Nelson
TEXTBOOK OF PEDIATRICS

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EDITION
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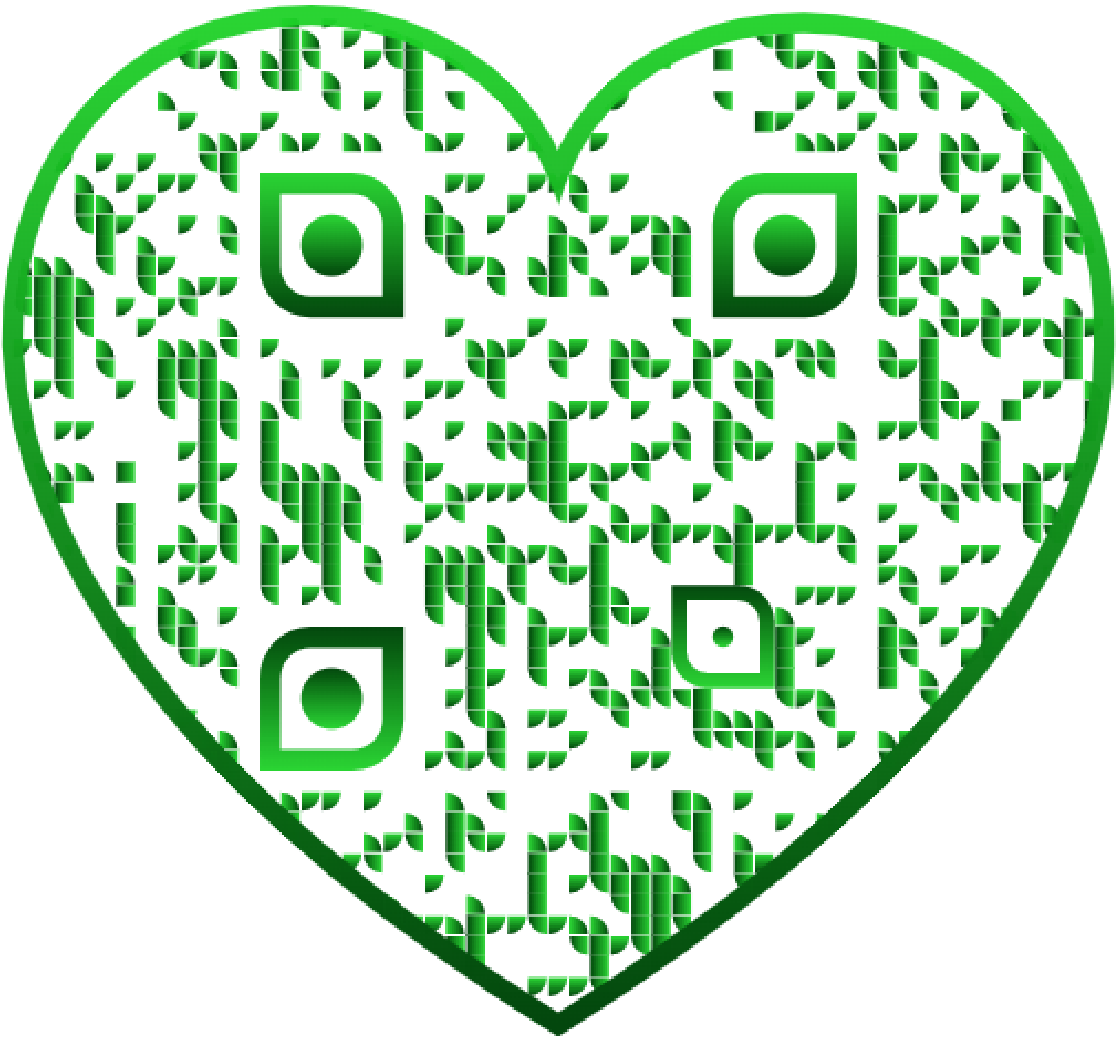

Nelson Textbook of Pediatrics

21 EDITION

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Dedication

To the Child's Physician who through their expressed confidence in past editions of this book have provided the stimulus for this revision. May we continue to be a resource of helpful information for clinicians who care for all of our children.

R.M. Kliegman

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Michigan State University
Grand Rapids, Michigan

Deformational Plagiocephaly

Stewart L. Adelson MD
Assistant Clinical Professor
Department of Psychiatry
Columbia University College of Physicians and Surgeons
Adjunct Clinical Assistant Professor
Weill Cornell Medical College of Cornell University
New York, New York

Gay, Lesbian, and Bisexual Adolescents

Shawn K. Ahlfeld MD
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Attending Neonatologist, Perinatal Institute
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Respiratory Tract Disorders

Osman Z. Ahmad MD
Fellow in Pediatric Gastroenterology
University of Alabama at Birmingham School of Medicine
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Clostridium difficile Infection

John J. Aiken MD, FACS, FAAP
Professor of Surgery
Division of Pediatric General and Thoracic Surgery
Medical College of Wisconsin
The Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Acute Appendicitis

Inguinal Hernias

Epigastric Hernia

Incisional Hernia

Cezmi A. Akdis MD
Professor of Immunology
Swiss Institute of Allergy and Asthma Research
Christine Kühne Center for Allergy Research and Education
Davos, Switzerland;
Medical Faculty, University of Zurich
Zurich, Switzerland

Allergy and the Immunologic Basis of Atopic Disease

Evaline A. Alessandrini MD, MSCE
Professor of Clinical Pediatrics
University of Cincinnati College of Medicine
Division of Emergency Medicine
Director, Quality Scholars Program in Health Care Transformation
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Outcomes and Risk Adjustment of Emergency Medical Services

Michael A. Alexander MD
Professor of Pediatrics and Rehabilitation Medicine
Thomas Jefferson Medical College
Philadelphia, Pennsylvania;
Emeritus Medical Staff
Nemours Alfred I. duPont Hospital for Children
Wilmington, Delaware

Evaluation of the Child for Rehabilitative Services

Omar Ali MD

Pediatric Endocrinology
Valley Children's Hospital
Madera, California

Hyperpituitarism, Tall Stature, and Overgrowth Syndromes
Hypofunction of the Testes
Pseudoprecocity Resulting from Tumors of the Testes
Gynecomastia

Karl E. Anderson MD, FACP
Professor of Preventive Medicine and Community Health and Internal Medicine
Director, Porphyria Laboratory and Center
University of Texas Medical Branch
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The Porphyrias

Kelly K. Anthony PhD, PLLC
Assistant Professor
Department of Psychiatry and Behavioral Sciences
Duke University Medical Center
Durham, North Carolina

Musculoskeletal Pain Syndromes

Alia Y. Antoon MD, DCH
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American Academy of Pediatrics
Honorary Pediatrician
MassGeneral Hospital for Children
Boston, Massachusetts

Burn Injuries
Cold Injuries

Susan D. Apkon MD

Professor
Department of Physical Medicine and Rehabilitation
University of Colorado
Denver, Colorado;
Chief, Pediatric Rehabilitation
Children's Hospital Colorado
Aurora, Colorado

Ambulation Assistance

Stacy P. Ardoin MD, MHS
Associate Professor of Clinical Medicine
Division of Adult and Pediatric Rheumatology
The Ohio State University Wexner Medical Center
Nationwide Children's Hospital
Columbus, Ohio

Systemic Lupus Erythematosus
Vasculitis Syndromes

Alexandre Arkader MD
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Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Common Fractures

Thaís Armangué MD, PhD
Pediatric Neurologist
Neuroimmunology Program
IDIBAPS—Hospital Clinic–Hospital Sant Joan de Déu (Barcelona)
University of Barcelona
Barcelona, Spain

Autoimmune Encephalitis

Carola A.S. Arndt MD
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Department of Pediatrics and Adolescent Medicine
Division of Pediatric Hematology-Oncology
Mayo Clinic
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Soft Tissue Sarcomas

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New Haven, Connecticut

Fever in the Older Child

David M. Asher MD
Supervisory Medical Officer and Chief
Laboratory of Bacterial and Transmissible Spongiform Encephalopathy Agents
Division of Emerging and Transfusion-Transmitted Diseases
US Food and Drug Administration
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Transmissible Spongiform Encephalopathies

Ann Ashworth PhD, Hon FRCPCH
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Department of Population Health
Nutrition Group
London School of Hygiene and Tropical Medicine
London, United Kingdom

Nutrition, Food Security, and Health

Amit Assa MD
Associate Professor of Pediatrics
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel;
Head, IBD Unit
Institute of Gastroenterology, Nutrition, and Liver Diseases

Schneider Children's Medical Center
Petah Tikva, Israel

Immunodeficiency Disorders

Barbara L. Asselin MD
Professor of Pediatrics and Oncology
Department of Pediatrics
University of Rochester School of Medicine and Dentistry
Golisano Children's Hospital and Wilmot Cancer Institute
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Epidemiology of Childhood and Adolescent Cancer

Christina M. Astley MD, ScD
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Harvard Medical School
Attending Physician
Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts

Autoimmune Polyglandular Syndromes

Joann L. Ater MD
Professor
Department of Pediatrics Patient Care
University of Texas MD Anderson Cancer Center
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Brain Tumors in Childhood
Neuroblastoma

Norrell Atkinson MD, FAAP
Assistant Professor of Pediatrics
Drexel University College of Medicine
Child Protection Program
St. Christopher's Hospital for Children

Philadelphia, Pennsylvania

Adolescent Sexual Assault

Erika U. Augustine MD
Associate Professor of Neurology and Pediatrics
Associate Director, Center for Health + Technology
University of Rochester Medical Center
Rochester, New York

Dystonia

Marilyn C. Augustyn MD
Professor of Pediatrics
Boston University School of Medicine
Boston Medical Center
Boston, Massachusetts

Impact of Violence on Children

Yaron Avitzur MD
Associate Professor
Department of Pediatrics
University of Toronto Faculty of Medicine
Division of Gastroenterology, Hepatology, and Nutrition
The Hospital for Sick Children
Toronto, Canada

Short Bowel Syndrome

Carlos A. Bacino MD
Professor and Vice Chair of Clinical Affairs
Department of Molecular and Human Genetics
Baylor College of Medicine
Director, Pediatrics Genetics Clinic
Texas Children's Hospital
Houston, Texas

Cytogenetics

Zinzi D. Bailey ScD, MSPH
Assistant Scientist
University of Miami Miller School of Medicine
Miami, Florida

Racism and Child Health

Binod Balakrishnan MBBS
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Medical College of Wisconsin
Division of Pediatric Critical Care
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Brain Death

Frances B. Balamuth MD, PhD, MSCE
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University of Pennsylvania Perelman School of Medicine
Associate Director of Research
Division of Emergency Medicine
Co-Director, Pediatric Sepsis Program
Children's Hospital of Philadelphia
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Triage of the Acutely Ill Child

Robert N. Baldassano MD
Colman Family Chair in Pediatric Inflammatory Bowel Disease and Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Center for Pediatric Inflammatory Bowel Disease
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Inflammatory Bowel Disease
Eosinophilic Gastroenteritis

Keith D. Baldwin MD, MSPT, MPH
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Department of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Physician
Neuromuscular Orthopaedics and Orthopaedic Trauma
Children's Hospital of Philadelphia
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Growth and Development
Evaluation of the Child
Torsional and Angular Deformities
Common Fractures

Christina Bales MD
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University of Pennsylvania Perelman School of MedicineMedical Director,
Intestinal Rehabilitation Program
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Intestinal Atresia, Stenosis, and Malrotation

William F. Balistreri MD
Medical Director Emeritus, Pediatric Liver Care Center
Division of Pediatric Gastroenterology, Hepatology, and Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Morphogenesis of the Liver and Biliary System
Manifestations of Liver Disease
Cholestasis
Metabolic Diseases of the Liver
Viral Hepatitis

Liver Disease Associated with Systemic Disorders
Mitochondrial Hepatopathies

Allison Ballantine MD, MEd
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Co-Director Med Ed Program, Graduate School of Education
Section Chief, Inpatient Services
Division of General Pediatrics
Children's Hospital of Philadelphia
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Malnutrition

Robert S. Baltimore MD
Professor of Pediatrics and Epidemiology
Clinical Professor of Nursing
Professor of Pediatrics and Epidemiology
Clinical Professor of Nursing
Yale School of Medicine
Associate Director of Hospital Epidemiology (for Pediatrics)
Yale–New Haven Hospital
New Haven, Connecticut

Listeria monocytogenes
Pseudomonas, Burkholderia, and Stenotrophomonas
Infective Endocarditis

Manisha Balwani MBBS, MS
Associate Professor of Medicine and Genetics and Genomic Sciences
Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
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The Porphyrias

Vaneeta Bamba MD
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Medical Director, Diagnostic and Research Growth Center
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Assessment of Growth

Brenda L. Banwell MD
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Grace R. Loeb Endowed Chair in Neurosciences
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Director, Pediatric Multiple Sclerosis Clinic
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Central Nervous System Vasculitis

Sarah F. Barclay PhD
Department of Medical Genetics
Cumming School of Medicine at University of Calgary
Alberta Children's Hospital Research Institute
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Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD)

Maria E. Barnes-Davis MD, PhD
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Attending Neonatologist
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Cincinnati Children's Hospital Medical Center
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The High-Risk Infant

Karyl S. Barron MD
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National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Amyloidosis

Donald Basel MBBCh
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Chief, Medical Genetics Division
Medical College of Wisconsin
Milwaukee, Wisconsin

Ehlers-Danlos Syndrome

Dorsey M. Bass MD
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Stanford University School of Medicine
Division of Pediatric Gastroenterology
Lucile Salter Packard Children's Hospital
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Rotaviruses, Caliciviruses, and Astroviruses

Mary T. Bassett MD, MPH
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Harvard T.H. Chan School of Public Health
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Racism and Child Health

Christian P. Bauerfeld MD
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Children's Hospital of Michigan
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Mechanical Ventilation

Rebecca A. Baum MD
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Positive Parenting and Support

Michael J. Bell MD
Professor, Pediatrics and Critical Care Medicine
Chief, Critical Care Medicine
Children's National Medical Center
The George Washington University School of Medicine
Washington, DC

Neurologic Emergencies and Stabilization

Nicole R. Bender MD
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Medical College of Wisconsin
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Morphology of the Skin
Dermatologic Evaluation of the Patient
Eczematous Disorders
Photosensitivity
Diseases of the Epidermis

Daniel K. Benjamin Jr, MD, PhD, MPH
Kiser-Arena Professor of Pediatrics
Duke Clinical Research Institute
Duke University Medical Center
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Principles of Antifungal Therapy

Candida

Michael J. Bennett PhD, FRCPath, FACB
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University of Pennsylvania Perelman School of Medicine
Director, Michael J. Palmieri Metabolic Disease Laboratory
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Disorders of Mitochondrial Fatty Acid β-Oxidation

Daniel Bernstein MD
Alfred Woodley Salter and Mabel G. Salter Endowed Professor in Pediatrics
Associate Dean for Curriculum and Scholarship
Stanford University School of Medicine
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Cardiac Development

The Fetal to Neonatal Circulatory Transition

History and Physical Examination in Cardiac Evaluation

Laboratory Cardiac Evaluation

Epidemiology and Genetic Basis of Congenital Heart Disease

Evaluation and Screening of the Infant or Child with Congenital Heart Disease

Acyanotic Congenital Heart Disease: Left-to-Right Shunt Lesions

Acyanotic Congenital Heart Disease: The Obstructive Lesions

Acyanotic Congenital Heart Disease: Regurgitant

Lesions

Cyanotic Congenital Heart Disease: Evaluation of the Critically Ill Neonate with Cyanosis and Respiratory Distress

Cyanotic Congenital Heart Lesions: Lesions Associated with Decreased Pulmonary Blood Flow

Cyanotic Congenital Heart Disease: Lesions Associated with Increased Pulmonary Blood Flow

Other Congenital Heart and Vascular Malformations

Pulmonary Hypertension

General Principles of Treatment of Congenital Heart Disease

Diseases of the Blood Vessels (Aneurysms and Fistulas)

Henry H. Bernstein DO, MHCM, FAAP
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Zucker School of Medicine at Hofstra/Northwell
Cohen Children's Medical Center of New York
New Hyde Park, New York

Immunization Practices

Diana X. Bharucha-Goebel MD
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Children's National Medical Center
Washington, DC;
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National Institutes of Health/NINDS
Neurogenetics Branch/NNDCS
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Muscular Dystrophies

Myasthenia Gravis

Giant Axonal Neuropathy

Holly M. Biggs MD, MPH
Medical Epidemiologist
Respiratory Viruses Branch, Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
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Parainfluenza Viruses

Samra S. Blanchard MD
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Peptic Ulcer Disease in Children

Joshua A. Blatter MD, MPH
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Washington University School of Medicine in St. Louis
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Congenital Disorders of the Lung

Archie Bleyer MD, FRCP (Glasg)
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Knight Cancer Center
Oregon Health & Science University
Chair, Institutional Review Board for St. Charles Health System
Portland, Oregon;
Professor of Pediatrics
University of Texas MD Anderson Cancer Center
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Principles of Cancer Treatment
The Leukemias

Nathan J. Blum MD
William H. Bennett Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief, Division of Developmental and Behavioral Pediatrics
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Philadelphia, Pennsylvania

Steven R. Boas MD, FAAP, FACSM
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President and CEO, The Cystic Fibrosis Institute
Glenview, Illinois;
Clinical Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Emphysema and Overinflation
α1-Antitrypsin Deficiency and Emphysema
Other Distal Airway Diseases
Skeletal Diseases Influencing Pulmonary Function

Walter O. Bockting PhD
Professor of Medical Psychology (in Psychiatry and Nursing)
Research Scientist, New York State Psychiatric Institute
Division of Gender, Sexuality, and Health
Department of Psychiatry
Columbia University Vagelos College of Physicians and Surgeons
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Gender and Sexual Identity
Transgender Care

Mark Boguniewicz MD
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Division of Allergy-Immunology
Department of Pediatrics
University of Colorado School of Medicine
National Jewish Health
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Ocular Allergies

Michael J. Boivin PhD, MPH
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Michigan State University College of Osteopathic Medicine
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Nodding Syndrome

Daniel J. Bonthius MD, PhD
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University of Iowa Carver College of Medicine
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Lymphocytic Choriomeningitis Virus

Brett J. Bordini MD, FAAP
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Division of Hospital Medicine
Nelson Service for Undiagnosed and Rare Diseases
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Plastic Bronchitis

Kristopher R. Bosse MD
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Molecular and Cellular Biology of Cancer

Bret L. Bostwick MD
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Baylor College of Medicine
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Genetics of Common Disorders

Kenneth M. Boyer MD
Professor and Woman's Board Chair, Emeritus
Department of Pediatrics
Rush University Medical Center
Chicago, Illinois

Toxoplasmosis (Toxoplasma gondii)

Jennifer M. Brady MD
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Perinatal Institute
Division of Neonatology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

The High-Risk Infant
Transport of the Critically Ill Newborn
Neonatal Resuscitation and Delivery Room Emergencies

Patrick W. Brady MD, MSc
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Attending Physician, Division of Hospital Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Safety in Healthcare for Children

Rebecca C. Brady MD
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Cincinnati Children's Hospital Medical Center
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Congenital and Perinatal Infections
Coccidioidomycosis (Coccidioides Species)

Samuel L. Brady MS, PhD
Clinical Medical Physicist
Cincinnati Children's Hospital
Associate Professor of Radiology
University of Cincinnati
Cincinnati, Ohio

Biologic Effects of Ionizing Radiation on Children

Amanda M. Brandow DO, MS
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Division of Pediatric Hematology/Oncology
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Milwaukee, Wisconsin

Enzymatic Defects
Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias
Hemolytic Anemias Secondary to Other Extracellular Factors
Polycythemia
Nonclonal Polycythemia

David T. Breault MD, PhD
Associate Professor of Pediatrics
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Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts

Diabetes Insipidus
Other Abnormalities of Arginine Vasopressin Metabolism and Action

Cora Collette Breuner MD, MPH
Professor of Pediatrics
Adjunct Professor of Orthopedics and Sports Medicine
University of Washington School of Medicine
Division of Adolescent Medicine
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Substance Abuse
Adolescent Pregnancy

Carolyn Bridgemohan MD
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Autism Spectrum Disorder

William J. Britt MD
Charles A. Alford Professor of Pediatrics
Professor of Microbiology and Neurobiology
University of Alabama Birmingham School of Medicine

Division of Pediatric Infectious Diseases
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Cytomegalovirus

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Fever Without a Focus in the Neonate and Young Infant

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Meconium Ileus, Peritonitis, and Intestinal Obstruction
Necrotizing Enterocolitis

J. Naylor Brownell MD
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Feeding Healthy Infants, Children, and Adolescents

Meghen B. Browning MD
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The Medical College of Wisconsin

Division of Pediatric Hematology-Oncology
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Pancreatic Tumors

Nicola Brunetti-Pierri MD
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Department of Translational Medicine
University of Naples Federico II
Associate Investigator, Telethon Institute of Genetics and Medicine (TIGEM)
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Management and Treatment of Genetic Disorders

Phillip R. Bryant DO
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Division of Rehabilitation Medicine
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Rehabilitation for Severe Traumatic Brain injury
Spinal Cord Injury and Autonomic Dysreflexia Management

Rebecca H. Buckley MD
J. Buren Sidbury Professor of Pediatrics
Professor of Immunology
Duke University School of Medicine
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Evaluation of Suspected Immunodeficiency
The T-, B-, and NK-Cell Systems
T Lymphocytes, B Lymphocytes, and Natural Killer Cells

Primary Defects of Antibody Production
Treatment of B-Cell Defects
Primary Defects of Cellular Immunity
Immunodeficiencies Affecting Multiple Cell Types

Cynthia Etzler Budek MS, APN/NP, CPNP-AC/PC
Pediatric Nurse Practitioner
Department of Pulmonary and Critical Care Medicine
Transitional Care/Pulmonary Habilitation Unit
Ann & Robert H. Lurie Children's Hospital of Chicago
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Other Conditions Affecting Respiration

Supinda Bunyavanich MD, MPH, MPhil
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Associate Director, Jaffe Food Allergy Institute
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Department of Genetics and Genomic Sciences
Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
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Diagnosis of Allergic Disease

Carey-Ann D. Burnham PhD D(ABMM), FIDSA, F(AAM)
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Barnes Jewish Hospital
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Diagnostic Microbiology

Gale R. Burstein MD, MPH
Clinical Professor
Department of Pediatrics

University at Buffalo Jacobs School of Medicine and Biomedical Sciences
Commissioner, Erie County Department of Health
Buffalo, New York

The Epidemiology of Adolescent Health Problems
Transitioning to Adult Care
The Breast
Menstrual Problems
Contraception
Sexually Transmitted Infections

Amaya L. Bustinduy MD, PhD, MPH
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London School of Hygiene and Tropical Medicine
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Schistosomiasis (Schistosoma)
Flukes (Liver, Lung, and Intestinal)

Jill P. Buyon MD
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NYU Langone Medical Center
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Neonatal Lupus

Miguel M. Cabada MD, MSc
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The University of Texas Medical Branch at Galveston
Galveston, Texas

Echinococcosis (Echinococcus granulosus and

Echinococcus multilocularis)

Michaela Cada MD, FRCPC, FAAP, MPH
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University of Toronto Faculty of Medicine
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Division of Hematology/Oncology
The Hospital for Sick Children
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Inherited Bone Marrow Failure Syndromes with Pancytopenia

Derya Caglar MD
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Department of Pediatrics
University of Washington School of Medicine
Attending Physician
Division of Emergency Medicine
Seattle Children's Hospital
Seattle, Washington

Drowning and Submersion Injury

Mitchell S. Cairo MD
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Departments of Pediatrics, Medicine, Pathology, Microbiology, and Immunology and Cell Biology and Anatomy
New York Medical College
Chief, Division of Pediatric Hematology, Oncology and Stem Cell Transplantation
Maria Fareri Children's Hospital at Westchester Medical Center
New York Medical College
Valhalla, New York

Lymphoma

Diane P. Calello MD
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Executive and Medical Director
New Jersey Poison Information and Education System
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Nonbacterial Food Poisoning

Lauren E. Camarda MD
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Bronchitis

Lindsay Hatzenbuehler Cameron MD, MPH
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Baylor College of Medicine
Pediatric Infectious Diseases
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Tuberculosis (Mycobacterium tuberculosis)

Bruce M. Camitta MD
Rebecca Jean Slye Professor of Pediatrics
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Medical College of Wisconsin
Midwest Children's Cancer Center
Milwaukee, Wisconsin

Polycythemia
Nonclonal Polycythemia
Anatomy and Function of the Spleen
Splenomegaly
Hyposplenism, Splenic Trauma, and Splenectomy

Anatomy and Function of the Lymphatic System
Abnormalities of Lymphatic Vessels
Lymphadenopathy

Angela J.P. Campbell MD, MPH
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Centers for Disease Control and Prevention
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Influenza Viruses
Parainfluenza Viruses

Rebecca F. Carlin MD
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Assistant Professor of Pediatrics
George Washington University School of Medicine and Health Sciences
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Sudden Infant Death Syndrome

Michael R. Carr MD
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Division of Cardiology
Northwestern University Feinberg School of Medicine
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Rheumatic Heart Disease

Robert B. Carrigan MD
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University of Pennsylvania Perelman School of Medicine

Pediatric Hand Surgeon
Children's Hospital of Philadelphia
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The Upper Limb

Michael S. Carroll
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Congenital Central Hypoventilation Syndrome

Rebecca G. Carter MD
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The Second Year
The Preschool Years

Mary T. Caserta MD
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Roseola (Human Herpesviruses 6 and 7)
Human Herpesvirus 8

Jennifer I. Chapman MD
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George Washington University School of Medicine and Health Sciences
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Children's National Medical Center
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Principles Applicable to the Developing World

Ira M. Cheifetz MD, FCCM, FAARC
Professor of Pediatrics and Anesthesiology
Duke University School of Medicine
Executive Director and Chief Medical Officer
Duke Children's Hospital
Associate Chief Medical Officer
Duke University Hospital
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Pediatric Emergencies and Resuscitation
Shock

Gisela G. Chelimsky MD
Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Gastroenterology
Children's Hospital Milwaukee
Milwaukee, Wisconsin

Chronic Overlapping Pain Conditions
Postural Tachycardia Syndrome

Thomas C. Chelimsky MD
Professor of Neurology
Medical College of Wisconsin
Milwaukee, Wisconsin

Chronic Overlapping Pain Conditions
Postural Tachycardia Syndrome

Wassim Chemaitilly MD
Associate Member and Director
Division of Endocrinology
Department of Pediatric Medicine
St. Jude Children's Research Hospital

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Physiology of Puberty
Disorders of Pubertal Development

Yuan-Tsong Chen MD, PhD
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Durham, North Carolina

Defects in Metabolism of Carbohydrates

Jennifer A. Chiriboga PhD
Pediatric and School Psychologist
Assistant Professor
Department of Counseling, Psychology, and Special Education
Duquesne University School of Psychology
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Anxiety Disorders

Yvonne E. Chiu MD
Associate Professor of Dermatology and Pediatrics
Medical College of Wisconsin
Department of Dermatology
Division of Pediatric Dermatology
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Morphology of the Skin
Dermatologic Evaluation of the Patient
Eczematous Disorders
Photosensitivity
Diseases of the Epidermis

Christine B. Cho MD
Assistant Professor of Pediatrics

Division of Allergy-Immunology
Department of Pediatrics
University of Colorado School of Medicine
National Jewish Health
Denver, Colorado

Ocular Allergies
Adverse Reactions to Drugs

Hey Jin Chong MD, PhD
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Infections in Immunocompromised Persons

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Development of the Hematopoietic System

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Ryan White Center for Pediatric Infectious Diseases and Global Health
Indiana University School of Medicine
Indianapolis, Indiana

Health Advice for Children Traveling Internationally

Robert H. Chun MD
Associate Professor of Pediatric Otolaryngology
Department of Otolaryngology and Communication Sciences

Medical College of Wisconsin
Milwaukee, Wisconsin

Acute Mastoiditis

Michael J. Chusid MD
Professor (Infectious Disease)
Department of Pediatrics
Medical College of Wisconsin
Medical Director, Infection Prevention and Control
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Infection Prevention and Control
Other Anaerobic Infections

Theodore J. Cieslak MD, MPH, FAAP, FIDSA
Associate Professor of Epidemiology
Associate Director, Center for Biosecurity, Biopreparedness, and Emerging Infectious Diseases
University of Nebraska Medical Center
College of Public Health
Omaha, Nebraska

Biologic and Chemical Terrorism

Donna J. Claes MD, MS, BS Pharm
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Pediatric Nephrology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Chronic Kidney Disease
End-Stage Renal Disease

Jeff A. Clark MD
Associate Professor

Department of Pediatrics
Wayne State University School of Medicine
Children's Hospital of Michigan
Detroit, Michigan

Respiratory Distress and Failure

John David Clemens MD, PhD (Hon)
Professor and Vice Chair
Department of Epidemiology
Founding Director, Center for Global Infectious Diseases
UCLA Fielding School of Public Health
Los Angeles, California;
International Centre for Diarrhoeal Disease Research
Dhaka, Bangladesh

International Immunization Practices

Thomas D. Coates MD
Professor of Pediatrics and Pathology
University of Southern California Keck School of Medicine
Head, Section of Hematology
Children's Center for Cancer and Blood Diseases
Children's Hospital of Los Angeles
Los Angeles, California

Neutrophils
Disorders of Phagocyte Function

Susan E. Coffin MD, MPH
Professor of Pediatrics
Distinguished Chair in the Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Associate Chief, Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Childcare and Communicable Diseases

Joanna S. Cohen MD
Associate Professor of Pediatrics and Emergency Medicine
George Washington University School of Medicine
Division of Pediatric Emergency Medicine
Children's National Medical Center
Washington, DC

Care of Abrasions and Minor Lacerations

Mitchell B. Cohen MD
Katharine Reynolds Ireland Endowed Chair in Pediatrics
Professor and Chair, Department of Pediatrics
University of Alabama at Birmingham School of Medicine
Physician-in-Chief
Children's of Alabama
Birmingham, Alabama

Clostridium difficile Infection

Michael Cohen-Wolkowiez MD
Professor of Pediatrics
Duke Clinical Research Institute
Duke University Medical Center
Durham, North Carolina

Principles of Antifungal Therapy

Robert A. Colbert MD, PhD
Acting Clinical Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Chief, Pediatric Translational Branch
National Institutes of Health
Bethesda, Maryland

Ankylosing Spondylitis and Other Spondylarthritides
Reactive and Postinfectious Arthritis

F. Sessions Cole III, MD

Assistant Vice-Chancellor for Children's Health
Park J. White Professor of Pediatrics
Professor of Cell Biology and Physiology
Washington University School of Medicine in St. Louis
Chief Medical Officer
Vice-Chairman, Department of Pediatrics
Director of Newborn Medicine
St. Louis Children's Hospital
St. Louis, Missouri

Inherited Disorders of Surfactant Metabolism
Pulmonary Alveolar Proteinosis

J. Michael Collaco MD, MS, MBA, MPH, PhD
Associate Professor of Pediatrics
Eudowood Division of Pediatric Respiratory Sciences
Johns Hopkins University School of Medicine
Baltimore, Maryland

Bronchopulmonary Dysplasia

John L. Colombo MD
Professor of Pediatrics
University of Nebraska College of Medicine
Division of Pediatric Pulmonology
Nebraska Regional Cystic Fibrosis Center
University of Nebraska Medical Center
Omaha, Nebraska

Aspiration Syndromes
Chronic Recurrent Aspiration

Joseph A. Congeni MD
Director, Sports Medicine Center
Akron Children's Hospital
Akron, Ohio;
Associate Professor of Pediatrics and Sports Medicine
Northeast Ohio Medical University

Rootstown, Ohio;
Clinical Associate Professor of Pediatrics and Sports Medicine
Ohio University College of Osteopathic Medicine
Athens, Ohio

Sports-Related Traumatic Brain Injury (Concussion)
Cervical Spinal Spine Injuries

Lindsay N. Conner MD, MPH
Department of Obstetrics and Gynecology
Benefis Health System
Great Falls, Montana

Breast Concerns

Sarah M. Creighton MBBS
Professor and Consultant Gynaecologist
Department of Women's Health
University College London Hospitals
London, United Kingdom

Female Genital Mutilation

James E. Crowe Jr, MD
Ann Scott Carell Chair and Professor of Pediatrics
Division of Pediatric Infectious Diseases
Professor of Pathology, Microbiology, and Immunology
Director, Vanderbilt Vaccine Center
Vanderbilt University School of Medicine
Nashville, Tennessee

Respiratory Syncytial Virus
Human Metapneumovirus

Steven J. Czinn MD
Professor and Chair
Department of Pediatrics
University of Maryland School of Medicine

Baltimore, Maryland

Peptic Ulcer Disease in Children

Aarti S. Dalal DO
Assistant Professor of Pediatrics
Washington University School of Medicine in St. Louis
Division of Pediatric Cardiology
St Louis Children's Hospital
St. Louis, Missouri

Syncope
Disturbances of Rate and Rhythm of the Heart
Sudden Death

Josep O. Dalmau MD, PhD
Research Professor ICREA-IDIBAPS
Service of Neurology
Hospital Clinic
University of Barcelona
Barcelona, Spain;
Adjunct Professor of Neurology
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania

Autoimmune Encephalitis

Lara A. Danziger-Isakov MD, MPH
Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Immunocompromised Host Infectious Disease
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Histoplasmosis (Histoplasma capsulatum)

Toni Darville MD
Professor of Pediatrics and Microbiology and Immunology

University of North Carolina at Chapel Hill
Chief, Division of Infectious Diseases
Vice-Chair of Pediatric Research
North Carolina Children's Hospital
Chapel Hill, North Carolina

Neisseria gonorrhoeae (Gonococcus)

Robert S. Daum MD, CM, MSc
Professor of Medicine
Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, Maryland

Haemophilus influenzae

Loren T. Davidson MD
Clinical Professor
Department of Physical Medicine and Rehabilitation
University of California, Davis School of Medicine
Davis, California;
Director, Spinal Cord Injury
Shriners Hospital for Children
Sacramento, California

Spasticity

Richard S. Davidson MD
Emeritus Professor of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

The Foot and Toes
Leg-Length Discrepancy
Arthrogryposis

H. Dele Davies MD, MS, MHCM
Vice-Chancellor for Academic Affairs
Dean for Graduate Studies
University of Nebraska Medical Center
Omaha, Nebraska

Chancroid (Haemophilus ducreyi)
Syphilis (Treponema pallidum)
Nonvenereal Treponemal Infections
Leptospira
Relapsing Fever (Borrelia)

Najat C. Daw MD
Professor
Division of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas

Neoplasms of the Kidney

Shannon L. Dean MD, PhD
Instructor in Neurology and Pediatrics
University of Rochester Medical Center
Rochester, New York

Dystonia

Helen M. Oquendo Del Toro, MD
Pediatric and Adolescent Gynecology
Clinical Assistant Professor
University of New Mexico
Department of Obstetrics and Gynecology
Albuquerque, New Mexico

Vulvovaginitis

David R. DeMaso MD

Psychiatrist-in-Chief
The Leon Eisenberg Chair in Psychiatry
Boston Children's Hospital;
George P. Gardner and Olga E. Monks Professor of Child Psychiatry
Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

Psychosocial Assessment and Interviewing
Psychopharmacology
Psychotherapy and Psychiatric Hospitalization
Somatic Symptom and Related Disorders
Rumination and Pica
Motor Disorders and Habits
Anxiety Disorders
Mood Disorders
Suicide and Attempted Suicide
Disruptive, Impulse-Control, and Conduct Disorders
Tantrums and Breath-Holding Spells
Lying, Stealing, and Truancy
Aggression
Self-Injurious Behavior
Childhood Psychoses

Mark R. Denison MD
Craig-Weaver Professor of Pediatrics
Professor of Pathology, Microbiology, and Immunology
Vanderbilt University Medical Center
Monroe Carell Jr Children's Hospital at Vanderbilt
Nashville, Tennessee

Coronaviruses

Arlene E. Dent MD, PhD
Associate Professor of Pediatrics
Center for Global Health and Diseases
Case Western Reserve University School of Medicine
Cleveland, Ohio

Ascariasis (Ascaris lumbricoides)
Trichuriasis (Trichuris trichiura)
Enterobiasis (Enterobius vermicularis)
Strongyloidiasis (Strongyloides stercoralis)
Lymphatic Filariasis (Brugia malayi, Brugia timori, and Wuchereria bancrofti)
Other Tissue Nematodes
Toxocariasis (Visceral and Ocular Larva Migrans)
Trichinellosis (Trichinella spiralis)

Robert J. Desnick MD, PhD
Dean for Genetics and Genomic Medicine
Professor and Chair Emeritus, Genetics and Genomic Sciences
Professor, Departments of Pediatrics, Oncological Sciences, and Obstetrics, Gynecology and Reproductive Science
Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
New York, New York

Lipidoses (Lysosomal Storage Disorders)
Mucolipidoses
Disorders of Glycoprotein Degradation and Structure
The Porphyrias

Robin R. Deterding MD
Professor of Pediatrics
University of Colorado School of Medicine
Chief, Pediatric Pulmonary Medicine
Director, Breathing Institute

Co-Chair, Children's Interstitial and Diffuse Lung Disease Research Network
Medical Director, Children's Colorado Innovation Center
Children's Hospital Colorado
Aurora, Colorado

Fibrotic Lung Disease

Prasad Devarajan MD, FAAP
Louise M. Williams Endowed Chair
Professor of Pediatrics and Developmental Biology
University of Cincinnati College of Medicine
Director of Nephrology and Hypertension
CEO, Dialysis Unit
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Multisystem Disease Associated with Hematuria
Tubulointerstitial Disease Associated with Hematuria
Vascular Disease Associated with Hematuria
Anatomic Abnormalities Associated with Hematuria
Lower Urinary Tract Causes of Hematuria
Acute Kidney Injury

Gabrielle A. deVeber MD, MHSc
Professor of Pediatrics
University of Toronto Faculty of Medicine
Children's Stroke Program
Division of Neurology
Senior Scientist Emeritus, Research Institute
Hospital for Sick Children
Toronto, Ontario, Canada

Pediatric Stroke

Vineet Dhar BDS, MDS, PhD,
Clinical Professor and Chairman

Department of Orthodontics and Pediatric Dentistry
Director, Advanced Specialty Education Program, Pediatric Dentistry
Diplomate, American Board of Pediatric Dentistry
University of Maryland School of Dentistry
Baltimore, Maryland

Development and Developmental Anomalies of the Teeth
Disorders of the Oral Cavity Associated with Other Conditions
Malocclusion
Cleft Lip and Palate
Syndromes with Oral Manifestations
Dental Caries
Periodontal Diseases
Dental Trauma
Common Lesions of the Oral Soft Tissues
Diseases of the Salivary Glands and Jaws
Diagnostic Radiology in Dental Assessment

Anil Dhawan MD, FRCPCH
Professor of Pediatric Hepatology
Pediatric Liver GI and Nutrition Centre
MowatLabs King's College London School of Medicine at King's College Hospital NSH Foundation Trust
London, United Kingdom

Liver and Biliary Disorders Causing Malabsorption

André A.S. Dick MD, MPH, FACS
Associate Professor of Surgery
Division of Transplantation
University of Washington School of Medicine

Section of Pediatric Transplantation
Seattle Children's Hospital
Seattle, Washington

Intestinal Transplantation in Children with Intestinal Failure

Harry C. Dietz III, MD
Victor A. McKusick Professor of Medicine and Genetics
Departments of Pediatrics, Medicine, and Molecular Biology and Genetics
Investigator, Howard Hughes Medical Institute
Institute of Genetic Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Marfan Syndrome

Daren A. Diiorio MD
Resident Physician
Department of Dermatology
Medical College of Wisconsin
Milwaukee, Wisconsin

Principles of Dermatologic Therapy
Cutaneous Bacterial Infections
Cutaneous Fungal Infections
Cutaneous Viral Infections
Arthropod Bites and Infestations

Linda A. DiMeglio MD, MPH
Professor
Department of Pediatrics
Indiana University School of Medicine
Indiana University Clinical and Translational Science Institute
Riley Hospital for Children
Indianapolis, Indiana

Hypophosphatasia
Hyperphosphatasia

Bradley P. Dixon MD, FASN
Associate Professor of Pediatrics and Medicine
Renal Section, Department of Pediatrics
University of Colorado School of Medicine
Kidney Center
Children's Hospital Colorado
Aurora, Colorado

Tubular Function
Renal Tubular Acidosis
Nephrogenic Diabetes Insipidus
Inherited Tubular Transport Abnormalities

Nomazulu Dlamini MBBS, PhD
Assistant Professor of Pediatrics
University of Toronto Faculty of Medicine
Staff Physician in Neurology
Director, Children's Stroke Program
Hospital for Sick Children
Toronto, Ontario, Canada

Pediatric Stroke

Sonam N. Dodhia MD
Resident Physician
New York-Presbyterian Hospital
New York, New York

Congenital Disorders of the Nose
Acquired Disorders of the Nose
Nasal Polyps
General Considerations and Evaluation of the Ear

Hearing Loss
Congenital Malformations of the Ear
External Otitis (Otitis Externa)
The Inner Ear and Diseases of the Bony Labyrinth
Traumatic Injuries of the Ear and Temporal Bone
Tumors of the Ear and Temporal Bone

Patricia A. Donohoue MD
Professor of Pediatrics
Chief, Pediatric Endocrinology
Medical College of Wisconsin
Medical Director, Pediatric Endocrinology
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Development and Function of the Gonads
Hypofunction of the Testes
Pseudoprecocity Resulting from Tumors of the Testes
Gynecomastia
Hypofunction of the Ovaries
Pseudoprecocity Resulting from Lesions of the Ovary
Disorders of Sex Development

Kevin J. Downes MD
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician, Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Tularemia (Francisella tularensis)
Brucella

Alexander J. Doyle MBBS, MDRes, FRCA
William Harvey Research Institute
Barts and The London School of Medicine
Queen Mary University of London
London, United Kingdom

Marfan Syndrome

Daniel A. Doyle MD
Associate Professor of Pediatrics
Thomas Jefferson University Sidney Kimmel Medical College
Philadelphia, Pennsylvania;
Chief, Division of Pediatric Endocrinology
Nemours Alfred I. duPont Hospital for Children
Wilmington, Delaware

Hormones and Peptides of Calcium Homeostasis and Bone Metabolism
Hypoparathyroidism
Pseudohypoparathyroidism (Albright Hereditary Osteodystrophy)
Hyperparathyroidism

Jefferson J. Doyle MBBChir, PhD, MHS
Assistant Professor of Ophthalmology
Wilmer Eye Institute
Johns Hopkins Hospital
Affiliate Member, Institute of Genetic Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Marfan Syndrome

Stephen C. Dreskin MD, PhD
Professor of Medicine and Immunology
Division of Allergy and Clinical Immunology

Department of Medicine
University of Colorado School of Medicine
Aurora, Colorado

Urticaria (Hives) and Angioedema

Sherilyn W. Driscoll MD
Division Chair, Pediatric Rehabilitation
Departments of Physical Medicine and Rehabilitation and Pediatric and Adolescent Medicine
Mayo Clinic Children's Center
Rochester, Minnesota

Specific Sports and Associated Injuries

Yigal Dror MD, FRCPC
Professor
Department of Pediatrics
University of Toronto Faculty of Medicine
Head, Hematology Section
Director, Marrow Failure and Myelodysplasia Program
The Hospital for Sick Children
Toronto, Ontario, Canada

The Inherited Pancytopenias

Jill N. D'Souza MD
Assistant Professor
Baylor College of Medicine
Division of Pediatric Otolaryngology – Head and Neck Surgery
Texas Children's Hospital
Houston, Texas

Congenital Anomalies of the Larynx, Trachea, and Bronchi

Howard Dubowitz MD, MS, FAAP
Professor of Pediatrics

Head, Division of Child Protection
Director, Center for Families
University of Maryland School of Medicine
Baltimore, Maryland

Abused and Neglected Children

J. Stephen Dumler MD
Professor and Chair
Joint Department of Pathology
Uniformed Services University of the Health Sciences
Walter Reed National Military Medical Center
Bethesda, Maryland

Spotted Fever Group Rickettsioses
Scrub Typhus (Orientia tsutsugamushi)
Typhus Group Rickettsioses
Ehrlichioses and Anaplasmosis
Q Fever (Coxiella burnetii)

Janet Duncan MSN, CPNP
Department of Psychosocial Oncology and Palliative Care
Boston Children's Hospital
Dana-Farber Cancer Institute
Boston, Massachusetts

Pediatric Palliative Care

Jeffrey A. Dvergsten MD
Assistant Professor of Pediatrics
Duke University School of Medicine
Division of Pediatric Rheumatology
Duke University Health System
Durham, North Carolina

Treatment of Rheumatic Diseases

Michael G. Earing MD
Professor of Internal Medicine and Pediatrics
Division of Adult Cardiovascular Medicine and Division of Pediatric Cardiology
Medical College of Wisconsin
Director, Wisconsin Adult Congenital Heart Disease Program (WAtCH)
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Congenital Heart Disease in Adults

Matthew D. Eberly MD
Associate Professor of Pediatrics
Program Director, Pediatric Infectious Diseases Fellowship
Uniformed Services University of the Health Sciences
Bethesda, Maryland

Primary Amebic Meningoencephalitis

S. Derrick Eddy MD
Sports Medicine Education Director
Akron Children's Hospital
Clinical Assistant Professor of Pediatrics
Northeast Ohio Medical University
Akron, Ohio

Cervical Spinal Spine Injuries

Marie E. Egan MD
Professor of Pediatrics (Respiratory) and Cellular and Molecular Physiology
Director, Cystic Fibrosis Center
Vice Chair for Research
Department of Pediatrics
Yale School of Medicine
New Haven, Connecticut

Cystic Fibrosis

Jack S. Elder MD, FACS
Chief of Pediatric Urology

Massachusetts General Hospital
Boston, Massachusetts

Congenital Anomalies and Dysgenesis of the Kidneys
Urinary Tract Infections
Vesicoureteral Reflux
Obstruction of the Urinary Tract
Anomalies of the Bladder
Neuropathic Bladder
Enuresis and Voiding Dysfunction
Anomalies of the Penis and Urethra
Disorders and Anomalies of the Scrotal Contents
Trauma to the Genitourinary Tract
Urinary Lithiasis

Elizabeth Englander PhD
Professor of Psychology
Founder and Director, Massachusetts Aggression Reduction Center
Bridgewater State University
Bridgewater, Massachusetts

Bullying, Cyberbullying, and School Violence

Elizabeth Enlow MD, MS
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Neonatology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Clinical Manifestations of Diseases in the Newborn Period

Stephen C. Eppes MD

Professor of Pediatrics
Sidney Kimmel Medical College at Thomas Jefferson University
Philadelphia, Pennsylvania;
Vice Chair, Department of Pediatrics
Division of Pediatric Infectious Diseases
Christiana Care Health System
Newark, Delaware

Lyme Disease (Borrelia burgdorferi)

Jessica Ericson MD
Assistant Professor of Pediatrics
Pennsylvania State University College of Medicine
Division of Pediatric Infectious Disease
Milton S. Hershey Medical Center
Hershey, Pennsylvania

Candida

Elif Erkan MD, MS
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Pediatric Nephrology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Nephrotic Syndrome

Yokabed Ermias MPH
Fellow, Division of Reproductive Health
Centers for Disease Control and Prevention
Atlanta, Georgia

Contraception

Ashley M. Eskew MD
Fellow, Reproductive Endocrinology and Infertility
Department of Obstetrics and Gynecology
Washington University School of Medicine in St. Louis

St. Louis, Missouri

Vulvovaginal and Müllerian Anomalies

Ruth A. Etzel MD, PhD
Milken Institute School of Public Health
George Washington University
Washington, DC

Overview of Environmental Health and Children

Matthew P. Fahrenkopf MD
Plastic Surgery Resident
Spectrum Health Hospitals
Michigan State University
Grand Rapids, Michigan

Deformational Plagiocephaly

Marni J. Falk MD
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Executive Director, Mitochondrial Medicine Frontier Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Mitochondrial Disease Diagnosis

John J. Faria MD
Assistant Professor of Otolaryngology and Pediatrics
University of Rochester
Rochester, New York

Acute Mastoiditis

John H. Fargo DO
Division of Pediatric Hematology/Oncology
Showers Family Center for Childhood Cancer and Blood Disorders
Akron Children's Hospital

Akron, Ohio

The Acquired Pancytopenias

Kristen A. Feemster MD, MPH, MSPHR
Director of Research for the Vaccine Education Center
Children's Hospital of Philadelphia
Medical Director of the Immunization Program and Acute Communicable Diseases
Philadelphia Department of Public Health
Adjunct Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania

Human Papillomaviruses

Susan Feigelman MD
Professor, Department of Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland

Developmental and Behavioral Theories
Assessment of Fetal Growth and Development
The First Year
The Second Year
The Preschool Years
Middle Childhood

Jeffrey A. Feinstein MD, MPH
Dunlevie Family Professor of Pulmonary Vascular Disease
Division of Pediatric Cardiology
Stanford University School of Medicine
Professor, by courtesy, of Bioengineering
Medical Director, Pediatric Pulmonary Hypertension Program
Lucile Packard Children's Hospital at Stanford
Palo Alto, California

Pulmonary Hypertension

Amy G. Feldman MD, MSCS
Assistant Professor of Pediatrics
University of Colorado School of Medicine
Denver, Colorado;
Program Director, Liver Transplant Fellowship
Children's Hospital Colorado Research Institute
Aurora, Colorado

Drug- and Toxin-Induced Liver Injury
Acute Hepatic Failure

Eric I. Felner MD, MS
Professor of Pediatrics
Division of Pediatric Endocrinology
Director, Pediatric Clerkships
Emory University School of Medicine
Atlanta, Georgia

Hormones of the Hypothalamus and Pituitary
Hypopituitarism

Edward C. Fels MD
Clinical Assistant Professor of Medicine
Tufts University School of Medicine
Boston, Massachusetts;
Maine Medical Center
Portland, Maine

Vasculitis Syndromes

Sing-Yi Feng MD, FAAP
Associate Professor
Division of Emergency Medicine
Department of Pediatrics
Children's Medical Center of Dallas

Medical Toxicologist
North Texas Poison Center
Parkland Memorial Hospital
The University of Texas Southwestern Medical Center at Dallas
Dallas, Texas

Envenomations

Thomas W. Ferkol Jr, MD
Alexis Hartmann Professor of Pediatrics
Director, Division of Pediatric Allergy, Immunology, and Pulmonary Medicine
Washington University School of Medicine in St. Louis
St. Louis, Missouri

Primary Ciliary Dyskinesia (Immotile Cilia Syndrome, Kartagener Syndrome)

Karin E. Finberg MD, PhD
Assistant Professor
Department of Pathology
Yale School of Medicine
New Haven, Connecticut

Iron-Refractory Iron-Deficiency Anemia

Jonathan D. Finder MD
Professor of Pediatrics
The University of Tennessee Health Science Center
Attending Pediatric Pulmonologist
Division of Pediatric Pulmonology
Le Bonheur Children's Hospital
Memphis, Tennessee

Bronchomalacia and Tracheomalacia
Congenital Disorders of the Lung

Laura H. Finkelstein MD
Assistant Professor, Department of Pediatrics

University of Maryland School of Medicine
Baltimore, Maryland

Assessment of Fetal Growth and Development
Middle Childhood

Kristin N. Fiorino MD
Associate Professor of Clinical Pediatrics
Suzie and Scott Lustgarten Motility Center
Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
University of Pennsylvania Perelman School of Medicine

Motility Disorders and Hirschsprung Disease

Philip R. Fischer MD
Professor of Pediatrics
Department of Pediatric and Adolescent Medicine
Mayo Clinic
Rochester, Minnesota

Adult Tapeworm Infections
Cysticercosis
Echinococcosis (Echinococcus granulosus and Echinococcus multilocularis)

Brian T. Fisher DO, MSCE
Assistant Professor of Pediatrics and Epidemiology
University of Pennsylvania Perelman School of Medicine
Fellowship Program Director
Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Actinomyces
Nocardia

Veronica H. Flood MD
Associate Professor
Department of Pediatrics
Division of Pediatric Hematology/Oncology
Medical College of Wisconsin
Milwaukee, Wisconsin

Hemostasis
Hereditary Clotting Factor Deficiencies (Bleeding Disorders)
von Willebrand Disease
Postneonatal Vitamin K Deficiency
Liver Disease
Acquired Inhibitors of Coagulation
Platelet and Blood Vessel Disorders

Francisco X. Flores MD
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director, Clinical Services and MARS Program
Division of Nephrology and Hypertension
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Clinical Evaluation of the Child with Hematuria
Isolated Renal Disease Associated with Hematuria
Clinical Evaluation of the Child with Proteinuria
Conditions Associated with Proteinuria

Joseph T. Flynn MD, MS
Dr. Robert O. Hickman Endowed Chair in Pediatric Nephrology
Professor of Pediatrics
University of Washington School of Medicine
Chief, Division of Nephrology

Seattle Children's Hospital
Seattle, Washington

Systemic Hypertension

Patricia M. Flynn MD
Senior Vice President and Medical Director of Quality and Patient Care
Deputy Clinical Director
Member, Department of Infectious Diseases
Arthur Ashe Chair in Pediatric AIDS Research
St. Jude Children's Research Hospital
Memphis, Tennessee

Infection Associated with Medical Devices
Cryptosporidium, Isospora, Cyclospora, and Microsporidia

Joel A. Forman MD
Associate Professor of Pediatrics and Preventive Medicine
Vice-Chair for Education
Department of Pediatrics
Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
New York, New York

Chemical Pollutants

Michael M. Frank MD
Professor Emeritus of Pediatrics, Medicine, and Immunology
Duke University School of Medicine
Durham, North Carolina

Urticaria (Hives) and Angioedema

Robert W. Frenck Jr, MD
Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director, Division of Infectious Diseases
Cincinnati Children's Hospital Medical Center

Cincinnati, Ohio

Liver Abscess

Deborah M. Friedman MD
Pediatric Cardiology
New York Medical College
Maria Fareri Children's Hospital
Westchester Medical Center
Valhalla, New York

Neonatal Lupus

Erika Friehling MD
Assistant Professor of Pediatrics
University of Pittsburgh School of Medicine
Division of Pediatric Hematology/Oncology
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Principles of Cancer Diagnosis
Principles of Cancer Treatment
The Leukemias

Stephanie A. Fritz MD, MSCI
Associate Professor of Pediatrics
University of Washington School of Medicine in St. Louis
Division of Infectious Diseases
St. Louis Children's Hospital
St. Louis, Missouri

Diphtheria (Corynebacterium diphtheriae)

Donald P. Frush MD, FACR, FAAP
Professor of Radiology
Lucile Packard Children's Hospital at Stanford
Stanford University School of Medicine
Stanford, California

Biologic Effects of Ionizing Radiation on Children

Anne M. Gadomski MD, MPH
Director, Bassett Research Institute
Bassett Medical Center
Cooperstown, New York;
Associate Professor of Pediatrics
Columbia University Medical Center
New York, New York

Strategies for Health Behavior Change

James T. Gaensbauer MD, MScPH
Assistant Professor of Pediatrics
University of Colorado School of Medicine
Pediatric Infectious Diseases
Denver Health Medical Center and Children's Hospital Colorado
Denver, Colorado

Staphylococcus

Sheila Gahagan MD, MPH
Professor of Clinical Pediatrics
Chief, Division of Academic General Pediatrics, Child Development, and Community Health
Martin Stein Endowed Chair, Developmental-Behavioral Pediatrics
University of California, San Diego School of Medicine
La Jolla, California

Overweight and Obesity

William A. Gahl MD, PhD
Clinical Director, National Human Genome Research Institute
Director, NIH Undiagnosed Diseases Program
National Institutes of Health
Bethesda, Maryland

Genetic Approaches to Rare and Undiagnosed

Diseases

Patrick G. Gallagher MD
Professor of Pediatrics, Genetics, and Pathology
Yale University School of Medicine
Attending Physician
Yale New Haven Children's Hospital
New Haven, Connecticut

Definitions and Classification of Hemolytic Anemias
Hereditary Spherocytosis
Hereditary Elliptocytosis, Hereditary Pyropoikilocytosis, and Related Disorders
Hereditary Stomatocytosis
Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis

Hayley A. Gans MD
Clinical Professor of Pediatrics
Stanford University School of Medicine
Division of Pediatric Infectious Diseases
Stanford, California

Measles
Rubella
Mumps

Cristina Garcia-Mauriño MD
Physician Scientist
Center for Vaccines and Immunity
The Research Institute at Nationwide Children's Hospital
Columbus, Ohio

Hansen Disease (Mycobacterium leprae)

Paula M. Gardiner MD, MPH
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Associate Research Director
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Complementary Therapies and Integrative Medicine

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Clinical Director
Division of Pediatric Endocrinology
Children's Hospital of UPMC
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Physiology of Puberty
Disorders of Pubertal Development

Gregory M. Gauthier MD, MS
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Division of Infectious Diseases
University of Wisconsin School of Medicine and Public Health
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Blastomycosis (Blastomyces dermatitidis)

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University of Pennsylvania Perelman School of Medicine
Division of Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Legionella

Anne A. Gershon MD

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Columbia University College of Physicians and Surgeons
Division of Pediatric Infectious Diseases
NewYork-Presbyterian Morgan Stanley Children's Hospital
New York, New York

Saied Ghadersohi MD
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Northwestern University Feinberg School of Medicine
Chicago, Illinois

Neoplasms of the Larynx, Trachea, and Bronchi

Mark Gibson MD
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Department of Obstetrics and Gynecology
Chief, Division of Reproductive Endocrinology
University of Utah School of Medicine
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Polycystic Ovary Syndrome and Hirsutism

Francis Gigliotti MD
Professor and Chief of Pediatric Infectious Diseases and Microbiology and Immunology
Vice Chair for Academic Affairs
University of Rochester Medical Center
School of Medicine and Dentistry
Rochester, New York

Pneumocystis jirovecii

Walter S. Gilliam MSEd, PhD
Professor of Child Psychiatry and Psychology
Child Study Center
Director, The Edward Zigler Center in Child Development and Social Policy
Yale School of Medicine

New Haven, Connecticut

Childcare

Salil Ginde MD, MPH
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Division of Pediatric Cardiology
Medical College of Wisconsin
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Congenital Heart Disease in Adults

John A. Girotto MD
Section Chief
Pediatric Plastic Surgery and Dermatology Center
Helen DeVos Children's Hospital
Grand Rapids, Michigan

Deformational Plagiocephaly

Samuel B. Goldfarb MD
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Pediatric Lung and Heart/Lung Transplant Programs
Division of Pulmonary Medicine
Medical Director, Solid Organ Transplant Center
Children's Hospital of Philadelphia
Professor of Clinical Pediatrics
University of Pennsylvania
Perelman School of Medicine
Philadelphia, Pennsylvania

Heart-Lung and Lung Transplantation

David L. Goldman MD
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Albert Einstein College of Medicine
Division of Pediatric Infectious Disease
Montefiore Medical Center
Bronx, New York

Cryptococcus neoformans and Cryptococcus gattii

Stanton C. Goldman MD
Division of Pediatric Hematology, Oncology, and Stem Cell Transplant
Medical City Children's Hospital
Texas Oncology, PA
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Neal D. Goldstein PhD, MBI
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Infectious Disease Epidemiologist
Christiana Care Health System
Newark, Delaware

Lyme Disease (Borrelia burgdorferi)

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Clark D. West Endowed Chair and Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Center for Acute Care Nephrology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

End-Stage Renal Disease

Joseph Gonzalez-Heydrich MD
Associate Professor of Psychiatry
Harvard Medical School
Senior Attending Psychiatrist
Boston Children's Hospital
Boston, Massachusetts

Childhood Psychoses

Denise M. Goodman MD, MS
Professor of Pediatrics

Northwestern University Feinberg School of Medicine
Attending Physician, Division of Critical Care Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Bronchitis
Chronic Respiratory Failure and Long-Term Mechanical Ventilation

Tracy S. Goodman MA
Technical Officer, Expanded Programme on Immunization
Department of Immunization, Vaccines, and Biologicals
World Health Organization
Geneva, Switzerland

International Immunization Practices

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Department of Pediatrics
Harvard Medical School
Chief, Division of Adolescent/Young Adult Medicine
Robert P. Masland Jr. Chair of Adolescent Medicine
Boston Children's Hospital
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Bone Structure, Growth, and Hormonal Regulation
Osteoporosis

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Professor of Pediatrics Research
Hasbro Children's Hospital and Warren Alpert Medical School of Brown University
Providence, Rhode Island;
Department of Pediatrics
Boston Children's Hospital and Harvard Medical School
Boston, Massachusetts;

Medical Director, The Progeria Research Foundation
Peabody, Massachusetts

Hutchinson-Gilford Progeria Syndrome (Progeria)

Collin S. Goto MD
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The University of Texas Southwestern Medical Center
Attending Physician
Division of Pediatric Emergency Medicine
Children's Medical Center
Dallas, Texas

Envenomations

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University of North Carolina School of Medicine
Chapel Hill, North Carolina

Neuroendocrine Cell Hyperplasia of Infancy

Neera K. Goyal MD
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Sidney Kimmel College of Medicine at Thomas Jefferson University
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The Newborn Infant
Jaundice and Hyperbilirubinemia in the Newborn
Kernicterus

Nicholas P. Goyeneche MD
Department of Physical Medicine and Rehabilitation
Ochsner Health Center–Covington
Covington, Louisiana

Management of Musculoskeletal Injury

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Vanderbilt University School of Medicine
Vanderbilt University Medical Center
Nashville, Tennessee

Coronaviruses

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Harvard Medical School
Division of Pediatric Critical Care Medicine
Boston Children's Hospital
Boston, Massachusetts

Home Mechanical Ventilation and Technology Dependence

John M. Greally DMed, PhD, FACMG
Professor of Genetics, Medicine, and Pediatrics
Albert Einstein College of Medicine
Department of Genetics
Children's Hospital at Montefiore
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Epigenome-Wide Association Studies and Disease

Cori M. Green MD, MSc
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Weill Cornell Medicine
New York-Presbyterian Komansky Children's Hospital
New York, New York

Strategies for Health Behavior Change

Michael Green MD, MPH
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University of Pittsburgh School of Medicine
Division of Infectious Diseases
Director, Antimicrobial Stewardship and Infection Prevention
UPMC Children's Hospital of Pittsburgh
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Infections in Immunocompromised Persons

Larry A. Greenbaum MD, PhD
Marcus Professor of Pediatrics
Director, Division of Pediatric Nephrology
Emory University School of Medicine
Children's Healthcare of Atlanta
Atlanta, Georgia

Vitamin D Deficiency (Rickets) and Excess
Vitamin E Deficiency
Vitamin K Deficiency
Micronutrient Mineral Deficiencies
Electrolyte and Acid-Base Disorders
Maintenance and Replacement Therapy
Deficit Therapy

V. Jordan Greenbaum MD
International Centre for Missing and Exploited Children
Alexandria, Virginia

Child Trafficking for Sex and Labor

James M. Greenberg MD
Professor of Pediatrics
Director, Division of Neonatology
University of Cincinnati College of Medicine
Co-Director, Perinatal Institute
Cincinnati Children's Hospital Medical Center
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Overview of Morbidity and Mortality
Clinical Manifestations of Diseases in the Newborn Period

Anne G. Griffiths MD
Pediatric Pulmonologist
Children's Respiratory and Critical Care Specialists
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Chronic or Recurrent Respiratory Symptoms

Kenneth L. Grizzle PhD
Associate Professor of Pediatrics
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Child Development Center
Children's Hospital of Wisconsin
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Math and Writing Disabilities
Child-Onset Fluency Disorder

Judith A. Groner MD
Clinical Professor of Pediatrics
The Ohio State University College of Medicine
Section of Ambulatory Pediatrics
Nationwide Children's Hospital
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Tobacco

Alfredo Guarino MD
Professor of Pediatrics
Department of Translational Medical Sciences
University of Naples Federico II
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Intestinal Infections and Infestations Associated with Malabsorption

Juan P. Gurria MD
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Cincinnati Children's Hospital Medical Center
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Meconium Ileus, Peritonitis, and Intestinal Obstruction

Anat Guz-Mark MD
Attending Physician
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Schneider Children's Medical Center of Israel
Petah Tikva, Israel;
Sackler Faculty of Medicine
Tel Aviv University
Tel Aviv, Israel;

Chronic Diarrhea

Gabriel G. Haddad MD
Distinguished Professor of Pediatrics and Neuroscience
Chairman, Department of Pediatrics
University of California, San Diego School of Medicine
Physician-in-Chief and Chief Scientific Officer
Rady Children's Hospital–San Diego

Diagnostic Approach to Respiratory Disease

Joseph Haddad Jr, MD
Lawrence Savetsky Professor Emeritus
Columbia University Irving Medical Center
New York, New York

Congenital Disorders of the Nose

Acquired Disorders of the Nose
Nasal Polyps
General Considerations and Evaluation of the Ear
Hearing Loss
Congenital Malformations of the Ear
External Otitis (Otitis Externa)
The Inner Ear and Diseases of the Bony Labyrinth
Traumatic Injuries of the Ear and Temporal Bone
Tumors of the Ear and Temporal Bone

Joseph F. Hagan Jr, MD, FAAP
Clinical Professor
Department of Pediatrics
The Robert Larner College of Medicine at the University of Vermont College of Medicine
Hagan, Rinehart, and Connolly Pediatricians, PLLC
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Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

James S. Hagood MD
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Director, Program in Rare and Interstitial Lung Disease
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Diagnostic Approach to Respiratory Disease

Suraiya K. Haider MD
Sleep Physician
Fairfax Neonatal Associates
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Pleurisy, Pleural Effusions, and Empyema

Goknur Haliloglu MD
Professor of Pediatrics
Department of Pediatric Neurology
Hacettepe University Children's Hospital
Ankara, Turkey

Nemaline Rod Myopathy
Core Myopathies
Myofibrillar Myopathies
Brain Malformations and Muscle Development
Arthrogryposis
Spinal Muscular Atrophies
Other Motor Neuron Diseases

Scott B. Halstead MD
Adjunct Professor
Department of Preventive Medicine and Biostatistics
Uniformed Services University of the Health Sciences
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Arboviral Infections
Dengue Fever, Dengue Hemorrhagic Fever, and Severe Dengue
Yellow Fever
Ebola and Other Viral Hemorrhagic Fevers
Hantavirus Pulmonary Syndrome

Allison R. Hammer MSN, APRN, CPNP-PC
Advanced Practice Nurse
Department of Otolaryngology – Head and Neck Surgery
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Foreign Bodies in the Airway

Margaret R. Hammerschlag MD
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Director, Pediatric Infectious Disease Fellowship Program
SUNY Down State Medical Center
Brooklyn, New York

Chlamydia pneumoniae
Chlamydia trachomatis
Psittacosis (Chlamydia psittaci)

Aaron Hamvas MD
Raymond and Hazel Speck Barry Professor of Neonatology
Northwestern University Feinberg School of Medicine
Head, Division of Neonatology
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Inherited Disorders of Surfactant Metabolism
Pulmonary Alveolar Proteinosis

James C. Harris MD
Professor of Pediatrics, Psychiatry and Behavioral Sciences, Mental Health, and History of Medicine
Division of Child and Adolescent Psychiatry
Director, Developmental Neuropsychiatry
Johns Hopkins University School of Medicine
Baltimore, Maryland

Disorders of Purine and Pyrimidine Metabolism

Douglas J. Harrison MD, MS
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Director of Patient Care and Programs
Co-Chair Pediatric Solid Tumor and Sarcoma Team
The Children's Cancer Hospital of MD Anderson
The University of Texas MD Anderson Cancer Center
Houston, Texas

Neuroblastoma

Corina Hartman MD
Pediatric Gastroenterology and Nutrition Unit
Lady Davis Carmel Medical Center
Haifa, Israel

Other Malabsorptive Syndromes

Mary E. Hartman MD, MPH
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Washington University School of Medicine in St. Louis
Division of Pediatric Critical Care Medicine
St. Louis Children's Hospital
St. Louis, Missouri

Pediatric Emergencies and Resuscitation

David B. Haslam MD
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University of Cincinnati College of Medicine
Director, Antimicrobial Stewardship Program
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Epidemiology of Infections
Healthcare-Acquired Infections
Non–Group A or B Streptococci
Enterococcus

H. Hesham Abdel-Kader Hassan MD, MSc
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Chief, Division of Pediatric Gastroenterology and Nutrition
The University of Arizona College of Medicine
Tucson, Arizona

Cholestasis

Fern R. Hauck MD, MS
Spencer P. Bass MD Twenty-First Century Professor of Family Medicine
Departments of Family Medicine and Public Health Sciences
University of Virginia School of Medicine
Charlottesville, Virginia

Sudden Infant Death Syndrome

Fiona P. Havers MD, MHS
Medical Epidemiologist
Epidemiology and Prevention Branch, Influenza Division
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
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Influenza Viruses

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Department of Pediatrics
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Washington University School of Medicine in St. Louis
Medical Director, Pediatric and Adolescent HIV Program
Medical Director, Infection Prevention
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Campylobacter
Yersinia
Nontuberculous Mycobacteria
Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Jacqueline T. Hecht PhD
Professor and Division Head
Pediatric Research Center
Vice-Chair for Research

Leah L. Lewis Distinguished Chair
Department of Pediatrics
McGovern Medical School at UTHealth
Associate Dean for Research
UTHealth School of Dentistry
Houston, Texas

General Considerations in Skeletal Dysplasias
Disorders Involving Cartilage Matrix Proteins
Disorders Involving Transmembrane Receptors
Disorders Involving Ion Transporters
Disorders Involving Transcription Factors
Disorders Involving Defective Bone Resorption
Other Inherited Disorders of Skeletal Development

Sabrina M. Heidemann MD
Professor
Department of Pediatrics
Wayne State University School of Medicine
Director, Intensive Care Unit
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Children's Hospital of Michigan
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Respiratory Distress and Failure

Jennifer R. Heimall MD
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University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Allergy and Immunology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Immunodeficiencies Affecting Multiple Cell Types

Cheryl Hemingway MBChB, PhD
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Great Ormond Street Hospital for Children
London, United Kingdom

Demyelinating Disorders of the Central Nervous System

J. Owen Hendley MD †
Professor of Pediatric Infectious Diseases
University of Virginia School of Medicine
Charlottesville, Virginia

Sinusitis
Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

Michelle L. Hernandez MD
Associate Professor of Pediatrics
University of North Carolina School of Medicine
Chief Medical Officer
UNC Center for Environmental Medicine, Asthma, and Lung Biology
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Hypersensitivity Pneumonia
Occupational and Environmental Lung Disease

Andrew D. Hershey MD, PhD, FAAN, FAHS
Professor of Pediatrics
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Endowed Chair and Director, Division of Neurology
Headache Medicine Specialist
Cincinnati Children's Medical Center
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Headaches

Cynthia E. Herzog MD
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University of Texas MD Anderson Cancer Center
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Retinoblastoma
Gonadal and Germ Cell Neoplasms
Neoplasms of the Liver
Benign Vascular Tumors
Melanoma
Nasopharyngeal Carcinoma
Adenocarcinoma of the Colon and Rectum
Desmoplastic Small Round Cell Tumor

Jesse P. Hirner MD
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Tumors of the Skin

Jessica Hochberg MD
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New York Medical College
Maria Fareri Children's Hospital at Westchester Medical Center
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Lymphoma

Deborah Hodes MBBS, BSc, DRCOG, FRCPCH
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University College London Hospitals
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Female Genital Mutilation

Holly R. Hoefgen MD
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Pediatric and Adolescent Gynecology
Washington University School of Medicine in St. Louis
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St. Louis Children's Hospital
St. Louis, Missouri

Vulvovaginitis

Lauren D. Holinger MD, FAAP, FACS
Paul H. Holinger MD Professor
Division of Pediatric Otolaryngology
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
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Other Laryngeal Neoplasms
Tracheal Neoplasms

Cynthia M. Holland-Hall MD, MPH
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Adolescent Physical and Social Development
Transitioning to Adult Care
The Breast

David K. Hooper MD, MS
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Medical Director of Kidney Transplantation

Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Renal Transplantation

Julie E. Hoover-Fong MD, PhD
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McKusick-Nathans Institute of Genetic Medicine
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Johns Hopkins University School of Medicine
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General Considerations in Skeletal Dysplasias
Disorders Involving Transmembrane Receptors

Jeffrey D. Hord MD
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The Acquired Pancytopenias

B. David Horn MD
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The Hip

Helen M. Horstmann MD
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Arthrogryposis

William A. Horton MD
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Oregon Health & Science University
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General Considerations in Skeletal Dysplasias
Disorders Involving Cartilage Matrix Proteins
Disorders Involving Transmembrane Receptors
Disorders Involving Ion Transporters
Disorders Involving Transcription Factors
Disorders Involving Defective Bone Resorption
Other Inherited Disorders of Skeletal Development

Peter J. Hotez MD, PhD
Dean, National School of Tropical Medicine
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Center for Vaccine Development
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Waco, Texas;
Baker Institute Fellow in Disease and Poverty
Rice University

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Hookworms (Necator americanus and Ancylostoma spp.)

Samantha A. House DO
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Wheezing in Infants: Bronchiolitis

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Liver Transplantation

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Medical Director, Division of STD Prevention and HIV/AIDS Surveillance
Director, Ratelle STD/HIV Prevention Training Center
Bureau of Infectious Disease and Laboratory Sciences
Massachusetts Department of Public Health
Jamaica Plain, Massachusetts

Neisseria gonorrhoeae (Gonococcus)

Felicia A. Scaggs Huang, MD
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Division of Infectious Diseases
Cincinnati Children's Hospital Medical Center

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Congenital and Perinatal Infections

Heather G. Huddleston MD
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Polycystic Ovary Syndrome and Hirsutism

Sarah P. Huepenbecker MD
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Washington University School of Medicine in St. Louis
St. Louis, Missouri

Gynecologic Neoplasms and Adolescent Prevention Methods for Human Papillomavirus

Vicki Huff PhD
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University of Texas MD Anderson Cancer Center
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Neoplasms of the Kidney

Winston W. Huh MD
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Los Angeles, California

Gonadal and Germ Cell Neoplasms
Adenocarcinoma of the Colon and Rectum

Stephen R. Humphrey MD

Assistant Professor
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Medical College of Wisconsin
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Principles of Dermatologic Therapy
Cutaneous Bacterial Infections
Cutaneous Fungal Infections
Cutaneous Viral Infections
Arthropod Bites and Infestations

Stephen P. Hunger MD
Professor and Jeffrey E. Perelman Distinguished Chair
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Director, Center for Childhood Cancer Research
Children's Hospital of Philadelphia
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Molecular and Cellular Biology of Cancer

David A. Hunstad MD
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Central Nervous System Infections
Animal and Human Bites
Rat Bite Fever
Monkeypox

Carl E. Hunt MD
Research Professor of Pediatrics
Uniformed Services University of the Health Sciences

Division of Neonatology
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Sudden Infant Death Syndrome

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Division of Developmental Biology
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Morphogenesis of the Liver and Biliary System

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Children's Hospital of Wisconsin
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Infectious Complications of Hematopoietic Stem Cell Transplantation

Patricia I. Ibeziako MBBS
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Boston Children's Hospital
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Somatic Symptom and Related Disorders

Samar H. Ibrahim MBChB
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Division of Pediatric Gastroenterology and Hepatology
Mayo Clinic
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Mitochondrial Hepatopathies

Allison M. Jackson MD, MPH, FAAP
Division Chief, Child and Adolescent Protection Center
Children's National Health System
Washington Children's Foundation
Professor of Child and Adolescent Protection
Associate Professor of Pediatrics
The George Washington University School of Medicine and Health Sciences
Washington, DC

Adolescent Sexual Assault

Elizabeth C. Jackson MD
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University of Cincinnati College of Medicine
Division of Nephrology
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Urinary Tract Infections

Mary Anne Jackson MD
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University of Missouri–Kansas City School of Medicine
Department of Pediatric Infectious Diseases
Children's Mercy Hospitals and Clinics
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Orbital Infections

Ashlee Jaffe MD, MEd
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Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician, Division of Rehabilitation Medicine
Children's Hospital of Philadelphia
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Spinal Cord Injury and Autonomic Dysreflexia Management

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Washington University School of Medicine in St. Louis
St. Louis, Missouri

Central Nervous System Infections

Tara C. Jatlaoui MD, MPH
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Contraception

Elena J. Jelsing MD
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Mayo Clinic Sports Medicine Center
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Specific Sports and Associated Injuries

M. Kyle Jensen MD
Associate Professor
Department of Pediatrics
University of Utah School of Medicine

Division of Pediatric Gastroenterology
Primary Children's Hospital
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Viral Hepatitis

Brian P. Jenssen MD, MSHP
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Tobacco and Electronic Nicotine Delivery Systems

Karen E. Jerardi MD, MEd
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Urinary Tract Infections

Chandy C. John MD, MS
Ryan White Professor of Pediatrics
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Health Advice for Children Traveling Internationally
Giardiasis and Balantidiasis
Malaria (Plasmodium)

Brian D. Johnston MD, MPH
Professor of Pediatrics
Associate Chief of Clinical Services

Division of General Pediatrics
University of Washington School of Medicine
Chief of Service, Department of Pediatrics
Harborview Medical Center
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Injury Control

Michael V. Johnston MD
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Professor of Pediatrics and Neurology
Johns Hopkins University School of Medicine
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Congenital Anomalies of the Central Nervous System
Encephalopathies

Richard B. Johnston Jr, MD
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University of Colorado School of Medicine
Aurora, Colorado;
National Jewish Health
Denver, Colorado

Monocytes, Macrophages, and Dendritic Cells
The Complement System
Disorders of the Complement System

Bridgette L. Jones MD
Associate Professor of Pediatrics
Division of Allergy, Asthma, and Immunology
University of Missouri – Kansas City School of Medicine
Division of Allergy, Asthma, and Immunology
Division of Clinical Pharmacology, Toxicology, and Therapeutic Innovation
Children's Mercy
Kansas City, Missouri

Principles of Drug Therapy

Marsha Joselow MSW, LICSW
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Boston Children's Hospital
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Pediatric Palliative Care

Cassandra D. Josephson MD
Professor of Pathology and Pediatrics
Emory University School of Medicine
Director of Clinical Research, Center for Transfusion and Cellular Therapies
Program Director, Transfusion Medicine
Fellowship Medical Director
Children's Healthcare of Atlanta Blood, Tissue, and Apheresis Services
Atlanta, Georgia

Red Blood Cell Transfusions and Erythropoietin Therapy

Platelet Transfusions

Neutrophil (Granulocyte) Transfusions

Plasma Transfusions

Risks of Blood Transfusions

Nicholas Jospe MD
Professor of Pediatrics
University of Rochester School of Medicine and Dentistry
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Diabetes Mellitus

Joel C. Joyce MD

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University of Chicago Pritzker School of Medicine
Chicago, Illinois

Hyperpigmented Lesions
Hypopigmented Lesions
Vesiculobullous Disorders
Nutritional Dermatoses

Marielle A. Kabbouche MD, FAHS
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University of Cincinnati College of Medicine
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Cincinnati Children's Medical Center
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Headaches

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University of Cincinnati College of Medicine
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Director, Post-Concussion Headache Program
Director, Headache Medicine Fellowship
Cincinnati Children's Medical Center
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Headaches

Deepak Kamat MD, PhD
Professor of Pediatrics
Vice Chair for Education
Wayne State University School of Medicine

Designated Institutional Official
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Fever

Beena D. Kamath-Rayne MD, MPH
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Attending Neonatologist, Division of Neonatology and Pulmonary Biology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Neonatal Resuscitation and Delivery Room Emergencies

Alvina R. Kansra MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Endocrinology
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Hypofunction of the Ovaries
Pseudoprecocity Resulting From Lesions of the Ovary

David M. Kanter MD
Assistant Professor
Department of Physical Medicine and Rehabilitation
State University of New York
SUNY Upstate Medical University
Syracuse, New York

Health and Wellness for Children With Disabilities

Aaron M. Karlin MD
Clinical Associate Professor
Department of Physical Medicine and Rehabilitation
Louisiana State University School of Medicine

Chair, Department of Physical Medicine and Rehabilitation
Section Head, Pediatric Rehabilitation
Ochsner Clinic Medical Center
Ochsner Children's Health Center
New Orleans, Louisiana

Management of Musculoskeletal Injury

Jacob Kattan MD, MSCR
Assistant Professor
Department of Pediatrics
Jaffe Food Allergy Institute
Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
New York, New York

Diagnosis of Allergic Disease

James W. Kazura MD
Distinguished University Professor
Adel A. Mahmoud Professorship in Global Health and Vaccines
Director, Center for Global Health and Diseases
Case Western Reserve University School of Medicine
Cleveland, Ohio

Ascariasis (Ascaris lumbricoides)
Trichuriasis (Trichuris trichiura)
Enterobiasis (Enterobius vermicularis)
Strongyloidiasis (Strongyloides stercoralis)
Lymphatic Filariasis (Brugia malayi, Brugia timori, and Wuchereria bancrofti)
Other Tissue Nematodes
Toxocariasis (Visceral and Ocular Larva Migrans)
Trichinellosis (Trichinella spiralis)

Gregory L. Kearns PharmD, PhD, FAAP

President, Arkansas Children's Research Institute
Senior Vice President and Chief Research Officer
Arkansas Children's
Ross and Mary Whipple Family Distinguished Research Scientist
Professor of Pediatrics
University of Arkansas for Medical Sciences
Little Rock, Arkansas

Principles of Drug Therapy

Andrea Kelly MD, MSCE
Associate Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Assessment of Growth

Desmond P. Kelly MD
Professor of Pediatrics
University of South Carolina School of Medicine Greenville
Chief Medical Research Officer
Health Sciences Center
Prisma Health-Upstate
Greenville, South Carolina

Neurodevelopmental and Executive Function and Dysfunction

Kevin J. Kelly MD
Professor of Pediatrics (Emeritus)
Department of Pediatrics
University of North Carolina School of Medicine
Chapel Hill, North Carolina

Hypersensitivity Pneumonia
Occupational and Environmental Lung Disease

Granulomatous Lung Disease
Eosinophilic Lung Disease
Interstitial Lung Disease

Matthew S. Kelly MD, MPH
Assistant Professor of Pediatrics
Division of Infectious Diseases
Duke University School of Medicine
Durham, North Carolina

Community-Acquired Pneumonia

Michael Kelly MD, PhD
Chief Research Officer
Akron Children's Hospital
Akron, Ohio

Anatomy and Function of the Lymphatic System
Abnormalities of Lymphatic Vessels
Lymphadenopathy

Kimberly M. Ken MD
Resident Physician
Department of Dermatology
University of Missouri School of Medicine
Columbia, Missouri

Disorders of the Sweat Glands
Disorders of Hair
Disorders of the Nails

Melissa A. Kennedy MD
Assistant Professor of Clinical Pediatrics
Division of Gastroenterology, Hepatology, and Nutrition
University of Pennsylvania Perelman School of Medicine
Children's Hospital of Philadelphia

Philadelphia, Pennsylvania

Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct

Eitan Kerem MD
Professor and Chair
Department of Pediatrics
Hadassah University Medical Center
Jerusalem, Israel

Effects of War on Children

Joseph E. Kerschner MD
Dean of the Medical School, Provost and Executive Vice President
Professor of Otolaryngology and Microbiology and Immunology
Medical College of Wisconsin
Milwaukee, Wisconsin

Otitis Media

Seema Khan MD
Associate Professor of Pediatrics
Division of Gastroenterology and Nutrition
George Washington University School of Medicine and Health Sciences
Children's National Medical Center
Washington, DC

Embryology, Anatomy, and Function of the Esophagus
Congenital Anomalies
Obstructing and Motility Disorders of the Esophagus
Dysmotility
Hiatal Hernia
Gastroesophageal Reflux Disease
Eosinophilic Esophagitis, Pill Esophagitis, and Infective Esophagitis

Esophageal Perforation
Esophageal Varices
Ingestions

Ameneh Khatami BHB, MBChB, MD
Clinical Senior Lecturer
Discipline of Child and Adolescent Health
University of Sydney
Department of Microbiology and Infectious Diseases
The Children's Hospital at Westmead
Sydney, Australia

Aeromonas and Plesiomonas

Soumen Khatua MD
Associate Professor of Pediatrics
Section Chief, Neuro-Oncology
Department of Pediatrics Patient Care
The University of Texas MD Anderson Cancer Center
Houston, Texas

Brain Tumors in Childhood

Alexandra Kilinsky DO
Fellow, Pediatric Hospital Medicine
Department of Pediatrics
Cohen Children's Medical Center of New York
New Hyde Park, New York

Immunization Practices

Chong-Tae Kim MD, PhD
Associate Professor
Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Rehabilitation Medicine
Children's Hospital of Philadelphia

Philadelphia, Pennsylvania

Rehabilitation for Severe Traumatic Brain Injury

Wendy E. Kim DO
Assistant Professor of Internal Medicine and Pediatrics
Division of Pediatric Dermatology
Loyola University Chicago Stritch School of Medicine
Evanston, Illinois

Diseases of the Dermis
Diseases of Subcutaneous Tissue
Disorders of the Mucous Membranes
Acne

Charles H. King MD
Professor Emeritus of International Health
Center for Global Health and Diseases
Case Western Reserve University School of Medicine
Cleveland, Ohio

Schistosomiasis (Schistosoma)
Flukes (Liver, Lung, and Intestinal)

Paul S. Kingma MD, PhD
Associate Professor of Pediatrics
University of Cincinnati of College of Medicine
Neonatal Director, Cincinnati Fetal Center
Co-Director, Cincinnati Bronchopulmonary Dysplasia Center
The Perinatal Institute
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Fetal Intervention and Surgery

Stephen L. Kinsman MD
Associate Professor of Pediatrics

Medical University of South Carolina
Charleston, South Carolina

Congenital Anomalies of the Central Nervous System

Priya S. Kishnani MD, MBBS
C.L. and Su Chen Professor of Pediatrics
Chief, Division of Medical Genetics
Duke University Medical Center
Durham, North Carolina

Defects in Metabolism of Carbohydrates

Bruce L. Klein MD
Associate Professor of Pediatrics
Johns Hopkins University School of Medicine
Interim Director, Pediatric Emergency Medicine
Director, Pediatric Transport
Johns Hopkins Children's Center
Baltimore, Maryland

Interfacility Transport of the Seriously Ill or Injured Pediatric Patient
Acute Care of Multiple Trauma
Care of Abrasions and Minor Lacerations

Bruce S. Klein MD
Professor of Pediatrics, Internal Medicine, and Medical Microbiology and Immunology
Chief, Pediatric Infectious Disease Division
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

Blastomycosis (Blastomyces dermatitidis)

Robert M. Kliegman MD
Professor and Chairman Emeritus
Department of Pediatrics

Medical College of Wisconsin
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Culture-Specific Beliefs
Refeeding Syndrome
Generalized Arterial Calcification of Infancy/Idiopathic Infantile Arterial Calcification
Arterial Tortuosity

William C. Koch MD
Associate Professor of Pediatrics
Virginia Commonwealth University School of Medicine
Division of Pediatric Infectious Diseases
Children's Hospital of Richmond at VCU
Richmond, Virginia

Parvoviruses

Patrick M. Kochanek MD, MCCM
Ake N. Grenvik Professor of Critical Care Medicine
Vice Chair, Department of Critical Care Medicine
Professor of Anesthesiology, Pediatrics, Bioengineering, and Clinical and Translational Science
Director, Safar Center for Resuscitation Research
UPMC Children's Hospital of Pittsburgh
John G. Rangos Research Center
Pittsburgh, Pennsylvania

Neurologic Emergencies and Stabilization

Eric Kodish MD
Professor of Pediatrics
Lerner College of Medicine
Cleveland Clinic
Cleveland, Ohio

Ethics in Pediatric Care

Stephan A. Kohlhoff MD
Associate Professor of Pediatrics and Medicine
Chief, Pediatric Infectious Diseases
SUNY Downstate Medical Center
Brooklyn, New York

Chlamydia pneumoniae
Psittacosis (Chlamydia psittaci)

Mark A. Kostic MD
Professor of Emergency Medicine and Pediatrics
Medical College of Wisconsin
Associate Medical Director
Wisconsin Poison Center
Milwaukee, Wisconsin

Poisoning

Karen L. Kotloff MD
Professor of Pediatrics
Division Head, Infectious Disease and Tropical Pediatrics
Center for Vaccine Development and Global Health
University of Maryland School of Medicine
Baltimore, Maryland

Acute Gastroenteritis in Children

Elliot J. Krane MD, FAAP
Professor of Pediatrics, and Anesthesiology, Perioperative, and Pain Medicine
Stanford University School of Medicine
Chief, Pediatric Pain Management
Stanford Children's Health
Lucile Packard Children's Hospital at Stanford
Stanford, California

Pediatric Pain Management

Peter J. Krause MD
Senior Research Scientist in Epidemiology (Microbial Diseases), Medicine (Infectious Diseases), and Pediatrics (Infectious Diseases)
Lecturer in Epidemiology (Microbial Diseases)
Yale School of Public Health
New Haven, Connecticut

Babesiosis (Babesia)

Richard E. Kreipe MD, FAAAP, FSAHM, FAED
Dr. Elizabeth R. McArnarney Professor in Pediatrics funded by Roger and Carolyn Friedlander
Department of Pediatrics, Division of Adolescent Medicine
University of Rochester Medical Center
Golisano Children's Hospital
Director, New York State ACT for Youth Center of Excellence
Medical Director, Western New York Comprehensive Care Center for Eating Disorders
Rochester, New York

Eating Disorders

Steven E. Krug MD
Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Division of Pediatric Emergency Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Emergency Medical Services for Children

Janet L. Kwiatkowski MD, MSCE
Professor
Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Hematology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Hemoglobinopathies

Jennifer M. Kwon MD
Professor of Child Neurology
Department of Neurology
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

Neurodegenerative Disorders of Childhood

Catherine S. Lachenauer MD
Assistant Professor of Pediatrics
Harvard Medical School
Director, Infectious Diseases Outpatient Practice
Boston Children's Hospital
Boston, Massachusetts

Group B Streptococcus

Stephan Ladisch MD
Professor of Pediatrics and Biochemistry/Molecular Biology
George Washington University School of Medicine
Center for Cancer and Immunology Research and
Center for Cancer and Blood Disorders
Children's Research Institute
Children's National Medical Center
Washington, DC

Histiocytosis Syndromes of Childhood

Oren J. Lakser MD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Associate Clinician Specialist
Division of Pulmonary Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Bronchiectasis
Pulmonary Abscess

Philip J. Landrigan MD, MSc, FAAP
Director, Global Public Health Program
Schiller Institute for Integrated Science and Society
Professor of Biology
Boston College
Chestnut Hill, Massachusetts

Chemical Pollutants

Gregory L. Landry MD
Professor Emeritus
Department of Pediatrics
University of Wisconsin – Madison
School of Medicine and Public Health
Madison, Wisconsin

Epidemiology and Prevention of Injuries
Heat Injuries
Female Athletes: Menstrual Problems and the Risk of Osteopenia
Performance-Enhancing Aids

Wendy G. Lane MD, MPH, FAAP
Associate Professor
Department Epidemiology and Public Health
Department of Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland

Abused and Neglected Children

A. Noelle Larson MD
Associate Professor, Orthopedic Surgery

Division of Pediatric Orthopedic Surgery
Mayo Clinic
Rochester, Minnesota

Benign Tumors and Tumor-Like Processes of Bone

Phillip S. LaRussa MD
Professor of Pediatrics
Columbia University College of Physicians and Surgeons
Division of Pediatric Infectious Diseases
NewYork-Presbyterian Morgan Stanley Children's Hospital
New York, New York

Varicella-Zoster Virus

Oren J. Lakser MD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Division of Pulmonary Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Bronchiectasis
Pulmonary Abscess

J. Todd R. Lawrence MD, PhD
Assistant Professor
Department of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

The Knee

Brendan Lee MD, PhD
Robert and Janice McNair Endowed Chair
in Molecular and Human Genetics

Professor and Chairman
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas

Integration of Genetics into Pediatric Practice
The Genetic Approach in Pediatric Medicine
The Human Genome
Patterns of Genetic Transmission
Cytogenetics
Genetics of Common Disorders

K. Jane Lee MD, MA
Associate Professor
Department of Pediatrics
Medical College of Wisconsin
Division of Pediatric Special Needs
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Brain Death

J. Steven Leeder PharmD, PhD
Marion Merrell Dow / Missouri Endowed Chair in Pediatric Pharmacology
Chief, Division of Pediatric Pharmacology and Medical Toxicology
Children's Mercy Hospitals and Clinics
Kansas City, Missouri;
Adjunct Professor
Department of Pharmacology, Toxicology, and Therapeutics
Kansas University School of Medicine
Kansas City, Kansas

Pediatric Pharmacogenetics, Pharmacogenomics, and Pharmacoproteomics

Jennifer W. Leiding MD

Assistant Professor of Pediatrics
University of South Florida College of Medicine
St. Petersburg, Florida

Immunodeficiencies Affecting Multiple Cell Types

Michael J. Lentze MD
Professor Emeritus of Pediatrics
Zentrum für Kinderheilkunde
Universitätsklinikum Bonn
Bonn, Germany

Enzyme Deficiencies

Steven O. Lestrud MD
Assistant Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Medical Director, Respiratory Care
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Bronchopulmonary Dysplasia
Chronic Respiratory Failure and Long-Term Mechanical Ventilation

Donald Y.M. Leung MD, PhD
Edelstein Family Chair of Pediatric Allergy-Immunology
National Jewish Health
Professor of Pediatrics
University of Colorado School of Medicine
Denver, Colorado

Atopic Dermatitis (Atopic Eczema)

Michael N. Levas MD
Associate Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Emergency Medicine

Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Violent Behavior

Rona L. Levy MSW, PhD, MPH
Professor and Director
Behavioral Medicine Research Group
Assistant Dean for Research
School of Social Work
University of Washington
Seattle, Washington

Pediatric Pain Management

B U.K. Li MD
Clinical Professor of Pediatrics
Medical College of Wisconsin
Division of Pediatric Gastroenterology
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Cyclic Vomiting Syndrome

Chris A. Liacouras MD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Co-Director, Center for Pediatric Eosinophilic Disorders
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Normal Digestive Tract Phenomena
Major Symptoms and Signs of Digestive Tract Disorders
Normal Development, Structure, and Function of the Stomach and Intestines
Pyloric Stenosis and Other Congenital Anomalies of

the Stomach
Intestinal Atresia, Stenosis, and Malrotation
Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct
Motility Disorders and Hirschsprung Disease
Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions
Foreign Bodies and Bezoars
Functional Abdominal Pain
Cyclic Vomiting Syndrome
Malformations
Ascites
Peritonitis

Christopher W. Liebig MD
Clinical Assistant Professor of Pediatrics
Northeast Ohio Medical University
Rootstown, Ohio;
Director, Sports Medicine in Mahoning Valley
Akron Children's Hospital
Boardman, Ohio

Sports-Related Traumatic Brain Injury (Concussion)

Paul H. Lipkin MD
Associate Professor of Pediatrics
Director, Medical Informatics
Director, Interactive Autism Network
Kennedy Krieger Institute
Johns Hopkins University School of Medicine
Baltimore, Maryland

Developmental and Behavioral Surveillance and

Screening

Deborah R. Liptzin MD, MS
Assistant Professor of Pediatrics
University of Colorado School of Medicine
Associate Director, Colorado chILD
Children's Hospital Colorado
Aurora, Colorado

Fibrotic Lung Disease

Andrew H. Liu MD
Professor
Department of Pediatrics
Children's Hospital Colorado
University of Colorado School of Medicine
Aurora, Colorado

Childhood Asthma

Lucinda Lo MD
Clinical Assistant Professor of Pediatrics
Physician Advisor, CDI and CM
University of Pennsylvania Perelman School of Medicine
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Malnutrition

Stanley F. Lo PhD
Associate Professor of Pathology
Medical College of Wisconsin
Technical Director, Clinical Chemistry, POCT, and Biochemical Genetics
Director, Reference Standards Library
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Laboratory Testing in Infants and Children

Reference Intervals for Laboratory Tests and Procedures

Kathleen A. Long MD
Department of Child Health
University of Missouri School of Medicine
Columbia, Missouri

Dermatologic Diseases of the Neonate

Sarah S. Long MD
Professor of Pediatrics
Drexel University College of Medicine
Division of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania

Pertussis (Bordetella pertussis and Bordetella parapertussis)

Anna Lena Lopez MD, MPH
Director, Institute of Child Health and Human Development
Research Associate Professor
University of the Philippines Manila–National Institutes of Health
Manila, Philippines

Cholera

Santiago M.C. Lopez MD
Assistant Professor of Pediatrics
University of South Dakota School of Medicine
Pediatric Infectious Diseases
Sanford Children's Hospital/Specialty Clinic
Sioux Falls, South Dakota

The Common Cold

Steven V. Lossef MD

Associate Professor of Radiology
George Washington University School of Medicine and Health Sciences
Head, Pediatric Interventional Radiology
Division of Diagnostic Imaging and Radiology
Children's National Medical Center
Washington, DC

Pertussis (Bordetella pertussis and Bordetella parapertussis)
Pleurisy, Pleural Effusions, and Empyema

Jennifer A. Lowry MD
Professor of Pediatrics
University of Missouri – Kansas City School of Medicine
Director, Division of Clinical Pharmacology, Toxicology, and Therapeutic Innovation
Children's Mercy
Kansas City, Missouri

Principles of Drug Therapy

Ian R. Macumber MD, MS
Assistant Professor of Pediatrics
University of Connecticut School of Medicine
Division of Nephrology
Connecticut Children's Medical Center
Hartford, Connecticut

Systemic Hypertension

Mark R. Magnusson MD, PhD
Co-Director, Diagnostic and Complex Care Center
Medical Director, Spina Bifida Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Chronic Fatigue Syndrome

Pilar L. Magoulas MS
Assistant Professor, Clinical Program
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas

Genetic Counseling

Prashant V. Mahajan MD, MPH, MBA
Professor of Emergency Medicine and Pediatrics
Vice-Chair, Department of Emergency Medicine
Division Chief, Pediatric Emergency Medicine
University of Michigan
Ann Arbor, Michigan

Heavy Metal Intoxication

Joseph A. Majzoub MD
Thomas Morgan Rotch Professor of Pediatrics
Harvard Medical School
Division of Endocrinology
Boston Children's Hospital
Boston, Massachusetts

Diabetes Insipidus
Other Abnormalities of Arginine Vasopressin Metabolism and Action

Robert J. Mann MD
The Karl and Patricia Betz Family
Endowed Director of Research
Helen DeVos Children's Hospital
Grand Rapids, Michigan

Deformational Plagiocephaly

Irini Manoli MD, PhD
National Human Genome Research Institute

National Institutes of Health
Bethesda, Maryland

Isoleucine, Leucine, Valine, and Related Organic Acidemias

Asim Maqbool MD
Associate Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Nutritional Requirements
Normal Digestive Tract Phenomena
Major Symptoms and Signs of Digestive Tract Disorders
Normal Development, Structure, and Function of the Stomach and Intestines
Pyloric Stenosis and Other Congenital Anomalies of the Stomach
Intestinal Atresia, Stenosis, and Malrotation
Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct
Motility Disorders and Hirschsprung Disease
Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions
Foreign Bodies and Bezoars
Cyclic Vomiting Syndrome
Peritoneal Malformations
Ascites

Peritonitis

Ashley M. Maranich MD
Program Director, Pediatrics Residency
Tripler Army Medical Center
Honolulu, Hawaii

Malassezia

Nicole Marcantuono MD
Associate Professor
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Thomas Jefferson Medical College
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Alfred I. du Pont Hospital for Children
Wilmington, Delaware

Evaluation of the Child for Rehabilitative Services

David Margolis MD
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Department of Pediatrics
Medical College of Wisconsin
Program Director, Bone Marrow Transplantation
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation

Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors

Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease

Late Effects of Hematopoietic Stem Cell

Transplantation

Mona Marin MD
Division of Viral Diseases
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia

Varicella-Zoster Virus

Joan C. Marini MD, PhD
Chief, Bone and Extracellular Matrix Branch
National Institute for Child Health and Development
National Institutes of Health
Bethesda, Maryland

Osteogenesis Imperfecta

Thomas C. Markello MD, PhD
Associate Staff Clinician,
Medical Genetics Branch
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

Genetic Approaches to Rare and Undiagnosed Diseases

Morri Markowitz MD
Professor of Pediatrics and Medicine
Albert Einstein College of Medicine
Director, Lead Poisoning Prevention and Treatment Program
The Children's Hospital at Montefiore
Bronx, New York

Lead Poisoning

Stacene R. Maroushek MD, PhD, MPH

Assistant Professor of Pediatrics
Divisions of Pediatric Infectious Diseases and General Pediatrics
University of Minnesota Medical School
Hennepin County Medical Center
Minneapolis, Minnesota

Medical Evaluation of the Foreign-Born Child
Principles of Antimycobacterial Therapy

Justin D. Marsh MD
Assistant Professor of Pediatric Ophthalmology
University of Missouri-Kansas City School of Medicine
Kansas City, Missouri

Growth and Development of the Eye
Examination of the Eye
Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
Childhood Glaucoma
Orbital Abnormalities
Orbital Infections

Injuries to the Eye

Kari L. Martin MD
Assistant Professor of Dermatology and Child Health
University of Missouri School of Medicine
Columbia, Missouri

Dermatologic Diseases of the Neonate
Cutaneous Defects
Ectodermal Dysplasias
Vascular Disorders
Cutaneous Nevi
Disorders of Keratinization
Disorders of the Sweat Glands
Disorders of Hair
Disorders of the Nails
Tumors of the Skin

Maria G. Martinez MD
Clinical Fellow, Pediatric Rehabilitation Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Health and Wellness for Children With Disabilities

Wilbert H. Mason MD, MPH
Professor Emeritus of Clinical Pediatrics
University of Southern California Keck School of Medicine
Chief, Pediatric Infectious Diseases
Children's Hospital of Los Angeles
Los Angeles, California

Measles
Rubella

Mumps

Reuben K. Matalon MD, PhD
Professor of Pediatrics and Genetics
University of Texas Medical Branch
University of Texas Children's Hospital
Galveston, Texas

N-Acetylaspartic Acid Aspartic Acid (Canavan Disease)

Sravan Kumar Reddy Matta, MD
Assistant Professor of Pediatrics
Division of Gastroenterology and Nutrition
Children's National Medical Center
Washington, DC

Embryology, Anatomy, and Function of the Esophagus
Congenital Anomalies
Obstructing and Motility Disorders of the Esophagus
Dysmotility
Hiatal Hernia
Gastroesophageal Reflux Disease

Aletha Maybank MD, MPH
Deputy Commissioner
Founding Director, Center for Health Equity
New York City Department of Health and Mental Hygiene
Long Island City, New York

Racism and Child Health

Robert L. Mazor MD
Clinical Associate Professor
Department of Pediatrics
University of Washington School of Medicine

Division of Critical Care and Cardiac Surgery
Clinical Director, CICU
Seattle Children's Hospital and Regional Medical Center
Seattle, Washington

Pulmonary Edema

Jennifer McAllister MD, IBCLC
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director, West Chester Hospital Special Care Nursery and University of Cincinnati Medical Center Newborn Nursery
Medical Director, NICU Follow Up Clinic–NAS Clinic
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Maternal Selective Serotonin Reuptake Inhibitors and Neonatal Behavioral Syndromes

Megan E. McCabe MD, FAAP
Director, Pediatric Residency Program
Director, Pediatric Critical Care Fellowship Program
The Children's Hospital at Montefiore
The University Hospital for Albert Einstein College of Medicine
Bronx, New York

Loss, Separation, and Bereavement

Megan E. McClean MD
Resident Physician
Department of Dermatology
University of Missouri School of Medicine
Columbia, Missouri

Cutaneous Nevi

Susanna A. McColley MD
Professor of Pediatrics

Northwestern University Feinberg School of Medicine
Associate Chief Research Officer for Clinical Trials
Stanley Manne Children's Research Institute
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Extrapulmonary Diseases with Pulmonary Manifestations
Pulmonary Tumors

Patrick T. McGann MD, MS
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Hematology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Anemia in the Newborn Infant

Margaret M. McGovern MD, PhD
Knapp Professor of Pediatrics
Physician-in-Chief
Stony Brook Children's Hospital
Dean for Clinical Affairs
Stony Brook University School of Medicine
Stony Brook, New York

Lipidoses (Lysosomal Storage Disorders)
Mucolipidoses
Disorders of Glycoprotein Degradation and Structure

Sharon A. McGrath-Morrow MD, MBA
Professor of Pediatrics
Eudowood Division of Pediatric Respiratory Sciences
Johns Hopkins University School of Medicine
Baltimore, Maryland

Bronchopulmonary Dysplasia

Jeffrey S. McKinney MD, PhD
Professor of Pediatrics
Vice Chair for Education
Harry W. Bass Jr. Professorship in Pediatric Education
Distinguished Teaching Professor
Division of Pediatric Infectious Diseases
UT Southwestern Medical Center
Dallas, Texas

Salmonella

Matthew J. McLaughlin MD
Assistant Professor of Pediatrics
University of Missouri–Kansas City School of Medicine
Division of Pediatric Physical Medicine and Rehabilitation
Children's Mercy Hospitals and Clinics
Kansas City, Missouri

Pediatric Pharmacogenetics, Pharmacogenomics, and Pharmacoproteomics

Rima McLeod MD
Professor of Ophthalmology and Visual Science and Pediatrics
Medical Director, Toxoplasmosis Center
University of Chicago Medicine
Chicago, Illinois

Toxoplasmosis (Toxoplasma gondii)

Asuncion Mejias MD, PhD, MSCS
Associate Professor of Pediatrics
Division of Infectious Diseases
The Ohio State University College of Medicine
Principal Investigator, Center for Vaccines and Immunity
The Research Institute at Nationwide Children's Hospital
Columbus, Ohio

Hansen Disease (Mycobacterium leprae)
Mycoplasma pneumoniae
Genital Mycoplasmas (Mycoplasma hominis, Mycoplasma genitalium, and Ureaplasma urealyticum)

Peter C. Melby MD
Professor of Internal Medicine (Infectious Diseases), Microbiology and Immunology, and Pathology
Director, Division of Infectious Diseases
Director, Center for Tropical Diseases
University of Texas Medical Branch (UTMB)
Galveston, Texas

Leishmaniasis (Leishmania)

Marlene D. Melzer-Lange MD
Professor of Pediatrics
Medical College of Wisconsin
Program Director, Project Ujima
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Violent Behavior

Matthew D. Merguerian MD, PhD
Fellow, Division of Pediatric Oncology
Department of Oncology
Johns Hopkins Hospital
Pediatric Oncology Branch
National Cancer Institute
Baltimore, Maryland

Definitions and Classification of Hemolytic Anemias
Hereditary Spherocytosis
Hereditary Elliptocytosis, Hereditary

Pyropoikilocytosis, and Related Disorders
Hereditary Stomatocytosis
Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis

Stephanie L. Merhar MD, MS
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Attending Neonatologist, Division of Neonatology and Pulmonary Biology
Research Director, NICU Follow-Up Clinic
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Nervous System Disorders

Diane F. Merritt MD
Professor
Department of Obstetrics and Gynecology
Director, Pediatric and Adolescent Gynecology
Washington University School of Medicine in St. Louis
St. Louis, Missouri

Gynecologic History and Physical Examination
Vaginal Bleeding in the Prepubertal Child
Breast Concerns
Neoplasms and Adolescent Prevention Methods for Human Papillomavirus
Vulvovaginal and Müllerian Anomalies

Kevin Messacar MD
Assistant Professor of Pediatrics
University of Colorado School of Medicine
Section of Pediatric Infectious Diseases
Section of Hospital Medicine
Children's Hospital Colorado

Aurora, Colorado

Nonpolio Enteroviruses

Marian G. Michaels MD, MPH
Professor of Pediatrics and Surgery
University of Pittsburgh School of Medicine
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Infections in Immunocompromised Persons

Thomas F. Michniacki
Pediatric Hematology/Oncology Fellow
Division of Pediatric Hematology/Oncology
University of Michigan Medical School
Ann Arbor, Michigan

Leukopenia
Leukocytosis

Mohamad A. Mikati MD
Wilburt C. Davison Professor of Pediatrics
Professor of Neurobiology
Chief, Division of Pediatric Neurology
Duke University Medical Center
Durham, North Carolina

Seizures in Childhood
Conditions That Mimic Seizures

Henry Milgrom MD
Professor of Pediatrics
National Jewish Health
University of Colorado School of Medicine
Denver, Colorado

Allergic Rhinitis

Jonathan W. Mink MD, PhD
Frederick A. Horner MD Endowed Professor in Pediatric Neurology
Professor of Neurology and Pediatrics
Chief, Division of Child Neurology
Vice-Chair, Department of Neurology
University of Rochester Medical Center
Rochester, New York

Mass Psychogenic Illness
Movement Disorders

R. Justin Mistovich MD
Assistant Professor
Department of Orthopaedic Surgery
Case Western Reserve University School of Medicine
MetroHealth Medical Center University Hospitals
Rainbow and Babies Children's Hospital
Cleveland, Ohio

The Spine
The Neck

Jonathan A. Mitchell PhD, MsC
Research Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia

Nutritional Requirements
Feeding Healthy Infants, Children, and Adolescents

Mark M. Mitsnefes MD, MS
Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Clinical and Translational Research Center
Division of Pediatric Nephrology
Cincinnati Children's Hospital Medical Center

Cincinnati, Ohio

Chronic Kidney Disease

Sindhu Mohandas MD
Assistant Professor of Pediatrics
Division of Infectious Diseases
Keck School of Medicine
University of Southern California
Los Angeles, California

Other Anaerobic Infections

Rachel Y. Moon MD
Professor of Pediatrics
Head, Division of General Pediatrics
University of Virginia School of Medicine
Charlottesville, Virginia

Sudden Infant Death Syndrome

Joan P. Moran BSN, RN
Infection Preventionist
Infection Prevention and Control
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Infection Prevention and Control

Eva Morava MD, PhD
Professor of Pediatrics
Tulane University Medical School
Clinical Biochemical Geneticist
Hayward Genetics Center
New Orleans, Louisiana

Congenital Disorders of Glycosylation

Megan A. Moreno MD, MSEd, MPH

Professor of Pediatrics
Division Chief, General Pediatrics and Adolescent Medicine
Vice Chair of Digital Health
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

Bullying, Cyberbullying, and School Violence
Media Violence

Esi Morgan MD, MSCE
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Rheumatology
James M. Anderson Center for Health Systems Excellence
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Treatment of Rheumatic Diseases

Peter E. Morrison DO
Senior Instructor
Department of Neurology
University of Rochester Medical Center
Rochester, New York

Ataxias

Lovern R. Moseley PhD
Clinical Assistant Professor of Psychiatry
Boston University School of Medicine
Boston, Massachusetts

Tantrums and Breath-Holding Spells
Lying, Stealing, and Truancy
Aggression
Self-Injurious Behavior

Yael Mozer-Glassberg MD
Head, Pediatric Liver Transplant Program
Institute of Gastroenterology, Nutrition, and Liver Diseases
Schneider Children's Medical Center of Israel
Petah Tikva, Israel

Immunoproliferative Small Intestinal Disease

Louis J. Muglia MD, PhD
Professor of Pediatrics
University of Cincinnati College of Medicine
Co-Director, Perinatal Institute
Director, Center for Prevention of Preterm Birth
Director, Division of Human Genetics
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

The Endocrine System

Kevin P. Murphy MD
Medical Director, Pediatric Rehabilitation
Sanford Health Systems
Bismarck, North Dakota;
Medical Director, Gillette Children's Specialty Healthcare
Duluth Clinic
Duluth, Minnesota

Management of Musculoskeletal Injury
Specific Sports and Associated Injuries

Timothy F. Murphy MD
SUNY Distinguished Professor of Medicine
Senior Associate Dean for Clinical and Translational Research
Jacobs School of Medicine and Biomedical Sciences
University at Buffalo, State University of New York
Buffalo, New York

Moraxella catarrhalis

Karen F. Murray MD
Professor and Interim-Chair
Chief, Division of Gastroenterology and Hepatology
Department of Pediatrics
University of Washington School of Medicine
Interim Pediatrician-In-Chief
Seattle Children's Hospital
Seattle, Washington

Tumors of the Digestive Tract

Thomas S. Murray MD, PhD
Associate Professor of Medical Sciences
Quinnipiac University Frank H Netter MD School of Medicine
Hamden, Connecticut

Listeria monocytogenes
Pseudomonas, Burkholderia, and Stenotrophomonas
Infective Endocarditis

Sona Narula MD
Assistant Professor of Clinical Neurology
Children's Hospital of Philadelphia
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania

Central Nervous System Vasculitis

Mindo J. Natale PsyD
Assistant Professor of Psychology
University of South Carolina School of Medicine
Senior Staff Psychologist
GHS Children's Hospital
Greenville, South Carolina

Neurodevelopmental and Executive Function and Dysfunction

Amy T. Nathan MD
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director, Perinatal Institute
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

The Umbilicus

Dipesh Navsaria MD, MPH, MSLIS, FAAP
Associate Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

William A. Neal MD
Professor Emeritus of Pediatrics
Division of Pediatric Cardiology
West Virginia University School of Medicine
Morgantown, West Virginia

Disorders of Lipoprotein Metabolism and Transport

Grace Nehme MD
Fellow, Department of Pediatrics
University of Texas MD Anderson Cancer Center
Houston, Texas

Neoplasms of the Kidney

Edward J. Nehus MD, MS
Assistant Professor of Clinical Pediatrics
University of Cincinnati College of Medicine
Division of Nephrology and Hypertension
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Introduction to Glomerular Diseases

Maureen R. Nelson MD
Associate Professor of Physical Medicine & Rehabilitation and Pediatrics
Baylor College of Medicine
Medical Director, Physical Medicine & Rehabilitation
The Children's Hospital of San Antonio
San Antonio, Texas

Birth Brachial Plexus Palsy

Caitlin M. Neri MD
Assistant Professor of Pediatrics
Boston University School of Medicine
Boston, Massachusetts

Complementary Therapies and Integrative Medicine

Mark I. Neuman MD, MPH
Associate Professor of Pediatrics and Emergency Medicine
Harvard Medical School
Department of Emergency Medicine
Boston Children's Hospital
Boston, Massachusetts

Fever in the Older Child

Mary A. Nevin MD, FAAP, FCCP
Associate Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Department of Pediatrics, Division of Pulmonary Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Pulmonary Hemosiderosis
Pulmonary Embolism, Infarction, and Hemorrhage

Jane W. Newburger MD

Commonwealth Professor of Pediatrics
Harvard Medical School
Associate Cardiologist-in-Chief, Research and Education
Director, Cardiac Neurodevelopmental Program
Boston Children's Hospital
Boston, Massachusetts

Kawasaki Disease

Jonathan Newmark MD, MM, FAAN
Adjunct Professor of Neurology
F. Edward Hebert School of Medicine
Uniformed Services University of the Health Sciences
Bethesda, Maryland;
Clinical Assistant Professor of NeurologyGeorge Washington University School of Medicine and Health Sciences
Staff Neurologist
Washington DC VA Medical Center
Washington, DC

Biologic and Chemical Terrorism

Linda S. Nield MD
Assistant Dean for Admissions
Professor of Medical Education and Pediatrics
West Virginia University School of Medicine
Morgantown, West Virginia

Fever

Omar Niss MD
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Hematology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Hemolytic Disease of the Newborn

Neonatal Polycythemia

Zehava L. Noah MD
Associate Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Division of Pediatric Critical Care Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Other Conditions Affecting Respiration

James J. Nocton MD
Professor of Pediatrics
Section of Pediatric Rheumatology
Medical College of Wisconsin
Milwaukee, Wisconsin

Mast Cell Activation Syndrome

Lawrence M. Nogee MD
Professor of Pediatrics
Eudowood Neonatal Pulmonary Division
Johns Hopkins University School of Medicine
Baltimore, Maryland

Inherited Disorders of Surfactant Metabolism
Pulmonary Alveolar Proteinosis

Corina Noje MD
Assistant Professor
Pediatric Critical Care Medicine
Department of Anesthesiology and Critical Care Medicine
Johns Hopkins University School of Medicine
Medical Director, Pediatric Transport
Johns Hopkins Bloomberg Children's Center
Baltimore, Maryland

Interfacility Transport of the Seriously Ill or Injured

Pediatric Patient

Laura E. Norton MD, MS
Assistant Professor of Pediatrics
Division of Pediatric Infectious Diseases and Immunology
University of Minnesota Medical School
Minneapolis, Minnesota

Botulism (Clostridium botulinum)

Anna Nowak-Węgrzyn MD, PhD
Professor of Pediatrics
Jaffe Food Allergy Institute
Division of Allergy and Immunology
Department of Pediatrics
Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
New York, New York

Serum Sickness
Food Allergy and Adverse Reactions to Foods

Stephen K. Obaro MD, PhD
Professor of Pediatric Infectious Diseases
Director, Pediatric International Research
University of Nebraska Medical Center
Omaha, Nebraska

Nonvenereal Treponemal Infections
Relapsing Fever (Borrelia)

Makram M. Obeid MD
Assistant Professor of Pediatrics and Adolescent Medicine
Pediatric Epileptologist, Division of Child Neurology
Department of Pediatrics and Adolescent Medicine
Department of Anatomy, Cell Biology and Physiology
American University of Beirut
Beirut, Lebanon

Conditions That Mimic Seizures

Hope L. O'Brien MD, MBA, FAHS, FAAN
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Program Director, Headache Medicine Education
Co-Director Young Adult Headache Program
Cincinnati Children's Medical Center
Cincinnati, Ohio

Headaches

Jean-Marie Okwo-Bele MD, MPH
Director, Department of Immunization, Vaccines, and Biologicals
World Health Organization
Geneva, Switzerland

International Immunization Practices

Joyce L. Oleszek MD
Associate Professor
Department of Physical Medicine and Rehabilitation
University of Colorado School of Medicine
Children's Hospital Colorado
Denver, Colorado

Spasticity

Scott E. Olitsky MD
Professor of Ophthalmology
University of Kansas School of Medicine
University of Missouri – Kansas City School of Medicine
Section Chief, Ophthalmology
Children's Mercy Hospitals and Clinics
Kansas City, Missouri

Growth and Development of the Eye
Examination of the Eye

Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
Childhood Glaucoma
Orbital Abnormalities
Orbital Infections
Injuries to the Eye

John M. Olsson MD, CPE
Professor of Pediatrics
Medical Director, Well Newborn Services
Division of General Pediatrics
University of Virginia School of Medicine
Charlottesville, Virginia

The Newborn

Amanda K. Ombrello MD
Associate Research Physician
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

Amyloidosis

Meghan E. O'Neill MD
Fellow in Neurodevelopment Disabilities
Kennedy Krieger Institute
Baltimore, Maryland

Developmental Delay and Intellectual Disability

Mutiat T. Onigbanjo MD
Assistant Professor
Department of Pediatrics
University of Maryland School of Medicine
Baltimore, Maryland

The First Year

Walter A. Orenstein MD, DSc (Hon)
Professor of Medicine, Pediatrics, and Global Health
Emory University
Associate Director, Emory Vaccines Center
Atlanta, Georgia;
Former Deputy Director for Immunization Programs
Bill & Melinda Gates Foundation
Seattle, Washington;
Former Director, National Immunization Program
Centers for Disease Control and Prevention
Atlanta, Georgia

Immunization Practices

Rachel C. Orscheln MD
Associate Professor of Pediatrics
Washington University School of Medicine in St. Louis
Director, Ambulatory Pediatric Infectious Diseases
Director, International Adoption Center
St. Louis Children's Hospital
St. Louis, Missouri

Bartonella

Marisa Osorio DO
Assistant Professor
Department of Rehabilitation Medicine
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, Washington

Ambulation Assistance

Christian A. Otto MD, MMSc
Director of TeleOncology
Associate Attending Physician
Memorial Sloan Kettering Cancer Center
New York, New York

Altitude-Associated Illness in Children (Acute Mountain Sickness)

Judith A. Owens MD, MPH
Professor of Neurology
Harvard Medical School
Director of Sleep Medicine
Boston Children's Hospital
Boston, Massachusetts

Sleep Medicine

Seza Özen MD
Professor of Paediatrics
Divisions of Paediatric Rheumatology
Hacettepe University
Ankara, Turkey

Behçet Disease

Lee M. Pachter DO

Professor of Pediatrics and Population Health
Sidney Kimmel Medical College and Jefferson College of Population Health
Thomas Jefferson University
Director, Community and Clinical Integration
Nemours Alfred I. duPont Hospital for Children
Wilmington, Delaware;
Director, Health Policy Program
Jefferson College of Population Health
Philadelphia, Pennsylvania

Overview of Pediatrics
Child Health Disparities
Cultural Issues in Pediatric Care

Amruta Padhye MD
Assistant Professor of Clinical Child Health
Division of Pediatric Infectious Diseases
University of Missouri School of Medicine
Columbia, Missouri

Diphtheria (Corynebacterium diphtheriae)

Suzinne Pak-Gorstein MD, PhD, MPH
Associate Professor of Pediatrics
Adjunct Associate Professor of Global Health
University of Washington School of Medicine
Seattle, Washington

Global Child Health

Jennifer Panganiban MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Non Alcoholic Fatty Liver Disease Clinic
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Nutritional Requirements

Diane E. Pappas MD, JD
Professor of Pediatrics
Director of Child Advocacy
University of Virginia School of Medicine
Charlottesville, Virginia

Sinusitis
Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

John J. Parent MD, MSCR
Assistant Professor of Pediatrics
Indiana University School of Medicine
Section of Cardiology
Riley Hospital for Children at Indiana University Health
Indianapolis, Indiana

Diseases of the Myocardium
Diseases of the Pericardium
Tumors of the Heart

Alasdair P.J. Parker MBBS (Lond), MRCP, MD, MA (Camb)
Consultant in Pediatric Neurology
Addenbrooke's Hospital
Associate Lecturer
University of Cambridge School of Clinical Medicine
Cambridge, United Kingdom

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Elizabeth Prout Parks MD, MSCE
Assistant Professor of Pediatrics

University of Pennsylvania Perelman School of Medicine
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Nutritional Requirements
Feeding Healthy Infants, Children, and Adolescents

Briana C. Patterson MD, MS
Associate Professor of Pediatrics
Division of Pediatric Endocrinology
Director, Pediatric Endocrine Fellowship Program
Emory University School of Medicine
Atlanta, Georgia

Hormones of the Hypothalamus and Pituitary
Hypopituitarism

Maria Jevitz Patterson MD, PhD
Professor Emeritus of Microbiology and Molecular Genetics
Michigan State University College of Human Medicine
East Lansing, Michigan

Syphilis (Treponema pallidum)

Anna L. Peters MD, PhD
Clinical Fellow
Division of Gastroenterology, Hepatology, and Nutrition
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Metabolic Diseases of the Liver

Timothy R. Peters MD
Professor of Pediatrics
Wake Forest School of Medicine
Division of Pediatric Infectious Diseases
Wake Forest Baptist Medical Center

Winston-Salem, North Carolina

Streptococcus pneumoniae (Pneumococcus)

Rachel A. Phelan MD, MPH
Assistant Professor of Pediatrics
Medical College of Wisconsin
Division of Hematology/Oncology/BMT
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation
Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors
Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease
Late Effects of Hematopoietic Stem Cell Transplantation

Anna Pinto MD, PhD
Lecturer of Neurology
Harvard Medical School
Co-Director, Sturge Weber Clinic
Department of Neurology
Boston Children's Hospital
Boston, Massachusetts

Neurocutaneous Syndromes

Brenda B. Poindexter MD, MS
Professor of Pediatrics
University of Cincinnati College of Medicine
Director of Clinical and Translational Research
Perinatal Institute
Cincinnati Children's Hospital Medical Center

Cincinnati, Ohio

The High-Risk Infant
Transport of the Critically Ill Newborn

Andrew J. Pollard FRCPCH, PhD, FMedSci
Professor of Paediatric Infection and Immunity
Department of Paediatrics
University of Oxford
Children's Hospital
Oxford, United Kingdom

Neisseria meningitidis (Meningococcus)

Diego Preciado MD, PhD
Professor of Pediatrics, Surgery, and Integrative Systems Biology
George Washington University School of Medicine and Health Sciences
Vice-Chief, Division of Pediatric Otolaryngology
Children's National Health System
Washington, DC

Otitis Media

Mark R. Proctor MD
Franc D. Ingraham Professor of Neurosurgery
Harvard Medical School
Neurosurgeon-in-Chief
Boston Children's Hospital
Boston, Massachusetts

Spinal Cord Injuries in Children
Spinal Cord Disorders

Howard I. Pryor II, MD
Instructor of Surgery
Division of Pediatric Surgery
Johns Hopkins University School of Medicine
Johns Hopkins Children's Center

Baltimore, Maryland

Acute Care of Multiple Trauma

Lee A. Pyles MD, MS
Associate Professor of Pediatrics
Division of Pediatric Cardiology
West Virginia University School of Medicine
Morgantown, West Virginia

Disorders of Lipoprotein Metabolism and Transport

Molly Quinn MD
Fellow, Reproductive Endocrinology and Infertility
Department of Obstetrics, Gynecology, and Reproductive Sciences
University of California, San Francisco
San Francisco, California

Polycystic Ovary Syndrome and Hirsutism

Elisabeth H. Quint MD
Professor of Obstetrics and Gynecology
Director, Fellowship in Pediatric and Adolescent Gynecology
University of Michigan Medical School
Ann Arbor, Michigan

Gynecologic Care for Girls with Special Needs

Amy E. Rabatin MD
Fellow, Pediatric Rehabilitation and Board Certified Sports Medicine
Department of Physical Medicine and Rehabilitation
Mayo Clinic Children's Center
Rochester, Minnesota

Specific Sports and Associated Injuries

C. Egla Rabinovich MD, MPH
Professor of Pediatrics
Duke University School of Medicine

Co-Chief, Division of Pediatric Rheumatology
Duke University Health System
Durham, North Carolina

Evaluation of Suspected Rheumatic Disease
Treatment of Rheumatic Diseases
Juvenile Idiopathic Arthritis
Scleroderma and Raynaud Phenomenon
Sjögren Syndrome
Miscellaneous Conditions Associated With Arthritis

Leslie J. Raffini MD
Associate Professor
Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Hematology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Hemostasis
Hereditary Predisposition to Thrombosis
Thrombotic Disorders in Children
Disseminated Intravascular Coagulation

Shawn L. Ralston MD, MS
Associate Professor and Vice Chair for Clinical Affairs
Department of Pediatrics
Geisel School of Medicine at Dartmouth
Chief, Section of Pediatric Hospital Medicine
Children's Hospital at Dartmouth-Hitchcock
Hanover, New Hampshire

Wheezing in Infants: Bronchiolitis

Sanjay Ram MD

Professor of Medicine
University of Massachusetts Medical School
Division of Infectious Diseases and Immunology
UMass Memorial Medical Center
Worcester, Massachusetts

Neisseria gonorrhoeae (Gonococcus)

Octavio Ramilo MD
Professor of Pediatrics
Henry G. Cramblett Chair in Medicine
The Ohio State University College of Medicine
Chief, Division of Infectious Diseases
Nationwide Children's Hospital
Columbus, Ohio

Mycoplasma pneumoniae

Kacy A. Ramirez MD
Assistant Professor of Pediatrics
Wake Forest School of Medicine
Division of Pediatric Infectious Diseases
Wake Forest Baptist Medical Center
Winston-Salem, North Carolina

Streptococcus pneumoniae (Pneumococcus)

Casey M. Rand BS
Project Manager, Center for Autonomic Medicine in Pediatrics
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Rapid-Onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD)
Congenital Central Hypoventilation Syndrome

Adam J. Ratner MD, MPH

Associate Professor of Pediatrics and Microbiology
New York University School of Medicine
Chief, Division of Pediatric Infectious Diseases
New York University Langone Medical Center
New York, New York

Aeromonas and Plesiomonas

Lee Ratner MD, PhD
Professor of Medicine
Professor of Molecular Microbiology and of Pathology and Immunology
Washington University School of Medicine in St. Louis
St. Louis, Missouri

Human T-Lymphotropic Viruses (1 and 2)

Gerald V. Raymond MD
Professor of Neurology
University of Minnesota School of Medicine
Chief of Pediatric Neurology
University of Minnesota Medical Center, Fairview
Minneapolis, Minnesota

Disorders of Very-Long-Chain Fatty Acids and Other Peroxisomal Functions

Ann M. Reed MD
Professor of Pediatrics
Chair, Department of Pediatrics
Physician-in-Chief
Duke Children's
Duke University
Durham, North Carolina

Juvenile Dermatomyositis

Shimon Reif MD
Chairman, Department of Pediatrics

Hadassah Medical Center
Hebrew University
Jerusalem, Israel

Diarrhea From Neuroendocrine Tumors

Megan E. Reller MD, PhD, MPH
Associate Professor of Medicine
Associate Research Professor of Global Health
Duke University Medical Center
Durham, North Carolina

Spotted Fever Group Rickettsioses
Scrub Typhus (Orientia tsutsugamushi)
Typhus Group Rickettsioses
Ehrlichioses and Anaplasmosis
Q Fever (Coxiella burnetii)

Caroline H. Reuter MD, MSCI
Associate Medical Director, Pharmacovigilance
Bioverativ
Waltham, Massachusetts

Group A Streptococcus

Jorge D. Reyes MD
Professor and Roger K. Giesecke Distinguished Chair
Department of Surgery
University of Washington School of Medicine
Chief, Division of Transplant Surgery
Seattle Children's Hospital
Seattle, Washington

Intestinal Transplantation in Children with Intestinal Failure
Liver Transplantation

Firas Rinawi MD
Attending Physician
Institute of Gastroenterology, Nutrition, and Liver Diseases
Schneider Children's Medical Center of Israel
Petah Tikva, Israel

Evaluation of Children with Suspected Intestinal Malabsorption

A. Kim Ritchey MD
Professor and Vice-Chair of International Affairs
Department of Pediatrics
University of Pittsburgh School of Medicine
Division of Hematology/Oncology
UPMC Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Principles of Cancer Diagnosis
Principles of Cancer Treatment
The Leukemias

Frederick P. Rivara MD, MPH
Seattle Children's Guild Endowed Chair in Pediatrics
Professor and Vice-Chair, Department of Pediatrics
University of Washington School of Medicine
Seattle, Washington

Injury Control

Eric Robinette MD
Attending Physician in Infectious Diseases
Akron Children's Hospital
Akron, Ohio

Osteomyelitis
Septic Arthritis

Angela Byun Robinson MD, MPH
Associate Professor
Cleveland Clinic Lerner College of Medicine
Staff, Pediatrics Institute
Cleveland Clinic Children's
Cleveland, Ohio

Juvenile Dermatomyositis
Miscellaneous Conditions Associated with Arthritis

Kristine Knuti Rodrigues MD, MPH
Assistant Professor of Pediatrics
University of Colorado School of Medicine
Department of Pediatrics
Denver Health Medical Center
Denver, Colorado

Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis)

David F. Rodriguez-Buritica MD
Assistant Professor
Department of Pediatrics
Division of Medical Genetics
McGovern Medical School at UTHealth
Houston, Texas

Disorders Involving Ion Transporters
Disorders Involving Transcription Factors
Disorders Involving Defective Bone Resorption

Rosa Rodríguez-Fernández MD, PhD
Hospital General Universitario Gregorio Marañón
Instituto de Investigación Sanitaria Gregorio Marañón (IISGM)
Madrid, Spain;

Center for Vaccines and Immunity
The Research Institute at Nationwide Children's Hospital
The Ohio State University College of Medicine
Columbus, Ohio

Genital Mycoplasmas (Mycoplasma hominis, Mycoplasma genitalium, and Ureaplasma urealyticum)

Genie E. Roosevelt MD, MPH
Professor of Emergency Medicine
University of Colorado School of Medicine
Department of Emergency Medicine
Denver Health Medical Center
Denver, Colorado

Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis)

David R. Rosenberg MD
Chair, Department of Psychiatry and Behavioral Neurosciences
Chief of Child Psychiatry and Psychology
Wayne State University School of Medicine
Detroit, Michigan

Anxiety Disorders

Cindy Ganis Roskind MD
Program Director
Pediatric Emergency Medicine Fellowship
Children's Hospital of New York–Presbyterian
Associate Professor of Pediatrics
Columbia University Irving Medical Center
Columbia University College of Physicians and Surgeons
New York, New York

Acute Care of Multiple Trauma

A. Catharine Ross PhD
Professor and Dorothy Foehr Huck Chair
Department of Nutritional Sciences
The Pennsylvania State University
College of Health and Human Development
University Park, Pennsylvania

Vitamin A Deficiencies and Excess

Joseph W. Rossano MD, MS
Chief, Division of Cardiology
Co-Executive Director, The Cardiac Center
Jennifer Terker Endowed Chair in Pediatric Cardiology
Associate Professor of Pediatrics
Children's Hospital of Philadelphia
University of Pennsylvania Perelman School of Medicine
Philadelphia, Pennsylvania

Heart Failure
Pediatric Heart and Heart-Lung Transplantation

Jennifer A. Rothman MD
Associate Professor
Department of Pediatrics
Division of Pediatric Hematology/Oncology
Duke University Medical Center
Durham, North Carolina

Iron-Deficiency Anemia
Other Microcytic Anemias

Ranna A. Rozenfeld MD
Professor of Pediatrics
The Warren Alpert Medical School
Brown University

Division of Pediatric Critical Care Medicine
Hasbro Children's Hospital
Providence, Rhode Island

Atelectasis

Colleen A. Ryan MD
Instructor in Psychiatry
Harvard Medical School
Boston Children's Hospital
Boston, Massachusetts

Motor Disorders and Habits

Monique M. Ryan M Med BS, FRACP
Professor of Paediatric Neurology
Director, Department of Neurology
Honorary Fellow, Murdoch Children's Research Institute
University of Melbourne
Royal Children's Hospital
Parkville, Victoria, Australia

Autonomic Neuropathies
Guillain-Barré Syndrome
Bell Palsy

Julie Ryu MD
Professor of Pediatrics
University of California, San Diego School of Medicine
Interim Chief, Division of Respiratory Medicine
Chief Research Informatics Officer
Department of Pediatrics
Rady Children's Hospital–San Diego
San Diego, California

H.P.S. Sachdev MD, FIAP, FAMS, FRCPCH
Senior Consultant
Departments of Pediatrics and Clinical Epidemiology

Sitaram Bhartia Institute of Science and Research
New Delhi, India

Vitamin B Complex Deficiencies and Excess

Vitamin C (Ascorbic Acid)

Manish Sadarangani MRCPCH, DPHIL, BM.BCh, MA
Assistant Professor of Pediatrics
Sauder Family Chair in Pediatric Infectious Diseases
University of British Columbia Faculty of Medicine
Director, Vaccine Evaluation Center
British Columbia Children's Hospital
Vancouver, British Columbia, Canada

Neisseria meningitidis (Meningococcus)

Rebecca E. Sadun MD, PhD
Assistant Professor of Adult and Pediatric Rheumatology
Departments of Medicine and Pediatrics
Duke University School of Medicine
Durham, North Carolina

Systemic Lupus Erythematosus

Mustafa Sahin MD, PhD
Professor of Neurology
Harvard Medical School
Director, Translational Neuroscience Center
Boston Children's Hospital
Boston, Massachusetts

Neurocutaneous Syndromes

Nina N. Sainath MD
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Feeding Healthy Infants, Children, and Adolescents

Robert A. Salata MD
Professor and Chairman, Department of Medicine
Case Western Reserve University School of Medicine
Physician-in-Chief
University Hospitals Case Medical Center
Cleveland, Ohio

Amebiasis
Trichomoniasis (Trichomonas vaginalis)
African Trypanosomiasis (Sleeping Sickness; Trypanosoma brucei complex)
American Trypanosomiasis (Chagas Disease; Trypanosoma cruzi)

Edsel Maurice T. Salvana MD
Clinical Associate Professor of Medicine
University of the Philippines College of Medicine
Director, Institute of Molecular Biology and Biotechnology
National Institutes of Health
Manila, The Philippines;
Adjunct Professor of Global Health
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Amebiasis
Trichomoniasis (Trichomonas vaginalis)
African Trypanosomiasis (Sleeping Sickness; Trypanosoma brucei complex)
American Trypanosomiasis (Chagas Disease; Trypanosoma cruzi)

Hugh A. Sampson MD
Kurt Hirschhorn Professor of Pediatrics
Jaffe Food Allergy Institute

Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
New York, New York

Anaphylaxis
Food Allergy and Adverse Reactions to Foods

Chase B. Samsel MD
Instructor in Psychiatry
Harvard Medical School
Boston Children's Hospital
Boston, Massachusetts

Rumination and Pica

Thomas J. Sandora MD, MPH
Associate Professor of Pediatrics
Harvard Medical School
Hospital Epidemiologist
Division of Infectious Diseases
Boston Children's Hospital
Boston, Massachusetts

Community-Acquired Pneumonia

Tracy L. Sandritter PharmD
Division of Clinical Pharmacology, Toxicology, and Therapeutic Innovation
Children's Mercy
Adjunct Clinical Professor
University of Missouri – Kansas City School of Pharmacy
Kansas City, Missouri

Principles of Drug Therapy

Wudbhav N. Sankar MD
Associate Professor
Department of Orthopaedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon

Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

The Hip

Eric J. Sarkissian MD
Resident Physician
Department of Orthopaedic Surgery
Stanford University School of Medicine
Stanford, California

Osgood-Schlatter Disease and Sinding-Larsen-Johansson Syndrome

Ajit A. Sarnaik MD
Associate Professor of Pediatrics
Wayne State University School of Medicine
Director, Pediatric Critical Care Medicine Fellowship Program
Children's Hospital of Michigan
Detroit, Michigan

Mechanical Ventilation

Ashok P. Sarnaik MD
Professor and Former Interim Chair
Department of Pediatrics
Wayne State University School of Medicine
Former Pediatrician-in-Chief
Children's Hospital of Michigan
Detroit, Michigan

Respiratory Distress and Failure

Harvey B. Sarnat MD, MS, FRCPC
Professor of Pediatrics, Pathology (Neuropathology), and Clinical Neurosciences
University of Calgary Cumming School of Medicine
Division of Pediatric Neurology
Alberta Children's Hospital Research Institute

Calgary, Alberta, Canada

Evaluation and Investigation of Neuromuscular Disorders
Developmental Disorders of Muscle
Endocrine and Toxic Myopathies
Metabolic Myopathies
Hereditary Motor-Sensory Neuropathies
Toxic Neuropathies

Joshua K. Schaffzin MD, PhD
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Infection Prevention and Control
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Liver Abscess

Laura E. Schanberg MD
Professor of Pediatrics
Duke University School of Medicine
Division of Pediatric Rheumatology
Duke University Medical Center
Durham, North Carolina

Systemic Lupus Erythematosus
Musculoskeletal Pain Syndromes

Michael S. Schechter MD, MPH
Professor of Pediatrics
Virginia Commonwealth University School of Medicine
Chief, Division of Pulmonary Medicine
Director, Cystic Fibrosis Center
Director, UCAN Community Asthma Program
Children's Hospital of Richmond at VCU

Richmond, Virginia

Cystic Fibrosis

Mark R. Schleiss MD
Professor of Pediatrics
American Legion and Auxiliary Heart Research Foundation Endowed Chair
Division of Pediatric Infectious Diseases and Immunology
University of Minnesota Medical School
Minneapolis, Minnesota

Principles of Antibacterial Therapy
Botulism (Clostridium botulinum)
Tetanus (Clostridium tetani)
Principles of Antiviral Therapy
Principles of Antiparasitic Therapy

Nina F. Schor MD, PhD
Deputy Director
National Institute of Neurological Disorders and Stroke
National Institute of Health
Bethesda, Maryland

Neurologic Evaluation

James W. Schroeder Jr, MD, FACS, FAAP
Associate Professor
Department of Otolaryngology – Head and Neck Surgery
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Congenital Anomalies of the Larynx, Trachea, and Bronchi
Foreign Bodies in the Airway
Laryngotracheal Stenosis and Subglottic Stenosis

Neoplasms of the Larynx, Trachea, and Bronchi

Elaine E. Schulte MD, MPH
Professor of Pediatrics
Albert Einstein College of Medicine
Vice Chair, Academic Affairs and Faculty Development
Division of Academic General Pediatrics
The Children's Hospital at Montefiore
Bronx, New York

Domestic and International Adoption

Mark A. Schuster MD, PhD
Founding Dean and CEO
Professor
Kaiser Permanente School of Medicine
Pasadena, California

Gay, Lesbian, and Bisexual Adolescents

Daryl A. Scott MD, PhD
Assistant Professor
Department of Molecular and Human Genetics
Baylor College of Medicine
Houston, Texas

The Genetic Approach in Pediatric Medicine

The Human Genome

Patterns of Genetic Transmission

J. Paul Scott MD
Professor
Department of Pediatrics
Division of Pediatric Hematology/Oncology
Medical College of Wisconsin
Blood Center of Southeastern Wisconsin
Milwaukee, Wisconsin

Hemostasis
Hereditary Clotting Factor Deficiencies (Bleeding Disorders)
von Willebrand Disease
Hereditary Predisposition to Thrombosis
Thrombotic Disorders in Children
Postneonatal Vitamin K Deficiency
Liver Disease
Acquired Inhibitors of Coagulation
Disseminated Intravascular Coagulation
Platelet and Blood Vessel Disorders

John P. Scott MD
Associate Professor of Anesthesiology and Pediatrics
Divisions of Pediatric Anesthesiology and Pediatric Critical Care
Medical College of Wisconsin
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Anesthesia and Perioperative Care
Procedural Sedation

Patrick C. Seed MD, PhD, FAAP, FIDSA
Children's Research Fund Chair in Basic Science
Professor of Pediatrics, Microbiology and Immunology
Northwestern University Feinberg School of Medicine
Division Head, Pediatric Infectious Diseases
Associate Chief Research Officer of Basic Science
Stanley Manne Children's Research Institute
Director, Host-Microbial Interactions, Inflammation, and Immunity (HMI3) Program
Ann & Robert H. Lurie Children's Hospital
Chicago, Illinois

The Microbiome and Pediatric Health
Shigella
Escherichia coli

Janet R. Serwint MD
Professor
Department of Pediatrics
Johns Hopkins University School of Medicine
Baltimore, Maryland

Loss, Separation, and Bereavement

Apurva S. Shah MD, MBA
Assistant Professor
Department of Orthopedic Surgery
University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Common Fractures

Dheeraj Shah MD, FIAP, MAMS
Professor
Department of Pediatrics
University College of Medical Sciences
Guru Teg Bahadur Hospital
New Delhi, India

Vitamin B Complex Deficiencies and Excess
Vitamin C (Ascorbic Acid)

Samir S. Shah MD, MSCE
Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Division of Hospital Medicine
Chief Metrics Officer

James M. Ewell Endowed Chair
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Quality and Value in Healthcare for Children
Fever Without a Focus in the Neonate and Young Infant
Osteomyelitis
Septic Arthritis

Ala Shaikhkhalil MD
Pediatric Nutrition Fellow
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Nutritional Requirements
Feeding Healthy Infants, Children, and Adolescents

Raanan Shamir MD
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Sackler Faculty of Medicine
Tel-Aviv University
Tel Aviv, Israel;
Chairman, Institute of Gastroenterology, Nutrition, and Liver Diseases
Schneider Children's Medical Center of Petah
Tikva, Israel

Disorders of Malabsorption
Chronic Diarrhea

Christina M. Shanti MD
Chief, Division of Pediatric Surgery
Children's Hospital of Michigan
Detroit, Michigan

Surgical Conditions of the Anus and Rectum

Bruce K. Shapiro MD
Professor of Pediatrics
The Arnold J. Capute MD, MPH Chair in Neurodevelopmental Disabilities
The Johns Hopkins University School of Medicine
Vice-President, Training
Kennedy Krieger Institute
Baltimore, Maryland

Developmental Delay and Intellectual Disability

Erin E. Shaughnessy MD, MSHCM
Division Chief, Hospital Medicine
Phoenix Children's Hospital
Phoenix, Arizona

Jaundice and Hyperbilirubinemia in the Newborn

Kernicterus

Bennett A. Shaywitz MD
Charles and Helen Schwab Professor in Dyslexia and Learning Development
Co-Director, Center for Dyslexia and Creativity
Chief, Child Neurology
Yale University School of Medicine
New Haven, Connecticut

Dyslexia

Sally E. Shaywitz MD
Audrey G. Ratner Professor in Learning Development
Co-Director, Center for Dyslexia and Creativity
Department of Pediatrics
Yale University School of Medicine
New Haven, Connecticut

Dyslexia

Oleg A. Shchelochkov MD
Medical Genomics and Metabolic Genetics Branch
National Human Genome Research Institute
National Institutes of Health
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An Approach to Inborn Errors of Metabolism

Nicole M. Sheanon MD, MS
Assistant Professor of Pediatrics
University of Cincinnati College of Medicine
Division of Endocrinology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

The Endocrine System

Benjamin L. Shneider MD
Professor of Pediatrics
Texas Children's Hospital
Baylor College of Medicine
Houston, Texas

Autoimmune Hepatitis

Stanford T. Shulman MD
Virginia H. Rogers Professor of Pediatric Infectious Diseases
Northwestern University Feinberg School of Medicine
Chief Emeritus, Division of Pediatric Infectious Diseases
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Group A Streptococcus
Rheumatic Heart Disease

Scott H. Sicherer MD
Elliot and Roslyn Jaffe Professor of Pediatrics, Allergy, and Immunology
Director, Jaffe Food Allergy Institute

Department of Pediatrics
Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
New York, New York

Allergy and the Immunologic Basis of Atopic Disease
Diagnosis of Allergic Disease
Allergic Rhinitis
Childhood Asthma
Atopic Dermatitis (Atopic Eczema)
Insect Allergy
Ocular Allergies
Urticaria (Hives) and Angioedema
Anaphylaxis
Serum Sickness
Food Allergy and Adverse Reactions to Foods
Adverse Reactions to Drugs

Mark D. Simms MD, MPH
Professor of Pediatrics
Medical College of Wisconsin
Medical Director
Child Development Center
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Language Development and Communication Disorders
Adoption

Jeffery M. Simmons MD, MSc
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Associate Division Director for Quality

Division of Hospital Medicine
Safety Officer
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Quality and Value in Healthcare for Children
Safety in Healthcare for Children

Eric A.F. Simões MBBS, DCH, MD
Professor of Pediatrics
University of Colorado School of Medicine
Division of Pediatric Infectious Diseases
Children's Hospital Colorado
Aurora, Colorado

Polioviruses

Kari A. Simonsen MD
Professor of Pediatrics
Division of Pediatric Infectious Disease
University of Nebraska Medical Center
Omaha, Nebraska

Leptospira

Keneisha Sinclair-McBride PhD
Assistant Professor of Psychology
Department of Psychiatry
Harvard Medical School
Staff Psychologist
Boston Children's Hospital
Boston, Massachusetts

Tantrums and Breath-Holding Spells
Lying, Stealing, and Truancy
Aggression
Self-Injurious Behavior

Vidya Sivaraman MD
Clinical Assistant Professor of Pediatrics
Division of Adult and Pediatric Rheumatology
The Ohio State University Wexner Medical Center
Nationwide Children's Hospital
Columbus, Ohio

Vasculitis Syndromes

Anne M. Slavotinek MB BS, PhD
Professor of Clinical Pediatrics
University of California San Francisco School of Medicine
Director, Medical Genetics and Genomics
UCSF Benioff Children's Hospital
San Francisco, California

Dysmorphology

Jessica R. Smith MD
Assistant Professor of Pediatrics
Harvard Medical School
Clinical Director, Thyroid Program
Boston Children's Hospital
Boston, Massachusetts

Thyroid Development and Physiology
Disorders of Thyroxine-Binding Globulin
Hypothyroidism
Thyroiditis
Goiter
Thyrotoxicosis
Carcinoma of the Thyroid
Autoimmune Polyglandular Syndromes
Multiple Endocrine Neoplasia Syndrome

Stephanie H. Smith MD
Resident Physician
Department of Obstetrics and Gynecology
Washington University School of Medicine in St. Louis
St. Louis, Missouri

Gynecologic Neoplasms and Adolescent Prevention Methods for Human Papillomavirus

Kim Smith-Whitley MD
Professor, Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Clinical Director, Division of Hematology
Director, Comprehensive Sickle Cell Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Hemoglobinopathies

Mary Beth F Son MD
Assistant Professor in Pediatrics
Harvard Medical School
Staff Physician, Division of Immunology
Boston Children's Hospital
Boston, Massachusetts

Kawasaki Disease

Laura Stout Sosinsky PhD
Research Scientist
Research and Evaluation Group
Public Health Management Corporation
Philadelphia, Pennsylvania

Childcare

Emily Souder MD
Drexel University College of Medicine

St. Christopher's Hospital for Children
Philadelphia, Pennsylvania

Pertussis (Bordetella pertussis and Bordetella parapertussis)

Joseph D. Spahn MD
Professor
Department of Pediatrics
University of Colorado School of Medicine
Aurora, Colorado

Childhood Asthma

Paul Spearman MD
Albert B. Sabin Professor of Pediatrics
University of Cincinnati College of Medicine
Director, Division of Infectious Diseases
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Human T-Lymphotropic Viruses (1 and 2)

Mark A. Sperling MD
Professor Emeritus and Chair
Department of Pediatrics
University of Pittsburgh School of Medicine
Professorial Lecturer
Department of Pediatrics
Division of Endocrinology and Diabetes
Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai
New York, New York

Hypoglycemia

David A. Spiegel MD
Professor
Department of Orthopaedic Surgery

University of Pennsylvania Perelman School of Medicine
Attending Orthopaedic Surgeon
Pediatric Orthopaedic Surgeon
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

The Spine
The Neck

Jaclyn B. Spitzer PhD
Professor Emerita of Audiology and Speech Pathology in Otolaryngology
Columbia University Irving Medical Center
New York, New York

Jürgen W. Spranger MD
Professor Emeritus of Pediatrics
University of Mainz School of Medicine
Children's Hospital
Mainz, Germany

Mucopolysaccharidoses

James E. Squires MD, MS
Assistant Professor in Pediatrics
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Manifestations of Liver Disease

Siddharth Srivastava MD, PhD
Instructor in Neurology
Harvard Medical School
Department of Neurology
Boston Children's Hospital
Boston, Massachusetts

Neurocutaneous Syndromes

Joseph W. St Geme III, MD

Professor of Pediatrics and Microbiology and Chair of the Department of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chair of the Department of Pediatrics and Physician-in-Chief
Leonard and Madlyn Abramson Endowed Chair in Pediatrics
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Amy P. Stallings MD
Assistant Professor of Pediatrics
Division of Pediatric Allergy and Immunology
Duke University School of Medicine
Durham, North Carolina

Urticaria (Hives) and Angioedema

Virginia A. Stallings MD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Director, Nutrition Center
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Nutritional Requirements
Feeding Healthy Infants, Children, and Adolescents

Kathryn C. Stambough MD
Resident Physician
Department of Obstetrics and Gynecology
Washington University School of Medicine in St. Louis
St. Louis, Missouri

Gynecologic History and Physical Examination

Lawrence R. Stanberry MD, PhD
Associate Dean for International Programs
Department of Pediatrics

Columbia University Vagelos College of Physicians and Surgeons
New York, New York

Herpes Simplex Virus

Charles A. Stanley MD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Division of Endocrinology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Disorders of Mitochondrial Fatty Acid β-Oxidation

Jeffrey R. Starke MD
Professor of Pediatrics
Baylor College of Medicine
Pediatric Infectious Diseases
Texas Children's Hospital
Houston, Texas

Tuberculosis (Mycobacterium tuberculosis)

Taylor B. Starr DO, MPH
Associate Professor of Pediatrics
Division of Adolescent Medicine
University of Rochester Medical Center
Rochester, New York

Eating Disorders

Andrew P. Steenhoff MBBCh, DCH, FAAP
Assistant Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Medical Director, Global Health Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Fever of Unknown Origin

Paracoccidioides brasiliensis
Sporotrichosis (Sporothrix schenckii)

Ronen E. Stein MD
Assistant Professor of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Attending Physician
Division of Gastroenterology, Hepatology, and Nutrition
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Inflammatory Bowel Disease
Eosinophilic Gastroenteritis

William J. Steinbach MD
Professor of Pediatrics, Molecular Genetics, and Microbiology
Chief, Pediatric Infectious DiseasesDuke University Medical Center
Durham, North Carolina

Principles of Antifungal Therapy
Aspergillus
Mucormycosis

Janet Stewart MD
Associate Professor Emerita
Department of Pediatrics
University of Colorado School of Medicine
Spina Bifida Clinic
Children's Hospital Colorado
Denver, Colorado

Meningomyelocele (Spina Bifida)

Gregory A. Storch MD
Ruth L. Siteman Professor of Pediatrics
Washington University School of Medicine in St. Louis
St. Louis Children's Hospital

St. Louis, Missouri

Diagnostic Microbiology
Polyomaviruses

Ronald G. Strauss MD
Professor Emeritus
Departments of Pediatrics and Pathology
University of Iowa Carver College of Medicine
Iowa City, Iowa;
Medical Director, Vitalant (formerly LifeSource)
Rosemont, Illinois

Red Blood Cell Transfusions and Erythropoietin Therapy
Platelet Transfusions
Neutrophil (Granulocyte) Transfusions
Plasma Transfusions
Risks of Blood Transfusions

Gina S. Sucato MD, MPH
Director, Adolescent Center
Washington Permanente Medical Group
Adjunct Investigator, Kaiser Permanente Washington Health Research Institute
Seattle, Washington

Menstrual Problems

Frederick J. Suchy MD
Professor of Pediatrics
Associate Dean for Child Health Research
University of Colorado School of Medicine
Denver, Colorado;
Chief Research Officer and Director
Children's Hospital Colorado Research Institute
Aurora, Colorado

Autoimmune Hepatitis
Drug- and Toxin-Induced Liver Injury
Acute Hepatic Failure
Fulminant Hepatic Failure
Cystic Diseases of the Biliary Tract and Liver
Diseases of the Gallbladder
Portal Hypertension and Varices

Kristen R. Suhrie MD
Assistant Professor
Department of Pediatrics
University of Cincinnati College of Medicine
Neonatologist, Perinatal Institute
Division of Neonatology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

High-Risk Pregnancies
The Fetus

Kathleen E. Sullivan MD, PhD
Professor of Pediatrics
University of Pennsylvania Perelman School of Medicine
Chief, Division of Allergy and Immunology
Frank R. Wallace Endowed Chair in Infectious Diseases
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Evaluation of Suspected Immunodeficiency
The T-, B-, and NK-Cell Systems
Primary Defects of Antibody Production
Treatment of B-Cell Defects
Primary Defects of Cellular Immunity

Immunodeficiencies Affecting Multiple Cell Types

Moira Szilagyi MD, PhD
Professor of Pediatrics
David Geffen School of Medicine at UCLA
Section Chief, Developmental Studies
UCLA Mattel Children's Hospital
Los Angeles, California

Foster and Kinship Care

Sammy M. Tabbah MD
Assistant Professor of Obstetrics and Gynecology
University of Cincinnati College of Medicine
Maternal-Fetal Medicine Specialist, Cincinnati Fetal Center
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

High-Risk Pregnancies
The Fetus

Robert R. Tanz MD
Professor of Pediatrics
Division of Academic General Pediatrics and Primary Care
Northwestern University Feinberg School of Medicine
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Acute Pharyngitis

Cristina Tarango MD
Associate Professor of Pediatrics
University of Cincinnati College of Medicine
Medical Director, Hemophilia Treatment Center
Clinical Director, Hematology Program
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Hemorrhage in the Newborn Infant
Nonimmune Hydrops

Nidale Tarek MD
Assistant Professor of Pediatrics
Department of Pediatrics and Adolescent Medicine
American University of Beirut
Beirut, Lebanon

Retinoblastoma
Neoplasms of the Liver
Desmoplastic Small Round Cell Tumor

Robert C. Tasker MBBS, MD
Professor of Neurology
Professor of Anesthesia
Harvard Medical School
Senior Associate, Critical Care Medicine
Director, Pediatric NeuroCritical Care Program
Boston Children's Hospital
Boston, Massachusetts

Outcomes and Risk Adjustment of Pediatric Emergency Medical Services

Dmitry Tchapyjnikov MD
Assistant Professor of Pediatrics and Neurology
Duke University Medical Center
Durham, North Carolina

Seizures in Childhood

Brenda L. Tesini MD
Assistant Professor of Medicine and Pediatrics
University of Rochester Medical Center
Division of Pediatric Infectious Diseases
Golisano Children's Hospital

Rochester, New York

Roseola (Human Herpesviruses 6 and 7)

Jillian L. Theobald MD, PhD
Assistant Professor of Emergency Medicine
Medical College of Wisconsin
Toxicologist, Wisconsin Poison Center
Milwaukee, Wisconsin

Poisoning

Beth K. Thielen MD, PhD
Fellow, Infectious Diseases and International Medicine
Department of Medicine
Fellow, Pediatric Infectious Diseases and ImmunologyDepartment of PediatricsUniversity of Minnesota Medical School
Minneapolis, Minnesota

Principles of Antiparasitic Therapy

Anita A. Thomas MD, MPH
Assistant Professor
Department of Pediatrics
University of Washington School of Medicine
Attending Physician
Division of Emergency Medicine
Seattle Children's Hospital
Seattle, Washington

Drowning and Submersion Injury

Cameron W. Thomas MD, MS
Assistant Professor of Pediatrics and Neurology
University of Cincinnati College of Medicine
Fetal and Neonatal Neurology Specialist, Division of Neurology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Nervous System Disorders

Courtney D. Thornburg MD, MS
Professor of Clinical Pediatrics
University of California San Diego School of Medicine
La Jolla, California;
Medical Director, Hemophilia and Thrombosis Treatment Center
Rady Children's Hospital, San Diego
San Diego, California

The Anemias
Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)
Pearson Syndrome
Acquired Pure Red Blood Cell Anemia
Anemia of Chronic Disease and Renal Disease
Congenital Dyserythropoietic Anemias
Physiologic Anemia of Infancy
Megaloblastic Anemias

Joel S. Tieder MD, MPH
Associate Professor of Pediatrics
Seattle Children's Hospital
University of Washington School of Medicine
Division of Hospital Medicine
Seattle Children's Hospital
Seattle, Washington

Brief Resolved Unexplained Events and Other Acute Events in Infants

Cynthia J. Tifft MD, PhD
Director, Pediatric Undiagnosed Diseases Program
Senior Staff Clinician

Medical Genetics Branch
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

Genetic Approaches to Rare and Undiagnosed Diseases

James K. Todd MD
Professor Emeritus of Pediatrics
Jules Amer Chair in Community Pediatrics
University of Colorado School of Medicine
Section Head, Epidemiology (Pediatrics)
Director, Epidemiology, Clinical Outcomes, and Clinical Microbiology
Children's Hospital Colorado
Denver, Colorado

Staphylococcus

Victor R. Tolentino Jr, JD, MPH, NP
Healthcare Consultant
Jackson Heights, New York

Principles Applicable to the Developing World

Camilo Toro MD
Senior Staff Clinician
Director, Adult Undiagnosed Diseases Program
National Human Genome Research Institute
National Institutes of Health
Bethesda, Maryland

Genetic Approaches to Rare and Undiagnosed Diseases

Richard L. Tower II, MD, MS
Assistant Professor
Department of Pediatrics

Division of Pediatric Hematology/Oncology
Medical College of Wisconsin
Children's Hospital of Wisconsin
Milwaukee, Wisconsin

Anatomy and Function of the Lymphatic System
Abnormalities of Lymphatic Vessels
Lymphadenopathy

Joseph M. Trapasso MD
Resident Physician
Department of Pediatrics
University of Texas Medical Branch
University of Texas Children's Hospital
Galveston, Texas

N-Acetylaspartic Acid (Canavan Disease)

Riccardo Troncone MD
Professor and Director
Department of Pediatrics
University of Naples Federico II
Napoli, Italy

Celiac Disease

Elaine Tsao MD
Assistant Professor
Department of Rehabilitation Medicine
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, Washington

Ambulation Assistance

David G. Tubergen MD
Medical Director, Host Program
MD Anderson Physicians Network

Houston, Texas

The Leukemias

Lisa K. Tuchman MD, MPH
Associate Professor of Pediatrics
Chief, Division of Adolescent and Young Adult Medicine
Center for Translational Science, Children's Research Institute
Children's National Health System
Washington, DC

Transitioning to Adult Care

Margaret A. Turk MD
Professor
Departments of Physical Medicine and Rehabilitation and Pediatrics
State University of New York
SUNY Upstate Medical University
Syracuse, New York

Health and Wellness for Children With Disabilities

David A. Turner MD
Associate Professor
Department of Pediatrics
Duke University School of Medicine
Director, Pediatric Critical Care Fellowship Program
Medical Director, Pediatric Intensive Care Unit
Duke University Medical Center
Durham, North Carolina

Shock

Christina Ullrich MD, PhD
Assistant Professor in Pediatrics
Department of Psychosocial Oncology and Palliative Care
Harvard Medical School
Boston Children's Hospital
Dana-Farber Cancer Institute

Boston, Massachusetts

Pediatric Palliative Care

Nicole Ullrich MD, PhD
Associate Professor of Neurology
Harvard Medical School
Director, Neurologic Neuro-Oncology
Associate Director, Clinical Trials
Neurofibromatosis Program
Boston Children's Hospital
Boston, Massachusetts

Neurocutaneous Syndromes

Krishna K. Upadhya MD, MPH
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Division of Adolescent and Young Adult Medicine
Children's National Health System
Washington, DC

Menstrual Problems

David K. Urion MD
Associate Professor and Charles F. Barlow Chair of Neurology
Harvard University Medical School
Director, Behavioral Neurology Clinics and Programs
Boston Children's Hospital
Boston, Massachusetts

Attention-Deficit/Hyperactivity Disorder

Taher Valika MD
Clinical Instructor of Otolaryngology – Head and Neck Surgery
Northwestern University Feinberg School of Medicine
Attending Physician, Otorhinolaryngology – Head and Neck Surgery
Ann & Robert H. Lurie Children's Hospital of Chicago
Chicago, Illinois

Laryngotracheal Stenosis and Subglottic Stenosis

George F. Van Hare MD
Professor of Pediatrics
Washington University School of Medicine in St Louis
Division of Pediatric Cardiology
St Louis Children's Hospital
St. Louis, Missouri

Syncope
Disturbances of Rate and Rhythm of the Heart
Sudden Death

Heather A. Van Mater MD, MS
Associate Professor of Pediatrics
Duke University School of Medicine
Division of Pediatric Rheumatology
Duke University Health System
Durham, North Carolina

Scleroderma and Raynaud Phenomenon

Charles D. Varnell Jr, MD, MS
Instructor of Pediatrics
University of Cincinnati College of Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Renal Transplantation

Ana M. Vaughan MD, MPH, FAAP
Assistant in Medicine
Division of Infectious Diseases
Associate Hospital Epidemiologist
Boston Children's Hospital
Instructor in Pediatrics
Harvard Medical School

Boston, Massachusetts

Childcare and Communicable Diseases

Timothy J. Vece MD
Associate Professor of Pediatrics
University of North Carolina School of Medicine
Medical Director, Airway Center
North Carolina Children's Hospital
Chapel Hill, North Carolina

Granulomatous Lung Disease
Eosinophilic Lung Disease
Interstitial Lung Disease

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Motor Disorders and Habits
Anxiety Disorders
Mood Disorders
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Disruptive, Impulse-Control, and Conduct Disorders
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Preface

Whoever saves one life it is considered as if they saved an entire world.

— Babylonian Talmud

The 21st edition of *Nelson Textbook of Pediatrics* continues its tradition of being an essential resource for general pediatric providers and pediatric subspecialists as they diagnose and treat infants, children, and adolescents throughout the world. The 21st edition has been thoroughly revised, updated, and edited to keep up with the huge advances in clinical care derived from basic, clinical, and population-based research. The promise that translational medicine will improve the lives of children has become a daily reality for most but not all children. Knowledge of human development, behavior, and diseases from the molecular to sociologic levels has led to greater understanding of health and illness in children and substantial improvements in health quality for those who have access to health care. These exciting scientific advances also provide hope to effectively address prevention and treatment of new and emerging diseases threatening children and their families.

The field of pediatrics encompasses advocacy for all children throughout the world and must address societal inequalities of important resources required for normal development, as well as protection from natural and man-made disasters. Unfortunately, many children throughout the world have not benefited from the significant advances in the prevention and treatment of health-related problems. For our increasing knowledge to benefit all children and youth, medical advances and good clinical practice must always be coupled with effective advocacy to overcome unconscious bias, lack of political will, and misplaced priorities.

This new edition of *Nelson Textbook of Pediatrics* attempts to provide the essential information that practitioners, house staff, medical students, and all other care providers involved in pediatric health care throughout the world need to understand to effectively address the enormous range of biologic, psychologic, and social problems that our children and youth face. In addition, pediatric subspecialists will benefit from the details of coexisting disorders often seen in their patients. Our goal is to be comprehensive yet concise and reader friendly, embracing both new advances in clinical science and the time-honored art of pediatric practice.

The 21st edition is reorganized and revised from the previous edition. There are many additions of new diseases and new chapters, as well as substantial expansion or significant modification of others. In addition, many more tables, photographs, imaging studies, and illustrative figures, as well as up-to-date references, have been added. This new edition has greatly benefited by the addition of four new associate editors with an extremely broad base of clinic experiences: Dr. Nathan Blum, Chief, Division of Developmental and Behavioral Pediatrics at the Children's Hospital of Philadelphia; Dr. Samir S. Shah, Director, Division of Hospital Medicine and Chief Metrics Officer, Cincinnati Children's Hospital Medical Center; Dr. Robert Tasker, Director, Pediatric NeuroCritical Care Medicine, Boston Children's Hospital; and Dr. Karen Wilson, Division Chief of General Pediatrics, Vice-Chair for Clinical and Translational Research, Kravis Children's Hospital at the Icahn School of Medicine at Mount Sinai, have all contributed to the planning and editing of the 21st edition.

Although, to an ill child and their family and physician, even the rarest disorder is of central importance, all health problems cannot possibly be covered with the same degree of detail in one general textbook of pediatrics. Thus, leading articles and subspecialty texts are referenced and should be consulted when more information is desired. In addition, as new recommendations or policies are developed, they will be updated on our website.

The outstanding value of the 21st edition of the textbook is due to its many expert and authoritative contributors. We are all indebted to these dedicated authors for their hard work, knowledge, thoughtfulness, and good judgment. Our sincere appreciation also goes to Jennifer Shreiner and Sarah Barth at Elsevier and to Carolyn Redman in the Pediatric Department of the Medical College of Wisconsin. We have all worked hard to produce an edition that will be helpful to those who provide care for children and youth and to those desiring to know more about children's health worldwide.

In this edition we have had informal assistance from many faculty and house staff of the department of pediatrics at the Medical College of Wisconsin, University of Pennsylvania Perelman School of Medicine, University of Cincinnati College of Medicine, Harvard Medical School, and the Kravis

Children's Hospital at the Icahn School of Medicine at Mount Sinai. The help of these individuals and of the many practicing pediatricians from around the world who have taken the time to offer thoughtful feedback and suggestions is always greatly appreciated and helpful.

Last and certainly not least, we especially wish to thank our families for their patience and understanding about the great time commitment we as editors have spent reading and editing this edition.

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PART I
The Field of Pediatrics

OUTLINE

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CHAPTER 1

Overview of Pediatrics

Lee M. Pachter

Pediatrics is the only discipline dedicated to all aspects of the care and well-being of infants, children, and adolescents, including their health—their physical, mental, social, and psychological growth and development—and their ability to achieve full potential as adults. Pediatricians must be concerned not only with specific organ systems, genetics, and biologic processes, but also with environmental, psychosocial, cultural, and political influences, all of which may have major impacts on the health and well-being of children and their families.

Children cannot advocate wholly for themselves. As the professionals whose purpose is to advance the well-being of children, pediatricians must be advocates for the individual child and for all children, irrespective of culture, religion, gender, sexual orientation, race, or ethnicity or of local, state, or national boundaries. The more politically, economically, or socially disenfranchised a population is, the greater the need for advocacy for its children and for those who support children. Youth are often among the most vulnerable persons in society, and thus their needs require special attention. As segmentation between nations blur through advances in media, transportation, technology, communication, and economics, a *global* , rather than a national or local, perspective for the field of pediatrics becomes both a reality and a necessity. The interconnectedness of health issues across the world has achieved widespread recognition in the wake of the Zika, Ebola, SARS, and AIDS epidemics; war and bioterrorism; the tsunami of 2004; the earthquake in Haiti in 2010; the displacement of families during the Syrian refugee crisis in 2016–2018; and the growing severity of drought, hurricanes, and cyclones brought about by climate change.

More than a century ago, pediatrics emerged as a medical specialty in response to increasing awareness that the health problems of children differ from those of adults, and that a child's response to disease and stress varies with age and development. In 1959 the United Nations issued the **Declaration of the Rights of the Child** , articulating the universal presumption that children everywhere have fundamental needs and rights. Today, an affirmation of those rights and an effort to satisfy those needs are more important than ever.

Vital Statistics About Children's Health Globally

From 1990 to 2010, the world population grew at an annual rate of 1.3% per year, down from 1.8% during the prior 20 yr. This rate continues to decline; in 2016 the growth rate was 1.13%. Worldwide, there are 2.34 billion children 18 yr and younger, which accounts for approximately one third (32%) of the world's population of 7.4 billion persons. In 2016 the average birthrate in the world was 18.5 births per 1,000 population, with a high of 44.8/1,000 in Niger to the lowest in Monaco at 6.6/1,000. The most populous countries—China, India, and the United States—have rates of 12.4, 19.3, and 12.5 per 1,000 population, respectively.

Despite global interconnectedness, the health of children and youth varies widely between and within regions and nations of the world, depending on several interrelated factors. These include (1) economic conditions; (2) educational, social, and cultural considerations; (3) health and social welfare infrastructure; (4) climate and geography; (5) agricultural resources and practices, which account for nutritional resources; (6) stage of industrialization and urbanization; (7) gene frequencies for certain disorders; (8) the ecology of infectious agents and their hosts; (9) social stability; and (10) political focus and stability. Although genetics, biology, and access to affordable and quality healthcare are important determinants, it has been shown that the *social* determinants of health—the physical environment, political and economic conditions, social and cultural considerations, and behavioral psychology—play as great a role, if not greater, in health outcomes.

To ensure that the needs of children and adults worldwide were not obscured by local needs, in 2000 the international community established 8 **Millennium Development Goals** (MDGs) to be achieved by 2015. Although all 8 MDGs impact child well-being, **MDG 4** was exclusively focused on children: to reduce the **under-five mortality rate (U5MR)** by two-thirds between 1990 and 2015. It was estimated that poor nutrition contributed to more than one third of the deaths worldwide in children <5 yr old, so many of the efforts to reach this goal centered on increasing household food security. Increasing measles vaccination, particularly in sub-Saharan Africa, was another strategy to reduce the U5MR.

There was some progress in achieving MDG 4; the worldwideU5MR decreased by 50% between 1990 and 2015. Although the goal of a two-thirds reduction was not achieved, deaths in children under5 dropped from 12.7 million in 1990 to about 6 million in 2015, despite growth in world population during the same period.

The U5MR can be further divided into neonatal (<1 mo of age), infant (<1 yr of age), and after infancy (1-5 yr of age) (Fig. 1.1). The leading causes of worldwide U5MR are preterm birth complications, pneumonia, perinatal asphyxia, diarrheal diseases, and malaria. Many of these causes are linked to **malnutrition** . Children in sub-Saharan Africa are 14 times more likely to die before age 5 yr than children in the developed areas of the world.

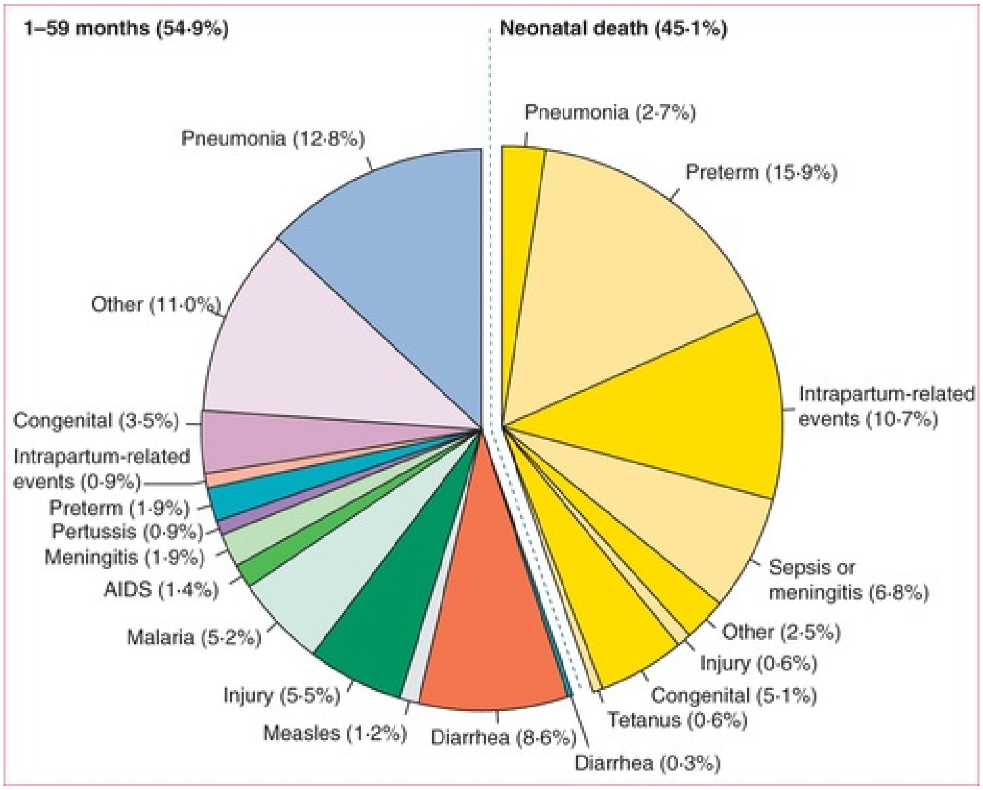

FIG. 1.1 **Global causes of under-five deaths, 2015. (From Oza LLS, Hogan D, Chu Y, et al: Global, regional, and national causes of under-5-mortality in 2000–15: an updated systematic analysis with implications for the sustainable development goals, *Lancet* 388:3027–3034, 2016, Fig 1, p 3029.)**

Causes of under-5 mortality differ greatly between developed and developing nations. In developing countries, 66% of deaths in children <5 yr old resulted from infectious and parasitic diseases. Among the 42 countries having 90% of childhood deaths, diarrheal disease accounted for 22% of deaths, pneumonia 21%, malaria 9%, AIDS 3%, and measles 1%. Neonatal causes contributed 33%. In the United States, pneumonia (and influenza) accounted for only 2% of under-5 deaths, with only negligible contributions from diarrheal diseases and malaria. **Unintentional injury** is the most common cause of death among U.S. children age 1-4 yr, accounting for approximately 33% of deaths, followed by congenital anomalies (11%), homicides (9%), and malignant neoplasms (8%). Other causes accounted for <5% of total mortality within this age-group (Table 1.1). **Violence** is a significant contributor to injury-related mortality in all child age-groups (Tables 1.2 and 1.3). Although unintentional injuries in developing countries are proportionately less important causes of mortality than in developed countries, the absolute rates and contributions of these injuries to morbidity are substantially greater.

Table 1.1

Ten Leading Causes of Death by Age Group, United States, 2015

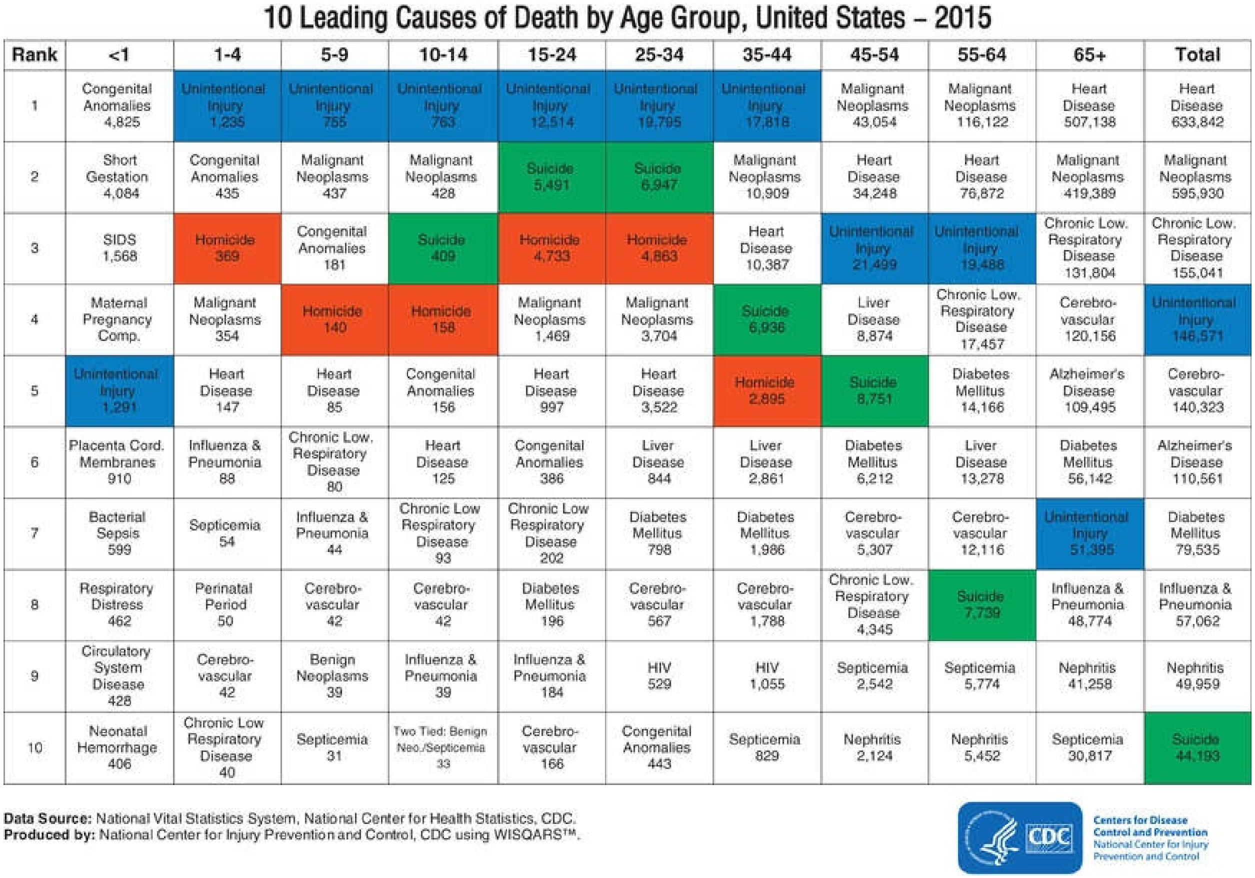

10 Leading Causes of Death by Age Group, United States – 2015

Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Congenital Anomalies 4,825	Unintentional Injury 1,235	Unintentional Injury 755	Unintentional Injury 763	Unintentional Injury 12,514	Unintentional Injury 19,795	Unintentional Injury 17,818	Malignant Neoplasms 43,054	Malignant Neoplasms 116,122	Heart Disease 507,138	Heart Disease 633,842
2	Short Gestation 4,084	Congenital Anomalies 435	Malignant Neoplasms 437	Malignant Neoplasms 428	Suicide 5,491	Suicide 6,947	Malignant Neoplasms 10,909	Heart Disease 34,248	Heart Disease 76,872	Malignant Neoplasms 419,389	Malignant Neoplasms 595,930
3	SIDS 1,568	Homicide 369	Congenital Anomalies 181	Suicide 409	Homicide 4,733	Homicide 4,863	Heart Disease 10,387	Unintentional Injury 21,499	Unintentional Injury 19,488	Chronic Low. Respiratory Disease 131,804	Chronic Low. Respiratory Disease 155,041
4	Maternal Pregnancy Comp.	Malignant Neoplasms 354	Homicide 140	Homicide 158	Malignant Neoplasms 1,469	Malignant Neoplasms 3,704	Suicide 6,936	Liver Disease 8,874	Chronic Low. Respiratory Disease 17,457	Cerebro-vascular 120,156	Unintentional Injury 146,571
5	Unintentional Injury 1,291	Heart Disease 147	Heart Disease 85	Congenital Anomalies 156	Heart Disease 997	Heart Disease 3,522	Homicide 2,895	Suicide 8,751	Diabetes Mellitus 14,166	Alzheimer's Disease 109,495	Cerebro-vascular 140,323
6	Placenta Cord. Membranes 910	Influenza & Pneumonia 88	Chronic Low. Respiratory Disease 80	Heart Disease 125	Congenital Anomalies 386	Liver Disease 844	Liver Disease 2,861	Diabetes Mellitus 6,212	Liver Disease 13,278	Diabetes Mellitus 56,142	Alzheimer's Disease 110,561
7	Bacterial Sepsis 599	Septicemia 54	Influenza & Pneumonia 44	Chronic Low Respiratory Disease 93	Chronic Low Respiratory Disease 202	Diabetes Mellitus 798	Diabetes Mellitus 1,986	Cerebro-vascular 5,307	Cerebro-vascular 12,116	Unintentional Injury 51,395	Diabetes Mellitus 79,535
8	Respiratory Distress 462	Perinatal Period 50	Cerebro-vascular 42	Cerebro-vascular 42	Diabetes Mellitus 196	Cerebro-vascular 567	Cerebro-vascular 1,788	Chronic Low. Respiratory Disease 4,345	Suicide 7,739	Influenza & Pneumonia 48,774	Influenza & Pneumonia 57,062
9	Circulatory System Disease 428	Cerebro-vascular 42	Benign Neoplasms 39	Influenza & Pneumonia 39	Influenza & Pneumonia 184	HIV 529	HIV 1,055	Septicemia 2,542	Septicemia 5,774	Nephritis 41,258	Nephritis 49,959
10	Neonatal Hemorrhage 406	Chronic Low Respiratory Disease 40	Septicemia 31	Two Tied: Benign Neo./Septicemia 33	Cerebro-vascular 166	Congenital Anomalies 443	Septicemia 829	Nephritis 2,124	Nephritis 5,452	Septicemia 30,817	Suicide 44,193

Data Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Courtesy Centers for Disease Control and Prevention, Atlanta.

Table 1.2

Ten Leading Causes of Injury Deaths by Age Group Highlighting Unintentional Injury Deaths, United States, 2015

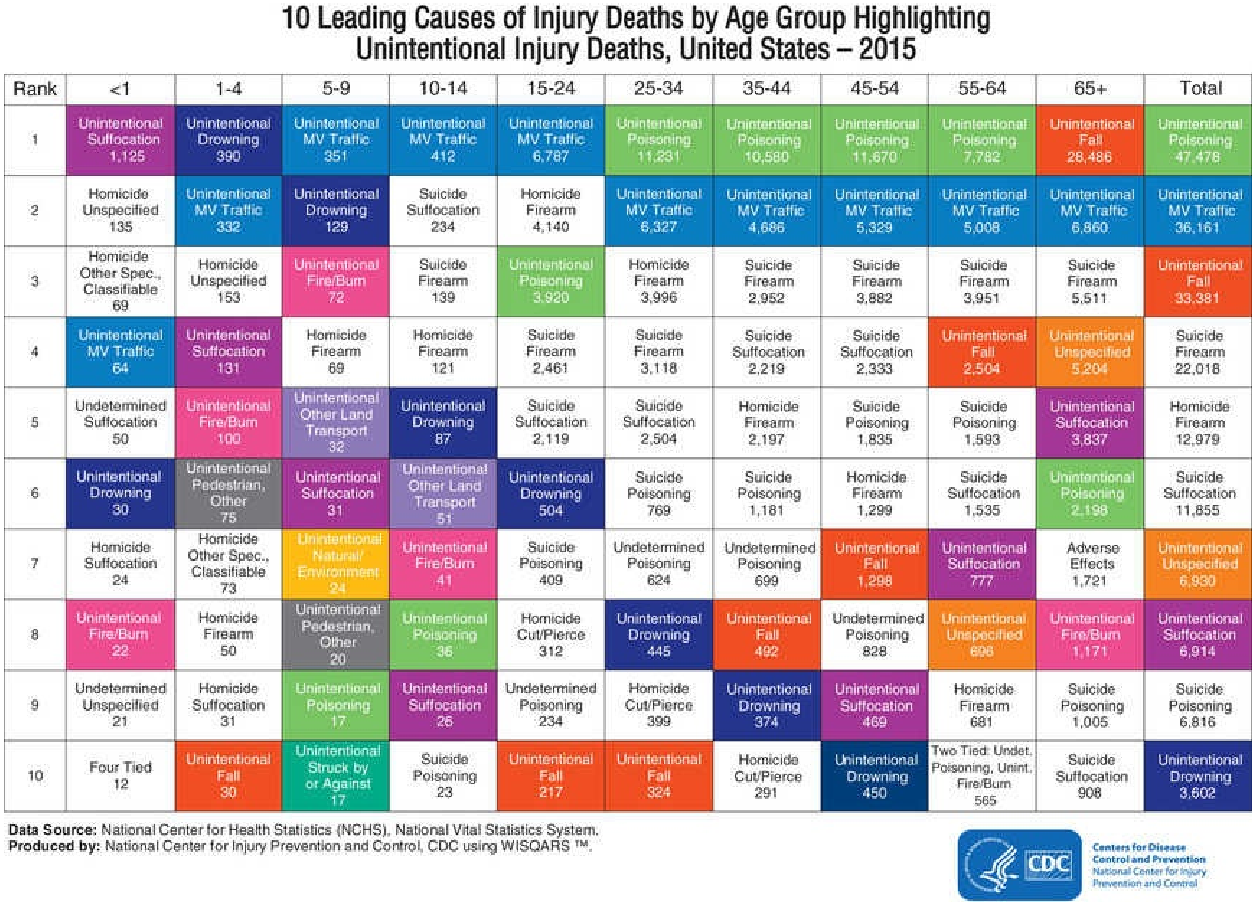

10 Leading Causes of Injury Deaths by Age Group Highlighting Unintentional Injury Deaths, United States – 2015

Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Unintentional Suffocation 1,125	Unintentional Drowning 390	Unintentional MV Traffic 351	Unintentional MV Traffic 412	Unintentional MV Traffic 6,787	Unintentional Poisoning 11,231	Unintentional Poisoning 10,580	Unintentional Poisoning 11,670	Unintentional Poisoning 7,782	Unintentional Fall 28,486	Unintentional Poisoning 47,478
2	Homicide Unspecified 135	Unintentional MV Traffic 332	Unintentional Drowning 129	Suicide Suffocation 234	Homicide Firearm 4,140	Unintentional MV Traffic 6,327	Unintentional MV Traffic 4,686	Unintentional MV Traffic 5,329	Unintentional MV Traffic 5,008	Unintentional MV Traffic 6,860	Unintentional MV Traffic 36,161
3	Homicide Other Spec., Classifiable 69	Homicide Unspecified 153	Unintentional Fire/Burn 72	Suicide Firearm 139	Unintentional Poisoning 3,920	Homicide Firearm 3,996	Suicide Firearm 2,952	Suicide Firearm 3,882	Suicide Firearm 3,951	Suicide Firearm 5,511	Unintentional Fall 33,381
4	Unintentional MV Traffic 64	Unintentional Suffocation 131	Homicide Firearm 69	Homicide Firearm 121	Suicide Firearm 2,461	Suicide Firearm 3,118	Suicide Suffocation 2,219	Suicide Suffocation 2,333	Unintentional Fall 2,504	Unintentional Unspecified 5,204	Suicide Firearm 22,018
5	Undetermined Suffocation 50	Unintentional Fire/Burn 100	Unintentional Other Land Transport 32	Unintentional Drowning 87	Suicide Suffocation 2,119	Suicide Suffocation 2,504	Homicide Firearm 2,197	Suicide Poisoning 1,835	Suicide Poisoning 1,593	Unintentional Suffocation 3,837	Homicide Firearm 12,979
6	Unintentional Drowning 30	Unintentional Pedestrian, Other 75	Unintentional Suffocation 31	Unintentional Other Land Transport 51	Unintentional Drowning 504	Suicide Poisoning 769	Suicide Poisoning 1,181	Homicide Firearm 1,299	Suicide Suffocation 1,535	Unintentional Poisoning 2,198	Suicide Suffocation 11,855
7	Homicide Suffocation 24	Homicide Other Spec., Classifiable 73	Unintentional Natural/ Environment 24	Unintentional Fire/Burn 41	Suicide Poisoning 409	Undetermined Poisoning 624	Undetermined Poisoning 699	Unintentional Fall 1,298	Unintentional Suffocation 777	Adverse Effects 1,721	Unintentional Unspecified 6,930
8	Unintentional Fire/Burn 22	Homicide Firearm 50	Unintentional Pedestrian, Other 20	Unintentional Poisoning 36	Homicide Cut/Pierce 312	Unintentional Drowning 445	Unintentional Fall 492	Undetermined Poisoning 828	Unintentional Unspecified 696	Unintentional Fire/Burn 1,171	Unintentional Suffocation 6,914
9	Undetermined Unspecified 21	Homicide Suffocation 31	Unintentional Poisoning 17	Unintentional Suffocation 26	Undetermined Poisoning 234	Homicide Cut/Pierce 399	Unintentional Drowning 374	Unintentional Suffocation 469	Homicide Firearm 681	Suicide Poisoning 1,005	Suicide Poisoning 6,816
10	Four Tied 12	Unintentional Fall 30	Unintentional Struck by or Against 17	Suicide Poisoning 23	Unintentional Fall 217	Unintentional Fall 324	Homicide Cut/Pierce 291	Unintentional Drowning 450	Two Tied: Undet. Poisoning, Unint. Fire/Burn 565	Suicide Suffocation 908	Unintentional Drowning 3,602

Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS ™.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Courtesy Centers for Disease Control and Prevention, Atlanta.

Table 1.3

Ten Leading Causes of Injury Deaths by Age Group Highlighting Violence-Related Injury Deaths, United States, 2015

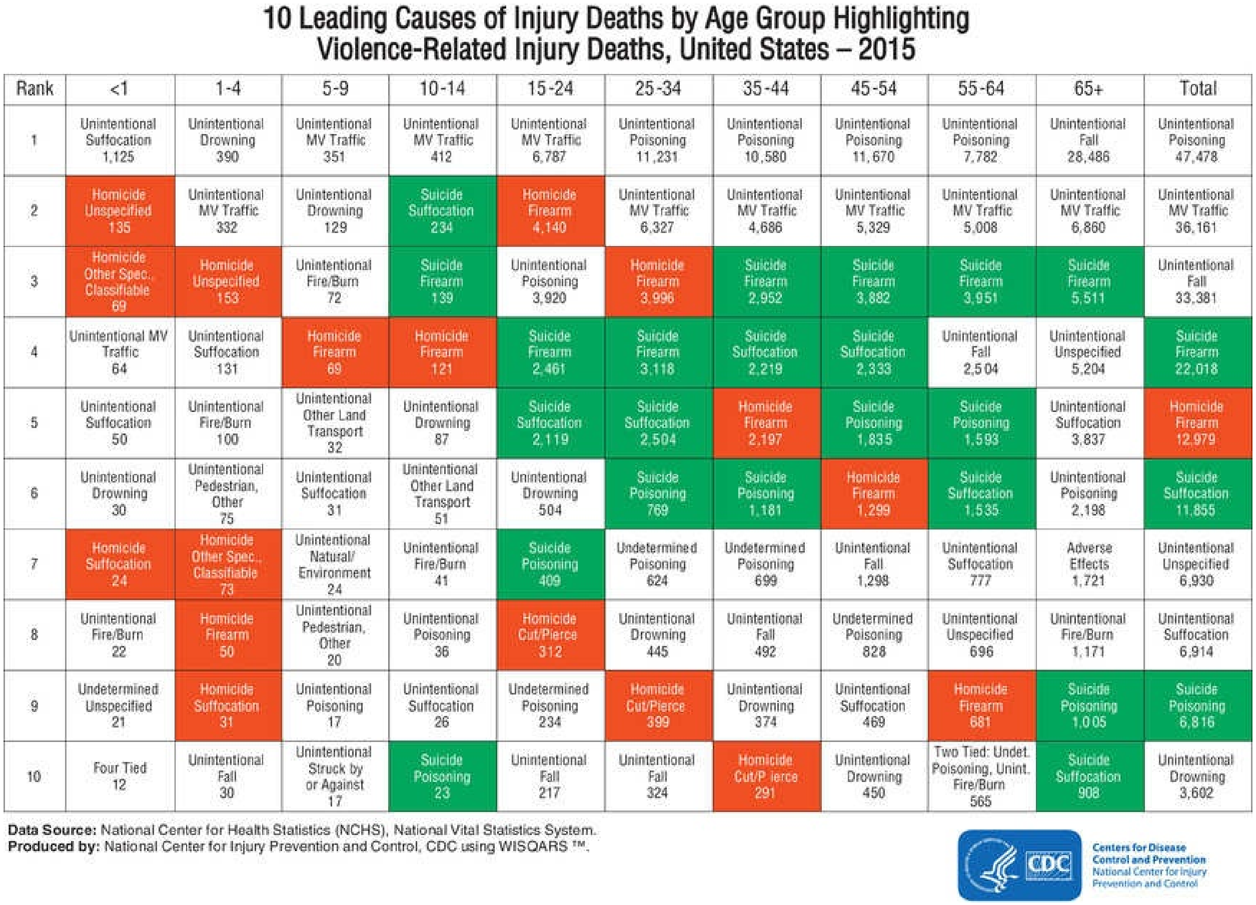

10 Leading Causes of Injury Deaths by Age Group Highlighting Violence-Related Injury Deaths, United States – 2015

Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Unintentional Suffocation 1,125	Unintentional Drowning 390	Unintentional MV Traffic 351	Unintentional MV Traffic 412	Unintentional MV Traffic 6,787	Unintentional Poisoning 11,231	Unintentional Poisoning 10,580	Unintentional Poisoning 11,670	Unintentional Poisoning 7,782	Unintentional Fall 28,486	Unintentional Poisoning 47,478
2	Homicide Unspecified 135	Unintentional MV Traffic 332	Unintentional Drowning 129	Suicide Suffocation 234	Homicide Firearm 4,140	Unintentional MV Traffic 6,327	Unintentional MV Traffic 4,686	Unintentional MV Traffic 5,329	Unintentional MV Traffic 5,008	Unintentional MV Traffic 6,860	Unintentional MV Traffic 36,161
3	Homicide Other Spec., Classifiable 69	Homicide Unspecified 153	Unintentional Fire/Burn 72	Suicide Firearm 139	Unintentional Poisoning 3,920	Homicide Firearm 3,996	Suicide Firearm 2,952	Suicide Firearm 3,882	Suicide Firearm 3,951	Suicide Firearm 5,511	Unintentional Fall 33,381
4	Unintentional MV Traffic 64	Unintentional Suffocation 131	Homicide Firearm 69	Homicide Firearm 121	Suicide Firearm 2,461	Suicide Firearm 3,118	Suicide Suffocation 2,219	Suicide Suffocation 2,333	Unintentional Fall 2,504	Unintentional Unspecified 5,204	Suicide Firearm 22,018
5	Unintentional Suffocation 50	Unintentional Fire/Burn 100	Unintentional Other Land Transport 32	Unintentional Drowning 87	Suicide Suffocation 2,119	Suicide Suffocation 2,504	Homicide Firearm 2,197	Suicide Poisoning 1,835	Suicide Poisoning 1,593	Unintentional Suffocation 3,837	Homicide Firearm 12,979
6	Unintentional Drowning 30	Unintentional Pedestrian, Other 75	Unintentional Suffocation 31	Unintentional Other Land Transport 51	Unintentional Drowning 504	Suicide Poisoning 769	Suicide Poisoning 1,181	Homicide Firearm 1,299	Suicide Suffocation 1,535	Unintentional Poisoning 2,198	Suicide Suffocation 11,855
7	Homicide Suffocation 24	Homicide Other Spec., Classifiable 73	Unintentional Natural/ Environment 24	Unintentional Fire/Burn 41	Suicide Poisoning 409	Undetermined Poisoning 624	Undetermined Poisoning 699	Unintentional Fall 1,298	Unintentional Suffocation 777	Adverse Effects 1,721	Unintentional Unspecified 6,930
8	Unintentional Fire/Burn 22	Homicide Firearm 50	Unintentional Pedestrian, Other 20	Unintentional Poisoning 36	Homicide Cut/Pierce 312	Unintentional Drowning 445	Unintentional Fall 492	Undetermined Poisoning 828	Unintentional Unspecified 696	Unintentional Fire/Burn 1,171	Unintentional Suffocation 6,914
9	Undetermined Unspecified 21	Homicide Suffocation 31	Unintentional Poisoning 17	Unintentional Suffocation 26	Undetermined Poisoning 234	Homicide Cut/Pierce 399	Unintentional Drowning 374	Unintentional Suffocation 469	Homicide Firearm 681	Suicide Poisoning 1,005	Suicide Poisoning 6,816
10	Four Tied 12	Unintentional Fall 30	Unintentional Struck by or Against 17	Suicide Poisoning 23	Unintentional Fall 217	Unintentional Fall 324	Homicide Cut/Pierce 291	Unintentional Drowning 450	Two Tied: Undet. Poisoning, Unint. Fire/Burn 565	Suicide Suffocation 908	Unintentional Drowning 3,602

Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS ™.

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Courtesy Centers for Disease Control and Prevention, Atlanta.

The **infant mortality rate** (deaths of children <1 yr old) accounts for 85% of the U5MR in industrialized countries, but only 70% in the least developed nations. Neonatal (<1 mo) death contributes substantially as well, growing in proportion as the U5MR decreases. Globally, the **neonatal mortality rate** of 19/1,000 live births represents 60% of the infant mortality rate and 45% of the U5MR. The neonatal mortality rate is responsible for 56% of the U5MR in industrialized nations, 45% in developing countries, but only 38% in the least-developed countries. More children <5 yr old in developing countries die from non–birth-related causes.

Across the globe, there are significant variations in child mortality rates by nation, by region, by economic status, and by level of industrial development, the categorizations employed by the World Bank (http://wdi.worldbank.org/table/2.18). As of 2015, 8 nations have a U5MR of ≥100 per 1,000 live births (all in the WHO African region) (Fig. 1.2). The average U5MR in low-income countries was 76/1,000 live births, and in high-income countries, 6/1,000. Income and wealth, however, are not the only determinants of mortality. For example, the United States has the 10th highest gross national income per capita, but ranked 57th in lowest infant mortality rate in 2016.

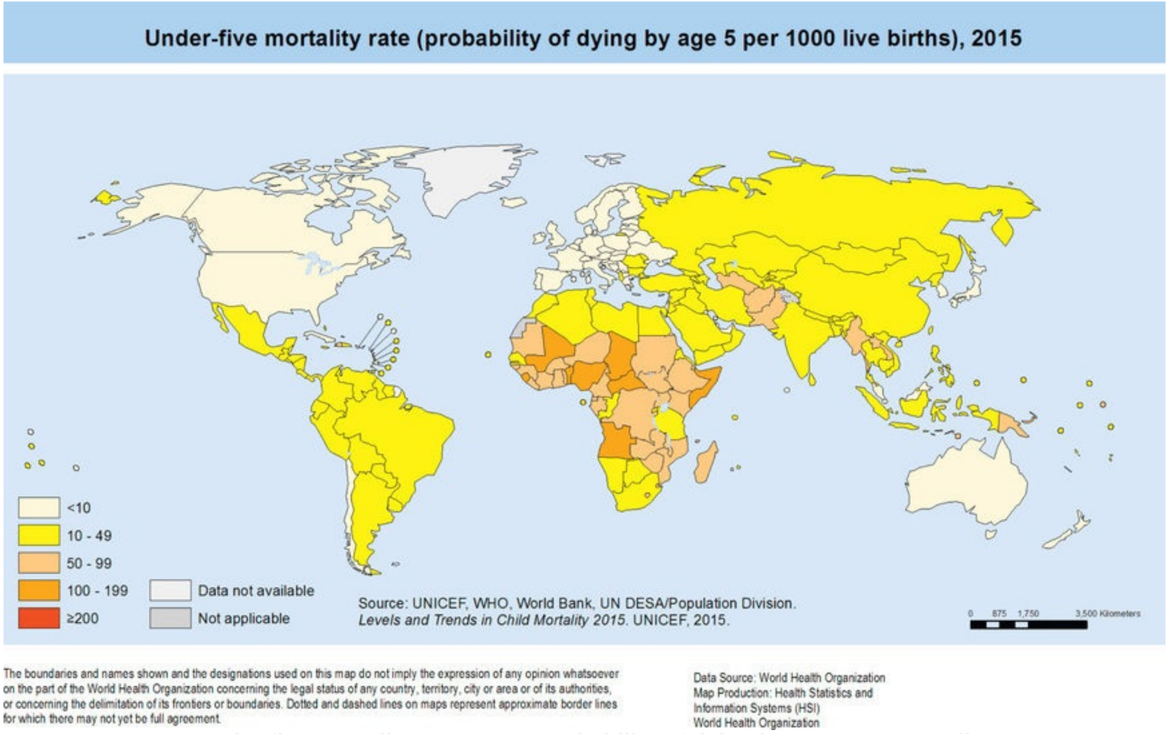
Under-five mortality rate (probability of dying by age 5 per 1000 live births), 2015
<10
10 - 49
50 - 99
100 - 199
≥200
Data not available
Not applicable
0 875 1,750 3,500 Kilometers

Source: UNICEF, WHO, World Bank, UN DESA/Population Division. *Levels and Trends in Child Mortality 2015*. UNICEF, 2015.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

FIG. 1.2 **Under-five mortality rate, 2015. Probability of dying by age 5 per 1000 live births. (Courtesy World Health Organization, Geneva, 2015.)**

In addition to mortality rates, causes of death vary by developmental status of the nation. In the United States the 3 leading causes of death among children <5 yr old were congenital anomalies, disorders related to gestation and low birthweight, and unintentional injuries. By contrast, in developing countries, most infant deaths are caused by pneumonia, diarrheal disease, and malaria.

The Changing Pediatric World

A profound improvement in child health within industrialized nations occurred in the 20th century with the introduction of vaccines, antibiotic agents, and improved hygienic practices. Efforts to control infectious diseases were complemented by better understanding of the role of nutrition in preventing illness and maintaining health. In the United States, Canada, and parts of Europe, new and continuing discoveries in these areas led to establishment of publicly funded **well-child clinics** for low-income families. Although the timing of infectious disease control was uneven around the globe, this focus on *control* was accompanied by significant decreases in morbidity and mortality in all countries.

In the later 20th century, with improved control of infectious diseases through more effective prevention and treatment (including the eradication of polio in the Western hemisphere), pediatric medicine in industrialized nations increasingly turned its attention to a broad spectrum of noninfectious acute and chronic conditions. These included potentially lethal conditions as well as temporarily or permanently handicapping conditions. Advances occurred in the diagnosis, care, and treatment of leukemia and other neoplasms, cystic fibrosis, sickle cell disease, diseases of the newborn infant, congenital heart disease, genetic defects, rheumatic diseases, renal diseases, and metabolic and endocrine disorders.

Until the 1970s and early 1980s, children affected with **sickle cell disease** often died within the 1st 3 yr of life often from overwhelming sepsis caused by encapsulated bacteria. In the 1980s a multicenter study showed that early initiation of *penicillin prophylaxis* led to an 84% risk reduction for pneumococcal sepsis. Life expectancy for those with sickle cell disease increased when penicillin prophylaxis was initiated early in life. The use of prophylactic penicillin became the standard of care, increasing the importance of early detection of sickle cell disease (which led to expanding universal *newborn screening*) and paving the way for advances in the chronic management of the disease, including transfusion therapy, radiographic screening for silent cerebral infarctions, and hydroxyurea as a disease-modifying therapy. The success of penicillin prophylaxis likely led to a more rapid rate of innovation in the diagnosis and management of the disease, since children with the condition now had increased life expectancy. Whereas in the preprophylaxis era children often died by age 3, now 95% of individuals born with sickle cell disease will live to their 18th birthday, and most will survive until their 5th decade.

The treatment of **acute lymphoblastic leukemia** (ALL), the most common pediatric malignancy, has also shown amazing advances. Five-year survival rates have increased from <10% in the 1960s to >90% in 2000–2005. **Cystic fibrosis** has shown improvements in survival as well. In the 1960s, most children with cystic fibrosis did not live until school age. With advances in pulmonary and nutritional therapies, as well as earlier initiation of these therapies secondary to earlier identification through newborn screening, a child born with cystic fibrosis in 2010 has a projected life expectancy of 39-56 yr.

These major advances in the management of chronic diseases of childhood were accomplished when significant improvement occurred in the prevention and treatment of acute infectious diseases, at least in industrial countries. This allowed human and economic resources to shift toward addressing chronic disease.

The New Morbidities

Given the advances in public health aimed at decreasing morbidity and mortality in infectious diseases (immunization, hygiene, antibiotics), along with the rise of technologic advances in clinical care, attention was given to the **new morbidities** —behavioral, developmental, and psychosocial conditions and problems shown to be increasingly associated with suboptimal health outcomes and quality of life. The American Academy of Pediatrics (AAP) **Committee on Psychosocial Aspects of Child and Family Health** asserted that the prevention, early detection, and management of these types of child health problems should be a central focus of the field of pediatrics, and that it would require an expansion in the knowledge base regarding (1) physical and environmental factors affecting behavior, (2) normal child behavior and development, (3) health behaviors as they pertain to child health, and (4) mild, moderate, and severe behavioral and developmental disorders. Accomplishing this would require reconceptualizing professional training, improving clinical communication and interviewing skills, expanding mental health resources for children, and shifting time allocation during child health supervision visits to address these concerns. In 2001 the Committee revisited this issue and reemphasized the need to address environmental and social aspects in addition to developmental and behavioral issues (Table 1.4). These included violence, firearms, substance use, and school problems, as well as poverty, homelessness, single-parent families, divorce, media, and childcare. Although this expanding list seems daunting and beyond the scope of what pediatricians typically addressed (i.e., physical health and development), many of these behavioral, environmental, and psychosocial issues (which fall under the category of social determinants of health) account for a large proportion of variance in health outcomes in children and youth. The role of pediatrics and the boundaries of clinical practice needed to change in order to address these salient contributors to child health and well-being. Newer models of clinical care that rely on close collaboration and coordination with other professionals committed to child welfare (e.g., social workers, psychologists, mental health providers, educators) were developed. As this model expanded, so did the role of the family, in particular the child's caregiver, from a passive recipient of professional services to a more equitable and inclusive partner in identifying the issues that needed to be addressed, as well as helping decide which therapeutic options had the “best fit” with the child, the family, and the condition.

Table 1.4

A Developmental History of the New Morbidities in Child Health*

THE NEW MORBIDITIES (1982–1993)	THE NEW MORBIDITIES REVISITED (2001)	THE “NEW” NEW MORBIDITIES (2010 to Present)
Behavioral disorders/mental health	School problems	Adverse childhood experiences (ACEs)
Family crisis	Mood and anxiety disorders	Toxic stress
Abuse & neglect	Adolescent suicide/homicide	Allostatic load
Long term disease	Firearms in home	Chronic illnesses of lifestyle (e.g., obesity, type-2 diabetes, hypertension)
Substance abuse	School violence	Behavioral conditions (autism, ADHD, depression, anxiety)
School difficulties	Drug and alcohol abuse	Food insecurity
	HIV infection	Oral health
	Effects of media	Witnessing community/interpersonal violence
	Poverty	Peer victimization/bullying
	Homelessness	Discrimination
	Single-parent families	
	Effects of divorce	
	Struggle of working parents	
	Childcare quality & policy	

* Each column adds further categories and refinements to prior columns.

ADHD, Attention-deficit/hyperactivity disorder; HIV human immunodeficiency virus.

The framing of salient child health issues under the “new morbidity” concept acknowledges that the determinants of health are heterogeneous but interconnected. Biology, genetics, healthcare, behaviors, social conditions, and environmental influences should not be viewed as mutually exclusive determinants; they exert their influences through complex interactions on multiple levels. For example, epigenetic changes that result from specific social and environmental conditions illustrate the influence of context on gene expression.

Studies have demonstrated that while each of these interrelated determinants are important for optimal health, development, and well-being, the greatest contributions to health outcomes occur in the behavioral, social, and environmental domains—the **social determinants of health** . From 40% to 70% of the relative variation in certain health outcomes is caused by social and economic conditions, health behaviors, and environmental factors. Whereas traditional medical education and clinical practice emphasized the biologic, genetic, and healthcare-related determinants of health, the recognition of the new morbidities as a focus of child healthcare provision reinforced the need to address social determinants as a key component of pediatric care, training, and research.

The "New" New Morbidities

The new morbidities concept brought into perspective the importance of addressing the social determinants of health, as well as the increasing prevalence and salience of chronic physical and behavioral health conditions in pediatric healthcare. Since then, advances in epidemiology, physiology, and epigenetics have expanded the scope of inquiry into the effects of a broad range of health determinants and provided more sophisticated explanatory models for the mechanisms that explain their effects (Table 1.4).

Adverse Childhood Experiences

Adverse childhood experiences (**ACEs**) are stressful events experienced during childhood that can have profound health consequences in childhood and throughout the life course into adulthood. ACEs were initially defined as *abuse* (physical, emotional, sexual), *neglect* (physical and emotional), and *household challenges/family dysfunction* (parental spousal abuse, mental illness in household, household substance abuse, incarceration of household member, parental separation or divorce). Retrospective studies have shown a graded dose-response effect of ACEs experienced in childhood on the future adult health of the child who experience the ACEs. For example, more childhood adversity was associated with significantly increased risk in later life of ischemic heart disease, chronic obstructive pulmonary disease, liver disease, depression, obesity, and cancer. People who suffered ≥6 ACEs as a child died almost 20 yr earlier than those who experienced no ACEs.

While the original conceptualization of ACEs included family-level psychosocial trauma, recent attempts have been made to expand the concept to include “macro” level stressors, such as those encountered in the neighborhood and community (Table 1.5). These include witnessing violence in the community, poverty, bullying and peer victimization, peer isolation, living in unsafe neighborhoods, low neighborhood social capital, living in foster care, and experiencing discrimination or racism.

Table 1.5

Classification of Adverse Childhood Experiences (ACEs)

CATEGORY	ITEMS
Abuse & neglect	Physical abuse*
	Physical neglect*
	Emotional abuse*
	Emotional neglect*
	Sexual abuse*
Family dysfunction	Intimate partner violence*
	Substance use in household*
	Mental illness in household*
	Parental separation or divorce*
	Family member incarcerated*
	Parental discord
Community-level adversity	Witnessing community violence
	Neighborhood safety
	Lack of neighborhood connectedness/trust
	Experiencing discrimination
Others	Being bullied/peer victimization
	Living in foster care
	Social isolation
	Low socioeconomic status/poverty

* Items included in original Kaiser ACE study.

ACEs and other psychosocial traumas may influence health through a number of mechanisms. ACEs are associated with adoption of risky behaviors such as substance use and early initiation of sexual activity, which in turn may increase the risk of chronic diseases such as lung cancer, liver disease, obesity, human papillomavirus (HPV) infection and cervical cancer, chronic lung disease, and premature mortality. Childhood trauma can also disrupt neurodevelopment during critical stages and contribute to social, emotional, and cognitive impairment. Finally, ACEs can result in toxic stress and lead to the dysregulation of normal physiologic processes.

Toxic Stress and Allostatic Load

The effects of stress are moderated by the intensity of the stress, the biologic response to the stress, and the social and physical environment in which the stress is experienced. **Toxic stress** occurs when a child experiences stressful events that are chronic, intense, or prolonged and are inadequately buffered by the child's social support system (most importantly, parents and adult caregivers). Toxic psychosocial stress influences physical health by producing **allostatic load** , or pathophysiologic dysregulation of normal regulatory systems. Allostatic load is the "wear and tear" that the body and its regulatory mechanisms experience in response to chronic, unbuffered stress. The systems that can be affected through allostatic load include the neuroendocrine, cardiovascular, immune, and metabolic systems. Dysregulation of stress hormones in the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) systems, inflammatory cytokines, hormones (e.g., insulin), immune factors (e.g., fibrinogen, C-reactive protein), and cardiovascular biomarkers (e.g., blood pressure) can occur from chronic stress and result in pathophysiologic conditions associated with chronic diseases. Chronic stress can also have effects at the genetic level. Studies of cellular aging have shown that chronic stress decreases telomere length, a determinant of aging on the cellular level. Epigenetic changes, including differential immune system DNA methylation, have been shown to occur after child abuse and posttraumatic stress disorder (PTSD), contributing to inflammatory and immune dysregulation.

Pediatrics, developmental psychology, basic sciences, and public health have contributed significant advances to the study of the behavioral, developmental, and social determinants of child health. The influence of psychosocial stress brought about by environmental challenges, while always acknowledged as important, has taken on a new level of salience as epidemiologists have linked its occurrence to significant morbidities throughout the life course, and as basic and clinical neuroscience has provided a multilevel framework for understanding how behavioral and psychosocial issues "get under the skin" to cause physiologic dysfunction and dysregulation.

Ecobiodevelopmental Framework

An ecobiodevelopmental framework has been proposed to integrate the environmental, biologic, and developmental factors into a model of health and illness (Fig. 1.3). This model posits that the ecology (or the physical and social environment) effects biology through the epigenetic and allostatic load mechanisms discussed above. The environment also influences development through life course science, which includes the effects of toxic exposures and childhood adversity on cognitive, behavioral, and physical health throughout the life course. Biology influences development though brain maturation and neuroplasticity, which in turn are also affected by inputs from the social and physical environment. The ecobiodevelopmental framework is consistent with the biopsychosocial model while adding a life course developmental dimension.

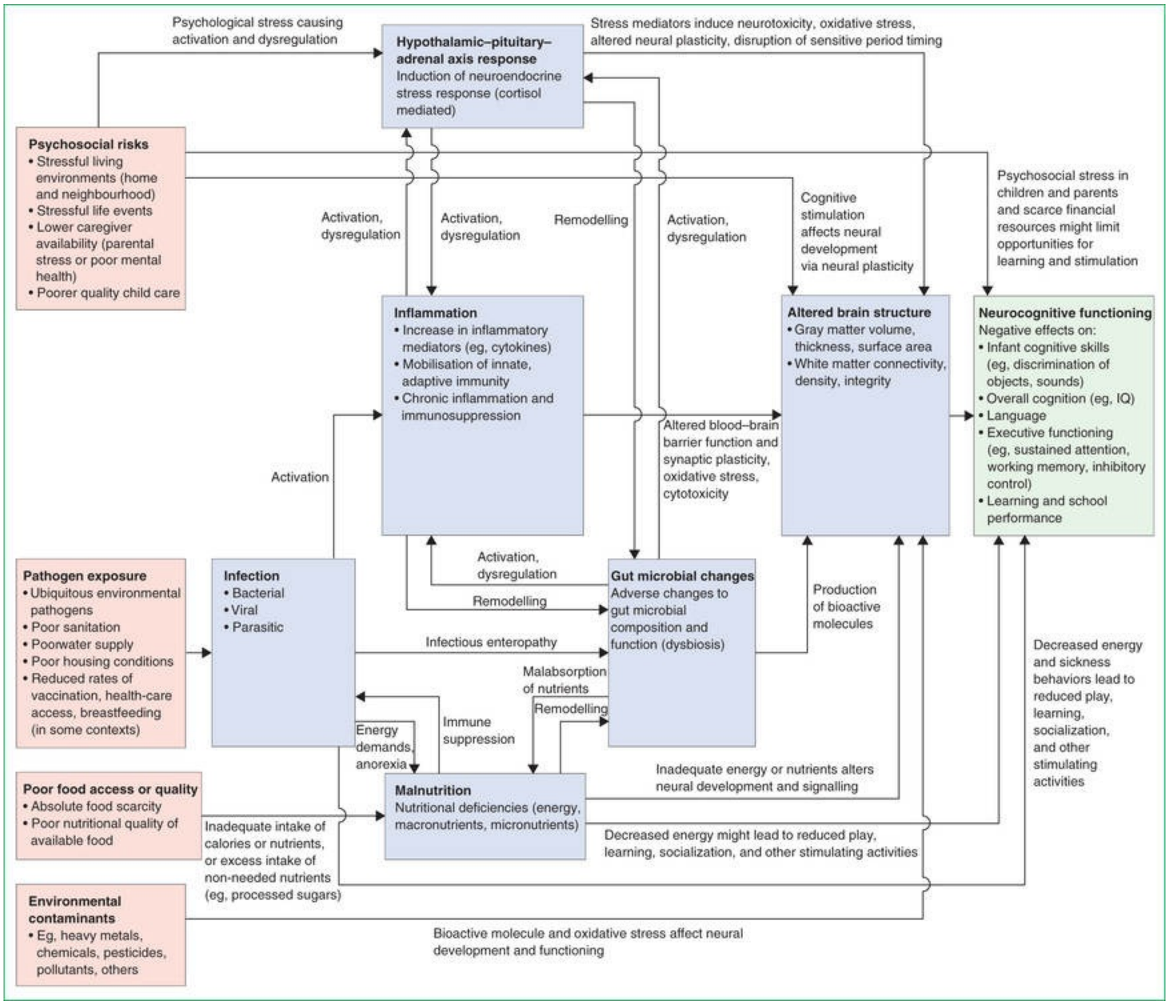
Psychological stress causing activation and dysregulation
Hypothalamic–pituitary–adrenal axis response
Induction of neuroendocrine stress response (cortisol mediated)
Stress mediators induce neurotoxicity, oxidative stress, altered neural plasticity, disruption of sensitive period timing
Psychosocial risks
• Stressful living environments (home and neighbourhood)
• Stressful life events
• Lower caregiver availability (parental stress or poor mental health)
• Poorer quality child care
Activation, dysregulation
Activation, dysregulation
Remodelling
Activation, dysregulation
Cognitive stimulation affects neural development via neural plasticity
Psychosocial stress in children and parents and scarce financial resources might limit opportunities for learning and stimulation
Inflammation
• Increase in inflammatory mediators (eg, cytokines)
• Mobilisation of innate, adaptive immunity
• Chronic inflammation and immunosuppression
Altered brain structure
• Gray matter volume, thickness, surface area
• White matter connectivity, density, integrity
Neurocognitive functioning
Negative effects on:
• Infant cognitive skills (eg, discrimination of objects, sounds)
• Overall cognition (eg, IQ)
• Language
• Executive functioning (eg, sustained attention, working memory, inhibitory control)
• Learning and school performance
Altered blood–brain barrier function and synaptic plasticity, oxidative stress, cytotoxicity
Activation
Activation, dysregulation
Remodelling
Pathogen exposure
• Ubiquitous environmental pathogens
• Poor sanitation
• Poorwater supply
• Poor housing conditions
• Reduced rates of vaccination, health-care access, breastfeeding (in some contexts)
Infection
• Bacterial
• Viral
• Parasitic
Gut microbial changes
Adverse changes to gut microbial composition and function (dysbiosis)
Infectious enteropathy
Production of bioactive molecules
Malabsorption of nutrients
Remodelling
Immune suppression
Energy demands, anorexia
Decreased energy and sickness behaviors lead to reduced play, learning, socialization, and other stimulating activities
Poor food access or quality
• Absolute food scarcity
• Poor nutritional quality of available food
Inadequate intake of calories or nutrients, or excess intake of non-needed nutrients (eg, processed sugars)
Malnutrition
Nutritional deficiencies (energy, macronutrients, micronutrients)
Inadequate energy or nutrients alters neural development and signalling
Decreased energy might lead to reduced play, learning, socialization, and other stimulating activities
Environmental contaminants
• Eg, heavy metals, chemicals, pesticides, pollutants, others
Bioactive molecule and oxidative stress affect neural development and functioning

FIG. 1.3 New proposed biologic pathways that mediate effects of selected stressful or adversarial poverty-associated risks to neurocognitive outcomes in children. Complex interactions among key poverty-related risk factors, focusing on primary biologic pathways related to malnutrition, infection and inflammation, and neuroendocrine responses to stress. (From Jensen SKG, Berens AE, Nelson CA: Effects of poverty on interacting biological systems underlying child development, *Lancet* 1:225–238, 2017, Fig 1, p 228.)

Chronic Illness and Children With Special Health Care Needs

The care of children with chronic conditions has become an increasingly larger part of clinical pediatrics, for both the pediatric subspecialist and the general pediatrician. **Children and youth with special health care needs (CSHCN)** are defined by the U.S. Maternal and Child Health Bureau as “those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally.” According to the 2011/12 **National Survey of Children's Health** (NSCH), >14.5 million, or 20% of U.S. children, have a special health need. The 2009–2010 **National Survey of Children with Special Health Care Needs** (NS-CSHCN) reports that almost one quarter (23%) of U.S. households with children have a child with a special need. The conditions these children have are extremely heterogeneous and include cerebral palsy, asthma, obesity, sickle cell disease, diabetes, learning disability, communication disorders, Down syndrome, heart conditions, migraine headaches, depression, conduct disorder, autism, and attention-deficit/hyperactivity disorder (Table 1.6). Most of these children need specialty care in addition to primary care. In the United States, 0.4–0.7% of children fall into the category of “highest medical complexity”; these children account for 15–33% of all healthcare spending for children. Children with medical complexity account for >70% of hospital readmissions.

Table 1.6

Heath Conditions in Children With Special Health Care Needs (CSHCN)*

Attention-deficit/hyperactivity disorder
Depression
Anxiety problems
Behavioral or conduct problems
Autism, pervasive developmental disorder, autism spectrum disorder
Developmental delay
Intellectual disability
Communication disorder

Asthma
Diabetes
Epilepsy or seizure disorder
Migraines or frequent headaches
Head injury, traumatic brain injury
Heart problems, including congenital heart disease
Blood problems, including anemia or sickle cell disease
Cystic fibrosis
Cerebral palsy
Muscular dystrophy
Down syndrome
Arthritis or joint problems
Allergies

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[*] List is not comprehensive and does not include all conditions that CSHCN may have.

Adapted from Child and Adolescent Health Measurement Initiative (2012). 2009/10 NS-CSHCN: Health Conditions and Functional Difficulties, Data Resource Center, supported by Cooperative Agreement 1-U59-MC06980-01 from the US Department of Health and Human Services, Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB). www.childhealthdata.org . Revised 01/27/2012.

Nine of 10 CSHCN have functional difficulties in the sensory, cognitive, movement, emotional, or behavioral domains (Table 1.7). More than 65% (7.2 million) of CSHCN have conditions that affect their daily activities, and >2.3 million families experience financial difficulties because of their children's special health needs. The fact that 25% of family members of CSHCN cut back work hours or stop working because of their child's special needs highlights the social and economic impact of child chronic illness, at both the individual and the national economic level.

Table 1.7

Functional Difficulties in Children With

Special Health Care Needs (CSHCN)*

Experiencing Difficulty With …

Breathing, or respiratory problem
Swallowing, digesting food, or metabolism
Blood circulation
Repeated or chronic physical pain, including headaches
Seeing, even when wearing glasses or contact lenses
Hearing, even when using a hearing aid or other devise
Taking care of self, such as eating, dressing, or bathing
Coordination or moving around
Using his/her hands
Learning, understanding, or paying attention
Speaking, communicating, or being understood
Feeling anxious or depressed
Behavior problems such as acting out, fighting, bullying, or arguing
Making and keeping friends

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* List is not comprehensive and does not include all functional difficulties that CSHCN may have.

Adapted from Child and Adolescent Health Measurement Initiative (2012). 2009/10 NS-CSHCN: Health Conditions and Functional Difficulties, Data Resource Center, supported by Cooperative Agreement 1-U59-MC06980-01 from the US Department of Health and Human Services, Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB). www.childhealthdata.org . Revised 01/27/2012.

Pediatricians are typically the “point persons” in the professional care of these children and provide data and expert opinion to procure needed services and resources to the child in the clinic, home, schools, and community. Such demands require an efficient model of chronic care.

Systems of Care

Population Health Approach

Because pediatric practice is increasingly spent working with patients and families who have chronic issues and conditions, new approaches to healthcare services delivery have been proposed. Whereas traditional practice models concentrate efforts toward the preventive and therapeutic needs of those patients who present for care, a **population health** approach to care refocuses efforts to emphasize the need to address health from a community- or population-level perspective, with emphasis on identifying and addressing the needs of individuals and families who do not seek regular care, or whose care is episodic and suboptimal from a prevention or management standpoint. Effectiveness of such a system would increase with advances in collaboration between healthcare providers and payers (insurance companies) to identify gaps in care, data surveillance systems, and electronic health records (EHRs), and with an expanded cadre of health care personnel such as care coordinators, nurse practitioners and physician assistants, social workers, health navigators, and community health workers. Healthcare reimbursement modifications, such as incorporating value-based and quality-of-care–based models, if implemented correctly, may further advance a population health approach to care.

Medical Home

The concept of the **patient and family–centered medical home (PFCMH)** approach to providing care has its origins in pediatrics in the late 20th century. As defined by AAP, a medical home provides care that is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective. Patients and family members are key active participants, working with clinicians to identify priorities for and approaches to care. A key aspect of the PFCMH is care coordination. According to AAP, *care coordination* “addresses interrelated medical, social, developmental, behavioral, educational and financial needs to achieve optimal health and wellness outcomes.” A *care coordinator* in the “point person” on the team who prospectively identifies the patient's and family's needs, concerns, and priorities for the healthcare visit, gathers pertinent information (lab results, consultations, educational plans, screening/testing results), communicates with subspecialists, and relays all important information to the clinical team before the patient/family visit. After a healthcare visit, the care coordinator works with the family to address any ongoing concerns, directs efforts to schedule follow up appointments and referrals, and communicates information to all necessary parties. The care coordinator typically is *not* a physician. The intended result of care coordination is an efficient and comprehensive interaction between the pediatric team and the family, between primary care and specialty care, between ambulatory and inpatient care teams, and between the pediatric care team and the community-based supports on which the patient and family depend.

Provision of care consistent with the elements of a medical home has been associated with more accurate and early diagnosis, fewer emergency department visits and inpatient hospitalizations, lower costs, fewer unmet needs, lower out-of-pocket medical costs, less impact on parental employment, fewer school absences, and better patient satisfaction. According to the 2011/12 National Survey of Children's Health, 54.4% of U.S. children received coordinated, comprehensive care within a medical home.

Medical and Health Neighborhood

While the medical home concept relates to practice transformation specific to primary care, a broadening of this concept has been proposed along 2 separate dimensions. The **medical neighborhood** expands the medical home concept and refers to coordinated and efficient integration between primary care pediatricians and the subspecialists, including integrated EHRs, efficient coordinated appointment scheduling, and enhanced communication. Such a system has the potential to provide a less stressful patient and family experience and could also lead to cost reduction and a decrease in medical errors.

Another expansion and modification of the medial home is the **health neighborhood** concept. The health neighborhood is based on the recognition of the importance of coordination with community-based and nonmedical providers to address comprehensively and efficiently the social determinants of health. Health neighborhoods include the healthcare providers (consistent with the medical home and neighborhood) but also involves services such as early intervention programs, the education system, childcare, community-based behavioral and mental health services, legal services, nutritional support services, and other clinical and community-based services that the patient and family need to access. The health neighborhood team helps families identify the needs of the patient, assists with referrals to appropriate agencies outside the healthcare system, and coordinates care.

Some nonmedical services may be co-located at the medical office. **Medical-legal partnerships** (MLPs) are collaborations between the healthcare and legal systems and embed legal aid personnel in the medical clinic. These lawyers and legal paraprofessionals can provide direct services to patients and families who have legal issues that may be affecting the child's health (e.g., housing code violations, utility shutoff, food insecurity, immigration issues, educational accommodations, guardianship). In addition to providing direct services, MLPs also train healthcare personnel in the legal and social determinants of health and work with physicians and others to advocate for policy change. Other nonmedical health neighborhood services that could be co-located in the medical center include supplemental nutrition assistance programs, parenting programs, behavioral health services, and family financial counseling.

Many, if not most, other services are located in the community. The health neighborhood model links families to these services and provides efficient on ongoing coordination and communication. Community health workers or health navigators are paraprofessional team members who are community and culturally informed and serve as a coordinating link between the family, the medical home, and needed community services. Community health workers and health navigators can also provide patient and family education.

Expanded care models such as these have the potential to achieve what the Institute for Healthcare Improvement calls the “triple aim” for healthcare, focusing on **care** (improving the patient experience with healthcare, quality care, and satisfaction), **health** (improving the health of populations), and **cost** (reducing per-capita healthcare costs) (Fig. 1.4).

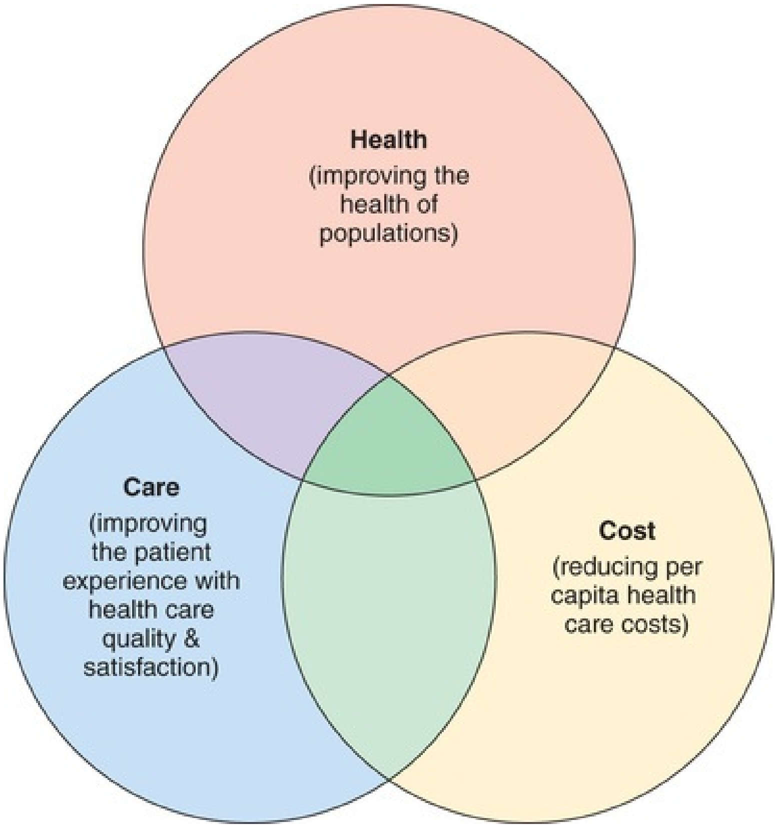
Health
(improving the health of populations)
Care
(improving the patient experience with health care quality & satisfaction)
Cost
(reducing per capita health care costs)

FIG. 1.4 The triple aim for healthcare. (Adapted from Berwick DM, Nolan TW, Whittington J: The triple aim: care, health, and cost, *Health Affairs* 27:759–769, 2008.)

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CHAPTER 2

Child Health Disparities

Lee M. Pachter

Health and illness are not distributed equally among all members in most societies. Differences exist in risk factors, prevalence and incidence, manifestations, severity, and outcome of health conditions, as well as in the availability and quality of healthcare. When these differences are modifiable and avoidable, they are referred to as **disparities** or **inequities** . The U.S. Department of Health and Human Services (DHHS) *Healthy People 2020* report defines *health disparity* as “a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group; religion; socioeconomic status; gender; age; mental health; cognitive, sensory, or physical disability; sexual orientation or gender identity; geographic location; or other characteristics historically linked to discrimination or exclusion.” The U.S. Centers for Disease Control and Prevention (CDC) define *health disparities* as “preventable differences in the burden of disease, injury, violence, or opportunities to achieve optimal health that are experienced by socially disadvantaged populations.” Health and healthcare disparities occur by nature of unequal distribution of resources that are inherent in societies that exhibit *social stratification* , which occurs in social systems that rank and categorize people into a hierarchy of unequal status and power. There exists a hierarchy of “haves and have nots” based on group classifications.

Although there are many differences regarding health status, not all these differences are considered disparities. The increased prevalence of sickle cell disease in people of African descent, or the increased prevalence of cystic fibrosis in white individuals of Northern European descent, would not be considered a disparity because—at least at present—the genetic risk is not easily modifiable. However, in 2003, funding was 8-fold greater per patient for cystic fibrosis than for sickle cell disease, which could be considered a disparity because it is modifiable.

Health and healthcare disparities have existed for centuries. A critical mass of research building in the mid-2000s corresponded to the U.S. Institute of Medicine's 2003 book, *Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare* . It reviewed the literature on racial and ethnic disparities in health and healthcare and found 600 citations.

Determinants of Health and Health Disparities

Fig. 2.1 displays a categorization of the multiple determinants of health and well-being. Applying this categorization to health disparities, conceptualizations of the root causes of health disparities emphasize the most modifiable determinants of health: the physical and social environment, psychology and health behaviors, socioeconomic position and status, and access to and quality of healthcare. Differential access to these resources result in differences in *material* resources (e.g., money, education, healthcare) or *psychosocial* factors (e.g., locus of control, adaptive or risky behaviors, stress, social connectedness) that may contribute to differences in health status.

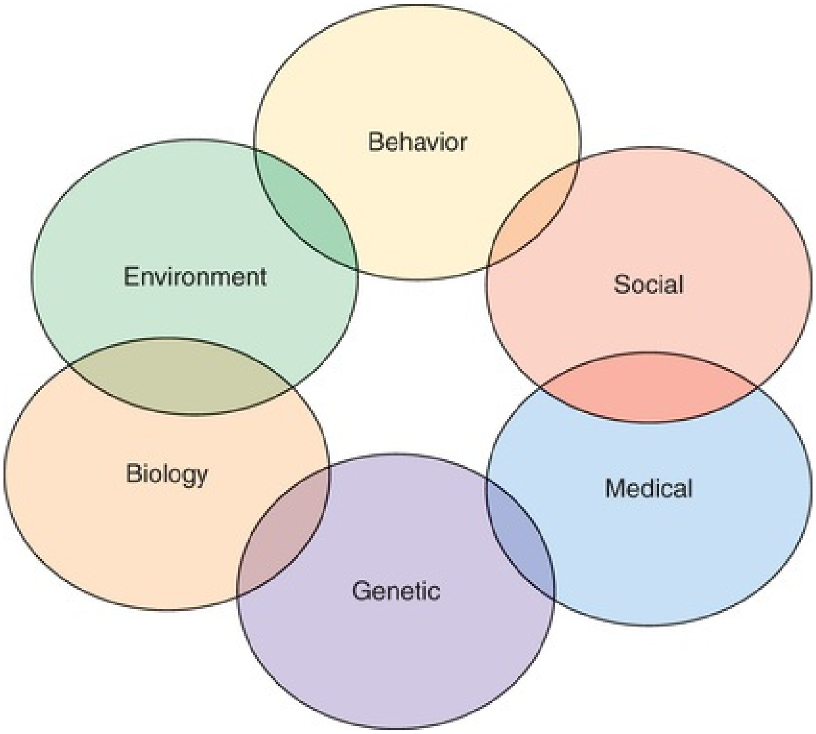

FIG. 2.1 **Determinants of health.**

Fig. 2.2 illustrates the complex relationships among multileveled factors and health outcomes. **Social stratification** factors such as socioeconomic status (SES), race, and gender have profound influences on environmental resources available to individuals and groups, including neighborhood factors (e.g., safety, healthy spaces), social connectedness and support, work opportunities, and family environment. Much of the differential access to these resources results from discrimination, on a systematic or interpersonal level. **Discrimination** is defined as negative beliefs, attitudes, or behaviors resulting from categorizing individuals based on perceived group affiliation, such as gender (sexism) or race/ethnicity (racism).

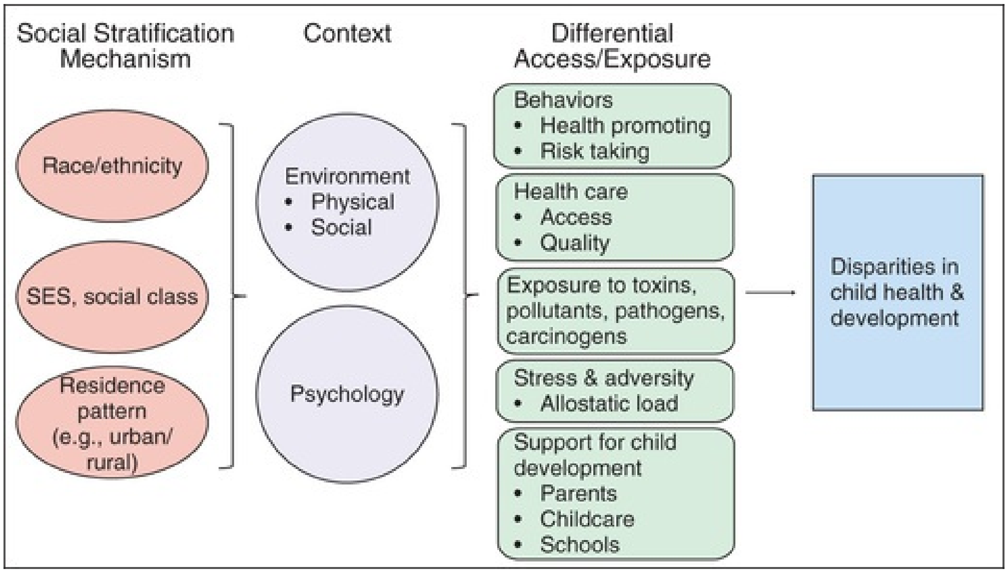
Social Stratification Mechanism
Context
Differential Access/Exposure
Race/ethnicity
SES, social class
Residence pattern (e.g., urban/ rural)
Environment
• Physical
• Social
Psychology
Behaviors
• Health promoting
• Risk taking
Health care
• Access
• Quality
Exposure to toxins, pollutants, pathogens, carcinogens
Stress & adversity
• Allostatic load
Support for child development
• Parents
• Childcare
• Schools
Disparities in child health & development

FIG. 2.2 **Child health disparities. SES, Socioeconomic status. (Data from Adler NE, Stewart J: Health disparities across the lifespan: meaning, methods, and mechanisms, *Ann NY Acad Sci* 1186(1):5–23, 2010.)**

SES, race/ethnicity, gender, and other social stratification factors also have effects on psychological functioning, including sense of control over one's life, expectations, resiliency, negative affect, and perceptions of and response to discrimination. Environmental and psychological context then have influence over more proximal determinants of health, including health-promoting or risk-promoting behaviors; access to and quality of healthcare and health education; exposure to pathogens, toxins, and carcinogens; pathophysiologic (biologic) and epigenetic response to stress; and the resources available to support optimal child development. Variability in these factors in turn results in differential health outcomes.

Psychosocial Stress and Allostatic Load

An understanding has emerged that helps explain how psychosocial stress influences disease and health outcomes (Fig. 2.3). This theory, **allostatic load** , provides insight into the processes and mechanisms that may contribute to health disparities. *Allostasis* refers to the normal physiologic changes that occur when individuals experience a stressful event. These internal reactions to an external stressor includes activation of the stress-response systems, such as increases in cortisol and epinephrine, changes in levels of inflammatory and immune mediators, cardiovascular reactivity, and metabolic and hormone activation. These are normal and adaptive responses to stress and result in physiologic stability in the face of an external challenge. After an acute external stress or challenge, these systems revert to normal baseline states. However, when the stressor becomes chronic and unbuffered by social supports, dysregulation of these systems may occur, resulting in pathophysiologic alterations to these responses, such as hyperactivation of the allostatic systems, or *burnout.* Over time this dysregulation contributes to increased risk of disease and dysfunction. This pathophysiologic response is called *allostatic load* .

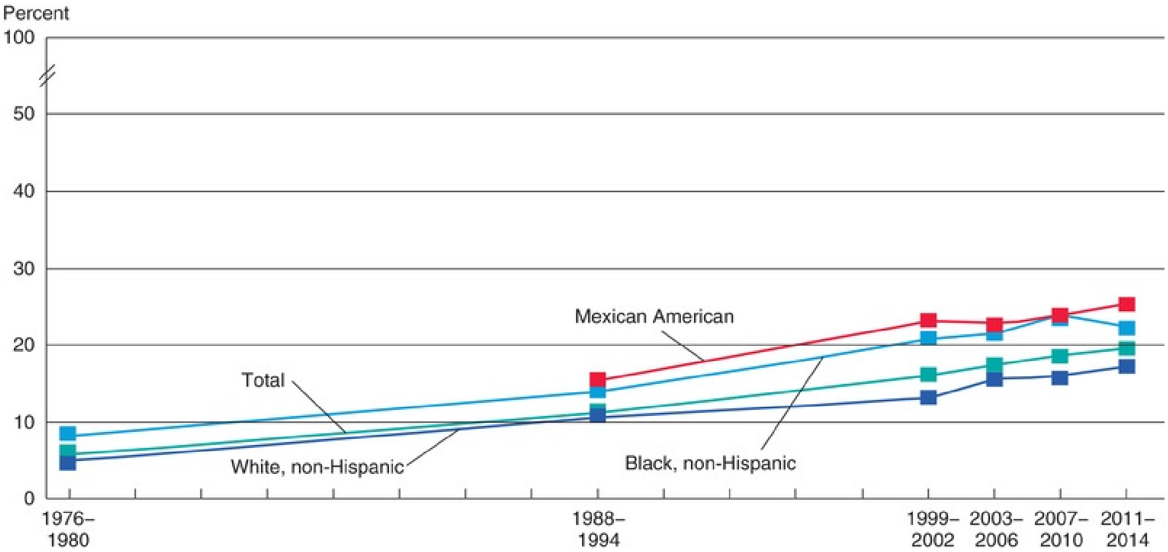

FIG. 2.3 **Percentage of children age 6-17 yr who are obese by race and Hispanic origin, selected years 1976–2014 (From National Center for Health Statistics, National Health and Nutrition Examination Survey. https://www.childstats.gov/americaschildren/health_fig.asp#health7 . Accessed July 2018.)**

Given the systems affected (e.g., metabolic, immune, inflammatory, cardiovascular), allostatic load may contribute to increase incidence of chronic diseases such as cardiovascular disease, stroke, diabetes, asthma, and depression. It is notable that these specific chronic diseases have increased prevalence in racial and ethnic minority groups. Racial and ethnic minorities experience significantly higher degrees of chronic psychosocial stress (see Fig. 2.2), which over time contributes to allostatic load and the resultant disparities in these chronic diseases. Many of these conditions are noted to occur in adulthood, demonstrating the life course consequences of chronic psychosocial stress and adversity that begins in childhood.

The allostatic load model provides a pathophysiologic mechanism through which social determinants of health contribute to health disparities. It complements other mechanisms noted in Fig. 2.2 , such as differential access to healthcare, increase in health risk behaviors, and increased exposure to pathogens, toxins, and other unhealthy agents.

The Hispanic Paradox

Whereas data suggest that minority racial and ethnic groups typically have worse health outcomes than the majority white group, this is not always the case. This finding demonstrates the complex interrelationship among race/ethnicity, minority status, and other factors that contribute to disparities, such as social class and SES.

Studies suggest that for many health outcomes, Hispanic/Latino populations do significantly better than other minority racial/ethnic groups and sometimes as well as the majority non-Hispanic white population. This finding has been called the *Hispanic Paradox* (also known as the Latino Paradox, Epidemiologic Paradox, Immigrant Paradox, and Health Immigrant Effect). Hispanic life expectancy is about 2 yr higher than for non-Hispanic whites, and mortality rates are lower for 7 of the 10 leading causes of death. Among child health issues, Hispanics in general have lower rates of prematurity and low birthweight than African Americans, and Mexican Americans have lower rates of asthma than African Americans and non-Hispanic whites.

Several hypotheses may explain these epidemiological findings. First, the relative advantages seen in Hispanic health are *greatest for non–U.S.-born Hispanics* , and many of the health advantages become nonsignificant in second- or third-generation U.S. Hispanics (as individuals spend more time in the United States). Thus, indigenous cultural beliefs and lifestyles brought over by Hispanic immigrants may provide a selective health advantage, including low rates of tobacco and illicit drug use, strong family support and community ties, and healthy eating habits. Health advantages disappear as immigrants become more acculturated to U.S. standards—poorer nutritional habits and tobacco, alcohol, and illicit drug use—supporting this theory. It is also hypothesized that those who immigrate to the United States are younger and healthier than those Hispanics who do not immigrate and stay in their country of origin, so there may be a *selection* bias; Hispanic immigrants may start out healthier on arrival. Recent immigrants also tend to reside in ethnic enclaves, and socially supportive residential environments are associated with better health outcomes. When immigrants acculturate to U.S. lifestyles, not only do they acquire unhealthy behaviors, but they also tend to lose the protective aspects of their original culture and lifestyle.

There are also differences in outcomes among different Hispanic/Latino subgroups. Selective advantages in Hispanics are usually found among Hispanics from Mexico or South/Central America. Puerto Rican Hispanics typically have *worse* outcomes, compared to other Hispanic groups and non-Hispanic whites. Puerto Rico is a U.S. territory (Puerto Ricans are *not* immigrants) and has many of the negative health profiles seen in the mainland (e.g., high rates of tobacco rates and other health risk behaviors), which further supports the importance of indigenous, healthy, cultural behaviors and lifestyle as an explanation for the healthy immigrant profile seen in Central and South American Hispanics.

Disparities in Child Health and Healthcare:

Tables 2.1 and 2.2 display some of the known disparities in child health and healthcare. As previously noted, health disparities may occur as a result of race/ethnicity,socioeconomic status (often operationalized through family income, sometimes using insurance status as a proxy), and residency patterns, such as urban and rural locale.

Table 2.1

Child Health Disparities

HEALTH INDICATOR	**RACE/ETHNICITY**	**FAMILY INCOME**	**RESIDENCE**
Child health status fair or poor	Black & Hispanic > White & Asian	Poor > Not Poor	
Children with special health care needs (CSHCN)	Black > White > Hispanic	Poor > Not Poor	
One or more chronic health conditions	Black > White > Hispanic > Asian	Poor > Not Poor	
Asthma	Mainland Puerto Rican > Black > White & Mexican American	Poor > Not Poor	Urban > Rural
Obesity	Hispanic & Black > White and Asian	Poor > Not Poor	Rural > Urban
Infant mortality	Black > Hispanic > White	Poor > Not Poor	
Low birthweight (<2,500 g.)	Black > White, Hispanic, American	Poor >	

	Indian/Native Alaskan, Asian/Pacific Islander Mainland Puerto Rican > Mexican American	Not Poor	
Preterm birth (<37 wk)	Black > American Indian/Native Alaskan, Hispanic, White, Asian/Pacific Islander Mainland Puerto Rican > Mexican American	Poor > Not Poor	
Seizure disorder, epilepsy	Black > White, Hispanic	Poor > Not Poor	
Bone, joint, or muscle problem	White > Black, Hispanic	Poor > Not Poor	
Ever breastfed	White, Hispanic, Asian > Black	Not Poor > Poor	Urban > Rural
No physical activity in the past week	Hispanic > Black, Asian > White Poor > Not Poor	Poor > Not Poor	
Hearing problem		Poor > Not Poor	
Vision problem		Poor > Not Poor	
Oral health problems (including caries and untreated caries)	Hispanic > Black > White, Asian	Poor > Not Poor	Rural > Urban
Attention-deficit/hyperactivity disorder (ADHD)	White, Black > Hispanic	Poor > Not Poor	Rural > Urban
Have ADHD but not taking medication	Hispanic, Black > White		
Anxiety problems	White > Black, Hispanic	Poor > Not Poor	
Depression		Poor > Not Poor	Rural > Urban
Behavior or conduct problem (ODD, conduct disorder)	Black > White, Hispanic	Poor > Not Poor	
Autism Spectrum Disorder	White > Black > Hispanic	Poor > Not Poor	
Learning disability	Black > White, Hispanic	Poor > Not Poor	Rural > Urban
Developmental delay	Black > White > Hispanic, Asian	Poor > Not Poor	
Risk of developmental delay, by parental concern	Hispanic > Black & White	Poor > Not Poor	
Speech or language problems		Poor > Not Poor	
Adolescent suicide attempts (consider, attempt, needed medical attention for an attempt)	Girls: Hispanic > Black & White Boys:Hispanic & Black > White		
Adolescent suicide rate	Girls: American Indian > White, Asian/Pacific Islander, Hispanic, Black Boys: American Indian & White > Hispanic, Black, Asian/Pacific Islander		
Child maltreatment (reported)	Black, American Indian/Alaskan Native, Multiracial > White, Hispanic, Asian, Pacific islander	Poor > Not Poor	
AIDS (adolescents)	Black > Hispanic > White		

AIDS, Acquired immunodeficiency syndrome; ODD, oppositional defiant disorder.

Table 2.2

Child Healthcare Disparities

HEALTHCARE INDICATOR	RACE/ETHNICITY	FAMILY INCOME	RESIDENCE
Did not receive any type of medical care in past 12 mo	Hispanic, Black, Asian > White	Poor > Not Poor	Rural > Urban
No well-child checkup or preventive visit in past 12 mo	Hispanic > White & Black	Poor > Not Poor	Rural > Urban
Delay in medical care	Hispanic > Black > White	Poor > Not Poor	
Unmet need in healthcare due to cost	Black > Hispanic > White > Asian	Poor > Not Poor	
No coordinated, comprehensive, or ongoing care in a medical home	Hispanic > Black & Asian > White	Poor > Not Poor	Rural > Urban
Problem accessing specialist care when needed	Hispanic & Black > White	Poor > Not Poor	
No preventative dental care visit in past 12 mo	Hispanic & Asian > Black > White	Poor > Not Poor	Rural > Urban
No vision screening in past 2 yr	Hispanic & Asian > Black & White	Poor > Not Poor	
Did not receive needed mental health treatment or counseling in past 12 mo	Black & Hispanic > White	Poor > Not Poor	
Not receiving a physician recommendation for HPV vaccination among 13-17-yr- old girls	Black & Hispanic > White		
Immunization rates: adolescent HPV vaccine	Girls: White > Black & Hispanic Boys: Black & Hispanic > White		

HPV, Human papillomavirus.

Child Health Disparities

Asthma

Disparities in asthma prevalence are seen by racial/ethnic group and SES. According to the 2015 U.S. National Health Interview Survey (NHIS), American Indian/Alaskan Native, Mainland Puerto Rican, and African American children have the highest prevalence of childhood asthma (14.4%, 13.9%, and 13.4%, respectively), followed non-Hispanic white (7.4%) and Asian (5.4%). The prevalence of childhood asthma in Hispanics is 8%, but when the Hispanic category is disaggregated, Mexican Americans have a prevalence of 7.3%, which is lower than that for non-Hispanic whites; Puerto Rican children have among the highest rates of asthma. The cause of this difference among Hispanic/Latino subgroups is debatable, but some data suggest that bronchodilator response may be different in the 2 groups, possibly based on genetic variants. Data also suggest that within the Mexican American population, differences in prevalence exist based on birthplace or generation (see earlier, The Hispanic Paradox): immigrant and first-generation Mexican American children have lower prevalence of asthma than Mexican American children who have lived in the United States longer. This may reflect the changes that occur as Latinos become more acculturated to U.S. behavioral norms the longer they reside in the United States (e.g., tobacco use, dietary patterns, environmental exposures).

Regarding SES, children living at <100% the federal poverty level have a childhood asthma prevalence of 10.7%, whereas those living at ≥200% the poverty level have a prevalence of 7.2%.

Obesity

In 2014 the percentage of Hispanic/Latino children in the National Health and Nutrition Examination Survey (NHANES) age 6-17 yr who were obese was 24.3%. The percentage of African American children who were obese was 22.5%. This compares to non-Hispanic whites (17.1%) and Asian (9.8%) (see Fig. 2.3). Dietary patterns, access to nutritious foods, and differing cultural norms regarding body habitus may account for some of these differences. The relationship between SES and childhood obesity is less clear. Some studies suggest that the racial and ethnic differences in childhood obesity become nonsignificant when factoring in family income, whereas other national survey studies suggest a relationship between family income and obesity rates in non-Hispanic whites but not among black or Mexican American children.

Infant Mortality

Highest rates of infant mortality are seen in non-Hispanic black infants. According to data from the 2007–2008 National Center for Health Statistics (NCHS)–linked Live Birth–Infant Death Cohort Files, the odds ratio for non-Hispanic black infant mortality is 2.32, compared to non-Hispanic white rates, and remains significant after controlling for maternal age, education, marital status, parity, plurality, nativity, tobacco use, hypertension, and diabetes. Compared with non-Hispanic whites, higher infant mortality is also seen in

Hispanic black and Hispanic white infants as well.

In 2012 the infant mortality rate for black, non-Hispanic (11.2/1,000 live births) and American Indian/Alaskan Native (8.4/1,000) infants was higher than for white, non-Hispanic (5.0/1,000), Hispanic (5.1/1,000), and Asian/Pacific Islander (4.1/1,000) (Fig. 2.4). There was variation in the U.S. Hispanic population: the Puerto Rican infant mortality rate was 6.9/1,000, compared to 5.0/1,000 for Mexican Americans and 4.1/1,000 for Central and South American origin.

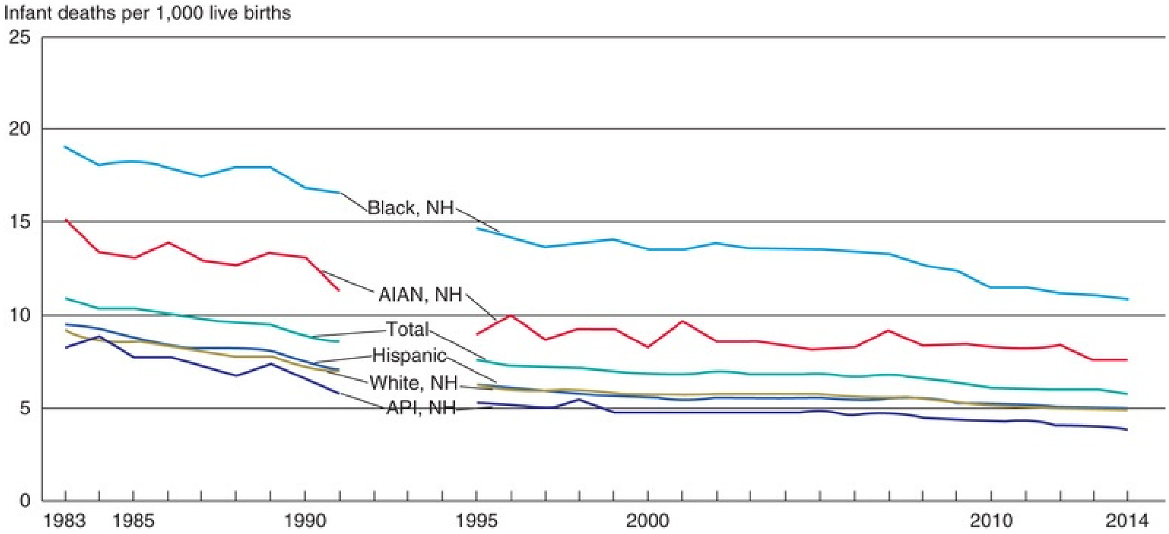

FIG. 2.4 Death rates among infants by race and Hispanic origin of mother, 1983–1991 and 1995–2014. AIAN, American Indian or Alaska Native; API, Asian or Pacific Islander; NH, non-Hispanic. (From National Center for Health Statistics, National Vital Statistics System. https://www.childstats.gov/americaschildren/health_fig.asp#health2 . Accessed July 2018.)

Prematurity and Low Birthweight

There are significant black-white differences in preterm birth and low birthweight (LBW) (Fig. 2.5). According to the 2014 NCHS National Vital Statistics System, LBW births (<2500 g) were significantly higher among black non-Hispanic women (13.2%) than white non-Hispanic (7.0%), American Indian/Alaskan Native (7.6%), Asian/Pacific Islander (8.1%), or Hispanic (7.1%) women. Among Hispanics, Puerto Rican women had higher rates of LBW births than Mexican Americans (9.5% vs 6.6%).

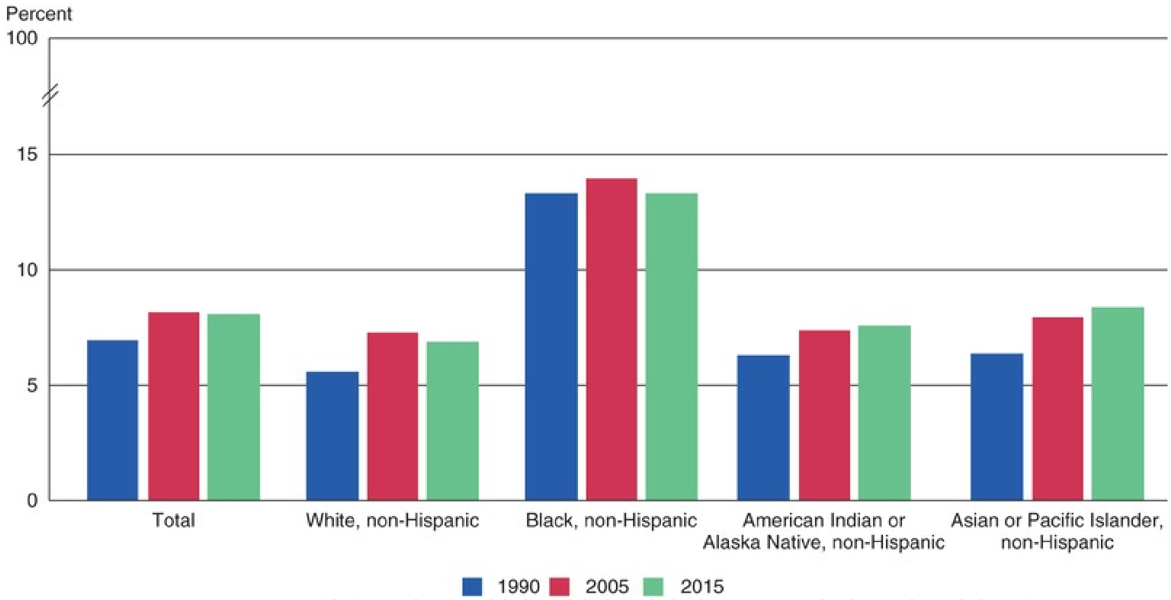

FIG. 2.5 **Percentage of infants born with low birthweight by race and Hispanic origin of mother, 1990, 2005, and 2015 (From National Center for Health Statistics, National Vital Statistics System. https://www.childstats.gov/americaschildren/health_fig.asp#health1b . Accessed July 2018.)**

Regarding preterm births (<37 wk), the black non-Hispanic rate was 13.2%, compared to 8.9% for white non-Hispanics, 8.5% for Asian/Pacific Islanders, 10.2% for American Indian/Alaskan Native, and 9% for Hispanics. Within the Hispanic group, the Puerto Rican preterm rate was higher than for Mexican Americans (11% vs 8.8%).

There are many hypotheses for the increased rates of preterm birth and LBW in black births. Risk factors such as inadequate prenatal care, genitourinary tract infections, increased exposure to environmental toxins, and increased tobacco use may account for some of the disparity, but not all, and neither do SES differences, since high-SES black women still have higher rates of premature and LBW births.

Increased **stress** has been presented as a potential mechanism. Studies have shown that minority women who experience perceptions of racism and discrimination have higher odds of delivering a preterm or LBW child than do minority women who have not perceived experiences with discrimination. **Residential segregation** is also a potential source of differences in preterm and LBW outcomes. Living in hypersegregated neighborhoods can decrease access to prenatal care, increased exposure to environmental pollutants, and increase psychosocial stress, all of which may contribute to increased risk.

Increased age at delivery in African American women does not lessen the risk of preterm or LBW delivery (as it does in white mothers). This has led to the theory that cumulative stress in black women, related to chronic exposure to factors such as socioeconomic deprivation and racial discrimination, leads to declining health at an earlier age compared with white women, and thus increases the risk for poor pregnancy outcomes. Called the **weathering hypothesis** , this has been proposed as an explanation for racial variations in pregnancy outcomes.

Oral Health

Significant differences exist in oral health status as well as preventive oral healthcare according to race/ethnicity, SES, and residency locale. Data from the 1994–2004 NHANES show that compared to non-Hispanic white children, black and Mexican American children had higher rates of caries and untreated caries and lower rates of receiving dental sealants. Children living at or below the federal poverty level also had higher rates of caries and untreated caries and lower rates of dental sealant applications, compared with nonpoor children.

Preventive oral healthcare may improve rates of caries and treat caries before further impairment ensues. Data from the 2004 Medical Expenditure Panel Survey revealed that only 34.1% of black and 32.9% of Hispanic children had a yearly visit to a dentist, compared to 52.5% of white children. Likewise, only 33.9% of low-income children had dentist visits, compared to 46.5% of middle-income children and 61.8% of high-income children.

According to the 2011/12 **National Survey of Children's Health (NSCH)** , parents reported fair to poor teeth condition at a higher rate in Asian non-Hispanic children (8.5%), black non-Hispanic children (7.6%), and Hispanic children (15.2%), compared to white children (4.2%). Hispanic and black non-Hispanic children had higher rates of oral health problems than white non-Hispanic and Asian non-Hispanic children as well.

Hearing Care

No data suggest that the prevalence of hearing loss (either congenital or acquired) is different among racial/ethnic or SES categories, but follow-up care after diagnosis of a hearing problem has been shown to be worse in certain groups. Higher “lost to follow-up” rates have been noted in children living in rural areas as well as with publically insured and nonwhite children. Much of this disparity is reduced when families have access to specialists.

Vision Problems

The parent-reported 2011/12 NSCH found no differences in the prevalence of correctable vision problem among white non-Hispanic, black non-Hispanic, Hispanic, and “other” racial/ethnic groups, or with regard to SES or urban/rural residence.

Immunization

Immunization against infectious agents was one of the major clinical and public health successes of the 20th century. Rates of life-threatening infectious diseases plummet after effective vaccines are introduced. The primary series of childhood immunizations against diphtheria, tetanus, pertussis, polio, rotavirus, measles, mumps, rubella, hepatitis A and B, *Haemophilus influenzae* type b, varicella, and *Streptococcus pneumoniae* have significantly decreased the incidence of illness caused by these agents.

Disparities in immunization rates had been noted regarding household income status, insurance status, and residential location. In response to these socioeconomic disparities, as well as higher rates of measles cases in the 1980s among racial and ethnic minority groups, a number of interventions were initiated, including the creation of the **Vaccines for Children program** (VFC), which eliminated the financial barrier to immunization by providing free immunizations to at-risk groups (Medicaid-eligible, uninsured, American Indian/Alaskan Native, or underinsured and vaccinated at a federally qualified health center or rural health clinic). Since VFC inception, disparities in immunization rates have either been eliminated or have significantly narrowed, showing that targeted public health programs can successfully eliminate health disparities.

Although rates of initial primary vaccine series demonstrate no or decreasing disparities, other vaccination rates do show differences. For example, black and Hispanic adolescent females have lower human papillomavirus (HPV) vaccination rates than whites. Reasons for this disparity include parental concerns about safety and no provider recommendation. Of interest, studies of HPV vaccination in adolescent males show that black and Hispanic male adolescents have higher rates of HPV vaccine coverage than whites.

Adolescent Suicide

In 2014 the highest rate of suicide for male adolescents was seen in American

Indian (20 per 100,000 population) and white (17/100,000) teens, compared to Hispanic (9/100,000), black (7/100,000), and Asian/Pacific Islander (6/100,000) teens. For female adolescents, highest suicide rates were seen in American Indian (12/100,000), compared to white (5/100,000), Asian/Pacific Islander (5/100,000), Hispanic (3/100,000), and Black (2/100,000) teens.

Hispanic female students in grades 9-12 were more likely to consider suicide (26%), report attempting suicide (15%), and require medical attention for a suicide attempt (5%), compared to black (19%, 10%, 4%) or White (23%, 10%, 3%) female students. Among male students, Hispanic and black students, compared to white students, were more likely to attempt suicide (8% and 7% vs 4%, respectively) and require medical attention for a suicide attempt (4% and 3% vs 1%).

Child Maltreatment

In 2014, reports of child abuse and neglect were higher in black (15.3 per 1,000 children), American Indian/Alaskan Native (13.4/1,000), and multiracial (10.6/1,000) children, compared to Hispanic (8.8/1,000), Pacific Islander (8.6/1,000), white (8.4/1,000), and Asian (1.7/1,000) children. **Poverty** , measured at the family as well as community level, is also a significant risk factor for maltreatment. Counties with high poverty concentration had >3 times the rate of child abuse deaths than counties with the lowest concentration of poverty. Nonetheless, race itself *should not be a marker* for child abuse or neglect.

Behavioral Health Disparities

Attention-Deficit/Hyperactivity Disorder (ADHD)

White and black children are more often diagnosed with ADHD (10.7% and 8.4%, respectively) than are Hispanic children (6.3%), according to NHIS data. Other studies have shown that both black and Hispanic children have lower odds of having an ADHD diagnosis than white children. Children reared in homes that are below the federal poverty level are diagnosed more often (11.6%) that those at or above the FPL (8.1%).

Children diagnosed with ADHD have different medication practices. Hispanic (43.8%) and black (40.9%) children with ADHD are more likely than white children (25.5%) *not* to be taking medication. The causes of this disparity are unknown but may include different patient and parental beliefs and perceptions about medication side effects and different prescribing patterns by clinicians.

Depression and Anxiety Disorders

According to the 2011/12 NSCH, there were no parent-reported differences in rates of childhood depression (2-17 yr) among racial/ethnic groups. Children living in poverty, as well as children living in rural areas, had higher rates of parent-reported depression. According to the 2015 **Youth Risk Behavior Survey** of adolescent in grades 9-12, Hispanic students had higher rates of reporting that they felt sad or hopeless (35.3%) compared to white (28.6%) and black (25.2%) students. This relationship existed for both male and female students.

The NSCH data noted that white children ages 2-17 yr had higher rates of anxiety than black or Hispanic children. "Poor" children had higher rates of anxiety than "not poor" children.

Autism Spectrum Disorder (ASD)

Compared with white children, black and Hispanic children are less likely to be diagnosed with ASD, and when diagnosed, are typically diagnosed at a later age and with more severe symptoms. This disparity in diagnosis and timing of diagnosis is concerning given that early diagnosis provides access to therapeutic services that are best initiated as early as possible. Reasons for these disparities may include differences in cultural behavioral norms, stigma, differences in parental knowledge of typical and atypical child development, poorer access to quality healthcare and screening services, differences in the quality of provider–patient communication, trust in providers, as well as differential access to specialists.

Behavioral or Conduct Problems

According to the 2011/12 NSCH, black children age 2-17 yr have higher rates of **oppositional defiant disorder** (ODD) or **conduct disorder** than white and Hispanic children. Children living in poverty have higher rates than those not living in poverty.

Developmental Delay

The 2011/12 NSCH found that black and white children age 2-17 yr had higher rates of developmental delay than Hispanic children (4.5% and 3.8% vs 2.7%, respectively). However, when parents of children age 4 mo to 5 yr were asked if they had concerns about their child's development (highly correlated with risk of developmental, behavioral, or social delays), Hispanic children had higher rates of moderate or high risk for developmental delay (32.5%) than did black (29.7%) or white (21.2%) children. This discrepancy may result from either overestimation of concerns in Hispanic mothers or underdiagnosis of Hispanic children by clinicians.

Children living below the poverty level have higher rates of developmental delay as well.

Disparities in Healthcare

In almost all areas, minority children have been identified as having worse access to needed healthcare, including receipt of any type of medical care within the past 12 mo, well-child or preventive visits, delay in care, having an unmet need due to healthcare cost, lack of care in a medical home, problems accessing specialist care when needed, lack of preventive dental care, vision screening, mental health counseling, and recommendations for adolescent immunizations (see Table 2.2). In addition, many of these healthcare indicators are found to be worse for children living in poverty, as well as those living in a rural area, compared to urban-dwelling children.

Approaches to Eradicating Disparities: Interventions

Much of the information regarding health disparities over the past 10-20 yr has focused on the identification of areas where health disparities exist. Additional work has expanded on simple description and acknowledged the multivariable nature of disparities. This has provided a more nuanced understanding of the complex interrelationships among factors such as race/ethnicity, socioeconomic status, social class, generation, acculturation, gender, and residency.

An example of a successful intervention that closed the disparity gap is the implementation of the VFC program, which, as noted earlier, significantly decreased the disparity in underimmunization rates noted among racial/ethnic groups and poor/underinsured children. This is an example of a **public health**

policy approach to intervention.

Interventions need to occur at the **clinical** level as well. The almost universal use of electronic health records (EHR) provides a unique opportunity for collecting clinical and demographic data that can be helpful in identify disparities and monitor the success of interventions. All EHR platforms should use a standardized approach to gathering information on patient race/ethnicity, SES, primary language preferences, and health literacy. The Institute of Medicine's 2009 report *Race, Ethnicity, and Language Data: Standardization for Health Care Quality Improvement* provides best practices information about capturing these data in the health record.

The advancing science of clinical **quality improvement** can also provide a framework for identifying clinical strategies to reduce disparities in care. Use of **PDSA** (Plan-Do-Study-Act) cycles targeting specific clinical issues where health disparities exist can result in practice transformation and help reduce differential outcomes.

Another practice-level intervention that has the potential to reduce disparities in care and outcomes is the **medical home** model, providing care that is accessible, family centered, continuous, comprehensive, compassionate, coordinated, and culturally effective. The use of care coordinators and community-based health navigators is an effective tool in helping to break down the multiple social and health system barriers that contribute to disparities.

Population health strategies have the advantage of addressing the determinants of disparities at both the clinic and the community levels. Techniques such as “hotspotting,” “cold-casing” (finding patients and families lost to follow up and not receiving care), and “geocoding,” combined with periodic community health needs assessments, identify the structural, systemic, environmental, and social factors that contribute to disparities and help guide interventions that are tailored to the local setting.

When developing strategies to address disparities, it is imperative to include patients and community members from the beginning of any process aimed at identification and intervention. Many potential interventions seem appropriate and demonstrate efficacy under ideal circumstances. However, if the intervention does not address the concerns of the end users—patients and communities—or fit the social or cultural context, it will likely be ineffective in the “real world.” Only by involving the community from the beginning, including defining the issues and problems, can the likelihood of success be optimized.

Health disparities are a consequence of the social stratification mechanisms inherent in many modern societies. Health disparities mirror other societal disparities in education, employment opportunities, and living conditions. While society grapples with the broader issues contributing to disparities, healthcare and public health can work to understand the multiple causes of these disparities and develop interventions that address the structural, clinical, and social root causes of these inequities.

2.1

Racism and Child Health

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Keywords

adverse childhood experiences
cultural humility
cultural safety
doll experiment
equity
implicit bias
infant mortality rate
institutional racism
internalized racism
interpersonal racism
microaggression
racial disparities
residential segregation
social determinants
stereotype threat
structural competency
structural racism

Racism as Social Determinant

An emerging body of evidence supports the role of racism in a range of adverse physical, behavioral, developmental, and mental health outcomes. Racial/ethnic patterning of health in the United States is long-standing, apparent from the first collection of vital statistics in the colonial period. However, the extensive data that document racial disparities have not settled the question of why groups of people, particularly of African and Native American Indian ancestry, face increased odds of shorter lives and poorer health (Table 2.3). The role of societal factors, not only factors related to the individual, is increasingly recognized in determining population health, but often omits racism among social determinants of health. This oversight occurs in the face of a long history of racial and ethnic subjugation in the United States that has been justified both explicitly and implicitly by racism. From the early 18th century, colonial America established racial categories that enshrined the superiority of whites, conferring rights specifically on white men, while denying these rights to others. Similar, perhaps less explicit, discrimination has continued through the centuries and remains a primary contributor to racial inequities in children's health.

Table 2.3

New Social and Health Inequities in the United States

	TOTAL	WHITE NON-HISPANIC	ASIAN*	HISPANIC OR LATINO	BLACK NON-HISPANIC †	NATIVE AMERICAN OR ALASKA NATIVE
Wealth: median household assets (2011)	$68,828	$110,500	$89,339	$7,683	$6,314	NR
Poverty: proportion living below poverty level, all ages (2014); children <18 yr (2014)	14.8%; 21.0%	10.1%; 12.0%	12.0%; 12.0%	23.6%; 32.0%	26.2%; 38.0%	28.3%; 35.0%
Unemployment rate (2014)	6.2%	5.3%	5.0%	7.4%	11.3%	11.3%
Incarceration: male inmates per 100,000 (2008)	982	610	185	836	3,611	1,573
Proportion with no health insurance, age <65 yr (2014)	13.3%	13.3%	10.8%	25.5%	13.7%	28.3%
Infant mortality per 1000 live births (2013)	6.0	5.1	4.1	5.0	10.8	7.6
Self-assessed health status (age-adjusted): proportion with fair or poor health (2014)	8.9%	8.3%	7.3%	12.2%	13.6%	14.1%
Potential life lost: person-years per	6621.1	6659.4	2954.4	4676.8	9490.6	6954.0

100,000 before age 75 yr (2014)						
Proportion reporting serious psychological distress [‡] in past 30 days, age ≥18 yr, age-adjusted (2013–14)	3.4%	3.4%	3.5%	1.9%	4.5%	5.4%
Life expectancy at birth (2014), yr	78.8	79.0	NR	81.8	75.6	NR
Diabetes-related mortality: age-adjusted mortality per 100,000 (2014)	20.9	19.3	15.0	25.1	37.3	31.3
Mortality related to heart disease: age-adjusted mortality per 100,000 (2014)	167.0	165.9	86.1	116.0	206.3	119.1

[*] Economic data and data on self-reported health and psychological distress are for Asians only; all other health data reported combine Asians and Pacific Islanders.

[†] Wealth, poverty, and potential life lost before age 75 yr are reported for the black population only; all other data are for the black non-Hispanic population.

[‡] Serious psychological distress in the past 30 days among adults 18 yr and older is measured using the Kessler 6 scale (range: 0–24; serious psychological distress ≥13).

NR, Not reported.

Wealth data from the US Census; poverty data for adults from National Center for Health Statistics (NCHS), and poverty data for children from National Center for Education Statistics; unemployment data from US Bureau of Labor Statistics; incarceration data from Kaiser Family Foundation; data on uninsured individuals from NCHS; data on infant mortality, self-assessed health status, potential life lost, serious psychological distress, life expectancy, diabetes-related mortality, and mortality related to heart disease from NCHS.

From Bailey ZD, Krieger N, Agénor M, et al: Structural racism and health inequities in the USA: evidence and interventions, *Lancet* 389:1453–463, 2017 (Table, p 1455).

For generations, racial/ethnic disparities have been documented beginning at birth and extending across life. In 2014, life expectancy at birth for blacks was almost 4 yr shorter than life expectancy of non-Hispanic whites, influenced heavily by disparities starting at birth (Table 2.3). The **infant mortality rate** (IMR), arguably the most important measure of national health, has shown a persistent relative black-white gap. Despite the substantial decline in U.S. IMR for all racial/ethnic groups, there is still at least a 2-fold higher risk of death in the 1st yr of life for black infants than for white infants (Table 2.3). NCHS data in 2014 showed a double-digit IMR *only* among non-Hispanic blacks, with 11.8 deaths per 1,000 live births, compared to 4.89/1,000 for non-Hispanic whites. In 2016 the black IMR slightly increased after many years of progressive decline, which may portend a further rise in the relative black-white gap. A troubling stagnation in IMR, with no recent decline, is found among Alaska Natives and American Indians. The 2005 IMR in American Indian or Alaskan Native women, 8.06 deaths/1000 live births, has remained essentially unchanged for a decade, with the 2014 IMR at 7.59/1,000.

Exposures that affect infant survival occur before birth. Prenatal maternal exposures to pesticides, lead, and other environmental toxins vary by race. Additionally, a higher prevalence of maternal obesity, diabetes, and substance/alcohol use before conception also adversely affects birth outcomes. A California study of maternal obesity based on claims data and vital records found that 22.3% of pregnant black women and 20.3% of Latina women had a body mass index (BMI) of 30-40, compared to 14.9% of white and 5.6% of Asian women. BMI >40 was more than twice as prevalent in black (5.7%) than white (2.6%) women.

The effects of racism are also stressful and toxic to the body, and evidence supports biologic effects of discrimination across the life span, especially for pregnant women. Racism can increase cortisol levels and lead to a cascade of effects, including impaired cell function, altered fat metabolism, increased blood glucose and blood pressure, and decreased bone formation (see Chapter 1 , Fig. 1.3). This can affect a growing fetus, leading to increased infant cortisol levels, lower birthweight (LBW), and prematurity. In New York City, white women had lower rates of adverse birth outcomes: 1.3% had preeclampsia, less than half the rate for black women (2.9%).

Although infant deaths occur more frequently among low-income groups of all race/ethnicities, these birth outcome disparities by race/ethnicity are found also in blacks with higher socioeconomic status (SES). College-educated black women are more likely than white high school–educated women to have a LBW infant, a principal risk factor for infant death. Another study examined California birth certificates of pregnant Arab American women after the September 11, 2001, terrorist attacks and found that those who experienced discrimination immediately after the 9/11 attacks had a higher relative risk of giving birth to an LBW infant in the following 6 mo than seen in births before this date.

The increased risk for populations of color continues from infancy into childhood; racial/ethnic disparities are seen across almost all health indicators, with most relative gaps remaining stagnant or worsening over the last 2 decades. Black children are about twice as likely to be diagnosed with **asthma** , more likely to be hospitalized for its treatment, and more likely to have fatal attacks. The black-white disparity in asthma has grown steadily over time. Native American children and youth (≤19 yr) also experience negative health outcomes, with the highest rates of **unintentional injury** and mortality rates at least twice as high as for other racial/ethnic groups. Additionally, according to a 2015

NCHS brief, Latino youth age 2-19 have the highest rates of **obesity** , defined as a BMI ≥95th percentile in the 2000 CDC sex/age-specific growth charts. The NCHS data show that 21.9% of Latino (followed by black) children qualified as obese from 2011 to 2014. Black children are more likely to be exposed to witnessed, personal, or family **violence** and have several-fold higher prevalence of **psychiatric distress** than their white counterparts, a racial difference that continues into adulthood.

Explaining Racial Disparities: A Taxonomy of Racism

Explanations of these ubiquitous racial gaps have focused on individual factors, including variation in individual genetic constitution, behavioral risks, poverty, and access to (and use of) healthcare services. Scientists agree that “race” is a social construct that is not based on biology, despite the persistence of the idea that racial categories reflect a racially distinctive genetic makeup that has a bearing on health. In fact, the genetic variation between individuals within a particular racial/ethnic group is far greater than the variability between “races.” Despite the genetic data, many groups have been “racialized” over time. Notably, the U.S. Census Bureau's demographic classifications reflect this process. In the mid-late 1800s the census counted “mulattos,” those of white and black ancestry, as another race.

Starting in the late 19th century, Eastern European immigrants and Jews were considered different races. As early as 1961, the U.S. Census identified Mexicans and Puerto Ricans as “white,” even as racial classification varied by geography. All states collected birth records by 1919, but there was little uniformity on how race was collected, if at all, across states. It was not until 1989, when the National Center for Health Statistics (NCHS) recommended assigning “infant race” as that of the mother, that standard guidance and categories were issued for states on collecting racial data at birth. Existing categories were changed and continue to change based on the economic, cultural, or political utility of the time, rather than actual genetic distinction.

Defining Racism

Racism has consistently structured U.S. society and is based on “white supremacy," a hierarchical idea that whites, the *dominant* group, are intrinsically superior to other groups who are not classified as "white." No single definition of racism exists, but one useful description is *racial prejudice backed by power and resources* . This conceptualization asserts that not only must there be prejudice, but also an interlocking system of institutions to produce and reproduce inequities in access to and utilization of resources and decision-making power. Even when considering variations in health behavior, lifestyles, economic status, and healthcare utilization, individual-level behavioral factors do not capture how broader shared social experiences shape outcomes. **Racial domination** or racism contributes to variation in the population's access to resources and exposure to disease, as well as the group experience of fair treatment and opportunity. Although many groups in the United States may encounter discrimination based on race/ethnicity, most of the modest literature on health effects of racism has focused on people of African descent, leaving a need to better understand the impact of racism on other nonwhite groups. Table 2.4 describes various pathways through which racism affects health.

Table 2.4

Pathways Between Racism and Health and Examples

- *Economic injustice and social deprivation*
    - Residential, educational, and occupational segregation to lower-quality neighborhoods, schools, and jobs (both historical de jure discrimination and contemporary de facto discrimination)
    - Lower salary for same work
    - Lower promotion rate despite comparable evaluations
- *Environmental and occupational health inequities*
    - Placement of bus garages and toxic waste sites
    - Selective government failure to prevent lead in drinking water (per Flint, Michigan, 2015–2016)
    - Disproportionate exposure of workers of color to occupational hazards
- *Psychosocial trauma*
    - Interpersonal racial discrimination, including microaggressions*
    - Exposure to racist media, including social media
- *Targeted marketing of health-harming substances*

        - Legal: cigarettes; sugar sweetened beverages
        - Illegal: heroin; illicit opioids
- *Inadequate healthcare*
    - Inadequate access to health insurance and healthcare facilities
    - Inadequate treatment caused by implicit or explicit racial bias
- *State-sanctioned violence and alienation from property and traditional lands*
    - Police violence
    - Forced urban "renewal" (use of eminent domain to force relocation of urban communities of color)
    - Genocide and forced removal of Native Americans
- *Political exclusion*
    - Voter restrictions (e.g. for ex-felons, ID requirements)
- *Maladaptive coping behaviors*
    - Increased tobacco and alcohol consumption
- *Stereotype threat*
    - Stigma of inferiority leading to physiologic arousal
    - Impaired patient-provider relationship

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[*] Small, often unintentional racial slights/insults (e.g., a judge asking a black defense attorney, "Can you wait outside until your attorney gets here?")

From Bailey ZD, Krieger N, Agénor M, et al: Structural racism and health inequities in the USA: evidence and interventions, *Lancet* 389:1453–1463, 2017 (Panel 2, p 1546).

While the empirical data on disparities for nonblack populations of color deserve greater research, useful frameworks exist to understand the disparities that public health has documented to date. A useful taxonomy of how racism operates in society has 4 categories: internalized racism, interpersonal racism, institutional racism, and structural racism. Each is relevant in considering the impact of racism on child health.

Internalized Racism

When the larger society characterizes marginalized racialized groups as “inferior,” these negative assessments may be accepted by members of those groups themselves, either consciously or unconsciously. The result is *devaluation* of personal abilities and intrinsic worth, as well as the capacity, of others also classified as being a part of a marginalized racialized group. The best-known documentation of *internalized racism* comes from the study of Kenneth and Mamie Clark known as the **doll experiment** , conducted in the 1940s. Black children, both boys and girls, were asked to choose between a black doll and a white doll according to attributes described by the interviewer. In response to positive attributes (e.g., *pretty, good, smart*), most children chose the white doll. The Clarks interpreted this finding to mean that black children had internalized the societal views of black inferiority and white superiority, even at the expense of their personal self-image. Repeated by a New York City high school student several decades later, the findings were much the same, with 15 of 21 children endorsing positive attributes to light-skinned dolls. Multiple studies confirm that racial identity is established in young children, both black and white, along with negative views of blackness. Developmentally, however, nonwhite youth often explore racial identity earlier than their white counterparts. In terms of health outcomes, depending on perceived inferiority or superiority of the group, racial identification is associated with self-esteem, mastery, and depressive symptoms. Low self-esteem is independently implicated in mental health disorders and may contribute to the phenomenon of **stereotype threat** , in which personal expectation of underperformance correlates with prevailing social stereotypes and adversely affects actual performance.

Interpersonal Racism

How racial beliefs affect interactions between individuals has been the most studied aspect of racism. *Interpersonal racism* refers to situations where one person from society's privileged racial group acts in a discriminatory manner that adversely affects another person or group of people. Such actions may be based on explicit beliefs or on implicit beliefs of which the perpetrating individual is not consciously aware. A burgeoning field is examining how experience of unfair treatment has *biologic* consequences, reflected in measurable increases in stress responses.

Such effects of interpersonal racism are best documented for **mental health** , where perceived unfair treatment serves as psychosocial stressors, and are weaker for physical health outcomes. A 2009 study of 5,147 5th-grade students found that compared to only 7% of whites who reported experiencing racial discrimination, 15% of Latinos and 20% of blacks self-reported enduring racial discrimination. Furthermore, discriminatory experiences have been strongly and consistently linked to greater risk for anxiety, depression, conduct disorder, psychological distress, ADHD, ODD, self-esteem, self-worth, and psychological adaptation and adjustment. Perceived racial discrimination can affect behavioral, mental, and physical health outcomes and is associated with: increased alcohol and drug use among Native Americans (age 9-16 yr), increased tobacco smoking for black youth (11-19 yr), higher depressive symptoms among Puerto Rican children, and insulin resistance among young females.

Understanding the enduring impact of childhood experience on adult health has increased with the study of **adverse childhood experiences** (ACEs) (see Chapter 1). ACEs have well-documented cumulative negative health effects that occur across the life span and are patterned by race/ethnicity. Early experience of racism is a proxy measure for **toxic stress** . The question, “Was [child's name] ever treated or judged unfairly because of [his/her] race or ethnic group?” is included in the U.S. Census Bureau's National Survey of Children's Health, a random sample of 91,000-102,000 households (depending on the year) to assess the health of children up to 17 yr old. Children of color from low-income households, especially Latino children, were reported to have the lowest level of health. However, exposure to racism among higher SES did not protect children from experiencing relatively poorer health. Children exposed to racism were also more likely (by 3.2%) to have a diagnosis of ADHD. Children exposed to racism were 2 times more likely to experience anxiety and depression.

Toxic stress increases cortisol levels in the body, increasing the risk of chronic disease. A 2010 study revealed that Mexican adolescents who perceived racism experienced greater cortisol output, after controlling for other stressors. Adolescents who experience racism with no support have been shown to have higher levels of blood pressure and obesity than those with emotional support, which can be protective.

Medical practice has not been exempt from these occurrences of interpersonal racism. Using variation in adherence to established clinical standards in diagnostic and treatment decisions across racialized groups, researchers have been assessing interpersonal racism in physician–patient interactions. The most comprehensive review of such bias in clinical care remains the 2003 study by the U.S. Institute of Medicine, in which the discriminatory treatment was inferred from examination of clinical decision-making rather than from directly observed interactions. For virtually every condition studied, black patients were less likely to receive recommended care. Such racial bias has been most extensively established in adults but also extends to children. A study conducted in an emergency department found pediatric patients (<21 yr) were less likely to receive medically indicated pain medication if they were black, mirroring the historical misconception of reduced pain sensitivity among blacks. Within this context, it is unsurprising that perceived interpersonal racism has been linked to healthcare utilization, including delays in seeking care or filling prescriptions and distrust of the health system.

Institutional Racism

Interpersonal racism clearly inflicts harms, but even if completely eliminated, racial inequities would persist because of institutional and structural racism. Broadly, *institutional racism* refers to patterns of discrimination based on policy, culture, or practice and carried out by state and nonstate institutions (e.g., corporations, universities, legal systems, cultural institutions) within various sectors (e.g., housing, education, criminal justice). Key to current residential segregation are banking practices dating to the post-Depression era. As an institution, the education system has been another tragic case of how racism impacts children's health. In addition, mass incarceration by the criminal justice system has dramatically increased in the United States while remaining relatively flat in other developed countries (Fig. 2.6). Over a lifetime, approximately 30% of African American men have been imprisoned.

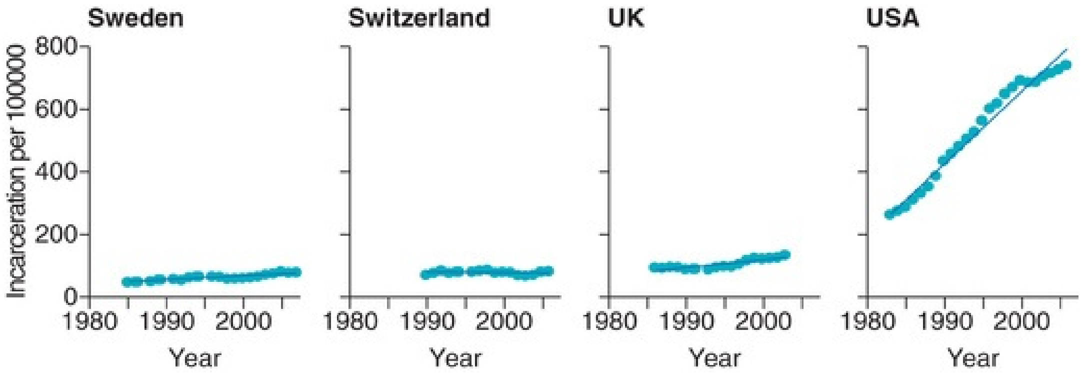

FIG. 2.6 **Trends in incarceration prevalence in developed democracies, 1981–2007. (Adapted from Wilderman C, Wang EA: Mass incarceration, public health, and widening inequality in the USA, *Lancet* 389:1464–1472, 2017, Fig 1.)**

In school, children of color can experience not only individual racism but also institutional racism, as documented by higher rates of disciplinary actions such as suspensions, and at younger ages than white children. According to a 2016 U.S. Department of Education civil rights survey, black children, who represent only 19% of national preschool students, account for a staggering 47% of at least 1 out-of-school suspension. Black preschoolers are 3.6 times more likely to be suspended than their white peers. Black females, representing 20% of female preschool population, account for 54% of out-of-school suspensions.

Unfortunately, this disparity persists as children continue through the school system: for kindergarten to grade 12 (K-12) students, black children are 3.8 times more likely to face out-of-school suspension than white peers. This inequity is particularly harmful because the educational system feeds into the criminal justice system. Black students are 2.2 times more likely to have either school-related arrests or law enforcement referrals than their white peers. The U.S. Department of Education survey also reveals racial inequities among children with disabilities. For K-12 children with disabilities covered under the Individuals with Disability in Education Act, 21% of multiracial females were issued with at least 1 out-of-school suspension, compared to 5% of white females.

In addition to the threat to educational and employment prospects, school suspensions also risk children's health. A 2016 brief from the Yale Child Study Center states that early suspensions and expulsions of children harm behavioral and social-emotional development, weakening a child's overall development. Furthermore, these forms of punishment may prevent the treatment of underlying health issues, such as mental health issues or disabilities, and cause increased stress for the entire family.

Institutional racism can function without apparent individual involvement and has powerful repercussions that persist centuries later. Both medical professional organizations and educational institutions have legacies of racial discrimination rooted in *scientific racism.* In 2008 the American Medical Association (AMA) issued a formal apology for its long history, dating to the 1870s, of endorsing explicitly racist practices, including exclusion of black physicians, silence on civil rights, and refusal to make any public statement on federally sponsored hospital segregation. Despite a focus on medical school desegregation in the 1960s and 1970s, the presence of black students in medical schools is actually declining. Low enrollment has become especially critical for black men, who in

2014 accounted for about 500 of the 20,000 medical students nationwide. If physicians hold stereotyped views about race that affect their clinical decision-making, the declining diversity of medical student bodies may well have consequences for the quality of medical care. This history of institutional racism on people of color contributes to the mistrust, apprehension, and fear projected toward the entire medical establishment.

Structural Racism

The institutional racism within medical institutions reinforces institutional racism in other sectors, creating a larger system of discrimination, *structural racism* . Structural racism can be described as “the totality of ways in which societies foster racial discrimination via mutually reinforcing systems of housing, education, employment, earnings, benefits, credit, media, healthcare, and criminal justice. These patterns and practices in turn reinforce discriminatory beliefs, values, and distribution of resources, which together affect risk of adverse health outcomes.” Institutional racism and structural racism are sometimes used interchangeably, but structural racism refers to overarching patterns beyond a single or even collection of institutions. Historically, government policies and practices have been largely responsible for the creation of these structures.

De facto and de jure urban residential segregation serves as a case study for how the mechanisms of structural racism operate across multiple sectors and can impact child health and development across the life course. In the 20th century, urban residential racial segregation was reinforced by the government-sanctioned policy and practice of *redlining* . This now-illegal practice was initiated by the U.S. Federal Housing Administration in 1934. Surveyors literally demarcated city maps with red ink to indicate those urban neighborhoods to be made ineligible for home loans. *Racial composition* was the most important driver of this categorization, and thus black neighborhoods were excluded from the federally financed, post-Depression home ownership boom and remained segregated. Through this segregation, existing resources were systematically removed (*disinvestment*) and led to further impoverished communities of color.

The effects of residential segregation were not restricted to the banking or housing sectors. **Residential segregation** ties together multiple systems, driving children's access to and quality of healthcare, education, and justice, as follows

◆ *Residential segregation and the healthcare system.* Healthcare institutions were explicitly racially segregated by law and inequitably resourced until passage of the 1964 Civil Rights Act. Vestiges of this segregation continue in recent hospital-level segregation and racial composition by hospital. In addition, institutions that provide mainly for uninsured or underserved residents are often financially unstable, leading to higher risk of closure in disinvested neighborhoods of color. On the provider level, fewer primary care and specialty physicians practice in disinvested, segregated neighborhoods, and those who are present are less likely to participate in Medicaid.

◆ *Residential segregation and the education system.* Schools have a similar history of racial segregation and, after a brief respite of integration peaking in 1980, the rates of segregation now resemble pre–Civil Rights levels of segregation. School segregation is related to high-risk health behaviors. Within these schools and in their neighborhoods, black children experience disproportionate penalization and criminalization in the educational and criminal justice systems, reinforcing institutional racism in other sectors and other forms of racism. A low-income black child is much more likely than a low-income white child to live in a segregated neighborhood. The result is that the black child will face not only the cumulative disadvantage in both family and neighborhood resources and experiences over time, but also the initiation of chains of disadvantage during sensitive periods of childhood key for development and adult transition (e.g., early childhood, adolescence).

◆ *Residential segregation and the criminal justice system.* Incarceration is concentrated in overpoliced and criminalized black communities. In the NCHS, almost 13% of black children had a parent imprisoned during their childhood (to age 17 yr), compared to about 6% of white children. Parental incarceration, which may start with a traumatic arrest in the home and later disrupt caregiving, create social stigma, deepen financial disadvantage, disconnect parents emotionally from children, and disrupt children's psychological development, has been independently associated with higher risk of children's antisocial behavior.

Most notably, experiences directly related to institutional and structural racism, operating through residential segregation (including financial hardship, parental imprisonment, and neighborhood violence), result in higher levels of ACEs for blacks and Latinos than whites. There has been growing, consistent evidence of the lifelong association between ACEs and a range of negative physical and mental health outcomes across the life course.

Structural racism, shown here with the example of residential segregation, affects child health through various direct and indirect, overlapping pathways, including the concentration of dilapidated housing, inferior quality of the social and built environment, exposure to pollutants and toxins, limited access to high-quality primary and secondary education, few well-paying jobs, overpolicing and criminalization, adverse experiences, and limited access to quality healthcare.

Opportunities to Address Racism

Racism as a determinant of health has strong empirical support, and there is promising evidence for community-wide approaches to its mitigation. Less is known about effective interventions in clinical settings. Most medical schools and subsequent training will not have prepared practitioners to examine the role of racism in their patients' lives or clinical care settings. Nonetheless, it is reasonable to expect that pediatricians can help address racism and promote racial justice in at least 3 ways: during individual patient encounters and at their practice sites, as members of institutions that provide medical care and training, and as respected community members.

Clinical Settings

A first step is understanding that racism affects everyone and personally assessing **implicit bias** . Such biases reflect reflexive patterns of thinking often using racial stereotypes stemming from living in a racially stratified society. The **Project Implicit Race Implicit Association Test** (https://implicit.harvard.edu/implicit/takeatest.html) is available online, and its results are confidential. The purpose of such tests is to create awareness, not apportion blame. Nonetheless, results are usually jarring for all participants, no matter their racial identity, many of whom will uncover negative racial biases of which they were unaware. Such individual assessments may contribute to addressing interpersonal racism as it triggers self-reflection. Further, a growing number of organizations offer training in understanding common behaviors associated with implicit bias, including microaggressions (see later) and inequitable hiring practices. Recognizing and undoing personal biases as pediatricians requires training to challenge existing thought processes and actions that are often difficult to see.

Pediatricians and other health workers have an entrusted role in families that requires a partnership. Recognizing the strengths of families and valuing their lived experiences of internalized and interpersonal racism as expertise fosters a more collaborative clinical interaction and relationship. This expertise cannot be readily captured by pedagogy or acquired by a pediatrician in training or clinical practice. Such an approach emphasizes respect for the expertise that caregivers bring to raising their child and begins with the presumption that caregivers want to do what is best for the child. By doing this, physicians can form a collaborative relationship, rather than one based on racial stereotypes and blame. Cultural competence is a widespread concept recognizing that *other cultures* exist that the dominant culture must learn to decode. In contrast, the concept of **cultural humility** , for which training is increasingly available, considers equality among cultures and a partnership approach to differences.

During clinical encounters with children and families, healthcare workers can use their authority to acknowledge racism. Pediatricians should broach “The Talk” with their patients who are black, young adolescent, and male. “The Talk” is the conversation that black parents typically initiate with their sons regarding interactions with police. In doing so, the pediatrician affirms the need for such conversations to promote safety and may provide opportunities to connect families to community resources. For all young children and youth of color, pediatricians should ask patients if they have they been treated unfairly because of their race, recognizing this can by a form of **bullying** . The experience of racism at all levels can be traumatic. Trauma consists of experiences or situations that are emotionally painful and distressing, and that overwhelm people's ability to cope, leaving them powerless. Pediatricians must consider adopting trauma-informed care practices that shift the paradigm from, “What is wrong with you?” to, “What has happened to you?”

In addition, healthcare providers must strive for **structural competency** , which is the “trained ability to discern how a host of issues defined clinically as symptoms, attitudes, or diseases also represent the downstream implications of a number of upstream decisions,” according to Johnathan M. Metzl and Helena Hansen. Consequently, it is helpful to ensure that clinical practices are aware of other social services that may enhance health and engagement with clinical care, such as need for legal counsel to address substandard housing, counter landlord harassment, or negotiate threatened evictions (http://medical-legalpartnership.org/), or the support of literacy by *prescribing* or distributing children's books in order to encourage parents to read to children (http://www.reachoutandread.org/).

Institutional Settings

The healthcare institution more broadly is also a setting where racial dynamics occur. Introducing conversations about race may uncover experiences that would not otherwise be apparent. A common outcome of implicit racial bias is **microaggressions** , actions and attitudes that may seem trivial or unimportant to the perpetrators but create a cumulative burden for those who perceive them. A physician of color might be asked for identification on entering a hospital, while white colleagues are not so queried. These microaggressions occur in interactions among staff as well with patients and may contribute to an unspoken and uncomfortable racial climate. While such interactions rarely would violate federal discrimination standards, interaction between co-workers shapes an entire practice and can be perceived by families.

Encouraging institutions to assess the impact of race among patients and staff is a first step. Healthcare delivery institutional settings can use both data and patient accounts to examine racial effects in the practice and experience by routinely disaggregating assessment measures by race/ethnicity. Patient-reported satisfaction or quality of care might be disaggregated by race. In addition, it is important to consider racial equity within the practice's employment structure: Are there discrepancies in hiring, retention, and salaries by race? Are there proper supervision and grievance procedures, particularly around issues related to racial microaggressions? Also, consider the images and language used to discuss and represent both patients and staff, particularly when alluding to race/ethnicity. Organizations such as **Race Forward** (https://www.raceforward.org) and organizational assessment tools developed by the **Race Matters Institute** can help to guide institutional assessments and internal change processes. Several local health departments have already incorporated antiracism training into staff professional development and introduced internal reforms to drive organizational change. Since institutional reform is closely associated with other models of productive practices, including quality improvement, collective impact, community engagement, and community mobilization, application of an antiracism lens should be judged by its contributions to organizational effectiveness as well as on its moral merits.

Education or training institutions have a special role in ensuring a workforce that is both diverse and informed. Patterns of student admissions should be scrutinized, as should the curriculum. Although many medical schools now include diversity training and provide instruction on cultural competency, such instruction is often brief (and sometimes delivered online). By contrast, approaches based on structural competency, cultural humility, and **cultural safety** have been implemented in health professionals' training in such countries as Canada and New Zealand. These approaches emphasize the value of gaining knowledge about structural racism, internalized scripts of racial superiority and inferiority, and the cultural and power contexts of health professionals and their patients or clients. Health professionals benefit from the scholarship of diverse disciplines about the origins and perpetuation of, as well as remedies to counter, racism. Finding class time for these topics encounters a *biomedical bias* that is widespread in medical education, although arguably successful medical practice also requires a host of skills in addition a firm grounding in pathophysiology and recommended treatments. Racism results in damaging disparities that cause ill health and shorten lives, which justifies the teaching hours committed to its understanding.

Pediatricians as Advocates for Antiracist Practices and Systems

Physicians are respected members of communities and wield the power, privilege, and responsibility for dismantling structural racism. A conceptual review of structural racism highlights the promise of place-based interventions that target geographically defined communities, to engage residents and a range of institutions (across sectors) in order to ensure equitable access to resources and services, remediating the processes set in motion decades earlier. Clinicians play a role in linking patients to services, programming, and other resources and advocating for responsiveness in addressing gaps. Over time, concentrated efforts across sectors in targeted areas have shown improvement in a host of social outcomes, including health outcomes. Similarly, providing access to higher-quality housing, either with housing vouchers or housing lotteries, had unexpected positive health impacts. These findings are encouraging, as are the social policy interventions and systemic change, including legislation such as the Civil Rights Act, the advent of Medicare and Medicaid, and tenement regulations, associated with the narrowing of racial gaps.

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CHAPTER 3

Global Child Health

Suzinne Pak-Gorstein

Global Burden and Trends in Child Health

The **under-five mortality rate (U5MR)** , also known as the **child mortality rate** , serves as a reliable gauge of child well-being. It measures the outcome of a country's health system and reflects a nation's social and economic development. The global U5MR fell by 53% between 1990 and 2015. Despite these gains, in 2016 an estimated 5.6 million children <5 yr old died worldwide, equivalent to *41 deaths per 1,000 live births*, or almost *15,000 child deaths each day* . The burden of the world's child mortality disproportionately falls on low- and middle-income regions of Africa and Asia (Fig. 3.1), with 86% of child deaths occurring in these regions and <1% in high-income countries. Consequently, a child born in sub-Saharan Africa is >15 times more likely to die by age 5 yr than a child born in a high-income country.

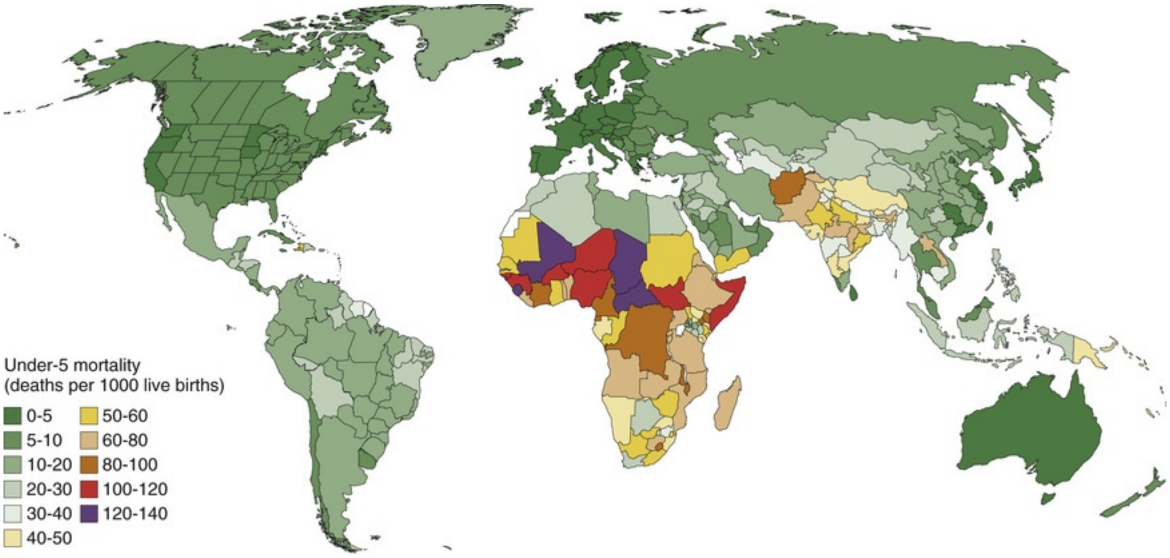

FIG. 3.1 Global under-five mortality rates, 2015. (Data from Global Burden of Disease 2016 Causes of Death Collaborators: Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016, *Lancet* 388:1151–1210, 2017.)

Improvements in child mortality have been uneven globally, regionally, and nationally. Rates of change in U5MR range from a decrease of 8.9% in the Maldives to an increase of 2.5% in Syria during 2000–2016. Significant disparities in child mortality persist and have become increasingly concentrated in specific regions of Africa and Asia, with one third of these deaths occurring in South Asia and half in sub-Saharan Africa.

While the number of child deaths has decreased dramatically over the past 2 decades, the early years of life remain one of a child's most vulnerable periods. Among the under-5 child deaths, almost half occurred within the 1st mo of life (2.7 million deaths in 2016). This estimate of **neonatal deaths** (<1 mo) translates into 19 per 1,000 live births. Declines in neonatal mortality occurred at slower rates, so that in 2015 the neonatal deaths made up 46% of all under-5 deaths (Fig. 3.2).

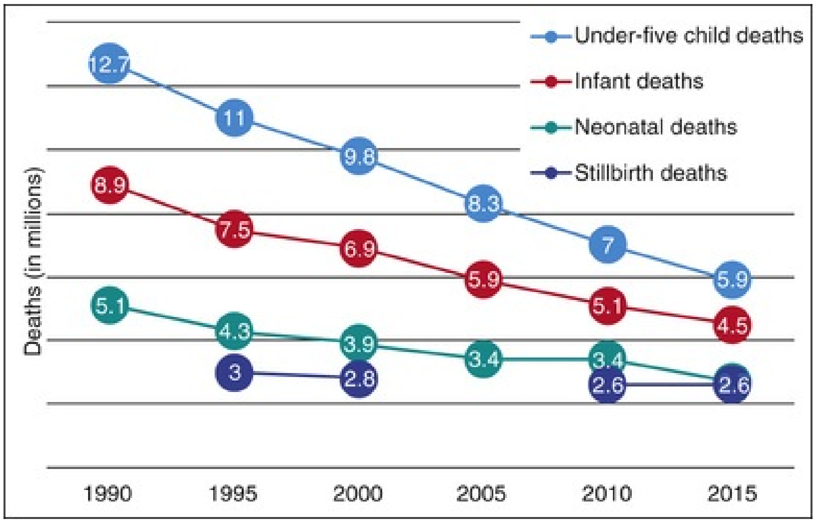

FIG. 3.2 Deaths for under-5 children, infants, neonates, and stillbirths, 1990–2015. (Adapted with data from United Nations Interagency Group for Child Mortality Estimation 2017. Stillbirth estimates for 1995 and 2009 from Cousens, 2011 [2010 rate from 2009]; 2000 rates from Lawn, 2012; and 2015 rate of 2.6 million from Blencow, 2016.)

Neonatal deaths account for a smaller percentage of child mortality in low- and middle-income countries compared to high-income countries (Fig. 3.3), but the absolute risk of death remains significantly higher. A child in sub-Saharan Africa or South Asia is 9 times more likely to die in the 1st mo of life than a child born in a high-income country.

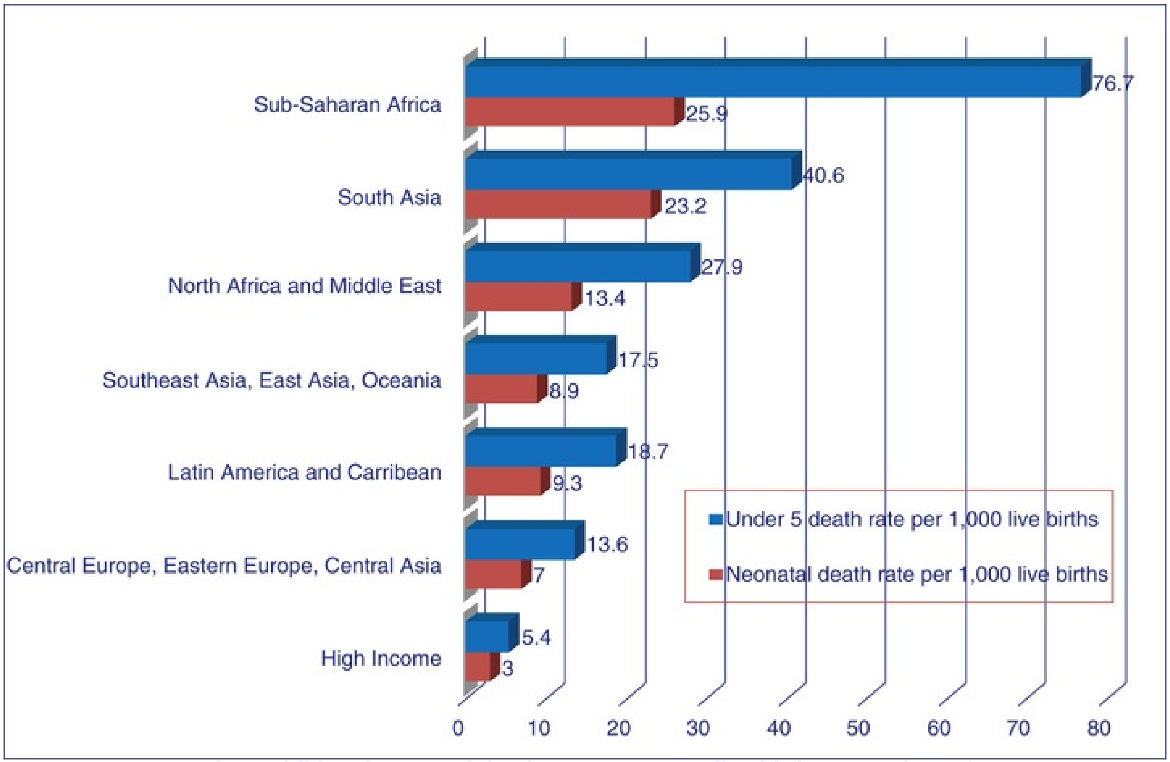

FIG. 3.3 **Under-5 child and neonatal death rates per 1,000 live births, 2016. (Data from Global Burden of Disease 2016: Global, regional, and national under-5 mortality, adult mortality, *Lancet* 390:1084–1150, 2017.)**

An estimated 1.7 million **stillborn** deaths (≥28 completed wk of gestation) burden families worldwide every year, which correlates to 13.1 deaths per 1,000 births. Global and national estimates of stillbirths vary widely because of inadequate data collection, reflecting the low prioritization of this vulnerable age-group. Progress to reduce stillbirth rates during the MDG era (UN Millennium Development Goals) has been slow, with the annual rate of reduction estimated to be half that for neonatal deaths between 2000 and 2015. Almost all stillbirths occur in low- and middle-income countries (98%), with three-quarters in sub-Saharan Africa and South Asia.

Most childhood deaths are caused by conditions that could be prevented or managed through improved access to simple, low-cost interventions. The most common causes of child death are *pneumonia* (13%), *diarrhea* (9%), and *malaria* (5%), which account for almost one third of all under-5 deaths and about 40% of under-5 deaths in sub-Saharan Africa (see Chapter 1 , Fig. 1.1). Neonatal deaths are caused by prematurity (16%), intrapartum-related complications such as birth asphyxia (11%), and neonatal sepsis (7%). In contrast, child deaths from infections in developed countries are less common, and injuries and congenital malformations account for higher proportions of under-5 deaths. **Undernutrition** , including fetal growth restriction, stunting and wasting, and micronutrient deficiencies, contributes up to 45% of under-5 deaths and leads to poor childhood development in low- and middle-income countries. Undernutrition has an enormous impact on child mortality because of the vicious cycle between nutrition and infection. Lowered immunity and mucosal damage from inadequate dietary intake leads to increased susceptibilty to pathogen invasion. Recurrent infections and immature microbiome impairs the child's ability to absorb nutrients.

Infants who start out life with a **low birthweight** (LBW) are at high risk of death, contributing 60–80% of all neonatal deaths. Most of these infants are premature (<37 wk of pregnancy) or had fetal growth restriction. About half of stillbirths take place during labor, ranging from 10.0% in developed regions to 59.3% in South Asia, which reflects the extent that timely, high-quality care at delivery can prevent many of these deaths.

Mortality among older children (5-14 yr) is low compared with the younger cohort, although 1 million children in this age-group died in 2016, equivalent to 3,000 children dying every day. Infectious diseases play a smaller role in deaths among these older children, with injuries from external causes such as drowning and motor vehicle crashes accounting for more than one quarter of the deaths and noncommunicable diseases for another quarter.

Child health should not be assessed based on mortality rates alone. Children surviving illness are often left with **lifelong disabilities** , burdening their families and impacting their economic productivity. Approximately 1 in 10 children are born with or acquire a disability, and 80% of these disabled children live in low- or middle-income countries. Neonatal disorders, infectious diseases, protein-energy and micronutrient deficiencies, hemoglobinopathies, and injuries are leading causes of disability in children. Child deaths can also lead to disability in the surviving mother. A woman who has a stillbirth is at risk of an obstetric fistula or death, with an estimated 78–98% of women with obstetric fistula having had a stillbirth. Also, perinatal loss with child death is a psychological trauma. Stillbirth, neonatal death, and child loss can lead to posttraumatic stress disorder, depression, anxiety, guilt, and in some settings, shame and social stigma, particularly in the mother, with significant impact on the health and well-being of the family.

Adolescents age 10-19 yr, who have benefited from the gains in child survival, grow up to find themselves in social settings where less attention and fewer resources are devoted to their well-being compared to their earlier years of growth. The paucity of support during this time of transition into adulthood diminishes the impact that child survival can have on their lives. Adolescents make up 18% of the world's population, approximately 1.8 billion in 2010, which is expected to increase to >2 billion by 2050. The vast majority of adolescents, 88%, live in low- and middle-income countries**.** In 2050, sub-Saharan Africa is projected to have more adolescents than any other region. While adolescent mortality rates are much lower than their younger-age cohorts, in low-income countries they face a lack of educational and employment opportunities, risk of injuries and violence, HIV/AIDS, mental health problems, marriage, and teenage pregnancy, preventing them from attaining their potential as they transition into adulthood. The decade of adolescence is a critical period when poverty and inequity frequently transfer to the next generation. The intergenerational transmission of poverty is most apparent among undereducated adolescent females. In many parts of the world, poor teenage females are likely to be married early, risking premature childbearing and higher rates of maternal mortality, and leading to infant and child undernutrition.

Social Determinants of Child Health

The gross national income level accounts for much of the difference in child mortality observed between countries, but other significant factors impact child health. Although the wealth of the United States places it in the 8th position with respect to gross domestic product (GDP) per capita (2016) in the world, the U.S. child mortality rate is ranked 56th in the world, at 5.8 deaths per 1,000 live births, which is higher than the United Kingdom (4.3), Cuba (4.4), Canada (4.5), Czech Republic (2.6), and Japan (2.0). *National estimates of mortality mask differences in health status among subpopulations within the same country.* In Burkina Faso the child mortality rate is 43.7/1,000 live births among children born to mothers with no education, whereas it is 16.7 per 1,000 among children born to mothers with at least secondary education. Similarly, in 2013, the infant mortality rate in the Dominican Republic was 14.0/1,000 live births for children in the highest wealth quintile, but 40.0/1,000 for children living in the lowest quintile.

Child health is influenced by socioeconomic factors that operate at multiple levels of the society. Disparities in these socioeconomic factors translate into child health inequities, as reflected by high rates of disease, poor nutrition, and disability. Fig. 3.4 outlines the immediate, underlying, and basic structural determinants of disease, malnutrition, and disability. Preventive and curative medical interventions focus on the immediate causes of poor health. However, inequities in child mortality and morbidity will persist unless the basic and underlying determinants of health are addressed.

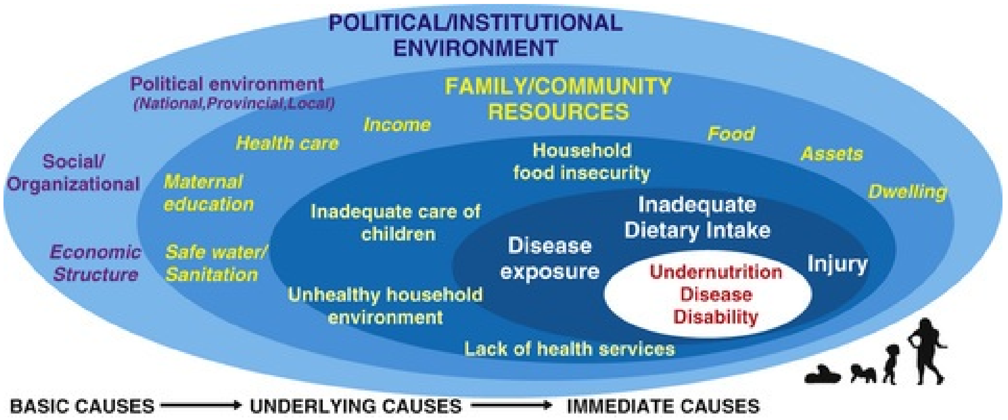
POLITICAL/INSTITUTIONAL ENVIRONMENT
Political environment (National,Provincial,Local)
Social/ Organizational
Economic Structure
FAMILY/COMMUNITY RESOURCES
Health care
Income
Food
Assets
Dwelling
Maternal education
Safe water/ Sanitation
Household food insecurity
Inadequate care of children
Inadequate Dietary Intake
Disease exposure
Injury
Undernutrition Disease Disability
Unhealthy household environment
Lack of health services
BASIC CAUSES → UNDERLYING CAUSES → IMMEDIATE CAUSES

FIG. 3.4 Socioecologic model: basic, underlying, and immediate determinants of child health. (Adapted with data from World Health Organization and Maternal and Child Epidemiology Estimation Group, 2017.)

Socioeconomic and Political Roots of Disparities in Global Health

The root causes of a child's health lie in the economic and political environments in which the child is born (Fig. 3.4). Growth of economies during the 1st half of the 20th century was associated with dramatic health improvements with falling mortality rates and rising life expectancy across all regions. However, the 2nd half observed significant disparities in global economies and health among and within many countries.

Between 1980 and 2016, the richest 1% of the world reaped twice as much of the world's income as the poorest 50% of the world (27% of income growth vs 12%) (World Inequality Report, 2018, http://wir2018.wid.world/). Almost all countries report income inequalities among its population, but a few countries, such as the United States, have seen income disparities at historical proportions (Fig. 3.5). Since 1980 the bottom half of Americans captured only 3% of the total growth. Growing income inequalities translates into greater differences in health outcomes, such as life expectancy, between the rich and the poor in the

United States (Fig. 3.6). More aggressive redistribution of wealth through taxes and transfers has spared Europe from such glaring disparities.

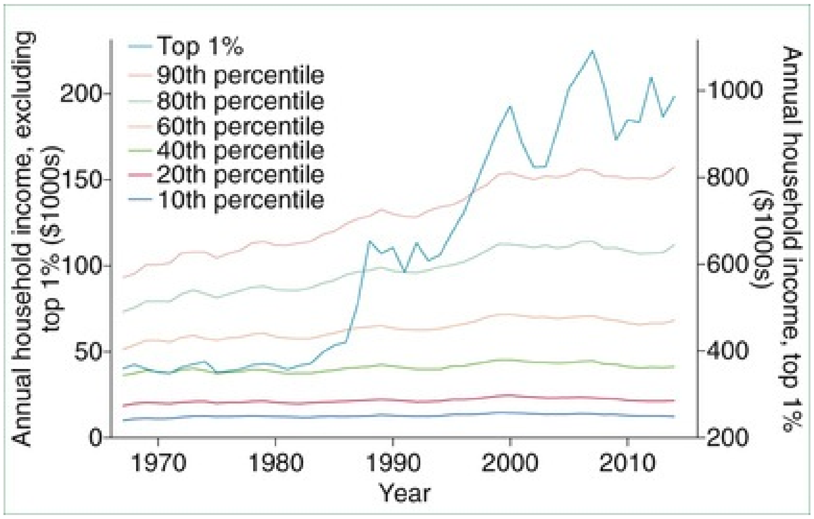

FIG. 3.5 Inflation-adjusted annual household income at selected percentiles, 1967–2014. All series show percentiles of the distribution except for top 1%, which shows the mean of the top 1%. All income series except for the top 1% are plotted against the left vertical axis, displaying incomes from $0 to $200,000. The top 1% is plotted against the right vertical axis, displaying incomes from $200,000 to $1,000,000. Income is expressed in 2014 US$. (Data from US Census Bureau Current Population Survey, 1968–2015, Annual Social and Economic Supplements and World Wealth and Income Database. From Bor J, Cohen GH, Galea S: Population health in an era of rising income inequality: USA, 1980–2015, *Lancet* 389:1475–1490, 2017, Fig 1.)

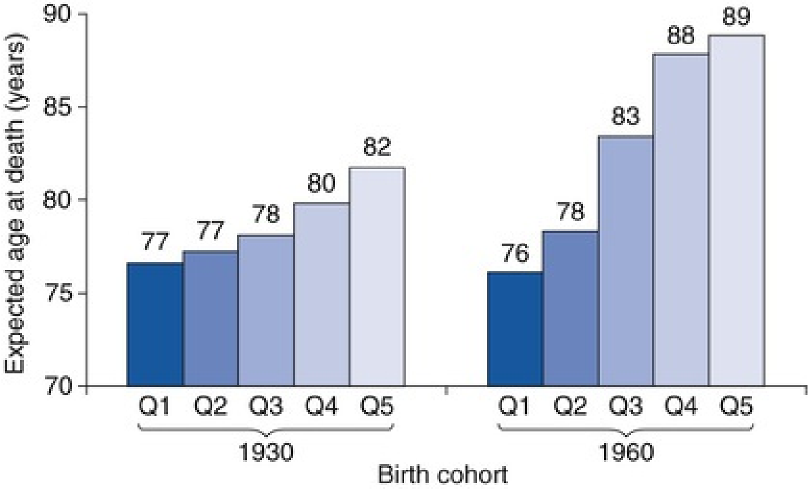

FIG. 3.6 Projected life expectancy for U.S. men at age 50 for 1930 and 1960 birth cohorts. By income quintile: Q1 (poorest) to Q5 (richest). (From Bor J, Cohen GH, Galea S: Population health in an era of rising income inequality: USA, 1980–2015, *Lancet*

389:1475–1490, 2017, Fig 5b; with data from National Academies of Sciences, Engineering, and Medicine: *The growing gap in life expectancy by income: implications for federal programs and policy responses,* Washington, DC, 2015, National Academies Press.)

Evidence supports that income inequality is not just a human rights issue, but also detrimental to economic growth. Wealthier households spend a smaller percentage of their own income, thereby dampening demand and slowing down economies. Poorer households face greater challenges to invest in health and educational opportunities, translating into less human capital, and obstacles to be productive and contribute to the economy. In extreme cases, inequalities can threaten social unrest, which further undermines economic activity.

Global disparities have grown between many wealthy and low-income countries, in large part from “austerity” measures, including structural adjustment programs, imposed on many postcolonial countries by the International Monetary Fund (IMF) and World Bank. In order to receive loans and pay off their debt, many of these countries were required to take on austerity measures that transformed their economies to produce cash crops and export natural resources to higher-income countries, rather than supporting local industries and investing in human capital and providing social services.

Foreign aid for healthcare programs has led to significant health improvements, with countries receiving more health aid demonstrating a more rapid rise in life expectancy and larger declines in child mortality than countries that received less health aid. National security concerns continue to drive U.S. assistance policy, which aims to reinforce ally countries, provide stability in conflict regions, promote democracy, and contribute to counterterrorism and law enforcement efforts abroad. Other goals, such as contributing humanitarian relief during natural disasters, poverty reduction, and health promotion, also drive assistance.

Sustainable Development Goals

The prioritization and planning of global development and international aid has been guided by international goals. In 2015, world leaders agreed to 17 goals, the **Sustainability Development Goals (SDGs)** , to improve global well-being by 2030 (Fig. 3.7). The SDGs were built on the eight **Millennium Development Goals (MDGs),** which were concrete, specific, and measurable targets set by the United Nations in 2000 to eradicate poverty, hunger, illiteracy, and disease by 2015. Significant, although uneven, progress had been made toward meeting the MDGs, falling short in improving the lives of the poorest and most disadvantaged countries, and bypassing social groups because of gender, age, disability, or ethnicity.

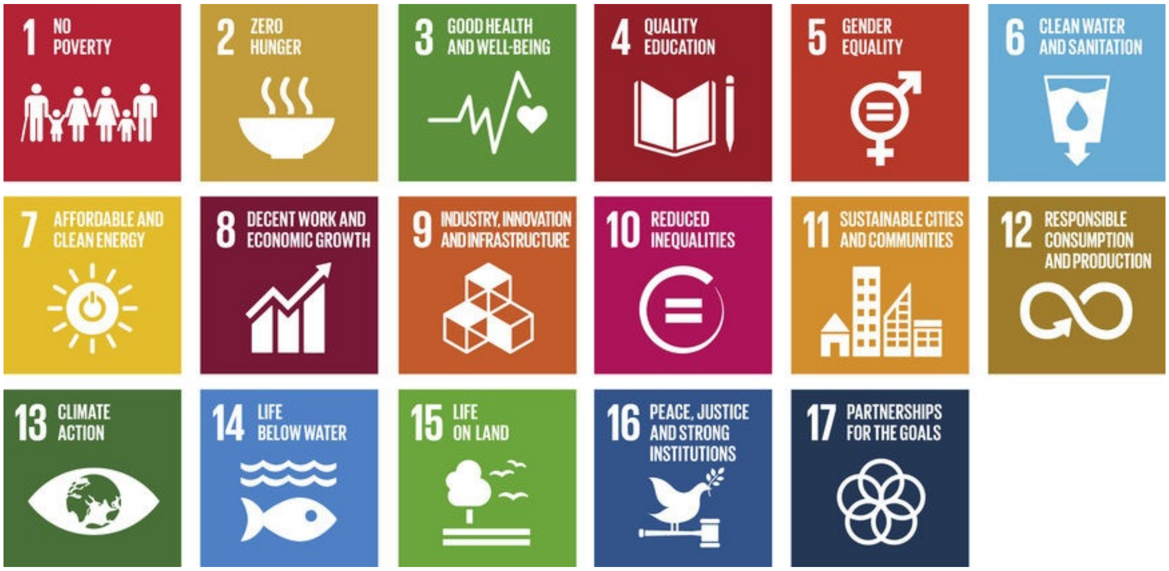
1 NO POVERTY
2 ZERO HUNGER
3 GOOD HEALTH AND WELL-BEING
4 QUALITY EDUCATION
5 GENDER EQUALITY
6 CLEAN WATER AND SANITATION
7 AFFORDABLE AND CLEAN ENERGY
8 DECENT WORK AND ECONOMIC GROWTH
9 INDUSTRY, INNOVATION AND INFRASTRUCTURE
10 REDUCED INEQUALITIES
11 SUSTAINABLE CITIES AND COMMUNITIES
12 RESPONSIBLE CONSUMPTION AND PRODUCTION
13 CLIMATE ACTION
14 LIFE BELOW WATER
15 LIFE ON LAND
16 PEACE, JUSTICE AND STRONG INSTITUTIONS
17 PARTNERSHIPS FOR THE GOALS

FIG. 3.7 Sustainable development goals (SDGs 1-17). (Courtesy United Nations Department of Public Information, 2016. http://www.un.org/sustainabledevelopment/sustainable-development-goals/)

Unlike the MDGs, in which health was prominently featured in 3 of the goals, the SDG-3 is the primary SDG that focuses on health-related subtargets, including the reduction of U5MR to 25 deaths per 1,000 live births and neonatal mortality rate to 12 deaths per 1,000 live births by 2030. The other 16 SDGs focus mainly on social and economic determinants and the environment. This reflects an important shift to broaden the global targets to include upstream determinants of health, including health systems and socioeconomic, gender-based, political, and environmental factors. As a social movement to support sustainable development, the SDGs were founded on the recognition that the world's environment, socioeconomic development, and human health are interconnected and dependent. Therefore the SDGs were formulated with core principles and values for **economic development, environmental sustainability**, and **social inclusion** for all.

The **Global Strategy for Women's, Children's and Adolescent's Health** 2016–2030 maps out the strategies to achieve the SDGs by centering on the goal of health for all women, children, and adolescents using evidence-based approaches, backed by innovative and sustainable financing mechanisms. An important component of the Global Strategy is the inclusion of adolescents as central to the 2030 Agenda for Sustainable Development. In alignment with the SDGs, the Global Strategy focuses on 3 pillars of action: (1) *ending preventable deaths* among women, children, and adolescents; (2) *ensuring their health and well-being* by ending malnutrition and ensuring access to family planning, reducing exposure to pollution, and achieving universal health coverage; and (3) *expanding enabling environments* by efforts such as eradicating extreme poverty, ensuring good-quality education, eliminating violence against women and girls, enhancing research and technologic capabilities, and encouraging innovation.

In addition to being much broader in scope, the Global Strategy focuses on *equity* in that the strategy is meant to apply to all people, including the marginalized and difficult-to-reach populations, in all situations, including during crisis. Thus, for example, health insurance coverage would not be assessed based simply on the national average of coverage, but also by how well the increases in coverage benefit *all* population groups, regardless of income or educational level.

Evidence-Based Interventions and Innovations to Address Child Health Inequities

Estimates indicate that most of the 5.6 million annual deaths in children <5 yr old could be averted by increasing coverage of proven low-cost interventions (Table 3.1). Childhood deaths from diarrheal illness and pneumonia can be prevented by simple measures such as vaccinations and exclusive breastfeeding until 6 mo of age. Deaths related to undernutrition, which predisposes children to infectious diseases, may be prevented by proper infant and young child feeding practices, micronutrient supplementation, and community-based screening and management of malnutrition.

Table 3.1

Essential Interventions Across the Continuum of Care to Improve Child Survival

HEALTH AND MULTISECTOR ACTIONS	
• Ensuring food security for the family (or mother and child) • Maternal education • Safe drinking water and sanitation • Handwashing with soap • Reduced household air pollution • Health education in schools	
AGE-SPECIFIC ACTIONS	
Prevention	**Treatment**
ADOLESCENCE AND PRE-PREGNANCY	
• Family planning • Preconception care	
PREGNANCY	
• Appropriate care for normal and high-risk pregnancies (maternal tetanus vaccination)	• Antenatal steroids for premature births • Intermittent preventive treatment for malaria
CHILDBIRTH	
• Maternal intrapartum care and monitoring	

• Skilled delivery
  • Thermal care for all newborns
  • Clean cord and skin care
  • Early initiation and exclusive breastfeeding within 1st hr
	• Newborn resuscitation (e.g., Healthy Babies Breathe)
	• Premature: surfactant administration, continuous positive airway pressure (CPAP), treatment of jaundice
	• Feeding support for small/preterm infants

PRENATAL PERIOD	
• Appropriate postnatal visits	• Extra care for small and sick babies (kangaroo mother care, treatment of infection, support for feeding, management of respiratory complications) • Antibiotics for newborns at risk and for treatment of bacterial infections (PROM, sepsis, meningitis, pneumonia)
INFANCY AND CHILDHOOD	
• Exclusive breastfeeding for 6 mo and continued breastfeeding up to at least 2 yr with appropriate complementary feeding from 6 mo	
• Monitoring and care for child growth and development • Routine immunization childhood diseases • Micronutrient supplementation, including vitamin A from 6 mo	• Case management of severe acute malnutrition

• Prevention of childhood diseases
  • Malaria (insecticide-treated bed nets)
  • Pneumonia
  • Diarrhea (rotavirus immunization)
  • Meningitis (meningococcal/Hib/pneumococcal vaccination)
  • Measles (vaccination)
• Prevention of mother-to-child HIV transmission
	• Management of childhood diseases
	  • Malaria (antimalarials)
	  • Pneumonia (case management, antibiotics)
	  • Diarrhea (ORS, zinc supplement, continued feeding)
	  • Meningitis (case management, antibiotics)
	  • Measles (vitamin A suppl)
	• Comprehensive care of children exposed to or infected with HIV (HAART)

HAART, Highly active antiretroviral therapy; ORS, oral rehydration solution (salts).

Adapted from Were W, Daelmans B, Bhutta ZA, et al. Children's health priorities and interventions, *BMJ* 351:h4300, 2015.

Addressing the SDGs to improve health of mothers, children, and adolescents takes a life course approach. Fig. 3.8 displays estimates of coverage for essential interventions across the continuum of care, indicating the wide range of coverage rates within countries that will need to be addressed if SDGs are to be attained.

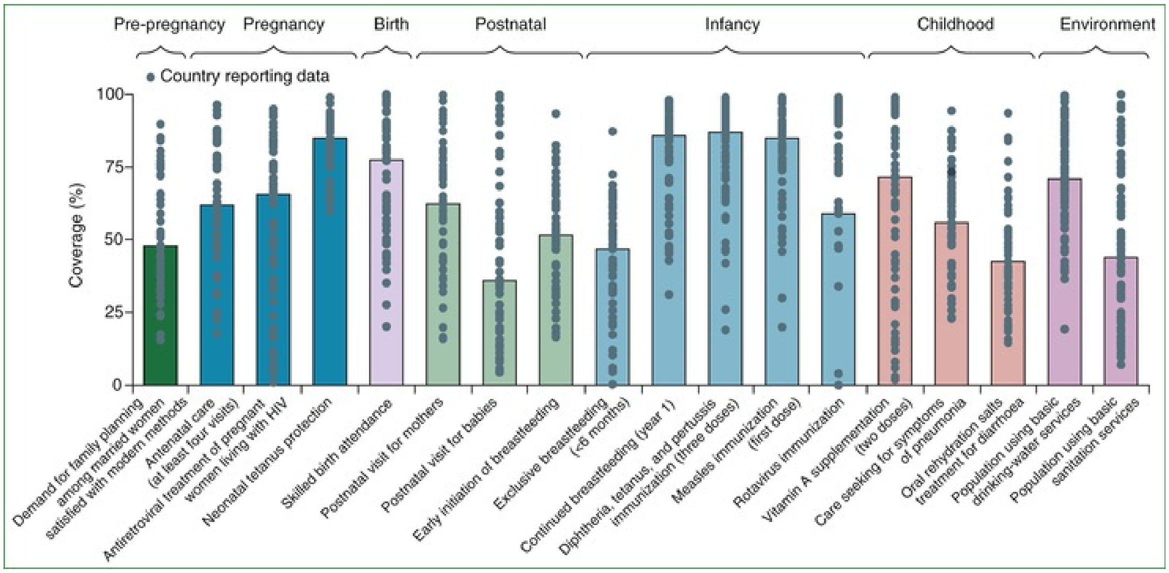

FIG. 3.8 Coverage of interventions across the continuum of care based on the most recent data since 2012 in Countdown countries. *Bars* show median national coverage of interventions; *dots* show country-specific data. (From Countdown to 2030 Collaboration: Tracking progress towards universal coverage for reproductive, maternal, newborn, and child health, *Lancet* 391:1538-1548, 2018. Fig 1.)

Vaccine-Preventable Diseases

In 2002 an estimated 1.5 million under-5 deaths were caused by vaccine-preventable diseases. Top contributors were pneumococcus and rotavirus, followed by *Haemophilus influenzae* B (Hib), measles, pertussis, and tetanus. The World Health Organization (WHO) **Expanded Program on Immunization** (EPI) has resulted in a dramatic reduction in deaths, illness, and disability from many of these diseases, as well as the near-elimination of poliomyelitis. Recommendations for routine immunizations have continued to grow with the development of new vaccines that have demonstrated significant lifesaving potential in industrialized countries (Table 3.2).

Table 3.2

Routine Immunizations Recommended by the World Health

Organization (2017)

VACCINE (ANTIGEN)	AGE AT 1st DOSE	DOSES IN PRIMARY SERIES	INTERVAL BETWEEN DOSES			BOOSTER DOSE	ADOLESCENT
			1st to 2nd	2nd to 3rd	3rd to 4th		
BCG (bacille Calmette-Guérin)	Birth	1					
Hepatitis B	Birth	3 (or 4)	4 wk w/ DTP2	4 wk w/ DTP3	(or 4 wk)		3 doses for high-risk groups if not previously immunized
OPV (oral polio vaccine)	bOPV + IPV IPV/bOPV IPV	4 1-2 IPV/2 bOPV 3	4 wk w/ DTP2 4-8 wk 4-8 wk	4 wk w/ DTP3 4-8 wk 4-8 wk	4-8 wk		
DTP (diphtheria, tetanus, and pertussis)	6 wk	3	4-8 wk	4-8 wk		3 boosters: 12-23 mo; 4-7 yr (Td); and 9-15 yr Td)	1 booster: 9-15 yr (Td)
Hib (*Haemophilus*	6 wk-59 mo	3 2-3	4 wk w/	4 wk w/		At least 6 mo after	

influenzae B)			DTP2 8 wk if only 2 doses 4 wk if 3 doses	DTP3 4 wk if 3 doses		last dose		
Pneumococcus (PCV10 or 13)	6 wk 6 wk	3 2-3	4 wk 8 wk	4 wk		Yes, if not given at 10 wk 9-15 mo		
Rotavirus	6 wk w/ DTP1 6 wk w/ DTP1	Rotarix: 6 wk w/ DTP1 Rota Teq: 6 wk w/ DTP1	4 wk w/ DTP2 4-10 wk w/ DTP2	4 wk w/ DTP3				
Measles	9 or 12 mo	2	4 wk					
Rubella	9 or 12 mo (w/ measles-containing vaccines)	1					1 dose (adolescent girls and/or childbearing-age women, if not previously vaccinated)	
HPV	9 yr (female)	2	6 mo				2 doses (female)	

CRS, Congenital rubella syndrome; IPV, inactivated polio vaccine; TB, tuberculosis.

Adapted from WHO Routine Guidelines for Immunization. http://www.who.int/immunization/policy/Immunization_routine_table2.pdf?ua=1 .

In 2015, 86% of the world's infants were vaccinated with 3 doses of diphtheria-tetanus-pertussis (DTP). Although vaccines are very effective in improving child survival, rates of coverage are low in many countries. In 2016 a total of 19.5 million children did not receive all routine lifesaving vaccinations, and 90,000 deaths were reported from measles. Although coverage rates are still improving, and lifesaving vaccines are still not available in many countries, progress has been made to expand availability to new countries every year. The lowest number of wild poliovirus cases (37) was reported in 2016.

Reaching Every Child, Everywhere

Global vaccine organizations aim for universal coverage of immunizations but face challenges within countries to attain this goal. Other lifesaving interventions have met barriers to attain universal coverage. Oral rehydration therapy (ORT) has been the evidence-based intervention recommended to prevent dehydration from diarrheal disease since the 1970s, yet only 2 in 5 children <5 yr with diarrheal illness receive this treatment. Many factors determine whether a child receives a lifesaving intervention. Characteristics of the healthcare system, social attitudes and practices, and the political climate impact whether universal coverage can be reached for evidence-based essential interventions. Innovations to strengthen vaccine coverage to reach every child in every district of a country range from programs such as **Reaching Every Child through Quality Improvement** (REC-QI) using community mapping techniques, to integrating service delivery mechanisms and strengthening the health system with improved surveillance.

Effective Delivery Strategies: Integrated Management of Childhood Illness

Weak health systems impede the ability of countries to deliver cost-effective interventions and lifesaving health messages for children. Such systems are characterized by insufficient numbers of health workers, low-quality training and supervision, and poorly functioning supply chains. The provision of child health services may focus on a single level, such as the health facility, but effective and lasting improvements can only be achieved with the integration of delivery at all levels, such as adequate referrals and follow-up between community, clinic, and health facility. Other important lifesaving strategies include outreach services (e.g., mass immunization, vitamin A campaigns) and community-based health promotion activities (Fig. 3.9).

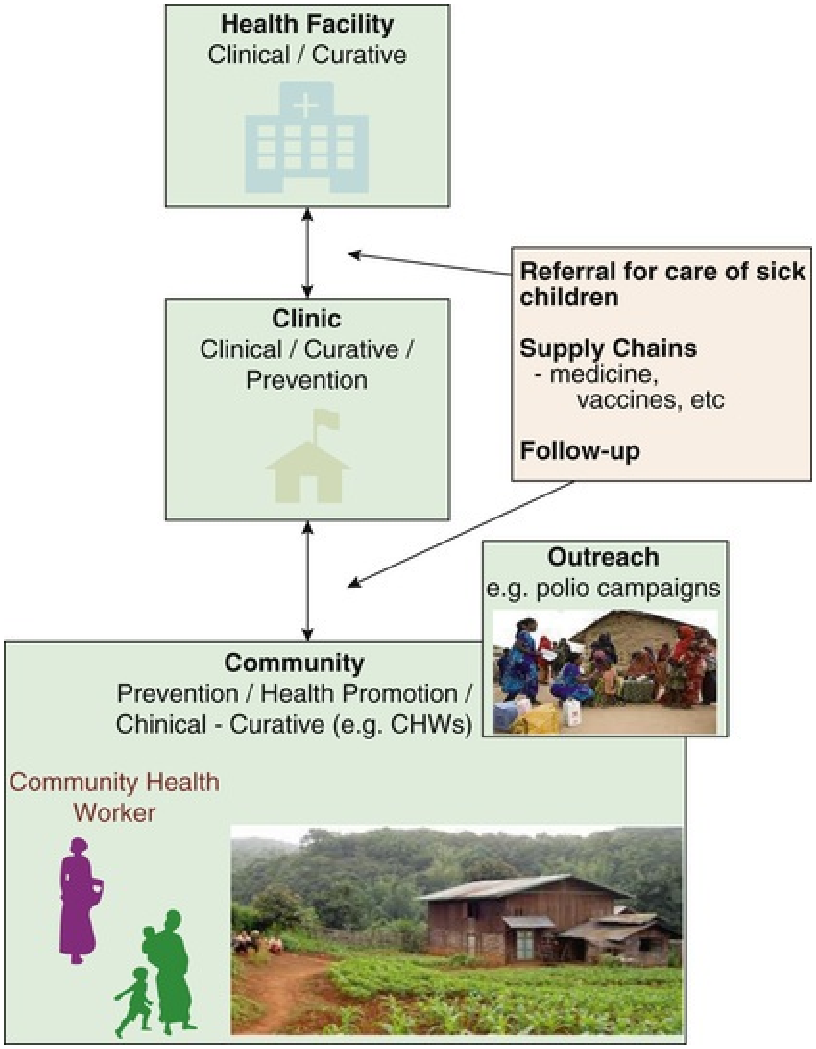
Health Facility
Clinical / Curative
Referral for care of sick children
Supply Chains
- medicine, vaccines, etc
Follow-up
Clinic
Clinical / Curative / Prevention
Outreach
e.g. polio campaigns
Community
Prevention / Health Promotion / Chinical - Curative (e.g. CHWs)
Community Health Worker

FIG. 3.9 **Health services delivery systems.**

The **Integrated Management of Childhood Illnesses** (IMCI) was launched in the mid-1990s by the United Nations Children's Fund (UNICEF) and WHO as an approach to reduce child mortality, illness, and disability and to promote improved growth and development in countries struggling with high child mortality rates. The IMCI was designed to increase coverage of evidence-based, high-impact interventions that address the top causes of child mortality by integrating health promotion, illness prevention, and disease treatment. The IMCI contains both preventive and curative elements, set forth through a series of clinical algorithms and guidelines for case management (see Fig. 3.10 for an example) and implemented by health care workers in collaboration with families and communities. One key component of the IMCI strategy involves training frontline healthcare workers to use the algorithms to identify signs of common childhood illness and to decide when a child needs referral to a hospital. In early 2003, guidelines for newborn care were added to create the **Integrated Management of Neonatal and Childhood Illnesses** (IMNCI).

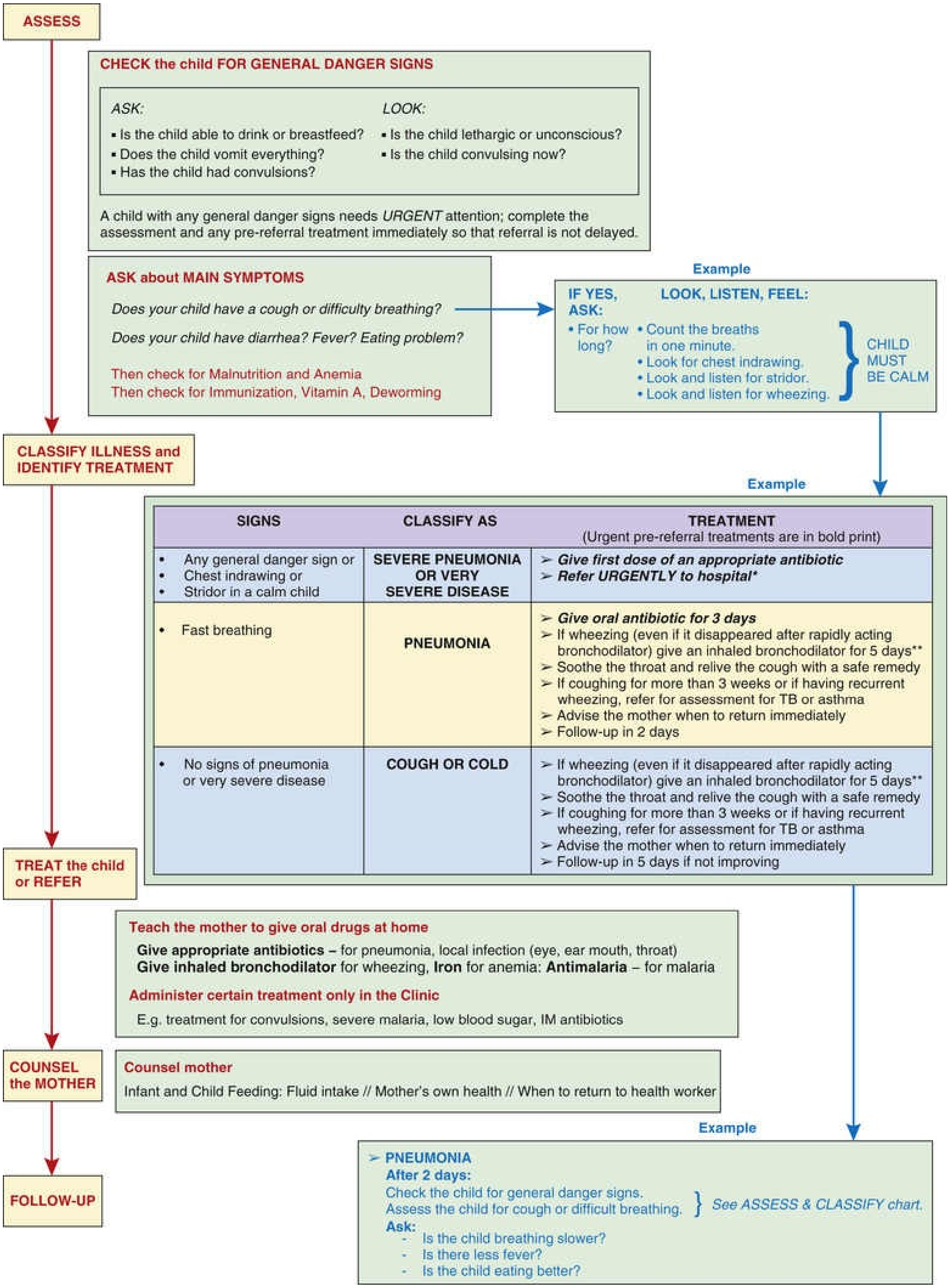

CHECK the child FOR GENERAL DANGER SIGNS

ASK:

- Is the child able to drink or breastfeed?
- Does the child vomit everything?
- Has the child had convulsions?

LOOK:

- Is the child lethargic or unconscious?
- Is the child convulsing now?

A child with any general danger signs needs *URGENT* attention; complete the assessment and any pre-referral treatment immediately so that referral is not delayed.

ASK about MAIN SYMPTOMS

Does your child have a cough or difficulty breathing?

Does your child have diarrhea? Fever? Eating problem?

Then check for Malnutrition and Anemia
Then check for Immunization, Vitamin A, Deworming

IF YES, ASK:

- For how long?

LOOK, LISTEN, FEEL:

- Count the breaths in one minute.
- Look for chest indrawing.
- Look and listen for stridor.
- Look and listen for wheezing.

} CHILD MUST BE CALM

SIGNS	CLASSIFY AS	TREATMENT (Urgent pre-referral treatments are in bold print)
• Any general danger sign or • Chest indrawing or • Stridor in a calm child	**SEVERE PNEUMONIA OR VERY SEVERE DISEASE**	➢ ***Give first dose of an appropriate antibiotic*** ➢ ***Refer URGENTLY to hospital****
• Fast breathing	**PNEUMONIA**	➢ ***Give oral antibiotic for 3 days*** ➢ If wheezing (even if it disappeared after rapidly acting bronchodilator) give an inhaled bronchodilator for 5 days** ➢ Soothe the throat and relive the cough with a safe remedy ➢ If coughing for more than 3 weeks or if having recurrent wheezing, refer for assessment for TB or asthma ➢ Advise the mother when to return immediately ➢ Follow-up in 2 days
• No signs of pneumonia or very severe disease	**COUGH OR COLD**	➢ If wheezing (even if it disappeared after rapidly acting bronchodilator) give an inhaled bronchodilator for 5 days** ➢ Soothe the throat and relive the cough with a safe remedy ➢ If coughing for more than 3 weeks or if having recurrent wheezing, refer for assessment for TB or asthma ➢ Advise the mother when to return immediately ➢ Follow-up in 5 days if not improving

Teach the mother to give oral drugs at home

Give appropriate antibiotics – for pneumonia, local infection (eye, ear mouth, throat)
Give inhaled bronchodilator for wheezing, **Iron** for anemia: **Antimalaria** – for malaria

Administer certain treatment only in the Clinic

E.g. treatment for convulsions, severe malaria, low blood sugar, IM antibiotics

Counsel mother

Infant and Child Feeding: Fluid intake // Mother's own health // When to return to health worker

➢ **PNEUMONIA**
After 2 days:
Check the child for general danger signs.
Assess the child for cough or difficult breathing.
} *See ASSESS & CLASSIFY chart.*
Ask:
- Is the child breathing slower?
- Is there less fever?
- Is the child eating better?

FIG. 3.10 Integrated Management of Childhood Illness (IMCI). (Adapted from WHO 2014. Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries; and WHO 2008. Integrated Management of Childhood

Illness Booklet
http://apps.who.int/iris/bitstream/handle/10665/43993/9789241597289_eng.pdf;jsessionid=43EF43A92
sequence=1)

As facility-based services alone do not provide adequate access to timely treatment of childhood illnesses, in early 2000 the **Integrated Community Case Management (i-CCM)** was implemented to train community health workers to instruct parents on home management of ill children, including ORS and zinc for diarrhea, antimalarial medicine for febrile children who test positive for malaria, and antibiotics for children with signs of pneumonia. **Community health workers** (CHWs) are members of communities that have selected them to provide basic health care with support and training from the health system. CHWs carry out health promotional activities such as promotion of proper infant and young child feeding, hand-hygiene practices, and use of bed nets. The i-CCM strategy involved training CHWs to screen and manage diseases, including mild to moderate cases of undernutrition, diarrheal disease, and pneumonia. CHWs schedule follow-up visits for ill children managed in the community, and refer serious cases in a timely manner to healthcare facilities. Community-based interventions are effective in extending healthcare delivery, are low cost, improve healthcare-seeking behavior, and can reduce infant and child mortality and morbidity.

Over 100 countries have adopted IMNCI and implement some or all of its components, not only improving health workers' skills but also strengthening health systems and improving family and community practices. After 20 yr of implementation, a review noted that IMNCI was associated with a 15% reduction in child mortality when activities were properly implemented in health facilities and communities. However, the implementation of IMNCI was found to be uneven between and within countries. In many countries the resources for CHW training and supervision, supply of medications, and referrals were limited or absent. IMNCI was only successful in countries with strong government leadership and a commitment to implement IMNCI in partnership with support groups such as UNICEF and WHO. In addition, the success of IMNCI required an adequate health system and a systematic approach to planning and implementation.

Social Protection Programs: Conditional and Unconditional Cash Transfers

Financial incentives are becoming widely used to improve healthcare coverage, alleviate poverty, and improve access to child health services. In industrialized countries, **cash transfers** is a common mechanism for ensuring that the poorest, most marginalized subgroups of the population, particularly with children, receive adequate support to meet their basic needs. Cash transfer programs are increasingly being used in low- and middle-income countries to support vulnerable populations.

Out-of-pocket expenses by households form the major share of total health expenditure in most low- and middle-income countries. Many social protection programs work to serve a dual purpose of reducing financial barriers and strengthening service delivery. Financial incentives may include cash transfers, microcredit, vouchers, and user fee removal and health insurance. Financial incentive programs may be unconditional, provided to eligible families without any requirements or expectations, based on the belief that families will use this type of financial support for their children's best interests. Other incentives are conditional on health promotion behavior targeting child health, such as providing cash or vouchers only to families who participate in preventive health behaviors, such as attending mother groups to learn about breastfeeding practices, visiting clinics for child vaccinations and growth monitoring, engaging in deworming, and ensuring their children receive vitamin A and iron supplementation. Some social protection programs are also directed toward education improvement by making cash transfers conditional on child school enrollment, attendance, and occasionally some measure of academic performance.

Challenges in Global Health

Adolescent Health

The Global Strategy, which directs countries to attain their SDGs, has called on nations to focus efforts to support adolescent health given their potential role in breaking the *intergenerational cycle* of poverty. The challenge to attain these health goals will be to effectively advocate governments to invest in this age-group as a means to improve the national productivity and economy. Considerable gaps in data on adolescents pose one of the greatest challenges to promoting their health and their rights.

Strategies to address the unmet needs of adolescent health efforts must highlight improving completion of secondary school education, particularly among females. The development of adolescents' capacities and values through education can empower an entire generation to become economically independent, positive contributors to society and break the cycle of poverty.

Other threats to adolescent health include mental health, substance abuse, sexual and reproductive health, and noncommunicable diseases (NCDs), such as obesity, which vary depending on country type (Fig. 3.11). A common theme for these threats is that interventions to combat these issues must attempt to influence individual behavior and attitudes while promoting healthy lifestyles. It is estimated that 20% of the world's adolescents have a mental health or behavioral problem. **Depression** is the single largest contributor to the global burden of disease for individuals age 15-19, and **suicide** is 1 of the 3 leading causes of mortality among people age 15-35. Efforts to tackle these problems will require an interdisciplinary approach, with more research needed to identify and evaluate interventions and effectively influence adolescent behavior in low- and middle-income countries.

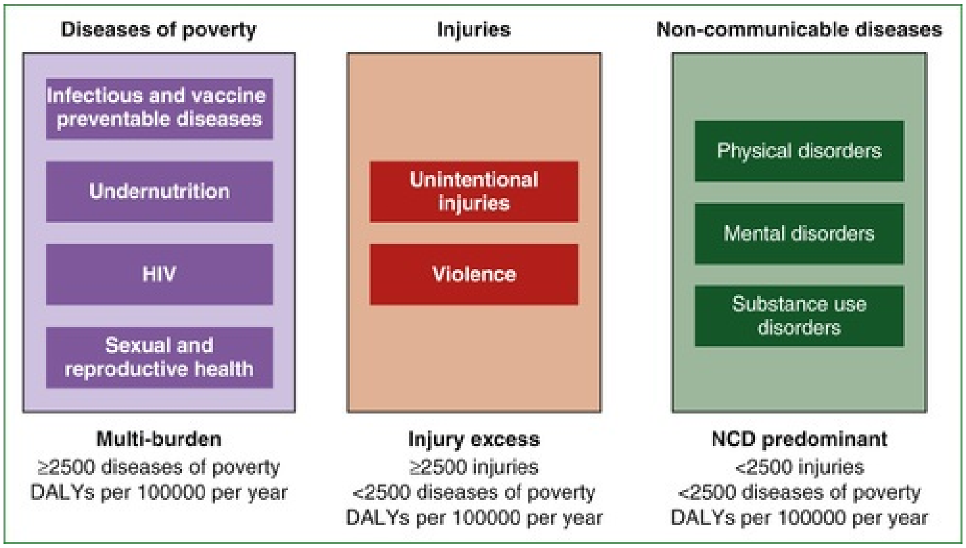
Diseases of poverty
Infectious and vaccine preventable diseases
Undernutrition
HIV
Sexual and reproductive health
Multi-burden
≥2500 diseases of poverty DALYs per 100000 per year
Injuries
Unintentional injuries
Violence
Injury excess
≥2500 injuries
<2500 diseases of poverty
DALYs per 100000 per year
Non-communicable diseases
Physical disorders
Mental disorders
Substance use disorders
NCD predominant
<2500 injuries
<2500 diseases of poverty
DALYs per 100000 per year

FIG. 3.11 Country categorization based on adolescent burden of disease. Categorization into 3 groups according to adolescent burden of disease and reflecting passage through epidemiologic transition. DALYs, Disability-adjusted life-years; HIV, human immunodeficiency virus; NCD, noncommunicable diseases. (From Patton GC, Sawyer SM, Santelli JS, et al: Our future: a Lancet commission on adolescent health and wellbeing, Lancet 387:2423–2478, 2016, Fig 7.)

Global Climate Change

Global climate change is currently the most urgent and alarming challenge to the environment. Contributing to environmental degradation, the loss of natural resources and change in climate undermine food and water sources. Climate change and increased frequency and severity of humanitarian crises adversely impact children health and nutrition, as well as threaten their education and development by disrupting school and home.

Conflict, Emergency Situations, and Migration

During times of crisis, children and adolescents are most vulnerable. Although the youngest are most likely to perish from disease or injuries, all children suffer as a result of food shortages, poor water and sanitation, interrupted education, and family separation or displacement. Approximately 214 million migrants live outside their countries of birth, which includes 33 million young children and adolescents under age 20 who have migrated either with their parents or unaccompanied. Many other children are directly or indirectly affected by migration, by parental separation, from deportation, or emigration.

Children and adolescents crossing borders may not be entitled to the same protection and rights as those who reside in a given country, leaving them at greater risk of discrimination and exploitation. A *rights-based* approach to migration is required to reinforce the steady buildup of national and international support. This approach must also address the root causes of migration (e.g., instability, inequality, discrimination, poverty) in the country of origin and should incorporate policies specifically targeted for young children and adolescents, girls and young women, and vulnerable populations, including those left behind when family members migrate.

Information and Communications Technology

Social network sites, mobile phones, programmers, and other stakeholders are implementing methods to appeal to youth in middle-income countries, harnessing this technology and their attention to increase awareness and build health skills. Parents and educators raise concern about the well-being and safety of children and adolescents who use these tools. The exposure to the immense amount of information on the internet places their privacy and psychological well-being at risk, since adults have not caught up to fully understand the implications.

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CHAPTER 4

Quality and Value in Healthcare for Children

Jeffrey M. Simmons, Samir S. Shah

The Need for Improvement in Quality and Value

Adults and children only receive recommended evidence-based care about half the time. The gap between knowledge and practice widens to a *chasm* in part because of variations in practice and disparities in care from doctor to doctor, institution to institution, geographic region to geographic region, and socioeconomic group to socioeconomic group. Furthermore, it is estimated that it takes about 17 yr for new knowledge to be adopted into clinical practice.

In addition to appropriate care that patients do not receive, U.S. healthcare systems also deliver much care that is unnecessary and waste many resources in doing so. This overuse and waste is one **key driver** of the disproportionate costs of care in the United States compared with other developed countries' delivery systems (in 2016, the United States spent about twice as much per capita, adjusting for gross domestic product (GDP), on healthcare compared to the average of peer wealthy nations). It is estimated that more than one quarter of all U.S. healthcare spending is waste. Gaps in appropriate care, combined with overuse and high costs, have driven conversations about the need to improve the value of care, which would mean better quality at lower overall costs. **Choosing Wisely** , an initiative initially sponsored by the American Board of Internal Medicine and subsequently endorsed by the American Academy of Pediatrics (AAP), asked medical societies to identify practices typically overused that clinicians could then make collective efforts to address.

Quality improvement (QI) science has become a predominant method utilized to close gaps and improve value. Initially focused on improving performance and reliability in care processes, more recently, in part inspired by the Institute for Healthcare Improvement's **Triple Aim** approach, QI is being used to improve value for *populations* of patients by focusing more on *outcomes* defined by patients' needs. The **Quadruple Aim** approach adds the 4th dimension of healthcare worker experience or *joy in work* to focus delivery systems on the need to enhance the resiliency of the clinical workforce in order to sustain high-value care approaches.

What Is Quality?

The Institute of Medicine (IOM) defines *quality* of healthcare as "the degree to which healthcare services for individuals and populations increases the likelihood of desired health outcomes and are consistent with current professional knowledge." This definition incorporates 2 key concepts related to healthcare quality: the direct relationship between the provision of healthcare services and health outcomes, and the need for healthcare services to be based on current evidence.

To measure healthcare quality, the IOM has identified *Six Dimensions of Quality* : **effectiveness** , **efficiency** , **equity** , **timeliness** , **patient safety** , and **patient-centered care** . Quality of care needs to be *effective,* which means that healthcare services should result in benefits and outcomes. Healthcare services also need to be *efficient,* which incorporates the idea of avoiding waste and improving system cost efficiencies. Healthcare quality should improve *patient safety* , which incorporates the concept of patient safety as 1 of the key elements in the Six Dimensions of Quality. Healthcare quality must be *timely* , thus incorporating the need for appropriate access to care (see Chapter 5). Healthcare quality should be *equitable* , which highlights the importance of minimizing variations as a result of ethnicity, gender, geographic location, and socioeconomic status (SES). Healthcare quality should be *patient centered ,* which underscores the importance of identifying and incorporating individual patient needs, preferences, and values in clinical decision-making. In pediatrics, the patient-centered dimension extends to family-centeredness, so that the needs, preferences, and values of parents and other child caregivers are considered in care decisions and system design.

The IOM framework emphasizes the concept that all Six Dimensions of Quality need to be met for the provision of *high-quality* healthcare. Collectively, these concepts represent *quality* in the overall *value* proposition of quality per cost. From the standpoint of the practicing physician, these 6 dimensions can be categorized into *clinical quality* and *operational quality* . To provide high-quality care to children, both aspects of quality—clinical and operational—must be met. Historically, physicians have viewed quality to be limited in scope to clinical quality, with the goal of improving clinical outcomes, while considering improving efficiency and patient access to healthcare as the role of healthcare plans, hospitals, and insurers. Healthcare organizations, which are subject to regular accreditation requirements, viewed the practice of clinical care delivery as the responsibility of physicians and limited their efforts to improve quality largely to process improvement to enhance efficiencies.

The evolving healthcare system requires physicians, healthcare providers, hospitals, and healthcare organizations to partner together and with patients to define, measure, and improve the overall quality of care delivered. Concrete examples of the evolving U.S. perspective include the widespread adoption of **Maintenance of Certification** (MOC) requirements by medical-certifying bodies, which require providers to engage in activities that improve care in their practices, and the core quality measurement features and population health incentives of the **Patient Protection and Affordable Care Act (ACA)** of 2010. The ACA also established the **Patient-Centered Outcomes Research Institute (PCORI)** to develop a portfolio of effectiveness and implementation research that requires direct engagement of patients and families to partner in setting research priorities, formulating research questions, and designing studies that will directly impact the needs of patients to improve the value of the research.

Framework for Quality

Quality is broader in scope than QI. The approach to quality includes 4 building blocks. *First* , the **standard for quality** must be defined (i.e., developing evidence-based guidelines, best practices, or policies that guide the clinician for the specific clinical situation). These guidelines should change based on new evidence. In 2000–2001 the AAP had published guidelines for care of children with attention-deficit/hyperactivity disorder (ADHD). Subsequently, in 2011, these were updated to highlight a greater emphasis on *behavioral interventions* rather than pharmacologic options based on new evidence. Similarly, the AAP has emphasized that guidelines evolve to include greater consideration of value in care, an example being the update to the clinical practice guideline for urinary tract infection in 2011, which called for a decrease in the use of screening radiologic tests and prophylactic antibiotics in certain populations of children due to a lack of cost-effectiveness. *Second* , **gaps in quality** need to be closed. One key gap is the difference between the recommended care and the actual care delivered to a patient. *Third* , quality needs to be **measured** . Quality measures can be developed as measures for accountability and measures for improvement. Accountability measures are developed with a high level of demonstrated rigor because these are used for measuring and comparing the quality of care at the state, regional, or health system (macro) level. Often, accountability measures are linked to **pay-for-performance (P4P)** incentive arrangements for enhanced reimbursement at the hospital and individual physician level. In contrast, improvement measures are metrics that can demonstrate the improvement accompanying a discrete QI project or program. These metrics need to be locally relevant, nimble, and typically have not had rigorous field testing. *Fourth* , the quality measurement approach should be used to **advocate** for providers and patients. For providers, meeting quality goals should be a key aspect of reimbursement if the system is designed to incentivize high-value care. At the population level, quality measurement strategies should advocate for preventive and early childhood healthcare, improving the value of care by decreasing costs across a patient's life span.

Lastly, many quality measurement systems have attempted to be more transparent with clinicians and patients about **costs** of care. Because more direct costs have been shifted to patients and families through widespread adoption of high-deductible insurance plans (i.e., families experience lower up-front insurance coverage costs but pay for certain acute healthcare expenses out-of-pocket until the preset deductible is met), better awareness of costs has become a more effective driver of improvement in value, in part by reducing overuse.

Developing Guidelines to Establish the Standard for Quality

Guidelines need to be developed based on accepted recommendations, such as the Grading of Recommendations Assessment, Development and Evaluation (**GRADE**) system for rating the quality and strength of the evidence, which is crucial for guideline development. Guidelines must adopt a high level of transparency in the development process. This is particularly relevant in the pediatric setting, where there may be limited research using methods such as randomized controlled trials (RCTs), which would have a high level of rating from an evidence standpoint. Because guidelines and policies related to quality need to be interpreted for specific settings, they should not be interpreted as “standards of care.”

Improving Quality

The applied science of QI currently in use in healthcare is also firmly grounded in the classic scientific method of observation, hypothesis, and planned experimentation. There are 4 key features of the applied science of quality improvement: appreciation of systems, understanding variation, knowledge theory, and psychology of change. In addition to this theoretical framework, statistical analytic techniques evolved to better evaluate variable systems over time. While each derives key features from this applied scientific foundation, multiple QI methodologies are currently in use in healthcare. At their most parsimonious level, each method can be described as a 3-step model: *Data* → *Information* → *Improvement.* Quality needs to be measured. Data obtained from measurement needs to be converted into meaningful information that can be analyzed, compared, and reported. Information must then be *actionable* to achieve improvements in clinical practice and health systems’ processes.

Model for Improvement

The Model for Improvement is structured around 3 key questions: (1) What are we trying to accomplish? (2) How will we know that a change is an improvement? and (3) What change can we make that will result in improvement? Clarifying the first question, the *goal* , is critical and is often a step skipped by clinicians, who typically already have change ideas in mind. The second question is about defining measures, with an emphasis on practicality and efficiency. The third question is about defining testable ideas for improvement, which are subsequently tested using a framework of rapid cycle improvement, also known as the **plan-do-study-act (PDSA) cycle** (Fig. 4.1*A*). The PDSA cycle is typically aimed at testing small, care process changes in iterative, rapid cycles. After discrete testing periods, results are analyzed, and the next cycle of change testing is planned and implemented (i.e., multiple PDSA cycles, often called a PDSA *ramp* , build on previous learning from PDSAs; Fig. 4.1*B*).

Valuable information can be obtained from PDSA cycles that are successful, and those that are not, to help plan the next iteration of the PDSA cycle. The PDSA cycle specifically requires that improvements be data driven. Many clinicians attempt to make changes for improvement in their practice based on clinical intuition rather than on interpretation of empirical data.

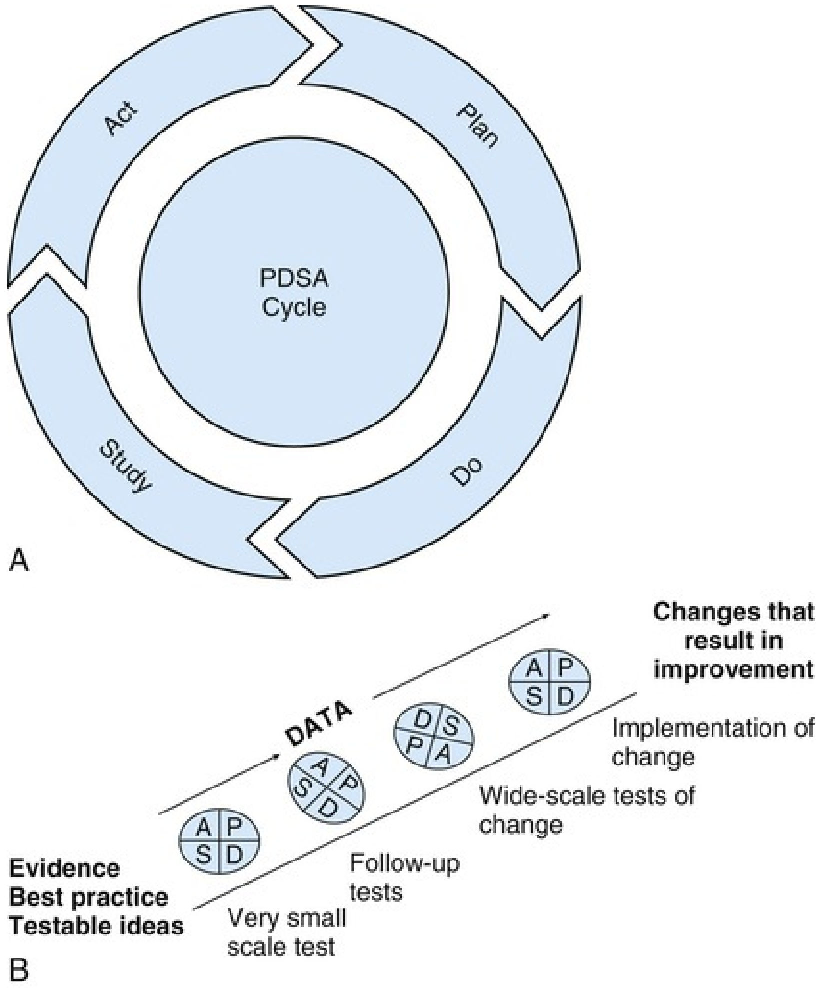
Act
Plan
PDSA Cycle
Study
Do
A
Changes that result in improvement
DATA
A P S D
D S P A
Implementation of change
Wide-scale tests of change
Follow-up tests
Evidence
Best practice
Testable ideas
Very small scale test
B

FIG. 4.1 **A,** The plan-do-study-act (PDSA) cycle. **B,** Use of PDSA cycles: a ramp. (From Langley GJ: The improvement guide: a practical guide to enhancing organizational performance, San Francisco, 1996, Jossey-Bass. © 1996 by Gerald J. Langley, Kevin M. Nolan, Thomas W. Nolan, L. Norman, and Lloyd P. Provost.)

The Model for Improvement has been successfully used in the Vermont Oxford Network (VON) to achieve improvements in care in the neonatal intensive care unit (NICU) setting. The VON is a global network of collaborating NICUs involved in several studies that have favorably impacted the care of newborns. An example of a successful VON QI effort is a project aimed at reducing rates of chronic lung disease in extremely-low-birthweight infants. Clinical teams participating in this improvement effort used special reports from the VON database, reviewed the available evidence with content faculty experts, and then identified improvement goals. The teams received QI training through conference calls and emails for 1 yr. This effort resulted in a 37% increase in early surfactant administration for preterm infants.

One successful QI collaborative using the improvement model in the outpatient setting is related to improvement in remission rates and reduction in systemic corticosteroid use among children with inflammatory bowel disease (IBD, Crohn disease or ulcerative colitis). This work was supported by the **ImproveCareNow Network** (https://improvecarenow.org/), a learning health system. A *learning health system* is a collaborative endeavor organized around communities of patients, clinicians, and researchers working together to integrate research with QI (i.e., knowledge dissemination and implementation) to improve care delivery while advancing clinical research. The network model leverages the inherent motivation of participants to engage and contribute in a collaborative manner. Participants are supported by development of standard processes, such as common approaches to data transfer, measurement, and reporting, as well as emphasis on data transparency, and share knowledge, tools, and resources to accelerate learning and facilitate uptake of useful innovations. For the IBD network, outpatient gastroenterology practices standardized treatment approaches to align with existing evidence though QI interventions adapted to local circumstances, and therapeutic decisions for individual patients remained at the discretion of physicians and their patients. This network also developed methods to more fully engage patients, particularly adolescents, and their caregivers through the use of social media, which helped drive improvement in some of the clinical behavior change aspects of the work.

Six Sigma

Six Sigma is related to the reduction in *undesirable variation in processes*. There are 2 types of variations in a process. **Random variation** refers to the variation that is inherent in a process simply because the process occurs within a system. Random variation in processes is expected in any system. In contrast, **special cause variation** refers to nonrandom variation that can impact a process and implies something in the system has been perturbed. For example, when tracking infection rates in a nursery, a sudden increase in the infection rates may be secondary to poor handwashing techniques by a new healthcare provider in the system. This would represent a special cause variation; once this provider's practice is improved, the system perturbation is resolved, and the infection rates will likely go back to the baseline level. Alternatively, improvement ideas are intended to perturb the system positively such that outcomes improve, ideally without exacerbating the variation in the system (Fig. 4.2). Six Sigma attempts to provide a structured approach to unwanted variations in healthcare processes. Six Sigma approaches have been successfully used in healthcare to improve processes in both clinical and nonclinical settings.

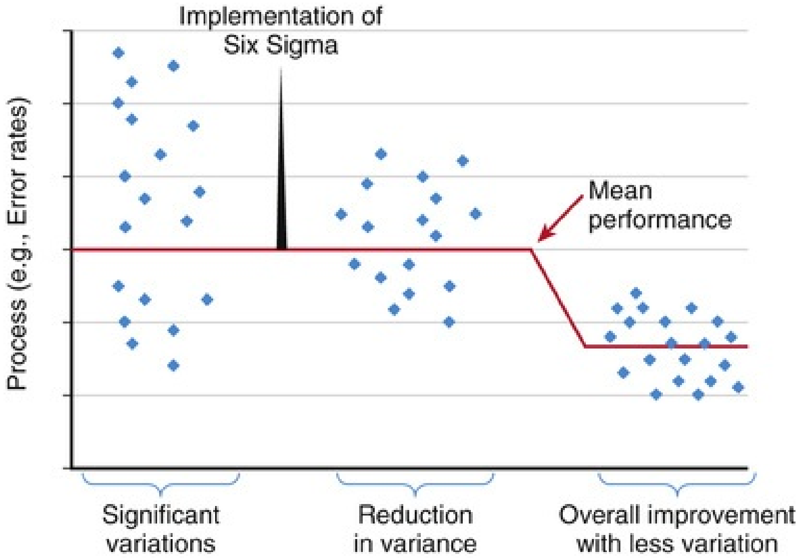

FIG. 4.2 **Improving quality by reducing variation.**

Lean Methodology

Lean methodology focuses on reducing waste within a process in a system. Fig. 4.3*A* illustrates the steps in the process of a patient coming to the emergency department (ED). After the initial registration, the patient is seen by a nurse and then the physician. In a busy ED, a patient may need to wait for hours before registration is complete and the patient is placed in the examination room. This wait time is a waste from the perspective of the patient and the family. Incorporating the registration process after placing the patient in the physician examination room can save time and minimize waste (Fig. 4.3*B*). Lean methods have been successfully used in several outpatient and inpatient settings with resulting improvements in efficiency. Lean principles have also been adopted as a core strategy for many children's hospitals and health systems with the goal of improving efficiencies and reducing waste. These efforts can improve aspects of quality while also typically reducing costs.

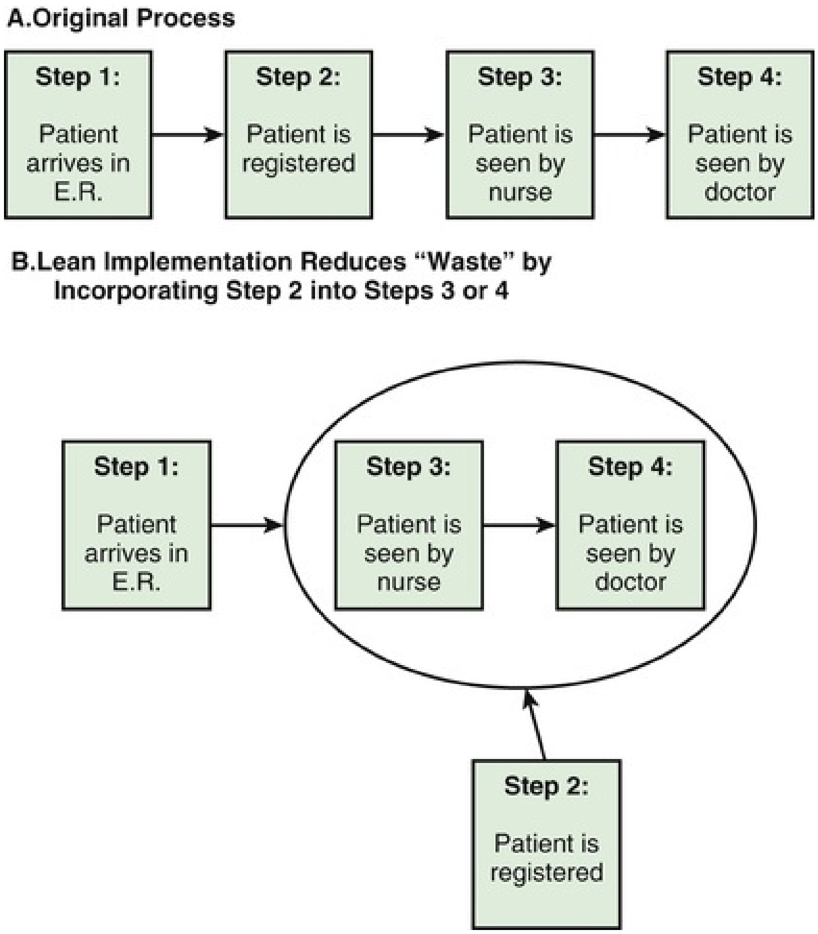
A.Original Process
Step 1:
Patient arrives in E.R.
Step 2:
Patient is registered
Step 3:
Patient is seen by nurse
Step 4:
Patient is seen by doctor
B.Lean Implementation Reduces "Waste" by Incorporating Step 2 into Steps 3 or 4
Step 1:
Patient arrives in E.R.
Step 3:
Patient is seen by nurse
Step 4:
Patient is seen by doctor
Step 2:
Patient is registered

FIG. 4.3 **A** and **B,** Lean methodology—waste reduction.

Management Sciences

Management sciences, also known as *operations management* , stems from operations research and refers to the use of mathematical principles to maximize efficiencies within systems. Management sciences principles have been successful in many European healthcare settings to optimize efficiencies in outpatient primary care office settings, inpatient acute care hospital settings, and surgical settings including operating rooms, as well as for effective planning of transport and hospital expansion policies. Management sciences principles are being explored for use in the U.S. healthcare system; one technique, **discrete event simulation** , was used at the Children's Hospital of Wisconsin to plan the expansion of the pediatric critical care services with the goal of improving quality and safety. The discrete event simulation model illustrated in Fig. 4.4 depicts the various steps of the process in a pediatric intensive care unit (PICU). Patients stratified across 3 levels of severity (low, medium, high) are admitted to the PICU, are initially seen by a nurse and physician, then stay in the PICU with ongoing care provided by physicians and nurses, and finally are discharged from the PICU. The discrete event simulation model is a computer model developed using real estimates of numbers of patients, number of physicians and nurses in a PICU, and patient outcomes. Discrete event simulation models are created using real historical data, which allows testing the *what if* scenarios, such as the impact on patient flow and throughput by increasing the number of beds and/or changing nurse and physician staffing.

DES Model

- Mathematically depicts a 24-bed PICU
- Depicts the patient experience from admission to discharge
- Factors the staffing of physicians and nurses in the PICU using historical experience
- DES Model starts with baseline and runs computer iterations to identify predicted outcomes with changing patient flow and staffing
- Results of DES Model provide insight into predicted outcomes of changing bed/staffing assumptions

Illustration of DES Model

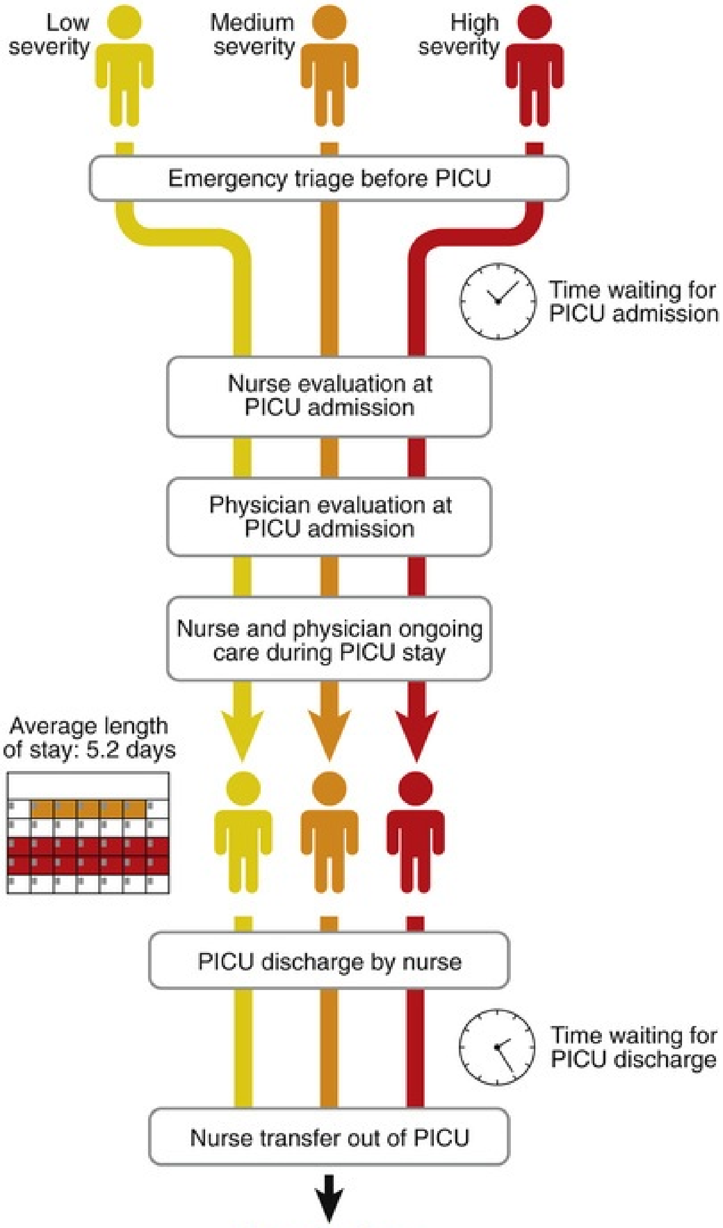
Low severity
Medium severity
High severity
Emergency triage before PICU
Time waiting for PICU admission
Nurse evaluation at PICU admission
Physician evaluation at PICU admission
Nurse and physician ongoing care during PICU stay
Average length of stay: 5.2 days
PICU discharge by nurse
Time waiting for PICU discharge
Nurse transfer out of PICU

Conclusions

- Simply adding new PICU beds will not improve patient flow in itself
- Critical ratio between MDs, RNs, and beds in PICU adjusted for patient severity is needed to maximize patient flow, safety, and outcomes

FIG. 4.4 Management sciences—discrete event stimulation. PICU, Pediatric intensive care unit.

Another management sciences technique, **cognitive mapping** , measures the soft aspects of management sciences, as illustrated in Fig. 4.5 . Cognitive mapping highlights the importance of perceptions and constructs of healthcare providers and the way these constructs are linked in a hierarchical manner. Goals and aspirations of individual healthcare providers are identified by structured interviews and are mapped to strategic issues and problems, and options. By using specialized computer software, complex relationships can be identified to better understand the relationships between different constructs in a system. A discrete event simulation model views patient throughput based on numbers of beds, physicians, and nurses, and accounts for differences in patient mix. It does not account for many other factors, such as individual unit characteristics related to culture. By interviewing healthcare providers, cognitive maps can be developed that can help to better inform decision-making.

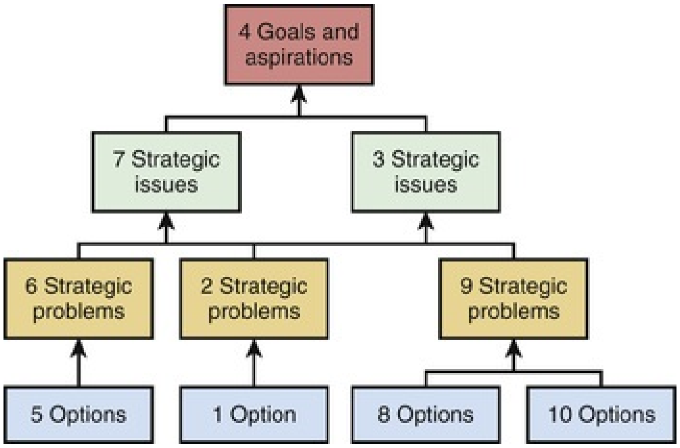
4 Goals and aspirations
7 Strategic issues
3 Strategic issues
6 Strategic problems
2 Strategic problems
9 Strategic problems
5 Options
1 Option
8 Options
10 Options

FIG. 4.5 Management sciences—cognitive mapping.

Tools for Organizing Quality Improvement Theory and Execution

QI efforts need to be organized around a theory of how the desired changes in outcome will be achieved. Multiple tools are available to help organize a QI team's thinking and execution. These tools typically help teams organize work into discrete projects or phases, and some of them also help teams develop change ideas.

Key driver diagrams (KDDs) are a tool to organize the theory of learning that underpins a QI project (Fig. 4.6), using the Model for Improvement. Important aspects of a KDD include a statement of the specific aim or improvement goal, a list of the key themes, or drivers, that are theorized to require improvement in order to achieve the aim, and lastly a list of the discrete change ideas or initiatives to be tested to determine whether or not they affect discrete drivers, and therefore the overall aim. Since most system outcomes are driven by multiple factors, a KDD allows a QI team to depict a theory that addresses multiple factors. Similarly, Lean and Six Sigma projects use a tool called an A3, that in addition to organizing the theory of a project, also prompts teams to assess the current state, and consider timelines and personnel for planned change (examples available at https://www.lean.org/common/display).

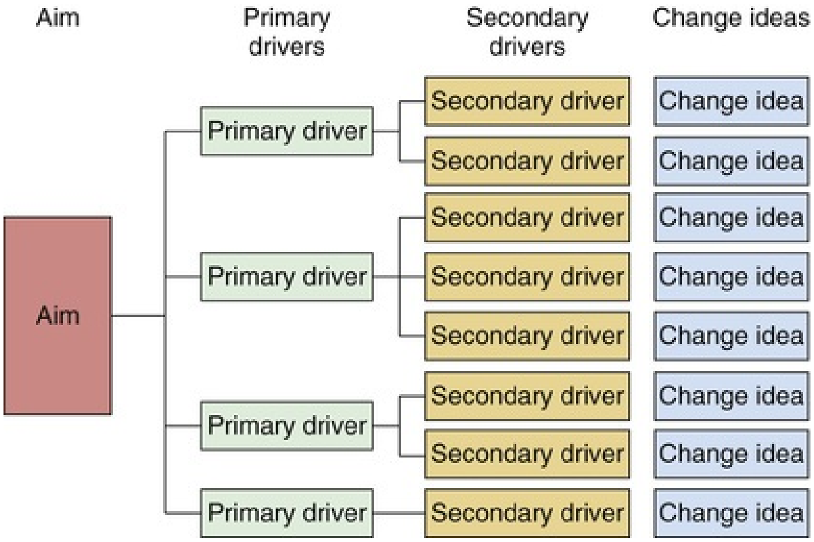
Aim
Primary drivers
Secondary drivers
Change ideas
Aim
Primary driver
Primary driver
Primary driver
Primary driver
Secondary driver
Secondary driver
Secondary driver
Secondary driver
Secondary driver
Secondary driver
Secondary driver
Secondary driver
Change idea
Change idea
Change idea
Change idea
Change idea
Change idea
Change idea
Change idea

FIG. 4.6 **Key driver diagram: theory of how to achieve an aim.**

There are additional QI tools to help assess the current state of a system to better understand how to improve it. One, the **failure modes and effects analysis (FMEA)** , also helps teams develop change ideas (Fig. 4.7). Starting with a map of the processes in the current system, FMEA then asks teams to investigate and brainstorm the many ways discrete processes can go wrong—the *failure modes* . Once failure modes are identified, teams begin to develop discrete interventions or countermeasures to address the failures (see Chapter 5). A similar tool, the **fishbone** or **cause-and-effect** diagram, is organized around key components in a system (e.g., people, material, machines) and helps teams catalog how deficiencies in each component can affect the overall outcome of a system.

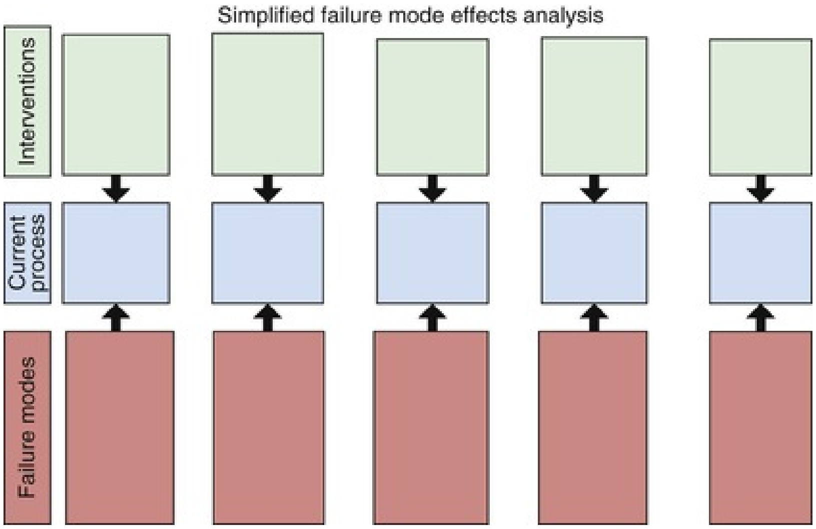
Simplified failure mode effects analysis
Interventions
Current process
Failure modes

FIG. 4.7 **Failure modes and effects analysis (FMEA).**

A final key tool to help teams prioritize action is a **Pareto chart** , which organizes system deficiencies in terms of their prevalence (Fig. 4.8). A Pareto chart typically displays the individual prevalence of discrete problems, determined by baseline analysis of data, as well as the cumulative prevalence, helping teams see which problems should be addressed first, to maximize impact on the overall outcome.

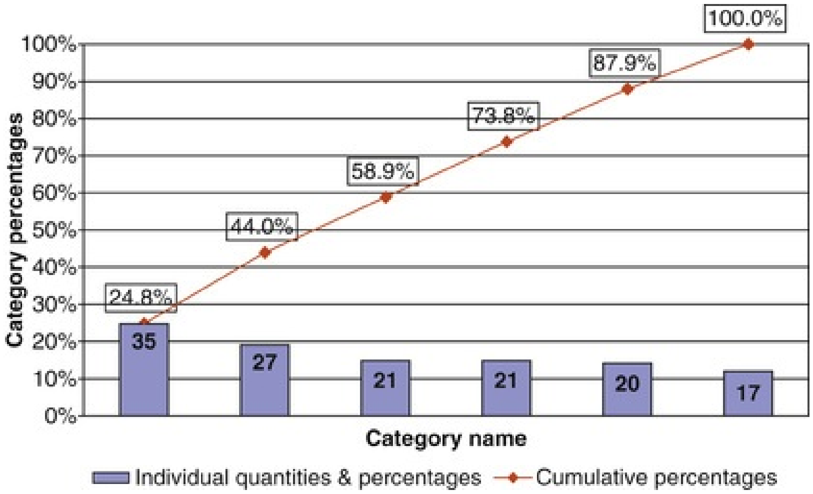

FIG. 4.8 Pareto chart.

Measuring Quality

Robust quality indictors should have clinical and statistical relevance. *Clinical relevance* ensures that the indicators are meaningful to patient care from the standpoint of patients and clinicians. *Statistical relevance* ensures that the indicators have measurement properties to allow an acceptable level of accuracy and precision. These concepts are captured in the national recommendations that quality measures must meet the criteria of being valid, reliable, feasible, and usable (Table 4.1). **Validity** of quality measures refers to the measure being an estimate of the true concept of interest. **Reliability** refers to the measure being reproducible and providing the same result if retested. It is important that quality measures are **feasible** in practice, with an emphasis on how the data to support the measures are collected. Quality measures must be **usable** , which means that they should be clinically meaningful. The **Agency for Healthcare Research and Quality** and the **National Quality Forum** have provided specific criteria to be considered when developing quality measures.

Table 4.1

Properties of Robust Quality Measures

ATTRIBUTE	RELEVANCE
Validity	Indicator accurately captures the concept being measured.
Reliability	Measure is reproducible.
Feasibility	Data can be collected using paper or electronic records.

Usability	Measure is useful in clinical practice.

Quality indicators can be used to measure the performance within 3 components of healthcare delivery: structure, process, and outcome. **Structure** refers to the *organizational characteristics* in healthcare delivery. Examples of organizational characteristics are the number of physicians and nurses in an acute care setting and the availability and use of systems such as electronic health records. **Process** measures estimate how services are provided; examples are the percentage of families of children with asthma who receive an asthma action plan as part of their office visit and percentage of hospitalized children who have documentation of pain assessments as part of their care. **Outcome** measures refer to the final health status of the child; examples are risk-adjusted survival in an intensive care unit setting, birthweight-adjusted survival in the NICU setting, and functional status of children with chronic conditions such as cystic fibrosis.

It is important to distinguish between measures for accountability and measures for improvement. Measures, particularly measures for accountability that may be linked to attribution and payment must be based on a rigorous process (Fig. 4.9). This can be resource intensive and time-consuming. In contrast, measures for improvement serve a different purpose—to track incremental improvements linked to specific QI efforts. These may not undergo rigorous testing, but they have limited applicability beyond the specific QI setting.

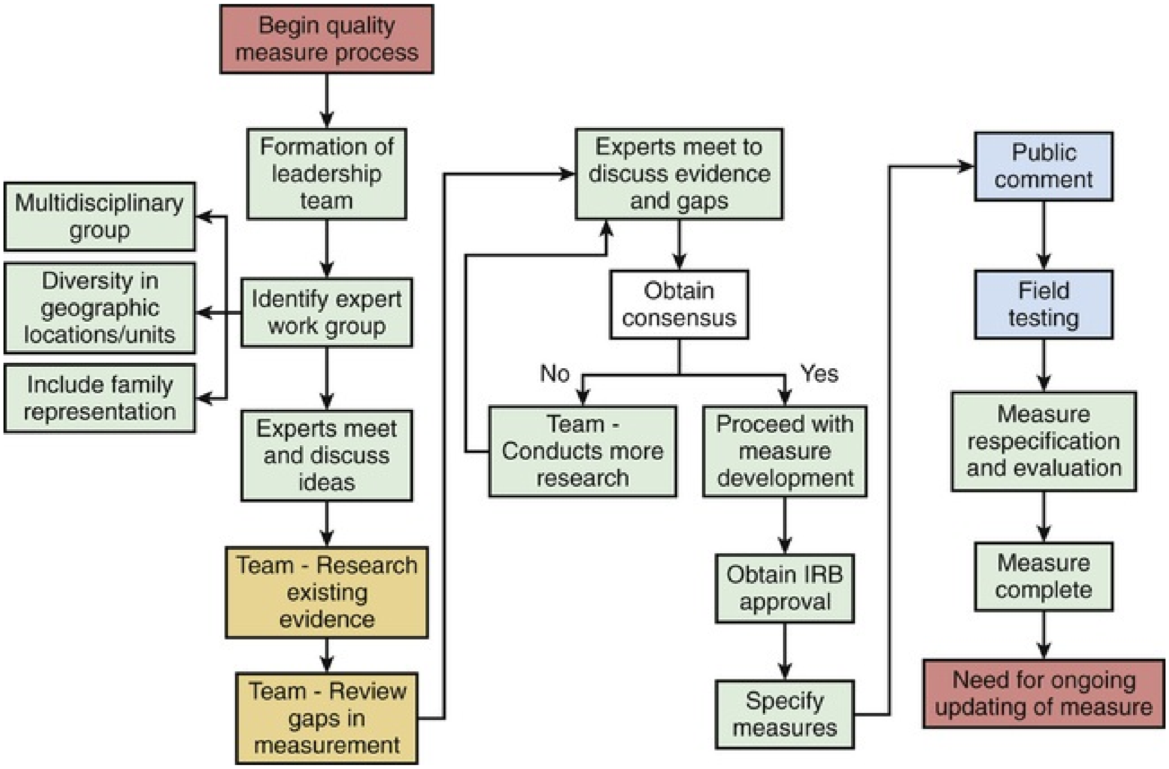
Begin quality measure process
Formation of leadership team
Multidisciplinary group
Diversity in geographic locations/units
Include family representation
Identify expert work group
Experts meet and discuss ideas
Team - Research existing evidence
Team - Review gaps in measurement
Experts meet to discuss evidence and gaps
Obtain consensus
No
Yes
Team - Conducts more research
Proceed with measure development
Obtain IRB approval
Specify measures
Public comment
Field testing
Measure respecification and evaluation
Measure complete
Need for ongoing updating of measure

FIG. 4.9 **Development of a rigorous quality measure.**

Quality data can be quantitative and qualitative. *Quantitative* data includes numerical data, which can be *continuous* (patient satisfaction scores represented as a percentage with higher numbers indicating better satisfaction) or *categorical* (patient satisfaction scores from a survey using a Likert scale indicating satisfactory, unsatisfactory, good, or superior care). Data can also be *qualitative* in nature, which includes nonnumerical data. Examples of qualitative data can include results from open-ended surveys related to the satisfaction of care in a clinic or hospital setting.

Data measuring quality of care can be obtained from a variety of sources, which include chart reviews, patient surveys, existing administrative data sources (billing data from hospitals), disease and specialty databases, and patient registries, which track individual patients over time. Sources of data vary in terms of reliability and accuracy, which will influence *rigor* and therefore appropriate-use cases for the data; many national databases invest significant resources in implementing processes to improve data reliability and accuracy.

It is important to distinguish between databases and data registries. *Databases* are data repositories that can be as simple as a Microsoft Excel spreadsheet or as complex as relational databases using sophisticated servers and information technology platforms. Databases can provide a rich source of aggregated data for both quality measurement and research. *Data registries* allow tracking individual patients over time; this dynamic and longitudinal characteristic is important for population health management and QI.

Data quality can become a significant impediment when using data from secondary sources, which can adversely impact the overall quality evaluation. Once data on the quality indicator have been collected, quality measurement can occur at 3 levels: (1) measuring quality status at one point in time (e.g., percent of children seen in a primary care office setting who received the recommended 2-year immunizations); (2) tracking performance over time (e.g., change in immunization rates in the primary care office setting for children 2 yr of age); and (3) comparing performance across clinical settings after accounting for epidemiologic confounders (e.g., immunization rates for children <2 yr of age in a primary care office setting stratified by race and SES as compared to the rates of other practices in community and national rates).

Pediatric quality measures are being developed nationally. Table 4.2 lists some currently endorsed pediatric national quality indicators.

Table 4.2

Examples of National Pediatric Quality Measures

NQF PEDIATRIC QUALITY INDICATORS	NQF-ENDORSED INPATIENT MEASURES AMONG PICUs	NQF-ENDORSED INPATIENT PEDIATRIC CARE MEASURES	NQF-ENDORSED OUTPATIENT PEDIATRIC CARE MEASURES
Neonatal bloodstream infection rate Transfusion reaction Gastroenteritis admission rate	PICU standardized mortality ratio PICU severity-adjusted length of stay PICU unplanned readmission rate	CAC-1 relievers for inpatient asthma CAC-2 systemic corticosteroids for inpatient asthma Admit decision time to ED departure time for admitted patients Follow-up after hospitalization for mental illness (FUH) NHSN Catheter-Associated Urinary Tract Infection (CAUTI) outcome measure NHSN Central Line-Associated Bloodstream Infection (CLABSI) outcome measure Percent of residents or patients assessed and appropriately given the pneumococcal vaccine (short stay) Restraint prevalence (vest and limb)	Appropriate testing for children with pharyngitis CAHPS clinician/group surveys (adult primary care, pediatric care, and specialist care surveys) Child and adolescent major depressive disorder: diagnostic evaluation Child and adolescent major depressive disorder: suicide risk assessment Follow-up after hospitalization for mental illness (FUH) Median time from ED arrival to ED departure for discharged ED patients

		Validated family-centered survey questionnaire for parents' and patients' experiences during inpatient pediatric hospital stay Nursing hours per patient day Preventive care and screening: screening for clinical depression and follow-up plan Skill mix (RN, LVN/LPN, UAP, and contract)	Pediatric symptom checklist (PSC)

CAC, Children's Asthma Care; CAHPS, Consumer Assessment of Healthcare Providers and Systems; ED, emergency department; HBIPS, hospital-based inpatient psychiatric services; LVN/LPN, licensed vocational/practical nurse; NHSN, National Healthcare Safety Network; NQF, National Quality Forum; PICU, pediatric intensive care unit; RACHS-1, risk adjustment for congenital heart surgery; RN, registered nurse; UAP, unlicensed assistive personnel.

Analyzing Quality Data

Three approaches have been used for analyzing and reporting data. The classic approach from a research paradigm has been applied to quality data for statistically comparing trends over time, and differences before and after an intervention. P-values are interpreted as being significant if ≤0.05, which suggests that the likelihood of seeing a difference as extreme as observed has a probability of ≤5% (type I error). Another approach from an improvement science paradigm uses techniques such as run charts and control charts to identify special cause variation. In the context of quality improvement, special cause variation in the desired direction is the intent, and these analytic techniques allow improvers to quickly recognize statistically significant changes in system performance over time. Lastly, quality data also have been reported on an individual patient level. This has gained popularity in the patient safety arena, where identifying individual patient events in the form of descriptive analysis (*stories*) may be more powerful in motivating a culture of change than statistical reporting of aggregate data in the form of rates of adverse patient safety events (see Chapter 5).

Comparing and Reporting Quality

There is an increasing emphasis on quality reporting in the United States. Many states have mandatory policies for the reporting of quality data. This reporting may be tied to reimbursement using the policy of P4P, which implies that reimbursements by insurers to hospitals and physicians will be partially based on the quality metrics. P4P can include both incentives and disincentives. *Incentives* relate to additional payments for meeting certain quality thresholds. *Disincentives* relate to withholding certain payments for not meeting those quality thresholds. An extension of the P4P concept relates to the implementation of the policy of **nonreimbursable hospital-acquired conditions** , formerly called *never events* by the Centers for Medicare and Medicaid Services. CMS has identified a list of hospital-acquired conditions, which are specific quality events that will result in no payment for care provided to patients, such as wrong-site surgery, catheter-associated bloodstream infection (CA-BSI), and decubitus ulcers. This approach has not yet been widely implemented for pediatric patients.

Quality reporting is also being used in a voluntary manner as a business growth strategy. Leading U.S. children's hospitals actively compete to have high ratings in national quality evaluations that are reported in publications such as *Parents* (formerly *Child)* magazine and *US News & World Report* . Many children's hospitals have also developed their own websites for voluntarily reporting their quality information for greater transparency. Although greater transparency may provide a competitive advantage to institutions, the underlying goal of transparency is to improve the quality of care being delivered, and for families to be able to make informed choices in selecting hospitals and physicians for their children.

Quality measures may also be used for purposes of certifying individual physicians as part of the Maintenance of Certification process. In the past, specialty and subspecialty certification in medicine, including pediatrics, was largely based on demonstrating a core fund of knowledge by being successful in an examination. No specific evidence of competency in actual practice needed to be demonstrated beyond successful completion of a training program. There continues to be significant variations in practice patterns even among physicians who are board certified, which highlights the concept that medical knowledge is important, but not sufficient for the delivery of high-quality care. Subsequently, the American Board of Medical Specialties, including its member board, the American Board of Pediatrics, implemented the MOC process in 2010. Within the MOC process, there is a specific requirement (Part IV) for the physician to demonstrate the assessment of quality of care and implementation of improvement strategies as part of recertification in pediatrics and pediatric subspecialties. Lifelong learning and the translation of learning into practice are the basis for the MOC process and an essential competency for physicians' professionalism. There are also discussions to adopt a similar requirement for Maintenance of Licensure for physicians by state medical regulatory boards.

The Accreditation Council for Graduate Medical Education requires residency programs to incorporate QI curriculum to ensure that systems-based practice and QI are part of the overall competencies within accredited graduate medical training programs. One form of continuing medical education, **performance improvement** , is used for ongoing physician education. These initiatives require physicians to measure the quality of care they deliver to their patients, to compare their performance to peers or known benchmarks, and to work toward improving their care by leveraging QI methods. This forms a feedback loop for continued learning and improvement in practice.

Prior to comparing quality measures data both within and across clinical settings, it is important to perform risk adjustment to the extent that is feasible. **Risk adjustment** is the statistical concept that utilizes measures of underlying severity or risk so that the outcomes can be compared in a meaningful manner. The importance of risk adjustment was highlighted in the PICU setting many years ago. The unadjusted mortality rate for large tertiary care centers was significantly higher than that for smaller hospital settings. By performing **severity of illness** risk adjustment, it was subsequently shown that the risks in tertiary care, large PICUs were higher because patients had higher levels of severity of illness. Although this concept is now intuitive for most clinicians, the use of severity of illness models in this study allowed a mathematical estimate of patient severity using physiologic and laboratory data, which allowed for the statistical adjustment of outcomes. This permits meaningful comparisons of the outcomes of large and small critical care units. Severity of illness models and the concepts of statistical risk adjustment are most developed in pediatric critical care. However, these concepts are relevant for all comparisons of outcomes in the hospital settings where sicker patients may be transferred to the larger institutions for care, and therefore would be expected to have poorer outcomes than other settings with less sick patients.

Risk adjustment can be performed at 3 levels. First, patients who are sicker can be excluded from the analysis, thereby allowing the comparisons to be within homogeneous groups. Although this approach is relatively simple to use, it is limited in that it would result in patient groups being excluded from the analysis. Second, risk stratification can be performed using measures of patient acuity; for example, in the **All-Patient Refined Diagnosis-Related Group** system, patients can be grouped or stratified into different severity criteria based on acuity weights. This approach may provide more homogeneous strata within which comparisons can be performed. Third, severity of illness risk adjustment can use clinical data to predict the outcomes for patient groups, such as the **Pediatric Risk of Mortality (PRISM)** scoring system in the PICU setting. In the PRISM score and its subsequent iterations, physiologic and laboratory perimeters are weighted on a statistical logistic scale to predict mortality risk within that PICU admission. By comparing the observed and expected outcomes (i.e., mortality or survival), a quantitative estimate of the performance of that PICU can be established, which can then be used to compare outcomes with other PICUs (standardized mortality ratio).

Risk adjustment systems have been effectively incorporated into specialty databases. For example, the **Virtual Pediatric Intensive Care Unit System (VPS)** represents the pediatric critical care database system in the United States. Comprising >100 PICUs and pediatric cardiac ICUs across the United States, as well as international PICUs, the VPS currently has >300,000 patients within its database. The VPS database emphasizes data validity and reliability to ensure that the resulting data are accurate. Data validity has been established using standard data definitions with significant clinical input. Data reliability is established using interrater reliability to ensure that the manual data collection that involves several data collectors within pediatric institutions is consistent. The PRISM scoring system is programmed into the VPS software to allow the rapid estimation of the severity of illness of individual patients. This in turn allows risk adjustment of the various outcomes, which are compared within institutions over time and across institutions for purposes of QI.

Implications of the U.S. Healthcare Reform for Quality

Regarding quality of healthcare for children, healthcare reform had 3 key implications. First, expanded insurance coverage optimized access and include expanded coverage for young adults to age 26 yr. Second, various initiatives related to quality, safety, patient-centered outcomes research, and innovation were implemented and funded. For example, the **Agency for Healthcare Research and Quality** (AHRQ) funded a national effort to establish 7 centers of excellence through the **Pediatric Quality Measurement Program** (PQMP) to improve existing pediatric quality measures and create new measures that can be used by states and in a variety of other settings to evaluate quality of care for children. Third, reform advocated a paradigm shift in the existing model of healthcare delivery from vertical integration toward a model of *horizontal* integration. This has led to the creation and rapid growth of integrated delivery systems and risk-sharing relationships of **accountable care organizations (ACOs)** . Population health outcomes from these changes remain uncertain, although it appears healthcare cost inflation may have slowed somewhat.

Another area of increasing emphasis is **population health** . This is important because it expands the traditional role of physicians to improve quality of care for individual patients also to improve the quality of care for larger populations. Populations can be defined by geographic constraints or disease/patient condition. Efforts to link payment and reimbursement for care delivery by physicians and health systems are being increasingly tied to measurable improvements in population health. To achieve a meaningful improvement in population outcome, physician practices will need to embrace the emerging paradigm of practice transformation, whose many facets include the adoption of a **medical home** , the seamless connectivity across the primary care and subspecialty continuum, and a strong connection between the medical and social determinants of healthcare delivery. To implement successful practice transformation, hospitals are increasingly adopting a broader view to evolve into healthcare systems that serve children across the entire range of the care continuum, including preventive and primary care, acute hospital care, and partnerships with community organizations for enhancing the social support structure. In addition, new risk-sharing payment models are evolving, resulting in the growth of entities such as ACOs, which represent a financial risk-sharing model across primary and subspecialty care and hospitals.

Information Technology and Quality Improvement

Health information technology (HIT) is a critical component in the effort to improve quality. HIT includes electronic health records, personal health records, and health information exchange. The purpose of a well-functioning **electronic health record** is to allow collection and storage of patient data in an electronic form, to allow this information to be efficiently provided to clinicians and healthcare providers, to have the ability to allow clinicians to enter patient care orders through the computerized physician order entry, and to have the infrastructure to provide clinical decision support that will improve physician decision-making at the individual patient level. The **personal health record** allows patients and families to be more actively engaged in managing their own health by monitoring their clinical progress and laboratory information, as well as to communicate with their physicians to make appointments, obtain medications, and have questions answered. Appropriate, timely, and seamless sharing of patient information across physician networks and healthcare organizations is critical to quality care and to achieve the full vision of a medical home for children. **Health information exchange** allows the sharing of healthcare information in an electronic format to facilitate the appropriate connections between providers and healthcare organizations within a community or region.

Expanding Individual Quality Improvement Initiatives to Scale

Despite the success of individual QI projects, the overall progress to achieve large-scale improvements to reach all children across the spectrum of geographic location and SES remains limited. This contributes to the health disparities that persist for children, with significant differences in access and quality of care. A potential factor that limits the full impact of QI is the lack of strategic alignment of improvement efforts with hospitals, health systems, and across states.

This challenge can be viewed from a system standpoint in being able to conduct and expand QI from a micro level (individual projects), to the meso level (regional), to the macro level (national and international). The learning from individual QI projects for addressing specific challenges can be expanded to the regional level by ensuring that there is optimal leadership, opportunity for education, and adoption of improvement science (Fig. 4.10). To further expand the learning to a national and international level, it is important to leverage implementation science to allow a strategic approach to the identification of the key factors that influence success. To leverage fully the synergies in order to impact the quality of care delivered to children, it is important for national and international healthcare organizations to collaborate effectively from a knowledge management and improvement standpoint (Table 4.3).

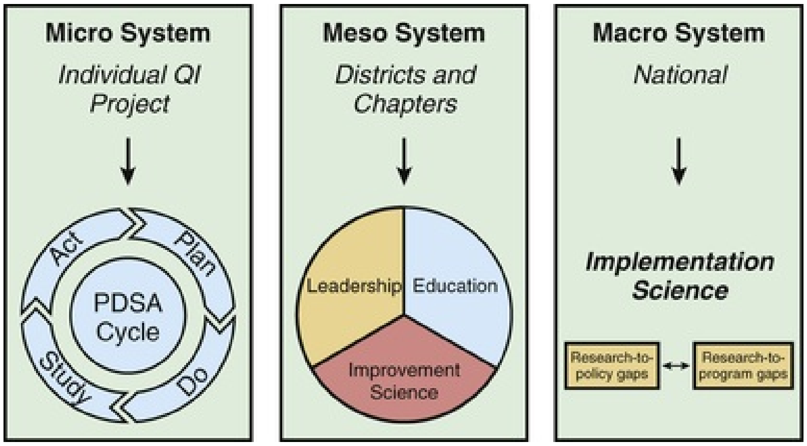
Micro System
Individual QI Project
Act
Plan
PDSA Cycle
Study
Do
Meso System
Districts and Chapters
Leadership
Education
Improvement Science
Macro System
National
Implementation Science
Research-to-policy gaps
Research-to-program gaps

FIG. 4.10 **Success ingredients for large-scale quality improvement.**

Table 4.3

National Organizations Involved in Pediatric Quality Improvement (QI)

ORGANIZATION	ROLE	ACTIVITIES
American Academy of Pediatrics (AAP)	Represents more than 60,000 pediatricians and pediatric subspecialists worldwide	Resources for QI to improve health for all children, best practices, advocacy, policy, research and practice, and medical home
American Board of Pediatrics (ABP)	Certifying board for pediatrics and pediatric subspecialties	Certification policies and resources for activities such as Maintenance of Certification (MOC)
American Medical Association (AMA)	Physician member association	Physician Consortium for Performance Improvement (PCPI)—physician-led initiative
Children's Hospital Association (CHA)	Formerly the National Association of Children's Hospitals and Related Institutions; and the Child Health Corporation of America	Databases, QI collaboratives, and policy
Institute for Healthcare Improvement (IHI)	QI organization for adult and pediatric care	QI collaboratives, QI educational workshops and materials
National Initiative for Child Health Quality (NICHQ)	QI organization for pediatric care	QI training, improvement networks
The Joint Commission	Hospital accreditation organization	Unannounced surveys to evaluate quality of care in hospitals
National Committee for Quality Assurance (NCQA)	QI organization	Healthcare Effectiveness Data and Information Set (HEDIS) and quality measures for improvement
National Quality Forum (NQF)	Multidisciplinary group including healthcare providers, purchases, consumers, and accrediting bodies	Endorsing national quality measures, convening expert groups, and setting national priorities

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CHAPTER 5

Safety in Healthcare for Children

Patrick W. Brady, Jeffrey M. Simmons

Children may be harmed by the healthcare that aims to make them better. Such harms include central line–associated bloodstream infections (CLA-BSIs) and medication overdoses. In 1991 the Harvard Medical Practice Study reviewed a large sample of adult medical records from New York State and found that adverse events occurred in an estimated 3.7% of hospitalizations. Most events gave rise to serious disability, and 13.6% led to death. The Institute of Medicine (IOM) estimated that as many as 98,000 Americans per year die in the hospital from medical errors.

Although fewer data are available for children, it is clear that children experience substantial healthcare-related harm. Nationally, hospitalized children experience approximately 1,700 CLA-BSIs and 84,000 adverse drug events each year. While the evidence is less robust, and not without controversy, substantial progress has been reported, particularly in **healthcare-associated conditions (HACs)** . Less strong epidemiologic estimates are available for adverse events in the ambulatory environment, but these events are likely more common than reported.

The **Solutions for Patient Safety (SPS)** collaborative started with the 8 children's hospitals in Ohio and has expanded to include >130 hospitals across the United States and Canada (http://www.solutionsforpatientsafety.org). The collaborative uses a learning network model to pursue the aim of eliminating serious harm across all children's hospitals. The American Academy of Pediatrics (AAP), Children's Hospital Association, and The Joint Commission (TJC) also have convened improvement collaboratives in pediatric safety. In addition, healthcare has recognized the high rates of healthcare worker injury and the critical role that the safety of healthcare providers plays in outcomes, burnout, and safe patient care.

Error vs Harm

Clinical leaders, improvers, and researchers often employ measures of error and harm to understand and improve safety, but the differences between these 2 measures can lead to confusion. **Errors** occur when a physician, nurse, or other member of the healthcare team does the wrong thing (*error of commission*) or fails to do the right thing (*error of omission*); errors of omission (e.g., not arriving at the right diagnosis) are considerably more difficult to measure. **Harm** , as defined by the Institute for Healthcare Improvement, is "unintended physical injury resulting from or contributed to by medical care (including the absence of indicated medical treatment), that requires additional monitoring, treatment, or hospitalization, or that results in death." Most errors in healthcare do not lead to harm; harm may be both preventable and nonpreventable (Fig. 5.1). A physician may erroneously fail to add a decimal point in a medication order for an aminoglycoside antibiotic, ordering a dose of 25 mg/kg rather than the intended dose of 2.5 mg/kg of gentamicin. If this error is caught by the computerized order entry system or the pharmacist, this would be an error with no resultant harm. If this error was not reviewed and caught by a pharmacist and reached the patient, who suffered acute kidney injury, this would be *preventable* harm since evidence shows that pharmacist review can reduce the risk of these errors 10-fold. Alternatively, if a patient received a first lifetime dose of amoxicillin and had anaphylaxis requiring treatment and hospital admission, this harm would be considered *nonpreventable* since no valid predictive tests are available for antibiotic allergy. Furthermore, the concept of **latent risk** , independent of any actual error, is inherent in any system where patients can be harmed. Among errors that do not lead to harm, **near misses** that do not reach patients—or high-risk situations that do not lead to harm because of good fortune or mitigation—are important learning opportunities about safety threats.

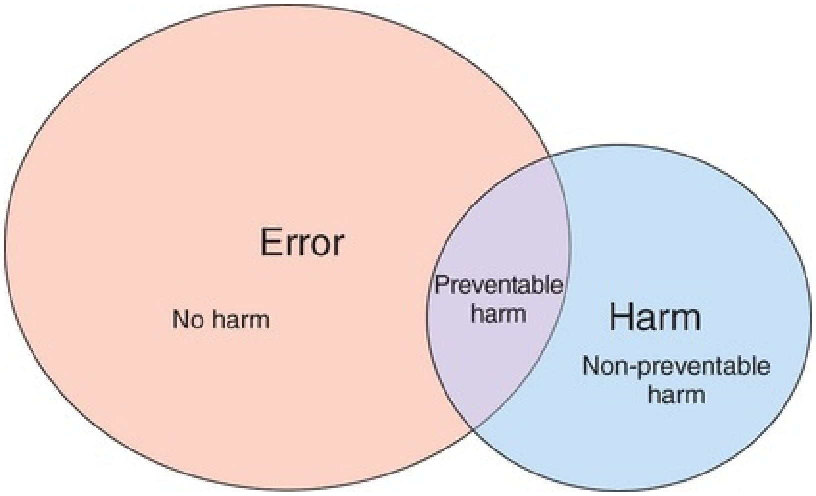

FIG. 5.1 **Overlap between error and harm.**

Several classification systems exist to rate harm severity, including the NCC-MERP for medication-related harm and the severity scales for all-cause harm. **Serious safety events (SSEs)** are deviations from expected practice followed by death or severe harm. The SPS collaborative has SSE elimination as its primary goal. **Sentinel events** or **never events** , such as a wrong-site surgery, are also targets of external reporting as well as for elimination through quality improvement (QI) initiatives (see Chapter 4). Increasingly, health systems are using a *composite serious harm index* , which combines a variety of preventable HACs (e.g., CLA-BSIs) to examine system safety performance over time across various patient populations and sites of care.

Safety Frameworks

Safety frameworks are conceptual models and tools to help clinicians, improvers, and researchers understand the myriad contributors to safe healthcare and safety events. Healthcare is delivered in a complex system with many care providers and technologies, such as electronic health records and continuous physiologic monitors. The Donabedian framework, which links structure, process, and outcome, can be a very useful tool. The **Systems Engineering Initiative for Patient Safety (SEIPS)** model, developed by human factors engineers and cognitive psychologists at the University of Wisconsin–Madison, provides more detailed tools to understand the work system and the complex interactions between people and task work and technology and the environment. The SEIPS 2.0 model more prominently includes the patient and family in co-producing care outcomes. Other available safety frameworks include those from the Institute for Healthcare Improvement. The “Swiss cheese” model illustrates how an organization's defenses prevent failures from leading to harm, but only when the holes of the Swiss cheese slices, representing different components of the system, do not line up properly.

Traditionally, safety science and improvement have focused on identifying *what went wrong* (near misses, errors, and harm) and then tried to understand and improve the system of care that led these events. There is increasing focus on *what goes right* . This framework, called **Safety-II** to contrast with Safety-I and its focus on learning from what goes wrong, brings focus on the much greater number of things that go right and how people act every day to create safety in complex and unpredictable systems. Safety-II seeks to learn from people, the greatest source of system resilience, particularly in the midst of high levels of risk and stress, as often seen in healthcare.

Identifying and Analyzing Harm, Errors, and Latent Threats

Health systems use a toolbox of processes to discover, understand, and mitigate unsafe conditions.

Incident Reporting Systems

Many health systems and hospitals offer employees access to a system to report errors, harms, or near misses. Most frequently, these are anonymous so that healthcare workers feel safe to submit an event in which they may have been involved, or when the harm involved someone in a position of authority. Ideally, these systems would facilitate smooth and efficient entry of enough information for further review but avoid excessive burden of time or cognitive load on the reporter. **Incident reporting** systems likely work best in the presence of a strong safety culture and when employees have some confidence that the event will be reviewed and actions taken. From studies that use more proactive assessment of harm and error, it is clear that incident reports dramatically *underreport* safety events. With this being the chief limitation, other mechanisms must also be in place to learn about safety. **Trigger tool** systems have been evaluated in pediatrics with encouraging results. These systems use *triggers* , such as the need for an antidote to an opioid overdose or the transfer of a patient to higher-level care, to facilitate targeted medical record review by trained nurses and physicians and elucidate any errors or system risks.

Simulation

Simulation is an excellent tool to better understand system and latent threats. *High-fidelity simulation* can allow clinicians to practice technical skills such as intubation in a safe environment; perhaps more importantly, simulation can help clinical teams improve non-technical skills such as using closed-loop communication and sharing a mental model (e.g., a team leader states, “I believe this patient has septic shock. We are rapidly infusing fluids and giving antibiotics. Blood pressure is normal for age. What other thoughts does the team have?”). It is often easier and more feasible to give feedback in a simulated scenario vs a real event.

Low-fidelity simulation on the hospital unit or in the clinic does not require costly simulated patients and may have advantages in identifying latent threats in the system. For example, a simulated scenario on a medical-surgical unit might identify that nurses do not know where to find a mask for continuous positive airway pressure (CPAP) to support an infant with respiratory failure. Identifying—and then mitigating—this latent threat in a simulated environment is preferable to doing so in an acutely deteriorating child.

Event Analysis

Several types of event analysis, including root cause analysis, apparent cause analysis, and common cause analysis, can help teams understand—and later mitigate—the causes of adverse events. Each model has its own strengths and weaknesses. **Root cause analysis (RCA)** is a useful, robust, and time-intensive process to ascertain the most fundamental, or *root* , causes of a safety event. TJC has required the use of RCA on sentinel events since 1997. Most health systems reserve this methodology primarily for sentinel events because RCAs can take months to complete and require convening a multidisciplinary team of experts. The safety event and its antecedents are reviewed in detail with a focus not on human behavior but instead on systems, hazards, and latent errors. The RCA team works to go beyond the event (e.g., enteral formula feeds connected to and administered through central line) to the proximal causes (e.g., “feeding tube and intravenous tubing are visually identical and are easily attached”) and root cause (e.g., “organization lacks a system to assess human factors risks as new equipment is procured and put into practice”). When root causes are identified and tied to robust improvement action plans, safety can be substantially improved. In addition to the time-intensive nature of RCAs, *hindsight bias* is a risk and needs to be managed carefully by the team. Additional challenges with RCAs include the potential to *overfit solutions* —designing protocols or procedures that may have reduced the risk of the specific safety event reviewed but also introduce new problems and increase the probability of other safety threats—as well as difficulties in spreading solutions to different care areas that often have different needs, processes, and goals.

Apparent cause analysis, common cause analysis, and failure modes and effects analysis are complementary learning methods. **Apparent cause analysis** is performed by a smaller team and is feasible for events that occur often (e.g., the wrong medication is sent from pharmacy). Apparent cause analysis uses a multidisciplinary team to look for proximal causes. Importantly, in each analysis the team works to determine how likely it is that such an event will occur in the future and how widespread the proximate causes are in the microsystem. As with apparent cause analysis, **common cause analysis** seeks to aggregate learning across events. A similar common cause, such as poor handoff procedures, may lead to different safety events (e.g., a missed lab check and a delayed diagnosis); common cause analysis aids leaders in determining this. **Failure mode and effects analysis (FMEA)** is a powerful tool that clinicians use to describe a process and identify *failure modes* , or ways in which each step might fail. A more robust and quantitative form of FMEA rates potential failure modes in 3 categories: probability of event occurring, its severity, and its ability to be detected. The product of these, called the *risk priority number* , can help a team identify which failure modes may lead to the greatest harm and thus which to target first.

Safety Culture

A broad and supportive safety culture likely drives both patient and employee safety outcomes. An organization with a mature safety culture fosters a culture of learning and treats errors as opportunities to improve the system, rather than as the personal failures of individual clinicians. *Just culture* differentiates the mistakes and wrong decisions that a clinician makes commensurate with their training and experience from willful violations and gross or repeated patterns of negligence. A safety culture prioritizes clear and consistent communication and teamwork. Several tools are available to measure safety culture, including the Safety Attitudes Questionnaire and the Agency for Healthcare Research and Quality (AHRQ) surveys on Patient Safety Culture. A strong safety culture supports transfer of responsibility within disciplines at handoffs and across disciplines (e.g., when a nurse is calling a physician with a new concern). Structured communication tools such as the **Situation-Background-Assessment-Recommendation** (SBAR) approach are valued in a safety culture, as are safety behaviors such as “repeat back or write back,” when a critical lab result is shared and repeated back by the receiving clinician. A safety culture also promotes teamwork and aims to ease authority gradients. Teamwork training can occur in simulation or in the clinical system. TeamSTEPPS (**Strategies and Tools to Enhance Performance and Patient Safety**) is a set of teamwork tools developed by AHRQ and the U.S. Department of Defense. It is an evidence-based training that facilitates learning in communication, leadership, situation monitoring, and mutual support.

Authority gradients are quite real in healthcare, and traditional medical culture may have done much to drive these. In a culture of safety, both junior and senior clinicians work together across disciplines to speak up when concerns are identified, to ask questions, and not to proceed if there is uncertainty about safe patient care. Unit/clinic and health system leaders have a critical role in supporting this culture, orienting new employees to its importance, and stepping in if authority gradients or disruptive behaviors contribute to safety events or unsafe conditions.

Reliability Science and High-Reliability Organizations

Reliability in healthcare is defined as the measurable capability of a process, procedure, or health service to perform its intended function in the required time under commonly occurring conditions. Most processes in healthcare organizations currently perform at **Level 1** reliability, meaning a success rate of only 80–90%. To achieve **Level 2** performance (≤5 failures/100 opportunities), processes must be *intentionally designed* with tools and concepts based on the principles of **human factors engineering** and **reliability science** . These processes include creating intentional redundancy, such as independent verification on high-risk medication dosing, and making the default action the desired action based on evidence, such as a default to an influenza vaccination for high-risk patients with asthma. Performance at **Level 3** (≤5 failures/1,000 opportunities), requires a well-designed system with low variation and cooperative relationships and a state of “mindfulness,” with attention to processes, structure, and their relationship to outcomes.

Healthcare can learn important safety lessons from disciplines such as human factors engineering and cognitive psychology. Industries that better leverage learnings from these disciplines—and robustly identify and mitigate threats and use simulation—include commercial aviation and nuclear power, termed *high-reliability organizations* . These organizations achieve exemplary safety records under dynamic and high-risk conditions through consistent application of 5 tenets: (1) a preoccupation with failure;—surprises and errors are thought of as learning opportunities, and learnings spread quickly through the organization; (2) reluctance to simplify interpretations—serious safety events receive an RCA; perspective of multiple stakeholders solicited on other safety events; (3) sensitivity to operations—proactive assessments and huddles target risks to patients and the organization; (4) a commitment to resilience—errors do not disable, and high-risk, uncommon scenarios are negotiated; and (5) deference to expertise—leaders defer to front-line experts when their knowledge is required.

Serious Harm Events and Healthcare-Associated Conditions

Substantial improvement in patient safety has occurred through improvement teams targeting *serious harm* events. The **serious harm event rate** is a composite metric that groups preventable HACs into 1 number (usually a rate per at-risk patient-days), so that an organization or collaborative can track progress on a variety of conditions with 1 metric and chart. Table 5.1 lists frequently targeted HACs. Commonalities among successful improvement teams targeting these HACs include multidisciplinary team membership, clear outcome definitions and measurement, learning systems around each HAC, and attention to both process and outcome measures. Much of the successes with CLA-BSIs was associated with targeted improvements to reliably adhere to a line insertion bundle and a line maintenance bundle. Fig. 5.2 illustrates coincident improvements in process measures and outcomes measure in a hypothetical CLA-BSI project. In this case, after improvement interventions targeted 2 process measures known to be important in CLA-BSI risk—the line insertion and the line maintenance bundles—the QI team saw improvement in both measures and coincident reduction in CLA-BSIs.

Table 5.1

Common Healthcare-Associated Conditions (HACs) Targeted in Quality Improvement Efforts with Interventions

HAC	**DEFINITION**	**COST PER EVENT**	**POTENTIALLY EFFECTIVE INTERVENTIONS**
Central line–associated bloodstream infections	Laboratory-confirmed bloodstream infection with central line in place at time of or 48 hr before onset of event (details at https://www.cdc.gov/nhsn)	$55,646	Line insurance bundle (e.g., handwashing, chlorhexidine scrub), maintenance bundle (catheter care, change dressing, discuss daily if catheter is needed)
Catheter-associated urinary tract infections	Urinary tract infection where an indwelling urinary catheter was in place >2 days on day of event (details at https://www.cdc.gov/nhsn)	$7,200	Protocols for reviewing and removing catheters daily, clear indications for inserting catheters, physician champions, audit and feedback of data
Adverse drug events	Harm associated with any dose of a drug (details at http://www.nccmerp.org/types-medication-errors)	$3,659	Pharmacist review of medication order, computerized physician order entry, co-ordering of laxatives in patients on opiates
Peripheral IV infiltrates	Moderate or serious harm (e.g., diminished pulses, >30% swelling) associated with a peripheral IV infiltrate (details at http://www.solutionsforpatientsafety.org)	—	Hourly reviews of IV status, limitations on use of desiccants through peripheral IVs, remove IVs when no longer needed
Pressure injuries	Localized damage to skin and/or underlying soft tissue usually over a bony prominence or related to a device (details at http://www.solutionsforpatientsafety.org)	—	Screening of high-risk patients (e.g., Braden Q Scale), regular turning of low-mobility patients, regular inspection and skin care; specialized device padding
Surgical site infections	Infection of incision or deep tissue space after operative procedure (details at https://www.cdc.gov/nhsn)	—	Surgical checklist, antimicrobial prophylaxis within 60 min before incision, preoperative baths, postoperative antibiotic redosing
Venous thromboembolism	Blood clot in deep vein, stratified as central line–associated vs not (details at https://www.cdc.gov/nhsn)	$27,686	Screening for high-risk patients, removal of central line catheters when no longer needed, targeted prophylaxis

IV, Intravenous line.

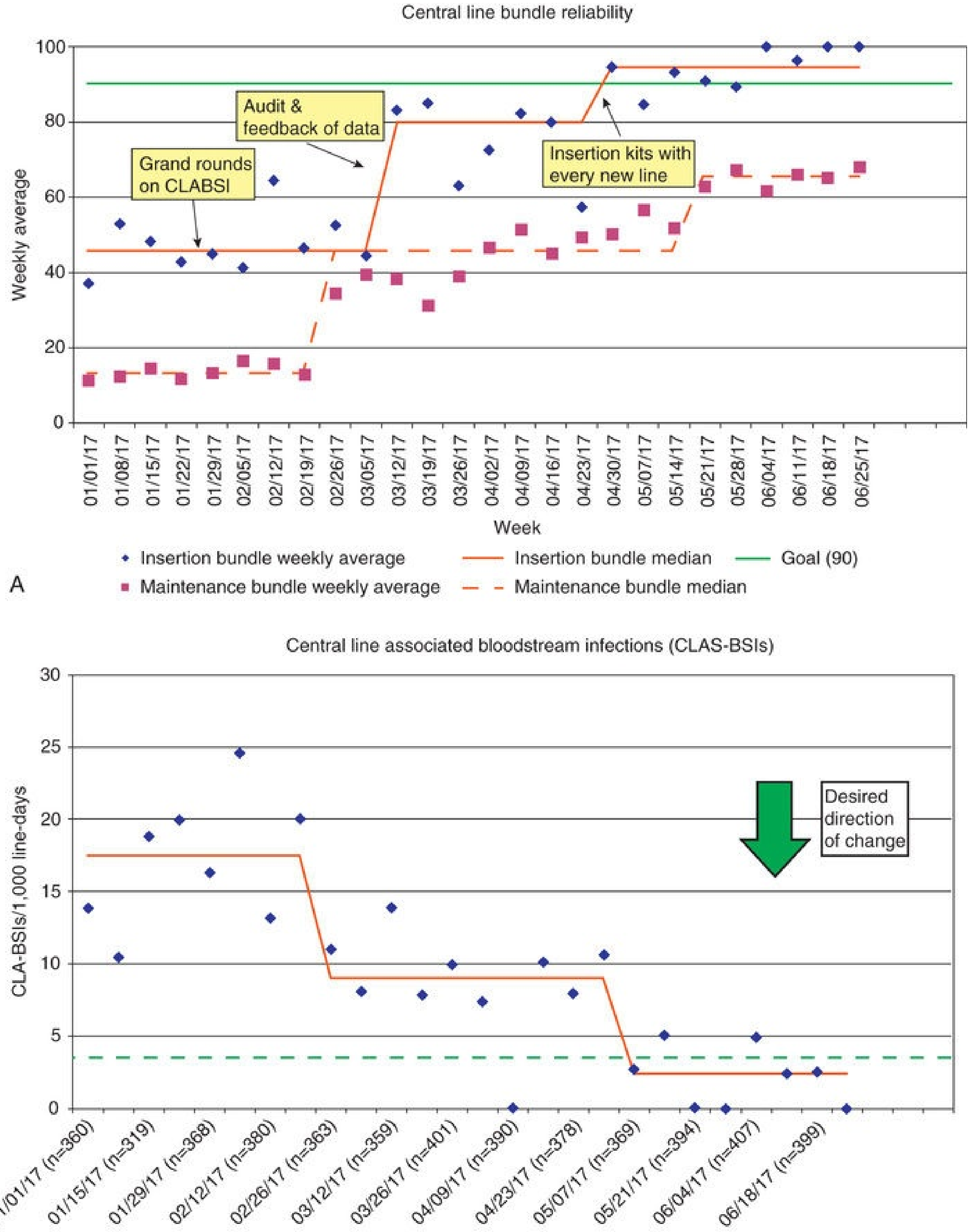

FIG. 5.2 Quality improvement interventions targeted process improvement in the **A,** line insertion bundle, where performance improved from 46% to 95%), and **B,** line maintenance bundle, where performance improved from 13% to 66%. Coincident with the improved bundle performance, the rate of

CLA-BSIs fell from 17.6 to 2.5 per 1,000 line-days.

A safety culture and experienced improvement teams are consistent drivers of success. A **learning network model** , as used in SPS, is effective in bringing project teams (e.g., groups with shared charters to reduce catheter-associated urinary tract infections) together from different hospitals to discuss lessons learned and common barriers faced and negotiated.

Safety Opportunities and Gaps

In addition to HACs, several other safety events are the targets of active study and improvement. Both the unrecognized clinical deterioration of hospitalized children and the poor handoffs across multiple stakeholders lead to substantial and preventable harm. Human factors interventions, such as *timeouts* , are also improving surgical safety.

Clinical Deterioration

The deterioration of hospitalized patients is rarely a sudden and unpredictable event; rather, it is preceded by abnormal vital signs and concerns from patients, families, and providers. **Rapid response systems** are designed to detect deterioration and then deploy teams with critical care expertise to provide treatment or escalate care to an intensive care unit (ICU). While there remains variation in how these teams are activated and how the rapid response teams are staffed (e.g., nurse vs physician led), all U.S. children's hospitals have some version of a rapid response system. The initiation of rapid response teams is associated with a significant reduction in codes outside the ICU and in-hospital mortality.

Pediatric early warning scores (PEWS) are used in most large children's hospitals to identify deteriorating patients by assigning scores based on the degree of abnormality in different body systems. Different versions of PEWS are often employed, but all include scores driven by age-based vital signs as well as nursing assessments in areas such as mental status and perfusion. Importantly, PEWS take these diverse exam elements and combine them into a single score, which when coupled with clear, expected actions (e.g., evaluation by physician at score of 5, evaluation by rapid response team at score of 7) may better detect deterioration and improve safety outcomes.

PEWS are one method of improving a clinician's *situation awareness*, the sense of what is going on around the clinician, the notion of what is important, and the anticipation of future consequences. Maintaining situation awareness can be challenging in dynamic, high-risk environments such as healthcare. Work at several children's hospitals to improve situation awareness has been associated with sustained and significant reductions in unrecognized clinical deterioration. This improvement work first designed systematic and proactive identification of high-risk *watcher* patients, those a nurse or physician felt were close to the edge of deterioration. High-risk patients are discussed at multidisciplinary bedside “huddles” and specific treatment plans and predictions outlined. Concerns are more fully addressed through the rapid response team as well as hospital-wide safety huddles and safety rounds. To gain a better sense of organization safety and performance threats, many hospitals in the SPS collaborative employ a daily safety or operations brief, where leaders from a variety of service lines (e.g., inpatient, pharmacy, perioperative care) can discuss unexpected events and rapidly develop solutions and follow-up plans to mitigate emerging threats that cross disciplines.

Handoffs/I-PASS

There is a growing evidence base on the consequences of poor handoffs and on complex interventions to improve handoffs and resultant safety outcomes. The best-studied handoff is resident-to-resident shift handoff in teaching hospitals. Use of the **I-PASS** mnemonic—*i* llness severity, *p* atient summary, *a* ction list, *s* ituation awareness and contingency planning, and *s* ynthesis by receiver—and the surrounding educational quality improvement curriculum was associated with a significant 23% reduction in medical errors and 30% reduction in adverse events in a 9-hospital study. Related work has described improved communication with work targeting ICU-to-floor, operating room–to-ICU, and inpatient medical team–to–primary care handoffs.

Surgical Safety

Initially, in response to the problem of wrong-patient or wrong-site surgeries, perioperative leaders have developed a set of safety strategies often termed the *tenets of surgical safety* , which are endorsed by the World Health Organization (http://www.who.int/patientsafety/safesurgery). The tenets are implemented as several discrete checklists at key points, or “timeouts,” in the workflow around a procedure or surgery. Several studies have demonstrated reduced harm to patients, and surgical checklists are adopted widely throughout developed and developing world surgical and procedural environments. Typically, checklists are used at 3 key times during a procedure: before induction of anesthesia, before skin incision or insertion of a device into any body cavity or orifice, and before a patient leaves the procedural area or operating room. Key aspects of the impact of this approach include multidisciplinary active participation, visual display of the checklist or other key tools as references, and attention to hierarchies and team-based communication. An evolving area of surgical and procedural safety is the use of simulation and video-based procedure review to improve surgical technique and perioperative team function and identify latent threats.

Ambulatory Safety

Adverse drug events and medication dosing errors are the best-studied safety events in the outpatient environment. A study of children receiving chemotherapy used direct observation by a trained nurse at home and found approximately 70 errors per 100 patients, many of which were serious or significant. Families often make dosing errors in administering liquid medications, particularly when using kitchen spoons rather than dosing syringes. A health literacy–informed pictogram reduces the rates of these errors. Dosing errors and nonadherence also can occur in cancer care, epilepsy, and transplant settings. Additional ambulatory safety threats include delays in diagnosis or treatment caused by mishandling of lab or imaging results and failures in care coordination.

Occupational Safety

The provision of healthcare can be a dangerous profession, with injury rates that surpass those of coal miners. The magnitude of this challenge and efforts to improve workplace safety have gained considerable attention the last several years. Nurses and physicians still typically view a needlestick injury or back strain from lifting a patient as simply “part of the job.” A culture of safety should include employee safety, and health systems should have mechanisms for employees to report injuries, near misses, and threats. Focused improvement efforts might include the roll-out of safer needle systems, education on safe processes, and easy access to lifts for larger children with limited mobility. Violence and patient interaction injuries, often from children with psychiatric disease or developmental disabilities, are a growing source of harm to clinicians.

Emerging Areas of Safety Research and Improvement

Diagnostic error is recognized as an increasingly common and impactful event. There are 2 systems of clinical decision-making. **System 1** is fast, instinctual, and largely unconscious. **System 2** is slow, effortful, and calculating. System 1 and its *heuristics* or *biases* allows for quick—almost automatic—decision-making, often by associating new information with existing patterns or beliefs (e.g., that red object on right side of road is a stop sign; I should stop). However, system 1 thinking can be dangerous in diagnostic thinking, particularly when new data are unconsciously made to fit the preconceived pattern, and are not seen as disconfirming. Many current efforts aim to better understand how well-described cognitive biases (e.g., premature closure, availability bias) play out in clinical care, and what system-based strategies can mitigate their effects (Tables 5.2 to 5.4). Diagnostic error is often an error of omission, making it difficult to measure or to produce valid epidemiologic estimates of its incidence. Despite this, many health systems are pursuing research and improvement to move clinicians from system 1 to system 2 thinking, such as being explicit on uncertainty (e.g., patients admitted from ED as “diagnosis unknown”) or using decision aids to prompt revisiting provisional diagnoses (Table 5.5).

Table 5.2

Cognitive Biases Related to Heuristic Failure

BIASES	DEFINITION
Anchoring	Locking into a diagnosis based on initial presenting features, failing to adjust diagnostic impressions when new information becomes available.
Confirmation bias	Looking for and accepting only evidence that confirms a diagnostic impression, rejecting or not seeking contradictory evidence.
Diagnostic momentum	Perpetuating a diagnostic label over time, usually by multiple providers both within and across healthcare systems, despite the label being incomplete or inaccurate.
Expertise bias/yin-yang out	Believing that a patient who has already undergone an extensive evaluation will have nothing more to gain from further investigations, despite the possibility that the disease process or diagnostic techniques may have evolved so as to allow for appropriate diagnosis.
Overconfidence	Believing one knows more than one does, acting on incomplete information or hunches, and

bias	prioritizing opinion or authority, as opposed to evidence.
Premature closure	Accepting the first plausible diagnosis before obtaining confirmatory evidence or considering all available evidence. “When the diagnosis is made, thinking stops.”
Unpacking principle	Failing to explore primary evidence or data in its entirety and subsequently failing to uncover important facts or findings, such as accepting a biopsy report or imaging study report without reviewing the actual specimen or image; especially important in undiagnosed and rare diseases.

From Bordini BJ, Stephany A, Kliegman R: Overcoming diagnostic errors in medical practice, *J Pediatr* 185:19–25, 2017 (Table I, p 20).

Table 5.3

Cognitive Biases Related to Errors of Attribution

BIASES	**DEFINITION**
Affective bias	Allowing emotions to interfere with a diagnosis, either positively or negatively; dislikes of patient types (“frequent flyers”).
Appeal to authority	Deferring to authoritative recommendations from senior, supervising, or “expert” clinicians, independent of the evidentiary support for such recommendations.
Ascertainment bias	Maintaining preconceived expectations based on patient or disease stereotypes.
Attribution error	Placing undue importance on the perceived internal characteristics or motivations of others, whether they are the patient, the patient's family, or other members of the evaluation team.
Countertransference	Being influenced by positive or negative subjective feelings toward a specific patient.
Outcome bias	Minimizing or overemphasizing the significance of a finding or result, often based on subjective feelings about a patient, a desired outcome, or personal confidence in one's own clinical skills. The use of “slightly” to describe abnormal results.
Psych-out bias	Maintaining biases about people with presumed mental illness.

From Bordini BJ, Stephany A, Kliegman R: Overcoming diagnostic errors in medical practice, *J Pediatr* 185:19–25, 2017 (Table II, p 21).

Table 5.4

Cognitive Biases Related to Errors of Context

BIASES	**DEFINITION**
Availability bias	Basing decisions on the most recent patient with similar symptoms, preferentially recalling recent and more common diseases.
Base-rate neglect	Prioritizing specific information (e.g., a lab value) pertaining to a case while ignoring general base rate information about the prevalence of disease in populations (pre-test probability).
Framing effect	Being influenced by how or by whom a problem is described or by the context in which the evaluation takes place.
Frequency bias	Believing that common things happen commonly and usually are benign in general practice.
Hindsight bias	Reinforcing diagnostic errors once a diagnosis is discovered despite these errors. May lead to a clinician overestimating the efficacy of his or her clinical reasoning and may reinforce ineffective techniques.
Posterior probability error	Considering the likelihood of a particular diagnosis in light of a patient's chronic illness. New headaches in a patient with a history of migraines may in fact be a tumor.
Representative	Basing decisions on an expected typical presentation. Not effective for atypical presentations.

bias	Overemphasis on disease-diagnostic criteria or “classic” presentations. “Looks like a duck, quacks like a duck.”
Sutton's slip	Ignoring alternate explanations for “obvious” diagnoses (Sutton's law is that one should first consider the obvious).
Thinking in silo	Restricting diagnostic considerations to a particular specialty or organ system. Each discipline has a set of diseases within its comfort zone, which reduces diagnostic flexibility or team-based communication.
Zebra retreat	Lacking conviction to pursue rare disorders even when suggested by evidence.

From Bordini BJ, Stephany A, Kliegman R: Overcoming diagnostic errors in medical practice, *J Pediatr* 185:19–25, 2017 (Table III, p 21).

Table 5.5

Solutions to Avoid Diagnostic Errors

1. Enhancing foundational knowledge in medical education
    - Teach symptoms and their differential pathophysiology, not just diseases.
    - Emphasize red flags and must-not-miss diagnoses.
2. Minimizing errors related to heuristic failure
    - Build understanding of system 1 and system 2 thought processes and the risks of heuristic failure.
    - Actively model and encourage counterfactual reasoning and hypothesis generation to enhance system 2 skills.
3. Mitigating errors of attribution
    - Increase awareness of biases toward specific patients by promoting self-reflection.
    - Use a team-based approach and diagnostic strategies that actively dispel biases.
4. Avoiding errors of context
    - Solicit input across a variety of specialties when appropriate.
    - Consciously acknowledge the risk of thinking in silo and actively seek explanations outside one's specialty.
5. Optimizing data gathering, analysis, and hypothesis generation
    - Develop differential diagnoses based on pathophysiology; consider alternatives and competing options.
    - Realize that diagnostic criteria for certain diseases do not account for atypical disease manifestations.
    - Rely on objective individual data, not just disease prevalence rates, when considering the pretest likelihood of a particular diagnosis.

- Avoid diagnostic momentum and question-accumulated diagnostic labels, regardless of who applied the label.

6. Improving hypothesis testing
    - Know the limitations of laboratory tests (i.e., false positives and negatives).
    - Do not be so quick to "rule out" a diagnosis: consider the posttest likelihood of disease in terms of a probabilistic analysis that applies specifically to the patient.
    - Acknowledge that the initial "working" diagnosis may not always be the final diagnosis.
    - Rely on evidence-based data and avoid authority- or overconfidence-based errors.
    - Recognize that diagnosis is an iterative and interactive process that should not be bounded by premature closure or anchoring. Be open to both confirmatory and nonconfirmatory data.
    - Both know and accept what you do not know.
7. Critical solutions for complex and undiagnosed and rare disease patients
    - Maintain healthy skepticism, especially with patients who come prediagnosed.
    - Analyze historical diagnostic data methodically and thoroughly and unpack all data completely. Examine actual studies, such as tissue specimens and imaging investigations, and do not rely on written reports.
    - Question the working diagnosis when findings or the clinical course does not fit.
    - Realize that patients can have more than one disease process.
    - Incorporate all data and avoid minimizing the significance of abnormal results. Do not ignore contradictory clinical, laboratory, or imaging data.
    - Never say "never" or "it cannot be."
    - Use a systematic team-based approach to enhance debiasing, broaden the collective knowledge base, and minimize context-related errors.
    - Be aware that patients with undiagnosed and rare diseases may have an atypical or rare manifestation of a recognizable common disease, or may have a rare disease.
    - Use extensive literature review and search strategies based on the

patient's phenotype and individual findings and hypotheses.

From Bordini BJ, Stephany A, Kliegman R: Overcoming diagnostic errors in medical practice. J Pediatr 185:19-25, 2017 (Table V, p. 24).

Alarm fatigue , when a healthcare provider is subject to so many interruptions that a potentially relevant alarm is not heard, is also an area of active research and improvement. In the hospital, many physiologic monitor alarms occur each day (up to 400 per patient in some environments), and nurses exposed to a high volume of alarms respond more slowly to them. Interventions currently being studied include removing monitors from patients unlikely to benefit from them and designing smart alarms that alert only when certain scenarios occur (e.g., bradycardia in context of hypoxia). Particularly in the case of bronchiolitis, the overuse of pulse oximetry monitors likely contributes to **overdiagnosis** —the identification of an existing abnormality but whose detection will have no net benefit for the patient. Overdiagnosis of hypoxemia in children with bronchiolitis may contribute to hospital admissions, prolong length of stay, and subject children to hospital-related harm.

Alert fatigue is related to alarm fatigue but refers to clinicians not processing an alert, such as a medication interaction from the electronic health record, when receiving a large burden of alerts often regarded as nonactionable.

The most important area of current and growing research may be how health care providers can partner with patients and families to improve the safety of care. Families often identify a wide number of errors and safety events that clinicians fail to report. More important than families simply reporting mistakes are early efforts to engage families more broadly and deeply to co-produce healthcare that is efficient, effective, and safe.

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CHAPTER 6

Ethics in Pediatric Care

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Pediatric ethics is the branch of bioethics that analyzes moral aspects of decisions made relating to the healthcare of children. In general terms, the **autonomy** -driven framework of adult medical ethics is replaced by a **beneficent** paternalism (or parentalism) in pediatrics. Pediatric ethics is distinctive because the pediatric clinician has an independent fiduciary obligation to act in a younger child's **best interest** that takes moral precedence over the wishes of the child's parent(s). For older children, the concept of **assent** suggests that the voice of the patient must be heard. These factors create the possibility of conflict among child, parent, and clinician. The approach to the ethical issues that arise in pediatric practice *must* include respect for parental responsibility and authority balanced with a child's developing capacity and autonomy. Heterogeneity of social, cultural, and religious views about the role of children adds complexity.

Assent and Parental Permission

The doctrine of *informed consent* has limited direct application to children and adolescents who lack decisional capacity. The capacity for informed decision-making in healthcare involves the ability to understand and communicate, to reason and deliberate, and to analyze conflicting elements of a decision using a set of personal values. The age at which a competent patient may legally exercise voluntary and informed consent for medical care varies from state to state and may be limited to specific conditions (sexually transmitted infections, family planning, drug or alcohol abuse).

In contrast to decisions about one's own care, a parent's right to direct a child's medical care is more limited. For this reason, the term *parental consent* is misleading. The concept of parental permission (rather than consent) reflects a *surrogate* or *proxy* decision made by a parent on behalf of a child. It is constrained both by the child's best interest and the independent obligation of clinicians to act in the child's best interest, even if this places them in conflict with a parent. In any given instance, the decision of what is or is not in a child's best interest may be difficult, especially given the diverse views of acceptable child rearing and child welfare. Parents are (and should be) granted wide discretion in raising their children. In cases involving a substantial risk of harm, the moral focus should be on avoiding or preventing harm to the child, not on a parental right to decide. While the term *best interests* may be too high of a threshold requirement, a minimum standard of *basic interests* is ethically obligatory.

Respect for children must account for both a child's vulnerability and developing capacity. This respect encompasses both the protective role of parental permission and the developmental role of **child assent** (the child's affirmative agreement). Understanding the concept of assent is one of the major conceptual challenges in pediatric ethics. The **dissent** (or disagreement) of a child is the opposite of assent and is also morally relevant. Pediatric ethics *requires* clinicians and parents to override a child's dissent when a proposed intervention is essential to the child's welfare. Otherwise, assent should be solicited and dissent honored. In seeking younger children's assent, a clinician should help them understand their condition, tell them what they can expect, assess their understanding and whether they feel pressured to assent, and solicit their willingness to participate. All efforts must be made to delineate situations in which the test or procedure will be done regardless of the child's assent/dissent, and in such cases the charade of soliciting assent should be avoided. There is an important distinction between soliciting assent and respectfully informing a child that a test or procedure will take place regardless of the child's decision. Optimally, an educational process can transpire (if time allows) to gain the trust and assent of the child-patient. When this cannot occur, pediatric ethics requires that clinicians apologize to a child for acting to override dissent.

Older children or adolescents may have the cognitive and emotional capacity to participate fully in healthcare decisions. If so, the adolescent should be provided with the same information given to an adult patient. In such situations the patient may be able to provide informed consent ethically but not legally. The adolescent's parent(s) remain in a guiding and protective role. The process of communication and negotiation will be more complex should disagreement arise between the parent and adolescent. Pediatricians can be effective intercessors when these situations arise, making use of communication skills in a respectful way that uses an ethical framework as recently described by Sisk et al.

Treatment of Critically Ill Children

Infants, children, and adolescents who become critically ill may recover fully, may die, or may survive with new or worsened limitations of function. Uncertainty about outcomes can make planning goals of care difficult, or if misunderstandings between patient, families, and medical staff occur, may drive conflict over treatment proposals. *Ethical issues* that arise during critical illness include balancing benefits, burdens, and harms of therapy in the face of uncertainty; maintaining a helpful degree of transparency and communication about medical standards of care at an institution; understanding and respecting religious and cultural differences that impact requests for or refusal of treatments; defining limits of therapy based on assessments of medical futility; recognizing the moral equivalence of not starting an ineffective treatment and stopping (although the 2 acts may seem very different to families and providers); and controversies such as withholding medically administered nutrition and hydration.

Transitioning the Goals of Care

Most acutely ill children who die in an intensive care unit do so after a decision has been made to forgo or withdraw **life-sustaining medical treatment (LSMT)** , and the same may apply in the chronically ill population. LSMT is justified when the anticipated benefit outweighs the burdens to the patient; the availability of technology does not in and of itself obligate its use. Decisions to use, limit, or withdraw LSMT should be made after careful consideration of all pertinent factors recognizable by both family and medical staff, including medical likelihood of particular outcomes, burdens on the patient and family, religious and cultural decision-making frameworks, and input by the patient when possible. Although fear of legal repercussions may sometimes drive treatment and medical advice, ultimately decisions should be based on what is thought to be best for the patient rather than based on fears of litigation.

The concept of **futility** has been used to support unilateral forgoing of LSMT against the wishes of patients and families by holding that clinicians should not provide futile (or useless) interventions. If *medical futility* is defined narrowly as the impossibility of achieving a desired physiologic outcome, forgoing a particular intervention is ethically justified. However, this approach may not adequately engage professionals and families in understanding facts and values that might allow the same therapy to reach other goals, and may leave medical and family stakeholders in permanent conflict. Guidance from critical care groups recommend restricting use of the word *futility* to situations of strict physiologic futility, and instead use process guidelines to evaluate and manage situations of *potentially inappropriate treatment* . If agreement cannot be reached through clear and compassionate communication efforts, further input should be sought from an ethics consultant or committee.

Communication about life-threatening or life-altering illness is challenging and requires skills learned through both modeling and practice. These *skills* include choosing a setting conducive to what may become one or more long conversations; listening carefully to children's and families' hopes, fears, understanding, and expectations; explaining medical information and uncertainties simply and clearly without complicated terms and concepts; conveying concern and openness to discussion; and being willing to share the burdens of decision-making with families by giving clear recommendations. Discussing difficult topics with children requires an understanding of child development and can be aided by professionals such as child psychologists or child life specialists. Such conversations and their outcomes have a major impact on the future care of the patient, on families, and on medical staff. For this reason, ongoing evaluation of goals and communication about them is needed with families and within complex medical teams as the course of the illness unfolds.

Experts recognize that good medical care involves providing for communication, symptom management, and a range of supportive services from the onset of acute illness. In this way, if an illness proves to be life-limiting despite aggressive therapies, the elements of palliative care are already in place. This concept has had difficulty gaining traction, especially in critical care settings, because of the mistaken conflation of broadly defined palliative measures with hospice care. **Palliative care** interventions focus on the relief of symptoms and conditions that may detract from quality of life regardless of the impact on a child's underlying disease process, and as such are important whether care is focused on cure or on transitioning to end-of-life care (see

Chapter 7). Some interventions regarded as life-sustaining, such as chemotherapy, may be ethically acceptable in the end-of-life setting if their use decreases pain and suffering rather than only prolonging dying.

Withholding and Withdrawing Life-Sustaining Treatment

Limitation of interventions or withdrawal of existing therapies are ethically acceptable if they are congruent with a plan of care focused on **comfort** and **improved quality** at the end of life rather than cure. The prevailing view in Western, traditional medical ethics is that there is no moral distinction between withholding or withdrawing interventions that are not medically indicated. Uncertainty in predicting a child's response to treatment may drive the initiation and continuation of interventions that are subsequently determined to be no longer supportive of shared goals of care. It is necessary to evaluate continually the results of these treatments and the evolution of the illness to recognize whether such interventions continue to be the best medical and moral choices. Maintaining the focus on the child rather than on the interests of parents or medical staff will help guide decision-making.

The decision about whether to attempt **cardiopulmonary resuscitation** (CPR) may become an issue to discuss with parents of children living with life-threatening or terminal conditions. All elements of end-of-life care approaches, including resuscitation status, should be supportive of agreed-on goals of care. It is imperative that decisions and plans are effectively communicated to all caregivers in order to avoid denying medically effective interventions and measures to ensure comfort. Orders about resuscitation status should clarify the plan regarding intubation and mechanical ventilation, the use of cardiac medications, chest compressions, and cardioversion. Because goals of care may change over time, a medical order regarding resuscitation is not irrevocable. Clinicians may assume that the absence of a **do-not-attempt-resuscitation (DNAR)** order obligates them to perform a prolonged resuscitation. This action may not be ethically supportable if resuscitative efforts will not achieve the desired physiologic end-point. In all cases, treatments should be tailored to the child's clinical condition, balancing benefits and burdens to the patient. Resuscitation should not be performed solely to mollify parental distress at the tragic time of the loss of their child.

Advance Directives

An *advance directive* is a mechanism that allows patients and/or appropriate surrogates to designate the desired medical interventions under applicable circumstances. Discussion and clarification of resuscitation status should be included in advance care planning, and for children attending school despite advanced illness, may need to be addressed in that setting. Decisions regarding resuscitation status in the out-of-hospital setting can be an important component of providing comprehensive care.

The 1991 federal Patient Self-Determination Act requires that healthcare institutions ask adult (>18 yr) patients whether they have completed an **advance directive** and, if not, inform them of their right to do so. Few states support creation of broad advance directives for minors because advance directives are traditionally created for persons with legal decision-making capacity. Some have moved in this direction, however, because it is recognized that minors may be capable of participating in decision-making, especially if they have experienced chronic disease. Most states have approved the implementation of **prehospital** or **portable DNAR orders** , through which adults may indicate their desire not to be resuscitated by emergency personnel. On a state-by-state basis, portable orders regarding resuscitation status may also apply to children. If DNAR orders exist for an infant or a child, it is important to communicate effectively about their intent among all potential caregivers, because nonmedical stakeholders such as teachers or sitters may not want to be in the position of interpreting or honoring them. Some institutions have established local policies and procedures by which an appropriately executed, outpatient DNAR order can be honored on a child's arrival in the emergency department. Key features may include a standardized document format, review by an attending physician, ongoing education, and involvement of a pediatric palliative medicine service.

In cases involving prenatal diagnosis of a lethal or significantly burdensome anomaly, parents may choose to carry their fetus/unborn child to term in order to cherish a short time with the infant after birth, but they do not feel that resuscitation or certain other aggressive measures would support their well-considered goals of care. In this setting, a birth plan explaining the reasons for each choice can be developed by the parents and medical staff before delivery and shared with involved medical staff. This approach gives staff a chance to find other caregivers if they are uncomfortable with the approach, without abandoning the care of the child. If, after evaluation at birth, the infant's condition is as had been expected, honoring the requested plan is ethically supportable and should be done in a way that optimizes comfort of the infant and family.

Many states use **Physician Orders for Life-Sustaining Treatment** or **Medical Orders for Life-Sustaining Treatment** approaches to communicating a patient or surrogates wishes regarding advance care planning. Other tools, such as **Five Wishes** , have been adapted for use by adolescent patients to elicit values and desires. It is important for pediatricians to learn which pathways for communicating goals of care are available in their own states.

Artificial Hydration and Nutrition

Issues surrounding withholding or withdrawing artificial hydration and nutrition are controversial, and interpretations are affected by parental, religious, and medical beliefs. Any adult or child who is fully dependent on the care of others will die as a result of not receiving hydration and nutrition. Case law has supported the withholding of artificially administered nutrition and hydration in the setting of adult vegetative or permanently unconscious patients who can be shown to have previously expressed a wish not to be maintained in such a state. This requires a valid advance directive, or for a surrogate decision maker to speak on behalf of the patient's known wishes. Because infants and many children have not reached a developmental stage in which such discussions would have been possible, decisions about stopping artificially administered nutrition and hydration as a limitation of treatment are more problematic. These decisions should be based on what families and caregivers decide best support comfort. In the child who is imminently dying, unaware of hunger, does not tolerate enteral feedings, and in whom family and staff agree that IV nutrition and hydration only prolong the dying process, it may be ethically supportable to withhold or withdraw these treatments based on a benefit-burden analysis.

The Doctrine of Double Effect

Treatment decisions at the end of life may include limitations of certain LSMT or may involve the use of analgesic or sedative medications that some fear may shorten life, thereby causing death. The doctrine of double effect (**DDE**) holds that an action with both good and bad effects is morally justifiable if the good effect is the only one intended, and the bad effect is foreseen and accepted, but not desired. In pediatrics, DDE is most commonly applied in end-of-life cases, when upward titration of medication (opiates) necessary to relieve pain, anxiety, or air hunger can be expected to result in a degree of respiratory depression. In such cases, meeting a provider's obligation to relieve suffering is the intended effect, and this obligation to the patient outweighs the acknowledged but unavoidable side effect. Choosing medications that adequately relieve symptoms with minimal adverse effects would be ethically preferable, but the obligation to provide comfort at the end of life outweighs the foreseeable occurrence of unavoidable side effects. Hastening death as a primary intention is not considered to be morally acceptable.

Providing pain medication guided by the DDE should not be confused with active euthanasia. The distinction is clear:

- In **active euthanasia** , causing death is chosen as a means of relieving the symptoms that cause suffering.
- Under DDE, adequate management of pain, anxiety, or air hunger is recognized as an obligation to dying patients, and is provided by careful titration of medications in response to symptoms. If death occurs sooner as a result, this is accepted.

In both cases the patient dies, and in both cases suffering ends, but immediate death is the intended consequence only in the case of euthanasia. Codes of ethics and legislation in many states support the obligation to provide pain and symptom relief at the end of life, even if this requires increasing doses of medication.

Neonatal Ethics

As neonatal care has evolved, the limits of viability of extremely premature infants are continuing to change. This introduces new elements of uncertainty to decision-making, often in emotionally fraught circumstances such as a precipitous premature delivery. In cases of uncertain prognosis, the American Academy of Pediatrics (AAP) supports parental desires as driving decision-making, while encouraging providers to recognize when treatments are inappropriate, and using a careful shared decision-making approach to developing plans of care.

The federal **Child Abuse Prevention and Treatment Act** of 1984 (CAPTA), which became known as “Baby Doe Regulations,” required state child protective services agencies to develop and implement mechanisms to report to a specific government agency treatment that providers believed was withheld from infants on the basis of disability. Exceptions were (1) an infant is chronically and irreversibly comatose, (2) if providing a treatment would merely prolong dying, would not be effective in ameliorating or correcting all the infant's life-threatening conditions, or would be futile in terms of the infant's survival, and (3) if the treatment would be virtually futile and inhumane. This legislation pertains *only* to infants and is intended to prevent discrimination on the basis of disability alone. One consequence of the legislation was a shift from potential undertreatment to widespread overtreatment (LSMT that does not serve the interests of the child) of severely disabled newborns. As parental involvement in decisions-making is again taking a more central role, and as palliative care approaches in infants have become more available and skilled, balanced approaches to valuing lives of disabled infants should be considered. Understanding institutional, regional, state, and national regulations related to care of infants is important in order to practice within regulatory frameworks while respecting family values and pursuing the interests of the patient.

Active euthanasia of severely suffering disabled newborns has been legalized in The Netherlands and Belgium, using protocols designed to minimize risk of abuse and maximize transparency. It is currently illegal in the United States, and although controversy surrounds the subject, the predominant view is that active euthanasia is not ethically acceptable in the care of infants and children, instead favoring palliative treatment and potential limitation of escalation.

Declaring Death and Organ Donation

Donation of solid organs necessary to support life can occur after a patient is declared dead based on either irreversible cessation of neurologic function of the brain and brainstem (death by neurologic criteria, or *brain death*) or a predetermined period of cardiac asystole called *circulatory death* . To avoid a potential conflict of interest by surgeons or others caring for a potential organ recipient, the request for organ donation should be separated from the clinical discussion of either brain death or withdrawal of LSMT. Although clinicians may be the first providers to enter discussion about death and organ donation with family members during conversations about outcomes and options, detailed discussion of organ donation should be done by other individuals who are specifically trained for this purpose. This decoupling of clinical decision-making from a request for organ donation by trained individuals, perhaps by providing families with expert information without a perceived conflict of interest, has been associated with improved donation rates.

Death by Neurologic Criteria

Death by neurologic criteria (**DBNC**), commonly referred to as “brain death,” may be difficult for families to understand when the child appears to be breathing (although on a ventilator), pink, and warm to the touch, and when language such as “life support” is used at the bedside by staff. Studies also document clinician misunderstanding of the diagnosis of DBNC. For these reasons, strict criteria adhering to nationally accepted guidelines must be used to determine when irreversible cessation of brain and brainstem function has occurred and adequately document these findings (see Chapter 85).

The states of New York and New Jersey allow families to object on “religious grounds” to the declaration of DBNC. In this situation the clinical determination of DBNC sets the stage for a discussion of forgoing LSMT, rather than the death of the patient. A unilateral decision not to initiate new or *escalate* existing interventions is ethically supportable under these circumstances, given the documented death of the patient. Even though it would seem to follow that a similar unilateral decision to withdraw existing interventions would also be supportable, this act is not in accordance with the intent of the state laws. Institutional procedures for conflict resolution, including involvement of the courts if necessary, should be followed.

Circulatory Death

Protocols allowing for **organ donation after determination of circulatory death (DDCD)** rather than after DBNC have been developed. DDCD can occur under either controlled (after planned withdrawal of LSMT) or uncontrolled (after failed CPR) circumstances, but in both cases require rapid removal of organs in order for subsequent transplantation to be successful. An increasing number of programs are pursuing DDCD protocols after federal legislation began requiring accredited hospitals to address the issue in hopes of decreasing organ shortages. Hospitals can make policy that either allows or disallows the process. In adults, consent for donation by either means can be obtained from patients or surrogates; for children, parents or guardians would make the decision to donate.

Ethical concerns about DDCD protocols focus on 2 principles that have served as the basis for organ donation: (1) the *dead donor* rule limiting the donation of vital organs to those who are irreversibly dead (either by circulatory or neurologic criteria, not both), and (2) the absence of conflict of interest between clinical care and organ procurement. With DDCD protocols, *irreversibility* has been declared at varying times after asystole occurs (usually 2-5 min), to avoid spontaneous return of circulation after forgoing CPR. To avoid a potential conflict of interest during the DDCD process, there is a requirement for strict decoupling of end-of-life care after discontinuation of LSMT and presence of the transplant team. Unlike in the setting of DBNC, a patient who is being considered for DDCD remains alive until after asystole has occurred. Careful evaluation by the transplantation team and organ procurement agency is performed before discontinuation of LSMT. Then, in most DDCD protocols, the medical caregivers from the ICU continue to care for the patient until after death by cardiac criteria has been declared, and only then is the surgical transplant team allowed into the room to procure organs.

It is *ethically imperative* to correctly diagnose the state of death, whether by neurologic criteria or prior to organ donation after cardiac death. Doing so avoids the danger of removing life-sustaining organs from a living person. Strict adherence to an ethically sound protocol is the best way to prevent both the perception and the potential reality of mistakes related to the pronunciation of death and organ procurement.

Religious or Cultural Objections to Treatment

Differences in religious beliefs or ethic-based cultural norms may lead to conflict between patients, families, and medical caregivers over the approach to medical care. Pediatricians need to remain sensitive to and maintain an attitude of respect for these differences, yet recognize that an independent obligation exists to provide effective medical treatment to the child. An adult with decision-making capacity is recognized as having the right to refuse treatment on religious or cultural grounds, but children who have not yet developed this capacity are considered a vulnerable population who has a right to treatment. In situations that threaten the life of the child or that may result in substantial harm, legal intervention should be sought if reasonable efforts toward collaborative decision-making are ineffective. If a child's life is imminently threatened, medical intervention is ethically justified despite parental objections.

Pediatric Ethics Committees and Ethics Consultation

Most hospitals have *institutional ethics committees* to assist with policy development, education, and case consultation. When these committees serve institutions caring for children, they may be referred to as *pediatric ethics committees* . Because of the important differences in approach between adult and pediatric ethics, member expertise on this committee should include those with special insight into the unique ethical issues arising in the care of children. Such committees generally provide ethics consultation advice without mandating action or being determinative. For the vast majority of decisions involving the medical treatment of children (including forgoing LSMT), pediatric clinicians and parents are in agreement about the desirability of the proposed intervention. Because of the ethical importance of assent, the views of older children should also be given considerable weight.

Pediatric ethics committees typically perform at least 3 different functions: (1) the drafting and review of institutional policy on such issues as DNAR orders and forgoing LSMT; (2) the education of healthcare professionals, patients, and families about ethical issues in healthcare; and (3) case consultation and conflict resolution. Although the process of *case consultation* may vary, ideally the committee (or consultant) should adopt a collaborative approach that uncovers all the readily available and relevant facts, considers the values of those involved, and balances the relevant interests, while arriving at a recommendation based on a consistent ethical analysis. One helpful approach involves consideration of the 4 following elements: (1) medical indications, (2) patient preferences, (3) quality of life, and (4) contextual features. Another framework based on principles would suggest attention to respect for persons, beneficence/nonmaleficence, and justice.

Pediatric ethics committees often play a constructive role when parents and medical staff cannot agree on the proper course of action. Over the past several decades, these committees have acquired considerable influence and are increasingly recognized by state courts as an important aid in decision-making. The membership, policies, and procedures of a pediatric ethics committee should conform to accepted professional standards.

Newborn Screening

The *Oxford Dictionary of Public Health* defines screening as "the identification of a previously unrecognized disease or disease precursor, using procedures or tests that can be conducted rapidly and economically on large numbers of people with the aim of sorting them into those who may have the condition(s)… and those who are free from evidence of the condition(s)." Several programs, such as newborn screening for inborn errors of metabolism (see Chapter 102 ; e.g., phenylketonuria and hypothyroidism), are rightly counted among the triumphs of contemporary pediatrics. The success of such programs sometimes obscures serious ethical issues that continue to arise in proposals to screen for other conditions for which the benefits, risks, and costs have not been clearly established. Advances in genetics and technology have led to exponential growth in the number of conditions for which screening programs might be considered, with insufficient opportunity to study each proposed testing program (see Chapter 95).

The introduction of screening efforts should be done in a carefully controlled manner that allows for the evaluation of the costs (financial, medical, and psychological) and benefits of screening, including the effectiveness of follow-up and treatment protocols. New programs should be considered *experimental* until the risks and benefits can be carefully evaluated. Screening tests that identify candidates for treatment must have demonstrated sensitivity, specificity, and high predictive value, lest individuals be falsely labeled and subject to possibly toxic treatments or to psychosocial risks. As newborn screening tests are being developed, parents should be given the opportunity to exercise informed parental permission or refusal. However, once a particular screening test has been clearly demonstrated to benefit the individual or public health, a formal, active parental permission process may not be ethically obligatory.

A persistent ethical issue is whether screening should be (1) voluntary ("opt in"), (2) routine, with the ability to "opt out" or refuse, or (3) mandatory. A **voluntary** approach entails an informed decision by parents before screening.

Concern is often expressed that seeking parental permission is ethically misguided for tests of clear benefit, such as phenylketonuria screening, because refusal would constitute neglect. **Routine** testing with an opt-out approach requires an explicit refusal of screening by parents who object to this intervention. The principal ethical justification for **mandatory** screening is the claim that society's obligation to promote child welfare through early detection and treatment of selected conditions supersedes any parental right to refuse this simple and low-risk medical intervention. Parental permission is clearly required when there is a research agenda (i.e., for incorporating experimental tests into established screening programs).

Genetics, Genomics, and Precision Medicine

Genetics refers to the study of particular genes, and **genomics** describes the entirety of an individual's genetic material. Genomics has been made possible by technologic advances that allowed the rapid and inexpensive sequencing now used in clinical care. The development of **precision medicine** is in large part predicated on genomic science and may have a major impact on the practice of pediatrics in the future. Efforts to undertake whole genome sequencing of newborns may yield actionable information to benefit the child, but also carry the risk of stigmatization, false positives, and unwanted information that could lead to anxiety and psychological distress.

Genetic testing of young children for late-onset disorders such as the *BRCA1* and *BRCA2* breast cancer risk genes has also been the subject of some ethical controversy. Knowledge of increased risk status may lead to lifestyle changes that can reduce morbidity and the risk of mortality, or may precipitate adverse emotional and psychological responses and discrimination. Because many adults choose not to be tested for late-onset disorders, one cannot assume that a child would want or will benefit from similar testing. Genetic testing of young children for late-onset disorders is generally inappropriate unless such testing will result in interventions that have been shown to reduce morbidity and mortality when initiated in childhood. Otherwise, such testing should be deferred until the child has the capacity to make an informed and voluntary choice.

Adolescent Healthcare

Adolescent Assent and Consent

Many adolescents are more like adults than children in their capacity to understand healthcare issues and to relate them to their life goals (see Chapter 132). Teenagers may lack legally defined competency, yet they may have developed the capacity meet the elements of informed consent for many aspects of medical care (see Chapter 137). There are also public health reasons for allowing adolescents to consent to their own healthcare with regard to reproductive decisions, such as contraception, abortion, and treatment of sexually transmitted infections. Strict requirements for parental permission may deter adolescents from seeking healthcare, with serious implications for their health and other community interests.

Counterbalancing these arguments are legitimate parental interests to maintain responsibility and authority for child rearing, including the opportunity to influence the sexual attitudes and practices of their children. Others claim that access to treatment such as contraception, abortion, or needle exchange programs implicitly endorses sexual activity or drug use during adolescence. Pediatricians should not impose their own moral beliefs in these disputes. Rather, they should provide unbiased evidence-based information and nonjudgmental support. One guiding principle should be encouragement of children and adolescents to begin taking responsibility, with guidance, for their own health. This requires some input from parents or guardians but also some privacy during decision-making as adolescents achieve developmentally anticipated separation from parental control.

Chronic Illness

The normal process of adolescent development involves gradually separating from parents, establishing self-confidence, asserting individuality, developing strong peer relationships, solidifying an ability to function independently outside the family, and taking on increasing autonomy in healthcare decisions. Most developmentally normal children older than age 14 yr understand the implications of well-explained medical options as well as the average adult, and their input into their own care should be respected. For children living with chronic illness, the ability to make medical decisions for themselves may either occur earlier than for those who have been previously healthy, or may occur later if, because of illness, they have not been able to achieve normal developmental milestones or psychological maturity. The clinician's role involves assessment of the individual adolescent patient's ability to understand the medical situation, to support the patient's efforts to express wishes regarding medical treatment, to value and encourage parental support and involvement, and to foster cooperation and mutual understanding. This may be difficult in situations in which parents and adolescents disagree about life-sustaining treatments such as organ transplantation or chemotherapy, but many such conflicts may be resolved by exploring the reasons for the disagreement. Overriding an adolescent's wishes should be done very infrequently, and only after careful consideration of the potential consequences of unwanted interventions.

Decisions in Terminally Ill Adolescents

Most adolescents share end-of-life decision making with family members, although communication may be challenging because of a growing sense of independence. Open communication and flexibility about treatment preferences may help teens cope with fears and uncertainties. Development of an age-appropriate advance directive may support the patient's emerging autonomy by clarifying the adolescent's wishes, while fostering a collaborative process among the patient, family, and medical caregivers. From the time of diagnosis of a life-threatening condition through the end-of-life phase, children should be included in a developmentally tailored process of communication and shared decision-making that builds a foundation of mutual respect and trust. Some experts believe that most adolescents are not yet fully capable of making a decision to forgo life-sustaining treatment. Careful case-by-case evaluation is required to make this determination, and assistance from developmental psychologists and ethics consultants may be helpful.

Research

The central ethical challenge of pediatric research is the need to balance protection of children from research risk against the ethical imperative of conducting studies to better the lives of future children. *Research* is defined in the federal regulations as “a systematic investigation designed to develop or contribute to generalizable knowledge.” For any research to be performed, the risks should be minimized and reasonable with respect to any anticipated benefits to the participants and the importance of the resulting knowledge. That some children derive a direct benefit from participation in research must also be considered, making it important to distinguish research with the prospect of direct benefit from nontherapeutic pediatric research. *Because children are a vulnerable population, there are restrictions on the research risks to which a child may be exposed,* in contrast to the risk level acceptable for research with consenting adults **.** These restrictions function by limiting the type of research that institutional review boards (IRBs) are permitted to approve and by specifying the conditions under which parents have the moral and legal authority to permit a child to participate in research.

Nontherapeutic research in children is the most ethically controversial because it holds no expected direct benefit for the individual. The prohibition against using a person (especially a child) solely as a means to an end has led some to argue that children should *never* be used in nontherapeutic research. The more widely held opinion is that children may be exposed to a limited degree of risk with IRB approval, parental permission, and assent if the child is capable. The federal regulations allow healthy children to participate in minimal-risk research regardless of the potential benefit to the child. More controversially, the regulations also state that children with a disorder or condition may be exposed to slightly more than minimal risk in nontherapeutic research if the child's experience is similar to everyday life with the condition and the anticipated knowledge is of vital importance for understanding the condition.

In pediatric research with the prospect of direct benefit, the risks must be justified by the anticipated benefit to the child, and the balance of anticipated benefit to the risk should be at least as favorable as that presented by available alternatives. *The welfare of an individual child must always come before the scientific goals of the research study.*

U.S. regulations for the protection of human research participants rest on 2 foundations: (1) independent review of the ethics and science of the research by an IRB **prior to** (2) voluntary and informed consent of the participant. Although it is not amenable to regulation, the *integrity* of the investigator is probably the most important element contributing to the protection of human research participants. The standard for informed consent in a research setting is higher than for clinical care because the risks and benefits are typically less clear, the investigator has a conflict of interest, and humans have historically been subjected to unauthorized risks when strict requirements for consent were not respected.

Adolescents who are competent may sometimes consent to be research participants. Younger children may participate in a process of assent, but this does not imply that a child's signature on an assent document is necessarily a legal or ethical requirement. Children should be given the opportunity to dissent, particularly for nontherapeutic research, when there cannot be a claim that participation is in the child's interest. In the United States, national regulations require that reasonable efforts be made at least to inform children who are capable of understanding that participation is *not* part of their care, and therefore they are free to refuse to participate. In the rare case that the research offers a direct benefit to the child that would not otherwise be available, the regulations do not require child assent but only parental permission.

In addition to the protection that informed consent or parental permission is intended to provide, virtually all research involving humans in the United States is reviewed by an IRB, as required by federal regulations for institutions receiving federal research funds and for drug research regulated by the U.S. Food and Drug Administration. For research that carries more than a minor increase over minimal risk without prospect of benefit to the child such that a local IRB cannot provide approval, there is a process for federal review of research that “presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.” Ultimately, the U.S. Secretary of Health and Human Services has the authority to approve such research.

Balancing Maternal and Fetal Interests

Some situations require balancing of maternal health and well-being with those of the fetus/unborn child to reach an ethically sound decision. For instance, innovative surgical treatment of a prenatally diagnosed anomaly may help the fetus/unborn child survive, but in the process place the mother at risk of injury or of loss of the pregnancy. Alternatively, a pregnant woman may object to cesarean delivery for various reasons despite advice that it may protect the fetus/unborn child during birth. Another important situation involves risk-taking behaviors during pregnancy that are known to injure the developing fetus/unborn child, such as drug or alcohol use. These issues raise conflicts over clinicians’ responsibility to the living, competent decision-maker—the pregnant mother—as opposed to the interests of the fetus/unborn child.

In certain cases, U.S. courts have decided that a woman can be required to undergo cesarean birth against her will when the risk to her health is minimal and the benefit to the otherwise normal, near-term fetus/unborn child is clear, as in a case of placenta previa. Other factors, such as prematurity, have led to the opposite legal conclusion in otherwise similar situations, because the benefit of intervention was less clear. In general, a clinician should not oppose a pregnant woman's refusal of a recommended intervention unless (1) the risk to the pregnant woman is minimal, (2) the intervention is clearly effective, and (3) the harm to the fetus/unborn child without the intervention would be certain, substantial, and irrevocable. Attempts should be made to persuade the pregnant woman to comply with recommendations in the interest of the fetus/unborn child when these 3 conditions exist, using support strategies such as the influence of other trusted caregivers, clergy, and ethics consultation or committee involvement. If these approaches fail and there is time, a clinician may seek judicial intervention as a last resort in the attempt to prevent harm to the fetus/unborn child.

Obstetricians and pediatricians may consider reporting women under child abuse or neglect statutes if ingesting alcohol or illicit drugs during pregnancy is believed to place the fetus/unborn child at risk of injury. However, clinicians must consider the likelihood of benefit from reporting, the harm to the child as well as to the mother if criminal charges or custody changes are sought, and the possible effects of reporting on driving pregnant women away from prenatal or postnatal care. The U.S. Supreme Court has held that drug testing of pregnant women without consent was a violation of the Fourth Amendment, which provides protection from unreasonable searches.

Justice and Pediatric Ethics

The most serious ethical problem in U.S. healthcare may be *inequality* in access to healthcare. Children are particularly vulnerable to this disparity, and pediatricians have a moral obligation to advocate for children as a class. Because children do not vote and do not have financial resources at their disposal, they are subject to a greater risk of being uninsured or underinsured. This lack of adequate and affordable healthcare has serious consequences in terms of death, disability, and suffering. The per capita proportion of healthcare funding spent on adults greatly exceeds that spent on children, and Medicare is available to all adults who turn 65 yr old, whereas Medicaid is limited to those beneath a specific income level. Pediatricians should be familiar with policy issues around the economics of childcare so that they will be better able to advocate for their own patients.

Emerging Issues

The ready availability of information on the internet and disease-specific social media support groups have encouraged parents to become more involved in advocating for specific approaches to the healthcare of their children, requiring physicians to remain aware of the quality of these information sources in order to counsel parents on treatment choices. Because the range of aggressive, innovative, or exceedingly expensive therapies has increased, without necessarily providing clear benefit to the patient, pediatricians must exercise care and judgment before agreeing to pursue these interventions. In addition, the growth of social media has presented expectations for clinicians to be quickly responsive, as well as challenges in maintaining privacy of medical information and professional boundaries. This will be an evolving issue, since the use of telemedicine is also gaining traction in certain sectors of healthcare, including the care of children and adolescents.

A growing number of parents are refusing to immunize their children because of fear of adverse reaction to vaccine. This raises the ethical problem of the *free rider* , in which a child may benefit from herd immunity because others have been immunized without contributing to this public good. Outbreaks of preventable infectious disease have been detected in communities where vaccine refusal is prevalent. Pediatricians should manage this issue with ethical sensitivity, educating parents about the safety profile of vaccines and encouraging appropriate immunization. More confrontational approaches are not generally effective or ethically warranted. Another emerging issue is children as stem cell or solid-organ donors. Here the risk/benefit balance should be carefully weighed, but in general, a permissive policy with regard to stem cell donation and a more restrictive approach to solid-organ donation are ethically justified.

Lastly, controversial medical and surgical interventions have raised awareness of situations in which families and children may not be in agreement with approaches that were recommended as “standard of care” in the past. Examples include delaying surgical treatment of sexual development disorders to determine the child's gender identity and arresting puberty through hormonal treatment to allow transgender or questioning children or adolescents to make decisions about gender identity before developing enduring secondary sexual characteristics. Attitudes about emerging technologies and treatments may be influenced by media coverage, special interest groups, and efforts by understandably desperate families to help their children. The clinician attempting to practice ethically must carefully consider all relevant facts in each case and try to focus families and caregivers on a reasonable *best interest* assessment for the child. The tension between finding optimal policy for groups of children and doing the right thing for an individual child raises formidable ethical challenges in this context. Ethics consultation may be helpful to frame the issues and design ethically supportable approaches to care.

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CHAPTER 7

Pediatric Palliative Care

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According to the World Health Organization (WHO), “Palliative care for children is the active total care of the child's body, mind and spirit and also involves giving support to the family. Optimally, this care begins when a life-threatening illness or condition is diagnosed and continues regardless of whether or not a child receives treatment directed at the underlying illness.” Provision of palliative care applies to children with a wide variety of diagnoses, including cancer, cystic fibrosis, complex or severe cardiac disease, neurodegenerative disorders, severe malformations, and trauma with life-threatening sequelae (Table 7.1). Medical and technologic advances have resulted in children living longer, often with significant dependence on expensive technologies. These children have *complex chronic conditions* across the spectrum of congenital and acquired life-threatening disorders. Children with complex chronic conditions benefit from integration of palliative care strategies. These children, who often survive near-death crises followed by the renewed need for rehabilitative and life-prolonging treatments, are best served by a system that is flexible and responsive to changing needs and blended goals of care.

Table 7.1

Conditions Appropriate for Pediatric Palliative Care

Conditions for Which Curative Treatment Is Possible but May Not Succeed
Advanced or progressive cancer or cancer with a poor prognosis Complex and severe congenital or acquired heart disease

Conditions for Which There Is Intensive Long-Term Treatment Aimed at Prolonging Life and Maintaining Quality of Life, but Premature Death Is Still Possible

Cystic fibrosis
Severe immunodeficiency
High-risk solid-organ transplant candidates and/or recipients (e.g., lung, multivisceral)
Chronic or severe respiratory failure
Muscular dystrophy
Complex multiple congenital malformation syndromes
Primary pulmonary hypertension
Severe chromosomal disorders (aneuploidy, deletions, duplications)

Progressive Conditions for Which There Is No Curative Option and in Which Treatment Is Almost Exclusively Palliative After Diagnosis

Progressive metabolic disorders (Tay-Sachs disease)
Batten disease
Severe forms of osteogenesis imperfecta

Conditions Involving Severe, Nonprogressive Disability, Causing Extreme Vulnerability to Health Complications

Severe cerebral palsy with recurrent infection or difficult-to-control symptoms
Severe neurologic sequelae of infectious disease
Hypoxic or anoxic brain injury
Brain malformations (e.g., holoprosencephaly, lissencephaly)

Adapted from The Together for Short Lives [formerly the Association for Children's Palliative Care (ACT)] Life-limiting/Life-threatening Condition Categories.
http://www.togetherforshortlives.org.uk/professionals/childrens_palliative_care_e
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Although often mistakenly understood as equivalent to *end-of-life care* , the scope and potential benefits of palliative care are applicable *throughout the illness trajectory* . Palliative care emphasizes optimization of quality of life, communication, and symptom control, goals that may be congruent with maximal treatment aimed at sustaining or prolonging life.

The mandate of the pediatrician and other pediatric clinicians to attend to children's physical, mental, and emotional health and development includes the provision of palliative care for those who live with a significant possibility of death before adulthood (Fig. 7.1). Such comprehensive physical, psychological, social, and spiritual care requires an interdisciplinary approach.

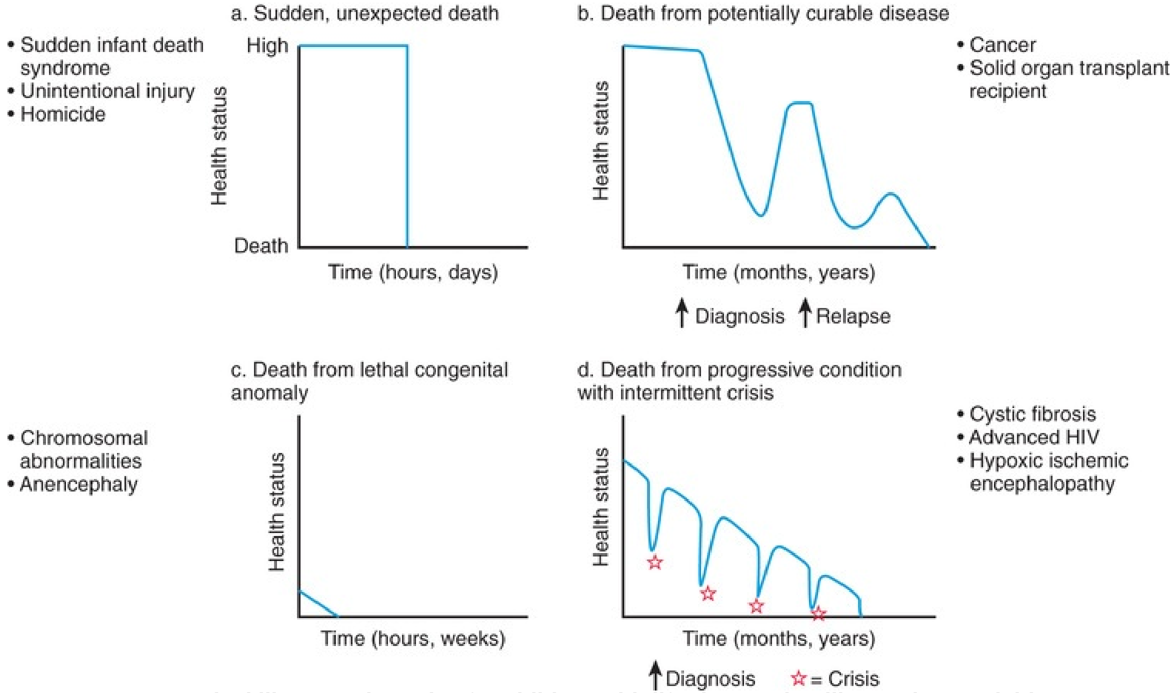

FIG. 7.1 **Typical illness trajectories for children with life-threatening illness. (From Field M, Behrman R, editors: When children die: improving palliative and end-of-life care for children and their families, Washington, DC, 2003, National Academies Press, p 74.)**

In the United States the healthcare and reimbursement structure, combined with frequent use of medical technology (e.g., home ventilatory support) or continuous home nursing, historically precluded formal enrollment of children on the hospice benefit when they were otherwise eligible (i.e., had estimated prognosis of ≤6 mo). Section 2302 of the Patient Protection and Affordable Care Act (ACA), the **Concurrent Care for Children Requirement (CCCR)** , eliminated the requirement that Medicaid patients <21 yr old forgo curative or life-prolonging therapies to be eligible for hospice. Although Medicaid programs in every state are now required to provide concurrent curative/life-prolonging treatment and hospice services for hospice-eligible children, development of systems to make such concurrent care a reality has been slow. A limitation of the CCCR is that it does not expand access to hospice for children with life-threatening illness who do not meet hospice eligibility criteria (i.e., have a prognosis that cannot be estimated to be <6 mo) or those not receiving Medicaid.

A number of state-based pediatric palliative care coalitions have formed in recent years to improve access to home-based pediatric hospice/palliative care services, using strategies such as Medicaid waivers or state plan amendments to increase coverage for hospice services. A growing number of home care agencies have also developed palliative care programs that serve as a bridge to hospice services for children not yet meeting hospice eligibility criteria. Some hospices have adopted an **open hospice** model with more flexible eligibility criteria. However, provision of hospice or palliative care for children is often also limited by the availability of clinicians who have training or experience in caring for seriously ill children.

Care Settings

Pediatric palliative care should be provided across settings, including hospital, outpatient, and home, as well as pediatric nursing facilities and sometimes inpatient hospice houses. **Home care** for the child with a life-threatening illness requires 24 hr/day access to experts in pediatric palliative care, a team approach, and an identified coordinator who serves as a link among hospitals, the community, and specialists and who may assist in preventing or arranging for hospital admissions, respite care, and increased home care support as needed. Adequate home care support and respite care, although sorely needed, is often not readily available because staffing or the high-tech skill required to care for these children is lacking. Furthermore, families may view using respite care as a personal failure, or they may worry that others cannot adequately care for their child's special needs or potential rapid escalation of symptoms.

At the end of life, children and families may need intensive support. About half of pediatric deaths occur in acute care hospitals, and end-of-life care may thus be provided in the home, hospital, pediatric nursing facility, or hospice house. Families need to feel safe and well cared for and given permission, if possible, to choose location of care. In tertiary care hospitals, most children die in the neonatal and pediatric intensive care units (ICUs). In some instances, when death at home for a child in the ICU is preferred, transport and even extubation at home may be possible, if clinical and logistical circumstances permit it.

The philosophy of palliative care can be successfully integrated into any hospital setting, including the ICU, when the focus of care also includes the prevention or amelioration of suffering and improving comfort and quality of life. All interventions that affect the child and family need to be assessed in relationship to these goals. This proactive approach asks the question, “What can we offer that will improve the quality of this child's life and provide the most meaning and sense of control and choice for their family?” instead of, “What therapies are we no longer going to offer this patient?” Staff may benefit from education, support, and guidance because pediatric palliative care, as with other types of intensive care, is an area of specialty. Regardless of the care setting, comprehensive palliative care requires an interdisciplinary approach that may include nurses, physicians, psychologists, psychiatrists, social workers, chaplains/clergy, child life specialists, and trained volunteers.

Communication, Advance Care Planning, and Anticipatory Guidance

Although accurate prognostication is a particular challenge in pediatrics, the medical team often recognizes a terminal prognosis before the prognosis is understood by parents or the child. This delay may impede informed decision-making about how the child lives at the end of life. Given the inherent prognostic uncertainty of a life-threatening diagnosis, discussions concerning resuscitation, symptom control, and end-of-life care planning should be initiated when the physician recognizes that a significant possibility of patient mortality exists. Having these conversations in the midst of a crisis is not ideal. Whenever possible, they should occur well in advance of the crisis or when the patient has recovered from a crisis but is at high risk for others.

Patients and families are most comfortable being cared for by physicians and other care providers with whom they have an established relationship. Even in the face of long-standing and highly connected relationships, *clinicians often hold assumptions about parent prognostic awareness, as well as parent readiness and willingness to have such discussions* . In an attempt to protect families, clinicians may avoid conversations that they perceive as promoting distress or hopelessness. However, parents greatly value honesty, and in fact such conversations can promote parent hopefulness, as well as trust and connection with the care team. At times, therefore, a *consultative* palliative care team provides the family with an opportunity to engage in sensitive conversations that do not as readily occur with the primary team, at least initially.

The population of individuals who die before reaching adulthood includes a disproportionate number of nonverbal and preverbal children and adolescents who are developmentally unable to make autonomous care decisions. Although parents are usually the primary decision-makers, these youth should be as fully involved in discussions and decisions about their care as appropriate for their developmental status. Using communication experts, child life therapists, chaplains, social workers, psychologists, or psychiatrists to allow children to express themselves through art, play, music, talk, and writing will enhance the provider's knowledge of the child's understanding and hopes. Tools such as **Five Wishes** (for adults), **Voicing My Choices** (for adolescents), and **My Wishes** (for school-age children), have in practice been useful in helping to introduce advance care planning to children, adolescents, and their families (www.agingwithdignity.org/index.php).

The Parents

For parents, **compassionate communication** with medical providers who understand their child's illness, treatment options, and family beliefs and goals are the cornerstone of caring for children with life-threatening illness. During this time, one of the most significant relationships is that with the child's pediatrician, who often has an enduring relationship with the child and family, including healthy siblings. Parents need to know that their child's pediatrician will not abandon them as the goals of care evolve. A family's goals may change with the child's evolving clinical condition and other variable factors. A flexible approach rooted in ongoing communication and guidance that incorporates understanding of the family's values, goals, and religious, cultural, spiritual, and personal beliefs is of paramount importance.

Pediatricians should recognize the important role they have in continuing to care for the child and family, since the primary goal of treatment may simultaneously be prolongation of life and comfort, relief of suffering, and promoting quality of life. Regular meetings between caregivers and the family are essential to reassess and manage symptoms, explore the impact of illness on immediate family members, and provide anticipatory guidance. At these meetings, important issues with lifelong implications for parents and their child may be discussed. Such discussions should be planned with care, ensuring that adequate time for in-depth conversation is allotted; a private, physical setting is arranged; devices are silenced; and that both parents and others who might be identified by the family as primary supports are present. Strategies for facilitating conversations related to goals of care and decision-making are detailed later.

Families may look to their pediatrician for assurance that all treatment options have been explored. Assisting a patient's family to arrange a second opinion may be helpful. Listening to families and children speak about the future even in the face of poor prognosis may help keep the focus on living even while the child may be dying. Hoping for a miracle can coexist for parents even as they are facing and accepting the more likely reality of death.

Parents also need to know about the availability of home care, respite services, web-based support (e.g., www.courageousparentsnetwork.org), educational materials, and support groups. Responding to parental requests or need for counseling referrals for themselves, other children, or family is essential. Also, attending to the concrete needs of families (e.g., financial, insurance, housing) can be paramount in freeing them of worries that might interfere or compete with their ability to be fully present in their child's care.

When closer to the patient's end of life, although broaching the topic may seem daunting, exploration of how parents envision their child's death, addressing their previous loss experiences (most often with death of an adult relative) and any misconceptions, is often a great relief to parents. Learning about cultural, spiritual, and family values regarding pain management, suffering, and the preferred place of end-of-life care is essential. Even mentioning funeral arrangements, possible autopsy, and organ/tissue donation can be helpful to give parents choices and know that these considerations can be discussed without fear. A major worry of many parents is how to involve and communicate with siblings, as well as the child, about the likelihood of impending death.

Ratings of “high satisfaction” with physician care have been directly correlated with receiving **clear communication** around end-of-life issues, delivered with sensitivity and caring; such communication included speaking directly to the child when appropriate. Communication is complicated by an assumed need for mutual protection in which the child wants to protect his or her parents, and likewise the parents want to protect their child, from painful information or sadness. Honoring the uniqueness of the child, as well as understanding and respecting the family's communication style, values, spirituality, and culture, is critical in these highly sensitive conversations. Evidence shows that parents who have open conversations with their child about death and dying do not regret having done so.

In communications with the child and family, the physician should avoid giving specific estimates of survival length, even when the child or family explicitly asks for them. These predictions are invariably inaccurate because population-based statistics do not predict the course for individual patients. A more honest approach may be to explore *ranges of time in general terms* (weeks to months, months to years) while recognizing that children with serious illness are also susceptible to acute events that cause rapid deterioration. The physician can also ask parents what they might do differently if they knew how long their child would live, then assist them in thinking through the options relating to their specific concerns (e.g., suggest celebrating upcoming holidays or important events earlier to take advantage of times when the child may be feeling better). It is generally wise to suggest that relatives who wish to visit might do so earlier rather than later, given the unpredictable trajectory of many conditions.

For the child and family, the integration of “bad news” is a *process,* not an event, and when done sensitively, does not take away hope or alter the relationship between the family and physician. The physician should expect that some issues previously discussed may not be fully resolved for the child and parents (e.g., do-not-resuscitate [DNR] orders, artificial nutrition or hydration) and may need to be revisited over time. Parents of a child with chronic illness may reject the reality of an impending death because past predictions may not have been accurate. Whether they are parents of a child with a chronic illness or a child whose death is the result of accident or sudden catastrophic illness, they may experience great anxiety, guilt, or despair.

The Child

Truthful communication that takes into account the child's developmental stage and unique lived experience can help to address the fear and anxiety commonly experienced among children with life-threatening illness. Responding in a developmentally appropriate fashion (Table 7.2) to a child's questions about death (e.g., “What's happening to me?” or “Am I dying?”) requires a careful exploration of what is already known by the child, what is really being asked (*the question behind the question*), and why the question is being asked at this particular time and in this setting. It may signal a need to be with someone who is comfortable listening to such unanswerable questions. Many children find nonverbal expression much easier than talking; art, play therapy, and storytelling may be more helpful than direct conversation.

Table 7.2

Developmental Questions, Thoughts, and Concepts of Dying, With Responsive Strategies

TYPICAL QUESTIONS AND STATEMENTS ABOUT DYING	THOUGHTS THAT GUIDE BEHAVIOR	DEVELOPMENTAL UNDERSTANDING OF DEATH	STRATEGIES AND RESPONSES
MONTHS TO 3 YR OF AGE			
“Mommy, don't cry.” “Daddy, will you still tickle me when I'm dead?”	Child has limited understanding of events, future and past, and of the difference between living and nonliving.	Child may have “sense” that something is wrong. Death is often viewed as continuous with life (analogous to being awake and being asleep).	Optimize comfort, and consistency; familiar persons, objects, routines. Use soothing songs, words, and touch. “I will always love you.” “I will always take care of you.” “I will tickle you forever.”
AGE 3-5 YR			
“I did something bad and so I will die.” “Can I eat anything I want in heaven?”	Concepts are simple and reversible. Variations between reality and fantasy.	Child may see death as temporary and reversible and not universal. Child may feel responsible for illness. Death may be perceived as an external force that can get you.	Assure child that illness not her fault. Provide consistent caregivers. Promote honest simple language. Use books to explain the life cycle and promote questions and answers. “You did not do anything to cause this.” “You are so special to us, and we will always

			love you.” “We know (God, Jesus, Grandma, Grandpa) are waiting to see you.”
AGE 5-10 YR			
“How will I die?” “Will it hurt?” “Is dying scary?”	Child begins to demonstrate organized, logical thought. Thinking becomes less esoteric. Child begins to problem-solve concretely, reason logically, and organize thoughts coherently. However, child has limited abstract reasoning.	Child begins to understand death as real and permanent. Death means that your heart stops, your blood does not circulate, and you do not breathe. It may be viewed as a violent event. Child may not accept death could happen to himself or to anyone he knows but starts to realize that people that he knows will die.	Be honest and provide specific details if they are requested. Help and support the child's need for control. Permit and encourage the child's participation in decision making. “We will work together to help you feel comfortable. It is very important that you let us know how you are feeling and what you need. We will always be with you, so you do not need to be afraid.”
AGE 10-18 YR			
“I'm afraid if I die my mom will just break down.” “I'm too young to die. I want to get married and have children.” “Why is God letting this happen?”	Abstract thoughts and logic possible. Body image is important. Child needs peer relationships for support and for validation. Child expresses altruistic values, such as staying alive for family (parents, siblings) and donating organs/tissue. Disbelief that she is dying.	Understand death as irreversible, inevitable and universal. Child needs reassurance of continued care and love. Search for meaning and purpose of life.	Reinforce child/adolescent's self-esteem, sense of worth, and self-respect. Allow need for privacy, independence, access to friends and peers. Tolerate expression of strong emotions and permit participation in decision-making. “I can't imagine how you must be feeling. Despite it all, you are doing an incredible job. I wonder how I can help?” “What's most important to you now?” “What are your hopes … your worries?” “You have taught me so much; I will always remember you.”

Adapted from Hurwitz C, Duncan J, Wolfe J: Caring for the child with cancer at the close of life, *JAMA* 292:2141–2149, 2003.

A child's perception of death depends on his or her conceptual understanding of *universality* (that all things inevitably die), *irreversibility* (that dead people cannot come back to life), *nonfunctionality* (that being dead means that all biologic functions cease), and *causality* (that there are objective causes of death).

Very young children may struggle with the concepts of irreversibility and nonfunctionality. For young school-age children, who are beginning to understand the finality of death, worries may include *magical thinking* in which their thoughts, wishes, or bad behavior might be the underlying cause for their illness. Older children seek more factual information to gain some control over the situation.

Children 's fears of death are often centered on the concrete fear of being separated from parents and other loved ones and what will happen to their parents rather than themselves. This can be true for teens and young adults as well. This fear may be responded to in different ways: some families may give reassurance that loving relatives will be waiting, while others use religious concepts to refer to an eternal spiritual connection.

Adolescents may have a conceptual understanding of death similar to that of adults, but working with the adolescent with life-threatening illness presents unique concerns and issues. The developmental work of adolescence includes separating from their parents, developing strong peer relationships, and moving towards independent adulthood. For this population, the teenager's developmental need to separate is complicated by the increasing dependence both physically and emotionally on their parents.

In addition to developmental considerations, understanding related to the child's life experiences, the length of the child's illness, the understanding of the nature and prognosis of the illness, the child's role in the family (peacemaker, clown, troublemaker, the good child) should be considered in communication with children.

The question of whether and when to involve adolescents in decision-making arises particularly often. There is no one answer to this question. Instead, numerous considerations should be taken into account, including the adolescent's chronological age, developmental stage, adolescent preference with regard to such participation, and the family's preferred approach to communication and decision-making.

Parents have an instinctive and strong desire to protect their children from harm. When facing the death of their child, many parents attempt to keep the reality of impending death hidden from their child, hoping the child can be *protected* from the harsh reality. Although it is important to respect parental wishes, it is also true that most children already have a sense of what is happening to their bodies, even when it has been purposely left unspoken. Children may blame themselves for their illness and the resulting hardships for their loved ones. Perpetuating the myth that “everything is going to be all right” takes away the chance to explore fears and provide reassurance. Assisting parents to understand that the key to honest communication is not telling a child he or she is dying but opening the door to conversation and validating what the child *already knows* . Honest communication also allows opportunities for memory and legacy making and saying goodbye.

School is the work of childhood and adolescence and is important in optimizing quality of life for a child seeking normalcy in the face of illness. Finding ways to help children and their families to maintain these connections through modification of the school day, and exploring options to promote educational and social connections into the home or into the hospital room, can be meaningful in the event that a child is not well enough to attend school. Video conferencing now can be readily arranged from almost any setting.

The Siblings

Brothers and sisters are at special risk both during their sibling's illness and after the death. Because of the extraordinary demands placed on parents to meet the needs of their ill child, healthy siblings may feel that their own needs are not being acknowledged or fulfilled. These feelings of neglect may then trigger guilt about their own good health and resentment toward their parents and ill sibling. Younger siblings may react to the stress by becoming seemingly oblivious to the turmoil around them. Some younger siblings may feel guilty for wishing the affected child would die so they could get their parents back (magical thinking). Parents need to know that these are normal responses, and siblings should be encouraged to maintain the typical routines of daily living. Siblings who are most involved with their sick brothers or sisters before death usually adjust better both at the time of and after the death. Acknowledging and validating sibling feelings, being honest and open, and appropriately involving them in the life of their sick sibling provide a good foundation for the grief process. It is often helpful to identify a person in the family (e.g., caring aunt) or school (e.g., counselor) to offer confidential and supportive opportunities for the sibling to reflect on their family experience, particularly as parents may be too overwhelmed to provide this at crucial times.

The Staff

Inadequate support for the staff providing palliative care can result in depression, emotional withdrawal, and other symptoms. Offering educational opportunities and emotional support for staff at various stages of caring for a child with life-threatening illness can be helpful in bettering patient/family care and preventing staff from experiencing compassion fatigue, burnout, and long-term repercussions, including leaving the field.

Goals of Care and Decision-Making

In the course of a child's life-limiting illness, a series of important decisions may arise in relation to location of care, medications with risks and benefits, not starting or discontinuing life-prolonging treatments, experimental treatments in research protocols, and use of integrative therapies (see Chapter 78). Such family decisions are greatly facilitated by opportunities for in-depth and guided discussions around **goals of care** for the child. This is often accomplished by eliciting parent (and child) understanding of the child's condition and asking open-ended questions that explore the parent's and child's hopes, worries, and family values. Goals-of-care conversations include what is most important for them as a family, considerations of their child's clinical condition, and their values and beliefs, including cultural, religious, and spiritual considerations. Table 7.3 presents specific questions that can effectively guide these discussions. The conversation should also include a review of previous discussions, active listening to concerns and issues as they are raised, opportunities to repeat back elements of the discussion to ensure clarity, and provision of honest, factual answers even in areas of uncertainty.

Table 7.3

Five Basic Questions to Guide "Goals of Care" Conversation

PHRASING FOR ADULT OR OLDER ADOLESCENT	PHRASING FOR CHILD
Tell us about your child as a person. What does your child enjoy?	Tell me about yourself before you got sick.
What is your understanding of your child's illness/condition?	Why are you in the hospital? What do you understand about your illness?

In light of your understanding, what is most important to you regarding your child's care?	What do you want others to know or do for you when taking care of you?
What are you hoping for? What are your worries?	I wonder if there is anything that is worrying you or that is keeping you up at night. Is there anything you wish you could talk about?
What gives you strength in the face of your child's illness/condition?	What helps you get through the day? What helps you feel good?

Decision-making should be focused on the goals of care, as opposed to limitations of care ; “This is what we can offer,” instead of, “There is nothing more we can do.” Rather than meeting specifically to discuss withdrawing support or a do-not-resuscitate (DNR) order, a more general discussion centered on the goals of care will naturally lead to considering which interventions are in the child's best interests and can present an opportunity for the clinicians to make recommendations based on these goals. By offering medical recommendations based on family goals and the clinical reality, the team can decrease the burden of responsibility for decision-making that parents carry.

Resuscitation Status

Many parents do not understand the legal mandate requiring attempted resuscitation for cardiorespiratory arrest unless a written DNR order is in place. In broaching this topic, rather than asking parents if they want to forgo cardiopulmonary resuscitation (CPR) for their child (and placing the full burden of decision-making on them), it is preferable to discuss whether or not resuscitative interventions are likely to benefit the child. *It is important to make recommendations based on overall goals of care and medical knowledge of potential benefit and/or harm of these interventions*. Once the goals of therapy are agreed on, the physician is required to write a formal order. Out-of-hospital DNR verification forms are available in many states, which if completed on behalf of the child, affirm that rather than initiating resuscitative efforts, emergency response teams are obligated to provide appropriate symptom management with comfort and relief of suffering with appropriate interventions when called to the scene.

Almost half of all states have implemented the **physician orders for life treatment (POLST) system** . A POLST order is completed for children with life-threatening illness, translating the expressed parent's and/or child's wishes for interventions to do or not do into actionable orders (www.polst.org). It is usually helpful to frame discussions about POLST as ways for parents to maintain some control, by communicating their goals and care preferences, so that they may be honored, irrespective of the setting. It may also be beneficial to write a letter that delineates decisions regarding resuscitation interventions and supportive care measures to be undertaken for the child, particularly if POLST are not available. The letter should be as detailed as possible, including recommendations for comfort medications and contact information for caregivers best known to the patient. Such a letter, given to the parents, with copies to involved caregivers and institutions, can be a useful communication aid, especially in times of crisis. In any case, if a child may die in the home setting, and the parents opt to use on out-of-hospital DNR verification form or POLST, plans to pronounce the child and provide support for the family must be in place. If the child has been referred to hospice, the hospice usually fulfills those responsibilities.

Conflicts in decision-making can occur within families, within healthcare teams, between the child and family, and between the family and professional caregivers (see Chapter 6). For children who are developmentally unable to provide guidance in decision-making (neonates, very young children, or children with cognitive impairment), parents and healthcare professionals may come to different conclusions as to what is in the child's best interests. Decision-making around the care of adolescents presents specific challenges, given the shifting boundary that separates childhood from adulthood. In some families and cultures, truth-telling and autonomy are secondary to maintaining the integrity of the family (see Chapter 11). Although frequently encountered, differences in opinion are often manageable for all involved when lines of communication are kept open, team and family meetings are held, and the goals of care are clear.

Symptom Management

Intensive symptom management is another cornerstone of pediatric palliative care. Alleviation of symptoms reduces suffering of the child and family and allows them to focus on other concerns and participate in meaningful experiences. Despite increasing attention to symptoms, and pharmacologic and technical advances in medicine, children often suffer from multiple symptoms. Table 7.4 provides key elements and general approaches to managing symptoms.

Table 7.4

Key Elements of Effective Symptom Management

Setting the Stage

- Establish and periodically revisit goals of care and ensure that goals are communicated to entire care team.
- Plan for symptoms (including unanticipated ones) before they occur.

Assessment

- Assess the child for symptoms regularly, using consistent and developmentally appropriate assessment tools.
  - Utilize self-report, if the child is able to reliably report symptoms.
- Evaluate all aspects of the symptom, including quality, frequency, duration, and intensity.
- Consider the holistic nature of symptoms.
- Explore the meaning that symptoms may have for families in their social, cultural, and religious context.
- Assess distress caused by the symptom.
- Evaluate the degree of functional impairment from the symptom.

Treatment

- Understand the pathophysiology of the symptom, and establish a complete differential diagnosis.
- Treat the underlying cause if possible, weighing benefits and risks, in the context of goals of care.
- Choose the least invasive route for medications—by mouth whenever possible.
- Prescribe regular medications for constant symptoms, and consider prn doses for breakthrough or uncontrolled symptoms.
- Consider all approaches (i.e., pharmacologic/nonpharmacologic and local/systemic).
- Partner with families to identify and address any barriers to optimal control of symptoms.
- Address spiritual, emotional, and existential suffering in addition to physical

suffering since these are often interrelated.

Ongoing Care

- Reassess the symptom and response to interventions regularly.
- For refractory symptoms, revisit the differential diagnosis and review potentially contributing factors.
- Effective interventions relieve the symptom and reduce distress and functional impairment.

Pain is a complex sensation triggered by actual or potential tissue damage and influenced by cognitive, behavioral, emotional, social, and cultural factors. Effective pain relief is essential to prevent *central sensitization* , a central hyperexcitation response that may lead to hypersensitivity and escalating pain, and to diminish a stress response that may have a variety of physiologic effects. Assessment tools include self-report tools for children who are able to communicate their pain verbally, as well as tools based on behavioral cues for children who are unable to do so because of their medical condition or a neurodevelopmental disorder. Tables 7.5 to 7.7 address management of pain (see also Chapter 76).

Table 7.5

Guidelines for Pain Management

- Use nonopioid analgesics as monotherapy for mild pain, and together with opioids for more severe pain.
    - Nonopioid analgesics include acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), salicylates, and selective cyclooxygenase (COX-2) inhibitors.
- For moderate or severe pain, start with a short-acting opioid at regular intervals.
    - When dose requirements have stabilized, consider converting opioid to a long-acting formulation with doses available for breakthrough or uncontrolled pain, as needed.
        - For uncontrolled pain, increase opioid dose by 30–50%; for severe pain, increase by 50–100%.

        - Avoid codeine and opioids with mixed-agonist activity (e.g., butorphanol, pentazocine).
- Administer medications by the simplest, most effective, and least distressing route.
- Dispel the myth that strong medications should be saved for extreme situations or the very end of life.
    - Opioids do not have a “ceiling effect,” and escalating symptoms can usually be treated with an increase in dose. If further titration does not provide adequate analgesia, the opioid may be rotated to another (see below).
- Clarify for families the differences among tolerance, physical dependence, and addiction.
- Anticipate and treat/prevent common analgesic side effects (gastritis with NSAIDs; constipation, pruritus, nausea, and sedation with opioids).
    - Always initiate a bowel regimen to prevent constipation when starting opioids.
    - Consider a stimulant for opioid-induced somnolence.
    - Pruritus rarely indicates a true allergy. If not responsive to an antihistamine, consider low-dose naloxone or switching opioids.
    - Consider switching to a different opioid for intolerable side effects or neurotoxicity (e.g., myoclonus).
    - Use an equianalgesic conversion table when switching opioids, and account for incomplete cross-tolerance with dose reduction.
- Consider the use of adjuvant drugs for specific pain syndromes, and for their opioid-sparing effect:
    - Antidepressants (e.g., amitriptyline, nortriptyline) and anticonvulsants (e.g., gabapentin, carbamazepine, topiramate) for neuropathic pain
    - Steroids or NSAIDs for bone pain
    - Sedatives and hypnotics for anxiety and muscle spasm
    - To enhance analgesia from opioids, consider clonidine or ketamine.
        - Use topical local anesthetics (lidocaine, prilocaine, bupivacaine) when possible
        - Consider anesthetic blocks for regional pain.
        - Consider palliative radiation therapy.
        - Consider psychological approaches (e.g., cognitive or

behavioral therapy) and integrative therapies (e.g., acupuncture, massage).

Table 7.6

Pharmacologic Approach to Symptoms Commonly Experienced by Children With Life-Threatening Illness

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pain—mild	Acetaminophen	15 mg/kg PO q4h, max 4 g/day	Available PO (including liquid), PR, or IV
	Ibuprofen	10 mg/kg PO q6h	PO (including liquid) only; avoid if risk of bleeding; use only in infants ≥6 mo. Use with caution in congestive heart failure. Chewable tablets contain phenylalanine.
	Choline magnesium trisalicylate	10-20 mg/kg PO tid (max 500-1000 mg/dose)	Trilisate may have less antiplatelet activity and therefore pose less risk for bleeding than other salicylates. Salicylates, however, have been associated with Reye syndrome in children <2 yr.
	Celecoxib	1-2 mg/kg (max 100 mg) PO q12-24h	Selective cyclooxygenase (COX-2) inhibitor has low risk of gastritis and low antiplatelet activity.
Pain—moderate/severe	Morphine immediate release (i.e., MSIR)	0.3 mg/kg PO q4h if <50 kg 5-10 mg PO q4h if >50 kg[*] [†]	Also available in IV/SQ formulation. [‡] [§]
	Oxycodone	0.1 mg/kg PO q4h if <50 kg 5-10 mg PO q4h if >50 kg[*] [†]	No injectable formulation. [‡] [§]
	Hydromorphone	0.05 mg/kg PO q4h if <50 kg 1-2 mg PO q4h if >50 kg[*] [†]	Also available in IV/SQ formulation. Injectable form very concentrated, facilitating subcutaneous delivery. [‡] [§]
	Fentanyl	0.5-1.5 µg/kg IV/SQ q30min[*] [†]	Rapid infusion may cause chest wall rigidity. [‡] [§]
	Methadone	Starting dose 0.1-0.2 mg/kg PO bid. May give tid if needed. Recommend consultation with experienced clinician for equivalence dosing from other opioids.[*] [†]	Only opioid with immediate and prolonged effect available as a liquid; do not adjust dose more often than every 72 hr because prolonged biologic half-life > therapeutic half-life. Knowledge of methadone pharmacokinetics is needed for converting to and from doses of other opioids. Also available IV/SQ. May cause QT interval prolongation (consider ECG), especially in adults

			on >200 mg/day or in those at risk for QT prolongation. Interacts with several antiretroviral agents. [§]
Pain—sustained release	MS Contin Kadian (contains sustained release pellets) Avinza (contains immediate and extended release beads) Oramorph	Total daily dose of MSIR divided bid-tid	Do not crush MS Contin. For those unable to swallow pills, Kadian and Avinza capsules may be opened and contents mixed with food but *cannot be chewed* . Kadian contents may be mixed in 10 mL water and given via 16-French G-tube. Avoid alcohol with Avinza. Larger-dose formulation may not be suitable for small children. [§]
	Oxycontin	Total daily dose of oxycodone divided bid-tid	Do not crush. [§]
	Transdermal fentanyl patch	Divide 24 hr PO morphine dose by 2 to determine starting dose of transdermal fentanyl. No data exist on the equianalgesic conversion from transdermal fentanyl to any oral opioid.	Smallest patch size may be too high for small children. For children >2 yr. Apply to upper back in young children. Patch may **not** be cut. Typically for patients taking at least 60 mg morphine/day or its equivalent. Not appropriate when dosage changes are frequent or for opioid-naïve patients. Fever >40°C results in higher serum concentrations. [§]
Pain—neuropathic	Nortriptyline	0.5 mg/kg PO at bedtime (max 150 mg/day)	Fewer anticholinergic side effects than amitriptyline. May cause constipation, sedation, postural hypotension, and dry mouth. May cause QT interval prolongation (consider ECG). At higher doses, monitor ECG and plasma levels.
	Gabapentin	Start at 5 mg/kg/day at bedtime and gradually increase to 10-15 mg/kg/day divided tid; titrate up by 5 mg/kg/day q 3-4 days as needed but not to exceed 50-75 mg/kg/day (3600 mg/day)	May cause neuropsychiatric events in children (aggression, emotional lability, hyperkinesia), usually mild but may require discontinuation of gabapentin. May cause dizziness, drowsiness, tremor, nystagmus, ataxia, and swelling.
	Pregabalin	Start at 1 mg/kg/dose PO at bedtime for 3 days, then increase to 1 mg/kg/dose bid. Increase every 3 days to 3 mg/kg/dose PO bid (max 6 mg/kg/dose).	
	Methadone	See previous listing	See previous listing.
Dyspnea	Morphine, immediate release (i.e., MSIR)	0.1 mg/kg PO q4h prn[*] [†]	All opioids may relieve dyspnea. For dyspnea, the starting dose is 30% of the dose that would be administered for pain. [§]
	Lorazepam	0.025-0.05 mg/kg IV/PO q6h,	See previous listing

		up to 2 mg/dose	
Respiratory secretions	Scopolamine patch	1.5 mg patch, change q72h (for children >8-12 yr old)	Excessive drying of secretions can cause mucus plugging of airways. Good for motion-induced nausea and vomiting. Handling patch and contacting eye may cause anisocoria and blurry vision. May fold patches, but do not cut them. Anticholinergic side effects possible.
	Glycopyrrolate	0.04-0.1 mg/kg PO q4-8h	Powerful antisialagogue. Excessive drying of secretions can cause mucus plugging of airways. Anticholinergic side effects possible. Quaternary ammonium structure limits its ability to cross lipid membranes, such as the blood-brain barrier (in contrast to atropine, scopolamine, and hyoscyamine sulfate), so may exert fewer central anticholinergic effects.
	Hyoscyamine sulfate	4 gtt PO q4h prn if <2 yr 8 gtt PO q4h prn if 2-12 yr Do not exceed 24 gtt/24 hr.	Anticholinergic side effects possible, including sedation. May be given sublingually.
	Atropine	1-2 gtt SL q4-6h prn	Give 0.5% ophthalmic drops sublingually.
Nausea	Metoclopramide	0.1-0.2 mg/kg/dose q6h, up to 10 mg/dose (prokinetic and mild nausea dosing). For chemotherapy-associated nausea, 0.5-1 mg/kg q6h prn PO/IV/SC; give with diphenhydramine and continue diphenhydramine for 24 hr after last dose of high-dose metoclopramide to prevent extrapyramidal reaction.	Helpful when dysmotility is an issue; may cause extrapyramidal reactions, particularly in children following IV administration of high doses. Contraindicated in complete bowel obstruction or pheochromocytoma. Avoid concomitant use with olanzapine.
	Ondansetron	0.15 mg/kg dose IV/PO q8h prn. No single IV dose should exceed 16 mg due to risk of QT prolongation.	Significant experience in pediatrics. Good empirical therapy for nausea in palliative care population. Oral dissolving tablet contains phenylalanine. Higher doses used with chemotherapy although single 32 mg IV dose is no longer available (risk for QT prolongation). Consider ECG monitoring in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or in patients taking other medications with potential to cause QT prolongation.
	Dexamethasone	0.1 mg/kg/dose tid PO/IV; max dose 10 mg/day	Also helpful with hepatic capsular distension, bowel wall edema, anorexia, increased ICP. May cause mood swings or psychosis.
	Lorazepam	See previous listing.	See previous listing
	Dronabinol	2.5-5 mg/m^2 /dose q3-4h	Available in 2.5 and 5 mg capsules.

			May remove liquid contents from capsules for children who cannot swallow capsules. Avoid in patients with sesame oil hypersensitivity or history of schizophrenia. May cause euphoria, dysphoria, or other mood changes. Tolerance to CNS side effects usually develops in 1-3 days of continuous use. Avoid in patients with depression or mania.
	Scopolamine patch	See previous listing.	See previous listing
	Olanzapine	4-6 yr: 1.25 mg PO daily 6-12 yr: 2.5 mg PO daily ≥12 yr: 5 mg daily	Little evidence to guide antiemetic dosing. Ranges largely derived from olanzapine dosing for other purposes. Avoid concomitant use with metoclopramide.
Anxiety	Lorazepam	See previous listing.	See previous listing.
Agitation	Haloperidol	0.01 mg/kg PO tid prn for acute onset: 0.025-0.050 mg/kg PO, may repeat 0.025 mg/kg in 1 hr prn	May cause extrapyramidal reactions, which can be reversed with diphenhydramine or Cogentin. Safety not established in children <3 yr.
Sleep disturbance/insomnia	Lorazepam	See previous listing.	See previous listing.
	Trazodone	Children 6-18 yr: 0.75-1 mg/kg/dose, given bid-tid if needed If >18 yr, start at 25-50 mg/dose, given bid-tid if needed	Potentially arrhythmogenic
Fatigue	Methylphenidate	0.3 mg/kg/dose titrated as needed, up to 60 mg/day	Rapid antidepressant effect; also improves cognition. Administer before meals to avoid appetite suppression. Use with caution in children at risk for cardiac arrhythmia. Available as liquid and chewable tablet.
Pruritus	Diphenhydramine	0.5-1 mg/kg q6h IV/PO (100 mg max per day)	May reverse phenothiazine-induced dystonic reactions. Topical formulation on large areas of the skin or open area may cause toxic reactions. May cause paradoxical reaction in young children.
	Hydroxyzine	0.5-1 mg/kg q6h IV/PO (600 mg max per day)	
Constipation	Docusate	40-150 mg/day PO in 1-4 divided doses	Stool softener available as liquid or capsule
	Miralax	<5 yr: ½ scoop (8.5 g) in 4 oz water daily >5 yr: 1 scoop (17 g) in 8 oz water daily	Tasteless powder may be mixed in beverage of choice. Now available over the counter.
	Lactulose	5-10 mL PO up to q2h until bowel movement	Bowel stimulant; dosing q2h may cause cramping.
	Senna	2.5 mL PO daily (for children >27 kg)	Bowel stimulant; available as granules

	Dulcolax	3-12 yr: 5-10 mg PO daily >12 yr 5-15 mg PO daily	Available in oral or rectal formulation
	Pediatric Fleets Enema	2.5 oz pediatric enema for children 2-11 yr; adult enema for children ≥12 yr	May repeat ×1 if needed. Do not use in neutropenic patients.
	Methylnaltrexone	10-20 kg: 2 mg SC 21-33 kg: 4 mg SC 34-46 kg: 6 mg SC 47.62 kg: 8 mg SC 63-114 kg: 12 mg SC ≥155 kg: 0.15 mg/kg SC Administer 1 dose every other day as needed; max 1 dose/24 hr	Peripherally acting opioid antagonist for opioid-induced constipation. Usually works within 30-60 min of administration.
Muscle spasm	Diazepam	0.5 mg/kg/dose IV/PO q6h prn Initial dose for children <5 yr: 5 mg dose; for children ≥5 yr: 10 mg/dose	May be irritating if given by peripheral IV line.
	Baclofen	5 mg PO tid, increase by 5 mg/dose as needed.	Helpful with neuropathic pain and spasticity; abrupt withdrawal may result in hallucinations and seizures; not for children <10 yr
Seizures	Lorazepam	0.1 mg/kg IV/PO/SL/PR; repeat q10min ×2	
	Diazepam	0.1 mg/kg q6h (max 5 mg/dose if <5 yr; max 10 mg/dose if >5 yr)	May be given PR as Diastat (0.2 mg/kg/dose q15min ×3 doses)
Neuroirritability	Gabapentin	See previous listing.	
	Clonidine	Starting dose: 0.05 mg/day. May increase every 3-5 days by 0.05 mg/day to 3-5 μg/kg/day given in divided doses 3-4 times/day; max dose 0.3 mg/day. May switch from oral to transdermal route once optimal oral dose is established. Transdermal dose is equivalent to the total oral daily dose (e.g., if total oral dose is 0.1 mg/day, apply 1 patch (delivers 0.1 mg/day). Change patch every 7 days.	Transdermal patch may contain metal (e.g., aluminum) that may cause burns if worn during MRI scan. Remove patch prior to MRI. Patch may be cut into ¼ or ½ fractions based on dose needed.
	Clonazepam	<10 yr or <30 kg: initial dose 0.01-0.03 mg/kg/day divided tid ≥10 yr (≥30 kg): initial dose up to 0.25 mg PO tid; may increase by 0.5-1 mg/day every 3 days Maintenance dose: 0.05-0.2 mg/kg/day up to 20 mg/day	
Anorexia	Megestrol acetate	10 mg/kg/day in 1-4 divided doses, may titrate up to 15	For children >10 yr. Acute adrenal insufficiency may occur with abrupt

		mg/kg/day or 800 mg/day	withdrawal after long-term use. Use with caution in patients with diabetes mellitus or history of thromboembolism. May cause photosensitivity.
	Dronabinol	See previous listing.	See previous listing.
	Cyproheptadine	Children ≥2 yr and adolescents: 0.08 mg/kg PO q8h; if no benefit in 5 days, increase dose by 0.04-0.08 mg/kg/dose Max daily dose: ≤6 yr: 12 mg/day; 7-14 yr: 16 mg/day; ≥15 yr: 32 mg/day	Potent antihistamine and serotonin antagonist

[*] Infants <6 mo should receive 25–30% of the usual opioid starting dose.

[†] Although the usual opioid starting dose is presented, dose may be titrated as needed. There is no ceiling/maximum dose for opioids.

[‡] Breakthrough dose is 10% of 24 hr dose. See Chapter 76 for information regarding titration of opioids.

[§] Side effects from opioids include constipation, respiratory depression, pruritus, nausea, urinary retention, physical dependence.

Note: **Some medications or dosing may not apply to infants (≤12 mo). Verify suitability and dosing of all medications before administering to neonates.**

IV, Intravenous(ly); PO, by mouth; PR, rectally; prn, as needed; gtt, drops; SC, subcutaneously; bid, twice daily; tid, 3 times daily; q4h, every 4 hours; q30min, every 30 minutes; CNS, central nervous system; ECG, electrocardiogram; ICP, intracranial pressure.

Adapted from Ullrich C, Wolfe J: Pediatric pain and symptom control. In Walsh TD, Caraceni AT, Fainsinger R, et al: *Palliative medicine* , Philadelphia, 2008, Saunders).

Table 7.7

Nonpharmacologic Approach to Symptoms Commonly Experienced by Children With Life-Threatening Illness

SYMPTOM	APPROACH TO MANAGEMENT
Pain	Prevent pain when possible by limiting unnecessary painful procedures, providing sedation, and giving preemptive analgesia before a procedure (e.g., including sucrose for procedures in neonates). Address coincident depression, anxiety, sense of fear or lack of control. Consider guided imagery, relaxation, hypnosis, art/pet/play therapy, acupuncture/acupressure, biofeedback, massage, heat/cold, yoga, transcutaneous electric nerve stimulation, distraction.
Dyspnea or air hunger	Suction oral secretions if present; positioning, comfortable loose clothing, fan to provide cool, blowing air. Limit volume of intravenous fluids; consider diuretics if fluid overload/pulmonary edema

	present. Behavioral strategies, including breathing exercises, guided imagery, relaxation, music, distraction.
Fatigue	Sleep hygiene (establish a routine, promote habits for restorative sleep). Regular, gentle exercise; prioritize or modify activities. Address potentially contributing factors (e.g., anemia, depression, side effects of medications). Aromatherapy* : peppermint, rosemary, basil.
Nausea/vomiting	Consider dietary modifications (bland, soft, adjust timing/volume of foods or feeds). Aromatherapy* : ginger, peppermint, lavender, acupuncture/acupressure.
Constipation	Increase fiber in diet, encourage fluids, ambulation (if possible).
Oral lesions/dysphagia	Oral hygiene and appropriate liquid, solid and oral medication formulation (texture, taste, fluidity). Treat infections, complications (mucositis, pharyngitis, dental abscess, esophagitis).
	Oropharyngeal motility study and speech (feeding team) consultation.
Anorexia/cachexia	Manage treatable lesions causing oral pain, dysphagia, or anorexia. Support caloric intake during phase of illness when anorexia is reversible. Acknowledge that anorexia/cachexia is intrinsic to the dying process and may not be reversible. Prevent/treat coexisting constipation.
Pruritus	Moisturize skin. Trim child's nails to prevent excoriation. Try specialized anti-itch lotions. Apply cold packs. Counterstimulation, distraction, relaxation.
Diarrhea	Evaluate/treat if obstipation. Assess and treat infection. Dietary modification.
Depression	Psychotherapy, behavioral techniques, setting attainable daily goals. Aromatherapy* : bergamot, lavender.
Anxiety	Psychotherapy (individual and family), behavioral techniques. Aromatherapy* : clary sage, angelica, mandarin, lavender.
Agitation/terminal restlessness	Evaluate for organic or drug causes. Educate family. Orient and reassure child; provide calm, nonstimulating environment, use familiar music, verse, voice, touch. Aromatherapy* : frankincense, ylang ylang.

* Best if aromatherapy is administered by a practitioner trained in aromatherapy use and safety and if child has choice of essential oil aroma that stimulates positive response.

From Sourkes B, Frankel L, Brown M, et al: Food, toys, and love: pediatric palliative care, *Curr Probl Pediatr Adolesc Health Care* 35:345–392, 2005.

Many children with life-threatening illness experience pain that requires **opioids** for adequate relief at some point in their illness trajectory. The WHO pain guidelines recommend the first step for mild pain and the second step for moderate to severe pain. Although it was previously recommended, prescribing *codeine* should generally be avoided because of its side effect profile and lack of superiority over nonopioid analgesics. Furthermore, relatively common genetic polymorphisms in the *CYP2D6* gene lead to wide variation in codeine metabolism. Specifically, 10–40% of individuals carry polymorphisms causing them to be *poor metabolizers* who cannot convert codeine to its active form, *morphine* , and therefore are at risk for inadequate pain control. Others are *ultrametabolizers* who may even experience respiratory depression from rapid generation of morphine from codeine. It is therefore preferable to use a known amount of the active agent, morphine.

It is important to explore with families, as well as members of the care team, misconceptions that they may have regarding respiratory suppression, addiction, dependence, the symbolic meaning of starting an opioid such as methadone or morphine and/or a morphine drip, and the potential for opioids to hasten death. *There is no association between administration or escalation of opioids and length of survival* . Evidence supports longer survival in individuals with symptoms that are well controlled.

Children also often experience a multitude of **nonpain symptoms** . A combination of both pharmacologic (Table 7.6) and nonpharmacologic (Table 7.7) interventions is often optimal. **Fatigue** is one of the most common symptoms in children with advanced illness. Children may experience fatigue as a physical symptom (e.g., weakness or somnolence), a decline in cognition (e.g., diminished attention or concentration), and impaired emotional function (e.g., depressed mood or decreased motivation). Because of its multidimensional and incapacitating nature, fatigue can prevent children from participating in meaningful or pleasurable activities, thereby impairing quality of life. Fatigue is usually multifactorial in etiology. A careful history may reveal contributing physical factors (uncontrolled symptoms, medication side effects), psychological factors (anxiety, depression), spiritual distress, or sleep disturbance. Interventions to reduce fatigue include treatment of contributing factors, exercise, pharmacologic agents, and behavior modification strategies. Challenges to effectively addressing fatigue include the common belief that fatigue is inevitable, lack of communication between families and care teams about it, and limited awareness of potential interventions for fatigue.

Dyspnea (the subjective sensation of shortness of breath) results from a mismatch between afferent sensory input to the brain and the outgoing motor signal from the brain. It may stem from respiratory causes (e.g., airway secretions, obstruction, infection) or other factors (e.g., cardiac) and may also be influenced by psychological factors (e.g., anxiety). Respiratory parameters such as respiratory rate and oxygen saturation correlate unreliably with the degree of dyspnea. Therefore, giving oxygen to a cyanotic or hypoxic child who is otherwise quiet and relaxed may relieve staff discomfort while having no impact on patient distress and may also add burden if the child cannot tolerate the mask or cannula. Dyspnea can be relieved with the use of regularly scheduled plus as-needed doses of opioids. Opioids work *directly* on the brainstem to reduce the sensation of respiratory distress, as opposed to relieving dyspnea by sedation. The dose of opioid needed to reduce dyspnea is as little as 25% of the amount that would be given for analgesia. Nonpharmacologic interventions, including guided imagery or hypnosis to reduce anxiety, or cool, flowing air, aimed toward the face, are also frequently helpful in alleviating dyspnea. While oxygen may relieve hypoxemia-related headaches, it is no more effective than blowing room air in reducing the distressing sensation of shortness of breath.

As death approaches, a buildup of secretions may result in noisy respiration sometimes referred to as a “death rattle.” Patients at this stage are usually unconscious, and noisy respirations are often more distressing for others than for the child. It is often helpful to discuss this anticipated phenomenon with families in advance, and if it occurs, to point out the child's lack of distress from it. If treatment is needed, an anticholinergic medication, such as glycopyrrolate, may reduce secretions.

Neurologic symptoms include **seizures** that are often part of the antecedent illness but may increase in frequency and severity toward the end of life. A plan for managing seizures should be made in advance, and anticonvulsants should be readily available in the event of seizure. Parents can be taught to use rectal diazepam at home. Increased **neuroirritability** accompanies some neurodegenerative disorders; it may be particularly disruptive because of the resultant break in normal sleep–wake patterns and the difficulty in finding respite facilities for children who have prolonged crying. Such neuroirritability may respond to gabapentin. Judicious use of sedatives, benzodiazepines, clonidine, nortriptyline, or methadone may also reduce irritability without inducing excessive sedation; such treatment can dramatically improve the quality of life for both child and caregivers. **Increased intracranial pressure** and **spinal cord compression** are most often encountered in children with brain tumors or metastatic and solid tumors. Depending on the clinical situation and the goals of care, radiation therapy, surgical interventions, and steroids are potential therapeutic options.

Delirium is an underrecognized brain disorder characterized by waxing-and-waning attention, confusion, and disorientation. Agitation may occur, as well as features of hypomania. Although delirium as a whole is often not diagnosed, the hypomanic form is particularly underrecognized. Delirium has a range of causes, including medications such as anticholinergics and benzodiazepines.

Environmental strategies to calm and orient the child while addressing potentially contributing factors are helpful. In some patients, antipsychotic/neuroleptic medications are indicated (see Chapter 33 and 47).

Feeding and hydration issues can raise ethical questions that evoke intense emotions in families and medical caregivers alike. Options that may be considered to artificially support nutrition and hydration in a child who can no longer feed by mouth include nasogastric and gastrostomy feedings or intravenous nutrition or hydration (see Chapter 55). These complex decisions require evaluating the risks and benefits of artificial feedings and taking into consideration the child's functional level and prognosis. At times, it may be appropriate to initiate a trial of tube feedings, with the understanding that they may be discontinued at a later stage of the illness. A commonly held but unsubstantiated belief is that artificial nutrition and hydration are comfort measures, without which a child may suffer from starvation or thirst. This may result in well-meaning but disruptive and invasive attempts to administer nutrition or fluids to a dying child. In dying adults, the sensation of thirst may be alleviated by careful efforts to keep the mouth moist and clean. There may also be deleterious side effects to artificial hydration in the form of increased secretions, need for frequent urination, edema, and exacerbation of dyspnea. For these reasons, it is important to educate families about anticipated decreases in appetite/thirst and therefore little need for nutrition and hydration as the child approaches death. In addition, exploring the meaning that provision of nutrition and hydration may hold for families, as well as helping families anticipate the changes in their child's appearance and exploring alternative ways that they may love and nurture their child, may ease distress around this issue.

Nausea and vomiting may be caused by medications or toxins, irritation to or obstruction of the gastrointestinal tract, motion, and emotions. Drugs such as metoclopramide, 5-hydroxytryptamine antagonists, corticosteroids, olanzapine, and aprepitant may be used and should be chosen depending on the underlying pathophysiology and neurotransmitters involved. Vomiting may accompany nausea but may also occur without nausea, as with increased intracranial pressure. **Constipation** is commonly encountered in children with neurologic impairment or children receiving medications that impair gastrointestinal motility (most notably opioids). Stool frequency and quantity should be evaluated in the context of the child's diet and usual bowel pattern. Children taking regular opioids should routinely be placed on stool softeners (docusate) in addition to a laxative agent (e.g., senna). For some patients, parenteral methylnaltrexone is also helpful in relieving opioid-induced constipation. **Diarrhea** may be particularly difficult for the child and family and may be treated with loperamide (an opioid that does not cross the blood-brain barrier), and in some cases, colestyramine or octreotide may be indicated. Paradoxical diarrhea, a result of overflow resulting from constipation, should also be included in the differential diagnosis.

Hematologic issues include consideration of anemia and thrombocytopenia or bleeding. If the child has symptomatic anemia (weakness, dizziness, shortness of breath, tachycardia), red blood cell transfusions may be considered. Platelet transfusions may be an option if the child has symptoms of bleeding. Life-ending hemorrhage is disturbing for all concerned, and a plan involving the use of fast-acting sedatives should be prepared in advance if such an event is a possibility.

Skin care issues include primary prevention of problems by ongoing and timely assessment (including observation of indwelling lines and tubes) and frequent turning and repositioning and alleviating pressure wherever possible (e.g., elevating heels off the bed with pillows). Pruritus may be secondary to systemic disorders or drug therapy. Treatment includes avoiding excessive use of drying soaps, using moisturizers, trimming fingernails, and wearing loose-fitting clothing, in addition to administering topical or systemic corticosteroids. Oral antihistamines and other specific therapies may also be indicated (e.g., cholestyramine in biliary disease). Opioids can cause histamine release from mast cells, but this does not account for most of the pruritus caused by opioids. A trial of diphenhydramine may provide relief; alternatively, rotating opioids or instituting a low dose of opioid antagonist may be needed for refractory pruritus.

Children with life-threatening illness may experience psychological symptoms such as **anxiety** and **depression.** Such symptoms are frequently multifactorial and sometimes interrelated with uncontrolled symptoms such as pain and fatigue. Diagnosing depression in the context of serious illness may pose challenges because neurovegetative symptoms may not be reliable indicators. Instead, expressions of hopelessness, helplessness, worthlessness, and guilt may be more useful. Pharmacologic agents such as antidepressants may be helpful, although their effect is often preceded by a significant lag phase. Because of its immediate and positive effect on mood, *methylphenidate* may be an effective antidepressant for children at end of life, when there may not be time for a traditional antidepressant to take effect. Interventions and opportunities for children to explore worries, hopes, and concerns in an open, supportive, and nonjudgmental setting are equally if not more important approaches to psychological distress. Skilled members from a variety of disciplines, including psychology, social work, chaplaincy, child life, and expressive therapy, may help children and their families in this regard. Such opportunities may create positive moments in which meaning, connection, and new definitions of hope are found.

Discussions with adolescent patients, or with the parents of any ill child, about possible therapies or interventions should include **integrative therapies** such as massage therapy, Reiki, acupuncture, clinical aromatherapy, prayer, and nutritional supplements. Many families use integrative therapy but do not bring it up with their physician unless explicitly asked (see Chapter 78). Although largely unproven, some of these therapies are inexpensive and provide relief to individual patients. Other therapies may be expensive, painful, intrusive, and even toxic. By initiating conversation and inviting discussion in a nonjudgmental way, the clinician can offer advice on the safety of different therapies and may help avoid expensive, dangerous, or burdensome interventions. Medical marijuana (**cannabis**) for pediatric use has been legalized by some states, and pediatricians are increasingly asked about it. In such cases, it is most helpful to use this opportunity to engage in a broader conversation about symptoms and symptom management, even in states where use of cannabis for pediatric medicinal purposes is legal.

Intensive Symptom Management

At the end of life, when intensive efforts to relieve the symptom have been exhausted, or when efforts to address suffering are incapable of providing relief with acceptable toxicity/morbidity or in an acceptable time frame, **palliative sedation** may be considered. Palliative sedation may relieve suffering from refractory symptoms by reducing a child's level of consciousness. It is most often used for intractable pain, dyspnea, or agitation, but is not limited to these distressing indications. Palliative sedation provides opportunities for parents, staff, and primary clinicians to discuss the indications and goals for sedation, as well as questions or concerns about this therapy, both before and after initiation of sedation.

The doctrine of double effect (DDE) is often invoked to justify escalation of symptom-relieving medications or palliative sedation for uncontrolled symptoms at the end of life. Use of DDE emphasizes the risk of hastening death posed by escalating opioids or sedation, which is theoretical and unproven (see Chapter 6

). There is mounting evidence that patients with well-controlled symptoms live longer.

Approaching End of Life

As death seems imminent, the major task of the physician and team are to help the child have as many good days as possible and not suffer. If not already in place, a referral **for hospice care** (usually provided in the *home* , not a hospice house for children) may provide the most comprehensive care for the child and family. Gently preparing the family for what to expect and offering choices, when possible, will allow them a sense of control in the midst of tragic circumstances. Before death, it can be very helpful to discuss the following:

- Support of siblings or other family members
- Resuscitation status
- Limiting technology when no longer beneficial to the child
- Cultural, spiritual, or religious needs
- Location of death
    - Who will pronounce if death occurs at home
- Funeral arrangements
    - Offering siblings choice and appropriate support to attend
- Autopsy and/or tissue/organ donation
    - Legacy building, benefits others, informs science and family

Offered the opportunity, families will often tolerate thinking and speaking about their hopes and fears regarding their child's end of life, and some even express relief when the door to such conversation in opened by the care team. It may help to let the family know these conversations are not about *whether* the child will die but *how* the child may die.

Families gain tremendous support from having a physician and team who will continue to stay involved in the child's care. If the child is at home or hospitalized, regular phone calls or visits, assisting with symptom management, and offering emotional support is invaluable for families.

In an intensive care setting, where technology can be overwhelming and put distance between the child and parent, the physician can offer discontinuation of that which is not benefiting the child or adding to quality of life. Less invasive ways to control symptoms, such as subcutaneous infusions or topical applications, may be helpful. Parents may be afraid to ask about holding or sleeping next to their child. They may need reassurance and assistance in holding, touching, and speaking with their child, despite tubes and technology, even if the child appears unresponsive.

It is believed that hearing and the ability to sense touch are often present until death; all family members should be encouraged to continue interacting with their loved one through the dying process. Parents may be afraid to leave the bedside so that their child will not die alone. Offering parents other supports such as chaplaincy/clergy, social work, and extended family members may be helpful. In most instances the moment of death cannot be predicted. Some propose that children wait to die until their parents are ready, an important event has passed, or they are given permission. Caregivers need not dispute this, nor the hope for a miracle often held by families until the child takes the last breath.

For the family, the moment of death is an event that is recalled in detail for years to come, and thus enhancing opportunity for dignity and limited suffering is essential. Research suggests that improved symptom control and easing of difficult moments at the time of death may lessen the long-term distress of bereaved parents. Clinical experience has shown that families often find solace in clinician presence, whether at home or in the hospital. After death, families should be given the option of remaining with their child for as long as they would like and should be prepared for changes in the child's body. During this time, physicians and other professionals may ask permission to say goodbye. The family may be invited to bathe and dress the body as a final act of caring for the child.

The physician's decision to attend the funeral is a personal one. Participation may serve the dual purpose of showing respect and helping the clinician cope with a personal sense of loss. If unable to attend services, families report highly valuing the importance of receiving a call, card, or note from the physician. To know that their child made a difference and will not be forgotten is often very important to families in their bereavement.

The Pediatrician

Although optimal palliative care for children entails caregivers from a variety of disciplines, pediatricians are well positioned to support children and their families, particularly if they have a long-standing relationship with multiple family members. A pediatrician who has cared for a family over time may already know and care for other family members, understand preexisting stressors for the family, and may be familiar with coping strategies used by family members. Pediatricians are familiar with the process of eliciting concerns and providing anticipatory guidance for parents, as well as developmentally appropriate explanations for children.

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CHAPTER 8

Domestic and International Adoption

Elaine E. Schulte

Adoption is a social, emotional, and legal process that provides a new family for a child when the birth family is unable or unwilling to parent. In the United States, about 1 million children <18 yr of age are adopted; 2–4% of all American families have adopted. Annually across the globe, approximately 250,000 children are adopted, with 30,000 of these between nations. In the United States, approximately 120,000 children are adopted every year. Of these, 49% are from private agencies, American Indian Tribes, stepparent, or other forms of kinship care. The remaining 51% of adoptions include public and international adoptions. Public adoptions account for the majority of these. Because of changing policies toward adoption and social change in several of the sending countries, the number of international adoptions has decreased dramatically over the last 10 yr. Public agencies support approximately 50% of total annual adoptions in the United States, private agencies facilitate 25% of adoptions, and independent practitioners (e.g., lawyers) handle 15% of adoptions. Compared to 19% of the general population, approximately 39% of adopted children have special healthcare needs.

Domestic Adoption

The **Adoption and Safe Families Act** (P.L. 105-89) requires children in foster care to be placed with adoptive families if they cannot be safely returned to their families within a reasonable time. In fiscal year (FY) 2014, there were an estimated 415,129 children in foster care, and 107,918 were waiting for adoption. Of the 238,230 children who exited foster care, 51% were reunited with parent(s) or primary caretakers(s), and 21% were adopted (see Chapter 9).

Many children awaiting adoption are less likely to be adopted because they are of school age, part of a sibling group, members of historically oppressed racial/ethnic groups, or because they have considerable physical, emotional, or developmental needs. A number of policy efforts are aimed at increasing adoption opportunities for these children, including federal adoption subsidies, tax credits, recruitment efforts to identify ethnically diverse adults willing to adopt, increased preplacement services, and expanding adoption opportunities to single adults, older couples, and gay/lesbian partners.

Although **same-sex couple adoption** is legal in more than a dozen countries worldwide, it is actively debated in the United States. Although legislation regarding same-sex couple adoption varies by state, increasing numbers of gay and lesbian partners have been able to adopt. Current estimates suggest that almost 2 million children, including 5% of all adopted children, are raised by gay and lesbian parents. Adopted children include those adopted domestically, those from foster care, and internationally adopted children. There is increasing evidence that children raised by same-sex couples are as physically or psychologically healthy, capable, and successful as those raised by opposite-sex couples. Pediatricians can advocate for adopted children by supporting gay and lesbian parents.

Open adoption , usually through an agency or privately, occurs when the birth mother arranges to continue to be involved, although in a limited manner, with the legally adopted family. This may occur through surrogacy or more often in an unplanned pregnancy.

Intercountry Adoption

Along with foster care adoptions, **international adoptions** are a way of providing stable, long-term care to vulnerable children throughout the world. There is concern that in some countries of origin, the rapid growth of international adoption has outpaced regulation and oversight to protect vulnerable children and families. Opportunities for financial gain have led to abuses, including the sale and abduction of children, bribery, and financial coercion of families, but the extent and scope of the potential concern is difficult to ascertain. Increasing global efforts, such as the **Hague Convention on Protection of Children and Co-operation in Respect of Intercountry Adoption** , have promoted political cooperation between nations and established international law to reduce potential for child abduction and child trafficking and to ensure that the best interests of the child are paramount in decision making.

Participating nations, including the United States, are working to address the myriad of sociopolitical conditions that create the need for out-of-family care, and are working to support children within their nation's borders. International adoption is increasingly considered a measure of last resort if the child cannot be cared for within his or her birth family (including extended relatives), the immediate community, or the larger national culture. As a result, children adopted internationally into the United States are more likely to enter their families at older ages or with complex medical, developmental, or social-emotional needs.

Although the vast majority of children adopted internationally *enter* the United States for purposes of adoption, a small but growing number of children *exit* the United States for adoption into other countries. For example, in FY 2014, 96 children exited the United States for adoption by families in other countries (e.g., Canada, Netherlands, Ireland, United Kingdom). Little is known about the circumstances surrounding these adoptions and the eventual outcomes of the children who are adopted internationally *from* the United States.

In 2015, U.S. families adopted 5,647 children from other countries (compared with a peak of 22,884 in 2004). Children from China, Ethiopia, South Korea, Ukraine, Bulgaria, and the Congo represented 65% of children adopted internationally into the United States in 2015; 42% were from China alone. Although individual experiences vary, most children placed for international adoption have some history of poverty and social hardship in their home countries, and most are adopted from orphanages or institutional settings. Many young infants are placed into **orphanage care** shortly after birth. Some older children have experienced family disruption resulting from parental illness, war, or natural disasters. Still others enter orphanage care after determination of significant abuse or neglect within their biological families. The effects of **institutionalization** and other life stresses may impact all areas of growth and development. As a result, many children require specialized support and understanding to overcome the impact of stress and early adversity and to reach their full potential.

Role of Pediatricians

Preadoption Medical Record Reviews

Preadoption medical record reviews are important for both domestic and international adoptions. Adoption agencies are making increased efforts to obtain biological family health information and genetic histories to share with adoptive families prior to adoption. Such information is often becomes increasingly relevant as the child ages. Pediatricians can help prospective adoptive parents understand the health and developmental history of a child and available background information from birth families in order to assess actual and potential medical risk factors to support adult decision-making about the family's ability to parent the waiting child.

Under the Hague Convention, U.S. agencies that arrange international adoptions must make efforts to obtain accurate and complete health histories on children awaiting adoption. The nature and quality of medical and genetic information, when available, vary greatly. Poor translation and use of medical terminology and medications that are unfamiliar to U.S.-trained physicians are common. Results of specific diagnostic studies and laboratory tests performed outside the United States should not be relied on and *should be repeated* once the child arrives in the United States. Paradoxically, review of the child's medical records may raise more questions than provide answers. Each medical diagnosis should be considered carefully before being rejected or accepted. Country-specific growth curves should be avoided because they may be inaccurate or may reflect a general level of poor health and nutrition in the country of origin. Instead, *serial growth* data should be plotted on U.S. standard growth curves; this may reveal a pattern of poor growth because of malnutrition or other chronic illness. Photographs or video files may provide the only objective information from which medical status can be determined. Full-face photographs may reveal dysmorphic features consistent with **fetal alcohol syndrome** (see Chapter 126.3) or findings suggestive of other congenital disorders.

Frank interpretations of available information should be shared with the prospective adoptive parents. The role of the healthcare provider is not to comment on the advisability of an adoption, but to inform the prospective parents of any significant health needs identified now or anticipated in the future.

Postadoption Medical Care

Arrival Visit–International Adoption

All internationally adopted children should have a thorough medical evaluation shortly after arriving in the United States. Many children may have acute or chronic medical problems that are not always immediately evident, including malnutrition, growth deficiencies; stool pathogens, anemia, elevated blood lead, dental decay, strabismus, birth defects, developmental delay, feeding and sensory difficulty, and social-emotional concerns. *All children who are adopted from other countries undergo comprehensive screening for infectious diseases and disorders of growth, development, vision, and hearing* (Tables 8.1 and 8.2). Regardless of test results before arrival, all children should be screened for **tuberculosis** with either a tuberculin skin test (TST) or interferon-γ release assays (IGRA). If the child's purified protein derivative (PPD) skin test is negative, it should be repeated in 4-6 mo; children may have false-negative tests because of poor nutrition. Additional tests (e.g., malaria) should be ordered depending on the prevalence of disease in the child's country of origin (see Chapter 10). **Immunization records** should be carefully reviewed. Internationally adopted children frequently have incomplete records or have been vaccinated using alternative schedules. Pediatricians may choose to check titers to determine which vaccines need to be given, or they can *choose to reimmunize* the child. The unique medical and developmental needs of internationally adopted children have led to the creation of specialty clinics throughout the United States, which may be a valuable resource for adoptive families at all stages in the adoption process and throughout the adopted child's life.

Table 8.1

Recommended Screening Tests for International Adoptees on U.S. Arrival

Screening Tests

Complete blood cell count
Blood lead level
Newborn screening (young infants)
Vision and hearing screening
Dental screening
Developmental testing

Other Screening Tests to Consider Based on Clinical Findings and Age of Child

Stool cultures for bacterial pathogens
Glucose-6-phosphate dehydrogenase deficiency screening
Sickle cell test
Urine pregnancy test

INFECTIOUS DISEASE SCREENING (see Table 8.2)

Table 8.2

Screening Tests for Infectious Diseases in International Adoptees

Recommended Tests

Hepatitis A total Ig (with reflex testing for IgM if total Ig is positive)
Hepatitis B virus serologic testing*
  - Hepatitis B surface antigen (HBsAg)
  - Antibody to hepatitis B surface antigen (anti-HBs)
  - Antibody to hepatitis B core antigen (anti-HBc)

Hepatitis C virus serologic testing*[†]
Syphilis serologic testing
  - Nontreponemal test (RPR, VDRL, or ART)
  - Treponemal test (MHA-TP or FTA-ABS)

HIV-1 and HIV-2 testing (ELISA if >18 mo, PCR if <18 mo)*
Complete blood cell count with red blood cell indices and differential (if eosinophilia, see Chapter 10)
Stool examination for ova and parasites (optimal: 3 specimens) with specific requests for *Giardia lamblia* and *Cryptosporidium* spp. testing
Tuberculin skin test (with CXR if >5 mm induration) or interferon-γ release assay*[†]

Optional Tests (for Special Populations or Circumstances)

GC/Chlamydia
Strongyloides spp.
Schistosoma spp.
Trypanosoma cruzi

ART, Automated reagin test; CXR, chest radiograph; ELISA, enzyme-linked immunosorbent assay; FTA-ABS, fluorescent treponemal antibody absorption; GC, gonococcus; HIV, human immunodeficiency virus; MHA-TP, microhemagglutination test for *Treponema pallidum* ; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories.

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[*] Repeat 3-6 mo after arrival.

[†] See Chapter 10 .

Growth Delays

Physical growth delays are common in internationally adopted children and may represent the combined result of many factors, such as unknown/untreated medical conditions, malnutrition, and psychological deprivation. It is more important to monitor growth over time, including preplacement measurements, since trend data may provide a more objective assessment of the child's nutritional and medical status. Children who present with low height-for-age (**growth stunting**) may have a history of inadequate nutrition as well as chronic adversity. Although most children experience a significant catch-up in physical growth following adoption, many remain shorter than their U.S. peers.

Developmental Delays

Many children adopted internationally exhibit delays in at least 1 area of development, but most exhibit significant gains within the 1st 12 mo after adoption. Children adopted at older ages are likely to have more variable outcomes. In the immediate post-adoption period, it may be impossible to determine with any certainty whether developmental delays will be transient or long-lasting. Careful monitoring of development within the first years of adoption can identify a **developmental trend** over time that may be more predictive of long-term functioning than assessment at any specific point in time. When in doubt, it is better to *refer early* for developmental intervention, rather than wait to see if the children will catch up.

Language Development

For both domestic and international adoptees, genetic or biologic risk factors for poor language development may be identified preadoptively, but it is unlikely that international adoptees will have had these delays identified before adoption. These children typically have not had an assessment in their native language and have had little exposure to English. It may not be possible to fully assess their language abilities until they have had a chance to learn English. Regardless of the age at adoption, most internationally adopted children will reach age-expected language skills over time.

If a child has language delays, referral to early intervention or the school district should be made. Clinicians may need to work with these groups to help them understand the unique circumstances surrounding an adopted child's language development. For example, English language acquisition in internationally adopted children depends on the age of adoption and native language skills. Placing the recently adopted, school-age child in an English as a Second Language class may not be sufficient if the child's language development in the primary language has been atypical.

Eating Concerns

Initial concerns about eating, sleep regulation, and repetitive (e.g., self-stimulating or self-soothing) behaviors are common, especially among children adopted following a high degree of neglect or developmental trauma. Feeding behaviors of international adoptees may be linked to orphanage feeding practices, or limited exposure to textured or solid foods during later infancy/toddlerhood. Children who have experienced chronic lack of food may not have developed an awareness of *satiation cues*, leading to hoarding or frequent vomiting. **Feeding concerns** often subside gradually with introduction of age-appropriate foods and parental support for positive feeding practices. Many children who were adopted after significant malnutrition may eat an excessive amount of food. Unless the child is eating to the point of vomiting (which would indicate little awareness of satiation cues), it is generally best to allow them to eat until satiation. Typically, within several months, the child will regulate food intake appropriately. Occasionally, additional support from a speech pathologist or feeding specialist is warranted to address possible sensory, physical, or psychological issues around proper feeding.

Sleep Concerns

Sleep is often disrupted as the child reacts to changes in routines and environments. Efforts to create continuity between the preadoption and postadoption environment can be helpful. Within the 1st 3-6 mo, as the child's emotional self-regulation improves, many sleep concerns subside. Similarly, stereotypical behaviors, such as rocking or head banging, often diminish within the 1st few mo after adoption.

Social and Emotional Development

Dyadic interactions between child and caretaker are a critical component to later regulatory functioning and social-emotional development. The amount and quality of individualized caretaking that children have received before their adoption, whether international, domestic, or through the foster care system, is usually unknown. In many cases, entry into a secure, stable home setting with consistent childcare routines is sufficient to support the child's emerging social-emotional development. Pediatricians can help parents remember that adoption is part of a child's history. Throughout one's childhood, prior experiences or biologic disposition may result in behavior that is confusing to the adoptive parents. The child's reactions may be subtle or difficult to interpret, interfering with the parents’ ability to respond in a sensitive manner. In these circumstances, additional support may be helpful to foster the emerging relationships and behavioral regulation in the newly formed family.

Racial Identity Development

Transracial adoption (where the racial background of the child differs from that of the parent/parents) accounts for a significant percentage of adoptions each year in the United States. In most of these adoptive placements, children of color have been adopted by white parents. Racial identity development, including ways to understand and respond to discrimination, is increasingly recognized as important in the overall development of children. Surveys of adults adopted transracially indicate that racial identity is of central importance at many ages and tends to increase in significance during young adulthood. Integrating race/ethnicity into identity can be a complex process for all children, but it may be especially complicated when they are raised in a family where racial differences are noted. Adults raised within interracial families have noted the value of attending racially diverse schools and of having adult role models (e.g., teachers, doctors, coaches) who share their racial background. Parents who adopt transracially are often encouraged to support interactions within diverse communities and to discuss race (and associated discrimination) often within the family. Black children raised by white families in white communities may have been sheltered from overt racism but need to be taught that many others (including law enforcement officers) will regard them as black with all the intense biases associated with race (see Chapter 2.1).

Toxic Stress

The cumulative amount of early adversity (e.g., numerous years within international orphanage care, extensive abuse/neglect prior to removal from biological family, or multiple foster care placements) experienced by a child before adoption, referred to as *toxic stress* , can impact both immediate placement stability and long-term functioning (see Chapter 2). The degree of presumed toxic stress may be helpful in interpreting a child's behavior and supporting family functioning.*

Family Support

The unique aspects to adoptive family formation can create familial stress and impact child and family functioning. Some adoptive families may have to address infertility, creation of a multiracial family, disclosure of adoptive status, concerns and questions the child may have about their biologic origins, and ongoing scrutiny by adoption agencies. With gay/lesbian parents, there are often additional psychosocial stressors, including continued barriers to legal recognition of both parents in a gay/lesbian partnership that can negatively impact family functioning. Although most families acclimate well to adoption-related stressors, some parents experience postadoption depression and may benefit from additional support to ease the family's transition.

Adoption Narrative

Families are encouraged to speak openly and repeatedly about adoption with their child, beginning in the toddler years and continuing through adolescence. Creating a *Lifebook* for the adopted child provides a way to support family communication about the child's history and significant relationships (including birth family members) and to document the child's important life transitions (e.g., through foster care or immigration to the United States). It is common, and normal, for children to have questions about adoption and their biological family throughout their development. An increase in cognitive understanding between ages 7 and 10 yr can sometimes increase adoption-related questions and distress. Youth who have questions about biological family members are increasingly able to access information via social media and web-based searching, raising the importance of ongoing open communication about adoption. Pediatricians may need to respond to increased concerns/questions when the adoptee's health and genetic history is incomplete or unknown. At any time, concerns about development, behavior, and social-emotional functioning may or may not be related to the child's adoption history.

The vast majority of adopted children and families adjust well and lead healthy, productive lives. Adoptions infrequently disrupt; disruption rates are higher among children adopted from foster care, which research associates with their age at adoption and a history of multiple placements before adoption. With increased understanding of the needs of families who adopt children from foster care, agencies are placing greater emphasis on the preparation of adoptive parents and ensuring the availability of a full range of postadoption services, including physical health, mental health, and developmental services for their adopted children.

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[*] See video at http://developingchild.harvard.edu/resources/multimedia/videos/three_core_conc .

CHAPTER 9

Foster and Kinship Care

Moira Szilagyi

The placement of children in out-of-home care has served the needs of children in many societies worldwide throughout history. The institution of **foster care** was developed in the United States as a temporary resource for children during times of family crisis and is rooted in the principle that children fare best when raised in family settings. The mission of foster care is to provide for the safety, permanency, and well-being of children while assisting their families with services to promote reunification.

Epidemiology

The number of children in foster care worldwide is unknown, although it has been estimated that 8 million may be in foster and residential care. On September 11, 2015, approximately 427,910 children in the United States resided in foster care, representing a slight increase since the nadir of 397,301 reached in 2012. Early in the millennium, foster care numbers decreased despite an increase in maltreatment reports, as child welfare offered families more preventive services and alternative placement with relatives or nonrelative caregivers (**kinship care**) as an alternative to court-ordered removal. The more recent increase in numbers appears to be related to the opioid epidemic. Over the last 15 years, reunification rates have stabilized while adoption of children from foster care has increased. Nationally, approximately 45% of children live with a nonrelative foster parent, 30% of children are in placement with a relative who is a certified foster parent, and just under 15% are in **congregate** (group) **care** .

Approximately 33% of children in foster care in the United States are younger than 5 yr, and 34% are older than 12 yr. Most children are white (41%); 24% are black, 21% are Hispanic of any race, and 7% are identified as ≥2 races. As foster care numbers declined by 25% beginning in 1999, the reduction in African American children was even greater as child welfare made efforts to reduce the disparities in investigation and removal. The average length of stay in foster care continues to decline (median in 2015, 20.4 mo), with a significant drop in the number who spend ≥2 yr from 31% in 2011 to 26% in 2015. Only approximately half of children achieve reunification, while 22% (53,000) are adopted and 6% reside with relatives. Among remaining children, 9% (20, 800) emancipate between ages 18 and 21 yr, 9% enter into long-term state guardianship, <1% run away, and 2% transfer to other institutions. There were 336 deaths reported in foster care in fiscal year 2015.

Only 4% of children reside in a preadoptive home, although they represent 12% of children awaiting adoption; 52% of children awaiting adoption reside with a foster parent who is a relative. The average number of placements a child experiences in foster care is not included in **Adoption and Foster Care Analysis and Reporting System (AFCARS)** , but important predictors of an increased number of different placements include severe behavioral and developmental problems, larger sibling group size, and longer time spent in foster care. Within 12 mo, almost all emancipated youth have at least 1 homeless night. Within a decade, less than half have achieved a high school degree, most are living in poverty, and many have psychiatric disorders, including posttraumatic stress disorder and depression.

Legislation in the United States

In the **United States the Adoption and Safe Families Act** (P.L. 105-89) requires that a permanency plan be made for each child no later than 12 mo after entry into foster care, and that a petition to terminate parental rights typically be filed when a child has been in foster care for at least 15 of the previous 22 mo. The **Fostering Connections and Promoting Adoptions Act** of 2009 (P.L. 110-351) focused on incentives for guardianship and adoption, supports for the young adults at the age of emancipation, and rights of Native American children to care within their tribe. This act also contained a clause requiring states to develop and coordinate healthcare systems for children in foster care in collaboration with Medicaid and pediatricians. In 2018 the **Family First Prevention Services Act** was signed into law. This legislation emphasizes providing evidence-based mental health and substance abuse services for families whose children are at imminent risk of entering foster care.

Early Childhood Trauma Leads to Poor Health Outcomes

Children in foster care have high rates of early childhood trauma and adversity. More than 60% are placed for neglect, 13% for physical abuse, and 5% are abandoned. Parental **substance abuse** is a factor in 32% of removals, and parent alcohol abuse in 6%. **Violence** in the home is common, with >80% having experienced domestic and/or community violence, but domestic violence is not included in the AFCARS reporting system as a reason for removal. Parental **mental illness** is also not reported as a reason for removal in AFCARS, but the literature indicates that birth parents have high rates of mental illness, criminal justice system involvement, substance abuse, unemployment, and cognitive impairment. Many children, particularly infants entering care, have had prenatal substance exposure, multiple caregivers of varying quality, and are from families with long involvement with child protective services.

Removal from the family of origin may compound prior trauma experiences, although some children experience relief at removal from a chaotic, abusive, or dangerous home. Most children miss their family, worry about their parents and siblings, and long for reunification. Separation, loss and grief, unpredictable contact with birth parents, placement changes, the process of terminating parental rights, and the sheer uncertainty of foster care may further erode a child's well-being.

Childhood trauma is correlated with poor developmental, behavioral, and health outcomes. Early trauma and chronic stress adversely affect the neurobiology of the developing brain, especially those areas involved in attention, emotional regulation, memory, executive function, and cognition. As a result, shortened attention span, hyperactivity, poorer cognitive function, aggression, and memory issues are problems encountered frequently among children in foster care. However, evidence shows that specific interventions, such as specially trained foster parents for children or youth and mentoring for adolescents in foster care, can improve outcomes, although replication and dissemination of these evidence-based interventions are limited.

Health Issues

Experiencing multiple childhood adversities and receiving fragmented and inadequate health services before placement into foster care mean that children enter foster care with a high prevalence of chronic medical, mental health, developmental, dental, and educational problems (Table 9.1). Thus they are defined as *children with special health care needs* (CSHCN). The greatest single healthcare need of this population is for high-quality, evidence-based trauma-informed mental health services to address the impacts of prior and ongoing trauma, loss, and unpredictability. In addition, children in foster care have higher rates of asthma, growth failure, obesity, vertically transmitted infections, and neurologic conditions than the general pediatric population. Adolescents need access to reproductive health and substance abuse services. Up to 60% of children <5 yr old have a developmental delay in at least 1 domain and >40% of school-age children qualify for special education services. Unfortunately, educational difficulties persist despite improvements in school attendance and performance after placement in foster care. Each placement change that is accompanied by a change in school sets children back academically by about 4 mo. Federal legislation requires child welfare to maintain children in their school of origin when possible, even if child welfare has to provide transportation to ensure this.

Table 9.1

Health Issues of Children in Foster Care

Chronic Medical Problems

Affect 40–60% of children.
Asthma, dermatologic, neurologic, obesity, growth failure, hearing, and vision problems are most common.

Abuse and Neglect

>70% of children have a history of abuse and neglect at entry into foster care.
Monitor at all health visits for abuse or neglect or poor care in the home.

Complex Chronic Medical Problems

Involves up to 10% of children in foster care.

Children may be dependent on medical technologies or may have multiple disabilities.

Mental Health Concerns

Affects 80% of children >4 yr of age.

Result of childhood trauma and adversity.

Most common diagnoses are adjustment disorder, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder.

Externalizing problems are more likely to result in therapy.

Minority children and those in kinship care have less access to mental health services.

Developmental Problems

60% of children <5 yr of age have at least 1 documented delay.

Typically affect communication, cognition, problem-solving, and personal-social domains, including emotional self-regulation.

Dental Problems

20–35% of children have significant dental disease.

Adolescent Health Issues

High rates of sexually transmitted infections, high-risk behaviors, and substance abuse.

Educational Problems

Half of special education placements relate to behavioral or emotional issues, not cognitive.

Only 32% of adolescents eventually graduate from high school; 32%

obtain a general equivalency diploma; 1–2% complete any amount of college.

Family Relationship Problems

100% of children have family relationship problems.

Although children in foster care are CSHCN, they often lack access to the services they need. Most public and private child welfare agencies do not have formal arrangements for accessing the needed array of health services and rely on local physicians and health clinics funded by Medicaid. Health histories are often sparse at admission because many have lacked regular care, or their biological parents may not be available or forthcoming. Once children enter foster care, there is often a diffusion of responsibility across caregivers and child welfare. Foster parents usually receive little information about a child's healthcare needs, but they are typically expected to decide when and where children receive healthcare services. Child welfare caseworkers are responsible for ensuring that a child's health needs are addressed but coordination across multiple healthcare providers may be daunting. Uncertainty about who is legally responsible for making healthcare treatment decisions and who may have access to health information may delay or result in the denial of healthcare services.

Healthcare for Children and Adolescents in Foster Care

The American Academy of Pediatrics (AAP) has published detailed healthcare standards for children in foster care, available on the *Healthy Foster Care America* website. The AAP recommends that children receive healthcare services in a medical home setting, where comprehensive healthcare is continuous over time (Table 9.2). Compassionate, culturally competent healthcare that is **trauma informed** means that health staff should understand, recognize, and respond to symptoms and risk factors of traumatic stress and provide an environment that offers physical, emotional, and psychological safety for children and caregivers. In foster care, attention must be paid to the effects of past trauma and the impact of ongoing uncertainty and loss on a child's health and well-being, as well as that of their birth and foster/kinship families.

Table 9.2

Trauma-Informed Pediatric Medical Home for Children in Foster Care

CHARACTERISTIC	APPLICATION IN FOSTER CARE
Comprehensive healthcare	Perform comprehensive admission assessment within 30 days of entry. Ensure access to mental health, developmental, and dental evaluation and services. Screen and refer as needed for abuse and neglect.
Coordination of care	Make timely referrals and follow up subspecialist visits. Communicate with caseworkers, foster parents, and legal professionals. Maintain a comprehensive medical record despite changes in placement.
Compassionate care	Understand and educate children, families, and other healthcare professionals on the impact of early childhood adversities, trauma, and ongoing uncertainties of foster care on the developing child. Promote positive purposeful parenting strategies and minimizing conflict among caregivers.
Child-centered and family-focused care	Prioritize the needs of children first and foremost. Partner with families to increase understanding of a child's needs. Focus on the strengths of children and caregivers. Understand the conflicts for the child of belonging in multiple families.
Continuity of care	Invite children to remain patients throughout their stay in foster care, and beyond when feasible.
Cultural competence	Extend this concept to include the microculture of foster care and the multiple transitions that can further erode a child's well-being. Understand the roles of caseworkers, foster parents, law guardians, etc. Understand the importance of quality visitation for family reunification.
Accessibility	Create a welcoming environment for children and all their families (birth, foster, kin, preadoptive).

The trauma-informed office is one in which symptoms such as dysregulation of sleep, behavioral problems, developmental delays, poor school function, and somatic complaints are recognized as potential effects of childhood trauma. Understanding the child's psychosocial context and history, as well as that of the caregiver, and exploring their strengths, assets, and challenges are the foundation of a trauma-informed approach. The office should have print resources for education of families and child welfare professionals and a list of helpful local community resources. Referral to trauma-informed pediatric mental health services, when available, should be considered in collaboration with caregivers, child welfare, and educators. **Continuity of care** is very important for the child in foster care and includes ongoing monitoring and management of progress and care. The AAP has several resources for caring for traumatized children.*

Several recommendations are specific to the care of children and youth in foster care. Children should be seen early and often when they first enter a new placement to identify all their health issues, and to support the child and caregivers through a major transition that involves considerable loss and adjustment, including the development of an attachment relationship with a new caregiver, for the child and many challenges for the foster/kinship parent.

The AAP recommends that every child in foster care have comprehensive medical, dental, developmental, and mental health assessments within 30 days of entering foster care. Almost every child in foster care deserves a full mental health evaluation to assess for the impact of trauma and loss on emotional well-being. *Psychotropic medication* should only be considered, if at all, after a thorough high-quality trauma-informed mental health evaluation by a pediatric-trained mental health professional. The pediatrician should remember that inattention, impulsivity, and hyperactivity may reflect the impact of past trauma on the developing brain rather than attention-deficit/hyperactivity disorder (see Chapter 49). Childhood trauma may impair cognition and memory (see Chapter 16), so that children <6 yr of age benefit from a comprehensive developmental assessment, whereas older children often benefit from a comprehensive educational assessment. The caseworker should provide consents for healthcare and any available health history and encourage the appropriate involvement of the birth parent. The primary care provider can help caseworkers and caregivers by obtaining and interpreting the results of these assessments. Pediatricians, caregivers, and caseworkers should share health information.

Foster/kinship parents are the major therapeutic intervention of the foster care system, and pediatricians are in a unique position to provide them with appropriate education and support. Important topics include positive parenting strategies, supporting children through transitions, providing a consistent and nurturing environment, and helping children heal from past trauma and adversity (Table 9.3). All caregivers may need extensive education about behavioral and emotional problems within the context of the child's trauma history to remove blame and promote healing. Minimizing conflict among caregivers is extremely important because children ideally have affection and loyalty for all their caregivers. Pediatricians can promote resilience by focusing on both caregiver and child strengths. For teens and young adults in foster care, the pediatrician can provide anticipatory guidance around education, identifying formation in the face of past trauma, independent decision-making, health promotion including reproductive health, healthy relationships, and developing the skills and competencies needed for a successful future life. The pediatrician can advocate for placement stability in a nurturing and responsive foster family where caregivers possess the appropriate skills to help children and youth heal.

Table 9.3

Trauma-Informed Anticipatory Guidance for Children in Foster Care

SITUATION	ANTICIPATORY GUIDANCE FOR FOSTER PARENTS
Preparing for visits	Educate foster/kinship parents about impact of visitation on children and ways to improve the experience for children. Send familiar object with child to visit. Have child draw picture to give birth parent. Reassure child that foster parent will be there when child returns from visits. Advise all caregivers to minimize conflict with and negativity toward each other. Ideally, visits are coached by trained professionals.
Returning from visits and other transitions	Greet child warmly and help with unpacking. Establish reentry rituals, such as quiet play, reading together, active play, having a healthy snack.
Relationship with birth parent(s)	Encourage caseworker to have birth parents keep child's rituals and routines consistent with those in foster/kinship home (vice versa when appropriate). Focus on birth parent's positive qualities; maintain a neutral or positive affect;.
Building on child's strengths	Encourage participation in child-directed play. Time-in with child. Encourage participation in normalizing activities (e.g., hobbies, sports) “Catch the child being good.” Give specific praise. Practice attentive listening. Provide child with words for emotions. Ignore negative behavior or redirect unless there is a safety issue.
Preparing for court dates	Foster/kinship parent, caseworker or law guardian should explain purpose of court hearings to child in simple terms.
School	If changing schools, visit school together a few times, and meet teacher. Check in regularly (weekly or monthly depending on need) with child's teacher.
Adolescent	Decide what issues demand firm limits and guidelines (e.g., curfews, no smoking, party at a friend's house), what issues are not important and can be left up to teen (e.g., hair length and color), and what issues are ideal for negotiation (e.g., transportation to school function, style of dress). Encourage responsible decision-making by recognizing and complimenting it. Encourage after-school activities. Teach driving when age and developmentally appropriate. Encourage teen to seek employment and teach job skills. Help teen to identify mentors and focus on the future.

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[*] https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/resilience/Pages/Becoming-a-Trauma-Informed-Practice.aspx .

CHAPTER 10

Medical Evaluation of the Foreign-Born Child

Stacene R. Maroushek

More than 210,000 foreign-born children (≤16 yr old) enter the United States each year as asylees (asylum seekers), refugees, and immigrants, including international adoptees (see Chapter 8). This number does not include undocumented children living and working in the United States, the U.S.-born children of foreign-born parents, or the approximately 2.7 million nonimmigrant visitors ≤16 yr old who legally enter the United States annually with temporary visas. With the exception of internationally adopted children, pediatric guidelines for screening these newly arrived children are sparse. The diverse countries of origin and patterns of infectious disease, the possibility of previous high-risk living circumstances (e.g., refugee camps, orphanages, foster care, rural/urban poor), the limited availability of reliable healthcare in many economically developing countries, the generally unknown past medical histories, and interactions with parents who may have limited English proficiency and/or varied educational and economic experiences, make the medical evaluation of immigrant children a challenging but important task.

Before admission into the United States, all immigrant children are required to have a medical examination performed by a physician designated by the U.S. Department of State in their **country of origin** . This examination is limited to completing legal requirements for screening for certain communicable diseases and examination for serious physical or mental problems that would prevent issuing a permanent residency visa. This evaluation is *not* a comprehensive assessment of the child's health, and except in limited circumstances, laboratory or radiographic screening for infectious diseases *is not required* for children <15 yr old. After entry into the United States, health screenings of refugees, but not other immigrants, are recommended to be done by the resettlement state. There is limited tracking of refugees as they move to different cities or states. Thus, many foreign-born children have had minimal pre- or postarrival screening for infectious diseases or other health issues.

Immunization requirements and records also vary depending on entry status. Internationally adopted children who are younger than 10 yr are exempt from Immigration and Nationality Act regulations pertaining to immunization of immigrants before arrival in the United States. Adoptive parents are required to sign a waiver indicating their intention to comply with U.S.-recommended immunizations, whereas older immigrants need only show evidence of up-to-date, not necessarily complete, immunizations before application for permanent resident (green card) status after arrival in the United States.

Infectious diseases are among the most common medical diagnoses identified in immigrant children after arrival in the United States. Children may be asymptomatic; therefore, diagnoses must be made by screening tests in addition to history and physical examination. Because of inconsistent perinatal screening for hepatitis B and hepatitis C viruses, syphilis, and HIV, and the high prevalence of certain intestinal parasites and tuberculosis, all foreign-born children should be screened for these infections on arrival in the United States. Table 10.1 lists suggested screening tests for infectious diseases. Table 10.2 lists incubation periods of common internationally acquired diseases. In addition to these infections, other medical and developmental issues, including hearing, vision, dental, and mental health assessments; evaluation of growth and development; nutritional assessment; lead exposure risk; complete blood cell count with red blood cell indices; microscopic urinalysis; newborn screening (this could also be done in non-neonates) and/or measurement of thyroid-stimulating hormone concentration; and examination for congenital anomalies (including fetal alcohol syndrome) should be considered as part of the initial evaluation of any immigrant child.*

Table 10.1

Screening Tests for Infectious Diseases in International Adoptees and Foreign-Born (Immigrant) Children

Recommended Tests

Hepatitis B virus serologic testing*

  - Hepatitis B surface antigen (HBsAg)
  - Antibody to hepatitis B surface antigen (anti-HBs)

Hepatitis C virus serologic testing* †

Hepatitis A virus serologic testing †

Varicella virus serologic testing †

Syphilis serologic testing

  - Nontreponemal test (RPR, VDRL, or ART)
  - Treponemal test (MHA-TP or FTA-ABS)

Human immunodeficiency viruses 1 *and* 2 testing (ELISA if >18 mo, PCR if <18 mo)*

Complete blood cell count with red blood cell indices and differential (if eosinophilia, see text)

Strongyloides serology

Stool examination for O&P (2-3 specimens) †

Stool examination for *Giardia lamblia* and *Cryptosporidium* antigen (1 specimen) †

Tuberculin skin test (with CXR if >5 mm induration) or interferon-γ release assay* †

Optional Tests (for Special Populations or Circumstances)

GC/Chlamydia

Chagas disease serology (endemic areas)

Malaria, thick and thin smears (endemic areas)

Filaria testing (endemic areas)

Urine for O&P for schistosomiasis, if hematuria present

Stool testing for enteric bacteria and viruses in children with diarrhea

ART, Automated reagin test; CXR, chest radiograph; ELISA, enzyme-linked immunosorbent assay; FTA-ABS, fluorescent treponemal antibody absorption; GC, gonococcus; MHA-TP, microhemagglutination test for *Treponema pallidum* ; O&P, ova and parasites; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories.

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[*] Repeat 3-6 mo after arrival.

[†] See text.

Table 10.2

Incubation Periods of Common Travel-Related Infections[*]

SHORT INCUBATION (<10 DAYS)	MEDIUM INCUBATION (10-21 DAYS)	LONG INCUBATION (>21 DAYS)
Malaria Arboviruses including dengue, yellow fever, Japanese encephalitis, Zika, chikungunya Hemorrhagic fevers: Lassa, Ebola, South American arenaviruses Respiratory viruses including severe acute respiratory syndrome Typhoid and paratyphoid Bacterial enteritis *Rickettsia* : spotted fever group—Rocky Mountain spotted fever, African tick typhus, Mediterranean spotted fever, scrub typhus, Q fever Bacterial pneumonia including *Legionella* Relapsing fever Amoebic dysentery Meningococcemia *Brucella* (rarely) Leptospirosis Fascioliasis Rabies (rarely) African trypanosomiasis (acute), East African (rarely)	Malaria Flaviviruses: tick-borne encephalitis and Japanese encephalitis Hemorrhagic fevers: Lassa, Ebola, Crimean-Congo Acute HIV infection Typhoid and paratyphoid *Giardia* *Rickettsia* : flea-borne, louse-borne, and scrub typhus, Q fever, spotted fevers (rare) Cytomegalovirus *Toxoplasma* Amoebic dysentery Histoplasmosis *Brucella* Leptospirosis Babesiosis Rabies East African trypanosomiasis (acute) Hepatitis A (rarely) Measles	Malaria Schistosomiasis Tuberculosis Acute HIV infection Viral hepatitis Filariasis *Rickettsia:* Q fever Secondary syphilis Epstein-Barr virus including mononucleosis Amoebic liver disease Leishmaniasis *Brucella* Bartonellosis (chronic) Babesiosis Rabies West African trypanosomiasis (chronic) Cytomegalovirus

[*] Diseases that commonly have variable incubation periods are shown more than once. However, most diseases may rarely have an atypical incubation period, and this is not shown here.

HIV, Human immunodeficiency virus.

From Freedman DO: Infections in returning travelers. In Bennett JE, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 324-2).

Children should be examined within 1 mo of arrival in the United States, or earlier if there are immediate health concerns, but foreign-born parents may not access the healthcare system with their children unless prompted by illness, school vaccination, or other legal requirements. *It is important to assess the completeness of previous medical screenings at any first visit with a foreign-born* *child.*

Clinicians should be aware of potential diseases in high-risk immigrant children and their clinical manifestations. Some diseases, such as central nervous system cysticercosis, may have incubation periods as long as several years, and thus may not be detected during initial screening. On the basis of findings at the initial evaluation, consideration should be given to a repeat evaluation 6 mo after arrival. In most cases, the longer the interval from arrival to development of a clinical syndrome, the less likely the syndrome can be attributed to a pathogen acquired in the country of origin.

Commonly Encountered Infections

Hepatitis B

See also Chapter 385 .

The prevalence of hepatitis B surface antigen (HBsAg) in refugee children ranges from 4–14%, depending on the country of origin, age, and year studied. Prevalence of markers of past hepatitis B virus (HBV) infection is higher. HBV infection is most prevalent in immigrants from Asia, Africa, and some countries in Central and Eastern Europe, as well as the former Soviet Union (e.g., Bulgaria, Romania, Russia, Ukraine), but also occurs in immigrants born in other countries. All immigrant children, even if previously vaccinated, coming from high-risk countries (HBsAg seropositivity >2%) should undergo serologic testing for HBV infection, including both HBsAg and antibody to HBsAg (anti-HBs), to identify current or chronic infection, past resolved infection, or evidence of previous immunization. Because HBV has a long incubation period (6 wk–6 mo), the child may have become infected at or near the time of migration, and initial testing might be falsely negative. Therefore, strong consideration should be given to a repeated evaluation 6 mo after arrival for all children, especially those from highly endemic countries. Chronic HBV infection is indicated by persistence of HBsAg for >6 mo. Children with HBsAg-positive test results should be evaluated to identify the presence of chronic HBV infection, which occurs in >90% of infants infected at birth or in the 1st yr of life and in 30% of children exposed at ages 1-5 yr. Once identified as being infected, additional testing should be done to assess for biochemical evidence of severe or chronic liver disease or liver cancer.

Hepatitis A

See Chapter 385 .

Hepatitis C

See also Chapter 385 .

The decision to screen children should depend on history (e.g., receipt of blood products; traditional percutaneous procedures such as tattooing, body piercing, circumcisions, or other exposures to reused, unsterile medical devices) and the prevalence of hepatitis C virus (HCV) infection in the child's country of origin. Children from Eastern Mediterranean and Western Pacific countries, Africa, China, and Southeast Asia should be considered for HCV infection screening. All children coming from Egypt, which has the highest known HCV seroprevalence (12% nationally and 40% in some villages), should be tested for hepatitis C.

Intestinal Pathogens

Fecal examinations for ova and parasites (O&P) by an experienced laboratory will identify a pathogen in 8–86% of immigrants and refugees The prevalence of intestinal parasites varies by country of origin, time period when studied, previous living conditions (including water quality, sanitation, and access to footwear) and age, with toddler/young school-age children being most affected. If documented predeparture treatment was given, an eosinophil count should be performed. An absolute eosinophil count of >400 cells/µL, if persistently elevated for 3-6 mo after arrival, should prompt further investigation for tissue-invasive parasites such as *Strongyloides* (see Chapter 321) and *Schistosoma* (Chapter 326) species (if no predeparture praziquantel given). If no documented predeparture treatment was given, 2 stool O&P specimens obtained from separate morning stools should be examined by the concentration method, and an eosinophil count performed. If the child is symptomatic, including evidence of poor physical growth, but no eosinophilia is present, a single stool specimen should also be sent for *Giardia lamblia* (see Chapter 308.1) and *Cryptosporidium parvum* (Chapter 309) antigen detection. All potentially pathogenic parasites found should be treated appropriately. All nonpregnant refugees >2 yr of age coming from sub-Saharan Africa and Southeast Asia should be presumptively treated with predeparture albendazole.

Tuberculosis

See also Chapter 242 .

Tuberculosis (TB) commonly is encountered in immigrants from all countries because *Mycobacterium tuberculosis* infects approximately 30% of the world's population. Latent TB infection rates can be up to 60% in some refugee children from North Africa and the Middle East. Prior to 2007, chest radiographs or tuberculin skin tests were generally not administered in children <15 yr of age, and reports indicate that 1–2% of these unscreened children may enter the United States with undiagnosed active TB disease.

Since 2007, TB *Technical Instructions for Medical Evaluation of Aliens* have required that children ages 2-14 yr undergo a TB skin test or interferon-γ release assay if they are medically screened in countries where the TB rate is ≥20 cases per 100,000 population. If the testing is positive, a chest radiograph is required. If the chest film suggests TB, cultures and 3 sputum smears are required, all before arrival in the United States. Check with the Centers for Disease Control and Prevention, Division of Global Migration and Quarantine, for the latest information (www.cdc.gov/ncidod/dq/technica.htm).

Congenital Syphilis

See Chapter 245 .

HIV Infection

See Chapter 302 .

Immunizations

See Chapter 197 .

Immigrant children and adolescents should receive immunizations according to the recommended schedules in the United States for healthy children and adolescents. Some immigrants will have written documentation of immunizations received in their birth or home country. Although immunizations such as bacille Calmette-Guérin, diphtheria and tetanus toxoids and pertussis (DTP), poliovirus, measles, and HBV vaccines often are documented, other immunizations, such as *Haemophilus influenzae* type b, mumps, and rubella vaccines, are given less frequently, and *Streptococcus pneumoniae* , human papillomavirus, meningococcal, and varicella vaccines are given rarely. When doubt exists, an equally acceptable alternative is to reimmunize the child. Because the rate of more serious local reactions after diphtheria, tetanus toxoid, and acellular pertussis vaccine increases with the number of doses administered, serologic testing for antibody to tetanus and diphtheria toxins before reimmunizing, or if a serious reaction occurs, can decrease risk.

In children older than 6 mo with or without written documentation of immunization, testing for antibodies to diphtheria and tetanus toxoid and poliovirus may be considered to determine whether the child has protective antibody concentrations. If the child has protective concentrations, the immunization series should be completed as appropriate for that child's age. In children older than 12 mo, measles, mumps, rubella, and varicella antibody concentrations may be measured to determine whether the child is immune; these antibody tests should not be performed in children younger than 12 mo because of the potential presence of maternal antibody.

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[*] For the most up-to-date guidelines, see: https://www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/domestic-guidelines.html .

CHAPTER 11

Cultural Issues in Pediatric Care

Lee M. Pachter

Pediatricians live and work in a multicultural world. Among the world's 7 billion people residing in over 200 countries, more than 6,000 languages are spoken. As the global population becomes more mobile, population diversity increases in all countries. In the United States, sources of ethnic and cultural diversity come from indigenous cultural groups such as Native Americans and Alaskan and Hawaiian natives, groups from U.S. territories such as Puerto Rico, recent immigrant groups, those whose heritage originates from the African diaspora, as well as others whose families and communities migrated to the United States from Europe and Asia generations ago but who have retained cultural identification. U.S. census estimates suggest that in 2016, almost 40% of the U.S. population self-identified as belonging to a racial/ethnic group other than non-Hispanic white. Recent immigrants comprise 13.5% of the U.S. population, but if U.S.-born children of these immigrants are included, 27% of the population are either new immigrants or first-generation Americans. Immigrants from China and India account for the largest groups coming to the United States, followed by those from Mexico. This national and international diversity allows for a heterogeneity of experience that enriches the lives of everyone. Much of this diversity is based on varied cultural orientation.

What Is Culture?

The concept of *culture* does not refer exclusively to racial and ethnic categorizations. A common definition of **cultural group** is a *collective that shares common heritage, worldviews, beliefs, values, attitudes, behaviors, practices, and identity* . Cultural groups can be based on identities such as gender orientation (gay/lesbian, bisexual, transgender), age (teen culture), being deaf or hearing impaired (deaf culture), and having neurodevelopmental differences (neurodiversity; neurotypical and neuroatypical). All these groups to a certain extent share common worldviews, attitudes, beliefs, values, practices, and identities.

Medical professionals can also be considered as belonging to a specific cultural group. Those who identify with the **culture of medicine** share common theories of well-being and disease, acceptance of the biomedical and biopsychosocial models of health, and common practices and rituals. As with other cultural groups, physicians and other healthcare professionals have a distinct language and share a common history, the same preparatory courses that must be mastered for entrance into training for the profession (a rite of passage). Medical professionals subscribe to common norms in medical practice. Young physicians learn a new way to describe health and illness that requires a new common vocabulary and an accepted structure for communicating a patient's history. These common beliefs, orientations, and practices are often not shared by those outside medicine. Therefore, *any* clinical interaction between a healthcare provider and a patient can be a potential *cross-cultural interaction* — between the culture of medicine and the culture of the patient—regardless of the race or ethnicity of the participants. A culturally informed and sensitized approach to clinical communication is a fundamental skill required of all medical professionals, regardless of the demographic makeup of one's patient population.

Culture and Identity

We are all members of multiple cultural groups. Our identification or affiliation with different groups is not fixed or unchangeable. With whom we self-identify may depend on specific situations and contexts and may change over time. A gay Latino physician may feel, at different times and in different situations, greatest affinity as a member of Latino culture, a member of the culture of medicine, a minority in the United States, or a gay man. An immigrant from India may initially feel great connection with her Indian culture and heritage, which may wane during periods of assimilation into American cultural life, then increase again in later life. Culturally informed clinicians should never assume that they know or understand the cultural identity of a person based solely on perception of ethnic, racial, or other group affiliation.

Intracultural Variability

There can be significantly different beliefs, values, and behaviors among members of the same cultural group. Often, there is as much variability *within* cultures as there is *between* cultures. The sources of this variability include differences in personal psychology and philosophy, family beliefs and practices, social context, and other demographic differences, as well as **acculturation** , defined as the changes in beliefs and practices resulting from continuous interactions with another culture. The literature on acculturation and health outcomes shows varied effects of cultural change on health and well-being. These differences are in part caused by overly simplistic ways of measuring acculturation in public health and health services research. The use of *proxies*, such as generational status (recent immigration, first generation) and socioeconomic status, as measures of acculturation does not allow for an understanding of the complex behavioral changes that occur during shifts in cultural orientation. Often, acculturation is seen as a *linear process* where individuals move from unacculturated to acculturated or assimilated into the host culture. This simplistic view does not take into account the reality that acculturation is **bidimensional** : the degree to which an individual continues to identify with her original cultural identity, and the degree to which the host cultural orientation is adopted. These are separate and independent processes. One can become *bicultural* (adopting the host culture while retaining aspects of the original culture), *assimilated* (host culture is adopted, but original culture is not retained), *separated* (original cultural orientation is retained, but host culture is not greatly adopted), or *marginalized* (does not adopt host culture and does not retain original culture). These variations in the acculturation process are determined not only by the individual going through the cultural change process but also by the degree of acceptance of diversity in the host culture. In theory, individuals who best adapt to the multicultural society are those who are **bicultural** , since they retain the strengths and assets of their heritage culture while being able to positively adjust to host cultural norms. Likewise, members of the majority culture who are able to take a bicultural perspective will have relative advantage in the multicultural society. This type of perspective is a foundation of cultural awareness and culturally informed practice.

Culturally Informed Care

Physicians and patients bring to their interactions diverse orientations from multiple cultural systems. These different belief systems and practices could have significant implications for the delivery of healthcare (Table 11.1). Consequently, physician cultural awareness, sensitivity, and humility is critical to successful patient–provider interaction.

Table 11.1

Culturally Informed Care

1. Respects the beliefs, values, and lifestyles of patients
2. Understands that health and illness are influenced by ethnic and cultural orientation, religious and spiritual beliefs, and linguistic considerations
3. Has insight into one's own cultural biases; doesn't see “cultural issues” as something that only affects the patient
4. Is sensitive to how differences in power and privilege affect the clinical encounter
5. Recognizes that the culturally constructed meaning of illness and health is as important a clinical issue as the biomedical aspects of disease
6. Sensitive to within group variations in beliefs and practices; avoids stereotyping

The culturally informed physician (1) attempts to understand and respect the beliefs, values, attitudes, and lifestyles of patients; (2) understands that health and illness are influenced by ethnic and cultural orientation, religious and spiritual beliefs, and linguistic considerations; (3) has insight into own cultural biases and does not see cultural issues as something that only affects the patient; (4) is sensitive to how differences in power and privilege may affect the quality of the clinical encounter; (5) recognizes that in addition to the physiologic aspects of disease, the culturally and psychologically constructed meaning of illness and health is a central clinical issue; and (6) is sensitive to intragroup variations in beliefs and practices and avoids stereotyping based on any group affiliation. These core components of culturally-informed care are important for interactions with *all* patients, regardless of race or ethnicity. Culturally sensitive clinical care is essentially *generally sensitive* clinical care.

Becoming culturally informed is a developmental process. Fig. 11.1 displays a framework that includes a continuum of perceptions and orientations to cultural awareness. Individuals in the *denial* stage perceive their own cultural orientation as the true one, with other cultures either undifferentiated or unnoticed. In the *defensive* stage, other cultures are acknowledged but regarded as inferior to one's own culture. The *minimization* stage is characterized by beliefs that fundamental similarities among people outweigh any differences, and downplays the role of culture as a source of human variation. The idea that one should be “color blind” is an example of a common belief of individuals in the minimization stage.

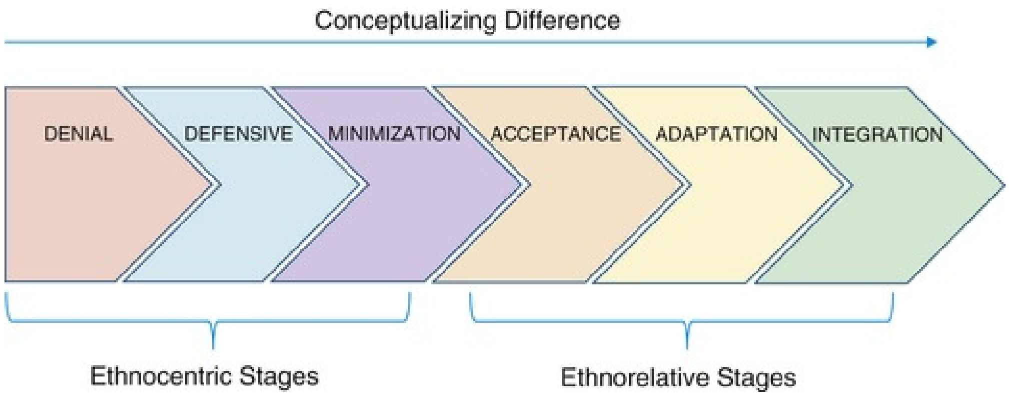

FIG. 11.1 **Development of intercultural sensitivity. (Adapted from Bennett MJ: A developmental approach to training for intercultural sensitivity, *Int J Intercultural Relations* 10(2):179–196, 1986.)**

As one moves to the *acceptance* stage, cultural differences are acknowledged. Further expansion and understanding lead to *adaptation* , where one not only acknowledges differences but can shift frames of reference and have a level of comfort outside one's own cultural frame. This eventually leads to further comfort with different worldviews seen at the *integration* stage, where individuals respect cultural differences and can comfortably interact across cultures, even incorporating aspects of different cultural orientations into their own.

Understanding Culture in the Context of Healthcare

Cultural orientation is just one of many different perspectives that individuals draw on as they make health and healthcare decisions. Individual psychology, past experiences, religious and spiritual views, social position, socioeconomic status, and family norms all can contribute to a person's health beliefs and practices. These beliefs and practices can also change over time and may be expressed differently in different situations and circumstances. Because of the significant variability in health beliefs and behaviors seen among members of the same cultural group, an approach to cultural competency that emphasizes a knowledge set of specific cultural health practices in different cultural groups could lead to false assumptions and stereotyping. Knowledge is important, but it only goes so far. Instead, an approach that focuses on the healthcare provider acquiring skills and attitudes relating to open and effective communication styles is a preferable approach to culturally effective and informed care. Such an approach does not rely on rote knowledge of facts that may change depending on time, place, and individuals. Instead, it provides a skills toolbox that can be used in all circumstances. The following skills can lead to a culturally informed approach to care:

1. *Don't assume.* Presupposing that a particular patient may have certain beliefs, or may act in a particular way based on their cultural group affiliation, could lead to incorrect assumptions. Sources of intracultural diversity are varied.
2. *Practice humility.* Cultural humility has been described by Hook et al. (2013) as “the ability to maintain an interpersonal stance that is other-oriented (or open to the other) in relation to aspects of cultural identity.” Cultural humility goes beyond cultural competency in that it requires the clinician to self-reflect and acknowledge that one's *own* cultural orientation enters into any transaction with a patient (see Chapter 2.1).

Cultural humility aims to fix power imbalances between the dominant (hospital-medical) culture and the patient. It recognizes the value of the patient's culture and incorporates the patient's life experiences and understanding outside the scope of the provider; it creates a collaboration and a partnership.

Cultural competency is an approach that typically focuses on the patient's culture, whereas cultural humility acknowledges that both physicians and patients have cultural orientations, and that a successful relationship requires give and take among those differing perspectives. It also includes an understanding that differences in social power, which are inherent in the physician–patient relationship, need to be understood and addressed so that open communication can occur.

3. *Understand privilege.* Members of the majority culture have certain privileges and benefits that are often unrecognized and unacknowledged. For example, they can have high expectations that they will be positively represented in media such as movies and television. Compared with minority groups, those in the majority culture have less

chance of being followed by security guards at stores, or having their bags checked. They have a greater chance of having a positive reception in a new neighborhood, or of finding food in the supermarket that is consistent with one's heritage. These privileges typically go unnoticed by members of the majority culture, but their absence is painfully recognized by members of nonmajority cultural groups. The culturally informed physician should try to be mindful of these privileges, and how they may influence the interaction between physicians and patients.

4. *Be inquisitive.* Because of the significant amount of intracultural diversity of beliefs and practices, the only way to know a particular patient's approach to issues concerning health and illness is through direct and effective communication. Asking about the patient's/family's perspective in an inquisitive and respectful manner will usually be met with open and honest responses, as long as the patient does not feel looked down on and the questions are asked in genuine interest. Obtaining a **health beliefs history** is an effective way of understanding clinical issues from the patient's and family's perspective (Table 11.2). The health beliefs history gathers information on the patient's views on the identification of health problems, causes, susceptibility, signs and symptoms, concerns, treatment, and expectations. Responses gathered from the health beliefs history can be helpful in guiding care plans and health education interventions.

Table 11.2

The Health Beliefs History

- What do you think is wrong with your child?
- Why do you think your child has gotten it [the illness]?
- What do you think caused it?
- Why do you think it started when it did?
- What do you think is happening inside the body?
- What are the symptoms that make you know your child has this illness?
- What problems does this illness cause your child?
- What are you most worried about with this illness?
- How long do you think it will last?
- How do you treat it?
- What will happen if it is not treated?
- What do you expect from the treatments?

Adapted from Kleinman A, Eisenberg L, Good B: Culture, illness, and care: clinical lessons from anthropologic and cross-cultural research, *Ann Intern Med* 88(2):251–258, 1978.

5. *Be flexible.* As members of the culture of medicine, clinicians have been educated and acculturated to the biomedical model as the optimal approach to health and illness. Patients and families may have health beliefs and practices that do not fully fit the biomedical model. Traditional beliefs and practices may be used in tandem with biomedical approaches. An individual's approach to health rarely is exclusively biomedical or traditional, and often a combination of multiple approaches. The health beliefs history provides clinicians with information regarding the nonbiomedical beliefs and practices that may be held by the patient. Culturally informed physicians should be flexible and find ways of integrating nonharmful traditional beliefs and practices into the medical care plan to make that plan fit the patient's needs and worldview. This will likely result in better adherence to treatment and prevention.

Obtaining a health beliefs history for a child with asthma, for example, may reveal that the family uses an alternative remedy when the symptoms first occur. If the symptoms do not resolve after giving the remedy, the family administers standard medical care. In this case, if the alternative remedy is safe and has no significant likelihood of causing adverse effects, the culturally informed physician might say, “I'm not sure if the remedy you're using is helpful or not, but I can say that if used as directed, it's not likely to be harmful. So if you think it may work, feel free to try it. But instead of waiting to give the prescription medicine until after you see if the remedy works, why don't you give it at the same time you give the remedy? Maybe they’ll work well together.” This approach shows respect for the family-held beliefs and practices while increasing timely adherence to the biomedical therapy.

At times, an alternative therapy the patient is using may be contraindicated or may have adverse effects. In this case it is advisable to recommend against the therapy, but whenever possible, one should attempt to replace the therapy with another, safer, culturally acceptable treatment. If a parent is giving a child tea containing harmful ingredients to treat a cold, the culturally informed physician could recommend stopping the practice and explain the concerns, but then recommend replacing the harmful tea with something safer that fits the family's cultural belief system, such as a weak herbal tea with no harmful ingredients. This requires an awareness and background knowledge of the cultural belief system, but this approach increases the chances that the family will follow through on the recommendation and feel that their beliefs are respected.

Awareness-Assessment-Negotiation Model

Providing care in the multicultural context can be challenging, but it offers opportunities for creativity and can result in improved long-term physician–patient relationships, which will ultimately improve the quality and outcomes of healthcare. Culturally informed care combines knowledge with effective communication skills, an open attitude, and the qualities of flexibility and humility.

The culturally informed physician should first become aware of common health beliefs and practices of patients in the practice. Reading literature on the particular groups could increase awareness, but with the caution that such information may be outdated (cultural beliefs and practices change over time) and not specific to the local context. The best approach to becoming aware of specific health beliefs and practices is to ask—enter into conversations with patients, families, and community members. One might say, “I've heard that there are ways of treating this illness [or staying healthy] that people believe work, but doctors don't know about. Sometimes they're recommended by grandparents or others in your community. They may be effective. Have you heard of any of these?” This approach shows genuine interest and openness, is not based on presumptions, and does not ask about behaviors or practices, only if the patient has *heard* of these practices. If the question elicits a positive response, the conversation can then continue, including asking whether the patient has personally tried any of the therapies, under what circumstances, and if they thought it was helpful. This approach shows respect for the patient as an individual and avoids stereotyping all members of a particular group as having a uniform set of cultural beliefs and practices.

The information obtained should be seen only as common ways that members of a community *may* interpret health-related issues. Assuming that all members subscribe to similar beliefs and practices would be incorrect and potentially damaging by promoting stereotypes. Since the unit of measurement in clinical care is the individual patient and family, clinicians must assess to what extent a specific patient may act on these general beliefs and under what circumstances. The health beliefs history can help the physician become aware of the specific beliefs and practices that a patient holds, and allow one to tailor the care to the individual patient.

Once the patient's explanatory model is elicited and understood, the clinician should be able to assess the congruity of this model and the biomedical model, finding similarities. Then the process of negotiating can occur. Integrating patient-held approaches to health with evidence-based biomedical standards of care will help place care within the lifestyle and worldview of patients, leading to increased adherence to medical care plans, better physician–patient communication, enhanced long-term therapeutic relationship, and improved patient (and physician) satisfaction.

11.1

Culture-Specific Beliefs

Robert M. Kliegman

Cultural group-specific practices that affect health-seeking behaviors are noted in Tables 11.3 and 11.4 .

Table 11.3

Cultural Values* Relevant to Health and Health-Seeking Behavior

CULTURAL GROUP	RELEVANT CULTURAL NORMS	
	Description of Norm	**Consequences of Failure to Appreciate**
Latino	*Fatalismo:* Fate is predetermined, reducing belief in the importance of screening and prevention.	Less preventive screening
	Simpática: Politeness/kindness in the face of adversity—expectation that the physician should be polite and pleasant, not detached.	Nonadherence to therapy, failure to make follow-up visits
	Personalismo: Expectation of developing a warm, personal relationship with the clinician, including introductory touching.	Refusal to divulge important parts of medical history, dissatisfaction with treatment
	Respeto: Deferential behavior on the basis of age, social stature, and economic position, including reluctance to ask questions.	Mistaking a deferential nod of the head/not asking questions for understanding; anger at not receiving due signs of respect
	Familismo: Needs of the extended family outrank those of the individual, and thus family may need to	Unnecessary conflict, inability to reach a decision

	be consulted in medical decision-making.	
Muslim	*Fasting* during the holy month of Ramadan: fasting from sunrise to sundown, beginning during the teen years. Women are exempted during pregnancy, lactation, and menstruation, and there are exemptions for illness, but an exemption may be associated with a sense of personal failure.	Inappropriate therapy; will not take medicines during daytime misinterpreted as noncompliance; misdiagnosed
	Modesty: Women's body, including hair, body, arms, and legs, not to be seen by men other than in immediate family. Female chaperone and/or husband must be present during exam, and only that part of the body being examined should be uncovered.	Deep personal outrage, seeking alternative care
	Touch: Forbidden to touch members of the opposite sex other than close family. Even a handshake may be inappropriate.	Patient discomfort, seeking care elsewhere
	After death , body belongs to God. Postmortem examination will not be permitted unless required by law; family may wish to perform after-death care.	Unnecessary intensification of grief and loss
	Cleanliness essential before prayer. Individual must perform ritual ablutions before prayer, especially elimination of urine and stool. Nurse may need to assist in cleaning if patient is incapable.	Affront to religious beliefs
	God's will: God causes all to happen for a reason, and only God can bring about healing.	Allopathic medicine will be rejected if it conflicts with religious beliefs, family may not seek healthcare.
	Patriarchal , extended family. Older male typically is head of household, and family may defer to him for decision-making.	Child's mother or even both parents may not be able to make decisions about child's care; emergency decisions may require additional time.
	Halal (permitted) vs *haram* (forbidden) foods and medications. Foods and medicine containing alcohol (some cough and cold syrups) or pork (some gelatin-coated pills) are not permitted.	Refusal of medication, religious effrontery
Native American	*Nature* provides the spiritual, emotional, physical, social, and biologic means for human life; by caring for the earth, Native Americans will be provided for. Harmonious living is important.	Spiritual living is required of Native Americans; if treatments do not reflect this view, they are likely not to be followed.
	Passive forbearance: Right of the individual to choose his or her path. Another family member cannot intervene.	Mother's failure to intervene in a child's behavior and/or use of noncoercive disciplinary techniques may be mistaken for neglect.
	Natural unfolding of the individual. Parents further the development of their children by limiting direct interventions and viewing their natural unfolding.	Many pediatric preventive practices will run counter to this philosophy.
	Talking circle format to decision-making. Interactive learning format including diverse tribal members.	Lecturing, excluding the views of elders, is likely to result in advice that will be disregarded.
African-American	Great heterogeneity in beliefs and culture among African-Americans.	Risk of stereotyping and/or making assumptions that do not apply to a specific patient or family.
	Extended family and variations in family size and childcare arrangements are common; matriarchal decision-making regarding healthcare.	Advice/instructions given only to the parent and not to others involved in health decision-making may not be effective.

	Parenting style often involves stricter adherence to rules than seen in some other cultures.	Advice regarding discipline may be disregarded if it is inconsistent with perceived norms; other parenting styles may not be effective.
	History-based widespread mistrust of medical profession and strong orientation toward culturally specific alternative/complementary medicine.	In patient noncompliance, physicians will be consulted as a last resort.
	Greater orientation toward others; the role of an individual is emphasized as it relates to others within a social network.	Compliance may be difficult if the needs of 1 individual are stressed above the needs of the group.
	Spirituality/religiosity important; church attendance central in most African American families.	Loss of opportunity to work with the church as an ally in healthcare
East and Southeast Asian	Long history of Eastern medicines (e.g., Chinese medicine) as well as more localized medical traditions.	May engage with multiple health systems (Western biomedical and traditional) for treatment of symptoms and diseases
	Extended families and care networks. Grandparents may provide day-to-day care for children while parents work outside of the home.	Parents may not be the only individuals a physician needs to communicate with in regard to symptoms, follow-through on treatments, and preventive behaviors.
	Sexually conservative. Strong taboos for premarital sexual relationships, especially for women.	Adolescents may be reluctant to talk about issues of sexuality, pregnancy, and birth control with physicians. Recent immigrants or native populations may have less knowledge regarding pregnancy prevention, sexually transmitted infections, and HIV.
	Infant/child feeding practices may overemphasize infant's or child's need to eat a certain amount of food to stay "healthy."	Guidelines for child nutrition and feeding practices may not be followed out of concern for child's well-being.
	Saving face. This is a complex value whereby an individual may lose prestige or respect of a 3rd party when a 2nd individual makes negative or contradictory statements.	Avoid statements that are potentially value laden or imply a criticism of an individual. Use statements such as, "We have now found that it is better to …," rather than criticizing a practice.

[*] Adherence to these or other beliefs will vary among members of a cultural group based on nation of origin, specific religious sect, degree of acculturation, age of patient, etc.

Table 11.4

Examples of Disease Beliefs and Health Practices in Select Cultures

CULTURAL GROUP	BELIEF OR PRACTICE
Latino	Use of traditional medicines (*nopales,* or cooked prickly pear cactus, as a hypoglycemic agent) along with allopathic medicine.
	Recognition of disorders not recognized in Western allopathic medicine (*empacho* , in which food adheres to the intestines or stomach), which are treated with folk remedies but also brought to the pediatrician.
	Cultural interpretation of disease (*caida de mollera* or "fallen fontanel") as a cultural interpretation of severe dehydration in infants.

Muslim	Female genital mutilation: practiced in some Muslim countries; the majority do not practice it, and it is not a direct teaching of the Koran.
	Koranic faith healers: use verses from the Koran, holy water, and specific foods to bring about recovery.
Native American	Traditional “interpreters” or “healers” interpret signs and answers to prayers. Their advice may be sought in addition or instead of allopathic medicine.
	Dreams are believed to provide guidance; messages in the dream will be followed.
East and Southeast Asian	Concepts of “hot” and “cold,” whereby a combination of hot and cold foods and other substances (e.g., coffee, alcohol) combine to cause illness. One important aspect is that Western medicines are considered “hot” by Vietnamese, and therefore nonadherence may occur if it is perceived that too much of a medicine will make their child's body “hot.” *Note:* Hot and cold do not refer to temperatures but are a typology of different foods; for example, fish is hot and ginger is cold. Foods, teas, and herbs are also important forms of medicine because they provide balance between hot and cold.

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CHAPTER 12

Maximizing Children's Health

Screening, Anticipatory Guidance, and Counseling

Joseph F. Hagan Jr, Dipesh Navsaria

Routine, scheduled care of well infants, children, and adolescents is an essential prevention effort for children and youth worldwide. Children's constantly changing development lends added value to regular and periodic encounters between children and their families and practitioners of pediatric healthcare. Health supervision visits from birth to age 21 yr are the platform for a young person's healthcare. The provision of **well care** in the medical home fosters strong relationships between the clinic or practice and the child and family, enabling the provision of appropriate surveillance, screening, and sick care.

To ensure the optimal health of the developing child, pediatric care in the United States and other countries evolved into regularly-scheduled visits to ensure adequate nutrition, to detect and immunize against infectious diseases, and to observe the child's development. Assessment of these key arenas remains essential to the well-child **health supervision** visit. However, contemporary analysis of changes in the population's health, coupled with the recognition that early life experiences and social factors impact health along the entire life course, have led to the addition of other components to the content of today's well-child encounter.

Stressful circumstances impair development, and **adverse childhood experiences** (ACEs) early in life increase the risk of disease (see Chapter 2). Adults who experienced abuse, violence, or other stressors as children have an increased risk for depression, heart disease, and other morbidities. Biology informs us that **stress** leads to increased heart rate and blood pressure and increased levels of inflammatory cytokines, cortisol, and other stress hormones, all of which impair brain activity, immune status, and cardiovascular function. There are both a causal model and evidence that ACEs, including those that could have been prevented, negatively impact the life course.

Preventive care for children and youth is a component of contemporary U.S. health reform activities and offers great opportunity for health cost savings. A healthy economy requires educated and healthy workers. For children to have a successful, meaningful, and useful educational experience, they must have physical, cognitive, and emotional health. Educational success, in particular, is tied to early childhood developmental competence. Thus, well-child care plays a vital role in promoting adult health, a concept endorsed by business leaders as essential to building the human infrastructure of the U.S. economy and society.

Although well-child care focuses on the health and well-being of the child, the reality is that children live in families. The context of the child within the family unit is also key to this primary goal and therefore also may necessitate the *addressing of needs* in the family, including the parents or other adults. Addressing of needs may be as straightforward as supportive listening, validation, and referral to an appropriate resource, whether in the community or the adult's own medical home. The importance of dual-generation approaches that benefit both the parent and the child is immense.

Periodicity Schedule and Guidelines

The frequency and content for well-child care activities are derived from evidence-based practice and research. In addition, federal agencies and professional organizations, such as the American Academy of Pediatrics (AAP), have developed evidence-informed, expert consensus guidelines for care. The *Recommendations for Preventive Pediatric Health Care* or **Periodicity Schedule** is a compilation of recommendations listed by age-based visits (Fig. 12.1). It is intended to guide practitioners of pediatric primary care to perform certain services and intentionally make observations at age-specific visits; it designates the standard for *preventive services* for U.S. children and youth and is referred to as such in some legislation. It is updated regularly and is available online.

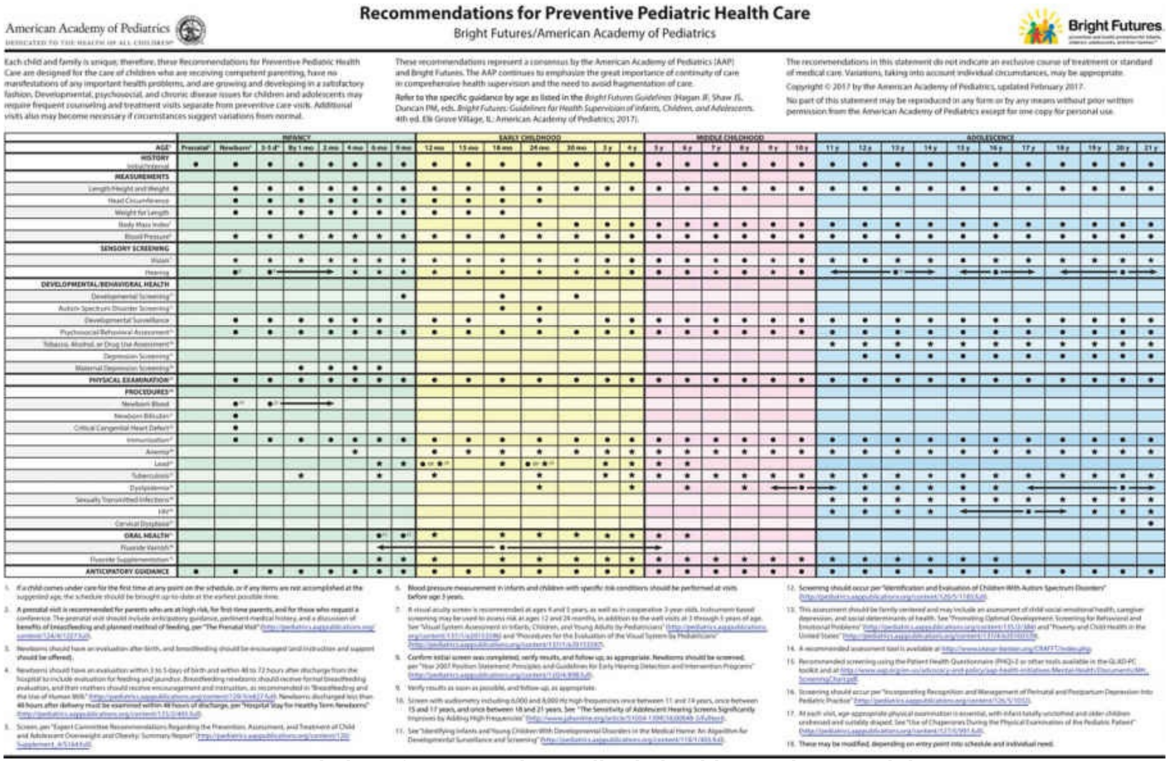

FIG. 12.1 **Recommendations for preventive pediatric healthcare. (From *Bright Futures* /American Academy of Pediatrics. Copyright 2017, American Academy of Pediatrics, Elk Grove Village, IL. https://www.aap.org/en-us/documents/periodicity_schedule.pdf .)**

Comprehensive guides for care of well infants, children, and adolescents have been developed based on the Periodicity Schedule to expand and further recommend how practitioners might accomplish the tasks outlined. The current guideline standard is *The Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents* , 4th edition (https://brightfutures.aap.org/Pages/default.aspx). These guidelines were developed by AAP under the leadership of the Maternal Child Health Bureau of the U.S. Department of Health and Human Services, in collaboration with the National Association of Pediatric Nurse Practitioners, American Academy of Family Physicians, American Medical Association, American Academy of Pediatric Dentistry, Family Voices, and others.

Tasks of Well-Child Care

The well-child encounter aims to promote the physical and emotional well-being of children and youth. Child health professionals, including pediatricians, family medicine physicians, nurse practitioners, and physician assistants, take advantage of the opportunity well-child visits provide to elicit parental questions and concerns, gather relevant family and individual health information, perform a physical examination, and initiate screening tests. The tasks of each well-child visit include the following:

1. Disease detection
2. Disease prevention
3. Health promotion
4. Anticipatory guidance

To achieve these outcomes, healthcare professionals employ techniques to screen for disease—or for the risk of disease—and provide advice about healthy behaviors. These activities lead to the formulation of appropriate anticipatory guidance and health advice.

Clinical detection of disease in the well-child encounter is accomplished by a careful physical examination and both surveillance and screening. In well-child care, **surveillance** occurs in every health encounter and is enhanced by repeated visits and observations with advancing developmental stages. It relies on the experience of a skilled clinician performing intentional observation over time. **Screening** is a more formal process using some form of validated assessment tool and has known sensitivity and specificity. For example, anemia *surveillance* is accomplished through taking a dietary history and seeking signs of anemia in the physical examination. Anemia *screening* is done by hematocrit or hemoglobin tests. Developmental *surveillance* relies on the observations of parents and the assessment of clinicians in pediatric healthcare who are experienced in child development. Developmental *screening* uses a structured developmental screening tool by personnel trained in its use or in the scoring and interpretation of parent report questionnaires.

The 2nd essential action of the well-child encounter, **disease prevention** , may include both *primary prevention* activities applied to a whole population and *secondary prevention* activities aimed at patients with specific factors of risk. For example, counseling about reducing fat intake is appropriate for all children and families. However, counseling is intensified for overweight and obese youth or in the presence of a family history of hyperlipidemia and its sequelae. The child and adolescent healthcare professional needs to individualize disease prevention strategies to the specific patient, family, and community.

Health promotion and **anticipatory guidance** activities distinguish the well-child health supervision visit from all other encounters with the healthcare system. Disease detection and disease prevention activities are germane to all interactions of children with physicians and other healthcare clinicians, but health promotion and anticipatory guidance shift the focus to wellness and to the strengths of the family (e.g., what is being done well and how this might be improved). This approach is an opportunity to help the family address relationship issues, broach important safety topics, access needed services, and engage with extended family, school, neighborhood, and community and spiritual organizations.

It is not possible to cover all the topics suggested by comprehensive guidelines such as *Bright Futures* in the average 18 min well-child visit. Child health professionals must prioritize the most important topics to cover. Consideration should be given to a discussion of the following:

- First and foremost, the agenda the parent or child brings to the health supervision visit.
- The topics where evidence suggests counseling is effective in behavioral change.
- The topics where there is a clear rationale for the issue's critical importance to health, such as sleep environment to prevent sudden unexpected infant death (SUID) or attention to diet and physical activity.
- A summary of the child's progress in emotional, cognitive, and social development, physical growth, and strengths.
- Issues that address the questions, concerns, or specific health problems relevant to the individual family.
- Community-specific problems that could significantly impact the child's health (e.g.,

neighborhood violence from which children need protection, absence of bike paths that would promote activity).

This approach must be directed at *all children* , including children and youth with special health care needs. CSHCN are no different from other children in their need for guidance about healthy nutrition, physical activity, progress in school, connection with friends, a healthy sense of self-efficacy, and avoidance of risk-taking behaviors. The existence of frequent visits to the medical home or specialists to address the special health needs sometimes masks the lack of general health supervision care. The coordination of specialty consultation, medication monitoring, and functional assessment, which should occur in their periodic visits, needs to be balanced with a discussion of the child's unique ways of accomplishing the emotional, social, and developmental tasks of childhood and adolescence. Comprehensive, integrated care planning for CSHCN should support partnerships between medical homes and families and youth through goal setting and negotiating next steps. In this process, chronic condition management and health surveillance (including adolescent engagement and planning for transition to adult care) occur within an effective patient care relationship, partnering to improve health outcomes and efficiencies of care provision.

Infancy and Early Childhood

Nutrition, physical activity, sleep, safety, and emotional, social, and physical growth, along with parental well-being, are critical for all children. For each well-child visit, there are topics specific to individual children based on their age, family situation, chronic health condition, or a parental concern, such as sleep environment to prevent SUID, activities to lose weight, and fences around swimming pools. Attention should also be focused on the family milieu and other social determinants of health, including screening for parental depression (especially maternal postpartum depression) and other mental illness, family violence, substance abuse, nutritional inadequacy, and lack of housing. It is equally important to identify, acknowledge, and empower family strengths. These issues are essential to the care of young children.

Answering parents’ questions while creating an environment where parents feel comfortable asking is the most important priority of the well-child visit. Promoting family-centered care and partnership with parents increases the ability to elicit parental concerns, especially about their child's development, learning, and behavior. Evidence-based approaches such as early literacy assessment and promotion (e.g., Reach Out and Read) provide a structure for enquiry, surveillance, and parent coaching efficiently within the health supervision visit.

It is important to identify children with developmental disorders as early as possible. Developmental surveillance at every visit combined with a structured developmental screening, neuromuscular screening, and autism screening at certain visits is a way to improve diagnosis, especially for some of the subtler delays or autism spectrum disorders for which early intervention is believed to be associated with reduced morbidity.

Middle Childhood and Adolescence

As the child enters school-age years, additional considerations emerge. Attention to their developing autonomy requires fostering a clinician–patient relationship separate from the clinician–child-family relationship, with increasing needs for privacy and confidentiality as the child ages. The 6 health behaviors that most significantly impact adolescent and adult morbidity and mortality are inadequate physical activity, poor nutrition, sexuality-related behaviors, substance use and abuse (including tobacco and vaporized nicotine), unintentional injury–related behaviors, and intentional injury–related behaviors. Emotional well-being and early diagnosis and treatment of mental health problems are equally important, with attention to the developmental tasks of adolescence: competence at school and other activities, connection to friends and family, autonomy, empathy, and a sense of self-worth.

Office Intervention for Behavioral and Mental Health Issues

One fifth of primary care encounters with children are for a behavioral or mental health problem or sickness visits complicated by a mental health issue. Pediatricians and other primary care clinicians seeing children must have reasonable comfort and knowledge for diagnosis, treatment, and referral criteria for attention-deficit/hyperactivity disorder (see Chapter 49), depression and other mood disorders (Chapter 39), anxiety (Chapter 38), and conduct disorder (Chapter 42), as well as an understanding of the pharmacology of the frequently prescribed psychotropic medications. Familiarity with available local mental health services and clinicians and knowledge of the types of services indicated are important for effective consultation or referral. With new understanding of the impact of lifestyle on mood disorders and anxiety, encouragement of behavioral change to implement regular exercise, a healthy diet, avoidance of substances, and judicious use of media has become an important responsibility of the primary care clinician. **Motivational interviewing** provides a structured approach that has been designed to help patients and parents identify the discrepancy between their desire for health and the outcomes of their current behavioral choices. It also allows the clinician to use proven strategies that lead to a patient-initiated plan for change.

Strength-Based Approaches and Framework

Questions about school or extracurricular accomplishments or competent personal characteristics should be integrated into the content of the well-child visit. Such inquiries set a positive context for the visit, deepen the partnership with the family, acknowledge the child's healthy development, and facilitate discussing social-emotional development with children and their parents. There is a strong relationship between appropriate social-emotional development (e.g., children's strong connection to their family, social friends, and mentors; competence; empathy; appropriate autonomy) and decreased participation in all the risk behaviors of adolescence (related to drugs, sex, and violence). An organized approach to the identification and encouragement of a child's strengths during health supervision visits provides both the child and the parent with an understanding of how to promote healthy achievement of the developmental tasks of childhood and adolescence. It also provides an opportunity to assess and comment on the relational health in the family. CSHCN often have a different timetable, but they have an equal need to be encouraged to develop strong family and peer connections, competence in a variety of arenas, ways to do things for others, and appropriate independent decision-making.

Office System Change for Quality Improvement

To facilitate the effective delivery of preventive services for children and youth, screening schedules and parent handouts, flow sheets, registries, and parent and youth previsit questionnaires are available in *The Bright Futures Guidelines Toolkit* ; online previsit tools are under construction. These efforts are part of a larger national effort that is built on a coordinated team approach in the office setting and the use of continuous measurement for improvement.

Evidence

Available evidence should be utilized in developing health-promotion and disease-detection recommendations. Revisions to the AAP Periodicity Schedule undergo rigorous evidence assessment; however, many highly valued well-child care activities have not been evaluated for efficacy. Lack of evidence is most often related to absence of systematic study and does not necessarily mean lack of benefit. Thus the clinical encounter with the well child is also guideline and recommendation driven and requires the integration of clinician goals, family needs, and community realities in seeking better health for the child. The evidence and rationale for recommendations in the Periodicity Schedule (see Fig. 12.1) and *Bright Futures Guidelines* regarding well-child care activities are a balance of evidence from research, clinical practice guidelines, professional recommendations, expert opinion, experience, and knowledge of the needs of the patient population in the context of community assets and challenges. Clinical or counseling decisions and recommendations may also be based on local legislation (e.g., seat belts), on commonsense measures not likely to be studied experimentally (e.g., lowering water heater temperatures, use of car seats), or on the basis of relational evidence (e.g., television watching associated with violent behavior in young children). Most important, sound clinical and counseling decisions are responsive to family needs and desires and support patient-centered decision-making.

Caring for the Child and Youth in the Context of the Family and Community

A successful primary care practice for children incorporates families, is family centered, and embraces the concept of the medical home. A **medical home** is defined as primary care that is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective. In a medical home, a clinician works in partnership with the family and patient to ensure that all medical and nonmedical needs of the child are met. Through this partnership, the child healthcare professional helps the family/patient access and coordinate specialty care, educational services, out-of-home care, family support, and other public and private community services that are important to the overall health of the child and family.

Ideally, health promotion activities occur not only in the medical home, but also through community members and other health and education professionals. To be most effective, communication and coordination around providing accurate, consistent information is key, with a clear understanding of the important role that the community plays in supporting healthy behaviors among families. Communities where children and families feel safe and valued and have access to positive activities and relationships provide the important base that the healthcare professional can build on and refer to for needed services that support health but are outside the realm of the healthcare system or primary care medical home. It is important for the medical home and community agencies to identify mutual resources, communicate well with families and each other, and partner in designing service delivery systems. This interaction is the practice of **community pediatrics** , whose unique feature is its concern for all the population: those who remain well but need preventive services, those who have symptoms but do not receive effective care, and those who do seek medical care in a physician's office or hospital.

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CHAPTER 13

Injury Control

Brian D. Johnston, Frederick P. Rivara

In all high-income countries of the world, and increasingly in many low- and middle-income countries, injuries are the most common cause of death during childhood and adolescence beyond the 1st few mo of life (Table 13.1 and Fig. 13.1). Injuries represent one of the most important causes of preventable pediatric morbidity and mortality in the United States. Identification of risk factors for injuries has led to the development of successful programs for prevention and control. Strategies for injury prevention and control should be pursued by the pediatrician in the office, emergency department (ED), hospital, and community setting and should be done in a multidisciplinary, multifaceted way.

Table 13.1

Injury Deaths in the United States, 2015* [N (Rate per 100,000)]

CAUSE OF DEATH	<1 yr	1-4 yr	5-9 yr	10-14 yr	15-19 yr	0-19 yr
ALL CAUSES	23,161 (583.4)	4045 (25.3)	2490 (12.2)	3013 (14.6)	10,812 (51.2)	43,521 (53.0)
ALL INJURIES	1616 (40.70)	1660 (10.40)	960 (4.70)	1468 (7.12)	8148 (39.03)	13,952 (16.99)
All unintentional	1219 (30.70)	1261 (7.90)	787 (3.85)	847 (4.11)	4152 (19.65)	8266 (10.07)
Motor vehicle occupant	26 (0.65)	80 (0.50)	111 (0.54)	144 (0.70)	748 (3.54)	1109 (1.35)
Pedestrian	12 (0.30)	175 (1.10)	98 (0.48)	117 (0.57)	329 (1.56)	731 (0.89)
Drowning	38 (0.96)	425 (2.66)	147 (0.72)	103 (0.50)	253 (1.20)	966 (1.18)
Fire and burn	13 (0.33)	107 (0.67)	78 (0.38)	52 (0.25)	35 (0.17)	285 (0.35)
Poisoning	9 (0.23)	34 (0.21)	13 (0.06)	28 (0.14)	771 (3.65)	855 (1.04)
Bicycle	0 (0.00)	6 (0.04)	15 (0.07)	38 (0.18)	45 (0.21)	104 (0.13)
Firearm	1 (0.03)	34 (0.21)	16 (0.08)	23 (0.11)	53 (0.25)	127 (0.15)
Fall	7 (0.16)	19 (0.12)	5 (0.02)	14 (0.07)	66 (0.31)	111 (0.14)
Suffocation	1023 (25.77)	118 (0.74)	35 (0.17)	39 (0.19)	43 (0.20)	1258 (1.53)
All intentional	276 (6.95)	339 (2.12)	146 (0.71)	585 (2.84)	3959 (18.74)	5305 (6.46)
Suicide	0 (0.00)	0 (0.00)	7 (0.03)	436 (2.11)	2117 (10.02)	2560 (3.12)

Firearm suicide	0 (0.00)	0 (0.00)	0 (0.00)	160 (0.78)	942 (4.46)	1102 (1.34)
Homicide	276 (6.95)	339 (2.12)	139 (0.68)	147 (0.71)	1816 (8.59)	2717 (3.13)
Firearm homicide	11 (0.28)	64 (0.40)	68 (0.33)	95 (0.46)	1611 (7.62)	1849 (2.25)
Undetermined intent	121 (3.05)	60 (0.38)	27 (0.13)	36 (0.17)	137 (0.65)	381 (0.46)

[*] *Injury data* from US Centers for Disease Control and Prevention (CDC): Web-based Injury Statistics Query and Reporting System (WISQARS) (website). National Center for Injury Prevention and Control, CDC (producer). https://www.cdc.gov/injury/wisqars/ .

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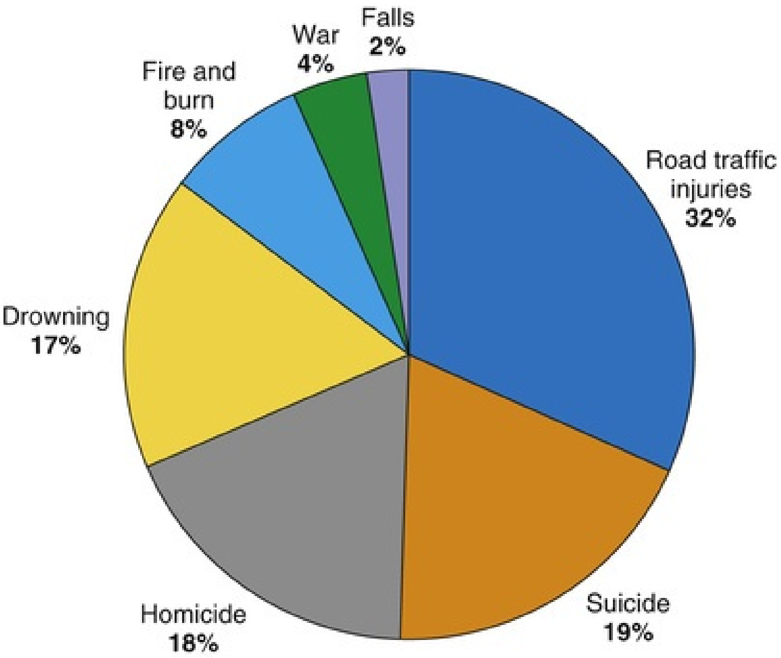

FIG. 13.1 **Global injury deaths to children, adolescents, and young adults, 0-29 yr of age, 2012. (From WHO: Injuries and Violence: The Facts 2012. Geneva: World Health Organization, 2014.)**

Injuries have identifiable risk and protective factors that can be used to define prevention strategies. The term *accidents* implies a chance event occurring without pattern or predictability. In fact, most injuries occur under fairly predictable circumstances to high-risk children and families. *Most injuries are preventable.*

Reduction of morbidity and mortality from injuries can be accomplished not only through *primary* prevention (averting the event or injury), but also through *secondary* and *tertiary* prevention. The latter 2 approaches include appropriate

emergency medical services (EMS) for injured children; **regionalized trauma care** for the child with multiple injuries, severe burns, or traumatic brain injury; and **specialized pediatric rehabilitation** services that attempt to return children to their previous level of functioning.

Injury control also encompasses *intentional injuries* (assaults and self-inflicted injuries). These injuries are important in adolescents and young adults, and in some populations, these rank 1st or 2nd as causes of death in these age-groups. Many of the same principles of injury control can be applied to these problems; for example, limiting access to firearms may reduce both unintentional shootings, homicides, and suicides.

Scope of the Problem

Mortality

In the United States, injuries cause 42% of deaths among 1-4 yr old children and 3.5 times more deaths than the next leading cause, congenital anomalies. For the rest of childhood and adolescence up to age 19 yr, 64% of deaths are a result of injuries, more than all other causes combined. In 2016, injuries caused 13,952 deaths (16.78 deaths per 100,000 population) among individuals ≤19 yr old in the United States, resulting in more years of potential life lost than any other cause. **Unintentional injuries** remained the leading cause of death among those <24 yr old in 2016 (see Table 13.1 and Fig. 13.1).

Motor vehicle injuries lead the list of injury deaths among school-age children and adolescents and are the 2nd leading cause of injury death for those age 1-4 yr. In children and adults, motor vehicle *occupant* injuries account for the majority of these deaths. During adolescence, occupant injuries are the leading cause of injury death, accounting for >50% of unintentional trauma mortality in this age-group.

Drowning ranks 2nd overall as a cause of unintentional injury deaths among those age 1-19 yr, with peaks in the preschool and later teenage years (see Chapter 91). In some areas of the United States, drowning is the leading cause of death from trauma for preschool-age children. The causes of drowning deaths vary with age and geographic area. In young children, bathtub and swimming pool drowning predominates, whereas in older children and adolescents, drowning occurs predominantly in natural bodies of water while the victim is swimming or boating.

Fire- and burn-related deaths account for 3% of all unintentional trauma deaths, with the highest rates among those <5 yr of age (see Chapter 92). Most deaths are a result of house fires and are caused by smoke inhalation or asphyxiation rather than severe burns. Children and elderly persons are at greatest risk for these deaths because of difficulty in escaping from burning buildings.

Suffocation accounts for approximately 87% of all unintentional deaths in children <1 yr old. Some cases result from choking on food items, such as hot dogs, candy, grapes, and nuts. Nonfood items that can cause choking include undersize infant pacifiers, small balls, and latex balloons. An increasing number of infant suffocation deaths represent sleep-related mortality in the presence of unsafe bedding, crib bumpers, or cosleeping with an impaired adult. In previous years these might have been classified as sudden infant death syndrome (see Chapter 402).

Homicide is the 3rd leading cause of injury death in children 1-4 yr old and the 3rd leading cause of injury death in adolescents (15-19 yr old) (Fig. 13.2). Homicide in the pediatric age-group falls into 2 patterns: infant (child) and adolescent. Child homicide involves children <5 yr old and represents child abuse (see Chapter 16). The perpetrator is usually a caretaker; death is generally the result of blunt trauma to the head and/or abdomen. The adolescent pattern of homicide involves peers and acquaintances and is caused by firearms in 88% of cases. The majority of these deaths involve handguns. Children between these 2 age-groups experience homicides of both types.

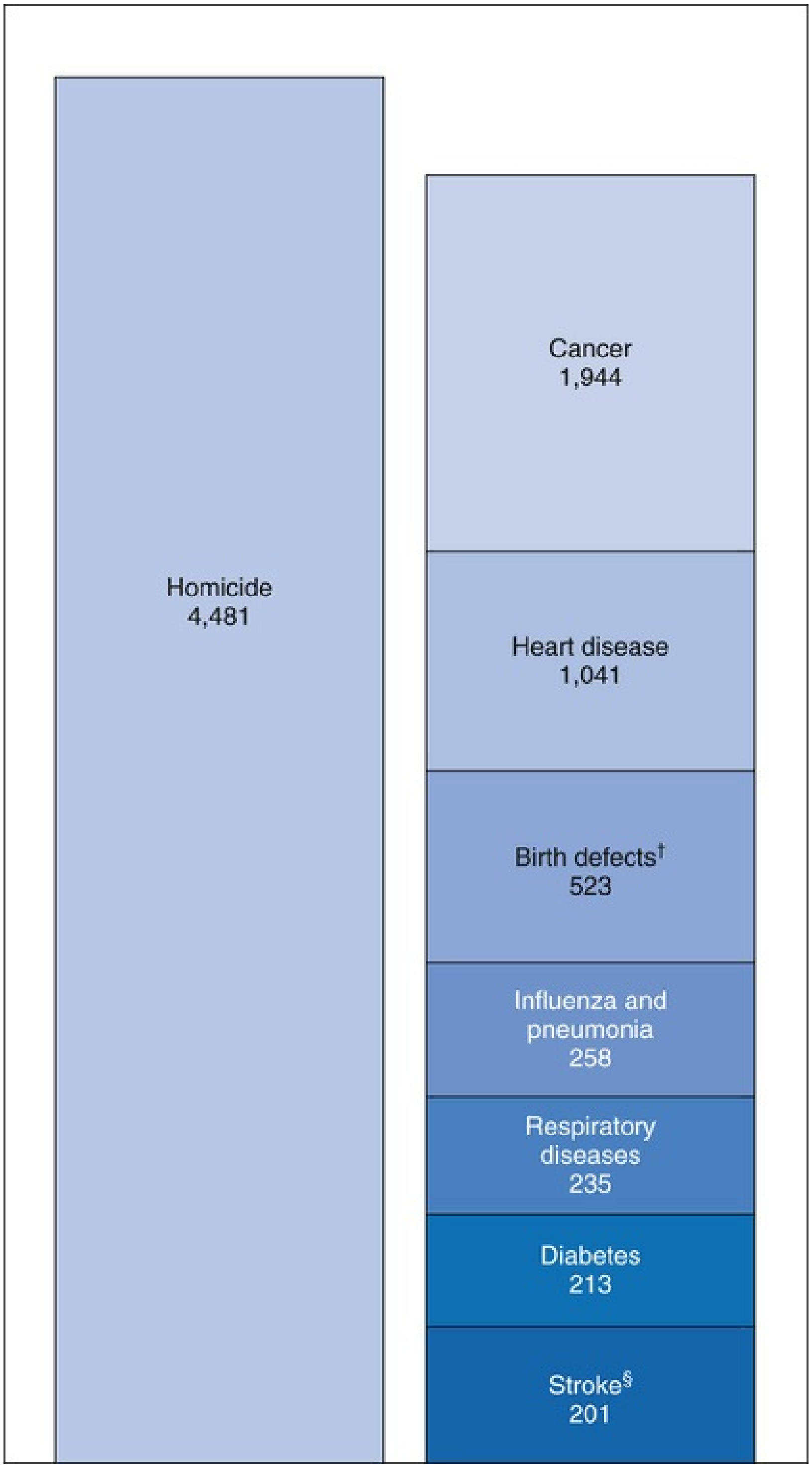

FIG. 13.2 Chart showing 3rd leading cause of death (homicide) among persons age 10-24 yr compared with 4th through 10th leading causes of death in the same age-group in the United States in 2013. *Does not include the 2 leading causes of death among persons age 10-24 yr in 2013: unintentional injuries (12,394 deaths) and suicide (5,264); † congenital anomalies; § cerebrovascular diseases. (From David-Ferdon C,

Simon TR, Spivak H, et al: CDC grand rounds: preventing youth violence, *MMWR* 64(7):172, 2015.)

Suicide is rare in children <10 yr old; only 1% of all suicides occur in children <15 yr. The suicide rate increases greatly after age 10 yr, with the result that suicide is now the 2nd leading cause of death for 15-19 yr olds. Native American teenagers are at the highest risk, followed by white males; black females have the lowest rate of suicide in this age-group. Approximately 40% of teenage suicides involve firearms (see Chapter 40).

There has been a sharp and substantial increase in unintentional **poisoning** deaths among teens and young adults. In 2016, unintentional poisonings were the 2nd leading cause of injury deaths among 15-24 yr olds. Many of these were from prescription analgesic and opioid medications such as fentanyl.

Nonfatal Injuries

Most childhood injuries do not result in death. Approximately 12% of children and adolescents receive medical care for an injury each year in hospital EDs, and at least as many are treated in physicians’ offices. Of these, 2% require inpatient care, and 55% have at least short-term temporary disability as a result of their injuries.

The distribution of nonfatal injuries is very different from that of fatal trauma (Fig. 13.3). **Falls** are the leading cause of both ED visits and hospitalizations. **Bicycle-related trauma** is the most common type of sports and recreational injury, accounting for approximately 300,000 ED visits annually. **Nonfatal injuries** , such as anoxic encephalopathy from near-drowning, scarring and disfigurement from burns, and persistent neurologic deficits from head injury, may be associated with severe morbidity, leading to substantial changes in the quality of life for victims and their families. In 2010, nonfatal injuries to U.S. children <19 yr old resulted in >$32 billion in direct medical and lifetime work loss costs.

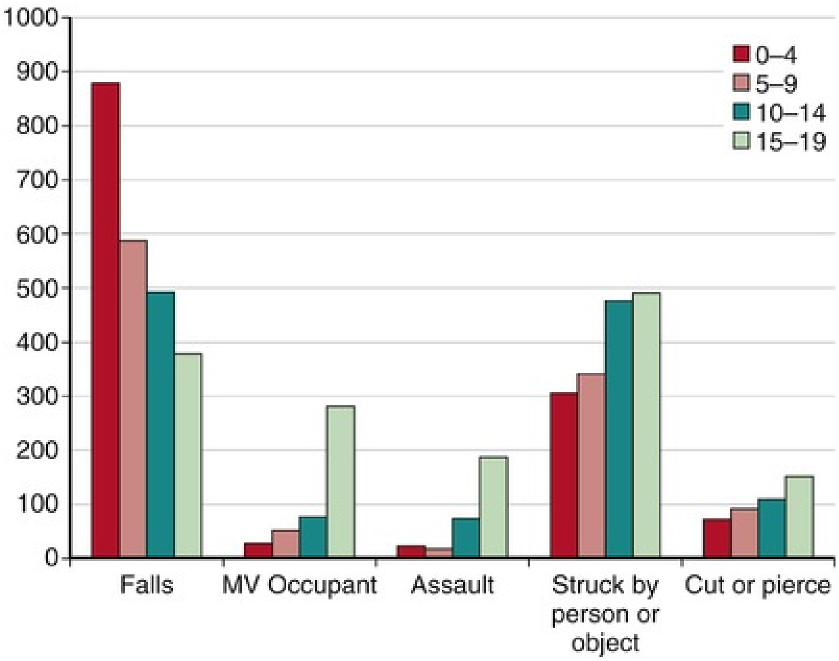

FIG. 13.3 **Emergency department visits for injuries, United States 2016. (Data from NEISS All Injury Program operated by the Consumer Product Safety Commission for numbers of injuries. U.S. Bureau of Census for population estimates.)**

Global Child Injuries

Child injuries are a global public health issue, and prevention efforts are necessary in low-, middle-, and high-income countries. Between 1990 and 2010 there was a 53% decrease in mortality of people of all ages from communicable, maternal, neonatal, and nutritional disorders, while injury mortality decreased by only 16% (Fig. 13.4).

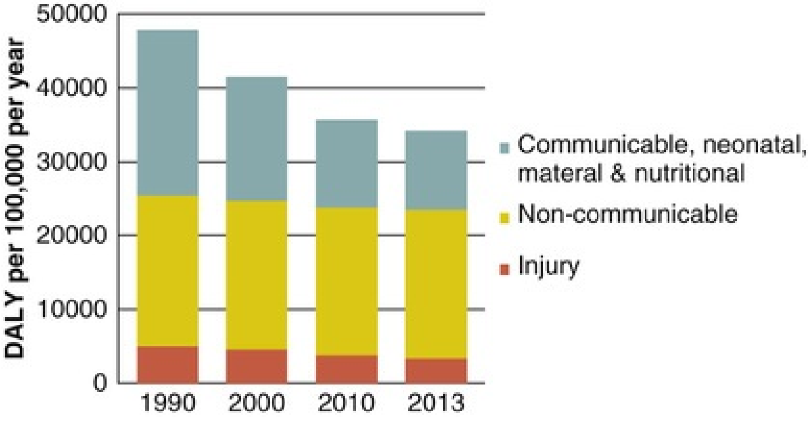

FIG. 13.4 Rates of disability-adjusted life-years (DALYs) loss per 100,000 per year by major grouping of cause. (Data from Institute for Health Metrics and Evaluation; GBD data visualization site. From Johnston BD: A safer world, *Injury Prev* 22(1):1–2, 2016.)

Worldwide, almost 1 million children and adolescents die from injuries and violence each year, and >90% of these deaths are in low- and middle-income countries. As child mortality undergoes an epidemiologic transition because of better control of infectious diseases and malnutrition, injuries have and will increasingly become the leading cause of death for children in the developing world, as it now is in all industrialized countries. Drowning is the 5th most common cause of death for 5-9 yr old children globally, and in some countries, such as Bangladesh, it is the leading cause of death among children beyond the 1st yr of life, with a rate 22 times greater than that in the Americas. An estimated 1 billion people do not currently have immediate access to roads; as industrialization and motorization spreads, the incidence of motor vehicle crashes, injuries, and fatalities will climb. The rate of child injury death in low- and middle-income countries is 3-fold higher than that in high-income countries and reflects both a higher incidence of many types of injuries and a much higher case fatality rate in those injured because of a lack of access to emergency and surgical care. As in high-income countries, prevention of child injuries and consequent morbidity and mortality is feasible with multifaceted approaches, many of which are low cost and of proven effectiveness.

Principles of Injury Control

Injury prevention once centered on attempts to pinpoint the innate characteristics of a child that result in greater frequency of injury. Most discount the theory of the “accident-prone child.” Although longitudinal studies have demonstrated an association between attention-deficit/hyperactivity disorder (ADHD) and increased rates of injury, the sensitivity and specificity of these traits as a test to identify individuals at high risk for injury are extremely low. The concept of *accident proneness* is counterproductive in that it shifts attention away from potentially more modifiable factors, such as product design or the environment. It is more appropriate to examine the physical and social environment of children with frequent rates of injury than to try to identify particular personality traits or temperaments, which are difficult to modify. Children at high risk for injury are likely to be relatively poorly supervised, to have disorganized or stressed families, and to live in hazardous environments.

Efforts to control injuries include education or persuasion, changes in product design, and modification of the social and physical environment. Efforts to persuade individuals, particularly parents, to change their behaviors have constituted the greater part of injury control efforts. Speaking with parents specifically about using child car-seat restraints and bicycle helmets, installing smoke detectors, and checking the tap water temperature is likely to be more successful than offering well-meaning but too-general advice about supervising the child closely, being careful, and childproofing the home. This information should be geared to the developmental stage of the child and presented in moderate doses in the form of anticipatory guidance at well-child visits. Table 13.2 lists important topics to discuss at each developmental stage. It is important to acknowledge that there are many barriers to prevention adherence beyond simple knowledge acquisition; pediatricians should be familiar with low-cost sources for safety equipment such as bicycle helmets, smoke detectors, trigger locks, and car seats in their community.

Table 13.2

Injury Prevention Topics for Anticipatory Guidance by the Pediatrician

Newborn

Car seats
Tap water temperature
Smoke detectors
Sleep safe environments

Infant

Car seats
Tap water temperature
Bath safety
Choking prevention

Toddler and Preschooler

Car seats and booster seats
Water safety
Poison prevention
Fall prevention

Primary School Child

Pedestrian skills training
Water skills training
Booster seats and seat belts
Bicycle helmets
Safe storage of firearms in the home

Middle School Child

Seatbelts
Safe storage of firearms in the home
Water skills training
Sports safety and concussion prevention

High School and Older Adolescent

Seatbelts
Alcohol and drug use, especially while driving and swimming
Mobile phone use while driving
Safe storage of firearms
Sports safety and concussion prevention
Occupational injuries

The most successful injury prevention strategies generally are those involving **changes in product design** . These passive interventions protect all individuals in the population, regardless of cooperation or level of skill, and are likely to be more successful than active measures that require repeated behavior change by the parent or child. The most important and effective product changes have been in motor vehicles, in which protection of the passenger compartment and use of airbags have had large effects on injury risk. Turning down the water heater temperature, installing smoke detectors, and using child-resistant caps on medicines and household products are other examples of effective product modifications. Many interventions require both active and passive measures. Smoke detectors provide passive protection when fully functional, but behavior change is required to ensure periodic battery changes and proper testing.

Modification of the environment often requires greater changes than individual product modification but may be very effective in reducing injuries. Safe roadway design, decreased traffic volume and speed limits in neighborhoods, and elimination or safe storage of guns in households are examples of such interventions. Included in this concept are changes in the social environment through legislation, such as laws mandating child seat restraint and seatbelt use, bicycle helmet use, and graduated driver's licensing laws.

Prevention campaigns combining 2 or more of these approaches have been particularly effective in reducing injuries. The classic example is the combination of legislation/regulation and education to increase child seat restraint and seatbelt use; other examples are programs to promote bike helmet use among school-aged children and improvements in occupant protection in motor vehicles.

Risk Factors for Childhood Injuries

Major factors associated with an increased risk of injuries to children include age, sex, race and ethnicity, socioeconomic status, rural-urban location, and the environment.

Age

Toddlers are at the greatest risk for burns, drowning, and falling. Poisonings become another risk as these children acquire mobility and exploratory behavior. Young school-age children are at greatest risk for pedestrian injuries, bicycle-related injuries (the most serious of which usually involve motor vehicles), motor vehicle occupant injuries, burns, and drowning. During the teenage years, there is a greatly increased risk from motor vehicle occupant trauma, a continued risk from drowning and burns, and the new risk of intentional trauma. Sports- and recreation-related injuries, including concussion, become more common, and more serious, as children age. Work-related injuries associated with child labor, especially for 14-16 yr olds, are an additional risk.

Injuries occurring at a particular age represent a period of vulnerability during which a child or an adolescent encounters a new task or hazard that they may not have the developmental skills to handle successfully. Toddlers do not have the judgment to know that medications can be poisonous or that some houseplants are not to be eaten; they do not understand the hazard presented by a swimming pool or an open second-story window. For young children, parents may inadvertently set up this mismatch between the skills of the child and the demands of the task. Many parents expect young school-age children to walk home from school, the playground, or the local convenience store, tasks for which most children are not developmentally ready. Likewise, the lack of skills and experience to handle many tasks during the teenage years contributes to an increased risk of injuries, particularly motor vehicle injuries. The high rate of motor vehicle crashes among 15-17 yr olds is caused in part by inexperience but also appears to reflect their level of cognitive development and emotional maturity. Alcohol, other drugs, and mobile phone use substantially add to these limitations.

Age also influences the severity of injury and the risk of long-term disability. Young school-age children have an incompletely developed pelvis. In a motor vehicle crash the seatbelt does not anchor onto the pelvis, but rides up onto the abdomen, resulting in the risk of serious abdominal injury. Proper restraint for 4-8 yr old children requires the use of booster seats. Children <2 yr old have much poorer outcomes from traumatic brain injuries than older children and adolescents, partly related to the severity of abusive head trauma.

Gender

Beginning at 1-2 yr of age and continuing throughout the life span, males have higher rates of fatal injury than females. During childhood, this does *not* appear to be primarily a result of developmental differences between the sexes, differences in coordination, or differences in muscle strength. Variation in *exposure* to risk may account for the male predominance in some types of injuries. Although males in all age-groups have higher rates of bicycle-related injuries, adjusting for exposure reduces this excess rate. Sex differences in rates of pedestrian injuries do *not* appear to be caused by differences in the amount of walking, but rather reflect differences in *behavior* between young females and males; whether these are genetic or the result of gender socialization is uncertain. Greater risk-taking behavior, combined with greater frequency of alcohol use, may lead to the disproportionately high rate of motor vehicle crashes among teenage males. The rate of violence-related injuries is higher among males because of their risk-taking behavior.

Race and Ethnicity

In the United States, Native Americans have the highest death rate from unintentional injuries, reflecting both the increased incidence and the poorer access to trauma care because of their rural location. African American children and adolescents have higher rates of fatal injuries than whites, whereas Asians have lower rates; rates for Hispanic children and adolescents are intermediate between those for blacks and those for whites. These discrepancies are even more pronounced for some injuries. The homicide rate for African Americans age 15-19 yr was 32.74 per 100,000 population in 2016, compared with 5.59/100,000 for American Indians and Alaskan Natives and 3.91/100,000 for whites and 2.18/100,000 for Asians. The suicide rate for Native American youth was 1.5 times the rate for whites and 2.7 times rates for blacks. The rate of firearm homicide deaths for African American youth ages 15-19 is 10-fold higher than that for whites and 17 times that of Asian American youth.

These disparities appear to be primarily related to poverty, the educational status of parents, and the presence of hazardous environments. Homicide rates among blacks are nearly equivalent to those among whites, when adjusted for socioeconomic status. *It is important to acknowledge racial disparities in injury rates and the importance of racism at all levels in society, but inappropriate to ascribe the etiology of these differences solely to the effect of race or ethnicity.*

Socioeconomic Status

Poverty is one of the most important risk factors for childhood injury. Mortality from fires, motor vehicle crashes, and drowning is 2-4 times higher in poor children. Death rates among both blacks and whites have an inverse relationship to income level: the higher the income level, the lower the death rate. Native Americans have especially high mortality rates. Other factors are single-parent families, teenage mothers, multiple care providers, family stress, and multiple siblings; these are primarily a function of poverty rather than independent risk factors.

Rural-Urban Location

Injury rates are generally higher in rural than in urban areas. Homicide rates are higher in urban areas, as is violent crime in general. However, suicide among adolescents is higher in rural than urban areas. Case fatality from injury is generally twice as high in rural areas than in urban areas, reflecting both the increased severity of some injuries (e.g., motor vehicle crashes occurring at higher speeds) and poorer access to EMS and definitive trauma care in rural areas. Some injuries are unique to rural areas, such as agricultural injuries to children and adolescents.

Environment

Poverty increases the risk of injury to children, at least in part through its effect on the environment. Children who are poor are at increased risk for injury because they are exposed to more hazards in their living environments. They may live in poor housing, which is more likely to be dilapidated and less likely to be protected by smoke detectors. The roads in their neighborhoods are more likely to be major thoroughfares. Their neighborhoods are more likely to experience higher levels of violence, and they are more likely to be victims of assault than children and adolescents living in the suburbs. The focus on the environment is also important because it directs attention away from relatively immutable factors, such as family dynamics, poverty, and race, and directs efforts toward factors that can be changed through interventions.

Mechanisms of Injury

Motor Vehicle Injuries

Motor vehicle injuries are the leading cause of serious and fatal injuries for children and adolescents. Large and sustained reductions in motor vehicle crash injuries can be accomplished by identifiable interventions.

Occupants

Injuries to passenger vehicle occupants are the predominant cause of motor vehicle deaths among children and adolescents. The peak injury and death rate for both males and females in the pediatric age-group occurs between 15 and 19 yr (see Table 13.1). Proper restraint use in vehicles is the single most effective method for preventing serious or fatal injury. Table 13.3 shows the recommended restraints at different ages. Fig. 13.5 provides examples of car safety seats.

Table 13.3

Recommended Child-Restraint Methods

	INFANTS	TODDLERS (1-3)	YOUNG CHILDREN
Recommended age/weight requirements	Birth to 1 yr or below weight limit of seat.	Older than 1 yr and weight 20-40 lb.	Weight 40-80 lb and height under 4 ft 9 in; generally between 4 and 8 yr of age.
Type of seat	Infant-only or rear-facing convertible.	Convertible or forward-facing harness seat.	Belt-positioning booster seat.
Seat position	Rear-facing only. Place in back seat of vehicle.	Can be rear-facing until 30 lb if seat allows; generally forward-facing. Place in back seat of vehicle.	Forward-facing. Place in back seat of vehicle.
Notes	Children should use rear-facing seat until at least 1 yr and at least 20 lb.	Harness straps should be at or above shoulder level.	Belt-positioning booster seats must be used with both lap and shoulder belts.
	Harness straps should be at or below shoulder level.	Most seats require top strap for forward-facing use.	Make sure that lap belt fits low and tightly across lap/upper thigh area, and that shoulder belt fits snugly, crossing chest and shoulder to avoid abdominal injuries.

Data from http://www.safercar.gov/parents/CarSeats.htm .

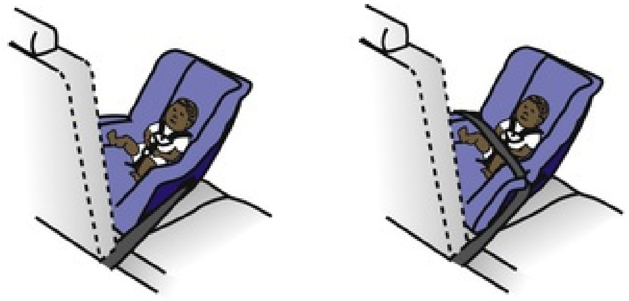

Rear-facing infant seat

A

Alternate seat belt position for the rear-facing infant seat depending on make and year of car and model of car seat

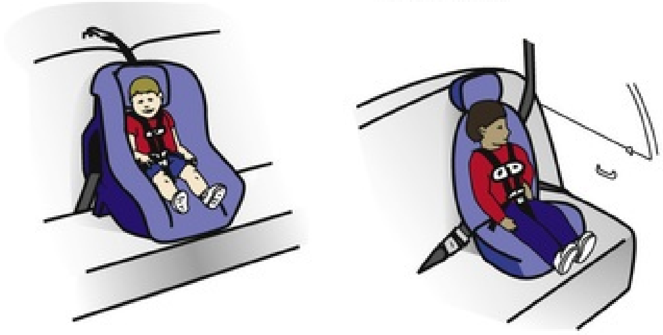

Forward-facing child harness seat

B

Forward-facing convertible harness seat

C

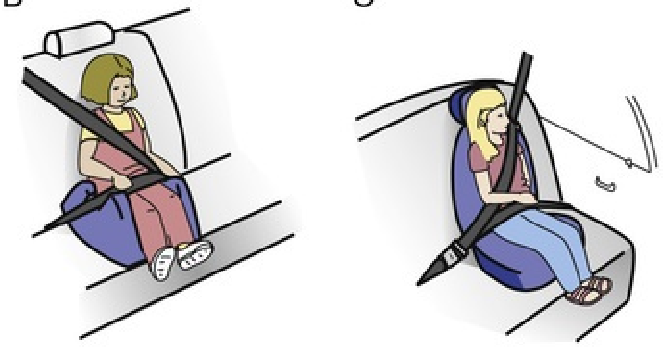

Low-back booster seat

D

High-back booster seat

E

FIG. 13.5 Car safety seats. A, Rear-facing infant seat. B, Forward-facing child harness seat. C, Forward-facing convertible harness seat. D, Low-back booster seat. E, High-back booster seat. (From Ebel BE, Grossman DC: Crash proof kids? An overview of current motor vehicle child occupant safety strategies, *Curr Probl Pediatr Adolesc Health Care* 33:33–64, 2003. Source: NHTSA.)

Much attention has been given to child occupants <8 yr old. Use of child-restraint devices, infant car seats, and booster seats can be expected to reduce fatalities by 71% and the risk of serious injuries by 67% in this age-group. All 50 states and the District of Columbia have laws mandating their use, although the upper age limit for booster seat requirements varies by state. Physician reinforcement of the positive benefits of child seat restraints has been successful in improving parent acceptance. Pediatricians should point out to parents that toddlers who normally ride restrained behave better during car trips than children who ride unrestrained.

A detailed guide and list of acceptable devices is available from the American Academy of Pediatrics (AAP)* and the National Highway Traffic Safety Administration (NHTSA). † Children weighing <20 lb may use an infant seat or may be placed in a convertible infant-toddler child-restraint device. Infants and toddlers <4 yr should be placed in the rear seat facing backward; older toddlers and young children can be placed in the rear seat in a forward-facing child harness seat until it is outgrown. Emphasis must be placed on the correct use of these seats, including placing the seat in the right direction, routing the belt properly, and ensuring that the child is buckled into the seat correctly. Government regulations specific to automobile and product design have made the fit between car seats and the car easier, quicker, and less prone to error. *Children <13 yr old should never sit in the front seat. Inflating airbags can be lethal to infants in rear-facing seats and to small children in the front passenger seat.*

Older children are often not adequately restrained. Many children ride in the rear seat restrained with lap belts only. **Booster seats** have been shown to decrease the risk of injury by 59% and should be used by children who weigh between 40 lb (about 4 yr of age) and 80 lb, are <8 yr of age, and are <4 ft 9 in (145 cm) tall. Many states have extended their car seat laws to include children of booster seat age as well. Shoulder straps placed behind the child or under the arm do not provide adequate crash protection and may increase the risk of serious injury. The use of lap belts alone has been associated with an increased risk of seatbelt-related injuries, especially fractures of the lumbar spine and hollow-viscus injuries of the abdomen. These flexion-distraction injuries of the spine are often accompanied by injuries to the abdominal organs.

The rear seat is clearly much safer than the front seat for both children and adults. One study of children <15 yr old found that the risk of injury in a crash was 70% lower for children in the rear seat compared with those sitting in the front seat. Frontal **airbags** present a risk of serious or fatal injury from the airbag itself for children <13 yr. Side airbags also pose a risk for children who are in the front seat and are leaning against the door at the time of a crash. The safest place for children is in the rear middle seat, properly restrained for their age and size. Educational and legislative interventions to increase the number of children traveling in the rear seat have been successful.

Transportation of **premature infants** presents special problems. The possibility of oxygen desaturation, sometimes associated with bradycardia, among premature infants while in child seat restraints has led the AAP to recommend an observed trial of infants born at <37 wk of gestational age in the seat before discharge and the use of oxygen or alternative restraints for infants who experience desaturation or bradycardia, such as seats that can be reclined and used as a car bed.

Children riding in the rear bed of pickup trucks are at special risk for injury because of the possibility of ejection from the truck and resultant serious injury.

Teenage Drivers

Drivers 15-17 yr old have more than twice the rate of collisions compared with motorists 18 yr and older. Formal driver education courses for young drivers appear to be ineffective as a primary means of decreasing the number of collisions, and in fact may increase risk by allowing younger teens to drive. The risk of serious injury and mortality is directly related to the speed at the time of the crash and inversely related to the size of the vehicle. Small, fast cars greatly increase the risk of a fatal outcome in the event of a crash.

The number of passengers traveling with teen drivers influences the risk of a crash. The risk of death for 17 yr old drivers is 50% greater when driving with 1 passenger compared with driving alone; this risk is 2.6-fold higher with 2 passengers and 3-fold higher with 3 or more passengers.

Teens driving at night are overrepresented in crashes and fatal crashes, with nighttime crashes accounting for >33% of teen motor vehicle fatalities. Almost 50% of fatal crashes involving drivers <18 yr old occur in the 4 hours before or after midnight. Teens are 5-10 times more likely to be in a fatal crash while driving at night compared with driving during the day. The difficulty of driving at night combined with the inexperience of teen drivers appears to be a deadly combination.

Another risk factor for motor vehicle crashes for people of all ages, including teens, is **distracted driving** . Distracting events can include *visual* distraction (taking eyes from the forward roadway), *manual* distraction (removing hands from vehicle controls), or *cognitive* distraction (taking attention from navigating the vehicle or responding to critical events). **Electronic devices** present all 3 modes of distraction in combination and are increasingly recognized as a major threat to driver safety, especially among teens. The uptick in motor vehicle fatality rates per vehicle mile driven is generally believed to be caused by distracted driving.

In 2017, 39.2% of teen drivers reported they had texted or emailed while driving in the last 30 days. Dialing on a cell phone increases the risk of a crash almost 3-fold, and texting may increase the risk as much as 6-fold. Although most states have banned text messaging for all drivers, the effect of state laws on prohibiting such behavior while driving is unknown. Parents should set limits on the use of these devices by their teens; technologic interventions that can block cell phone signals in a moving vehicle are also be available and should be considered by parents for their teens.

Graduated driver's licensing (GDL) programs consist of a series of steps over a designated period before a teen can receive full, unrestricted driving privileges. In a 3-stage graduated license, the student driver must first pass vision and knowledge-based tests, followed by obtaining a learner's permit, and once a specific age has been achieved and driving skills advanced, the student driver is eligible to take the driving test. Once given a provisional license, the new driver will have a specified time to do low-risk driving. GDL usually places initial restrictions on the number of passengers (especially teenage) allowed in the vehicle and limits driving at night. The number of crashes decreased 10–30% among the youngest drivers in states with a GDL system. The characteristics of GDL programs vary substantially across states. Optimal safety benefits depend on parent monitoring and engagement with teens around driving restrictions and responsibilities. Parent-teen driving contracts are available and help to facilitate these discussions.

Alcohol use is a major cause of motor vehicle trauma among adolescents. The combination of inexperience in driving and inexperience with alcohol is particularly dangerous. Approximately 20% of all deaths from motor vehicle crashes in this age-group are the result of alcohol intoxication, with impairment of driving seen at blood alcohol concentrations (BACs) as low as 0.05 g/dL. In 2017, approximately 16.5% of adolescents reported riding with a driver who had been drinking, and 5.5% reported driving after drinking. All states have adopted a *zero tolerance policy* to adolescent drinking while driving, which defines any measurable alcohol content as legal intoxication. All adolescent motor vehicle injury victims should have their BAC measured in the ED and should be screened for high-risk alcohol use with a validated screening test (e.g., CRAFFT, Alcohol Use Disorders Identification Test [AUDIT]) to identify those with alcohol abuse problems (see Chapter 140.1). Individuals who have evidence of alcohol abuse should not leave the ED or hospital without plans for appropriate alcohol abuse treatment. Interventions for problem drinking can be effective in decreasing the risk of subsequent motor vehicle crashes. Even brief interventions in the ED using motivational interviewing can be successful in decreasing adolescent problem drinking.

Another cause of impaired driving is **marijuana use.** In 2017, nearly 20% of high school students reported using marijuana in the prior 30 days. Marijuana is currently legal (2018) for adult use in 9 U.S. states and for medical use in 30 states, while being considered in many others; the effects of this on adolescent injury remains to be determined. Marijuana is often co-ingested with alcohol or other drugs, and blood thresholds for biologic impairment have not been standardized. It is therefore difficult to estimate the independent effect of marijuana on crash risk.

All-Terrain Vehicles

All-terrain vehicles (ATVs) in many parts of the United States are an important cause of injuries to children and adolescents. These vehicles can attain high speeds, especially with low-weight children, and are prone to rollover because of their high center of gravity. Orthopedic and head injuries are the most common serious injuries seen among children involved in ATV crashes. Helmets can significantly decrease the risk and severity of head injuries among ATV riders, but current use is very low. Voluntary industry efforts to decrease the risk of injuries appear to have had little effect in making ATVs safer. The AAP recommends that children <16 yr old should not ride on ATVs.

Bicycle Injuries

Each year in the United States, approximately 161,000 children and adolescents are treated in EDs for bicycle-related injuries, making this one of the most common reasons that children with trauma visit EDs. The majority of severe and fatal bicycle injuries involve **head trauma** . A logical step in the prevention of these head injuries is the use of helmets. **Helmets** are very effective, reducing the risk of all head injury by 85% and the risk of traumatic brain injury by 88%. Helmets also reduce injuries to the mid and upper face by as much as 65%. Pediatricians can be effective advocates for the use of bicycle helmets and should incorporate this advice into their anticipatory guidance schedules for parents and children. Appropriate helmets are those with a firm polystyrene liner that fit properly on the child's head. Parents should avoid buying a larger helmet to give the child “growing room.”

Promotion of helmet use can and should be extended beyond the pediatrician's office. Community education programs spearheaded by coalitions of physicians, educators, bicycle clubs, and community service organizations have been successful in promoting the use of bicycle helmets to children across the socioeconomic spectrum, resulting in helmet use rates of ≥70% with a concomitant reduction in the number of head injuries. Passage of bicycle helmet laws also leads to increased helmet use.

Consideration should also be given to other types of preventive activities, although the evidence supporting their effectiveness is limited. Bicycle paths are a logical method for separating bicycles and motor vehicles.

Pedestrian Injuries

Pedestrian injuries are a major cause of traumatic death for children and adolescents in the United States and in most high-income countries. In low-income countries, a much higher proportion of road traffic fatalities are pedestrians, especially among 5-14 yr olds. Although case fatality rates are <5%, serious nonfatal injuries constitute a much larger problem, resulting in 34,498 ED visits annually for children and adolescents. Pedestrian injuries are the most important cause of traumatic coma in children and a frequent cause of serious lower-extremity fractures, particularly in school-age children.

Most injuries occur during the day, with a peak in the after-school period. Improved lighting or reflective clothing would be expected to prevent few injuries. Surprisingly, approximately 30% of pedestrian injuries occur while the individual is in a marked crosswalk, perhaps reflecting a false sense of security and decreased vigilance in these areas. The risk of pedestrian injury is greater in neighborhoods with high traffic volumes, speeds >25 miles/hr, absence of play space adjacent to the home, household crowding, and low socioeconomic status.

One important risk factor for childhood pedestrian injuries is the developmental level of the child. Children <5 yr old are at risk for being run over in the driveway. Few children <9 or 10 yr of age have the developmental skills to successfully negotiate traffic 100% of the time. Young children have poor ability to judge the distance and speed of traffic and are easily distracted by playmates or other factors in the environment. Many parents are not aware of this potential mismatch between the abilities of the young school-age child and the skills needed to cross streets safely. The use of mobile phones and devices has become increasingly common while walking and can increase the risk of being struck by a motor vehicle.

Prevention of pedestrian injuries is difficult but should consist of a multifaceted approach. Education of the child in pedestrian safety should be initiated at an early age by the parents and continue into the school-age years. Younger children should be taught never to cross streets when alone; older children should be taught (and practice how) to negotiate quiet streets with little traffic. Major streets should not be crossed alone until the child is at least 10 yr of age and has been observed to follow safe practices.

Legislation and police enforcement are important components of any campaign to reduce pedestrian injuries. Right-turn-on-red laws increase the hazard to pedestrians. In many cities, few drivers stop for pedestrians in crosswalks, a special hazard for young children. Engineering changes in roadway design are extremely important as passive prevention measures. Most important are measures to slow the speed of traffic and to route traffic away from schools and residential areas; these efforts are endorsed by parents and can decrease the risk of injuries and death by 10–35%. Other modifications include networks of 1-way streets, proper placement of transit or school bus stops, sidewalks in urban and suburban areas, stripping in rural areas to delineate the edge of the road, and curb parking regulations. Comprehensive traffic “calming” schemes using these strategies have been very successful in reducing child pedestrian injuries in Sweden, The Netherlands, Germany, and increasingly, the United States.

Ski- and Snowboard-Related Head Injuries

The increasing use of helmets in snow sports, such as skiing and snowboarding, is encouraging since head injuries are the most common cause of death in these sports, and helmets reduce the risk of head injury by ≥50%. Use of helmets does not result in skiers or snow boarders taking more risks and should be encouraged in all snow sports at all ages, not just for young children.

Fire- and Burn-Related Injuries

See Chapter 92 .

Poisoning

See Chapter 77 .

Drowning

See Chapter 91 .

Traumatic Brain Injury

See Chapter 85 .

Firearm Injuries

Injuries to children and adolescents involving firearms occur in 3 different situations: unintentional injury, suicide attempt, and assault. The injury may be fatal or may result in permanent sequelae. **Unintentional firearm injuries** and deaths have continued to decrease and accounted for 127 deaths in 2016, representing only a very small fraction of all firearm injuries among children and adolescents. The majority of these deaths occur to teens during hunting or recreational activities. **Suicide** is the 2nd most common cause of death from all causes in both males and females age 10-19 yr. During the 1950s to 1970, suicide rates for children and adolescents more than doubled; firearm suicide rates peaked in 1994 and decreased by 59% from this peak by 2010 before gradually increasing, paralleling increases in the overall suicide rate. The difference in the rate of suicide death between males and females is related to the differences in method used during attempts. Girls die less often in suicide attempts because they use less lethal means (mainly drugs) and perhaps have a lower degree of intent. The use of firearms in a suicidal act confers an approximately 90% case fatality rate.

Homicides are 3rd only to motor vehicle crashes and suicide among causes of death in teenagers >15 yr old. In 2016, 1816 adolescents age 15-19 yr were homicide victims; African American teenagers accounted for 63% of the total, making homicides the most common cause of death among black teenagers. Over 85% of homicides among teenage males involved firearms, mostly handguns.

In the United States, approximately 36% of households owned guns in 2016. Handguns account for approximately 30% of the firearms in use today, yet they are involved in 80% of criminal and other firearm misuse. Home ownership of guns increases the risk of adolescent suicide 3- to 10-fold and the risk of adolescent homicide up to 4-fold. In homes with guns, the risk to the occupants is far greater than the chance that the gun will be used against an intruder; for every death occurring in self-defense, there may be 1.3 unintentional deaths, 4.6 homicides, and 37 suicides.

Of all firearms, **handguns** pose the greatest risk to children and adolescents. Access to handguns by adolescents is surprisingly common and is not restricted to those involved in gang or criminal activity. Stricter approaches to reduce youth access to handguns, rather than all firearms, would appear to be the most appropriate focus of efforts to reduce shooting injuries in children and adolescents.

Locking and unloading guns as well as storing ammunition locked in a different location substantially reduces the risk of a suicide or unintentional firearm injury among youth by up to 73%. Because up to 30% of handgun-owning households have at least 1 firearm stored unsafely, one potential approach to reducing these injuries could focus on improving household firearm storage practices where children and youth reside or visit. The evidence regarding the effectiveness of office-based counseling to influence firearm storage practice is mixed; the most effective programs are those in which devices are dispensed along with advice.

Adolescents with mental health conditions and alcoholism are at particularly high risk for firearm injury. In the absence of conclusive evidence, physicians should continue to work with families to eliminate access to guns in these households.

Falls

Falls are the leading cause of **nonfatal injury** in children and adolescents. Altogether, there were 2.3 million falls that led to ED visits in 2016 for children and adolescents; approximately 2.9% of these visits led to a hospitalization or transfer. There have been relatively few in-depth analytic studies of falls, except in particular circumstances, such as playground injuries. Strategies to prevent falls depend on the environmental circumstances and social context in which they occur. *Window falls* have been successfully prevented with the use of devices that prevent egress, and injuries from *playground falls* can be mitigated through the use of proper surfacing, such as woodchips or other soft, energy-absorbing materials. Alcohol may also contribute to falls among teenagers, and these injuries can be reduced by general strategies to reduce teen alcohol use.

Violent Behavior and Aggression

Although the current rates of homicide are much lower than at their peak in the late 1980s and early 1990s, the problem of violence and assault remains large. The origins of adult and teen violence occur during childhood. Almost all adults who commit violent acts have a history of violent behavior during childhood or adolescence. Longitudinal studies following groups of individuals from birth have found that aggression occurs early and that most children learn to control this aggression in childhood. Children who later become violent adolescents and adults do not learn to control this aggressive behavior.

The most successful interventions for violence target young children and their families. These include home visits by nurses and paraprofessionals beginning in the prenatal period and continuing for the 1st few yr of life to provide support and guidance to parents, especially parents without other resources. Enrollment in early childhood education programs (e.g., Head Start) beginning at age 3 yr has been shown to be effective in improving school success, keeping children in school, and decreasing the chance that the child will be a delinquent adolescent. School-based interventions, including curricula to increase the social skills of children and improve the parenting skills of caregivers, have long-term effects on violence and risk-taking behavior. Early identification of behavior problems by primary care pediatricians can best be accomplished through the routine use of formal screening tools. Interventions in adolescence, such as family therapy, multisystemic therapy, and therapeutic foster care, can decrease problem behavior and a subsequent decline into delinquency and violence.

Psychosocial Consequences of Injuries

Many children and their parents have substantial psychosocial sequelae from trauma. Studies in adults indicate that 10–40% of hospitalized injured patients will have **posttraumatic stress disorder** (PTSD; see Chapter 38). Among injured children involved in motor vehicle crashes, 90% of families will have symptoms of acute stress disorder after the crash, although the diagnosis of acute stress disorder is poorly predictive of later PTSD. Standardized questionnaires that collect data from the child, the parents, and the medical record at the time of initial injury can serve as useful screening tests for later development of PTSD.

Early mental health intervention, with close follow-up, is important for the treatment of PTSD and for minimizing its effect on the child and family.

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CHAPTER 14

Impact of Violence on Children

Marilyn C. Augustyn, Barry S. Zuckerman

The reach of violence, whether as the victim, perpetrator, or witness, whether in person or through the media, is far, deep, and long-standing across the globe. In the home, it is estimated that 80–95% of such aggression is witnessed by a child. *Exposure to violence* disrupts the healthy development of children in a myriad of ways. Pediatric clinicians must be competent to address these issues in impacted children and families under their care (**trauma-informed care**). Clinicians also have a wider responsibility to advocate on local, state, national, and international levels for safer environments in which all children can grow and thrive.

Witnessing violence is detrimental to children. Because their scars as bystanders are emotional and not physical, the pediatric clinician may not fully appreciate their distress and thereby miss an opportunity to provide needed interventions. For children not living in war zones, the source of first exposure to violence is often **intimate partner violence (IPV).** In the United States alone, >1 in 15 children witness IPV each year, and worldwide approximately 275 million children are exposed to IPV yearly. Exposure to IPV in infancy and toddlerhood impacts attachment relationships, and school-age children who witness IPV have difficulties in developing and maintaining friendships, as well as an increased likelihood of developing maladaptive peer relations.

Another source of witnessed violence is **community violence** , a serious problem in the United States that disproportionately affects children from low-income areas. Approximately 22% of children witness violence in their family or in their community each year; *witnessed violence* includes assaults and bullying, sexual victimization, maltreatment by a caregiver, and theft or vandalism. Almost 60% of children will experience or witness violence during childhood. Witnessing acts of violence may be a significant stressor in children's lives. Witnessed community violence is related to internalizing problems such as depression and posttraumatic stress disorder (PTSD) as well as externalizing problems, including delinquent behavior, aggression, and substance abuse.

The most ubiquitous source of witnessing violence for U.S. children is **media violence** , sometimes referred to as **virtual violence** . This form of violence is not experienced physically; rather it is experienced in realistic ways through technology and ever more intense and realistic games. There is an ever-widening array of screens that are part of children's everyday lives, including computers, tablets, and cell phones, in addition to long-standing platforms, such as televisions and movies. Recent tragic events, including mass shootings and acts of terrorism, have increased the specter of fear among children as these events are reenacted for them on the multiple screens they encounter. Although exposure to media/virtual violence cannot be equated to exposure to real-life violence, many studies confirm that media/virtual violence *desensitizes* children to the meaning and impact of violent behavior. Violent video game exposure is associated with: an increased composite aggression score; increased aggressive behavior; increased aggressive cognitions; increased aggressive affect, increased desensitization, and decreased empathy; and increased physiological arousal. Violent video game use is a risk factor for adverse outcomes; however, insufficient data exist to examine any potential link between violent video game use and delinquency or criminal behavior. Table 14.1 lists interventions to reduce exposure to media violence.

Table 14.1

Public Health Recommendations to Reduce Effects of Media Violence on Children and Adolescents

Parents should:

- Be made aware of the risks associated with children viewing violent imagery, as it promotes aggressive attitudes, antisocial behavior, fear, and desensitization.
- Review the nature, extent, and context of violence in media available to their children before children view.
- Assist children's understanding of violent imagery appropriate to their developmental level.

Professionals should:

- Offer support and advice to parents who allow their children unsupervised access to extreme violent imagery, as this could be seen as a form of emotional abuse and neglect.
- Educate all young people in critical film appraisal, in terms of realism, justification, and consequences.
- Exercise greater control over access to inappropriate violent media entertainment by young people in secure institutions.
- Use violent film material in anger management programs under guidance.

Media producers should:

- Reduce violent content, and promote antiviolence themes and publicity campaigns.
- Ensure that when violence is presented, it is in context and associated with remorse, criticism, and penalty.
- Ensure that violent action is not justified, or its consequences understated.

Policymakers should:

- Monitor the nature, extent, and context of violence in all forms of media, and implement appropriate guidelines, standards, and penalties.
- Ensure that education in media awareness is a priority and a part of school curricula.

From Browne KD, Hamilton-Giachritsis C: The influence of violent media on children and adolescents: a public-health approach, *Lancet* 365:702–710, 2005.

Impacts of Violence

All types of violence have a profound impact on health and development both psychologically and behaviorally; it may influence how children view the world and their place in it. Children can come to see the world as a dangerous and unpredictable place. This fear may thwart their exploration of the environment, which is essential to learning in childhood. Children may experience overwhelming terror, helplessness, and fear, even if they are not immediately in danger. Preschoolers are most vulnerable to threats that involve the safety (or perceived safety) of their caretakers. High exposure to violence in older children correlates with poorer performances in school, symptoms of anxiety and depression, and lower self-esteem. Violence, particularly IPV, can also teach children especially powerful early lessons about the role of violence in relationships. Violence may change the way that children view their future; they may believe that they could die at an early age and thus take more risks, such as drinking alcohol, abusing drugs, not wearing a seatbelt, and not taking prescribed medication.

Some children exposed to severe and/or chronic violence may suffer from PTSD, exhibiting constricted emotions, difficulty concentrating, autonomic disturbances, and reenactment of the trauma through play or action (see Chapter 38). Based on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for PTSD in children ≤6 yr old, >50% of preschoolers may experience clinically significant symptoms of PTSD after exposure to IPV. Although young children may not fully meet these criteria, certain behavioral changes are associated with exposure to trauma, such as sleep disturbances, aggressive behavior, new fears, and increased anxiety about separations (clinginess). A challenge in treating and diagnosing pediatric PTSD is that a child's caregiver exposed to the same trauma may be suffering from it as well.

Diagnosis and Follow-Up

The simplest way to recognize whether violence has become a problem in a family is to screen both the parents and the children (after approximately 8 yr of age) on a regular basis. This practice is particularly important during pregnancy and the immediate postpartum period, when women may be at highest risk for being abused. It is important to assure families that they are not being singled out, but that all families are asked about their exposure to violence. A direct approach may be useful: “Violence is a major problem in our world today and one that impacts everyone in our society. So I ask all my patients and families about violence that they are experiencing in their lives. …” In other cases, beginning with general questions and then moving to the specific may be helpful: “Do you feel safe in your home and neighborhood? Has anyone ever hurt you or your child?” When violence has impacted the child, it is important to gather details about symptoms and behaviors.

The pediatric clinician can effectively counsel many parents and children who have been exposed to violence. Regardless of the type of violence to which the child has been exposed, the following components are part of the guidance: (1)

careful review of the facts and details of the event, (2) gaining access to support services, (3) providing information about the symptoms and behaviors common in children exposed to violence, (4) assistance in restoring a sense of stability to the family in order to enhance the child's feelings of safety, and (5) helping parents talk to their children about the event. When the symptoms are chronic (>6 mo) or not improving, if the violent event involved the death or departure of a parent, if the caregivers are unable to empathize with the child, or if the ongoing safety of the child is a concern, it is important that the family be referred to mental health professionals for additional treatment.

14.1

Bullying, Cyberbullying, and School Violence

Megan A. Moreno, Elizabeth Englander

Keywords

aggression
bullying
cyberbullying
online harassment
peer victimization
perpetrator
school climate
target

Bullying and Cyberbullying

Bullying behavior affects people throughout the life span, but much of the focus has been on children and adolescents. In the past, bullying was sometimes considered a rite of passage, or was written off as “kids being kids.” It is now recognized that bullying can have profound short- and long-term negative consequences on all those involved, including perpetrators, targets, and bystanders. The consequences of bullying can affect a child's social experiences, academic progress, and health.

Bullying is defined as any unwanted aggressive behavior by another youth or group of youths that involves an observed or perceived power imbalance and is repeated multiple times or is highly likely to be repeated. Generally, sibling aggression and dating violence are excluded, but research has associated these problems with *peer bullying* . Digital technology was initially viewed as a context in which bullying can occur. Further research studies have suggested that **cyberbullying** is not merely bullying that occurs through electronic communications, but rather a type of bullying with distinct elements, such as the potential for a single event to “go viral” and the use of technology as a tool to achieve power imbalance.

It is thought that bullying and cyberbullying are more alike than dissimilar, and that surveillance efforts, as well as prevention and intervention approaches, should address both types of bullying.

Bullying Roles and Nomenclature

Bullying represents a dynamic social interaction in which an individual may play different roles at different stages. A child can be a perpetrator of bullying, a target of bullying, a witness or bystander, or simply a child whose environment is affected by pervasive bullying. In any bullying experience, the roles that each child plays may be fluid; such that a target of bullying may then become a perpetrator, or vice versa. Thus, common nomenclature has evolved to refer to children as *perpetrators* of bullying or *targets* of bullying to represent a present state, rather than labeling a child as a bully or a victim, which suggests a static role and may impact that child's self-image.

Epidemiology

Bullying is a widespread problem during childhood and adolescence. Current estimates suggest that school-based bullying likely affects 18–31% of children and youth and that cyberbullying affects 7–15% of youth. Apparent rates of bullying are influenced by the questions that are asked; the word “bully” is stigmatized, and absent that label, youth are more willing to acknowledge having engaged in activities that can be categorized as bullying. Estimates of bullying prevalence are typically based on self-reported victimization (not perpetration), but here too, language can influence results. Targets of other types of social conflict may overestimate or underestimate their bullying victimization unless precise language is used during assessment.

Risk Factors

Certain groups are more vulnerable to bullying, including youth who are lesbian, gay, bisexual, transgender, and questioning (LGBTQ); immigrant and racial minority youth; obese youth; and youth with disabilities. However, it is important to recognize that while these individual risk factors exist, the context and situation can also present unique risk factors. Some studies have found that African Americans are bullied more often than Latinos, whereas other studies have found no group differences. Contextual factors, such as the school climate or prevalence of a particular ethnic group in a school setting, may be important factors in a given bullying situation. The 2015 **Youth Risk Behavior Survey** found that white students were much more likely than black teens to report being bullied at school or online. Thus, it is important to recognize that in any bullying situation, an individual is embedded within a situation that is within a larger social context. This *person by situation by context* approach is useful to consider in identifying why bullying takes place in some situations but not others.

Bullying may occur with other high-risk behaviors. Students who carry weapons, smoke, and drink alcohol >5-6 days/wk are at greatest risk for moderate bullying. Those who carry weapons, smoke, have >1 alcoholic drink/day, have above-average academic performance, moderate/high family affluence, and feel irritable or bad-tempered daily are at greatest risk for engaging in frequent bullying. Negative parenting behavior is related to a moderately increased risk of becoming a *bully/victim* (youth who are both perpetrators and targets) and small to moderate effects on being targeted for bullying at school.

Some risk factors may be specific to cyberbullying. Among preadolescent children, more access to technology (e.g., cell phone ownership) predicts cyberbullying behaviors and some types of digital victimization. Also, communications through digital technology can be misperceived as hostility, and those misperceptions can in turn increase electronic forms of bullying.

Consequences of Bullying

Involvement in any type of bullying is associated with poorer psychosocial adjustment; perpetrators, targets, and those both perpetrator and target report greater health problems and poorer emotional and social adjustment. Bullying consequences of both traditional and cyber forms of bullying are particularly significant in the areas of physical health, mental health, and academic achievement. Being the target of bullying is typically viewed as particularly stressful. The impact of this stress has been shown to affect the developing brain and to be associated with changes to the stress response system, which confers an increased risk for future health and academic difficulties. The long-term consequences of being bullied as a child include increased risk for depression, poor self-esteem, and abusive relationships. Negative outcomes for perpetrating bullying include higher risks of depression as well as substance abuse. Mental health consequences for both perpetrator and target include, across types of bullying, increased risks of depression, poor-self-esteem, increased suicidality, and anxiety. Academic difficulties include increased risk of poor school performance, school failure, and dropping out.

School Violence

Epidemiology

School violence is a significant problem in the United States. Almost 40% of U.S. schools report a least 1 violent incident to police, with >600,000 victims of violent crime per year. Among 9th to 12th graders, 8% were threatened or injured on school property in the last 12 mo, and 14% were involved in a physical fight over the last year. Still, school-associated violent deaths are rare. Seventeen homicides of children age 5-18 yr occurred at school during the 2009–2010 school year. Of all youth homicides, <2% occur at school. While urban schools experience more episodes of violence, the rare rampage gun violence that happens in rural and suburban schools demonstrates that no region is immune to lethal violence.

Risk Factors

Bullying and weapon carrying may be important precursors to more serious school violence. Among perpetrators of violent deaths at school, 20% had been bullying victims, and 6% carried a weapon to school in the last 30 days. Nonlethal violence, mental health problems, racial tensions, student attacks on teachers, and the effects of rapid economic change in communities can all lead to school violence. Individual risk factors for violence include prior history of violence, drug, alcohol, or tobacco use, association with delinquent peers, poor family functioning, poor grades in school, and poverty in the community.

Family risk factors include early childbearing, low parental attachment and involvement, authoritarian or permissive parenting styles (see Chapter 19), and poverty. There is more school violence in areas with higher crime rates and more street gangs, which take away students' ability to learn in a safe environment and leave many children with traumatic stress and grief reactions.

Treatment and Prevention of Bullying and School Violence

Pediatric providers are in a unique position to screen, treat, and advocate for reducing the impact of bullying and school violence by assisting those affected and seeking to prevent further occurrences.

Signs and Symptoms

Signs of a child being involved in bullying or exposed to school violence include physical complaints such as insomnia, stomachaches, headaches, and new-onset enuresis. **Psychological symptoms,** such as depression (see Chapter 39), loneliness, anxiety (see Chapter 38), and suicidal ideation, may occur. **Behavioral changes,** such as irritability, poor concentration, school avoidance, and substance abuse, are common. **School problems,** such as academic failure, social problems, and lack of friends, can also occur. Additional vigilance is warranted for those children who represent vulnerable groups for bullying and aggression, including youth with disabilities, obesity, or minority, immigrant, or LGBTQ status.

Screening for Bullying

Assessing bullying and cyberbullying involvement is an important part of pediatric visits. Several tools can be helpful for clinicians, including the *Bright Futures Guidelines*, which recommend screening at each well-child visit. In these discussions, begin by normalizing the discussion; for example, practitioners can let the patient know that bullying is a topic they discuss with all their patients. It is advisable to define bullying based on the Uniform Definition, but using readily understandable and developmentally appropriate language. Physicians can ask patients if they have had experiences where there was repeated cruelty between peers, either as a target of that cruelty or seeing the cruelty, or even being angry or mean toward others. Asking a patient if he or she is a bully is not likely to generate either trust or an honest answer. Asking about exposures to peer victimization or school violence is also important. Throughout these discussions, it is critical to provide support and empathy while engaging a patient.

One tool to help providers begin and navigate these discussions is a *Practice Enhancement Tool* developed by the **Massachusetts Aggression Reduction Center** (MARC) and Children's Hospital Boston (Fig. 14.1). It begins by defining bullying in readily understandable language and then asks, “Is there any one kid, or a bunch of kids, that pick on you or make feel bad over and over again?” The Tool also guides the practitioner in asking about problematic digital experiences and asks whom the child has spoken to about the problem, and whether that has helped. Finally, it guides the practitioner through emphasizing the usefulness of talking about social problems and discusses how the physician can assist the patient.

MARC/BACPAC Pediatric Questionnaire:
Bullying & Cyberbullying

Date of office visit:__________

Child's name: ______________________	Gender: ☐Male ☐Female	Parent present during interview? ☐Yes ☐No
Child's grade: ______________________	Child's age: ________ years _______ months	Subjective complaints (eg, H/A, tics, sleep): ______________________ ______________________
IEP? ☐Yes ☐No	Neurodev / Psych Dx (if established): ______________________	

BEGIN BY STATING:

"You probably know that grownups today are very worried about bullying. I'd like to ask you a little bit about that, but I want to make sure you understand what I mean. When I ask about bullying, I mean another kid (or group of kids) who picks on someone or is mean to them on purpose, over and over again – not just one time."

1. Do you see bullying happen at your school?

☐ **Yes** ☐ **No**

2. Is there any one kid or a bunch of kids that pick on you or make you feel bad over and over again?

☐ **Yes** (inquire as to the frequency):

(_____ times daily; _____ times a week; _____ times a month; _____ times a year).

IF NO, SKIP TO **#3**

If YES:

Where does this happen? (check all that apply):

☐ classroom ☐ lunchroom ☐ hallways

☐ stairwell ☐ bathroom ☐ locker-room

☐ playground ☐ bus ☐ other: ____________________

What did he or she do to you? (check all that apply):

☐ made fun of me ☐ kids laughed ☐ name-calling

☐ rumors ☐ made up lies ☐ got me in trouble

☐ pushed, shoved, hit, threw stuff ☐ other:____________________________

3. How about on the computer at home? Has anyone been mean to you or made fun of you on the internet?

☐ **Yes** (Details):

____

____

If **NO** to both **#2** and **#3, END HERE.** Otherwise, continue.

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4. It's very important that you understand that if you are being bullied that it is *never* your fault. Bullying is wrong and people should *never* bully others. Have you told any adults about the kids that are bothering you?

☐ **Yes** (Who have you told?)

- ☐ Parent
- ☐ Teacher
- ☐ Other: ______________________________

If Yes.....**Were the adults able to stop the bullying?**

☐ **Yes** ☐ **No**

If Yes.....**Did talking about it make you feel better?**

☐ **Yes** ☐ **No** ("That's ok. Sometimes talking does help though.")

5. "Sometimes it feels good just to talk about things. I wish you and I had more time to talk about it today. Would you like to have a chance to talk about it sometime soon?"

☐ **Yes** (if YES, refer to):

____

____

☐ **No**

IF NO...

..."Would you like me to try to help? As your doctor, I can talk with the school officials and try to make sure that the bullying stops. While I cannot promise that everything will be better, I know that if we do nothing the bullying will likely continue and probably get worse. I want you to be happy and safe at school — is it okay with you if I talk to your school about this?"

☐ **Yes**
(Who would you like me to talk to? Principal / Nurse / Counselor / Teacher / Other: ____________)

☐ **No**

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MARC/BACPAC Pediatric Questionnaire: **Bullying & Cyberbullying**

Guide to the bullying/cyberbullying checklist/interview

"Warm up" questions: briefly acknowledge these but do not discuss at length. No need to note the child's answers.

- Are the kids in your school friendly?
- Tell me about one child at your school who you like.
- Tell me about one child at your school who is not friendly.

(Brief acknowledgement, e.g.: "Ok" or "that's good.")

Note: It's fine to skip the warm-up questions if you have already chatted with the child.

Websites for parents/ teachers/students:

The Massachusetts Aggression Reduction Center (MARC): **MARCcenter.org**

Bullying And Cyberbullying Prevention and Advocacy Collaborative (BACPAC) at Boston Children's Hospital: **bostonchildrens.org/BACPAC**

Stop Bullying Now from the U.S. government: **stopbullying.gov**

When a child is being bullied

There are three venues through which you can help this child:

1. **BY GIVING THEM A "SAFE ADULT" AT SCHOOL THEY CAN ALWAYS SPEAK WITH (EG, THE SCHOOL NURSE, THE SCHOOL ADJUSTMENT COUNSELOR);**
2. **BY GIVING THEIR PARENTS GUIDANCE ABOUT HOW TO COPE (THROUGH HANDOUTS, WEBSITES); AND**
3. **BY OFFERING THEM SUPPORT FROM YOURSELF.**

If child consents to your involvement, seek written parental consent to share information with the school in writing. The more details the child can provide as to who, what, where, how, the more power the school will have to act. Explain this to the child/parent and do your best to gently get details for your letter to the school. If child or parent will not consent to communication with school, provide advice / handouts (**MARCcenter.org**) to help the parent advocate themselves for their child with the school. Always document in your note the conversation in the office.

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FIG. 14.1 **MARC/BACPAC* pediatric questionnaire on bullying and cyberbullying. *Massachusetts Aggression Reduction Center and Bullying And Cyberbullying Prevention and Advocacy Collaborative. (Copyright ©2013 Peter C. Raffalli, MD, and Elizabeth Englander, PhD.)**

Children who are aggressive, overly confident, lacking in empathy, or having persistent conduct problems may need careful screening. It is important to bear in mind that bullying is a dynamic process, and a child may be involved as both a perpetrator and a target at different time points. The physical, behavioral, psychological, and academic symptoms of bullying may overlap with other conditions, such as medical illness, learning problems, and psychological disorders. Thus, labeling the behavior as *bullying* rather than the child as a “bully” is recommended.

Management of bullying and school violence involves several steps. First, ensure that all parties understand the relevant information (the patient, parents, and school). Second, assess a child's need for specialized counseling or social skills interventions. Extracurricular activities, (e.g., drama clubs, mentoring programs, sports) can be discussed as avenues to help to increase the child's social skills and self-esteem. Third, ensure that the patient has adequate support, including at home and at school. Peers are a particularly effective source of support, and patients can be encouraged to spend time with friends, but parents and educators are also important sources of emotional support. Many children benefit from planning their actions in unstructured settings (e.g., discussing where they could sit during lunch), while some benefit from role-playing. Finally, the clinician should identify safety issues, such as suicidal ideation and plans, substance abuse, and other high-risk behaviors.

When bullying or cyberbullying is suspected or confirmed, the parents and child should be offered education and resources. Some resources include the government-supported website www.stopbullying.gov , as well as MARC. Both provide free downloadable literature that can be offered to parents and families.

Addressing cases of bullying or exposure to violence in clinic often requires a cross-disciplinary approach. Involving teachers or school counselors, as well as outside referrals to psychologists, social workers, or counselors, may be warranted. Parental mental health and resource risk factors should also be addressed.

Prevention

Pediatric clinicians can reasonably expect their patients’ schools to provide violence and bullying prevention programs. Rather than focusing on only changing a target of bullying, successful interventions use whole school approaches that involve multiple stakeholders. **School climate** has been shown to have significant effects on bullying prevalence, so these approaches are essential to primary prevention. These broad-based programs simultaneously include school-wide rules and sanctions, teacher training, classroom curriculum, and high levels of student engagement. Addressing access to firearms, involving community organizations and parents, and supporting youth mental health are important in creating a safe school climate.

Prevention programs for cyberbullying are at a nascent stage, reflecting uncertainty about the prevalence of the practice, who is perpetrating it and from where, and how students respond when they are victimized. Many schools have established cyberbullying policies and are increasingly involved with teaching youth about guidelines for appropriate online interactions and monitoring for cyberbullying problems. As of 2016, 23 states included cyberbullying in their state antibullying laws, while 48 states included "electronic harassment." Although legal remedies are frequently not the most productive answer to bullying and cyberbullying incidents, pediatric physicians should be aware of local laws and be prepared to refer parents to more information about these laws when necessary. Studies suggest that preventive interventions designed to address bullying have effects on cyberbullying, and vice versa.

The American Academy of Pediatrics (AAP) provides a free online **Family Media Use Plan** that allows families to develop rules for digital media use and prompts for discussions about safety and online relationships with the goal of preventing negative consequences of online behavior and interactions. The tool is designed for ongoing discussions with family members about online experiences and family rules and values.

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Resources

AAP Family Media Use Plan . www.healthychildren.org/MediaUsePlan .

Federal Partners for Bullying Prevention . www.stopbullying.gov .

Boston Children's Hospital. *Bulling And Cyberbullying Prevention and Advocacy Cooperative* . http://www.childrenshospital.org/centers-and-services/bullying-and-cyberbullying-prevention-and-advocacy-collaborative-bacpac-program .

14.2

Media Violence

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Keywords

apps
social media
traditional media
violent video games
vlogs

Today's youth are growing up in a media-rich environment of both traditional and digital media. *Traditional* media includes television (TV), radio, and periodicals; *digital* media includes online content that promote interactive and social engagement. The online world allows youth instant access to entertainment, information, and knowledge; social contact; and marketing. Social and interactive media allow media users to act as both creators and consumers of content. Examples include applications (apps), multiplayer video games, YouTube videos, and video blogs (vlogs).

One of the earliest studies that has been linked to media effects on aggression and violence was the “bobo doll” experiment in which children who observed an aggressive adult model were more likely to be aggressive toward a doll afterward. It has been widely accepted that media exposure can affect behavior; the advertising industry is grounded in the concept that media exposure can change purchasing behavior. Exposure to sexual content in media has been linked to earlier sexual initiation. However, applying these same constructs to media violence has been controversial. Some suggest that other concepts may be important to consider, such as “dose-response” effects of media, or gene-environment interactions.

There are 3 main types of media in which children may be exposed to violence: video games, traditional media, and social media. **Violent video game** exposure is associated with several outcomes, including increases in composite aggression score, aggressive behavior, aggressive cognitions, aggressive affect, and desensitization; decreased empathy; and increased physiological arousal.

Movies and TV often model violent behavior for the purposes of entertainment. Media violence does not always portray the real human cost or suffering caused by violence. Special effects can make virtual violence more believable and appealing than in the real world. For some children, exposure to media violence can lead to anxiety, depression, posttraumatic stress disorder, or sleep disorders and nightmares. Repeated exposure to the behavioral scripts provided by entertainment media can lead to increased feelings of hostility, expectations for aggression, desensitization to violence, and increased likelihood of interacting and responding to others with violence.

Social media presents similar risks of exposure to virtual violence, but because of the interactive nature of the medium, this content can feel more personal or targeted. Social media combines peer and media effects and thereby represents a powerful motivator of behavior, whether content created by adolescents themselves or content they find and share with peers. The Facebook Influence Model describes 13 distinct constructs in which social media may influence users, such as establishing *social norms* and connection to identity. Thus, exposure to violent content on social media may have influence in promoting a social norm, or connecting this type of content to one's own identity.

Screening

It is important for pediatricians to screen and counsel patients and families about media use and exposure to violent content. Both the quantity and the quality of media are critical factors in media effects on children. When heavy media use by a child is identified, pediatricians should evaluate the child for aggressive behaviors, fears, or sleep disturbances and intervene appropriately.

Recommendations (see Table 14.1)

Pediatricians can counsel parents to help their children *avoid exposure to any form of media violence under age 8 yr* . These younger children do not have the capacity to distinguish fantasy from reality.

Parents should *select and co-view media with their children* , including playing video games with them, watching movies together, and co-viewing social media content. Parents can then assess these games and shows in regard to what they are teaching about communication and interactions with others.

Parents should *feel empowered to place restrictions* on games or shows that reward shooting, killing, or harming other people. Media are powerful teachers, and parents can make choices about how much violence they want their children to learn. Parents can use industry ratings, such as from the Motion Picture Association of America and the Entertainment Software Ratings Board, as well as resources such as Commonsense Media, to guide media selections.

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Resources

AAP Family Media Use Plan . www.healthychildren.org/MediaUsePlan .

Commonsense Media . www.commonsensemedia.org .

14.3

Effects of War on Children

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Keywords

biologic warfare
chemical warfare
child exploitation
gang warfare
posttraumatic stress disorder
terrorism
violence
war

The adverse consequences of war on children are devastating and long-lasting—death, injury, disfigurement, pain and other physical and cognitive disabilities, acute and chronic psychological suffering, temporary and permanent loss of family members, abduction, rape, conscription into armed service, forced relocation, epidemics, famine, drought, and residual trauma lasting decades after hostilities have ceased. The impact of war on children is detailed annually by the Secretary General of the United Nations, and in the 2016 report he described the increasing intensity of human rights violations in a large number of armed conflict situations throughout the world that included mass abduction of children, coercive conscription, death of children or their parents, attacks on schools, and sexual violence. Exploitation in the form of human trafficking has significantly increased in areas of conflict. Slavery, forced marriages, prostitution, and child labor are often a consequence of displacement, which has seen an increase in the past decade due to the increasing number of intrastate conflicts, especially in the Middle East and Northern Africa. In 2017, UNHCR **(Office of the United Nations High Commissioner for Refugees),** the UN

Refugee Agency, reported the astounding statistic of 65.6 million people forcibly displaced worldwide.

Mortality and morbidity related to the long-term effects of war and civil strife are often higher than that occurring during actual fighting. War and violence are not listed as leading causes of childhood mortality, but the regions with the highest levels of child mortality, especially among children <5 yr of age, are the same locations involved in military conflicts. Nations experiencing conflict devote substantial portions of their budgets to military expenditures at the expense of the healthcare infrastructure; a substantial proportion of deaths attributed to malnutrition, environmentally related infectious disease, or inadequate immunization are related to the effects of war. Children experiencing the trauma of wartime violence are at risk for long-term health sequelae, with greater risk for obesity, hypertension, stroke, and cardiovascular disease.

During wartime, customary patterns of behavior are forced to change, overcrowding is frequent, and essential resources, such as water and food staples, may be polluted or contaminated. War is associated with plagues and epidemics, and novel disease entities can develop. Reemergence of polio or cholera and the increased virulence of tuberculosis have been associated with conflict-affected regions and large population displacements.

The morbidity of children exposed to conflicts is significant (Table 14.2). Many more children are physically harmed than killed. Children bear the psychological scars of war resulting from exposure to violent events, loss of primary caregivers, and forced removal from their homes. Impressment of children into service as **soldiers** or agents is a form of *exploitation* associated with long-term problems of adjustment, because child soldiers often lack the appropriate education and socialization and thus their moral compass is often misaligned. They are often incapable of understanding the sources of conflict or why they have been targeted. Their thought processes are more concrete; it is easier for them to dehumanize their adversaries. Children, who themselves are exposed to violence and cruelty, frequently become the worst perpetrators of atrocities.

Table 14.2

Impact of War on Children

Physical

Death
Rape
Abduction
Injuries
Amputations and fractures
Head trauma
Ballistic wounds
Blast injuries
Burns
Chemical and biologic induced
Malnutrition and starvation
Infectious disease
Displacement

Psychosocial

Loss of caregivers and family members
Separation from community
Lack of education
Inappropriate socialization
Acute stress reaction
Posttraumatic stress disorder
Depression
Maladaptive behavior

Exploitation

Conscription as soldiers
Coerced involvement in terrorist activities
Prostitution
Slavery
Forced adoption

After cessation of hostilities, children are still at risk for life-endangering injuries from **landmines** , unexploded ordnance, and other explosive remnants of war. Prior to the signing of the international treaty to ban landmines in 1997, an estimated 20,000-25,000 casualties occurred annually from landmines. Since the ban, the number of casualties from landmines and explosive devices had been declining until 2015, when there was a significant increase in causalities attributed to the increasing number of conflicts. Approximately 40% of these casualties occur in children. Injuries and death tended to occur while children were either playing or involved in household chores, and in contrast to adults, a large proportion of the injuries involved upper-extremity amputation. After the end of armed conflict, the continued proliferation of small arms and light weapons, which are easily handled by children, continues to take its toll on human life and hinders stabilization in postconflict societies.

Susceptibility of Children in Times of War

Children do not have the physical or intellectual capabilities to defend themselves. It is easier for adults to victimize children than other adults. Older children's curiosity, desire for adventure, and imperfect assessment of risk often lead them to participate in dangerous behavior. Younger children, because of their small size and immature physiology, are more susceptible to disease and starvation and are more likely to sustain fatal injuries from ballistic projectiles and explosive devices such as mines. **Blast injuries** , a common cause of violence-related injuries, have a more devastating impact on children than adults. Specific types of military engagement can have a disproportionate effect on children. In a survey of war-related mortality in Iraq from 2003–2008, it was found that approximately 10% of the violence-related fatalities were children. Most children succumbed to either small arms gunfire or suicide bombs (35%). Compared with adults, a proportionately higher rate of children died as a result of the indiscriminant use of weaponry such as mortars, missiles, and aircraft-delivered bombs; 40% of the total casualties in these types of attacks were children.

During times of war, there is a breakdown of social inhibitions and cultural norms. Exploitation of children, such as forced marriages or involuntary conscription, are rationalized as being beneficial for the greater cause. Aberrant behavior such as rape, torture, and pillaging, which would be inconceivable in times of peace, is common during war. Children may be attacked, kidnapped, or used as human shields.

The changing nature of war has adversely affected children. Conventional warfare in which armies of professional soldiers representing different countries battle each other has become less common. **Intrastate conflicts** in the form of civil war are more frequent. In 2013, there were 33 active intrastate armed conflicts in the world as documented by the Uppsala Conflict Data Program (UCDP). These conflicts are often rooted in factious ethnic, political, or religious ideologies, and the participants are frequently nonprofessional irregulars who lack discipline and accountability to higher echelons, and are directed by those who do not acknowledge or respect international accords governing warfare. Often the military resources of the antagonists are disproportionate, leading the weaker protagonist to develop compensatory tactics that can include guerrilla, paramilitary, and terrorist activities, while the stronger side often resorts to the disproportionate use of force. Low-intensity conflicts have become more common. These types of conflicts are often characterized by military activities targeting civilian populations with the goal of disrupting normal routines and generating publicity for the perpetrators. Sites of violence can be remote from the battleground when one or both parties to a conflict resort to terrorist activities.

Terrorism and organized urban-based **gang warfare** have become prevalent. Violence perpetrated by terrorists groups or gangs is designed to coerce and intimidate both individuals and entire societies. Children are often intended victims of political- or religious-motivated violence because this serves to maximize the impact of terrorism. The destruction of the New York City World Trade Center Towers in 2001 and the nearly 3,000 fatalities showed that highly organized and motivated terrorists have few inhibitions and can strike anywhere. **Biologic** and **chemical** weapons of mass destruction have been employed, with the most recent example being the use of poisonous gases in the Syrian civil war. Children are more susceptible to chemical and biologic toxins because of their higher respiratory rates, more permeable skin, and other developmental vulnerabilities (see Chapter 741).

The media and internet have had a significant role in exacerbating the effects of war on children. Media coverage of war and terrorist events is extensive and visual, and social media promulgated via the internet is a convenient tool for disseminating **propaganda** and graphic video material designed to recruit volunteers and shock opponents. Children, more impressionable than adults, often view this material uncontrolled. Uncensored pictures of victims, unbridled violence, people in shock, or family members searching through ruins for relatives may traumatize children and even encourage inappropriate behavior. Overt broadcast propaganda glorifying war and violence may sway children to participate in militaristic or antisocial activities.

Psychological Impact of War

Exposure to war and violence can have a significant impact on a child's psychosocial development. Displacement, loss of caregivers, physical suffering, and the lack of appropriate socialization all contribute to abnormal child development (see Table 14.2). Often the reactions are age specific (Table 14.3). Preschoolers may have an increase in somatic complaints and sleep disturbances and display acting-out behaviors such as tantrums or excessively clinging behavior. School-age children may show regressive behavior such as enuresis and thumb sucking. They, too, have an increase in somatic complaints; there is often a negative impact on school performance. For teenagers, psychological withdrawal and depression are common. Adolescents often exhibit trauma-stimulated acting-out behavior. Motivated by the desire for revenge, they may be quick to join in the violence and contribute to the continuation of conflict.

Table 14.3

Manifestations of Stress Reactions in Children and Adolescents Exposed to War, Terrorism, and Urban Violence

Children ≤6 Yr

Excessive fear of separation
Clinging behavior
Uncontrollable crying or screaming
Freezing (persistent immobility)
Sleep disorders
Terrified affect
Regressive behavior
Expressions of helplessness and passivity

Children 7-11 Yr

Decline in school performance
Truancy
Sleep disorders
Somatization
Depressive affect
Abnormally aggressive or violent behavior
Irrational fears
Regressive and childish behavior
Expressions of fearfulness, withdrawal, and worry

Adolescents 12-17 Yr

Decline in school performance
Sleep disturbances
Flashbacks
Emotional numbness
Antisocial behavior
Substance abuse
Revenge fantasies
Suicidal ideation
Withdrawal

There is an increased incidence of both **acute stress reactions** and **posttraumatic stress disorder** (PTSD; see Chapter 38). The true incidence is difficult to assess because of the heterogeneous nature of war, degree of exposure to violence, and methodologic challenges related to the precise characterization of PTSD. Risk factors for having a more serious psychological response to a violent event include severity of the incident, personal involvement (physical injury, proximity, loss of a relative), prior history of exposure to traumatic events, female gender, and a dysfunctional parental response to the same event. Children may develop PTSD many years after the traumatic event. Children do not have to be directly exposed to violent activity, and media coverage of terrorist events may be sufficient to trigger PTSD.

The trauma experienced by children during war can have lifelong effects. Studies on children imprisoned in concentration camps or evacuated from their homes in London during the Battle of Britain show that these individuals were at greater risk for PTSD, anxiety disorders, and a higher level of dissatisfaction with life when surveyed decades after the traumatic events. Trauma may have a **transgenerational effect** with epigenetic alterations and environmental influences causing children of PTSD victims to display a wide variety of psychological disorders. On the positive side, children are more resilient than adults. With appropriate support from family and community, together with timely and intensive psychological intervention, children can recover and lead normal, productive lives despite the searing trauma that they may have experienced.

Efforts to Protect Children From the Effects of War

International Conventions

War and terror violate the human rights of children, including the right to life, the right to be nurtured and protected, the right to develop appropriately, the right to be with family and community, and the right to a healthy existence. Several international treaties and conventions have been ratified, beginning with the **Fourth Geneva Convention** (1949) that set forth guidelines regarding appropriate treatment of children in times of war. The **United Nations Convention on the Rights of the Child** (1990) delineated specific human rights inherent to every child (defined as any individual younger than 18 yr), and the subsequent **First Optional Protocol** (2000), which prohibits conscripting or recruiting children for military activities. The **Third Optional Protocol** in 2014 established methods for communicating complaints of human rights violations involving children to the United Nations Committee on the Rights of the Child and sets up procedures by which the Committee can conduct inquiries into alleged human rights violations among signatory nations. The **Rome Statute of the International Criminal Court** enacted in 2002 declared that the conscription or enlistment of children younger than 15 yr is a prosecutable war crime. A decade since the ratification of the Rome Statute, the number of armed conflicts in which children were serving as soldiers had decreased from 36 to 16 worldwide.

Although these treaties and conventions define the extent of protection afforded to children, the means of enforcement available to the international community is limited. Individuals, motivated by religious fervor, nationalistic zeal, or ethnic xenophobia, are unlikely to curb their activities because of fear of prosecution. These treaties better serve in heightening awareness regarding the protected status of children in wartime, and perhaps deter high-ranking leaders who fear being held accountable for war crimes.

Humanitarian Efforts

Several organizations, either nongovernmental or under UN auspices, are involved in mitigating the effects of war on children. The International Red Cross, UNICEF, UNHCR, International Rescue Committee, World Health Organization, and Médicins Sans Frontières (Doctors Without Borders), have had a significant impact on reducing violence-related casualties in war-torn regions. The infusion of humanitarian aid into developing countries often improves overall mortality and morbidity by increasing the level of medical and social services available to the general population. Other organizations, such as Amnesty International, Stockholm International Peace Research Institute, and Physicians for Human Rights, actively monitor human rights abuses involving children and other civilian groups. In 2005 the UN Security Council approved the establishment of a monitoring and reporting system designed to protect children exposed to war. UN-led task forces conduct active surveillance in war-stricken regions reporting on the *6 grave violations against children during armed conflict* : the killing or injuring of children, recruitment of child soldiers, attacks directed against schools or hospitals, sexual violence against children, abduction of children, and denial of humanitarian access for children.

Role of Pediatricians and Allied Health Professionals

War is a chronic condition, and health providers need to be prepared to treat childhood casualties resulting from military or terrorist activity, as well as caring for children suffering from the aftermath of war or related violence. Community and hospital pediatricians need to be involved in community disaster planning. General disaster planning should not ignore the unique needs and requirements of children; in planning for a possible chemical attack, appropriate resuscitation equipment suitable for children needs to be stockpiled. The signs of biologic infection, chemical intoxication, or radiation injury are different for children, and pediatricians and emergency personnel need to be aware of these differences (see Chapters 736 and 741). Surveys of pediatricians and other healthcare providers indicate that many feel unprepared for bioterrorism attacks. Professional organizations (e.g., AAP, CDC) have published position papers; there is a special section in the AAP *Red Book* that presents guidelines for treating specific pathogens likely to be used in **biologic warfare** . In regions where violent terrorist activity is likely, pediatricians, nurses, and rescue personnel should consider becoming certified in the Red Cross Basic and Advanced Trauma Life Support programs.

Pediatricians need to be aware of the potential effects of war and terror on parents and children. Loss or separation from parents or caregivers has a devastating impact on children (see Chapter 30). Parents, who themselves are under tremendous strain, may not be sensitive to the effects that the same stressors have on their children. Parents and caregivers must be made cognizant of the effect that media coverage can have on their children and their role in the intermediation of the repetitive broadcast of real-time acts of violence and incendiary communications designed to enlist support for specific causes. Pediatricians should draw out both parents and children and encourage them to talk freely about their feelings. Child healthcare providers can be instrumental in educating parents to be more aware of inappropriate responses by children to war and violence. When necessary, pediatricians can serve their families by referring them to appropriate support services.

Just as it is important to administer first aid for physical trauma, it is also critical to provide psychologic first aid to victims of trauma. An excellent source of online information for both providers and caregivers is the **National Child Traumatic Stress Network** (www.nctsn.org). In day-to-day patient interactions, a pediatrician is most likely to confront situations related to stress reactions such as PTSD or depressive disorders. Recognition of PTSD is essential so that early treatment can be initiated. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) stipulates that for a diagnosis of PTSD, there has to be manifestations from each of 4 symptom clusters: *intrusion* , *avoidance* , *negative alterations in cognitions and mood* , and *alterations in arousal and reactivity* . DSM-5 also established a special preschool subtype of PTSD that has the same 4 symptom clusters but with specific manifestations typical of preschoolers exposed to trauma. Clues to the presence of PTSD and acute anxiety reactions include changes in behavior, school performance, affect, and sleep patterns and an increase in somatic complaints. Even when the triggering event is neither temporally nor physically proximate, it should not dissuade the pediatrician from making an appropriate referral to mental health professionals who are expert in childhood stress disorders.

Medical professional standards demand that the physician treat all patients equitably without regard to their background. Both international law and professional medical societies ban physicians from actively participating in **torture** or other activities that infringe on human rights, including those of children. It is difficult to countenance any situation in which a health professional, even acting as a representative of his country, might directly or indirectly injure a minor. On the positive side, many pediatricians and other physicians have treated children during war either as members of the armed services or volunteers, often under adverse conditions, refusing to abandon their patients even when it has put their own life at risk. Pediatricians and pediatric organizations have been at the forefront in advocating for peaceful coexistence, assisting in relief efforts, and attempting to alleviate the disparities in healthcare resulting from war.

Health professionals have an important role in preventing the atrocities that occur to children. In their role as advocates for the rights of children, pediatricians can be instrumental in focusing public attention on the precarious situation of children exposed to the brutality and mayhem of organized violence. They can promulgate the message that war and terror should not be allowed to rob children of their childhood.

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CHAPTER 15

Child Trafficking for Sex and Labor

V. Jordan Greenbaum

Human trafficking violates the fundamental human rights of child and adult victims and impacts families, communities, and societies. Trafficked persons originate from countries worldwide and may belong to any racial, ethnic, religious, socioeconomic, or cultural group. They may be of any gender. According to the United Nations *Protocol to Prevent, Suppress and Punish Trafficking in Persons* , **child trafficking** refers to the "recruitment, transportation, transfer, harboring or receipt of a person" under 18 yr old for purposes of exploitation. Two major types of trafficking involve **forced labor** and **sexual exploitation** (Table 15.1). While adult sex trafficking requires demonstration of force, fraud, coercion, deception, or the abuse of power as a means of exploitation, these are *not* required for persons younger than 18 yr. Interpretation of the international protocol varies across the globe; U.S. law does not require movement of a victim to qualify as human trafficking. In addition, minors who "consent" to commercial sex in the absence of a third party (trafficker) are victims of commercial sexual exploitation, because their age precludes true informed consent.

Table 15.1

Types of Exploitation Included in Child Trafficking

Sexual Exploitation

- Prostitution of a child
- Production of child sexual exploitation materials (child pornography)
- Exploitation in context of travel and tourism
- Engaging child in sex-oriented business

Child marriage or forced marriage
Live online sexual abuse

Labor Exploitation

Occurs in a variety of sectors, such as agriculture, manufacturing, textiles, food/hospitality services; domestic work; construction, magazine sales, health and beauty, and cleaning services

Forced Begging

Forced Criminality

Forced Engagement in Armed Conflict

Illegal Adoption

The word *victim* is used in this chapter in the legal sense and refers to a person who has been harmed as a result of a crime or other event. It is not intended to imply any subjective interpretation of the person's feelings about his/her situation or imply any judgment about that person's resilience.

Child trafficking may occur within the confines of the child's home country (*domestic* trafficking) or may cross national borders (*international* , or *transnational* , trafficking). Globally, victims tend to be trafficked within their own country or to a country in the same region. In the United States, most identified *child sex trafficking* victims are U.S. citizens or legal residents; few statistical data exist on victims of child labor trafficking. Variations in definitions of terms, problems with data collection, and underrecognition of victims complicate estimates of the prevalence of human trafficking, but the International Labour Organization estimates that 5.5 million of the world's children are victims of forced labor (this includes human trafficking). In a study of 55,000 officially identified trafficking victims, the United Nations Office on Drugs and Crime estimated that approximately 17% were girls and 10% boys. However, laws that define sexual exploitation in terms of girls and women, as well as cultural views regarding gender roles, lead to underreporting of boys, especially as victims of sex trafficking, so their numbers may be higher than estimated.

Factors creating vulnerability to human trafficking exist at the individual, family, community, and societal levels (Table 15.2). **Age** is an important risk factor for adolescents since they are at a stage in their development at which they have limited life experience, a desire to demonstrate their independence from parental control, and a level of brain maturation that favors risk-taking and impulsive behaviors over careful situational analysis and other executive functions. They are also very interested in social media and are savvy at internet use, which render them susceptible to online recruitment and solicitation.

Table 15.2

Vulnerability Factors for Child Trafficking

Individual

- Member of marginalized group (racial, ethnic, sexual minority, caste, etc.)
- History of sexual/physical abuse or neglect
- Limited education
- Substance misuse
- Homeless status; runaway; told to leave home
- History of child welfare and/or juvenile justice involvement (U.S., sex trafficking)
- Untreated mental health or behavioral condition
- Significantly older intimate partner

Family

- Poverty
- Violence, substance misuse, other dysfunction
- Migration

Community

- Limited resources (economic, educational, social support)
- Tolerance of trafficking/exploitation
- Social or political upheaval
- Natural disaster
- Violence
- Limited knowledge of trafficking/exploitation

Increased tourism, travel to area

Societal

Cultural beliefs about roles and rights of children
Gender bias/discrimination
Tolerance of marginalization, exploitation
Sexual objectification of girls
Tolerance of violence
Economic disparities

Recruitment of child victims for labor or sex trafficking often involves false promises of romance, job opportunities, or a better life. Children may remain in their exploitative situation for a number of reasons, including **fear of violence** to themselves or their loved ones should they attempt escape; **guilt and shame** for believing the fraudulent recruitment scheme or engaging in illegal and/or socially condemned activities; **humiliation** and fear of criticism by authorities; **debt bondage** (believing they owe the trafficker exorbitant amounts of money and cannot leave until the debt is paid), and fear of **arrest** and/or deportation. Many children do not recognize their victimization. Girls who believe their trafficker is a boyfriend may view their commercial sexual activities as demonstrations of their love; boys engaging in commercial sex to obtain shelter or food while living on the street may feel they are exploiting buyers rather than being victimized. Traffickers may use violence, economic manipulation, and psychological manipulation to control their victims.

Clinical Presentation

Trafficked persons may seek medical care for any of the myriad physical and emotional consequences of exploitation. They may present with traumatic injuries inflicted by traffickers, buyers, or others or injuries related to unsafe working conditions. They may present with a history of sexual assault, or symptoms/signs of sexually transmitted infections (STIs) and infections related to overcrowded, unsanitary conditions. They may request testing for HIV or complain of signs/symptoms of HIV or infections endemic to the victim's home country (e.g., malaria, schistosomiasis, tuberculosis). Other clinical presentations may involve pregnancy and complications of pregnancy or abortion; malnutrition and/or dehydration; exhaustion; conditions related to exposure to toxins, chemicals, and dust; and signs and symptoms of posttraumatic stress disorder (PTSD), major depression, suicidality, behavioral problems with aggression, and somatization. Some children may have preexisting chronic medical conditions that have been inadequately treated before or during the exploitation (e.g., diabetes, seizure disorder, asthma). Trafficked persons may also seek care for medical issues related to their children.

Many of the same factors that keep victims trapped in their exploitative conditions also preclude them from disclosing their situation to others. *Most victims presenting for medical care at clinics, hospitals, and emergency departments do not self-identify as trafficked persons.* Consequently, it is incumbent on the medical professional to be aware of risk factors so that potential victims may be recognized and offered services. A trafficked child may present to a medical facility alone, in the company of a parent/guardian (who may or may not be aware of the trafficking situation), a friend or other person not involved in the trafficking, a person working for the trafficker (who may pose as a friend or relative), or the trafficker. Traffickers may be male or female, adult or juvenile, and they may be family members, acquaintances, friends, or strangers. On occasion, children are brought in by law enforcement or child protective services, as known or suspected victims. Table 15.3 lists possible indicators of labor or sex trafficking. In some cases, the best indicator is the **chief complaint** , which may be a condition frequently associated with trafficking (e.g., teen pregnancy, STI symptoms/signs (especially with history of prior STI), preventable work-related injury). The practitioner may become concerned about possible trafficking on recognizing the presence of 1 or more **risk factors** (runaway status; recent migration and current work in sector known for labor trafficking).

Table 15.3

Possible Indicators of Child Trafficking

Indicators at Presentation

Chief complaint of acute physical or sexual assault
Chief complaint of suicide attempt
Child accompanied by unrelated adult or juvenile

Child or parent accompanied by domineering person who appears in hurry to leave; child/parent appears intimidated, fearful
Child or accompanying person provides inconsistent or unlikely history of events
Child does not know city he or she is in, or address where staying

Physical Findings

Child withdrawn and with flat affect; fearful; very anxious; intoxicated; or with inappropriate affect
Motel key(s), multiple cell phones, large amounts of cash, or a few expensive items (clothing, nails, etc.)
Tattoos (especially with street names or sexual innuendo)
Evidence of remote or acute inflicted injury (suspicious burns, bruising, signs of strangulation, fractures, closed head injury, thoracoabdominal trauma)
Malnutrition and/or poor hygiene
Poor dentition and/or dental trauma
Late presentation of illness/injury

Approach to the Potentially Trafficked Child

When interacting with a possible victim of trafficking, the medical provider should use a **trauma-informed, human rights–based, culturally appropriate, and gender-sensitive approach** (Table 15.4). This involves being aware that trauma experienced by children may influence their thoughts about themselves and others, their beliefs and perceptions of the world, and their behavior. Hostility, withdrawal, or distrust may be reactions to trauma and should be met with a sensitive, nonjudgmental, empathic response by the provider. Physical safety of the patient and staff are critical, and protocols should be in place to address security issues that may arise if the trafficker is on the premises. Psychological safety of the patient may be facilitated by separating them from any accompanying person when obtaining the medical history, conducting the visit in a warm, child-friendly environment, taking adequate time to build rapport and begin to establish trust, and ensuring that any interpreter used is not from the same community as the patient and is trained in human trafficking.

Table 15.4

Elements of Human Rights–Based, Trauma-Informed Approach to Patient Care

Basic Rights

- Best interest of the child to be primary concern in all actions involving the child
- Protection from discrimination because of gender, race, ethnicity, culture, socioeconomic status, disability, religion, language, country of origin, or other status
- Right to express views and be heard, appropriate to child's age and development
- Right to obtain information relevant to child, to be given in a way that children understand
- Right to privacy and confidentiality
- Right to highest attainable standard of health and to access healthcare services
- Right to dignity, self-respect
- Right to consideration of special needs (age, disability, etc.)
- Right to respect of cultural and religious beliefs and practices

Trauma-Informed Care

- Strength-based approach; facilitate patient resilience and empowerment.
- Obtain medical history in private, safe place, outside presence of persons accompanying child to visit.
- Explain all processes in way child understands, and obtain assent for each step; discuss limits of confidentiality and mandated reporting.
- Encourage patient to express views and to participate in decision-making regarding referrals and care.
- Foster patient's sense of control during evaluation.
- Ask only the questions needed to assess safety, health, and well-being. Avoid asking irrelevant questions about trauma, to avoid unnecessarily

triggering anxiety and distress.
Minimize retraumatization during history, examination, and diagnostic testing (avoid triggers of stress when possible).
Monitor for signs of distress, both verbal and nonverbal.
Allow patient option to choose gender of provider, if feasible.
Have trained personnel present during examination to assist with providing support and reassurance.
Avoid making promises provider cannot fulfill.
Put information gathered to good use.
Conduct safety assessment and create plan.
Be prepared to make referrals and offer resources.

Respect for the **patient's rights** is essential, including the right to an explanation of the purpose of the questions being asked, and the reasons for, and elements of, the examination and diagnostic evaluation. Informed assent by the patient for all steps of the process should be obtained when possible. The limits of confidentiality should be explained in a way the child understands so that they are able to choose what information to disclose. A **risk assessment** should include a discussion with the patient of safety concerns (involving current risks and perceived risks after discharge). While many trafficked persons have committed crimes during their period of exploitation, it is critical to treat the child with respect and compassion, viewing the patient as a victim of exploitation rather than a criminal offender. Every attempt should be made to understand and respect cultural and religious influences that may affect the child's views of their bodies, their condition, and their desired treatment.

In some cases the provider may become concerned about the possibility of human trafficking only after speaking with the child and obtaining the medical history. Social or other vulnerability factors may come to light, prompting concern about exploitation. In such cases the provider may consider asking additional questions, if this can be done in a nontraumatizing manner. Such questions might include the following:

◆ “Many children who have to live on the street have a hard time getting money for food and shelter. Sometimes they have to exchange sex to get what they need. Has this ever happened to you or anyone you know?”

◆ When asking about sexual history: “Has anyone ever asked you or forced you to have sex when you really didn't want to? Do you feel comfortable telling me about it?”

◆ “If you feel comfortable, can you tell me a little bit about your job? Who offered you the job? Is the work you do what you expected when you agreed to the job? Are you allowed to keep all of the money you earn, or send it home? Where, and with whom, do you live? When you are not working, are you allowed to come and go from the place you stay?”

Such questions may open the door to a discussion of exploitation and facilitate the provider identifying appropriate resources and referrals.

All elements of the medical history and review of systems are important, but special attention should be paid to reproductive history (including sexual orientation and identity, prior history of sex partners, STIs, pregnancy/abortions, condom use); injury history; substance use/misuse; and mental health history and current symptoms. Rates of substance misuse, depression, PTSD, depression, and suicidality are very high, and questioning may highlight the need for emergency care or nonurgent referrals. It also provides an opportunity for anticipatory guidance aimed at harm reduction: a discussion of condom use, STIs, HIV/AIDS, and substance use may prove invaluable, since many victims lack accurate information on these topics. It is important to identify any chronic conditions, especially if untreated, and to assess vaccination status. Many trafficked persons have had very poor healthcare in the past and lack basic primary care. It is important to ask questions about signs/symptoms of infections endemic to the child's home country or to countries in which the child has been trafficked (e.g., tuberculosis, dengue, malaria; see Chapter 10).

Examination and Diagnostic Testing

A thorough physical examination allows the provider to assess and treat acute and chronic medical conditions, collect forensic evidence (as appropriate), assess nutritional and developmental status, and document recent and remote injuries. Diagnostic testing may identify pregnancy, STIs, HIV, non–sexually transmitted infections, vitamin and mineral deficiencies, anemia, toxic exposures, drugs, or alcohol. A sexual assault evidence kit may reveal trace evidence or DNA from offenders. Informed assent for the exam, assault kit, and diagnostic tests is important, as is careful explanation of each step during the process, and monitoring of the patient for signs of distress and anxiety. Those who have been sex-trafficked may experience particular distress during the anogenital examination, the oral exam, and when injuries are photographed. A trauma-trained chaperone is very helpful in providing comfort and support to the patient. The examination should be conducted outside the presence of anyone suspected of being involved in the trafficking situation. After the exam the provider should explain the results, ask the child if they have any questions about the exam, and give them the opportunity to discuss concerns about their bodies. Trafficked persons may harbor anxiety about a variety of issues, including possible infertility, future health, or possible permanent damage from work-related injuries and toxic conditions.

Providers may follow U.S. Centers for Disease Control and Prevention (CDC) guidelines on STI testing and prophylaxis. Additional resources on laboratory testing for sexually and non–sexually transmitted diseases may be obtained from the CDC (https://www.cdc.gov/) or World Health Organization (WHO) websites (http://www.who.int/en/). In general, STIs of greatest relevance include *Neisseria gonorrhoeae* , *Chlamydia trachomatis* , *Trichomonas vaginalis* , HIV, syphilis, and hepatitis B and C viruses. Methods of testing and decisions to treat (e.g., positive test results vs prophylaxis vs syndromic treatment) will depend on national guidelines as well as on medical resources, which may be limited in some countries or regions. However, consideration should be given to the high likelihood that the patient may be lost to follow-up after the visit, so the decision to delay treatment until test results are available may lead to lack of needed medication. Testing and treatment decisions need to be outlined in a protocol. Emergency contraception and other methods of birth control (especially long-acting reversible contraception) should be discussed with the patient as feasible.

Many child victims of trafficking (and children of trafficked adults) have experienced nutritional deprivation, lack of immunizations, and general poor health, especially if they are from low-resource countries or are born into the trafficking situation. Guidance on **medical screening** and care for immigrant children (see Chapter 10) may also be obtained from the CDC or American Academy of Pediatrics (AAP) *Red Book* or *Immigrant Child Health Toolkit* .* Consideration should be given to vaccine-preventable diseases (including tetanus if there are open wounds) and common diseases in the child's home country. Domestic or international victims may have iron deficiency, hemoglobinopathies, vitamin D deficiency, and undiagnosed vision or hearing problems. Crowded, unhygienic living conditions during the trafficking period raise the risks of tuberculosis, scabies, and diarrheal illnesses. Toxic levels of lead or chemicals may be present, and vitamin/mineral deficiencies should be considered. A **developmental assessment** is important, given the high likelihood of poor primary care in the past and possible harsh living conditions.

Documentation of health and injuries is extremely important and should be detailed and accurate. Body diagrams and photographs (if not traumatizing to the child) are helpful, as are written descriptions of injury location, type (e.g., contusion, laceration), size, shape, and color. All photographs should include patient identifiers and a measuring instrument when possible. Distance photographs to establish injury location may be supplemented with close-up photographs from various angles. Physical signs of untreated illness, malnutrition, and other conditions need to be documented carefully. When documenting the medical history, direct quotes should be used when possible (quotes of provider and of victim statements). Records, including written, video, audio, and photographic records, should be stored in a secure health information system, with limited access and password protection. Strict protocols for patient confidentiality and privacy should be established and followed.

Referrals and Resources

Healthcare providers must comply with mandatory reporting laws in their state or country, but in doing so, should make every effort to avoid causing harm to the child or their family. In the event the parent is the trafficking victim rather than the child, care should be taken to make reports and referrals only with the victim's consent (unless child's safety/health are at risk). For those practicing within the United States, assistance on interpreting laws, working with suspected victims, making reports to authorities, and identifying local referral sources may be obtained by contacting the **National Human Trafficking Resource Center** (1-888-3737-888). The NHTRC has trained staff to assist victims and professionals alike, including interpreters for over 100 languages. Additional assistance may be obtained by contacting state or local law enforcement and antitrafficking task forces or local child advocacy centers. In some countries, “helplines” and “hotlines” may be used to seek assistance for suspected trafficking victims. It is important for the healthcare provider to be aware of local, state, and national resources for trafficking victims. Exploited persons have numerous needs that extend beyond the range of the healthcare provider's ability to respond. A multidisciplinary team approach is needed to ensure the child is provided with necessary food, shelter, crisis management, language interpretation, immigration assistance, mental health and medical care, educational needs, and other services. Such a team may include local victim service providers, shelter staff, behavioral health professionals, child protective services (CPS) workers, law enforcement, child advocacy center staff, sexual assault providers, and victim advocates. Table 15.5 lists potential health-related referrals.

Table 15.5

Potential Health Referrals for Trafficked Persons

Behavioral health assessment and treatment (emergent or nonurgent): trauma-focused, preferably conducted by professional trained in trauma therapies*
Substance abuse assessment/treatment
Obstetrician/gynecologist
Specialized medical service
Primary medical home (for immunizations including HPV, periodic STI testing, monitoring of growth and development, family planning, anticipatory guidance, nutrition/hygiene counseling, etc.)
Physical therapy, occupational therapy
Developmental assessment
Dentist
Optometrist or audiologist
Resources for LGBTQ
HIV clinic

Child advocacy center (for 2nd opinion on exam; forensic interview, behavioral health services)

HPV, Human papillomavirus; HIV, human immunodeficiency virus; LGBTQ, lesbian, gay, bisexual, transgender, and questioning; STI, sexually transmitted infection.

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[*] Appropriate therapy may differ with victims from varied cultures; there is a very limited evidence-base for effectiveness of behavioral health therapy for trafficked children. However, therapies with an evidence base for child sexual assault/abuse are often used in the U.S.

Trafficked victims may face considerable **social stigma** and **discrimination** . They may be viewed as consenting participants, illegal immigrants who deserve maltreatment, or “bad kids” who are responsible for their own actions. In some countries, laws on sexual exploitation do not include boys, and cultural beliefs foster the attitude that males cannot be victimized. Variations in the age of consent may result in a child being considered an adult in one country and a child in another. For these reasons and others, it is important for the healthcare provider to advocate for the child's victim status when interacting with other professionals and emphasize the need for comprehensive, sustained, trauma-informed services.

Prior to discharge, the provider should ensure the patient understands the results of the evaluation and the treatment plan, has a safety plan, and is aware of options for future care. When referrals are being made, it is helpful for the provider to take steps to ensure services are actually obtained by following up with the referral staff, sending medical records (as appropriate and with victim consent), and assisting the victim with arrangements as feasible. It is also helpful to counsel the victim on their basic human rights, including their right to medical care. If responsible for long-term care of the child, the provider should consider that treatment needs change over time, so treatment plans must be reevaluated periodically. Continuity of care is important but can be challenging when the child is moved to another city, is transported back to the home country, or is re-trafficked. Communication and collaboration with external agencies and healthcare providers can be extremely helpful, along with assignment of a case manager to help ensure referrals are in place in destination towns or villages.

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[*] https://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Council-on-Community-Pediatrics/Pages/Section-1-Clinical-Care.aspx#q1 .

CHAPTER 16

Abused and Neglected Children

Howard Dubowitz, Wendy G. Lane

The abuse and neglect (**maltreatment**) of children are pervasive problems worldwide, with short- and long-term physical and mental health and social consequences. Child healthcare professionals have an important role in helping address this problem. In addition to their responsibility to identify maltreated children and help ensure their protection and health, child healthcare professionals can also play vital roles related to prevention, treatment, and advocacy. Rates and policies vary greatly among nations and, often, within nations. Rates of maltreatment and provision of services are affected by the overall policies of the country, province, or state governing recognition and responses to child abuse and neglect. Two broad approaches have been identified: a *child and family welfare* approach and a *child safety* approach. Although overlapping, the focus in the former is the family as a whole, and in the latter, on the child perceived to be at risk. The United States has primarily had a child safety approach.

Definitions

Abuse is defined as acts of commission and **neglect** as acts of omission. The U.S. government defines *child abuse* as “any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm.” Some states also include other household members. Children may be found in situations in which no actual harm has occurred, and no imminent risk of serious harm is evident, but potential harm may be a concern. Many states include *potential harm* in their child abuse laws. Consideration of potential harm enables preventive intervention, although predicting potential harm is inherently difficult. Two aspects should be considered: the likelihood of harm and the severity of that harm.

Physical abuse includes beating, shaking, burning, and biting. **Corporal punishment** , however, is increasingly being prohibited. The Global Initiative to End All Corporal Punishment of Children reported that 52 countries have prohibited corporal punishment in all settings, including the home. Governments in 55 other countries have expressed a commitment to full prohibition. In the United States, corporal punishment in the home is lawful in all states, but 31 states have banned corporal punishment in public.

The threshold for defining corporal punishment as abuse is unclear. One can consider any injury beyond transient redness as abuse. If parents spank a child, it should be limited to the buttocks, should occur over clothing, and should never involve the head and neck. When parents use objects other than a hand, the potential for serious harm increases. Acts of serious violence (e.g., throwing a hard object, slapping an infant's face) should be seen as abusive even if no injury ensues; significant risk of harm exists. While some child healthcare professionals think that **hitting** is acceptable under limited conditions, almost all know that more constructive approaches to discipline are preferable. The American Academy of Pediatrics clearly opposed the use of corporal punishment in a recent policy statement. Although many think that hitting a child should never be accepted, and many studies have documented the potential harm, there remains a reluctance in the United States to label hitting as abuse, unless there is an injury. It is clear that the emotional impact of being hit may leave the most worrisome scar, long after the bruises fade and the fracture heals.

Sexual abuse has been defined as “the involvement of dependent, developmentally immature children and adolescents in sexual activities which they do not fully comprehend, to which they are unable to give consent, or that violate the social taboos of family roles.” Sexual abuse includes exposure to sexually explicit materials, oral-genital contact, genital-to-genital contact, genital-to-anal contact, and genital fondling. Any touching of *private parts* by parents or caregivers in a context other than necessary care is inappropriate.

Neglect refers to omissions in care, resulting in actual or potential harm. *Omissions* include inadequate healthcare, education, supervision, protection from hazards in the environment, and unmet physical needs (e.g., clothing, food) and emotional support. A preferable alternative to focusing on caregiver omissions is to instead consider the *basic needs* (or rights) of children (e.g., adequate food, clothing, shelter, healthcare, education, nurturance). Neglect occurs when a need is not adequately met and results in actual or potential harm, whatever the reasons. A child whose health is jeopardized or harmed by not receiving necessary care experiences **medical neglect** . Not all such situations necessarily require a report to child protective services (CPS); less intrusive initial efforts may be appropriate.

Psychological abuse includes verbal abuse and humiliation and acts that scare or terrorize a child. Although this form of abuse may be extremely harmful to children, resulting in depression, anxiety, poor self-esteem, or lack of empathy, CPS seldom becomes involved because of the difficulty in proving such allegations. Child healthcare professionals should still carefully consider this form of maltreatment, even if the concern fails to reach a legal or agency threshold for reporting. These children and families can benefit from counseling and social support. Many children experience more than one form of maltreatment; CPS are more likely to address psychological abuse in the context of other forms of maltreatment.

Within in the United States and internationally, problems of **trafficking** in children, for purposes of cheap labor and sexual exploitation, expose children to all the forms of abuse just noted (see Chapter 15).

Incidence and Prevalence

Global

Child abuse and neglect are not rare and occur worldwide. Based on international studies, the World Health Organization (WHO) has estimated that 18% of girls and 8% of boys experience sexual abuse as children, while 23% of children report being physically abused (Figs. 16.1 and 16.2). In addition, many children experience emotional abuse and neglect. Surveys reported by United Nations Children's Fund (UNICEF) confirm these reports; one survey conducted in the Middle East reported that 30% of children had been beaten or tied up by parents, and in a survey in a Southeast Asian country, 30% of mothers reported having hit their child with an object in the past 6 mo.

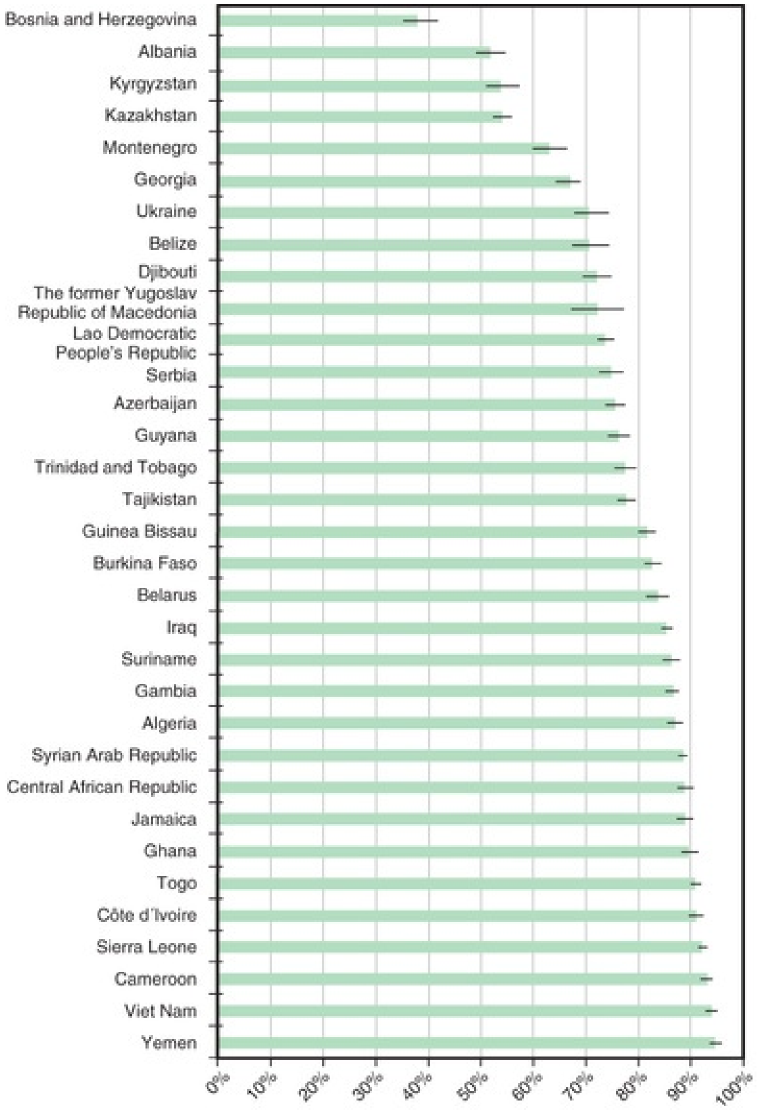

FIG. 16.1 Percentage of children ages 2-14 yr who experienced any violent discipline (physical punishment and/or psychological aggression) in the past month, by country. (United Nations Children's Fund, Hidden in Plain Sight: A statistical analysis of violence against children. UNICEF, New York, 2014, Fig 2. http://www.data.unicef.org/resources/hidden-in-plain-sight .)

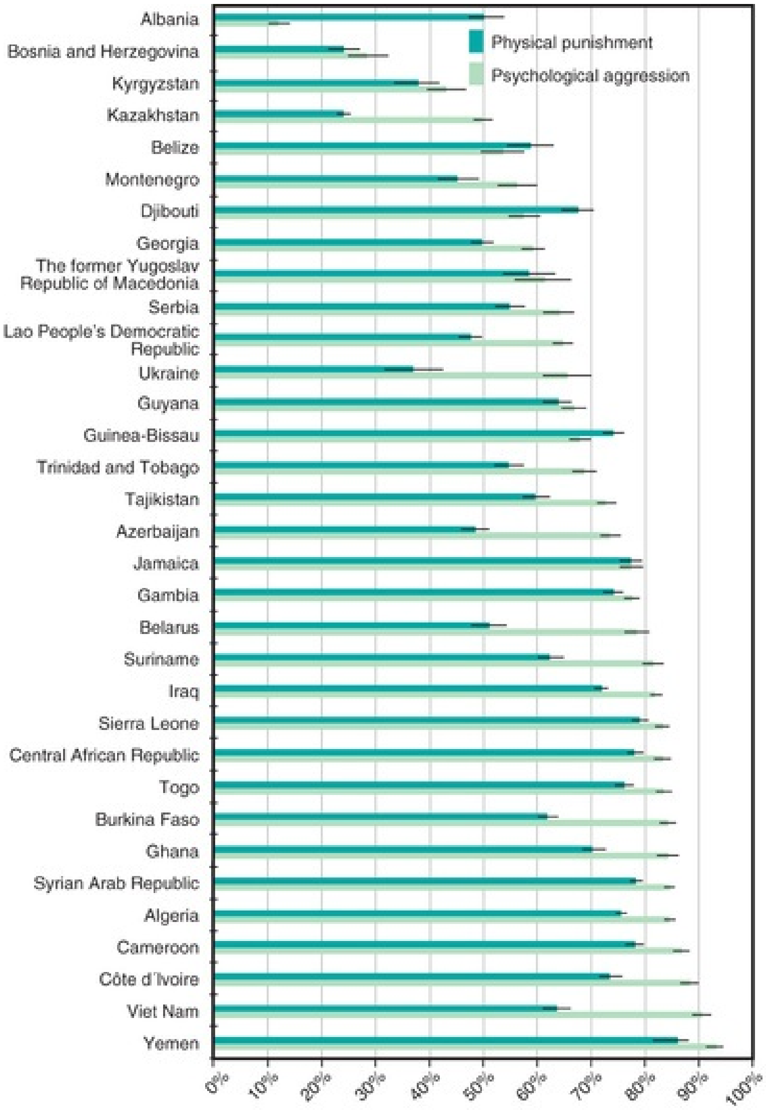

FIG. 16.2 Percentage of children ages 2-14 yr who experienced psychological aggression and percentage of children ages 2-14 yr who experienced physical punishment in the past month, by country, 2005–2006. (United Nations Children's Fund, Hidden in Plain Sight: A statistical analysis of violence against children. UNICEF, New York, Fig 2. http://www.data.unicef.org/resources/hidden-in-plain-sight .)

United States

Abuse and neglect mostly occur behind closed doors and often are a well-kept secret. Nevertheless, there were 4 million reports to CPS involving 7.2 million children in the United States in 2015. Of the 683,000 children with substantiated reports (9.2 per 1,000 children), 78.3% experienced neglect (including 1.9%

medical neglect), 17.2% physical abuse, 8.4% sexual abuse, and 6.2% psychological maltreatment. While there had been a decline in rates beginning in the early 1990s, rates increased in 2014 and 2015 from prior years. Likewise, the rate of hospitalized children with serious physical abuse has not declined in recent years. Medical personnel made 9.1% of all reports.

Other sources independent from the official CPS statistics cited above confirm the prevalence of child maltreatment. In a community survey, 3% of parents reported using very severe violence (e.g., hitting with fist, burning, using gun or knife) against their child in the prior year. Considering a natural disinclination to disclose socially undesirable information, such rates are both conservative and alarming.

Etiology

Child maltreatment seldom has a single cause; rather, multiple and interacting biopsychosocial **risk factors** at 4 levels usually exist. To illustrate, at the *individual level* , a child's disability or a parent's depression or substance abuse predispose a child to maltreatment. At the *familial level* , intimate partner (or domestic) violence presents risks for children. Influential *community factors* include stressors such as dangerous neighborhoods or a lack of recreational facilities. Professional inaction may contribute to neglect, such as when the treatment plan is not clearly communicated. Broad *societal factors* , such as poverty and its associated burdens, also contribute to maltreatment. WHO estimates the rate of homicide of children is approximately 2-fold higher in low-income compared to high-income countries (2.58 vs 1.21 per 100,000 population), but clearly homicide occurs in high-income countries too. Children in all social classes can be maltreated, and child healthcare professionals need to guard against biases concerning low-income families.

In contrast, **protective factors** , such as family supports, or a mother's concern for her child, may buffer risk factors and protect children from maltreatment. Identifying and building on protective factors can be vital to intervening effectively. One can say to a parent, “I can see how much you love [child's name]. What can we do to keep her out of the hospital?” Child maltreatment results from a complex interplay among risk and protective factors. A single mother who has a colicky baby and who recently lost her job is at risk for maltreatment, but a loving grandmother may be protective. A good understanding of factors that contribute to maltreatment, as well as those that are protective, should guide an appropriate response.

Clinical Manifestations

Child abuse and neglect can manifest in many ways. A critical element of physical abuse is the lack of a plausible history other than inflicted trauma. The onus is on the clinician to carefully consider the differential diagnosis and not jump to conclusions.

Bruises are the most common manifestation of physical abuse. Features suggestive of inflicted bruises include (1) bruising in a preambulatory infant (occurring in just 2% of infants), (2) bruising of padded and less exposed areas (buttocks, cheeks, ears, genitalia), (3) patterned bruising or burns conforming to shape of an object or ligatures around the wrists, and (4) multiple bruises, especially if clearly of different ages (Fig. 16.3 and Table 16.1). Earlier suggestions for estimating the age of bruises have been discredited. It is very difficult to precisely determine the ages of bruises.

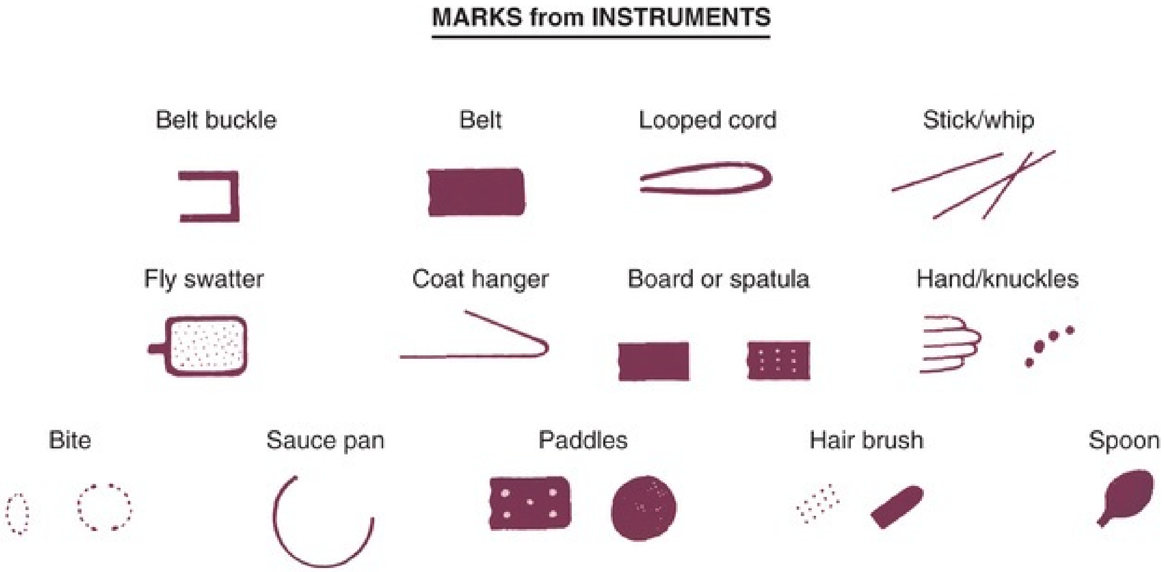

FIG. 16.3 A variety of instruments may be used to inflict injury on a child. Often the choice of an instrument is a matter of convenience. Marks tend to silhouette or outline the shape of the instrument. The possibility of intentional trauma should prompt a high degree of suspicion when injuries to a child are geometric, paired, mirrored, of various ages or types, or on relatively protected parts of the body. Early recognition of intentional trauma is important to provide therapy and prevent escalation to more serious injury.

Table 16.1

Injury Patterns

METHOD OF INJURY/IMPLEMENT	PATTERN OBSERVED
Grip/grab	Relatively round marks that correspond to fingertips and/or thumb
Closed-fist punch	Series of round bruises that correspond to knuckles of the hand
Slap	Parallel, linear bruises (usually petechial) separated by areas of central sparing
Belt/electrical cord	Loop marks or parallel lines of petechiae (the width of the belt/cord) with central sparing; may see triangular marks from the end of the belt, small circular lesions caused by the holes in the tongue of the belt, and/or a buckle pattern
Rope	Areas of bruising interspersed with areas of abrasion
Other objects/household implements	Injury in shape of object/implement (e.g., rods, switches, and wires cause linear bruising)
Human bite	Two arches forming a circular or oval shape, may cause bruising and/or abrasion
Strangulation	Petechiae of the head and/or neck, including mucous membranes; may see subconjunctival hemorrhages
Binding/ligature	Marks around the wrists, ankles, or neck; sometimes accompanied by petechiae or edema distal to the ligature mark Marks adjacent to the mouth if the child has been gagged
Excessive *hincar* *	Abrasions/burns, especially to knees
Hair pulling	Traumatic alopecia; may see petechiae on underlying scalp, or swelling or tenderness of the scalp (from subgaleal hematoma)
Tattooing or intentional scarring	Abusive cases have been described, but can also be a cultural phenomenon (e.g., Maori body ornamentation)

* Punishment by kneeling on salt or other rough substance.

Other conditions such as birthmarks and congenital dermal melanocytosis (e.g., mongolian spots) can be confused with bruises and abuse. These skin markings are not tender and do not rapidly change color or size. An underlying medical explanation for bruises may exist, such as blood dyscrasias (hemophilia) or connective tissue disorders (Ehlers-Danlos syndrome). The history or examination usually provides clues to these conditions. Henoch-Schönlein purpura, the most common vasculitis in young children, may be confused with abuse. The pattern and location of bruises caused by abuse are usually different from those due to a coagulopathy. Noninflicted bruises are characteristically anterior and over bony prominences, such as shins and forehead. The presence of a medical disorder does not preclude abuse.

Cultural practices can cause bruising. Cao gio, or *coining,* is a Southeast Asian folkloric therapy. A hard object is vigorously rubbed on the skin, causing petechiae or purpura. *Cupping* is another approach, popular in the Middle East. A heated glass is applied to the skin, often on the back. As it cools, a vacuum is formed, leading to perfectly circular bruises. The context here is important, and such circumstances should not be considered abusive (see Chapter 11).

A careful history of bleeding problems in the patient and first-degree relatives is needed. If a bleeding disorder is suspected, a complete blood count including platelet count, prothrombin time, and partial thromboplastin time should be obtained. More extensive testing, such as factors VIII, IX and XIII activity and von Willebrand evaluation, should be considered in consultation with a hematologist.

Bites have a characteristic pattern of 1 or 2 opposing arches with multiple bruises. They can be inflicted by an adult, another child, an animal, or the patient. Forensic odontologists have previously developed guidelines for distinguishing adult from child and human from animal bites. However, several studies have identified problems with the accuracy and consistency of bite mark analysis.

Burns may be inflicted or caused by inadequate supervision. Scalding burns may result from immersion or splash. *Immersion burns*, when a child is forcibly held in hot water, show clear delineation between the burned and healthy skin and uniform depth. They may have a sock or glove distribution. Splash marks are usually absent, unlike when a child inadvertently encounters hot water. Symmetric burns are especially suggestive of abuse, as are burns of the buttocks and perineum (Fig. 16.4). Although most often accidental, splash burns may also result from abuse. Burns from hot objects such as curling irons, radiators, steam irons, metal grids, hot knives, and cigarettes leave patterns representing the object (Fig. 16.5). A child is likely to draw back rapidly from a hot object; thus burns that are extensive and deep reflect more than fleeting contact and are suggestive of abuse.

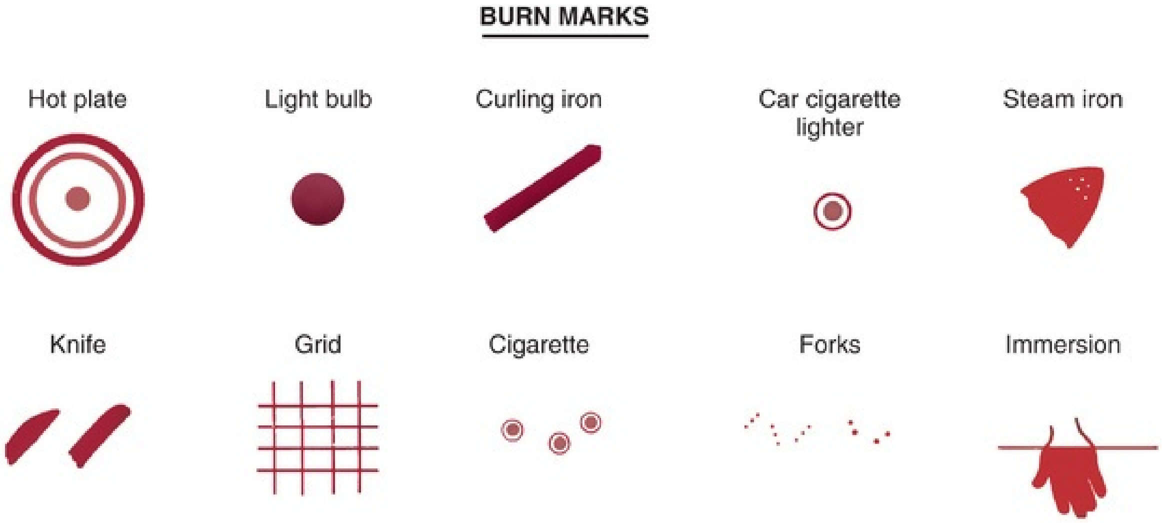
BURN MARKS
Hot plate
Light bulb
Curling iron
Car cigarette lighter
Steam iron
Knife
Grid
Cigarette
Forks
Immersion

FIG. 16.4 Marks from heated objects cause burns in a pattern that duplicates that of the object. Familiarity with the common heated objects that are used to traumatize children facilitates recognition of possible intentional injuries. The location of the burn is important in determining its cause. Children tend to explore surfaces with the palmar surface of the hand and rarely touch a heated object repeatedly for long.

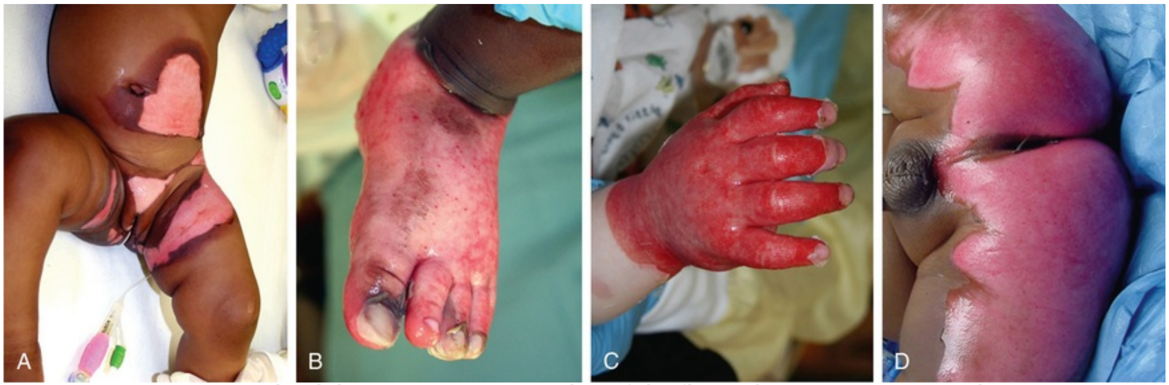

FIG. 16.5 **Immersion injury patterns. A, Sparing of the flexoral creases. B, Immersion "stocking" burn. C, Immersion "glove" burn. D, Immersion buttocks burn. (From Jenny C: Child abuse and neglect: diagnosis, treatment, and evidence, Philadelphia, 2011, Saunders, p. 225, Fig 28-3)**

Several conditions mimic abusive burns, such as brushing against a hot radiator, car seat burns, hemangiomas, and folk remedies such as moxibustion. Impetigo may resemble cigarette burns. *Cigarette burns* are usually 7-10 mm across, whereas impetigo has lesions of varying size. Noninflicted cigarette burns are usually oval and superficial.

Neglect frequently contributes to childhood burns. Children, home alone, may be burned in house fires. A parent taking drugs may cause a fire and may be unable to protect a child. Exploring children may pull hot liquids left unattended onto themselves. Liquids cool as they flow downward so that the burn is most severe and broad proximally. If the child is wearing a diaper or clothing, the fabric may absorb the hot water and cause burns worse than otherwise expected. Some circumstances are difficult to foresee, and a single burn resulting from a momentary lapse in supervision should not automatically be seen as neglectful parenting.

Concluding whether a burn was inflicted depends on the history, burn pattern, and the child's capabilities. A delay in seeking healthcare may result from the burn initially appearing minor, before blistering or becoming infected. This circumstance may represent reasonable behavior and should not be automatically deemed neglectful. A home investigation is often valuable (e.g., testing the water temperature).

Fractures that strongly suggest abuse include classic metaphyseal lesions, posterior rib fractures, and fractures of the scapula, sternum, and spinous processes, especially in young children (Table 16.2). These fractures all require more force than would be expected from a minor fall or routine handling and activities of a child. Rib and sternal fractures rarely result from cardiopulmonary resuscitation (CPR), even when performed by untrained adults. The recommended 2-finger or 2-thumb technique recommended for infants since 2005 may produce anterolateral rib fractures. In abused infants, rib (Fig. 16.6), metaphyseal (Fig. 16.7), and skull fractures are most common. Femoral and humeral fractures in nonambulatory infants are also very worrisome for abuse. With increasing mobility and running, toddlers can fall with enough rotational force to cause a spiral, femoral fracture. Multiple fractures in various stages of healing are suggestive of abuse; nevertheless, underlying conditions need to be considered. Clavicular, femoral, supracondylar humeral, and distal extremity fractures in children older than 2 yr are most likely noninflicted unless they are multiple or accompanied by other signs of abuse. Few fractures are pathognomonic of abuse; all must be considered in light of the history and the child's developmental level. Fractures may present as an irritable fussy child.

Table 16.2

Specificity of Radiologic Findings for Fractures

High Specificity*

Classic metaphyseal lesions
Rib fractures, especially posteromedial
Scapular fractures
Spinous process fractures
Sternal fractures

Moderate Specificity

Multiple fractures, especially bilateral
Fractures of different ages
Epiphyseal separations
Vertebral body fractures and subluxations
Digital fractures
Complex skull fractures
Pelvic fractures

Common but Low Specificity

Subperiosteal new bone formation
Clavicular fractures
Long-bone shaft fractures
Linear skull fractures

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* Highest specificity applies in infants.

From Kleinman PK: *Diagnostic imaging of child abuse* , ed 3, Cambridge, UK, 2015, Cambridge University Press, p 24.

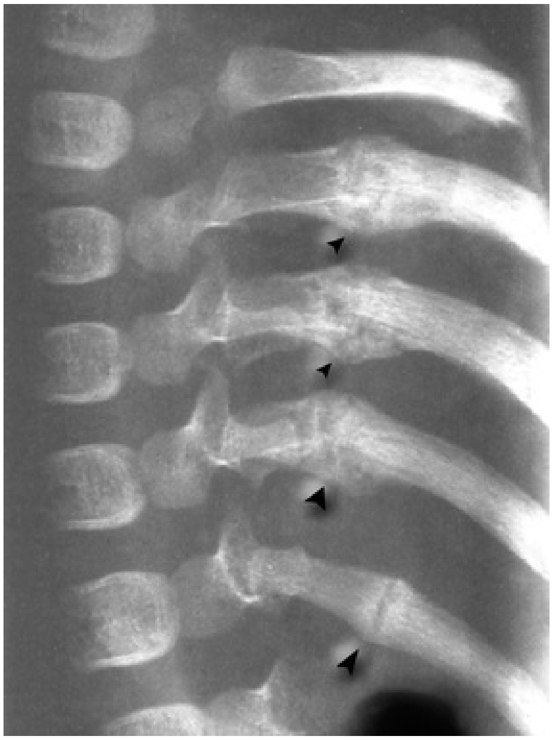

FIG. 16.6 High-detail oblique view of the ribs of a 6 mo old infant shows multiple healing posteromedial rib fractures (*arrowheads*). The level of detail in this image is far greater than what would be present on a standard chest radiograph. (From Dwek JR: The radiographic approach to child abuse, Clin Orthop Relat Res 469:776–789, 2011, p 780, Fig 4.)

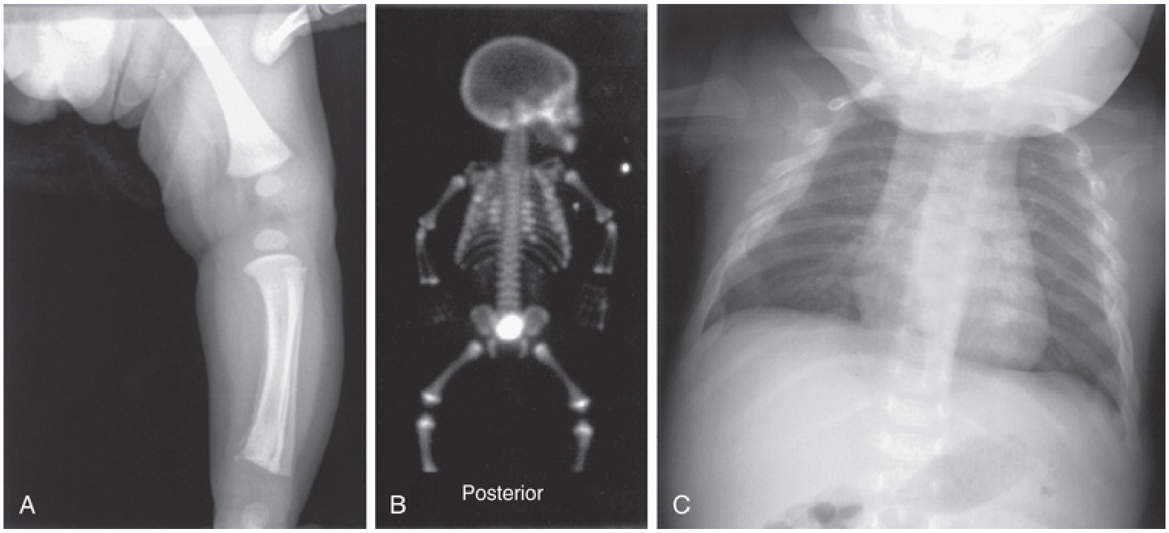

FIG. 16.7 **A,** Metaphyseal fracture of the distal tibia in a 3 mo old infant admitted to the hospital with severe head injury. There is also periosteal new bone formation of the tibia, perhaps from previous injury. **B,** Bone scan

of same infant. Initial chest radiograph showed a single fracture of the right posterior 4th rib. A radionuclide bone scan performed 2 days later revealed multiple previously unrecognized fractures of the posterior and lateral ribs. **C,** Follow-up radiographs 2 wk later showed multiple healing rib fractures. This pattern of fracture is highly specific for child abuse. The mechanism of these injuries is usually violent squeezing of the chest.

The differential diagnosis includes conditions that increase susceptibility to fractures, such as osteopenia and osteogenesis imperfecta, metabolic and nutritional disorders (e.g., scurvy, rickets), renal osteodystrophy, osteomyelitis, congenital syphilis, and neoplasia. Some have pointed to possible rickets and low but subclinical levels of vitamin D as being responsible for fractures thought to be abusive. The evidence to date does not support this supposition. Features of congenital or metabolic conditions associated with nonabusive fractures include family history of recurrent fractures after minor trauma, abnormally shaped cranium, dentinogenesis imperfecta, blue sclera, craniotabes, ligamentous laxity, bowed legs, hernia, and translucent skin. *Subperiosteal new bone formation* is a nonspecific finding seen in infectious, traumatic, and metabolic disorders. In young infants, new bone formation may be a normal physiologic finding, usually bilateral, symmetric, and <2 mm in depth.

The evaluation of a fracture should include a skeletal radiologic survey in children <2 yr old when abuse seems possible (Table 16.3). Multiple radiographs with different views are needed; “babygrams” (1 or 2 films of the entire body) should be avoided. If the survey is normal, but concern for an occult injury remains, a radionucleotide bone scan should be performed to detect a possible acute injury. Follow-up films after 2 wk may also reveal fractures not apparent initially.

Table 16.3

Radiologic Skeletal Survey for Infants and Children Under 2 Yr of Age*

- Anteroposterior (AP) and lateral views of skull (Townes view optional; add if any fracture seen)
- Lateral spine (cervical spine [C-spine] may be included on skull radiographs; AP spine is included on AP chest and AP pelvis views to include entire spine)
- AP view, right posterior oblique, left posterior oblique view of chest—rib

technique

- AP pelvis
- AP view of each femur
- AP view of each leg
- AP view of each humerus
- AP view of each forearm
- Posteroanterior (PA) view of each hand
- AP (dorsoventral) view of each foot

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[*] Images are checked by a radiologist before the patient leaves. Poorly positioned or otherwise suboptimal images should be repeated. Lateral views are added for positive or equivocal findings in the extremities. Coned views of positive or equivocal findings (i.e., at ends of long bones, ribs) may be obtained.

Adapted from Coley BD: *Caffey's pediatric diagnostic imaging* , ed 12, vol 2, Philadelphia, 2013, Mosby/Elsevier, p 1588 (Box 144-1).

In corroborating the history and the injury, the age of a fracture can be crudely estimated (Table 16.4). Soft tissue swelling subsides in 2-21 days. Subperiosteal new bone is visible within 6-21 days. Loss of definition of the fracture line occurs in 10-21 days. Soft callus can be visible after 9 days and hard callus at 14-90 days. These ranges are shorter in infancy and longer in children with poor nutritional status or a chronic underlying disease. Fractures of flat bones such as the skull do not form callus and cannot be aged, although soft tissue swelling indicates approximate recency (within the prior week).

Table 16.4

Timetable of Radiologic Changes in Children's Fractures* (in Days)

CATEGORY	EARLY	PEAK	LATE
1. Subperiosteal new bone formation	4-10	10-14	14-21
2. Loss of fracture line definition		10-14	14-21
3. Soft callus		10-14	14-21
4. Hard callus	14-21	21-42	42-90

[*] Repetitive injuries may prolong all categories. The time points tend to increase from early infancy into childhood.

Adapted from Kleinman PK: *Diagnostic imaging of child abuse* , ed 3, Cambridge, UK, 2015, Cambridge University Press, p 215.

Abusive head trauma (AHT) results in the most significant morbidity and mortality. Abusive injury may be caused by direct impact, asphyxia, or shaking. Subdural hematomas (Fig. 16.8), retinal hemorrhages, especially when extensive and involving multiple layers, and diffuse axonal injury strongly suggest AHT, especially when they occur together. The poor neck muscle tone and relatively large heads of infants make them vulnerable to acceleration-deceleration forces associated with shaking, leading to AHT. Children may lack external signs of injury, even with serious intracranial trauma. Signs and symptoms may be nonspecific, ranging from lethargy, vomiting (without diarrhea), changing neurologic status or seizures, and coma. In all preverbal children, an index of suspicion for AHT should exist when children present with these signs and symptoms.

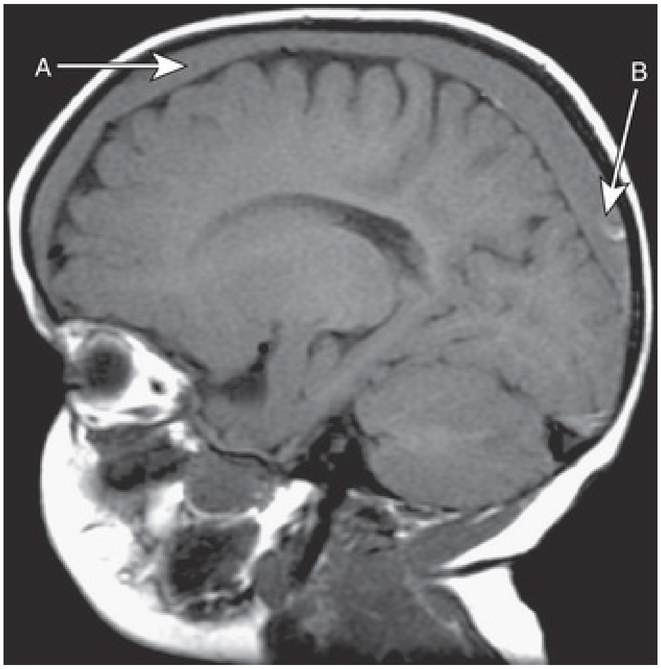

FIG. 16.8 **CT scan indicating intracranial bleeding.** ***A arrow,*** **Older blood.** ***B arrow,*** **New blood.**

Acute intracranial trauma is best evaluated by initial and follow-up CT. MRI is helpful in differentiating extra axial fluid, determining timing of injuries, assessing parenchymal injury, and identifying vascular anomalies. MRI is best obtained 5-7 days after an acute injury. Glutaric aciduria type 1 can present with intracranial bleeding and should be considered. Other causes of subdural hemorrhage in infants include arteriovenous malformations, coagulopathies, birth trauma, tumor, and infections. When AHT is suspected, injuries elsewhere —skeletal and abdominal—should be ruled out.

Retinal hemorrhages are an important marker of AHT (Fig. 16.9). Whenever AHT is being considered, a dilated indirect eye examination by a pediatric ophthalmologist should be performed. Although retinal hemorrhages can be found in other conditions, hemorrhages that are multiple, involve >1 layer of the retina, and extend to the periphery are very suspicious for abuse. The mechanism is likely repeated acceleration-deceleration from shaking. Traumatic retinoschisis points strongly to abuse.

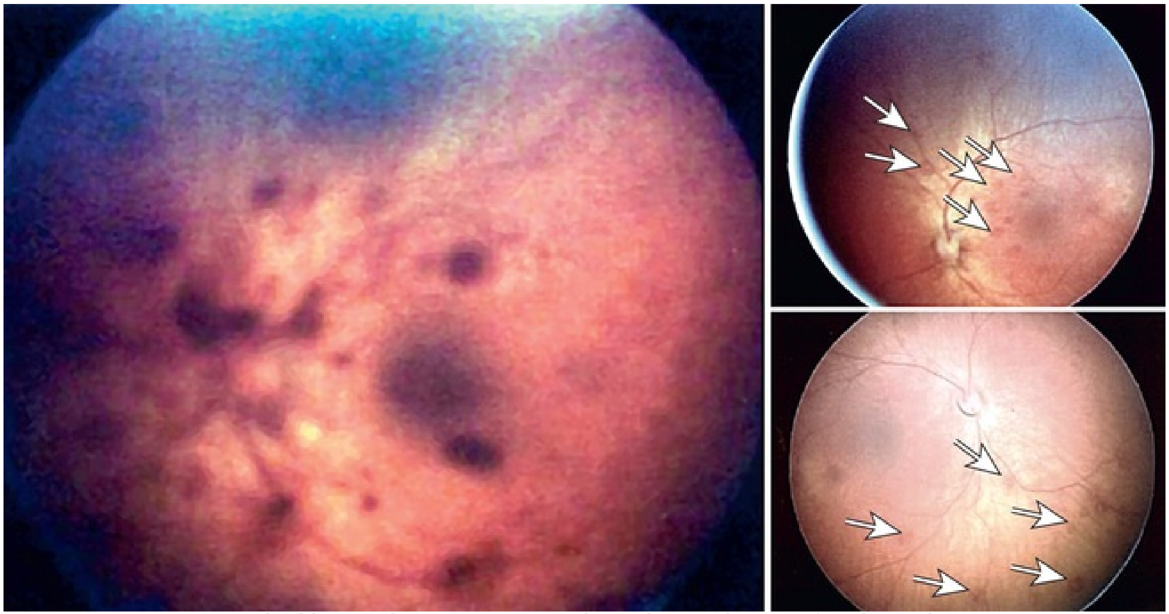

FIG. 16.9 **Retinal hemorrhages. *Arrows* point to hemorrhages of various sizes.**

With other causes of retinal hemorrhages, the pattern is usually different than seen in child abuse. After birth, many newborns have them, but they disappear in 2-6 wk. Coagulopathies (particularly leukemia), retinal diseases, carbon monoxide poisoning, or glutaric aciduria may be responsible. Severe, noninflicted, direct crush injury to the head can rarely cause an extensive hemorrhagic retinopathy. CPR rarely, if ever, causes retinal hemorrhage in infants and children; if present, there a few hemorrhages in the posterior pole.

Hemoglobinopathies, diabetes mellitus, routine play, minor noninflicted head trauma, and vaccinations do not appear to cause retinal hemorrhage in children. Severe coughing or seizures rarely cause retinal hemorrhages that could be confused with AHT.

The dilemma frequently posed is whether minor, everyday forces can explain the findings seen in AHT. Simple linear skull fractures in the absence of other suggestive evidence can be explained by a short fall, although even that is rare (1-2%), and underlying brain injury from short falls is exceedingly rare. Timing of brain injuries in cases of abuse is not precise. In fatal cases, however, the trauma most likely occurred very soon before the child became symptomatic.

Other manifestations of AHT may be seen. *Raccoon eyes* occur in association with subgaleal hematomas after traction on the anterior hair and scalp, or after a blow to the forehead. Neuroblastoma can present similarly and should be considered. Bruises from attempted strangulation may be visible on the neck. Choking or suffocation can cause hypoxic brain injury, often with no external signs.

Abdominal trauma accounts for significant morbidity and mortality in abused children. Young children are especially vulnerable because of their relatively large abdomens and lax abdominal musculature. A forceful blow or kick can cause hematomas of solid organs (liver, spleen, kidney) from compression against the spine, as well as hematoma (duodenal) or rupture (stomach) of hollow organs. Intraabdominal bleeding may result from trauma to an organ or from shearing of a vessel. More than 1 organ may be affected. Children may present with cardiovascular failure or an acute condition of the abdomen, often after a delay in care. Bilious vomiting without fever or peritoneal irritation suggests a duodenal hematoma, often caused by abuse.

The manifestations of abdominal trauma are often subtle, even with severe injuries. Bruising of the abdominal wall is unusual, and symptoms may evolve slowly. Delayed perforation may occur days after the injury; bowel strictures or a pancreatic pseudocyst may occur weeks or months later. Child healthcare professionals should consider screening for occult abdominal trauma when other evidence of physical abuse exists. Screening should include liver and pancreatic enzyme levels, and testing urine for blood. Children with lab results indicating possible injury should have abdominal CT performed. CT or ultrasound should also be performed if there is concern about possible splenic, adrenal, hepatic, or reproductive organ injury.

Oral lesions may present as bruised lips, bleeding, torn frenulum, and dental trauma or caries (neglect).

Neglect

Neglect is the most prevalent form of child maltreatment, with potentially severe and lasting sequelae. It may manifest in many ways, depending on which needs are not adequately met. Nonadherence to medical treatment, for example, may aggravate the condition, as may a delay in seeking care. Inadequate food may manifest as impaired growth; inattention to obesity may compound that problem. Poor hygiene may contribute to infected cuts or lesions. Inadequate supervision contributes to injuries and ingestions. Children's needs for mental healthcare, dental care, and other health-related needs may be unmet, manifesting as neglect in those areas. Educational needs, particularly for children with learning disabilities, are often not met.

The evaluation of possible neglect requires addressing critical questions: “Is this neglect?” and “Have the circumstances harmed the child, or jeopardized the child's health and safety?” For example, suboptimal treatment adherence may lead to few or no clear consequences. Inadequacies in the care that children receive naturally fall along a continuum, requiring a range of responses tailored to the individual situation. Legal considerations or CPS policies may discourage physicians from labeling many circumstances as neglect. Even if neglect does not meet a threshold for reporting to CPS, child healthcare professionals can still help ensure children's needs are adequately met.

General Principles for Assessing Possible Abuse and Neglect

The heterogeneity of circumstances in situations of child maltreatment precludes specific detailing of varied assessments. The following are useful general principles.

- Given the complexity and possible ramifications of determining child maltreatment, an **interdisciplinary assessment** is optimal, with input from all involved professionals. Consultation with a physician expert in child maltreatment is recommended.

◆ A thorough **history** should be obtained from the parent(s) optimally via separate interviews.

◆ Verbal children should be interviewed separately, in a developmentally appropriate manner. **Open-ended questions** (e.g., “Tell me what happened”) are best. Some children need more directed questioning (e.g., “How did you get that bruise?”); others need multiple-choice questions. Leading questions must be avoided (e.g., “Did your daddy hit you?”).

◆ A thorough **physical examination** is necessary.

◆ Careful **documentation** of the history and physical is essential. Verbatim quotes are valuable, including the question that prompted the response. Photographs are helpful.

◆ For **abuse** : What is the evidence for concluding abuse? Have other diagnoses been ruled out? What is the likely mechanism of the injury? When did the injury likely occur?

◆ For **neglect** : Do the circumstances indicate that the child's needs have not been adequately met? Is there evidence of actual harm? Is there evidence of potential harm and on what basis? What is the nature of the neglect? Is there a pattern of neglect?

◆ Are there indications of other forms of maltreatment? Has there been prior CPS involvement?

◆ A child's **safety** is a paramount concern. What is the risk of imminent harm, and of what severity?

◆ What is contributing to the maltreatment? Consider the categories described in the section on etiology.

◆ What **strengths/resources** are there? This is as important as identifying problems.

◆ What **interventions** have been tried, with what results? Knowing the nature of these interventions can be useful, including from the parent's perspective.

◆ What is the **prognosis** ? Is the family motivated to improve the circumstances and accept help, or resistant? Are suitable resources, formal and informal, available?

◆ Are there other children in the home who should be assessed for maltreatment?

General Principles for Addressing Child Maltreatment

The heterogeneity of circumstances also precludes specific details regarding how to address different types of maltreatment. The following are general principles.

◆ Treat any medical problems.

◆ Help ensure the child's **safety** , often in conjunction with CPS; this is a priority.

◆ Convey concerns of maltreatment to parents, kindly but forthrightly. Avoid blaming. It is natural to feel anger toward parents of maltreated children, but they need support and deserve respect.

◆ Have a means of addressing the difficult emotions child maltreatment can evoke.

◆ Be empathic, and state interest in helping or suggest another pediatrician.

◆ Know your national and state laws and/or local CPS policies on reporting child maltreatment. In the United States, the legal threshold for reporting is typically “reason to believe” (or similar language such as “reason to suspect”); one does not need to be certain. Physical abuse and moderate to severe neglect warrant a report. In less severe neglect, less intrusive interventions may be an appropriate initial response. For example, if an infant's mild failure to thrive is caused by an error in mixing the formula, parent education and perhaps a visiting nurse should be tried. In contrast, severe failure to thrive may require hospitalization, and if the contributing factors are particularly serious (e.g., psychotic mother), out-of-home placement may be needed. CPS can assess the home environment, providing valuable insights.

◆ Reporting child maltreatment is never easy. Parental inadequacy or culpability is at least implicit, and parents may express considerable anger. Child healthcare professionals should supportively inform families directly of the report; it can be explained as an effort to clarify the situation and provide help, as well as a professional (and legal) responsibility. Explaining what the ensuing process is likely to entail (e.g., a visit from a CPS worker and sometimes a police officer) may ease a parent's anxiety. Parents are frequently concerned that they might lose their child. Child healthcare professionals can cautiously reassure parents that CPS is responsible for helping children and families and that, in most instances, children remain with their parents. When CPS does not accept a report or when a report is not substantiated, they may still offer voluntary supportive services such as food, shelter, parenting resources, and childcare. Child healthcare professionals can be a useful liaison between the family and the public agencies and should try to remain involved after reporting to CPS.

◆ Help address contributory factors, prioritizing those most important and amenable to being remedied. Concrete needs should not be overlooked; accessing nutrition programs, obtaining health insurance, enrolling children in preschool programs, and help finding safe housing can make a valuable difference. Parents may need their own problems addressed to enable them to provide adequate care for their children.

◆ Establish specific **objectives** (e.g., no hitting, diabetes will be adequately controlled), with measurable **outcomes** (e.g., urine dipsticks, hemoglobin A1c). Similarly, advice should be specific and limited to a few reasonable steps. A written contract can be very helpful.

◆ Engage the family in developing the plan, solicit their input and agreement.

◆ Build on **strengths** ; there are always some. These provide a valuable way to engage parents.

◆ Encourage informal supports (e.g., family, friends; invite fathers to office visits). This is where most people get their support, not from professionals. Consider support available through a family's religious affiliation.

◆ Consider children's **specific needs** . Too often, maltreated children do not receive direct services.

◆ Be knowledgeable about community resources, and facilitate appropriate referrals.

◆ Provide support, follow-up, review of progress, and adjust the plan if needed.

◆ Recognize that maltreatment often requires long-term intervention with ongoing support and monitoring.

Outcomes of Child Maltreatment

Child maltreatment often has significant short- and long-term medical, mental health, and social sequelae. Physically abused children are at risk for many problems, including conduct disorders, aggressive behavior, posttraumatic stress disorder (PTSD), anxiety and mood disorders, decreased cognitive functioning, and poor academic performance. Neglect is similarly associated with many potential problems. Even if a maltreated child appears to be functioning well, healthcare professionals and parents need to be sensitive to the possibility of later problems. Maltreatment is associated with increased risk in adolescence and adulthood for health risk behaviors (e.g., smoking, alcohol/drug abuse), mental health problems (e.g., anxiety, depression, suicide attempt), physical health problems (e.g., heart disease, arthritis), and mental health problems. Maltreated children are at risk for becoming abusive parents. The neurobiologic effects of child abuse and neglect on the developing brain may partly explain some of these sequelae.

Some children appear to be resilient and may not exhibit sequelae of maltreatment, perhaps because of protective factors or interventions. The benefits of intervention have been found in even the most severely neglected children, such as those from Romanian orphanages, who were adopted—the earlier the better.

Prevention of Child Abuse and Neglect

An important aspect of prevention is that many of the efforts to strengthen families and support parents should promote children's health, development, and safety, as well as prevent child abuse and neglect. Medical responses to child maltreatment have typically occurred after the fact; preventing the problem is preferable. Child healthcare professionals can help in several ways. An ongoing relationship offers opportunities to develop trust and knowledge of a family's circumstances. Astute observation of parent–child interactions can reveal useful information.

Parent and child education regarding medical conditions helps to ensure implementation of the treatment plan and to prevent neglect. Possible barriers to treatment should be addressed. Practical strategies such as writing down the plan can help. In addition, anticipatory guidance may help with child rearing, diminishing the risk of maltreatment. Hospital-based programs that educate parents about infant crying and the risks of shaking the infant may help prevent abusive head trauma.

Screening for major psychosocial risk factors for maltreatment (depression, substance abuse, intimate partner violence, major stress), and helping address identified problems, often through referrals, may help prevent maltreatment. The primary care focus on prevention offers excellent opportunities to screen briefly for psychosocial problems. The traditional organ system–focused review of systems can be expanded to probe areas such as feelings about the child, the parent's own functioning, possible depression, substance abuse, intimate partner violence, disciplinary approaches, stressors, and supports. The **Safe Environment for Every Kid** (SEEK) model offers a promising approach for pediatric primary care to identify and help address prevalent psychosocial problems. This can strengthen families; support parents; promote children's health, development, and safety; and help prevent child maltreatment.

Obtaining information directly from children or youth is also important, especially given that separate interviews with teens have become the norm. Any concerns identified on such screens require at least brief assessment and initial management, which may lead to a referral for further evaluation and treatment. More frequent office visits can be scheduled for support and counseling while monitoring the situation. Other key family members (e.g., fathers) might be invited to participate, thereby encouraging informal support. Practices might arrange parent groups through which problems and solutions are shared.

Child healthcare professionals also need to recognize their limitations and facilitate referrals to other community resources. Finally, the problems underpinning child maltreatment, such as poverty, parental stress, substance abuse, and limited child-rearing resources, require policies and programs that enhance families' abilities to care for their children adequately. Child healthcare professionals can help advocate for such policies and programs.

Advocacy

Child healthcare professionals can assist in understanding what contributed to the child's maltreatment. When advocating for the best interest of the child and family, addressing risk factors at the individual, family, and community levels is optimal. At the individual level, an example of advocating on behalf of a child is explaining to a parent that an active toddler is behaving normally and not intentionally challenging the parent. Encouraging a mother to seek help dealing with a violent spouse (e.g., saying, “You and your life are very important”), asking about substance abuse, and helping parents obtain health insurance for their children are all forms of advocacy.

Efforts to improve family functioning, such as encouraging fathers’ involvement in child care, are also examples of advocacy. Remaining involved after a report to CPS and helping ensure appropriate services are provided is advocacy as well. In the community, child health professionals can be influential advocates for maximizing resources devoted to children and families. These include parenting programs, services for abused women and children, and recreational facilities. Lastly, child healthcare professionals can play an important role in advocating for policies and programs at the local, state, and national levels to benefit children and families. Child maltreatment is a complex problem that has no easy solutions. Through partnerships with colleagues in child protection, mental health, education, and law enforcement, child health professionals can make a valuable difference in the lives of many children and families.

16.1

Sexual Abuse

Wendy G. Lane, Howard Dubowitz

Keywords

chlamydia
hymen
nucleic acid amplification testing
NAAT
sexual abuse
sexual assault
sexually explicit behavior
sexually transmitted infection
STI

See also Chapter 145 .

Approximately 18% of females and 7% of males in the United States will be sexually abused at some point during their childhood. Whether children and families share this information with their pediatrician will depend largely on the pediatrician's comfort with and openness to discussing possible sexual abuse with families. Pediatricians may play a number of different roles in addressing sexual abuse, including identification, reporting to child protective services (CPS), testing for and treating sexually transmitted infections (STIs), and providing support and reassurance to children and families. Pediatricians may also play a role in the prevention of sexual abuse by advising parents and children about ways to help keep safe from sexual abuse. In many U.S. jurisdictions, general pediatricians will play a *triage* role, with the definitive medical evaluation conducted by a child abuse specialist.

Definition

Sexual abuse may be defined as any sexual behavior or action toward a child that is unwanted or exploitative. Some legal definitions distinguish sexual abuse from **sexual assault** : abuse being committed by a caregiver or household member, and assault being committed by someone with a noncustodial relationship or no relationship with the child. For this chapter, the term *sexual abuse* will encompass both abuse and assault. It is important to note that sexual abuse does not have to involve direct touching or contact by the perpetrator. Showing pornography to a child, filming or photographing a child in sexually explicit poses, and encouraging or forcing one child to perform sex acts on another all constitute sexual abuse.

Presentation of Sexual Abuse

Children who have been sexually abused sometimes provide a clear, spontaneous disclosure to a trusted adult. Often the signs of sexual abuse are subtle. For some children, behavioral changes are the first indication that something is amiss. **Nonspecific behavior changes** such as social withdrawal, acting out, increased clinginess or fearfulness, distractibility, and learning difficulties may be attributed to a variety of life changes or stressors. Regression in developmental milestones, including new-onset bed-wetting or encopresis, is another behavior that caregivers may overlook as an indicator of sexual abuse. Teenagers may respond by becoming depressed, experimenting with drugs or alcohol, or running away from home. Because nonspecific symptoms are very common among children who have been sexually abused, it should almost always be included in one's differential diagnosis of child behavior changes.

Some children may not exhibit behavioral changes or provide any other indication that something is wrong. For these children, sexual abuse may be discovered when another person witnesses the abuse or discovers evidence such as sexually explicit photographs or videos. Pregnancy may be another way that sexual abuse is identified. Other children, some with and some without symptoms, will not be identified at any point during their childhood.

Caregivers may become concerned about the possibility of sexual abuse when children exhibit **sexually explicit behavior** . This behavior includes that which is outside the norm for a child's age and developmental level. For preschool and school-age children, sexually explicit behavior may include compulsive masturbation, attempting to perform sex acts on adults or other children, or asking adults or children to perform sex acts on them. Teenagers may become sexually promiscuous and even engage in prostitution. Older children and teenagers may respond by sexually abusing younger children. It is important to recognize that this behavior could also result from accidental exposure (e.g., child enters parents’ bedroom at night and sees them having sex), or from neglect (e.g., adults watching pornographic movies where a child can see them).

Role of General Pediatrician in Assessment and Management of Possible Sexual Abuse

Before determining where and how a child with suspected sexual abuse is evaluated, it is important to assess for and rule out any medical problems that can be confused with abuse. A number of **genital findings** may raise concern about abuse but often have alternative explanations. Genital redness in a prepubertal child is more often caused by nonspecific vulvovaginitis, eczema, or infection with staphylococcus, group A streptococcus, *Haemophilus* , or yeast. Lichen sclerosis is a less common cause of redness. Vaginal discharge can be caused by STIs, but also by poor hygiene, vaginal foreign body, early in the onset of puberty, or infection with *Salmonella* , *Shigella* , or *Yersinia* . Genital ulcers can be caused by herpes simplex virus (HSV) and syphilis, but also by

Epstein-Barr virus, varicella-zoster virus, Crohn disease, and Behçet disease. Genital bleeding can be caused by urethral prolapse, vaginal foreign body, accidental trauma, and vaginal tumor.

Although other medical conditions may need to be evaluated, any possible sexual abuse should be investigated (Fig. 16.10). Where and how a child with suspected sexual abuse is evaluated should be determined by duration since the last incident of abuse likely occurred, and whether the child is prepubertal or postpubertal. For the *prepubertal child* , if abuse has occurred in the previous 72 hr, and history suggests direct contact, forensic evidence collection (e.g., external genital, vaginal, anal, and oral swabs, sometimes referred to as a “rape kit”) is indicated, and the child should be referred to a site equipped to collect forensic evidence. Depending on the jurisdiction, this site may be an emergency department (ED), a child advocacy center, or an outpatient clinic. If the last incident of abuse occurred >72 hr prior, the likelihood of recovering forensic evidence is extremely low, making forensic evidence collection unnecessary. For *postpubertal females* , many experts recommend forensic evidence collection up to 120 hr following the abuse—the same time limit as for adult women. The extended time frame is justified because some studies have demonstrated that semen can remain in the postpubertal vaginal vault for >72 hr.

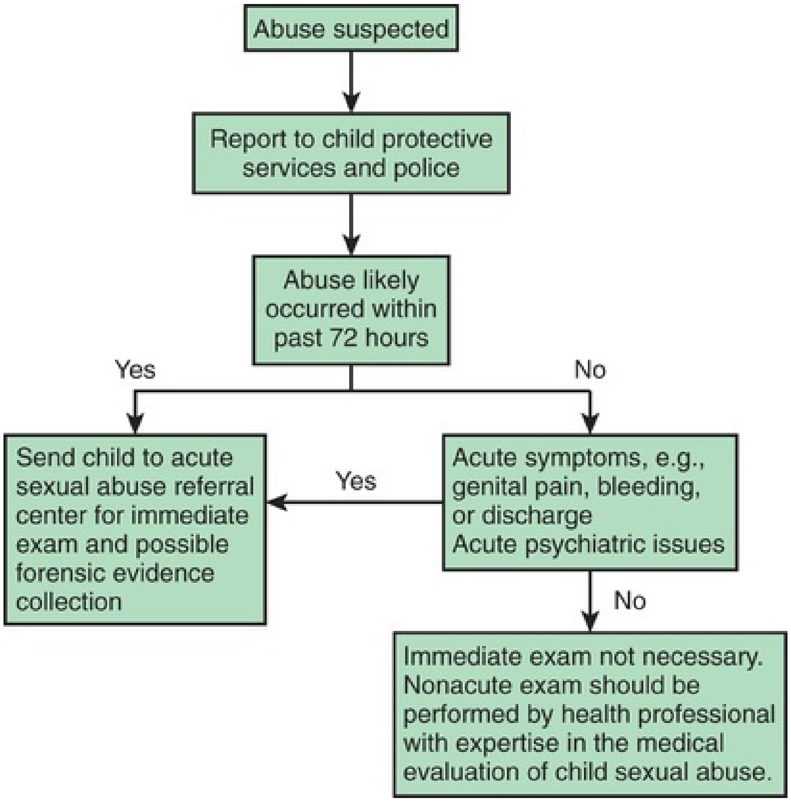
Abuse suspected
Report to child protective services and police
Abuse likely occurred within past 72 hours
Yes
No
Send child to acute sexual abuse referral center for immediate exam and possible forensic evidence collection
Yes
Acute symptoms, e.g., genital pain, bleeding, or discharge
Acute psychiatric issues
No
Immediate exam not necessary. Nonacute exam should be performed by health professional with expertise in the medical evaluation of child sexual abuse.

FIG. 16.10 Triage protocol for children with suspected sexual abuse.

The site to which a child is referred may be different when the child does not present until after the cutoff for an acute examination. Because EDs may not have a child abuse expert and can be busy, noisy, and lacking in privacy, examination at an alternate location such as a child advocacy center or outpatient clinic is recommended. If the exam is not urgent, waiting until the next morning is recommended because it is easier to interview and examine a child who is not tired and cranky. Referring physicians should be familiar with the triage procedures in their communities, including the referral sites for both acute and chronic exams, and whether there are separate referral sites for prepubertal and postpubertal children.

Children with suspected sexual abuse may present to the pediatrician's office with a clear disclosure of abuse or subtler indicators. A private, brief conversation between pediatrician and child can provide an opportunity for the child to speak in his or her own words without the parent speaking for the child. Doing this may be especially important when the caregiver does not believe the child, or is unwilling or unable to offer emotional support and protection. Telling caregivers that a private conversation is part of the routine assessment for the child's concerns can help comfort a hesitant parent.

When speaking with the child, experts recommend establishing rapport by starting with general and open-ended questions, such as, “Tell me about school,” and “What are your favorite things to do?” Questions about sexual abuse should be nonleading (e.g., “Who touched you there?”). A pediatrician should explain that sometimes children are hurt or bothered by others, and that he or she wonders whether that might have happened to the child. Open-ended questions, such as, “Can you tell me more about that?” allow the child to provide additional information and clarification in his or her own words. It is not necessary to obtain extensive information about what happened because the child will usually have a forensic interview once a report is made to CPS and an investigation begins. Very young children and those with developmental delay may lack the verbal skills to describe what happened. In this situation the caregiver's history may provide enough information to warrant a report to CPS without interviewing the child.

All 50 U.S. states mandate that professionals report suspected maltreatment to CPS. The specific criteria for “reason to suspect” are generally not defined by state law. It is clear that *reporting does not require certainty that abuse has occurred.* Therefore, it may be appropriate to report a child with sexual behavior concerns when no accidental sexual exposure can be identified, and when the child does not clearly confirm or deny abuse.

Physical Examination of the Child With Suspected Sexual Abuse

Unfortunately, many physicians are unfamiliar with genital anatomy and examination, particularly in the prepubertal child (Figs. 16.11 and 16.12). Because about 95% of children who undergo a medical evaluation following sexual abuse have normal examinations, the role of the primary care provider is often simply to be able to distinguish a normal exam from findings indicative of common medical concerns or trauma. The absence of physical findings can often be explained by the type and timing of sexual contact that has occurred. Abusive acts such as fondling, or even digital penetration, can occur without causing injury. In addition, many children do not disclose abuse until days, weeks, months, or even years after the abuse has occurred. Because genital injuries usually heal rapidly, injuries are often completely healed by the time a child presents for medical evaluation. A normal genital examination does not rule out the possibility of abuse and should not influence the decision to report to CPS.

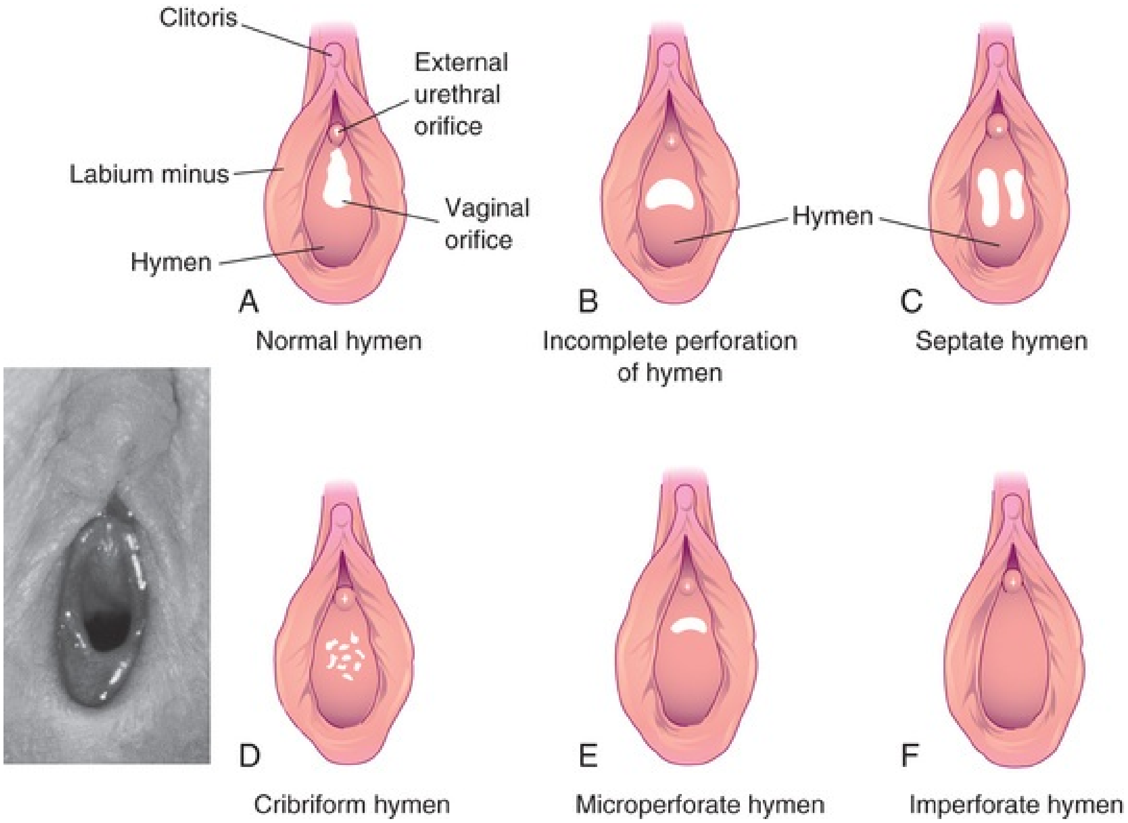
Clitoris
External urethral orifice
Labium minus
Vaginal orifice
Hymen
Hymen
A
Normal hymen
B
Incomplete perforation of hymen
C
Septate hymen
D
Cribriform hymen
E
Microperforate hymen
F
Imperforate hymen

FIG. 16.11 Congenital anomalies of the hymen. A-F, Different types of hymen abnormalities. Photograph shows a normal hymen, as in A. (From Moore KL, Persaud TVN. The developing human, ed 7, Philadelphia, 2003, Elsevier.)

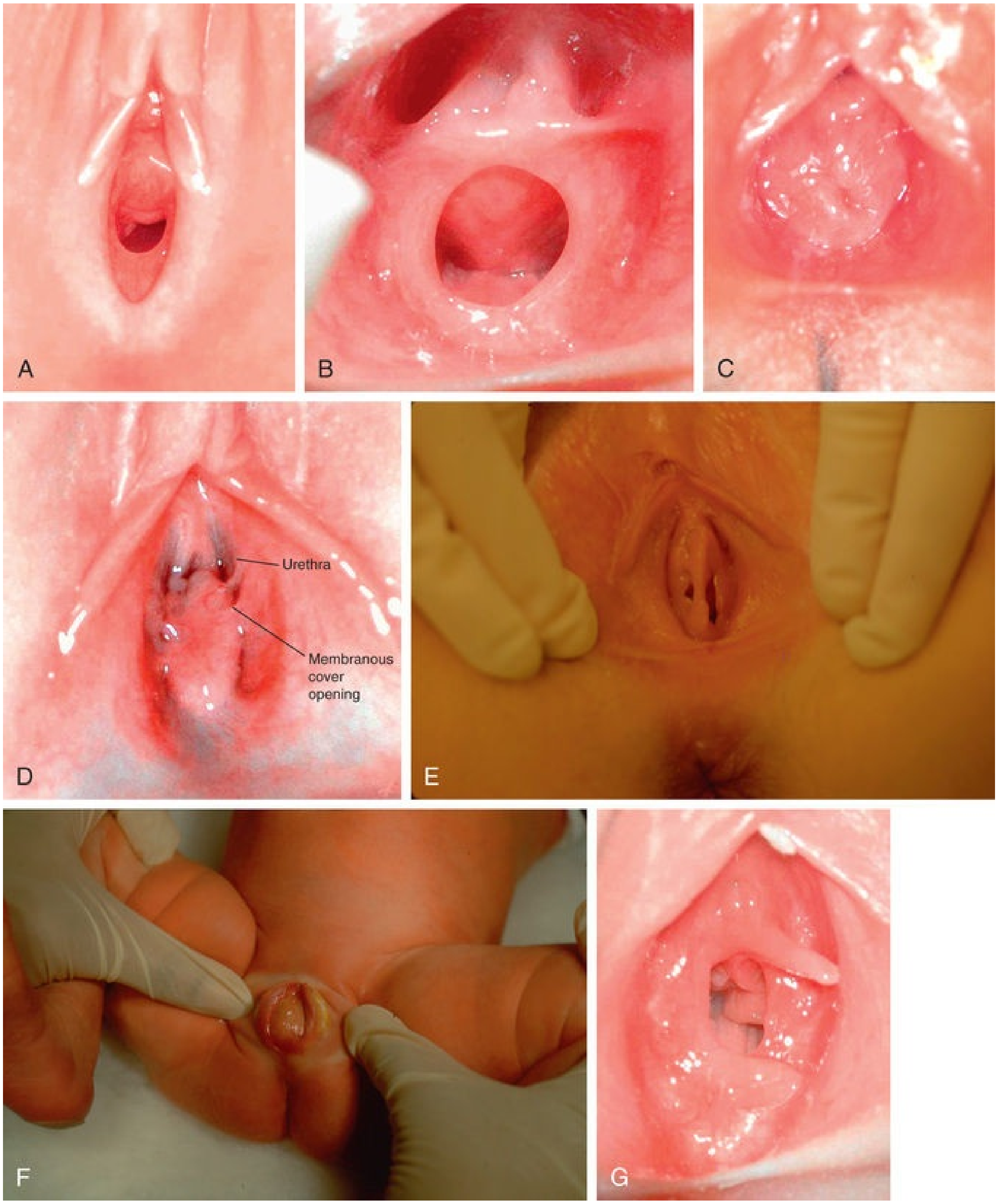

FIG. 16.12 Types of hymens. A, Crescentic. B, Annular. C, Redundant. D, Microperforate. E, Septated. F, Imperforate. G, Hymeneal tags. (A-F, From Perlman SE, Nakajima ST, Hertweck SP. Clinical protocols in pediatric and adolescent gynecology, London, 2004, Parthenon Publishing Group; G, From McCann JJ, Kerns DL. The anatomy of child and adolescent sexual abuse, St. Louis, 1999, InterCorp.)

Even with the high proportion of normal genital exams, there is value in conducting a thorough physical examination. Unsuspected injuries or medical problems, such as labial adhesions, imperforate hymen, or urethral prolapse, may be identified. In addition, reassurance about the child's physical health may allay anxiety for the child and family.

Few findings on the genital examination are diagnostic for sexual abuse. In the acute time frame, lacerations or bruising of the labia, penis, scrotum, perianal tissues, or perineum are indicative of trauma. Likewise, hymenal bruising and lacerations and perianal lacerations extending deep to the external anal sphincter indicate penetrating trauma. In the nonacute time frame, perianal scars and scars of the posterior fourchette or fossa indicate trauma and/or sexual activity. A complete transection of the hymen to the base between the 4 and 8 o'clock in the supine position (i.e., absence of hymenal tissue in the posterior rim) is considered diagnostic for trauma (Fig. 16.12). For these findings, the cause of injury must be elucidated through the child and caregiver history. If there is any concern that the finding may be the result of sexual abuse, CPS should be notified and a medical evaluation performed by an experienced child abuse pediatrician.

Testing for STIs is not indicated for all children but is warranted in certain situations (Table 16.5). *Culture* was once considered the gold standard for the diagnosis of vaginal gonorrhea (see Chapter 219) and chlamydia (Chapter 252) infections in children. However, several studies demonstrated that *nucleic acid amplification testing* (NAAT) for gonorrhea and chlamydia by either vaginal swab or urine in prepubertal females is as sensitive, and possibly more sensitive, than culture. Current guidelines from the Centers for Disease Control and Prevention (CDC) allow for NAAT testing by vaginal swab or urine as an alternative to culture in females. Because obtaining vaginal swabs can be uncomfortable for prepubertal children, urine testing is preferable. Culture remains the preferred method for testing of rectal and pharyngeal specimens in males and females. Few data are available on the use of urine NAAT testing in prepubertal boys. Therefore the CDC continues to recommend urine or urethral culture for boys. Many child abuse experts perform urine NAAT testing on prepubertal boys because urethral swabs are uncomfortable, and good data support urine NAAT testing in females. For all NAAT testing in both genders, the child should *not* receive presumptive treatment at testing. Instead, a positive NAAT test should be confirmed by culture or an alternate NAAT test before treatment. Because gonorrhea and chlamydia in prepubertal children do not typically cause ascending infection, waiting for a definitive diagnosis before treatment will not increase the risk for pelvic inflammatory disease. Testing for

Trichomonas vaginalis is by culture (Diamond media or InPouch; Biomed Diagnostics, White City, OR) or wet mount. *Wet mount* requires the presence of vaginal secretions, viewing must be immediate for optimal results, and sensitivity is only 44–68%; therefore false-negative tests are common. Experts have determined that insufficient data exist to recommend commercially available *Trichomonas* NAATs for prepubertal children. However, there is also no reason to suspect that test performance in children would be different from adults.

Table 16.5

Indications for STI Screening in Children With Suspected Sexual Abuse

1. Child has experienced penetration or has evidence of recent or healed penetrative injury to the genitals, anus, or oropharynx.
2. Child has been abused by a stranger.
3. Child has been abused by a perpetrator known to be infected with a sexually transmitted infection (STI) or at high risk for STIs (e.g., intravenous drug abusers, men who have sex with men, persons with multiple sexual partners, those with a history of STIs).
4. Child has a sibling, other relative, or another person in the household with an STI.
5. Child lives in an area with a high rate of STI in the community.
6. Child has signs or symptoms of STIs (e.g., vaginal discharge or pain, genital itching or odor, urinary symptoms, genital lesions or ulcers).
7. Child or parent requests STI testing.

From Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2015, *MMWR* 64(RR3):1–137, 2015.

A number of STIs should raise concern for abuse (Table 16.6). In a prepubertal child, **gonorrhea** or **syphilis** beyond the neonatal period indicates that the child has had some contact with infected genital secretions, almost always as a result of sexual abuse. There is some evidence to indicate that **chlamydia** in children up to 3 yr of age may be perinatally acquired. Chlamydia in children >3 yr old is diagnostic of contact with infected genital secretions, almost always a result of sexual abuse. In children <3 yr old, sexual abuse should still be strongly considered beyond the neonatal period. **HIV** is diagnostic for sexual abuse if other means of transmission have been excluded. Because of the potential for transmission either perinatally or through nonsexual contact, the presence of **genital warts** has a low specificity for sexual abuse. The possibility of sexual abuse should be considered and addressed with the family, especially in children whose warts first appear beyond 5 yr of age. Type 1 or 2 genital herpes is concerning for sexual abuse, but not diagnostic given other possible routes of transmission. For human papillomavirus (HPV) and HSV, the American Academy of Pediatrics (AAP) recommends reporting to CPS unless perinatal or horizontal transmission is considered likely.

Table 16.6

Implications of Commonly Encountered Sexually Transmitted or Sexually Associated Infections for Diagnosis and Reporting of Sexual Abuse Among Infants and Prepubertal Children

ST/SA CONFIRMED	EVIDENCE FOR SEXUAL ABUSE	SUGGESTED ACTION
Gonorrhea*	Diagnostic	Report †
Syphilis*	Diagnostic	Report †
HIV ‡	Diagnostic	Report †
Chlamydia trachomatis *	Diagnostic	Report †
Trichomonas vaginalis *	Highly suspicious	Report †
Genital herpes	Highly suspicious (HSV-2 especially)	Report † , §
Condylomata acuminata (anogenital warts)*	Suspicious	Consider report † , § , **
Bacterial vaginosis	Inconclusive	Medical follow-up

[*] If not likely to be perinatally acquired, and rare vertical transmission is excluded.

[†] Reports should be made to the agency in the community mandated to receive reports of suspected child abuse or neglect.

[‡] If not likely to be acquired perinatally or through transfusion.

[§] Unless a clear history of autoinoculation exists.

[**] Report if evidence exists to suspect abuse, including history, physical examination, or other identified infections.

HIV, Human immunodeficiency virus; HSV, herpes simplex virus; SA, sexually associated; ST, sexually transmitted.

From Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2015, *MMWR* 64(RR3):1-137, 2015 (Table 6).

Additional Management

Because HIV testing identifies antibodies to the virus and not the human immunodeficiency virus itself, and because it may take several months for seroconversion, repeat testing at 6 wk and 3 mo after the last suspected exposure is indicated. Repeat testing for syphilis is also recommended. Hepatitis B and HPV vaccination (for children ≥9 yr) should be given if the child has not been previously vaccinated or vaccination is incomplete.

Sexual Abuse Prevention

Pediatricians can play a role in the prevention of sexual abuse by educating parents and children about sexual safety at well-child visits. During the genital exam the pediatrician can inform the child that only the doctor and select adult caregivers should be permitted to see their private parts, and that a trusted adult should be told if anyone else attempts to do so. Pediatricians can raise parental awareness that older kids or adults may try to engage in sexual behavior with children. The pediatrician can teach parents how to minimize the opportunity for perpetrators to access children, for example, by limiting one-adult/one-child situations and being sensitive to any adult's unusual interest in young children. In addition, pediatricians can help parents talk to children about what to do if confronted with a potentially abusive situation. Some examples include telling children to say “no,” to leave, and to tell a parent and/or another adult. If abuse does occur, the pediatrician can tell parents how to recognize possible signs and symptoms, and how to reassure the child that she or he was not at fault. Lastly, pediatricians can provide parents with suggestions about how to maintain open communication with their children so that these conversations can occur with minimal parent and child discomfort.

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16.2

Medical Child Abuse (Factitious Disorder by Proxy, Munchausen Syndrome by Proxy)

Howard Dubowitz, Wendy G. Lane

Keywords

apnea
bleeding
factitious disorder by proxy
MCA
medical child abuse
Munchausen syndrome by proxy
recurrent sepsis
seizures

The term *Munchausen syndrome* is used to describe situations in which adults falsify their own symptoms. In *Munchausen syndrome by proxy* , a parent, typically a mother, simulates or causes disease in her child. Several terms have been suggested to describe this phenomenon: factitious disorder by proxy, pediatric condition falsification, and currently, **medical child abuse (MCA)** . In some instances, such as partial suffocation, child abuse may be most appropriate.

The core dynamic of MCA is that a parent falsely presents a child for medical attention. This may occur by fabricating a history, such as reporting seizures that never occurred. A parent may directly cause a child's illness, by exposing a child to a toxin, medication, or infectious agent (e.g., injecting stool into an intravenous line). Signs or symptoms may also be manufactured, such as when a parent smothers a child, or alters laboratory samples or temperature measurements. Each of these actions may lead to unnecessary medical care, sometimes including intrusive tests and surgeries. The “problems” often recur repeatedly over several years. In addition to the physical concomitants of testing and treatment, there are potentially serious and lasting social and psychological sequelae.

Child healthcare professionals are typically misled into thinking that the child really has a medical problem. Parents, sometimes working in a medical field, may be adept at constructing somewhat plausible presentations. A convincing seizure history may be offered, and a normal electroencephalogram (EEG) cannot fully rule out the possibility of a seizure disorder. Even after extensive testing fails to lead to a diagnosis or treatment proves ineffective, health professionals may think they are confronting a new or rare disease. Unwittingly, this can lead to continued testing (leaving no stone unturned) and interventions, thus perpetuating the MCA. Pediatricians generally rely on and trust parents to provide an accurate history. As with other forms of child maltreatment, an accurate diagnosis of MCA requires that the pediatrician maintain a healthy skepticism under certain circumstances.

Clinical Manifestations

The presentation of MCA may vary in nature and severity. Consideration of MCA should be triggered when the reported symptoms are repeatedly noted by only 1 parent, appropriate testing fails to confirm a diagnosis, and seemingly appropriate treatment is ineffective. At times, the child's symptoms, their course, or the response to treatment may be incompatible with any recognized disease. Preverbal children are usually involved, although older children may be convinced by parents that they have a particular problem and become dependent on the increased attention; this may lead to feigning symptoms.

Symptoms in young children are mostly associated with proximity of the offending caregiver to the child. The mother may present as a devoted or even model parent who forms close relationships with members of the healthcare team. While appearing very interested in her child's condition, she may be relatively distant emotionally. She may have a history of Munchausen syndrome, although not necessarily diagnosed as such.

Bleeding is a particularly common presentation. This may be caused by adding dyes to samples, adding blood (e.g., from the mother) to the child's sample, or giving the child an anticoagulant (e.g., warfarin).

Seizures are another common manifestation, with a history easy to fabricate, and the difficulty of excluding the problem based on testing. A parent may report that another physician diagnosed seizures, and the myth may be continued if there is no effort to confirm the basis for the “diagnosis.” Alternatively, seizures may be induced by toxins, medications (e.g., insulin), water, or salts. Physicians need to be familiar with the substances available to families and the possible consequences of exposure.

Apnea is also a common presentation. The observation may be falsified or created by partial suffocation. A history of a sibling with the same problem, perhaps dying from it, should be cause for concern. Parents of children hospitalized for brief resolved unexplained events (or apparent life-threatening events) have been videotaped attempting to suffocate their child while in the hospital.

Gastrointestinal signs or symptoms are another common manifestation. Forced ingestion of medications such as ipecac may cause chronic vomiting, or laxatives may cause diarrhea.

The **skin** , easily accessible, may be burned, dyed, tattooed, lacerated, or punctured to simulate acute or chronic skin conditions. **Recurrent sepsis** may be caused by infectious agents being administered; intravenous lines during hospitalization may provide a convenient portal. Urine and blood samples may be contaminated with foreign blood or stool.

Diagnosis

In assessing possible MCA, several explanations should be considered in addition to a true medical problem. Some parents may be extremely anxious and genuinely concerned about possible problems. This anxiety may result from a personality trait, the death of neighbor's child, or something read on the internet. Alternatively, parents may believe something told to them by a trusted physician despite subsequent evidence to the contrary and efforts to correct the earlier misdiagnosis. Physicians may unwittingly contribute to a parent's belief that a real problem exists by, perhaps reasonably, persistently pursuing a medical diagnosis. There is a need to discern commonly used hyperbole (e.g., exaggerating height of fever) in order to evoke concern and perhaps justify an ED visit. In the end, a diagnosis of MCA rests on clear evidence of a child repeatedly being subjected to unnecessary medical tests and treatment, primarily stemming from a parent's actions. Determining the parent's underlying psychopathology is the responsibility of mental health professionals.

Once MCA is suspected, gathering and reviewing **all** the child's medical records from all sources is an onerous but critical first step. It is often important to confer with other treating physicians about what specifically was conveyed to the family. A mother may report that the child's physician insisted that a certain test be done, when instead it was the mother who demanded the test. It is also necessary to confirm the basis for a given diagnosis, rather than simply accepting a parent's account.

Pediatricians may face the dilemma of when to accept that all plausible diagnoses have been reasonably ruled out, the circumstances fit MCA, and further testing and treatment should cease. The likelihood of MCA must be balanced with concerns about possibly missing an important diagnosis. Consultation with a pediatrician expert in child abuse is recommended. In evaluating possible MCA, specimens should be carefully collected, with no opportunity for tampering with them. Similarly, temperature measurements should be closely observed.

Depending on the severity and complexity, hospitalization may be needed for careful observation to help make the diagnosis. In some instances, such as repeated apparent life-threatening events, covert video surveillance accompanied by close monitoring (to rapidly intervene in case a parent attempts to suffocate a child) can be valuable. Close coordination among hospital staff is essential, especially since some may side with the mother and resent even the possibility of MCA being raised. Parents should not be informed of the evaluation for MCA until the diagnosis is made. Doing so could naturally influence their behavior and jeopardize establishing the diagnosis. All steps in making the diagnosis and all pertinent information should be very carefully documented, perhaps using a “shadow chart” to which the parent does not have access.

Treatment

Once the diagnosis is established, the medical team and CPS should determine the treatment plan, which may require out-of-home placement and should include mental healthcare for the offending parent as well as for other affected children. Further medical care should be carefully organized and coordinated by one primary care provider. CPS should be encouraged to meet with the family only after the medical team has informed the offending parent of the diagnosis; their earlier involvement may hamper the evaluation. Parents often respond with resistance, denial, and threats. It may be prudent to have hospital security in the vicinity.

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CHAPTER 17

Strategies for Health Behavior Change

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To improve the health of children, pediatricians often ask patients and caregivers to make behavioral changes. These may be lifestyle changes to manage a chronic condition (e.g., obesity, asthma), adherence with the recommended timing and frequency of medications, or recommendations to seek assistance from other health providers (e.g., dieticians, mental health providers, physical, occupational, or speech therapists). However, change is difficult and can cause distress, and families often express reluctance or ambivalence to change due to perceived barriers. When families do not believe change is needed or possible, pediatricians may become discouraged or uncomfortable in providing care. This can make it difficult for clinicians to form an alliance with families, which is central to finding a solution to most problems identified in the medical setting.

Many healthcare problems may require complex, multifaceted interventions, but the first step is always to engage the family in identifying the healthcare problem driving the need for behavior change. Once a problem is identified and agreed on, clinicians and families need to set an achievable goal and identify specific behaviors that can help families reach their goal. It is important to be specific and precise about the actual behavior and not simply identify the *category* of the behavior. When counseling a patient on weight loss for obesity, for example, one might discuss 3 possible approaches: making dietary changes, increasing exercise, and decreasing screen time. The choice of which behavior to focus on should come from the patient but needs to be specific. It is not enough for the patient to state he will exercise more. Instead, the clinician should help the patient identify a more specific goal, such as playing basketball with his friends 3 times a week at the park near home. This takes in to account the action, context, setting, and time of the new behavioral goal. Specific examples of problems that would necessitate a behavior change to improve outcomes are used throughout the chapter.

Unified Theory of Behavior Change

There are several theories of health-related behavior change. Each highlights a different concept, but frameworks that unite these theories suggest that the factor most predictive of whether one will perform a behavior is the *intention* to do so. The **unified theory of behavior change** examines behavior along 2 dimensions: influences on intent and moderators of the intention-behavior relationship (Fig. 17.1). Five main factors that influence one's decision to perform a behavior are expectancies, social norms/normative influences, self-concept/self-image, emotions, and self-efficacy. Table 17.1 provides specific examples on how to explore influences of intent when guiding families in decision-making, such as deciding to start a stimulant medication for a child diagnosed with attention-deficit/hyperactivity disorder (ADHD). It is not necessary to ask about each influence, but these principles are particularly useful when guiding patients who may be resistant to change.

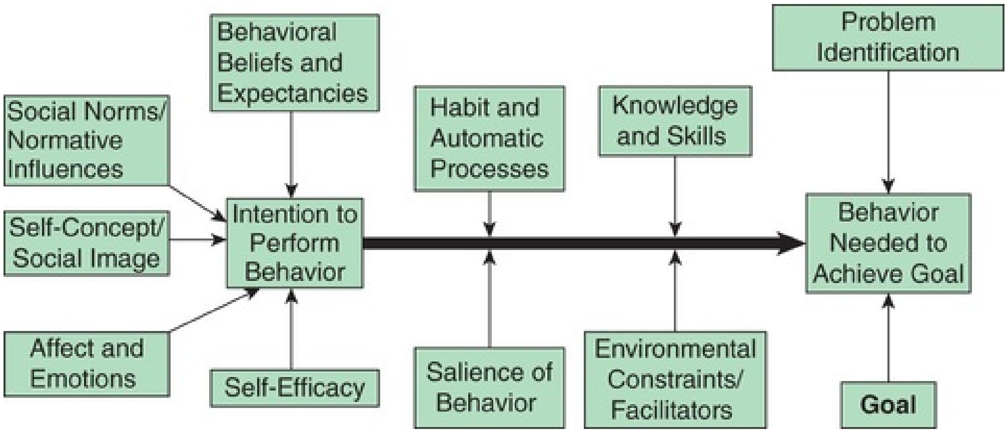
Behavioral Beliefs and Expectancies
Problem Identification
Social Norms/ Normative Influences
Habit and Automatic Processes
Knowledge and Skills
Self-Concept/ Social Image
Intention to Perform Behavior
Behavior Needed to Achieve Goal
Affect and Emotions
Self-Efficacy
Salience of Behavior
Environmental Constraints/ Facilitators
Goal

FIG. 17.1 The 5 constructs that influence one's intent to perform a behavior and the 4 influences that determine whether an intent will lead to performing the behavior. Problem identification (*box* at upper right) is where the process of thinking about health behavior changes begins. A clinician can then help the patient decide on which behavior can help the patient to meet the health goal. Once this is decided, to help with behavior change, clinicians should think about intent, influences of intent, and the factors that may facilitate or impede intent from leading to action.

Table 17.1

Influences of Intent and Possible Use During a Patient Encounter (Specifically, Starting Stimulant for ADHD)

INFLUENCE OF INTENT	STRATEGIES TO ENGAGE FAMILIES USING INFLUENCES OF INTENT	POSSIBLE FACTORS INFLUENCING THE DECISION
Beliefs and expectancies Perceived advantages and disadvantages of performing a behavior.	Ask questions about their beliefs and experiences. “What do you know already know about stimulants?” “Have you heard about other children's experiences taking stimulants?” “What do you expect will happen if your child takes a stimulant?” Ask permission to give information addressing their prior beliefs or experiences. “Is it all right if I give you some information addressing your concerns?”	“I know that stimulants helped my nephew do better in school.” “I heard stimulants stunt children's growth.”
Social norms Pressures to (or not) perform a behavior because of what is standard among social groups.	Share information about the normative nature of the behavior and ways to cope if performing a behavior that is not the social norm. “I have a lot of patients who have improved in school after starting a stimulant.”	“Do other parents give their children stimulants if they are diagnosed with ADHD?” “What would my mother think if she found out my child was taking a stimulant?”
Self-concept/self-image Overall sense of self and whether behavior is congruent with that and with the image they want to project to others.	Interact with family in a partnering, supportive, respectful manner. Identify strengths. Reframe any negative images they foresee may happen with the behavior. “I am sure your in-laws will be so happy when your child is doing better in school.”	“Am I a good parent if I give my child medications that affect his brain?” “What will other parents at school think if I allow my child to start a stimulant? What will my in-laws think?”
Emotions Emotional reactions to performing behaviors, in intensity and direction (positive or negative).	Allow patients to express their feelings. Suggest ways to manage negative or avoidant feelings. “Many parents are scared to start stimulants at first. However, once their child is succeeding in school, they realize the benefits outweighed the risks. Let's talk more about your fears.”	“I am so nervous about my child starting to take a stimulant.” “I am so upset with how my child is doing in school and really do not know what to do next.” “I am so relieved that there is a medication that may help improve my child's grades and chance of going to college.”
Self-efficacy Perceived confidence they can perform the behavior.	Provide information, model the behavior, encourage success, and teach skills. Explore what obstacles they foresee and how confident they are they can overcome obstacles. Help	“Will I be able to remember to give my child his medication every day?”

	strategize ways to overcome obstacles. “Do you feel confident you will be able to get your child to take the medication?” “Let's brainstorm how we can prevent any of the side effects.” “Many of my patients have a large breakfast before taking the medication. Can I help you figure out how to fit that into your schedule?”	“Will I be able to make sure my child has a large breakfast in the morning before taking her medication?”

ADHD, Attention-deficit/hyperactivity disorder.

Once a decision to make a change is made, 4 factors determine whether an intention leads to carrying out the behavior: knowledge and skills, environmental facilitators and constraints, salience of the behavior, and habits. The pediatrician can help ensure intent leads to behavior change by addressing these factors during the visit. In the ADHD example, the clinician can help the family build their knowledge by providing handouts on stimulants, nutritional pamphlets on how to minimize the appetite-suppressant effects of the medication on weight, and information on how the family can explain to others the need for medication. Asking about morning routines will help identify potential barriers in remembering to take the medication. Lastly, clinicians can help families think about cues for remembering to give the medication in the morning, since their morning routines, or habits, will have to be adjusted to adhere to this medication.

By using these principles of behavior change, pediatricians can guide their patients toward change during an encounter by ensuring they leave with (1) a strong positive intention to perform the behavior; (2) the perception that they have the skills to accomplish it; (3) a belief that the behavior is socially acceptable and consistent with their self-image; (4) a positive feeling about the behavior; (5) specific strategies in overcoming potential barriers in performing the behavior; and (6) a set of identified cues and enablers to help build new habits.

Transtheoretical Model of Health Behavior Change

It is difficult to counsel families to change a behavior when they may not agree there is a problem or when they are not ready to build an intention to change. The **transtheoretical model of health behavior change** places an individual's motivation and readiness to change on a continuum. The premise of this model is that behavior change is a process, and as someone attempts to change, they move through 5 stages (although not always in a linear fashion): *precontemplation* (no current intention of making a change), *contemplation* (considering change), *preparation* (creating an intention, planning, and committing to change), *action* (has changed behavior for a short time), and *maintenance* (sustaining long-term change). Assessing a patient's stage of change and then targeting counseling toward that stage can help build a *therapeutic alliance* , in contrast to counseling a patient to do something she is not ready for, which can disrupt therapeutic alliance and lead to resistance. Table 17.2 further describes stages of change and gives examples for counseling that targets the adolescent's stage of change in reducing marijuana smoking.

Table 17.2

Stages of Change and Strategies for Counseling*

STAGE/DEFINITION	GOAL AND STRATEGY	SPECIFIC EXAMPLES
Precontemplation Not considering change. May be unaware that a problem exists.	Establish a therapeutic relationship. Increase awareness of need to change.	“I understand you are only here because your parents are worried and that you don't feel that smoking marijuana is a big deal.” “Can I ask if smoking marijuana has created any problems for you now? I know your parents were worried about your grades.” “It's up to you to decide if and when you are ready to cut back on smoking marijuana.” “Is it okay if I give you some information about marijuana use?” “I know it can be hard to change a habit when you feel under pressure. It is totally up to you to decide if cutting back is right for you. Is it okay if I ask you about this during our next visit?”
Contemplation Beginning to consider making a change, but still feeling ambivalent about making a change.	Identify ambivalence. Help develop discrepancy between goals and current behaviors. Ask about pros and cons of changing problem behavior. Support patient toward making a change.	“I'm hearing that you do agree that sometimes your marijuana use does get in the way, especially with school. However, it helps relax you and it would be hard to make a change right now.” “What would be one benefit of cutting back? What would be a drawback to cutting back? Do you think your smoking will cause problems in the future?” “After talking about this, if you feel you want to cut back, the next step would be to think about how to best do that. We wouldn't need to jump right into a plan. Why don't you think about what we discussed, and we can meet next week if you are ready to make a plan?”

Preparation Preparing for action. Reduced ambivalence and exploration of options for change.	Help patient set a goal and prepare a concrete plan. Offer a menu of choices. Identify supports and barriers.	“It's great that you are thinking about ways to cut back on your smoking. I understand your initial goal is to stop smoking during the week.” “I can give you some other options of how to relax and reduce stress during the week.” “We need to figure out how to react to your friends after school who you normally smoke with.” “Do you have other friends who you can see after school instead, who would support this decision?”
Action Taking action; actively implementing plan.	Provide positive feedback. Identify unexpected barriers and create coping strategies.	“Congratulations on cutting back. Have you noticed any differences in your schoolwork? I'm so happy to hear your grades improved.” “Has it been difficult to not see your friends after school? How have you reacted when they get annoyed you don't want to smoke with them?” “Let's continue to track your progress.”
Maintenance Continues to change behavior and maintains healthier lifestyle.	Reinforce commitment and affirm ability to change. Create coping plans when relapse does occur. Manage triggers.	“You really are committed to going to a good college and improving your grades. I'm so happy the hard work has paid off.” “I understand that it was hard to say no to smoking with your friends last week when it was someone's birthday. How did you feel after? Are there triggers that we can think about preventing in the future?”

[*] This table uses an example of an adolescent who is initially resistant to cutting back on smoking marijuana. His parents caught him smoking in his room and arranged for him to see the pediatrician.

Adapted from *Implementing mental health priorities in practice: substance use,* American Academy of Pediatrics. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/substance-use.aspx .

Common Factors Approach

Conversations around behavior change are most effective when they take place in a context of a trusting, mutually respectful relationship. The traditional medical model assumes that patients and their families come with questions and needs, and that the pediatrician's job is to offer specific advice and advocate for its acceptance. This approach fails when families are reluctant, ambivalent, demoralized, or unfamiliar with the healthcare system or the treatment choices offered. A context more supportive of behavior change can be developed when pediatricians use communication strategies that facilitate collaboration and building therapeutic alliance.

The **common factors approach** is an evidence-based communication strategy that is effective in facilitating behavior change. The skills central to a common factors approach are consistent across multiple forms of psychotherapy and can be viewed as generic aspects of treatment that can be used across a wide range of symptoms to build a therapeutic alliance between the physician and patient. This alliance predicts outcomes of counseling more than the specific modality of treatment. The common factors approach has been implemented and studied in pediatric primary care for children with mental health problems. Children who were treated by pediatricians trained in the common factors approach had improved functioning compared to those who saw pediatricians without this training.

A common factors approach distinguishes between the impact of the patient–provider alliance and the pediatrician's use of skills that influence patient behavior change across a broad range of conditions. Interpersonal skills that help build alliances with patients include showing empathy, warmth, and positive regard. Skills that influence behavior change include a clinician's ability to provide optimism, facilitate treatment engagement, and maintain the focus on achievable goals. This can be done by clearly explaining the condition and treatment approaches while keeping the discussion focused on immediate and practical concerns.

Interpersonal Skills: HEL^2 P^3

The interpersonal skills that facilitate an affective bond between the patient and clinician can be remembered by the HEL^2 P^3 mnemonic (Table 17.3). These skills include providing **hope** , **empathy** , and **loyalty** ; using the patient's **language** ; **partnering** with the family; asking **permission** to raise more sensitive questions or to give advice; and creating a **plan** that is initiated by the family. These interpersonal skills should help operationalize the common factors approach by increasing a patient's optimism, feelings of well-being, and willingness to work toward improved health, while also targeting feelings of anger, ambivalence, and hopelessness.

Table 17.3

Hope, Empathy, Language, Loyalty, Permission, Partnership, Plan (HEL^2 P^3)*

SKILL	EXAMPLES
Hope for improvement: Develop strengths.	“I have seen other children like you with similar feelings of sadness, and they have gotten better.”
Empathy: Listen attentively.	“It must be hard for you that you no longer get pleasure in playing soccer.”
Language: Use family's language. Check understanding.	“Let me make sure I understand what you are saying. You no longer feel like doing things that make you happy in the past?”
Loyalty: Express support and commitment.	“You are free to talk to me about anything while we work through this.”
Permission: Ask permission to explore sensitive subjects. Offer advice. **Partnership:** Identify and overcome barriers.	“I would like to ask more questions that you may find more sensitive, is that okay?” “Is it okay with you if I give you my opinion on what may be the problem here?”
Plan: Establish a plan, or at least a first step family can take.	“If we work together, maybe we can think through solutions for the problems you identified.”

[*] This table illustrates the **interpersonal skills** highlighted in the common factors approach. In this example the clinician is responding to an adolescent struggling with depression and resistant to seeking help.

Adapted with data from Foy JM, Kelleher KJ, Laraque D; American Academy of Pediatrics: Enhancing pediatric mental health care: strategies for preparing a primary care practice, *Pediatrics* 125(Suppl 3):S87–S108, 2010.

Structuring a patient encounter using common factors to facilitate behavior change uses these steps: eliciting concerns while setting an agenda and agreeing on the nature of the problem; establishing a plan; and responding to anger and demoralization and emphasizing hope.

Elicit Concerns: Set the Agenda and Agree on the Problem

The first step of the visit is to elicit both the child's and the parent's concerns and agree on the focus for the visit. This can be accomplished by using open-ended questions and asking “anything else?” until nothing else is disclosed. It is important to show you have time and are interested in their concerns by making eye contact, listening attentively, minimizing distractions, and responding with empathy and interest. Engage both the child and the parent by taking turns eliciting their concerns. It is helpful to summarize their story to reassure them you have heard and understand what they are saying. Keep the session organized, and manage rambling by gently interrupting, paraphrasing, asking for additional concerns, and refocusing the conversation.

By the end of this step in the visit, all parties should feel reassured that their problems were heard and accurately described. The next step is to agree on the problem to be addressed during that visit. If the parent and child do not agree on the issue, try to find a common thread that will address the concerns of both.

Establish a Plan

Once a problem is agreed on, the pediatrician can partner with families to develop acceptable and achievable plans for treatment or further evaluation. Families should take the lead in developing goals and the strategies to attain them, and information should be given in response to patients' expressed needs. Pediatricians can involve families by offering choices and asking for feedback. Advice should be given only after asking a family's permission to do so. If the family asks for advice, the clinician should respond by considering principles of behavior change, as described earlier. Advice should be tailored toward the family's willingness to act, concerns for barriers, and attitudes and should be as specific and practical as possible. Once an initial plan is established, it is important to partner in monitoring responses and to provide continued support.

Respond to Anger and Demoralization and Emphasize Hope

The common factors approach is particularly helpful in engaging families in situations where anger and demoralization could prevent patients from being able to use the clinician's advice. Focusing the conversation on goals for the future and how to achieve them is more productive than discussing how problems began. This "solution-focused therapy" approach grew out of the need for clinicians to help people in a brief encounter. Hopelessness can be relieved by pediatricians helping patients to identify and build on strengths and past success, reframing events and feelings, and breaking down overwhelming goals into small, concrete steps that are more readily accomplished. In general, pediatricians can use the **elicit-provide-elicit model** . First, ask if they want to hear your thoughts about the situation. Provide guidance in a neutral way, and then ask the family what they think about what you just stated.

Table 17.4 provides an example of how to use common factors in practice using a scenario of an adolescent female who has been teased for using albuterol before physical education class for her exercise-induced asthma. The clinician in the scenario attempts to address both the patient's and her mother's concerns.

Table 17.4

Common Factors Approach in Practice*

GOAL	SPECIFIC SKILLS	EXAMPLES
Elicit child and parents' concerns.	Use open-ended questions and ask, “What else?” until nothing else is listed, while engaging both parties and demonstrating empathy.	“Hi, Jacqueline and Mrs. Smith. How have things been since last time? What are your biggest concerns for today?” “What else do you think we should put on the agenda for today?” “I am sorry to hear that you have had more asthma symptoms around gym time, Jacqueline. I'd like to ask you a few more questions to get a better understanding of what has changed, if that's okay with you.” “I understand this is upsetting you, Mrs. Smith, and that you worry that Jacqueline is not going to the nurse before gym to use her inhaler pump anymore. Let's hear from Jacqueline.”
	Agree on the problem.	“Can we all agree that managing the asthma symptoms around gym time is the most pressing issue for today? Should we focus on that today?”
	Manage rambling.	“What you're saying is really important, but I want to be sure we have time to talk about controlling your daughter's asthma symptoms during gym. Is it okay if we go back to that topic?”
Partner with families to find acceptable forms of treatment.	Develop acceptable plans for treatment of further diagnoses.	“I believe we can develop a plan to help deal with this. Is it okay to start talking about next steps?” “I know these asthma symptoms are concerning to your mom. But, Jacqueline, is this something you can act on now?” “I am happy to give suggestions on how to more easily use your inhaler before gym, without the other kids noticing. But what were you thinking, Jacqueline?” “Let's make a specific plan on where you can keep your inhaler so the other kids don't see it.”
	Address barriers to treatment.	“Is there anything that makes you worry that this may not work?”
Increase expectations that treatment will be helpful.	Respond to hopelessness, anger, and frustration.	“I realize it wasn't your choice to come here, Jacqueline, but I'm interested in hearing how you feel about this issue.” “It must be really hard for you, Jacqueline, when the kids tease you about your inhaler.” “It must be frustrating for the school nurse to call you in the middle of the day at work, Mrs. Smith.” “I would be angry, too, if I felt my mom didn't understand how it felt when I got teased for going to the nurse's office.”
	Emphasize hope.	“We've managed difficult things before. Remember when Jacqueline kept getting admitted for her asthma when she was younger? We have come a long way since then, and I'm sure we can manage this as well.”

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* Jacqueline is an adolescent female who has had asthma since she was an infant. Despite

multiple hospitalizations as an infant, her asthma had been under control except for during exercise, including physical education (PE) class. She had been going to the nurse's office to take albuterol before PE class, but recently she had been teased for having to take medication before PE. She has begun to skip treatments to avoid the teasing. However, her mother has now been called a few times to pick her up from school due to her asthma symptoms. Mrs. Smith is a single mother who cannot miss work and is very frustrated. She was not aware of the bullying Jacqueline has undergone.

This scenario is adapted from the American Academy of Pediatrics curricula on common factors. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Pages/Module-1-Brief-Intervention.aspx .

Motivational Interviewing

Motivational interviewing (MI) is a goal-oriented, supportive counseling style that complements the $HEL^2 P^3$ framework and is useful when patients or families remain ambivalent about making health-related behavior changes. MI is designed to enhance intrinsic motivation in patients by exploring their perspectives and ambivalence. It is also aligned with the transtheoretical model's continuum of change, where the pediatrician not only tailors counseling to a patient's stage of change, but does so with the goal of moving the patient toward the next stage. It is particularly effective for those not interested in change or not ready to make a commitment. MI has been shown to be an effective intervention strategy for decreasing high-risk behaviors, improving chronic disease control, and increasing adherence to preventive health measures.

MI is a collaborative approach in which the pediatrician respects patients' perspective and treats them as the "expert" on their values, beliefs, and goals. *Collaboration, acceptance, compassion,* and *evocation* are the foundation of MI and are referred to as the "spirit" of the approach. The clinician is a "guide," respecting patients' autonomy and their ability to make their own decision to change. The pediatrician expresses genuine concern and demonstrates that he or she understands and validates the patient's or family's struggle. Using open-ended questions, the pediatrician evokes the patient's own motivation for change.

Expressing empathy facilitates behavior change by accepting the patient's beliefs and behaviors. This contrasts to *direct persuasion*, which often leads to resistance. The pediatrician must reinforce that ambivalence is normal and use skillful reflective listening, showing the patient an understanding of the situation.

Developing a discrepancy between current behaviors (or treatment choices) and treatment goals motivates change and helps move the patient from the precontemplative stage to the contemplative stage or from the contemplative stage to preparation, as described in the transtheoretical model. Through MI the clinician can guide patients in understanding that their current behaviors may not be consistent with their stated goals and values.

Rolling with resistance , or not pushing back when suggestions are declined, is a strategy again to align with the patient. Resistance is usually a sign that a different approach is needed. As necessary, the clinician can ask permission to give new perspectives.

Self-efficacy, or a patient's belief in her ability to perform the behavior, is a key element for change and a powerful motivator. Clinicians can express confidence in the patient's ability to achieve change and support the patient's self-efficacy.

The process by which MI is used in a patient encounter involves the following 4 parts:

1. *Engagement* is the rapport-building part of the encounter. In addition to using the skills presented in the HEL^2 P^3 framework, the MI approach highlights the use of open-ended questions, affirmations, reflective listening, and summaries (**OARS**). **Open-ended questions** should be inviting and probing enabling the patient to think through and come to a better understanding of the problem and elicit their internal motivation. **Affirmations** provide positive feedback, express appreciation about a patient's strengths and can reinforce autonomy and self-efficacy. **Reflective listening** demonstrates that the clinician understands the patient's thoughts and feelings without judgement or interruption. It should be done frequently and can encourage the patient to be more open. **Summarizing** the conversation in a succinct way reinforces that you are listening, pulls together all information, and allows the patient to hear his own motivations and ambivalence.
2. *Focusing* the visit is done to clarify the patient's priorities, stage of readiness, and to identify the problem where there is ambivalence. If a patient remains resistant to change, ask permission to give information or share ideas and then ask for feedback on what they think about what you said. In the **elicit-ask-elicit model** , a clinician can deliver information about an unhealthy behavior or lifestyle decision in a nonpaternalistic manner.
3. *Evocation* is when the clinician assesses their patients’ reasons for

change and helps them to explore advantages, disadvantages, and barriers to change. It is important to reinforce the patient's **change talk.** Examples of change talk include an expression of desire (“I want to…”), ability (“I can…”), reasons (“There are good reasons to…”), or a need for change (“I need to…”). Clinician can use “readiness rulers” by asking their patients to rate on a scale from 1 to 10 how important and confident they are in making change. The clinician should then respond by asking why the patient did not choose a lower number and should follow up asking what it would take to bring it to a higher number.

4. The *planning* stage is similar to that described in the discussion of a common factors approach and occurs once a patient is in the preparation stage on the continuum of change. A clinician can guide their patient through this stage by having them write down responses to statements such as, “The changes I want to make are…,” “The most important reasons to make this change are…,” “Some people who can support me are…,” and “They can help me by ….” A concrete plan should include specific actions and a way to factor in accountability and rewards. Table 17.5 uses a visit for counseling about obesity to demonstrate the process of motivational interviewing.

Table 17.5

Counseling for Obesity Using a Motivational Interviewing (MI) Approach

ACTION	SPECIFIC SKILLS	EXAMPLES
Engagement*	**O** pen-ended questions	“Now that we have finished the majority of the visit, I'd like to talk about your weight. Is that okay? How do you feel about your size?” “Mrs. Smith, how do you feel about Jimmy's weight?”
	A ffirmations	“You definitely have shown how strong you are having dealt with kids teasing you about your size.” “Remember when you were having difficulty with school? You were able to make a few changes, and now you are doing well. I am confident we can do the same with your weight.”
	R eflective listening	“You are feeling like your son is the same size as everyone in your family, and you aren't concerned right now.” “Having your family watch TV before bed really works for your family, Mrs. Smith.” “You're not terribly excited about having to think of ways to cook differently.”
	S ummary	“So far, we have discussed how challenging it would be to

	statements	lose weight and make changes for the whole family, but you are willing to consider some simple changes.”
Focusing	Set the agenda.	“We could talk about increasing the amount of exercise Jimmy has every week, reducing screen time, or making a dietary change. What do you think would work best?” “Great, so we will talk about soda. What do you like about it? How many times a week do you drink it?”
Evocation	Reinforce any change talk. Change ruler.	“Those are great reasons for thinking about cutting back on soda.” “On a scale of 1 to 10, how confident are you (or important is it) that you can cut back on soda?” “A 5. Why didn't you answer a 3?” “What would it take to bring it to a 7?”
Planning	Focus on how to make the change, not “why” anymore. Be concrete.	“Maybe completely eliminating soda is too difficult right now. Do you want to think of a couple of times during the week where you can reward yourself with a soda?” “What will you drink after school instead of soda?”

[*] **OARS** is used to engage the patient and build rapport.

Adapted from *Changing the conversation about childhood obesity,* American Academy of Pediatrics, Institute for Healthy Childhood Weight. https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/Changing-the-conversation-about-Childhood-Obesity.aspx .

Shared Decision-Making

Shared decision-making has many similarities to the processes previously described in that it emphasizes moving physicians away from a paternalistic approach in dictating treatment to one where patients and clinicians collaborate in making a medical decision, particularly when multiple evidence-based treatments options exist. The pediatrician or clinician offers different treatment options and describes the risks and benefits for each one. The patient or caregiver expresses their values, preferences, and treatment goals, and a decision is made together.

Shared decision-making is often facilitated by using evidence-based decision aids such as pamphlets, videos, web-based tools, or educational workshops. Condition-specific or more generic decision aids have been created and facilitate the process of shared decision-making. Studies in adults show that such aids improve knowledge and satisfaction, reduce decisional conflict, and increase the alignment between patient preferences and treatment options. More study is needed to assess behavioral and physiologic outcomes specifically when involving children in the decision-making process.

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PART II

Growth, Development, and Behavior

OUTLINE

Chapter 18 Developmental and Behavioral Theories
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Chapter 21 The Newborn
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CHAPTER 18

Developmental and Behavioral Theories

Susan Feigelman

The field of pediatrics is dedicated to optimizing the growth and development of each child. Pediatricians require knowledge of normal growth, development, and behavior in order to effectively monitor children's progress, identify delays or abnormalities in development, help obtain needed services, and counsel parents and caretakers. To alter factors that increase or decrease risk, pediatricians need to understand how biologic and social forces interact within the parent–child relationship, within the family, and between the family and the larger society. Growth is an indicator of overall well-being, status of chronic disease, and interpersonal and psychologic stress. By monitoring children and families over time, pediatricians are uniquely situated to observe the interrelationships between physical growth and cognitive, motor, and emotional development. Observation is enhanced by familiarity with developmental and behavioral theories that inform one about typical patterns of development and provide guidance for prevention or intervention for behavior problems. Familiarity with theories of health behavior may assist in guiding patients and families in disease management and wellness care.

Biopsychosocial Model and Ecobiodevelopmental Framework: Models of Development

The **medical model** presumes that a patient presents with signs and symptoms and a physician focuses on diagnosing and treating diseases of the body. This model neglects the psychologic aspect of a person who exists in the larger realm of the family and society. In the **biopsychosocial model** , societal and community systems are simultaneously considered along with more proximal systems that make up the person and the person's environment (Fig. 18.1). A patient's symptoms are examined and explained in the context of the patient's existence. This basic model can be used to understand health and both acute and chronic disease.

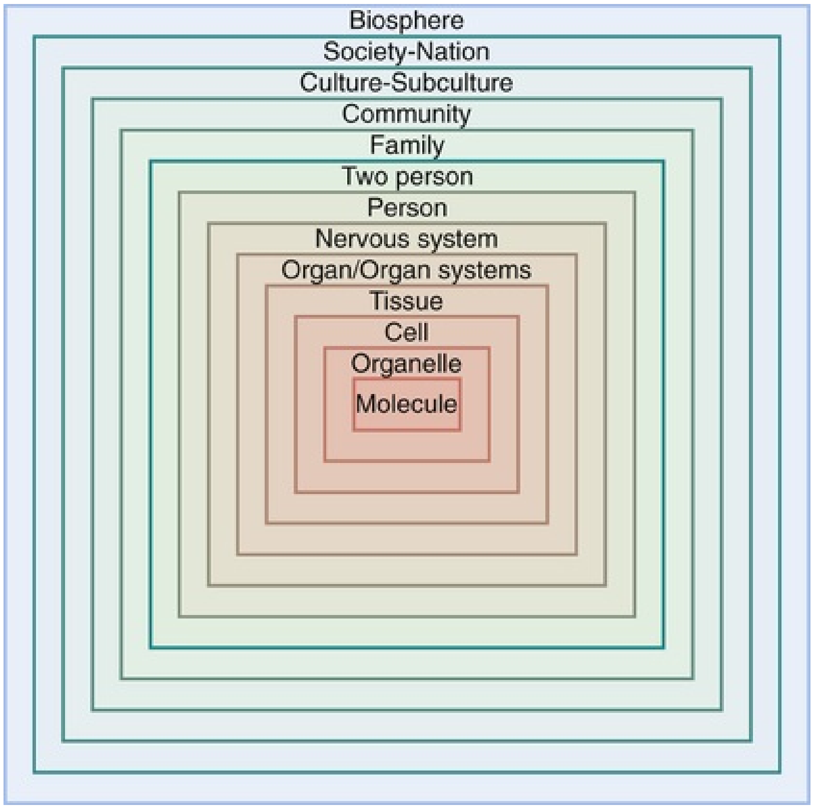
Biosphere
Society-Nation
Culture-Subculture
Community
Family
Two person
Person
Nervous system
Organ/Organ systems
Tissue
Cell
Organelle
Molecule

FIG. 18.1 **Continuum and hierarchy of natural systems in the biopsychosocial model. (From Engel GL: The clinical application of the biopsychosocial model, *Am J Psychiatry* 137:535–544, 1980.)**

With the advances in neurology, genomics (including epigenetics), molecular biology, and the social sciences, a more accurate model, the **ecobiodevelopmental framework** , has emerged. This framework emphasizes how the ecology of childhood (social and physical environments) interacts with biologic processes to determine outcomes and life trajectories. Early influences, particularly those producing **toxic levels of stress** , affect the individual through modification of gene expression, without change in DNA sequencing. These

epigenetic changes , such as DNA methylation and histone acetylation (see Chapter 100), are influenced by the early life experiences (the environment). Stress responses may produce alterations in brain structure and function, leading to disruption of later coping mechanisms. These changes will produce long-lasting effects on the health and well-being of the individual and may be passed on to future generations (Fig. 18.2).

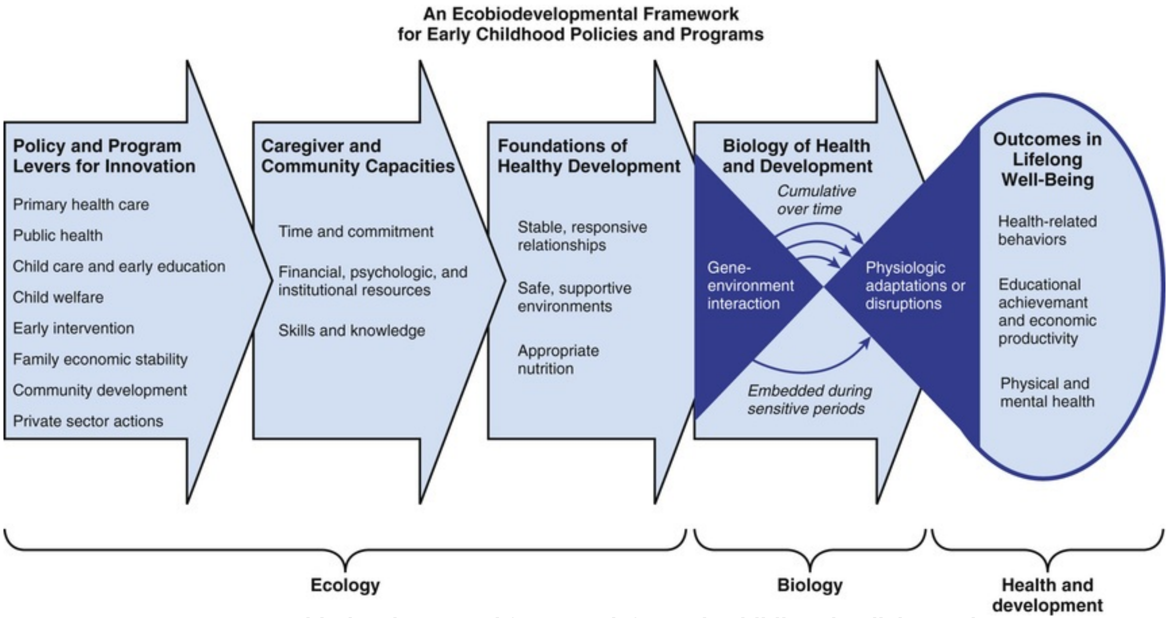
An Ecobiodevelopmental Framework for Early Childhood Policies and Programs
Policy and Program Levers for Innovation
Primary health care
Public health
Child care and early education
Child welfare
Early intervention
Family economic stability
Community development
Private sector actions
Caregiver and Community Capacities
Time and commitment
Financial, psychologic, and institutional resources
Skills and knowledge
Foundations of Healthy Development
Stable, responsive relationships
Safe, supportive environments
Appropriate nutrition
Biology of Health and Development
Cumulative over time
Gene-environment interaction
Physiologic adaptations or disruptions
Embedded during sensitive periods
Outcomes in Lifelong Well-Being
Health-related behaviors
Educational achievemant and economic productivity
Physical and mental health
Ecology
Biology
Health and development

FIG. 18.2 **An ecobiodevelopmental framework for early childhood policies and programs. (Adapted from Center on the Developing Child (2010). The foundations of lifelong health are built in early childhood. Available at: http://developingchild.harvard.edu .)**

Critical to learning and remembering (and therefore development) is **neuronal plasticity** , which permits the central nervous system to reorganize neuronal networks in response to environmental stimulation, both positive and negative. An overproduction of neuronal precursors eventually leads to about 100 billion neurons in the adult brain. Each neuron develops on average 15,000 synapses by 3 yr of age. During early childhood, synapses in frequently used pathways are preserved, whereas less-used ones atrophy, a process termed “pruning.” Changes in the strength and number of synapses and reorganization of neuronal circuits also play important roles in brain plasticity. Increases or decreases in synaptic activity result in persistent increases or decreases in synaptic strength. Thus experience (**environment**) has a direct effect on the physical and therefore functional properties of the brain. Children with different talents and temperaments (already a combination of genetics and environment) further elicit different stimuli from their (differing) environments.

Periods of rapid development generally correlate with periods of great changes in synaptic numbers in relevant areas of the brain. Accordingly, sensory deprivation during the time when synaptic changes should be occurring has profound effects. For example, the effects of strabismus leading to amblyopia in one eye may occur quickly during early childhood; likewise, patching the eye with good vision to reverse amblyopia in the other eye is less effective in late childhood (see Chapter 641). Early experience is particularly important because learning proceeds more efficiently along established synaptic pathways.

Early traumatic experiences modify the expression of stress mediators (in particular the hypothalamic-pituitary-adrenal axis) and neurotransmitters, leading to changes in brain structure and function. These effects may be persistent, leading to alterations and dysfunction in the stress response throughout life. Chronic stress has negative effects on cognitive functions, including memory and emotional regulation. Positive and negative experiences do not determine the ultimate outcome, but shift the probabilities by influencing the child's ability to respond adaptively to future stimuli. The plasticity of the brain continues into adolescence, with further development of the prefrontal cortex, which is important in decision-making, future planning, and emotional control; neurogenesis persists in adulthood in certain areas of the brain.

Biologic Influences

Biologic influences on development include genetics, in utero exposure to teratogens, the long-term negative effects of low birthweight (neonatal morbidities plus increased rates of subsequent adult-onset obesity, coronary heart disease, stroke, hypertension, and type 2 diabetes), postnatal illnesses, exposure to hazardous substances, and maturation. Adoption and twin studies consistently show that heredity accounts for approximately 40% of the variance in IQ and in other personality traits, such as sociability and desire for novelty, whereas shared environment accounts for another 50%. The negative effects on development of prenatal exposure to teratogens, such as mercury and alcohol, and of postnatal insults, such as meningitis and traumatic brain injury, have been extensively studied (see Chapters 115 and 120). Any chronic illness can affect growth and development, either directly or through changes in nutrition, parenting, school attendance, or peer interactions.

Most children follow similar motor developmental sequences; the age at which children walk independently is similar around the world, despite great variability in child-rearing practices. The attainment of other skills, such as the use of complex sentences, is less tightly bound to a maturational schedule. Maturational changes also generate behavioral challenges at predictable times. Decrements in growth rate and sleep requirements around 2 yr of age often generate concern about poor appetite and refusal to nap. Although it is possible to accelerate many developmental milestones (toilet-training a 12 mo old or teaching a 3 yr old to read), *the long-term benefits of such precocious accomplishments are questionable.*

In addition to physical changes in size, body proportions, and strength, maturation brings about hormonal changes. Sexual differentiation, both somatic and neurologic, begins in utero. Both stress and reproductive hormones affect brain development as well as behavior throughout development. Steroid production by the fetal gonads leads to differences in brain structures between males and females.

Temperament describes the stable, early-appearing individual variations in behavioral dimensions, including emotionality (crying, laughing, sulking), activity level, attention, sociability, and persistence. The classic theory proposes 9 dimensions of temperament (Table 18.1). These characteristics lead to 3 common constellations: (1) the easy, highly adaptable child, who has regular biologic cycles; (2) the difficult child, who is inflexible, moody, and easily frustrated; and (3) the slow-to-warm-up child, who needs extra time to adapt to new circumstances. Various combinations of these clusters also occur. Temperament has long been described as biologic or "inherited." Monozygotic twins are rated by their parents as temperamentally similar more often than are dizygotic twins. Estimates of heritability suggest that genetic differences account for approximately 20–60% of the variability of temperament within a population. The remainder of the variance is attributed to the child's environment. Maternal prenatal stress and anxiety is associated with child temperament, possibly through stress hormones. However, certain polymorphisms of specific genes moderate the influence of maternal stress on infant temperament. Children who are easily frustrated, fearful, or irritable may elicit negative parental reactions, making these children even more susceptible to negative parenting behaviors and to poor adjustment to adversity. Longitudinal twin studies of adult personality indicate that changes in personality over time largely result from nonshared environmental influences, whereas stability of temperament appears to result from genetic factors.

Table 18.1

Temperamental Characteristics: Descriptions and Examples

CHARACTERISTIC	DESCRIPTION	EXAMPLES*
Activity level	Amount of gross motor movement	“She's constantly on the move.” “He would rather sit still than run around.”
Rhythmicity	Regularity of biologic cycles	“He's never hungry at the same time each day.” “You could set a watch by her nap.”
Approach and withdrawal	Initial response to new stimuli	“She rejects every new food at first.” “He sleeps well in any place.”
Adaptability	Ease of adaptation to novel stimulus	“Changes upset him.” “She adjusts to new people quickly.”
Threshold of responsiveness	Intensity of stimuli needed to evoke a response (e.g., touch, sound, light)	“He notices all the lumps in his food and objects to them.” “She will eat anything, wear anything, do anything.”
Intensity of reaction	Energy level of response	“She shouts when she is happy and wails when she is sad.” “He never cries much.”
Quality of mood	Usual disposition (e.g., pleasant, glum)	“He does not laugh much.” “It seems like she is always happy.”
Distractibility	How easily diverted from ongoing activity	“She is distracted at mealtime when other children are nearby.” “He doesn't even hear me when he is playing.”
Attention span and persistence	How long a child pays attention and sticks with difficult tasks	“He goes from toy to toy every minute.” “She will keep at a puzzle until she has mastered it.”

* Typical statements of parents, reflecting the range for each characteristic from very little to very much.

Based on data from Chess S, Thomas A: *Temperament in clinical practice,* New York, 1986, Guilford.

The concept of temperament can help parents understand and accept the characteristics of their children without feeling responsible for having caused them. Children who have difficulty adjusting to change may have behavior problems when a new baby arrives or at the time of school entry. In addition, pointing out the child's temperament may allow for adjustment in parenting styles. Behavioral and emotional problems may develop when the temperamental characteristics of children and parents are in conflict. For example, if parents who keep an irregular schedule have a child who is not readily adaptable, behavioral difficulties are more likely than if the child has parents who have predictable routines.

Psychologic Influences: Attachment and

Contingency

The influence of the child-rearing environment dominates most current models of development. Infants in hospitals and orphanages, devoid of opportunities for attachment, have severe developmental deficits. **Attachment** refers to a biologically determined tendency of a young child to seek proximity to the parent during times of stress and also to the relationship that allows securely attached children to use their parents to reestablish a sense of well-being after a stressful experience. Insecure attachment may be predictive of later behavioral and learning problems.

At all stages of development, children progress optimally when they have adult caregivers who pay attention to their verbal and nonverbal cues and respond accordingly. In early infancy, such contingent responsiveness to signs of overarousal or underarousal helps maintain infants in a state of quiet alertness and fosters autonomic self-regulation. **Contingent responses** (reinforcement depending on the behavior of the other) to nonverbal gestures create the groundwork for the shared attention and reciprocity that are critical for later language and social development. Children learn best when new challenges are just slightly more difficult than what they have already mastered, a degree of difficulty dubbed the “zone of proximal development.” Psychologic forces, such as attention problems (see Chapter 49) or mood disorders (see Chapter 39), will have profound effects on many aspects of an older child's life.

Social Factors: Family Systems and the Ecologic Model

Contemporary models of child development recognize the critical importance of influences outside the mother–child dyad. Fathers play critical roles, both in their direct relationships with their children and in supporting mothers. As traditional nuclear families become less dominant, the influence of other family members (grandparents, foster and adoptive parents, same-sex partners) becomes increasingly important. Children are increasingly raised by unrelated caregivers while parents work or while they are in foster care.

Families function as systems, with internal and external boundaries, subsystems, roles, and rules for interaction. In families with rigidly defined parental subsystems, children may be denied any decision-making, exacerbating rebelliousness. In families with poorly defined parent–child boundaries, children may be required to take on responsibilities beyond their years or may be recruited to play a spousal role.

Family systems theory recognizes that individuals within systems adopt implicit roles. Although birth order does not have long-term effects on personality development, within families the members take on different roles. One child may be the troublemaker, whereas another is the negotiator and another is quiet. Changes in one person's behavior affects every other member of the system; roles shift until a new equilibrium is found. The birth of a new child, attainment of developmental milestones such as independent walking, the onset of nighttime fears, and the death of a grandparent are all changes that require renegotiation of roles within the family and have the potential for healthy adaptation or dysfunction.

The family system, in turn, functions within the larger systems of extended family, subculture, culture, and society. Bronfenbrenner's ecologic model depicts these relationships as concentric circles, with the parent–child dyad at the center (with associated risks and protective factors) and the larger society at the periphery. Changes at any level are reflected in the levels above and below. The shift from an industrial economy to one based on service and information is an obvious example of societal change with profound effects on families and children.

Unifying Concepts: The Transactional Model, Risk, and Resilience

The **transactional model** proposes that a child's status at any point in time is a function of the interaction between biologic and social influences. The influences are bidirectional: biologic factors, such as temperament and health status, both affect the child-rearing environment and are affected by it. A premature infant may cry little and sleep for long periods; the infant's depressed parent may welcome this behavior, setting up a cycle that leads to poor nutrition and inadequate growth. The child's failure to thrive may reinforce the parent's sense of failure as a parent. At a later stage, impulsivity and inattention associated with early, prolonged undernutrition may lead to aggressive behavior. The cause of the aggression in this case is not the prematurity, the undernutrition, or the maternal depression, but the interaction of all these factors (Fig. 18.3). Conversely, children with biologic risk factors may nevertheless do well developmentally if the child-rearing environment is supportive. Premature infants with electroencephalographic evidence of neurologic immaturity may be at increased risk for cognitive delay. This risk may only be realized when the quality of parent–child interaction is poor. When parent–child interactions are optimal, prematurity carries a reduced risk of developmental disability.

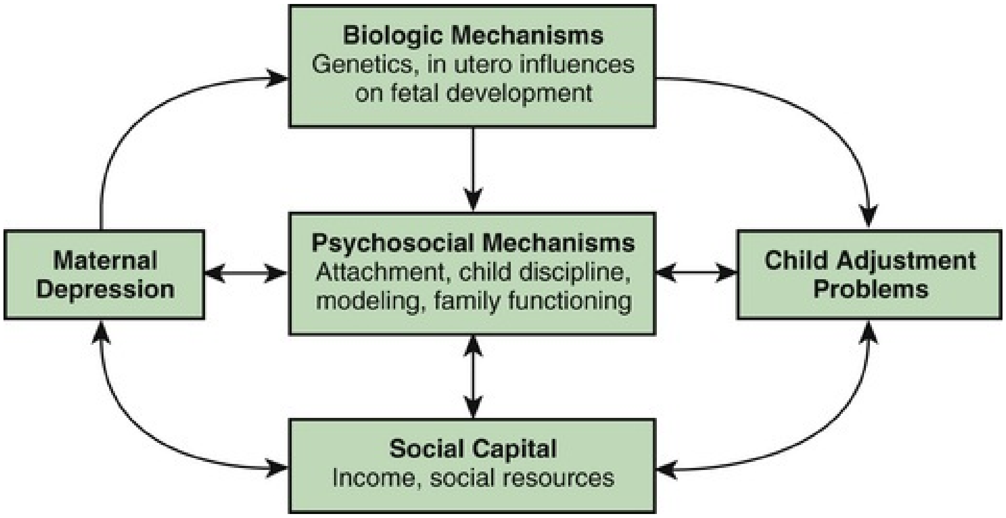
Biologic Mechanisms
Genetics, in utero influences on fetal development
Maternal Depression
Psychosocial Mechanisms
Attachment, child discipline, modeling, family functioning
Child Adjustment Problems
Social Capital
Income, social resources

FIG. 18.3 Theoretical model of mutual influences on maternal depression and child adjustment. (From Elgar FJ, McGrath PJ, Waschbusch DA, et al: Mutual influences on maternal depression and child adjustment problems, *Clin Psychol Rev* 24:441–459, 2004.)

An estimate of developmental risk can begin with risk factors, such as low income, limited parental education, and lack of neighborhood resources. Stress and anxiety in pregnancy are associated with cognitive, behavioral, and emotional problems in the child. Early stress may have effects on aging mediated by shortening of telomere length, a link to health disparities. Risk for negative outcomes over time increases exponentially as a result of declining plasticity and accumulation of risk factors (both behavioral and environmental). Interventions are most effective in young children; over time, risk increases as the ability to change decreases.

Children growing up in poverty experience multiple levels of developmental risk: increased exposure to biologic risk factors, such as environmental lead and undernutrition; lack of stimulation in the home; and decreased access to interventional education and therapeutic experiences. As they respond by withdrawal or acting out, they further discourage positive stimulation from those around them. Children of adolescent mothers are also at risk. When early intervention programs provide timely, intensive, comprehensive, and prolonged services, at-risk children show marked and sustained upswings in their developmental trajectory. Early identification of children at developmental risk, along with early intervention to support parenting, is critically important.

Children can have appropriate developmental trajectories despite childhood trauma. **Resilience** is the ability to withstand, adapt to, and recover from adversities. There are several resilience factors that can be modified: a positive appraisal or outlook and good executive functioning (see Chapter 48); nurturing parenting (see Chapter 19); good maternal mental health, good self-care skills, and consistent household routines; and an understanding of trauma. The personal histories of children who overcome poverty often include at least one trusted adult (parent, grandparent, teacher) with whom the child has a special, supportive, close relationship. Pediatric providers are positioned to target and bolster resilience in their patients and families.

Developmental Domains and Theories of Emotion and Cognition

Child development can also be tracked by the child's developmental progress in particular domains, such as gross motor, fine motor, social, emotional, language, and cognition. Within each of these categories are *developmental lines* or sequences of changes leading up to particular attainments. Developmental lines in the gross motor domain, from rolling to creeping to independent walking, are clear. Others, such as the line leading to the development of conscience, are subtler.

The concept of a developmental line implies that a child passes through successive stages. Several psychoanalytic theories are based on stages as qualitatively different epochs in the development of emotion and cognition (Table 18.2). In contrast, behavioral theories rely less on qualitative change and more on the gradual modification of behavior and accumulation of competence.

Table 18.2

Classic Developmental Stage Theories

	INFANCY (0-1 YR)	**TODDLERHOOD (2-3 YR)**	**PRESCHOOL (3-6 YR)**	**SCHOOL AGE (6-12 YR)**	**ADOLESCE (12-20 YR)**
Freud: psychosexual	Oral	Anal	Phallic/oedipal	Latency	Genital

Erikson: psychosocial	Basic trust vs mistrust	Autonomy vs shame and doubt	Initiative vs guilt	Industry vs inferiority	Identity vs role diffusion
Piaget: cognitive	Sensorimotor	Sensorimotor	Preoperational	Concrete operations	Formal operations
Kohlberg: moral	—	Preconventional: avoid punishment/obtain rewards (stages 1 and 2)	Conventional: conformity (stage 3)	Conventional: law and order (stage 4)	Postconventional: moral principles

Psychoanalytic Theories

At the core of **Freudian theory** is the idea of body-centered (or broadly, “sexual”) drives; the emotional health of both the child and the adult depends on adequate resolution of these conflicts. Although Freudian ideas have been challenged, they opened the door to subsequent theories of development.

Erikson recast Freud's stages in terms of the emerging personality (see Table 18.2). The child's sense of basic trust develops through the successful negotiation of infantile needs. As children progress through these psychosocial stages, different issues become salient. It is predictable that a toddler will be preoccupied with establishing a sense of autonomy, whereas a late adolescent may be more focused on establishing meaningful relationships and an occupational identity. Erikson recognized that these stages arise in the context of Western European societal expectations; in other cultures, the salient issues may be quite different.

Erikson's work calls attention to the intrapersonal challenges facing children at different ages in a way that facilitates professional intervention. Knowing that the salient issue for school-age children is industry vs inferiority, pediatricians inquire about a child's experiences of mastery and failure and (if necessary) suggest ways to ensure adequate successes.

Cognitive Theories

Cognitive development is best understood through the work of **Piaget** . A central tenet of Piaget's work is that cognition changes in *quality*, not just quantity (see Table 18.2). During the sensorimotor stage, an infant's thinking is tied to immediate sensations and a child's ability to manipulate objects. The concept of “in” is embodied in a child's act of putting a block into a cup. With the arrival of language, the nature of thinking changes dramatically; symbols increasingly take the place of objects and actions. Piaget described how children actively construct knowledge for themselves through the linked processes of **assimilation** (taking in new experiences according to existing schemata) and **accommodation** (creating new patterns of understanding to adapt to new information). In this way, children are continually and actively reorganizing cognitive processes.

Piaget's basic concepts have held up well. Challenges have included questions about the timing of various stages and the extent to which context may affect conclusions about cognitive stage. Children's understanding of cause and effect may be considerably more advanced in the context of sibling relationships than in the manipulation and perception of inanimate objects. In many children, logical thinking appears well before puberty (even in toddlers), the age postulated by Piaget. Of undeniable importance is Piaget's focus on cognition as a subject of empirical study, the universality of the progression of cognitive stages, and the image of a child as actively and creatively interpreting the world.

Piaget's work is of special importance to pediatricians for 3 reasons: (1) Piaget's observations provide insight into many puzzling behaviors of infancy, such as the common exacerbation of sleep problems at 9 and 18 mo of age; (2) Piaget's observations often lend themselves to quick replication in the office, with little special equipment; and (3) open-ended questioning, based on Piaget's work, can provide insights into children's understanding of illness and hospitalization.

Based on cognitive development, **Kohlberg** developed a theory of moral development in 6 stages, from early childhood through adulthood. Preschoolers' earliest sense of right and wrong is egocentric, motivated by externally applied controls. In later stages, children perceive equality, fairness, and reciprocity in their understanding of interpersonal interactions through perspective taking. Most youth will reach stage 4, conventional morality, by mid- to late adolescence. The basic theory has been modified to distinguish morality from social conventions. Whereas moral thinking considers interpersonal interactions, justice, and human welfare, social conventions are the agreed-on standards of behavior particular to a social or cultural group. Within each stage of development, children are guided by the basic precepts of moral behavior, but they also may take into account local standards, such as dress code, classroom behavior, and dating expectations. Additional studies have even demonstrated some protomorality in infants.

Behavioral Theory

This theoretical perspective distinguishes itself by its lack of concern with a child's inner experience. Its sole focus is on observable behaviors and measurable factors that either increase or decrease the frequency with which these behaviors occur. No stages are implied; children, adults, and indeed animals all respond in the same way. In its simplest form, the behaviorist orientation asserts that behaviors that are reinforced occur more frequently; behaviors that are punished or ignored occur less frequently. Reinforcement may be further divided into *positive* reinforcement, when a reward or attention increases the chance of a behavior occurring, and *negative* reinforcement, when removal of an aversive stimulus increases the frequency of the behavior. For example, a teacher who allows students who do the homework Monday through Thursday not to do the assignment on Friday, is using negative reinforcement to motivate homework completion during the week.

The strengths of behavioral theory are its simplicity, wide applicability, and conduciveness to scientific verification. A behavioral approach lends itself to interventions for various common problems, such as temper tantrums, aggressive preschool behavior, and eating disorders in which behaviors are broken down into discrete units. In cognitively limited children and children with autism spectrum disorder, behavioral interventions using **applied behavior analysis** approaches have demonstrated the ability to teach new, complex behaviors. Applied behavior analysis has been particularly useful in the treatment of early-diagnosed autism (see Chapter 54). However, when misbehavior is symptomatic of an underlying emotional, perceptual, or family problem, an exclusive reliance on behavior therapy risks leaving the cause untreated. Behavioral approaches can be taught to parents for application at home.

Theories Used in Behavioral Interventions

An increasing number of programs or interventions (within and outside the physician's office) are designed to influence health behaviors; some of these models are based on behavioral or cognitive theory or may have attributes of both. The most commonly employed models are the Health Belief Model, Theory of Reasoned Action, Theory of Planned Behavior, Social Cognitive Theory, and Transtheoretical Model, also known as Stages of Change Theory (see Chapter 17). Pediatricians should be aware of these models and their similarities and differences (Table 18.3). Interventions based on these theories have been designed for children and adolescents in community, clinic, and hospital-based settings.

Table 18.3

Similar or Identical Elements Within 5 Theories of Health Behavior

CONCEPT	**GENERAL TENET OF THE CONCEPT “ENGAGING IN THE BEHAVIOR IS LIKELY IF …”**	**HEALTH BELIEF MODEL**	**THEORY OF REASONED ACTION**	**THEORY OF PLANNED BEHAVIOR**	**SOCIAL COGNITIVE THEORY**	**T M**
ATTITUDINAL BELIEFS						
Appraisal of positive and negative aspects of the behavior and its expected outcome	The positive aspects outweigh the negative aspects.	Benefits, barriers/health motive	Behavioral beliefs and evaluation of those beliefs (attitudes)	Behavioral beliefs and evaluation of those beliefs (attitudes)	Outcome expectations/expectancies	Pr ba
SELF-EFFICACY BELIEFS/BELIEFS ABOUT CONTROL OVER THE BEHAVIOR						
Belief in one's ability to perform the behavior; confidence	One believes in one's ability to perform the behavior.	Self-efficacy	—	Perceived behavioral control	Self-efficacy	Se
NORMATIVE AND NORM-RELATED BELIEFS AND ACTIVITIES						
Belief that others want one to engage in the behavior (and one's motivation to comply); may include actual support of others	One believes that people important to one want one to engage in the behavior; person has others' support.	Cues from media, friends (cues to action)	Normative beliefs and motivation to comply (subjective norms)	Normative beliefs and motivation to comply (subjective norms)	Social support	H (p
Belief that others (e.g., peers) are engaging in the behavior	One believes that other people are engaging in the behavior.	—	—	—	Social environment/norms; modeling	So of
Responses to one's behavior that increase or decrease the likelihood one will engage in the behavior;	One receives positive reinforcement from others or creates positive reinforcements for oneself.	Cues from media, friends (cues to action)	—	—	Reinforcement	Re m co ch

may include reminders						
RISK-RELATED BELIEFS AND EMOTIONAL RESPONSES						
Belief that one is at risk if one does not engage in the behavior, and that the consequences may be severe; may include actually experiencing negative emotions or symptoms and coping with them	One feels at risk with regard to a negative outcome or disease.	Perceived susceptibility/severity (perceived threat)	—	—	Emotional coping responses/expectancies about environmental cues	D ch
INTENTION/COMMITMENT/PLANNING						
Intending or planning to perform the behavior; setting goals or making a commitment to perform the behavior	One has formed strong behavioral intentions to engage in the behavior; one has set realistic goals or made a firm commitment to engage in the behavior.	—	Behavioral intentions	Behavioral intentions	Self-control/self-regulation	C (s lil ch

From Noar SM, Zimmerman RS: Health behavior theory and cumulative knowledge regarding health behaviors: are we moving in the right direction? *Health Educ Res* 20:275–290, 2005, Table 1.

Motivational interviewing is a technique often used in clinical settings to bring about behavior change, as discussed in detail in Chapter 17 . Briefly, the goal is to enhance an individual's motivation to change behavior by exploring and overcoming ambivalence. The therapist is a partner rather than an authority figure and recognizes that, ultimately, the patient has control over his or her choices.

Statistics Used in Describing Growth and Development

(See Chapter 27 .)

In everyday use, the term *normal* is synonymous with *healthy* . In a statistical sense, *normal* means that a set of values generates a normal (bell-shaped or gaussian) distribution. This is the case with anthropometric quantities, such as height and weight, and with many developmental measures, such as intelligence quotient (IQ). For a **normally distributed measurement** , a histogram with the quantity (height, age) on the *x* axis and the frequency (the number of children of that height, or the number who stand on their own at that age) on the *y* axis generates a bell-shaped curve. In an ideal bell-shaped curve, the peak corresponds to the arithmetic **mean** (average) of the sample, as well as to the median and the mode. The **median** is the value above and below which 50% of the observations lie; the **mode** is the value having the highest number of observations. Distributions are termed *skewed* if the mean, median, and mode are not the same number.

The extent to which observed values cluster near the mean determines the width of the bell and can be described mathematically by the **standard deviation (SD)** . In the ideal normal curve, a range of values extending from 1 SD below the mean to 1 SD above the mean includes approximately 68% of the values, and each "tail" above and below that range contains 16% of the values. A range encompassing ±2 SD includes 95% of the values (with the upper and lower tails each comprising approximately 2.5% of the values), and ±3 SD encompasses 99.7% of the values (Table 18.4 and Fig. 18.4).

Table 18.4

Relationship Between Standard Deviation (SD) and Normal Range for Normally Distributed Quantities

OBSERVATIONS INCLUDED IN THE NORMAL RANGE		PROBABILITY OF A "NORMAL" MEASUREMENT DEVIATING FROM THE MEAN BY THIS AMOUNT	
SD	**%**	**SD**	**%**
±1	68.3	≥1	16.0
±2	95.4	≥2	2.3
±3	99.7	≥3	0.13

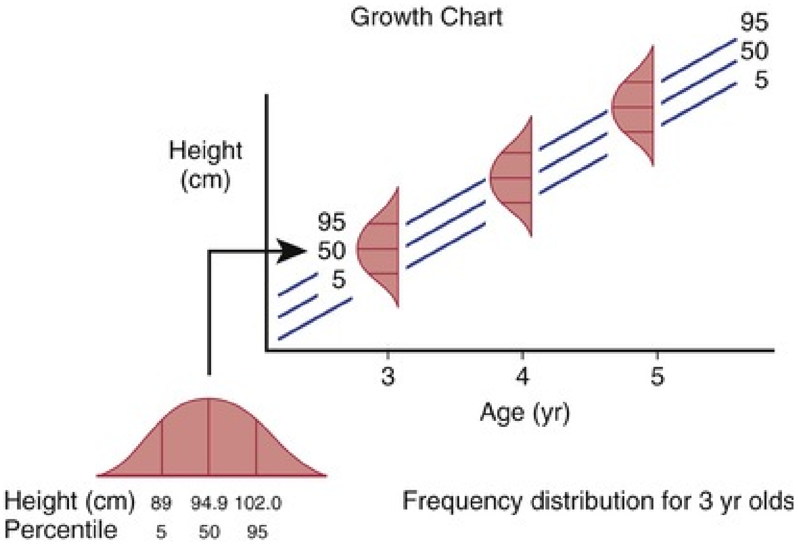

FIG. 18.4 **Relationship between percentile lines on the growth curve and frequency distributions of height at different ages.**

For any single measurement, its distance away from the mean can be expressed in terms of the number of SDs (also called a ***z* score**); one can then consult a table of the normal distribution to find out what percentage of measurements fall within that distance from the mean. Software to convert anthropometric data into z scores for epidemiologic purposes is available. A measurement that falls “outside the normal range”—arbitrarily defined as 2, or sometimes 3, SDs on either side of the mean—is atypical, but not necessarily indicative of illness. The further a measurement (height, weight, IQ) falls from the mean, the greater is the probability that it represents not simply normal variation, but rather a different, potentially pathologic condition.

Another way of relating an individual to a group uses percentiles. The **percentile** is the percentage of individuals in the group who have achieved a certain measured quantity (e.g., height of 95 cm) or a developmental milestone (e.g., walking independently). For anthropometric data, the percentile cutoffs can be calculated from the mean and SD. The 5th, 10th, and 25th percentiles correspond to −1.65 SD, −1.3 SD, and −0.7 SD, respectively. Fig. 18.4 demonstrates how frequency distributions of a particular parameter (height) at different ages relate to the percentile lines on the growth curve.

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CHAPTER 19

Positive Parenting and Support

Rebecca A. Baum

No force may be more important to a child's development than the family. Many factors contribute to the family's influence, including family structure, functioning, economics, and stress. Parenting provides the foundation to promote healthy child development and to protect against adverse outcomes. The term **positive parenting** describes an approach to parenting that achieves these goals.

The Importance of Parenting

Interactions between parents and their children provide stimulation that promotes the development of language, early cognitive skills, and school readiness. Less frequent participation in interactive parenting practices, such as reading aloud to children, eating family meals, and participating in family outings, predicts an increased risk of developmental delay in low-income families. Interventions that increase parents' reading to children promote positive developmental outcomes such as early language and literacy development.

The affective nature of the parent–child interaction is important for both cognitive and social emotional development. Persistent maternal depression has been linked to decreases in child IQ scores at school entry. Early exposure to positive parenting has been associated with lower rates of childhood depression, risky behavior, delinquency, injuries, behavior problems, and bullying, with increased likelihood of empathy and prosocial behavior. The beneficial effects of early maternal sensitivity on social competence have been found to persist into adulthood, suggesting that early life experiences have a long-term impact.

Positive parenting practices, such as using a warm, supporting approach during conflict, and negative practices, such as maternal aggression, have been associated with MRI changes in adolescent brain development in boys. Animal models have been used to demonstrate the detrimental effects of stressful early life experiences, characterized by maternal separation or decreased maternal responsiveness. Offspring raised in these environments were more likely to exhibit fearful behavior. Differences were noted in brain architecture and epigenetic changes that alter gene expression (see Chapter 100). Importantly in these animal models, increased maternal nurturing could protect against these changes.

The Role of the Family

Parenting occurs in the context of a family unit, and there is significant diversity among families. Family makeup has changed greatly over the last several decades in the United States, with increases in cultural, ethnic, and spiritual diversity and in single-parent families. In 2014, based on U.S. Census Bureau data, 26% of children lived in single-parent families, and 62% lived in households with 2 married parents. These patterns differ when race and ethnicity are considered; the majority of children in white and Asian American families live in households with married parents, whereas only 31% of black children do, with about half (57%) living in single-parent households. Although children can thrive in all types of family environments, data suggest that, on average, children living in single-parent families fare less well than their counterparts. Children in single-parent households are 3 times more likely to be living below the poverty line than those in families with 2 married parents. Mothers are the primary breadwinner in 40% of families, an increase from 10% in 1960, yet families led by unmarried mothers tend to fare worse than those led by unmarried fathers.

Families are also changing how they spend time together. Media use for both parents and children has increased dramatically with the advent of tablets and smartphones. Over the last several decades, as women have entered the workforce, increasing numbers of children participate in childcare, and in after-school activities. Racial, ethnic, and economic disparities are found in those participating in these activities as well. More children from economically advantaged families participate in extracurricular activities; low-income and black families worry more about the availability of high-quality programming for their children.

The U.S. Census Bureau projects that by 2040 the majority of the U.S. population will consist of minorities, with steady increases in foreign-born populations and individuals reporting 2 or more ethnicities. This diversity will impact family composition, as well as family values and approaches to parenting. *Culture* refers to a pattern of social norms, values, language, and behavior shared by a group of individuals, and parents are thus affected by their culture. Parenting approaches to self-regulation vary across cultures with respect to promoting attention, compliance, delayed gratification, executive function, and effortful control.

Parenting Styles

Three styles of parenting are authoritative, authoritarian, and permissive, each with varying approaches to parental control and responsiveness. A fourth style, neglectful parenting, has also been suggested. **Authoritative parenting** describes a parenting style that is warm, responsive, and accepting but that also sets expectations for behavior and achievement. Differences are approached with reasoning and discussion rather than by exerting control. **Authoritarian parenting** is characterized by a high degree of parental control in which obedience is expected. Punishment is often employed to foster compliance rather than verbal discussion. **Permissive parenting** refers to an approach characterized by warmth and acceptability but with few rules or expectations, and the child's autonomy is highly valued. This contrasts with **neglectful parenting,** similarly characterized by few rules or expectations, but also by limited parental warmth or responsiveness.

Studies have found that an authoritative parenting style is most likely to be associated with positive child outcomes across multiple domains, including educational achievement and social-emotional competence. Parental supervision, consistency, and open communication reduce risky behaviors in adolescents. Harsh, inconsistent, and coercive discipline and physical punishment have been associated with increases in emotional and behavioral problems and may be a risk factor for child maltreatment. Much of the initial research on parenting styles was based on select U.S. populations (white middle-class families). Some suggest that an authoritarian parenting style may be beneficial in certain environments, and further work is needed to account for the economic and demographic changes in U.S. families.

Child Temperament

As evidenced by the effects of family structure, culture/ethnicity, and economics, parenting does not occur in isolation. The child also brings to the parent–child relationship their own personality, or **temperament,** a collection of traits that stay relatively constant over time (see Chapter 18). Nine traits have been identified in child temperament: activity level, predictability of behavior, reaction to new environments, adaptability, intensity, mood, distractibility, persistence, and sensitivity. Most infants (65%) fit into 1 of 3 groups: easy (40%), difficult (10%), and slow to warm up (15%), and these patterns are relatively stable over time. Although variations in temperament traits are part of normal human variations, certain behavioral difficulties have been associated with certain temperament types. For example, a difficult temperament has been associated with the development of externalizing behavior (e.g., acting-out, disruptive, and aggressive behavior) and not surprisingly, a slow-to-warm-up temperament with internalizing behavior (e.g., anxious and moody behavior).

Temperament traits are relatively stable, but how the child functions is affected by the environment, especially by parenting and the "goodness of fit" between the parent and child. Children with difficult temperament characteristics respond more negatively to neglectful parenting, and children of all temperament groups respond positively to responsive and sensitive parenting. Moreover, childhood traits such as low adaptability, impulsivity, and low frustration tolerance may lead some parents to engage in more negative parenting practices. These findings illustrate the interactive nature between parent and child, with parental behavior shaping child behavior, and vice versa.

Child Behavioral Problems

Emotional and behavioral problems are common in childhood. Indeed, many patterns of challenging behavior are normative in childhood, such as the tantrums and negativism seen in toddlers. Approximately 7.4% of children 4-17 yr of age have emotional and behavioral problems, defined as either elevated symptoms or serious overall difficulties. Emotional and behavioral problems have been associated with mother-only households, poverty, and developmental disorders. In preschool children, rates of clinically significant challenging behavior have been estimated at 8–17%, again with an increased prevalence among children living in poverty. The association between challenging behavior and poverty is likely multifactorial, mediated by increases in family stress, more negative parenting behaviors, lower-quality childcare, parental mental health issues, and community violence. Evidence also suggests that some types of challenging behavior apparent at a young age may persist. In one study, a high percentage of preschoolers identified as having both internalizing and externalizing behavior at age 3 yr continued to have similar difficulties at 6 yr.

Other risk factors for the development of challenging behavior include trauma and developmental problems. **Adverse childhood experiences (ACEs)** , defined as abuse and neglect, caregiver substance use, caregiver depression, and domestic violence or criminality, are often present during childhood. In the National Survey of Child and Adolescent Well-Being, 42% of children under 6 yr of age in the child welfare system had experienced 4 or more ACEs. Further, there was a cumulative relationship between emotional and behavioral problems and ACE exposure, with children exposed to 4 or more ACEs almost 5 times more likely to have internalizing problems than children not exposed to ACEs. A similar relationship was found for externalizing problems. Studies involving children with developmental disabilities suggest emotional and behavioral problems occur more frequently in this group than in typically developing children. These children may have delays in self-regulation and communication skills as well as increased family stress, which contribute to the increased likelihood of behavioral challenges.

Defining Positive Parenting

The precise definition of the components of positive parenting are lacking. Positive parenting must ensure the child's safety, health, and nutrition as well as developmental promotion. Common attributes of positive parenting include: caring, leading, providing, teaching, and communicating with the child in a consistent and unconditional manner. To account for the long-term goals of successful parenting in promoting optimal emotional, behavioral, and developmental outcomes, some suggest the term **purposeful parenting** and related characteristics (Table 19.1). The characterization of an ideal approach to parenting will evolve with ever-changing societal norms, but key components such as those in Table 19.1 will likely remain fundamental.

Table 19.1

Components of Purposeful Parenting

ATTRIBUTE	DEFINING ACTIONS

Protective	Ensure the child's emotional, developmental, and physiologic needs are met. Provide a safe environment. Balance the need for safety with the child's need for exploration and independence.
Personal	Show unconditional love and acceptance. Be kind and gentle. Avoid name-calling and harsh language. Label emotions and behaviors to help children understand their feelings. Teach and model helpful behavior rather than just saying “no.”
Progressive	Adapt parenting skills and discipline to meet the child's developmental needs. Learn about child development to know what to expect. Notice and praise new skills and desirable behaviors.
Positive	Be warm, supportive, and optimistic, even during times of misbehavior. Avoid harsh or physical punishments. Provide encouragement and reward effort, not just a positive result.
Playful	Enjoy child-led time together to encourage exploration, foster creativity, and learn new skills. Read together.
Purposeful	Take care of your needs as a parent. Keep the long-terms goals of parenting in mind. Preferentially use teaching instead of punishment to encourage desirable behavior. Be consistent with routines and expectations. Try to understand the reason behind the child's behavior.

Adapted from the work of Andrew Garner and the Ohio Chapter, American Academy of Pediatrics. http://ohioaap.org/wp-content/uploads/2013/07/BPoM_PurposefulParenting.pdf .

Parenting as an Intervention

The influence of parenting practices on child behavior, development, and overall adjustment has led to efforts to teach parenting as a method of primary prevention. The Video Interaction Project (VIP) uses a coaching and education model with recorded parent–child interactions to foster positive parenting behavior. These parenting behaviors range from reading aloud to encouraging interactive play. In an urban, low-income, primary care setting, parent and child outcomes for the VIP group were compared to those from a lower-intensity intervention (parent mailings encouraging positive parenting behaviors) and a control group. VIP produced the most robust impacts on socioemotional outcomes, including increased attention and decreased distress with separation, hyperactivity, and externalizing behavior in toddlers.

Positive parenting as a public health intervention has resulted in decreased rates of substantiated child maltreatment cases, out-of-home placements, and child maltreatment injuries. Other effective public health approaches include home-visiting programs, which have been deployed to at-risk families in an effort to improve maternal and child outcomes. The Maternal, Infant and Early Childhood Home Visiting Program, authorized as part of the Affordable Care

Act of 2010 and again in 2015, is part of the Medicare Access and Children's Health Insurance Program (CHIP) Reauthorization Act. A key component of home-visiting programs is the promotion of positive parenting behavior to foster child developmental and school readiness. Group parenting programs have been deployed as primary prevention to promote emotional and behavioral adjustment in young children. There is moderate-quality evidence that group-based parenting programs may improve parent–child interactions. These programs typically employ praise, encouragement, and affection and have been associated with improved self-esteem and social and academic competence.

Parenting behaviors have also been employed as an *intervention* to treat emotional and behavioral problems in young children. Parenting interventions such as Incredible Years, Triple P Positive Parenting Program, and New Forrest Parenting Program are effective for at least short-term improvements in child conduct problems, parental mental health, and parenting practices. Also called *parent training programs* , most teach the importance of play, rewards, praise, and consistent discipline and allow parents to practice new skills. This active-learning component distinguishes parent training programs from educational programs, which have been shown to be less effective.

Teaching emotional communication skills and positive parent–child interaction skills are associated with parent training programs that demonstrate a greater increase in parenting skills (Table 19.2). Several components are associated with programs that show greater improvements in child externalizing behavior: teaching parents to use time-out correctly, respond consistently, and interact positively with their children. All successful programs require parents to practice parenting skills during the program.

Table 19.2

Parent Training Program Components

COMPONENT	ACTIVITIES
Knowledge about child development and behavior	Providing developmentally-appropriate environment Learning about child development Promoting positive emotional development
Positive parent–child interactions	Learning the importance of positive, non–discipline-focused interactions Using skills that promote positive interactions Providing positive attention
Responsiveness and warmth	Responding sensitively to the child's emotional needs Providing appropriate physical contact and affection
Emotional communication	Using active listening to foster communication

	Helping children identify and express emotion
Disciplinary communication	Setting clear, appropriate, and consistent expectations Establishing limits and rules Choosing and following through with appropriate consequences
Discipline and behavior management	Understanding child misbehavior Understanding appropriate discipline strategies Using safe and appropriate monitoring and supervision practices Using reinforcement techniques Using problem solving for challenging behavior Being consistent
Promoting children's social skills and prosocial behavior	Teaching children to share, cooperate, and get along with others Using good manners
Promoting children's cognitive or academic skills	Fostering language and literacy development Promoting school readiness

Adapted from US Centers for Disease Control and Prevention: Parent training programs: insight for practitioners, Atlanta, 2009, CDC.

Parents have been found to benefit from participation in parenting programs. Before their participation, parents experienced a loss of control, self-blame, social isolation, and difficulty dealing with their child's emotional and behavioral problems, all of which improved after participation. The few studies that have assessed the long-term efficacy of parent-training programs suggest overall positive child outcomes, but also periods of relapse during which the use of positive parenting skills decreased. Use of social supports is associated with positive child outcomes and may be an important program component when considering long-term success.

The Role of the Pediatrician

Pediatricians and other pediatric practitioners have a primary responsibility to support the needs of parents and their children. Numerous programs and interventions have been developed to be delivered effectively and efficiently in the primary care setting.

The American Academy of Pediatrics published Bright Futures and the associated Guidelines for Preventive Care to standardize child health promotion and prevention in primary care. A substantial amount of the content in Bright Futures maps to the positive-parenting domains of safety, feeding, developmental promotion, and protection. Implementing Bright Futures guidelines in health supervision visits is an important way for pediatric practitioners to support the promotion of positive parenting in practice.

Reading aloud to children is a powerful strategy to promote language development, early literacy, and positive parent–child interaction. The Reach Out and Read program is a primary care–based intervention that trains practitioners to encourage parents to read with their child and provides books to at-risk families. In the absence of a formal partnership with Reach Out and Read, practitioners should promote the benefits of reading aloud to children and support parents in their efforts to develop habits that incorporate reading into daily routines.

In addition to VIP described earlier, other primary care models to promote parenting have been studied. The Healthy Steps for Young Children program is a strengths-based approach delivered in the primary care setting from infancy to age 3 yr. Healthy Steps promotes changes in parents' knowledge, beliefs, and psychologic health and changes in parenting behaviors using a variety of methods delivered in the office setting by the practitioner and Healthy Steps specialists and through home visits. Extensive evaluations have shown improvements in parental well-being, parenting practices, and parent–child attachment and decreased child behavior problems. Another promising approach uses community health workers and nurses to provide parenting education and allow mothers to practice parenting skills outside the office setting.

If participation in a formal parenting program is not possible, pediatric practitioners can still implement a systematic approach to support the needs of parents and their children. Practitioners can take advantage of materials in the public domain from national organizations devoted to child and family health, such as ZERO TO THREE (https://www.zerotothree.org/ and the American Academy of Pediatrics https://www.aap.org/). The U.S. Centers for Disease Control and Prevention (CDC) also provides evidenced-based parenting resources (https://www.cdc.gov/parents/essentials/index.html). Additional components include early identification of parents' concerns, addressing concerns in a supportive and nonjudgmental way, and providing linkage to treatment services when appropriate.

Parents want more information about child development, but parents of children with behavior problems often feel stigmatized and isolated. Practitioners are encouraged to be supportive and optimistic in their interactions with families, to develop a partnership aimed at promoting parent and child health (see Chapter 17). Practitioners may also encourage parents to practice new skills briefly in the office setting before trying a new skill at home. Active modeling by the practitioner using “teachable moments” may also be effective.

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CHAPTER 20

Assessment of Fetal Growth and Development

Susan Feigelman, Laura H. Finkelstein

The developing fetus is affected by social and environmental influences, including maternal nutritional status; substance use (both legal and illicit); and psychologic trauma. Correspondingly, the psychologic alterations experienced by the parents during the gestation profoundly impact the lives of all members of the family. Growing evidence implicates the importance of these and other maternal and paternal experiences that occur during and prior to the pregnancy (and even among members of earlier generations) on the subsequent development of the individual (epigenetic effects; see Chapter 100). The complex interplay among these forces and the somatic and neurologic transformations occurring in the fetus influence growth and behavior at birth, through infancy, and potentially throughout the individual's life.

Somatic Development

Embryonic Period

Table 20.1 lists milestones of prenatal development. By 6 days postconception age, as implantation begins, the embryo consists of a spherical mass of cells with a central cavity (the *blastocyst*). By 2 wk, implantation is complete and the uteroplacental circulation has begun; the embryo has 2 distinct layers, *endoderm* and *ectoderm* , and the amnion has started to form. By 3 wk, the 3rd primary germ layer *(mesoderm)* has appeared, along with a primitive neural tube and blood vessels. Paired heart tubes have begun to pump.

Table 20.1

Milestones of Prenatal Development

WK	DEVELOPMENTAL EVENTS
1	Fertilization and implantation; beginning of *embryonic* period
2	Endoderm and ectoderm appear (bilaminar embryo)
3	First missed menstrual period; mesoderm appears (trilaminar embryo); somites begin to form
4	Neural folds fuse; folding of embryo into human-like shape; arm and leg buds appear; crown-rump length 4-5 mm
5	Lens placodes, primitive mouth, digital rays on hands
6	Primitive nose, philtrum, primary palate
7	Eyelids begin; crown-rump length 2 cm
8	Ovaries and testes distinguishable
9	*Fetal* period begins; crown-rump length 5 cm; weight 8 g
12	External genitals distinguishable
20	Usual lower limit of viability; weight 460 g; length 19 cm
25	Third trimester begins; weight 900 g; length 24 cm
28	Eyes open; fetus turns head down; weight 1,000-1,300 g
38	Term

During wk 4-8, lateral folding of the embryologic plate, followed by growth at the cranial and caudal ends and the budding of arms and legs, produces a human-like shape. Precursors of skeletal muscle and vertebrae (somites) appear, along with the branchial arches that will form the mandible, maxilla, palate, external ear, and other head and neck structures. Lens placodes appear, marking the site of future eyes; the brain grows rapidly. By the end of wk 8, as the embryonic period closes, the rudiments of all major organ systems have developed; the crown-rump length is 3 cm.

Fetal Period

From the 9th wk on (fetal period), somatic changes consist of rapid body growth as well as differentiation of tissues, organs, and organ systems. Fig. 20.1 depicts changes in body proportion. By wk 10, the face is recognizably human. The midgut returns to the abdomen from the umbilical cord, rotating counterclockwise to bring the stomach, small intestine, and large intestine into their normal positions. By wk 12, the gender of the external genitals becomes clearly distinguishable. Lung development proceeds, with the budding of bronchi, bronchioles, and successively smaller divisions. By wk 20-24, primitive alveoli have formed and surfactant production has begun; before that time, the absence of alveoli renders the lungs useless as organs of gas exchange.

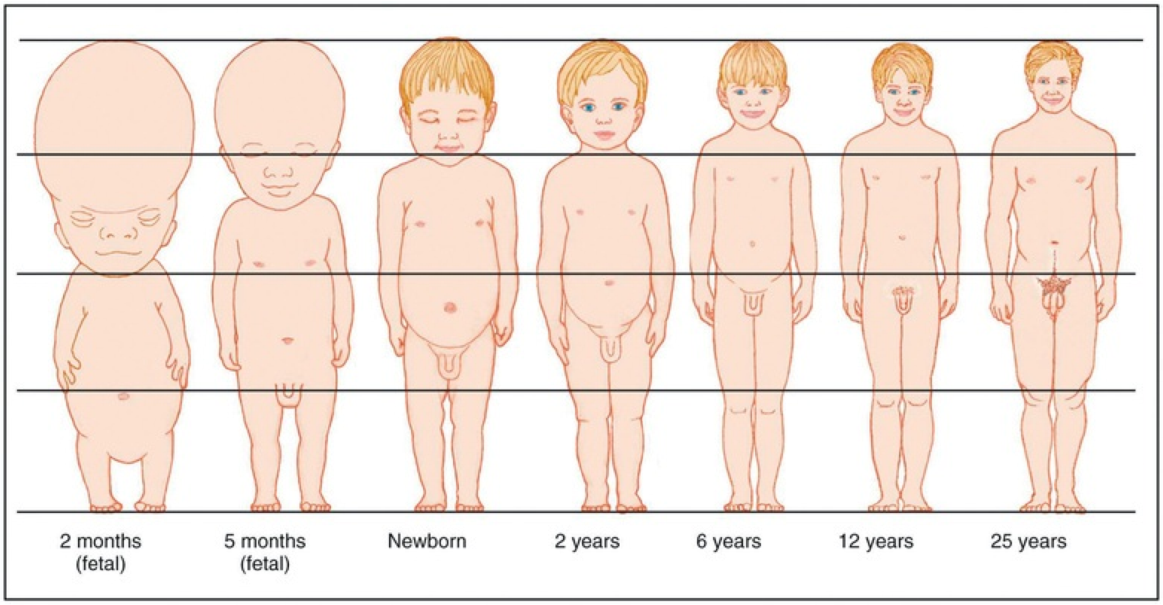

FIG. 20.1 **Changes in body proportions. Approximate changes in body proportions from fetal life through adulthood. (From Leifer G: *Introduction to maternity & pediatric nursing,* Philadelphia, 2011, WB Saunders, pp 347–385, Fig. 15-2.)**

During the 3rd trimester, weight triples and length doubles as body stores of protein, fat, iron, and calcium increase.

Neurologic Development

During the 3rd wk, a neural plate appears on the ectodermal surface of the trilaminar embryo. Infolding produces a neural tube that will become the central nervous system and a neural crest that will become the peripheral nervous system. Neuroectodermal cells differentiate into neurons, astrocytes, oligodendrocytes, and ependymal cells, whereas microglial cells are derived from mesoderm. By the 5th wk, the 3 main subdivisions of forebrain, midbrain, and hindbrain are evident. The dorsal and ventral horns of the spinal cord have begun to form, along with the peripheral motor and sensory nerves. Myelinization begins at midgestation and continues for years.

By the end of the embryonic period (wk 8), the gross structure of the nervous system has been established. On a cellular level, neurons migrate outward to form the 6 cortical layers. Migration is complete by the 6th mo, but differentiation continues. Axons and dendrites form synaptic connections at a rapid pace, making the central nervous system vulnerable to teratogenic or hypoxic influences throughout gestation. Fig. 20.2 shows rates of increase in DNA (a marker of cell number), overall brain weight, and cholesterol (a marker of myelinization). The prenatal and postnatal peaks of DNA probably represent rapid growth of neurons and glia, respectively. The glial cells are important in shaping the brain and neuronal circuits. The various types of glial cells are needed for the formation of axonal myelin sheaths, a range of functions in the formation and maintenance of neural pathways, and removal of waste (the brain has no lymphoid system for this task).

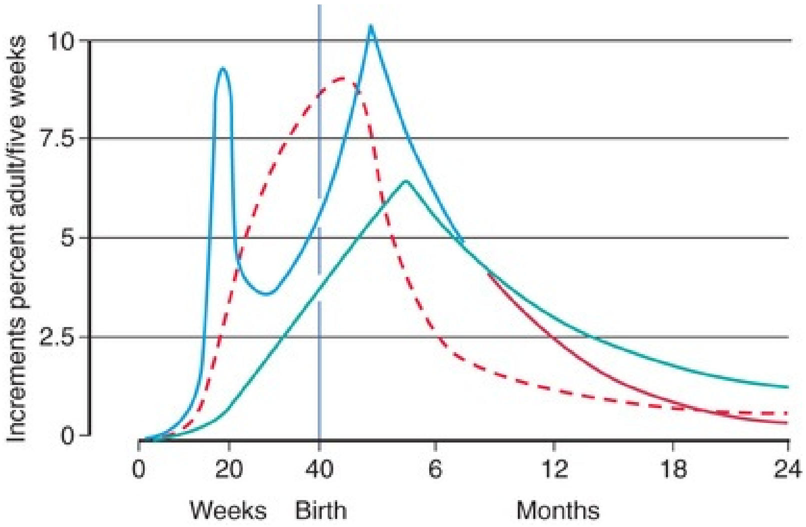

FIG. 20.2 Velocity curves of the various components of human brain growth. *Blue line,* DNA; *red line,* brain weight; *green line,* cholesterol. (From Brasel JA, Gruen RK. In Falkner F, Tanner JM, editors: *Human growth: a comprehensive treatise,* New York, 1986, Plenum Press, pp 78–95.)

By the time of birth, the structure of the brain is complete. However, many cells will undergo *apoptosis* (cell death). Synapses will be pruned back substantially, and new connections will be made, largely as a result of experience. Many psychiatric and developmental disorders are thought to result at least in part from disruptions in the **functional connectivity** of brain networks. Disorders of connectivity may begin during fetal life; MRI studies provide a developmental timetable for such connections that lend support to the possible role of disruptions in the establishment of such connections.

Behavioral Development

No behavioral evidence of neural function is detectable until the 3rd mo. Reflexive responses to tactile stimulation develop in a craniocaudal sequence.

By wk 13-14, breathing and swallowing motions appear. The grasp reflex appears at 17 wk and is well developed by 27 wk. Eye opening occurs around 26-28 wk. By midgestation, the full range of neonatal movements can be observed.

During the 3rd trimester, fetuses respond to external stimuli with heart rate elevation and body movements, which can be observed with ultrasound (see Chapter 115). Reactivity to auditory (vibroacoustic) and visual (bright light) stimuli vary, depending on their behavioral state, which can be characterized as quiet sleep, active sleep, or awake. Individual differences in the level of fetal activity are usually noted by mothers. Fetuses will preferentially turn to light patterns in the configuration of the human face. Fetal movement is affected by maternal medications and diet, increasing after ingestion of caffeine. Behavior may be entrained to the mother's diurnal rhythms: asleep during the day, active at night. Abnormal fetal movement patterns are found in neonates with subsequent muscular or neurologic abnormalities.

Fetal movement increases in response to a sudden auditory tone but decreases after several repetitions. This demonstrates **habituation** , a basic form of learning in which repeated stimulation results in a response decrement. If the tone changes in pitch, the movement increases again, which is evidence that the fetus distinguishes between a familiar, repeated tone and a novel tone. Habituation improves in older fetuses and decreases in neurologically impaired or physically stressed fetuses. Similar responses to visual and tactile stimuli have been observed.

Psychologic Changes in Parents

Many psychologic changes occur during pregnancy. An unplanned pregnancy may be met with anger, denial, or depression. Ambivalent feelings are the norm, whether or not the pregnancy was planned. Elation at the thought of producing a baby and the wish to be the perfect parent compete with fears of inadequacy and of the lifestyle changes that parenting will impose. Parents of an existing child may feel protective of the child, worried that the child may feel less valued. Old conflicts may resurface as a woman psychologically identifies with her own mother and with herself as a child. The father-to-be faces similar mixed feelings, and problems in the parental relationship may intensify.

Tangible evidence that a fetus exists as a separate being, whether as a result of ultrasonic visualization or awareness of fetal movements known as *quickening* (at 16-20 wk), often heightens a woman's feelings. Parents worry about the fetus's healthy development and mentally rehearse what they will do if the child is malformed, including their response to evidence of abnormality through ultrasound, amniocentesis, or other fetal laboratory tests. Toward the end of pregnancy, a woman becomes aware of patterns of fetal activity and reactivity and begins to ascribe to her fetus an individual personality and an ability to survive independently. Appreciation of the psychologic vulnerability of the expectant parents and of the powerful contribution of fetal behavior facilitates supportive clinical intervention.

Threats to Fetal Development

Mortality and morbidity are highest during the prenatal period (see Chapter 112). An estimated 50% of all pregnancies end in spontaneous abortion, including 10–15% of all clinically recognized pregnancies. The majority occur in the 1st trimester. Some occur as a result of chromosomal or other abnormalities.

Teratogens associated with gross physical and mental abnormalities include various infectious agents (e.g., toxoplasmosis, rubella, syphilis, Zika virus); chemical agents (e.g., mercury, thalidomide, antiepileptic medications, ethanol), high temperature, and radiation (see Chapters 115.6 and 736).

Teratogenic effects may also result in decreased growth and cognitive or behavioral deficits that only become apparent later in life. Nicotine has vasoconstrictor properties and may disrupt dopaminergic and serotonergic pathways. Prenatal exposure to cigarette smoke is associated with lower birthweight, stunting, and smaller head circumference, as well as changes in neonatal neurodevelopmental assessments. Later, these children are at increased risk for learning problems, attention and behavior disorders, and long-term health effects. Alcohol is a significant teratogen affecting physical development, cognition, and behavior (see Chapter 126.3). The effects of prenatal exposure to cocaine, also occurring through alternations in placental blood flow and in direct toxic effects to the developing brain, have been followed in several cohorts and are less dramatic than previously believed. Exposed adolescents show small but significant effects in behavior and functioning but may not show cognitive impairment. The associated risk factors, including other prenatal exposures (alcohol and cigarette co-use) as well as “toxic” postnatal environments frequently characterized by instability, multiple caregivers, and violence exposure remain significant (see Chapters 14 and 16).

The association between an inadequate nutrient supply to the fetus and low birthweight has been recognized for decades; this adaptation on the part of the fetus presumably increases the likelihood that the fetus will survive until birth. For any potential fetal insult, the extent and nature of its effects are determined by characteristics of the host as well as the dose and timing of the exposure. Inherited differences in the metabolism of ethanol, timing of exposure, and the mother's diet may explain the variability in fetal alcohol effects. Organ systems are most vulnerable during periods of maximum growth and differentiation, generally during the 1st trimester (**organogenesis**) (http://www2.epa.gov/children/children-are-not-little-adults details critical periods and specific developmental abnormalities).

Fetal adaptations or responses to an adverse situation in utero, termed **fetal programming** or **developmental plasticity** , have lifelong implications for the individual. Fetal programming may prepare the fetus for an environment that matches that experienced in utero. Fetal programming in response to some environmental and nutritional signals in utero increases the risk of cardiovascular disease, diabetes, and obesity in later life. These adverse long-term effects appear to represent a mismatch between fetal and neonatal environmental conditions and the conditions that the individual will confront later in life; a fetus deprived of adequate calories may or may not as a child or teenager face famine. One proposed mechanism for fetal programming is **epigenetic imprinting** , in which 1 of 2 alleles is turned off through environmentally induced epigenetic modification (see Chapters 97 and 100). Exposure to psychoactive drugs in utero produces drug–protein receptor interactions, affecting both nervous system development and neurotransmitter function. This dysregulation causes long-lasting effects on fetal growth and adult function and may have effects on future generations through these epigenetic changes.

Just as the fetal adaptations to the in utero environment may increase the likelihood of later metabolic conditions, the fetus adapts to the mother's psychologic distress. In response to the stressful environment, physiologic changes involving the hypothalamic-pituitary-adrenal axis and the autonomic nervous system occur. Dysregulation of these systems may explain the associations observed in some but not all studies between maternal distress and negative infant outcomes, including low birthweight, spontaneous abortion, prematurity, and decreased head circumference. In addition, children born to mothers experiencing high stress levels have been found to have higher rates of inattention, impulsivity, conduct disorders, and cognitive changes. Although these changes may have been adaptive in primitive cultures, they are maladaptive in modern societies, leading to psychopathology. Genetic variability, timing of stress during sensitive periods, and the quality of postnatal parenting can attenuate or exacerbate these associations.

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CHAPTER 21

The Newborn

John M. Olsson

(See also Chapter 113 .)

Regardless of gestational age, the newborn (neonatal) period begins at birth and includes the 1st mo of life. During this time, marked physiologic transitions occur in all organ systems, and the infant learns to respond to many forms of external stimuli. Because infants thrive physically and psychologically only in the context of their social relationships, any description of the newborn's developmental status has to include consideration of the parents' role as well.

Parental Role in Mother–Infant Attachment

Parenting a newborn infant requires dedication because a newborn's needs are urgent, continuous, and often unclear. Parents must attend to an infant's signals and respond empathically. Many factors influence parents' ability to assume this role.

Prenatal Factors

Pregnancy is a period of psychologic preparation for the profound demands of parenting. Women may experience ambivalence, particularly (but not exclusively) if the pregnancy was unplanned. If financial concerns, physical illness, prior miscarriages or stillbirths, or other crises interfere with psychologic preparation, the neonate may not be welcomed. For adolescent mothers, the demand that they relinquish their own developmental agenda, such as an active social life, may be especially burdensome.

The early experience of being mothered may establish unconsciously held expectations about nurturing relationships that permit mothers to “tune in” to their infants. These expectations are linked with the quality of later infant–parent interactions. Mothers whose early childhoods were marked by traumatic separations, abuse, or neglect may find it especially difficult to provide consistent, responsive care. Instead, they may reenact their childhood experiences with their own infants, as if unable to conceive of the mother–child relationship in any other way. **Bonding** may be adversely affected by several risk factors during pregnancy and in the postpartum period that undermine the mother–child relationship and may threaten the infant's cognitive and emotional development (Table 21.1).

Table 21.1

Prenatal Risk Factors for Attachment

Recent death of a loved one
Previous loss of or serious illness in another child
Prior removal of a child
History of depression or serious mental illness
History of infertility or pregnancy loss
Troubled relationship with parents
Financial stress or job loss
Marital discord or poor relationship with the other parent
Recent move or no community ties
No friends or social network
Unwanted pregnancy
No good parenting model
Experience of poor parenting
Drug and/or alcohol abuse
Extreme immaturity

From Dixon SD, Stein MT: *Encounters with children: pediatric behavior and development*, ed 4, Philadelphia, 2006, Mosby, p 131.

Social support during pregnancy, particularly support from the father and close family members, is also important. Conversely, conflict with or abandonment by the father during pregnancy may diminish the mother's ability to become absorbed with her infant. Anticipation of an early return to work may make some women reluctant to fall in love with their babies because of anticipated separation. Returning to work should be delayed for at least 6 wk, by which time feeding and basic behavioral adjustments have been established.

Many decisions have to be made by parents in anticipation of the birth of their child. One important choice is that of how the infant will be nourished. Among the important benefits of **breastfeeding** is its promotion of bonding. Providing breastfeeding education for the parents at the prenatal visit by the pediatrician and by the obstetrician during prenatal care can increase maternal confidence in breastfeeding after delivery and reduce stress during the newborn period (see Chapter 56).

Peripartum and Postpartum Influences

The continuous presence during labor of a woman trained to offer friendly support and encouragement (a **doula**) results in shorter labor, fewer obstetric complications (including cesarean section), and reduced postpartum hospital stays. Early skin-to-skin contact between mothers and infants immediately after birth may correlate with an increased rate and longer duration of breastfeeding. Most new parents value even a brief period of uninterrupted time in which to get to know their new infant, and increased mother–infant contact over the 1st days of life may improve long-term mother–child interactions. Nonetheless, early separation, although predictably very stressful, does not inevitably impair a mother's ability to bond with her infant. Early discharge home from the maternity ward may undermine bonding, particularly when a new mother is required to resume full responsibility for a busy household.

Postpartum depression may occur in the 1st wk or up to 6 mo after delivery and can adversely affect neonatal growth and development. Screening tools, such as the **Edinburgh Postnatal Depression Scale (EPDS)** , are available for use during neonatal and infant visits to the pediatric provider. On the EPDS, scores of 0-8 indicate a low likelihood of depression (Table 21.2). Cutoff-score recommendations for further evaluation of depression have ranged from 9 to 13; thus any woman scoring 9 or above should be evaluated further. If postpartum depression is present, referral for mental healthcare will greatly accelerate recovery.

Table 21.2

Edinburgh Postnatal Depression Scale

Instructions for Users

1. The mother is asked to underline the response that comes closest to how she has been feeling in the previous 7 days.
2. All 10 items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others.
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.
5. The Edinburgh Postnatal Depression Scale may be used at 6-8 wk to screen postnatal women. The child health clinic, a postnatal checkup, or a home visit may provide a suitable opportunity for its completion.

Edinburgh Postnatal Depression Scale

Name:
Address:
Baby's age:

Because you have recently had a baby, we would like to know how you are feeling. Please underline the answer that comes closest to how you have felt in the past 7 days, not just how you feel today.

Here is an example, already completed.

I have felt happy:

Yes, all the time
Yes, most of the time
No, not very often
No, not at all

This would mean: “I have felt happy most of the time” during the past week. Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
    - As much as I always could
    - Not quite so much now
    - Definitely not so much now

Not at all
2. I have looked forward with enjoyment to things
As much as I ever did
Rather less than I used to
Definitely less than I used to
Hardly at all
*3. I have blamed myself unnecessarily when things went wrong
Yes, most of the time
Yes, some of the time
Not very often
No, never
4. I have been anxious or worried for no good reason
No, not at all
Hardly ever
Yes, sometimes
Yes, very often
*5. I have felt scared or panicky for no very good reason
Yes, quite a lot
Yes, sometimes
No, not much
No, not at all
*6. Things have been getting on top of me
Yes, most of the time I haven't been able to cope at all
Yes, sometimes I haven't been coping as well as usual
No, most of the time I have coped quite well
No, I have been coping as well as ever
*7. I have been so unhappy that I have had difficulty sleeping
Yes, most of the time
Yes, sometimes
Not very often
No, not at all
*8. I have felt sad or miserable
Yes, most of the time
Yes, quite often
Not very often
No, not at all
*9. I have been so unhappy that I have been crying

Yes, most of the time
Yes, quite often
Only occasionally
No, never

*10. The thought of harming myself has occurred to me

Yes, quite often
Sometimes
Hardly ever
Never

Response categories are scored 0, 1, 2, and 3 according to increased severity of the symptom. Items marked with an asterisk (*) are reverse-scored (i.e., 3, 2, 1, and 0). The total score is calculated by adding the scores for each of the 10 items. Users may reproduce the scale without further permission provided they respect copyright (which remains with the *British Journal of Psychiatry*) by quoting the names of the authors, the title, and the source of the paper in all reproduced copies.

From Currie ML, Rademacher R: The pediatrician's role in recognizing and intervening in postpartum depression, *Pediatr Clin North Am* 51:785–801, 2004.

The Infant's Role in Mother–Infant Attachment

The in utero environment contributes greatly but not completely to the future growth and development of the fetus. Abnormalities in maternal-fetal placental circulation and maternal glucose metabolism or the presence of maternal infection can result in abnormal fetal growth. Infants may be small or large for gestational age as a result. These abnormal growth patterns not only predispose infants to an increased requirement for medical intervention, but also may affect their ability to respond behaviorally to their parents.

Physical Examination

Examination of the newborn should include an **evaluation of growth** (see Chapter 20) and an **observation of behavior** . The average term newborn weighs approximately 3.4 kg (7.5 lb); boys are slightly heavier than girls. Average weight does vary by ethnicity and socioeconomic status. The average length and head circumference are about 50 cm (20 in) and 35 cm (14 in), respectively, in term infants. Each newborn's growth parameters should be plotted on growth curves specific for that infant's gestational age to determine the appropriateness of size. Likewise, specific growth charts for conditions associated with variations in growth patterns have also been developed. The infant's response to being examined may be useful in assessing its vigor, alertness, and tone. Observing how the parents handle their infant, their comfort and affection, is also important. The order of the physical examination should be from the least to the most intrusive maneuver. Assessing visual tracking and response to sound and noting changes of tone with level of activity and alertness are very helpful. Performing this examination and sharing impressions with parents is an important opportunity to facilitate bonding (see Chapter 113).

Interactional Abilities

Soon after birth, neonates are alert and ready to interact and nurse. This first alert-awake period may be affected by maternal analgesics and anesthetics or fetal hypoxia. Neonates are nearsighted, having a fixed focal length of 8-12 inches, approximately the distance from the breast to the mother's face, as well as an inborn visual preference for faces. Hearing is well developed, and infants preferentially turn toward a female voice. These innate abilities and predilections increase the likelihood that when a mother gazes at her newborn, the baby will gaze back. The initial period of social interaction, usually lasting about 40 minutes, is followed by a period of somnolence. After that, briefer periods of alertness or excitation alternate with sleep. If a mother misses her baby's first alert-awake period, she may not experience as long a period of social interaction for several days. The hypothalamic-midbrain-limbic-paralimbic-cortical circuit of the parents interacts to support responses to the infants that are critical for effective parenting (e.g., emotion, attention, motivation, empathy, decision-making).

Modulation of Arousal

Adaptation to extrauterine life requires rapid and profound physiologic changes, including aeration of the lungs, rerouting of the circulation, and activation of the intestinal tract. The necessary behavioral changes are no less profound. To obtain nourishment, to avoid hypo- and hyperthermia, and to ensure safety, neonates must react appropriately to an expanded range of sensory stimuli. Infants must become aroused in response to stimulation, but not so overaroused that their behavior becomes disorganized. Underaroused infants are not able to feed and interact; overaroused infants show signs of **autonomic instability** , including flushing or mottling, perioral pallor, hiccupping, vomiting, uncontrolled limb movements, and inconsolable crying.

Behavioral States

The organization of infant behavior into discrete behavioral states may reflect an infant's inborn ability to regulate arousal. *Six states* have been described: quiet sleep, active sleep, drowsy, alert, fussy, and crying. In the **alert state** , infants visually fixate on objects or faces and follow them horizontally and (within a month) vertically; they also reliably turn toward a novel sound, as if searching for its source. When overstimulated, they may calm themselves by looking away, yawning, or sucking on their lips or hands, thereby increasing parasympathetic activity and reducing sympathetic nervous activity. The behavioral state determines an infant's muscle tone, spontaneous movement, electroencephalogram pattern, and response to stimuli. In **active sleep** , an infant may show progressively less reaction to a repeated heelstick (habituation), whereas in the **drowsy state** , the same stimulus may push a child into fussing or crying.

Mutual Regulation

Parents actively participate in an infant's state regulation, alternately stimulating and soothing. In turn, they are regulated by the infant's signals, responding to cries of hunger with a letdown of milk (or with a bottle). Such interactions constitute a system directed toward furthering the infant's physiologic homeostasis and physical growth. At the same time, they form the basis for the emerging psychologic relationship between parent and child. Infants come to associate the presence of the parent with the pleasurable reduction of tension (as in feeding) and show this preference by calming more quickly for their mother than for a stranger. This response in turn strengthens a mother's sense of efficacy and her connection with her baby.

Implications for the Pediatrician

The pediatrician can support healthy newborn development in several ways.

Optimal Practices

A **prenatal pediatric visit** allows pediatricians to assess potential threats to bonding (e.g., tense spousal relationship) and sources of social support. **Supportive hospital policies** include the use of birthing rooms rather than operating suites and delivery rooms; encouraging the father or a trusted relative or friend to remain with the mother during labor or the provision of a professional doula; the practice of giving the newborn infant to the mother immediately after drying and a brief assessment; placement of the newborn in the mother's room rather than in a central nursery; and avoiding in-hospital distribution of infant formula. Such policies ("Baby Friendly Hospital") have been shown to significantly increase breastfeeding rates (see Chapter 113.3). After discharge, **home visits** by nurses and lactation counselors can reduce early feeding problems and identify emerging medical conditions in either mother or baby. Infants requiring transport to another hospital should be brought to see the mother first, if at all possible. On discharge home, fathers can shield mothers from unnecessary visits and calls and take over household duties, allowing mothers and infants time to get to know each other without distractions. The **first office visit** should occur during the 1st 2 wk after discharge to determine how smoothly the mother and infant are making the transition to life at home. Babies who are discharged early, those who are breastfeeding, and those who are at risk for jaundice should be seen 1-3 days after discharge.

Assessing Parent–Infant Interactions

During a feeding or when infants are alert and face-to-face with their parents, it is normal for the dyad to appear absorbed in one another. Infants who become overstimulated by the parent's voice or activity may turn away or close their eyes, leading to a premature termination of the encounter. Alternatively, the infant may be ready to interact, but the parent may appear preoccupied. Asking a new mother about her own emotional state, and inquiring specifically about a history of depression, facilitates referral for therapy, which may provide long-term benefits to the child. Pediatricians may detect postpartum depression using the EPDS at well-child visits during the 1st yr (see Table 21.2).

Teaching About Individual Competencies

The **Newborn Behavior Assessment Scale (NBAS)** provides a formal measure of an infant's neurodevelopmental competencies, including state control, autonomic reactivity, reflexes, habituation, and orientation toward auditory and visual stimuli. This examination can also be used to demonstrate to parents an infant's capabilities and vulnerabilities. Parents might learn that they need to undress their infant to increase the level of arousal or to swaddle the infant to reduce overstimulation by containing random arm movements. The NBAS can be used to support the development of positive early parent–infant relationships. Demonstration of the NBAS to parents in the 1st wk of life has been shown to correlate with improvements in the caretaking environment months later.

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CHAPTER 22

The First Year

Mutiat T. Onigbanjo, Susan Feigelman

The prenatal period and the 1st yr of life provide the platform for remarkable growth and development, setting the trajectory for a child's life. **Neural plasticity** , the ability of the brain to be shaped by experience, both positive and negative, is at its peak. Total brain volume doubles in the 1st yr of life and increases by an additional 15% over the 2nd yr. Total brain volume at age 1 mo is approximately 36% of adult volume but by age 1 yr is approximately 72% (83% by 2 yr) (Fig. 22.1).

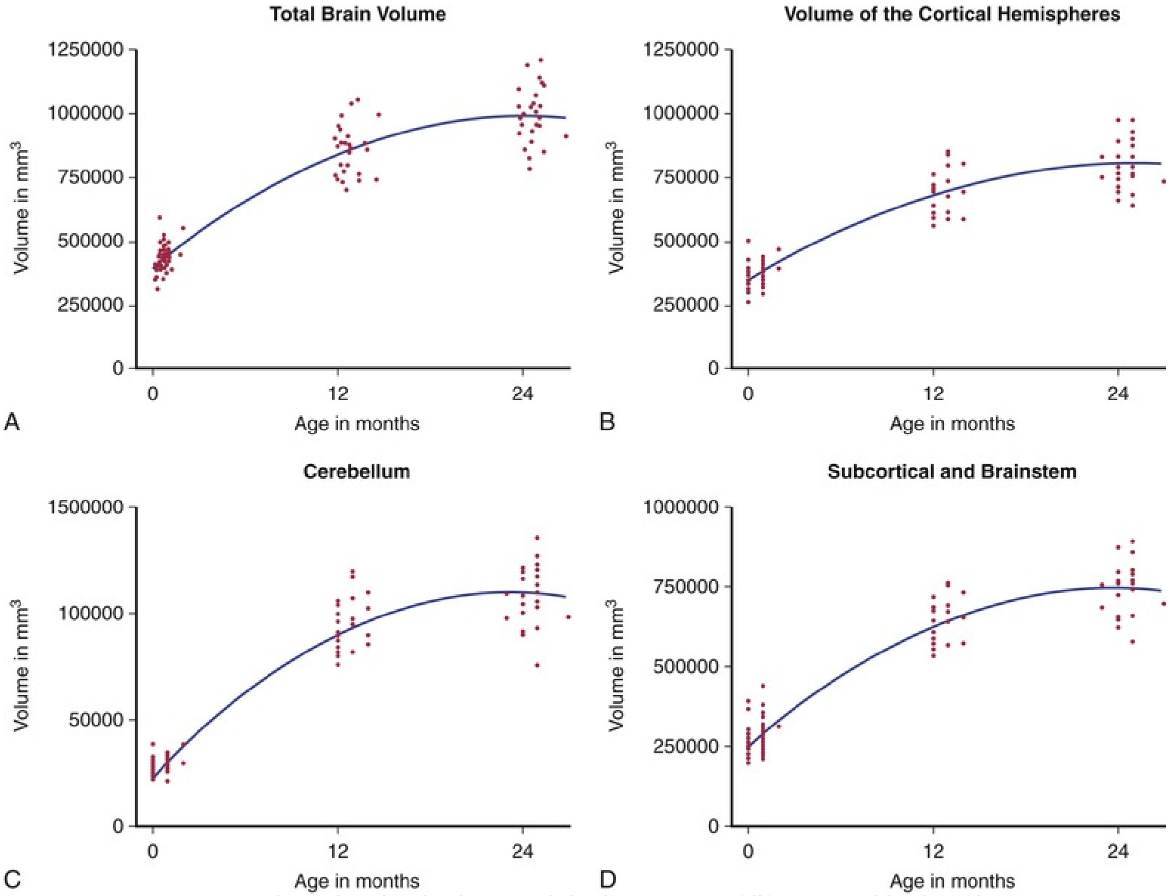

FIG. 22.1 Scatterplots showing brain growth in the 1st 2 yr of life. A, Total brain volume by age at scan. B, Cortical hemispheres. C, Cerebellum. D, Subcortical region and brainstem. (From Knickmeyer RC, Gouttard S, Kang C, et al: A structural MRI study of human brain development from birth to 2 years, *J Neurosci* 28(47):12176–12182, 2008.)

The acquisition of seemingly “simple” skills, such as swallowing, reflect a series of intricate and highly coordinated processes involving multiple levels of neural control distributed among several physiologic systems whose nature and relationships mature throughout the 1st yr of life. Substantial learning of the basic tools of language (phonology, word segmentation) occurs during infancy. Speech processing in older individuals requires defined and precise neuronal networks; the infant brain possesses a structural and functional organization similar to that of adults, suggesting that structural neurologic processing of speech may guide infants to discover the properties of their native language. Myelination of the cortex begins at 7-8 mo gestation and continues into adolescence and young adulthood. It proceeds posterior to anterior, allowing progressive maturation of sensory, motor, and finally associative pathways. Given the importance of iron, cholesterol, and other nutrients in myelination, adequate stores throughout infancy are critical (see Chapter 56). Insufficient interactions with caregivers or the wider environment may alter experience-dependent processes that are critical to brain structure development and function during infancy. Although for some processes, subsequent stimulation may allow catch-up, as the periods of plasticity close during the rapid developmental changes occurring in infancy, more permanent deficits may result.

The infant acquires new competences in all developmental domains. The concept of **developmental trajectories** recognizes that complex skills build on simpler ones; it is also important to realize how development in each domain affects functioning in all the others. All growth parameters should be plotted using the World Health Organization charts, which show how children from birth through 72 mo "should" grow under optimal circumstances (see Chapter 23 , Figs. 23.1 and 23.2). Table 22.1 presents an overview of key milestones by domain; Table 22.2 presents similar information arranged by age. Table 22.3 presents age at time of x-ray appearance of centers of ossification. Parents often seek information about "normal development" during this period and should be directed to reliable sources, including the American Academy of Pediatrics website (healthychildren.org).

Table 22.1

Developmental Milestones in 1st 2 Yr of Life

MILESTONE	AVERAGE AGE OF ATTAINMENT (MO)	DEVELOPMENTAL IMPLICATIONS
GROSS MOTOR		
Holds head steady while sitting	2	Allows more visual interaction
Pulls to sit, with no head lag	3	Muscle tone
Brings hands together in midline	3	Self-discovery of hands
Asymmetric tonic neck reflex gone	4	Can inspect hands in midline
Sits without support	6	Increasing exploration
Rolls back to stomach	6.5	Truncal flexion, risk of falls
Walks alone	12	Exploration, control of proximity to parents
Runs	16	Supervision more difficult
FINE MOTOR		
Grasps rattle	3.5	Object use
Reaches for objects	4	Visuomotor coordination
Palmar grasp gone	4	Voluntary release
Transfers object hand to hand	5.5	Comparison of objects
Thumb-finger grasp	8	Able to explore small objects
Turns pages of book	12	Increasing autonomy during book time
Scribbles	13	Visuomotor coordination
Builds tower of 2 cubes	15	Uses objects in combination
Builds tower of 6 cubes	22	Requires visual, gross, and fine motor coordination

COMMUNICATION AND LANGUAGE		
Smiles in response to face, voice	1.5	More active social participant
Monosyllabic babble	6	Experimentation with sound, tactile sense
Inhibits to “no”	7	Response to tone (nonverbal)
Follows 1-step command with gesture	7	Nonverbal communication
Follows 1-step command without gesture	10	Verbal receptive language (e.g., “Give it to me”)
Says “mama” or “dada”	10	Expressive language
Points to objects	10	Interactive communication
Speaks first real word	12	Beginning of labeling
Speaks 4-6 words	15	Acquisition of object and personal names
Speaks 10-15 words	18	Acquisition of object and personal names
Speaks 2-word sentences (e.g., “Mommy shoe”)	19	Beginning grammatization, corresponds with 50-word vocabulary
COGNITIVE		
Stares momentarily at spot where object disappeared	2	Lack of object permanence (out of sight, out of mind; e.g., yarn ball dropped)
Stares at own hand	4	Self-discovery, cause and effect
Bangs 2 cubes	8	Active comparison of objects
Uncovers toy (after seeing it hidden)	8	Object permanence
Egocentric symbolic play (e.g., pretends to drink from cup)	12	Beginning symbolic thought
Uses stick to reach toy	17	Able to link actions to solve problems
Pretend play with doll (e.g., gives doll bottle)	17	Symbolic thought

Table 22.2

Emerging Patterns of Behavior During the 1st Yr of Life*

NEONATAL PERIOD (1ST 4 WK)	
Prone:	Lies in flexed attitude; turns head from side to side; head sags on ventral suspension
Supine:	Generally flexed and a little stiff
Visual:	May fixate face on light in line of vision; doll's eye movement (oculocephalic reflex) of eyes on turning of the body
Reflex:	Moro response active; stepping and placing reflexes; grasp reflex active
Social:	Visual preference for human face
AT 1 MO	
Prone:	Legs more extended; holds chin up; turns head; head lifted momentarily to plane of body on ventral suspension
Supine:	Tonic neck posture predominates; supple and relaxed; head lags when pulled to sitting position
Visual:	Watches person; follows moving object
Social:	Body movements in cadence with voice of other in social contact; beginning to smile
AT 2 MO	
Prone:	Raises head slightly farther; head sustained in plane of body on ventral suspension
Supine:	Tonic neck posture predominates; head lags when pulled to sitting position
Visual:	Follows moving object 180 degrees
Social:	Smiles on social contact; listens to voice and coos
AT 3 MO	

Prone:	Lifts head and chest with arms extended; head above plane of body on ventral suspension
Supine:	Tonic neck posture predominates; reaches toward and misses objects; waves at toy
Sitting:	Head lag partially compensated when pulled to sitting position; early head control with bobbing motion; back rounded
Reflex:	Typical Moro response has not persisted; makes defensive movements or selective withdrawal reactions
Social:	Sustained social contact; listens to music; says “aah, ngah”
AT 4 MO	
Prone:	Lifts head and chest, with head in approximately vertical axis; legs extended
Supine:	Symmetric posture predominates, hands in midline; reaches and grasps objects and brings them to mouth
Sitting:	No head lag when pulled to sitting position; head steady, tipped forward; enjoys sitting with full truncal support
Standing:	When held erect, pushes with feet
Adaptive:	Sees raisin, but makes no move to reach for it
Social:	Laughs out loud; may show displeasure if social contact is broken; excited at sight of food
AT 7 MO	
Prone:	Rolls over; pivots; crawls or creep-crawls (Knobloch)
Supine:	Lifts head; rolls over; squirms
Sitting:	Sits briefly, with support of pelvis; leans forward on hands; back rounded
Standing:	May support most of weight; bounces actively
Adaptive:	Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; rakes at raisin
Language:	Forms polysyllabic vowel sounds
Social:	Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact
AT 10 MO	
Sitting:	Sits up alone and indefinitely without support, with back straight
Standing:	Pulls to standing position; “cruises” or walks holding on to furniture
Motor:	Creeps or crawls
Adaptive:	Grasps objects with thumb and forefinger; pokes at things with forefinger; picks up pellet with assisted pincer movement; uncovers hidden toy; attempts to retrieve dropped object; releases object grasped by other person
Language:	Repetitive consonant sounds (“mama,” “dada”)
Social:	Responds to sound of name; plays peek-a-boo or pat-a-cake; waves bye-bye
AT 1 YR	
Motor:	Walks with one hand held; rises independently, takes several steps (Knobloch)
Adaptive:	Picks up raisin with unassisted pincer movement of forefinger and thumb; releases object to other person on request or gesture
Language:	Says a few words besides “mama,” “dada”
Social:	Plays simple ball game; makes postural adjustment to dressing

[*] Data are derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others.

Data from Knobloch H, Stevens F, Malone AF: *Manual of developmental diagnosis,* Hagerstown, MD, 1980, Harper & Row.

Table 22.3

Time of Radiographic Appearance of Centers of Ossification in Infancy and Childhood

BOYS—AGE AT APPEARANCE*	**BONES AND EPIPHYSEAL CENTERS**	**GIRLS—AGE AT APPEARANCE***
HUMERUS, HEAD		
3 wk		3 wk
CARPAL BONES		
2 mo ± 2 mo	Capitate	2 mo ± 2 mo
3 mo ± 2 mo	Hamate	2 mo ± 2 mo
30 mo ± 16 mo	Triangular †	21 mo ± 14 mo
42 mo ± 19 mo	Lunate †	34 mo ± 13 mo
67 mo ± 19 mo	Trapezium †	47 mo ± 14 mo
69 mo ± 15 mo	Trapezoid †	49 mo ± 12 mo
66 mo ± 15 mo	Scaphoid †	51 mo ± 12 mo
No standards available	Pisiform †	No standards available
METACARPAL BONES		
18 mo ± 5 mo	II	12 mo ± 3 mo
20 mo ± 5 mo	III	13 mo ± 3 mo
23 mo ± 6 mo	IV	15 mo ± 4 mo
26 mo ± 7 mo	V	16 mo ± 5 mo
32 mo ± 9 mo	I	18 mo ± 5 mo
FINGERS (EPIPHYSES)		
16 mo ± 4 mo	Proximal phalanx, 3rd finger	10 mo ± 3 mo
16 mo ± 4 mo	Proximal phalanx, 2nd finger	11 mo ± 3 mo
17 mo ± 5 mo	Proximal phalanx, 4th finger	11 mo ± 3 mo
19 mo ± 7 mo	Distal phalanx, 1st finger	12 mo ± 4 mo
21 mo ± 5 mo	Proximal phalanx, 5th finger	14 mo ± 4 mo
24 mo ± 6 mo	Middle phalanx, 3rd finger	15 mo ± 5 mo
24 mo ± 6 mo	Middle phalanx, 4th finger	15 mo ± 5 mo
26 mo ± 6 mo	Middle phalanx, 2nd finger	16 mo ± 5 mo
28 mo ± 6 mo	Distal phalanx, 3rd finger	18 mo ± 4 mo
28 mo ± 6 mo	Distal phalanx, 4th finger	18 mo ± 5 mo
32 mo ± 7 mo	Proximal phalanx, 1st finger	20 mo ± 5 mo
37 mo ± 9 mo	Distal phalanx, 5th finger	23 mo ± 6 mo
37 mo ± 8 mo	Distal phalanx, 2nd finger	23 mo ± 6 mo
39 mo ± 10 mo	Middle phalanx, 5th finger	22 mo ± 7 mo
152 mo ± 18 mo	Sesamoid (adductor pollicis)	121 mo ± 13 mo
HIP AND KNEE		
Usually present at birth	Femur, distal	Usually present at birth
Usually present at birth	Tibia, proximal	Usually present at birth
4 mo ± 2 mo	Femur, head	4 mo ± 2 mo
46 mo ± 11 mo	Patella	29 mo ± 7 mo
FOOT AND ANKLE ‡		

* To nearest month.

† Except for the capitate and hamate bones, the variability of carpal centers is too great to make them very useful clinically.

‡ Standards for the foot are available, but normal variation is wide, including some familial variants, so this area is of little clinical use.

Values represent mean ± standard deviation, when applicable.

The norms present a composite of published data from the Fels Research Institute, Yellow

Springs, OH (Pyle SI, Sontag L: *AJR Am J Roentgenol* 49:102, 1943), and unpublished data from the Brush Foundation, Case Western Reserve University, Cleveland, OH, and the Harvard School of Public Health, Boston, MA. Compiled by Lieb, Buehl, and Pyle.

Age 0-2 Months

In the full-term infant, **myelination** is present by the time of birth in the dorsal brainstem, cerebellar peduncles, and posterior limb of the internal capsule. The cerebellar white matter acquires myelin by 1 mo of age and is well myelinated by 3 mo. The subcortical white matter of the parietal, posterior frontal, temporal, and calcarine cortex is partially myelinated by 3 mo of age. In this period the infant experiences tremendous growth. Physiologic changes allow the establishment of effective feeding routines and a predictable sleep–wake cycle. The social interactions that occur as parents and infants accomplish these tasks lay the foundation for cognitive and emotional development.

Physical Development

A newborn's weight may initially decrease 10% (vaginal delivery) to 12% (cesarean section) below birthweight in the 1st wk as a result of excretion of excess extravascular fluid and limited nutritional intake. Nutrition improves as colostrum is replaced by higher-fat content breast milk, and when infants learn to latch on and suck more efficiently, and as mothers become more comfortable with feeding techniques. Infants regain or exceed birthweight by 2 wk of age and should grow at approximately 30 g (1 oz) per day during the 1st mo (see Table 27.1). This is the period of fastest postnatal growth. Arms are held to the sides. Limb movements consist largely of uncontrolled writhing, with apparently purposeless opening and closing of the hands. Smiling occurs involuntarily. Eye gaze, head turning, and sucking are under better control and thus can be used to demonstrate infant perception and cognition. An infant's preferential turning toward the mother's voice is evidence of recognition memory.

Six **behavioral states** have been described (see Chapter 21). Initially, sleep and wakefulness are evenly distributed throughout the 24 hr day (Fig. 22.2). Neurologic maturation accounts for the consolidation of sleep into blocks of 5 or 6 hr at night, with brief awake, feeding periods. Learning also occurs; infants whose parents are consistently more interactive and stimulating during the day learn to concentrate their sleeping during the night.

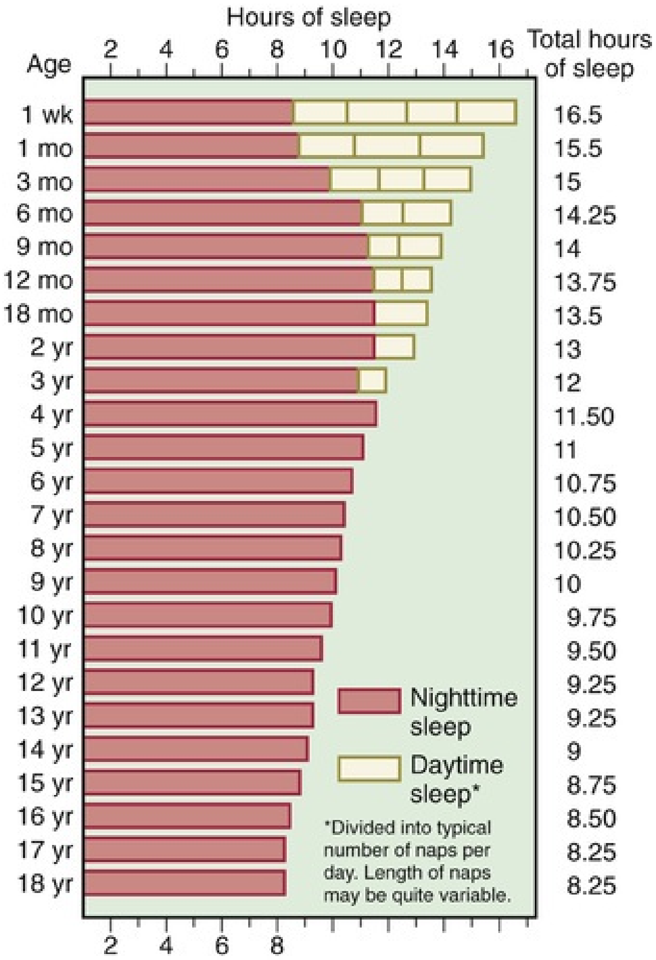

FIG. 22.2 Typical sleep requirements in children. (From Ferber R: *Solve your child* 's *sleep problems* , New York, 1985, Simon & Schuster.)

Cognitive Development

Infants can differentiate among patterns, colors, and consonants. They can recognize facial expressions (smiles) as similar, even when they appear on different faces. They also can match abstract properties of stimuli, such as contour, intensity, or temporal pattern, across sensory modalities. Infants at 2 mo of age can discriminate rhythmic patterns in native vs non-native language. Infants appear to seek stimuli actively, as though satisfying an innate need to make sense of the world. These phenomena point to the integration of sensory inputs in the central nervous system. Caretaking activities provide visual, tactile, olfactory, and auditory stimuli, all of which support the development of cognition. Infants **habituate** to the familiar, attending less to repeated stimuli and increasing their attention to novel stimuli.

Emotional Development

The infant is dependent on the environment to meet his or her needs. The consistent availability of a trusted adult to meet the infant's urgent needs creates the conditions for **secure attachment** . Basic **trust vs mistrust,** the first of Erikson's psychosocial stages (see Chapter 18), depends on attachment and reciprocal maternal bonding. Crying occurs in response to stimuli that may be obvious (a soiled diaper) but are often obscure (see Chapter 22.1). Infants who are consistently picked up and held in response to distress cry less at 1 yr and show less aggressive behavior at 2 yr. Infants cry in response to the cry of another infant, which has been interpreted as an early sign of empathy.

Implications for Parents and Pediatricians

Success or failure in establishing feeding and sleep cycles influences parents' feelings of competence. When things go well, the parents' anxiety and ambivalence, as well as the exhaustion of the early weeks, decrease. Infant issues (e.g., colic) or familial conflict may prevent this from occurring. With physical recovery from delivery and hormonal normalization, the mild postpartum “blues” that affects many mothers passes. If the mother continues to feel sad, overwhelmed, and anxious, the possibility of moderate to severe **postpartum depression,** found in 10–15% of postpartum women, needs to be considered. Major depression that arises during pregnancy or in the postpartum period threatens the mother–child relationship and is a risk factor for later cognitive and behavioral problems. The pediatrician may be the first professional to encounter the depressed mother and should be instrumental in assisting her in seeking treatment (see Chapter 21).

Age 2-6 Months

At about age 2 mo, the emergence of voluntary (social) smiles and increasing eye contact mark a change in the parent–child relationship, heightening the parents' sense of being loved reciprocally. During the next months, an infant's range of motor and social control and cognitive engagement increases dramatically. Mutual regulation takes the form of complex social interchanges, resulting in strong mutual attachment and enjoyment. Routines are established. Parents are less fatigued.

Physical Development

Between 3 and 4 mo of age, the rate of growth slows to approximately 20 g/day (see Table 27.1 and Figs. 23.1 and 23.2). By age 4 mo, birthweight is doubled. Early reflexes that limited voluntary movement recede (e.g., **primitive reflexes** ; see Chapter 608). Disappearance of the asymmetric tonic neck reflex means that infants can begin to examine objects in the midline and manipulate them with both hands. Waning of the early grasp reflex allows infants both to hold objects and to let them go voluntarily. A novel object may elicit purposeful, although inefficient, reaching. The quality of spontaneous movements also changes, from larger writhing to smaller, circular movements that have been described as “fidgety.” Abnormal or absent fidgety movements may constitute a risk factor for later neurologic abnormalities.

Increasing control of truncal flexion makes intentional rolling possible. Once infants can hold their heads steady while sitting, they can gaze across at things rather than merely looking up at them, opening up a new visual range. They can begin taking food from a spoon. At the same time, maturation of the visual system allows greater depth perception.

In this period, infants achieve stable state regulation and regular sleep–wake cycles. Total sleep requirements are approximately 14-16 hr/24 hr, with about 9-10 hr concentrated at night and 2 naps/day. Approximately 70% of infants sleep for a 6-8 hr stretch by age 6 mo (see Fig. 22.2). By 4-6 mo, the sleep electroencephalogram shows a mature pattern, with demarcation of rapid eye movement and 3 stages of non–rapid eye movement sleep. The sleep cycle remains shorter than in adults (50-60 min vs approximately 90 min). As a result, infants arouse to light sleep or wake frequently during the night, setting the stage for behavioral sleep problems (see Chapter 31).

Cognitive Development

The overall effect of these developments is a qualitative change. At 4 mo of age, infants are described as “hatching” socially, becoming interested in a wider world. During feeding, infants no longer focus exclusively on the mother, but become distracted. In the mother's arms, the infant may literally turn around, preferring to face outward.

Infants at this age also explore their own bodies, staring intently at their hands, vocalizing, blowing bubbles, and touching their ears, cheeks, and genitals. These explorations represent an early stage in the understanding of cause and effect as infants learn that voluntary muscle movements generate predictable tactile and visual sensations. They also have a role in the emergence of a sense of self, separate from the mother. This is the 1st stage of personality development. Infants come to associate certain sensations through frequent repetition. The proprioceptive feeling of holding up the hand and wiggling the fingers always accompanies the sight of the fingers moving. Such “self” sensations are consistently linked and reproducible at will. In contrast, sensations that are associated with “other” occur with less regularity and in varying combinations. The sound, smell, and feel of the mother sometimes appear promptly in response to crying, but sometimes do not. The satisfaction that the mother or another loving adult provides continues the process of attachment.

Emotional Development and Communication

Babies interact with increasing sophistication and range. The primary **emotions** of anger, joy, interest, fear, disgust, and surprise appear in appropriate contexts as distinct facial expressions. When face-to-face, the infant and a trusted adult can match affective expressions (smiling or surprise) approximately 30% of the time. Initiating games (singing, hand games) increases social development. Such face-to-face behavior reveals the infant's ability to share emotional states, the 1st step in the development of communication. Infants of depressed parents show a different pattern, spending less time in coordinated movement with their parents and making fewer efforts to reengage. Rather than anger, they show sadness and a loss of energy when the parents continue to be unavailable.

Implications for Parents and Pediatricians

Motor and sensory maturation makes infants at 3-6 mo exciting and interactive. Some parents experience their 4 mo old child's outward turning as a rejection, secretly fearing that their infants no longer love them. For most parents, this is a happy period. Most parents excitedly report that they can hold conversations with their infants, taking turns vocalizing and listening. Pediatricians share in the enjoyment, as the baby coos, makes eye contact, and moves rhythmically. Infants who do not show this reciprocal language and movements are at risk for autism spectrum disorders or other developmental disabilities (see Chapters 52 and 54). If this visit does not feel joyful and relaxed, causes such as social stress, family dysfunction, parental mental illness, or problems in the infant–parent relationship should be considered. Parents can be reassured that responding to an infant's emotional needs cannot spoil the infant. Giving vaccines and drawing blood while the child is seated on the parent's lap or nursing at the breast increases pain tolerance.

Age 6-12 Months

With achievement of the sitting position, increased mobility, and new skills to explore the world around them, 6-12 mo old infants show advances in cognitive understanding and communication, and new tensions arise in regard to attachment and separation. Infants develop will and intentions, characteristics that most parents welcome but still find challenging to manage.

Physical Development

Growth slows more (see Table 27.1 and Figs. 23.1 and 23.2). By the 1st birthday, birthweight has tripled, length has increased by 50%, and head circumference has increased by 10 cm (4 in). The ability to sit unsupported (6-7 mo) and to pivot while sitting (around 9-10 mo) provides increasing opportunities to manipulate several objects at a time and to experiment with novel combinations of objects. These explorations are aided by the emergence of a thumb–finger grasp (8-9 mo) and a neat pincer grasp by 12 mo. Voluntary release emerges at 9 mo. Many infants begin crawling and pulling to stand around 8 mo, followed by cruising. Some walk by 1 yr. Motor achievements correlate with increasing myelinization and cerebellar growth. These gross motor skills expand infants' exploratory range and create new physical dangers, as well as opportunities for learning. Tooth eruption occurs, usually starting with the mandibular central incisors. Tooth development reflects skeletal maturation and bone age, although there is wide individual variation (see Table 22.3 and Chapter 333).

Cognitive Development

The 6 mo old infant has discovered his hands and will soon learn to manipulate objects. At first, everything is mouthed. In time, novel objects are picked up, inspected, passed from hand to hand, banged, dropped, and then mouthed. Each action represents a nonverbal idea about what things are for (in Piagetian terms, a *schema* ; see Chapter 18). The complexity of an infant's play, how many different schemata are brought to bear, is a useful index of cognitive development at this age. The pleasure, persistence, and energy with which infants tackle these challenges suggest the existence of an intrinsic drive or mastery motivation. Mastery behavior occurs when infants feel secure; those with less secure attachments show limited experimentation and less competence.

A major milestone is the achievement by 9 mo of **object permanence** (**constancy**), the understanding that objects continue to exist, even when not seen. At 4-7 mo of age, infants look down for a yarn ball that has been dropped but quickly give up if it is not seen. With object constancy, older infants persist in searching. They will find objects hidden under a cloth or behind the examiner's back. Peek-a-boo brings unlimited pleasure as the child magically brings back the other player. Events seem to occur as a result of the child's own activities.

Emotional Development

The advent of object permanence corresponds with qualitative changes in social and communicative development. Infants look back and forth between an approaching stranger and a parent and may cling or cry anxiously, demonstrating **stranger anxiety** . Separations often become more difficult. Infants who have been sleeping through the night for months begin to awaken regularly and cry, as though remembering that the parents are nearby or in the next room.

A new demand for **autonomy** also emerges. Poor weight gain at this age often reflects a struggle between an infant's emerging independence and parent's control of the feeding situation. Use of the 2-spoon method of feeding (1 for the child and 1 for the parent), finger foods, and a high chair with tray table can avert potential problems. Tantrums make their first appearance as the drives for autonomy and mastery come in conflict with parental controls and the infant's still-limited abilities.

Communication

Infants at 7 mo of age are adept at nonverbal communication, expressing a range of emotions and responding to vocal tone and facial expressions. About 9 mo of age, infants become aware that emotions can be shared between people; they show parents toys as a way of sharing their happy feelings. Between 8 and 10 mo of age, babbling takes on a new complexity, with multisyllabic sounds (“ba-da-ma”) called **canonical babbling** . Babies can discriminate between languages. Infants in bilingual homes learn the characteristics and rules that govern 2 different languages. Social interaction (attentive adults taking turns vocalizing with the infant) profoundly influences the acquisition and production of new sounds. The first true word (i.e., a sound used consistently to refer to a specific object or person) appears in concert with an infant's discovery of object permanence. Picture books now provide an ideal context for verbal language acquisition. With a familiar book as a shared focus of attention, a parent and child engage in repeated cycles of pointing and labeling, with elaboration and feedback by the parent. The addition of sign language may support infant development while enhancing parent–infant communication.

Implications for Parents and Pediatricians

With the developmental reorganization that occurs around 9 mo of age, previously resolved issues of feeding and sleeping reemerge. Pediatricians can prepare parents at the 6 mo visit so that these problems can be understood as the result of developmental progress and not regression. Parents should be encouraged to plan ahead for necessary, and inevitable, separations (e.g., babysitter, daycare). Routine preparations may make these separations easier. Dual parent employment has not been consistently found to be harmful or beneficial for long-term cognitive or social-emotional outcomes. Introduction of a **transitional object** may allow the infant to self-comfort in the parents' absence. The object cannot have any potential for asphyxiation or strangulation.

Infants' wariness of strangers often makes the 9 mo examination difficult, particularly if the infant is temperamentally prone to react negatively to unfamiliar situations. Initially, the pediatrician should avoid direct eye contact with the child. Time spent talking with the parent and introducing the child to a small, washable toy will be rewarded with more cooperation. The examination can be continued on the parent's lap when feasible.

22.1

Infant Crying and Colic

Susan Feigelman

Crying or fussiness is present in all babies but reaches medical attention in about 20% of infants younger than 2 mo. Although usually a transient and normal infant behavior, crying is often associated with parental concern and distress. On average, babies cry 2 hr/day, peaking at 6 wk of age. Premature infants will have peak crying at 6 wk corrected age (Fig. 22.3). Small-for-gestational-age and premature babies may be at higher risk. The peak period of infant crying usually occurs in the evenings and early part of the night. Excessive crying or fussiness persisting longer than 3-5 mo may be associated with behavioral problems in an older child (anxiety, aggression, hyperactivity), decreased duration of breastfeeding, or postnatal depression, but it is uncertain which is the cause or effect. Most infants with crying/fussiness do not have gastroesophageal reflux, lactose intolerance, constipation, or cow's milk protein allergy.

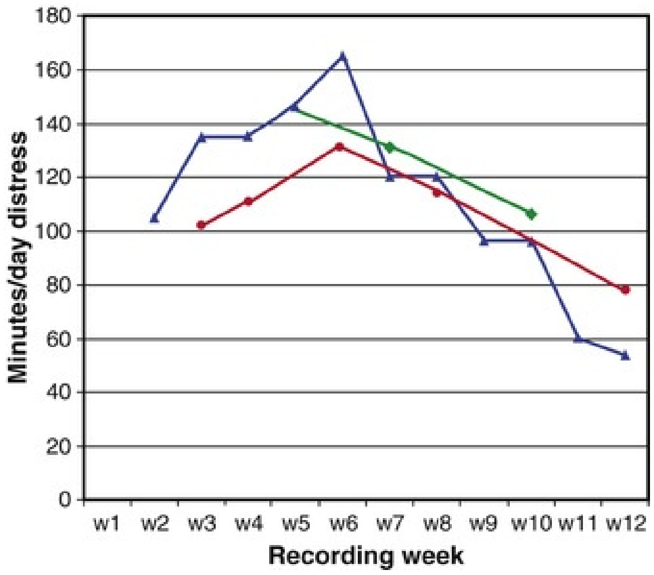

FIG. 22.3 Crying amounts and patterns from three North American studies illustrating similarities in crying pattern. (From Barr RG, Trent RB, Cross J: Age-related incidence curve of hospitalized shaken baby syndrome cases: convergent evidence for crying as a trigger to shaking, *Child Abuse Neglect*

30(1):7–16, 2006.)

Acute-onset uncontrollable crying could be caused by a medical condition. Potentially overlooked conditions to consider include corneal abrasion, tourniquet effect of a hair wrapped around a digit or penis, occult fracture, urinary tract infection, acute abdomen including inguinal hernia, or anomalous coronary artery. Breastfeeding mothers should be questioned about medications, drugs, and diet. Gastrointestinal distress can result from a maternal diet high in cruciferous vegetables. Most of the time, the etiology of a serious problem can be discovered with a careful history and physical examination.

Crying is a normal part of neurobehavioral development. Infants have various signals for their needs and for getting attention from a caregiver. These behaviors progressively increase in intensity in many infants, from changes in breathing and color, to postural and movement changes, and then to calm vocalizations. These precry cues, if not attended to, will eventually lead to active crying. Some infants may go directly to crying, perhaps based on temperament; these infants may be less easily consolable, more intense, or more responsive to sensory stimuli. Management of crying/fussiness should include teaching caregivers about precry cues and responding to the signal for feeding in a calm, relaxed manner. If sensory overstimulation is a factor, creating a nondistracting, calm environment may help, as well as swaddling. When lack of sensory stimulation is present, mother–infant skin-to-skin contact and carrying the infant may be beneficial. In all situations, reassurance that this is both normal and transient, with only 5% of infants persisting beyond 3 mo of age, helps the family cope. Teaching families about expectations for normal crying behavior can reduce emergency department visits.

The emotional significance of any experience depends on both the individual child's temperament and the parent's responses (see Table 18.1); differing feeding schedules produce differing reactions. Hunger generates increasing tension; as the urgency peaks, the infant cries, the parent offers the breast or bottle, and the tension dissipates. Infants fed “on demand” consistently experience this link among their distress, the arrival of the parent, and relief from hunger. Most infants fed on a fixed schedule quickly adapt their hunger cycle to the schedule. Those who cannot adapt, because they are temperamentally prone to irregular biologic rhythms, experience periods of unrelieved hunger as well as unwanted feedings when they already feel full. Similarly, infants who are fed at the parents' convenience, with neither attention to the infant's hunger cues nor a fixed schedule, may not consistently experience feeding as the pleasurable reduction of tension. Infants with early dysregulation often show increased irritability and physiologic instability (spitting, diarrhea, poor weight gain) as well as later behavioral problems. Infants with excess crying after 4-6 mo may have neurobehavioral dysregulation and may be at higher risk of other behavior problems (sleep, behavior, feeding).

Colic is characterized by the “rule of 3.” It occurs in a healthy, thriving infant beginning in the 2nd or 3rd week of life, lasts about 3 hr/day, occurs 3 days/wk, lasts for more than 3 wk, and resolves by 3 or 4 mo of age. It is equally common in breast- and bottle-fed infants, although prevalence is variable (up to 20%). There is no racial, socioeconomic status, or gender risk for colic. Colic is a diagnosis of exclusion following a careful history and physical examination. Few cases will be found to have an organic etiology. Although all babies have crying episodes, colicky babies cry excessively and are difficult to settle. The fussiness is not associated with hunger or any other form of discomfort. Colicky babies may be more reactive to the same stimulus and may cry louder than other babies. Although crying periods are a normal developmental phenomenon, babies with colic can cause parents to become anxious, distraught, frustrated, and sleep deprived. Mothers are at higher risk for postpartum depression if they report inconsolable crying episodes lasting more than 20 min. Depression may lead to cessation of breastfeeding. The risk of abuse increases as parents may use aggressive means to quiet the child, resulting in the **shaken baby syndrome** .

There is no specific treatment for colic, but practitioners should provide advice and reassurance to parents. Parents must be counseled about the problem, the importance of implementing a series of calm, systematic steps to sooth the infant, and having a plan for stress relief, such as time-out for parents and substitute caregivers. Parents can be advised that that colic is self-limited with no adverse effects on the child. Public health programs, such as the **Period of PURPLE Crying** (http://purplecrying.info/) and **Take 5 Safety Plan for Crying** , are invaluable tools for parents. These programs inform parents that all babies go through periods of crying, deflecting parental guilt and self-recrimination. Most importantly, parents are reminded that it is better to allow the baby to cry than engage in shaking that leads to head trauma. Although babies with colic will have inconsolable periods when there is no relief, parents can try some simple steps. Predictable daily schedules may help, ensuring the baby has adequate sleep. Parents should provide appropriate stimulation throughout the day when baby is in an alert/awake period. The sleep environment should be free of stimulation. Swaddling, rocking, white noise, and movement (e.g., stroller, car ride) help some babies settle. Infants who are carried by a parent show different physiologic changes than when held in a sitting position, although there is no evidence that continuous carrying is effective in colic management. A study in a hunter–gatherer society showed that children who are continuously carried by their mothers display similar crying periods as those in Western societies.

Some studies have found differences in **fecal microflora** between babies with excess crying and controls. Results include fewer bifidobacteria and lactobacilli and more coliform bacteria such as *Escherichia coli* . None has been conclusive, however, and each study was found to have limitations such as lack of precise inclusion criteria, lack of blinded observers, and variability in outcome measurements.

If the child appears to have gastrointestinal symptoms, breastfeeding mothers may try elimination of milk, beans, and cruciferous vegetables. In allergic families, mothers may try a stricter elimination of food allergens (milk, egg, wheat, nuts, soy, and fish), although nutritional status should be monitored. For formula-fed infants, changing from milk-based to soy-based or other lactose-free formulas had no effect in most studies. A protein hydrolysate formula may moderately improve symptoms.

The cause of colic in not known, and no medical intervention has been consistently effective. Colic has been described as a “functional gastrointestinal disorder” and has been associated with later development of **migraine** . Simethicone has not been shown to be better than placebo. Anticholinergic medications should not be used in infants younger than 6 mo. Early studies of probiotics look promising, but evidence is insufficient to recommend their routine use. Among various complementary therapies, certain **herbal teas** , sugar solutions, Gripe water (containing herbal supplements), and fennel extract may have benefit, but the evidence is weak. Baby massage may be helpful, but chiropractic manipulation should not be performed in young children. Acupuncture was effective in 1 trial, and singing while in utero may produce babies who cry less.

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CHAPTER 23

The Second Year

Rebecca G. Carter, Susan Feigelman

The 2nd year of life is a time of rapid growth of development, particularly in the realms of social-emotional and cognitive skills as well as motor development. The toddler's newly found ability to walk allows separation and independence; however, the toddler continues to need secure attachment to the parents. At approximately 18 mo of age, the emergence of symbolic thought and language causes a reorganization of behavior, with implications across many developmental domains.

Age 12-18 Months

Physical Development

While overall rate of growth continues to decline, the toddler continues to experience considerable brain growth and myelination in the 2nd yr of life, resulting in an increase in head circumference of 2 cm over the year (Figs. 23.1 and 23.2). Toddlers have relatively short legs and long torsos, with exaggerated lumbar lordosis and protruding abdomens.

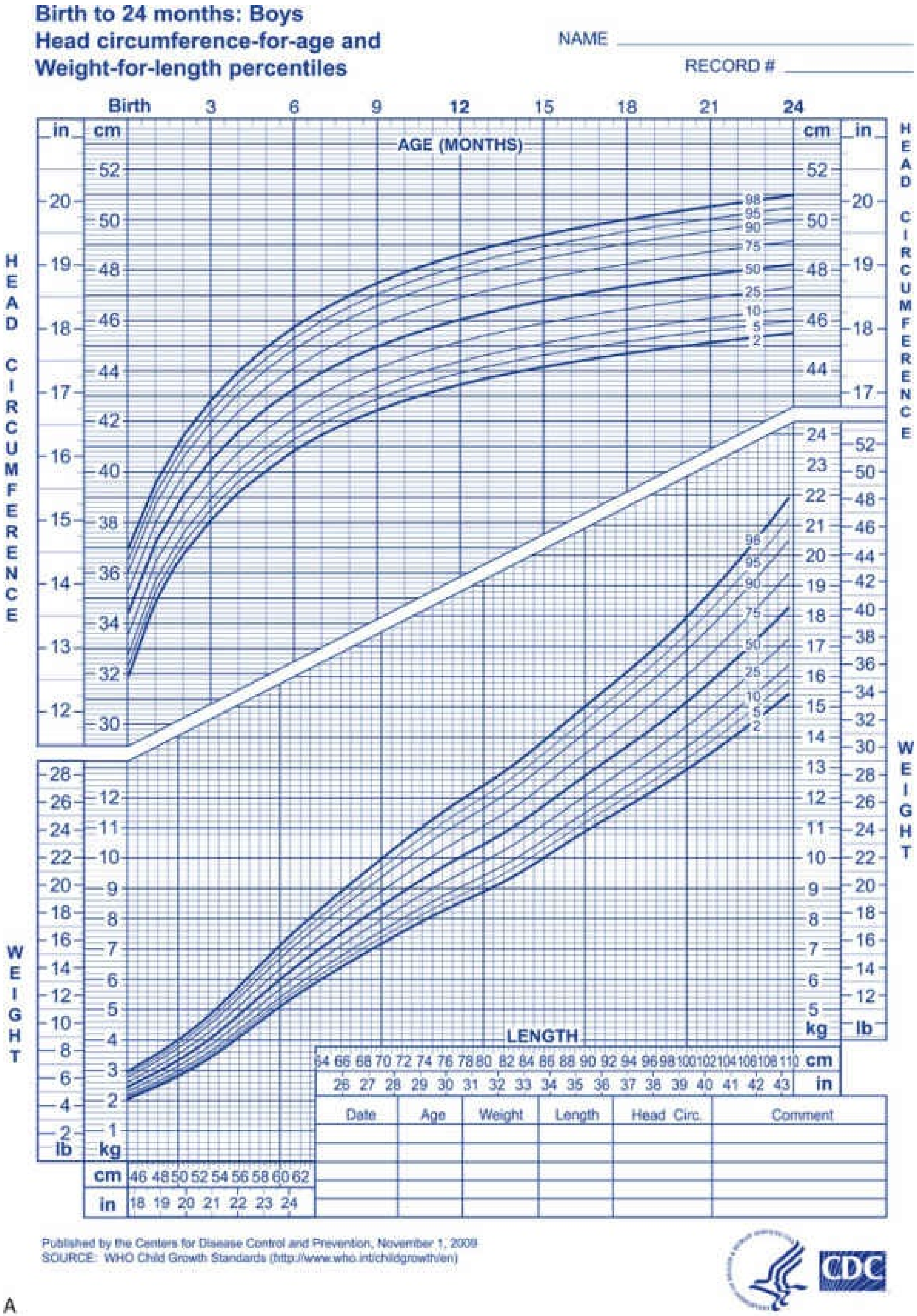

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

A

A, Weight for length and head circumference for age for boys, birth to 24 mo. (Courtesy World Health Organization: WHO Child Growth Standards, 2014.)

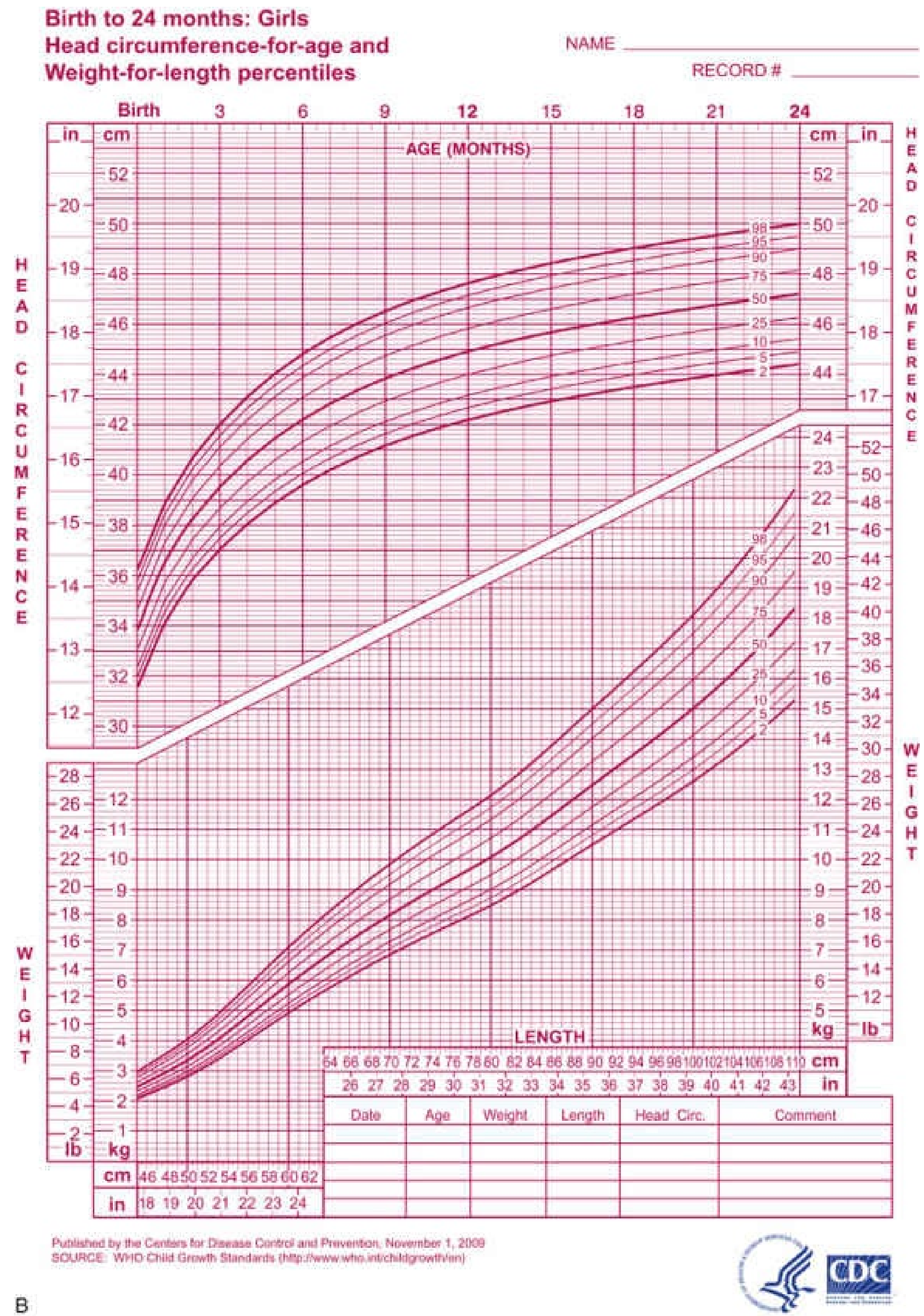

B

B, Weight for length and head circumference for age for girls, birth to 24 mo. (Courtesy World Health Organization: WHO Child Growth Standards, 2014.)

FIG. 23.1 The World Health Organization Growth Charts.

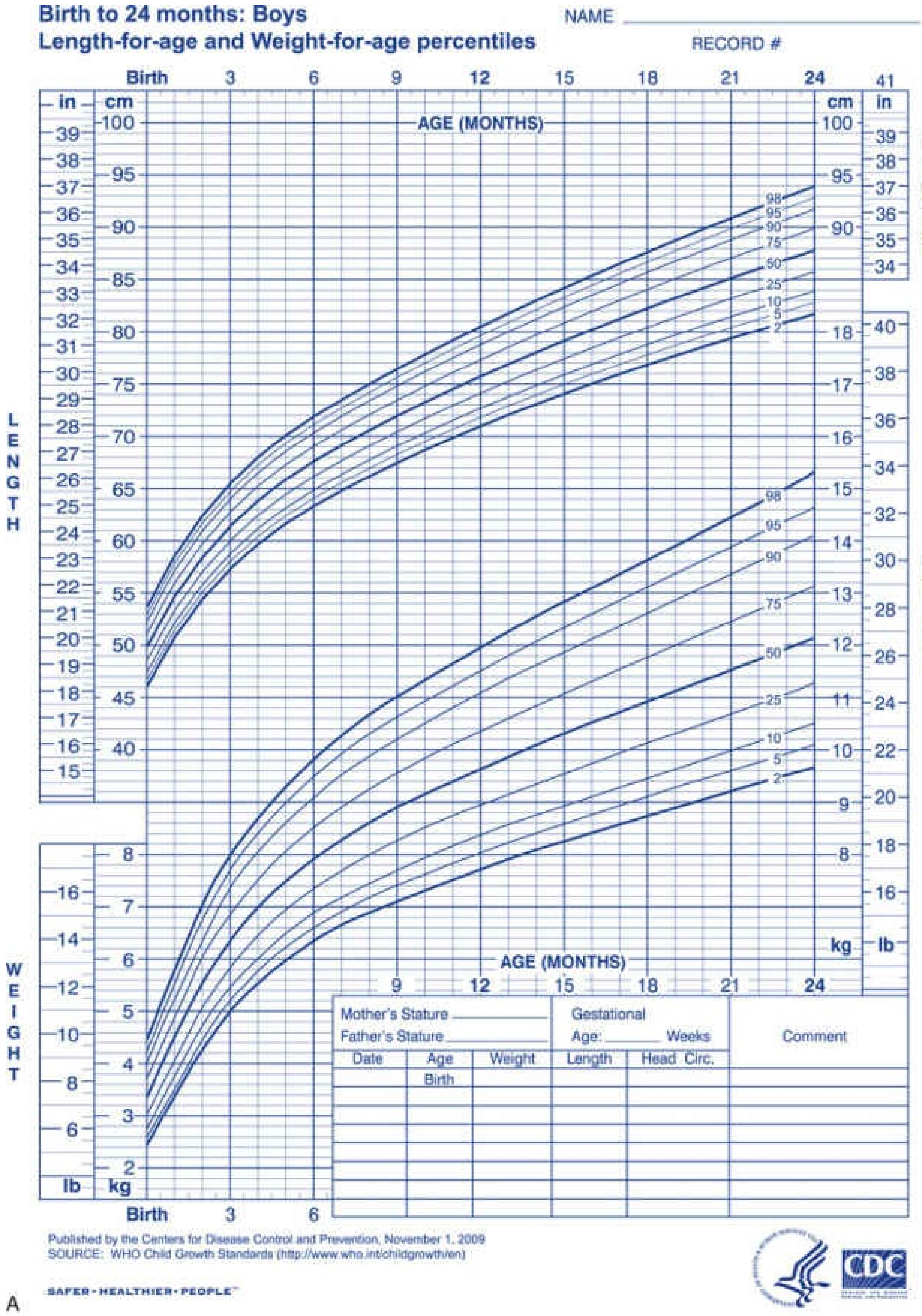

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

A

A, Length for age and weight for age for boys, birth to 24 mo. (Courtesy World Health Organization: WHO Child Growth

Standards, 2014.)

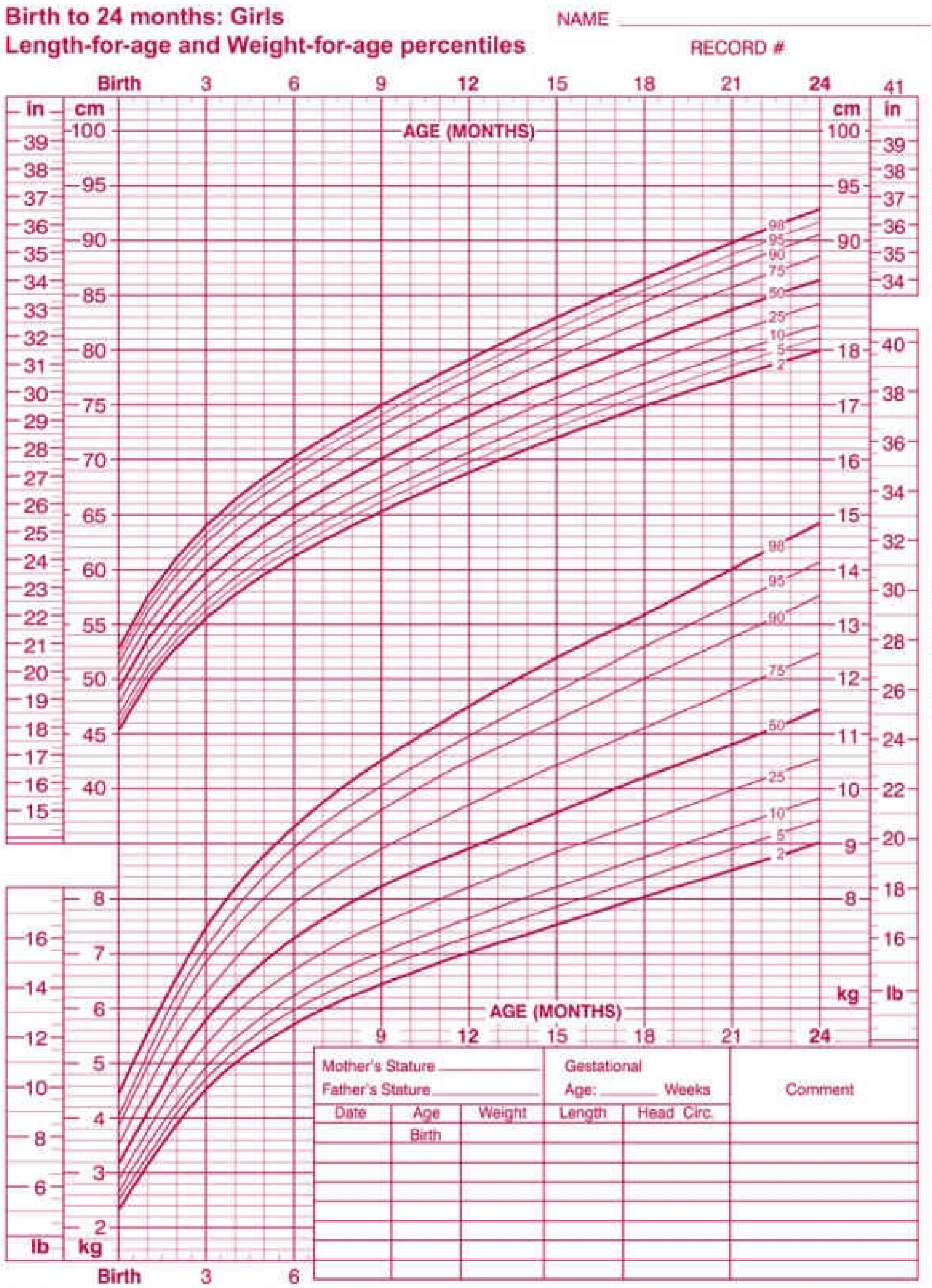

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

B

B, Length for age and weight for age for girls, birth to 24 mo. (Courtesy World Health Organization: WHO Child Growth Standards, 2014.)

FIG. 23.2 **The World Health Organization Growth Charts.**

Most children begin to walk independently at about 12-15 mo of age. Early walking is not associated with advanced development in other domains. Infants initially toddle with a wide-based gait, with the knees bent and the arms flexed at the elbow; the entire torso rotates with each stride; the toes may point in or out, and the feet strike the floor flat. The appearance is that of genu varum (**bowleg**). Subsequent refinement leads to greater steadiness and energy efficiency. After several months of practice, the center of gravity shifts back and the torso stabilizes, while the knees extend and the arms swing at the sides for balance. The feet are held in better alignment, and the child is able to stop, pivot, and stoop without toppling over (see Chapters 692 and 693).

Cognitive Development

Exploration of the environment increases in parallel with improved dexterity (reaching, grasping, releasing) and mobility. Learning follows the precepts of Piaget's **sensorimotor stage** (see Chapter 18). Toddlers manipulate objects in novel ways to create interesting effects, such as stacking blocks or filling and dumping buckets. Playthings are also more likely to be used for their intended purposes (combs for hair, cups for drinking). Imitation of parents and older siblings or other children is an important mode of learning. Make-believe play (**symbolic play**) centers on the child's own body, such as pretending to drink from an empty cup (Table 23.1 ; see also Table 22.1).

Table 23.1

Emerging Patterns of Behavior From 1-5 Yr of Age*

15 MO	
Motor:	Walks alone; crawls up stairs
Adaptive:	Makes tower of 3 cubes; makes a line with crayon; inserts raisin in bottle
Language:	Jargon; follows simple commands; may name a familiar object (e.g., ball); responds to his/her name
Social:	Indicates some desires or needs by pointing; hugs parents
18 MO	
Motor:	Runs stiffly; sits on small chair; walks up stairs with 1 hand held; explores drawers and wastebaskets

Adaptive:	Makes tower of 4 cubes; imitates scribbling; imitates vertical stroke; dumps raisin from bottle
Language:	10 words (average); names pictures; identifies 1 or more parts of body
Social:	Feeds self; seeks help when in trouble; may complain when wet or soiled; kisses parent with pucker
24 MO	
Motor:	Runs well, walks up and down stairs, 1 step at a time; opens doors; climbs on furniture; jumps
Adaptive:	Makes tower of 7 cubes (6 at 21 mo); scribbles in circular pattern; imitates horizontal stroke; folds paper once imitatively
Language:	Puts 3 words together (subject, verb, object)
Social:	Handles spoon well; often tells about immediate experiences; helps to undress; listens to stories when shown pictures
30 MO	
Motor:	Goes up stairs alternating feet
Adaptive:	Makes tower of 9 cubes; makes vertical and horizontal strokes, but generally will not join them to make cross; imitates circular stroke, forming closed figure
Language:	Refers to self by pronoun “I”; knows full name
Social:	Helps put things away; pretends in play
36 MO	
Motor:	Rides tricycle; stands momentarily on 1 foot
Adaptive:	Makes tower of 10 cubes; imitates construction of “bridge” of 3 cubes; copies circle; imitates cross
Language:	Knows age and sex; counts 3 objects correctly; repeats 3 numbers or a sentence of 6 syllables; most of speech intelligible to strangers
Social:	Plays simple games (in “parallel” with other children); helps in dressing (unbuttons clothing and puts on shoes); washes hands
48 MO	
Motor:	Hops on 1 foot; throws ball overhand; uses scissors to cut out pictures; climbs well
Adaptive:	Copies bridge from model; imitates construction of “gate” of 5 cubes; copies cross and square; draws man with 2-4 parts besides head; identifies longer of 2 lines
Language:	Counts 4 pennies accurately; tells story
Social:	Plays with several children, with beginning of social interaction and role-playing; goes to toilet alone
60 MO	
Motor:	Skips
Adaptive:	Draws triangle from copy; names heavier of 2 weights
Language:	Names 4 colors; repeats sentence of 10 syllables; counts 10 pennies correctly
Social:	Dresses and undresses; asks questions about meaning of words; engages in domestic role-playing

[*] Data derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others. After 6 yr, the Wechsler Intelligence Scales for Children (WISC-IV) and other scales offer the most precise estimates of cognitive development. To have their greatest value, they should be administered only by an experienced and qualified person.

Emotional Development

Infants who are approaching the developmental milestone of taking their 1st steps may be irritable. Once they start walking, their predominant mood changes markedly. Toddlers are often elated with their new ability and with the power to control the distance between themselves and their parents. Exploring toddlers orbit around their parents, moving away and then returning for a reassuring touch before moving away again. A child with **secure attachment** will use the parent as a secure base from which to explore independently. Proud of her or his accomplishments, the child illustrates Erikson's **stage of autonomy and separation** (see Chapter 18). The toddler who is overly controlled and discouraged from active exploration will feel doubt, shame, anger, and insecurity. All children will experience tantrums, reflecting their inability to delay gratification, suppress or displace anger, or verbally communicate their emotional states. The quality of the parent–child relationship may moderate negative behavioral effects of childcare arrangements when parents work.

Linguistic Development

Receptive language precedes *expressive* language. By the time infants speak their first words around 12 mo of age, they already respond appropriately to several simple statements, such as “no,” “bye-bye,” and “give me.” By 15 mo, the average child points to major body parts and uses 4-6 words spontaneously and correctly. Toddlers also enjoy **polysyllabic jargoning** (see Tables 22.1 and 23.1) and do not seem upset that no one understands. Most communication of wants and ideas continues to be nonverbal.

Implications for Parents and Pediatricians

Parents who cannot recall any other milestone tend to remember when their child began to walk, perhaps because of the symbolic significance of walking as an act of independence and because of the new demands that the ambulating toddler places on the parent. All toddlers should be encouraged to explore their environment; however, a child's ability to wander out of sight also increases the risks of injury and the need for supervision, making **childproofing** an integral focus of physician visits.

In the office setting, many toddlers are comfortable exploring the examination room, but cling to the parents under the stress of the examination. Performing most of the physical examination in the parent's lap may help allay fears of separation. Infants who become more, not less, distressed in their parents' arms or who avoid their parents at times of stress may be insecurely attached. Young children who, when distressed, turn to strangers rather than parents for comfort are particularly worrisome. Children raised in **toxic stressful environments** have increased vulnerability to disease. The conflicts between independence and security manifest in issues of discipline, temper tantrums, toilet training, and changing feeding behaviors. Parents should be counseled on these matters within the framework of normal development.

Parents may express concern about poor food intake as growth slows. The growth chart should provide reassurance. Many children still take 2 daytime naps, although the duration steadily decreases and may start to condense to 1 longer nap (see Fig. 22.2).

Age 18-24 Months

Physical Development

Motor development during this period is reflected in improvements in balance and agility and the emergence of running and stair climbing. Height and weight increase at a steady rate during this year, with a gain of 5 in and 5 lb. By 24 mo, children are about half their ultimate adult height. Head growth slows slightly, with 85% of adult head circumference achieved by age 2 yr, leaving only an additional 5 cm (2 in) gain over the next few years (see Fig. 23.1 and Table 27.1).

Cognitive Development

At approximately 18 mo of age, several cognitive changes coalesce, marking the conclusion of the sensorimotor period. These can be observed during *self-initiated play* . **Object permanence** is firmly established; toddlers anticipate where an object will end up, even though the object was not visible while it was being moved. Cause and effect are better understood, and toddlers demonstrate flexibility in problem solving (e.g., using a stick to obtain a toy that is out of reach, figuring out how to wind a mechanical toy). Symbolic transformations in play are no longer tied to the toddler's own body; thus a doll can be “fed” from an empty plate. As with the reorganization that occurs at 9 mo (see Chapter 22), the cognitive changes at 18 mo correlate with important changes in the emotional and linguistic domains (see Table 23.1).

Emotional Development

The relative independence of the preceding half-year often gives way to increased clinginess about 18 mo. This stage, described as “rapprochement,” may be a reaction to growing awareness of the possibility of separation. Many parents report that they cannot go anywhere without having a small child attached to them. **Separation anxiety** will manifest at bedtime. Many children use a special blanket or stuffed toy as a **transitional object** , which functions as a symbol of the absent parent. The transitional object remains important until the transition to symbolic thought has been completed and the symbolic presence of the parent fully internalized. Despite the attachment to the parent, the child's use of “no” is a way of declaring independence. Individual differences in **temperament** , in both the child and the parents, play a critical role in determining the balance of conflict vs cooperation in the parent–child relationship. As effective language emerges, conflicts often become less frequent.

Self-conscious awareness and internalized standards of behavior first appear at this age. Toddlers looking in a mirror will, for the first time, reach for their own face rather than the mirror image if they notice something unusual on their nose. They begin to recognize when toys are broken and may hand them to their parents to fix. Language becomes a means of impulse control, early reasoning, and connection between ideas. When tempted to touch a forbidden object, they may tell themselves “no, no.” This is the very beginning of the formation of a conscience. The fact that they often go on to touch the object anyway demonstrates the relative weakness of **internalized inhibitions** at this stage.

Linguistic Development

Perhaps the most dramatic developments in this period are linguistic. Labeling of objects coincides with the advent of symbolic thought. After the realization occurs that words can stand for objects or ideas, a child's vocabulary grows from 10-15 words at 18 mo to between 50 and 100 at 2 yr. After acquiring a vocabulary of about 50 words, toddlers begin to combine them to make simple sentences, marking the beginning of grammar. At this stage, toddlers understand **2-step commands** , such as “Give me the ball and then get your shoes.” Language also gives the toddler a sense of control over the surroundings, as in “night-night” or “bye-bye.” The emergence of verbal language marks the end of the sensorimotor period. As toddlers learn to use symbols to express ideas and solve problems, the need for cognition based on direct sensation and motor manipulation wanes.

Implications for Parents and Pediatricians

With children's increasing mobility, physical limits on their explorations become less effective; words become increasingly important for behavior control as well as cognition. Children with delayed language acquisition often have greater behavior problems and frustrations due to problems with communication. Language development is facilitated when parents and caregivers use clear, simple sentences; ask questions; and respond to children's incomplete sentences and gestural communication with the appropriate words. Television viewing, as well as television as background noise, decreases parent–child verbal interactions, whereas looking at picture books and engaging the child in 2-way conversations stimulates language development. In the world of constant access to tablets, phones, and screens, parents and children have more distractions from direct language engagement.

In the office setting, certain procedures may lessen the child's **stranger anxiety** . Avoid direct eye contact initially. Perform as much of the examination as feasible with the child on the parent's lap. Pediatricians can help parents understand the resurgence of problems with separation and the appearance of a transitional object as a developmental phenomenon. Parents must understand the importance of exploration. Rather than limiting movement, parents should place toddlers in safe environments or substitute one activity for another. Methods of discipline, including **corporal punishment** (which is not recommended), should be discussed; effective alternatives will usually be appreciated. Helping parents to understand and adapt to their children's different temperamental styles can constitute an important intervention (see Table 18.1). Developing daily routines is helpful to all children at this age. Rigidity in those routines reflects a need for mastery over a changing environment.

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CHAPTER 24

The Preschool Years

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The emergence of language and exposure of children to an expanding social sphere represent the critical milestones for children ages 2-5 yr. As toddlers, children learn to walk away and come back to the secure adult or parent. As preschoolers, they explore emotional separation, alternating between stubborn opposition and cheerful compliance, between bold exploration and clinging dependence. Increasing time spent in classrooms and playgrounds challenges a child's ability to adapt to new rules and relationships. Emboldened by their growing array of new skills and accomplishments, preschool children also are increasingly cognizant of the constraints imposed on them by the adult world and their own limited abilities.

Structural Development of the Brain

The preschool brain experiences dramatic changes in its anatomic and physiologic characteristics, with increases in cortical area, decreases in cortical thickness, and changing cortical volume. These changes are not uniform across the brain and vary by region. Gray and white matter tissue properties change dramatically, including diffusion properties in the major cerebral fiber tracts. Dramatic increases occur in brain metabolic demands. In general, more brain regions are required in younger than in older children to complete the same cognitive task. This duplication has been interpreted as a form of “scaffolding,” which is discarded with increasing age. The preschool brain is characterized by growth and expansion that will be followed in later years by “pruning.”

Physical Development

Somatic and brain growth slows by the end of the 2nd yr of life, with corresponding decreases in nutritional requirements and appetite, and the emergence of “picky” eating habits (see Table 27.1). Increases of approximately 2 kg (4-5 lb) in weight and 7-8 cm (2-3 in) in height per year are expected. Birthweight quadruples by 2.5 yr of age. An average 4 yr old weighs 40 lb and is 40 in tall. The head will grow only an additional 5-6 cm between ages 3 and 18 yr. Current growth charts, with growth parameters, can be found on the U.S. Centers for Disease Control and Prevention website (http://www.cdc.gov/growthcharts/) and in Chapter 27 . Children with early **adiposity rebound** (increase in body mass index) are at increased risk for adult obesity.

The preschooler has genu valgum (**knock-knees**) and mild pes planus (**flatfoot**). The torso slims as the legs lengthen. Growth of sexual organs is commensurate with somatic growth. Physical energy peaks, and the need for sleep declines to 11-13 hr/24 hr, with the child eventually dropping the nap (see Fig. 22.2). Visual acuity reaches 20/30 by age 3 yr and 20/20 by age 4 yr. All 20 primary teeth should have erupted by 3 yr of age (see Chapter 333).

Most children walk with a mature gait and run steadily before the end of their 3rd yr (see Table 23.1). Beyond this basic level, there is wide variation in ability as the range of motor activities expands to include throwing, catching, and kicking balls; riding on bicycles; climbing on playground structures; dancing; and other complex pattern behaviors. Stylistic features of gross motor activity, such as tempo, intensity, and cautiousness, also vary significantly. Although toddlers may walk with different styles, **toe walking** should not persist.

The effects of such individual differences on cognitive and emotional development depend in part on the demands of the social environment. Energetic, coordinated children may thrive emotionally with parents or teachers who encourage physical activity; lower-energy, more cerebral children may thrive with adults who value quiet play.

Handedness is usually established by the 3rd yr. Frustration may result from attempts to change children's hand preference. Variations in fine motor development reflect both individual proclivities and different opportunities for learning. Children who are restricted from drawing with crayons, for example, develop a mature pencil grasp later.

Bowel and bladder control emerge during this period, with “readiness” for toileting having large individual and cultural variation. Girls tend to potty “train” faster and earlier than boys. Bed-wetting is common up to age 5 yr (see Chapter

558). Many children master toileting with ease, particularly once they are able to verbalize their bodily needs. For others, **toilet training** can involve a protracted power struggle. Refusal to defecate in the toilet or potty is relatively common, associated with constipation, and can lead to parental frustration. Defusing the issue with a temporary cessation of training (and a return to diapers) often allows toilet mastery to proceed.

Implications for Parents and Pediatricians

The normal decrease in appetite at this age may cause parental concern about nutrition; growth charts should reassure parents that the child's intake is adequate. Children normally modulate their food intake to match their somatic needs according to feelings of hunger and satiety. Daily intake fluctuates, at times widely, but intake over a week is relatively stable. Parents should provide a predictable eating schedule, with 3 meals and 2 snacks per day, allowing the child to choose how much to eat in order to avoid power struggles and to allow the child to learn to respond to satiety cues. However, it is important to obtain thorough diet histories for children at this age to advise parents about healthy choices and encourage physical activity to decrease long-term obesity risks and improve learning and cognitive development.

Highly active children face increased risks of injury, and parents should be counseled about safety precautions. Parental concerns about possible hyperactivity may reflect inappropriate expectations, heightened fears, or true overactivity. Children who engage in ongoing impulsive activity with no apparent regard for personal safety or those harming others on a regular basis should be evaluated further.

Language, Cognition, and Play

These 3 domains all involve **symbolic function** , a mode of dealing with the world that emerges during the preschool period.

Language

Our understanding of the acquisition of language is evolving. Preschool children command significant computational skills and understanding of statistical patterns that allow them to learn about both language and causation. The 2 and 3 yr old child employs frequency distributions to identify phonetic units distinguishing words in his or her native language from other languages.

Language development occurs most rapidly between 2 and 5 yr of age. Vocabulary increases from 50-100 words to more than 2,000. Sentence structure advances from telegraphic phrases (“Baby cry”) to sentences incorporating all the major grammatical components. As a rule of thumb, between ages 2 and 5 yr, the number of words the child puts in a typical sentence should, at a minimum, equal the child's age (2 by age 2 yr, 3 by age 3 yr, and so on). By 21-24 mo, most children are using possessives (“My ball”), progressives (the “-ing” construction, as in “I playing”), questions, and negatives. By age 4 yr, most children can count to 4 and use the past tense; by age 5 yr, they can use the future tense. Young children do not use figurative speech; they will only comprehend the literal meaning of words. Referring to an object as “light as a feather” may produce a quizzical look on a child.

It is important to distinguish between **speech** (the production of intelligible sounds) and **language** , which refers to the underlying mental act. Language includes both expressive and receptive functions. *Receptive* language (understanding) varies less in its rate of acquisition than does *expressive* language; therefore, it has greater prognostic importance (see Chapters 28 and 52).

Language acquisition depends critically on environmental input. Key determinants include the amount and variety of speech directed toward children and the frequency with which adults ask questions and encourage verbalization. Children raised in poverty typically perform lower on measures of language development than children from economically advantaged families, who tend to be exposed to many more words in the preschool period.

Although experience influences the rate of language development, many linguists believe that the basic mechanism for language learning is “hard-wired” in the brain. Children do not simply imitate adult speech; they abstract the complex rules of grammar from the ambient language, generating implicit hypotheses. Evidence for the existence of such implicit rules comes from analysis of grammatical errors, such as the overgeneralized use of “-s” to signify the plural and “-ed” to signify the past (“We seed lots of mouses.”).

Language is linked to both cognitive and emotional development. Language delays may be the 1st indication of an intellectual disability, autism spectrum disorder, or child neglect or maltreatment. Language plays a critical part in the regulation of behavior through internalized “private speech” in which a child repeats adult prohibitions, first audibly and then mentally. Language also allows children to express feelings, such as anger or frustration, without acting them out; consequently, language-delayed children show higher rates of tantrums and other externalizing behaviors.

Preschool language development lays the foundation for later success in school. Approximately 35% of U.S. children may enter school lacking the language skills that are the prerequisites for acquiring literacy. Children from socially and economically disadvantaged backgrounds have an increased risk of school problems, making early detection, along with referral and enrichment, highly crucial for later development. Although children typically learn to read and write in elementary school, critical foundations for literacy are established during the preschool years. Through repeated early exposure to written words, children learn about the uses of writing (telling stories or sending messages) and about its form (left to right, top to bottom). Early errors in writing, like errors in speaking, reveal that literacy acquisition is an active process involving the generation and revision of hypotheses. Programs such as Head Start are especially important for improving language skills for children from bilingual homes. Such parents should be reassured that although **bilingual children** may initially appear to lag behind their monolingual peers in acquiring language, they learn the differing rules governing both languages, and generally have the same number of total words between the languages. Bilingual children do not follow the same course of language development as monolingual children, but rather create a different system of language cues. Several cognitive advantages have been repeatedly demonstrated among bilingual compared to monolingual children.

Picture books have a special role in familiarizing young children with the printed word and in the development of verbal language. Children's vocabulary and receptive language improve when their parents or caregivers consistently read to them. Reading aloud with a young child is an interactive process in which a parent repeatedly focuses the child's attention on a particular picture, asks questions, and then gives the child feedback (**dialogic reading**). The elements of shared attention, active participation, immediate feedback, repetition, and graduated difficulty make such routines ideal for language learning. Programs in which physicians provide books to preschool children have shown improvement in language skills among the children (e.g., Reach Out and Read).

The period of rapid language acquisition is also when **developmental**

dysfluency and **stuttering** are most likely to emerge (see Chapter 52.1); these can be traced to activation of the cortical motor, sensory, and cerebellar areas. Common difficulties include pauses and repetitions of initial sounds. Stress or excitement exacerbates these difficulties, which generally resolve on their own. Although 5% of preschool children will stutter, it will resolve in 80% of those children by age 8 yr. Children with stuttering should be referred for evaluation if it is severe, persistent, or associated with anxiety, or if parental concern is elicited. Treatment includes guidance to parents to reduce pressures associated with speaking.

Cognition

The preschool period corresponds to Piaget's **preoperational** (prelogical) **stage,** characterized by magical thinking, egocentrism, and thinking that is dominated by perception, not abstraction (see Table 18.2). **Magical thinking** includes confusing coincidence with causality, *animism* (attributing motivations to inanimate objects and events), and unrealistic beliefs about the power of wishes. A child might believe that people cause it to rain by carrying umbrellas, that the sun goes down because it is tired, or that feeling resentment toward a sibling can actually make that sibling sick. **Egocentrism** refers to a child's inability to take another's point of view and does not connote selfishness. A child might try to comfort an adult who is upset by bringing the adult a favorite stuffed animal. After 2 yr of age, the child develops a concept of herself or himself as an individual and senses the need to feel “whole.”

Piaget demonstrated the dominance of **perception** over logic. In one experiment, water is poured back and forth between a tall, thin vase and a low, wide dish, and children are asked which container has more water. Invariably, they choose the one that looks larger (usually the tall vase), even when the examiner points out that no water has been added or taken away. Such misunderstandings reflect young children's developing hypotheses about the nature of the world, as well as their difficulty in attending simultaneously to multiple aspects of a situation.

Recent work indicating that preschool children do have the ability to understand **causal relationships** has modified our understanding of the ability of preschool children to engage in abstract thinking (see Chapter 18).

Imitation , central to the learning experience of preschool children, is a complex act because of differences in the size of the operators (the adult and the child), different levels of dexterity, and even different outcomes. A child who watches an adult unsuccessfully attempt a simple act (unscrew a lid) will imitate the action—but often with the intended outcome, not the demonstrated but failed outcome. Thus “imitation” goes beyond the mere repetition of observed movements.

By age 3, children have self-identified their sex and are actively seeking understanding of the meaning of **gender identification** . There is a developmental progression from rigidity (boys and girls have strict gender roles) in the early preschool years to a more flexible realistic understanding (boys and girls can have a variety of interests).

Play

Play involves learning, physical activity, socialization with peers, and practicing adult roles. Play increases in complexity and imagination, from simple imitation of common experiences, such as shopping and putting baby to bed (2 or 3 yr of age), to more extended scenarios involving singular events, such as going to the zoo or going on a trip (3 or 4 yr of age), to the creation of scenarios that have only been imagined, such as flying to the moon (4 or 5 yr of age). By age 3 yr, **cooperative play** is seen in activities such as building a tower of blocks together; later, more structured **role-play activity** , as in playing house, is seen. Play also becomes increasingly governed by rules, from early rules about asking (rather than taking) and sharing (2 or 3 yr of age), to rules that change from moment to moment, according to the desires of the players (4 and 5 yr of age), to the beginning of the recognition of rules as relatively immutable (5 yr of age). Electronic forms of play (games) are best if interactive and educational and should remain limited in duration.

Play also allows for resolution of conflicts and anxiety and for creative outlets. Children can vent anger safely (spanking a doll), take on superpowers (dinosaur and superhero play), and obtain things that are denied in real life (an imaginary friend or stuffed animal). Creativity is particularly apparent in drawing, painting, and other artistic activities. Themes and emotions that emerge in a child's drawings often reflect the emotional issues of greatest importance for the child.

Difficulty distinguishing fantasy from reality colors a child's perception of what the child views in the media, through programming and advertising. One fourth of young children have a television set in their bedroom; a TV in the bedroom is associated with more hours of watching. The number of hours that most preschoolers watch TV exceeds guidelines (1 hr/day for 2-5 year olds). Interactive quality educational programming in which children develop social relationships with the characters can increase learning if paired with adult interaction around the storyline. However, exposure to commercial TV with violent content is associated with later behavior problems, and because children younger than 8 yr are not able to comprehend the concept of persuasive intent, they are more vulnerable to TV advertising.

Implications for Parents and Pediatricians

The significance of language as a target for assessment and intervention cannot be overestimated, because of its central role as an indicator of cognitive and emotional development and a key factor in behavioral regulation and later school success. As language emerges, parents can support emotional development by using words that describe the child's feeling states (“You sound angry right now”) and urging the child to use words to express rather than act out feelings. Active imaginations will come into play when children offer explanations for misbehavior. A parent's best way of dealing with untruths is to address the event, not the child, and have the child participate in “making things right.”

Parents should have a regular time each day for reading or looking at books with their children. Programs such as **Reach Out and Read,** in which pediatricians give out picture books along with appropriate guidance during primary care visits, have been effective in increasing reading aloud and thereby promoting language development, particularly in lower-income families. TV and similar media should be limited to 1 hr/day of quality programming for children aged 2-5 yr, and parents should be watching the programs with their children and debriefing their young children afterward. At-risk children, particularly those living in poverty, can better meet future school challenges if they have early high-quality child care and learning experiences (e.g., Head Start).

Preoperational thinking constrains how children understand experiences of illness and treatment. Children begin to understand that bodies have “insides” and “outsides.” Children should be given simple, concrete explanations for medical procedures and given some control over procedures if possible. Children should be reassured that they are not to blame when receiving a vaccine or venipuncture. An adhesive bandage will help to make the body “whole” again in a child's mind.

The active imagination that fuels play and the magical, animist thinking characteristic of preoperational cognition can also generate intense fears. More than 80% of parents report at least 1 fear in their preschool children. Refusal to take baths or to sit on the toilet may arise from the fear of being washed or flushed away, reflecting a child's immature appreciation of relative size. Attempts to demonstrate rationally that there are no monsters in the closet often fail, inasmuch as the fear arises from preoperational thinking. However, this same thinking allows parents to be endowed with magical powers that can banish the monsters with “monster spray” or a night-light. Parents should acknowledge the fears, offer reassurance and a sense of security, and give the child some sense of control over the situation. Use of the **Draw-a-Person** , in which a child is asked to draw the best person he or she child can, may help elucidate a child's viewpoint.

Emotional and Moral Development

Emotional challenges facing preschool children include accepting limits while maintaining a sense of self-direction, reigning in aggressive and sexual impulses, and interacting with a widening circle of adults and peers. At 2 yr of age, behavioral limits are predominantly external; by 5 yr of age, these controls need to be internalized if a child is to function in a typical classroom. Success in achieving this goal relies on prior emotional development, particularly the ability to use internalized images of trusted adults to provide a secure environment in times of stress. The love a child feels for important adults is the main incentive for the development of self-control.

Children learn what behaviors are acceptable and how much power they wield vis-à-vis important adults by testing limits. **Limit testing** increases when it elicits attention, even though that attention is often negative, and when limits are inconsistent. Testing often arouses parental anger or inappropriate solicitude as a child struggles to separate, and it gives rise to a corresponding parental challenge: letting go. Excessively tight limits can undermine a child's sense of initiative, whereas overly loose limits can provoke anxiety in a child who feels that no one is in control.

Control is a central issue. Young children cannot control many aspects of their lives, including where they go, how long they stay, and what they take home from the store. They are also prone to lose internal control, that is, to have **temper tantrums** . Fear, overtiredness, hunger, inconsistent expectations, or physical discomfort can also evoke tantrums. Tantrums normally appear toward the end of the 1st yr of life and peak in prevalence between 2 and 4 yr of age. Tantrums lasting more than 15 min or regularly occurring more than 3 times/day may reflect underlying medical, emotional, developmental, or social problems.

Preschool children normally experience complicated feelings toward their parents that can include strong attachment and possessiveness toward the parent of the opposite sex, jealousy and resentment of the other parent, and fear that these negative feelings might lead to abandonment. These emotions, most of which are beyond a child's ability to comprehend or verbalize, often find expression in highly labile moods. The resolution of this crisis (a process extending over years) involves a child's unspoken decision to identify with the parents rather than compete with them. Play and language foster the development of emotional controls by allowing children to express emotions and role-play.

Curiosity about genitals and adult sexual organs is normal, as is **masturbation** . Excessive masturbation interfering with normal activity, acting out sexual intercourse, extreme modesty, or mimicry of adult seductive behavior all suggest the possibility of sexual abuse or inappropriate exposure (see Chapter 16.1). Modesty appears gradually between 4 and 6 yr of age, with wide variations among cultures and families. Parents should begin to teach children about “private” body areas before school entry.

Moral thinking is constrained by a child's cognitive level and language abilities but develops as the child continues her or his identity with the parents. Beginning before the 2nd birthday, the child's sense of right and wrong stems from the desire to earn approval from the parents and avoid negative consequences. The child's impulses are tempered by external forces; the child has not yet internalized societal rules or a sense of justice and fairness. Over time, as the child internalizes parental admonitions, words are substituted for aggressive behaviors. Finally, the child accepts personal responsibility. Actions will be viewed by damage caused, not by intent. Empathic responses to others' distress arise during the 2nd yr of life, but the ability to consider another child's point of view remains limited throughout this period. In keeping with a child's inability to focus on more than one aspect of a situation at a time, fairness is taken to mean equal treatment, regardless of circumstance. A 4 yr old will acknowledge the importance of taking turns, but will complain if he or she “didn't get enough time.” Rules tend to be absolute, with guilt assigned for bad outcomes, regardless of intentions.

Implications for Parents and Pediatricians

The importance of the preschooler's sense of control over his or her body and surroundings has implications for practice. Preparing the patient by letting the child know how the visit will proceed is reassuring. Tell the child what will happen, but do not ask permission unless you are willing to deal with a “no” answer. A brief introduction to “private parts” is warranted before the genital examination.

The visit of the 4 or 5 yr old should be entertaining, because of the child's ability to communicate, as well as the child's natural curiosity. Physicians should realize that all children are occasionally difficult. Guidance emphasizing appropriate expectations for behavioral and emotional development and acknowledging normal parental feelings of anger, guilt, and confusion should be part of all visits at this time. Parents should be queried about daily routines and their expectations of child behavior. Providing children with **acceptable choices** (all options being acceptable to the parent) and encouraging independence in self-care activities (feeding, dressing, and bathing) will reduce conflicts.

Although some cultures condone the use of **corporal punishment** for disciplining of young children, it is not a consistently effective means of behavioral control. As children habituate to repeated spanking, parents have to spank ever harder to achieve the desired response, increasing the risk of serious injury. Sufficiently harsh punishment may inhibit undesired behaviors, but at great psychologic cost. Children mimic the corporal punishment that they receive; children who are spanked will have more aggressive behaviors later. Whereas spanking is the use of force, externally applied, to produce behavior change, **discipline** is the process that allows the child to internalize controls on behavior. Alternative discipline strategies should be offered, such as the “countdown” for transitions along with consistent limit setting, “time-outs” or “time-ins” (breaks from play with caregiver present and interacting), clear communication of rules, and frequent approval with positive reinforcement of productive play and behavior (see Chapter 19). Punishment should be immediate, specific to the behavior, and time-limited. *Time-out for approximately 1 min/yr of age is very effective.* A kitchen timer allows the parent to step back from the situation; the child is free when the timer rings. Although one strategy might not work for all children uniformly, consistency is integral to healthy learning and growth.

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CHAPTER 25

Middle Childhood

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Middle childhood (6-11 yr of age) is the period in which children increasingly separate from parents and seek acceptance from teachers, other adults, and peers. Children begin to feel under pressure to conform to the style and ideals of the peer group. Self-esteem becomes a central issue, as children develop the cognitive ability to consider their own self-evaluations and their perception of how others see them. For the first time, they are judged according to their ability to produce socially valued outputs, such as getting good grades, playing a musical instrument, or hitting home runs.

Physical Development

Growth occurs *discontinuously,* in 3-6 irregularly timed spurts each year, but varies both within and among individuals. Growth during the period averages 3-3.5 kg (6.6-7.7 lb) and 6-7 cm (2.4-2.8 in) per year (Fig. 25.1). The head grows only 2 cm in circumference throughout the entire period, reflecting a slowing of brain growth. Myelination continues into adolescence, with peak gray matter at 12-14 yr. Body habitus is more erect than previously, with long legs compared with the torso.

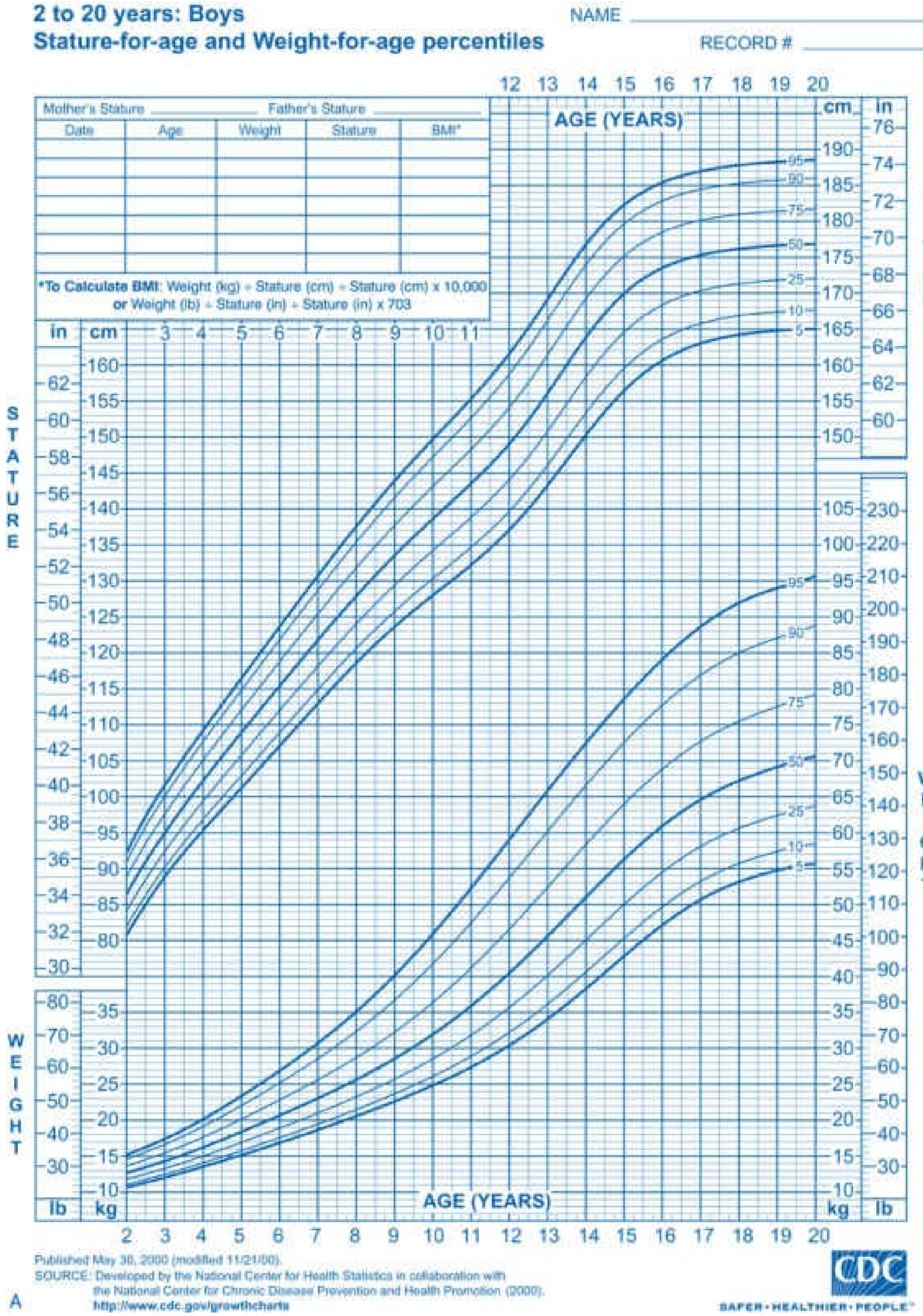

A, Stature (height) for age and weight for boys age 2-20 yr.
(Courtesy National Center for Health Statistics, in

collaboration with the National Center for Chronic Disease
Prevention and Health Promotion, 2000.
http://www.cdc.gov/growthcharts .)

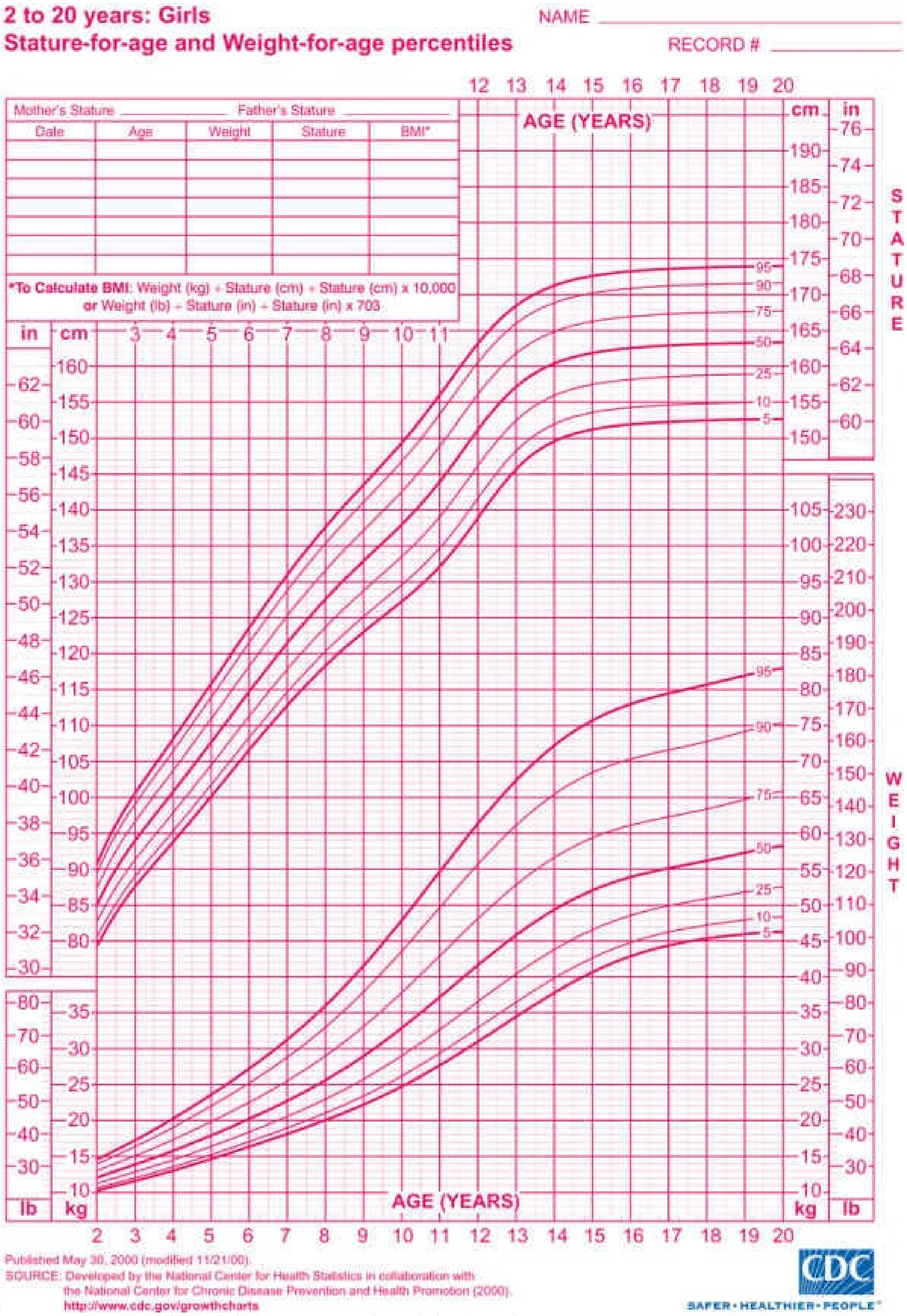

B

B, Stature (height) for age and weight for girls, age 2-20 yr. (Courtesy National Center for Health Statistics, 2000.)

FIG. 25.1

Growth of the midface and lower face occurs gradually. Loss of deciduous (baby) teeth is a more dramatic sign of maturation, beginning around 6 yr of age. Replacement with adult teeth occurs at a rate of about 4 per year, so that by age 9 yr, children will have 8 permanent incisors and 4 permanent molars. Premolars erupt by 11-12 yr of age (see Chapter 333). Lymphoid tissues hypertrophy and reach maximal size, often giving rise to impressive tonsils and adenoids.

Muscular strength, coordination, and stamina increase progressively, as does the ability to perform complex movements, such as dancing or shooting baskets. Such higher-order motor skills are the result of both maturation and training; the degree of accomplishment reflects wide variability in innate skill, interest, and opportunity.

Physical fitness has declined among school-age children. Sedentary habits at this age are associated with increased lifetime risk of obesity, cardiovascular disease, lower academic achievement, and lower self-esteem. The number of overweight children and the degree of overweight have been increasing, although recently at a slower rate (see Chapter 60). Only 15% of middle and junior high schools require physical education class at least 3 days/wk. One quarter of youth do not engage in any free-time physical activity, despite the recommendation for at least 1 hr of physical activity per day.

Perceptions of **body image** develop early during this period; children as young as 5 and 6 yr express dissatisfaction with their body image; by ages 8 and 9 yr many of these youth report trying to diet, often using ill-advised regimens. Loss-of-control (binge) eating occurs among approximately 6% of children at this age.

Prior to puberty, the sensitivity of the hypothalamus and pituitary changes, leading to increased gonadotropin synthesis. Interest in gender differences and sexual behavior increases progressively until puberty. Although this is a period when sexual drives are limited, masturbation is common, and children may be interested in differences between genders. Rates of maturation differ by geography, ethnicity, and country. Sexual maturity occurs earlier for both genders in the United States. Differences in maturation rates have implications for differing expectations of others based on sexual maturation.

Implications for Parents and Pediatricians

Middle childhood is generally a time of excellent health. However, children have variable sizes, shapes, and abilities. Children of this age compare themselves with others, eliciting feelings about their physical attributes and abilities. Fears of being “abnormal” can lead to avoidance of situations in which physical differences might be revealed, such as gym class or medical examinations. Children with actual physical disabilities may face special stresses. Medical, social, and psychologic risks tend to occur together.

Children should be asked about risk factors for **obesity** . Participation in physical activity, including organized sports or other organized activities, can foster skill, teamwork, and fitness as well as a sense of accomplishment, but pressure to compete when the activity is no longer enjoyable has negative effects. Counseling on establishing healthy eating habits and limited screen time should be given to all families. Prepubertal children should not engage in high-stress, high-impact sports, such as power lifting or tackle football, because skeletal immaturity increases the risk of injury (see Chapter 713).

Cognitive Development

The thinking of early elementary school-age children differs qualitatively from that of preschool children. In place of magical, egocentric, and perception-bound cognition, school-age children increasingly apply rules based on observable phenomena, factor in multiple dimensions and points of view, and interpret their perceptions using physical laws. Piaget documented this shift from preoperational to **concrete** (logical) **operations** . When 5 yr olds watch a ball of clay being rolled into a snake, they might insist that the snake has “more” because it is longer. In contrast, 7 yr olds typically reply that the ball and the snake must weigh the same because nothing has been added or taken away or because the snake is both longer and thinner. This cognitive reorganization occurs at different rates in different contexts. In the context of social interactions with siblings, young children often demonstrate an ability to understand alternate points of view long before they demonstrate that ability in their thinking about the physical world. Understanding time and space constructs occurs in the later part of this period.

The concept of **school readiness** has evolved. The American Academy of Pediatrics recommends following an “interactional relational” model in which the focus is on the child, the environment, and the resulting interactions. This model explicitly asserts that all children can learn and that the educational process is reciprocal between the child and the school. It is developmentally based, recognizing the importance of early experiences for later development. Rather than delaying school entry, high-quality early-education programs may be the key to ultimate school success.

School makes increasing cognitive demands on the child. Mastery of the elementary curriculum requires that many perceptual, cognitive, and language processes work efficiently (Table 25.1), and children are expected to attend to many inputs at once. The 1st 2-3 yr of elementary school are devoted to acquiring the fundamentals: reading, writing, and basic mathematics skills. By 3rd grade, children need to be able to sustain attention through a 45 min period, and the curriculum requires more complex tasks. The goal of reading a paragraph is no longer to decode the words, but to understand the content; the goal of writing is no longer spelling or penmanship, but composition. The volume of work increases along with the complexity.

Table 25.1

Selected Perceptual, Cognitive, and Language Processes Required for Elementary School Success

PROCESS	DESCRIPTION	ASSOCIATED PROBLEMS
PERCEPTUAL		
Visual analysis	Ability to break a complex figure into components and understand their spatial relationships	Persistent letter confusion (e.g., between *b, d,* and *g*); difficulty with basic reading and writing and limited “sight” vocabulary
Proprioception and motor control	Ability to obtain information about body position by feel and unconsciously program complex movements	Poor handwriting, requiring inordinate effort, often with overly tight pencil grasp; special difficulty with timed tasks
Phonologic processing	Ability to perceive differences between similar-sounding words and to break down words into constituent sounds	Delayed receptive language skill; attention and behavior problems secondary to not understanding directions; delayed acquisition of letter-sound correlations (phonetics)
COGNITIVE		
Long-term memory, both storage and recall	Ability to acquire skills that are “automatic” (i.e., accessible without conscious thought)	Delayed mastery of the alphabet (reading and writing letters); slow handwriting; inability to progress beyond basic mathematics
Selective attention	Ability to attend to important stimuli and ignore distractions	Difficulty following multistep instructions, completing assignments, and behaving well; problems with peer interaction
Sequencing	Ability to remember things in order; facility with time concepts	Difficulty organizing assignments, planning, spelling, and telling time
LANGUAGE		
Receptive language	Ability to comprehend complex constructions, function words (e.g., if,	Difficulty following directions; wandering attention during lessons and stories; problems with reading

	when, only, except), nuances of speech, and extended blocks of language (e.g., paragraphs)	comprehension; problems with peer relationships
Expressive language	Ability to recall required words effortlessly (word finding), control meanings by varying position and word endings, and construct meaningful paragraphs and stories	Difficulty expressing feelings and using words for self-defense, with resulting frustration and physical acting out; struggling during “circle time” and in language-based subjects (e.g., English)

Cognitive abilities interact with a wide array of attitudinal and emotional factors in determining classroom performance. These factors include *external rewards* (eagerness to please adults and approval from peers) and *internal rewards* (competitiveness, willingness to work for a delayed reward, belief in one's abilities, and ability to risk trying when success is not ensured). Success predisposes to success, whereas failure impacts self-esteem and reduces self-efficacy, diminishing a child's ability to take future risks.

Children's intellectual activity extends beyond the classroom. Beginning in the 3rd or 4th grade, children increasingly enjoy strategy games and wordplay (puns and insults) that exercise their growing cognitive and linguistic mastery. Many become experts on subjects of their own choosing, such as sports trivia, or develop hobbies, such as special card collections. Others become avid readers or take on artistic pursuits. Whereas board and card games were once the usual leisure-time activity of youth, video, computer, and other electronic games currently fill this need.

Implications for Parents and Pediatricians

Pediatricians have an important role in preparing their patients for school entrance by promoting health through immunizations, adequate nutrition, appropriate recreation, and screening for physical, developmental, and cognitive disorders. The American Academy of Pediatrics recommends that pediatric providers promote the “5 Rs” of early education: (1) reading as a daily family activity; (2) rhyming, playing, and cuddling together; (3) routines and regular times for meals, play, and sleep; (4) reward through praise for successes; and (5) reciprocal nurturing relationships.

Concrete operations allow children to understand simple explanations for illnesses and necessary treatments, although they may revert to prelogical thinking when under stress. A child with pneumonia may be able to explain about white cells fighting the “germs” in the lungs, but may still secretly harbor the belief that the sickness is a punishment for disobedience.

As children are faced with more abstract concepts, academic and classroom behavior problems emerge and come to the pediatrician's attention. Referrals may be made to the school for remediation or to community resources (medical or psychologic) when appropriate. The causes may be one or more of the following: deficits in perception (vision and hearing); specific learning disabilities (see Chapters 50 and 51); global cognitive delay (intellectual disability; Chapter 53); deficits in attention and executive function (Chapters 48 and 49); and attention deficits secondary to family dysfunction, depression, anxiety, or chronic illness. Children whose learning style does not fit the classroom culture may have academic difficulties and need assessment before failure sets in. Simply having a child repeat a failed grade rarely has any beneficial effect and often seriously undercuts the child's self-esteem. In addition to finding the problem areas, identifying each child's strengths is important. Educational approaches that value a wide range of talents (“multiple intelligences”) beyond the traditional reading, writing, and mathematics may allow more children to succeed.

The change in cognition allows the child to understand “if/when” clauses. Increased responsibilities and expectations accompany increased rights and privileges. Discipline strategies should move toward negotiation and a clear understanding of consequences, including removal of privileges for infringements.

Social, Emotional, and Moral Development

Social and Emotional Development

In middle childhood, energy is directed toward creativity and productivity. Changes occur in 3 spheres: the home, the school, and the neighborhood. Of these, the home and family remains the most influential. Increasing independence is marked by the first sleepover at a friend's house and the first time at overnight camp. Parents should make demands for effort in school and extracurricular activities, celebrate successes, and offer unconditional acceptance when failures occur. Regular chores, associated with an allowance, provide an opportunity for children to contribute to family functioning and learn the value of money. These responsibilities may be a testing ground for psychologic separation, leading to conflict. Siblings have critical roles as competitors, loyal supporters, and role models.

The beginning of school coincides with a child's further separation from the family and the increasing importance of teacher and peer relationships. Social groups tend to be same-sex, with frequent changing of membership, contributing to a child's growing social development and competence. Popularity, a central ingredient of self-esteem, may be won through possessions (having the latest electronic gadgets or the right clothes), as well as through personal attractiveness, accomplishments, and actual social skills. Children are aware of racial differences and are beginning to form opinions about racial groups that impact their relationships. **Gender identification** , which began in early childhood, continues to evolve and can have significant implications for peer relationships and self-awareness.

Some children conform readily to the peer norms and enjoy easy social success. Those who adopt individualistic styles or have visible differences may be teased or bullied. Such children may be painfully aware that they are different, or they may be puzzled by their lack of popularity. Children with deficits in social skills may go to extreme lengths to win acceptance, only to meet with repeated failure. Attributions conferred by peers, such as funny, stupid, bad, or fat, may become incorporated into a child's self-image and affect the child's personality, as well as school performance. Parents may have their greatest effect indirectly, through actions that change the peer group (moving to a new community or insisting on involvement in structured after-school activities). Children who identify with a gender different from their sex of birth, or whose manner and dress reflect those more typically seen as “opposite” their birth sex, may be subject to teasing or, **bullying** . This can magnify the confusion for these children, who are formulating their own concept of “self.”

In the neighborhood, real dangers, such as busy streets, bullies, violence, and strangers, tax school-age children's common sense and resourcefulness (see Chapter 14). Interactions with peers without close adult supervision call on increasing conflict resolution skills. Media exposure to adult materialism, sexuality, substance use, and violence may be frightening, reinforcing children's feeling of powerlessness in the larger world. Compensatory fantasies of being powerful may fuel the fascination with heroes and superheroes. A balance between fantasy and an appropriate ability to negotiate real-world challenges indicates healthy emotional development.

Moral Development

Although by age 6 yr most children will have a **conscience** (internalized rules of society), they vary greatly in their level of moral development. For the younger youth, many still subscribe to the notion that rules are established and enforced by an authority figure (parent or teacher), and decision-making is guided by self-interest (avoidance of negative and receipt of positive consequences). The needs of others are not strongly considered in decision-making. As they grow older, most will recognize not only their own needs and desires but also those of others, although personal consequences are still the primary driver of behavior. Social behaviors that are socially undesirable are considered wrong. By age 10-11 yr, the combination of peer pressure, a desire to please authority figures, and an understanding of **reciprocity** (treat others as you wish to be treated) shapes the child's behavior.

Implications for Parents and Pediatricians

Children need unconditional support as well as realistic demands as they venture into a world that is often frightening. A daily query from parents over the dinner table or at bedtime about the good and bad things that happened during the child's day may uncover problems early. Parents may have difficulty allowing the child independence or may exert excessive pressure on their children to achieve academic or competitive success. Children who struggle to meet such expectations may have behavior problems or psychosomatic complaints.

Many children face stressors that exceed the normal challenges of separation and success in school and the neighborhood. Divorce affects almost 50% of children. Domestic violence, parental substance abuse, and other mental health problems may also impair a child's ability to use home as a secure base for refueling emotional energies. In many neighborhoods, random violence makes the normal development of independence extremely dangerous. Older children may join gangs as a means of self-protection and a way to attain recognition and to belong to a cohesive group. Children who bully others and those who are victims of bullying should be evaluated, since bullying is associated with mood disorders, family problems, and school adjustment problems. Parents should reduce exposure to hazards where possible. Because of the risk of unintentional firearm injuries to children, parents should be encouraged to ask parents of playmates whether a gun is kept in their home and, if so, how it is secured. The high prevalence of adjustment disorders among school-age children attests to the effects of such overwhelming stressors on development.

Pediatrician visits are infrequent in this period; therefore each visit is an opportunity to assess children's functioning in all contexts (home, school, neighborhood). Maladaptive behaviors, both internalizing and externalizing, occur when stress in any of these environments overwhelms the child's coping responses. Because of continuous exposure and the strong influence of media (programming and advertisements) on children's beliefs and attitudes, parents must be alert to exposures from television and Internet. An average American youth spends over 6 hr/day with a variety of media, and 65% of these children have a TV in their bedrooms. Parents should be advised to remove the TV from their children's rooms, limit viewing to 2 hr/day, and monitor what programs children watch. The **Draw-a-Person** (for ages 3-10 yr, with instructions to “draw a complete person”) and **Kinetic Family Drawing** (beginning at age 5 yr, with instructions to “draw a picture of everyone in your family doing something”) are useful office tools to assess a child's functioning.

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CHAPTER 26

Adolescence

See Part XII, Chapter 132 , Adolescent Physical and Social Development.

CHAPTER 27

Assessment of Growth

Vaneeta Bamba, Andrea Kelly

Growth can be considered a vital sign in children, and aberrant growth may be the first sign of an underlying pathologic condition. The most powerful tool in growth assessment is the **growth chart** (Figs. 23.1 , 23.2 , 25.1 , and 27.1), used in combination with accurate measurements of height, weight, head circumference, and calculation of the body mass index.

Techniques to Measure Growth

Growth assessment requires accurate and precise measurements. For infants and toddlers age <2 yr, weight, length, and head circumference are obtained. **Head circumference** is measured with a flexible tape measure starting at the supraorbital ridge around to the occipital prominence in the back of the head, locating the maximal circumference. **Height** and **weight** measures should be performed with the infant naked, and ideally, repeated measures will be performed on the same equipment. **Recumbent length** is most accurately measured by two examiners (one to position the child). Hair ornaments and hairstyles that interfere with measurements and positioning should be removed. The child's head is positioned against an inflexible measuring board in the **Frankfurt plane** , in which the outer canthi of the eyes are in line with the external auditory meatus and are perpendicular to the long axis of the trunk. Legs should be fully extended, and feet are maintained perpendicular to the plane of the supine infant. For older children (>2 yr) who can stand unassisted, standing heights should be obtained without shoes, using a stadiometer with the head in the Frankfurt plane, and the back of the head, thoracic spine, buttocks, and heels approximating the vertical axis of one another and the stadiometer.

Measurements obtained using alternative means, such as marking examination paper at the foot and head of a supine infant or using a tape measure or wall growth chart with a book or ruler on the head can lead to inaccuracy and render the measurement useless.

Measurements for height and weight should be plotted on the age-appropriate growth curve. Comparing measurements with previous growth trends, repeating measures that are inconsistent, and plotting results longitudinally are essential for monitoring growth. Calculation of interim linear height velocity, such as centimeters per year (cm/yr), allows more precise comparison of growth rate to the norm (Table 27.1).

Table 27.1

Growth Velocity and Other Growth Characteristics by Age

INFANCY	CHILDHOOD	ADOLESCENCE
Birth-12 mo: 24 cm/yr 12-24 mo: 10 cm/yr 24-36 mo: 8 cm/yr	6 cm/yr Slowly decelerates before pubertal onset Height typically does not cross percentile lines	Sigmoid-shaped growth Adolescent growth spurt accounts for about 15% of adult height Peak height velocity Girls: 8 cm/yr Boys: 10 cm/yr

If a child is growing faster or more slowly than expected, measurement of body proportions, which follow a predictable sequence of changes with development, are useful. The head and trunk are relatively large at birth, with progressive lengthening of the limbs throughout development, particularly during puberty. The **upper-to-lower body segment ratio** (**U/L ratio**) provides an assessment of truncal growth relative to limb growth. The **lower-body segment** is defined as the length from the top of the symphysis pubis to the floor, and the **upper-body segment** is the total height minus the lower-body segment. The U/L ratio equals approximately 1.7 at birth, 1.3 at 3 yr, and 1.0 after 7 yr. Higher U/L ratios are characteristic of short-limb dwarfism, as occurs with Turner syndrome or bone disorders, whereas lower ratios suggest hypogonadism or Marfan syndrome.

Arm span also provides assessment of proportionality and is measured as the distance between the tips of the middle fingers while the patient stands with the back against the wall with arms outstretched horizontally at a 90-degree angle to the trunk. This span should be close to height, although the proportion changes with age.

Growth Curves

The American Academy of Pediatrics (AAP) and the U.S. Centers for Disease Control and Prevention (CDC) recommend use of the 2006 World Health Organization (WHO) growth curves for children age 0-24 mo and the 2000 CDC growth curves for children age 2-19 yr (https://www.cdc.gov/growthcharts). There are 5 standard gender-specific charts: (1) weight for age, (2) height (length and stature) for age, (3) head circumference for age, (4) weight for height (length and stature) for infants, and (5) body mass index for age (Fig. 27.1 ; see also Figs. 23.1 , 23.2 , and 25.1). Clinicians should confirm that the correct CDC and WHO growth charts are used in electronic medical records to ensure accurate characterization of growth.

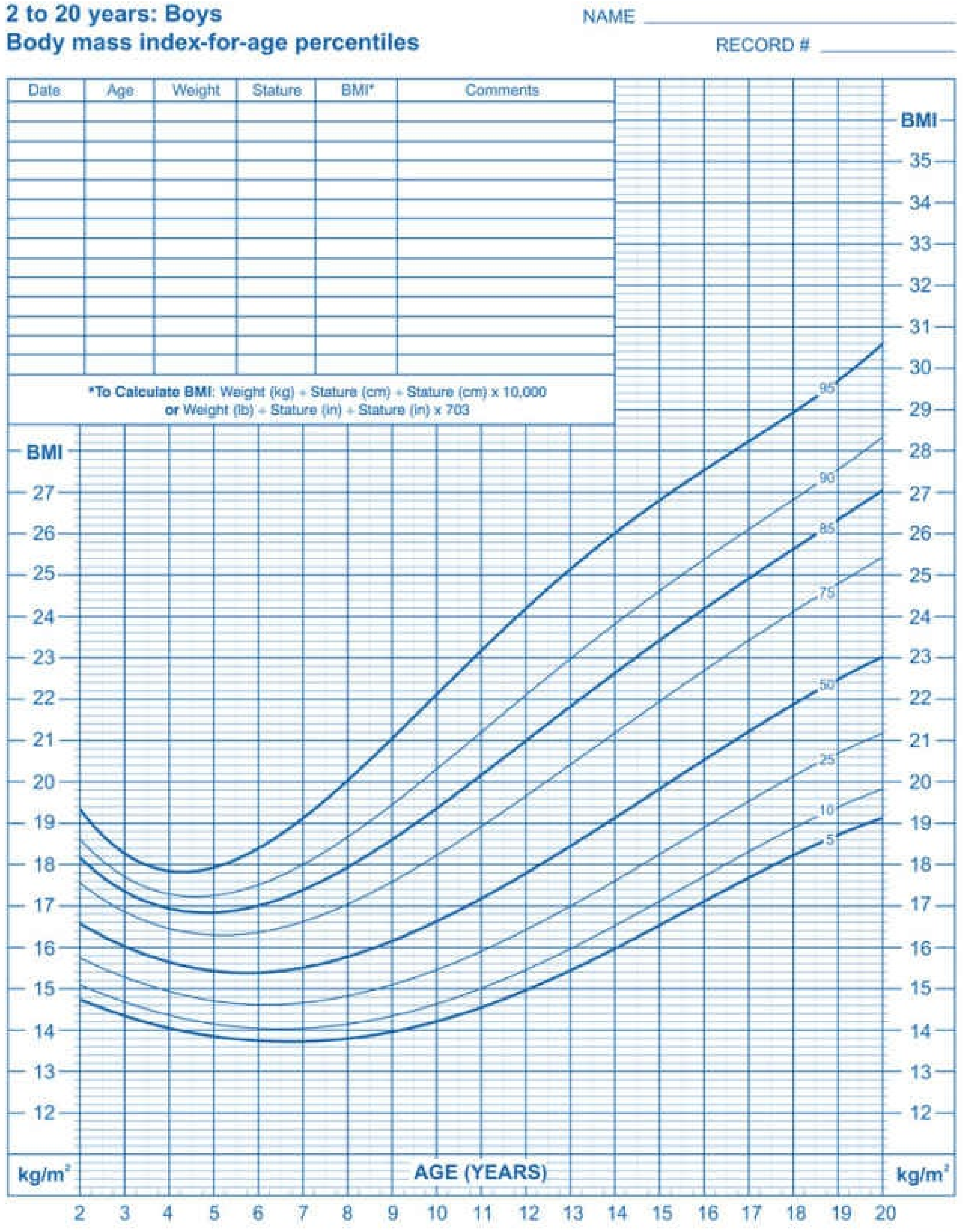

Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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A

A, Body mass index (BMI) percentiles for boys, age 2-20 yr. (Official Centers for Disease Control [CDC] growth charts, as described in this chapter. The 85th to 95th percentile is at risk for overweight; >95th percentile is overweight; <5th percentile is underweight. Technical information and interpretation and management guides are available at

www.cdc.gov/nchs . Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000. http://www.cdc.gov/growthcharts)

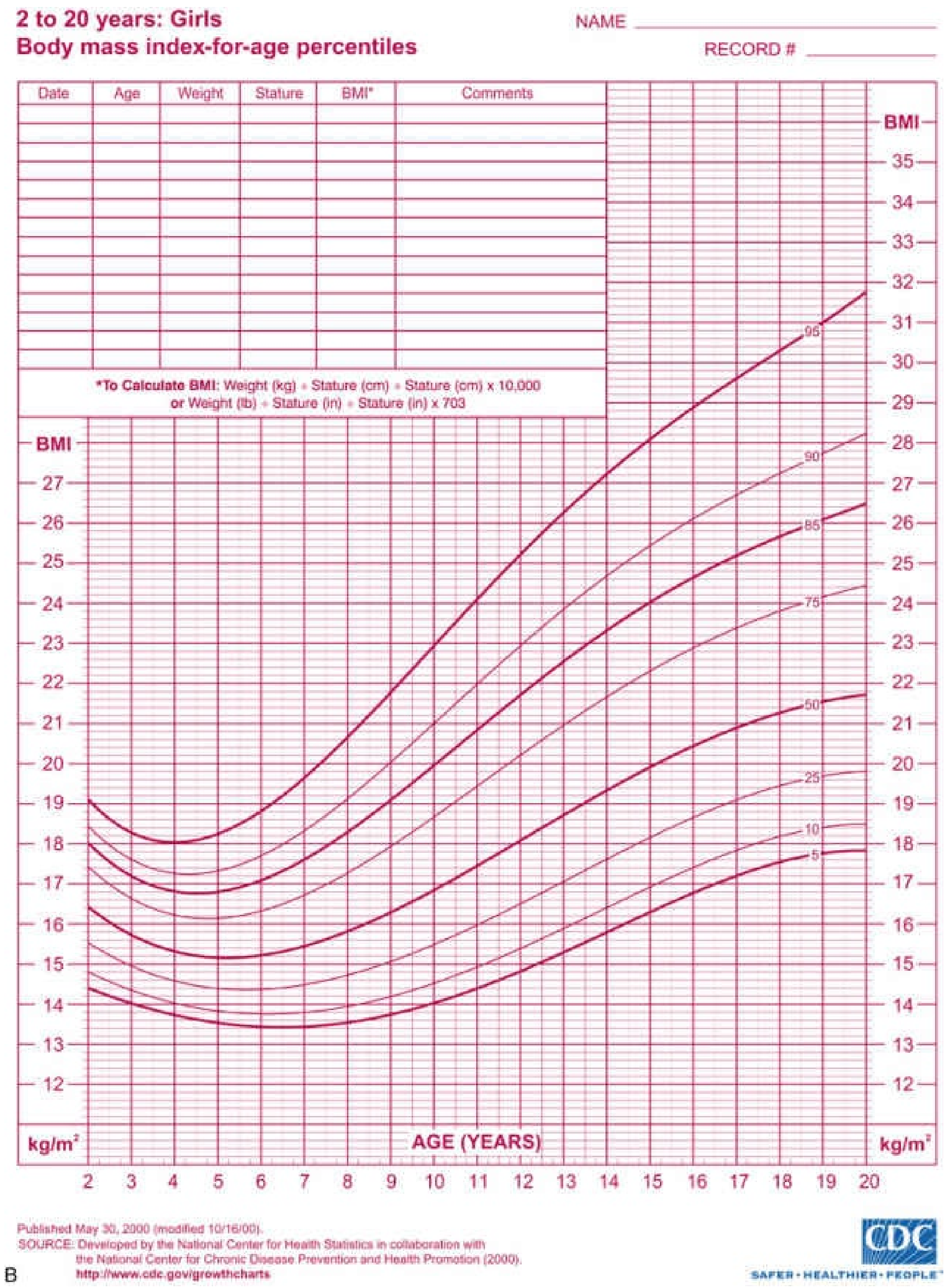

B, Body mass index (BMI) percentiles for girls, age 2-20 yr.

FIG. 27.1

The WHO curves describe growth differently than the CDC curves (Fig. 27.2). The WHO curves are **growth standards** that describe how children grow under optimal conditions, whereas the CDC curves are **growth references** that describe how children grew in a specific time and place. The WHO growth curves are based on longitudinal growth studies in which cohorts of newborns were chosen from six countries (Brazil, Ghana, India, Norway, Oman, United States) using specific inclusion and exclusion criteria; all infants were breastfed for at least 12 months and were predominantly breastfed for the first 4 mo of life. They were measured regularly from birth to 23 mo during 1997–2003. In contrast, the CDC curves are based on cross-sectional data from different studies during different time points. Growth curves for children age 2-59 mo were based on the National Health and Nutrition Examination Survey (NHANES), which included a cross section of the U.S. population. These data were supplemented with additional participants in a separate nutrition surveillance study.

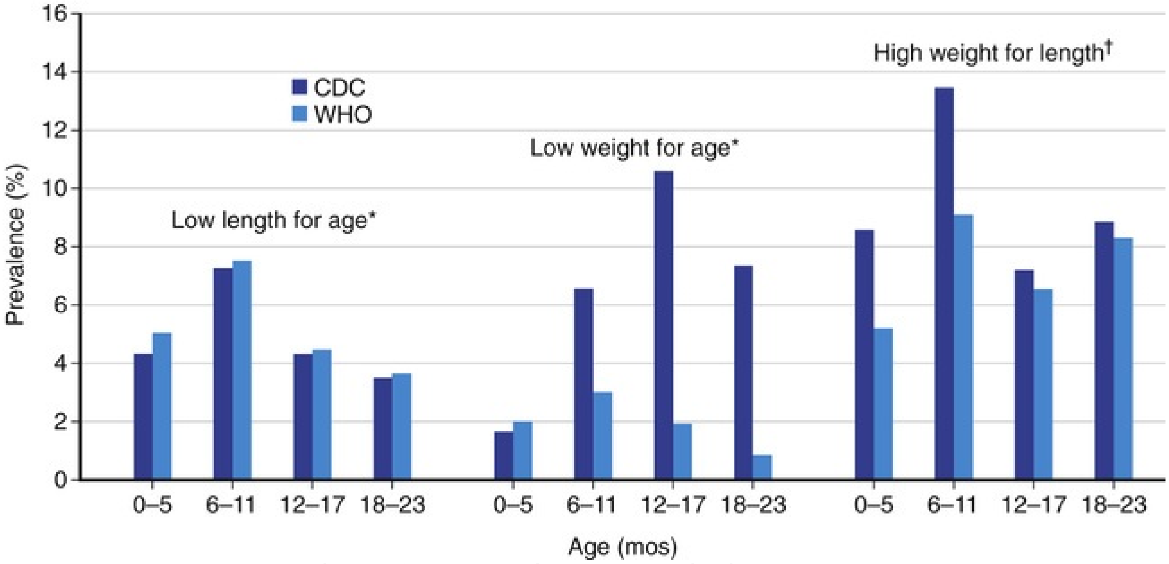

FIG. 27.2 Comparison of WHO and CDC growth chart prevalence of low length for age, low weight for age, and high weight for length among children age <24 mo, United States, 1999–2004. *, ≤5th percentile on the CDC charts; ≤2.3rd percentile on the WHO charts. †, ≥95th percentile on the CDC charts; ≥97.7th percentile on the WHO charts. (Data from the National Health and Nutrition Examination Survey, 1999–2004; from Grummer-Strawn LM, Reinold C, Krebs NF; Centers for Disease Control and Prevention: Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States, *MMWR Recomm Rep* 59(RR-9):1–15, 2010.)

Several deficiencies of the older charts have been corrected, such as the overrepresentation of bottle-fed infants and the reliance on a local dataset for the infant charts. The disjunction between length and height when transitioning from the infant curves to those for older children is improved.

Each chart is composed of percentile curves, which indicate the percentage of children at a given age on the *x* axis whose measured value falls below the corresponding value on the *y* axis. The 2006 WHO growth curves include values that are 2 standard deviations (SD) above and below median (2nd and 98th percentiles), whereas the 2000 CDC growth curves include 3rd and 97th percentiles. On the WHO weight chart for boys age 0-24 mo (see Fig. 23.2*A*), the 9 mo age line intersects the 25th percentile curve at 8.3 kg, indicating that 25% of 9 mo old boys in the WHO cohorts weigh less than 8.3 kg (75% weigh more). Similarly, a 9 mo old boy weighing more than 11 kg is heavier than 98% of his peers. The median or 50th percentile is also termed the **standard value** , in the sense that the standard length for a 7 mo old girl is 67.3 cm (see Fig. 23.2*B*). The weight-for-length charts (see Fig. 23.1) are constructed in an analogous fashion, with length or stature in place of age on the *x* axis; the median or standard weight for a girl measuring 100 cm is 15 kg.

Extremes of height or weight can also be expressed in terms of the age for which they would represent the standard or median. For instance, an 18 mo old girl who is 74.9 cm (2nd percentile) is at the 50th percentile for a 13 mo old. Thus the height age is 13 mo. Weight age can also be expressed this way.

In assessing adolescents, caution must be used in applying cross-sectional charts. Growth during adolescence is linked temporally to the onset of puberty, which varies widely. Normal variations in the timing of the growth spurt can lead to misdiagnosis of growth abnormalities. By using cross-sectional data based on chronological age, the charts combine youth who are at different stages of maturation. Data for 12 yr old boys include both earlier-maturing boys who are at the peak of their growth spurts and later-maturing ones who are still growing at their prepubertal rate. The net results are an artificially blunted growth peak, and the appearance that adolescents grow more gradually and for a longer duration than in actuality.

When additional insight is necessary, growth charts derived from longitudinal data, such as the **height velocity charts** of Tanner and colleagues, are recommended. The longitudinal component of these velocity curves are based on British children from the 1950s–1960s, and cross-sectional data from U.S. children were superimposed. More recently, height velocity curves based on longitudinal data from a multiethnic study conducted at five U.S. sites included standard deviation scores for height velocity for earlier- and later-maturing adolescents to facilitate the identification of poor or accelerated linear growth.

Specialized growth charts have been developed for U.S. children with various conditions, including very low birthweight, small for gestational age, trisomy 21, Turner syndrome, and achondroplasia, and should be used when appropriate.

Facilitating identification of obesity, the charts include curves for plotting **body mass index (BMI)** for ages 2-20 yr rather than weight for height (see Fig. 27.1). Methodological steps have ensured that the increase in the prevalence of obesity has not unduly raised the upper limits of normal. BMI can be calculated as weight in kilograms/(height in meters)^2 or weight in pounds/(height in inches)^2 × 703, with fractions of pounds and inches expressed as decimals. Because of variable weight and height gains during childhood, BMI must be interpreted relative to age and sex; BMI percentile provides a more standardized comparison. For example, a 6 yr old girl with BMI of 19.7 kg/m^2 (97th percentile) is obese, whereas a 15 yr old girl with BMI of 19.7 kg/m^2 (50th percentile) is normal weight.

Normal Growth

Height is highly correlated with genetics, specifically parental height. Calculation of sex-adjusted **midparental height** is important when assessing growth in a child to avoid misclassification of abnormal growth. The average difference in stature between men and women is 5 inches (13 cm); therefore 5 inches (13 cm) is subtracted from father's height before averaging with mother's height in a female, whereas 5 inches (13 cm) is added to mother's height before averaging with father's height in a male:

- Boys: [(Maternal height + 5 inches) + Paternal height]/2
- Girls: [Maternal height + (Paternal height − 5 inches)]/2

Furthermore, generally 4 inches (2 SD) is applied above and below this value to provide a *genetic target height range* . For example, if the mother is 63 inches tall and the father 70 inches tall, the daughter's sex-adjusted midparental height is 64 inches ± 4 inches, for a target height range of 60-68 inches. The son of these same parents would have a sex-adjusted midparental height of 69 inches, with a range of 65-73 inches. Note that these general guidelines do not address extreme differences between parental heights that may affect individual target height range.

Growth can be divided into four major phases: fetal, infantile, childhood, and adolescence. Growth rate varies by age (see Table 27.1). Different factors are of different importance in each phase, and the various contributors to poor growth may feature more in one phase than another. Long-term height may be permanently compromised if one entire phase is characterized by poor growth. Therefore, early detection and prevention are critical. **Fetal growth** is the fastest growth phase, with maternal, placental, fetal, and environmental factors playing key roles. Birthweight does not necessarily correlate with adult height, although factors that inhibit fetal growth may have long-lasting effects, as seen in children with intrauterine growth retardation. **Infantile growth** is particularly sensitive to nutrition as well as congenital conditions. Genetic height gradually becomes influential; indeed, crossing of percentiles in the 1st 2 yr of life is common as children begin to approach their genetic potential. **Childhood growth** is often the most steady and predictable. During this phase the height percentile channel is fairly consistent in otherwise healthy children.

Adolescent growth is associated with a decrease in growth velocity prior to the onset of puberty; this deceleration tends to be more pronounced in males. During pubertal development, sex hormones (testosterone and estrogen) are the primary drivers of growth and enhance growth hormone secretion, thereby facilitating pubertal growth acceleration. Girls typically experience growth acceleration during Tanner Stage 3 for breast development, whereas this acceleration occurs during Tanner Stage 4 for pubic hair development in boys. Boys not only achieve greater height velocities than girls during puberty, but also grow approximately 2 yr longer than girls, both of which contribute to the taller average height of adult men compared with adult women.

Abnormal Growth

Growth is a dynamic process. A child measured at the 5th percentile for stature may be growing normally, may be failing to grow, or may be recovering from growth failure, depending on the trajectory of the growth curve (Fig. 27.3). Growth failure must be distinguished from short stature. **Growth failure** is defined as achievement of height velocity that is less than expected for a child's age and sex (and pubertal development if relevant) or a downward crossing of more than 2 percentile lines for height on the growth chart. **Short stature** is defined as growing either below expected genetic potential or growing below −2 SD for age and sex. For some children, however, growth parameters <−2 SD may be normal, and differentiating appropriately small vs pathologically small is crucial. Midparental height, ethnicity, and other factors that may be inherent in the child's genetic potential for growth are important considerations in the assessment of growth. For children with particularly tall or short parents, overdiagnosing and underdiagnosing growth disorders are risks if parental heights are not taken into account. In the setting of familial short stature or tall status, more specialized charts can help determine if a child is even shorter or taller than expected for parental heights, to prevent misdiagnosis of growth disorders.

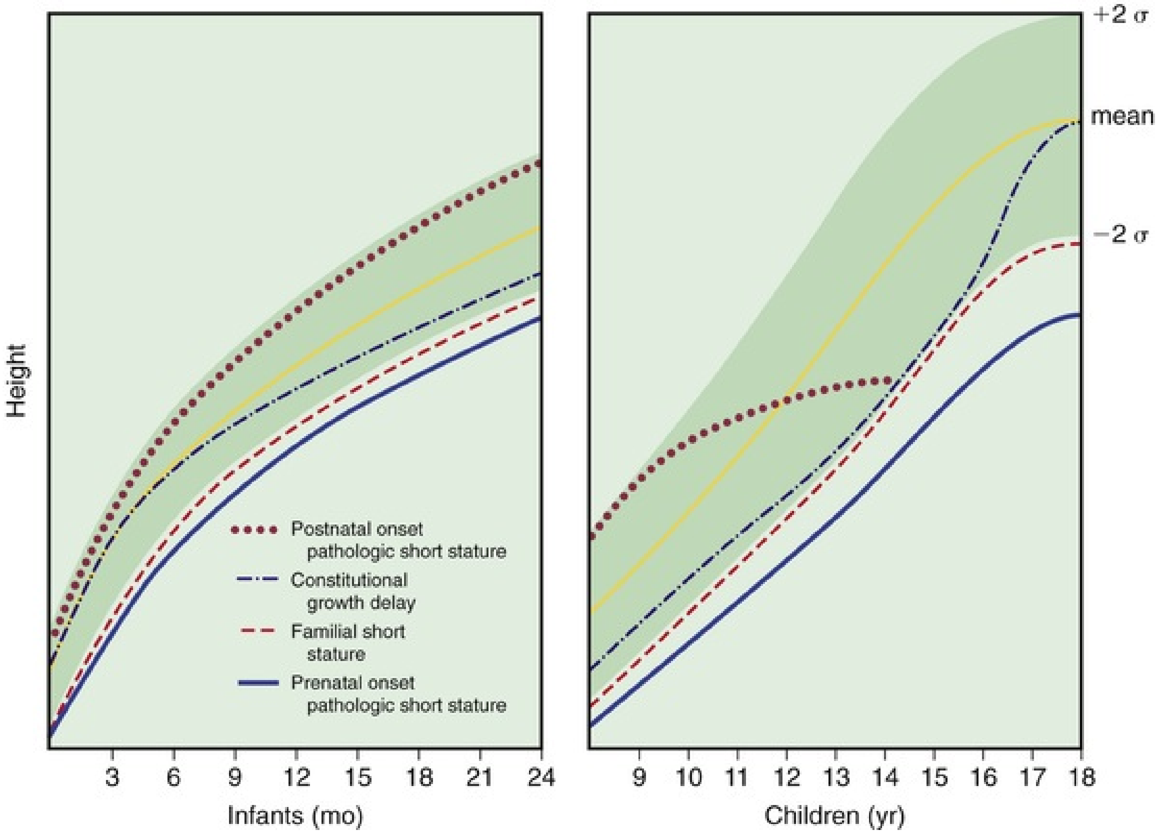

FIG. 27.3 Height-for-age curves of the 4 general causes of proportional

short stature: postnatal onset pathologic short stature, constitutional growth delay, familial short stature, and prenatal onset short stature. (From Mahoney CP: Evaluating the child with short stature, *Pediatr Clin North Am* 34:825, 1987.)

For **premature infants** , overdiagnosis of growth failure can be avoided by using growth charts developed specifically for this population. A cruder method, subtracting the weeks of prematurity from the postnatal age when plotting growth parameters, does not capture the variability in growth velocity that very-low-birthweight (VLBW) infants demonstrate. Although VLBW infants may continue to show **catch-up growth** through early school age, most achieve weight catch-up during the 2nd year and height catch-up by 3-4 yr, barring medical complications (see Chapter 117).

Abnormal growth may be caused by a variety of factors, including congenital conditions, systemic disease, endocrine disorders, nutritional deficiency (see Chapter 57), psychosocial conditions, constitutional delay, or familial disorders (Tables 27.2 and 27.3). In congenital pathologic short stature, an infant may or may not be born small, but growth gradually tapers throughout infancy (Fig. 27.3). Causes include chromosome or genetic abnormalities (Turner syndrome, skeletal dysplasia, trisomy 21; see Chapter 98), perinatal infection, extreme prematurity, and teratogens (phenytoin, alcohol) (see Chapter 115.5). Linear growth deceleration with or without changes in weight can occur at the onset or as a result of a systemic illness or chronic inflammation. Medications such as high-dose glucocorticoids may also impact growth. Analysis of growth patterns requires consideration of weight status. Poor linear growth in the setting of decreasing BMI suggests a nutritional or gastrointestinal issue, whereas poor linear growth in the context of good or robust BMI suggests a hormonal condition (hypothyroidism, growth hormone deficiency, cortisol excess).

Table 27.2

Common Causes of Decreased Growth and Short Stature

- Variation of normal
    - Familial short stature
    - Constitutional delay
    - Delayed puberty
- Nutrition and gastrointestinal conditions

- Malnutrition
- Celiac disease
- Inflammatory bowel disease

Genetic conditions
- Turner syndrome
- Prader-Willi syndrome
- 22q deletion syndrome
- Trisomy 21
- Skeletal dysplasias: achondroplasia, SHOX haploinsufficiency, osteogenesis imperfecta

Endocrine conditions
- Hypothyroidism
- Growth hormone deficiency
- Poorly controlled diabetes mellitus
- Poorly controlled diabetes insipidus
- Metabolic bone disease: rickets, hypophosphatasia
- Glucocorticoid excess

Psychosocial causes

Renal conditions
- Renal tubular acidosis
- Nephrotic syndrome

Medications
- Glucocorticoids
- Inappropriate sex steroid exposure
- Antiepileptic medications

Table 27.3

Common Causes of Increased Growth and Tall Stature

Variation of normal
- Constitutional tall stature
- Familial tall stature

Endocrine conditions
- Growth hormone excess
- Precocious puberty
- Congenital adrenal hyperplasia

- Obesity
- Genetic conditions
    - Marfan syndrome
    - Klinefelter syndrome
    - Sotos syndrome

Not all decreased growth is abnormal; variations of growth include constitutional growth (and pubertal) delay and familial short stature. In **constitutional growth delay** , weight and height decrease near the end of infancy, parallel the norm through middle childhood, and accelerate toward the end of adolescence with achievement of normal adult height. In **familial short stature** , both the infant/child and the parent(s) are small; growth runs parallel to and just below the normal curves.

Although **tall or accelerated growth** may be a variation of normal, unexpected increase in growth may also signal an underlying condition (Table 27.3). Typically, obese individuals grow more quickly than their peers because of peripheral aromatization of estrogen and effects on bone maturation. Despite early taller stature, obese children are not ultimately taller than anticipated for genetic height. Early onset of puberty, growth hormone excess, and sex steroid exposure can also lead to accelerated growth. Several of these conditions may ultimately lead to short stature in adulthood. Genetic conditions associated with tall stature and overgrowth include Sotos, Klinefelter, and Marfan syndromes (see Chapter 576).

Evaluation of Abnormal Growth

Evaluation of abnormal growth should include confirmation that the data are accurate and plotted correctly. Comparisons should be made with previous measurements. If poor or rapid growth or short or tall stature is a concern, a radiograph of the left hand and wrist, the **bone age** , can provide information about skeletal maturation. Skeletal development represents physiologic rather than chronological age. Reference standards for bone maturation facilitate estimation of bone age (see Table 22.3). A delayed bone age (skeletal age younger than chronological age) suggests catch-up potential for linear growth. Advanced bone age suggests a rapid maturation of the skeleton that may lead to earlier cessation of growth. Bone age should be interpreted with the guidance of a pediatric endocrinologist. Skeletal age correlates well with stage of pubertal development and may be helpful in predicting adult height in early- or late-maturing adolescents. In familial short stature the bone age is normal (comparable to chronological age), whereas constitutional delay, endocrinologic short stature, and undernutrition may be associated with delay in bone age comparable to the height age.

Laboratory testing is also useful in assessment of growth and may be tailored to suspected etiology based on the patient history and physical examination. Initial assessment includes comprehensive metabolic panel, complete blood count, sedimentation rate, C-reactive protein, thyroid-stimulating hormone, thyroxine, celiac panel, and insulin-like growth factor (IGF)-I and IGF-BP3, which are surrogate markers for growth hormone secretion (see Chapter 573). A karyotype to exclude Turner syndrome is an essential component of the evaluation of short stature in females and should be performed even in the absence of characteristic physical features (see Chapter 604). If there is concern for abnormal timing of puberty contributing to growth pattern, gonadotropins (luteinizing hormone, follicle-stimulating hormone), and estradiol or testosterone may also be assessed. A urinalysis can provide additional information about renal function. Evaluation by a (pediatric) nutritionist for caloric needs assessment may be useful in patients with malnutrition, underweight status, or slow weight gain. Additional testing and referral to specialists should be performed as indicated.

Other Growth Considerations

Obesity

Obesity affects large numbers of children (see Chapter 60). The CDC defines *obesity* as BMI ≥95th percentile for age and sex, and *overweight* as BMI 85th to <95th percentile for age and sex. Although widely accepted as the best clinical measure of underweight and overweight, BMI may not provide an accurate index of adiposity because it does not differentiate lean tissue and bone from fat. In otherwise healthy individuals, lean body mass is largely represented by BMI at lower percentiles. BMI >80–85% largely reflects increased body fat with a nonlinear relationship between BMI and adiposity. In the setting of chronic illness, increased body fat may be present at low BMI, whereas in athletes, high BMI may reflect increased muscle mass. Measurement of the triceps, subscapular, and suprailiac skinfold thickness have been used to estimate adiposity. Other methods of measuring fat, such as hydrodensitometry, bioelectrical impedance, and total body water measurement, are used in research, but not in clinical evaluation, but whole body dual-energy x-ray absorptiometry (DXA) is beginning to emerge as a tool for measuring body fat and lean body mass.

Dental Development

Dental development includes mineralization, eruption, and exfoliation (Table 27.4). Initial mineralization begins as early as the 2nd trimester (mean age for central incisors, 14 wk) and continues through 3 yr of age for the primary (deciduous) teeth and 25 yr of age for the secondary (permanent) teeth. Mineralization begins at the crown and progresses toward the root. Eruption begins with the central incisors and progresses laterally. Exfoliation begins at about 6 yr of age and continues through 12 yr. Eruption of the permanent teeth may follow exfoliation immediately or may lag by 4-5 mo. The timing of dental development is poorly correlated with other processes of growth and maturation. **Delayed eruption** is usually considered when no teeth have erupted by approximately 13 mo of age (mean + 3 SD). Common causes include congenital or genetic disorders, endocrine disorders (e.g., hypothyroidism, hypoparathyroidism), familial conditions, and (the most common) idiopathic conditions. Individual teeth may fail to erupt because of mechanical blockage (crowding, gum fibrosis). Causes of **early exfoliation** include hypophosphatasia, histiocytosis X, cyclic neutropenia, leukemia, trauma, and idiopathic factors. Nutritional and metabolic disturbances, prolonged illness, and certain medications (tetracycline) frequently result in discoloration or malformations of the dental enamel. A discrete line of pitting on the enamel suggests a time-limited insult.

Table 27.4

Chronology of Human Dentition of Primary (Deciduous) and Secondary (Permanent) Teeth

	CALCIFICATION		AGE AT ERUPTION		AGE AT SHEDDING	
	Begins at	**Complete at**	**Maxillary**	**Mandibular**	**Maxillary**	**Mandibular**
PRIMARY TEETH						
Central incisors	5th fetal mo	18-24 mo	6-8 mo	5-7 mo	7-8 yr	6-7 yr
Lateral incisors	5th fetal mo	18-24 mo	8-11 mo	7-10 mo	8-9 yr	7-8 yr

Cuspids (canines)	6th fetal mo	30-36 mo	16-20 mo	16-20 mo	11-12 yr	9-11 yr
First molars	5th fetal mo	24-30 mo	10-16 mo	10-16 mo	10-12 yr	10-12 yr
Second molars	6th fetal mo	36 mo	20-30 mo	20-30 mo	10-12 yr	11-13 yr
SECONDARY TEETH						
Central incisors	3-4 mo	9-10 yr	7-8 yr	6-7 yr		
Lateral incisors	Max, 10-12 mo	10-11 yr	8-9 yr	7-8 yr		
	Mand, 3-4 mo					
Cuspids (canines)	4-5 mo	12-15 yr	11-12 yr	9-11 yr		
First premolars (bicuspids)	18-21 mo	12-13 yr	10-11 yr	10-12 yr		
Second premolars (bicuspids)	24-30 mo	12-14 yr	10-12 yr	11-13 yr		
First molars	Birth	9-10 yr	6-7 yr	6-7 yr		
Second molars	30-36 mo	14-16 yr	12-13 yr	12-13 yr		
Third molars	Max, 7-9 yr	18-25 yr	17-22 yr	17-22 yr		
	Mand, 8-10 yr					

Mand, Mandibular; Max, maxillary.

Adapted from a chart prepared by P.K. Losch, Harvard School of Dental Medicine, who provided the data for this table.

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CHAPTER 28

Developmental and Behavioral Surveillance and Screening

Paul H. Lipkin

In healthy development, a child will acquire new skills beginning prenatally and extending into at least young adulthood. The roots of this acquisition of skills lie in the development of the nervous system, with additional influences from the health status of other organ systems and the physical and social environment in which the development occurs. *Development* and its milestones are divided into the “streams” of gross motor, fine motor, verbal language (expressive and receptive), social language, and self-help. *Behavior* can be categorized into observable, spontaneous, and responsive behaviors in the settings of home, school, and community.

Although typical development is associated with a wide variability of skill acquisition in each of these streams, specific developmental and behavioral disorders are seen in approximately 1 of every 6 children and may affect the health, function, and well-being of the child and family for a lifetime. These disorders include rare conditions that often cause severe impairments, such as cerebral palsy and autism, and relatively common conditions such as attention-deficit/hyperactivity disorder, speech language disorders, and behavioral and emotional disorders that affect as many as 1 in 4 children. The more common conditions are generally perceived as “less severe,” but these too can have major short-term and long-term impact on the child's health and daily functioning in the home, school, and community and can affect lifelong well-being. Because of their high prevalence in children; their impact on health, social, and economic status; and their effect on the child, the home, and the community, these disorders require the attention of the pediatrician throughout childhood. In addition, both the child and the family benefit from the early identification and treatment of many of these conditions, including the most severe. It is therefore incumbent on the pediatric clinician to conduct regular **developmental surveillance** and periodic **developmental screening** at primary care health supervision visits aimed at early identification and treatment.

Among the many types of developmental or behavioral conditions, the most common include *language problems,* affecting at least 1 in 10 children (see Chapter 52); *behavior or emotional disorders*, affecting up to 25% of children, with 6% considered serious; *attention-deficit/hyperactivity disorder,* affecting 1 in 10 children (Chapter 49); and *learning disabilities*, affecting up to 10% (Chapters 50 and 51). Less common and more disabling are the *intellectual disabilities* (1–2%; Chapter 53); *autism spectrum disorders* (1 in 59 children; Chapter 54); *cerebral palsy* and related *motor impairments* (0.3%, or 1 in 345 children; Chapter 616); *hearing impairment*, also referred to as deafness, hard-of-hearing, or hearing loss (0.12%; Chapter 655); and nonrefractive *vision impairment* (0.8%; Chapter 639).

Developmental and Behavioral Surveillance

General health surveillance is a critical responsibility of the primary care clinician and is a key component of health supervision visits. Regular developmental and behavioral surveillance should be performed at every health supervision visit from infancy through young adulthood. Surveillance of a child's development and behavior includes both obtaining historical information on the child and family and making observations at the office visit (Tables 28.1 and 28.2).

Table 28.1

Key Components of Developmental and Behavioral Surveillance

History

1. Parental developmental concerns
2. Developmental history
    a. Streams of developmental milestone achievement
        i. Gross motor

        - ii. Fine motor
        - iii. Verbal speech and language
            - (1) Expressive
            - (2) Receptive
        - iv. Social language and self-help
    - b. Patterns of abnormality
        - i. Delay
        - ii. Dissociation
        - iii. Deviancy or deviation
        - iv. Regression
3. Behavior history
    - a. Interactions
        - i. Familiar settings (e.g. home, school): parents, siblings, other familiar people, peers, other children
        - ii. Interaction in unfamiliar settings (e.g., community): unfamiliar adults and children
    - b. Patterns of abnormality
        - i. Noncompliance, disruption (including tantrums), aggression, impulsivity, increased activity, decreased attention span, decreased social engagement, decreased auditory or visual attention
        - ii. Deviation or atypical behaviors
            - (1) Repetitive play, rituals, perseverative thought or action, self-injury
4. Risk factor identification: medical, family, and social history (including social determinants of health)
5. Protective factor identification (also including social determinants)

Developmental Observation

1. Movement: gross and fine motor skills
2. Verbal communication: expressive speech and language, language understanding
3. Social engagement and response
4. Behavior: spontaneous and responsive with caregiver and with staff
5. Related neurologic function on physical examination

Table 28.2

“Red Flags” in Developmental Screening and Surveillance*

These indicators suggest that development is seriously disordered and that the child should be promptly referred to a developmental or community pediatrician.

Positive Indicators

Presence of Any of the Following:

- Loss of developmental skills at any age
- Parental or professional concerns about vision, fixing, or following an object or a confirmed visual impairment at any age (simultaneous referral to pediatric ophthalmology)
- Hearing loss at any age (simultaneous referral for expert audiologic or ear, nose, and throat assessment)
- Persistently low muscle tone or floppiness
- No speech by 18 mo, especially if the child does not try to communicate by other means, such as gestures (simultaneous referral for urgent hearing test)
- Asymmetry of movements or other features suggestive of cerebral palsy, such as increased muscle tone
- Persistent toe walking
- Complex disabilities
- Head circumference above the 99.6th centile or below 0.4th centile; also, if circumference has crossed 2 centiles (up or down) on the appropriate chart or is disproportionate to parental head circumference
- An assessing clinician who is uncertain about any aspect of assessment but thinks that development may be disordered

Negative Indicators

Activities That the Child Cannot Do:

- Sit unsupported by 12 mo
- Walk by 18 mo (boys) or 2 yr (girls) (check creatine kinase urgently)

Walk other than on tiptoes
Run by 2.5 yr
Hold object placed in hand by 5 mo (corrected for gestation)
Reach for objects by 6 mo (corrected for gestation)
Point at objects to share interest with others by 2 yr

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[*] Most children do not have “red flags” and thus require quality screening to detect any problems.

Adapted from Horridge KA. Assessment and investigation of the child with disordered development. *Arch Dis Child Educ Pract Ed* 96:9–20, 2011.

Key historical elements include (1) eliciting and attending to the parents' or caregivers' concerns around the child's development or behavior; (2) obtaining a history of the child's developmental skills and behavior at home, with peers, in school, and in the community; and (3) identifying the risks, strengths, and protective factors for development and behavior in the child and family, including the social determinants of health. During the office visit, the clinician should make and document direct observations of the child's developmental skills and behavioral interactions. Skills in all streams of development should be considered along with observations of related neurologic functioning made on physical examination.

With this history and observation, the clinician should create and maintain a longitudinal record of the child's development and behavior for tracking the child across visits. It is often helpful to obtain information from and share information with other professionals involved with the child, including childcare professionals, home visitors, teachers, after-school providers, and developmental therapists. This provides a complete picture of the child's development and behavior and allows collaborative tracking of the child's progress.

The Developmental and Behavioral Histories

Developmental surveillance includes tracking a child's achievement of milestones, which represent key readily recognizable skills that usually occur in a predictable sequence and at predictable age ranges during childhood. The developmental skill areas can be divided into **gross motor** , **fine motor** , **verbal speech and language** (expressive and receptive), **social language** , and **self-help** . Tracking milestones will reveal that most children achieve the milestones in a typical pattern and within typical age ranges. However, the pediatrician or the parent may recognize concerning patterns of development, such as delay, dissociation, deviancy or deviation, or regression.

Developmental delay occurs when development is occurring in its usual sequence but at a slower rate, with milestones achieved later than the normal range (see Chapter 53). Delay can occur in a single area of development or across several streams and can be expressed as a *developmental quotient* (DQ). The DQ is calculated by dividing the age at which the child is functioning developmentally (*developmental age* ; DA) by *chronologic age* (CA) and multiplying by 100 (DQ = DA/CA × 100). A DQ of 100 indicates that the child is developing at the mean or average rate, whereas a DQ below 70 is approximately 2 standard deviations (SD) below the mean and suggests a significant delay that requires further evaluation.

Developmental dissociation indicates delay in a single stream with typical development in other streams. A child with autism may have delays in verbal or social language but normal motor skills. *Deviancy* or *deviation* is defined by development occurring out of sequence, as when a child stands before sitting (as in diplegic cerebral palsy) or has better expressive vocabulary than receptive understanding of words (language and autism spectrum disorders). *Regression* refers to a loss of skills. It may also be identified earlier or more subtly by a slowing or lack of advancement in skills. Although uncommon, regression is described in as many as 1 in 4 children with autism and is also seen in rarer neurologic disorders, such as Rett syndrome and Duchenne muscular dystrophy (see Chapter 53.1).

Behavioral surveillance is conducted by obtaining a history of a child's behavior and interactions across settings, including home, daycare, school, and community, and in situations such as eating, sleeping, and play. In addition, interactions may differ based on who the child is with (parent or guardian, sibling, peers, strangers). Concerns may include limited engagement or socializing, compliance, tantrums, aggression, impulsivity, activity level, auditory or visual attention, and attention span. Deviations from usual behavior may also occur, including repetitive play, ritualistic behaviors, perseverative thoughts or actions, and self-injury.

Observation

Observations of the child's developmental skills and behavioral interactions should be made in the examining room, with documentation in the medical record, and combined with the examination of other neurologic functioning, such as muscle tone, reflexes, and posture.

Developmental observations may include a child's gross and fine motor movements, both on the floor and on the examination table. Spoken language and response to others' communications, as well as interactions and engagement with the parent or guardian, should be noted. If siblings are in the room, the interaction between the child and a sibling may also be informative. Impulsivity, attention problems, tantrums, noncompliance, oppositionality, and aggression may be observed along with interactions with the clinician, but one should inquire about whether these behaviors are seen in *other settings* , given the possible unfamiliarity or discomfort of the child with the healthcare professional or in healthcare settings.

If inquiring about and observing the child's development and behavior suggests normal or typical patterns of development and behavior, discussions can be held about future milestones and usual behavior management strategies employable at home. If problems or concerns are identified by the parent or clinician, however, formal developmental screening, evaluation, or management should be considered, along with early follow-up and review.

Developmental and Behavioral Screening

Periodic episodic screening for developmental and behavioral conditions should be conducted on every child, as done for other health conditions such as anemia, lead poisoning, hearing, and congenital metabolic disorders. Developmental and behavioral screenings are centered on administration of low-cost, brief, and standardized tests designed for such purposes in the primary care office setting. These tests can be implemented by health assistants at age-determined visits, with interpretation of the results and referral or treatment initiation by the pediatric healthcare clinician as indicated.

The American Academy of Pediatrics provides recommendations and guidelines on age-specific developmental screening for implementation in the primary care medical home. Developmental screening using a formal, validated, and standardized test is recommended during the 1st 3 yr of life at the preventive care visit at 9 m, 18 mo, and 30 mo. Tests recommended at these ages screen development across all the streams. In addition, an autism screening test is recommended at the 18 and 24 mo visits. Table 28.3 provides recommended screening tests for general development and for autism. It is also recommended that a child have a screening test administered any time that a parent, guardian, or child health or early childhood professional has concerns identified during developmental surveillance, or through screening performed at early childhood programs. Although routine formal screening before the child's entry into elementary school is not included in current guidelines, the primary care clinician should be vigilant about surveillance regarding development at the 4 or 5 yr old visit and perform formal screening if concerns are identified, because of the potential impact on learning and school services.

Table 28.3

Standardized Tools for General Developmental Screening

SCREENING TEST	AGE RANGE	NUMBER OF ITEMS	ADMINISTRATION TIME	PUBLICATION INFORMATION	REF*
Ages & Stages Questionnaires-3 (ASQ3)	2-60 mo	30	10-15 min	Paul H. Brookes Publishing 800-638-3775 www.brookespublishing.com	1
Parents' Evaluation of Developmental Status (PEDS)	0-8 y	10	2-10 min	Ellsworth & Vandermeer Press 888-729-1697 www.pedstest.com	2
Parents' Evaluation of Developmental Status: Developmental Milestones (PEDS:DM) Screening Version	0-8 y	6-8 items at each age level	4-6 min	Ellsworth & Vandermeer Press 888/729-1697 or www.pedstest.com	2
Survey of Well-being of Young Children (SWYC) †	Dev: 1-65 mo Autism: 16-35 mo	Dev: 10 Autism: 7	Dev: <5 min Autism: <5 min	www.theswyc.org	3-6

[*] Key reference sources:

1. Squires J, Potter L, Bricker D: The ASQ user's guide, ed 3, Baltimore, MD, 2009, Paul H Brookes Publishing.

2. Glascoe FP, Marks KP, Poon JK, et al, editors: Identifying and addressing developmental-behavioral problems: a practical guide for medical and non-medical professionals, trainees, researchers and advocates, Nolensville, TN, 2013, PEDStest.com .
3. Sheldrick RC, Perrin EC: Evidence-based milestones for surveillance of cognitive, language, and motor development, Acad Pediatr 13(6):577–586, 2013.
4. Smith N, Sheldrick R, Perrin E: An abbreviated screening instrument for autism spectrum disorders, Infant Ment Health J 34(2):149–155, 2012.
5. Salisbury LA, Nyce JD, Hannum CD, et al: Sensitivity and specificity of 2 autism screeners among referred children between 16 and 48 months of age, *J Dev Behav Pediatr* 39(3):254–258, 2018.
6. Publications and user's manual available at www.theswyc.org .

† Initial validation studies have been completed. Further validation on large populations is currently in progress. Dev, Development.

Each of the screening visits offers special opportunities to identify specific developmental conditions. At the 9 mo screening, critical areas of development are vision, hearing, gross motor, fine motor, and receptive language. It is at this age that disabilities may be identified in vision or hearing, as well as cerebral palsy and other neuromotor disorders. At 18 mo, expressive language and social language development are particularly important areas. Conditions identified at this age may include those considered at 9 mo, although in milder forms, as well as autism spectrum, language, and intellectual disorders. By the 30 mo visit, the child's behavioral interactions become an additional area of focus, with problems emerging tied to attention and disruptive behavior disorders. While universal screening is not recommended at later ages, developmental surveillance may identify children in need of screening or evaluation for problems in learning, attention, and behavior.

Additional screening for *behavioral conditions* should be considered, although there is currently no recommended consensus on the ages at which behavioral screening should occur. One possibility would be to provide behavioral screening at the 30 mo, 4 or 5 yr, and 8 yr visits to identify problems emerging in the toddler, preschool, and early elementary years. For older children, visits during preadolescent or adolescent ages also offer an opportunity for surveillance and possible screening for behavioral and emotional problems meriting professional assistance or intervention. Table 28.4 provides recommended behavior screening tools.

Table 28.4

Standardized Tools for General Behavioral Screening

SCREENING TEST	**AGE RANGE**	**NUMBER OF ITEMS**	**ADMINISTRATION TIME**	**PUBLICATION INFORMATION**	**REF***
Ages & Stages Questionnaire: Social-Emotional-2 (ASQ:SE-2) (2015)	2-60 mo	9 age-specific forms with 19-33 items	10 min	Paul H. Brookes Publishing, 800-638-3775 www.agesandstages.com	1, 2
Brief Infant Toddler Social Emotional Assessment (BITSEA)	12-36 mo	42	7-10 min	Pearson Assessments †	3
Pediatric Symptom Checklist–17 items (PSC-17b))	4-16 yr PSC-35 Youth self-report: ≥11 yr	17	<5 min	Website ‡	4
Strengths and Difficulties Questionnaire (SDQ)	4-17 yr 3-4 yr old version available Youth self-report 11-16 yr	25; 22 for 3-4 yr olds	5-10 min	www.sdqinfo.org	5

* Key reference sources:

1. Squires J, Bricker DD, Twombly E: Ages & Stages Questionnaires: Social-Emotional-2 (ASQ:SE-2): a parent-completed, child-monitoring system for social-

emotional behaviors, Baltimore, MD, 2016, Paul H Brookes Publishing.
2. Briggs RD, Stettler EM, Johnson Silver, E, et al: Social-emotional screening for infants and toddlers in primary care, Pediatrics 129(2):1–8, 2012.
3. Briggs-Gowan MJ, Carter AS, Irwin JR, et al: The Brief-Infant Toddler Social and Emotional Assessment: screening for social-emotional problems and delays in competence, J Pediatr Psychol 29:143–155, 2004.
4. Gardner W, Lucas A, Kolko DJ, Campo JV: Comparison of the PSC-17 and alternative mental health screens in an at-risk primary care sample, J Am Acad Child Adolesc Psychiatry 46:611–618, 2007.
5. Stone LL, Otten R, Engels RC, et al: Psychometric properties of the parent and teacher versions of the Strengths and Difficulties Questionnaire for 4- to 12-year-olds: a review. Clin Child Fam Psychol Rev 13(3):254–274, 2010.

[†] http://www.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8007-352 .

[‡] http://www.massgeneral.org/psychiatry/services/psc_about.aspx .

Evidence-Based Tools

Tables 28.3 , 28.4 , and 28.5 show a range of measures useful for early identification of developmental and behavioral problems, including autism spectrum disorders. Because well-child visits are brief and with broad agendas (health surveillance and screening, physical examination, immunization, anticipatory guidance, safety and injury prevention, and developmental promotion), tools relying on parent completion with office staff administration and scoring are well suited for primary care settings. Such tests may be completed in advance of appointments, either online or in writing, whether at home or while waiting for the pediatric visit to begin. If a test is scored in advance of the visit, the pediatric clinician can enter the room with results in hand for review and discussion, including a description of the child's development and behavior compared with peers, general information on child development and behavior, any areas of concern, referrals needed, and information to share with the child's daycare, preschool, or other community providers, when applicable.

Table 28.5

Standardized Tools for Language and Autism Screening

SCREENING TEST	AGE RANGE	NUMBER OF ITEMS	ADMINISTRATION TIME	PURCHASE/ OBTAINMENT INFORMATION	REF*
LANGUAGE					
Communication and Symbolic Behavior Scales: Developmental Profile (CSBS-DP): Infant Toddler Checklist	6-24 mo	24	5-10 min	Paul H. Brookes Publishing Co 800/638-3775 www.brookespublishing.com	1
AUTISM					
Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F)	16-48 mo	20 (avg)	5-10 min	www.m-chat.org/ Follow up interview †	2
Social Communication Questionnaire (SCQ)	4+ yr	40 (avg)	5-10 min	Western Psychological Services www.wpspublish.com	3, 4

* Key reference sources:

1. Wetherby AM, Prizant BM: Communication and Symbolic Behavior Scales: Developmental Profile, Baltimore, MD, 2002, Paul H Brookes Publishing.
2. Robins DL, Casagrande K, Barton M, et al: Validation of the Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F), Pediatrics

133(1):37–45, 2014.
3. Rutter M, Bailey A, Lord C: The Social Communication Questionnaire (SCQ) manual, Los Angeles, 2003, Western Psychological Services.
4. Corsello C, Hus V, Pickles A, et al: Between a ROC and a hard place: decision making and making decisions about using the SCQ, J Child Psychol Psychiatry 48(9):932–940, 2007.

[†] http://www2.gsu.edu/~psydlr/Diana_L._Robins,_Ph.D._files/M-CHATInterview.pdf .

Screening Test Properties

Each of the tests provided in Tables 28.3 to 28.5 meets accepted psychometric test criteria. The test has norms, with standardized questions or milestones based on administration to parents of a large sample of children with typical development. These norms are used for comparing an individual child's performance on the test with that of the large sample of typically developing children. In addition, the tests demonstrate accepted standards of *reliability* , or the ability to produce consistent results; *predictive validity* , or the ability to predict later test performance or development; *sensitivity* , or accuracy in the identification of delayed development or disability; and *specificity* , or accuracy in the identification of children who are not delayed. Some of the screening tests are general, evaluating multiple areas of development or behavior (sometimes referred to as “broad band”). Others are domain specific, evaluating one area of development (e.g., language), or disorder specific, aimed at identifying a specific developmental disorder (sometimes referred to as “narrow band”).

Beyond Surveillance and Screening

Comprehensive Evaluation

When a developmental or behavioral concern is identified through surveillance or screening, the primary care physician's role is to ensure that the child receives an appropriate diagnostic evaluation, related medical testing, and indicated developmental interventions and medical treatment. When a concern is identified, a full diagnostic evaluation should be performed by a professional with appropriate training and experience. In the case of developmental concerns, this may be a pediatric specialist, such as a neurodevelopmental pediatrician/neurologist or a developmental-behavioral pediatrician, or a related developmental professional, depending on resources in the local community. Related professionals may include early childhood educators, psychologists, speech/language pathologists, audiologists, physical therapists, and occupational therapists, many of whom are available through the local early intervention system. Such an evaluation would typically include more detailed standardized developmental testing. The primary care physician should ensure that hearing and vision assessments are completed. For the child with motor concerns, the physician should pay particular attention to the motor and neurologic evaluation. Children with language delays should have hearing, speech, language, and learning skills (e.g., reading, phonics) evaluated.

The primary care pediatrician should also perform a comprehensive medical evaluation of the child to identify any related health conditions. Physical examination including head circumference should be reviewed to identify growth abnormalities and dysmorphic features. For the child with motor delay and decreased or normal muscle tone, serum creatine kinase and thyroid function testing are recommended to rule out muscular dystrophy and thyroid disease, respectively. When there is increased tone, MRI or referral to a neurologist should be considered. For the child with suspected autism or intellectual disability (or global developmental delay), chromosomal microarray and fragile X testing are recommended (see Chapter 53).

Referral and Intervention

Children with significant developmental delays or an identified developmental disability are entitled to and usually benefit from early intervention with therapy services directed at delayed or atypical development. The U.S. Individuals with Disabilities Education Act (IDEA) entitles any child with a disability or developmental delay to receive local education and related services, including therapy, from as early as birth, for known or high-risk conditions that lead to such delay or disability, through age 21 yr. These interventions enhance the child's development through early intervention and family support as well as individualized public education with the goal of reducing public costs. The pediatric clinician should therefore refer every child with developmental concerns to the local early intervention program or agency (ages 0-3 yr), public school program (≥3 yr), or local therapy providers. Typical service needs include special education for the child with intellectual or learning concerns, physical or occupational therapy for children with motor delays, speech language therapy for the child with language or social communication difficulties, and behavioral therapy services for the child with social engagement or other behavior problems.

Likewise, the child with specific behavior concerns should be referred to an appropriate pediatric or mental health professional who can perform a thorough evaluation and assist the family to alleviate the problems or concerns. Such professionals may include those trained in developmental-behavioral pediatrics, neurodevelopmental disabilities, adolescent medicine, child and adolescent psychiatry, pediatric psychology, psychiatric advanced practice nursing, and social work. Such an evaluation is similar to developmental evaluation in its aim of determining a diagnosis, as well as developing a treatment program that may include psychotherapeutic and medication management. Associated medical or developmental disorders should be considered and further evaluated as needed.

Ongoing Management

Children with developmental or behavioral disorders should be identified as *children with special healthcare needs* in the medical home, with a program of chronic condition management initiated by the clinical program staff, including its medical and nonmedical staff. In doing so, the clinician and family should work together to outline the child's short- and long-term goals and management plan. This includes a program of regular monitoring and follow-up of the child's development and behavior, referrals, treatment, and surveillance for identification and treatment of related medical, developmental, or behavioral comorbidities that may arise. Some children and families may warrant assignment of a case manager either within the medical home or in a related local agency. The pediatric clinician or other medical home staff should participate in care coordination activities as needed and assist the family and other professionals in decision-making on medical care, therapies, and educational services.

The family can be further assisted during the screening and referral phases or later with ongoing care by referral to support service programs, such as respite care, parent-to-parent programs, and advocacy organizations. Some children may qualify for additional state or federal benefit programs, including insurance, supplemental security income, and state programs for children with special healthcare needs. Families often seek out information, support, or connection to other families with similarly affected children and find benefit in local or national networks (e.g., Family Voices, Family to Family Health Information centers) and condition-specific associations.

Implementation

The principles and professional guidelines for developmental-behavioral surveillance and screening have been solidified to identify children with developmental disabilities, including the specific conditions of intellectual disability, autism, motor disorders, and behavioral-emotional problems. Specific algorithms are included in these guidelines to assist the clinician with implementation. However, pediatricians have reported difficulties in putting these into practice, with obstacles and barriers identified and policy changes made to ensure that screening and referral can be implemented. (See Bibliography online for specific guidelines.)

Implementation projects have identified key factors for successful incorporation of developmental surveillance and screening into practice. Successful office-based screening requires development of a comprehensive office-based system that extends from the child's home to the front office and into the clinic visit, rather than solely centered on the time in the clinic room. This requires utilizing office and medical support staff for scheduling, advance test distribution, and initiation of the surveillance and screening procedures before the preventive care visit. The pediatric staff must choose screening tests that are not only valid for screening of the specific condition at the recommended ages, but also appropriate to the population being served (including reading level and language). The tests chosen should be able to be completed by the caregiver in a short time and at low cost. Staff training on billing and coding for these procedures ensures appropriate payment.

Practice systems should also be developed for referral and tracking of children who have problems identified through screening. This should include systems for referral to early intervention, community therapy, developmental professionals, and medical consultants. Office representatives or the clinician should establish working relationships with local community programs and resources to assist the child and family.

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Resources

American Academy of Pediatrics. *Screening in Practices Initiative: Screening Technical Assistance & Resource (STAR) Center* . https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Screening/Pages/default.aspx .

US Centers for Disease Control and Prevention (CDC). *Learn the Signs, Act Early Program* . https://www.cdc.gov/ncbddd/actearly/index.html .

US Department of Health and Human Services, Administration for Children and Families. *Birth to 5: Watch Me Thrive!* . http://www.acf.hhs.gov/programs/ecd/watch-me-thrive .

CHAPTER 29

Childcare

Laura Stout Sosinsky, Walter S. Gilliam

In the United States, approximately half of all children under the age of 3 yr and 60–75% of children age 3-5 yr had at least 1 regular nonparental childcare arrangement in 2012. Young children of employed mothers spend on average 36 hr per week in a childcare arrangement.

Childcare provision is affected by many factors, derived from family demand, childcare supply, and child/family policy. With increasing movement of mothers into the workplace across the globe, the prime reason most families use childcare is to support employment of both parents. At childbirth, unpaid maternity leave is the typical solution among U.S. mothers. The U.S. Federal leave program allows for 12 wk of unpaid job-protected leave during pregnancy or after childbirth, but only covers approximately 50% of the workforce because companies with <50 employees, with part-time employees, and those working in informal labor markets are exempt. Four states and several cities have passed paid family leave laws.

In part because of the financial burden of an unpaid maternity leave, many mothers return to work, and their children may begin childcare in the 1st few weeks after birth. In a 2000 Family and Medical Leave Act survey, only 10% of respondents reported taking more than 60 days for maternity leave. Approximately 44% of mothers in 2005–2007 were working by the time their 1st child was 3-4 mo of age, and approximately 63% of mothers were working by the time their 1st child was 12 mo. Some mothers face work requirements if they are receiving public benefits because of the reforms to welfare passed by the U.S. Congress in 1996. Many mothers feel strong financial motivation or even pressure to work, especially in single-parent households, or have strong incentive to work for short- and long-term financial security, or because interest and preference, or all these. Employment is not the only factor driving childcare use; young children of unemployed mothers spend on average 21 hr/wk in childcare. Many parents want their children to have childcare experiences for the potential benefits that early learning environments can give to their children, particularly preschoolers. Given these realities, childcare quality is of great concern, yet the quality of childcare and early education environments varies widely, and the supply of high-quality childcare is largely deemed inadequate.

Provision, Regulation, and Use of Childcare in America

Childcare Settings

Childcare settings vary widely and fall into 4 broad categories, listed here from the least to the most formal: (1) relative care; (2) in-home nonrelative care, such as nannies, babysitters, or au pairs; (3) family childcare, in which the caregiver provides care in her own home for up to 6 young children, often including children of mixed ages, siblings, or the provider's own children; and (4) center-based care, provided in nonresidential facilities for children grouped by age.

Parents more often use home-based care for infants and toddlers, partly because of greater preference, flexibility, and availability, and sometimes because of lower cost. Use of center-based childcare is greater among preschoolers (children 3-5 yr old). Childcare centers and early education programs are administered by a wide array of businesses and organizations, including for-profit independent companies and chains, religious organizations, public and private schools, nonprofit community organizations, cooperatives, and public agencies. **Preschool** programs (e.g., Head Start, **prekindergarten**) also may play an important role in childcare. Although early education programs may have a greater focus on educational activities and often provide only limited hours of care daily, the health and safety issues involved with preschool programs are similar to those presented by other group childcare settings.

Childcare Licensing, Regulation, and Accreditation

Poor-quality childcare settings and unsafe environments that do not meet children's basic physical and emotional needs can result in neglect, toxic stress, injury, or even death. Licensing and regulatory requirements establish the minimum requirements necessary to protect the health and safety of children in childcare. For the most part, licensing standards mandate basic health and safety standards, such as sanitary practices, child and provider vaccinations, access to a healthcare professional, and facilities and equipment safety, as well as basic structural and caregiver characteristics, such as the ratio of children to staff, group sizes, and minimum caregiver education and training requirements. Most childcare centers and preschools and many family daycare providers are subject to state **licensing and regulation** . All states regulate centers, as does the District of Columbia, and most states regulate family childcare providers.* Childcare programs that are subject to licensing must comply with their state's requirements to legally operate. Many early care and education providers are subject to monitoring by multiple agencies and organizations.

Many providers are legally exempt from licensing standards. However, the 2014 Child Care Development Block Grant (CCDBG) reauthorization required states and territories to expand their monitoring of legally exempt providers to protect the health and safety of children receiving subsidized childcare. Exemptions for various types of programs vary by state. The smallest homes (3-4 children in care) are typically license exempt, encompassing relative, friend, and neighbor caregivers as well as babysitters, nannies, and au pairs. These providers may fall outside of any regulatory scrutiny, and some may not even think of themselves as offering “childcare.” Fewer children (≥4) are cared for in large home-based settings, typically by nonrelatives. Depending on the state, small family childcare homes may be exempt if there are few children in care, and large/group family childcare homes may be exempt if they are open part-day. Unlike exemption rules for homecare providers, which typically are based on size, centers are often exempted if overseen by other organizations such as schools, churches, or local governments, and thus have some external oversight. Many of these entities provide part-day or part-week Head Start or preschool programs, and about half the states also explicitly exempt such part-time programs.

Homes and centers that fall under state-licensing guidelines face different requirements, which can have a direct impact on the quality of children's experiences. Size differs greatly between the 2 types of contexts, and such size differences are built into regulations in terms of the maximum number of children who can be cared for in a group and the number of adults that must be present. The most common state-required maximum group size in **centers** is 8 for infants, 12 for toddlers, and 20 for preschoolers; centers may have numerous classrooms of these sizes. For centers, regulations explicitly state an allowable ratio of children to adults. The most common ratios are 4 : 1 for infants, 6 : 1 for toddlers, and 10 : 1 for preschoolers, meaning that typically there would be 2 adults in a group. However, other states permit ratios that are 5 : 1 or 6 : 1 for infants ≤9 mo of age. Furthermore, most states' child/staff ratio requirements increase as children age; for children 27 mo old, only a handful of states have ratios of 4 : 1.

States license **homes** in 2 categories, small and large, with typical maximums of 6 and 12, respectively (including the provider's own children). More than 75% of licensed homes fall within the small category. Thus the total size of a typical home is smaller than just 1 classroom in a center. States less often explicitly lay out child/adult ratios for homes, given that many homes involve one provider caring for all the children. Some states restrict the number of younger children who may be in care or explicitly provide ratios (especially for large homes), although these restrictions vary greatly across states.

Health and safety conditions may be unsatisfactory in unlicensed settings. In most states, licensing and regulatory standards have been found to be inadequate to promote optimal child development, and in many states, standards are so low as to endanger child health and safety. Therefore, even licensed providers may be providing care at quality levels far below professional recommendations. A small portion of providers become accredited by National Association for the Education of Young Children (NAEYC), National Association for Family Child Care (NAFCC), or other organizations by voluntarily meeting high-quality, developmentally appropriate, professionally recommended standards. The accreditation process goes well beyond health and safety practices and structural and caregiver characteristics, to examine the quality of child–caregiver interactions, which are crucial for child development, as described in the next section. Evidence indicates that childcare programs that complete voluntary accreditation through NAEYC improve in quality and provide an environment that better facilitates children's overall development. Only 10% of childcare centers and 1% of family childcare homes are accredited. This is partly the result of a lack of knowledge, resources, and incentives for providers to improve quality, but also because of expenses providers incur in the process of becoming accredited.

State childcare licensing agencies are playing a larger role in various initiatives designed to improve the quality of childcare, working through the infrastructure of the early care and education system. Several states have quality initiatives called *quality ratings and improvement systems (QRIS)*, such as tiered quality strategies (e.g., tiered reimbursement systems for participating providers who achieve levels of quality beyond basic licensing requirements), public funding to facilitate accreditation, professional development systems, and program assessments and technical assistance.

Childcare's Role in Child Health and Development

Characteristics of Childcare and Associations With Child Developmental Outcomes

High-quality childcare is characterized by warm, responsive, and stimulating interactions between children and caregivers. In high-quality interactions, caregivers express positive feelings toward their children; are emotionally involved, engaged, and aware of the child's needs and sensitive and responsive to their initiations; speak directly with children in a manner that is elaborative and stimulating while being age appropriate; and ask questions and encourage children's ideas and verbalizations. Structural quality features of the setting, including ratio of children to adults, group size, and caregiver education and training, act indirectly on child outcomes by facilitating high-quality child–caregiver interactions. It would be difficult for even the most sensitive and stimulating provider to engage in high-quality interactions with each child, if the provider was the sole caregiver of 10 toddlers.

Practices in childcare centers can support or undermine the potential for caregivers to provide high-quality individualized interactions with young children in their care and support development. **Primary caregiving** is the practice of assigning 1 teacher the primary responsibility for the care of a small group of children within a larger group setting; this teacher takes the lead role in providing intentional and individual care for the child's routine needs and establishes relationships with the children and families in their care. This practice is consistent with research showing that infants who experience stable, consistent, sensitive, and responsive care from their primary caregivers develop more **secure attachment** relationships (see Chapters 18 , 19 , and 22) and more positive developmental outcomes. To enact primary caregiving, centers need to have child-to-staff ratios and staffing arrangements consistent with this practice. Several states' child/staff ratio licensing requirements (e.g., 4 : 1 for 6 or 9 mo old infants) are consistent with staffing arrangements conducive to creating and maintaining primary caregiving relationships, but other states' ratios are much larger and rise even higher during the infant/toddler years.

The quality, quantity, type of setting, and stability of childcare experienced by young children contribute to child development. Childcare use by itself does not affect mother–child attachment. Only when combined with low maternal sensitivity and responsiveness does poor-quality childcare, larger quantities of childcare, or multiple childcare arrangements predict greater likelihood of insecure attachment.

Adjusting for family factors (parental income, education, race/ethnicity, family structure, parental sensitivity), the quality of childcare has a unique and consistent but small association with child outcomes across most domains of development. The type of childcare setting has unique effects, controlling for quality, with results from numerous studies demonstrating that center-based care is associated with better language and preacademic performance than home-based care. Quantity of care (hours per week) may also have unique effects, but findings are mixed, with some studies demonstrating small associations between greater quantity and elevated behavior problems, and other studies finding no associations for most children. **Instability** in childcare—over the course of a day, such as with rotating staff or multiple arrangements, or over time, with frequent staff turnover or changes in arrangements—does have negative effects on children's language and internalizing problems. Also, since childcare settings naturally have packages of quality characteristics, which are a mix of lower- and higher-quality indicators, the bundle of features in a childcare arrangement may be another meaningful way for a parent to consider the potential effects of an arrangement on their child.

When a healthcare provider talks with a parent about the childcare arrangement, it is also important to consider the individual child's characteristics, health concerns, dispositions, and even physiologic responses to the environment. As with all environments, childcare is experienced differently by different children. An average environment can often sufficiently compensate for the typical regulatory capacities of most children, but when an environment lacks adequate support for a child's unique needs, healthy development can be further compromised. Some children may be more vulnerable to poor childcare (or particularly responsive to good childcare), such as children with difficult or fearful temperaments, especially if their home environments are characterized by more risk factors, such as poverty or high conflict with a parent.

Several large studies have found that most U.S. childcare is of “poor to mediocre” quality. In one study, only 14% of centers (8% of center-based infant care) were found to provide developmentally appropriate care, while 12% scored at minimal levels that compromised health and safety (40% for infant care). In another study, 58% of family daycare homes provided adequate or custodial care, and only 8% provided good care. Children with the greatest amount of family risk may be the most likely to receive childcare that is substandard in quality. Many children from lower-risk families also receive lower-quality care, and despite their advantages at home, these children may not be protected from the negative effects of poor-quality care.

Affordable, accessible, high-quality childcare is difficult to find. Middle-class families spend approximately 6% of their annual income on childcare expenses, whereas poor families spend approximately 33% (on par with housing expenses). Infant and toddler care is particularly expensive, with fewer available slots. For a married couple with children, the average cost of full-time center care for 1 infant ranges from 7% to approximately 19% of the state median income, depending on the state. In 38 states the cost of infant care exceeds 10% of the state's median income for a 2-parent family. The average cost of center care for one 4 yr old exceeds 10% of the median household income in 21 states and the District of Columbia. For single parents, the average cost of center-based infant care exceeds 25% of median income in every state. The average cost of family childcare is only slightly lower.

In addition to the stress of meeting such a high expense, many parents worry that their child will feel unhappy in group settings, will suffer from separation from the parents, or will be subjected to neglect or abuse. This worry is especially likely among low-income parents with more risk factors, fewer resources, and fewer high-quality options available. Parents are the purchasers but not the recipients of care and are not in the best position to judge its quality. Many parents are 1st-time purchasers of childcare with little experience and very immediate needs, selecting care in a market that does little to provide them with useful information about childcare arrangements. In many states, efforts are underway to improve quality and provide parents with this information, but several states do not have a quality rating and information system, and programs in states that do are still emerging, and testing of effectiveness is still underway.

To inform their care decisions, parents may turn to their child's pediatrician as the only professional with expertise in child development with whom they have regular and convenient contact.

Pediatricians may frequently be asked to provide input regarding child health in out-of-home childcare settings. **Standards and guidelines** are provided by the American Academy of Pediatrics, the American Public Health Association, and the National Resource Center for Health and Safety in Child Care and Early Education, in *Stepping Stones to Caring for Our Children: National Health and Safety Performance Standards—Guidelines for Early Care and Education Programs* (3rd edition, 2013). *Caring for our Children Basics* (2014), which is based on the larger resource document, represents the **minimum** health and safety standards experts believe should be in place where children are cared for outside their homes. The intent is for the guidelines to serve as a resource for states and other entities as they work to improve health and safety standards in licensing and quality rating improvement systems. The guidelines include sections on program activities for healthy development (e.g., monitoring children's development, obtaining consent for age-appropriate developmental and behavioral screenings), health promotion and protection (e.g., active opportunities for physical activity; safe sleep practices and SIDS risk reduction; diaper-changing and hand hygiene procedures; emergency procedures; recognizing and reporting suspected child abuse, neglect, and exploitation), and nutrition and food service (e.g., care for children with food allergies; preparing, feeding, and storing human milk).

Pediatricians most often may encounter questions from parents and caregivers regarding sick children, exposure to and prevention of risks in childcare, and support for children with special needs in childcare. Guidelines in these areas are summarized in the next sections.

Sick Children

When children are ill, they may be excluded from out-of-home arrangements, and settings under state licensure are required to exclude children with certain conditions. *Stepping Stones* offers guidelines and recommendations regarding the conditions under which sick children should and should not be excluded from group programs. State laws typically mirror these guidelines but may be stricter in some states. *Caring for Our Children Basics* (2014) summarizes guidelines for inclusion, exclusion, or dismissal of children based on signs or symptoms or illness (Table 29.1).

Table 29.1

Conditions That Do and Do Not Require Exclusion From Group Childcare Settings

CONDITIONS THAT REQUIRE EXCLUSION	COMMENTS
If any of these 3 key criteria for exclusion of children who are ill are met, the child should be temporarily excluded, regardless of the type of illness:	
Illness preventing the child from participating comfortably in activities, as determined by the childcare provider	Providers should specify in their policies, approved by the facility's healthcare consultant, what severity level of illness the facility can manage, and how much and what types of illness will be addressed: • Severity level 1 consists of children whose health condition is accompanied by high interest and complete involvement in activity, associated with an absence of symptoms of illness (e.g., children recovering from pinkeye, rash, or chickenpox) but who need further recuperation time. • Severity level 2 encompasses children whose health condition is accompanied by a medium activity level because of symptoms (e.g., children with low-grade fever, children at beginning of illness, children in early recovery period of illness) • Severity level 3 consists of children whose health condition is accompanied by a low activity level because of symptoms that preclude much involvement.
Illness resulting in a greater need for care than the childcare staff can provide without compromising the health and safety of the other children, as determined by the childcare provider	
Illness that poses a risk of spread of harmful diseases to others	
In addition to the above key criteria, temporary exclusion is recommended when the child has any of the following conditions:	
Fever (temperature above 38°C [101°F] orally, above 38.9°C [102°F] rectally, or above 37.8°C [100°F] or higher taken axillary [armpit] or measured by an equivalent method) and behavior change or other signs and symptoms (e.g., sore throat, rash, vomiting, diarrhea)	Accompanied by behavior changes or other signs or symptoms of illness until medical professional evaluation finds the child able to be included at the facility
Acute change in behavior including lethargy/lack of responsiveness, inexplicable irritability or persistent crying, difficult breathing, or having a quickly spreading rash	Until evaluation by a medical professional finds the child able to be included at the facility
Diarrhea (defined by watery stools or decreased form of stool that is not associated with changes of diet). Exclusion is required for all diapered children whose stool is not contained in the diaper and toilet-trained children if the diarrhea is causing soiled pants or clothing.	Readmission after diarrhea can occur when diapered children have their stool contained by the diaper (even if the stools remain loose) and when toilet-trained children are continent. Special circumstances that require specific exclusion criteria include the following:

	• Toxin-producing *Escherichia coli* or *Shigella* infection, until stools are formed and test results of 2 stool cultures obtained from stools produced 24 hr apart do not detect these organisms • *Salmonella* serotype Typhi infection, until diarrhea resolves and, in children <5 yr old, 3 negative stool cultures obtained at 24 hr intervals
Blood or mucus in stool	Not explained by dietary change, medication, or hard stools
Vomiting illness	More than 2 times in previous 24 hr, unless vomiting is determined to be caused by a noninfectious condition and child remains adequately hydrated
Abdominal pain	Persistent (continues >2 hr) or intermittent associated with fever or other signs or symptoms
Mouth sores with drooling	Unless the child's primary care provider or local health department authority states that the child is noninfectious
Rash with fever or behavior changes	Until the primary care provider has determined that the illness is not an infectious disease
Active tuberculosis	Until the child's primary care provider or local health department states child is on appropriate treatment and can return
Impetigo	Until treatment has been started
Streptococcal pharyngitis (i.e., strep throat or other streptococcal infection)	Until 24 hr after treatment has been started
Purulent conjunctivitis	Defined as pink or red conjunctiva with white or yellow eye discharge, until after treatment has been initiated
Pediculosis (head lice)	Until after 1st treatment *Note:* Exclusion is not necessary before end of the program day.
Scabies	Until after treatment has been given
Varicella-zoster virus (chickenpox)	Until all lesions have dried or crusted (usually 6 days after onset of rash)
Rubella	Until 6 days after onset of rash
Pertussis	Until 5 days of appropriate antibiotic treatment
Mumps	Until 5 days after onset of parotid gland swelling
Measles	Until 4 days after onset of rash
Hepatitis A virus	Until 1 wk after onset of illness or jaundice if child's symptoms are mild or as directed by health department
Any child determined by the local health department to be contributing to the transmission of illness during an outbreak	
CONDITIONS THAT DO NOT REQUIRE EXCLUSION	**COMMENTS**
Common colds, runny noses	Regardless of color or consistency of nasal discharge
A cough not associated with an infectious disease or a fever	
Watery, yellow or white discharge or crusting eye discharge without fever, eye pain, or eyelid redness	
Presence of bacteria or viruses in urine or feces in the absence of illness symptoms (e.g., diarrhea)	Exceptions include children infected with highly contagious organisms capable of causing serious illness.
Pinkeye (bacterial conjunctivitis), indicated by pink or red eyelids after sleep	If 2 unrelated children in the same program have conjunctivitis, the organism causing the conjunctivitis may have a higher risk for transmission, and a child healthcare professional should be consulted.

Fever without any signs or symptoms of illness in children >6 mo old regardless of whether acetaminophen or ibuprofen was given	If the child is behaving normally but has fever <38.9°C (102°F) rectally or the equivalent, child should be monitored but does not need to be excluded for fever alone.
Rash without fever and without behavioral changes	
Lice or nits	Exclusion for treatment of an active lice infestation may be delayed until end of the day.
Ringworm	Exclusion for treatment may be delayed until end of the day.
Molluscum contagiosum	Do not require exclusion or covering of lesions
Thrush (i.e., white spots or patches in mouth or on cheeks or gums)	
Fifth disease	Once the rash has appeared
Methicillin-resistant *Staphylococcus aureus* (MRSA) without an infection or illness that would otherwise require exclusion	Known MRSA carriers or colonized individuals should not be excluded.
Cytomegalovirus infection	
Chronic hepatitis B infection	
HIV infection	
Asymptomatic children who have been previously evaluated and found to be shedding potentially infectious organisms in the stool	Children who are continent of stool or who are diapered with formed stools that can be contained in the diaper may return to care
Children with chronic infections conditions who can be accommodated in the program according to federal legal requirement in Americans with Disabilities Act (ADA)	ADA requires that childcare programs make reasonable accommodations for children with disabilities and/or chronic illnesses, considering each child individually.

Adapted from American Academy of Pediatrics (AAP), American Public Health Association, National Resource Center for Health and Safety in Child Care and Early Education: *Stepping stones to caring for our children: national health and safety performance standards—guidelines for early care and education programs* , ed 3, Elk Grove Village, IL, 2013, AAP, pp 46–52. http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/ .

The caregiver/teacher should determine if the illness (1) prevents the child from participating comfortably in activities; (2) results in a need for care that is greater than the staff can provide without compromising the health and safety of other children; (3) poses a risk of spread of harmful diseases to others; or (4) causes a fever and behavior change or other signs and symptoms (e.g., sore throat, rash, vomiting, diarrhea). An unexplained temperature above 100°F (37.8°C) (armpit) in a child <6 mo old should be medically evaluated. Any infant <2 mo old with fever should receive immediate medical attention.

Most families need to arrange to keep sick children at home, such as staying home from work or having backup plans with an alternative caregiver. Alternative care arrangements outside the home for sick children are relatively rare but may include either (1) care in the child's own center, if it offers special provisions designed for the care of ill children (sometimes called the **infirmary model** or **sick daycare**), or (2) care in a center that serves only children with illness or temporary conditions. Although it is important that such arrangements emphasize preventing further spread of disease, one study found no occurrence of additional transmission of communicable disease in children attending a sick center. The impact of group care of ill children on their subsequent health and on the health of their families and community is unknown.

Caring for Our Children Basics also provides guidelines for control of infectious disease outbreaks and for exclusion of any child or staff member who is suspected of contributing to transmission of the illness, who is not adequately immunized when there is an outbreak of a vaccine-preventable disease, or when the circulating pathogen poses an increased risk to the individual.

Childcare and Child Health

A disproportionate number of **sudden infant death syndrome (SIDS)** deaths occur in childcare centers or family-based childcare homes (approximately 20%). Infants who are back-sleepers at home but are put to sleep on their front in childcare settings have a higher risk of SIDS. Providers and parents should be made aware of the importance of placing infants on their backs to sleep (see Chapter 402).

Children enrolled in childcare are also of an age that places them at increased risk for acquiring **infectious diseases** . Participation in group settings elevates exposure. Children enrolled in such settings have a higher incidence of illness (upper respiratory tract infections, otitis media, diarrhea, hepatitis A infections, skin conditions, and asthma) than those cared for at home, especially in the preschool years; these illnesses have no long-term adverse consequences. Childcare providers who follow childcare licensure guidelines for handwashing, diapering, and food handling, and who manage child illness appropriately, can reduce communicable illnesses.

Debate surrounds whether childcare exposure serves as a risk or protective factor for asthma. One cross-sectional study found that preschoolers in childcare had increased risk of the common cold and otitis media, and children who began childcare before age 2 yr had increased risk of developing recurrent otitis media and asthma. However, a longitudinal study found that children exposed to older children at home or to other children at childcare during the 1st 6 mo of life were less likely to have frequent wheezing from ages 6-13 yr, suggesting that childcare exposure may protect against the development of asthma and frequent wheezing later in childhood. A 10 yr follow-up of a birth cohort found no association between childcare attendance and respiratory infections, asthma, allergic rhinitis, or skin-prick test reactivity. Another study found that in the 1st yr of elementary school, children who had attended childcare had fewer absences from school, half as many episodes of asthma, and less acute respiratory illness than their peers who had never attended childcare. These results may be related to protection against respiratory illness as a result of early exposure or a shift in the age-related peak of illness, although selection of illness-prone children into homecare may play a role. Other factors may also be relevant to this issue, such as children in childcare potentially being less exposed to passive smoking than children at home.

Childcare and Children With Special Needs

The needs of children with mental, physical, or emotional disabilities who, because of their chronic illness, require special care and instruction may require particular attention when it comes to their participation in most childcare settings. Guiding principles of services for children with disabilities advocate supporting children in natural environments, including childcare. Furthermore, the Americans with Disabilities Act and Section 504 of the Rehabilitation Act of 1973 prohibit discrimination against children and adults with disabilities by requiring equal access to offered programs and services.

Although many childcare providers and settings are unprepared to identify or administer services for children with special needs, childcare could be utilized for delivery of support services to these children and for linking families to services, such as early intervention and physician referrals. Furthermore, pediatricians can draw on childcare providers for important evaluative data regarding a child's well-being, since these providers have extensive daily contact with the child and may have broad, professional understanding of normative child development. A childcare provider may be the first to identify a child's potential language delay. Childcare providers are also necessary and valuable partners in the development and administration of early intervention service plans.

Children with special needs may be eligible for services under the **Individuals with Disabilities Education Act** (**IDEA** ; see Chapters 48 and 51). The purpose of this law is to provide “free appropriate public education,” regardless of disability or chronic illness, to all eligible children, birth to 21 yr, in a natural and/or least restrictive environment. Eligible children include those with mental, physical, or emotional disabilities who, because of their disability or chronic illness, require special instruction to learn. As a part of these services, a formal plan of intervention is to be developed by the service providers, families, and the children's healthcare providers. Federal funds are available to implement a collaborative early intervention system of services for eligible infants and toddlers from birth to 3 yr and their families. These services include screening, assessment, service coordination, and collaborative development of an **individualized family service plan (IFSP)** . The IFSP describes early intervention services for the infant or toddler and family, including family support and the child's health, therapeutic, and educational needs. An understanding of the child's routines and real-life opportunities and activities, such as eating, playing, interacting with others, and working on developmental skills, is crucial to enhancing a child's ability to achieve the functional goals of the IFSP. Therefore it is critical that childcare providers be involved in IFSP development or revision, with parental consent. Childcare providers should also become familiar with the child's IFSP and understand the providers' role and the resources available to support the family and childcare provider.

Additionally, IDEA provides support for eligible preschool-age children to receive services through the local school district. This includes development of a written **individualized education program (IEP)** , with implementation being the responsibility of the local education agency in either a public or a private preschool setting. As with IFSPs, childcare providers should become familiar with the preschooler's special needs as identified in the IEP and may become involved, with parental consent, in IEP development and review meetings. For children who have or may be at risk for developmental delay, a diagnosis is important for obtaining and coordinating services and further evaluation. To this end, pediatricians can partner with childcare providers to screen and monitor children's behavior and development.

Role of Pediatric Providers in Childcare

Advising Parents on Childcare Selection

Organized professional guidance in choosing childcare is insufficient. Pediatricians can help parents understand the importance of high-quality care for their child's development by describing this care and providing referrals and advice on finding and selecting high-quality childcare (Table 29.2). In addition, pediatricians can help parents determine how to adjust childcare arrangements to best meet their child's specific needs (e.g., allergies, eating and sleeping habits, temperament and stress-regulation capacities). For most parents, finding childcare that they can afford, access, manage, and accept as a good environment for their child is a difficult and often distressing process. Many parents also worry about how their child will fare in childcare (e.g., Will their child feel distressed by group settings, suffer from separation from the parents, or even be subjected to neglect or abuse?). These worries are especially likely among low-income parents with fewer family and community resources. A few parents may think of childcare only as “babysitting” and may not consider the consequences for their child's cognitive, linguistic, and social development, focusing solely on whether the child is safe and warm. These parents may be less likely to select a high-quality childcare arrangement, which is especially problematic if the family is facing socioeconomic challenges that already place them at risk of receiving lower-quality care for their children. For these parents, it is vital to stress the importance of quality and its implications for their child's cognitive, language, and behavioral development and school readiness.

Table 29.2

Childcare Information Resources

ORGANIZATION	SPONSOR	WEBSITE AND CONTACT INFORMATION
Child Care Aware	Child Care Aware of America (formerly National Association of Child Care Resource and Referral Agencies)	http://www.childcareaware.org
Healthy Child Care America	American Academy of Pediatrics (AAP)	http://www.healthychildcare.org
National Association for the Education of Young Children (NAEYC)		http://www.naeyc.org
National Association for Sick Child Daycare (NASCD)		http://www.nascd.com
National Resource Center for Health and Safety in Child Care and Early Education (NRC)		http://www.nrckids.org For 2013 report from AAP, APHA, NRC, *Stepping Stones to Caring for Our Children: National Health and Safety Performance Standards—Guidelines for Early Care and Education Programs*, ed 3, go to: http://nrckids.org/index.cfm/products/stepping-stones-to-caring-

		for-our-children-3rd-edition-ss3/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/
Office of Child Care (OCC)	U.S. Department of Health and Human Services, Administration for Children and Families	http://www.acf.hhs.gov/programs/occ
Office of Child Care Technical Assistance Network (CCTAN)	U.S. Department of Health and Human Services, Administration for Children and Families, Office of Child Care	https://childcareta.acf.hhs.gov/

Advising Parents on Childcare Health Issues

Parents of infants should be advised to ensure that childcare providers put infants on their back to sleep to prevent SIDS. Also, pediatricians should emphasize the importance of following vaccination schedules; most states require compliance for children to participate in licensed group childcare settings.

When children are ill, parents should be advised to follow guidelines for inclusion and exclusion (see Table 29.1). Parents may disagree with childcare staff about whether a child meets or does not meet the exclusion criteria. However, professional guidelines state that “if … the reason for exclusion relates to the child's ability to participate or the caregiver's/teacher's ability to provide care for the other children, the caregiver/teacher should not be required to accept responsibility for the care of the child.”*

Helping Children With Special Needs

Pediatricians should work with parents and communicate with other service providers and early intervention staff to identify problems, remove access barriers, and coordinate service delivery for children with special needs. They should also encourage involvement of parents and childcare providers in IFSP or IEP plan development.

Consulting and Partnering With Childcare Providers

Most state regulations mandate that licensed programs have a formal relationship with a healthcare provider. Additional state efforts include mental health consultation models to support providers, who are often not well trained in managing child behavior, and build capacity to raise quality for all children. Early childhood mental health consultation links a mental health professional with an early education and care provider in an ongoing problem-solving and capacity-building relationship.

Pediatricians can provide consultation to childcare providers about measures to protect and maintain the health and safety of children and staff. This may include consultation regarding promoting practices to prevent SIDS; preventing and reducing the spread of communicable disease; reducing allergen, toxin, and parasite exposure; ensuring vaccinations for children and staff; removing environmental hazards; and preventing injuries.

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CHAPTER 30

Loss, Separation, and Bereavement

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All children will experience involuntary separations, whether from illness, death, or other causes, from loved ones at some time in their lives. Relatively brief separations of children from their parents, usually produce minor transient effects, but more enduring and frequent separation may cause sequelae. The potential impact of each event must be considered in light of the age, stage of development, and experiences of the child, the particular relationship with the absent person, and the nature of the situation.

Separation and Loss

Separations may be from temporary causes, such as vacations, parental job requirements, natural disasters or civil unrest, or parental or sibling illness requiring hospitalization. More long-term separations occur as a result of divorce, placement in foster care, or immigration, whereas permanent separation may occur because of death. The initial reaction of young children to separation of any duration may involve crying, either of a tantrum-like, protesting type, or of a quieter, sadder type. Children's behavior may appear subdued, withdrawn, fussy, or moody, or they may demonstrate resistance to authority. Specific problems may include poor appetite, behavior issues such as acting against caregiver requests, reluctance to go to bed, sleep problems, or regressive behavior, such as requesting a bottle or bed-wetting. School-age children may experience impaired cognitive functioning and poor performance in school. Some children may repeatedly ask for the absent parent and question when the absent parent will return. The child may go to the window or door or out into the neighborhood to look for the absent parent; a few may even leave home or their place of temporary placement to search for their parents. Other children may not refer to the parental absence at all.

A child's response to reunion may surprise or alarm an unprepared parent. A parent who joyfully returns to the family may be met by wary or cautious children. After a brief interchange of affection, children may seem indifferent to the parent's return. This response may indicate anger at being left or wariness that the event will happen again, or the young child may feel, as a result of **magical thinking** (see Chapter 24), as if the child caused the parent's departure. For example, if the parent who frequently says “Stop it, or you'll give me a headache” is hospitalized, the child may feel at fault and guilty. Because of these feelings, children may seem more closely attached to the present parent than to the absent one, or even to the grandparent or babysitter who cared for them during their parent's absence. Some children, particularly younger ones, may become more clinging and dependent than they were before the separation, while continuing any regressive behavior that occurred during the separation. Such behavior may engage the returned parent more closely and help to reestablish the bond that the child felt was broken. Such reactions are usually transient, and within 1-2 wk, children will have recovered their usual behavior and equilibrium. Recurrent separations may tend to make children wary and guarded about reestablishing the relationship with the repeatedly absent parent, and these traits may affect other personal relationships. Parents should be advised not to try to modify a child's behavior by threatening to leave.

Divorce

More sustained experiences of loss, such as divorce or placement in foster care, can give rise to the same kinds of reactions noted earlier, but they are more intense and possibly more lasting. Currently in the United States, approximately 40% of marriages end in divorce. Divorce has been found to be associated with negative parent functioning, such as parental depression and feelings of incompetence; negative child behavior, such as noncompliance and whining; and negative parent–child interaction, such as inconsistent discipline, decreased communication, and decreased affection. Greater childhood distress is associated with greater parental distress. Continued parental conflict and loss of contact with the noncustodial parent, usually the father, is common.

Two of the most important factors that contribute to morbidity of the children in a divorce include *parental psychopathology* and *disrupted parenting* before the separation. The year following the divorce is the period when problems are most apparent; these problems tend to dissipate over the next 2 yr. Depression may be present up to 5 yr later, and educational or occupational decline may occur even 10 yr later. It is difficult to sort out all confounding factors. Children may suffer when exposed to parental conflict that continues after divorce and that in some cases may escalate. The degree of *interparental conflict* may be the most important factor associated with child morbidity. A continued relationship with the noncustodial parent when there is minimal interparental conflict is associated with more positive outcomes.

School-age children may become depressed, may seem indifferent, or may be extremely angry. Other children appear to deny or avoid the issue, behaviorally or verbally. Most children cling to the hope that the actual placement or separation is not real and only temporary. The child may experience guilt by feeling that the loss, separation, or placement represents rejection and perhaps punishment for misbehavior. Children may protect a parent and assume guilt, believing that their own “badness” caused the parent to depart. Children who feel that their misbehavior caused their parents to separate may have the fantasy that their own trivial or recurrent behavioral patterns caused their parents to become angry at each other. A child might perceive that outwardly blaming parents is emotionally risky; parents who discover that a child harbors resentment might punish the child further for these thoughts or feelings. Some children have behavioral or psychosomatic symptoms and unwittingly adopt a “sick” role as a strategy for reuniting their parents.

In response to divorce of parents and the subsequent separation and loss, older children and adolescents usually show intense anger. Five years after the breakup, approximately 30% of children report intense unhappiness and dissatisfaction with their life and their reconfigured family; another 30% show clear evidence of a satisfactory adjustment; and the remaining children demonstrate a mixed picture, with good achievement in some areas and faltering achievement in others. After 10 yr, approximately 45% do well, but 40% may have academic, social, or emotional problems. As adults, some are reluctant to form intimate relationships, fearful of repeating their parents' experience.

Parental divorce has a moderate long-term negative impact on the adult mental health status of children, even after controlling for changes in economic status and problems before divorce. Good adjustment of children after a divorce is related to ongoing involvement with two psychologically healthy parents who minimize conflict and to the siblings and other relatives who provide a positive support system. Divorcing parents should be encouraged to avoid adversarial processes and to use a trained mediator to resolve disputes if needed. Joint-custody arrangements may reduce ongoing parental conflict, but children in joint custody may feel overburdened by the demands of maintaining a strong presence in two homes.

When the primary care provider is asked about the effects of divorce, parents should be informed that different children may have different reactions, but that the parents' behavior and the way they interact will have a major and long-term effect on the child's adjustment. The continued presence of both parents in the child's life, with minimal interparental conflict, is most beneficial to the child.

Move/Family Relocation

A significant proportion of the U.S. population changes residence each year. The effects of this movement on children and families are frequently overlooked. For children, the move is essentially involuntary and out of their control. When changes in family structure such as divorce or death precipitate moves, children face the stresses created by both the precipitating events and the move itself. Parental sadness surrounding the move may transmit unhappiness to the children. Children who move lose their old friends, the comfort of a familiar bedroom and house, and their ties to school and community. They not only must sever old relationships, but also are faced with developing new ones in new neighborhoods and new schools. Children may enter neighborhoods with different customs and values, and because academic standards and curricula vary among communities, children who have performed well in one school may find themselves struggling in a new one. Frequent moves during the school years are likely to have adverse consequences on social and academic performance.

Migrant children and children who emigrate from other countries present with special circumstances. These children not only need to adjust to a new house, school, and community, but also need to adjust to a new culture and in many cases a new language. Because children have faster language acquisition than adults, they may function as translators for the adults in their families. This powerful position may lead to role reversal and potential conflict within the family. In the evaluation of migrant children and families, it is important to ask about the circumstances of the migration, including legal status, violence or threat of violence, conflict of loyalties, and moral, ethical, and religious differences.

Parents should prepare children well in advance of any move and allow them to express any unhappy feelings or misgivings. Parents should acknowledge their own mixed feelings and agree that they will miss their old home while looking forward to a new one. Visits to the new home in advance are often useful preludes to the actual move. Transient periods of regressive behavior may be noted in preschool children after moving, and these should be understood and accepted. Parents should assist the entry of their children into the new community, and whenever possible, exchanges of letters and visits with old friends should be encouraged.

Separation Because of Hospitalization

Potential challenges for hospitalized children include coping with separation, adapting to the new hospital environment, adjusting to multiple caregivers, seeing very sick children, and sometimes experiencing the disorientation of intensive care, anesthesia, and surgery. To help mitigate potential problems, a preadmission visit to the hospital can help by allowing the child to meet the people who will be offering care and ask questions about what will happen. Parents of children <5-6 yr old should room with the child if feasible. Older children may also benefit from parents staying with them while in the hospital, depending on the severity of their illness. Creative and active recreational or socialization programs with child life specialists, chances to act out feared procedures in play with dolls or mannequins, and liberal visiting hours, including visits from siblings, are all helpful. Sensitive, sympathetic, and accepting attitudes toward children and parents by the hospital staff are very important. Healthcare providers need to remember that parents have the best interest of their children at heart and know their children the best. Whenever possible, school assignments and tutoring for hospitalized children should be available to engage them intellectually and prevent them from falling behind in their scholastic achievements.

The psychologic aspects of illness should be evaluated from the outset, and physicians should act as a model for parents and children by showing interest in a child's feelings, allowing them a venue for expression, and demonstrating that it is possible and appropriate to communicate about discomfort. Continuity of medical personnel may be reassuring to the child and family.

Military Families

More than 2 million children live in military families in the United States, and approximately 50% of them obtain medical care in the community rather than at a military medical facility. Children whose parents are serving in the military may experience loss and separation in multiple ways. These include frequent relocations, relocation to foreign countries, and duty-related separation from parents. In recent years the most impactful experiences have been repeated wartime deployments of parents and the death of parents during military service. All branches of the military have increased their focus on preparing and supporting military families for a service member's deployment in order to improve family coping. Military families composed of young parents and young children are at risk for child maltreatment in the context of repeated or prolonged deployments.

Parental/Sibling Death

Approximately 5–8% of U.S. children will experience parental death; rates are much higher in other parts of the world more directly affected by war, AIDS, and natural disasters. Anticipated deaths from chronic illness may place a significant strain on a family, with frequent bouts of illness, hospitalization, disruption of normal home life, absence of the ill parent, and perhaps more responsibilities placed on the child. Additional strains include changes in daily routines, financial pressures, and the need to cope with aggressive treatment options.

Children can and should continue to be involved with the sick parent or sibling, but they need to be prepared for what they will see in the home or hospital setting. The stresses that a child will face include visualizing the physical deterioration of the family member, helplessness, and emotional lability. Forewarning the child that the family member may demonstrate physical changes, such as appearing thinner or losing hair, will help the child to adjust. These warnings combined with simple yet specific explanations of the need for equipment, such as a nasogastric tube for nutrition, an oxygen mask, or a ventilator, will help lessen the child's fear. Children should be honestly informed of what is happening, in language they can understand, allowing them choices, but with parental involvement in decision-making. They should be encouraged, but not forced, to see their ill family member. Parents who are caring for a dying spouse or child may be too emotionally depleted to be able to tend to their healthy child's needs or to continue regular routines. Children of a dying parent may suffer the loss of security and belief in the world as a safe place, and the surviving parent may be inclined to impose his or her own need for support and comfort onto the child. However, the well parent and caring relatives must keep in mind that children need to be allowed to remain children, with appropriate support and attention. Sudden, unexpected deaths lead to more anxiety and fear because there is no time for preparation, and explanations for the death can cause uncertainty.

Grief and Bereavement

Grief is a personal, emotional state of bereavement or an anticipated response to loss, such as a death. Common reactions include sadness, anger, guilt, fear, and at times, relief. The normality of these reactions needs to be emphasized. Most bereaved families remain socially connected and expect that life will return to some new, albeit different, sense of normalcy. The pain and suffering imposed by grief should never be automatically deemed “normal” and thus neglected or ignored. In **uncomplicated grief** reactions, the steadfast concern of the pediatrician can help promote the family's sense of well-being. In more distressing reactions, as seen in traumatic grief of sudden death, the pediatrician may be a major, first-line force in helping children and families address their loss.

Participation in the care of a child with a life-threatening or terminal illness is a profound experience. Parents experience much anxiety and worry during the final stages of their child's life. In one study, 45% of children dying from cancer died in the pediatric intensive care unit, and parents report that 89% of their children suffered “a lot” or “a great deal” during the last month of life. Physicians consistently underreport children's symptoms in comparison to parents' reports. Better ways are needed to provide care for dying children. Providers need to maintain honest and open communication, provide appropriate pain management, and meet the families' wishes as to the preferred location of the child's death, in some cases in their own home. Inclusion of multiple disciplines, such as hospice, clergy, nursing, pain service, child life specialists, and social work, often helps to support families fully during this difficult experience.

The practice of withholding information from children and parents regarding a child's diagnosis and prognosis has generally been abandoned, because physicians have learned that protecting parents and patients from the seriousness of their child's condition does not alleviate concerns and anxieties. Even very young children may have a real understanding of their illness. Children who have serious diseases and are undergoing aggressive treatment and medication regimens, but who are told by their parents that they are okay, are not reassured. These children understand that something serious is happening to them, and they are often forced to suffer in silence and isolation because the message they have been given by their parents is to not discuss it and to maintain a cheerful demeanor. Children have the right to know their diagnosis and should be informed early in their treatment. The content and depth of the discussion needs to be tailored to the child's personality and developmental level of understanding. Parents have choices as to how to orchestrate the disclosure. Parents may want to be the ones to inform the child themselves, may choose for the pediatric healthcare provider to do so, or may do it in partnership with the pediatrician.

A **death** , especially the death of a family member, is the most difficult loss for a child. Many changes in normal patterns of functioning may occur, including loss of love and support from the deceased family member, a change in income, the possible need to relocate, less emotional support from surviving family members, altering of routines, and a possible change in status from sibling to only child. Relationships between family members may become strained, and children may blame themselves or other family members for the death of a parent or sibling. Bereaved children may exhibit many of the emotions discussed earlier as a result of the loss, in addition to behaviors of withdrawal into their own world, sleep disturbances, nightmares, and symptoms such as headache, abdominal pains, or possibly similar to those of the family member who has died. Children 3-5 yr of age who have experienced a family bereavement may show regressive behaviors such as bed-wetting and thumb sucking. School-age children may exhibit nonspecific symptoms, such as headache, abdominal pain, chest pain, fatigue, and lack of energy. Children and adolescents may also demonstrate enhanced anxiety if these symptoms resemble those of the family member who died. The presence of secure and stable adults who can meet the child's needs and who permit discussion about the loss is most important in helping a child to grieve. The pediatrician should help the family understand this necessary presence and encourage the protective functioning of the family unit. More frequent visits to the healthcare professional may be necessary to address these symptoms and provide reassurance when appropriate. Suggested availability of clergy or mental health providers can provide additional support and strategies to facilitate the transitions after the death.

Death, separation, and loss as a result of **natural catastrophes** and **human-made disasters** have become increasingly common events in children's lives. Exposure to such disasters occurs either directly or indirectly, where the event is experienced through the media. Examples of **indirect exposure** include televised scenes of earthquakes, hurricanes, tsunamis, tornadoes, and domestic and international terrorist attacks. Children who experience personal loss in disasters tend to watch more television coverage than children who do not. Children without a personal loss watch as a way of participating in the event and may thus experience repetitive exposure to traumatic scenes and stories. The loss and devastation for a child who personally lives through a disaster are significant; the effect of the simultaneous occurrence of disaster and personal loss complicates the bereavement process as grief reactions become interwoven with posttraumatic stress symptoms (see Chapter 38). After a death resulting from aggressive or traumatic circumstances, access to expert help may be required. Under conditions of threat and fear, children seek proximity to safe, stable, protective figures.

It is important for parents to grieve with their children. Some parents want to protect their children from their grief, so they put on an outwardly brave front or do not talk about the deceased family member or traumatic event. Instead of the desired protective effect, the child receives the message that demonstrating grief or talking about death is wrong, leading the child to feel isolated, grieve privately, or delay grieving. The child may also conclude that the parents did not really care about the deceased because they seem to have forgotten the person so easily or demonstrate no emotion. The parents' efforts to avoid talking about the death may cause the parents to isolate themselves from their children at a time when the children most need them. Children need to know that their parents love them and will continue to protect them. Children need opportunities to talk about their relative's death and associated memories. A surviving sibling may feel guilty simply because he or she survived, especially if the death was the result of an accident that involved both children. Siblings' grief, especially when compounded by feelings of guilt, may manifest as regressive behavior or anger. Parents should be informed of this possibility and encouraged to discuss it with their children.

Developmental Perspective

Children's responses to death reflect the family's current culture, their past heritage, their experiences, and the sociopolitical environment. Personal experience with terminal illness and dying may also facilitate children's comprehension of death and familiarity with mourning. Developmental differences exist in children's efforts to make sense of and master the concept and reality of death and profoundly influence their grief reactions.

Children younger than 3 yr have little or no understanding of the concept of death. Despair, separation anxiety, and detachment may occur at the withdrawal of nurturing caretakers. Young children may respond in reaction to observing distress in others, such as a parent or sibling who is crying, withdrawn, or angry. Young children also express signs and symptoms of grief in their emotional states, such as irritability or lethargy, and in severe cases, mutism. If the reaction is severe, failure to thrive may occur.

Preschool children are in the preoperational cognitive stage, in which communication takes place through play and fantasy (see Chapter 24). They do not show well-established cause-and-effect reasoning. They feel that death is reversible, analogous to someone going away. In attempts to master the finality and permanence of death, preschoolers frequently ask unrelenting, repeated questions about when the person who died will be returning. This makes it difficult for parents, who may become frustrated because they do not understand why the child keeps asking and do not like the constant reminders of the person's death. The primary care provider has a very important role in helping families understand the child's struggle to comprehend death. Preschool children typically express magical explanations of death events, sometimes resulting in guilt and self-blame (“He died because I wouldn't play with him”; “She died because I was mad at her”). Some children have these thoughts but do not express them verbally because of embarrassment or guilt. Parents and primary care providers need to be aware of magical thinking and must reassure preschool children that their thoughts had nothing to do with the outcome. Children of this age are often frightened by prolonged, powerful expressions of grief by others. Children conceptualize events in the context of their own experiential reality, and therefore consider death in terms of sleep, separation, and injury. Young children express grief intermittently and show marked affective shifts over brief periods.

Younger school-age children think concretely, recognize that death is irreversible, but believe it will not happen to them or affect them, and begin to understand biologic processes of the human body (“You'll die if your body stops working”). Information gathered from the media, peers, and parents forms lasting impressions. Consequently, they may ask candid questions about death that adults will have difficulty addressing (“He must have been blown to pieces, huh?”).

Children approximately 9 yr and older do understand that death is irreversible and that it may involve them or their families. These children tend to experience more anxiety, overt symptoms of depression, and somatic complaints than do younger children. School-aged children are often left with anger focused on the loved one, those who could not save the deceased, or those presumed responsible for the death. Contact with the pediatrician may provide great reassurance, especially for the child with somatic symptoms, and particularly when the death followed a medical illness. School and learning problems may also occur, often linked to difficulty concentrating or preoccupation with the death. Close collaboration with the child's school may provide important diagnostic information and offer opportunities to mobilize intervention or support.

At **12-14 yr of age** , children begin to use symbolic thinking, reason abstractly, and analyze hypothetical, or “what if,” scenarios systematically. Death and the end of life become concepts rather than events. Teenagers are often ambivalent about dependence and independence and may withdraw emotionally from surviving family members, only to mourn in isolation. Adolescents begin to understand complex physiologic systems in relationship to death. Since they are often egocentric, they may be more concerned about the impact of the death on themselves than about the deceased or other family members. Fascination with dramatic, sensational, or romantic death sometimes occurs and may find expression in *copycat behavior,* such as cluster suicides, as well as *competitive behavior,* to forge emotional links to the deceased person (“He was my best friend”). Somatic expression of grief may revolve around highly complex syndromes such as eating disorders (see Chapter 41) or conversion reactions (Chapter 35), as well as symptoms limited to the more immediate perceptions (stomachaches). *Quality of life* takes on meaning, and the teenager develops a focus on the future. Depression, resentment, mood swings, rage, and risk-taking behaviors can emerge as the adolescent seeks answers to questions of values, safety, evil, and fairness. Alternately, adolescents may seek philosophic or spiritual explanations (“being at peace”) to ease their sense of loss. The death of a peer may be especially traumatic.

Families often struggle with how to inform their children of the death of a family member. The answer depends on the child's developmental level. It is best to avoid misleading euphemisms and metaphor. A child who is told that the relative who died “went to sleep” may become frightened of falling asleep, resulting in sleep problems or nightmares. Children can be told that the person is “no longer living” or “no longer moving or feeling.” Using examples of pets that have died sometimes can help children gain a more realistic idea of the meaning of death. Parents who have religious beliefs may comfort their children with explanations, such as, “Your sister's soul is in heaven,” or “Grandfather is now with God,” provided those beliefs are honestly held. If these are not religious beliefs that the parents share, children will sense the insincerity and experience anxiety rather than the hoped-for reassurance. Children's books about death can provide an important source of information, and when read together, these books may help the parent to find the right words while addressing the child's needs.

Role of the Pediatrician in Grief

The pediatric healthcare provider who has had a longitudinal relationship with the family will be an important source of support in the disclosure of bad news and in critical decision-making, during both the dying process and the bereavement period. The involvement of the healthcare provider may include being present at the time the diagnosis is disclosed, at the hospital or home at the time of death, being available to the family by phone during the bereavement period, sending a sympathy card, attending the funeral, and scheduling a follow-up visit. Attendance at the funeral sends a strong message that the family and their child are important, respected by the healthcare provider, and can also help the pediatric healthcare provider to grieve and reach personal closure about the death. A family meeting 1-3 mo later may be helpful because parents may not be able to formulate their questions at the time of death. This meeting allows the family time to ask questions, share concerns, and review autopsy findings (if one was performed), and allows the healthcare provider to determine how the parents and family are adjusting to the death.

Instead of leaving the family feeling abandoned by a healthcare system that they have counted on, this visit allows them to have continued support. This is even more important when the healthcare provider will be continuing to provide care for surviving siblings. The visit can be used to determine how the mourning process is progressing, detect evidence of marital discord, and evaluate how well surviving siblings are coping. This is also an opportunity to evaluate whether referrals to support groups or mental health providers may be of benefit. Continuing to recognize the child who has died is important. Families appreciate the receipt of a card on their child's birthday, around holidays, or the anniversary of their child's death.

The healthcare provider needs to be an *educator* about disease, death, and grief. The pediatrician can offer a safe environment for the family to talk about painful emotions, express fears, and share memories. By giving families permission to talk and modeling how to address children's concerns, the pediatrician demystifies death. Parents often request practical help. The healthcare provider can offer families resources, such as literature (both fiction and nonfiction), referrals to therapeutic services, and tools to help them learn about illness, loss, and grief. In this way the physician reinforces the sense that other people understand what they are going through and helps to normalize their distressing emotions. The pediatrician can also facilitate and demystify the grief process by sharing basic tenets of **grief therapy** . There is no single right or wrong way to grieve. Everyone grieves differently; mothers may grieve differently than fathers, and children mourn differently than adults. Helping family members to respect these differences and reach out to support each other is critical. Grief is not something to “get over,” but a lifelong process of adapting, readjusting, and reconnecting.

Parents may need help in knowing what constitutes **normal grieving** . Hearing, seeing, or feeling their child's presence may be a normal response. Vivid memories or dreams may occur. The pediatrician can help parents to learn that, although their pain and sadness may seem intolerable, other parents have survived similar experiences, and their pain will lessen over time.

Pediatricians are often asked whether children should attend the **funeral** of a parent or sibling. These rituals allow the family to begin their mourning process. Children >4 yr old should be given a choice. If the child chooses to attend, the child should have a designated, trusted adult who is not part of the immediate family and who will stay with the child, offer comfort, and be willing to leave with the child if the experience proves to be overwhelming. If the child chooses not to attend, the child should be offered additional opportunities to share in a ritual, go to the cemetery to view the grave, tell stories about the deceased, or obtain a keepsake object from the deceased family member as a remembrance.

In the era of regionalized tertiary care medicine, the primary care provider and medical home staff may not be informed when one of their patients dies in the hospital. Yet, this communication is critically important. Families assume their pediatrician has been notified and often feel hurt when they do not receive some symbol of condolence. Because of their longitudinal relationship with the family, primary care providers may offer much needed support. There are practical issues, such as the need to cancel previously made appointments and to alert office and nursing staff so that they are prepared should the family return for a follow-up visit or for ongoing health maintenance care with the surviving siblings. Even minor illnesses in the surviving siblings may frighten children. Parents may contribute to this anxiety because their inability to protect the child who has died may leave them with a sense of guilt or helplessness. They may seek medical attention sooner or may be hypervigilant in the care of the siblings because of guilt over the other child's death, concern about their judgment, or the need for continued reassurance. A visit to the pediatrician can do much to allay their fears.

Clinicians must remain vigilant for risk factors in each family member and in the family unit as a whole. Primary care providers, who care for families over time, know bereft patients' premorbid functioning and can identify those at current or future risk for physical and psychiatric morbidity. Providers must focus on symptoms that interfere with a patient's normal activities and compromise a child's attainment of developmental tasks. Symptom duration, intensity, and severity, in context with the family's culture, can help identify **complicated grief** reactions in need of therapeutic attention. Descriptive words such as “unrelenting,” “intense,” “intrusive,” or “prolonged” should raise concern. Total absence of signs of mourning, specifically an inability to discuss the loss or express sadness, also suggests potential problems.

No specific sign, symptom, or cluster of behaviors identifies the child or family in need of help. Further assessment is indicated if the following occur: (1) persistent somatic or psychosomatic complaints of undetermined origin (headache, stomachache, eating and sleeping disorders, conversion symptoms, symptoms related to the deceased's condition, hypochondriasis); (2) unusual circumstances of death or loss (sudden, violent, or traumatic death; inexplicable, unbelievable, or particularly senseless death; prolonged, complicated illness; unexpected separation); (3) school or work difficulties (declining grades or school performance, social withdrawal, aggression); (4) changes in home or family functioning (multiple family stresses, lack of social support, unavailable or ineffective functioning of caretakers, multiple disruptions in routines, lack of safety); and (5) concerning psychologic factors (persistent guilt or blame, desire to die or talk of suicide, severe separation distress, disturbing hallucinations, self-abuse, risk-taking behaviors, symptoms of trauma such as hyperarousal or severe flashbacks, grief from previous or multiple deaths). Children who are intellectually impaired may require additional support.

Finally, pediatric healthcare providers need to recognize that the loss of a patient will have an impact on them, both as a health professional and as a caring individual. Identifying one's responses to the loss (grief, guilt, anger, sadness) and finding time to process these feelings is important. Providers cope with these experiences in many ways. Strong coping mechanisms foster resilience and allow providers to continue to engage with patients and families in meaningful ways even in the face of grief and loss.

Treatment

Suggesting interventions outside the natural support network of family and friends can often prove useful to grieving families. Bereavement counseling should be readily offered if needed or requested by the family. Interventions that enhance or promote attachments and security, as well as give the family a means of expressing and understanding death, help to reduce the likelihood of future or prolonged disturbance, especially in children. Collaboration between pediatric and mental health professionals can help determine the timing and appropriateness of services.

Interventions for children and families who are struggling to cope with a loss in the community include gestures such as sending a card or offering food to the relatives of the deceased and teaching children the etiquette of behaviors and rituals around bereavement and mutual support. Performing community service or joining charitable organizations, such as fund-raising in memory of the deceased, may be useful. In the wake of a disaster, parents and older siblings can give blood or volunteer in search and recovery efforts. When a loss does not involve an actual death (e.g., parental divorce, geographic relocation), empowering the child to join or start a “divorced kids' club” in school or planning a “new kids in town” party may help. Participating in a constructive activity moves the family away from a sense of helplessness and hopelessness and helps them find meaning in their loss.

Psychotherapeutic services may benefit the entire family or individual members. Many support or self-help groups focus on specific types of losses (sudden infant death syndrome, suicide, widow/widowers, AIDS) and provide an opportunity to talk with other people who have experienced similar losses. Family, couple, sibling, or individual counseling may be useful, depending on the nature of the residual coping issues. Combinations of approaches may work well for children or parents with evolving needs. A child may participate in family therapy to deal with the loss of a sibling and use individual treatment to address issues of personal ambivalence and guilt related to the death.

The question of **pharmacologic intervention** for grief reactions often arises. Explaining that medication does not cure grief and often does not reduce the intensity of some symptoms (separation distress) can help. Although medication can blunt reactions, the psychologic work of grieving still must occur. The pediatrician must consider the patient's premorbid psychiatric vulnerability, current level of functioning, other available supports, and the use of additional therapeutic interventions. Medication as a first line of defense rarely proves useful in normal or uncomplicated grief reactions. In certain situations (severe sleep disruption, incapacitating anxiety, intense hyperarousal), an anxiolytic or antidepressant may help to achieve symptom relief and provide the patient with the emotional energy to mourn. Medication used in conjunction with some form of psychotherapy, and in consultation with a psychopharmacologist, has optimal results.

Children who are **refugees** and may have experienced war, violence, or personal torture, while often resilient, may experience posttraumatic stress disorder if exposures were severe or repeated (see Chapter 14.3). Sequelae such as depression, anxiety, and grief need to be addressed, and mental health therapy is indicated. Cognitive-behavioral therapy, use of journaling and narratives to bear witness to the experiences, and use of translators may be essential.

Spiritual Issues

Responding to patients' and families' spiritual beliefs can help in comforting them during family tragedies. Offering to call members of pastoral care teams or their own spiritual leader can provide needed support and can aid in decision-making. Families have found it important to have their beliefs and their need for hope acknowledged in end-of-life care. The majority of patients report welcoming discussions on spirituality, which may help individual patients cope with illness, disease, dying, and death. In addressing spirituality, physicians need to follow certain guidelines, including maintaining respect for the patient's beliefs, following the patient's lead in exploring how spirituality affects the patient's decision-making, acknowledging the limits of their own expertise and role in spirituality, and maintaining their own integrity by not saying or doing anything that violates their own spiritual or religious views. Healthcare providers should not impose their own religious or nonreligious beliefs on patients, but rather should listen respectfully to their patients. By responding to spiritual needs, physicians may better aid their patients and families in end-of-life care and bereavement and take on the role of healers.

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CHAPTER 31

Sleep Medicine

Judith A. Owens

Basics of Sleep and Chronobiology

Sleep, with its counterpart of wakefulness, is a highly complex and intricately regulated neurobiologic system that both influences and is influenced by all physiologic systems in the body, as well as by the environment and sociocultural practices. The concept of **sleep regulation** is based on what is usually referred to as the “2-process model” because it requires the simultaneous operation of 2 basic, highly coupled processes that govern sleep and wakefulness. The **homeostatic process** (“Process S”), regulates the length and depth of sleep and is thought to be related to the accumulation of adenosine and other sleep-promoting chemicals (“somnogens”), such as cytokines, during prolonged periods of wakefulness. This sleep pressure appears to build more quickly in infants and young children, thus limiting the duration that wakefulness can be sustained during the day and necessitating periods of daytime sleep (i.e., naps). The endogenous **circadian rhythms** (“Process C”) influence the internal organization of sleep and the timing and duration of daily sleep–wake cycles and govern predictable patterns of alertness throughout the 24 hr day.

The “master circadian clock” that controls sleep–wake patterns, of which melatonin secretion is the principal biomarker, is located in the suprachiasmatic nucleus in the ventral hypothalamus. In addition, “circadian clocks” are present in virtually every cell in the body, which in turn govern the timing of multiple other physiologic systems (e.g., cardiovascular reactivity, hormone levels, renal and pulmonary functions). Because the human circadian clock is slightly longer than 24 hr, intrinsic circadian rhythms must be synchronized or “entrained” to the 24 hr day cycle by environmental cues called *zeitgebers*. The **dark–light cycle** is the most powerful of the zeitgebers; light signals are transmitted to the suprachiasmatic nucleus via the circadian photoreceptor system within the retina (functionally and anatomically separate from the visual system), which switch the pineal gland's production of the hormone melatonin off (light) or on (dark). Circadian rhythms are also synchronized by other external time cues, such as timing of meals and alarm clocks.

Sleep propensity, the relative level of sleepiness or alertness experienced at any given time during a 24 hr period, is partially determined by the homeostatic *sleep drive* , which in turn depends on the duration and quality of previous sleep and the amount of time awake since the last sleep period. Interacting with this *sleep homeostat* is the 24 hr cyclic pattern or rhythm characterized by clock-dependent periods of maximum sleepiness (*circadian troughs*) and maximum alertness (*circadian nadirs*). There are two periods of maximum sleepiness, one in the late afternoon (approximately 3:00-5:00 PM) and one toward the end of the night (around 3:00-5:00 AM), and two periods of maximum alertness, one in mid-morning and one in the evening just before the onset of natural sleep, the so-called forbidden zone or second-wind phenomenon, which allows for the maintenance of wakefulness in the face of accumulated sleep drive.

There are significant health, safety, and performance consequences of failure to meet basic sleep needs, termed *insufficient/inadequate sleep* or **sleep loss** . Sufficient sleep is a biologic imperative, necessary for optimal brain and body functioning. **Slow-wave sleep (SWS)** (i.e., N3, delta, or deep sleep) appears to be the most restorative form of sleep; it is entered relatively quickly after sleep onset, is preserved in the face of reduced total sleep time, and increases (rebounds) after a night of restricted sleep. These restorative properties of sleep may be linked to the “glymphatic system,” which increases clearance of metabolic waste products, including β-amyloid, produced by neural activity in the awake brain. **Rapid eye movement (REM)** sleep (stage R or “dream” sleep) appears to be involved in numerous important brain processes, including completion of vital cognitive functions (e.g., consolidation of memory), promoting the plasticity of the central nervous system (CNS), and protecting the brain from injury. Sufficient amounts of these sleep stages are necessary for optimal cognitive functioning and emotional and behavioral self-regulation.

Partial sleep loss (i.e., sleep restriction) on a chronic basis accumulates in a **sleep debt** and over several days produces deficits equivalent to those seen under conditions of 1 night of total sleep deprivation. If the sleep debt becomes large enough and is not voluntarily repaid by obtaining sufficient recovery sleep, the body may respond by overriding voluntary control of wakefulness. This results in periods of decreased alertness, dozing off, and unplanned napping, recognized as *excessive daytime sleepiness.* The sleep-restricted individual may also experience very brief (several seconds) repeated daytime microsleeps, of which the individual may be completely unaware, but which nonetheless may result in significant lapses in attention and vigilance. There is also a relationship between the amount of sleep restriction and performance on cognitive tasks, particularly those requiring sustained attention and higher-level cognitive skills (*executive functions* ; see Chapter 48), with a decay in performance correlating with declines in sleep amounts.

It has also been increasingly recognized that what may be globally described as "deficient" sleep involves alterations in both amount and *timing* of sleep. Misalignment of intrinsic circadian rhythms with extrinsic societal demands, such a shift work and early school start times, is associated with deficits in cognitive function and self-regulation, increased emotional and behavioral problems and risk-taking behaviors, and negative impacts on health, such as increased risk of cardiovascular disease, obesity, and metabolic dysfunction.

Insufficient quantity of sleep, mistimed sleep, and poor-quality sleep in children and adolescents frequently result in excessive daytime sleepiness and decreased daytime alertness levels. **Sleepiness** in children may be recognizable as drowsiness, yawning, and other classic "sleepy behaviors," but can also manifest as mood disturbance, including complaints of moodiness, irritability, emotional lability, depression, and anger; fatigue and daytime lethargy, including increased somatic complaints (headaches, muscle aches); cognitive impairment, including problems with memory, attention, concentration, decision-making, and problem solving; daytime behavior problems, including hyperactivity, impulsivity, and noncompliance; and academic problems, including chronic tardiness related to insufficient sleep and school failure resulting from chronic daytime sleepiness.

Developmental Changes in Sleep

Sleep disturbances, as well as many characteristics of sleep itself, have some distinctly different features in children from sleep and sleep disorders in adults. Changes in sleep architecture and the evolution of sleep patterns and behaviors reflect the physiologic/chronobiologic, developmental, and social/environmental changes that are occurring across childhood. These trends may be summarized as the gradual assumption of more adult sleep patterns as children mature:

1. Sleep is *the* primary activity of the brain during early development; for example, by age 2 yr, the average child has spent 9500 hr (approximately 13 mo) asleep vs 8000 hr awake, and between 2 and 5 yr, the time asleep is equal to the time awake.
2. There is a gradual decline in the average 24 hr sleep duration from infancy through adolescence, which involves a decrease in both diurnal and nocturnal sleep amounts. The decline in daytime sleep (scheduled napping) results in termination of naps typically by age 5 yr. There is also a gradual continued decrease in nocturnal sleep amounts into late adolescence; however, the typical adolescent still requires 8-10 hr of sleep per night.
3. There is also a decline in the relative percentage of REM sleep from birth (50% of sleep) through early childhood into adulthood (25–30%), and a similar initial predominance of SWS that peaks in early childhood, drops off abruptly after puberty (40–60% decline), and then further decreases over the life span. This SWS preponderance in early life has clinical significance; for example, the high prevalence of partial arousal parasomnias (sleepwalking and sleep terrors) in preschool and early school-age children is related to the relative increased percentage of SWS in this age-group.
4. The within-sleep **ultradian cycle** lengthens from about 50 min in the term infant to 90-110 min in the school-age child. This has clinical significance in that typically a brief arousal or awakening occurs during the night at the termination of each ultradian cycle. As the length of the cycles increase, there is a concomitant decrease in the number of these end-of-cycle arousals (night wakings).
5. A gradual shift in the circadian sleep–wake rhythm to a delayed (later) sleep onset and offset time, linked to pubertal stage rather than chronological age, begins with pubertal onset in middle childhood and accelerates in early to mid-adolescence. This biologic phenomenon often coincides with environmental factors, which further delay bedtime and advance wake time and result in insufficient sleep duration, including exposure to electronic “screens” (television, computer) in the evening, social networking, academic and extracurricular demands, and early (before 8:30 AM) high school start times.
6. Increasing irregularity of sleep–wake patterns is typically observed across childhood into adolescence; this is characterized by increasingly

larger discrepancies between school night and non–school night bedtimes and wake times, and increased “weekend oversleep” in an attempt to compensate for chronic weekday sleep insufficiency. This phenomenon, often referred to as “social jet lag,” not only fails to adequately address performance deficits associated with insufficient sleep on school nights, but further exacerbates the normal adolescent phase delay and results in additional circadian disruption (analogous to that experienced by shift workers).

Table 31.1 lists normal developmental changes in children's sleep.

Table 31.1

Normal Developmental Changes in Children's Sleep

AGE CATEGORY	SLEEP DURATION* AND SLEEP PATTERNS	ADDITIONAL SLEEP ISSUES	SLEEP DISORDERS
Newborn (0-2 mo)	Total sleep: 10-19 hr per 24 hr (average, 13-14.5 hr), may be higher in premature babies Bottle-fed babies generally sleep for longer periods (2-5 hr bouts) than breastfed babies (1-3 hr). Sleep periods are separated by 1-2 hr awake. No established nocturnal-diurnal pattern in 1st few wk; sleep is evenly distributed throughout the day and night, averaging 8.5	American Academy of Pediatrics issued a revised recommendation in 2016 advocating against bed-sharing in the 1st yr of life, instead encouraging proximate but separate sleeping surfaces for mother and infant for at least the 1st 6 mo and preferably 1st yr of life. Safe sleep practices for infants: • Place baby on his or her back to sleep at night and during nap times. • Place baby on a firm mattress with well-fitting sheet in safety-approved crib. • Do not use pillows or comforters. • Standards require crib bars to be no farther apart than $2\frac{3}{8}$ in. • Make sure baby's face and head stay uncovered and clear of blankets and other coverings during sleep.	Most sleep issues perceived as problematic at this stage represent a discrepancy between parental expectations and developmentally appropriate sleep behaviors. Newborns who are extremely fussy and persistently difficult to console, as noted by parents, are more likely to have underlying medical issues such as colic, gastroesophageal reflux, and formula intolerance.

	hr at night and 5.75 hr during day.		
Infant (2-12 mo)	Recommended sleep duration (4-12 mo) is 12-16 hr (note that there is great individual variability in sleep times during infancy).	Sleep regulation or self-soothing involves the infant's ability to negotiate the sleep–wake transition, both at sleep onset and following normal awakenings throughout the night. The capacity to self-soothe begins to develop in the 1st 12 wk of life and is a reflection of both neurodevelopmental maturation and learning. Sleep consolidation, or “sleeping through the night,” is usually defined by parents as a continuous sleep episode without the need for parental intervention (e.g., feeding, soothing) from the child's bedtime through the early morning. Infants develop the ability to consolidate sleep between 6 wk and 3 mo.	Behavioral insomnia of childhood; sleep-onset association type Sleep-related rhythmic movements (head banging, body rocking)
Toddler (1-2 yr)	Recommended sleep amount is 11-14 hr (including naps). Naps decrease from 2 to 1 nap at average age of 18 mo.	Cognitive, motor, social, and language developmental issues impact sleep. Nighttime fears develop; transitional objects and bedtime routines are important.	Behavioral insomnia of childhood, sleep-onset association type Behavioral insomnia of childhood, limit-setting type
Preschool (3-5 yr)	Recommended sleep amount is 10-13 hr (including naps). Overall, 26% of 4 yr olds and just 15% of 5 yr olds nap.	Persistent cosleeping tends to be highly associated with sleep problems in this age-group.	Behavioral insomnia of childhood, limit-setting type
		Sleep problems may become chronic.	Sleepwalking, sleep terrors, nighttime fears/nightmares, obstructive sleep apnea syndrome
Middle childhood (6-12 yr)	Recommended sleep amount is 9-12 hr.	School and behavior problems may be related to sleep problems.	Nightmares
		Media and electronics, such as television, computer, video games, and the Internet, increasingly compete for sleep time. Irregularity of sleep–wake schedules reflects increasing discrepancy between school	Obstructive sleep apnea syndrome
			Insufficient sleep

		and non–school night bedtimes and wake times.	
Adolescence (13-18 yr)	Recommended sleep amount is 8-10 hr. Later bedtimes; increased discrepancy between sleep patterns on weekdays and weekends	Puberty-mediated phase delay (later sleep onset and wake times), relative to sleep-wake cycles in middle childhood Earlier required wake times Environmental competing priorities for sleep	Insufficient sleep Delayed sleep–wake phase disorder Narcolepsy Restless legs syndrome/periodic limb movement disorder

[*] All recommended sleep amounts from Paruthi S, Brooks LJ, D'Ambrosio C, et al: Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. *J Clin Sleep Med* 12:785–786, 2016.

Common Sleep Disorders

Childhood sleep problems may be conceptualized as resulting from (1) inadequate duration of sleep for age and sleep needs (insufficient sleep quantity); (2) disruption and fragmentation of sleep (poor sleep quality) as a result of frequent, repetitive, and brief arousals during sleep; and (3) misalignment of sleep–wake timing with circadian rhythms or CNS-mediated **hypersomnia** (excessive daytime sleepiness and increased sleep needs). Insufficient sleep is usually the result of difficulty initiating (*delayed sleep onset*) or maintaining sleep (*prolonged night wakings*), but, especially in older children and adolescents, may also represent a conscious lifestyle decision to sacrifice sleep in favor of competing priorities, such as homework and social activities. The underlying causes of delayed sleep onset/prolonged night wakings or sleep fragmentation may in turn be related to primarily behavioral factors (e.g., bedtime resistance resulting in shortened sleep duration) or medical causes (e.g., obstructive sleep apnea causing frequent, brief arousals).

Certain pediatric populations are relatively more vulnerable to acute or chronic sleep problems. These include children with medical problems, such as chronic illnesses or pain conditions (e.g., cystic fibrosis, asthma, idiopathic juvenile arthritis) and acute illnesses (e.g., otitis media); children taking stimulants s (e.g., psychostimulants, caffeine), sleep-disrupting medications (e.g., corticosteroids), or daytime-sedating medications (some anticonvulsants, α-agonists); hospitalized children; and children with a variety of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), depression, bipolar disorder, and anxiety disorders. Children with neurodevelopmental disorders such as autism, intellectual disability, blindness, and some chromosomal syndromes (e.g., Smith-Magenis, fragile X) have especially high rates of sleep disturbances for a wide variety of reasons. They may have comorbid medical issues or may be taking sleep-disrupting medications, may be more prone to nocturnal seizures, may be less easily entrained by environmental cues and thus more vulnerable to circadian disruption, and are more likely to have psychiatric and behavioral comorbidities that further predispose them to disrupted sleep.

Insomnia of Childhood

Insomnia is defined as difficulty initiating and/or maintaining sleep that occurs despite age-appropriate time and opportunity for sleep and results in some degree of impairment in daytime functioning for the child and/or family (ranging from fatigue, irritability, lack of energy, and mild cognitive impairment to effects on mood, school performance, and quality of life). Insomnia may be of a short-term and transient nature (usually related to an acute event) or may be characterized as long-term and chronic. Insomnia is a set of *symptoms* with many possible etiologies (e.g., pain, medication, medical/psychiatric conditions, learned behaviors). As with many behavioral issues in children, insomnia is often primarily defined by parental concerns rather than by objective criteria, and therefore should be viewed in the context of family (maternal depression, stress), child (temperament, developmental level), and environmental (cultural practices, sleeping space) considerations.

While current terminology (*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, 2015; *International Classification of Sleep Disorders*, 3rd edition, 2014) groups most types of insomnia in both children and adults under a single category of Chronic Insomnia Disorder, the descriptor of Behavioral Insomnia of Childhood and its subtypes (Sleep Onset Association and Limit Setting) remains a useful construct, particularly for young children (0-5 yr) in clinical practice. One of the most common presentations of insomnia found in infants and toddlers is the **sleep-onset association type.** In this situation the child learns to fall asleep only under certain conditions or associations, which typically require parental presence, such as being rocked or fed, and does not develop the ability to self-soothe. During the night, when the child experiences the type of brief arousal that normally occurs at the end of an ultradian sleep cycle or awakens for other reasons, the child is not able to get back to sleep without those same associations being present. The infant then “signals” the parent by crying (or coming into the parents' bedroom, if the child is ambulatory) until the necessary associations are provided. The presenting complaint is typically one of prolonged night waking requiring caregiver intervention and resulting in insufficient sleep (for both child and parent).

Management of **night wakings** should include establishment of a set sleep schedule and bedtime routine and implementation of a behavioral program. The treatment approach typically involves a program of rapid withdrawal (extinction) or more gradual withdrawal (graduated extinction) of parental assistance at sleep onset and during the night. **Extinction** (“cry it out”) involves putting the child to bed at a designated bedtime, “drowsy but awake,” to maximize sleep propensity and then systematically ignoring any protests by the child until a set time the next morning. Although it has considerable empirical support, extinction is often not an acceptable choice for families. **Graduated extinction** involves gradually weaning the child from dependence on parental presence; typically, the parent leaves the room at “lights out” and then returns or “checks” periodically at fixed or successively longer intervals during the sleep–wake transition to provide brief reassurance until the child falls asleep. The exact interval between checks is generally determined by the parents' tolerance for crying and the child's temperament. The goal is to allow the infant or child to develop skills in self-soothing during the night, as well as at bedtime. In older infants and young children, the introduction of more appropriate sleep associations that will be readily available to the child during the night (transitional objects, such as a blanket or toy), in addition to positive reinforcement (stickers for remaining in bed), is often beneficial. If the child has become habituated to awaken for nighttime feedings (learned hunger), these feedings should be slowly eliminated. Parents must be consistent in applying behavioral programs to avoid inadvertent, intermittent reinforcement of night wakings. They should also be forewarned that crying behavior often temporarily escalates at the beginning of treatment (*postextinction burst*).

Bedtime problems, including stalling and refusing to go to bed, are more common in preschool-age and older children. This type of insomnia is frequently related to inadequate **limit setting** and is often the result of parental difficulties in setting limits and managing behavior in general and the inability or unwillingness to set consistent bedtime rules and enforce a regular bedtime. The situation may be exacerbated by the child's oppositional behavior. In some cases the child's resistance at bedtime is the result of an underlying problem in falling asleep that is caused by other factors (medical conditions such as asthma or medication use; a sleep disorder such as restless legs syndrome; anxiety) or a mismatch between the child's intrinsic circadian rhythm (“night owl”) and parental expectations regarding an “appropriate” bedtime.

Successful treatment of limit-setting sleep problems generally involves a combination of parent education regarding appropriate limit setting, decreased parental attention for bedtime-delaying behavior, establishment of bedtime routines, and positive reinforcement (sticker charts) for appropriate behavior at bedtime. Other behavioral management strategies that have empirical support include **bedtime fading** , or temporarily setting the bedtime closer to the actual sleep-onset time and then gradually advancing the bedtime to an earlier target bedtime. Older children may benefit from being taught relaxation techniques to help themselves fall asleep more readily. Following the principles of healthy sleep practices for children is essential (Table 31.2).

Table 31.2

Basic Principles of Healthy Sleep for Children

1. **Have a set bedtime and bedtime routine** for your child.
2. **Bedtime and wake-up time should be about the same time on school nights and non–school nights.** There should not be more than about 1 hr difference from one day to another.
3. **Make the hour before bed shared quiet time.** Avoid high-energy activities, such as rough play, and stimulating activities, such as watching television or playing computer games, just before bed.
4. **Don 't send your child to bed hungry.** A *light* snack (e.g., milk and cookies) before bed is a good idea. Heavy meals within 1 hr or 2 of bedtime, however, may interfere with sleep.
5. **Avoid products containing caffeine for at least several hours before bedtime.** These include caffeinated sodas, coffee, tea, and chocolate.
6. **Make sure your child spends time outside every day,** whenever possible, and is involved in regular exercise.
7. **Keep your child** 's **bedroom quiet and dark.** A low-level night light is acceptable for children who find completely dark rooms frightening.
8. **Keep your child** 's **bedroom at a comfortable temperature** during the night (<24°C [75°F]).

9. **Don 't use your child** 's **bedroom for time-out or punishment.**
10. **Keep the television set out of your child** 's **bedroom.** Children can easily develop the bad habit of “needing” the television to fall asleep. It is also much more difficult to control your child's viewing if the set is in the bedroom.

A 3rd type of childhood insomnia is related to a mismatch between parental expectations regarding time in bed and the child's intrinsic sleep needs. If, as illustrated in Fig. 31.1 , a child's typical sleep time is 10 hr but the “sleep window” is set for 12 hr (7 PM to 7 AM), the result is likely to be a prolonged sleep onset of 2 hr, an extended period of wakefulness during the night, or early morning waking (or a combination); these periods are usually characterized by “normal” wakefulness in the child that is not accompanied by excessive distress. This situation is important to recognize because the solution—reducing the time in bed to actual sleep time—is typically simple and effective.

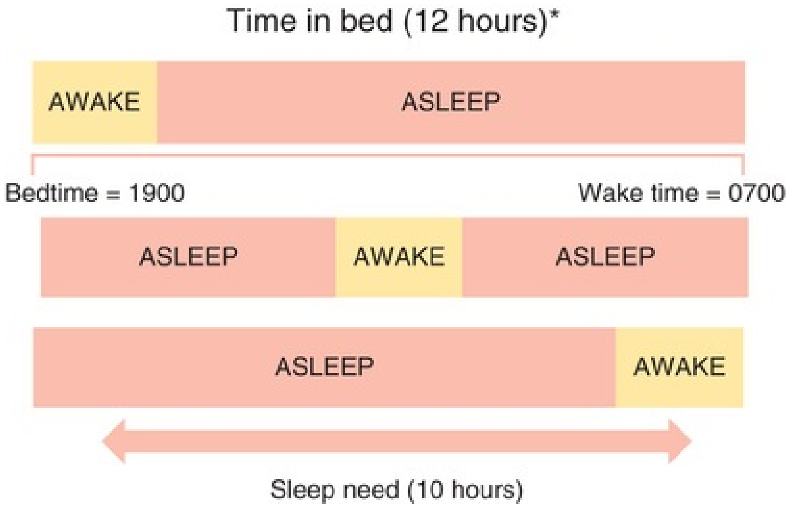

FIG. 31.1 Mismatch between sleep needs/duration and time in bed, resulting in insomnia.

Another form of insomnia that is more common in older children and adolescents is often referred to as *psychophysiologic*, *primary*, or *learned* insomnia. **Primary insomnia** occurs mainly in adolescents and is characterized by a combination of learned sleep-preventing associations and heightened physiologic arousal resulting in a complaint of sleeplessness and decreased daytime functioning. A hallmark of primary insomnia is excessive worry about sleep and an exaggerated concern of the potential daytime consequences. The physiologic arousal can be in the form of cognitive **hypervigilance** , such as “racing” thoughts; in many individuals with insomnia, an increased baseline level of arousal is further intensified by this secondary anxiety about sleeplessness. Treatment usually involves educating the adolescent about the principles of healthy sleep practices (Table 31.3), institution of a consistent sleep–wake schedule, avoidance of daytime napping, instructions to use the bed for sleep only and to get out of bed if unable to fall asleep (*stimulus control*), restricting time in bed to the actual time asleep (*sleep restriction*), addressing maladaptive cognitions about sleep, and teaching relaxation techniques to reduce anxiety.

Table 31.3

Basic Principles of Healthy Sleep for Adolescents

1. **Wake up and go to bed at about the same time** every night. Bedtime and wake-up time should not differ from school to non–school nights by more than approximately 1 hr.
2. **Avoid sleeping in on weekends** to “catch up” on sleep. This makes it more likely that you will have problems falling asleep.
3. If you take **naps** , they should be **short** (no more than 1 hr) and **scheduled in the early to mid-afternoon** . However, if you have a problem with falling asleep at night, napping during the day may make it worse and should be avoided.
4. **Spend time outside** every day. Exposure to sunlight helps to keep your body's internal clock on track.
5. **Exercise regularly.** Exercise may help you fall asleep and sleep more deeply.
6. **Use your bed for sleeping only.** Don't study, read, listen to music, or watch television on your bed.
7. **Make the 30-60 minutes before bedtime a quiet or wind-down time** . Relaxing, calm, enjoyable activities, such as reading a book or listening to calm music, help your body and mind slow down enough to let you get to sleep. Don't study, watch exciting/scary movies, exercise, or get involved in “energizing” activities just before bed.
8. Eat regular meals, and **don 't go to bed hungry** . A light snack before bed

is a good idea; eating a full meal within 1 hr before bed is not.

9. **Avoid** eating or drinking products containing **caffeine** from dinnertime to bedtime. These include caffeinated sodas, coffee, tea, and chocolate.
10. **Do not use alcohol.** Alcohol disrupts sleep and may cause you to awaken throughout the night.
11. Smoking (e.g., cigarettes) disturbs sleep. Although you should not smoke at all, if you do, **do not smoke at least 2 hr before bed** .
12. **Do not use sleeping pills, melatonin, or other nonprescription sleep aids** to help you sleep unless specifically recommended by your doctor. These can be dangerous, and the sleep problems often return when you stop taking the medicine.

Behavioral treatments for insomnia, even in young children, appear to be highly effective and well tolerated. Several studies have failed to demonstrate long-term negative effects of behavioral strategies such as “sleep training” on parent–child relationships and attachment, psychosocial-emotional functioning, and chronic stress. In general, hypnotic medications or supplements such as melatonin are infrequently needed as an adjunct to behavioral therapy to treat insomnia in typically developing and healthy children.

Obstructive Sleep Apnea Syndrome

Sleep-related breathing disorder (SRBD) in children encompasses a broad spectrum of respiratory disorders that occur exclusively in sleep or that are exacerbated by sleep, including primary snoring and upper airway resistance syndrome, as well as apnea of prematurity (see Chapter 122.2) and central apnea (see Chapter 446.2). **Obstructive sleep apnea syndrome (OSAS)** , the most important clinical entity within the SRBD spectrum, is characterized by repeated episodes of prolonged upper airway obstruction during sleep despite continued or increased respiratory effort, resulting in complete (*apnea*) or partial (*hypopnea* ; ≥30% reduction in airflow accompanied by ≥3% O_2 desaturation and/or arousal) cessation of airflow at the nose and/or mouth, as well as in disrupted sleep. Both intermittent hypoxia and the multiple arousals resulting from these obstructive events likely contribute to significant metabolic, cardiovascular, and neurocognitive-neurobehavioral morbidity.

Primary snoring is defined as snoring without associated ventilatory abnormalities on overnight polysomnogram (e.g., apneas or hypopneas, hypoxemia, hypercapnia) or respiratory-related arousals and is a manifestation of the vibrations of the oropharyngeal soft tissue walls that occur when an individual attempts to breathe against increased upper airway resistance during sleep. Although generally considered nonpathologic, primary snoring in children may still be associated with subtle breathing abnormalities during sleep, including evidence of increased respiratory effort, which in turn may be associated with adverse neurodevelopmental outcomes.

Etiology

OSAS results from an anatomically or functionally narrowed upper airway; this typically involves some combination of decreased upper airway patency (upper airway obstruction and/or decreased upper airway diameter), increased upper airway collapsibility (reduced pharyngeal muscle tone), and decreased drive to breathe in the face of reduced upper airway patency (reduced central ventilatory drive) (Table 31.4). Upper airway obstruction varies in degree and level (i.e., nose, nasopharynx/oropharynx, hypopharynx) and is most frequently caused by adenotonsillar hypertrophy, although tonsillar size does not necessarily correlate with degree of obstruction, especially in older children. Other causes of airway obstruction include allergies associated with chronic rhinitis or nasal obstruction; craniofacial abnormalities, including hypoplasia or displacement of the maxilla and mandible; gastroesophageal reflux with resulting pharyngeal reactive edema (see Chapter 349); nasal septal deviation (Chapter 404); and velopharyngeal flap cleft palate repair. Reduced upper airway tone may result from neuromuscular diseases, including hypotonic cerebral palsy and muscular dystrophies (see Chapter 627), or hypothyroidism (Chapter 581). Reduced central ventilatory drive may be present in some children with Arnold-Chiari malformation (see Chapter 446); rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (Chapter 60.1); and meningomyelocele (Chapter 609.4). In other situations the etiology is mixed; individuals with Down syndrome (see Chapter 98.2), because of their facial anatomy, hypotonia, macroglossia, and central adiposity, as well as the increased incidence of hypothyroidism, are at particularly high risk for OSAS, with some estimates of prevalence as high as 70%.

Table 31.4

Anatomic Factors That Predispose to

Obstructive Sleep Apnea Syndrome and Hypoventilation in Children

Nose

Anterior nasal stenosis
Choanal stenosis/atresia
Deviated nasal septum
Seasonal or perennial rhinitis
Nasal polyps, foreign body, hematoma, mass lesion

Nasopharyngeal and Oropharyngeal

Adenotonsillar hypertrophy
Macroglossia
Cystic hygroma
Velopharyngeal flap repair
Cleft palate repair
Pharyngeal mass lesion

Craniofacial

Micrognathia/retrognathia
Midface hypoplasia (e.g., trisomy 21, Crouzon disease, Apert syndrome)
Mandibular hypoplasia (Pierre Robin, Treacher Collins, Cornelia de Lange syndromes)
Craniofacial trauma
Skeletal and storage diseases
Achondroplasia
Storage diseases (e.g., glycogen; Hunter, Hurler syndromes)

Although many children with OSAS are of normal weight, an increasingly large percentage are overweight or obese, and many of these children are school-age or younger (see Chapter 60). There is a significant correlation between weight and SRBD (e.g., habitual snoring, OSAS, sleep-related hypoventilation).

Although adenotonsillar hypertrophy also plays an important etiologic role in overweight/obese children with OSAS, mechanical factors related to an increase in the amount of adipose tissue in the throat (pharyngeal fat pads), neck (increased neck circumference), and chest wall and abdomen can increase upper airway resistance, worsen gas exchange, and increase the work of breathing, particularly in the supine position and during REM sleep. A component of blunted central ventilatory drive in response to hypoxia/hypercapnia and hypoventilation may occur as well (see Chapter 446.3), particularly in children with morbid or syndrome-based (e.g., Prader-Willi) obesity. Overweight and obese children and adolescents are at particularly high risk for metabolic and cardiovascular complications of SRBD, such as insulin resistance and systemic hypertension. Morbidly obese children are also at increased risk for postoperative complications as well as residual OSAS after adenotonsillectomy.

Epidemiology

Overall prevalence of parent-reported snoring in the pediatric population is approximately 8%; “always” snoring is reported in 1.5–6%, and “often” snoring in 3–15%. When defined by parent-reported symptoms, the prevalence of OSAS is 4–11%. The prevalence of pediatric OSAS as documented by overnight sleep studies using ventilatory monitoring procedures (e.g., in-lab polysomnography, home studies) is 1–4% overall, with a reported range of 0.1–13%. Prevalence is also affected by the demographic characteristics such as age (increased prevalence between 2 and 8 yr), gender (more common in boys, especially after puberty), race/ethnicity (increased prevalence in African American and Asian children), history of prematurity, and family history of OSAS.

Pathogenesis

The upregulation of inflammatory pathways, as indicated by an increase in peripheral markers of inflammation (e.g., C-reactive protein, interleukins), appears to be linked to metabolic dysfunction (e.g., insulin resistance, dyslipidemia, alterations in neurohormone levels such as leptin) in both obese and nonobese children with OSAS. Systemic inflammation and arousal-mediated increases in sympathetic autonomic nervous system activity with altered vasomotor tone may be key contributors to increased cardiovascular risk due to alterations in vascular endothelium in both adults and children with OSA. Other potential mechanisms that may mediate cardiovascular sequelae in adults and children with OSA include elevated systemic blood pressure and ventricular dysfunction. Mechanical stress on the upper airway induced by chronic snoring may also result in both local mucosal inflammation of adenotonsillar tissues and subsequent upregulation of inflammatory molecules, most notably leukotrienes.

One of the primary mechanisms by which OSAS is believed to exert negative influences on cognitive function appears to involve repeated episodic arousals from sleep leading to sleep fragmentation and sleepiness. Equally important, intermittent hypoxia may lead directly to systemic inflammatory vascular changes in the brain. Levels of inflammatory markers such as C-reactive protein and interleukin-6 are elevated in children with OSAS and are also associated with cognitive dysfunction.

Clinical Manifestations

The clinical manifestations of OSAS may be divided into sleep-related and daytime symptoms. The most common nocturnal manifestations of OSAS in children and adolescents are loud, frequent, and disruptive snoring; breathing pauses; choking or gasping arousals; restless sleep; and nocturnal diaphoresis. Many children who snore do not have OSAS, but few children with OSAS do not snore (caregivers may not be aware of snoring in older children and adolescents). Children, like adults, tend to have more frequent and more severe obstructive events in REM sleep and when sleeping in the supine position. Children with OSAS may adopt unusual sleeping positions, keeping their necks hyperextended to maintain airway patency. Frequent arousals associated with obstruction may result in nocturnal awakenings but are more likely to cause fragmented sleep.

Daytime symptoms of OSAS include mouth breathing and dry mouth, chronic nasal congestion or rhinorrhea, hyponasal speech, morning headaches, difficulty swallowing, and poor appetite. Children with OSAS may have *secondary enuresis*, postulated to result from the disruption of the normal nocturnal pattern of atrial natriuretic peptide secretion by changes in intrathoracic pressure associated with OSAS. Partial arousal parasomnias (sleepwalking and sleep terrors) may occur more frequently in children with OSAS, related to the frequent associated arousals and an increased percentage of SWS.

One of the most important but frequently overlooked sequelae of OSAS in children is the effect on mood, behavior, learning, and academic functioning. The neurobehavioral consequences of OSAS in children include daytime sleepiness with drowsiness, difficulty in morning waking, and unplanned napping or dozing off during activities, although evidence of frank hypersomnolence tends to be less common in children compared to adults with OSA (except in very obese children or those with severe disease). Mood changes include increased irritability, mood instability and emotional dysregulation, low frustration tolerance, and depression or anxiety. Behavioral issues include both "internalizing" (i.e., increased somatic complaints and social withdrawal) and "externalizing" behaviors, including aggression, impulsivity, hyperactivity, oppositional behavior, and conduct problems. There is substantial overlap between the clinical impairments associated with OSAS and the diagnostic criteria for ADHD, including inattention, poor concentration, and distractibility (see Chapter 49).

Many of the studies that have looked at changes in behavior and neuropsychologic functioning in children after treatment (usually adenotonsillectomy) for OSAS have largely documented significant improvement in outcomes, both short term and long term, including daytime sleepiness, mood, behavior, academics, and quality of life. However, most studies failed to find a dose-dependent relationship between OSAS in children and specific neurobehavioral-neurocognitive deficits, suggesting that other factors may influence neurocognitive outcomes, including individual genetic susceptibility, racial/ethnic background, environmental influences (e.g., passive smoking exposure), and comorbid conditions, such as obesity, shortened sleep duration, and other sleep disorders.

Diagnosis

The 2012 revised American Academy of Pediatrics clinical practice guidelines provide excellent information for the evaluation and management of uncomplicated childhood OSAS (Table 31.5). No physical examination findings are truly pathognomonic for OSAS, and most healthy children with OSAS appear normal; however, certain physical examination findings may suggest OSAS. Growth parameters may be abnormal (obesity, or less frequently, failure to thrive), and there may be evidence of chronic nasal obstruction (hyponasal speech, mouth breathing, septal deviation, "adenoidal facies") as well as signs of atopic disease (i.e., "allergic shiners"). Oropharyngeal examination may reveal enlarged tonsils, excess soft tissue in the posterior pharynx, and a narrowed posterior pharyngeal space, as well as dental features consistent with obstruction (e.g., teeth crowding, narrow palate, short frenulum). Any abnormalities of head position, such as forward head posture, and facial structure, such as retrognathia, micrognathia, and midfacial hypoplasia, best appreciated by inspection of the lateral facial profile, increase the likelihood of OSAS and should be noted. In severe cases the child may have evidence of pulmonary hypertension, right-sided heart failure, and cor pulmonale; systemic hypertension may occur, especially in obese children.

Table 31.5

American Academy of Pediatrics Clinical Practice Guideline: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome (OSAS)

Key Action Statement 1: Screening for OSAS

As part of routine health maintenance visits, clinicians should inquire whether the child or adolescent snores. If the answer is affirmative or if a child or adolescent presents with signs or symptoms of OSAS, clinicians should perform a more focused evaluation. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)

Key Action Statement 2A: Polysomnography

If a child or adolescent snores on a regular basis and has any of the complaints or findings of OSAS, clinicians should either (1) obtain a polysomnogram (Evidence Quality: Grade A; Recommendation Strength: Recommendation) *or* (2) refer the patient to a sleep specialist or otolaryngologist for a more extensive evaluation (Evidence Quality: Grade D; Recommendation Strength: Option.)

Key Action Statement 2B: Alternative Testing

If polysomnography is not available, clinicians may order alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap polysomnography, or ambulatory polysomnography. (Evidence Quality: Grade C; Recommendation Strength: Option.)

Key Action Statement 3: Adenotonsillectomy

If a child is determined to have OSAS, has a clinical examination consistent with adenotonsillar hypertrophy, and does not have a contraindication to surgery, the clinician should recommend adenotonsillectomy as the first line of treatment. If the child has OSAS but does not have adenotonsillar hypertrophy, other treatment should be considered (see Key Action Statement 6). Clinical judgment is required to determine the benefits of adenotonsillectomy compared with other treatments in obese children with varying degrees of adenotonsillar hypertrophy. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)

Key Action Statement 4: High-Risk Patients Undergoing Adenotonsillectomy

Clinicians should monitor high-risk patients undergoing adenotonsillectomy as inpatients postoperatively. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)

Key Action Statement 5: Reevaluation

Clinicians should clinically reassess all patients with OSAS for persisting signs and symptoms after therapy to determine whether further treatment is required. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)

Key Action Statement 5B: Reevaluation of High-Risk Patients

Clinicians should reevaluate high-risk patients for persistent OSAS after adenotonsillectomy, including those who had a significantly abnormal baseline polysomnogram, have sequelae of OSAS, are obese, or remain symptomatic after treatment, with an objective test (see Key Action Statement 2), or refer such patients to a sleep specialist. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)

Key Action Statement 6: Continuous Positive Airway Pressure (CPAP)

Clinicians should refer patients for CPAP management if symptoms/signs or objective evidence of OSAS persists after adenotonsillectomy or if adenotonsillectomy is not performed. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)

Key Action Statement 7: Weight Loss

Clinicians should recommend weight loss in addition to other therapy if a child/adolescent with OSAS is overweight or obese. (Evidence Quality: Grade C; Recommendation Strength: Recommendation.)

Key Action Statement 8: Intranasal Corticosteroids

Clinicians may prescribe topical intranasal corticosteroids for children with mild OSAS in whom adenotonsillectomy is contraindicated or for children with mild postoperative OSAS. (Evidence Quality: Grade B; Recommendation Strength: Option.)

Adapted from Marcus CL, Brooks LJ, Draper KA, et al: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 130:576–584, 2012.

Because no combination of clinical history and physical findings can accurately predict which children with snoring have OSAS, the gold standard for diagnosing OSAS remains an in-lab overnight **polysomnogram (PSG)** . Overnight PSG is a technician-supervised, monitored study that documents physiologic variables during sleep; sleep staging, arousal measurement, cardiovascular parameters, and body movements (electroencephalography, electrooculography, chin and leg electromyography, electrocardiogram, body position sensors, and video recording), and a combination of breathing monitors (oronasal thermal sensor and nasal air pressure transducer for airflow), chest/abdominal monitors (e.g., inductance plethysmography for respiratory effort, pulse oximeter for O_2 saturation, end-tidal or transcutaneous CO_2 for CO_2 retention, snore microphone). The PSG parameter most often used in evaluating for sleep-disordered breathing is the **apnea-hypopnea index (AHI)** , which indicates the number of apneic and hypopneic (both obstructive and central) events per hour of sleep. Currently, there are no universally accepted PSG normal reference values or parameters for diagnosing OSAS in children, and it is still unclear which parameters best predict morbidity. Normal preschool and school-age children generally have a total AHI <1.5 (obstructive AHI <1), and this is the most widely used cutoff value for OSA in children ≤12 yr old; in older adolescents the adult cutoff of an AHI ≥5 is generally used. When AHI is between 1 and 5 obstructive events per hour, assessment of additional PSG parameters (e.g., elevated CO_2 indicating obstructive hypoventilation, O_2 desaturation, respiratory-related arousals), clinical judgment regarding risk factors for SRBD, presence and severity of clinical symptoms, and evidence of daytime sequelae should determine further management.

Treatment

At present, no universally accepted guidelines exist regarding the indications for treatment of pediatric SRBD, including primary snoring and OSAS. Current recommendations largely emphasize weighing what is known about the potential cardiovascular, metabolic, and neurocognitive sequelae of SRBD in children in combination with the individual healthcare professional's clinical judgment. The decision of whether and how to treat OSAS specifically in children depends on several parameters, including severity (nocturnal symptoms, daytime sequelae, sleep study results), duration of disease, and individual patient variables such as age, comorbid conditions, and underlying etiologic factors. In the case of moderate (AHI 5-10) to severe (AHI >10) disease, the decision to treat is usually straightforward, and most pediatric sleep experts recommend that any child with AHI >5 should be treated. However, a large randomized trial of early adenotonsillectomy vs watchful waiting with supportive care demonstrated that 46% of the control group children normalized on PSG (vs 79% of early adenotonsillectomy group) during the 7 mo observation period.

In the majority of cases of pediatric OSAS, adenotonsillectomy is the first-line treatment in any child with significant adenotonsillar hypertrophy, even in the presence of additional risk factors such as obesity. Adenotonsillectomy in uncomplicated cases generally (70–90% of children) results in complete resolution of symptoms; regrowth of adenoidal tissue after surgical removal occurs in some cases. Groups considered at high risk include young children (<3 yr) as well as those with severe OSAS documented by PSG, significant clinical sequelae of OSAS (e.g., failure to thrive), or associated medical conditions, such as craniofacial syndromes, morbid obesity, and hypotonia. All patients should be reevaluated postoperatively to determine whether additional evaluation, a repeat PSG, and treatment are required. The American Academy of Sleep Medicine recommends that in high-risk groups (children with obesity, craniofacial anomalies, Down syndrome, or moderate-severe OSAS) or in children with continued symptoms of OSAS, a follow-up sleep study about 6 wk after adenotonsillectomy is indicated. Also, a number of studies have suggested that children who are underweight, normal weight, or overweight/obese at baseline all tend to *gain weight* after AT, and thus clinical vigilance is required during follow-up.

Additional treatment measures that may be appropriate include weight loss, **positional therapy** (attaching a firm object, such as a tennis ball, to the back of a sleep garment to prevent the child from sleeping in the supine position) and aggressive treatment of additional risk factors when present, such as asthma, seasonal allergies, and gastroesophageal reflux. Evidence suggests that intranasal corticosteroids and leukotriene inhibitors may be helpful in reducing upper airway inflammation in mild OSAS. Other surgical procedures (e.g., uvulopharyngopalatoplasty) and maxillofacial surgery (e.g., mandibular distraction osteogenesis) are seldom performed in children. Oral appliances, such as mandibular advancing devices and palatal expanders, may be considered in select cases; consultation with a pediatric dentist or orthodontist is recommended. Neuromuscular reeducation or repatterning of the oral and facial muscles with exercises to address abnormal tongue position and low upper airway tone (i.e., **myofunctional therapy**) have been shown to be beneficial in addressing pediatric OSAS as well as alleviating chewing and swallowing problems in children able to cooperate with the behavioral program.

Continuous or **bilevel positive airway pressure (CPAP** or **BiPAP)** is the most common treatment for OSAS in adults and can be used successfully in children and adolescents. Positive airway pressure (PAP) may be recommended if removing the adenoids and tonsils is not indicated, if there is residual disease following adenotonsillectomy, or if there are major risk factors not amenable to surgery (obesity, hypotonia). PAP delivers humidified, warmed air through an interface (mask, nasal pillows) that, under pressure, effectively “splints” the upper airway open. Optimal pressure settings (that abolish or significantly reduce respiratory events without increasing arousals or central apneas) are determined in the sleep lab during a full-night PAP titration. Careful attention should be paid to education of the child and family, and desensitization protocols should usually be implemented to increase the likelihood of adherence. Efficacy studies at the current pressure and retitrations should be conducted periodically with long-term use (at least annually) or in association with significant weight changes or resurgence of SRBD symptoms.

Parasomnias

Parasomnias are episodic nocturnal behaviors that often involve cognitive disorientation and autonomic and skeletal muscle disturbance. Parasomnias may be further characterized as occurring primarily during non-REM sleep (partial arousal parasomnias) or in association with REM sleep, including nightmares, hypnogogic hallucinations, and sleep paralysis; other common parasomnias include sleep-talking and hypnic jerks or “sleep starts.”

Etiology

Partial arousal parasomnias represent a dissociated sleep–wake state, the neurobiology of which remains unclear, although genetic factors and an intrinsic oscillation of subcortical-cortical arousal with sleep have been proposed. These episodic events, which include sleepwalking, sleep terrors, and confusional arousals, are more common in preschool and school-age children because of the relatively higher percentage of SWS in younger children. Partial arousal parasomnias typically occur when SWS predominates, in the 1st third of the night. In contrast, **nightmares** , which are much more common than partial arousal parasomnias but are often confused with them, tend to be concentrated in the last third of the night, when REM sleep is most prominent. Any factor associated with an increase in the relative percentage of SWS (certain medications, previous sleep restriction) may increase the frequency of events in a predisposed child. There appears to be a genetic predisposition for both sleepwalking and night terrors. Partial arousal parasomnias may also be difficult to distinguish from nocturnal seizures. Table 31.6 summarizes similarities and differences among these nocturnal arousal events.

Table 31.6

Key Similarities and Differentiating Features Between Non-REM and REM Parasomnias as Well as Nocturnal Seizures

	CONFUSIONAL AROUSALS	SLEEP TERRORS	SLEEPWALKING	NIGHTMARES	NOCTURNAL SEIZURES
Time	Early	Early	Early-mid	Late	Any
Sleep stage	SWA	SWA	SWA	REM	Any
EEG discharges	−	−	−	−	+
Scream	−	++++	−	++	+
Autonomic activation	+	++++	+	+	+
Motor activity	−	+	+++	+	++++
Awakens	−	−	−	+	+
Duration (min)	0.5-10; more gradual offset	1-10; more gradual offset	2-30; more gradual offset	3-20	5-15; abrupt onset and offset
Postevent confusion	+	+	+	−	+
Age	Child	Child	Child	Child, young adult	Adolescent, young adult
Genetics	+	+	+	−	±
Organic CNS lesion	−	−	−	−	++++

CNS, Central nervous system; EEG, electroencephalogram; REM, rapid eye movement; SWA, slow-wave arousal.

From Avidan A, Kaplish N: The parasomnias: epidemiology, clinical features and diagnostic approach. *Clin Chest Med* 31:353–370, 2010.

Epidemiology

Many children sleepwalk on at least one occasion; the lifetime prevalence by age 10 yr is 13%. **Sleepwalking** (somnambulism) may persist into adulthood, with the prevalence in adults of approximately 4%. The prevalence is approximately 10 times greater in children with a family history of sleepwalking. The peak prevalence of **sleep terrors** is 34% at age 1-5 yr, decreasing to 10% by age 7; the age at onset is usually between 4 and 12 yr. Because of the common genetic predisposition, the likelihood of developing sleepwalking after age 5 is almost 2-fold higher in children with a history of sleep terrors. Although sleep terrors can occur at any age from infancy through adulthood, most individuals outgrow sleep terrors by adolescence. **Confusional arousals** (sleep drunkenness, sleep inertia) usually occur with sleepwalking and sleep terrors; prevalence rates have been estimated at >15% in children age 3-13 yr.

Clinical Manifestations

The partial arousal parasomnias have several features in common. Because they typically occur at the transition out of “deep” sleep or SWS, partial arousal parasomnias have clinical features of both the *awake* (ambulation, vocalizations) and the *sleeping* (high arousal threshold, unresponsiveness to environment) states, usually with amnesia for the events. External (noise) or internal (obstruction) factors may trigger events in some individuals. The duration is typically a few minutes (sleep terrors) up to 30-40 min (confusional arousals). Sleep terrors are sudden in onset and characteristically involve a high degree of autonomic arousal (tachycardia, dilated pupils). Confusional arousals typically arise more gradually from sleep, may involve thrashing around but usually not displacement from bed, and are often accompanied by slow mentation, disorientation, and confusion on forced arousal from SWS or on waking in the morning. Sleepwalking may be associated with safety concerns (e.g., falling out of windows, wandering outside). The child's avoidance of, or increased agitation with, comforting by parents or attempts at awakening is also common to all partial arousal parasomnias.

Treatment

Management of partial arousal parasomnias involves some combination of parental education and reassurance, healthy sleep practices, and avoidance of exacerbating factors such as sleep restriction and caffeine. Particularly in the case of sleepwalking, it is important to institute safety precautions such as use of gates in doorways and at the top of staircases, locking of outside doors and windows, and installation of parent notification systems such as bedroom door alarms. **Scheduled awakenings** is a behavioral intervention that involves having the parent wake the child 15-30 min before the time of night that the 1st parasomnia episode occurs and is most likely to be successful in situations where partial arousal episodes occur on a nightly basis. Pharmacotherapy is rarely necessary but may be indicated in cases of frequent or severe episodes, high risk of injury, violent behavior, or serious disruption to the family. The primary pharmacologic agents used are potent SWS suppressants, primarily benzodiazepines and tricyclic antidepressants.

Sleep-Related Movement Disorders: Restless Legs Syndrome/Periodic Limb Movement Disorder and Rhythmic Movements

Restless legs syndrome (**RLS**), also termed *Willis-Ekbom disease* , is a chronic neurologic disorder characterized by an almost irresistible urge to move the legs, often accompanied by uncomfortable sensations in the lower extremities. Both the urge to move and the sensations are usually worse at rest and in the evening and are at least partially relieved by movement, including walking, stretching, and rubbing, but only if the motion continues. RLS is a clinical diagnosis that is based on the presence of these key symptoms (Table 31.7).

Table 31.7

Diagnostic Criteria for Restless Legs Syndrome

A. An urge to move legs, usually accompanied by or in response to uncomfortable and unpleasant sensations in the legs, characterized by the following:
    1. The urge to move the legs begins or worsens during periods of rest or inactivity.
    2. The urge to move the legs is partially or totally relieved by movement.
    3. The urge to move the legs is worse in the evening or at night than during the day, or occurs only in the evening or at night.

B. The symptoms in Criterion A occur at least three times per week and have persisted for at least 3 months.

C. The symptoms in Criterion A are accompanied by significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning.

D. The symptoms in Criterion A are not attributable to another mental disorder or medical condition (e.g., arthritis, leg edema, peripheral ischemia, leg cramps) and are not better explained by a behavioral condition (e.g., positional discomfort, habitual foot tapping).

E. The symptoms are not attributable to the physiological effects of a drug or abuse or medication (e.g., akathisia).

From American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed, 2013, p 410.

Periodic limb movement disorder (**PLMD**) is characterized by periodic, repetitive, brief (0.5-10 sec), and highly stereotyped limb jerks typically occurring at 20-40 sec intervals. These movements occur primarily during sleep, usually occur in the legs, and frequently consist of rhythmic extension of the big toe and dorsiflexion at the ankle. The diagnosis of **periodic limb movements (PLMs)** requires overnight PSG to document the characteristic limb movements with anterior tibialis electromyography leads.

Etiology

“Early-onset” RLS (onset of symptoms before 35-40 yr of age), often termed *primary* RLS, appears to have a particularly strong genetic component, with a 6-7–fold increase in prevalence in first-degree relatives of RLS patients. The mode of inheritance is complex, and several genetic loci have been identified (*MEIS1*, *BTBD9*, *MAP2K5*). Low serum iron levels (even without anemia) in both adults and children may be an important etiologic factor for the presence and severity of both RLS symptoms and PLMs. As a marker of decreased iron stores, serum ferritin levels in both children and adults with RLS are frequently low; (<50 µg/mL). The postulated underlying mechanism is related to the role of iron as a cofactor in tyrosine hydroxylation, a rate-limiting step in dopamine synthesis; in turn, dopaminergic dysfunction has been implicated, particularly in the genesis of the sensory component of RLS, as well as in PLMD. Certain medical conditions, including diabetes mellitus, end-stage renal disease, cancer, idiopathic juvenile arthritis, hypothyroidism, and pregnancy, may also be associated with RLS/PLMD, as are specific medications (e.g., antihistamines such as diphenhydramine, antidepressants, H_2 blockers such as cimetidine) and substances (notably, caffeine).

Epidemiology

Previous studies found prevalence rates of RLS in the pediatric population ranging from 1–6%; approximately 2% of 8-17 yr olds meet the criteria for “definite” RLS. Prevalence rates of PLMs >5 per hour in clinical populations of children referred for sleep studies range from 5–27%; in survey studies of PLM symptoms, rates are 8–12%. About 40% of adults with RLS have symptoms before age 20 yr; 20% report symptoms before age 10. Familial cases usually have a younger age of onset. Several studies in referral populations have found that PLMs occur in as many as 25% of children diagnosed with ADHD.

Clinical Manifestations

In addition to the urge to move the legs and the sensory component (paresthesia-like, tingling, burning, itching, crawling), most RLS episodes are initiated or exacerbated by rest or inactivity, such as lying in bed to fall asleep or riding in a car for prolonged periods. A unique feature of RLS is that the timing of symptoms also appears to have a circadian component, in that they often peak in the evening hours. Some children may complain of “growing pains,” although this is considered a nonspecific feature. Because RLS symptoms are usually worse in the evening, bedtime struggles and difficulty falling asleep are two of the most common presenting complaints. In contrast to patients with RLS, individuals with PLMs are usually unaware of these movements, but children may complain of morning muscle pain or fatigue; these movements may result in arousals during sleep and consequent significant sleep disruption. Parents of children with RLS/PLMD may report that their child is a restless sleeper, moves around, or even falls out of bed during the night.

The differential diagnosis includes growing pains, leg cramps, neuropathy, arthritis, myalgias, nerve compression (“leg fell asleep”), and dopamine antagonist–associated akathisia.

Treatment

The decision of whether and how to treat RLS depends on the level of severity (intensity, frequency, and periodicity) of sensory symptoms, the degree of interference with sleep, and the impact of daytime sequelae in a particular child or adolescent. With PLMs, for an index (PLMs/hr) <5, usually no treatment is recommended; for an index >5, the decision to specifically treat PLMs should be based on the presence or absence of nocturnal symptoms (restless or nonrestorative sleep) and daytime clinical sequelae.

The acronym **AIMS** represents a comprehensive approach to the treatment of RLS: **avoidance** of exacerbating factors, such as caffeine and drugs, that increase symptoms; **iron** supplementation when appropriate; **muscle** activity, with increased physical activity, muscle relaxation, and application of heat/cold compresses; and **sleep,** with a regular sleep schedule and sufficient sleep for age. Iron supplements should be instituted if serum ferritin levels are <50 µg/L; it should be kept in mind that ferritin is an acute-phase reactant and thus may be falsely elevated (i.e., normal) in the setting of a concomitant illness. The recommended dose of oral ferrous sulfate is typically 3-6 mg/kg/day for 3 mo. If there is no response to oral iron, intravenous iron compounds may be needed. Medications that increase dopamine levels in the CNS, such as ropinirole and pramipexole, are effective in relieving RLS/PLMD symptoms in adults; data in children are extremely limited. Dopaminergic therapy may lead to a loss of therapeutic response. Some recommend gabapentin enacarbil or other related alpha-2 delta ligands that bind to the alpha-2 delta subunit of the voltage-activated calcium channel.

Sleep-related rhythmic movements , including head banging, body rocking, and head rolling, are characterized by repetitive, stereotyped, and rhythmic movements or behaviors that involve large muscle groups. These behaviors typically occur with the transition to sleep at bedtime, but also at nap times and after nighttime arousals. Children typically engage in these behaviors as a means of soothing themselves to (or back to) sleep; these are much more common in the 1st yr of life and usually disappear by preschool age. In most cases, rhythmic movement behaviors are benign, because sleep is not significantly disrupted, and associated significant injury is rare. These behaviors typically occur in normally developing children and in the majority of cases do not indicate some underlying neurologic or psychologic problem. Usually, the most important aspect in management of sleep-related rhythmic movements is reassurance to the family that this behavior is normal, common, benign, and self-limited.

Narcolepsy

Hypersomnia is a clinical term that is used to describe a group of disorders characterized by recurrent episodes of **excessive daytime sleepiness (EDS)** , reduced baseline alertness, and/or prolonged nighttime sleep periods that interfere with normal daily functioning (Table 31.8). The many potential causes of EDS can be broadly grouped as “extrinsic” (e.g., secondary to insufficient and/or fragmented sleep) or “intrinsic” (e.g., resulting from an increased need for sleep). **Narcolepsy** is a chronic, lifelong CNS disorder, typically presenting in adolescence and early adulthood, characterized by profound daytime sleepiness resulting in significant functional impairment. More than half of patients with narcolepsy also present with **cataplexy** (type 1), defined as the sudden, brief, partial or complete loss of skeletal muscle tone, typically triggered by strong emotion (e.g., laughter, surprise, anger), with retained consciousness. Other symptoms frequently associated with narcolepsy, including hypnogogic/hypnopompic (immediately before falling asleep/awakening) typically visual hallucinations and sleep paralysis, may be conceptualized as representing the “intrusion” of REM sleep features into the waking state. Other REM-related features include observance of eye movements and twitches at sleep onset and vivid dreams. Rapid weight gain, especially near symptom onset, is frequently observed, and young children with narcolepsy have been reported to develop precocious puberty.

Table 31.8

Diagnostic Criteria for Narcolepsy

A. Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring at least three times per week over the past 3 months.

B. The presence of at least one of the following:

1. Episodes of cataplexy, defined as either (a) or (b), occurring at least a few time per month:
    a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.
    b. In children or individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.
2. Hypocretin deficiency, as measured using cerebrospinal fluid (CSF) hypocretin-1 immunoreactivity values (less than or equal to one-third of values obtained in healthy subjects tested using the same assay, or less than or equal to 110 pg/mL). Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.
3. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency less than or equal to 15 minutes, or a multiple sleep latency test showing a mean sleep latency less than or equal to 8 minutes and two or more sleep-onset REM periods.

Specify whether:

Narcolepsy without cataplexy but with hypocretin deficiency: Criterion B requirements of low CSF hypocretin-1 levels and positive polysomnography/multiple sleep latency test are met, but no cataplexy is present (Criterion B1 not met).

Narcolepsy with cataplexy but without hypocretin deficiency: In this rare sub-type (less than 5% of narcolepsy cases), Criterion B requirements of cataplexy and positive polysomnography/multiple sleep latency test are met, but CSF hypocretin-1 levels are normal (Criterion B2 not met).

Autosomal dominant cerebellar ataxia, deafness, and narcolepsy: This sub-type is caused by exon 21 DNA (cytosine-5)-methyltransferase-1 mutations and is characterized by late-onset (age 30-40 years) narcolepsy (with low or intermediate CSF hypocretin-1 levels), deafness, cerebellar ataxia, and eventually dementia.

Autosomal dominant narcolepsy, obesity, and type 2 diabetes: Narcolepsy, obesity, and type 2 diabetes are low CSF hypocretin-1 levels have been described in rare cases and are associated with a mutation in the myelin oligodendrocyte glycoprotein gene.

Narcolepsy without cataplexy but with hypocretin deficiency: This sub-type is for narcolepsy that develops secondary to medical conditions that cause infectious (e.g., Whipple's disease, sarcoidosis), traumatic, or tumoral destruction of hypocretin neurons.

Severity:

Mild: Infrequent cataplexy (less than once per week), need for naps only once or twice per day, and less disturbed nocturnal sleep.

Moderate: Cataplexy once daily or every few days, disturbed nocturnal sleep and need for multiple naps daily.

Severe: Drug-resistant cataplexy with multiple attacks daily, nearly constant sleepiness, and disturbed nocturnal sleep (i.e., movements, insomnia, and vivid dreaming).

From American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed, 2013, pp 372–373.

Etiology

The genesis of narcolepsy with cataplexy (type 1) is thought to be related to a specific deficit in the hypothalamic orexin/hypocretin neurotransmitter system involving the selective loss of cells that secrete hypocretin/orexin in the lateral hypothalamus. *Hypocretin* neurons stimulate a range of wake-promoting neurons in the brainstem, hypothalamus, and cortex and basal forebrain that produce neurochemicals to sustain the wake state and prevent lapses into sleep.

The development of narcolepsy most likely involves autoimmune mechanisms, possibly triggered by streptococcal, influenza virus, H1N1, and other viral infections, likely in combination with a genetic predisposition and environmental factors. A 12-13–fold increase in narcolepsy type 1 cases, especially in children, was reported in parts of Europe in 2009–2010 following immunization with the AS03 adjuvanted H1N1 influenza vaccine. Human leukocyte antigen testing also shows a strong association with narcolepsy; the majority of individuals with this antigen do not have narcolepsy, but most (>90%) patients with narcolepsy with cataplexy are HLA-DQB1*0602–positive. Patients with narcolepsy without cataplexy (type 2) are increasingly thought to have a significantly different pathophysiology; they are much less likely to be HLA-DQB1*0602–positive (4–50%), and cerebrospinal fluid (CSF) hypocretin levels are normal in most patients.

Although the majority of cases of narcolepsy are considered idiopathic (autoimmune), secondary narcolepsy can be caused by lesions to the posterior hypothalamus induced by traumatic brain injury, tumor, stroke, and neuroinflammatory processes such as post-streptococcal PANDAS (see Chapter 210), as well as by neurogenetic diseases such as Prader-Willi syndrome (Chapter 98.8), Niemann-Pick type C (Chapter 104.4), myotonic dystrophy (Chapter 627.6), and Norrie disease.

Epidemiology

Narcolepsy is a rare disorder with a prevalence of approximately 0.025–0.05%. The risk of developing narcolepsy with cataplexy in a first-degree relative of a narcoleptic patient is estimated at 1–2%. This represents an increase of 10-40–fold compared to the general population, but the risk remains very low, reinforcing the likely role for other etiologic factors.

Clinical Manifestations and Diagnosis

The typical onset of symptoms of narcolepsy is in adolescence and early adulthood, although symptoms may initially present in school-age and even younger children. The early manifestations of narcolepsy are often ignored, misinterpreted, or misdiagnosed as other medical, neurologic, or psychiatric conditions, and the appropriate diagnosis is frequently delayed for years. The onset may be abrupt or slowly progressive.

The most prominent clinical manifestation of narcolepsy is profound daytime sleepiness, characterized by both an increased baseline level of daytime drowsiness and the repeated occurrence of sudden and unpredictable sleep episodes. These "sleep attacks" are often described as "irresistible," in that the child or adolescent is unable to stay awake despite considerable effort, and occur even in the context of normally stimulating activities (e.g., during meals, in conversation). Very brief (several seconds) sleep attacks may also occur in which the individual may "stare off," appear unresponsive, or continue to engage in an ongoing activity (*automatic behavior*). EDS may also be manifested by increased nighttime sleep needs and extreme difficulty waking in the morning or after a nap.

Cataplexy is considered virtually pathognomonic for narcolepsy but can develop several years after the onset of EDS. Manifestations are triggered by strong positive (laughing, joy) or negative (fright, anger, frustration) emotions and predominantly include facial slackening, head nodding, jaw dropping, and less often, knees buckling or complete collapse with falling to the ground. The cataplectic attacks are typically brief (seconds to minutes), the patient is awake and aware, and episodes are fully reversible, with complete recovery of normal tone when the episode ends. A form of cataplexy unique to children known as **cataplectic facies** is characterized by prolonged tongue protrusion, ptosis, slack jaw, slurred speech, grimacing, and gait instability. Additionally, children may have positive motor phenomenon similar to dyskinesias or motor tics, with repetitive grimacing and tongue thrusting. The cataplectic attacks are typically brief (seconds to minutes) but in children may last for hours or days (**status cataplecticus**).

Hypnogogic/hypnopompic hallucinations usually involve vivid visual but also auditory and sometimes tactile sensory experiences during transitions between sleep and wakefulness, either at sleep offset (hypnopompic) or sleep onset (hypnogogic). **Sleep paralysis** is the inability to move or speak for a few seconds or minutes at sleep onset or offset and often accompanies the hallucinations. Other symptoms associated with narcolepsy include disrupted nocturnal sleep, impaired cognition, inattention and ADHD-like symptoms, and behavioral and mood dysregulation.

Several pediatric screening questionnaires for EDS, including the modified Epworth Sleepiness Scale, help to guide the need for further evaluation in clinical practice when faced with the presenting complaint of daytime sleepiness. Physical examination should include a detailed neurologic assessment. Overnight PSG and a multiple sleep latency test (MSLT) are strongly recommended components in the evaluation of a patient with profound unexplained daytime sleepiness or suspected narcolepsy. The purpose of the overnight PSG is to evaluate for primary sleep disorders (e.g., OSAS) that may cause EDS. The MSLT involves a series of 5 opportunities to nap (20 min long), during which patients with narcolepsy demonstrate a pathologically shortened mean sleep-onset latency (≤8 min, typically <5 min) as well as at least 2 periods of REM sleep occurring immediately after sleep onset. Alternatively, a diagnosis can be made by findings of low CSF hypocretin-1 concentration (typically ≤110 pg/mL) with a standardized assay.

Treatment

An individualized narcolepsy treatment plan usually involves education, good sleep hygiene, behavioral changes, and medication. Scheduled naps during the day are often helpful. Wake-promoting medications such as modafinil or armodafinil may be prescribed to control the EDS, although these are not approved for use in children by the U.S. Food and Drug Administration (FDA), and potential side effects include rare reports of Stevens-Johnson syndrome and reduced efficacy of hormone-based contraceptives. Psychostimulants are approved for ADHD in children and can be used for EDS; side effects include appetite suppression, mood lability, and cardiovascular effects. Antidepressants (serotonin reuptake inhibitors, venlafaxine) may be used to reduce cataplexy. Sodium oxybate, also not currently FDA-approved for use in children, is a unique drug that appears to have a positive impact on daytime sleepiness, cataplexy, and nocturnal sleep disruption; reported side effects include dizziness, weight loss, enuresis, exacerbation of OSAS, depression, and risk of respiratory depression, especially when combined with CNS depressants, including alcohol. Pitolisant, a histamine (H_3) receptor agonist, has been shown to improve cataplexy and EDS in adult patients with narcolepsy. The goal for the child should be to allow the fullest possible return of normal functioning in school, at home, and in social situations.

Delayed Sleep–Wake Phase Disorder

Delayed sleep–wake phase disorder (**DSWPD**), a circadian rhythm disorder, involves a significant, persistent, and intractable phase shift in sleep–wake schedule (later sleep onset and wake time) that conflicts with the individual's normal school, work, and lifestyle demands. DSWPD may occur at any age but is most common in adolescents and young adults.

Etiology

Individuals with DSPD may start out as “night owls”; that is, they have an underlying predisposition or circadian “eveningness” preference for staying up late at night and sleeping late in the morning, especially on weekends, holidays, and summer vacations. The underlying pathophysiology of DSWPD is still unknown, although some theorize that it involves an intrinsic abnormality in the circadian oscillators that govern the timing of the sleep period.

Epidemiology

Studies indicate that the prevalence of DSWPD may be as high as 7–16% in adolescents and young adults.

Clinical Manifestations

The most common clinical presentation is sleep-initiation insomnia when the individual attempts to fall asleep at a “socially acceptable” desired bedtime and experiences very delayed sleep onset (often after 1-2 AM), accompanied by daytime sleepiness. Patients may have extreme difficulty arising in the morning even for desired activities, with pronounced confusion on waking (*sleep inertia*). Sleep maintenance is generally not problematic, and no sleep-onset insomnia is experienced if bedtime coincides with the preferred sleep-onset time (e.g., on weekends, school vacations). School tardiness and frequent absenteeism with a decline in academic performance often occur. Patients may also develop “secondary” psychophysiologic insomnia as a result of spending prolonged time in bed attempting to fall asleep at bedtime.

Treatment

The treatment of DSWPD usually has three components, all directed toward the goals of shifting the sleep–wake schedule to an earlier, more desirable time and maintaining the new schedule. The initial step involves shifting the sleep–wake schedule to the desired earlier times, usually with gradual (i.e., in 15-30 min increments every few days) advancement of bedtime in the evening and rise time in the morning. More significant phase delays (i.e., larger difference between current sleep onset and desired bedtime) may require *chronotherapy,* which involves delaying bedtime and wake time by 2-3 hr every 24 hr “forward around the clock” until the target bedtime is reached. Because melatonin secretion is highly sensitive to light, exposure to light in the morning (either natural light or a “light box,” which typically produces light at around 10,000 lux) and avoidance of evening light exposure (especially from screens emitting predominantly blue light, such as computers and laptops) are often beneficial. Exogenous oral melatonin supplementation may also be used; larger, mildly sedating doses (5 mg) are typically given at bedtime, but some studies have suggested that physiologic doses of oral melatonin (0.3-0.5 mg) administered in the afternoon or early evening (5-7 hr before the habitual sleep-onset time) may be more effective in advancing the sleep phase.

Health Supervision

It is especially important for pediatricians to screen for and recognize sleep disorders in children and adolescents during healthcare encounters. The well-child visit is an opportunity to educate parents about normal sleep in children and to teach strategies to prevent sleep problems from developing (primary prevention) or becoming chronic, if problems already exist (secondary prevention). Developmentally appropriate screening for sleep disturbances should take place in the context of every well-child visit and should include a range of potential sleep problems; Table 31.9 outlines a simple sleep screening algorithm, the “BEARS.” Because parents may not always be aware of sleep problems, especially in older children and adolescents, it is also important to question the child directly about sleep concerns. The recognition and evaluation of sleep problems in children require both an understanding of the association between sleep disturbances and daytime consequences (e.g., irritability, inattention, poor impulse control) and familiarity with the developmentally appropriate differential diagnoses of common presenting sleep complaints (difficulty initiating and maintaining sleep, episodic nocturnal events). An assessment of sleep patterns and possible sleep problems should be part of the initial evaluation of every child presenting with behavioral or academic problems, especially ADHD.

Table 31.9

BEARS Sleep Screening Algorithm

The BEARS instrument is divided into 5 major sleep domains, providing a comprehensive screen for the major sleep disorders affecting children 2-18 yr old. Each sleep domain has a set of age-appropriate “trigger questions” for use in the clinical interview.

B = Bedtime problems
E = Excessive daytime sleepiness
A = Awakenings during the night
R = Regularity and duration of sleep
S = Snoring

	EXAMPLES OF DEVELOPMENTALLY APPROPRIATE TRIGGER QUESTIONS		
	Toddler/Preschool Child (2-5 yr)	**School-Age Child (6-12 yr)**	**Adolescent (13-18 yr)**
1. Bedtime problems	Does your child have any problems going to bed? Falling asleep?	Does your child have any problems at bedtime? (P) Do you any problems going to bed? (C)	Do you have any problems falling asleep at bedtime? (C)
2. Excessive daytime sleepiness	Does your child seem overtired or sleepy a lot during the day? Does your child still take naps?	Does your child have difficulty waking in the morning, seem sleepy during the day, or take naps? (P) Do you feel tired a lot? (C)	Do you feel sleepy a lot during the day? In school? While driving? (C)
3. Awakenings during the night	Does your child wake up a lot at night?	Does your child seem to wake up a lot at night? Any sleepwalking or nightmares? (P) Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)	Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)
4. Regularity and duration of sleep	Does your child have a regular bedtime and wake time? What are they?	What time does your child go to bed and get up on school days? Weekends? Do you think your child is getting enough sleep? (P)	What time do you usually go to bed on school nights? Weekends? How much sleep do you usually get? (C)
5. Snoring	Does your child snore a lot or have difficulty breathing at night?	Does your child have loud or nightly snoring or any breathing difficulties at night? (P)	Does your teenager snore loudly or nightly? (P)

C, Child; P, parent.

Effective preventive measures include educating parents of newborns about normal sleep amounts and patterns. The ability to regulate sleep, or control internal states of arousal to fall asleep at bedtime and to fall back asleep during the night, begins to develop in the 1st 8-12 wk of life. Thus it is important to recommend that parents put their 2-4 mo old infants to bed “drowsy but awake” if they want to avoid dependence on parental presence at sleep onset and foster the infant's ability to self-soothe. Other important sleep issues include discussing the importance of regular bedtimes, bedtime routines, and transitional objects for toddlers, and providing parents and children with basic information about healthy sleep practices, recommended sleep amounts at different ages, and signs that a child is not getting sufficient sleep (wakes with difficulty at required time in morning, sleeps longer given opportunity on weekends and vacation days).

The cultural and family context within which sleep problems in children occur should be considered. For example, bed-sharing of infants and parents is a common and accepted practice in many racial/ethnic groups, and these families may not share the goal of independent self-soothing in young infants. *Anticipatory guidance* needs to balance cultural awareness with the critical importance of "safe sleep" conditions in sudden infant death syndrome prevention (i.e., sleeping in the supine position, avoidance of bed-sharing but encouragement of room-sharing in the 1st yr of life) (see Chapter 402). On the other hand, the institution of cosleeping by parents as an attempt to address a child's underlying sleep problem (so-called reactive cosleeping), rather than as a conscious family decision, is likely to yield only a temporary respite from the problem and may set the stage for more significant sleep issues.

Evaluation of Pediatric Sleep Problems

The clinical evaluation of a child presenting with a sleep problem involves obtaining a careful medical history to assess for potential medical causes of sleep disturbances, such as allergies, concomitant medications, and acute or chronic pain conditions. A developmental history is important because of the increased risk of sleep problems in children with neurodevelopmental disorders. Assessment of the child's current level of functioning (school, home) is a key part of evaluating possible mood, behavioral, and neurocognitive sequelae of sleep problems. Current sleep patterns, including the usual sleep duration and sleep–wake schedule, are often best assessed with a **sleep diary,** in which a parent (or adolescent) records daily sleep behaviors for an extended period (1-2 wk). A review of sleep habits, such as bedtime routines, daily caffeine intake, and the sleeping environment (e.g., temperature, noise level), may reveal environmental factors that contribute to the sleep problems. Nocturnal symptoms that may be indicative of a medically based sleep disorder, such as OSAS (loud snoring, choking or gasping, sweating) or PLMs (restless sleep, repetitive kicking movements), should be elicited. Home video recording may be helpful in the evaluation of potential parasomnia episodes and the assessment of snoring and increased work of breathing in children with OSAS. An overnight sleep study (PSG) is not routinely warranted in the evaluation of a child with sleep problems unless there are symptoms suggestive of OSAS or PLMs, unusual features of episodic nocturnal events, or unexplained daytime sleepiness.

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PART III

Behavioral and Psychiatric Disorders

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CHAPTER 32

Psychosocial Assessment and Interviewing

Heather J. Walter, David R. DeMaso

It is estimated that 20% of children living in the United States experience a mental illness in a given year, at a cost of almost $14 billion. In children, mental illness is more prevalent than leukemia, diabetes, and AIDS combined; more money is spent on mental disorders than on any other childhood illness, including asthma, trauma, and infectious diseases. Although nearly 1 in 5 youths suffers from a psychiatric disorder, 75–85% do not receive specialty mental health services. Those who do, primarily receive services in nonspecialty sectors (primary care, schools, child welfare, juvenile justice), where mental health expertise may be limited. Untreated or inadequately treated psychiatric disorders persist over decades, become increasingly intractable to treatment, impair adherence to medical treatment regimens, and incur progressively greater social, educational, and economic consequences over time.

Aims of Assessment

A psychosocial assessment in the pediatric setting should determine whether there are signs and symptoms of cognitive, developmental, emotional, behavioral, or social difficulties and characterize these signs and symptoms sufficiently to determine their appropriate management. The focus of the assessment varies with the nature of the presenting problem and the clinical setting. Under emergency circumstances, the focus may be limited to an assessment of “dangerousness to self or others” for the purpose of determining the safest level of care. In routine circumstances (well-child visits), the focus may be broader, involving a screen for symptoms and functional impairment in the major psychosocial domains. The challenge for the pediatric practitioner will be to determine as accurately as possible whether the presenting signs and symptoms are likely to meet criteria for a psychiatric disorder and whether the severity and complexity of the disorder suggest referral to a mental health specialist or management in the pediatric setting.

Presenting Problems

Infants may come to clinical attention because of problems with eating and/or sleep regulation, concerns about failure to gain weight and length, poor social responsiveness, limited vocalization, apathy or disinterest, and response to strangers that is excessively fearful or overly familiar. Psychiatric disorders most commonly diagnosed during this period are rumination and reactive attachment disorders.

Toddlers are assessed for concerns about sleep problems, language delay, motor hyperactivity, extreme misbehavior, extreme shyness, inflexible adherence to routines, difficulty separating from parents, struggles over toilet training, dietary issues, and testing limits. Developmental delays and more subtle physiologic, sensory, and motor processing problems can be presented as concerns. Problems with “goodness of fit” between the child's temperament and the parents' expectations can create relationship difficulties that also require assessment (see Chapter 19). Psychiatric disorders most commonly diagnosed during this period are autism spectrum disorder (ASD) and reactive attachment disorders.

Presenting problems in **preschoolers** include elimination difficulties, sibling jealousy, lack of friends, self-destructive impulsiveness, multiple fears, nightmares, refusal to follow directions, somatization, speech that is difficult to understand, and temper tantrums. Psychiatric disorders most commonly diagnosed in this period are ASD communication, oppositional, attention-deficit/hyperactivity disorder (ADHD), anxiety (separation, selective mutism), reactive attachment, gender dysphoria, and sleep disorders.

Older children are brought to clinical attention because of concerns about angry or sad mood, bedwetting, overactivity, impulsiveness, distractibility, learning problems, arguing, defiance, nightmares, school refusal, bullying or being bullied, worries and fears, somatization, communication problems, tics, and withdrawal or isolation. Psychiatric disorders most commonly diagnosed during this period are ADHD, oppositional, anxiety (generalized, phobias), elimination, somatic symptom, specific learning, and tic disorders.

Adolescents are assessed for concerns about the family situation, experimentation with sexuality and drugs, delinquency and gang involvement, friendship patterns, issues of independence, identity formation, self-esteem, and morality. Psychiatric disorders most often diagnosed during this period are anxiety (panic, social anxiety), depressive, bipolar, psychotic, obsessive-compulsive, impulse control, conduct, substance-related, and eating disorders.

General Principles of the Psychosocial Interview

Psychosocial interviewing in the context of a routine pediatric visit requires adequate time and privacy. The purpose of this line of inquiry should be explained to the child and parents ("to make sure things are going OK at home, at school, and with friends"), along with the limits of **confidentiality** . Thereafter, the first goal of the interview is to build **rapport** with both the child and the parents (see Chapters 17 and 34 for further discussion of strategies for engaging families).

With the parents, this rapport is grounded in respect for the parents' knowledge of their child, their role as the central influence in their child's life, and their desire to make a better life for their child. Parents often feel anxious or guilty because they believe that problems in a child imply that their parenting skills are inadequate. Parents' experiences of their own childhood influence the meaning a parent places on a child's feelings and behavior. A good working alliance allows mutual discovery of the past as it is active in the present and permits potential distortions to be modified more readily. Developmentally appropriate overtures can facilitate rapport with the child. Examples include playing peek-a-boo with an infant, racing toy cars with a preschooler, commenting on sports with a child who is wearing a baseball cap, and discussing music with a teenager who is wearing a rock band T-shirt.

After an overture with the child, it is helpful to begin with **family-centered interviewing,** in which the parent is invited to present any psychosocial concerns (learning, feelings, behavior, peer relationships) about the child. With adolescent patients, it is important to conduct a separate interview to give the adolescent an opportunity to confirm or refute the parent's presentation and to present the problem from his or her perspective. Following the family's undirected presentation of the primary problem, it is important to shift to direct questioning to clarify the duration, frequency, and severity of symptoms, associated distress or functional impairment, and the developmental and environmental context in which the symptoms occur.

Because of the high degree of comorbidity of psychosocial problems in children, after eliciting the presenting problem, the pediatric practitioner should then briefly screen for problems in all the major developmentally appropriate categories of cognitive, developmental, emotional, behavioral, and social disturbance, including problems with mood, anxiety, attention, behavior, thinking and perception, substance use, social relatedness, eating, elimination, development, language, and learning. This can be preceded by a transition statement such as, “Now I'd like to ask about some other issues that I ask all parents and kids about.”

A useful guide for this area of inquiry is provided by the **11 Action Signs** (Table 32.1), designed to give frontline clinicians the tools needed to recognize early symptoms of mental disorders. *Functional impairment* can be assessed by inquiring about symptoms and function in the major life domains, including home and family, school, peers, and community. These domains are included in the **HEADSS** (Home, Education, Activities, Drugs, Sexuality, Suicide/Depression) Interview Guide, often used in the screening of adolescents (Table 32.2).

Table 32.1

Mental Health Action Signs

- Feeling very sad or withdrawn for more than 2 weeks
- Seriously trying to harm or kill yourself, or making plans to do so
- Sudden overwhelming fear for no reason, sometimes with a racing heart or fast breathing
- Involvement in many fights, using a weapon, or wanting to badly hurt others
- Severe out-of-control behavior that can hurt yourself or others
- Not eating, throwing up, or using laxatives to make yourself lose weight
- Intense worries or fears that get in the way of your daily activities
- Extreme difficulty in concentrating or staying still that puts you in physical danger or causes school failure
- Repeated use of drugs or alcohol

- Severe mood swings that cause problems in relationships
- Drastic changes in your behavior or personality

From The Action Signs Project, Center for the Advancement of Children's Mental Health at Columbia University.

Table 32.2

HEADSS* Screening Interview for Taking a Rapid Psychosocial History

Parent Interview

Home

- How well does the family get along with each other?

Education

- How well does your child do in school?

Activities

- What does your child like to do?
- Does your child do anything that has you really concerned?
- How does your child get along with peers?

Drugs

- Has your child used drugs or alcohol?

Sexuality

- Are there any issues regarding sexuality or sexual activity that are of concern to you?

Suicide/Depression

- Has your child ever been treated for an emotional problem?
- Has your child ever intentionally tried to hurt him/herself or made threats to others?

Adolescent Interview

Home

- How do you get along with your parents?

Education

- How do you like school and your teachers?
- How well do you do in school?

Activities

- Do you have a best friend or group of good friends?
- What do you like to do?

Drugs

- Have you used drugs or alcohol?

Sexuality

- Are there any issues regarding sexuality or sexual activity that are of concern to you?

Suicide/Depression

- Everyone feels sad or angry some of the time. How about you?
- Did you ever feel so upset that you wished you were not alive or so angry

you wanted to hurt someone else badly?

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[*] HEADSS, Home, Education, Activities, Drugs, Sexuality, Suicide/Depression.

From Cohen E, MacKenzie RG, Yates GL: HEADSS, a psychosocial risk assessment instrument: implications for designing effective intervention programs for runaway youth, *J Adolesc Health* 12:539–544, 1991.

The nature and severity of the presenting problem(s) can be further characterized through a standardized self-, parent-, or teacher-informant symptom rating scale; Table 32.3 lists selected scales in the public domain. A *rating scale* is a type of measure that provides a relatively rapid assessment of a specific construct with an easily derived numerical score that is readily interpreted. The use of symptom rating scales can ensure efficient, systematic coverage of relevant symptoms, quantify symptom severity, and document a baseline against which treatment effects can be measured. Functional impairment also can be assessed with self- and other-reported rating scales.

Table 32.3

Select List of Mental Health Rating Scales in the Public Domain

INSTRUMENTS	FOR AGES (yr)	INFORMANT: NUMBER OF ITEMS	TIME TO COMPLETE (min)	AVAILABLE AT
BROAD BAND				
Pediatric Symptom Checklist (PSC)	4-18	Parent: 35, 17 Youth: 35, 17	5-10	www.massgeneral.org/psychiatry/services/psc_home
SNAP-IV Rating Scale	6-18	Parent, Teacher: 90	10	http://www.crfht.ca/files/8913/7597/8069/SNAPIV_
Strengths and Difficulties Questionnaire (SDQ)	4-18	Parent, Teacher, Child: 25	5	www.sdqinfo.com
NARROW BAND				
Anxiety				
Self-Report for Childhood Anxiety Related	8-18	Parent, Child: 41	5	http://www.pediatricbipolar.pitt.edu/content.asp?id=

Emotional Disorders (SCARED)				
Attention and Behavior				
Vanderbilt ADHD Diagnostic Rating Scale	6-12	Parent: 55 Teacher: 43	10	http://www.nichq.org/childrens-health/adhd/resource scales
Autism				
Modified Checklist for Autism in Toddlers (M-CHAT)	16-30 mo	Parent: 23	5-10	https://www.m-chat.org/index.php
Depression				
Center for Epidemiological Studies Depression Scale for Children (CES-DC)	6-18	Child: 20	5	https://www.brightfutures.org/mentalhealth/pdf/prof
Mood and Feelings Questionnaire (MFQ)–Short Version	7-18	Parent: 34 Child: 33	<5	www.devepi.duhs.duke.edu/mfq.html
Patient Health Questionnaire–9 (PHQ-9)	12/13+	9	<5	http://www.phqscreeners.com/sites/g/files/g1001626 9_English.pdf

ADHD, Attention-deficit/hyperactivity disorder.

Clinical experience and methodological studies suggest that parents and teachers are more likely than the child to report externalizing problems (disruptive, impulsive, overactive, or antisocial behavior). Children may be more likely to report anxious or depressive feelings, including suicidal thoughts and acts, of which the parents may be unaware. Discrepancies across informants are common and can shed light on whether the symptoms are pervasive or contextual. Although concerns have been raised about children's competence as self-reporters (because of limitations in linguistic skills; self-reflection; emotional awareness; ability to monitor behavior, thoughts, and feelings; tendency toward social desirability), children and adolescents can be reliable and valid self-reporters.

Clinicians are encouraged to become familiar with the psychometric characteristics and appropriate use of at least 1 broad-band symptom rating scale, such as the *Strengths and Difficulties Questionnaire* (SDQ),* the *Pediatric Symptom Checklist* (PSC), † or the *Swanson, Nolan, and Pelham–IV* (SNAP-IV). ‡ These measures are available in multiple languages. If the clinical interview or broad-band rating scale suggests difficulties in one or more specific symptom areas, the clinician can follow with a psychometrically sound, relevant narrow-band instrument, such as the *Vanderbilt ADHD Diagnostic Rating Scale* for attention, behavior, and learning problems; the *Center for Epidemiological Studies Depression Scale for Children* (CES-DC), *Mood and Feelings Questionnaire* (MFQ), or *Patient Health Questionnaire-9* (PHQ-9) for depression; or the *Screen for Child Anxiety Related Emotional Disorders* (SCARED) for anxiety.

Children and adolescents scoring above standardized rating scale cutpoints in most cases should be referred to a qualified mental health professional for assessment and treatment, because scores above cutpoint are highly correlated with clinically significant psychiatric disorders. Youths scoring just below or only slightly above cutpoints (e.g., subsyndromal or mild mood, anxiety, or disruptive behavior disorders) may be appropriate for management in the pediatric primary care or subspecialty settings, as may youths scoring well above cutpoints for certain neurodevelopmental disorders (ADHD, autism spectrum, tic).

The safety of the child in the context of the home and community is of paramount importance. The interview should sensitively assess whether the child has been exposed to any frightening events, including abuse, neglect, bullying, marital discord, or domestic or community violence; whether the child shows any indication of dangerousness to self or others or a severely altered mental status (psychosis, intoxication, delirium, rage, hopelessness); or whether the child (if age appropriate) has been involved in any risky behavior, including running away, staying out without permission, truancy, gang involvement, experimentation with substances, and unprotected sexual encounters. The interview also should assess the capacity of the parents to adequately provide for the child's physical, emotional, and social needs or whether parental capacity has been diminished by psychiatric disorder, family dysfunction, or the sequelae of disadvantaged socioeconomic status. Any indications of threats to the child's safety should be immediately followed by thorough assessment and protective action.

Indications for Referral

There is variability in the level of **confidence** pediatric practitioners perceive in diagnosing psychosocial problems in children and adolescents. Pediatric practitioners who have familiarity with psychiatric diagnostic criteria may feel confident diagnosing certain disorders, particularly the neurodevelopmental and other biologically based disorders (ADHD, ASD, tic disorders, enuresis, encopresis, insomnia, anorexia). The disorders about which some pediatric practitioners might have less diagnostic confidence include the disruptive/impulse control/conduct, depressive, bipolar, anxiety, psychotic, obsessive-compulsive, trauma-related, somatic symptom, and substance-related disorders. Pediatric practitioners should refer to a mental health practitioner whenever they experience diagnostic uncertainty with a child who has distressing or functionally impairing psychosocial symptoms. Children found to have indicators of dangerousness on initial assessment always should be immediately referred to a mental health professional.

Psychiatric Diagnostic Evaluation

The objectives of the psychiatric diagnostic evaluation of the child and adolescent are to determine whether *psychopathology* or *developmental risk* is present and if so, to establish an explanatory formulation and a differential diagnosis, and to determine whether treatment is indicated and if so, to develop a treatment plan and facilitate the parents' and child's involvement in the plan. The aims of the diagnostic evaluation are to clarify the reasons for the referral; to obtain an accurate accounting of the child's developmental functioning and the nature and extent of the child's psychosocial difficulties, functional impairment, and subjective distress; and to identify potential individual, family, or environmental factors that might account for, influence, or ameliorate these difficulties. The issues relevant to diagnosis and treatment planning can span genetic, constitutional, and temperamental factors; individual psychodynamics; cognitive, language, and social skills; family patterns of interaction and child-rearing practices; and community, school, and socioeconomic influences.

The focus of the evaluation is *developmental* ; it seeks to describe the child's functioning in various realms and to assess the child's adaptation in these areas relative to that expected for the child's age and phase of development. The developmental perspective extends beyond current difficulties to vulnerabilities that can affect future development and as such are important targets for preventive intervention. Vulnerabilities may include subthreshold or subsyndromal difficulties that, especially when manifold, often are accompanied by significant distress or impairment and as such are important as potential harbingers of future problems.

Throughout the assessment, the clinician focuses on identifying a realistic balance of vulnerabilities and strengths in the child, in the parents, and in the parent–child interactions. From this strength-based approach, over time a hopeful family narrative is co-constructed to frame the child's current developmental progress and predict the child's ongoing progress within the scope of current risk and protective factors.

Although the scope of the evaluation will vary with the clinical circumstance, the comprehensive psychiatric diagnostic evaluation has 12 major components: the presenting problem(s) and the context in which they occur; a review of psychiatric symptoms; a history of psychiatric treatment; a medical history, a developmental history; an educational history; a family history; a mental status examination; a biopsychosocial clinical formulation; a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) diagnosis; a risk assessment; and a treatment plan. For infants and young children, the presenting problem and historical information is derived from parents and other informants. As children mature, they become increasingly important contributors to the information base, and they become the primary source of information in later adolescence. Information relevant to formulation and differential diagnosis is derived in multiple ways, including directive and nondirective questioning, interactive play, and observation of the child alone and together with the caregiver(s).

The explication of the **presenting problem(s)** includes information about onset, duration, frequency, setting, and severity of symptoms; associated distress and/or functional impairment; and predisposing, precipitating, perpetuating, and ameliorating contextual factors. The **symptom review** assesses potential comorbidity in the major domains of child and adolescent psychopathology, including problems with intellectual, communication, motor, learning, and developmental capabilities; attention deficits; angry, sad, or elated mood; anxiety; obsessions or compulsions; trauma or stress reactions; somatic symptoms; eating, elimination, sleep, or gender disturbances; disruptive, impulse-control, or conduct problems; psychosis; or substance abuse or addiction. The **history of psychiatric treatment** includes gathering information about prior emergency mental health assessments, psychiatric hospitalizations, day treatment, psychotherapy, pharmacotherapy, and nontraditional treatments.

The **medical history** includes information about the source of primary care, the frequency of health supervision, past and current medical illnesses and treatments, and the youth and family's history of adherence to medical treatment. A systematic review of organ or functional systems facilitates the identification of abnormalities that require investigation or monitoring by the pediatric practitioner, as well as the identification of cautionary factors related to the prescription of psychotropic medication. The **developmental history** includes information about the circumstances of conception, pregnancy, or adoption; pre-, peri-, or postnatal insults; attachment and temperament; cognitive, motor, linguistic, emotional, social, and moral development; health habits, sexuality, and substance use (as age appropriate), coping and defensive structure, future orientation, and perceived strengths. The **educational history** includes schools attended; typical grades, attendance, and behavior; classroom accommodations; special education services; disciplinary actions; social relationships; extracurricular activities; and barriers to learning. The **family history** assesses family composition; sociodemographic and neighborhood characteristics; domiciliary arrangements; parenting capacities; family function; medical/psychiatric histories of family members; and cultural/religious affiliations.

Orientation is tested by the ability to correctly identify time (date, month, year, season), place (hospital, clinic, city, state, country), and name, as well as remember (recall) 3 objects. **Attention/calculation** testing is age dependent and includes counting forward by 3s, or more classically, counting backward from 100 by 7 (“serial 7s”) or 5. **Language** is tested by pointing to familiar objects (clock, pen) and asking the patient to name them, as well as having the patient follow a 3-step command. Language is also tested by having the patient write a sentence, as well as having the patient read another sentence and perform the command in that sentence.

The **mental status examination** assesses appearance, relatedness, cognition, communication, mood, affective expression, behavior, memory, orientation, and perception.

The evaluation culminates in a biopsychosocial formulation, diagnosis, and risk assessment. The **biopsychosocial formulation** is derived from an assessment of *vulnerabilities* and *strengths* in the biologic, psychological, and social domains and serves to identify targets for intervention and treatment. In the *biologic* domain, major vulnerabilities include a family history of psychiatric disorder and personality or behavior problems, as well as a personal history of pre-, peri-, or postnatal insults; cognitive or linguistic impairments; chronic physical illness; and a difficult temperament. In the *psychological* domain, major vulnerabilities include failure to achieve developmental tasks, unresolved unconscious conflicts, and maladaptive coping and defensive styles. In the *social* domain, major vulnerabilities include parental incapacity; unskilled parenting; family dysfunction; social isolation; unfavorable school setting; unsupportive community structures; and sociodemographic disadvantage. Major strengths include cognitive and linguistic capability; physical health and attractiveness; stable, moderate temperamental characteristics; and stable supportive parenting, family, peer, and community structures. The biopsychosocial formulation can be organized to reflect predisposing, precipitating, perpetuating, and protective (ameliorating) factors (the “4 Ps”) influencing the development of the observed psychopathology.

The **diagnosis** must be made in accordance with the nomenclature in DSM-5. This nomenclature categorizes cross-sectional phenomenology into discrete clinical syndromes and seeks to improve diagnostic accuracy at the expense of theories of causation and dimensional presentations. By DSM-5 convention, if diagnostic criteria are met, the diagnosis is given (except where hierarchical rules apply); consequently, psychiatric comorbidity is a common occurrence. The **risk assessment** includes a careful assessment of risk status, including suicidality, homicidality, assaultiveness, self-injuriousness, and involvement in risky behavior or situations.

The psychiatric diagnostic evaluation culminates in a **treatment plan** that brings the broad array of targeted psychosocial interventions to the service of the child. Diagnoses drive the choice of evidence-based psychotherapeutic and psychopharmacologic treatments. The formulation drives the selection of interventions targeted at biologic, psychological, and social vulnerabilities and strengths. Many of these treatments and interventions are described in the succeeding chapters.

Special Considerations in the Diagnostic Evaluation of Infants and Young Children

Psychiatric evaluation of infants and young children includes the domains of physiology, temperament, language and motor development, affective behavior, social behavior, and communication. Although much of the information in these domains will be derived from parent report, much also can be gleaned from nonverbal behavior and observation of the parent–child interaction. Observations should include predominant affective tone of parent and child (positive, negative, apathetic); involvement in the situation (curiosity, disinterest); social responsiveness (mutuality of gaze, auditory responsiveness); and reactions to transitions (including separation).

A screen for maternal depression* is critical at this stage, as is an assessment of the mother's (or other caregiver's) ability to respond rapidly on a contingent basis to the child's expressed needs, regulate the child's rapid shifts of emotion and behavior, and provide a stimulus shelter to prevent the child from being overwhelmed.

Standardized screening instruments—*Ages and Stages Questionnaires, Brief Infant-Toddler Social & Emotional Assessment, Early Childhood Screening Assessment, Modified Checklist for Autism in Toddlers, Parents' Evaluation of Developmental Status,* and *Survey of Well-being of Young Children* —designed for this age-group can be helpful in systematizing the evaluation. In addition, the *Infant, Toddler and Preschool Mental Status Exam* (ITP-MSE) is a reference tool that describes how traditional categories of the mental status examination can be adapted to observations of young children. Additional categories, including sensory and state regulation, have been added that reflect important areas of development in young children.

Diagnostic systems that are more age appropriate than DSM-5 have been developed for infants and young children. These systems include the *Research Diagnostic Criteria–Preschool Age* (RDC-PA) and *Zero to Three Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood-Revised* (DC: 0-3R). The DC: 0-3R includes a relationship classification that assesses the range of interactional adaptation in each parent–child relationship and regulation disorders of sensory processing that identify a range of constitutionally and maturationally based sensory reactivity patterns, motor patterns, and behavior patterns that together can dysregulate a child internally and impact the child's interactions with caregivers.

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[*] http://www.sdqinfo.org/py/sdqinfo/b0.py .

[†] http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst .

[‡] http://psychiatryassociatespc.com/doc/SNAP-IV_Parent&Teacher.pdf .

[*] See http://www.medicalhomeportal.org/clinical-practice/screening-and-prevention/maternal-depression for several examples.

CHAPTER 33

Psychopharmacology

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Psychopharmacology is the first-line treatment for several child and adolescent psychiatric disorders (e.g., ADHD, schizophrenia, bipolar) and is used adjunctively with psychosocial treatments for other disorders (or coexisting conditions), including anxiety, depression, autism spectrum, tic, trauma-related, and obsessive-compulsive disorders. Although pediatric primary care practitioners (PCPs) may routinely manage medications for attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression, they may be called on to manage psychotropic medications with which they have had less experience. As such, it is useful for PCPs to be familiar with basic information about child and adolescent psychopharmacology. Before prescribing a psychotropic medication, PCPs should review full prescribing information for each medication (in package inserts or at reliable websites such as the National Institutes of Health *DailyMed* *) to obtain complete and up-to-date information about indications, contraindications, warnings, interactions, and precautions.

Pediatric prescribers should be aware of "best practice" principles that underlie medication assessment and management by child and adolescent psychiatrists (Table 33.1), so as to consider extrapolation of these principles to prescribing in the primary care setting. The use of medication involves a series of interconnected steps, including performing an assessment, constructing working diagnoses and an explanatory formulation, deciding on treatment and a monitoring plan, obtaining treatment assent/consent, and implementing treatment.

Table 33.1

Best Principles for Use of Psychotropic Medications With Children and Adolescents

1. Before initiating pharmacotherapy, a psychiatric evaluation is completed.
2. Before initiating pharmacotherapy, a medical history is obtained, and a medical evaluation is considered when appropriate.
3. The prescriber communicates with other professionals to obtain collateral history and collaborate in the monitoring of outcome and side effects during the medication trial.
4. The prescriber develops a psychosocial and psychopharmacologic treatment plan based on the best available evidence.
5. The prescriber develops a plan to monitor the patient during the medication trial.
6. The prescriber is cautious when the medication trial cannot be appropriately monitored.
7. The prescriber educates the patient and family about the patient's diagnosis and treatment plan.
8. The prescriber obtains and documents informed consent before initiating the medication trial and at appropriate intervals during the trial.
9. The informed-consent process focuses on the risks and benefits of the proposed and alternative treatments.
10. The medication trial should involve an adequate dose of medication for an adequate duration.
11. The prescriber reassesses the patient if the patient fails to respond to the medication trial as expected.
12. The prescriber has a clear rationale for using medication combinations.
13. The prescriber has a specific plan for medication discontinuation.

Adapted from American Academy of Child and Adolescent Psychiatry: Practice parameter on the use of psychotropic medication in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 48(9):961–973, 2009.

Questions remain about the quality of the evidence supporting the use of many psychotropic medications in children and adolescents. Therefore, cognitive, emotional, and behavioral symptoms are targets for medication treatment when (1) there is no or insufficient response to available evidence-based psychosocial interventions, (2) the patient's symptoms convey significant risk of harm, or (3) the patient is experiencing significant distress or functional impairment. Common target symptoms include agitation, aggression, anxiety, depression, hyperactivity, inattention, impulsivity, mania, obsessions, compulsions, and psychosis (Table 33.2). All these can be quantitatively measured with standardized symptom rating scales to establish baseline symptom severity and facilitate “treating to target.”

Table 33.2

Target Symptom Approach to Psychopharmacologic Management

TARGET SYMPTOM	MEDICATION CONSIDERATIONS
Agitation	Atypical antipsychotic Typical antipsychotic Anxiolytic
Aggression	Stimulant Atypical antipsychotic
Anxiety	Antidepressant Anxiolytic (only situational anxiety)
Depression	Antidepressant
Hyperactivity, inattention, impulsivity	Stimulant α-Agonist Atomoxetine
Mania	Atypical antipsychotic Lithium
Obsessions, compulsions	Antidepressant
Psychosis	Atypical antipsychotic Typical antipsychotic
Tics	α-Agonist Atypical antipsychotic Typical antipsychotic

Adapted from Shaw RJ, DeMaso DR: *Clinical manual of pediatric psychosomatic medicine: mental health consultation with physically ill children and adolescents,* Washington, DC, 2006, American Psychiatric Press, p 306.

Stimulants and Other ADHD Medications

Stimulants are sympathomimetic drugs that act both in the central nervous system (CNS) and peripherally by enhancing dopaminergic and noradrenergic transmission (Table 33.3). Strong evidence exists for the effectiveness of these medications for the treatment of ADHD and aggression, as well as moderate evidence for the treatment of hyperactivity in autism spectrum disorder (ASD). In some cases, stimulants are used adjunctively with antidepressants in the treatment of depression and as monotherapy for fatigue or malaise associated with chronic physical illnesses.

Table 33.3

Select Medications for Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms

GENERIC (BRAND) APPROXIMATE DURATION OF ACTION	FDA APPROVED (Pediatric age range in years)	TARGET SYMPTOMS	DAILY STARTING DOSE	DAILY THERAPEUTIC DOSAGE RANGE*	SELECT MEDICAL MONITORING AND PRECAUTION
STIMULANTS					
Long Acting					
OROS methylphenidate (Concerta) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	18 mg	Age 6-12: 18-54 mg Age >12: 18-72 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse potential for GI obstruction
Dexmethylphenidate (Focalin XR) † 10-12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	5 mg	5-30 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Amphetamine combination (Adderall XR) † 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	5 mg	5-30 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Lisdexamfetamine (capsule † and chewable) (Vyvanse) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	20 mg	20-70 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Methylphenidate transdermal (Daytrana)	ADHD (6+)	Inattention Hyperactivity Impulsivity	10 mg	10-30 mg	Personal and family CV history; persona

12 hr					seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse skin reactions
Methylphenidate suspension (Quillivant XR) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	20 mg	20-60 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Intermediate Acting					
Methylphenidate (Metadate CD, Ritalin LA) 8 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	10 mg	10-60 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Dextroamphetamine (Dexedrine Spansule) 8 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	5 mg	5-40 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Methylphenidate chewable (Quillichew ER) 8 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	20 mg	20-60 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Short Acting					
Dexmethylphenidate (Focalin) 4-5 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	5 mg	5-20 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Methylphenidate	ADHD (6+)	Inattention	5 mg	5-60 mg	Personal and

(Ritalin, Methylin) 4 hr		Hyperactivity Impulsivity			family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Amphetamine combination (Adderall) 4-5 hr	ADHD (3+)	Inattention Hyperactivity Impulsivity	Age 3-5: 2.5 mg Age ≥6: 5 mg	5-40 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
Dextroamphetamine (Dexedrine) 4 hr	ADHD (3+)	Inattention Hyperactivity Impulsivity	Age 3-5: 2.5 mg Age ≥6: 5 mg	5-40 mg	Personal and family CV history; persona seizure history; Ht, Wt, BP, P; bipolar or psychotic symptoms; substance abuse
SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITOR					
Atomoxetine (Strattera) 24 hours	ADHD (6+)	Inattention Hyperactivity Impulsivity	<70 kg: 0.5 mg/kg/day >70 kg: 40 mg	<70 kg: 0.5-1.2 mg/kg/day >70 kg: 40-100 mg	Personal and family CV history; BP, P; liver injury; suicidal ideation bipolar or psychotic symptoms
ALPHA (α)-AGONISTS					
Short Acting					
Clonidine (Catapres) 4 hr	None	Inattention Hyperactivity Impulsivity	0.05 mg	27-40.5 kg: 0.05-0.2 mg 40.5-45 kg: 0.05-0.3 mg >45 kg: 0.05-0.4 mg	CV history; BP, P; rebound hypertension; cardiac conduction abnormalities
Guanfacine (Tenex) 6 hr	None	Inattention Hyperactivity Impulsivity	0.5 mg	27-40.5 kg: 0.5-2 mg 40.5-45 kg: 0.5-3 mg >45 kg: 0.5-4 mg	CV history; BP, P; rebound hypertension; cardiac conduction abnormalities
Long Acting					
Clonidine (Kapvay) 12 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	0.1 mg	0.1-0.4 mg	CV history; BP, P; rebound hypertension; cardiac conduction

					abnormalities
Guanfacine (Intuniv) 24 hr	ADHD (6+)	Inattention Hyperactivity Impulsivity	1 mg	*Monotherapy*: 25-33.9 kg: 2-3 mg 34-41.4 kg: 2-4 mg 41.5-49.4 kg: 3-5 mg 49.5-58.4 kg: 3-6 mg 58.5-91 kg: 4-7 mg >91 kg: 5-7 mg *Adjunctive* (with stimulant): 0.05-0.12 mg/kg/day	CV history; BP, P; rebound hypertension, cardiac conduction abnormalities

[*] Doses shown in table may exceed maximum recommended dose for some children.

[†] Capsule contents may be sprinkled on soft food.

FDA, U.S. Food and Drug Administration; CV, cardiovascular; Ht, height; Wt, weight; BP, blood pressure; P, pulse; GI, gastrointestinal.

No major differences in efficacy or tolerability have been found between different classes of stimulants, and no consistent patient profile identifies those who will respond preferentially to one class over another. The most common (generally dose-dependent) side effects of stimulants include headache, stomachache, appetite suppression, weight loss, blood pressure (BP) and heart rate increases, and delayed sleep onset. Less common side effects include irritability (particularly prominent in younger children), aggression, social withdrawal, and hallucinations (visual or tactile). Amphetamine preparations prescribed concurrently with serotonergic antidepressants can be associated with the development of serotonin syndrome.

Stimulants have been associated with elevations in mean BP (<5 mm Hg) and pulse (<10 beats/min); a subset of individuals (5–10%) may have greater increases. The rate of sudden death in pediatric patients taking stimulants is comparable to children in the general population; the hazard ratio for serious cardiovascular (CV) events is 0.75 (although up to a 2-fold increase in risk could not be ruled out). Moreover, a case series analysis of children with a CV incident and treatment with methylphenidate demonstrated an increased risk of arrhythmia (incidence rate ratio, 1.61) that was highest in the presence of congenital heart disease. The U.S. Food and Drug Administration (FDA) recommends that stimulants should be avoided in the presence of structural cardiac abnormalities (e.g., postoperative tetralogy of Fallot, coronary artery abnormalities, subaortic stenosis, hypertrophic cardiomyopathy) and patient symptoms (syncope, palpitations, arrhythmias) or family history (e.g., unexplained sudden death) suggestive of CV disease. In these circumstances, cardiology consultation is recommended before prescribing. Routine electrocardiograms (ECGs) are not recommended in the absence of cardiac risk factors.

Atomoxetine is a selective inhibitor of presynaptic norepinephrine reuptake; it increases dopamine and norepinephrine in the prefrontal cortex (Table 33.3). It is less effective for the treatment of ADHD and aggression than stimulants, but atomoxetine has a longer duration of action (approximately 24 hr). Atomoxetine can have an onset of action within 1-2 wk of starting treatment, but there is an incrementally increasing response for up to 24 wk or longer. Common side effects of atomoxetine include nausea, headache, abdominal pain, insomnia, somnolence, erectile dysfunction, irritability, fatigue, decreased appetite, weight loss, and dizziness, along with nonclinical increases in heart rate and BP. Potential serious neuropsychiatric reactions include psychosis, mania, panic attacks, aggressive behavior, depression, seizures, and suicidal thinking. Atomoxetine carries an FDA warning regarding the risk of suicidal thinking and the need to monitor this closely. Atomoxetine also has been associated with hepatotoxicity and should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Because of the risk of sudden death, atomoxetine generally should be avoided in youth with known serious structural cardiac abnormalities, cardiomyopathy, heart rhythm abnormalities, or other serious cardiac problems.

The α-adrenergic agents **clonidine** and **guanfacine** , along with the longer-acting preparation of each, are presynaptic adrenergic agonists that appear to stimulate inhibitory presynaptic autoreceptors in the CNS (Table 33.3). The extended-release formulation of guanfacine has moderate to strong evidence for the monotherapy of ADHD and weaker evidence as adjunctive therapy to stimulant medication. Combination stimulant/α-agonist therapy is superior to monotherapy with either and to placebo for improving inattention and working memory. Extended-release guanfacine also has moderate evidence for effective treatment of ADHD with comorbid oppositional defiant disorder (ODD), favorably affecting both symptom clusters, as well as for the treatment of agitation in autism.

Sedation, somnolence, headache, abdominal pain, hypotension, bradycardia, cardiac conduction abnormalities, dry mouth, depression, and confusion are potential side effects of clonidine and guanfacine. Abrupt withdrawal can result in rebound hypertension; overdose can result in death.

Antidepressants

Antidepressant drugs act on pre- and postsynaptic receptors affecting the release and reuptake of brain neurotransmitters, including norepinephrine, serotonin, and dopamine (Table 33.4). There is strong evidence for the effectiveness of antidepressant medications in the treatment of anxiety and obsessive-compulsive disorders and weaker evidence for the treatment of depressive disorders. Suicidal thoughts have been reported during treatment with all antidepressants. The overall risk difference of suicidal ideation/attempts across all randomized controlled trials (RCTs) of antidepressants and indications has been reported as 0.7%, corresponding to a *number needed to harm* of 143. All antidepressants carry an FDA warning for suicidality; careful monitoring is recommended during the initial stages of treatment and following dose adjustments.

Table 33.4

Select Medications for Depression and Anxiety in Children and Adolescents

GENERIC (BRAND)	FDA APPROVED (Pediatric age range in years)	TARGET SYMPTOMS	DAILY STARTING DOSE	DAILY THERAPEUTIC DOSAGE RANGE*	SELECT MEDICAL MONITORING AND PRECAUTION
SELECTIVE SEROTONIN REUPTAKE INHIBITORS					
Citalopram (Celexa)	None	Depression Anxiety Obsessions/compulsions	10 mg	10-40 mg	Suicidal ideation QT prolongation at doses >40 mg; abnormal bleeding; mania; SS, DS
Escitalopram (Lexapro)	Depression (12-17)	Depression Anxiety Obsessions/compulsions	5 mg	5-20 mg	Suicidal ideation abnormal bleeding; mania; SS, DS
Fluoxetine (Prozac)	Depression (8-17) OCD (7-	Depression Anxiety Obsessions/compulsions	Age 6-12: 10 mg	Depression: 10-20 mg Anxiety,	Suicidal ideation abnormal bleeding; mania;

	17)		Age 13-17: 20 mg	OCD: 10-60 mg	SS
Sertraline (Zoloft)	OCD (6-17)	Depression Anxiety Obsessions/compulsions	Age 6-12: 12.5-25 mg Age 13-17: 25-50 mg	12.5-200 mg	Suicidal ideation abnormal bleeding; mania; SS, DS
ATYPICAL ANTIDEPRESSANTS					
Bupropion (Wellbutrin XL)	None	Depression	150 mg	150-300 mg	Suicidal ideation neuropsychiatric reaction, seizures (>300 mg/day), BP; mania; contraindicated i patients with seizure and eatin disorders
Duloxetine (Cymbalta)	Anxiety (7-17)	Depression Anxiety	30 mg	30-60 mg	Suicidal ideation BP, P; liver damage; severe skin reactions; abnormal bleeding; mania; SS, DS
Mirtazapine (Remeron)	None	Depression	7.5 mg	7.5-45 mg	Suicidal ideation weight; somnolence; agranulocytosis; QT prolongation mania; SS, DS
Venlafaxine (Effexor XR)	None	Depression Anxiety	37.5 mg	37.5-225 mg	Suicidal ideation BP; abnormal bleeding; mania; SS, DS
TRICYCLIC ANTIDEPRESSANTS					
Clomipramine (Anafranil)	OCD (10-17)	Obsessions Compulsions	25 mg	25-200 mg	Suicidal ideation BP; P; ECG; blood level; mania; SS; seizures; DS
ANXIOLYTIC AGENTS (SITUATIONAL USE)					
Lorazepam (Ativan)	None	Anxiety	0.5 mg	0.5-2 mg	Respiratory depression; sedation; physica and psychologica dependence; paradoxical reactions
Clonazepam (Klonopin)	None	Panic	0.5 mg	0.5-1 mg	Respiratory depression; sedation; physica and psychologica

					dependence; paradoxical reactions; suicida ideation
Hydroxyzine (Atarax, Vistaril)	Anxiety	Anxiety	50 mg	Age <6: 50 mg Age >6: 50-100 mg	QT prolongation

* Doses shown in table may exceed maximum recommended dose for some children.

OCD, Obsessive-compulsive disorder; BP, blood pressure; P, pulse; ECG, electrocardiogram; SS, serotonin syndrome; DS, discontinuation syndrome.

The **selective serotonin reuptake inhibitor (SSRI)** fluoxetine outperforms all other antidepressants (both SSRI and non-SSRI) studied and is the only SSRI separating from placebo in studies of depressed *preadolescents* . SSRIs have a large margin of safety. Side effects to SSRIs generally manifest in the first few weeks of treatment, and many will resolve with time. More common side effects include nausea, irritability, insomnia, appetite changes, weight loss/gain, headaches, dry mouth, dizziness, bruxism, diaphoresis, tremors, akathisia, restlessness, and behavioral activation. Approximately 5% of youth taking SSRIs, particularly children, develop **behavioral activation** (increased impulsivity, agitation, and irritability) that can be confused with mania, but the activation symptoms typically resolve when the dose is decreased or the medication discontinued. Sexual side effects are common, including decreased libido, anorgasmia, and erectile dysfunction. There is an increased risk of bleeding, especially when used with aspirin or nonsteroidal antiinflammatory drugs (NSAIDs).

SSRIs can be associated with abnormal heart rhythms, and citalopram causes dose-dependent QT-interval prolongation, contraindicating doses >40 mg/day. Patients with diabetes may experience hypoglycemia during SSRI treatment and hyperglycemia on discontinuation. **Discontinuation symptoms** (e.g., dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania) are common with short-acting SSRIs (sertraline, citalopram, escitalopram), leading to a recommendation for divided doses if these medications are used at higher doses and graduated reduction if discontinued.

The **serotonin syndrome** is characterized by the triad of mental status changes (e.g., agitation, hallucinations, delirium, coma), autonomic instability (e.g., tachycardia, labile BP, dizziness, diaphoresis, flushing, hyperthermia), and neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination). Serotonin syndrome results from excessive agonism of the CNS and peripheral nervous system serotonergic receptors and can be caused by a range of drugs, including SSRIs, valproate, and lithium. Interactions that can cause serotonin syndrome include SSRIs with linezolid (antibiotic with monoamine oxidase inhibitor properties) and with antimigraine preparations, as well as with amphetamine preparations, trazodone, buspirone, and venlafaxine. Serotonin syndrome is generally self-limited and can resolve spontaneously after the serotonergic agents are discontinued. Patients with severe disease require the control of agitation, autonomic instability, and hyperthermia as well as administration of 5-hydroxytryptamine (5-HT_{2A} , serotonin) antagonists (e.g., cyproheptadine).

The **non-SSRI antidepressants** include bupropion, duloxetine, venlafaxine, and mirtazapine (Table 33.4). These medications all lack rigorous evidence to support their effectiveness in children and adolescents, and as such should not be considered first-line options. *Bupropion*, a **norepinephrine-dopamine reuptake inhibitor (NDRI)** , appears to have an indirect mixed-agonist effect on dopamine and norepinephrine transmission. No rigorous studies of bupropion for anxiety or depression have been conducted with children or adolescents, although some evidence suggests that bupropion may be effective for smoking cessation and ADHD in youth. Common side effects include irritability, nausea, anorexia, headache, and insomnia. Dose-related seizures (0.1% risk at 300 mg/day and 0.4% risk at 400 mg/day) have occurred with bupropion, so it is contraindicated in those with epilepsy, eating disorders, or at risk for seizures.

Duloxetine and venlafaxine are **serotonin-norepinephrine reuptake inhibitors (SNRIs)** . *Duloxetine* has FDA approval for treatment of generalized anxiety disorder in children and adolescents, but studies of duloxetine for depression in youth have been negative. There is some evidence in adults that duloxetine can be useful for fibromyalgia and chronic musculoskeletal pain, an effect that has also been observed in children and adolescents. Common side effects of duloxetine include nausea, diarrhea, decreased weight, and dizziness. Increases in heart rate and BP have been noted, and BP should be monitored at each visit and with each dosage change. In addition, there have been reports of hepatic failure, sometimes fatal; duloxetine should be discontinued and not resumed in patients who develop jaundice or other evidence of liver dysfunction. Duloxetine also has been associated with severe skin reactions (erythema multiforme and Stevens-Johnson syndrome).

Venlafaxine has only negative trials for the treatment of depression in children and adolescents, but does have favorable evidence for the treatment of anxiety. Side effects are similar to SSRIs, including hypertension, irritability, insomnia, headaches, anorexia, nervousness, and dizziness, and dropout rates are high in clinical trials of venlafaxine. BP should be monitored at each visit and with each dosage change. Discontinuation symptoms (e.g., dysphoric mood, irritability, agitation, dizziness, sensory disturbances, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, seizures) are more pronounced with venlafaxine than the other non-SSRI antidepressants. In addition, suicidal thinking and agitation may be more common with venlafaxine than with other antidepressants, requiring close monitoring. In light of the substantial adverse effects, venlafaxine likely should be considered to be a third-line medication.

Mirtazapine is both a noradrenergic and a specific serotonergic antidepressant. Mirtazapine has only negative trials for the treatment of depression in youth and has no rigorous evidence of effectiveness for any other child or adolescent psychiatric disorder. Mirtazapine is associated with a risk for substantial weight gain and more rarely, hypotension, elevated liver enzymes, agranulocytosis, and QT prolongation. While its sedating properties have led to its adjunctive use for insomnia in adults with depressive/anxiety disorders, there is no evidence for use of mirtazapine in childhood sleep disorders.

The **tricyclic antidepressants (TCAs)** have mixed mechanisms of action; for example, clomipramine is primarily serotonergic, and imipramine is both noradrenergic and serotonergic. With the advent of the SSRIs, the lack of efficacy studies, particularly in depression, and more serious side effects, the use of TCAs in children has declined. *Clomipramine* is used in the treatment of obsessive-compulsive disorder (Table 33.4). Unlike the SSRIs, the TCAs may be helpful in pain disorders. They have a narrow therapeutic index, with overdoses being potentially fatal. Anticholinergic symptoms (e.g., dry mouth, blurred vision, constipation) are the most common side effects. TCAs can have cardiac conduction effects in doses >3.5 mg/kg. BP and ECG monitoring is indicated at doses above this level.

Anxiolytic agents, including lorazepam, clonazepam, and hydroxyzine, have been effectively used for the short-term relief of the symptoms of acute anxiety (Table 33.4). They are less effective as chronic (>4 mo) anxiolytic medications, particularly when one is used as monotherapy. Chronic use carries a significant risk of physical and psychological dependence.

Antipsychotics

Based on their mechanism of action, antipsychotic medications can be divided into first-generation (blocking dopamine D_2 receptors) and second-generation (mixed dopaminergic and serotonergic antagonists) agents (Table 33.5).

Table 33.5

Select Medications for Psychosis, Mania, Irritability, Agitation, Aggression, and Tourette Disorder in Children and Adolescents

GENERIC (BRAND)	FDA APPROVED (Pediatric age range in years)	TARGET SYMPTOMS	DAILY STARTING DOSE	DAILY THERAPEUTIC DOSAGE RANGE*	SELECT MEDICAL MONITORIN AND PRECAUTIO
SECOND-GENERATION ANTIPSYCHOTICS					
Aripiprazole (Abilify) Available in liquid preparation	Bipolar (10-17) Schizophrenia (13-17) Irritability in autism (6-17) Tourette (6-17)	Mania Psychosis Irritability Aggression Agitation Vocal/motor tics	Bipolar, schizophrenia: 2 mg Autism: 2 mg Tourette: 2 mg	Bipolar, schizophrenia: 10-30 mg Autism: 5-15 mg Tourette: 5-20 mg	BMI, BP, P, fasting glucose and lipids, abnormal movements; compulsive behaviors; neuroleptic malignant syndrome; leukopenia, neutropenia, agranulocytosis seizures
Olanzapine (Zyprexa) Available in liquid, dissolvable, and IM preparations	Bipolar (13-17) Schizophrenia (13-17)	Mania Psychosis Agitation	2.5 mg	2.5-20 mg	BMI, BP, P, fasting glucose and lipids, abnormal movements; ski rash (DRESS); neuroleptic malignant syndrome; leukopenia, neutropenia, agranulocytosis seizures
Quetiapine (Seroquel)	Bipolar (10-17) Schizophrenia (13-17)	Mania Psychosis Agitation	25 mg bid	Bipolar: 400-600 mg Schizophrenia: 400-800 mg	BMI, BP, P, fasting glucose and lipids, abnormal

					movements; ophthalmologic exam; neurolep malignant syndrome; leukopenia, neutropenia, agranulocytosis seizures; QT prolongation
Risperidone (Risperdal) Available in liquid and dissolvable preparations	Bipolar (10-17) Schizophrenia (13-17) Irritability in autism (5-17)	Mania Psychosis Irritability Aggression Agitation	Bipolar, schizophrenia: 0.5 mg Autism: <20 kg: 0.25 mg ≥20 kg: 0.5 mg	Bipolar, schizophrenia: 1-6 mg Autism: 0.5-3 mg	BMI, BP, P, fasting glucose and lipids, prolactin, abnormal movements; neuroleptic malignant syndrome; leukopenia, neutropenia, agranulocytosis seizures
Paliperidone (Invega) Available in liquid and IM preparations	Schizophrenia (12-17)	Psychosis	3 mg	<51 kg: 3-6 mg ≥51 kg: 3-12 mg	BMI, BP, P, fasting glucose and lipids, prolactin, abnormal movements, QT prolongation; neuroleptic malignant syndrome; potential for GI obstruction; leukopenia, neutropenia, agranulocytosis seizures
Lurasidone (Latuda)	Schizophrenia (13-17)	Psychosis	40 mg	40-80 mg	BMI, BP, P, fasting glucose and lipids, prolactin, abnormal movements; neuroleptic malignant syndrome; leukopenia, neutropenia, agranulocytosis seizures
Asenapine (Saphris)	Bipolar (10-17)	Mania Psychosis	2.5 mg twice daily	5-20 mg	BMI, BP, P, fasting glucose and lipids, prolactin,

					abnormal movements; QT prolongation; neuroleptic malignant syndrome; leukopenia, neutropenia, agranulocytosis seizures
FIRST-GENERATION ANTIPSYCHOTIC					
Haloperidol (Haldol) Available in liquid and IM preparations	Psychosis Tourette disorder Severe behavioral disorders Agitation (3-17)	Mania Psychosis Irritability Aggression Agitation Vocal/motor tics	0.05 mg/kg/day	0.05-0.15 mg/kg/day	BP, P; abnorma movements; QT prolongation; neuroleptic malignant syndrome; encephalopathy when combined with lithium; leukopenia, neutropenia, agranulocytosis
MOOD STABILIZER					
Lithium carbonate Available in liquid preparation	Bipolar (12-17)	Mania	Acute mania: 1800 mg/day Target level: 1.0-1.5 mEq/L	Long-term control: 900-1200 mg/day Target level: 0.6-1.2 mEq/L	Serum level, CBC/diff, thyro function, BUN/creatine, UA, electrolytes FBS; ECG; encephalopathy when combined with haloperido

[*] Doses shown in table may exceed maximum recommended dose for some children.

BMI, Body mass index; BP, blood pressure; P, pulse; IM, intramuscular; GI, gastrointestinal; CBC/diff, complete blood count with differential; BUN, blood urea nitrogen; UA, urinalysis; FBS, fasting blood sugar; ECG, electrocardiogram.

The **second-generation** (or **atypical**) **antipsychotics (SGAs)** have relatively strong antagonistic interactions with 5-HT_2 receptors and perhaps more variable activity at central adrenergic, cholinergic, and histaminic sites, which might account for the varying side effects, particularly metabolic, noted among these agents. The SGAs have moderate evidence for the treatment of agitation in autism and for the treatment of schizophrenia, bipolar disorder, and aggression. Haloperidol is a high-potency antipsychotic that is the **first-generation** (or **typical**) **antipsychotic** most commonly used in treatment of agitation and schizophrenia.

The SGAs have significant side effects, including sedation, extrapyramidal symptoms, weight gain, metabolic syndrome, diabetes, hyperlipidemia, hyperprolactinemia, hematologic effects (e.g., leukopenia, neutropenia), elevated liver transaminases, seizures, and CV effects (Table 33.6). They have an FDA warning for increased risk of diabetes. Youth appear to be more sensitive to sedation, extrapyramidal side effects (except akathisia), withdrawal dyskinesia, prolactin abnormalities, weight gain, hepatotoxicity, and metabolic abnormalities. The development of diabetes or tardive dyskinesia appears less prevalent than in adults, although this may be a function of short follow-up periods because these side effects may not emerge until adulthood.

Table 33.6

Adverse Effects for Select Antipsychotic Medications

ADVERSE EFFECT	ARIPIPRAZOLE (ABILIFY)	OLANZAPINE (ZYPREXA)	QUETIAPINE (SEROQUEL)	RISPERIDONE (RISPERDAL)	
Weight gain	0/+	+++	++	++	++
QTc interval	0/+	0/+	+	+	+
Sedation	0/+	+/++	++	+	0/+
Prolactin increase	0	+	0	+++	+++
Lipid increase	0/+	+++	++	+	+
Diabetes	0/+	+++	++	+	+
Anticholinergic	0	++	+/++	0	0
Acute parkinsonism	+	0/+	0	++	++
Akathisia	++	+	+	+	+
Tardive dyskinesia	0/+	0/+	0/+	0/+	0/+
Withdrawal dyskinesia	+/++	0/+	0/+	+	+
Orthostasis	0/+	++	++	+	+
Seizures	0/+	0/+	0/+	0/+	0/+

0 = none; 0/+ = minimal; + = mild; ++ = moderate; +++ = severe.

Adapted from Correll CU: Antipsychotic medications. In Dulcan MK, editor: *Dulcan's textbook of child and adolescent psychiatry,* ed 2, Washington, DC, 2016, American Psychiatric Press, pp 795–846.

The management of adverse effects should be proactive with baseline assessment and ongoing monitoring (Table 33.7). Abnormal movements (dystonia, akathisia, tardive dyskinesia) need periodic assessment using a standardized instrument such as the *Abnormal Involuntary Movement Scale* (AIMS). Valbenazine is FDA approved for the treatment of tardive dyskinesia in adults. The need for antiparkinsonian agents may be a consideration, particularly for patients at risk for acute dystonia or who have a previous history of dystonic reactions. CV effects of SGAs include prolongation of the QTc interval, tachycardia, orthostatic hypertension, and pericarditis. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline ECG with subsequent monitoring should be considered, along with cardiology consultation before prescribing. Alternative pharmacology should be considered if the resting heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 milliseconds (msec), respectively.

Table 33.7

Metabolic Monitoring Parameters Based on ADA/APA Consensus Guidelines

	BASELINE	WEEK 4	WEEK 8	WEEK 12	EVERY 3 MO THEREAFTER	ANNUALLY
Medical history*	X			X		X
Weight (BMI)	X	X	X	X	X	X
Waist circumference	X			X		X
Blood pressure	X			X		X
Fasting glucose/HbA$_{1c}$	X			X		X
Fasting lipids	X			X		X

* Personal and family history of obesity, hypertension, and cardiovascular disease.

BMI, Body mass index; Hb, hemoglobin.

From American Diabetes Association (ADA), American Psychiatric Association (APA), American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes, *Diabetes Care* 27:596–601, 2004.

The cytochrome P450 (CYP) enzymes metabolize the antipsychotics and as such necessitate that the PCP and psychiatrist are alert for potential drug-drug interactions that may impact the serum levels of all patient medications. CYP3A4 is mainly relevant to lurasidone, quetiapine, olanzapine, and haloperidol, whereas CYP2D6 predominately clears aripiprazole and risperidone. Asenapine is metabolized by CYP1A2 as well as direct glucuronidation by UGT1A4. Because <10% of paliperidone undergoes CYP first-pass metabolism, there is a lower likelihood of drug-drug interactions.

Primary prevention strategies to manage weight and metabolic dysfunction include educating the youth and family about healthy lifestyle behaviors and selecting an agent that has the lowest likelihood of impacting metabolic status. Secondary strategies would include intensifying healthy lifestyle instructions, consideration of switching agents, and a weight loss treatment program. Consideration of weight management interventions and increased monitoring of blood glucose and lipid levels should be implemented if weight gain exceeds the 90th percentile of body mass index (BMI) for age, or a change of 5 BMI units in youth who were obese at the initiation of treatment. Tertiary strategies, where diabetes, hypertension, obesity, or another metabolic abnormality has occurred, require more intensive weight reduction interventions, changing medication, and consultation with a medical subspecialist. Metformin has been used to treat severe weight gain associated with antipsychotic medication. Extrapyramidal adverse effects are generally dose and titration rate dependent and may respond to dose or titration rate reductions. More disabling effects may benefit from adjunctive treatment (e.g., anticholinergics, antihistamines).

Neuroleptic malignant syndrome is a rare, potentially fatal reaction that can occur during antipsychotic therapy. The syndrome generally manifests with fever, muscle rigidity, autonomic instability, and delirium. It is associated with elevated serum creatine phosphokinase levels, a metabolic acidosis, and high end-tidal CO_2 excretion. It has been estimated to occur in 0.2–1% of patients treated with dopamine-blocking agents. Malnutrition and dehydration in the context of an organic brain syndrome and simultaneous treatment with lithium and antipsychotic agents (particularly haloperidol) can increase the risk. Mortality rates may be as high as 20–30% as a result of dehydration, aspiration, kidney failure, and respiratory collapse. Differential diagnosis of neuroleptic malignant syndrome includes infections, heat stroke, malignant hyperthermia, lethal catatonia, agitated delirium, thyrotoxicosis, serotonin syndrome, drug withdrawal, and anticholinergic or amphetamine, ecstasy, and salicylate toxicity.

Mood Stabilizers

Because of their limited evidence of effectiveness and concerns about safety, mood-stabilizing medications (see Table 33.5) have limited use in the treatment of child and adolescent psychiatric disorders. For the treatment of bipolar mania in adolescents, atypical antipsychotics are considered first-line therapy.

Of the mood stabilizers, **lithium** alone has rigorous support for the treatment of bipolar mania. Lithium's mechanism of action is not well understood;

proposed theories relate to neurotransmission, endocrine effects, circadian rhythm, and cellular processes. Common side effects include polyuria and polydipsia, hypothyroidism, hyperparathyroidism, weight gain, nausea, abdominal pain, diarrhea, acne, and CNS symptoms (sedation, tremor, somnolence, memory impairment). Periodic monitoring of lithium levels along with thyroid and renal function is needed. Lithium serum levels of 0.8-1.2 mEq/L are targeted for acute episodes and 0.6-0.9 mEq/L are targeted for maintenance therapy. Acute overdose (level > 1.5 mEq/L) manifests with neurologic symptoms (e.g., tremor, ataxia, nystagmus, hyperreflexia, myoclonus, slurred speech, delirium, coma, seizures), and altered renal function. Toxicity is enhanced when dehydrated or with drugs that affect renal function, such as NSAIDs or angiotensin-converting enzyme (ACE) inhibitors. Neuroleptic malignant syndrome has been reported in patients concurrently taking antipsychotic drugs and lithium.

Medication Use in Physical Illness

There are special considerations in the use of psychotropic medications with physically ill children. Between 80% and 95% of most psychotropic medications are protein bound, the exceptions being lithium (0%), methylphenidate (10–30%), and venlafaxine (25–30%). As a result, psychotropic levels may be directly affected because albumin binding is reduced in many physical illnesses. Metabolism is primarily through the liver and gastrointestinal (GI) tract, with excretion via the kidney. Therefore, dosages may need to be adjusted in children with hepatic or renal impairment.

Hepatic Disease

Lower doses of medications may be required in patients with hepatic disease. Initial dosing of medications should be reduced, and titration should proceed slowly. In steady-state situations, changes in protein binding can result in elevated unbound medication, resulting in increased drug action even in the presence of normal serum drug concentrations. Because it is often difficult to predict changes in protein binding, it is important to maintain attention to the clinical effects of psychotropic medications and not rely exclusively on serum drug concentrations.

In acute hepatitis, there is generally no need to modify dosing because metabolism is only minimally altered. In chronic hepatitis and cirrhosis, hepatocytes are destroyed, and doses may need to be modified.

Medications with high baseline rates of liver clearance (e.g., haloperidol, sertraline, venlafaxine, TCAs) are significantly affected by hepatic disease. For drugs that have significant hepatic metabolism, intravenous administration may be preferred because parenteral administration avoids first-pass liver metabolic effects, and the dosing and action of parenteral medications are similar to those in patients with normal hepatic function. Valproic acid can impair the metabolism of the hepatocyte disproportionate to the degree of hepatocellular damage. In patients with valproate-induced liver injury, low albumin, high prothrombin, and high ammonia levels may be seen without significant elevation in liver transaminases.

Gastrointestinal Disease

Medications with anticholinergic side effects can slow GI motility, affecting absorption and causing constipation. SSRIs increase gastric motility and can cause diarrhea. SSRIs can increase the risk of GI bleeding, especially when administered with NSAIDs. Extended-release or controlled-release preparations of medications can reduce GI side effects, particularly where gastric distress is related to rapid increases in plasma drug concentrations.

Renal Disease

With the exceptions of lithium and gabapentin, psychotropic medications do not generally require significant dosing adjustments in kidney failure. It is important to monitor serum concentrations in renal insufficiency, particularly for medications with a narrow therapeutic index; cyclosporine can elevate serum lithium levels by decreasing lithium excretion. Patients with kidney failure and those on dialysis appear to be more sensitive to TCA side effects, possibly because of the accumulation of hydroxylated tricyclic metabolites.

Because most psychotropic medications are highly protein bound, they are not significantly cleared by dialysis. Lithium is essentially completely removed by dialysis, and the common practice is to administer lithium after dialysis. Patients on dialysis often have significant fluid shifts and are at risk for dehydration, with neuroleptic malignant syndrome more likely in these situations.

Cardiac Disease

Antipsychotics, TCAs, and citalopram (>40 mg/day) can lead to prolongation of the QTc interval, with increased risk of ventricular tachycardia and ventricular fibrillation, particularly in patients with structural heart disease. Patients with a baseline QTc interval of >440 msec should be particularly considered at risk. The normal QTc value in children is 400 msec (±25-30 msec). A QTc value that exceeds 2 SD (>450-460 msec) is considered too long and may be associated with increased mortality. An increase in the QTc from baseline of >60 msec is also associated with increased mortality.

There is increased risk of morbidity and mortality in patients with preexisting cardiac conduction problems. Some of the calcium channel–blocking agents (e.g., verapamil) can slow atrioventricular conduction and can theoretically interact with TCAs. Patients with Wolff-Parkinson-White syndrome who have a short PR interval (<0.12 sec) and widened QRS interval associated with paroxysmal tachycardia are at high risk for life-threatening ventricular tachycardia that may be exacerbated by the use of antipsychotics, TCAs, and citalopram.

Respiratory Disease

Anxiolytic agents can increase the risk of respiratory suppression in patients with pulmonary disease. In these situations, SSRIs and buspirone are good alternative medications to consider in treating disabling anxiety. Possible airway compromise caused by acute laryngospasm should be considered when dopamine-blocking antipsychotic agents are used.

Neurologic Disease

Psychotropic medications can be used safely with epilepsy following consideration of potential interactions among the medication, the seizure disorder, and the anticonvulsant. Any behavioral toxicity of anticonvulsants used either alone or in combination should be considered before proceeding with psychotropic treatment. Simplification of combination anticonvulsant therapy or a change to another agent can result in a reduction of behavioral or emotional symptoms and obviate the need for psychotropic intervention. Clomipramine and bupropion possess significant seizure-inducing properties and should be avoided when the risk of seizures is present.

Principles for Psychotropic Prescribing in Primary Care

Because nonpsychiatrist physicians (predominantly pediatricians) provide three quarters and two thirds, respectively, of all child and adolescent mental health visits in which new psychotropic medications are initiated, it can be helpful for PCPs to develop consultative relationships with child and adolescent psychiatrists who can advise about safe and effective psychotropic prescribing. If such consultation is not readily available, PCPs may benefit from following a standardized approach to prescribing that is feasible in the primary care setting (Table 33.8). This approach emphasizes baseline assessment with standardized rating scales to identify target symptoms and their level of severity; selection of FDA-approved medications for the target symptom and patient age range; adherence to recommendations regarding therapeutic dosage ranges; follow-up rating scale assessment to monitor medication response; sufficient duration of the medication trial; and switching to an alternative FDA-approved medication if the first medication trial is ineffective. Generally, consultation with a physician experienced in managing the child's disorder should occur if one is considering using multiple psychotropic medications, doses outside of therapeutic range, or non-FDA-approved medications.

Table 33.8

Principles for Psychotropic Prescribing in Primary Care

1. Identify potential target symptoms through the systematic use (e.g., at all well-child visits) of broad-band mental health screening instruments, such as the Pediatric Symptom Checklist or the Strengths and Difficulties Questionnaire.
2. Establish the baseline severity of identified target symptom(s) through the use of narrow-band symptom rating scales, such as the following (selected from instruments in the public domain):
    a. Depression
        - Mood and Feelings Questionnaire
        - Centers for Epidemiologic Studies Depression Scale
        - Patient Health Questionnaire-9

b. Anxiety
    - Screen for Child Anxiety Related Disorders

c. ADHD, Behavior Problems
    - Vanderbilt ADHD Diagnostic Rating Scale
    - SNAP-IV 19

d. Aggression
    - Outburst Monitoring Scale

3. Select a medication that is FDA approved for the target symptom and age range; titrate as tolerated from starting dose to therapeutic dosage range.
4. *Treat to target* : Readminister baseline symptom rating scale at regular intervals (at least monthly) to assess treatment response (reduction in rating scale score), with the goal of remission (rating scale score below clinical cutpoint).
5. If medication trial is unsuccessful after adherence to therapeutic dose for adequate duration (typically 1-2 mo), consider 2nd trial of alternative medication with FDA approval for target symptom and age range, following same principles as for 1st trial.
6. If 2nd medication trial is unsuccessful, consultation with a child and adolescent psychiatrist is recommended before resorting to medication doses outside therapeutic range, polypharmacy, or non–FDA-approved medications.

ADHD, Attention-deficit/hyperactivity disorder; FDA, U.S. Food and Drug Administration.

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[*] https://dailymed.nlm.nih.gov/dailymed/index.cfm .

CHAPTER 34

Psychotherapy and Psychiatric Hospitalization

Heather J. Walter, David R. DeMaso

Psychotherapy

Psychotherapy is the first-line treatment for most child and adolescent psychiatric disorders, because this type of treatment generally produces outcomes similar to pharmacotherapy, with less risk of harm. Even with disorders such as schizophrenia, bipolar disorder, and attention-deficit/hyperactivity disorder (ADHD) for which *medication is the first-line treatment* , adjunctive psychotherapy can convey considerable additional benefit. Because pediatric primary care practitioners (PCPs) likely will be referring youth with psychiatric disorders for psychotherapy, they should be familiar with basic information about child and adolescent psychotherapy.

Overall, psychotherapy is moderately effective in reducing psychiatric symptomatology and achieving remission of illness. In a 2017 multilevel meta-analysis of almost 500 randomized trials over 5 decades, there was a 63% probability that a youth receiving psychotherapy fared better than a youth in a control condition. Effects varied across multiple moderators, including the problem targeted in treatment. Thus, the mean posttreatment and follow-up effect sizes were highest for anxiety, followed by behavior/conduct, ADHD, and depression, and lowest for multiple concurrent comorbidities. Effect sizes varied according to outcome measure informant, with youth and parents generally reporting larger effects than teachers. Ethnicity moderator tests showed no significant differences in treatment benefit between majority Caucasian samples and majority non-Caucasian samples.

A variety of psychotherapeutic programs have been developed, with varying levels of effectiveness (Table 34.1). Differences between therapeutic approaches may be less pronounced in practice than in theory. The quality of the therapist–patient alliance is consistently an important predictor of treatment outcome. A positive working relationship, expecting change to occur, facing problems assertively, increasing mastery, and attributing change to the participation in the therapy have all been connected to effective therapy.

Table 34.1

Effective Psychotherapies for Specific Behavioral Health Disorders

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DISORDER	WELL ESTABLISHED[*]	PROBABLY EFFICACIOUS[†]
Anorexia	Family therapy: behavioral	Family therapy: systemic
		Individual insight-oriented psychotherapy
Anxiety	Individual CBT	CBT + parent component
		CBT + medication
ADHD	Behavioral parent training	Combined training interventions
	Behavioral classroom management	
	Behavioral peer interventions	
	Organization (executive function) training	
Autism	Individual, comprehensive ABA	Individual, focused ABA + DSP
	Teacher-implemented ABA + DSP	Focused DSP parent training
Bipolar	None	Family psychoeducation + skill building
Depression, child	Group CBT	Behavior therapy
	Group CBT + parent component	
Depression adolescent	Group CBT	Group CBT + parent component
	Individual interpersonal psychotherapy	Individual CBT
		Individual CBT + parent/family component
Insomnia	Individual CBT	
ODD and CD, child	Individual/parent management training	Group CBT
	Individual CBT	Group/parent management training
	Problem-solving skill training	
	Group assertiveness training	
	Multidimensional treatment foster care	
	Multisystemic therapy	
ODD and CD, adolescent	Combined behavioral therapy, CBT, and family therapy	CBT
	Treatment foster care	
OCD	None	Individual CBT
		Family-focused individual CBT
Personality Disorders	None	Dialectical behavioral therapy
PTSD	Trauma-focused CBT	Group CBT
Social phobia	None	Group CBT
Specific phobia	None	None
Substance use	Group CBT	Family-based treatment, behavioral

	Individual CBT	Motivational interviewing
	Family-based treatment, ecologic	
Self-injury	Individual + family CBT + parent training	Family-based therapy
	Psychodynamic individual + family	

[*] Two or more consistent randomized controlled trials demonstrating superiority of treatment over control groups; conducted by independent investigators working at different research settings.

[†] Same as above, but lacking independent investigator criterion.

ADHD, Attention-deficit/hyperactivity disorder CBT, cognitive-behavioral therapy; ABA, applied behavioral analysis; DSP, developmental social-pragmatic; ODD, oppositional defiant disorder; CD, conduct disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.

Adapted from Society of Clinical Child and Adolescent Psychology: Effective child psychotherapy. http://effectivechildtherapy.org/content/ebp-options-specific-disorders . Accessed March 5, 2017.

All psychotherapy interventions involve a series of interconnected steps, including performing an assessment, constructing working diagnoses and an explanatory formulation, deciding on treatment and a monitoring plan, obtaining treatment assent/consent, and implementing treatment. Psychotherapists ideally develop a treatment plan by combining known evidence-based therapies with clinical judgment and patient/family preference to arrive at a specific intervention plan for the individual patient.

Behavior Therapy

Behavior therapy is based on both classic (Pavlovian) and operant (Skinnerian) conditioning. Both approaches do not concern themselves with the inner motives of the individual, but instead address the antecedent stimuli and consequent responses. The treatment begins with a behavioral assessment with interview, observation, diary, and rating scale components, along with a functional analysis of the setting context, immediately preceding external events, and real-world consequences of the behavior. A treatment plan is developed to modify the maladaptive functions of the behavior, using tools such as positive and negative reinforcement, social and tangible rewards, shaping, modeling, and prompting to increase positive behavior, and extinction, stimulus control, punishment, response cost, overcorrection, differential reinforcement of incompatible behavior, graded exposure/systematic desensitization, flooding, modeling, and role-playing to decrease negative behavior.

Behavior therapy has shown applicability to anxiety disorders, obsessive-compulsive and related disorders, behavior disorders, **A** DHD, and autism spectrum disorder.

Cognitive-Behavioral Therapy

Cognitive-behavioral therapy (CBT) is based on social and cognitive learning theories and extends behavior therapy to address the influence of cognitive processes on behavior. CBT is a problem-oriented treatment centered on correcting problematic patterns in *thinking* and *behavior* that lead to emotional difficulties and functional impairments. The CBT therapist seeks to identify and change cognitive distortions (e.g., learned helplessness, irrational fears), identify and avoid distressing situations, and identify and practice distress-reducing behavior. Self-monitoring (daily thought records), self-instruction (brief sentences asserting thoughts that are comforting and adaptive), and self-reinforcement (rewarding oneself) are key tools used to facilitate achievement of the CBT goals. Table 34.2 outlines the key descriptive features of CBT that can be used by PCPs when describing CBT to patients and their family members.

Table 34.2

Core Components and Characteristics of Cognitive-Behavioral Therapy

- One 60- to 90-minute session each week, typically for 6-12 weeks
- Symptom measures typically are collected frequently.
- Treatment is goal-oriented and collaborative with patient as an active participant.
- Treatment is focused on changing current problematic thoughts or behaviors.
- Weekly homework typically is assigned.

From Coffey SF, Banducci AN, Vinci C: Common questions about cognitive behavior therapy for psychiatric disorders. *Am Fam Physician* 92:807–812, 2015.

CBT has good-quality evidence for the treatment of depression, anxiety, obsessive-compulsive disorders (OCDs), behavior disorders, substance abuse, and insomnia (see Table 34.1). For many childhood psychiatric disorders, CBT alone provides outcomes comparable to psychotropic medication alone, and the combination of both may convey additional benefit in symptom and harm reduction.

Modified versions of CBT have shown applicability to the treatment of other disorders. **Trauma-focused cognitive-behavioral therapy (TF-CBT)** involves a combination of psychoeducation; teaching effective relaxation, affective modulation, and cognitive coping and processing skills; engaging in a trauma narrative; mastering trauma reminders; and enhancing future safety and development. TF-CBT is considered the first-line treatment for posttraumatic stress disorder (PTSD).

Dialectical behavioral therapy (DBT) is a CBT approach targeted at emotional and behavioral dysregulation by synthesizing or integrating the seemingly opposite strategies of acceptance and change. Dialectic conflicts (wanting to die vs wanting to live) often exist in the same patient and are important to address. The 4 skills modules—*mindfulness* (the practice of being fully aware and present in the moment), *distress tolerance* (how to tolerate emotional pain), *interpersonal effectiveness* (how to maintain self-respect and effective communication in relationships with others), and *emotion regulation* (how to manage complex emotions)—are balanced in terms of acceptance and change. Patients who receive DBT typically have multiple problems; the treatment targets, in order of priority within a given session, are *life-threatening* behaviors, such as suicidal and self-injurious behaviors or communications; *therapy-interfering* behaviors, such as coming late to sessions, cancelling appointments, and being noncollaborative in working toward treatment goals; *quality-of-life* behaviors, including relationship and occupational problems and financial crises; and skills acquisition to help patients achieve their goals. DBT has shown promise for the treatment of personality disorders, suicidal behavior, bipolar disorder, and other manifestations of emotional-behavioral dysregulation.

Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT) focuses on interpersonal issues that lead to psychological distress. Patients are viewed to having biopsychosocial strengths and vulnerabilities that determine the manner in which they cope or respond to an interpersonal crisis (**stressor**). Symptom resolution, improved interpersonal functioning, and increased social support are the IPT targets. IPT has proved to be a well-established treatment for adolescent depression.

Psychodynamic Psychotherapy

At the core of psychodynamic psychotherapy lies a *dynamic* interaction between different dimensions of the mind. This approach is based on the belief that much of one's mental activity occurs outside one's awareness. The patient is often unaware of internal conflicts because threatening or painful emotions, impulses, and memories are repressed. Behavior is then controlled by what the patient does not know about himself or herself. Therapy objectives are to increase self-understanding, increase acceptance of feelings, and develop realistic relationships between self and others. This therapy is nondirective to allow a patient's characteristic patterns to emerge, so that self-understanding and a corrective emotional experience can then be fostered.

Psychodynamic psychotherapy has shown applicability for the treatment of anxiety and depression as well as maladaptive aspects of personality. Brief, time-limited psychodynamic psychotherapy can be appropriate for youth who are in acute situational distress. Long-term therapy can be appropriate when the biologic or social factors destabilizing the child's adaptation and development are chronic, or the psychological difficulties caused by comorbidities are complex, or if entrenched conflicts and developmental interferences are present.

Supportive Psychotherapy

Supportive psychotherapy aims to minimize levels of emotional distress through the provision of individual and contextual support. The goal is to reduce symptoms, and treatment is focused on the “here and now.” The therapist is active and helpful in providing the patient with symptomatic relief by helping the patient to contain and manage anxiety, sadness, and anger. The therapist provides support and encouragement to bolster a patient's existing coping mechanisms, facilitates problem-solving, and provides social and instrumental support for ameliorating or lessening contextual precipitants. CBT-informed techniques are often combined with supportive psychotherapy. Probably the most common psychotherapy employed by therapists, supportive psychotherapy has shown comparable results to CBT in a number of research studies.

Family Therapy

The core premise in family therapy is that dysfunctional family interaction patterns precipitate and/or perpetuate an individual's emotional or behavioral difficulties. Family dysfunction can take a variety of forms, including enmeshment, disengagement, role-reversal or confusion, and maladaptive communication patterns. Family therapy begins with an assessment of the family system, including observing patterns of interaction, assessing family beliefs and the meanings attached to behaviors, defining social and cultural contexts, exploring the presenting problem in the context of individual and family development, assessing the family's style of dealing with problems, and identifying family strengths and weaknesses.

Family therapy techniques are drawn from 2 major theoretical models: structural and behavioral. *Structural* family therapy develops structures believed to foster well-functioning families, including clear and flexible boundaries between individuals, well-defined roles, and an appropriate balance between closeness and independence. *Behavioral* family therapy focuses on behavioral sequences that occur in daily life and attempts to interrupt unhelpful patterns and strengthen positive patterns through effective communication and problem solving.

Family therapy has shown established applicability in anorexia nervosa and substance use and may be a promising treatment for depression.

Parenting Interventions

(See Chapter 19 for more details)

Parenting interventions seek to improve both the parent–child relationship and parenting skills using the principles of behavior therapy previously described. They can be provided in individual or group therapy formats. Core relationship recommendations include spending quality time with the child, increasing verbal interaction, showing physical affection, providing contingent praise, and engaging in child-directed play. Core parenting skills include increasing reinforcement of positive behaviors, decreasing reinforcement of negative behaviors, ignoring merely annoying behaviors, applying consequences for dangerous/destructive behaviors, and making parental responses predictable, contingent, and immediate. Parenting interventions have shown applicability for behavior disorders and ADHD.

Common Elements of Evidence-Based Psychotherapies

A major challenge for the practitioner is selecting the “right intervention” for the "right person" in the "right setting," and delivering the intervention in the "right way" (to meet the needs of patients and families). This challenge has led to interest in identifying common **practice elements** across efficacious evidence-based therapies that could be "matched" in a flexible way to patients of a certain age, gender, and race/ethnicity who have certain psychiatric disorders. Table 34.3 provides the major practice elements for 3 of the most common child and adolescent psychiatric disorders: anxiety, depression, and disruptive behaviors. These practice elements, when made available to patients with psychiatric disorders in a system of care, are estimated to be relevant to approximately two thirds of the patients. Six of the practice elements—problem-solving skills, psychoeducation of the parent, relaxation skills, self-monitoring, cognitive/coping skills, and psychoeducation of the child—are applicable to all 3 disorders and as such could be considered "core skills" for the child and adolescent psychotherapist.

Table 34.3

Practice Elements in Interventions for 3 Common Child and Adolescent Psychiatric Disorders

	ANXIETY DISORDERS	DEPRESSION	DISRUPTIVE BEHAVIOR
Directed play			X
Limit setting			X
Time-out			X
Cost response			X
Activity scheduling		X	
Maintenance		X	X
Skill building		X	
Social skills training		X	X
Therapist praise/rewards			X
Natural and logical consequences	X		X
Communication skills	X		X
Assertiveness training	X		
Parent monitoring	X		X
Modeling	X		
Ignoring	X		X
Parent praise	X		X
Problem solving	X	X	X
Parent coping	X		X
Psychoeducation, parent	X	X	X
Relaxation	X	X	X
Tangible rewards	X		X
Self-monitoring	X	X	X
Cognitive/coping	X	X	X
Psychoeducation, child	X	X	X

Exposure	X		

Adapted from Chorpita BF, Daleiden EL, Weisz JR: Identifying and selecting the common elements of evidence based interventions: a distillation and matching model, *Ment Health Serv Res* 7(1):5–20, 2005.

Psychoeducation is the education of the parent and child about the cause, course, prognosis, and treatment of the disorder. **Problem solving** is techniques, discussions, or activities designed to bring about solutions to targeted problems, with the intention of imparting a skill for how to approach and solve future problems in a similar manner. **Relaxation** is techniques designed to create and maintain the physiologic relaxation response. **Self-monitoring** is the repeated measurement of a target metric by the child. **Cognitive/coping** skills consist of techniques designed to alter interpretations of events through examination of the child's reported thoughts, accompanied by exercises designed to test the validity of the reported thoughts. PCPs can incorporate some of these elements into their anticipatory guidance work with pediatric patients.

Modular Therapy Packages

Of considerable importance to day-to-day clinical work is the manner in which common therapy practice elements are selected, sequenced, repeated, or selectively applied. This **coordination** of psychotherapeutic elements is particularly relevant for patients presenting with multiple concurrent psychiatric disorders. The *Modular Approach to Therapy for Children* (MATCH) is a multidisorder intervention system that incorporates treatment procedures (practice elements) and treatment logic (coordination) corresponding to efficacious interventions for childhood anxiety, depression, and behavior problems, with modifications to allow the system to operate as a single protocol. Compared with standard manualized treatments for individual disorders and with usual care, the modular package outperformed both comparators on multiple clinical and service outcome measures when assessed over a 2-yr period, although additional, independently derived evidence is needed to categorize this treatment approach as well established.

Common Elements of Treatment Engagement Interventions

Treatment engagement is conceptualized as a multidimensional construct targeting *cognitive, attendance,* and *adherence* domains. Research has identified several key factors addressing these domains that are associated with treatment engagement: accessibility promotion, psychoeducation about services, appointment reminders, assessment of treatment barriers, patient assessment, expectation setting, modeling, and homework assignments (Table 34.4). To promote treatment engagement, the first 7 of these factors can be addressed by the PCP and the medical home team as soon as a mental health problem is identified that would benefit from treatment (see Chapter 17 for further discussion).

Table 34.4

Select Psychotherapy Engagement Elements

ELEMENT	DEFINITION
Accessibility promotion	Any strategy used to make services convenient and accessible in order to proactively encourage and increase participation in treatment; e.g., hiring a co-located therapist or referring to a local community-based therapist with whom the practice has an ongoing collaborative relationship
Psychoeducation about services	Provision of information about services or the service delivery system; e.g., type of therapy being recommended, information about the therapist, session frequency and duration
Appointment reminders	Providing information about the day, time, and location of the therapy office for the initial appointment via mail, text, phone, email, etc., to increase session attendance
Assessment of treatment barriers	Discussion to elicit and identify barriers that hinder participation in treatment; e.g. transportation, scheduling, childcare, previous experiences with therapy, stigma
Assessment	Measurement of the patient's strengths/needs through a variety of methods; e.g., mental health screening instruments, interviews, recorded reviews during which the referring practitioner can motivate treatment engagement
Modeling	Vehicle to convey information about specific roles of the therapist; e.g., introductory video or brochure
Expectation setting	Instillation of hope regarding the efficacy of therapy and the patient's ability to participate successfully in treatment
Homework assignment	Therapeutic tasks given to the patient to complete outside the therapy session to reinforce or facilitate knowledge or skills that are consistent with the treatment plan

Adapted from Lindsey MA, Brandt NE, Becker KD, et al: Identifying the common elements of treatment engagement interventions in children's mental health services, *Clin Child Fam Psychol Rev* 17:283–298, 2014; and Becker KD, Lee BR, Daleiden EL, et al: The common elements of engagement in children's mental health services: which elements for which outcomes? *J Clin Child Adolesc Psychol* 44(1):30–43, 2015.

Psychotherapy in the Medical Home

Recognizing that up to one half of visits to PCPs involve a mental health problem, and that an estimated one fifth of pediatric patients have a functionally impairing psychiatric disorder, in the context of limited access to specialty mental health services in community or hospital settings, a number of models have been developed to deliver psychotherapy in primary care. Two prominent models, both originally developed for adult populations, are collaborative care and primary care behavioral health.

Collaborative care integrates physical and mental healthcare for patients who have a psychiatric disorder in a treatment model that provides both psychotropic medication and psychotherapy delivered by an interdisciplinary care team of PCPs, social workers, and care managers supported by a consulting psychiatrist. The role of the consulting psychiatrist is to advise the PCPs about psychotropic medication management and the therapists about brief psychotherapeutic interventions. The 4 critical elements of collaborative care are team-driven, population-focused, measurement-guided, and evidence-based. These elements guide a treatment approach in which evidence-based, measurement-guided (e.g., symptom rating scale scores as treatment targets) mental healthcare is delivered by the multidisciplinary team to the entire patient population as indicated, such that the patient perceives a seamless integration of medical and mental healthcare.

In children and adolescents, randomized controlled trials (RCT) have shown that collaborative care for behavior problems, adolescent depression, and adolescent substance use is associated with more favorable treatment adherence, symptom reduction, disorder remission, and consumer satisfaction outcomes than usual care, with or without specialty referral. In a meta-analysis and systematic review, overall integrated medical-mental healthcare for children and adolescents led to improved mental health outcomes compared with usual care. Larger effects were observed for treatment trials targeting diagnoses and elevated symptoms relative to prevention trials, as well as for collaborative care models relative to other integrated mental healthcare.

Primary care behavioral health employs an on-site mental health professional (psychologist, social worker, mental health counselor) to provide focused assessment of patients with mental health, health behavior, and substance use problems and short-term therapy as well as health/mental health promotion and prevention interventions. Mental health clinicians typically collaborate with primary care physicians to develop treatment plans, monitor patient progress, and flexibly provide care to meet patients' changing needs. The model uses a “wide net” approach aimed at serving the entire primary care population, with emphasis on brief, focused interventions. Key features of the model include “warm handoffs,” in which the physician introduces the mental health clinician directly to the patient, and “curbside consultations,” in which the physician and mental health clinician have frequent informal interactions to discuss patients.

A limited evidence base supports the primary care behavioral health model, but the research literature on brief intervention is increasing and encouraging. Brief interventions lasting only 1 session are effective for multiple child psychiatric disorders, particularly anxiety and behavior problems and among children (vs adolescents), and are most effective for CBT approaches. Psychosocial interventions delivered by PCPs (rather than behavioral health clinicians) have not been found to be effective in a Cochrane review.

Psychiatric Hospitalization

Youth with severe psychiatric disorders require initial evaluation, treatment planning, and stabilization by child-trained behavioral health clinicians. Psychiatric hospital programs address the serious risks and severe impairments caused by the most acute and complex forms of psychiatric disorder that cannot be managed effectively at any other level of care. The goal is to produce rapid clinical stabilization that allows an expeditious, safe, and appropriate treatment transition to a less intensive level of mental healthcare outside the hospital.

High levels of illness severity combined with significant functional impairment signal a need for hospitalization. Admission criteria must include significant signs and symptoms of active psychiatric disorder. Functional admission indicators generally include a significant risk of self-harm or harm to others, although in some cases the patient is unable to meet basic self-care or healthcare needs, jeopardizing well-being. Serious emotional disturbances that prevent participation in family, school, or community life can also rise to a level of global impairment that can only be addressed on an inpatient basis.

Discharge planning begins at admission, when efforts are made to coordinate care with services and resources that are already in place for the child or adolescent in the community. Step-down care might be needed in partial hospital or residential settings if integrated services in a single location are still indicated after sufficient clinical stabilization has occurred in the hospital setting. Transition from the hospital entails active collaboration and communication with PCPs in the child's medical home. In some cases the PCP resumes the pharmacologic treatment of these youth once stabilized.

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CHAPTER 35

Somatic Symptom and Related Disorders

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Pediatric psychosomatic medicine deals with the relation between physical and psychological factors in the causation or maintenance of disease states. The process whereby distress is experienced and expressed in physical symptoms is referred to as **somatization** or **psychosomatic illness** . Even though present in virtually every psychiatric disorder, physical symptoms are most prominent in the various somatic symptom and related disorders.

In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), illnesses previously referred to as “somatoform disorders” are classified as **somatic symptom and related disorders (SSRDs).** In children and adolescents, the SSRDs include **somatic symptom disorder** (Table 35.1), **conversion disorder** (Table 35.2), **factitious disorders** (Table 35.3), **illness anxiety disorder** (Table 35.4), and other **specified/unspecified somatic symptom disorders** (Table 35.5), as well as psychological factors affecting other medical conditions (Table 35.6).

Table 35.1

DSM-5 Diagnostic Criteria for Somatic Symptom Disorder

A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.

B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns, as manifested by at least one of the following:

1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
2. Persistent high level of anxiety about health and symptoms.
3. Excessive time and energy devoted to these symptoms or health concerns.

C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically >6 mo).

Specify if:

With predominant pain (previously known as “pain disorder” in DSM IV-TR): for individuals whose somatic symptoms predominantly involve pain.

Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (>6 mo).

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 311.

Table 35.2

DSM-5 Diagnostic Criteria for Conversion Disorder or Functional Neurologic Symptom Disorder

A. One or more symptoms of altered voluntary motor or sensory function.

B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurologic or medical conditions.

C. The symptom is not better explained by another medical or mental disorder.

D. The symptom causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify symptom type: weakness or paralysis, abnormal movements, swallowing symptoms, speech symptom, attacks/seizures, anesthesia/sensory loss, special sensory symptom (e.g., visual, olfactory, hearing), or mixed symptoms.

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 318.

Table 35.3

DSM-5 Diagnostic Criteria for Factitious Disorders

Factitious Disorder Imposed on Self

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.
B. The individual presents himself or herself to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Specify if: single episode or recurrent episodes.

Factitious Disorder Imposed on Another (Previously “Factitious Disorder by Proxy”)

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, in another, associated with identified deception.
B. The individual presents another individual (victim) to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Note : The perpetrator, not the victim, receives this diagnosis.
Specify if: single episode or recurrent episodes.

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 324.

Table 35.4

DSM-5 Diagnostic Criteria for Illness Anxiety Disorder

A. Preoccupation with having or acquiring a serious illness.

B. Somatic symptoms are not present, or, if present, are only mild in intensity. If another medical condition is present or there is a high risk for developing a medical condition (e.g., strong family history is present), the preoccupation is clearly excessive or disproportionate.

C. There is a high level of anxiety about health, and the individual is easily alarmed about personal health status.

D. The individual performs excessive health-related behaviors (e.g., repeatedly checks his or her body for signs of illness) or exhibits maladaptive avoidance (e.g., avoids doctor appointments and hospitals).

E. Illness preoccupation has been present for at least 6 mo, but the specific illness that is feared may change over that time.

F. The illness-related preoccupation is not better explained by another mental disorder.

Specify whether: care-seeking type or care-avoidant type.

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 315.

Table 35.5

DSM-5 Diagnostic Criteria for Other Specified/Unspecified Somatic Symptom and Related Disorders

Other Specified

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet full criteria for any of the disorders in the *somatic symptom and related disorders* diagnostic class. Examples of presentations that can be specified using the “other specified” designation include the following:

1. Brief somatic symptom disorder: duration of symptoms is <6 mo.
2. Brief illness anxiety disorder: duration of symptoms is <6 mo.
3. Illness anxiety disorder without excessive health-related behaviors: Criterion D for illness anxiety disorder is not met (see Table 35.4).
4. *Pseudocyesis* : a false belief of being pregnant that is associated with objective signs and reported symptoms of pregnancy.

Unspecified

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in functioning predominate but do not meet criteria for any of the other disorders in the *somatic symptom and related disorders* diagnostic class.

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 327.

Table 35.6

DSM-5 Diagnostic Criteria for Psychological Factors Affecting Other Medical Conditions

A. A medical symptom or condition (other than a mental disorder) is present.

B. Psychological or behavioral factors adversely affect the medical condition in one of the following ways:

1. The factors have influenced the course of the medical condition, as shown by a close temporal association between the psychological factors and the development or exacerbation of, or delayed recovery from, the medical condition.
2. The factors interfere with the treatment of the medical condition (e.g., poor adherence).

3. The factors constitute additional well-established health risks for the individual.
4. The factors influence the underlying pathophysiology, precipitating or exacerbating symptoms or necessitating medical attention.

C. The psychological and behavioral factors in Criterion B are not better explained by another mental disorder (e.g., panic disorder, major depressive disorder, posttraumatic stress disorder).

Specify if: mild, moderate, severe, or extreme.

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 322.

With the exception of illness anxiety disorder, in which there is a high level of anxiety about health in the absence of significant somatic symptoms, and psychological factors affecting other medical conditions, in which psychological and/or behavioral factors adversely affect a medical condition, SSRDs are classified on the basis of physical symptoms associated with significant distress and impairment, with or without the presence of a diagnosed medical condition. The symptoms form a continuum that can range from pain to disabling neurologic symptoms and generally interfere with school/home life and peer relationships.

Most patients with SSRDs are seen by primary care practitioners or by pediatric subspecialists, who may make specialty-specific diagnoses such as visceral hyperalgesia, chronic fatigue syndrome, psychogenic syncope, or noncardiac chest pain. Even within psychiatry, SSRDs are variously referred to as **functional** or **psychosomatic disorders** or as **medically unexplained symptoms** . The nosologic heterogeneity across the pediatric subspecialties contributes to the varying diagnostic labels. There is a significant overlap in the symptoms and presentation of patients with somatic symptoms who have received different diagnoses from different specialties. Moreover, SSRDs share similarities in etiology, pathophysiology, neurobiology, psychological mechanisms, patient characteristics, and management and treatment response, which is indicative of a single spectrum of somatic disorders.

It is helpful for healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered physically or psychologically based. In contrast, a *biobehavioral continuum* of disease better characterizes illness as occurring across a spectrum ranging from a predominantly biologic to a predominantly psychosocial etiology.

Epidemiology

Between 10% and 30% of children worldwide experience physical symptoms that are seemingly unexplained by a physical illness. Estimated prevalence varies greatly between studies based on the type of symptoms and the study methodology. The frequency and heterogeneity of complaints increase with age, with symptoms occurring more frequently in girls than boys.

Many children with persistent complaints of abdominal pain meet criteria for somatic symptom disorder with predominant pain in DSM-5. Headaches and back, limb, and chest pain are also frequently occurring pain symptoms in adolescents. Prevalence rates of conversion disorder in adolescents are 0.3–10%. Nonepileptic seizures, loss of consciousness, and motor symptoms are common conversion symptoms across cultures.

Risk Factors

Individual

Temperament/Coping Styles

Somatic symptoms have been found to be more common in children who are conscientious, sensitive, insecure, internalizers, and anxious, and in those who strive for high academic achievement. Somatization may also occur in children who are unable to verbalize emotional distress. Somatic symptoms are often seen as a form of psychological defense against intrapsychic distress that allows the child to avoid confronting anxieties or conflicts, a process referred to as “primary gain.” The symptoms may also lead to what is described as “secondary gain” if the symptom results in the child being allowed to avoid unwanted responsibilities or consequences.

Learned Behavior

Somatic complaints may be reinforced through a decrease in responsibilities or expectations by others and through receiving attention and sympathy. Many children may have an antecedent underlying general medical condition that may then be reinforced by parental and peer attention as well as additional medical attention in the form of unnecessary tests and investigations.

Psychiatric Comorbidity

There is an association between somatization and other psychiatric illness, in particular depressive and anxiety disorders. A familial link exists between SSRDs and other psychiatric disorders (e.g., higher rates of anxiety and depression in family members).

Childhood Physical Illness

There appears to be a connection between childhood physical illness and the later development of somatization. Many children with an SSRD have other medical conditions. An antecedent history (e.g., accident, viral illness) may trigger onset of symptoms and lead to prolonged recovery or recurrence of symptoms after illness should have subsided. Children who tend to somatize may have a tendency to experience normal somatic sensations as “intense, noxious, and disturbing,” referred to as *somatosensory amplification* .

Family and Environmental

Symptom Modeling

Multiple studies have found evidence that a significant proportion of patients with SSRD had recently encountered similar symptoms in their local environment or live with family members who complain of similar physical symptoms (e.g., child with nonepileptic seizures who has parent or sibling with seizure disorder).

Parental Responses

Parent beliefs about the significance of symptoms influence the extent of symptoms the child reports. Having a somatic complaint may be more acceptable or noticed in some households than the expression of strong emotions (e.g., anxiety, fear, anger). In such an environment, a child may garner minimal attention for emotional distress, but obtain more attention and sympathy for physical symptoms. Multiple studies have shown that parental protectiveness predicts child functional disability and parental responses (e.g., discouraging activity, expressing concern, providing comfort) may serve inadvertently to reinforce and maintain illness behaviors.

School and Family Stressors

External environmental factors (e.g., school stress, change in family situation) are common in children presenting with an SSRD. Common school stressors include bullying, beginning the school year, fear of academic failure, or participation in extracurricular school activities. Dysfunction and less support within the family system are common. Transitions within the family system, including death of a family member, birth of a sibling, parental divorce, physical punishment by parents, and increased arguments between parents, have all been linked to somatic symptoms. Nevertheless, a significant minority of patients with SSRD do not appear to have obvious psychosocial precipitants for their symptoms. It is unclear whether recorded stressful events are absent in these patients because they were unwilling or unable to report relevant stressors or because the stressors were simply absent.

Trauma

Elevated rates of childhood trauma (e.g., sexual, physical, or emotional abuse) have been found in patients with SSRD, although the trauma prevalence rates in studies vary widely.

Genetic and Biologic Vulnerabilities

Genetic and biologic vulnerabilities (e.g., increased pain sensitivity) are thought to contribute to SSRDs. Research has suggested some unifying mechanisms, including aberrant functions of efferent neural pathways, such as the autonomic nervous system and hypothalamic-pituitary axis, and alterations in central processing of sensory input. Hyperactivity of the anterior cingulate cortex has been found in patients with conversion disorder, along with impaired activity of the dorsolateral prefrontal cortex. In chronic pain studies, including migraine and tension-type headaches, there appears to be progressive loss of gray matter density in brain structures involved in registering pain, such as the somatosensory cortex, anterior cingulate cortex, and insula. Additionally, when there is a strong expectation of pain, the anterior insular cortex is activated in proportion to this expectation.

Assessment

The majority of patients with SSRD present in the pediatric setting rather than the mental health setting. It is important for pediatric practitioners to make their diagnosis based on positive symptoms and signs (distressing somatic symptoms plus abnormal thoughts, feelings, and behaviors in response to these symptoms) rather than the absence of a medical explanation. As such, the evaluation of suspected disorders should include an assessment of biologic, psychological, social, and developmental realms, both separately and in relation to each other. An integrated approach in which both pediatric and mental health clinicians are involved in the assessment, management, and treatment is indicated.

Medical

The presence of a physical illness does not exclude the possibility of somatization playing an important role in the child's presentation. Somatic symptoms early in a disease course that can be directly attributed to a specific physical illness (e.g., acute respiratory illness) may evolve into psychologically based symptoms, particularly in situations where the child may experience benefit from adopting the sick role. Somatic symptoms may also occur in excess of what would be expected of the symptoms experienced in an existing physical illness. Physical findings may occur secondary to the effects of the somatic symptom disorder, especially when chronic or severe (e.g., deconditioning, disuse atrophy and contractures from prolonged immobilization, nutritional deficiency, gastroparesis and constipation from chronic poor oral intake).

A comprehensive medical workup to rule out serious physical illness must be carefully balanced with efforts to avoid unnecessary and potentially harmful tests and procedures. The physical examination will find that the child's symptoms may fluctuate in different contexts, may be anatomically inconsistent, or may be in excess of what would be expected from the physical findings.

Psychosocial

If somatization is suspected, mental health consultation should be included early in the diagnostic workup. The reason for consultation should be carefully explained to the family to help avoid the perception that their child's symptoms are not being taken seriously by the pediatric team (i.e., “it's in her head”). It should be explained that a complete workup involves a thorough assessment of the physical and psychological domains of the child, and that the psychiatric consultation can provide further understanding of the origins of the child's distress, what perpetuates it, and which treatments are likely to be most effective.

The mental health evaluation should include a careful assessment of the psychological and social stressors and risk factors, including a thorough family psychiatric and medical history. The nature of current physical symptoms and any history of prior episodes of somatic symptoms should be included in the assessment, in addition to the child's emotional, social, and academic functioning; coping strategies; and family functioning. The evaluation should provide the clinical team with a biopsychosocial explanation of the child's symptoms, which will inform the treatment plan.

Differential Diagnoses

The primary differential diagnosis is between an SSRD and a physical illness. Importantly, however, these disorders are not mutually exclusive and often coexist. Mood and anxiety disorders frequently include the presence of physical symptoms, which tend to remit with treatment of the primary mood or anxiety symptoms, and which appear distinct from physical complaints seen in SSRDs. Chronic pain syndromes may be caused by fibromyalgia and small fiber autonomic neuropathy.

Management

With the completion of medical and psychological assessments, a multidisciplinary team meeting of pediatric and mental health clinicians should be arranged to review all the specialty evaluations and tests and discuss diagnostic impressions and treatment recommendations. This should occur to ensure consensus on the diagnosis and treatment plan and facilitate adequate and consistent communication among all providers.

An informing meeting or conference with the family should be facilitated after the team meeting to convey the multidisciplinary team's diagnostic impressions and treatment recommendations to the patient and family. Pediatric and mental health clinicians together should communicate the diagnosis (or diagnoses) in a way that families can understand using a comprehensive biopsychosocial formulation. Medical and psychosocial findings should be acknowledged and discussed.

Patients and families with SSRD often present with the belief that there is primarily a medical cause for their problem, and psychosocial contributors are often resisted. After exhaustive medical investigations yield no unifying results, labeling the symptoms as “psychiatric” can effectively shift the search for the cause onto family functioning, resulting in children and parents feeling blamed for the symptoms. The team should help the family move toward an understanding of the mind–body connection and shift their approach from searching for the cause of the symptoms to increasing family functioning. Providing education about the benefits of treatment and risks of no treatment is helpful to move the family through the treatment steps.

Treatment

An integrated multidisciplinary rehabilitation model provides a useful framework for treatment that shifts the focus away from finding a cure for symptoms, and instead emphasizes a return to normal adaptive functioning. This includes increased activities of daily living, improved nutrition, enhanced mobility, return to school and socialization with peers.

Cognitive behavioral therapy (CBT) is the evidence-based intervention of choice. CBT interventions modify symptom experience (including pain perception) and restore central nervous system abnormalities associated with functional impairment. CBT techniques (e.g., relaxation training, biofeedback, hypnosis) can be used to teach patients the control they can have over certain physiologic processes, such as autonomic system activity. Cognitive restructuring is effective in addressing and altering dysfunctional thoughts regarding symptoms and their implications for functioning. Treatments that encourage active coping strategies and emotional expression and modulation, and that limit patient reliance on emotional support provided by parents, are helpful in reducing symptoms and improving functioning. Modifying parental response patterns that are overprotective and potentially reinforcing (e.g., allowing the child to sleep late or to stay home from school in response to symptoms) help to decrease disability.

Psychopharmacologic treatment may be considered when psychiatric comorbidities are present, specifically, depressive and anxiety disorders. A combination of pharmacotherapy, physical therapy, and psychological interventions in multicomponent management programs has been shown to be effective.

Treatment Setting

The majority of patients can be managed in the outpatient setting with appropriate mental health follow-up. Scheduled follow-up visits with the primary care provider are important to maintain alliance and investment in treatment, prevent “doctor shopping,” and avoid unnecessary invasive tests and procedures.

Because of the nature of their symptoms, most patients with SSRD do not present in mental health settings for their physical complaints, and only patients who display prominent emotional symptoms or who have a concurrent mental disorder are referred to mental health services. Pediatric specialists treat “their own” specialty somatic syndromes within their service, as a natural consequence of the large number of patients with these disorders presenting at their clinics. The management in these clinics is often monodisciplinary and comprises primarily medically based treatments and interventions. The existence of various syndrome-specific clinics perpetuates the separate, specialty-dominated approach to SSRDs and can perpetuate fragmented care rather than moving toward a more integrated model. Although specialized clinics play an important role in providing the expertise needed in the evaluation of these patients, these clinics are often not prepared to manage patients who have symptoms involving multiorgan systems. These patients may attend several clinics simultaneously and receive several parallel, uncoordinated treatments.

A **medical home model** with mental health clinicians working in collaboration with pediatric practitioners and/or different pediatric specialists may prove to be the most suitable approach for patients with SSRD. Integrated pediatric and mental health services improve communication, decrease fragmentation of services, and decrease the stigma and resistance some families may have with attending mental health clinics. A treatment program with comprehensive multidisciplinary services and CBT showed immediate, clinically relevant benefits that were sustained at the 1 yr follow-up in a randomized controlled trial.

Patients with profound and pervasive functional impairment likely will need more intensive psychiatric treatment (e.g., medical-psychiatric partial hospital program or inpatient unit). Multidisciplinary inpatient rehabilitation programs have much to offer these patients because they are designed to support both physical and psychological recovery. Families feel reassured that multidisciplinary staff can continue to monitor symptoms, thus ensuring that any missed diagnoses will be recognized quickly.

Children with a high level of impairment often miss a significant amount of school; communication with the school is often crucial in helping a successful transition back and improving overall functioning. In addition to discussions with the school guidance counselor and nurse, a letter for the school providing education and recommended approaches for the patient's symptoms is often beneficial. These interventions can be formalized by having the school work with the family and medical team to develop either a 504 plan for accommodations needed in regular education settings, or an individualized educational plan (IEP) if the child needs special education services. Ongoing communication between the school and the primary care provider for monitoring of further symptoms is recommended.

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CHAPTER 36

Rumination and Pica

36.1

Rumination Disorder

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Rumination disorder is the repeated regurgitation of food, where the regurgitated food may be rechewed, reswallowed, or spit out, for a period of at least 1 mo following a period of normal functioning. Regurgitation is typically frequent and daily; it does not occur during sleep. It is not caused by an associated gastrointestinal illness or other medical conditions (e.g., gastroesophageal reflux, pyloric stenosis). It does not occur exclusively during the course of anorexia nervosa, bulimia nervosa, binge-eating disorder, or avoidant/restrictive food intake disorder. If the symptoms occur in the context of an intellectual developmental disorder or another neurodevelopmental disorder, the symptoms must be sufficiently severe to warrant additional clinical attention.

Weight loss and failure to make expected weight are common features in infants with rumination disorder. Infants may display a characteristic position of straining and arching the back with the head held back, making sucking movements with their tongue. In infants and older individuals with intellectual disability, the rumination behavior may appear to have a self-soothing or self-stimulating function. Malnutrition may occur in older children and adults, particularly when the regurgitation is associated with restricted food intake (which may be designed to avoid regurgitation in front of others). They may attempt to hide the regurgitation behavior or avoid eating among others.

Epidemiology

Originally thought of as a disorder predominantly seen in infants and those with intellectual disability, rumination disorder has also been recognized in healthy individuals across the life span and can be overlooked in adolescents. In otherwise healthy children, rumination disorder typically appears in the 1st year of life, generally between ages 3 and 12 mo. The disorder can have an episodic course or can occur continuously until treatment is initiated. In infants the disorder frequently remits spontaneously but can be protracted with problematic and even life-threatening malnutrition. Additional complications related to the secondary effects of malnutrition include growth delay and negative effects on development and learning potential.

Etiology and Differential Diagnosis

Risk factors for rumination disorder in infants and young children include a disturbed relationship with primary caregivers, lack of an appropriately stimulating environment, neglect, stressful life situations, learned behavior reinforced by pleasurable sensations, distraction from negative emotions, and inadvertent reinforcement (attention) from primary caregivers. Risk factors for rumination disorder in adolescents include similar early childhood factors along with female gender and comorbid anxiety and depression. The differential diagnosis includes congenital gastrointestinal system anomalies, pyloric stenosis, Sandifer syndrome, gastroparesis, hiatal hernia, increased intracranial pressure, diencephalic tumors, adrenal insufficiency, and inborn errors of metabolism. Older children and adults with anorexia nervosa or bulimia nervosa may also engage in regurgitation because of concerns about weight gain. The diagnosis of rumination disorder is appropriate only when the severity of the disturbance exceeds that routinely associated with a concurrent physical illness or mental disorder.

Treatment

The 1st step in treatment begins with a behavioral analysis to determine if the disorder serves as a self-stimulation purpose and/or is socially motivated. The behavior may begin as self-stimulation, but it subsequently becomes reinforced and maintained by the social attention given to the behavior. The central focus of behavioral treatment is to reinforce correct eating behavior while minimizing attention to rumination. Diaphragmatic breathing and postprandial gum chewing, when used as a competing response, have been shown to be helpful. **Aversive conditioning** techniques (e.g., withdrawal of positive attention, introducing bitter/sour flavors when regurgitating) are considered when a child's health is jeopardized but can be more reasonable and useful in adolescents. Additional techniques shown to be useful in adolescents include reswallowing all regurgitation, use of paradoxical intention, and guided progressive food trials.

Successful behavioral treatment requires the child's primary caregivers to be involved in the intervention. The caretakers need education and counseling on responding adaptively to the child's behavior as well as altering any maladaptive responses. No current evidence supports a psychopharmacologic intervention for rumination disorder. In more severe or intractable cases (e.g., severe dehydration, malnutrition), an intensive integrated medical-behavioral treatment program on a medical or medical-psychiatric unit may be necessary.

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36.2

Pica

Chase B. Samsel, Heather J. Walter, David R. DeMaso

Pica involves the persistent eating of nonnutritive, nonfood substances (e.g., paper, soap, plaster, charcoal, clay, wool, ashes, paint, earth) over a period of at least 1 mo. The eating behavior is inappropriate to the developmental level (e.g., the normal mouthing and tasting of objects in infants and toddlers), and therefore a minimum age of 2 yr is suggested. The eating behavior is not part of a culturally supported or socially normative practice. A diagnosis of pica may be assigned in the presence of any other feeding and eating disorder.

Epidemiology

Pica can occur throughout life but occurs most frequently in childhood. It appears to be more common in those with intellectual disability and autism spectrum disorders, and to a lesser degree in obsessive-compulsive and schizophrenic disorders. The prevalence of pica is unclear, although it appears to increase with the severity of an intellectual disability. It usually remits in childhood but can continue into adolescence and adulthood. **Geophagia** (eating earth) is associated with pregnancy and is not seen as abnormal in some cultures (e.g., rural or preindustrial societies in parts of Africa and India). Children with pica are at increased risk for lead poisoning, iron-deficiency anemia, mechanical bowel problems, intestinal obstruction, intestinal perforations, dental injury, and parasitic infections. Pica can be fatal based on substances ingested.

Etiology and Differential Diagnosis

Numerous etiologies have been proposed but not proved, ranging from psychosocial causes to physical ones. They include nutritional deficiencies (e.g., iron, zinc, calcium), low socioeconomic factors (e.g., lead paint exposure), child abuse and neglect, family disorganization (e.g., poor supervision), mental disorder, learned behavior, underlying (but undetermined) biochemical disorder, and cultural and familial factors. The differential diagnosis includes anorexia nervosa, factitious disorder, and nonsuicidal self-injury in personality disorders. A separate diagnosis of pica should be made only if the eating behavior is sufficiently severe enough to warrant additional clinical attention.

Treatment

Combined behavioral, social, and medical approaches are generally indicated for pica. Assessment for neglect and family supervision combined with psychiatric assessment for concurrent mental disorders and developmental delay are important in developing an effective intervention strategy for pica. Behavioral interventions, particularly applied behavioral analysis in patients with intellectual disability or autism spectrum disorders, are increasingly found to be helpful. The sequelae related to an ingested item can require specific treatment (e.g., lead toxicity, iron-deficiency anemia, parasitic infestation). Ingestion of hair can require medical or surgical intervention for a gastric bezoar.

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CHAPTER 37

Motor Disorders and Habits

Colleen A. Ryan, Heather J. Walter, David R. DeMaso

Motor disorders are interrelated sets of psychiatric symptoms characterized by abnormal motor movements and associated phenomena. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), **motor disorders** include tic, stereotypic movement, and developmental coordination disorders. **Tic disorders** (Tourette, persistent motor or vocal tic, provisional tic, other specified/unspecified tic) and **stereotypic movement disorder** are addressed in this chapter, along with habits. Although not DSM-5 motor disorders, **habits** present as repetitive and often problematic motor behaviors (e.g., thumb sucking, teeth grinding).

37.1

Tic Disorders

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Tourette disorder (TD) , **persistent (chronic) motor or vocal tic disorder (PTD)** , and **provisional tic disorders** are characterized by involuntary, rapid, repetitive, single or multiple motor and/or vocal/phonic tics that wax and wane in frequency but have persisted for >1 yr since first tic onset (<1 yr for provisional tic disorder) (Table 37.1). PTD is differentiated from TD in that PTD is limited to either motor or vocal tics (not both), whereas TD has both motor and vocal tics at some point in the illness (although not necessarily concurrently). The tic disorders are hierarchical in order (i.e., TD followed by PTD followed by provisional tic disorder), such that once a tic disorder at one level of the hierarchy is diagnosed, a lower-hierarchy diagnosis cannot be made. **Other specified/unspecified tic disorders** are presentations in which symptoms characteristic of a tic disorder that cause significant distress or impairment predominate but do not meet the full criteria for a tic or other neurodevelopmental disorder.

Table 37.1

DSM-5 Diagnostic Criteria for Tic Disorders

Note: A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization.

Tourette Disorder

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.

B. The tics may wax and wane in frequency but have persisted for >1 yr since first tic onset.

C. Onset is before age 18 yr.

D. The disturbance is not attributable to the physiologic effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington disease, postviral encephalitis).

Persistent (Chronic) Motor or Vocal Tic Disorder

A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal.

B. The tics may wax and wane in frequency but have persisted for >1 yr since first tic onset.

C. Onset is before age 18 yr.

D. The disturbance is not attributable to the physiologic effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington disease, postviral encephalitis).

E. Criteria have never been met for Tourette disorder.

Specify if:

With motor tics only

With vocal tics only

Provisional Tic Disorder

A. Single or multiple motor and/or vocal tics.

B. The tics have been present for <1 yr since first tic onset.

C. Onset is before age 18 yr.

D. The disturbance is not attributable to the physiologic effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington disease, postviral encephalitis).

E. Criteria have never been met for Tourette disorder or persistent (chronic) motor or vocal tic disorder.

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p. 81.

Description

Tics are sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations. *Simple motor tics* (e.g., eye blinking, neck jerking, shoulder shrugging, extension of the extremities) are fast, brief movements involving one or a few muscle groups. *Complex motor tics* involve sequentially and/or simultaneously produced, relatively coordinated movements that can seem purposeful (e.g., brushing back one's hair bangs, tapping the foot, imitating someone else's movement [**echopraxia**], or making a sexual or obscene gesture [**copropraxia**]). *Simple vocal tics* (e.g., throat clearing, sniffing, coughing) are solitary, meaningless sounds and noises. *Complex vocal tics* involve recognizable word or utterances (e.g., partial words [syllables], words out of context, coprolalia [obscenities or slurs], **palilalia** [repeating one's own sounds or words], or **echolalia** [repeating the last heard word or phrase]).

Sensory phenomena (premonitory urges) that precede and trigger the urge to tic have been described. Individuals with tics can suppress them for varying periods of time, particularly when external demands exert their influence, when deeply engaged in a focused task or activity, or during sleep. Tics are often suggestible and are worsened by anxiety, excitement, or exhaustion. Parents have described increasing frequency of tics at the end of the day. Research has not supported volitional suppressing of tics leading to tic rebound.

Clinical Course

Onset of tics is typically between ages 4 and 6 yr. The frequency of tics tends to wax and wane with peak tic severity between ages 10 and 12 yr and marked attenuation of tic severity in most individuals (65%) by age 18-20 yr. A small percentage will have worsening tics into adulthood. New onset of tics in adulthood is very rare and most often is associated with exposure to drugs or insults to the central nervous system. Tics manifest similarly in all age-groups and changes in affected muscle groups and vocalizations occur over time. Some individuals may have tic-free periods of weeks to months.

Epidemiology

Prevalence rates for all tics range from 6–18% for boys and 3–11% for girls, with the rate of TD alone estimated as 0.8%. In general, PTD/TD has a male preponderance with a gender ratio varying from 2 : 1 to 4 : 1. Evidence supports higher rates in white youth than black or Hispanic youth.

Differential Diagnosis

The differential diagnosis includes the repetitive movements of childhood (Table 37.2). Tics may be difficult to differentiate from stereotypies. Although stereotypies may resemble tics, **stereotypies** are typically rhythmic movements and do not demonstrate the change in body location or movement type over time that is typical of tics. **Compulsions** may be difficult to differentiate from tics when tics have premonitory urges. Tics should be differentiated from a variety of developmental and benign movement disorders (e.g., benign paroxysmal torticollis, Sandifer syndrome, benign jitteriness of newborns, shuddering attacks). Tics may present in various neurologic illnesses (e.g., Wilson disease, neuroacanthocytosis, Huntington syndrome, various frontal-subcortical brain lesions), but it is rare for tics to be the only manifestation of these disorders.

Table 37.2

Repetitive Movements of Childhood

MOVEMENT	DESCRIPTION	TYPICAL DISORDERS WHERE PRESENT
Tics	Sudden rapid, recurrent, nonrhythmic, stereotyped, vocalization or motor movement	Transient tics, Tourette disorder, persistent tic disorder
Dystonia	Involuntary, sustained, or intermittent muscle contractions that cause twisting and repetitive movements, abnormal postures, or both	*DYT1* gene, Wilson disease, myoclonic dystonia, extrapyramidal symptoms caused by dopamine-blocking agents
Chorea	Involuntary, random, quick, jerking movements, most often of the proximal extremities, that flow from joint to joint. Movements are abrupt, nonrepetitive, and arrhythmic and have variable frequency and intensity	Sydenham chorea, Huntington chorea
Stereotypies	Stereotyped, rhythmic, repetitive movements or patterns of speech, with lack of variation over time	Autism, stereotypic movement disorder, intellectual disability
Compulsions	A repetitive, excessive, meaningless activity or mental exercise that a person performs in an attempt to avoid distress or worry	Obsessive-compulsive disorder, anorexia, body dysmorphic disorder, trichotillomania, excoriation disorder
Myoclonus	Shock-like involuntary muscle jerk that may affect a single body region, one side of the body, or the entire body; may occur as a single jerk or repetitive jerks	Hiccups, hypnic jerks, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, mitochondrial encephalopathies, metabolic disorders
Akathisia	Unpleasant sensations of "inner" restlessness, often prompting movements in an effort to reduce the sensations	Extrapyramidal adverse effects from dopamine-blocking agents; anxiety
Volitional behaviors	Behavior that may be impulsive or caused by boredom, such as tapping peers or making sounds (animal noises)	Attention-deficit/hyperactivity disorder, oppositional defiant disorder, sensory integration disorders

Adapted from Murphy TK, Lewin AB, Storch EA, et al: Practice parameter for the assessment and treatment of children and adolescents with chronic tic disorders, *J Am Acad Child Adolesc Psychiatry* 52(12):1341–1359, 2013.

Individuals presenting with tics in the context of declining motor or cognitive function should be referred for neurologic assessment. Substances/medications that are reported to worsen tics include selective serotonin reuptake inhibitors (SSRIs), lamotrigine, and cocaine. If tics develop in close temporal relationship to the use of a substance or medication and then remit when use of the substance is discontinued, a causal relationship is possible. Although a long-standing clinical concern, controlled studies show no evidence that stimulants commonly increase tics.

Comorbidities

Comorbid psychiatric disorders are common, often with both patient and family viewing the accompanying condition as more problematic than the tics. There is a bidirectional association between PTD/TD (especially TD) and obsessive-compulsive disorder (OCD), with 20–60% of TD patients meeting OCD criteria and 20–40% of OCD patients reporting tics (Fig. 37.1). Attention-deficit/hyperactivity disorder (ADHD) occurs in approximately 50% of all childhood PTD/TD, but estimates in clinically referred patients suggest much higher rates (60–80%). PTD/TD is often accompanied by behavior problems, including poor frustration tolerance, temper outbursts, and oppositionality. Learning disabilities have been found in >20% of these patients. Concurrent anxiety and depression have also been observed. Some patients with PTD/TD will display symptoms of autism spectrum disorder (ASD); careful assessment is required to determine which disorder is primary.

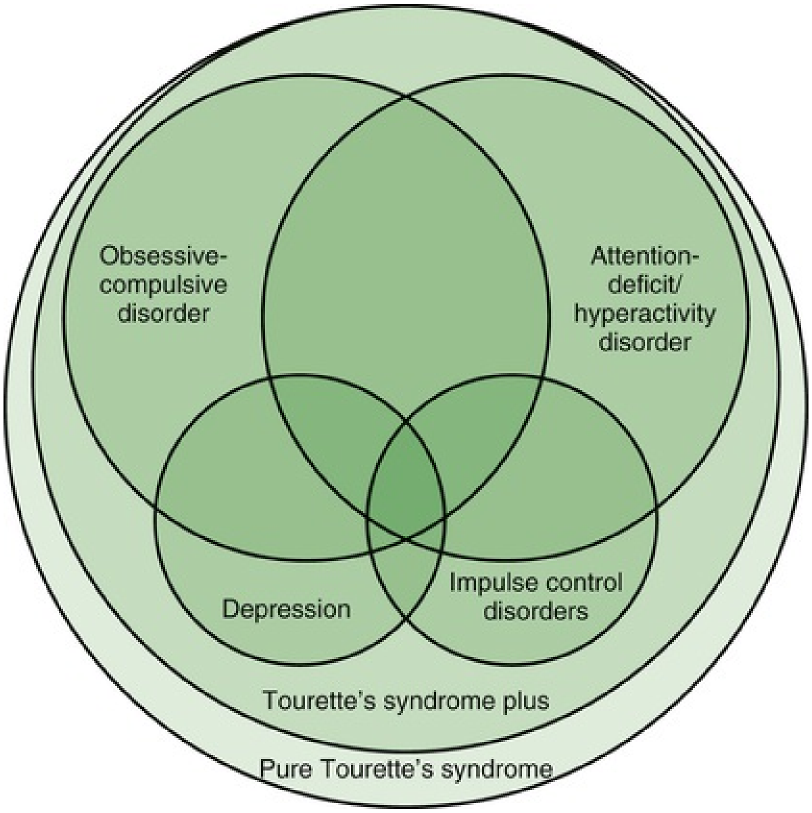
Obsessive-compulsive disorder
Attention-deficit/hyperactivity disorder
Depression
Impulse control disorders
Tourette's syndrome plus
Pure Tourette's syndrome

FIG. 37.1 **Schematic representation of the behavioral spectrum in Tourette's syndrome. The size of each area is proportional to the estimated prevalence of the symptoms; the background color intensity is proportional to the complexity of the**

clinical presentation. (From Cavanna AE, Seri S: Tourette's syndrome. *BMJ* 347:f4964, 2013.)

Etiology

Tics are proposed to be the result of dysfunctional corticostriatal-thalamocortical motor pathways in the basal ganglia, striatum, and frontal lobes associated with abnormalities in the dopamine, serotonin, and norepinephrine neurotransmitter systems. Male predominance in PTD/TD may be attributable to influences of sex hormones on the neurodevelopment of these motor pathways, as reflected by the effects of antiandrogens in the treatment of TD.

Family studies suggest a 10-100–fold increased risk of PTD/TD among first-degree relatives compared to rates in the general population. Twin studies also support a genetic link, with approximately 80% of monozygotic twins and 30% of dizygotic twins showing concordance for PTD/TD. Candidate-gene association and nonparametric linkage studies have not identified specific susceptibility genes for PTD/TD.

Autoimmune-mediated mechanisms have been hypothesized as having a potential etiologic role in some tic disorders. The **pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)** designation has been used to describe cases of acute childhood onset of OCD and/or tics following a streptococcal infection. **Pediatric acute-onset neuropsychiatric syndrome (PANS)** has been used to describe a subtype of acute childhood-onset OCD (tics are not a required feature) in which a link to a prior streptococcal infection is not evident, suggesting that other infectious agents may also be responsible. In addition to a diagnosis of OCD and tics, children with PANS/PANDAS have been reported with symptoms of separation anxiety, nightmares, personality change, oppositional behaviors, and deterioration in math skills and handwriting. Although some studies suggest a prior history of infections may increase the risk for developing tic disorder, this remains controversial.

Premorbid stress has been hypothesized to act as a sensitizing agent in the pathogenesis of TD among susceptible individuals by affecting stress-responsive biologic systems such as the hypothalamic-pituitary-adrenal axis.

Sequelae

Many individuals with mild to moderate tics express minimal to no distress or functional impairment and may even be unaware of their tics. Even individuals with moderate to severe tics can experience minimal functional impairment, but psychological distress may occur. Infrequently, the presence of tics can lead to social isolation, social victimization, inability to work or attend school, or impaired quality of life.

Screening

Pediatricians should routinely screen for unusual movements and vocalizations. As an adjunct to a verbal screen, commonly used broad-band symptom rating scales such as the *Child Behavior Checklist* (CBCL) and the *Swanson, Nolan, and Pelham* (SNAP) include specific tic questions. Often families are unaware that frequent sniffing, coughing, or blinking may be indicative of tics, attributing these behaviors to medical problems (e.g., allergies, visual problems). A careful assessment of the timing, triggers, and specific characteristics may differentiate tics from other medical problems. If differentiation is difficult, a referral to a pediatric specialist in the affected system is warranted.

Assessment

If the screening suggests the presence of a tic disorder, a more comprehensive evaluation should ensue, including the age of onset, types of tics, tic frequency, alleviating and aggravating factors, and a family history of tics. Symptom rating scales specific for tics (e.g., the *Motor Tic, Obsessions and Compulsions, Vocal Tic Evaluation Survey* [MOVES], *Tic Self Report Scale* , *Tourette's Disorder Scale* , *Parent Tic Questionnaire* [PTQ], and *Child Tourette's Disorder Impairment Scale–Parent Version* can supplement the assessment. For clinician-rated tic severity, the most commonly used instruments are the *Yale Global Tic Severity Scale* (YGTSS), *Tourette Syndrome Severity Scale* (TSSS), and *Tourette Syndrome Global Scale* (TSGS).

A medical workup should be considered for new-onset tics, particularly for presentations characterized by sudden onset, atypicality, or mental status abnormalities. Basic laboratory measures (hemogram, renal/hepatic function panel, thyroid panel, and ferritin, along with urine drug screen for adolescents) should be considered. For new, sudden onset or severe symptom exacerbation, pediatric practitioners may assess for concurrent acute infection (e.g., culture, rapid viral tests). Electroencephalography and brain imaging are not routinely recommended and should be reserved for patients with other neurologic findings that might suggest an autoimmune encephalitis syndrome (limbic encephalitis). Comorbid psychiatric disorders (e.g., OCD, ADHD, ASD) should be investigated.

Treatment

The decision to treat tics is made with the child and family based on the level of impairment and distress caused by the tics. If tics are mild in severity, there may be no need for intervention after psychoeducation is provided.

Psychoeducation should include common symptom presentations, implications of concurrent conditions, course and prognosis, and treatment options (including no treatment). The youth's typical exacerbating and alleviating factors should be reviewed. The clinician can direct the family and youth to informational websites, including the Tourette Association of America (www.tourette.org).

Almost 75% of children with TD/PTD receive some form of classroom accommodation (most often ignoring the tics and permission to leave the room as needed). The accommodations may need to be formalized in an individualized education plan (IEP) if a child needs special education services or a 504 plan if the child just needs accommodations in the regular classroom.

Referral to a behavioral treatment specialist should be considered when tics are distressing or functionally impairing. The behavioral interventions with the strongest empirical support are **habit reversal therapy (HRT)** and **comprehensive behavioral intervention for tics (CBIT)** . The basic components of HRT include premonitory urge awareness training and building a competing response to the urge to tic (Table 37.3). Based on HRT, CBIT also includes relaxation training and a functional intervention designed to mitigate against tic-generating situations. A course of HRT/CBIT treatment typically takes several months or 8-10 sessions. In children and adolescents with TD, CBIT has been found to reduce significantly the severity of tics compared to education and supportive therapy. This finding has been supported by a meta-analysis of behavior therapy (HRT/CBIT) for TD, in which a medium to large effect size has been shown for behavioral therapy relative to comparison conditions.

Table 37.3

Components of Habit Reversal Procedure

Increase Individual's Awareness of Habit

Response description—have individual describe behavior to therapist in detail while reenacting the behavior and looking in a mirror.

Response detection—inform individual of each occurrence of the behavior until each occurrence is detected without assistance.

Early warning—have individual practice identifying earliest signs of the target behavior.

Situation awareness—have individual describe all situations in which the target behavior is likely to occur.

Teach Competing Response to Habit

The competing response must result in isometric contraction of muscles involved in the habit, be capable of being maintained for 3 min, and be socially inconspicuous and compatible with normal ongoing activities but incompatible with the habit (e.g., clenching one's fist, grasping and clenching an object). For vocal tics and stuttering, deep relaxed breathing with a slight exhale before speech has been used as the competing response.

Sustain Compliance

Habit inconvenience review—have individual review in detail all problems associated with target behavior.

Social support procedure—family members and friends provide high levels of praise when a habit-free period is noted.

Public display—individual demonstrates to others that he or she can control the target behavior in situations in which the behavior occurred in the past.

Facilitate Generalization—Symbolic Rehearsal Procedure

For each situation identified in situation awareness procedure, individual imagines himself or herself beginning the target behavior but stopping and engaging in the competing response.

From Carey WB, Crocker AC, Coleman WL, et al, editors: *Developmental-behavioral pediatrics*, ed 4, Philadelphia, 2009, Elsevier/Saunders, p 639.

Medications should be considered when the tics are causing severe impairment in the quality of life, or when psychiatric comorbidities are present. The only U.S. Food and Drug Administration (FDA)–approved medications to treat TD in children and adolescents are 2 first-generation (typical) antipsychotics (haloperidol, pimozide) and 1 second-generation (atypical) antipsychotic (aripiprazole). Alpha-agonists (clonidine, guanfacine) are also a consideration as first-line agents because of their more favorable side effect profile than the first- or second-generation antipsychotics (see Chapter 33).

Both antipsychotic and α-adrenergic medications have significant benefit compared with placebo for the pharmacologic treatment of youth with tic disorders. There have been no significant differences between the first- and second-generation antipsychotic agents tested.

Children with tic disorders may benefit from SSRIs for the treatment of comorbid OCD, anxiety, or depressive disorders. Augmentation of SSRIs with an atypical antipsychotic has been a consideration in patients with concurrent tic disorders and OCD responding poorly to an SSRI alone. The presence of tics does not preclude the use of stimulants to address comorbid ADHD. However, close clinical monitoring is required for possible exacerbation of tics during stimulant treatment. Anger and rage outbursts are not uncommon among youth with tics (up to 80% in clinically referred samples). Behavioral therapies (CBT, parent management training) that address anger management may be useful. There are no controlled pharmacologic studies in youth with tic disorders with anger outbursts. There also is no rigorous scientific evidence to support the use of deep brain stimulation, repetitive magnetic stimulation, or dietary supplements in the treatment of TD or PTD.

37.2

Stereotypic Movement Disorder

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In DSM-5, **stereotypic movement disorder (SMD)** is defined as a neurodevelopmental disorder characterized by repetitive, seemingly driven, and apparently purposeless motor behavior *(stereotypy)* that interferes with social, academic, or other activities and may result in self-injury. The onset of SMD is the early developmental period (often before age 3 yr), and the symptoms are not attributable to the physiologic effects of a substance or neurologic condition and are not better explained by another neurodevelopmental or mental disorder. The disorder is considered *mild* if symptoms are easily suppressed by sensory stimulus or distraction, and *severe* if continuous monitoring and protective measures are required to prevent serious injury, with *moderate* falling between mild and severe.

Description

Examples of stereotypic movements include hand shaking or waving, body rocking, head banging, self-biting, and hitting one's own body. The presentation depends on the nature of the stereotypic movement and level of the child's awareness of the behavior. Among typically developing children, the repetitive movements may be stopped when attention is directed to the movements or when the child is distracted from performing them. Among children with intellectual disability, the behaviors may be less responsive to such efforts. Each individual presents with his or her own uniquely patterned behavior. Stereotypic movements may occur many times during a day, lasting a few seconds to several minutes or longer. The behaviors may occur in multiple contexts, including when the individual is excited, stressed, fatigued, or bored.

Clinical Course

Stereotypic movements typically begin within the 1st 3 yr of life. In children who develop complex motor stereotypies, the great majority exhibit symptoms before 24 mo of age. In most typically developing children, these movements resolve over time. Among individuals with intellectual disability, the stereotyped behaviors may persist for years, although the pattern may change over time.

Epidemiology

Simple stereotypic movements are common in typically developing young children. Some children may bang their head on their mattress as they are falling asleep or may sit and rock when bored or overstimulated. Self-injurious habits, such as self-biting or head banging, can occur in up to 25% of typically developing toddlers (often during tantrums), but they are *almost invariably* associated with developmental delay in children older than age 5 yr. *Complex* stereotypic movements are much less common (occurring in approximately 3–4% of children). Between 4% and 16% of individuals with intellectual disability engage in stereotypic movements.

Comorbidity

Stereotypic movements are a common manifestation of a variety of neurogenetic disorders, such as Lesch-Nyhan, Rett, fragile X, Cornelia de Lange, and Smith-Magenis syndromes.

Differential Diagnosis

According to DSM-5, stereotypic movements must be differentiated from normal development, ASDs, tic disorders, OCDs, and other neurologic and medical conditions. Simple stereotypic movements occurring in the context of typical development usually resolve with age. Stereotypic movements may be a presenting symptom of ASD, but SMD does not include the deficits in social communication characteristic of ASD. When ASD is present, SMD is diagnosed only when there is self-injury or when the stereotypic behaviors are sufficiently severe to become a focus of treatment. Typically, SMD has an earlier age of onset than the tic disorders, and the movements are fixed in their pattern. SMD is distinguished from OCD by the absence of obsessions as well as the nature of the repetitive behaviors, which in OCD are purposeful (e.g., in response to obsessions). The diagnosis of stereotypic movements requires the exclusion of habits, mannerisms, paroxysmal dyskinesias, and benign hereditary chorea. A neurologic history and examination are required to assess features suggestive of other disorders, such as myoclonus, dystonia, and chorea.

Etiology

There is a possible evolutionary link between repetitive abnormal grooming-like behaviors and early human experience with adversity. Brain regions implicated in this model (e.g., amygdala, hippocampus) are those involved in navigating human experience through unpredictable, anxiety-provoked emotional states, as well as regions (e.g., nucleus accumbens) related to pleasure and reward seeking. The latter involves the hypothesis that individuals experience some level of gratification from performing the habit behavior.

Social isolation with insufficient stimulation (e.g., severe neglect) is a risk factor for self-stimulation that may progress into stereotypies, particularly repetitive rocking or spinning. Environmental stress may trigger stereotypic behaviors. Repetitive self-injurious behavior may be a behavioral phenotype in neurogenetic syndromes (e.g., Lesch-Nyhan, Rett, and Cornelia de Lange syndromes). Lower cognitive functioning is also linked to greater risk of stereotypic behaviors.

Treatment

The initial approach to helping children with mild stereotypy is for parents to ignore the undesired behavior, encourage substitute behavior, and not convey worry to their child. These behaviors may disappear with time and elimination of attention in young children. However, in children with intellectual disability or ASDs, stereotypies may be more refractory to treatment than in typically developing children and may necessitate referral to a behavioral psychologist, developmental-behavioral pediatrician, or child and adolescent psychiatrist for behavioral and psychopharmacologic management. The pediatrician should consider and rule out neglect of the child, which can be associated with repetitive rocking, spinning, or other stereotypic movements.

Behavior therapy is the mainstay of treatment, using a variety of strategies, including habit reversal, relaxation training, self-monitoring, contingency management, competing responses, and negative practice. The environment should also be modified to reduce risk of injury to those engaging in self-injurious behavior.

Atypical antipsychotic medications appear to be helpful in reducing stereotypic movements in youth with ASD. Patients with anxiety and obsessive-compulsive behaviors treated with SSRIs may show improvement in their stereotypic movements.

Habits

Habits involve an action or pattern of behavior that is repeated often. Habits are common in childhood and range from usually benign and transient behaviors (e.g., thumb sucking, nail biting) to more problematic (e.g., trichotillomania, bruxism). In DSM-5, habits are not included as a diagnostic category because they are not viewed as disorders causing clinically significant distress or impairment in functioning. Treatment with HRT has been effective as a first-line approach (see Table 37.3).

Thumb Sucking

Thumb sucking is common in infancy and in as many as 25% of children age 2 yr and 15% of children age 5 yr. Thumb sucking beyond 5 yr may be associated with sequelae (e.g., paronychia, anterior open bite). As with other rhythmic patterns of behavior, thumb sucking is self-soothing. Basic behavioral management, including encouraging parents to ignore thumb sucking and instead focus on praising the child for substitute behaviors, is often effective treatment. Simple reminders and reinforcers can also be considered, such as giving the child a sticker (or other reward) for each block of time that he or she does not suck the thumb. In rare cases, mechanical devices placed on the thumb or in the mouth to prevent thumb sucking or noxious agents (bitter salves) placed on the thumb may be part of the treatment plan.

Bruxism

Bruxism or teeth grinding is common (5–30% of children), can begin in the first 5 yr of life, and may be associated with daytime anxiety. Persistent bruxism can manifest as muscular or temporomandibular joint pain. Untreated bruxism can cause problems with dental occlusion. Helping the child find ways to reduce anxiety might relieve the problem; bedtime can be made more relaxing by reading or talking with the child and allowing the child to discuss fears. Praise and other emotional support are useful. Persistent bruxism requires referral to a dentist given the risk for dental occlusion.

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CHAPTER 38

Anxiety Disorders

David R. Rosenberg, Jennifer A. Chiriboga

Anxiety, defined as dread or apprehension, is not considered pathologic, is seen across the life span, and can be adaptive (e.g., the anxiety one might feel during an automobile crash). Anxiety has both a cognitive-behavioral component, expressed in worrying and wariness, and a physiologic component, mediated by the autonomic nervous system. Anxiety disorders are characterized by **pathologic anxiety,** in which anxiety becomes disabling, interfering with social interactions, development, and achievement of goals or quality of life, and can lead to low self-esteem, social withdrawal, and academic underachievement. The average age of onset of anxiety disorder is 11 yr. Diagnosis of a particular anxiety disorder in a child requires significant interference in the child's psychosocial and academic or occupational functioning, which can occur even with subthreshold symptoms that do not meet criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Anxiety may have physical manifestations such as weight loss, pallor, tachycardia, tremors, muscle cramps, paresthesias, hyperhidrosis, flushing, hyperreflexia, and abdominal tenderness.

Separation anxiety disorder (SAD), childhood-onset social phobia or social anxiety disorder, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), phobias, posttraumatic stress disorder (PTSD), and panic disorder (PD) are all defined by the occurrence of either diffuse or specific anxiety, often related to predictable situations or cues. Anxiety disorders are the most common psychiatric disorders of childhood, occurring in 5–18% of all children and adolescents, prevalence rates comparable to physical disorders such as asthma and diabetes. Anxiety disorders are often comorbid with other psychiatric and medical disorders (including a second anxiety disorder); significant impairment in day-to-day functioning is common. High levels of fear in adolescence are also a significant risk factor for experiencing later episodes of major depression in adulthood. Anxiety and depressive disorder in adolescence predict increased risk of anxiety and depressive symptoms (including suicide attempts) in adulthood, underscoring the need to diagnose and treat these underreported, yet prevalent, conditions early.

Because anxiety is both a normal phenomenon and, when highly activated, strongly associated with impairment, the pediatrician must be able to differentiate normal anxiety from abnormal anxiety across development (Fig. 38.1 and Table 38.1). Anxiety has an identifiable developmental progression for most children; most infants exhibit stranger wariness or anxiety beginning at 7-9 mo of age. **Behavioral inhibition** to the unfamiliar (withdrawal or fearfulness to novel stimuli associated with physiologic arousal) is evident in approximately 10–15% of the population at 12 mo of age and is moderately stable. Most children who show behavioral inhibition do not develop impairing levels of anxiety. A family history of anxiety disorders and maternal overinvolvement or enmeshment predicts later clinically significant anxiety in behaviorally inhibited infants. The infant who is excessively clingy and difficult to calm during pediatric visits should be followed for signs of increasing levels of anxiety.

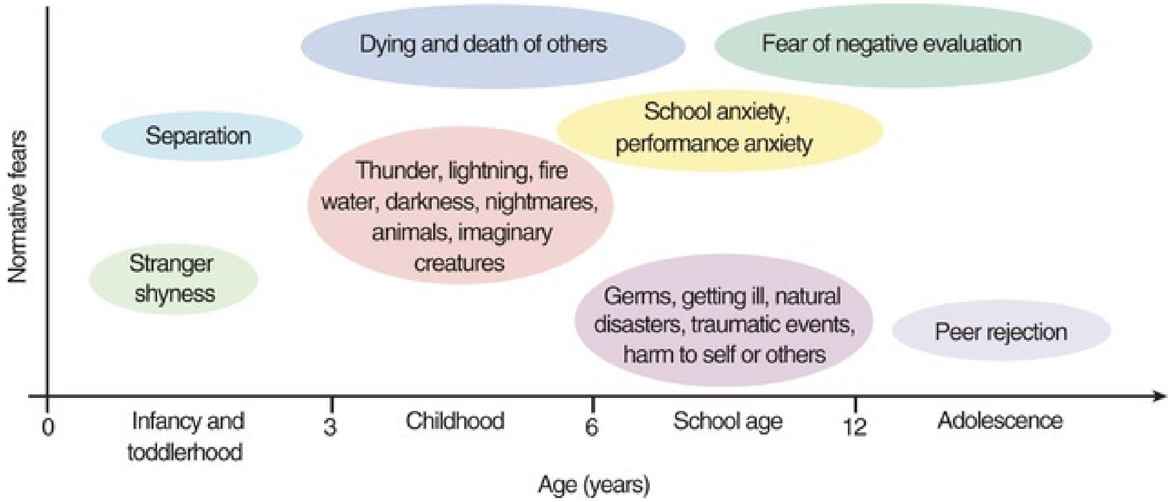

FIG. 38.1 Normative fears throughout childhood and adolescence. (From Craske MG, Stein MB: Anxiety. *Lancet* 388:3048–3058, 2016.)

Table 38.1

Differential Diagnosis of Anxiety Disorders

Shyness
Substance use
Substance use withdrawal
Hyperthyroidism
Arrhythmias
Pheochromocytoma
Mast cell disorders
Carcinoid syndrome
Anaphylaxis
Hereditary angioedema
Lupus
Autoimmune encephalitis
Body dysmorphic disorder
Autism spectrum disorder
Major depressive disorder
Delusional disorder
Oppositional defiant disorder
Embarrassing medical condition

Preschoolers typically have specific fears related to the dark, animals, and imaginary situations, in addition to normative separation anxiety. Preoccupation with orderliness and routines (*just right* phenomena) often takes on a quality of anxiety for preschool children. Parents' reassurance is usually sufficient to help the child through this period. Although most school-age children abandon the imaginary fears of early childhood, some replace them with fears of bodily harm or other worries (Table 38.2). In adolescence, general worrying about school performance and worrying about social competence are common and remit as the teen matures.

Table 38.2

DSM-5 Diagnostic Criteria for Specific Phobia

A. Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.

B. The phobic object or situation almost always provokes immediate fear or anxiety.

C. The phobic object or situation is actively avoided or endured with intense fear or anxiety.

D. The fear or anxiety is out of proportion to the actual danger posed by the specific object or situation and to the sociocultural context.

E. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

F. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

G. The disturbance is not better explained by the symptoms of another mental disorder, including fear, anxiety and avoidance or situations associated with panic-like symptoms or other incapacitating symptoms (as in agoraphobia); objects or situations related to obsessions (as in obsessive-compulsive disorder); remainders of traumatic events (as in posttraumatic stress disorder); separation from home or attachment figures (as in separation anxiety disorder); or social situations (as in social anxiety disorder).

Specify if:

Code based on the phobic stimulus:

Animal (e.g., spiders, insects, dogs).
Natural environment (e.g., heights, storms, water).
Blood-injection-injury (e.g., needles, invasive medical procedures).
Situational (e.g., airplanes, elevators, enclosed places).
Other (e.g., situations that may lead to choking or vomiting; in children, e.g., loud sounds or costumed characters).

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 197–198.

Genetic or temperamental factors contribute more to the development of some anxiety disorders, whereas environmental factors are closely linked to the cause of others. Specifically, behavioral inhibition appears to be a heritable tendency and is linked with social phobia, generalized anxiety, and selective mutism. OCD and other disorders associated with OCD-like behaviors, such as Tourette syndrome and other tic disorders, tend to have high genetic risk as well (see Chapter 37.1). Environmental factors, such as parent–infant attachment and exposure to trauma, contribute more to SAD and PTSD. Parental anxiety disorder is associated with an increased risk of anxiety disorder in offspring. Differences in the size of the amygdala and hippocampus are noted in patients with anxiety symptoms.

Separation anxiety disorder is one of the most common childhood anxiety disorders, with a prevalence of 3.5–5.4%. Approximately 30% of children presenting to an outpatient anxiety disorder clinic have SAD as a primary diagnosis. Separation anxiety is developmentally normal when it begins about 10 mo of age and tapers off by 18 mo. By 3 yr of age, most children can accept the temporary absence of their mother or primary caregiver.

SAD is more common in prepubertal children, with an average age of onset of 7.5 yr. Girls are more frequently affected than boys. SAD is characterized by unrealistic and persistent worries about separation from the home or a major attachment figure. Concerns include possible harm befalling the affected child or the child's primary caregivers, reluctance to go to school or to sleep without being near the parents, persistent avoidance of being alone, nightmares involving themes of separation, numerous somatic symptoms, and complaints of subjective distress. The first clinical sign might not appear until 3rd or 4th grade, typically after a holiday or a period where the child has been home because of illness, or when the stability of the family structure has been threatened by illness, divorce, or other psychosocial stressors.

Symptoms vary depending on the child's age: Children <8 yr often have associated school refusal and excessive fear that harm will come to a parent; children 9-12 yr have excessive distress when separated from a parent; and those 13-16 yr often have school refusal and physical complaints. SAD may be more likely to develop in children with lower levels of psychosocial maturity. Parents are often unable to be assertive in returning the child to school. Mothers of children with SAD often have a history of an anxiety disorder. In these cases the pediatrician should screen for parental depression or anxiety. Often, referral for parental treatment or family therapy is necessary before SAD and concomitant school refusal can be successfully treated.

Comorbidity is common in SAD. In children with comorbid tic disorders and anxiety, SAD is especially associated with tic severity. SAD is a predictor for early onset of PD. Children with SAD compared to those without SAD are 3 times more likely to develop PD in adolescence.

When a child reports recurring acute severe anxiety, antidepressant or anxiolytic medication is often necessary. Controlled studies of tricyclic antidepressants (TCAs, imipramine) and benzodiazepines (clonazepam) show that these agents are not generally effective. Data support the use of cognitive-behavioral therapy (CBT) *and* selective serotonin reuptake inhibitors (SSRIs) (see Chapter 33 , Table 33.4). Adverse events with SSRI treatment, including suicidal and homicidal ideation, are uncommon. CBT alone is associated with less insomnia, fatigue, sedation, and restlessness than SSRIs. Combining SSRIs with CBT may be the best approach to achieving a positive response; long-term SSRI treatment can provide additional benefit.

Childhood-onset social phobia (social anxiety disorder) is characterized by excessive anxiety in social settings (including the presence of unfamiliar peers, or unfamiliar adults) or performance situations, leading to social isolation, and is associated with social scrutiny and fear of doing something embarrassing (Table 38.3). Fear of social settings can also occur in other disorders, such as GAD. Avoidance or escape from the situation usually dissipates anxiety in **social phobia (SP),** unlike GAD, where worry persists.

Table 38.3

DSM-5 Diagnostic Criteria for Social Anxiety Disorder (Social Phobia)

A. Marked fear or anxiety about 1 or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).

B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing; will lead to rejection or offend others).

C. The social situations almost always provoke fear or anxiety.

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

D. The social situations are avoided or endured with intense fear or anxiety.

E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The fear, anxiety, or avoidance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

I. The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder.

J. If another medical condition (e.g., Parkinson disease, obesity, disfigurement from burns or injury) is present, the anxiety or avoidance is clearly unrelated or is excessive.

Specify if:

Performance only: If the fear is restricted to speaking or performing in public.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, pp 202–203.

Children and adolescents with SP often maintain the desire for involvement with family and familiar peers. When severe, the anxiety can manifest as a panic attack. SP is associated with a decreased quality of life, with increased likelihood of having failed at least 1 grade, and a 38% likelihood of not graduating from high school. Its onset is typically during or before adolescence and is more common in girls. A family history of SP or extreme shyness is common. Approximately 70–80% of patients with SP have at least 1 comorbid psychiatric disorder. Most shy patients do not have SP.

Social effectiveness therapy for children (SET-C), alone or with SSRIs, is considered the treatment of choice for SP (see Table 33.4). SSRI and SET-C are superior to placebo in reducing social distress and behavioral avoidance and increasing general functioning. SET-C may be better than SSRI in reducing these symptoms. SET-C, but not SSRI, may be superior to placebo in improving social skills, decreasing anxiety in specific social interactions, and enhancing social competence. SSRIs have a maximum effect by 8 wk; SET-C provides continued improvement through 12 wk. A combination of SSRI and CBT is superior to either treatment alone in reducing severity of anxiety in children with SP and other anxiety disorders. β-Adrenergic blocking agents are used to treat SP, particularly the subtype with performance anxiety and stage fright. β-Blockers are not approved by the U.S. Food and Drug Administration (FDA) for SP.

School refusal , which occurs in approximately 1–2% of children, is associated with anxiety in 40–50% of cases, depression in 50–60% of cases, and oppositional behavior in 50% of cases. Younger anxious children who refuse to attend school are more likely to have SAD, whereas older anxious children usually refuse to attend school because of SP. Somatic symptoms, especially abdominal pain and headaches, are common. There may be increasing tension in the parent–child relationship or other indicators of family disruption (domestic violence, divorce, or other major stressors) contributing to school refusal.

Management of school refusal typically requires parent management training and family therapy. Working with school personnel is always indicated; anxious children often require special attention from teachers, counselors, or school nurses. Parents who are coached to calmly send the child to school and to reward the child for each completed day of school are usually successful. In cases of ongoing school refusal, referral to a child and adolescent psychiatrist and psychologist is indicated. SSRI treatment may be helpful. Young children with affective symptoms have a good prognosis, whereas adolescents with more insidious onset or with significant somatic complaints have a more guarded prognosis.

Selective mutism is conceptualized as a disorder that overlaps with SP. Children with selective mutism talk almost exclusively at home, although they are reticent in other settings, such as school, daycare, or even relatives' homes. The mutism must be present for ≥1 mo. Often, one or more stressors, such as a new classroom or conflicts with parents or siblings, drive an already shy child to become reluctant to speak. It may be helpful to obtain history of normal language use in at least one situation to rule out any communication disorder (fluency disorder), neurologic disorder, or pervasive developmental disorder (autism, schizophrenia) as a cause of mutism. Fluoxetine in combination with behavioral therapy is effective for children whose school performance is severely limited by their symptoms (see Chapter 52). Other SSRIs may also be effective.

Panic disorder is a syndrome of recurrent, discrete episodes of marked fear or discomfort in which patients experience abrupt onset of physical and psychological symptoms called *panic attacks* (Table 38.4). Physical symptoms can include palpitations, sweating, shaking, shortness of breath, dizziness, chest pain, and nausea. Children can present with acute respiratory distress but without fever, wheezing, or stridor, ruling out organic causes of the distress. The associated psychological symptoms include fear of death, impending doom, loss of control, persistent concerns about having future attacks, and avoidance of settings where attacks have occurred (agoraphobia, Table 38.5).

Table 38.4

DSM-5 Diagnostic Criteria for Panic Disorder

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time 4 (or more) of the following symptoms occur:

Note: The abrupt surge can occur from a calm state or an anxious state.

1. Palpitations, pounding heart, or accelerated heart rate.
2. Sweating.
3. Trembling or shaking.
4. Sensations of shortness of breath or smothering.
5. Feelings of choking.
6. Chest pain or discomfort.
7. Nausea or abdominal distress.
8. Feeling dizzy, unsteady, light-headed, or faint.
9. Chills or heart sensations.
10. Paresthesias (numbness or tingling sensations).
11. Derealizations (feeling or unreality) or depersonalization (being detached from one-self).
12. Fear of losing control or “going crazy.”
13. Fear of dying.

Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as 1 of the 4 required symptoms.

B. At least 1 of the attacks has been followed by 1 mo (or more) of 1 or both of the following:

1. Persistent concern or worry about additional panic attacks or their

consequences (e.g., losing control, having a heart attack, “going crazy”).
    2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; or in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

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Table 38.5

DSM-5 Diagnostic Criteria for Agoraphobia

A. Marked fear or anxiety about 2 (or more) if the following 5 situations:
    1. Using public transportation (e.g., automobiles, buses, trains, ships, planes).
    2. Being in open spaces (e.g., parking lots, marketplaces, bridges).
    3. Being in enclosed places (e.g., shops, theaters, cinemas).
    4. Standing in line or being in a crowd.
    5. Being outside of the home alone.

B. The individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of a developing panic-like symptoms or other incapacitating or embarrassing symptoms (e.g., fear or falling in the elderly, fear of incontinence).

C. The agoraphobic situations almost always provoke fear or anxiety.

D. The agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety.

E. The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context.

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important area of functioning.

H. If another medical condition (e.g., inflammatory bowel disease, Parkinson disease) is present, the fear, anxiety, or avoidance is clearly excessive.

I. The fear, anxiety, or avoidance is not better explained by the symptoms or another mental disorder—for example, the symptoms are not confined to specific phobia, situational type; do not involve only social situations (as in social anxiety disorder); and are not related exclusively to obsessions (as in obsessive-compulsive disorder), reminders or traumatic events (as in posttraumatic stress disorder), or fear of separation (as in separation anxiety disorder).

Note: Agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 217–218.

PD is uncommon before adolescence, with the peak age of onset at 15-19 yr, occurring more often in girls. The postadolescence prevalence of PD is 1–2%. Early-onset PD and adult-onset PD do not differ in symptom severity or social functioning. *Early-onset* PD is associated with greater comorbidity, which can result from greater familial loading for anxiety disorders in the early-onset subtype. Children of parents with PD are much more likely to develop PD. A predisposition to react to autonomic arousal with anxiety may be a specific risk factor leading to PD. Twin studies suggest that 30–40% of the variance is attributed to genetics. The increasing rates of panic attack are also directly related to earlier sexual maturity. Cued panic attacks can be present in other anxiety disorders and differ from the uncued “out-of-the-blue” attacks in PD.

No randomized controlled trials (RCTs) have evaluated the effectiveness of antidepressant medication in youth with PD. Open-label studies with SSRIs appear to show effectiveness in the treatment of adolescents (see Table 33.4).

CBT may also be helpful. The recovery rate is approximately 70%.

Generalized anxiety disorder occurs in children who often experience unrealistic worries about different events or activities for at least 6 mo with at least 1 somatic complaint (Table 38.6). The diffuse nature of the anxiety symptoms differentiates it from other anxiety disorders. Worries in children with GAD usually center around concerns about competence and performance in school and athletics. GAD often manifests with somatic symptoms, including restlessness, fatigue, problems concentrating, irritability, muscle tension, and sleep disturbance. Given the somatic symptoms characteristic of GAD, the differential diagnosis must consider other medical causes. Excessive use of caffeine or other stimulants in adolescence is common and should be determined with a careful history. When the history or physical examination is suggestive, the pediatrician should rule out hyperthyroidism, hypoglycemia, lupus, pheochromocytoma, and other disorders (see Table 38.1 ; Fig. 38.2).

Table 38.6

DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance).

B. The individual finds it difficult to control the worry.

C. The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms having been present for more days than not for the past 6 mo):

Note: Only 1 item is required in children.

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or other medical condition (e.g., hyperthyroidism).

F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, remainders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 222.

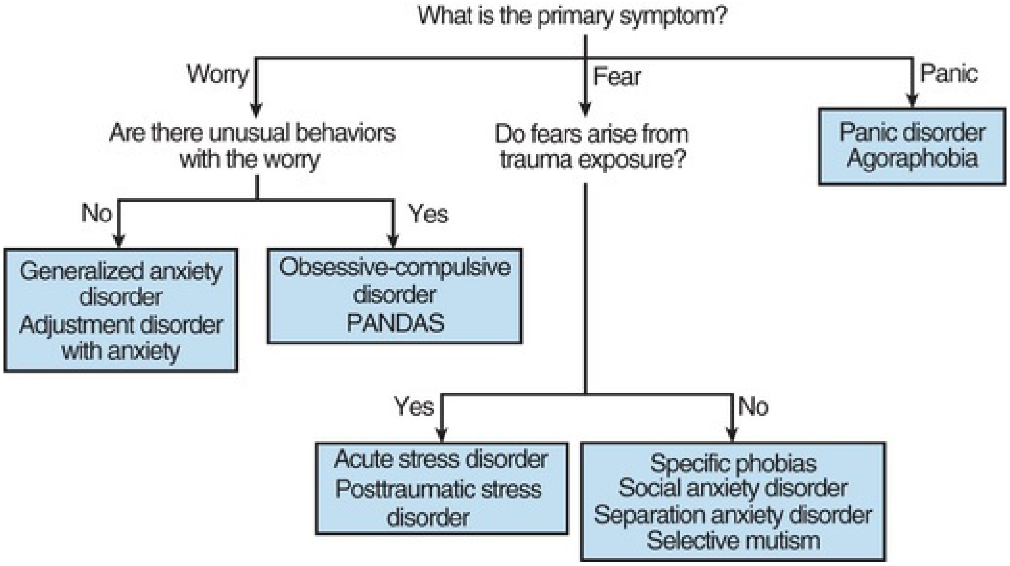
What is the primary symptom?
Worry
Fear
Panic
Are there unusual behaviors with the worry
Do fears arise from trauma exposure?
Panic disorder
Agoraphobia
No
Yes
Generalized anxiety disorder
Adjustment disorder with anxiety
Obsessive-compulsive disorder
PANDAS
Yes
No
Acute stress disorder
Posttraumatic stress disorder
Specific phobias
Social anxiety disorder
Separation anxiety disorder
Selective mutism

FIG. 38.2 **Evaluation of worry, fear, and panic. *PANDAS* , Pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus pyogenes* . (From Kliegman RM, Lye PS, Bordini B, et al, editors: *Nelson pediatric symptom-based diagnosis,* Philadelphia, 2018, Elsevier, p 429).**

Children with GAD are extremely self-conscious and perfectionistic and struggle with more intense distress than is evident to parents or others around them. They often have other anxiety disorders, such as simple phobia and PD. Onset may be gradual or sudden, although GAD seldom manifests until puberty. Boys and girls are equally affected before puberty, when GAD becomes more prevalent in girls. The prevalence of GAD ranges from 2.5–6% of children. Hypermetabolism in frontal precortical area and increased blood flow in the right dorsolateral prefrontal cortex may be present.

Children with GAD are good candidates for CBT, an SSRI, or their combination (see Table 33.4). Buspirone may be used as an adjunct to SSRI therapy. The combination of CBT and SSRI often results in a superior response in pediatric patients with anxiety disorders, including GAD. The recovery rate is approximately 80%.

It is important to distinguish children with GAD from those who present with specific repetitive thoughts that invade consciousness (**obsessions**) or repetitive rituals or movements that are driven by anxiety (**compulsions**). The most common obsessions are concerned with bodily wastes and secretions, the fear that something calamitous will happen, or the need for sameness. The most common compulsions are handwashing, continual checking of locks, and touching. At times of stress (bedtime, preparing for school), some children touch certain objects, say certain words, or wash their hands repeatedly.

Obsessive-compulsive disorder is diagnosed when the thoughts or rituals cause distress, consume time, or interfere with occupational or social functioning (Table 38.7). In the DSM-5, OCD and related disorders, such as trichotillomania, excoriation, body dysmorphic disorder, and hoarding, are listed separately and are no longer included under anxiety disorders.

Table 38.7

DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder

A. Presence of obsessions, compulsions, or both:

Obsessions are defined by (1) and (2):

1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.

2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).

Compulsions are defined by (1) and (2):

1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hr per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The obsessive-compulsive symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating disorder, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).

Specify if:

With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.

With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.

With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.

Specify if:

Tic-related: The individual has a current or past history of a tic disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, p 237.

OCD is a chronically disabling illness characterized by repetitive, ritualistic behaviors over which the patient has little or no control. OCD has a lifetime prevalence of 1–3% worldwide, and as many as 80% of all cases have their onset in childhood and adolescence. Common obsessions include contamination (35%) and thoughts of harming loved ones or oneself (30%). Washing and cleaning compulsions are common in children (75%), as are checking (40%) and straightening (35%). Many children are observed to have visuospatial irregularities, memory problems, and attention deficits, causing academic problems not explained by OCD symptoms alone.

The *Children's Yale-Brown Obsessive-Compulsive Scale* (C-YBOCS) and the *Anxiety Disorders Interview Schedule for Children* (ADIS-C) are reliable and valid methods for identifying children with OCD. The C-YBOCS is helpful in following the progression of symptoms with treatment. The *Leyton Obsessional Inventory* (LOI) is a self-report measure of OCD symptoms that is quite sensitive. Patients with OCD have consistently identified abnormalities in the frontostriatal-thalamic circuitry associated with severity of illness and treatment response. Comorbidity is common in OCD, with 30% of patients having comorbid tic disorders, 26% comorbid major depression, and 24% comorbid developmental disorders.

Consensus guidelines recommend that children and adolescents with OCD begin treatment with either CBT alone or CBT in combination with SSRI, when symptoms are moderate to severe (YBOCS >21). In OCD patients with comorbid tics, SSRIs are no more effective than placebo, and the combination of CBT and SSRI is superior to CBT; CBT alone is superior to placebo. Pediatric OCD patients with comorbid tics should begin treatment with CBT alone or combined CBT and SSRI. Pediatric patients with OCD who have a family history of OCD may be significantly less responsive to CBT alone than patients without a family history.

There are 4 FDA-approved medications for pediatric OCD: fluoxetine, sertraline, fluvoxamine, and clomipramine. *Clomipramine,* a heterocyclic antidepressant and nonselective serotonin and norepinephrine reuptake inhibitor, is only indicated when a patient has failed 2 or more SSRI trials. There may be a role for glutamate-modulating medications in the treatment of OCD. The glutamate inhibitor *riluzole* (Rilutek) is FDA approved for amyotrophic lateral sclerosis (see Chapter 630.3) and has a good safety record. The most common adverse event with riluzole is transient increase in liver transaminases. Riluzole in children with treatment-resistant OCD may be beneficial and is well tolerated. Other glutamate-modulating agents, such as memantine, *N* -acetylcysteine, and D -cycloserine, have been used with some success in patients with OCD. Referral of patients with OCD to a mental health professional is always indicated.

In 10% of children with OCD, symptoms are triggered or exacerbated by group A β-hemolytic streptococcal infection (see Chapter 210). Group A β-hemolytic streptococci trigger antineuronal antibodies that cross-react with basal ganglia neural tissue in genetically susceptible hosts, leading to swelling of this region and resultant obsessions and compulsions. This subtype of OCD, called **pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS),** is characterized by sudden and dramatic onset or exacerbation of OCD or tic symptoms, associated neurologic findings, and a recent streptococcal infection. Increased antibody titers of antistreptolysin O and antideoxyribonuclease B correlates with increased basal ganglia volumes. Plasmapheresis is effective in reducing OCD symptoms in some patients with PANDAS and also decreasing enlarged basal ganglia volume. OCD has also followed episodes of acute disseminated encephalomyelitis (see Chapter 618.4) The pediatrician should be aware of the infectious cause of some cases of tic disorders, and OCD and follow management guidelines (see Chapter 37).

Children with **phobias** avoid specific objects or situations that reliably trigger physiologic arousal (e.g., dogs, spiders) (see Table 38.2). The fear is excessive and unreasonable and can be cued by the presence or anticipation of the feared trigger, with anxiety symptoms occurring immediately. Neither obsessions nor compulsions are associated with the fear response; phobias only rarely interfere with social, educational, or interpersonal functioning. Assault by a relative and verbal aggression between parents can influence the onset of specific phobias. The parents of phobic children should remain calm in the face of the child's anxiety or panic. Parents who become anxious themselves may reinforce their children's anxiety, and the pediatrician can usefully interrupt this cycle by calmly noting that phobias are not unusual and rarely cause impairment. The prevalence of specific phobias in childhood is 0.5–2%.

Systematic desensitization is a form of behavior therapy that gradually exposes the patient to the fear-inducing situation or object, while simultaneously teaching relaxation techniques for anxiety management. Successful repeated exposure leads to extinguishing anxiety for that stimulus. When phobias are particularly severe, SSRIs can be used with behavioral intervention. Low-dose SSRI treatment may be especially effective for some children with severe, refractory choking phobia.

Posttraumatic stress disorder is typically precipitated by an extreme stressor (see Chapter 14). PTSD is an anxiety disorder resulting from the long- and short-term effects of trauma that cause behavioral and physiologic sequelae in toddlers, children, and adolescents (Table 38.8). Another diagnostic category, **acute stress disorder** , reflects that traumatic events often cause acute symptoms that may or may not resolve. Previous trauma exposure, a history of other psychopathology, and symptoms of PTSD in parents predict childhood-onset PTSD. Many adolescent and adult psychopathologic conditions, such as conduct disorder, depression, and some personality disorders, might relate to previous trauma. PTSD is also linked to mood disorders and disruptive behavior. Separation anxiety is common in children with PTSD. The lifetime prevalence of PTSD by age 18 yr is approximately 6%. Up to 40% show symptoms, but do not fulfill the diagnostic criteria.

Table 38.8

DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder

Posttraumatic Stress Disorder

Note: The following criteria apply to adults, adolescents, and children older than 6 yr. For children 6 yr and younger, see corresponding criteria below.

A. Exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:

1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others.

3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., 1st responders collecting human remains; police officers repeatedly exposed to details of child abuse).

Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of 1 (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: In children older than 6 yr, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

2. Recurrent distressing dreams in which the content and/or effect of the dream are related to the traumatic event(s).

Note: In children, there may be frightening dreams without recognizable content.

3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the more extreme expression being a complete loss or awareness of present surroundings.)

Note: In children, trauma-specific reenactment may occur in play.

4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
5. Marked physiologic reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by 1 or both of the following:

1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic

event(s).

2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:

1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., “I am bad,” “No one can be trusted,” “The world is completely dangerous,” “My whole nervous system is permanently ruined”).
3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest or participation in significant activities.
6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:

1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed by verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 mo.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

Posttraumatic Stress Disorder for Children 6 Yr and Younger

A. In children 6 yr and younger, exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:

1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others, especially primary caregivers.

Note: Witnessing does not include events that are only in electronic media, television, movies, or pictures.

3. Learning that the traumatic event(s) occurred to a parent or caregiving figure.

B. Presence of 1 (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:

1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: Spontaneous and intrusive memories may not necessarily appear distressing and may be expressed as play reenactment.

2. Recurrent distressing dreams in which the content and/or effect of the dream is related to the traumatic event(s).

Note: It may not be possible to ascertain that the frightening content is related to the traumatic event.

3. Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Such trauma-specific reenactment may occur in play.
4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. One (or more) of the following symptoms, representing either persistent avoidance of stimuli associated with the traumatic event(s) or negative alterations in cognitions and mood associated with the traumatic event(s), must be present, beginning after the event(s) or worsening after the event(s):

Persistent Avoidance of Stimuli

1. Avoidance of or efforts to avoid activities, places, or physical reminders that arouse recollections or the traumatic event(s).
2. Avoidance of or efforts to avoid people, conversations, or interpersonal situations that around recollections of the traumatic event(s).

Negative Alterations in Cognitions

3. Substantially increased frequency of negative emotional states (e.g., fear, guilt, sadness, shame, confusion).
4. Markedly diminished interest or participation in significant

activities, including constriction of play.
   5. Socially withdrawn behavior.
   6. Persistent reduction in expression of positive emotions.

D. Alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:

   1. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal and physical aggression toward people or objects (including extreme temper tantrums).
   2. Hypervigilance.
   3. Exaggerated startle response.
   4. Problems with concentration.
   5. Sleep disturbance (e.g., difficulty falling asleep or staying asleep or restless sleep).

E. The duration of the disturbance is more than 1 mo.

F. The disturbance causes clinically significant distress or impairment in relationships with parents, siblings, peers, or other caregivers or with school behavior.

G. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication or alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and the individual experiences persistent or recurrent symptoms of either of the following:

   1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
   2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

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Events that pose actual or threatened physical injury, harm, or death to the child, child's caregiver, or others close to the child, and that produce considerable stress, fear, or helplessness, are required to make the diagnosis of PTSD. Three clusters of symptoms are also essential for diagnosis: reexperiencing, avoidance, and hyperarousal. Persistent **reexperiencing** of the stressor through intrusive recollections, nightmares, and reenactment in play are typical responses in children. Persistent **avoidance** of reminders and numbing of emotional responsiveness, such as isolation, amnesia, and avoidance, constitute the 2nd cluster of behaviors. Symptoms of **hyperarousal,** such as hypervigilance, poor concentration, extreme startle responses, agitation, and sleep problems, complete the symptom profile of PTSD. Occasionally, children regress in some of their developmental milestones after a traumatic event. Avoidance symptoms are usually observable in younger children, whereas older children may better describe reexperiencing and hyperarousal symptoms. Repetitive play involving the event, psychosomatic symptoms, and nightmares may also be observed.

Initial interventions after a trauma should focus on reunification with a parent and attending to the child's physical needs in a safe place. Aggressive treatment of pain, and facilitating a return to comforting routines, including regular sleep, is indicated. Long-term treatment may include individual, group, school-based, or family therapy, as well as pharmacotherapy, in selected cases. *Individual* treatment involves transforming the child's concept of himself or herself as victim to that of survivor and can occur through play therapy, psychodynamic therapy, or CBT. *Group* work is also helpful for identifying which children might need more intensive assistance. Goals of *family* work include helping the child establish a sense of security, validating the child's emotions, and anticipating situations when the child will need more support from the family.

Clonidine or *guanfacine* may be helpful for sleep disturbance, persistent arousal, and exaggerated startle response. Recent RCTs in children and adolescents with PTSD found no significant difference between SSRI and placebo. SSRIs may be considered in pediatric patients with PTSD who have comorbid conditions responsive to SSRIs, including depression, affective numbing, and anxiety (see Table 33.4). As for many other anxiety disorders, CBT is the psychotherapeutic intervention with the most empirical support.

Anxiety Associated With Medical Conditions

It is prudent to rule out organic conditions such as hyperthyroidism, caffeinism (carbonated beverages), hypoglycemia, central nervous system disorders (delirium, encephalopathy, brain tumors), migraine, asthma, lead poisoning, cardiac arrhythmias, and rarely, pulmonary embolism, hyperparathyroidism, systemic lupus erythematosus, anaphylaxis, porphyria, or pheochromocytoma, before making a diagnosis of an anxiety disorder (see Table 38.1). Some *prescription* drugs with side effects that can mimic anxiety include antiasthmatic agents, corticosteroids, sympathomimetics, SSRIs (initiation), anticholinergic agents, and antipsychotics. *Nonprescription* drugs causing anxiety include diet pills, antihistamines, stimulant drugs of abuse, drug withdrawal, and cold medicines.

Chronic illness is also an underlying cause of anxiety. Children are not often emotionally and cognitively competent to understand the implications of a serious and prolonged illness. In addition to the physiologic implications of illness, they must also attend to the hospitalizations, procedures, and medications that permeate their everyday schedule. This experience affects their schooling, friendships, activities, and dynamics of the nuclear family, including the experiences of their well siblings.

School issues surrounding both prolonged absences and school reentry following a medical condition can cause or reinforce and escalate existing anxiety. School is a foundation not only for learning, but it is central to children's social experiences and feelings of normalcy. It is often impeded and stunted by illness. Academic struggles can result from missing classes, medication use, and emotional status. Children with chronic conditions are also socially disadvantaged, with friendship networks hampered by unstable attendance or social rejection for being different. Consulting with the school psychologist can be beneficial in preparing teachers and classmates before the child returns to school. An agreement between the student and school staff should be implemented, outlining a plan for taking medication, needing rest, or consulting on other needs. If the child and family agree, an informational meeting with students and teachers can normalize the situation. Explaining the condition makes it less scary for children who *catastrophize* or worry about contagion. Classmates and teachers are a natural accessible resource and can be a valuable support community. Medication may also be warranted to supplement social supports.

The experiences of the **siblings** of children with chronic illness are often forgotten, with familial resources focused on medical-financial consequences and the emotional and physical functioning of the ill child. It is not uncommon for the siblings of ill children to experience depression and anxiety as well. Assessing their social support systems, communication opportunities with parents and emotional outlets are critical to maintaining healthy functioning. Maintaining a redefined schedule of after-school activities and social engagements are helpful in allowing siblings to continue in school.

Safety and Efficacy Concerns About SSRIs

No empirical evidence suggests the superiority of one SSRI over another. Data are limited on combining medications. SSRIs are usually well tolerated by most children and adolescents. The FDA issued a “black box” warning of increased agitation and suicidality among adolescents and children taking SSRIs. This warning was based on review of studies in children and adolescents with major depression and not anxiety disorders. Close monitoring is always warranted.

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CHAPTER 39

Mood Disorders

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Mood disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in emotional self-regulation. Classically, the mood disorders have been divided into depressive and bipolar disorders, representing the two emotional polarities, *dysphoric* (“low”) and *euphoric* (“high”) mood.

39.1

Major and Other Depressive Disorders

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The depressive disorders include major depressive, persistent depressive, disruptive mood dysregulation, other specified/unspecified depressive, premenstrual dysphoric, and substance/medication-induced disorders, as well as depressive disorder caused by another medical condition (Fig. 39.1).

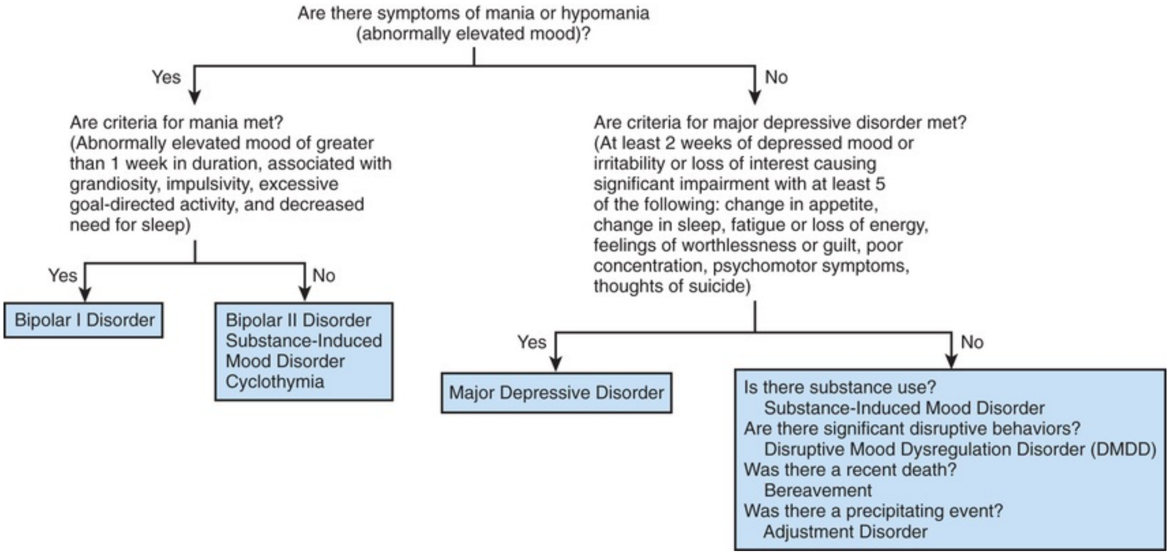
Are there symptoms of mania or hypomania (abnormally elevated mood)?
Yes
No
Are criteria for mania met? (Abnormally elevated mood of greater than 1 week in duration, associated with grandiosity, impulsivity, excessive goal-directed activity, and decreased need for sleep)
Yes
No
Bipolar I Disorder
Bipolar II Disorder
Substance-Induced Mood Disorder
Cyclothymia
Are criteria for major depressive disorder met? (At least 2 weeks of depressed mood or irritability or loss of interest causing significant impairment with at least 5 of the following: change in appetite, change in sleep, fatigue or loss of energy, feelings of worthlessness or guilt, poor concentration, psychomotor symptoms, thoughts of suicide)
Yes
No
Major Depressive Disorder
Is there substance use?
Substance-Induced Mood Disorder
Are there significant disruptive behaviors?
Disruptive Mood Dysregulation Disorder (DMDD)
Was there a recent death?
Bereavement
Was there a precipitating event?
Adjustment Disorder

FIG. 39.1 Evaluation of mood disorders. (From Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis,* Philadelphia, 2018, Elsevier, p 426.)

Description

Major depressive disorder (MDD) is characterized by a distinct period of at least 2 wk (an *episode*) in which there is a depressed or irritable mood and/or loss of interest or pleasure in almost all activities that is present for most of the day, nearly every day (Table 39.1). Major depression is associated with characteristic vegetative and cognitive symptoms, including disturbances in appetite, sleep, energy, and activity level; impaired concentration; thoughts of worthlessness or guilt; and suicidal thoughts or actions. Major depression is considered *mild* if few or no symptoms in excess of those required to make the diagnosis are present, and the symptoms are mildly distressing and manageable and result in minor functional impairment. Major depression is considered *severe* if symptoms substantially in excess of those required to make the diagnosis are present, and the symptoms are highly distressing and unmanageable and markedly impair function. *Moderate* major depression is intermediate in severity between mild and severe.

Table 39.1

DSM-5 Diagnostic Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).

Note: In children and adolescents, can be irritable mood.

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

Note: In children, consider failure to make expected weight gain.

4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiologic effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 125–126.

Persistent depressive disorder is characterized by depressed or irritable mood for more days than not, for at least 1 yr (in children and adolescents). As with major depression, this chronic form of depression is associated with characteristic vegetative and cognitive symptoms; however, the cognitive symptoms of persistent depression are less severe (e.g., low self-esteem rather than worthlessness, hopelessness rather than suicidality). As with major depression, persistent depressive disorder is characterized as mild, moderate, or severe (Table 39.2).

Table 39.2

DSM-5 Diagnostic Criteria for Persistent Depressive Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 yr.

Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr.

B. Presence, while depressed, of 2 (or more) of the following:

1. Poor appetite or overeating.
2. Insomnia or hypersomnia.
3. Low energy or fatigue.
4. Low self-esteem.
5. Poor concentration or difficulty making decisions.
6. Feelings of hopelessness.

C. During the 2 yr period (1 yr for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 mo at a time.

D. Criteria for a major depressive disorder may be continuously present for 2 yr.

E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

G. The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: Because the criteria for a major depressive episode include 4 symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 yr but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.

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Overall, the clinical presentation of major and persistent depressive disorders in children and adolescents is similar to that in adults. The prominence of the symptoms can change with age: irritability and somatic complaints may be more common in children, and energy, activity level, appetite, and sleep disturbances may be more common in adolescents. Because of the cognitive and linguistic immaturity of young children, symptoms of depression in that age-group may be more likely to be observed than self-reported.

The core feature of **disruptive mood dysregulation disorder (DMDD)** is severe, persistent irritability evident most of the day, nearly every day, for at least 12 mo in multiple settings (at home, at school, with peers). The irritable mood is interspersed with frequent (≥3 times/wk) and severe (verbal rages, physical aggression) temper outbursts (Table 39.3). This diagnosis is intended to characterize more accurately the extreme irritability that some investigators had considered a developmental presentation of bipolar disorder, and to distinguish extreme irritability from the milder presentations characteristic of oppositional defiant disorder (ODD) and intermittent explosive disorder.

Table 39.3

DSM-5 Diagnostic Criteria for Disruptive Mood Dysregulation Disorder

A. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.

B. The temper outbursts are inconsistent with developmental level.

C. The temper outbursts occur, on average, 3 or more times per week.

D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).

E. Criteria A-D have been present for 12 or more months. Throughout that time, the individual has not had a period lasting 3 or more consecutive months without all of the symptoms in Criteria A-D.

F. Criteria A and D are present in at least 2 of 3 settings (i.e., at home, at school, with peers) and are severe in at least 1 of these.

G. The diagnosis should not be made for the first time before age 6 yr or after age 18 yr.

H. By history or observation, the age at onset of Criteria A-E is before 10 yr.

I. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.

Note: Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, should not be considered as a symptom of mania or hypomania.

J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, persistent depressive disorder [dysthymia]).

Note: The diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, or bipolar disorder, though it can coexist with others, including major depressive disorder, attention-deficit/hyperactivity disorder, conduct disorder, and substance use disorders. Individuals whose symptoms meet criteria for both disruptive mood dysregulation disorder and oppositional defiant disorder should only be given the diagnosis of disruptive mood dysregulation disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of disruptive mood dysregulation disorder should not be assigned.

K. The symptoms are not attributable to the physiologic effects of a substance or to another medical or neurologic condition.

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Other specified/unspecified depressive disorder (subsyndromal depressive disorder) applies to presentations in which symptoms characteristic of a depressive disorder are present and cause clinically significant distress or functional impairment, but do not meet the full criteria for any of the disorders in this diagnostic class.

Epidemiology

The overall prevalence of parent-reported diagnosis of depressive disorder in the United States (excluding DMDD) among 3-17 yr old children is approximately 2.1% (current) and 3.9% (ever); the prevalence rate increases to 12.8% (lifetime) for 12-17 yr olds. The male:female ratio (excluding DMDD) is approximately 1 : 1 during childhood and beginning in early adolescence rises to 1 : 1.5-3.0 in adulthood.

Based on rates of chronic and severe persistent irritability, which is the core feature of DMDD, the overall 6 mo to 1 yr prevalence has been estimated in the 2–5% range. In 3 community samples, the 3 mo prevalence rate of DMDD ranged from 0.8–3.3%, with the highest rates occurring in preschoolers (although DSM-5 does not permit this diagnosis until age 6 yr). Approximately

5–10% of children and adolescents are estimated to have **subsyndromal (unspecified) depression** .

Clinical Course

Major depression may first appear at any age, but the likelihood of onset greatly increases with puberty. Incidence appears to peak in the 20s. The median duration of a major depressive episode is about 5-8 mo for clinically referred youth and 3-6 mo for community samples. The course is quite variable in that some individuals rarely or never experience remission, whereas others experience many years with few or no symptoms between episodes. Persistent depressive disorder often has an early and insidious onset and by definition, a chronic course (average untreated duration in both clinical and community samples: 3.5 yr).

Prepubertal depressive disorders exhibit more heterotypic than homotypic continuity; depressed children appear to be more likely to develop nondepressive psychiatric disorders in adulthood than depressive disorders. Adolescents exhibit greater homotypic continuity, with the probability of recurrence of depression reaching 50–70% after 5 yr. The persistence of even mild depressive symptoms during remission is a powerful predictor of recurrence; other negative prognostic factors include more severe symptoms, longer time to remission, history of maltreatment, and comorbid psychiatric disorders. Up to 20% of depressed adolescents develop a bipolar disorder; the risk is higher among adolescents who have a high family loading for bipolar disorder, who have psychotic depression, or who have had pharmacologically induced mania.

Differential Diagnosis

A number of psychiatric disorders, general medical conditions, and medications can generate symptoms of depression or irritability and must be distinguished from the depressive disorders. The psychiatric disorders include autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and bipolar, anxiety, trauma- and stressor-related, disruptive/impulse control/conduct, and substance-related disorders. Medical conditions include neurologic disorders (including autoimmune encephalitis), endocrine disorders (including hypothyroidism and Addison disease), infectious diseases, tumors, anemia, uremia, failure to thrive, chronic fatigue disorder, and pain disorder. Medications include narcotics, chemotherapy agents, β-blockers, corticosteroids, and contraceptives. The diagnosis of a depressive disorder should be made after these and other potential explanations for the observed symptoms have been ruled out.

Comorbidity

Major and persistent depressive disorders often co-occur with other psychiatric disorders. Depending on the setting and source of referral, 40–90% of youths with a depressive disorder have other psychiatric disorders, and up to 50% have ≥2 comorbid diagnoses. The most common comorbid diagnosis is an **anxiety disorder** and as such may reflect a common diathesis; other common comorbidities include ADHD and disruptive behavior, eating, and substance use disorders. The development of depressive disorders can both lead to and follow the development of the comorbid disorders.

Preliminary data suggest that DMDD occurs with other psychiatric disorders, including other depressive disorders, ADHD, conduct disorder, and substance use disorders, from 60–90% of the time. Because the symptoms of DMDD overlap in part with symptoms of bipolar disorder, ODD, and intermittent explosive disorder, by *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) convention, hierarchical diagnostic rules apply. Thus, bipolar disorder takes precedence over DMDD if a manic/hypomanic episode has ever occurred, and DMDD takes precedence over ODD and intermittent explosive disorder if full criteria for DMDD are met.

Sequelae

Approximately 60% of youths with MDD report thinking about **suicide,** and 30% attempt suicide. Youths with depressive disorders are also at high risk of substance abuse, impaired family and peer relationships, early pregnancy, legal problems, educational and occupational underachievement, and poor adjustment to life stressors, including physical illness.

Children with DMDD have displayed elevated rates of social impairments, school suspension, and service use. Irritability in adolescence has predicted the development of major depressive and dysthymic disorders and generalized anxiety disorder (but not bipolar disorder) 20 yr later, as well as lower educational attainment and income.

Etiology and Risk Factors

Current models of vulnerability to depressive disorders are grounded in gene and environment pathways. Genetic studies have demonstrated the heritability of depressive disorders, with monozygotic twin studies finding concordance rates of 40–65%. In families, both bottom-up (children to parents) and top-down (parents to children) studies have shown a 2-4–fold bidirectional increase in depression among first-degree relatives. The exact nature of genetic expression remains unclear. Cerebral variations in structure and function (particularly serotonergic), the function of the hypothalamic-pituitary-adrenal axis, difficult temperament/personality (i.e., negative affectivity), and ruminative, self-devaluating cognitive style have been implicated as components of biologic vulnerability. The great majority of depressive disorders arise in youths with long-standing psychosocial difficulties, among the most predictive of which are physical/sexual abuse, neglect, chronic illness, school difficulties (bullying, academic failure), social isolation, family or marital disharmony, divorce/separation, parental psychopathology, and domestic violence. Longitudinal studies demonstrate the greater importance of environmental influences in children who become depressed than in adults who become depressed. Factors shown to be protective against the development of depression include a positive relationship with a parent; better family function; closer parental supervision, monitoring, and involvement; a prosocial peer group; higher IQ; and greater educational aspirations.

Prevention

Numerous experimental trials have sought to demonstrate the effectiveness of psychological or educational strategies in preventing the onset of depressive disorders in children and adolescents. These programs generally have provided information about the link between depressed mood and depressogenic thoughts and behaviors, as well as training in skills intended to modify these thoughts and behaviors. A Cochrane review found small effects of these programs on depression symptoms when implemented universally vs no intervention, with selective programs (targeted at high-risk groups) performing better than universal programs; however, the effect of prevention programs was null compared with attention controls.

Screening/Case Finding

Adolescents presenting in the primary care setting should be queried, along with their parent(s), about depressed mood as part of the routine clinical interview. A typical screening question would be, “Everyone feels sad or angry some of the time, how about you (or your teen)?” The parents of younger children can be queried about overt signs of depression, such as tearfulness, irritability, boredom, or social isolation. A number of standardized screening instruments widely used in the primary care setting (e.g., *Pediatric Symptom Checklist* , *Strengths and Difficulties Questionnaire* , *Vanderbilt ADHD Diagnostic Rating Scales*) have items specific to sad mood, and as such can be used to focus the interview.

The role of universal depression screening using standardized depression-specific instruments is unclear. A Cochrane review found that the use of depression screening in primary care has little or no impact on the recognition, management, or outcome of depression. Nonetheless, the U.S. Preventive Services Task Force (PSTF) recommends the universal use of depression screening instruments, but only among adolescents and only when systems are in place to ensure adequate follow-up. Targeted screening of known high-risk groups (e.g., youth who are homeless, refugees, attracted to the same sex, involved with child welfare or juvenile justice), or youth experiencing known psychosocial adversities (see Etiology and Risk Factors earlier) or self-reporting a dysphoric mood, may be a higher-yield case-finding strategy than universal screening.

Early Intervention

Youth (and/or their parents) presenting in the primary care setting who self-report, or respond affirmatively to queries about, a distressing life experience or a depressed or irritable mood should be offered the opportunity to talk about the situation with the pediatric practitioner (separately with the older youth as indicated). By engaging in active listening (e.g., “I hear how upset you have been feeling, tell me more about what happened to make you feel that way”), the pediatric practitioner can begin to assess the onset, duration, context, and severity of the symptoms and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., suicidality, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner (or co-located behavioral health therapist) can schedule a follow-up appointment within 1-2 wk to conduct a depression assessment. At this follow-up visit, to assist with decision-making about appropriate level of care, a depression-specific screening standardized rating scale can be administered to assess symptom severity (Table 39.4), and additional risk factors can be explored (see Etiology and Risk Factors earlier).

Table 39.4

Depression-Specific Rating Scales

NAME OF INSTRUMENT	INFORMANT(S)	AGE RANGE	NUMBER OF ITEMS
Beck Depression Inventory	Youth	13+ yr	21
Beck Depression Inventory for Youth	Youth	7-14 yr	20
Center for Epidemiologic Studies-Depression-Children	Youth	6-18 yr	20
Children's Depression Rating Scale-Revised	Youth, Parent, Clinician	6-18 yr	47
Children's Depression Inventory, Second Edition	Youth, Parent, Teacher	7-17 yr	28/17/12
Depression Self-Rating Scale	Youth	7-13 yr	18
Mood and Feelings Questionnaire	Youth, Parent	7-18 yr	33-34
Patient Health Questionnaire-9	Youth	12/13+ yr	9
Preschool Feelings Checklist	Parent	3-5.6 yr	20
PROMIS Emotional Distress-Depressive Symptoms	Youth, Parent	Youth: 8-17 yr Parent: 5-17 yr	8/6
Reynolds Child Depression Scale	Youth	8-13 yr	30
Reynolds Adolescent Depression Scale, Second Edition	Youth	11-20 yr	30

Treatment decisions should be guided by the understanding that depression in youth is highly responsive to placebo (50–60%) or brief nonspecific intervention (15–30%). The goal of treatment is **remission,** defined as a period of at least 2 wk with no or very few depressive symptoms, and ultimately **recovery,** defined as a period of at least 2 mo with no or very few depressive symptoms. Assessment of remission and recovery can be aided using the depression-specific standardized rating scales, in which remission is defined as scores below the scale-specific clinical cutpoint.

For mild symptoms (manageable and not functionally impairing) and in the absence of major risk factors (e.g., suicidality; psychosis; substance use; history of depression, mania, or traumatic exposures; parental psychopathology, particularly depression; severe family dysfunction), **guided self-help** (anticipatory guidance) with watchful waiting and scheduled follow-up may suffice. Guided self-help can include provision of educational materials (e.g., pamphlets, books, workbooks, apps, internet sites) that provide information to the youth about coping adaptively with depressogenic situations, as well as advice to parents about strengthening the parent–child relationship and modifying depressogenic exposures (e.g., taking action against bullying, increasing opportunities for social interaction and support, protecting child from exposure to marital discord). Additional self-help activities that have shown promise in improving mild depressive symptoms include physical exercise, relaxation therapy (e.g., yoga, mindfulness), and a regular sleep schedule.

For youths who continue to have mild depression after a few weeks of guided self-help, supportive therapy by a mental health professional (ideally co-located in the primary care, school, or community setting) may be an appropriate subsequent step. **Supportive psychotherapy** , which can be delivered in individual or group formats, focuses on teaching thoughts (e.g., positive self-talk) and behaviors (e.g., pleasurable activities, relaxation, problem solving, effective communication) known to ameliorate depressive symptoms, as well as providing concrete social or material problem-solving assistance to the youth or family as needed.

Treatment

For youths who have not responded to approximately 4-8 wk of supportive psychotherapy, or who from the outset exhibit moderate to severe, comorbid, or recurrent depression or suicidality, or who have a history of mania, traumatic exposures, or severe family dysfunction or psychopathology, assessment and treatment in the specialty mental health setting by a child-trained mental health clinician should be considered.

For moderate to severe depression, specific manualized psychotherapies, antidepressant medication, or a combination of both should be considered. At present, there is insufficient evidence on which to base definitive conclusions about the relative effectiveness of these treatments.

Clinical trials of acute treatments have generated support for the efficacy of cognitive-behavioral therapy (CBT)/behavioral activation therapy and interpersonal therapy as monotherapies in depressed youth, but overall effect sizes are modest (0.35 and 0.26, respectively). For children age 12 and younger, meta-analyses suggest no benefit of CBT over no treatment. CBT focuses on identifying and correcting cognitive distortions that may lead to depressed mood and teaches problem-solving, behavior activation, social communication, and emotional regulation skills to combat depression. Interpersonal therapy focuses on enhancing interpersonal problem solving and social communication to decrease interpersonal conflicts. Each of these therapies typically involves 8-12 weekly visits. Limited evidence suggests that family therapy may be more effective than no treatment in decreasing depression and improving family functioning.

Two selective serotonin reuptake inhibitors (SSRIs), **fluoxetine** and **escitalopram,** are the only antidepressants approved by the U.S. Food and Drug Administration (FDA) for the treatment of depression in youth, and fluoxetine alone is approved for preadolescents. Randomized controlled trials (RCTs) of the effectiveness of antidepressants are mixed, but meta-analyses of RCTs have been fairly consistent in their disappointing findings.

Based on a 2007 meta-analysis, approximately 60% of youths with MDD responded to antidepressants from multiple medication classes (vs 50% for placebo), but only about 30% of medicated depressed youths experienced symptom remission. Fluoxetine consistently demonstrated greater efficacy and was the only SSRI separating from placebo in studies of depressed preadolescents. The absolute risk for suicidal thoughts in youths treated with antidepressant medication was approximately 3%, vs 2% of those given placebo.

In another Cochrane review, antidepressants from multiple classes decreased symptom severity in children and adolescents with depressive disorders and increased remission/response in adolescents, but the effects were small and may not have been clinically significant. Fluoxetine and escitalopram possibly outperformed other antidepressants for safety and effectiveness.

In a 2016 meta-analysis of all classes of antidepressants prescribed for MDD in children and adolescents, only fluoxetine was statistically significantly more effective than placebo. Duloxetine and venlafaxine had adverse tolerability profiles, and youths taking venlafaxine were suggested to have a significantly increased risk for suicidality.

These findings converge in the suggestion that fluoxetine should be considered first-line therapy among antidepressants unless other factors (e.g., comorbidities, side effect profiles, personal/family history of response to a specific medication) favor an alternative antidepressant. Considering both efficacy and tolerability findings, next-best choices may be escitalopram (for adolescents) and sertraline (for children and adolescents). In light of the accumulated findings, antidepressants should be used cautiously in youth and likely should limited to patients (especially adolescents) with moderate to severe depression for whom psychosocial interventions are either ineffective or not feasible.

Clinical severity, comorbidity, family conflict, low drug concentration, nonadherence, anhedonia, sleep difficulties, subsyndromal manic symptoms, and child maltreatment have all been related to treatment resistance. Approximately 50% of depressed youth failing to respond to the 1st SSRI respond after switching to a 2nd antidepressant plus CBT, vs approximately 40% who respond to a 2nd medication alone. For youth with psychotic depression, augmenting the antidepressant with an atypical antipsychotic medication should be considered, while monitoring closely for side effects.

Before initiating antidepressant medication, baseline symptom severity should be assessed using a standardized rating scale (see Table 39.4). The initial dose of fluoxetine for moderate to severe major depressive disorder generally would be 10 mg for children age 6-12 yr and 20 mg for adolescents age ≥13. Clinical response, tolerability, and emergence of behavioral activation, mania, or suicidal thoughts should be assessed weekly (per FDA recommendation) for the 1st 4 wk. If the youth has safely tolerated the antidepressant, the baseline standardized symptom rating scale should be readministered to assess response to treatment. Because the findings from a recent meta-analysis suggest that treatment gains in response to SSRI medications are greatest early in treatment and minimal after 4 wk, if substantial improvement in the rating scale score has not occurred at 4 wk despite confirmation of adherence to the medication regimen, consultation from a child and adolescent psychiatrist should be considered.

Because of the high rate of recurrence, successful treatment should continue for 6-12 mo. The findings from one RCT suggested that the addition of relapse-prevention CBT to ongoing medication management reduces the risk of relapse more than medication management alone, even after the end of treatment. When treatment concludes, all antidepressants (except possibly fluoxetine because of long half-life) should be discontinued gradually to avoid withdrawal symptoms (gastrointestinal upset, disequilibrium, sleep disruption, flulike symptoms, sensory disturbances). Patients with recurrent (≥2 episodes), chronic, or severe major depression may require treatment beyond 12 mo.

To date, there are no rigorous studies evaluating the effectiveness of pharmacologic or psychosocial treatment approaches to persistent depressive disorder or DMDD. The aforementioned treatments for MDD may prove helpful in persistent depressive disorder. In suspected cases of DMDD, child and adolescent psychiatry consultation may be helpful to clarify diagnosis and suggest treatment approaches.

Level of Care

Most children and adolescents with mild to moderate depressive disorders can be safely and effectively treated as outpatients, provided that a clinically appropriate schedule of visits can be maintained through the phases of treatment. Inpatient treatment should be considered for youth who present with a high risk of suicide, serious self-harm, or self-neglect, or when the family is not able to provide an appropriate level of supervision or follow-up with outpatient treatment recommendations, or when comprehensive assessment for diagnostic clarity is needed. When considering inpatient admission for a young person with depression, the benefits of inpatient treatment needs to be balanced against potential detrimental effects, such as the loss of family and community support.

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39.2

Bipolar and Related Disorders

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Description

The bipolar and related disorders include bipolar I, bipolar II, cyclothymic, and other specified/unspecified bipolar and related disorders, as well as bipolar and related disorder caused by another medical condition.

A **manic episode** is characterized by a distinct period of at least 1 wk in which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy that is present for most of the day, nearly every day (or any duration if hospitalization is necessary). The episode is associated with characteristic cognitive and behavioral symptoms, including disturbances in self-regard, speech, attention, thought, activity, impulsivity, and sleep (Table 39.5). To diagnose **bipolar I disorder** , criteria must be met for at least 1 manic episode, and the episode must not be better explained by a psychotic disorder. The manic episode may have been preceded and may be followed by hypomanic or major depressive episodes. Bipolar I disorder is rated as mild, moderate, or severe in the same way as the depressive disorders (see Description section of Chapter 39.1).

Table 39.5

DSM-5 Diagnostic Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hr of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A-D constitute a manic episode. At least 1 lifetime manic episode is required for the diagnosis of bipolar I disorder.

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To diagnose **bipolar II disorder** , criteria must be met for at least 1 hypomanic episode and at least 1 major depressive episode. A **hypomanic episode** is similar to a manic episode but is briefer (at least 4 days) and less severe (causes less impairment in functioning, is not associated with psychosis, and would not require hospitalization) (Table 39.6). In bipolar II disorder, there must never have been a manic disorder, the episodes must not be better explained by a psychotic disorder, and the symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania must cause clinically significant distress or functional impairment. Bipolar II disorder is also rated as mild, moderate, or severe.

Table 39.6

DSM-5 Diagnostic Criteria for a Hypomanic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:

   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hr of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The disturbance is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that 1 or 2 symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note: Criteria A-F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, p 124.

Cyclothymic disorder is characterized by a period of at least 1 yr (in children and adolescents) in which there are numerous periods with hypomanic and depressive symptoms that do not meet criteria for a hypomanic episode or a major depressive episode, respectively.

Other specified/unspecified bipolar and related disorders (**subsyndromal bipolar disorder**) applies to presentations in which symptoms characteristic of a bipolar and related disorder are present and cause distress or functional impairment, but do not meet the full criteria for any of the disorders in this diagnostic class. Although this diagnosis (formerly known as “bipolar disorder, not otherwise specified”) had frequently been applied to children with severe and chronic mood and behavioral dysregulation who did not precisely fit other diagnostic categories, the empirical support for the validity of this practice has been sparse. Children who formerly received this diagnosis may meet criteria for DMDD (see Chapter 39.1).

In adolescents, the clinical manifestations of mania are similar to those in adults, and **psychosis** (delusions, hallucinations) often is an associated symptom. Mood in a manic episode is often described as euphoric, excessively cheerful, high, or “feeling on top of the world.” During the episode, the adolescent may engage in multiple new projects that are initiated with little knowledge of the topic and often at unusual hours (middle of the night). Inflated self-esteem is usually present, ranging from uncritical self-confidence to marked grandiosity, and may reach delusional proportions. The adolescent may sleep little if at all for days and still feel rested and full of energy. Speech can be rapid, pressured, and loud and characterized by jokes, puns, amusing irrelevancies, and theatricality. Frequently there is a “flight of ideas,” evidenced by an almost continuous flow of accelerated speech, with abrupt shifts from one topic to another. Distractibility is evidenced by an inability to censor irrelevant extraneous stimuli, which often prevents an individual with mania from engaging in a rational conversation. The expansive mood, grandiosity, and poor judgment often lead to reckless involvement in activities with high potential for personal harm.

Controversy surrounds the applicability of the diagnostic criteria for mania to *prepubertal* children. It may be developmentally normal for children to be elated, expansive, grandiose, or talkative, reducing the specificity of these symptoms to this disorder. In addition, the distractibility, overactivity, impulsivity, and irritability formerly ascribed to bipolar disorder by some investigators may be better explained by a diagnosis of ADHD, with or without comorbid ODD. The presentation of severe and pervasive irritability formerly diagnosed as “bipolar disorder” may be better captured by the diagnosis of DMDD.

Epidemiology

The lifetime prevalence of bipolar disorder I among adults worldwide is approximately 0.6% for bipolar I disorder, 0.4% for bipolar II disorder, and 1.4% for subsyndromal bipolar disorder. Bipolar I disorder affects men and women equally, whereas bipolar II disorder is more common in women. Lifetime rates of mania among youth have ranged from 0.1% to 1.7%. Since the 1990s, there has been a significant increase in the diagnosis of bipolar disorder in the United States that was not mirrored in the United Kingdom. The estimated annual number of U.S. office-based visits of youth with a diagnosis of bipolar disorder increased from 25 per 100,000 population in 1994–1995 to 1,003/100,000 in 2002–2003. U.S. hospital discharge diagnoses increased from 1.4 to 7.3/10,000 in 9-13 yr old children and from 5.1 to 20.4/10,000 in 14-19 yr olds. These increases were not found in U.K. hospital discharges, questioning whether bipolar disorder was being overdiagnosed in the United States, with resultant increases in prescribing of antipsychotic and mood-stabilizing medications.

Clinical Course

The mean age of onset of the 1st manic episode is approximately 18 yr for bipolar I disorder. Premorbid problems are common in bipolar disorder, especially temperamental difficulties with mood and behavioral regulation. Premorbid anxiety also is common. The early course of adolescent-onset bipolar I disorder appears to be more chronic and refractory to treatment than adult-onset bipolar disorder. Comorbidity predicts functional impairment, and age at onset predicts duration of episodes. Sleep impairment and family conflict are inversely related to favorable treatment response, suggesting important targets for treatment. The bipolar disorders are highly recurrent, and 70–80% of bipolar I patients will have additional mood episodes. Recurrent episodes can approximate 4 in 10 years, with the interepisode interval shortening as the patient ages. Although the majority of patients with bipolar I return to a fully functional level between episodes, approximately one-third continue to be symptomatic and functionally impaired between episodes.

The initial presentation of bipolar I disorder is often an MDD. Switching from a depressive episode to a manic episode by adulthood may occur in 10–20% of youth, both spontaneously and during depression treatment. Factors that predict the eventual development of mania in depressed youth include a depressive episode characterized by rapid onset, psychomotor retardation, and psychotic features; a family history of affective disorders, especially bipolar disorder; and a history of mania or hypomania after antidepressant therapy.

The mean age of onset of bipolar II disorder is 20 yr. The illness most often begins with a depressive episode and is not recognized as bipolar II disorder until a hypomanic episode occurs, in about 12% of individuals with the initial diagnosis of major depression. Many individuals experience several episodes of major depression before experiencing the first recognized hypomanic episode. Anxiety, substance misuse, or eating disorders may also precede the onset of bipolar II, complicating its detection. About 5–15% of individuals with bipolar II disorder will ultimately develop a manic episode, which changes the diagnosis to bipolar I disorder.

Depression in bipolar I or II usually has an earlier age of onset, more frequent episodes of shorter duration, an abrupt onset and offset, is linked to comorbid substance misuse, and is triggered by stressors. Atypical symptoms such as hypersomnia, lability, and weight instability are also common in bipolar depression, reported in up to 90% of cases vs 50% in unipolar depression. Psychosis, psychomotor retardation, and catatonia are also more characteristic of bipolar depression, whereas somatic complaints are more frequent in unipolar depression. A family history of mania is also a relevant discriminating factor.

Provision of clinical services is poor for youth with bipolar disorder. In one healthcare system study spanning 2 yr follow-up after diagnosis, despite complex drug regimens, medication appointments were infrequent, averaging 1 visit every 2 mo. More than half of patients needed 1 or more hospitalizations, and almost half had psychiatric emergency department visits. In a national study, 38% of youths diagnosed with bipolar disorder had received no treatment at all.

Differential Diagnosis

Numerous psychiatric disorders, general medical conditions, and medications can generate manic-like symptoms and must be distinguished from the bipolar and related disorders. The psychiatric disorders include ADHD, ODD, and intermittent explosive, posttraumatic stress, depressive, anxiety, substance abuse, and borderline personality disorders. Medical conditions include neurologic disorders, endocrine disorders, infectious diseases, tumors, anemia, uremia, and vitamin deficiencies. Medications include androgens, bronchodilators, cardiovascular medications, corticosteroids, chemotherapy agents, thyroid preparations, and certain psychiatric medications (benzodiazepines, antidepressants, stimulants). The diagnosis of a bipolar disorder should be made after these other explanations for the observed symptoms have been ruled out.

For bipolar II disorder, the main differential is unipolar depression (MDD) or cyclothymic disorder.

Comorbidity

The most common simultaneous comorbidities (ADHD, ODD, conduct disorder, anxiety) may be difficult to distinguish from mania because of considerable symptom overlap. Substance use also is a common comorbidity in adolescents, and presentations that appear to be manic may remit when the substances of abuse are discontinued.

Sequelae

The lifetime risk of **suicide** in individuals with bipolar disorder is estimated to be at least 15 times that of the general population. Factors associated with suicide attempts include female gender, young age at illness onset, depressive polarity of first illness episode or of current or most recent episode, comorbid anxiety disorder, any comorbid substance use disorder, borderline personality disorder, and first-degree family history of suicide. By contrast, completed suicides are associated with male sex and a first-degree family history of suicide. Despite patients with bipolar disorder having normal or even superior cognition before diagnosis, bipolar disorder has been associated with decrements in executive function and verbal memory. Youths with bipolar disorder are also at high risk for substance abuse, antisocial behavior, impaired academic performance, impaired family and peer relationships, and poor adjustment to life stressors.

Etiology and Risk Factors

Twin studies of adults suggest the heritability of bipolar disorder may be 60–90%, while shared and unique environmental factors may account for 30–40% and 10–20%, respectively. Offspring of parents with bipolar disorders are at high risk for early-onset bipolar disorders as well as anxiety and behavioral disorders and mood dysregulation. There is an average 10-fold increased risk among adult relatives of individuals with bipolar disorder, with the magnitude of risk increasing with the degree of kinship. Bipolar disorder and schizophrenia likely share a genetic origin, reflected in familial co-aggregation of the two disorders.

Studies to date suggest key roles for the amygdala, anterior paralimbic cortices, and their connections in the emotional dysregulation of bipolar disorder. Some of these abnormalities are apparent by adolescence, whereas others appear to progress over adolescence into young adulthood.

Dysthymic (sad), *cyclothymic* (labile), or *hyperthymic* (irritable) temperaments may presage eventual bipolar disorder. Premorbid anxiety and dysphoria also are common. Environmental factors such as irritable and negative parenting styles, physical and sexual abuse, poor social support, and prenatal alcohol exposure may interact with genetic vulnerability to produce early onset of bipolar illness as well as negative prognostic indicators. *Affective lability* in particular has been associated with high levels of childhood trauma, and gradual sensitization to stressors has been linked to episode recurrence.

Prevention

Although empirical support is sparse, one study demonstrated the effectiveness of family-focused treatment vs an educational control in hastening and sustaining recovery from mood symptoms in a high-familial-risk cohort of youths with subsyndromal symptoms of mania. Family-focused treatment is a manualized psychoeducational intervention designed to reduce family stress, conflict, and affective arousal by enhancing communication and problem solving between youths and their caregivers. Pharmacologic interventions for subsyndromal mania have produced equivocal results.

Case Finding

Cardinal manic symptoms of elation, increased energy, and grandiosity occurring in adolescents as a discrete episode representing an unequivocal and uncharacteristic change in functioning should alert pediatric practitioners to the possibility of bipolar disorder. High scores on parent-completed versions of mania-specific rating scales (e.g., *General Behavior Inventory, Child Mania Rating Scale*, *Young Mania Rating Scale*) have been associated with increased likelihood of a bipolar diagnosis. However, in general, screening tools for bipolar disorder have suboptimal psychometric properties when applied to young people. Because of the complexity of diagnosing and treating bipolar disorders, any suspected cases should be referred to the specialty mental health setting for comprehensive assessment and treatment.

Treatment

For mania in bipolar I disorder, medication is the primary treatment. Studies have demonstrated the superiority of **antipsychotics** over mood stabilizers in the treatment of mania, with haloperidol, risperidone, and olanzapine ranked as the most efficacious agents and quetiapine, risperidone, and olanzapine ranked as the most tolerable agents. Taken together, risperidone and olanzapine may have the best overall efficacy and tolerability. Asenapine has also been found to be effective and well tolerated. The FDA has approved aripiprazole, risperidone, quetiapine, and asenapine for the treatment of bipolar disorder from age 10 yr, and olanzapine from age 13 years. The choice of antipsychotic medication is based on factors such as side effect profiles, comorbidities, adherence, and positive response of a family member.

Among traditional **mood stabilizer** s, only lithium is FDA approved for the treatment of bipolar disorder from age 12 yr, and its efficacy and tolerability compared to placebo has been demonstrated in RCTs. There also is meta-analytic evidence that lithium reduces the risk of suicide and total deaths in patients with both unipolar and bipolar depressive disorder.

No published RCT evidence supports the efficacy of other mood stabilizers (e.g., divalproex sodium, topiramate, carbamazepine, oxcarbazepine, lamotrigine) in the treatment of youth with bipolar disorder, and retrospective cohort studies suggest that those who receive antipsychotics are less likely to discontinue treatment and less likely to receive treatment augmentation than youth who receive mood stabilizers. None of the mood-stabilizing medications (other than lithium) have FDA approval for the treatment of bipolar disorder in youth, and as such, likely should not be first-line treatments.

Medication trials should be systematic and their duration sufficient (generally 6-8 wk) to determine the agent's effectiveness. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Because these medications are associated with significant side effects, careful monitoring of baseline and follow-up indices is imperative.

The regimen needed to stabilize acute mania should be maintained for 12-24 mo. Maintenance therapy is often needed for adolescents with bipolar I disorder, and some patients need lifelong medication. Any attempts to discontinue prophylactic medication should be done gradually while closely monitoring the patient for relapse.

Antidepressants *alone* should not be prescribed for depressive symptoms in bipolar I disorder because of the risk of manic switch. However, in an RCT, olanzapine/fluoxetine combination was superior to placebo in youth with depression in bipolar I and has been FDA approved for this indication in patients age 10-17 yr. For treatment of depression in bipolar II, antidepressant medication (preferably SSRIs or bupropion) may be used cautiously. Comorbid ADHD can be treated with a stimulant once a mood-stabilizer has been initiated.

Psychotherapy is a potentially important adjunctive treatment for the bipolar disorders. Therapies with some evidence of efficacy, primarily as adjunctive to pharmacotherapy, include multifamily psychoeducational psychotherapy and family-focused treatment (probably efficacious), child and family-focused CBT (possibly efficacious), dialectical behavioral therapy, and interpersonal and social rhythm therapy (experimental). Active components of these therapies include family involvement and psychoeducation, along with self-regulation, cognitive restructuring, communication, problem-solving, and emotion regulation skills. Factors that adversely influence response to therapy include high-conflict families and sleep impairment, suggesting the importance of targeting these factors in treatment.

Level of Care

Most youths with bipolar disorders can be safely and effectively treated as outpatients, provided that an appropriate schedule of visits and laboratory monitoring can be maintained through the course of treatment. Youths who are suicidal or psychotic typically require inpatient care.

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CHAPTER 40

Suicide and Attempted Suicide

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Youth suicide is a major public health problem. In 2014 for all youth between ages 10 and 19 yr in the United States, suicide was the 2nd leading cause of death, with approximately 5,500 lives lost each year. The suicide rate for youth age 15-19 yr was 9.8 per 100,000 persons (14.2 for males, 5.1 for females), while the rate for youth age 10-14 yr was 2.0/100,000 (2.4 for males, 1.6 for females). There are numerous psychiatric, social, cultural, and environmental risk factors for suicidal behavior, and knowledge of these risk factors can facilitate identification of youths at highest risk (Fig. 40.1).

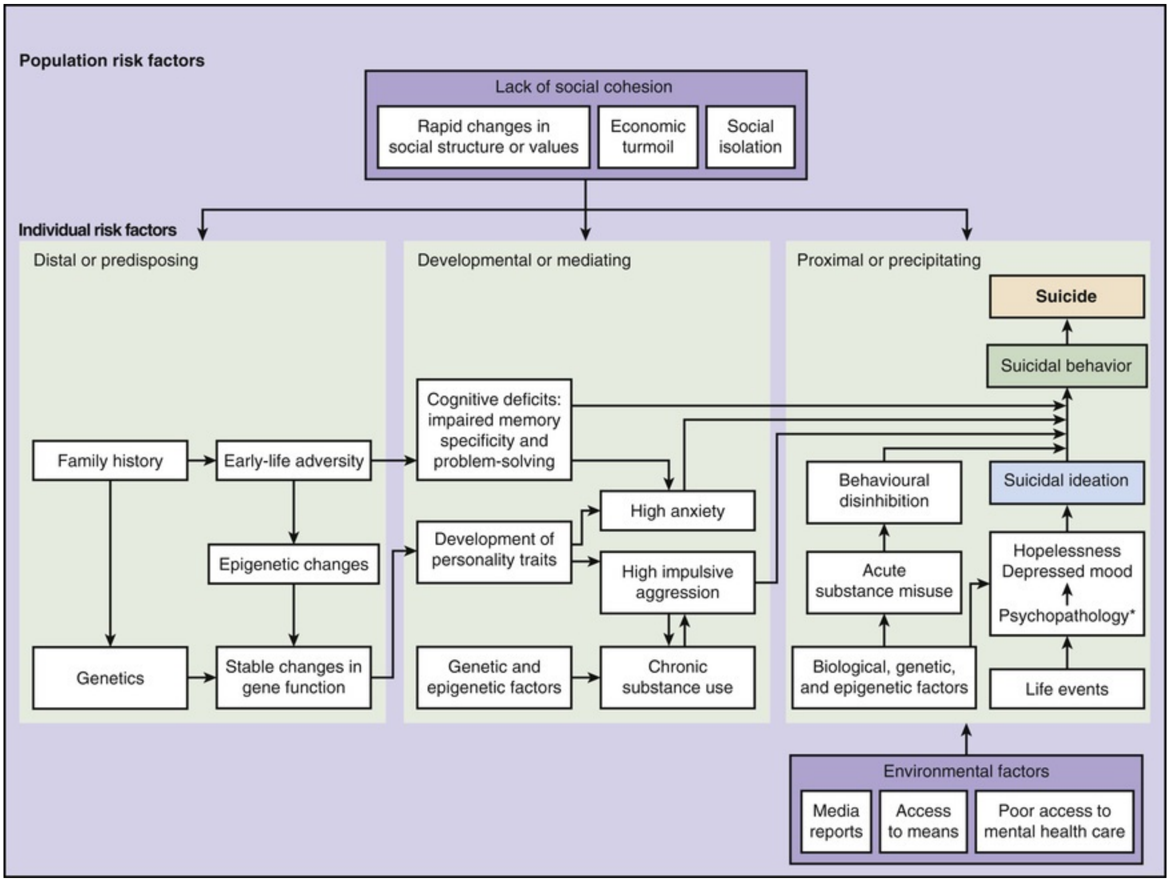
Population risk factors
Lack of social cohesion
Rapid changes in social structure or values
Economic turmoil
Social isolation
Individual risk factors
Distal or predisposing
Developmental or mediating
Proximal or precipitating
Suicide
Suicidal behavior
Cognitive deficits: impaired memory specificity and problem-solving
Family history
Early-life adversity
Behavioural disinhibition
Suicidal ideation
High anxiety
Development of personality traits
Epigenetic changes
High impulsive aggression
Acute substance misuse
Hopelessness
Depressed mood
Psychopathology*
Genetics
Stable changes in gene function
Genetic and epigenetic factors
Chronic substance use
Biological, genetic, and epigenetic factors
Life events
Environmental factors
Media reports
Access to means
Poor access to mental health care

FIG. 40.1 **Model for suicide risk. Suicide risk is modulated by a range of factors at both the population and the individual levels. Individual risk factors can be grouped into *distal* (or predisposing), *developmental* (or mediating), and *proximal* (or precipitating) factors, and many of these factors interact to contribute to the risk of developing suicidal behaviors. *Any single mental illness associated with suicide risk, or a combination of mental illnesses, including major depressive disorder, bipolar disorder, schizophrenia, and personality disorders; the presence of a depressive episode is often a sign of increased risk of suicide. (From Turecki D, Brent DA: Suicide and suicidal behaviours. Lancet 387:1227–1238, 2016.)**

Epidemiology

Suicidal Ideation and Attempts

Based on the 2015 Youth Risk Behavior Survey, almost one third of 9th through 12th grade students in the United States felt so sad or hopeless almost every day for ≥2 wk in a row during the previous year that they stopped doing usual activities. During that same period, 18% of the students reported that they had seriously considered attempting suicide, and 9% reported that they had actually attempted suicide one or more times. A suicide attempt in the previous year that resulted in an injury, poisoning, or overdose that had to be treated by a physician or nurse was reported by 3% of students.

It is estimated that for every completed youth suicide, as many as 200 suicide attempts are made. Poisoning, suffocation, and firearms are the most common causes of suicide, whereas ingestion of medication is the most common method of *attempted* suicide (Fig. 40.2). The 15-19 yr old age-group is the most likely to intentionally harm themselves by ingestion, receive treatment in the emergency department (ED), and survive. Attempts are more common in adolescent females than males (approximately 3 : 1-4 : 1) and in Hispanic females than their non-Hispanic counterparts. Gay, lesbian, bisexual, transgender, and bullied youths also have disproportionately high rates of suicide attempts. Attempters who have made prior suicide attempts, who used a method other than ingestion, who have a plan (nonimpulsive), who have no regret, and who still want to die are at increased risk for completed suicide.

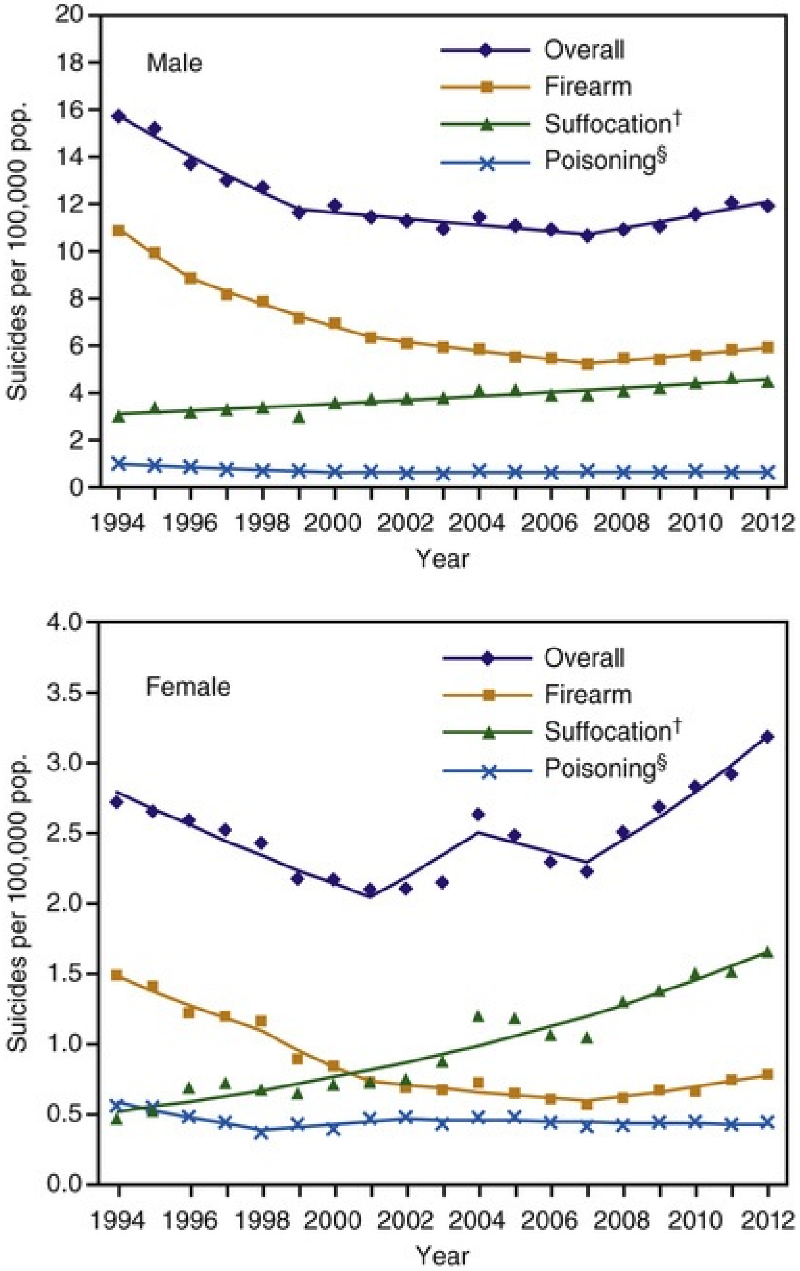

* Symbols (diamond, square, triangle, x) representing joinpoints are displayed on the line graphs because, for both males and females, some of the suicide rates were best fitted by multiple segments of lines (number of joinpoints >0).

† Including hanging.

§ Including drug overdose.

FIG. 40.2 Age-adjusted suicide rates among persons aged 10-24 yr, by sex and mechanism—United States, 1994–2012; **top** , males; **bottom** , females. *Symbols* ,* See footnotes on figure. (From Sullivan EM, Annest JL, Simon TR, et al: Suicide trends among persons aged 10-24 years – United States, 1994-2012. MMWR 64(8):201-205, 2015. Fig, p. 203.)

Suicide Completions

In the United States, *completed* suicide is very rare before age 10. Rates of completed suicide increase steadily across adolescence into young adulthood, peaking in the early 20s. The male:female ratio for completed suicide rises with age from 3 : 1 in children to approximately 4 : 1 in 15-24 yr olds, and to >6 : 1 among 20-24 yr olds.

In 2015 among 10-19 yr olds, the highest suicide rates, 21.8 and 16.6 per 100,000, were among Native American males and females, respectively, followed by white males (10.6/100,000). The groups with the lowest rates were Asian/Pacific Islander females, Hispanic females, and black females (2.4, 2.3, and 1.9/100,000, respectively). **Firearms** are the most common method used to complete suicide in the United States, accounting for 50% of all suicide deaths in 2015 (Fig. 40.2). The next most prevalent methods are **suffocation** (27%) and **poisoning** (15%). Firearms are the most lethal method of suicide completion; the death rate with respect to firearms is approximately 80–90%, whereas the death rate is only 1.5–4% for overdoses. Among males, firearms are the most frequently used method of suicide (55%); among females, poisoning is the most common method (34%).

From 1999 through 2014, the age-adjusted suicide rate in the United States increased 24%, from 10.5 to 13.0/100,000, with the pace of increase greater after 2006. Rates increased for both males and females and for all ages 10-74; the percent increase among females was greatest for those age 10-14, and for males, those age 45-64.

Risk Factors

In addition to age, race/ethnicity, and a history of a previous suicide attempt, multiple risk factors predispose youths to suicide (see Fig. 40.1).

Preexisting Mental Disorder

Approximately 90% of youths who complete suicide have a preexisting psychiatric illness, most often major depression. Among females, chronic anxiety, especially panic disorder, also is associated with suicide attempts and completion. Among males, conduct disorder and substance use convey increased risk. Comorbidity of a substance use disorder, a depressive disorder, and conduct disorder are linked to suicide by firearm. Schizophrenia spectrum disorders are linked to suicide attempts and completions.

Cognitive Distortions

Negative self-attributions can contribute to the hopelessness typically associated with suicidality; hopelessness may contribute to approximately 55% of the explained variance in continued suicidal ideation. Many youth who are suicidal hold negative views of their own competence, have poor self-esteem, engage in catastrophic thinking, and have difficulty identifying sources of support or reasons to live. Many young people lack the coping strategies necessary to manage strong emotions and instead tend to *catastrophize* and engage in *all-or-nothing* thinking.

Biologic Factors

Postmortem studies show observable differences between the brains of individuals who have completed suicide and those who died from other causes. The brain systems that may be related to suicide completion are the serotonergic system, adrenergic system, and the hypothalamic-pituitary axis. Family history of mental disorders also is linked to completed suicide.

Social, Environmental, and Cultural Factors

Of youths who attempt suicide, 65% can name a precipitating event for their action. Most adolescent suicide attempts are precipitated by **stressful life events** (e.g., academic or social problems; being bullied; trouble with the law; questioning one's sexual orientation or gender identify; newly diagnosed medical condition; recent or anticipated loss).

Suicide attempts may also be precipitated by exposure to news of another person's suicide or by reading about or viewing a suicide portrayed in a romantic light in the media. Media coverage of suicide is linked to fluctuating incidence rates of suicides, particularly among adolescents. Glorification or sensationalization of suicide in the media has found to be associated with an increase in suicides. When media coverage includes a detailed description of specific means used, the use of that particular method may increase in the overall population.

For some immigrants, suicidal ideation can be associated with high levels of acculturative stress, especially in the context of family separation and limited access to supportive resources. Physical and sexual abuse can also increase one's risk of suicide, with 15–20% of female suicide attempters having had a history of abuse. The general association between family conflict and suicide attempts is strongest in children and early adolescents. Family psychopathology and a family history of suicidal behavior also convey excess risk. The lack of supportive social relations with peers, parents, and school personnel interacts in increasing the risk of suicide among youth.

Protective Factors

Protective factors can provide a counterbalance for those contemplating suicide. These may include a sense of family responsibility, life satisfaction, future orientation, social support, coping and problem-solving skills, religious faith, intact reality testing, and solid therapeutic relationships (e.g., pediatrician, teacher, therapist).

Assessment and Intervention

The U.S. Preventive Services Task Force has concluded that there is insufficient evidence to recommend universal suicide screening in the primary care setting for children and adolescents. Pediatric practitioners should consider suicide potential and the need for mental health assessment in the context of concerning information elicited in child/parent psychosocial histories (e.g., HEADSS Psychosocial Risk Assessment; see Chapter 32 , Table 32.2), general screening measure scores out of the normal range (e.g., Pediatric Symptom Checklist Internalizing Sub-Scale; see Chapter 28), or self-reported statements or behaviors from patients and parents.

All suicidal ideation and attempts should be taken seriously and require a thorough assessment by a child-trained mental health clinician to evaluate the youth's current state of mind, underlying psychiatric conditions, and ongoing risk of harm. **Emergency** mental health assessment is needed for immediate threat to self (i.e., suicidal intent and plan); **urgent** mental health assessment (48-72 hr) is needed for severe psychiatric symptoms, significant change in overall functioning, and suicidal ideation without intent or plan. **Routine** mental health assessment is appropriate for mild to moderate psychiatric symptoms without suicidal ideation.

Pediatric practitioners should expect the mental health clinician to evaluate the presence and degree of suicidality and underlying risk factors. The reliability and validity of child interviewing are affected by children's level of cognitive development as well as their understanding of the relationship between their emotions and behavior. Confirmation of the youth's suicidal behavior can be obtained from information gathered by interviewing others who know the child or adolescent. A discrepancy between patient and parent reports is not unusual, with both children and adolescents being more likely to disclose suicidal ideation and suicidal actions than their parents.

In the mental health assessment, **suicidal ideation** can be assessed by explicit questions posed in a nonjudgmental, noncondescending, matter-of-fact approach. The *Ask Suicide-Screening Questionnaire* (ASQ) is a validated 4-item measure shown in the ED setting to have high sensitivity and negative predictive value in identifying youth at risk for suicide ideation and behavior: (1) “In the past few weeks, have you felt that you or your family would be better off if you were dead?” (2) “In the past few weeks, have you wished you were dead?” (3) “In the past few weeks, have you been having thoughts about killing yourself?” and (4) “Have you ever tried to kill yourself?” If a “yes” response is given to any of these 4 questions, the patient is asked, (5) “Are you having thoughts of killing yourself right now?” Another common screening test is the *Columbia Suicide Severity Rating Scale* (C-SSRS) *Screener* (Table 40.1).

Table 40.1

Columbia Suicide Severity Rating Scale Screener

1. Have you wished you were dead or wished you could go to sleep and not wake up?
2. Have you actually had any thoughts about killing yourself?
    If “Yes” to 2, answer questions 3, 4, 5, and 6.
    If “No” to 2, go directly to question 6.
3. Have you thought about how you might do this?
4. Have you had any intention of acting on these thoughts of killing yourself, as opposed to you having the thoughts but you definitely would not act on them?
5. Have you started to work out or worked out the details of how to kill

yourself? Do you intend to carry out this plan?
6. Have you done anything, started to do anything, or prepared to do anything to end your life?

Response Protocol to Screening (based on last item answered "Yes")

Item 1— Mental Health Referral at discharge
Item 2— Mental Health Referral at discharge
Item 3— Care Team Consultation (Psychiatric Nurse) and Patient Safety Monitor/Procedures
Item 4— Psychiatric Consultation and Patient Safety Monitor/Procedures
Item 5— Psychiatric Consultation and Patient Safety Monitor/Procedures
Item 6— If over 3 months ago, Mental Health Referral at discharge
If 3 months ago or less, Psychiatric Consultation and Patient Safety Monitor

From Posner K. Columbia Lighthouse Project. The Columbia-Suicide Severity Rating Scale (C-SSRS) Screener–Recent. http://www.cssrs.columbia.edu/scales_practice_cssrs.html .

The assessment of a suicidal attempt should include a detailed exploration of the hours immediately preceding the attempt to identify precipitants as well as the circumstances of the attempt itself, to understand fully the patient's intent and potential lethality. The calculation of the level of suicide concern is complex, requiring a determination across a spectrum of risk. At the low end of the risk spectrum are youth with thoughts of death or wanting to die, but without suicidal thoughts, intent, or plan. Those with highly specific suicide plans, preparatory acts or suicide rehearsals, and clearly articulated intent are at the high end. A suicidal history, presently impaired judgment (as seen in altered mental states including depression, mania, anxiety, intoxication, substance abuse, psychosis, trauma-reactive, hopelessness, rage, humiliation, impulsivity), as well as poor social support, further exacerbates the heightened risk. Among adolescents who consider self-harm, those who carry out (**enactors**) self-injury are more likely to have family or friends (or think that their peers) engaged in self-harm, and are more impulsive than those who only have thoughts of self-harm (**ideators**).

For youth who are an imminent danger to themselves (i.e, have *active* ["I want to die”] or *implied* [“I can't see any reason to go on living”] suicidal intent), inpatient level of psychiatric care is necessary to ensure safety, clarify diagnoses, and comprehensively plan treatment. These patients can be hospitalized voluntarily or involuntarily. It is helpful for the pediatric practitioner to have an office protocol to follow in these situations. This protocol should take into consideration state laws regarding involuntary hospitalization, transportation options, nearest emergency assessment site, necessary forms for hospitalization, and available emergency mental health consultants.

For those youth suitable for treatment in the outpatient setting (e.g., suicidal ideation without intent, intact mental status, few or no other risk factors for suicidality, willing and able to participate in outpatient treatment; has caregivers able to provide emotional support, supervision, safeguarding, and adherence to follow-up), an appointment should be scheduled within a few days with a mental health clinician. Ideally, this appointment should be scheduled before leaving the assessment venue, because almost 50% of those who attempt suicide fail to follow through with the mental health referral. A procedure should be in place to contact the family if the family fails to complete the referral.

Through follow-up office visits, pediatric practitioners can help support and facilitate the implementation of psychotherapies (e.g., cognitive-behavioral therapy, dialectical behavioral therapy, mentalization-based treatment, family therapy) that target the specific psychiatric disorders and the emotional dysphoria or behavioral dysregulation that accompany suicidal ideation or behavior. In conjunction with a child and adolescent child psychiatrist, psychotropic medications may be used as indicated to treat underlying psychiatric disorders. Pediatric practitioners also can encourage social connectedness to peers and to community organizations (e.g., school or church), as well as promote help-seeking (e.g., talking to a trusted adult when distressed) and wellness (e.g., sleep, exercise, relaxation, nutrition) behaviors. In the event of a completed suicide, pediatricians can offer support to the family, particularly by monitoring for adverse bereavement responses in siblings and parents.

Prevention

The aforementioned risk factors associated with suicide are relatively common and individually not strong predictors of suicide. The assessment is complicated by patients who may attempt to conceal their suicide thoughts and by those who express suicidal thoughts without serious intent. Suicide screening has been challenging because most screening instruments have variable sensitivity and specificity. In addition, the burden of follow-up mental health evaluations for those who screen positive has been daunting. Although primary care–feasible screening tools may be help to identify some adults at increased risk for suicide, they have, to date, demonstrated limited ability to detect suicide risk in adolescents.

Prevention strategies in the **pediatric medical home** include training staff to recognize and respond to the *warning signs* of suicide (Table 40.2), screening for and treating depression, educating patients/parents about warning signs for suicide, and restricting access to modes of lethal self-harm. Young people have increased rates of suicide attempts and completions if they live in homes where firearms are present and available. When recommended by their primary care providers, most parents restrict access of their children to guns and medications. Pediatric practitioners should consider counseling parents to remove firearms from the home entirely or securely lock guns and ammunition in separate locations. Anecdotal evidence suggests youths frequently know where guns and keys to gun cabinets are kept, even though parents may think they do not. The same recommendation applies to restricting access to potentially lethal prescription and nonprescription medications (e.g., containers of >25 acetaminophen tablets) and alcohol. These approaches emphasize the importance of restriction of access to means for suicide to prevent self-harm.

Table 40.2

Warning Signs of Suicide

Seek help as soon as possible by contacting a mental health professional or by calling the National Suicide Prevention Lifeline at **1-800-273-TALK** if you or someone you know exhibits any of the following signs:

- Threatening to hurt or kill oneself or talking about wanting to hurt or kill oneself.
- Looking for ways to kill oneself by seeking access to firearms, available pills, or other means.
- Talking or writing about death, dying, or suicide when these actions are out of the ordinary for the person.
- Feeling hopeless.
- Feeling rage or uncontrolled anger or seeking revenge.

- Acting reckless or engaging in risky activities, seemingly without thinking.
- Feeling trapped, “like there's no way out.”
- Increasing alcohol or drug use.
- Withdrawing from friends, family, and society.
- Feeling anxious, agitated, or unable to sleep, or sleeping all the time.
- Experiencing dramatic mood changes.
- Seeing no reason for living, or having no sense of purpose in life.

Developed by the US Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA). https://www.nimh.nih.gov/health/topics/suicide-prevention/suicide-prevention-studies/warning-signs-of-suicide.shtml .

Screening for suicide in **schools** is also fraught with problems related to low specificity of the screening instrument and paucity of referral sites, as well as poor acceptability among school administrators. **Gatekeeper** (e.g., student support personnel) **training** appears effective in improving skills among school personnel and is highly acceptable to administrators but has not been shown to prevent suicide. School curricula (e.g., *Signs of Suicide*) have shown some preventive potential by teaching students to recognize the signs of depression and suicide in themselves and others and providing them with specific action steps necessary for responding to these signs. Peer helpers have not generally been shown to be efficacious.

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CHAPTER 41

Eating Disorders

Richard E. Kreipe, Taylor B. Starr

Eating disorders (EDs) are characterized by body dissatisfaction related to overvaluation of a thin body ideal, associated with dysfunctional patterns of cognition and weight control behaviors that result in significant biologic, psychological, and social complications. Although usually affecting white, adolescent females, EDs also affect males and cross all racial, ethnic, and cultural boundaries. Early intervention in EDs improves outcome.

Definitions

Anorexia nervosa (AN) involves significant overestimation of body size and shape, with a relentless pursuit of thinness that, in the **restrictive** subtype, typically combines excessive dieting and compulsive exercising. In the **binge-purge** subtype, patients might intermittently overeat and then attempt to rid themselves of calories by vomiting or taking laxatives, still with a strong drive for thinness (Table 41.1).

Table 41.1

DSM-5 Diagnostic Criteria for Anorexia Nervosa

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.

B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.

C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Specify whether:

Restricting type (ICD-10-CM code F50.01): During the last 3 mo, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

Binge-eating/purging type (ICD-10-CM code F50.02): During the last 3 mo, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Specify if:

In partial remission : After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.

In full remission : After full criteria for anorexia nervosa were previously met, none of the criteria has been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based, for adults, on current body mass index (BMI) (see below) or, for children and adolescents, on BMI percentile. **The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used.** The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

Mild : BMI ≥ 17 kg/m^2
Moderate : BMI 16-16.99 kg/m^2
Severe : BMI 15-15.99 kg/m^2
Extreme : BMI < 15 kg/m^2

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 338–339.

Bulimia nervosa (BN) is characterized by episodes of eating large amounts of food in a brief period, followed by compensatory vomiting, laxative use, exercise, or fasting to rid the body of the effects of overeating in an effort to avoid obesity (Table 41.2).

Table 41.2

DSM-5 Diagnostic Criteria for Bulimia Nervosa

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
    1. Eating, in a discrete period of time (e.g., within any 2 hr period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
    2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.

C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo.

D. Self-evaluation is unduly influenced by body shape and weight.

E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specify if:

In partial remission : After full criteria for bulimia nervosa were previously met, some, but not all, of the criteria have been met for a sustained period of time.

In full remission : After full criteria for bulimia nervosa were previously met, none of the criteria has been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based on the frequency of inappropriate compensatory behaviors (see below). The level of severity may be increased to reflect other symptoms and the degree of functional disability.

Mild : An average of 1-3 episodes of inappropriate compensatory behaviors per week.

Moderate : An average of 4-7 episodes of inappropriate compensatory behaviors per week.

Severe : An average of 8-13 episodes of inappropriate compensatory behaviors per week.

Extreme : An average of 14 or more episodes of inappropriate compensatory behaviors per week.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 345.

Children and adolescents with EDs may not fulfill criteria for AN or BN in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and may fall into a subcategory of **atypical anorexia nervosa,** or a more appropriately defined category of **avoidant/ restrictive food intake disorder (ARFID).** In these conditions, food intake is restricted or avoided because of adverse feeding or eating experiences or the sensory qualities of food, resulting in significant unintended weight loss or nutritional deficiencies and problems with social interactions (Table 41.3).

Table 41.3

DSM-5 Diagnostic Criteria for Avoidant/Restrictive Food Intake Disorder

A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:
   1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children).
   2. Significant nutritional deficiency.
   3. Dependence on enteral feeding or oral nutritional supplements.
   4. Marked interference with psychosocial functioning.

B. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.

C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.

D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

Specify if:

In remission : After full criteria for avoidant/restrictive food intake disorder were previously met, the criteria have not been met for a sustained period of time.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, p 334.

Binge eating disorder (BED) , in which binge eating is not followed regularly by any compensatory behaviors (vomiting, laxatives), is a stand-alone category in DSM-5 but shares many features with obesity (see Chapter 60). **Eating disorder–not otherwise specified (ED-NOS)** , often called “disordered eating,” can worsen into full syndrome EDs.

Epidemiology

The classic presentation of AN is an early to middle adolescent female of above-average intelligence and socioeconomic status who is a conflict-avoidant, risk-aversive perfectionist and is struggling with disturbances of anxiety and/or mood. BN tends to emerge in later adolescence, sometimes evolving from AN, and is typified by impulsivity and features of borderline personality disorder associated with depression and mood swings. The 0.5–1% and 3–5% incidence rates among younger and older adolescent females for AN and BN, respectively, probably reflect ascertainment bias in sampling and underdiagnosis in cases not fitting the common profile. The same may be true of the significant gender disparity, in which female patients account for approximately 85% of patients with diagnosed EDs. In some adolescent female populations, ≥10% have ED-NOS.

No single factor causes the development of an ED; sociocultural studies indicate a complex interplay of culture, ethnicity, gender, peers, and family. The **gender** dimorphism is presumably related to females having a stronger relationship between body image and self-evaluation, as well as the influence of the Western culture's thin body ideal. Race and ethnicity appear to moderate the association between risk factors and disordered eating, with African American and Caribbean females reporting lower body dissatisfaction and less dieting than Hispanic and non-Hispanic white females. Because peer acceptance is central to healthy adolescent growth and development, especially in early adolescence, when AN tends to have its initial prevalence peak, the potential influence of peers on EDs is significant, as are the relationships among peers, body image, and eating. Teasing by peers or by family members (especially males) may be a contributing factor for overweight females.

Family influence in the development of EDs is even more complex because of the interplay of environmental and genetic factors; shared elements of the family environment and immutable genetic factors account for approximately equal amounts of the variance in disordered eating. There are associations between parents' and children's eating behaviors; dieting and physical activity levels suggest parental reinforcement of body-related societal messages. The influence of inherited genetic factors on the emergence of EDs during adolescence is also significant, but not directly. Rather, the risk for developing an ED appears to be mediated through a genetic predisposition to *anxiety* (see Chapter 38), *depression* (see Chapter 39), or *obsessive-compulsive traits* that may be modulated through the internal milieu of puberty. There is no evidence to support the outdated notion that parents or family dynamics cause an ED. Rather, the family dynamics may represent responses to having a family member with a potentially life-threatening condition. The supportive influence on recovery of parents as nurturing caregivers cannot be overestimated.

Pathology and Pathogenesis

The emergence of EDs coinciding with the processes of adolescence (e.g., puberty, identity, autonomy, cognition) indicates the central role of development. A history of sexual trauma is not significantly more common in EDs than in the population at large, but when present makes recovery more difficult and is more common in BN. EDs may be viewed as a final common pathway, with a number of *predisposing* factors that increase the risk of developing an ED, *precipitating* factors often related to developmental processes of adolescence triggering the emergence of the ED, and *perpetuating* factors that cause an ED to persist. EDs often begin with dieting but gradually progress to unhealthy habits that lessen the negative impact of associated psychosocial problems to which the affected person is vulnerable because of premorbid biologic and psychological characteristics, family interactions, and social climate. When persistent, the biologic effects of starvation and malnutrition (e.g., true loss of appetite, hypothermia, gastric atony, amenorrhea, sleep disturbance, fatigue, weakness, depression), combined with the psychological rewards of increased sense of mastery and reduced emotional reactivity, actually maintain and reward pathologic ED behaviors.

This positive reinforcement of behaviors and consequences, generally viewed by parents and others as negative, helps to explain why persons with an ED characteristically deny that a problem exists and resist treatment. Although noxious, purging can be reinforcing because of a reduction in anxiety triggered by overeating; purging also can result in short-term, but reinforcing, improvement in mood related to changes in neurotransmitters. In addition to an imbalance in neurotransmitters, most notably serotonin and dopamine, alterations in functional anatomy also support the concept of EDs as brain disorders. The cause-and-effect relationship in central nervous system (CNS) alterations in EDs is not clear, nor is their reversibility.

Clinical Manifestations

Except for ARFID, in which weight loss is *unintentional,* a central feature of EDs is the overestimation of body size, shape, or parts (e.g., abdomen, thighs) leading to intentional weight control practices to reduce weight (AN) or prevent weight gain (BN). Associated practices include severe restriction of caloric intake and behaviors intended to reduce the effect of calories ingested, such as compulsive exercising or purging by inducing vomiting or taking laxatives. Eating and weight loss habits commonly found in EDs can result in a wide range of energy intake and output, the balance of which leads to a wide range in weight, from extreme loss of weight in AN to fluctuation around a normal to moderately high weight in BN. Reported eating and weight control habits thus inform the initial primary care approach (Table 41.4).

Table 41.4

Eating and Weight Control Habits Commonly Found in Children and Adolescents With an Eating Disorder (ED)

HABIT	**PROMINENT FEATURE**		**CLINICAL COMMENTS REGARDING ED HABITS**	
	Anorexia Nervosa	**Bulimia Nervosa**	**Anorexia Nervosa**	**Bulimia Nervosa**
Overall intake	Inadequate energy (calories), although volume of food and beverages may be high because of very low caloric density of intake as a result of "diet" and nonfat choices	Variable, but calories normal to high; intake in binges is often "forbidden" food or drink that differs from intake at meals	Consistent inadequate caloric intake leading to wasting of the body is an essential feature of diagnosis	Inconsistent balance of intake, exercise and vomiting, but severe caloric restriction is short-lived
Food	Counts and limits calories, especially from fat; emphasis on "healthy food choices" with reduced caloric density Monotonous, limited "good" food choices, often leading to vegetarian or vegan diet Strong feelings of guilt after eating more than planned	Aware of calories and fat, but less regimented in avoidance than AN Frequent dieting interspersed with overeating, often triggered by depression, isolation, or anger	Obsessive-compulsive attention to nutritional data on food labels and may have "logical" reasons for food choices in highly regimented pattern, such as sports participation or family history of lipid disorder	Choices less structured, with more frequent diets

	leads to exercise and renewed dieting			
Beverages	Water or other low- or no-calorie drinks; nonfat milk	Variable, diet soda common; may drink alcohol to excess	Fluids often restricted to avoid weight gain	Fluids ingested to aid vomiting or replace losses
Meals	Consistent schedule and structure to meal plan Reduced or eliminated caloric content, often starting with breakfast, then lunch, then dinner Volume can increase with fresh fruits, vegetables, and salads as primary food sources	Meals less regimented and planned than in AN; more likely impulsive and unregulated, often eliminated following a binge-purge episode	Rigid adherence to “rules” governing eating leads to sense of control, confidence, and mastery	Elimination of a meal following a binge-purge only reinforces the drive for binge later in the day
Snacks	Reduced or eliminated from meal plan	Often avoided in meal plans, but then impulsively eaten	Snack foods removed early because “unhealthy”	Snack “comfort foods” can trigger a binge
Dieting	Initial habit that becomes progressively restrictive, although often appearing superficially “healthy” Beliefs and “rules” about the patient's idiosyncratic nutritional requirements and response to foods are strongly held	Initial dieting gives way to chaotic eating, often interpreted by the patient as evidence of being “weak” or “lazy”	Distinguishing between healthy meal planning with reduced calories and dieting in ED may be difficult	Dieting tends to be impulsive and short-lived, with “diets” often resulting in unintended weight gain
Binge eating	None in restrictive subtype, but an essential feature in binge-purge subtype	Essential feature, often secretive Shame and guilt prominent afterward	Often “subjective” (more than planned but not large)	Relieves emotional distress, may be planned
Exercise	Characteristically obsessive-compulsive, ritualistic, and progressive May excel in dance, long-distance running	Less predictable May be athletic, or may avoid exercise entirely	May be difficult to distinguish active thin vs ED	Males often use exercise as means of “purging”
Vomiting	Characteristic of binge-purge subtype May chew, then spit out, rather than	Most common habit intended to reduce effects of	Physiologic and emotional instability prominent	Strongly “addictive” and self-punishing, but does not eliminate calories

	swallow, food as a variant	overeating Can occur after meal as well as a binge		ingested—many still absorbed
Laxatives	If used, generally to relieve constipation in restrictive subtype, but as a cathartic in binge-purge subtype	Second most common habit used to reduce or avoid weight gain, often used in increasing doses for cathartic effect	Physiologic and emotional instability prominent	Strongly “addictive,” self-punishing, but ineffective means to reduce weight (calories are absorbed in small intestine, but laxatives work in colon)
Diet pills	Very rare, if used; more common in binge-purge subtype	Used to either reduce appetite or increase metabolism	Use of diet pills implies inability to control eating	Control over eating may be sought by any means

AN, Anorexia nervosa; BN, bulimia nervosa.

Although weight control patterns guide the initial pediatric approach, an assessment of common symptoms and findings on physical examination is essential to identify targets for intervention. When reported symptoms of excessive weight loss (feeling tired and cold; lacking energy; orthostasis; difficulty concentrating) are explicitly linked by the clinician to their associated physical signs (hypothermia with acrocyanosis and slow capillary refill; loss of muscle mass; bradycardia with orthostasis), it becomes more difficult for the patient to deny that a problem exists. Furthermore, awareness that bothersome symptoms can be eliminated by healthier eating and activity patterns can increase a patient's motivation to engage in treatment. Tables 41.5 and 41.6 detail common symptoms and signs that should be addressed in a pediatric assessment of a suspected ED.

Table 41.5

Symptoms Commonly Reported by Patients With an Eating Disorder (ED)

SYMPTOMS	DIAGNOSIS		CLINICAL COMMENTS REGARDING ED SYMPTOMS
	Anorexia Nervosa	Bulimia Nervosa	
Body image	Feels fat, even with extreme emaciation, often with specific body distortions (e.g., stomach, thighs); strong drive for thinness, with self-efficacy closely tied to appraisal of body shape, size, and/or weight	Variable body image distortion and dissatisfaction, but drive for thinness is less than desire to avoid gaining weight	Challenging patient's body image is both ineffective and countertherapeutic clinically Accepting patient's expressed body image but noting its discrepancy with symptoms and signs reinforces concept

			that patient can “feel” fat but also “be” too thin and unhealthy
Metabolism	Hypometabolic symptoms include feeling cold, tired, and weak and lacking energy May be both bothersome and reinforcing	Variable, depending on balance of intake and output and hydration	Symptoms are evidence of body's “shutting down” in an attempt to conserve calories with an inadequate diet Emphasizing reversibility of symptoms with healthy eating and weight gain can motivate patients to cooperate with treatment
Skin	Dry skin, delayed healing, easy bruising, gooseflesh Orange-yellow skin on hands	No characteristic symptom; self-injurious behavior may be seen	Skin lacks good blood flow and ability to heal in low weight Carotenemia with large intake of β-carotene foods; reversible
Hair	Lanugo-type hair growth on face and upper body Slow growth and increased loss of scalp hair	No characteristic symptom	Body hair growth conserves energy Scalp hair loss can worsen during refeeding “telogen effluvium” (resting hair is replaced by growing hair) Reversible with continued healthy eating
Eyes	No characteristic symptom	Subconjunctival hemorrhage	Caused by increased intrathoracic pressure during vomiting
Teeth	No characteristic symptom	Erosion of dental enamel erosion Decay, fracture, and loss of teeth	Intraoral stomach acid resulting from vomiting etches dental enamel, exposing softer dental elements
Salivary glands	No characteristic symptom	Enlargement (no to mild tenderness)	Caused by chronic binge eating and induced vomiting, with parotid enlargement more prominent than submandibular; reversible
Heart	Dizziness, fainting in restrictive subtype Palpitations more common in binge-purge subtype	Dizziness, fainting, palpitations	Dizziness and fainting due to postural orthostatic tachycardia and dysregulation at hypothalamic and cardiac level with weight loss, as a result of hypovolemia with binge-purge Palpitations and arrhythmias often caused by electrolyte disturbance Symptoms reverse with weight gain and/or cessation of binge-purge
Abdomen	Early fullness and discomfort with eating	Discomfort after a binge	Weight loss is associated with reduced volume and

	Constipation Perceives contour as “fat,” often preferring well-defined abdominal musculature	Cramps and diarrhea with laxative abuse	tone of GI tract musculature, especially the stomach Laxatives may be used to relieve constipation or as a cathartic Symptom reduction with healthy eating can take weeks to occur
Extremities and musculoskeletal	Cold, blue hands and feet	No characteristic symptoms Self-cutting or burning on wrists or arms	Energy-conserving low body temperature with slow blood flow most notable peripherally Quickly reversed with healthy eating
Nervous system	No characteristic symptom	No characteristic symptom	Neurologic symptoms suggest diagnosis other than ED
Mental status	Depression, anxiety, obsessive-compulsive symptoms, alone or in combination	Depression; PTSD; borderline personality disorder traits	Underlying mood disturbances can worsen with dysfunctional weight control practices and can improve with healthy eating AN patients might report emotional “numbness” with starvation preferable to emotionality associated with healthy eating

AN, Anorexia nervosa; BN, bulimia nervosa; ED, eating disorder; GI, gastrointestinal; PTSD, posttraumatic stress disorder.

Table 41.6

Signs Commonly Found in Patients With Eating Disorder (ED) Relative to Prominent Feature of Weight Control

PHYSICAL SIGN	PROMINENT FEATURE		CLINICAL COMMENTS RELATED TO ED SIGNS
	Restrictive Intake	Binge Eating/Purging	
General appearance	Thin to cachectic, depending on balance of intake and output Might wear bulky clothing to hide thinness and might resist being examined	Thin to overweight, depending on the balance of intake and output through various means	Examine in hospital gown Weight loss more rapid with reduced intake and excessive exercise Binge eating can result in large weight gain, regardless of purging behavior Appearance depends on balance of intake and output and overall weight control habits
Weight	Low and falling (if previously overweight, may be normal or high); may be falsely elevated if patient	Highly variable, depending on	Weigh in hospital gown with no underwear, after voiding (measure urine SG)

	drinks fluids or adds weights to body before being weighed	balance of intake and output and state of hydration Falsification of weight is unusual	Remain in gown until physical exam completed to identify possible fluid loading (low urine SG, palpable bladder) or adding weights to body
Metabolism	Hypothermia: temp <35.5°C (95.9°F), pulse <60 beats/min Slowed psychomotor response with very low core temperature	Variable, but hypometabolic state is less common than in AN	Hypometabolism related to disruption of hypothalamic control mechanisms as a result of weight loss Signs of hypometabolism (cold skin, slow capillary refill, acrocyanosis) most evident in hands and feet, where energy conservation is most active
Skin	Dry Increased prominence of hair follicles Orange or yellow hands	Calluses over proximal knuckle joints of hand (Russell's sign)	Carotenemia with large intake of β-carotene foods Russell's sign: maxillary incisors abrasion develops into callus with chronic digital pharyngeal stimulation, usually on dominant hand
Hair	Lanugo-type hair growth on face and upper body Scalp hair loss, especially prominent in parietal region	No characteristic sign	Body hair growth conserves energy Scalp hair loss "telogen effluvium" can worsen weeks after refeeding begins, as hair in resting phase is replaced by growing hair
Eyes	No characteristic sign	Subconjunctival hemorrhage	Increased intrathoracic pressure during vomiting
Teeth	No characteristic sign	Eroded dental enamel and decayed, fractured, missing teeth	Perimolysis, worse on lingual surfaces of maxillary teeth, is intensified by brushing teeth without preceding water rinse
Salivary glands	No characteristic sign	Enlargement, relatively nontender	Parotid > submandibular involvement with frequent and chronic binge eating and induced vomiting
Throat	No characteristic sign	Absent gag reflex	Extinction of gag response with repeated pharyngeal stimulation
Heart	Bradycardia, hypotension, and orthostatic pulse differential >25 beats/min	Hypovolemia if dehydrated	Changes in AN resulting from central hypothalamic and intrinsic cardiac function Orthostatic changes less prominent if athletic, more prominent if associated with purging
Abdomen	Scaphoid, organs may be palpable but not enlarged, stool-filled left lower quadrant	Increased bowel sounds if recent laxative use	Presence of organomegaly requires investigation to determine cause Constipation prominent with weight loss

Extremities and musculoskeletal system	Cold, acrocyanosis, slow capillary refill Edema of feet Loss of muscle, subcutaneous, and fat tissue	No characteristic sign, but may have rebound edema after stopping chronic laxative use	Signs of hypometabolism (cold) and cardiovascular dysfunction (slow capillary refill and acrocyanosis) in hands and feet Edema, caused by capillary fragility more than hypoproteinemia in AN, can worsen in early phase of refeeding
Nervous system	No characteristic sign	No characteristic sign	Water loading before weigh-ins can cause acute hyponatremia
Mental status	Anxiety about body image, irritability, depressed mood, oppositional to change	Depression, evidence of PTSD, more likely suicidal than AN	Mental status often improves with healthier eating and weight; SSRIs only shown to be effective for BN

AN, Anorexia nervosa; BN, bulimia nervosa; PTSD, posttraumatic stress disorder; SG, specific gravity; SSRIs, selective serotonin reuptake inhibitors.

Differential Diagnosis

In addition to identifying symptoms and signs that deserve targeted intervention for patients who have an ED, a comprehensive history and physical examination are required to rule out other conditions in the differential diagnosis. Weight loss can occur in any condition with increased *catabolism* (e.g., hyperthyroidism, malignancy, occult chronic infection) or *malabsorption* (e.g., inflammatory bowel disease, celiac disease) or in other disorders (Addison disease, type 1 diabetes mellitus, stimulant abuse), but these illnesses are generally associated with other findings and are not usually associated with decreased caloric intake. Patients with **inflammatory bowel disease** can reduce intake to minimize abdominal cramping; eating can cause abdominal discomfort and early satiety in AN because of gastric atony associated with significant weight loss, not malabsorption. Likewise, signs of weight loss in AN might include hypothermia, acrocyanosis with slow capillary refill, and neutropenia similar to some features of sepsis, but the overall picture in EDs is one of relative cardiovascular stability compared with sepsis. **Endocrinopathies** are also in the differential of EDs. With BN, voracious appetite in the face of weight loss might suggest diabetes mellitus, but blood glucose levels are normal or low in EDs. Adrenal insufficiency mimics many physical symptoms and signs found in restrictive AN but is associated with elevated potassium levels and hyperpigmentation. Thyroid disorders may be considered, because of changes in weight, but the overall presentation of AN includes symptoms of both underactive and overactive thyroid, such as hypothermia, bradycardia, and constipation, as well as weight loss and excessive physical activity, respectively.

In the CNS, craniopharyngiomas and Rathke pouch tumors can mimic some of the findings of AN, such as weight loss and growth failure, and even some body image disturbances, but the latter are less fixed than in typical EDs and are associated with other findings, including evidence of increased intracranial pressure. **Mitochondrial neurogastrointestinal encephalomyopathy** , caused by a mutation in the *TYMP* gene, presents with gastrointestinal dysmotility, cachexia, ptosis, peripheral neuropathy, ophthalmoplegia, and leukoencephalopathy. Symptoms begin during the 2nd decade of life and are often initially diagnosed as AN. Early satiety, vomiting, cramps, constipation, and pseudoobstruction result in weight loss often before the neurologic features are noticed (see Chapter 616.2). Acute or chronic oromotor dysfunction and obsessive-compulsive disorder may mimic an eating disorder. Fear of choking may lead to **avoidance-restrictive food intake disorder** .

Any patient with an atypical presentation of an ED, based on age, sex, or other factors not typical for AN or BN, deserves a scrupulous search for an alternative explanation. In ARFID, disturbance in the neurosensory processes associated with eating, not weight loss, is the central concern and must be recognized for appropriate treatment. Patients can have both an underlying illness and an ED. The core features of dysfunctional eating habits—body image disturbance and change in weight—can coexist with conditions such as diabetes mellitus, where patients might manipulate their insulin dosing to lose weight.

Laboratory Findings

Because the diagnosis of an ED is made clinically, there is no confirmatory laboratory test. Laboratory abnormalities, when found, are the result of malnutrition, weight control habits, or medical complications; studies should be chosen based on history and physical examination. A routine screening battery typically includes complete blood count, erythrocyte sedimentation rate (should be normal), and biochemical profile. Common abnormalities in ED include low white blood cell count with normal hemoglobin and differential; hypokalemic, hypochloremic metabolic alkalosis from severe vomiting; mildly elevated liver enzymes, cholesterol, and cortisol levels; low gonadotropins and blood glucose with marked weight loss; and generally normal total protein, albumin, and renal function. An electrocardiogram may be useful when profound bradycardia or arrhythmia is detected; the ECG usually has low voltage, with nonspecific ST or T-wave changes. Although prolonged QTc has been reported, prospective studies have not found an increased risk for this. Nonetheless, when a prolonged QTc is present in a patient with ED, it may increase the risk for ventricular dysrhythmias.

Complications

No organ is spared the harmful effects of dysfunctional weight control habits, but the most concerning targets of medical complications are the heart, brain, gonads, and bones. Some **cardiac** findings in EDs (e.g., sinus bradycardia, hypotension) are *physiologic* adaptations to starvation that conserve calories and reduce afterload. Cold, blue hands and feet with slow capillary refill that can result in tissue perfusion insufficient to meet demands also represent energy-conserving responses associated with inadequate intake. All these acute changes are reversible with restoration of nutrition and weight. Significant orthostatic pulse changes, ventricular dysrhythmias, or reduced myocardial contractility reflect myocardial impairment that can be lethal. In addition, with extremely low weight, **refeeding syndrome** (a result of the rapid drop in serum phosphorus, magnesium, and potassium with excessive reintroduction of calories, especially carbohydrates), is associated with acute tachycardia and heart failure and neurologic symptoms. With long-term malnutrition, the myocardium appears to be more prone to tachyarrhythmias, the second most common cause of death in these patients after suicide. In BN, dysrhythmias can also be related to electrolyte imbalance.

Clinically, the primary CNS area affected acutely in EDs, especially with weight loss, is the **hypothalamus.** Hypothalamic dysfunction is reflected in problems with thermoregulation (warming and cooling), satiety, sleep, autonomic cardioregulatory imbalance (orthostasis), and endocrine function (reduced gonadal and excessive adrenal cortex stimulation), all of which are reversible. Anatomic studies of the brain in ED have focused on AN, with the most common finding being increased ventricular and sulcal volumes that normalize with weight restoration. Persistent gray matter deficits following recovery, related to the degree of weight loss, have been reported. Elevated medial temporal lobe cerebral blood flow on positron emission tomography, similar to that found in psychotic patients, suggests that these changes may be related to body image distortion. Also, visualizing high-calorie foods is associated with exaggerated responses in the visual association cortex that are similar to those seen in patients with specific phobias. Patients with AN might have an imbalance between serotonin and dopamine pathways related to neurocircuits in which dietary restraint reduces anxiety.

Reduced **gonadal** function occurs in male and female patients; it is clinically manifested in AN as amenorrhea in female patients and erectile dysfunction in males. It is related to understimulation from the hypothalamus as well as cortical suppression related to physical and emotional stress. Amenorrhea precedes significant dieting and weight loss in up to 30% of females with AN, and most adolescents with EDs perceive the absence of menses positively. The primary health concern is the negative effect of decreased ovarian function and estrogen on **bones** . Decreased bone mineral density (BMD) with osteopenia or the more severe osteoporosis is a significant complication of EDs (more pronounced in AN than BN). Data do not support the use of sex hormone replacement therapy because this alone does not improve other causes of low BMD (low body weight, lean body mass, low insulin-like growth factor-1, high cortisol).

Treatment

Principles Guiding Primary Care Treatment

The approach in primary care should facilitate the acceptance by the ED patient (and parents) of the diagnosis and initial treatment recommendations. A **nurturant-authoritative** approach using the biopsychosocial model is useful. A pediatrician who explicitly acknowledges that the patient may disagree with the diagnosis and treatment recommendations and may be ambivalent about changing eating habits, while also acknowledging that recovery requires strength, courage, willpower, and determination, demonstrates *nurturance* . Parents also find it easier to be nurturing once they learn that the development of an ED is neither a willful decision by the patient nor a reflection of poor parenting. Framing the ED as a “coping mechanism” for a complex variety of issues with both positive and negative aspects avoids blame or guilt and can prepare the family for professional help that will focus on strengths and restoring health, rather than on the deficits in the adolescent or the family.

The *authoritative* aspect of a physician's role comes from expertise in health, growth, and physical development. A goal of primary care treatment should be attaining and maintaining health—not merely weight gain—although weight gain is a means to the goal of wellness. Providers who frame themselves as consultants to the patient with authoritative knowledge about health can avoid a countertherapeutic authoritarian stance. Primary care health-focused activities include monitoring the patient's physical status, setting limits on behaviors that threaten the patient's health, involving specialists with expertise in EDs on the treatment team, and continuing to provide primary care for health maintenance, acute illness, or injury.

The **biopsychosocial model** uses a broad ecologic framework, starting with the biologic impairments of physical health related to dysfunctional weight control practices, evidenced by symptoms and signs. Explicitly linking ED behaviors to symptoms and signs can increase motivation to change. In addition, there are usually unresolved psychosocial conflicts in both the intrapersonal (self-esteem, self-efficacy) and the interpersonal (family, peers, school) domains. Weight control practices initiated as coping mechanisms become reinforced because of positive feedback. That is, external rewards (e.g., compliments about improved physical appearance) and internal rewards (e.g., perceived mastery over what is eaten or what is done to minimize the effects of overeating through exercise or purging) are more powerful to maintain behavior than negative feedback (e.g., conflict with parents, peers, and others about eating) is to change it. Thus, when definitive treatment is initiated, more productive alternative means of coping must be developed.

Nutrition and Physical Activity

The primary care provider generally begins the process of prescribing nutrition, although a dietitian should be involved eventually in the meal planning and nutritional education of patients with AN or BN. Framing food as fuel for the body and the source of energy for daily activities emphasizes the health goal of increasing the patient's energy level, endurance, and strength. For patients with AN and low weight, the nutrition prescription should work toward gradually increasing weight at the rate of about 0.5-1 lb/wk, by increasing energy intake by 100-200 kcal increments every few days, toward a target of approximately 90% of average body weight for sex, height, and age. Weight gain will not occur until intake exceeds output, and eventual intake for continued weight gain can exceed 4,000 kcal/day, especially for patients who are anxious and have high levels of thermogenesis from nonexercise activity. Stabilizing intake is the goal for patients with BN, with a gradual introduction of “forbidden” foods while also limiting foods that might trigger a binge.

When initiating treatment of an ED in a primary care setting, the clinician should be aware of common cognitive patterns. Patients with AN typically have all-or-none thinking (related to perfectionism) with a tendency to overgeneralize and jump to catastrophic conclusions, while assuming that their body is governed by rules that do not apply to others. These tendencies lead to the dichotomization of foods into good or bad categories, having a day ruined because of one unexpected event, or choosing foods based on rigid self-imposed restrictions. These thoughts may be related to neurocircuitry and neurotransmitter abnormalities associated with executive function and rewards. Weight loss in the absence of body shape, size, or weight concerns should raise suspicion about ARFID, because the emotional distress associated with "forced" eating is not associated with gaining weight, but with the neurosensory experience of eating.

A standard nutritional balance of 15–20% calories from protein, 50–55% from carbohydrate, and 25–30% from fat is appropriate. The fat content may need to be lowered to 15–20% early in the treatment of AN because of continued fat phobia. With the risk of low BMD in patients with AN, calcium and vitamin D supplements are often needed to attain the recommended 1,300 mg/day intake of calcium. Refeeding can be accomplished with frequent small meals and snacks consisting of a variety of foods and beverages (with minimal diet or fat-free products), rather than fewer high-volume high-calorie meals. Some patients find it easier to take in part of the additional nutrition as canned supplements (medicine) rather than food. Regardless of the source of energy intake, the risk for refeeding syndrome (see Complications earlier) increases with the degree of weight loss and the rapidity of caloric increases. Therefore, if the weight has fallen below 80% of expected weight for height, refeeding should proceed carefully (not necessarily slowly) and possibly in the hospital (Table 41.7).

Table 41.7

Potential Indications for Inpatient Medical Hospitalization of Patients With Anorexia Nervosa

Physical and Laboratory

Heart rate <50 beats/min

Other cardiac rhythm disturbances
Blood pressure <80/50 mm Hg
Postural hypotension resulting in >10 mm Hg decrease or >25 beats/min increase
Hypokalemia
Hypophosphatemia
Hypoglycemia
Dehydration
Body temperature <36.1°C (97°F)
<80% healthy body weight
Hepatic, cardiac, or renal compromise

Psychiatric

Suicidal intent and plan
Very poor motivation to recover (in family and patient)
Preoccupation with ego-syntonic thoughts
Coexisting psychiatric disorders

Miscellaneous

Requires supervision after meals and while using the restroom
Failed day treatment

Patients with AN tend to have a highly structured day with restrictive intake, in contrast to BN, which is characterized by a lack of structure, resulting in chaotic eating patterns and binge-purge episodes. All patients with AN, BN, or ED-NOS benefit from a daily structure for healthy eating that includes 3 meals and at least 1 snack a day, distributed evenly over the day, based on balanced meal planning. Breakfast deserves special emphasis because it is often the first meal eliminated in AN and is often avoided the morning after a binge-purge episode in BN. In addition to structuring meals and snacks, patients should plan structure in their activities. Although overexercising is common in AN, completely prohibiting exercise can lead to further restriction of intake or to surreptitious exercise; inactivity should be limited to situations in which weight loss is dramatic or there is physiologic instability. Also, healthy exercise (once a day, for no more than 30 min, at no more than moderate intensity) can improve mood and make increasing calories more acceptable. Because patients with AN often are unaware of their level of activity and tend toward progressively increasing their output, exercising without either a partner or supervision is not recommended.

Primary Care Treatment

Follow-up primary care visits are essential in the management of EDs. Close monitoring of the response of the patient and the family to suggested interventions is required to determine which patients can remain in primary care treatment (patients with early, mildly disordered eating), which patients need to be referred to individual specialists for co-management (mildly progressive disordered eating), and which patients need to be referred for interdisciplinary team management (EDs). Between the initial and subsequent visits, the patient can record daily caloric intake (food, drink, amount, time, location), physical activity (type, duration, intensity), and emotional state (e.g., angry, sad, worried) in a journal that is reviewed jointly with the patient in follow-up. Focusing on the recorded data helps the clinician to identify dietary and activity deficiencies and excesses, as well as behavioral and mental health patterns, and helps the patient to become objectively aware of the relevant issues to address in recovery.

Given the tendency of patients with AN to overestimate their caloric intake and underestimate their activity level, before reviewing the journal record it is important at each visit to measure weight, without underwear, in a hospital gown after voiding; urine specific gravity; temperature; and blood pressure and pulse in supine, sitting, and standing positions as objective data. In addition, a targeted physical examination focused on hypometabolism, cardiovascular stability, and mental status, as well as any related symptoms, should occur at each visit to monitor progress (or regression).

Referral to Mental Health Services

In addition to referral to a registered dietitian, mental health and other services are important elements of treatment of ED patients. Depending on availability and experience, these services can be provided by a psychiatric social worker, psychologist, or psychiatrist, who should team with the primary care provider. ARFID presents the challenge of working with patients' negative experience of eating, or fear of trauma such as vomiting or choking, while also addressing inadequate nutritional needs. Although patients with AN often are prescribed a selective serotonin reuptake inhibitor (SSRI) because of depressive symptoms, there is no evidence of efficacy for patients at low weight; **food** remains the initial treatment of choice to treat depression in AN. **SSRIs** , very effective in reducing binge-purge behaviors regardless of depression, are considered a standard element of therapy in BN. SSRI dosage in BN, however, may need to increase to an equivalent of >60 mg of fluoxetine to maintain effectiveness.

Cognitive-behavioral therapy , which focuses on restructuring “thinking errors” and establishing adaptive patterns of behavior, is more effective than interpersonal or psychoanalytic approaches in ED patients. **Dialectical behavioral therapy** , in which distorted thoughts and emotional responses are challenged, analyzed, and replaced with healthier ones, with an emphasis on “mindfulness,” requires adult thinking skills and is useful for older patients with BN. **Group therapy** can provide much needed support, but it requires a skilled clinician. Combining patients at various levels of recovery who experience variable reinforcement from dysfunctional coping behaviors can be challenging if group therapy patients compete with each other to be “thinner” or take up new behaviors such as vomiting.

The younger the patient, the more intimately the parents need to be involved in therapy. The only treatment approach with evidence-based effectiveness in the treatment of AN in children and adolescents is **family-based treatment** , exemplified by the Maudsley approach. This 3-phase intensive outpatient model helps parents play a positive role in restoring their child's eating and weight to normal, then returns control of eating to the child, who has demonstrated the ability to maintain healthy weight, and then encourages healthy progression in the other domains of adolescent development. Features of effective family treatment include (1) an agnostic approach in which the cause of the disease is unknown and irrelevant to weight gain, emphasizing that parents are *not* to blame for EDs; (2) parents being actively nurturing and supportive of their child's healthy eating while reinforcing limits on dysfunctional habits, rather than an authoritarian “food police” or complete hands-off approach; and (3) reinforcement of parents as the best resource for recovery for almost all patients, with professionals serving as consultants and advisors to help parents address challenges.

Referral to an Interdisciplinary Eating Disorder Team

The treatment of a child or adolescent diagnosed with an ED is ideally provided by an interdisciplinary team (physician, nurse, dietitian, mental health provider) with expertise treating pediatric patients. Because such teams, often led by specialists in adolescent medicine at medical centers, are not widely available, the primary care provider might need to convene such a team. Adolescent medicine–based programs report encouraging treatment outcomes, possibly related to patients entering earlier into care and the stigma that some patients and parents may associate with psychiatry-based programs. Specialty centers focused on treating EDs are generally based in psychiatry and often have separate tracks for younger and adult patients. The elements of treatment noted earlier (cognitive-behavioral, dialectical behavioral, family-based), as well as individual and group treatment, should all be available as part of interdisciplinary team treatment. Comprehensive services ideally include intensive outpatient and partial hospitalization as well as inpatient treatment. Regardless of the intensity, type, or location of the treatment services, the patient, parents, and primary care provider are essential members of the treatment team. A recurring theme in effective treatment is helping patients and families reestablish connections that are disrupted by the ED.

Inpatient medical treatment of EDs is generally limited to patients with AN, to stabilize and treat life-threatening starvation and to provide supportive mental health services. Inpatient medical care may be required to avoid refeeding syndrome in severely malnourished patients, provide nasogastric tube feeding for patients unable or unwilling to eat, or initiate mental health services, especially family-based treatment, if this has not occurred on an outpatient basis (see Table 41.7). Admission to a general pediatric unit is advised only for short-term stabilization in preparation for transfer to a medical unit with expertise in treating pediatric EDs. Inpatient psychiatric care of EDs should be provided on a unit with expertise in managing the often challenging behaviors (e.g., hiding or discarding food, vomiting, surreptitious exercise) and emotional problems (e.g., depression, anxiety). Suicidal risk is small, but patients with AN might threaten suicide if made to eat or gain weight in an effort to “get their parents to back off.”

An ED **partial hospital program** offers outpatient services that are less intensive than round-the-clock inpatient care. Generally held 4-5 days/wk for 6 to 9 hr each session, partial hospital program services typically are group-based and include eating at least 2 meals as well as opportunities to address issues in a setting that more closely approximates “real life” than inpatient treatment. That is, patients sleep at home and are free-living on weekends, exposing them to challenges that can be processed during the 25-40 hr each week in program, as well as sharing group and family experiences.

Supportive Care

In relation to pediatric EDs, support groups are primarily designed for parents. Because their daughter or son with an ED often resists the diagnosis and treatment, parents often feel helpless and hopeless. Because of the historical precedent of blaming parents for causing EDs, parents often express feelings of shame and isolation (www.maudsleyparents.org). Support groups and multifamily therapy sessions bring parents together with other parents whose families are at various stages of recovery from an ED in ways that are educational and encouraging. Patients often benefit from support groups after intensive treatment or at the end of treatment because of residual body image or other issues after eating and weight have normalized.

Prognosis

With early diagnosis and effective treatment, ≥80% of youth with AN recover: They develop normal eating and weight control habits, resume menses, maintain average weight for height, and function in school, work, and relationships, although some still have poor body image. With weight restoration, fertility returns as well, although the weight for resumption of menses (approximately 92% of average body weight for height) may be lower than the weight for ovulation. The prognosis for BN is less well established, but outcome improves with multidimensional treatment that includes SSRIs and attention to mood, past trauma, impulsivity, and any existing psychopathology. Since the diagnosis of ARFID was only established in 2013, little is known about its long-term prognosis, although anecdotal evidence suggests that weight restoration is not actively resisted as it is in AN. Atypical AN and ED-NOS may still have significant morbidity.

Prevention

Given the complexity of the pathogenesis of EDs, prevention is difficult. Targeted preventive interventions can reduce risk factors in older adolescents and college-age women. Universal prevention efforts to promote healthy weight regulation and discourage unhealthy dieting have not shown effectiveness in middle school students. Programs that include recovered patients or focus on the problems associated with EDs can inadvertently normalize or even glamorize EDs and should be discouraged.

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CHAPTER 42

Disruptive, Impulse-Control, and Conduct Disorders

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The disruptive, impulse-control, and conduct disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in self-regulation of anger, aggression, defiance, and antisocial behaviors. The disruptive, impulse-control, and conduct disorders include oppositional defiant, intermittent explosive, conduct, other specified/unspecified disruptive/impulse control/conduct, and antisocial personality disorders, as well as pyromania and kleptomania.

Description

Oppositional defiant disorder (ODD) is characterized by a pattern lasting at least 6 mo of angry, irritable mood, argumentative/defiant behavior, or vindictiveness exhibited during interaction with at least 1 individual who is not a sibling (Table 42.1). For preschool children, the behavior must occur on most days, whereas in school-age children, the behavior must occur at least once a week. The severity of the disorder is considered *mild* if symptoms are confined to only 1 setting (e.g., at home, at school, at work, with peers), *moderate* if symptoms are present in at least 2 settings, and *severe* if symptoms are present in ≥4 settings.

Table 42.1

DSM-5 Diagnostic Criteria for Oppositional Defiant Disorder

A. A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 mo as evidenced by at least 4 symptoms from any of the following categories, and exhibited during interaction with at least 1 individual who is not a sibling:

Angry/Irritable Mood

1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

Argumentative/Defiant Behavior

4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

Vindictiveness

8. Has been spiteful or vindictive at least twice within the past 6 mo.

   Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 yr, the behavior should occur on most days for a period of at least 6 mo unless otherwise noted (Criterion A8). For individuals 5 yr or older, the behavior should occur at least once per week for at least 6 mo, unless otherwise noted (Criterion A8). While these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.

C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 462–463.

Intermittent explosive disorder (IED) is characterized by recurrent verbal or physical aggression that is grossly disproportionate to the provocation or to any precipitating psychosocial stressors (Table 42.2). The outbursts, which are impulsive and/or anger-based rather than premeditated and/or instrumental, typically last <30 min and frequently occur in response to a minor provocation by a close intimate.

Table 42.2

DSM-5 Diagnostic Criteria for Intermittent Explosive Disorder

A. Recurrent behavioral outbursts representing a failure to control aggressive impulses as manifested by either of the following:
    1. Verbal aggression (e.g., temper tantrums, tirades, verbal arguments or fights) or physical aggression toward property, animals, or other individuals, occurring twice weekly, on average, for a period of 3 mo. The physical aggression does not result in damage or destruction of property and does not result in physical injury to animals or other individuals.
    2. Three behavioral outbursts involving damage or destruction of property and/or physical assault involving physical injury against animals or other individuals occurring with a 12 mo period.

B. The magnitude of aggressiveness expressed during the recurrent outbursts is grossly out of proportion to the provocation or to any precipitating psychosocial stressors.

C. The recurrent aggressive outbursts are not premeditated (i.e., they are impulsive and/or anger-based) and are not committed to achieve some tangible objective (e.g., money, power, intimidation).

D. The recurrent aggressive outbursts cause either marked distress in the individual or impairment in occupational or interpersonal functioning, or as associated with financial or legal consequences.

E. Chronological age is at least 6 yr (or equivalent developmental level).

F. The recurrent aggressive outbursts are not better explained by another mental disorder (e.g., major depressive disorder, bipolar disorder, disruptive mood dysregulation disorder, a psychotic disorder, antisocial personality disorder, borderline personality disorder) and are not attributable to another medical condition (e.g., head trauma, Alzheimer disease) or to the physiologic effects of a substance (e.g., a drug of abuse, a medication). For children ages 6-18 yr, aggressive behavior that occurs as part of an adjustment disorder should not be considered for this diagnosis.
Note: This diagnosis can be made in addition to the diagnosis of attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, or autism spectrum disorder when recurrent impulsive aggressive outbursts are in excess of those usually seen in these disorders and warrant clinical attention.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, p 466.

Conduct disorder (CD) is characterized by a repetitive and persistent pattern over at least 12 mo of serious rule-violating behavior in which the basic rights of others or major societal norms or rules are violated (Table 42.3). The symptoms of CD are divided into 4 major categories: aggression to people and animals, destruction of property, deceitfulness or theft, and serious rule violations (e.g., truancy, running away). Three subtypes of CD (which have different prognostic significance) are based on the age of onset: childhood-onset type, adolescent-onset type, and unspecified. A small proportion of individuals with CD exhibit characteristics (lack of remorse/guilt, callous/lack of empathy, unconcerned about performance, shallow/deficient affect) that qualify for the “with limited prosocial emotions” specifier. CD is classified as *mild* when few if any symptoms over those required for the diagnosis are present, and the symptoms cause relatively minor harm to others. CD is classified as *severe* if many symptoms over those required for the diagnosis are present, and the symptoms cause considerable harm to others. *Moderate* severity is intermediate between mild and severe.

Table 42.3

DSM-5 Diagnostic Criteria for Conduct Disorder

A. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least 3 of the following 15 criteria in the past 12 mo from any of the categories below, with at least 1 criterion present in the past 6 mo:

Aggression to People and Animals

1. Often bullies, threatens, or intimidates others.
2. Often initiates physical fights.
3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun).
4. Has been physically cruel to people.
5. Has been physically cruel to animals.
6. Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery).
7. Has forced someone into sexual activity.

Destruction of Property

8. Has deliberately engaged in fire setting with the intention of causing serious damage.
9. Has deliberately destroyed others' property (other than by fire setting).

Deceitfulness or Theft

10. Has broken into someone else's house, building, or car.
11. Often lies to obtain good or favors or to avoid obligations (i.e., “cons” others).
12. Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery).

Serious Violations of Rules

13. Often stays out at night despite parental prohibitions, beginning before age 13 yr.

14. Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period.
15. Is often truant from school, beginning before age 13 yr.

B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

C. If the individual is age 18 yr or older, criteria are not met for antisocial personality disorder.

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Other specified/unspecified disruptive/impulse-control/CD (sub-syndromal disorder) applies to presentations in which symptoms characteristic of the disorders in this class are present and cause clinically significant distress or functional impairment, but do not meet full diagnostic criteria for any of the disorders in this class.

Epidemiology

The prevalence of ODD is approximately 3%, and in preadolescents is more common in males than females (1.4 : 1). One-year prevalence rates for IED and CD approximate 3% and 5%, respectively. For CD, prevalence rates rise from childhood to adolescence and are higher among males than females. The prevalence of these disorders has been shown to be higher in lower socioeconomic classes. This class of disorders constitutes the most frequent referral problem for youth, accounting for one third to one half of all cases seen in mental health clinics. Racial/ethnic minority youth with these disorders utilize specialty mental health services at lower rates than their white peers.

Clinical Course

Oppositional *behavior* can occur in all children and adolescents at times, particularly during the toddler and early teenage periods when establishing autonomy and independence are normative developmental tasks. Oppositional behavior becomes a concern when it is intense, persistent, and pervasive and when it affects the child's social, family, and academic life.

Some of the earliest manifestations of oppositionality are stubbornness (3 yr), defiance and temper tantrums (4-5 yr), and argumentativeness (6 yr). Approximately 65% of children with ODD exit from the diagnosis after a 3 yr follow-up; earlier age at onset of oppositional symptoms conveys a poorer prognosis. ODD often precedes the development of CD (approximately 30% higher likelihood with comorbid attention-deficit/hyperactivity disorder [ADHD]), but also increases the risk for the development of depressive and anxiety disorders. The defiant and vindictive symptoms carry most of the risk for CD, whereas the angry, irritable mood symptoms carry most of the risk for anxiety and depression.

IED usually begins in late childhood or adolescence and appears to follow a chronic and persistent course over many years.

The onset of CD may occur as early as the preschool years, but the first significant symptoms usually emerge during the period from middle childhood through middle adolescence; onset is rare after age 16 yr. Symptoms of CD vary with age as the individual develops increased physical strength, cognitive abilities, and sexual maturity. Symptoms that emerge first tend to be less serious (e.g., lying), while those emerging later tend to be more severe (e.g., sexual or physical assault). Severe behaviors emerging at an early age convey a poor prognosis. In the majority of individuals, the disorder remits by adulthood; in a substantial fraction, antisocial personality disorder develops. Individuals with CD also are at risk for the later development of mood, anxiety, posttraumatic stress, impulse control, psychotic, somatic symptom, and substance-related disorders.

Differential Diagnosis

The disorders in this diagnostic class share a number of characteristics with each other as well as with disorders from other classes, and as such must be carefully differentiated. ODD can be distinguished from CD by the absence of physical aggression and destructiveness and by the presence of angry, irritable mood. ODD can be distinguished from IED by the lack of serious aggression (physical assault). IED can be distinguished from CD by the lack of predatory aggression and other, nonaggressive symptoms of CD.

The **oppositionality** seen in ODD must be distinguished from that seen in

ADHD, depressive and bipolar disorders (including disruptive mood dysregulation disorder), language disorders, intellectual disability, and social anxiety disorder. ODD should not be diagnosed if the behaviors occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder, or if criteria are met for disruptive mood dysregulation disorder. IED should not be diagnosed if the behavior can be better explained by a depressive, bipolar, disruptive mood dysregulation, psychotic, antisocial personality, or borderline personality disorder. The **aggression** seen in CD must be distinguished from that seen in ADHD and intermittent explosive, depressive, bipolar, and adjustment disorders.

Comorbidity

Rates of ODD are much higher in children with ADHD, which suggests shared temperamental risk factors. Depressive, anxiety, and substance use disorders are most often comorbid with IED. ADHD and ODD are both common in individuals with CD, and this comorbid presentation predicts worse outcomes. CD also may occur with anxiety, depressive, bipolar, learning, language, and substance-related disorders.

Sequelae

The disruptive, impulse-control, and conduct disorders are associated with a wide range of psychiatric disorders in adulthood and with many other adverse outcomes, such as suicidal behavior, physical injury, delinquency and criminality, legal problems, substance use, unplanned pregnancy, social instability, marital failure, and academic and occupational underachievement.

Etiology and Risk Factors

At the individual level, a number of neurobiologic markers (lower heart rate and skin conductance reactivity, reduced basal cortisol reactivity, abnormalities in the prefrontal cortex and amygdala, serotonergic abnormalities) have been variously associated with aggressive behavior disorders. Other biologic risk factors include pre-, peri-, and postnatal insults; cognitive and linguistic impairment, particularly language-based learning deficits; difficult temperamental characteristics, particularly negative affectivity, poor frustration tolerance, and impulsivity; certain personality characteristics (novelty seeking, reduced harm avoidance, and reward dependence); and certain cognitive characteristics (cognitive rigidity, hostile attributions for ambiguous social cues).

At the family level, a consistently demonstrated risk factor is **ineffective parenting** . Parents of behaviorally disordered children are more inconsistent in their use of rules; issue more and unclear commands; are more likely to respond to their child based on their own mood rather than the child's behavior; are less likely to monitor their children's whereabouts; and are relatively unresponsive to their children's prosocial behavior. Complicating this association is the consistent finding that *temperamentally difficult children are more likely to elicit negative parenting responses*, including physical punishment, which can exacerbate anger and oppositionality in the child. Other important family-level influences include impaired parent–child attachment, child maltreatment (physical and sexual abuse), exposure to marital conflict and domestic violence, family poverty and crime, and **family genetic liability** (family history of the disorders in this class along with substance use, depressive, bipolar, schizophrenic, somatization, and personality disorders, as well as ADHD, have all been shown to be associated with the development of behavior disorders).

Peer-level influence on the development of behavior problems include peer rejection in childhood and antisocial peer groups. Neighborhood influences include social processes such as collective efficacy and social control.

Prevention

A useful conduct problem prevention program is the *Fast Track* (http://fasttrackproject.org), a multicomponent school-based intervention comprising a classroom curriculum targeted at conflict resolution and interpersonal skills, parent training, and interventions targeted at the school environment. Implemented in 1st through 10th grade, former program participants at age 25 had a lower prevalence of any externalizing, internalizing, or substance abuse problem than program nonparticipants. Program participants also had lower violent and drug crime conviction scores, lower risky sexual behavior scores, and higher well-being scores. Another useful prevention program, the *Seattle Social Development Project* (http://ssdp-tip.org/SSDP/index.html), is also a multicomponent school-based intervention of teacher, parent, and student components targeting classroom management, interpersonal problem-solving, child behavior management, and academic support skills. Implemented in 1st through 6th grades, outcomes at age 19 yr demonstrated that the intervention decreased lifetime drug use and delinquency for participant males compared with males in comparator communities, but had no significant effects on females.

Screening/Case Finding

The parents of children presenting in the primary care setting should be queried about angry mood or aggressive, defiant, or antisocial behavior as part of the routine clinical interview. A typical screening question would be, “Does [name] have a lot of trouble controlling [his/her] anger or behavior?” A number of standardized broad-band screening instruments widely used in the primary care setting *(Pediatric Symptom Checklist* , *Strengths and Difficulties Questionnaire* , *Vanderbilt ADHD Diagnostic Rating Scales)* have items specific to angry mood and aggressive behavior, and as such can be used to focus the interview.

Early Intervention

Youth (and/or their parents) presenting in the primary care setting who self-report or respond affirmatively to queries about difficulties managing angry mood or aggressive or antisocial behavior should be afforded the opportunity to talk about the situation with the pediatric practitioner (separately with the older youth as indicated). By engaging in active listening (e.g., “I hear how you have been feeling. Tell me more about what happened to make you feel that way”), the pediatric practitioner can establish a therapeutic rapport and begin to assess the onset, duration, context, and severity of the symptoms, and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., homicidality, assaultiveness, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within 1-2 wk to conduct a behavior assessment. At this follow-up visit, to assist with decision-making about appropriate level of care, a behavior screening instrument can be administered (Table 42.4) and additional risk factors explored (see Etiology and Risk Factors earlier).

Table 42.4

Anger/Aggression-Specific Screening Instruments

NAME OF INSTRUMENT	INFORMANT(S)	AGE RANGE	NUMBER OF ITEMS
Children's Aggression Scale	Parent, Teacher	5-18 yr	33 (P), 23 (T)
Eyberg Child Behavior Inventory	Parent	2-16 yr	36
Outburst Monitoring Scale	Parent	12-17 yr	20
Sutter-Eyberg Student Behavior Inventory–Revised	Teacher	2-16 yr	38
Vanderbilt ADHD Diagnostic Rating Scales	Parent, Teacher	6-12 yr	55 (P), 43 (T)

For mild symptoms (manageable by the parent and not functionally impairing) and in the absence of major risk factors (homicidality, assaultiveness, psychosis, substance use, child maltreatment, parental psychopathology, or severe family dysfunction), **guided self-help** (anticipatory guidance) with watchful waiting and scheduled follow-up may suffice. Guided self-help can include provision of educational materials (pamphlets, books, videos, workbooks, internet sites) that provide information to the youth about dealing with anger-provoking situations, and advice to parents about strengthening the parent–child relationship, effective parenting strategies, and the effects of adverse environmental exposures on the development of behavior problems. In a Cochrane review, media-based parenting interventions had a moderate positive effect on child behavior problems, either alone or as an adjunct to medication. An example of a self-help program for parents is the *Positive Parenting Program* (Triple P; www.triplep.net), online version, in which parents can purchase 4 modules of instruction addressing techniques for positive parenting and strategies for encouraging good behavior, teaching new emotional and behavioral skills, and managing misbehavior (see Chapter 19).

If the problematic behavior is occurring predominantly at school, the parent can be advised about the role of a special education evaluation in the assessment and management of the child's misbehavior, including the development of a behavioral intervention plan to prevent disciplinary actions that is formalized in an individualized educational plan (IEP) or 504 plan.

If a mental health clinician has been co-located or integrated into the primary care setting, all parents of young children (universal prevention), as well as the parents of youth with mild behavior problems (indicated prevention), can be provided with a brief version of **parent training** . Programs targeted at toddlers through 12 yr olds have been found to be effective in improving parenting skills, parental mental health, and child emotional and behavior problems. For example, *Incredible Years* (http://www.incredibleyears.com) has a 6-8 session universal prevention version to help parents promote their 2-6 yr old children's emotional regulation, social competence, problem solving, and reading readiness. A 12-20 session version is designed to strengthen parent–child interactions, reduce harsh discipline, and foster parents' ability to promote children's social, emotional, and language development in their toddler to school-age children. A randomized trial in pediatric practices found that Incredible Years significantly improved parenting practices and 2-4 yr olds' disruptive behaviors compared to a wait-list control. Similarly, for children with behavior problems, the Triple P program has seminar (three 90 min sessions), brief (15-30 min consultations), and primary care (four 20-30 min consultations) versions for the parents of youth from birth to the teenage years, specifically designed for implementation in the primary care setting. The Triple P interventions, supported by an extensive evidence base, focus on strengthening the parent–child relationship, identifying and monitoring the frequency of a problem behavior, and implementing and reviewing the effects of a targeted behavior plan.

Treatment

For youth who continue to have mild to moderate behavior problems after several weeks of guided self-help or a brief course of parent training, or who from the outset exhibit moderate to severe or comorbid aggression, homicidality, assaultiveness, psychosis, or substance use, or who have a history of child maltreatment or severe family dysfunction or psychopathology, assessment and treatment in the specialty mental health setting by a child-trained mental health clinician should be provided.

The youth's problem behavior may predominantly occur at home, at school, with peers, or in the community, or it may be pervasive. If possible, interventions need to address each context specifically, rather than assuming generalizability of treatment. Thus, for behaviors mostly manifested in the home setting, parent training would be the treatment of choice, whereas for behaviors manifested mostly at school, consultation with the teacher and recommendation of a special education evaluation for service eligibility can be useful. When there are pervasive problems, including aggression toward peers, cognitive-behavioral therapy with the child/teen can be employed in addition to the other interventions.

Parent training has been extensively studied for the treatment of youth problem behavior. These programs, typically 10-15 wk in duration, focus on some combination of the following components: understanding social learning principles, developing a warm supportive relationship with the child, encouraging child-directed interaction and play, providing a predictable structured household environment, setting clear simple household rules, consistently praising and materially rewarding positive behavior, consistently ignoring annoying behavior (followed by praise when the annoying behavior ceases), and consistently giving consequences (e.g., time-out, loss of privileges) for dangerous or destructive behavior. Other important targets for parenting training include understanding developmentally appropriate moods and behavior, managing difficult temperamental characteristics, fostering the child's social and emotional development, and protecting the child from traumatic exposures. Specific parent training programs include *Parent–Child Interaction Therapy* , *Triple P* , *Helping the Noncompliant Child*, *Incredible Years*, and *Parent Management Training Oregon.* Predictors of nonresponse to these interventions have included greater initial symptom severity as well as involvement of the parent with child protection services.

Adherence to the complete treatment regimen has limited the effectiveness of parent training programs. Estimates of premature termination are as high as 50–60%, and termination within 5 treatment sessions is not uncommon. Predictors of premature termination of parent training programs have included single-parent status, low family income, low parental education levels, young maternal age, minority group status, and life stresses.

Cognitive behavioral therapy (CBT) for youth with disruptive behavior also has been extensively studied. Common CBT techniques for disruptive behavior include identifying the antecedents and consequences of disruptive or aggressive behavior, learning strategies for recognizing and regulating anger expression, problem-solving and cognitive restructuring (perspective-taking) techniques, and modeling and rehearsing social appropriate behaviors that could replace angry or aggressive reactions. Programs typically are delivered in 16-20 weekly sessions.

Multicomponent treatments for serious behavior disorders such as CD target the broader social context. **Multidimensional Treatment Foster Care** , delivered in a foster care setting for 6-9 mo, typically includes foster parent training and support; family therapy for biologic parents; youth anger management, social skills, and problem-solving training; school-based behavioral interventions and academic support; and psychiatric consultation and medication management, when needed. **Multisystemic Therapy** , typically lasting 3-5 mo, generally includes social competence training, parent and family skills training, medications, academic engagement and skills building, school interventions and peer mediation, mentoring and after-school programs, and involvement of child-serving agencies. These multicomponent programs have been designated “probably efficacious” because of the limited rigorous supporting evidence. Predictors of nonresponse to multicomponent treatments have included higher frequency of rule-breaking behavior and predatory aggression, higher psychopathy scores, and comorbid mood disorders.

Two classes of medication, **stimulants** and **atypical antipsychotics** , have strong evidence for the management of impulsive, anger-driven aggressive behavior, although neither is approved by the U.S. Food and Drug Administration (FDA) for this indication. Resource limitations may necessitate provision of pharmacotherapy in the primary care setting; the safety and efficacy of this practice can be enhanced by regular consultation with a child and adolescent psychiatrist. Several studies have shown favorable effects of stimulants on oppositional behavior and aggression in youths with ADHD. The doses of stimulants used for aggression are similar to those used for ADHD (average dose for methylphenidate, approximately 1 mg/kg/day). There is evidence for efficacy of risperidone in reducing aggression and conduct problems in children age 5-18 yr. The suggested usual daily dose of risperidone for severe aggression is 1.5-2 mg for children and 2-4 mg for adolescents. The initial starting doses are 0.25 mg for children and 0.5 mg for adolescents, titrating upward to the usual daily dose, as indicated and tolerated.

Medication trials should be systematic, and the duration of trials should be sufficient (generally 6-8 wk for atypical antipsychotics) to determine the agent's effectiveness. The short-term goal of treatment is to achieve at least a 50% reduction in aggressive symptoms, as assessed by a standardized rating scale (see Table 42.4); the ultimate goal is to achieve symptom remission (below clinical cutpoint on rating scale). A 2nd medication of the same class can be considered if there is insufficient evidence of response to the maximal tolerated dose by 8 weeks. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Discontinuation of the medication should be considered after a symptom-free interval.

Level of Care

Most children and adolescents with a behavior disorder can be safely and effectively treated in the outpatient setting. Youths with intractable CD may benefit from residential or specialized foster care treatment, where more intensive treatments can be provided.

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CHAPTER 43

Tantrums and Breath-Holding Spells

Lovern R. Moseley, Keneisha Sinclair-McBride, David R. DeMaso, Heather J. Walter

Temper tantrums are common during the first few years of life. They are typically developmentally normative expressions of children's frustration with their own limitations or anger about not being able to get their way. It is important for parents to recognize the differences between tantrum types and precipitants in order to determine the best course of action to manage the ensuing behavior. Dealing with tantrum behavior can become very frustrating for parents, but many tantrums can be averted by a parent's awareness or attunement to certain cues given by their child, particularly in the early years. In particular, parents should be aware that when a child is tired, hungry, or feeling ill or has to make a transition, it can be expected that the child will be more likely to have a tantrum because children are more easily overwhelmed. In this case, it is advised that parents plan ahead and take a preventive stance by being aware of *triggers* and minimizing the potential for a tantrum. For example, parents should not make a tired or hungry child accompany them on an extended outing unless absolutely necessary. Additionally, depending on the child's developmental level, it is helpful to have a clear discussion ahead of time about the expectations in certain scenarios. When children are able to demonstrate good control, their behavior should be acknowledged and praised. This will increase the likelihood that they will engage in the desired response more often, even in frustrating situations.

In the case of children who engage in tantrum behavior to get their way, parents may feel more inclined to respond to such defiance with yelling or threats, which can reinforce and even escalate the oppositional behavior. Parents should attempt to avert defiance by giving the child choices; once the child has begun a tantrum, he or she can be placed in time-out. If the tantrum was to avoid a task, the child should be required to complete the task once time-out is over. Parents should state the reason the child is being placed in time-out, but they should not discuss the reasons before or during time-out. Once the time-out is over and the child is calm, it may be helpful for parents to discuss with the child the reasons for the child's frustration and their expectations for how the child will respond in the future.

Breath-holding spells occasionally occur during a tantrum and can be frightening to parents. These are reflexive events in which the crying child becomes apneic, pale, or cyanotic, may lose consciousness, and occasionally will have a brief seizure. Parents are best advised to ignore breath holding once it has started. Without reinforcement, breath holding generally disappears.

Subtypes of breath-holding spells include cyanotic, pallid, or mixed episodes. *Cyanotic spells* are the dominant type. *Pallid spells* may be similar to vasovagal-related syncopal events in older children and may be initiated by similar stimuli. *Iron deficiency* with or without anemia may be present, and some children with breath-holding spells respond to iron therapy. There is no increased risk of seizure disorders in children who have had a short seizure during a breath-holding spell. Medical conditions to rule-out in breath-holding spells (usually pallid) include seizures, Chiari crisis, dysautonomia, cardiac arrhythmias, and central nervous system lesions.

The first key to the office **management** of temper tantrums and breath-holding spells is to help parents intervene before the child is highly distressed. The parent can be instructed to calmly remind the child of the expected behavior and the potential consequence if the expected behavior does not occur. If the child does not comply, he or she should be placed in time-out for a period approximating 1 min for each year of age. Time-out can be effectively used in children up to age 10 yr. Parents should also be advised to be mindful of their own reactions to their child's tantrum behavior, to avoid an escalation of the child's behavior caused by an angry parental response.

If behavioral measures such as time-out fail, pediatricians must assess other aspects of parent–child interactions, such as the frequency of positive interactions, the consistency of parental responses to child behavior, and the way that parents handle anger, before making further recommendations. In the absence of frequent positive parent–child interactions, time-out may not be effective, and inconsistent responding to problem behavior increases the likelihood of the behavior continuing. Children can be frightened by the intensity of their own angry feelings and by angry feelings they arouse in their parents.

Parents should model the anger control that they want their children to exhibit. Some parents are unable to see that if they lose control themselves, their own angry behavior does not help their children to internalize appropriate behavior. Advising parents to calmly provide simple choices will help the child to feel more in control and to develop a sense of *autonomy*. Providing the child with options also typically helps reduce the child's feelings of anger and shame, which can later have adverse effects on social and emotional development. Providing choice also reduces power struggles between the parent and child and can aid in enhancing the parent–child relationship and building problem-solving skills.

When tantrum behavior, including breath holding, does not respond to parent coaching or is accompanied by head banging or high levels of aggression, referral for a mental health evaluation is indicated. Further evaluation is also recommended if tantrum behavior persists into the latency period and preteen years.

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CHAPTER 44

Lying, Stealing, and Truancy

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Lying

There are various reasons why a child might lie. For children between ages 2 and 4 yr, lying can be used as a method of playing with language. By observing the reactions of parents, preschoolers learn about expectations for honesty in communication. Lying can also be a form of fantasy for children, who describe things as they wish them to be rather than as they are. To avoid an unpleasant confrontation, a child who has not done something that a parent wanted may say that it has been done. The child's sense of time and reason does not permit the realization that this only postpones a confrontation. It is important for the parent to keep in mind that lying behavior in this age-group is rarely malicious or premeditated.

In **older children** , lying is generally an effort to cover up something that they do not want to accept in their own behavior. The lie is invented to achieve a temporary good feeling and to protect the child against a loss of self-esteem. Lying in this age-group is also an attempt to avoid a negative consequence for misbehavior. Older children are also more likely to intentionally leave out critical parts of a story in an attempt to deceive or avoid a negative consequence. **Habitual lying** can also be promoted by poor adult modeling. Many adolescents lie to avoid adults' disapproval. Alternatively, lying may be used as a method of rebellion. **Chronic lying** can occur in combination with several other antisocial behaviors and is a sign of underlying psychopathology or family dysfunction.

Parents should address lying by giving the child a clear message of what is acceptable. Sensitivity and support combined with limit setting are necessary for a successful intervention. While habitual lying can become frustrating for parents, they should be discouraged from making accusations or focusing on catching their child in a lie and instead should work toward creating an atmosphere that makes it easier for their child to tell the truth. Parents should let the child know that telling the truth about a difficult situation will allow the parents to help them better problem-solve the issue at hand. Should a situation arise where the parents are aware of the details, the lie should be confronted while providing the facts of what is known and also stating the desired or expected behavior. If a parent is aware that a child took a cookie without permission and the child denies it, the parent can state, “I am disappointed that you took the cookie without permission. I need you to ask me first.” The child is then reminded of how he can get things that he desires in an acceptable way; an appropriate consequence can then be given. Parents should be encouraged to address the expectations for their home and children in a family meeting or in regular discussions with their child outside the context of the child's lying.

Regardless of age or developmental level, when lying becomes a common way of managing conflict, intervention is warranted. If this behavior cannot be resolved through the parents' understanding of the situation and the child's understanding that lying is not a reasonable alternative, a mental health evaluation is indicated.

Stealing

Many children steal something at some point in their lives. Often, when very young children steal, the behavior is an impulsive action to acquire something they want. A common example is the child who takes candy or a toy from the store shelf. If a parent notices this behavior, the situation is a teaching opportunity and should be used to talk with the child about having to pay for things at the store and not taking things without permission. It should not be expected that a very young child will be aware of all the rules around shopping or stealing. It may also be difficult for a child who has been used to being able to freely take whatever she wants to be aware of all the expected behaviors across different settings. When preschoolers and school-age children begin to steal frequently even after they have been told not to, the behavior may be a response to stressful environmental circumstances and requires further exploration and evaluation.

For some **older children** , stealing can be an expression of anger or revenge for perceived frustrations with parents or other authority figures. In such instances, stealing becomes one way the child and adolescent can manipulate and attempt to control their world. Stealing can also be learned from adults. Some children will report that the behavior is “exciting” for them, and they may also engage in the behavior for peer approval. In some cases, youth living in poverty may engage in the behavior as a survival mechanism.

It is important for parents to help the child undo the theft through some form of restitution. The child should be made to return the stolen articles or render their equivalent either in money that the child can earn or in services. When stealing is part of a pattern of broader conduct problems, referral for a mental health evaluation is warranted.

Truancy

Truancy and running away are never developmentally appropriate. **Truancy** may represent disorganization within the home, caretaking needs of younger siblings, developing conduct problems, or emotional problems including depression or anxiety. When truancy occurs in **younger children** , there are usually psychosocial concerns with the parents or adult caretakers in the home that prevent them from following through with the regular demands for their children. It is important to consider whether parents are struggling with housing and food insecurity, making school attendance less of a priority. Parents with intellectual disability or their own mental health or substance abuse problems may become overwhelmed with managing the home and caring for their children, and thus might not consistently ensure their child gets to school. Also, children might decide to remain at home to take care of parents who are impaired.

Truancy is more common in **older children** and can be a function of multiple factors, including but not limited to learning difficulties, social anxiety, depression, traumatic exposure, bullying, peer pressure, and substance use. In any of these cases, the child should be referred for further evaluation to assess the barriers to returning to school. Best practices for dealing with truancy resulting from *school avoidance* and *anxiety* include addressing the underlying psychological symptoms causing the school avoidance and empowering parents, children, and school staff to work on a consistent plan for a return to school.

Younger children may threaten **running away** out of frustration or a desire to “get back at” parents. Older children who run away are almost always expressing a serious underlying problem within themselves or their family, including violence, abuse, and neglect. Adolescent runaways are at high risk for substance abuse, unsafe sexual activity (e.g., sexual exploitation), and other risk-taking behaviors.

Youth exhibiting truancy or running away should be referred for a mental health evaluation.

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CHAPTER 45

Aggression

Lovern R. Moseley, Keneisha Sinclair-McBride, David R. DeMaso, Heather J. Walter

Aggressive behavior is a serious symptom associated with significant morbidity and mortality. Early intervention is indicated for persistent aggressive behavior, because children may not simply "grow out of it." Aggressive tendencies are heritable, although environmental factors can promote aggression in susceptible children. Both enduring and temporary stressors affecting a family can increase aggressive behavior in children. Aggression in childhood is correlated with both poverty and chaotic family situations, including chronic unemployment, family discord, and exposure to community and domestic violence, criminality, and psychiatric disorders. Children born to teenage mothers and parents with limited resources and support are also at risk. Boys are almost universally reported to be more aggressive than girls. A *difficult temperament* and later aggressiveness are related. When children with temperament difficulties elicit punitive caregiving within the family environment, it can set up a cycle of increasing aggression. Aggressive children often misinterpret social cues in such a way that they perceive hostile intent in ambiguous or benign interactions, and then may react with verbal or physical aggression toward peers and parents.

It is important to differentiate the causes and motives for childhood aggression. Intentional aggression may be primarily instrumental, i.e. to achieve an end, primarily hostile, i.e. to inflict physical or psychological pain, or primarily angry and impulsive. Children who are callous, not empathetic, and often aggressive require mental health intervention. These children are at high risk for suspension from school and eventual school failure. Because learning disorders are common in this population, aggressive children should be referred for screening. Aggressive behavior is often present in a variety of other psychological conditions, including attention-deficit/hyperactivity, oppositional defiant, intermittent explosive, conduct, and disruptive mood dysregulation disorders (see Chapters 39 and 42).

Aggressive behavior in **boys** is relatively consistent from the preschool period through adolescence. Without effective intervention, a boy with a high level of aggressive behavior between 3 and 6 yr of age has a high probability of carrying this behavior into adolescence. The developmental progression of aggression among **girls** is less well studied. Fewer girls show physically aggressive behavior in early childhood. However, **interpersonal coercive behavior** , especially in peer relationships, is seen in girls. This behavior may be related to the development of physical aggression for girls in adolescence (e.g., fighting) or other conduct problems (e.g., stealing).

Children exposed to aggressive models on television, in video games, or in play have more aggressive behavior compared with children not exposed to these models. Parents' anger and aggressive or harsh punishment can model behavior that children may imitate when they are physically or psychologically hurt. Parents' abuse may be transmitted to the next generation by several modes: children imitate aggression that they have witnessed; abuse can cause brain injury, which itself predisposes the child to violence; and internalized rage often results from abuse.

Aggressive behavior in youth is often oriented toward peers through **bullying** (see Chapter 14.1). While it is developmentally normative for children to engage in some teasing behavior, bullying has a more serious tone. Bullying is defined as *unwanted aggressive behavior* in which there is a real or perceived *imbalance of power or strength* between the bully and the victim. Typically, it involves a pattern of behavior repeated over time. Although most often perceived as physical aggression, bullying can take on a variety of forms, including **relational bullying** , the most common form engaged in by girls. **Cyberbullying** is a particular risk during the middle and high school years because of increased exposure and access to multiple social media platforms at this developmental stage. Parents should be advised to closely monitor their child's social media exposure through both smartphone- and internet-based platforms and maintain open communication with their children. Children may bully others because of impulse control and social skills deficits, strong need for power and negative dominance, satisfaction in causing harm to others, or psychological or material rewards. Children who bully are at risk for a variety of negative school and psychological outcomes.

Victims of bullying are particularly at risk for negative outcomes, especially if the behavior is not addressed by adults. Victimization experiences are associated with school avoidance and school dropout, social isolation, somatic symptoms, and increased psychological problems such as depression and anxiety. There have been numerous cases of suicide in children who reported a prior history of being bullied. Should a concern arise around bullying in the school setting, parents should be advised to reach out to their child's teacher, school counselor, and school administrative staff to have the bullying behavior addressed. Many schools also have a *bullying intervention protocol* that can be implemented, and state departments of education have antibullying policies with formal protocols to address concerns. Given the significant psychological risks for victims of bullying, it is essential that victims be referred for mental health evaluation.

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CHAPTER 46

Self-Injurious Behavior

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Self-injurious behavior can be defined as intentional self-inflicted damage to the surface of an individual's body of a type likely to induce bleeding, bruising, or pain, with the expectation that the injury will lead to only minor or moderate physical harm.

Self-injurious behaviors and **cutting** in particular have been documented in children as young as 7 yr, with increasing rates among preteens, adolescents, and young adults. Rates of self-injury are generally higher in females than in males, but cutting and other self-injurious behaviors occur in both sexes. It is estimated that in the United States, approximately 20% or more of adolescents have engaged in some form of self-injury at some point in their lives. There are no significant race, ethnicity, or class differences among youth who engage in self-injurious behavior. Youth identified as those with the highest risk include females age 15-19 and males 20-24, with cutting being the most common form of self-injury. For those youth who engage in self-injurious behavior for the first time, approximately 20% will repeat the behavior within the same year, with cutting being the most likely repeated self-injurious behavior.

Common types of self-injury include cutting, scratching, burning, carving, piercing, hitting or punching, biting, picking at wounds, and digging nails into the skin. The most common areas of injury are the arms, legs, and torso. Females with significant psychiatric symptomatology have been found to cut on parts of their body other than their arms (breasts, genitals, groin, neck). Objects used in cutting include razors, scissors, broken glass, hard plastic, knives, staples, paperclips, or any other object sharp enough to cause injury.

Usually, self-injurious behavior does not occur with the intention of **suicide** but can unintentionally result in significant harm or even death. Although self-injury and suicide are often seen as distinct behaviors, research exploring the attitudes of youth who have engaged in self-injury indicates that there is a strong identification with suicide and death for this population, making self-injurious behavior a significant clinical issue that cannot be ignored or minimized. Some youth engage in repeated self-injury without ever attempting suicide, but studies suggest that 50–75% of adolescents who have a history of self-injurious behavior will make a suicide attempt at some point.

Youth have reported many avenues of exposure before engaging in self-injurious behavior. They often report that they have **friends** who cut to attempt to alleviate negative emotions, so they try it as well. Youth may also share their stories of self-injury on websites and **social media** , possibly contributing to experimentation in those who view the postings. Impressionable youth have also reported learning about cutting for the first time from hearing reports of celebrities who have engaged in the behavior.

Self-injurious behavior is associated with depression, anxiety, peer victimization, social isolation, low self-esteem, substance abuse, eating disorders, impulsivity, poor school performance, delinquency, and neglectful or highly punitive parenting practices, as well as a history of physical or sexual abuse. The behavior may begin as an impulsive response to internal distress for younger adolescents, but for those who are older, the behavior can take on a self-reinforcing function. Youth may feel a sense of *relief* or *mastery* over negative emotions once the behavior has been completed. Some youth report that they engage in self-injurious behavior when feeling overwhelmed or in a state of panic, in order to feel that they can “breathe again,” or when they are feeling numb, the self-injury pain allows them to “feel something” again. Cutting may also serve as a *distraction* from emotional pain, provide a sense of *control* over the body, or be used as a form of *self-punishment* for a perceived wrongdoing. Youth often report that they are unable to resist the urge to engage in the behavior and will continue to feel increasing levels of distress until they have completed the self-injury; they view it as a way to regulate affect. Others also look forward to and enjoy the behavior and tend to plan and think about when they will be able to do it again. Youth who view the cutting behavior as an enjoyable, private, and positive coping strategy tend to have more dependence on the behavior and more resistance to stopping it.

Some adolescents and young adults have engaged in repeated acts of self-injury for years without sharing this behavior with others or without the behavior being known. They will often go to great lengths to keep the behavior a secret.

Some individuals wear bracelets to cover scars on their arms or wear long sleeves in summer to hide the scarring. They report feeling ashamed of the behavior and fear rejection or disappointment from family and friends should they find out. At times, fear of being rejected or a disappointment to others can increase feelings of depression and anxiety and can serve to perpetuate the behavior. There is also a cohort of adolescents who are more open about showing their scars and sharing their behavior with others; their discussion about the behavior can tend to seem provocative. In either case, the behavior is a way to communicate or manage some level of *distress* . Many youth who engage in self-injurious behavior may never be seen in a hospital emergency department or by a mental health professional.

Parents should be advised to monitor their child's and adolescent's media access and be aware of their peer group. Maintaining open communication can assist parents in recognizing an increase in concerning behaviors and patterns of behaviors. Parents should also be encouraged to talk with their child about their use of and exposure to drugs and alcohol, because substance use can accompany involvement in self-injurious behavior. Learning that their child has been engaging in self-injury can be frightening for parents because they are unsure of what to do or why their child is engaging in this behavior. It is important that they seek mental health services for their child. It is also recommended that the adolescent receive a full assessment for risk of suicide when self-injury is a concern.

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) has classified **nonsuicidal self-injury (NSSI)** as a condition requiring further study before consideration for possible placement in forthcoming editions of DSM. Proposed diagnostic criteria include self-inflicted injury without suicidal intent occurring on 5 or more days in the past year, with lack of suicidal intent either stated by the individual or inferred by the individual's repeated engagement in a behavior that he knows is not likely to result in death. The individual expects that the self-injurious behavior will relieve a negative feeling or thought, resolve an interpersonal difficulty, or induce a positive feeling state. The self-injurious behavior is associated with interpersonal difficulties or negative feelings or thoughts, preoccupation with the intended behavior that is difficult to control, or frequent thoughts about the intended behavior. The proposed criteria also specify that the behavior is not socially sanctioned (e.g., body piercing, tattooing) and is not restricted to skin picking or nail biting. Finally, the behavior must be associated with significant *distress* or functional impairment.

Self-injurious behavior in individuals with developmental disabilities often occurs in association with stereotypic movement disorder (see Chapter 37.2).

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CHAPTER 47

Childhood Psychoses

Joseph Gonzalez-Heydrich, Heather J. Walter, David R. DeMaso

Psychosis is a severe disruption of thought, perception, and behavior resulting in **loss of reality testing.** Psychosis can occur as part of a mood disorder, such as major depressive disorder or bipolar I disorder; between mood disorder episodes, as in schizoaffective disorder; or without mood disorder episodes, as in schizophrenia. Transient psychotic episodes can arise during times of psychological or physiologic stress in patients who are vulnerable because of personality, developmental, or genetic disorders. Delusions, hallucinations, disorganized thinking, and grossly disorganized behavior (positive symptoms) are key features that define psychoses across disorders, likely because of shared pathophysiologic mechanisms. Negative symptoms, on the other hand, are most typical of schizophrenia.

Delusions are fixed, unchangeable, false beliefs held despite conflicting evidence. They may include a variety of themes (persecutory, referential, somatic, religious, grandiose). Delusions are considered bizarre if they are clearly implausible. **Hallucinations** are vivid, clear, perceptual-like experiences that occur without external stimulus and have the full force and impact of normal perceptions. They may occur in any sensory modality; auditory hallucinations are the most common. **Disorganized thinking** is typically inferred from an individual's speech (loose associations, tangentiality, or incoherence). **Grossly disorganized behavior** may range from childlike silliness to catatonic behavior. **Negative symptoms** include diminished emotional expression, avolition, alogia (lack of speech), anhedonia (inability to experience pleasure), and asociality. Negative symptoms generally account for a substantial portion of the long-term morbidity associated with schizophrenia.

Given the centrality of hallucinations and delusions in making a diagnosis of a psychotic illness, their differentiation from developmentally normal *fantasy* is essential. When children are *imagining,* they control the fantasy and do not have the perceptual experience of seeing and hearing. When children are *hallucinating,* they do not control the hallucination. Almost two thirds of children will endorse at least 1 psychotic-like experience, most often a hallucination, and when not persistent or accompanied by distress, these experiences are not usually a cause for concern. The largest population-based study to date evaluating psychotic symptoms and neurocognition in youth 11-21 yr old found that those who endorsed more psychotic-like experiences than is typical for their age had reduced accuracy across neurocognitive domains, reduced global functioning, and increased risk of depression, anxiety, behavioral disorders, substance use, and suicidal ideation. Thus, psychotic-like symptoms that are frequent, distressing, and cause impairment signal a need for further evaluation and monitoring; however, only a small minority of these children will develop full-blown psychotic illnesses.

47.1

Schizophrenia Spectrum and Other Psychotic Disorders

Joseph Gonzalez-Heydrich, Heather J. Walter, David R. DeMaso

Schizophrenia spectrum and other psychotic disorders as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) include brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder, psychotic disorder caused by another medical condition, catatonia associated with another mental disorder, catatonic disorder due to another medical condition, unspecified catatonia, delusional disorder, schizotypal personality disorder, and other specified/unspecified schizophrenia spectrum and other psychotic disorders.

Description

The **schizophrenia spectrum** and other psychotic disorders are primarily characterized by the active (or positive) symptoms of psychosis, specifically delusions, hallucinations, disorganized speech, or grossly disorganized or catatonic behavior. **Brief psychotic disorder** is characterized by the duration of 1 or more of these symptoms for at least 1 day but <1 mo followed by complete resolution. Emergence of symptoms may or may not be preceded by an identifiable stressor (Table 47.1). Although brief, the level of impairment in this disorder may be severe enough that supervision is required to ensure that basic needs are met and the individual is protected from the consequences of poor judgment and cognitive impairment.

Table 47.1

DSM-5 Diagnostic Criteria for Brief Psychotic Disorder

A. Presence of 1 (or more) of the following symptoms. At least 1 of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.

   Note: Do not include a symptom if it is a culturally sanctioned response.

B. Duration of an episode of the disturbance is at least 1 day but less than 1 mo, with eventual full return to premorbid level of functioning.

C. The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

With marked stressor(s) (brief reactive psychosis): If symptoms occur in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the individual's culture.

Without marked stressor(s) : If the symptoms do not occur in response to events that, singly or together, would be would be markedly stressful to almost anyone in similar circumstances in the individual's culture.

With postpartum onset : If onset is during pregnancy or within 4 wk postpartum.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, p 94.

If 2 or more psychotic symptoms persist from 1 mo up to 6 mo, the condition is called **schizophreniform disorder** (Table 47.2). To meet DSM-5 criteria for **schizophrenia** , 2 or more psychotic symptoms must have been present for a significant time during 1 mo (unless suppressed by treatment), and the level of psychosocial functioning must be markedly below the level achieved before the onset (or there is failure in children to achieve the expected level of functioning). In addition, there must be continuous signs of the disturbance (prodromal, active, or residual symptoms) for at least 6 mo (Table 47.3).

Table 47.2

DSM-5 Diagnostic Criteria for Schizophreniform Disorder

A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least 1 of these must be (1), (2), or (3):
    1. Delusions.
    2. Hallucinations.
    3. Disorganized speech (e.g., frequent derailment or incoherence).
    4. Grossly disorganized or catatonic behavior.
    5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. An episode of the disorder lasts at least 1 mo but less than 6 mo. When the diagnosis must be made without waiting for recovery, it should qualified as “provisional.”

C. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

D. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

With good prognostic features : This specifier requires the presence of at least 2 of the following features: onset of prominent psychotic symptoms within 4 wk of the first noticeable change in usual behavior or functioning; confusion or perplexity; good premorbid social and occupational functioning; and absence of blunted or flat affect.

Without good prognostic features : This specifier is applied if 2 or more of the above features have not been present.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, pp 96–97.

Table 47.3

DSM-5 Diagnostic Criteria for Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least 1 of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in 1 or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 mo. This 6 mo period must include at least 1 mo of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by 2 or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least a month (or less if successfully treated).

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 99–100.

Individuals with schizophrenia can display inappropriate affect, dysphoric mood, disturbed sleep patterns, and lack of interest in eating, or food refusal. Depersonalization, derealization, somatic concerns, and anxiety and phobias are common. Cognitive deficits are observed, including decrements in declarative memory, working memory, language function, and other executive functions, as well as slower processing speed. These individuals may have no insight or awareness of their disorder, which is a predictor of nonadherence to treatment, higher relapse rates, and poorer illness course. Hostility and aggression can be associated with schizophrenia, although spontaneous or random assault is uncommon. Aggression is more frequent for younger males and for individuals with a past history of violence, non-adherence with treatment, substance abuse, and impulsivity.

The essential features of schizophrenia are the same in childhood as in adulthood, but it is more difficult to make the diagnosis. In children, delusions and hallucinations may be less elaborate, visual hallucinations may be more common, and disorganized speech may be better attributed to an autism spectrum or communication disorder. In a review of 35 studies of youth with schizophrenia, the most frequent psychotic symptoms were auditory hallucinations (82%), delusions (78%), thought disorder (66%), disorganized or bizarre behavior (53%), and negative symptoms (50%).

Epidemiology

Brief psychotic disorders have been reported to account for 9% of first-onset psychosis in the United States, with a 2 : 1 ratio in favor of females. The incidence of schizophreniform disorders in the United States appears as much as 5-fold less than that of schizophrenia. The lifetime prevalence of schizophrenia is approximately 0.3–0.7%, although variations are reported by race/ethnicity, across countries, and by geographic origin for immigrants. The male:female ratio is approximately 1.4 : 1. Males generally have worse premorbid adjustment, lower educational achievement, more prominent negative symptoms, and more cognitive impairment than females.

Clinical Course

Brief psychotic disorder most often appears in adolescence or early adulthood, with the average age of onset in the mid-30s, but can occur throughout the life span. A diagnosis of brief psychotic disorder requires full remission within 1 mo of onset and gradual return to premorbid level of function. The age of onset of schizophreniform disorder is similar to that of schizophrenia. Recovery from an episode of the disorder is within 6 mo; however, about two thirds of patients relapse and eventually receive a diagnosis of schizophrenia or schizoaffective disorder. Abrupt onset, confusion, absence of blunted affect, and good premorbid functioning predict a better outcome in schizophreniform disorder.

Schizophrenia typically develops between the late teens and the mid-30s; onset before adolescence is rare. The peak age at onset for the first psychotic episode is in the early to mid-20s for males and in the late 20s for females. The onset may be abrupt or insidious, but the majority of individuals manifest a slow and gradual development of symptoms, with about half of individuals complaining of depressive symptoms. The predictors of course and outcome are largely unexplained. The course appears to be favorable in approximately 20% of cases, and a small number of individuals are reported to recover completely. However, many remain chronically ill, with exacerbations and remissions of active symptoms, whereas others experience progressive deterioration. Most individuals diagnosed with schizophrenia require daily living supports. Positive symptoms tend to diminish over time, and negative symptoms are the most persistent, along with cognitive deficits.

Differential Diagnosis

The differential diagnosis for the psychotic disorders is broad and includes reactions to substances/medications (dextromethorphan, LSD, hallucinogenic mushrooms, psilocybin, peyote, cannabis, stimulants, inhalants; corticosteroids, anesthetics, anticholinergics, antihistamines, amphetamines); medical conditions causing psychotic-like symptoms (Table 47.4); and other psychiatric disorders (depressive, bipolar, obsessive-compulsive, factitious, body dysmorphic, posttraumatic stress, autism spectrum, communication, personality). The differential diagnosis can be difficult because many conditions that can be mistaken for psychosis also increase the risk for it.

Table 47.4

Select Neurologic and Systemic Causes of Depression and/or Psychosis

CATEGORY	DISORDERS
Head trauma	Traumatic brain injury Subdural hematoma
Infectious	Lyme disease Prion diseases Neurosyphilis Viral infections/encephalitides (HIV infection/encephalopathy, herpes encephalitis, cytomegalovirus. Epstein-Barr virus) Whipple disease Cerebral malaria Systemic infection
Inflammatory	Autoimmune encephalitis Celiac disease

	Systemic lupus erythematosus Sjögren syndrome Temporal arteritis Hashimoto encephalopathy Sydenham chorea Sarcoidosis
Neoplastic	Primary or secondary cerebral neoplasm Systemic neoplasm Paraneoplastic encephalitis
Endocrine or acquired metabolic	Hepatic encephalopathy Uremic encephalopathy Dialysis dementia Hypo/hyperparathyroidism Hypo/hyperthyroidism Addison disease, Cushing disease Postpartum Vitamin deficiency: vitamin B_{12} , folate, niacin, vitamin C. thiamine Gastric bypass–associated nutritional deficiencies Hypoglycemia Hyponatremia
Vascular	Stroke Cerebral autosomal dominant aneriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Degenerative	Progressive supranuclear palsy Huntington disease Corticobasal ganglionic degeneration Multisystem atrophy, striatonigral degeneration, olivopontocerebellar atrophy Idiopathic basal ganglia calcifications, Fahr disease Neuroacanthosis Neurodegeneration with brain iron accumulation (NBIA) Adrenoleukodystrophy Metachromatic leukodystrophy
Demyelinating, dysmyelinating	Multiple sclerosis Acute disseminated encephalomyelitis Adrenoleukodystrophy Metachromatic leukodystrophy
Inherited metabolic	Wilson disease Posterior hom syndrome Tay-Sachs disease Neuronal ceroid lipofuscinosis Niemann-Pick disease type C Acute intermittent porphyria Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) Cerebrotendinous xanthomatosis Homocystinuria Ornithine transcarbamylase deficiency
Syndromes	Williams Prader-Willi Fragile X Deletion 22q11.2 ROHHAD
Epilepsy	Ictal Interictal Postictal Forced normalization

	Postepilepsy surgery Lafora progressive myoclonic epilepsy
Medications	Analgesics Androgens (anabolic steroids) Antiarrhythmics Anticonvulsants Anticholinergics Antibiotics Antihypertensives Antineoplastic agents β-Blocking agents Corticosteroids Cyclosporin Dopamine agonists Oral contraceptives Sedatives/hypnotics Selective serotonin reuptake inhibitors (SSRIs) (serotonin syndrome)
Drugs of abuse	Alcohol Amphetamines Cocaine Hallucinogens Marijuana and synthetic cannabinoids Methylenedioxymethamphetamine (MDMA, Ecstasy) Phencyclidine
Drug withdrawal syndromes	Alcohol Barbiturates Benzodiazepines Amphetamines SSRIs
Toxins	Heavy metals Inhalants
Other	Normal-pressure hydrocephalus Ionizing radiation Decompression sickness

ROHHAD, Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, autonomic dysregulation.

Modified from Perez DL, Murray ED, Price BH: Depression and psychosis in neurological practice. In Daroff RB, Jankovic J, Mazziotta JC, et al, editors: *Bradley's neurology in clinical practice,* 7th ed, Philadelphia, 2015, Elsevier.

Autoimmune encephalitis caused by anti–*N* -methyl-D -aspartate (NMDA) receptor or other autoantibodies may manifest with psychosis, anxiety, depression, agitation, aggression, delusions, catatonia, visual or auditory hallucinations, disorientation, and paranoia in combination with sleep disturbances, autonomic dysfunction (hypoventilation), dyskinesias, movement disorders, seizures, memory loss, and a depressed level of consciousness (Fig. 47.1). The electroencephalogram (EEG), cerebrospinal fluid (CSF), and MRI are usually, but not always, abnormal. The constellation of psychosis and encephalitic features should suggest the diagnosis, although at presentation, behavioral problems may be the dominant feature (see Chapter 616.4).

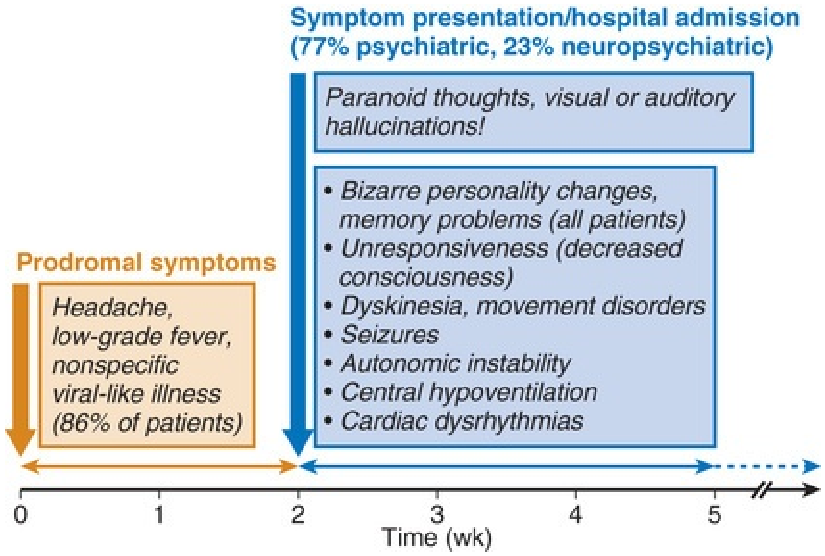
Symptom presentation/hospital admission
(77% psychiatric, 23% neuropsychiatric)
Paranoid thoughts, visual or auditory hallucinations!
• Bizarre personality changes, memory problems (all patients)
• Unresponsiveness (decreased consciousness)
• Dyskinesia, movement disorders
• Seizures
• Autonomic instability
• Central hypoventilation
• Cardiac dysrhythmias
Prodromal symptoms
Headache, low-grade fever, nonspecific viral-like illness (86% of patients)
0
1
2
3
4
5
Time (wk)

FIG. 47.1 **Clinical characteristics of patients with anti–NMDA receptor encephalitis. (Modified from Wandinger KP, Saschenbrecker S, Stoecker W, Dalmau J: Anti-NMDA-receptor encephalitis: a severe multistage, treatable disorder presenting with psychosis, J Neuroimmunol 231:86-91, 2011, Fig 2.)**

Determining when identifiable medical conditions are causing delirium with prominent psychotic symptoms may be difficult (Table 47.5 and Table 47.6). In general, delirium due to medical causes is often associated with abnormalities in vital signs and the neurologic examination (including level of consciousness). A positive family or prior personal history of serious psychiatric illness is less likely. When psychotic symptoms are caused by identifiable medical conditions, there are often impairments in attention, orientation, recent memory, and intellectual function. Hallucinations may be caused by medical illness, but are often tactile, visual, or olfactory, whereas auditory hallucinations are more common in primary psychotic disorders. Patients whose hallucinations are caused by medical illness are more likely than patients with primary psychotic disorders to be aware that the hallucinations do not represent reality.

Table 47.5

Special Problems in the Differential Diagnosis of Delirium*

CLINICAL FEATURE	DELIRIUM	DEMENTIAS	SCHIZOPHRENIA	DEPRESSION

Course	Acute onset; hours, days, or more	Insidious onset, months or years, progressive	Insidious onset, ≥6 mo, acute psychotic phases	Insidious onset, at least 2 wk, often months
Attention	Markedly impaired attention and arousal	Normal early; impairment later	Normal to mild impairment	Mild impairment
Fluctuation	Prominent in attention arousal; disturbed day/night cycle	Prominent fluctuations absent; lesser disturbances in day/night cycle	Absent	Absent
Perception	Misperceptions; hallucinations, usually visual, fleeting; paramnesia	Perceptual abnormalities much less prominent; paramnesia	Hallucinations, auditory with personal reference	May have mood-congruent hallucinations
Speech and language	Abnormal clarity, speed, and coherence; disjointed and dysarthric; misnaming; characteristic dysgraphia	Early anomia; empty speech; abnormal comprehension	Disorganized, with a bizarre theme	Decreased amount of speech
Other cognition	Disorientation to time, place; recent memory and visuospatial abnormalities	Disorientation to time, place; multiple other higher cognitive deficits	Disorientation to person; concrete interpretations	Mental slowing; indecisiveness; memory retrieval difficulty
Behavior	Lethargy or delirium; nonsystematized delusions; emotional lability	Disinterested; disengaged; disinhibited; delusions and other psychiatric symptoms	Systematized delusions; paranoia; bizarre behavior	Depressed mood; anhedonia; lack of energy; sleep and appetite disturbances
Electroencephalogram	Diffuse slowing; low-voltage fast activity; specific patterns	Normal early; mild slowing later	Normal	Normal

* The characteristics listed are the usual ones and not exclusive.

From Mendez MF, Padilla CR: Delirium. In Daroff RB, Jankovic J, Mazziotta JC, et al, editors: *Bradley's neurology in clinical practice,* 7th ed, Philadelphia, 2015, Elsevier.

Table 47.6

Features Suggesting Neurologic Disease in Patients With Psychiatric Symptoms

Atypical Psychiatric Features

Late or very early age of onset
Acute or subacute onset
Lack of significant psychosocial stressors
Catatonia

Diminished comportment
Cognitive decline
Intractability despite adequate therapy
Progressive symptoms

History of Present Illness

New or worsening headache
Inattention
Somnolence
Incontinence
Focal neurologic complaints such as weakness, sensory changes, incoordination, or gait difficulty
Neuroendocrine changes
Anorexia/weight loss

Patient Medical History

Risk factors for cerebrovascular disease or central nervous system infections
Malignancy
Immunocompromised status
Significant head trauma
Seizures
Movement disorder
Hepatobiliary disorders
Abdominal crises of unknown cause
Biologic relatives with similar diseases or complaints

Unexplained Diagnostic Abnormalities

Screening laboratory tests
Neuroimaging studies or possibly imaging of other systems
Electroencephalogram
Cerebrospinal fluid

From Perez DL Murray ED, Price BH: Depression and psychosis in neurological practice. In Daroff RB, Jankovic J, Mazziotta JC, editors: *Bradley's neurology in clinical practice*, 7th ed, Philadelphia, 2015, Elsevier.

The diagnosis of a psychotic disorder should be made only after other explanations for the observed symptoms have been thoroughly considered. Mistakenly diagnosing psychosis when it is not present can lead to inappropriate use of antipsychotics with all their attendant risks, and mistakenly dismissing psychotic symptoms as nonpsychotic manifestations of, for example, autism or trauma can lead to long delays in treatment of the psychosis. The persistence, frequency, and form of possible psychotic symptoms, as well the degree of accompanying distress and functional regression, need to be considered in determining the likelihood of an underlying psychotic pathophysiology.

Comorbidity

In a review of 35 studies of youth with schizophrenia, rates of comorbidity approximated 34% for posttraumatic stress disorder, 34% for attention-deficit/hyperactivity and/or disruptive behavior disorders, and 32% for substance abuse/dependence.

Sequelae

Follow-up studies of early-onset schizophrenia suggest moderate to severe impairment across the life span. Poor outcome is predicted by low premorbid functioning, insidious onset, higher rates of negative symptoms, childhood onset, and low intellectual functioning. When followed into adulthood, youth with schizophrenia demonstrated greater social deficits, lower levels of employment, and were less likely to live independently, relative to those with other childhood psychotic disorders.

Approximately 5–6% of individuals with schizophrenia die by suicide, approximately 20% attempt suicide on one or more occasions, and many more have suicidal ideation. Life expectancy is reduced in individuals with schizophrenia because of associated medical conditions; a shared vulnerability for psychosis and medical disorders may explain some of the medical comorbidity of schizophrenia.

Etiology and Risk Factors

Etiologic evidence for schizophrenia supports a neurodevelopmental and neurodegenerative model, with multiple genetic and environmental exposures playing important roles. It has been hypothesized that although psychotic disorders likely have their origins in early development, it is not until youth are in their mid-teens that the underlying neural structures manifest the disabling functional deficits and resultant psychotic symptoms.

Genetic Factors

The lifetime risk of developing schizophrenia is 5-20 times higher in first-degree relatives of affected probands than the general population. Concordance rates of 40–60% and 5–15% have been reported, respectively, in monozygotic and dizygotic twins. Genome-wide association studies have implicated variants in >100 different genes as leading to statistically significant but small increases in the risk for schizophrenia (odds ratios of about 1.4). The risk for schizophrenia increases with increasing burden of these common risk alleles, and approximately 30% of the risk of schizophrenia is attributable to common genetic variants. Rare variants of larger effect have also been implicated as increasing risk. Some rare copy number variants where stretches of the genome encompassing many genes are either duplicated or deleted have been shown to increase the risk of schizophrenia more markedly, with odds ratios of 2-25. Although these copy number variants, including such “hot spots” as 1q21.1, 15q13.3, and 22q11.2, may be responsible for 0.5–1.0% of typical adolescent/adult-onset schizophrenia, data indicate that they are responsible for about 12% of schizophrenia cases with onset before age 13 yr. There is increasing evidence that the same genetic risk alleles impart risk for multiple disorders (e.g., depression).

Environmental Factors

In utero exposure to maternal famine, advanced paternal age, prenatal infections, obstetric complications, marijuana use, and immigration have been hypothesized to contribute to the development of schizophrenia. Environmental exposures may mediate disease risk through direct neurologic damage, gene-environment interactions, epigenetic effects, or de novo mutations. There is no evidence that psychological or social factors alone cause schizophrenia. Rather, environmental factors potentially interact with biologic risk factors to mediate the timing of onset, course, and severity of the disorder. Expressed emotion within the family setting can influence the onset and exacerbation of acute episodes and relapse rates.

Neuroanatomic Abnormalities

Increased lateral ventricle volumes, along with reductions in hippocampus, thalamus, and frontal lobe volumes, have been reported in schizophrenia. Youth in particular have reductions in gray matter volumes and reduced cortical folding. Neurotransmitter systems, particularly central nervous system dopamine circuits, are hypothesized to have a key role in the pathophysiology of schizophrenia. The dopamine hypothesis is derived in part from the identification of D_2 receptor blockade as the mechanism for the action of antipsychotic medications.

Prevention

There has been significant interest in prospectively identifying youth at risk for schizophrenia spectrum and other psychotic disorders in an effort to provide early intervention before the development of a full-blown psychotic disorder. Various names, including *attenuated psychosis syndrome* (APS), *clinical high risk* (CHR), psychosis risk syndrome, ultrahigh risk, at-risk mental state, and prodromal stage, have been used to describe patients who present with troubling symptoms suggestive of early psychosis.

APS or CHR is characterized by the presence of delusions, hallucinations, or disorganized speech in attenuated forms. Affected individuals may express a variety of unusual or odd beliefs or may have unusual perceptual experiences, including frank hallucinations, but retain insight into their unreality; their speech may be generally understandable but vague; and their behavior may be unusual but not grossly disorganized. Individuals who had been socially active may become withdrawn. The symptoms are described as present at least once per week for the past month and have begun or worsened over the past year. Although the symptoms are less severe and more transient than in a psychotic disorder, 20–40% with these attenuated symptoms appear to go on to a psychotic disorder within several years of symptom presentation. There is evidence that premorbid lower cognitive and social skills as well as a history of substance abuse contribute to the risk of developing a full-blown psychotic disorder in individuals with APS/CHR.

Some evidence indicates that antipsychotic medication may delay conversion of attenuated to full-blown psychosis and ameliorate attenuated symptoms in active treatment, yet there appear to be no lasting effects after the medication is withdrawn. Additionally, the known adverse effects of antipsychotics argue against their being used broadly to prevent psychosis in patients with APS/CHR, given that about two thirds of them do not go on to develop a psychotic disorder.

Antidepressants have been associated with symptomatic improvement in adolescents with APS/CHR. Psychological interventions, including social skills, cognitive, and interaction training programs, as well as educational family interventions and cognitive-behavioral therapy (CBT), are reported to improve symptoms and psychosocial functioning in youth with early symptoms and decrease the rate of conversion to psychosis.

Despite improvements in diagnostic predictive validity, significant concern remains regarding a high *false-positive* rate (identifying an individual as prodromal who does not go on to develop psychosis) that may cause individuals to be stigmatized or exposed to unnecessary treatment. In this context, youth with early symptoms suggestive of psychosis should be referred to a child and adolescent psychiatrist or other qualified mental health specialist, and/or a specialized research program.

Screening/Case Finding

Pediatric practitioners can make general inquiries of youth and their parents regarding problems with thinking or perceptions. For the older youth, such questions as “Does your mind ever play tricks on you?,” “Do you hear voices talking to you when no one is there?,” and “Does your mind ever feel confused?” can help elicit symptoms. For younger children, the clinician must ensure that the child understands the questions. True psychotic symptoms are generally confusing to the individual. Highly descriptive, detailed, organized, and situation-specific reports are less likely to represent true psychosis. Overt evidence of psychosis is not always present on mental status examination, but in the absence of this, the validity of symptom reports should be scrutinized. Youth presenting with possible psychosis warrant assessment and treatment by a child and adolescent psychiatrist or other qualified mental health specialist.

Assessment

The diagnostic assessment of schizophrenia in youth is uniquely complicated, and misdiagnosis is common. Most children who report hallucinations do not meet criteria for schizophrenia, and many do not have a psychotic illness. The persistence, frequency, and form of possible psychotic symptoms; the presence of distress; functional impairment; and insight need to be considered in arriving at a diagnosis. Expertise in childhood psychopathology and experience in assessing reports of psychotic symptoms in youth are important prerequisite skills for clinicians evaluating youth for possible psychosis. Comprehensive diagnostic assessments, which reconcile mental status findings with the rigorous application of diagnostic criteria, help improve accuracy.

There are no neuroimaging, psychological, or laboratory tests that establish a diagnosis of schizophrenic spectrum disorders. The medical evaluation focuses on ruling out nonpsychiatric causes of psychosis, while also establishing baseline laboratory parameters for monitoring medication therapy. Routine laboratory testing typically includes blood counts, basic metabolic panel, and liver, renal, and thyroid function. More extensive evaluation is indicated for atypical presentations, such as a gross deterioration in cognitive and motor abilities, focal neurologic symptoms, or delirium. Neuroimaging may be indicated when neurologic symptoms are present, or an EEG may be indicated for a clinical history suggestive of seizures. Toxicology screens are indicated for acute onset or exacerbations of psychosis, when exposure to drugs of abuse cannot be ruled out. Genetic testing is indicated if there are associated dysmorphic or syndromic features. Tests to rule out specific syndromes or diseases are indicated for clinical presentations suggestive of a specific syndrome (e.g., amino acid screens for inborn errors of metabolism, ceruloplasmin for Wilson disease, porphobilinogen for acute intermittent porphyria, NMDA receptor antibodies for autoimmune encephalitis). Neuropsychological testing cannot establish the diagnosis but may be important for documenting cognitive deficits for academic planning.

Treatment

It is important to recognize hallmark phases in the assessment and management of schizophrenia. In the **prodrome phase** , most patients experience functional deterioration (i.e., social withdrawal, idiosyncratic preoccupations, unusual behaviors, academic failure, deteriorating self-care skills, and/or dysphoria) before the onset of psychotic symptoms. The **acute phase** is characterized by prominent positive symptoms and deterioration in functioning. The **recuperative/recovery phase** is marked by a several-month period of impairment and predominantly negative symptoms. The **residual phase** (if reached) has no positive symptoms, although negative symptoms may cause continued impairment.

Treatment goals include decreasing psychotic symptomatology, directing the child toward a developmentally typical trajectory, and reintegrating the child into the home and community. Children and families facing schizophrenia spectrum disorders require an array of mental health services to address their psychological, social, educational, and cultural needs. Given the insidious onset and chronic course of these disorders, the patient must be followed longitudinally, with periodic reassessment to hone diagnostic accuracy and tailor services to meet the patient's and family's needs. Integrated psychopharmacologic, psychotherapeutic, psychoeducational, and case management services are often necessary.

Psychoeducation about the illness with an assessment of the potential role of stigma in treatment participation is critical for improving adherence with treatment recommendations. Assessing a child's strengths and vulnerabilities as well as available environmental resources is critical in devising an effective treatment plan. School and community liaison work to develop and maintain a day-to-day schedule for the patient is important. Specialized educational programs should be considered within the school system. Cognitive remediation has led to some promising gains in planning ability and cognitive flexibility. Effective and collaborative communication among the family, the pediatrician, a child and adolescent psychiatrist, and other mental health providers increases the potential for the patient's optimal functioning.

Pharmacotherapy

First-generation (typical) and second-generation (atypical) antipsychotic medications have been shown to be effective in reducing psychotic symptoms. These antipsychotics appear to outperform placebo and to have approximately equal effectiveness, except for *ziprasidone* and *clozapine,* which may be less and more effective than the others, respectively. Risperidone, aripiprazole, quetiapine, olanzapine, and lurasidone are FDA-approved second-generation antipsychotics for treating schizophrenia in patients 13 yr and older, and *paliperidone* for those 12 yr and older. Several of the first-generation antipsychotics are also FDA approved for children and adolescents. The choice of which agent to use first is typically based on U.S. Food and Drug Administration approval status, side effect profile, patient and family preference, clinician familiarity, and cost. *Depot* antipsychotics have not been studied in pediatric age groups and have inherent risks with long-term exposure to side effects. Although clozapine is effective in treating both positive and negative symptoms, its risk for agranulocytosis and seizures limits its use to those patients with treatment-resistant disorders. Ziprasidone and paliperidone are associated with QT prolongation; this finding along with the inferior effectiveness of ziprasidone limits its use with children and adolescents.

Most patients require long-term treatment and are at significant risk for relapse if their medication is discontinued, and more than three quarters of youth with schizophrenia discontinue their medication within 180 days. As such, the goal is to maintain the medication at the lowest effective dose to minimize potential adverse events. Many patients will continue to experience some degree of positive or negative symptoms, requiring ongoing treatment. Patients should maintain regular physician contact to monitor symptom course, side effects, and adherence.

Electroconvulsive therapy (ECT) may be used with severely impaired adolescents if medications are either not helpful or cannot be tolerated. It has not been systematically studied in children.

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47.2

Psychosis Associated With Epilepsy

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Schizophrenia spectrum and other psychotic disorders include psychotic disorder due to another medical condition (Table 47.7). **Psychosis associated with epilepsy** has been reported in children and adults. Also called *schizophrenic-like psychosis of epilepsy*, the disorder manifests with delusions or hallucinations associated with poor insight. The characterization is complicated by the fact that anticonvulsant drugs can cause psychosis and antipsychotic drugs can lower the seizure threshold, producing seizures.

Table 47.7

DSM-5 Diagnostic Criteria for Psychotic Disorder Due to Another Medical Condition

A. Prominent hallucinations or delusions.

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiologic consequence of another medical condition.

C. The disturbance is not better explained by another mental disorder.

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify whether:

With delusions : If delusions are the predominant symptom.

With hallucinations : If hallucinations are the predominant symptom.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 115–116.

Psychosis associated with epilepsy can be further differentiated into ictal, interictal, and postictal psychosis. Ictal-induced psychosis is a form of **nonconvulsive status epilepticus** , usually complex partial status that can last for hours to days and is associated with periods of impaired consciousness. Brief interictal psychosis can last days to weeks and is associated with paranoia, delusions, and auditory hallucinations. Chronic interictal psychosis resembles schizophrenia and manifests with paranoia, visual hallucinations, and catatonia. Postictal psychosis is the most common type (observed in 2–7% of patients with epilepsy) and lasts up to 1 wk and then spontaneously remits.

The diagnosis requires a strong index of suspicion and EEG monitoring. Treatment requires appropriate anticonvulsant drugs and, if the psychosis persists, initiating low-dose antipsychotic medication.

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47.3

Catatonia in Children and Adolescents

Joseph Gonzalez-Heydrich, Heather J. Walter, David R. DeMaso

Catatonia is a poorly defined state presenting as an unusual manifestation of decreased or increased muscle tone and decreased responsiveness (although agitation may be present) occurring in association with a broad array of conditions affecting children, adolescents, and adults. These conditions include psychosis, autism spectrum disorder, developmental disorders, drug-induced conditions, mood disorders, and a wide range of medical disorders (Table 47.8). Not surprising given its ill-defined nature, the prevalence of catatonia in children and adolescents is unknown, although it is generally believed to be significantly underdiagnosed. Recognition of catatonia by a clinician is important because the disorder is generally very responsive to treatment with benzodiazepines and/or ECT.

Table 47.8

Conditions Associated With Catatonia

- Psychotic disorders
  - Paranoid schizophrenia, catatonic schizophrenia, psychosis, autism, Prader-Willi syndrome, intellectual impairment
- Mood disorders
  - Bipolar disorder: manic or mixed episodes
- Major depressive disorder
- Medical conditions
  - Endocrine abnormalities, infections, electrolyte imbalances, mutations in *SCN2A* gene
- Neurologic conditions
  - Epilepsy, strokes, traumatic brain injury, multiple sclerosis,

	infectious and autoimmune encephalitis
Drugs	Withdrawal: benzodiazepines, L -dopa, gabapentin Overdose: LSD, phencyclidine (PCP), cocaine, MDMA (Ecstasy), disulfiram, levetiracetam

Adapted from Weder ND, Muralee S, Penland H, Tampi RR: Catatonia: a review, *Ann Clin Psychiatry* 20(2):97–107, 2008, Table 2.

Diagnosis and Treatment

Catatonia is defined as 3 or more of the 12 symptoms listed in Table 47.9 . An important next step is the evaluation (and possible elimination) of medications being administered to the child for their potential to induce catatonic symptoms, a not-infrequent side effect of many medical and psychiatric medications. Of particular importance, antipsychotics should be discontinued because they have been associated with an increased incidence of malignant catatonia or neuroleptic malignant syndrome.

Table 47.9

DSM-5 Diagnostic Criteria for Catatonic Disorder Due to Another Medical Condition

A. The clinical picture is dominated by 3 (or more) of the following symptoms:

1. Stupor (i.e., no psychomotor activity; not actively relating to environment).
2. Catalepsy (i.e., passive induction of a posture held against gravity).
3. Waxy flexibility (i.e., slight, even resistance to positioning by examiner).
4. Mutism (i.e., no, or very little, verbal response [*Note:* not applicable if there is an established aphasia]).
5. Negativism (i.e., opposing or not responding to instructions or external stimuli).
6. Posturing (i.e., spontaneous and active maintenance of a posture

against gravity).

7. Mannerism (i.e., odd, circumstantial caricature of normal actions).
8. Stereotypy (i.e., repetitive, abnormally frequent, non–goal-directed movements).
9. Agitation, not influenced by external stimuli.
10. Grimacing.
11. Echolalia (i.e., mimicking another's speech).
12. Echopraxia (i.e., mimicking another's movements).

B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiologic consequence of another medical condition.

C. The disturbance is not better explained by another mental disorder (e.g., a manic episode).

D. The disturbance does not occur exclusively during the course of a delirium.

E. The disturbance causes clinically significant distress or impairment in social, occupational, or other areas of functioning.

Coding note: Include the name of the medical condition in the name of the mental disorder (e.g., F06.1 catatonic disorder due to hepatic encephalopathy). The other medical condition should be coded and listed separately immediately before the catatonic disorder due to the medical condition (e.g., K71.90 hepatic encephalopathy; F06.1 catatonic disorder due to hepatic encephalopathy).

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 120–121.

Benzodiazepines (typically lorazepam) and ECT are effective in adults and appear to be effective in children. Fig. 47.2 shows a treatment algorithm using a lorazepam challenge test (oral, intravenous, or intramuscular lorazepam, 1-2 mg). If the challenge test does reverse symptoms, increasing doses of lorazepam are indicated, with careful monitoring to avoid side effects. ECT may be indicated alone (if no improvement with lorazepam) or in combination with lorazepam if some but incomplete improvement is noted.

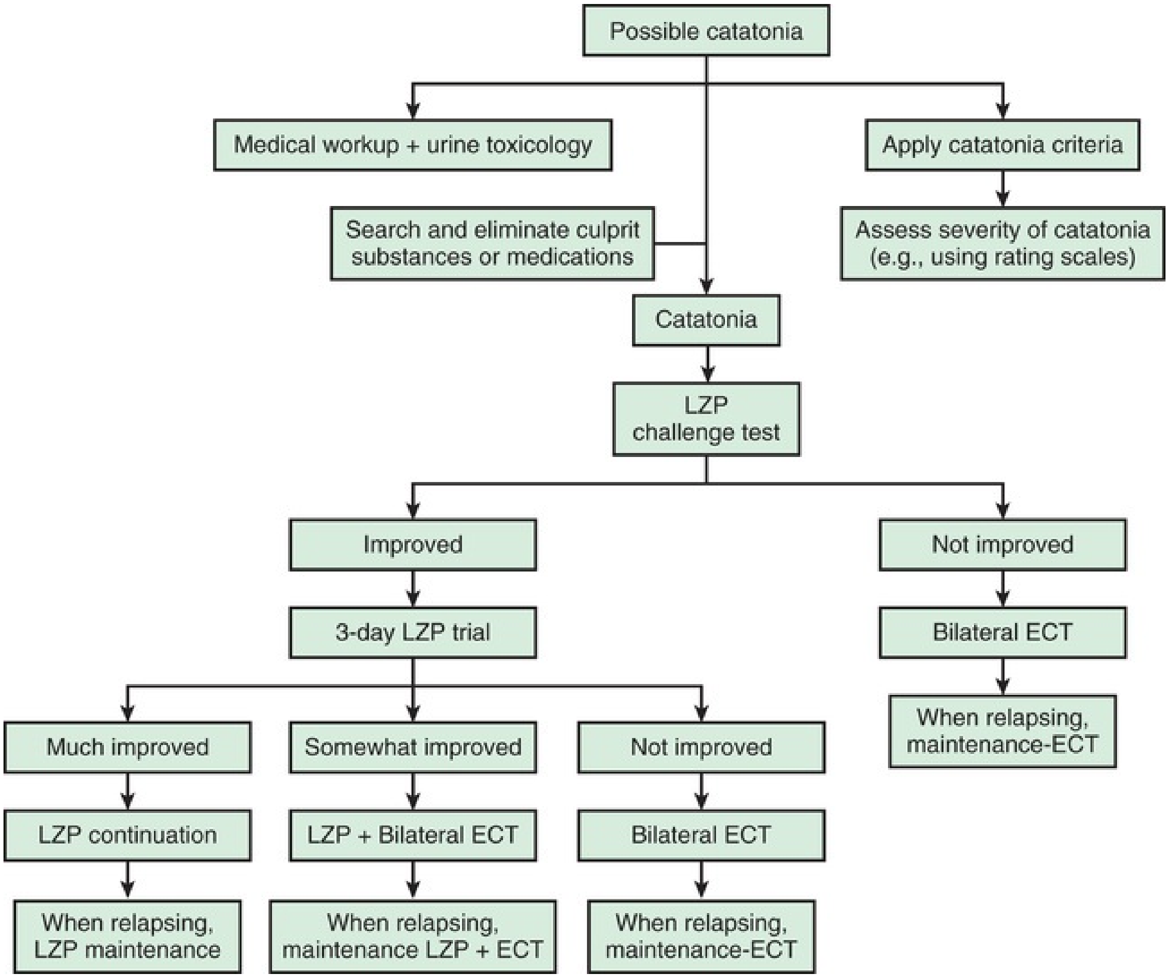
Possible catatonia
Medical workup + urine toxicology
Apply catatonia criteria
Search and eliminate culprit substances or medications
Assess severity of catatonia (e.g., using rating scales)
Catatonia
LZP challenge test
Improved
Not improved
3-day LZP trial
Bilateral ECT
When relapsing, maintenance-ECT
Much improved
Somewhat improved
Not improved
LZP continuation
LZP + Bilateral ECT
Bilateral ECT
When relapsing, LZP maintenance
When relapsing, maintenance LZP + ECT
When relapsing, maintenance-ECT

FIG. 47.2 **Evaluation, diagnosis, and treatment of catatonia in children and adolescents. ECT, Electroconvulsive therapy; LZP, lorazepam. (From Dhossche DM, Wilson C, Wachtel LE: Catatonia in childhood and adolescents: implications for the DSM-5, Prim Psychiatry 17(4):23–26, 2010.)**

The outlook for catatonia is greatly impacted by that of the associated condition(s). The long-term outcome for patients treated with ECT is unknown, but mortality rates in catatonic patients declined after the introduction of ECT in treatment.

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47.4

Acute Phobic Hallucinations of Childhood

Joseph Gonzalez-Heydrich, Heather J. Walter, David R. DeMaso

Among adults, hallucinations are viewed as synonymous with “psychosis” and as harbingers of serious psychopathology. In children, hallucinations can be part of normal development and more often than in adults can be associated with nonpsychotic psychopathology, psychosocial stressors, drug intoxication, or physical illness. The first clinical task in evaluating youth who report hallucinations is to sort out those associated with severe mental illness from those derived from other causes (Fig. 47.3).

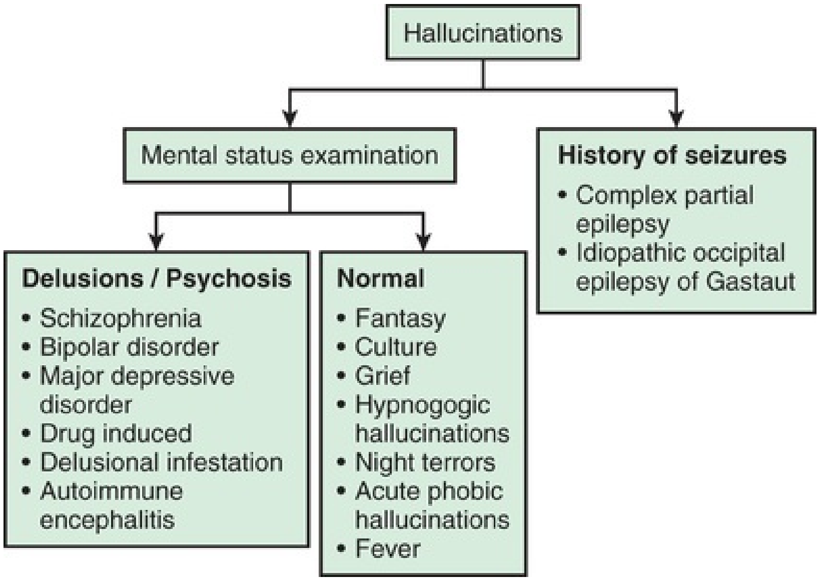
Hallucinations
Mental status examination
History of seizures
• Complex partial epilepsy
• Idiopathic occipital epilepsy of Gastaut
Delusions / Psychosis
• Schizophrenia
• Bipolar disorder
• Major depressive disorder
• Drug induced
• Delusional infestation
• Autoimmune encephalitis
Normal
• Fantasy
• Culture
• Grief
• Hypnogogic hallucinations
• Night terrors
• Acute phobic hallucinations
• Fever

FIG. 47.3 **Evaluation of hallucinations.**

Clinical Manifestations

Hallucinations are perceptions (typically auditory, visual, tactile, or olfactory) that occur in the absence of identifiable external stimuli. Hallucinations can be further categorized as *nondiagnostic* (hearing footsteps, knocking, or one's name) and *diagnostic* (hearing one or more voices saying words other than one's own name).

In children with nonpsychotic hallucinations, the other symptoms of psychosis are absent. *Nonpsychotic* hallucinations typically occur in the context of severe traumatic stress, developmental difficulties, social and emotional deprivation, parents whose own psychopathology promotes a breakdown in the child's sense of reality, cultural beliefs in mysticism, and unresolved mourning. *Auditory* hallucinations of voices telling the child to do “bad things” may be more often associated with disruptive behavior disorders than psychotic diagnoses. Hearing a voice invoking suicide is often associated with depression. Trauma-related auditory hallucinations are commonly associated with posttraumatic stress disorder or a brief psychotic disorder with marked stressors. The content of the hallucinations may be relevant in understanding the underlying psychopathology and developmental issues.

Diagnosis and Differential Diagnosis

Acute phobic hallucinations are benign and common and occur in previously healthy preschool children. The hallucinations are often visual or tactile, last 10-60 min, and occur at any time but most often at night. The child is quite frightened and might complain that bugs or snakes are crawling over him or her and attempt to remove them. The cause is unknown. The differential diagnosis includes drug overdose or poisoning, high fever, encephalitis, and psychosis. The child's fear is not alleviated by reassurance by the parents or physician, and the child is not amenable to reason. Findings on physical and mental status examinations are otherwise normal. Symptoms can persist for 1-3 days, slowly abating over 1-2 wk.

The differential diagnosis of hallucinations comprises a broad range of mental disorders, including diagnoses in which hallucinations are not the hallmark feature, but may be viewed as associated symptoms (posttraumatic stress disorder, nonpsychotic mood disorders, and disruptive, impulse-control, and conduct disorders); diagnoses that are defined by psychotic features (brief psychotic disorder, schizophrenia, major depressive or bipolar disorder with psychotic features); and at-risk clinical states (poor reality testing). In addition, other medical conditions can manifest with hallucinations, including drug intoxications (cannabis, LSD, cocaine, amphetamines, barbiturates), medication side effects (e.g., corticosteroids, anticholinergics, stimulants), and physical illnesses (e.g., thyroid, parathyroid, and adrenal disorders; Wilson disease; electrolyte imbalances; infections; migraines; seizures; neoplasms).

Treatment

The evaluation of the underlying condition directs the type of treatment needed. Nonpsychotic hallucinations suggest the need for disorder-specific psychotherapy (e.g., trauma-focused CBT for posttraumatic stress disorder) and perhaps adjunctive medication (e.g., antidepressant for depression or anxiety, brief trial of antipsychotic for agitation). CBT focused on helping the youth understand the origin of the hallucinations and on developing coping strategies for stressful situations may be helpful for older children and adolescents. True psychotic hallucinations suggest the need for antipsychotic medication.

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PART IV

Learning and Developmental Disorders

OUTLINE

Chapter 48 Neurodevelopmental and Executive Function and Dysfunction
Chapter 49 Attention-Deficit/Hyperactivity Disorder
Chapter 50 Dyslexia
Chapter 51 Math and Writing Disabilities
Chapter 52 Language Development and Communication Disorders
Chapter 53 Developmental Delay and Intellectual Disability
Chapter 54 Autism Spectrum Disorder

CHAPTER 48

Neurodevelopmental and Executive Function and Dysfunction

Desmond P. Kelly, Mindo J. Natale

Terminology and Epidemiology

A **neurodevelopmental function** is a basic brain process needed for learning and productivity. **Executive function (EF)** is an umbrella term used to describe specific neurocognitive processes involved in the regulating, guiding, organizing, and monitoring of thoughts and actions to achieve a specific goal. Processes considered to be “executive” in nature include inhibition/impulse control, cognitive/mental flexibility, emotional control, initiation skills, planning, organization, working memory, and self-monitoring. **Neurodevelopmental and/or executive dysfunctions** reflect any disruptions or weaknesses in these processes, which may result from neuroanatomic or psychophysiologic malfunctioning. **Neurodevelopmental variation** refers to differences in neurodevelopmental functioning. Wide variations in these functions exist within and between individuals. These differences can change over time and need not represent pathology or abnormality.

Neurodevelopmental and/or executive dysfunction places a child at risk for developmental, cognitive, emotional, behavioral, psychosocial, and adaptive challenges. Preschool-age children with neurodevelopmental or executive dysfunction may manifest delays in developmental domains such as language, motor, self-help, or social-emotional development and self-regulation. For the school-age child, an area of particular focus is academic skill development. The *Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition* (DSM-5) classifies **academic disorder** within the group of neurodevelopmental disorders as **specific learning disorder (SLD)** , with broadened diagnostic criteria recognizing impairments in reading, written expression, and mathematics. In the

International Classification of Diseases, Tenth Edition (ICD-10), neurodevelopmental disorders include **specific developmental disorders of scholastic skills** with specific reading disorder, mathematics disorder, and disorder of written expression. **Dyslexia** is categorized separately in ICD-10 under “Symptoms and Signs Not Elsewhere Classified.” **Frontal lobe and executive function deficit** is also included in this category. **Disorders of executive function** have traditionally been viewed as a component of **attention-deficit/hyperactivity disorder *(* ADHD)** , which is also classified in DSM-5 as a neurodevelopmental disorder.

There are no prevalence estimates specifically for neurodevelopmental dysfunction, but overall estimates for learning disorders range from 3–10% with a similar range reported for ADHD. These disorders frequently co-occur. The range in prevalence is likely related to differences in definitions and criteria used for classification and diagnosis, as well as differences in methods of assessment.

Etiology and Pathogenesis

Neurodevelopmental and executive dysfunction may result from a broad range of etiologic factors, including genetic, medical, psychological, environmental, and sociocultural influences.

There is a high degree of **heritability** reported in learning and attention disorders, with estimates ranging from 45–80%. Specific genes have been identified that are associated with reading disorders, including the *DYX2* locus on chromosome 6p22 and the *DYX3* locus on 2p12. Neuroimaging studies have confirmed links between gene variations and variations in cortical thickness in areas of the brain known to be associated with learning and academic performance, such as the temporal regions. Chromosomal abnormalities can lead to unique patterns of dysfunction, such as visual-spatial deficits in girls diagnosed with Turner syndrome (see Chapter 98.4) or executive and language deficits in children with fragile X syndrome (Chapter 98.5). Chromosome 22q11.2 deletion syndrome (velocardiofacial-DiGeorge syndrome; Chapter 98.3) has been associated with predictable patterns of neurodevelopmental and executive dysfunction that can be progressive, including a higher prevalence of intellectual disability, as well as deficits in visual-spatial processing, attention, working memory, verbal learning, arithmetic, and language.

Genetic vulnerabilities may be further influenced by **perinatal** factors, including very low birthweight, severe intrauterine growth restriction, perinatal hypoxic-ischemic encephalopathy, and prenatal exposure to substances such as alcohol and drugs. Increased risk of neurodevelopmental and executive dysfunction has also been associated with environmental toxins, including lead (see Chapter 739); drugs such as cocaine; infections such as meningitis, HIV, and Zika; and brain injury secondary to intraventricular hemorrhage, periventricular leukomalacia, or head trauma. The academic effects of concussion in children and adolescents, although usually temporary, have been well characterized, including impaired concentration and slowed processing speed. Repeated injuries have a much higher likelihood of long-term negative neurocognitive effects.

Early **psychological trauma** may result in both structural and neurochemical changes in the developing brain, which may contribute to neurodevelopmental and executive dysfunction. Findings suggest that the effects of exposure to trauma or abuse early in the developmental course can induce disruption of the brain's regulatory system and may influence right hemisphere function with associated risk for problems with information processing, memory, focus, and self-regulation. Environmental and sociocultural deprivation can lead to, or potentiate, neurodevelopmental and executive dysfunction, and numerous studies have indicated that parent/caregiver executive functioning impacts the development of EFs in offspring.

With regard to **pathogenesis** , investigations of neuroanatomic substrates have yielded important information about the underlying mechanisms in neurodevelopmental and executive dysfunction. Multiple neurobiologic investigations have identified differences in the left parietotemporal and left occipitotemporal brain regions of individuals with dyslexia compared to those without reading difficulties (see Chapter 50). Studies have also described the neural circuitry, primarily in the parietal cortex, underlying mathematical competencies such as the processing of numerical magnitude and mental arithmetic. The associations between executive dysfunction and the *prefrontal/frontal cortex* have been well established, and insults to the frontal lobe regions often result in dysfunction of executive abilities (e.g., poor inhibitory control). Although the prefrontal/frontal cortex may be the primary control region for EFs, there is considerable interconnectivity between the brain's frontal regions and other areas, such as *arousal* systems (reticular activating system), *motivational and emotional* systems (limbic system), *cortical association* systems (posterior/anterior; left/right hemispheres), and *input/output* systems (frontal motor/posterior sensory areas).

Core Neurodevelopmental Functions

The neurodevelopmental processes that are critical to a child's successful functioning may best be understood as falling within **core neurodevelopmental domains** . Notwithstanding such classification of domains, the clinical distinctions often made regarding “cognitive” processes (e.g., intelligence, EF, attention, language, memory) are relatively artificial because these brain functions are highly integrated.

Sensory and Motor Function

Sensory development (e.g., auditory, visual, tactile, proprioceptive) begins well before birth. This neurodevelopmental process is crucial in helping children experience, understand, and manipulate their environments. Sensory development progresses in association with environmental exposure and with the development of other cognitive processes, such as motor development. Through sensory experiences, children's brains mature as new neuronal pathways are created and existing pathways are strengthened.

There are three distinct, yet related, forms of neuromotor ability: fine motor, graphomotor, and gross motor coordination. **Fine motor function** reflects the ability to control the muscles and bones to produce small, exact movements. Deficits in fine motor function can disrupt the ability to communicate in written form, to excel in artistic and crafts activities, and can interfere with learning a musical instrument or mastering a computer keyboard. The term **dyspraxia** relates to difficulty in developing an ideomotor plan and activating coordinated and integrated visual-motor actions to complete a task or solve a motor problem, such as assembling a model. **Graphomotor function** refers to the specific motor aspects of written output. Several subtypes of graphomotor dysfunction can significantly impede writing. Children who harbor weaknesses of visualization during writing have trouble picturing the configurations of letters and words as they write (orthographics), with poorly legible written output with inconsistent spacing between words. Others have weaknesses in orthographic memory and may labor over individual letters and prefer printing (manuscript) to cursive writing. Some exhibit signs of finger agnosia and have trouble localizing their fingers while they write, needing to keep their eyes very close to the page and applying excessive pressure to the pencil. Others struggle producing the highly coordinated motor sequences needed for writing, a phenomenon also described as **dyspraxic dysgraphia** . It is important to emphasize that a child may show excellent fine motor dexterity (as revealed in mechanical or artistic domains) but very poor graphomotor fluency (with labored or poorly legible writing).

Gross motor function refers to control of large muscles. Children with gross motor incoordination often have problems in processing “outer spatial” information to guide gross motor actions. Affected children may be inept at catching or throwing a ball because they cannot form accurate judgments about trajectories in space. Others demonstrate diminished body position sense. They do not efficiently receive or interpret proprioceptive and kinesthetic feedback from peripheral joints and muscles. They are likely to evidence difficulties when activities demand balance and ongoing tracking of body movement. Others are unable to satisfy the motor praxis demands of certain gross motor activities. It may be difficult for them to recall or plan complex motor procedures such as those needed for dancing, gymnastics, or swimming.

Language

Language is one of the most critical and complex cognitive functions and can be broadly divided into **receptive** (auditory comprehension/understanding) and e**xpressive** (speech and language production and/or communication) functions. Children who primarily experience receptive language problems may have difficulty understanding verbal information, following instructions and explanations, and interpreting what they hear. Expressive language weaknesses can result from problems with speech production and/or problems with higher-level language development. **Speech production difficulties** include oromotor problems affecting articulation, verbal fluency, and naming. Some children have trouble with sound sequencing within words. Others find it difficult to regulate the rhythm or prosody of their verbal output. Their speech may be dysfluent, hesitant, and inappropriate in tone. Problems with word retrieval can result in difficulty finding exact words when needed (as in a class discussion) or substituting definitions for words (circumlocution).

The basic components of language include **phonology** (ability to process and integrate the individual sounds in words), **semantics** (understanding the meaning of words), **syntax** (mastery of word order and grammatical rules), **discourse** (processing and producing paragraphs and passages), **metalinguistics** (ability to think about and analyze how language works and draw inferences), and **pragmatics** (social understanding and application of language). Children who evidence higher-level expressive language impediments have trouble formulating sentences, using grammar acceptably, and organizing spoken (and possibly written) narratives.

To one degree or another, all academic skills are taught largely through language, and thus it is not surprising that children who experience language dysfunction often experience problems with academic performance. In fact, some studies suggest that up to 80% of children who present with a specific learning disorder also experience language-based weaknesses. Additionally, the role of language in executive functioning cannot be understated, since language serves to guide cognition and behavior.

Visual-Spatial/Visual-Perceptual Function

Important structures involved in the development and function of the visual system include the retina, optic cells (e.g., rods and cones), the optic chiasm, the optic nerves, the brainstem (control of automatic responses, e.g., pupil dilation), the thalamus (e.g., lateral geniculate nucleus for form, motion, color), and the primary (visual space and orientation) and secondary (color perception) visual processing regions located in and around the occipital lobe. Other brain areas, considered to be outside of the primary visual system, are also important to visual function, helping to process *what* (temporal lobe) is seen and *where* it is located in space (parietal lobe). It is now well documented that the left and right cerebral hemispheres interact considerably in visual processes, with each hemisphere possessing more specialized functions, including left hemisphere processing of details, patterns, and linear information and right hemisphere processing of the gestalt and overall form.

Critical aspects of visual processing development in the child include appreciation of **spatial relations** (ability to perceive objects accurately in space in relation to other objects), **visual discrimination** (ability to differentiate and identify objects based on their individual attributes, e.g., size, shape, color, form, position), and **visual closure** (ability to recognize or identify an object even when the entire object cannot be seen). Visual-spatial processing dysfunctions are rarely the cause of reading disorders, but some investigations have established that deficits in orthographic coding (visual-spatial analysis of character-based systems) can contribute to reading disorders. Spelling and writing can emerge as a weakness because children with visual processing problems usually have trouble with the precise visual configurations of words. In mathematics, these children often have difficulty with visual-spatial orientation, with resultant difficulty aligning digits in columns when performing calculations and difficulty managing geometric material. In the social realm, intact visual processing allows a child to make use of visual or physical cues when communicating and interpreting the paralinguistic aspects of language. Secure visual functions are also necessary to process proprioceptive and kinesthetic feedback and to coordinate movements during physical activities.

Intellectual Function

A useful definition of **intellectual function** is the capacity to think in the abstract, reason, problem-solve, and comprehend. The concept of intelligence has had many definitions and theoretical models, including Spearman's unitary concept of “the g-factor,” the “verbal and nonverbal” theories (e.g., Binet, Thorndike), the 2-factor theory from Catell (crystallized vs fluid intelligence), Luria's simultaneous and successive processing model, and more recent models that view intelligence as a global construct composed of more-specific cognitive functions (e.g., auditory and visual-perceptual processing, spatial abilities, processing speed, working memory).

The expression of intellect is mediated by many factors, including language development, sensorimotor abilities, genetics, heredity, environment, and neurodevelopmental function. When an individual's measured intelligence is >2 standard deviations below the mean (a standard score of <70 on most IQ tests) and accompanied by significant weaknesses in adaptive skills, the diagnosis of **intellectual disability** may be warranted (see Chapter 53).

Functionally, some common characteristics distinguish children with deficient intellectual functioning from those with average or above-average abilities. Typically, those at the lowest end of the spectrum (e.g., profound or severe intellectual deficiencies) are incapable of independent function and require a highly structured environment with constant aid and supervision. At the other end of the spectrum are those with unusually well-developed intellect (“gifted”). Although this level of intellectual functioning offers many opportunities, it can also be associated with functional challenges related to socialization and learning and communication style. Individuals whose intellect falls in the below-average range (sometimes referred to as the “borderline” or “slow learner” range) tend to experience greater difficulty processing and managing information that is abstract, making connections between concepts and ideas, and generalizing information (e.g., may be able to comprehend a concept in one setting but are unable to carry it over and apply it in different situation). In general, these individuals tend to do better when information is presented in more concrete and explicit terms, and when working with rote information (e.g., memorizing specific material). Stronger intellect has been associated with better-developed concept formation, critical thinking, problem solving, understanding and formulation of rules, brainstorming and creativity, and *metacognition* (ability to “think about thinking”).

Memory

Memory is a term used to describe the cognitive mechanism by which information is acquired, retained, and recalled. Structurally, some major brain areas involved in memory processing include the hippocampus, fornix, temporal lobes, and cerebellum, with connections in and between most brain regions. The memory system can be partitioned into subsystems based on processing sequences; the form, time span, and method of recall; whether memories are conscious or unconsciously recalled; and the types of memory impairments that can occur.

Once information has been identified (through auditory, visual, tactile, and/or other sensory processes), it needs to be **encoded and registered** , a mental process that constructs a representation of the information into the memory system. The period (typically seconds) during which this information is being held and/or manipulated for registration, and ultimately encoded, consolidated, and retained, is referred to as **working memory** . Other descriptors include **short-term memory** and **immediate memory** . **Consolidation** and **storage** represent the process by which information in short-term memory is transferred into **long-term memory** . Information in long-term memory can be available for hours or as long as a life span. Long-term memories are generally thought to be housed, in whole or in part, in specific brain regions (e.g., cortex, cerebellum). Ordinarily, consolidation in long-term memory is accomplished in 1 or more of 4 ways: pairing 2 bits of information (e.g., a group of letters and the English sound it represents); storing procedures (consolidating new skills, e.g., the steps in solving mathematics problems); classifying data in categories (filing all insects together in memory); and linking new information to established rules, patterns, or systems of organization (rule-based learning).

Once information finds its way into long-term memory, it must be accessed. In general, information can be retrieved spontaneously (a process known as **free recall**) or with the aid of cues (**cued or recognition recall**). Some other common descriptors of memory include **anterograde memory** (capacity to learn from a single point in time forward), **retrograde memory** (capacity to recall information that was already learned), and **explicit memory** (conscious awareness of recall), **implicit memory** (subconscious recall: no awareness that the memory system is being activated), **procedural memory** (memory for how to do things), and **prospective memory** or *remembering to remember* . **Automatization** reflects the ability to instantaneously access what has been learned in the past with no expenditure of effort. Successful students are able to automatically form letters, master mathematical facts, and decode words.

Social Cognition

The development of effective social skills is heavily dependent on secure **social cognition,** which consists of mental processes that allow an individual to understand and interact with the social environment. Although some evidence shows that social cognition exists as a discrete area of neurodevelopmental function, multiple cognitive processes are involved with social cognition. These include the ability to recognize, interpret, and make sense of the thoughts, communications (verbal and nonverbal), and actions of others; the ability to understand that others' perceptions, perspectives, and intentions might differ from one's own (commonly referred to as “theory of mind”); the ability to use language to communicate with others socially (pragmatic language); and the ability to make inferences about others and the environment based on contextual information. It can also be argued that social cognition involves processes associated with memory and EFs such as flexibility.

Executive Function

The development of EFs begins very early on in the developmental course (early indications of inhibitory control and even working memory have been found in infancy), matures significantly during the preschool years, and continues to develop through adolescence and well into adulthood. Some studies suggest that secure EF may be more important than intellectual ability for academic success and have revealed that a child's ability to delay gratification early in life predicts competency, attention, self-regulation, frustration tolerance, aptitude, physical and mental health, and even substance dependency in adolescence and adulthood. Conversely, deficits in other areas of neurodevelopment, such as language development, impact EF.

Attention is far from a unitary, independent, or specific brain function. This may be best illustrated through the phenotype associated with ADHD) (see Chapter 49). Disordered attention can result from faulty mechanisms in and across subdomains of attention. These subdomains include *selective* attention (ability to focus attention on a particular stimulus and to discriminate relevant from irrelevant information), *divided* attention (ability to orient to more than one stimulus at a given time), *sustained* attention (ability to maintain one's focus), and *alternating* attention (capacity to shift focus between stimuli).

Attention problems in children can manifest at any point, from arousal through output. Children with diminished alertness and arousal can exhibit signs of mental fatigue in a classroom or when engaged in any activity requiring sustained focus. They are apt to have difficulty allocating and sustaining their concentration, and their efforts may be erratic and unpredictable, with extreme performance inconsistency. Weaknesses of determining saliency often result in focusing on the wrong stimuli, at home, in school, and socially, and missing important information. **Distractibility** can take the form of listening to extraneous noises instead of a teacher, staring out the window, or constantly thinking about the future. Attention dysfunction can affect the output of work, behavior, and social activity. It is important to appreciate that most children with attentional dysfunction also harbor other forms of neurodevelopmental dysfunction that can be associated with academic disorders (with some estimates suggesting up to 60% comorbidity).

Inhibitory control (IC) can be described as one's ability to restrain, resist, and not act (cognitively or behaviorally/emotionally) on a thought. IC may also be seen as one's ability to stop thoughts or ongoing actions. Deficits in this behavioral/impulse regulation mechanism are a core feature of the **combined** or **hyperactive impulsive** presentation of ADHD and have a significant adverse impact on a child's overall functioning. In everyday settings, children with weak IC may exhibit difficulties with self-control and self-monitoring of their behavior and output (e.g., impulsivity), may not recognize their own errors or mistakes, and often act prematurely and without consideration of the potential consequences of their actions. In the social context, disinhibited children may interrupt others and demonstrate other impulsive behaviors that often interfere with interpersonal relationships. The indirect consequences of poor IC often lead to challenges with behavior, emotional, and academic functioning and social interaction (Table 48.1).

Table 48.1

Symptom Expression of Executive Dysfunction

EXECUTIVE FUNCTION DEFICIT	SYMPTOM EXPRESSION
Disinhibition	Impulsivity/poor behavioral regulation Interrupts “Blurts things out”
Shifting	Problems with transitioning from one task/activity to another Unable to adjust to unexpected change Repeats unsuccessful problem-solving approaches
Initiation	Difficulty independently beginning tasks/activities Lacks initiative Difficulty developing ideas or making decisions
Working memory	Challenges following multistep instruction (e.g., only completes 1 of 3 steps) Forgetfulness
Organization and planning	Fails to plan ahead Work is often disorganized Procrastinates and does not complete tasks “Messy” child
Self-monitoring	Fails to recognize errors and check work Does not appreciate impact of actions on others Poor self-awareness
Affect control	Experiences behavioral and emotional outbursts (e.g., tantrums) Easily upset/frustrated Frequent mood changes

Working memory (WM) can be defined as the ability to hold, manipulate, and store information for short periods. This function is critical to be able to complete multistep problems and more complex instructions and tasks. In its simplest form, WM involves the interaction of short-term verbal and visual processes (e.g., memory, phonologic, awareness, and spatial skills) with a centralized control mechanism that is responsible for coordinating all the cognitive processes involved (e.g., temporarily suspending information in memory while working with it). Developmentally, WM capacity can double or triple between the preschool years and adolescence. When doing math, a child with WM dysfunction might carry a number and then forget what he intended to do after carrying that number. WM is an equally important underlying function for reading, where it enables the child to remember the beginning of a paragraph when she arrives at the end of it. In writing, WM helps children remember what they intend to express in written form while they are performing another task, such as placing a comma or working on spelling a word correctly. WM also enables the linkage between new incoming information in short-term memory with prior knowledge or skills held in longer-term memory.

Initiation refers to the ability to independently begin an activity, a task, or thought process (e.g., problem-solve). Children who present with initiation difficulties often have trouble “getting going” or “getting started.” This can be exhibited behaviorally, such that the child struggles to start on physical activities such as getting out of bed or beginning chores. Cognitively, weaknesses in initiation may manifest as difficulty coming up with ideas or generating plans. In school, children who have poor initiation abilities may be delayed in or unable to start homework assignments or tests. In social situations, initiation challenges may cause a child to have difficulty beginning conversations, calling on friends, or going out to be with friends.

Deficits in “primary” initiation are relatively rare and are often associated with significant neurologic conditions and treatments (e.g., traumatic brain injury, anoxia, effects of radiation treatment in childhood cancer). More often, initiation deficits are secondary to other executive problems (e.g., disorganization) or behavioral (e.g., oppositional/defiant behaviors), developmental (e.g., autism spectrum disorder), or emotional (e.g., depression, anxiety) disorders.

Planning refers to the ability to effectively generate, sequence, and put into motion the steps and procedures necessary to realize a specific goal. In real-world settings, children who struggle with planning are typically described by caregivers and teachers as being inept at independently gathering what is required to solve a problem, or as unable to complete more weighty assignments. Another common complaint is that these children exhibit poor time management skills. **Organization** is an ability that represents a child's proficiency in arranging, ordering, classifying, and categorizing information. Common daily life challenges associated with organizational difficulties in childhood include problems with gathering and managing materials or items. When children struggle with organization, indirect consequences may include becoming overwhelmed with information and being unable to complete a task or activity. Effective organization is a vital component in learning (more specifically, in memory/retention); many studies along with clinical experience have shown that poor organization significantly impacts how well a child recalls information. Planning and organizing depend on **discrimination** ability, which refers to the child's ability to determine what is and is not valuable when trying to problem-solve or organize.

Emotional control is the ability to regulate emotions in order to realize goals and direct one's behavior, thoughts, and actions. It has been well established that affective/emotional states have an impact on many aspects of functioning. Conversely, executive function or dysfunction often contributes to modulation or affect. While emotional control is highly interrelated with different EFs (e.g., disinhibition, self-monitoring), separating it conceptually facilitates an appreciation for and recognition of the often-overlooked role that a child's emotional state plays in cognitive and behavioral functioning. Children with weak emotional control may exhibit explosive outbursts, poor temper/anger control, and oversensitivity. Clearly, understanding a child's emotional state is vital to understanding its impact not only on executive functioning, but also on functioning as a whole (e.g., socially, mentally, behaviorally, academically).

Any discussion involving emotional control should also recognize **motivation** . *Motivation/effort* may be defined as the reason or reasons one acts or behaves in a certain way. Less motivated children are less likely to engage and utilize all their abilities. Such a disposition not only interferes with application of executive skills, but also results in less than optimal performance and functioning. The less success a child feels, the less likely the child is to put forth effort and to persevere when things become more challenging. If a child's initial efforts are met with a negative reaction, the likelihood that the child will continue putting forth adequate effort diminishes. If left unchecked, a child's overall level of functioning will likely be compromised. More importantly, the child's sense of personal efficacy (e.g., self-esteem) and competence may suffer.

Clinical Manifestations

The symptoms and clinical manifestations of neurodevelopmental and executive dysfunction differ with age. **Preschool-age children** might present with delayed language development, including problems with articulation, vocabulary development, word finding, and rhyming. They often experience early challenges with learning colors, shapes, letters, and numbers; the alphabet; and days of the week. Children with visual processing deficits may have difficulty learning to draw and write and have problems with art activities. These children might also have trouble discriminating between left and right. They might encounter problems recognizing letters and words. Difficulty following instructions, overactivity, and distractibility may be early symptoms of emerging executive dysfunction. Difficulties with fine motor development (e.g., grasping crayons/pencils, coloring, drawing) and social interaction may develop.

School-age children with neurodevelopmental and executive dysfunctions can vary widely in clinical presentations. Their specific patterns of academic performance and behavior represent final common pathways of neurodevelopmental strengths and deficits interacting with environmental, social, or cultural factors; temperament; educational experience; and intrinsic resilience (Table 48.2). Children with language weaknesses might have problems integrating and associating letters and sounds, decoding words, deriving meaning, and being able to comprehend passages. Children with early signs of a mathematics weakness might have difficulty with concepts of quantity or with adding or subtracting without using concrete representation (e.g., their fingers when calculating). Difficulty learning time concepts and confusion with directions (right/left) might also be observed. Poor fine motor control and coordination and poor planning can lead to writing problems. Attention and behavioral regulation weaknesses observed earlier can continue, and together with other executive functioning weaknesses (e.g., organization, initiation skills), further complicate the child's ability to acquire and generalize new knowledge. Children with weaknesses in WM may struggle to remember the steps necessary to complete an activity or problem-solve. In social settings, these children often have difficulty keeping up with more complex conversations.

Table 48.2

Neurodevelopmental Dysfunction Underlying Academic Disorders*

ACADEMIC DISORDER	POTENTIAL UNDERLYING NEURODEVELOPMENTAL DYSFUNCTION
Reading	Language Phonologic processing Verbal fluency Syntactic and semantic skills Memory Working memory Sequencing Visual-spatial Attention
Written expression, spelling	Language Phonologic processing Syntactic and semantic skills Graphomotor Visual-spatial Memory Working memory Sequencing Attention

Mathematics	Visual-spatial Memory Working memory Language Sequencing Graphomotor Attention

[*] Isolated neurodevelopmental dysfunction can lead to a specific academic disorder, but more often there is a combination of factors underlying weak academic performance. In addition to the dysfunction in neurodevelopmental domains as listed in the table, the clinician must also consider the possibility of limitations of intellectual and cognitive abilities or associated social and emotional problems.

In **middle school children** the shift in cognitive, academic, and regulatory demands can cause further difficulties for those with existing neurodevelopmental and executive challenges. In reading and writing, middle school children might present with transposition and sequencing errors; might struggle with root words, prefixes, and suffixes; might have difficulty with written expression; and might avoid reading and writing altogether. Challenges completing word problems in math are common. Difficulty with recall of information might also be experienced. Although observable in both lower and more advanced grades, behavioral, emotional, and social difficulties tend to become more salient in middle school children who experience cognitive or academic problems.

High school students can present with deficient reading comprehension, written expression, and slower processing efficiency. Difficulty in answering open-ended questions, dealing with abstract information, and producing executive control (e.g., self-monitoring, organization, planning, self-starting) is often reported.

Academic Problems

Reading disorders (see Chapter 50) can stem from any number of neurodevelopmental dysfunctions, as described earlier (see Table 48.2). Most often, language and auditory processing weaknesses are present, as evidenced by poor phonologic processing that results in deficiencies at the level of decoding individual words and, consequently, a delay in *automaticity* (e.g., acquiring a repertoire of words readers can identify instantly) that causes reading to be slow, laborious, and frustrating. Deficits in other core neurodevelopmental domains might also be present. Weak WM might make it difficult for a child to hold sounds and symbols in mind while breaking down words into their component sounds, or might cause reading comprehension problems. Some children experience temporal-ordering weaknesses and struggle with reblending phonemes into correct sequences. Memory dysfunction can cause problems with recall and summarization of what was read. Some children with higher-order cognitive deficiencies have trouble understanding what they read because they lack a strong grasp of the concepts in a text. Although relatively rare as a cause of reading difficulty, problems with visual-spatial functions (e.g., visual perception) can cause children difficulty in recognizing letters. It is not unusual for children with reading problems to avoid reading practice, and a delay in reading proficiency becomes increasingly pronounced and difficult to remediate.

Spelling and writing impairments share many related underlying processing deficits with reading, so it is not surprising that the 2 disorders often occur simultaneously in school-age children (see Table 48.2). Core neurodevelopmental weaknesses that underlie *spelling difficulties* include phonologic and decoding difficulties, orthographic problems (coding letters and words into memory), and morphologic deficits (use of suffixes, prefixes, and root words). Problems in these areas can manifest as phonetically poor, yet visually comparable approximations to the actual word (*faght* for *fight*), spelling that is phonetically correct but visually incorrect (*fite* for *fight*), and inadequate spelling patterns (*played* as *plade).* Children with memory disorders might misspell words because of coding weaknesses. Others misspell because of poor auditory WM that interferes with their ability to process letters. Sequencing weaknesses often result in transposition errors when spelling.

Writing difficulties have been classified as **disorder of written expression** , or **dysgraphia** (see Table 48.2). Although many of the same dysfunctions described for reading and spelling can contribute to problems with writing, written expression is the most complex of the language arts, requiring synthesis of many neurodevelopmental functions (e.g., auditory, visual-spatial, memory, executive; see Chapter 51.2). Weaknesses in these functions can result in written output that is difficult to comprehend, disjointed, and poorly organized. The child with WM challenges can lose track of what the child intended to write. Attention deficits can make it difficult for a child to mobilize and sustain the mental effort, pacing, and self-monitoring demands necessary for writing. In many cases, writing is laborious because of an underlying *graphomotor dysfunction* (e.g., fluency does not keep pace with ideation and language production). Thoughts may also be forgotten or underdeveloped during writing because the mechanical effort is so taxing.

Weaknesses in mathematical ability, known as **mathematics disorder** or **dyscalculia** , require early intervention because math involves the assimilation of both procedural knowledge (e.g., calculations) and higher-order cognitive processes (e.g., WM) (see Table 48.2). There are many reasons why children experience failure in mathematics (see Chapter 51.1). It may be difficult for some to grasp and apply math concepts effectively and systematically; good mathematicians are able to use both verbal and perceptual conceptualization to understand such concepts as fractions, percentages, equations, and proportion. Children with language dysfunctions have difficulty in mathematics because they have trouble understanding their teachers' verbal explanations of quantitative concepts and operations and are likely to experience frustration in solving word problems and in processing the vast network of technical vocabulary in math. Mathematics also relies on visualization. Children who have difficulty forming and recalling visual imagery may be at a disadvantage in acquiring mathematical skills. They might experience problems writing numbers correctly, placing value locations, and processing geometric shapes or fractions. Children with executive dysfunction may be unable to focus on fine detail (e.g., operational signs), might take an impulsive approach to problem solving, engage in little or no self-monitoring, forget components of the problem, or commit careless errors. When a child's memory system is weak, the child might have difficulty recalling appropriate procedures and automatizing mathematical facts (e.g., multiplication tables). Moreover, children with mathematical disabilities can have superimposed mathematics **phobias** ; anxiety over mathematics can be especially debilitating.

Nonacademic Problems

The impulsivity and lack of effective self-monitoring of children with executive dysfunction can lead to unacceptable actions that were unintentional. Children struggling with neurodevelopmental dysfunction can experience excessive performance anxiety, sadness, or clinical depression; declining self-esteem; and chronic fatigue. Some children lose motivation. They tend to give up and exhibit **learned helplessness,** a sense that they have no control over their destiny. Therefore they feel no need to exert effort and develop future goals. These children may be easily led toward dysfunctional interpersonal relationships, detrimental behaviors (e.g., delinquency), and the development of mental health disorders, such as mood disorders (see Chapter 39) or conduct disorder (Chapter

42).

Assessment and Diagnosis

Pediatricians have a critical role in identifying and treating the child with neurodevelopmental or executive dysfunction (Fig. 48.1). They have knowledge of the child's medical and family history and social-environmental circumstances and have the benefit of longitudinal contact over the course of routine health visits. Focused **surveillance and screening** will lead to early identification of developmental-behavioral and preacademic difficulties and interventions to facilitate optimal outcomes.

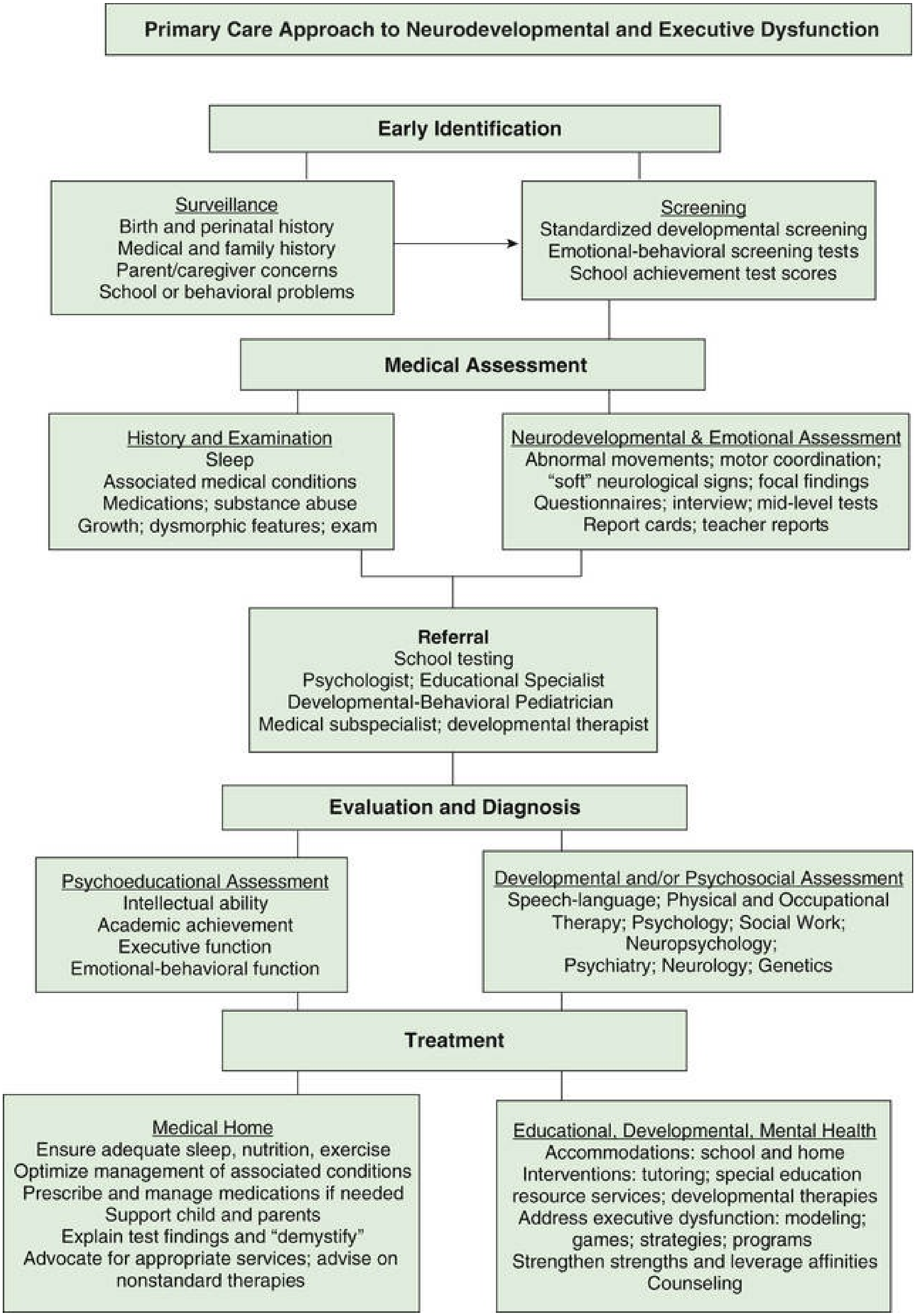
Primary Care Approach to Neurodevelopmental and Executive Dysfunction
Early Identification
Surveillance
Birth and perinatal history
Medical and family history
Parent/caregiver concerns
School or behavioral problems
Screening
Standardized developmental screening
Emotional-behavioral screening tests
School achievement test scores
Medical Assessment
History and Examination
Sleep
Associated medical conditions
Medications; substance abuse
Growth; dysmorphic features; exam
Neurodevelopmental & Emotional Assessment
Abnormal movements; motor coordination;
"soft" neurological signs; focal findings
Questionnaires; interview; mid-level tests
Report cards; teacher reports
Referral
School testing
Psychologist; Educational Specialist
Developmental-Behavioral Pediatrician
Medical subspecialist; developmental therapist
Evaluation and Diagnosis
Psychoeducational Assessment
Intellectual ability
Academic achievement
Executive function
Emotional-behavioral function
Developmental and/or Psychosocial Assessment
Speech-language; Physical and Occupational
Therapy; Psychology; Social Work;
Neuropsychology;
Psychiatry; Neurology; Genetics
Treatment
Medical Home
Ensure adequate sleep, nutrition, exercise
Optimize management of associated conditions
Prescribe and manage medications if needed
Support child and parents
Explain test findings and "demystify"
Advocate for appropriate services; advise on
nonstandard therapies
Educational, Developmental, Mental Health
Accommodations: school and home
Interventions: tutoring; special education
resource services; developmental therapies
Address executive dysfunction: modeling;
games; strategies; programs
Strengthen strengths and leverage affinities
Counseling

FIG. 48.1 Primary care approach to neurodevelopmental and executive dysfunction.

A **family history** of a parent who still struggles with reading or time management, or an older sibling who has failed at school, should spur an increased level of monitoring. **Risk factors** in the medical history, such as extreme prematurity or chronic medical conditions, should likewise be flagged. Children with low birthweight and those born prematurely who appear to have been spared more serious neurologic problems might only manifest academic problems later in their school career. **Nonspecific physical complaints** or unexpected **changes in behavior** might be presenting symptoms. Warning signs might be subtle or absent, and parents might have concerns about their child's learning progress but may be reluctant to share these with the pediatrician unless prompted, such as through completion of **standardized developmental screening questionnaires** or direct questioning regarding possible concerns. There should be a low threshold for initiating further school performance screening and assessment if there are any “red flags.”

Review of **school report cards** can provide very useful information. In addition to patterns of grades in the various academic skill areas, it is also important to review ratings of classroom behavior and work habits. Group-administered **standardized tests** provide further information, although interpretation is required because poor scores could result from a learning disorder, ADHD, anxiety, lack of motivation, or some combination. Conversely, a discrepancy between above-average scores on standardized tests and unsatisfactory classroom performance could signal motivation or adjustment issues. Challenges related to **homework** can provide further insight regarding executive, academic skill, and behavioral factors.

Underlying or associated medical problems should be ruled out. Any suspicion of sensory difficulty should warrant referral for **vision or hearing testing** . The influence of chronic medical problems or potential side effects of medications should be considered. **Sleep deprivation** is increasingly being recognized as a contributor to academic problems, especially in middle and high school. **Substance abuse** must always be a consideration as well, especially in the adolescent previously achieving well who has shown a rapid decline in academic performance.

The physician should be alert for dysmorphic physical features, minor congenital anomalies, or constellations of physical findings (e.g., cardiac and palatal anomalies in velocardiofacial syndrome) and should perform a detailed neurologic examination, including an assessment of fine and gross motor coordination and any involuntary movements or soft neurologic signs. Special investigations (e.g., genetic deletion-duplication microarray, electroencephalogram, MRI) are not always indicated in the absence of specific medical findings or a family history. Measures of brain function, such as functional MRI, offer insight into possible areas of neurodevelopmental dysfunction but remain primarily research tools.

Early signs of executive dysfunction can also be subtle and easily overlooked or misinterpreted. Informal inquiry might include questions about how children complete schoolwork or tasks, how organized or disorganized they are, how much guidance they need, whether they think through problems or respond and react too quickly, what circumstances or individuals affect their ability to employ EFs, how easily they begin tasks and activities, and how well they plan, manage belongings, and control their emotions.

Pediatricians who are interested in performing further assessment before referral, or who are practicing in areas where psychological testing resources are limited, can utilize standardized rating scales and inventories or brief, individually administered tests to narrow potential diagnoses and guide next steps in diagnosis and treatment. Such instruments, completed by the parents, teachers, and the child (if old enough), can provide information about emotions and behavior, patterns of academic performance, and traits associated with specific neurodevelopmental dysfunctions (see Chapter 32). Screening instruments such as the *Pediatric Symptom Checklist* and behavioral questionnaires such as the *Child Behavior Checklist* (CBCL) and *Behavior Assessment System for Children, Second Edition* (BASC-2) can aid in evaluation. Instruments more specifically focused on academic disorders, such as the *Learning Disabilities Diagnostic Inventory,* can be completed by the child's teacher to reveal the extent to which skill patterns in a particular area (e.g., reading, writing) are consistent with those of individuals known to have a learning disability.

Executive functions can be further assessed by instruments such as the *Behavior Rating Inventory of Executive Function, Second Edition* (BRIEF2), which provides a comprehensive measure of real-world behaviors that are closely tied to executive functioning in children age 5-18 yr. An alternative rating inventory of EF in children is the *Comprehensive Executive Function*

Inventory (CEFI). Tests that can be directly administered to gauge intellectual functioning include the *Kaufman Brief Intelligence Test, Second Edition* (KBIT-2) and *Peabody Picture Vocabulary Test*, *Fourth Edi* tion (PPVT 4; assessing receptive vocabulary). A relatively brief test of academic skills is the *Wide Range Achievement Test 4* (WRAT4). It should be recognized that these are midlevel tests that can provide descriptive estimates of function but are not diagnostic.

Children who are struggling academically are entitled to evaluations in school. Such assessments are guaranteed in the United States under Public Law 101-476, the **Individuals with Disabilities Education Act (IDEA)** . One increasingly common type of evaluation supported by IDEA is referred to as a **response to intervention (RtI)** model (see Chapter 51.1). In this model, students who are struggling with academic skills are initially provided research-based instruction. If a child does not respond to this instruction, an individualized evaluation by a multidisciplinary team is conducted. Children found to have attentional dysfunction and other disorders might qualify for educational accommodations in the regular classroom under Section 504 of the Rehabilitation Act of 1973 (**504 plan**).

The pediatrician should advise and support parents regarding steps to request evaluations by the school. Multidisciplinary evaluations are focused primarily on determining whether a student meets the eligibility criteria for special education services and to assist in developing an **individualized educational plan (IEP)** for those eligible for these services. Independent evaluations can provide second opinions outside the school setting. The multidisciplinary team should include a psychologist and preferably an educational diagnostician who can undertake a detailed analysis of academic skills and subskills to pinpoint where breakdowns are occurring in the processes of reading, spelling, writing, and mathematics. Other professionals should become involved, as needed, such as a speech-language pathologist, occupational therapist, and social worker. A mental health specialist can be valuable in identifying family-based issues or psychiatric disorders that may be complicating or aggravating neurodevelopmental dysfunctions.

In some cases, more in-depth examination of a child's **neurocognitive status** is warranted. This is particularly true for children who present with developmental or cognitive difficulties in the presence of a medical condition (e.g., epilepsy, traumatic brain injury, childhood cancers/brain tumors, genetic conditions). A **neuropsychological evaluation** involves comprehensive assessment to understand brain functions across domains. Neuropsychological data are often analyzed together with other tests, such as MRI, to look for supporting evidence of any areas of difficulty (e.g., memory weaknesses associated with temporal lobe anomalies). Neuropsychologists can also provide more in-depth evaluation of EFs. Assessment of EFs is typically completed in an examination setting using tools specifically designed to identify any weaknesses in these functions. Although few tools are currently available to assess EF in preschool-age children, the assessment of school-age children is better established. Problems with EFs should be evaluated across measures and in different settings, particularly within the context of the child's daily demands.

Treatment

In addition to addressing any underlying or associated medical problems, the pediatrician can play an important role as a **consultant and advocate** in overseeing and monitoring the implementation of a comprehensive multidisciplinary management plan for children with neurodevelopmental dysfunctions. Most children require several of the following forms of intervention.

Demystification

Many children with neurodevelopmental dysfunctions have little or no understanding of the nature or sources of their academic difficulties. Once an appropriate descriptive assessment has been performed, it is important to explain to the child the nature of the dysfunction while delineating the child's strengths. This explanation should be provided in nontechnical language, communicating a sense of optimism and a desire to be helpful and supportive.

Bypass Strategies (Accommodations)

Numerous techniques can enable a child to circumvent neurodevelopmental dysfunctions. Such bypass strategies are ordinarily used in the regular classroom. Examples of bypass strategies include using a calculator while solving mathematical problems, writing essays with a word processor, presenting oral instead of written reports, solving fewer mathematical problems, being seated near the teacher to minimize distraction, presenting correctly solved mathematical problems visually, and taking standardized tests untimed. These bypass strategies do not cure neurodevelopmental dysfunctions, but they minimize their academic and nonacademic effects and can provide a scaffold for more successful academic achievement.

Treatment of Neurodevelopmental Dysfunctions

Interventions can be implemented at home and in school to strengthen the weak links in academic skills. Reading specialists, mathematics tutors, and other professionals can use diagnostic data to select techniques that use a student's neurodevelopmental strengths to improve decoding skills, writing ability, or mathematical computation skills. **Remediation** need not focus exclusively on specific academic areas. Many students need assistance in acquiring study skills, cognitive strategies, and productive organizational habits.

Early identification is critical so that appropriate instructional interventions can be introduced to minimize the long-term effects of academic disorders. Any interventions should be empirically supported (e.g., phonologically based reading intervention has been shown to significantly improve reading skills in school-age children). Remediation may take place in a resource room or learning center at school and is usually limited to children who have met the educational criteria for special education resource services described earlier.

Interventions that can be implemented at home could include drills to aid the automatization of subskills, such as arithmetic facts or letter formations, or the use of phonologically based reading programs.

Treatment of Executive Dysfunction

Interventions to strengthen EFs can be implemented throughout childhood but are most effective if started at a young age. Preschool-age children first experience EFs by way of the **modeling, boundaries, and rules** observed and put in place by their parents/caregivers, and this modeled behavior must gradually become “internalized” by the child. Early **play** has been shown to be effective in promoting executive skills in younger children with games such as peek-a-boo (WM); pat-a-cake (WM and IC); follow the leader, Simon says, and “ring around the rosie” (self-control); imitation activities (attention and impulse control); matching and sorting games (organization and attention); and imaginary play (attention, WM, IC, self-monitoring, cognitive flexibility).

In school-age children it is crucial to establish consistent **cognitive and behavioral routines** that foster and maximize independent, goal-oriented problem solving and performance through mechanisms that include modification of the child's environment, modeling and guidance with the child, and positive reinforcement strategies. Interventions should promote **generalization** (teaching executive routines in the context of a problem, not as a separate skill) and should move from the external to the internal (from “external support” with active and directive modeling to an “internal process”). An intervention could proceed from external modeling of multistep problem-solving routines and external guidance in developing and implementing everyday routines, to practicing application and use of routines in everyday situations, to a gradual fading of external support and cueing of internal generation and use of executive skills. Such approaches should make the child a part of intervention planning, should avoid labeling, reward effort not outcomes, make interventions positive, and hold the child responsible for his or her efforts. Studies have consistently shown that a combination of medication and behavioral treatments are most effective, although evidence for long term efficacy is lacking. It is important that any treatment plans aimed at bolstering attention and executive functioning also include interventions that address the specific deficits associated with any comorbid diagnoses.

In addition to behavioral approaches, computerized **training programs** have been shown to strengthen WM skills in children using a computer game model. Generalized and lasting improvements in WM have been reported. Also evidencing positive outcomes are curriculum-based **classroom programs** , such as the *Tools of the Mind* (Tools) and *Promoting Alternative Thinking Strategies* (PATHS). Other promising approaches to EF intervention include **aerobic exercise,** shown to improve EFs through prefrontal cortex stimulation. **Martial arts** such as tae kwon do, which stresses discipline and self-regulation, has demonstrated improvements that generalize in many aspects of EFs and attention (e.g., sustained focus). Approaches that use **mindfulness techniques** are also gaining prominence. Formal **parenting interventions** have also demonstrated strong evidence for effectiveness. Four programs that have the most empirical support are the *Triple P, Parent-Child Interaction Therapy* (PCIT)*, Incredible Years,* and *New Forest Parenting Programme* .

Table 48.3 outlines interventions to target the specific components of EF. Although interventions may target each component separately, success will be determined by how well treatments can be integrated across settings and generalized to other areas of function. Whenever possible, working with more than one EF simultaneously is encouraged as a means of scaffolding intervention and building on previously mastered skills.

Table 48.3

Executive Function Categories: Presenting Symptoms, Suggested Dysfunction, and Potential Interventions

SYMPTOM/PRESENTING COMPLAINT	SUSPECTED AREA OF DYSFUNCTION	POSSIBLE "REAL WORLD" INTERVENTIONS
Acts before thinking Interrupts Poor behavioral and/or emotional control	Disinhibition/impulsivity	Increase structure in environment to set limits for inhibition problems. Make behavior and work expectations clear and explicit; review with child. Post rules in view; point to them when child breaks rule. Teach response-delay techniques (e.g., counting to 10 before acting).
Cannot follow multistep instructions Forgetful	Working memory	Repeat instructions as needed. Keep instructions clear and concise. Provide concrete references.
Struggles starting assignments/tasks Lacks initiative/motivation Has trouble developing ideas/strategies	Initiation	Increase structure of tasks. Establish and rely on routine. Break tasks into smaller, manageable steps. Place child with partner or group for modeling and cuing from peers.
Does not plan ahead Uses trial-and-error approach	Planning	Practice with tasks with only a few steps first. Teach simple flow charting as a planning tool. Practice with planning tasks (e.g., mazes). Ask child to verbalize plan before beginning work. Ask child to verbalize second plan if first does not work. Ask child to verbalize possible consequences of actions before beginning. Review incidents of poor planning/anticipation with child.
Work/belongings is/are "messy" Random/haphazard problem solving Procrastinates/does not complete tasks	Organization	Increase organization of classroom and activities to serve as model, and help child grasp structure of new information. Present framework of new information to be learned at the outset, and review again at the end of a lesson. Begin with tasks with only few steps and increase gradually.
Gets "stuck" Trouble transitioning Does not adapt to change	Flexibility/shifting	Increase routine to the day. Make schedule clear and public. Forewarn of any changes in schedule. Give "2-minute warning" of time to change. Make changes from one task to the next or one topic to the next, clear and explicit. Shifting may be a problem of inhibiting, so apply

		strategies for inhibition problems.

Developmental Therapy

Speech-language pathologists offer intervention for children with various forms of language disability. Occupational therapists focus on sensorimotor skills, including the motor skills of students with writing problems, and physical therapists address gross motor incoordination.

Curriculum Modifications

Many children with neurodevelopmental dysfunctions require alterations in the school curriculum to succeed, especially as they progress through secondary school. Students with memory weaknesses might need to have their courses selected for them so that they do not have an inordinate cumulative memory load in any single semester. The timing of foreign language learning, the selection of a mathematics curriculum, and the choice of science courses are critical issues for many of these struggling adolescents.

Strengthening of Strengths

Affected children need to have their affinities, potentials, and talents identified clearly and exploited widely. It is as important to augment strengths as it is to attempt to remedy deficiencies. Athletic skills, artistic inclinations, creative talents, and mechanical abilities are among the potential assets of certain students who are underachieving academically. Parents and school personnel need to create opportunities for such students to build on these assets and to achieve respect and praise for their efforts. These well-developed personal assets can ultimately have implications for the transition into young adulthood, including career or college selection.

Individual and Family Counseling

When academic difficulties are complicated by family problems or identifiable psychiatric disorders, **psychotherapy** may be indicated. Mental health professionals may offer long-term or short-term therapy. Such intervention may involve the child alone or the entire family. Cognitive-behavioral therapy is especially effective for mood and anxiety disorders. It is essential that the therapist have a firm understanding of the nature of a child's neurodevelopmental dysfunctions.

Nonstandard Therapies

A variety of treatment methods for neurodevelopmental dysfunctions have been proposed that currently have little to no known scientific evidence of efficacy. This list includes dietary interventions (vitamins, elimination of food additives or potential allergens), neuromotor programs or medications to address vestibular dysfunction, eye exercises, filters, tinted lenses, and various technologic devices. Parents should be cautioned against expending the excessive amounts of time and financial resources usually demanded by these remedies. In many cases, it is difficult to distinguish the nonspecific beneficial effects of increased support and attention paid to the child from the supposed target effects of the intervention.

Medication

Psychopharmacologic agents may be helpful in lessening the toll of some neurodevelopmental dysfunctions. Most often, **stimulants** are used in the treatment of children with attention deficits. Although most children with attention deficits have other associated dysfunctions, such as language disorders, memory problems, motor weaknesses, or social skill deficits, medications such as methylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts, as well as nonstimulants such as **α_2 -adrenergic agonists** and **atomoxetine** , can be important adjuncts to treatment by helping some children focus more selectively and control their impulsivity. When depression or excessive anxiety is a significant component of the clinical picture, **antidepressants** or **anxiolytics** may be helpful. Other drugs may improve behavioral control (see Chapter 33). Children receiving medication need regular follow-up visits that include a history to check for side effects, a review of current behavioral checklists, a complete physical examination, and appropriate modifications of the medication dose. Periodic trials off medication are recommended to establish whether the medication is still necessary.

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CHAPTER 49

Attention-Deficit/Hyperactivity Disorder

David K. Urion

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood, among the most prevalent chronic health conditions affecting school-aged children, and one of the most extensively studied neurodevelopmental disorders of childhood. ADHD is characterized by inattention, including increased distractibility and difficulty sustaining attention; poor impulse control and decreased self-inhibitory capacity; and motor overactivity and motor restlessness (Table 49.1 and Fig. 49.1). Definitions vary in different countries (Table 49.2). Affected children usually experience academic underachievement, problems with interpersonal relationships with family members and peers, and low self-esteem. ADHD often co-occurs with other emotional, behavioral, language, and learning disorders (Table 49.3). Evidence also suggests that for many people, the disorder continues with varying manifestations across the life cycle, leading to significant under- and unemployment, social dysfunction and increased risk of antisocial behaviors (e.g., substance abuse), difficulty maintaining relationships, encounters with the law, death from suicide, and, if untreated, accidents (Figs. 49.2 and 49.3).

Table 49.1

DSM-5 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder (ADHD)

A. A persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. **Inattention:** Six (or more) of the following symptoms of inattention have persisted for ≥6 mo to a degree that is inconsistent with development level and that negatively impacts directly on social and academic/occupational activities:
    a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
    b. Often has difficulty sustaining attention in tasks or play activities.
    c. Often does not seem to listen when spoken to directly.
    d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
    e. Often has difficulty organizing tasks and activities.
    f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork, homework).
    g. Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, tools).
    h. Is often easily distracted by extraneous stimuli.
    i. Is often forgetful in daily activities.
2. **Hyperactivity/impulsivity:** Six (or more) of the following symptoms of inattention have persisted for ≥6 mo to a degree that is inconsistent with development level and that negatively impacts directly on social and academic/occupational activities.
    a. Often fidgets with hands or feet or squirms in seat.
    b. Often leaves seat in classroom or in other situations in which remaining seated is expected.
    c. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness).
    d. Often has difficulty playing or engaging in leisure activities quietly.
    e. Is often “on the go” or often acts as if “driven by a motor.”

f. Often talks excessively.
Impulsivity.
g. Often blurts out answers before questions have been completed.
h. Often has difficulty awaiting turn.
i. Often interrupts or intrudes on others (e.g., butts into conversations or games).

B. Several inattentive or hyperactive/impulsive symptoms were present before 12 yr of age.

C. Several inattentive or hyperactive/impulsive symptoms are present in 2 or more settings (e.g., at school [or work] or at home) and is documented independently.

D. There is clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. Symptoms do not occur exclusively during the course of schizophrenia, or another psychotic disorder, and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Code Based on Type

314.01 Attention-deficit/hyperactivity disorder, combined presentation: if both Criteria A1 and A2 are met for the past 6 mo.

314.00 Attention-deficit/hyperactivity disorder, predominantly inattentive presentation: if Criterion A1 is met but Criterion A2 is not met for the past 6 mo.

314.01 Attention-deficit/hyperactivity disorder, predominantly hyperactive-impulsive presentation: if Criterion A2 is met but Criterion A1 is not met for the past 6 mo.

Specify if:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis are present, and if the symptoms result in no more than minor impairments in social and occupational functioning.

Moderate: Symptoms or functional impairment between “mild” and “severe” are present.

Severe: Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, Washington, DC, 2000, and *Fifth Edition*, (Copyright 2013). American Psychiatric Association.

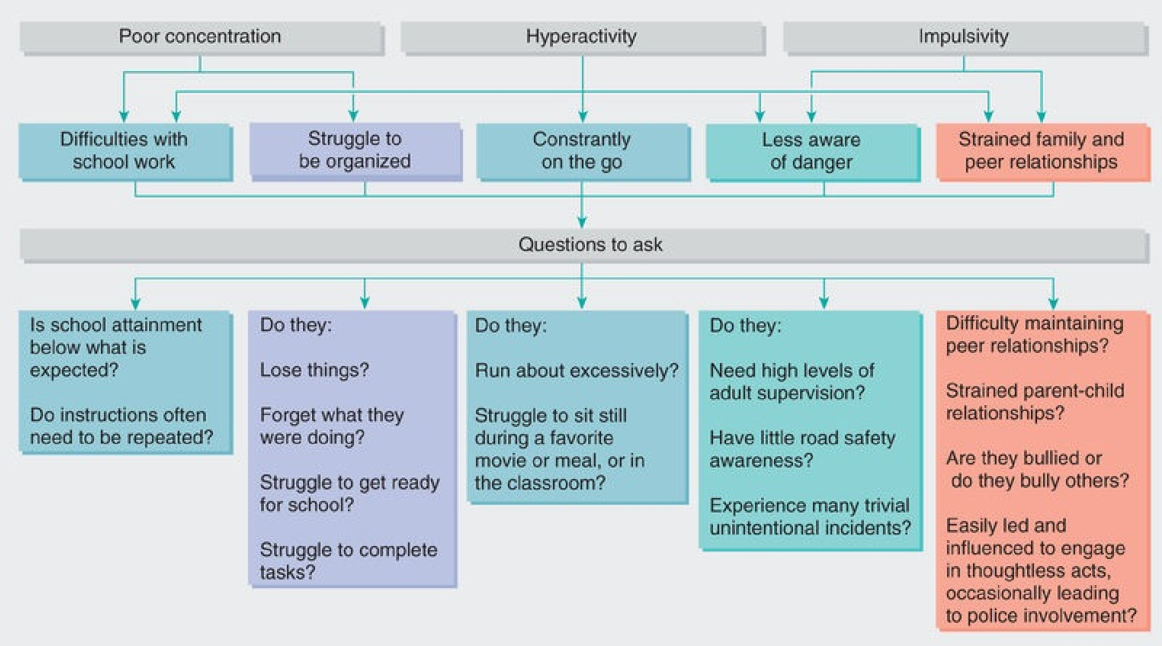
Poor concentration
Hyperactivity
Impulsivity
Difficulties with school work
Struggle to be organized
Constantly on the go
Less aware of danger
Strained family and peer relationships
Questions to ask
Is school attainment below what is expected?
Do instructions often need to be repeated?
Do they:
Lose things?
Forget what they were doing?
Struggle to get ready for school?
Struggle to complete tasks?
Do they:
Run about excessively?
Struggle to sit still during a favorite movie or meal, or in the classroom?
Do they:
Need high levels of adult supervision?
Have little road safety awareness?
Experience many trivial unintentional incidents?
Difficulty maintaining peer relationships?
Strained parent-child relationships?
Are they bullied or do they bully others?
Easily led and influenced to engage in thoughtless acts, occasionally leading to police involvement?

FIG. 49.1 How to assess children for attention-deficit/hyperactivity disorder. (From Verkuijl N, Perkins M, Fazel M: Childhood attention-deficit/hyperactivity disorder, BMJ 350:h2168, 2015, Fig 2, p 146.)

Table 49.2

Differences Between U.S. and European Criteria for ADHD or HKD

DSM-5 ADHD	ICD-10 HKD
SYMPTOMS	
Either or both of the following: At least 6 of 9 inattentive symptoms At least 6 of 9 hyperactive or impulsive symptoms	*All of the following:* At least 6 of 8 inattentive symptoms At least 3 of 5 hyperactive symptoms At least 1 of 4 impulsive symptoms

PERVASIVENESS	
Some impairment from symptoms is present in >1 setting	Criteria are met for >1 setting

ADHD, Attention-deficit/hyperactivity disorder; HKD, hyperkinetic disorder; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* ; ICD-10, *International Classification of Diseases, Tenth Edition* .

From Biederman J, Faraone S: Attention-deficit hyperactivity disorder, *Lancet* 366:237–248, 2005.

Table 49.3

Differential Diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD)

Psychosocial Factors

Response to physical or sexual abuse
Response to inappropriate parenting practices
Response to parental psychopathology
Response to acculturation
Response to inappropriate classroom setting

Diagnoses Associated With ADHD Behaviors

Fragile X syndrome
Fetal alcohol syndrome
Pervasive developmental disorders
Obsessive-compulsive disorder
Gilles de la Tourette syndrome
Attachment disorder with mixed emotions and conduct

Medical and Neurologic Conditions

Thyroid disorders (including general resistance to thyroid hormone)
Heavy metal poisoning (including lead)
Adverse effects of medications
Effects of abused substances
Sensory deficits (hearing and vision)
Auditory and visual processing disorders
Neurodegenerative disorder, especially leukodystrophies

Posttraumatic head injury
Postencephalitic disorder

Note: Coexisting conditions with possible ADHD presentation include oppositional defiant disorder, anxiety disorders, conduct disorder, depressive disorders, learning disorders, and language disorders. Presence of one or more of the symptoms of these disorders can fall within the spectrum of normal behavior, whereas a range of these symptoms may be problematic but fall short of meeting the full criteria for the disorder.

From Reiff MI, Stein MT: Attention-deficit/hyperactivity disorder evaluation and diagnosis: a practical approach in office practice, *Pediatr Clin North Am* 50:1019–1048, 2003. Adapted from Reiff MI: Attention-deficit/hyperactivity disorders. In Bergman AB, editor: *20 Common problems in pediatrics,* New York, 2001, McGraw-Hill, p 273.

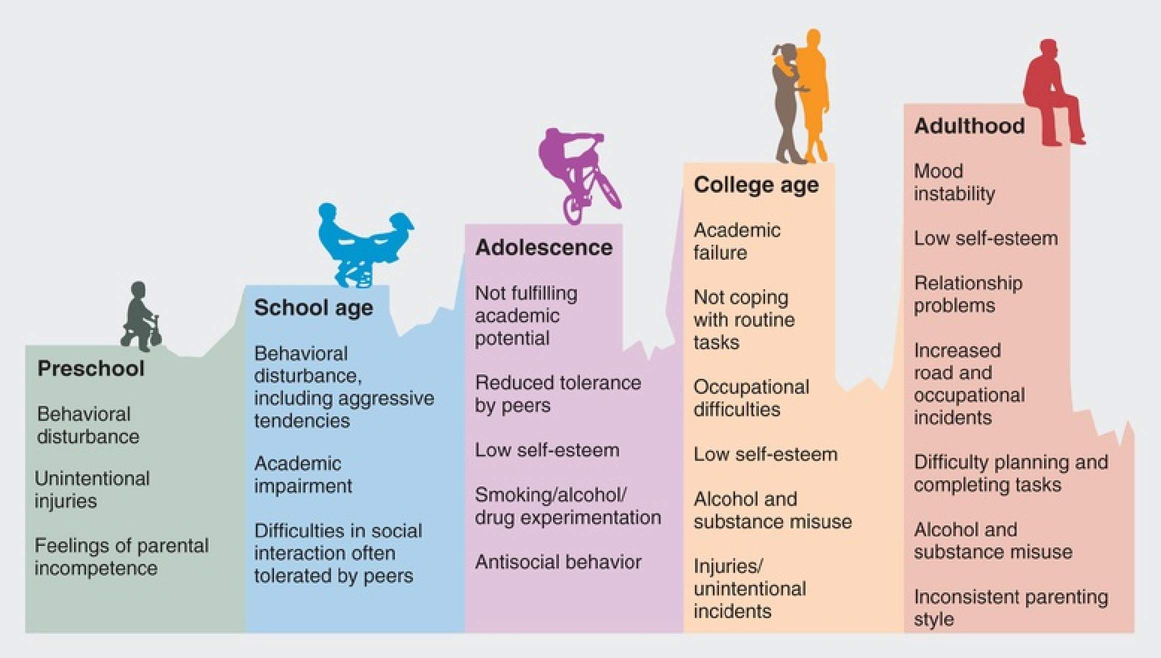
Preschool
Behavioral disturbance
Unintentional injuries
Feelings of parental incompetence
School age
Behavioral disturbance, including aggressive tendencies
Academic impairment
Difficulties in social interaction often tolerated by peers
Adolescence
Not fulfilling academic potential
Reduced tolerance by peers
Low self-esteem
Smoking/alcohol/drug experimentation
Antisocial behavior
College age
Academic failure
Not coping with routine tasks
Occupational difficulties
Low self-esteem
Alcohol and substance misuse
Injuries/unintentional incidents
Adulthood
Mood instability
Low self-esteem
Relationship problems
Increased road and occupational incidents
Difficulty planning and completing tasks
Alcohol and substance misuse
Inconsistent parenting style

FIG. 49.2 Possible developmental impacts of attention-deficit/hyperactivity disorder. (From Verkuijl N, Perkins M, Fazel M: Childhood attention-deficit/hyperactivity disorder, *BMJ* 350:h2168, 2015, Fig 1, p 145.)

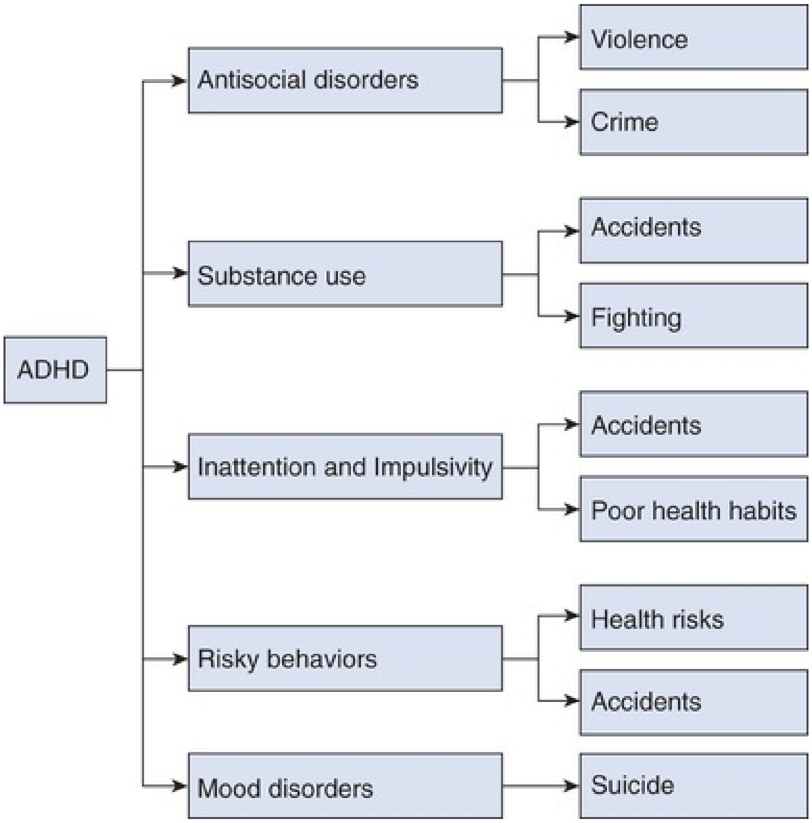
ADHD
Antisocial disorders
Violence
Crime
Substance use
Accidents
Fighting
Inattention and Impulsivity
Accidents
Poor health habits
Risky behaviors
Health risks
Accidents
Mood disorders
Suicide

FIG. 49.3 Pathways to premature death in persons with attention-deficit/hyperactivity disorder (ADHD). (From Faraone SV: Attention deficit hyperactivity disorder and premature death, *Lancet* 385:2132–2133, 2015.)

Etiology

No single factor determines the expression of ADHD; ADHD may be a final common pathway for a variety of complex brain developmental processes. Mothers of children with ADHD are more likely to experience birth complications, such as toxemia, lengthy labor, and complicated delivery. Maternal drug use has also been identified as a risk factor in the development of ADHD. Maternal smoking, alcohol use during pregnancy, and prenatal or postnatal exposure to lead are frequently linked to the attentional difficulties associated with development of ADHD, but less clearly to hyperactivity. Food coloring and preservatives have inconsistently been associated with increased hyperactivity in children with ADHD.

There is a strong genetic component to ADHD. Genetic studies have primarily implicated 2 candidate genes, the dopamine transporter gene *(DAT1)* and a particular form of the dopamine 4 receptor gene *(DRD4)*, in the development of ADHD. Additional genes that might contribute to ADHD include *DOCK2*, associated with a pericentric inversion 46N inv(3)(p14:q21) involved in cytokine regulation; a sodium-hydrogen exchange gene; and *DRD5, SLC6A3, DBH, SNAP25, SLC6A4,* and *HTR1B.*

Structural and functional abnormalities of the brain have been identified in children with ADHD. These include dysregulation of the frontal subcortical circuits, small cortical volumes in this region, widespread small-volume reduction throughout the brain, and abnormalities of the cerebellum, particularly midline/vermian elements (see Pathogenesis). Brain injury also increases the risk of ADHD. For example, 20% of children with severe traumatic brain injury are reported to have subsequent onset of substantial symptoms of impulsivity and inattention. However, ADHD may also increase the risk of traumatic brain injury.

Psychosocial family stressors can also contribute to or exacerbate the symptoms of ADHD, including poverty, exposure to violence, and undernutrition or malnutrition.

Epidemiology

Studies of the prevalence of ADHD worldwide have generally reported that 5–10% of school-age children are affected, although rates vary considerably by country, perhaps in part because of differing sampling and testing techniques. Rates may be higher if symptoms (inattention, impulsivity, hyperactivity) are considered in the absence of functional impairment. The prevalence rate in adolescent samples is 2–6%. Approximately 2% of adults meet criteria for ADHD. ADHD is often underdiagnosed in children and adolescents. Youth with ADHD are often undertreated with respect to what is known about the needed and appropriate doses of medications. Many children with ADHD also present with comorbid neuropsychiatric diagnoses, including oppositional defiant disorder, conduct disorder, learning disabilities, and anxiety disorders. The incidence of ADHD appears increased in children with neurologic disorders such as the epilepsies, neurofibromatosis, and tuberous sclerosis (see Table 49.3).

Pathogenesis

Brain MRI studies in children with ADHD indicate a reduction or even loss of the normal hemispheric asymmetry in the brain, as well as smaller brain volumes of specific structures, such as the prefrontal cortex and basal ganglia. Children with ADHD have approximately a 5–10% reduction in the volume of these brain structures. MRI findings suggest low blood flow to the striatum. Functional MRI data suggest deficits in dispersed functional networks for selective and sustained attention in ADHD that include the striatum, prefrontal regions, parietal lobe, and temporal lobe. The prefrontal cortex and basal ganglia are rich in dopamine receptors. This knowledge, plus data about the dopaminergic mechanisms of action of medication treatment for ADHD, has led to the **dopamine hypothesis,** which postulates that disturbances in the dopamine system may be related to the onset of ADHD. Fluorodopa positron emission tomography (PET) scans also support the dopamine hypothesis through the identification of low levels of dopamine activity in adults with ADHD.

Clinical Manifestations

Development of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria leading to the diagnosis of ADHD has occurred mainly in field trials with children 5-12 yr of age (see Table 49.1 and Fig. 49.1). The DSM-5 notably expanded the accepted age of onset for symptoms of ADHD, and studies utilizing these broader criteria demonstrate a good correlation with data from DSM-IV criteria–based studies. The current DSM-5 criteria state that the behavior must be developmentally inappropriate (substantially different from that of other children of the same age and developmental level), must begin before age 12 yr, must be present for at least 6 mo, must be present in 2 or more settings and reported as such by independent observers, and must not be secondary to another disorder. DSM-5 identifies three presentations of ADHD. The **inattentive** presentation is more common in females and is associated with relatively high rates of internalizing symptoms (anxiety and low mood). The other two presentations, **hyperactive-impulsive** and **combined** , are more often diagnosed in males (see Fig. 49.1).

Clinical manifestations of ADHD may change with age (see Fig. 49.2). The symptoms may vary from motor restlessness and aggressive and disruptive behavior, which are common in preschool children, to disorganized, distractible, and inattentive symptoms, which are more typical in older adolescents and adults. ADHD is often difficult to diagnose in preschoolers because distractibility and inattention are often considered developmental norms during this period.

Diagnosis and Differential Diagnosis

A diagnosis of ADHD is made primarily in clinical settings after a thorough evaluation, including a careful history and clinical interview to rule in or to identify other causes or contributing factors; completion of behavior rating scales by different observers from at least 2 settings (e.g., teacher and parent); a physical examination; and any necessary or indicated laboratory tests that arise from conditions suspected based on history and/or physical examination. It is important to systematically gather and evaluate information from a variety of sources, including the child, parents, teachers, physicians, and when appropriate, other caretakers, over the course of both diagnosis and subsequent management.

Clinical Interview and History

The clinical interview allows a comprehensive understanding of whether the symptoms meet the diagnostic criteria for ADHD. During the interview, the clinician should gather information pertaining to the history of the presenting problems, the child's overall health and development, and the social and family history. The interview should emphasize factors that might affect the development or integrity of the central nervous system or reveal chronic illness, sensory impairments, sleep disorders, or medication use that might affect the child's functioning. Disruptive social factors, such as family discord, situational stress, and abuse or neglect, can result in hyperactive or anxious behaviors. A family history of first-degree relatives with ADHD, mood or anxiety disorders, learning disability, antisocial disorder, or alcohol or substance abuse might indicate an increased risk of ADHD and comorbid conditions.

Behavior Rating Scales

Behavior rating scales are useful in establishing the magnitude and pervasiveness of the symptoms, but are not sufficient alone to make a diagnosis of ADHD. A variety of well-established behavior rating scales have obtained good results in discriminating between children with ADHD and controls. These measures include, but are not limited to, the *Vanderbilt ADHD Diagnostic*

Rating Scale, the *Conner Rating Scales* (parent and teacher), *ADHD Rating Scale 5,* the *Swanson, Nolan, and Pelham Checklist* (SNAP), and the *ADD-H: Comprehensive Teacher Rating Scale* (ACTeRS). Other broad-band checklists, such as the *Achenbach Child Behavior Checklist* (CBCL) or *Behavioral Assessment Scale for Children* (BASC), are useful, particularly when the child may be experiencing coexisting problems in other areas (anxiety, depression, conduct problems). Some, such as the BASC, include a validation scale to help determine the reliability of a given observer's assessment of the child.

Physical Examination and Laboratory Findings

No laboratory tests are available to identify ADHD in children. The presence of hypertension, ataxia, or symptoms of a sleep or thyroid disorder should prompt further neurologic or endocrine diagnostic evaluation. Impaired fine motor movement and poor coordination and other subtle neurologic motor signs (difficulties with finger tapping, alternating movements, finger-to-nose, skipping, tracing a maze, cutting paper) are common but not sufficiently specific to contribute to a diagnosis of ADHD. The clinician should also identify any possible vision or hearing problems. The clinician should consider testing for elevated lead levels in children who present with some or all of the diagnostic criteria, if these children are exposed to environmental factors that might put them at risk (substandard housing, old paint, proximity to highway with deposition of lead in topsoil from automobile exhaust years ago). Behavior in the structured laboratory setting might not reflect the child's typical behavior in the home or school environment. Thus, computerized attentional tasks and electroencephalographic assessments are not needed to make the diagnosis, and compared to the clinical gold standard, these are subject to false-positive and false-negative errors. Similarly, observed behavior in a physician's office is not sufficient to confirm or rule-out the diagnosis of ADHD.

Differential Diagnosis

Chronic illnesses, such as migraine headaches, absence seizures, asthma/allergies, hematologic disorders, diabetes, and childhood cancer, affect up to 20% of U.S. children and can impair children's attention and school performance, because of either the disease itself or the medications used to treat or control the underlying illness (medications for asthma, corticosteroids, anticonvulsants, antihistamines) (see Table 49.3). In older children and adolescents, **substance abuse** can result in declining school performance and inattentive behavior (see Chapter 140).

Sleep disorders , including those secondary to chronic upper airway obstruction from enlarged tonsils and adenoids, often result in behavioral and emotional symptoms that can resemble or exacerbate ADHD (see Chapter 31). Periodic leg movements of sleep/restless leg syndrome has been associated with attentional symptoms, and inquiry regarding this should be made during the history. Behavioral and emotional disorders can cause disrupted sleep patterns as well.

Depression and anxiety disorders can cause many of the same symptoms as ADHD (inattention, restlessness, inability to focus and concentrate on work, poor organization, forgetfulness) but can also be comorbid conditions (see Chapters 38 and 39). Obsessive-compulsive disorder can mimic ADHD, particularly when recurrent and persistent thoughts, impulses, or images are intrusive and interfere with normal daily activities. Adjustment disorders secondary to major life stresses (death of a close family member, parents' divorce, family violence, parents' substance abuse, a move, shared social trauma such as bombings or other attacks) or parent–child relationship disorders involving conflicts over discipline, overt child abuse and/or neglect, or overprotection can result in symptoms similar to those of ADHD.

Although ADHD is believed to result from primary impairment of attention, impulse control, and motor activity, there is a high prevalence of comorbidity with other neuropsychiatric disorders (see Table 49.3). Of children with ADHD, 15–25% have learning disabilities, 30–35% have developmental language disorders, 15–20% have diagnosed mood disorders, and 20–25% have coexisting anxiety disorders. Children with ADHD can also have concurrent diagnoses of sleep disorders, memory impairment, and decreased motor skills.

Treatment

Psychosocial Treatments

Once the diagnosis of ADHD has been established, the parents and child should be educated with regard to the ways ADHD can affect learning, behavior, self-esteem, social skills, and family function. The clinician should set goals for the family to improve the child's interpersonal relationships, develop study skills, and decrease disruptive behaviors. Parent support groups with appropriate professional consultation to such groups can be very helpful.

Behaviorally Oriented Treatments

Treatments geared toward behavioral management often occur in the time frame of 8-12 sessions. The goal of such treatment is for the clinician to identify targeted behaviors that cause impairment in the child's life (disruptive behavior, difficulty in completing homework, failure to obey home or school rules) and for the child to work on progressively improving his or her skill in these areas. The clinician should guide the parents and teachers in setting appropriate expectations, consistently implementing rewards to encourage desired behaviors and consequences to discourage undesired behaviors. In short-term comparison trials, stimulants have been more effective than behavioral treatments used alone in improving core ADHD symptoms for most children. Behavioral interventions are modestly successful at improving core ADHD symptoms and are considered the first-line treatment in preschool-age children with ADHD. In addition, behavioral treatment may be particularly useful for children with comorbid anxiety, complex comorbidities, family stressors, and when combined with medication.

Medications

The most widely used medications for the treatment of ADHD are the presynaptic dopaminergic agonists, commonly called **psychostimulant** medications, including methylphenidate, dexmethylphenidate, amphetamine, and various amphetamine and dextroamphetamine preparations. Longer-acting, once-daily forms of each of the major types of stimulant medications are available and facilitate compliance with treatment and coverage over a longer period (see Table 49.3). When starting a stimulant, the clinician can select either a methylphenidate-based or an amphetamine-based compound. If a full range of methylphenidate dosages is used, approximately 25% of patients have an optimal response on a low dose (<0.5 mg/kg/day for methylphenidate, <0.25 mg/kg/day for amphetamines), 25% on a medium dose (0.5-1.0 mg/kg/day for methylphenidate, 0.25-0.5 mg/kg/day for amphetamines), and 25% on a high dose (1.0-1.5 mg/day for methylphenidate, 0.5-0.75 mg/kg/day for amphetamine); another 25% will be unresponsive or will have side effects, making that drug particularly unpalatable for the family (See Table 33.2 for more information on dosing).

Over the first 4 wk of treatment, the physician should increase the medication dose as tolerated (keeping side effects minimal to absent) to achieve maximum benefit. If this strategy does not yield satisfactory results, or if side effects prevent further dose adjustment in the presence of persisting symptoms, the clinician should use an alternative class of stimulants that was not used previously. If a methylphenidate compound is unsuccessful, the clinician should switch to an amphetamine product. If satisfactory treatment results are not obtained with the 2nd stimulant, clinicians may choose to prescribe *atomoxetine,* a noradrenergic reuptake inhibitor that has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD in children, adolescents, and adults. Atomoxetine should be initiated at a dose of 0.3 mg/kg/day and titrated over 1-3 wk to a maximum total daily dosage of 1.2-1.4 mg/kg/day. The dose should be divided into twice-daily portions. Once-daily dosing appears to be associated with a high incidence of treatment failure. Long-acting *guanfacine* and *clonidine* are also FDA approved for the treatment of ADHD (see Chapter 33). These medications can also treat motor and vocal tics and so may be a reasonable choice in a child with a comorbid tic disorder. Drugs to treat ADHD do not increase the incidence of tics in children predisposed to a tic disorder. In the past, tricyclic antidepressants have been used to treat ADHD, but TCAs are rarely used now because of the risk of sudden death, particularly if an overdose is taken.

The clinician should consider careful monitoring of medication a necessary component of treatment in children with ADHD. When physicians prescribe medications for the treatment of ADHD, they tend to use lower-than-optimal doses. Optimal treatment usually requires somewhat higher doses than tend to be found in routine practice settings. All-day preparations are also useful to maximize positive effects and minimize side effects, and regular medication follow-up visits should be offered (≥4 times/yr) as opposed to the twice-yearly medication visits often used in standard community care settings.

Medication alone may not be sufficient to treat ADHD in children, particularly when children have multiple psychiatric disorders or a stressed home environment. When children do not respond to medication, it may be appropriate to refer them to a mental health specialist. Consultation with a child psychiatrist, developmental-behavioral pediatrician, or psychologist can also be beneficial to determine the next steps for treatment, including adding other components and supports to the overall treatment program. Evidence suggests that children who receive careful medication management, accompanied by frequent treatment follow-up, all within the context of an educative, supportive relationship with the primary care provider, are likely to experience behavioral gains.

Stimulant drugs used to treat ADHD may be associated with an increased risk of adverse cardiovascular events, including sudden cardiac death, myocardial infarction, and stroke, in young adults and rarely in children. In some of the reported cases, the patient had an underlying disorder, such as hypertrophic obstructive cardiomyopathy, which is made worse by sympathomimetic agents. These events are rare but nonetheless warrant consideration before initiating treatment and during monitoring of therapy with stimulants. Children with a positive personal or family history of cardiomyopathy, arrhythmias, or syncope require an electrocardiogram and possible cardiology consultation before a stimulant is prescribed (Fig. 49.4).

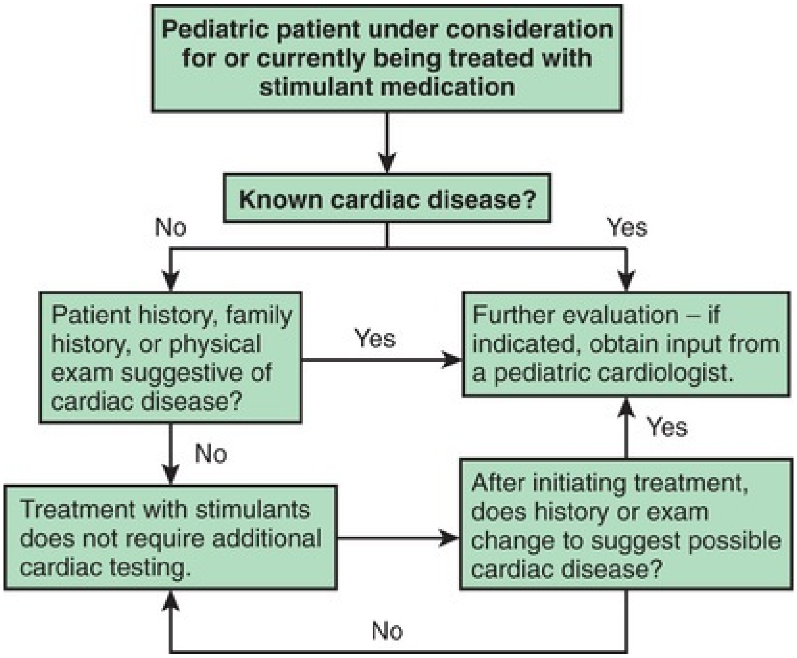
Pediatric patient under consideration for or currently being treated with stimulant medication
Known cardiac disease?
No
Yes
Patient history, family history, or physical exam suggestive of cardiac disease?
Yes
Further evaluation – if indicated, obtain input from a pediatric cardiologist.
No
Yes
Treatment with stimulants does not require additional cardiac testing.
After initiating treatment, does history or exam change to suggest possible cardiac disease?
No

FIG. 49.4 Cardiac evaluation of children and adolescents with ADHD receiving or being considered for stimulant medications. (From Perrin JM, Friedman RA, Knilans TK: Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder, *Pediatrics* 122:451–453, 2008.)

Prognosis

A childhood diagnosis of ADHD often leads to persistent ADHD throughout the life span. From 60–80% of children with ADHD continue to experience symptoms in adolescence, and up to 40–60% of adolescents exhibit ADHD symptoms into adulthood. In children with ADHD, a reduction in hyperactive behavior often occurs with age. Other symptoms associated with ADHD can become more prominent with age, such as inattention, impulsivity, and disorganization, and these exact a heavy toll on young adult functioning. Risk factors in children with untreated ADHD as they become adults include engaging in risk-taking behaviors (sexual activity, delinquent behaviors, substance use), educational underachievement or employment difficulties, and relationship difficulties. With proper treatment, the risks associated with ADHD, including injuries, can be significantly reduced. Consistent treatment with medication and adjuvant therapies appears to lower the risk of adverse outcomes, such as substance abuse.

Prevention

Parent training can lead to significant improvements in preschool children with ADHD symptoms, and parent training for preschool youth with ADHD can reduce oppositional behavior. To the extent that parents, teachers, physicians, and policymakers support efforts for earlier detection, diagnosis, and treatment, prevention of long-term adverse effects of ADHD on affected children's lives should be reconsidered within the lens of prevention. Given the effective treatments for ADHD now available, and the well-documented evidence about the long-term effects of untreated or ineffectively treated ADHD on children and youth, prevention of these consequences should be within the grasp of physicians and the children and families with ADHD for whom we are responsible.

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CHAPTER 50

Dyslexia

Sally E. Shaywitz, Bennett A. Shaywitz

The most current definition of *dyslexia* is now codified in U.S. Federal law (First Step Act of 2018, PL: 115–391): “The term *dyslexia* means an unexpected difficulty in reading for an individual who has the intelligence to be a much better reader, most commonly caused by a difficulty in the phonological processing (the appreciation of the individual sounds of spoken language), which affects the ability of an individual to speak, read, and spell.” In typical readers, development of reading and intelligence quotient (IQ) are dynamically linked over time. In dyslexic readers, however, a developmental uncoupling occurs between reading and IQ (Fig. 50.1), such that reading achievement is significantly below what would be expected given the individual's IQ. The discrepancy between reading achievement and IQ provides the long-sought empirical evidence for the seeming paradox between cognition and reading in individuals with developmental dyslexia, and this discrepancy is now recognized in the Federal definition as unexpected difficulty in reading.

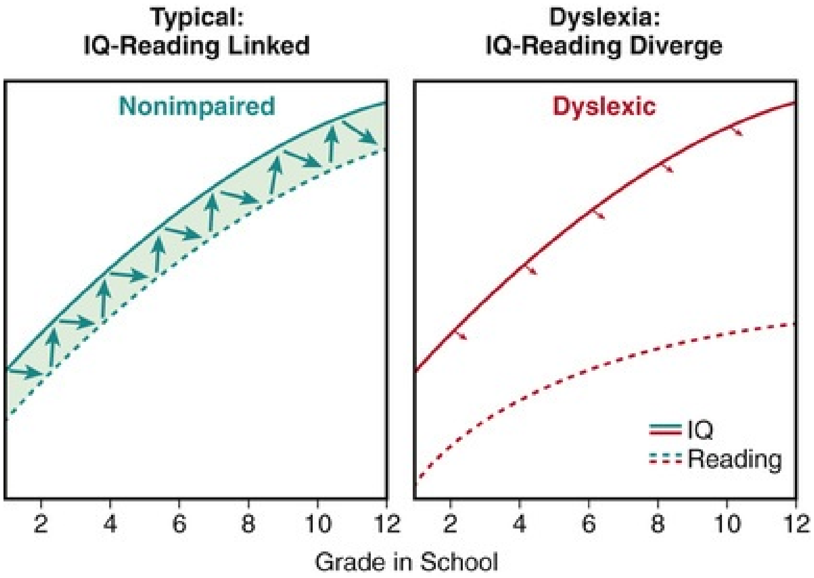

FIG. 50.1 **Uncoupling of reading and IQ over time: empirical evidence for a definition of dyslexia. Left , In typical readers, reading and IQ development are dynamically linked over time. Right, In contrast, reading and IQ development are dissociated in dyslexic readers, and one does not influence the other. (Data adapted from Ferrer E, Shaywitz BA, Holahan JM, et al: Uncoupling of reading and IQ over time: empirical evidence for a definition of dyslexia, *Psychol Sci* 21(1):93–101, 2010.)**

Etiology

Dyslexia is familial, occurring in 50% of children who have a parent with dyslexia, in 50% of the siblings of dyslexic persons, and in 50% of the parents of dyslexic persons. Such observations have naturally led to a search for genes responsible for dyslexia, and at one point there was hope that heritability would be related to a small number of genes. Genome-wide association studies (GWAS), however, have demonstrated that a large number of genes are involved, each producing a small effect. Advances in genetics have confirmed what the GWAS suggested, that complex traits such as reading are the work of thousands of genetic variants, working in concert (see Chapter 99). Thus, pediatricians should be wary of recommending any genetic test to their patients that purports to diagnose dyslexia in infancy or before language and reading have even emerged. It is unlikely that a single gene or even a few genes will reliably identify people with dyslexia. Rather, dyslexia is best explained by **multiple genes** , each contributing a small amount toward the expression of dyslexia.

Epidemiology

Dyslexia is the most common and most comprehensively studied of the learning disabilities, affecting 80% of children identified as having a learning disability. Dyslexia may be the most common neurobehavioral disorder affecting children, with prevalence rates ranging from 20% in unselected population-based samples to much lower rates in school-identified samples. The low prevalence rate in school-identified samples may reflect the reluctance of schools to identify dyslexia. Dyslexia occurs with equal frequency in boys and girls in survey samples in which *all* children are assessed. Despite such well-documented findings, schools continue to identify more boys than girls, probably reflecting the more rambunctious behavior of boys who come to the teacher's attention because of misbehavior, while girls with reading difficulty, who are less likely to be misbehaving, are also less likely to be identified by the schools. Dyslexia fits a dimensional model in which reading ability and disability occur along a *continuum*, with dyslexia representing the lower tail of a normal distribution of reading ability.

Pathogenesis

Evidence from a number of lines of investigation indicates that dyslexia reflects deficits within the language system, and more specifically, within the **phonologic component** of the language system engaged in processing the sounds of speech. Individuals with dyslexia have difficulty developing an awareness that spoken words can be segmented into smaller elemental units of sound (phonemes), an essential ability given that reading requires that the reader map or link printed symbols to sound. Increasing evidence indicates that disruption of attentional mechanisms may also play an important role in reading difficulties.

Functional brain imaging in both children and adults with dyslexia demonstrates an inefficient functioning of left hemisphere posterior brain systems, a pattern referred to as the *neural signature of dyslexia* (Fig. 50.2). Although functional magnetic resonance imaging (fMRI) consistently demonstrates differences between *groups* of dyslexic compared to typical readers, brain imaging is not able to differentiate an *individual* case of a dyslexic reader from a typical reader and thus is not useful in diagnosing dyslexia.

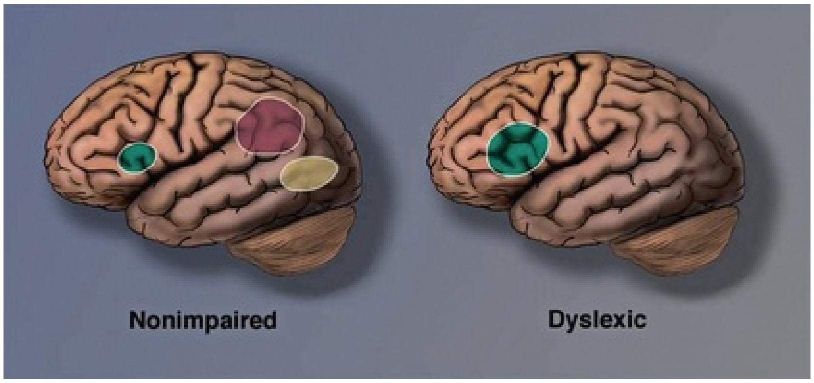

FIG. 50.2 A neural signature for dyslexia. The *left* side of the figure shows a schematic of left hemisphere brain systems in in typical (nonimpaired) readers. The 3 systems for reading are an anterior system in the region of the inferior frontal gyrus (Broca's area), serving articulation and word analysis, and 2 posterior systems, 1 in the occipitotemporal region serving word analysis, and a 2nd in the occipitotemporal region (the word-form area) serving the rapid, automatic, fluent identification of words. In dyslexic readers (*right* side of figure), the 2 posterior systems are functioning inefficiently and appear underactivated. This pattern of underactivation in left posterior reading systems is referred to as the neural signature for dyslexia. (Adapted from Shaywitz S: *Overcoming dyslexia: a new and complete science-based program for reading problems at any level.* New York, 2003, Alfred A. Knopf. Copyright 2003 by S. Shaywitz. Adapted with permission.)

Clinical Manifestations

Reflecting the underlying phonologic weakness, children and adults with dyslexia manifest problems in both spoken and written language. Spoken language difficulties are typically manifest by mispronunciations, lack of glibness, speech that lacks fluency with many pauses or hesitations and “ums,” word-finding difficulties with the need for time to summon an oral response, and the inability to come up with a verbal response quickly when questioned; these reflect *sound-based,* not semantic or knowledge-based, difficulties.

Struggles in decoding and word recognition can vary according to age and developmental level. The cardinal signs of dyslexia observed in school-age children and adults are a labored, effortful approach to reading involving decoding, word recognition, and text reading. Listening comprehension is typically robust. Older children improve reading accuracy over time, but without commensurate gains in reading fluency; they remain slow readers. Difficulties in spelling typically reflect the phonologically based difficulties observed in oral reading. Handwriting is often affected as well.

History often reveals early subtle language difficulties in dyslexic children. During the preschool and kindergarten years, at-risk children display difficulties playing rhyming games and learning the names for letters and numbers. Kindergarten assessments of these language skills can help identify children at risk for dyslexia. Although a dyslexic child enjoys and benefits from being read to, the child might avoid reading aloud to the parent or reading independently.

Dyslexia may coexist with attention-deficit/hyperactivity disorder (see Chapter 49); this comorbidity has been documented in both referred samples (40% comorbidity) and nonreferred samples (15% comorbidity).

Diagnosis

A large achievement gap between typical and dyslexic readers is evident as early as 1st grade and persists (Fig. 50.3). These findings provide strong evidence and impetus for early screening and identification of and early intervention for young children at risk for dyslexia. One source of potentially powerful and highly accessible screening information is the teacher's judgment about the child's reading and reading-related skills. Evidence-based screening can be carried out as early as kindergarten, and also in grades 1-3, by the child's teacher. The teachers' responses to a small set of questions (10-12 questions) predict a pool of children who are at risk for dyslexia with a high degree of accuracy. Screening takes less than 10 minutes, is completed on a tablet, and is extremely efficient and economical. Children found to be at-risk will then have further assessment and, if diagnosed as dyslexic, should receive evidence-based intervention.

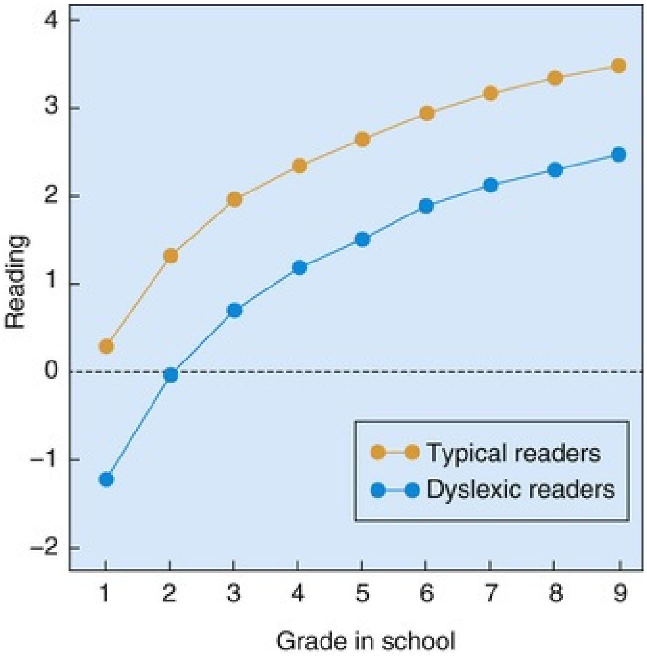

FIG. 50.3 **Reading from grades 1 through 9 in typical and dyslexic readers. The achievement gap between typical and dyslexic readers is evident as early as 1st grade and persists through adolescence. (Adapted from Ferrer E, Shaywitz BA, Holahan JM, et al: Achievement gap in reading is present as early as first grade and persists through adolescence, *J Pediatr* 167:1121–1125, 2015.)**

Dyslexia is a clinical diagnosis, and history is especially critical. The clinician seeks to determine through history, observation, and psychometric assessment, if there are unexpected difficulties in reading (based on the person's intelligence, chronological/grade, level of education or professional status) and associated linguistic problems at the level of phonologic processing. No single test score is pathognomonic of dyslexia. The diagnosis of dyslexia should reflect a thoughtful synthesis of all clinical data available.

Dyslexia is distinguished from other disorders that can prominently feature reading difficulties by the unique, circumscribed nature of the *phonologic deficit*, one that does not intrude into other linguistic or cognitive domains. A core assessment for the diagnosis of dyslexia in children includes tests of language, particularly phonology; reading, including real and pseudowords; reading fluency; spelling; and tests of intellectual ability. Additional tests of memory, general language skills, and mathematics may be administered as part of a more comprehensive evaluation of cognitive, linguistic, and academic function. Some schools use a **response to intervention (RtI)** approach to identifying reading disabilities (see Chapter 51.1). Once a diagnosis has been made, dyslexia is a permanent diagnosis and need not be reconfirmed by new assessments.

For informal screening, in addition to a careful history, the primary care physician in an office setting can listen to the child read aloud from the child's own grade-level reader. Keeping a set of graded readers available in the office serves the same purpose and eliminates the need for the child to bring in schoolbooks. **Oral reading** is a sensitive measure of reading accuracy and fluency. The most consistent and telling sign of a reading disability in an accomplished young adult is slow and laborious reading and writing. In attempting to read aloud, most children and adults with dyslexia display an effortful approach to decoding and recognizing single words, an approach in children characterized by hesitations, mispronunciations, and repeated attempts to sound out unfamiliar words. In contrast to the difficulties they experience in decoding single words, persons with dyslexia typically possess the vocabulary, syntax, and other higher-level abilities involved in comprehension.

The failure either to recognize or to measure the lack of fluency in reading is perhaps the most common error in the diagnosis of dyslexia in older children and accomplished young adults. Simple word identification tasks will not detect dyslexia in a person who is accomplished enough to be in honors high school classes or to graduate from college or obtain a graduate degree. Tests relying on the accuracy of word identification alone are inappropriate to use to diagnose dyslexia because they show little to nothing of the *struggle* to read. Because they assess reading accuracy but not automaticity (speed), the types of reading tests used for school-age children might provide misleading data on bright adolescents and young adults. The most critical tests are those that are *timed* ; they are the most sensitive in detecting dyslexia in a bright adult. Few standardized tests for young adult readers are administered under timed and untimed conditions; the *Nelson-Denny Reading Test* is an exception. The helpful *Test of Word Reading Efficiency* (TOWRE) examines simple word reading under timed conditions. Any scores obtained on testing must be considered relative to peers with the same degree of education or professional training.

Management

The management of dyslexia demands a life-span perspective. Early in life the focus is on **remediation** of the reading problem. Applying knowledge of the importance of early language, including vocabulary and phonologic skills, leads to significant improvements in children's reading accuracy, even in predisposed children. As a child matures and enters the more time-demanding setting of middle and then high school, the emphasis shifts to the important role of providing accommodations. Based on the work of the National Reading Panel, evidence-based reading intervention methods and programs are identified. Effective intervention programs provide systematic instruction in 5 key areas: phonemic awareness, phonics, fluency, vocabulary, and comprehension strategies. These programs also provide ample opportunities for writing, reading, and discussing literature.

Taking each component of the reading process in turn, effective interventions improve phonemic awareness: the ability to focus on and manipulate phonemes (speech sounds) in spoken syllables and words. The elements found to be most effective in enhancing **phonemic awareness** , reading, and spelling skills include teaching children to manipulate phonemes with letters; focusing the instruction on 1 or 2 types of phoneme manipulations rather than multiple types; and teaching children in small groups. Providing instruction in phonemic awareness is necessary but not sufficient to teach children to read. Effective intervention programs include teaching **phonics** , or making sure that the beginning reader understands how letters are linked to sounds (phonemes) to form letter-sound correspondences and spelling patterns. The instruction should be explicit and systematic; phonics instruction enhances children's success in learning to read, and systematic phonics instruction is more effective than instruction that teaches little or no phonics or teaches phonics casually or haphazardly. Important but often overlooked is starting children on reading connected text early on, optimally at or near the beginning of reading instruction.

Fluency is of critical importance because it allows the automatic, rapid recognition of words, and while it is generally recognized that fluency is an important component of skilled reading, it has proved difficult to teach. Interventions for vocabulary development and reading comprehension are not as well established. The most effective methods to teach reading comprehension involve teaching vocabulary and strategies that encourage active interaction between the reader and the text. Emerging science indicates that it is not only teacher content knowledge but the teacher's skill in engaging the student and focusing the student's attention on the reading task at hand that is required for effective instruction.

For those in high school, college, and graduate school, provision of **accommodations** most often represents a highly effective approach to dyslexia. Imaging studies now provide neurobiologic evidence of the need for extra time for dyslexic students; accordingly, college students with a childhood history of dyslexia require extra time in reading and writing assignments as well as examinations. Many adolescent and adult students have been able to improve their reading accuracy, but without commensurate gains in reading speed. The accommodation of extra time reconciles the individual's often high cognitive ability and slow reading, so that the exam is a measure of that person's ability rather than his disability. Another important accommodation is teaching the dyslexic student to listen to texts. Excellent text-to-speech programs and apps available for Apple and Android systems include Voice Dream Reader, Immersive Reader (in OneNote as part of Microsoft Office), Kurzweil Firefly, Read & Write Gold, Read: OutLoud, and Natural Reader. Voice-to-text programs are also helpful, often part of the suite of programs as well as the popular Dragon Dictate. Voice to text is found on many smartphones. Other helpful accommodations include the use of laptop computers with spelling checkers, access to lecture notes, tutorial services, and a separate quiet room for taking tests.

In addition, the impact of the primary phonologic weakness in dyslexia mandates special consideration during oral examinations so that students are not graded on their lack of glibness or speech hesitancies but on their content knowledge. Unfortunately, speech hesitancies or difficulties in word retrieval often are wrongly confused with insecure content knowledge. The major difficulty in dyslexia, reflecting problems accessing the sound system of spoken language, causes great difficulty learning a 2nd language. As a result, an often-necessary accommodation is a waiver or partial waiver of the foreign language requirement; the dyslexic student may enroll in a course on the history or culture of a non–English-speaking country.

Prognosis

Application of evidence-based methods to young children (kindergarten to grade 3), when provided with sufficient intensity and duration, can result in improvements in reading accuracy and, to a much lesser extent, fluency. In older children and adults, interventions result in improved accuracy, but not an appreciable improvement in fluency. Accommodations are critical in allowing the dyslexic child to demonstrate his or her knowledge. Parents should be informed that with proper support, dyslexic children can succeed in a range of future occupations that might seem out of their reach, including medicine, law, journalism, and writing.

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CHAPTER 51

Math and Writing Disabilities

51.1

Math Disabilities

Kenneth L. Grizzle

Keywords

dyscalculia
math disability
Individual with Disabilities Education Act
IDEA
individualized education plan
IEP
response to intervention
specific learning disorder with impairment in mathematics

Data from the U.S. National Center for Educational Statistics for 2009 showed that 69% of U.S. high school graduates had taken algebra 1, 88% geometry, 76% algebra 2/trigonometry, and 35% precalculus. These percentages are considerably higher than those for 20 years earlier. However, concerns remain about the limited literacy level in mathematics for children, adolescents, and those entering the workforce; poor math skills predict numerous social, employment, and emotional challenges. The need for number and math literacy extends beyond the workplace and into daily lives, and weaknesses in this area can negatively impact daily functioning. Research into the etiology and treatment of **math disabilities** falls far behind the study of reading disabilities (see Chapter 50). Therefore the knowledge needed to identify, treat, and minimize the impact of math challenges on daily functioning and education is limited.

Math Learning Disability Defined

Understanding learning challenges associated with mathematics requires a basic appreciation of domain-specific terminology and operations. The *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5) has published diagnostic criteria for learning disorders. Specific types of learning challenges are subsumed under the broad term of **specific learning disorder (SLD)** . The DSM identifies the following features of a SLD with an **impairment in math:** difficulties mastering number sense, number facts, or fluent calculation and difficulties with math reasoning. Symptoms must be present for a minimum of 6 mo and persist despite interventions to address the learning challenges. **Number sense** refers to a basic understanding of quantity, number, and operations and is represented as nonverbal and symbolic. Examples of number sense include an understanding that each number is 1 more or 1 less than the previous or following number; knowledge of number words and symbols; and the ability to compare the relative magnitude of numbers and perform simple arithmetic calculations.

The DSM-5 definition can be contrasted with an **education-defined learning disability in mathematics** . Two math-related areas are identified as part of the **Individuals with Disabilities Education Act (IDEA):** mathematics calculation and mathematics problem solving. Operationally, this is reflected in age-level competency in arithmetic and math calculation, word problems, interpreting graphs, understanding money and time concepts, and applying math concepts to solve quantitative problems. The federal government allows states to choose the way a *learning disability* (LD) is identified if the procedure is “research based.” Referred to specifically in IDEA as methods for identifying an LD are a **discrepancy model** and “use of a process based on the child's response to scientific, research-based intervention.” The former refers to identifying a LD based on a pronounced discrepancy between intellectual functioning and academic achievement. The latter, referred to as a **response to intervention**

(RtI) model, requires school systems to screen for a disability, intervene using empirically supported treatments for the identified disability, closely monitor progress, and make necessary adjustments to the intervention as needed. If a child is not responding adequately, a multidisciplinary team evaluation is used to develop an **individualized educational plan (IEP)** .

It is important that primary care providers understand the RtI process because many states require or encourage this approach to identifying LDs. Confusion can be avoided by helping concerned parents understand that a school may review their child's records, screen the skills of concern, and provide intervention with close progress monitoring, before initiating the process for an IEP. Traditional psychoeducation testing (IQ and achievement) may only be completed if a child has not responded well to specific interventions. The RtI approach is a valuable, empirically supported way to approach and identify a potential learning disability, but very different from a medical approach to diagnosis and treatment.

Terminology

The term **dyscalculia** , often used in medicine and research but seldom used by educators, is reserved for children with a SLD in math when there is a pattern of deficits in learning arithmetic facts and accurate, fluent calculations. The term **math learning disability (MLD** *)* is used generically here, with dyscalculia used when limiting the discussion to children with deficient math calculation skills. A distinction is also made between children with a MLD and those who are **low achieving (LA) in math;** both groups have received considerable research focus. Although not included in either definition above, research into math deficits typically requires that individuals identified with MLD have math achievement scores below the 10th percentile across multiple grade levels. These children start out poorly in math and continue poor performance across grades, despite interventions. LA math students consistently score below the 25th percentile on math achievement tests across grades, but show more typical entry-level math skills.

Epidemiology

Prevalence

Depending on how MLD is defined and assessed, the prevalence varies. Based on findings from multiple studies, approximately 7% of children will show a MLD profile before high school graduation. An additional 10% of students will be identified as LA. Because research in the area typically requires that individuals show deficits for consecutive years, the respective prevalence estimates are lower than the 10th percentile cutoff for being identified as MLD or the 25th percentile cutoff for being identified as LA. It is not unusual for children to score below the criterion one year and above the criterion in subsequent years. These children do not show the same cognitive deficits associated with a MLD. Unlike dyslexia, boys are at greater risk to experience MLD. This is found in epidemiologic research in the United States (risk ratio, 1.6-2.2 : 1) and various European countries.

Risk Factors

Genetics

The heritability of math skills is estimated to be approximately 0.50. The heritability or genetic influence on math skills is consistent across the continuum from high to low math skills. This research emphasizes that although math skills are learned across time, the stability of math performance is the result of genetic influences. Math heritability appears to be the product of multiple genetic markers, each having a small effect.

Medical/Genetic Conditions

Numerous genetic syndromes are associated with math problems. Although most children with **fragile X syndrome** have an *intellectual disability* (ID), approximately 50% of girls with the condition do not. Of those without an ID, ≥75% have a math disability by the end of 3rd grade and are already scoring below average in mathematics in kindergarten and 1st grade. For girls with fragile X MLD, weak working memory seems to play an important role. The frequency of MLD in girls with **Turner syndrome (TS)** is the same as found in girls with fragile X syndrome. A consistent finding is girls with TS complete math calculations at significantly slower speed than typically developing students. Although girls with TS have weak calculation skills, their ability to complete math problems not requiring explicit calculation is similar to that of their peers. The percentage of children with the **22q11.2 deletion syndrome**

(22q11.2ds) with MLD is not clear. Younger children with this genetic condition (6-10 yr old) showed similar number sense and calculation skills as typically developing children but weaker math problem solving. Older children with 22q11.2ds showed slower speed in their general number sense and calculations, but accuracy was maintained. Weak counting skills and magnitude comparison have been found in this group of children, suggesting weak visual-spatial processing. Children with **myelomeningocele** are at greater risk for math difficulties than their unaffected peers. Almost 30% of these children have MLD without an additional diagnosed learning disorder, and >50% have both math and reading learning disorders. While broad, deficits are most pronounced in speed of math calculation and written computation.

Comorbidities

It is estimated that 30–70% of those with MLD will also have reading disability. This is especially important because children with MLD are less likely to be referred for additional educational assistance and intervention than students with reading problems. Unfortunately, children identified with both learning challenges perform poorer across psychosocial and academic measures than children with MLD alone. Having a MLD places a child at greater risk for not only other learning challenges but also psychiatric disorders, including attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder, generalized anxiety disorder, and major depressive disorder. Individuals with MLD have been found to have increased social isolation and difficulties developing social relationships in general.

Causes of Math Learning Disability

There is a consensus that individuals with MLD are a heterogeneous group, with multiple potential broad and specific deficits driving their learning difficulties. Research into the causes of MLD has focused on math-specific processes and broad cognitive deficits, with an appreciation that these two factors are not always independent.

Broad Cognitive Processes

Intelligence

Intelligence affects learning, but if intellectual functioning were the primary driver of poor math performance, the math skills of low-IQ children would be similar or worse than individuals with MLD. On the contrary, children with MLD have significantly poorer math achievement than children with low IQ. Children with MLD have severe deficits in math not accounted for by their cognitive functioning. Individuals with lower cognition may have difficulty learning mathematics, but their math skills are likely to be commensurate with their intelligence.

Working Memory

Working memory refers to the ability to keep information in mind while using the information in other mental processes. Working memory is composed of 3 core systems: the central executive, the language-related phonologic loop, and the visual-based sketch pad. The central executive coordinates the functioning of the other two systems. All three play a role in various aspects of learning and in the development and application of math skills in particular; children with MLD have shown deficits in each area.

Processing Speed

Individuals with MLD are often slower to complete math problems than their typically developing peers, a result of their poor fact retrieval rather than broader speed of processing deficits. However, young children later identified with a MLD when beginning school have number-processing speed that is considerably slower than same-age same-grade peers.

Math-Specific Processes

Procedural Errors

The type of errors made by children with a MLD are typical for any child, the difference being that children with a learning disability show a 2-3 yr lag in understanding the concept. An example of a common error a 1st grade child with a MLD might make when “counting on” is to undercount: “6 + 2= ?;” “6, 7” rather than starting at 6 and counting an additional 2 numbers. As children with math deficits get older, it is common to subtract a larger number from a smaller number. For example, in the problem “63 − 29 = 46,” the child makes the mistake of subtracting 3 from 9. Another common error is not decreasing the number in the 10s column when borrowing: “64 − 39 = 35.” For both adding and subtracting, there is a lack of understanding of the commutative property of numbers and a tendency to use repeated addition rather than fact retrieval. It is not that children with a MLD do not develop these skills, it is that they develop them much later than their peers, thereby making the transition to complicated math concepts much more challenging.

Memory for Math Facts

Committing math facts to or retrieving facts from memory have consistently been found to be problematic for children with MLD. Weak fact encoding or retrieval alone do not determine a MLD diagnosis. Many math curricula in the United States do not include development of math facts as a part of the instructional process, resulting in children not knowing basic facts.

Unlike dyslexia, in which deficits have been isolated and identified as causal (see Chapter 50), factors involved in the development of a MLD are much more heterogeneous. Alone, none of the processes previously outlined fully accounts for MLD, although all have been implicated as problematic for those struggling with math.

Treatment and Interventions

The most effective interventions for MLD are those that include explicit instruction on solving specific types of problems and that take place over several weeks to several months. Skill-based instruction is a critical component; general math problem solving will not carry over across various math skills, unless the skill is part of a more complex math concept. Clear, comprehensive guidelines for effective interventions for students struggling with math have been provided by the U.S. Department of Education in the form of a *Practice Guide* released through the What Works Clearinghouse. This document gives excellent direction in the identification and treatment of children with math difficulties in the educational system. Although not intended for medical personnel or parents, the guide is available free of charge and can be helpful for parents when talking to teachers about their child's learning. Table 51.1 lists additional resources for parents concerned about their young child's development of math facts.

Table 51.1

Parent Resources for the Child With Math

Learning Disability

Let's Talk About Math . Available from: http://www.zerotothree.org/parenting-resources/early-math-video-series . Accessed January 2, 2017.

Mixing in Math . Available from: https://mixinginmath.terc.edu/aboutMiM/what_isMiM.php . Accessed January 2, 2017.

PBS Parents. Math resources available to parents through the Public Broadcasting Service website. Accessed January 28, 2017:

http://www.pbs.org/parents/earlymath/index.html
http://www.pbs.org/parents/education/math/

US Department of Education: *Helping your child learn mathematics* . Available from: https://www2.ed.gov/parents/academic/help/math/index.html . Accessed January 28, 2017.

Awareness that most public school systems have implemented some form of a RtI to identify learning disabilities allows the primary care physician to encourage parents to return to the school seeking an intervention to address their child's concern. Receiving special education services in the form of an IEP may be necessary for some children. However, the current approach to identifying children with a learning disability allows school systems to intervene earlier, when problems arise, and potentially avoid the need for an IEP. Pediatricians with patients whose parents have received feedback from school with any of the risk factors outlined in Table 51.2 should encourage the parents to discuss an intervention plan with the child's teacher.

Table 51.2

Risk Factors for a Specific Learning Disability Involving Mathematics

The child is at or below the 20th percentile in any math area, as reflected by standardized testing or ongoing measures of progress monitoring.

The teacher expresses concerns about the child's ability to “take the next step” in math.

There is a positive family history for math learning disability (this alone will not initiate an intervention).

Parents think they have to “reteach” math concepts to their child.

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51.2

Writing Disabilities

Kenneth L. Grizzle

Keywords

dysgraphia
transcription
specific language impairment
pragmatic language
higher-level language
executive functions
working memory
504 plan
individual education plan

Oral language is a complex process that typically develops in the absence of formal instruction. In contrast, *written language* requires instruction in acquisition (word reading), understanding (reading comprehension), and expression (spelling and composition). Unfortunately, despite reasonable pedagogy, a subset of children struggle with development in one or several of these areas. The disordered output of written language is currently referred to within the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5) as a **specific learning disorder with impairment in written expression** (Table 51.3).

Table 51.3

DSM-5 Diagnostic Criteria for Specific Learning Disability With Impairment in Written Expression

A. Difficulties learning and using academic skills that have persisted for at least 6 mo, despite the provision of interventions that target those difficulties.

  Difficulties with written expression (e.g., makes multiple grammatical or punctuation errors within sentences; employs poor paragraph organization; written expression of ideas lacks clarity).

B. The affected academic skills are substantially and quantifiably below those expected for the individual's chronological age, and cause significant interference with academic or occupational performance, or with activities of daily living, as confirmed by individually administered standardized achievement measures and comprehensive clinical assessment. For individuals age 17 yr and older, a documented history of impairing learning difficulties may be substituted for the standardized assessment.

C. The learning difficulties begin during school-age years but may not become fully manifest until the demands for those affected academic skills exceed the individual's limited capacities (e.g., as in timed tests, reading or writing lengthy complex reports for a tight deadline, excessively heavy academic loads).

D. The learning difficulties are not better accounted for by intellectual disabilities, uncorrected visual or auditory acuity, other mental or neurologic disorders, psychosocial adversity, lack of proficiency in the language of academic instruction, or inadequate educational instruction.

315.2 (F81.81) With impairment in written expression:

Spelling accuracy
Grammar and punctuation accuracy
Clarity or organization of written expression

Specify current severity:

Mild: Some difficulties learning skills in 1 or 2 academic domains, but of mild enough severity that the individual may be able to compensate or function well when provided with appropriate accommodations or support services, especially during the school years.

Moderate: Marked difficulties learning skills in ≥1 academic domain(s), so that the individual is unlikely to become proficient without some intervals of intensive and specialized teaching during the school years. Some accommodations or supportive services at least part of the day at school, in the workplace, or at home may be needed to complete activities accurately and efficiently.

Severe: Severe difficulties learning skills, affecting several academic domains, so that the individual is unlikely to learn those skills without ongoing intensive individualized and specialized teaching for most of the school years. Even with an array of appropriate accommodations or services at home, at school, or in the workplace, the individual may not be able to complete all activities efficiently.

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 66–67.

Various terminology has been used when referring to individuals with writing deficits; this subchapter uses the term **impairment in written expression (IWE)** rather than “writing disorder” or “disorder of written expression.” **Dysgraphia** is often used when referring to children with writing problems, sometimes synonymously with IWE, although the two are related but distinct conditions. Dysgraphia is primarily a deficit in motor output (paper/pencil skills), and IWE is a conceptual weakness in developing, organizing, and elaborating on ideas in writing.

The diagnoses of a IWE and dysgraphia are made largely based on phenotypical presentation; spelling, punctuation, grammar, clarity, and organization are factors to consider with IWE concerns. Aside from these potentially weak writing characteristics, however, no other guidelines are offered. Based on clinical experience and research into the features of writing samples of children with disordered writing skills, one would expect to see limited output, poor organization, repetition of content, and weak sentence structure and spelling, despite the child taking considerable time to produce a small amount of content. For those with comorbid dysgraphia, the legibility of their writing product will also be poor, sometimes illegible.

Epidemiology

The incidence of IWE is estimated at 6.9–14.7%, with the relative risk for IWE 2-2.9 times higher for boys than girls. One study covering three U.S. geographic regions found considerably higher rates of IWE in the Midwest and Southeast than in the West.

The risk for writing problems is much greater among select populations; >50% of children with oral language disorders reportedly have IWE. The relationship between attention-deficit/hyperactivity disorder (ADHD) and learning disorders in general is well established, including IWE estimates in the 60% range for the combined and inattentive presentations of ADHD. Because of the importance of working memory and other executive functions in the writing process, any child with weakness in these areas will likely find the writing process difficult (see Chapter 48).

Skill Deficits Associated With Impaired Writing

Written language, much like reading, occurs along a developmental trajectory that can be seamless as children master skills critical to the next step in the process. Mastery of motor control that allows a child to produce letters and letter sequences frees up cognitive energy to devote to spelling words and eventually stringing words into sentences, paragraphs, and complex composition. Early in the development of each individual skill, considerable cognitive effort is required, although ideally the lower-level skills of motor production, spelling, punctuation, and capitalization (referred to as **writing mechanics** or **writing conventions**) will gradually become automatic and require progressively less mental effort. This effort can then be devoted to higher-level skills, such as planning, organization, application of knowledge, and use of varied vocabulary. For children with writing deficits, breakdowns can occur at one, some, or every stage.

Transcription

Among preschool and primary grade children, there is a wide range of what is considered “developmentally typical” as it relates to letter production and spelling. However, evidence indicates that poor writers in later grades are slow to produce letters and write their name in preschool and kindergarten. Weak early spelling and reading skills (letter identification and phonologic awareness; see Chapter 50) and weak oral language have also been found to predict weak writing skills in later elementary grades. Children struggling to master early **transcription** skills tend to write slowly, or when writing at reasonable speed, the legibility of their writing degrades. Output in quantity and variety is limited, and vocabulary use in poor spellers is often restricted to words they can spell.

As children progress into upper elementary school and beyond, a new set of challenges arise. They are now expected to have mastered lower-level transcription skills, and the focus turns to the application of these skills to more complex text generation. In addition to transcription, this next step requires the integration of additional cognitive skills that have yet to be tapped by young learners.

Oral Language

Language, although not speech, has been found to be related to writing skills. Writing difficulties are associated with deficits in both expression and comprehension of oral language. Writing characteristics of children with **specific language impairment (SLI)** can differ from their unimpaired peers early in the school experience, and persist through high school (see Chapter 52). In preschool and kindergarten, as a group, children with language disorders show poorer letter production and ability to print their name. Poor spelling and weak vocabulary also contribute to the poor writing skills. Beyond primary grades, the written narratives of SLI children tend to be evaluated as “lower quality with poor organization" and weaker use of varied vocabulary.

Pragmatic language and higher-level language deficits also negatively impact writing skills. **Pragmatic language** refers to the social use of language, including, though not limited to greeting and making requests; adjustments to language used to meet the need of the situation or listener; and following conversation rules verbally and nonverbally. **Higher-level language** goes beyond basic vocabulary, word form, and grammatical skills and includes making inferences, understanding and appropriately using figurative language, and making cause-and-effect judgments. Weaknesses in these areas, with or without intact foundational language, can present challenges for students in all academic areas that require writing. For example, whether producing an analytic or narrative piece, the writer must understand the extent of the reader's background knowledge and in turn what information to include and omit, make an argument for a cause-and-effect relationship, and use content-specific vocabulary or vocabulary rich in imagery and nonliteral interpretation.

Executive Functions

Writing is a complicated process and, when done well, requires the effective integration of multiple processes. Executive functions (EFs) are a set of skills that include planning, problem solving, monitoring and making adjustments as needed (see Chapter 48). Three recursive processes have consistently been reported as involved in the writing process: *translation* of thought into written output, *planning,* and *reviewing.* Coming up with ideas, while challenging for many, is simply the first step when writing a narrative (story). Once an idea has emerged, the concept must be developed to include a plot, characters, and story line and then coordinated into a coherent whole that is well organized and flows from beginning to end. Even if one develops ideas and begins to write them down, *persistence* is required to complete the task, which requires *self-regulation.* Effective writers rely heavily on EFs, and children with IWE struggle with this set of skills. Poor writers seldom engage in the necessary planning and struggle to self-monitor and revise effectively.

Working Memory

Working memory (WM) refers to the ability to hold, manipulate, and store information for short periods. The more space available, the more memory can be devoted to problem solving and thinking tasks. Nevertheless, there is limited space in which information can be held, and the more effort devoted to one task, the less space is available to devote to other tasks. WM has consistently been shown to play an important role in the writing process, because weak WM limits the space available. Further, when writing skills that are expected to be *automatic* continue to require effort, precious memory is required, taking away what would otherwise be available for higher-level language.

The *Simple View of Writing* is an approach that integrates each of the 4 ideas just outlined to describe the writing process (Fig. 51.1). At the base of the triangle are transcription and executive functions, which support, within WM, the ability to produce text. Breakdowns in any of these areas can lead to poor writing, and identifying where the deficit(s) are occurring is essential when deciding to treat the writing problem. For example, children with weak **graphomotor** skills (e.g., dysgraphia) must devote considerable effort to the accurate production of written language, thereby increasing WM use devoted to lower-level transcription and limiting memory that can be used for developing discourse. The result might be painfully slow production of a legible story, or a passage that is largely illegible. If, on the other hand, a child's penmanship and spelling have developed well, but their ability to persist with challenging tasks or to organize their thoughts and develop a coordinated plan for their paper is limited, one might see very little information written on the paper despite considerable time devoted to the task. Lastly, even when skills residing at the base of this triangle are in place, students with a language disorder will likely produce text that is more consistent with their language functioning than their chronological grade or age (Fig. 51.1).

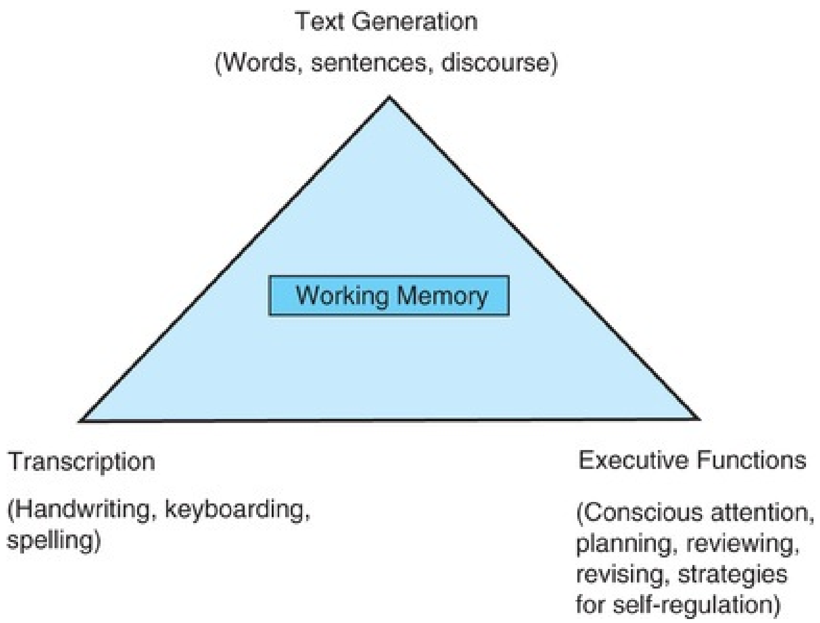
Text Generation
(Words, sentences, discourse)
Working Memory
Transcription
(Handwriting, keyboarding, spelling)
Executive Functions
(Conscious attention, planning, reviewing, revising, strategies for self-regulation)

FIG. 51.1 **Simple view of writing. (From Berninger VW: Preventing written expression disabilities through early and continuing assessment and intervention for handwriting and/or spelling problems: research into practice. In Swanson HL, Harris KR, Graham S, editors: *Handbook of learning disabilities,* New York, 2003, The Guilford Press.)**

Treatment

Poor writing skills can improve with effective treatment. Weak graphomotor skills may not necessarily require intervention from an **occupational therapist (OT),** although *Handwriting Without Tears* is a curriculum frequently used by OTs when working with children with poor penmanship. An empirically supported writing program has been developed by Berninger, but it is not widely used inside or outside school systems *(PAL Research-Based Reading and Writing Lessons).* For children with dysgraphia, lower-level transcription skills should be emphasized to the point of becoming automatic. The connection between transcription skills and composition should be included in the instructional process; that is, children need to see how their work at letter production is related to broader components of writing. Further, because of WM constraints that frequently impact the instructional process for students with learning disorders, all components of writing should be taught within the same lesson.

Explicit instruction of writing strategies combined with implementation and coaching in self-regulation will likely produce the greatest gains for students with writing deficits. Emphasis will vary depending on the deficit specific to the child. A well-researched and well-supported intervention for poor writers is **self-**

regulated strategy development (SRSD) . The 6 stages in this model include developing and activating a child's background knowledge; introducing and discussing the strategy that is being taught; modeling the strategy for the student; assisting the child in memorization of the strategy; supporting the child's use of the strategy during implementation; and independent use of the strategy. SRSD can be applied across various writing situations and is supported until the student has developed mastery. The model can emphasize or deemphasize the areas most needed by the child.

Educational Resources

Children with identified learning disorders can potentially qualify for formal education programming through special education or a section 504 plan. **Special education** is guided on a federal level by the **Individual with Disabilities Education Act (IDEA)** and includes development of an **individual education plan** (see Chapter 48). A **504 plan** provides accommodations to help children succeed in the regular classroom. Accommodations that might be provided to a child with IWE, through an IEP or a 504 plan, include dictation to a scribe when confronted with lengthy writing tasks, additional time to complete exams that require writing, and use of technology such as keyboarding, speech-to-text software, and writing devices that record teacher instruction. When recommending that parents pursue assistive technology for their child as a potential accommodation, the physician should emphasize the importance of instruction to mastery of the device being used. Learning to use technology effectively requires considerable time and is initially likely to require additional effort, which can result in frustration and avoidance.

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CHAPTER 52

Language Development and Communication Disorders

Mark D. Simms

Most children learn to communicate in their native language without specific instruction or intervention other than exposure to a language-rich environment. Normal development of speech and language is predicated on the infant's ability to hear, see, comprehend, remember, and socially interact with others. The infant must also possess sufficient motor skills to imitate oral motor movements.

Normal Language Development

Language can be subdivided into several essential components. **Communication** consists of a wide range of behaviors and skills. At the level of basic verbal ability, **phonology** refers to the correct use of speech sounds to form words, **semantics** refers to the correct use of words, and **syntax** refers to the appropriate use of grammar to make sentences. At a more abstract level, verbal skills include the ability to link thoughts together coherently and to maintain a topic of conversation. **Pragmatic** abilities include verbal and nonverbal skills that facilitate the exchange of ideas, including the appropriate choice of language for the situation and circumstance and the appropriate use of body language (i.e., posture, eye contact, gestures). Social pragmatic and behavioral skills also play an important role in effective interactions with communication partners (i.e., engaging, responding, and maintaining reciprocal exchanges).

It is customary to divide language skills into **receptive** (hearing and understanding) and **expressive** (talking) abilities. Language development usually follows a fairly predictable pattern and parallels general intellectual development (Table 52.1).

Table 52.1

Normal Language Milestones: Birth to 5 Years

HEARING AND UNDERSTANDING	TALKING
BIRTH TO 3 MONTHS	
Startles to loud sounds Quiets or smiles when spoken to Seems to recognize your voice and quiets if crying Increases or decreases sucking behavior in response to sound	Makes pleasure sounds (cooing, gooing) Cries differently for different needs Smiles when sees you
4-6 MONTHS	
Moves eyes in direction of sounds Responds to changes in tone of your voice Notices toys that make sounds Pays attention to music	Babbling sounds more speech-like, with many different sounds, including *p*, *b*, and *m* Vocalizes excitement and displeasure Makes gurgling sounds when left alone and when playing with you
7 MONTHS TO 1 YEAR	
Enjoys games such as peek-a-boo and pat-a-cake Turns and looks in direction of sounds Listens when spoken to Recognizes words for common items, such as *cup, shoe,* and *juice* Begins to respond to requests *(Come here; Want more?)*	Babbling has both long and short groups of sounds, such as *tata upup bibibibi.* Uses speech or noncrying sounds to get and keep attention Imitates different speech sounds Has 1 or 2 words *(bye-bye, dada, mama),* although they might not be clear
1-2 YEARS	
Points to a few body parts when asked Follows simple commands and understands simple questions *(Roll the ball; Kiss the baby; Where's your shoe?)* Listens to simple stories, songs, and rhymes Points to pictures in a book when named	Says more words every month Uses some 1-2 word questions *(Where kitty? Go bye-bye? What's that?)* Puts 2 words together *(more cookie, no juice, mommy book)* Uses many different consonant sounds at the beginning of words
2-3 YEARS	
Understands differences in meaning (e.g., go–stop, in–on, big–little, up–down) Follows 2-step requests *(Get the book and put it on the table.)*	Has a word for almost everything Uses 2-3 word “sentences” to talk about and ask for things Speech is understood by familiar listeners most of the time Often asks for or directs attention to objects by naming them
3-4 YEARS	
Hears you when you call from another room Hears television or radio at the same loudness level as other family members Understands simple *who, what, where, why* questions	Talks about activities at school or at friends' homes Usually understood by people outside the family Uses a lot of sentences that have ≥4 words Usually talks easily without repeating syllables or words
4-5 YEARS	
Pays attention to a short story and answers simple questions about it Hears and understands most of what is said at home and in	Voice sounds as clear as other children's Uses sentences that include details *(I like to read my books)*

school	Tells stories that stick to a topic Communicates easily with other children and adults Says most sounds correctly except a few, such as *l, s, r, v, z, ch, sh,* and *th* Uses the same grammar as the rest of the family

Adapted from American Speech-Language-Hearing Association, 2005. http://www.asha.org/public/speech/development/chart.htm .

Receptive Language Development

The peripheral auditory system is mature by 26 wk gestation, and the fetus responds to and discriminates speech sounds. Anatomic asymmetry in the *planum temporale* , the structural brain region specialized for language processing, is present by 31 wk gestation. At birth, the full-term newborn appears to have functionally organized neural networks that are sensitive to different properties of language input. The normal newborn demonstrates preferential response to human voices over inanimate sound and recognizes the mother's voice, reacting stronger to it than to a stranger's voice. Even more remarkable is the ability of the newborn to discriminate sentences in their “native” (mother's) language from sentences in a “foreign” language. In research settings, infants of monolingual mothers showed a preference for only that language, whereas infants of bilingual mothers showed a preference for both exposed languages over any other language.

Between 4 and 6 mo, infants visually search for the source of sounds, again showing a preference for the human voice over other environmental sounds. By 6 mo, infants can passively follow the adult's line of visual regard, resulting in a “joint reference” to the same objects and events in the environment. The ability to share the same experience is critical to the development of further language, social, and cognitive skills as the infant “maps” specific meanings onto his or her experiences. By 8-9 mo, the infant can actively show, give, and point to objects. Comprehension of words often becomes apparent by 9 mo, when the infant selectively responds to his or her name and appears to comprehend the word “no.” Social games, such as “peek-a-boo,” “so big,” and waving “bye-bye” can be elicited by simply mentioning the words. At 12 mo, many children can follow a simple, 1-step request without a gesture (e.g., “Give it to me”).

Between 1 and 2 yr, comprehension of language accelerates rapidly. Toddlers can point to body parts on command, identify pictures in books when named, and respond to simple questions (e.g., “Where's your shoe?”). The 2 yr old is able to follow a 2-step command, employing unrelated tasks (e.g., “Take off your shoes, then go sit at the table”), and can point to objects described by their use (e.g., “Give me the one we drink from”). By 3 yr, children typically understand simple “wh-” question forms (e.g., who, what, where, why). By 4 yr, most children can follow adult conversation. They can listen to a short story and answer simple questions about it. A 5 yr old typically has a receptive vocabulary of more than 2000 words and can follow 3- and 4-step commands.

Expressive Language Development

Cooing noises are established by 4-6 wk of age. Over the 1st 3 mo of life, parents may distinguish their infant's different vocal sounds for pleasure, pain, fussing, tiredness, and so on. Many 3 mo old infants vocalize in a reciprocal fashion with an adult to maintain a social interaction (“vocal tennis”). By 4 mo, infants begin to make bilabial (“raspberry”) sounds, and by 5 mo, monosyllables and laughing are noticeable. Between 6 and 8 mo, polysyllabic *babbling* (“lalala” or “mamama”) is heard, and the infant might begin to communicate with gestures. Between 8 and 10 mo, babbling makes a phonologic shift toward the particular sound patterns of the child's native language (i.e., they produce more native sounds than nonnative sounds). At 9-10 mo, babbling becomes truncated into specific words (e.g., “mama,” “dada”) for their parents.

Over the next several months, infants learn 1 or 2 words for common objects and begin to imitate words presented by an adult. These words might appear to come and go from the child's repertoire until a stable group of 10 or more words is established. The rate of acquisition of new words is approximately 1 new word per week at 12 mo, but it accelerates to approximately 1 new word per day by 2 yr. The first words to appear are used primarily to label objects (nouns) or to ask for objects and people (requests). By 18-20 mo, toddlers should use a minimum of 20 words and produce *jargon* (strings of word-like sounds) with language-like inflection patterns (rising and falling speech patterns). This jargon usually contains some embedded true words. Spontaneous 2-word phrases (pivotal speech), consisting of the flexible juxtaposition of words with clear intention (e.g., “Want juice!” or “Me down!”), is characteristic of 2 yr olds and reflects the emergence of grammatical ability (syntax).

Two-word, combinational phrases do not usually emerge until children have acquired 50-100 words in their lexicon. Thereafter, the acquisition of new words accelerates rapidly. As knowledge of grammar increases, there is a proportional increase in verbs, adjectives, and other words that serve to define the relation between objects and people (predicates). By 3 yr, sentence length increases, and the child uses pronouns and simple present-tense verb forms. These 3-5 word sentences typically have a subject and verb but lack conjunctions, articles, and complex verb forms. The *Sesame Street* character Cookie Monster (“Me want cookie!”) typifies the “telegraphic” nature of the 3 yr old's sentences. By 4-5 yr, children should be able to carry on conversations using adult-like grammatical forms and use sentences that provide details (e.g., “I like to read my books”).

Variations of Normal

Language milestones have been found to be largely universal across languages and cultures, with some variations depending on the complexity of the grammatical structure of individual languages. In Italian (where verbs often occupy a prominent position at the beginning or end of sentences), 14 mo olds produce a greater proportion of verbs compared with English speaking infants. Within a given language, development usually follows a predictable pattern, paralleling general cognitive development. Although the sequences are predictable, the exact timing of achievement is not. There are marked variations among normal children in the rate of development of babbling, comprehension of words, production of single words, and use of combinational forms within the first 2-3 yr of life.

Two basic patterns of language learning have been identified, analytic and holistic. The *analytic* pattern is the most common and reflects the mastery of increasingly larger units of language form. The child's analytic skills proceed from simple to more complex and lengthy forms. Children who follow a *holistic* or gestalt learning pattern might start by using relatively large chunks of speech in familiar contexts. They might memorize familiar phrases or dialog from movies or stories and repeat them in an overgeneralized fashion. Their sentences often have a formulaic pattern, reflecting inadequate mastery of the use of grammar to flexibly and spontaneously combine words appropriately in the child's own unique utterance. Over time, these children gradually break down the meanings of phrases and sentences into their component parts, and they learn to analyze the linguistic units of these memorized forms. As this occurs, more original speech productions emerge, and the child is able to assemble thoughts in a more flexible manner. Both analytic and holistic learning processes are necessary for normal language development to occur.

Language and Communication Disorders

Epidemiology

Disorders of speech and language are very common in preschool-age children. Almost 20% of 2 yr olds are thought to have delayed onset of language. By age 5 yr, approximately 6% of children are identified as having a speech impairment, 5% as having both speech and language impairment, and 8% as having language impairment. Boys are nearly twice as likely to have an identified speech or language impairment as girls.

Etiology

Normal language ability is a complex function that is widely distributed across the brain through interconnected neural networks that are synchronized for specific activities. Although clinical similarities exist between acquired aphasia in adults and childhood language disorders, unilateral focal lesions acquired in early life do not seem to have the same effects in children as in adults. Risk factors for **neurologic injury** are absent in the vast majority of children with language impairment.

Genetic factors appear to play a major role in influencing how children learn to talk. Language disorders cluster in families. A careful family history may identify current or past speech or language problems in up to 30% of first-degree relatives of proband children. Although children exposed to parents with language difficulty might be expected to experience poor language stimulation and inappropriate language modeling, studies of twins have shown the concordance rate for low language test score and/or a history of speech therapy to be approximately 50% in dizygotic pairs, rising to over 90% in monozygotic pairs. Despite strong evidence that language disorders have a genetic basis, consistent genetic mutations have not been identified. Instead, multiple genetic regions and epigenetic changes may result in heterogeneous genetic pathways causing language disorders. Some of these genetic pathways disrupt the timing of early prenatal neurodevelopmental events affecting migration of nerve cells from the germinal matrix to the cerebral cortex. Several single nucleotide polymorphisms (SNPs) involving noncoding regulatory genes, including

CNTNAP2 (contactin-associated-protein-like-2) and *KIAA0319* , are strongly associated with early language acquisition and are also believed to affect early neuronal structural development.

In addition, other environmental, hormonal, and nutritional factors may exert **epigenetic** influences by dysregulating gene expression and resulting in aberrant sequencing of the onset, growth, and timing of language development **.**

Pathogenesis

Language disorders are associated with a fundamental deficit in the brain's capacity to process complex information rapidly. Simultaneous evaluation of words (semantics), sentences (syntax), *prosody* (tone of voice), and social cues can overtax the child's ability to comprehend and respond appropriately in a verbal setting. Limitations in the amount of information that can be stored in verbal working memory can further limit the rate at which language information is processed. Electrophysiologic studies show abnormal latency in the early phase of auditory processing in children with language disorders. Neuroimaging studies identify an array of anatomic abnormalities in regions of the brain that are central to language processing. MRI scans in children with **specific language impairment (SLI)** may reveal white matter lesions and volume loss, ventricular enlargement, focal gray matter heterotopia within the right and left parietotemporal white matter, abnormal morphology of the inferior frontal gyrus, atypical patterns of asymmetry of language cortex, or increased thickness of the corpus callosum in a minority of affected children. Postmortem studies of children with language disorders found evidence of atypical symmetry in the plana temporale and cortical dysplasia in the region of the sylvian fissure. In support of a genetic mechanism affecting cerebral development, a high rate of atypical perisylvian asymmetries has also been documented in the parents of children with SLI.

Clinical Manifestations

Primary disorders of speech and language development are often found in the absence of more generalized cognitive or motor dysfunction. However, disorders of communication are also the most common comorbidities in persons with generalized cognitive disorders (intellectual disability or autism), structural anomalies of the organs of speech (e.g., velopharyngeal insufficiency from cleft palate), and neuromotor conditions affecting oral motor coordination (e.g., dysarthria from cerebral palsy or other neuromuscular disorders).

Classification

Each professional discipline has adopted a somewhat different classification system, based on cluster patterns of symptoms. The American Psychiatric Association (APA) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) organized communication disorders into: (1) language disorder (which combines expressive and mixed receptive-expressive language disorders), speech sound disorder (phonologic disorder), and childhood-onset fluency disorder (stuttering); and (2) social (pragmatic) communication disorder, which is characterized by persistent difficulties in the social uses of verbal and nonverbal communication (Table 52.2). In clinical practice, childhood speech and language disorders occur as a number of distinct entities.

Table 52.2

DSM-5 Diagnostic Criteria for Communication Disorders

Language Disorder

A Persistent difficulties in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production that include the following:
    1. Reduced vocabulary (word knowledge and use).
    2. Limited sentence structure (ability to put words and word endings together to form sentences based on the rules of grammar and morphology).
    3. Impairments in discourse (ability to use vocabulary and connect sentences to explain or describe a topic or series of events or have a conversation).

B. Language abilities are substantially and quantifiably below those expected for age, resulting in functional limitations in effective communication, social participation, academic achievement, or occupational performance, individually or in any combination.

C. Onset of symptoms is in the early developmental period.

D. The difficulties are not attributable to hearing or other sensory impairment, motor dysfunction, or another medical or neurologic condition and are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

Speech Sound Disorder

A. Persistent difficulty with speech sound production that interferes with speech intelligibility or prevents verbal communication of messages.

B. The disturbance causes limitations in effective communication that interfere with social participation, academic achievement, or occupational performance, individually or in any combination.

C. Onset of symptoms is in the early developmental period.

D. The difficulties are not attributable to congenital or acquired conditions, such as cerebral palsy, cleft palate, deafness or hearing loss, traumatic brain injury, or other medical or neurologic conditions.

Social (Pragmatic) Communication Disorder

A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following:

   1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context.
   2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on a playground, talking differently to a child than to an adult, and avoiding use of overly formal language.
   3. Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction.
   4. Difficulties understanding what is not explicitly stated (e.g., making inferences) and nonliteral or ambiguous meanings of language (e.g., idioms, humor, metaphors, multiple meanings that depend on the context for interpretation).

B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination.

C. The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities).

D. The symptoms are not attributable to another medical or neurologic condition or to low abilities in the domains of word structure and grammar, and are not better explained by autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 42, 44, 47–48.

Language Disorder or Specific Language Impairment

The condition DSM-5 refers to as **language disorder** is also referred to as **specific language impairment (SLI)** , **developmental dysphasia** , or **developmental language disorder** . SLI is characterized by a significant discrepancy between the child's overall cognitive level (typically nonverbal measures of intelligence) and functional language level. These children also follow an atypical pattern of language acquisition and use. Closer examination of the child's skills might reveal deficits in understanding and use of word meaning (semantics) and grammar (syntax). Often, children are delayed in starting to talk. Most significantly, they usually have difficulty understanding spoken language. The problem may stem from insufficient understanding of single words or from the inability to deconstruct and analyze the meaning of sentences. Many affected children show a *holistic* pattern of language development, repeating memorized phrases or dialog from movies or stories (echolalia). In contrast to their difficulty with spoken language, children with SLI appear to learn visually and demonstrate their ability on nonverbal tests of intelligence.

After children with SLI become fluent talkers, they are generally less proficient at producing oral narratives than their peers. Their stories tend to be shorter and include fewer propositions, main story ideas, or story grammar elements. Older children include fewer mental state descriptions (e.g., references to what their characters think and how they feel). Their narratives contain fewer cohesive devices, and the story line may be difficult to follow.

Many children with SLI show difficulties with **social interaction,** particularly with same-age peers. Social interaction is mediated by oral communication, and a child deficient in communication is at a distinct disadvantage in the social arena. Children with SLI tend to be more dependent on older children or adults, who can adapt their communication to match the child's level of function. Generally, social interaction skills are more closely correlated with language level than with nonverbal cognitive level. Using this as a guide, one usually sees a developmental progression of increasingly more sophisticated social interaction as the child's language abilities improve. In this context, social ineptitude is not necessarily a sign of asocial distancing (e.g., autism) but rather a delay in the ability to negotiate social interactions.

Higher-Level Language Disorder

As children mature, the ability to communicate effectively with others depends on mastery of a range of skills that go beyond basic understanding of words and rules of grammar. Higher-level language skills include the development of advanced vocabulary, the understanding of word relationships, reasoning skills (including drawing correct inferences and conclusions), the ability to understand things from another person's perspective, and the ability to paraphrase and rephrase with ease. In addition, higher-order language abilities include pragmatic skills that serve as the foundation for social interactions. These skills include knowledge and understanding of one's conversational partner, knowledge of the social context in which the conversation is taking place, and general knowledge of the world. Social and linguistic aspects of communication are often difficult to separate, and persons who have trouble interpreting these relatively abstract aspects of communication typically experience difficulty forming and maintaining relationships.

DSM-5 identified **social (pragmatic) communication disorder (SPCD)** as a category of communication disorder (Table 52.2). Symptoms of pragmatic difficulty include extreme literalness and inappropriate verbal and social interactions. Proper use and understanding of humor, slang, and sarcasm depend on correct interpretation of the meaning and the context of language and the ability to draw proper inferences. Failure to provide a sufficient referential base to one's conversational partner—to take the perspective of another person—results in the appearance of talking or behaving randomly or incoherently. SPCD often occurs in the context of another language disorder and has been recognized as a symptom of a wide range of disorders, including right-hemisphere damage to the brain, Williams syndrome, and nonverbal learning disabilities. SPCD can also occur independently of other disorders. Children with **autism spectrum disorder (ASD)** often have symptoms of SPCD, but SPCD is not diagnosed in these children because the symptoms are a component of ASD. In school settings, children with SPCD may be socially ostracized and bullied.

Intellectual Disability

Most children with a mild degree of intellectual disability learn to talk at a slower-than-normal rate; they follow a normal sequence of language acquisition and eventually master basic communication skills. Difficulties may be encountered with higher-level language concepts and use. Persons with moderate to severe degrees of intellectual disability can have great difficulty in acquiring basic communication skills. About half of persons with an intelligence quotient (IQ) of <50 can communicate using single words or simple phrases; the rest are typically nonverbal.

Autism Spectrum Disorder

A disordered pattern of language development is one of the core features of ASD (see Chapter 54). The language profile of children with ASD is often indistinguishable from that in children with SLI or SPCD. The key characteristics of ASD that distinguish it from SLI or SPCD are lack of reciprocal social relationships; limitation in the ability to develop functional, symbolic, or pretend play; hyper- or hyporeactivity to sensory input; and an obsessive need for sameness and resistance to change. Approximately 40% of children with ASD also have intellectual disability, which can limit their ability to develop functional communication skills. Language abilities can range from absent to grammatically intact, but with limited pragmatic features and odd prosody patterns. Some individuals with ASD have highly specialized, but isolated, “savant” skills, such as calendar calculations and **hyperlexia** (the precocious ability to recognize written words beyond expectation based on general intellectual ability). Parents report regression in language and social skills (**autistic regression**) in approximately 20–25% of children with ASD, usually between 12 and 36 mo of age. The cause of the regression is not known, but it tends to be associated with an increased risk for comorbid intellectual disability and more severe ASD (Fig. 52.1).

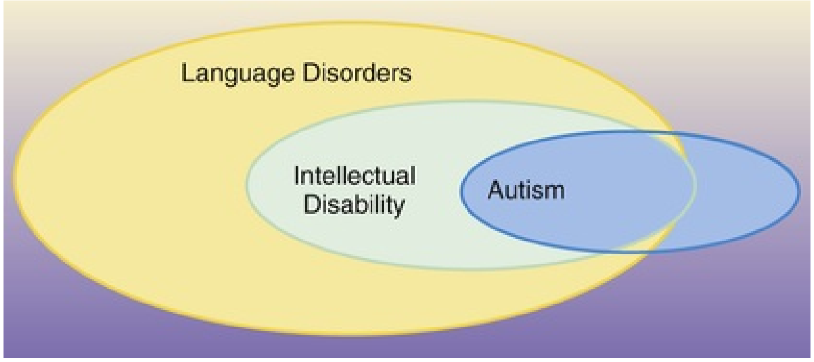

FIG. 52.1 Relationship of autism, language disorders, and intellectual disability. (From Simms MD, Schum RL: Preschool children who have atypical patterns of development, *Pediatr Rev* 21:147–158, 2000.)

Asperger Syndrome

Asperger syndrome is characterized by difficulties in social interaction, eccentric behaviors, and abnormally intense and circumscribed interests despite normal cognitive and verbal ability. Affected individuals may engage in long-winded, verbose monologs about their topics of special interest, with little regard to the reaction of others. Adults with Asperger syndrome generally have a more favorable prognosis of than those with “classic” autism. Prior to 2013, Asperger syndrome was classified as distinct from autism; however, DSM-5 no longer recognizes Asperger as a separate neurodevelopmental disorder. More severely affected individuals are now considered to be at the “high functioning” end of the autism spectrum (see Chapter 54), whereas mildly impaired individuals may be diagnosed with SPCD.

Selective Mutism

Selective mutism is defined as a failure to speak in specific social situations despite speaking in other situations, and it is typically a symptom of an underlying **anxiety disorder** . Children with selective mutism can speak normally in certain settings, such as within their home or when they are alone with their parents. They fail to speak in other social settings, such as at school or at other places outside their home. Other symptoms associated with selective mutism can include excessive shyness, withdrawal, dependency on parents, and oppositional behavior. Most cases of selective mutism are not the result of a single traumatic event, but rather the manifestation of a chronic pattern of anxiety. Mutism is not passive-aggressive behavior. Selectively mute children often report that they want to speak in social settings but are afraid to do so. Often, one or both parents of a child with selective mutism has a history of anxiety symptoms, including childhood shyness, social anxiety, or panic attacks. Mutism is highly functional for the child in that it reduces anxiety and protects the child from the perceived challenge of social interaction. Treatment of selective mutism should utilize cognitive behavioral strategies focused on reducing the general anxiety and increasing speaking in social situation (see Chapter 38). Occasionally, selective serotonin reuptake inhibitors are helpful in conjunction with cognitive-behavioral therapy. Selective mutism reflects a difficulty of *social interaction*, not a disorder of language processing.

Isolated Expressive Language Disorder

More often seen in boys than girls, **isolated expressive language disorder** ("late talker syndrome") is a diagnosis best made in retrospect. These children have age-appropriate receptive language and social ability. Once they start talking, their speech is clear. There is no increased risk for language or learning disability as they progress through school. A family history of other males with a similar developmental pattern is often reported. This pattern of language development likely reflects a variation of normal.

Motor Speech Disorders

Dysarthria

Motor speech disorders can originate from neuromotor disorders such as cerebral palsy, muscular dystrophy, myopathy, and facial palsy. The resulting **dysarthria** affects both speech and nonspeech functions (smiling and chewing). Lack of strength and muscular control manifests as slurring of words and distorting of vowels. Speech patterns are often slow and labored. Poor velopharyngeal function can result in mixed nasal resonance (hyper- or hyponasal speech). In many cases, feeding difficulty, drooling, open-mouth posture, and protruding tongue accompany the dysarthric speech.

Childhood Apraxia of Speech

Difficulty in planning and coordinating movements for speech production can result in inconsistent distortion of speech sounds. The same word may be pronounced differently each time. Intelligibility tends to decline as the length and complexity of the child's speech increases. Consonants may be deleted and sounds transposed. As they try to talk spontaneously, or imitate other's speech, children with **childhood apraxia of speech** may display oral groping or struggling behaviors. Children with childhood apraxia of speech frequently have a history of early feeding difficulty, limited sound production as infants, and delayed onset of spoken words. They may point, grunt, or develop an elaborate gestural communication system in an attempt to overcome their verbal difficulty. Apraxia may be limited to oral-motor function, or it may be a more generalized problem affecting fine and/or gross motor coordination.

Speech Sound Disorder

Children with **speech sound disorder (SSD)** , previously called *phonologic disorder,* are often unintelligible, even to their parents. Articulation errors are not the result of neuromotor impairment, but rather seem to reflect an inability to correctly process the words they hear (Table 52.2). As a result, they lack understanding of how to fit sounds together properly to create words. In contrast to children with childhood apraxia of speech, those SSD are fluent, although unintelligible, and produce a consistent, highly predictable pattern of articulation errors. Children with SSD are at high risk for later reading and learning disability.

Hearing Impairment

Hearing loss can be a major cause of delayed or disordered language development (see Chapter 655). Approximately 16-30 per 1,000 children have mild to severe hearing loss, significant enough to affect educational progress. In addition to these “hard of hearing” children, approximately another 1 : 1,000 are **deaf** (profound bilateral hearing loss). Hearing loss can be present at birth or acquired postnatally. Newborn screening programs can identify many forms of congenital hearing loss, but children can develop progressive hearing loss or acquire deafness after birth.

The most common types of hearing loss are attributable to conductive (middle ear) or sensorineural deficit. Although it is not possible to accurately predict the impact of hearing loss on a child's language development, the type and degree of hearing loss, the age of onset, and the duration of the auditory impairment clearly play important roles. Children with significant hearing impairment often have problems developing facility with language and often have related academic difficulties. Presumably, the language impairment is caused by lack of exposure to fluent language models, starting in infancy.

Approximately 30% of hearing-impaired children have at least 1 other disability that affects development of speech and language (e.g., intellectual disability, cerebral palsy, craniofacial anomalies). Any child who shows developmental warning signs of a speech or language problem should have a hearing assessment by an audiologist.

Hydrocephalus

Some children with **hydrocephalus** may be described as having “cocktail-party syndrome.” Although they may use sophisticated words, their comprehension of abstract concepts is limited, and their pragmatic conversational skills are weak. As a result, they speak superficially about topics and appear to be carrying on a monolog (see Chapter 609.11).

Rare Causes of Language Impairment

Hyperlexia

Hyperlexia is the precocious development of reading single words that spontaneously occurs in some young children (2-5 yr) without specific instruction. It is often associated with ASD or SLI. It stands in contrast to precocious reading development in young children who do not have any other developmental disorders. A typical manifestation is a child with SLI orally reading single words or matching pictures with single words. Although hyperlexic children show early and well-developed word-decoding skills, they usually do not have precocious ability for comprehension of text. Rather, text comprehension is closely intertwined with oral comprehension, and children who have difficulty decoding the syntax of language are also at risk for having reading comprehension problems.

Landau-Kleffner Syndrome (Verbal Auditory Agnosia)

Children with Landau-Kleffner syndrome have a history of normal language development until they experience a regression in their ability to comprehend spoken language, **verbal auditory agnosia** . The regression may be sudden or gradual, and it usually occurs between 3 and 7 yr of age. Expressive language skills typically deteriorate, and some children may become mute. Despite their language regression, these children typically retain appropriate play patterns and the ability to interact in a socially appropriate manner. An electroencephalogram (EEG) might show a distinct pattern of status epilepticus in sleep (continuous spike wave in slow-wave sleep), and up to 80% of children with Landau-Kleffner syndrome eventually exhibit clinical seizures. A number of treatment approaches have been reported, including antiepileptic medication, corticosteroids, and intravenous gamma globulin, with varying results. The prognosis for return of normal language ability is uncertain, even with resolution of the EEG abnormality. Epileptic interictal discharges are more frequently found on EEGs of children with language impairments than in otherwise normally developing children, even in those without any history of language regression. However, this phenomenon is believed to represent a manifestation of an underlying disorder of brain structure or function that is distinct from the language impairment, because there has been little evidence of improvement in language function when the EEG was normalized after antiepileptic administration. Unless there is a clear pattern of either seizure symptoms or regression in language ability, a routine EEG is not recommended as part of the evaluation for a child with speech and/or language impairment.

Metabolic and Neurodegenerative Disorders

(See also Part X.)

Regression of language development may accompany loss of neuromotor function at the outset of a number of metabolic diseases, including lysosomal storage disorders (metachromatic leukodystrophy), peroxisomal disorders (adrenal leukodystrophy), ceroid lipofuscinosis (Batten disease), and mucopolysaccharidosis (Hunter disease, Hurler disease). Recently, creatine transporter deficiency was identified as an X-linked disorder that manifests with language delay in boys and with mild learning disability in female carriers.

Screening

Developmental surveillance at each well child visit should include specific questions about normal language developmental milestones and observations of the child's behavior. **Clinical judgment,** defined as eliciting and responding to parents' concerns, can detect the majority of children with speech and language problems. The AAP recommends clinicians employ standardized developmental screening questionnaires and observation checklists at select well child visits. (see Chapter 28).

In 2015 the U.S. Preventive Services Task Force reviewed screening for SLI in young children in primary care settings and found inadequate evidence to support screening in the absence of parental or clinician concern about children's speech, language, hearing, or development. When either parents or physicians are concerned about speech or language development for reasons such as highlighted in Table 52.3 , the child should be referred for further evaluation and intervention (see Diagnostic Evaluation).

Table 52.3

Speech and Language Screening

REFER FOR SPEECH–LANGUAGE EVALUATION IF:		
AT AGE	**RECEPTIVE**	**EXPRESSIVE**
15 mo	Does not look/point at 5-10 objects	Is not using 3 words
18 mo	Does not follow simple directions (“get your shoes”)	Is not using Mama, Dada, or other names
24 mo	Does not point to pictures or body parts when they are named	Is not using 25 words
30 mo	Does not verbally respond or nod/shake head to questions	Is not using unique 2-word phrases, including noun–verb combinations
36 mo	Does not understand prepositions or action words; does not follow 2-step directions	Has a vocabulary of <200 words; does not ask for things; echolalia to questions; language regression after attaining 2-word phrases

Noncauses of Language Delay

Twinning, birth order, “laziness,” exposure to multiple languages (bilingualism), tongue-tie (ankyloglossia), or otitis media are not adequate explanations for significant language delay. Normal twins learn to talk at the same age as normal single-born children, and birth-order effects on language development have not been consistently found. The drive to communicate and the rewards for successful verbal interaction are so strong that children who let others talk for them usually cannot talk for themselves and are not “lazy.” Toddlers exposed to more than one language can show a mild delay in starting to talk, and they can initially mix elements (vocabulary and syntax) of the different languages they are learning (code switching). However, they learn to segregate each language by 24-30 mo and are equal to their monolingual peers by 3 yr of age. An extremely tight lingual frenulum (tongue-tie) can affect feeding and speech articulation but does not prevent the acquisition of language abilities. Prospective studies also show that frequent ear infections and serous otitis media in early childhood do not result in persisting language disorder.

Diagnostic Evaluation

It is important to distinguish developmental delay (abnormal timing) from abnormal patterns or sequences of development. A child's language and communication skills must also be interpreted within the context of the child's overall cognitive and physical abilities. It is also important to evaluate the child's use of language to communicate with others in the broadest sense (communicative intent). Thus a multidisciplinary evaluation is often warranted. At a minimum, this should include psychologic evaluation, neurodevelopmental pediatric assessment, and speech-language examination.

Psychologic Evaluation

There are two main goals for the psychologic evaluation of a young child with a communication disorder. Nonverbal cognitive ability must be assessed to determine if the child has an intellectually disability, and the child's social behaviors must be assessed to determine whether ASD is present. Additional diagnostic considerations may include emotional disorders such as anxiety, depression, mood disorder, obsessive-compulsive disorder, academic learning disorders, and attention-deficit/hyperactivity disorder (ADHD).

Cognitive Assessment

Intellectual disability is defined as deficits in cognitive abilities and adaptive behaviors. In this context, children with intellectual disability show delayed development of communication skills; however, delayed communication does not necessarily signal intellectual disability. Therefore, a broad-based cognitive assessment is an important component to the evaluation of children with language delays, including evaluation of both verbal and nonverbal skills. If a child has intellectual disability, both verbal and nonverbal scores will be low compared to norms (≤2nd percentile). In contrast, a typical cognitive profile for a child with SLI includes a significant difference between nonverbal and verbal abilities, with nonverbal IQ being greater than verbal IQ and the nonverbal score being within an average range.

Evaluation of Social Behaviors

Social interest is the key difference between children with a primary language disorder (SLI) and those with a communication disorder secondary to ASD. Children with SLI have an interest in social interaction, but they may have difficulty enacting their interest because of their limitations in communication. In contrast, autistic children show little social interest.

Relationship of Language and Social Behaviors to Mental Age

Cognitive assessment provides a mental age for the child, and the child's behavior must be evaluated in that context. Most 4 yr old children typically engage peers in interactive play, but most 2 yr olds are playful but primarily focused on interactions with adult caretakers. A 4 yr old with mild to moderate intellectual disability and a mental age of 2 yr might not yet play with peers because of cognitive limitation, not a lack of desire for social interaction.

Speech and Language Evaluation

A certified **speech-language pathologist** should perform a speech and language evaluation. A typical evaluation includes assessment of language, speech, and the physical mechanisms associated with speech production. Both expressive and receptive language is assessed by a combination of standardized measures and informal interactions and observations. All components of language are assessed, including syntax, semantics, pragmatics, and fluency. Speech assessment similarly uses a combination of standardized measures and informal observations. Assessment of physical structures includes oral structures and function, respiratory function, and vocal quality. In many settings, a speech-language pathologist works in conjunction with an **audiologist,** who can do appropriate hearing evaluation of the child. If an audiologist is not available in that setting, a separate referral should be made. No child is too young for a speech-language or hearing evaluation. A referral for evaluation is appropriate whenever there is suspicion of language impairment.

Medical Evaluation

Careful history and physical examination should focus on the identification of potential contributors to the child's language and communication difficulties. A **family history** of delay in talking, need for speech and language therapy, or academic difficulty can suggest a genetic predisposition to language disorders. **Pregnancy history** might reveal risk factors for prenatal developmental anomalies, such as polyhydramnios or decreased fetal movement patterns. Small size for gestational age at birth, symptoms of neonatal encephalopathy, or early and persistent oral-motor feeding difficulty may presage speech and language difficulty. **Developmental history** should focus on the age when various language skills were mastered and the sequences and patterns of milestone acquisition. Regression or loss of acquired skills should raise immediate concern.

Physical examination should include measurement of height (length), weight, and head circumference. The skin should be examined for lesions consistent with phakomatosis (e.g., tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome) and other disruptions of pigment (e.g., hypomelanosis of Ito). Anomalies of the head and neck, such as white forelock and hypertelorism (Waardenburg syndrome), ear malformations (Goldenhar syndrome), facial and cardiac anomalies (Williams syndrome, velocardiofacial syndrome), retrognathism of the chin (Pierre Robin anomaly), or cleft lip/palate, are associated with hearing and speech abnormalities. **Neurologic examination** might reveal muscular hypertonia or hypotonia, both of which can affect neuromuscular control of speech. Generalized muscular hypotonia, with increased range of motion of the joints, is frequently seen in children with SLI. The reason for this association is not clear, but it might account for the fine and gross motor clumsiness often seen in these children. However, mild hypotonia is not a sufficient explanation for the impairment of expressive and receptive language.

No routine diagnostic studies are indicated for SLI or isolated language disorders. When language delay is a part of a generalized cognitive or physical disorder, referral for further genetic evaluation, chromosome testing (e.g., fragile X testing, microarray comparative genomic hybridization), neuroimaging studies, and EEG may be considered, if clinically indicated.

Treatment

The federal Individuals with Disabilities Education Act (IDEA) requires that schools provide early intervention and **special education** services to children who have learning difficulties. This includes children with speech and language disorders. Services are provided to children from birth through 21 yr of age. States have various methods for providing services, including speech and language therapy for young children, such as *Birth-to-Three* , *Early Childhood* , and *Early Learning* programs. Children can also receive therapy from nonprofit service agencies, hospital and rehabilitation centers, and speech pathologists in private practice.

Of concern is that many children with identified speech and language deficits do not receive appropriate intervention services. Population-based surveys in both the United States and Canada have found that less than half of children identified by kindergarten entry receive **speech and language interventions** , even when their parents have been educated about the nature of their child's condition. In one study, children with deficits in speech sound production were much more likely to receive services (41%) than those who had problems with language alone (9%). These findings are troubling because poor educational outcome, especially in reading, and impaired social-behavioral adjustment are more highly associated with language than with speech sound disorders. Therefore the children at greatest risk are least likely to receive intervention services. Boys were twice as likely to receive speech intervention as girls, regardless of their speech-language diagnosis. Social and demographic factors did not appear to influence whether identified children received interventions services.

Speech-language therapy includes a variety of goals. Sometimes both speech and language activities are incorporated in therapy. The speech goals focus on development of more intelligible speech. Language goals can focus on expanding vocabulary (lexicon) and understanding of the meaning of words (semantics), improving syntax by using proper forms or learning to expand single words into sentences, and social use of language (pragmatics). Therapy can include individual sessions, group sessions, and mainstream classroom integration. **Individual** sessions may use drill activities for older children or play activities for younger children to target specific goals. **Group** sessions can include several children with similar language goals to help them practice peer communication activities and to help them bridge the gap into more naturalistic communication situations. **Classroom** integration might include the therapist team-teaching or consulting with the teacher to facilitate the child's use of language in common academic situations.

For children with severe language impairment, alternative methods of communication are often included in therapy, such as manual sign language, use of pictures (e.g., Picture Exchange Communication System), and computerized devices for speech output. Often the ultimate goal is to achieve better spoken language. Early use of **signs** or **pictures** can help the child establish better functional communication and understand the symbolic nature of words to facilitate the language process. There is no evidence that use of signs or pictures interferes with development of oral language if the child has the capacity to speak. Many clinicians believe that these alternative methods accelerate the learning of language. These methods also reduce the frustration of parents and children who cannot communicate for basic needs.

Parents can consult with their child's speech-language therapist about home activities to enhance language development and extend therapy activities through appropriate language-stimulating activities and recreational reading. Parents' language activities should focus on emerging communication skills that are within the child's repertoire, rather than teaching the child new skills. The speech pathologist can guide parents on effective modeling and eliciting communication from their child.

Recreational **reading** focuses on expanding the child's comprehension of language. Sometimes the child's avoidance of reading is a sign that the parent is presenting material that is too complex for the child. The speech-language therapist can guide the parent in selecting an appropriate level of reading material.

Prognosis

Children with mild isolated expressive language disorder (“late talkers”) have an excellent prognosis for both language, learning, and social-emotional adjustment.

Over time, children with SLI respond to therapeutic/educational interventions and show a trend toward improvement of communication skills. Adults with a history of childhood language disorder continue to show evidence of impaired language ability, even when surface features of the communication difficulty have improved considerably. This suggests that many persons find successful ways of adapting to their impairment. Although the majority of children improve their communication ability with time, 50–80% of preschoolers with language delay and normal nonverbal intelligence continue to experience difficulty with language and social development up to 20 yr beyond the initial diagnosis. Language disorders often interfere with the child's ability to conceptualize the increasingly complex and ambiguous worlds of social relationship and emotions. Consequently, in later childhood and adolescence, children with persisting symptoms of SLI are about twice as likely as their typical-language peers to show clinical levels of emotional problems and twice as likely to show behavioral difficulties.

A Danish study found that adults with SLI were less likely to have completed formal education beyond high school, and that they had lower occupational and socioeconomic success than the general population; 56% had a paid job (vs 84% of same-age general population), of whom 35% were unskilled and 40% skilled workers. About 80% of the adults reported difficulty reading while in school, most had received remedial teaching, and 50% continued to report reading difficulty as adults (vs 5% of Danish adults). Lower nonverbal intelligence and comorbid psychiatric or neurologic disorders independently contributed to a worse prognosis. These results were consistent with previous reports of adult outcomes of children with SLI from Canada and the United Kingdom.

Academic Disorders

Early language difficulty is strongly related to later **reading disorder** . Approximately 50% of children with early language difficulty develop reading disorder, and 55% of children with reading disorder have a history of impaired early oral language development. By the time they enter kindergarten, many children with early language deficits may have improved significantly, and they may begin to show early literacy skills, identifying and sounding out letters. However, as they progress through school, they are often unable to keep up with the increasing demands for both oral and written language. Despite their ability to read words, these children lack oral and reading comprehension, may read slowly, and struggle with a wide range of academic subjects. This “illusory recovery” of early language skill may result in children losing speech-language services or other special education support in early grades, only to be identified later with academic problems. In addition, children with subtle but persisting language impairments may appear inattentive or anxious in language-rich classroom environments and may be misdiagnosed as having an attention disorder.

A study from Australia found that at 7-9 yr of age, children with communication impairments were reported by their parents and teachers to be making slower progress in reading, writing, and overall school achievement than other children their age. The children reported a higher incidence of bullying, poorer peer relationships, and less overall enjoyment of school than their typically developing peers.

Comorbid Disorders

Emotional and Behavioral Difficulty

Early language disorder, particularly difficulty with auditory comprehension, appears to be a specific risk factor for later emotional dysfunction. Boys and girls with language disorder have a higher-than-expected rate of **anxiety disorder** (principally social phobia). Boys with language disorder are more likely to develop symptoms of ADHD, conduct disorder, and antisocial personality disorder compared with normally developing peers. Language disorders are common in children referred for psychiatric services, but they are often underdiagnosed, and their impact on children's behavior and emotional development is often overlooked.

Preschoolers with language difficulty frequently express their frustration through anxious, socially withdrawn, or aggressive behavior. As their ability to communicate improves, parallel improvements are usually noted in their behavior, suggesting a cause-and-effect relationship between language and behavior. However, the persistence of emotional and behavioral problems over the life span of persons with early language disability suggests a strong biologic or genetic connection between language development and subsequent emotional disorders.

The full impact of environmental and education support on these emotional and behavioral difficulties is not known at this time, but many children with SLI need psychologic support. Efforts should be made to support the child's resilience, emotional competency, and coping abilities. Parents and teachers should be encouraged to strengthen the child's prosocial behavior and reduce noncompliant and aggressive behaviors.

Motor and Coordination Delays

Approximately one third to one half of children with speech and/or language disorders have some degree of motor coordination impairment that may have an important impact on their ability to carry out activities of daily living (dressing, eating, bathing), school tasks (writing, drawing, coloring), and social/recreational activities (participation in sports and other playground activities). Motor difficulties are not related to the type of language impairment (i.e., they are found both in children with only receptive delays and in those with both expressive and receptive delays). The patterns of motor difficulty seen in children with language impairment are not distinctly “abnormal,” and the motor profiles of children with language impairment resemble those of younger children, suggesting that they result from delayed maturation of motor development rather than from a neurologic impairment. Several researchers have postulated that language impairments and motor difficulties may have a common neurodevelopmental basis. Because attention may be focused on the child's language delays, the need for intervention and support for the child's comorbid motor impairment may be overlooked.

52.1

Childhood-Onset Fluency Disorder

Kenneth L. Grizzle

Keywords

childhood-onset fluency disorder
cluttering
physical concomitants
stammering, stuttering

Developmental stuttering is a childhood speech disorder that is not associated with stroke, traumatic brain injury, or other possible medical conditions and that interrupts the normal flow of speech through repeated or prolonged sounds, syllables, or single-syllable words. (Table 52.4 lists definitions of terminology.) All speakers experience **speech dysfluencies** . During the toddler and preschool years, children often make repetitions of sounds, syllables, or words, particularly at the beginning of sentences (normal dysfluencies). However, dysfluencies found in individuals who stutter are distinct from those experienced by typically developing speakers. Specifically, children who stutter show greater part-word repetition (“b-b-b-b-but”), single-syllable word repetition (“My, my, my”), and sound prolongation (“MMMMMM-an”), and the frequency of their stuttering is much greater than found in normal dysfluencies. Other types of dysfluency that are not exclusive to children who stutter include *interjections* (“well, uhh, umm”), *revisions* (“I thought…I mean”), and *phrase repetitions* (“Did you say–Did you say”). The perspective of the speaker also characterizes differences between those children who stutter and a typical dysfluency. Children who stutter have decided on a word to use but are unable to “get the word out,” while a typically developing child may struggle to express herself because she is unable to retrieve the word, changes thought, or is distracted.

Table 52.4

Terminology Related to Childhood-Onset Fluency Disorder

TERM	DEFINITION
Stuttering	A speech disorder manifested through abnormal speech patterns referred to as *dysfluencies*
Childhood-onset fluency disorder	Term used in DSM-5 that is synonymous with *stuttering*
Stammering	The clinical term used in the United Kingdom rather than stuttering; stammering also used informally to describe halting speech
Cluttering	A speech disorder characterized by excessively rapid and irregular rate of speech
Dysfluency	Speech disruptions that can occur in normal or disordered speech

Multiple nonspeech features can accompany stuttering. **Physical concomitants** that occur at the onset and as the condition persists include movements of the head (head turning or jerking), face (eye blinking/squinting, grimacing, opening or tightly closing the jaw), and neck (tightening) and irregular inhalations and exhalations. *Fear* and *anxiety* about speaking in a large-group setting, such as in front of a class or in interpersonal social interactions, are **emotional symptoms** associated with stuttering. As with all social beings, children closely monitor the reactions of those with whom they associate, especially as they get older. It is not difficult to imagine the impact a single or series of negative interactions or comments could have on a child's future attempts to interact verbally with another or in a large social setting. Consider also the potential **social challenges** associated with entering a classroom for the first time, transitioning to middle/high school/college, beginning a job, dating, and so on. Not surprisingly, *avoidance* is a common way of coping with the anxiety created by the fear of stuttering.

In the *Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition* (DSM-5), the term *stuttering* has been removed from the diagnostic classification, and the disorder is referred to as **childhood-onset fluency disorder** (Table 52.5). Note that impact on functional behavior is a component of the psychiatric diagnosis of this condition. In contrast, communication disorder specialists would consider possible anxiety and avoidance of various activities and situations a common concomitant of childhood-onset fluency disorder (stuttering) and not necessarily a requirement for the diagnosis to be made.

Table 52.5

DSM-5 Diagnostic Criteria for Childhood-Onset Fluency Disorder (Stuttering)

A. Disturbances in the normal fluency and time patterning of speech that are inappropriate for the individual's age and language skills, persist over time, and are characterized by frequent and marked occurrences of one (or more) of the following:
    1. Sound and syllable repetitions.
    2. Sound prolongations of consonants as well as vowels.
    3. Broken words (e.g., pauses within a word).
    4. Audible or silent blocking (filled or unfilled pauses in speech).
    5. Circumlocutions (word substitutions to avoid problematic words).
    6. Words produced with an excess of physical tension.

    7. Monosyllabic whole-word repetitions (e.g., “I-I-I-I see him”).

B. The disturbance causes anxiety about speaking or limitations in effective communication, social participation, or academic or occupational performance, individually or in any combination.

C. The onset of symptoms is in the early developmental period.
Note: Later-onset cases are diagnosed as 307.0 [F98.5] adult-onset fluency disorder.

D. The disturbance is not attributable to a speech-motor or sensory deficit, dysfluency associated with neurologic insult (e.g., stroke, tumor, trauma), or another medical condition and is not better explained by another mental disorder.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, pp 45–46.)

Stuttering is distinct from other disordered speech output conditions such as cluttering in several ways. Unlike stuttering, for which distinct episodes can be identified and even counted, **cluttering** affects the entire speech output. In addition to elevated repetitions of partial words (as in stuttering), whole words, and phrases, those who clutter show speech bursts that are often choppy, and articulation can be slurred and imprecise. The level of awareness of how their speech affects those listening, unlike children who stutter, is minimal for those who clutter. **Stammering** and stuttering are terms used interchangeably, although the former is used in the United Kingdom and the latter in the United States. “Stammer” is also used informally to describe when an individual is struggling to express himself and may speak in a halting or “bumbling” manner.

Epidemiology

Although prevalence studies have produced a range of estimates for developmental stuttering, it appears that 0.75–1% of the population is experiencing this condition at any one time. Incidence rates are considerably higher: Estimates to date suggest an incidence rate of approximately 5%, with rates considerably higher among young children than older children or adolescents. Seldom does a child begin stuttering before 2 yr of age or after 12 yr; in fact, the mean age of onset is 2-4 yr, and most children stop stuttering within 4 yr of onset. Symptoms will disappear within 4 wk for a minority of children. Although studies have consistently shown that the male:female ratio favors males, the magnitude of the pattern increases as children get older. The ratio among children <5 yr is approximately 2 : 1 and jumps to 4 : 1 among adolescents and young adults.

Genetics

There is convergent evidence of a genetic link for childhood-onset fluency disorder. Concordance rates among MZ twins range from 20–83%, and for DZ twins, 4–19%. Family aggregation studies suggest increased incidence rate of approximately 15% among first-degree relatives of those affected, 3 times higher than the 5% rate for the general population. The variance in risk for stuttering attributed to genetic effects is high, ranging from 70–85%. Although evidence is limited, stuttering appears to be a polygenic condition, and several genes increase susceptibility.

Etiology

Brain structure and function abnormalities found in stutterers include deficits in white matter in the left hemisphere, overactivity in the right cortical region, and underactivity in the auditory cortex. Abnormal basal ganglia activation has also been identified among stutterers.

Comorbidities

Despite the widely held belief in a high degree of comorbidity between childhood-onset fluency disorder and other communication disorders, research to date does not necessarily support this assertion. Speech-language pathologists (SLPs) consistently report higher rates of comorbidity on their caseload, although this would be expected in clinical samples. Speech sound (phonologic) disorders are the most commonly reported comorbidities, and 30–40% of children on SLP caseloads are also experiencing problems with phonology. However, studies have not found greater incidence of phonologic disorders among those who stutter compared to a control group. Similarly, SLPs report a much higher percentage of children with language disorders among their patients who stutter than the approximately 7% expected in the population at large, yet the language functioning among stutters apparently is no different than in the general population. The same pattern holds for learning disorder (LD). The incidence of various types of LDs associated with a language disorder is well documented, so one would expect to see increased frequency within a clinical population.

The perception of communication disorder professionals and people in general is that children who stutter experience more **anxiety** than their nonstuttering peers. This in fact is supported by clinical research that has found considerably higher rates of psychopathology, specifically social anxiety and generalized anxiety disorder, among adolescents who stutter. The frequency of reported anxiety increases with age. To date, however, the lack of controlled studies should not lead to the assumption that stuttering itself places a child or adolescent at greater risk for a psychiatric disorder of any type. This is not meant to suggest that anxiety has no impact on a stuttering child's behavior in specific situations; as indicated earlier in this chapter, children who stutter frequently avoid situations that demand speaking.

Children who stutter have consistently been found to be bullied more than peers. In one study, stutterers were almost 4 times more likely to be bullied than their nonstuttering counterparts. About 45% of those who stuttered reported being the victim of bullying.

Developmental Progression

Onset of stuttering typically occurs between 2 and 4 yr of age. Severity of symptoms vary, from pronounced stuttering within a few days of onset to gradual worsening of symptoms across months. Symptoms may ebb and flow, including disappearing for weeks before returning, especially among young children. From 40–75% of young children who stutter will stop spontaneously, typically within months of starting. Although predicting which child will stop stuttering is difficult, risk factors for persisting include stuttering for >1 yr, continued stuttering after age 6 yr, and experiencing other speech or language problems.

Treatment

Several factors should be considered when deciding to refer a younger child with childhood-onset fluency disorder for therapy. If there is a positive family history for stuttering, if symptoms have been present for >4 wk, and if the dysfluencies are impacting the child's social, behavioral, and emotional functioning, referral is warranted. Although there is no cure for stuttering, behavioral therapies are available that are developed and implemented by SLPs. Treatment emphasizes managing stuttering while speaking by regulating rate of speech and breathing and helping the child gradually progress from the fluent production of syllables to more complex sentences. Approaches to treatment may include parents directly in the process, although even if not active participants, parents play an important role in the child coping with stuttering. Treatment in preschool-age children has been shown to improve stuttering. Management of stuttering is also emphasized in older children. For school-age children, treatment includes improving not only fluency but also concomitants of the condition. This includes recognizing and accepting stuttering and appreciating others' reaction to the child when stuttering, managing secondary behaviors, and addressing avoidance behaviors. The broad focus allows for minimizing the adverse effects of the condition. To date, no evidence supports the use of a pharmacologic agent to treat stuttering in children and adolescents.

Preschool children with normal developmental dysfluency can be observed with parental education and reassurance. Parents should not reprimand the child or create undue anxiety.

Preschool or older children with stuttering should be referred to a speech pathologist. Therapy is most effective if started during the preschool period. In addition to the risks noted in Table 52.5 , indications for referral include 3 or more dysfluencies per 100 syllables (b-b-but; th-th-the; you, you, you), avoidances or escapes (pauses, head nod, blinking), discomfort or anxiety while speaking, and suspicion of an associated neurologic or psychotic disorder.

Most preschool children respond to interventions taught by speech pathologists and to behavioral feedback by parents. Parents should not yell at the child, but should calmly praise periods of fluency (“That was smooth”) or nonjudgmentally note episodes of stuttering (“That was a bit bumpy”). The child can be involved with self-correction and respond to requests (“Can you say that again?”) made by a calm parent. Such treatment greatly improves dysfluency, but it may never be eliminated.

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CHAPTER 53

Developmental Delay and Intellectual Disability

Bruce K. Shapiro, Meghan E. O'Neill

Intellectual disability (ID) refers to a group of disorders that have in common deficits of adaptive and intellectual function and an age of onset before maturity is reached.

Definition

Contemporary conceptualizations of ID emphasize functioning and social interaction rather than test scores. The definitions of ID by the World Health Organization (WHO) *International Classification of Diseases, Tenth Edition* (ICD-10), the U.S. Individuals with Disabilities Education Act (IDEA), the American Psychiatric Association (APA) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), and the American Association on Intellectual and Developmental Disabilities (AAIDD) all include significant impairment in general intellectual function (reasoning, learning, problem solving), social skills, and adaptive behavior. This focus on conceptual, social, and practical skills enables the development of individual treatment plans designed to enhance functioning. Consistent across these definitions is onset of symptoms before age 18 yr or adulthood.

Significant impairment in general intellectual function refers to performance on an individually administered test of intelligence that is approximately 2 standard deviations (SD) below the mean. Generally these tests provide a standard score that has a mean of 100 and SD of 15, so that intelligence quotient (IQ) scores <70 would meet these criteria. If the standard error of measurement is considered, the upper limits of significantly impaired intellectual function may extend to an IQ of 75. Using a score of 75 to delineate ID might double the number of children with this diagnosis, but the requirement for impairment of adaptive skills limits the false positives. Children with ID often show a variable pattern of strengths and weaknesses. Not all their subtest scores on IQ tests fall into the significantly impaired range.

Significant impairment in adaptive behavior reflects the degree that the cognitive dysfunction impairs daily function. **Adaptive behavior** refers to the skills required for people to function in their everyday lives. The AAIDD and DSM-5 classifications of adaptive behavior addresses three broad sets of skills: conceptual, social, and practical. **Conceptual skills** include language, reading, writing, time, number concepts, and self-direction. **Social skills** include interpersonal skills, personal and social responsibility, self-esteem, gullibility, naiveté, and ability to follow rules, obey laws, and avoid victimization. Representative **practical skills** are performance of activities of daily living (dressing, feeding, toileting/bathing, mobility), instrumental activities of daily living (e.g., housework, managing money, taking medication, shopping, preparing meals, using phone), occupational skills, and maintenance of a safe environment. For a deficit in adaptive behavior to be present, a significant delay in at least 1 of the 3 skill areas must be present. The rationale for requiring only 1 area is the empirically derived finding that people with ID can have varying patterns of ability and may not have deficits in all 3 areas.

The requirement for adaptive behavior deficits is the most controversial aspect of the diagnostic formulation. The controversy centers on two broad areas: whether impairments in adaptive behavior are necessary for the construct of ID, and what to measure. The adaptive behavior criterion may be irrelevant for many children; adaptive behavior is impaired in virtually all children who have IQ scores <50. The major utility of the adaptive behavior criterion is to confirm ID in children with IQ scores in the 65-75 range. It should be noted that deficits in adaptive behavior are often found in disorders such as autism spectrum disorder (ASD; see Chapter 54) and attention-deficit/hyperactivity disorder (ADHD; see Chapter 49) in the presence of typical intellectual function.

The issues of measurement are important as well. The independence of the 3 domains of adaptive behavior has not been validated. The relationship between adaptive behavior and IQ performance is insufficiently explored. Most adults with mild ID do not have significant impairments in practical skills. Adaptive behavior deficits also must be distinguished from *maladaptive behavior* (e.g., aggression, inappropriate sexual contact).

Onset before age 18 yr or adulthood distinguishes dysfunctions that originate during the developmental period. The diagnosis of ID may be made after 18 yr of age, but the cognitive and adaptive dysfunction must have been manifested before age 18.

The term “mental retardation” should not be used because it is stigmatizing, has been used to limit the achievements of the individual, and has not met its initial objective of assisting people with the disorder. The term *intellectual disability* is increasingly used in its place, but has not been adopted universally. In the United States, Rosa's law (Public Law 111-256) was passed in 2010 and now mandates that the term mental retardation be stripped from federal health, education, and labor policy. As of 2013, at least 9 states persist in using the outdated terminology. In Europe the term *learning disability* is often used to describe ID.

Global developmental delay (GDD) is a term often used to describe young children whose limitations have not yet resulted in a formal diagnosis of ID. In DSM-5, GDD is a diagnosis given to children <5 yr of age who display significant delay (>2 SD) in acquiring early childhood developmental milestones in 2 or more domains of development. These domains include receptive and expressive language, gross and fine motor function, cognition, social and personal development, and activities of daily living. Typically, it is assumed that delay in 2 domains will be associated with delay across all domains evaluated, but this is not always the case. Furthermore, not all children who meet criteria for a GDD diagnosis at a young age go on to meet criteria for ID after age 5 yr. Reasons for this might include maturational effects, a change in developmental trajectory (possibly from an intervention), reclassification to a different disability category, or imprecise use of the GDD diagnosis initially. Conversely, in patients with more severe delay, the GDD term is often inappropriately used beyond the point when the child clearly has ID, often by 3 yr of age.

It is important to distinguish the medical diagnosis of GDD from the federal disability classification of “developmental delay” that may be used by education agencies under IDEA. This classification requires that a child have delays in only 1 domain of development with subsequent need for special education. Each state determines its own precise definition and terms of eligibility under the broader definition outline by IDEA, and many states use the label for children up to age 9 yr.

Etiology

Numerous identified causes of ID may occur prenatally, during delivery, postnatally, or later in childhood. These include infection, trauma, prematurity, hypoxia-ischemia, toxic exposures, metabolic dysfunction, endocrine abnormalities, malnutrition, and genetic abnormalities. However, more than two thirds of persons with ID will not have a readily identifiable underlying diagnosis that can be linked to their clinical presentation, meriting further medical evaluation. For those who then undergo further genetic and metabolic workup, about two thirds will have an etiology that is subsequently discovered. There does appear to be 2 overlapping populations of children with ID with differing corresponding etiologies. *Mild* ID (IQ 50-70) is associated more with environmental influences, with the highest risk among children of low socioeconomic status. *Severe* ID (IQ <50) is more frequently linked to biologic and genetic causes. Accordingly, diagnostic yield is generally higher among persons with more severe disability (>75%) than among those with mild disability (<50%). With continued advancement of technologic standards and expansion of our knowledge base, the number of identified biologic and genetic causes is expected to increase.

Nongenetic risk factors that are often associated with mild ID include low socioeconomic status, residence in a developing country, low maternal education, malnutrition, and poor access to healthcare. The most common biologic causes of mild ID include genetic or chromosomal syndromes with multiple, major, or minor congenital anomalies (e.g., velocardiofacial, Williams, and Noonan syndromes), intrauterine growth restriction, prematurity, perinatal insults, intrauterine exposure to drugs of abuse (including alcohol), and sex chromosomal abnormalities. Familial clustering is common.

In children with severe ID, a biologic cause (usually prenatal) can be identified in about three fourths of all cases. Causes include chromosomal (e.g., Down, Wolf-Hirschhorn, and deletion 1p36 syndromes) and other genetic and epigenetic disorders (e.g., fragile X, Rett, Angelman, and Prader-Willi syndromes), abnormalities of brain development (e.g., lissencephaly), and inborn errors of metabolism or neurodegenerative disorders (e.g., mucopolysaccharidoses) (Table 53.1). *Nonsyndromic* severe ID may be a result of inherited or de novo gene mutations, as well as microdeletions or microduplications not detected on standard chromosome analysis. Currently, >700 genes are associated with nonsyndromic ID. Inherited genetic abnormalities may be mendelian (autosomal dominant de novo, autosomal recessive, X-linked) or nonmendelian (imprinting, methylation, mitochondrial defects; see Chapter 97). De novo mutations may also cause other phenotypic features such as seizures or autism; the presence of these features suggests more pleotropic manifestations of genetic mutations. Consistent with the finding that disorders altering early embryogenesis are the most common and severe, the earlier the problem occurs in development, the more severe its consequences tend to be.

Table 53.1

Identification of Cause in Children With Significant Intellectual Disability

CAUSE	EXAMPLES	% OF TOTAL
Chromosomal disorder	Trisomies 21, 18, 13 Deletions 1p36, 4p, 5p, 11p, 12q, 17p Microdeletions; 47,XXX Klinefelter and Turner syndromes	~20
Genetic syndrome	Fragile X, Prader-Willi, Angelman, and Rett syndromes	~20
Nonsyndromic autosomal mutations	Variations in copy number; de novo mutations in *SYNGAP1* , *GRIK2* , *TUSC3,* oligosaccharyl transferase, and others	~10
Developmental brain abnormality	Hydrocephalus ± meningomyelocele; schizencephaly, lissencephaly	~8
Inborn errors of metabolism or neurodegenerative disorder	Phenylketonuria, Tay-Sachs disease, various storage diseases	~7
Congenital infections	HIV, toxoplasmosis, rubella, cytomegalovirus, syphilis, herpes simplex	~3
Familial intellectual disability	Environment, syndromic, or genetic	~5
Perinatal causes	Hypoxic-ischemic encephalopathy, meningitis, intraventricular hemorrhage, periventricular leukomalacia, fetal alcohol syndrome	4
Postnatal causes	Trauma (abuse), meningitis, hypothyroidism	~4
Unknown		20

Adapted from Stromme P, Hayberg G: Aetiology in severe and mild mental retardation: a population based study of Norwegian children, *Dev Med Child Neurol* 42:76–86, 2000.

Etiologic workup is recommended in all cases of GDD or ID. Although there are only about 80 disorders (all of which are metabolic in nature) for which treatment may ameliorate the core symptoms of ID, several reasons beyond disease modification should prompt providers to seek etiologic answers in patients with ID. These include insight into possible associated medical or behavioral comorbidities; information on prognosis and life expectancy; estimation of recurrence risk for family planning counseling, potential validation, and closure for the family; increased access to services or specific supports; and better understanding of underlying pathology with the hope of new eventual treatment options. When surveyed, families of children with ID with no identified underlying etiology almost universally report that they would want to know of an etiologic diagnosis if given the choice.

Epidemiology

The prevalence of ID depends on the definition, method of ascertainment, and population studied, both in terms of geography and age. According to the statistics of a normal distribution, 2.5% of the population should have ID (based on IQ alone), and 75% of these individuals should fall into the mild to moderate range. Variability in rates across populations likely results from the heavy influence of external environmental factors on the prevalence of mild ID. The prevalence of severe ID is relatively stable. Globally, the prevalence of ID has been estimated to be approximately 16.4 per 1,000 persons in low-income countries, approximately 15.9/1,000 for middle-income countries, and approximately 9.2/1,000 in high-income countries. A meta-analysis of worldwide studies from 1980–2009 yielded an overall prevalence of 10.4/1000. ID occurs more in boys than in girls, at 2 : 1 in mild ID and 1.5 : 1 in severe ID. In part this may be a consequence of the many X-linked disorders associated with ID, the most prominent being fragile X syndrome (see Chapter 98.5).

In 2014–2015 in the United States, approximately 12/1000 students 3-5 yr old and 6.2/1000 students 6-21 yr old received services for ID in federally supported school programs. In 2012 the National Survey of Children's Health reported an estimated prevalence of ID among American children (age 2-17 yr) of 1.1%. For several reasons, fewer children than predicted are identified as having mild ID. Because it is more difficult to diagnose mild ID than the more severe forms, professionals might defer the diagnosis and give the benefit of the doubt to the child. Other reasons that contribute to the discrepancy are use of instruments that underidentify young children with mild ID, children diagnosed as having ASD without their ID being addressed, misdiagnosis as a language disorder or specific learning disability, and a disinclination to make the diagnosis in poor or minority students because of previous overdiagnosis. In some cases, behavioral disorders may divert the focus from the cognitive dysfunction.

Beyond potential underdiagnosis of mild ID, the number of children with mild ID may be decreasing as a result of public health and education measures to prevent prematurity and provide early intervention and Head Start programs. However, although the number of schoolchildren who receive services under a federal disability classification of ID has decreased since 1999, when *developmental delay* is included in analysis of the data, the numbers have not changed appreciably.

The prevalence of severe ID has not changed significantly since the 1940s, accounting for 0.3–0.5% of the population. Many of the causes of severe ID involve genetic or congenital brain malformations that can neither be anticipated nor treated at present. In addition, new populations with severe ID have offset the decreases in the prevalence of severe ID that have resulted from improved healthcare. Although prenatal diagnosis and subsequent pregnancy terminations could lead to a decreasing incidence of Down syndrome (see Chapter 98.2), and newborn screening with early treatment has virtually eliminated ID caused by phenylketonuria and congenital hypothyroidism, continued high prevalence of fetal exposure to illicit drugs and improved survival of very-low-birthweight premature infants has counterbalanced this effect.

Pathology and Pathogenesis

The limitations in our knowledge of the neuropathology of ID are exemplified by 10–20% of brains of persons with severe ID appearing entirely normal on standard neuropathologic study. Most of these brains show only mild, nonspecific changes that correlate poorly with the degree of ID, including microcephaly, gray matter heterotopias in the subcortical white matter, unusually regular columnar arrangement of the cortex, and neurons that are more tightly packed than usual. Only a minority of the brain shows more specific changes in dendritic and synaptic organization, with dysgenesis of dendritic spines or cortical pyramidal neurons or impaired growth of dendritic trees. The programming of the central nervous system (CNS) involves a process of *induction* ; CNS maturation is defined in terms of genetic, molecular, autocrine, paracrine, and endocrine influences. Receptors, signaling molecules, and genes are critical to brain development. The maintenance of different neuronal phenotypes in the adult brain involves the same genetic transcripts that play a crucial role in fetal development, with activation of similar intracellular signal transduction mechanisms.

As the ability to identify genetic aberrations that correspond to particular phenotypes expands through the use of next-generation sequencing, more will be elucidated about the pathogenesis of ID at a genetic and molecular level. This expanding pathophysiologic knowledge base may serve as a framework with which to develop targeted therapies to bypass or correct newly identified defects. For example, use of histone deacetylase (HDAC) inhibitors has been shown to rescue structural and functional neural deficits in mouse models of Kabuki syndrome, a disorder of histone methylation that leads to variable levels of ID and characteristic facial features (see Chapter 100).

Clinical Manifestations

Early diagnosis of ID facilitates earlier intervention, identification of abilities, realistic goal setting, easing of parental anxiety, and greater acceptance of the child in the community. Most children with ID first come to the pediatrician's attention in infancy because of dysmorphisms, associated developmental disabilities, or failure to meet age-appropriate developmental milestones (Tables 53.2 and 53.3). There are no specific physical characteristics of ID, but dysmorphisms may be the earliest signs that bring children to the attention of the pediatrician. They might fall within a genetic syndrome such as Down syndrome or might be isolated, as in microcephaly or failure to thrive. Associated developmental disabilities include seizure disorders, cerebral palsy, and ASD.

Table 53.2

Physical Examination of a Child With Suspected Developmental Disabilities

ITEM	POSSIBLE SIGNIFICANCE
General appearance	May indicate significant delay in development or obvious syndrome
Stature	
Short stature	Malnutrition, many genetic syndromes are associated with short stature (e.g., Turner, Noonan)
Obesity	Prader-Willi syndrome
Large stature	Sotos syndrome
Head	
Macrocephaly	Alexander syndrome, Canavan disease, Sotos syndrome, gangliosidosis, hydrocephalus, mucopolysaccharidosis, subdural effusion
Microcephaly	Virtually any condition that can restrict brain growth (e.g., malnutrition, Angelman syndrome, Cornelia de Lange syndrome, fetal alcohol effects)
Face	
Coarse, triangular, round, or flat face; hypotelorism or hypertelorism; slanted or short palpebral fissure; unusual nose, maxilla, and mandible	Specific measurements may provide clues to inherited, metabolic, or other diseases such as fetal alcohol syndrome, cri du chat (5p−) syndrome, or Williams syndrome.

Eyes	
Prominent	Crouzon, Seckel, and fragile X syndromes
Cataract	Galactosemia, Lowe syndrome, prenatal rubella, hypothyroidism
Cherry-red spot in macula	Gangliosidosis (GM_1), metachromatic leukodystrophy, mucolipidosis, Tay-Sachs disease, Niemann-Pick disease, Farber lipogranulomatosis, sialidosis type III
Chorioretinitis	Congenital infection with cytomegalovirus, toxoplasmosis, Zika virus, or rubella
Corneal cloudiness	Mucopolysaccharidosis types I and II, Lowe syndrome, congenital syphilis
Ears	
Low-set or malformed pinnae	Trisomies such as Down syndrome, Rubinstein-Taybi syndrome, CHARGE syndrome, cerebrooculofacioskeletal syndrome, fetal phenytoin effects
Hearing	Loss of acuity in mucopolysaccharidosis; hyperacusis in many encephalopathies
Heart	
Structural anomaly or hypertrophy	CHARGE syndrome, velocardiofacial syndrome, glycogenosis type II, fetal alcohol effects, mucopolysaccharidosis type I; chromosomal anomalies such as Down syndrome; maternal PKU; chronic cyanosis may impair cognitive development.
Liver	
Hepatomegaly	Fructose intolerance, galactosemia, glycogenosis types I-IV, mucopolysaccharidosis types I and II, Niemann-Pick disease, Tay-Sachs disease, Zellweger syndrome, Gaucher disease, ceroid lipofuscinosis, gangliosidosis
Genitalia	
Macroorchidism	Fragile X syndrome
Hypogenitalism	Prader-Willi, Klinefelter, and CHARGE syndromes
Extremities	
Hands, feet; dermatoglyphics, creases	May indicate a specific entity such as Rubinstein-Taybi syndrome or may be associated with chromosomal anomaly
Joint contractures	Signs of muscle imbalance around the joints; e.g., with meningomyelocele, cerebral palsy, arthrogryposis, muscular dystrophy; also occurs with cartilaginous problems such as mucopolysaccharidosis
Skin	
Café au lait spots	Neurofibromatosis, tuberous sclerosis, chromosomal aneuploidy, ataxia-telangiectasia, multiple endocrine neoplasia type 2b Fanconi anemia, Gaucher disease Syndromes: basal cell nevus, McCune-Albright, Silver-Russell, Bloom, Chediak-Higashi, Hunter, Bannayan-Riley-Ruvalcaba, Maffucci
Seborrheic or eczematoid rash	PKU, histiocytosis
Hemangiomas and telangiectasia	Sturge-Weber syndrome, Bloom syndrome, ataxia-telangiectasia
Hypopigmented macules, streaks, adenoma sebaceum	Tuberous sclerosis, hypomelanosis of Ito
Hair	
Hirsutism	De Lange syndrome, mucopolysaccharidosis, fetal phenytoin effects, cerebrooculofacioskeletal syndrome, trisomy 18, Wiedemann-Steiner syndrome (hypertrichosis cubiti)
Neurologic	
Asymmetry of strength and tone	Focal lesion, hemiplegic cerebral palsy
Hypotonia	Prader-Willi, Down, and Angelman syndromes; gangliosidosis; early cerebral palsy; muscle disorders (dystrophy or myopathy)

Hypertonia	Neurodegenerative conditions involving white matter, cerebral palsy, trisomy 18
Ataxia	Ataxia-telangiectasia, metachromatic leukodystrophy, Angelman syndrome

CHARGE, Coloboma, heart defects, atresia choanae, retarded growth, genital anomalies, ear anomalies (deafness); CATCH-22, cardiac defects, abnormal face, thymic hypoplasia, cleft palate, hypocalcemia—defects on chromosome 22; PKU, phenylketonuria.

From Simms M: Intellectual and developmental disability. In Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis,* Philadelphia, 2018, Elsevier, Table 24.11, p 376.

Table 53.3

Examples of Minor Anomalies and Associated Syndromes[*] [†]

AREA	ANOMALY/SYNDROME
Head	Flat occiput: Down syndrome, Zellweger syndrome; prominent occiput: trisomy 18 Delayed closure of sutures: hypothyroidism, hydrocephalus Craniosynostosis: Crouzon syndrome, Pfeiffer syndrome Delayed fontanel closure: hypothyroidism, Down syndrome, hydrocephalus, skeletal dysplasias
Face	Midface hypoplasia: fetal alcohol syndrome, Down syndrome Triangular facies: Russell-Silver syndrome, Turner syndrome Coarse facies: mucopolysaccharidoses, Sotos syndrome Prominent nose and chin: fragile X syndrome Flat facies: Apert syndrome, Stickler syndrome Round facies: Prader-Willi syndrome
Eyes	Hypertelorism: fetal hydantoin syndrome, Waardenburg syndrome Hypotelorism: holoprosencephaly sequence, maternal phenylketonuria effect Inner canthal folds/Brushfield spots: Down syndrome; slanted palpebral fissures: trisomies Prominent eyes: Apert syndrome, Beckwith-Wiedemann syndrome Lisch nodules: neurofibromatosis Blue sclera: osteogenesis imperfecta, Turner syndrome, hereditary connective tissue disorders
Ears	Large pinnae/simple helices: fragile X syndrome Malformed pinnae/atretic canal: Treacher Collins syndrome, CHARGE syndrome Low-set ears: Treacher Collins syndrome, trisomies, multiple disorders
Nose	Anteverted nares/synophrys: Cornelia de Lange syndrome; broad nasal bridge: fetal drug effects, fragile X syndrome Low nasal bridge: achondroplasia, Down syndrome Prominent nose: Coffin-Lowry syndrome, Smith-Lemli-Opitz syndrome
Mouth	Long philtrum/thin vermilion border: fetal alcohol effects Cleft lip and palate: isolated or part of a syndrome Micrognathia: Pierre Robin sequence, trisomies, Stickler syndrome Macroglossia: hypothyroidism, Beckwith-Wiedemann syndrome
Teeth	Anodontia: ectodermal dysplasia Notched incisors: congenital syphilis Late dental eruption: Hunter syndrome, hypothyroidism Talon cusps: Rubinstein-Taybi syndrome Wide-spaced teeth: Cornelia de Lange syndrome, Angelman syndrome
Hair	Hirsutism: Hurler syndrome Low hairline: Klippel-Feil sequence, Turner syndrome Sparse hair: Menkes disease, argininosuccinic acidemia

	Abnormal hair whorls/posterior whorl: chromosomal aneuploidy (e.g., Down syndrome) Abnormal eyebrow patterning: Cornelia de Lange syndrome
Neck	Webbed neck/low posterior hairline: Turner syndrome, Noonan syndrome
Chest	Shield-shaped chest: Turner syndrome
Genitalia	Macroorchidism: fragile X syndrome Hypogonadism: Prader-Willi syndrome
Extremities	Short limbs: achondroplasia, rhizomelic chondrodysplasia Small hands: Prader-Willi syndrome Clinodactyly: trisomies, including Down syndrome Polydactyly: trisomy 13, ciliopathies Broad thumb: Rubinstein-Taybi syndrome Syndactyly: de Lange syndrome Transverse palmar crease: Down syndrome Joint laxity: Down syndrome, fragile X syndrome, Ehlers-Danlos syndrome Phocomelia: Cornelia de Lange syndrome
Spine	Sacral dimple/hairy patch: spina bifida
Skin	Hypopigmented macules/adenoma sebaceum: tuberous sclerosis Café au lait spots and neurofibromas: neurofibromatosis Linear depigmented nevi: hypomelanosis of Ito Facial port-wine hemangioma: Sturge-Weber syndrome Nail hypoplasia or dysplasia: fetal alcohol syndrome, trisomies

[*] Increased incidence of minor anomalies have been reported in cerebral palsy, intellectual disability, learning disabilities, and autism.

[†] The presence of 3 or more minor anomalies implies a greater chance that the child has a major anomaly and a diagnosis of a specific syndrome.

CHARGE, Coloboma, heart defects, atresia choanae, retarded growth, genital anomalies, ear anomalies (deafness).

Modified from Levy SE, Hyman SL. Pediatric assessment of the child with developmental delay, *Pediatr Clin North Am* 40:465-477, 1993.

Most children with ID do not keep up with their peers' developmental skills. In early infancy, failure to meet age-appropriate expectations can include a lack of visual or auditory responsiveness, unusual muscle tone (hypo- or hypertonia) or posture, and feeding difficulties. Between 6 and 18 mo of age, gross motor delay (lack of sitting, crawling, walking) is the most common complaint. Language delay and behavior problems are common concerns after 18 mo (Table 53.4). For some children with mild ID, the diagnosis remains uncertain during the early school years. It is only after the demands of the school setting increase over the years, changing from “learning to read” to “reading to learn,” that the child's limitations are clarified. Adolescents with mild ID are typically up to date on current trends and are conversant as to “who,” “what,” and “where.” It is not until the “why” and “how” questions are asked that their limitations become apparent. If allowed to interact at a superficial level, their mild ID might not be appreciated, even by professionals, who may be their special education teachers or healthcare providers. Because of the stigma associated with ID, adolescents may use euphemisms to avoid being thought of as “stupid” or “retarded” and may refer to themselves as learning disabled, dyslexic, language disordered, or slow learners. Some people with ID emulate their social milieu to be accepted. They may be social chameleons and assume the morals of the group to whom they are attached. Some would rather be thought “bad” than “incompetent.”

Table 53.4

Common Presentations of Intellectual Disability by Age

AGE	AREA OF CONCERN
Newborn	Dysmorphic syndromes, (multiple congenital anomalies), microcephaly Major organ system dysfunction (e.g., feeding, breathing)
Early infancy (2-4 mo)	Failure to interact with the environment Concerns about vision and hearing impairments
Later infancy (6-18 mo)	Gross motor delay
Toddlers (2-3 yr)	Language delays or difficulties
Preschool (3-5 yr)	Language difficulties or delays Behavior difficulties, including play Delays in fine motor skills: cutting, coloring, drawing
School age (>5 yr)	Academic underachievement Behavior difficulties (e.g., attention, anxiety, mood, conduct)

Children with ID have a nonprogressive disorder; loss of developmental milestones or progressive symptoms suggest another disorder (see Chapter 53.1).

Diagnostic Evaluation

Intellectual disability is one of the most frequent reasons for referral to pediatric genetic providers, with separate but similar diagnostic evaluation guidelines put forth by the American College of Medical Genetics, the American Academy of Neurology, the American Academy of Pediatrics (AAP), and the American Academy of Child and Adolescent Psychiatry. ID is a diagnosis of great clinical heterogeneity, with only a subset of syndromic etiologies identifiable through classic dysmorphology. If diagnosis is not made after conducting an appropriate history and physical examination, chromosomal microarray is the recommended first step in the diagnostic evaluation of ID. Next-generation sequencing represents the new diagnostic frontier, with extensive gene panels (exome or whole genome) that increase the diagnostic yield and usefulness of genetic testing in ID. Other commonly used medical diagnostic testing for children with

ID includes neuroimaging, metabolic testing, and electroencephalography (Fig. 53.1).

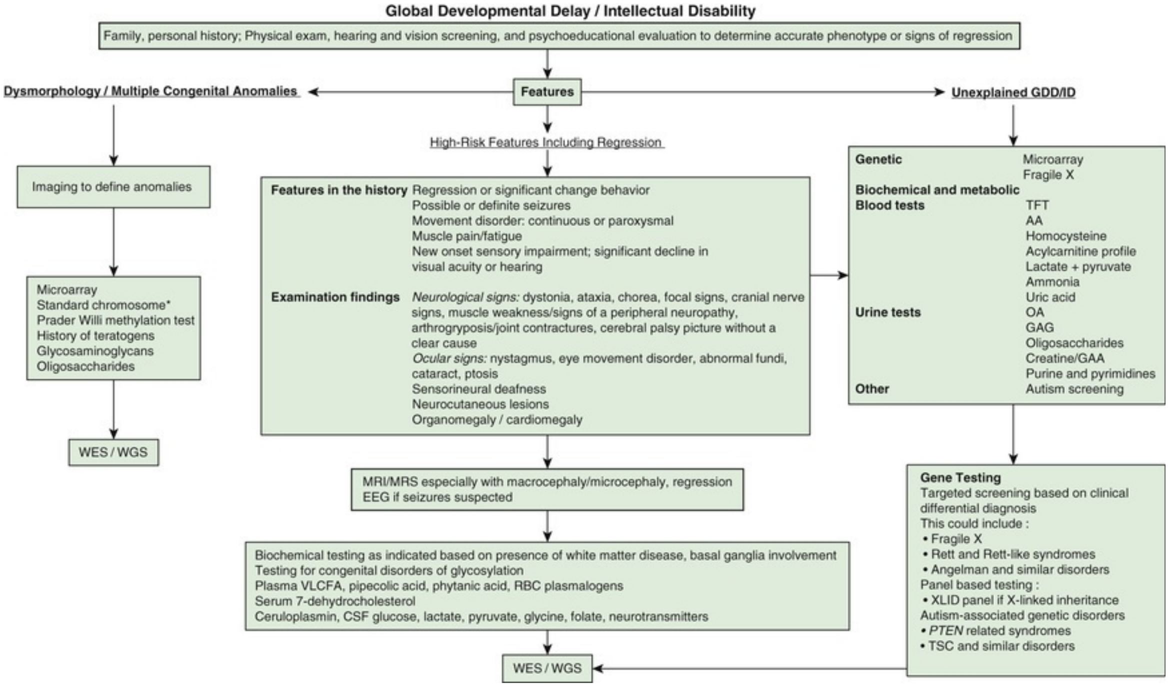
Global Developmental Delay / Intellectual Disability
Family, personal history; Physical exam, hearing and vision screening, and psychoeducational evaluation to determine accurate phenotype or signs of regression
Features
Dysmorphology / Multiple Congenital Anomalies
Unexplained GDD/ID
High-Risk Features Including Regression
Imaging to define anomalies
Microarray
Standard chromosome*
Prader Willi methylation test
History of teratogens
Glycosaminoglycans
Oligosaccharides
WES / WGS
Features in the history
Regression or significant change behavior
Possible or definite seizures
Movement disorder: continuous or paroxysmal
Muscle pain/fatigue
New onset sensory impairment; significant decline in visual acuity or hearing
Examination findings
Neurological signs: dystonia, ataxia, chorea, focal signs, cranial nerve signs, muscle weakness/signs of a peripheral neuropathy, arthrogryposis/joint contractures, cerebral palsy picture without a clear cause
Ocular signs: nystagmus, eye movement disorder, abnormal fundi, cataract, ptosis
Sensorineural deafness
Neurocutaneous lesions
Organomegaly / cardiomegaly
Genetic
Microarray
Fragile X
Biochemical and metabolic
Blood tests
TFT
AA
Homocysteine
Acylcarnitine profile
Lactate + pyruvate
Ammonia
Uric acid
Urine tests
OA
GAG
Oligosaccharides
Creatine/GAA
Purine and pyrimidines
Other
Autism screening
MRI/MRS especially with macrocephaly/microcephaly, regression
EEG if seizures suspected
Biochemical testing as indicated based on presence of white matter disease, basal ganglia involvement
Testing for congenital disorders of glycosylation
Plasma VLCFA, pipecolic acid, phytanic acid, RBC plasmalogens
Serum 7-dehydrocholesterol
Ceruloplasmin, CSF glucose, lactate, pyruvate, glycine, folate, neurotransmitters
Gene Testing
Targeted screening based on clinical differential diagnosis
This could include :
• Fragile X
• Rett and Rett-like syndromes
• Angelman and similar disorders
Panel based testing :
• XLID panel if X-linked inheritance
Autism-associated genetic disorders
• PTEN related syndromes
• TSC and similar disorders
WES / WGS

FIG. 53.1 **Algorithm for the evaluation of the child with unexplained global developmental delay (GDD) or intellectual disability (ID). AA, amino acids; ASD, autistic spectrum disorder; CK, creatine kinase; CSF, cerebrospinal fluid; FBC, full blood count; GAA, guanidinoacetic acid; GAG, glycosaminoglycans; LFT, liver function test; OA, organic acids; TFT, thyroid function tests; TSC, tuberous sclerosis complex; U&E, urea and electrolytes; VLCFA, very long chain fatty acids; WES, whole exome sequencing; WGS, whole genome sequencing; X-linked intellectual disability genes.**

Decisions to pursue an etiologic diagnosis should be based on the medical and family history, physical examination, and the family's wishes. Table 53.5 summarizes clinical practice guidelines and the yields of testing to assist in decisions about evaluating the child with GDD or ID. Yield of testing tends increase with worsening severity of delays.

Table 53.5

Suggested Evaluation of the Child With Intellectual Disability (ID) or Global Developmental Delay (GDD)

TEST	COMMENT
In-depth history	Includes pre-, peri-, and postnatal events (including seizures); developmental attainments; and 3-generation pedigree in family history (focusing on neurologic or developmental abnormalities, miscarriages, consanguinity, etc.)

Physical examination	Particular attention to minor or subtle dysmorphisms; growth issues; neurocutaneous findings; eye and skull abnormalities; hepatosplenomegaly; and neurologic examination for focality Behavioral phenotype
Vision and hearing evaluation	Essential to detect and treat; can mask as developmental delay
Gene microarray analysis	A 15% yield overall Better resolution than with karyotype; may identify up to twice as many abnormalities as karyotyping
Karyotype	Yield of 4% in ID/GDD (18.6% if syndromic features, 3% excluding trisomy 21) Best for inversions and balanced insertions, reciprocal translocations, and polyploidy
Fragile X screen	Combined yield of 2% Preselection on clinical grounds can increase yield to 7.6%
Next-generation gene sequencing	Detects inherited and de novo point mutations, especially in nonsyndromic severe intellectual disability Whole exome sequencing (WES, introduced in 2010) gives an additional yield of about 30–40%. Although not yet used clinically, pilot studies of whole genome sequencing (WGS) reveal additional yield of about 15%.
Neuroimaging	MRI preferred; positive findings increased by abnormalities of skull contour or microcephaly and macrocephaly, or focal neurologic examination (30–40% if indicated, 10–14% if screening). Identification of specific etiologies is rare; most conditions that are found do not alter the treatment plan; need to weigh risk of sedation against possible yield.
Thyroid (T_4 , TSH)	Near 0% in settings with universal newborn screening program
Serum lead	If there are identifiable risk factors for excessive environmental lead exposure (e.g., low socioeconomic status, home built before 1950)
Metabolic testing	Yield of 0.2–4.6% based on clinical indicators and tests performed Urine organic acids, plasma amino acids, ammonia, lactate, and capillary blood gas Focused testing based on clinical findings is warranted if lack of newborn screen results or suggestive history/exam (e.g., regression, consanguinity, hepatosplenomegaly, course facies). Tandem mass spectrometry newborn screening has allowed for identification of many disorders in perinatal period and have decreased yield in older children; other disorders have emerged, such as congenital disorders of glycosylation (yield 1.4%) and disorders of creatine synthesis and transport (yield 2.8%).
MECP2 for Rett syndrome	1.5% of females with criteria suggestive of Rett (e.g., acquired microcephaly, loss of skills) 0.5% of males
EEG	May be deferred in absence of history of seizures
Repeated history and physical examination	Can give time for maturation of physical and behavioral phenotype; new technology may be available for evaluation.

EEG, Electroencephalogram; CGH, comparative genomic hybridization; MECP2, methyl CpG–binding protein 2; T_4 , thyroxine; TSH, thyroid-stimulating hormone.

Data from Michelson DJ et al: Evidence report. Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of Child Neurology, Neurology 77:1629-35, 2011; Curry CJ et al: Evaluation of mental retardation: recommendations of a Consensus Conference: American College of Medical Genetics, Am J Med Genet 12:72:468-477, 1997;

Shapiro BK, Batshaw ML: Mental retardation. In Burg FD et al: *Gellis and Kagan's current pediatric therapy* , ed 18, Philadelphia, 2005, Saunders; and Shevell M et al: Practice parameter: evaluation of the child with global developmental delay, *Neurology* 60:367–380, 2003.

Microarray analysis has replaced a karyotype as first-tier testing given that it discerns abnormalities that are far below the resolution of a karyotype. Microarray analysis may identify variants of unknown significance or benign variants and therefore should be used in conjunction with a genetic consultation. Karyotyping has a role when concerns for inversions, balanced insertions, and reciprocal translocations are present. Fluorescence in situ hybridization (FISH) and subtelomeric analysis have been largely replaced by microarray analysis but are occasionally used for specific indications. If microarray analysis is not diagnostic, whole exome sequencing increases the diagnostic yield in many children with nonsyndromic severe ID. Starting with whole exome sequencing may be more cost-effective and may substantially reduce time to diagnosis with higher ultimate yields compared with the traditional diagnostic pathway.

Molecular genetic testing for fragile X syndrome is recommended for all children presenting with GDD. Yields are highest in males with moderate ID, unusual physical features, and/or a family history of ID, or for females with more subtle cognitive deficits associated with severe shyness and a relevant family history, including premature ovarian failure or later-onset ataxia-tremor symptoms. For children with a strong history of X-linked ID, specific testing of genes or the entire chromosome may be revealing. Testing for Rett syndrome (MECP2, methyl CpG–binding protein 2) should be considered in girls with moderate to severe disability.

A child with a progressive neurologic disorder, developmental regression, or acute behavioral changes needs metabolic investigation as shown in Figure 53.1 . Some are advocating that metabolic testing should be done more frequently in children with ID because of the possibility of detecting a condition that could be treatable (Fig. 53.2 and Table 53.6). A child with seizure-like episodes should have an electroencephalogram (EEG), although this testing is generally not helpful outside the scope of ruling out seizures. **MRI of the brain** may provide useful information in directing the care of a child with micro- or macrocephaly, change in head growth trajectory, asymmetric head shape, new or focal neurologic findings, or seizure. MRI can detect a significant number of subtle markers of cerebral dysgenesis in children with ID, but these markers do not usually suggest a specific etiologic diagnosis.

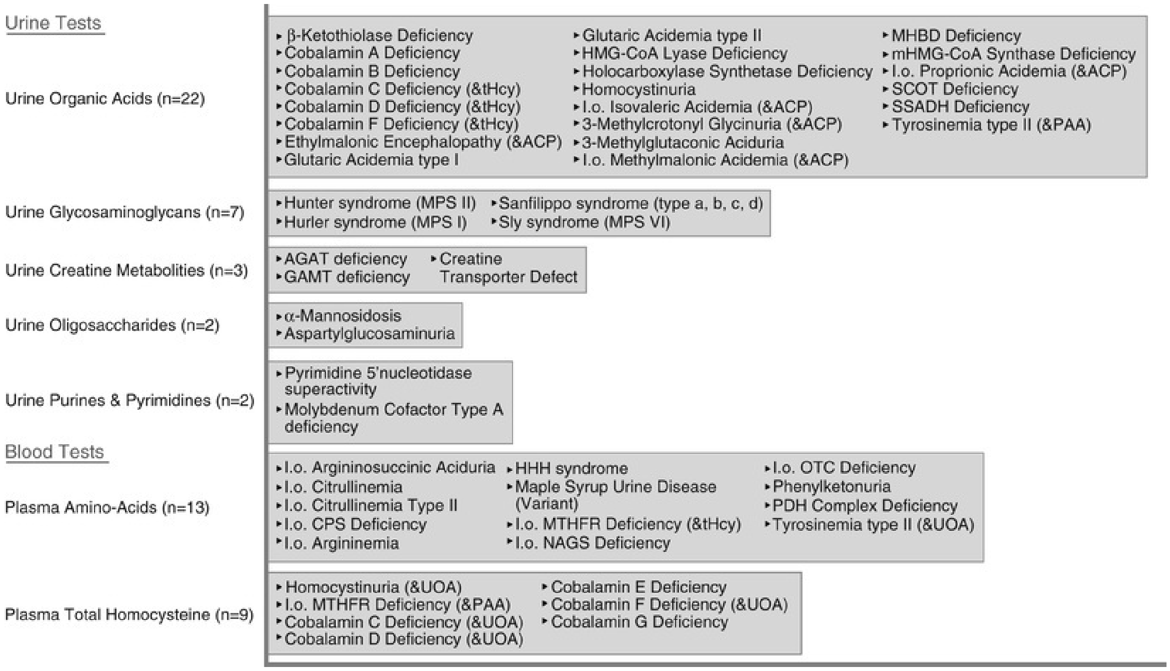
Urine Tests
Urine Organic Acids (n=22)
β-Ketothiolase Deficiency
Cobalamin A Deficiency
Cobalamin B Deficiency
Cobalamin C Deficiency (&tHcy)
Cobalamin D Deficiency (&tHcy)
Cobalamin F Deficiency (&tHcy)
Ethylmalonic Encephalopathy (&ACP)
Glutaric Acidemia type I
Glutaric Acidemia type II
HMG-CoA Lyase Deficiency
Holocarboxylase Synthetase Deficiency
Homocystinuria
I.o. Isovaleric Acidemia (&ACP)
3-Methylcrotonyl Glycinuria (&ACP)
3-Methylglutaconic Aciduria
I.o. Methylmalonic Acidemia (&ACP)
MHBD Deficiency
mHMG-CoA Synthase Deficiency
I.o. Proprionic Acidemia (&ACP)
SCOT Deficiency
SSADH Deficiency
Tyrosinemia type II (&PAA)
Urine Glycosaminoglycans (n=7)
Hunter syndrome (MPS II)
Hurler syndrome (MPS I)
Sanfilippo syndrome (type a, b, c, d)
Sly syndrome (MPS VI)
Urine Creatine Metabolites (n=3)
AGAT deficiency
GAMT deficiency
Creatine Transporter Defect
Urine Oligosaccharides (n=2)
α-Mannosidosis
Aspartylglucosaminuria
Urine Purines & Pyrimidines (n=2)
Pyrimidine 5'nucleotidase superactivity
Molybdenum Cofactor Type A deficiency
Blood Tests
Plasma Amino-Acids (n=13)
I.o. Argininosuccinic Aciduria
I.o. Citrullinemia
I.o. Citrullinemia Type II
I.o. CPS Deficiency
I.o. Argininemia
HHH syndrome
Maple Syrup Urine Disease (Variant)
I.o. MTHFR Deficiency (&tHcy)
I.o. NAGS Deficiency
I.o. OTC Deficiency
Phenylketonuria
PDH Complex Deficiency
Tyrosinemia type II (&UOA)
Plasma Total Homocysteine (n=9)
Homocystinuria (&UOA)
I.o. MTHFR Deficiency (&PAA)
Cobalamin C Deficiency (&UOA)
Cobalamin D Deficiency (&UOA)
Cobalamin E Deficiency
Cobalamin F Deficiency (&UOA)
Cobalamin G Deficiency

FIG. 53.2 Summary of treatable inherent errors of metabolism (IEM) that can be detected by metabolic tests in affected children, each of which is affordable and accessible and has the potential to identify at least 2 IEM (and up to 22). Each bar represents the yield of the specific screening test and lists the number and types of treatable IEM it can identify. PAA, Plasma amino acids; tHcy, total homocysteine; ACP, plasma acylcarnitine profile; UOA, urine organic acids. (From van Karnebeek CD, Stockler S: Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review, *Mol Genet Metab* 105:368–381, 2012, Fig 1, p 374.)

Table 53.6

Treatable Intellectual Disability Endeavor (TIDE) Diagnostic Protocol

Tier 1: Nontargeted Metabolic Screening to Identify 54 (60%) Treatable IEM

Blood
- Plasma amino acids
- Plasma total homocysteine
- Acylcarnitine profile
- Copper, ceruloplasmin

Urine
- Organic acids

Purines and pyrimidines
Creatine metabolites
Oligosaccharides
Glycosaminoglycans
Amino acids (when indicated)

Tier 2: Current Practice Adhering to International Guidelines* (1 or more of:)

Audiology
Ophthalmology
Cytogenetic testing (array CGH)
Thyroid studies
Complete blood count (CBC)
Lead
Metabolic testing
Brain MRI and 1H spectroscopy (where available)
Fragile X
Targeted gene sequencing/molecular panel
Other

Tier 3: Targeted Workup to Identify 35 (40%) Treatable IEM Requiring Specific Testing

According to patient's symptomatology and clinician's expertise
Utilization of digital tools (www.treatable-id.org)
Specific biochemical/gene test
Whole blood manganese
Plasma cholestanol
Plasma 7-dehydroxycholesterol:cholesterol ratio
Plasma pipecolic acid and urine α-amino adipic semialdehyde (AASA)
Plasma very-long-chain fatty acids
Plasma vitamin B_{12} and folate
Serum and CSF lactate to pyruvate ratio
Enzyme activities (leukocytes): arylsulfatase A, biotinidase, glucocerebrosidase, fatty aldehyde dehydrogenase

Urine deoxypyridinoline
CSF amino acids
CSF neurotransmitters
CSF-to-plasma glucose ratio
CoQ measurement: fibroblasts
Molecular analysis: *CA5A, NPC1, NPC2, SC4MOL, SLC18A2, SLC19A3, SLC30A10, SLC52A2, SLC52A3, PDHA1, DLAT, PDHX, SPR, TH* genes

IEM, Inborn errors of metabolism; CSF, cerebrospinal fluid; CGH, comparative genomic hybridization; CoQ, coenzyme Q (ubiquinone).

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* Low threshold for ordering tests.

Adapted from Van Karnebeek CD, Stockler-Ipsiroglu S. Early identification of treatable inborn errors of metabolism in children with intellectual disability: The Treatable Intellectual Disability Endeavor protocol in British Columbia, *Paediatr Child Health* 19(9):469–471, 2014.

Some children with subtle physical or neurologic findings can also have determinable biologic causes of their ID (see Tables 53.2 and 53.3). How intensively one investigates the cause of a child's ID is based on the following factors:

- What is the degree of delay, and what is the age of the child? If milder or less pervasive delays are present, especially in a younger child, etiologic yield is likely to be lower.
- Is the medical history, family history, or physical exam suggestive of a specific disorder, increasing the likelihood that a diagnosis will be made? Are the parents planning on having additional children, and does the patient have siblings? If so, one may be more

likely to intensively seek disorders for which prenatal diagnosis or a specific early treatment option is available.

◆ What are the parents' wishes? Some parents have little interest in searching for the cause of the ID, whereas others become so focused on obtaining a diagnosis that they have difficulty following through on interventions until a cause has been found. The entire spectrum of responses must be respected, and supportive guidance should be provided in the context of the parents' education.

Differential Diagnosis

One of the important roles of pediatricians is the early recognition and diagnosis of cognitive deficits. The developmental surveillance approach to early diagnosis of ID should be multifaceted. Parents' concerns and observations about their child's development should be listened to carefully. Medical, genetic, and environmental risk factors should be recognized. Infants at high risk (prematurity, maternal substance abuse, perinatal insult) should be registered in newborn follow-up programs in which they are evaluated periodically for developmental lags in the 1st 2 yr of life; they should be referred to early intervention programs as appropriate. Developmental milestones should be recorded routinely during healthcare maintenance visits. The AAP has formulated a schema for developmental surveillance and screening (see Chapter 28).

Before making the diagnosis of ID, other disorders that affect cognitive abilities and adaptive behavior should be considered. These include conditions that mimic ID and others that involve ID as an associated impairment. Sensory deficits (severe hearing and vision loss), communication disorders, refractory seizure disorders, poorly controlled mood disorders, or unmanaged severe attention deficits can mimic ID; certain progressive neurologic disorders can appear as ID before regression is appreciated. Many children with cerebral palsy (see Chapter 616.1) or ASD (Chapter 54) also have ID. Differentiation of isolated **cerebral palsy** from ID relies on motor skills being more affected than cognitive skills and on the presence of pathologic reflexes and tone changes. In **autism spectrum disorders,** language and social adaptive skills are more affected than nonverbal reasoning skills, whereas in ID, there are usually more equivalent deficits in social, fine motor, adaptive, and cognitive skills.

Diagnostic Psychologic Testing

The formal diagnosis of ID requires the administration of individual tests of intelligence and adaptive functioning.

The *Bayley Scales of Infant and Toddler Development* (BSID-III), the most commonly used infant intelligence test, provides an assessment of cognitive, language, motor, behavior, social-emotional, and general adaptive abilities between 1 mo and 42 mo of age. Mental Developmental Index (MDI) and Psychomotor Development Index (PDI, a measure of motor competence) scores are derived from the results. The BSID-III permits the differentiation of infants with severe ID from typically developing infants, but it is less helpful in distinguishing between a typical child and one with mild ID.

The most commonly used psychologic tests for children older than 3 yr are the Wechsler Scales. The *Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition* (WPPSI-IV) is used for children with mental ages of 2.5-7.6 yr. The *Wechsler Intelligence Scale for Children, Fifth Edition* (WISC-V) is used for children who function above a 6 yr mental age. Both scales contain numerous subtests in the areas of verbal and performance skills. Although children with ID usually score below average on all subscale scores, they occasionally score in the average range in one or more performance areas.

Several normed scales are used in practice to evaluate adaptive functioning. For example, the *Vineland Adaptive Behavior Scale* (VABS-3) uses semistructured interviews with parents and caregivers/teachers to assess adaptive behavior in 4 domains: communication, daily living skills, socialization, and motor skills. Other tests of adaptive behavior include the *Woodcock-Johnson Scales of Independent Behavior–Revised*, the AAIDD Diagnostic *Adaptive Behavior Scale* (DABS), and the *Adaptive Behavior Assessment System* (ABAS-3). There is usually (but not always) a good correlation between scores on the intelligence and adaptive scales. However, it is important to recognize that adaptive behavior can by influenced by environmentally based opportunities as well as family or cultural expectations. Basic practical adaptive skills (feeding, dressing, hygiene) are more responsive to remedial efforts than is the IQ score. Adaptive abilities are also more variable over time, which may be related to the underlying condition and environmental expectations.

Complications

Children with ID have higher rates of vision, hearing, neurologic, orthopedic, and behavioral or emotional disorders than typically developing children. These other problems are often detected later in children with ID. If untreated, the associated impairments can adversely affect the individual's outcome more than the ID itself.

The more severe the ID, the greater are the number and severity of associated impairments. Knowing the cause of the ID can help predict which associated impairments are most likely to occur. Fragile X syndrome and fetal alcohol syndrome (see Chapter 126.3) are associated with a high rate of behavioral disorders; Down syndrome has many medical complications (hypothyroidism, obstructive sleep apnea, congenital heart disease, atlantoaxial subluxation). Associated impairments can require ongoing physical therapy, occupational therapy, speech-language therapy, behavioral therapy, adaptive and mobility equipment, glasses, hearing aids, and medication. Failure to identify and treat these impairments adequately can hinder successful habilitation and result in difficulties in the school, home, and neighborhood environment.

Prevention

Examples of primary programs to prevent ID include the following:

◆ Increasing the public's awareness of the adverse effects of alcohol and other drugs of abuse on the fetus (the most common preventable cause of ID in the Western world is fetal alcohol exposure).

◆ Encouraging safe sexual practices, preventing teen pregnancy, and promoting early prenatal care with a focus on preventive programs to limit transmission of diseases that may cause congenital infection (syphilis, toxoplasmosis, cytomegalovirus, HIV).

◆ Preventing traumatic injury by encouraging the use of guards, railings, and window locks to prevent falls and other avoidable injuries in the home; using appropriate seat restraints when driving; wearing a safety helmet when biking or skateboarding; limiting exposure to firearms.

◆ Preventing poisonings by teaching parents about locking up medications and potential poisons.

◆ Implementing immunization programs to reduce the risk of ID caused by encephalitis, meningitis, and congenital infection.

Presymptomatic detection of certain disorders can result in treatment that prevents adverse consequences. State newborn screening by tandem mass spectrometry (now including >50 rare genetic disorders in most states), newborn hearing screening, and preschool lead poisoning prevention programs are examples. Additionally, screening for comorbid conditions can help to limit the extent of disability and maximize level of functioning in certain populations. Annual thyroid, vision, and hearing screening in a child with Down syndrome is an example of presymptomatic testing in a disorder associated with ID.

Treatment

Although the core symptoms of ID itself are generally not treatable, many associated impairments are amenable to intervention and therefore benefit from early identification. Most children with an ID do not have a behavioral or emotional disorder as an associated impairment, but challenging behaviors (aggression, self-injury, oppositional defiant behavior) and mental illness (mood and anxiety disorders) occur with greater frequency in this population than among children with typical intelligence. These behavioral and emotional disorders are the primary cause for out-of-home placements, increased family stress, reduced employment prospects, and decreased opportunities for social integration. Some behavioral and emotional disorders are difficult to diagnose in children with more severe ID because of the child's limited abilities to understand, communicate, interpret, or generalize. Other disorders are masked by the ID. The detection of ADHD (see Chapter 49) in the presence of moderate to severe ID may be difficult, as may be discerning a thought disorder (psychosis) in someone with autism and ID.

Although mental illness is generally of biologic origin and responds to medication, **behavioral disorders** can result from a mismatch between the child's abilities and the demands of the situation, organic problems, and family difficulties. These behaviors may represent attempts by the child to communicate, gain attention, or avoid frustration. In assessing the challenging behavior, one must also consider whether it is inappropriate for the child's *mental age*, rather than the *chronological age*. When intervention is needed, an environmental change, such as a more appropriate classroom setting, may improve certain behavior problems. Behavior management techniques are useful; psychopharmacologic agents may be appropriate in certain situations.

No medication has been found that improves the core symptoms of ID. However, several agents are being tested in specific disorders with known biologic mechanisms (e.g., mGluR5 inhibitors in fragile X syndrome, mTOR inhibitors in tuberous sclerosis), with the hope for future pharmacologic options that could alter the natural course of cognitive impairment seen in patients with these disorders. Currently, medication is most useful in the treatment of associated behavioral and psychiatric disorders. Psychopharmacology is generally directed at specific symptom complexes, including ADHD (stimulant medication), self-injurious behavior and aggression (antipsychotics), and anxiety, obsessive-compulsive disorder, and depression (selective serotonin reuptake inhibitors). Even if a medication proves successful, its use should be reevaluated at least yearly to assess the need for continued treatment.

Supportive Care and Management

Each child with ID needs a medical home with a pediatrician who is readily accessible to the family to answer questions, help coordinate care, and discuss concerns. Pediatricians can have effects on patients and their families that are still felt decades later. The role of the pediatrician includes involvement in prevention efforts, early diagnosis, identification of associated deficits, referral for appropriate diagnostic and therapeutic services, interdisciplinary management, provision of primary care, and advocacy for the child and family. The management strategies for children with an ID should be multimodal, with efforts directed at all aspects of the child's life: health, education, social and recreational activities, behavior problems, and associated impairments. Support for parents and siblings should also be provided.

Primary Care

For children with an ID, primary care has the following important components:

- Provision of the same primary care received by all other children of similar chronological age.
- Anticipatory guidance relevant to the child's level of function: feeding, toileting, school, accident prevention, sexuality education.
- Assessment of issues that are relevant to that child's disorder, such as dental examination in children who exhibit bruxism, thyroid function in children with Down syndrome, and cardiac function in Williams syndrome (see Chapter 454.5).

The AAP has published a series of guidelines for children with specific genetic disorders associated with ID (Down syndrome, fragile X syndrome, and Williams syndrome). Goals should be considered and programs adjusted as needed during the primary care visit. Decisions should also be made about what additional information is required for future planning or to explain why the child is not meeting expectations. Other evaluations, such as formal psychologic or educational testing, may need to be scheduled.

Interdisciplinary Management

The pediatrician has the responsibility for consulting with other disciplines to make the diagnosis of ID and coordinate treatment services. Consultant services may include psychology, speech-language pathology, physical therapy, occupational therapy, audiology, nutrition, nursing, and social work, as well as medical specialties such as neurodevelopmental disabilities, neurology, genetics, physical medicine and rehabilitation, psychiatry, developmental-behavioral pediatricians, and surgical specialties. Contact with early intervention and school personnel is equally important to help prepare and assess the adequacy of the child's individual family service plan or individual educational plan. The family should be an integral part of the planning and direction of this process. Care should be family centered and culturally sensitive; for older children, their participation in planning and decision-making should be promoted to whatever extent possible.

Periodic Reevaluation

The child's abilities and the family's needs change over time. As the child grows, more information must be provided to the child and family, goals must be reassessed, and programming needs should be adjusted. A periodic review should include information about the child's health status as well as the child's functioning at home, at school, and in other community settings. Other information, such as formal psychologic or educational testing, may be helpful. Reevaluation should be undertaken at routine intervals (every 6-12 mo during early childhood), at any time the child is not meeting expectations, or when the child is moving from one service delivery system to another. This is especially true during the transition to adulthood, beginning at age 16, as mandated by the IDEA Amendments of 2004, and lasting through age 21, when care should be transitioned to adult-based systems and providers.

Federal and Education Services

Education is the single most important discipline involved in the treatment of children with an ID. The educational program must be relevant to the child's needs and address the child's individual strengths and weaknesses. The child's developmental level, requirements for support, and goals for independence provide a basis for establishing an **individualized education program (IEP)** for school-age children, as mandated by federal legislation.

Beyond education services, families of children with ID are often in great need of federal or state-provided social services. All states offer developmental disabilities programs that provide home and community-based services to eligible children and adults, potentially including in-home supports, care coordination services, residential living arrangements, and additional therapeutic options. A variety of Medicaid waiver programs are also offered for children with disabilities within each state. Children with ID who live in low socioeconomic status households should qualify to receive supplemental security income (SSI). Of note, in 2012, an estimated >40% of children with ID did not receive SSI benefits for which they would have been eligible, indicating an untapped potential resource for many families.

Leisure and Recreational Activities

The child's social and recreational needs should be addressed. Although young children with ID are generally included in play activities with children who have typical development, adolescents with ID often do not have opportunities for appropriate social interactions. Community participation among adults with ID is much lower than that of the typical population, stressing the importance of promoting involvement in social activities such as dances, trips, dating, extracurricular sports, and other social-recreational events at an early age. Participation in sports should be encouraged (even if the child is not competitive) because it offers many benefits, including weight management, development of physical coordination, maintenance of cardiovascular fitness, and improvement of self-image.

Family Counseling

Many families adapt well to having a child with ID, but some have emotional or social difficulties. The risks of parental depression and child abuse and neglect are higher in this group of children than in the general population. The factors associated with good family coping and parenting skills include stability of the marriage, good parental self-esteem, limited number of siblings, higher socioeconomic status, lower degree of disability or associated impairments (especially behavioral), parents' appropriate expectations and acceptance of the diagnosis, supportive extended family members, and availability of community programs and respite care services. In families in whom the emotional burden of having a child with ID is great, family counseling, parent support groups, respite care, and home health services should be an integral part of the treatment plan.

Transition to Adulthood

Transition to adulthood in adolescents with intellectual disabilities can present a stressful and chaotic time for both the individual and the family, just as it does among young adults of typical intelligence. A successful transition strongly correlates to later improved quality of life but requires significant advanced planning. In moving from child to adult care, families tend to find that policies, systems, and services are more fragmented, less readily available, and more difficult to navigate. Several domains of transition must be addressed, such as education and employment, health and living, finances and independence, and social and community life. Specific issues to manage include transitioning to an adult healthcare provider, determining the need for decision-making assistance (e.g., guardianship, medical power of attorney), securing government benefits after aging out of youth-based programs (e.g., SSI, medical assistance), agreeing on the optimal housing situation, applying for state disability assistance programs, and addressing caretaker estate planning as it applies to the individual with ID (e.g., special needs trusts).

Following graduation from high school, options for continued education or entry into the workforce should be thoroughly considered, with the greater goal of ultimate community-based employment. Although employment is a critical element of life adaptation for persons with ID, only 15% are estimated to have jobs, with significant gaps in pay and compensation compared to workers without disability. Early planning and expansion of opportunities can help to reduce barriers to employment. Post–secondary education possibilities might involve community college or vocational training. Employment selection should be “customized” to the individual's interests and abilities. Options may include participation in competitive employment, supported employment, high school–to–work transition programs, job-coaching programs, and consumer-directed voucher programs.

Prognosis

In children with severe ID, the prognosis is often evident by early childhood.

Mild ID might not always be a lifelong disorder. Children might meet criteria for GDD at an early age, but later the disability can evolve into a more specific developmental disorder (communication disorder, autism, specific learning disability, or borderline normal intelligence). Others with a diagnosis of mild ID during their school years may develop sufficient adaptive behavior skills that they no longer fit the diagnosis as adolescents or young adults, or the effects of maturation and plasticity may result in children moving from one diagnostic category to another (from moderate to mild ID). Conversely, some children who have a diagnosis of a specific learning disability or communication disorder might not maintain their rate of cognitive growth and may fall into the range of ID over time.

The apparent higher prevalence of ID in low- and middle-income countries is of concern given the limitations in available resources. **Community-based rehabilitation (CBR)** is an effort promoted by WHO over the past 4 decades as a means of making use of existing community resources for persons with disabilities in low-income countries with the goal of increasing inclusion and participation within the community. CBR is now being implemented in >90 countries, although the efficacy of such programs has not been established.

The long-term outcome of persons with ID depends on the underlying cause, degree of cognitive and adaptive deficits, presence of associated medical and developmental impairments, capabilities of the families, and school and community supports, services, and training provided to the child and family (Table 53.7). As adults, many persons with mild ID are capable of gaining economic and social independence with functional literacy, but they may need periodic supervision (especially when under social or economic stress). Most live successfully in the community, either independently or in supervised settings.

Table 53.7

Severity of Intellectual Disability and Adult-Age Functioning

LEVEL	MENTAL AGE AS ADULT	ADULT ADAPTATION
Mild	9-11 yr	Reads at 4th-5th grade level; simple multiplication and division; writes simple letter, lists; completes job application; basic independent job skills (arrive on time, stay at task, interact with coworkers); uses public transportation, might qualify for driver's license; keeps house, cooks using recipes
Moderate	6-8 yr	Sight-word reading; copies information (e.g., address from card to job application);

		matches written number to number of items; recognizes time on clock; communicates; some independence in self-care; housekeeping with supervision or cue cards; meal preparation, can follow picture recipe cards; job skills learned with much repetition; uses public transportation with some supervision
Severe	3-5 yr	Needs continuous support and supervision; might communicate wants and needs, sometimes with augmentative communication techniques
Profound	<3 yr	Limitations of self-care, continence, communication, and mobility; might need complete custodial or nursing care

Data from World Health Organization: *International Statistical Classification of Diseases and Related Health Problems,* 10th revision, Geneva, 2011, WHO.

For persons with moderate ID, the goals of education are to enhance adaptive abilities and “survival” academic and vocational skills so they are better able to live and function in the adult world (Table 53.7). The concept of supported employment has been very beneficial to these individuals; the person is trained by a coach to do a specific job in the setting where the person is to work, bypassing the need for a “sheltered workshop” experience and resulting in successful work adaptation in the community. These persons generally live at home or in a supervised setting in the community.

As adults, people with severe to profound ID usually require extensive to pervasive supports (Table 53.7). These individuals may have associated impairments, such as cerebral palsy, behavioral disorders, epilepsy, or sensory impairments, that further limit their adaptive functioning. They can perform simple tasks in supervised settings. Most people with this level of ID can live in the community with appropriate supports.

The life expectancy of people with mild ID is similar to the general population, with a mean age at death in the early 70s. However, persons with severe and profound ID have a decreased life expectancy at all ages, presumably from associated serious neurologic or medical disorders, with a mean age at death in the mid-50s. Given that persons with ID are living longer and have high rates of comorbid health conditions in adulthood (e.g., obesity, hypertension, diabetes), ID is now one of the costliest ICD-10 diagnoses, with an average lifetime cost of 1-2 million dollars per person. Thus the priorities for pediatricians are to improve healthcare delivery systems during childhood, facilitate the transition of care to adult providers, and ensure high-quality, integrated community-based services for all persons with ID.

53.1

Intellectual Disability With Regression

Bruce K. Shapiro, Meghan E. O'Neill

The patients discussed in Chapter 53 with intellectual disability (ID) usually have a static and nonprogressive disease course. They may acquire new developmental milestones, although at a slower rate than unaffected children, or they may remain fixed at a particular developmental stage. Regression of milestones in these children may be caused by increasing spasticity or contractures, new-onset seizures or a movement disorder, or the progression of hydrocephalus.

Nonetheless, **regression** or loss of milestones should suggest a **progressive encephalopathy** caused by an *inborn error of metabolism*, including disorders of energy metabolism and storage disorders, or a *neurodegenerative disorder*, including disorders of the whole brain (diffuse encephalopathies), white matter (leukodystrophies), cerebral cortex, and basal ganglia as well as spinocerebellar disorders (Table 53.8) (see Chapters 616 and 617).

Table 53.8

Causes of Progressive Encephalopathy

Onset Before Age 2 Years

Acquired Immunodeficiency Syndrome Encephalopathy *

Disorders of Amino Acid Metabolism

- Guanidinoacetate methyltransferase deficiency*
- Homocystinuria (21q22)*
- Maple syrup urine disease (intermediate and thiamine response forms)*
- Phenylketonuria
- Guanidinoacetate methyltransferase deficiency*
- Hyperammonemic disorders

Disorders of Lysosomal Enzymes

- Ganglioside storage disorders
    - GM_1 gangliosidosis
    - GM_2 gangliosidosis (Tay-Sachs disease, Sandhoff disease)
- Gaucher disease type II (glucosylceramide lipidosis)*
- Globoid cell leukodystrophy (Krabbe disease)
- Glycoprotein degradation disorders
- I-cell disease
    - Mucopolysaccharidoses*
    - Type I (Hurler Syndrome)*
    - Type III (Sanfilippo disease)
- Niemann-Pick disease type A (sphingomyelin lipidosis)
- Sulfatase deficiency disorders
- Metachromatic leukodystrophy (sulfatide lipidoses)
- Multiple sulfatase deficiency

Carbohydrate-Deficient Glycoprotein Syndromes
Hypothyroidism *
Mitochondrial Disorders

- Alexander disease
- Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke
- Progressive infantile poliodystrophy (Alpers disease)
- Subacute necrotizing encephalomyelopathy (Leigh disease)
- Trichopoliodystrophy (Menkes disease)

Neurocutaneous Syndromes

- Chediak-Higashi syndrome
- Neurofibromatosis*
- Tuberous sclerosis*

Other Disorders of Gray Matter

Infantile ceroid lipofuscinosis (Santavuori-Haltia disease)
Infantile neuroaxonal dystrophy
Lesch-Nyhan disease*
Progressive neuronal degeneration with liver disease
Rett syndrome

Progressive Hydrocephalus *
Other Disorders of White Matter

Aspartoacylase deficiency (Canavan disease)
Galactosemia: Transferase deficiency*
Neonatal adrenoleukodystrophy
Pelizaeus-Merzbacher disease
Progressive cavitating leukoencephalopathy

Onset After Age 2 Years

Disorders of Lysosomal Enzymes

Gaucher disease type III (glucosylceramide lipidosis)
Globoid cell leukodystrophy (late-onset Krabbe disease)
Glycoprotein degradation disorders
Aspartylglycosaminuria
Mannosidosis type II
GM_2 gangliosidosis (juvenile Tay-Sachs disease)
Metachromatic leukodystrophy (late-onset sulfatide lipidoses)
Mucopolysaccharidoses types II and VII
Niemann-Pick type C (sphingomyelin lipidosis)

Infectious Disease

Acquired immunodeficiency syndrome encephalopathy*
Congenital syphilis*
Subacute sclerosing panencephalitis

Other Disorders of Gray Matter

- Ceroid lipofuscinosis
    - Juvenile
    - Late infantile (Bielschowsky-Jansky disease)
- Huntington disease
- Mitochondrial disorders
    - Late-onset poliodystrophy
    - Myoclonic epilepsy and ragged-red fibers
- Progressive neuronal degeneration with liver disease
- Xeroderma pigmentosum

Other Disorders of White Matter

- Adrenoleukodystrophy
- Alexander disease
- Cerebrotendinous xanthomatosis
- Progressive cavitating leukoencephalopathy

Other Diseases

- Wilson disease
- Friedreich ataxia
- Pantothenate kinase neurodegeneration
- Neurodegeneration with brain iron accumulation

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[*] Denotes the most common conditions and those with disease-modifying treatment.

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CHAPTER 54

Autism Spectrum Disorder

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Definition

Autism spectrum disorder (ASD) is a neurobiologic disorder with onset in early childhood. The key features are impairment in social communication and social interaction accompanied by restricted and repetitive behaviors. The presentation of ASD can vary significantly from one individual to another, as well as over the course of development for a particular child. There is currently no diagnostic biomarker for ASD. Accurate diagnosis therefore requires careful review of the history and direct observation of the child's behavior.

Diagnostic Criteria and Symptoms

The diagnostic criteria in the *Diagnostic and Statistical Manual, Fifth Edition* (DSM-5) focus on symptoms in two primary domains (Table 54.1). To meet criteria for ASD, the symptoms need to have been present since the early developmental period, significantly impact functioning, and not be better explained by the diagnoses of intellectual disability (ID) or global developmental delay (GDD; Chapter 53). Table 54.2 provides associated features not included in DSM-5 criteria.

Table 54.1

DSM-5 Diagnostic Criteria for Autism Spectrum Disorder

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:

1. Deficits in social-emotional reciprocity.
2. Deficits in nonverbal communicative behaviors used for social interaction.
3. Deficits in developing, maintaining, and understanding relationships.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least 2 of the following, currently or by history:

1. Stereotyped or repetitive motor movements, use of objects, or speech.
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior.
3. Highly restricted, fixated interests that are abnormal in intensity or focus.
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.

C. Symptoms must be present in the early developmental period (may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, (Copyright 2013). American Psychiatric Association, pp 50–51.

Table 54.2

Associated Features of Autism Not in DSM-5 Criteria

Atypical language development and abilities

- Age <6 yr: frequently disordered and delayed in comprehension; two-thirds have difficulty with expressive phonology and grammar
- Age ≥6 yr: disordered pragmatics, semantics, and morphology,

with relatively intact articulation and syntax (i.e., early difficulties are resolved)

Motor abnormalities: motor delay; hypotonia; catatonia; deficits in coordination, movement preparation and planning, praxis, gait, and balance

For version with full references, see *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, Washington DC, 2013, American Psychiatric Association. Adapted from Lai MC, Lombardo MV, Baron-Cohen S: Autism, *Lancet* 383:896–910, 2014.

Previously, ASD was grouped under the heading of *pervasive developmental disorders* (PDDs) and included a variety of subdiagnoses, including autistic disorder, PDD not otherwise specified (PDD-NOS), and **Asperger disorder** . Research did not support these as distinct conditions; in the current diagnostic framework, any individual previously diagnosed with 1 of these conditions should be diagnosed with ASD.

Symptoms can present early in infancy, with reduced response to name and unusual use of objects being strong predictors for risk of ASD. However, symptoms before age 12 mo are not as reliably predictive of later diagnosis. Individuals with milder severity may not present until preschool or school age, when the social demands for peer interaction and group participation are higher.

Social Communication and Social Interaction

Individuals with ASD have difficulty understanding and engaging in social relationships. The problems are pervasive and impact 3 major areas: reciprocal social interactions (social-emotional reciprocity), nonverbal communication, and understanding of social relationships. The presentation can vary with severity and developmental functioning. Diagnosis of ASD requires the presence of symptoms from all 3 categories (Table 54.3).

Table 54.3

Signs and Symptoms of Possible Autism in Preschool Children (or Equivalent Mental Age)

Social Interaction and Reciprocal Communication Behaviors

Spoken Language

Language delay (in babbling or using words; e.g., using <10 words by age 2 yr).

Regression in, or loss of, use of speech.

Spoken language (if present) may include unusual features, such as vocalizations that are not speech-like; odd or flat intonation; frequent repetition of set words and phrases (echolalia); reference to self by name or “you” or “she” or “he” beyond age 3 yr.

Reduced and/or infrequent use of language for communication; e.g., use of single words, although able to speak in sentences.

Responding to Others

Absent or delayed response to name being called, despite normal hearing.

Reduced or absent responsive social smiling.

Reduced or absent responsiveness to other people's facial expressions or feelings.

Unusually negative response to the requests of others (“demand avoidance” behavior).

Rejection of cuddles initiated by parent or caregiver, although the child may initiate cuddles.

Interacting With Others

Reduced or absent awareness of personal space, or unusually intolerant of people entering their personal space.

Reduced or absent social interest in others, including children of own age—may reject others; if interested in others, child may approach others inappropriately, seeming to be aggressive or disruptive.

Reduced or absent imitation of others' actions.

Reduced or absent initiation of social play with others; plays alone.

Reduced or absent enjoyment of situations that most children like; e.g., birthday parties.

Reduced or absent sharing of enjoyment.

Eye Contact, Pointing, and Other Gestures

- Reduced or absent use of gestures and facial expressions to communicate (although may place an adult's hand on objects).
- Reduced and poorly integrated gestures, facial expressions, body orientation, eye contact (looking at people's eyes when speaking), and speech used in social communication.
- Reduced or absent social use of eye contact (assuming adequate vision).
- Reduced or absent “joint attention” (when 1 person alerts another to something by means of gazing, finger pointing, or other verbal or nonverbal indication for the purpose of sharing interest). This would be evident in the child from lack of:
  - Gaze switching
  - Following a point (looking where the other person points to—may look at hand)
  - Using pointing at or showing objects to share interest

Ideas and Imagination

- Reduced or absent imagination and variety of pretend play.

Unusual or Restricted Interests and/or Rigid and Repetitive Behaviors

- Repetitive “stereotypic” movements such as hand flapping, body rocking while standing, spinning, and finger flicking.
- Repetitive or stereotyped play; e.g., opening and closing doors.
- Over focused or unusual interests.
- Excessive insistence on following own agenda.
- Extremes of emotional reactivity to change or new situations; insistence on things being “the same.”
- Overreaction or underreaction to sensory stimuli, such as textures, sounds, or smells.
- Excessive reaction to the taste, smell, texture, or appearance of food, or having extreme food fads.

Adapted from Baird G, Douglas HR, Murphy MS: Recognizing and diagnosing autism in children and young people: summary of NICE guidance. *BMJ* 343:d6360, 2011, Box 1, p 901.

Social-Emotional Reciprocity

Reduced social interactions in ASD may range from active avoidance or reduced social response to having an interest in, but lacking ability to initiate or sustain, an interaction with peers or adults. A young child with ASD may not respond when his name is called, may exhibit limited showing and sharing behaviors, and may prefer solitary play. In addition, the child may avoid attempts by others to play and may not participate in activities that require taking turns, such as peek-a-boo and ball play. An older child with ASD may have an interest in peers but may not know how to initiate or join in play. The child may have trouble with the rules of conversation and may either talk at length about an area of interest or abruptly exit the interaction. Younger children often have limited capacity for imaginative or pretend play skills. Older children may engage in play but lack flexibility and may be highly directive to peers. Some children with ASD interact well with adults but struggle to interact with same-age peers.

Nonverbal Communicative Behavior

Difficulties with nonverbal communication may manifest as reduced use of eye contact and gestures such as pointing. Children may also show reduced awareness or response to the eye gaze or pointing of others. They may use eye contact only when communicating a highly preferred request or may have difficulty coordinating the use of nonverbal with verbal communication. Children with ASD may have limited range of facial expression or expressed emotion.

Developing, Maintaining, and Understanding Relationships

Children with ASD have limited insight regarding social relationships. They have difficulty understanding the difference between a true friend and a casual acquaintance. They have trouble picking up on the nuances of social interactions and understanding social expectations for polite behavior. They may have reduced understanding of personal boundaries and may stand too close to others. In addition, they can have trouble understanding and inferring others' emotions and are less likely to share emotion or enjoyment with others. Adolescents and young adults have difficulty engaging in group interactions and navigating romantic relationships.

Restrictive and Repetitive Behavior

Diagnosis of ASD requires the presence of 2 of the 4 symptoms of restrictive and repetitive patterns of behavior discussed next.

Stereotyped Motor Movements or Speech

Stereotyped (or stereotypic) movements and repetitive behaviors may include hand flapping, finger movements, body rocking and lunging, jumping, running and spinning, and repetitive speech such as echoing words immediately after they are said. Repetitive patterns of play may be present, such as lining up objects, repetitively turning light switches on and off or opening and closing doors, spinning objects, or arranging toys in a specific manner. These repetitive patterns may not be seen in very young toddlers but may develop as they get older. Stereotyped movements can change over time and in older children are seen more often in individuals with lower cognitive functioning.

Insistence on Sameness

Children with ASD have difficulty tolerating transitions or change. They may insist on certain routines or schedules and can become very distressed with unexpected events or new situations. They may repeat scripts from shows or movies or watch the same portion of a video repeatedly. Intolerance for change causes significant impairment and impact on child and family function.

Restricted Interests

This symptom may manifest as intense interests that seem out of the norm in comparison to same-age peers. Younger children may play with a limited range of toys or may insist on retaining a small object in each hand. Older children may have a strong preference for a particular story or movie. The area of interest may be shared by peers (e.g., Disney movies, Legos, Thomas the Train) but *unusual* in its intensity. Other affected children may have interests that are both intense and odd, such as an interest in brands of vehicles, license plate numbers, or fans and heating systems. These interests interfere with social interactions; a child may only want to talk about her area of interest or may insist that peers act out a particular story in a rigid and inflexible manner.

Hypo- or Hyperreactivity to Sensory Input

Children with ASD may be overly sensitive to sensory input, such as noise, smells, or texture. Children may scream when they hear a siren or vacuum and may gag and choke with certain foods or odors. They may refuse to wear certain clothing or may become very distressed with bathing or with cutting nails and hair. Conversely, some affected children seem to crave sensory input. They may engage in repetitive jumping or hugging and may smell or lick objects or people. Young children may inappropriately touch the face or hair of others.

Diagnosing ASD with DSM-5 criteria can be challenging in very young children because of reduced expression of repetitive behaviors, particularly stereotyped behavior and intense interests. Studies monitoring development in high-risk young children who have an older sibling with ASD indicate these additional symptoms may emerge over time. This creates a dilemma for specialty clinicians evaluating very young children for ASD, because they may not be able to endorse sufficient symptoms to make an early diagnosis and access specialized intervention services.

Severity Levels Defined in DSM-5

Severity level in ASD is based on the level of support the individual requires in each of the major domains impacted—social communication and restricted and repetitive behavior. Levels range from –“needing support” (level 1), to –“needing substantial support” (level 2), to –“needing very substantial support” (level 3) (Table 54.4).

Table 54.4

DSM-5 Severity Levels for Autism Spectrum Disorder

SEVERITY LEVEL	SOCIAL COMMUNICATION	RESTRICTED, REPETITIVE BEHAVIORS
Level 3 “Requiring very substantial support”	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. *For example,* a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great

	only and responds to only very direct social approaches	distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. *For example,* a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication	Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. *For example,* a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

From the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* (Copyright 2013). American Psychiatric Association, p 52.

Specifiers Defined in DSM-5

Formal diagnosis of ASD also includes documenting associated conditions including whether the individual has cognitive and/or language impairment, any related medical, genetic or environmental factors and any other neurodevelopmental or behavioral health conditions, including catatonia (Table 54.5). This process helps to better characterize the presentation in an individual child and ensures that the diagnosis has been made by considering the symptoms in the context of the child's current cognitive and language abilities.

Table 54.5

Common Co-occurring Conditions in Autism Spectrum Disorder (ASD)

COMORBIDITY	**INDIVIDUALS WITH AUTISM AFFECTED**	**COMMENTS**
DEVELOPMENTAL DISORDERS		
Intellectual disability	~45%	Prevalence estimate is affected by the diagnostic boundary and definition of intelligence (e.g., whether verbal ability is used as a criterion).

		In individuals, discrepant performance between subtests is common.
Language disorders	Variable	In DSM-IV, language delay was a defining feature of autism (autistic disorder), but is no longer included in DSM-5. An autism-specific language profile (separate from language disorders) exists, but with substantial interindividual variability.
Attention-deficit/hyperactivity disorder	28–44%	In DSM-IV, not diagnosed when occurring in individuals with autism, but no longer so in DSM-5.
Tic disorders	14–38%	~6·5% have Tourette syndrome.
Motor abnormality	≤79%	See Table 54.2 .
GENERAL MEDICAL DISORDERS		
Epilepsy	8–35%	Increased frequency in individuals with intellectual disability or genetic syndromes. Two peaks of onset: early childhood and adolescence. Increases risk of poor outcome.
Gastrointestinal problems	9–70%	Common symptoms include chronic constipation, abdominal pain, chronic diarrhea, and gastroesophageal reflux. Associated disorders include gastritis, esophagitis, gastroesophageal reflux disease, inflammatory bowel disease, celiac disease, Crohn disease, and colitis.
Immune dysregulation	≤38%	Associated with allergic and autoimmune disorders.
Genetic disorders	10–20%	Collectively called *syndromic autism.* Examples include fragile X syndrome (21–50% of individuals affected have autism), Rett syndrome (most have autistic features but with profiles different from idiopathic autism), tuberous sclerosis complex (24–60%), Down syndrome (5–39%), phenylketonuria (5–20%), CHARGE syndrome* (15–50%), Angelman syndrome (50–81%), Timothy syndrome (60–70%), and Joubert syndrome (~40%).
Sleep disorders	50–80%	Insomnia is the most common.
PSYCHIATRIC DISORDERS		
Anxiety	~40%	Common across all age-groups. Most common are social anxiety disorder (13–29% of individuals with autism) and generalized anxiety disorder (13–22%). High-functioning individuals are more susceptible (or symptoms are more detectable).
Depression	12–70%	Common in adults, less common in children. High-functioning adults who are less socially impaired are more susceptible (or symptoms are more detectable).
Obsessive-compulsive disorder (OCD)	7–24%	Shares the repetitive behavior domain with autism that could cut across nosologic categories. Important to distinguish between repetitive behaviors that do not involve intrusive, anxiety-causing thoughts or obsessions (part of autism) and those that do (and are part of OCD).
Psychotic disorders	12–17%	Mainly in adults. Most commonly recurrent hallucinosis. High frequency of autism-like features (even a diagnosis of ASD) preceding adult-onset (52%) and childhood-onset schizophrenia (30–50%).
Substance use disorders	≤16%	Potentially because individual is using substances as self-medication to relieve anxiety.
Oppositional defiant disorder	16–28%	Oppositional behaviors could be a manifestation of anxiety, resistance to change, stubborn belief in the correctness of own point of view, difficulty seeing another's point of view, poor awareness of the effect of own behavior on others, or no interest in social compliance.

Eating disorders	4–5%	Could be a misdiagnosis of autism, particularly in females, because both involve rigid behavior, inflexible cognition, self-focus, and focus on details.
PERSONALITY DISORDERS †		
Paranoid personality disorder	0–19%	Could be secondary to difficulty understanding others' intentions and negative interpersonal experiences.
Schizoid personality disorder	21–26%	Partly overlapping diagnostic criteria.
Schizotypal personality disorder	2–13%	Some overlapping criteria, especially those shared with schizoid personality disorder.
Borderline personality disorder	0–9%	Could have similarity in behaviors (e.g., difficulties in interpersonal relationships, misattributing hostile intentions, problems with affect regulation), which requires careful differential diagnosis. Could be a misdiagnosis of autism, particularly in females.
Obsessive-compulsive personality disorder	19–32%	Partly overlapping diagnostic criteria.
Avoidant personality disorder	13–25%	Could be secondary to repeated failure in social experiences.
BEHAVIORAL DISORDERS		
Aggressive behaviors	≤68%	Often directed toward caregivers rather than noncaregivers. Could be a result of empathy difficulties, anxiety, sensory overload, disruption of routines, and difficulties with communication.
Self-injurious behaviors	≤50%	Associated with impulsivity and hyperactivity, negative affect, and lower levels of ability and speech. Could signal frustration in individuals with reduced communication, as well as anxiety, sensory overload, or disruption of routines. Could also become a repetitive habit. Could cause tissue damage and need for restraint.
Pica	~36%	More likely in individuals with intellectual disability. Could be a result of a lack of social conformity to cultural categories of what is deemed edible, or sensory exploration, or both.
Suicidal ideation or attempt	11–14%	Risks increase with concurrent depression and behavioral problems, and after being teased or bullied.

[*] Coloboma of the eye; heart defects; atresia of the choanae; retardation of growth and development, or both; genital and urinary abnormalities, or both; and ear abnormalities and deafness.

[†] Particularly in high-functioning adults.

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* ; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth edition.*

Adapted from Lai MC, Lombardo MV, Baron-Cohen S: Autism, *Lancet* 383:896–910, 2014.

Epidemiology

The prevalence of ASD is estimated at 1 in 59 persons by the U.S. Centers for Disease Control and Prevention (CDC). The prevalence increased significantly over the past 25 years, primarily because of improved diagnosis and case finding as well as inclusion of less severe presentations within the **autism** spectrum. There is a 4:1 male predominance. The prevalence is increased in siblings (up to 10% recurrence rate) and particularly in identical twins. There are no racial or ethnic differences in prevalence. Individuals from racial minorities and lower socioeconomic status are at risk for later diagnosis.

Etiology

The etiology of ASD is thought to result from disrupted neural connectivity and is primarily impacted by genetic variations affecting early brain development. Animal models and studies of individuals with ASD indicate changes in brain volume and neural cell density in the limbic system, cerebellum, and frontotemporal regions. One study documented changes in early brain development, characterized as "hyperexpansion of cortical surface area," at age 6-12 mo on brain MRI, which correlated with later development of impaired social skills. Functional studies show abnormalities of processing information, particularly related to foundational social skills such as facial recognition. The disruptions in early brain development likely are responsive the treatment. Early developmental therapies in young children with ASD have demonstrated the capacity for normalization of electrophysiologic response to visual stimuli, including faces.

Numerous **genes** involved in brain development and synaptic function have been associated with ASD. Mutations that include large genetic deletions or duplications and small sequencing changes have been implicated; these can be inherited or occur de novo. Heterozygous mutations in genes, such as present in deletion or duplication of 15q11.2 or 16p11.2, may have variable expression within a family. Rare recessive mutations have been implicated in some populations with high levels of consanguinity. Patients with a number of genetic syndromes (e.g., fragile X, Down, Smith-Lemli-Opitz, Rett, Angelman, Timothy, Joubert) as well as disorders of metabolism and mitochondrial function have higher rates of ASD than the general population (Table 54.5).

There is also evidence for **environmental** contributions to ASD. Older maternal or paternal age may increase the risk of ASD. In addition, factors influencing the intrauterine environment, such as maternal obesity or overweight, short interval from prior pregnancy, premature birth, and certain prenatal infections (e.g., rubella, cytomegalovirus) are associated with ASD. An epigenetic model is considered one explanation for the etiology; individuals with genetic vulnerability may be more sensitive to environmental factors influencing early brain development.

Despite frequent concerns from families that **vaccines** or the preservatives in vaccines lead to ASD, *there is no evidence to support this claim.* Multiple research studies and meta-analyses have failed to show an association of vaccines with ASD.

Differential Diagnosis

The differential diagnosis of ASD is complex because many conditions in the differential can also occur with ASD. The most important conditions to consider in young children are language disorder (see Chapter 52), intellectual disability or global developmental delay (Chapter 53), and hearing loss (Chapter 655). Children with **language disorder** may have impairments in social communication and play; their social and play skills, however, are typically on par with their language level. In addition, they do not have associated restricted and repetitive behavior or atypical use of language, such as scripting. The diagnosis of **social communication disorder** is also distinguished from ASD by the lack of restrictive and repetitive behaviors. Children with **intellectual disability (ID)** or **global developmental delay (GDD)** may have delays in social and communication skills as well as stereotyped behavior. However, social and communication skills are typically commensurate with their cognitive and adaptive functioning. Children with **hearing loss** may present with some “red flags” for ASD, such as poor response to name. However, they typically develop nonverbal communication and play skills as expected and do not have stereotyped or restricted behavior patterns.

In older children, disorders of attention, learning, and mood regulation must be considered in the differential diagnosis of ASD. Children with **attention-deficit/hyperactivity disorder (ADHD)** may present with reduced eye contact and response to name caused by poor attention rather than lack of social awareness. Children with ADHD, however, do not have associated impairments in shared enjoyment and social reciprocity or repetitive behaviors. Children with **social anxiety** or other anxiety disorders may present with some symptoms suggestive of ASD. Shy children may have reduced eye contact and social initiation. Anxious children can be resistant to change and prefer familiar routines. Children with anxiety, however, typically will have preserved social interest and insight and will not exhibit high levels of stereotyped behaviors.

Reactive attachment disorder can be difficult to distinguish from ASD, particularly in younger children with history of trauma. However, social behaviors in these children generally improve with positive caretaking.

The differentiation of ASD from **obsessive-compulsive disorder (OCD)** , tics, and stereotyped behaviors can sometimes be challenging. In general, stereotyped behaviors may be calming or preferred, whereas tics and compulsive routines are distressing to the individual. Children with OCD have intense interests as well as repetitive behaviors and rituals but do not have impairment in social communication or interaction. Children with **stereotypic movement disorder** will not have impaired social skills or other types of restricted and repetitive behaviors. Children with **Landau Kleffner syndrome (LKS)** present with loss of skills in language comprehension (auditory verbal agnosia) and verbal expression (aphasia) associated with onset of epileptic seizures during sleep (see Chapter 52). In contrast to ASD, children with LKS present with typical early development followed by loss of language function at age 3-6 yr.

Comorbid Conditions

Up to 50% of individuals with ASD have intellectual disability, ranging in severity from mild to severe (Table 54.5). Intellectual disability is associated with higher rates of both identified genetic conditions and epilepsy. Children with ASD often have associated language impairments, including delays in expressive, receptive, and pragmatic (social) language skills. Language function can range widely from nonverbal status to age appropriate. Gastrointestinal (GI) problems such as constipation, esophagitis, and gastroesophageal reflux disease (GERD) are reported in up to 70% of children with ASD. Epilepsy occurs in up to 35% of children with ASD and presents in 2 peaks, in early childhood and in adolescence. Epilepsy or electrical seizures without motor manifestations may be a cause of **regression** in young children with ASD.

Children with ASD are at higher risk for disorders of attention, including reduced attention for nonpreferred activities and excessive attention for preferred activities. A subset of children will also meet full criteria for a diagnosis of ADHD. There are higher rates of anxiety (~40%) and mood disorders in ASD, particularly during adolescence. Children with ASD are also at increased risk for being bullied and may present with secondary irritability, anxiety, or depression.

Sleep problems, including delayed sleep onset, frequent night waking, and abnormal sleep architecture, are reported in 50–80% of children with ASD.

There is some evidence for baseline abnormalities in melatonin secretion. The use of screen-based activities such as television, computers, or tablets before bedtime can inhibit melatonin secretion. Children with ASD also have higher rates of feeding and toileting problems resulting from resistance to change, sensory sensitivity, and repetitive behavior patterns. Many children with ASD have restrictive feeding patterns and food selectivity. They also have higher rates of overweight, possibly because of diets higher in carbohydrates, reduced physical activity, use of food rewards to regulate behavior, and side effects from medications used for managing mood and behavior.

Disruptive behaviors such as self-injury and aggression are common in ASD patients, but most common in individuals with lower cognitive function and limited language. Sleep deprivation, nutritional deficits, pain, epilepsy, and medication side effects may contribute to disruptive behaviors.

Screening

The American Academy of Pediatrics recommends screening for ASD for *all* children at age 18 mo and 24 mo (see Chapter 28). Screening should also occur when there is increased risk for ASD, such as a child with an older sibling who has ASD, or concern for possible ASD. Screening can be done by parent checklist or direct assessment. The most frequently used screening tool is the *Modified Checklist for Autism, Revised/Follow-Up Interview* (MCHAT-R/FU), a 20-item parent report measure, with additional parent interview completed for intermediate scores. The MCHAT-R/FU can be used from age 16-30 mo.

Assessment

Diagnostic assessment should include medical evaluation and assessment of the child's cognitive, language, and adaptive function. Assessment may occur in a single multidisciplinary visit or through a series of visits with different developmental specialists. Multidisciplinary evaluation with clinicians who have expertise with ASD is optimal for diagnostic accuracy and treatment planning. Developmental-behavioral pediatricians, neurodevelopmental disability specialists, neurologists, psychiatrists, and psychologists are qualified to make a formal diagnosis of ASD. Other specialists, including speech-language pathologists and occupational therapists, should also be included depending on the child's age and the presenting concerns.

Assessment of ASD includes direct observation of the child to evaluate social skills and behavior. Informal observation can be supplemented with structured diagnostic tools such as the *Autism Diagnostic Observation Schedule, Second Edition* (ADOS-2) and *Autism Diagnostic Observation Schedule, Toddler module* (ADOS-T). These structured play-based assessments provide social prompts and opportunities to evaluate the frequency and quality of a child's social responsiveness to, initiation, and maintenance of social interactions; the capacity for joint attention and shared enjoyment; the child's behavioral flexibility; and presence of repetitive patterns of behavior. The ADOS-2 and ADOS-T are not required for accurate diagnosis and do not stand alone, but rather can be used to augment a careful history and observation. The *Childhood Autism Rating Scale, Second Edition* (CARS-2) is a 15-item direct clinical observation instrument that can assist clinicians in the diagnosis of ASD. The *Autism Diagnostic Interview-Revised* (ADI-R) is a lengthy clinical interview tool that is used primarily in research settings since it takes several hours to administer. Other tools include standardized rating scales that parents and teachers can complete to report on the child's social skills and behaviors.

Medical evaluation should include a thorough history and detailed physical examination of the child, including direct behavioral observations of communication and play. In addition, the examination should include measurement of head circumference, careful evaluation for dysmorphic features, and screening for tuberous sclerosis with Wood lamp exam. Children with ASD should have genetic testing (described later), an audiology examination to rule out hearing loss, and in children with pica, a lead test (Table 54.6).

Table 54.6

Medical and Genetic Evaluation of Children With Autism Spectrum Disorder

Physical Examination

Dysmorphic physical features
Muscle tone and reflexes
Head circumference
Wood lamp examination for tuberous sclerosis

Diagnostic Testing

Chromosomal microarray (CMA) in all individuals
Fragile X DNA test in males
Audiology evaluation
Lead test in children with pica

Additional Targeted Genetic Testing

Fragile X DNA test in females with symptoms suggestive of fragile X, family history of X-linked intellectual disability, tremor, ataxia, or premature ovarian failure
MeCP2 sequencing in females
PTEN mutation testing if head circumference >2.5 SD above the mean
MeCP2 deletion/duplication testing in males with significant developmental regression, drooling, respiratory infections, and hypotonia
Karyotype if unable to obtain CMA or if balanced translocation suspected

Additional Targeted Diagnostic Testing

EEG in children with seizures, staring spells, or developmental regression
Brain MRI in children with microcephaly, focal neurologic findings, or developmental regression
Metabolic testing in children with developmental regression, hypotonia, seizures, food intolerance, hearing loss, ataxia, or course facial features

Data from Schaefer GB, Mendelsohn NJ: Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions, *Genet Med* 15(5):399–407, 2013.

There are currently several specialty-specific clinical guidelines for genetic evaluation of children diagnosed with ASD. Genetic testing is shown to impact clinical decision-making, but no studies have evaluated the impact of genetic testing on the outcome for the child. The American College of Medical Genetics recommends a tiered approach to genetic testing.

First Tier

All children with ASD should have a **chromosomal microarray (CMA)** . CMA will be positive in 10–15% of individuals with ASD. The rate is increased to almost 30% in individuals who have complex presentations, such as associated microcephaly, dysmorphic features, congenital anomalies, or seizures. CMA technology will identify copy number variants but not DNA sequencing errors, balanced translocations, or abnormalities in trinucleotide repeat length. *Fragile X DNA testing is therefore recommended for all boys with ASD*. Fragile X testing should also be considered in girls with physical features suggestive of fragile X syndrome or with a family history of fragile X, X-linked pattern of intellectual disability, tremor/ataxia, or premature ovarian failure.

Second Tier

Girls with ASD should have testing for mutation in the *MeCP2* gene if CMA is normal. Boys who have hypotonia, drooling, and frequent respiratory infections should have *MeCP2* deletion/duplication testing. All individuals with ASD and a head circumference greater than 2.5 standard deviations (SD) above the mean should have testing for mutation in the *PTEN* gene because there is a risk for hamartoma tumor disorders (Cowden, Proteus-like, Bannayan-Riley-Ruvakaba syndromes) in these individuals. Cytogenetic testing (karyotype) has a lower yield than CMA. Karyotype is recommended if microarray is not available and in children with suspected balanced translocation, such as history of multiple prior miscarriages.

Further medical diagnostic testing is indicated by the child's history and presentation. Brain imaging is indicated in cases of microcephaly, significant developmental regression, or focal findings on neurologic examination. Because of the high rate (up to 25%) of macrocephaly in ASD, imaging is not indicated for macrocephaly alone. MRI is not recommended for minor language regression (loss of a few words) during the 2nd year of life that is often described in toddlers with ASD. Children with concern for seizures, spells, or developmental regression should have an electroencephalogram (EEG). Metabolic screening is indicated for children with signs of a metabolic or mitochondrial disorder, such as developmental regression, weakness, fatigue, lethargy, cyclic vomiting, or seizures (see Chapters 53 and 102).

Treatment and Management

Educational

The primary treatment for ASD is done outside the medical setting and includes developmental and educational programming. Numerous resources have been developed that can help families in the complex process of treatment planning (Table 54.7). Intensive behavioral therapies have the strongest evidence to date. Earlier age at initiation of treatment and higher intensity of treatment are associated with better outcomes. Programming must be individualized, and no approach is successful for all children. In addition, research treatments are often conducted with a high level of intensity and fidelity that are difficult to scale up or reproduce in community settings. Higher cognitive, play, and joint attention skills and lower symptom severity at baseline are predictors for better outcomes in core symptoms, intellectual function, and language function.

Table 54.7

Autism Resources for Families

- Autism Speaks First 100 Days kit
    - https://www.autismspeaks.org/family-services/tool-kits/100-day-kit
- Autism Speaks Toolkits–dental, transition, guardianship
    - https://www.autismspeaks.org/family-services/tool-kits
- AACAP Autism Spectrum Disorder Parent's Medication Guide
    - https://www.aacap.org/App_Themes/AACAP/Docs/resource_cent
- Sexuality information for individuals with developmental disability
    - http://vkc.mc.vanderbilt.edu/healthybodies/

Behavioral approaches based on the principles of **applied behavioral analysis (ABA)** involve direct incremental teaching of skills within a traditional behavioral framework using reinforcement of desired behavior, careful data collection, and analysis and adjustment of the treatment program based on review of data. Comprehensive models integrating behavioral and developmental approaches that build on key foundational skills, such as joint attention, shared enjoyment, and reciprocal communication, show strong evidence of efficacy for young children, particularly toddlers, with ASD.

Examples include the *Early Start Denver Model* (ESDM), *Joint Attention Symbolic Play Engagement and Regulation* (JASPER), and *Social Communication/Emotional Regulation/Transactional Support* (SCERTS). Parent training models also show promise for younger children.

Educational approaches such as the *Treatment and Education of Autistic and Communication Handicapped Children* (TEACCH) incorporate structured teaching, visual supports, and adjustment of the environment to the individual needs of students with ASD, such as difficulty with communication, understanding time, and need for routine. These approaches have demonstrated efficacy for improved cognitive and adaptive skills. For older children with more severe symptoms, approaches that use behavioral principles in addition to adjusting the environment may be most effective.

Speech and language therapy can help build vocabulary, comprehension, and pragmatic skills. Children with ASD benefit from visual supports for comprehension, understanding expectations, and communicating their needs. **Augmentative communication** approaches using photographs or picture icons can improve comprehension and ability to communicate. There are a range of options with varying levels of complexity, flexibility, and technology. Using augmentative communication does not inhibit acquisition of verbal language. On the contrary, supporting a child's language development with augmentative supports can facilitate the development of spoken language, even in older children.

Additional strategies to build social skills are used for school age children and adolescents and may be administered in the school or community setting by a variety of specialists, including speech therapists, psychologists, and counselors. **Social skills programs** that include training peer mentors have higher rates of efficacy. Occupational and physical therapy may be indicated for individuals with motor delay and difficulty acquiring adaptive skills such as dressing and toileting.

For some high school students with ASD, training in life skills and vocational skills is critical for maximizing independence in adulthood. Training may focus on basic self-care (e.g., dressing, hygiene), functional academics (e.g., money management, banking skills), learning to fill out a job application, and understanding how to behave with strangers and in work settings. Social skills and job coaching may be needed even for adolescents with strong cognitive and academic function, because they may struggle with social perception and may be vulnerable to exploitation by others.

Co-occurring Conditions

Additional medical or behavioral health treatment is often required for management of co-occurring conditions in ASD. Seizures occur in up to 35% of children with ASD and should be managed with appropriate antiepileptic therapy (see Chapter 611). GI problems (e.g., constipation, esophagitis, GERD) may present with nonspecific irritability, sleep disturbance, self-injury, aggression, and signs of pain or discomfort, such as crying, and can be managed with the same approaches used in typically developing children.

Management of co-occurring attention and mood disorders is similar to that for typically developing children. Strategies to increase structure and organization in the environment and use of visual supports (e.g., schedules) can improve attention and reduce anxiety. Some children with ASD benefit from modified cognitive-behavioral therapy to address anxiety and OCD.

Strategies to promote **sleep hygiene** and use of behavioral approaches, such as structured bedtime routines, can address delayed sleep onset. Other medical problems, such as epilepsy or GERD, can also contribute to poor sleep and should be treated directly. In cases refractory to behavioral approaches, medications may be used. (For further discussion of management of sleep problems, see Chapter 31 .)

Structured behavioral approaches for delayed toilet training in concert with treatment to prevent constipation are often needed for children with ASD. For children with highly restrictive diets, nutrition counseling and behaviorally based feeding therapy may be needed to address poor caloric intake or lack of nutritional quality. Because of limited diets, children with ASD may be at risk for low levels of calcium, vitamin D, and iron. Children who are overweight may have poor nutrition as a result of restrictive diets.

Irritability is a nonspecific symptom and can be a reflection of pain, anxiety, distress, or lack of sleep. Children with ASD are prone to irritability because of their difficulty tolerating change and their limited communication skills. Management of irritability includes evaluating carefully for medical problems that may be causing pain, as well as for any factors in the child's home or school environment that may be causing distress. Possible causes of distress range from common experiences such as changes in the routine to undisclosed abuse or bullying. Treatment should be targeted first at any underlying cause. Medications are often used to treat irritability in ASD but should only be used after appropriate behavioral and communication supports have been implemented.

Pharmacology

There are currently no medications that treat the core symptoms of ASD. Medications can be used to target specific co-occurring conditions or symptoms (Table 54.8 ; see also Table 54.5). Families should be cautioned, however, that the effect size may be lower and the rate of medication side effects higher in children with ASD.

Table 54.8

Common Pharmacologic Treatments in Autism Spectrum Disorder (ASD)

TARGET SYMPTOM	MEDICATION CLASS*	EFFECTS	SIDE EFFECTS	MONITORING
Hyperactivity and/or Inattention	Stimulants	Decreased hyperactivity, impulsivity, improved attention	Activation, irritability, emotional lability, lethargy/social withdrawal, stomach ache, reduced appetite, insomnia, increased stereotypy	Height, weight, BP, HR
	α_2 -Agonists	Decreased hyperactivity, impulsivity, improved attention	Drowsiness, irritability, enuresis, decreased appetite, dry mouth, hypotension	Height, weight, BP, HR
	Selective norepinephrine reuptake inhibitor	Decreased hyperactivity, impulsivity, improved attention	Irritability, decreased appetite, fatigue, stomach ache, nausea, vomiting, racing heart rate	Height, weight, BP, HR
Anxiety	Selective serotonin reuptake inhibitors	Decreased anxiety	Activation, hyperactivity, inattention, sedation, change in appetite, insomnia, stomach ache, diarrhea Citalopram: prolonged QTc interval	Weight, BP, HR
Irritability	Atypical antipsychotics (risperidone, aripiprazole)	Decreased irritability, aggression, self-injurious behavior, repetitive behavior, hyperactivity	Somnolence, weight gain, extrapyramidal movements, drooling, tremor, dizziness, vomiting, gynecomastia	Weight, BP, HR Monitor CBC, cholesterol, ALT, AST, prolactin, glucose or hemoglobin A_{1c}
Insomnia	Melatonin	Shortened sleep onset	Nightmares, enuresis	—

* Specific medications names are provided in parentheses when there is a FDA-approved indication for the use of the medication to treat the symptom in children with ASD. Further information about these medications is available in Chapter 33 .

BP, Blood pressure; HR, heart rate; CBC, complete blood count; ALT, alanine transaminase; AST, aspartate transaminase.

Preliminary data suggest that intranasal therapy with neuropeptide oxytocin may improve social functioning in children with ASD, particularly those with low pretreatment oxytocin levels.

There is evidence to support use of stimulant medication, **atomoxetine** and α-agonists for ADHD in ASD. Selective serotonin reuptake inhibitors (SSRI) can be used for anxiety and OCD and in adolescents may also be useful for depression. Benzodiazepines may be useful for situational anxiety, for example, triggered by dental and medical procedures or air travel. Medications used to treat ADHD and anxiety may result in activation or irritability in ASD and require careful monitoring.

Melatonin can be used to improve sleep onset but will not address night waking. **Clonidine** or **trazodone** may be used for sleep onset and maintenance. No medications are specifically labeled for treatment of insomnia in ASD.

The α-adrenergic agonists may be helpful in children who present with significant behavioral dysregulation. There are two atypical antipsychotic medications that have U.S. Food and Drug Administration (FDA) recommendation for irritability and aggression in children with ASD. Both **risperidone** and **aripiprazole** have several studies documenting efficacy for reducing irritability, aggression, and self-injury. Secondary improvements in attention and repetitive behavior were also noted. Side effects include weight gain and metabolic syndrome as well as tardive dyskinesia and extrapyramidal movements. Careful laboratory monitoring is recommended. Mood-stabilizing antiepileptic medications have also been used to treat irritability.

Complementary and Alternative Medicine

Families of children with ASD often use complementary and alternative medicine (CAM) approaches. These treatments can include supplements, dietary changes, and body or physical treatments. There is a limited evidence to inform families, who often learn about these treatments from friends and family members, alternative medicine providers, or the internet. For most therapies, evidence is insufficient to show benefit. There is strong evidence that secretin and facilitated communication are not effective. Some therapies, such as hyperbaric oxygen, chelation, and high-dose vitamins, are potentially harmful. For children with restrictive diets, taking a daily multivitamin and 400 IU vitamin D may be indicated, although there is no evidence to support megadoses of vitamins. Similarly, for children with evidence of gluten sensitivity, a trial of gluten-free diet may be indicated. However, current evidence does not support this as a treatment for all children with ASD.

When discussing CAM with a family, it is best to use open and collaborative communication, encouraging them to share their current practices and any questions. Specifically ask if they use any herbal treatments, supplements, or other therapies, such as acupuncture, massage, or chiropractic treatment, and what they have observed since trying the treatment. Provide accurate information regarding potential benefit and risk for any treatment. Educate about “red flags” such as treatments that are marketed as a cure for multiple conditions, that report no risk of side effects, or that are marketed by the clinician recommending the treatment. Encourage families to identify a target symptom, “try one thing at a time,” and monitor response carefully.

Transition

Navigating a successful transition to adult care is a key role for the pediatric provider. This process should ideally start as early as age 12-13 yr. Parents are faced with a complex and disconnected system of diverse agencies that they need to navigate. Use of structured-visit templates and care coordinators can help ensure that families and their youth with ASD are able to make appropriate decisions about secondary and postsecondary educational programming, vocational training, guardianship, finances, housing, and medical care. High school educational programming should include individualized and meaningful vocational training, as well as instruction regarding sexuality, relationships, safety and abuse prevention, finances, travel training, and general self-advocacy. Individuals with ASD who are higher functioning will need help accessing supports for college or postsecondary skills training and may benefit from referral to their state vocational rehabilitative services as well as personal life coaches or counselors. Families who have adult children with more significant cognitive disability need information about the range of adult disability services, how to apply for supplemental security income (SSI), and the process for considering guardianship or medical and financial conservatorship for their adult child. These decisions are complex and must be individualized for the adult with ASD and the family.

Outcome

Autism spectrum disorder is a lifelong condition. Although a minority of individuals respond so well to therapy that they no longer meet criteria for the diagnosis, most will make progress but continue to have some impairment in social and behavioral function as adults. Adult outcome studies are sobering, indicating that many adults with ASD are socially isolated, lack gainful employment or independent living, and have higher rates of depression and anxiety. It is not clear if these data can be extrapolated to younger children currently receiving intensive educational therapies. There is a growing network of adult self-advocates who promote the unique strengths in individuals with ASD. Outcome as measured by developmental progress and functional independence is better for individuals who have higher cognitive and language skills and lower ASD severity at initial diagnosis.

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PART V
Nutrition

OUTLINE

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CHAPTER 55

Nutritional Requirements

Asim Maqbool, Elizabeth Prout Parks, Ala Shaikhkhalil, Jennifer Panganiban, Jonathan A. Mitchell, Virginia A. Stallings

Nutrition for infants, children, and adolescents should maintain current weight and support normal growth and development. Growth during infancy is rapid, critical for neurocognitive development, and has the highest energy and nutrient requirements relative to body size than any other period of growth. It is followed by growth during childhood, when 60% of total growth occurs, and finally by puberty. Nutrition and growth during the 1st 3 yr of life predict adult stature and some health outcomes. The major risk period for **growth stunting** (impaired linear growth) is between 4 and 24 mo of age. Therefore, it is critical to identify nutrient deficiencies promptly and to address them aggressively early in life, because missing them can impart lasting adverse effects on later growth and development.

Dietary intake should provide energy requirements as well as the essential macronutrient and micronutrient needs for sustaining the function of multiple vital processes. Nutrient deficiencies can limit growth, impair immune function, affect neurodevelopment, and increase morbidity and mortality. Worldwide, malnutrition and undernutrition are the leading causes of acquired immunodeficiency, and a major factor underlying morbidity and mortality in children <5 yr of age.

The transition in food supply and type of nutrition chosen in many developing countries, coincident with population change, from traditional to Western diet has resulted in increased life expectancy and adult stature. Unfortunately, the Western diet in these populations is also frequently accompanied by decreased physical activity and, in parallel, decreases in the incidence and prevalence of communicable (infectious) diseases along with increases in the incidence and prevalence of noncommunicable diseases such as type 2 diabetes, cardiovascular

(CV) disease, obesity, inflammatory bowel disease (IBD), and certain cancers. Consequently, it is important to view the impact of nutrition on health from various perspectives: to prevent deficiency, to promote adequacy, and to prevent or reduce the risk for acquiring diseases associated with excess intakes, such as obesity, diabetes, and CV disease.

Advances in our understanding of the roles of some nutrients such as vitamin D, polyunsaturated fatty acids (PUFAs), and fiber have changed our focus from recommendations about preventing deficiency to recommendations about nutritional intake associated with optimal health. The 2006 World Health Organization (WHO) growth charts, which now are recommended *for all children until age 2 yr* , are not only descriptive but also proscriptive on how children with adequate nutrition and health care should grow. Therefore, identifying and providing appropriate and adequate nutrition in infancy and childhood are critical to supporting normal growth and development as well as providing the foundation for lifelong health and well-being.

Dietary Reference Intakes

The **dietary reference intake (DRI)** established by the Food and Nutrition Board of the U.S. Institutes of Medicine (IOM) provides guidance on the nutrient needs for individuals and groups across different life stages and by gender (see Tables 55.1 to 55.4).

Key concepts on DRI concepts include the **estimated average requirement (EAR)** , the **recommended dietary allowance (RDA),** and the tolerable **upper limit** of intake **(UL)** (Fig. 55.1). The EAR is the average level of daily nutrient intake that is estimated to meet the requirements for 50% of the population, assuming normal distribution. The RDA is an estimate of the daily average nutrient intake that meets the nutritional needs of >97% of the individuals in a population, and it can be used as a guideline for individuals to avoid deficiency. When an EAR cannot be derived, an RDA cannot be calculated; therefore, an **adequate intake (AI)** is developed as a guideline for individuals based on the best available data and scientific consensus. The UL denotes the highest average daily intake with no associated adverse health effects for almost all individuals in a particular group. Fig. 55.2 shows the relationships among EAR, RDA, and UL.

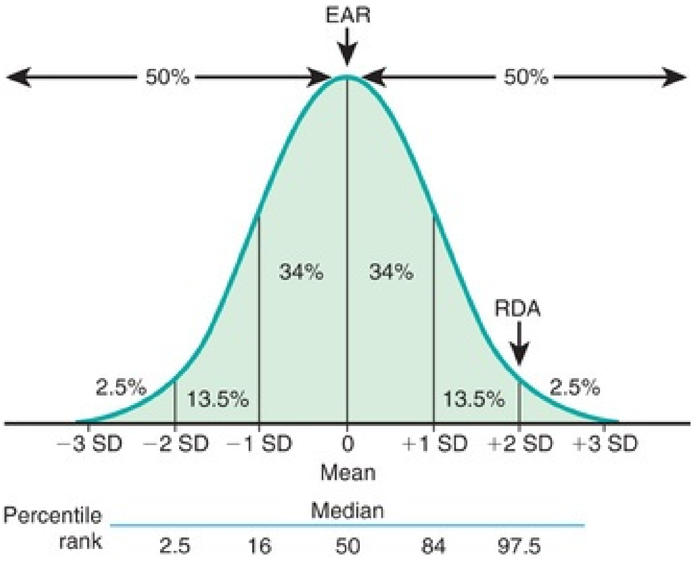

FIG. 55.1 Dietary reference intakes. Normal requirement distribution of hypothetical nutrient showing percentile rank and placement of the estimated average requirement (EAR) and the recommended dietary allowance (RDA) on the distribution; SD, standard deviation.

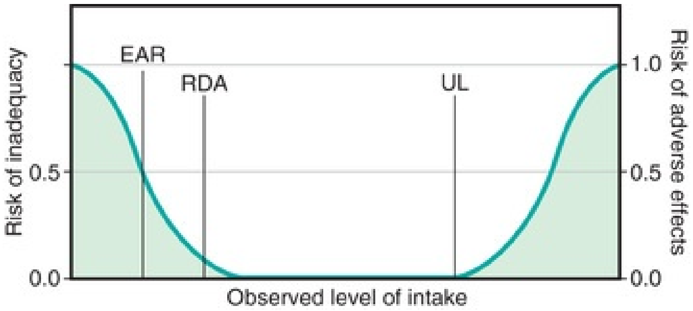

FIG. 55.2 Dietary reference intakes: the relationship among the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper limit of intake (UL). This figure shows that the EAR is the intake at which the risk of inadequacy is estimated to be 0.5 (50%). The RDA is the intake at which the risk of inadequacy would be very small, only 0.02-0.03 (2–3%). At intakes between the RDA and the UL, the risk of inadequacy and of excess are estimated to be close to 0.0. At intakes above the UL, the potential risk of adverse effects can increase.

Energy

Energy includes both food intake *and* metabolic expenditure. Deficits and excesses of energy intake yield undesirable health consequences. *Inadequate* energy intake can lead to growth faltering, catabolism of body tissues, and inability to provide adequate energy substrate. *Excess* energy intakes can increase the risk for obesity. Adequacy of energy intake in adults is associated with maintenance of a healthy weight. The three components of energy expenditure in adults are the *basal metabolic rate* (BMR), *thermal effect* of food (e.g., energy required for digestion and absorption), and *energy* for physical activity. In children, additional energy intake is required to support growth and development.

Estimated energy requirement (EER) is the average dietary energy intake predicted to maintain energy balance in a healthy individual and takes into account age, gender, weight, stature, and level of physical activity (Table 55.1). The 2015–2020 **Dietary Guidelines for Americans** refer to the 2008 Physical Activity Guidelines for Americans. These guidelines recommend ≥60 min of moderate- or vigorous-intensity aerobic physical daily for children and adolescents. This activity should include vigorous intensity physical activity at least 3 days per week. In addition, as part of their ≥60 min of daily physical activity, children and adolescents are advised to incorporate muscle- and bone-strengthening activity for ≥3 days a week, to maintain a healthy weight and to prevent or delay progression of chronic noncommunicable diseases such as obesity and CV disease.

Table 55.1

Equations to Estimate Energy Requirement

INFANTS AND YOUNG CHILDREN: EER (kcal/day) = TEE + ED	
0-3 mo	$\text{EER} = (89 \times \text{weight [kg]} - 100) + 175$
4-6 mo	$\text{EER} = (89 \times \text{weight [kg]} - 100) + 56$
7-12 mo	$\text{EER} = (89 \times \text{weight [kg]} - 100) + 22$
13-36 mo	$\text{EER} = (89 \times \text{weight [kg]} - 100) + 20$
CHILDREN AND ADOLESCENTS 3-18 yr: EER (kcal/day) = TEE + ED	
Boys	
3-8 yr	$\text{EER} = 88.5 - (61.9 \times \text{age [yr]} + \text{PA} \times [(26.7 \times \text{weight [kg]} + (903 \times \text{height [m]})] + 20$
9-18 yr	$\text{EER} = 88.5 - (61.9 \times \text{age [yr]} + \text{PA} \times [(26.7 \times \text{weight [kg]} + (903 \times \text{height [m]})] + 25$
Girls	
3-8 yr	$\text{EER} = 135.3 - (30.8 \times \text{age [yr]} + \text{PA} [(10 \times \text{weight [kg]} + (934 \times \text{height [m]})] + 20$
9-18 yr	$\text{EER} = 135.3 - (30.8 \times \text{age [yr]} + \text{PA} [(10 \times \text{weight [kg]} + (934 \times \text{height [m]})] + 25$

EER, Estimated energy requirement; TEE, total energy expenditure; ED, energy deposition (energy required for growth /new tissue accretion).

PA indicates the physical activity coefficient:

For boys:

PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4)

PA = 1.13 (low active, estimated physical activity level 1.4-1.6)

PA = 1.26 (active, estimated physical activity level 1.6-1.9)

PA = 1.42 (very active, estimated physical activity level 1.9-2.5)

For girls:

PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4)

PA = 1.16 (low active, estimated physical activity level 1.4-1.6)

PA = 1.31 (active, estimated physical activity level 1.6-1.9)

PA = 1.56 (very active, estimated physical activity level 1.9-2.5)

Adapted from Kleinman RE, editor: *Pediatric nutrition handbook,* ed 7, Elk Grove Village, IL, 2013, American Academy of Pediatrics.

The EER was determined based on empirical research in healthy persons at different levels of physical activity, including levels different from recommended levels. They do not necessarily apply to children with acute or chronic diseases. EER is estimated by equations that account for *total energy expenditure* (TEE) and *energy deposition* (ED) for healthy growth. EERs for infants, relative to body weight, are approximately twice those for adults because of the increased metabolic rate and requirements for weight maintenance and tissue accretion (growth).

Dietary nutrients that provide energy include *fats* (approximately 9 kcal/g), *carbohydrates* (4 kcal/g), and *protein* (4 kcal/g). These nutrients are called **macronutrients** . If alcohol is consumed, it also contributes to energy intake (7 kcal/g). The EER does not specify the relative energy contributions of macronutrients. Once the minimal intake of each macronutrient is attained (e.g., sufficient protein intake to meet specific amino acid requirements, sufficient fat intake to meet linoleic acid and α-linolenic acid needs for brain development), the remainder of the intake is used to meet energy requirements, with some degree of freedom and interchangeability among fat, carbohydrate, and protein. This argument forms the basis for the **acceptable macronutrient distribution ranges (AMDRs)** , expressed as a function of total energy intake (Table 55.2).

Table 55.2

Acceptable Macronutrient Distribution Ranges

AMDA (% OF ENERGY)		
Macronutrient	**Age 1-3 yr**	**Age 4-18 yr**
Fat	30-40	25-35
ω6 PUFAs (linoleic acid)	5-10	5-10

ω3 PUFAs (α-linolenic acid)	0.6-1.2	0.6-1.2
Carbohydrate	45-65	45-65
Protein	5-20	10-30

PUFAs, Polyunsaturated fatty acids.

Adapted from Otten JJ, Hellwig JP, Meyers LD, editors; Institute of Medicine: *Dietary reference intakes: the essential guide to nutrient requirements* , Washington, DC, 2006, National Academies Press.

Fat

Fat is the most calorically dense macronutrient, providing approximately 9 kcal/g. For infants, human milk and formula are the main dietary sources of fat, whereas older children obtain fat from animal products, vegetable oils, and margarine. The AMDR for fats is 30–40% of total energy intake for children 1-3 yr and 25–35% for children 4-18 yr of age. In addition to being energy dense, fats provide essential fatty acids that have body structural and functional roles (e.g., cholesterol moieties are precursors for cell membranes, hormones, and bile acids). Fat intake facilitates absorption of fat-soluble vitamins (vitamins A, D, E, and K). Both roles are relevant to neurologic and ocular development (Table 55.3).

Table 55.3

Dietary Reference Intakes: Macronutrients

FUNCTION	LIFE STAGE GROUP		RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
TOTAL DIGESTIBLE CARBOHYDRATE					
RDA based on its role as the primary energy source for the brain AMDR based on its role as a source of kcal to maintain body weight	*Infants*			Major types: starches and sugars, grains, and vegetables (corn, pasta, rice, potatoes, and breads) are sources of starch. Natural sugars are found in fruits and juices. Sources of added sugars: soft drinks, candy, fruit drinks,	No defined intake level for potential adverse effects of total digestible carbohydrate is identified, but the upper end of the AMDR was based on decreasing risk of chronic disease and providing adequate intake of other nutrients. It is suggested that the maximal intake of added sugars be limited to providing no more than 10% of energy.
	0-6 mo	60*			
	7-12 mo	95*			
	Children				
	>1 yr	**130**			
	Pregnancy				
	≤18 yr	**175**			
	19-30 yr	**175**			

			desserts, syrups, and sweeteners[†]	
TOTAL FIBER				
Improves laxation, reduces risk of coronary artery (heart) disease, assists in maintaining normal blood glucose levels	*Infants*		Includes dietary fiber naturally present in grains (e.g., oats, wheat, unmilled rice) and functional fiber synthesized or isolated from plants or animals and shown to be of benefit to health	Dietary fiber can have variable compositions; therefore it is difficult to link a specific source of fiber with a particular adverse effect, especially when phytate is also present in the natural fiber source. As part of an overall healthy diet, a high intake of dietary fiber will not produce deleterious effects in healthy persons. Occasional adverse GI symptoms are observed when consuming some isolated or synthetic fibers, but serious chronic adverse effects have not been observed because of the bulky nature of fibers. Excess consumption is likely to be self-limiting; therefore, UL was not set for individual functional fibers.
	0-6 mo	ND		
	7-12 mo	ND		
	Children			
	1-3 yr	190*		
	4-8 yr	25*		
	Males			
	9-13 yr	31*		
	14-18 yr	38*		
	19-21 yr	38*		
	Females			
	9-13 yr	26*		
	14-18 yr	26*		
	19-21 yr	25*		
	Pregnancy			
	≤18 yr	28*		
	19-21 yr	28*		
TOTAL FAT				
Energy source When found in foods, is a source of ω3 and ω6 PUFAs Facilitates absorption of fat-soluble vitamins	*Infants*		*Infants:* Human milk or infant formula *Older children:* Butter, margarine, vegetable oils, whole milk, visible fat on meat and poultry products, invisible fat in fish, shellfish, some plant products such as seeds and nuts, bakery products	UL is not set because there is no defined intake of fat at which adverse effects occur. High fat intake will lead to obesity. Upper end of AMDR is also based on reducing risk of chronic disease and providing adequate intake of other nutrients.[†] Low fat intake (with high carbohydrate) has been shown to increase plasma triacylglycerol concentrations and decrease HDL cholesterol.
	0-6 mo	31*		
	7-12 mo	30*		
	1-18 yr	Insufficient evidence to determine AI or EAR; see AMDR, Table 55.2.		
ω6 POLYUNSATURATED FATTY ACIDS				
Essential component of structural membrane lipids, involved with cell signaling Precursor of eicosanoids Required for normal skin function	*Infants*		Nuts, seeds; vegetable oils such as soybean, safflower, corn oil	There is no defined intake of ω6 level at which adverse effects occur. Upper end of AMDR is based on the lack of evidence that demonstrates long-term safety and human in vitro studies that show increased free radical formation and lipid peroxidation with higher amounts of ω6 fatty acids.
	0-6 mo	4.4*		
	7-12 mo	4.6*		
	Children			
	1-3 yr	7*		
	4-8 yr	10*		
	Males			
	9-13 yr	12*		
	14-18 yr	16*		
	19-21 yr	17*		

	Females			Lipid peroxidation is thought to be a component of atherosclerotic plaques.
	9-13 yr	10*		
	14-18 yr	11*		
	19-21 yr	12*		
	Pregnancy			
	≤18 yr	13*		
	19-21 yr	13*		
	Lactation			
	≤18 yr	13*		
	19-21 yr	13*		
ω3 POLYUNSATURATED FATTY ACIDS				
Involved with neurologic development and growth Precursor of eicosanoids	*Infants*		Vegetable oils, e.g., soybean, canola, flax seed oil; fish oils, fatty fish, walnuts; † smaller amounts in meats and eggs	No defined intake levels for potential adverse effects of ω3 PUFAs are identified. Upper end of AMDR is based on maintaining appropriate balance with ω6 fatty acids and the lack of evidence that demonstrates long-term safety, along with human in vitro studies that show increased free radical formation and lipid peroxidation with higher amounts of PUFAs. Because the longer-chain *n* -3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are biologically more potent than their precursor, linolenic acid, much of the work on adverse effects of this group of fatty acids has been on DHA and EPA. Lipid peroxidation is thought to be a component in the development of atherosclerotic plaques.
	0-6 mo	0.5*		
	7-12 mo	0.5*		
	Children			
	1-3 yr	0.7*		
	4-8 yr	0.9*		
	Males			
	9-13 yr	1.2*		
	14-18 yr	1.6*		
	19-21 yr	1.6*		
	Females			
	9-13 yr	1.0*		
	14-18 yr	1.1*		
	19-21 yr	1.1*		
	Pregnancy			
	≤18 yr	1.4*		
	19-21 yr	1.4*		
	Lactation			
	≤18 yr	1.3*		
	19-21 yr	1.3*		
SATURATED AND *TRANS* FATTY ACIDS				
The body can synthesize its needs for saturated fatty acids from other sources.		No dietary requirement	Saturated fatty acids are present in animal fats (meat fats and butter fat), and coconut and palm kernel oils. *Trans* fat: stick margarines, foods containing hydrogenated or partially hydrogenated vegetable shortenings	There is an incremental increase in plasma total and LDL cholesterol concentrations with increased intake of saturated or *trans* fatty acids; therefore, saturated fat intake should be limited to <10% with no *trans* fat. † ‡
CHOLESTEROL				

		No dietary requirement	Sources: liver, eggs, foods that contain eggs, e.g., cheesecake, custard pie	
PROTEIN AND AMINO ACIDS [‡]				
Major structural component of all cells in the body Functions as enzymes, in membranes, as transport carriers, and as some hormones During digestion and absorption, dietary protein is broken down to amino acids, which become the building blocks of these structural and functional compounds. Nine indispensable amino acids must be provided in the diet; the body can make the other amino acids needed to synthesize specific structures from other amino acids.	*Infants*		Proteins from animal sources, e.g., meat, poultry, fish, eggs, milk, cheese, yogurt, provide all 9 indispensable amino acids in adequate amounts and are considered “complete protein.” Protein from plants, legumes, grains, nuts, seeds, and vegetables tend to be deficient in ≥1 of the indispensable amino acids and are called “incomplete protein.” Vegan diets adequate in total protein content can be “complete” by combining sources of incomplete protein, which lack different indispensable amino acids.	No defined intake levels for potential adverse effects of protein are identified. Upper end of AMDR was based on complementing AMDR for carbohydrate and fat for the various age-groups. Lower end of AMDR is set at approximately the RDA.
	0-6 mo	9.1*		
	7-12 mo	**11.0**		
	Children			
	1-3 yr	**13**		
	4-8 yr	**19**		
	Males			
	9-13 yr	**34**		
	14-18 yr	**52**		
	≥19 yr	**56**		
	Females			
	9-13 yr	**34**		
	≥14 yr	**46**		
	≤18 yr			
	19-21 yr	**71**		

[*] Adequate intake.

[†] 2015–2020 Dietary Guidelines for Americans. US Department of Health and Human Services. https://health.gov/dietaryguidelines/2015/ .

[‡] Based on 1.5 g/kg/day for infants, 1.1 g/kg/day for 1-3 yr, 0.95 g/kg/day for 4-13 yr, 0.85 g/kg/day for 14-18 yr, 0.8 g/kg/day for adults, and 1.1 g/kg/day for pregnant (using pre-pregnancy weight) and lactating women.

Note: Starred (*) numbers are AI; **bold** numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake.

AMDR is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. With consumption in excess of the AMDR, there is a potential for increasing the risk of chronic diseases and/or insufficient intakes of essential nutrients.

ND amounts are not determinable because of a lack of data regarding adverse effects in this age-group and concern with regard to a lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

AI, Adequate intake; AMDR, acceptable macronutrient distribution range; EAR, estimated average requirement; GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ND, not determinable; PUFAs, polyunsaturated fatty acids; RDA, recommended dietary allowance; UL, upper limit of normal.

Adapted from Food and Nutrition Board, Institute of Medicine: *Dietary reference intakes for, energy, carbohydrate fiber, fat, fatty acids, cholesterol, protein, and amino acids.* https://www.nap.edu/read/10490/chapter/32 .

Triglycerides are the most common form of dietary fat and are composed of 1 glycerol molecule with 3 fatty acids. Triglycerides are found in animal and vegetable fats. Simple sugars (i.e., refined grains and high sugar drinks) are converted to triglycerides in the liver. Elevated serum triglycerides are a risk factor for CV disease and metabolic syndrome. Decreasing simple sugars and increasing complex carbohydrate intake reduces serum triglyceride levels.

Dietary saturated fatty acids (found primarily in animal fat and dairy products), *trans* fats (found in hydrogenated margarines and oils), and **cholesterol** increase the low-density lipoprotein (LDL) fraction of serum cholesterol, which is a risk factor for the development of atherosclerosis (Fig. 55.3). Autopsy studies demonstrate that atherosclerosis begins early in childhood, even in infancy. Therefore, dietary advice to optimize CV health should be given starting from age 2 yr, when sufficient fat intake to sustain growth and brain development is less of a concern.

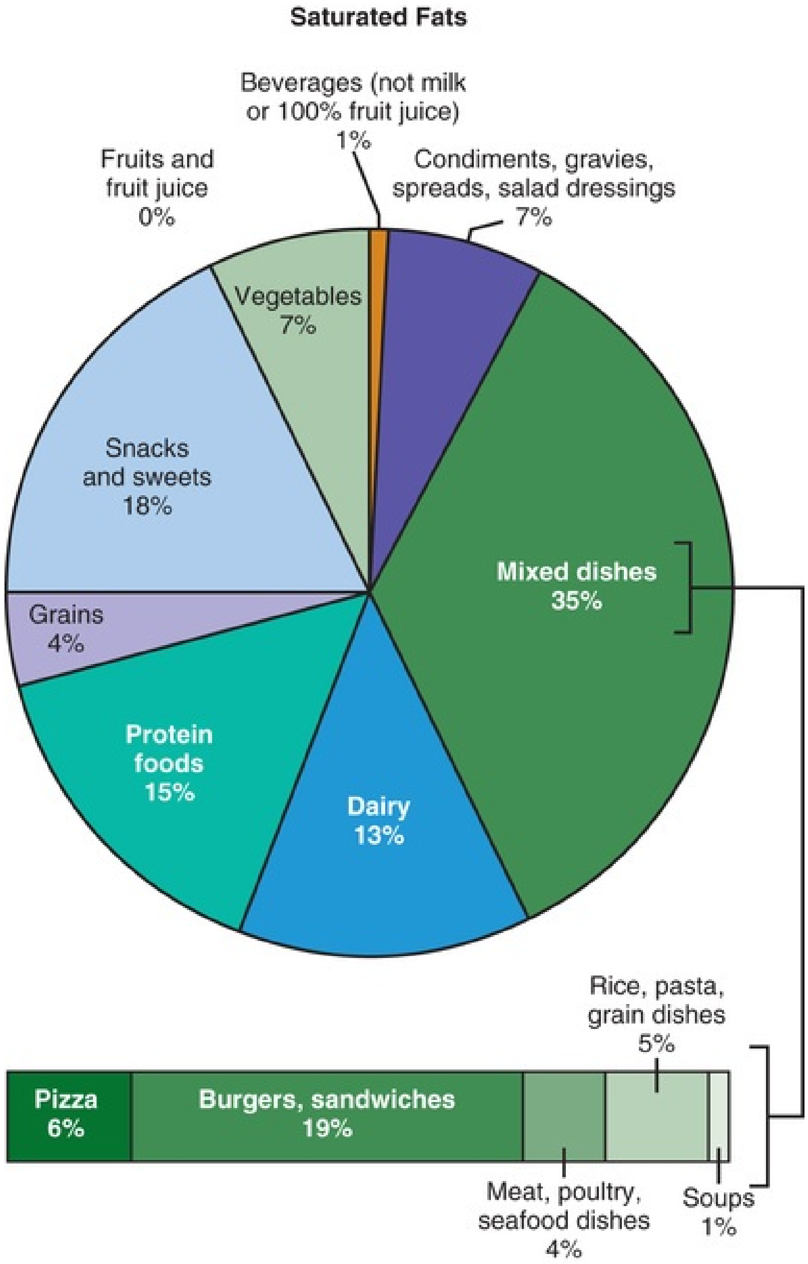

FIG. 55.3 Food category sources of saturated fats in the U.S. population age 2 yr and older. Estimates based on day 1 dietary recalls from WWEIA, National Health and Nutrition Examination Survey (NHANES), 2009–2010. (From What We Eat in America (WWEIA) category analysis for the 2015 Dietary Guidelines Advisory Committee. https://health.gov/dietaryguidelines/2015/guidelines/chapter-2/a-closer-look-at-current-intakes-and-recommended-shifts/#figure-2-12 .)

Because saturated and monounsaturated fats can be synthesized endogenously to support adequate structural and physiologic requirements, there is no AI or RDA set for these dietary components. *Trans* fats, a by-product of the hydrogenation of vegetables oils to form margarine, *have no known health benefits in humans. Trans* fats do not have an AI or RDA defined. In fact, *trans* fats behave like saturated fats. An UL has not been set for cholesterol, saturated, or *trans* fats because there is a continuous positive linear association between intake of these fats and increased risk for CV disease, without a threshold level. Diets low in saturated fats and cholesterol without *trans* fats are therefore preferred.

Efforts continue to reduce or eliminate *trans* fats from the diet. For optimal CV health in the general population, rather than limiting fat intake, advice should focus in most cases on changing the type of fat consumed. With respect to preventing obesity, all types of fatty acids have the same energy content and can contribute to increasing the risk for obesity. The current 2015–2020 Dietary Guidelines for Americans no longer restrict how much energy should come from fat intake, but continue to recommend that <10% of total daily calories come from saturated fat, with no *trans* fat intake. Furthermore, these guidelines do not specify limits on dietary cholesterol intake, because there is no clear strong evidence of the relationship between dietary and blood cholesterol.

Humans are incapable of synthesizing the precursor omega (ω) 3 (α-linolenic acid; ALA) and ω6 (linoleic acid; LA) PUFAs and depend on diet for these 2 essential fatty acids (EFAs). Safflower and sunflower oil are good sources of linoleic acid. Walnut and flaxseed oil are good sources of ALA. **Essential fatty acid deficiency** with LA is associated with desquamating skin rashes, alopecia, thrombocytopenia, impaired immunity, and growth deficits but is rare in the general population. EFAs are enzymatically elongated and desaturated into longer-chain fatty acids; ALA can be converted to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) ω3 PUFAs. LA is converted to arachidonic acid (ARA). Long-chain PUFAs such as DHA and ARA have a variety of cellular structural and functional roles; they influence membrane fluidity and function in gene expression and modulate the inflammatory response. ARA and DHA are present in breast milk, often supplemented in infant formulas, and are required for normal growth and development. DHA is present in the retina and is involved in the visual evoked response in infants.

The conversion of ALA to EPA and DHA and of LA to ARA is influenced by many factors, including type and amounts of dietary fats, and by enzymatic substrate affinity among competing ω3, ω6, ω9, saturated, and *trans* fatty acids. Approximately 0.5% of dietary ALA is converted to DHA, and 5% of ALA intake is converted to EPA; therefore, dietary intake of longer-chain PUFAs is an important determinant of serum and tissue long-chain PUFA status. The biologic activity and health benefits of ALA are thought to be derived from the longer-chain PUFA products EPA and DHA. Consistent with these findings of limited conversion of ALA to EPA and DHA, and that EPA and DHA appear to confer the biologic role and health benefits, the dietary reference intake (DRI) stipulates that up to 10% of the AI for ω3 PUFA (ALA being the major dietary constituent) can be replaced by DHA and EPA to support normal neural development and growth.

The ratio of dietary intake of each type of PUFA influences their relative amounts in different tissue compartments. A dietary ω6:ω3 PUFA ratio of 4-5 : 1 may be beneficial in reducing risk of disease and may be associated with improved health outcomes, compared with the current 15-30 : 1 ratio observed in U.S. diets.

Protein

Protein and amino acids have structural and functional roles in every cell in the body. Dietary protein intake is required to replenish the turnover of protein and to meet amino acid needs for growth. Dietary protein also provides approximately 4 kcal/g as an energy substrate when intake is in excess of needs, or during periods of catabolism. Inadequate energy intake or inadequate protein intake increases catabolism of body protein reservoirs (i.e., lean body mass) for energy and free amino acids required to support normal physiologic function. Nitrogen from protein turnover is excreted in urine, stool, and other bodily excretions. Increased protein intake may be required for rare hypermetabolic states, such as extensive burn injury. Protein-energy malnutrition, although relatively rare in the noninstitutionalized U.S. population, is more common in the developing world. Protein-energy malnutrition impairs brain, immune system, and intestinal mucosal functions (see Chapter 59).

The DRI for protein is provided in Table 55.3 . According to the 2015–2020 Dietary Guidelines for Americans, the average intake of protein from poultry, meat, eggs, nuts, seeds, and soy products are close to the recommended amounts for all ages. Protein intake is higher than recommended amounts in adolescent males (mostly from meats, poultry, and eggs). Intake of seafood protein is low across all age and sex groups. An UL for protein has not been set. Some athletes may have increased protein needs, of approximately 2 g/kg/day, to prevent loss of fat-free mass or lean body mass. Certain conditions may require a modest increase in protein intake, including conditions with high protein turnover, inflammatory conditions, or postsurgical states, as well as with cystic fibrosis, critical illnesses, burn injuries, compensated liver disease, and bariatric surgery (e.g., laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass). Intake of protein or specific amino acids needs to be limited in some health conditions, such as renal disease and decompensated liver disease, and metabolic diseases such as phenylketonuria and maple syrup urine disease, in which specific amino acids can be toxic.

The amino acid content of dietary protein is also important. Certain amino acids are **indispensable** , and humans depend on dietary sources to meet adequacy and prevent deficiency. Certain amino acids are termed **conditional essential/indispensable** , meaning they become essential in patients affected by some diseases or during a certain life stage, such as with cysteine, tyrosine, and arginine in newborns because of enzyme immaturity (Table 55.4). Human milk contains both the indispensable and conditionally indispensable amino acids and therefore meets the protein requirements for infants. Breast milk is considered the optimal protein source for infants and is the reference amino acid composition by which biologic quality is determined for infants. If a single amino acid in a food protein source is low or absent but is required to support normal metabolism, that specific amino acid becomes the limiting nutrient in that food. For soy-based infant formula, supplementing the formula with the limiting amino acid (methionine) is necessary. Certain amino acid–like substances, such as creatinine, are used by some athletes and may enhance performance. Such supplementation should be monitored for potential side effects.

Table 55.4

Indispensable, Dispensable, and Conditionally Indispensable Amino Acids in the Human Diet

INDISPENSABLE	DISPENSABLE	CONDITIONALLY INDISPENSABLE*	PRECURSORS OF CONDITIONALLY INDISPENSABLE
Histidine† Isoleucine Leucine Lysine Methionine Phenylalanine Threonine Tryptophan Valine	Alanine Aspartic acid Asparagine Glutamic acid Serine	Arginine Cysteine Glutamine Glycine Proline Tyrosine	Glutamine/glutamate, aspartate Methionine, serine Glutamic acid/ammonia Serine, choline Glutamate Phenylalanine

[*] *Conditionally indispensable* is defined as requiring a dietary source when endogenous synthesis

cannot meet metabolic need.

[†] Although histidine is considered indispensable, unlike the other 8 indispensable amino acids, it does not fulfill the criteria of reducing protein deposition and inducing negative nitrogen balance promptly on removal from the diet.

Adapted from Otten JJ, Hellwig JP, Meyers LD, editors; Institute of Medicine: *Dietary reference intakes: the essential guide to nutrient requirements* , Washington, DC, 2006, National Academies Press.

To ensure appropriate growth and to promote satiety, children should consume the recommended amount of protein. Specific recommendations for appropriate dietary protein sources to meet indispensable amino acid requirements are available for groups adopting specific diets, such as vegetarians and vegans. Inclusion of legumes and corn, as well as the use of a variety of food sources to provide all of the required amino acids is a strategy advocated for vegetarians and vegans (see Chapter 56).

Carbohydrates

Carbohydrates are abundant in many foods, including cereals, grains, fruits, and vegetables, and provide approximately 4 kcal/g. Dietary carbohydrates include *monosaccharides,* which contain 1 sugar molecule (glucose, fructose); *disaccharides,* which contain 2 sugar molecules (sucrose, lactose); *oligosaccharides* or *polysaccharides,* which contain multiple sugar molecules in a chain or complex configuration (e.g., starch); and *sugar alcohols.* **Glucose** serves as the essential energy source for erythrocytes and the central nervous system and a major energy source for all other cells. The requirements for carbohydrates are based on the average minimum amount of glucose utilized by the brain. Chronic low carbohydrate intake results in ketosis. Although an UL for carbohydrates has not been set, a maximal intake of <10% of total energy intake from added sugars has been proposed in the 2015–2020 Dietary Guidelines for Americans. Added sugars include syrups and other caloric *sweeteners* (Fig. 55.4). These added sugars do not contribute essential nutrients and function to sweeten foods and beverages to which they are added. Naturally occurring sugars, such as in milk (lactose) or fruits, are not included. Higher intakes of added sugar can displace other macro- and micronutrients and increase risk for nutrient deficiency and excessive energy intake. There is no advantage or benefit from discretionary calorie intake such as consuming added sugars. In fact, the excess calories from added sugars may make it difficult to meet nutrient needs while remaining within recommended total calorie intake.

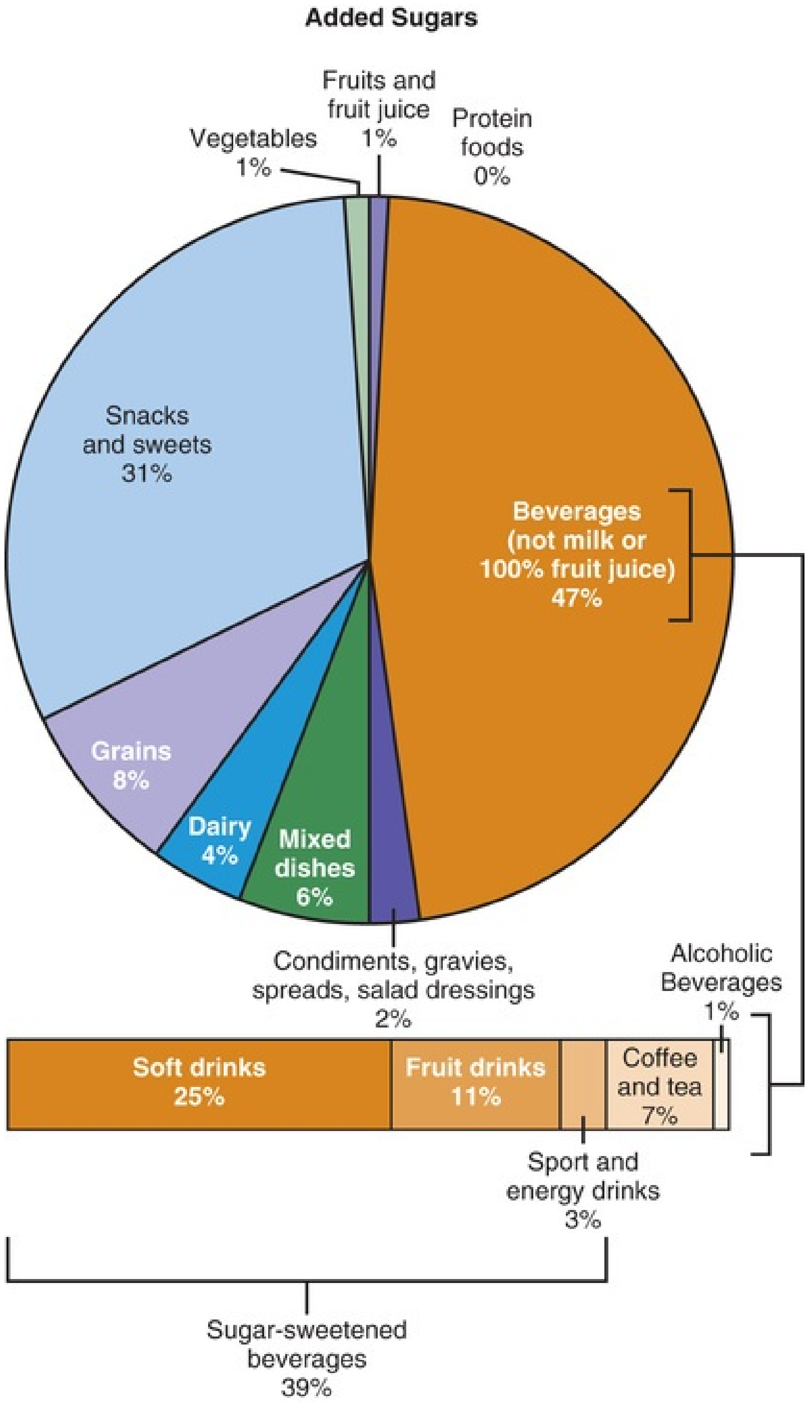

FIG. 55.4 Food category sources of added sugars in the U.S. population age 2 yr and older. Estimates based on day 1 dietary recalls from WWEIA, NHANES, 2009–2010. (From What We Eat in America (WWEIA) category analysis for the 2015 Dietary Guidelines Advisory Committee. https://health.gov/dietaryguidelines/2015/guidelines/chapter-2/a-closer-look-at-current-intakes-and-recommended-shifts/#figure-2-10 .)

The recommended AMDR for carbohydrates is based on data suggesting a risk for coronary artery disease (CAD) with diets high in carbohydrates and low in fat (see Table 55.2). These diets, compared to diets with higher fat intake, result in high triglyceride levels, low high-density lipoprotein (HDL) cholesterol, and small LDL cholesterol particles, and are associated with a high risk of CAD, especially in sedentary overweight individuals. Diets within the AMDR for carbohydrates and fats minimize the risks of diabetes, obesity, and CAD. Diets with less than the minimum AMDR for carbohydrate most likely do not meet the AI for fiber (see Table 55.3).

Most carbohydrates are present as starches or sugars in food. Simple sugars (monosaccharides and disaccharides) are often added to foods and beverages during food preparation, processing, and packaging to enhance their palatability, as well as acting as preservatives. Nondiet soft drinks, juice drinks, iced tea, and sport drinks are among the major contributors to added sugars in the diet of U.S. children and adolescents. Added sugars increase the risk for obesity, diabetes, and dental caries. Fructose is one such added sugar in the form of high-fructose corn syrup, which is ubiquitous in the U.S. diet. Fructose increases HDL and triglyceride production in the liver and serum uric acid, which increases systolic blood pressure and is associated with nonalcoholic fatty liver disease and metabolic syndrome. Excessive fructose intake, such as in the form of fruit juices, is associated with diarrhea, abdominal pain, and failure to thrive in children.

The **glycemic index** is a measure of peak blood glucose concentration 2 hr after ingestion of a given food compared with a reference standard (slice of white bread). The glycemic index has predictable effects on blood glucose, hemoglobin A_{1c} , insulin, triglycerides, and HDL cholesterol. Lower–glycemic index foods are recommended and may reduce the risk of insulin resistance and CV disease (e.g., oat bran, muesli, barley carrots, nonstarchy vegetables, most fruits).

Fiber

Fiber consists of *nondigestible* carbohydrates mostly derived from plant sources, such as whole grains, fruits, and vegetables, that escape digestion and reach the colon almost 100% intact. These compounds were previously classified as being *water soluble* vs *insoluble*, which may be a less meaningful health distinction but still commonly used. The DRI classification lists **dietary fiber** (nondigestible carbohydrates and lignin that are intrinsic and intact in plants), **functional fiber** (fiber with known physiologic benefits in humans), and **total fiber** (dietary plus functional).

Although fiber intake does not contribute significantly to energy intake, it does have several important roles. The metabolic fate of fiber is influenced primarily by colonic bacteria, which render it susceptible to fermentation, depending on the structure of the fiber (e.g., pectin, oat bran). Common by-products of colonic fermentation include carbon dioxide, methane (in addition to other gases), **oligofructose** (also known as a *prebiotic,* a substrate that nourishes beneficial commensurate gastrointestinal microbiota), and **short-chain fatty acids (SCFAs)** . The common SCFAs produced by fermentation include acetate, butyrate, and propionate. There is dynamic interplay between the colonic bacterial milieu and the diet. SCFAs influence colonic physiology by stimulating colonic blood flow and fluid and electrolyte uptake. Butyrate is the preferred fuel for the colonocyte and may have a role in maintaining the normal phenotype in these cells.

Dietary fiber may have an important role in reducing dysplasia risk by diluting toxins, carcinogens, and tumor promoters; decreasing transit time, thereby decreasing colonic mucosal exposure; and promoting toxin expulsion in the fecal stream. Dietary fiber that is resistant to colonic degradation may also play a role in maintaining and promoting stool bulk and in regulating intraluminal pressure and colonic wall resistance, disordered colonic motility, or both. Lack of certain types of dietary fiber is associated with constipation and diverticulosis.

All types of dietary fiber slow gastric emptying and promote satiety, and thus may help to regulate appetite. Dietary fiber may decrease the rate of release and absorption of simple sugars and may help regulate blood sugar concentration, with lower postprandial level. Dietary fiber has a low glycemic index and may have a beneficial effect on insulin sensitivity. Fiber also binds luminal cholesterol and reduces absorption and enterohepatic circulation of the cholesterol in bile salts (with the intake of more viscous forms of dietary fiber, such as pectin). Guar gum, oat products, and pectin (previously categorized as soluble fiber) lower serum cholesterol, whereas insoluble fiber (e.g., flax, wheat bran) may reduce serum triglycerides. However, fiber such as psyllium, resistant dextrins, and resistant starch may lower both serum LDL cholesterol and triglycerides. The older classifications of the benefits of soluble vs insoluble fiber types are thus not always consistent. Decreased fiber intake in Western society has been associated with the increasing incidence and prevalence of diabetes, obesity, CV disease, colon cancer, and IBD.

Data are insufficient to establish an EAR for dietary fiber. AI for dietary fiber has been established based on the intake levels associated with reducing risk for CV disease and in lowering or normalizing serum cholesterol (see Table 55.3). A UL has not been established for fiber, which is not thought to be harmful to human health. Several recommendations address dietary fiber intake in children based on body weight or as a proportion of daily calories consumed. The prevailing approach, however, is based on expert consensus and uses a rule of thumb guided by safety considerations, with improved laxation and reduced risk of future chronic diseases as goals. The equation for fiber intake in children follows:

$$\text{Range of grams of fiber per day} = \text{Age [yr]} + 5 \text{ to Age [yr]} + 10.$$

It is noteworthy that the recommendation does not specify type of fiber, and it predates the newer definition of fiber. Difficulties in making better recommendations for fiber intake goals in children include the lack of consensus on defining fiber and inadequate randomized double-blinded placebo-controlled trials with well-defined, clinically meaningful end-points.

Certain types of fiber intake are associated with increased risk for gastrointestinal (GI) symptoms along the functional abdominal pain, functional GI disorders, and IBD spectrum. Some fiber types may exert symptoms on the basis of their digestibility, by-product formation, and interactions with GI microbiota. Restriction of **fermentable** (i.e., to produce methane, CO_2 , and hydrogen) **oligosaccharides** (e.g., fructooligosaccharides such as onions), **disaccharides** (e.g., lactose), **monosaccharides** (e.g., fructose), **and polyols** (e.g., sorbitol) **(FODMAP)** or substitution with lower-FODMAP foods may be beneficial. Substitutions within the same food groups can shift from a high-FODMAP diet to a low-FODMAP diet, which may provide GI symptom relief. For example, substituting cucumber for celery would be exchanging a high-FODMAP food for a low-FODMAP food.

Lastly, dietary management in certain diseases may put such children at risk of low fiber intake. For example, children with celiac disease are advised gluten-free diets. As such, these children are at risk of inadequate fiber intake, for which alternative, gluten-free sources of fiber should be recommended, such as tapioca, flax, corn, rice, sorghum, and quinoa.

Micronutrients

(See Chapters 61-67 .)

Vitamins and trace minerals, the dietary **micronutrients** , are essential for growth and development and contribute to a host of physiologic functions. Many U.S. children have suboptimal intake of iron, zinc, potassium, calcium, vitamin D, and vitamin K, and excess intake of sodium. Dietary recommendations for micronutrients were originally established to prevent deficiency and currently also include the impact of micronutrients on long-term health outcomes (Table 55.5). Food fortification is an effective strategy to prevent some nutrient deficiencies and has been successfully implemented to prevent iodine and folate deficiency.

Table 55.5

Dietary Reference Intakes for Vitamins

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDER
Biotin (vitamin B$_7$)	Coenzyme in synthesis of fat, glycogen, and amino acids	*Infants* (µg/day)			Liver Smaller amounts in fruits and meats	No adverse effects of biotin in humans or animals have been found; this does not mean there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of biotin are limited, caution may be warranted.	None
		0-6 mo	5*	ND			
		7-12 mo	6*	ND			
		Children (µg/day)					
		1-3 yr	8*	ND			
		4-8 yr	12*	ND			
		Males (µg/day)					
		9-13 yr	20*	ND			
		14-18 yr	25*	ND			
		19-21 yr	30*	ND			
		Females (µg/day)					
		9-13 yr	20*	ND			
		14-18 yr	25*	ND			
		19-21 yr	30*	ND			
		Pregnancy (µg/day)					
		≤18 yr	30*	ND			
		19-21 yr	30*	ND			
		Lactation (µg/day)					
		≤18 yr	35*	ND			
		19-21 yr	35*	ND			
Choline	Precursor for acetylcholine,	*Infants* (mg/day)			Milk, liver, eggs,	Fishy body odor, sweating,	Patients v trimethyl

	phospholipids, and betaine	0-6 mo	125*	ND	peanuts	salivation, hypotension, hepatotoxicity	renal dise disease, depressio Parkinso may be at adverse e with chol intakes at AIs have for cholin there are to assess a dietary choline is at all stag life cycle, choline requireme be met by endogeno synthesis of these s
		7-12 mo	150*	ND			
		Children (mg/day)					
		1-3 yr	200*	1,000			
		4-8 yr	250*	1,000			
		Males (mg/day)					
		9-13 yr	375*	2,000			
		14-18 yr	550*	3,000			
		19-21 yr	550*	3,500			
		Females (mg/day)					
		9-13 yr	375*	2,000			
		14-18 yr	400*	3,000			
		19-21 yr	425*	3,500			
		Pregnancy (mg/day)					
		≤18 yr	450*	3,000			
		19-21 yr	450*	3,500			
		Lactation (mg/day)					
		≤18 yr	550*	3,000			
		19-21 yr	550*	3,500			
Folate (folic acid, vitamin B_9 , folacin); pteroyl-polyglutamates given as dietary folate equivalents (DFEs) 1 DFE = 1 µg food folate = 0.6 µg folate from fortified food, or as supplement consumed with food = 0.5 µg of supplement taken on empty stomach	Coenzyme in metabolism of nucleic and amino acids Prevents megaloblastic anemia	*Infants* (µg/day)			Enriched cereal, grains, dark leafy vegetables, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	Masks neurologic complications in people with vitamin B_{12} deficiency No adverse effects associated with folate from food or supplements have been reported; this does not mean that there is no potential for adverse effects resulting from high intakes. Because data on adverse effects of folate are limited, caution may be warranted. UL for folate applies to synthetic forms obtained from	In view of ev linking poor intake with n defects, all w who can bec pregnant shou consume 400 from supple fortified food addition to in food folate fr varied diet.
		0-6 mo	65*	ND			
		7-12 mo	80*	ND			
		Children (µg/day)					
		1-3 yr	**150**	300			
		4-8 yr	**200**	400			
		Males (µg/day)					
		9-13 yr	**300**	600			
		14-18 yr	**400**	800			
		19-21 yr	**400**	1,000			
		Females (µg/day)					
		9-13 yr	**300**	600			
		14-18 yr	**400**	800			
		19-21 yr	**400**	1,000			
		Pregnancy (µg/day)					
		≤18 yr	**600**	800			
		19-21 yr	**600**	1,000			
		Lactation (µg/day)					
		≤18 yr	**500**	800			
		19-21 yr	**500**	1,000			

						supplements and/or fortified foods.	
Niacin (vitamin B_3) Includes nicotinic acid amide, nicotinic acid (pyridine-3 carboxylic acid), and derivatives that exhibit biologic activity of nicotinamide Given as niacin equivalents (NE) 1 mg niacin = 60 mg tryptophan Age 0-6 mo: preformed niacin (not NE).	Coenzyme or cosubstrate in many biologic reduction and oxidation reactions, thus required for energy metabolism	*Infants* (mg/day)			Meat, fish, poultry, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	No evidence of adverse effects from consuming naturally occurring niacin in food Adverse effects from niacin-containing supplements can include flushing and GI distress. UL for niacin applies to synthetic forms obtained from supplements, fortified food, or a combination of these.	Extra niacin required by p treated with hemodialysis peritoneal dia those with malabsorptio syndrome.
		0-6 mo	2*	ND			
		7-12 mo	4*	ND			
		Children (mg/day)					
		1-3 yr	**6**	10			
		4-8 yr	**8**	15			
		Males (mg/day)					
		9-13 yr	**12**	20			
		14-18 yr	**16**	30			
		19-21 yr	**16**	35			
		Females (mg/day)					
		9-13 yr	**12**	20			
		14-18 yr	**14**	30			
		19-21 yr	**14**	35			
		Pregnancy (mg/day)					
		≤18 yr	**18**	30			
		19-21 yr	**18**	35			
		Lactation (mg/day)					
		≤18 yr	**17**	30			
		19-21 yr	**17**	35			
Pantothenic acid (vitamin B_5)	Coenzyme in fatty acid metabolism	*Infants* (mg/day)			Chicken, beef, potatoes, oats, cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli, whole grains	No adverse effects associated with pantothenic acid from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intakes. Because data on adverse effects of pantothenic acid are limited, caution may be warranted.	None
		0-6 mo	1.7*	ND			
		7-12 mo	1.8*	ND			
		Children (mg/day)					
		1-3 yr	2*	ND			
		4-8 yr	3*	ND			
		Males (mg/day)					
		9-13 yr	4*	ND			
		14-18 yr	5*	ND			
		19-21 yr	5*	ND			
		Females (mg/day)					
		9-13 yr	4*	ND			
		14-18 yr	5*	ND			
		19-21 yr	5*	ND			
		Pregnancy (mg/day)					
		≤18 yr	6*	ND			
		19-21 yr	6*	ND			
		Lactation (mg/day)					
		≤18 yr	7*	ND			
		19-21 yr	7*	ND			
Riboflavin (vitamin	Coenzyme in	*Infants* (mg/day)			Organ meats,	No adverse	None

B_2)	numerous redox reactions	0-6 mo	0.3*	ND	milk, bread products, fortified cereals	effects associated with vitamin B_2 consumption from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intake. Because data on adverse effects of vitamin B_2 are limited, caution may be warranted.	
		7-12 mo	0.4*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	ND			
		4-8 yr	**0.6**	ND			
		Males (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.3**	ND			
		19-21 yr	**1.3**	ND			
		Females (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.0**	ND			
		19-21 yr	**1.1**	ND			
		Pregnancy (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
		Lactation (mg/day)					
		≤18 yr	**1.6**	ND			
		19-21 yr	**1.6**	ND			
Thiamin (vitamin B_1 , aneurin)	Coenzyme in metabolism of carbohydrates and branched-chain amino acids	*Infants* (mg/day)			Enriched, fortified, or whole-grain products, bread and bread products, mixed foods whose main ingredient is grain, ready-to-eat cereals	No adverse effects associated with vitamin B_1 consumption from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intake. Because data on adverse effects of vitamin B_1 are limited, caution may be warranted.	Persons who have increase for vitamin B those being t with hemodia persons with malabsorptio syndrome.
		0-6 mo	0.2*	ND			
		7-12 mo	0.3*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	ND			
		4-8 yr	**0.6**	ND			
		Males (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.2**	ND			
		19-21 yr	**1.2**	ND			
		Females (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.0**	ND			
		19-21 yr	**1.1**	ND			
		Pregnancy (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
		Lactation (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
Vitamin A Includes provitamin A carotenoids that are dietary precursors of retinol Given as	Required for normal vision, gene expression, reproduction, embryonic development, and immune function	*Infants* (µg/day)			Liver, dairy products, fish, dark-colored fruit, leafy vegetable	Teratologic effects, liver toxicity (from preformed vitamin A only)	Persons w alcohol ir preexistir disease, hyperlipi severe pr malnutriti be distinc
		0-6 mo	400*	600			
		7-12 mo	500*	600			
		Children (µg/day)					
		1-3 yr	**300**	600			
		4-8 yr	**400**	900			
		Males (µg/day)					

retinol activity equivalents (RAEs) 1 RAE = 1 µg retinol, 12 µg β-carotene, 24 µg α-carotene, or 24 µg β-cryptoxanthin To calculate RAEs from REs of provitamin A carotenoids in food, divide REs by 2. For preformed vitamin A in food or supplements and for provitamin A carotenoids in supplements, 1 RE = 1 RAE		9-13 yr	**600**	1,700			susceptib adverse e excess pr vitamin A β-Caroter suppleme advised o serve as a provitami source fo at risk for A deficie
		14-18 yr	**900**	2,800			
		19-21 yr	**900**	3,000			
		Females (µg/day)					
		9-13 yr	**600**	1,700			
		14-18 yr	**700**	2,800			
		19-21 yr	**700**	3,000			
		Pregnancy (µg/day)					
		≤18 yr	**750**	2,800			
		19-21 yr	**770**	3,000			
		Lactation (µg/day)					
		≤18 yr	**1,200**	2,800			
		19-21 yr	**1,300**	3,000			
Pyridoxine (vitamin B_6) Comprises a group of 6 related compounds: pyridoxal, pyridoxine, pyridoxamine, and 5′-phosphates (PLP, PNP, PMP)	Coenzyme in metabolism of amino acids, glycogen, and sphingoid bases	*Infants* (mg/day)			Fortified cereals, organ meats, fortified soy-based meat substitutes	No adverse effects associated with vitamin B_6 from food have been reported; this does not mean there is no potential for adverse effects resulting from high intake. Because data on adverse effects of vitamin B_6 are limited, caution may be warranted. Sensory neuropathy has occurred from high intakes of supplemental forms.	None
		0-6 mo	0.1*	ND			
		7-12 mo	0.3*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	30			
		4-8 yr	**0.6**	40			
		Males (mg/day)					
		9-13 yr	**1.0**	60			
		14-18 yr	**1.3**	80			
		19-21 yr	**1.3**	100			
		Females (mg/day)					
		9-13 yr	**1.0**	60			
		14-18 yr	**1.2**	80			
		19-21 yr	**1.3**	100			
		Pregnancy (mg/day)					
		≤18 yr	**1.9**	80			
		19-21 yr	**1.9**	100			
		Lactation (mg/day)					
		≤18 yr	**2.0**	80			
		19-21 yr	**2.0**	100			
Cobalamin (vitamin B_{12})	Coenzyme in nucleic acid	*Infants* (µg/day)			Fortified cereals,	No adverse effects have	Because 10–3 older people

	metabolism Prevents megaloblastic anemia	0-6 mo	0.4*	ND	meat, fish, poultry	been associated with consumption of the amounts of vitamin B_{12} normally found in food or supplements; this does not mean there is no potential for adverse effects resulting from high intake. Because data on adverse effects of vitamin B_{12} are limited, caution may be warranted.	malabsorb fo vitamin B_{12} , >50 yr are ad meet their RI mainly by co foods fortifie vitamin B_{12} c supplement c vitamin B_{12} .
		7-12 mo	0.5*	ND			
		Children (µg/day)					
		1-3 yr	**0.9**	ND			
		4-8 yr	**1.2**	ND			
		Males (µg/day)					
		9-13 yr	**1.8**	ND			
		14-18 yr	**2.4**	ND			
		19-21 yr	**2.4**	ND			
		Females (µg/day)					
		9-13 yr	**1.8**	ND			
		14-18 yr	**2.4**	ND			
		19-21 yr	**2.4**	ND			
		Pregnancy (µg/day)					
		≤18 yr	**2.6**	ND			
		19-21 yr	**2.6**	ND			
		Lactation (µg/day)					
		≤18 yr	**2.8**	ND			
		19-21 yr	**2.8**	ND			
Vitamin C (ascorbic acid, dehydroascorbic acid)	Cofactor for reactions requiring reduced copper or iron metalloenzyme and as a protective antioxidant	*Infants* (mg/day)			Citrus fruit, tomatoes, tomato juice, potatoes, Brussels sprouts, cauliflower, broccoli, strawberries, cabbage, spinach	GI disturbances, kidney stones, excess iron absorption	Smokers additiona mg/day o C over th needed by nonsmoke Nonsmok regularly to tobacco should en they meet RDA for C.
		0-6 mo	40*	ND			
		7-12 mo	50*	ND			
		Children (mg/day)					
		1-3 yr	**15**	400			
		4-8 yr	**25**	650			
		Males (mg/day)					
		9-13 yr	**45**	1,200			
		14-18 yr	**75**	1,800			
		19-21 yr	**90**	2,000			
		Females (mg/day)					
		9-13 yr	**45**	1,200			
		14-18 yr	**65**	1,800			
		19-21 yr	**75**	2,000			
		Pregnancy (mg/day)					
		≤18 yr	**80**	1,800			
		19-21 yr	**85**	2,000			
		Lactation (mg/day)					
		≤18 yr	**115**	1,800			
		19-21 yr	**120**	2,000			
Vitamin E (α-tocopherol α-Tocopherol includes *RRR*-α- tocopherol, the only form of α-tocopherol that	A metabolic function has not yet been identified. Vitamin E's major function appears to be	*Infants* (mg/day)			Vegetable oil, unprocessed cereal grains, nuts, fruit, vegetables, meat	No evidence of adverse effects from consuming vitamin E naturally occurring in food	Patients recei anticoagulant should be mo when taking supplements.
		0-6 mo	4*	ND			
		7-12 mo	5*	ND			
		Children (mg/day)					
		1-3 yr	**6**	200			
		4-8 yr	**7**	300			
		Males (mg/day)					

occurs naturally in foods, and the *2R* -stereoisomeric forms of α-tocopherol (*RRR*- , *RSR*- , RRS-, and *RSS*- α-tocopherol) that occur in fortified foods and supplements It does not include the *2S* -stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements	as a nonspecific chain-breaking antioxidant.	9-13 yr	**11**	600		Adverse effects from vitamin E–containing supplements may include hemorrhagic toxicity. UL for vitamin E applies to any form of α-tocopherol obtained from supplements, fortified foods, or a combination of these.	
		14-18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Females (mg/day)					
		9-13 yr	**11**	600			
		14-18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Pregnancy (mg/day)					
		≤18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Lactation (mg/day)					
		≤18 yr	**19**	800			
		19-21 yr	**19**	1,000			
Vitamin K	Coenzyme during synthesis of many proteins involved in blood clotting and bone metabolism	*Infants* (µg/day)			Green vegetables (collards, spinach, salad greens, broccoli), Brussels sprouts, cabbage, plant oil, margarine	No adverse effects associated with vitamin K consumption from food or supplements have been reported in humans or animals; this does not mean there is no potential for adverse effects resulting from high intake. Because data on adverse effects of vitamin K are limited, caution may be warranted.	Patients recei anticoagulant should monit vitamin K int
		0-6 mo	2.0*	ND			
		7-12 mo	2.5*	ND			
		Children (µg/day)					
		1-3 yr	30*	ND			
		4-8 yr	55*	ND			
		Males (µg/day)					
		9-13 yr	60*	ND			
		14-18 yr	75*	ND			
		19-21 yr	120*	ND			
		Females (µg/day)					
		9-13 yr	60*	ND			
		14-18 yr	75*	ND			
		19-21 yr	90*	ND			
		Pregnancy (µg/day)					
		≤18 yr	75*	ND			
		19-21 yr	90*	ND			
		Lactation (µg/day)					
		≤18 yr	75*	ND			
		19-21 yr	90*	ND			

[*] Adequate intake. *RDA for vitamin D in IU/day: 400 if <1 yr age, 600 if >1 yr, lactating, or pregnant.

Note: Starred (*) numbers are AI, and **bold** numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97–98% of members in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake.

UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, or inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

ND amounts are not determinable because of a lack of data of adverse effects in this age-group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

AI, Adequate intake; GI, gastrointestinal; ND, not determinable; PLP, pyridoxal phosphate; PMP, pyridoxamine phosphate; PNP, pyridoxine phosphate; RDA, recommended dietary allowance; UL, upper limit of normal.

Data from Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride, 1997; Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6 , folate, vitamin B_{12} , pantothenic acid, biotin, and choline, 1998; Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids, 2000; Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc, 2001; Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids, 2002/2005; Dietary reference intakes for calcium and vitamin D, 2011. These reports may be accessed via www.nap.edu . Accessed on January 18, 2017.

Breast milk provides optimal intake of most nutrients, including iron and zinc. Although present in lower amounts compared with infant formula, iron and zinc are more bioavailable and are sufficient to meet infant needs until approximately 4-6 mo of age. After 4-6 mo, iron and zinc are required from complementary foods, such as iron-fortified cereal and pureed meats.

Iron

Iron requirements are relatively higher during infancy and childhood than later in life and are higher for menstruating females than for males of similar age-groups (see Chapter 67). Iron present in animal protein is more bioavailable than that found in vegetables and other foods because it is already incorporated into heme moieties in blood and muscle. **Iron deficiency** is the most common micronutrient deficiency in the world and is associated with iron-deficiency anemia and neurocognitive deficits in some children. **Zinc deficiency** affects millions of children and is associated with increased risk for impaired linear growth (stunting), impaired immune function, and increased risk for respiratory and diarrheal diseases.

Vitamin D

Breast milk is a poor source of vitamin D. Vitamin D insufficiency is more common than previously thought in infants and children. Vitamin D is central to calcium and bone metabolism but is also an important determinant of various nonosseous health outcomes (see Chapter 64). Children of all ages with darker skin and those who do not consume fortified dairy products should be screened for vitamin D deficiency. The DRI for vitamin D is based on its effects on calcium status and bone health. The goal is to achieve serum 25-hydroxyvitamin D levels >50 nmol/L (30 ng/dL). The American Academy of Pediatrics (AAP) recommends total vitamin D intake of 400 IU/day for infants and children. A supplement is recommended for all breastfed infants to ensure sufficient intake. In 2010, IOM increased the RDA of vitamin D to 600 units daily for healthy children 1-18 yr of age.

Calcium

Calcium is key to bone health. Adequacy is determined in part by bone mineral content and bone mineral density (BMD). The main storage organs for calcium are the bones and teeth. Bone mineral accretion occurs primarily during childhood, with peak bone mass being achieved by the 2nd to 3rd decade of life. Calcium recommendations vary by age and were updated in 2011. These changes include a change from an AI to RDA, in terms of strength of evidence for recommendations, and increased UL in 9-18 yr olds (Table 55.6). There are no adequate biomarkers to assess calcium status in healthy children, because serum calcium is tightly regulated (regardless of intake and total body calcium) by changes in parathyroid hormone and calcitriol levels. Maintaining adequate serum calcium level despite inadequate intake could come at the expense of BMD. Therefore, in the long term, reduced BMD could serve as a surrogate marker of calcium intake and status. It is important to note that other variables influence BMD. Assessments of calcium status should include calcium intake in the diet. It is also important to educate families on additional and alternative sources of calcium (including calcium supplementation) if calcium intake is determined to be low.

Table 55.6

Dietary Reference Intakes for Select Micronutrients and Water

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	AI (mg/day)	UL (mg/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPEC CONS
Sodium	Maintains fluid volume outside of cells and thus normal cell function	*Infants*			Processed foods with added sodium chloride (salt), benzoate, phosphate; salted meats, bread, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table Salt is about 40% sodium by weight.	Hypertension Increased risk of cardiovascular disease and stroke	AI ab nu ad oth an ne los en rec lev act Pe in hig hu res ex mi tha UL ap he wi hy thu hig wh hy wh car pro
		0-6 mo	120	ND			
		7-12 mo	370	ND			
		Children					
		1-3 yr	1,000	1,500			
		4-8 yr	1,200	1,900			
		Males					
		9-13 yr	1,500	2,200			
		14-21 yr	1,500	2,300			
		Females					
		9-13 yr	1,500	2,200			
		13-21 yr	1,500	2,300			
		Pregnancy and Lactation					
		≥14 yr	1,500	2,300			
Chloride	With sodium, maintains fluid volume outside of cells and thus normal cell function	*Infants*			Processed foods with added sodium chloride (salt), benzoate, phosphate; salted	In concert with sodium, results in hypertension	Ch us so as vo dia AI eq am
		0-6 mo	180	ND			
		7-12 mo	570	ND			
		Children					
		1-3 yr	1,500	2,300			
		4-8 yr	1,900	2,900			
		Males					
		9-13 yr	2,300	3,400			

		14-21 yr	2,300	3,600	meats, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table Salt is about 60% chloride by weight.		be so co ch
		Females					
		9-13 yr	2,300	3,400			
		13-21 yr	2,300	3,600			
		Pregnancy and Lactation					
		≥14 yr	2,300	3,600			
Potassium	Maintains fluid volume inside/outside of cells and thus normal cell function; acts to blunt the rise of blood pressure in response to excess sodium intake, and decrease markers of bone turnover and recurrence of kidney stones	*Infants*			Fruits and vegetables, dried peas, dairy products, meats, nuts	None documented from food alone, but potassium from supplements or salt substitutes can result in hyperkalemia and possibly sudden death if excess is consumed by persons with chronic renal insufficiency (kidney disease) or diabetes.	Perso for ca diseas inhibit potass diureti carefu consu contai and m consu AI.
		0-6 mo	400	None set			
		7-12 mo	700				
		Children					
		1-3 yr	3,000	No UL			
		4-8 yr	3,800				
		Males					
		9-13 yr	4,500				
		14-21 yr	4,700				
		Females					
		9-13 yr	4,500				
		13-21 yr	4,700				
		Pregnancy					
		≥14 yr	4,700				
		Lactation					
		≥14 yr	5,100				
Vitamin D (calciferol) 1 µg calciferol = 40 IU vitamin D DRI values are based on absence of adequate exposure to sunlight.	Maintains serum calcium and phosphorus concentrations	*Infants (µg/day)* *			Fish liver oils, flesh of fatty fish, liver and fat from seals and polar bears, eggs from hens that have been fed vitamin D, fortified milk products, fortified cereals	Elevated plasma 25(OH)D concentration causing hypercalcemia	Patien glucoc might additi
		0-6 mo	10	**25**			
		7-12 mo	10	**38**			
		Children (µg/day) *					
		1-3 yr	**15**	**63**			
		4-8 yr	**15**	**75**			
		Males (µg/day) *					
		9-21 yr	**15**	**100**			
		Females (µg/day) *					
		9-21 yr	**15**	**100**			
		Pregnancy (µg/day) *					
		≤18 yr	15	**100**			
		Lactation (µg/day)					
		≤18 yr	15	**100**			
		19-21 yr	**15**	**100**			
Calcium	Essential role in blood clotting, muscle contraction, nerve transmission, and bone and tooth formation	*Infants*			Milk, cheese, yogurt, corn tortillas, calcium-set tofu, Chinese cabbage, kale, broccoli	Kidney stones, hypercalcemia, milk alkali syndrome, renal insufficiency	Amen (exerc nervos reduce absor
		0-6 mo	200	**1,000**			
		7-12 mo	260	**1,500**			
		Children					
		1-3 yr	**700**	**2,500**			
		4-8 yr	**1,000**	**2,500**			
		Males					
		9-18 yr	**1,300**	3,000			
		19-21 yr	**1,000**	**2,500**			
		Females					

		9-18 yr	**1,300**	**3,000**			
		19-21 yr					
		Pregnancy					
		≤18 yr	**1,300**	**3,000**			
		19-21 yr	**1,000**	**2,500**			
		Lactation					
		≤18 yr	**1,300**	**3,000**			
		19-21 yr	**1,000**	**2,500**			
Iron	Critical component of enzymes, cytochromes, myoglobin, and hemoglobin	*Infants*			Heme sources: meat, poultry, fish Nonheme sources: dairy, eggs, plant-based foods, breads, cereals, breakfast foods	GI distress	Pe de aci inc de Co po bio an rec ch olc Ne de rep inf de RI inc me to los me Ve ve rec su or for GI inc los ble Irc ca zir an su be do sta
		0-6 mo	0.27	40			
		7-12 mo	**11**	40			
		Children					
		1-3 yr	**7**	40			
		4-8 yr	**10**	40			
		Males					
		9-13 yr	**8**	40			
		14-18 yr	**11**	45			
		19-21 yr	**8**	45			
		Females					
		9-13 yr	**8**	40			
		14-18 yr	**15**	45			
		19-21 yr	**18**	45			
		Pregnancy					
		≤18 yr	**27**	45			
		19-21 yr	**27**	45			
		Lactation					
		≤18 yr	**10**	45			
		19-21 yr	**9**	45			
Zinc	Essential for proper growth and development; important catalyst for 100	*Infants*			Meats, shellfish, legumes, fortified cereals, whole grains	Acutely, zinc supplements cause GI irritation and headache; chronic effects of zinc supplementation	Zi int iro an the su
		0-6 mo	2	4			
		7-12 mo	**3**	5			
		Children					
		1-3 yr	**3**	7			

	specific enzymes	4-8 yr	**5**	12		include impaired immune function, changes in lipoprotein and cholesterol levels, and reduced copper status.	be do sta Zi ca wi im gr
		Males					
		9-13 yr	**8**	23			
		14-18 yr	**11**	34			
		19-21 yr	**11**	40			
		Females					
		9-13 yr	**8**	23			
		14-18 yr	**9**	34			
		19-21 yr	**8**	40			
		Pregnancy					
		≤18 yr	**12**	34			
		19-21 yr	**11**	40			
		Lactation					
		≤18 yr	**13**	34			
		19-21 yr	**12**	40			
Water	Maintains homeostasis in the body Allows transport of nutrients to cells and removal and excretion of waste products of metabolism	*Infants* (L/day)			All beverages, including water Moisture in foods High-moisture foods include watermelon, meats, and soups	No UL because normally functioning kidneys can handle >0.7 L (24 oz) of fluid per hour Symptoms of water intoxication include hyponatremia, which can result in heart failure, and rhabdomyolysis (skeletal muscle tissue injury), which can lead to kidney failure.	Re int ar me ge pe ad hy Pe ad hy ab the AI fo ter cli Al co wa be co so wa mo fo M ac ab tot Th co be me ad ma hy
		0-6 mo	0.7	None set			
		7-12 mo	0.8				
		Children					
		1-3 yr	1.3				
		4-8 yr	1.7				
		Males (L/day)					
		9-13 yr	2.4				
		14-18 yr	3.3				
		≥19 yr	3.7				
		Females (L/day)					
		9-13 yr	2.1				
		14-18 yr	2.3				
		≥19 yr	2.7				
		Pregnancy (L/day)					
		≥14 yr	3.0				
		Lactation (L/day)					
		≥14 yr	3.8				

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[*] Vitamin D RDA in IU/day: 40 if <1 yr, 600 if >1 yr of age or pregnant or lactating.

Note: **Bold** numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97–98% of members in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of a group, but lack of data prevents specifying with confidence the percentage covered by this intake.

UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, or inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

ND amounts are not determinable because of a lack of data on adverse effects in this age-group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

ACE, Angiotensin-converting enzyme; AI, adequate intake; ARB, angiotensin receptor blocker; GI, gastrointestinal; ND, not determinable; RDA, recommended dietary allowance; UL, upper limit of normal.

Adapted from Food and Nutrition Board, US Institute of Medicine: *Dietary reference intakes for water, potassium, sodium, chloride, and sulfate* (website). http://www.nap.edu/openbook.php?record_id=10925 ; and Ross AC, US Institute of Medicine, Committee to Review Dietary Reference Intakes for Vitamin D and Calcium: *Dietary reference intakes: calcium, vitamin D,* Washington, DC, 2011, National Academies Press, pp xv, 536.

Vitamin K

Vitamin K is an important determinant of bone health and an important cofactor for coagulation factors (factors II, VII, IX, and X; protein C and S) (see Chapter 66).

Electrolytes

Potassium (K^+) and sodium (Na^+) are the main intra- and extracellular cations, respectively, and are involved in transport of fluids and nutrients across the cellular membrane. The AI for **potassium** is related to its effects in maintaining a healthy blood pressure, reducing risk for nephrolithiasis, and supporting bone health. Moderate potassium deficiency occurs even in the absence of hypokalemia and can result in increased blood pressure, stroke, and other CV disease.

Most American children have potassium intake below the current recommendations, and blacks have lower potassium intake than whites. For people at increased risk of hypertension and who are salt sensitive, reducing sodium intake and increasing potassium intake is advised. Leafy green vegetables, vine fruit (e.g., tomatoes, eggplant, zucchini, pumpkin) and root vegetables (e.g., yams, beets) are good sources of potassium (see Table 55.6).

People with impaired renal function may need to reduce potassium intake, because hyperkalemia can increase risk for fatal cardiac arrhythmias among these patients.

Most dietary **sodium** (as sodium chloride, or table salt) in the United States is found in processed foods, breads, and condiments (Fig. 55.5). Sodium salt is added to foods to serve as a food preservative and enhance palatability. Sodium has an AI, but given the risk of table salt–related hypertension, an UL has also been set. The UL threshold may be even lower in blacks, who on average are more sodium salt sensitive, and for those with hypertension or preexisting renal disease. Dietary sodium intake also displaces potassium intake. Elevated sodium:potassium ratios can increase the risk for nephrolithiasis. Intakes of <2,300 mg (approximately 1 tsp) per day are recommended. The average daily salt intake for most people in the United States and Canada exceeds both the AI and UL. For populations with or at risk for hypertension and renal disease, *sodium intake should be decreased to <1,500 mg/day and potassium intake increased to >4,700 mg/day.* For persons with hypertension, additional dietary guidelines are available from the Dietary Approaches to Stop Hypertension (DASH) eating plan.

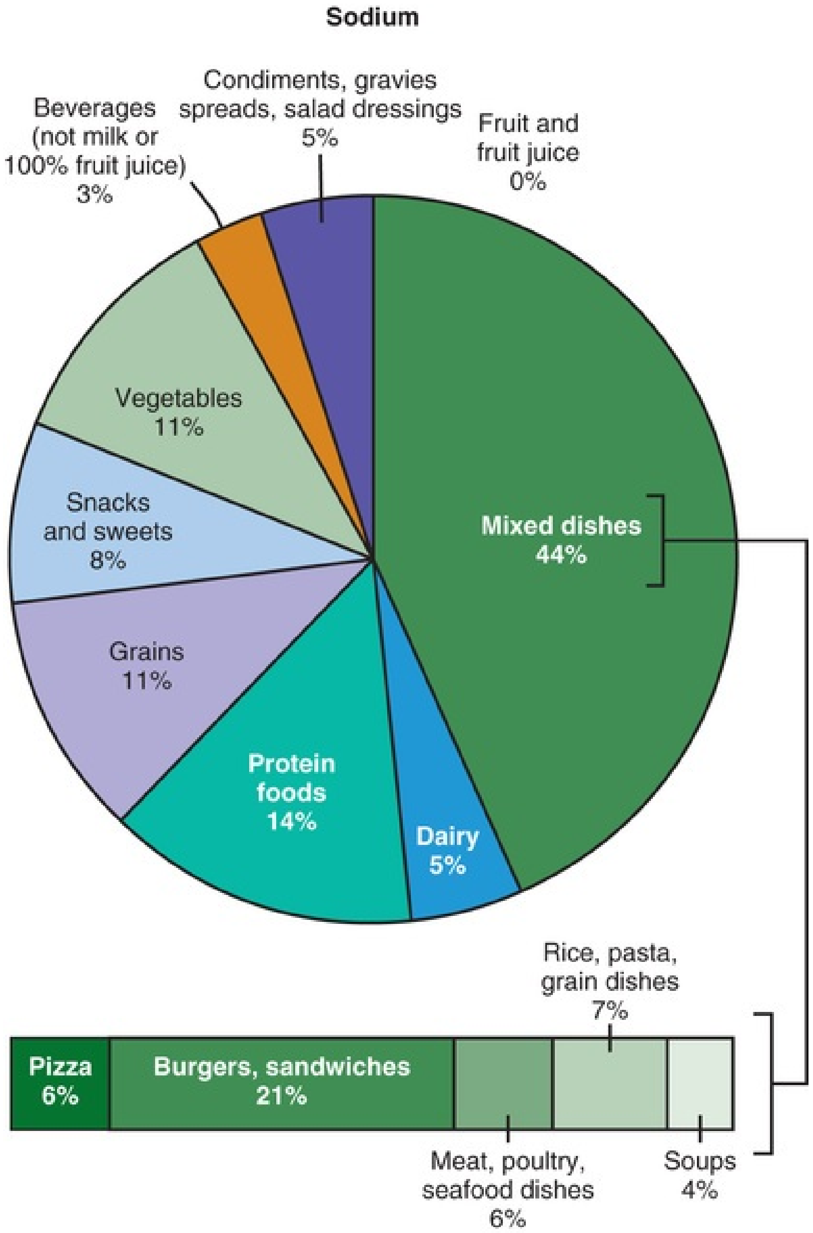

FIG. 55.5 Food category sources of sodium in the U.S. population age 2 yr and older. Estimates based on day 1 dietary recalls from WWEIA, NHANES, 2009–2010. (From What We Eat in America (WWEIA) category analysis for the 2015 Dietary Guidelines Advisory Committee. https://health.gov/dietaryguidelines/2015/guidelines/chapter-2/a-closer-look-at-current-intakes-and-recommended-shifts/#figure-2-14 .)

Water

The daily water requirement and water content as a proportion of body weight are highest in infants and decrease with age. Water intake is achieved with liquid and food intake, and losses include excretion in the urine and stool as well as insensible and evaporative losses through the skin and respiratory tract. An AI has been established for water (see Table 55.6). Special considerations are required by life stages and by BMR, physical activity, body proportions (surface area to volume), environment, and underlying medical conditions. Breast milk and infant formula provide adequate water, and additional water or other fluid intake is not required until complementary foods are introduced. Water contains no calories; the concern is that water intake will decrease breast milk intake and displace the intake of essential nutrients during this phase of rapid rate of growth and metabolically very active life stage. The relatively higher fluid needs of infants and young children can be explained in part by the high ratio of body surface area to volume in infancy, high respiratory rate, and period of rapid growth.

The consequences of inadequate fluid intake include impaired thermoregulation and heat dissipation, reduced activity tolerance and performance, and reduced intravascular fluid and dehydration. This inadequate fluid intake may be reflected by decreased urine input. These deficits can result in an increased compensatory heart rate, hypotension, and syncope, and if uncorrected, renal injury or nephrolithiasis. “Free water” is defined as water in the body that can be removed by ultrafiltration and in which substances can be dissolved. Excess free water intake is usually better tolerated by healthy adults than by younger children, who are at increased risk for **water intoxication** . Hyponatremia can result from excess free water intake coupled with inadequate sodium intake. Fluid intake requirements and restrictions are also influenced by any underlying renal and hormonal disorders, including diabetes, the syndrome of inappropriate antidiuretic hormone secretion, and diabetes insipidus.

Measuring Nutritional Adequacy

The U.S. Centers for Disease Control and Prevention (CDC) and AAP recommend the use of the WHO charts to monitor growth of all infants and children (breastfed and bottle-fed or infant formula–fed) from birth to 2 yr, and the use of the CDC 2000 growth charts for children 2-20 yr (see Chapters 18 and 27). The WHO growth charts are derived from longitudinal and cross-sectional data obtained from a sample of healthy breastfed infants and children (0-5 yr) who were receiving adequate nutritional intake and medical care in Brazil, Ghana, India, Norway, Oman, and the United States. Consequently, the WHO growth charts are not only descriptive of population average and distribution, but also describe growth of adequately nourished healthy children under best-care practices.

In the clinical setting, the 2.3rd and 97.7th percentiles on the WHO growth charts are used to identify *insufficient* and *excessive* growth from birth to 2 yr, respectively. In contrast, the 5th and 95th percentiles are recommended for the equivalent identification in the CDC growth charts from 2-20 yr (Table 55.7). Note that length, weight, and weight-for-length are used in the WHO growth charts from birth to 2 yr. *Body mass index* (BMI) can be calculated but is not recommended for use in children <2 yr. Stature, weight, and BMI are used in the CDC 2000 growth charts from 2-20 yr of age. These charts can be used to categorize children 2-20 yr as *underweight* (<5th BMI percentile), normal weight (5–85th), overweight (85–95th), and obese (≥95th BMI percentile). Severe obesity is defined as BMI ≥120% of the 95th percentile, or BMI ≥35 kg/m^2 (whichever is lower). This assessment corresponds to approximately the 99th percentile or a BMI *z* score ≥2.33. Severe obesity that exceeds the 99th percentile is tracked on a specialized percentile curve for obesity. Furthermore, adult classification is used for BMI ≥27 kg/m^2 in adolescents over age 18 for consideration of medication and bariatric surgery.

Table 55.7

Growth Chart Comparisons for Measuring Growth from Birth to 20 Years

GROWTH CHART	AGE RANGE	GROWTH METRICS	INSUFFICIENT GROWTH PERCENTILE	EXCESSIVE GROWTH PERCENTILE	BMI STATUS PERCENTILE
World Health Organization, 2006	Birth to 2 yr	Weight, length, weight-for-length, and head circumference	<2.3rd	>97.7th	—
US Centers for Disease Control and Prevention, 2000	2-20 yr	Weight, height, body mass index (BMI)	<5th	>95th	Under (<5th) Normal (5–85th) Over (85–95th) Obese (>95th) Severe Obesity (≥120% of 95th, or ≥35 kg/m^2)

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CHAPTER 56

Feeding Healthy Infants, Children, and Adolescents

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Early feeding and nutrition are of importance in the origin of adult diseases such as type 2 diabetes, hypertension, obesity, and the metabolic syndrome. Therefore, appropriate feeding practices should be established in the neonatal period and continued throughout childhood and adolescence to adulthood. Healthful feeding in children requires partnerships between family members, the healthcare system, schools, the community, and the government.

Feeding During the First Year of Life

Breastfeeding

The American Academy of Pediatrics (AAP) and World Health Organization (WHO) have declared breastfeeding and the administration of human milk to be the normative practice for infant feeding and nutrition. **Breastfeeding** has documented short- and long-term medical and neurodevelopmental advantages and rare contraindications (Tables 56.1 and 56.2 and Table 56.3). Thus the decision to breastfeed should be considered a public health issue and not only a lifestyle choice. The AAP and the WHO recommend that infants should be exclusively breastfed or given breast milk for 6 mo. Breastfeeding should be continued with the introduction of complementary foods for 1 yr or longer, as mutually desired by mother and infant. The success of breastfeeding initiation and continuation depends on multiple factors, such as education about breastfeeding, hospital breastfeeding practices and policies, routine and timely follow-up care, and family and societal support (Table 56.4 and Table 56.5).

Table 56.1

Selected Beneficial Properties of Human Milk Compared With Infant Formula

FACTOR	ACTION
ANTIBACTERIAL FACTORS	
Secretory IgA	Specific antigen-targeted antiinfective action
Lactoferrin	Immunomodulation, iron chelation, antimicrobial action, antiadhesive, trophic for intestinal growth
κ-Casein	Antiadhesive, bacterial flora
Oligosaccharides	Prevention of bacterial attachment
Cytokines	Antiinflammatory, epithelial barrier function
GROWTH FACTORS	
Epidermal growth factor	Luminal surveillance, repair of intestine
Transforming growth factor (TGF)	Promotes epithelial cell growth (TGF-β) Suppresses lymphocyte function (TGF-β)
Nerve growth factor	Promotes neural growth
ENZYMES	
Platelet-activating factor (PAF)–acetylhydrolase	Blocks action of PAF
Glutathione peroxidase	Prevents lipid oxidation
Nucleotides	Enhance antibody responses, bacterial flora

Adapted from Hamosh M: Bioactive factors in human milk, *Pediatr Clin North Am* 48:69–86, 2001.

Table 56.2

Absolute and Relative Contraindications to Breastfeeding Because of Maternal Health Conditions

MATERNAL HEALTH CONDITION	DEGREE OF RISK
HIV and HTLV infection	In the United States, breastfeeding is contraindicated. In other settings, health risks of not breastfeeding must be weighed against the risk of transmitting virus to the infant.
Tuberculosis infection	Breastfeeding is contraindicated until completion of approximately 2 wk of appropriate maternal therapy.
Varicella-zoster infection	Infant should not have direct contact to active lesions. Infant should receive immune globulin.
Herpes simplex infection	Breastfeeding is contraindicated with active herpetic lesions of the breast.
CMV infection	May be found in milk of mothers who are CMV seropositive. Transmission through human milk causing symptomatic illness in term infants is uncommon.
Hepatitis B infection	Infants routinely receive hepatitis B immune globulin and hepatitis B vaccine if mother is HBsAg positive. No delay in initiation of breastfeeding is required.
Hepatitis C infection	Breastfeeding is not contraindicated.

Alcohol intake	Limit maternal alcohol intake to <0.5 g/kg/day (for a woman of average weight, this is the equivalent of 2 cans of beer, 2 glasses of wine, or 2 oz of liquor).
Cigarette smoking	Discourage cigarette smoking, but smoking is not a contraindication to breastfeeding.
Chemotherapy, radiopharmaceuticals	Breastfeeding is generally contraindicated.

CMV, Cytomegalovirus; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

Data from Schanler RJ, Krebs NF, Mass SB, editors: *Breastfeeding handbook for physicians* , ed 2, Elk Grove Village, IL, 2014, American Academy of Pediatrics, pp 223–226.

Table 56.3

Conditions for Which Human Milk May Have a Protective Effect

Diarrhea
Otitis media
Urinary tract infection
Necrotizing enterocolitis
Septicemia
Infant botulism
Insulin-dependent diabetes mellitus
Celiac disease
Crohn disease
Childhood cancer
Lymphoma
Leukemia
Recurrent otitis media
Allergy
Hospitalizations
Infant mortality

Table 56.4

Ten Hospital Practices to Encourage and Support Breastfeeding* ‡

1. Have a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in the skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.

4. Help women initiate breastfeeding within 1 hour of birth.
5. Show women how to breastfeed and how to maintain lactation, even if they are separated from their newborns.
6. Give newborns no food or drink other than breast milk unless medically indicated.
7. Practice rooming-in; allow mothers and newborns to remain together 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no pacifiers or artificial nipples to breastfeeding infants. [†]
10. Foster the establishment of breastfeeding support groups and refer to them on discharge from the hospital or birth center.
COMPONENTS OF SAFE POSITIONING FOR THE NEWBORN WHILE SKIN-TO-SKIN [**]
1. Infant's face can be seen.
2. Infant's head is in “sniffing” position.
3. Infant's nose and mouth are not covered.
4. Infant's head is turned to one side.
5. Infant's neck is straight, not bent.
6. Infant's shoulders and chest face mother.
7. Infant's legs are flexed.
8. Infant's back is covered with blankets.
9. Mother-infant dyad is monitored continuously by staff in the delivery environment and regularly on the postpartum unit.
10. When mother wants to sleep, infant is placed in bassinet or with another support person who is awake and alert.

[*] The 1994 report of the Healthy Mothers, Health Babies National Coalition Expert Work Group recommend that the UNICEF-WHO Baby Friendly Hospital Initiative be adapted for use in the United States as the United States Breastfeeding Health Initiative, using the adapted ten hospital practices above.

[†] The American Academy of Pediatrics endorsed the UNICEF-WHO Ten Steps to Successful Breastfeeding, but does not support a categorical ban on pacifiers because of their role in reducing the risk of sudden infant death syndrome and their analgesic benefit during painful procedures when breastfeeding cannot provide the analgesia.

[‡] Data from Baby-Friendly USA. Guidelines and evaluation criteria for facilities seeking baby-friendly designation. Sandwich (MA): Baby Friendly USA, 2010. Available at https://www.babyfriendlyusa.org/for-facilities/practice-guidelines/. Accessed 10 December 2018. From ACOG Committee Opinion: Optimizing support for breastfeeding as part of obstetric practice. Obstet Gynecol 132(4):e187-e195, 2018 (Box 1, p. e191 and Box 2, p. e192).

[**] Data from Ludington-Hoe SM, Morgan K. Infant assessment and reduction of sudden unexpected postnatal collapse risk during skin-to-skin contact. Newborn Infant Nurs Rev 2014;14:28-33.

Table 56.5

Recommendations on Breastfeeding Management for Healthy Term Infants

1. Exclusive breastfeeding for about 6 months
    - Breastfeeding preferred; alternatively expressed mother's milk, or donor breast milk

- To continue for at least the first year and beyond as long as mutually desired by mother and child
- Complementary foods rich in iron and other micronutrients should be introduced at about 6 mo of age

2. Peripartum policies and practices that optimize breastfeeding initiation and maintenance should be compatible with the AAP and Academy of Breastfeeding Medicine Model Hospital Policy and include the following:
   - Direct skin-to-skin contact with mothers immediately after delivery until the first feeding is accomplished and encouraged throughout the postpartum period
   - Delay in routine procedures (weighing, measuring, bathing, blood tests, vaccines, and eye prophylaxis) until after the first feeding is completed
   - Delay in administration of intramuscular vitamin K until after the first feeding is completed but within 6 hr of birth
   - Ensure 8-12 feedings at the breast every 24 hr
   - Ensure formal evaluation and documentation of breastfeeding by trained caregivers (including position, latch, milk transfer, examination) at least once for each nursing shift
   - Give no supplements (water, glucose water, commercial infant formula, or other fluids) to breastfeeding newborn infants unless medically indicated using standard evidence-based guidelines for the management of hyperbilirubinemia and hypoglycemia
   - Avoid routine pacifier use in the postpartum period
   - Begin daily oral vitamin D drops (400 IU) at hospital discharge
3. All breastfeeding infants should be seen by a pediatrician within 48 to 72 hr after discharge from the hospital
   - Evaluate hydration and elimination patterns
   - Evaluate body weight gain (body weight loss no more than 7% from birth and no further weight loss by day 5: assess feeding and consider more frequent follow-up)
   - Discuss maternal/infant issues
   - Observe feeding
4. Mother and infant should sleep in proximity to each other to facilitate breastfeeding
5. Pacifier should be offered, while placing infant in back-to-sleep-position,

no earlier than 3 to 4 weeks of age and after breastfeeding has been established

From American Academy of Pediatrics (AAP): Breast-feeding and the use of human milk, *Pediatrics* 129:e827–e841, 2012.

Feedings should be initiated soon after birth unless medical conditions preclude them. Mothers should be encouraged to nurse at each breast at each feeding starting with the breast offered second at the last feeding. It is not unusual for an infant to fall asleep after the 1st breast and refuse the 2nd. It is preferable to empty the 1st breast before offering the 2nd to allow complete emptying of both breasts and therefore better milk production. Table 56.6 summarizes patterns of milk supply in the 1st week.

Table 56.6

Patterns of Milk Supply

DAY OF LIFE	MILK SUPPLY
Day 1	Some milk (~5 mL) may be expressed.
Days 2-4	Lactogenesis; milk production increases.
Day 5	Milk present; fullness and leaking are felt.
Day 6 onward	Breasts should feel “empty” after feeding.

Adapted from Neifert MR: Clinical aspects of lactation: promoting breastfeeding success, *Clin Perinatol* 26:281–306, 1999.

New mothers should be instructed about infant hunger cues, correct nipple latch, positioning of the infant on the breast, and feeding frequency. It is also suggested that someone trained in lactation observe a feeding to evaluate positioning, latch, milk transfer, maternal responses, and infant satiety. Attention to these issues during the birth hospitalization allows dialog with the mother and family and can prevent problems that could occur with improper technique or knowledge of breastfeeding. As part of the discharge teaching process, issues on infant feeding, elimination patterns, breast engorgement, breast care, and maternal nutrition should be discussed. A follow-up appointment is recommended within 24-48 hr after hospital discharge.

Nipple Pain

Nipple pain is one of the most common complaints of breastfeeding mothers in the immediate postpartum period. Poor infant positioning and improper latch are the most common reasons for nipple pain beyond the mild discomfort felt early in breastfeeding. If the problem persists and the infant refuses to feed, evaluation for nipple candidiasis is indicated. If candidiasis is present, the mother should be treated with an antifungal cream that is wiped off of the breast before feeding, and the infant treated with an oral antifungal medication.

Tongue-tie (ankyloglossia) has been associated with nipple pain, poor latching, and poor weight gain in breastfed and bottle-fed infants. *Frenotomy* is a minor surgical procedure with few complications and has been suggested as a treatment option for ankyloglossia. Nonetheless, there is considerable disagreement about the significance of ankyloglossia and the value of frenotomy. It is often difficult to assess the severity of ankyloglossia on physical examination; a combination of physical assessment and functional feeding difficulty is more useful. Nonetheless, about 50% of infants with ankyloglossia have no feeding problems, and most infants with nursing problems do not have ankyloglossia. Lactation consultants often recommend frenotomy, whereas pediatricians provide lactation management approaches and wait at least 2-3 wk before considering frenotomy. During that time many feeding issues resolve, thus avoiding frenotomy.

Engorgement

In the 2nd stage of lactogenesis, physiologic fullness of the breast occurs. Breasts may become engorged: firm, overfilled, and painful as the pattern and volume of milk production adjusts to the infant's feeding schedule. Incomplete removal of milk as a result of poor breastfeeding technique or infant illness can cause engorgement. Breastfeeding immediately at signs of infant hunger will eventually prevent this from occurring. To reduce engorgement, breasts should be softened before infant feeding with a combination of hot compresses and expression of milk. To reduce inflammation and pain, between feedings a supportive bra should be worn, cold compresses applied, and oral nonsteroidal antiinflammatory drugs (NSAIDs) administered.

Mastitis

Mastitis occurs in 2–3% of lactating women and is usually unilateral, manifesting with localized warmth, tenderness, edema, and erythema after the

2nd postdelivery week. Sudden onset of breast pain, myalgia, and fever with fatigue, nausea, vomiting, and headache can also occur. Organisms implicated in mastitis include *Staphylococcus aureus*, *Escherichia coli*, group A streptococcus, *Haemophilus influenzae*, *Klebsiella pneumoniae,* and *Bacteroides* species. Diagnosis is confirmed by physical examination. Oral antibiotics and analgesics, while promoting breastfeeding or emptying of the affected breast, usually resolve the infection. A **breast abscess** is a less common complication of mastitis, but it is a more serious infection that requires intravenous antibiotics and incision and drainage, along with temporary cessation of feeding from that breast.

Inadequate Milk Intake

Insufficient milk intake, dehydration, and jaundice in the infant can occur within the 1st week of life. Signs include lethargy, delayed stooling, decreased urine output, weight loss >7–10% of birth weight, hypernatremic dehydration, inconsolable crying, and increased hunger. Insufficient milk intake may be caused by insufficient milk production, failure of established breastfeeding, and health conditions in the infant that prevent proper breast stimulation. Parents should be counseled that breastfed neonates feed 8-12 times/day with a minimum of 8 times/day. Careful attention to prenatal history can identify maternal factors associated with this problem (failure of breasts to enlarge during pregnancy or within the 1st few days after delivery). Direct observation of breastfeeding can help identify improper technique. If a large volume of milk is expressed manually after breastfeeding, the infant might not be extracting enough milk, eventually leading to decreased milk output. Late preterm infants (34-36 wk) are at risk for insufficient milk syndrome because of poor suck and swallow patterns or medical issues.

Jaundice

Breastfeeding jaundice is related to insufficient fluid intake during the 1st week of life and is a common reason for hospital readmission of healthy breastfed infants (see Chapter 123.3). Breastfeeding jaundice is associated with dehydration and hypernatremia. **Breast milk jaundice** is a different disorder that causes persistently high serum indirect bilirubin in thriving healthy well-fed infants. Breast milk contains inhibitors of glucuronyl transferase and causes enhanced absorption of bilirubin from the gut. Breast milk jaundice becomes evident later than breastfeeding jaundice and generally declines in the 2nd to 3rd wk of life. Infants with severe or persistent jaundice should be evaluated for other medical causes. Persistently high bilirubin levels may require changing from breast milk to infant formula for 24-48 hr and/or treatment with phototherapy without cessation of breastfeeding. Breastfeeding should resume after the decline in serum bilirubin. Parents should be reassured and encouraged to continue collecting breast milk during the period the infant is taking formula.

Breast Milk Collection

The pumping of breast milk is a common practice when the mother and baby are separated. Good handwashing and hygiene should be emphasized. Electric breast pumps are generally more efficient and better tolerated by mothers than mechanical pumps or manual expression. Collection kits should be cleaned with hot soapy water, rinsed, and air-dried after each use. Glass or plastic containers should be used to collect the milk, and milk should be refrigerated and then used within 48 hr. Expressed breast milk can be frozen and used for up to 6 mo. Milk should be thawed rapidly by holding under running tepid water and used completely within 24 hr after thawing. *Milk should never be microwaved.*

Growth of the Breastfed Infant

The rate of weight gain of the breastfed infant differs from that of the formula-fed infant; the infant's risk for excess weight gain during late infancy may be associated with bottle feeding. The WHO growth charts are based on growth patterns of healthy breastfed infants through the 1st year of life. These standards (http://www.who.int/childgrowth) are the result of a study in which >8,000 children were selected from 6 countries. The infants were selected based on being breastfed, having good health care, high socioeconomic status, and nonsmoking mothers, so that they reflect the growth pattern of breastfed infants in optimal conditions and can be used as prescriptive rather than normative curves. Charts are available for growth monitoring. The U.S. Centers for Disease Control and Prevention (CDC) recommend use of the WHO growth charts for infants 0-23 mo of age and CDC growth charts for ages 24 mo to 20 yr (see Chapter 27).

Formula Feeding (Fig. 56.1)

Despite efforts to promote exclusive breastfeeding through 6 mo, <50% of women continue to breastfeed at 6 mo. Most women make their infant feeding choices early in pregnancy. Parental preference is the most common reason for using infant formula. However, infant formula is also indicated for infants whose intake of breast milk is contraindicated for infant factors (e.g., inborn errors of metabolism) and maternal factors (see Table 56.2). In addition, infant formula is used as a supplement to support inadequate weight gain in breastfed infants.

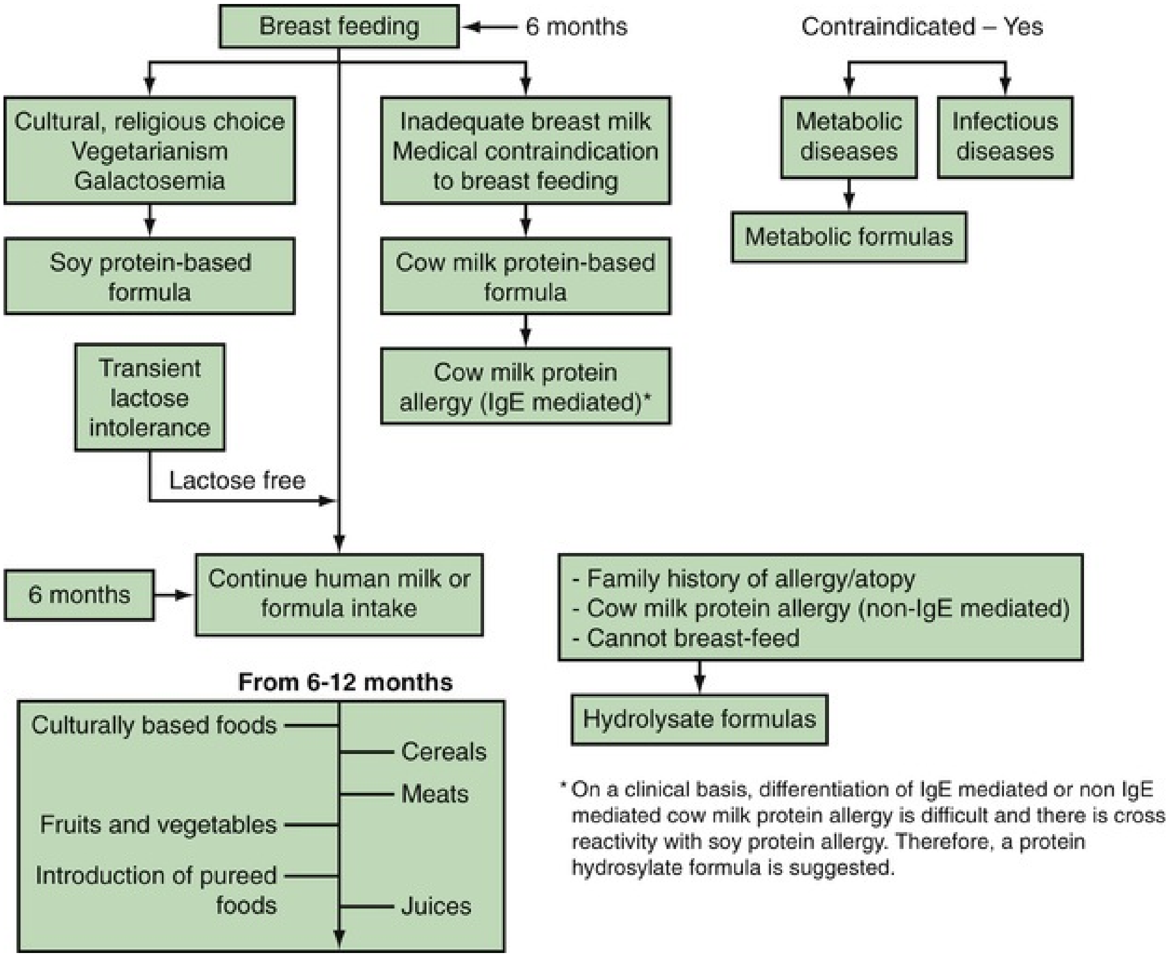
Breast feeding
6 months
Contraindicated – Yes
Cultural, religious choice
Vegetarianism
Galactosemia
Inadequate breast milk
Medical contraindication to breast feeding
Metabolic diseases
Infectious diseases
Metabolic formulas
Soy protein-based formula
Cow milk protein-based formula
Transient lactose intolerance
Cow milk protein allergy (IgE mediated)*
Lactose free
6 months
Continue human milk or formula intake
- Family history of allergy/atopy
- Cow milk protein allergy (non-IgE mediated)
- Cannot breast-feed
From 6-12 months
Hydrolysate formulas
Culturally based foods
Cereals
Meats
Fruits and vegetables
Introduction of pureed foods
Juices

* On a clinical basis, differentiation of IgE mediated or non IgE mediated cow milk protein allergy is difficult and there is cross reactivity with soy protein allergy. Therefore, a protein hydrosylate formula is suggested.

FIG. 56.1 **Feeding algorithm for term infants. (From Gamble Y, Bunyapen C, Bhatia J: Feeding the term infant. In Berdanier CD, Dwyer J, Feldman EB, editors: *Handbook of nutrition and food* , Boca Raton, FL, 2008, CRC Press, pp 271–284, Fig 15-3.)**

Infant formulas marketed in the United States are safe and nutritionally adequate as the sole source of nutrition for healthy infants for the 1st 6 mo of life. Infant formulas are available in ready-to-feed, concentrated liquid or powder forms. Ready-to-feed products generally provide 19-20 kcal/30 mL (1 oz) and approximately 64-67 kcal/dL. Concentrated liquid products, when diluted according to instructions, provide a preparation with the same concentration. Powder formulas come in single or multiple servings and when mixed according to instructions will result in similar caloric density.

Although infant formulas are manufactured in adherence to good manufacturing practices and are regulated by the U.S. Food and Drug Administration (FDA), there are potential safety issues. Ready-to-feed and concentrated liquid formulas are commercially sterile, but powder preparations are not. Although the number of bacterial colony-forming units per gram (CFU/g) of powder formula is generally lower than allowable limits, outbreaks of infections with *Cronobacter sakazakii* (previously *Enterobacter sakazakii*) have been documented, especially in premature infants. The powder preparations can contain other coliform bacteria but have not been linked to disease in healthy term infants. Care must be taken in following the mixing instructions to avoid over- or underdilution, to use boiled or sterilized water, and to use the specific scoops provided by the manufacturer because scoop sizes vary. Water that has been boiled should be allowed to cool fully to prevent degradation of heat-labile nutrients, specifically vitamin C. Well water should be tested regularly for bacteria and toxin contamination. Municipal water can contain variable concentrations of fluoride, and if the concentrations are high, bottled water that is defluoridated should be used to avoid toxicity.

Parents should be instructed to use proper handwashing techniques when preparing formula and feedings for the infant. Guidance on formula storage should also be given. Once opened, ready-to-feed and concentrated liquid containers can be covered with aluminum foil or plastic wrap and stored in the refrigerator for no longer than 48 hr. Powder formula should be stored in a cool, dry place; once opened, cans should be covered with the original plastic cap or aluminum foil, and the powdered product can be used within 4 wk. Once prepared, all bottles, regardless of type of formula, should be used within 24 hr. Formula should be used within 2 hr of removal from the refrigerator, and once a feeding has started, that formula should be used within 1 hr or be discarded. Prepared formula stored in the refrigerator should be warmed by placing the container in warm water for about 5 min. Formula should *not* be heated in a microwave because it can heat unevenly and result in burns, despite appearing to be at the right temperature when tested.

Formula feedings should be ad libitum, with the goal of achieving growth and development to the child's genetic potential. The usual intake to allow a weight gain of 25-30 g/day will be 140-200 mL/kg/day in the 1st 3 mo of life. The rate of weight gain declines from 3-12 mo of age.

Cow's Milk Protein–Based Formulas

Intact cow's milk protein–based formulas in the United States contain a protein concentration varying from 1.8-3 g/100 kcal (or 1.4-1.8 g/dL), considerably higher than in mature breast milk (1.2-1.3 g/100 kcal; 0.9-1.0 g/dL). This increased concentration is designed to meet the needs of the youngest infants, but leads to excess protein intake for older infants. In contrast, breast milk content varies over time to match protein needs at various ages. The whey:casein ratio varies in infant formula from 18 : 82 to 60 : 40; one manufacturer markets a formula that is 100% whey. The predominant whey protein is β-globulin in cow's milk and α-lactalbumin in human milk. This and other differences between human milk and cow's milk–based formulas result in different plasma amino acid profiles in infants on different feeding patterns, but clinical significance has not been demonstrated.

The primary source of fat in cow's milk protein–based infant formulas is plant or a mixture of plant and animal oils. Fat provides 40–50% of the energy in cow's milk–based formulas. Fat blends are better absorbed than dairy fat and provide saturated, monounsaturated, and polyunsaturated fatty acids (PUFAs). All infant formulas are supplemented with long-chain PUFAs, docosahexaenoic acid (DHA), and arachidonic acid (ARA) at varying concentrations. ARA and DHA are found at varying concentrations in human milk and vary by geographic region and maternal diet. DHA and ARA are derived from single-cell microfungi and microalgae and are classified as “generally recognized as safe” (GRAS) for use in infant formulas at approved concentrations and ratios. The routine supplementation of milk formula with long-chain PUFAs to improve the physical, neurodevelopmental, or visual outcomes of term infants cannot be recommended based on the current evidence.

Lactose is the major carbohydrate in breast milk and in standard cow's milk–based formulas for term infants. Formulas for term infants may also contain modified starch or other complex carbohydrates. Carbohydrates constitute 67-75 g/L of cow's milk–based formula.

Soy Formulas

Soy protein–based formulas on the market are all free of cow's milk–based protein and lactose. Carbohydrates are provided by sucrose, corn syrup solids, and maltodextrins to provide 67 kcal/dL. They meet the vitamin, mineral, and electrolyte guidelines from the AAP and the FDA for feeding term infants. The protein is a soy isolate supplemented with L -methionine, L -carnitine, and taurine to provide a protein content of 2.45-2.8 g/100 kcal, or 1.7-1.9 g/dL.

The quantity of specific fats varies by manufacturer and is usually similar to the manufacturer's corresponding cow's milk–based formula. The fat content is 5.0-5.5 g/100 kcal, or 3.4-3.6 g/dL. The oils used in both cow's milk and soy formula include soy, palm, sunflower, olein, safflower, and coconut. DHA and ARA are also added.

In term infants, although soy protein–based formulas have been used to provide nutrition resulting in normal growth patterns, there are few indications for use in place of cow's milk–based formula. Indications for soy formula include galactosemia, preference for a vegetarian diet, and hereditary lactase deficiency, because soy-based formulas are lactose free. Most healthy infants with acute gastroenteritis can be managed after rehydration with continued use of breast milk or cow's milk–based formulas and do not require a lactose-free formula, such as soy-based formula. However, soy protein–based formulas may be indicated when documented secondary lactose intolerance occurs. Soy protein–based formulas have no advantage over cow's milk protein–based formulas as a supplement for the breastfed infant, unless the infant has one of the indications noted previously, and are not recommended for preterm infants. The routine use of soy protein–based formula has no proven value in the prevention or management of infantile colic, fussiness, or atopic disease. Infants with documented cow's milk protein–induced enteropathy or enterocolitis often are also sensitive to soy protein. They should be provided formula derived from extensively hydrolyzed protein or synthetic amino acids. Soy formulas contain *phytoestrogens,* which have been shown to have physiologic activity in rodent models, but there is no conclusive evidence of adverse developmental effects in infants fed soy formula.

Protein Hydrolysate Formulas

Protein hydrolysate formulas may be *partially hydrolyzed* , containing oligopeptides with a molecular weight of <5000 daltons (range 3,000-10,000 Da), or *extensively hydrolyzed* , containing peptides with a molecular weight <3000 Da. Partially hydrolyzed proteins formulas have fat blends similar to cow's milk–based formulas, and carbohydrates are supplied by corn maltodextrin or corn syrup solids. Because the protein is not extensively hydrolyzed, these formulas should not be fed to infants who are allergic to cow's milk protein. In studies of formula-fed infants who are at high risk of developing atopic disease, there is modest evidence that childhood atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow's milk–based formula. Comparative studies of the various hydrolyzed formulas have also indicated that not all formulas have the same protective benefit. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed in preventing atopic disease. Extensively hydrolyzed formulas are recommended for infants intolerant to cow's milk or soy proteins. These formulas are lactose free and can include medium-chain triglycerides, making them useful in infants with gastrointestinal malabsorption as a consequence of cystic fibrosis, short gut syndrome, prolonged diarrhea, and hepatobiliary disease.

Amino Acid Formulas

Amino acid formulas are peptide-free formulas that contain mixtures of essential and nonessential amino acids. They are designed for infants with cow's milk–based protein allergy who failed to thrive on extensively hydrolyzed protein formulas. The effectiveness of amino acid formulas to prevent atopic disease has not been studied.

Milk and Other Fluids in Infants and Toddlers

Neither breastfed nor formula-fed infants require additional water unless dictated by a specific condition involving excess water loss, such as diabetes insipidus. Vomiting and spitting up are common in infants. When weight gain and general well-being are noted, no change in formula is necessary.

Whole cow's milk should not be introduced until 12 mo of age. In children 12-24 mo of age for whom overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or cardiovascular disease, the use of reduced-fat milk is appropriate. Otherwise, whole milk is recommended until age 24 mo, changing to 1% milk at 24 mo for healthy children. Regardless of the type, all animal milk consumed should be pasteurized. Infants and young children are particularly susceptible to infections such as *E. coli* , *Campylobacter* , and *Salmonella* found in **raw or unpasteurized milk** . For cultural and other reasons, such as parental preference, **goat's milk** is sometimes given in place of formula, although this is not recommended. Goat's milk has been shown to cause significant electrolyte disturbances and anemia because it has low folic acid concentrations.

Nondairy alternatives to milk from plant-based (e.g., soy, hemp, pea, rice) and nut-based (e.g., almond, cashew, peanut) sources have become popular. When counseling parents, it is important to emphasize that the overall nutritional content of plant-based milk alternatives *is not* equivalent to cow's milk. Although most are fortified with vitamin D and calcium, with the exception of some soy-, hemp-, and pea-based milk alternatives, most products have a lower protein content. Concurrently, plant-based products such as soy and rice milk tend to have added oils and sugars, giving them a higher energy content than cow's milk. Secondary to a lower protein content, these alternative milks *should not be given to infants.* Nut-based milks may be suitable to toddlers ≥24 mo of age without allergies who have an otherwise adequate diet.

Complementary Feeding

The timely introduction of **complementary foods** (solid and liquid foods other than breast milk or formula, also called **weaning foods**) during infancy is important for nutritional and developmental reasons (Table 56.7). The ability of exclusive breastfeeding to meet macronutrient and micronutrient requirements becomes limited with increasing age of the infant. The recommendation for timing of complementary food initiation is based on the benefits on neurodevelopment and prevention of future comorbidities from exclusive breastfeeding after 6 mo. The AAP, WHO, and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition all recommend exclusive breastfeeding for the 1st 6 mo. Similar data on the benefits of the exclusive use of formula for 6 mo have not been published.

Table 56.7

Important Principles for Weaning

Begin at 6 mo of age.
At the proper age, encourage a cup rather than a bottle.
Introduce 1 new food at a time.
Energy density should exceed that of breast milk.
Iron-containing foods (meat, iron-supplemented cereals) are required.
Zinc intake should be encouraged with foods such as meat, dairy products, wheat, and rice.
Phytate intake should be low to enhance mineral absorption.
Breast milk should continue to 12 mo of age; formula or cow's milk is then substituted.
Give no more than 24 oz/day of cow's milk.
Fluids other than breast milk, formula, and water should be discouraged.
Give no more than 4-6 oz/day of 100% fruit juice; no sugar-sweetened beverages.

Adapted from American Academy of Pediatrics: *Pediatric nutrition handbook* , ed 6, Elk Grove Village, IL, 2008, American Academy of Pediatrics.

Some foods are more nutritionally appropriate than others to complement breast milk or infant formula. The food consumption patterns of U.S. infants and toddlers demonstrate that almost all infants ≤12 mo consumed some form of milk every day; infants >4 mo consumed more formula than human milk, and by 9-11 mo, 20% consumed whole cow's milk and 25% consumed nonfat or reduced-fat milk.

The most common complementary foods between 4 and 11 mo of age are infant cereals. Almost 45% of infants between 9 and 11 mo of age consumed noninfant cereals. Infant eating patterns also vary, with up to 61% of infants 4-11 mo of age consuming no vegetables. French fries were the most frequently consumed vegetables in toddlers. Positive changes in the last decade include increased duration of breastfeeding, delayed introduction of complementary foods, and decreased juice consumption. Continuing concerns include lack of fruits and vegetables; diets low in iron, essential fatty acids, fiber, and whole grains; and diets high in saturated fat and sodium. Table 56.7 summarizes the AAP recommendations for initiating complementary foods.

The complementary foods should be varied to ensure adequate macro- and micronutrient intake. In addition to complementary foods introduced at 6 mo of age, continued breastfeeding or the use of infant formula for the entire 1st year of life should be encouraged. Overconsumption of energy-dense complementary foods can lead to excessive weight gain in infancy, resulting in an increased risk of obesity in childhood.

Feeding Toddlers and Preschool-Age Children

Toddlerhood is a period when eating behavior and healthful habits can be established and is often a confusing and anxiety-generating period for parents. Growth after the 1st year slows, motor activity increases, and appetite decreases. Birth weight triples during the 1st year of life and quadruples by the 2nd year, reflecting this slowing in growth velocity. Eating behavior is erratic, and the child appears distracted from eating as he explores the environment. Children consume a limited variety of foods and often only “like” a particular food for a period and then reject the favored food. The use of growth charts to demonstrate adequate growth and provide guidance about typical behavior and eating habits will help allay parents' concerns. Important goals of early childhood nutrition are to foster healthful eating habits and offer foods that are developmentally appropriate.

Feeding Practices

The period starting after 6 mo until 15 mo is characterized by the acquisition of self-feeding skills because the infant can grasp finger foods, learn to use a spoon, and eat soft foods (Table 56.8). Around 12 mo of age, the child learns to drink from a cup and may still breastfeed or desire formula bottle feeding. Bottle weaning should begin around 12-15 mo, and bedtime bottles should be discouraged because of the association with **dental carries** . Unless being used at mealtime, the sippy cup should only contain water to prevent caries. Sugar-sweetened beverages and 100% fruit juice should also be discouraged from being used in bottles in all infants at all times. Cups without a lid can be used for no more than 4-6 oz/day of 100% fruit juice for toddlers.

Table 56.8

Feeding Skills Birth to 36 Months

AGE (mo)	FEEDING/ORAL SENSORIMOTOR SKILLS
Birth to 4-6	Nipple feeding, breast or bottle Hand on bottle during feeding (2-4 mo) Maintains semiflexed posture during feeding Promotion of infant–parent interaction
6-9 (transition feeding)	Feeding more in upright position Spoon feeding thin, pureed foods Both hands to hold bottle Finger feeding introduced Vertical munching of easily dissolvable solids Preference for parents to feed
9-12	Cup drinking Eats lumpy, mashed food Finger feeding for easily dissolvable solids Chewing includes rotary jaw action
12-18	Self-feeding; grasps spoon with whole hand Holds cup with 2 hands Drinking with 4-5 consecutive swallows Holding and tipping bottle
>18-24	Swallowing with lip closure Self-feeding predominates Chewing broad range of food Up-down tongue movements
24-36	Circulatory jaw rotations Chewing with lips closed One-handed cup holding and open cup drinking with no spilling Using fingers to fill spoon Eating wide range of solid food Total self-feeding, using fork

Adapted from Arvedson JC: Swallowing and feeding in infants and young children. *GI Motility online,* 2006. doi:10.1038/gimo17.

Juices should not be given before 12 mo of age. The volume of juices should be limited to 4 oz/day in children 1-3 yr old, to 4-6 oz/day for 4-6 yr olds, and to 8 oz/day for 7-18 yr olds. Children taking medications metabolized by CYP3A4 must avoid grapefruit juices.

In the 2nd year of life, self-feeding becomes a norm and provides the opportunity for the family to eat together with less stress. Self-feeding allows the child to limit her intake. Child feeding is an interactive process. Children receive cues regarding appropriate feeding behaviors from parents. Parents should praise positive and ignore negative eating behaviors unless the behavior jeopardizes the health and safety of the child. In addition, parents should eat with their toddlers and not simply feed them, in order to model positive eating behaviors.

The 2 yr old child should progress from small pieces of soft food to prepared table foods with precautions. At this stage, the child is not capable of completely chewing and swallowing foods, and particular attention should be paid to foods with a choking risk. Hard candies, nuts, and raw carrots should be avoided. Hot dogs, sausages, and grapes should be sliced lengthwise. Caregivers should always be vigilant and present during feeding, and the child should be placed in a high chair or booster seat. The AAP discourages eating in the presence of distractions such as television, tablets, mobile devices, and other screens, or eating in a car where an adult cannot adequately observe the child.

Young children have a natural preference for sweetened foods and beverages that begins in infancy. Reluctance to accept new foods is a common developmental phase. A new food should be offered multiple times (8-15) over a period of months for acceptance by the child.

Toddlers need to eat 3 healthy meals and 2 snacks daily. Milk continues to be an important source of nutrition. Guidelines for vitamin D supplementation recommend a daily vitamin D intake of 600 IU/day for children and adolescents who are ingesting <1000 mL/day of vitamin D–fortified milk or formula. Toddlers and preschool children often fail to meet the recommended servings of fruits, vegetables, and fiber, whereas intakes of food with fat and added sugar are high. Giving vegetables at the beginning of the meal and increasing the portion size of vegetables served during meals can be an effective strategy for increasing vegetable consumption in preschool children.

Eating in the Daycare Setting

Many U.S. toddlers and preschool children attend daycare and receive meals and snacks in this setting. There is a wide variation in the quality of the food offered and the level of supervision during meals. Parents are encouraged to assess the quality of the food served at daycare by asking questions, visiting the center, and taking part in parent committees. Free or reduced-price snacks and meals are provided in daycare centers for low- and medium-income communities through the U.S. Department of Agriculture (USDA) **Child and Adult Care Food Program** . Participating programs are required to provide meals and snacks that meet the meal regulations set by the USDA, guaranteeing a certain level of food quality. However, often for monetary reasons, many daycare centers still struggle to provide high-quality meals and snacks.

Feeding School-Age Children and Adolescents

MyPlate

The USDA MyPlate (www.choosemyplate.gov) is a basis for building an optimal diet for children and adults (Fig. 56.2). MyPlate is based on the 2010 **Dietary Guidelines for Americans** and replaced MyPyramid. MyPlate provides a visual representation of the different food groups and portion sizes designed for the general public. In addition to food group information, the website provides discretionary calorie information, weight management strategies, and tools to track calories and physical activity goals. A personalized eating plan based on these guidelines provides, on average over a few days, all the essential nutrients necessary for health and growth, while limiting nutrients associated with chronic disease development. MyPlate can also be used as an interactive tool that allows customization of recommendations, based on age, sex, physical activity, and for some populations, weight and height. Print materials from the USDA are also available for families without internet access.

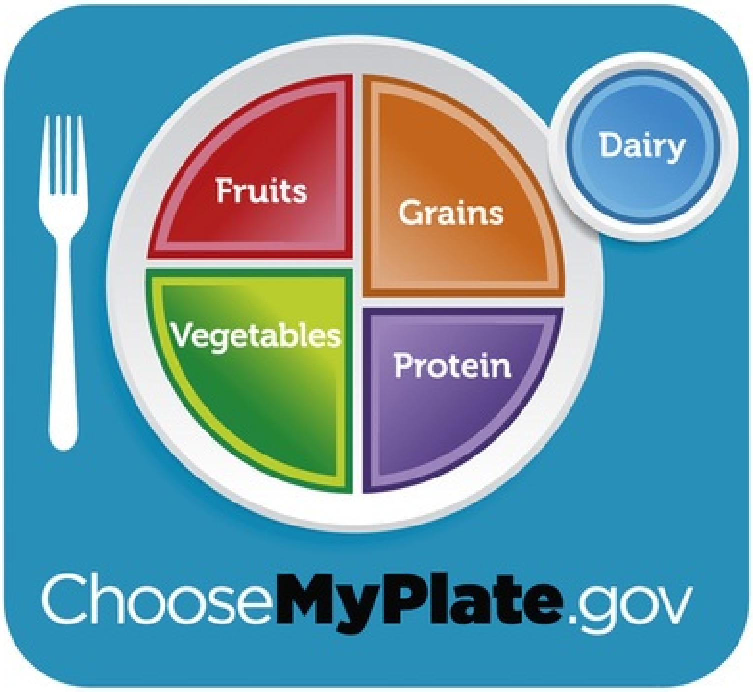

FIG. 56.2 MyPlate food guide. (From US Department of Agriculture: http://www.choosemyplate.gov/ .)

Recommendations based on MyPlate emphasize making half the plate vegetables and fruits and half the plate protein and grains, with protein having the smallest section. Protein replaces the meat category since many protein sources are not from animals. A separate dairy section is included. Physical activity recommendations to achieve a healthful energy balance are not visually displayed but are provided on the website. MyPlate has removed foods that have low nutritional value, such as sweetened sugar beverages and sweetened bakery products.

In the United States and an increasing number of other countries, the vast majority of children and adolescents do not consume a diet that follows the recommendations of MyPlate. The intake of discretionary calories is much higher than recommended, with frequent consumption of sweetened sugar beverages (soda, juice drinks, iced tea, sport drinks), snack foods, high-fat meat (bacon, sausage), and high-fat dairy products (cheese, ice cream). Intake of dark-green and orange vegetables (vs fried white potatoes), whole fruits, reduced-fat dairy products, and whole grains is typically lower than recommended. Furthermore, unhealthful eating habits, such as larger-than-recommended portion sizes; food preparation that adds fat, sugar, or salt; skipping breakfast and/or lunch; grazing; or following fad diets are prevalent and associated with a poorer diet quality. MyPlate offers a helpful and customer-friendly tool to assist pediatricians counseling families on optimal eating plans for short- and long-term health.

Eating at Home

At home, much of what children and adolescents eat is under the control of their parents. Typically, parents shop for groceries and control, to some extent, what food is available in the house. Modeling of healthful eating behavior by parents is a critical determinant of the food choices of children and adolescents. Counseling to improve diet should include guiding parents in using their influence to make healthier food choices available and attractive at home.

Regular family meals sitting at a table, as opposed to eating alone or watching a TV or other screen, are associated with improved diet quality, perhaps because of increased opportunities for **positive parenting** during meals. Many families with busy schedules and other stressors are unable to provide the ideal meal setting. Another parenting challenge is to control the excess appetite of some children and adolescents. Children should be supported to eat at a slower pace and to chew their food properly. Conversation at the dinner table should be encouraged to prolong eating to at least 15 min. Offering vegetables while children are hungry at the beginning of the meal has been shown to increase vegetable consumption. Useful strategies, when the child is still hungry after a meal, include a 15-20 min pause (allow child to engage in another activity) before a 2nd serving or offering foods that are insufficiently consumed, such as vegetables, whole grains, or fruits.

Eating at School

The **National School Lunch Program** and the **School Breakfast Program** provide low-cost meals to more than 5 billion children nationwide. Guidelines for meals are taken from the Dietary Guidelines for Americans and the 2005 Dietary Reference. Recommendations include the use of age-grade portion sizes and the amounts of vegetables and fruits, grains, and fats (Table 56.9). The training and equipment for school food service staff, school community engagement, parent education, and food industry involvement are among the necessary components. The target year is 2020 for achieving recommendations for sodium. In the meantime, while schools are working on implementing changes, parents should be encouraged to examine the weekly menu with their child and assist with their choices. If children bring their lunch from home, recommendations for what constitutes a healthful lunch should be provided by the pediatrician. Parents can be directed to www.choosemyplate.org for healthful lunch ideas. In addition, parties within classrooms should be limited to once a month.

Table 56.9

Revised National School Lunch Program and School Breakfast Program Recommendations

- Portion sizes of food are to be based on age-grade groups.
- School lunches and breakfasts will have a minimum and maximum calorie level, maximum saturated fat content, and a maximum sodium content.
- Foods must contain zero grams of *trans* fat per serving.

- The inclusion of unsaturated vegetable oils is encouraged within calorie limits.
- Vegetables and fruits are not interchangeable.
- Vegetable offerings at lunch must include ½ cup equivalent of the following: dark-green vegetables, bright-orange vegetables, and legumes.
- No more than half of fruit servings may be in the form of juice.
- At least one half of bread/grain offered must be whole grain.
- Milk must be fat free if flavored and either fat free or 1% fat if plain.
- Students must select a fruit option at breakfast with their meal, and either a fruit or a vegetable at lunch, for the meal to be reimbursable.

Adapted from the National Academies of Engineering, Science and Medicine: *School meals: building blocks for healthy children*, Washington, DC, 2010, National Academies Press.

Eating Out

The number of meals eaten outside the home or brought home from takeout restaurants has increased in all age-groups of the U.S. population. The increased convenience of this meal pattern is undermined by the generally lower nutritional value of the meals, compared to home-cooked meals. Typically, meals consumed or purchased in fast-food or casual restaurants are of large portion size, are dense in calories, and contain large amounts of saturated fat, salt, and sugar and low amounts of whole grains, fruits, and vegetables. Although still a problem currently, *trans* fat is being phased out of most commercial restaurants and prepared foods. Although an increasing number of restaurants offer healthier alternatives, the vast majority of what is consumed at restaurants does not fit MyPlate recommendations.

With increasing age, an increasing number of meals and snacks are also consumed during peer social gatherings at friends' houses and parties. When a large part of a child's or adolescent's diet is consumed on these occasions, the diet quality can suffer, because food offerings are typically of low nutritional value. Parents and pediatricians need to guide teens in navigating these occasions while maintaining a healthful diet and enjoying meaningful social interactions. These occasions often are also opportunities for teens to consume alcohol; consequently, adult supervision is important.

Nutrition Issues of Importance Across Pediatric Ages

Food Environment

Most families have some knowledge of nutrition and intend to provide their children with a healthful diet. The discrepancy between this fact and the actual quality of the diet consumed by U.S. children is often explained by challenges in the environment for families to make healthful food choices. Because the final food choice is made by individual children or their parents, interventions to improve diet have focused on individual knowledge and behavior changes, but these have had limited success (Fig. 56.3). Understanding the context of food and lifestyle choices helps in understanding lack of changes or “poor compliance” and can decrease the frustration often experienced by the pediatricians who might “blame the victim” for behavior that is not entirely under their control. In recent time, national initiatives have been launched to increase access to vegetables and fruits and increase public awareness of healthful eating (e.g., Let's Move!).

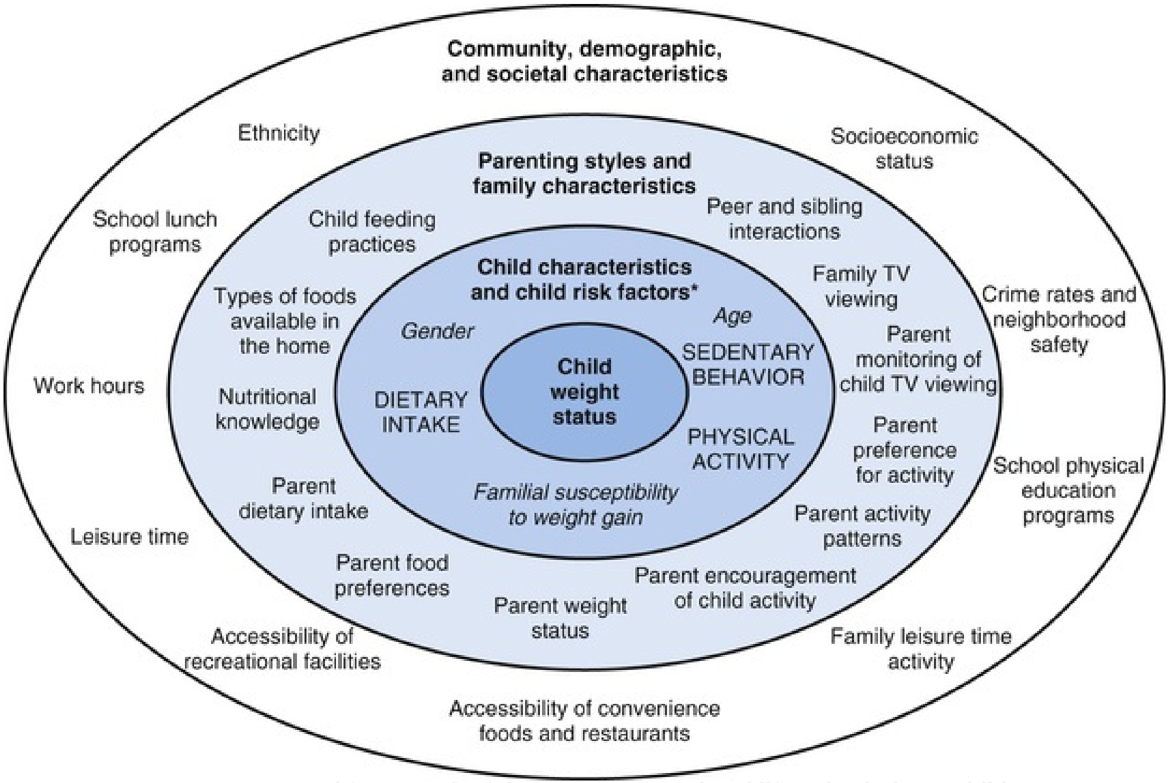
Community, demographic, and societal characteristics
Ethnicity
Socioeconomic status
School lunch programs
Work hours
Leisure time
Accessibility of recreational facilities
Accessibility of convenience foods and restaurants
Family leisure time activity
School physical education programs
Crime rates and neighborhood safety
Parenting styles and family characteristics
Child feeding practices
Peer and sibling interactions
Family TV viewing
Parent monitoring of child TV viewing
Parent preference for activity
Parent activity patterns
Parent encouragement of child activity
Parent weight status
Parent food preferences
Parent dietary intake
Nutritional knowledge
Types of foods available in the home
Child characteristics and child risk factors*
Gender
Age
SEDENTARY BEHAVIOR
PHYSICAL ACTIVITY
DIETARY INTAKE
Familial susceptibility to weight gain
Child weight status

FIG. 56.3 **A conceptual framework of the context of food and lifestyle choices. Child risk factors (shown in uppercase lettering) refer to child behaviors associated with the development of overweight. Characteristics of the child (shown in italic lettering) interact with child risk factors and contextual factors to influence the development of overweight (i.e., moderator variables). (From Davison KK, Birch LL: Childhood overweight: a contextual model and recommendations for future research, *Obes Rev* 2:159–171, 2001. © 2001 The International Association for the Study of Obesity.)**

While **taste** is the main determinant of food choice, many other complex determinants influence that choice including **cost** and marketing strategies. **Marketing** includes strategies as diverse as shelf placements, association of cartoon characters with food products, coupons, and special offers or pricing, all of which influence food purchase choices. Television advertising is an important part of how children and adolescents hear about food, with an estimated 40,000 TV commercials per year, as seen by the average U.S. child, many of which are for food, compared to the few hours of nutrition education they receive in school. Additional food advertisement increasingly occurs as brand placement in movies and TV shows, on websites, and even video games.

Using Food as Reward

It is a prevalent habit to use food as a reward or sometimes withdraw food as punishment. Most parents use this practice occasionally, and some use it almost systematically, starting at a young age. The practice is also commonly used in other settings where children spend time, such as daycare, school, or even athletic settings. Although it might be a good idea to limit some unhealthful but desirable food categories to special occasions, using food as a reward is problematic. Limiting access to some foods and making its access contingent on a particular accomplishment increases the desirability of that type of food. Conversely, encouraging the consumption of some foods renders them less desirable. Therefore, phrases such as, “Finish your vegetables, and you will get ice cream for dessert,” can result in establishing unhealthful eating habits once the child has more autonomy in food choices. Parents should be counseled on such issues and encouraged to choose items other than food as reward, such as inexpensive toys or sporting equipment, family time, special family events, or collectible items. Similar types of behavior are also seen in schools and extracurricular events. Instead of rewards of food (e.g., pizza, candy), daycare providers, teachers, and counselors should be encouraged to use alternative rewards, such as minutes of free time, sitting in the teacher's chair, being the teacher's helper, and homework-free nights.

Cultural Considerations in Nutrition and Feeding

Food choices, food preparation, eating patterns, and infant feeding practices all have very deep cultural roots. In fact, beliefs, attitudes, and practices surrounding food and eating are some of the most important components of cultural identity. Therefore, it is not surprising that in multicultural societies, great variability exists in the cultural characteristics of the diet. Even in a world where global marketing forces tend to reduce geographic differences in the types of food, or even brands, that are available, most families, especially during family meals at home, are still much influenced by their cultural background. Therefore, pediatricians should become familiar with the dietary characteristics of various cultures in their community, so that they can identify and address, in a nonjudgmental way and avoiding stereotypes, the potential nutritional issues related to the diet of their patients.

Vegetarianism

Vegetarianism is the practice of following a diet that excludes animal flesh foods, including beef, pork, poultry, fish, and shellfish. There are several variants of the diet, some of which also exclude eggs and/or some products produced from animal labor, such as dairy products and honey. It is important to understand different variations in vegetarianism, as follows:

- Veganism: excludes all animal products. It may be part of a larger practice of abstaining from the use of animal products for any purpose.
- Ovovegetarianism: includes eggs but not dairy products.
- Lactovegetarianism: includes dairy products but excludes eggs.
- Lactoovovegetarianism: includes eggs and dairy products.
- Flexitarian: a vegetarian who will occasionally eat meat.
- Pescatarian: consumes fish, but often self-labeled a vegetarian.

Another expression used for vegetarianism and veganism is “plant-based diets.”

Other dietary practices commonly associated with vegetarianism include *fruitarian* diet (fruits, nuts, seeds, and other plant matter gathered without harm to the plant), *Su vegetarian* diet (excludes all animal products as well as onion, garlic, scallions, leeks, or shallots), *macrobiotic* diet (includes whole grains and beans and, in some cases, fish), and *raw vegan* diet (includes fresh and uncooked fruits, nuts, seeds, and vegetables). The safety of these restrictive diets has not been studied in children. These diets can be very limited in macro- and micronutrients and are not recommended for children. While being on a vegetarian or vegan diet does not appear to increase the risk of an eating disorder, some teenagers with disordered eating may choose such diets to aid in limiting their caloric intake.

Vegetarianism is considered a healthful and viable diet; both the U.S.

Academy of Nutrition and Dietetics and the Dietitians of Canada have found that a properly planned and well-balanced vegetarian diet can satisfy the nutritional goals for all stages of life. Compared with nonvegetarian diets, vegetarian diets have lower intakes of saturated fat, cholesterol, and animal protein and relatively higher levels of complex carbohydrates, fiber, magnesium, potassium, folate, vitamins C and E, and phytochemicals. Vegetarians have a lower body mass index, cholesterol level, and blood pressure and are at decreased risk for cancer and ischemic heart disease. Specific nutrients of concern in vegetarian diets include the following:

◆ **Iron** (see Chapter 55): Vegetarian diets may have similar levels of iron as nonvegetarian diets, but iron from vegetable sources has lower bioavailability than iron from meat sources, and iron absorption may be inhibited by other dietary constituents, such as phytate (found in leafy green vegetables and whole grains). Iron stores are lower in vegetarians and vegans than in nonvegetarians; and iron deficiency is more common in vegetarian and vegan women and children. Foods rich in iron include iron-fortified cereals, black beans, cashews, kidney beans, lentils, oatmeal, raisins, black-eyed peas, soybeans, sunflower seeds, chickpeas, molasses, chocolate, and tempeh. Iron absorption can be increased by eating food containing ascorbic acid (vitamin C) along with foods containing iron.

◆ **Vitamin B_{12} :** Plants are not a good source of B_{12} (see Chapter 62.7). Vitamin B_{12} can be obtained through dairy products and eggs; vegans need fortified foods or supplements. Breastfeeding by vegan mothers can place an infant at risk for vitamin B_{12} deficiency.

◆ **Fatty acids:** Vegetarians and vegans may be at risk for insufficient eicosapentaenoic acid (EPA) and DHA. The inclusion of sources of linolenic acid (precursor of EPA and DHA), such as walnuts, soy products, flaxseed oil, and canola oil, is recommended.

◆ **Calcium and vitamin D:** Without supplementation, vegan diets are low in calcium and vitamin D, putting vegans at risk for impaired bone mineralization (see Chapter 64). Serum hydroxyvitamin D levels should be monitored in vegans and supplemented for levels <30 dL. Calcium sources include leafy greens with low oxalate, such as broccoli, kale, and Chinese cabbage. Calcium and vitamin D are found in fortified almond, soy milk, and orange juice.

◆ **Zinc:** The bioavailability of zinc in plant sources tends to be low because of the presence of phytates and fiber that inhibit zinc absorption (see Chapter 67). Zinc is found in soy products, legumes, grains, cheese, and nuts.

◆ **Iodine:** Plant-based diets can be low in iodine, and therefore vegetarians and vegans who do not consume iodized salt or sea vegetables (which have variable

> iodine content) may be at risk of iodine deficiency. The exclusive use of sea salt or kosher salt could further increase that risk, because these are typically not iodized, and iodized salt is not used in processed foods.

Organic Foods

Parents may prefer organic foods to feed children secondary to concerns regarding chemical and hormonal content of animals and produce. **Organic food** is defined as produce and ingredients that are grown without the use of pesticides, synthetic fertilizers, sewage sludge, genetically modified organisms, or ionizing radiation. Animals that produce meat, poultry, eggs, and dairy products are not given antibiotics or growth hormones. In the United States, certification must be obtained, and USDA regulations must be followed to market food as “organic.” The nutritional differences between organic and conventional foods may not be clinically relevant. Children consuming organic foods have lower or no detectable levels of pesticides in their urine compared to those consuming nonorganic foods. It remains unclear whether such a reduction in exposure to chemicals is clinically significant. Organic foods have higher levels of PUFAs (α-linolenic acid, very-long-chain *n-3* fatty acids), α-tocopherol, and iron and lower levels of cadmium, selenium, and iodine. Similarly, despite concerns of parents, the amount of bovine growth hormone in conventional milk is thought to be neither significant nor biologically active in humans. Additionally, milk consumption from estrogen-treated cows does not result in endocrine disruptions in infants. However, other chemicals in the environment, such as bisphenol-A (found in plastics), nitrates, endocrine disruptors, and phthalates, should be avoided. Organic certification of a food also suggests the food source is not from a genetically modified nutrient.

Genetically modified organisms (GMOs) in themselves may not be harmful. However, GMOs are modified to be resistant to the effects of herbicides, including glyphosate and 2,4-dichlorophenoxyacetic acid (2,4-D), which give GMOs a selective growth advantage. Nonetheless, glyphosate and 2,4-D have been designated by the International Agency for Research on Cancer as probable and possible human carcinogens, respectively.

Because the cost of organic foods is generally higher than that of other foods, a prudent approach is to explain to families that the scientific basis for choosing organic foods is uncertain, and that large-scale human studies to evaluate these issues will be difficult to carry out. If it is their preference, however, and they can afford the added cost, there is no reason not to eat organic foods.

Nutrition as Part of Complementary and Alternative Medicine, Functional Foods, Dietary Supplements, Vitamin Supplements, and Botanical and Herbal Products

The use of nutrition or nutritional supplements as complementary or alternative medicine is increasing, despite limited data on safety and efficacy, especially in children. Many parents assume that if a food or supplement is “natural” or “organic,” there is no potential for risk and some potential for benefit. However, adverse effects of some dietary supplements have been documented, and some supplements have been discovered to contain common allergens. Dietary supplements, including botanical and herbal products, are regulated differently than medication in the United States. Manufacturers do not have to prove safety or efficacy before marketing the supplement; the potential for adverse effects or simply for inefficacy is therefore high. It is difficult for pediatricians to compete against the aggressive marketing through multimedia sources of food supplements to families of healthy and chronically ill children. Pediatricians must also compete against word of mouth, the internet, and advice from people without a scientific background and those with significant conflicts of interest.

Pediatricians are often asked by parents if their children need to receive a **daily multivitamin** . Unless the child follows a particular diet that may be poor in one or more nutrients for health, cultural, or religious reasons, or if the child has a chronic health condition that puts the child at risk for deficiency in one or more nutrients, multivitamins are not indicated. Many children do not follow all the guidelines of MyPlate, and parents and pediatricians may be tempted to use multivitamin supplements to ensure nutrient deficiencies are avoided. Use of a daily multivitamin supplement can result in a false impression that the child's diet is complete and in decreased efforts to meet dietary recommendations with food rather than the intake of supplements (see Chapter 55). The average U.S. diet provides more than a sufficient amount of most nutrients, including most vitamins. Therefore, multivitamins should not be routinely recommended.

Food Safety

Constantly keeping food safety issues in mind is an important aspect of feeding infants, children, and adolescents. In addition to choking hazards and food allergies, pediatricians and parents should be aware of food safety issues related to infectious agents and environmental contaminants. **Food poisoning** with bacteria, viruses, or their toxins is most common with raw or undercooked food, such as oysters, beef, and eggs, or cooked foods that have not been handled or stored properly. The specific bacteria and viruses involved in food poisoning are described in Chapter 740 . Many chemical contaminants, such as heavy metals, pesticides, and organic compounds, are present in various foods, usually in small amounts. Because of concerns regarding their child's neurologic development and cancer risk, many questions arise from parents, especially after media coverage of isolated incidents. A recurring debate is the balance between the benefits of seafood for the growing brain and cardiovascular health and the risk of mercury contamination from consuming large, predatory fish species. Pediatricians need to become familiar with reliable sources of information, such as the websites of the U.S. Environmental Protection Agency (EPA), FDA, and CDC. The **Food Safety Modernization Act** provides the FDA with authority to have stricter control over food production and distribution. The FDA can require that manufacturers develop food safety plans. A good source of information for patients and parents can be found at www.foodsafety.gov .

Preventive Nutrition Counseling in Pediatric Primary Care

An important part of the primary care well child visit focuses on nutrition and growth because most families turn to pediatricians for guidance on child nutrition. Preventive nutrition is one of the cornerstones of preventive pediatrics and a critical aspect of anticipatory guidance. The first steps of nutrition counseling are nutritional status assessments, primarily done through growth monitoring and dietary intake assessment. Although **dietary assessment** is somewhat simple in infants who have a relatively monotonous diet, it is more challenging at older ages. The goals of dietary assessment in the primary care setting need to include an idea of the eating patterns (time, location, and environment) and usual diet by asking the parent to describe the child's dietary intake on a typical day or in the last 24 hr. Alternatively, a basic assessment of the child's consumption of vegetables, fruits, whole grains, low-fat or nonfat dairy products, 100% fruit juice, and sugar-sweetened beverages should be assessed. Pediatricians should encourage regularly scheduled meals and 1 or 2 healthy snacks (depending on the child's age). For more ambitious goals of dietary assessment, referral to a registered dietician with pediatric experience is recommended.

After understanding the child's usual diet, existing or anticipated nutritional problems should be addressed, such as diet quality, dietary habits, and portion size. For a few nutritional problems, a lack of knowledge can be addressed with nutrition education, but key nutritional issues, such as overeating or poor food choices, are not solely the result of lack of parents' knowledge. Therefore, nutrition education alone is insufficient in these situations, and pediatricians need to acquire training in behavior-modification techniques or refer to specialists to assist their patients in engaging in healthful feeding and eating behaviors. The physical, cultural, and family environment in which the child lives should always be considered so that nutrition counseling is relevant and changes are feasible.

One important aspect of nutrition counseling is providing families with sources of additional information and behavioral change tools. Although some handouts are available from government agencies, the AAP, and other professional organizations for families without internet access, an increasing number of families rely on the internet to find nutrition information. Therefore, pediatricians need to become familiar with common websites so that they can point families to reliable and unbiased sources of information. Perhaps the most useful websites for children are the AAP and USDA MyPlate sites and those of the CDC, FDA, National Institutes of Health, The National Academies, and Food and Nutrition Board for government sources. Other professional resources include the American Heart Association and Academy of Nutrition and Dietetics. Pediatricians should also be aware of sites that provide biased or even dangerous information so that they can warn families accordingly. Examples include dieting sites, sites that openly promote dietary supplements or other food products, and the sites of “nonprofit” organizations that are mainly sponsored by food companies or that have other social or political agendas.

U.S. Food Assistance Programs

Several programs exist in the United States to ensure sufficient and high-quality nutrition for children of families who cannot always afford optimal nutrition. One of the most utilized federal programs is the **Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).** This program provides nutrition supplements to a large proportion of pregnant women, postpartum women, and children up to their 5th birthday. One of its strengths is that in order to qualify, families need to regularly visit a WIC nutritionist, who can be a useful resource for nutritional counseling. For older children, federal programs provide school lunches, breakfasts, and after-school meals, as well as daycare and summer nutrition. Lower-income families are also eligible for the **Supplemental Nutrition Assistance Program (SNAP)** , formerly known as the Food Stamp Program. This program provides funds directly to families to purchase various food items in regular food stores.

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CHAPTER 57

Nutrition, Food Security, and Health

Ann Ashworth

Malnutrition as the Intersection of Food Insecurity and Health Insecurity

Undernutrition is usually an outcome of three factors, often in combination: household food supply, childcare practices, and access to health and water/sanitation services. In famine and emergency settings, food shortage is the foremost factor, but in many countries with widespread undernutrition, food production or access to food might not be the most limiting factor. More important causes might be repeated childhood infections, especially diarrheal diseases associated with an unsafe environment and lack of exclusive breastfeeding, or inadequate complementary feeding practices, or the lack of time families have available for appropriate infant or maternal care. Fig. 57.1 shows some of the many causal factors on the pathway to undernutrition and how they extend from household and community levels to national/international levels. Inequitable distribution of resources because of political, economic, and agricultural policies often denies families their right to adequate land, water, food, healthcare, education, and a safe environment, all of which can influence nutritional status.

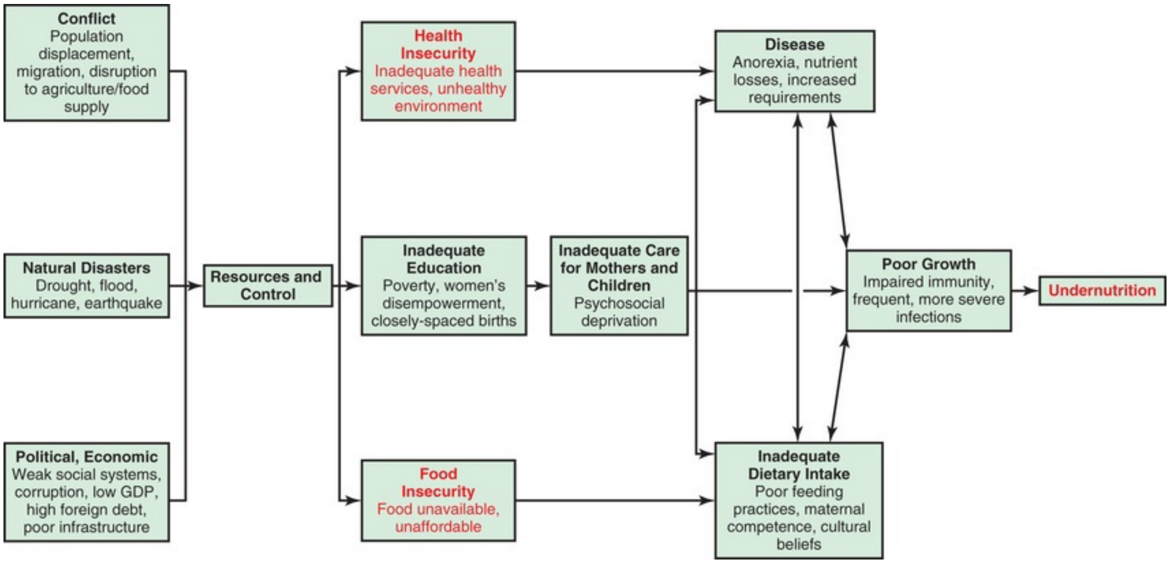
Conflict
Population displacement, migration, disruption to agriculture/food supply
Natural Disasters
Drought, flood, hurricane, earthquake
Political, Economic
Weak social systems, corruption, low GDP, high foreign debt, poor infrastructure
Resources and Control
Health Insecurity
Inadequate health services, unhealthy environment
Inadequate Education
Poverty, women's disempowerment, closely-spaced births
Inadequate Care for Mothers and Children
Psychosocial deprivation
Food Insecurity
Food unavailable, unaffordable
Disease
Anorexia, nutrient losses, increased requirements
Poor Growth
Impaired immunity, frequent, more severe infections
Inadequate Dietary Intake
Poor feeding practices, maternal competence, cultural beliefs
Undernutrition

FIG. 57.1 Basic, underlying, and immediate causes of undernutrition.

Families with few economic resources who know how to care for their children and are enabled to do so can often use available food and health services to produce well-nourished children. If food resources and health services are not available in a community, not utilized, or not accessible to some families, children might become undernourished. Undernutrition is not confined to low-income countries. It has been noted in chronically ill patients in neonatal and pediatric intensive care units in high-income countries and among patients with burns, human immunodeficiency virus (HIV) infection, tuberculosis, cystic fibrosis, chronic diarrhea syndromes, malignancies, bone marrow transplantation, and inborn errors of metabolism. Severe malnutrition has been reported in affluent communities in infants whose families believe in fad diets, as well as in infants with food allergies fed nutritionally inadequate foods such as rice "milk," which has a very low protein and micronutrient content (Figs. 57.2 and 57.3).

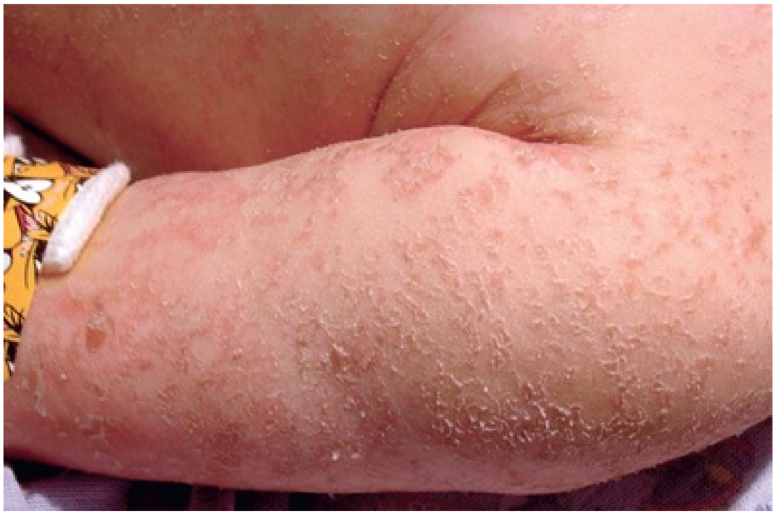

FIG. 57.2 A 14 mo old girl with "flaky paint" dermatitis. (From Katz KA, Mahlberg MH, Honig PJ, et al: Rice nightmare: kwashiorkor in 2 Philadelphia-area infants fed Rice Dream beverage, *J Am Acad Dermatol* 52(5 Suppl 1):S69–S72, 2005.)

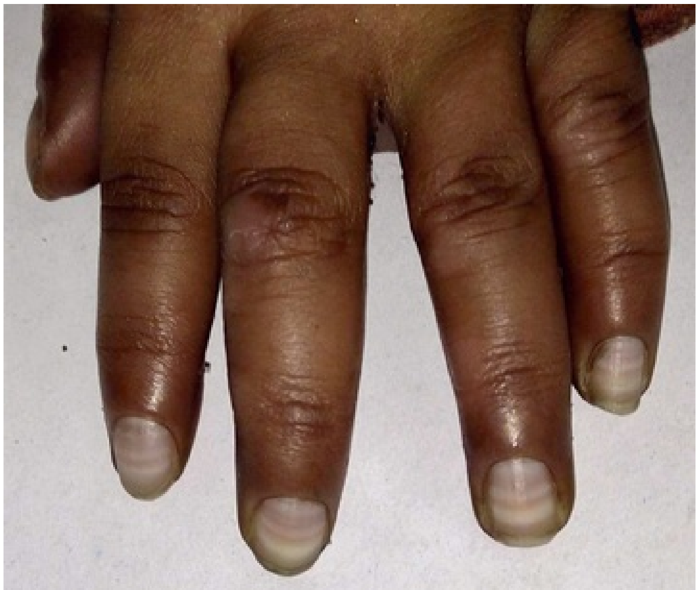

FIG. 57.3 Paired, transverse, homogeneous, and smooth bordered lines noted in all finger nails suggestive of Muehrcke lines in an infant fed diluted cow's milk since birth. (From Williams V, Jayashree M: Muehrcke lines in an infant, *J Pediatr* 189:234, 2017.)

Food Security

Food security exists when all people, at all times, have access to sufficient, safe, nutritious food to maintain a healthy and active life. Four main dimensions of food security can be identified: availability, access, utilization, and stability. **Availability** refers to the *supply* of food, reflecting the level of food production, food stocks, and net trade. **Access** is at the household level, reflecting purchasing power, household food production, and food/cash transfers received through social "safety net" programs. The **utilization** dimension recognizes that even when a household has access to food, it is not necessarily shared equitably within a household. **Stability** refers to being "food secure" at all times: Examples of situations that affect stability are the "lean seasons" before a harvest, natural disasters, political unrest, and rising food prices. To be food secure, all four dimensions must be met simultaneously.

Measuring Food Insecurity

The most commonly used measurement of food insecurity is *undernourishment* (chronic hunger), which is the proportion of the population who are unable to meet daily energy requirements for light activities. It is an estimate calculated by the **Food and Agriculture Organization (FAO)** based on country-level food balance sheets. It does not take nutrient adequacy into account, but has the advantage of being available for almost all countries annually (although with a time lag) and assists in monitoring global trends. In addition, FAO measures food access by asking individuals about their experiences over the last 12 mo, such as whether they ran out of food or skipped meals. The responses are graded from mild to severe food insecurity. This relatively simple monitoring tool, the **Food Insecurity Experience Scale** , provides timely information to guide decision-making at national and local levels.

In 2017, FAO estimated that about 821 million people, or 10.9% of the world's population, were undernourished, 98% of whom were in developing countries. The majority are rural poor people subsisting on small plots of land or hired as laborers, and urban poor people who lack the means to grow or buy food. Alongside the 0.82 billion people who are underfed are 1.9 billion who are overfed, reflecting global inequalities and the “double burden of malnutrition” in low- and middle-income countries.

Nutrition, Food Security, and Poverty

Household food security tracks income closely. With rising incomes, very poor households first increase their dietary energy intake to avert hunger. If incomes rise further, there is a shift to more expensive staple foods and then to a more varied diet with a greater proportion of energy from animal sources, fruits/vegetables, and fats/sugars, and less from cereals, roots, and tubers. National economic growth tends to be accompanied by reductions in stunting, but economic growth can pass by poor persons if they work in unaffected sectors, or are unable to take advantage of new opportunities because of lack of education, access to credit, or transportation, or if governments do not channel resources accruing from economic growth to healthcare, education, social protection, and other public services and infrastructure. There is good evidence that economic growth reduces poverty but does not necessarily reduce undernutrition.

Food Security and Nutrition Targets

The period of Millennium Development Goals (MDGs) ended in 2015. All developing regions except sub-Saharan Africa achieved the target to halve the proportion of people living in extreme poverty, with the proportion falling from 47% in 1990 to 14% in 2015. Reductions in hunger were broadly consistent with those of poverty reduction, and rates of undernourishment in developing regions fell from 23% in 1990 to 13% in 2015. The prevalence of underweight children (another MDG indicator of “hunger”) fell from 29% in 1990 to 15% in 2015 for the developing regions combined. Rural children are almost twice as likely to be underweight as urban children, and the poorest quintile is almost 3 times as likely to be underweight as the richest quintile.

Eradicating poverty and hunger continue to be core targets of the **Sustainable Development Goals** , as agreed by 193 countries of the United Nations General Assembly in September 2015, and are to be achieved by 2030. In addition, in 2012 the World Health Assembly agreed to 6 global nutrition targets to be reached by 2025, measured against a 2010 baseline, and the United Nations Secretary-General launched the **Zero Hunger Challenge** with 5 objectives that “would boost economic growth, reduce poverty and safeguard the environment” and “would foster peace and stability” (Table 57.1).

Table 57.1

Global Food Security and Nutrition Targets

ZERO HUNGER CHALLENGE OBJECTIVES	WORLD HEALTH ASSEMBLY GLOBAL NUTRITION TARGETS FOR 2025
1. Access to an adequate and stable food supply for all 2. Elimination of stunting in children <2 yr, and no malnutrition in pregnancy and early childhood 3. Sustainable food systems 4. Doubling of smallholder productivity and income, particularly for women 5. No loss or waste of food, and responsible consumption	1. A 40% reduction in the number of stunted children <5 yr 2. A 50% reduction in anemia in women of reproductive age 3. A 30% reduction in low birthweight 4. No increase in childhood overweight 5. Increase exclusive breastfeeding rates to at least 50% in the 1st 6 mo 6. Reduce and maintain childhood wasting to <5%

Future Food Security

Between now and 2050 the world's population is expected to exceed 9 billion, and an increase in food supply of 70–100% will be needed to feed this larger, more urban, and more affluent populace. Over this same period, the world's food supply is expected to diminish unless action is taken. Accelerating the decline in fertility rates and reducing overconsumption are basic but difficult actions to bridge the gap between increasing demand and diminishing supply. Equally challenging actions include limiting climate disruption, increasing the efficiency of food production, reducing waste, and reducing the demand for meat and dairy foods.

◆ *Limit climate disruption.* Drought, floods, and other extreme weather events are becoming more prevalent and destroy crops and livestock, often on a huge scale. Rising sea levels will lead to loss of productive land through inundation and salinization. Acidification of oceans will reduce marine harvests. Because curbing greenhouse gas emissions is essential to minimize climate disruption, the goals are (1) to cut fossil fuel use by at least half of present levels by 2050 so as to reduce carbon dioxide (CO_2) emissions and (2) change livestock husbandry and agronomic practices to reduce methane and nitrous oxide (N_2O) emissions.

◆ *Increase efficiency of food production.* Expanding the area of agricultural land to any large extent (e.g., by deforestation) is not a sustainable option because of adverse consequences on ecosystems and biodiversity, although some expansion of food production could be achieved by switching good-quality land away from first-generation biofuels. For example, almost 40% of the U.S. corn harvest in 2016–2017 went to biofuels. Efforts to increase the intensity of production need to be environmentally sustainable. These include optimizing yields by soil and water conservation, removal of technical and financial constraints faced by farmers, and breeding resource-efficient crops and livestock that are also climate resilient and pest/disease resistant.

- *Reduce waste*. From 30–40% of food is wasted, between harvesting and the market, during retail, at home, and in the food service industry. Better transport and storage facilities in developing countries, less stringent sell-by dates, lower cosmetic standards for fruits and vegetables, and ending supersized portions would help reduce waste.
- *Change diets*. As wealth increases, so does the demand for processed foods, meat, dairy products, and fish. About one third of global cereal production is fed to animals, so reducing consumption of meat from grain-fed livestock and increasing the proportion derived from the most efficient sources (pigs and poultry) would allow more people to be fed from the same amount of land.

Undernutrition

The greatest risk of undernutrition (underweight, stunting, wasting, and micronutrient deficiencies) occurs in the first 1000 days, from conception to 24 mo of age, and this early damage to growth and development can have adverse consequences in later life on health, intellectual ability, school achievement, work productivity, and earnings. Governments and agencies are therefore advised to focus interventions on this critical window of opportunity. For folate deficiency, which increases the risk of birth defects, this particular window is before conception.

Measurement of Undernutrition

The term **malnutrition** encompasses both ends of the nutrition spectrum, from undernutrition to overweight. Many poor nutritional outcomes begin in utero and are manifest as low birthweight (LBW, <2,500 g). Preterm delivery and fetal growth restriction are the 2 main causes of LBW, with prematurity relatively more common in richer countries and fetal growth restriction relatively more common in poorer countries.

Nutritional status is often assessed in terms of anthropometry (Table 57.2). International standards of normal child growth under optimum conditions from birth to 5 yr have been established by the World Health Organization (WHO). To compile the standards, longitudinal data from birth to 24 mo of healthy, breastfed, term infants were combined with cross-sectional measurements of children ages 18-71 mo. The standards allow normalization of anthropometric measures in terms of *z* scores (standard deviation [SD] scores). A z-score is the child's height (weight) minus the median height (weight) for the child's age and sex divided by the relevant SD. The standards are applicable to all children everywhere, having been derived from a large, multicountry study reflecting diverse ethnic backgrounds and cultural settings.

Table 57.2

Classification of Undernutrition

CLASSIFICATION	INDEX	GRADING
Gomez (underweight)	90–75% of median weight-for-age	Grade 1 (mild)
	75-60%	Grade 2 (moderate)
	<60%	Grade 3 (severe)
Waterlow (wasting)	90–80% of median weight-for-height	Mild
	80–70% <70%	Moderate Severe
Waterlow (stunting)	95–90% of median height-for-age	Mild
	90–85%	Moderate
	<85%	Severe
WHO (wasting)	< −2 to > −3 SD weight-for-height	Moderate
	< −3	Severe
WHO (stunting)	< −2 to > −3 SD height-for-age	Moderate
	<−3	Severe
WHO (wasting) (for age-group 6-59 mo)	115-125 mm mid-upper arm circumference	Moderate

	<115 mm	Severe

SD, Standard deviation; WHO, World Health Organization.

Height-for-age (or length-for-age for children <2 yr) is a measure of linear growth, and a deficit represents the cumulative impact of adverse events, usually in the first 1000 days from conception, that result in *stunting,* or chronic malnutrition. A low height-for-age typically reflects socioeconomic disadvantage. A low **weight-for-height** , or *wasting* , usually indicates acute malnutrition. Conversely, a high weight-for-height indicates *overweight* . **Weight-for-age** is the most commonly used index of nutritional status, although a low value has limited clinical significance because it does not differentiate between wasting and stunting. Weight-for-age has the advantage of being somewhat easier to measure than indices that require height measurements. In humanitarian emergencies and some community or outpatient settings, **mid-upper arm circumference** is used for screening wasted children (Fig. 57.4).

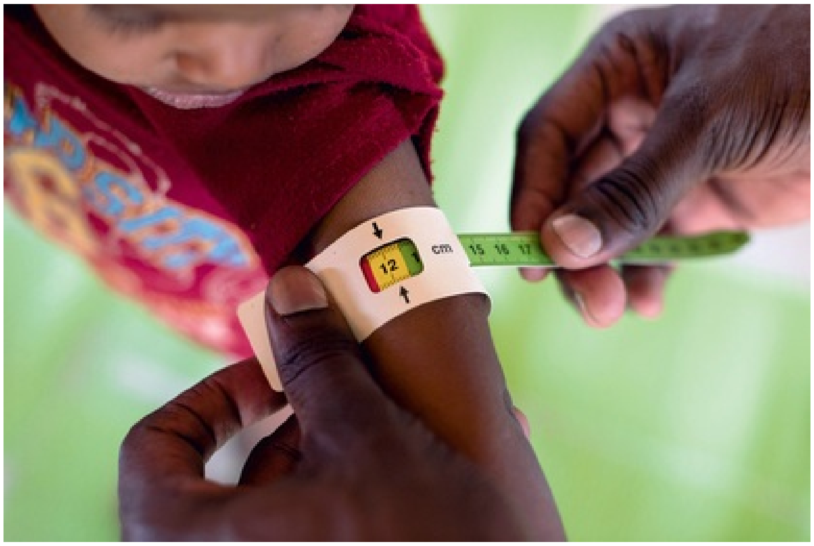

FIG. 57.4 Measuring mid-upper arm circumference. (Courtesy of Nyani Quarmyne/Panos Pictures.)

Body mass index (BMI) is calculated by dividing weight in kilograms by the square of height in meters. For children, BMI is age and gender specific. **BMI-for-age** can be used from birth to 20 yr and is a screening tool for *thinness* (less than −2 SD), *overweight* (between +1 SD and +2 SD), and *obesity* (greater than +2 SD). To diagnose obesity, additional measures of adiposity are desirable because a high BMI can result from high muscularity, and not only from excess subcutaneous fat.

Micronutrient deficiencies are another dimension of undernutrition. Those of particular public health significance are vitamin A, iodine, iron, and zinc deficiencies.

Vitamin A deficiency is caused by a low intake of retinol (in animal foods) or its carotenoid precursors, mainly beta carotene (in orange-colored fruits and vegetables and dark-green leaves) (see Chapter 61). The prevalence of *clinical deficiency* is assessed from symptoms and signs of xerophthalmia (principally night blindness and Bitot spots). *Subclinical deficiency* is defined as serum retinol concentration ≤0.70 µmol/L. Vitamin A deficiency is the leading cause of preventable blindness in children. It is also associated with a higher morbidity and mortality among young children.

Iodine deficiency is the main cause of preventable intellectual impairment (see Chapter 67). An enlarged thyroid (goiter) is a sign of deficiency. Severe deficiency in pregnancy causes fetal loss and permanent damage to the brain and central nervous system in surviving offspring (cretinism). It can be prevented by iodine supplementation before conception or during the 1st trimester of pregnancy. Postnatal iodine deficiency is associated with impaired mental function and growth retardation. The median urinary iodine concentration in children age 6-12 yr is used to assess the prevalence of deficiency in the general population, and a median of <100 µg/L indicates insufficient iodine intake.

Iron-deficiency anemia is common in childhood either from low iron intakes or poor absorption, or as a result of illness or parasite infestation (see Chapter 67). Women also have relatively high rates of anemia as a result of menstrual blood loss, pregnancy, low iron intake, poor absorption, and illness. Hemoglobin cutoffs to define anemia are 110 g/L for children 6-59 mo, 115 g/L for children 5-11 yr, and 120 g/L for children 12-14 yr. Cutoffs to define anemia for nonpregnant women are 120 g/L, 110 g/L for pregnant women, and 130 g/L for men.

Zinc deficiency increases the risk of morbidity and mortality from diarrhea, pneumonia, and possibly other infectious diseases (see Chapter 67). Zinc deficiency also has an adverse effect on linear growth. Deficiency at the population level is assessed from dietary zinc intakes or serum zinc concentrations.

Prevalence of Undernutrition

It is estimated that approximately 16% of births worldwide in 2013 were LBW. Rates of LBW are highest (28%) in southern Asia, which are twice those of sub-Saharan Africa. Globally, in 2015, 14% of children <5 yr of age were *underweight* (weight-for-age < −2 SD). The global prevalence of *stuntin* g (height-for-age < −2 SD) has declined from 33% in 2000 to 22% in 2017, with the greatest reductions occurring in Asia. Stunting prevalence is highest in the African region (30%). *Wasting* (weight-for-height < −2 SD) affects 7% of children <5 yr, with minimal change in prevalence over the past 2 decades. These figures represent 151 million stunted children, and 51 million wasted children.

Asia carries most of the global burden of underweight children because of the combination of large population size and high prevalence. In 2017, 55% of all stunted children and 69% of all wasted children lived in Asia. Africa carries most of the remaining global burden. For children <5 yr, the global prevalence is estimated to be 33% for *vitamin A deficiency,* 29% for *iodine deficiency,* 17% for *zinc deficiency,* and 18% for *iron-deficiency anemia* . Prevalence of micronutrient deficiencies tends to be highest in Africa. For pregnant women, the estimated prevalence of vitamin A deficiency is 15% and for iron-deficiency anemia, 19%.

Rates of clinical deficiency of vitamin A in children <5 yr have been declining, probably as a result of high-dose vitamin A supplementation programs and measles vaccination (because measles leads to sizable urinary loss of vitamin A), but subclinical deficiency remains widespread (>90 million children). Large-scale availability of iodized salt has reduced rates of iodine deficiency substantially, and iodized salt reaches an estimated 75% of households. In contrast, progress in reducing rates of iron-deficiency anemia is slow, and rates remain largely static.

Consequences of Undernutrition

The most profound consequence of undernutrition is premature death (Table 57.3). Fetal growth restriction together with suboptimal breastfeeding in the 1st month of life contribute to 19% of all deaths in children <5 yr (1.3 million deaths/yr). When the effects of stunting, wasting, and deficiencies of vitamin A and zinc are also considered, these 6 items jointly contribute to 45% of global child deaths (3.1 million deaths/yr), and many more are disabled or stunted for life. Anemia contributes to over one quarter of maternal deaths.

Table 57.3

Global Deaths in Children <5 yr Attributed to Nutritional Conditions

CONDITION	ATTRIBUTABLE DEATHS	% OF TOTAL DEATHS <5 YR
(a) Fetal growth restriction (<1 mo)	817,000	11.8
(b) Stunting (1-59 mo)	1,017,000	14.7
(c) Wasting (1-59 mo)	875,000	12.6
(d) Zinc deficiency (12-59 mo)	116,000	1.7
(e) Vitamin A deficiency (6-59 mo)	157,000	2.3
(f) Suboptimal breastfeeding (0-23 mo)	804,000	11.6
Joint effects of (a) + (f)	1,348,000	19.4
Joint effects of all 6 factors	3,097,000	44.7

From Black RE, Victora CG, Walker SP, et al: Maternal and child undernutrition and overweight in low- and middle-income countries, *Lancet* 382:427–451, 2013.

The risk of child death from infectious diseases increases even with mild undernutrition, and as the severity of undernutrition increases, the risk increases exponentially (Table 57.4). Undernutrition impairs immune function and other host defenses; consequently, childhood infections are more severe and longer-lasting in undernourished children and more likely to be fatal than the same illnesses in well-nourished children. Infections can adversely affect nutritional status, and young children can quickly enter a cycle of repeated infections and ever-worsening malnutrition. Even for the survivors, physical and cognitive damage as a result of undernutrition can impact their future health and economic well-being. For girls, the cycle of undernutrition is passed on to the next generation when undernourished women give birth to LBW babies.

Table 57.4

Hazard Ratios for All-Cause and Cause-Specific Deaths Associated With Stunting, Wasting, and Underweight in Children <5 yr

STANDARD DEVIATION (SD) SCORE	DEATHS				
	All	Pneumonia	Diarrhea	Measles	Other Infections
Height/length-for-age					
< −3	5.5	6.4	6.3	6.0	3.0
−3 to < −2	2.3	2.2	2.4	2.8	1.9
−2 to < −1	1.5	1.6	1.7	1.3	0.9
≥ −1	1.0	1.0	1.0	1.0	1.0
Weight-for-length					

< −3	11.6	9.7	12.3	9.6	11.2
−3 to < −2	3.4	4.7	3.4	2.6	2.7
−2 to < −1	1.6	1.9	1.6	1.0	1.7
≥ −1	1.0	1.0	1.0	1.0	1.0
Weight-for-age					
< −3	9.4	10.1	11.6	7.7	8.3
−3 to < −2	2.6	3.1	2.9	3.1	1.6
−2 to < −1	1.5	1.9	1.7	1.0	1.5
≥ −1	1.0	1.0	1.0	1.0	1.0

From Black RE, Victora CG, Walker SP, et al: Maternal and child undernutrition and overweight in low- and middle-income countries, *Lancet* 382:427–451, 2013.

Fetal growth restriction and early childhood undernutrition have consequences for adult chronic illness. LBW is associated with an increased risk of hypertension, stroke, and type 2 diabetes in adults. The increased risk is thought to reflect “fetal programming,” a process by which fetal undernutrition leads to permanent changes in the structure and metabolism of organs and systems that manifest as disease in later life. The risk is exacerbated by low weight gain during the first 2 yr of life. The increased risk of adult chronic disease from undernutrition early in life is a particular challenge to low-income countries with rapid economic growth.

Stunting before age 3 yr is associated with poorer motor and cognitive development and altered behavior in later years. The effect is 6-13 DQ (developmental quotient) points. Iodine and iron deficiencies also lead to loss of cognitive potential. Indications are that children living in areas of chronic iodine deficiency have an average reduction in IQ (intelligence quotient) of 12-13.5 points compared with children in iodine-sufficient areas. Iron deficiency has a detrimental effect on the motor development of children <4 yr and on cognition of school-age children. The estimated deficit is 1.73 IQ points for each 10 g/L decrease in hemoglobin concentration.

Undernutrition can have substantial economic consequences for survivors and their families. The consequences can be quantified in 5 categories: (1) increased costs of healthcare, either neonatal care for LBW babies or treatment of illness for infants and young children; (2) productivity losses (and thus reduced earnings) associated with smaller stature and muscle mass; (3) productivity losses from reduced cognitive ability and poorer school performance; (4) increased costs of chronic diseases associated with fetal and early child malnutrition; and (5) consequences of maternal undernutrition on future generations. The impact of nutrition on earnings appears to be independent of the effects of childhood deprivation.

Key Interventions

Interventions to address child undernutrition can be divided into those that address immediate causes (*nutrition-specific interventions*) and those that address underlying causes (*nutrition-sensitive interventions*) (Table 57.5). In the short-term, nutrition-specific interventions (e.g., salt iodization) can have substantial impact even in the absence of economic growth, and micronutrient interventions (supplementation and fortification) are consistently ranked as the most cost-effective investment. There is increased attention to nutrition-sensitive interventions as the best means of sustainably eliminating malnutrition, and to multisectoral policies that harness the synergism between the two types of intervention (e.g., cross-sectoral linkages among agriculture, nutrition, and health).

Table 57.5

Examples of Nutrition-Specific and Nutrition-Sensitive Interventions

NUTRITION-SPECIFIC INTERVENTIONS	NUTRITION-SENSITIVE INTERVENTIONS
• Promotion and support for exclusive breastfeeding for 6 mo, and continued breastfeeding for at least 2 yr • Promotion of adequate, timely, and safe complementary feeding from 6 mo • Increased micronutrient intake through dietary diversity • Micronutrient supplements for pregnant women (iron/folate) and young children (vitamin A, iron, zinc) in deficient areas • Zinc supplements to children during and after diarrhea (10-20 mg/day for 2 wk) • Prevention and treatment of severe acute malnutrition • Crop biofortification, food fortification, salt iodization • Reduced heavy physical activity in pregnancy	• Increased access to affordable, nutritious food; smallholder agriculture; credit and microfinance • Postharvest food processing and preservation • Vaccination against neonatal and childhood illness; access to healthcare • Improved water/sanitation and hygiene (e.g., handwashing with soap) • Education; women's empowerment; gender equality • Social protection (e.g., cash transfers) • Malaria prevention (vector control/bednets); intermittent preventive treatment during pregnancy and in children 3-59 mo • Birth spacing; delaying pregnancy until after 18 yr of age

To reduce the adverse consequences of undernutrition on mortality, morbidity, and cognitive development, interventions must encompass both fetal and postnatal periods. Preventing LBW is essential, with emphasis on prevention of low maternal BMI and anemia, and in the longer term, prevention of low maternal stature. Other measures include smoking cessation, birth spacing, delaying pregnancy until after 18 yr of age, and intermittent preventive treatment of malaria. In the postnatal period, promotion and support of exclusive breastfeeding is a high priority. Although the Baby Friendly Hospital Initiative has a marked benefit on rates of exclusive breastfeeding in hospital, postnatal counseling from community workers or volunteers is needed to facilitate continuation of exclusive breastfeeding at home for 6 mo (see Chapter 56). Most studies show a lower risk of HIV transmission with exclusive breastfeeding than with mixed breastfeeding. The risk of HIV transmission by breastfeeding is approximately 5–20%, depending on duration, but can be reduced to <2% with antiretroviral drugs. Even without antiretroviral drugs, exclusively breastfed children of HIV-infected mothers in low-income countries have lower mortality than non-breastfed children, because the latter are at increased risk of death from diarrhea and pneumonia.

Interventions to improve infant feeding must be designed for the local setting and thus require careful formative research during their development. Messages should be few, feasible, and culturally appropriate. For complementary feeding, nutrient-rich energy-dense mixtures of foods and responsive feeding are often emphasized. Where adequate complementary feeding is difficult to achieve and subclinical deficiencies are common, high-dose vitamin A supplementation every 6 mo in children 6-59 mo of age reduces all-cause mortality and death due to diarrhea by 12%, and zinc supplementation can reduce 1-4 yr mortality by 18%, diarrhea incidence by 13%, and pneumonia by 19%. Monitoring of child growth provides an early alert to a nutrition or health problem but is only worthwhile if accompanied by good counseling and growth promotion activities. The impact of growth monitoring and promotion will depend on coverage, intensity of contact, health worker performance and communication skills, adequacy of resources, and the motivation and ability of families to follow agreed actions.

Clinical Manifestations and Treatment of Undernutrition

Treatment of vitamin and mineral deficiencies is discussed in Chapters 61-67 . Treatment of LBW and intrauterine growth restriction is discussed in Chapter 117 .

Severe Acute Malnutrition

Severe acute malnutrition is defined as severe wasting and/or bilateral edema.

Severe wasting is extreme thinness diagnosed by a weight-for-length (or height) < −3 SD of the WHO Child Growth Standards. In children ages 6-59 mo, a mid-upper arm circumference <115 mm also denotes extreme thinness: a color-banded tape (see Fig. 57.4) is a convenient way of screening children in need of treatment.

Bilateral edema is diagnosed by grasping both feet, placing a thumb on top of each, and pressing gently but firmly for 10 sec. A pit (dent) remaining under each thumb indicates bilateral edema.

This definition of severe acute malnutrition distinguishes wasted/edematous children from those who are stunted, since stunted children (although underweight) are not a priority for acute clinical care because their deficits in height and weight cannot be corrected in the short term. The previous name *protein-energy malnutrition* is avoided because it oversimplifies the complex, multideficiency etiology. Other terms are *marasmus* (severe wasting), *kwashiorkor* (characterized by edema), and *marasmic-kwashiorkor* (severe wasting and edema).

Children with severe acute malnutrition have had a diet insufficient in energy and nutrients relative to their needs. The magnitude of the deficits will differ depending on the duration of inadequacy, quantity and diversity of food consumed, presence of antinutrients (e.g., phytate), individual variation in requirements, and number and severity of coexisting infections and their duration. Infections can lead to profound nutrient deficits and imbalances: For example, amino acids are diverted to form acute-phase proteins, and potassium, magnesium, vitamin A, and zinc are lost through diarrhea, and losses of glycine and taurine are linked to small bowel bacterial overgrowth. Ingested microbes can cause villous atrophy and loss of nutrients from maldigestion and malabsorption, as well as disruption of gut barrier function leading to microbial translocation, chronic immune activation, and altered gut microbiome (environmental enteric dysfunction). Deficits can also arise from increased nutrient utilization in response to noxae (e.g., cysteine and methionine to detoxify dietary cyanogens).

Heterogeneity in the extent and nature of the deficits and imbalances, reflecting the diverse pathways to severe acute malnutrition, helps explain why affected children differ in their clinical presentation and degree of metabolic disturbance. Children who develop edematous malnutrition are more likely than nonedematous children to have been exposed to noxae that generate oxidative stress and/or to have greater deficits in free radical–scavenging antioxidants (glutathione, vitamins A, C, and E, and essential fatty acids) or cofactors (zinc, copper, selenium).

Clinical Manifestations of Severe Acute Malnutrition (Table 57.6)

Severe wasting is most visible on the thighs, buttocks, and upper arms, as well as over the ribs and scapulae, where loss of fat and skeletal muscle is greatest (Fig. 57.5). Wasting is preceded by failure to gain weight and then by weight loss. The skin loses turgor and becomes loose as subcutaneous tissues are broken down to provide energy. The face may retain a relatively normal appearance, but eventually becomes wasted and wizened. The eyes may be sunken from loss of retroorbital fat, and lacrimal and salivary glands may atrophy, leading to lack of tears and a dry mouth. Weakened abdominal muscles and gas from bacterial overgrowth of the upper gut may lead to a distended abdomen. Severely wasted children are often fretful and irritable.

Table 57.6

Clinical Signs of Malnutrition

SITE	SIGNS
Face	Moon face (kwashiorkor), simian facies (marasmus)
Eye	Dry eyes, pale conjunctiva, Bitot spots (vitamin A), periorbital edema
Mouth	Angular stomatitis, cheilitis, glossitis, spongy bleeding gums (vitamin C), parotid enlargement
Teeth	Enamel mottling, delayed eruption
Hair	Dull, sparse, brittle hair; hypopigmentation; flag sign (alternating bands of light and normal color); broomstick eyelashes; alopecia
Skin	Loose and wrinkled (marasmus); shiny and edematous (kwashiorkor); dry, follicular hyperkeratosis; patchy hyper- and hypopigmentation (“crazy paving” or “flaky paint” dermatoses); erosions; poor wound healing
Nails	Koilonychia; thin and soft nail plates, fissures, or ridges
Musculature	Muscle wasting, particularly buttocks and thighs; Chvostek or Trousseau sign (hypocalcemia)
Skeletal	Deformities, usually as a result of calcium, vitamin D, or vitamin C deficiencies
Abdomen	Distended: hepatomegaly with fatty liver; ascites may be present
Cardiovascular	Bradycardia, hypotension, reduced cardiac output, small vessel vasculopathy
Neurologic	Global developmental delay, loss of knee and ankle reflexes, impaired memory
Hematologic	Pallor, petechiae, bleeding diathesis
Behavior	Lethargic, apathetic, irritable on handling

From Grover Z, Ee LC: Protein energy malnutrition, *Pediatr Clin North Am* 56:1055–1068, 2009.

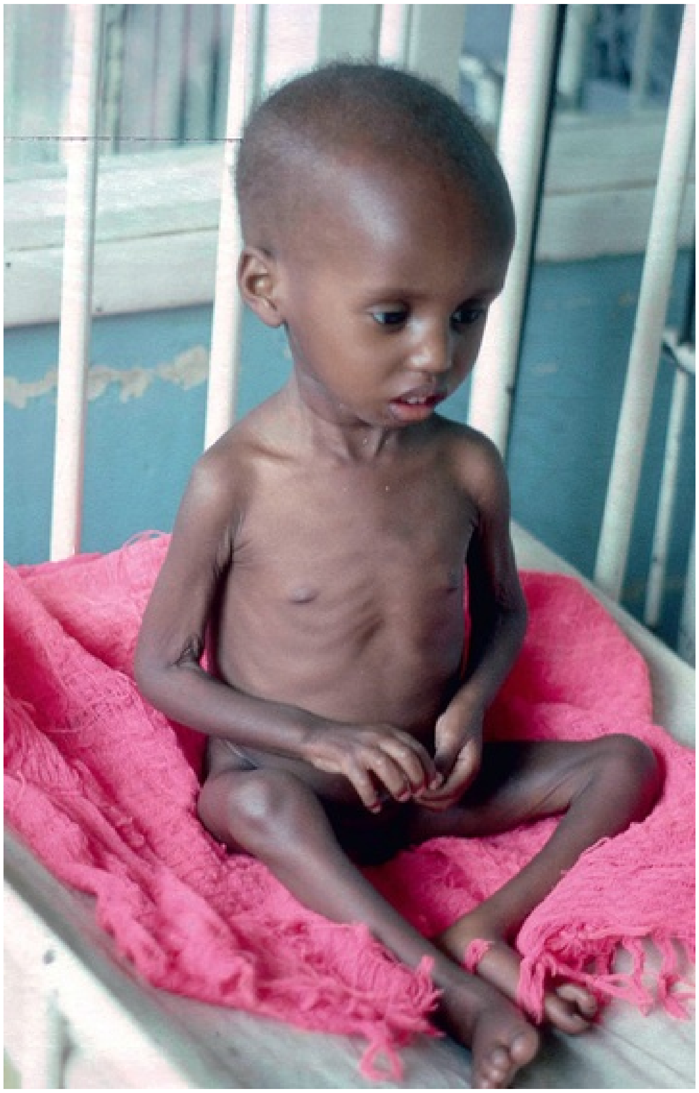

FIG. 57.5 Child with severe wasting.

In **edematous malnutrition** the edema is most likely to appear first in the feet and then in the lower legs. It can quickly develop into generalized edema affecting also the hands, arms, and face (Fig. 57.6). Skin changes typically occur over the swollen limbs and include dark, crackled peeling patches ("flaky paint" dermatosis) with pale skin underneath that is easily infected (see Figs. 57.2 and 57.6). The hair is sparse and easily pulled out and may lose its curl. In dark-haired children the hair may turn pale or reddish. The liver is often enlarged with fat. Children with edema are miserable and apathetic, and often refuse to eat.

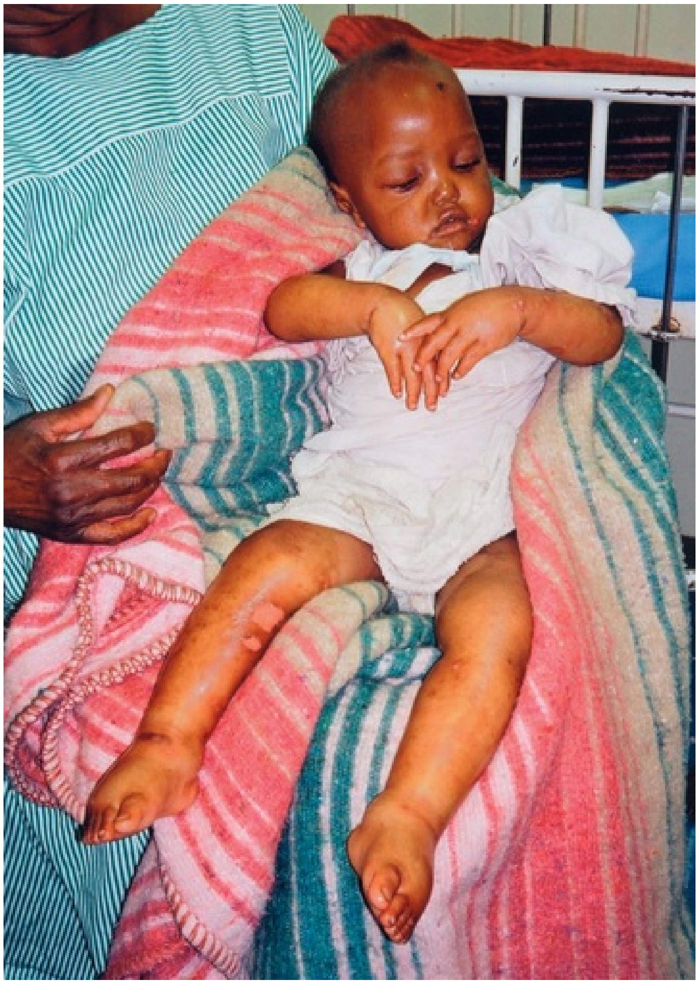

FIG. 57.6 Child with generalized edema.

Pathophysiology

When a child's intake is insufficient to meet daily needs, physiologic and metabolic changes take place in an orderly progression to conserve energy and prolong life. This process is called *reductive adaptation* . Fat stores are mobilized to provide energy. Later, protein in muscle, skin, and the gastrointestinal tract is mobilized. Energy is conserved by reducing physical activity and growth, reducing basal metabolism and the functional reserve of organs, and reducing inflammatory and immune responses. These changes have important consequences:

- The liver makes glucose less readily, making the child more prone to hypoglycemia. It produces less albumin, transferrin, and other transport proteins. It is less able to cope with excess dietary protein and to excrete toxins.

◆ Heat production is less, making the child more vulnerable to hypothermia.

◆ The kidneys are less able to excrete excess fluid and sodium, and fluid easily accumulates in the circulation, increasing the risk of fluid overload.

◆ The heart is smaller and weaker and has a reduced output, and fluid overload readily leads to death from cardiac failure.

◆ Sodium builds up inside cells due to leaky cell membranes and reduced activity of the sodium-potassium pump, leading to excess body sodium, fluid retention, and edema.

◆ Potassium leaks out of cells and is excreted in urine, contributing to electrolyte imbalance, fluid retention, edema, and anorexia.

◆ Loss of muscle protein is accompanied by loss of potassium, magnesium, zinc, and copper.

◆ The gut produces less gastric acid and enzymes. Motility is reduced, and bacteria may colonize the stomach and small intestine, damaging the mucosa and deconjugating bile salts. Digestion and absorption are impaired.

◆ Cell replication and repair are reduced, increasing the risk of bacterial translocation through the gut mucosa.

◆ Immune function is impaired, especially cell-mediated immunity. The usual responses to infection may be absent, even in severe illness, increasing the risk of undiagnosed infection.

◆ Red blood cell mass is reduced, releasing iron, which requires glucose and amino acids to be converted to ferritin, increasing the risk of hypoglycemia and amino acid imbalances. If conversion to ferritin is incomplete, unbound iron promotes pathogen growth and formation of free radicals.

◆ Micronutrient deficiencies limit the body's ability to deactivate free radicals, which cause cell damage. Edema and hair/skin changes are outward signs of cell damage.

When prescribing treatment, it is essential to take these changes in function into account. Otherwise, organs and systems will be overwhelmed, and death will rapidly ensue.

Principles of Treatment

Fig. 57.7 shows the 10 steps of treatment, which are separated into 2 phases, stabilization and rehabilitation. These steps apply to all clinical forms and all geographic locations, including North America and Europe. The aim of the **stabilization** phase is to repair cellular function, correct fluid and electrolyte imbalance, restore homeostasis, and prevent death from the interlinked triad of hypoglycemia, hypothermia, and infection. The aim of the **rehabilitation** phase is to restore wasted tissues (i.e., catch-up growth). It is essential that treatment proceeds in an ordered progression and that the metabolic machinery is repaired before any attempt is made to promote weight gain. Pushing ahead too quickly risks inducing the potentially fatal “refeeding syndrome” (see Chapter 58).

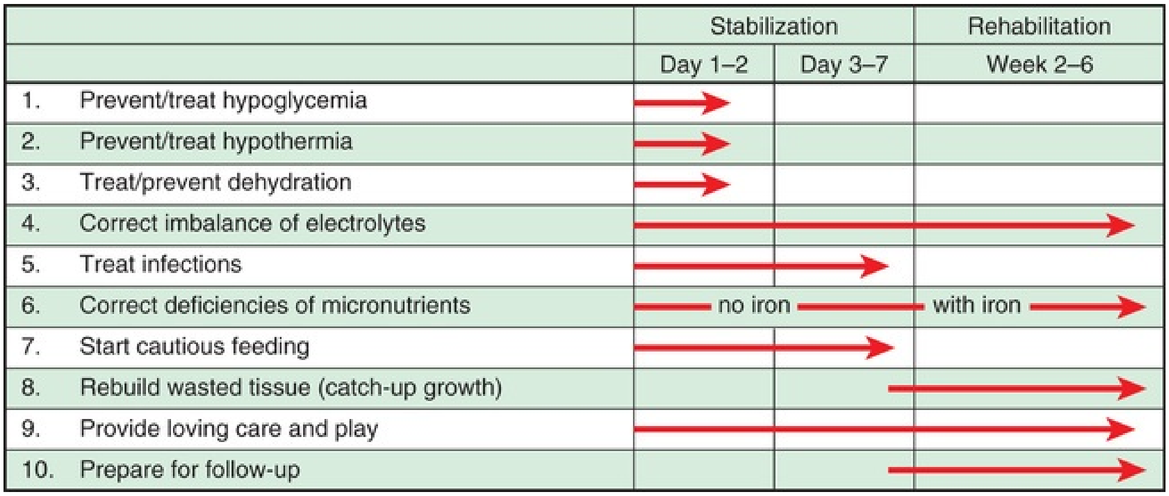

	Stabilization		Rehabilitation
	Day 1–2	Day 3–7	Week 2–6
1. Prevent/treat hypoglycemia	→		
2. Prevent/treat hypothermia	→		
3. Treat/prevent dehydration	→		
4. Correct imbalance of electrolytes	→	→	→
5. Treat infections	→	→	
6. Correct deficiencies of micronutrients	no iron	→	with iron →
7. Start cautious feeding	→	→	
8. Rebuild wasted tissue (catch-up growth)		→	→
9. Provide loving care and play	→	→	→
10. Prepare for follow-up		→	→

FIG. 57.7 The 10 steps of treatment for severe acute malnutrition and their approximate time frames.

Caregivers bring children to health facilities because of illness, rarely because of their malnutrition. A common mistake among healthcare providers is to focus on the illness and treat as for a well-nourished child. This approach ignores the deranged metabolism in malnourished children and can be fatal. Such children should be considered as severely malnourished with a complication, and treatment should follow the 10 steps. Two other potentially fatal mistakes are to treat edema with a diuretic and to give a high-protein diet in the early phase of treatment.

Emergency Treatment

Table 57.7 summarizes the therapeutic directives for malnourished children with shock and other emergency conditions. Note that treatment of shock in these children is different (less rapid, smaller volume, different fluid) from treatment of shock in well-nourished children, because shock from dehydration and shock from sepsis often coexist and are difficult to differentiate on clinical grounds. Thus the physician must be guided by the response to treatment: children with dehydration respond to intravenous (IV) fluid, whereas those with septic shock will not respond. Since severely malnourished children can quickly succumb to fluid overload, they must be monitored closely.

Table 57.7

Emergency Treatment in Severe Malnutrition

CONDITION	IMMEDIATE ACTION
Shock • Lethargic or unconscious *and* • Cold hands *Plus* either: • Slow capillary refill (>3 sec) *or* • Weak fast pulse	1. Give oxygen. 2. Give sterile 10% glucose (5 mL/kg) rapidly by IV injection. 3. Give IV fluid at 15 mL/kg over 1 hr, using: • Ringer lactate with 5% dextrose *or* • Half-normal saline[*] with 5% dextrose *or* • Half-strength Darrow solution with 5% dextrose • If all the above are unavailable, Ringer lactate 4. Measure and record pulse and respirations at the start and every 10 min. If there are signs of improvement (pulse and respiration rates fall) repeat IV drip, 15 mL/kg for 1 more hr. Then switch to oral or nasogastric rehydration with ReSoMal, 5-10 mL/kg in alternate hr (see Table 57.8 step 3). If there are no signs of improvement, assume septic shock and: 1. Give maintenance fluid IV (4 mL/kg/hr) while waiting for blood. 2. Order 10 mL/kg fresh whole blood and transfuse slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood. 3. Give furosemide, 1 mL/kg IV at start of transfusion.
Hypoglycemia Blood glucose <3 mmol/L	See Table 57.8 step 1 for treatment.
Severe dehydration	Do *not* give IV fluids except in shock. See Table 57.8 step 3 for treatment.
Very severe anemia Hgb <4 g/dL	If very severe anemia (or Hgb 4-6 g/dL *and* respiratory distress): 1. Give whole blood 10 mL/kg slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood. 2. Give furosemide 1 mL/kg IV at the start of the transfusion.
Emergency eye care Corneal ulceration	If corneal ulceration: 1. Give vitamin A immediately (age <6 mo: 50,000 IU; 6-12 mo: 100,000 IU; >12 mo: 200,000 IU) 2. Instill 1 drop atropine (1%) into affected eye to relax the eye and prevent the lens from pushing out.

[*] Some would recommend 5% dextrose in normal saline.

Hgb, Hemoglobin; IV, intravenous(ly).

Stabilization

Table 57.8 summarizes the therapeutic directives for stabilization steps 1-7 (Fig. 57.7). Giving broad-spectrum antibiotics (Table 57.9) and feeding frequent small amounts of F75 (a specially formulated low-lactose milk with 75 kcal and 0.9 g protein per 100 mL to which potassium, magnesium, and micronutrients are added), will reestablish metabolic control, treat edema, and restore appetite.

The parenteral route should be avoided; children who lack appetite should be fed by nasogastric tube, because nutrients delivered within the gut lumen help in its repair. Table 57.10 provides recipes for preparing the special feeds and their nutrient composition. Of the 2 recipes for F75, one requires no cooking, and the other is cereal based and has a lower osmolality, which may benefit children with persistent diarrhea. F75 is also available commercially; maltodextrins replace some of the sugar, and potassium, magnesium, minerals, and vitamins are already added.

Table 57.8

Therapeutic Directives for Stabilization of Malnourished Children

STEP	PREVENTION	TREATMENT
1. Prevent/treat hypoglycemia blood glucose <3 mmol/L.	Avoid long gaps without food and minimize need for glucose: 1. Feed immediately. 2. Feed every 3 hr day and night (2 hr if ill). 3. Feed on time. 4. Keep warm. 5. Treat infections (they compete for glucose). *Note:* Hypoglycemia and hypothermia often coexist and are signs of severe infection.	If conscious: 1. Give 10% glucose (50 mL), or a feed (see step 7), or 1 tsp sugar under tongue, whichever is quickest. 2. Feed every 2 hr for at least 1st day. Initially give ¼ of feed every 30 min. 3. Keep warm. 4. Start broad-spectrum antibiotics. If unconscious: 1. Immediately give sterile 10% glucose (5 mL/kg) rapidly by IV. 2. Feed every 2 hr for at least 1st day. Initially give ¼ of feed every 30 min. Use nasogastric (NG) tube if unable to drink. 3. Keep warm. 4. Start broad-spectrum antibiotics.
2. Prevent/treat hypothermia axillary <35°C (95°F); rectal <35.5°C (95.9°F).	Keep warm and dry and feed frequently. 1. Avoid exposure. 2. Dress warmly, including head and cover with blanket. 3. Keep room hot; avoid drafts. 4. Change wet clothes and bedding. 5. Do not bathe if very ill. 6. Feed frequently day and night. 7. Treat infections.	Actively rewarm. 1. Feed. 2. Skin-to-skin contact with caregiver ("kangaroo technique") or dress in warmed clothes, cover head, wrap in warmed blanket and provide indirect heat (e.g., heater; transwarmer mattress; incandescent lamp). 3. Monitor temperature hourly (or every 30 min if using heater). 4. Stop rewarming when rectal temperature is 36.5°C (97.7°F).
3. Prevent/treat dehydration.	Replace stool losses. 1. Give ReSoMal after each watery stool. ReSoMal (37.5 mmol Na/L) is a low-	Do *not* give IV fluids unless the child is in shock. 1. Give ReSoMal 5 mL/kg every 30 min for 1st 2 hr orally or NG tube. 2. Then give 5-10 mL/kg in alternate hours for up to

	sodium rehydration solution for malnutrition.	10 hr. Amount depends on stool loss and eagerness to drink. Feed in the other alternate hour. 3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins). 4. Stop when rehydrated (≥3 signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate).
4. Correct electrolyte imbalance—deficit of potassium and magnesium, excess sodium.		1. Give extra potassium (4 mmol/kg/day) and magnesium (0.6 mmol/kg/day) for at least 2 wk (see Table 57.12). *Note:* Potassium and magnesium are already added in Nutriset F75 and F100 packets.
5. Prevent/treat infections.	Minimize risk of cross-infection. 1. Avoid overcrowding. 2. Wash hands. 3. Give measles vaccine to unimmunized children age >6 mo.	Infections are often silent. Starting on 1st day, give broad-spectrum antibiotics to all children. 1. For antibiotic choices/schedule, see Table 57.9 . 2. Ensure all doses are given, and given on time. 3. Cover skin lesions so that they do not become infected. *Note:* Avoid steroids because they depress immune function.
6. Correct micronutrient deficiencies.	*Note:* Folic acid, multivitamins, zinc, copper, and other trace minerals are already added in Nutriset F75 and F100 packets.	Do *not* give iron in the stabilization phase. 1. Give vitamin A on day 1 (<6 mo 50,000 units; 6-12 mo 100,000 units; >12 mo 200,000 units) if child has any eye signs of vitamin A deficiency or has had recent measles. Repeat this dose on days 2 and 14. 2. Give folic acid, 1 mg (5 mg on day 1). 3. Give zinc (2 mg/kg/day) and copper (0.3 mg/kg/day). These are in the electrolyte/mineral solution and Combined Mineral Vitamin mix (CMV) and can be added to feeds and ReSoMal. 4. Give multivitamin syrup or CMV.
7. Start cautious feeding.		1. Give 8-12 small feeds of F75 to provide 130 mL/kg/day, 100 kcal/kg/day, and 1-1.5 g protein/kg/day. 2. If gross edema, reduce volume to 100 mL/kg/day. 3. Keep a 24-hr intake chart. Measure feeds carefully. Record leftovers. 4. If child has poor appetite, coax and encourage to finish the feed. If unfinished, reoffer later. Use NG tube if eating ≤80% of the amount offered. 5. If breastfed, encourage continued breastfeeding but also give F75. 6. Transfer to F100 when appetite returns (usually within 1 wk) and edema has been lost or is reduced. 7. Weigh daily and plot weight.

Table 57.9

Recommended Antibiotics for Malnourished Children*

GIVE	
If no complications	Amoxicillin, 25 mg/kg PO twice daily for 5 days
If complications (shock, hypoglycemia, hypothermia, skin lesions, respiratory or urinary tract infections, or lethargy/sickly)	Gentamicin, 7.5 mg/kg IV or IM once daily for 7 days *and* Ampicillin, 50 mg/kg IV or IM every 6 hr for 2 days, then amoxicillin, 25-40 mg/kg PO every 8 hr for 5 days

[*] Local resistance patterns may require these to be adjusted: Ensure that there is Gram-negative cover.

If specific infections are identified, add appropriate antibiotics.

For persistent diarrhea or small bowel overgrowth, add metronidazole, 7.5 mg/kg PO every 8 hr for 7 days.

PO, Orally; IM, intramuscularly; IV, intravenously.

Table 57.10

Recipes for Milk Formulas F75 and F100

	F75 [b] (STARTER)	**F75 [c] (STARTER) (CEREAL-BASED)**	**F100 [d] (CATCH-UP)**
Dried skimmed milk (g)	25	25	80
Sugar (g)	100	70	50
Cereal flour (g)	—	35	—
Vegetable oil (g)	30	30	60
Electrolyte/mineral solution (mL) [a]	20	20	20
Water: make up to (mL)	1000	1000	1000
Content/100 mL			
Energy (kcal)	75	75	100
Protein (g)	0.9	1.1	2.9
Lactose (g)	1.3	1.3	4.2
Potassium (mmol)	4.0	4.2	6.3
Sodium (mmol)	0.6	0.6	1.9
Magnesium (mmol)	0.43	0.46	0.73
Zinc (mg)	2.0	2.0	2.3
Copper (mg)	0.25	0.25	0.25
% Energy from protein	5	6	12
% Energy from fat	32	32	53
Osmolality (mOsm/L)	413	334	419

[a] See Table 57.12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).

[b] A comparable F75 can be made from 35 g dried whole milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 300 mL full-cream cow's milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.

[c] This lower-osmolality formula may be helpful for children with dysentery or persistent diarrhea. Cook for 4 min.

[d] A comparable F100 can be made from 110 g dried whole milk, 50 g sugar, 30 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 880 mL full-cream cow's milk, 75 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.

Whisk at high speed to prevent oil from separating out.

Dehydration status is easily misdiagnosed in severely wasted children, because the usual signs (e.g., slow skin pinch, sunken eyes) may be present even without dehydration. Rehydration must therefore be closely monitored for signs of fluid overload. Serum electrolyte levels can be misleading because of sodium leaking from the blood into cells and potassium leaking out of cells. Keeping the intake of electrolytes and nutrients constant (see Table 57.8) allows systems to stabilize more quickly than adjusting intake in response to laboratory results.

Table 57.11 provides a recipe for the special rehydration solution used in severe malnutrition (ReSoMal). Therapeutic **Combined Mineral Vitamin mix (CMV)** contains electrolytes, minerals, and vitamins and is added to ReSoMal and feeds. If unavailable, potassium, magnesium, zinc, and copper can be added as an electrolyte/mineral stock solution (Table 57.12 provides a recipe), and a multivitamin supplement can be given separately.

Table 57.11

Recipe for Rehydration Solution for Malnutrition (ReSoMal)

INGREDIENT	AMOUNT
Water	2 L
WHO ORS	One 1-L sachet*
Sucrose	50 g
Electrolyte/mineral solution †	40 mL

* Sachet contains 2.6 g sodium chloride, 2.9 g trisodium citrate dihydrate, 1.5 g potassium chloride, and 13.5 g glucose.

† See Table 57.12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).

ReSoMal contains 37.5 mmol sodium and 40 mmol potassium/L.

WHO ORS, World Health Organization Oral Rehydration Solution.

Table 57.12

Recipe for Concentrated Electrolyte/Mineral Solution*

INGREDIENT	**g**	**mol/20 mL**
Potassium chloride: KCl	224.0	24 mmol
Tripotassium citrate	81.0	2 mmol
Magnesium chloride: $MgCl_2 \cdot 6H_2O$	76.0	3 mmol
Zinc acetate: Zn acetate$\cdot 2H_2O$	8.2	300 µmol
Copper (cupric) sulfate: $CuSO_4 \cdot 5H_2O$	1.4	45 µmol
Water: make up to	2500 mL	

[*] Make fresh each month. Use cooled boiled water.

Add 20 mL when preparing 1 L of feed or ReSoMal.

Rehabilitation

The signals for entry to the rehabilitation phase are reduced or minimal edema and return of appetite.

A controlled transition over 3 days is recommended to prevent refeeding syndrome (see Chapter 58). After the transition, unlimited amounts should be given of a high-energy, high-protein milk formula such as F100 (100 kcal and 3 g protein per 100 mL), or a **ready-to-use therapeutic food (RUTF)** , or family foods modified to have comparable energy and protein contents.

To make the transition, for 2 days replace F75 with an equal volume of F100, then increase each successive feed by 10 mL until some feed remains uneaten (usually at about 200 mL/kg/day). After this transition, give 150-220 kcal/kg/day and 4-6 g protein/kg/day, and continue to give potassium, magnesium, and micronutrients. Add iron (3 mg/kg/day). If breastfed, encourage continued breastfeeding. Children with severe malnutrition have developmental delays, so loving care, structured play, and sensory stimulation during and after treatment are essential to aid recovery of brain function.

Community-Based Treatment

Many children with severe acute malnutrition can be identified in their communities before medical complications arise. If these children have a good appetite and are clinically well, they can be rehabilitated at home through community-based therapeutic care, which has the added benefit of reducing their exposure to nosocomial infections and providing continuity of care after recovery. It also reduces the time caregivers spend away from home and their opportunity costs and can be cost-effective for health services.

Fig. 57.8 shows the criteria for inpatient and outpatient care. To maximize coverage and compliance, community-based therapeutic care has 4 main elements: community mobilization and sensitization, active case finding, therapeutic care, and follow-up after discharge.

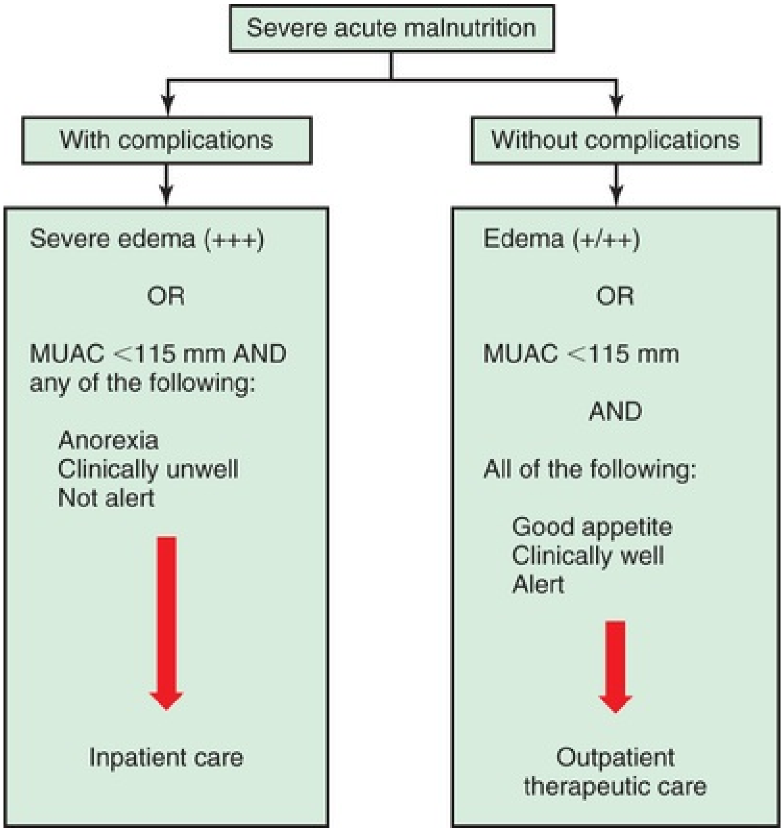
Severe acute malnutrition
With complications
Without complications
Severe edema (+++)
OR
MUAC <115 mm AND
any of the following:
Anorexia
Clinically unwell
Not alert
Inpatient care
Edema (+/++)
OR
MUAC <115 mm
AND
All of the following:
Good appetite
Clinically well
Alert
Outpatient
therapeutic care

FIG. 57.8 Flow diagram for inpatient care (*left*) and outpatient care (*right*) in the child with severe acute malnutrition. MUAC, Mid-upper arm circumference.

Community-based therapeutic care comprises steps 8-10 (Fig. 57.7), plus a broad-spectrum antibiotic (step 5). RUTF is usually provided, especially in times of food shortage. RUTF is specially designed for rehabilitating children with severe acute malnutrition at home. It is high in energy and protein and has electrolytes and micronutrients added. The most widely used RUTF is a thick paste that contains milk powder, peanuts, vegetable oil, and sugar. Pathogens cannot grow in it because of its low moisture content. Hospitalized children who have completed steps 1-7 and the transition can be transferred to community-based care for completion of their rehabilitation, thereby reducing their hospital stay to about 7-10 days.

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CHAPTER 58

Refeeding Syndrome

Robert M. Kliegman

The **refeeding syndrome** may occur if high-energy feeding is started too soon or too vigorously, and it may lead to sudden death with signs of heart failure. Early accounts of the syndrome were among starved survivors of wartime sieges and concentration camps and among prisoners of war when given sudden access to unlimited food. The refeeding syndrome occurs in malnourished individuals as a result of untimely, overzealous oral, enteral, or parenteral (highest risk) feeding, and the risk is not widely recognized. Refeeding syndrome has also been seen among malnourished patients with anorexia nervosa with a body mass index (BMI) <70% median values. Onset is usually 24-48 hr after the start of high-energy feeding and is characterized by breathlessness, rapid pulse, increased venous pressure, rapid enlargement of the liver, and watery diarrhea. Other features are noted in Table 58.1 .

Table 58.1

Clinical Signs and Symptoms of Refeeding Syndrome

HYPOPHOSPHATEMIA	HYPOKALEMIA	HYPOMAGNESEMIA	VITAMIN/THIAMINE DEFICIENCY	SODIUM RETENT
Cardiac Hypotension Decreased stroke volume ***Respiratory*** Impaired diaphragm contractility Dyspnea Respiratory failure ***Neurologic*** Paresthesia Weakness Confusion Disorientation	***Cardiac*** Arrhythmias ***Respiratory*** Failure ***Neurologic*** Weakness Paralysis ***Gastrointestinal*** Nausea Vomiting Constipation ***Muscular*** Rhabdomyolysis	***Cardiac*** Arrhythmias ***Neurologic*** Weakness Tremor Tetany Seizures Altered mental status Coma ***Gastrointestinal*** Nausea Vomiting Diarrhea	Encephalopathy Lactic acidosis Death	Fluid ove Pulmonar edema Cardiac compro

Lethargy Areflexic paralysis Seizures Coma ***Hematologic*** Leukocyte dysfunction Hemolysis Thrombocytopenia ***Other*** Death	Muscle necrosis ***Other*** Death	**Other** Refractory hypokalemia and hypocalcemia Death		

Data from Kraft MD, Btaiche IF, Sacks GS: Review of RFS, *Nutr Clin Pract* 20:625–633, 2005. From Fuentebella J, Kerner JA: Refeeding syndrome, *Pediatr Clin North Am* 56:1201–1210, 2009.

An increase in the supply of energy (usually carbohydrates) is accompanied by an increase in sodium pump activity, and too sudden a supply risks causing a rapid release of accumulated sodium from cells, causing expansion of extracellular and plasma volumes. At the same time there is increased uptake by cells of glucose, potassium, magnesium, and phosphate. A sudden lowering of serum potassium, magnesium, and phosphate concentrations is an important feature of the refeeding syndrome.

The key to preventing the syndrome is to minimize the risk of its occurrence. It can be avoided by following the World Health Organization (WHO) guidelines for the treatment of malnutrition (see Chapter 57). Of particular relevance to minimizing the risk is the initial **stabilization phase** , which includes providing maintenance amounts of energy and protein and correcting electrolyte imbalances and micronutrient deficiencies, followed by a controlled transition to high-energy feeding. Milk-based diets are desirable because milk is a good source of phosphate. No or minimal edema and return of appetite are signs of readiness for the transition. Monitoring for sudden increases in pulse and respiration rates during the transition to high-energy feeding is advisable to detect these early warning signs. Should refeeding syndrome occur, prompt treatment with a single parenteral dose of digoxin and furosemide has been useful.

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CHAPTER 59

Malnutrition

Lucinda Lo, Allison Ballantine

Failure to thrive (FTT) has classically been the term used to describe children who are not growing as expected. Studies have advocated using the term **malnutrition** to describe this cohort of children with specifically defined classification based on anthropometric measurements. In this chapter, malnutrition refers to **undernutrition** and is defined as an imbalance between nutrient requirements and intake or delivery that then results in deficits—of energy, protein, or micronutrients—that may negatively affect growth and development. Malnutrition may be illness related or non–illness related, or both. Illness-related malnutrition may be caused by one or more diseases, infections, or congenital anomalies, as well as by injury or surgery. Non–illness-related causes include environmental, psychosocial, or behavioral factors. Often, one cause may be primary and exacerbated by another. Patients with malnutrition may present with growth deceleration, faltering growth, or even weight loss, as measured by anthropometric parameters, including weight, height/length, skinfolds, and mid-upper arm circumference (see Chapter 57).

Clinical Manifestations

Inadequate weight-for–corrected age, failure to gain adequate weight over a period of time (weight gain velocity), height velocity, weight-for-height, body mass index (BMI), and developmental outcomes help define malnutrition (see Chapter 57). These growth and anthropometric parameters should be measured serially and plotted on growth charts appropriate for the child's sex, age (corrected if premature), and, if known, genetic disorders, such as trisomy 21. The American Academy of Pediatrics (AAP) and U.S. Centers for Disease Control and Prevention (CDC) recommend the 2006 World Health Organization

(WHO) charts for children up to 2 yr of age who are measured supine for length. The CDC 2000 growth charts are recommended for children and adolescents (age 2-20 yr) when measured with a standing height. The severity of malnutrition (mild, moderate, or severe) may be determined by plotting the z score (standard deviation [SD] from the mean) for each of these anthropometric values (Table 59.1).

Table 59.1

Comprehensive Malnutrition Indicators

INDICATORS[*]	**SEVERE MALNUTRITION**	**MODERATE MALNUTRITION**	**MILD MALNUTRITION**
Weight-for-length z score	≥ −3 z score or worse	−2.0 to 2.99 z score	−1.0 to −1.99 z score [†]
BMI-for-age z score	≥ −3 z score or worse	−2.0 to 2.99 z score	−1.0 to −1.99 z score [†]
Weight-for-length/height z score	≥ −3 z score or worse	No data available	No data available
Mid-upper arm circumference (<5 yr of age)	≥ −3 z score or worse	−2.0 to 2.99 z score	−1.0 to −1.99 z score
Weight gain velocity (≤2 yr of age)	≤25% of norm	26–50% of norm	51–75% of the norm
Weight loss (2-20 yr of age)	>10% of UBW	>7.5% UBW	>5% UBW
Deceleration in weight-for-length/height or BMI-for-age	Deceleration across 3 z score lines	Deceleration across 2 z score lines	Deceleration across 1 z score line
Inadequate nutrient intake	≤25% of estimated energy − protein need	26–50% of estimated energy − protein need	51–75% of estimated energy − protein need

[*] It is recommended that when a child meets more than one malnutrition acuity level, the provider should document the severity of the malnutrition at the highest acuity level to ensure that an appropriate treatment plan and appropriate intervention, monitoring, and evaluation are provided.

[†] Needs additional positive diagnostic criteria to make a malnutrition diagnosis.

BMI, Body mass index; UBW, usual body weight.

Use clinical judgment when applying these diagnostic criteria.

Adapted from Becker PJ, Carney LN, Corkins MR, et al: Consensus Statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: Indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *J Acad Nutr Diet* 114(12):1988-2000, 2014.

Etiology and Diagnosis

The most common mechanisms for illness-related causes of insufficient growth include (1) failure to ingest sufficient calories, or starvation (e.g., cardiac failure, fluid restriction), (2) increased nutrient losses (e.g., protein-losing enteropathy, chronic diarrhea), (3) increased metabolic demands, as seen in extensive burn injuries, and (4) altered nutrient absorption or utilization (e.g., cystic fibrosis, short bowel syndrome). More than one mechanism can exist simultaneously (Fig. 59.1). *Acute malnutrition* is defined as having a duration of <3 mo (see Chapter 57).

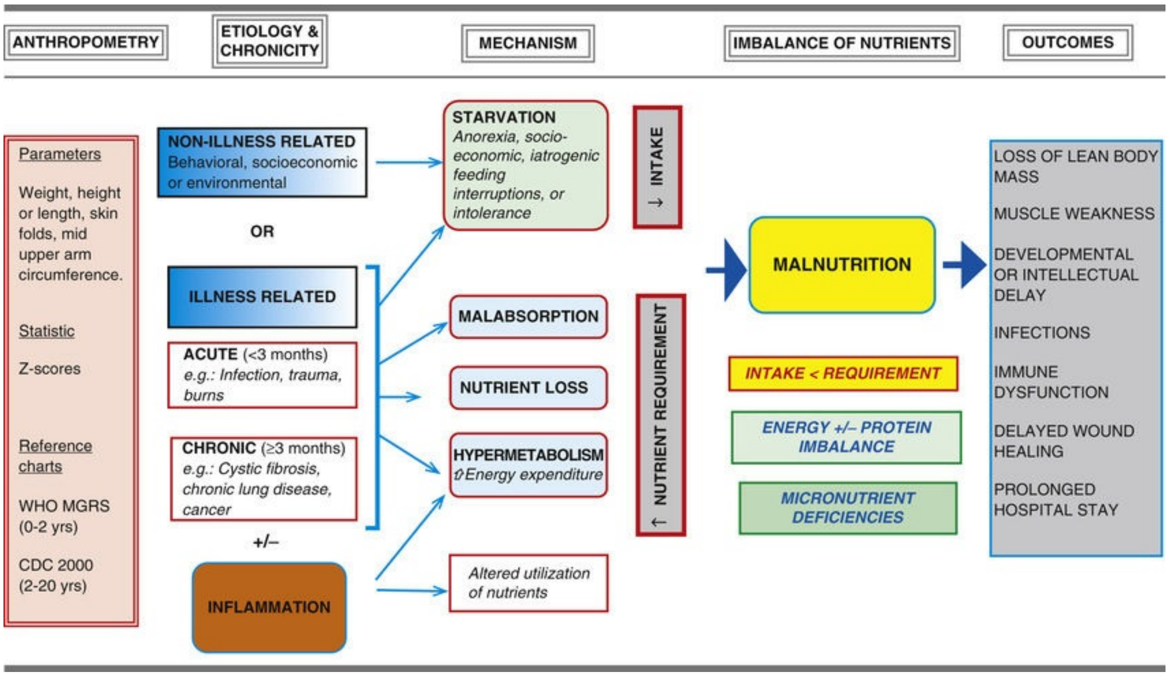
ANTHROPOMETRY
ETIOLOGY & CHRONICITY
MECHANISM
IMBALANCE OF NUTRIENTS
OUTCOMES
Parameters
Weight, height or length, skin folds, mid upper arm circumference.
Statistic
Z-scores
Reference charts
WHO MGRS (0-2 yrs)
CDC 2000 (2-20 yrs)
NON-ILLNESS RELATED
Behavioral, socioeconomic or environmental
OR
ILLNESS RELATED
ACUTE (<3 months) e.g.: Infection, trauma, burns
CHRONIC (≥3 months) e.g.: Cystic fibrosis, chronic lung disease, cancer
+/–
INFLAMMATION
STARVATION
Anorexia, socio-economic, iatrogenic feeding interruptions, or intolerance
MALABSORPTION
NUTRIENT LOSS
HYPERMETABOLISM
⇧Energy expenditure
Altered utilization of nutrients
↓ INTAKE
↑ NUTRIENT REQUIREMENT
MALNUTRITION
INTAKE < REQUIREMENT
ENERGY +/– PROTEIN IMBALANCE
MICRONUTRIENT DEFICIENCIES
LOSS OF LEAN BODY MASS
MUSCLE WEAKNESS
DEVELOPMENTAL OR INTELLECTUAL DELAY
INFECTIONS
IMMUNE DYSFUNCTION
DELAYED WOUND HEALING
PROLONGED HOSPITAL STAY

FIG. 59.1 **Defining malnutrition in hospitalized children (ASPEN). CDC, Centers for Disease Control and Prevention; MGRS, Multicenter Growth Reference Study; WHO, World Health Organization. From Mehta NM, Corkins MR, Lyman B, et al: Defining pediatric malnutrition: A paradigm shift toward etiology-related definitions. JPEN J Parenter Enteral Nutr 37(4):460-481, 2013.**

A complete history should include a detailed nutritional, family, and prenatal history; the quantity, quality, and frequency of meals; and further information regarding the onset of the growth failure (Table 59.2). A comprehensive physical examination is necessary to elicit underlying etiologies (Table 59.3). Puberty is often delayed or stalled in malnutrition, so Tanner stage should be carefully noted during the initial evaluation of preteens and adolescents. Tanner staging cannot be used as a marker for nutritional status, but it is influenced by malnourishment. Puberty will usually resume progression when the malnourished state improves. Laboratory evaluation of children with malnutrition should be judicious and based on findings from the history and physical examination. Obtaining the state's newborn screening results, a complete blood count, and urinalysis represent a reasonable initial screen.

Table 59.2

Approach to Malnutrition Based on Signs and Symptoms

HISTORY/PHYSICAL EXAMINATION	DIAGNOSTIC CONSIDERATION
Spitting, vomiting, food refusal	Gastroesophageal reflux, chronic tonsillitis, food allergies, eosinophilic esophagitis
Diarrhea, fatty stools	Malabsorption, intestinal parasites, milk protein intolerance, pancreatic insufficiency, celiac disease, immunodeficiency, inflammatory bowel disease
Snoring, mouth breathing, enlarged tonsils	Adenoid hypertrophy, obstructive sleep apnea
Recurrent wheezing, pulmonary infections	Asthma, aspiration, food allergy, cystic fibrosis, immunodeficiency
Recurrent infections	HIV or congenital primary immunodeficiency diseases, anatomic defects
Travel to/from developing countries	Parasitic or bacterial infections of gastrointestinal tract

Table 59.3

Findings in Failure to Thrive in Infancy

CAUSE	APPROXIMATE PERCENTAGE OF ALL CASES	HISTORY	SYSTEM-SPECIFIC PHYSICAL FINDINGS	SYSTEM-SPECIFIC LABORATORY STUDIES
Psychosocial	Up to 50% or more	Vague, inconsistent feeding history, history of bottle propping	None, may have soft neurologic signs	None
CNS	13%	Poor feeding, gross developmental delay, vomiting	Grossly abnormal neurologic findings	Frequent gross abnormalities on EEG and MRI scan or grossly abnormal tests of neuromuscular function
Gastrointestinal	10%	Chronic vomiting and/or diarrhea, abnormal stools, crying with feedings, nocturnal cough/snoring	Often negative, may have abdominal distention	Abnormal barium, pH probe, or endoscopic study; abnormal stool findings (pH, reducing substances, fat stain, Wright

				stain)
Cardiac	9%	Slow feeding, dyspnea and diaphoresis with feeding, restlessness and diaphoresis during sleep	Often cyanotic or have signs of congestive heart failure	Abnormal echocardiogram, ECG, catheterization findings
Genetic	8%	May have positive family history or a history of developmental delay	Often have facies typical of a syndrome, skeletal abnormalities, neurologic abnormalities, or visceromegaly	May have typical radiographic findings, chromosomal abnormalities, abnormal metabolic screens
Pulmonary	3.5%	Chronic or recurrent dyspnea with feedings, tachypnea	Grossly abnormal chest examination findings	Abnormal chest radiographs
Renal	3.5%	May be negative or may have history of polyuria	Often negative, may have flank masses	Abnormal urinalysis, frequently elevated BUN and creatinine, signs of renal osteodystrophy on radiographs
Endocrine	3.5%	With hypothyroidism, constipation and decreased activity level; with diabetes, polyuria, polydipsia	With hypothyroidism, no wasting but mottling, umbilical hernia, often open posterior fontanelle. With diabetes, often without specific abnormality, but may have signs of dehydration, ketotic breath, and hyperpnea. With hypopituitarism and isolated growth hormone deficiency, growth normal until 9 mo or later, then plateaus, but normal weight for height; delayed tooth eruption	Decreased T_4 , increased TSH; glucosuria and hyperglycemia; abnormal pituitary function study results

BUN, Blood urea nitrogen; *CNS,* central nervous system; *CT,* computed tomography; *ECG,* electrocardiogram; *EEG,* electroencephalogram; T_4 , thyroxine; *TSH,* thyroid-stimulating hormone.

From Carrasco MM, Wolford JE: Child abuse and neglect. In Zitelli BJ, McIntire SC, Nowalk AJ, editors: Atlas of pediatric physical diagnosis, ed 7, Philadelphia, 2018, Elsevier, Table 6.6.

Additional measurements that are useful for following the progress of the acutely malnourished child are mid-upper arm circumference (MUAC) and hand-grip strength. MUAC is a particularly useful anthropometric measure when weight may be distorted by use of corticosteroids or fluid status (e.g., ascites, edema).

For children 6 yr and older, **hand-grip strength** may be a more acute measurement of response to nutritional intervention than MUAC, because muscle function reacts earlier to changes in nutritional status than does muscle mass. The *dynamometer* is a simple, noninvasive, and low-cost instrument for measuring baseline functional status and tracking progress throughout the therapeutic course. Hand-grip strength can help to identify the presence of malnutrition, but the current lack of reference ranges for mild, moderate, and severe malnutrition in large populations limit the ability to use hand-grip strength to quantify the degree of malnutrition.

Treatment

While an illness-related etiology of mild malnutrition is being investigated, caloric supplementation should occur simultaneously. Both the medical workup and the initiation of supplemental oral feeds should occur in the outpatient setting with close follow-up. Consider including a speech therapist for a suck-and-swallow evaluation if the history suggests difficulty with oral feeds. If a child has not responded after 2-3 mo of outpatient management. consider hospitalization for potential initiation of nasogastric tube feeds, further diagnostic and laboratory evaluation, assessment and observed implementation of adequate nutrition, and evaluation of the parent–child feeding interaction. Additional indications for hospitalization include moderate or severe malnutrition, since the potential for refeeding syndrome requires close monitoring (see Chapter 58). The type of caloric supplementation is based on the severity of malnutrition and the underlying medical condition. The response to feeding depends on the specific diagnosis, medical treatment, and severity of malnutrition.

The same anthropometric measures used to diagnosis malnutrition should be used to measure progress and recovery from the malnourished state. Multivitamin supplementation should be given to all children with malnutrition to meet the recommended dietary allowance, because these children usually have iron, zinc, and vitamin D deficiencies, as well as increased micronutrient demands with catch-up growth.

Therapy for the psychosocial factors should be specific for the underlying issue, such as maternal depression or insufficient funds for food. In addition, parent education should focus on what is normal infant development and on correcting any parental misconceptions about feeding and temperament, as well as learning the infant cues for hunger, satiety, and sleep. Some children who develop feeding aversion behaviors will require treatment by a specialized feeding team. If abuse or purposeful neglect is a concern, the family should be referred to the child protective services team.

Prognosis

Malnutrition, regardless of cause, is concerning because of the detrimental effect on physical and intellectual growth and development. Early diagnosis and treatment of acute malnutrition allow children to catch up to and sometimes even surpass their peers who were not malnourished. The long-term sequelae of malnutrition in young infants and children have been conflicting, and there is no clear consensus regarding the long-term emotional, cognitive, and metabolic effects. Despite inconclusive long-term outcomes in children who have malnutrition, investigators support early nutritional interventions for children who have poor growth.

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CHAPTER 60

Overweight and Obesity

Sheila Gahagan

Epidemiology

Obesity is an important pediatric public health problem associated with risk of complications in childhood and increased morbidity and mortality throughout adult life. Obesity is now linked to more deaths than underweight. In 2014, according to the World Health Organization (WHO), more than 1.9 billion persons ≥20 yr old were overweight or obese.

In the United States, 37% of adults are obese, and 35% are overweight. In children the prevalence of obesity increased 300% over approximately 40 yr. According to the National Health and Nutrition Examination Survey (NHANES), 2013–2014, 34% of children 2-19 yr old were overweight or obese, with 17% in the obese range. Risk for obesity in children 2-19 yr old varies significantly by race/ethnicity, with >20% for minority children compared with 15% for white children. Across all racial groups, higher maternal education confers protection against childhood obesity.

The first 1000 days, the period from conception to age 2 yr, are increasingly recognized as a modifiable period related to risk for childhood obesity. Parental obesity correlates with a higher risk for obesity in the children. Prenatal factors, including high preconceptual weight, gestational weight gain, high birthweight, and maternal smoking, are associated with increased risk for later obesity. Paradoxically, intrauterine growth restriction with early infant catch-up growth is associated with the development of central adiposity and adult-onset cardiovascular (CV) risk. Breastfeeding is modestly protective for obesity based on dose and duration. Infants with high levels of negative reactivity (temperament) are more at risk for obesity than those with better self-regulation.

Body Mass Index

Obesity or increased adiposity is defined using the **body mass index (BMI)** , an excellent proxy for more direct measurement of body fat. BMI = weight in kg/(height in meters)^2 . Adults with a BMI ≥30 meet the criterion for obesity, and those with a BMI 25-30 fall in the overweight range. During childhood, levels of body fat change beginning with high adiposity during infancy. Body fat levels decrease for approximately 5.5 yr until the period called *adiposity rebound*, when body fat is typically at the lowest level. Adiposity then increases until early adulthood (Fig. 60.1). Consequently, obesity and overweight are defined using BMI percentiles for children ≥2 yr old and weight/length percentiles for infants <2 yr old. The criterion for **obesity** is BMI ≥95th percentile and for **overweight** is BMI between 85th and 95th percentiles.

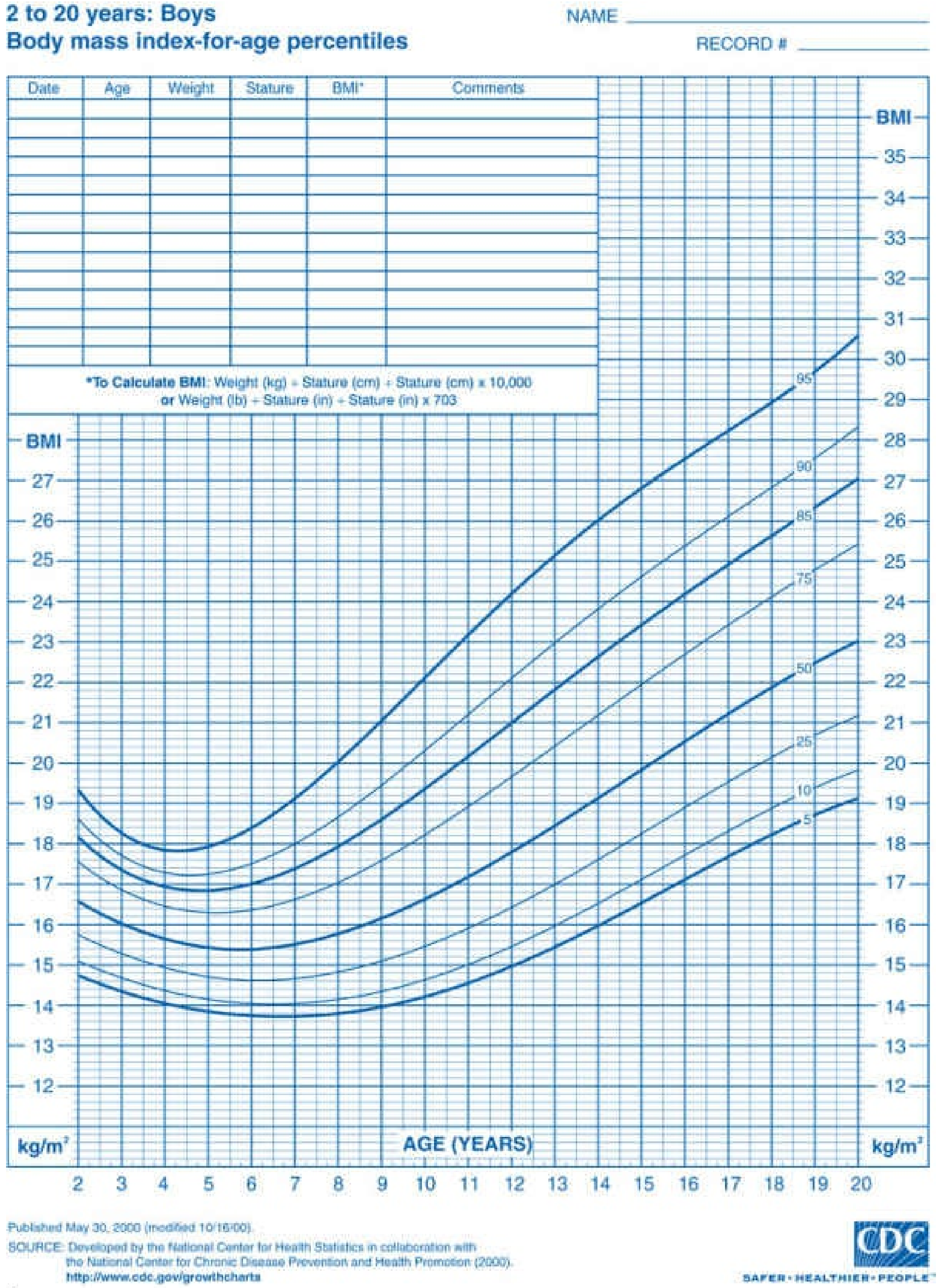

Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

A

A, Body mass index (BMI)-for-age profiles for boys and men. (Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion,

2000. See www.cdc.gov/growthcharts .)

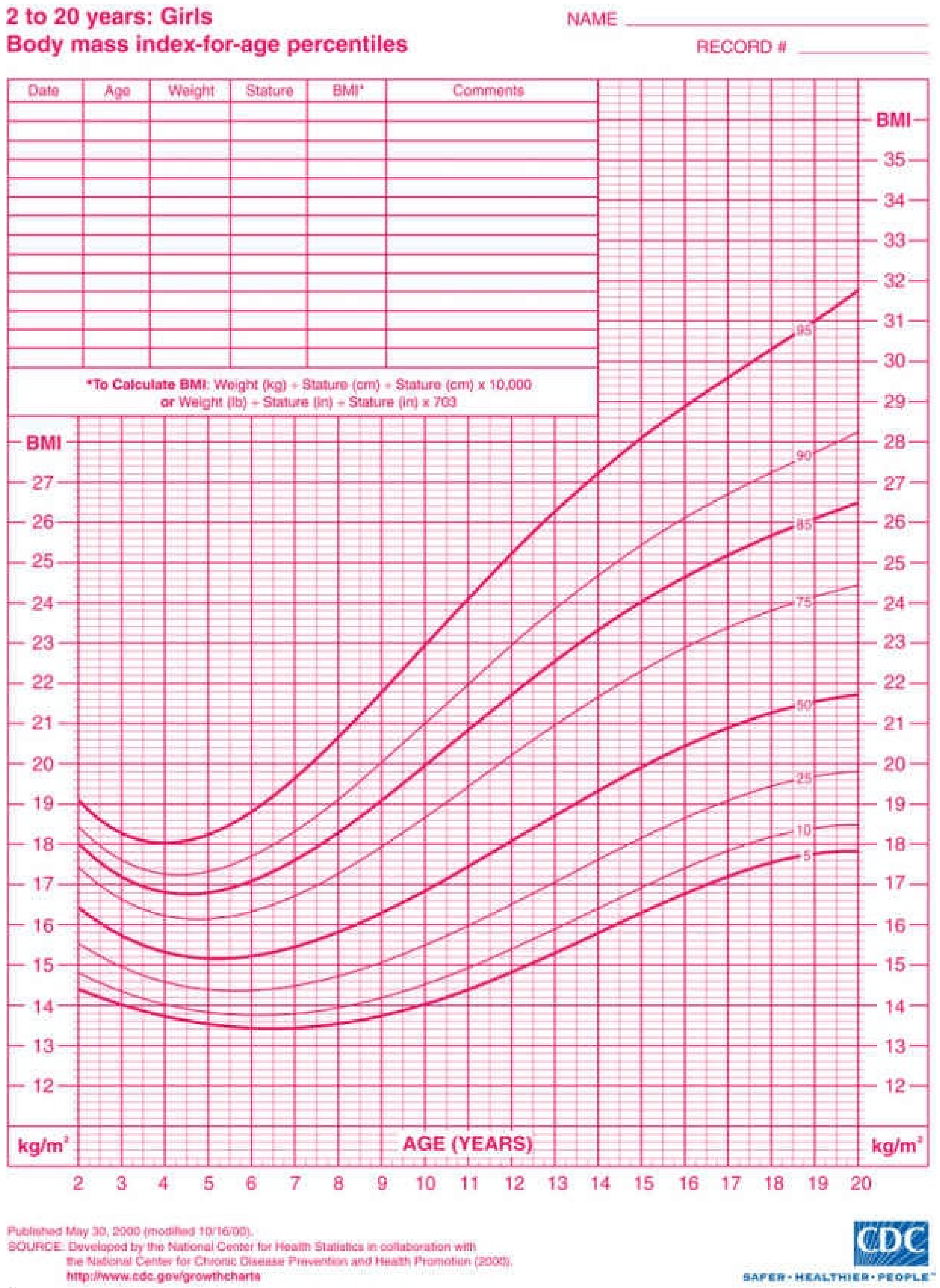

B

B, BMI-for-age profiles for girls and women.

FIG. 60.1

Etiology

Humans have the capacity to store energy in adipose tissue, allowing improved survival in times of famine. Simplistically, obesity results from an imbalance of caloric intake and energy expenditure. Even incremental but sustained caloric excess results in excess adiposity. Individual adiposity is the result of a complex interplay among genetically determined body habitus, appetite, nutritional intake, **physical activity (PA)** , and energy expenditure. Environmental factors determine levels of available food, preferences for types of foods, levels of PA, and preferences for types of activities. Food preferences play a role in consumption of energy-dense foods. Humans innately prefer sweet and salty foods and tend initially to reject bitter flavors, common to many vegetables. Repeated exposure to healthy foods promotes their acceptance and liking, especially in early life. This human characteristic to adapt to novel foods can be used to promote healthy food selection.

Environmental Changes

Over the last 4 decades, the food environment has changed dramatically related to urbanization and the food industry. As fewer families routinely prepare meals, foods prepared by a food industry have higher levels of calories, simple carbohydrates, and fat. The price of many foods has declined relative to the family budget. These changes, in combination with marketing pressure, have resulted in larger portion sizes and increased snacking between meals. The increased consumption of high-carbohydrate beverages, including sodas, sport drinks, fruit punch, and juice, adds to these factors.

Fast food is consumed by one third of U.S. children each day and by two thirds of children every week. A typical fast food meal can contain 2000 kcal and 84 g of fat. Many children consume 4 servings of high-carbohydrate beverages per day, resulting in an additional 560 kcal of low nutritional value. Sweetened beverages have been linked to increased risk for obesity. The dramatic increase in the use of high-fructose corn syrup to sweeten beverages and prepared foods is another important environmental change, leading to availability of inexpensive calories.

Since World War II, levels of PA in children and adults have declined. According to the 2012 NHANES survey, 25% of 12-15 yr olds met PA guidelines of 60 min of PA per day. Decline in PA is related to many factors, including changes in the built environment, more reliance on cars, lower levels of active transportation, safety issues, and increasingly sedentary lifestyles. Many sectors of society do not engage in PA during leisure time. For children, budgetary constraints and pressure for academic performance have led to less time devoted to physical education in schools. Perception of poor neighborhood safety also leads to lower levels of PA. Furthermore, screens (televisions, tablets, smartphones, computers) offer compelling sedentary activities that do not burn calories.

Sleep plays a role in risk for obesity. Over the last 4 decades, children and adults have decreased the amount of time spent sleeping. Reasons for these changes may relate to increased time at work, increased time watching television, and a generally faster pace of life. Chronic partial sleep loss can increase risk for weight gain and obesity, with the impact possibly greater in children than in adults. In studies of young, healthy, lean men, short sleep duration was associated with decreased leptin levels and increased ghrelin levels, along with increased hunger and appetite. *Sleep debt* also results in decreased glucose tolerance and insulin sensitivity related to alterations in glucocorticoids and sympathetic activity. Some effects of sleep debt might relate to *orexins*, peptides synthesized in the lateral hypothalamus that can increase feeding, arousal, sympathetic activity, and neuropeptide Y activity.

Genetics

Genetic determinants also have a role in individual susceptibility to obesity (Table 60.1). Findings from genome-wide association studies explain a very small portion of interindividual variability in obesity. One important example, the *FTO* gene at 16q12, is associated with adiposity in childhood, probably explained by increased energy intake. Monogenic forms of obesity have also been identified, including **melanocortin-4 receptor (MC4R)** deficiency, associated with early-onset obesity and food-seeking behavior. Mutations in *MC4R* are a common cause of monogenetic obesity but a rare cause of obesity in general. Deficient activation of *MC4R* is seen in patients with

proopiomelanocortin (POMC) deficiency, a prohormone precursor of adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH), resulting in adrenal insufficiency, light skin, hyperphagia, and obesity.

Table 60.1

Endocrine and Genetic Causes of Obesity

DISEASE	SYMPTOMS	LABORATORY
ENDOCRINE		
Cushing syndrome	Central obesity, hirsutism, moon face, hypertension	Dexamethasone suppression test
GH deficiency	Short stature, slow linear growth	Evoked GH response, IGF-1
Hyperinsulinism	Nesidioblastosis, pancreatic adenoma, hypoglycemia, Mauriac syndrome	Insulin level
Hypothyroidism	Short stature, weight gain, fatigue, constipation, cold intolerance, myxedema	TSH, FT_4
Pseudohypoparathyroidism	Short metacarpals, subcutaneous calcifications, dysmorphic facies, mental retardation, short stature, hypocalcemia, hyperphosphatemia	Urine cAMP after synthetic PTH infusion
GENETIC		
Albright hereditary osteodystrophy	Short stature, skeletal defects, PTH resistance	*GNAS* gene
Alström syndrome	Cognitive impairment, retinitis pigmentosa, diabetes mellitus, hearing loss, hypogonadism, cardiomyopathy	*ALMS1* gene
Bardet-Biedl syndrome	Retinitis pigmentosa, renal abnormalities, polydactyly, syndactyly, hypogonadism	*BBS1* gene
BDNF/TrkB deficiency	Hyperactivity, impaired concentration, limited attention span, impaired short-term memory and pain sensation	*BDNF/TrkB* gene
Biemond syndrome	Cognitive impairment, iris coloboma, hypogonadism, polydactyly	
Carpenter syndrome	Polydactyly, syndactyly, cranial synostosis, mental retardation	Mutations in *RAB23* gene, located on chromosome 6 in humans
Cohen syndrome	Mid-childhood-onset obesity, short stature, prominent maxillary incisors, hypotonia, mental retardation, microcephaly, decreased visual activity	Mutations in *VPS13B* gene (often called *COH1*) at locus 8q22
Deletion 9q34	Early-onset obesity, mental retardation, brachycephaly, synophrys, prognathism, behavior and sleep disturbances	Deletion 9q34
Down syndrome	Short stature, dysmorphic facies, mental retardation	Trisomy 21
ENPP1 gene mutations	Insulin resistance, childhood obesity	Gene mutation on chromosome 6q
Fröhlich syndrome	Hypothalamic tumor	
FTO gene polymorphism, plus upstream regulatory and downstream activation	Dysregulation of orexigenic hormone acyl-ghrelin, poor postprandial appetite suppression	Homozygous for *FTO* AA allele

genes		
KSR2 deficiency	Mild hyperphagia and reduced basal metabolic rate, insulin resistance often with acanthosis nigricans, irregular menses, early development of type 2 diabetes mellitus	*KSR2* gene
Leptin or leptin receptor gene deficiency	Early-onset severe obesity, infertility (hypogonadotropic hypogonadism), hyperphagia, infections	Leptin
Melanocortin 4 receptor gene mutation	Early-onset severe obesity, increased linear growth, hyperphagia, hyperinsulinemia Most common known genetic cause of obesity Homozygous worse than heterozygous	*MC4R* mutation
PCSK1 deficiency	Small bowel enteropathy, hypoglycemia, hypothyroidism, ACTH deficiency, diabetes insipidus	*PCSK1* gene
Prader-Willi syndrome	Neonatal hypotonia, slow infant growth, small hands and feet, mental retardation, hypogonadism, hyperphagia leading to severe obesity, paradoxically elevated ghrelin	Partial deletion of chromosome 15 or loss of paternally expressed genes
Proopiomelanocortin (POMC) deficiency	Obesity, red hair, adrenal insufficiency due to ACTH deficiency, hyperproinsulinemia, hyperphagia, pale skin, cholestatic jaundice	Loss-of-function mutations of *POMC* gene
Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD)	Often confused with congenital central hypoventilation syndrome (CCHS); presentation ≥1.5 yr with weight gain, hyperphagia, hypoventilation, cardiac arrest, central diabetes insipidus, hypothyroidism, GH deficiency, pain insensitivity, hypothermia, precocious puberty, neural crest tumors	Unknown genes May be a paraneoplastic disorder
SH2B1 deficiency	Hyperphagia, disproportionate hyperinsulinemia, early speech and language delay that often resolves, behavioral problems including aggression	*SH2B1* gene
SIM1 deficiency	Hyperphagia with autonomic dysfunction (characterized by low systolic blood pressure), speech and language delay, neurobehavioral abnormalities including autistic-type behaviors	*SIM1* gene
TUB deficiency	Retinal dystrophy, deafness	*TUB* gene
Turner syndrome	Ovarian dysgenesis, lymphedema, web neck, short stature, cognitive impairment	XO chromosome

ACTH, Adrenocorticotropic hormone; cAMP, cyclic adenosine monophosphate; FT_4 , free thyroxine; GH, growth hormone; IGF, insulin-like growth factor; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

In addition, evidence suggests that appetitive traits are moderately heritable. For example, some genes associated with appetite also relate to weight, and vice-versa. In addition, there are genetic conditions associated with obesity, such as **Prader-Willi syndrome,** which results from absence of paternally expressed imprinted genes in the 15q11.2–q13 region. Prader-Willi syndrome is characterized by insatiable appetite and food seeking. In the era of genomic medicine, it will be increasingly possible to identify risks according to specific genes and consider gene-environment interactions. Epigenetic environmental modification of genes may have a role in the development of obesity, especially during fetal and early life.

Microbiome

It is increasingly recognized the human gut microbiota play a role in regulating metabolism. This novel area of research raises questions about the role of antibiotics in the pathway to obesity and the possibility that probiotics could be therapeutic for certain individuals.

Endocrine and Neural Physiology

Monitoring of “stored fuels” and short-term control of food intake (appetite and satiety) occurs through neuroendocrine feedback loops linking adipose tissue, the gastrointestinal (GI) tract, and the central nervous system (CNS) (Figs. 60.2 and 60.3). GI hormones, including cholecystokinin, glucagon-like peptide 1, peptide YY, and vagal neuronal feedback promote satiety. *Ghrelin* stimulates appetite. Adipose tissue provides feedback regarding energy storage levels to the brain through hormonal release of adiponectin and leptin. These hormones act on the arcuate nucleus in the hypothalamus and on the solitary tract nucleus in the brainstem and in turn activate distinct neuronal networks. Adipocytes secrete *adiponectin* into the blood, with reduced levels in response to obesity and increased levels in response to fasting. Reduced adiponectin levels are associated with lower insulin sensitivity and adverse CV outcomes. *Leptin* is directly involved in satiety; low leptin levels stimulate food intake, and high leptin levels inhibit hunger in animal models and in healthy human volunteers. However, the negative feedback loop from leptin to appetite may be more adapted to preventing starvation than excess intake.

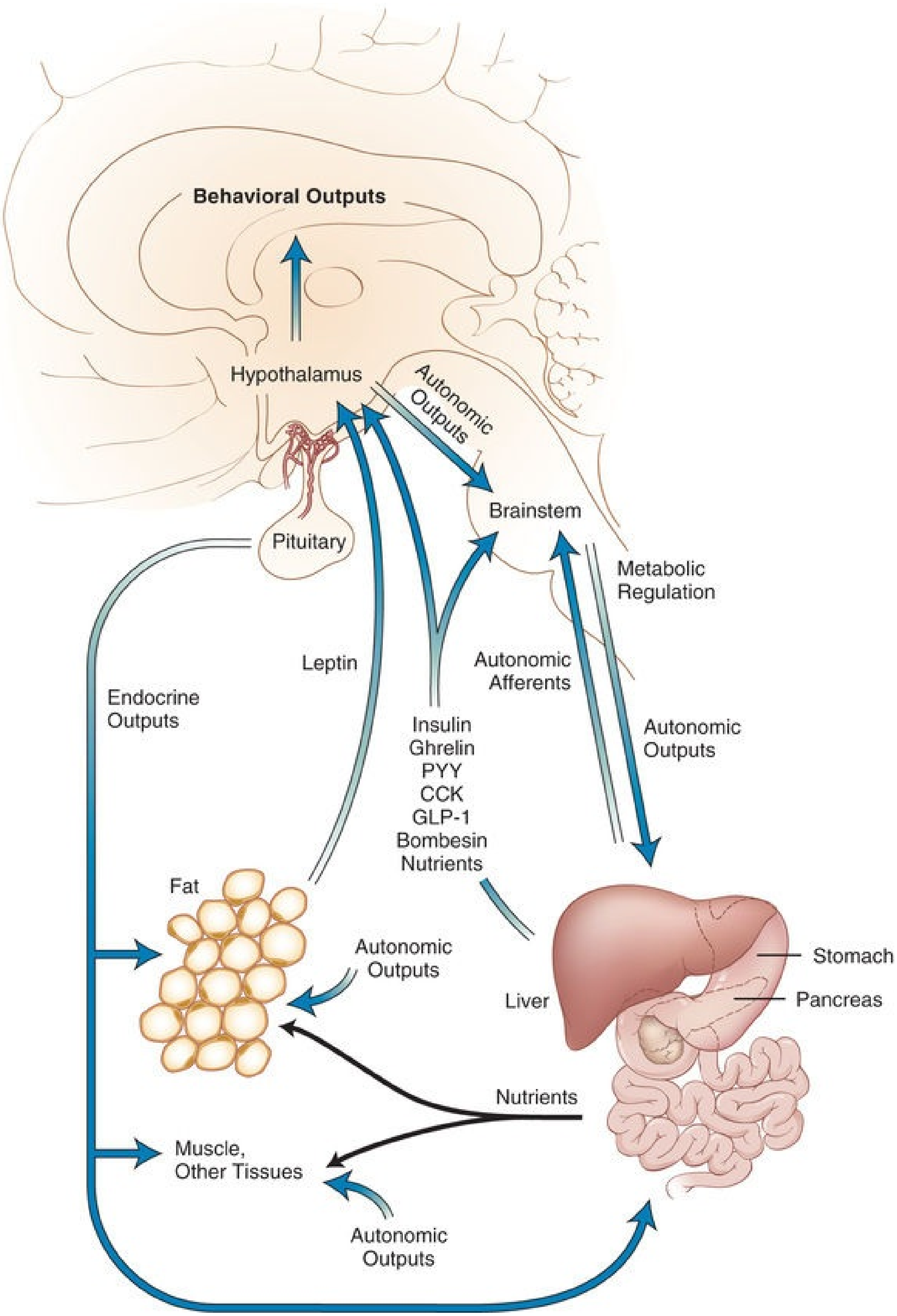
Behavioral Outputs
Hypothalamus
Autonomic Outputs
Brainstem
Pituitary
Metabolic Regulation
Leptin
Autonomic Afferents
Endocrine Outputs
Insulin
Ghrelin
PYY
CCK
GLP-1
Bombesin
Nutrients
Autonomic Outputs
Fat
Autonomic Outputs
Stomach
Pancreas
Liver
Nutrients
Muscle, Other Tissues
Autonomic Outputs

FIG. 60.2 Regulation of energy homeostasis by the brain-gut-adipose axis. CCK, Cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology,*

ed 13, Philadelphia, 2016, Elsevier, p 1610.)

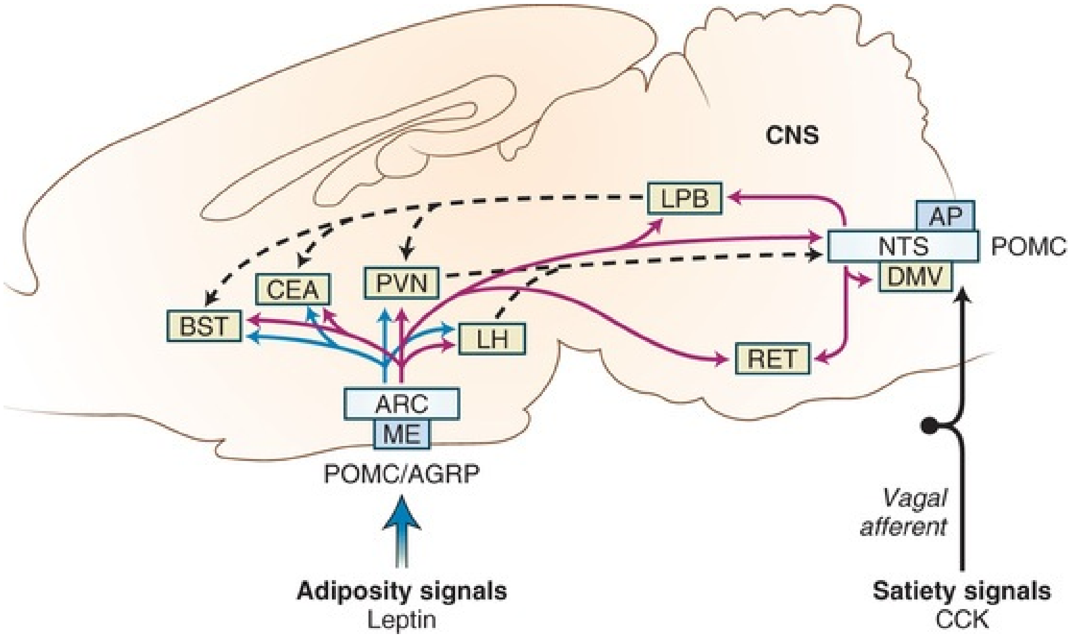

FIG. 60.3 Brain structures involved in energy homeostasis. Receipt of long-term adipostatic signals and acute satiety signals by neurons in arcuate nucleus and brainstem, respectively. *Pale-blue boxes* indicate nuclei containing proopiomelanocortin (POMC) neurons; *tan boxes* indicate nuclei containing melanocortin-4 receptor (MC4R) neurons that may serve to integrate adipostatic and satiety signals; and *darker-blue boxes* show some circumventricular organs involved in energy homeostasis. *Magenta arrows* designate a subset of projections of POMC neurons; *blue arrows* show a subset of projections of agouti-related peptide (AGRP) neurons. AP, Area postrema; ARC, arcuate nucleus; BST, bed nucleus of stria terminalis; CCK, cholecystokinin; CEA, central nucleus of amygdala; CNS, central nervous system; DMV, dorsal motor nucleus of vagus; LH, lateral hypothalamic area; LPB, lateral parabrachial nucleus; ME, median eminence; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus of hypothalamus; RET, reticular formation. (Modified from Fan W, Ellacott KL, Halatchev IG, et al: Cholecystokinin-mediated suppression of feeding involves the brainstem melanocortin system, *Nat Neurosci* 7:335–336, 2004.)

Numerous neuropeptides in the brain, including peptide YY (PYY), agouti-related peptide, and orexin, appear to affect appetite stimulation, whereas melanocortins and α-melanocortin–stimulating hormone are involved in satiety (Fig. 60.3). The neuroendocrine control of appetite and weight involves a negative-feedback system, balanced between short-term control of appetite and long-term control of adiposity (including leptin). PYY reduces food intake via the vagal-brainstem-hypothalamic pathway. Developmental changes in PYY are evident as infants have higher PYY levels than school-age children and adults. Obese children have lower fasting levels of PYY than adults. Weight loss may restore PYY levels in children, even though this does not happen in adults. In addition, patients homozygous for the *FTO* obesity-risk allele demonstrate poor regulation of the orexigenic hormone acyl-ghrelin and have poor postprandial appetite suppression.

Comorbidities

Complications of pediatric obesity occur during childhood and adolescence and persist into adulthood. An important reason to prevent and treat pediatric obesity is the increased risk for morbidity and mortality later in life. The Harvard Growth Study found that boys who were overweight during adolescence were twice as likely to die from CV disease as those who had normal weight. More immediate comorbidities include type 2 diabetes, hypertension, hyperlipidemia, and **nonalcoholic fatty liver disease** (NAFLD) (Table 60.2). Insulin resistance increases with increasing adiposity and independently affects lipid metabolism and CV health. The **metabolic syndrome** (central obesity, hypertension, glucose intolerance, and hyperlipidemia) increases risk for CV morbidity and mortality. NAFLD has been reported in 34% of patients treated in pediatric obesity clinic. NAFLD is now the most common chronic liver disease in U.S. children and adolescents. It can present with advanced fibrosis or nonalcoholic steatohepatitis and may result in cirrhosis and hepatocellular carcinoma. Insulin resistance is often associated. Furthermore, NAFLD is independently associated with increased risk of CV disease.

Table 60.2

Obesity-Associated Comorbidities

DISEASE	POSSIBLE SYMPTOMS	LABORATORY CRITERIA
CARDIOVASCULAR		
Dyslipidemia	HDL <40, LDL >130, total cholesterol >200 mg/dL	Fasting total cholesterol, HDL, LDL, triglycerides
Hypertension	SBP >95% for sex, age, height	Serial testing, urinalysis, electrolytes, blood urea nitrogen, creatinine
ENDOCRINE		
Type 2 diabetes mellitus	Acanthosis nigrans, polyuria, polydipsia	Fasting blood glucose >110, hemoglobin A_{1c} , insulin level, C-peptide, oral glucose tolerance test
Metabolic syndrome	Central adiposity, insulin resistance, dyslipidemia, hypertension, glucose intolerance	Fasting glucose, LDL and HDL cholesterol
Polycystic	Irregular menses, hirsutism, acne,	Pelvic ultrasound, free testosterone, LH, FSH

ovary syndrome	insulin resistance, hyperandrogenemia	
GASTROINTESTINAL		
Gallbladder disease	Abdominal pain, vomiting, jaundice	Ultrasound
Nonalcoholic fatty liver disease (NAFLD)	Hepatomegaly, abdominal pain, dependent edema, ↑ transaminases Can progress to fibrosis, cirrhosis	AST, ALT, ultrasound, CT, or MRI
NEUROLOGIC		
Pseudotumor cerebri	Headaches, vision changes, papilledema	Cerebrospinal fluid opening pressure, CT, MRI
Migraines	Hemicrania, headaches	None
ORTHOPEDIC		
Blount disease (tibia vara)	Severe bowing of tibia, knee pain, limp	Knee radiographs
Musculoskeletal problems	Back pain, joint pain, frequent strains or sprains, limp, hip pain, groin pain, leg bowing	Radiographs
Slipped capital femoral epiphysis	Hip pain, knee pain, limp, decreased mobility of hip	Hip radiographs
PSYCHOLOGIC		
Behavioral complications	Anxiety, depression, low self-esteem, disordered eating, signs of depression, worsening school performance, social isolation, problems with bullying or being bullied	Child Behavior Checklist, Children's Depression Inventory, Peds QL, Eating Disorder Inventory 2, subjective ratings of stress and depression, Behavior Assessment System for Children, Pediatric Symptom Checklist
PULMONARY		
Asthma	Shortness of breath, wheezing, coughing, exercise intolerance	Pulmonary function tests, peak flow
Obstructive sleep apnea	Snoring, apnea, restless sleep, behavioral problems	Polysomnography, hypoxia, electrolytes (respiratory acidosis with metabolic alkalosis)

ALT, Alanine transaminase; AST, aspartate transaminase; CT, computed tomography; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; MRI, magnetic resonance imaging; Peds QL, Pediatric Quality of Life Inventory; SBP, systolic blood pressure.

Obesity may also be associated with chronic inflammation. Adiponectin, a peptide with antiinflammatory properties, occurs in reduced levels in obese patients compared to insulin-sensitive, lean persons. Low adiponectin levels correlate with elevated levels of free fatty acids and plasma triglycerides as well as a high BMI, and high adiponectin levels correlate with peripheral insulin sensitivity. Adipocytes secrete peptides and cytokines into the circulation, and proinflammatory peptides such interleukin (IL)-6 and tumor necrosis factor (TNF)-α occur in higher levels in obese patients. Specifically, IL-6 stimulates production of C-reactive protein (CRP) in the liver. CRP is a marker of inflammation and might link obesity, coronary disease, and subclinical inflammation.

Some complications of obesity are mechanical, including obstructive sleep apnea and orthopedic complications. Orthopedic complications include Blount disease and slipped femoral capital epiphysis (see Chapters 697 and 698.4).

Mental health problems can coexist with obesity, with the possibility of bidirectional effects. These associations are modified by gender, ethnicity, and socioeconomic status. Self-esteem may be lower in obese adolescent girls than in nonobese peers. Some studies have found an association between obesity and adolescent depression. There is considerable interest in the co-occurrence of eating disorders and obesity. Obese youth are also at risk for bullying based on their appearance.

Identification

Overweight and obese children are often identified as part of routine medical care. The child and family may be unaware that the child has increased adiposity. They may be unhappy with the medical provider for raising this issue and may respond with denial or apparent lack of concern. It is often necessary to begin by helping the family understand the importance of healthy weight for current and future health. Forging a good therapeutic relationship is important because obesity intervention requires a chronic disease management approach. Intervention and successful resolution of this problem require considerable effort by the family and the child over an extended period in order to change eating and activity behaviors.

Evaluation

The evaluation of the overweight or obese child begins with examination of the growth chart for weight, height, and BMI trajectories; consideration of possible medical causes of obesity; and detailed exploration of family eating, nutritional, and activity patterns. A complete pediatric history is used to uncover comorbid disorders. The family history focuses on the adiposity of other family members and the family history of obesity-associated disorders. The physical examination adds data that can lead to important diagnoses. Laboratory testing is guided by the need to identify comorbidities.

Examination of the **growth chart** reveals the severity, duration, and timing of obesity onset. Children who are overweight (BMI in 85–95th percentile) are less likely to have developed comorbid conditions than those who are obese (BMI ≥95th percentile). Those with a BMI ≥99th percentile are more likely to have coexisting medical problems. Once obesity severity is determined, the BMI trajectory is examined to elucidate when the child became obese. Several periods during childhood are considered *sensitive* periods, or times of increased risk for developing obesity, including infancy, adiposity rebound (when body fat is lowest at approximately age 5.5 yr), and adolescence. An abrupt change in BMI might signal the onset of a medical problem or a period of family or personal stress for the child. Examination of the weight trajectory can further reveal how the problem developed. A young child might exhibit high weight and high height because linear growth can increase early in childhood if a child consumes excess energy. At some point the weight percentile exceeds the height percentile, and the child's BMI climbs into the obese range. Another example is a child whose weight rapidly increases when she reduces her activity level and consumes more meals away from home. Examination of the height trajectory can reveal endocrine problems, which often occur with slowing of linear growth.

Consideration of possible medical causes of obesity is essential, even though endocrine and genetic causes are rare (see Table 60.1). Growth hormone deficiency, hypothyroidism, and Cushing syndrome are examples of endocrine disorders that can lead to obesity. In general, these disorders manifest with slow linear growth. Because children who consume excessive amounts of calories tend to experience accelerated linear growth, short stature warrants further evaluation. Genetic disorders associated with obesity may manifest extreme hyperphagia, or they can have coexisting dysmorphic features, cognitive impairment, vision and hearing abnormalities, or short stature. In some children with congenital disorders such as myelodysplasia or muscular dystrophy, lower levels of PA can lead to secondary obesity. Some medications, such as atypical antipsychotics, can cause excessive appetite and hyperphagia, resulting in obesity (Table 60.3). Rapid weight gain in a child or adolescent taking one of these medications might require its discontinuation. Poor linear growth and rapid changes in weight gain are indications for evaluation of possible medical causes.

Table 60.3

Medications Associated With Obesity

Prednisone and other glucocorticoids
Thioridazine

Olanzapine
Clozapine
Quetiapine
Risperidone
Lithium
Amitriptyline and other tricyclic antidepressants
Paroxetine
Valproate
Carbamazepine
Gabapentin
Cyproheptadine
Propranolol and other β-blockers

Exploration of family eating, nutritional, and activity patterns begins with a description of regular meal and snack times and family habits for walking, bicycle riding, active recreation, and **screen time** (TV, computer, video games). It is useful to request a 24-hr dietary recall with special attention to intake of fruits, vegetables, and water, as well as high-calorie foods and high-carbohydrate beverages. When possible, evaluation by a nutritionist is extremely helpful. This information will form the basis for incremental changes in eating behavior, caloric intake, and PA during the intervention.

Initial assessment of the overweight or obese child includes a complete review of bodily systems focusing on the possibility of comorbid conditions (see Table 60.2). Developmental delay and visual and hearing impairment can be associated with genetic disorders. Difficulty sleeping, snoring, or daytime sleepiness suggests sleep apnea. Abdominal pain might suggest NAFLD. Symptoms of polyuria, nocturia, or polydipsia may be the result of type 2 diabetes. Hip or knee pain can be caused by secondary orthopedic problems, including Blount disease and slipped capital femoral epiphysis. Irregular menses may be associated with polycystic ovary syndrome. Acanthosis nigricans can suggest insulin resistance and type 2 diabetes (Fig. 60.4).

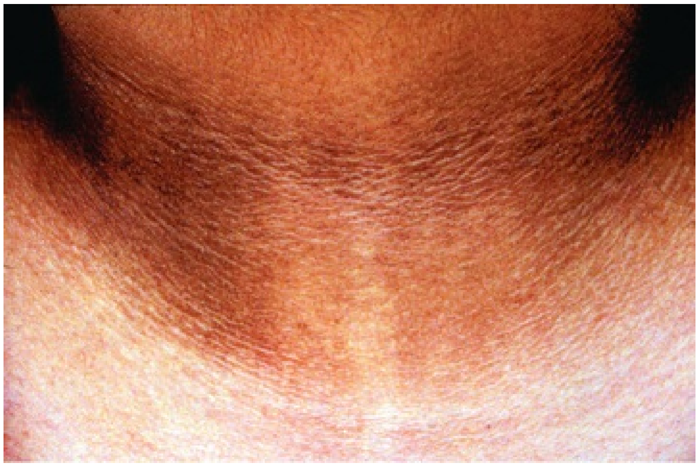

FIG. 60.4 Acanthosis nigricans. (From Gahagan S: Child and adolescent obesity, *Curr Probl Pediatr Adolesc Health Care* 34:6–43, 2004.)

The family history begins with identifying other obese family members. Parental obesity is an important risk for child obesity. If all family members are obese, focusing the intervention on the entire family is reasonable. The child may be at increased risk for developing type 2 diabetes if a family history exists. Patients of African American, Hispanic, or Native American heritage are also at increased risk for developing type 2 diabetes. Identification of a family history of hypertension, CV disease, or metabolic syndrome indicates increased risk for developing these obesity-associated conditions. If the clinician helps the family to understand that childhood obesity increases risk for developing these chronic diseases, this educational intervention might serve as motivation to improve their nutrition and PA.

Physical examination should be thorough, focusing on possible comorbidities (see Table 60.2). Careful screening for hypertension using an appropriately sized blood pressure cuff is important. Systematic examination of the skin can reveal acanthosis nigricans, suggesting insulin resistance, or hirsutism, suggesting polycystic ovary syndrome. Tanner staging can reveal premature adrenarche secondary to advanced sexual maturation in overweight and obese girls.

Laboratory testing for fasting plasma glucose, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol, and liver function tests are recommended as part of the initial evaluation for newly identified pediatric obesity (Table 60.4). Overweight children (BMI 85–95th percentile) who have a family history of diabetes mellitus or signs of insulin resistance should also be evaluated with a fasting plasma glucose test. Other laboratory testing should be guided by history or physical examination findings. Fig. 60.5 provides a recommended approach to categorization, evaluation, and treatment.

Table 60.4

Normal Laboratory Values for Recommended Tests

LABORATORY TEST	NORMAL VALUE
Glucose	<110 mg/dL
Insulin	<15 mU/L
Hemoglobin A_{1c}	<5.7%
AST (age 2-8 yr)	<58 U/L
AST (age 9-15 yr)	<46 U/L
AST (age 15-18 yr)	<35 U/L
ALT	<35 U/L
Total cholesterol	<170 mg/dL
LDL	<110 mg/dL
HDL	>45 mg/dL
Triglycerides (age 0-9 yr)	<75 mg/dL
Triglycerides (age 10-19 yr)	<90 mg/dL

AST, Aspartate transaminase; ALT, alanine transaminase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

From Children's Hospital of Wisconsin: *The NEW (nutrition, exercise and weight management) kids program* (PDF file). http://www.chw.org/display/displayFile.asp?docid=33672&filename=/Groups/NEWKids/NewKidsReferral.PDF .

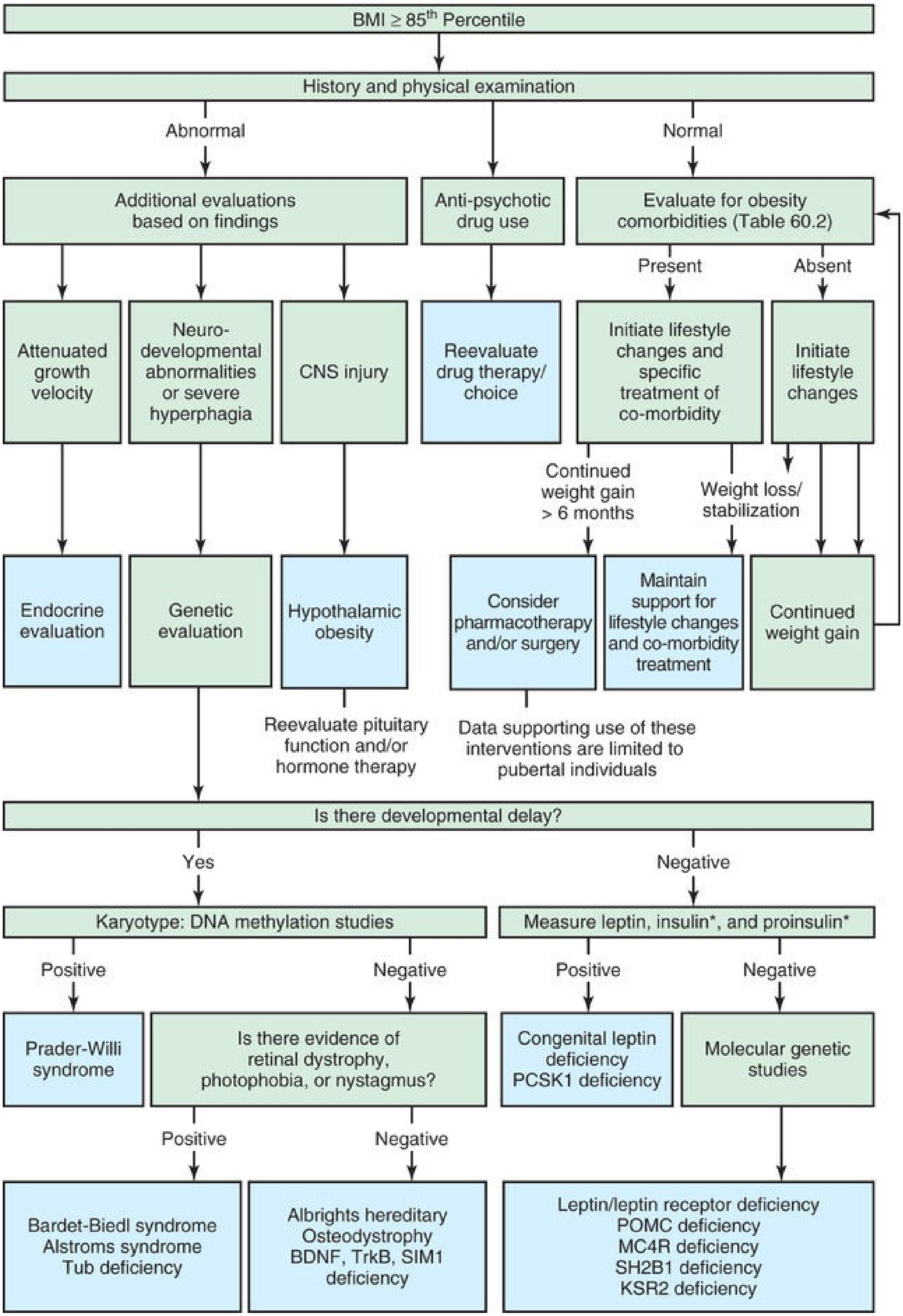
BMI ≥ 85th Percentile
History and physical examination
Abnormal
Normal
Additional evaluations based on findings
Anti-psychotic drug use
Evaluate for obesity comorbidities (Table 60.2)
Present
Absent
Attenuated growth velocity
Neuro-developmental abnormalities or severe hyperphagia
CNS injury
Reevaluate drug therapy/ choice
Initiate lifestyle changes and specific treatment of co-morbidity
Initiate lifestyle changes
Continued weight gain > 6 months
Weight loss/ stabilization
Endocrine evaluation
Genetic evaluation
Hypothalamic obesity
Consider pharmacotherapy and/or surgery
Maintain support for lifestyle changes and co-morbidity treatment
Continued weight gain
Reevaluate pituitary function and/or hormone therapy
Data supporting use of these interventions are limited to pubertal individuals
Is there developmental delay?
Yes
Negative
Karyotype: DNA methylation studies
Measure leptin, insulin*, and proinsulin*
Positive
Negative
Positive
Negative
Prader-Willi syndrome
Is there evidence of retinal dystrophy, photophobia, or nystagmus?
Congenital leptin deficiency PCSK1 deficiency
Molecular genetic studies
Positive
Negative
Bardet-Biedl syndrome Alstroms syndrome Tub deficiency
Albrights hereditary Osteodystrophy BDNF, TrkB, SIM1 deficiency
Leptin/leptin receptor deficiency POMC deficiency MC4R deficiency SH2B1 deficiency KSR2 deficiency

FIG. 60.5 Diagnosis and management flow chart. *Measure insulin and proinsulin in patients with clinical features of PCSK1 deficiency. BMI, Body mass index; CNS, central nervous system. (From Farooqi SOR, O'Rahilly S: Genetic obesity syndromes. In Grant S, editor: *The genetics of obesity,* New York, 2014, Springer, pp 23–32; originally adapted from August GP, Caprio S, Fennoy I, et al: Prevention and treatment of pediatric obesity: an Endocrine Society clinical practice guideline based on expert opinion, *J Clin Endocrinol Metab* 93:4576–4599, 2008.)

Intervention

Evidence shows that some interventions result in modest but significant and sustained improvement in body mass. Based on behavior change theories, treatment includes specifying **target behaviors** , **self-monitoring** , **goal setting** , **stimulus control** , and promotion of **self-efficacy** and **self-management** skills. **Behavior changes** associated with improving BMI include drinking lower quantities of sugar-sweetened beverages, consuming higher-quality diets, increasing exercise, decreasing screen time, and self-weighing. Most successful interventions have been *family based* and consider the child's developmental age. “Parent-only” treatment can be as effective as “parent–child” treatment. Because obesity is multifactorial, not all children and adolescents will respond to the same approach. For example, *loss-of-control eating,* associated with weight gain and obesity, predicts poor outcome in response to family-based treatment. Furthermore, clinical treatment programs are expensive and not widely available. Therefore, interest has grown in novel approaches such as internet-based treatments and guided self-help.

It is important to begin with clear recommendations about **appropriate caloric intake** for the obese child (Table 60.5). Working with a dietitian is essential. Meals should be based on fruits, vegetables, whole grains, lean meat, fish, and poultry. Prepared foods should be chosen for their nutritional value, with attention to calories and fat. Foods that provide excessive calories and low nutritional value should be reserved for infrequent treats.

Table 60.5

Recommended Caloric Intake Designated by Age and Gender

LIFE-STAGE	AGE	RELATIVELY SEDENTARY LEVEL	MODERATE LEVEL OF	ACTIVE

GROUP	(yr)	OF ACTIVITY (kcal)	ACTIVITY (kcal)	(kcal)
Child	2-3	1,000	1,000-1,400	1,000-1,400
Female	4-8	1,200	1,400-1,600	1,400-1,800
	9-13	1,600	1,600-2,000	1,800-2,200
	14-18	1,800	2,000	2,400
Male	4-8	1,400	1,400-1,600	1,600-2,000
	9-13	1,800	1,800-2,200	2,000-2,600
	14-18	2,200	2,400-2,800	2,800-3,200

Adapted from U.S. Department of Agriculture: *Dietary guidelines for Americans* , 2005. http://www.health.gov/DIETARYGUIDELINES/dga2005/document/html/chapter2.htm .

Weight reduction diets in adults generally do not lead to sustained weight loss. Therefore the focus should be on changes that can be maintained for life. Attention to eating patterns is helpful. Families should be encouraged to plan *family meals,* including breakfast. It is almost impossible for a child to make changes in nutritional intake and eating patterns if other family members do not make the same changes. Dietary needs also change developmentally; adolescents require greatly increased calories during their growth spurts, and adults who lead inactive lives need fewer calories than active, growing children.

Psychologic strategies are helpful. The **“traffic light” diet** groups foods into those that can be consumed without any limitations (green), in moderation (yellow), or reserved for infrequent treats (red) (Table 60.6). The concrete categories are very helpful to children and families. This approach can be adapted to any ethnic group or regional cuisine. **Motivational interviewing** begins with assessing how ready the patient is to make important behavioral changes. The professional then engages the patient in developing a strategy to take the next step toward the ultimate goal of healthy nutritional intake. This method allows the professional to take the role of a coach, helping the child and family reach their goals. Other behavioral approaches include family rules about where food may be consumed (e.g., “not in the bedroom”).

Table 60.6

“Traffic Light” Diet Plan

FEATURE	GREEN LIGHT FOODS	YELLOW LIGHT FOODS	RED LIGHT FOODS

Quality	Low-calorie, high-fiber, low-fat, nutrient-dense	Nutrient-dense, but higher in calories and fat	High in calories, sugar, and fat
Types of food	Fruits, vegetables	Lean meats, dairy, starches, grains	Fatty meats, sugar, sugar-sweetened beverages, fried foods
Quantity	Unlimited	Limited	Infrequent or avoided

Increasing PA without decreasing caloric intake is unlikely to result in weight loss. However, **aerobic exercise** training has been shown to improve metabolic profiles in obese children and adolescents. Furthermore, it can increase aerobic fitness and decrease percent body fat even without weight loss. Therefore, increasing PA can decrease risk for CV disease, improve well-being, and contribute to weight loss. Increased PA can be accomplished by walking to school, engaging in PA during leisure time with family and friends, or enrolling in organized sports. Children are more likely to be active if their parents are active. As with family meals, family PA is recommended. When adults lose significant weight, they may regain that weight despite eating fewer calories. The body may adapt to weight loss by reducing the basal metabolic rate (BMR), thus requiring fewer calories. One approach to this phenomenon is to increase PA.

Active pursuits can replace more sedentary activities. The American Academy of Pediatrics recommends that screen time be restricted to no more than 2 hr/day for children >2 yr old and that children <2 yr old not watch television. TV watching is often associated with eating, and many highly caloric food products are marketed directly to children during child-oriented television programs.

Pediatric healthcare providers should assist families to develop goals to change nutritional intake and PA. They can also provide the child and family with needed information. The family should not expect immediate lowering of BMI percentile related to behavioral changes, but can instead count on a gradual decrease in the rate of BMI percentile increase until it stabilizes, followed by a gradual decrease. Referral to multidisciplinary, comprehensive pediatric weight management programs is ideal for obese children whenever possible.

Pharmacotherapy for weight loss in the pediatric population is understudied. Randomized controlled trials (RCTs) have evaluated many medications, including metformin, orlistat, sibutramine, and exanatide (Table 60.7). Available medications result in modest weight loss or BMI improvement, even when combined with behavioral interventions. Various classes of drugs are of interest, including those that decrease energy intake or act centrally as **anorexiants** , those that affect the availability of nutrients through intestinal or renal tubular reabsorption, and those that affect metabolism. The only U.S. Food and Drug

Administration (FDA)–approved medication for obesity in children <16 yr old is *orlistat,* which decreases absorption of fat, resulting in modest weight loss. Complications include flatulence, oily stools, and spotting. This agent offers little benefit to severely obese adolescents. Because multiple redundant neural mechanisms act to protect body weight, promoting weight loss is extremely difficult. Thus there is considerable interest in combining therapies that simultaneously target multiple weight-regulating pathways. One example, approved for adults, combines *phentermine,* a noradrenergic agent, with *topiramate,* a γ-aminobutyric acid (GABA)–ergic medication. This combination resulted in a mean 10.2-kg weight loss vs 1.4 kg in the placebo group. Side effects are common and include dry mouth, constipation, paresthesias, insomnia, and cognitive dysfunction. Another promising example is the combination of amylin (decreases food intake and slows gastric emptying) with leptin, which has no anorexigenic effects when given alone. This combination requires injection and is in clinical trials in adults. Another FDA-approved drug for adults is *lorcaserin,* a selective serotonin 2C receptor agonist. Establishing long-term safety and tolerability in children is a challenge because medications of interest have CNS effects or interfere with absorption of nutrients. Teratologic effects must be considered for use in adolescent girls.

Table 60.7

Medications for Weight Management With Mechanism of Action, Availability, and Dosing

MEDICATION	MECHANISM OF ACTION	AVAILABLE FOR CHRONIC USE		MEAN PERCENTAGE WEIGHT LOSS		ADVANTAGES	DISADV
		USA	**European Union**	**Placebo**	**Drug**		
Phentermine, 15-30 mg PO	Sympathomimetic	For short-term use	No	Not stated in label	Not stated in label	Inexpensive	Side effe no long-t
Orlistat, 120 mg PO tid before meals	Pancreatic lipase inhibitor	Yes	Yes	−2.6%[†]	−6.1%[†]	Not absorbed; long-term data[*]	Modest side effe
Lorcaserin, 10 mg PO bid	5-HT_{2c} serotonin agonist with little affinity for other serotonergic receptors	Yes	No	−2.5%	−5.8%	Mild side effects; long-term data[*]	Expensiv weight l
Phentermine/topiramate ER, 7.5 mg/46 mg or	Sympathomimetic anticonvulsant	Yes	No	−1.2%	−7.8% (mid-	Robust weight loss; long-term	Expensiv

15 mg/92 mg PO indicated as rescue (requires titration)	(GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)				dose) −9.8% (full dose)	data[*]	
Naltrexone SR/bupropion SR, 32 mg/360 mg PO (requires titration)	Opioid receptor antagonist; dopamine and noradrenaline reuptake inhibitor	Yes	Yes	−1.3%	−5.4%	Reduces food craving; long-term data[*]	Moderat expensiv effect pr
Liraglutide, 3.0 mg injection (requires titration)	GLP-1 receptor agonist	Yes	Yes	−3%	−7.4% (full dose)	Side effect profile; long-term data[*]	Expensiv injectabl

[*] Data from randomized controlled trials lasting >52 wk.

[†] Assuming the average patient in the orlistat and placebo groups weighed 100 kg at baseline.

Information is from U.S. product labels, except where noted. The data supporting these tables are derived from the prescribing information labeling approved by the US Food and Drug Administration.

ER, Extended release; SR, sustained release; PO, orally; bid, twice daily; tid, 3 times daily.

Adapted from Bray GA, Frühbeck G, Ryan DH, Wilding JPH: Management of obesity, *Lancet* 387:1947–1965, 2016, p 1950.

Hormone replacement therapy is available for patients with leptin deficiency and may become available for patients with POMC deficiency. Setmelanotide binds to and activates MC4R and may be useful for patients with POMC deficiency–associated obesity.

In some cases it is reasonable to refer adolescents for **bariatric surgery** evaluation. The American Pediatric Surgical Association guidelines recommends that surgery be considered only in children with complete or near-complete skeletal maturity, a BMI ≥40, and a medical complication resulting from obesity, *after* they have failed 6 mo of a multidisciplinary weight management program. Surgical approaches include the Roux-en-Y and the adjustable gastric band (Fig. 60.6). In obese adults, bariatric surgery reduces the risk of developing type 2 diabetes mellitus. In obese adult patients with existing type 2 diabetes, bariatric surgery improves diabetic control. Nutritional complications of bariatric surgery include malabsorption and vitamin (A, B_1 , B_2 , B_6 , B_{12} , D, E, K) and mineral (copper, iron) deficiencies that require supplementation.

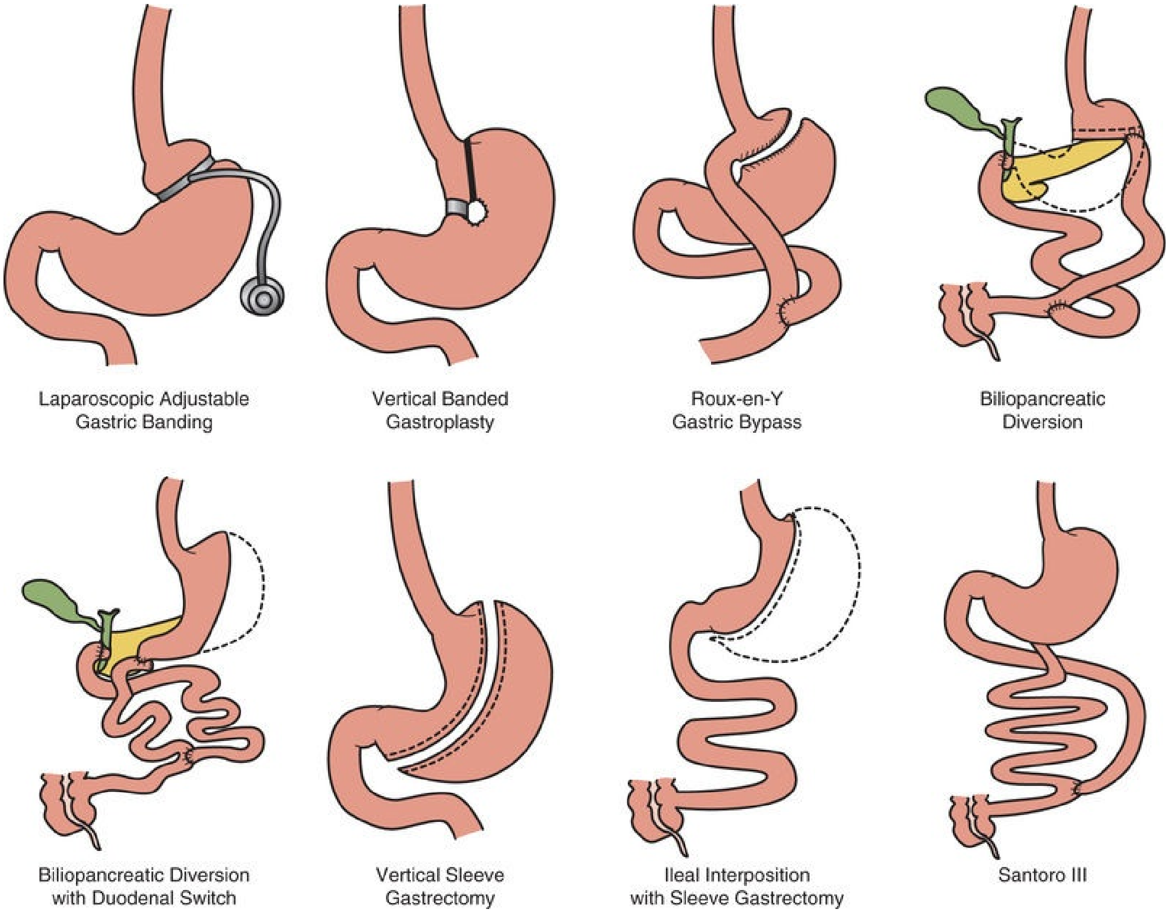
Laparoscopic Adjustable Gastric Banding
Vertical Banded Gastroplasty
Roux-en-Y Gastric Bypass
Biliopancreatic Diversion
Biliopancreatic Diversion with Duodenal Switch
Vertical Sleeve Gastrectomy
Ileal Interposition with Sleeve Gastrectomy
Santoro III

FIG. 60.6 **Bariatric surgical procedures. Laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass, and vertical sleeve gastrectomy techniques.**

Prevention

Prevention of child and adolescent obesity is essential for public health in the United States and most other countries (Tables 60.8 and 60.9). Efforts by pediatric providers can supplement national and community public health programs. The National Institutes of Health (NIH) and U.S. Centers for Disease Control and Prevention (CDC) recommend a variety of initiatives to combat the current obesogenic environment, including promotion of breastfeeding, access to fruits and vegetables, walkable communities, and 60 min/day of activity for children. The U.S. Department of Agriculture (USDA) sponsors programs promoting 5.5 cups of fruits and vegetables per day. Incentives for the food industry to promote consumption of healthier foods should be considered. Marketing of unhealthy foods to children is now being regulated. Changes in federal food programs are expected, including commodity foods, the Women, Infant, and Children Supplemental Food Program (WIC), and school lunch programs, to meet the needs of today's children.

Table 60.8

Proposed Suggestions for Preventing Obesity

Pregnancy

Normalize body mass index (BMI) before pregnancy.
Do not smoke.
Maintain moderate exercise as tolerated.
In women with gestational diabetes, provide meticulous glucose control.
Monitor gestational weight gain within Institute of Medicine (IOM) recommendations.

Postpartum and Infancy

Breastfeeding: exclusive for 4-6 mo; continue with other foods for 12 mo.
Postpone introduction of baby foods to 4-6 mo and juices to 12 mo.

Families

Eat meals as a family in a fixed place and time.
Do not skip meals, especially breakfast.
Do not allow television during meals.
Use small plates, and keep serving dishes away from the table.
Avoid unnecessary sweet or fatty foods and sugar-sweetened drinks.
Remove televisions from children's bedrooms; restrict times for TV viewing and video games.
Do not use food as a reward.

Schools

Eliminate candy and cookie sales as fundraisers.
Review the contents of vending machines, and replace with healthier choices; eliminate sodas.

Avoid financial support for sports teams from beverage and food industries.
Install water fountains and hydration stations.
Educate teachers, especially physical education and science faculty, about basic nutrition and the benefits of physical activity (PA).
Educate children from preschool through high school on appropriate diet and lifestyle.
Mandate minimum standards for physical education, including 60 min of strenuous exercise 5 times weekly.
Encourage “the walking school bus”: groups of children walking to school with adult supervision.

Communities

Increase family-friendly exercise and safe play facilities for children of all ages.
Develop more mixed residential-commercial developments for walkable and bicyclable communities.
Discourage the use of elevators and moving walkways.
Provide information on how to shop and prepare healthier versions of culture-specific foods.

Healthcare Providers

Explain the biologic and genetic contributions to obesity.
Give age-appropriate expectations for body weight in children.
Work toward classifying obesity as a disease to promote recognition, reimbursement for care, and willingness and ability to provide treatment.

Industry

Mandate age-appropriate nutrition labeling for products aimed at children (e.g., “red light/green light” foods, with portion sizes).
Encourage marketing of interactive video games in which children must exercise to play.
Use celebrity advertising directed at children for healthful foods to promote breakfast and regular meals.

Reduce portion size (drinks and meals).

Government and Regulatory Agencies

Classify childhood obesity as a legitimate disease.

Find novel ways to fund healthy lifestyle programs (e.g., with revenues from food and drink taxes).

Subsidize government-sponsored programs to promote the consumption of fresh fruits and vegetables.

Provide financial incentives to industry to develop more healthful products and to educate the consumer on product content.

Provide financial incentives to schools that initiate innovative PA and nutrition programs.

Allow tax deductions for the cost of weight loss and exercise programs.

Provide urban planners with funding to establish bicycle, jogging, and walking paths.

Ban advertising of fast foods, non-nutritious foods, and sugar-sweetened beverages directed at preschool children, and restrict advertising to school-age children.

Ban toys as gifts to children for purchasing fast foods.

Adapted from Speiser PW, Rudolf MCJ, Anhalt H, et al: Consensus statement: childhood obesity, *J Clin Endocrinol Metab* 90:1871–1887, 2005.

Table 60.9

Anticipatory Guidance: Establishing Healthy Eating Habits in Children

Do not punish a child during mealtimes with regard to eating. The emotional atmosphere of a meal is very important. Interactions during meals should be pleasant and happy.

Do not use foods as rewards.

Parents, siblings, and peers should model healthy eating, tasting new foods, and eating a well-balanced meal.

Children should be exposed to a wide range of foods, tastes, and textures.

New foods should be offered multiple times. Repeated exposure leads to acceptance and liking.

Forcing a child to eat a certain food will decrease the child's preference for that food. Children's wariness of new foods is normal and should be expected. Offering a variety of foods with low-energy density helps children balance energy intake.

Parents should control what foods are in the home. Restricting access to foods in the home will increase rather than decrease a child's desire for that food.

Children tend to be more aware of satiety than adults, so allow children to respond to satiety, and stop eating. Do not force children to "clean their plate."

Adapted from Benton D: Role of parents in the determination of food preferences of children and the development of obesity, *Int J Obes Relat Metab Disord* 28:858–869, 2004. Copyright 2004. Reprinted by permission from Macmillan Publishers Ltd.

Pediatric prevention efforts begin with careful monitoring of weight and BMI percentiles at healthcare maintenance visits. Attention to changes in BMI percentiles can alert the pediatric provider to increasing adiposity before the child becomes overweight or obese. All families should be counseled about healthy nutrition for their children, because the current prevalence of overweight and obesity in adults is 65%. Therefore, approximately two thirds of all children can be considered at risk for becoming overweight or obese at some time in their lives. Those who have an obese parent are at increased risk. Prevention efforts begin with promotion of *exclusive breastfeeding for 6 mo* and total breastfeeding for 12 mo. Introduction of infant foods at 6 mo should focus on cereals, fruits, and vegetables. Lean meats, poultry, and fish may be introduced later in the 1st year of life. Parents should be specifically counseled to *avoid introducing highly sugared beverages and foods in the 1st year* of life. Instead, they should expose their infants and young children to a rich variety of fruits, vegetables, grains, lean meats, poultry, and fish to facilitate acceptance of a diverse and healthy diet. Parenting matters, and **authoritative** parents are more likely to have children with a healthy weight than those who are authoritarian or permissive. Families who eat regularly scheduled meals together are less likely to have overweight or obese children. Child health professionals can address a child's nutritional status and provide expertise in child growth and development.

Child health professionals can also *promote PA* during regular healthcare maintenance visits. Parents who spend some of their leisure time in PA promote healthy weight in their children. Beginning in infancy, parents should be cognizant of their child's developmental capability and need for PA. Because TV, computer, and video game time can replace health-promoting PA, physicians should counsel parents to limit screen time for their children. Snacking during TV watching should be discouraged. Parents can help their children to understand that television commercials intend to sell a product. Children can learn that their parents will help them by responsibly choosing healthy foods.

Because obesity is determined by complex multifactorial conditions, prevention will take efforts at multiple levels of social organization. Successful programs include **EPODE** (Ensemble Prévenons l'Obésité Des Enfants), a multilevel prevention strategy that began in France and has been adopted by more than 500 communities in 6 countries. **Shape Up Somerville** is a citywide campaign to increase daily PA and healthy eating in Somerville, MA, since 2002. The **“Let's Move”** campaign was championed by former First Lady Michelle Obama. Since community and environmental factors are related to pediatric obesity risk, changes in local environments, daycare centers, schools, and recreational settings can have a public health impact. Programs can empower families to adopt practices that promote healthy lifestyles for children and adolescents. The most successful programs are comprehensive and rely on 4 strategies: political commitment to change, resources to support social marketing and changes, support services, and evidence-based practices. Community-wide programs are important because neighborhood environmental factors (e.g., poverty) have been associated with obesity in its residents. There is considerable interest in focusing these efforts early in the life cycle. Beginning obesity prevention during pregnancy and engaging health systems, early childhood programs, and community systems to support healthier life cycles is an approach with great promise.

60.1

Rapid-Onset Obesity With Hypothalamic Dysfunction,

Hypoventilation, and Autonomic Dysregulation (ROHHAD)

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Keywords

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ROHHAD—rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation—is a rare, poorly understood disease of childhood onset, the first sign of which is sudden, rapid, and extreme weight gain in a previously healthy child. The acronym describes the presenting symptoms and the typical order in which they will manifest or unfold, as the condition evolves over months to years. Despite its rarity, ROHHAD must be considered whenever rapid-onset obesity is observed in a child, because in the absence of appropriate treatment, a high mortality rate is associated with the severe central hypoventilation that will invariably develop.

The diagnosis is initially considered after the observation of rapid-onset obesity (15-20 lb gain) after age 1.5 yr, accompanied by at least 1 additional sign of hypothalamic dysfunction. Central hypoventilation may not be present at diagnosis but will develop over time, and artificial ventilatory support will be required at least during sleep, if not 24 hr/day. Signs of autonomic nervous system dysregulation typically occur after the weight gain, hypothalamic dysfunction, and hypoventilation have been identified. Additionally, approximately 40% of ROHHAD patients will have a tumor of neural crest origin, typically ganglioneuroma or ganglioneuroblastoma.

ROHHAD is distinct from **late-onset congenital central hypoventilation syndrome (LO-CCHS** ; see later and Chapter 446.2). ROHHAD is primarily distinguished from LO-CCHS by the presence of obesity and other signs of hypothalamic dysfunction and by the absence of CCHS-related *PHOX2B* mutation. Approximately 100 cases of ROHHAD have been described in the literature to date.

Clinical Manifestations

Children with ROHHAD initially appear healthy, with an unremarkable history. The initial symptoms present between ages 18 mo and 7 yr. Typically, the 1st symptom observed is **rapid-onset obesity** , with weight gain of 15-20 lb in 6-12 mo. This is a sign of **hypothalamic dysfunction (HD)** in these patients. The 2nd common sign of HD, seen in most ROHHAD patients, is **disordered water balance** , including hyper- and hyponatremia and both adipsia and polydipsia. Growth hormone (GH) deficiency is also observed in most patients. In some this manifests clinically as slowed growth rate and short stature, whereas in others a failed GH stimulation test is the only evidence. Other symptoms of HD, occurring in >25–50% of ROHHAD patients, include hyperprolactinemia, poor thermoregulation, central hypothyroidism, adrenal insufficiency, and delayed or precocious puberty. The number of hypothalamic abnormalities that will be observed and the sequential order in which they will appear are variable, and some symptoms may not manifest for months to 1-2 yr after the initial diagnosis. However, all ROHHAD patients will present with at least 1 of these signs of HD.

Sleep-disordered breathing (SDB) is one of the key symptoms of ROHHAD, often manifesting as one of the most severe features of the phenotype, with the greatest potential for fatal complications. More than half of ROHHAD patients have initial **obstructive sleep apnea (OSA)** ; although SDB is known to be associated with obesity, and OSA is often seen in obese individuals, the extent that SDB is tied to obesity in ROHHAD patients is not yet well defined. However, over time, as the ROHHAD phenotype unfolds, SDB will evolve beyond what could potentially be explained as obesity related. All ROHHAD patients will eventually develop **central alveolar hypoventilation** , requiring artificial ventilatory support, even when the upper airway obstruction is relieved as an intervention for OSA. About half of ROHHAD patients will require artificial ventilation only during sleep, while half will require continuous artificial ventilation (during sleep and wakefulness). More than 40% of children with ROHHAD will have a cardiorespiratory arrest before their hypoventilation is identified and treated. Unfortunately, many ROHHAD patients die from cardiorespiratory arrest because of unrecognized or inadequately managed hypoventilation. Thus, if a ROHHAD diagnosis is suspected, it is crucial that a comprehensive respiratory physiology evaluation is performed, including overnight polysomnography and awake physiologic recording in activities of daily living (ADLs).

All ROHHAD patients have symptoms of **autonomic nervous system (ANS) dysregulation** , but as described for signs of HD, the exact symptoms and the order and timing of their appearance will vary between patients. The most common manifestations of ANS dysregulation in ROHHAD are ophthalmologic, including pupillary dysfunction, strabismus, and alacrima. Many ROHHAD patients will have gastrointestinal dysmotility, presenting as either chronic constipation or chronic diarrhea. Other signs of ANS dysregulation include altered sweating, decreased body temperature, decreased sensitivity to pain, and cold hands and feet indicating altered vasomotor tone. Bradycardia is seen in some ROHHAD patients, typically related to extreme hypothermia.

Neural crest tumors are observed in at least 40% of ROHHAD patients, most frequently ganglioneuromas and ganglioneuroblastomas of the chest or abdomen; rarely a neuroblastoma has been reported. These tumors can occur at any age, so proactive imaging evaluation to identify the tumors is essential.

Most patients do not have **behavioral or psychologic disorders** . For those who do, however, the disorders can be quite severe, including anxiety, depression, rage, lethargy, irritability, aggressiveness, psychosis, and obsessive-compulsive disorder. Developmental disorders described include neurocognitive delay, developmental regression, attention-deficit/hyperactivity disorder, and pervasive developmental disorder. These disorders are most likely caused by poorly managed hypoventilation because the majority of ROHHAD patients have no behavioral issues and a normal IQ.

Seizures have been reported in some ROHHAD patients, likely caused by episodes of hypoxemia, when hypoventilation either has not yet been diagnosed or has been inadequately managed.

Diagnosis

The diagnostic criteria for ROHHAD include **r** apid-onset obesity after 1.5 years of age, central hypoventilation beginning after age 1.5 yr, and ≥1 of the following signs of HD: disordered water balance, hyperprolactinemia, failed GH stimulation test, central hypothyroidism, corticotropin deficiency, and altered onset of puberty. Additionally, it should be confirmed that no CCHS-related *PHOX2B* gene mutation is present, to rule out a diagnosis of CCHS or LO-CCHS.

Since no single diagnostic test is currently available for ROHHAD, diagnosis must be based on observation of the clinical presentation and therefore requires expert consultation in several specialties, including respiratory physiology, endocrinology, autonomic medicine, cardiology, oncology, nutrition, critical care, and psychiatry. When a child with rapid-onset obesity is seen by a general pediatrician or family physician, the trajectory of weight gain should signal prompt consideration of a ROHHAD diagnosis, with immediate referral to a center with expertise in this unique constellation of symptoms. Early recognition is critical for a positive outcome in children with ROHHAD. If alveolar hypoventilation is not identified and aggressively managed, cardiorespiratory arrest can occur and has proved fatal in many cases.

Initial evaluations should include overnight polysomnography to identify OSA or central hypoventilation, awake comprehensive physiologic recording in activities of daily living, cardiac evaluation to evaluate for cor pulmonale, endocrine function evaluation, screening for neural crest tumors (chest radiograph, abdominopelvic ultrasound), and a psychiatric evaluation, especially if any behavioral, psychologic, or developmental disorders are seen or suspected. Brain imaging should be performed to rule out intracranial lesions that may account for the observed hypothalamic-pituitary abnormalities. If the criteria are met, and a ROHHAD diagnosis is made, successful management requires ongoing cooperation among the various specialists, with a team leader to orchestrate all testing, to provide integrated care for the child.

Management

There is currently no cure for ROHHAD. Rather, treatment consists of early identification, meticulous monitoring, and symptomatic management of the various symptoms as they develop. Comprehensive initial evaluations should determine the nature and severity of hypoventilation, HD, and ANS dysregulation, and appropriate interventions should be implemented. Obesity is very difficult to control, but in consultation with a nutritionist and endocrinologist, the trajectory of advancing weight gain can be diminished with moderate exercise and calorie restriction, leading to improved body mass index (BMI) with advancing age. Specific signs of HD and ANS dysregulation should be evaluated by a pediatric endocrinologist and expert in pediatric autonomic medicine, respectively, and treated as necessary. Such treatments or management strategies may include hormone replacement; regimented fluid intake; ophthalmologic assessment and treatment; longitudinal monitoring of peripheral, core, and ambient temperature; and management of constipation with stool softeners. Disordered water balance to prevent dehydration should be addressed, as well as regulation of heart rate, since bradycardia is seen in some patients (usually with decreased core temperature).

Neural crest tumors should be assessed and resected by a pediatric surgeon together with a pediatric oncologist, because the sheer size of these benign tumors creates serious compromise to surrounding tissues. If no tumor is identified initially, screening should continue every 6 mo until age 7 yr and thereafter annually.

Most critical is the management of hypoventilation. Initial intervention for OSA will likely involve surgical relief of the upper airway obstruction. This will usually unveil central hypoventilation, and initiation of supported ventilation will be required. If no central hypoventilation is identified, the patient should continue to be vigilantly monitored by a respiratory physiologist because all ROHHAD patients will eventually develop central hypoventilation requiring artificial ventilation. Optimal oxygenation and ventilation can then be maintained using a mechanical ventilator with mask or tracheostomy. This should be accompanied by highly trained home nursing and continuous monitoring with oximetry and capnography during sleep, with spot checks during wakefulness. The goal should be to maintain hemoglobin saturation values of ≥95% and end-tidal CO_2 values of 35-45 mm Hg, with vigilant evaluation for awake hypoventilation necessitating artificial ventilation up to 24 hr/day as necessary.

Given that the ROHHAD phenotype evolves with advancing age, ongoing care requires regularly scheduled evaluation of all the systems involved to identify and treat further symptoms as they appear. Comprehensive evaluation should ideally occur at a **Center of Excellence** for ROHHAD and should include respiratory physiology assessment both asleep and awake (in ADLs including varied levels of exertion, concentrational tasks, quiet play, and eating), screening of chest and abdomen for neural crest tumors in the adrenals or along the sympathetic chain, evaluation of the hypothalamic-pituitary axis with hormonal replacement as necessary, age-appropriate noninvasive evaluation of ANS dysregulation, comprehensive cardiac evaluation for evidence of recurrent hypoxemia, and neurocognitive testing. These evaluations should initially occur at 3-6 mo intervals, but this schedule may be altered with advancing age, depending on each patient's clinical condition.

Without proper management, oxygen deprivation can lead to irreversible deterioration in patients. However, with prompt diagnosis and aggressive management, including careful attention to the child's airway, breathing, and circulation, complications can be minimized and the prognosis can be quite favorable, although long-term outcome remains unknown but the focus of an international registry (https://clinicaltrials.gov/show/NCT03135730).

Etiology: Studies and Hypotheses

Despite advances made in the characterization of the ROHHAD phenotype and early identification, the cause of the disease is unknown. The interrelationships among the observed symptoms, as well as the mechanisms that underlie them, remain to be elucidated.

Genetic Studies

Because the related but seemingly distinct disorder CCHS has a genetic basis (*PHOX2B* mutation), ROHHAD may be genetic as well. ROHHAD patients do not have CCHS-related *PHOX2B* mutations, however, and no numerical or structural chromosomal rearrangements have been described. The sporadic occurrence of ROHHAD, without familial recurrence, is consistent with de novo mutations. Exome-sequencing analysis of 7 ROHHAD family trios did not identify any causative de novo protein-altering mutations, or any candidates under autosomal recessive or autosomal dominant inheritance models, even when a replication cohort of 28 additional ROHHAD probands was included.

Another genetic mutation model that can account for sporadic occurrence of a phenotype is a *somatic mutation* model, in which mutations occur postzygotically and are thus only present in a subset of an individual's cells. Consistent with a somatic mutation hypothesis, 2 pairs of monozygotic twins discordant for the ROHHAD phenotype have been reported. The exomes (from blood samples) of 1 twin pair were compared, but no discordant coding mutations were identified. The challenge is that the "correct" tissue needs to be sampled for the somatic mutation to be identified. In other phenotypes caused by somatic mutations, such as Proteus syndrome, the mutation causes overgrowth, so the affected (mutated) tissue is visible and can be sampled and sequenced. In ROHHAD, presumably the affected (mutated) cells are in the hypothalamus and/or ANS, which cannot be sampled and sequenced from living individuals. The neural crest tumors in many ROHHAD patients might represent an additional affected tissue. The exomes of neural crest tumors from 4 ROHHAD patients were compared to the exomes of blood samples from the same patients, but no tumor-specific mutations were identified.

The observation of monozygotic twins discordant for the ROHHAD phenotype could be consistent with a somatic genetic mutation, but could also suggest an alternative, nongenetic etiology. For example, epigenetic variation can account for some discordance between monozygotic twins and also can play a role in diseases involving respiratory and autonomic function, such as Prader-Willi syndrome (see later) and Rett syndrome.

Paraneoplastic/Autoimmune Hypothesis

Paraneoplastic syndromes are rare disorders caused by a neoplasm triggering an altered immune response that aberrantly attacks and destroys neurons, leading to the nervous system symptoms. An autoimmune or paraneoplastic basis for ROHHAD has been suggested based on neural crest tumors occurring in 40% of ROHHAD patients and 2 early cases with autopsies revealing low-density lesions in the basal ganglia and neuronal loss from lymphocytic infiltration of the hypothalamus, thalamus, midbrain, and pons. Autopsy of another ROHHAD patient revealed similar findings of hypothalamic inflammation with lymphocytic infiltrates and gliosis, although other autopsies have found no such pathology. Some cerebrospinal fluid (CSF) analyses have revealed pleocytosis, elevated neopterins, and oligoclonal bands consistent with intrathecal synthesis of oligoclonal immunoglobulin G. However, other studies report a lack of oligoclonal IgG and antineuronal antibodies, as well as clear CSF microscopies and cultures. Thus the evidence so far is conflicting, with some reports supporting the autoimmune hypothesis, while others do not. Further, the onset of ROHHAD symptoms often precedes the diagnosis of a neural crest tumor in ROHHAD patients, and in many cases, neural crest tumors have not been discovered with MRI or even an autopsy, although these tumors are often difficult to detect. However, this is also seen in other paraneoplastic syndromes, such as opsoclonus-myoclonus, where only some cases are associated with a neoplasm, the remainder being idiopathic.

After a patient with idiopathic HD was treated with immune globulin therapy, several other studies pursued similar treatments with immunoglobulins and corticosteroids in ROHHAD patients. After high-dose cyclophosphamide treatment, some ROHHAD patients reported symptomatic and neurophysiologic improvements while others had poor clinical results. Notably, reports indicate that immunotherapy has not consistently halted unfolding and advancing of the unique constellation of symptoms described in ROHHAD. Even with complete tumor resection and immunoablation, only partial recovery has been reported. The lack of return to baseline has been attributed to late treatment, where early rapid progressive disease left residual damage. This would be consistent with an immune-mediated hypothesis, in which an autoimmune process is initiated by a neural crest tumor but maintained in its absence, resulting in irreversible injury that prevents complete symptom resolution.

Neurocristopathy

Neurocristopathies are disorders caused by abnormal development of any of the tissues or systems that develop from the embryonic neural crest cell lineage. Given that the systems involved in the ROHHAD phenotype (hypothalamus, ANS, endocrine system) share a neural crest origin, ROHHAD fits into this class. One could then hypothesize that the observed symptoms are caused by abnormal development of neural crest cells at an early embryonic stage. This is indeed the case for the related disorder, CCHS, caused by mutations in the gene *PHOX2B*, which is important for the development of the ANS from neural crest cells. Under this hypothesis, the neural crest tumors seen in ROHHAD patients, rather than being the trigger for the rest of the phenotype (as proposed by the paraneoplastic theory), would be a result of the same abnormal development that caused the rest of the phenotype.

Differential Diagnosis

As noted earlier, **congenital central hypoventilation syndrome** is a rare pediatric disorder of the ANS and respiratory control. CCHS is caused by mutations in the *PHOX2B* gene, which plays an important role in the differentiation and development of the ANS from neural crest progenitor cells. The hallmark feature of CCHS is life-threatening hypoventilation while sleeping (and in some cases, also while awake). As with ROHHAD patients, CCHS patients require artificial ventilatory support, typically by tracheostomy and mechanical ventilator. Unlike ROHHAD, however, CCHS usually presents in the newborn period, although late-onset CCHS has been diagnosed in later childhood, adolescence, and even adulthood. CCHS also presents with other symptoms of ANS dysregulation, including altered heart rate regulation and altered vasomotor tone, altered temperature regulation, ophthalmologic manifestations, and reduced gastrointestinal motility. However, CCHS patients are not obese and do not typically have HD. When hypoventilation is observed, a simple blood test can confirm a CCHS diagnosis by looking for *PHOX2B* mutations. If *PHOX2B* mutations are not identified and the other features of the ROHHAD phenotype are identified, a ROHHAD diagnosis must be considered.

Prader-Willi syndrome (PWS) is similar to ROHHAD in that childhood obesity is one of the most prominent features; however, many important differences set these two conditions apart. PWS is caused by chromosomal abnormalities at chromosome 15q11-q13, specifically by a lack of the paternal contribution at this region (from genomic deletion, uniparental disomy, or imprinting error). Infants with PWS present with neonatal hypotonia and failure to thrive (malnutrition). Later, children with PWS develop extreme hyperphagia and obesity. Other major symptoms include mild intellectual impairment, maladaptive behaviors, short stature caused by GH insufficiency, hypogonadism, and SDB. In addition, many PWS patients show signs of ANS dysregulation, including altered temperature perception and regulation, strabismus, and high pain threshold. Although there are several apparently overlapping symptoms (pediatric obesity, SDB, ANS dysregulation), ROHHAD patients do not have the characteristic PWS genomic abnormality, hypogonadism, or consistent neurocognitive impairment. ROHHAD patients also are healthy in the neonatal period, showing none of the early PWS symptoms.

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CHAPTER 61

Vitamin A Deficiencies and Excess

A. Catharine Ross

Overview of Vitamin A

Vitamin A is a fat-soluble micronutrient that cannot be synthesized de novo by mammals; thus it is an obligatory dietary factor. The term **vitamin A** is generally used to refer to a group of compounds that possess the biologic activity of all-*trans* retinol (Fig. 61.1). As a fat-soluble micronutrient, vitamin A is recognized as being essential for all vertebrates for normal vision, reproduction, cell and tissue differentiation, and functions of the immune system. Vitamin A plays critical roles in neonatal development. It is required for normal embryonic development, hematopoiesis, immune response, metabolism, and growth and differentiation of many types of cells.

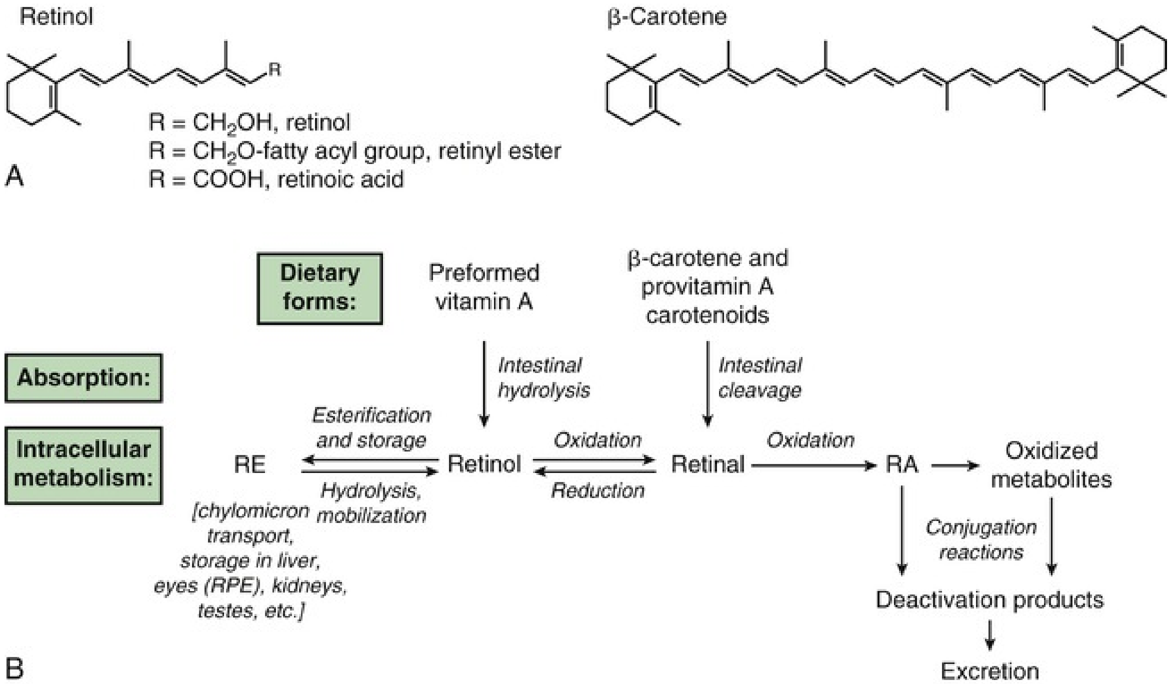
Retinol
β-Carotene
R
R = CH2OH, retinol
R = CH2O-fatty acyl group, retinyl ester
R = COOH, retinoic acid
A
Dietary forms:
Preformed vitamin A
β-carotene and provitamin A carotenoids
Absorption:
Intestinal hydrolysis
Intestinal cleavage
Intracellular metabolism:
Esterification and storage
RE
Retinol
Oxidation
Retinal
Oxidation
RA
Oxidized metabolites
Hydrolysis, mobilization
Reduction
[chylomicron transport, storage in liver, eyes (RPE), kidneys, testes, etc.]
Conjugation reactions
Deactivation products
Excretion
B

FIG. 61.1 **A,** Vitamin A structures. **B,** Overview of vitamin A metabolism. RA, All-*trans* retinoic acid; RE, retinyl ester; RPE, retinal pigment epithelium.

Vitamin A can be obtained from the diet from preformed vitamin A (retinyl esters, such as retinyl palmitate) primarily in foods of animal origin. Organ meats (especially liver, kidney) are very rich in vitamin A, whereas other meats, milk, and cheese contain moderate levels. Other sources of vitamin A include several provitamin A carotenoids, which are found naturally in many fruits and vegetables, especially yellow-orange vegetables (pumpkin, squash, sweet potato), and leafy green vegetables (chard, spinach, broccoli). One of the most abundant carotenoids is β-carotene. Several *cultivars* or biofortified forms of sweet potatoes have been introduced to elevate carotene intake in areas of the world where vitamin A deficiency still is prevalent. α-Carotene and oxygenated carotenoids, such as β-cryptoxanthin, found in oranges, also possess vitamin A activity, at a lower bioactivity. In the body, these precursors are used for the synthesis of 2 essential metabolites of vitamin A. **All-*trans* retinoic acid** is the form required for cell differentiation and regulation of gene transcription and is the most bioactive form of vitamin A; **11-*cis* retinal** is the form required for vision as the light-absorbing chromophore of the visual pigments rhodopsin and iodopsin.

Metabolism of Vitamin A

Vitamin A compounds in foods must first be released through normal digestive processes. Retinyl esters must first be hydrolyzed in the intestinal lumen to liberate unesterified retinol for absorption across the mucosal barrier. Once in the enterocyte, most of the retinol is reesterified, forming new retinyl esters for inclusion in chylomicrons. Approximately 70–90% of dietary preformed vitamin A is absorbed provided there is ≥10 g fat in the meal; otherwise the absorption efficiency is lower. Chronic intestinal disorders or lipid malabsorption can result in vitamin A deficiency. Provitamin-A carotenoids are transported from the intestinal lumen into the enterocytes by specific transporters, then either incorporated intact into chylomicrons or cleaved to form *retinal*, a precursor for retinol; β-carotene becomes retinol through this process. The estimated efficiency of absorption of carotenoids is 20–50%, lower than for preformed vitamin A. Moreover, the efficiency is reduced when the body's vitamin A status is high, and because vitamin A status may vary, there is significant interindividual variability in absorption efficiency. The carotene cleavage enzyme β-carotene monooxygenase, present in the enterocyte and in other tissues at lower levels, exhibits certain single nucleotide polymorphisms (SNPs) that, at least in vitro, reduce the efficiency of conversion of β-carotene to retinol. Clinical studies suggest a similar effect in vivo.

Once retinol is esterified in the enterocyte, retinyl ester is then packaged into nascent chylomicrons, which are secreted into the lymphatic vessels, enter the systemic circulation, and are then transported to and taken up by various tissues. When vitamin A status is adequate, in most mammals, including humans, the liver is the major site of chylomicron vitamin A uptake and storage, with potentially high levels of retinyl esters within hepatic stellate cells (HSCs). As vitamin A status deteriorates into the deficient range, vitamin A stores are mobilized from the HSCs, such that the released retinol can be taken up and utilized by extrahepatic tissues. Circulating retinol is bound to a specific transport protein, **retinol-binding protein (RBP)** , which in turn binds to the thyroid hormone transport protein, **transthyretin (TTR)** ; this complex delivers plasma retinol (as well as the thyroid hormone) to a large number of vitamin A target tissues. The major physiologic mediator of retinol uptake by cells in many tissues is Stra6, a widely expressed multitransmembrane domain protein that functions as a cell surface receptor for retinol bound to RBP. Stra6 is not significantly expressed in the liver, but a homologous receptor may perform the similar function. Within target tissues, retinol is either esterified into retinyl esters for storage or oxidized into retinoic acid for function. In the eye, 11-*cis* -retinal is formed, bound to the protein rhodopsin (rods) or iodopsin (cones), where it functions as a light-sensing receptor.

Vitamin A Status in Neonates

Neonates begin life with low levels of vitamin A, in plasma, liver, and extrahepatic tissues, compared with those in adults. Normal plasma levels of retinol are 20-50 µg/dL in infants and increase gradually as children become older. Median serum retinol values are 1.19 µmol/L in both boys and girls ages 4-8 yr; 1.4 and 1.33 µmol/L in boys and girls, respectively, ages 9-13; and 1.71 and 1.57 µmol/L in boys and girls, ages 14-18 (for conversion, 1 µmol/L = 28.6 µg/dL). Values of 1.96 and 1.85 µmol/L are found in 19-30 yr old adult men and women, respectively. Fig. 61.2 shows the distribution of serum retinol concentrations in U.S. children.

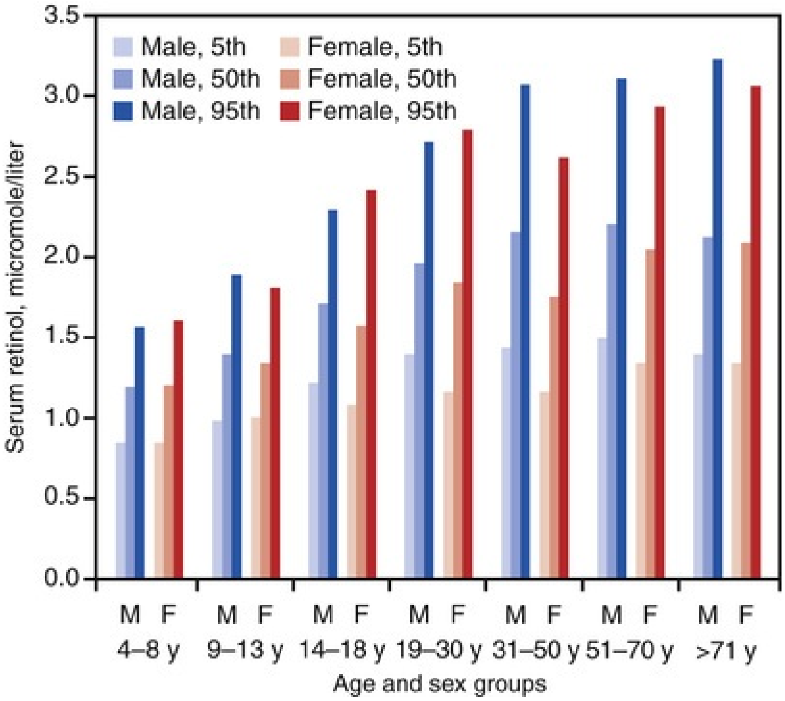

FIG. 61.2 Distribution of serum retinol concentrations in U.S. children and adults by age and sex in the National Health and Nutrition Examination Survey (NHANES).

Retinol levels are even lower in neonates in developing countries, where vitamin A intakes may be low and vitamin A deficiency is a common and significant nutritional problem. Lower vitamin A stores and plasma retinol concentrations are seen in low-birthweight infants and in preterm newborns. Malnutrition, particularly protein deficiency, can cause vitamin A deficiency because of the impaired synthesis of RBP.

Inflammation Causing Low Plasma Retinol

Inflammation is a cause of reduced levels of plasma retinol as a result of reduced synthesis of RBP and TTR. This condition may mimic a lack of vitamin A, but will not be corrected by supplementation. In U.S. adults, those with moderately elevated levels of C-reactive protein (CRP), indicative of mild inflammation, had lower average plasma retinol levels. The extent to which inflammation is a factor in low plasma retinol in children is uncertain but likely significant in acute infectious diseases such as measles, and possibly in chronic inflammatory conditions such as cystic fibrosis.

Functions of Vitamin A and Mechanisms of Action

Except for its role in vision, the pleiotropic actions of this micronutrient are mediated by all-*trans* -retinoic acid (RA), which is a ligand for specific nuclear transcription factors, the **retinoid receptors** ; RARs and RXRs regulate the expression of several hundred genes. When an RAR is activated by RA, an RAR-RXR complex is formed, which binds to and activates specific DNA sequences present in retinoid-responsive genes, RAREs and RXREs. Genes can be either induced or repressed, depending on additional co-activators or co-repressors recruited to the RAR-RXR complex. Retinoid-regulated genes are involved in several fundamental biologic activities, including regulation of cell division, death, and differentiation. The term *retinoids* applies to both natural and synthetic compounds with vitamin A activity and is most often used in the context of vitamin A acting at the gene level. Numerous synthetic retinoids have gained clinical acceptance in the treatment of skin disorders and certain cancers.

During embryonic development, retinoic acid is among the most important signaling molecules that determine body patterning (morphogenesis). Many physiologic processes are sensitive to a deficiency or excess of vitamin A or RA, including reproduction, growth, bone development, and the functions of the respiratory, gastrointestinal, hematopoietic, and immune systems. Vitamin A, presumably by enhancing immune function and host defense, is particularly important in developing countries; studies show that vitamin A supplementation or therapy reduces morbidity and mortality from various infectious diseases, including measles (see Chapter 273).

Vitamin A plays a critical role in vision, mediated by 11-*cis* retinal. The human retina contains 2 distinct photoreceptor systems: the *rods,* in which rhodopsin senses light of low-intensity, and the *cones*, in which iodopsins detect different colors; 11-*cis* -retinal is the prosthetic group on both these visual proteins. The mechanism of vitamin A action is similar for rods and cones, based on *photoisomerization* of 11-*cis* to all-*trans* retinal (change shape when exposed to light), which initiates signal transduction via the optic nerve to the brain, resulting in visual sensation. After isomerization (also known as photobleaching), a series of reactions serves to regenerate the 11-*cis* retinal for resynthesis of rhodopsin and iodopsin; accessory cells, including retinal pigment epithelium and Müller cells, are involved in this recycling process.

Vitamin A Deficiency

If the growing child has a well-balanced diet and obtains vitamin A from foods rich in vitamin A or provitamin A (Table 61.1), the risk of vitamin A deficiency is small. However, even subclinical vitamin A deficiency can have serious consequences.

Table 61.1

Vitamin A Characteristics

NAMES AND SYNONYMS	CHARACTERISTICS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	SOURC
Retinol (vitamin A_1); 1 µg retinol = 3.3 IU vitamin A = 1 RAE Provitamins A: the plant pigments α-,	Fat-soluble; heat-stable; destroyed by oxidation, drying Bile necessary for absorption Stored in liver Protected by vitamin E	In vision, as retinal, for synthesis of the visual pigments rhodopsin and iodopsin In growth, reproduction,	Nyctalopia Photophobia, xerophthalmia, Bitôt spots, conjunctivitis, keratomalacia leading to blindness Faulty	Anorexia, slow growth, drying and cracking of skin, enlargement of liver and spleen, swelling and	Live liver Dair prod exce milk Egg forti marg

β-, and γ-carotenes and cryptoxanthin have partial retinol activity: 12 µg β-carotene, or 24 µg other provitamin A carotenoids = 1 µg retinol		embryonic and fetal development, bone growth, immune and epithelial functions, via retinoic acid as a ligand for specific nuclear transcription factors, regulating genes involved in many fundamental cellular processes	epiphyseal bone formation Defective tooth enamel Keratinization of mucous membranes and skin Retarded growth Impaired resistance to infection, anemia, reproductive failure, fetal abnormalities	pain of long bones, bone fragility, increased intracranial pressure, alopecia, carotenemia Fetal abnormalities	forti skim Caro from plan gree vege yello fruit vege

RAE, Retinol activity equivalent.

Deficiency states in developed countries are rare, except in some impoverished populations (see Chapter 57), or after mistakes in food preparation or with fad diets, but are common in many developing countries and often associated with global malnutrition. In the clinical setting, vitamin deficiencies can also occur as complications in children with various chronic disorders or diseases. Information obtained in the medical history related to dietary habits can be important in identifying the risk of such nutritional problems. Except for vitamin A, toxicity from excess intake of vitamins is rare. Table 61.1 summarizes the food sources, functions, and deficiency and excess symptoms of the vitamins.

Clinical Manifestations of Vitamin A Deficiency

The most obvious symptoms of vitamin A deficiency are associated with changes in epithelial cell morphology and functions. In the intestines, mucus-secreting goblet cells are affected, and loss of an effective barrier against pathogens can cause diarrhea or impairment of epithelial barrier function. Similarly, mucus secretion by the epithelium is essential in the respiratory tract for the disposal of inhaled pathogens and toxicants. Characteristic epithelial changes result from vitamin A deficiency, including proliferation of basal cells, hyperkeratosis, and formation of stratified cornified squamous epithelium. Squamous metaplasia of the renal pelves, ureters, vaginal epithelium, and the pancreatic and salivary ducts can lead to increased infections in these areas. In the urinary bladder, loss of epithelial integrity can result in pyuria and hematuria. In the skin, vitamin A deficiency manifests as dry, scaly, hyperkeratotic patches, typically on the arms, legs, shoulders, and buttocks. The combination of defective epithelial barriers to infection, low immune response, and lowered response to inflammatory stress, all from insufficient vitamin A, can cause poor growth and serious health problems in children.

The most characteristic and specific signs of vitamin A deficiency are *eye lesions*, but these may manifest rather late in the progression of vitamin A deficiency, develop insidiously, and rarely occur before age 2 yr. An earlier symptom of vitamin A deficiency is delayed dark adaptation, as a result of reduced resynthesis of rhodopsin; this may progress to **night blindness** . Photophobia is a common symptom. The retinal pigment epithelium (RPE), the structural element of the retina, undergoes keratinization. When the RPE degenerates, the rods and cones have no support and eventually break down, resulting in blindness.

As vitamin A deficiency progresses, the corneal and conjunctival epithelial tissues of the eye become severely altered because of a lack of sufficient RA for normal epithelial cell differentiation. The cornea protects the eye from the environment and is also important in light refraction. Stages in vitamin A deficiency include corneal keratinization and opacity, susceptibility to infection, and formation of dry, scaly layers of cells (**xerophthalmia**) (Figs. 61.3 and 61.4)**.** The conjunctival membrane undergoes keratinization and may develop foamy-appearing plaques (**Bitôt spots** ; Fig. 61.5). When lymphocytes infiltrate the cornea in later stages of infection, it degenerates irreversibly (**keratomalacia** and **corneal ulceration**), resulting in irreversible blindness. These eye lesions are primarily diseases of the young and are a major cause of blindness in developing countries. Although rates of xerophthalmia have fallen, the number of affected children is still too high. Treatment with vitamin A, up to the stage of keratomalacia, is effective in rapidly repleting the individual and saving vision.

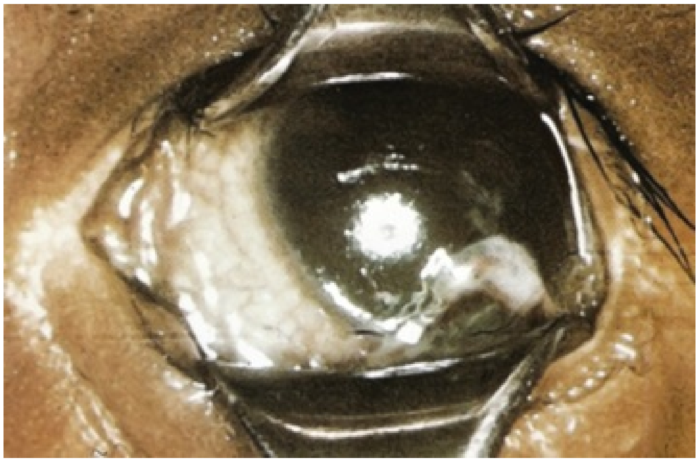

FIG. 61.3 Advanced xerophthalmia with an opaque, dull cornea and some damage to the iris in a 1 yr old boy. (From Oomen HAPC: Vitamin A deficiency, xerophthalmia and blindness, *Nutr Rev* 6:161–166, 1974.)

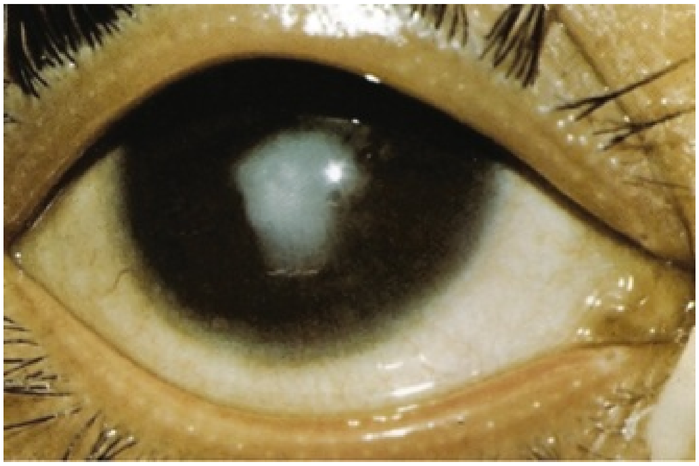

FIG. 61.4 Recovery from xerophthalmia, showing a permanent eye lesion. (From Bloch CE: Blindness and other disease arising from deficient nutrition [lack of fat soluble A factor], *Am J Dis Child* 27:139, 1924.)

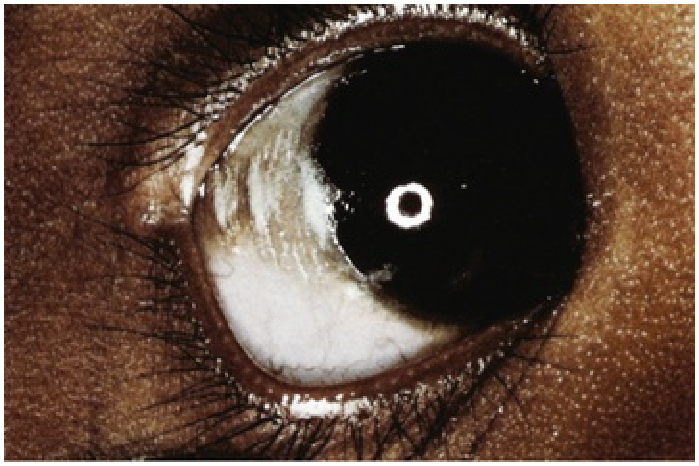

FIG. 61.5 Bitôt spots with hyperpigmentation seen in a 10 mo old Indonesian boy. (From Oomen HAPC: Vitamin A deficiency, xerophthalmia and blindness, *Nutr Rev* 6:161–166, 1974.)

Other clinical signs of vitamin A deficiency include poor overall growth, diarrhea, susceptibility to infections, anemia, apathy, intellectual impairment, and increased intracranial pressure, with wide separation of the cranial bones at the sutures. There may be vision problems as a consequence of bone overgrowth causing pressure on the optic nerve.

Malnutrition , particularly protein deficiency, can cause vitamin A deficiency through impaired synthesis of retinol transport protein. In developing countries, subclinical or clinical zinc deficiency can increase the risk of vitamin A deficiency. There is also some evidence of marginal zinc intakes in U.S. children.

Diagnosis

Dark adaptation tests can be used to assess early-stage vitamin A deficiency. Although Bitôt spots develop relatively early, those related to active vitamin A deficiency are usually confined to preschool-age children. Xerophthalmia is a very characteristic lesion of vitamin A deficiency. For detection of less severe deficiency (marginal vitamin A status), methods include conjunctival impression cytology, relative dose response, and modified relative dose response tests. A diet history is useful in suggesting or ruling out low intake as a cause of symptoms. Marginal vitamin A status is relatively prevalent among pregnant and lactating women in low-resource (and therefore poor dietary intake) areas of the world. Although plasma retinol level is not a completely accurate indicator of vitamin A status, various guidelines have been proposed for categorizing vitamin

A status based on serum retinol. In children, plasma retinol <0.35 µmol/L is considered *very deficient,* 0.35-0.7 µmol/L *deficient,* 0.7-1.05 µmol/L *marginal,* and >1.05 µmol/L *adequate.* It has long been thought that a liver vitamin A concentration >20 µg/g is needed to support a normal rate of secretion of retinol-RBP into plasma, and therefore normal delivery of retinol to peripheral tissues.

Epidemiology and Public Health Issues

Vitamin A deficiency and xerophthalmia still occur throughout much of the developing, income-poor world and are linked to undernourishment and complicated by illness. Various public health programs to provide large doses of vitamin A periodically have been instituted. Vitamin A supplementation is considered part of the strategy of the World Health Organization (WHO) Millennium Development Goals to reduce <5 yr mortality. Neonatal supplementation may be most effective in populations with a high incidence of maternal vitamin A deficiency. Other strategies being tested include improving the content of β-carotene in staple foods through plant breeding (biofortification).

Dietary Reference Intakes for the Healthy Population

Table 61.2 summarizes the dietary reference intakes for infants and children. Dietary reference intake values include the estimated average requirement (EAR), which is the mean biologic requirement for the nutrient for the age-sex group of interest; the recommended dietary allowance (RDA), which is set to cover the physiological needs of >97% of the population (thus the needs of many people are more than met by consuming the RDA); and the upper level of normal (UL), an intake level above which risk of adverse effects may increase; the UL pertains only to chronic consumption of preformed vitamin A. The RDA is expressed as retinol activity equivalents (RAEs; 1 RAE = 1 µg all-*trans* retinol; equivalents for provitamin-A in foods = 12 µg β-carotene, 24 µg α-carotene, or 24 µg β-cryptoxanthin). From infancy to age 18 yr, the RDA increases as a result of increased body size, becoming higher for boys than girls during adolescence. During pregnancy the RDA is 750-770 µg, and during lactation it increases to 1,200-1,300 µg to ensure sufficient vitamin A content during breastfeeding.

Table 61.2

Dietary Reference Intakes for Vitamin A in Children

AGE RANGE	RECOMMENDED DIETARY ALLOWANCE (RDA) (µg retinol equivalents per day)	UPPER LEVEL (UL) (µg retinol equivalents per day)	COMMENTS
0-6 mo	400	600	The recommended intake for infants is an adequate intake, based on the amount of vitamin A normally present in breast milk.
7-12 mo	500	600	
1-3 yr	300	600	The UL applies only to preformed vitamin A (retinol).
4-8 yr	400	900	
9-13 yr	600	1,700	
14-18 yr	900, male; 700, female	2,800	

It is noteworthy that, especially for young children, the UL is only about 2 times higher than the RDA. This suggests that for children whose diet is good, care should be taken not to overuse dietary supplements (vitamin-mineral supplements) containing preformed vitamin A, and/or to avoid excessive consumption of foods that are very rich in vitamin A, such as liver.

Vitamin A for Treatment of Deficiency

A daily supplement of 1,500 µg of vitamin A is sufficient for treating latent vitamin A deficiency, after which intake at the RDA level should be the goal. In children without overt signs of vitamin A deficiency but suspected low reserves of vitamin A, rates of morbidity and mortality, as from viral infections such as measles, have been reduced by a weekly doses of vitamin A at the RDA level. More often, higher doses of 30-60 mg of retinol (100,000-200,000 IU/child) are given once or twice, under careful monitoring to avoid toxicity associated with excess vitamin A. Xerophthalmia is treated by giving 1,500 µg/kg body weight orally for 5 days, followed by intramuscular injection of 7,500 µg of vitamin A in oil, until recovery. In neonatal rats, vitamin A given as a supplemental dose only transiently increased retinol levels in most tissues, although liver vitamin A remained higher more persistently.

Vitamin A is also used in preterm infants to improve respiratory function and prevent development of chronic lung disease. An analysis of 9 randomized controlled trials found that vitamin A appears to be beneficial in reducing death or oxygen requirement with no difference in neurodevelopmental outcomes.

Hypervitaminosis A

Chronic hypervitaminosis A results from excessive ingestion of preformed vitamin A (retinol or retinyl ester), generally for several weeks or months. Hypervitaminosis A is most often caused by vitamin A–containing supplements or food faddism, including high intakes of organ meats. Chronic daily intakes of 15,000 µg and 6,000 µg can be toxic in adults and children, respectively. Because there is no antidote for hypervitaminosis A, and vitamin A is readily stored in liver and other tissues, it is most important to prevent toxicity. Symptoms may subside rapidly on withdrawal of the vitamin, but the rate of improvement depends on the amount of vitamin A stored in tissues. Extreme hypervitaminosis A is fatal. Signs of subacute or chronic toxicity can include headache, vomiting (early signs), anorexia, dry itchy desquamating skin, and seborrheic cutaneous lesions. With chronic hypervitaminosis A, one may observe fissuring at the corners of the mouth, alopecia and coarsening of the hair, bone abnormalities and swelling, enlargement of the liver and spleen, diplopia, increased intracranial pressure, irritability, stupor, limited motion, dryness of the mucous membranes, and desquamation of the palms and the soles of the feet. Radiographs may show *hyperostosis* affecting several long bones, especially in the middle of the shafts (Fig. 61.6). Serum levels of vitamin A are elevated, mostly as retinyl esters carried in lipoproteins, which may result in tissue damage and release of liver enzymes into plasma. Hypercalcemia and/or liver cirrhosis may be present. Hypervitaminosis A is distinct from cortical hyperostosis (see Chapter 720).

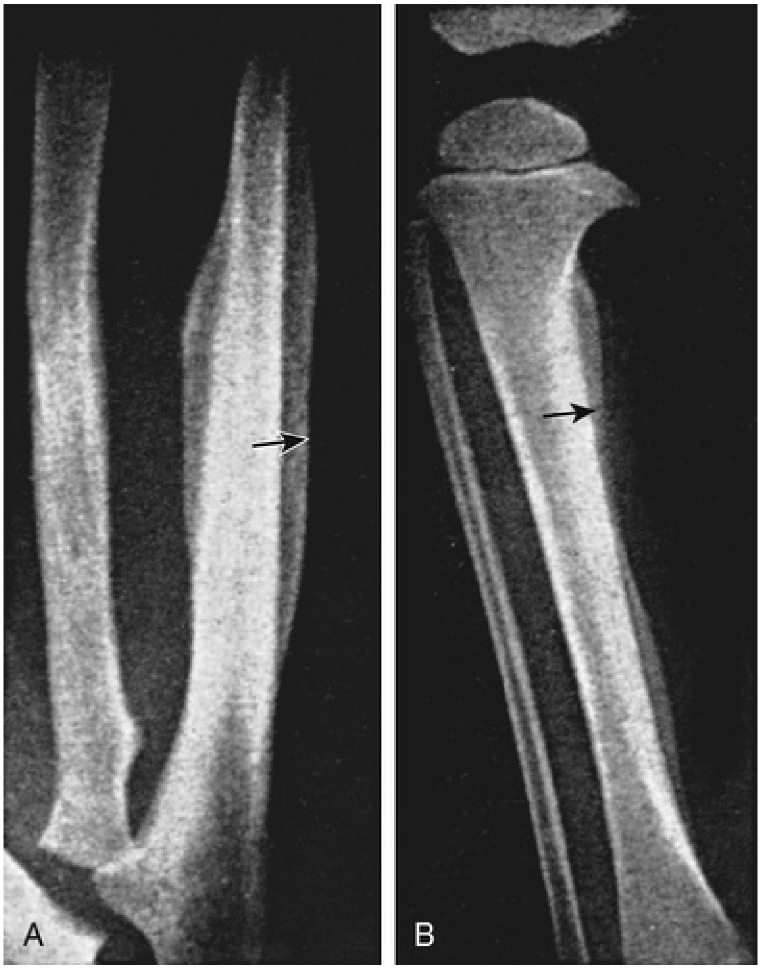

FIG. 61.6 Hyperostosis of the ulna and tibia in 21 mo old infant, resulting from vitamin A positioning. A, Long, wavy cortical hyperostosis of the ulna (*arrow*). B, Long, wavy cortical hyperostosis of the right tibia (*arrow*), with a striking absence of metaphyseal changes. (From Caffey J: *Pediatric x-ray diagnosis* , ed 5, Chicago, 1967, Year Book, p 994.)

In young children, signs of vitamin A toxicity include vomiting and bulging fontanels, neither of which is specific. Combined with anorexia, pruritus, and a lack of weight gain, vitamin A toxicity should be considered. Less common symptoms include diplopia, papilledema, cranial nerve palsies, and other symptoms suggesting **pseudotumor cerebri.**

If high levels of vitamin A or synthetic retinoids are taken early in pregnancy, **severe congenital malformations** may occur in the fetus. **Teratogenicity** has been associated with therapeutic doses (0.5-1.5 mg/kg) of oral 13-*cis* -retinoic acid (e.g., Accutane), generally taken for the treatment of acne or cancer, during the 1st trimester of pregnancy. A high incidence (>20%) of spontaneous abortions and birth defects, including characteristic craniofacial abnormalities, has prompted the U.S. Food and Drug Administration (FDA) to enact more stringent prescription regulations for such drugs in women of childbearing age, to attempt to reduce these birth defects.

Carotenoids, even in high doses, are not associated with toxicity but can cause yellowing of the skin (**carotenodermia**), including palms of the hands, and high levels in serum (carotenemia); this relatively benign state disappears slowly when carotene intake is reduced. Children with liver disease, diabetes mellitus, or hypothyroidism are more susceptible. Food faddism, such as excessive consumption of carotene-rich foods and juices, may be a cause of carotenodermia.

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CHAPTER 62

Vitamin B Complex Deficiencies and Excess

H.P.S. Sachdev, Dheeraj Shah

Vitamin B complex includes a number of water-soluble nutrients, including thiamine (vitamin B_1), riboflavin (B_2), niacin (B_3), pyridoxine (B_6), folate, cobalamin (B_{12}), biotin, and pantothenic acid. *Choline* and *inositol* are also considered part of the B complex and are important for normal body functions, but specific deficiency syndromes have not been attributed to a lack of these factors in the diet.

B-complex vitamins serve as coenzymes in many metabolic pathways that are functionally closely related. Consequently, a lack of one of the vitamins has the potential to interrupt a chain of chemical processes, including reactions that are dependent on other vitamins, and ultimately can produce diverse clinical manifestations. Because diets deficient in any one of the B-complex vitamins are often poor sources of other B vitamins, manifestations of several vitamin B deficiencies usually can be observed in the same person. It is therefore a general practice in a patient who has evidence of deficiency of a specific B vitamin to treat with the entire B-complex group of vitamins.

62.1

Thiamine (Vitamin B_1)

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Keywords

beriberi
cardiopathy
peripheral neuropathy
thiamine deficiency
Wernicke encephalopathy

Thiamine diphosphate, the active form of thiamine, serves as a cofactor for several enzymes involved in carbohydrate catabolism such as pyruvate dehydrogenase, transketolase, and α-ketoglutarate. These enzymes also play a role in the hexose monophosphate shunt that generates nicotinamide adenine dinucleotide phosphate (NADP) and pentose for nucleic acid synthesis. Thiamine is also required for the synthesis of acetylcholine (ACh) and γ-aminobutyric acid (GABA), which have important roles in nerve conduction. Thiamine is absorbed efficiently in the gastrointestinal (GI) tract and may be deficient in persons with GI or liver disease. The requirement of thiamine is increased when carbohydrates are taken in large amounts and during periods of increased metabolism, such as fever, muscular activity, hyperthyroidism, pregnancy, and lactation. Alcohol affects various aspects of thiamine transport and uptake, contributing to the deficiency in alcoholics.

Pork (especially lean), fish, and poultry are good nonvegetarian **dietary sources** of thiamine. Main sources of thiamine for vegetarians are rice, oat, wheat, and legumes. Most ready-to-eat breakfast cereals are enriched with thiamine. Thiamine is water soluble and heat labile; most of the vitamin is lost when the rice is repeatedly washed and the cooking water is discarded. The breast milk of a well-nourished mother provides adequate thiamine; breastfed infants of thiamine-deficient mothers are at risk for deficiency. Thiamine antagonists (coffee, tea) and thiaminases (fermented fish) may contribute to thiamine deficiency. Most infants and older children consuming a balanced diet obtain an adequate intake of thiamine from food and do not require supplements.

Thiamine Deficiency

Deficiency of thiamine is associated with severely malnourished states, including malignancy and following surgery. The disorder (or spectrum of disorders) is classically associated with a diet consisting largely of polished rice (oriental beriberi); it can also arise if highly refined wheat flour forms a major part of the diet, in alcoholic persons, and in food faddists (occidental beriberi). Thiamine deficiency has often been reported from inhabitants of refugee camps consuming the polished rice–based monotonous diets. Low thiamine concentrations are also noted during critical illnesses.

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is a rare autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus, and sensorineural hearing loss, responding in varying degrees to thiamine treatment. The syndrome occurs because of mutations in the *SLC19A2* gene, encoding a thiamine transporter protein, leading to abnormal thiamine transportation and cellular vitamin deficiency. Another dependency state, **biotin and thiamine–responsive basal ganglia disease** , results from mutations in the *SLC19A3* gene; presents with lethargy, poor contact, and poor feeding in early infancy; and responds to combined treatment with biotin and thiamine. Thiamine and related vitamins may improve the outcome in children with Leigh encephalomyelopathy and type 1 diabetes mellitus.

Clinical Manifestations

Thiamine deficiency can develop within 2-3 mo of a deficient intake. Early symptoms of thiamine deficiency are nonspecific, such as fatigue, apathy, irritability, depression, drowsiness, poor mental concentration, anorexia, nausea, and abdominal discomfort. As the condition progresses, more-specific manifestations of **beriberi** develop, such as peripheral neuritis (manifesting as tingling, burning, paresthesias of the toes and feet), decreased deep tendon reflexes, loss of vibration sense, tenderness and cramping of the leg muscles, heart failure, and psychologic disturbances. Patients can have ptosis of the eyelids and atrophy of the optic nerve. Hoarseness or aphonia caused by paralysis of the laryngeal nerve is a characteristic sign. Muscle atrophy and tenderness of the nerve trunks are followed by ataxia, loss of coordination, and loss of deep sensation. Later signs include increased intracranial pressure, meningismus, and coma. The clinical picture of thiamine deficiency is usually divided into a dry (**neuritic**) type and a wet (**cardiac**) type. The disease is wet or dry depending on the amount of fluid that accumulates in the body because of cardiac and renal dysfunction, even though the exact cause for this edema is unknown. Many cases of thiamine deficiency show a mixture of both features and are more properly termed **thiamine deficiency with cardiopathy and peripheral neuropathy** .

The classic clinical triad of **Wernicke encephalopathy** —mental status changes, ocular signs, and ataxia—is rarely reported in infants and young children with severe deficiency secondary to malignancies or feeding of defective formula. An epidemic of life-threatening thiamine deficiency was seen in infants fed a defective soy-based formula that had undetectable thiamine levels. Manifestations included emesis, lethargy, restlessness, ophthalmoplegia, abdominal distention, developmental delay, failure to thrive (malnutrition), lactic acidosis, nystagmus, diarrhea, apnea, seizures, and auditory neuropathy. An acute presentation with tachycardia, moaning, and severe metabolic acidosis responding to parenteral thiamine has been occasionally reported in infants of mothers consuming polished and frequently washed rice.

Death from thiamine deficiency usually is secondary to cardiac involvement. The initial signs are cyanosis and dyspnea, but tachycardia, enlargement of the liver, loss of consciousness, and convulsions can develop rapidly. The heart, especially the right side, is enlarged. The electrocardiogram (ECG) shows an increased QT interval, inverted T waves, and low voltage. These changes, as well as the cardiomegaly, rapidly revert to normal with treatment, but without prompt treatment, cardiac failure can develop rapidly and result in death. In fatal cases of beriberi, lesions are principally located in the heart, peripheral nerves, subcutaneous tissue, and serous cavities. The heart is dilated, and fatty degeneration of the myocardium is common. Generalized edema or edema of the legs, serous effusions, and venous engorgement are often present. Degeneration of myelin and axon cylinders of the peripheral nerves, with wallerian degeneration beginning in the distal locations, is also common, particularly in the lower extremities. Lesions in the brain include vascular dilation and hemorrhage.

Diagnosis

The diagnosis is often suspected based on clinical setting and compatible symptoms. A high index of suspicion in children presenting with unexplained cardiac failure may sometimes be lifesaving. Objective biochemical tests of thiamine status include measurement of erythrocyte transketolase activity and the thiamine pyrophosphate effect. The biochemical diagnostic criteria of thiamine deficiency consist of low erythrocyte transketolase activity and high thiamine pyrophosphate effect (normal range: 0–14%). Urinary excretion of thiamine or its metabolites (thiazole or pyrimidine) after an oral loading dose of thiamine may also be measured to help identify the deficiency state. MRI changes of thiamine deficiency in infants are characterized by bilateral symmetric hyperintensities of the basal ganglia and frontal lobe, in addition to the lesions in the mammillary bodies, periaqueductal region, and thalami described in adults.

Prevention

A maternal diet containing sufficient amounts of thiamine prevents thiamine deficiency in breastfed infants, and infant formulas marketed in all developed countries provide recommended levels of intake. During complementary feeding, adequate thiamine intake can be achieved with a varied diet that includes meat and enriched or whole-grain cereals. When the staple cereal is polished rice, special efforts need to be made to include legumes and/or nuts in the ration. Thiamine and other vitamins can be retained in rice by *parboiling,* a process of steaming the rice in the husk before milling. Improvement in cooking techniques, such as not discarding the water used for cooking, minimal washing of grains, and reduction of cooking time helps to minimize the thiamine losses during the preparation of food. Thiamine supplementation should be ensured during total parenteral nutrition (TPN).

Treatment

In the absence of GI disturbances, oral administration of thiamine is effective. Children with cardiac failure, convulsions, or coma should be given 10 mg of thiamine intramuscularly (IM) or intravenously (IV) daily for the 1st wk. This treatment should then be followed by 3-5 mg/day of thiamine orally (PO) for at least 6 wk. The response is dramatic in infants and in those having predominantly cardiovascular manifestations, whereas the neurologic response is slow and often incomplete. Epilepsy, mental disability, and language and auditory problems of varying degree have been reported in survivors of severe infantile thiamine deficiency.

Patients with beriberi often have other B-complex vitamin deficiencies; therefore, all other B-complex vitamins should also be administered. Treatment of TRMA and other dependency states require higher dosages (100-200 mg/day).

The anemia responds well to thiamine administration, and insulin for associated diabetes mellitus can also be discontinued in many patients with TRMA syndrome.

Thiamine Toxicity

There are no reports of adverse effects from consumption of excess thiamine by ingestion of food or supplements. A few isolated cases of pruritus and anaphylaxis have been reported in patients after parenteral administration of vitamin B_1 .

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62.2

Riboflavin (Vitamin B_2)

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Keywords

ariboflavinosis
angular cheilosis
glossitis
riboflavin deficiency

Riboflavin is part of the structure of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide, which participate in oxidation-reduction (redox) reactions in numerous metabolic pathways and in energy production via the mitochondrial respiratory chain. Riboflavin is stable to heat but is destroyed by light. Milk, eggs, organ meats, legumes, and mushrooms are rich dietary sources of riboflavin. Most commercial cereals, flours, and breads are enriched with riboflavin.

Riboflavin Deficiency

The causes of riboflavin deficiency (**ariboflavinosis**) are mainly related to malnourished and malabsorptive states, including GI infections. Treatment with some drugs, such as probenecid, phenothiazine, or oral contraceptives (OCs), can also cause the deficiency. The side chain of the vitamin is photochemically destroyed during phototherapy for hyperbilirubinemia, since it is involved in the photosensitized oxidation of bilirubin to more polar excretable compounds.

Isolated complex II deficiency , a rare mitochondrial disease manifesting in infancy and childhood, responds favorably to riboflavin supplementation and thus can be termed a dependency state. **Brown-Vialetto-Van Laere syndrome (BVVLS)** , a rare, potentially lethal neurologic disorder characterized by rapidly progressive neurologic deterioration, peripheral neuropathy, hypotonia, ataxia, sensorineural hearing loss, optic atrophy, pontobulbar palsy, and respiratory insufficiency, responds to treatment with high doses of riboflavin if treated early in the disease course. Mutations in *SLC52A2* gene (autosomal recessive), encoding riboflavin transporter proteins, have been identified in children with BVVLS.

Clinical Manifestations

Clinical features of nutritional riboflavin deficiency include cheilosis, glossitis, keratitis, conjunctivitis, photophobia, lacrimation, corneal vascularization, and seborrheic dermatitis. Cheilosis begins with pallor at the angles of the mouth and progresses to thinning and maceration of the epithelium, leading to fissures extending radially into the skin (Fig. 62.1). In glossitis the tongue becomes smooth, with loss of papillary structure (Fig. 62.2). Normochromic, normocytic anemia may also be seen because of the impaired erythropoiesis. A low riboflavin content of the maternal diet has been linked to congenital heart defects, but the evidence is weak.

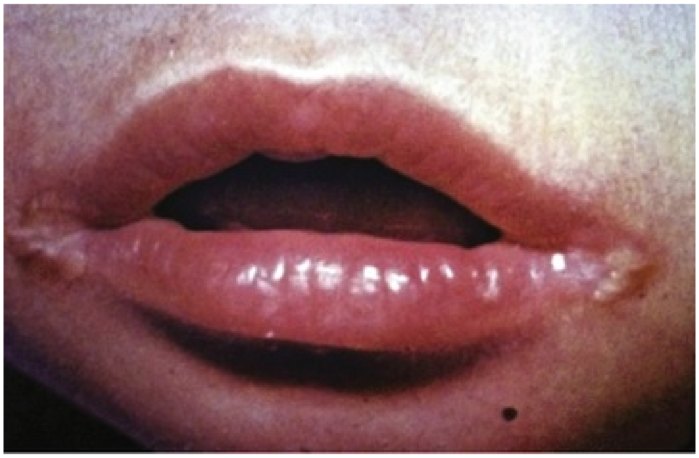

FIG. 62.1 Angular cheilosis with ulceration and crusting. (Courtesy of National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India.)

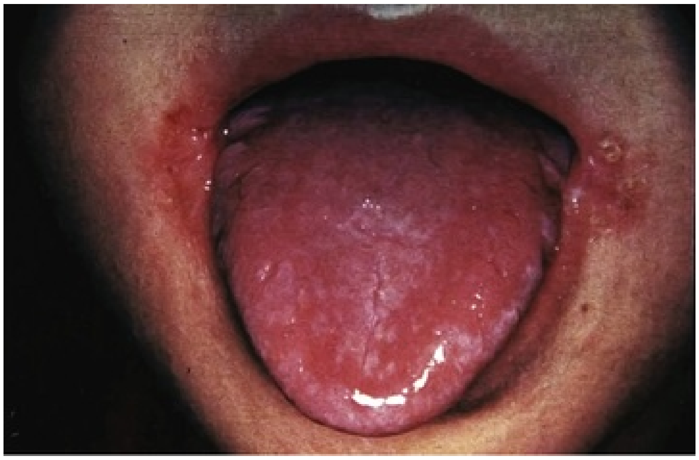

FIG. 62.2 Glossitis as seen in riboflavin deficiency. (From Zappe HA, Nuss S, Becker K, et al: *Riboflavin deficiency in Baltistan* . http://www.rzuser.uni-heidelberg.de/%7Ecn6/baltista/ribofl_e.htm .)

Diagnosis

Most often, the diagnosis is based on the clinical features of angular cheilosis in a malnourished child, who responds promptly to riboflavin supplementation. A functional test of riboflavin status is done by measuring the activity of erythrocyte glutathione reductase (EGR), with and without the addition of FAD. An EGR activity coefficient (ratio of EGR activity with added FAD to EGR activity without FAD) of >1.4 is used as an indicator of deficiency. Urinary excretion of riboflavin <30 µg/24 hr also suggests low intakes.

Prevention

Table 62.1 lists the recommended daily allowance of riboflavin for infants, children, and adolescents. Adequate consumption of milk, milk products, and eggs prevents riboflavin deficiency. Fortification of cereal products is helpful for those who follow vegan diets or who are consuming inadequate amounts of milk products for other reasons.

Table 62.1

Water-Soluble Vitamins

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETA SOUR
Thiamine (vitamin B_1)	Coenzyme in carbohydrate metabolism Nucleic acid synthesis Neurotransmitter synthesis	Neurologic (dry beriberi): irritability, peripheral neuritis, muscle tenderness, ataxia Cardiac (wet beriberi): tachycardia, edema, cardiomegaly, cardiac failure	3-5 mg/day PO thiamine for 6 wk	Polished rice–based diets Malabsorptive states Severe malnutrition Malignancies Alcoholism	Me esp por live Ric (un wh ger enr cer leg
Riboflavin (vitamin B_2)	Constituent of flavoprotein enzymes important in redox reactions: amino acid, fatty acid, and carbohydrate metabolism and cellular respiration	Glossitis, photophobia, lacrimation, corneal vascularization, poor growth, cheilosis	3-10 mg/day PO riboflavin	Severe malnutrition Malabsorptive states Prolonged treatment with phenothiazines, probenecid, or OCPs	Milk, produc fortifie cereals vegetal
Niacin (vitamin B_3)	Constituent of NAD and NADP, important in respiratory chain, fatty acid synthesis, cell differentiation, and DNA processing	Pellagra manifesting as diarrhea, symmetric scaly dermatitis in sun-exposed areas, and	50-300 mg/day PO niacin	Predominantly maize-based diets Anorexia nervosa Carcinoid	Me pou Cer leg gre veg

		neurologic symptoms of disorientation and delirium		syndrome	
Pyridoxine (vitamin B_6)	Constituent of coenzymes for amino acid and glycogen metabolism, heme synthesis, steroid action, neurotransmitter synthesis	Irritability, convulsions, hypochromic anemia Failure to thrive Oxaluria	5-25 mg/day PO for deficiency states 100 mg IM or IV for pyridoxine-dependent seizures	Prolonged treatment with INH, penicillamine, OCPs	Fortifie to-eat c meat, f poultry banana potatoe
Biotin	Cofactor for carboxylases, important in gluconeogenesis, fatty acid and amino acid metabolism	Scaly periorificial dermatitis, conjunctivitis, alopecia, lethargy, hypotonia, and withdrawn behavior	1-10 mg/day PO biotin	Consumption of raw eggs for prolonged periods Parenteral nutrition with infusates lacking biotin Valproate therapy	Liver, c meats,

Pantothenic acid (vitamin B_5)	Component of coenzyme A and acyl carrier protein involved in fatty acid metabolism	Experimentally produced deficiency in humans: irritability, fatigue, numbness, paresthesias (burning feet syndrome), muscle cramps		Isolated deficiency extremely rare in humans	Be me pou sea egg Yea soy mu
Folic acid	Coenzymes in amino acid and nucleotide metabolism as an acceptor and donor of 1-carbon units	Megaloblastic anemia Growth retardation, glossitis Neural tube defects in progeny	0.5-1 mg/day PO folic acid	Malnutrition Malabsorptive states Malignancies Hemolytic anemias Anticonvulsant therapy	Enrich cereals leafy vegetal citrus f papaya
Cobalamin (vitamin B_{12})	As deoxyadenosylcobalamin, acts as cofactor for lipid and carbohydrate metabolism As methylcobalamin, important for conversion of homocysteine to methionine and folic acid metabolism	Megaloblastic anemia, irritability, developmental delay, developmental regression, involuntary movements, hyperpigmentation	1,000 µg IM vitamin B_{12}	Vegan diets Malabsorptive states Crohn disease Intrinsic factor deficiency (pernicious anemia)	Organ sea foo poultry yolk, n fortifie to-eat c

Ascorbic acid (vitamin C)	Important for collagen synthesis, metabolism of cholesterol and neurotransmitters Antioxidant functions and nonheme iron absorption	Scurvy manifesting as irritability, tenderness and swelling of legs, bleeding gums, petechiae, ecchymoses, follicular hyperkeratosis, and poor wound healing	100-200 mg/day PO ascorbic acid for up to 3 mo	Predominantly milk-based (non–human milk) diets Severe malnutrition	Citrus fruit ju pepper berries tomato caulifl leafy g vegetal

[*] For healthy breastfed infants, the values represent adequate intakes, that is, the mean intake of apparently “normal” infants.

PO, Orally, IM, intramuscularly; IV, intravenously; INH, isoniazid; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; OCP, oral contraceptive pill; RDA, recommended dietary allowance.

From Dietary reference intakes (DRIs): *Recommended dietary allowances and adequate intakes, vitamins,* Food and Nutrition Board, Institute of Medicine, National Academies. http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Nutrition/DRI-Tables/2_%20RDA%20and%20AI%20Values_Vitamin%20and%20Elements.pdf?la=en .

Treatment

Treatment includes oral administration of 3-10 mg/day of riboflavin, often as an ingredient of a vitamin B–complex mix. The child should also be given a well-balanced diet, including milk and milk products.

Riboflavin Toxicity

No adverse effects associated with riboflavin intakes from food or supplements have been reported, and the upper safe limit for consumption has not been established. Although the photosensitizing property of vitamin B_2 suggests some potential risks, limited absorption in high-intake situations precludes such concerns.

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62.3

Niacin (Vitamin B_3)

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Keywords

dermatitis
dementia
niacin deficiency
pellagra

Niacin (nicotinamide or nicotinic acid) forms part of two cofactors, nicotinamide adenine dinucleotide (NAD) and NADP, which are important in several biologic reactions, including the respiratory chain, fatty acid and steroid synthesis, cell differentiation, and DNA processing. Niacin is rapidly absorbed from the stomach and the intestines and can also be synthesized from tryptophan in the diet.

Major dietary sources of niacin are meat, fish, and poultry for nonvegetarians and cereals, legumes, and green leafy vegetables for vegetarians. Enriched and fortified cereal products and legumes also are major contributors to niacin intake. Milk and eggs contain little niacin but are good sources of tryptophan, which can be converted to NAD (60 mg tryptophan = 1 mg niacin).

Niacin Deficiency

Pellagra , the classic niacin deficiency disease, occurs chiefly in populations where corn (maize), a poor source of tryptophan, is the major foodstuff. A severe dietary imbalance, such as in anorexia nervosa and in war or famine conditions, also can cause pellagra. Pellagra can also develop in conditions associated with disturbed tryptophan metabolism, such as carcinoid syndrome and Hartnup disease.

Clinical Manifestations

The early symptoms of pellagra are vague: anorexia, lassitude, weakness, burning sensation, numbness, and dizziness. After a long period of deficiency, the classic triad of dermatitis, diarrhea, and dementia appears. **Dermatitis** , the most characteristic manifestation of pellagra, can develop suddenly or insidiously and may be initiated by irritants, including intense sunlight. The lesions first appear as symmetric areas of erythema on exposed surfaces, resembling sunburn, and might go unrecognized. The lesions are usually sharply demarcated from the surrounding healthy skin, and their distribution can change frequently. The lesions on the hands and feet often have the appearance of a glove or stocking (Fig. 62.3). Similar demarcations can also occur around the neck (**Casal necklace**) (Fig. 62.3). In some cases, vesicles and bullae develop (wet type). In others there may be suppuration beneath the scaly, crusted epidermis; in still others the swelling can disappear after a short time, followed by desquamation (Fig. 62.4). The healed parts of the skin might remain pigmented. The cutaneous lesions may be preceded by or accompanied by stomatitis, glossitis, vomiting, and diarrhea. Swelling and redness of the tip of the tongue and its lateral margins is often followed by intense redness, even ulceration, of the entire tongue and the papillae. Nervous symptoms include depression, disorientation, insomnia, and delirium.

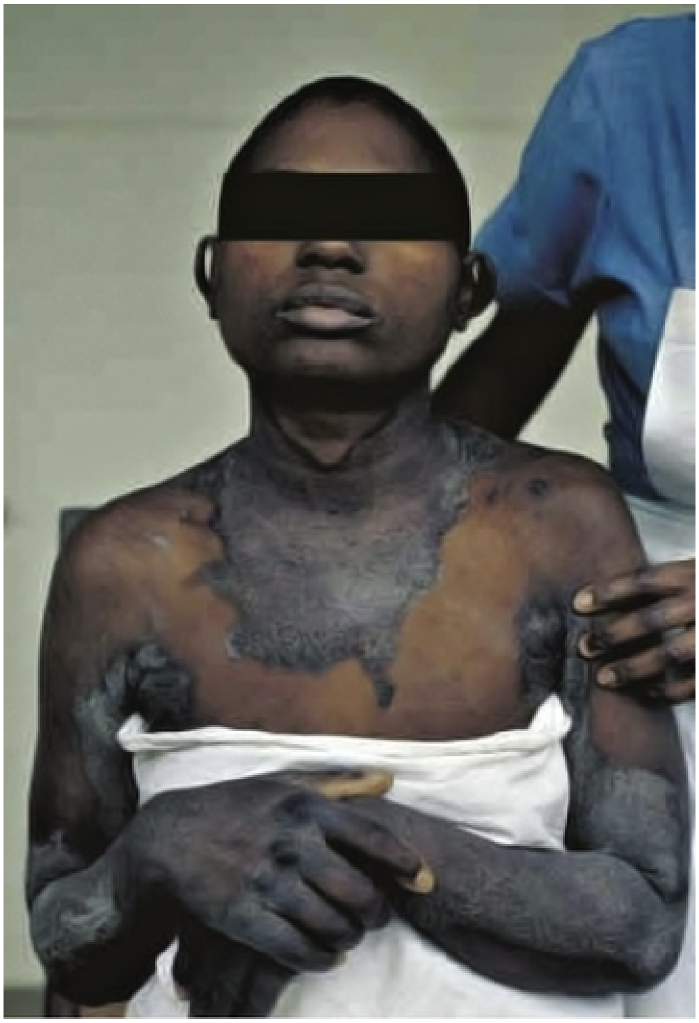

FIG. 62.3 Characteristic skin lesions of pellagra on hands and lesions on the neck (Casal necklace). (Courtesy of Dr. J.D. MacLean, McGill Centre for Tropical Diseases, Montreal.)

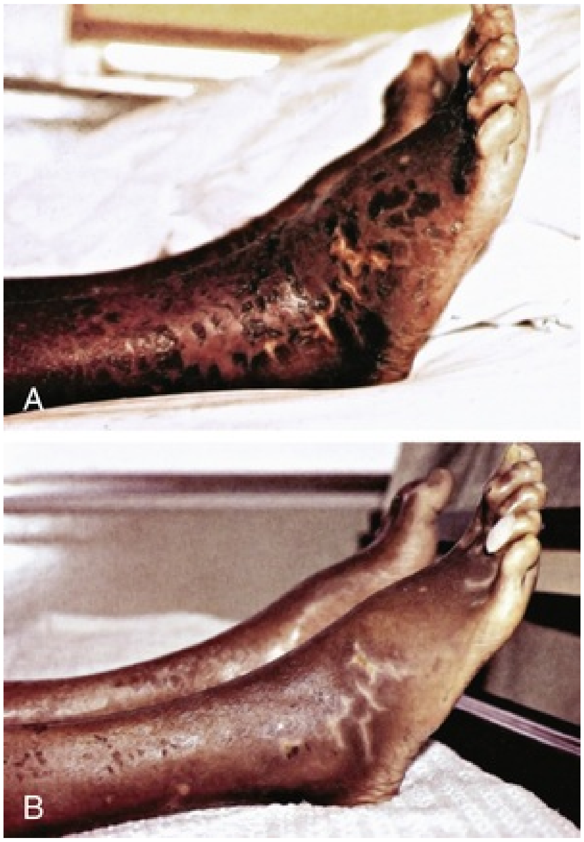

FIG. 62.4 Clinical manifestations of niacin deficiency before (**A**) and after (**B**) therapy. (From Weinsier RL, Morgan SL: *Fundamentals of clinical nutrition* , St Louis, 1993, Mosby, p 99.)

The classic symptoms of pellagra usually are not well developed in infants and young children, but anorexia, irritability, anxiety, and apathy are common. Young patients might also have sore tongues and lips and usually have dry scaly skin. Diarrhea and constipation can alternate, and anemia can occur. Children who have pellagra often have evidence of other nutritional deficiency diseases.

Diagnosis

Because of lack of a good functional test to evaluate niacin status, the diagnosis of deficiency is usually made from the physical signs of glossitis, GI symptoms, and a symmetric dermatitis. Rapid clinical response to niacin is an important confirmatory test. A decrease in the concentration and/or a change in the proportion of the niacin metabolites N^1 -methyl-nicotinamide and 2-pyridone in the urine provide biochemical evidence of deficiency and can be seen before the appearance of overt signs of deficiency. Histopathologic changes from the affected skin include dilated blood vessels without significant inflammatory infiltrates, ballooning of the keratinocytes, hyperkeratosis, and epidermal necrosis.

Prevention

Adequate intakes of niacin are easily met by consumption of a diet that consists of a variety of foods and includes meat, eggs, milk, and enriched or fortified cereal products. The **dietary reference intake (DRI)** is expressed in milligram niacin equivalents (NE) in which 1 mg NE = 1 mg niacin or 60 mg tryptophan. An intake of 2 mg of niacin is considered adequate for infants 0-6 mo of age, and 4 mg is adequate for infants 7-12 mo. For older children, the recommended intakes are 6 mg for 1-3 yr of age, 8 mg for 4-8 yr, 12 mg for 9-13 yr, and 14-16 mg for 14-18 yr of age.

Treatment

Children usually respond rapidly to treatment. A liberal and varied diet should be supplemented with 50-300 mg/day of niacin; in severe cases or in patients with poor intestinal absorption, 100 mg may be given IV. The diet should also be supplemented with other vitamins, especially other B-complex vitamins. Sun exposure should be avoided during the active phase of pellagra, and the skin lesions may be covered with soothing applications. Other coexisting nutrient deficiencies such as iron-deficiency anemia should be treated. Even after successful treatment, the diet should continue to be monitored to prevent recurrence.

Niacin Toxicity

No toxic effects are associated with the intake of naturally occurring niacin in foods. Shortly after the ingestion of large doses of nicotinic acid taken as a supplement or a pharmacologic agent, a person often experiences a burning, tingling, and itching sensation as well as flushing on the face, arms, and chest. Large doses of niacin also can have nonspecific GI effects and can cause cholestatic jaundice or hepatotoxicity. Tolerable upper intake levels for children are approximately double the recommended dietary allowance.

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62.4

Vitamin B_6 (Pyridoxine)

H.P.S. Sachdev, Dheeraj Shah

Keywords

pyridoxine deficiency
pyridoxine-dependent epilepsy
vitamin B_6

Vitamin B_6 includes a group of closely related compounds: pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives. **Pyridoxal 5′-phosphate (PLP)** and, to a lesser extent, pyridoxamine phosphate function as coenzymes for many enzymes involved in amino acid metabolism, neurotransmitter synthesis, glycogen metabolism, and steroid action. If vitamin B_6 is lacking, glycine metabolism can lead to oxaluria. The major excretory product in the urine is 4-pyridoxic acid.

The vitamin B_6 content of human milk and infant formulas is adequate. Good food sources of the vitamin include fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, and certain vegetables. Large losses of the vitamin can occur during high-temperature processing of foods or milling of cereals, whereas parboiling of rice prevents its loss.

Vitamin B_6 Deficiency

Because of the importance of vitamin B_6 in amino acid metabolism, high protein intakes can increase the requirement for the vitamin; the recommended daily allowances are sufficient to cover the expected range of protein intake in the population. The risk of deficiency is increased in persons taking medications that inhibit the activity of vitamin B_6 (e.g., isoniazid, penicillamine, corticosteroids, phenytoin, carbamazepine), in young women taking oral progesterone-estrogen OCs, and in patients receiving maintenance dialysis.

Clinical Manifestations

The vitamin B_6 deficiency symptoms seen in infants are listlessness, irritability, seizures, vomiting, and failure to thrive. Peripheral neuritis is a feature of deficiency in adults but is not usually seen in children. Electroencephalogram (EEG) abnormalities have been reported in infants as well as in young adults in controlled depletion studies. Skin lesions include cheilosis, glossitis, and seborrheic dermatitis around the eyes, nose, and mouth. Microcytic anemia can occur in infants but is not common. Oxaluria, oxalic acid bladder stones, hyperglycinemia, lymphopenia, decreased antibody formation, and infections also are associated with vitamin B_6 deficiency.

Several types of vitamin B_6 **dependence syndromes** , presumably resulting from errors in enzyme structure or function, respond to very large amounts of pyridoxine. These syndromes include pyridoxine-dependent epilepsy, a vitamin B_6 –responsive anemia, xanthurenic aciduria, cystathioninuria, and homocystinuria (see Chapter 103). Pyridoxine-dependent epilepsy involves mutations in the *ALDH7A1* gene causing deficiency of antiquitin, an enzyme involved in dehydrogenation of L -α-aminoadipic semialdehyde.

Diagnosis

The activity of aspartate (glutamic-oxaloacetic) transaminase (AST) and alanine (glutamic-pyruvic) transaminase (ALT) is low in vitamin B_6 deficiency; tests measuring the activity of these enzymes before and after the addition of PLP may be useful as indicators of vitamin B_6 status. Abnormally high xanthurenic acid excretion after tryptophan ingestion also provides evidence of deficiency. Plasma PLP assays are being used more often, but factors such as inflammation, renal function, and hypoalbuminemia can influence the results. Ratios between substrate-products pairs (e.g., PAr index, 3-hydroxykynurenine/xanthurenic acid ratio, oxoglutarate/glutamate ratio) may attenuate such influence. Quantification of a large number of metabolites, using mass spectrometry–based metabolomics, are being evaluated as functional biomarkers of pyridoxine status.

Vitamin B_6 deficiency or dependence should be suspected in all infants with **seizures** . If more common causes of infantile seizures have been eliminated, 100 mg of pyridoxine can be injected, with EEG monitoring if possible. If the seizure stops, vitamin B_6 deficiency should be suspected. In older children, 100 mg of pyridoxine may be injected IM while the EEG is being recorded; a favorable response of the EEG suggests pyridoxine deficiency.

Prevention

Deficiency is unlikely in children consuming diets that meet their energy needs and contain a variety of foods. Parboiling of rice prevents the loss of vitamin B_6 from the grains. The DRIs for vitamin B_6 are 0.1 mg/day for infants up to 6 mo of age; 0.3 mg/day for 6 mo to 1 yr; 0.5 mg/day for 1-3 yr; 0.6 mg/day for 4-8 yr; 1.0 mg/day for 9-13 yr; and 1.2-1.3 mg/day for 14-18 yr. Infants whose mothers have received large doses of pyridoxine during pregnancy are at increased risk for seizures from pyridoxine dependence, and supplements during the 1st few weeks of life should be considered. Any child receiving a pyridoxine antagonist, such as isoniazid, should be carefully observed for neurologic manifestations; if these develop, vitamin B_6 should be administered or the dose of the antagonist should be decreased.

Treatment

Intramuscular or intravenous administration of 100 mg of pyridoxine is used to treat convulsions caused by vitamin B_6 deficiency. One dose should be sufficient if adequate dietary intake follows. For pyridoxine-dependent children, daily doses of 2-10 mg IM or 10-100 mg PO may be necessary.

Vitamin B_6 Toxicity

Adverse effects have not been associated with high intakes of vitamin B_6 from food sources. However, ataxia and sensory neuropathy have been reported with dosages as low as 100 mg/day in adults taking vitamin B_6 supplements for several months.

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62.5

Biotin

H.P.S. Sachdev, Dheeraj Shah

Keywords

basal ganglia disease
biotin receptor
vitamin H

Biotin (vitamin B_7 or vitamin H) functions as a cofactor for enzymes involved in carboxylation reactions within and outside mitochondria. These biotin-dependent carboxylases catalyze key reactions in gluconeogenesis, fatty acid metabolism, and amino acid catabolism.

There is limited information on the biotin content of foods; biotin is believed to be widely distributed, making a deficiency unlikely. *Avidin* found in raw egg whites acts as a biotin antagonist. Signs of biotin deficiency have been demonstrated in persons who consume large amounts of raw egg whites over long periods. Deficiency also has been described in infants and children receiving enteral and parenteral nutrition formula that lack biotin. Treatment with valproic acid may result in a low biotinidase activity and/or biotin deficiency.

The clinical findings of biotin deficiency include scaly periorificial dermatitis, conjunctivitis, thinning of hair, and alopecia (Fig. 62.5). Central nervous system (CNS) abnormalities seen with biotin deficiency are lethargy, hypotonia, seizures, ataxia, and withdrawn behavior. Biotin deficiency can be successfully treated using 1-10 mg of biotin orally daily. The adequate dietary intake values for biotin are 5 µg/day for ages 0-6 mo, 6 µg/day for 7-12 mo, 8 µg/day for 1-3 yr, 12 µg/day for 4-8 yr, 20 µg/day for 9-13 yr, and 25 µg/day for 14-18 yr. No toxic effects have been reported with very high doses.

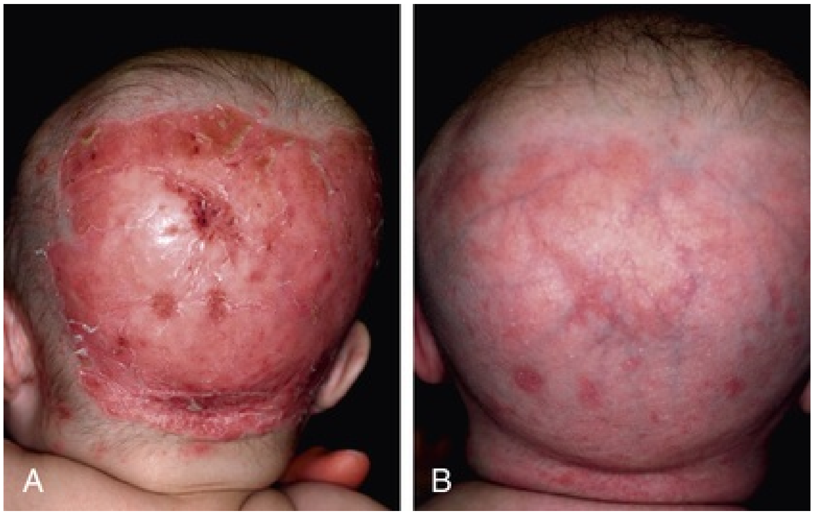

FIG. 62.5 **A,** Scalp rash before treatment with biotin. **B,** After 3 wk of biotin treatment. (From Ito T, Nishie W, Fujita Y, et al: Infantile eczema caused by formula milk. *Lancet* 381:1958, 2013.)

Biotin-responsive basal ganglia disease or **biotin and thiamine–responsive basal ganglia disease** is a rare childhood neurologic disorder characterized by encephalopathy, seizures, extrapyramidal manifestations, altered signals in basal ganglia (bilateral involvement of caudate nuclei and putamen with sparing of globus pallidus) on MRI, and homozygous missense mutation in the *SLC19A3* gene. Chapter 103 describes conditions involving deficiencies in the enzymes holocarboxylase synthetase and biotinidase that respond to treatment with biotin.

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62.6

Folate

H.P.S. Sachdev, Dheeraj Shah

Keywords

folic acid deficiency
megaloblastic anemia
neural tube defects

Folate exists in a number of different chemical forms. **Folic acid** (pteroylglutamic acid) is the synthetic form used in fortified foods and supplements. Naturally occurring folates in foods retain the core chemical structure of pteroylglutamic acid but vary in their state of reduction, the single-carbon moiety they bear, or the length of the glutamate chain. These polyglutamates are broken down and reduced in the small intestine to dihydro- and tetrahydrofolates, which are involved as coenzymes in amino acid and nucleotide metabolism as acceptors and donors of 1-carbon units. Folate is important for CNS development during embryogenesis.

Rice and cereals are rich dietary sources of folate, especially if enriched. Beans, leafy vegetables, and fruits such as oranges and papaya are good sources as well. The vitamin is readily absorbed from the small intestine and is broken down to monoglutamate derivatives by mucosal polyglutamate hydrolases. A high-affinity proton-coupled folate transporter (PCFT) seems to be essential for absorption of folate in intestine and in various cell types at low pH. The vitamin is also synthesized by colonic bacteria, and its half-life is prolonged by enterohepatic recirculation.

Folate Deficiency

Because of folate's role in protein, DNA, and RNA synthesis, the risk of deficiency is increased during periods of rapid growth or increased cellular metabolism. Folate deficiency can result from poor nutrient content in diet, inadequate absorption (celiac disease, inflammatory bowel disease), increased requirement (sickle cell anemia, psoriasis, malignancies, periods of rapid growth as in infancy and adolescence), or inadequate utilization (long-term treatment with high-dose nonsteroidal antiinflammatory drugs; anticonvulsants such as phenytoin and phenobarbital; methotrexate). Rare causes of deficiency are hereditary folate malabsorption, inborn errors of folate metabolism (methylene tetrahydrofolate reductase, methionine synthase reductase, and glutamate formiminotransferase deficiencies), and cerebral folate deficiency. A loss-of-function mutation in the gene coding for PCFT is the molecular basis for hereditary folate malabsorption. A high-affinity blocking autoantibody against the membrane-bound folate receptor in the choroid plexus preventing its transport across the blood-brain barrier is the likely cause of the infantile cerebral folate deficiency.

Clinical Manifestations

Folic acid deficiency results in megaloblastic anemia and hypersegmentation of neutrophils. Nonhematologic manifestations include glossitis, listlessness, and growth retardation not related to anemia. An association exists between low maternal folic acid status and **neural tube defects** , primarily spina bifida and anencephaly, and the role of periconceptional folic acid in their prevention is well established (see Chapter 481.1).

Hereditary folate malabsorption manifests at 1-3 mo of age with recurrent or chronic diarrhea, failure to thrive (malnutrition), oral ulcerations, neurologic deterioration, megaloblastic anemia, and opportunistic infections. **Cerebral folate deficiency** manifests at 4-6 mo of age with irritability, microcephaly, developmental delay, cerebellar ataxia, pyramidal tract signs, choreoathetosis, ballismus, seizures, and blindness as a result of optic atrophy. 5-Methyltetrahydrofolate levels are normal in serum and red blood cells (RBCs) but greatly depressed in the cerebrospinal fluid (CSF).

Diagnosis

The diagnosis of folic acid deficiency anemia is made in the presence of macrocytosis along with low folate levels in serum or RBCs. Normal serum folic acid levels are 5-20 ng/mL; with deficiency, levels are <3 ng/mL. Levels of RBC folate are a better indicator of chronic deficiency. The normal RBC folate level is 150-600 ng/mL of packed cells. The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation also are seen.

Cerebral folate deficiency is associated with low levels of 5-methyltetrahydrofolate in CSF and normal folate levels in the plasma and RBCs. Mutations in the *PCFT* gene are demonstrated in the hereditary folate malabsorption.

Prevention

Breastfed infants have better folate nutrition than nonbreastfed infants throughout infancy. Consumption of folate-rich foods and food fortification programs are important to ensure adequate intake in children and in women of childbearing age. The DRIs for folate are 65 µg of dietary folate equivalents (DFE) for infants 0-6 mo of age and 80 µg of DFE for infants 6-12 mo. (1 DFE = 1 µg food folate = 0.6 µg of folate from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach.) For older children, the DRIs are 150 µg of DFE for ages 1-3 yr; 200 µg DFE for 4-8 yr; 300 µg DFE for 9-13 yr; and 400 µg DFE for 14-18 yr. All women desirous of becoming pregnant should consume 400-800 µg folic acid daily; the dose is 4 mg/day in those having delivered a child with neural tube defect. To be effective, supplementation should be started at least 1 mo before conception and continued through the 1st 2-3 mo of pregnancy. The benefit of periconceptional folate supplementation in prevention of congenital heart defects, orofacial clefts, and autistic spectrum disorders is unclear. Preconceptional folate supplementation continued throughout pregnancy may marginally reduce the risk of delivering a small-for-gestational-age infant. Providing iron and folic acid tablets for prevention of anemia in children and pregnant women is a routine strategy in at-risk populations. Mandatory fortification of cereal flours with folic acid coupled with health-education programs has been associated with a substantial reduction in incidence of neural tube defects in many countries.

Treatment

When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. Folic acid therapy should be continued for 3-4 wk or until a definite hematologic response has occurred. Maintenance therapy with 0.2 mg of folate is adequate. Prolonged treatment with oral folinic acid is required in cerebral folate deficiency, and the response may be incomplete. High-dose intravenous folinic acid may help in refractory cases. Treatment of hereditary folate malabsorption may be possible with intramuscular folinic acid; some patients may respond to high-dose oral folinic acid therapy.

Folate Toxicity

No adverse effects have been associated with consumption of the amounts of folate normally found in fortified foods. Excessive intake of folate supplements might obscure and potentially delay the diagnosis of vitamin B_{12} deficiency. Massive doses given by injection have the potential to cause neurotoxicity.

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62.7

Vitamin B_{12} (Cobalamin)

H.P.S. Sachdev, Dheeraj Shah

Keywords

cyanocobalamin
hydroxocobalamin
intrinsic factor
methyl cobalamin

Vitamin B_{12} , in the form of deoxyadenosylcobalamin, functions as a cofactor for isomerization of methylmalonyl-CoA to succinyl-CoA, an essential reaction in lipid and carbohydrate metabolism. Methylcobalamin is another circulating form of vitamin B_{12} and is essential for methyl group transfer during the conversion of homocysteine to methionine. This reaction also requires a folic acid cofactor and is important for protein and nucleic acid biosynthesis. Vitamin

B_{12} is important for hematopoiesis, CNS myelination, and mental and psychomotor development (Fig. 62.6).

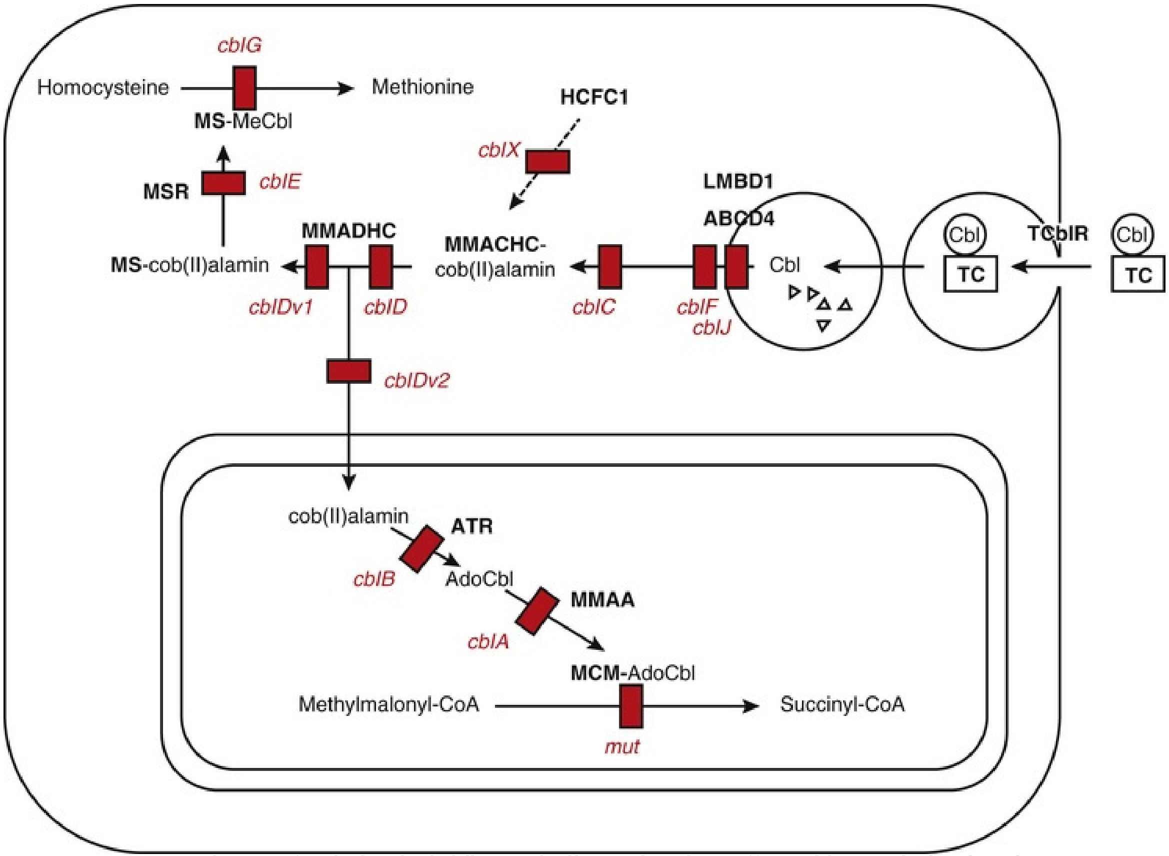
cblG
Homocysteine
Methionine
MS-MeCbl
HCFC1
cblX
MSR
cblE
LMBD1
ABCD4
MMADHC
MMACHC-
cob(II)alamin
MS-cob(II)alamin
Cbl
Cbl
TCblR
Cbl
TC
TC
cblDv1
cblD
cblC
cblF
cblJ
cblDv2
cob(II)alamin
ATR
cblB
AdoCbl
MMAA
cblA
MCM-AdoCbl
Methylmalonyl-CoA
Succinyl-CoA
mut

FIG. 62.6 Scheme of cobalamin (Cbl) metabolism. The sites affected by methylmalonyl-CoA mutase deficiency (*mut*) and the inborn errors of cobalamin metabolism (*cblA-cblG, cblJ,* and *cblX*) are shown in *red.* The cblA disorder is caused by defects in the MMAA protein; the cblB disorder by defects in the cob(I)alamin adenosyltransferase (MMAB) protein; the cblC disorder by defects in the MMACHC protein; the cblD, cblD variant 1 (*cblDv1*), and cblD variant 2 (*cblDv2*) disorders are caused by defects in the MMADHC protein; cblE disorder is caused by defects in the methionine synthase reductase (MSR) protein; cblG disorder by defects in the methionine synthase (MS) protein; cblJ disorder by mutations in the ABCD4 protein; cblX disorder by mutations in the HCFC1 protein, and the mut disorder by defects in methylmalonyl-CoA mutase (MCM). The protein affected in the cblF disorder is unknown. MCM-AdoCbl, Holomethylmalonyl-CoA mutase (mutase with bound adenosylcobalamin); MS-cob(II)alamin, methionine synthase with bound cob(II)alamin; MS-MeCbl, holomethionine synthase (synthase with bound methylcobalamin; TC, transcobalamin. (From *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, Vol 1, Philadelphia, 2015, Elsevier, p 318.)

Dietary sources of vitamin B_{12} are almost exclusively from animal foods. Organ meats, muscle meats, seafood (mollusks, oysters, fish), poultry, and egg yolk are rich sources. Fortified ready-to-eat cereals and milk and their products are the important sources of the vitamin for vegetarians. Human milk is an adequate source for breastfeeding infants if the maternal serum B_{12} levels are adequate. Vitamin B_{12} is absorbed from ileum at alkaline pH after binding with intrinsic factor. Enterohepatic circulation, direct absorption, and synthesis by intestinal bacteria are additional mechanisms helping to maintain the vitamin B_{12} nutriture.

Vitamin B_{12} Deficiency

Deficiency of vitamin B_{12} caused by inadequate dietary intake occurs primarily in persons consuming strict vegetarian or vegan diets. Prevalence of vitamin B_{12} deficiency is high in predominantly vegetarian or lactovegetarian populations. Breastfeeding infants of B_{12} -deficient mothers are also at risk for significant deficiency. Malabsorption of B_{12} occurs in celiac disease, ileal resections, Crohn disease, *Helicobacter pylori* infection, and autoimmune atrophic gastritis (pernicious anemia). Use of metformin, proton pump inhibitors, and histamine (H_2) receptor antagonists may increase the risk of deficiency. **Hereditary intrinsic factor deficiency** and **Imerslund-Gräsbeck disease** are inborn errors of metabolism leading to vitamin B_{12} malabsorption. Mutations in the hereditary intrinsic factor gene cause hereditary intrinsic factor deficiency, whereas mutations in any of the 2 subunits (cubilin and amnionless) of the intrinsic factor receptor cause Imerslund-Gräsbeck disease.

Clinical Manifestations

The hematologic manifestations of vitamin B_{12} deficiency are similar to manifestations of folate deficiency and are discussed in Chapter 481.2 . Irritability, hypotonia, developmental delay, developmental regression, and involuntary movements (predominantly coarse tremors) are the common neurologic symptoms in infants. Older children with vitamin B_{12} deficiency may show poor growth and poor school performance, whereas sensory deficits, paresthesias, peripheral neuritis, and psychosis are seen in adults. Hyperpigmentation of the knuckles and palms is another common observation with B_{12} deficiency in children (Fig. 62.7). Maternal B_{12} deficiency may also be an independent risk factor for fetal neural tube defects.

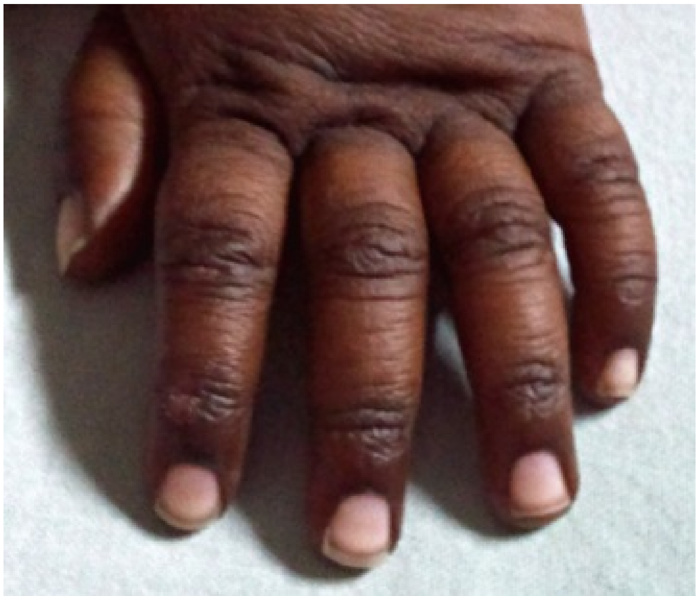

FIG. 62.7 Hyperpigmentation of knuckles in an infant with vitamin B_{12} deficiency and megaloblastic anemia.

Diagnosis

See Chapter 481.2 .

Treatment

The hematologic symptoms respond promptly to parenteral administration of 250-1,000 µg vitamin B_{12} . Children with severe deficiency and those with neurologic symptoms need repeated doses, daily or on alternate days in first week, followed by weekly for the 1st 1-2 mo and then monthly. Children having only hematologic presentation recover fully within 2-3 mo, whereas those with neurologic disease need at least 6 mo of therapy. Children with a continuing malabsorptive state and those with inborn errors of vitamin B_{12} malabsorption need lifelong treatment. Prolonged daily treatment with high-dose (1,000-2,000 µg) oral vitamin B_{12} preparations is also equally effective in achieving hematologic and neurologic responses in elderly patients, but the data are inadequate in children and young adults.

Prevention

Vitamin B_{12} DRIs are 0.4 µg/day at age 0-6 mo, 0.5 µg/day at 6-12 mo, 0.9 µg/day at 1-3 yr, 1.2 µg/day at 4-8 yr, 1.8 µg/day at 9-13 yr, 2.4 µg/day at 14-18 yr and in adults, 2.6 µg/day in pregnancy, and 2.8 µg/day in lactation. Pregnant and breastfeeding women should ensure an adequate consumption of animal products to prevent cobalamin deficiency in infants. Strict vegetarians, especially vegans, should ensure regular consumption of vitamin B_{12} . Food fortification with the vitamin helps to prevent deficiency in predominantly vegetarian populations.

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CHAPTER 63

Vitamin C (Ascorbic Acid) Deficiency and Excess

Dheeraj Shah, H.P.S. Sachdev

Vitamin C is important for synthesis of collagen at the level of hydroxylation of lysine and proline in precollagen. It is also involved in neurotransmitter metabolism (conversion of dopamine to norepinephrine and tryptophan to serotonin), cholesterol metabolism (conversion of cholesterol to steroid hormones and bile acids), and the biosynthesis of carnitine. Vitamin C functions to maintain the iron and copper atoms, cofactors of the metalloenzymes, in a reduced (active) state. Vitamin C is an important antioxidant (electron donor) in the aqueous milieu of the body. Vitamin C enhances nonheme iron absorption, the transfer of iron from transferrin to ferritin, and the formation of tetrahydrofolic acid and thus can affect the cellular and immunologic functions of the hematopoietic system.

Dietary Needs and Sources of Vitamin C

Humans depend on dietary sources for vitamin C. An adequate intake is 40 mg for ages 0-6 mo and 50 mg for 6-12 mo. For older children the recommended dietary allowance is 15 mg for ages 1-3 yr, 25 mg for 4-8 yr, 45 mg for 9-13 yr, and 65-75 mg for 14-18 yr. The recommended dietary allowances during pregnancy and lactation are 85 mg/day and 120 mg/day, respectively. The requirement for vitamin C is increased during infectious and diarrheal diseases. Children exposed to smoking or environmental tobacco smoke also require increased amounts of foods rich in vitamin C. The best food sources of vitamin C are citrus fruits and fruit juices, peppers, berries, melons, guava, kiwifruit, tomatoes, cauliflower, and green leafy vegetables. Vitamin C is easily destroyed by prolonged storage, overcooking, and processing of foods.

Absorption of vitamin C occurs in the upper small intestine by an active process or by simple diffusion when large amounts are ingested. Vitamin C is not stored in the body but is taken up by all tissues; the highest levels are found in the pituitary and adrenal glands. The brain ascorbate content in the fetus and neonate is markedly higher than the content in the adult brain, a finding probably related to its function in neurotransmitter synthesis.

When a mother's intake of vitamin C during pregnancy and lactation is adequate, the newborn will have adequate tissue levels of vitamin C related to active placental transfer, subsequently maintained by the vitamin C in breast milk or commercial infant formulas. Breast milk contains sufficient vitamin C to prevent deficiency throughout infancy. Infants consuming pasteurized or boiled animal milk are at significant risk of developing deficiency if the other sources of vitamin C are also lacking in the diet. Neonates whose feeding has been delayed because of a clinical condition can also have ascorbic acid deficiency. For patients receiving total parenteral nutrition (TPN), 80 mg/day is recommended for full-term infants and 25 mg/kg/day for preterm infants. Parents and children who choose a limited (selective) diet or those on fad diets are at risk for vitamin C deficiency.

Vitamin C Deficiency

A deficiency of vitamin C results in the clinical presentation of **scurvy** . Children fed predominantly heat-treated (ultrahigh-temperature or pasteurized) milk or unfortified formulas and not receiving fruits and fruit juices are at significant risk for symptomatic disease. Infants and children on highly restrictive diets, devoid of most fruits and vegetables, are at risk of acquiring severe vitamin C deficiency. Such diets are occasionally promoted with unsubstantiated claims of benefit in autism and other developmental disorders, In scurvy, there is defective formation of connective tissues and collagen in skin, cartilage, dentine, bone, and blood vessels, leading to their fragility. In the long bones, osteoid is not deposited by osteoblasts, cortex is thin, and the trabeculae become brittle and fracture easily.

Clinical Features

The early manifestations of vitamin C deficiency are irritability, loss of appetite, low-grade fever, musculoskeletal pain, and tenderness in the legs. These signs and symptoms are followed by leg swelling—most marked at the knees and the ankles—and **pseudoparalysis** . The infant might lie with the hips and knees semiflexed and the feet rotated outward. Subperiosteal hemorrhages in the lower-limb bones sometimes acutely increase the swelling and pain, and the condition might mimic acute osteomyelitis or arthritis. A “rosary” at the costochondral junctions and depression of the sternum are other typical features (Fig. 63.1). The angulation of scorbutic beads is usually sharper than that of a rachitic rosary. Gum changes are seen in older children after teeth have erupted, manifested as bluish purple, spongy swellings of the mucous membrane, especially over the upper incisors (Fig. 63.2). **Anemia,** a common finding in infants and young children with scurvy, is related to impaired iron absorption and coexistent hematopoietic nutrient deficiencies, including iron, vitamin B_{12} , and folate. Hemorrhagic manifestations of scurvy include petechiae, purpura, and ecchymoses at pressure points; epistaxis; gum bleeding; and the characteristic perifollicular hemorrhages (Fig. 63.3). Other manifestations are poor wound and fracture healing, hyperkeratosis of hair follicles, arthralgia, and muscle weakness.

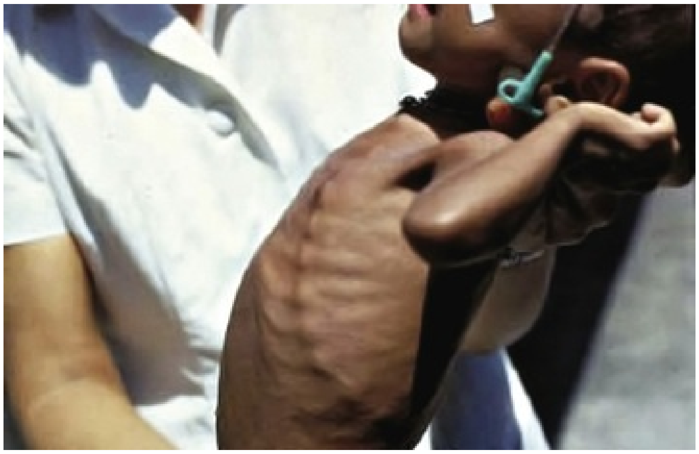

FIG. 63.1 Scorbutic “rosary.” (Courtesy of Dr. J.D. MacLean, McGill Centre for Tropical Diseases, Montreal.)

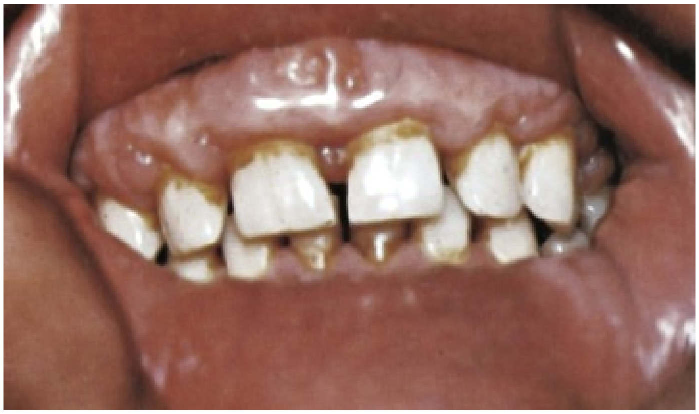

FIG. 63.2 Gingival lesions in advanced scurvy. (From *Nutrition* , ed 4, Kalamazoo, MI, 1980, The Upjohn Company, p 80. Used with permission of Pfizer, Inc.)

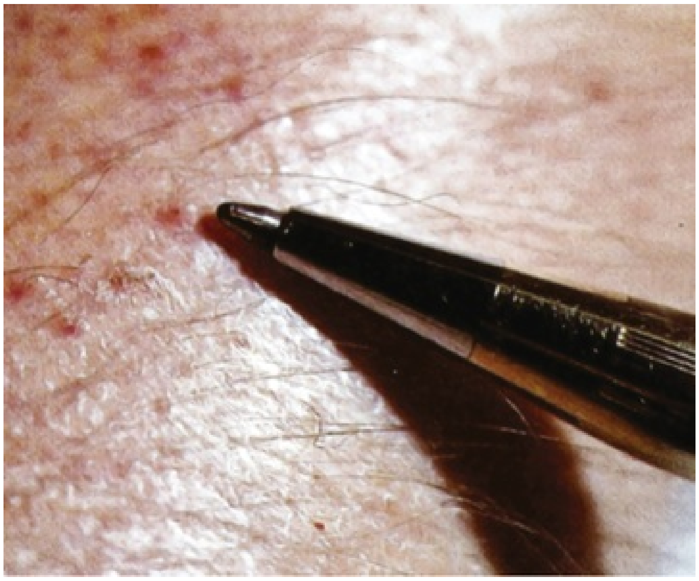

FIG. 63.3 Perifollicular petechiae in scurvy. (From Weinsier RL, Morgan SL: *Fundamentals of clinical nutrition* , St Louis, 1993, Mosby, p 85.)

Laboratory Findings and Diagnosis

The diagnosis of vitamin C deficiency is usually based on the characteristic clinical picture, the radiographic appearance of the long bones, and a history of poor vitamin C intake. A high index of suspicion is required in children on restrictive diets, particularly those with autism and other developmental disorders, and they should be evaluated for scurvy whenever they present with difficulty in walking or bone pains. The typical radiographic changes occur at the distal ends of the long bones and are particularly common at the knees. The shafts of the long bones have a ground-glass appearance because of trabecular atrophy. The cortex is thin and dense, giving the appearance of *pencil outlining* of the diaphysis and epiphysis. The *white line of Fränkel*, an irregular but thickened white line at the metaphysis, represents the zone of well-calcified cartilage. The epiphyseal centers of ossification also have a ground-glass appearance and are surrounded by a sclerotic ring (Fig. 63.4). The more specific but late radiologic feature of scurvy is a zone of rarefaction under the white line at the metaphysis. This zone of rarefaction *(Trümmerfeld zone)*, a linear break in the bone that is proximal and parallel to the white line, represents area of debris of broken-down bone trabeculae and connective tissue. A *Pelkan spur* is a lateral prolongation of the white line and may be present at cortical ends. Epiphyseal separation can occur along the line of destruction, with either linear displacement or compression of the epiphysis against the shaft (Fig. 63.5). Subperiosteal hemorrhages are not visible using plain radiographs during the active phase of scurvy. However, during healing the elevated periosteum becomes calcified and radiopaque (Fig. 63.5), sometimes giving a dumbbell or club shape to the affected bone. MRI can demonstrate acute as well as healing subperiosteal hematomas along with periostitis, metaphyseal changes, and heterogeneous bone marrow signal intensity, even in absence of changes in plain radiographs. Gelatinous transformation of bone marrow, on aspiration, has been reported in children with suspected malignancy.

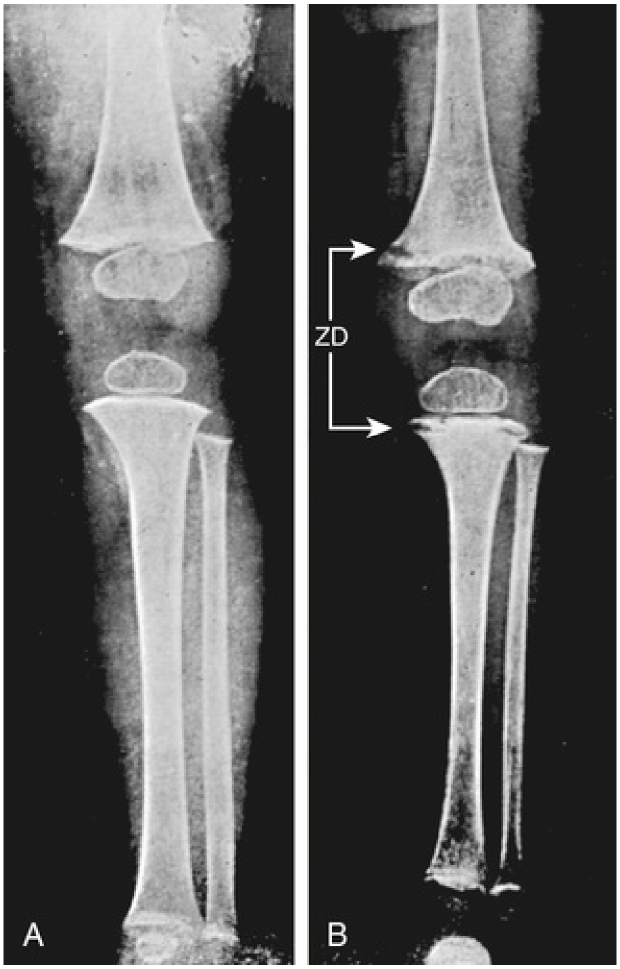

FIG. 63.4 Radiographs of a leg. A, An early scurvy “white line” is visible on the ends of the shafts of the tibia and fibula; sclerotic rings (Wimberger sign) are shown around the epiphyses of the femur and tibia. B, More advanced scorbutic changes; zones of destruction (ZD) are evident in the femur and tibia. Pelkan spur is also seen at the cortical end.

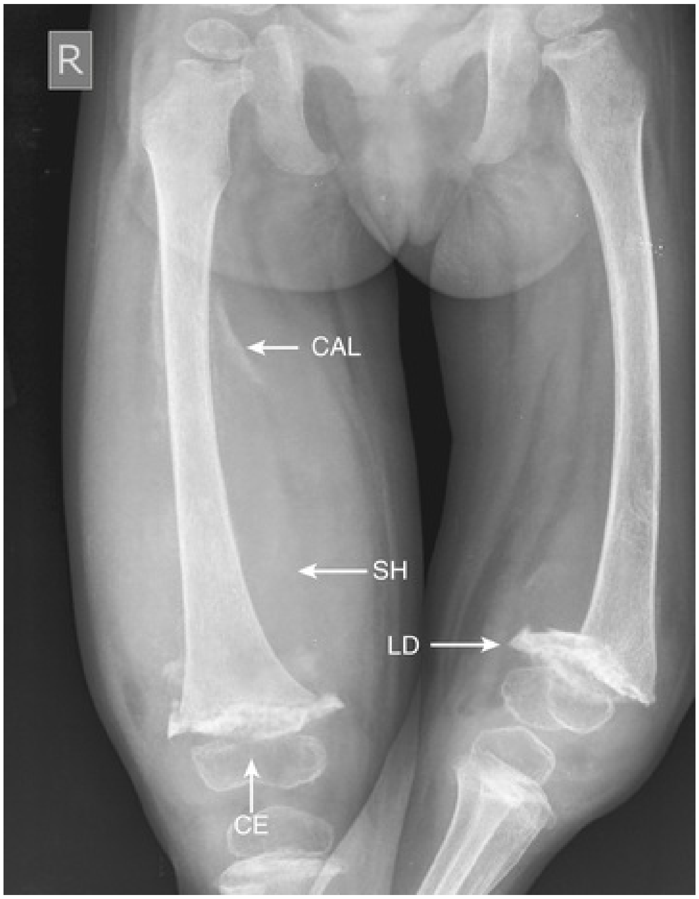

FIG. 63.5 Large subperiosteal hematoma (SH) with areas of calcification (CAL) is seen along the shaft of right femur of a child with advanced scurvy. Epiphyseal separation is seen in both knees, with linear displacement (LD) in left knee and compression (CE) against the shaft in right knee.

Biochemical tests are not very useful in the diagnosis of scurvy, because they do not reflect the tissue status. A plasma ascorbate concentration of <0.2 mg/dL usually is considered deficient. Leukocyte concentration of vitamin C is a better indicator of body stores, but this measurement is technically more difficult to perform. Leukocyte concentrations of ≤10 µg/10^8 white blood cells are considered deficient and indicate latent scurvy, even in the absence of clinical signs of deficiency. Saturation of the tissues with vitamin C can be estimated from the urinary excretion of the vitamin after a test dose of ascorbic acid. In healthy children, 80% of the test dose appears in the urine within 3-5 hr after parenteral administration. Generalized nonspecific aminoaciduria is common in scurvy, whereas plasma amino acid levels remain normal.

Differential Diagnosis

Scurvy is often misdiagnosed as arthritis, osteomyelitis, nonaccidental trauma (child abuse), malignancy, or acrodynia. The early irritability and bone pain are sometimes attributed to nonspecific pains or other nutritional deficiencies. Copper deficiency results in a radiographic picture similar to that of scurvy. Henoch-Schönlein purpura, thrombocytopenic purpura, or leukemia is sometimes suspected in children presenting with hemorrhagic manifestations.

Treatment

Vitamin C supplements of 100-200 mg/day orally or parenterally ensure rapid and complete cure. The clinical improvement is seen within 1 week in most cases, but the treatment should be continued for up to 3 mo for complete recovery.

Prevention

Breastfeeding protects against vitamin C deficiency throughout infancy. In children consuming milk formula, fortification with vitamin C must be ensured. Children consuming heat-treated milk or plant-based beverages (e.g., almond milk, soy milk) should consume adequate vitamin C–rich foods in infancy. Dietary or medicinal supplements are required in children on restrictive diets deficient in vitamin C, severely malnourished children, and those with chronic debilitating conditions (e.g., malignancies, neurologic disorders). Providing antenatal supplements of vitamin C to smoking mothers may mitigate some of the harmful effects of smoking on fetal and infant lung development and function.

Vitamin C Toxicity

Daily intake of <2 g of vitamin C is generally without adverse effects in adults. Larger doses can cause gastrointestinal problems, such as abdominal pain and osmotic diarrhea. Hemolysis has rarely been reported after high doses of ascorbic acid. Megadoses of vitamin C should be avoided in patients with a history of urolithiasis or conditions related to excessive iron accumulation, such as thalassemia and hemochromatosis. Data are sparse regarding vitamin C toxicity in children. The following values for tolerable upper intake levels are extrapolated from data for adults based on body weight differences: ages 1-3 yr, 400 mg; 4-8 yr, 650 mg; 9-13 yr, 1,200 mg; and 14-18 yr, 1,800 mg.

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CHAPTER 64

Vitamin D Deficiency (Rickets) and Excess

Larry A. Greenbaum

Rickets

Bone consists of a protein matrix called *osteoid* and a mineral phase, principally composed of calcium and phosphate, mostly in the form of *hydroxyapatite* . **Osteomalacia** occurs with inadequate mineralization of bone osteoid in children and adults. **Rickets** is a disease of growing bone caused by unmineralized matrix at the growth plates in children only before fusion of the epiphyses. Because growth plate cartilage and osteoid continue to expand but mineralization is inadequate, the growth plate thickens. Circumference of the growth plate and metaphysis is also greater, increasing bone width at the growth plates and causing classic clinical manifestations, such as widening of the wrists and ankles. The general softening of the bones causes them to bend easily when subject to forces such as weight bearing or muscle pull. This softening leads to a variety of bone deformities.

Rickets is principally caused by vitamin D deficiency and was rampant in northern Europe and the United States during the early years of the 20th century. Although largely corrected through public health measures that provided children with adequate vitamin D, rickets remains a persistent problem in developed countries, with many cases still secondary to preventable nutritional vitamin D deficiency. It remains a significant problem in developing countries and may be secondary to nutritional vitamin D deficiency and inadequate intake of calcium (Table 64.1).

Table 64.1

Physical and Metabolic Properties and Food Sources of Vitamins D, E, and K

NAMES AND SYNONYMS	CHARACTERISTICS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	SOURCES
VITAMIN D					
Vitamin D_3 (3-cholecalciferol), which is synthesized in the skin, and vitamin D_2 (from plants or yeast) are biologically equivalent; 1 μg = 40 IU vitamin D.	Fat-soluble, stable to heat, acid, alkali, and oxidation; bile necessary for absorption; hydroxylation in the liver and kidney necessary for biologic activity	Necessary for GI absorption of calcium; also increases absorption of phosphate; direct actions on bone, including mediating resorption	Rickets in growing children; osteomalacia; hypocalcemia can cause tetany and seizures	Hypercalcemia, which can cause emesis, anorexia, pancreatitis, hypertension, arrhythmias, CNS effects, polyuria, nephrolithiasis, renal failure	Exposure to sunlight (UV light); fish oils, fatty fish, egg yolks, and vitamin D–fortified formula, milk, cereals, bread
VITAMIN E					
Group of related compounds with similar biologic activities; α-tocopherol is the most potent and most common form	Fat-soluble; readily oxidized by oxygen, iron, rancid fats; bile acids necessary for absorption	Antioxidant; protection of cell membranes from lipid peroxidation and formation of free radicals	Red cell hemolysis in premature infants; posterior column and cerebellar dysfunction; pigmentary retinopathy	Unknown	Vegetable oils, seeds, nuts, green leafy vegetables, margarine
VITAMIN K					
Group of naphthoquinones with similar biologic activities; K_1 (phylloquinone) from diet; K_2 (menaquinones) from intestinal bacteria	Natural compounds are fat-soluble; stable to heat and reducing agents; labile to oxidizing agent, strong acids, alkali, light; bile salts necessary for intestinal absorption	Vitamin K–dependent proteins include coagulation factors II, VII, IX, and X; proteins C, S, Z; matrix Gla protein, osteocalcin	Hemorrhagic manifestations; long-term bone and vascular health	Not established; analogs (no longer used) caused hemolytic anemia, jaundice, kernicterus, death	Green leafy vegetables, liver, certain legumes and plant oils; widely distributed

CNS, Central nervous system; GI, gastrointestinal; UV, ultraviolet.

Etiology

There are many causes of rickets, including vitamin D disorders, calcium deficiency, phosphorus deficiency, and distal renal tubular acidosis (Table 64.2).

Table 64.2

Causes of Rickets

Vitamin D Disorders

- Nutritional vitamin D deficiency
- Congenital vitamin D deficiency
- Secondary vitamin D deficiency
- Malabsorption
- Increased degradation
- Decreased liver 25-hydroxylase
- Vitamin D–dependent rickets types 1A and 1B
- Vitamin D–dependent rickets types 2A and 2B
- Chronic kidney disease

Calcium Deficiency

- Low intake
- Diet
- Premature infants (rickets of prematurity)
- Malabsorption
- Primary disease
- Dietary inhibitors of calcium absorption

Phosphorus Deficiency

- Inadequate intake
- Premature infants (rickets of prematurity)
- Aluminum-containing antacids

Renal Losses

- X-linked hypophosphatemic rickets*
- Autosomal dominant hypophosphatemic rickets*
- Autosomal recessive hypophosphatemic rickets types 1 and 2*
- Hereditary hypophosphatemic rickets with hypercalciuria

Overproduction of fibroblast growth factor-23
Tumor-induced rickets*
McCune-Albright syndrome*
Epidermal nevus syndrome*
Neurofibromatosis*
Fanconi syndrome
Dent disease
Distal renal tubular acidosis

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* Disorders secondary to excess fibroblast growth factor-23.

Clinical Manifestations

Most manifestations of rickets are a result of skeletal changes (Table 64.3). **Craniotabes** is a softening of the cranial bones and can be detected by applying pressure at the occiput or over the parietal bones. The sensation is similar to the feel of pressing into a Ping-Pong ball and then releasing. Craniotabes may also be secondary to osteogenesis imperfecta, hydrocephalus, and syphilis. It is a normal finding in many newborns, especially near the suture lines, but typically disappears within a few months of birth. Widening of the costochondral junctions results in a **rachitic “rosary** ,” which feels like the beads of a rosary as the examiner's fingers move along the costochondral junctions from rib to rib (Fig. 64.1). Growth plate widening is also responsible for the enlargement at the wrists and ankles (Fig. 64.2). The horizontal depression along the lower anterior chest known as *Harrison groove* occurs from pulling of the softened ribs by the diaphragm during inspiration. Softening of the ribs also impairs air movement and predisposes patients to atelectasis and pneumonia. Valgus or varus deformities of the legs are common; **windswept deformity** occurs when one leg is in extreme valgus and the other is in extreme varus (Fig. 64.3).

Table 64.3

Clinical Features of Rickets

General

Failure to thrive (malnutrition)

Listlessness
Protruding abdomen
Muscle weakness (especially proximal)
Hypocalcemic dilated cardiomyopathy
Fractures (pathologic, minimal trauma)
Increased intracranial pressure

Head

Craniotabes
Frontal bossing
Delayed fontanel closure (usually closed by 2 yr)
Delayed dentition
  No incisors by age 10 mo
  No molars by age 18 mo
Caries
Craniosynostosis

Chest

Rachitic rosary
Harrison groove
Respiratory infections and atelectasis*

Back

Scoliosis
Kyphosis
Lordosis

Extremities

Enlargement of wrists and ankles
Valgus or varus deformities
Windswept deformity (valgus deformity of one leg with varus deformity of

other leg)
Anterior bowing of tibia and femur
Coxa vara
Leg pain

Hypocalcemic Symptoms [†]

Tetany
Seizures
Stridor caused by laryngeal spasm

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[*] These features are most frequently associated with the vitamin D deficiency disorders.

[†] These symptoms develop only in children with disorders that produce hypocalcemia (see Table 64.4).

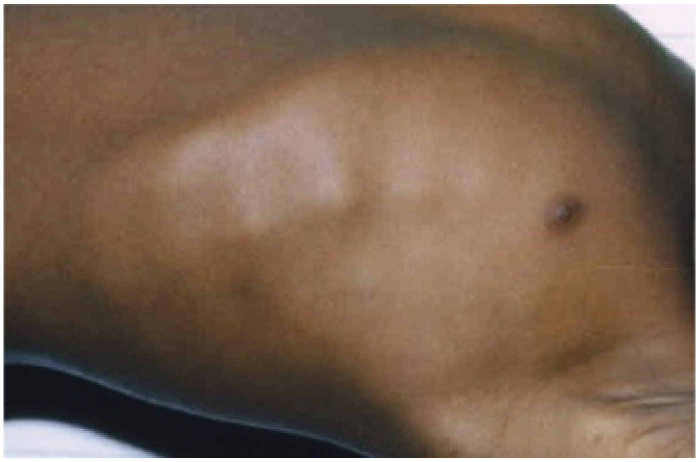

FIG. 64.1 Rachitic “rosary” in a child with rickets. (Courtesy of Dr. Thomas D. Thacher, Rochester, MN.)

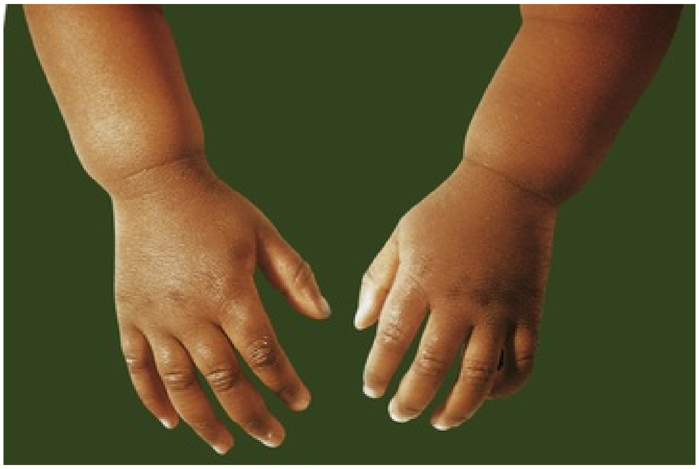

FIG. 64.2 Hands and forearms of a young child with rickets show prominence above the wrist, resulting from flaring and poor mineralization of lower end of the radius and ulna. (From Bullough PG: *Orthopaedic pathology,* ed 5, St Louis, 2010, Mosby, Fig 8-31.)

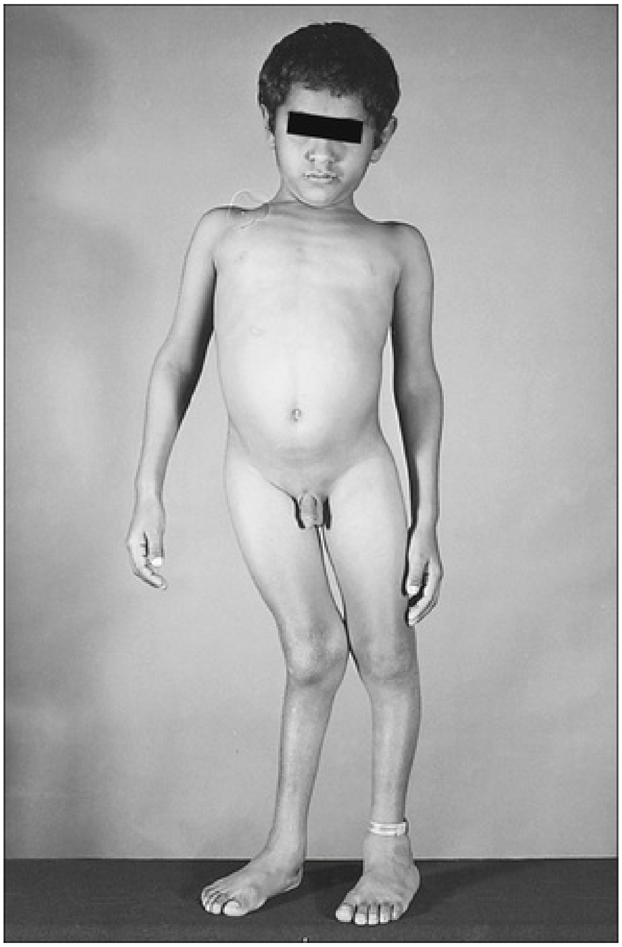

FIG. 64.3 Windswept deformity of the legs in an older child with rickets. (From Rickets and osteomalacia. In Hochberg MC, Silman AJ, Smolen JS, et al, editors: *Rheumatology,* 4e. London, 2008, Mosby, Fig 192-6.)

The clinical presentation of rickets may vary based on the etiology. Changes in the lower extremities tend to be the dominant feature in X-linked hypophosphatemic rickets. Symptoms secondary to hypocalcemia occur only in those forms of rickets associated with decreased serum calcium.

The chief complaint in a child with rickets is quite variable. Many children present because of skeletal deformities, whereas others have difficulty walking owing to a combination of deformity and weakness. Other common presenting complaints include failure to thrive (malnutrition) and symptomatic hypocalcemia (see Chapters 588 to 590).

Radiology

Rachitic changes are most easily visualized on posteroanterior radiographs of the wrist, although characteristic rachitic changes can be seen at other growth plates (Figs. 64.4 and 64.5). Decreased calcification leads to thickening of the growth plate. The edge of the metaphysis loses its sharp border, which is described as *fraying*. The edge of the metaphysis changes from a convex or flat surface to a more concave surface. This change to a concave surface is termed *cupping* and is most easily seen at the distal ends of the radius, ulna, and fibula. There is widening of the distal end of the metaphysis, corresponding to the clinical observation of thickened wrists and ankles, as well as the rachitic rosary. Other radiologic features include coarse trabeculation of the diaphysis and generalized rarefaction.

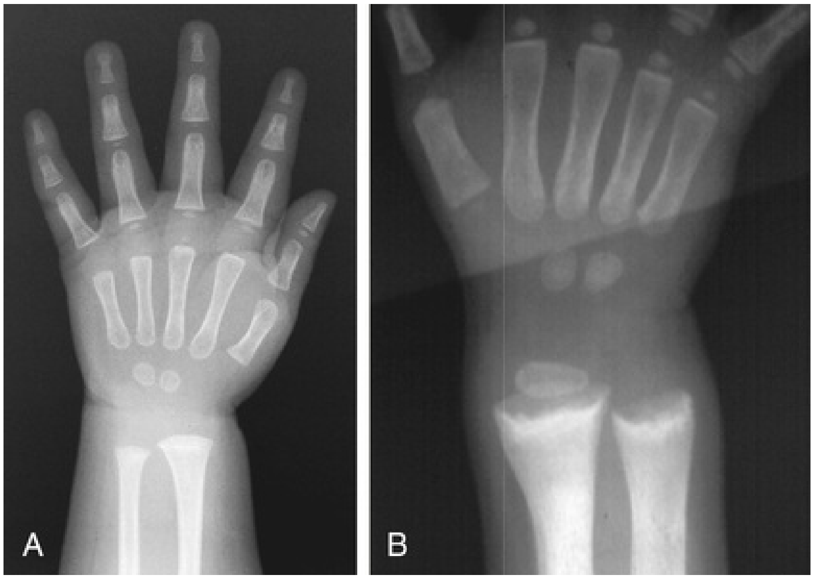

FIG. 64.4 Radiographs of the wrist in **A,** normal child; and **B,** child with rickets, who has metaphyseal fraying and cupping of the distal radius and ulna.

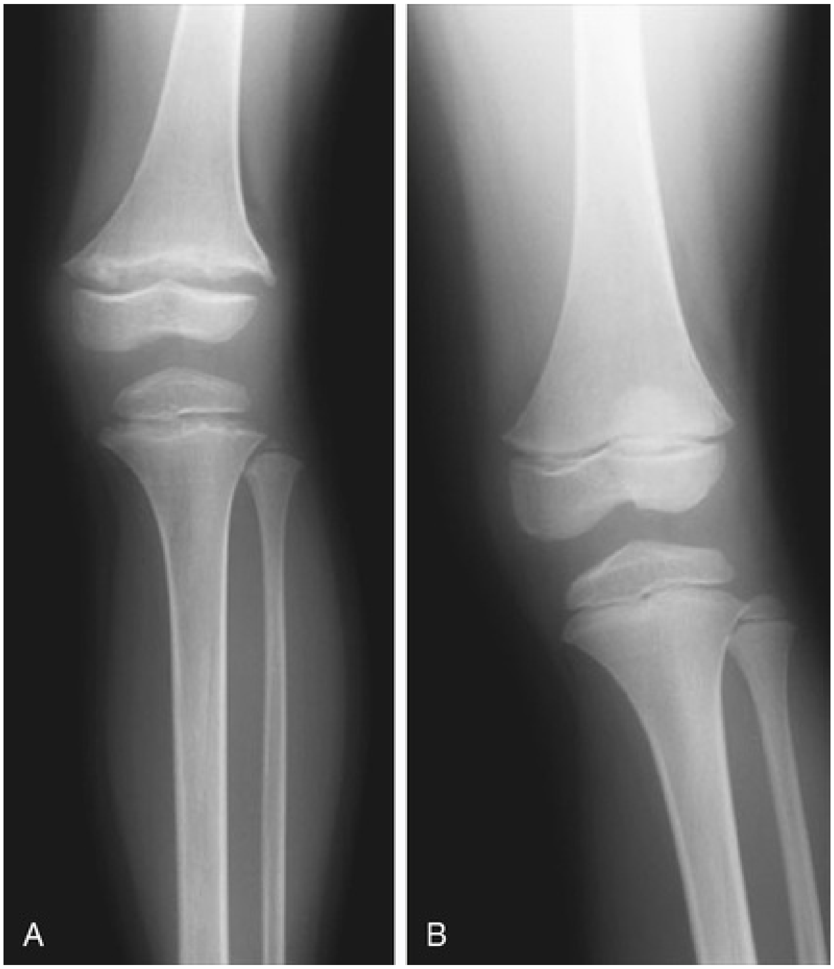

FIG. 64.5 Radiographs of the knees in 7 yr old girl with distal renal tubular acidosis and rickets. A, At initial presentation, there is widening of the growth plate and metaphyseal fraying. B, Dramatic improvement after 4 mo of therapy with alkali.

Diagnosis

The diagnosis of rickets is based on the presence of classic radiographic abnormalities. It is supported by physical examination findings, history, and laboratory results consistent with a specific etiology (Table 64.4).

Table 64.4

Laboratory Findings in Various Disorders Causing Rickets

Disorder	Ca	Pi	PTH	25-(OH)D	1,25-$(OH)_2$ D	ALP	URINE Ca	URINE Pi
Vitamin D deficiency	N, ↓	↓	↑	↓	↓, N, ↑	↑	↓	↑
VDDR, type 1A	N, ↓	↓	↑	N	↓	↑	↓	↑
VDDR, type 1B	N, ↓	↓	↑	↓	N	↑	↓	↑

VDDR, type 2A	N, ↓	↓	↑	N	↑↑	↑	↓	↑
VDDR, type 2B	N, ↓	↓	↑	N	↑↑	↑	↓	↑
Chronic kidney disease	N, ↓	↑	↑	N	↓	↑	N, ↓	↓
Dietary Pi deficiency	N	↓	N, ↓	N	↑	↑	↑	↓
XLH[*]	N	↓	N, ↑	N	RD	↑	↓	↑
ADHR[*]	N	↓	N	N	RD	↑	↓	↑
HHRH	N	↓	N, ↓	N	↑	↑	↑	↑
ARHR, type 1 or type 2[*]	N	↓	N	N	RD	↑	↓	↑
Tumor-induced rickets [†]	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dent's disease	N	↓	N	N	N	↑	↑	↑
Dietary Ca deficiency	N, ↓	↓	↑	N	↑	↑	↓	↑

[*] Elevated fibroblast growth factor-23 (FGF-23).

[†] FGF-23 elevated in some patients.

ADHR, Autosomal dominant hypophosphatemic rickets; ALP, alkaline phosphatase; ARHR, autosomal recessive hypophosphatemic rickets; Ca, calcium; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; N, normal; Pi, inorganic phosphorus; PTH, parathyroid hormone; RD, relatively decreased (because it should be increased given the concurrent hypophosphatemia); VDDR, vitamin D–dependent rickets; XLH, X-linked hypophosphatemic rickets; 1,25-(OH)$_2$ D, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ↓, decreased; ↑, increased; ↑↑, extremely increased.

Clinical Evaluation

Because the majority of children with rickets have a nutritional deficiency, the initial evaluation should focus on a **dietary history,** emphasizing intake of both vitamin D and calcium. Most children in industrialized nations receive vitamin D from formula, fortified milk, or vitamin supplements. Along with the amount, the exact composition of the formula or milk is pertinent, because rickets has occurred in children given products that are called “milk” (e.g., soy milk) but are deficient in vitamin D and minerals.

Cutaneous synthesis mediated by sunlight exposure is an important source of vitamin D. It is important to ask about time spent outside, sunscreen use, and clothing, especially if there may be a cultural reason for increased covering of the skin. Because winter sunlight is ineffective at stimulating cutaneous synthesis of vitamin D, the season is an additional consideration. Children with increased skin pigmentation are at increased risk for vitamin D deficiency because of decreased cutaneous synthesis.

The presence of **maternal** risk factors for nutritional vitamin D deficiency, including diet and sun exposure, is an important consideration when a neonate or young infant has rachitic findings, especially if the infant is breastfed (Table 64.5

). Determining a child's intake of dairy products, the main dietary source of calcium, provides a general sense of calcium intake. High dietary fiber can interfere with calcium absorption.

Table 64.5

Risk Factors for Nutritional Rickets and Osteomalacia and Their Prevention

Maternal Factors

- Vitamin D deficiency
    - Dark skin pigmentation
    - Full body clothing cover
    - High latitude during winter/spring season
    - Other causes of restricted sun (UVB) exposure, e.g., predominant indoor living, disability, pollution, cloud cover
    - Low–vitamin D diet
- Low-calcium diet
    - Poverty, malnutrition, special diets

Infant/Childhood Factors

- Neonatal vitamin D deficiency secondary to maternal deficiency/vitamin D deficiency
    - Lack of infant supplementation with vitamin D
    - Prolonged breastfeeding without appropriate complementary feeding from 6 mo
    - High latitude during winter/spring season
    - Dark skin pigmentation and/or restricted sun (UVB) exposure, e.g., predominant indoor living, disability, pollution, cloud cover
    - Low–vitamin D diet
- Low-calcium diet
    - Poverty, malnutrition, special diets

Preventive Measures

Sun exposure (UVB content of sunlight depends on latitude and season)
Vitamin D supplementation
Strategic fortification of the habitual food supply
Normal calcium intake

Adapted from Munns CF, Shaw N, Kiely M, et al: Global consensus recommendations on prevention and management of nutritional rickets, *J Clin Endocrinol Metab* 101:394-415, 2016, p 401.

The child's **medication** use is relevant, because certain medications, such as the anticonvulsants phenobarbital and phenytoin, increase degradation of vitamin D, and phosphate binders or aluminum-containing antacids interfere with the absorption of phosphate.

Malabsorption of vitamin D is suggested by a history of liver or intestinal disease. Undiagnosed liver or intestinal disease should be suspected if the child has gastrointestinal (GI) symptoms, although occasionally rickets is the presenting complaint. Fat malabsorption is often associated with diarrhea or oily stools, and there may be signs or symptoms suggesting deficiencies of other fat-soluble vitamins (A, E, and K; see Chapters 61 , 65 , and 66).

A history of **renal disease** (proteinuria, hematuria, urinary tract infections) is an additional significant consideration, given the importance of chronic kidney disease as a cause of rickets. Polyuria can occur in children with chronic kidney disease or Fanconi syndrome.

Children with rickets might have a history of dental caries, poor growth, delayed walking, waddling gait, pneumonia, and hypocalcemic symptoms.

The family history is critical, given the large number of **genetic causes** of rickets, although most of these causes are rare. Along with bone disease, it is important to inquire about leg deformities, difficulties with walking, or unexplained short stature, because some parents may be unaware of their diagnosis. Undiagnosed disease in the mother is not unusual in X-linked hypophosphatemia. A history of an unexplained sibling death during infancy may be present in the child with cystinosis, the most common cause of Fanconi syndrome in children.

The physical examination focuses on detecting manifestations of rickets (see Table 64.3). It is important to observe the child's gait, auscultate the lungs to detect atelectasis or pneumonia, and plot the patient's growth. Alopecia suggests vitamin D–dependent rickets type 2.

The initial **laboratory tests** in a child with rickets should include serum calcium, phosphorus, alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D (1,25-D), creatinine, and electrolytes (see Table 64.4 for interpretation). Urinalysis is useful for detecting the glycosuria seen with Fanconi syndrome and low-molecular-weight proteinuria (positive dipstick for protein) in Fanconi syndrome or Dent disease. Evaluation of urinary excretion of calcium (24 hr collection for calcium or calcium:creatinine ratio) is helpful if hereditary hypophosphatemic rickets with hypercalciuria or Dent disease is suspected. Direct measurement of other fat-soluble vitamins (A, E, and K) or indirect assessment of deficiency (prothrombin time for vitamin K deficiency) is appropriate if malabsorption is a consideration.

Vitamin D Disorders

Vitamin D Physiology

Vitamin D can be synthesized in skin epithelial cells and therefore technically is not a vitamin. Cutaneous synthesis is normally the most important source of vitamin D and depends on the conversion of 7-dehydrochlesterol to vitamin D_3 (3-cholecalciferol) by ultraviolet B (UVB) radiation from the sun. The efficiency of this process is decreased by melanin; therefore, more sun exposure is necessary for vitamin D synthesis in people with increased skin pigmentation. Measures to decrease sun exposure, such as covering the skin with clothing or applying sunscreen, also decrease vitamin D synthesis. Children who spend less time outside have reduced vitamin D synthesis. The winter sun away from the equator is ineffective at mediating vitamin D synthesis.

There are few natural dietary sources of vitamin D. Fish liver oils have a high vitamin D content. Other good dietary sources include fatty fish and egg yolks. Most children in industrialized countries receive vitamin D via fortified foods, especially formula and milk (both of which contain 400 IU/L) and some breakfast cereals and breads. Supplemental vitamin D may be vitamin D_2 (which comes from plants or yeast) or vitamin D_3 . Breast milk has a low vitamin D content, approximately 12-60 IU/L.

Vitamin D is transported bound to vitamin D–binding protein to the liver, where 25-hydroxlase converts vitamin D into 25-hydroxyvitamin D (25-D), the most abundant circulating form of vitamin D. Because there is little regulation of this liver hydroxylation step, measurement of 25-D is the standard method for determining a patient's vitamin D status. The final step in activation occurs in the kidney, where the enzyme 1α-hydroxylase adds a second hydroxyl group, resulting in 1,25-D. The 1α-hydroxylase is upregulated by PTH and hypophosphatemia and inhibited by hyperphosphatemia and 1,25-D. Most 1,25-D circulates bound to vitamin D–binding protein.

1,25-Dihydroxyvitamin D acts by binding to an intracellular receptor, and the complex affects gene expression by interacting with vitamin D response elements. In the intestine, this binding results in a marked increase in calcium absorption, which is highly dependent on 1,25-D. There is also an increase in phosphorus absorption, but this effect is less significant because most dietary phosphorus absorption is vitamin D independent. 1,25-D also has direct effects on bone, including mediating resorption. 1,25-D directly suppresses PTH secretion by the parathyroid gland, thus completing a negative feedback loop. PTH secretion is also suppressed by the increase in serum calcium mediated by 1,25-D. 1,25-D inhibits its own synthesis in the kidney and increases the synthesis of inactive metabolites.

Nutritional Vitamin D Deficiency

Vitamin D deficiency remains the most common cause of rickets globally and is prevalent, even in industrialized countries. Because vitamin D can be obtained from dietary sources or from cutaneous synthesis, most patients in industrialized countries have a combination of risk factors that lead to vitamin D deficiency.

Etiology

Vitamin D deficiency most frequently occurs in infancy because of a combination of poor intake and inadequate cutaneous synthesis. Transplacental transport of vitamin D, mostly 25-D, typically provides enough vitamin D for the 1st 2 mo of life unless there is severe maternal vitamin D deficiency. Infants who receive formula receive adequate vitamin D, even without cutaneous synthesis. Because of the low vitamin D content of breast milk, breastfed infants rely on cutaneous synthesis or vitamin supplements. Cutaneous synthesis can be limited because of the ineffectiveness of the winter sun in stimulating vitamin D synthesis; avoidance of sunlight because of concerns about cancer, neighborhood safety, or cultural practices; and decreased cutaneous synthesis because of increased skin pigmentation.

The effect of skin pigmentation explains why most cases of nutritional rickets in the United States and northern Europe occur in breastfed children of African descent or other dark-pigmented populations. The additional impact of the winter sun is supported by such infants more often presenting in the late winter or spring. In some groups, complete covering of infants or the practice of not taking infants outside has a significant role, explaining the occurrence of rickets in infants living in areas of abundant sunshine, such as the Middle East. Because the mothers of some infants can have the same risk factors, decreased maternal vitamin D can also contribute, both by leading to reduced vitamin D content in breast milk and by lessening transplacental delivery of vitamin D. Rickets caused by vitamin D deficiency can also be secondary to unconventional dietary practices, such as vegan diets that use unfortified soy milk or rice milk.

Clinical Manifestations

The clinical features are typical of rickets (see Table 64.3), with a significant minority presenting with symptoms of hypocalcemia. Prolonged laryngospasm is occasionally fatal. These children have an increased risk of pneumonia and muscle weakness leading to a delay in motor development.

Laboratory Findings

Table 64.4 summarize the principal laboratory findings. Hypocalcemia is a variable finding because the elevated PTH acts to increase the serum calcium concentration. The hypophosphatemia is caused by PTH-induced renal losses of phosphate, combined with a decrease in intestinal absorption.

The wide variation in 1,25-D levels (low, normal, or high) is secondary to the upregulation of renal 1α-hydroxylase caused by concomitant hypophosphatemia and hyperparathyroidism. Because serum levels of 1,25-D are much lower than the levels of 25-D, even with low levels of 25-D there is often enough 25-D still present to act as a precursor for 1,25-D synthesis in the presence of upregulated 1α-hydroxylase. The level of 1,25-D is only low when there is severe vitamin D deficiency.

Some patients have a metabolic acidosis secondary to PTH-induced renal bicarbonate wasting. There may also be generalized aminoaciduria.

Diagnosis and Differential Diagnosis

The diagnosis of nutritional vitamin D deficiency is based on the combination of a history of poor vitamin D intake and risk factors for decreased cutaneous synthesis, radiographic changes consistent with rickets, and typical laboratory findings (see Table 64.4). A normal PTH level almost never occurs with vitamin D deficiency and suggests a primary phosphate disorder.

Treatment

Children with nutritional vitamin D deficiency should receive vitamin D and adequate nutritional intake of calcium and phosphorus. There are 2 strategies for administration of vitamin D. With **stoss therapy** , vitamin D (300,000-600,000 IU) is administered orally (preferred) or intramuscularly as 2-4 doses over 1 day (vitamin D_3 is preferred to D_2 because of longer half-life of D_3). Since the doses are observed, stoss therapy is ideal in patients in whom adherence to therapy is questionable. The alternative strategy is daily vitamin D with a minimum dose of 2,000 IU/day for a minimum of 3 mo. Either strategy should be followed by daily vitamin D intake of 400 IU/day if <1 yr old or 600 IU/day if >1 yr old. It is important to ensure that children receive adequate dietary calcium (minimum of 500 mg/day) and phosphorus; this dietary intake is usually provided by milk, formula, and other dairy products, although calcium supplements may be needed in some patients.

Children who have symptomatic hypocalcemia might need intravenous (IV) calcium acutely, followed by oral calcium supplements, which typically can be tapered over 2-6 wk in children who receive adequate dietary calcium. Transient use of IV or oral 1,25-D (**calcitriol**) is often helpful in reversing hypocalcemia in the acute phase by providing active vitamin D during the delay as supplemental vitamin D is converted to active vitamin D. Calcitriol doses are typically 0.05 µg/kg/day. IV calcium is initially given as an acute bolus for symptomatic hypocalcemia (20 mg/kg calcium chloride or 100 mg/kg calcium gluconate). Some patients require a continuous IV calcium drip, titrated to maintain the desired serum calcium level. These patients should transition to enteral calcium, and most infants require approximately 1,000 mg of elemental calcium.

Prognosis

Most children with nutritional vitamin D deficiency have an excellent response to treatment, with radiologic healing occurring within a few months. Laboratory test results should also normalize rapidly. Many of the bone malformations improve dramatically, but children with severe disease can have permanent deformities and short stature. Rarely, patients benefit from orthopedic intervention for leg deformities, although this is generally not done until the metabolic bone disease has healed, there is clear evidence that the deformity will not self-resolve, and the deformity is causing functional problems.

Prevention

Most cases of nutritional rickets can be prevented by universal administration of 400 IU of vitamin D to infants <1 yr old. Older children with risk factors for inadequate intake should receive 600 IU/day. Vitamin D may be administered as a component of a multivitamin or as a vitamin D supplement.

Congenital Vitamin D Deficiency

Congenital rickets is quite rare in industrialized countries and occurs when there is severe maternal vitamin D deficiency during pregnancy. Maternal risk factors include poor dietary intake of vitamin D, lack of adequate sun exposure, and closely spaced pregnancies. These newborns can have symptomatic hypocalcemia, intrauterine growth retardation, and decreased bone ossification, along with classic rachitic changes. Subtler maternal vitamin D deficiency can have an adverse effect on neonatal bone density and birthweight, cause a defect in dental enamel, and predispose infants to neonatal hypocalcemic tetany. Treatment of congenital rickets includes vitamin D supplementation and adequate intake of calcium and phosphorus. Use of prenatal vitamins containing vitamin D (600 IU) prevents this entity.

Secondary Vitamin D Deficiency

Etiology

Along with inadequate intake, vitamin D deficiency can result from inadequate absorption, decreased hydroxylation in the liver, and increased degradation. Because vitamin D is fat soluble, its absorption may be decreased in patients with a variety of liver and GI diseases, including cholestatic liver disease, defects in bile acid metabolism, cystic fibrosis and other causes of pancreatic dysfunction, celiac disease, and Crohn disease. Malabsorption of vitamin D can also occur with intestinal lymphangiectasia and after intestinal resection.

Severe liver disease, which usually is also associated with malabsorption, can cause a decrease in 25-D formation as a result of insufficient enzyme activity. Because of the large reserve of 25-hydroxlase activity in the liver, vitamin D deficiency caused by liver disease usually requires a loss of >90% of liver function. A variety of medications increase the degradation of vitamin D by inducing the cytochrome P450 (CYP) system. Rickets from vitamin D deficiency can develop in children receiving anticonvulsants (e.g., phenobarbital, phenytoin) or antituberculosis medications (e.g., isoniazid, rifampin).

Treatment

Treatment of vitamin D deficiency attributable to malabsorption requires high doses of vitamin D. Because of its better absorption, 25-D (25-50 µg/day or 5-7 µg/kg/day) is superior to vitamin D_3 . The dose is adjusted based on monitoring of serum levels of 25-D. Alternatively, patients may be treated with 1,25-D, which also is better absorbed in the presence of fat malabsorption, or with parenteral vitamin D. Children with rickets as a result of increased degradation of vitamin D by the CYP system require the same acute therapy as indicated for nutritional deficiency (discussed earlier), followed by long-term administration of high doses of vitamin D (e.g., 1,000 IU/day), with dosing titrated based on serum levels of 25-D. Some patients require as much as 4,000 IU/day.

Vitamin D–Dependent Rickets, Type 1

Children with vitamin D–dependent rickets **type 1A** , an autosomal recessive disorder, have mutations in the gene encoding renal 1α-hydroxylase, preventing conversion of 25-D into 1,25-D. These patients normally present during the 1st 2 yr of life and can have any of the classic features of rickets (see Table 64.3), including symptomatic hypocalcemia. They have normal levels of 25-D but low levels of 1,25-D (see Table 64.4). Occasionally, 1,25-D levels are at the lower limit of normal, inappropriately low given the high PTH and low serum phosphorus levels, both of which should increase the activity of renal 1α-hydroxylase and cause elevated levels of 1,25-D. As in nutritional vitamin D deficiency, renal tubular dysfunction can cause a metabolic acidosis and generalized aminoaciduria.

Vitamin D–dependent rickets **type 1B** is secondary to a mutation in the gene for a 25-hydroxylase. Patients have low levels of 25-D but normal levels of 1,25-D (see Table 64.4).

Treatment

Vitamin D–dependent rickets type 1A responds to long-term treatment with 1,25-D (calcitriol). Initial doses are 0.25-2 μg/day, and lower doses are used once the rickets has healed. Especially during initial therapy, it is important to ensure adequate intake of calcium. The dose of calcitriol is adjusted to maintain a low-normal serum calcium level, a normal serum phosphorus level, and a high-normal serum PTH level. Targeting a low-normal calcium concentration and a high-normal PTH level avoids excessive dosing of calcitriol, which can cause hypercalciuria and nephrocalcinosis. Therefore, patient monitoring includes periodic assessment of urinary calcium excretion, with a target of <4 mg/kg/day.

Vitamin D–dependent rickets type 1B may respond to pharmacologic doses of vitamin D_2 (3,000 U/day) as a result of alternative enzymes with 25-hydroxylase activity or residual activity of the mutant protein.

Vitamin D–Dependent Rickets, Type 2

Patients with vitamin D–dependent rickets **type 2A** have mutations in the gene encoding the vitamin D receptor, preventing a normal physiologic response to 1,25-D. Levels of 1,25-D are extremely elevated in this autosomal recessive disorder (see Table 64.4). Most patients present during infancy, although rickets in less severely affected patients might not be diagnosed until adulthood. Less severe disease is associated with a partially functional vitamin D receptor. Approximately 50–70% of children have **alopecia** , which tends to be associated with a more severe form of the disease and can range from alopecia areata to alopecia totalis. Epidermal cysts are a less common manifestation.

Vitamin D–dependent rickets **type 2B** appears to result from overexpression of a hormone response element–binding protein that interferes with the actions of 1,25-D. Alopecia may be present.

Treatment

Some patients respond to extremely high doses of vitamin D_2 (25-D or 1,25-D), especially patients without alopecia. This response is caused by a partially functional vitamin D receptor in patients with vitamin D–dependent rickets type 2A, but may also occur in vitamin D–dependent rickets type 2B. All patients should be given a 3-6 mo trial of high-dose vitamin D and oral calcium. The initial dose of 1,25-D should be 2 μg/day, but some patients require doses as high as 50-60 µg/day. Calcium doses are 1,000-3,000 mg/day. Patients who do not respond to high-dose vitamin D may be treated with long-term IV calcium, with possible transition to very high dose oral calcium supplements. Treatment of patients who do not respond to vitamin D is difficult.

Chronic Kidney Disease

With chronic kidney disease, there is decreased activity of 1α-hydroxylase in the kidney, leading to diminished production of 1,25-D. In chronic kidney disease, unlike the other causes of vitamin D deficiency, patients have hyperphosphatemia as a result of decreased renal excretion (see Table 64.4 and Chapter 550.2).

Treatment

Therapy requires the use of a form of vitamin D that can act without 1-hydroxylation by the kidney (calcitriol), which both permits adequate absorption of calcium and directly suppresses the parathyroid gland. Because hyperphosphatemia is a stimulus for PTH secretion, normalization of the serum phosphorus level through a combination of dietary phosphorus restriction and use of oral phosphate binders is as important as the use of activated vitamin D.

Calcium Deficiency

Pathophysiology

Rickets secondary to inadequate dietary calcium is a significant problem in some countries in Africa, although there are cases in other regions of the world, including industrialized countries. Because breast milk and formula are excellent sources of calcium, this form of rickets develops after children have been weaned from breast milk or formula and is more likely to occur in children who are weaned early. Rickets develops because the diet has low calcium content, typically <200 mg/day if <12 mo old or <300 mg/day if >12 mo old. The child has minimal intake of dairy products or other sources of calcium. In addition, because of reliance on grains and green leafy vegetables, the diet may be high in phytate, oxalate, and phosphate, which decrease absorption of dietary calcium. In industrialized countries, rickets caused by calcium deficiency can occur in children who consume an unconventional diet. Examples include children with milk allergy who have low dietary calcium and children who transition from formula or breast milk to juice, soda, or a calcium-poor soy drink, without an alternative source of dietary calcium.

This type of rickets can develop in children who receive intravenous nutrition without adequate calcium. Malabsorption of calcium can occur in celiac disease, intestinal abetalipoproteinemia, and after small bowel resection. There may be concurrent malabsorption of vitamin D.

Clinical Manifestations

Children with calcium deficiency have the classic signs and symptoms of rickets (see Table 64.3). Presentation can occur during infancy or early childhood, although some cases are diagnosed in teenagers. Because calcium deficiency occurs after the cessation of breastfeeding, it tends to occur later than the nutritional vitamin D deficiency that is associated with breastfeeding. In Nigeria, nutritional vitamin D deficiency is most common at 4-15 mo of age, whereas calcium deficiency rickets typically occurs at 15-25 mo.

Diagnosis

Laboratory findings include increased levels of ALP, PTH, and 1,25-D (see Table 64.4). Calcium levels may be normal or low, although symptomatic hypocalcemia is uncommon. There is decreased urinary excretion of calcium, and serum phosphorus levels may be low as a result of renal wasting of phosphate from secondary hyperparathyroidism. In some children, there is coexisting nutritional vitamin D deficiency, with low 25-D levels.

Treatment

Treatment focuses on providing adequate calcium, typically as a dietary supplement (doses of 700 [age 1-3 yr], 1,000 [4-8 yr], and 1,300 [9-18 yr] mg/day of elemental calcium are effective). Vitamin D supplementation is necessary if there is concurrent vitamin D deficiency (discussed earlier). Prevention strategies include discouraging early cessation of breastfeeding and increasing dietary sources of calcium. In countries such as Kenya, where many children have diets high in cereal with negligible intake of cow's milk, school-based milk programs have been effective in reducing the prevalence of rickets.

Phosphorus Deficiency

Inadequate Intake

With the exception of starvation or severe anorexia, it is almost impossible to have a diet that is deficient in phosphorus, because phosphorus is present in most foods. Decreased phosphorus absorption can occur in diseases associated with malabsorption (celiac disease, cystic fibrosis, cholestatic liver disease), but if rickets develops, the primary problem is usually malabsorption of vitamin D and/or calcium.

Isolated malabsorption of phosphorus occurs in patients with long-term use of **aluminum-containing antacids** . These compounds are very effective at chelating phosphate in the GI tract, leading to decreased absorption. This decreased absorption results in hypophosphatemia with secondary osteomalacia in adults and rickets in children. This entity responds to discontinuation of the antacid and short-term phosphorus supplementation.

Fibroblast Growth Factor-23

Fibroblast growth factor-23 (**FGF-23**) is a humoral mediator that decreases renal tubular reabsorption of phosphate and therefore decreases serum phosphorus. FGF-23, synthesized by osteocytes, also decreases the activity of renal 1α-hydroxylase, resulting in a decrease in the production of 1,25-D. Increased levels of FGF-23 cause many of the renal phosphate-wasting diseases (see Table 64.2).

X-Linked Hypophosphatemic Rickets

Among the genetic disorders causing rickets because of hypophosphatemia, X-linked hypophosphatemic rickets (**XLH**) is the most common, with a prevalence of 1/20,000. The defective gene is on the X chromosome, but female carriers are affected, so it is an X-linked dominant disorder.

Pathophysiology

The defective gene is called *PHEX* because it is a *ph* osphate-regulating gene with homology to *e* ndopeptidases on the *X* chromosome. The product of this gene appears to have an indirect role in inactivating FGF-23. Mutations in *PHEX* lead to increased levels of FGF-23. Because the actions of FGF-23 include inhibition of phosphate reabsorption in the proximal tubule, phosphate excretion is increased. FGF-23 also inhibits renal 1α-hydroxylase, leading to decreased production of 1,25-D.

Clinical Manifestations

These patients have rickets, but abnormalities of the lower extremities and poor growth are the dominant features. Delayed dentition and tooth abscesses are also common. Some patients have hypophosphatemia and short stature without clinically evident bone disease.

Laboratory Findings

Patients have high renal excretion of phosphate, hypophosphatemia, and increased ALP; PTH and serum calcium levels are normal (see Table 64.4). Hypophosphatemia normally upregulates renal 1α-hydroxylase and should lead to an increase in 1,25-D, but these patients have low or inappropriately normal levels of 1,25-D.

Treatment

Patients respond well to a combination of oral phosphorus and 1,25-D (calcitriol). The daily need for phosphorus supplementation is 1-3 g of elemental phosphorus divided into 4 or 5 doses. Frequent dosing helps to prevent prolonged decrements in serum phosphorus because there is a rapid decline after each dose. In addition, frequent dosing decreases diarrhea, a complication of high-dose oral phosphorus. Calcitriol is administered at 30-70 ng/kg/day in 2 doses. Burosumab-twza is a monoclonal antibody to FGF-23 that is an approved alternative approach for treating XLH in children >1 yr.

Complications of treatment occur when there is not an adequate balance between phosphorus supplementation and calcitriol. Excess phosphorus, by decreasing enteral calcium absorption, leads to secondary hyperparathyroidism, with worsening of the bone lesions. In contrast, excess calcitriol causes hypercalciuria and nephrocalcinosis and can even cause hypercalcemia. Therefore, laboratory monitoring of treatment includes serum calcium, phosphorus, ALP, PTH, and urinary calcium, as well as periodic renal ultrasound to evaluate patients for nephrocalcinosis. Because of variation in the serum phosphorus level and the importance of avoiding excessive phosphorus dosing, normalization of ALP levels is a more useful method of assessing the therapeutic response than measuring serum phosphorus. For children with significant short stature, growth hormone is an effective option. Children with severe deformities might need osteotomies, but these procedures should be done only when treatment has led to resolution of the bone disease.

Prognosis

The response to therapy is usually good, although frequent dosing can lead to problems with compliance. Girls generally have less severe disease than boys, probably because of the X-linked inheritance. Short stature can persist despite healing of the rickets. Adults generally do well with less aggressive treatment, and some receive calcitriol alone. Adults with bone pain or other symptoms improve with oral phosphorus supplementation and calcitriol.

Autosomal Dominant Hypophosphatemic Rickets

Autosomal dominant hypophosphatemic rickets (**ADHR**) is much less common than XLH. There is incomplete penetrance and variable age of onset. Patients with ADHR have a mutation in the gene encoding FGF-23 (*FGF23*). The mutation prevents degradation of FGF-23 by proteases, leading its level to increase. The actions of FGF-23 include decreased reabsorption of phosphate in the renal proximal tubule, which results in hypophosphatemia, and inhibition of the 1α-hydroxylase in the kidney, causing a decrease in 1,25-D synthesis.

In ADHR, as in XLH, abnormal laboratory findings are hypophosphatemia, elevated ALP level, and a low or inappropriately normal 1,25-D level (see Table 64.4). Treatment is similar to the approach used in XLH.

Autosomal Recessive Hypophosphatemic Rickets

Autosomal recessive hypophosphatemic rickets (**ARHR**) **type 1** is an extremely rare disorder caused by mutations in the gene encoding dentin matrix protein 1 (*DMP1*). ARHR **type 2** occurs in patients with mutations in the *ENPP1* gene. Mutations in *ENPP1* also cause generalized arterial calcification of infancy. Both types of ARHR are associated with elevated levels of FGF-23, leading to renal phosphate wasting, hypophosphatemia, and low or inappropriately normal levels of 1,25-D. Treatment is similar to the approach used in XLH, although monitoring for arterial calcification is prudent in patients with *ENPP1* mutations.

Hereditary Hypophosphatemic Rickets With Hypercalciuria

Hereditary hypophosphatemic rickets with hypercalciuria (**HHRH**) is a rare disorder that is mainly found in the Middle East.

Pathophysiology

This autosomal recessive disorder is caused by mutations in the gene for a sodium-phosphate co-transporter in the proximal tubule (*SLC34A3*). The renal phosphate leak causes hypophosphatemia, which then stimulates production of 1,25-D. The high level of 1,25-D increases intestinal absorption of calcium, suppressing PTH. Hypercalciuria ensues as a result of the high absorption of calcium and the low level of PTH, which normally decreases renal excretion of calcium.

Clinical Manifestations

The dominant symptoms of HHRH are rachitic leg abnormalities (see Table 64.3), muscle weakness, and bone pain. Patients can have short stature, with a disproportionate decrease in the length of the lower extremities. The severity of the disease varies, and some family members have no evidence of rickets but have kidney stones secondary to hypercalciuria.

Laboratory Findings

Laboratory findings include hypophosphatemia, renal phosphate wasting, elevated serum ALP levels, and elevated 1,25-D levels. PTH levels are low (see Table 64.4).

Treatment

Therapy for HHRH patients relies on oral phosphorus replacement (1-2.5 g/day of elemental phosphorus in 5 divided doses). Treatment of the hypophosphatemia decreases serum levels of 1,25-D and corrects the hypercalciuria. The response to therapy is usually excellent, with resolution of pain, weakness, and radiographic evidence of rickets.

Overproduction of FGF-23

Tumor-induced osteomalacia is more common in adults; in children it can produce classic rachitic findings. Most tumors are mesenchymal in origin and are usually benign, small, and located in bone. These tumors secrete FGF-23 and produce a biochemical phenotype similar to XLH, including urinary phosphate wasting, hypophosphatemia, elevated ALP levels, and low or inappropriately normal 1,25-D levels (see Table 64.4). Curative treatment is excision of the tumor. If the tumor cannot be removed, treatment is identical to that for XLH.

Renal phosphate wasting leading to hypophosphatemia and rickets (or osteomalacia in adults) is a potential complication in **McCune-Albright syndrome** , an entity that includes the triad of polyostotic fibrous dysplasia, hyperpigmented macules, and polyendocrinopathy (see Chapter 578.6). Affected patients have inappropriately low levels of 1,25-D and elevated ALP levels. The renal phosphate wasting and inhibition of 1,25-D synthesis are related to the polyostotic fibrous dysplasia. Patients have elevated FGF-23, presumably caused by the dysplastic bone. Hypophosphatemic rickets can also occur in children with isolated polyostotic fibrous dysplasia. Although it is rarely possible, removal of the abnormal bone can cure this disorder in children with McCune-Albright syndrome. Most patients receive the same treatment as children with XLH. Bisphosphonate treatment decreases the pain and fracture risk associated with the bone lesions.

Rickets is an unusual complication of **epidermal nevus syndrome** (see Chapter 670). Patients have hypophosphatemic rickets caused by renal phosphate wasting and an inappropriately normal or low level of 1,25-D from excessive production of FGF-23. The timing of presentation with rickets varies from infancy to early adolescence. Hypophosphatemia and rickets have resolved after excision of the epidermal nevi in some patients, but not in others. In most the skin lesions are too extensive to be removed, necessitating treatment with phosphorus supplementation and 1,25-D. Rickets caused by phosphate wasting is an extremely rare complication in children with **neurofibromatosis** (see Chapter 614.1).

Raine syndrome , an autosomal recessive disorder caused by mutations in the *FAM20C* gene, is an osteosclerotic bone dysplasia that is often fatal in the neonatal period. However, patients who survive into childhood may develop rickets from increased levels of FGF-23.

Fanconi Syndrome

Fanconi syndrome is secondary to generalized dysfunction of the renal proximal tubule (see Chapter 547.1). There are renal losses of phosphate, amino acids, bicarbonate, glucose, urate, and other molecules that are normally reabsorbed in the proximal tubule. Some patients have partial dysfunction, with less generalized losses. The most clinically relevant consequences are hypophosphatemia caused by phosphate losses and proximal renal tubular acidosis caused by bicarbonate losses. Patients have rickets as a result of hypophosphatemia, with exacerbation from the chronic metabolic acidosis, which causes bone dissolution. Failure to thrive (malnutrition) is a consequence of both rickets and renal tubular acidosis. Treatment is dictated by the etiology (see Chapter 547).

Dent Disease

Dent disease is an X-linked disorder usually caused by mutations in the gene encoding a chloride channel expressed in the kidney (*CLCN5*). Some patients have mutations in the *OCRL1* gene, which can also cause Lowe syndrome (see Chapter 549.3). Affected males have variable manifestations, including hematuria, nephrolithiasis, nephrocalcinosis, rickets, and chronic kidney disease. Almost all patients have low-molecular-weight proteinuria and hypercalciuria. Other, less universal abnormalities are aminoaciduria, glycosuria, hypophosphatemia, and hypokalemia. Rickets occurs in approximately 25% of patients, and it responds to oral phosphorus supplements. Some patients also need 1,25-D, but this treatment should be used cautiously because it can worsen the hypercalciuria.

Rickets of Prematurity

Rickets in very-low-birthweight infants has become a significant problem, as the survival rate for this group of infants has increased (see Chapter 117.2).

Pathogenesis

The transfer of calcium and phosphorus from mother to fetus occurs throughout pregnancy, but 80% occurs during the 3rd trimester. Premature birth interrupts this process, with rickets developing when the premature infant does not have an adequate supply of calcium and phosphorus to support mineralization of the growing skeleton.

Most cases of rickets of prematurity occur in infants with a birthweight <1,000 g. It is more likely to develop in infants with lower birthweight and younger gestational age. Rickets occurs because unsupplemented breast milk and standard infant formula do not contain enough calcium and phosphorus to supply the needs of the premature infant. Other risk factors include cholestatic jaundice, a complicated neonatal course, prolonged use of parenteral nutrition, the use of soy formula, and medications such as diuretics and corticosteroids.

Clinical Manifestations

Rickets of prematurity occurs 1-4 mo after birth. Infants can have nontraumatic fractures, especially of the legs, arms, and ribs. Most fractures are not suspected clinically. Because fractures and softening of the ribs lead to decreased chest compliance, some infants have respiratory distress from atelectasis and poor ventilation. This rachitic respiratory distress usually develops >5 wk after birth, distinguishing it from the early-onset respiratory disease of premature infants. These infants have poor linear growth, with negative effects on growth persisting beyond 1 yr of age. An additional long-term effect is enamel hypoplasia. Poor bone mineralization can contribute to dolichocephaly. There may be classic rachitic findings, such as frontal bossing, rachitic rosary (see Fig. 64.1), craniotabes, and widened wrists and ankles (see Table 64.3). Most infants with rickets of prematurity have no clinical manifestations, and the diagnosis is based on radiographic and laboratory findings.

Laboratory Findings

Because of inadequate intake, the serum phosphorus level is low or low-normal in patients with rickets of prematurity. The renal response is appropriate, with conservation of phosphate leading to a low urine phosphate level; tubular reabsorption of phosphate is >95%. Most patients have normal levels of 25-D, unless there has been inadequate intake or poor absorption (discussed earlier). The hypophosphatemia stimulates renal 1α-hydroxylase, so levels of 1,25-D are high or high-normal. These high levels can contribute to bone demineralization because 1,25-D stimulates bone resorption. Serum levels of calcium are low, normal, or high, and patients often have hypercalciuria. Elevated serum calcium levels and hypercalciuria are secondary to increased intestinal absorption and bone dissolution caused by elevated 1,25-D levels and inability to deposit calcium in bone because of an inadequate phosphorus supply. The hypercalciuria indicates that phosphorus is the limiting nutrient for bone mineralization, although increased provision of phosphorus alone often cannot correct the mineralization defect; increased calcium is also necessary. Thus there is an inadequate supply of calcium and phosphorus, but the deficiency in phosphorus is greater.

Alkaline phosphatase levels are often elevated, but some affected infants have normal levels. In some cases, normal ALP levels may be secondary to resolution of the bone demineralization because of an adequate mineral supply despite the continued presence of radiologic changes, which take longer to resolve. However, ALP levels may be normal despite active disease. No single blood test is 100% sensitive for the diagnosis of rickets. The diagnosis should be suspected in infants with ALP >5-6 times the upper limit of normal (UL) for adults (unless there is concomitant liver disease) or phosphorus <5.6 mg/dL. The diagnosis is confirmed by radiologic evidence of rickets, which is best seen on x-ray films of the wrists and ankles. Films of the arms and legs might reveal fractures. The rachitic rosary may be visible on chest radiograph. Unfortunately, x-ray films cannot show early demineralization of bone because changes are not evident until there is >20–30% reduction in the bone mineral content.

Diagnosis

Because many premature infants have no overt clinical manifestations of rickets, screening tests are recommended. These tests should include weekly measurements of calcium, phosphorus, and ALP. Periodic measurement of the serum bicarbonate concentration is also important, because metabolic acidosis causes dissolution of bone. At least 1 screening radiograph for rickets at 6-8 wk of age is appropriate in infants who are at high risk for rickets; additional films may be indicated in high-risk infants.

Prevention

Provision of adequate amounts of calcium, phosphorus, and vitamin D significantly decreases the risk of rickets of prematurity. Parenteral nutrition is often necessary initially in very premature infants. In the past, adequate parenteral calcium and phosphorus delivery was difficult because of limits secondary to insolubility of these ions when their concentrations were increased. Current amino acid preparations allow higher concentrations of calcium and phosphate, decreasing the risk of rickets. Early transition to enteral feedings is also helpful. These infants should receive either human milk fortified with calcium and phosphorus or preterm infant formula, which has higher concentrations of calcium and phosphorus than standard formula. Soy formula should be avoided because there is decreased bioavailability of calcium and phosphorus. Increased mineral feedings should continue until the infant weighs 3-3.5 kg. These infants should also receive approximately 400 IU/day of vitamin D through formula and vitamin supplements.

Treatment

Therapy for rickets of prematurity focuses on ensuring adequate delivery of calcium, phosphorus, and vitamin D. If mineral delivery has been good and there is no evidence of healing, it is important to screen for vitamin D deficiency by measuring serum 25-D. Measurement of PTH, 1,25-D, and urinary calcium and phosphorus may be helpful in some cases.

Distal Renal Tubular Acidosis

Distal renal tubular acidosis usually manifests with failure to thrive. Patients have a metabolic acidosis with an inability to acidify the urine appropriately. Hypercalciuria and nephrocalcinosis are typically present. The many etiologies include autosomal recessive and autosomal dominant forms. Rickets is variable and responds to alkali therapy (see Fig. 64.5 and Chapter 547.2).

Hypervitaminosis D

Etiology

Hypervitaminosis D is caused by excessive intake of vitamin D. It can occur with long-term high intake or with a substantial, acute ingestion (see Table 64.1

). Most cases are secondary to misuse of prescribed or nonprescription vitamin D supplements, but other cases have been secondary to accidental overfortification of milk, contamination of table sugar, and inadvertent use of vitamin D supplements as cooking oil. The recommended upper limits for long-term vitamin D intake are 1,000 IU for children <1 yr old and 2,000 IU for older children and adults. Hypervitaminosis D can also result from excessive intake of synthetic vitamin D analogs (25-D, 1,25-D). Vitamin D intoxication is never secondary to excessive exposure to sunlight, probably because ultraviolet irradiation can transform vitamin D_3 and its precursor into inactive metabolites.

Pathogenesis

Although vitamin D increases intestinal absorption of calcium, the dominant mechanism of the hypercalcemia is excessive bone resorption.

Clinical Manifestations

The signs and symptoms of vitamin D intoxication are secondary to hypercalcemia. GI manifestations include nausea, vomiting, poor feeding, constipation, abdominal pain, and pancreatitis. Possible cardiac findings are hypertension, decreased QT interval, and arrhythmias. The central nervous system effects of hypercalcemia include lethargy, hypotonia, confusion, disorientation, depression, psychosis, hallucinations, and coma. Hypercalcemia impairs renal concentrating mechanisms, which can lead to polyuria, dehydration, and hypernatremia. Hypercalcemia can also lead to acute renal failure, nephrolithiasis, and nephrocalcinosis, which can result in chronic renal insufficiency. Deaths are usually associated with arrhythmias or dehydration.

Laboratory Findings

The classic findings in vitamin D intoxication are hypercalcemia, elevated levels of 25-D (>100 ng/mL), hypercalciuria, and suppressed PTH. Hyperphosphatemia is also common. Hypercalciuria can lead to nephrocalcinosis, which is visible on renal ultrasound. Hypercalcemia and nephrocalcinosis can lead to renal insufficiency.

Surprisingly, levels of 1,25-D are usually normal. This may result from downregulation of renal 1α-hydroxylase by the combination of low PTH, hyperphosphatemia, and a direct effect of 1,25-D. The level of free 1,25-D may be high because of displacement from vitamin D–binding proteins by 25-D. Anemia is sometimes present; the mechanism is unknown.

Diagnosis and Differential Diagnosis

The diagnosis is based on the presence of hypercalcemia and an elevated serum 25-D level, although children with excess intake of 1,25-D or another synthetic vitamin D preparation have normal levels of 25-D. With careful sleuthing, there is usually a history of excess intake of vitamin D, although in some situations (overfortification of milk by a dairy) the patient and family may be unaware.

The differential diagnosis of vitamin D intoxication focuses on other causes of **hypercalcemia** . Hyperparathyroidism produces hypophosphatemia, whereas vitamin D intoxication usually causes hyperphosphatemia. Williams syndrome is often suggested by phenotypic features and accompanying cardiac disease. Idiopathic infantile hypercalcemia occurs in children taking appropriate doses of vitamin D. Subcutaneous fat necrosis is a common cause of hypercalcemia in young infants; skin findings are usually present. The hypercalcemia of familial benign hypocalciuric hypercalcemia is mild, asymptomatic, and associated with hypocalciuria. Hypercalcemia of malignancy is an important consideration. High intake of calcium can also cause hypercalcemia, especially in the presence of renal insufficiency. Questioning about calcium intake should be part of the history in a patient with hypercalcemia. Occasionally, patients are intentionally taking high doses of calcium and vitamin D.

Treatment

The treatment of vitamin D intoxication focuses on control of hypercalcemia. Many patients with hypercalcemia are dehydrated as a result of polyuria from nephrogenic diabetes insipidus, poor oral intake, and vomiting. Rehydration lowers the serum calcium level by dilution and corrects prerenal azotemia. The resultant increased urine output increases urinary calcium excretion. Urinary calcium excretion is also increased by high urinary sodium excretion. The mainstay of the initial treatment is aggressive therapy with normal saline, often in conjunction with a loop diuretic to further increase calcium excretion; this is often adequate for treating mild or moderate hypercalcemia. More significant hypercalcemia usually requires other therapies. Glucocorticoids decrease intestinal absorption of calcium by blocking the action of 1,25-D. There is also a decrease in the levels of 25-D and 1,25-D. The usual dosage of prednisone is 1-2 mg/kg/24 hr.

Calcitonin, which lowers calcium by inhibiting bone resorption, is a useful adjunct, but its effect is usually not dramatic. There is an excellent response to IV or oral bisphosphonates in vitamin D intoxication. Bisphosphonates inhibit bone resorption through their effects on osteoclasts. Hemodialysis using a low or 0 dialysate calcium can rapidly lower serum calcium in patients with severe hypercalcemia that is refractory to other measures.

Along with controlling hypercalcemia, it is imperative to eliminate the source of excess vitamin D. Additional sources of vitamin D such as multivitamins and fortified foods should be eliminated or reduced. Avoidance of sun exposure, including the use of sunscreen, is prudent. The patient should also restrict calcium intake.

Prognosis

Most children make a full recovery, but hypervitaminosis D may be fatal or can lead to chronic kidney disease. Because vitamin D is stored in fat, levels can remain elevated for months, necessitating regular monitoring of 25-D, serum calcium, and urine calcium.

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CHAPTER 65

Vitamin E Deficiency

Larry A. Greenbaum

Vitamin E is a fat-soluble vitamin and functions as an antioxidant, but its precise biochemical functions are not known. Vitamin E deficiency can cause hemolysis or neurologic manifestations and occurs in premature infants, in patients with malabsorption, and in an autosomal recessive disorder affecting vitamin E transport. Because of its role as an antioxidant, there is considerable research on vitamin E supplementation in chronic illnesses.

Pathogenesis

The term *vitamin E* denotes a group of 8 compounds with similar structures and antioxidant activity. The most potent member of these compounds is **α-tocopherol** , which is also the main form in humans. The best dietary sources of vitamin E are vegetable oils, seeds, nuts, green leafy vegetables, and margarine (see Table 64.1).

The majority of vitamin E is located within cell membranes, where it prevents lipid peroxidation and the formation of free radicals. Other antioxidants, such as ascorbic acid, enhance the antioxidant activity of vitamin E. The importance of other functions of vitamin E is still being delineated.

Premature infants are particularly susceptible to vitamin E deficiency, because there is significant transfer of vitamin E during the last trimester of pregnancy. Vitamin E deficiency in premature infants causes thrombocytosis, edema, and hemolysis, potentially causing anemia. The risk of symptomatic vitamin E deficiency was increased by the use of formulas for premature infants that had a high content of polyunsaturated fatty acids (PUFAs). These formulas led to a high content of PUFAs in red blood cell membranes, making them more susceptible to oxidative stress, which could be ameliorated by vitamin E.

Oxidative stress was augmented by aggressive use of iron supplementation; iron increases the production of oxygen radicals. The incidence of hemolysis as a result of vitamin E deficiency in premature infants decreased secondary to the use of formulas with a lower content of PUFAs, less-aggressive use of iron, and provision of adequate vitamin E.

Because vitamin E is plentiful in common foods, primary dietary deficiency is rare except in premature infants and in severe, generalized malnutrition. Vitamin E deficiency does occur in children with fat malabsorption secondary to the bile acid needed for vitamin E absorption. Although symptomatic disease is most common in children with cholestatic liver disease, it can occur in patients with cystic fibrosis, celiac disease, short bowel syndrome, and Crohn disease. The autosomal recessive disorder **abetalipoproteinemia** causes fat malabsorption, and vitamin E deficiency is a common complication (see Chapter 104).

In **ataxia with isolated vitamin E deficiency (AVED)** , a rare autosomal recessive disorder, there are mutations in the gene for α-tocopherol transfer protein (*TTPA*). Patients with this disorder are unable to incorporate vitamin E into lipoproteins before their release from the liver, leading to reduced serum levels of vitamin E. There is no associated fat malabsorption, and absorption of vitamin E from the intestine occurs normally.

Clinical Manifestations

A severe, progressive neurologic disorder occurs in patients with prolonged vitamin E deficiency. Clinical manifestations do not appear until after 1 yr of age, even in children with cholestasis since birth. Patients may have cerebellar disease, posterior column dysfunction, and retinal disease. Loss of deep tendon reflexes is usually the initial finding. Subsequent manifestations include limb ataxia (intention tremor, dysdiadochokinesia), truncal ataxia (wide-based, unsteady gait), dysarthria, ophthalmoplegia (limited upward gaze), nystagmus, decreased proprioception (positive Romberg test), decreased vibratory sensation, and dysarthria. Some patients have pigmentary retinopathy. Visual field constriction can progress to blindness. Cognition and behavior can also be affected. Myopathy and cardiac arrhythmias are less common findings.

In premature infants, hemolysis as a result of vitamin E deficiency typically develops during the 2nd mo of life. Edema may also be present.

Laboratory Findings

Serum vitamin E levels increase in the presence of high serum lipid levels, even when vitamin E deficiency is present. Therefore, vitamin E status is best determined by measuring the ratio of vitamin E to serum lipids; a ratio <0.8 mg/g is abnormal in older children and adults; <0.6 mg/g is abnormal in infants <1 yr. Premature infants with hemolysis caused by vitamin E deficiency also often have elevated platelet counts.

Neurologic involvement can cause abnormal somatosensory evoked potentials and nerve conduction studies. Abnormalities on electroretinography can precede physical examination findings in patients with retinal involvement.

Diagnosis and Differential Diagnosis

Premature infants with unexplained hemolytic anemia after the 1st mo of life, especially if thrombocytosis is present, either should be empirically treated with vitamin E or should have serum vitamin E and lipid levels measured. Children with neurologic findings and a disease that causes fat malabsorption should have their vitamin E status evaluated.

Because children with AVED do not have symptoms of malabsorption, a correct diagnosis requires a high index of suspicion. **Friedreich ataxia** has been misdiagnosed in some patients (see Chapter 615.1). Children with unexplained ataxia should be screened for vitamin E deficiency.

Treatment

For correction of deficiency in neonates, the dose of vitamin E is 25-50 units/day for 1 wk, followed by adequate dietary intake. Children with deficiency as a result of malabsorption should receive 1 unit/kg/day, with the dose adjusted based on levels; ongoing treatment is necessary. Children with AVED normalize their serum vitamin E levels with high doses of vitamin E and require ongoing treatment.

Prognosis

The hemolytic anemia in infants resolves with correction of the vitamin E deficiency. Some neurologic manifestations of vitamin E deficiency may be reversible with early treatment, but many patients have little or no improvement. Importantly, treatment prevents progression.

Prevention

Premature infants should receive sufficient vitamin E through formula or breast milk fortifier and formula without a high content of PUFAs. Children at risk for vitamin E deficiency as a result of malabsorption should be screened for deficiency and given adequate vitamin E supplementation. Vitamin preparations with high content of all the fat-soluble vitamins are available.

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CHAPTER 66

Vitamin K Deficiency

Larry A. Greenbaum

Vitamin K is necessary for the synthesis of clotting factors II, VII, IX, and X; deficiency of vitamin K can result in clinically significant bleeding. Vitamin K deficiency typically affects infants, who experience a transient deficiency related to inadequate intake, or patients of any age who have decreased vitamin K absorption. Mild vitamin K deficiency can affect long-term bone and vascular health (see Chapters 124.4 and 507).

Pathogenesis

Vitamin K is a group of compounds that have a common naphthoquinone ring structure (see Table 64.1). **Phylloquinone** , called *vitamin* K_1 , is present in a variety of dietary sources, with green leafy vegetables, liver, and certain legumes and plant oils having the highest content. Vitamin K_1 is the form used to fortify foods and as a medication in the United States. *Vitamin* K_2 is a group of compounds called **menaquinones** , which are produced by intestinal bacteria. There is uncertainty regarding the relative importance of intestinally produced vitamin K_2 . Menaquinones are also present in meat, especially liver, and cheese. A menaquinone is used pharmacologically in some countries.

Vitamin K is a cofactor for γ-glutamyl carboxylase, an enzyme that performs posttranslational carboxylation, converting glutamate residues in proteins to **γ-carboxyglutamate (Gla)** . The Gla residues, by facilitating calcium binding, are necessary for protein function.

The classic Gla-containing proteins involved in blood coagulation that are decreased in vitamin K deficiency are factors II (prothrombin), VII, IX, and X. Vitamin K deficiency causes a decrease in proteins C and S, which inhibit blood coagulation, and protein Z, which also has a role in coagulation. All these proteins are made only in the liver, except for protein S, a product of various tissues.

Gla-containing proteins are also involved in bone biology (osteocalcin and protein S) and vascular biology (matrix Gla protein and protein S). Based on the presence of reduced levels of Gla, these proteins appear more sensitive than the coagulation proteins to subtle vitamin K deficiency. Evidence suggests that mild vitamin K deficiency might have a deleterious effect on long-term bone strength and vascular health.

Because it is fat soluble, vitamin K requires the presence of bile salts for its absorption. Unlike other fat-soluble vitamins, there are limited body stores of vitamin K. In addition, there is high turnover of vitamin K, and the vitamin K–dependent clotting factors have a short half-life. Thus, symptomatic vitamin K deficiency can develop within weeks when there is inadequate supply because of low intake or malabsorption.

There are 3 forms of **vitamin K deficiency bleeding (VKDB)** of the newborn (see Chapter 124.4). *Early* VKDB was formerly called *classic hemorrhagic disease of the newborn* and occurs at 1-14 days of age. Early VKDB is secondary to low stores of vitamin K at birth as a result of the poor transfer of vitamin K across the placenta and inadequate intake during the 1st few days of life. In addition, there is no intestinal synthesis of vitamin K_2 because the newborn gut is sterile. Early VKDB occurs mostly in breastfed infants as a consequence of the low vitamin K content of breast milk (formula is fortified). Delayed feeding is an additional risk factor.

Late VKDB most often occurs at 2-12 wk of age, although cases can occur up to 6 mo after birth. Almost all cases are in breastfed infants because of the low vitamin K content of breast milk. An additional risk factor is occult malabsorption of vitamin K, as occurs in children with undiagnosed cystic fibrosis or cholestatic liver disease (e.g., biliary atresia, α_1 -antitrypsin deficiency). Without vitamin K prophylaxis, the incidence is 4-10 per 100,000 newborns.

The third form of VKDB of the newborn occurs *at birth* or shortly thereafter. It is secondary to maternal intake of medications (warfarin, phenobarbital, phenytoin) that cross the placenta and interfere with vitamin K function.

VKDB as a result of fat malabsorption can occur in children of any age. Potential etiologies include cholestatic liver disease, pancreatic disease, and intestinal disorders (celiac sprue, inflammatory bowel disease, short bowel syndrome). Prolonged diarrhea can cause vitamin K deficiency, especially in breastfed infants. Children with cystic fibrosis are most likely to have vitamin K deficiency if they have pancreatic insufficiency and liver disease.

Beyond infancy, low dietary intake by itself never causes vitamin K deficiency. However, the combination of poor intake and the use of broad-spectrum antibiotics that eliminate the intestine's vitamin K_2 –producing bacteria can cause vitamin K deficiency. This scenario is especially common in the intensive care unit. Vitamin K deficiency can also occur in patients who receive total parenteral nutrition (TPN) without vitamin K supplementation.

Clinical Manifestations

In early VKDB, the most common sites of bleeding are the gastrointestinal (GI) tract, mucosal and cutaneous tissue, umbilical stump, and postcircumcision site; intracranial bleeding is less common. GI blood loss can be severe enough to require a transfusion. In contrast, the most common site of bleeding in late VKDB is intracranial, although cutaneous and GI bleeding may be the initial manifestation. Intracranial bleeding can cause convulsions, permanent neurologic sequelae, or death. In some patients with late VKDB, the presence of an underlying disorder may be suggested by jaundice or failure to thrive (malnutrition). Older children with vitamin K deficiency can present with bruising, mucocutaneous bleeding, or more serious bleeding.

Laboratory Findings

In patients with bleeding as a result of vitamin K deficiency, the prothrombin time (PT) is prolonged. The PT must be interpreted based on the patient's age, because it is normally prolonged in newborns (see Chapters 124.4 and 502). The partial thromboplastin time (PTT) is usually prolonged but may be normal in early deficiency. Factor VII has the shortest half-life of the coagulation factors and is the first to be affected by vitamin K deficiency, but isolated factor VII deficiency does not affect PTT. The platelet count and fibrinogen level are normal.

When there is mild vitamin K deficiency, the PT is normal, but there are elevated levels of the undercarboxylated forms of the proteins that are normally carboxylated in the presence of vitamin K. These undercarboxylated proteins are called *proteins induced by vitamin K absence* (PIVKA). Measurement of undercarboxylated factor II (PIVKA-II) can be used to detect mild vitamin K deficiency. Determination of blood vitamin K levels is less useful because of significant variation based on recent dietary intake; levels do not always reflect tissue stores.

Diagnosis and Differential Diagnosis

The diagnosis is established by the presence of a prolonged PT that corrects rapidly after administration of vitamin K, which stops the active bleeding. Other possible causes of bleeding and a prolonged PT include **disseminated intravascular coagulation (DIC)** , liver failure, and rare hereditary deficiencies of clotting factors. DIC, which is usually secondary to sepsis, is associated with thrombocytopenia, low fibrinogen, and elevated D-dimers. Severe liver disease results in decreased production of clotting factors; the PT does not fully correct with administration of vitamin K. Children with a hereditary disorder have a deficiency in a specific clotting factor (I, II, V, VII, X).

Coumarin derivatives inhibit the action of vitamin K by preventing its recycling to an active form after it functions as a cofactor for γ-glutamyl carboxylase. Bleeding can occur with overdosage of the common anticoagulant **warfarin** or with ingestion of rodent poison, which contains a coumarin derivative. High doses of salicylates also inhibit vitamin K regeneration, potentially leading to a prolonged PT and clinical bleeding.

Treatment

Infants with VKDB should receive 1 mg of parenteral vitamin K. The PT should decrease within 6 hr and normalize within 24 hr. For rapid correction in adolescents, the parenteral dose is 2.5-10 mg. In addition to vitamin K, a patient with severe, life-threatening bleeding should receive an infusion of fresh-frozen plasma (FFP), which corrects the coagulopathy rapidly. Children with vitamin K deficiency caused by malabsorption require chronic administration of high doses of oral vitamin K (2.5 mg twice/wk to 5 mg/day). Parenteral vitamin K may be necessary if oral vitamin K is ineffective.

Prevention

Administration of either oral or parenteral vitamin K soon after birth prevents early VKDB of the newborn. In contrast, a single dose of oral vitamin K does not prevent a substantial number of cases of late VKDB. However, a single intramuscular (IM) injection of vitamin K (1 mg), the current practice in the United States, is almost universally effective, except in children with severe malabsorption. This increased efficacy of the IM form is thought to be the result of a depot effect. Concerns about an association between parenteral vitamin K at birth and the later development of malignancy are unsubstantiated.

Discontinuing the offending medications before delivery can prevent VKDB attributable to maternal medications. If this is not possible, administration of vitamin K to the mother may be helpful. In addition, the neonate should receive parenteral vitamin K immediately after birth. If parenteral vitamin K does not correct the coagulopathy rapidly, the child should receive FFP.

Children who are at high risk for malabsorption of vitamin K should receive supplemental vitamin K and periodic measurement of the PT.

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CHAPTER 67

Micronutrient Mineral Deficiencies

Larry A. Greenbaum

Micronutrients include vitamins (see Chapters 61-66) and trace elements. By definition, a **trace element** is <0.01% of the body weight. Trace elements have a variety of essential functions (Table 67.1). With the exception of iron deficiency, trace element deficiency is uncommon in developed countries, but some deficiencies (iodine, zinc, selenium) are important public health problems in a number of developing countries. Because of low nutritional requirements and plentiful supply, deficiencies of some of the trace elements are extremely rare in humans and typically occur in patients receiving unusual diets or prolonged total parenteral nutrition (TPN) without adequate delivery of a specific trace element. Trace element deficiencies can also occur in children with short bowel syndrome or malabsorption. Excess intake of trace elements is uncommon but can result from environmental exposure or overuse of supplements (Table 67.1).

Table 67.1

Trace Elements

ELEMENT	PHYSIOLOGY	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	DIETARY SOURCES
Chromium	Potentiates the action of insulin	Impaired glucose tolerance, peripheral neuropathy, and encephalopathy	Unknown	Meat, grains, fruits, and vegetables
Copper	Absorbed via specific intestinal transporter Circulates bound to ceruloplasmin Enzyme cofactor (superoxide dismutase,	Microcytic anemia, osteoporosis, neutropenia, neurologic symptoms, depigmentation of hair and skin	Acute: nausea, emesis, abdominal pain, coma, and hepatic necrosis Chronic toxicity (liver and brain injury) occurs in **Wilson disease** (see	Vegetables, grains, nuts, liver, margarine, legumes, corn oil

	cytochrome oxidase, and enzymes involved in iron metabolism and connective tissue formation)		Chapter 384.2) and secondary to excess intake (see Chapter 384.3).	
Fluoride	Incorporated into bone	Dental caries (see Chapter 338)	Chronic: dental fluorosis (see Chapter 333)	Toothpaste, fluoridated water
Iodine	Component of thyroid hormone (see Chapter 580)	Hypothyroidism (see Chapters 579 and 580)	Hypothyroidism and goiter (see Chapters 581 and 583); maternal excess can cause congenital hypothyroidism and goiter (see Chapter 584.1).	Saltwater fish, iodized salt
Iron	Component of hemoglobin, myoglobin, cytochromes, and other enzymes	Anemia (see Chapter 482), decreased alertness, impaired learning	Acute (see Chapter 77): nausea, vomiting, diarrhea, abdominal pain, and hypotension Chronic excess usually secondary to hereditary disorders (see Chapter 489); causes organ dysfunction.	Meat, fortified foods Deficiency can also result from blood loss (hookworm infestation, menorrhagia)
Manganese	Enzyme cofactor	Hypercholesterolemia, weight loss, decreased clotting proteins[*]	Neurologic manifestations, cholestatic jaundice	Nuts, meat, grains, tea
Molybdenum	Enzyme cofactor (xanthine oxidase and others)	Tachycardia, tachypnea, night blindness, irritability, coma[*]	Hyperuricemia and increased risk of gout	Legumes, grains, liver
Selenium	Enzyme cofactor (prevents oxidative damage)	Cardiomyopathy (**Keshan disease**), myopathy	Nausea, diarrhea, neurologic manifestations, nail and hair changes, garlic odor	Meat, seafood, whole grains, garlic
Zinc	Enzyme cofactor Constituent of zinc-finger proteins, which regulate gene transcription	Decreased growth, dermatitis of extremities and around orifices, impaired immunity, poor wound healing, hypogonadism, diarrhea Supplements are beneficial in diarrhea and improve neurodevelopmental outcomes.	Abdominal pain, diarrhea, vomiting Can worsen copper deficiency	Meat, shellfish, whole grains, legumes, cheese

[*] These deficiency states have been reported only in case reports associated with parenteral nutrition or highly unusual diets.

For a number of reasons, children are especially susceptible to trace element deficiency. First, growth creates an increased demand for most trace elements. Second, some organs are more likely to sustain permanent damage because of trace element deficiency during childhood. The developing brain is particularly vulnerable to the consequences of certain deficiency states (iron, iodide). Similarly, adequate fluoride is most critical for dental health during childhood. Third, children, especially in the developing world, are more prone to gastrointestinal disorders that can cause trace element deficiencies because of malabsorption.

A normal diet provides adequate intake of most trace elements. However, the intake of certain trace elements varies significantly in different geographic locations. Iodide-containing food is plentiful near the ocean, but inland areas often have inadequate sources, leading to goiter and **hypothyroidism** . **Iodine deficiency** is not a problem in the United States because of the widespread use of iodized salt; however, symptomatic iodine deficiency (goiter, hypothyroidism) is common in many developing countries. Selenium content of the soil and consequently of food is also quite variable. Dietary **selenium deficiency** (associated with cardiomyopathy) occurs in certain locations, such as some parts of China.

The consequences of severe isolated trace mineral deficiency are illustrated in certain genetic disorders. The manifestations of **Menkes disease** are caused by a mutation in the gene coding for a protein that facilitates intestinal copper absorption (see Chapters 617.5 and 682). This mutation results in severe copper deficiency; subcutaneous copper is an effective treatment. The recessive disorder **acrodermatitis enteropathica** is secondary to malabsorption of zinc (see Chapter 691). These patients respond dramatically to zinc supplementation.

Children can have apparently asymptomatic deficiencies of certain trace elements but still benefit from supplementation. As an example, zinc is highly effective in treating children before or during diarrheal illnesses in the developing world.

Zinc deficiency is quite common in the developing world and is often associated with malnutrition or other micronutrient deficiencies (iron). Chronic zinc deficiency is associated with dwarfism, hypogonadism, dermatitis, and T-cell immunodeficiency. Diets rich in phytates bind zinc, impairing its absorption. Zinc supplementation in at-risk children reduces the incidence and severity of diarrhea, pneumonia, and possibly malaria. In developing countries, children who have diarrhea may benefit from zinc supplementation, especially if there is underlying malnutrition.

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PART VI

Fluid and Electrolyte Disorders

OUTLINE

Chapter 68 Electrolyte and Acid-Base Disorders
Chapter 69 Maintenance and Replacement Therapy
Chapter 70 Deficit Therapy
Chapter 71 Fluid and Electrolyte Treatment of Specific Disorders

CHAPTER 68

Electrolyte and Acid-Base Disorders

68.1

Composition of Body Fluids

Larry A. Greenbaum

Keywords

total body water
fluid compartments
edema
intracellular fluid
extracellular fluid
osmolality
hyperglycemia
pseudohyponatremia
point-of-care testing

Total Body Water

Total body water (TBW) as a percentage of body weight varies with age (Fig. 68.1). The fetus has very high TBW, which gradually decreases to approximately 75% of birthweight for a term infant. Premature infants have higher TBW than term infants. During the 1st yr of life, TBW decreases to approximately 60% of body weight and remains at this level until puberty. At puberty, the fat content of females increases more than that in males, who acquire more muscle mass than females. Because fat has very low water content and muscle has high water content, by the end of puberty, TBW in males remains at 60%, but TBW in females decreases to approximately 50% of body weight. The high fat content in overweight children causes a decrease in TBW as a percentage of body weight. During dehydration, TBW decreases and thus is a smaller percentage of body weight.

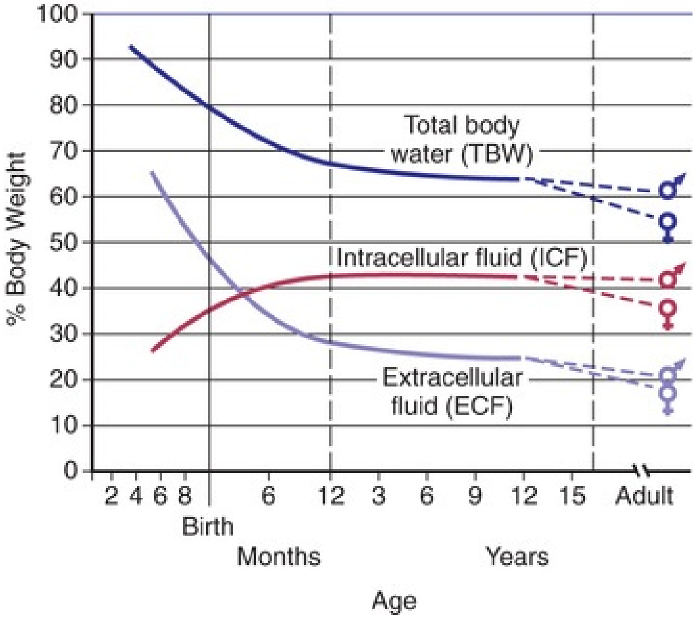

FIG. 68.1 Total body water, intracellular fluid, and extracellular fluid as a percentage of body weight as a function of age. (From Winters RW: Water and electrolyte regulation. In Winters RW, editor: *The body fluids in pediatrics* , Boston, 1973, Little, Brown.)

Fluid Compartments

TBW is divided between 2 main compartments: **intracellular fluid (ICF)** and **extracellular fluid (ECF)** . In the fetus and newborn, the ECF volume is larger than the ICF volume (Fig. 68.1). The normal postnatal diuresis causes an immediate decrease in the ECF volume. This is followed by continued expansion of the ICF volume, which results from cellular growth. By 1 yr of age, the ratio of ICF volume to ECF volume approaches adult levels. The ECF volume is approximately 20–25% of body weight, and the ICF volume is approximately 30–40% of body weight, close to twice the ECF volume (Fig. 68.2). With puberty, the increased muscle mass of males causes them to have a higher ICF volume than females. There is no significant difference in the ECF volume between postpubertal females and males.

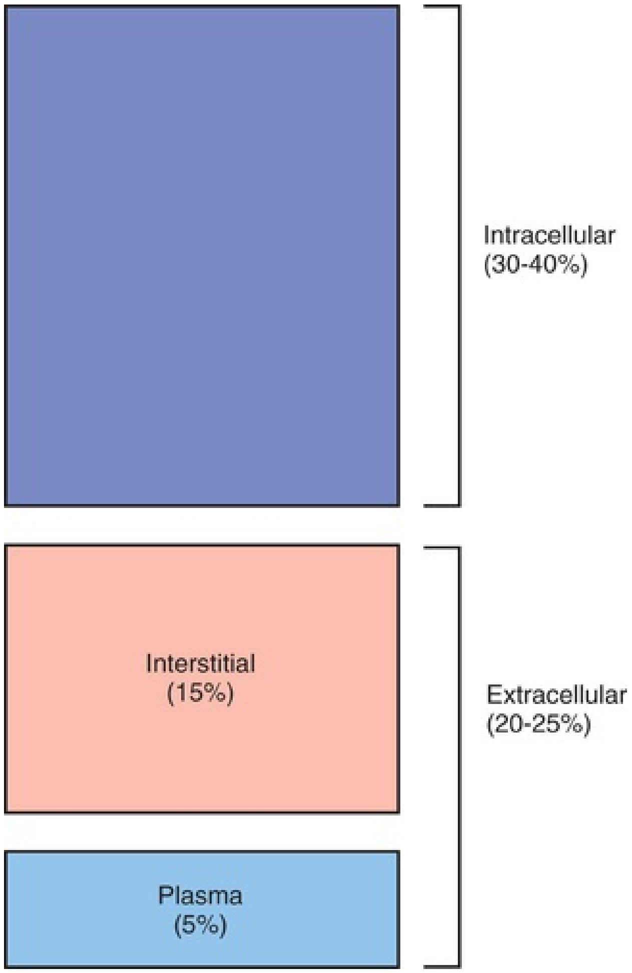

FIG. 68.2 Compartments of total body water, expressed as percentages of body weight, in an older child or adult.

The ECF is further divided into the plasma water and the interstitial fluid (see Fig. 68.2). The *plasma water* is 5% of body weight. The blood volume, given a hematocrit of 40%, is usually 8% of body weight, although it is higher in newborns and young infants; in premature newborns it is approximately 10% of body weight. The volume of plasma water can be altered by pathologic conditions, including dehydration, anemia, polycythemia, heart failure, abnormal plasma osmolality, and hypoalbuminemia. The *interstitial fluid*, normally 15% of body weight, can increase dramatically in diseases associated with edema, such as heart failure, protein-losing enteropathy, liver failure, nephrotic syndrome, and sepsis. An increase in interstitial fluid also occurs in patients with ascites or pleural effusions.

There is a delicate equilibrium between the intravascular fluid and the interstitial fluid. The balance between hydrostatic and oncotic forces regulates the intravascular volume, which is critical for proper tissue perfusion. The *intravascular fluid* has a higher concentration of albumin than the interstitial fluid, and the consequent oncotic force draws water into the intravascular space. The maintenance of this gradient depends on the limited permeability of albumin across the capillaries. The hydrostatic pressure of the intravascular space, which is caused by the pumping action of the heart, drives fluid out of the intravascular space. These forces favor movement into the interstitial space at the arterial ends of the capillaries. The decreased hydrostatic forces and increased oncotic forces, which result from the dilutional increase in albumin concentration, cause movement of fluid into the venous ends of the capillaries. Overall, there is usually a net movement of fluid out of the intravascular space to the interstitial space, but this fluid is returned to the circulation via the *lymphatics* .

An imbalance in these forces may cause expansion of the interstitial volume at the expense of the intravascular volume. In children with hypoalbuminemia, the decreased oncotic pressure of the intravascular fluid contributes to the development of **edema** . Loss of fluid from the intravascular space may compromise the intravascular volume, placing the child at risk for inadequate blood flow to vital organs. This is especially likely in diseases in which capillary leak occurs because the loss of albumin from the intravascular space is associated with an increase in the albumin concentration in the interstitial space, further compromising the oncotic forces that normally maintain intravascular volume. In contrast, with **heart failure** , there is an increase in venous hydrostatic pressure from expansion of the intravascular volume, which is caused by impaired pumping by the heart, and the increase in venous pressure causes fluid to move from the intravascular space to the interstitial space. Expansion of the intravascular volume and increased intravascular pressure also cause the edema that occurs with acute glomerulonephritis.

Electrolyte Composition

The composition of the solutes in the ICF and ECF are very different (Fig. 68.3). **Sodium** (Na^+) and **chloride** (Cl^-) are the dominant cation and anion, respectively, in the ECF. The sodium and chloride concentrations ([Na^+], [Cl^-]) in the ICF are much lower. **Potassium** (K^+) is the most abundant cation in the ICF, and its concentration ([K^+]) within the cells is approximately 30 times higher than in the ECF. Proteins, organic anions, and phosphate are the most plentiful anions in the ICF. The dissimilarity between the anions in the ICF and the ECF is largely determined by the presence of intracellular molecules that do not cross the cell membrane, the barrier separating the ECF and the ICF. In contrast, the difference in the distribution of cations—Na^+ and K^+ —relies on activity of the Na^+ ,K^+ -adenosine triphosphatase (ATPase) pump and membrane ion channels.

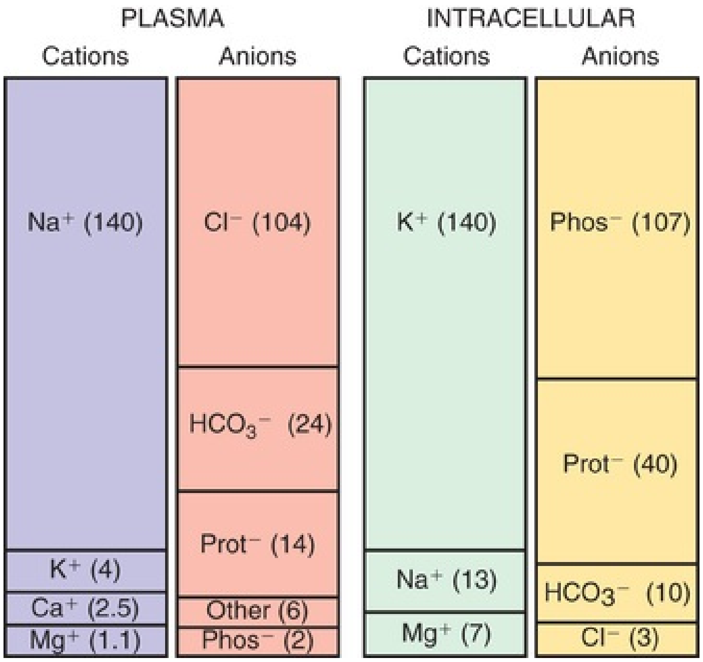

FIG. 68.3 Concentrations of the major cations and anions in the intracellular space and the plasma, expressed in mEq/L.

The difference in the electrolyte compositions of the ECF and the ICF has important ramifications in the evaluation and treatment of electrolyte disorders. Serum concentrations of electrolytes—[Na^+], [K^+], and [Cl^-]—do not always reflect total body content. Intracellular [K^+] is much higher than the serum concentration. A shift of K^+ from the **intracellular space (ICS)** can maintain a normal or even an elevated serum [K^+] despite massive losses of K^+ from the ICS. This effect is seen in diabetic ketoacidosis, in which significant K^+ depletion is masked by transmembrane shift of K^+ from the ICF to the ECF. Therefore, for K^+ and phosphorus, electrolytes with a high intracellular concentration, serum level may not reflect total body content. Similarly, the serum **calcium** concentration ([Ca^{2+}]) does not reflect total body content of Ca^{2+} , which is largely contained in bone and teeth (see Chapter 64).

Osmolality

The ICF and the ECF are in **osmotic equilibrium** because the cell membrane is permeable to water. If the osmolality in 1 compartment changes, then water movement leads to a rapid equalization of osmolality, with a shift of water between the ICS and **extracellular space (ECS)** . Clinically, the primary process is usually a change in the osmolality of the ECF, with resultant shift of water into the ICF if ECF osmolality decreases, or vice versa if ECF osmolality increases. The *ECF osmolality* can be determined and *usually equals ICF osmolality* . **Plasma osmolality** , normally 285-295 mOsm/kg, is measured by the degree of freezing-point depression. The plasma osmolality can also be *estimated* by a calculation based on the following formula:

$$\text{Osmolality} = 2\times[\text{Na}]+[\text{glucose}]/18+[\text{BUN}]/2.8$$

Glucose and blood urea nitrogen (BUN) are reported in mg/dL. Division of these values by 18 and 2.8, respectively, converts the units into mmol/L. Multiplication of the [Na^+] value by 2 accounts for its accompanying anions, principally Cl^- and bicarbonate. The calculated osmolality is usually slightly lower than measured osmolality.

Urea is not only confined to the ECS because it readily crosses the cell membrane, and its intracellular concentration approximately equals its extracellular concentration. Whereas an elevated [Na^+] causes a shift of water from the ICS, with **uremia** there is no osmolar gradient between the two compartments and consequently no movement of water. The only exception is during **hemodialysis** , when the decrease in extracellular urea is so rapid that intracellular urea does not have time to equilibrate. This **disequilibrium**

syndrome may result in shift of water into brain cells and leads to severe symptoms. Ethanol, because it freely crosses cell membranes, is another ineffective osmole. In the case of glucose, the effective osmolality can be calculated as follows:

$$\text{Effective osmolality} = 2\times[\text{Na}]+[\text{glucose}]/18$$

The *effective osmolality* (also called the *tonicity*) determines the osmotic force that is mediating the shift of water between the ECF and the ICF.

Hyperglycemia causes an increase in the plasma osmolality because it is not in equilibrium with the ICS. During hyperglycemia, there is shift of water from the ICS to the ECS. This shift causes dilution of the Na^+ in the ECS, causing hyponatremia despite elevated plasma osmolality. The magnitude of this effect can be calculated as follows:

$$[\text{Na}]_{\text{corrected}} = [\text{Na}]_{\text{measured}} + 1.6\times([\text{glucose}]-100\ \text{mg/dL})/100$$

where $[\text{Na}]_{\text{measured}}$ = Na^+ concentration measured by the clinical laboratory and $[\text{Na}]_{\text{corrected}}$ = corrected Na^+ concentration (the Na^+ concentration if the glucose concentration were normal and its accompanying water moved back into the cells). The $[\text{Na}]_{\text{corrected}}$ is the more reliable indicator of the ratio of total body Na^+ to TBW, the usual determinant of the $[Na^+]$.

Normally, measured osmolality and calculated osmolality are within 10 mOsm/kg. However, there are some clinical situations in which this difference does not occur. The presence of **unmeasured osmoles** causes measured osmolality to be significantly elevated in comparison with the calculated osmolality. An **osmolal gap** is present when the difference between measured osmolality exceeds calculated osmolality by >10 mOsm/kg. Examples of unmeasured osmoles include ethanol, ethylene glycol, methanol, sucrose, sorbitol, and mannitol. These substances increase measured osmolality but are not part of the equation for calculating osmolality. The presence of an osmolal gap is a clinical clue to the presence of unmeasured osmoles and may be diagnostically useful when there is clinical suspicion of poisoning with methanol or ethylene glycol.

Pseudohyponatremia is a second situation in which there is discordance between measured osmolality and calculated osmolality. Lipids and proteins are the solids of the serum. In patients with elevated serum lipids or proteins, the water content of the serum decreases because water is displaced by the larger amounts of solids. Some instruments measure [Na^+] by determining the amount of Na^+ per liter of serum, including the solid component. When the solid component increases, there is a decrease in [Na^+] per liter of serum, despite a normal concentration when based on the amount of Na^+ per liter of serum water. *It is the concentration of Na^+ in serum water that is physiologically relevant.* A similar problem occurs when using instruments that require dilution of the sample prior to measurement of Na^+ (indirect potentiometry). In both situations, the plasma osmolality is normal despite the presence of pseudohyponatremia, because the method for measuring osmolality is not appreciably influenced by the percentage of serum that is composed of lipids and proteins. Pseudohyponatremia is diagnosed by the finding of a normal measured plasma osmolality despite hyponatremia. This laboratory artifact does not occur if the [Na^+] in water is measured directly with an ion-specific electrode, as with arterial blood gas (ABG) analyzers. **Pseudohypernatremia** may occur in patients with very low levels of serum proteins by a similar mechanism.

When there are no unmeasured osmoles and pseudohyponatremia is not a concern, the calculated osmolality provides an accurate estimate of the plasma osmolality. Measurement of plasma osmolality is useful for detecting or monitoring unmeasured osmoles and confirming the presence of true hyponatremia. Whereas many children with high plasma osmolality are dehydrated—as seen with hypernatremic dehydration or diabetic ketoacidosis—high osmolality does not always equate with dehydration. A child with salt poisoning or uremia has an elevated plasma osmolality but may be volume-overloaded.

Point-of-Care Testing

Point-of-care (POC) testing offers a number of advantages, including rapid turnaround and usually smaller blood sample volume required. POC devices may provide more accurate results in certain situations, such as pseudohyponatremia (see earlier) and pseudohyperkalemia (see Chapter 68.4). However, the agreement between POC and the laboratory is variable, and thus caution is needed when interpreting results. Because of bias, POC and laboratory results should not be used on an alternating basis when following critical trends (e.g., during correction of hypernatremia or hyponatremia; see Chapter 68.3).

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Composition of Body Fluids

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68.2

Regulation of Osmolality and Volume

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Keywords

volume overload
sodium
water
aldosterone
renin-angiotensin system
salt craving
intravascular volume
osmolality
diabetes insipidus
syndrome of inappropriate antidiuretic hormone
SIADH
free water
osmotic diuresis
polydipsia

The regulation of plasma **osmolality** and the intravascular **volume** is controlled by independent systems for water balance, which determines osmolality, and sodium balance, which determines volume status. Maintenance of normal osmolality depends on control of water balance. Control of volume status depends on regulation of sodium balance. When present, volume depletion takes precedence over regulation of osmolality, and retention of water contributes to the maintenance of intravascular volume.

Regulation of Osmolality

The plasma osmolality is tightly regulated and maintained at 285-295 mOsm/kg.

Modification of water intake and excretion maintains normal plasma osmolality. In the steady state the combination of water intake and water produced by the body from oxidation balances water losses from the skin, lungs, urine, and gastrointestinal (GI) tract. Only water intake and urinary losses can be regulated.

Osmoreceptors in the hypothalamus sense plasma osmolality (see Chapter 572). An elevated effective osmolality leads to secretion of **antidiuretic hormone (ADH)** by neurons in the supraoptic and paraventricular nuclei in the hypothalamus. The axons of these neurons terminate in the posterior pituitary. Circulating ADH binds to its V_2 receptors in the collecting duct cells of the kidney, and causes insertion of water channels (aquaporin-2) into the renal collecting duct cells. This produces increased permeability to water, permitting resorption of water into the hypertonic renal medulla. Urine concentration increases and water excretion decreases. Urinary water losses cannot be eliminated because there is obligatory excretion of urinary solutes, such as urea and sodium. The regulation of ADH secretion is tightly linked to plasma osmolality, responses being detectable with a 1% change in osmolality. ADH secretion virtually disappears when plasma osmolality is low, allowing excretion of maximally dilute urine. The resulting loss of free water (i.e., water without Na^+) corrects plasma osmolality. ADH secretion is not an all-or-nothing response; there is a graded adjustment as the osmolality changes.

Water intake is regulated by hypothalamic osmoreceptors, which stimulate thirst when the serum osmolality increases. Thirst occurs with a small increase in the serum osmolality. *Control of osmolality is subordinate to maintenance of an adequate intravascular volume.* When volume depletion is present, both ADH secretion and thirst are stimulated, regardless of the plasma osmolality. The sensation of thirst requires moderate volume depletion but only a 1–2% change in the plasma osmolality.

A number of conditions can limit the kidney's ability to excrete adequate water to correct low plasma osmolality. In the **syndrome of inappropriate antidiuretic hormone (SIADH)** , ADH continues to be produced despite a low plasma osmolality (see Chapters 68.3 and 575).

The glomerular filtration rate (GFR) affects the kidney's ability to eliminate water. With a decrease in the GFR, less water is delivered to the collecting duct, limiting the amount of water that can be excreted. The impairment in the GFR must be quite significant to limit the kidney's ability to respond to an excess of water.

The **minimum urine osmolality** is approximately 30-50 mOsm/kg. This places an upper limit on the kidney's ability to excrete water; sufficient solute must be present to permit water loss. Massive water intoxication may exceed this limit, whereas a lesser amount of water is necessary in the child with a diet that has very little solute. This can produce severe hyponatremia in children who receive little salt and have minimal urea production as a result of inadequate protein intake. Volume depletion is an extremely important cause of decreased water loss by the kidney despite a low plasma osmolality. This “appropriate” secretion of ADH occurs because volume depletion takes precedence over the osmolality in the regulation of ADH.

The **maximum urine osmolality** is approximately 1,200 mOsm/kg. The obligatory solute losses dictate the minimum volume of urine that must be produced, even when maximally concentrated. Obligatory water losses increase in patients with high salt intake or high urea losses, as may occur after relief of a urinary obstruction or during recovery from acute kidney injury. An increase in urinary solute and thus water losses occurs with an **osmotic diuresis** , which occurs classically from glycosuria in diabetes mellitus as well as iatrogenically after mannitol administration. There are developmental changes in the kidney's ability to concentrate the urine. The maximum urine osmolality in a newborn, especially a premature newborn, is less than that in an older infant or child. This limits the ability to conserve water and makes such a patient more vulnerable to hypernatremic dehydration. Very high fluid intake, as seen with **psychogenic polydipsia** , can dilute the high osmolality in the renal medulla, which is necessary for maximal urinary concentration. If fluid intake is restricted in patients with this condition, the kidney's ability to concentrate the urine may be somewhat impaired, although this defect corrects after a few days without polydipsia. This may also occur during the initial treatment of central diabetes insipidus with desmopressin acetate; the renal medulla takes time to achieve its normal maximum osmolality.

Regulation of Volume

An appropriate intravascular volume is critical for survival; both volume depletion and volume overload may cause significant morbidity and mortality. Because sodium is the principal extracellular cation and is restricted to the ECF, adequate body sodium is necessary for maintenance of intravascular volume. The principal extracellular anion, Cl^- , is also necessary, but for simplicity, Na^+ balance is considered the main regulator of volume status because body content of sodium and that of chloride usually change proportionally, given the need for equal numbers of cations and anions. In some situations, Cl^- depletion is considered the dominant derangement causing volume depletion (metabolic alkalosis with volume depletion).

The kidney determines sodium balance because there is little homeostatic control of sodium intake, even though **salt craving** does occasionally occur, typically in children with chronic renal salt loss. The kidney regulates Na^+ balance by altering the percentage of filtered Na^+ that is resorbed along the nephron. Normally, the kidney excretes <1% of the Na^+ filtered at the glomerulus. In the absence of disease, extrarenal losses and urinary output match intake, with the kidney having the capacity to adapt to large variations in sodium intake. When necessary, urinary sodium excretion can be reduced to virtually undetectable levels or increased dramatically.

The most important determinant of renal Na^+ excretion is the volume status of the child; it is the effective intravascular volume that influences urinary Na^+ excretion. The *effective intravascular volume* is the volume status that is sensed by the body's regulatory mechanisms. Heart failure is a state of volume overload, but the effective intravascular volume is low because poor cardiac function prevents adequate perfusion of the kidneys and other organs. This explains the avid renal Na^+ retention often present in patients with heart failure.

The **renin-angiotensin system** is an important regulator of renal Na^+ excretion. The juxtaglomerular apparatus produces renin in response to decreased effective intravascular volume. Specific stimuli for renin release are decreased perfusion pressure in the afferent arteriole of the glomerulus, decreased delivery of sodium to the distal nephron, and β_1 -adrenergic agonists, which increase in response to intravascular volume depletion. Renin, a proteolytic enzyme, cleaves angiotensinogen, producing angiotensin I. Angiotensin-converting enzyme (ACE) converts angiotensin I into angiotensin II. The actions of angiotensin II include direct stimulation of the proximal tubule to increase sodium resorption and stimulation of the adrenal gland to increase aldosterone secretion. Through its actions in the distal nephron—specifically, the late distal convoluted tubule and the collecting duct—aldosterone increases sodium resorption. Aldosterone also stimulates potassium excretion, increasing urinary losses. Along with decreasing urinary loss of sodium, angiotensin II acts as a vasoconstrictor, which helps maintain adequate blood pressure in the presence of volume depletion.

Volume expansion stimulates the synthesis of **atrial natriuretic peptide (ANP)** , which is produced by the atria in response to atrial wall distention. Along with increasing the GFR, ANP inhibits Na^+ resorption in the medullary portion of the collecting duct, facilitating an increase in urinary Na^+ excretion.

Volume overload occurs when Na^+ intake exceeds output. Children with kidney failure have impaired ability to excrete Na^+ . The GFR is low at birth, limiting a newborn's ability to excrete an Na^+ load. In other situations, there is a loss of the appropriate regulation of renal Na^+ excretion. This loss occurs in patients with excessive aldosterone, as seen in primary hyperaldosteronism or renal artery stenosis, where excess renin production leads to high aldosterone levels. In acute glomerulonephritis, even without significantly reduced GFR, the normal intrarenal mechanisms that regulate Na^+ excretion malfunction, causing excessive renal retention of Na^+ and volume overload.

Renal retention of Na^+ occurs during volume depletion, but this appropriate response causes the severe excess in total body Na^+ that is present in heart failure, liver failure, nephrotic syndrome, and other causes of hypoalbuminemia. In these diseases the effective intravascular volume is decreased, causing the kidney and the various regulatory systems to respond, leading to renal Na^+ retention and edema formation.

Volume depletion usually occurs when Na^+ losses exceed intake. The most common etiology in children is gastroenteritis. Excessive losses of sodium may also occur from the skin in children with burns, in sweat from patients with cystic fibrosis, or after vigorous exercise. Inadequate intake of Na^+ is uncommon except in neglect, in famine, or with an inappropriate choice of liquid diet in a child who cannot take solids. Urinary Na^+ wasting may occur in a range of renal diseases, from renal dysplasia to tubular disorders, such as Bartter syndrome. The neonate, especially if premature, has a mild impairment in the ability to conserve Na^+ . Iatrogenic renal Na^+ wasting takes place during diuretic therapy. Renal Na^+ loss occurs as a result of derangement in the normal regulatory systems. An absence of aldosterone, seen most frequently in children with **congenital adrenal hyperplasia** caused by 21-hydroxylase deficiency, causes sodium wasting (see Chapter 594).

Isolated disorders of water balance can affect volume status and Na^+ balance. Because the cell membrane is permeable to water, changes in TBW influence both the extracellular volume and the intracellular volume. In isolated water loss, as occurs in diabetes insipidus, the impact is greater on the ICS because it has a greater volume than the ECS. Thus, compared with other types of dehydration, hypernatremic dehydration has less impact on plasma volume; most of the fluid loss comes from the ICS. Yet, significant water loss eventually affects intravascular volume and will stimulate renal Na^+ retention, even if total body Na^+ content is normal. Similarly, with acute water intoxication or SIADH, there is an excess of TBW, but most is in the ICS. However, there is some effect on the intravascular volume, which causes renal excretion of Na^+ . Children with SIADH or water intoxication have high urine Na^+ concentration, despite hyponatremia. This finding reinforces the concept of independent control systems for water and Na^+ , but the 2 systems interact when pathophysiologic processes dictate, and control of effective intravascular volume always takes precedence over control of osmolality.

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Regulation of Osmolality and Volume

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68.3

Sodium

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Keywords

- renal salt wasting
- hyponatremia
- hypernatremia
- dehydration
- syndrome of inappropriate antidiuretic hormone
- SIADH
- pseudohyponatremia
- osmolality
- salt poisoning
- sweat
- aldosterone
- free water
- water balance
- diabetes insipidus
- cerebral edema
- seizures
- vaptan

Sodium Metabolism

Body Content and Physiologic Function

Sodium is the dominant cation of the ECF (see Fig. 68.3), and it is the principal determinant of extracellular osmolality. Na^+ is therefore necessary for the maintenance of intravascular volume. Less than 3% of Na^+ is intracellular. More than 40% of total body Na^+ is in bone; the remainder is in the interstitial and intravascular spaces. The low intracellular [Na^+], approximately 10 mEq/L, is maintained by Na^+ ,K^+ -ATPase, which exchanges intracellular Na^+ for extracellular K^+ .

Sodium Intake

A child's diet determines the amount of Na^+ ingested—a predominantly cultural determination in older children. An occasional child has salt craving because of an underlying salt-wasting renal disease or adrenal insufficiency. Children in the United States tend to have very high salt intakes because their diets include a large amount of “junk” food or fast food. Infants receive sodium from breast milk (approximately 7 mEq/L) and formula (7-13 mEq/L, for 20 calorie/oz formula).

Sodium is readily absorbed throughout the GI tract. Mineralocorticoids increase sodium transport into the body, although this effect has limited clinical significance. The presence of glucose enhances sodium absorption owing to the presence of a co-transport system. This is the rationale for including sodium and glucose in oral rehydration solutions (see Chapter 366).

Sodium Excretion

Sodium excretion occurs in stool and sweat, but the kidney regulates Na^+ balance and is the principal site of Na^+ excretion. There is some Na^+ loss in stool, but it is minimal unless diarrhea is present. Normally, sweat has 5-40 mEq/L of sodium. Sweat Na^+ concentration is increased in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism. The higher sweat losses in these conditions may cause or contribute to Na^+ depletion.

Sodium is unique among electrolytes because water balance, not Na^+ balance, usually determines its concentration. When the $[Na^+]$ increases, the resultant higher plasma osmolality causes increased thirst and increased secretion of ADH, which leads to renal conservation of water. Both these mechanisms increase the water content of the body, and the $[Na^+]$ returns to normal. During hyponatremia, the decrease in plasma osmolality stops ADH secretion, and consequent renal water excretion leads to an increase in the $[Na^+]$. Even though water balance is usually regulated by osmolality, volume depletion does stimulate thirst, ADH secretion, and renal conservation of water. Volume depletion takes precedence over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia.

The excretion of Na^+ by the kidney is not regulated by the plasma osmolality. The patient's effective plasma volume determines the amount of sodium in the urine. This is mediated by a variety of regulatory systems, including the renin-angiotensin-aldosterone system and intrarenal mechanisms. In hyponatremia or hypernatremia, the underlying pathophysiology determines the amount of urinary Na^+, not the serum [Na^+].

Hypernatremia

Hypernatremia is a [Na^+] >145 mEq/L, although it is sometimes defined as >150 mEq/L. Mild hypernatremia is fairly common in children, especially among infants with gastroenteritis. Hypernatremia in hospitalized patients may be iatrogenic—caused by inadequate water administration or, less often, by excessive Na^+ administration. Moderate or severe hypernatremia has significant morbidity because of the underlying disease, the effects of hypernatremia on the brain, and the risks of overly rapid correction.

Etiology and Pathophysiology

There are 3 basic mechanisms of hypernatremia (Table 68.1). *Sodium intoxication* is frequently iatrogenic in a hospital setting as a result of correction of metabolic acidosis with sodium bicarbonate. Baking soda, a putative home remedy for upset stomach, is another source of sodium bicarbonate; the hypernatremia is accompanied by a profound metabolic alkalosis. In hyperaldosteronism, there is renal retention of sodium and resultant hypertension; hypernatremia may not be present or is usually mild.

Table 68.1

Causes of Hypernatremia

Excessive Sodium

- Improperly mixed formula
- Excess sodium bicarbonate
- Ingestion of seawater or sodium chloride
- Intentional salt poisoning (child abuse or Munchausen syndrome by proxy)
- Intravenous hypertonic saline
- Hyperaldosteronism

Water Deficit

Nephrogenic Diabetes Insipidus

Acquired
X-linked (OMIM 304800)
Autosomal recessive (OMIM 222000)
Autosomal dominant (OMIM 125800)

Central Diabetes Insipidus

Acquired
Autosomal recessive (OMIM 125700)
Autosomal dominant (OMIM 125700)
Wolfram syndrome (OMIM 222300/598500)

Increased Insensible Losses

Premature infants
Radiant warmers
Phototherapy
Inadequate intake:
    Ineffective breastfeeding
    Child neglect or abuse
    Adipsia (lack of thirst)

Water and Sodium Deficits

Gastrointestinal Losses

Diarrhea
Emesis/nasogastric suction
Osmotic cathartics (lactulose)

Cutaneous Losses

Burns
Excessive sweating

Renal Losses

Osmotic diuretics (mannitol)
Diabetes mellitus
Chronic kidney disease (dysplasia and obstructive uropathy)
Polyuric phase of acute tubular necrosis
Postobstructive diuresis

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

The classic causes of hypernatremia from a *water deficit* are **nephrogenic** and **central diabetes insipidus** (see Chapters 548 and 574). Hypernatremia develops in diabetes insipidus only if the patient does not have access to water or cannot drink adequately because of immaturity, neurologic impairment, emesis, or anorexia. Infants are at high risk because of their inability to control their own water intake. Central diabetes insipidus and the genetic forms of nephrogenic diabetes insipidus typically cause massive urinary water losses and very dilute urine. The water losses are less dramatic, and the urine often has the same osmolality as plasma when nephrogenic diabetes insipidus is secondary to intrinsic renal disease (obstructive uropathy, renal dysplasia, sickle cell disease).

The other causes of a water deficit are also secondary to an imbalance between losses and intake. Newborns, especially if premature, have high insensible water losses. Losses are further increased if the infant is placed under a radiant warmer or with the use of phototherapy for hyperbilirubinemia. The renal concentrating mechanisms are not optimal at birth, providing an additional source of water loss. Ineffective breastfeeding, often in a primiparous mother, can cause severe hypernatremic dehydration. **Adipsia** , the absence of thirst, is usually secondary to damage to the hypothalamus, such as from trauma, tumor, hydrocephalus, or histiocytosis. Primary adipsia is rare.

When hypernatremia occurs in conditions with *deficits of sodium and water*, the water deficit exceeds the sodium deficit. This occurs only if the patient is unable to ingest adequate water. Diarrhea results in depletion of both Na^+ and water. Because diarrhea is hypotonic—typical Na^+ concentration of 35-65 mEq/L—water losses exceed Na^+ losses, potentially leading to hypernatremia. Most children with gastroenteritis do not have hypernatremia because they drink enough hypotonic fluid to compensate for stool water losses (see Chapter 366). Fluids such as water, juice, and formula are more hypotonic than the stool losses, allowing correction of the water deficit and potentially even causing hyponatremia. Hypernatremia is most likely to occur in the child with diarrhea who has inadequate intake because of emesis, lack of access to water, or anorexia.

Osmotic agents, including mannitol, and glucose in **diabetes mellitus** , cause excessive renal losses of water and Na^+ . Because the urine is hypotonic (Na^+ concentration of approximately 50 mEq/L) during an osmotic diuresis, water loss exceeds Na^+ loss, and hypernatremia may occur if water intake is inadequate. Certain chronic kidney diseases, such as renal dysplasia and obstructive uropathy, are associated with tubular dysfunction, leading to excessive losses of water and Na^+ . Many children with such diseases have disproportionate water loss and are at risk for hypernatremic dehydration, especially if gastroenteritis supervenes. Similar mechanisms occur during the polyuric phase of acute kidney injury and after relief of urinary obstruction (postobstructive diuresis). Patients with either condition may have an osmotic diuresis from urinary losses of urea and an inability to conserve water because of tubular dysfunction.

Essential hypernatremia is rare in children and is thought to occur with injury to the hypothalamic-posterior pituitary axis. It is euvolemic, nonhypertensive, and associated with hypodipsia, possibly related to a reset osmol sensor.

Clinical Manifestations

Most children with hypernatremia are dehydrated and show the typical clinical signs and symptoms (see Chapter 70). Children with hypernatremic dehydration tend to have better preservation of intravascular volume because of the shift of water from the ICS to the ECS. This shift maintains blood pressure and urine output and allows hypernatremic infants to be less symptomatic initially and potentially to become more dehydrated before medical attention is sought. Breastfed infants with hypernatremia are often profoundly dehydrated, with failure to thrive (malnutrition). Probably because of intracellular water loss, the pinched abdominal skin of a dehydrated, hypernatremic infant has a “doughy” feel.

Hypernatremia, even without dehydration, causes central nervous system

(CNS) symptoms that tend to parallel the degree of Na^+ elevation and the acuity of the increase. Patients are irritable, restless, weak, and lethargic. Some infants have a high-pitched cry and hyperpnea. Alert patients are very thirsty, even though nausea may be present. Hypernatremia may cause fever, although many patients have an underlying process that contributes to the fever. Hypernatremia is associated with hyperglycemia and mild hypocalcemia; the mechanisms are unknown. Beyond the sequelae of dehydration, there is no clear direct effect of hypernatremia on other organs or tissues, except the brain.

Brain hemorrhage is the most devastating consequence of untreated hypernatremia. As the extracellular osmolality increases, water moves out of brain cells, leading to a decrease in brain volume. This decrease can result in tearing of intracerebral veins and bridging blood vessels as the brain moves away from the skull and the meninges. Patients may have subarachnoid, subdural, and parenchymal hemorrhages. Seizures and coma are possible sequelae of the hemorrhage, although seizures are more common during correction of hypernatremia. The cerebrospinal fluid protein is often elevated in infants with significant hypernatremia, probably because of leakage from damaged blood vessels. Neonates, especially if premature, seem especially vulnerable to hypernatremia and excessive sodium intake. There is an association between rapid or hyperosmolar sodium bicarbonate administration and the development of intraventricular hemorrhages in neonates. Even though central pontine myelinolysis is classically associated with overly rapid correction of hyponatremia, both central pontine and extrapontine myelinolysis can occur in children with hypernatremia (see Treatment). Thrombotic complications occur in severe hypernatremic dehydration, including stroke, dural sinus thrombosis, peripheral thrombosis, and renal vein thrombosis. This is secondary to dehydration and possibly hypercoagulability associated with hypernatremia.

Diagnosis

The etiology of hypernatremia is usually apparent from the history. Hypernatremia resulting from water loss occurs only if the patient does not have access to water or is unable to drink. In the absence of dehydration, it is important to ask about sodium intake. Children with excess salt intake do not have signs of dehydration, unless another process is present. Severe Na^+ intoxication causes signs of volume overload, such as pulmonary edema and weight gain. **Salt poisoning** is associated with an elevated fractional excretion of

Na^+ , whereas hypernatremic dehydration causes a low fractional excretion of Na^+ . Gastric sodium concentrations are often elevated in salt poisoning. In hyperaldosteronism, hypernatremia is usually mild or absent and is associated with edema, hypertension, hypokalemia, and metabolic alkalosis.

When there is isolated water loss, the signs of volume depletion are usually less severe initially because much of the loss is from the ICS. When pure water loss causes signs of dehydration, the hypernatremia and water deficit are usually severe. In the child with renal water loss, either central or nephrogenic diabetes insipidus, the urine is inappropriately dilute and urine volume is not low. The urine is maximally concentrated and urine volume is low if the losses are extrarenal or caused by inadequate intake. With extrarenal causes of loss of water, the urine osmolality should be >1,000 mOsm/kg. When diabetes insipidus is suspected, the evaluation may include measurement of ADH and a water deprivation test, including a trial of desmopressin acetate (synthetic ADH analog) to differentiate between nephrogenic diabetes insipidus and central diabetes insipidus (see Chapters 548 and 574). A water-deprivation test is unnecessary if the patient has simultaneous documentation of hypernatremia and poorly concentrated urine (osmolality lower than that of plasma). In children with central diabetes insipidus, administration of desmopressin acetate increases the urine osmolality above the plasma osmolality, although maximum osmolality does not occur immediately because of the decreased osmolality of the renal medulla as a result of the chronic lack of ADH. In children with nephrogenic diabetes insipidus, there is no response to desmopressin acetate. Hypercalcemia or hypokalemia may produce a nephrogenic diabetes insipidus–like syndrome.

With combined Na^+ and water deficits, analysis of the urine differentiates between renal and nonrenal etiologies. When the losses are extrarenal, the kidney responds to volume depletion with low urine volume, concentrated urine, and Na^+ retention (urine [Na^+] <20 mEq/L, fractional excretion of Na^+ <1%). With renal causes, the urine volume is not appropriately low, the urine is not maximally concentrated, and the urine [Na^+] may be inappropriately elevated.

Treatment

As hypernatremia develops, the brain generates **idiogenic osmoles** to increase the intracellular osmolality and prevent the loss of brain water. This mechanism is not instantaneous and is most prominent when hypernatremia has developed gradually. If the serum [Na^+] is lowered rapidly, there is movement of water from the serum into the brain cells to equalize the osmolality in the 2 compartments. The resultant brain swelling manifests as seizures or coma.

Because of the associated dangers, *chronic hypernatremia should not be corrected rapidly.* The goal is to decrease the serum [Na^+] by <10 mEq/L every 24 hr. The most important component of correcting moderate or severe hypernatremia is frequent monitoring of the serum [Na^+] value so that fluid therapy can be adjusted to provide adequate correction, neither too slow nor too fast. If a child has seizures as a result of brain edema secondary to rapid correction, administration of hypotonic fluid should be stopped. An infusion of 3% saline can acutely increase the serum [Na^+], reversing the cerebral edema.

Chapter 70 outlines a detailed approach to the child with hypernatremic dehydration. Acute, severe hypernatremia, usually secondary to sodium administration, can be corrected more rapidly with 5% dextrose in water (D5W) because idiogenic osmoles have not had time to accumulate. This fact balances the high morbidity and mortality rates associated with hypernatremia with the dangers of overly rapid correction. When hypernatremia is severe and is caused by sodium intoxication, it may be impossible to administer enough water to correct the hypernatremia rapidly without worsening the volume overload. In this situation, dialysis allows for removal of the excess Na^+, with the precise strategy dependent on the mode of dialysis. In less severe cases, the addition of a loop diuretic increases the removal of excess Na^+ and water, decreasing the risk of volume overload. With Na^+ overload, hypernatremia is corrected with Na^+-free intravenous (IV) fluid (D5W).

Hyperglycemia from hypernatremia is not usually a problem and is not treated with insulin because the acute decrease in glucose may precipitate cerebral edema by lowering plasma osmolality. Rarely, the glucose concentration of IV fluids must be reduced (from 5% to 2.5% dextrose in water). The secondary hypocalcemia is treated as needed.

It is important to address the underlying cause of the hypernatremia, if possible. The child with central diabetes insipidus should receive desmopressin acetate. Because this treatment reduces renal excretion of water, excessive intake of water must be avoided to prevent both overly rapid correction of the hypernatremia and the development of hyponatremia. Over the long term, reduced sodium intake and the use of medications can somewhat ameliorate the water losses in nephrogenic diabetes insipidus (see Chapter 548). The daily water intake of a child receiving tube feeding may need to be increased to compensate for high losses. The patient with significant ongoing losses, such as through diarrhea, may need supplemental water and electrolytes (see Chapter 69). Sodium intake is reduced if it contributed to the hypernatremia.

Hyponatremia

Hyponatremia, a very common electrolyte abnormality in hospitalized patients, is a serum sodium level <135 mEq/L. Both total body sodium and TBW determine the serum sodium concentration. Hyponatremia exists when the ratio of water to Na^+ is increased. This condition can occur with low, normal, or high levels of body Na^+ . Similarly, body water can be low, normal, or high.

Etiology and Pathophysiology

Table 68.2 lists the causes of hyponatremia. **Pseudohyponatremia** is a laboratory artifact present when the plasma contains very high concentrations of protein (multiple myeloma, IVIG infusion) or lipid (hypertriglyceridemia, hypercholesterolemia). It does not occur when a direct ion-selective electrode determines the $[Na^+]$ in undiluted plasma, a technique that is used by ABG analyzers or POC instruments (see Chapter 68.1). In true hyponatremia, the measured osmolality is low, whereas it is normal in pseudohyponatremia. **Hyperosmolality,** as may occur with hyperglycemia, causes a low $[Na^+]$ because water moves down its osmotic gradient from the ICS into the ECS, diluting the $[Na^+]$. However, because the manifestations of hyponatremia are a result of the low plasma osmolality, patients with hyponatremia resulting from hyperosmolality do not have symptoms of hyponatremia. When the etiology of the hyperosmolality resolves, such as hyperglycemia in diabetes mellitus, water moves back into the cells, and the $[Na^+]$ rises to its “true” value. Mannitol or sucrose, a component of intravenous immune globulin (IVIG) preparations, may cause hyponatremia because of hyperosmolality.

Table 68.2

Causes of Hyponatremia

PSEUDOHYPONATREMIA

Hyperlipidemia
Hyperproteinemia

HYPEROSMOLALITY

- Hyperglycemia
- Iatrogenic (mannitol, sucrose, glycine)

HYPOVOLEMIC HYPONATREMIA
EXTRARENAL LOSSES

- Gastrointestinal (emesis, diarrhea)
- Skin (sweating or burns)
- Third space losses (bowel obstruction, peritonitis, sepsis)

RENAL LOSSES

- Thiazide or loop diuretics
- Osmotic diuresis
- Postobstructive diuresis
- Polyuric phase of acute tubular necrosis
- Juvenile nephronophthisis (OMIM 256100/606966/602088/604387/611498)
- Autosomal recessive polycystic kidney disease (OMIM 263200)
- Tubulointerstitial nephritis
- Obstructive uropathy
- Cerebral salt wasting
- Proximal (type II) renal tubular acidosis (OMIM 604278)*
- Lack of aldosterone effect (high serum potassium):
    - Absence of aldosterone (e.g., 21-hydroxylase deficiency [OMIM 201910])
    - Pseudohypoaldosteronism type I (OMIM 264350/177735)
    - Urinary tract obstruction and/or infection
    - Addison disease

EUVOLEMIC HYPONATREMIA

- Syndrome of inappropriate antidiuretic hormone secretion
- Nephrogenic syndrome of inappropriate antidiuresis (OMIM 304800)

- Desmopressin acetate
- Glucocorticoid deficiency
- Hypothyroidism
- Antidepressant medications
- Water intoxication
  - Iatrogenic (excess hypotonic intravenous fluids)
  - Feeding infants excessive water products
  - Swimming lessons
  - Tap water enema
  - Child abuse
  - Psychogenic polydipsia
  - Diluted formula
  - Beer potomania
  - Exercise-induced hyponatremia

HYPERVOLEMIC HYPONATREMIA

- Heart failure
- Cirrhosis
- Nephrotic syndrome
- Acute, chronic kidney injury
- Capillary leak caused by sepsis
- Hypoalbuminemia caused by gastrointestinal disease (protein-losing enteropathy)

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[*] Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Classification of hyponatremia is based on the patient's volume status. In **hypovolemic hyponatremia** the child has lost Na^+ from the body. The water balance may be positive or negative, but Na^+ loss has been higher than water loss. The pathogenesis of the hyponatremia is usually a combination of Na^+ loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and this fluid contains Na^+ . Most fluid that is lost has a lower [Na^+] than that of plasma. Viral diarrhea fluid has an average [Na^+] of 50 mEq/L. Replacing diarrhea fluid, which has [Na^+] of 50 mEq/L, with formula, which has only approximately 10 mEq/L of Na^+ , reduces [Na^+]. Intravascular volume depletion interferes with renal water excretion, the body's usual mechanism for preventing hyponatremia. The volume depletion stimulates ADH synthesis, resulting in renal water retention. Volume depletion also decreases the GFR and enhances water resorption in the proximal tubule, thereby reducing water delivery to the collecting duct.

Diarrhea as a result of gastroenteritis is the most common cause of hypovolemic hyponatremia in children. Emesis causes hyponatremia if the patient takes in hypotonic fluid, either intravenously or enterally, despite the emesis. Most patients with emesis have either a normal [Na^+] or hypernatremia. Burns may cause massive losses of isotonic fluid and resultant volume depletion. Hyponatremia develops if the patient receives hypotonic fluid. Losses of sodium from sweat are especially high in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism, although high losses can also occur in a hot climate. Third space losses are isotonic and can cause significant volume depletion, leading to ADH production and water retention, which can cause hyponatremia if the patient receives hypotonic fluid. In diseases that cause volume depletion through extrarenal Na^+ loss, the urine Na^+ level should be low (<10 mEq/L) as part of the renal response to maintain the intravascular volume. The only exceptions are diseases that cause both extrarenal and renal Na^+ losses: adrenal insufficiency and pseudohypoaldosteronism.

Renal Na^+ loss may occur in a variety of situations. In some situations the urine [Na^+] is >140 mEq/L; thus hyponatremia may occur without any fluid intake. In many cases the urine Na^+ level is less than the serum [Na^+]; thus the intake of hypotonic fluid is necessary for hyponatremia to develop. In diseases associated with urinary Na^+ loss, the urine Na^+ level is >20 mEq/L despite volume depletion. This may not be true if the urinary Na^+ loss is no longer occurring, as is frequently the case if diuretics are discontinued. Because loop diuretics prevent generation of a maximally hypertonic renal medulla, the patient can neither maximally dilute nor concentrate the urine. The inability to maximally retain water provides some protection against severe hyponatremia.

The patient receiving thiazide diuretics can concentrate the urine and is at higher risk for severe hyponatremia. Osmotic agents, such as glucose during diabetic ketoacidosis, cause loss of both water and Na^+ . Urea accumulates during renal failure and then acts as an osmotic diuretic after relief of urinary tract obstruction and during the polyuric phase of acute tubular necrosis. Transient tubular damage in these conditions further impairs Na^+ conservation. The serum $[Na^+]$ in these conditions depends on $[Na^+]$ of the fluid used to replace the losses. Hyponatremia develops when the fluid is hypotonic relative to the urinary losses.

Renal salt wasting occurs in hereditary kidney diseases, such as juvenile nephronophthisis and autosomal recessive polycystic kidney disease. Obstructive uropathy, most often a result of posterior urethral valves, produces salt wasting, but patients with the disease may also have hypernatremia as a result of impaired ability to concentrate urine and high-water loss. Acquired tubulointerstitial nephritis, usually secondary to either medications or infections, may cause salt wasting, along with other evidence of tubular dysfunction. CNS injury may produce cerebral salt wasting, which is theoretically caused by the production of a natriuretic peptide that causes renal salt wasting. In type II **renal tubular acidosis (RTA)** , usually associated with Fanconi syndrome (see Chapter 547.1), there is increased excretion of Na^+ and bicarbonate in the urine. Patients with Fanconi syndrome also have glycosuria, aminoaciduria, and hypophosphatemia because of renal phosphate wasting.

Aldosterone is necessary for renal Na^+ retention and for the excretion of K^+ and acid. In congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, the block of aldosterone production results in hyponatremia, hyperkalemia, and metabolic acidosis. Decreased aldosterone secretion may be seen in Addison disease (adrenal insufficiency). In pseudohypoaldosteronism, aldosterone levels are elevated, but there is no response because of either a defective Na^+ channel or a deficiency of aldosterone receptors. A lack of tubular response to aldosterone may occur in children with urinary tract obstruction, especially during an acute urinary tract infection.

In **hypervolemic hyponatremia** there is an excess of TBW and Na^+ , although the increase in water is greater than the increase in Na^+ . In most conditions that cause hypervolemic hyponatremia, there is a decrease in the *effective blood volume* , resulting from third space fluid loss, vasodilation, or poor cardiac output. The regulatory systems sense a decrease in effective blood volume and attempt to retain water and Na^+ to correct the problem. ADH causes renal water retention, and the kidney, under the influence of aldosterone and other intrarenal mechanisms, retains sodium. The patient's sodium concentration decreases because water intake exceeds sodium intake and ADH prevents the normal loss of excess water.

In these disorders, there is low urine [Na^+] (<10 mEq/L) and an excess of both TBW and Na^+ . The only exception is in patients with renal failure and hyponatremia. These patients have an expanded intravascular volume, and hyponatremia can therefore appropriately suppress ADH production. Water cannot be excreted because very little urine is being made. Serum Na^+ is diluted through ingestion of water. Because of renal dysfunction, the urine [Na^+] may be elevated, but urine volume is so low that urine Na^+ excretion has not kept up with Na^+ intake, leading to sodium overload. The urine [Na^+] in renal failure varies. In patients with acute glomerulonephritis, because it does not affect the tubules, the urine Na^+ level is usually low, whereas in patients with acute tubular necrosis, it is elevated because of tubular dysfunction.

Patients with hyponatremia and no evidence of volume overload or volume depletion have **euvolemic hyponatremia.** These patients typically have an excess of TBW and a slight decrease in total body Na^+ . Some of these patients have an increase in weight, implying that they are volume-overloaded. Nevertheless, from a clinical standpoint, they usually appear normal or have subtle signs of fluid overload. In SIADH the secretion of ADH is not inhibited by either low serum osmolality or expanded intravascular volume (see Chapter 575). The result is that the child with SIADH is unable to excrete water. This results in dilution of the serum Na^+ and hyponatremia. The expansion of the extracellular volume because of the retained water causes a mild increase in intravascular volume. The kidney increases Na^+ excretion to decrease intravascular volume to normal; thus the patient has a mild decrease in body Na^+ . SIADH typically occurs with disorders of the CNS (infection, hemorrhage, trauma, tumor, thrombosis, Guillain-Barré syndrome), but lung disease (infection, asthma, positive pressure ventilation) and malignant tumors (producing ADH) are other potential causes. A variety of medications may cause SIADH, including recreational use of 3,4-methylenedioxymethylamphetamine (MDMA, or “Ecstasy”), opiates, antiepileptic drugs (carbamazepine, oxcarbazepine, valproate), tricyclic antidepressants, vincristine, cyclophosphamide, and selective serotonin reuptake inhibitors (SSRIs). The diagnosis of SIADH is one of exclusion, because other causes of hyponatremia must be eliminated (Table 68.3). Because SIADH is a state of intravascular volume expansion, low serum uric acid and BUN levels are supportive of the diagnosis. A rare gain-of-function mutation in the renal ADH receptor causes **nephrogenic syndrome of inappropriate antidiuresis** . Patients with this X-linked disorder appear to have SIADH but have undetectable levels of ADH.

Table 68.3

Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion

- Absence of:
  - Renal, adrenal, or thyroid insufficiency
  - Heart failure, nephrotic syndrome, or cirrhosis
  - Diuretic ingestion
  - Dehydration
- Urine osmolality >100 mOsm/kg (usually > plasma)
- Serum osmolality <280 mOsm/kg and serum sodium <135 mEq/L
- Urine sodium >30 mEq/L
- Reversal of "sodium wasting" and correction of hyponatremia with water restriction

Hyponatremia in hospitalized patients is frequently caused by inappropriate production of ADH and administration of hypotonic IV fluids (see Chapter 69). Causes of inappropriate ADH production include stress, medications such as narcotics or anesthetics, nausea, and respiratory illness. The synthetic analog of ADH, desmopressin acetate, causes water retention and may cause hyponatremia if fluid intake is not appropriately limited. The main uses of desmopressin acetate in children are for the management of central diabetes insipidus and nocturnal enuresis.

Excess water ingestion can produce hyponatremia. In these cases, [Na^+] decreases as a result of dilution. This decrease suppresses ADH secretion, and there is a marked water diuresis by the kidney. Hyponatremia develops only because the intake of water exceeds the kidney's ability to eliminate water. This condition is more likely to occur in infants because their lower GFR limits their ability to excrete water.

Hyponatremia may develop in infants <6 mo of age when caregivers offer water to their infant as a supplement, during hot weather, or when they run out of formula. Hyponatremia may result in transient seizures, hypothermia, and poor tone. With cessation of water intake, the hyponatremia rapidly corrects. Infants <6 mo of age should not be given water to drink; infants 6-12 mo of age should not receive >1-2 ounces. If the infant appears thirsty, the parent should offer formula or breastfeed the child.

In some situations the water intoxication causes acute hyponatremia and is caused by a massive **acute water load** . Causes include infant swimming lessons, inappropriate use of hypotonic IV fluids, water enemas, and forced water intake as a form of child abuse. Chronic hyponatremia occurs in children who receive water but limited sodium and protein. The minimum urine osmolality is approximately 50 mOsm/kg, the kidney can excrete 1 L of water only if there is enough solute ingested to produce 50 mOsm for urinary excretion. Because Na^+ and urea (a breakdown product of protein) are the principal urinary solutes, a lack of intake of Na^+ and protein prevents adequate water excretion. This occurs with the use of diluted formula or other inappropriate diets. Subsistence on beer, a poor source of Na^+ and protein, causes hyponatremia because of the inability to excrete the high water load ("beer potomania"). **Exercise-induced hyponatremia** , reported frequently during marathons, is caused by excessive water intake, salt losses from sweat, and secretion of ADH.

The pathogenesis of the hyponatremia in glucocorticoid deficiency (adrenal insufficiency) is multifactorial and includes increased ADH secretion. In hypothyroidism there is an inappropriate retention of water by the kidney, but the precise mechanisms are not clearly elucidated.

Cerebral salt wasting , an uncommon disorder in children, may be confused with SIADH and is often associated with CNS injury or lesions. Cerebral salt wasting produces renal salt losses and hypovolemia (orthostatic hypotension and elevated hematocrit, BUN, or creatinine).

Clinical Manifestations

Hyponatremia causes a decrease in the osmolality of the ECS. Because the ICS then has a higher osmolality, water moves from the ECS to the ICS to maintain osmotic equilibrium. The increase in intracellular water causes cells to swell. Although cell swelling is not problematic in most tissues, it is dangerous for the brain, which is confined by the skull. As brain cells swell, there is an increase in intracranial pressure, which impairs cerebral blood flow. Acute, severe hyponatremia can cause brainstem herniation and apnea; respiratory support is often necessary. Brain cell swelling is responsible for most of the symptoms of hyponatremia. Neurologic symptoms of hyponatremia include anorexia, nausea, emesis, malaise, lethargy, confusion, agitation, headache, seizures, coma, and decreased reflexes. Patients may have hypothermia and Cheyne-Stokes respirations. Hyponatremia can cause muscle cramps and weakness; rhabdomyolysis can occur with water intoxication.

The symptoms of hyponatremia are mostly a result of the decrease in extracellular osmolality and the resulting movement of water down its osmotic gradient into the ICS. Brain swelling can be significantly obviated if the hyponatremia develops gradually, because brain cells adapt to the decreased extracellular osmolality by reducing intracellular osmolality. This reduction is achieved by extrusion of the main intracellular ions (K^+ , Cl^-) and a variety of small organic molecules. This process explains why the range of symptoms in hyponatremia is related to both the serum [Na^+] and its rate of decrease. A patient with chronic hyponatremia may have only subtle neurologic abnormalities with a serum [Na^+] of 110 mEq/L, but another patient may have seizures because of an acute decline in serum [Na^+] from 140 to 125 mEq/L.

Diagnosis

The history usually points to a likely etiology of the hyponatremia. Most patients with hyponatremia have a history of volume depletion. Diarrhea and diuretic use are common causes of hyponatremia in children. A history of polyuria, perhaps with enuresis, and/or salt craving is present in children with primary kidney diseases or absence of aldosterone effect. Children may have signs or symptoms suggesting a diagnosis of hypothyroidism or adrenal insufficiency (see Chapters 581 and 593). Brain injury raises the possibility of SIADH or cerebral salt wasting, with the caveat that SIADH is much more likely. Liver disease, nephrotic syndrome, renal failure, or congestive heart failure may be acute or chronic. The history should include a review of the patient's intake, both intravenous and enteral, with careful attention to the amounts of water, Na^+ , and protein.

The traditional first step in the diagnostic process is determination of the plasma osmolality. This is done because some patients with a low serum [Na^+] do not have low osmolality. The clinical effects of hyponatremia are secondary to the associated low osmolality. Without a low osmolality, there is no movement of water into the intracellular space.

A patient with hyponatremia can have a low, normal, or high osmolality. A normal osmolality in combination with hyponatremia occurs in pseudohyponatremia. Children with elevation of serum glucose concentration or of another effective osmole (mannitol) have a high plasma osmolality and hyponatremia. The presence of a low osmolality indicates “true” hyponatremia. Patients with low osmolality are at risk for neurologic symptoms and require further evaluation to determine the etiology of the hyponatremia.

In some situations, true hyponatremia is present despite a normal or elevated plasma osmolality. The presence of an ineffective osmole, usually urea, increases the plasma osmolality, but because the osmole has the same concentration in the ICS, it does not cause fluid to move into the ECS. There is no dilution of the serum Na^+ by water, and the [Na^+] remains unchanged if the ineffective osmole is eliminated. Most importantly, the ineffective osmole does not protect the brain from edema caused by hyponatremia. Therefore, a patient may have symptoms of hyponatremia despite having a normal or increased osmolality because of uremia.

In patients with true hyponatremia, the next step in the diagnostic process is to clinically evaluate the volume status. Patients with hyponatremia can be hypovolemic, hypervolemic, or euvolemic. The diagnosis of volume depletion relies on the usual findings with dehydration (see Chapter 70), although subtle volume depletion may not be clinically apparent. Children with hypervolemia are **edematous** on physical examination. They may have ascites, pulmonary edema, pleural effusion, or hypertension.

Hypovolemic hyponatremia can have renal or nonrenal causes. The urine [Na^+] is very useful in differentiating between renal and nonrenal causes. When the losses are nonrenal and the kidney is working properly, there is renal retention of Na^+ , a normal homeostatic response to volume depletion. Thus the urinary [Na^+] is low, typically <10 mEq/L, although Na^+ conservation in neonates is less avid. When the kidney is the cause of the Na^+ loss, the urine [Na^+] is >20 mEq/L, reflecting the defect in renal Na^+ retention. The interpretation of the urine Na^+ level is challenging with diuretic therapy because it is high when diuretics are being used but low after the diuretic effect is gone. This becomes an issue only when diuretic use is surreptitious. The urine [Na^+] is not useful if a metabolic alkalosis is present; the urine [Cl^-] must be used instead (see Chapter 68.7).

Differentiating among the nonrenal causes of hypovolemic hyponatremia is usually facilitated by the history. Although the renal causes are more challenging to distinguish, a high serum [K^+] is associated with disorders in which the Na^+ wasting is caused by absence of or ineffectiveness of aldosterone.

In the patient with hypervolemic hyponatremia, the urine [Na^+] is a helpful parameter. It is usually <10 mEq/L, except in the patient with renal failure.

Treatment

The management of hyponatremia is based on the pathophysiology of the specific etiology. The management of all causes requires judicious monitoring and avoidance of an overly quick normalization of the serum [Na^+]. A patient with severe symptoms (seizures), no matter the etiology, should be given a bolus of hypertonic saline to produce a small, rapid increase in serum sodium. *Hypoxia worsens cerebral edema*, and *hyponatremia may exacerbate hypoxic cell swelling*. Therefore, pulse oximetry should be monitored and hypoxia aggressively corrected.

With all causes of hyponatremia, it is important to avoid overly rapid correction, which may cause **central pontine myelinolysis (CPM)** . This syndrome, which occurs within several days of rapid correction of hyponatremia, produces neurologic symptoms, including confusion, agitation, flaccid or spastic quadriparesis, and death. There are usually characteristic pathologic and radiologic changes in the brain, especially in the pons, but extrapontine lesions are quite common and may cause additional symptoms. Despite severe symptoms, full recovery does occur in some patients.

CPM is more common in patients who are treated for *chronic* hyponatremia than for acute hyponatremia. Presumably, this difference is based on the adaptation of brain cells to the hyponatremia. The reduced intracellular osmolality, an adaptive mechanism for chronic hyponatremia, makes brain cells susceptible to dehydration during rapid correction of the hyponatremia, which may be the mechanism of CPM. Even though CPM is rare in pediatric patients, it is advisable to avoid correcting the serum [Na^+] by >10 mEq/L/24 hr or >18 mEq/L/48 hr. Desmopressin is a potential option if the serum [Na^+] is increasing too rapidly. This guideline *does not* apply to acute hyponatremia, as may occur with water intoxication, because the hyponatremia is more often symptomatic, and the adaptive decrease in brain osmolality has not had time to occur. The consequences of brain edema in acute hyponatremia exceed the small risk of CPM.

Patients with hyponatremia can have severe neurologic symptoms, such as seizures and coma. The seizures associated with hyponatremia generally are poorly responsive to anticonvulsants. The child with hyponatremia and severe symptoms needs treatment that will quickly reduce cerebral edema. This goal is best accomplished by increasing the extracellular osmolality so that water moves down its osmolar gradient from the ICS to the ECS.

Intravenous hypertonic saline rapidly increases serum [Na^+], and the effect on serum osmolality leads to a decrease in brain edema. Each mL/kg of 3% NaCl increases the serum [Na^+] by approximately 1 mEq/L. A child with active symptoms often improves after receiving 4-6 mL/kg of 3% NaCl.

The child with **hypovolemic hyponatremia** has a deficiency in Na^+ and may have a deficiency in water. The cornerstone of therapy is to replace the Na^+ deficit and any water deficit present. The first step in treating any dehydrated patient is to restore the intravascular volume with isotonic saline. Ultimately, complete restoration of intravascular volume suppresses ADH production, thereby permitting excretion of the excess water. Chapter 70 discusses the management of hyponatremic dehydration.

The management of **hypervolemic hyponatremia** is difficult; patients have an excess of both water and Na^+ . Administration of Na^+ leads to worsening volume overload and edema. In addition, patients are retaining water and Na^+ because of their ineffective intravascular volume or renal insufficiency. The cornerstone of therapy is water and Na^+ restriction, because patients have volume overload. Diuretics may help by causing excretion of both Na^+ and water. Vasopressin antagonists (**vaptans**), by blocking the action of ADH and causing a water diuresis, are effective in correcting the hypervolemic hyponatremia caused by heart failure. Vaptans are contraindicated if there are moderate to severe CNS symptoms.

Hyponatremic patients with low albumin from nephrotic syndrome have a better response to diuretics after an infusion of 25% albumin; the [Na^+] often normalizes as a result of expansion of the intravascular volume. A child with heart failure may have an increase in renal water and Na^+ excretion if there is an improvement in cardiac output. This improvement will “turn off” the regulatory hormones causing renal water (ADH) and Na^+ (aldosterone) retention. The patient with renal failure cannot respond to any of these therapies except fluid restriction. Insensible fluid losses eventually result in an increase in the [Na^+] as long as insensible and urinary losses are greater than intake. A more definitive approach in children with renal failure is to perform dialysis, which removes water and Na^+ .

In **isovolumic hyponatremia** there is usually an excess of water and a mild Na^+ deficit. Therapy is directed at eliminating the excess water. The child with acute excessive water intake loses water in the urine because ADH production is turned off as a result of the low plasma osmolality. Children may correct their hyponatremia spontaneously over 3-6 hr. For acute, symptomatic hyponatremia as a result of water intoxication, hypertonic saline may be needed to reverse cerebral edema. For chronic hyponatremia from poor solute intake, the child needs an appropriate formula, and excess water intake should be eliminated.

Children with **iatrogenic hyponatremia** caused by the administration of hypotonic IV fluids should receive 3% saline if symptomatic. Subsequent management is dictated by the patient's volume status. The hypovolemic child should receive isotonic IV fluids. The child with nonphysiologic stimuli for ADH production should undergo fluid restriction. Prevention of this iatrogenic complication requires judicious use of IV fluids (see Chapter 69).

Specific hormone replacement is the cornerstone of therapy for the hyponatremia of hypothyroidism or cortisol deficiency. Correction of the underlying defect permits appropriate elimination of the excess water.

SIADH is a condition of excess water, with limited ability of the kidney to excrete water. The mainstay of its therapy is fluid restriction with normal sodium intake. Furosemide and NaCl supplementation are effective in the patient with SIADH and *severe* hyponatremia. Even in a patient with SIADH, furosemide causes an increase in water and Na^+ excretion. The loss of Na^+ is somewhat counterproductive, but this Na^+ can be replaced with hypertonic saline. Because the patient has a net loss of water and the urinary losses of Na^+ have been replaced, there is an increase in the [Na^+], but no significant increase in blood pressure. Vaptans, which block the action of ADH and cause a water diuresis, are effective at correcting **euvolemic hyponatremia** , but overly rapid correction is a potential complication. Vaptans are not appropriate for treating symptomatic hyponatremia because it can take a few hours before the water diuresis occurs.

Treatment of chronic SIADH is challenging. Fluid restriction in children is difficult for nutritional and behavioral reasons. Other options are long-term furosemide therapy with Na^+ supplementation, an oral vaptan (tolvaptan), or oral urea.

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68.4

Potassium

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Keywords

hyperkalemia
hypokalemia
aldosterone
pseudohyperkalemia
congenital adrenal hyperplasia
hypertension

Gordon syndrome
pseudohypoaldosteronism
Bartter syndrome
Gitelman syndrome
hypokalemic periodic paralysis

Potassium Metabolism

Body Content and Physiologic Function

The intracellular [K^+], approximately 150 mEq/L, is much higher than the plasma [K^+] (see Fig. 68.3). The majority of body K^+ is contained in muscle. As muscle mass increases, there is an increase in body K^+ . Thus an increase in body K^+ occurs during puberty, and it is more significant in males. The majority of extracellular K^+ is in bone; <1% of total body K^+ is in plasma.

Because most K^+ is intracellular, the plasma concentration does not always reflect the total body K^+ content. A variety of conditions alter the distribution of K^+ between the intracellular and extracellular compartments. Na^+ ,K^+ -ATPase maintains the high intracellular [K^+] by pumping Na^+ out of the cell and K^+ into the cell. This activity balances the normal leak of K^+ out of cells via potassium channels that is driven by the favorable chemical gradient. Insulin increases K^+ movement into cells by activating Na^+ ,K^+ -ATPase. Hyperkalemia stimulates insulin secretion, which helps mitigate the hyperkalemia. Acid-base status affects K^+ distribution, probably via K^+ channels and the Na^+ ,K^+ -ATPase. A decrease in pH drives potassium extracellularly; an increase in pH has the opposite effect. β-Adrenergic agonists stimulate the Na^+ ,K^+ -ATPase, increasing cellular uptake of K^+ . This increase is protective, in that hyperkalemia stimulates adrenal release of catecholamines. α-Adrenergic agonists and exercise cause a net movement of K^+ out of the ICS. An increase in plasma osmolality, as with mannitol infusion, leads to water movement out of the cells, and K^+ follows as a result of solvent drag. The serum [K^+] increases by approximately 0.6 mEq/L with each 10 mOsm rise in plasma osmolality.

The high intracellular concentration of K^+ , the principal intracellular cation, is maintained through Na^+ ,K^+ -ATPase. The resulting chemical gradient is used to produce the resting membrane potential of cells. K^+ is necessary for the electrical responsiveness of nerve and muscle cells and for the contractility of cardiac, skeletal, and smooth muscle. The changes in membrane polarization that occur during muscle contraction or nerve conduction make these cells susceptible to changes in serum [K^+]. The ratio of intracellular to extracellular K^+ determines the threshold for a cell to generate an action potential and the rate of cellular repolarization. The intracellular [K^+] affects cellular enzymes. K^+ is necessary for maintaining cell volume because of its important contribution to intracellular osmolality.

Potassium Intake

Potassium is plentiful in food. Dietary consumption varies considerably, even though 1-2 mEq/kg is the recommended intake. The intestines normally absorb approximately 90% of ingested K^+ . Most absorption occurs in the small intestine, whereas the colon exchanges body K^+ for luminal Na^+ . Regulation of intestinal losses normally has a minimal role in maintaining potassium homeostasis, although renal failure, aldosterone, and glucocorticoids increase colonic secretion of K^+ . The increase in intestinal losses in the setting of renal failure and hyperkalemia, which stimulates aldosterone production, is clinically significant, helping to protect against hyperkalemia.

Potassium Excretion

Some loss of K^+ occurs in sweat but is normally minimal. The colon has the ability to eliminate some K^+ . In addition, after an acute K^+ load, much of the K^+ , >40%, moves intracellularly, through the actions of epinephrine and insulin, which are produced in response to hyperkalemia. This process provides transient protection from hyperkalemia, but most ingested K^+ is eventually excreted in the urine. The kidneys principally regulate long-term K^+ balance, and they alter excretion in response to a variety of signals. K^+ is freely filtered at the glomerulus, but 90% is resorbed before reaching the distal tubule and collecting duct, the principal sites of K^+ regulation that have the ability to absorb and secrete K^+ . The amount of tubular secretion regulates the amount of K^+ that appears in the urine. The plasma [K^+] directly influences secretion in the distal nephron. As the [K^+] increases, secretion increases.

The principal hormone regulating potassium secretion is **aldosterone** , which is released by the adrenal cortex in response to increased plasma K^+ . Its main site of action is the cortical collecting duct, where aldosterone stimulates Na^+ movement from the tubule into the cells. This movement creates a negative charge in the tubular lumen, facilitating K^+ excretion. In addition, the increased intracellular Na^+ stimulates the basolateral Na^+ ,K^+ -ATPase, causing more K^+ to move into the cells lining the cortical collecting duct. Glucocorticoids, ADH, a high urinary flow rate, and high Na^+ delivery to the distal nephron also increase urinary K^+ excretion. Insulin, catecholamines, and urinary ammonia decrease K^+ excretion. Whereas ADH increases K^+ secretion, it also causes water resorption, decreasing urinary flow. The net effect is that ADH has little overall impact on K^+ balance. Alkalosis causes potassium to move into cells, including the cells lining the collecting duct. This movement increases K^+ secretion, and because acidosis has the opposite effect, it decreases K^+ secretion.

The kidney can dramatically vary K^+ excretion in response to changes in intake. Normally, approximately 10–15% of the filtered load is excreted. In an adult, excretion of K^+ can vary from 5-1,000 mEq/day.

Hyperkalemia

Hyperkalemia—because of the potential for lethal arrhythmias—is one of the most alarming electrolyte abnormalities.

Etiology and Pathophysiology

Three basic mechanisms cause hyperkalemia (Table 68.4). In the individual patient, the etiology is sometimes multifactorial.

Table 68.4

Causes of Hyperkalemia

Spurious Laboratory Value

Hemolysis
Tissue ischemia during blood drawing
Thrombocytosis
Leukocytosis

Familial pseudohyperkalemia (OMIM 609153/611184/612126)

Increased Intake

Intravenous or oral
Blood transfusions

Transcellular Shifts

Acidosis
Rhabdomyolysis
Tumor lysis syndrome
Tissue necrosis
Hemolysis/hematomas/gastrointestinal bleeding
Succinylcholine
Digitalis intoxication
Fluoride intoxication
β-Adrenergic blockers
Exercise
Hyperosmolality
Insulin deficiency
Malignant hyperthermia (OMIM 145600/601887)
Hyperkalemic periodic paralysis (OMIM 170500)

Decreased Excretion

- Renal failure
- Primary adrenal disease
  - Acquired Addison disease
  - 21-Hydroxylase deficiency (OMIM 201910)
  - 3β-Hydroxysteroid dehydrogenase deficiency (OMIM 201810)
  - Lipoid congenital adrenal hyperplasia (OMIM 201710)
  - Adrenal hypoplasia congenita (OMIM 300200)
  - Aldosterone synthase deficiency (OMIM 203400/610600)
  - Adrenoleukodystrophy (OMIM 300100)
- Hyporeninemic hypoaldosteronism

    - Urinary tract obstruction
    - Sickle cell disease (OMIM 603903)
    - Kidney transplant
    - Lupus nephritis
- Renal tubular disease
    - Pseudohypoaldosteronism type I (OMIM 264350/177735)
    - Pseudohypoaldosteronism type II (OMIM 145260)
    - Bartter syndrome, type 2 (OMIM 241200)
    - Urinary tract obstruction
    - Kidney transplant
- Medications
    - Renin inhibitors
    - Angiotensin-converting enzyme inhibitors
    - Angiotensin II blockers
    - Potassium-sparing diuretics
    - Calcineurin inhibitors
    - Nonsteroidal antiinflammatory drugs
    - Trimethoprim
    - Heparin
    - Drospirenone (in some oral contraceptives)

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Spurious hyperkalemia or **pseudohyperkalemia** is very common in children because of the difficulties in obtaining blood specimens. This laboratory result is usually caused by hemolysis during a heelstick or phlebotomy, but it can be the result of prolonged tourniquet application or fist clenching, either of which causes local potassium release from muscle.

The serum [K^+] is normally 0.4 mEq/L higher than the plasma value, secondary to K^+ release from cells during clot formation. This phenomenon is exaggerated with thrombocytosis because of K^+ release from platelets. For every 100,000/m^3 increase in the platelet count, the serum [K^+] rises by approximately 0.15 mEq/L. This phenomenon also occurs with the marked white blood cell (WBC) count elevations sometimes seen with leukemia. Elevated WBC counts, typically >200,000/m^3 , can cause a dramatic elevation in the serum [K^+].

Analysis of a plasma sample usually provides an accurate result. It is important to analyze the sample promptly to avoid K^+ release from cells, which occurs if the sample is stored in the cold, or cellular uptake of K^+ and spurious hypokalemia, which occurs with storage at high temperatures. Pneumatic tube transport can cause pseudohyperkalemia if cell membranes are fragile (leukemia). Occasionally, heparin causes lysis of leukemic cells and a false elevation of the plasma sample; a blood gas syringe has less heparin and may provide a more accurate reading than a standard tube. There are rare genetic disorders causing in vitro leakage of K^+ from red blood cells (RBCs) that may causes familial pseudohyperkalemia.

Because of the kidney's ability to excrete K^+ , it is unusual for excessive intake, by itself, to cause hyperkalemia. This condition can occur in a patient who is receiving large quantities of IV or oral K^+ for excessive losses that are no longer present. Frequent or rapid blood transfusions can acutely increase the [K^+] because of the K^+ content of blood, which is variably elevated. Increased intake may precipitate hyperkalemia if there is an underlying defect in K^+ excretion.

The ICS has a very high [K^+], so a shift of K^+ from the ICS to the ECS can have a significant effect on the plasma [K^+]. This shift occurs with metabolic acidosis, but the effect is minimal with an organic acid (lactic acidosis, ketoacidosis). A respiratory acidosis has less impact than a metabolic acidosis. Cell destruction, as seen with rhabdomyolysis, tumor lysis syndrome, tissue necrosis, or hemolysis, releases K^+ into the extracellular milieu. The K^+ released from RBCs in internal bleeding, such as hematomas, is resorbed and enters the ECS.

Normal doses of succinylcholine or β-blockers and fluoride or digitalis intoxication all cause a shift of K^+ out of the intracellular compartment. *Succinylcholine should not be used during anesthesia in patients at risk for hyperkalemia.* β-Blockers prevent the normal cellular uptake of K^+ mediated by binding of β-agonists to the β_2 -adrenergic receptors. K^+ release from muscle cells occurs during exercise, and levels can increase by 1-2 mEq/L with high activity. With an increased plasma osmolality, water moves from the ICS, and K^+ follows. This process occurs with hyperglycemia, although in nondiabetic patients the resultant increase in insulin causes K^+ to move intracellularly. In **diabetic ketoacidosis (DKA)** , the absence of insulin causes potassium to leave the ICS, and the problem is compounded by the hyperosmolality. The effect of hyperosmolality causes a transcellular shift of K^+ into the ECS after mannitol or hypertonic saline infusions. **Malignant hyperthermia** , which is triggered by some inhaled anesthetics, causes muscle release of potassium (see Chapter 629.2). **Hyperkalemic periodic paralysis** is an autosomal dominant disorder caused by a mutated Na^+ channel. It results in episodic cellular release of K^+ and attacks of paralysis (see Chapter 629.1).

The kidneys excrete most of the daily K^+ intake, so a decrease in kidney function can cause hyperkalemia. Newborn infants in general, and especially premature infants, have decreased kidney function at birth and thus are at increased risk for hyperkalemia despite an absence of intrinsic renal disease. Neonates also have decreased expression of K^+ channels, further limiting K^+ excretion.

A wide range of primary **adrenal disorders** , both hereditary and acquired, can cause decreased production of aldosterone, with secondary hyperkalemia (see Chapters 593 and 594). Patients with these disorders typically have metabolic acidosis and salt wasting with hyponatremia. Children with subtle adrenal insufficiency may have electrolyte problems only during acute illnesses. The most common form of **congenital adrenal hyperplasia** , 21-hydroxylase deficiency, typically manifests in male infants as hyperkalemia, metabolic acidosis, hyponatremia, and volume depletion. Females with this disorder usually are diagnosed as newborns because of their ambiguous genitalia; treatment prevents the development of electrolyte problems.

Renin, via angiotensin II, stimulates aldosterone production. A deficiency in renin, a result of kidney damage, can lead to decreased aldosterone production. **Hyporeninemia** occurs in many kidney diseases, with some of the more common pediatric causes listed in Table 68.4 . These patients typically have hyperkalemia and a metabolic acidosis, without hyponatremia. Some of these patients have impaired renal function, partially accounting for the hyperkalemia, but the impairment in K^+ excretion is more extreme than expected for the degree of renal insufficiency.

A variety of **renal tubular disorders** impair renal excretion of K^+ . Children with **pseudohypoaldosteronism type 1** have hyperkalemia, metabolic acidosis, and salt wasting (kidney, colon, sweat) leading to hyponatremia and volume depletion; aldosterone values are elevated. In the autosomal recessive variant, there is a defect in the renal Na^+ channel that is normally activated by aldosterone. Patients with this variant have severe symptoms (failure to thrive, diarrhea, recurrent respiratory infections, miliaria-rubra like rash), beginning in infancy. Patients with the autosomal dominant form have a defect in the aldosterone receptor, and the disease is milder, often remitting in adulthood. **Pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension),** also called **Gordon syndrome,** is an autosomal dominant disorder characterized by hypertension caused by salt retention and impaired excretion of K^+ and acid, leading to hyperkalemia and hyperchloremic metabolic acidosis. Activating mutations in either *WNK1* or *WNK4* , both serine-threonine kinases located in the distal nephron, cause Gordon syndrome. Patients may respond well to thiazide diuretics. In **Bartter syndrome** , caused by mutations in the potassium channel *ROMK* (type 2 Bartter syndrome), there can be transient hyperkalemia in neonates, but hypokalemia subsequently develops (see Chapter 549.1).

Acquired renal tubular dysfunction, with an impaired ability to excrete K^+ , occurs in a number of conditions. These disorders, all characterized by **tubulointerstitial disease,** are often associated with impaired acid secretion and a secondary metabolic acidosis. In some affected children, the metabolic acidosis is the dominant feature, although a high K^+ intake may unmask the defect in K^+ handling. The tubular dysfunction can cause renal salt wasting, potentially leading to hyponatremia. Because of the tubulointerstitial damage, these conditions may also cause hyperkalemia as a result of hyporeninemic hypoaldosteronism.

The risk of hyperkalemia resulting from **medications** is greatest in patients with underlying renal insufficiency. The predominant mechanism of medication-induced hyperkalemia is impaired renal excretion, although ACE inhibitors may worsen hyperkalemia in anuric patients, probably by inhibiting GI potassium loss, which is normally upregulated in renal insufficiency. The hyperkalemia caused by trimethoprim generally occurs only at the very high doses used to treat *Pneumocystis jiroveci* pneumonia. Potassium-sparing diuretics may easily cause hyperkalemia, especially because they are often used in patients receiving oral K^+ supplements. Oral contraceptives containing drospirenone, which blocks the action of aldosterone, may cause hyperkalemia and should not be used in patients with decreased renal function.

Clinical Manifestations

The most important effects of hyperkalemia result from the role of K^+ in membrane polarization. The cardiac conduction system is usually the dominant concern. Changes in the electrocardiogram (ECG) begin with peaking of the T waves. This is followed, as K^+ level increases, by ST-segment depression, an increased PR interval, flattening of the P wave, and widening of the QRS complex. However, the correlation between K^+ level and ECG changes is poor. This process can eventually progress to ventricular fibrillation. Asystole may also occur. Some patients have paresthesias, fasciculations, weakness, and even an ascending paralysis, but cardiac toxicity usually precedes these clinical symptoms, emphasizing the danger of assuming that an absence of symptoms implies an absence of danger. Chronic hyperkalemia is generally better tolerated than acute hyperkalemia.

Diagnosis

The etiology of hyperkalemia is often readily apparent. Spurious hyperkalemia is very common in children, so obtaining a 2nd potassium measurement is often appropriate. If there is a significant elevation of WBC or platelet count, the 2nd measurement should be performed on a plasma sample that is evaluated promptly. The history should initially focus on potassium intake, risk factors for transcellular shifts of K^+ , medications that cause hyperkalemia, and signs of renal insufficiency, such as oliguria and edema. Initial **laboratory evaluation** should include creatinine, BUN, and assessment of the acid-base status. Many etiologies of hyperkalemia cause **metabolic acidosis** , which worsens hyperkalemia through the transcellular shift of K^+ out of cells. Renal insufficiency is a common cause of the combination of metabolic acidosis and hyperkalemia, also seen in diseases associated with aldosterone insufficiency or aldosterone resistance. Children with absent or ineffective aldosterone often have hyponatremia and volume depletion because of salt wasting. Genetic diseases, such as congenital adrenal hyperplasia and pseudohypoaldosteronism, usually manifest in infancy and should be strongly considered in the infant with hyperkalemia and metabolic acidosis, especially if hyponatremia is present.

It is important to consider the various etiologies of a transcellular K^+ shift. In some of these disorders, the K^+ level continues to increase, despite the elimination of all K^+ intake, especially with concurrent renal insufficiency. This increase is potentially seen in tumor lysis syndrome, hemolysis, rhabdomyolysis, and other causes of cell death. All these entities can cause concomitant hyperphosphatemia and hyperuricemia. **Rhabdomyolysis** produces an elevated creatinine phosphokinase (CPK) value and hypocalcemia, whereas children with hemolysis have hemoglobinuria and a decreasing hematocrit. For the child with diabetes, elevated blood glucose suggests a transcellular shift of K^+ .

Treatment

The plasma K^+ level, the ECG, and the risk of the problem worsening determine the aggressiveness of the therapeutic approach. High serum [K^+] and the presence of ECG changes require vigorous treatment. An additional source of concern is the patient in whom plasma K^+ levels are rising despite minimal intake. This situation can happen if there is cellular release of K^+ (tumor lysis syndrome), especially in the setting of diminished excretion (renal failure).

The first action in a child with a concerning elevation of plasma [K^+] is to stop all sources of additional K^+ (oral, intravenous). Washed RBCs can be used for patients who require blood transfusions. If the [K^+] is >6.5 mEq/L, an ECG should be obtained to help assess the urgency of the situation. Peak T waves are the first sign of hyperkalemia, followed by a prolonged PR interval, and when most severe, prolonged QRS complex. Life-threatening ventricular arrhythmias may also develop. The treatment of hyperkalemia has 2 basic goals: (1) to stabilize the heart to prevent life-threatening arrhythmias and (2) to remove K^+ from the body. The treatments that acutely prevent arrhythmias all have the advantage of working quickly (within minutes) but do not remove K^+ from the body. **Calcium** stabilizes the cell membrane of heart cells, preventing arrhythmias; it is given intravenously over a few minutes, and its action is almost immediate. Calcium should be given over 30 min in a patient receiving digitalis; otherwise the calcium may cause arrhythmias. **Bicarbonate** causes potassium to move intracellularly, lowering the plasma [K^+]; it is most efficacious in a patient with a metabolic acidosis. **Insulin** causes K^+ to move intracellularly but must be given with **glucose** to avoid hypoglycemia. The combination of insulin and glucose works within 30 min. Nebulized **albuterol** , by stimulation of β_1 -adrenergic receptors, leads to rapid intracellular movement of K^+ . This has the advantage of not requiring an IV route of administration, allowing it to be given concurrently with the other measures.

It is critical to begin measures that remove K^+ from the body. In patients who are not anuric, a **loop diuretic** increases renal excretion of K^+ . A high dose may be required in a patient with significant renal insufficiency. **Sodium polystyrene sulfonate** (**SPS** ; Kayexalate) is an exchange resin that is given either rectally or orally. **Patiromer** is an oral exchange resin for treating hyperkalemia. Some patients require **dialysis** for acute K^+ removal. Dialysis is often necessary if the patient has either severe renal failure or an especially high rate of endogenous K^+ release, as is sometimes present with tumor lysis syndrome or rhabdomyolysis. Hemodialysis rapidly lowers plasma [K^+]. Peritoneal dialysis is not nearly as quick or reliable, but it is usually adequate as long as the acute problem can be managed with medications and the endogenous release of K^+ is not high.

Long-term management of hyperkalemia includes reducing intake through dietary changes and eliminating or reducing medications that cause hyperkalemia (see Chapter 550). Some patients require medications to increase potassium excretion, such as SPS, patiromer and loop or thiazide diuretics. Some infants with chronic renal failure may need to start dialysis to allow adequate caloric intake without hyperkalemia. It is unusual for an older child to require dialysis principally to control chronic hyperkalemia. The disorders caused by aldosterone deficiency respond to replacement therapy with fludrocortisone.

Hypokalemia

Hypokalemia is common in children, with most cases related to gastroenteritis.

Etiology and Pathophysiology

There are 4 basic mechanisms of hypokalemia (Table 68.5). **Spurious hypokalemia** occurs in patients with leukemia and very elevated WBC counts if plasma for analysis is left at room temperature, permitting the WBCs to take up K^+ from the plasma. With a transcellular shift, there is no change in total body K^+ , although there may be concomitant potassium depletion resulting from other factors. Decreased intake, extrarenal losses, and renal losses are all associated with total body K^+ depletion.

Table 68.5

Causes of Hypokalemia

Spurious Laboratory Value

High white blood cell count

Transcellular Shifts

Alkalemia
Insulin
α-Adrenergic agonists
Drugs/toxins (theophylline, barium, toluene, cesium chloride, hydroxychloroquine)
Hypokalemic periodic paralysis (OMIM 170400)
Thyrotoxic period paralysis
Refeeding syndrome

Decreased Intake

Anorexia nervosa

Extrarenal Losses

Diarrhea
Laxative abuse
Sweating
Sodium polystyrene sulfonate (Kayexalate) or clay ingestion

Renal Losses

With Metabolic Acidosis

Distal renal tubular acidosis (OMIM 179800/602722/267300)
Proximal renal tubular acidosis (OMIM 604278)*
Ureterosigmoidostomy
Diabetic ketoacidosis

Without Specific Acid–Base Disturbance

Tubular toxins: amphotericin, cisplatin, aminoglycosides
Interstitial nephritis
Diuretic phase of acute tubular necrosis

- Postobstructive diuresis
- Hypomagnesemia
- High urine anions (e.g., penicillin or penicillin derivatives)

With Metabolic Alkalosis

- Low urine chloride
  - Emesis or nasogastric suction
  - Chloride-losing diarrhea (OMIM 214700)
  - Cystic fibrosis (OMIM 219700)
  - Low-chloride formula
  - Posthypercapnia
  - Previous loop or thiazide diuretic use
- High urine chloride and normal blood pressure
  - Gitelman syndrome (OMIM 263800)
  - Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
  - Autosomal dominant hypoparathyroidism (OMIM 146200)
  - EAST syndrome (OMIM 612780)
  - Loop and thiazide diuretics (current)
- High urine chloride and high blood pressure
  - Adrenal adenoma or hyperplasia
  - Glucocorticoid-remediable aldosteronism (OMIM 103900)
  - Renovascular disease
  - Renin-secreting tumor
  - 17β-Hydroxylase deficiency (OMIM 202110)
  - 11β-Hydroxylase deficiency (OMIM 202010)
  - Cushing syndrome
  - 11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
  - Licorice ingestion
  - Liddle syndrome (OMIM 177200)

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[*] Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Because the intracellular [K$^+$] is much higher than the plasma level, a significant amount of K$^+$ can move into cells without greatly changing the intracellular [K$^+$]. **Alkalemia** is one of the more common causes of a transcellular shift. The effect is much greater with a *metabolic* alkalosis than with a respiratory alkalosis. The impact of exogenous insulin on K$^+$ movement into the cells is substantial in patients with DKA. Endogenous insulin may be the cause when a patient is given a bolus of glucose. Both endogenous (epinephrine in stress) and exogenous (albuterol) β-adrenergic agonists stimulate cellular uptake of K$^+$. Theophylline overdose, barium intoxication, administration of cesium chloride (a homeopathic cancer remedy), and toluene intoxication from paint or glue sniffing can cause a transcellular shift hypokalemia, often with severe clinical manifestations. Children with **hypokalemic periodic paralysis,** a rare autosomal dominant disorder, have acute cellular uptake of K$^+$ (see Chapter 629). **Thyrotoxic periodic paralysis,** which is more common in Asians, is an unusual initial manifestation of hyperthyroidism. Affected patients have dramatic hypokalemia as a result of a transcellular shift of potassium. Hypokalemia can occur during refeeding syndrome (see Chapters 58 and 364.8).

Inadequate K$^+$ intake occurs in **anorexia nervosa** ; accompanying bulimia and laxative or diuretic abuse exacerbates the K$^+$ deficiency. Sweat losses of K$^+$ can be significant during vigorous exercise in a hot climate. Associated volume depletion and hyperaldosteronism increase renal losses of K$^+$ (discussed later). Diarrheal fluid has a high concentration of K$^+$, and hypokalemia as a result of diarrhea is usually associated with metabolic acidosis resulting from stool losses of bicarbonate. In contrast, normal acid-base balance or mild metabolic alkalosis is seen with laxative abuse. Intake of SPS or ingestion of clay because of pica increases stool losses of potassium.

Urinary potassium wasting may be accompanied by a metabolic acidosis (proximal or distal RTA). In DKA, although it is often associated with normal plasma [K$^+$] from transcellular shifts, there is significant total body K$^+$ depletion from urinary losses because of the osmotic diuresis, and the K$^+$ level may decrease dramatically with insulin therapy (see Chapter 607). Both the polyuric phase of acute tubular necrosis and postobstructive diuresis cause transient, highly variable K^+ wasting and may be associated with metabolic acidosis. Tubular damage, which occurs either directly from medications or secondary to interstitial nephritis, is often accompanied by other tubular losses, including magnesium, Na^+ , and water. Such tubular damage may cause a secondary RTA with metabolic acidosis. Isolated magnesium deficiency causes renal K^+ wasting. **Penicillin** is an anion excreted in the urine, resulting in increased K^+ excretion because the penicillin anion must be accompanied by a cation. Hypokalemia from penicillin therapy occurs only with the *sodium* salt of penicillin, not with the potassium salt.

Urinary K^+ wasting is often accompanied by a metabolic alkalosis. This condition is usually associated with increased aldosterone, which increases urinary K^+ and acid losses, contributing to the hypokalemia and the metabolic alkalosis. Other mechanisms often contribute to both the K^+ losses and the metabolic alkalosis. With emesis or nasogastric suction, there is gastric loss of K^+ , but this is fairly minimal, given the low K^+ content of gastric fluid, approximately 10 mEq/L. More important is the gastric loss of hydrochloric acid (HCl), leading to metabolic alkalosis and a state of volume depletion. The kidney compensates for metabolic alkalosis by excreting bicarbonate in the urine, but there is obligate loss of K^+ and Na^+ with the bicarbonate. The volume depletion raises aldosterone levels, further increasing urinary K^+ losses and preventing correction of metabolic alkalosis and hypokalemia until the volume depletion is corrected.

Urinary chloride (Cl^-) is low as a response to the volume depletion. Because the volume depletion is secondary to Cl^- loss, this is a **state of Cl^- deficiency** . There were cases of Cl^- deficiency resulting from infant formula deficient in Cl^- , which caused a metabolic alkalosis with hypokalemia and low urine [Cl^-]. Current infant formula is not deficient in Cl^- . A similar mechanism occurs in cystic fibrosis because of Cl^- loss in sweat. In **congenital chloride-losing diarrhea** , an autosomal recessive disorder, there is high stool loss of Cl^- , leading to metabolic alkalosis, an unusual sequela of diarrhea. Because of stool K^+ losses, Cl^- deficiency, and metabolic alkalosis, patients with this disorder have hypokalemia. During respiratory acidosis, there is renal compensation, with retention of bicarbonate and excretion of Cl^- . After the respiratory acidosis is corrected, the patients have Cl^- deficiency and post–hypercapnic alkalosis with secondary hypokalemia. Patients with Cl^- deficiency, metabolic alkalosis, and hypokalemia have a urinary [Cl^-] of <10 mEq/L. Loop and thiazide diuretics lead to hypokalemia, metabolic alkalosis, and Cl^- deficiency. During treatment, these patients have high urine chloride levels resulting from the effect of the diuretic. However, after the diuretics are discontinued, there is residual Cl^- deficiency, the urinary [Cl^-] is appropriately low, and neither the hypokalemia nor the alkalosis resolves until the Cl^- deficiency is corrected.

The combination of metabolic alkalosis, hypokalemia, high urine [Cl^-], and normal blood pressure is characteristic of Bartter syndrome, Gitelman syndrome, and current diuretic use. Patients with any of these conditions have high urinary losses of Cl^- despite a state of relative volume depletion with secondary hyperaldosteronism (high plasma renin). Bartter and Gitelman syndromes are autosomal recessive disorders caused by defects in tubular transporters (see Chapter 549). **Bartter syndrome** is usually associated with hypercalciuria, and often with nephrocalcinosis, whereas children with **Gitelman syndrome** have low urinary calcium losses but hypomagnesemia because of urinary magnesium losses. Some patients with Bartter syndrome have hypomagnesemia. A transient antenatal form of Bartter syndrome is associated with severe polyhydramnios and mutations in *MAGED2* .

Some patients with hypoparathyroidism and hypocalcemia caused by an activating mutation of the calcium-sensing receptor (**autosomal dominant hypoparathyroidism**) have hypokalemia, hypomagnesemia, and metabolic alkalosis. The reason is that activation of the calcium-sensing receptor in the loop of Henle impairs tubular resorption of sodium and chloride, causing volume depletion and secondary hyperaldosteronism. **EAST syndrome** , an autosomal recessive disorder caused by mutations in the gene for a potassium channel in the kidney, inner ear, and brain, consists of *e* pilepsy, *a* taxia, *s* ensorineural hearing loss, and *t* ubulopathy (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).

In the presence of high aldosterone levels, there is urinary loss of K^+ , hypokalemia, metabolic alkalosis, and elevated urinary [Cl^-]. Also, renal retention of Na^+ leads to hypertension. Primary hyperaldosteronism caused by adenoma or hyperplasia is much less common in children than in adults (see Chapters 597 and 598). **Glucocorticoid-remediable aldosteronism** , an autosomal dominant disorder that leads to high levels of aldosterone (but low renin levels), is often diagnosed in childhood, although hypokalemia is not always present.

Increased aldosterone levels may be secondary to increased renin production. Renal artery stenosis leads to hypertension from increased renin and secondary hyperaldosteronism. The increased aldosterone can cause hypokalemia and metabolic alkalosis, although most patients have normal electrolyte levels. Renin-producing tumors, which are extremely rare, can cause hypokalemia.

A variety of disorders cause hypertension and hypokalemia without increased aldosterone levels. Some are a result of increased levels of mineralocorticoids other than aldosterone. Such increases occur in two forms of **congenital adrenal hyperplasia** (see Chapter 594). In **11β-hydroxylase deficiency** , which is associated with virilization, the value of 11-deoxycorticosterone is elevated, causing variable hypertension and hypokalemia. A similar mechanism, increased 11-deoxycorticosterone, occurs in **17α-hydroxylase deficiency** , but patients with this disorder are more uniformly hypertensive and hypokalemic, and they have a defect in sex hormone production. **Cushing syndrome** , frequently associated with hypertension, less frequently causes metabolic alkalosis and hypokalemia, secondary to the mineralocorticoid activity of cortisol. In **11β-hydroxysteroid dehydrogenase deficiency** , an autosomal recessive disorder, the enzymatic defect prevents the conversion of cortisol to cortisone in the kidney. Because cortisol binds to and activates the aldosterone receptor, children with this deficiency have all the features of excessive mineralocorticoids, including hypertension, hypokalemia, and metabolic alkalosis. Patients with this disorder, which is also called **apparent mineralocorticoid excess** , respond to spironolactone therapy, which blocks the mineralocorticoid receptor. An acquired form of 11β-hydroxysteroid dehydrogenase deficiency occurs from the ingestion of substances that inhibit this enzyme. A classic example is glycyrrhizic acid, which is found in natural licorice. **Liddle syndrome** is an autosomal dominant disorder that results from an activating mutation of the distal nephron sodium channel that is normally upregulated by aldosterone. Patients have the characteristics of hyperaldosteronism—hypertension, hypokalemia, and alkalosis—but low serum renin and aldosterone levels. These patients respond to the potassium-sparing diuretics (triamterene and amiloride) that inhibit this sodium channel (see Chapter 549.3). Hypertension exacerbated by pregnancy and syndrome of apparent mineralocortical excess are associated with hypokalemia and low renin levels.

Clinical Manifestations

The heart and skeletal muscle are especially vulnerable to hypokalemia. ECG changes include a flattened T wave, a depressed ST segment, and the appearance of a U wave, which is located between the T wave (if still visible) and the P wave. Ventricular fibrillation and torsades de pointes may occur, although usually only in the context of underlying heart disease. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias, such as supraventricular tachycardia, ventricular tachycardia, and heart block (see Chapter 462).

The clinical consequences of hypokalemia in skeletal muscle include muscle weakness and cramps. Paralysis is a possible complication, generally only at $[K^+]$ <2.5 mEq/L. It usually starts in the legs and moves to the arms. Respiratory paralysis may require mechanical ventilation. Some patients have rhabdomyolysis; the risk increases with exercise. Hypokalemia slows GI motility. This effect manifests as constipation; with K^+ levels <2.5 mEq/L, an ileus may occur. Hypokalemia impairs bladder function, potentially leading to urinary retention.

Hypokalemia causes **polyuria** and **polydipsia** by impairing urinary concentrating ability, which produces nephrogenic diabetes insipidus. Hypokalemia stimulates renal ammonia production, an effect that is clinically significant if hepatic failure is present, because the liver cannot metabolize the ammonia. Consequently, hypokalemia may worsen hepatic encephalopathy. Chronic hypokalemia may cause kidney damage, including interstitial nephritis and renal cysts.

Diagnosis

Most causes of hypokalemia are readily apparent from the history. It is important to review the child's diet, GI losses, and medications. Both emesis and diuretic use can be surreptitious. The presence of **hypertension** suggests excess mineralocorticoid effects or levels. Concomitant electrolyte abnormalities are useful clues. The combination of hypokalemia and metabolic acidosis is characteristic of diarrhea and distal and proximal RTA. A concurrent metabolic alkalosis is characteristic of emesis or nasogastric losses, aldosterone excess, use of diuretics, and Bartter and Gitelman syndromes. Fig. 68.4 shows an approach to persistent hypokalemia.

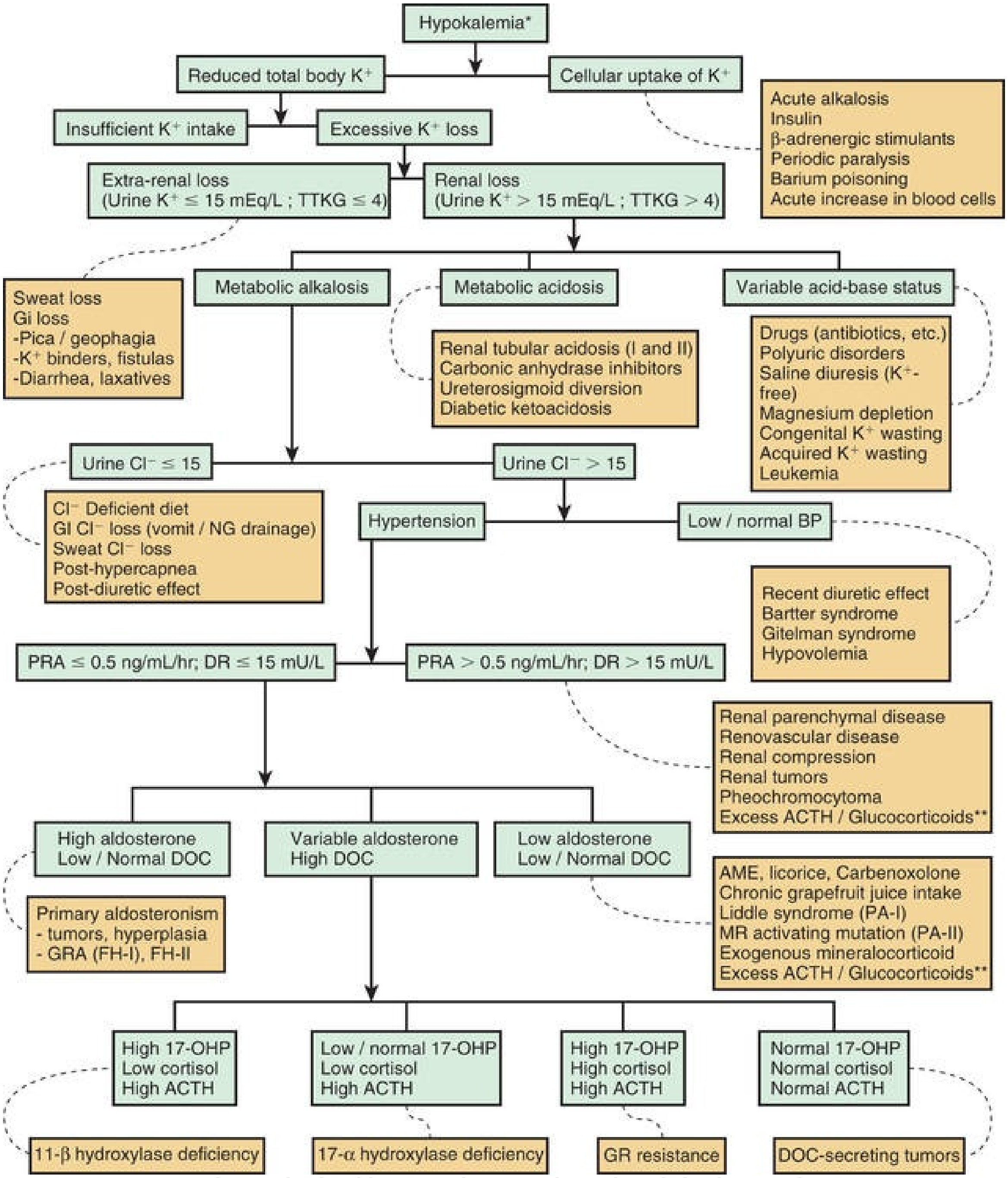
Hypokalemia*
Reduced total body K⁺
Cellular uptake of K⁺
Acute alkalosis
Insulin
β-adrenergic stimulants
Periodic paralysis
Barium poisoning
Acute increase in blood cells
Insufficient K⁺ intake
Excessive K⁺ loss
Extra-renal loss (Urine K⁺ ≤ 15 mEq/L ; TTKG ≤ 4)
Renal loss (Urine K⁺ > 15 mEq/L ; TTKG > 4)
Sweat loss
Gi loss
-Pica / geophagia
-K⁺ binders, fistulas
-Diarrhea, laxatives
Metabolic alkalosis
Metabolic acidosis
Variable acid-base status
Renal tubular acidosis (I and II)
Carbonic anhydrase inhibitors
Ureterosigmoid diversion
Diabetic ketoacidosis
Drugs (antibiotics, etc.)
Polyuric disorders
Saline diuresis (K⁺-free)
Magnesium depletion
Congenital K⁺ wasting
Acquired K⁺ wasting
Leukemia
Urine Cl⁻ ≤ 15
Urine Cl⁻ > 15
Cl⁻ Deficient diet
GI Cl⁻ loss (vomit / NG drainage)
Sweat Cl⁻ loss
Post-hypercapnea
Post-diuretic effect
Hypertension
Low / normal BP
Recent diuretic effect
Bartter syndrome
Gitelman syndrome
Hypovolemia
PRA ≤ 0.5 ng/mL/hr; DR ≤ 15 mU/L
PRA > 0.5 ng/mL/hr; DR > 15 mU/L
Renal parenchymal disease
Renovascular disease
Renal compression
Renal tumors
Pheochromocytoma
Excess ACTH / Glucocorticoids**
High aldosterone Low / Normal DOC
Variable aldosterone High DOC
Low aldosterone Low / Normal DOC
Primary aldosteronism
- tumors, hyperplasia
- GRA (FH-I), FH-II
AME, licorice, Carbenoxolone
Chronic grapefruit juice intake
Liddle syndrome (PA-I)
MR activating mutation (PA-II)
Exogenous mineralocorticoid
Excess ACTH / Glucocorticoids**
High 17-OHP Low cortisol High ACTH
Low / normal 17-OHP Low cortisol High ACTH
High 17-OHP High cortisol High ACTH
Normal 17-OHP Normal cortisol Normal ACTH
11-β hydroxylase deficiency
17-α hydroxylase deficiency
GR resistance
DOC-secreting tumors

FIG. 68.4 Diagnostic algorithm to evaluate persistent hypokalemia. *Spurious hypokalemia must be excluded. **Hypokalemia is uncommon in uncomplicated edematous disorders and in conditions associated with excessive glucocorticosteroids. Conditions associated with high circulating levels of glucocorticosteroids often have normal renin activity. 17-OHP, 17-Hydroxyprogesterone; ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; BP, blood pressure; Cl^- , chloride; DOC, 11-deoxycorticosterone; DR, direct renin assay; GI, gastrointestinal; FH-II, familial hyperaldosteronism type II; GR, glucocorticoid receptor; GRA (FH-I), glucocorticoid remediable aldosteronism (familial hyperaldosteronism type I); K^+ , potassium; MR, mineralocorticoid receptor; PA-I, pseudoaldosteronism type I; PA-II, pseudoaldosteronism type II; PRA, plasma renin activity; TTKG, transtubular potassium gradient. (From Shoemaker LR, Eaton BV, Buchino JJ: A three-year-old with

persistent hypokalemia, *J Pediatr* 151:696–699, 2007.)

If a clear etiology is not apparent, the measurement of urinary K^+ distinguishes between renal and extrarenal losses. The kidneys should conserve K^+ in the presence of extrarenal losses. Urinary K^+ losses can be assessed with a 24 hr urine collection, spot K^+ :creatinine ratio, fractional excretion of K^+ , or calculation of the *transtubular K^+ gradient* (TTKG), which is the most widely used approach in children:

$$\mathrm{TTKG} = [\mathrm{K}]_{\mathrm{urine}}/[\mathrm{K}]_{\mathrm{plasma}} \times (\text{plasma osmolality}/\text{urine osmolality})$$

where $[K]_{urine}$ = urine potassium concentration and $[K]_{plasma}$ = plasma potassium concentration.

The urine osmolality must be greater than the serum osmolality for the result of this calculation to be valid. A TTKG >4 in the presence of hypokalemia suggests excessive urinary losses of K^+ . The urinary K^+ excretion value can be misleading if the stimulus for renal loss, such as a diuretic, is no longer present.

Treatment

Factors that influence the treatment of hypokalemia include the K^+ level, clinical symptoms, renal function, the presence of transcellular shifts of K^+ , ongoing losses, and the patient's ability to tolerate oral K^+ . Severe, symptomatic hypokalemia requires aggressive treatment. Supplementation is more cautious if renal function is decreased because of the kidney's limited ability to excrete excessive K^+ . The plasma potassium level does not always provide an accurate estimation of the total body K^+ deficit because there may be shifts of K^+ from the ICS to the plasma. Clinically, such shifts occur most often with metabolic acidosis and the insulin deficiency of DKA; the plasma $[K^+]$ measurement underestimates the degree of total body K^+ depletion. When these problems are corrected, K^+ moves into the ICS, so more K^+ supplementation is required to correct the hypokalemia. Likewise, the presence of a transcellular shift of K^+ into the cells indicates that the total body K^+ depletion is less severe. In an isolated transcellular shift, as in hypokalemic periodic paralysis, K^+ supplementation should be used cautiously, given the risk of hyperkalemia when the transcellular shift resolves. This caution is especially required in thyrotoxic periodic paralysis, which responds dramatically to propranolol, with correction of weakness and hypokalemia. Patients who have ongoing losses of K^+ need correction of the deficit and replacement of the ongoing losses.

Because of the risk of hyperkalemia, intravenous K^+ should be used very cautiously. Oral K^+ is safer, but not as rapid in urgent situations. Liquid preparations are bitter tasting; microencapsulated or wax matrix formulations are less irritating than tablets to the gastric mucosa. Oral dosing is variable depending on the clinical situation. A typical starting dose is 1-2 mEq/kg/day, with a maximum of 60 mEq/day in divided doses. The dose of IV potassium is 0.5-1.0 mEq/kg, usually given over 1 hr. The adult maximum dose is 40 mEq. Conservative dosing is generally preferred. Potassium chloride is the usual choice for supplementation, although the presence of concurrent electrolyte abnormalities may dictate other options. Patients with acidosis and hypokalemia can receive potassium acetate or potassium citrate. If hypophosphatemia is present, some of the potassium deficit can be replaced with potassium phosphate. It is sometimes possible to decrease ongoing K^+ losses. For patients with excessive urinary losses, potassium-sparing diuretics are effective, but they need to be used cautiously in patients with renal insufficiency. If hypokalemia, metabolic alkalosis, and volume depletion are present (with gastric losses), restoration of intravascular volume with adequate NaCl will decrease urinary K^+ losses. Correction of concurrent hypomagnesemia is important because it may cause hypokalemia. Disease-specific therapy is effective in many of the genetic tubular disorders.

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68.5

Magnesium

Larry A. Greenbaum

Keywords

hypomagnesemia
hypermagnesemia
Gitelman syndrome
nephrocalcinosis
hypocalcemia
tetany
seizures
preeclampsia

Magnesium Metabolism

Body Content and Physiologic Function

Magnesium is the 4th most common cation in the body and the 3rd most common intracellular cation (see Fig. 68.3). From 50–60% of body magnesium is in bone, where it serves as a reservoir because 30% is exchangeable, allowing movement to the ECS. Most intracellular magnesium is bound to proteins; only approximately 25% is exchangeable. Because cells with higher metabolic rates have higher magnesium concentrations, most intracellular magnesium is present in muscle and liver.

The normal plasma magnesium concentration is 1.5-2.3 mg/dL (1.2-1.9 mEq/L; 0.62-0.94 mmol/L), with some variation among clinical laboratories. Infants have slightly higher plasma magnesium concentrations than older children and adults. Only 1% of body magnesium is extracellular (60% ionized; 15% complexed; 25% protein bound). In the United States, serum magnesium is reported as mg/dL (Table 68.6). Values in the left-column unit are converted into the right-column unit by multiplying the conversion factor (e.g., calcium of

10 mg/dL × 0.25 = 2.5 mmol/L). Dividing the right-column unit by the conversion factor converts to the units of the left-column unit.

Table 68.6

Conversion Factors for Calcium, Magnesium, and Phosphorus

	UNIT	CONVERSION FACTOR	UNIT
Calcium	mg/dL	0.25	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.5	mEq/L
Magnesium	mg/dL	0.411	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.822	mEq/L
Phosphorus	mg/dL	0.32	mmol/L

Magnesium is a necessary cofactor for hundreds of enzymes. It is important for membrane stabilization and nerve conduction. Adenosine triphosphate (ATP) and guanosine triphosphate need associated magnesium when they are used by ATPases, cyclases, and kinases.

Magnesium Intake

Between 30% and 50% of dietary magnesium is absorbed. Good dietary sources include green vegetables, cereals, nuts, meats, and hard water, although many foods contain magnesium. Human milk contains approximately 35 mg/L of magnesium; formula contains 40-70 mg/L. The small intestine is the major site of magnesium absorption, but the regulation of magnesium absorption is poorly understood. There is passive absorption, which permits high absorption in the presence of excessive intake. It probably occurs by a paracellular mechanism. Absorption is diminished in the presence of substances that complex with magnesium (free fatty acids, fiber, phytate, phosphate, oxalate); increased intestinal motility and calcium also decrease magnesium absorption. Vitamin D and parathyroid hormone (PTH) may enhance absorption, although this effect is limited. Intestinal absorption does increase when intake is decreased, possibly by a saturable, active transport system. If there is no oral intake of magnesium, obligatory secretory losses prevent the complete elimination of intestinal losses.

Magnesium Excretion

Renal excretion is the principal regulator of magnesium balance. There is no defined hormonal regulatory system, although PTH may increase tubular resorption. Approximately 15% of resorption occurs in the proximal tubule, and 70% in the thick ascending limb (TAL) of the loop of Henle. Proximal resorption may be higher in neonates. High serum magnesium levels inhibit resorption in the TAL, suggesting that active transport is involved. Approximately 5–10% of filtered magnesium is resorbed in the distal tubule. Hypomagnesemia increases absorption in the TAL and the distal tubule.

Hypomagnesemia

Hypomagnesemia is relatively common in hospitalized patients, although most cases are asymptomatic. Detection requires a high index of suspicion because magnesium is not measured in most basic metabolic panels.

Etiology and Pathophysiology

Gastrointestinal and renal losses are the major causes of hypomagnesemia (Table 68.7). Diarrheal fluid contains up to 200 mg/L of magnesium; gastric contents have only approximately 15 mg/L, but high losses can cause depletion. Steatorrhea causes magnesium loss as a result of the formation of magnesium-lipid salts; restriction of dietary fat can decrease losses. The potassium-lowering agent patiromer binds magnesium and may cause hypomagnesemia.

Table 68.7

Causes of Hypomagnesemia

Gastrointestinal Losses

Diarrhea
Nasogastric suction or emesis
Inflammatory bowel disease
Celiac disease
Cystic fibrosis
Intestinal lymphangiectasia
Small bowel resection or bypass
Pancreatitis

- Protein-calorie malnutrition
- Patiromer
- Hypomagnesemia with secondary hypocalcemia (OMIM 602014)*

Renal Disorders

- Medications
    - Amphotericin
    - Cisplatin
    - Cyclosporine, tacrolimus
    - Loop diuretics
    - Mannitol
    - Pentamidine
    - Proton pump inhibitors
    - Aminoglycosides
    - Thiazide diuretics
    - Epidermal growth factor receptor inhibitors (cetuximab)
- Diabetes
- Acute tubular necrosis (recovery phase)
- Postobstructive nephropathy
- Chronic kidney diseases
    - Interstitial nephritis
    - Glomerulonephritis
    - Post–renal transplantation
- Hypercalcemia
- Intravenous fluids
- Primary aldosteronism
- Genetic diseases
    - Gitelman syndrome (OMIM 263800)
    - Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
    - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM 248250)
    - Familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement (OMIM 248190)
    - Autosomal recessive renal magnesium wasting with normocalciuria (OMIM 611718)

    - Renal cysts and diabetes syndrome (OMIM 137920)
    - Autosomal dominant hypomagnesemia (OMIM 160120/613882/154020)
    - EAST syndrome (OMIM 612780)
    - Autosomal dominant hypoparathyroidism (OMIM 146200)
    - Mitochondrial disorders (OMIM 500005)
- Hypomagnesemia after transient neonatal hyperphenylalaninemia
- Hypomagnesemia with impaired brain development
- Hypomagnesemia with metabolic syndrome
- Hyperuricemia, pulmonary hypertension, renal failure, alkalosis syndrome (HUPRA)
- HNF1B nephropathy

Miscellaneous Causes

- Poor intake
- Hungry bone syndrome
- Insulin administration
- Pancreatitis
- Intrauterine growth restriction
- Infants of diabetic mothers
- Exchange transfusion

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* This disorder is also associated with renal magnesium wasting.

EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Hypomagnesemia with secondary hypocalcemia , a rare autosomal recessive disorder, is caused by decreased intestinal absorption of magnesium and renal magnesium wasting. Patients with this disorder have mutations in a gene expressed in intestine and kidney; *TRPM6* codes for a transient receptor potential cation channel. The patients have seizures, tetany, tremor, or restlessness at 2-8 wk of life as a result of severe hypomagnesemia (0.2-0.8

mg/dL) and secondary hypocalcemia.

Renal losses may occur because of **medications** that are direct tubular toxins. Amphotericin frequently causes significant magnesium wasting and is typically associated with other tubular defects (especially potassium wasting). Cisplatin produces dramatic renal magnesium losses. Diuretics affect tubular handling of magnesium. Loop diuretics cause a mild increase in magnesium excretion, and thiazide diuretics have even less effect. Chronic use of proton pump inhibitors may cause hypomagnesemia. Potassium-sparing diuretics reduce magnesium losses. Osmotic agents, such as mannitol, glucose in diabetes mellitus, and urea in the recovery phase of acute tubular necrosis, increase urinary magnesium losses. Epidermal growth factor (EGF) receptor inhibitors cause renal magnesium wasting. IV fluid, by expanding the intravascular volume, decreases renal resorption of sodium and water, thereby impairing magnesium resorption. Hypercalcemia inhibits magnesium resorption in the loop of Henle, although this inhibition does not occur in hypercalcemia caused by familial hypercalcemic hypocalciuria or lithium.

A number of rare genetic diseases cause renal magnesium loss. Gitelman and Bartter syndromes, both autosomal recessive disorders, are the most common entities (see Chapter 549). **Gitelman syndrome** , caused by a defect in the thiazide-sensitive Na^+ -Cl^- co-transporter in the distal tubule, is usually associated with hypomagnesemia. Hypomagnesemia occurs in a minority of patients with **Bartter syndrome** , which can be caused by mutations in multiple genes necessary for Na^+ and Cl^- reabsorption in the loop of Henle. In both disorders there is hypokalemic metabolic alkalosis. Typically, hypomagnesemia is not severe and is asymptomatic, although tetany as a result of hypomagnesemia occasionally occurs.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (Michelis-Castrillo syndrome) , an autosomal recessive disorder, is caused by mutations in the gene for claudin 16 (paracellin-1), located in the tight junctions of the TAL of the loop of Henle. Patients with the disease have severe renal wasting of magnesium and calcium with secondary hypomagnesemia and nephrocalcinosis; serum calcium levels are normal. Chronic renal failure frequently occurs during childhood. Other features include kidney stones, urinary tract infections, hematuria, increased PTH levels, tetany, seizures, incomplete distal RTA, hyperuricemia, polyuria, and polydipsia. Patients with **familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement** have mutations in the gene for claudin 19.

Autosomal recessive renal magnesium wasting with normocalciuria is caused by mutations in the EGF gene. Clinical manifestations include seizures, mild to moderate psychomotor retardation, and brisk tendon reflexes.

Autosomal dominant renal magnesium wasting is caused by mutations in a number of different genes. A dominant-negative mutation in the gene encoding the Na^+ ,K^+ -ATPase γ subunit is associated with hypomagnesemia, increased urinary magnesium losses, hypocalciuria, and normocalcemia. Patients may present with seizures; most are asymptomatic, despite serum magnesium levels of 0.8-1.5 mg/dL. Mutations in *CNNM2* , which encodes a protein that mediates magnesium-sensitive sodium currents, cause isolated hypomagnesemia. A mutation in *KCNA1* , a gene that encodes a K^+ channel, also causes an autosomal dominant form of hypomagnesemia; symptoms may be severe.

Renal cysts and diabetes syndrome , which is caused by mutations in the gene for hepatocyte nuclear factor-1β, is associated with hypomagnesemia, despite the frequent presence of renal insufficiency. The hypomagnesemia is usually mild but may cause symptomatic hypocalcemia. **EAST syndrome** is caused by mutations in a potassium channel, and patients with this autosomal recessive disorder have hypokalemia, metabolic alkalosis, and hypomagnesemia. **Autosomal dominant hypoparathyroidism** is caused by an activating mutation in the calcium-sensing receptor, which also senses magnesium levels in the kidney (see Chapter 589). The mutated receptor inappropriately perceives that magnesium and calcium levels are elevated, leading to urinary wasting of both cations. Hypomagnesemia, if present, is usually mild. A mutation in a mitochondrially encoded transfer RNA is associated with hypomagnesemia, hypertension, and hypercholesterolemia. Hypomagnesemia is occasionally present in children with other mitochondrial disorders.

Poor intake is an unusual cause of hypomagnesemia, although it can be seen in children who are hospitalized and receive only IV fluids without magnesium. In **hungry bone syndrome** , which most frequently occurs after parathyroidectomy in patients with hyperparathyroidism, magnesium moves into bone as a result of accelerated bone formation. These patients usually have hypocalcemia and hypophosphatemia through the same mechanism. A similar mechanism can occur during the **refeeding phase of protein-calorie malnutrition** in children, with high magnesium use during cell growth depleting the patient's limited reserves. Insulin therapy stimulates uptake of magnesium by cells, and in DKA, in which total body magnesium is low because of osmotic losses, hypomagnesemia frequently occurs. In **pancreatitis** there is saponification of magnesium and calcium in necrotic fat, causing both hypomagnesemia and hypocalcemia.

Transient hypomagnesemia in newborns , which is sometimes idiopathic, is more common in infants of diabetic mothers, presumably as a result of maternal depletion from osmotic losses. Other maternal diseases that cause magnesium losses predispose infants to hypomagnesemia. Hypomagnesemia is more common in infants with intrauterine growth restriction. Hypomagnesemia may develop in newborn infants who require exchange transfusions because of magnesium removal by the citrate in banked blood.

Clinical Manifestations

Hypomagnesemia causes secondary hypocalcemia by impairing the release of PTH by the parathyroid gland and through blunting of the tissue response to PTH. Thus, hypomagnesemia is part of the differential diagnosis of hypocalcemia. It usually occurs only at magnesium levels <0.7 mg/dL. The dominant manifestations of hypomagnesemia are caused by hypocalcemia: tetany, presence of Chvostek and Trousseau signs, and seizures. However, with severe hypomagnesemia, these same signs and symptoms may be present despite normocalcemia. Persistent hypocalcemia caused by hypomagnesemia is a rare cause of rickets.

Many causes of hypomagnesemia also result in hypokalemia. Hypomagnesemia may produce renal potassium wasting and hypokalemia that corrects only with magnesium therapy. ECG changes with hypomagnesemia include flattening of the T wave and lengthening of the ST segment. Arrhythmias may occur, almost always in the setting of underlying heart disease.

Diagnosis

The etiology of hypomagnesemia is often readily apparent from the clinical situation. The child should be assessed for GI disease, adequate intake, and kidney disease, with close attention paid to medications that may cause renal magnesium wasting. When the diagnosis is uncertain, an evaluation of urinary magnesium losses distinguishes between renal and nonrenal causes. The *fractional excretion of magnesium* (FE_{Mg}) is calculated via the following formula:

$$FE_{Mg} = (U_{Mg} \times P_{Cr})/([0.7 \times P_{Mg}] \times U_{Cr}) \times 100$$

where U_{Mg} = urinary magnesium concentration, P_{Cr} = plasma creatinine concentration, P_{Mg} = plasma magnesium concentration, and U_{Cr} = urinary magnesium concentration. The plasma magnesium concentration is multiplied by 0.7 because approximately 30% is bound to albumin and not filtered at the glomerulus.

The FE_{Mg} does not vary with age, but it does change according to the serum magnesium concentration. The FE_{Mg} ranges from 1–8% in children with normal magnesium levels. In the patient with hypomagnesemia as a result of extrarenal causes, FE_{Mg} should be low because of renal conservation, typically <2%. The FE_{Mg} is inappropriately elevated in the setting of renal magnesium wasting; values are usually >4% and frequently >10%. The measurement should not be made during a magnesium infusion, because the acute increase in serum magnesium increases urinary magnesium. Other approaches for evaluating urinary magnesium losses include calculation of 24 hr urinary magnesium losses and the urine magnesium/creatinine ratio, both of which vary with age.

The genetic causes of renal magnesium loss are distinguished on the basis of the measurement of other serum and urinary electrolytes. Children with Gitelman or Bartter syndrome have hypokalemia and metabolic alkalosis.

Treatment

Severe hypomagnesemia is treated with parenteral magnesium. Magnesium sulfate is given at a dose of 25-50 mg/kg (0.05-0.1 mL/kg of a 50% solution; 2.5-5.0 mg/kg of elemental magnesium). It is administered as a slow IV infusion, although it may be given intramuscularly in neonates. The rate of IV infusion should be slowed if a patient experiences diaphoresis, flushing, or a warm sensation. The dose is often repeated every 6 hr (every 8-12 hr in neonates), for a total of 2-3 doses, before the plasma magnesium concentration is rechecked. Lower doses are used in children with renal insufficiency.

Long-term therapy is usually given orally. Preparations include magnesium gluconate (5.4 mg elemental magnesium/100 mg), magnesium oxide (60 mg elemental magnesium/100 mg), and magnesium sulfate (10 mg elemental magnesium/100 mg). Sustained-release preparations include Slow-Mag (60 mg elemental magnesium/tablet) and Mag-Tab SR (84 mg elemental magnesium/tablet). Oral magnesium dosing should be divided to decrease cathartic side effects. Alternatives to oral magnesium are intramuscular injections and nighttime nasogastric infusion, both designed to minimize diarrhea. Magnesium supplementation must be used cautiously in the context of renal insufficiency.

Hypermagnesemia

Clinically significant hypermagnesemia is almost always secondary to excessive intake. It is unusual, except in neonates born to mothers who are receiving IV magnesium for preeclampsia or eclampsia (see Chapter 119.5).

Etiology and Pathophysiology

There is no feedback mechanism to prevent magnesium absorption from the GI tract. Magnesium is present in high amounts in certain laxatives, enemas, cathartics used to treat drug overdoses, and antacids. It is also usually present in total parenteral nutrition (TPN), and neonates may receive high amounts transplacentally if maternal levels are elevated. Usually the kidneys excrete excessive magnesium, but this ability is diminished in patients with chronic renal failure. In addition, neonates and young infants are vulnerable to excessive magnesium ingestion because of their reduced GFR. Most pediatric cases not related to maternal hypermagnesemia occur in infants as a result of excessive use of antacids or laxatives. Mild hypermagnesemia may occur in chronic renal failure, familial hypocalciuric hypercalcemia, DKA, lithium ingestion, milk-alkali syndrome, and tumor lysis syndrome. The hypermagnesemia in DKA occurs despite significant intracellular magnesium depletion as a result of urinary losses; hypomagnesemia often occurs after insulin treatment.

Clinical Manifestations

Symptoms usually do not appear until the plasma magnesium level is >4.5 mg/dL. Hypermagnesemia inhibits acetylcholine release at the neuromuscular junction, producing hypotonia, hyporeflexia, and weakness; paralysis occurs at high concentrations. The neuromuscular effects may be exacerbated by aminoglycoside antibiotics. Direct CNS depression causes lethargy and sleepiness; infants have a poor suck. Elevated magnesium values are associated with hypotension because of vascular dilation, which also causes flushing. Hypotension can be profound at higher concentrations from a direct effect on cardiac function. ECG changes include prolonged PR interval, QRS complex, and QT interval. Severe hypermagnesemia (>15 mg/dL) causes complete heart block and cardiac arrest. Other manifestations of hypermagnesemia include nausea, vomiting, and hypocalcemia.

Diagnosis

Except for the case of the neonate with transplacental exposure, a high index of suspicion and a good history are necessary to make the diagnosis of hypermagnesemia. Prevention is essential; magnesium-containing compounds should be used judiciously in children with renal insufficiency.

Treatment

Most patients with normal renal function rapidly clear excess magnesium. Intravenous hydration and loop diuretics can accelerate this process. In severe cases, especially in patients with underlying renal insufficiency, dialysis may be necessary. Hemodialysis works faster than peritoneal dialysis. Exchange transfusion is another option in newborn infants. Supportive care includes monitoring of cardiorespiratory status, provision of fluids, monitoring of electrolyte levels, and the use of pressors for hypotension. In acute emergencies, especially in the context of severe neurologic or cardiac manifestations, 100 mg/kg of IV calcium gluconate is transiently effective.

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Magnesium

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68.6

Phosphorus

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Keywords

hypophosphatemia
hyperphosphatemia
vitamin D
rickets
FGF-23
phosphate binders
parathyroid hormone
PTH
refeeding hypophosphatemia
hungry bone syndrome
hypoparathyroidism
hyperparathyroidism
osteomalacia
chronic kidney disease
rhabdomyolysis
tumor lysis
familial tumoral calcinosis

Approximately 65% of plasma phosphorus is in phospholipids, but these compounds are insoluble in acid and are not measured by clinical laboratories. It is the phosphorus content of **plasma phosphate** that is determined. The result is reported as either phosphate or phosphorus, although even when the term *phosphate* is used, it is actually the *phosphorus* concentration that is measured and reported. The result is that the terms phosphate and phosphorus are often used interchangeably. The term *phosphorus* is preferred when referring to the plasma concentration. Conversion from the units used in the United States (mg/dL) to mmol/L is straightforward (see Table 68.6).

Phosphorus Metabolism

Body Content and Physiologic Function

Most phosphorus is in bone or is intracellular, with <1% in plasma. At a physiologic pH, there are monovalent and divalent forms of phosphate because the pK_a (ionization constant of acid) of these forms is 6.8. Approximately 80% is divalent, and the remainder is monovalent at a pH of 7.4. The remainder can be filtered by the glomerulus, with most existing as free phosphate and a small percentage complexed with calcium, magnesium, or sodium. Phosphate is the most plentiful intracellular anion, although the majority is part of a larger compound (ATP).

More than that of any other electrolyte, the phosphorus concentration varies with age (Table 68.8). The teleologic explanation for the high concentration during childhood is the need for phosphorus to facilitate growth. There is diurnal variation in the plasma phosphorus concentration, with the peak during sleep.

Table 68.8

Serum Phosphorus Levels During Childhood

AGE	PHOSPHORUS LEVEL (mg/dL)
0-5 day	4.8-8.2
1-3 yr	3.8-6.5
4-11 yr	3.7-5.6
12-15 yr	2.9-5.4
16-19 yr	2.7-4.7

Phosphorus, as a component of adenosine triphosphate (ATP) and other trinucleotides, is critical for cellular energy metabolism. It is necessary for cell signaling and nucleic acid synthesis, and it is a component of cell membranes and other structures. Along with calcium, phosphorus is necessary for skeletal mineralization. A net positive phosphorus balance is required during growth, with the growing skeleton especially vulnerable to deficiency.

Phosphorus Intake

Phosphorus is readily available in food. Milk and milk products are the best sources of phosphorus; high concentrations are present in meat and fish. Vegetables have more phosphorus than fruits and grains. GI absorption of phosphorus is fairly proportional to intake, with approximately 65% of intake being absorbed, including a small amount that is secreted. Absorption, almost exclusively in the small intestine, occurs via a paracellular diffusive process and a vitamin D–regulated transcellular pathway. However, the impact of the change in phosphorus absorption caused by vitamin D is relatively small compared with the effect of variations in phosphorus intake.

Phosphorus Excretion

Despite the wide variation in phosphorus absorption dictated by oral intake, excretion matches intake, except for the needs for growth. The kidney regulates phosphorus balance, which is determined by intrarenal mechanisms and hormonal actions on the nephron.

Approximately 90% of plasma phosphate is filtered at the glomerulus, although there is some variation based on plasma phosphate and calcium concentrations. There is no significant secretion of phosphate along the nephron. Resorption of phosphate occurs mostly in the proximal tubule, although a small amount can be resorbed in the distal tubule. Normally, approximately 85% of the filtered load is resorbed. A sodium-phosphate co-transporter mediates the uptake of phosphate into the cells of the proximal tubule.

The dietary phosphorus determines the amount of phosphate resorbed by the nephron. There are both acute and chronic changes in phosphate resorption that are based on intake. Many of these changes appear to be mediated by intrarenal mechanisms that are independent of regulatory hormones. Fibroblast growth factor-23 (**FGF-23**) inhibits renal resorption of phosphorus in the proximal tubule, and its level increases in the setting of hyperphosphatemia. FGF-23 also inhibits synthesis of calcitriol in the kidney by decreasing 1α-hydroxylase activity.

Secreted in response to a low plasma calcium level, PTH decreases resorption of phosphate, increasing the urinary phosphate level. This process appears to have a minimal effect during normal physiologic variation in PTH levels. However, it does impact the setting of pathologic changes in PTH synthesis.

Low plasma phosphorus stimulates the 1α-hydroxylase in the kidney that converts 25-hydroxyvitamin D (25-D) to 1,25-dihydroxyvitamin D (1,25-D; calcitriol). Calcitriol increases intestinal absorption of phosphorus and is necessary for maximal renal resorption of phosphate. The effect of a change in calcitriol on urinary phosphate is significant only when the level of calcitriol was initially low, arguing against a role for calcitriol in nonpathologic conditions.

Hypophosphatemia

Because of the wide variation in normal plasma phosphorus levels, the definition of hypophosphatemia is age dependent (see Table 68.8). The normal range reported by a laboratory may be based on adult normal values and therefore may be misleading in children. A serum phosphorus level of 3 mg/dL, a normal value in an adult, indicates clinically significant hypophosphatemia in an infant.

The plasma phosphorus level does not always reflect the total body stores because only 1% of phosphorus is extracellular. Thus, a child may have significant phosphorus deficiency despite a normal plasma phosphorus concentration when there is a shift of phosphorus from the ICS.

Etiology and Pathophysiology

A variety of mechanisms cause hypophosphatemia (Table 68.9). A transcellular shift of phosphorus into cells occurs with processes that stimulate cellular usage of phosphorus (glycolysis). Usually, this shift causes only a minor, transient decrease in plasma phosphorus, but if intracellular phosphorus deficiency is present, the plasma phosphorus level can decrease significantly, producing symptoms of acute hypophosphatemia. Glucose infusion stimulates insulin release, leading to entry of glucose and phosphorus into the cells. Phosphorus is then used during glycolysis and other metabolic processes. A similar phenomenon can occur during the treatment of DKA, and patients with DKA are typically phosphorus depleted because of urinary phosphorus losses.

Table 68.9

Causes of Hypophosphatemia

Transcellular Shifts

- Glucose infusion
- Insulin
- Refeeding
- Total parenteral nutrition
- Respiratory alkalosis
- Tumor growth
- Bone marrow transplantation
- Hungry bone syndrome

Decreased Intake

- Nutritional
- Premature infants
- Low phosphorus formula
- Antacids and other phosphate binders

Renal Losses

- Hyperparathyroidism
- Parathyroid hormone–related peptide
- X-linked hypophosphatemic rickets (OMIM 307800)
- Overproduction of fibroblast growth factor-23
  - Tumor-induced rickets
  - McCune-Albright syndrome (OMIM 174800)
  - Epidermal nevus syndrome
  - Neurofibromatosis
  - Autosomal dominant hypophosphatemic rickets (OMIM 193100)
  - Autosomal recessive hypophosphatemic rickets, types 1 and 2 (OMIM 241520/613312)
  - Fanconi syndrome
- Dent disease (OMIM 300009/300555)
- Hypophosphatemic rickets with hypercalciuria (OMIM 241530)
- Volume expansion and intravenous fluids
- Metabolic acidosis
- Diuretics
- Glycosuria

Glucocorticoids
Kidney transplantation

Multifactorial

Vitamin D deficiency
Vitamin D–dependent rickets type 1 (OMIM 264700)
Vitamin D–dependent rickets type 2 (OMIM 277440)
Alcoholism
Sepsis
Dialysis

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Refeeding of patients with protein-calorie malnutrition causes anabolism, which leads to significant cellular demand for phosphorus. The increased phosphorus uptake for incorporation into newly synthesized compounds containing phosphorus leads to hypophosphatemia, which can be severe and symptomatic. **Refeeding hypophosphatemia** occurs frequently during treatment of severe anorexia nervosa. It can occur during treatment of children with malnutrition from any cause, such as cystic fibrosis, Crohn disease, burns, neglect, chronic infection, or famine. Hypophosphatemia usually occurs within the 1st 5 days of refeeding and is prevented by a gradual increase in nutrition with appropriate phosphorus supplementation. TPN without adequate phosphorus can cause hypophosphatemia.

Phosphorus moves into the ICS during a respiratory alkalosis and during recovery from a respiratory acidosis. An acute decrease in the carbon dioxide concentration, by raising the intracellular pH, stimulates glycolysis, leading to intracellular use of phosphorus and hypophosphatemia. Because a metabolic alkalosis has less effect on the intracellular pH (CO_2 diffuses across cell membranes much faster than bicarbonate), transcellular phosphorus movement is minimal with a metabolic alkalosis.

Tumors that grow rapidly, such as those associated with leukemia and lymphoma, may use large amounts of phosphorus, leading to hypophosphatemia. A similar phenomenon may occur during the hematopoietic reconstitution that follows bone marrow transplantation. In **hungry bone syndrome** there is avid bone uptake of phosphorus, along with calcium and magnesium, which can produce plasma deficiency of all 3 ions. Hungry bone syndrome is most common after parathyroidectomy for hyperparathyroidism because the stimulus for bone dissolution is acutely removed, but bone synthesis continues.

Nutritional phosphorus deficiency is unusual because most foods contain phosphorus. However, infants are especially susceptible because of their high demand for phosphorus to support growth, especially of the skeleton. Very-low-birthweight infants have particularly rapid skeletal growth, and phosphorus deficiency and rickets may develop if they are fed human milk, or formula for term infants. There is also a relative deficiency of calcium. The provision of additional calcium and phosphorus, using breast milk fortifier or special premature infant formula, prevents this complication. Phosphorus deficiency, sometimes with concomitant calcium and vitamin D deficiencies, occurs in infants who are not given enough milk or who receive a milk substitute that is nutritionally inadequate.

Antacids containing aluminum hydroxide (e.g., Maalox, Mylanta) bind dietary phosphorus and secreted phosphorus, preventing absorption. This process can cause phosphorus deficiency and rickets in growing children. A similar mechanism causes hypophosphatemia in patients who are overtreated for hyperphosphatemia with phosphorus binders. In children with kidney failure, the addition of dialysis to phosphorus binders increases the risk of iatrogenic hypophosphatemia in these normally hyperphosphatemic patients. This complication, which is more common in infants, can worsen renal osteodystrophy.

Excessive renal losses of phosphorus occur in a variety of inherited and acquired disorders. Because PTH inhibits the resorption of phosphorus in the proximal tubule, **hyperparathyroidism** causes hypophosphatemia (see Chapter 591). The dominant clinical manifestation, however, is hypercalcemia, and the hypophosphatemia is usually asymptomatic. The phosphorus level in hyperparathyroidism is not extremely low, and there is no continued loss of phosphorus because a new steady state is achieved at the lower plasma phosphorus level. Renal excretion therefore does not exceed intake over the long term. Occasional malignancies produce PTH-related peptide, which has the same actions as PTH and causes hypophosphatemia and hypercalcemia.

A variety of diseases cause renal phosphate wasting, hypophosphatemia, and rickets resulting from excess FGF-23 (see Chapter 64). These disorders include

X-linked hypophosphatemic rickets, tumor-induced osteomalacia, autosomal dominant hypophosphatemic rickets, and autosomal recessive hypophosphatemic rickets types 1 and 2.

Fanconi syndrome is a generalized defect in the proximal tubule leading to urinary wasting of bicarbonate, phosphorus, amino acids, uric acid, and glucose (see Chapter 547.1). The clinical sequelae result from the metabolic acidosis and hypophosphatemia. In children an underlying genetic disease, usually cystinosis, often causes Fanconi syndrome, but it can be secondary to a variety of toxins and acquired diseases. Some patients have incomplete Fanconi syndrome, and phosphorus wasting may be one of the manifestations.

Dent disease , an X-linked disorder, can cause renal phosphorus wasting and hypophosphatemia, although the latter is not present in most cases. Other possible manifestations of Dent disease include tubular proteinuria, hypercalciuria, nephrolithiasis, rickets, and decreased kidney function. Dent disease may be secondary to mutations in a gene that encodes a chloride channel or the *OCRL1* gene, which may also cause Lowe syndrome (see Chapter 547.1). **Hypophosphatemic rickets with hypercalciuria** is a rare autosomal recessive disorder, principally described in kindreds from the Middle East (see Chapter 64). Mutations in a sodium-phosphate co-transporter cause hypophosphatemia in this disorder, and complications may include nephrolithiasis and osteoporosis.

Metabolic acidosis inhibits resorption of phosphorus in the proximal tubule. In addition, metabolic acidosis causes a transcellular shift of phosphorus out of cells because of intracellular catabolism. This released phosphorus is subsequently lost in the urine, leading to significant phosphorus depletion, even though the plasma phosphorus level may be normal. This classically occurs in DKA, in which renal phosphorus loss is further increased by the osmotic diuresis. With correction of the metabolic acidosis and the administration of insulin, both of which cause a transcellular movement of phosphorus into the cells, there is a marked decrease in the plasma phosphorus level.

Volume expansion from any cause, such as hyperaldosteronism or SIADH, inhibits resorption of phosphorus in the proximal tubule. This effect also occurs with high rates of IV fluids. Thiazide and loop diuretics can increase renal phosphorus excretion, but the increase is seldom clinically significant. Glycosuria and glucocorticoids inhibit renal conservation of phosphorus. Hypophosphatemia is common after kidney transplantation as a result of urinary phosphorus losses. Possible explanations include preexisting secondary hyperparathyroidism from chronic renal failure, glucocorticoid therapy, and upregulation of FGF-23 before transplantation. The hypophosphatemia usually resolves in a few months.

Both acquired and genetic causes of **vitamin D deficiency** are associated with hypophosphatemia (see Chapter 64). The pathogenesis is multifactorial. By impairing intestinal calcium absorption, vitamin D deficiency causes secondary hyperparathyroidism that leads to increased urinary phosphorus wasting. An absence of vitamin D decreases intestinal absorption of phosphorus and directly decreases renal resorption of phosphorus. The dominant clinical manifestation is rickets, although some patients have muscle weakness that may be related to phosphorus deficiency.

Alcoholism is the most common cause of severe hypophosphatemia in adults. Fortunately, many of the risk factors that predispose alcoholic adults to hypophosphatemia are not usually present in adolescents (malnutrition, antacid abuse, recurrent DKA episodes). Hypophosphatemia often occurs in sepsis, but the mechanism is not clear. Aggressive, protracted hemodialysis, as might be used for the treatment of methanol or ethylene glycol ingestion, can cause hypophosphatemia.

Clinical Manifestations

There are acute and chronic manifestations of hypophosphatemia. **Rickets** occurs in children with long-term phosphorus deficiency. The clinical features of rickets are described in Chapter 64 .

Severe hypophosphatemia, typically at levels <1.0-1.5 mg/dL, may affect every organ in the body because phosphorus has a critical role in maintaining adequate cellular energy. Phosphorus is a component of ATP and is necessary for glycolysis. With inadequate phosphorus, 2,3-diphosphoglycerate levels in RBCs decrease, impairing release of oxygen to the tissues. Severe hypophosphatemia can cause hemolysis and dysfunction of WBCs. Chronic hypophosphatemia causes proximal muscle weakness and atrophy. In the intensive care unit, phosphorus deficiency may slow weaning from mechanical ventilation or cause acute respiratory failure. **Rhabdomyolysis** is the most common complication of acute hypophosphatemia, usually in the setting of an acute transcellular shift of phosphorus into cells in a child with chronic phosphorus depletion (anorexia nervosa). The rhabdomyolysis is actually somewhat protective, in that cellular release of phosphorus occurs. Other manifestations of severe hypophosphatemia include cardiac dysfunction and neurologic symptoms, such as tremor, paresthesia, ataxia, seizures, delirium, and coma.

Diagnosis

The history and basic laboratory evaluation often suggest the etiology of hypophosphatemia. The history should investigate nutrition, medications, and familial disease. Hypophosphatemia and rickets in an otherwise healthy young child suggests a genetic defect in renal phosphorus conservation, Fanconi syndrome, inappropriate use of antacids, poor nutrition, vitamin D deficiency, or a genetic defect in vitamin D metabolism. The patient with Fanconi syndrome usually has metabolic acidosis, glycosuria, aminoaciduria, and a low plasma uric acid level. Measurement of 25-D and 1,25-D, calcium, and PTH differentiates among the various vitamin D deficiency disorders and primary renal phosphate wasting (see Chapter 64). Hyperparathyroidism is easily distinguished by the presence of elevated plasma PTH and calcium values.

Treatment

The plasma phosphorus level, the presence of symptoms, the likelihood of chronic depletion, and the presence of ongoing losses dictate the approach to therapy. Mild hypophosphatemia does not require treatment unless the clinical situation suggests that chronic phosphorus depletion is present or that losses are ongoing. Oral phosphorus can cause diarrhea, so the doses should be divided. IV therapy is effective in patients who have severe deficiency or who cannot tolerate oral medications. IV phosphorus is available as either sodium phosphate or potassium phosphate, with the choice usually based on the patient's plasma potassium level. Starting doses are 0.08-0.16 mmol/kg over 6 hr. The oral preparations of phosphorus are available with various ratios of sodium and potassium. This is an important consideration because some patients may not tolerate the potassium load, whereas supplemental potassium may be helpful in some diseases, such as Fanconi syndrome and malnutrition. Oral maintenance dosages are 2-3 mmol/kg/day in divided doses, although the maintenance dose varies considerably between patients.

Increasing dietary phosphorus is the only intervention needed in infants with inadequate intake. Other patients may also benefit from increased dietary phosphorus, usually from dairy products. Phosphorus-binding antacids should be discontinued in patients with hypophosphatemia. Certain diseases require specific therapy (see Chapter 64).

Hyperphosphatemia

Etiology and Pathophysiology

Renal insufficiency is the most common cause of hyperphosphatemia, with the severity proportional to the degree of kidney impairment (see Chapter 550). This occurs because GI absorption of the large dietary intake of phosphorus is unregulated, and the kidneys normally excrete this phosphorus. As renal function deteriorates, increased excretion of phosphorus is able to compensate. When kidney function is <30% of normal, hyperphosphatemia usually develops, although this varies considerably depending on dietary intake. Many of the other causes of hyperphosphatemia are more likely to develop in the setting of renal insufficiency (Table 68.10).

Table 68.10

Causes of Hyperphosphatemia

Transcellular Shifts

- Tumor lysis syndrome
- Rhabdomyolysis
- Acute hemolysis
- Diabetic ketoacidosis and lactic acidosis

Increased Intake

- Enemas and laxatives
- Cow's milk in infants
- Treatment of hypophosphatemia
- Vitamin D intoxication

Decreased Excretion

- Renal failure

Hypoparathyroidism or pseudohypoparathyroidism (OMIM 146200/603233/103580/241410/203330)
Acromegaly
Hyperthyroidism
Tumoral calcinosis with hyperphosphatemia (OMIM 211900)

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Cellular content of phosphorus is high relative to plasma phosphorus, and cell lysis can release substantial phosphorus. This is the etiology of hyperphosphatemia in **tumor lysis syndrome** , **rhabdomyolysis** , and **acute hemolysis** . These disorders cause concomitant potassium release and the risk of hyperkalemia. Additional features of tumor lysis and rhabdomyolysis are hyperuricemia and hypocalcemia, whereas indirect hyperbilirubinemia and elevated lactate dehydrogenase (LDH) values are often present with hemolysis. An elevated CPK level is suggestive of rhabdomyolysis. During lactic acidosis or DKA, use of phosphorus by cells decreases, and phosphorus shifts into the ECS. This problem reverses when the underlying problem is corrected, and especially with DKA, patients subsequently become hypophosphatemic as a result of previous renal phosphorus loss.

Excessive intake of phosphorus is especially dangerous in children with renal insufficiency. Neonates are at risk because renal function is normally reduced during the 1st few months of life. In addition, they may erroneously be given doses of phosphorus that are meant for an older child or adult. In infants fed cow's milk, which has higher phosphorus content than breast milk or formula, hyperphosphatemia may develop. **Fleet Enema** has a high amount of phosphorus that can be absorbed, especially in the patient with an ileus; infants and children with Hirschsprung disease are especially vulnerable. There is often associated hypernatremia from sodium absorption and water loss from diarrhea. Sodium phosphorus laxatives may cause hyperphosphatemia if the dose is excessive or if renal insufficiency is present. Hyperphosphatemia occurs in children who receive overaggressive treatment for hypophosphatemia. **Vitamin D intoxication** causes excessive GI absorption of both calcium and phosphorus, and the suppression of PTH by hypercalcemia decreases renal phosphorus excretion.

The absence of PTH in **hypoparathyroidism** or PTH responsiveness in

pseudohypoparathyroidism causes hyperphosphatemia because of increased resorption of phosphorus in the proximal tubule of the kidney (see Chapters 589 and 590). The associated hypocalcemia is responsible for the clinical symptoms. The hyperphosphatemia in hyperthyroidism or acromegaly is usually minor. It is secondary to increased resorption of phosphorus in the proximal tubule from the actions of thyroxine or growth hormone. Excessive thyroxine can also cause bone resorption, which may contribute to the hyperphosphatemia and cause hypercalcemia. Patients with **familial tumoral calcinosis** , a rare autosomal recessive disorder, have hyperphosphatemia as a result of decreased renal phosphate excretion and heterotopic calcifications. The disease may be secondary to mutations in the genes for a glycosyltransferase, the phosphatonin FGF-23, or the gene for Klotho, which encodes the co-receptor for FGF-23.

Clinical Manifestations

The principal clinical consequences of hyperphosphatemia are hypocalcemia and systemic calcification. The hypocalcemia is probably caused by tissue deposition of calcium-phosphorus salt, inhibition of 1,25-D production, and decreased bone resorption. Symptomatic hypocalcemia is most likely to occur when the phosphorus level increases rapidly or when diseases predisposing to hypocalcemia are present (chronic renal failure, rhabdomyolysis). Systemic calcification occurs because the solubility of phosphorus and calcium in the plasma is exceeded. This is believed to occur when plasma calcium × plasma phosphorus, both measured in mg/dL, is >70. Clinically, this condition is often apparent in the conjunctiva, where it manifests as a foreign body feeling, erythema, and injection. More ominous manifestations are hypoxia from pulmonary calcification and renal failure from nephrocalcinosis.

Diagnosis

Plasma creatinine and BUN levels should be assessed in any patient with hyperphosphatemia. The history should focus on intake of phosphorus and the presence of chronic diseases that may cause hyperphosphatemia. Measurement of K^+ , uric acid, calcium, LDH, bilirubin, hemoglobin, and CPK may be indicated if rhabdomyolysis, tumor lysis, or hemolysis is suspected. With mild hyperphosphatemia and significant hypocalcemia, measurement of the serum PTH level distinguishes between hypoparathyroidism and pseudohypoparathyroidism.

Treatment

The treatment of acute hyperphosphatemia depends on its severity and etiology. Mild hyperphosphatemia in a patient with reasonable renal function spontaneously resolves; the resolution can be accelerated by dietary phosphorus restriction. If kidney function is not impaired, IV fluids can enhance renal phosphorus excretion. For more significant hyperphosphatemia or a situation such as tumor lysis or rhabdomyolysis, in which endogenous phosphorus generation is likely to continue, addition of an oral phosphorus binder prevents absorption of dietary phosphorus and can remove phosphorus from the body by binding what is normally secreted and absorbed by the GI tract. Phosphorus binders are most effective when given with food. Binders containing aluminum hydroxide are especially efficient, but calcium carbonate is an effective alternative and may be preferred if there is a need to treat concomitant hypocalcemia. Preservation of renal function, as with high urine flow in rhabdomyolysis or tumor lysis, is an important adjunct because it will permit continued excretion of phosphorus. If the hyperphosphatemia is not responding to conservative management, especially if renal insufficiency is supervening, dialysis may be necessary to increase phosphorus removal.

Dietary phosphorus restriction is necessary for diseases causing chronic hyperphosphatemia. However, such diets are often difficult to follow, given the abundance of phosphorus in a variety of foods. Dietary restriction is often sufficient in conditions such as hypoparathyroidism and mild renal insufficiency. For more problematic hyperphosphatemia, such as with moderate renal insufficiency and end-stage renal disease, phosphorus binders are usually necessary. They include calcium carbonate, calcium acetate, sevelamer, ferric citrate, sucroferric oxyhydroxide, and lanthanum. Aluminum-containing phosphorus binders are no longer used in patients with **chronic kidney disease** because of the risk of aluminum toxicity. Dialysis directly removes phosphorus from the blood in patients with end-stage renal disease, but it is only an adjunct to dietary restriction and phosphorus binders; removal by dialysis does not keep up with normal dietary intake.

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68.7

Acid-Base Balance

Larry A. Greenbaum

Keywords

metabolic acidosis
metabolic alkalosis
respiratory acidosis
respiratory alkalosis
mixed disorder
simple disorder
metabolic compensation
respiratory compensation
anion gap
lactic acidosis
ketoacidosis
renal tubular acidosis
acidemia
alkalemia
chloride
hypoxia
mechanical ventilation
poisoning
salicylates

Acid-Base Physiology

Terminology

Chronic, mild derangements in acid-base status may interfere with normal growth and development, whereas acute, severe changes in pH can be fatal. Control of acid-base balance depends on the kidneys, the lungs, and intracellular and extracellular buffers.

A normal pH is 7.35-7.45. There is an inverse relationship between the pH and the hydrogen ion concentration($[H^+]$). At a pH of 7.40, $[H^+]$ is 40 nmol/L. A normal serum sodium concentration, 140 mEq/L, is 1 million times higher.

Maintaining a normal pH is necessary because hydrogen ions are highly reactive and are especially likely to combine with proteins, altering their function.

An **acid** is a substance that releases (“donates”) a hydrogen ion (H^+). A **base** is a substance that accepts a hydrogen ion. An acid (HA) can dissociate into a hydrogen ion and a conjugate base (A^-), as follows:

$$HA \leftrightarrow H^+ + A^-$$

A strong acid is highly dissociated, so in this reaction, there is little HA. A weak acid is poorly dissociated; not all the hydrogen ions are released from HA. A^- acts as a base when the reaction moves to the left. These reactions are in equilibrium. When HA is added to the system, there is dissociation of some HA until the concentrations of H^+ and A^- increase enough that a new equilibrium is reached. Addition of hydrogen ions causes a decrease in A^- and an increase in HA. Addition of A^- causes a decrease in hydrogen ions and an increase in HA.

Buffers are substances that attenuate the change in pH that occurs when acids or bases are added to the body. Given the extremely low $[H^+]$ in the body at physiologic pH, without buffers a small amount of hydrogen ions could cause a dramatic decline in the pH. Buffers prevent the decrease in pH by binding the added hydrogen ions, as follows:

$$A^- + H^+ \rightarrow HA$$

The increase in $[H^+]$ drives this reaction to the right. Similarly, when base is added to the body, buffers prevent the pH from increasing by releasing hydrogen ions, as follows:

$$HA \rightarrow A^- + H^+$$

The best buffers are weak acids and bases. This is because a buffer works best when it is 50% dissociated (half HA and half A^-). The pH at which a buffer is 50% dissociated is its pK_a (ionization constant of acid). The best physiologic buffers have a pK_a close to 7.40. The concentration of a buffer and its pK_a

determine the buffer's effectiveness (buffering capacity). When the pH is lower than the pK_a of a buffer, there is more HA than A^-. When the pH is higher than the pK_a, there is more A^- than HA.

Physiologic Buffers

The bicarbonate and nonbicarbonate buffers protect the body against major changes in pH. The **bicarbonate buffer system** is routinely monitored clinically and is based on the relationship between carbon dioxide (CO_2) and bicarbonate (HCO_3^-):

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$$

CO_2 acts as an acid in that, after combining with water, it releases an H^+; bicarbonate acts as its conjugate base in that it accepts an H^+. The pK_a of this reaction is 6.1. The **Henderson-Hasselbalch equation** expresses the relationship among pH, pK_a, and the concentrations of an acid and its conjugate base. This relationship is valid for any buffer. The Henderson-Hasselbalch equation for bicarbonate and CO_2 is as follows:

$$pH = 6.1 + \log[HCO_3^-]/[CO_2]$$

The **Henderson-Hasselbalch equation** for the bicarbonate buffer system has 3 variables: pH, bicarbonate concentration ($[HCO_3^-]$), and carbon dioxide concentration ($[CO_2]$). Thus, if any 2 of these variables are known, it is possible to calculate the 3rd. When one is using the Henderson-Hasselbalch equation, it is important that CO_2 and bicarbonate have the same units. CO_2 is reported clinically as mm Hg and must be multiplied by its solubility constant, 0.03 mmol/L/mm Hg, before the equation can be used. Mathematical manipulation of the Henderson-Hasselbalch equation produces the following relationship:

$$[H^+] = 24 \times P\text{CO}_2/[HCO_3^-]$$

At a normal $[H^+]$ of 40 nmol (pH 7.40), the partial pressure of carbon dioxide ($P\text{CO}_2$), which is expressed as mm Hg in this equation, is 40 when the $[HCO_3^-]$ is 24 mEq/L. This equation emphasizes that $[H^+]$, and thus pH, can be determined by the ratio of $P\text{CO}_2$ and $[HCO_3^-]$.

The bicarbonate buffer system is very effective because of the high concentration of bicarbonate in the body (24 mEq/L) and because it is an open system. The remaining body buffers are in a closed system. The bicarbonate buffer system is an open system because the lungs increase CO_2 excretion when the blood CO_2 concentration increases. When acid is added to the body, the following reaction occurs:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

In a closed system, the CO_2 would increase. The higher CO_2 concentration would lead to an increase in the reverse reaction:

$$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$$

This would increase $[H^+]$, limiting the buffering capacity of bicarbonate. However, because the lungs excrete the excess CO_2, the reverse reaction does not increase; this fact enhances the buffering capacity of bicarbonate. The same principle holds with the addition of base, because the lungs decrease CO_2 excretion and prevent the CO_2 level from falling. The lack of change in $[CO_2]$ dramatically increases the buffering capacity of bicarbonate.

The **nonbicarbonate buffers** include proteins, phosphate, and bone. Protein buffers consist of extracellular proteins, mostly albumin and intracellular proteins, including hemoglobin. Proteins are effective buffers, largely because of the presence of the amino acid *histidine,* which has a side chain that can bind or release H^+. The pK_a of histidine varies slightly, depending on its position in the protein molecule, but its average pK_a is approximately 6.5. This is close enough to a normal pH (7.4) to make histidine an effective buffer. Hemoglobin and albumin have 34 and 16 histidine molecules, respectively.

Phosphate can bind up to 3 hydrogen molecules, so it can exist as PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^{1-}$, or H_3PO_4. However, at a physiologic pH, most phosphate exists as either HPO_4^{2-} or $H_2PO_4^{1-}$. $H_2PO_4^{1-}$ is an acid, and HPO_4^{2-} is its conjugate base:

$$H_2PO_4^{1-} \leftrightarrow H^+ + HPO_4^{2-}$$

The pK_a of this reaction is 6.8, making phosphate an effective buffer. The concentration of phosphate in the ECS is relatively low, limiting the overall buffering capacity of phosphate; it is less important than albumin. However, phosphate is found at a much higher concentration in the urine, where it is an important buffer. In the ICS, most phosphate is covalently bound to organic molecules (ATP), but it still serves as an effective buffer.

Bone is an important buffer. Bone is *basic* —it is composed of compounds such as sodium bicarbonate and calcium carbonate—and thus dissolution of bone releases base. This release can buffer an acid load, although at the expense of bone density, if it occurs over an extended period. In contrast, bone formation, by consuming base, helps buffer excess base.

Clinically, we measure the extracellular pH, but it is the intracellular pH that affects cell function. Measurement of the intracellular pH is unnecessary because changes in the intracellular pH parallel the changes in the extracellular pH. However, the change in the intracellular pH tends to be less than the change in the extracellular pH because of the greater buffering capacity in the ICS.

Normal Acid-Base Balance

The lungs and kidneys maintain a normal acid-base balance. Carbon dioxide generated during normal metabolism is a weak acid. The lungs prevent an increase in the P_{CO_2} in the blood by excreting the CO_2 that the body produces. CO_2 production varies according to the body's metabolic needs, increasing with physical activity. The rapid pulmonary response to changes in the CO_2 concentration occurs via central sensing of the P_{CO_2} and a subsequent increase o decrease in ventilation to maintain a normal P_{CO_2} (35-45 mm Hg). An increase in ventilation decreases the P_{CO_2}, and a decrease in ventilation increases the P_{CO_2}.

The kidneys excrete endogenous acid. An adult normally produces approximately 1-2 mEq/kg/24 hr of H^+. Children normally produce 2-3 mEq/kg/24 hr of H^+. The 3 principal sources of H^+ are dietary protein metabolism, incomplete metabolism of carbohydrates and fat, and stool losses of bicarbonate. Because metabolism of protein generates H^+, endogenous acid production varies with protein intake. The complete oxidation of carbohydrates or fats to CO_2 and water does not generate H^+; the lungs remove the CO_2. However, incomplete metabolism of carbohydrates or fats produces H^+. Incomplete glucose metabolism can produce lactic acid, and incomplete triglyceride metabolism can produce keto acids, such as β-hydroxybutyric acid and acetoacetic acid. There is always some baseline incomplete metabolism that contributes to endogenous acid production. This factor increases in pathologic conditions, such as **lactic acidosis** and **diabetic ketoacidosis (DKA)**. Stool loss of bicarbonate is the 3rd major source of endogenous acid production. The stomach secretes H^+, but most of the remainder of the GI tract secretes bicarbonate, and the net effect is a loss of bicarbonate from the body. To secrete bicarbonate, the cells of the intestine produce hydrogen ions that are released into the bloodstream. For each bicarbonate molecule lost in the stool, the body gains 1 H^+. This source of endogenous acid production is normally minimal but may increase dramatically in a patient with diarrhea.

The hydrogen ions formed from endogenous acid production are neutralized by bicarbonate, potentially causing the bicarbonate concentration to decrease. The kidneys regenerate this bicarbonate by secreting H^+. The lungs cannot regenerate bicarbonate, even though loss of CO_2 lowers the $[H^+]$, as shown in the following reaction:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

A decrease in $[CO_2]$ causes the reaction to move to the right, which decreases $[H^+]$, but it also lowers $[HCO_3^-]$. During a metabolic acidosis, hyperventilation can lower $[CO_2]$, decrease $[H^+]$, and thus increase pH. The underlying metabolic acidosis is still present. Similarly, the kidneys cannot correct an abnormally high [CO_2], as shown in the following reaction:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

An increase in [HCO_3^-] also causes the reaction to move to the right, which increases [CO_2] while simultaneously decreasing [H^+]. During a respiratory acidosis, increased renal generation of bicarbonate can decrease [H^+] and increase pH, but cannot repair the respiratory acidosis. Both the lungs and the kidneys can affect [H^+] and thus pH. However, only the lungs can regulate [CO_2], and only the kidneys can regulate [HCO_3^-].

Renal Mechanisms

The kidneys regulate the serum bicarbonate concentration by modifying acid excretion in the urine. This requires a 2-step process. First, the renal tubules resorb the bicarbonate that is filtered at the glomerulus. Second, there is tubular secretion of H^+ . The urinary excretion of H^+ generates bicarbonate that neutralizes endogenous acid production. The tubular actions necessary for renal acid excretion occur throughout the nephron (Fig. 68.5).

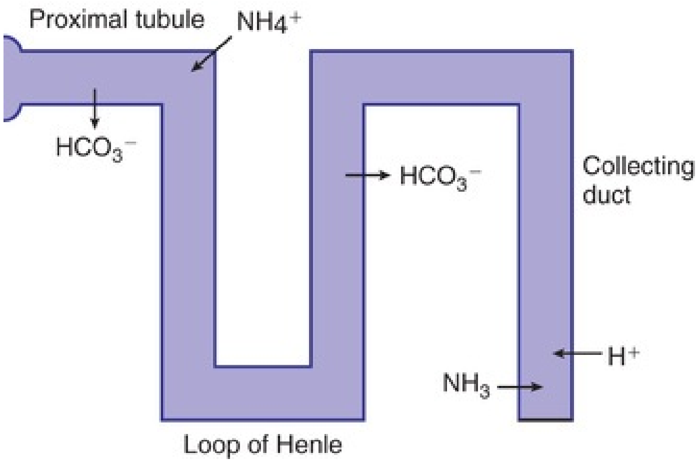

FIG. 68.5 **Tubular sites involved in acid-base balance. The proximal tubule is the site where most filtered bicarbonate is reclaimed, even though other sites along the nephron, especially the thick ascending limb of the loop of Henle, resorb some of the filtered bicarbonate. The collecting duct is the principal location for the hydrogen ion**

secretion that acidifies the urine. The proximal tubule generates the ammonia that serves as a urinary buffer in the collecting duct.

The resorption of filtered bicarbonate is a necessary first step in renal regulation of the acid-base balance. A normal adult has a GFR of approximately 180 L/24 hr. This fluid enters Bowman's space with [HCO_3^-] that is essentially identical to the plasma concentration, normally 24 mEq/L. Multiplying 180 L by 24 mEq/L indicates that >4,000 mEq of bicarbonate enters Bowman's space each day. This bicarbonate, if not reclaimed along the nephron, would be lost in the urine and would cause a profound metabolic acidosis.

The proximal tubule reclaims approximately 85% of the filtered bicarbonate (Fig. 68.6). The final 15% is reclaimed beyond the proximal tubule, mostly in the ascending limb of the loop of Henle. Bicarbonate molecules are not transported from the tubular fluid into the cells of the proximal tubule. Rather, hydrogen ions are secreted into the tubular fluid, leading to conversion of filtered bicarbonate into CO_2 and water. The secretion of H^+ by the cells of the proximal tubule is coupled to generation of intracellular bicarbonate, which is transported across the basolateral membrane of the proximal tubule cell and enters the capillaries. The bicarbonate produced in the cell replaces the bicarbonate filtered at the glomerulus.

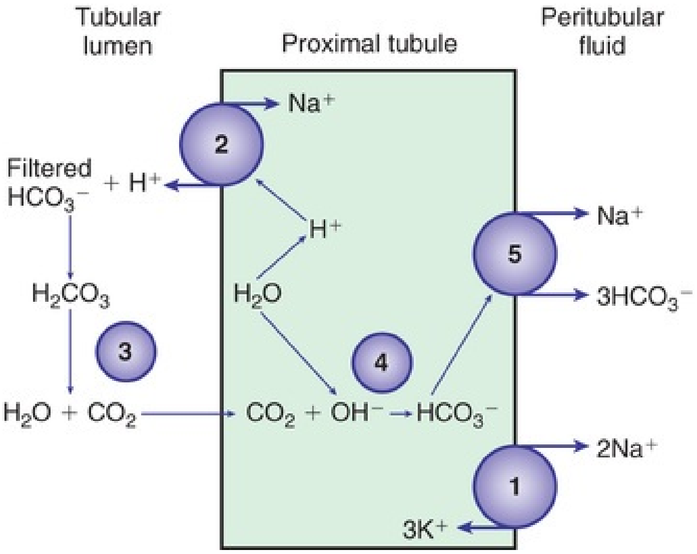

FIG. 68.6 **Resorption of filtered bicarbonate in the proximal tubule. The Na^+ ,K^+ -ATPase *(1)* excretes sodium across the basolateral cell membrane, maintaining a low intracellular sodium concentration. The low intracellular sodium concentration provides the energy for the Na^+ ,H^+ antiporter *(2)* , which exchanges sodium from the tubular lumen for intracellular hydrogen ions. The hydrogen ions that are secreted into**

the tubular lumen then combine with filtered bicarbonate to generate carbonic acid. CO_2 and water are produced from carbonic acid (H_2CO_3). This reaction is catalyzed by luminal carbonic anhydrase *(3)* . CO_2 diffuses into the cell and combines with OH^- ions to generate bicarbonate. This reaction is catalyzed by an intracellular carbonic anhydrase *(4)* . The dissociation of water generates an OH^- ion and an H^+ ion. The Na^+ ,H^+ antiporter *(2)* secretes the hydrogen ions. Bicarbonate ions cross the basolateral membrane and enter the blood via the $3HCO_3^-/1Na^+$ co-transporter *(5)* . The energy for the $3HCO_3^-/1Na^+$ co-transporter comes from the negatively charged cell interior, which makes it electrically favorable to transport a net negative charge (i.e., 3 bicarbonates and only 1 sodium) out of the cell.

Increased bicarbonate resorption by the cells of the proximal tubule—the result of increased H^+ secretion—occurs in a variety of clinical situations. Volume depletion increases bicarbonate resorption. This is partially mediated by activation of the renin-angiotensin system; angiotensin II increases bicarbonate resorption. Increased bicarbonate resorption in the proximal tubule is one of the mechanisms that accounts for the metabolic alkalosis that may occur in some patients with volume depletion. Other stimuli that increase bicarbonate resorption include hypokalemia and an increased P_{CO_2} . This partially explains the observations that hypokalemia causes a metabolic alkalosis, and that a respiratory acidosis leads to a compensatory increase in serum [HCO_3^-].

Stimuli that decrease bicarbonate resorption in the proximal tubule may cause a decrease in the serum [HCO_3^-]. A decrease in the P_{CO_2} (respiratory alkalosis) decreases proximal tubule bicarbonate resorption, partially mediating the decrease in serum [HCO_3^-] that compensates for a respiratory alkalosis. PTH decreases proximal tubule bicarbonate resorption; hyperparathyroidism may cause a mild metabolic acidosis. A variety of medications and diseases cause a metabolic acidosis by impairing bicarbonate resorption in the proximal tubule. Examples are the medication acetazolamide, which directly inhibits carbonic anhydrase, and the many disorders that cause proximal RTA (see Chapter 547.1).

After reclaiming filtered bicarbonate, the kidneys perform the 2nd step in renal acid-base handling, the excretion of the acid created by endogenous acid production. Excretion of acid occurs mostly in the collecting duct, with a small role for the distal tubule.

Along with secretion of H^+ by the tubular cells lining the collecting duct, adequate excretion of endogenous acid requires the presence of urinary buffers. The hydrogen pumps in the collecting duct cannot lower the urine pH below 4.5. The [H^+] at pH 4.5 is <0.04 mEq/L; it would require >25 L of water with a pH of 4.5 to excrete 1 mEq H^+ . A 10-kg child, with an endogenous acid production of 20 mEq H^+ each day, would need to have a daily urinary output of >500 L without the presence of urinary buffers. As in the blood, buffers in the urine attenuate the decrease in pH that occurs with the addition of H^+ . The 2 principal urinary buffers are phosphate and ammonia.

Urinary **phosphate** is proportional to dietary intake. Whereas most of the phosphate filtered at the glomerulus is resorbed in the proximal tubule, the urinary phosphate concentration is usually much greater than the serum phosphate concentration. This arrangement allows phosphate to serve as an effective buffer through the following reaction:

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^{1-}$$

The p*K* a of this reaction is 6.8, making phosphate an effective buffer as the urinary pH decreases from 7.0 to 5.0 within the collecting duct. Although phosphate is an effective buffer, its buffering capacity is limited by its concentration; there is no mechanism for increasing urinary phosphate excretion in response to changes in acid-base status.

In contrast, **ammonia** production can be modified, allowing for regulation of acid excretion. The buffering capacity of ammonia (NH_3) is based on the reaction of ammonia with hydrogen ions to form ammonium:

$$NH_3 + H^+ \rightarrow NH_4^+$$

The cells of the proximal tubule are the source of the excreted ammonia, mostly through metabolism of glutamine through the following reactions:

$$\text{Glutamine} \rightarrow NH_4^+ + \text{glutamate}^-$$

$$\text{Glutamate}^- \rightarrow NH_4^+ + \alpha\text{-ketoglutarate}^{3-}$$

The metabolism of glutamine generates 2 ammonium ions. In addition, the metabolism of α-ketoglutarate generates 2 bicarbonate molecules. The ammonium ions are secreted into the lumen of the proximal tubule, whereas the bicarbonate molecules exit the proximal tubule cells via the basolateral Na^+ ,$3HCO_3{}^-$ co-transporter (see Fig. 68.6). This arrangement would seem to accomplish the goal of excreting H^+ (as $NH_4{}^+$) and regenerating bicarbonate molecules. However, the ammonium ions secreted in the proximal tubule do not remain within the tubular lumen. Cells of the TAL of the loop of Henle resorb the ammonium ions. The result is that there is a high medullary interstitial concentration of ammonia, but the tubular fluid entering the collecting duct does not have significant amounts of ammonium ions. Moreover, the hydrogen ions that were secreted with ammonia, as ammonium ions, in the proximal tubule enter the bloodstream, canceling the effect of the bicarbonate generated in the proximal tubule. The excretion of ammonium ions, and thus of hydrogen ions, depends on the cells of the collecting duct.

The cells of the collecting duct secrete H^+ and regenerate bicarbonate, which is returned to the bloodstream (Fig. 68.7). This bicarbonate neutralizes endogenous acid production. Phosphate and ammonia buffer the H^+ secreted by the collecting duct. Ammonia is an effective buffer because of the high concentrations in the medullary interstitium and because the cells of the collecting duct are permeable to ammonia but not to ammonium. As ammonia diffuses into the lumen of the collecting duct, the low urine pH causes almost all the ammonia to be converted into ammonium. This process maintains a low luminal ammonia concentration. Because the luminal pH is lower than the pH in the medullary interstitium, there is a higher concentration of ammonia within the medullary interstitium than in the tubular lumen, favoring movement of ammonia into the tubular lumen. Even though the concentration of ammonium in the tubular lumen is higher than in the interstitium, the cells of the collecting duct are impermeable to ammonium, preventing back-diffusion of ammonium out of the tubular lumen and permitting ammonia to be an effective buffer.

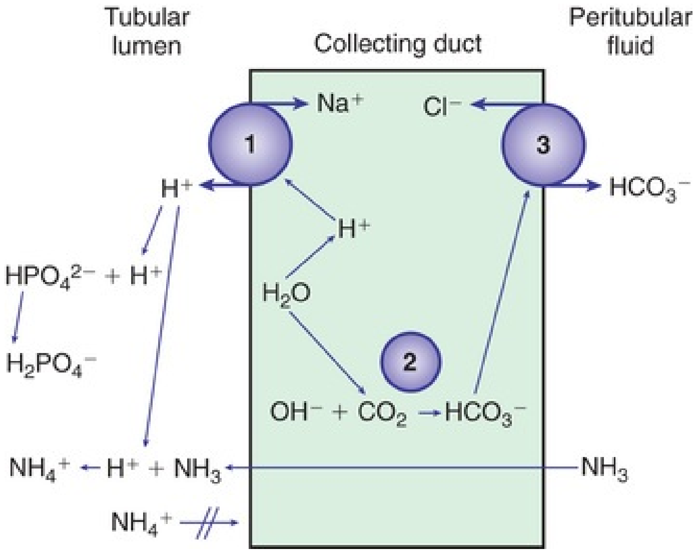

FIG. 68.7 Secretion of hydrogen ions in the collecting duct. The dissociation of water generates an OH^- ion and an H^+ ion. The H^+ -ATPase *(1)* secretes hydrogen ions into the tubular lumen. Bicarbonate is formed when an OH^- ion combines with CO_2 in a reaction mediated by carbonic anhydrase *(2)* . Bicarbonate ions cross the basolateral membrane and enter the blood via the HCO_3^-/Cl^- exchanger *(3)* . The hydrogen ions in the tubular lumen are buffered by phosphate and ammonia (NH_3). NH_3 can diffuse from the peritubular fluid into the tubular lumen, but ammonium (NH_4^+) cannot pass through the cells of the collecting duct.

The kidneys adjust H^+ excretion according to physiologic needs. There is variation in endogenous acid production, largely a result of diet and pathophysiologic stresses, such as diarrheal losses of bicarbonate, which increase the need for acid excretion. H^+ excretion is increased by upregulation of H^+ secretion in the collecting duct, causing the pH of the urine to decrease. This response is fairly prompt, occurring within hours of an acid load, but it is limited by the buffering capacity of the urine; the hydrogen pumps in the collecting duct cannot lower the pH to <4.5. A more significant increase in acid excretion requires upregulation of ammonia production by the proximal tubule so that more ammonia is available to serve as a buffer in the tubular lumen of the collecting duct. This response to a low serum pH reaches its maximum within 5-6 days; ammonia excretion can increase approximately 10-fold over the baseline value.

Acid excretion by the collecting duct increases in a number of different clinical situations. The extracellular pH is the most important regulator of renal acid excretion. A decrease in the extracellular pH from either a respiratory or a metabolic acidosis causes an increase in renal acid excretion. Aldosterone stimulates H^+ excretion in the collecting duct, causing an increase in the serum bicarbonate concentration. This explains the metabolic alkalosis that occurs with primary hyperaldosteronism or secondary hyperaldosteronism caused by volume depletion. Hypokalemia increases acid secretion, by both stimulating ammonia production in the proximal tubule and increasing H^+ secretion in the collecting duct. Hypokalemia therefore tends to produce a metabolic alkalosis. Hyperkalemia has the opposite effects, which may cause a metabolic acidosis.

In patients with an increased pH, the kidney has 2 principal mechanisms for correcting the problem. First, less bicarbonate is resorbed in the proximal tubule, leading to an increase in urinary bicarbonate losses. Second, in a limited number of specialized cells, the process for secretion of H^+ by the collecting duct can be reversed (Fig. 68.7), leading to secretion of bicarbonate into the tubular lumen and secretion of hydrogen ions into the peritubular fluid, where they enter the bloodstream.

Clinical Assessment of Acid-Base Disorders

The following rearrangement of the Henderson-Hasselbalch equation emphasizes the relationship among Pco_2 , bicarbonate concentration, and hydrogen ion concentration:

$$[H^+] = 24 \times Pco_2 / [HCO_3^-]$$

An increase in the Pco_2 or a decrease in $[HCO_3^-]$ increases $[H^+]$; the pH decreases. A decrease in the Pco_2 or an increase in $[HCO_3^-]$ decreases $[H^+]$; th pH increases.

Terminology

Acidemia is a pH below normal (<7.35), and **alkalemia** is a pH above normal (>7.45). An **acidosis** is a pathologic process that causes an increase in $[H^+]$, and an **alkalosis** is a pathologic process that causes a decrease in $[H^+]$. Whereas acidemia is always accompanied by an acidosis, a patient can have an acidosis and a low, normal, or high pH. For example, a patient may have a mild metabolic acidosis but a simultaneous, severe respiratory alkalosis; the net result may be alkalemia. Acidemia and alkalemia indicate the pH abnormality; acidosis and alkalosis indicate the pathologic process that is taking place.

A **simple acid-base disorder** is a single primary disturbance. During a simple metabolic disorder, there is respiratory compensation. With a metabolic acidosis, the decrease in the pH increases the ventilatory drive, causing a decrease in P_{CO_2}. The decrease in the carbon dioxide concentration ([CO_2]) leads to an increase in the pH. This appropriate respiratory compensation is expected with a primary metabolic acidosis. Despite the decrease in [CO_2], appropriate respiratory compensation is not a respiratory alkalosis, even though it is sometimes erroneously called a “compensatory” respiratory alkalosis. A low P_{CO_2} can result either from a primary respiratory alkalosis or from appropriate respiratory compensation for a metabolic acidosis. Appropriate respiratory compensation also occurs with a primary metabolic alkalosis, although in this case [CO_2] increases to attenuate the increase in the pH. The respiratory compensation for a metabolic process happens quickly and is complete within 12-24 hr; it cannot overcompensate for or normalize the pH.

During a primary respiratory process, there is metabolic compensation, mediated by the kidneys. The kidneys respond to a respiratory acidosis by increasing H^+ excretion, thereby increasing bicarbonate generation and raising the serum [HCO_3^-]. The kidneys increase bicarbonate excretion to compensate for a respiratory alkalosis; [HCO_3^-] decreases. Unlike respiratory compensation which occurs rapidly, it takes 3-4 days for the kidneys to complete appropriate metabolic compensation. There is, however, a small and rapid compensatory change in [HCO_3^-] during a primary respiratory process. The expected appropriate metabolic compensation for a respiratory disorder depends on whether the process is acute or chronic.

A **mixed acid-base disorder** is present when there is >1 primary acid-base disturbance. An infant with bronchopulmonary dysplasia may have a respiratory acidosis from chronic lung disease and a metabolic alkalosis from the furosemide used to treat the chronic lung disease. More dramatically, a child with pneumonia and sepsis may have severe acidemia as a result of a combined metabolic acidosis caused by lactic acid and respiratory acidosis caused by ventilatory failure.

There are formulas for calculating the appropriate metabolic or respiratory compensation for the 6 primary simple acid-base disorders (Table 68.11). The appropriate compensation is expected in a simple disorder; it is not optional. If a patient does not have the appropriate compensation, a mixed acid-base disorder is present. A patient has a primary metabolic acidosis with a serum $[HCO_3^-]$ of 10 mEq/L. The expected respiratory compensation is $[CO_2]$ of 23 mm Hg ± 2 ($1.5 \times 10 + 8 \pm 2 = 23 \pm 2$; Table 68.11). If the patient's $[CO_2]$ is >25 mm Hg, a concurrent respiratory acidosis is present; $[CO_2]$ is higher than expected. A patient may have a respiratory acidosis despite a CO_2 level below the “normal” value of 35-45 mm Hg. In this example, $[CO_2]$ <21 mm Hg indicates a concurrent respiratory alkalosis; $[CO_2]$ is lower than expected.

Table 68.11

Appropriate Compensation During Simple Acid-Base Disorders

DISORDER	EXPECTED COMPENSATION
Metabolic acidosis	$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in serum $[HCO_3^-]$
Respiratory Acidosis	
Acute	$[HCO_3^-]$ increases by 1 for each 10 mm Hg increase in P_{CO_2}
Chronic	$[HCO_3^-]$ increases by 3.5 for each 10 mm Hg increase in P_{CO_2}
Respiratory Alkalosis	
Acute	$[HCO_3^-]$ falls by 2 for each 10 mm Hg decrease in P_{CO_2}
Chronic	$[HCO_3^-]$ falls by 4 for each 10 mm Hg decrease in P_{CO_2}

Diagnosis

A systematic evaluation of an arterial blood gas (ABG) sample, combined with the clinical history, can usually explain the patient's acid-base disturbance. Assessment of an ABG sample requires knowledge of normal values (Table 68.12). In most cases, this is accomplished through a 3-step process (Fig. 68.8):

Table 68.12

Normal Values of Arterial Blood Gases

pH	7.35-7.45
[HCO_3^-]	20-28 mEq/L
PCO_2	35-45 mm Hg

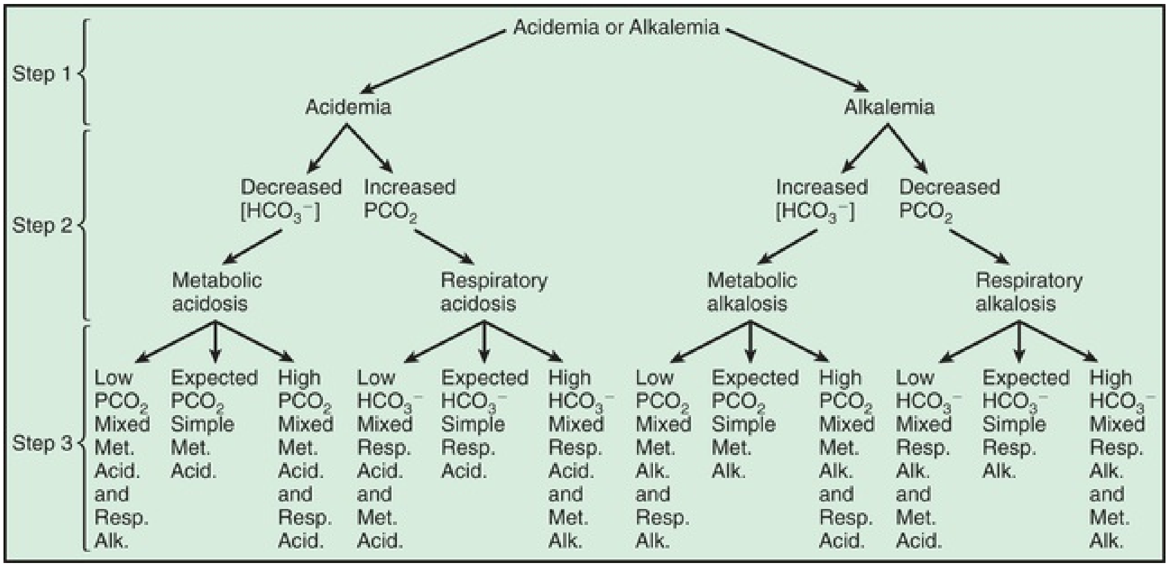
Step 1
Step 2
Step 3
Acidemia or Alkalemia
Acidemia
Alkalemia
Decreased [HCO_3^-]
Increased PCO_2
Increased [HCO_3^-]
Decreased PCO_2
Metabolic acidosis
Respiratory acidosis
Metabolic alkalosis
Respiratory alkalosis
Low PCO_2 Mixed Met. Acid. and Resp. Alk.
Expected PCO_2 Simple Met. Acid.
High PCO_2 Mixed Met. Acid. and Resp. Acid.
Low HCO_3^- Mixed Resp. Acid. and Met. Acid.
Expected HCO_3^- Simple Resp. Acid.
High HCO_3^- Mixed Resp. Acid. and Met. Alk.
Low PCO_2 Mixed Met. Alk. and Resp. Alk.
Expected PCO_2 Simple Met. Alk.
High PCO_2 Mixed Met. Alk. and Resp. Acid.
Low HCO_3^- Mixed Resp. Alk. and Met. Acid.
Expected HCO_3^- Simple Resp. Alk.
High HCO_3^- Mixed Resp. Alk. and Met. Alk.

FIG. 68.8 **Three-step process for interpreting acid-base disturbances. In step 1, determine whether the pH is low (acidemia) or high (alkalemia). In step 2, establish an explanation for the acidemia or alkalemia. In step 3, calculate the expected compensation (see Table 68.11) and determine whether a mixed disturbance is present. Met. Acid., metabolic acidosis; Met. Alk., metabolic alkalosis; Resp. Acid., respiratory acidosis; Resp. Alk., respiratory alkalosis.**

1. Determine whether acidemia or alkalemia is present.
2. Determine a cause of the acidemia or alkalemia.
3. Determine whether a mixed disorder is present.

Most patients with an acid-base disturbance have an abnormal pH, although there are 2 exceptions. One exception is in the patient with a mixed disorder in which the 2 processes have opposite effects on pH (a metabolic acidosis and a respiratory alkalosis) and cause changes in [H^+] that are comparable in magnitude, although opposite. The other exception is in the patient with a simple chronic respiratory alkalosis; in some cases the appropriate metabolic compensation is enough to normalize the pH. In both situations the presence of an acid-base disturbance is deduced because of the abnormal CO_2 and bicarbonate levels. Determining the acid-base disturbance in these patients requires proceeding to the 3rd step of the process.

The 2nd step requires inspection of the serum bicarbonate and CO_2 concentrations to determine a cause of the abnormal pH (Fig. 68.8). In most cases, there is only 1 obvious explanation for the abnormal pH. In some mixed disorders, however, there may be 2 possibilities (e.g., a high P_{CO_2} and a low $[HCO_3^-]$ in a patient with acidemia). In such cases the patient has 2 causes for abnormal pH—a metabolic acidosis and a respiratory acidosis, in this instance—and it is unnecessary to proceed to the 3rd step.

The 3rd step requires determining whether the patient's compensation is appropriate. It is assumed that the primary disorder was diagnosed in the 2nd step, and the expected compensation is calculated (Table 68.11). If the compensation is appropriate, a simple acid-base disorder is present. If the compensation is not appropriate, a mixed disorder is present. The identity of the 2nd disorder is determined by deciding whether the compensation is too little or too much compared with what was expected (see Fig. 68.8).

The history is always useful in evaluating and diagnosing patients with acid-base disturbances. It is especially helpful in a respiratory process. The expected metabolic compensation for a respiratory process changes according to whether the process is **acute** or **chronic** , which can be deduced only from the history. The metabolic compensation for an acute respiratory acidosis is less than that for a chronic respiratory acidosis. In a patient with a respiratory acidosis, a small increase in $[HCO_3^-]$ would be consistent with a simple acute respiratory acidosis or a mixed disorder (a chronic respiratory acidosis and a metabolic acidosis). Only the history can differentiate among the possibilities. Knowledge of the length of the respiratory process and the presence or absence of a risk factor for a metabolic acidosis (diarrhea) allows the correct conclusion to be reached.

An alternative to the **physiologic** approach just described (which includes calculation of the anion gap; see later) is the **physiochemical** approach, often called the **Stewart method** . Some view this approach as superior to the physiologic approach, but it requires multiple calculations and additional laboratory values and is thus more challenging to use in the clinical setting. The physiochemical approach requires measurement of the blood pH and P_{CO_2} and calculation of the apparent strong ion difference (SIDa), the effective strong ion difference (SIDe), the strong ion gap (SIG), and the total concentration of weak acids (A_{TOT}).

Metabolic Acidosis

Metabolic acidosis occurs frequently in hospitalized children; diarrhea is the most common etiology. For a patient with an unknown medical problem, the presence of a metabolic acidosis is often helpful diagnostically, because it suggests a relatively narrow differential diagnosis.

Patients with a metabolic acidosis have a low serum [HCO_3^-], although not every patient with a low serum [HCO_3^-] has a metabolic acidosis. The exception is the patient with a respiratory alkalosis, which causes a decrease in the serum [HCO_3^-] as part of appropriate renal compensation. In a patient with an isolated metabolic acidosis, there is a predictable decrease in the blood [CO_2], as follows:

$$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$$

A mixed acid-base disturbance is present if the respiratory compensation is not appropriate. If the P_{CO_2} is greater than predicted, the patient has a concurrent respiratory acidosis. A lower P_{CO_2} than predicted indicates a concurrent respiratory alkalosis or, less frequently, an isolated respiratory alkalosis. Because the appropriate respiratory compensation for a metabolic acidosis **never normalizes** the patient's pH, the presence of a normal pH and a low [HCO_3^-] occurs only if some degree of respiratory alkalosis is present. In this situation, distinguishing an isolated chronic respiratory alkalosis from a mixed metabolic acidosis and acute respiratory alkalosis may be possible only clinically. In contrast, the combination of a low serum pH and a low [HCO_3^-] occurs only if a metabolic acidosis is present.

Etiology and Pathophysiology

There are many causes of a metabolic acidosis (Table 68.13), resulting from 3 basic mechanisms:

Table 68.13

Causes of Metabolic Acidosis

Normal Anion Gap

- Diarrhea
- Renal tubular acidosis (RTA)
  - Distal (type I) RTA (OMIM 179800/602722/267300)*
  - Proximal (type II) RTA (OMIM 604278) †
  - Mixed (type III) RTA (OMIM 259730)
  - Hyperkalemic (type IV) RTA (OMIM 201910/264350/177735/145260) ‡
  - Urinary tract diversions
  - Posthypocapnia
  - Ammonium chloride intake

Increased Anion Gap

Lactic Acidosis

- Tissue hypoxia
  - Shock
  - Hypoxemia
  - Severe anemia
- Liver failure
- Malignancy
- Intestinal bacterial overgrowth
- Inborn errors of metabolism
- Medications
  - Nucleoside reverse transcriptase inhibitors
  - Metformin
  - Propofol
  - Linezolid

Ketoacidosis

- Diabetic ketoacidosis
- Starvation ketoacidosis
- Alcoholic ketoacidosis

Kidney Failure
Poisoning

Ethylene glycol
Methanol
Salicylate
Toluene
Paraldehyde

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[*] Along with these genetic disorders, distal RTA may be secondary to renal disease or medications.

[†] Most cases of proximal RTA are not caused by this primary genetic disorder. Proximal RTA is usually part of Fanconi syndrome, which has multiple etiologies.

[‡] Hyperkalemic RTA can be secondary to a genetic disorder (some of the more common are listed) or other etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

1. Loss of bicarbonate from the body
2. Impaired ability to excrete acid by the kidney
3. Addition of acid to the body (exogenous or endogenous)

Diarrhea, the most common cause of metabolic acidosis in children, causes a loss of bicarbonate from the body. The amount of bicarbonate lost in the stool depends on the volume of diarrhea and [HCO_3^-] of the stool, which tends to increase with more severe diarrhea. The kidneys attempt to balance the losses by increasing acid secretion, but metabolic acidosis occurs when this compensation is inadequate. Diarrhea often causes volume depletion as a result of losses of sodium and water, potentially exacerbating the acidosis by causing shock and a lactic acidosis. In addition, diarrheal losses of potassium lead to hypokalemia. Moreover, the volume depletion causes increased production of aldosterone. This increase stimulates renal retention of sodium, helping to maintain intravascular volume, but also leads to increased urinary losses of potassium, exacerbating the hypokalemia.

There are 4 forms of renal tubular acidosis (RTA): distal (type I), proximal (type II), mixed (type III) and hyperkalemic (type IV) (see Chapter 547). In **distal** RTA, children may have accompanying hypokalemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis. Failure to thrive because of chronic metabolic acidosis is the most common presenting complaint. Patients with distal RTA cannot acidify their urine and thus have a urine pH >5.5 despite a metabolic acidosis.

Proximal RTA is rarely present in isolation. In most patients, proximal RTA is part of **Fanconi syndrome** , a generalized dysfunction of the proximal tubule. The dysfunction leads to glycosuria, aminoaciduria, and excessive urinary losses of phosphate and uric acid. The presence of a low serum uric acid level, glycosuria, and aminoaciduria is helpful diagnostically. Chronic hypophosphatemia leads to rickets in children (see Chapter 64). Rickets and/or failure to thrive may be the presenting complaint. The ability to acidify the urine is intact in proximal RTA; thus untreated patients have a urine pH <5.5. However, bicarbonate therapy increases bicarbonate losses in the urine, and the urine pH increases. A mixed RTA (combined distal and proximal) occurs in patients with autosomal recessive osteopetrosis caused by mutations in the gene for carbonic anhydrase II.

In **hyperkalemic** RTA, renal excretion of acid and potassium is impaired. Hyperkalemic RTA is the result of hyperkalemia, absence of aldosterone, or inability of the kidney to respond to aldosterone. In severe **aldosterone deficiency** , as occurs with congenital adrenal hyperplasia because of 21α-hydroxylase deficiency, the hyperkalemia and metabolic acidosis are accompanied by hyponatremia and volume depletion from renal salt wasting. Incomplete aldosterone deficiency causes less severe electrolyte disturbances; children may have isolated hyperkalemic RTA, hyperkalemia without acidosis, or isolated hyponatremia. Patients may have aldosterone deficiency caused by decreased renin production by the kidney; renin normally stimulates aldosterone synthesis. Children with hyporeninemic hypoaldosteronism usually have either isolated hyperkalemia or hyperkalemic RTA. The manifestations of aldosterone resistance depend on the severity of the resistance. In the autosomal recessive form of **pseudohypoaldosteronism** type I, which is the result of an absence of the sodium channel that normally responds to aldosterone, there is often severe salt wasting and hyponatremia. In contrast, the aldosterone resistance in kidney transplant recipients usually produces either isolated hyperkalemia or hyperkalemic RTA; hyponatremia is unusual. Similarly, the medications that cause hyperkalemic RTA do not cause hyponatremia. Pseudohypoaldosteronism type II, an autosomal recessive disorder also known as **Gordon syndrome** , is a unique cause of hyperkalemic RTA because the genetic defect causes volume expansion and hypertension.

Children with abnormal urinary tracts, usually secondary to congenital malformations, may require diversion of urine through intestinal segments. Ureterosigmoidostomy, anastomosis of a ureter to the sigmoid colon, almost always produces a metabolic acidosis and hypokalemia. Consequently, ileal conduits are now the more commonly used procedure, although there is still a risk of a metabolic acidosis.

The appropriate metabolic compensation for a chronic respiratory alkalosis is a decrease in renal acid excretion. The resultant decrease in the serum $[HCO_3^-]$ lessens the alkalemia caused by the respiratory alkalosis. If the respiratory alkalosis resolves quickly, the patient continues to have a decreased serum $[HCO_3^-]$, causing acidemia as the result of a metabolic acidosis. This resolves over 1-2 days through increased acid excretion by the kidneys.

Lactic acidosis typically occurs when inadequate oxygen delivery to the tissues leads to anaerobic metabolism and excess production of lactic acid. Lactic acidosis may be secondary to shock, severe anemia, or hypoxemia. When the underlying cause of the lactic acidosis is alleviated, the liver is able to metabolize the accumulated lactate into bicarbonate, correcting the metabolic acidosis. There is normally some tissue production of lactate metabolized by the liver. In children with severe liver dysfunction, impairment of lactate metabolism may produce a lactic acidosis. Rarely, a metabolically active malignancy grows so fast that its blood supply becomes inadequate, with resultant anaerobic metabolism and lactic acidosis. Patients who have **short bowel syndrome** resulting from small bowel resection can have bacterial overgrowth. In these patients, excessive intestinal bacterial metabolism of glucose into D -lactic acid can cause a lactic acidosis. Lactic acidosis occurs in a variety of **inborn errors of metabolism** , especially those affecting mitochondrial oxidation (see Chapters 105.4 and 106). **Medications** also can cause lactic acidosis. Nucleoside reverse transcriptase inhibitors that are used to treat HIV infection inhibit mitochondrial replication; lactic acidosis is a rare complication, although elevated serum lactate concentrations without acidosis are quite common. Metformin, used to treat type 2 diabetes mellitus, is most likely to cause a lactic acidosis in patients with renal insufficiency. High dosages and prolonged use of propofol can cause lactic acidosis. Propylene glycol is a diluent in a variety of oral and IV medications; excessive intake causes a lactic acidosis, principally from accumulation of D-lactic acid. Linezolid is another medication that may cause a lactic acidosis

In **insulin-dependent diabetes mellitus**, inadequate insulin leads to hyperglycemia and DKA (see Chapter 607). Production of acetoacetic acid and β-hydroxybutyric acid causes the metabolic acidosis. Administration of insulin corrects the underlying metabolic problem and permits conversion of acetoacetate and β-hydroxybutyrate into bicarbonate, which helps correct the metabolic acidosis. However, in some patients, urinary losses of acetoacetate and β-hydroxybutyrate may be substantial, preventing rapid regeneration of bicarbonate. In these patients, full correction of the metabolic acidosis requires renal regeneration of bicarbonate, a slower process. The hyperglycemia causes an osmotic diuresis, usually producing volume depletion, along with substantial losses of potassium, sodium, and phosphate.

In **starvation ketoacidosis** the lack of glucose leads to keto acid production, which in turn can produce a metabolic acidosis, although it is usually mild as a result of increased acid secretion by the kidney. In **alcoholic ketoacidosis**, which is much less common in children than in adults, the acidosis usually follows a combination of an alcoholic binge with vomiting and poor intake of food. The acidosis is potentially more severe than with isolated starvation, and the blood glucose level may be low, normal, or high. Hypoglycemia and acidosis also suggest an inborn error of metabolism.

Renal failure causes a metabolic acidosis because of the need for the kidneys to excrete the acid produced by normal metabolism. With mild or moderate renal insufficiency, the remaining nephrons are usually able to compensate by increasing acid excretion. When the GFR is <20–30% of normal, the compensation is inadequate, and a metabolic acidosis develops. In some children, especially those with chronic renal failure because of tubular damage, the acidosis develops at a higher GFR because of a concurrent defect in acid secretion by the distal tubule (distal RTA).

A variety of **toxic ingestions** can cause a metabolic acidosis (see Chapter 77). **Salicylate** intoxication is now much less common because aspirin is no longer recommended for fever control in children. Acute salicylate intoxication occurs after a large overdose. Chronic salicylate intoxication is possible with gradual buildup of the drug. Especially in adults, respiratory alkalosis may be the dominant acid-base disturbance. In children the metabolic acidosis is usually the more significant finding. Other symptoms of salicylate intoxication are fever, seizures, lethargy, and coma. Hyperventilation may be particularly marked. Tinnitus, vertigo, and hearing impairment are more likely with chronic salicylate intoxication.

Ethylene glycol , a component of antifreeze, is converted in the liver to glyoxylic and oxalic acids, causing a severe metabolic acidosis. Excessive oxalate excretion causes calcium oxalate crystals to appear in the urine, and calcium oxalate precipitation in the kidney tubules can cause renal failure. The toxicity of **methanol** ingestion also depends on liver metabolism; formic acid is the toxic end product that causes the metabolic acidosis and other sequelae, which include damage to the optic nerve and CNS. Symptoms may include nausea, emesis, visual impairment, and altered mental status. **Toluene** inhalation and **paraldehyde** ingestion are other potential causes of a metabolic acidosis.

Many **inborn errors of metabolism** cause a metabolic acidosis (see Chapters 102-105). The metabolic acidosis may be the result of excessive production of keto acids, lactic acid, and other organic anions. Some patients have accompanying hypoglycemia or hyperammonemia. In most patients the acidosis occurs episodically, only during acute decompensations, which may be precipitated by ingestion of specific dietary substrates, the stress of a mild illness, or poor compliance with dietary or medical therapy. In a few inborn errors of metabolism, patients have a chronic metabolic acidosis.

Clinical Manifestations

The underlying disorder usually produces most of the signs and symptoms in children with a mild or moderate metabolic acidosis. The clinical manifestations of the acidosis are related to the degree of acidemia; patients with appropriate respiratory compensation and less severe acidemia have fewer manifestations than those with a concomitant respiratory acidosis. At a serum pH <7.2, there may be impaired cardiac contractility and an increased risk of arrhythmias, especially if underlying heart disease or other predisposing electrolyte disorders are present. With acidemia, there may be a decrease in the cardiovascular response to catecholamines, potentially exacerbating hypotension in children with volume depletion or shock. Acidemia causes vasoconstriction of the pulmonary vasculature, which is especially problematic in newborn infants with **persistent pulmonary hypertension** (see Chapter 122.09).

The normal respiratory response to metabolic acidosis—compensatory hyperventilation—may be subtle with mild metabolic acidosis, but it causes discernible increased respiratory effort with worsening acidemia. The acute metabolic effects of acidemia include insulin resistance, increased protein degradation, and reduced ATP synthesis. Chronic metabolic acidosis causes failure to thrive in children. Acidemia causes potassium to move from the ICS to the ECS, thereby increasing the serum [K^+]. Severe acidemia impairs brain metabolism, eventually resulting in lethargy and coma.

Diagnosis

The etiology of a metabolic acidosis is often apparent from the history and physical examination. Acutely, diarrhea and shock are common causes of a metabolic acidosis. Shock, which causes a lactic acidosis, is usually apparent on physical examination and can be secondary to dehydration, acute blood loss, sepsis, or heart disease. Failure to thrive suggests a chronic metabolic acidosis, as with renal insufficiency or RTA. New onset of polyuria occurs in children with undiagnosed diabetes mellitus and DKA. Metabolic acidosis with seizures and/or a depressed sensorium, especially in an infant, warrants consideration of an inborn error of metabolism. Meningitis and sepsis with lactic acidosis are more common explanations for metabolic acidosis with neurologic signs and symptoms. Identification of a toxic ingestion (e.g., ethylene glycol, methanol) is especially important because of the potentially excellent response to specific therapy. A variety of medications can cause a metabolic acidosis, whether prescribed or accidentally ingested. Hepatomegaly and metabolic acidosis may occur in children with sepsis, congenital or acquired heart disease, hepatic failure, or inborn errors of metabolism.

Basic laboratory tests in a child with a metabolic acidosis should include measurements of BUN, serum creatinine, serum glucose, urinalysis, and serum electrolytes. Metabolic acidosis, hyperglycemia, glycosuria, and ketonuria support a diagnosis of DKA. Starvation causes ketosis, but the metabolic acidosis, if present, is usually mild (HCO_3^- >18 mEq/L). Most children with ketosis from poor intake and metabolic acidosis have a concomitant disorder, such as gastroenteritis with diarrhea, that explains the metabolic acidosis. Alternatively, metabolic acidosis with or without ketosis occurs in inborn errors of metabolism; patients with these disorders may have hyperglycemia, normoglycemia, or hypoglycemia. Adrenal insufficiency may cause metabolic acidosis and hypoglycemia. Metabolic acidosis with hypoglycemia also occurs with liver failure. Metabolic acidosis, normoglycemia, and glycosuria occur in children when type II RTA is part of Fanconi syndrome; the defect in resorption of glucose by the proximal tubule of the kidney causes the glycosuria.

The serum [K^+] is often abnormal in children with a metabolic acidosis. Even though a metabolic acidosis causes potassium to move from the ICS to the ECS, many patients with a metabolic acidosis have a low serum [K^+] because of excessive body losses of K^+ . With diarrhea, there are high stool losses of K^+ and, often, secondary renal losses of K^+ , whereas in type I or type II RTA, there are increased urinary losses of K^+ . In DKA, urinary losses of K^+ are high, but the shift of K^+ out of cells because of a lack of insulin and metabolic acidosis is especially significant. Consequently, the initial serum [K^+] can be low, normal, or high, even though total body K^+ is almost always decreased. The serum [K^+] is usually increased in patients with acidosis caused by renal insufficiency; urinary K^+ excretion is impaired. The combination of metabolic acidosis, hyperkalemia, and hyponatremia occurs in patients with severe aldosterone deficiency (adrenogenital syndrome) or aldosterone resistance. Patients with less severe, type IV RTA often have only hyperkalemia and metabolic acidosis. Very ill children with metabolic acidosis may have an elevated serum K^+ as a result of a combination of renal insufficiency, tissue breakdown, and a shift of K^+ from the ICS to the ECS secondary to the metabolic acidosis.

The **plasma anion gap** is useful for evaluating patients with a metabolic acidosis. It divides patients into two diagnostic groups, those with normal anion gap and those with increased anion gap. The following formula determines the anion gap:

$$\text{Anion gap} = [\text{Na}^+] - [\text{Cl}^-] + [\text{HCO}_3^-]$$

A normal anion gap is 4-11, although there is variation among laboratories. Approximately 11 mEq of the anion gap is normally secondary to albumin. A 1 g/dL decrease in the albumin concentration decreases the anion gap by approximately 2.5 mEq/L. Thus, if the albumin is not close to 4 g/dL, the anion gap should be corrected for the albumin concentration:

$$\text{Anion gap (corrected for albumin)} = [\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-] + 2.5\,(4 - \text{albumin})$$

The number of serum anions must equal the number of serum cations to maintain electrical neutrality (Fig. 68.9). The anion gap is the difference between the measured cation (Na^+) and the measured anions (Cl^- + bicarbonate). The anion gap is also the difference between the unmeasured cations (K^+ , magnesium, calcium) and the unmeasured anions (albumin, phosphate, urate, sulfate). An increased anion gap occurs when there is an increase in unmeasured anions. With a lactic acidosis, there is endogenous production of lactic acid, which is composed of positively charged hydrogen ions and negatively charged lactate anions. The hydrogen ions are largely buffered by serum bicarbonate, resulting in a decrease in [HCO_3^-]. The hydrogen ions that are not buffered by bicarbonate cause the serum pH to decrease. The lactate anions remain, causing the increase in the anion gap.

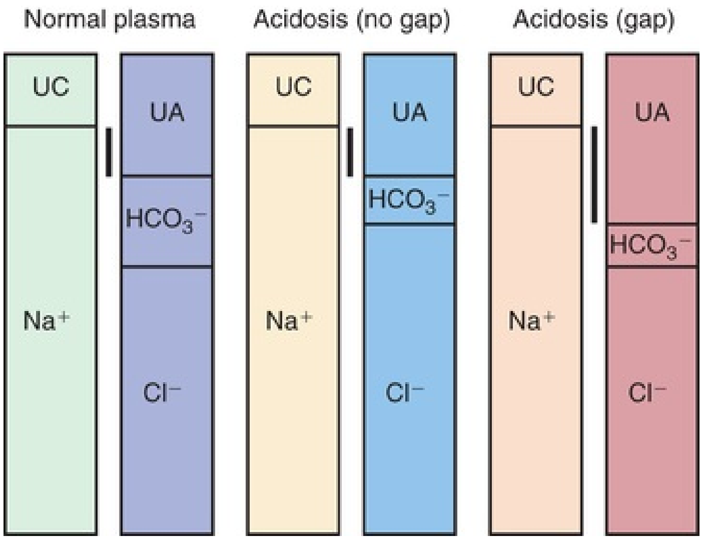

FIG. 68.9 **Anion gap. The anion gap is the difference between the sodium concentration and the combined concentrations of chloride and bicarbonate *(vertical bars)* . In both a gap and a nongap metabolic acidosis, there is a decrease in the bicarbonate concentration. There is an increase in unmeasured anions (UA) in patients with a gap metabolic acidosis. In a nongap metabolic acidosis, there is an increase in the serum chloride concentration. UC, Unmeasured cations.**

An increase in unmeasured anions, along with H^+ generation, is present in all causes of an increased gap metabolic acidosis (see Table 68.13). In DKA, the keto acids β-hydroxybutyrate and acetoacetate are the unmeasured anions. In renal failure there is retention of unmeasured anions, including phosphate, urate, and sulfate. The increase in unmeasured anions in renal failure is usually less than the decrease in [HCO_3^-]. Renal failure is thus a mix of an increased-gap and a normal-gap metabolic acidosis. The normal-gap metabolic acidosis is especially prominent in children with renal failure as a result of tubular damage, as occurs with renal dysplasia or obstructive uropathy, because these patients have a concurrent RTA. The unmeasured anions in toxic ingestions vary: formate in methanol intoxication, glycolate in ethylene glycol intoxication, and lactate and keto acids in salicylate intoxication. In inborn errors of metabolism the unmeasured anions depend on the specific etiology and may include keto acids, lactate, and other organic anions. In a few inborn errors of metabolism the acidosis occurs without generation of unmeasured anions; thus the anion gap is normal.

A **normal–anion gap metabolic acidosis** occurs when there is a decrease in [HCO_3^-] without an increase in the unmeasured anions. With diarrhea, there is a loss of bicarbonate in the stool, causing a decrease in the serum pH and [HCO_3^-]; the serum [Cl^-] increases to maintain electrical neutrality (see Fig. 68.9). **Hyperchloremic metabolic acidosis** is an alternative term for a normal–anion gap metabolic acidosis. Calculation of the anion gap is more precise than using [Cl^-] to differentiate between a normal-gap and an increased-gap metabolic acidosis, in that the anion gap directly determines the presence of unmeasured anions. Electrical neutrality dictates that the [Cl^-] increases or decreases according to the serum [Na^+], making [Cl^-] a less reliable predictor of unmeasured anions than the more direct measure, calculation of the anion gap.

An increase in unmeasured cations, such as calcium, potassium, and magnesium, decreases the anion gap. Conversely, a decrease in unmeasured cations is a very unusual cause of an increased anion gap. Because of these variables, the broad range of a normal anion gap, and other variables, the presence of a normal or an increased anion gap is not always reliable in differentiating among the causes of a metabolic acidosis, especially when the metabolic acidosis is mild. In some patients there is more than one explanation for the metabolic acidosis, such as the child with diarrhea and lactic acidosis as a result of poor perfusion. The anion gap should not be interpreted in dogmatic isolation; consideration of other laboratory abnormalities and the clinical history improves its diagnostic utility.

Treatment

The most effective therapeutic approach for patients with a metabolic acidosis is repair of the underlying disorder, if possible. The administration of insulin in DKA and the restoration of adequate perfusion with IV fluids in lactic acidosis because of hypovolemia or shock eventually result in normalization of the acid-base balance. In other diseases the use of bicarbonate therapy is indicated because the underlying disorder is irreparable. Children with metabolic acidosis caused by RTA or chronic renal failure require long-term base therapy. Patients with acute renal failure and metabolic acidosis need base therapy until their kidneys' ability to excrete hydrogen normalizes. In other disorders the cause of the metabolic acidosis eventually resolves, but base therapy is necessary during the acute illness. In salicylate poisoning, alkali administration increases renal clearance of salicylate and decreases the amount of salicylate in brain cells. Short-term base therapy is often necessary in other poisonings (ethylene glycol, methanol) and inborn errors of metabolism (pyruvate carboxylase deficiency, propionic acidemia). Some inborn errors of metabolism require long-term base therapy.

The use of base therapy in DKA and lactic acidosis is controversial; *there is little evidence that it improves patient outcome, and it has a variety of potential side effects.* The risks of giving sodium bicarbonate include the possibility of causing hypernatremia or volume overload. Furthermore, the patient may have overcorrection of the metabolic acidosis once the underlying disorder resolves, because metabolism of lactate or keto acids generates bicarbonate. The rapid change from acidemia to alkalemia can cause a variety of problems, including hypokalemia and hypophosphatemia. Bicarbonate therapy increases the generation of CO_2 , which can accumulate in patients with respiratory failure. Because CO_2 readily diffuses into cells, the administration of bicarbonate can lower the intracellular pH, potentially worsening cell function. Base therapy is usually reserved for children with severe acute lactic acidosis and severe DKA.

Oral base therapy is given to children with chronic metabolic acidosis. Sodium bicarbonate tablets are available for older children. Younger children generally take citrate solutions; the liver generates bicarbonate from citrate. Citrate solutions are available as sodium citrate, potassium citrate, and a 1 : 1 mix of sodium citrate and potassium citrate. The patient's potassium needs dictate the choice. Children with type I or type II RTA may have hypokalemia and benefit from potassium supplements, but most children with chronic renal failure cannot tolerate additional potassium.

Oral or IV base can be used in acute metabolic acidosis; IV therapy is generally used when a rapid response is necessary. Sodium bicarbonate may be given as a bolus, usually at a dose of 1 mEq/kg, in an emergency situation. Another approach is to add sodium bicarbonate or sodium acetate to the patient's IV fluids, remembering to remove an equal amount of sodium chloride from the solution to avoid giving an excessive sodium load. Careful monitoring is mandatory so that the dose of base can be titrated appropriately. Tris(hydroxymethyl)aminomethane (**tromethamine, THAM**) is an option in patients with a metabolic acidosis and a respiratory acidosis, because it neutralizes acids without releasing CO_2 . THAM also diffuses into cells and therefore provides intracellular buffering.

Hemodialysis is another option for correcting a metabolic acidosis, and it is an appropriate choice in patients with renal insufficiency, especially if significant uremia or hyperkalemia is also present. Hemodialysis is advantageous for correcting the metabolic acidosis caused by methanol or ethylene glycol intoxication, because hemodialysis efficiently removes the offending toxin. In addition, these patients often have a severe metabolic acidosis that does not respond easily to IV bicarbonate therapy. Peritoneal dialysis is another option for correcting the metabolic acidosis due to renal insufficiency.

Many causes of metabolic acidosis require specific therapy. Administration of a glucocorticoid and a mineralocorticoid is necessary in patients with adrenal insufficiency. Patients with DKA require insulin therapy, whereas patients with lactic acidosis respond to measures that alleviate tissue hypoxia. Along with correction of acidosis, patients with methanol or ethylene glycol ingestion should receive an agent that prevents the breakdown of the toxic substance to its toxic metabolites. Fomepizole has supplanted ethanol as the treatment of choice. These agents work by inhibiting alcohol dehydrogenase, the enzyme that performs the first step in the metabolism of ethylene glycol or methanol. There are a variety of disease-specific therapies for patients with a metabolic acidosis resulting from an inborn error of metabolism.

Metabolic Alkalosis

Metabolic alkalosis in children is most often secondary to emesis or diuretic use. The serum bicarbonate concentration is increased with a metabolic alkalosis, although a respiratory acidosis also leads to a compensatory elevation of the serum [HCO_3^-]. With a simple metabolic alkalosis, however, the pH is elevated; alkalemia is present. Patients with a respiratory acidosis are acidemic. By decreasing ventilation, a metabolic alkalosis causes appropriate respiratory compensation. $P\text{CO}_2$ increases by 7 mm Hg for each 10 mEq/L increase in the serum [HCO_3^-]. Appropriate respiratory compensation never exceeds a $P\text{CO}_2$ of 55-60 mm Hg. The patient has a concurrent respiratory alkalosis if the $P\text{CO}_2$ is lower than the expected compensation. A greater-than-expected $P\text{CO}_2$ occurs with a concurrent respiratory acidosis.

Etiology and Pathophysiology

The kidneys normally respond promptly to a metabolic alkalosis by increasing base excretion. Two processes are therefore usually present to produce a metabolic alkalosis:(1) the generation of the metabolic alkalosis, which requires the addition of base to the body, and (2) the maintenance of the metabolic alkalosis, which requires impairment in the kidney's ability to excrete base.

The etiologies of a metabolic alkalosis are divided into 2 categories on the basis of urinary chloride level (Table 68.14). The alkalosis in patients with a **low urinary [Cl^-]** is maintained by **volume depletion** ; thus volume repletion is necessary for correction of the alkalosis. The volume depletion in these patients is caused by losses of Na^+ and K^+ , but the loss of Cl^- is usually greater than the losses of Na^+ and K^+ combined. Because Cl^- losses are the dominant cause of the volume depletion, these patients require Cl^- to correct the volume depletion and metabolic alkalosis; they are said to have **Cl^- -responsive metabolic alkalosis.** In contrast, the alkalosis in a patient with an elevated urinary [Cl^-] does not respond to volume repletion and so is termed **Cl^- -resistant metabolic alkalosis.**

Table 68.14

Causes of Metabolic Alkalosis

Chloride-Responsive (Urinary Chloride <15 mEq/L)

- Gastric losses
  - Emesis

Nasogastric suction
Diuretics (loop or thiazide)
Chloride-losing diarrhea (OMIM 214700)
Low chloride formula
Cystic fibrosis (OMIM 219700)
Posthypercapnia

Chloride-Resistant (Urinary Chloride >20 mEq/L)

High Blood Pressure

Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism (OMIM 103900)
Renovascular disease
Renin-secreting tumor
17α-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)

Normal Blood Pressure

Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 241200/607364/602522/601678/300971/601198/613090)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Base administration

EAST, Epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Emesis or nasogastric suction results in **loss of gastric fluid** , which has a high content of HCl. Generation of H^+ by the gastric mucosa causes simultaneous release of bicarbonate into the bloodstream. Normally, the hydrogen ions in gastric fluid are reclaimed in the small intestine (by neutralizing secreted bicarbonate). Thus there is no net loss of acid. With loss of gastric fluid, this does not occur, and a metabolic alkalosis develops. This period is the *generation phase* of the metabolic alkalosis.

The *maintenance phase* of the metabolic alkalosis from gastric losses is caused by the volume depletion (“chloride depletion” from gastric loss of HCl). Volume depletion interferes with urinary loss of bicarbonate, the normal renal response to a metabolic alkalosis. During volume depletion, several mechanisms prevent renal bicarbonate loss. First, there is a reduction in the GFR, so less bicarbonate is filtered. Second, volume depletion increases resorption of sodium and bicarbonate in the proximal tubule, limiting the amount of bicarbonate that can be excreted in the urine. This effect is mediated by angiotensin II and adrenergic stimulation of the kidney, both of which are increased in response to volume depletion. Third, the increase in aldosterone during volume depletion increases bicarbonate resorption and H^+ secretion in the collecting duct.

In addition to volume depletion, gastric losses are usually associated with hypokalemia as a result of both gastric loss of K^+ and, most importantly, increased urinary K^+ losses. The increased urinary losses of K^+ are mediated by aldosterone, through volume depletion, and by the increase in intracellular K^+ secondary to the metabolic alkalosis, which causes K^+ to move into the cells of the kidney, causing increased K^+ excretion. Hypokalemia contributes to the maintenance of the metabolic alkalosis by decreasing bicarbonate loss. Hypokalemia increases H^+ secretion in the distal nephron and stimulates ammonia production in the proximal tubule. Ammonia production enhances renal excretion of H^+ .

A metabolic alkalosis can develop in patients receiving **loop** or **thiazide diuretics.** Diuretic use leads to volume depletion, which increases angiotensin II, aldosterone, and adrenergic stimulation of the kidney. Diuretics increase the delivery of sodium to the distal nephron, further enhancing acid excretion. Moreover, these diuretics cause hypokalemia, which increases acid excretion by the kidney. The increase in renal acid excretion generates the metabolic alkalosis, and the decrease in bicarbonate loss maintains it. In addition, patients who are receiving diuretics have a “contraction alkalosis.” Diuretic use causes fluid loss without bicarbonate; thus the remaining body bicarbonate is contained in a smaller total body fluid compartment. The [HCO_3^-] increases, helping to generate the metabolic alkalosis.

Diuretics are often used in patients with edema, such as those with nephrotic syndrome, heart failure, or liver failure. In many of these patients, metabolic alkalosis resulting from diuretic use develops despite the continued presence of edema. This is because the effective intravascular volume is low, and it is the effective intravascular volume that stimulates the compensatory mechanisms that cause and maintain a metabolic alkalosis. Many of these patients have a decreased effective intravascular volume before they begin diuretic therapy, increasing the likelihood of diuretic-induced metabolic alkalosis.

Diuretic use increases chloride excretion in the urine. Consequently, while a patient is receiving diuretics, the urine [Cl^-] is typically high (>20 mEq/L). After the diuretic effect has worn off, the urinary [Cl^-] is low (<15 mEq/L) because of appropriate renal Cl^- retention in response to volume depletion. Thus, categorization of diuretics on the basis of urinary [Cl^-] depends on the timing of the measurement. However, the metabolic alkalosis from diuretics is clearly Cl^- responsive; it is corrected after adequate volume repletion. This is the rationale for including this process among the chloride-responsive causes of a metabolic alkalosis.

Most patients with diarrhea have a metabolic acidosis as a result of stool losses of bicarbonate. In **chloride-losing diarrhea** , an autosomal recessive disorder, there is a defect in the normal intestinal exchange of bicarbonate for chloride, causing excessive stool losses of chloride (see Chapter 364). In addition, stool losses of H^+ and K^+ cause metabolic alkalosis and hypokalemia, both of which are exacerbated by increased renal H^+ and K^+ losses from volume depletion. Treatment is with oral supplements of K^+ and NaCl. Use of a gastric proton pump inhibitor (PPI), by decreasing gastric HCl production, reduces both the volume of diarrhea and the need for electrolyte supplementation.

Formulas with extremely low Cl^- content have led to Cl^- deficiency and volume depletion. There is secondary metabolic alkalosis and hypokalemia. **Cystic fibrosis** can rarely cause metabolic alkalosis, hypokalemia, and hyponatremia because of excessive NaCl losses in sweat (see Chapter 432). The volume depletion causes the metabolic alkalosis and hypokalemia through increased urinary losses, whereas the hyponatremia, a less common finding, is secondary to Na^+ loss combined with renal water conservation in an effort to protect the intravascular volume (“appropriate” ADH production).

A **posthypercapnic metabolic alkalosis** occurs after the correction of a chronic respiratory acidosis. This is typically seen in patients with chronic lung disease who are started on mechanical ventilation. During chronic respiratory acidosis, appropriate renal compensation leads to an increase in the serum [HCO_3^-]. Because it is still present after acute correction of the respiratory acidosis, this [HCO_3^-] causes a metabolic alkalosis. The metabolic alkalosis persists because the patient with a chronic respiratory acidosis is intravascularly depleted because of the Cl^- loss that occurred during the initial metabolic compensation for the primary respiratory acidosis. In addition, many children with a chronic respiratory acidosis receive diuretics, which further decrease the intravascular volume. The metabolic alkalosis responds to correction of the intravascular volume deficit.

The **chloride-resistant** causes of metabolic alkalosis can be subdivided according to blood pressure status. Patients with **hypertension** either have increased aldosterone levels or act as if they do. Aldosterone levels are elevated in children with adrenal adenomas or hyperplasia. Aldosterone causes renal retention of sodium, with resultant hypertension. Metabolic alkalosis and hypokalemia result from aldosterone-mediated renal excretion of H^+ and K^+. The urinary Cl^- level is not low because these patients are volume-overloaded, not volume-depleted. The volume expansion and hypertension allow normal excretion of Na^+ and Cl^- despite the presence of aldosterone. This is known as the *mineralocorticoid escape phenomenon.*

In **glucocorticoid-remediable aldosteronism** , an autosomal dominant disorder, excess production of aldosterone results from the presence of an aldosterone synthase gene regulated by adrenocorticotropic hormone (ACTH) (see Chapter 594.8). Glucocorticoids effectively treat this disorder by inhibiting ACTH production by the pituitary, downregulating the inappropriate aldosterone production. Renovascular disease and renin-secreting tumors both cause excessive renin, leading to an increase in aldosterone, although hypokalemia and metabolic alkalosis are less common findings than hypertension. In 2 forms of **congenital adrenal hyperplasia** , 11β-hydroxylase deficiency and 17α-hydroxylase deficiency, there is excessive production of the mineralocorticoid 11-deoxycorticosterone (see Chapters 594.2 and 594.4). Hypertension, hypokalemia, and metabolic alkalosis are more likely in 17α-hydroxylase deficiency than in 11β-hydroxylase deficiency. These disorders respond to glucocorticoids because the excess production of 11-deoxycorticosterone is under the control of ACTH.

Cushing syndrome frequently causes hypertension. Cortisol has some mineralocorticoid activity, and high levels can produce hypokalemia and metabolic alkalosis in patients with Cushing syndrome.

Cortisol can bind to the mineralocorticoid receptors in the kidney and function as a mineralocorticoid. This binding normally does not occur because 11β-hydroxysteroid dehydrogenase in the kidney converts cortisol to cortisone, which does not bind to the mineralocorticoid receptor. In 11β-hydroxysteroid dehydrogenase deficiency, also called **apparent mineralocorticoid excess** , cortisol is not converted in the kidney to cortisone. Cortisol is therefore available to bind to the mineralocorticoid receptor in the kidney and act as a mineralocorticoid. Patients with this deficiency, despite low levels of aldosterone, are hypertensive and hypokalemic, and they have a metabolic alkalosis. The same phenomenon can occur with excessive intake of natural licorice, a component of which, glycyrrhizic acid, inhibits 11β-hydroxysteroid dehydrogenase. The autosomal dominant disorder **Liddle syndrome** is secondary to an activating mutation of the sodium channel in the distal nephron (see Chapter 549.3). Upregulation of this sodium channel is one of the principal actions of aldosterone. Because this Na^+ channel is continuously open, children with Liddle syndrome have the features of hyperaldosteronism, including hypertension, hypokalemia, and metabolic alkalosis, but low serum levels of aldosterone.

Bartter and Gitelman syndromes are autosomal recessive disorders associated with **normal blood pressure** , elevated urinary Cl^- , metabolic alkalosis, and hypokalemia (see Chapter 549). In **Bartter syndrome** , patients have a defect in Na^+ and Cl^- resorption in the loop of Henle. This leads to excessive urinary losses of Na^+ and Cl^- , and as in patients receiving loop diuretics, volume depletion and secondary hyperaldosteronism occur, causing hypokalemia and metabolic alkalosis. **Gitelman syndrome** is usually milder than Bartter syndrome. Patients have renal Na^+ and Cl^- wasting with volume depletion caused by mutations in the gene encoding the thiazide-sensitive Na^+ -Cl^- transporter in the distal tubule. As in patients receiving a thiazide diuretic, affected patients have volume depletion and secondary hyperaldosteronism with hypokalemia and metabolic alkalosis. Children with Gitelman syndrome have hypocalciuria and hypomagnesemia. Some patients with autosomal dominant hypoparathyroidism have hypokalemia and metabolic alkalosis from impaired

Na^+ and Cl^- resorption in the loop of Henle. **EAST syndrome** causes hypokalemia, metabolic alkalosis and hypomagnesemia.

Excessive base intake can cause a metabolic alkalosis. Affected patients do not have low urine [Cl^-], unless there is associated volume depletion. In the absence of volume depletion, excess base is rapidly corrected via renal excretion of bicarbonate. Rarely, massive base intake can cause a metabolic alkalosis by overwhelming the kidney's ability to excrete bicarbonate. This may occur in infants who are given baking soda as a “home remedy” for colic or stomach upset. Each teaspoon of baking soda has 42 mEq of sodium bicarbonate. Infants have increased vulnerability because of a lower GFR, limiting the rate of compensatory renal bicarbonate excretion. A metabolic alkalosis may also occur in patients who receive a large amount of sodium bicarbonate during cardiopulmonary resuscitation. Blood products are anticoagulated with citrate, which is converted into bicarbonate by the liver. Patients who receive large amounts of blood products may have a metabolic alkalosis. Iatrogenic metabolic alkalosis can occur as a result of acetate in TPN. Aggressive use of bicarbonate therapy in a child with a lactic acidosis or DKA may cause a metabolic alkalosis. This event is especially likely in a patient in whom the underlying cause of the lactic acidosis is successfully corrected (restoration of intravascular volume in a patient with severe dehydration). Once the cause of the lactic acidosis resolves, lactate can be converted by the liver into bicarbonate, which when combined with infused bicarbonate can create a metabolic alkalosis. A similar phenomenon can occur in a child with DKA because the administration of insulin allows keto acids to be metabolized, producing bicarbonate. However, this phenomenon rarely occurs because of judicious use of bicarbonate therapy in DKA and because there are usually significant pretreatment losses of keto acids in the urine, preventing massive regeneration of bicarbonate. Base administration is most likely to cause a metabolic alkalosis in patients who have an impaired ability to excrete bicarbonate in the urine. This impairment occurs in patients with concurrent volume depletion or renal insufficiency.

Clinical Manifestations

The symptoms in patients with a metabolic alkalosis are often related to the underlying disease and associated electrolyte disturbances. Children with Cl^- -responsive causes of metabolic alkalosis often have symptoms related to volume depletion, such as thirst and lethargy. In contrast, children with Cl^- -

unresponsive causes may have symptoms related to hypertension.

Alkalemia causes potassium to shift into the ICS, producing a decrease in the extracellular [K^+]. Alkalemia leads to increased urinary losses of K^+ . Increased K^+ losses are present in many of the conditions that cause a metabolic alkalosis. Therefore, most patients with a metabolic alkalosis have hypokalemia, and their symptoms may be related to the hypokalemia (see Chapter 68.4).

The symptoms of a metabolic alkalosis are caused by the associated alkalemia. The magnitude of the alkalemia is related to the severity of the metabolic alkalosis and the presence of concurrent respiratory acid-base disturbances. During alkalemia, the ionized calcium concentration decreases as a result of increased binding of calcium to albumin. The decrease in the ionized calcium concentration may cause symptoms of **tetany** (**carpopedal spasm**).

Arrhythmias are a potential complication of a metabolic alkalosis, and the risk for arrhythmia increases if there is concomitant hypokalemia. Alkalemia increases the risk of digoxin toxicity, and antiarrhythmic medications are less effective in the presence of alkalemia. In addition, alkalemia may decrease cardiac output. A metabolic alkalosis causes a compensatory increase in the P_{CO_2} by decreasing ventilation. In patients with underlying lung disease, the decrease in ventilatory drive can cause hypoxia. In patients with normal lungs, the hypoventilation seen in severe metabolic alkalosis can cause hypoxia.

Diagnosis

Measurement of the urine [Cl^-] is the most helpful test in differentiating among the causes of a metabolic alkalosis. The urine [Cl^-] is low in patients with a metabolic alkalosis resulting from volume depletion, unless there is a defect in renal handling of Cl^- . The urine [Cl^-] is superior to the urine [Na^+] in assessment of volume status in patients with a metabolic alkalosis, because the normal renal response to a metabolic alkalosis is to excrete bicarbonate. Because bicarbonate is negatively charged, it can be excreted only with a cation, usually Na^+ and K^+ . Therefore, a patient with a metabolic alkalosis may excrete Na^+ in the urine despite the presence of volume depletion, which normally causes avid Na^+ retention. The urine [Cl^-] is usually a good indicator of **volume status** , and it differentiates Cl^- -resistant and Cl^- -responsive causes of a metabolic alkalosis.

Diuretics and gastric losses are the most common causes of metabolic alkalosis and are usually apparent from the patient history. Occasionally, metabolic alkalosis, usually with hypokalemia, may be a clue to the presence of bulimia or surreptitious diuretic use (see Chapter 41). Patients with bulimia have a low urine Cl^- level, indicating that they have volume depletion as a result of an extrarenal etiology, but there is no alternative explanation for their volume depletion. Surreptitious diuretic use may be diagnosed by obtaining a urine toxicology screen for diuretics. The urine $[Cl^-]$ is increased while a patient is using diuretics but is low when the patient stops taking them. Rarely, children with mild Bartter or Gitelman syndrome are misdiagnosed as having bulimia or abusing diuretics. The urine $[Cl^-]$ is always elevated in Bartter and Gitelman syndromes, and the urine toxicology screen for diuretics has a negative result. Metabolic alkalosis with hypokalemia is occasionally the initial manifestation of cystic fibrosis. An elevated sweat Cl^- finding is diagnostic.

Patients with a metabolic alkalosis and a high urinary $[Cl^-]$ are subdivided according to blood pressure status. Children with normal blood pressure may have Bartter or Gitelman syndrome. Excess base administration is another diagnostic possibility, but it is usually apparent from the history. In patients with sodium bicarbonate ingestion (baking soda), which may be unreported by the parent, the metabolic alkalosis usually occurs with significant hypernatremia. In addition, unless volume depletion is superimposed, the metabolic alkalosis from base ingestion resolves itself once the source of base is eliminated.

Measuring serum concentrations of renin and aldosterone differentiates children with a metabolic alkalosis, a high urinary $[Cl^-]$, and elevated blood pressure. Both renin and aldosterone are elevated in children with either renovascular disease or a renin-secreting tumor. Aldosterone is high and renin is low in patients with adrenal adenomas or hyperplasia and glucocorticoid-remediable aldosteronism. Renin and aldosterone are low in children with Cushing syndrome, Liddle syndrome, licorice ingestion, and 17α-hydroxylase, 11β-hydroxylase, and 11β-hydroxysteroid dehydrogenase deficiencies. An elevated 24 hr urine cortisol value is diagnostic of Cushing syndrome, which is suspected from the presence of the other classic features of this disease (see Chapter 597). Elevations of 11-deoxycorticosterone values are seen in 17α-hydroxylase and 11β-hydroxylase deficiency.

Treatment

The approach to treatment of metabolic alkalosis depends on the severity of the alkalosis and the underlying etiology. In children with a mild metabolic alkalosis ($[HCO_3^-]$ <32 mEq/L), intervention is often unnecessary, although this depends on the specific circumstances. In a child with congenital heart disease who is receiving a stable dose of a loop diuretic, a mild alkalosis does not require treatment. In contrast, intervention may be appropriate in a child with a worsening mild metabolic alkalosis because of nasogastric suction. The presence of a concurrent respiratory acid-base disturbance also influences therapeutic decision-making. A patient with a concurrent respiratory acidosis should have some increase in bicarbonate from metabolic compensation; thus the severity of the pH elevation is more important than $[HCO_3^-]$. In contrast, a patient with a respiratory alkalosis and a metabolic alkalosis is at risk for severe alkalemia; treatment may be indicated, even if the increase in bicarbonate value is only mild.

Intervention is usually necessary in children with moderate or severe metabolic alkalosis. The most effective approach is to address the underlying etiology. In some children, nasogastric suction may be decreased or discontinued. Alternatively, the addition of a gastric PPI reduces gastric secretion and losses of HCl. Diuretics are an important cause of metabolic alkalosis, and if a change is tolerated, they should be eliminated or the dose reduced. Adequate potassium supplementation or the addition of a potassium-sparing diuretic is also helpful in a child with a metabolic alkalosis from diuretics. Potassium-sparing diuretics not only decrease renal K^+ losses but, by blocking the action of aldosterone, also decrease H^+ secretion in the distal nephron, increasing urinary bicarbonate excretion. Many children cannot tolerate discontinuation of diuretic therapy; thus potassium supplementation and potassium-sparing diuretics are the principal therapeutic approach. Arginine HCl may also be used to treat chloride-responsive metabolic acidosis if sodium or potassium salts are not appropriate. Arginine HCl may raise the serum K^+ levels during administration. Rarely, in cases of severe metabolic alkalosis, acetazolamide is an option. A carbonic anhydrase inhibitor, acetazolamide decreases resorption of bicarbonate in the proximal tubule, causing significant bicarbonate loss in the urine. The patient receiving this drug must be monitored closely, because acetazolamide produces major losses of potassium in the urine and increases fluid losses, potentially necessitating a reduction in dosage of other diuretics.

Most children with a metabolic alkalosis have one of the **chloride-responsive** etiologies. In these situations, administration of sufficient sodium chloride and potassium chloride to correct the volume deficit and the potassium deficit is necessary to correct the metabolic alkalosis. This approach may not be an option in the child who has volume depletion due to diuretics, because volume repletion may be contraindicated. Adequate replacement of gastric losses of sodium and potassium in a child with a nasogastric tube can minimize or prevent the development of the metabolic alkalosis. With adequate intravascular volume and a normal serum [K^+], the kidney excretes the excess bicarbonate within 2 days.

In children with the **chloride-resistant** causes of a metabolic alkalosis that are associated with hypertension, volume repletion is contraindicated because it would exacerbate the hypertension and would not repair the metabolic alkalosis. Ideally, treatment focuses on eliminating the excess aldosterone effect. Adrenal adenomas can be resected, licorice intake can be eliminated, and renovascular disease can be repaired. Glucocorticoid-remediable aldosteronism, 17α-hydroxylase deficiency, and 11β-hydroxylase deficiency respond to the administration of glucocorticoids. The mineralocorticoid effect of cortisol in 11β-hydroxysteroid dehydrogenase deficiency can be decreased with the use of spironolactone, which blocks the mineralocorticoid receptor. In contrast, the metabolic alkalosis in children with Liddle syndrome does not respond to spironolactone; however, either triamterene or amiloride is effective therapy because both agents block the sodium channel that is constitutively active in Liddle syndrome.

In children with Bartter or Gitelman syndrome, therapy includes oral potassium and sodium supplementation; potassium-sparing diuretics may be helpful in select cases. Children with Gitelman syndrome often require magnesium supplementation, whereas children with severe Bartter syndrome often benefit from indomethacin.

Respiratory Acidosis

A respiratory acidosis is an inappropriate increase in blood carbon dioxide tension (P_{CO_2}). CO_2 is a by-product of metabolism and is removed from the body by the lungs. During a respiratory acidosis, the effectiveness of CO_2 removal by the lungs is decreased. A respiratory acidosis is secondary to either pulmonary disease, such as severe bronchiolitis, or nonpulmonary disease, such as a narcotic overdose. Even though body production of CO_2 can vary, normal lungs are able to accommodate this variation; excess production of CO_2 is not an isolated cause of a respiratory acidosis. With impairment of alveolar ventilation, the rate of body production of CO_2 may affect the severity of the respiratory acidosis, but this is usually not a significant factor.

A respiratory acidosis causes a decrease in the blood pH, but there is normally a metabolic response that partially compensates, minimizing the severity of the acidemia. The acute metabolic response to a respiratory alkalosis occurs within minutes. The metabolic compensation for an *acute* respiratory acidosis is secondary to titration of acid by nonbicarbonate buffers. This buffering of H^+ causes a predictable increase in the serum $[HCO_3^-]$: Plasma bicarbonate increases by 1 for each 10 mm Hg increase in the P_{CO_2} (acute compensation).

With a *chronic* respiratory acidosis, there is more significant metabolic compensation and thus less severe acidemia than in an acute respiratory acidosis with the same increase in P_{CO_2}. During a chronic respiratory acidosis, the kidneys increase acid excretion. This response occurs over 3-4 days and causes a predictable increase in the serum $[HCO_3^-]$: Plasma bicarbonate increases by 3.5 for each 10 mm Hg increase in the P_{CO_2} (chronic compensation).

The increase of serum $[HCO_3^-]$ during a chronic respiratory acidosis is associated with a decrease in body chloride. After acute correction of a chronic respiratory acidosis, the plasma bicarbonate continues to be increased, and the patient has a metabolic alkalosis. Because of the Cl^- deficit, this is a chloride-responsive metabolic alkalosis; it corrects once the patient's Cl^- deficit is replaced.

A **mixed disorder** is present if the metabolic compensation is inappropriate. A higher-than-expected bicarbonate value occurs in the setting of a concurrent metabolic alkalosis, and a lower-than-expected bicarbonate value occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory acidosis requires clinical knowledge of the acuity of the process, because the expected compensation is different, depending on whether the process is acute or chronic.

The P_{CO_2} cannot be interpreted in isolation to determine whether a patient has a respiratory acidosis. A respiratory acidosis is always present if a patient has acidemia and an elevated P_{CO_2}. However, an elevated P_{CO_2} also occurs as appropriate respiratory compensation for a simple metabolic alkalosis. The patient is *alkalemic* ; this is not a respiratory acidosis. During a mixed disturbance, a patient can have a respiratory acidosis and a normal or even low P_{CO_2}. This condition may occur in a patient with a metabolic acidosis. A respiratory acidosis is present if the patient does not have appropriate respiratory compensation (the P_{CO_2} is higher than expected from the severity of the metabolic acidosis).

Etiology and Pathophysiology

The causes of a respiratory acidosis are either pulmonary or nonpulmonary (Table 68.15). CNS disorders can decrease the activity of the central respiratory center, reducing ventilatory drive. A variety of medications and illicit drugs suppress the respiratory center. The signals from the respiratory center need to be transmitted to the respiratory muscles via the nervous system. Respiratory muscle failure can be secondary to disruption of the signal from the CNS in the spinal cord, the phrenic nerve, or the neuromuscular junction. Disorders directly affecting the muscles of respiration can prevent adequate ventilation, causing a respiratory acidosis.

Table 68.15

Causes of Respiratory Acidosis

Central Nervous System Depression

- Encephalitis
- Head trauma
- Brain tumor
- Central sleep apnea
- Primary pulmonary hypoventilation (Ondine curse)
- Stroke
- Hypoxic brain damage
- Obesity-hypoventilation (pickwickian) syndrome
- Increased intracranial pressure
- Medications
    - Narcotics
    - Barbiturates
    - Anesthesia
    - Benzodiazepines

    - Propofol
    - Alcohols

Disorders of Spinal Cord, Peripheral Nerves, or Neuromuscular Junction

- Diaphragmatic paralysis
- Guillain-Barré syndrome
- Poliomyelitis
- Acute flaccid myelitis
- Spinal muscular atrophies
- Tick paralysis
- Botulism
- Myasthenia
- Multiple sclerosis
- Spinal cord injury
- Medications
    - Vecuronium
    - Aminoglycosides
    - Organophosphates (pesticides)

Respiratory Muscle Weakness

- Muscular dystrophy
- Hypothyroidism
- Malnutrition
- Hypokalemia
- Hypophosphatemia
- Medications
    - Succinylcholine
    - Corticosteroids

Pulmonary Disease

- Pneumonia

Pneumothorax
Asthma
Bronchiolitis
Pulmonary edema
Pulmonary hemorrhage
Acute respiratory distress syndrome
Neonatal respiratory distress syndrome
Cystic fibrosis
Bronchopulmonary dysplasia
Hypoplastic lungs
Meconium aspiration
Pulmonary thromboembolus
Interstitial fibrosis

Upper Airway Disease

Aspiration
Laryngospasm
Angioedema
Obstructive sleep apnea
Tonsillar hypertrophy
Vocal cord paralysis
Extrinsic tumor
Extrinsic or intrinsic hemangioma

Miscellaneous

Flail chest
Cardiac arrest
Kyphoscoliosis
Decreased diaphragmatic movement due to ascites or peritoneal dialysis

Mild or moderate lung disease often causes a respiratory alkalosis as a result of hyperventilation secondary to hypoxia or stimulation of lung mechanoreceptors or chemoreceptors. Only more severe lung disease causes a respiratory acidosis. Upper airway diseases, by impairing air entry into the lungs, may decrease ventilation, producing a respiratory acidosis.

Increased production of CO_2 is never the sole cause of a respiratory acidosis, but it can increase the severity of the disease in a patient with decreased ventilation of CO_2 . Increased production of CO_2 occurs in patients with fever, hyperthyroidism, excess caloric intake, and high levels of physical activity. Increased respiratory muscle work also increases CO_2 production.

Clinical Manifestations

Patients with a respiratory acidosis are often tachypneic in an effort to correct the inadequate ventilation. Exceptions include patients with a respiratory acidosis resulting from CNS depression and patients who are on the verge of complete respiratory failure secondary to fatigue of the respiratory muscles.

The symptoms of respiratory acidosis are related to the severity of the **hypercarbia** . Acute respiratory acidosis is usually more symptomatic than chronic respiratory acidosis. Symptoms are also increased by concurrent hypoxia or metabolic acidosis. In a patient breathing room air, hypoxia is always present if a respiratory acidosis is present. The potential CNS manifestations of respiratory acidosis include anxiety, dizziness, headache, confusion, asterixis, myoclonic jerks, hallucinations, psychosis, coma, and seizures.

Acidemia, no matter the etiology, affects the cardiovascular system. An arterial pH <7.2 impairs cardiac contractility and the normal response to catecholamines, in both the heart and the peripheral vasculature. Hypercapnia causes vasodilation, most dramatically in the cerebral vasculature, but hypercapnia produces vasoconstriction of the pulmonary circulation. Respiratory acidosis increases the risk of cardiac **arrhythmias** , especially in a child with underlying cardiac disease.

Diagnosis

The history and physical findings often point to a clear etiology. For the obtunded patient with poor respiratory effort, evaluation of the CNS is often indicated. This may include imaging studies (CT or MRI) and, potentially, a lumbar puncture for cerebrospinal fluid analysis. A toxicology screen for illicit drugs may also be appropriate. A response to naloxone is both diagnostic and therapeutic. In many of the diseases affecting the respiratory muscles, there is evidence of weakness in other muscles. Stridor is a clue that the child may have upper airway disease. Along with a physical examination, a chest radiograph is often helpful in diagnosing pulmonary disease.

In many patients, respiratory acidosis may be multifactorial. A child with bronchopulmonary dysplasia, an intrinsic lung disease, may worsen because of respiratory muscle dysfunction caused by severe hypokalemia resulting from long-term diuretic therapy. Conversely, a child with muscular dystrophy, a muscle disease, may worsen because of aspiration pneumonia.

For a patient with respiratory acidosis, calculation of the gradient between the alveolar oxygen concentration and the arterial oxygen concentration, the A-a O_2 gradient, is useful for distinguishing between poor respiratory effort and intrinsic lung disease. The A-a O_2 gradient is increased if the hypoxemia is caused by intrinsic lung disease (see Chapter 400).

Treatment

Respiratory acidosis is best managed by treatment of the underlying etiology. In some patients the response is very rapid, such as after the administration of naloxone to a patient with a narcotic overdose. In contrast, in the child with pneumonia, a number of days of antibiotic therapy may be required before the respiratory status improves. In many children with a chronic respiratory acidosis, there is no curative therapy, although an acute respiratory illness superimposed on a chronic respiratory condition is usually reversible.

All patients with an *acute* respiratory acidosis are hypoxic and therefore need to receive supplemental oxygen. Mechanical ventilation is necessary in some children with respiratory acidosis. Children with significant respiratory acidosis caused by CNS disease usually require mechanical ventilation because such a disorder is unlikely to respond quickly to therapy. In addition, hypercarbia causes cerebral vasodilation, and the increase in intracranial pressure can be dangerous in a child with an underlying CNS disease. Readily reversible CNS depression, as from a narcotic overdose, may not require mechanical ventilation. Decisions on mechanical ventilation for other patients depend on a number of factors. Patients with severe hypercarbia—P_{CO_2} >75 mm Hg—usually require mechanical ventilation (see Chapter 89.1). The threshold for intubation is lower if there is concomitant metabolic acidosis, a slowly responsive underlying disease, or hypoxia that responds poorly to oxygen, or if the patient appears to be tiring and respiratory arrest seems likely.

In patients with a *chronic* respiratory acidosis the respiratory drive is often less responsive to hypercarbia and more responsive to hypoxia. Thus, with chronic respiratory acidosis, excessive use of oxygen can blunt the respiratory drive and therefore increase the P_{CO_2}. In these patients, oxygen must be used cautiously.

When possible, it is best to avoid mechanical ventilation in a patient with chronic respiratory acidosis because extubation is often difficult. However, an acute illness may necessitate mechanical ventilation in a child with chronic respiratory acidosis. When intubation is necessary, the P_{CO_2} should be lowered only to the patient's normal baseline, and this should be done gradually. These patients normally have an elevated serum $[HCO_3^-]$ as a result of metabolic compensation for their respiratory acidosis. A rapid lowering of the P_{CO_2} can cause a severe metabolic alkalosis, potentially leading to complications, including cardiac arrhythmias, decreased cardiac output, and decreased cerebral blood flow. In addition, prolonged mechanical ventilation at a normal P_{CO_2} causes the metabolic compensation to resolve. When the patient is subsequently extubated, the patient will no longer benefit from metabolic compensation, causing a more severe acidemia because of the respiratory acidosis.

Respiratory Alkalosis

A respiratory alkalosis is an inappropriate reduction in the blood CO_2 concentration. This is usually secondary to hyperventilation, initially causing removal of CO_2 to surpass production. Eventually, a new steady state is achieved, with removal equaling production, although at a lower CO_2 tension (P_{CO_2}). A respiratory alkalosis that is not the result of hyperventilation may occur in children receiving extracorporeal membrane oxygenation or hemodialysis, with CO_2 lost directly from the blood in the extracorporeal circuit.

With a simple respiratory alkalosis, the pH increases but there is a normal metabolic response that attenuates some of the change in the blood pH. A metabolic response to an acute respiratory alkalosis occurs within minutes, mediated by hydrogen ion release from nonbicarbonate buffers. The metabolic response to an acute respiratory alkalosis is predictable: Plasma bicarbonate falls by 2 for each 10 mm Hg decrease in the P_{CO_2} (acute compensation).

A chronic respiratory alkalosis leads to more significant metabolic compensation because of the actions of the kidneys, which decrease acid secretion, producing a decrease in the serum [HCO_3^-]. Both the proximal and distal tubules decrease acid secretion. Metabolic compensation for a respiratory alkalosis develops gradually and takes 2-3 days to produce the full effect: Plasma bicarbonate falls by 4 for each 10 mm Hg decrease in the P_{CO_2} (chronic compensation).

A chronic respiratory alkalosis is the only acid-base disturbance in which appropriate compensation may *normalize the pH,* although >7.4.

A **mixed disorder** is present if the metabolic compensation is inappropriate. A higher-than-expected HCO_3^- level occurs in the setting of a concurrent metabolic alkalosis, and a lower-than-expected HCO_3^- level occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory alkalosis requires clinical knowledge of the acuity of the process, because the expected compensation differs according to whether the process is acute or chronic.

A low P_{CO_2} value does not always indicate a respiratory alkalosis. The P_{CO_2} also decreases as part of the appropriate respiratory compensation for a metabolic acidosis; this is not a respiratory alkalosis. A metabolic acidosis is the dominant acid-base disturbance in a patient with acidemia and a low P_{CO_2}, even though there could still be a concurrent respiratory alkalosis. In contrast, a respiratory alkalosis is always present in a patient with alkalemia and a low P_{CO_2}. Even a normal P_{CO_2} value may be consistent with a respiratory alkalosis in a patient with a metabolic alkalosis, because an elevated P_{CO_2} is expected as part of appropriate respiratory compensation for the metabolic alkalosis.

Etiology and Pathophysiology

A variety of stimuli can increase the ventilatory drive and cause a respiratory alkalosis (Table 68.16). Arterial hypoxemia or tissue **hypoxia** stimulates peripheral chemoreceptors to signal the central respiratory center in the medulla to increase ventilation. The resultant greater respiratory effort increases the oxygen content of the blood (P_{O_2}) but depresses the P_{CO_2}. The effect of hypoxemia on ventilation begins when the arterial oxygen saturation (Sa_{O_2}) decreases to approximately 90% (P_{O_2} = 60 mm Hg), and hyperventilation increases as hypoxemia worsens. Acute hypoxia is a more potent stimulus for hyperventilation than chronic hypoxia; thus chronic hypoxia, as occurs in cyanotic heart disease, causes a much less severe respiratory alkalosis than an equivalent degree of acute hypoxia. The many causes of hypoxemia or tissue hypoxia include primary lung disease, severe anemia, and carbon monoxide (CO) poisoning.

Table 68.16

Causes of Respiratory Alkalosis

Hypoxemia or Tissue Hypoxia

- Pneumonia
- Pulmonary edema
- Cyanotic heart disease
- Congestive heart failure
- Asthma
- Severe anemia
- High altitude
- Laryngospasm
- Aspiration
- Carbon monoxide poisoning
- Pulmonary embolism
- Interstitial lung disease
- Hypotension

Lung Receptor Stimulation

- Pneumonia
- Pulmonary edema
- Asthma
- Pulmonary embolism
- Hemothorax
- Pneumothorax
- Respiratory distress syndrome (adult or infant)

Central Stimulation

- Central nervous system disease
    - Subarachnoid hemorrhage
    - Encephalitis or meningitis
    - Trauma
    - Brain tumor
    - Stroke
- Fever
- Pain
- Anxiety (panic attack)
- Psychogenic hyperventilation or anxiety
- Liver failure
- Sepsis
- Pregnancy
- Mechanical ventilation
- Hyperammonemia
- Extracorporeal membrane oxygenation or hemodialysis
- Medications
    - Salicylate intoxication
    - Theophylline
    - Progesterone
    - Exogenous catecholamines
    - Caffeine

The lungs contain chemoreceptors and mechanoreceptors that respond to irritants and stretching and send signals to the respiratory center to increase ventilation. Aspiration or pneumonia may stimulate the chemoreceptors, whereas pulmonary edema may stimulate the mechanoreceptors. Most of the diseases that activate these receptors may also cause hypoxemia and can therefore potentially lead to hyperventilation by 2 mechanisms. Patients with primary lung disease may initially have a respiratory alkalosis, but worsening of the disease, combined with respiratory muscle fatigue, often causes respiratory failure and the development of a respiratory acidosis.

Hyperventilation in the absence of lung disease occurs with direct stimulation of the central respiratory center. This occurs with CNS diseases such as meningitis, hemorrhage, and trauma. Central hyperventilation caused by lesions, such as infarcts or tumors near the central respiratory center in the midbrain, increases the rate and depth of the respiratory effort. This respiratory pattern portends a poor prognosis because these midbrain lesions are frequently fatal. Systemic processes may cause centrally mediated hyperventilation. Although the exact mechanisms are not clear, liver disease causes a respiratory alkalosis that is usually proportional to the degree of liver failure. **Pregnancy** causes a chronic respiratory alkalosis, probably mediated by progesterone acting on the respiratory centers. **Salicylates** , although often causing a concurrent metabolic acidosis, directly stimulate the respiratory center to produce a respiratory alkalosis. The respiratory alkalosis during sepsis is probably caused by cytokine release.

Hyperventilation may be secondary to an underlying disease that causes pain, stress, or anxiety. In psychogenic hyperventilation or in **panic attacks** , there is no disease process accounting for the hyperventilation. This disorder may occur in a child who has had an emotionally stressful experience. Alternatively, it may be part of a panic disorder, especially if there are repeated episodes of hyperventilation. In such a patient the symptoms of acute alkalemia increase anxiety, potentially perpetuating the hyperventilation.

A respiratory alkalosis is quite common in children receiving mechanical ventilation because the respiratory center is not controlling ventilation. In addition, these children may have a decreased metabolic rate and thus less CO_2 production because of sedation and paralytic medications. Normally, decreased CO_2 production and the resultant hypocapnia decrease ventilation, but this physiologic response cannot occur in a child who cannot reduce ventilatory effort.

Clinical Manifestations

The disease process causing the respiratory alkalosis is usually more concerning than the clinical manifestations. Chronic respiratory alkalosis is usually asymptomatic because metabolic compensation decreases the magnitude of the alkalemia.

Acute respiratory alkalosis may cause chest tightness, palpitations, lightheadedness, circumoral numbness, and paresthesias of the extremities. Less common manifestations include tetany, seizures, muscle cramps, and syncope. The lightheadedness and syncope probably result from the reduction in cerebral blood flow caused by hypocapnia. The reduction in cerebral blood flow is the rationale for using hyperventilation to treat children with increased intracranial pressure (ICP). The paresthesias, tetany, and seizures may be partially related to the reduction in ionized calcium that occurs because alkalemia causes more calcium to bind to albumin. A respiratory alkalosis also causes a mild reduction in the serum potassium level. Patients with psychogenic hyperventilation tend to be most symptomatic as a result of the respiratory alkalosis, and these symptoms, along with a sensation of breathlessness, exacerbate the hyperventilation.

Diagnosis

In many patients, hyperventilation producing a respiratory alkalosis is not clinically detectable, even with careful observation of the patient's respiratory effort. Metabolic compensation for a respiratory alkalosis causes a low serum [HCO_3^-]. When hyperventilation is not appreciated and only serum electrolytes are evaluated, there is often a presumptive diagnosis of a metabolic acidosis. If a respiratory alkalosis is suspected, only ABG determination can make the diagnosis.

Hyperventilation does not always indicate a primary respiratory disorder. In some patients the hyperventilation is appropriate respiratory compensation for a metabolic acidosis. With a primary metabolic acidosis, acidemia is present, and the serum HCO_3^- level is usually quite low if there is clinically detectable hyperventilation. In contrast, the serum HCO_3^- level never goes below 17 mEq/L as part of the metabolic compensation for acute respiratory alkalosis, and simple acute respiratory alkalosis causes alkalemia.

The etiology of a respiratory alkalosis is often apparent from the physical examination or history, and it may consist of lung disease, neurologic disease, or cyanotic heart disease. **Hypoxemia** is a common cause of hyperventilation, and it is important to diagnose because it suggests a significant underlying disease that requires expeditious treatment. Hypoxemia may be detected on physical examination (cyanosis) or by pulse oximetry. However, normal pulse oximetry values do not eliminate hypoxemia as the etiology of the hyperventilation. There are 2 reasons why pulse oximetry is not adequate for eliminating hypoxemia as a cause of a respiratory alkalosis. First, pulse oximetry is not very sensitive at detecting a mildly low arterial PO_2 (PaO_2). Second, the hyperventilation during respiratory alkalosis causes PaO_2 to increase, possibly to a level that is not identified as abnormal by pulse oximetry. Only ABG measurement can eliminate hypoxia as an explanation for a respiratory alkalosis. Along with hypoxemia, it is important to consider processes that cause **tissue hypoxia without necessarily causing hypoxemia** . Examples are CO poisoning, severe anemia, and heart failure.

Lung disease without hypoxemia may cause hyperventilation. Although lung disease is often apparent by history or physical examination, a chest radiograph may detect more subtle disease. The patient with a pulmonary embolism may have benign chest radiograph findings, normal $Pa\textsc{o}_2$, and isolated respiratory alkalosis, although hypoxia may eventually occur. Diagnosis of a pulmonary embolism requires a high index of suspicion and should be considered in children without another explanation for respiratory alkalosis, especially if risk factors are present, such as prolonged bed rest and a hypercoagulable state (e.g., nephrotic syndrome, lupus anticoagulant).

Treatment

There is seldom a need for specific treatment of respiratory alkalosis. Rather, treatment focuses on the underlying disease. Mechanical ventilator settings are adjusted to correct **iatrogenic** respiratory alkalosis, unless the hyperventilation has a therapeutic purpose (e.g., treatment of increased ICP).

For the patient with hyperventilation secondary to anxiety, efforts should be undertaken to reassure the child, usually enlisting the parents. Along with reassurance, patients with **psychogenic hyperventilation** may benefit from benzodiazepines. During an acute episode of psychogenic hyperventilation, rebreathing into a paper bag increases the patient's $P\textsc{co}_2$. Using a paper bag instead of a plastic bag allows adequate oxygenation but permits [CO_2] in the bag to increase. The resultant increase in the patient's $P\textsc{co}_2$ decreases the symptoms of the respiratory alkalosis that tend to perpetuate the hyperventilation. Rebreathing should be performed only when other causes of hyperventilation have been eliminated; pulse oximetry during the rebreathing is prudent.

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CHAPTER 69

Maintenance and Replacement Therapy

Larry A. Greenbaum

Maintenance intravenous (IV) fluids are used in a child who cannot be fed enterally. Along with maintenance fluids, children may require concurrent **replacement fluids** if they have continued excessive losses, as may occur with drainage from a nasogastric (NG) tube or with high urine output because of nephrogenic diabetes insipidus. If dehydration is present, the patient also needs to receive **deficit** replacement (see Chapter 70). A child awaiting surgery may need only maintenance fluids, whereas a child with diarrheal dehydration needs maintenance and deficit therapy and also may require replacement fluids if significant diarrhea continues.

Maintenance Therapy

Children normally have large variations in their daily intake of water and electrolytes. The only exceptions are patients who receive fixed dietary regimens orally, via a gastric tube, or as IV total parenteral nutrition (TPN). Healthy children can tolerate significant variations in intake because of the many homeostatic mechanisms that can adjust absorption and excretion of water and electrolytes (see Chapter 68). The calculated water and electrolyte needs that form the basis of maintenance therapy are not absolute requirements. Rather, these calculations provide reasonable guidelines for a starting point to estimate IV therapy. Children do not need to be started on IV fluids simply because their intake is being monitored in a hospital and they are not taking “maintenance fluids” orally, unless there is a pathologic process present that necessitates high fluid intake.

Maintenance fluids are most often necessary in preoperative and postoperative surgical patients; many nonsurgical patients also require maintenance fluids. It is important to recognize when it is necessary to begin maintenance fluids. A normal teenager who is given nothing by mouth (NPO) overnight for a morning procedure does not require maintenance fluids because a healthy adolescent can easily tolerate 12 or 18 hr without oral intake. In contrast, a 6 mo old child waiting for surgery should begin receiving IV fluids within 8 hr of the last feeding. Infants become dehydrated more quickly than older patients. A child with obligatory high urine output from nephrogenic diabetes insipidus should begin receiving IV fluids soon after being classified as NPO.

Maintenance fluids are composed of a solution of water, glucose, sodium (Na^+), and potassium (K^+). This solution has the advantages of simplicity, long shelf life, low cost, and compatibility with peripheral IV administration. Such a solution accomplishes the major objectives of maintenance fluids (Table 69.1). Patients lose water, Na^+ , and K^+ in their urine and stool; water is also lost from the skin and lungs. Maintenance fluids replace these losses, thereby avoiding the development of dehydration and Na^+ or K^+ deficiency.

Table 69.1

Goals of Maintenance Fluids

- Prevent dehydration
- Prevent electrolyte disorders
- Prevent ketoacidosis
- Prevent protein degradation

The glucose in maintenance fluids provides approximately 20% of the normal caloric needs of the patient, prevents the development of starvation ketoacidosis, and diminishes the protein degradation that would occur if the patient received no calories. Glucose also provides added osmoles, thus avoiding the administration of hypotonic fluids that may cause hemolysis.

Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins. This fact is typically not problematic for a patient receiving IV fluids for a few days. A patient receiving maintenance IV fluids is receiving inadequate calories and will lose 0.5–1% of weight each day. It is imperative that patients not remain on maintenance therapy indefinitely; TPN should be used for children who cannot be fed enterally for more than a few days, especially patients with underlying malnutrition.

Prototypical maintenance fluid therapy does not provide electrolytes such as calcium, phosphorus, magnesium, and bicarbonate. For most patients, this lack is not problematic for a few days, although there are patients who will not tolerate this omission, usually because of excessive losses. A child with proximal renal tubular acidosis wastes bicarbonate in urine. Such a patient will rapidly become acidemic unless bicarbonate (or acetate) is added to the maintenance fluids. It is important to remember the limitations of maintenance fluid therapy.

Maintenance Water

Water is a crucial component of maintenance fluid therapy because of the obligatory daily water losses. These losses are both measurable (urine, stool) and not measurable (**insensible losses** from the skin and lungs). Failure to replace these losses leads to a child who is thirsty, uncomfortable, and ultimately dehydrated.

The goal of maintenance water is to provide enough water to replace these losses. Although urinary losses are approximately 60% of the total, the normal kidney can greatly modify water losses, with daily urine volume potentially varying by more than a factor of 20. Maintenance water is designed to provide enough water so that the kidney does not need to significantly dilute or concentrate the urine. It also provides a margin of safety, so that normal homeostatic mechanisms can adjust urinary water losses to prevent overhydration and dehydration. This adaptability obviates the need for absolute precision in determining water requirements. This fact is important, given the absence of absolute accuracy in the formulas for calculation of water needs.

Table 69.2 provides a system for calculating maintenance water on the basis of the patient's weight and emphasizes the high water needs of smaller, less mature patients. This approach is reliable, although calculations based on weight do overestimate the water needs of an overweight child, in whom it is better to base the calculations on the lean body weight, which can be estimated by using the 50th percentile of body weight for the child's height. It is also important to remember that there is an upper limit of 2.4 L/24 hr in adult-sized patients. IV fluids are written as an hourly rate. The formulas in Table 69.3 enable rapid calculation of the rate of maintenance fluids.

Table 69.2

Body Weight Method for Calculating Daily Maintenance Fluid Volume

BODY WEIGHT	FLUID PER DAY
0-10 kg	100 mL/kg
11-20 kg	1,000 mL + 50 mL/kg for each kg >10 kg
>20 kg	1,500 mL + 20 mL/kg for each kg >20 kg*

* The maximum total fluid per day is normally 2,400 mL.

Table 69.3

Hourly Maintenance Water Rate

For body weight 0-10 kg: 4 mL/kg/hr
For body weight 10-20 kg: 40 mL/hr + 2 mL/kg/hr × (wt – 10 kg)
For body weight >20 kg: 60 mL/hr + 1 mL/kg/hr × (wt – 20 kg)*

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* The maximum fluid rate is normally 100 mL/hr.

Intravenous Solutions

The components of available solutions are shown in Table 69.4 . These solutions are available with 5% dextrose (D5), 10% dextrose (D10), or without dextrose. Except for Ringer lactate (lactated Ringer, LR), they are also available with added potassium (10 or 20 mEq/L). A *balanced IV fluid* contains a base (lactate or acetate), a more physiologic chloride concentration than NS, and additional physiologic concentrations of electrolytes such as potassium, calcium, and magnesium. Examples include LR and PlasmaLyte, and there is evidence suggesting benefit versus NS in certain clinical situations. A hospital pharmacy can also prepare custom-made solutions with different concentrations of sodium or potassium. In addition, other electrolytes, such as calcium, magnesium, phosphate, acetate, and bicarbonate, can be added to IV solutions. Custom-made solutions take time to prepare and are much more expensive than commercial solutions. The use of custom-made solutions is necessary only for patients who have underlying disorders that cause significant electrolyte imbalances. The use of commercial solutions saves time and expense.

Table 69.4

Composition of Intravenous Solutions*

FLUID	$[Na^+]$	$[Cl^-]$	$[K^+]$	$[Ca^{2+}]$	$[LACTATE^-]$
Normal saline (0.9% NaCl)	154	154	—	—	—
Half-normal saline (0.45% NaCl)	77	77	—	—	—
0.2 normal saline (0.2% NaCl)	34	34	—	—	—
Ringer lactate	130	109	4	3	28

* Electrolyte concentrations in mEq/L.

A normal plasma osmolality is 285-295 mOsm/kg. Infusing an IV solution peripherally with a much lower osmolality can cause water to move into red blood cells, leading to hemolysis. Thus, IV fluids are generally designed to have an osmolality that is either close to 285 or greater (fluids with moderately higher osmolality do not cause problems). Thus, 0.2NS (osmolality = 68) should not be administered peripherally, but D5 0.2NS (osmolality = 346) or D5 ½ NS + 20 mEq/L potassium chloride (KCl) with an osmolality of 472 can be administered.

Controversy surrounds the appropriate sodium content of maintenance fluids, considering the observation that **hypotonic** fluids may cause hyponatremia, which may have serious sequelae. Hypotonic fluids seem more physiologic given the low Na^+ content of breast milk and formula. However, hospitalized children often have impaired water excretion because of volume depletion or nonosmotic stimuli for antidiuretic hormone (ADH) production, such as respiratory disease, central nervous system (CNS) disease, stress, pain, nausea, and medications (e.g., narcotics). Hypotonic fluids increase the risk of hyponatremia; *hence, isotonic fluids with 5% dextrose are recommended as standard maintenance fluid except in neonates* .

Glucose

Maintenance fluids usually contain D5, which provides 17 calories/100 mL and nearly 20% of the daily caloric needs. This level is enough to prevent ketone production and helps minimize protein degradation, but the child will lose weight on this regimen. The weight loss is the principal reason why a patient needs to be started on TPN after a few days of maintenance fluids if enteral feedings are still not possible. Maintenance fluids are also lacking in such crucial nutrients as protein, fat, vitamins, and minerals.

Selection of Maintenance Fluids

An isotonic fluid (NS, LR, PlasmaLyte) with 5% dextrose and KCl (10-20 mEq/L is usually added to NS) is recommended for maintenance IV fluids. Surgical patients typically receive isotonic fluids (NS, LR) during surgery and in the recovery room for 6-8 hr postoperatively; the rate is typically approximately two-thirds the calculated maintenance rate, with dextrose added if clinically indicated. Subsequent maintenance fluids have the addition of 5% dextrose and 10-20 mEq/L KCl based on the serum K^+ and the clinical setting. Electrolytes should be measured at least daily in all children receiving >50% of maintenance fluids intravenously unless the child is receiving prolonged IV fluids (TPN).

These guidelines assume that no disease process is present that would require an adjustment in either the volume or the electrolyte composition of maintenance fluids. Neonates, and especially premature infants, are outside the scope of these guidelines given their unique physiology. Children with renal insufficiency may be hyperkalemic or unable to excrete K^+ and may not tolerate 10 or 20 mEq/L of potassium. Patients with persistent ADH production because of an underlying disease process (syndrome of inappropriate ADH secretion, congestive heart failure, nephrotic syndrome, liver disease) should receive less than maintenance fluids. Children with meningitis are fluid-restricted unless intravascular volume depletion is present (see Chapter 621.1). Treatment is individualized, and careful monitoring is critical.

In children with complicated pathophysiologic derangements, it may be necessary to adjust empirically the electrolyte composition and rate of maintenance fluids on the basis of electrolyte measurements and assessment of fluid balance. In all children it is critical to monitor weight, urine output, and electrolytes carefully to identify overhydration or underhydration, hyponatremia, and other electrolyte disturbances, and then adjust the rate or composition of the IV solution accordingly.

Variations in Maintenance Water and Electrolytes

The calculation of maintenance water is based on standard assumptions regarding water losses. In some patients, however, these assumptions are incorrect. To identify such situations, it is helpful to understand the source and magnitude of normal water losses. Table 69.5 lists the 3 sources of normal water loss.

Table 69.5

Sources of Water Loss

- Urine: 60%
- Insensible losses: ≈35% (skin and lungs)
- Stool: 5%

Urine is the most important contributor to normal water loss. Insensible losses represent approximately one third of total maintenance water (40% in infants; 25% in adolescents and adults). Insensible losses are composed of evaporative losses from the skin and lungs that cannot be quantitated. The evaporative losses from the skin do not include sweat, which would be considered an additional (sensible) source of water loss. Stool normally represents a minor source of water loss.

Maintenance water and electrolyte needs may be increased or decreased, depending on the clinical situation. This may be obvious, as in the infant with profuse diarrhea, or subtle, as in the patient who has decreased insensible losses while receiving mechanical ventilation. It is helpful to consider the sources of normal water and electrolyte losses and to determine whether any of these sources is being modified in a specific patient. It is then necessary to adjust maintenance water and electrolyte calculations.

Table 69.6 lists a variety of clinical situations that modify normal water and electrolyte losses. The skin can be a source of very significant water loss, particularly in neonates, especially premature infants, who are under radiant warmers or are receiving phototherapy. Very-low-birthweight infants can have insensible losses of 100-200 mL/kg/24 hr. Burns can result in massive losses of water and electrolytes, and there are specific guidelines for fluid management in children with burns (see Chapter 92). Sweat losses of water and electrolytes, especially in a warm climate, can also be significant. Children with cystic fibrosis and some children with pseudohypoaldosteronism have increased sodium losses from the skin.

Table 69.6

Adjustments in Maintenance Water

SOURCE	CAUSES OF INCREASED WATER NEEDS	CAUSES OF DECREASED WATER NEEDS
Skin	Radiant warmer	Incubator (premature infant)
	Phototherapy	
	Fever	
	Sweat	
	Burns	
Lungs	Tachypnea	Humidified ventilator
	Tracheostomy	
Gastrointestinal tract	Diarrhea	—
	Emesis	
	Nasogastric suction	
Renal	Polyuria	Oliguria/anuria
Miscellaneous	Surgical drain	
	Third spacing	

Fever increases evaporative losses from the skin. These losses are somewhat predictable, leading to a 10–15% increase in maintenance water needs for each 1°C (1.8°F) increase in temperature above 38°C (100.4°F). These guidelines are for a patient with a persistent fever; a 1 hr fever spike does not cause an appreciable increase in water needs.

Tachypnea or a tracheostomy increases evaporative losses from the lungs. A humidified ventilator causes a decrease in insensible losses from the lungs and can even lead to water absorption via the lungs; a ventilated patient has a decrease in maintenance water requirements. It may be difficult to quantify the changes that take place in the individual patient in these situations.

Replacement Fluids

The gastrointestinal (GI) tract is potentially a source of considerable water loss. GI water losses are accompanied by electrolytes and thus may cause disturbances in intravascular volume and electrolyte concentrations. GI losses are often associated with loss of potassium, leading to hypokalemia. Because of the high bicarbonate concentration in stool, children with diarrhea usually have a **metabolic acidosis** , which may be accentuated if volume depletion causes hypoperfusion and a concurrent lactic acidosis. Emesis or losses from an NG tube can cause a **metabolic alkalosis** (see Chapter 68).

In the absence of vomiting, diarrhea, or NG drainage, GI losses of water and electrolytes are usually quite small. All GI losses are considered excessive, and the increase in the water requirement is equal to the volume of fluid losses. Because GI water and electrolyte losses can be precisely measured, an appropriate replacement solution can be used.

It is impossible to predict the losses for the next 24 hr; it is better to replace excessive GI losses as they occur. The child should receive an appropriate maintenance fluid that does not consider the GI losses. The losses should then be replaced after they occur, with use of a solution with a similar electrolyte concentration as the GI fluid. The losses are usually replaced every 1-6 hr, depending on the rate of loss, with very rapid losses being replaced more frequently.

Diarrhea is a common cause of fluid loss in children and can result in dehydration and electrolyte disorders. In the unusual patient with significant diarrhea and a limited ability to take oral fluid, it is important to have a plan for replacing excessive stool losses. The volume of stool should be measured, and an equal volume of replacement solution should be given. Data are available on the average electrolyte composition of diarrhea in children (Table 69.4). With this information an appropriate replacement solution can be designed. The solution shown in Table 69.7 replaces stool losses of Na^+ , K^+ , Cl^- , and bicarbonate. Each 1 mL of stool should be replaced by 1 mL of this solution. The average electrolyte composition of diarrhea is just an average, and there may be considerable variation. It is therefore advisable to consider measuring the electrolyte composition of a patient's diarrhea if the amount is especially excessive or if the patient's serum electrolyte levels are problematic.

Table 69.7

Replacement Fluid for Diarrhea

Average Composition of Diarrhea

Sodium: 55 mEq/L
Potassium: 25 mEq/L
Bicarbonate: 15 mEq/L

Approach to Replacement of Ongoing Losses

Solution: D5 ½ NS + 30 mEq/L sodium bicarbonate + 20 mEq/L KCl
Replace stool mL/mL every 1-6 hr

D5, 5% dextrose; NS, normal saline.

Loss of gastric fluid , through emesis or NG suction, is also likely to cause dehydration, in that most patients with either condition have impaired oral intake of fluids. Electrolyte disturbances, particularly hypokalemia and metabolic alkalosis, are also common. These complications can be avoided by judicious use of a replacement solution. The composition of gastric fluid shown in Table 69.8 is the basis for designing a replacement solution.

Table 69.8

Replacement Fluid for Emesis or Nasogastric Losses

Average Composition of Gastric Fluid

Sodium: 60 mEq/L
Potassium: 10 mEq/L
Chloride: 90 mEq/L

Approach to Replacement of Ongoing Losses

Solution: normal saline + 10 mEq/L KCl
Replace output mL/mL every 1-6 hr

Patients with gastric losses frequently have hypokalemia, although the K^+ concentration of gastric fluid is relatively low. The associated urinary K^+ loss is an important cause of hypokalemia in this situation (see Chapter 68). These patients may need additional potassium either in their maintenance fluids or in their replacement fluids to compensate for prior or ongoing urinary losses. Restoration of the patient's intravascular volume, by decreasing aldosterone synthesis, lessens the urinary K^+ losses.

Urine output is normally the largest cause of water loss. Diseases such as renal failure and syndrome of inappropriate ADH secretion can lead to a decrease in urine volume. The patient with oliguria or anuria has a decreased need for water and electrolytes; continuation of maintenance fluids produces fluid overload. In contrast, postobstructive diuresis, the polyuric phase of acute tubular necrosis, diabetes mellitus, and diabetes insipidus increase urine production. To prevent dehydration, the patient must receive more than standard maintenance fluids when urine output is excessive. The electrolyte losses in patients with polyuria are variable. In diabetes insipidus the urine electrolyte concentration is usually low, whereas children with diseases such as juvenile nephronophthisis and obstructive uropathy usually have increased losses of both water and sodium.

The approach to decreased or increased urine output is similar (Table 69.9). The patient receives fluids at a rate to replace insensible losses. This is accomplished by a rate of fluid administration that is 25–40% of the normal maintenance rate, depending on the patient's age. Replacing insensible losses in the anuric child will theoretically maintain an even fluid balance, with the caveat that 25–40% of the normal maintenance rate is only an estimate of insensible losses. In the individual patient, this rate is adjusted on the basis of monitoring of the patient's weight and volume status. Most children with renal insufficiency receive little or no potassium because the kidney is the principal site of K^+ excretion.

Table 69.9

Adjusting Fluid Therapy for Altered Renal Output

Oliguria/Anuria

Replacement of insensible fluid losses (25–40% of maintenance) with D5 ½ NS
Replace urine output mL/mL with D5 ½ NS ± KCl

Polyuria

Replacement of insensible fluid losses (25–40% of maintenance) with D5 ½ NS ± KCl
Measure urine electrolytes
Replace urine output mL/mL with solution based on measured urine electrolytes

D5, 5% dextrose; NS, normal saline.

For the **oliguric** child, it is important to add a urine replacement solution to prevent dehydration. This issue is especially important in the patient with acute renal failure, in whom output may increase, potentially leading to volume depletion and worsening of renal failure if the patient remains on only insensible fluids. A replacement solution of D5 ½ NS is usually appropriate initially, although its composition may have to be adjusted if urine output increases significantly.

Most children with **polyuria** (except in diabetes mellitus; see Chapter 607) should be started on replacement of insensible fluid plus urine losses. This approach avoids the need to attempt to calculate the volume of urine output that is "normal" so that the patient can be given replacement fluid for the excess. In these patients, urine output is, by definition, excessive, and it is often helpful to measure Na^+ and K^+ concentrations of the urine to help in formulating the urine replacement solution.

Surgical drains and chest tubes can produce measurable fluid output. These fluid losses should be replaced when they are significant. They can be measured and replaced with an appropriate solution. **Third space losses** , which manifest as edema and ascites, are caused by a shift of fluid from the intravascular space into the interstitial space. Although these losses cannot be quantitated easily, third space losses can be large and may lead to intravascular volume depletion, despite the patient's weight gain. Replacement of third space fluid is empirical but should be anticipated in patients who are at risk, such as children who have burns or abdominal surgery. Third space losses and chest tube output are isotonic, so they usually require replacement with an isotonic fluid, such as NS or LR. Adjustments in the amount of replacement fluid for third space losses are based on continuing assessment of the patient's intravascular volume status. Protein losses from chest tube drainage can be significant, occasionally necessitating that 5% albumin be used as a replacement solution.

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CHAPTER 70

Deficit Therapy

Larry A. Greenbaum

Dehydration, most often caused by gastroenteritis, is a common problem in children. Most cases can be managed with oral rehydration (see Chapter 366). *Even children with mild to moderate hyponatremic or hypernatremic dehydration can be managed with oral rehydration.*

Clinical Manifestations

The 1st step in caring for the child with dehydration is to assess the degree of dehydration (Table 70.1), which dictates both the urgency of the situation and the volume of fluid needed for rehydration. The infant with mild dehydration (3–5% of body weight dehydrated) has few clinical signs or symptoms. The infant may be thirsty; the alert parent may notice a decline in urine output. The history is most helpful. The infant with moderate dehydration has clear physical signs and symptoms. Intravascular space depletion is evident from an increased heart rate and reduced urine output. This patient needs fairly prompt intervention. The infant with severe dehydration is gravely ill. The decrease in blood pressure indicates that vital organs may be receiving inadequate perfusion. Immediate and aggressive intervention is necessary. If possible, the child with severe dehydration should initially receive intravenous (IV) therapy. For older children and adults, mild, moderate, or severe dehydration represents a lower percentage of body weight lost. This difference occurs because water accounts for a higher percentage of body weight in infants (see Chapter 68).

Table 70.1

Clinical Evaluation of Dehydration

Mild dehydration (<5% in an infant; <3% in an older child or adult): Normal or increased pulse; decreased urine output; thirsty; normal physical findings

Moderate dehydration (5–10% in an infant; 3–6% in an older child or adult): Tachycardia; little or no urine output; irritable/lethargic; sunken eyes and fontanel; decreased tears; dry mucous membranes; mild delay in elasticity (skin turgor); delayed capillary refill (>1.5 sec); cool and pale

Severe dehydration (>10% in an infant; >6% in an older child or adult): Peripheral pulses either rapid and weak or absent; decreased blood pressure; no urine output; very sunken eyes and fontanel; no tears; parched mucous membranes; delayed elasticity (poor skin turgor); very delayed capillary refill (>3 sec); cold and mottled; limp, depressed consciousness

Clinical assessment of dehydration is only an estimate; thus the patient must be continually reevaluated during therapy. The degree of dehydration is underestimated in hypernatremic dehydration because the movement of water from the intracellular space (ICS) to the extracellular space (ECS) helps preserve the intravascular volume.

The history usually suggests the etiology of the dehydration and may predict whether the patient will have a normal sodium concentration (isotonic dehydration), hyponatremic dehydration, or hypernatremic dehydration. The neonate with dehydration caused by poor intake of breast milk often has hypernatremic dehydration. **Hypernatremic dehydration** is likely in any child with losses of hypotonic fluid and poor water intake, as may occur with diarrhea, and poor oral intake because of anorexia or emesis. **Hyponatremic dehydration** occurs in the child with diarrhea who is taking in large quantities of low-salt fluid, such as water or formula.

Some children with dehydration are appropriately thirsty, but in others the lack of intake is part of the pathophysiology of the dehydration. Even though decreased urine output is present in most children with dehydration, good urine output may be deceptively present if a child has an underlying renal defect, such as diabetes insipidus or a salt-wasting nephropathy, or in infants with hypernatremic dehydration.

Physical examination findings are usually proportional to the degree of dehydration. Parents may be helpful in assessment of the child for the presence of sunken eyes, because this finding may be subtle. Pinching and gently twisting the skin of the abdominal or thoracic wall detects tenting of the skin (turgor, elasticity). Tented skin remains in a pinched position rather than springing quickly back to normal. It is difficult to properly assess tenting of the skin in premature infants or severely malnourished children. Activation of the sympathetic nervous system causes **tachycardia** in children with intravascular volume depletion; diaphoresis may also be present. Postural changes in blood pressure are often helpful for evaluating and assessing the response to therapy in children with dehydration. **Tachypnea** in children with dehydration may be present secondary to a metabolic acidosis from stool losses of bicarbonate or lactic acidosis from shock (see Chapter 88).

Laboratory Findings

Several laboratory findings are useful for evaluating the child with dehydration. The serum sodium concentration determines the type of dehydration. **Metabolic acidosis** may be a result of stool bicarbonate losses in children with diarrhea, secondary renal insufficiency, or lactic acidosis from shock. The anion gap is useful for differentiating among the various causes of a metabolic acidosis (see Chapter 68). Emesis or nasogastric losses usually cause a **metabolic alkalosis** . The serum potassium (K^+) concentration may be low as a result of diarrheal losses. In children with dehydration as a result of emesis, gastric K^+ losses, metabolic alkalosis, and urinary K^+ losses all contribute to hypokalemia. Metabolic acidosis, which causes a shift of K^+ out of cells, and renal insufficiency may lead to hyperkalemia. A combination of mechanisms may be present; thus, it may be difficult to predict the child's acid-base status or serum K^+ level from the history alone.

The blood urea nitrogen (BUN) value and serum creatinine concentration are useful in assessing the child with dehydration. Volume depletion without parenchymal renal injury may cause a disproportionate increase in the BUN with little or no change in the creatinine concentration. This condition is secondary to increased passive resorption of urea in the proximal tubule as a result of appropriate renal conservation of sodium and water. The increase in the BUN with moderate or severe dehydration may be absent or blunted in the child with poor protein intake, because urea production depends on protein degradation. The BUN may be disproportionately increased in the child with increased urea production, as occurs with a gastrointestinal bleed or with the use of glucocorticoids, which increase catabolism. A significant elevation of the creatinine concentration suggests renal insufficiency, although a small, transient increase can occur with dehydration. **Acute kidney injury** (see Chapter 550.1) because of volume depletion is the most common etiology of renal insufficiency in a child with volume depletion, but occasionally the child may have previously undetected chronic renal insufficiency or an alternative explanation for the acute renal failure. **Renal vein thrombosis** is a well-described sequela of severe dehydration in infants; findings may include thrombocytopenia and hematuria (see Chapter 540.2).

Hemoconcentration from dehydration causes increases in hematocrit, hemoglobin, and serum proteins. These values normalize with rehydration. A normal hemoglobin concentration during acute dehydration may mask an underlying anemia. A decreased albumin level in a dehydrated patient suggests a chronic disease, such as malnutrition, nephrotic syndrome, or liver disease, or an acute process, such as capillary leak. An acute or chronic protein-losing enteropathy may also cause a low serum albumin concentration.

Calculation of the Fluid Deficit

Determining the fluid deficit necessitates clinical determination of the percentage of dehydration and multiplication of this percentage by the patient's weight; a child who weighs 10 kg and is 10% dehydrated has a fluid deficit of 1 L.

Approach to Severe Dehydration

The child with dehydration needs acute intervention to ensure that there is adequate tissue perfusion. This resuscitation phase requires rapid restoration of the circulating intravascular volume and treatment of **shock** with an isotonic solution, such as normal saline (NS), Ringer lactate (lactated Ringer solution, LR), or PlasmaLyte (see Chapter 88). The child is given a fluid bolus, usually 20 mL/kg of the isotonic fluid, over approximately 20 min. The child with severe dehydration may require multiple fluid boluses and may need to receive the boluses as fast as possible. In a child with a known or probable metabolic alkalosis (e.g., child with isolated vomiting), LR or PlasmaLyte should not be used because the lactate or acetate would worsen the alkalosis. However, LR or

PlasmaLyte may be preferable to NS in shock since it is a balanced solution (see Chapter 69); NS may cause a hyperchloremic metabolic acidosis.

Colloids, such as blood, 5% albumin, and plasma, are rarely needed for fluid boluses. A crystalloid solution (NS or LR) is satisfactory, with both lower risk of infection and lower cost. Blood is obviously indicated in the child with significant anemia or acute blood loss. Plasma is useful for children with a coagulopathy. The child with hypoalbuminemia may benefit from 5% albumin, although there is evidence that albumin infusions increase mortality in adults. The volume and the infusion rate for colloids are generally modified compared with crystalloids (see Chapter 500).

The initial resuscitation and rehydration phase is complete when the child has an adequate intravascular volume. Typically, the child shows clinical improvement, including a lower heart rate, normalization of blood pressure, improved perfusion, better urine output, and a more alert affect.

With adequate intravascular volume, it is appropriate to plan the fluid therapy for the next 24 hr. A general approach is outlined in Table 70.2 , with the caveat that there are many different approaches to correcting dehydration. A balanced solution can be substituted for NS. In isonatremic or hyponatremic dehydration, the entire fluid deficit is corrected over 24 hr; a slower approach is used for hypernatremic dehydration (discussed later). The volume of isotonic fluids that the patient has received is subtracted from this total. The remaining fluid volume is then administered over 24 hr. The potassium concentration may need to be decreased or, less frequently, increased, depending on the clinical situation. Potassium is not usually included in the IV fluids until the patient voids and normal renal function is documented by measurement of BUN and creatinine. Children with significant ongoing losses need to receive an appropriate replacement solution (see Chapter 69).

Table 70.2

Fluid Management of Dehydration

Restore intravascular volume:
    Isotonic fluid (NS or LR): 20 mL/kg over 20 min
    Repeat as needed
Calculate 24 hr fluid needs: maintenance + deficit volume
Subtract isotonic fluid already administered from 24 hr fluid needs
Administer remaining volume over 24 hr using 5% dextrose NS + 20

mEq/L KCl
Replace ongoing losses as they occur

LR, Ringer lactate; NS, normal saline.

Monitoring and Adjusting Therapy

The formulation of a plan for correcting a child's dehydration is only the beginning of management. *All calculations in fluid therapy are only approximations*. This statement is especially true for the assessment of percentage dehydration. It is equally important to monitor the patient during treatment and to modify therapy on the basis of the clinical situation. Table 70.3 lists the cornerstones of patient monitoring. The patient's vital signs are useful indicators of intravascular volume status. The child with decreased blood pressure and an increased heart rate will probably benefit from a fluid bolus.

Table 70.3

Monitoring Therapy

Vital signs:
    Pulse
    Blood pressure
Intake and output:
    Fluid balance
    Urine output
Physical examination:
    Weight
    Clinical signs of depletion or overload
Electrolytes

The patient's intake and output are critically important in the dehydrated child. The child who, after 8 hr of therapy, has more output than input because of continuing diarrhea needs to be started on a replacement solution. See the guidelines in Chapter 69 for selecting an appropriate replacement solution. Urine output is useful for evaluating the success of therapy. Good urine output indicates that rehydration has been successful.

Signs of dehydration on physical examination suggest the need for continued rehydration. Signs of fluid overload, such as edema and pulmonary congestion, are present in the child who is overhydrated. An accurate daily weight measurement is critical for the management of the dehydrated child. There should be a gain in weight during successful therapy.

Measurement of serum electrolyte levels at least daily is appropriate for any child who is receiving IV rehydration. Such a child is at risk for sodium, potassium, and acid-base disorders. It is always important to look at trends. For example, a sodium concentration ([Na^+]) of 144 mEq/L is normal; but if the [Na^+] was 136 mEq/L 12 hr earlier, there is a distinct risk that the child will be hypernatremic in 12 or 24 hr. It is advisable to be proactive in adjusting fluid therapy.

Both hypokalemia and hyperkalemia are potentially serious (see Chapter 68). Because dehydration can be associated with acute renal failure and hyperkalemia, potassium is withheld from IV fluids until the patient has voided. The potassium concentration in the patient's IV fluids is not rigidly prescribed. Rather, the patient's serum K^+ level and underlying renal function are used to modify potassium delivery. The patient with an elevated creatinine value and K^+ level of 5 mEq/L does not receive any potassium until the serum K^+ level decreases. Conversely, the patient with a K^+ level of 2.5 mEq/L may require additional potassium.

Metabolic acidosis can be quite severe in dehydrated children. Although normal kidneys eventually correct this problem, a child with renal dysfunction may be unable to correct a metabolic acidosis, and a portion of the patient's IV sodium chloride may have to be replaced with sodium bicarbonate or sodium acetate.

The serum K^+ level is modified by the patient's acid-base status. Acidosis increases serum K^+ by causing intracellular K^+ to move into the ECS. Thus, as acidosis is corrected, the serum potassium concentration ([K^+]) decreases. Again, it is best to anticipate this problem and to monitor the serum [K^+] and adjust potassium administration appropriately.

Hyponatremic Dehydration

The pathogenesis of hyponatremic dehydration usually involves a combination of sodium and water loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and the lost fluid contains sodium. Most fluid that is lost has a lower sodium concentration, so patients with only fluid loss would have hypernatremia. Diarrhea has, on average, a sodium concentration of 50 mEq/L. Replacing diarrheal fluid with water, which has almost no sodium, causes a reduction in the serum [Na^+]. The volume depletion stimulates synthesis of antidiuretic hormone (ADH), resulting in reduced renal water excretion. Therefore, the body's usual mechanism for preventing hyponatremia, renal water excretion, is blocked. The risk of hyponatremia is further increased if the volume depletion is a result of loss of fluid with a higher sodium concentration, as may occur with renal salt wasting, third space losses, or diarrhea with high sodium content (cholera).

The initial goal in treating hyponatremia is correction of intravascular volume depletion with isotonic fluid. An overly rapid (>12 mEq/L over 1st 24 hr) or overcorrection in the serum [Na^+] (>135 mEq/L) is associated with an increased risk of **central pontine myelinolysis** (see Chapter 68). Most patients with hyponatremic dehydration do well with the same basic strategy outlined in Table 70.2 . Again, K^+ delivery is adjusted according to the initial serum K^+ level and the patient's renal function. Potassium is not given until the patient voids.

The patient's [Na^+] is monitored closely to ensure appropriate correction, and the sodium concentration of the fluid is adjusted accordingly. Patients with ongoing losses require an appropriate replacement solution (see Chapter 69). Patients with neurologic symptoms (seizures) as a result of hyponatremia need to receive an acute infusion of hypertonic (3%) saline to increase the serum [Na^+] rapidly (see Chapter 68).

Hypernatremic Dehydration

Hypernatremic dehydration is the most dangerous form of dehydration because of complications of hypernatremia itself and of its therapy. Hypernatremia can cause serious neurologic damage, including central nervous system hemorrhages and thrombosis. This damage appears to be secondary to the movement of water from the brain cells into the hypertonic extracellular fluid (ECF), causing brain cell shrinkage and tearing blood vessels within the brain (see Chapter 68).

The movement of water from the ICS to the ECS during hypernatremic dehydration partially protects the intravascular volume. Unfortunately, because the initial manifestations are milder, children with hypernatremic dehydration are often brought for medical attention with more profound dehydration.

Children with hypernatremic dehydration are often lethargic, and they may be irritable when touched. Hypernatremia may cause fever, hypertonicity, and hyperreflexia. More severe neurologic symptoms may develop if cerebral bleeding or thrombosis occurs.

Overly rapid treatment of hypernatremic dehydration may cause significant morbidity and mortality. **Idiogenic osmoles** are generated within the brain during the development of hypernatremia; they increase the osmolality within the cells of the brain, providing protection against brain cell shrinkage caused by movement of water out of the cells and into the hypertonic ECF. Idiogenic osmoles dissipate slowly during the correction of hypernatremia. With overly rapid lowering of the extracellular osmolality during the correction of hypernatremia, an osmotic gradient may be created that causes water movement from the ECS into the cells of the brain, producing cerebral edema. Symptoms of the resultant cerebral edema can range from seizures to brain herniation and death.

To minimize the risk of **cerebral edema** during the correction of hypernatremic dehydration, *the serum sodium concentration should not decrease by >10 mEq/L every 24 hr.* The deficits in severe hypernatremic dehydration may need to be corrected over 2-4 days (Table 70.4).

Table 70.4

Treatment of Hypernatremic Dehydration

Restore intravascular volume:
  Normal saline: 20 mL/kg over 20 min (repeat until intravascular volume restored)
  Determine time for correction on basis of initial sodium concentration:
    - [Na] 145-157 mEq/L: 24 hr
    - [Na] 158-170 mEq/L: 48 hr
    - [Na] 171-183 mEq/L: 72 hr
    - [Na] 184-196 mEq/L: 84 hr

Administer fluid at constant rate over time for correction:
  Typical fluid: 5% dextrose + half-normal saline (with 20 mEq/L KCl unless contraindicated)
  Typical rate: 1.25-1.5 times maintenance

Follow serum sodium concentration
Adjust fluid on basis of clinical status and serum sodium concentration:
- Signs of volume depletion: administer normal saline (20 mL/kg)
- Sodium decreases too rapidly; either:
  - Increase sodium concentration of IV fluid
  - Decrease rate of IV fluid
- Sodium decreases too slowly; either:
  - Decrease sodium concentration of IV fluid
  - Increase rate of IV fluid

Replace ongoing losses as they occur

The initial resuscitation of hypernatremic dehydration requires restoration of the intravascular volume with NS. LR should not be used because it is more hypotonic than NS and may cause too rapid a decrease in the serum [Na$^+$], especially if multiple fluid boluses are necessary.

To avoid cerebral edema during correction of hypernatremic dehydration, the fluid deficit is corrected slowly. The rate of correction depends on the initial sodium concentration (Table 70.4). There is no general agreement on the choice or the rate of fluid administration for correcting hypernatremic dehydration; these factors are not nearly as important as vigilant monitoring of the serum [Na$^+$] and adjustment of the therapy according to the result. The rate of decrease of the serum [Na$^+$] is roughly related to the "free water" delivery, although there is considerable variation between patients. Free water is water without sodium. NS contains no free water, half-normal saline (½ NS) is 50% free water, and water is 100% free water. Smaller patients, to achieve the same decrease in the sodium concentration, tend to need higher amounts of free water delivery per kilogram because of **higher insensible fluid losses** . Five percent dextrose (D5) with ½ NS is usually an appropriate starting solution for correction of a patient with hypernatremic dehydration. Some patients, especially infants with ongoing high insensible water losses, may rarely need to receive D5 0.2NS, which should be used with great caution and constant monitoring. Others require D5 NS. A child with dehydration as a result of pure free water loss, as usually occurs with diabetes insipidus, usually needs a more hypotonic fluid than a child with depletion of both sodium and water from diarrhea.

Adjustment in the sodium concentration of the IV fluid is the most common approach to modify the rate of decrease in the serum concentration (see Table

70.4). For difficult-to-manage patients with severe hypernatremia, having two IV solutions (e.g., D5 ½ NS and D5 NS, both with the same concentration of potassium) at the bedside can facilitate this approach by allowing for rapid adjustments of the rates of the 2 fluids. If the serum [Na$^+$] decreases too rapidly, the rate of D5 NS can be increased and the rate of D5 ½ NS can be decreased by the same amount. Adjustment in the total rate of fluid delivery is another approach to modifying free water delivery. For example, if the serum [Na$^+$] is decreasing too slowly, the rate of the IV fluid can be increased, thereby increasing the delivery of free water. There is limited flexibility in modifying the rate of the IV fluid because patients generally should receive 1.25-1.5 times the normal maintenance fluid rate. Nevertheless, in some situations, it can be a helpful adjustment.

Because increasing the rate of the IV fluid increases the rate of decline of the sodium concentration, signs of volume depletion are treated with additional isotonic fluid boluses. The serum [K$^+$] and the level of renal function dictate the potassium concentration of the IV fluid; potassium is withheld until the patient voids. Patients with hypernatremic dehydration need an appropriate replacement solution if they have ongoing, excessive losses (see Chapter 69).

Seizures and a depressed level of consciousness are the most common manifestations of **cerebral edema** from an overly rapid decrease of the serum [Na$^+$] during correction of hypernatremic dehydration. Signs of increased intracranial pressure or impending herniation may develop quite rapidly (see Chapter 85). Acutely, increasing the serum [Na$^+$] through an infusion of 3% sodium chloride can reverse the cerebral edema. Each 1 mL/kg of 3% NaCl increases the serum [Na$^+$] by approximately 1 mEq/L. An infusion of 4 mL/kg often results in resolution of the symptoms. This strategy is similar to that used for treating symptomatic hyponatremia (see Chapter 68).

Many patients with mild to moderate hypernatremic dehydration as a result of gastroenteritis can be managed with oral rehydration (see Chapter 366). In patients with severe hypernatremia, oral fluids must be used cautiously. Infant formula, because of its low sodium concentration, has a high free water content, and especially if added to IV therapy, it may contribute to a rapid decrease in the serum [Na$^+$]. Less hypotonic fluid, such as an oral rehydration solution, may be more appropriate initially. If oral intake is allowed, its contribution to free water delivery must be taken into account, and adjustment in the IV fluid is usually appropriate. Judicious monitoring of the serum [Na$^+$] is critical.

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CHAPTER 71

Fluid and Electrolyte Treatment of Specific Disorders

Acute Diarrhea

See Chapter 366 .

Pyloric Stenosis

See Chapter 355.1 .

Perioperative Fluids

See Chapter 74 .

PART VII
Pediatric Drug Therapy

OUTLINE

Chapter 72 Pediatric Pharmacogenetics, Pharmacogenomics, and Pharmacoproteomics

Chapter 73 Principles of Drug Therapy

Chapter 74 Anesthesia and Perioperative Care

Chapter 75 Procedural Sedation

Chapter 76 Pediatric Pain Management

Chapter 77 Poisoning

Chapter 78 Complementary Therapies and Integrative Medicine

CHAPTER 72

Pediatric Pharmacogenetics, Pharmacogenomics, and Pharmacoproteomics

Jonathan B. Wagner, Matthew J. McLaughlin, J. Steven Leeder

Interindividual variability in the response to similar doses of a given medication is an inherent characteristic of both adult and pediatric populations. **Pharmacogenetics** , the role of genetic factors in drug disposition and response, has resulted in many examples of how variations in human genes can lead to interindividual differences in pharmacokinetics and drug response at the level of individual patients. Pharmacogenetic variability contributes to the broad range of drug responses observed in children at any given age or developmental stage. Therefore, it is expected that children will benefit from the promise of **personalized medicine** —identifying the right drug for the right patient at the right time (Fig. 72.1). However, pediatricians are keenly aware that children are not merely small adults. Numerous maturational processes occur from birth through adolescence such that utilization of information resulting from the Human Genome Project and related initiatives must take into account the changing patterns of gene expression that occur over development to improve pharmacotherapeutics in children.

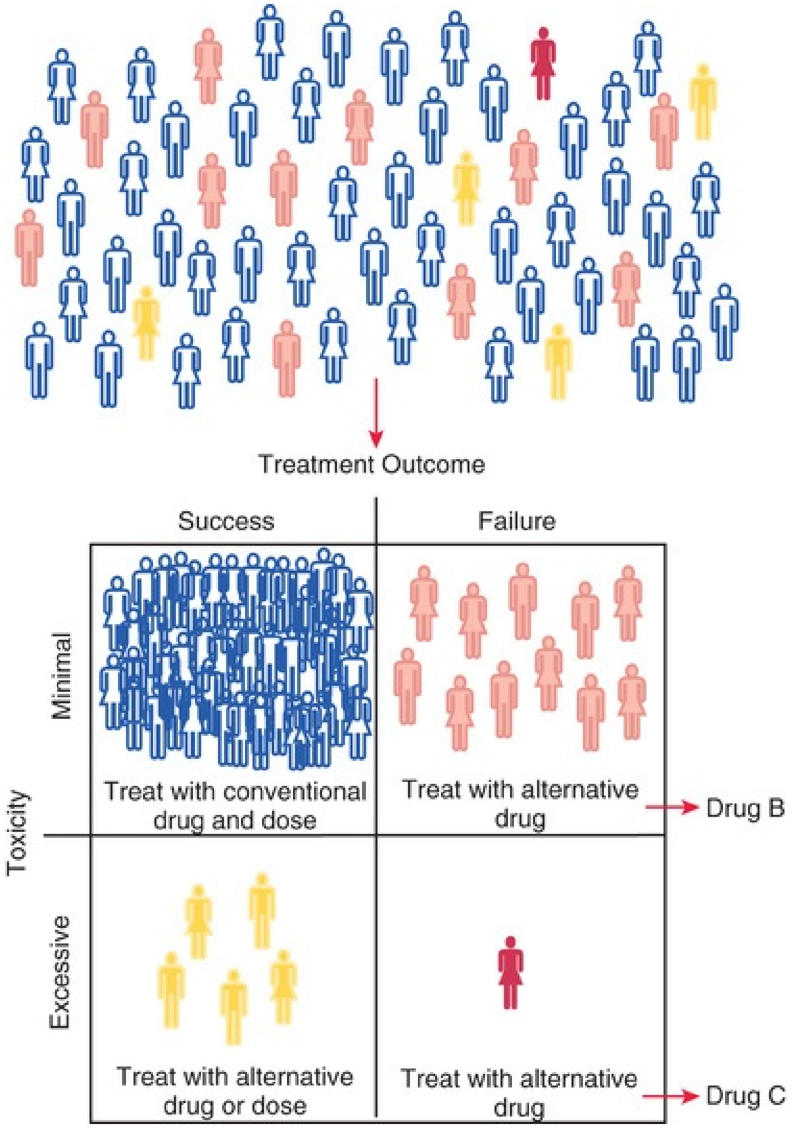
Treatment Outcome
Success
Failure
Toxicity
Minimal
Excessive
Treat with conventional drug and dose
Treat with alternative drug
Drug B
Treat with alternative drug or dose
Treat with alternative drug
Drug C

FIG. 72.1 The promise of genomic medicine to human health and disease. The goal of personalized medicine is to identify subgroups of patients who will respond favorably to a given drug with a minimum of side effects, as well as those who will not respond or who will show excessive toxicity with standard doses. A further benefit of pharmacogenomics is the ability to select the most appropriate alternative drug for patients who cannot be treated successfully with conventional drugs and doses. (Adapted from Yaffe SJ, Aranda JV: *Neonatal and pediatric pharmacology,* ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)

Definition of Terms

The terms pharmacogenomics and pharmacogenetics tend to be used interchangeably, and precise, consensus definitions are often difficult to determine. **Pharmacogenetics** classically is defined as the study or clinical testing of genetic variations that give rise to interindividual response to drugs. Examples of pharmacogenetic traits include specific adverse drug reactions, such as unusually prolonged respiratory muscle paralysis due to succinylcholine, hemolysis associated with antimalarial therapy, and isoniazid-induced neurotoxicity, all of which were found to be a consequence of inherited variations in enzyme activity. The importance of pharmacogenetic differences has become better understood and is exemplified by the half-life of several drugs being more similar in monozygotic twins than in dizygotic twins. However, it is important to note that in addition to pharmacogenetic differences, environmental factors (diet, smoking status, concomitant drug or toxicant exposure), physiologic variables (age, sex, disease, pregnancy), and patient adherence all contribute to variations in drug metabolism and response. Likewise, ethnicity is another potential genetic determinant of drug variability. Chinese patients who are HLA-B*1502 positive have an increased risk of carbamazepine-induced Stevens-Johnson syndrome; white patients who are HLA-B*5701 positive have an increased risk of hypersensitivity to abacavir (Table 72.1).

Table 72.1

Examples of Effects of Gene Polymorphisms on Drug Response

GENE	ENZYME/TARGET	DRUG	CLINICAL RESPONSE
BCHE	Butyrylcholinesterase	Succinylcholine	Prolonged paralysis
CYP2C9	Cytochrome P450 2C9	Warfarin	Individuals having ≥1 reduced function alleles require lower doses of warfarin for optimal anticoagulation, especially initial anticoagulant control.
CYP2C19	Cytochrome P450 2C19	Clopidogrel	Individuals having ≥1 loss-of-function alleles have reduced capacity to form pharmacologically active metabolite of clopidogrel and reduced antiplatelet effect.
CYP2D6	Cytochrome P450 2D6	Codeine	Poor metabolizers—individuals with 2 loss-of-function alleles—do not metabolize codeine to morphine and thus experience no analgesic effect. Ultrarapid metabolizers—individuals with ≥3 functional alleles—may experience morphine toxicity.
G6PD	Glucose-6-phosphate dehydrogenase	Primaquine (others)	Hemolysis
*HLA-A*3101*	Human leukocyte antigen A31	Carbamazepine	Carriers of *HLA-A*3101* allele have increased risk of SJS and TEN from carbamazepine.
*HLA-B*1502*	Human leukocyte antigen B15	Allopurinol	Han Chinese carriers of *HLA-B*1502* allele have increased risk of SJS and TEN from carbamazepine.
*HLA-B*5701*	Human leukocyte antigen B57	Abacavir Flucloxacillin	Carriers of *HLA-B*5701* allele have increased risk of hypersensitivity reactions to abacavir- and

			flucloxacillin-induced liver injury.
*HLA-B*5801*	Human leukocyte antigen B58	Allopurinol	Carriers of *HLA-B*5801* allele have increased risk of severe cutaneous adverse reactions to allopurinol, including hypersensitivity reactions, SJS, and TEN.
NAT2	*N* -Acetyltransferase 2	Isoniazid, hydralazine	Individuals homozygous for “slow acetylation” polymorphisms are more susceptible to isoniazid toxicity, or hydralazine-induced systemic lupus erythematosus.
SLCO1B1	Organic anion–transporting protein (OATP) 1B1	Simvastatin	Carriers of the *SLCO1B1*5* allele are at increased risk for musculoskeletal side effects from simvastatin.
TPMT	Thiopurine *S* -methyltransferase	Azathioprine 6-Mercaptopurine	Individuals homozygous for an inactivating mutation have severe toxicity if treated with standard doses of azathioprine or 6-mercaptopurine; rapid metabolism causes undertreatment.
UGT1A1	Uridine diphospho-glucuronosyltransferase 1A1	Irinotecan	*UGT1A1*28* allele is associated with decreased glucuronidation of SN-38, the active metabolite of irinotecan, and increased risk of neutropenia.
VKORC1	Vitamin K oxidoreductase complex 1	Warfarin	Individuals with a haplotype associated with reduced expression of VKORC1 protein (therapeutic target of warfarin) require lower doses of the drug for stable anticoagulation.

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Pharmacogenomics represents the marriage of pharmacology and genomics and can be defined as the broader application of genome-wide technologies and strategies to identify both disease processes that represent new targets for drug development and factors predictive of efficacy and risk of adverse drug reactions.

Pharmacokinetics describes what the body does to a drug. It is often studied in conjunction with **pharmacodynamics** , which explores what a drug does to the body. The **pharmacokinetic properties** of a drug are determined by the genes that control the drug's disposition in the body (absorption, distribution, metabolism, excretion). Drug-metabolizing enzymes and drug transporters play a particularly important role in this process (Table 72.2), and the functional consequences of genetic variations in many drug-metabolizing enzymes have been described between individuals of both similar and different ethnic groups. The most common clinical manifestation of pharmacogenetic variability in drug biotransformation is an increased risk of concentration-dependent toxicity caused by reduced clearance and consequent drug accumulation. However, an equally important manifestation of this variability is lack of efficacy caused by variations in metabolism of prodrugs that require biotransformation to be converted into a pharmacologically active form of a medication. The pharmacogenetics of drug receptors and other target proteins involved in signal transduction or disease pathogenesis can also be expected to contribute significantly to interindividual variability in drug disposition and response.

Table 72.2

Some Important Relationships Between Drugs and Cytochrome P450 (CYP) Enzymes[*] and P-Glycoprotein Transporter

ENZYME	DRUG SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	Caffeine, clomipramine (*Anafranil*[†]), clozapine (*Clozaril*[†]), theophylline	Cimetidine (*Tagamet*[†]) Fluvoxamine (*Luvox*[†]) Ciprofloxacin (*Cipro*)	Omeprazole (*Prilosec*[†]) Tobacco
CYP2C9	Diclofenac (*Voltaren*[†]), ibuprofen (*Motrin*[†]), piroxicam (*Feldene*[†]), Losartan (*Cozaar*), irbesartan (*Avapro*), celecoxib (*Celebrex*), tolbutamide (*Orinase*[†]), warfarin (*Coumadin*[†]), phenytoin (*Dilantin*)	Fluconazole (*Diflucan*) Fluvastatin (*Lescol*) Amiodarone (*Cordarone*) Zafirlukast (*Accolate*)	Rifampin (*Rifadin*[†])
CYP2C19	Omeprazole, lansoprazole (*Prevacid*), pantoprazole (*Protonix*), (S)-mephenytoin, *(S)*-citalopram (*Lexapro*); nelfinavir (*Viracept*), diazepam (*Valium*[†]), voriconazole (*Vfend*)	Cimetidine Fluvoxamine	Rifampin
CYP2D6	**CNS-active agents:** Atomoxetine (*Strattera*), amitriptyline (*Elavil*[†]), desipramine (*Norpramin*[†]), imipramine (*Tofranil*[†]), paroxetine (*Paxil*), haloperidol (*Haldol*[†]), risperidone (*Risperdal*), thioridazine (*Mellaril*[†])	Fluoxetine (*Prozac*[†]) Paroxetine (*Paxil*)	
	Antiarrhythmic agents: Mexiletine (*Mexitil*), propafenone (*Rythmol*)	Amiodarone (*Cordarone*[†]) Quinidine (*Quinidex*[†])	
	β-Blockers: Propranolol (*Inderal*[†]), metoprolol (*Lopressor*[†]), timolol (*Blocadren*[†])	Terbinafine	
	Narcotics: Codeine, dextromethorphan, hydrocodone (*Vicodin*[†])		
	Others: Tamoxifen (*Nolvadex*)	Cimetidine Ritonavir	
CYP3A4	**Calcium channel blockers:** Diltiazem (*Cardizem*[†]), felodipine (*Plendil*), nimodipine (*Nimotop*), nifedipine (*Adalat*[†]), nisoldipine (*Sular*), nitrendipine, verapamil (*Calan*[†])	Amiodarone	Barbiturates Carbamazepine (*Tegretol*[†]) Phenytoin (*Dilantin*[†])
	Immunosuppressive agents: Cyclosporine A (*Sandimmune*, *Neoral*[†]), tacrolimus (*Prograf*)		Efavirenz (*Sustiva*)

	Corticosteroids: Budesonide (*Pulmicort*), cortisol, 17β-estradiol, progesterone, testosterone	Fluconazole Ketoconazole (*Nizoral* †) Itraconazole (*Sporanox*)	Nevirapine (*Viramune*)
	Macrolide antibiotics: Clarithromycin (*Biaxin*), erythromycin (*Erythrocin* †), troleandomycin (*TAO*)	Clarithromycin Erythromycin Troleandomycin	
	Anticancer agents: Cyclophosphamide (*Cytoxan* †), gefitinib (*Iressa*), ifosfamide (*Ifex*), tamoxifen, vincristine (*Oncovin* †), vinblastine (*Velban* †),	Imatinib	Rifampin Ritonavir ‡
	Benzodiazepines: Alprazolam (*Xanax* †), midazolam (*Versed* †), triazolam (*Halcion* †)		St. John's wort
	Opioids: Alfentanil (*Alfenta* †), fentanyl (*Sublimaze* †), sufentanil (*Sufenta* †)		
	HMG-CoA reductase inhibitors: Lovastatin (*Mevacor*) †, simvastatin (*Zocor*), atorvastatin (*Lipitor*)		
	HIV protease inhibitors: Indinavir (*Crixivan*), nelfinavir, ritonavir (*Norvir*), saquinavir (*Invirase, Fortovase*), amprenavir (*Agenerase*)	Ritonavir ‡ Indinavir	
	Others: Quinidine (*Quinidex* †), sildenafil (*Viagra*), eletriptan (*Relpax*), ziprasidone (*Geodon*)	Grapefruit juice Nefazodone (*Serzone*)	
P-glycoprotein	Aldosterone, amprenavir, atorvastatin, cyclosporine, dexamethasone (*Decadron* †), digoxin (*Lanoxin* †), diltiazem, domperidone (*Motilium*), doxorubicin (*Adriamycin* †), erythromycin, etoposide (*VePesid*), fexofenadine (*Allegra*), hydrocortisone, indinavir, ivermectin (*Stromectol*), lovastatin, loperamide (*Imodium* †), nelfinavir, ondansetron (*Zofran*), paclitaxel (*Taxol*), quinidine, saquinavir, simvastatin, verapamil, vinblastine, vincristine	Amiodarone Carvedilol (*Coreg*) Clarithromycin Cyclosporine Erythromycin Itraconazole Ketoconazole Quinidine Ritonavir ‡ Tamoxifen Verapamil	Amprenavir Clotrimazole (*Mycelex* †) Phenothiazine Rifampin Ritonavir ‡ St. John's wort

* www.drug-interactions.com .

† Also available generically.

‡ Can be both an inhibitor and an inducer.

CNS, Central nervous system.

From *Med Lett* 2003;45:47.

Therapeutic drug monitoring (TDM) programs recognize that all patients are unique and that the serum concentration-time data for an individual patient theoretically can be used to optimize pharmacotherapy. TDM programs have been the earliest application of personalized medicine; however, routine TDM does not necessarily translate to improved patient outcome in all situations.

The concept of **personalized medicine** is based on the premise that the information explosion accompanying the application of genomic technologies to patient-related problems will allow (1) stratification of patient populations according to their response to a particular medication (e.g., lack of drug efficacy or excessive toxicity) and (2) stratification of diseases into specific subtypes that are categorized according to genomic criteria and by response to particular treatments. Personalized medicine has become supplanted by **individualized medicine** , which takes into consideration the vast amount of information that can be collected from an individual patient and applied to inform decisions for that patient. **Precision medicine** is an emerging approach for disease treatment and prevention that considers individual variability in genes, environment, and lifestyle for each person; it reflects the progression in delivery of care for more accurately diagnosing or treating a patient at an individual level. As the amount of data specific to an individual patient increases (e.g., genomic data, electronic health records), precision medicine can be further divided into **precision diagnosis** and **precision therapeutics** ; pharmacokinetics, pharmacodynamics, and pharmacogenomics all represent tools that can be applied to implement precision therapeutics for children.

Genetic polymorphisms (**variations**) result when copies of a specific gene present within a population do not have identical nucleotide sequences. The term **allele** refers to one of a series of alternative DNA sequences for a particular gene. In humans, there are 2 copies of every gene. An individual's genotype for a given gene is determined by the set of alleles that the individual possesses. The most common form of genetic variation involves a single base change at a given location, referred to as a **single nucleotide polymorphism (SNP)** (see Chapter 95). At the other end of the spectrum are **copy number variations (CNVs)** , which refer to the deletion or duplication of identical or near-identical DNA sequences that may be thousands to millions of bases in size. CNVs occur less frequently than SNPs, but may constitute 0.5–1% of an individual's genome and thereby contribute significantly to phenotypic variation. **Haplotypes** are collections of SNPs and other allelic variations that are located close to each other; when inherited together, these create a catalog of haplotypes, or **HapMap** . When the alleles at a particular gene locus on both chromosomes are identical, a **homozygous** state exists, whereas the term **heterozygous** refers to the situation in which different alleles are present at the same gene locus. The term **genotype** refers to an individual's genetic constitution, whereas the observable characteristics or physical manifestations constitute the **phenotype** , which is the net consequence of genetic and environmental effects (see Chapters 94 –101).

Pharmacogenetics focuses on the phenotypical consequences of allelic variation in single genes. **Pharmacogenetic polymorphisms** are monogenic traits that are functionally relevant to drug disposition and action and are caused by the presence (within one population) of >1 allele (at the same gene locus) and >1 phenotype with regard to drug interaction with the organism. The key elements of pharmacogenetic polymorphisms are heritability, the involvement of a single gene locus, functional relevance, and the fact that distinct phenotypes are observed within the population only after drug challenge.

Developmental or Pediatric Pharmacogenetics and Pharmacogenomics

Our current understanding of pharmacogenetic principles involves enzymes responsible for **drug biotransformation** . Individuals are classified as being “fast,” “rapid,” or “extensive” metabolizers at one end and “slow” or “poor” metabolizers at the other end of the continuum. This may or may not also include an “intermediate” metabolizer group, depending on the particular enzyme. With regard to biotransformation, children are more complex than adults; fetuses and newborns may be phenotypically “slow” or “poor” metabolizers for certain drug-metabolizing pathways because of their stage of development and may acquire a phenotype consistent with their genotype at some point later in the developmental process as they mature. Examples of drug-metabolizing pathways that are significantly affected by **ontogeny** include glucuronidation and some of the **cytochrome P450 (CYP)** activities. It is also apparent that not all infants acquire drug metabolism activity at the same rate, a result of interactions between genetics and environmental factors. Interindividual variability in the trajectory (i.e., rate and extent) of acquired drug biotransformation capacity may be considered a **developmental phenotype** (Fig. 72.2). This helps to explain the considerable variability in some CYP activities observed immediately after birth.

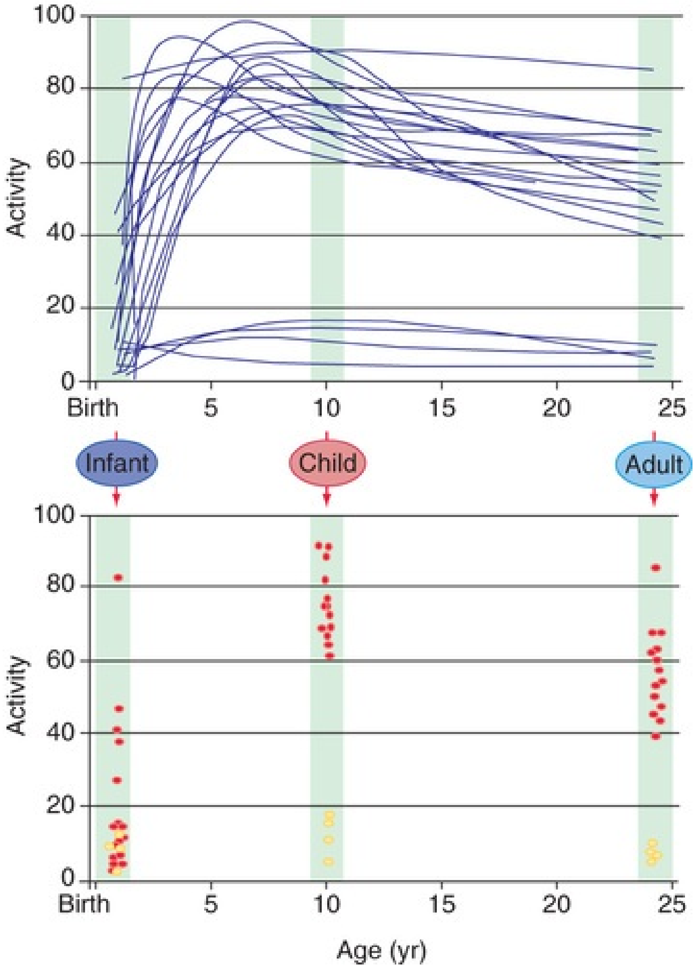

FIG. 72.2 “Developmental” phenotypes. Variability in developmental changes in gene expression and functional enzyme activity are superimposed on pharmacogenetic determinants. Top, Developmental profile of a theoretical drug-metabolizing enzyme over a 25 yr span in 20 individuals. Bottom, At maturity (adults), allelic variation within the coding region of the gene gives rise to 2 distinct phenotypes: high activity in 92% of the population (“extensive metabolizers”; *red circles*) and low activity in 8% of the population (“poor metabolizers”; *yellow circles*). However, there is also interindividual variability in the rate at which functional activity is acquired after birth. For example, the 2 phenotypes may not be readily distinguishable in newborn infants immediately after birth. Furthermore, there may be discrete periods during childhood in which the genotype-phenotype relationship may differ from that observed in adults (e.g., developmental stages at which enzyme activity appears to be greater in children than in adults). (Adapted from Leeder JS: Translating pharmacogenetics and pharmacogenomics into drug development for clinical pediatric and beyond, *Drug Discov Today* 9:567–573, 2004.)

In contrast to pharmacogenetic studies that typically target single genes, **pharmacogenomic** analyses are considerably broader in scope and focus on complex and highly variable drug-related phenotypes with targeting of many genes. Genome-wide genotyping technologies and massively parallel “next-generation” sequencing platforms for genomic analyses continue to evolve and allow evaluation of genetic variation at more than 1 million sites throughout an individual genome for SNP and CNV analyses. Genome-wide association studies (GWAS) have been conducted in several pediatric settings, in part to identify novel genes involved in disease pathogenesis that can lead to new therapeutic targets. GWAS are also being applied to identify genetic associations with response to drugs, such as warfarin and clopidogrel, and risk for drug-induced toxicity, including statin-induced myopathy and flucloxacillin hepatotoxicity. The "Manhattan plot," a form of data presentation for GWAS, is becoming more common in many medical journals (Fig. 72.3*A*). Whole genome and exome sequencing have been applied in a diagnostic setting to identify disease-causing genetic variation, usually in the context of rare, undiagnosed diseases that would otherwise require a "diagnostic odyssey" lasting several years before a definitive diagnosis is made (and thereby delaying therapeutic intervention). Contained within this genome sequence is the **pharmacogenome** , and an area of intense interest is the development of bioinformatics tools to determine a patient's drug metabolism and response genotype from whole genome sequence data.

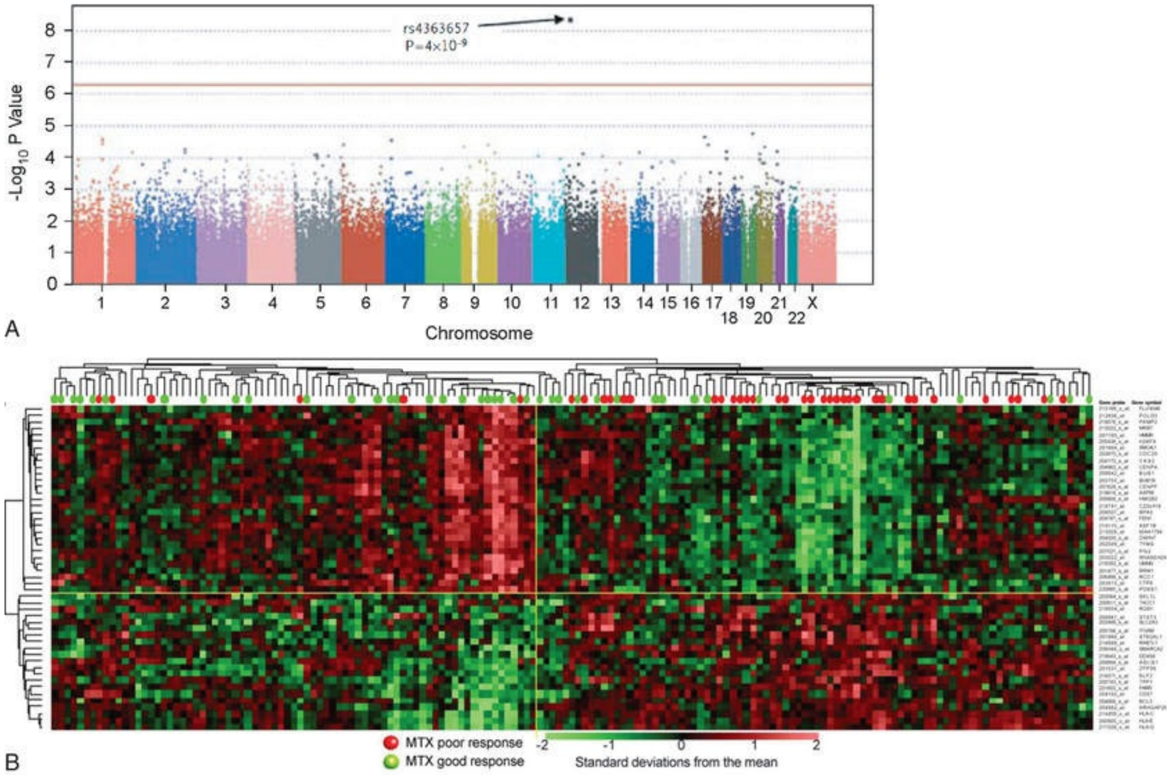

FIG. 72.3 Presentations of pharmacogenomic data. A, Manhattan plot from a genome-wide association study (GWAS). Derived from its similarity to the Manhattan skyline, the Manhattan plot presents the genome-wide significance of several hundred thousand single nucleotide polymorphisms (SNPs) distributed throughout the genome with the trait or phenotype of interest. In this example, each SNP included on the "chip"

is plotted along the *x* axis according to its chromosomal coordinate, with each color representing an individual chromosome from chromosome 1 to the X chromosome. The *y* axis represents the inverse $\log_{10}$ of the *p* value for the association: the higher the value on the *y*- axis, the smaller the *p* value. A value of "15" corresponds to a *p* value of 10^{-15} . SNPs exceeding a particular threshold are subject to further verification and validation. B, "Heat map" constructed from gene expression data. In a heat map the level of expression of many genes, as obtained from microarray analysis, is presented as a 2-dimensional matrix of values. Each column represents an individual patient, and each row is an individual RNA transcript designated by the gene name. The level of gene expression is indicated by the color of each rectangle on a continuum from high expression *(red)* to low expression *(green).* In this example, acute lymphoblastic leukemia (ALL) patients are clustered by their response to methotrexate (MTX); patients responding to MTX have markedly different patterns of gene expression compared to nonresponders. One of the goals of personalized medicine is to use genomic information (e.g., microarray data) to identify signatures of drug response (or risk of drug toxicity), to select the most appropriate drug among available options for each patient. (*A,* Reprinted with permission from Search Collaborative Group. SLCO1B1 variants and statin-induced myopathy: a genome-wide study, *N Engl J Med* 359:789–799, 2008; *B,* from Sorich MJ et al. In vivo response to methotrexate forecasts outcome of acute lymphoblastic leukemia and has a distinct gene expression profile, *PLoS Med* 5(4):e83, 2008.)

Investigating differential gene expression before and after drug exposure has the potential to correlate gene expression with variable drug responses and uncover the mechanisms of tissue-specific drug toxicities. These types of studies use **microarray technology** to monitor global changes in expression of thousands of genes (the **transcriptome**) simultaneously. Genomic sequencing technologies can also be applied to RNA (RNA-Seq) and result in a more complete and quantitative assessment of the transcriptome. Gene expression profiling data from microarrays or RNA-Seq analyses are used to improve disease classification and risk stratification and are common in oncology. This approach has been widely used to address treatment resistance in acute lymphoblastic leukemia and has provided clinically relevant insights into the mechanistic basis of drug resistance and the genomic basis of interindividual variability in drug response. Subsets of transcripts, or gene expression "signatures," are being investigated as potential prognostic indicators for identifying patients at risk for treatment failure (Fig. 72.3*B*).

Pharmacoproteomic and Metabolomic Tools

Proteomic studies use many different techniques to detect, quantify, and identify proteins in a sample **(expression proteomics)** and to characterize protein function in terms of activity and protein-protein or protein–nucleic acid interactions (**functional proteomics**). Mass spectrometry–based analyses are able to provide quantitative data regarding protein abundance, and several studies have been applied to pediatric liver samples, for example, to generate more accurate developmental trajectories for several drug-metabolizing enzymes and transporters.

Metabolomics and metabonomics utilize sophisticated analytical platforms, such as nuclear magnetic resonance (NMR) spectroscopy and liquid or gas chromatography coupled with mass spectral detection, to measure the concentrations of all small molecules present in a sample. **Metabolomics** refers to the complete set of low-molecular-weight molecules (metabolites) present in a living system (cell, tissue, organ or organism) at a particular developmental or pathologic state. **Metabonomics** is defined as the study of how the metabolic profile of biologic systems change in response to alterations caused by pathophysiologic stimuli, toxic exposures, or dietary changes. **Pharmacometabonomics** involves prediction of the outcome, efficacy, or toxicity of a drug or xenobiotic intervention in an individual patient based on a mathematical model of preintervention metabolite signatures.

Drug Biotransformation: Applications to Pediatric Therapy

The major consequence of pharmacogenetic polymorphisms in drug-metabolizing enzymes is concentration-dependent toxicity caused by impaired drug clearance. In certain cases, reduced conversion of prodrug to therapeutically active compounds is also of clinical importance (see Table 72.2). Chemical modification of drugs by biotransformation reactions generally results in termination of biologic activity through decreased affinity for receptors or other cellular targets as well as more rapid elimination from the body. The process of drug biotransformation can be very complex but is characterized by 3 important features: (1) the concept of broad **substrate specificity** , in which a single isozyme may metabolize a large variety of chemically diverse compounds; (2) many different enzymes may be involved in the biotransformation of a single drug (**enzyme multiplicity**); and (3) a given drug may undergo several different types of reactions. One example of this **product multiplicity** occurs with racemic warfarin, in which at least 7 different hydroxylated metabolites are produced by different CYP isoforms.

Drug biotransformation reactions are conveniently classified into 2 main types, which occur sequentially and serve to terminate biologic activity and enhance elimination (see Chapter 73). **Phase I** reactions introduce or reveal (through oxidation, reduction, or hydrolysis) a functional group within the substrate drug molecule that serves as a site for a phase II conjugation reaction. **Phase II** reactions involve conjugation with endogenous substrates, such as acetate, glucuronic acid, glutathione, glycine, and sulfate. These reactions further increase the polarity of an intermediate metabolite, make the compound more water soluble, and thereby enhance its renal excretion. Interindividual variability in drug biotransformation activity (for both phase I and phase II reactions) is a consequence of the complex interplay among genetic (genotype, sex, race or ethnic background) and environmental (diet, disease, concurrent medication, other xenobiotic exposure) factors. The pathway and rate of a given compound's biotransformation are a function of each individual's unique phenotype with respect to the forms and amounts of drug-metabolizing enzymes expressed.

The CYP enzymes (CYPs) are quantitatively the most important of the **phase I enzymes** . These heme-containing proteins catalyze the metabolism of many lipophilic endogenous substances (steroids, fatty acids, fat-soluble vitamins, prostaglandins, leukotrienes, thromboxanes) as well as exogenous compounds, including a multitude of drugs and environment toxins. CYP nomenclature is based on evolutionary considerations and uses the root symbol *CYP* for *cytochrome P450.* CYPs that share at least 40% homology are grouped into families denoted by an Arabic number after the CYP root. Subfamilies, designated by a letter, appear to represent clusters of highly related genes. Members of the human CYP2 family, for example, have >67% amino acid sequence homology. Individual P450s in a subfamily are numbered sequentially (e.g., CYP3A4, CYP3A5). CYPs that have been identified as being important in human drug metabolism are predominantly found in the CYP1, CYP2, and CYP3 gene families. Importantly, enzyme activity may be induced or inhibited by various agents (see Table 72.2).

Phase II enzymes include arylamine *N* -acetyltransferases (NAT1, NAT2), uridine diphospho-glucuronosyltransferases (UGTs), epoxide hydrolase, glutathione *S* -transferases (GSTs), sulfotransferases (SULTs), and methyltransferases (catechol *O* -methyltransferase, thiopurine *S* -methyltransferase, several *N* -methyltransferases). As with the CYPs, UGTs, SULTs, and GSTs are gene families with multiple individual isoforms, each having its own preferred substrates, mode of regulation, and tissue-specific pattern of expression.

For most CYPs, genotype-phenotype relationships are influenced by development in that fetal expression is limited (with the exception of CYP3A7) and functional activity is acquired postnatally in isoform-specific patterns. Clearance of some compounds appears to be greater in children relative to adults, and the correlation between genotype and phenotype in neonatal life through adolescence may be obscured.

CYP2D6

The *CYP2D6* gene locus is highly polymorphic, with >110 allelic variants identified to date (http://www.imm.ki.se/CYPalleles/cyp2d6.htm ; see Table 72.2). Individual alleles are designated by the gene name *(CYP2D6)* followed by an asterisk, and an Arabic number. By convention, *CYP2D6*1* designates the fully functional wild-type allele. Allelic variants are the consequence of point mutations, single–base pair deletions or additions, gene rearrangements, or deletion of the entire gene, resulting in a reduction or complete loss of activity. Inheritance of 2 recessive, nonfunctional or “null' alleles results in the **poor-metabolizer (PM) phenotype** , which is found in approximately 5–10% of whites and approximately 1–2% of Asians. In whites the *3, *4, *5, and *6 alleles are the most common loss-of-function alleles and account for approximately 98% of PM phenotypes. In contrast, CYP2D6 activity on a population basis tends to be lower in Asian and African American populations because of a lower frequency of nonfunctional alleles (*3, *4, *5, and *6) *and* a relatively high frequency of population-selective alleles associated with decreased activity (“reduced function” alleles) relative to the wild-type *CYP2D6*1* allele. The *CYP2D6*10* allele occurs at a frequency of approximately 50% in Asians, whereas *CYP2D6*17* and *CYP2D6*29* occur at relatively high frequencies in persons of black African origin.

In addition to nonfunctional and partial-function alleles, the presence of gene duplication and multiplication events (≥3 copies of *CYP2D6* gene in tandem on a single chromosome) further complicates the prediction of phenotype from genotype information. The concept of “activity score” has been developed to simplify translation of *CYP2D6* genotype information into a predicted phenotype of CYP2D6 activity for a particular patient. Fully functional alleles (**1, *2, *35,* etc.) are assigned a value of “1”, reduced-function alleles (**9, *10, *17, *29*) are assigned a value of “0.5”, and nonfunctional alleles (**3-*6,* etc.*)* are assigned a value of “0”; for duplications/multiplication events, the allele score is multiplied by the number of copies detected (*10 × 2 = 0.5 × 2 = “1”). The activity score for an individual is the sum of the scores for each chromosome, with poor metabolizers (PMs) defined by a score of “0”, whereas a score of “0.5” indicates an **intermediate-metabolizer (IM) phenotype** , and a score >2 indicating an **ultrarapid-metabolizer (UM) phenotype** ; scores of 1 to 2 are referred to as **extensive metabolizers (EMs)** . The activity score classification system has been adopted by the Clinical Pharmacogenetics Implementation Consortium (CPIC; see below). In the past, individuals with an activity score of “1” have been referred to as “IMs,” and any reference to IM status in literature before 2012 likely refers to a genotype with the equivalent of 1 functional allele, in contrast to the current definition (0.5).

CYP2D6 is involved in the biotransformation of >40 therapeutic entities, including several β-receptor antagonists, antiarrhythmics, antidepressants, antipsychotics, and morphine derivatives [†] (see Table 72.2). CYP2D6 substrates commonly encountered in pediatrics include selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine), risperidone, atomoxetine, promethazine, tramadol, and codeine. Furthermore, over-the-counter cold remedies (e.g., dextromethorphan, diphenhydramine, chlorpheniramine) are also CYP2D6 substrates. An analysis of CYP2D6 ontogeny in vitro that utilized a relatively large number of samples revealed that CYP2D6 protein and activity remain relatively constant after 1 wk of age up to 18 yr. Similarly, results from an in vivo longitudinal phenotyping study involving >100 infants over the 1st year of life demonstrated considerable interindividual variability in CYP2D6 activity, but no relationship between CYP2D6 activity and postnatal age between 2 wk and 12 mo. Furthermore, a cross-sectional study involving 586 children reported that the distribution of CYP2D6 phenotypes in children was comparable to that observed in adults by at least 10 yr of age. Thus, both available in vitro and in vivo data, although based on phenotype data rather than information on drug clearance from pharmacokinetic studies, imply that genetic variation is more important than developmental factors as a determinant of CYP2D6 variability in children.

One consequence of CYP2D6 developmental pharmacogenetics may be the syndrome of irritability, tachypnea, tremors, jitteriness, increased muscle tone, and temperature instability in neonates born to mothers receiving SSRIs during pregnancy. Controversy exists as to whether these symptoms reflect a neonatal withdrawal (hyposerotonergic) state or represent manifestations of serotonin toxicity analogous to the hyperserotonergic state associated with the SSRI-induced serotonin syndrome in adults. Delayed expression of CYP2D6 (and CYP3A4) in the 1st few weeks of life is consistent with a hyperserotonergic state caused by delayed clearance of paroxetine and fluoxetine (CYP2D6) or sertraline (CYP3A4) in neonates exposed to these compounds during pregnancy. Furthermore, decreases in plasma SSRI concentrations and resolution of symptoms would be expected with increasing postnatal age and maturation of these pathways. Given that treatment of a “withdrawal” reaction may include administration of an SSRI, there is considerable potential for increased toxicity in affected neonates. Resolution of the question whether symptoms are caused by withdrawal vs a hyperserotonergic state is essential for appropriate management of SSRI-induced neonatal adaptation syndromes. Until further data are available, it would be prudent to consider newborns and infants <28 days of age as CYP2D6 PMs.

In older children, drug accumulation and resultant concentration-dependent toxicities in CYP2D6 genotypic poor metabolizers should be anticipated in the same way that they are in adults due to the risk of significant morbidity and mortality. Although a fluoxetine-related death has been reported in a 9 yr old child with a CYP2D6 PM genotype, experience with paroxetine indicates that the risk of drug accumulation may also occur, under certain conditions, in individuals at the opposite end of the activity spectrum. For example, chronic dosing of paroxetine may lead to greater-than-anticipated drug accumulation in children classified as CYP2D6 EMs. In fact, the largest decreases in paroxetine clearance observed with ascending doses are seen in patients who have the greatest clearance at the initial dose level (10 mg/day) and are predicted to have the greatest CYP2D6 activity based on CYP2D6 genotype. This seemingly paradoxical effect appears to involve oxidation of paroxetine within the CYP2D6 active site to form a reactive intermediate that is associated with irreversible modification of the CYP2D6 protein in or near the active site and loss of enzyme activity. As a consequence, CYP2D6 activity progressively declines such that drug accumulation may occur over time, placing CYP2D6 EM patients also at increased risk of concentration-dependent toxicity.

Theoretically, younger children may experience decreased efficacy or therapeutic failure with drugs such as codeine and tramadol that are dependent on functional CYP2D6 activity for conversion to the pharmacologically active species. CYP2D6 catalyzes the *O* -demethylation of codeine to morphine. Infants and children appear capable of converting codeine to morphine and achieving morphine:codeine ratios comparable to those of adults. However, in one study, morphine and its metabolites were not detected in 36% of children receiving codeine making the level of analgesia from codeine unreliable in the studied pediatric population. Interestingly, levels of morphine and its metabolites were not related to CYP2D6 phenotype. Finally, *ultrarapid* CYP2D6 metabolism of codeine may result in opiate intoxication, including maternal ultrarapid metabolism of codeine, which can result in high serum and breast milk concentrations of morphine and may have adverse effects in the breastfed neonate.

Rapid metabolism and clearance of CYP2D6 substrates may also contribute to poor therapeutic response because of an inability to achieve adequate plasma concentrations, even when medications are dosed at the maximum approved dose level. The product label for atomoxetine (Strattera) indicates that CYP2D6 PMs have a systemic exposure to the drug (e.g., amount of drug in body over time as determined by area under plasma concentration-time curve) that is 10 times greater than in typical individuals (EMs), and yet the same starting dose of 0.5 mg/kg is recommended for all patients. A genotype-stratified pharmacokinetic study of atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) confirmed an 11-14-fold difference in average systemic exposure between PM and EM groups. However, the most informative finding was the 50-fold range in exposure (30-fold, if exposure corrected for actual mg dose administered) between the PM participant with the highest exposure and the UM participant (3 functional alleles) with the lowest exposure. Using the results of this single-dose study to simulate atomoxetine exposure at steady state for each study participant revealed that even at the maximum recommended dose of atomoxetine, exposure was likely to be subtherapeutic for the majority of patients with ≥1 functional *CYP2D6* alleles.

Avoiding ineffective treatment at one end of the spectrum and excessive toxicity at the other are potential benefits of individualizing doses based on genomic information for medications dependent on a polymorphic clearance pathway, such as CYP2D6. The CPIC has published several guidelines that include CYP2D6 substrates, such as the CPIC guideline for codeine,[*] SSRIs, [†] and tricyclic antidepressants. [‡] Although pediatric data are sparse, these links serve as valuable sources of information regarding the effect of genotype on the dose-exposure relationship for several CYP2D6 substrates.

CYP2C9

Although several clinically useful compounds are substrates for CYP2C9 [§] (see Table 72.2), the effects of allelic variation are most profound for drugs with a narrow therapeutic index, such as phenytoin, warfarin, and tolbutamide. In vitro studies show a progressive increase in CYP2C9 expression from 1–2% of mature levels in the 1st trimester to approximately 30% at term. Considerable variability (approximately 35-fold) in expression is apparent over the 1st 5 mo of life, with about half the samples studied exhibiting values equivalent to those observed in adults. One interpretation of these data is that broad interindividual variability exists in the rate at which CYP2C9 expression is acquired after birth, and in general, the ontogeny of CYP2C9 activity in vivo, as inferred from pharmacokinetic studies of phenytoin in newborns, is consistent with the in vitro results. The apparent half-life of phenytoin is prolonged (approximately 75 hours) in preterm infants, but decreases to approximately 20 hr in term newborns. By 2 wk of age, the half-life has further declined to 8 hr. The appearance of concentration-dependent (saturable) metabolism of phenytoin, reflecting the functional acquisition of CYP2C9 activity, does not appear until approximately 10 days of age. The maximal velocity of phenytoin metabolism has been reported to decrease from an average of 14 mg/kg/day in infants to 8 mg/kg/day in adolescents, which may reflect changes in the ratio of liver mass to total body mass observed over this period of development, as has been observed for warfarin.

Several allelic variants of *CYP2C9* have been reported, but not all have been evaluated for their functional consequences. The *CYP2C9*2* allele is associated with approximately 5.5-fold decreased intrinsic clearance for *S* -warfarin relative to the wild-type enzyme. Allelic variations resulting in amino acid changes within the enzyme active site, such as the *CYP2C9*3, CYP2C9*4,* and *CYP2C9*5* alleles, are associated with activities that are approximately 5% of the wild-type protein. Approximately one third of the white population carries a variant *CYP2C9* allele (typically *2 and *3 alleles), whereas the *2 and *3 alleles are virtually nonexistent in African American, Chinese, Japanese, or Korean populations. In contrast, the *5 allele has been detected in blacks but not in whites. The risk of bleeding complications in patients treated with warfarin and with concentration-dependent toxicity in patients treated with phenytoin is most pronounced for individuals with a *CYP2C9*3/*3* genotype. Although the relationship between the *CYP2C9* genotype and warfarin dosing and pharmacokinetics has not been as extensively studied in children, consequences of allelic variation can be expected to be similar to those observed in adults. In adults, *CYP2C9* and *VKORC1* genotype and patient age, sex, and weight can account for 50–60% of the variation in warfarin dose requirements. A large part of the variation is still unknown, but may be at least partially attributed to interactions with other drugs and foods.

CYP2C19

In vitro, CYP2C19 protein and catalytic activity can be detected at levels representing 12–15% of mature values by 8 wk of gestation and remain essentially unchanged throughout gestation and at birth. Over the 1st 5 mo of postnatal age, CYP2C19 activity increases linearly. Adult levels are achieved by 10 yr of age, although variability in expression is estimated to be approximately 21-fold between 5 mo and 10 yr of age. The major source of this variability is likely pharmacogenetic in nature. The CYP2C19 PM phenotype (also known as *mephenytoin hydroxylase deficiency*) is present in 3–5% of the white population and 20–25% of Asians. Although 25 variant alleles have been reported to date, the 2 most common variant alleles, *CYP2C19*2* and *CYP2C19*3*, result from single-base substitutions that introduce premature stop codons and, consequently, truncated polypeptide chains that possess no functional activity. Despite consistent increases in CYP2C19 activity observed in vitro over the 1st 5 months of life, the results of an in vivo phenotyping study with omeprazole in Mexican children revealed a broad range of activity and implied that 17% of infants <4 mo of age could be classified as PMs (no PMs were detected beyond that point). In contrast, 20% of children 3–9 mo old were classified as ultrarapid metabolizers (UMs) compared with 6% of infants 1-3 mo of age. For omeprazole, pharmacokinetic parameters comparable to those observed in adults are achieved by age 2 yr.

CYP2C19 also plays an important role in the metabolism of lansoprazole. In Japanese adults treated with lansoprazole, amoxicillin, and clarithromycin for *Helicobacter pylori* infection, the eradication rate for CYP2C19 PMs (97.8%) and heterozygous EMs (1 functional *CYP2C19* allele; 92.1%) was significantly greater than that observed in homozygous EMs (72.7%). Initial treatment did not eradicate *H. pylori* in 35 patients, 34 of whom had at least 1 functional *CYP2C19* allele, and eradication could be achieved with higher lansoprazole doses in almost all cases. Given that the frequency of the functional *CYP2C19*1* allele is considerably greater in whites (0.84 [84%]) than Japanese (0.55 [55%]), eradication failure can be expected to occur more frequently in whites. Because proton pump inhibitors are widely used in children, pharmacogenetic as well as developmental considerations should guide pediatric dosing strategies.

CYP3A4, CYP3A5, and CYP3A7

The **CYP3A** subfamily consists of four members in humans (CYPs 3A4, 3A5, 3A7, and 3A43) and is quantitatively the most important group of CYPs in terms of human hepatic drug biotransformation. These isoforms catalyze the oxidation of many different therapeutic entities, several of which are of potential importance to pediatric practice [†] (see Table 72.2). CYP3A7 is the predominant CYP isoform in fetal liver and can be detected in embryonic liver as early as 50–60 days' gestation. CYP3A4, the major CYP3A isoform in adults, is essentially absent in fetal liver, but increases gradually throughout childhood. Over the 1st 6 mo of life, CYP3A7 expression exceeds that of CYP3A4, although its catalytic activity toward most CYP3A substrates is rather limited compared with CYP3A4. CYP3A4 is also abundantly expressed in intestine, where it contributes significantly to the first-pass metabolism of oral drugs, which are substrates (e.g., midazolam). CYP3A5 is polymorphically expressed and is present in approximately 25% of adult liver samples studied in vitro.

Several methods have been proposed to measure CYP3A activity. Using these various phenotyping probes, CYP3A4 activity has been reported to vary widely (up to 50-fold) among individuals, but the population distributions of activity are essentially unimodal and evidence for polymorphic activity has been elusive. Although 20 allelic variants have been identified (http://www.imm.ki.se/CYPalleles/cyp3a4.htm), most occur relatively infrequently and do not appear to be of clinical importance. Of interest to pediatrics is the *CYP3A4*1B* allele present in the *CYP3A4* promoter region. The clinical significance of this allelic variant appears limited with respect to drug biotransformation activity, despite in vitro assays showing 2-fold increased activity over the wild-type *CYP3A4*1* allele. Although no association appears to exist between the *CYP3A4*1B* allele and age of menarche, a significant relationship does exist between the number of *CYP3A4*1B* alleles and the age at onset of puberty, as defined by Tanner breast score. In one study, 90% of 9 yr old girls with a *CYP3A4*1B/*1B* genotype had a Tanner breast score of ≥2 vs 56% of *CYP3A4*1A/*1B* heterozygotes and 40% of girls homozygous for the *CYP3A4*1A* allele. Because CYP3A4 plays an important role in testosterone catabolism, it was proposed that the estradiol:testosterone ratio may be shifted toward higher values in the presence of the *CYP3A4*1B* allele and might trigger the hormonal cascade that accompanies puberty. Intestinal CYP3A4 activity is inhibited by grapefruit juice and may result in higher levels of the many drugs metabolized by this enzyme; very large quantities of grapefruit juice may also inhibit the hepatic CYP3A4.

Polymorphic *CYP3A5* expression is largely caused by an SNP in intron 3 that creates a cryptic splice site and gives rise to messenger RNA splice variants that retain part of intron 3 with a premature stop codon. The truncated mRNA transcripts associated with this allele, *CYP3A5*3*, cannot be translated into a functional protein. Individuals with at least one wild-type *CYP3A5*1* allele express functional CYP3A5 protein, whereas those homozygous for *CYP3A5*3 (CYP3A5*3/*3)* do not express appreciable amounts of functional protein. Approximately 60% of African Americans show functional hepatic CYP3A5 activity, compared with only 33% of European Americans.

Clinically important consequences of *CYP3A5* allelic variation have been reported in children. In pediatric heart transplant patients with a *CYP3A5*1/*3* genotype, tacrolimus concentrations were approximately 25% of those observed in patients with *CYP3A5*3/*3* genotypes, when corrected for dose, in the highly vulnerable period immediately after transplant (≤2 wk), and 50% less at 3, 6, and 12 mo after transplant. Thus, larger doses of tacrolimus are required in patients with functional CYP3A5 protein to achieve comparable blood levels and to minimize the risk of rejection. Of concern, <15% of tacrolimus concentrations in the immediate posttransplant period were within the therapeutic target range, highlighting the need for prospective, precision-guided tacrolimus trials in the pediatric population. In addition to *CYP3A5* expressor genotype, younger age was associated with lower tacrolimus concentrations. The same age and genotype relationship is observed for renal transplantation. Conversely, the same age- and genotype-tailored treatment is more challenging in liver transplantation unless the donor *CYP3A5* is known. In pediatric liver transplant recipients, *CYP3A5* expressor genotype was not associated with tacrolimus concentrations and dosing. This implies that hepatic metabolism, from the donor liver and genotype status, plays a larger role in tacrolimus concentrations than intestinal metabolism or the recipient's *CYP3A5* genotype status. Collectively, these pediatric tacrolimus datasets have informed the CPIC to recommend a 1.5-2-fold increase in tacrolimus dosing, followed by close plasma drug monitoring, in children and adolescents with at least one *CYP3A5*1* allele (https://cpicpgx.org/guidelines/guideline-for-tacrolimus-and-cyp3a5/).

Glucuronosyl Transferases (UGTs)

The UGT gene superfamily catalyzes the conjugation (with glucuronic acid) of several drugs used clinically in pediatrics, including morphine, acetaminophen, nonsteroidal antiinflammatory drugs, and benzodiazepines. The effect of development on glucuronidation capacity has been well described and is illustrated by hyperbilirubinemia, **gray baby syndrome** (cardiovascular collapse associated with high doses of chloramphenicol in newborns), and the 3.5-fold increase in morphine clearance observed in premature neonates at 24-39 wk postconception age. As with the CYPs, there are multiple UGT isoforms, and the acquisition of functional UGT activity appears to be isoform and substrate specific.

UGT1A1 is the major UGT gene product responsible for bilirubin glucuronidation, and >100 genetic alterations have been reported (Table 72.3), most of which are rare and are more properly considered *mutations* rather than gene polymorphisms. Inheritance of 2 defective alleles is associated with reduced bilirubin-conjugating activity and gives rise to clinical conditions such as Crigler-Najjar and Gilbert syndromes. More frequently occurring polymorphisms involve a dinucleotide (TA) repeat in the atypical TATA box of the *UGT1A1* promoter. The wild-type *UGT1A1*1* allele has 6 repeats (TA_6), and the TA_5 *(UGT1A1*33)*, TA_7 *(UGT1A1*28)*, and TA_8 *(UGT1A1*34)* variants are all associated with reduced activity. *UGT1A1*28*, the most frequent variant, is a contributory factor to prolonged neonatal jaundice. This variant is also associated with impaired glucuronidation and thus toxicity of the active metabolite SN-38 of the chemotherapeutic agent irinotecan. Allelic variations in *UGT1A7* and *UGT1A9* have also been associated with irinotecan toxicity in adults with colorectal cancer.

Table 72.3

Internet Resources for Pharmacogenetics and Pharmacogenomics*

INTRODUCTION TO PHARMACOGENOMICS	
http://www.pharmgkb.org/ http://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/personalized-medicine/art-20044300	
PHARMACOGENETICS: ALLELIC VARIANTS OF DRUG-METABOLIZING ENZYMES	
CYP2C9	http://www.cypalleles.ki.se/cyp2c9.htm
CYP2C19	http://www.cypalleles.ki.se/cyp2c19.htm
CYP2D6	http://www.cypalleles.ki.se/cyp2d6.htm
CYP3A4	http://www.cypalleles.ki.se/cyp3a4.htm
CYP3A5	http://www.cypalleles.ki.se/cyp3a5.htm

UGTs	https://www.pharmacogenomics.pha.ulaval.ca/ugt-alleles-nomenclature/
NAT1 and NAT2	http://nat.mbg.duth.gr/
PHARMACOGENETICS: SUBSTRATES OF DRUG-METABOLIZING ENZYMES	
http://medicine.iupui.edu/clinpharm/ddis/clinical-table http://www.mayomedicallaboratories.com/it-mmfiles/Pharmacogenomic_Associations_Tables.pdf	
PHARMACOGENETICS-BASED DOSING GUIDELINES	
Dosing guidelines incorporating pharmacogenetic data developed by the Clinical Pharmacogenetics Implementation Consortium are available on the CPIC web page https://cpicpgx.org/ , which is mirrored at PharmGKB: https://www.pharmgkb.org/page/cpic , *or* through the National Guidelines Clearinghouse website, a publically accessible resource for evidence-based clinical guidelines sponsored by the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health Services, at https://www.guideline.gov/search?q=CPIC .	
CYP2D6, CYP2C19, and antidepressants: https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/ CYP2D6 and codeine: https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/ CYP2D6, CYP2C19, and SSRIs: https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/ CYP3A5 and tacrolimus: https://cpicpgx.org/guidelines/guideline-for-tacrolimus-and-cyp3a5/ HLA-B and abacavir and allopurinol: https://cpicpgx.org/guidelines/guideline-for-abacavir-and-hla-b/ https://cpicpgx.org/guidelines/guideline-for-allopurinol-and-hla-b/ https://cpicpgx.org/guidelines/guideline-for-carbamazepine-and-hla-b/ SLCO1B1 and simvastatin: https://cpicpgx.org/guidelines/guideline-for-simvastatin-and-slco1b1/ TPMT and thiopurines: https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/	

[*] All sites were accessible on July 14, 2017.

The consequences of allelic variation in the UGT2B family are less certain. The predominant routes of morphine elimination include biotransformation to the pharmacologically active 6-glucuronide (M6G) and the inactive 3-glucuronide (M3G). M6G formation is almost exclusively catalyzed by UGT2B7, whereas several UGTs in the UGT1A subfamily and UGT2B7, both contribute to M3G formation. Increased M6G:morphine ratios have been reported in individuals homozygous for the SNPs constituting the *UGT2B7*2* allele. Although individuals genotyped as *UGT2B7*2/*2* may produce higher-than-anticipated concentrations of pharmacologically active morphine and its metabolites, prospective studies addressing phenotype-genotype correlations and the consequences of morphine analgesia have had conflicting results.

Thiopurine *S* -Methyltransferase

Thiopurine *S* -methyltransferase (**TPMT**) is a cytosolic enzyme that catalyses the *S* -methylation of aromatic and heterocyclic sulfur-containing compounds, such as 6-mercaptopurine (6MP), azathioprine, and 6-thioguanine, used in the treatment of acute lymphoblastic leukemia (ALL), inflammatory bowel disease (IBD), and juvenile idiopathic arthritis and the prevention of renal allograft rejection. To exert its cytotoxic effects, 6MP requires metabolism to thioguanine nucleotides by a multistep process initiated by hypoxanthine guanine phosphoribosyltransferase. TPMT prevents thioguanine nucleotide production by methylating 6MP (Fig. 72.4*A*). TPMT activity is usually measured in erythrocytes, with erythrocyte activity reflecting what is found in other tissues, including liver and leukemic blasts. Although approximately 89% of whites and blacks have high TPMT activity and 11% have intermediate activity, 1 in 300 individuals inherits TPMT deficiency as an autosomal recessive trait (Fig. 72.4*B*). In newborn infants, peripheral blood TPMT activity is 50% greater than in race-matched adults and shows a distribution of activity consistent with the polymorphism characterized in adults. No data currently indicate how long this higher activity is maintained, although TPMT activities were comparable to previously reported adult values in a population of Korean schoolchildren age 7–9 yr. In patients with intermediate or low activity, more drug is shunted toward production of cytotoxic thioguanine nucleotides. TPMT can also methylate 6-thioinosine 5′-monophosphate to generate a methylated metabolite capable of inhibiting de novo purine synthesis (Fig. 72.4*C*).

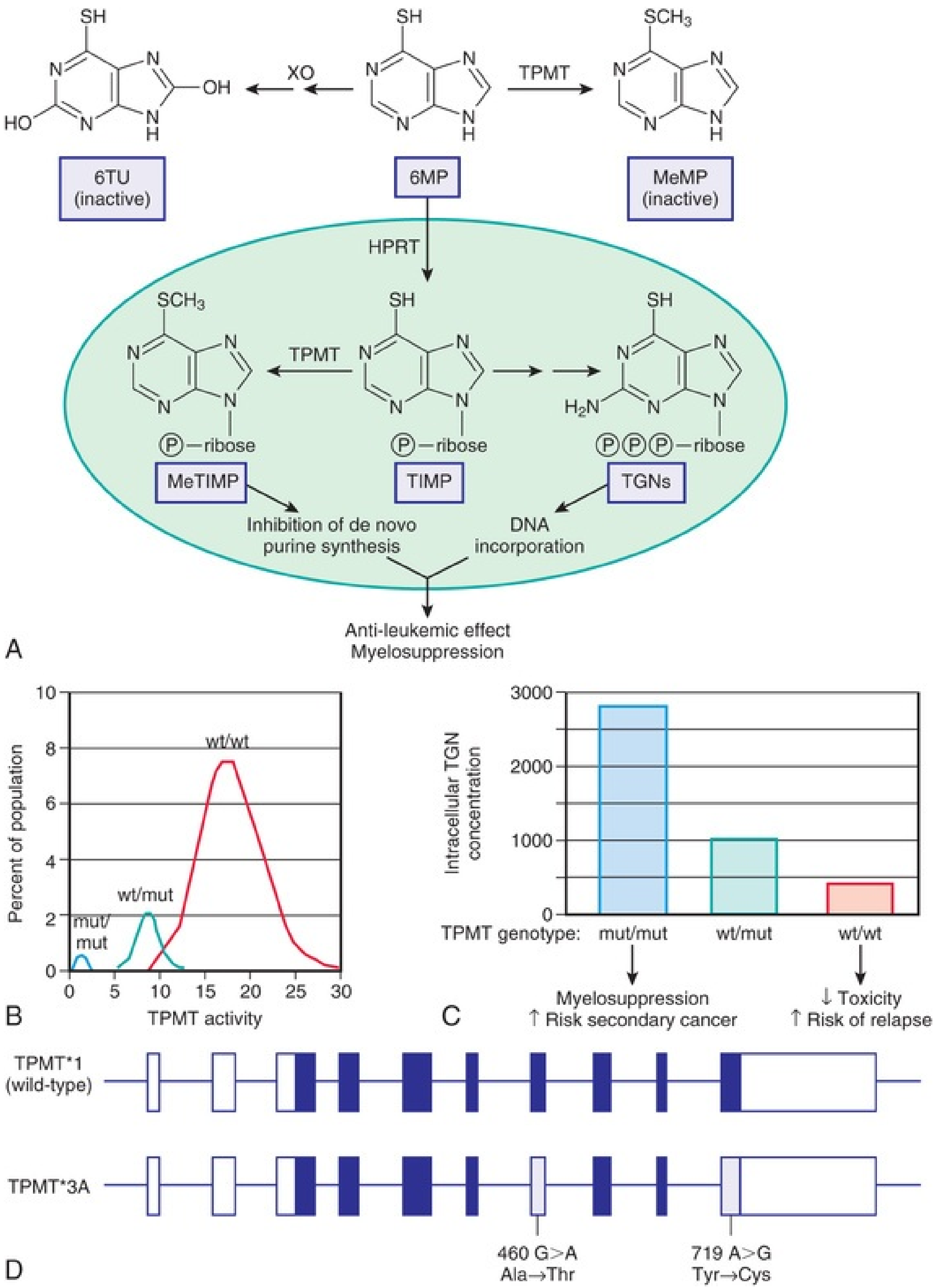
SH
N
N
OH
HO
N
N
H
XO
TPMT
SCH3
6TU
(inactive)
6MP
MeMP
(inactive)
HPRT
SCH3
SH
SH
TPMT
H2N
P — ribose
P — ribose
P P P — ribose
MeTIMP
TIMP
TGNs
Inhibition of de novo
purine synthesis
DNA
incorporation
Anti-leukemic effect
Myelosuppression
A
10
8
6
4
2
0
Percent of population
wt/wt
wt/mut
mut/
mut
0
5
10
15
20
25
30
TPMT activity
B
3000
2000
1000
0
Intracellular TGN
concentration
TPMT genotype:
mut/mut
wt/mut
wt/wt
Myelosuppression
↑ Risk secondary cancer
↓ Toxicity
↑ Risk of relapse
C
TPMT*1
(wild-type)
TPMT*3A
460 G>A
Ala→Thr
719 A>G
Tyr→Cys
D

FIG. 72.4 **Thiopurine *S* -methyltransferase (TPMT) polymorphism. A, 6-Mercaptopurine (6MP) undergoes metabolism to thioguanine nucleotides (TGNs) to exert its cytotoxic effects. TPMT and xanthine oxidase reduce the amount of 6MP available for the bioactivation pathway to TGNs. TPMT can also methylate 6-thioinosine 5′-monophosphate (TIMP) to generate a methylated compound capable of inhibiting de novo purine synthesis. B, Distribution of TPMT activity in humans. Of the population, 89% has high activity, whereas 11% has intermediate activity. Approximately 1 in 300**

individuals homozygous for 2 loss-of-function alleles has very low activity. C, Correlation between the TPMT genotype and intracellular TGN concentrations. In TPMT poor metabolizers, more 6MP is available to go down the bioactivation pathway to form TGNs; this situation is associated with an increased risk of myelosuppression. D, The most common variant TPMT allele is the result of 2 mutations that give rise to an unstable protein product that undergoes proteolytic degradation. 6TU, 6-Thiouric acid; MeMP, 6-methylmercaptopurine; HPRT, 6-thiomethylinosine 5-monophosphate; MeTIMP, hypoxanthine-guanine phosphoribosyl transferase; wt, wild type; mut, mutant. (Modified with permission from Relling MV, Dervieux T: Pharmacogenetics and cancer therapy, *Nat Rev Cancer* 11:99–108, 2001; copyright 2001, Macmillan Magazines Ltd.)

Multiple SNP variants have been identified in the *TPMT* gene, and a GWAS from 2 independent pediatric ALL cohorts confirmed that TPMT activity is a monogenic pharmacogenetics trait; 3 variants (*TPMT*2, *3A, *3C*) account for 98% of whites with low activity and have high predictive capacity for TPMT phenotype. *TPMT*3A* is the most common and is characterized by 2 nucleotide transition mutations, G460A and A719G, that lead to 2 amino acid substitutions, Ala154Thr and Tyr240Cys (Fig. 72.4*D*). The *TPMT*3A* allele occurs more frequently in white (9.5%) and Hispanic (7.0%) patients and is absent in black patients. In contrast, *TPMT*3C* is reported to be the predominant variant allele in black patients (12.2%), and only rarely observed in white or Hispanic patients; overall, black patients have lower TPMT activities than nonblack patients. The *3A and *3C variants each result in loss of functional activity through the production of unstable proteins that are subject to accelerated proteolytic degradation.

The relatively few patients with low to absent TPMT activity (0.3%) are at increased risk for **severe myelosuppression** if treated with routine doses of thiopurines; thus they require a 10-15-fold reduction in dose to minimize this risk. Furthermore, if not dosed properly, patients may be at increased risk for relapse as a result of inadequate or a lack of treatment with thiopurines. Given the expanding use of 6MP and azathioprine in pediatrics to treat IBD and juvenile arthritis and to prevent renal allograft rejection, TPMT pharmacogenetics is not trivial, and a CPIC guideline assists with genotype-guided dosing. [†] However, *TPMT* genotype is not the only determinant of intolerance to thiopurines. Multiple studies have also implicated genetic variation in *NUDT15*, a nucleotide diphosphatase that converts thioguanine triphosphate to thioguanine monophosphate, thereby reducing incorporation of thioguanine into DNA; reduction or loss of this activity results in greater-than-expected thioguanine incorporation into DNA and thus increased cytotoxicity. Reduced-function *NUDT15* alleles are more common in Hispanic patients and those with Asian ancestry, and patients who have inherited 2 reduced-function alleles tolerate thiopurine doses that are much lower (10%) than normal. Thus it is reasonable to expect that both *TPMT* and *NUDT15* genotype will need to be considered for individualized thiopurine treatment.

Pharmacogenetics of Drug Transporters

There are several major types of membrane transporters, including organic anion transporters (OATs), organic anion–transporting polypeptides (OATPs), organic cation transporters (OCTs), and the adenosine triphosphate–binding cassette (ABC) transporters, such as P-glycoprotein and the multidrug-resistant proteins. Membrane transporters are heavily involved in drug disposition and actively transport substrate drugs between organs and tissues. Drug transporters are expressed at numerous epithelial barriers, such as intestinal epithelial cells, hepatocytes, renal tubular cells, and the blood-brain barrier (BBB) (Fig. 72.5). Transporters often are also determinants of drug resistance, and many drugs work by affecting the function of transporters. As such, polymorphisms in the genes encoding these proteins may have a significant effect on the absorption, distribution, metabolism, and excretion as well as the pharmacodynamic effect of a wide variety of compounds.

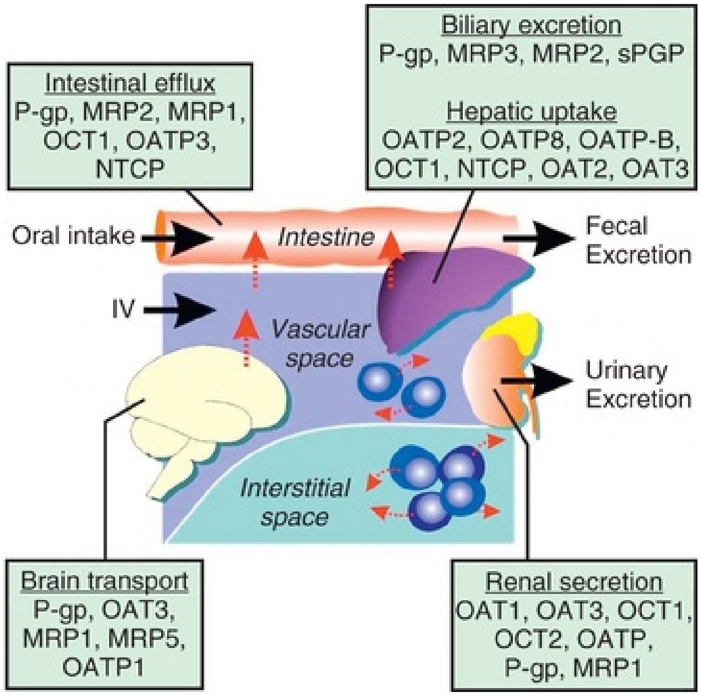
Biliary excretion
P-gp, MRP3, MRP2, sPGP
Hepatic uptake
OATP2, OATP8, OATP-B, OCT1, NTCP, OAT2, OAT3
Intestinal efflux
P-gp, MRP2, MRP1, OCT1, OATP3, NTCP
Oral intake
Intestine
Fecal Excretion
IV
Vascular space
Urinary Excretion
Interstitial space
Brain transport
P-gp, OAT3, MRP1, MRP5, OATP1
Renal secretion
OAT1, OAT3, OCT1, OCT2, OATP, P-gp, MRP1

FIG. 72.5 Schematic diagram of important transport proteins and their known locations in humans. *Spheres* correspond to drug molecules. (Reprinted with permission from American Pharmacists Association. Ritschel WA, Kearns GL, editors. *Handbook of basic pharmacokinetics including clinical applications,* ed 7, Washington, DC, 2009, American Pharmacists Association, p 45.)

Adenosine Triphosphate–Binding Cassette Superfamily

The ATP-binding cassette (ABC) transporters belong to the largest known transporter gene family and translocate a variety of substrates, including chemotherapy agents. ABC multidrug transporter expression has been implicated in tumor cell resistance to anticancer therapy, altered disposition of chemotherapy drugs, and toxic side effects associated with chemotherapy. More recently, the genetic heterogeneity of several ABC transporter genes has been described. Apart from having at least one ATP-binding domain, these transporters are characterized by a signature sequence of amino acid residues within the domain. In humans the ABC transporters function as efflux pumps, which together with detoxification enzymes, constitute a complex, integrated, "chemoimmunologic defense" system against drugs and other foreign chemicals. A variety of epithelial barriers, including the kidney, liver, and BBB have abundant expression of ABC transporters, such as P-glycoprotein (P-gp; also known as *MDR1*), and multidrug-resistant proteins (MRPs) 1, 2, and 3. Powered by ATP, these transporters actively extrude substrates from the respective cell and organ.

Considerable genetic variation has been reported in the superfamily of ABC transporter genes. Many studies have investigated the relationship between *ABCB1* genotype or haplotype and P-gp expression, activity, or drug response, yielding inconsistent results, largely due to methodological limitations. No association between genotype and drug disposition or response would be expected if the drug of interest were not substrate for P-gp. However, even when drugs are tested for transport by P-gp using in vitro systems, the results are not necessarily conclusive, as is the case for carbamazepine. On the other hand, an association between *ABCB1* genotype and drug response was observed in patients receiving antidepressants that were ABC substrates (e.g., citalopram, paroxetine, amitriptyline, venlafaxine)., but not in drugs that were not substrates (e.g., mirtazapine).

Studies conducted in children need to also consider the ontogeny of P-gp expression. Based on studies using human lymphocytes, it appears that P-gp activity is high at birth, decreases between 0 and 6 mo, and stabilizes between 6 mo and 2 yr of age. In contrast, P-gp can be detected in human neural stem/progenitor cells and decreases with differentiation. Furthermore, P-gp has been proposed as an endothelial marker for development of the BBB, and expression increases with postnatal age as the BBB matures. Proteomic analysis of the ontogeny of hepatic P-gp has demonstrated that P-gp expression increases through infancy, achieving 50% of adult expression at approximately 3 yr and reaching a plateau during adolescence. Thus the developmental patterns of P-gp expression likely are tissue specific, but data still are sparse in this regard. Nevertheless, expression of P-gp at a young age in gut and liver likely represents a protective mechanism in which both endogenous and exogenous toxins are efficiently excreted from the body. However, developmental patterns of expression in tissues of drug response, such as lymphocytes and tumors, may also affect the efficacy of intracellular drugs. For example, polymorphisms in the gene have been shown to be predictive of the ability to wean corticosteroids after heart transplantation, as well as the susceptibility to and clinical outcome of treatment for pediatric ALL. On the other hand, immaturity of P-gp expression in the developing BBB may contribute to discrete periods of increased susceptibility to drug toxicity in the central nervous system. However, for most other drugs, including immunosuppressants and protease inhibitors, studies investigating the effect of *ABCB1* polymorphisms in drug disposition and response have yielded conflicting results. In one study investigating the relationship between *ABCB1* genotype and cyclosporin pharmacokinetics, an effect of genotype on oral availability was only apparent in children >8 yr of age. Although these results require further replication, the implication is that a better understanding of transporter ontogeny is required to properly design and interpret pharmacogenetic studies of *ABCB1* in pediatric populations.

Organic Anion–Transporting Polypeptides

Organic anion–transporting polypeptides (OATPs) in the solute carrier organic anion transporter (SLCO) are a family of glycoprotein transporters with 12 transmembrane-spanning domains expressed in various epithelial cells. There are 11 OATPs in humans, some of which are ubiquitously expressed and others whose expression is restricted to specific tissues. Typical substrates include bile salts, hormones and their conjugates, toxins, and various drugs. The solute carrier, human OATP 1A2 (OATP1A2, OATP-A, OATP1, and OATP) is highly expressed in the intestine, kidney, cholangiocytes, and BBB and may be important in the absorption, distribution, and excretion of a broad array of clinically important drugs. Several nonsynonymous polymorphisms have been identified in the gene encoding OATP1A2, SLCO1A2 (SLC21A3), with some of these variants demonstrating functional changes in the transport of OATP1A2 substrates.

OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3) are liver-specific transporters and promote the cellular uptake of endogenous substrates, such as bilirubin, bile acids, DHEA-sulfate, and leukotriene C4, as well as various drugs, including several statins, methotrexate, and enalapril. Allelic variation in OATP1B1 (specifically the *SLCO1B1*5* allele) results in reduced clearance and increased systemic exposure of several statin drugs (atorvastatin, pravastatin, simvastatin) and has been associated with an increased risk of musculoskeletal side effects from simvastatin. The expression of OATP1B1 in human pediatric liver tissue was independent of age in all samples, but age dependency was demonstrated in samples homozygous for the *SLCO1B1* reference sequence (i.e., *SLCO1B1*1A/*1A* genotype). Therefore, not only genotype, but also growth and development, may influence OATP1B1 protein expression in the developing child. To date, only one study has investigated the effect of *SLCO1B1* genotype on statin disposition in children, reporting a genotype-phenotype relationship for pravastatin that was discordant with the relationship observed in adults. However, data with simvastatin in dyslipidemic children and adolescents (LDL >130 mg/dL) suggest that the genotype-phenotype relationships observed in adults are also present in this population, but the magnitude of the genetic effect may be greater in pediatric patients.

Several studies have confirmed that the 2 SNPs determining the most common *SLCO1B1* haplotypes (**1a, *1b, *5,* and **15*), rs4149056 and rs2306283, are associated with decreased clearance of high-dose methotrexate in children with ALL. Genotyping for *SLCO1B1* may be helpful in identifying patients at increased risk of toxicity from reduced clearance or increased accumulation of methotrexate. In the pediatric liver proteomic analysis, OATP1B3 expression was age dependent, with a 3-fold difference observed between neonates and adults. Similar to P-gp, expression steadily increased during childhood; however, 50% of adult level expression was much earlier (6 mo) compared with P-gp.

Organic Cation Transporters

Organic cation transporters (OCTs) in the SCL22A subfamily are primarily expressed on the basolateral membrane of polarized epithelia and mediate the renal secretion of small organic cations. Originally, OCT1 (also known as SLC22A1) was thought to be primarily expressed in liver, but recent studies have also localized its expression to the apical side of proximal and distal renal tubules. Hepatic OCT1 expression was found to be age dependent with almost a 5-fold difference between neonates and adults. OCT2 (SLC22A2) is predominantly expressed on the basolateral surface of proximal renal tubules. In adults, allelic variation in OCT1 and OCT2 is associated with increased renal clearance of metformin. The role of genetic variation of OCT1 and OCT2 has not been studied in children, but developmental factors appear to be operative. Neonates possess very limited ability to eliminate organic cations, but this function increases rapidly during the 1st few months of life, and when standardized for body weight or surface area, it tends to exceed adult levels during the toddler stage.

Polymorphisms in Drug Receptors

Receptors are the targets for drugs and endogenous transmitters because of their inherent molecular recognition sites. Drugs and transmitters bind to the receptor to produce a pharmacologic effect. Variability in the receptor protein or the ion channel may determine the magnitude of the pharmacologic response. Polymorphisms of the β_2 -adrenergic receptor gene *(ADRB2)* are associated with variable responses to bronchodilator drugs.

Drug responses are seldom monogenic events because multiple genes are involved in both drug binding to the pharmacologic target and the subsequent downstream signal transduction events that ultimately manifest collectively as a therapeutic effect. Although genotypes at a particular locus may show a statistically significant effect on the outcome of interest, they may account for only a relatively small amount of the overall population variability for that outcome. A particular group of SNPs in the corticotropin-releasing hormone receptor 1 gene *(CRHR1)* is associated with a statistically significant improvement in forced expiratory volume in 1 second (FEV_1), but accounts for only 6% of the overall variability in response to inhaled corticosteroids. A series of subsequent studies has determined that allelic variation in several genes in the steroid pathway contributes to overall response to this form of therapy.

The listing and classification of receptors is a major initiative of the International Union of Pharmacology (IUPHAR). The list of receptors and voltage-gated ion channels is available on the IUPHAR website (http://www.iuphar-db.org). The effect of growth and development on the activities and binding affinities of these receptors, effectors, and ion channels has been studied in animals to some extent but remains to be elucidated in humans.

Current and Future Applications in Pediatrics

Progress in the treatment of acute lymphoblastic leukemia shows how the application of pharmacogenomic principles can improve pediatric drug therapy (see Chapter 522.1). Despite improved understanding of the genetic determinants of drug response, however, many complexities remain to be resolved. Patients with ALL who have 1 wild-type allele and intermediate TPMT activity tend to have a better response to 6MP therapy than patients with 2 wild-type alleles and full activity. Reduced TPMT activity also places patients at risk for irradiation-induced secondary brain tumors and etoposide-induced acute myeloid leukemia. Pharmacogenetic polymorphisms of several additional genes, such as *NUDT15,* also have the potential to influence successful treatment of ALL. Multiple genetic and treatment-related factors interact to create patient subgroups with varying degrees of risk. These represent an opportunity for pharmacogenomic approaches to identify subgroups of patients who will benefit from specific treatment regimens and those who will be at risk for short-term and long-term toxicities (Fig. 72.6).

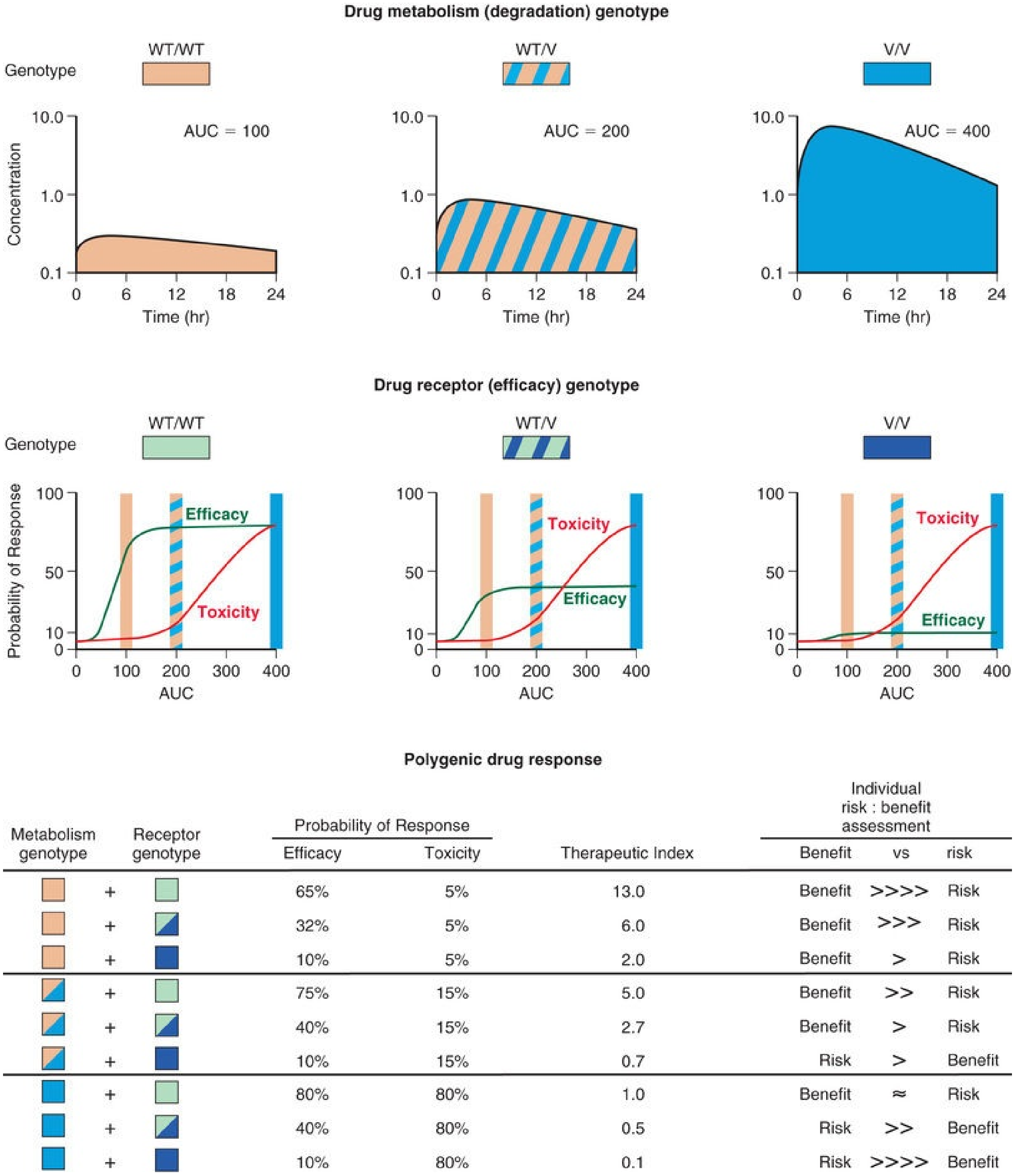

Polygenic drug response

Metabolism genotype		Receptor genotype	Probability of Response Efficacy	 Toxicity	Therapeutic Index	Individual risk : benefit assessment Benefit	 vs	 risk
🟧	+	🟩	65%	5%	13.0	Benefit	>>>>	Risk
🟧	+	◪	32%	5%	6.0	Benefit	>>>	Risk
🟧	+	■	10%	5%	2.0	Benefit	>	Risk
◩	+	🟩	75%	15%	5.0	Benefit	>>	Risk
◩	+	◪	40%	15%	2.7	Benefit	>	Risk
◩	+	■	10%	15%	0.7	Risk	>	Benefit
🟦	+	🟩	80%	80%	1.0	Benefit	≈	Risk
🟦	+	◪	40%	80%	0.5	Risk	>>	Benefit
🟦	+	■	10%	80%	0.1	Risk	>>>>	Benefit

FIG. 72.6 **Polygenic determinants of drug response. The potential effects of 2 genetic polymorphisms are illustrated. In each panel, there is a profile for individuals who have 2 wild-type alleles (WT/WT), those who are heterozygous for 1 wild-type and 1 variant (V) allele (WT/V), and those who have 2 variant alleles (V/V) for the depicted gene. The top panels illustrate a potential polymorphism involving a drug-metabolizing enzyme where variant alleles result in decreased drug metabolism and greater exposure (as shown by the increasing area under the concentration-time curve [AUC]). The middle panels illustrate a potential polymorphism involving a drug receptor and depicts variant alleles which result in decreased receptor sensitivity. Note that for each receptor type, there are 3 possibilities for drug exposure. The bottom table shows the 9 resulting combinations of drug-metabolism and drug-receptor genotypes and the**

corresponding drug-response phenotypes calculated from data shown in the middle panels. These phenotypes allow for calculation of a therapeutic index (i.e., efficacy:toxicity; here this ranges from 13 [65%:5%] to 0.1 [10%:80%]), which results in the ability to perform an individualized risk/benefit assessment. (Adapted from Evans WE, McLeod HL: Pharmacogenomics—drug disposition, drug targets, and side effects, *N Engl J Med* 348:538–549, 2003.)

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[†] For an updated list, see http://www.mayomedicallaboratories.com/it-mmfiles/Pharmacogenomic_Associations_Tables.pdf .

[*] https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/ .

[†] https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/ .

[‡] https://cpicpgx.org/guidelines/guideline-for-tricyclic-antidepressants-and-cyp2d6-and-cyp2c19/ .

[§] http://www.mayomedicallaboratories.com/it-mmfiles/Pharmacogenomic_Associations_Tables.pdf .

[†] For an updated list, see http://www.mayomedicallaboratories.com/it-mmfiles/Pharmacogenomic_Associations_Tables.pdf .

[†] https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/ .

CHAPTER 73

Principles of Drug Therapy

Tracy L. Sandritter, Bridgette L. Jones, Gregory L. Kearns, Jennifer A. Lowry

The clinical pharmacology of a given drug reflects a multifaceted set of properties that pertain to not only the disposition and action of drugs, but also the response (e.g., adverse effects, therapeutic effects, therapeutic outcomes) to their administration or use. The 3 most important facets of clinical pharmacology are pharmacokinetics, pharmacodynamics, and pharmacogenomics. **Pharmacokinetics** describes the movement of a drug throughout the body and the concentrations (or amounts) of a drug that reach a given body space or tissue and its residence time there. Pharmacokinetics of a drug are conceptualized by considering the characteristics that collectively are the determinants of the dose-concentration-effect relationship: absorption, distribution, metabolism, and excretion. **Pharmacodynamics** describes the relationship between drug dose or drug concentration and response. The response may be desirable *(effectiveness)* or untoward *(toxicity)*. Although in clinical practice the response to drugs in different patient populations is often described by a standard dosing or concentration range, response is best conceptualized along a continuum where the relationship between dose and response(s) is not linear. **Pharmacogenomics** is the study of how variant forms of human genes contribute to interindividual variability in drug response. The finding that drug responses can be influenced by the patient's genetic profile has offered great hope for realizing individualized pharmacotherapy, in which the relationship between genotype and phenotype (either disease and/or drug response) is predictive of drug response (see Chapter 72). In the developing child, ontogeny has the potential to modulate drug response through altering both pharmacokinetics and pharmacodynamics.

General Pharmacokinetic and

Pharmacodynamic Principles

A drug effect is produced only when an exposure (both amount and duration) occurs that is sufficient to produce a drug-receptor interaction capable of modulating the cellular milieu and inducing a physiologic response. Thus, exposure-response relationships for a given drug represent an interface between pharmacokinetics and pharmacodynamics, which can be simply conceptualized by consideration of 2 profiles: plasma concentration vs effect (Fig. 73.1) and plasma concentration vs time (Fig. 73.2).

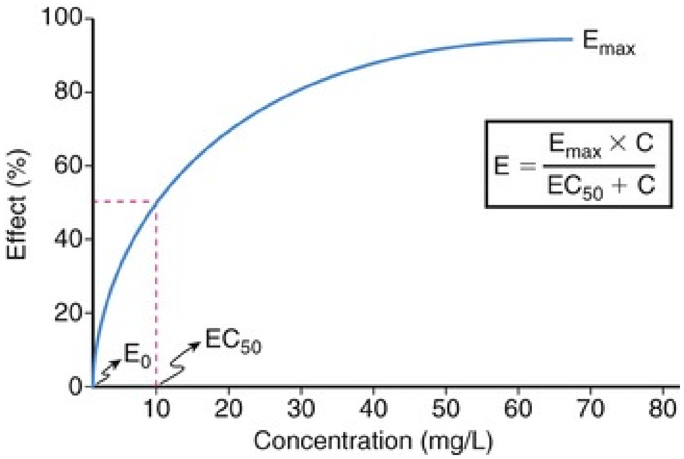

FIG. 73.1 **Plasma concentration vs effect curve. The percent effect is measured as a function of increasing drug concentration in the plasma. E_0 , Dose at which no effect is seen in the population; EC_{50} , dose of a drug required to produce a specified effect in 50% of the population; E_{max} , concentration associated with the maximal effect that can be produced by a drug. (From Abdel-Rahman SM, Kearns GL: The pharmacokinetic-pharmacodynamic interface: determinants of anti-infective drug action and efficacy in pediatrics. In Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors: *Textbook of pediatric infectious disease,* ed 6, Philadelphia, 2009, Saunders-Elsevier, pp 3156–3178; reproduced with permission.)**

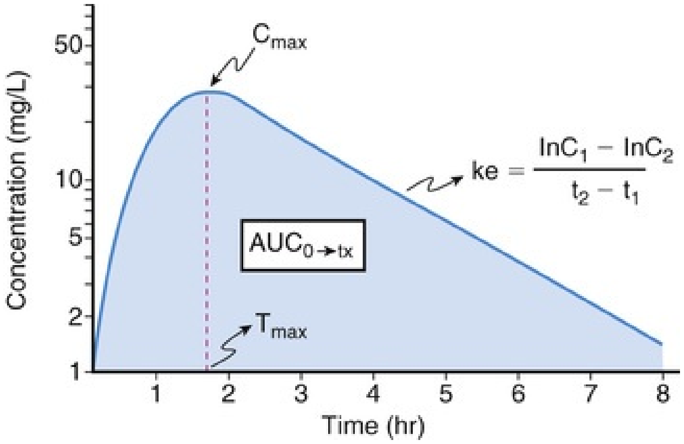

FIG. 73.2 **Semilogarithmic plot of the plasma concentration vs time curve for a hypothetical drug following extravascular administration. The area under the plasma level-time curve (AUC) is a concentration- and time-dependent measure of systemic drug exposure. After administration, the drug is absorbed and reaches the maximal concentration (C_{max}) at its peak time (T_{max}). Following completion of drug absorption and distribution, plasma drug concentrations decline in an apparent monoexponential manner in which the slope of the apparent elimination phase represents the apparent elimination rate constant (ke). (From Abdel-Rahman SM, Kearns GL: The pharmacokinetic-pharmacodynamic interface: determinants of anti-infective drug action and efficacy in pediatrics. In Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors: *Textbook of pediatric infectious disease,* ed 6, Philadelphia, 2009, Saunders-Elsevier, pp 3156–3178; reproduced with permission.)**

The relationship between drug concentration and effect for most drugs is not linear (Fig. 73.1). At a drug concentration of zero, the effect from the drug is generally zero or not perceptible (E_0). After drug administration and with dose escalation, the concentration increases, as does the effect, first in an apparent linear fashion (at low drug concentrations), followed by a nonlinear increase in effect to an asymptotic point in the relationship where a maximal effect (E_{max}) is attained that does not perceptibly change with further increases in drug concentration. The point in the concentration-effect relationship where the observed effect represents 50% of the E_{max} is defined as **EC_{50}** , a common pharmacodynamic term used to compare concentration-effect relationships between patients (or research participants) and between drugs that may be in a given drug class.

Because it is rarely possible to measure drug concentrations at or near the receptor, it is necessary to utilize a surrogate measurement to assess **exposure-response relationships** . In most cases this surrogate is represented by the plasma drug concentration vs time curve. For drugs whose pharmacokinetic properties are best described by first-order (vs zero- or mixed-order) processes, a semilogarithmic plot of plasma drug concentration vs time data for an agent given by an extravascular route of administration (e.g., intramuscular, subcutaneous, intracisternal, peroral, transmucosal, transdermal, rectal) produces a pattern depicted by Fig. 73.2 . The ascending portion of this curve represents a time during which the liberation of a drug from its formulation, dissolution of the drug in a biologic fluid (e.g., gastric or intestinal fluid, interstitial fluid; a prerequisite for absorption), and absorption of the drug are rate limiting relative to its elimination. After the time (T_{max}) where maximal plasma concentrations (C_{max}) are observed, the plasma concentration decreases as metabolism and elimination become rate limiting; the terminal portion of this segment of the plasma concentration vs time curve is representative of drug elimination from the body. Finally, the area under the plasma concentration vs time curve (**AUC**), a concentration- and time dependent parameter reflective of the degree of systemic exposure from a given drug dose, can be determined by integrating the plasma concentration data over time.

Being able to characterize the pharmacokinetics of a specific drug allows the clinician to use the data to adjust “normal” dosing regimens and individualize them to produce the degree of systemic exposure associated with desired pharmacologic effects. For drugs where a therapeutic plasma concentration range or “target” systemic exposure (i.e., AUC) is known, a priori knowledge of pharmacokinetic parameters for a given population or patient within a population can facilitate the selection of a drug dosing regimen. Along with information on the pharmacodynamic behavior of a drug and the status of the patient (e.g., age, organ function, disease state, concomitant medications), the application of pharmacokinetics allows the practitioner to exercise a real degree of adaptive control over therapeutic decision-making through the selection of a drug and dosing regimen with the greatest likelihood of producing both efficacy and safety.

Impact of Ontogeny on Drug Disposition

Development represents a continuum of biologic events that enable adaptation, somatic growth, neurobehavioral maturation, and eventually reproduction. The impact of development on the pharmacokinetics of a given drug is determined to a great degree by age-related changes in body composition and the acquisition of function in organs and organ systems important in determining drug metabolism and excretion. Although it is often convenient to classify pediatric patients on the basis of postnatal age in providing drug therapy, with neonates ≤1 mo of age, infants 1-24 mo, children 2-12 yr, and adolescents 12-18 yr, it is important to recognize that the changes in physiology are not linearly related to age and may not correspond to these age-defined breakpoints. In fact, the most dramatic changes in drug disposition occur during the 1st 18 mo of life, when the acquisition of organ function is most dynamic. It is important to note that the pharmacokinetics of a given drug may be altered in pediatric patients because of *intrinsic* (e.g., gender, genotype, ethnicity, inherited diseases) or *extrinsic* (e.g., acquired diseases, xenobiotic exposure, diet) factors that may occur during the 1st 2 decades of life.

Selection of an appropriate drug dose for a neonate, infant, child, or adolescent requires an understanding of the basic pharmacokinetic properties of a given compound and how the process of development impacts each facet of drug disposition. Accordingly, it is most useful to conceptualize pediatric pharmacokinetics by examining the impact of development on the physiologic variables that govern drug **absorption, distribution, metabolism, and elimination (ADME)** .

Pediatrics encompasses a broad range of ages at which certain stages of life profoundly influence drug response and disposition. Dramatic pharmacokinetic, pharmacodynamic, and psychosocial changes occur as preterm infants mature toward term, as infants mature through the 1st few years of life, and as children reach puberty and adolescence (Fig. 73.3). To meet the needs of these different pediatric groups, different formulations are needed for drug delivery that can influence drug absorption and disposition, and different psychosocial issues influence compliance, timing of drug administration, and reactions to drug use. These additional factors must be considered in conjunction with known pharmacokinetic and pharmacodynamic influences of age when developing an optimal, patient-specific drug therapy strategy.

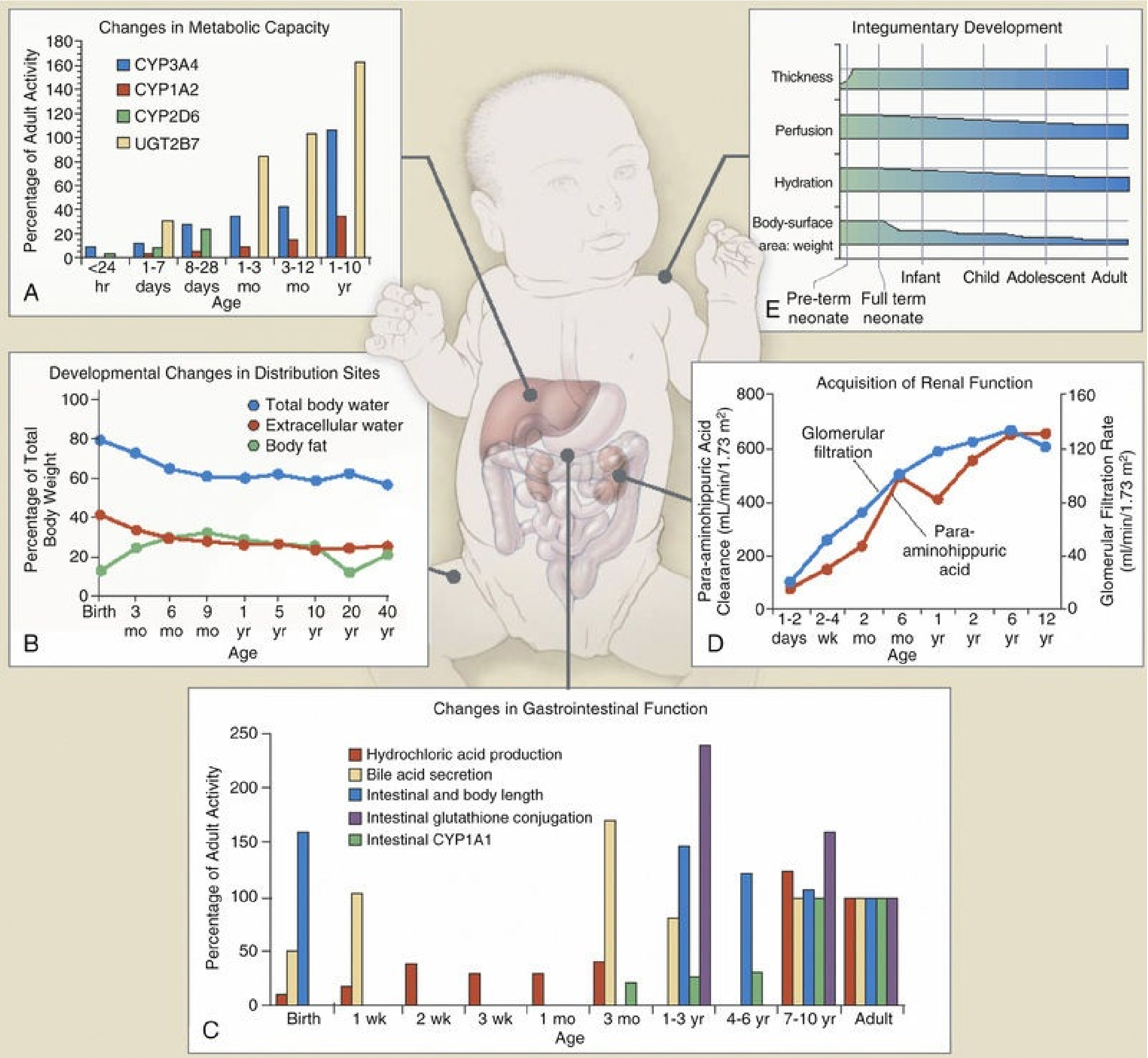

FIG. 73.3 Developmental changes in physiologic factors that influence drug disposition in infants, children, and adolescents. Physiologic changes in multiple organ systems during development are responsible for age-related differences in drug disposition. As reflected by panel A, the activity of many cytochrome P450 (CYP) isoforms and a single glucuronosyltransferase (UGT) isoform is markedly diminished during the 1st 2 mo of life. In addition, the acquisition of adult activity over time is enzyme and isoform specific. Panel B shows age-dependent changes in body composition, which influence the apparent volume of distribution of drugs. Infants in the 1st 6 mo of life have markedly expanded total-body water and extracellular water, expressed as a percentage of total body weight, compared with older infants and adults. Panel C summarizes the age-dependent changes in both structure and function of the gastrointestinal tract. As with hepatic drug-metabolizing enzymes (A), the activity of CYP1A1 in the intestine is low during early life. Panel D shows the effect of postnatal development on the processes of active tubular secretion, represented by the clearance of paraaminohippuric acid and the glomerular filtration rate, both of which approximate adult activity by 6-12 mo of age. Panel E shows age dependence in the thickness, extent of perfusion, and extent of hydration of the skin and the relative size of the skin-surface area (reflected by the ratio of body surface area to body weight). Although skin thickness is similar in infants and adults, the extent of perfusion and hydration diminishes from infancy to adulthood. (From Kearns GL et al: Developmental pharmacology—drug disposition, action, therapy in infants and children, *N Engl J Med* 349:1160–1167, 2003. Copyright © 2003, reproduced with permission.)

Drug Absorption

Drug absorption mainly occurs through passive diffusion, but active transport or facilitated diffusion may also be necessary for drug entry into cells. Several physiologic factors affect this process, one or more of which may be altered in certain disease states (e.g., inflammatory bowel disease, diarrhea), and thus produce changes in drug bioavailability. The rate and extent of absorption can be significantly affected by a child's normal growth and development.

Peroral Absorption

The most important factors that influence drug absorption from the gastrointestinal (GI) tract are related to the physiology of the stomach, intestine, and biliary tract (Fig. 73.3*C* and Table 73.1). The rate and extent of peroral absorption of drugs depend primarily on the pH-dependent *passive diffusion* and *motility* of the stomach and intestinal tract, because both these factors will influence transit time of the drug. Gastric pH changes significantly throughout development, with the highest (alkaline) values occurring during the neonatal period. In the fully mature neonate the gastric pH ranges from 6-8 at birth and drops to 2-3 within a few hours of birth. However, after the 1st 24 hr of life, the gastric pH increases because of the immaturity of the parietal cells. As the parietal cells mature, the gastric acid secretory capacity increases (pH decreases) over the 1st few months of life, reaching adult levels by age 3-7 yr. As a result, the peroral bioavailability of acid-labile drugs (e.g., penicillin, ampicillin) is increased. In contrast, the absorption of weak organic acids (e.g., phenobarbital, phenytoin) is relatively decreased, a condition that may necessitate administration of larger doses in very young patients to achieve therapeutic plasma levels.

Table 73.1

Developmental Alterations in Intestinal Drug Absorption

PHYSIOLOGIC ALTERATION	NEONATES	INFANTS	CHILDREN
Gastric pH	>5	4 to 2	Normal (2-3)
Gastric emptying time	Irregular	Increased	Slightly increased
Intestinal motility	Reduced	Increased	Slightly increased
Intestinal surface area	Reduced	Near adult	Adult pattern
Microbial colonization	Reduced	Near adult	Adult pattern
Biliary function	Immature	Near adult	Adult pattern

Direction of alteration given relative to expected normal adult pattern.

Data from Morselli PL: Development of physiological variables important for drug kinetics. In Morselli PL, Pippenger CE, Penry JK, editors: *Antiepileptic drug therapy in pediatrics,* New York, 1983, Raven Press.

Gastric emptying time is prolonged throughout infancy and childhood as a result of reduced motility, which may impair drug passage into the intestine, where most absorption takes place. Gastric emptying rates reach or exceed adult values by 6-8 mo of life. As such, intestinal motility is important for the rate of drug absorption and, as with other factors, is dependent on the age of the child. Consequently, the rate of absorption of drugs with limited water solubility (e.g., phenytoin, carbamazepine) can be dramatically altered consequent to changes in GI motility. In older infants and young children, more rapid rates of intestinal drug transit can reduce the bioavailability for some drugs (e.g., phenytoin) and drug formulations (e.g., sustained-release) by reducing their residency time at the absorption surfaces in the small intestine.

Neonates, particularly premature neonates, have a reduced bile acid pool and biliary function, resulting in a decreased ability to solubilize and absorb lipophilic drugs. Biliary function develops in the 1st few months of life, but it may be difficult for the neonate and young infant to absorb fat-soluble vitamins because low concentrations of bile acids are necessary for their absorption.

Extravascular Drug Absorption

Intravenous (IV) drug administration is assumed to be the most dependable and accurate route for drug delivery, with a bioavailability of 100%. Absorption of drugs from tissues and organs (e.g., intramuscular, transdermal, rectal) can also be affected by development (Table 73.2). Intramuscular (IM) blood flow changes with age, which can result in variable and unpredictable absorption. Reduced muscular blood flow in the 1st few days of life, the relative inefficiency of muscular contractions (useful in dispersing an IM drug dose), and an increased percentage of water per unit of muscle mass may delay the rate and extent of drugs given intramuscularly to the neonate. Muscular blood flow increases into infancy, and thus the bioavailability of drugs given by the IM route is comparable to that seen in children and adolescents.

Table 73.2

Influence of Ontogeny on Drug Absorption

PHYSIOLOGIC ALTERATION	NEONATES	INFANTS	CHILDREN
Oral absorption	Erratic	Increased	Near adult
Intramuscular absorption	Variable	Increased	Near adult
Percutaneous absorption	Increased	Increased	Near adult
Rectal absorption	Very efficient	Efficient	Near adult

Direction of alteration given relative to expected normal adult pattern.

Data from Morselli PL: Development of physiological variables important for drug kinetics. In Morselli PL, Pippenger CE, Penry JK, editors: *Antiepileptic drug therapy in pediatrics,* New York, 1983, Raven Press.

In contrast, *mucosal* permeability (rectal and buccal) in the neonate is increased and thus may result in enhanced absorption by this route. *Transdermal* drug absorption in the neonate and very young infant is increased because of the thinner and more hydrated stratum corneum (Fig. 73.3*E*). In addition, the ratio of body surface area to body weight is greater in infants and children than in adults. Collectively, these developmental differences may predispose the child to increased exposure and risk for toxicity for drugs or chemicals placed on the skin (e.g., silver sulfadiazine, topical corticosteroids, benzocaine, diphenhydramine), with higher likelihood of occurrence during the 1st 8-12 mo of life.

Normal developmental differences in drug absorption from most all extravascular routes of administration can influence the dose–plasma concentration relationship in a manner sufficient to alter pharmacodynamics. The presence of disease states that influence a physiologic barrier for drug absorption or the time that a drug spends at a given site of absorption can further influence drug bioavailability and effect.

Drug Distribution

Drug distribution is influenced by a variety of drug-specific physiochemical factors, including the role of drug transporters, blood-tissue protein binding, blood-tissue pH, and perfusion. However, age-related changes in drug distribution are primarily related to developmental changes in body composition and the quantity of plasma proteins capable of drug binding. Age-dependent changes in the relative sizes of **body water** —*total body water* (TBW) and *extracellular water* (ECW)—and fat compartments may alter the apparent *volume of distribution* (VD) for a given drug. The absolute amounts and distribution of body water and fat depend on a child's age and nutritional status. Also, certain disease states (e.g., ascites, dehydration, burn injuries, skin disruption involving large surface area) can influence body water compartment sizes and thereby, further impact the VD for certain drugs.

Newborns have a much higher proportion of body mass in the form of water (approximately 75% TBW) than older infants and children (Fig. 73.3*B*). In addition, the percentage of ECW changes (decreases) from the newborn stage (approximately 45%) into adulthood (20–30%). In fact, the increase of TBW in the neonate is attributable to ECW. The reduction in TBW is rapid in the 1st year of life, with adult values (approximately 55%) achieved by approximately 12 yr of age. In contrast, the percentage of *intracellular water* (ICW) as a function of body mass remains stable from the 1st months of life through adulthood. The impact of developmental changes in body water spaces are exemplified by drugs such as the aminoglycoside antibiotics; compounds that distribute predominantly throughout the extracellular fluid space and have a higher VD (0.4-0.7 L/kg) in neonates and infants than in adults (0.2-0.3 L/kg).

Body fat percentage and composition increase during normal development. The body fat percentage in a neonate is approximately 16% (60% water and 35% lipid). Despite the relatively low body fat content in the neonate, it is important to note that the lipid content in the developing central nervous system (CNS) is high, which has implications for the distribution of lipophilic drugs (e.g., propranolol) and their CNS effects during this period. The body fat percentage tends to increase up to about age 10 yr, then changes composition with respect to puberty and sex to approach adult body fat composition (26% water and 71% lipid). In addition, a sex difference exists as the child transitions into adolescence. Whereas the total body fat in males is reduced to 50% between 10 and 20 yr of life, the reduction in females is not as dramatic and decreases 28–25% during this same developmental stage.

Albumin, total proteins, and total globulins (e.g., α_1 -acid glycoprotein) are the most important circulating proteins responsible for **drug binding** in plasma. The absolute concentration of these proteins is influenced by age, nutrition, and disease (Table 73.3). The concentrations of almost all circulating plasma proteins are reduced in the neonate and young infant (approximately 80% of adult) and reach adult values by 1 yr of age. A similar pattern of maturation is observed with α_1 -acid glycoprotein (an acute-phase reactant capable of binding basic drugs), for which neonatal plasma concentrations are approximately 3 times lower than in maternal plasma and attain adult values by approximately 1 yr of age.

Table 73.3

Factors Influencing Drug Binding in Pediatric Patients

PHYSIOLOGIC ALTERATION	NEONATES	INFANTS	CHILDREN
Plasma albumin	Reduced	Near adult	Near adult
Fetal albumin	Present	Absent	Absent
Total proteins	Reduced	Decreased	Near adult
Total globulins	Reduced	Decreased	Near adult
Serum bilirubin	Increased	Normal	Adult pattern
Serum free fatty acids	Increased	Normal	Adult pattern

Direction of alteration given relative to expected normal adult pattern.

Data from Morselli PL: Development of physiological variables important for drug kinetics. In Morselli PL, Pippenger CE, Penry JK, editors: *Antiepileptic drug therapy in pediatrics,* New York, 1983, Raven Press.

The extent of drug binding to proteins in the plasma may influence distribution characteristics. Only free, unbound drug can be distributed from the vascular space into other body fluids and, ultimately, to tissues where drug-receptor interaction occurs. Drug protein binding depends on a number of age-related variables, including the absolute amount of proteins and their available binding sites, the conformational structure of the binding protein (e.g., reduced binding of acidic drugs to glycated albumin in patients with poorly controlled diabetes mellitus), the affinity constant of the drug for the protein, the influence of pathophysiologic conditions that either reduce circulating protein concentrations (e.g., ascites, major burn injury, chronic malnutrition, hepatic failure) or alter their structure (e.g., diabetes, uremia), and the presence of endogenous or exogenous substances that may compete for protein binding (i.e., protein displacement interactions).

Developmentally associated changes in drug binding can occur because of altered protein concentrations and binding affinity. Circulating fetal albumin in the neonate has significantly reduced binding affinity for acid drugs such as phenytoin, which is extensively (94–98%) bound to albumin in adults, compared to 80–85% in the neonate. The resultant 6-8-fold difference in the free fraction can result in CNS adverse effects in the neonate when total plasma phenytoin concentrations are within the generally accepted “therapeutic range” (10-20 mg/L). The importance of reduced drug-binding capacity of albumin in the neonate is exemplified by interactions between endogenous ligands (e.g., bilirubin, free fatty acids) and drugs with greater binding affinity (e.g., ability of sulfonamides to produce kernicterus).

Drug transporters such as P-glycoprotein and multidrug-resistant proteins 1 and 2 can influence drug distribution. These drug transporters can greatly influence the extent that drugs cross membranes in the body and whether drugs can penetrate or are secreted from the target sites (inside cancer cells or microorganisms or crossing the blood-brain barrier). Thus, drug resistance to cancer chemotherapy, antibiotics, or epilepsy may be conferred by these drug transport proteins and their effect on drug distribution. Growing evidence on the ontogeny of drug transport proteins demonstrates their presence as early as 12 wk gestation and low levels in the neonatal period, which rapidly increase to adult values by 1 to 2 yr of age, depending on the transporter. In addition, genetic variation can affect drug transporter expression and function but may not be readily apparent until adult levels are obtained (see Chapter 72).

Drug Metabolism

Metabolism reflects the biotransformation of an endogenous or exogenous molecule by one or more enzymes to moieties that are more hydrophilic and thus can be more easily eliminated by excretion, secretion, or exhalation. Although metabolism of a drug generally reduces its ability to produce a pharmacologic action, metabolism also can result in metabolites that have significant potency and thereby contribute to the drug's overall pharmacodynamic profile (e.g., biotransformation of the tricyclic antidepressant amitriptyline to nortriptyline; codeine to morphine; cefotaxime to desacetyl cefotaxime; theophylline to caffeine). In the case of prodrugs (e.g., zidovudine, enalapril, fosphenytoin) or some drug salts or esters (e.g., cefuroxime axetil, clindamycin phosphate), biotransformation is required to produce a pharmacologically active moiety. Finally, for some drugs, cellular injury and associated adverse reactions are the result of drug metabolism (e.g., acetaminophen hepatotoxicity, Stevens-Johnson syndrome associated with sulfamethoxazole).

The primary organ responsible for drug metabolism is the liver, although the kidney, intestine, lung, adrenals, blood (phosphatases, esterases), and skin can also biotransform certain compounds. Drug metabolism occurs primarily in the endoplasmic reticula of cells through 2 general classes of enzymatic processes: phase I (nonsynthetic) and phase II (synthetic) reactions. **Phase I** reactions include oxidation, reduction, hydrolysis, and hydroxylation reactions. **Phase II** reactions primarily involve conjugation with an endogenous ligand (e.g., glycine, glucuronide, glutathione or sulfate). Many drug-metabolizing enzymes demonstrate an ontogenic profile with generally low activity at birth and maturation over months to years (Table 73.4 and Fig. 73.3*A*).

Table 73.4

Impact of Development on Drug Metabolism

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Cytochrome P450 activity	Reduced	Increased	Slightly increased
Phase II enzyme activity	Reduced	Increased	Near adult
Blood esterase activity	Reduced	Normal (by 1 yr)	Adult pattern
Presystemic enzyme activity	Reduced	Increased	Near adult

Direction of alteration given relative to expected normal adult pattern.

Data from Morselli PL: Development of physiological variables important for drug kinetics. In Morselli PL, Pippenger CE, Penry JK, editors: *Antiepileptic drug therapy in pediatrics,* New York, 1983, Raven Press.

Many enzymes are capable of catalyzing the biotransformation of drugs and xenobiotics, but quantitatively the most important are represented by cytochrome P450 (**CYP**), a supergene family with at least 16 primary enzymes. The specific CYP isoforms responsible for the majority of human drug metabolism are represented by CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These enzymes represent the products of genes that in some cases are polymorphically expressed, with allelic variants producing enzymes generally resulting in either no or reduced catalytic activity (a notable exception being the **17* allele of CYP2C19, which may have increased activity) (see Chapter 72). At birth the concentration of drug-oxidizing enzymes in fetal liver (corrected for liver weight) appears similar to that in adult liver. However, the activity of these oxidizing enzyme systems is reduced, which results in slow clearance (and prolonged elimination) of many drugs that are substrates for them (e.g., phenytoin, caffeine, diazepam). Postnatally, the hepatic CYPs appear to mature at different rates. Within hours after birth, CYP2E1 activity increases rapidly, with CYP2D6 being detectable soon thereafter. CYP2C (CYP2C9 and CYP2C19) and CYP3A4 are present within the 1st mo of life, a few months before CYP1A2. CYP3A4 activity in young infants may exceed that observed in adults, as reflected by the clearance of drugs that are substrates for this enzyme (e.g., cyclosporine, tacrolimus).

Compared to phase I drug-metabolizing enzymes, the impact of development on the activity of phase II enzymes (acetylation, glucuronidation, sulfation) is not characterized as well. Phase II enzyme activity is decreased in the newborn and increases into childhood. Conjugation of compounds metabolized by isoforms of glucuronosyltransferase (**UGT**) (e.g., morphine, bilirubin, chloramphenicol) is reduced at birth but can exceed adult values by 3-4 yr of age. Also, the ontogeny of UGT expression is isoform specific. Newborns and infants primarily metabolize the common analgesic acetaminophen by sulfate conjugation, since the UGT isoforms responsible for its glucuronidation (UGT1A1 and UGT1A9) have greatly reduced activity. As children age, the glucuronide conjugate becomes predominant in the metabolism of therapeutic doses of acetaminophen. In contrast, the glucuronidation of morphine (a UGT2B7 substrate) can be detected as early as 24 wk gestation.

The activity of certain hydrolytic enzymes, including blood esterases, is also reduced during the neonatal period. Blood esterases are important for the metabolic clearance of cocaine, and the reduced activity of these plasma esterases in the newborn may account for the delayed metabolism (prolonged effect) of local anesthetics in the neonate. In addition, this may account for the prolonged effect that cocaine has on the fetus with prenatal exposures. Adult esterase activity is achieved by 10-12 mo of age.

The development of **presystemic clearance** or “first-pass” metabolism is unclear given the involvement of multiple enzymes and transporters in the small intestine, many of which have patterns of developmental expression that may be more or less concordant. However, given that the activity of almost all drug-metabolizing enzymes is markedly reduced in the neonate, the extent of bioavailability of drugs given by the peroral route that may be subjected to significant presystemic clearance in older children and adults would appear to be greatly increased during the 1st days to weeks of life. It is important for the clinician to recognize that estimates of bioavailability for a host of drugs available in reference texts and therapeutic compendia are most often derived from studies conducted in young adults. Thus, estimates of the rate and extent of absorption (including a propensity to be affected by presystemic clearance) from adults cannot be accurately used to extrapolate how a peroral drug dose may need to be age-adjusted for a neonate or infant.

With regard to the impact of development on drug metabolism, it must be recognized that most therapeutic drugs are polyfunctional substrates for a host of enzymes and transporters. It is the isoform-specific ontogenic profile (Fig. 73.3) that must be considered in the context of deducing how development can affect the metabolic portion of drug clearance. True developmental dependence of drug clearance must also consider the role of pharmacogenetic constitution on the activity of enzymes and transporters (see Chapter 72) and the impact of ontogeny on the nonmetabolic routes (e.g., renal drug excretion, salivary/biliary drug excretion, pulmonary drug excretion), which contribute to the overall drug clearance (Total CL = $CL_{hepatic} + CL_{renal} + CL_{nonrenal}$).

Renal Drug Elimination

The kidney is the primary organ responsible for the elimination of drugs and their metabolites. The development of renal function begins during early fetal development and is complete by early childhood (Fig. 73.3*D* and Table 73.5). Total renal drug clearance (CL_{renal}) can be conceptualized by considering the following equation:

Table 73.5

Impact of Development on Renal Drug Elimination

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Glomerular filtration	Reduced	Normal (by 1 yr)	Adult pattern
Active tubular secretion	Reduced	Near normal	Adult pattern
Active tubular reabsorption	Reduced	Near normal	Adult pattern
Active drug excretion	Reduced	Near normal	Adult pattern
Passive drug excretion	Reduced	Increased	Adult pattern
Excretion of basic drugs	Increased	Increased	Near normal

Direction of alteration given relative to expected normal adult pattern.

Data from Morselli PL: Development of physiological variables important for drug kinetics. In Morselli PL, Pippenger CE, Penry JK, editors: *Antiepileptic drug therapy in pediatrics,* New York, 1983, Raven Press.

$$CL_{renal} = (GFR + ATS) - ATR$$

where glomerular filtration rate (GFR), active tubular secretion (ATS), and active tubular reabsorption (ATR) of drugs can contribute to overall clearance. As for hepatic drug metabolism, only free (unbound) drug and metabolite can be filtered by a normal glomerulus and secreted or reabsorbed by a renal tubular transport protein.

Renal clearance is limited in the newborn because of anatomic and functional immaturity of the nephron unit. In both the term and the preterm neonate, GFR averages 2-4 mL/min/1.73 m^2 at birth. During the 1st few days of life, a decrease in renal vascular resistance results in a net increase in renal blood flow and a redistribution of intrarenal blood flow from a predominantly medullary to a cortical distribution. All these changes are associated with a commensurate increase in GFR. In term neonates, GFR increases rapidly over the 1st few months of life and approaches adult values by 10-12 mo (Fig. 73.3*D*). The rate of GFR acquisition is blunted in preterm neonates because of continued nephrogenesis in the early postnatal period. In young children 2-5 yr of age, GFR may exceed adult values, especially during periods of increased metabolic demand (e.g., fever).

In addition, a relative glomerular/tubular imbalance results from a more advanced maturation of glomerular function. Such an imbalance may persist up to 6 mo of age and may account for the observed decrease in the ATS of drugs commonly used in neonates and young infants (e.g., β-lactam antibiotics). Finally, some evidence suggests that ATR is reduced in neonates and that it appears to mature at a slower rate than the GFR.

Altered renal drug clearance in the newborn and infants result in the different dosing recommendations seen in pediatrics. The aminoglycoside antibiotic gentamicin provides an illustrative example. In adolescents and young adults with normal values for GFR (85-130 mL/min/1.73 m^2), the recommended dosing interval for gentamicin is 8 hours. In young children who may have a GFR >130 mL/min/1.73 m^2 , a gentamicin dosing interval of every 6 hr may be necessary in selected patients who have serious infections that require maintaining steady-state peak and trough plasma concentrations near the upper boundary of the recommended therapeutic range. In contrast, to maintain “therapeutic” gentamicin plasma concentrations in neonates during the 1st few weeks of life, a dosing interval of 18-24 hr is required.

The impact of developmental differences in GFR on the elimination characteristics of a given drug can be assessed by estimating the apparent elimination rate constant *(Kel)* for a drug by using the following equation:

$$\begin{aligned}&\text{Kel (in reduced renal function)}\\&\quad = \text{Kel}_{\text{normal}} \bullet \{[(\text{GFR}_{\text{observed}}/\text{GFR}_{\text{normal}}) - 1] \bullet \text{Fel}\} + 1\end{aligned}$$

where the *Fel* represents the fraction of the drug excreted unchanged in an adult with normal renal function; $GFR_{observed}$ is the value calculated (from creatinine clearance or age-appropriate estimation equation) for the patient (in mL/min/1.73 m^2); and GFR_{normal} is the average value considered for a healthy adult (120 mL/min/1.73 m^2). Kel_{normal} is estimated from the average elimination $T_{1/2}$ for a drug taken from the medical literature using the following equation:

$$Kel_{normal}\,[hr^{-1}] = 0.693/T_{1/2\ normal}\,[hr]$$

Likewise, the elimination half-life ($T_{1/2}$) for a drug in patients with reduced renal function can be estimated as follows:

$$T_{1/2}\ (\text{in reduced renal function}) = 0.693/Kel\ (\text{in reduced function})$$

An estimate of the drug elimination $T_{1/2}$ in patients with reduced renal function with knowledge of the desired interdose excursion in steady-state plasma concentrations can allow determination of the desired drug dosing interval.

Impact of Ontogeny on Pharmacodynamics

Although it is generally accepted that developmental differences exist in drug action, there is little evidence of true age related pharmacodynamic variation among children of differing age-groups and adults. **Drug action** is typically mediated by interaction of a small molecule with 1 or more receptors that may be located either on or in a cell. **Drug effect** is mediated at the receptor by 4 main biochemical mechanisms involved in cell signaling. *Binding* of the receptors on the cell surface or within the cell activates downstream pathways that mediate a specific cellular action. Some receptors act as *enzymes*, whereby on ligand binding the enzyme phosphorylates downstream effector proteins, thereby activating or inhibiting a cellular signal (e.g., guanosine triphosphate–binding regulatory protein, also known as G-protein–coupled receptors). Other receptors mediate their actions through *ion channels*, whereby on ligand binding the cell's membrane potential or ionic composition is altered, allowing cellular activation or inhibition. Lastly, some receptors act as *transcription factors,* which when bound by a ligand activate transcription of specific genes within the cell.

Drug action is concentration dependent, with onset and offset generally associated with appearance and disappearance, respectively, of the drug at the receptor(s) in an amount that is sufficient to initiate the cascade of biologic effects that terminate in drug action (see Fig. 73.1). The *minimum effective concentration* of a drug is that observed with the immediate onset of effect, whereas the duration of action is predicated on the maintenance of drug concentrations at the receptor within a range associated with the desirable pharmacologic action(s). Receptor binding by a drug may have varying consequences. Drugs that are **agonists** bind to and activate the receptor, directly or indirectly achieving the desired effect. An agonist binding to a receptor results in the same biologic effect as binding of the endogenous ligand. **Partial agonist** binding results in activation of the receptor, but maximal effect is not achieved, even in the presence of receptor saturation. **Antagonists** bind to a receptor, preventing binding of other molecules, thereby preventing activation of the receptor.

Evidence supports developmental differences in receptor number, density, distribution, function, and ligand affinity for some drugs. Human data are limited, so much of what is known has been derived from animal studies. In the CNS, unique developmental aspects of drug-receptor interaction affect therapeutic efficacy of both analgesics and sedatives in neonates. The number of γ-aminobutyric acid (GABA) receptors, which mediate inhibitory signal transduction in the CNS, is reduced in newborns compared to adults. Functional differences have also been observed between neonatal and adult brain on GABA receptor activation. These changes may explain observed differences in dosing of drugs such as midazolam in infants and in part may explain seizures experienced by infants on benzodiazepine exposure. Another CNS example is the μ-opioid receptor, whereby receptor number is reduced in newborns and receptor distribution also differs between newborns and adults.

For the clinician, consideration of age-dependent differences in pharmacodynamics is particularly relevant when associated with **adverse drug reactions** (e.g., higher incidence of valproic acid-associated hepatotoxicity in young infants; greater frequency of paradoxical CNS reactions to diphenhydramine in infants; weight gain associated with atypical antipsychotic drugs in adolescents) or when drugs have a narrow therapeutic index (Fig. 73.4). The age-associated pharmacodynamics of warfarin observed in children with congenital heart disease is related to developmental differences in serum concentrations of vitamin K–dependent coagulation factors (II, VII, IX, X) between children and adults. Developmental differences in drug action have been observed between prepubertal children and adults in regard to warfarin action. Prepubertal children exhibit a more profound response, demonstrated by lower protein C concentration, prothrombin fragments 1 and 2, and greater rise in INR, to comparable doses of warfarin. Thus, when age-dependent pharmacodynamics of a given drug is evident, the use of simple allometric approaches for “scaling” the pediatric dose from the usual adult dose may not produce the desired pharmacologic effects. Pharmacokinetic and pharmacodynamic (PK/PD) modeling techniques that use known developmental changes in body composition, enzyme function, renal function, effector proteins, and receptors are being used to predict optimal dosing in children. However, data regarding differences in pharmacodynamic response across the age continuum remain lacking and limit the application of these techniques to accurately predict dose-response relationships in the pediatric population.

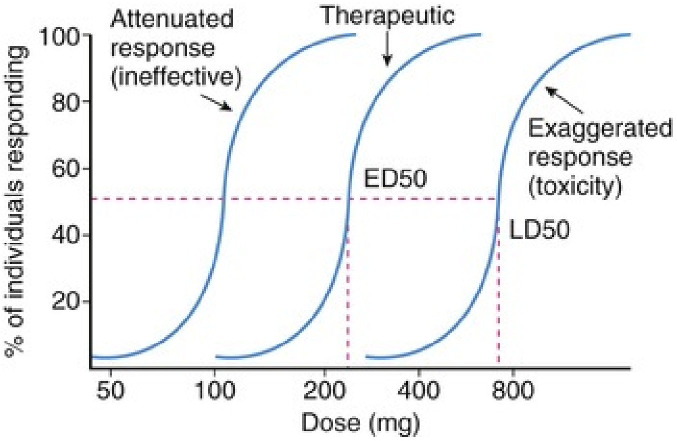

FIG. 73.4 Quantal dose–effect curve. Age-related pharmacokinetic variation may result in alterations in drug concentration at the receptor resulting in ineffective, therapeutic or toxic results. LD50, Dose at which 50% of the population is lethal. The ratio of the LD50 to the ED50 is an indication of the therapeutic index, which is a reflection of drug potency relative to its concentration.

Surrogate Endpoints

Biomarkers and surrogate endpoints (markers) are ideally simple, reliable, inexpensive, and easily obtainable measures of a biologic response or disease phenotype that can be used to facilitate either clinical research or patient care. **Biomarkers** have been defined by the U.S. National Institutes of Health as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” A **surrogate endpoint** is defined “as a biomarker that is intended to substitute for a specific clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.” Reliable surrogate endpoints predict a specific physiologic event (e.g., intraesophageal pH to assess gastroesophageal reflux) that may be used diagnostically, prognostically, or in predicting a specific drug response (therapeutic, subtherapeutic, or adverse) or potentially the impact of ontogeny on pharmacodynamics. Specific examples of surrogate endpoints used in pediatric pharmacology include measurement of esophageal pH to assess the action of prokinetic or acid-modifying drugs and pulmonary function tests (e.g., FEV_1) to evaluate the effect of drugs on pulmonary function in patients with conditions such as asthma and cystic fibrosis. Biomarkers used in pediatric studies to assess drug disposition or effect include hemoglobin A_{1c} plasma concentration (to assess efficacy of peroral hypoglycemic agents), urinary leukotriene concentrations (to assess effects of nonsteroidal antiinflammatory drugs), and minimal inhibitory concentration (MIC) and minimal bacteriocidal concentration (MBC) of drugs to select antiinfective agents.

Additional Considerations in Pediatric Therapeutics

Pediatric Dose and Regimen Selection

Incomplete developmental profiles for hepatic and extrahepatic drug-metabolizing enzymes and drug transporters that may influence drug clearance and bioavailability prevent the use of simple formulas or allometric scaling for effective pediatric dose prediction. Although these approaches may have some clinical utility in older children (>8 yr) and adolescents whose organ function and body composition approximate that of young adults, their utility is severely limited in neonates, infants, and young children, in whom ontogeny produces dramatic differences in drug disposition. This is especially problematic for therapeutic drugs whose doses cannot be easily individualized using patient-specific pharmacokinetic data obtained from therapeutic drug monitoring. In the absence of such pharmacokinetic data or established pediatric dosing guidelines, alternate methods must often be employed.

To date, >20 different approaches for initial selection of a drug dose for pediatric patients have been described. The majority use either total body weight (BW) or body surface area (BSA) as surrogates that reflect the developmental changes of body composition or organ function, which collectively are the major determinants of drug disposition. Selection based on BW or BSA will generally produce similar relationships between drug dose and resultant plasma concentration, except for those drugs whose apparent volume of distribution (VD) corresponds to the extracellular fluid pool (i.e., VD <0.3 L/kg), in which a BSA-based approach is preferable. In contrast, for drugs whose apparent VD exceeds the extracellular fluid space (i.e., VD >0.3 L/kg), a BW-based approach for dose selection is preferable, which is the most frequently used method in pediatrics. When the pediatric dose for a given drug is not known, these principles can be used to best approximate a proper dose for the initiation of treatment, as illustrated by the following equations:

$$\begin{aligned}&\text{Child dose (if VD} < 0.3\ \text{L/kg)}\\&\quad = (\text{Child BSA in m}^2/1.73\ \text{m}^2) * \text{Adult dose}\end{aligned}$$

$$\text{Infant dose (if VD} \geq 0.3\ \text{L/kg)} = (\text{Infant BW in kg}/70\ \text{kg}) * \text{Adult dose}$$

It should be noted that this approach assumes that the child's weight, height, and body composition are age appropriate and normal, and that the “reference” normal adult has a BW and BSA of 70 kg and 1.73 m^2 , respectively. It is useful only for selection of dose size and does not offer information regarding dosing interval, because the equations contain no specific variable that describes potential age-associated differences in drug clearance.

Similar to obese adults, **obesity in children** would be expected to result in to alterations in drug pharmacokinetics. Unfortunately, few data exist on drug dosing in obese pediatric patients. Alterations in VD, which is important for loading-dose calculations, is related to the lipophilicity or water solubility of the medication to be administered. Some limited data are available on the impact of obesity on VD in children with the antibiotics cefazolin and tobramycin. The impact of obesity in pediatric patients on absorption and drug metabolism (phase I and II pathways) is not known. No validated estimate of GFR in obese children exists, but current information suggests that serum creatinine concentration may be higher or no different in obese children than in those of normal weight. Drug dosing in normal-weight children typically uses age-based dosing, allometric scaling, BSA, or BW. These same estimates can be used in obese children, although use of an adjusted BW should be considered. Variations on weight used in adults include ideal body weight (IBW), lean body weight, adjusted body weight, and total body weight. However, in children, standards for calculating adjusted weights may not be standardized (e.g., IBW). When dosing medications in obese children, it is important to consider information regarding drug dosing in obese adults, recommended adult maximum doses, and the physiochemical properties of the drug to be given.

In neonates and young infants with developmental immaturity in GFR or ATS, it is often necessary to adjust the "normal" dosing interval (i.e., that used for older infants and children who have attained developmental competence of renal function) for drugs with significant (>50%) renal elimination, to prevent excessive drug accumulation (and possible associated toxicity) with administration of multiple doses. To accomplish this therapeutic goal, it is necessary to estimate the apparent elimination half-life ($T_{1/2}$) of the drug (see equations earlier).

Therapeutic Drug Monitoring

Clinically, systemic drug exposure is usually evaluated through assessing the plasma drug concentration, a surrogate measurement for a drug reaching its pharmacologic receptor(s). In the patient, drug level monitoring can be used to facilitate 2 approaches for evaluating the dose-concentration-effect relationship: single-concentration (e.g., trough or random level) therapeutic drug monitoring (TDM) and multilevel pharmacokinetic-based TDM. Both lead to dose individualization for a given patient.

Drug-level monitoring largely entails measurement of drug concentrations in plasma (primarily) or other biologic fluids at some point during a drug's dosing interval. These levels are then compared with those that are “desired” for a given drug based on published information and used to adjust the dose/dosing regimen. For *single* trough-level measurement (at the end of a dosing interval) or random-level measurement (nonspecific time point during a dosing interval), adjustment of the medications dose is done empirically without pharmacokinetic parameters. In using a TDM approach, it should be recognized that for many drugs which are therapeutically monitored in the clinical setting (e.g., aminoglycoside antibiotics, vancomycin, phenytoin, phenobarbital, cyclosporine, tacrolimus, mycophenolate mofetil, selected antiretroviral drugs, acyclovir), “desired” plasma concentrations are generally determined from studies in adult patients where drug disposition and disease states may be quite different from those in infants and children.

Clinical pharmacokinetics represents a proactive approach where *multiple* plasma drug concentrations are used to estimate pharmacokinetic parameters for a specific patient to a specific drug at that point in time (e.g., apparent elimination rate constant, elimination $T_{1/2}$, apparent VD, total plasma clearance, AUC), which are then used to calculate a dosing regimen required to attain a desired level of systemic exposure (e.g., AUC, steady-state peak/trough plasma drug concentrations) that would portend a desired pharmacologic response. Of these 2 approaches, the use of drug-level data for performing clinical pharmacokinetics provides the better approach for individualizing dose/dosing regimen and maintaining some adaptive control over the dose-concentration-effect relationship. This approach is particularly useful for patients who may have “abnormal” pharmacokinetics because of their age and/or disease states. Approaches used to enable the performance of clinical pharmacokinetics include the manual use of established formulas for calculating pharmacokinetic parameters (generally using a simple 1-compartment open model consequent to the few plasma drug-level observations obtained in clinical patient care) or computer-based algorithms (e.g., bayesian estimation, population-based pharmacokinetic approaches).

Common to both of the aforementioned approaches is the need to accurately assess plasma drug concentrations in a given patient. Fig. 73.5 represents a hypothetical general steady-state plasma concentration vs time profile for a drug given by an extravascular route, illustrating the following general principles to recognize and follow when plasma drug-level monitoring is used in patients as a “tool” to individualize drug treatment:

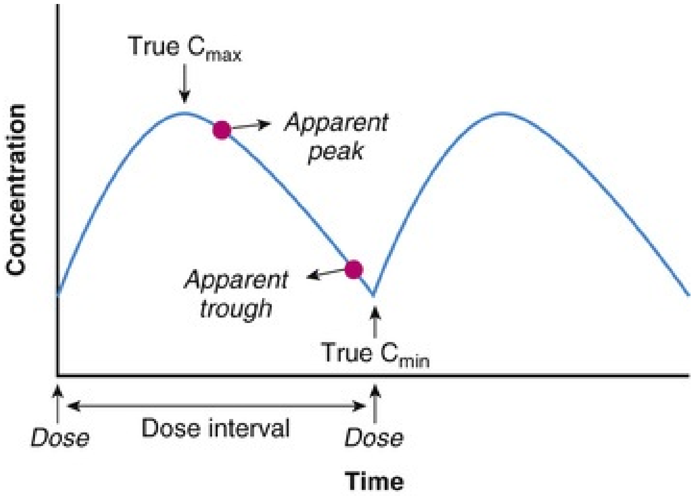

FIG. 73.5 Plasma concentration vs time profile for a hypothetical drug at steady state. When dose size, route of administration, time of administration, and dosing interval remain constant, the resultant true peak (C_{max}) and trough (C_{min}) plasma concentrations and AUC from dose to dose are identical. Apparent values for C_{max} and C_{min} are denoted to illustrate the potential difference from true values that can result when the actual times for obtaining samples for either therapeutic drug monitoring or clinical pharmacokinetic applications are not realized.

◆ When a drug reaches a pharmacokinetic steady state (a period corresponding to 5 times the apparent elimination $T_{1/2}$ for a given drug), both the excursion between the peak (C_{max}) and trough (C_{min}) plasma concentration and the AUC are identical between dose intervals provided that (1) the dose is not changed; (2) an exact dose-to-dose interval is maintained for drug administration; and (3) the route or rate of drug administration between dosing intervals has not changed.

◆ Steady-state plasma drug concentrations provide the best surrogate for assessing exposure-response relationships for a given drug. These drug concentrations provide the most accurate estimation of patient-specific pharmacokinetic parameters. Plasma concentrations assessed before the attainment of steady state can be useful for evaluating exaggerated drug response or predicting eventual steady-state drug levels and exposure.

◆ To reliably interpret any drug plasma concentration, it is imperative that the clinician know and consider the following:

1. The expected pharmacokinetic profile for a given drug (e.g., time after dosing required for completion of drug absorption [for extravascularly administered drugs] and distribution)
2. The exact time that the drug was administered
3. For drugs given by IV infusion, the total duration of infusion (including time required to flush the dose from the IV tubing)
4. Pertinent limitations of the analytic method used to measure the plasma drug level (e.g., range of linearity, potential for analytic interference from concomitant drugs)
5. The method used to obtain the blood specimen(s) used for plasma level determination (e.g., venous puncture vs cutaneous puncture; use of vascular

catheter different from one used for drug administration)

6. Whether the blood specimen was adequate for accurate drug-level measurement (e.g., sufficient volume, presence or absence of hemolysis or lipemia)
7. The *exact* time that the blood specimens were obtained in relationship to the time of drug administration and the drug dosing interval

This last point is illustrated by Fig. 73.5 , which denotes the “true” peak (C_{max}) and trough (C_{min}) plasma concentrations in relationship to apparent values. This situation frequently occurs when “peak” and “trough” blood levels are ordered, and nursing/phlebotomy procedures allow some period of leeway as to when they can be obtained. When such a discrepancy is realized, and the exact timing of the samples relative to dose administration is known, corrections can be made to insure pharmacokinetic parameters estimated from the data are accurate. If such a discrepancy is not realized, errant parameter estimation and dose regimen calculation/determination may result, thereby compromising safety or efficacy of drug treatment.

Drug Formulation and Administration

One of the more unique challenges in pediatric therapeutics is the drug formulation itself. Despite the increasing sensitivity for the need to study pediatric drugs before their use in children and to have available “pediatric-friendly” formulations, many drug products formulated only for adult use are routinely given to pediatric patients. Their use can result in inaccurate dosing (e.g., administration of a fixed dose to children with widely varying body weights), loss of desired performance characteristics of the formulation (e.g., crushing sustained-release tablet, cutting transdermal patch), and exposure of infants and children to excipients (e.g., binding agents, preservatives) in amounts capable of producing adverse effects.

Peroral Drug Administration

One of the principal determinants of peroral drug administration in children is the ability to get the drug into the body. Peroral formulations are often expelled by children because of poor taste and texture. This is a significant issue, especially when considering that taste sensation differs because of development and on an interindividual basis. Solid peroral formulations such as tablets and capsules are not easily administered to the majority of infants and children because of their inability to swallow them easily and safely. Incomplete development of swallowing coordination may result in choking or aspiration when solid peroral formulations are given to infants and small children. Further, solid peroral formulations limit the ability for dose titration and dosing flexibility. Drug developers are working to address this limitation with new techniques suitable for both oral and peroral drug administration that encompass both products (e.g., dispersible peroral tablets, oral films, titratable granules, oral melts) and drug administration devices (e.g., dosing straws, graduated cylinders for peroral granules).

With regard to dosing accuracy with peroral formulations, **liquids** (e.g., drops, solutions, syrups, suspensions, elixirs) are preferred for infants and young children. The utility of these formulations is often limited by palatability when taste-masking of the active ingredient(s) cannot be effectively achieved. In the case of suspension formulations, improper reconstitution and/or resuspension before dose administration can introduce problems related to accuracy of dosing. Other potential limitations of peroral liquid formulations (e.g., those that may be extemporaneously compounded by the pharmacist from drug powder or from solid peroral dosage forms of a given drug) include potential problems related to drug stability, contamination (chemical or bacterial), portability, and for some products the need for refrigeration.

Administration of liquid medications can be associated with risk if the device for administering the medication is not appropriate (e.g., use of a kitchen teaspoon vs 5.0 mL dosing spoon) or is used improperly to insure the drug dose is measured appropriately for the patient's age or weight. The low cost and convenience of hypodermic syringes has prompted many physicians and pharmacists to dispense them with liquid medications in order to improve accuracy. While this approach would seemingly be associated with greater accuracy in dosing, parents/caregivers can have difficulty in reading the graduations on a syringe, and the plastic caps on the plungers of syringes can produce a choking hazard for infants and young children. These problems can be obviated by education of parents/caregivers on how to reliably use peroral dosing syringes, which pharmacists should dispense with every liquid drug formulation.

Parenteral Drug Administration

In contrast to adults, in whom vascular access is relatively easy to obtain, difficulties are often present in the infant and young child, resulting from the smaller diameter of peripheral vessels (relative to size of IV cannula), developmentally associated differences in body composition (e.g., body fat distribution), and use of topical anesthetic agents, which can produce venous constriction. The small peripheral blood vessels in infants and young children can also limit the volume and rate of parenteral drug administration due to issues of capacity and with drugs capable of producing venous irritation, which induces infusion-related pain.

An underappreciated complicating issue for parenteral drug administration to infants is the relative lack of formulations in concentrations suitable for IV administration. Errors consequent to improper dilution of adult formulations necessary to ensure appropriate osmolarity and volume for IV administration (the most common resulting in a 10-fold overdose) are not uncommon. Morphine, a drug commonly used in neonates, infants, and children, is commonly available in an 8 mg/mL concentration. A usual 0.1 mg/kg morphine dose for a 1 kg infant using this formulation would require a nurse or pharmacist to accurately withdraw 0.013 mL and administer it into a length of IV tubing with a dead space volume that may exceed that of the dose by 100-fold. In this situation, accuracy of dose and infusion time can be significantly compromised. Although underdosing is often a serious problem when attempting to administer very small volumes, overdoses also occur from inaccurate extemporaneous dilutions. Moreover, attempts to compensate for the volumes present within the IV tubing further predispose the patient to receive an incorrect, possibly unsafe, dose. Whenever such concentrated drug formulations are the only source for use, appropriate alteration of the stock parenteral solution should be performed and manufactured by the pharmacy department. Also, many errors can be avoided by the use of standard dilutions that all practitioners are aware of and using standardized approaches for IV drug administration that minimize complications associated with unrealized drug dilution and errant infusion times (e.g., pediatric syringe pumps attached to low-volume tubing).

Although used rather infrequently, intramuscular (IM) drug administration offers a route of administration for many drugs when venous access is not immediately available or when a therapeutic drug regimen involves use of a single or limited number of doses. While appealing with respect to immediacy, this route of administration can be associated with problems (e.g., muscle/nerve damage, sterile abscess formation, variable rate of drug absorption because of developmental differences in vascular perfusion of muscle beds), especially in the neonate and small infant. Lastly, the decision to use the IM route must take into consideration the physicochemical properties (e.g., pH, osmolarity, solubility) of the drug formulation and any diluent used to prepare it.

Other Routes for Drug Administration

Neonates, infants, children, and adolescents with certain pulmonary conditions (e.g., reactive airway disease, viral-induced bronchiolitis, asthma, cystic fibrosis) frequently receive drugs (e.g., corticosteroids, β-adrenergic agonists, antimicrobial agents, mucolytic drugs) by **inhalation** . The pulmonary surface area in pediatric patients of all ages is a very effective, easily traversable barrier for drug absorption. Rate-limiting factors for pulmonary drug absorption include physicochemical factors associated with the drug and delivery system (e.g., particle size, diffusion coefficient, chemical stability of drug molecule in the lung) and physical factors that influence intrapulmonary drug disposition (e.g., active vs passive drug delivery to tracheobronchial tree, respiratory minute volume, internal airway diameter), many of which are developmentally determined. For drugs formulated for delivery using a metered-dose inhaler (either drug powder or suspended particles using a carrier gas), developmental factors (e.g., incoordination of device actuation with inhalation, inability to follow instructions for clearing of airway, passive inhalation with actuation of delivery device) either prevent their use (as in infants and small children) or limit the bioavailability of the drug to be administered. In these instances, specific devices (e.g., masks, spacer chambers) and methods of delivery (e.g., continuous aerosolization by mask) can be used to improve the efficiency of drug delivery and thus drug efficacy.

In pediatric patients, **percutaneous** drug administration is generally reserved for agents intended to produce a local effect within the dermis. Development has an impact on the barrier of the skin that, if not recognized and controlled for with proper drug administration techniques, can produce situations in which systemic toxicity can result. Similar therapeutic challenges occur when **transmucosal** routes (e.g., buccal, sublingual, rectal) are used for drug administration. Specifically, unpredictable systemic bioavailability may complicate treatment consequent to variability in the rate and/or extent of drug absorption. As a consequence, transmucosal drug administration to pediatric patients is no longer widely used as a matter of convenience but, rather, when the condition of the patient does not enable drug administration by the peroral or the parenteral routes. Direct **intraosseous** drug administration through puncture of the tibia is occasionally used in infants and small children for administration of drugs and crystalloid fluids given acutely during resuscitation efforts. It is particularly useful when vascular access sufficient for drug administration cannot be immediately accomplished, since the onset of action by the intraosseous route is comparable to that after IV administration.

Adherence and Compliance

The success of drug treatment in a pediatric patient depends on the successful administration of the drug. Physical and cognitive immaturity makes the infant and the child a dependent creature in almost all respects, including those related to therapeutic drug administration. Until a child reaches an age at which the child can physically self-administer a drug in an accurate, proficient manner and can mentally assume this responsibility (generally 7-14 yr of age, depending on the individual child), **compliance** with a drug regimen becomes the responsibility of an adult. In a hospital environment, compliance is ensured through the actions of physicians, nurses, and pharmacists who, collectively through an integrated system of medical care, assume this responsibility. On discharge, the responsibility is transferred to parents/guardians or other adult caregivers in an environment that is generally nonmedical. At this juncture, therapeutic compliance morphs into **adherence** , as defined by the potential for conflicting demands, such as multiple adult caregivers, different external environments (e.g., home, daycare, school), and parents tending to the needs of multiple children, to introduce variability (anticipated and unpredictable) in drug administration. Whether treatment is for a self-limiting (e.g., antibiotic administration) or chronic (e.g., asthma, diabetes) condition, challenges to therapeutic adherence can serve as rate-limiting events in the determination of drug safety and efficacy in infants and young children.

In contrast to the period encompassing infancy and childhood, adolescence poses its own unique challenges to therapeutic adherence. During this period, psychosocial maturation almost always lags behind physical maturation. Development of cognitive and physical skills in most adolescents enables them to self-administer a prescribed medication in a proper manner with little to no supervision. However, psychodynamic issues experienced by a substantial number of adolescents (e.g., complete understanding of the ramifications of undertreatment, disease progression, and roles of disease prevention and health maintenance; perceptions of immortality and associated lack of need for treatment; disorganized patterns of thinking capable of confounding treatment schedules; defiant/oppositional behavior toward authority figures) can often precipitate therapeutic failure, through either undertreatment or overtreatment, the latter occasionally leading to drug toxicity.

Unfortunately, the only approach that can be used to facilitate therapeutic compliance and adherence in the pediatric patient is the combination of *vigilance* (on behalf of all caregivers) and repetitive *education* coupled with positive reinforcement. When children reach the age of assent (generally by 7 yr in children who have normal neurobehavioral development), they have the beginning level of cognitive ability sufficient to engender understanding about their medical condition(s) and how effective treatment can be used to improve their life. Through diligent patient education and reeducation, older children and adolescents can assume a level of responsibility for active partnership in their overall medical management, one that will mature as educational efforts, driven by a shared desire for an optimal outcome, are regularly made.

Drug-Drug Interactions

Pharmacokinetic and pharmacodynamic properties of drugs may be altered when ≥2 drugs are administered to a patient (Table 73.6). Interactions largely occur at the level of drug *metabolism* but may occur at the level of drug *absorption* (e.g., inhibition of intestinal CYP3A4 activity by grapefruit juice or St. John's wort and consequent reduction in presystemic clearance of CYP3A4 substrates), distribution (e.g., displacement of warfarin plasma protein binding by ibuprofen with consequent increased hemorrhagic risk), or elimination (e.g., inhibition of

ATS of β-lactam antibiotics by probenecid). Also, drug-drug interactions may occur at the level of the *receptor* (through competitive antagonism); many of which are intentional and produce therapeutic benefit in pediatric patients (e.g., antihistamine reversal of histamine effects, naloxone reversal of opiate adverse effects).

Table 73.6

Mechanism of Drug Interactions [1]

	EXAMPLE DRUG COMBINATION	RESULT
PHARMACODYNAMIC		
Additive		Use of multiple drugs with similar adverse effect profiles can lead to additive effects:
	Fentanyl + midazolam Class 1A antiarrhythmic [2] + erythromycin [3] Vancomycin + an aminoglycoside [4]	Increased sedation Increased QT prolongation Increased potential for nephrotoxicity
Synergy	Penicillin + an aminoglycoside [4]	Improved bactericidal efficacy against some gram-positive organisms; penicillin inhibits bacterial cell wall synthesis, which for some gram-positive organisms can improve the intracellular penetration of the aminoglycoside
Antagonism	Opioid + naloxone	Competitive receptor antagonism; decreased efficacy of the opioid, reversal of sedation, respiratory depression, and hypotension
	Donepezil + an anticholinergic	Oppositional effects; acetylcholinesterase inhibitors such as donepezil increase acetylcholine concentrations by slowing the degradation of acetylcholine, and anticholinergic drugs antagonize the effect of acetylcholine
PHARMACOKINETIC		
Absorption	Inhibition of P-gp [5] :	
	Amiodarone + digoxin	Increased digoxin concentration; gut P-gp is an efflux transporter that takes drugs from cell cytoplasm and transports them back into the intestinal lumen for excretion, limiting bioavailability
	Complex formation:	
	Oral quinolone and tetracycline antibiotics + divalent/trivalent cations (eg, Ca^{2+}, Mg^{2+}, Fe^{3+}, Al^{3+})	Decreased antibiotic concentrations due to binding in the gut
Distribution	Ceftriaxone + endogenous bilirubin	Displacement of bilirubin from albumin binding site, increased risk of kernicterus in neonates
Metabolism	Induction of CYP isozymes [5], [6] :	
	Rifampin + protease inhibitors [7]	Decreased serum concentrations of protease inhibitors metabolized by CYP3A4 due to induction of CYP3A4-mediated metabolism; may result in subtherapeutic levels and resistance
	Inhibition of CYP isozymes [5] ,	

	[6] :	
	Azole antifungals[8] + CYP3A4 substrates	Increased serum concentrations of CYP3A4 substrates due to inhibition of CYP3A4-mediated metabolism; may result in drug toxicity
Elimination	Penicillin + probenecid	Decreased tubular secretion of penicillin resulting in increased serum concentrations
	Methotrexate + aspirin	Inhibition of tubular secretion of methotrexate resulting in increased methotrexate concentrations

[1] Drug interactions from The Medical Letter. Available at: www.medicalletter.org/subDIO .

[2] Disopyramide, procainamide, quinidine

[3] Woosley RL, Romero KA: QT drugs list. Available at: www.crediblemeds.org

[4] Gentamicin, tobramycin, amikacin, streptomycin, neomycin

[5] Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2017; September 18 (epub). Available at: www.medicalletter.org/downloads/CYP_PGP_Tables.pdf

[6] Cytochrome P450 (CYP) isozymes that can affect drug metabolism include CYP1A2, 2C8, 2C9, 2C19, 2D6, and 3A4.

[7] Some protease inhibitors metabolized by CYP3A4 include atazanavir, darunavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, and saquinavir.

[8] Itraconazole, ketoconazole, posaconazole, and voriconazole are strong inhibitors of CYP3A4. Fluconazole is a moderate CYP3A4 inhibitor.

This table is not an all-inclusive list of drug interactions. The prescriber is encouraged to assess the possibility of drug interactions when prescribing medications. This table does not address the chemical compatibility of drugs (eg, IV-line compatibility).

CYP = cytochrome P-450; P-gp = P-glycoprotein.

Modified from Rizack M, Hillman C: *The Medical Letter Handbook of Adverse Drug Interactions.* New Rochelle, NY, The Medical Letter, 1989. IBM Micromedex DRUGDEX, Copyright IBM Corporation 2018; Med Lett Drugs Ther 2018;60:e160.

Drug interactions may also occur at a pharmaceutical level as a result of a physicochemical incompatibility of 2 medications when combined. Such interactions generally alter the chemical structure of one or both constituents and thereby renders them inactive and potentially dangerous (e.g., IV infusion of crystalline precipitate or unstable suspension). Ceftriaxone should be avoided in infants <28 days of age if they are receiving or expected to receive IV calcium-containing products, due to reports of neonatal deaths resulting from crystalline deposits in the lungs and kidneys. Alternatively, 2 drugs simultaneously administered perorally may form a complex that can inhibit drug absorption (eg., co-administration of doxycycline with a food or drug containing divalent cations).

Drug-drug interactions at the level of drug metabolism can be somewhat predictable based on a priori knowledge of a given drug's biotransformation profile. Although such information can be derived from the primary literature, it may not be immediately translated into a useful clinical context because of limitations associated with in vitro to in vivo extrapolation, including (1) use of animal models for characterizing metabolism; (2) extrapolating enzyme kinetics derived from pooled human liver microsomes or recombinant human drug-metabolizing enzymes to estimates of in vivo drug clearance; (3) extrapolating in vitro data obtained from fully competent (i.e., adult activity) hepatic microsomes to estimates of clearance in patients who may have developmental or disease-associated compromise in enzyme activity; (4) inaccurate accounting for pharmacogenetic variation in drug-metabolizing activity (i.e., constitutive activity) and the contribution of multiple different drug-metabolizing enzymes in overall drug biotransformation; and (5) the potential role of enzyme induction or inhibition in vivo that is not reflected by conditions used for in vitro metabolism studies.

Despite these limitations, information pertaining to a drug's impact on drug-metabolizing enzymes (e.g., substrate, inducer, inhibitor) can be useful in understanding if the drug has the potential to compete for, induce, or inhibit the metabolism of another drug (e.g., enzyme inhibition enhanced effect vs enzyme induction → diminished effect) of a drug-drug interaction. While multiple sources for this information exist (e.g., primary and secondary literature, drug product labeling), it may not be complete or updated. In examining multiple information sources pertaining to this topic, the authors have found the website https://www.pharmgkb.org/ (accessed 21 February 2017) to be the most complete and useful for understanding drug metabolism pathways.

Extensive databases of reported and/or potential (e.g., theoretical mechanism- or metabolism-based) drug interactions exist and are widely available via the internet,* some of which provide some assessment as to their potential significance. Also, many computer-based information systems used by hospital and community pharmacies will routinely screen a patient's medication profile (generally restricted to prescription drugs) against new prescriptions to evaluate the potential for drug-drug interactions. When using drug-drug interaction databases or online resources, it is advisable to use multiple sources to check for complete information because information regarding interactions is evolving, and all databases may not be fully complete or may provide different information. The clinician is subsequently challenged with determining whether drug-drug or drug-food interactions found by searching these databases is of sufficient magnitude as to be clinically significant. Utilizing primary literature should be assessed when information is not available in online sources.

Over-the-counter (OTC) preparations, herbal supplements, and certain foods also have the potential to produce interactions with drugs. These are often quite challenging for the clinician, especially for alternative therapies, in that their composition (or potency) may not be completely discernible from the product labels, and the disposition of many natural products has not been studied in either children or adults. Further, many patients and their parents do not consider alternative therapies (including nutriceuticals) to be “medicines” (and consequently will not disclose their use during a routine medication history) but rather safe “nutritional supplements” despite absent regulation for their testing. An assessment should therefore begin with a thorough medication history that includes discussions of which OTC medications and herbal products are used as well as the regularity of their use. This will allow the clinician to identify the primary ingredients contained in these products and query their potential for producing clinically significant drug-drug interactions.

The provision of individualized, optimal drug therapy requires that the clinician make an assessment of potential drug-drug interactions and their significance. This requires knowledge of the interaction, the patient's condition, concomitant treatments (prescriptions, OTC drugs, alternative medicines), the impact of development on the dose-concentration-response relationship and a consideration of the risk vs benefit profile of the drug being prescribed. The clinician must be cognizant that if he or she treats a potential drug-drug interaction as a contraindication to drug use, it is possible that an alternative drug choice could produce a treatment associated with either less benefit or greater risk. Although many drugs have the potential to cause drug interactions, not all cases are deemed clinically relevant. For patients with complex histories requiring multiple medications, consultation with a clinical pharmacologist or pharmacist can help provide guidance on drug-drug interactions and their potential to impact therapy.

Adverse Drug Reactions

The World Health Organization has defined adverse drug reactions (ADRs) as “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.” There are 2 traditional pharmacologic classifications. **Type A** , generally referred to as “side effects,” are dose-dependent and predictable reactions that account for 85–90% of all ADRs. **Type B** reactions, generally referred to as “idiosyncratic” or “allergies,” are not dose dependent and are unpredictable and account for approximately 10–15% of all ADRs. Patients sometimes misinterpret some side effects as allergies (e.g., diarrhea with amoxicillin/clavulanate), which may be perpetuated through the patient's medical record.

In the pediatric population, ADRs are common occurrences that produce a major burden to patients and the healthcare system. While ADRs have not been as thoroughly studied in children as in adults, their significance has been widely recognized in pediatrics for >25 yr. Studies concerning ADRs in pediatric patients suggest the following:

1. Approximately 9% of all pediatric patients admitted to the hospital experience an ADR during their treatment.
2. The apparent incidence of ADRs in children in outpatient clinics is approximately 1.5%.
3. ADRs have been reported as being responsible for up to 10% of pediatric admissions to children's hospitals, with a pooled estimate data of about 3%.
4. Approximately 40% of ADRs occurring in hospitalized children are potentially life threatening.

In considering these “statistics,” it should be recognized that the true incidence of ADRs in children is not known because of generalized underreporting by healthcare providers (physicians > nurses > pharmacists), parents/caregivers, and patients (who may not recognize signs/symptoms and/or may be unable to report them) and in many countries (including the United States) the lack of a standardized surveillance and real-time reporting system.

Despite the limitations associated with determining the incidence of ADRs in children, it is estimated that their occurrence in patients 0-4 yr of age (3.8%) is more than double that seen at any other time during childhood or adolescence. In the outpatient setting, children age 0-4 yr accounted for 43% of clinic and emergency department visits for ADRs. One study reported that 60% of the ADRs occurred in those <1 yr. The reasons for this are not currently known but may involve developmental differences in pharmacokinetics and pharmacodynamics (i.e., altered dose-concentration-effect relationship), age-associated differences in physiologic “systems” that modulate drug- and metabolite-mediated cellular injury (e.g., immune system), and therapeutic use of drugs known to have a relatively high incidence of producing ADRs (e.g., delayed hypersensitivity reactions associated with β-lactam antibiotics). Also, it is important to recognize that infants can experience ADRs from drugs that are not directly administered to them therapeutically, but rather from maternal drug exposure (transplacental, breastfeeding). Examples include neonatal abstinence syndrome associated with maternal opiate use, production of a hyperserotonergic state in neonates born to mothers who received selective serotonin reuptake inhibitors during pregnancy, and opiate toxicity in breastfed infants whose mothers were taking codeine for pain management. In these cases, drug accumulation caused by reduced activity of drug-metabolizing enzymes associated with development and, potentially, pharmacogenetically determined phenotypical changes, which in concert can produce a level of systemic drug exposure capable of producing an exaggerated response or frank toxicity.

Specific ADRs occur at a much greater frequency in infants and children than in adults. Examples include aspirin-associated Reye syndrome, cefaclor-associated serum sickness–like reactions, lamotrigine-induced cutaneous toxicity, and valproic acid (VPA)–induced hepatotoxicity in infants <2 yr of age. It is not clear whether the age predilection for these specific ADRs is associated with developmental differences in drug biotransformation, related to both metabolite formation and detoxification, or alternatively, has a pharmacogenetic basis. Also, children experience **hypersensitivity reactions** to drugs such as anticonvulsants (e.g., phenytoin, carbamazepine, phenobarbital), sulfonamides (e.g., sulfamethoxazole, sulfasalazine), minocycline, cefaclor, and abacavir. These specific ADRs are not characteristic of type I (i.e., immediate) hypersensitivity reactions (e.g., true penicillin allergy) or anaphylactoid reactions, but rather have been previously classified as *idiosyncratic* with respect to their origin. A relatively common constellation of symptoms (fever, rash, and lymphadenopathy) suggests that abnormal activation/regulation of the immune system is a predominant component of the pathogenesis. Data from in vitro studies of sulfamethoxazole hypersensitivity also support this assertion. In addition, a requisite role for metabolic bioactivation (for anticonvulsants, sulfamethoxazole, and cefaclor) and possibly genetic factors such as allelic variants in HLA-B (e.g., HLA-B*6001 and HLA-B*1502 associated with hypersensitivity reactions to abacavir and carbamazepine) appears also to be involved in their etiology.

Personalized Medicine

The general concept of personalized medicine involves the application of genomic information to predicting a disease, disease severity, and therapeutic response (see Chapter 72). This “new vision of medicine” has been described as the “3 Ps”: predictive, personalized, and preventive. In children, however, ontogeny should also be considered when discussing personalizing therapy. Thus the aim of pediatric personalized medicine is uniquely to combine genetic variation with developmental stage to provide a tailored preventive, diagnostic, and therapeutic regimen.

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[*] For example, http://www.medscape.com/druginfo/druginterchecker ; http://www.drugs.com/ ; http://www.umm.edu/adam/drug_checker.htm ; all accessed 21 February 2017.

CHAPTER 74

Anesthesia and Perioperative Care

John P. Scott

The continuum of anesthesia includes varying degrees of sedation (i.e., mild, moderate, or deep) and general anesthesia. All forms of **sedation** are characterized by some preservation of purposeful movement (see Chapter 75), whereas **general anesthesia** is defined by the complete loss of consciousness. Potent pharmacologic agents are required to suppress the perception and physiologic response to noxious stimuli. Perioperatively, the anesthesiologist is responsible for providing analgesia while preserving physiologic and metabolic stability (Table 74.1). This responsibility begins with the performance of a comprehensive preanesthesia history (Table 74.2). Although anesthetic risk has greatly decreased with advancements in pharmacology and monitoring technology, the persistent risk of perioperative morbidity and mortality demands vigilance. The risk is elevated in certain disease states (Table 74.3).

Table 74.1

Goals of Anesthesia

Analgesia
Amnesia
Hypnosis
Akinesia
Maintenance of physiologic homeostasis
Vigilance

Table 74.2

The Preanesthetic History

Child's previous anesthetic and surgical procedures:

- Review previous anesthetic records:
    - Ease of mask ventilation
    - Grade of laryngoscopy; type and size of laryngoscope; endotracheal tube size
    - Issues during emergence (awakening) from anesthesia (postoperative vomiting, emergence delirium)
    - History of hyperthermia or acidosis in the child or family members.

Perinatal problems (especially for infants):

- Prematurity
- Need for supplemental oxygen or intubation and ventilation
- History of apnea and bradycardia
- History of cardiovascular compromise

Other major illnesses and hospitalizations

Family history of anesthetic complications, malignant hyperthermia, or pseudocholinesterase deficiency

Respiratory problems:

- Long-term exposure to environmental tobacco smoke
- Obstructive breathing score
- STBUR (snoring, trouble breathing, un-refreshed)
- Cyanosis (especially in infants <6 mo of age)
- Recurrent respiratory infections
- Recent lower respiratory tract infection
- Previous laryngotracheitis (croup) or laryngomalacia
- Reactive airway disease
- Airway abnormalities, facial anomalies, mucopolysaccharidosis

Cardiac problems:

- Murmur or history of congenital heart disease
- Dysrhythmia
- Exercise intolerance
- Syncope
- Cyanosis

Gastrointestinal problems:

- Reflux and vomiting
- Feeding difficulties
- Failure to thrive

  - Liver disease

- Exposure to infectious pathogens
- Neuromuscular problems:
  - Neuromuscular diseases
  - Developmental delay
  - Myopathy
  - Seizure disorder
- Hematologic problems:
  - Anemia
  - Bleeding diathesis
  - Tumor
  - Immunocompromise
  - Prior blood transfusions and reactions
- Renal problems:
  - Renal insufficiency, oliguria, anuria
  - Fluid and electrolyte abnormalities
- Psychosocial considerations:
  - Drug abuse, use of cigarettes or alcohol
  - Physical or sexual abuse
  - Family dysfunction
  - Previous traumatic medical or surgical experience
  - Psychosis, anxiety, depression
- Gynecologic considerations:
  - Sexual history (sexually transmitted infections)
  - Possibility of pregnancy
- Current medications:
  - Prior administration of corticosteroids
- Allergies:
  - Drugs
  - Iodine
  - Latex products
  - Surgical tape
  - Food (especially soya and egg albumin)
- Dental condition (loose or cracked teeth)
- When and what the child last ate (especially in emergency procedures)

Table 74.3

Specific Pediatric Diseases and Their Anesthetic Implications

DISEASE	IMPLICATIONS
RESPIRATORY SYSTEM	
Asthma	Intraoperative bronchospasm that may be life threatening
	Pneumothorax or atelectasis
	Optimal preoperative medical management is essential.
Difficult airway	Special equipment and personnel may be required.
	Should be anticipated with dysmorphic features or storage diseases
	Patients with trisomy 21 may require atlantooccipital joint evaluation.
	Increased risk with acute airway obstruction, epiglottitis, laryngotracheobronchitis, or airway foreign body
Bronchopulmonary dysplasia	Barotrauma with positive pressure ventilation
	Oxygen toxicity, pneumothorax a risk
Cystic fibrosis	Airway reactivity, bronchorrhea, increased intraoperative pulmonary shunt and hypoxia
	Risk of pneumothorax, pulmonary hemorrhage
	Atelectasis, risk of prolonged postoperative ventilation
	Patient should be assessed for cor pulmonale.
Sleep apnea	Pulmonary hypertension and cor pulmonale must be excluded.
	Careful postoperative observation for obstruction required
CARDIAC	
	Bacterial endocarditis prophylaxis as indicated
	Use of air filters; careful purging of air from the intravenous equipment
	Physician must understand the effects of various anesthetics on the hemodynamics of specific lesions.
	Possible need for preoperative evaluation of myocardial function and pulmonary vascular resistance
	Provide information about pacemaker function and ventricular device function.
HEMATOLOGIC	
Sickle cell disease	Possible need for simple or exchange transfusion based on preoperative hemoglobin concentration and percentage of hemoglobin S
	Avoid hypoxemia, hypothermia, dehydration, and hyperviscosity states.
Oncology	Pulmonary evaluation of patients who have received bleomycin, *bis* -chloroethyl-nitrosourea, chloroethyl-cyclohexyl-nitrosourea, methotrexate, or radiation to the chest
	Avoidance of high oxygen concentration
	Cardiac evaluation of patients who have received anthracyclines; risk of severe myocardial depression with volatile agents
	Potential for coagulopathy
RHEUMATOLOGIC	
	Limited mobility of the temporomandibular joint, cervical spine, arytenoid cartilages
	Careful preoperative evaluation required
	Possible difficult airway
GASTROINTESTINAL	
Esophageal, gastric	Potential for reflux and aspiration
Liver	Altered metabolism of many anesthetic drugs
	Potential for coagulopathy and uncontrollable intraoperative bleeding
RENAL	
	Altered electrolyte and acid-base status
	Altered clearance of many anesthetic drugs
	Need for preoperative dialysis in selected cases

	Succinylcholine to be used with extreme caution and only when the serum potassium level has recently been shown to be normal
NEUROLOGIC	
Seizure disorder	Avoidance of anesthetics that may lower the seizure threshold
	Optimal control ascertained preoperatively
	Preoperative serum anticonvulsant measurements
Increased intracranial pressure	Avoidance of agents that increase cerebral blood flow
	Maintain cerebral perfusion pressure.
Neuromuscular disease	Avoidance of depolarizing relaxants; at risk for hyperkalemia
	Patient may be at risk for malignant hyperthermia; avoid volatile anesthetics in myopathies.
Developmental delay	Patient may be uncooperative during induction and emergence.
Psychiatric	Monoamine oxidase inhibitor (or cocaine) may interact with meperidine, resulting in hyperthermia and seizures.
	Selective serotonin reuptake inhibitors may induce or inhibit various hepatic enzymes that may alter anesthetic drug clearance.
	Illicit drugs may have adverse effects on cardiorespiratory homeostasis and may potentiate the action of anesthetics.
ENDOCRINE	
Diabetes	Greatest risk is unrecognized intraoperative hypoglycemia; intraoperative blood glucose level monitoring needed especially when insulin is administered.
SKIN	
Burns	Difficult airway
	Fluid shifts
	Bleeding
	Risk of rhabdomyolysis and hyperkalemia from succinylcholine following burns for many months
IMMUNOLOGIC	
	Retroviral drugs may inhibit benzodiazepine clearance.
	Immunodeficiency requires careful infection control practices.
	Cytomegalovirus-negative blood products, irradiation, or leukofiltration may be required.
METABOLIC	
	Careful assessment of glucose homeostasis in infants

Preanesthetic Evaluation

All children presenting for surgery should undergo a preanesthetic history and multiorgan system assessment with assignment of **American Society of Anesthesiologists Physical Status (ASA-PS)** (Table 74.4). Children of ASA-PS I-II generally require a brief history, notation of medical allergies, and physical examination focusing on the neurologic and cardiorespiratory systems, with no additional testing. Patients with complex medical history of ASA-PS ≥III require a more comprehensive preanesthetic assessment often with ancillary preoperative testing. Children should be screened for anesthetic risks, including drug allergies, previous reactions to anesthetics, and family history of problems with anesthesia (e.g., sudden perioperative death, hyperthermia after surgery), which may indicate risk of malignant hyperthermia.

Table 74.4

American Society of Anesthesiology Physical Status Classification

Class 1: Healthy patient, no systemic disease
Class 2: Mild systemic disease with no functional limitations (mild chronic renal failure, iron-deficiency anemia, mild asthma)
Class 3: Severe systemic disease with functional limitations (hypertension, poorly controlled asthma or diabetes, congenital heart disease, cystic fibrosis)
Class 4: Severe systemic disease that is a constant threat to life (critically and/or acutely ill patients with major systemic disease)
Class 5: Moribund patients not expected to survive 24 hr, with or without surgery
Additional classification: “E”—emergency surgery

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Respiratory System

Recent respiratory tract infections should be noted. *Clear rhinorrhea without fever is not associated with increased anesthetic risk*. Respiratory illnesses associated with fever, mucopurulent nasal discharge, productive cough, or lower respiratory symptoms (wheezing, rales) are associated with increased airway reactivity and anesthetic complications for up to 6 wk thereafter. There may also be increased risk of perioperative laryngospasm and bronchospasm, reduced mucociliary clearance, atelectasis, and hypoxemia. It is recommended that elective procedures requiring general anesthesia be postponed 4-6 wk in this setting.

Children with reactive airway disease require a thorough preanesthetic assessment. Acute, potentially fatal bronchospasm can occur during induction of anesthesia and endotracheal intubation for routine, minor surgery in children with asthma. Children at increased risk for anesthetic complications have experienced asthma exacerbations requiring (1) hospital admission within the previous year; (2) emergency department (ED) care within the last 6 mo; (3) previous intensive care unit (ICU) admission; or (4) previous parenteral systemic corticosteroids. Ideally, children should be free of wheezing for least several days before surgery, even if this necessitates increased controller medication administration (β-adrenergic agonist and corticosteroids). Active wheezing is an indication for delaying elective surgery. Chronic respiratory conditions such as bronchopulmonary dysplasia and cystic fibrosis are also associated with significant intraoperative risks. Every effort should be made to ensure that children with such disorders achieve optimal respiratory status before surgery.

Airway Evaluation

Induction of general anesthesia is associated with reduced spontaneous ventilation and airway reflexes. Prediction of difficult bag-mask ventilation and/or intubation before anesthesia is critical. Congenital anomalies associated with airway compromise include micrognathia, macroglossia, and thoracic anomalies (Table 74.5). Conditions that impair mouth opening (e.g., temporomandibular joint disease) should also be noted. A history of wheezing or stridor may indicate postoperative airway complications and difficult intraoperative airway management. It is also essential to ask about a history of sleep-disordered breathing using the **STBUR** (snoring, trouble breathing, un-refreshed) index, which may be predictive of perioperative respiratory complications.

Table 74.5

Common Difficult Airway Syndromes

Achondroplasia
Airway tumors, hemangiomas
Apert syndrome
Beckwith-Wiedemann syndrome
Choanal atresia
Cornelia de Lange syndrome
Cystic hygroma/teratoma
DiGeorge syndrome
Fractured mandible

Goldenhar syndrome
Juvenile rheumatoid arthritis
Mucopolysaccharidosis
Pierre Robin syndrome
Smith-Lemli-Opitz syndrome
Treacher-Collins syndrome
Trisomy 21
Turner syndrome

Cardiovascular System

Most anesthetic agents possess myocardial depressant properties. All patients should be screened for the presence of heart disease. Important cardiovascular considerations include history of congenital heart disease (CHD), cyanosis, arrhythmias, or cardiomyopathy. Room-air pulse oximetry should be performed as part of the preanesthetic evaluation. Accurate diagnosis of cardiac murmurs in neonates is essential. A history of cardiac dysrhythmias should be investigated because inhalational anesthetics may be arrhythmogenic. A pediatric cardiologist should evaluate children with known CHD undergoing surgery. Preoperative ancillary studies may include electrocardiogram (ECG), echocardiogram, or cardiac catheterization. Lesions associated with increased anesthetic risk include single-ventricle heart disease, fixed obstructive outflow tract lesions (aortic valve and pulmonary valve stenosis), and cardiomyopathy. Children with these conditions should be cared for by a **cardiac anesthesia service** . Antibiotic prophylaxis for the prevention of bacterial endocarditis may also be indicated, and the American Heart Association (AHA) guidelines should be followed.

Hematologic System

Evidence of coagulopathy should be sought. Easy bruising, familial bleeding disorders, and anticoagulant (e.g., aspirin, heparin, warfarin) use should be discussed. Preoperative adequacy of hemostatic function (e.g., platelet count, fibrinogen, prothrombin time, partial thromboplastin time) and correction of coagulopathic disorders may be indicated for complex procedures associated with significant risk of perioperative hemorrhage. In neonates, assurance of vitamin K prophylaxis and adequate coagulation status is critical before any major surgery. Although anemia may be well tolerated in healthy children, anesthesia and surgery increase oxygen consumption. Preoperative anemia should be corrected in the setting of reduced oxygen delivery or expected blood loss. In the patient with life threatening hemorrhage (trauma), massive transfusion protocols of 1 : 1:1 replacement of packed red blood cells:fresh-frozen plasma:platelets should be used.

Neurologic System

A history of neurologic and neuromuscular disorders should be sought. Preoperative developmental assessments may be helpful in interpreting age-dependent variation in the response to pain. Maintenance of appropriate perioperative anticonvulsant therapy is essential in children with seizure disorders because the seizure threshold may be lowered perioperatively. Children with obstructive hydrocephalus typically require ventriculoperitoneal (VP) shunt insertion to divert cerebrospinal fluid (CSF) and to prevent intracranial hypertension (ICH). Repeated shunt malfunction is common, and these children my present for shunt revision with signs of ICH (vomiting, altered mentation, sundowning). Similarly, shunt patency and function should be ensured preoperatively in children with VP shunts presenting for nonneurosurgical procedures.

Psychological Assessment

Surgery and painful medical procedures are psychologically traumatic events for children and families. Children who require anesthesia may experience fear and anxiety. They may also sense stressful signals from parents and caregivers. Many children undergoing surgery have new-onset negative behavioral changes postoperatively. These maladaptive behavioral responses may include enuresis, separation anxiety, temper tantrums, and nighttime crying, as well as fear of strangers, doctors, and hospitals. Sleep quality may be altered postoperatively, resulting in further behavioral compromise. Risk factors for postoperative behavioral changes include preoperative anxiety and emergence excitation. Need for recurrent procedures is another risk factor. Preoperative psychological preparation programs decrease the incidence of postoperative behavioral changes. **Parental presence during induction (PPI)** has not been shown to improve postoperative behavior (see later). Oral midazolam (0.5 mg/kg) may decrease negative behavioral changes after surgery. Midazolam has the benefit of providing rapid-onset anxiolysis and amnesia.

Genetic Evaluation

Children with genetic conditions may have syndrome-specific anesthetic considerations. For example, children with trisomy 21 may have cardiac anomalies, macroglossia, upper airway obstruction, and hypothyroidism (see Chapter 98.2). Atlantoaxial instability, common in trisomy 21, has been linked to cervical dislocation and spinal cord trauma with neck extension during intubation. Some anesthesiologists recommend extension and flexion lateral neck films to detect instability before surgery. For children with other known genetic disorders it is essential to review specific anesthetic considerations.

Preoperative Preparation

Preoperative Fasting

Preoperative fasting guidelines have been developed to reduce the incidence of aspiration of gastric contents during anesthesia. Aspiration may lead to laryngospasm, bronchospasm, and postoperative pneumonitis. Aspiration of gastric contents may be a potentially lethal complication in children with chronic lung disease or critical illness. Table 74.6 lists preoperative fasting guidelines (e.g., nothing by mouth, or nil per os [NPO] status). Clear, sweet liquids (e.g., Pedialyte, 5% dextrose in water [D5W]) facilitate gastric emptying, prevent hypoglycemia, and may be given up to 2 hr before anesthesia. Breast milk may be given to infants up to 4 hr before surgery. Solids should be avoided for 6-8 hr before surgery. Many conditions delay gastric emptying and may require prolonged periods of fasting.

Table 74.6

Guidelines for Preoperative Fasting (“2-4-6-8 Rule”)*

TIME BEFORE SURGERY (hr)	ORAL INTAKE
2	Clear, sweet liquids
4	Breast milk
6	Infant formula, fruit juices, gelatin
8	Solid food

* These are general guidelines and may differ among hospitals.

The Full Stomach

Gastric emptying may be delayed for up to 96 hr after an acute episode of trauma or surgical illness. Because of the serious complications of aspiration of gastric contents, it is desirable to secure the airway as rapidly as possible during induction of anesthesia in patients at risk for having a full stomach. Under these circumstances, rapid sequence induction of anesthesia is indicated (**rapid sequence induction** ; see Chapter 89).

Parental Presence During Induction of Anesthesia

Parents may expect to be with their child during the induction of anesthesia. Removing a fearful child from the comforting arms of a parent is stressful for the child, parents, and caregivers. When parental separation cannot be achieved comfortably with premedication and behavioral modification (patient education and desensitization to the operative environment), there may be a need to defer parent–child separation until general anesthesia is induced. Premedication with the oral benzodiazepine midazolam more frequently provides calm, smooth induction conditions than PPI without pharmacologic preparation. Although PPI in the hands of a confident, competent anesthesia practitioner may replace the need for preoperative medication, it does not reliably predict smooth induction. PPI has not been shown to decrease emergence delirium or postoperative behavioral changes, and it does not appear to be superior to premedication with oral midazolam.

General Anesthesia

Analgesia

Pediatric anesthesiologists are responsible for providing analgesia to children for procedures within operating room (OR) and non-OR settings (Table 74.7). Multimodal techniques exist to provide pain relief during operative procedures for children of all ages, including critically ill infants. Effective analgesia is essential to blunt physiologic responses to painful stimuli (surgery) and modulate the deleterious physiologic and metabolic consequences. The response to painful and stressful stimuli may provoke **systemic inflammatory response**

syndrome (SIRS) , which has been linked to increased catabolism, physiologic instability, and mortality (see Chapter 88).

Table 74.7

Definitions of Anesthesia Care

Monitored Anesthesia Care

A designated anesthesia service in which an anesthesiologist has been requested to participate in the care of a patient undergoing a diagnostic or therapeutic procedure.

Monitored anesthesia care includes all aspects of anesthesia care: a preprocedure assessment, intraprocedure care, and postprocedure anesthesia management.

During monitored anesthesia care, the anesthesiologist or a member of the anesthesia care team provides a number of specific services, which may include but are not limited to the following:

- Discussing anesthesia care with the family and child, obtaining consent for anesthesia, allaying anxiety and answering questions—family-centered anesthesia care.
- Monitoring of vital signs, maintenance of the patient's airway, and continual evaluation of vital functions.
- Diagnosing and treating clinical problems that occur during the procedure.
- Administering sedatives, analgesics, hypnotics, anesthetic agents, or other medications as necessary to ensure patient safety and comfort.
- Providing other medical services as needed to accomplish the safe completion of the procedure.

Anesthesia care often includes the administration of medications for which the loss of normal protective reflexes or loss of consciousness is likely.

Monitored anesthesia care refers to those clinical situations in which the patient remains able to protect the airway for the majority of the procedure.

If the patient is rendered unconscious and/or loses normal protective reflexes for an extended period, this is considered a general anesthetic.

Light Sedation

Administration of anxiolysis or analgesia that obtunds consciousness but does not obtund normal protective reflexes (cough, gag, swallow, hemodynamic), or spontaneous ventilation.

Deep Sedation

Sedation that obtunds consciousness and normal protective reflexes or possesses a significant risk of blunting normal protective reflexes (cough, gag, swallow, hemodynamic), hemodynamic and respiratory insufficiency may occur.

General Anesthesia

Administration of hypnosis, sedation, and analgesia that results in the loss of normal protective reflexes.

Regional Anesthesia

Induction of neural blockade (either central, neuraxial, epidural, or spinal; or peripheral nerve block, e.g., digital nerve block, brachial plexus block), which provides analgesia and is associated with regional motor blockade.

Consciousness is not obtunded.

Special expertise is required.

Frequently, in children, anxiolysis and sedation are also necessary for this technique to be successful.

Regional anesthesia (e.g., caudal epidural blockade) is used to supplement general anesthesia and provide postoperative analgesia.

Local Anesthesia

Provision of analgesia by local infiltration of an appropriate anesthetic agent.

Does not require the presence or involvement of an anesthesiologist, although an anesthesiologist may provide local anesthesia services.

No Anesthesiologist

An anesthesiologist will not be involved in the care of the child.

Hypnosis and Amnesia

The attenuation of both consciousness **(hypnosis)** and conscious recall **(amnesia)** is critical during pediatric anesthesia care. Awareness during procedures may be as physically and psychologically deleterious as the experience of pain. A primary goal of anesthetic management is to minimize fear and anxiety during both painful and nonpainful procedures. Many drugs provide anxiolysis and amnesia for such events (Table 74.8). However, it is important to remember that sedative-hypnotic agents may alter consciousness without producing analgesia; *analgesia* and *hypnosis* are not synonymous. It is also possible to provide analgesia (local, spinal, or epidural) without altering consciousness.

Table 74.8

Selected Drugs Used in Anesthesia

DRUG	USES AND IMPLICATIONS
MUSCLE RELAXANTS	
Succinylcholine	A depolarizing neuromuscular blocking agent with rapid onset and offset properties
	Used to facilitate endotracheal intubation and maintain muscle relaxation in emergency situations; rarely used
	Associated with the development of malignant hyperthermia in susceptible patients
	Degraded by plasma cholinesterase, which may be deficient in some individuals; such a deficiency may result in prolonged effect
	Fasciculations may be associated with immediate increases in intracranial and intraocular pressures as well as postoperative muscle pain.
Vecuronium, rocuronium, *cis* -atracurium, all aminosteroids	Nondepolarizing neuromuscular blockers
	Have less rapid onset than succinylcholine but are longer acting
	Prolonged ICU use may lead to profound muscle weakness.
	Vecuronium and rocuronium are metabolized by the liver and excreted in bile; they are the most commonly used neuromuscular blocking agents.
	cis -Atracurium is metabolized by plasma cholinesterase and therefore may be of benefit in patients with hepatic or renal disease.
HYPNOTICS	
Propofol	Rapid-acting hypnotic amnestic agent

	No analgesic properties
	Respiratory depressant
	Increases seizure threshold
	Antiemetic
	Propofol infusion syndrome may occur with prolonged intravenous infusion (>24 hr).
Etomidate	Cardiovascular stability on induction
	Inhibits corticosteroid synthesis
	Increases ICU mortality after use
	Associated with myoclonus and pain on injection
Ketamine	Hypnotic analgesic
	Causes sialorrhea and should be co-administered with an antisialogue, such as atropine or glycopyrrolate
	Induces endogenous catecholamine release and tachycardia
	Bronchodilator
	Increases intracranial and intraocular pressures
	Decreases the seizure threshold
SEDATIVE-ANXIOLYTICS	
Benzodiazepines	Produce sedation, anxiolysis, amnesia, and hypnosis
	All agents raise the seizure threshold, are metabolized by the liver, and depress respiration, especially when administered with opioids.
	Effective as premedication
	Diazepam may be painful on injection and has active metabolites.
	Midazolam can be administered by various routes.
	Lorazepam has no active metabolites.
	Reversed with flumazenil
Dexmedetomidine	Produces anxiolysis, sedation, sympatholysis, by α_2 -receptor stimulation centrally; has mild analgesic properties
	Side effects include hypertension, hypotension, and bradycardia.
	Commonly used for procedural and ICU sedation
	Continuous infusion for ICU sedation
ANALGESIC-SEDATIVES	
Opioids	Gold standard for providing analgesia
	All cause respiratory depression.
	Morphine and, to a lesser extent, hydromorphone may cause histamine release.
	The synthetic opioids fentanyl, sufentanil, and short-acting alfentanil may have a greater propensity to cause chest wall rigidity when administered rapidly or in high doses and are also associated with the rapid development of tolerance. These drugs have particular utility in cardiac surgery because of the hemodynamic stability associated with their use.
	Remifentanil is an ultrashort-acting synthetic opioid that is metabolized by plasma cholinesterase; it may have particular utility when deep sedation and analgesia are required along with the ability to assess neurologic status intermittently.
INHALATIONAL AGENTS	
Nitrous oxide	Produces amnesia and analgesia at low concentrations
	Danger of hypoxic gas mixture if the oxygen concentration is not monitored and preventive safety mechanisms are not in place
Potent vapors, sevoflurane, desflurane, isoflurane	“Complete anesthetics”—induce hypnosis, analgesia, and amnesia
	All are myocardial depressants, and some are vasodilators.
	May trigger malignant hyperthermia in susceptible individuals
	Sevoflurane is used for induction of anesthesia in children.
	All bronchodilate at equipotent concentrations.
	Isoflurane and desflurane are associated with laryngospasm and should not be used for anesthesia induction.

Sedation describes a medically induced state in the continuum between wakefulness and general anesthesia (see Table 74.7). **General anesthesia** is characterized by unconsciousness, amnesia, and reduced physiologic reflexes. Cardiorespiratory reflexes (**airway-protective and vasomotor reflexes**) are reduced with general anesthesia. *Light (minimal) sedation* is anxiolysis with minimally reduced reflexes or airway patency. *Deep sedation* occurs when cardiorespiratory reflexes are obtunded or lost. Respiratory depression and hemodynamic compromise may be profound. As sedation deepens toward general anesthesia, loss of airway patency, loss of airway-protective reflexes, and loss of cardiovascular stability occur. Individuals providing sedation and anesthesia for children must be able to detect and support cardiorespiratory insufficiency.

Akinesia (Immobility or Muscular Relaxation)

Akinesia , the absence of movement, is commonly indicated to ensure safe and adequate operative conditions. Neuromuscular blocking agents (NMBAs) may be used to produce akinesia (see Table 74.8). However, the absence of movement is not indicative of hypnosis, amnesia, or analgesia. Whenever NMBAs are used, *analgesia and sedation must be provided.*

Monitoring

Administration of anesthesia increases the need to monitor and support physiologic integrity and homeostasis due to potentially life-threatening physiologic consequences (see Tables 74.7 and 74.8). Consequently, ASA mandates routine monitoring of oxygenation, ventilation, and circulation during the provision of anesthesia. This includes assessment of continuous pulse oximetry, capnography, electrocardiography, intermittent blood pressure measurements (every 5 min), and temperature when temperature instability is anticipated. The use of advanced invasive or noninvasive monitors varies based on procedural complexity and ASA-PS.

Specific Medications

Inhalational Anesthetics

Inhalational anesthetics are frequently used for the induction and maintenance of general anesthesia in children. Pediatric inhalational anesthetics include sevoflurane, isoflurane, and desflurane. Although halothane is the prototypical pediatric inhalational anesthetic, it has been replaced by sevoflurane and is no longer used in the United States.

The **minimum alveolar concentration (MAC)** of an inhalational anesthetic is the alveolar concentration (expressed as percent at 1 atmosphere) that provides sufficient depth of anesthesia for surgery in 50% of patients. For potent inhalational agents, the alveolar concentration of an anesthetic reflects the arterial concentration of anesthetic in the blood perfusing the brain. Thus the MAC is an indication of anesthetic potency and is analogous to the **ED_{50}** (effective dose in 50% of recipients) of a drug. MAC is age dependent. MAC is lower in premature than in full-term infants and decreases from term through infancy to preadolescence. In adolescence, MAC again increases, falling thereafter.

Respiratory Effects.

The advantages of inhalational anesthesia are rapid onset and offset with the convenient route of delivery and respiratory excretion. These agents provide profound analgesia and amnesia. Inhalational anesthetic agents are poorly soluble in blood but rapidly equilibrate between alveolar gas and blood. They are airway irritants that may provoke laryngospasm. All inhalational anesthetics depress ventilation in a dose-dependent manner. Thus, expired carbon dioxide (CO_2) and Pa_{CO_2} (arterial partial pressure of CO_2) will increase in spontaneously breathing children. Inhalational anesthetics also shift the CO_2 response curve to the right, thus decreasing the normal increase in minute ventilation with increasing Pa_{CO_2}. Inhalational anesthesia decreases end-expiratory lung volume (functional residual capacity). Small lung volumes are associated with reduced lung compliance, increased pulmonary vascular resistance, and restrictive lung defects. Volatile agents depress normal hypoxic pulmonary vasoconstriction, increasing intrapulmonary arteriovenous shunting and hypoxemia.

Cardiovascular Effects.

All volatile anesthetic agents reduce cardiac output and peripheral vascular resistance; hypotension is common. This is accentuated in hypovolemic patients and more pronounced in neonates. Inhalational anesthetics also depress baroreceptor and heart rate responses. The administration of inhalational anesthesia may result in decreased tissue oxygen delivery. Perioperatively, cellular metabolism increases, creating a potential imbalance between oxygen demand and oxygen delivery. Development of intraoperative dysoxia is a sign of this imbalance. All volatile inhalational anesthetic agents cause **cerebrovasodilation** and uncouple cerebral blow flow with cerebral metabolic rate. Although inhalational anesthetics decrease cerebral oxygen consumption, they may also disproportionately increase cerebral oxygen blood flow. Thus, inhalational anesthetics should be used with caution in children who have elevated intracranial pressure (ICP) or impaired cerebral perfusion (i.e., traumatic brain injury).

Sevoflurane

Sevoflurane is the most commonly used inhalational agent for induction and maintenance of general anesthesia in children. Sevoflurane is not a significant airway irritant and is a useful induction agent when co-administered with nitrous oxide. Emergence from sevoflurane anesthesia is rapid; however, there is a significant incidence of **emergence delirium** , especially with inadequate pain control. This effect may be attenuated with adequate analgesia and supplemental hypnotic agents (e.g., midazolam, dexmedetomidine, propofol), although hypnotics may delay recovery from anesthesia. Metabolism of sevoflurane by cytochrome P450 (CYP) yields free fluoride, which may be potentially nephrotoxic. Sevoflurane degradation by desiccated CO_2 absorbents at low fresh gas flows (<2 L/min) may produce the nephrotoxin Compound A. Large-scale studies of sevoflurane-associated renal injury in humans are lacking. However, the U.S. Food and Drug Administration (FDA) has recommended maintenance of fresh gas flow rates >2 L/min for surgical cases lasting >2 MAC hr.

Isoflurane

Isoflurane is a pungent volatile anesthetic and airway irritant, not suitable for induction because of the high incidence of complications, such as laryngospasm. However, maintenance of anesthesia with isoflurane is common after induction with sevoflurane or an intravenous (IV) hypnotic. Emergence from anesthesia with isoflurane is slower than for sevoflurane. Isoflurane administration in the setting of desiccated CO_2 absorbents may yield the production of carbon monoxide.

Desflurane

Desflurane is a potent airway irritant associated with coughing, breath holding, and laryngospasm and is *not* useful for induction. Desflurane has the lowest solubility and potency of all commonly used volatile agents. It is frequently administered for maintenance of anesthesia. Emergence from desflurane anesthesia is rapid due to its low tissue solubility.

Nitrous Oxide

Nitrous oxide (N_2O) is a tasteless, colorless, odorless gas with potent analgesic properties. It produces a state of euphoria (thus its nickname, “laughing gas”). The MAC of N_2O is >100; consequently, it may not be used as a sole agent to maintain anesthesia. N_2O produces little hemodynamic or respiratory depression. N_2O is typically used in combination with volatile and IV anesthetic agents during maintenance of general anesthesia. The deleterious effects of N_2O include postoperative nausea and vomiting and, with long-term use (i.e., days), bone marrow suppression. N_2O diffuses out of blood rapidly and is contraindicated in patients with closed gas-filled body cavities (pneumothorax, lung cysts, bowel injury).

Intravenous Anesthetic Agents

Intravenous anesthetics may be administered for induction and maintenance of anesthesia in bolus form or as continuous infusions. Common IV agents include propofol, opioids, benzodiazepines, ketamine, dexmedetomidine, and barbiturates. For children with vascular access, IV induction should be routine. All IV agents affect cardiorespiratory function.

Propofol

Propofol is the most commonly administered IV induction agent. Administered in doses of 2-5 mg/kg, propofol rapidly produces unconsciousness. Propofol may burn and itch on injection. After induction of anesthesia, propofol is a useful agent for maintaining hypnosis and amnesia and may be used as a sole anesthetic agent for nonpainful procedures (e.g., radiation therapy) and imaging studies. When combined with opioids, propofol provides excellent anesthesia for brief painful procedures, such as lumbar puncture and bone marrow aspiration.

Although hemodynamic stability, and even spontaneous respirations, may be maintained during propofol administration, it remains a potent anesthetic that obtunds airway reflexes, respiration, and hemodynamic function, and should not be considered a “sedation agent.” Propofol frequently induces both respiratory depression and hypotension. Extrapyramidal symptoms are a rarer complication. Prolonged use may cause hemodynamic collapse, bradycardia, metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidemia, profound shock, and death (**propofol infusion syndrome)** . Prolonged propofol administration (>24-48 hr) in the ICU in children is not recommended. Propofol is formulated in 10% soy emulsion with egg emulsifiers and was once thought to be contraindicated in patients with soy or egg allergy. According to the American Academy of Allergy, Asthma, and Immunology, however, patients with soy and egg allergies may safely receive propofol for anesthesia.

Etomidate

Etomidate is an imidazole derivative used for the induction of anesthesia, frequently in emergent situations. Its onset of action is slower than propofol. Etomidate lacks significant cardiovascular depressant effects, making it a popular induction agent in patients with hemodynamic compromise, cardiac disease, and septic shock. However, etomidate inhibits 11β-hydroxylase, thereby suppressing mineralocorticoid and glucocorticoid synthesis for up to 72 hr after a single induction dose. Etomidate is associated with increased mortality when used as a sedative in the ICU (for which it is now contraindicated), even with a single induction dose. Any decision to use etomidate must weigh the short-term benefits of hemodynamic stability with the serious risks of adrenal suppression.

Ketamine

Ketamine (1-3 mg/kg IV) produces rapid induction of general anesthesia that lasts for 15-30 min. Ketamine is effective when given intramuscularly, subcutaneously, nasally, or orally. However, the dose must be increased for alternative routes. Ketamine dissociates connections between the cerebral cortex and limbic system *(dissociative anesthesia)* through inhibition of *N* -methyl-D -aspartate receptors. Ketamine is also an analgesic and may be used as a sole IV agent to provide general anesthesia. It has few side effects and generally preserves blood pressure and cardiac output. However, ketamine increases myocardial oxygen demand and should be used cautiously in patients with impaired myocardial oxygen delivery or ventricular outflow tract obstruction. With low-dose (1-2 mg/kg) ketamine, airway reflexes and spontaneous ventilation may be maintained; at higher doses (3-5 mg/kg), loss of airway reflexes, apnea, and respiratory depression occur. Aspiration of gastric contents remains a risk during deep sedation with ketamine. IV ketamine is a useful general anesthetic agent for short procedures.

Ketamine has been linked to disturbing postanesthetic dreams and hallucinations following emergence from anesthesia. In adults the incidence of this effect is 30–50%; in prepubertal children it may be 5–10%. Benzodiazepines (e.g., midazolam) reduce these sequelae and should be routinely given to children receiving ketamine. Ketamine is also a potent secretagogue, enhancing oral and bronchial secretions. An antisialogue, such as atropine or glycopyrrolate, should also be considered before the administration of ketamine. Ketamine is a bronchodilator and is a useful agent for sedating asthmatic patients in the ICU. Ketamine has been reported to increase ICP and therefore is contraindicated in patients with elevated ICP.

Opioids

Opioids are superb analgesics for painful procedures and postprocedural pain (see Chapter 75). Opioids are respiratory depressants that suppress CO_2 responsiveness and can produce apnea. Importantly, in equianalgesic doses, all opioids are equally potent respiratory depressants. Other inhalational or IV anesthetics generally potentiate opioid-induced respiratory depression.

Morphine is a long-acting opioid analgesic with important age-dependent pharmacokinetics. Large doses of morphine (0.5-2 mg/kg), combined with N_2O provide adequate analgesia for painful procedures. Equivalent doses of morphine per kilogram are associated with higher blood levels in neonates than in older children, with plasma concentrations approximating 3 times those of adults. Morphine exhibits a longer elimination half-life (14 hr) in young children than in adults (2 hr). The immature blood-brain barrier of neonates is more permeable to morphine. Morphine is often associated with hypotension and bronchospasm from histamine release and should be used with caution in children with asthma. Morphine has renally excreted active metabolites and is relatively contraindicated in renal failure. Because of morphine's prolonged duration of action and cardiorespiratory side effects, the fentanyl class of synthetic opioids has increased in popularity for perioperative analgesia.

Fentanyl is a potent synthetic opioid with a shorter duration of action and a more stable hemodynamic profile than morphine. Fentanyl attenuates the hemodynamic response to surgery and provides stable operating conditions. Effective analgesia and anesthesia may be provided with IV fentanyl administered as a 2-3 µg/kg bolus followed by a 1-3 µg/kg/hr continuous infusion. Nitrous-narcotic anesthetic techniques that incorporate fentanyl are effective for maintenance of stable hemodynamics while still providing adequate hypnosis and analgesia. Fentanyl is the most commonly used *synthetic* opioid, but other formulations of varying potency are available (alfentanil < fentanyl < sufentanil). *Sufentanil* is 10 times more potent than fentanyl and is frequently used during pediatric cardiac anesthesia. *Alfentanil* is approximately ¼ as potent as fentanyl. *Remifentanil* has very rapid onset and offset of action. In doses of 0.25 µg/kg/min, surgical anesthesia can be maintained with this agent. Remifentanil is metabolized through nonspecific ester hydrolysis and has a short elimination half-life (<10 min) advantageous for rapid emergence from anesthesia. Unfortunately, this short duration of action has been linked to inadequate postprocedural analgesia and increased need for postprocedural opioid analgesic supplementation, limiting remifentanil's use.

Benzodiazepines

Benzodiazepines induce hypnosis, anxiolysis, sedation, and amnesia and have anticonvulsant properties. In high doses, benzodiazepines cause respiratory depression and are synergistic with opioids and barbiturates in their respiratory depressant effects. Benzodiazepines are γ-aminobutyric acid (GABA) agonists.

Midazolam is the most commonly used benzodiazepine in pediatric anesthesia. Short acting and water soluble, it can be injected without pain. It is a potent hypnotic-anxiolytic-anticonvulsant and is approximately 4 times more potent than diazepam. Midazolam may be administered orally, nasally, rectally, intravenously, or intramuscularly. Midazolam (0.10-0.15 mg/kg IV) has minimal effect on respiratory rate, heart rate, or blood pressure and provides excellent preoperative anxiolysis and amnesia. Premedication with oral midazolam (0.5-1.0 mg/kg) mixed in sweet-flavored syrup induces anxiolysis in approximately 90% of children without hemodynamic or respiratory depressant effects. However, children may experience loss of coordination (head control), blurred vision, and rarely dysphoria. A child sedated with midazolam should not be left unattended. Most children rapidly accept an inhalational anesthetic by face mask after oral midazolam premedication. The widespread use of preoperative oral midazolam has decreased the practice of PPI.

Dexmedetomidine

Dexmedetomidine is a central α_2 adrenergic receptor agonist similar to clonidine. Dexmedetomidine lacks respiratory depressant effects and produces anxiolysis, sedation, mild analgesia, and sympatholysis. Interestingly, rapid bolus administration may produce hypertension and bradycardia, whereas continuous infusions may produce hypotension and bradycardia. Dexmedetomidine is frequently used for sedation in ICU patients as well as for procedures. Dexmedetomidine has become a popular adjuvant for general anesthesia during pediatric cardiac surgery.

Barbiturates

Sodium thiopental is the classic barbiturate IV induction agent, although it is now rarely used. Side effects of thiopental include respiratory depression, apnea, and hypotension. Induction with 3-5 mg/kg of thiopental produces unconsciousness within seconds, lasting 5-10 min. Thiopental is not useful for maintenance of anesthesia, which requires other IV or inhalational anesthetics. Pentobarbital is a barbiturate frequently administered IV for sedation in children during imaging procedures of intermediate duration (e.g., imaging studies) that require akinesia. **Pentobarbital** is a potent respiratory depressant, particularly when combined with opioids and benzodiazepines. Pentobarbital has a prolonged duration of action. Pentobarbital sedation for nonpainful procedures generally results in delayed emergence. **Sodium methohexital** (Brevital) is another IV induction agent, similar to sodium thiopental in respiratory depressant effects. Barbiturates lack analgesic properties, and painful procedures require supplemental analgesia.

Neuromuscular Blocking Agents

Neuromuscular blockade is performed to facilitate endotracheal intubation and akinesia during surgery. NMBAs may be *depolarizing* (e.g., succinylcholine) or *nondepolarizing* (e.g., vecuronium, rocuronium, cisatracurium). **Succinylcholine** has a high-risk profile in children. Its use is associated with postoperative pain from muscle spasms; hyperkalemia; elevated intracranial, intraocular, and intragastric pressures; malignant hyperthermia; myoglobinuria; and renal damage. Consequently, succinylcholine is now rarely used, except to provide rapid relief of laryngospasm. Endotracheal intubation is most often facilitated with nondepolarizing NMBAs. **Rocuronium** is most commonly used for intubation because of its rapid onset of action. For procedures that last >40 min, **vecuronium** and **cisatracurium** are also suitable to induce muscle relaxation for intubation. After intubation, repeat administration of NMBAs may be indicated to maintain muscle relaxation to facilitate surgery. Prolonged use of nondepolarizing NMBAs in critical illness may contribute to myopathy, especially when combined with high-dose corticosteroids.

Induction of General Anesthesia

The primary goal of induction of general anesthesia is the rapid and safe transition to a state of unconsciousness. Induction in children is usually achieved by inhalational anesthetics, although IV agents are indicated when patients have IV access. Many children will not tolerate the establishment of vascular access before induction of anesthesia, and it is routine to induce anesthesia by face mask with inhaled anesthetics. Before the induction of anesthesia, monitors applied may include pulse oximetry, ECG, and noninvasive blood pressure cuff. The child is then cautiously introduced to the face mask, which contains a high gas flow (5-7 L/min O_2), frequently mixed with N_2O. Inhalation of N_2O and O_2 for 60-90 sec induces a state of euphoria. Nitrous oxide blunts the airway responses to potent volatile inhalational agents, and sevoflurane may then be safely introduced into the inhaled gas mixture. This leads to unconsciousness within 30-60 sec while the child continues to breathe spontaneously.

Following induction, IV access is obtained, and comprehensive intraoperative monitoring initiated. Thereafter, definitive airway management is performed. Airway management for short procedures (i.e., myringotomy tubes) frequently includes a mask airway and spontaneous ventilation; this is safe when the airway is secure, and patent and aspiration risk is low. Longer procedures (>30-60 min) are not usually performed with mask airways. Definitive artificial airways include laryngeal mask airways and endotracheal tubes. The **laryngeal mask** is a supraglottic airway generally reserved for procedures in spontaneously ventilating patients and does not effectively prevent the aspiration of gastric contents.

For complex surgical procedures, **endotracheal intubation** in required (e.g., intraabdominal, intrathoracic, airway). Although endotracheal intubation may be performed under deep inhalational anesthesia, the depth of anesthesia required to attenuate airway reflexes may produce hemodynamic instability. Therefore, NMBAs are frequently administered to facilitate intubation. The depolarizing NMBA succinylcholine is rarely used, and nondepolarizing NMBAs such as rocuronium and vecuronium are most frequently used (see earlier). After muscle relaxation, direct laryngoscopy and endotracheal intubation can be performed. Correct endotracheal tube (ETT) placement is confirmed by direct laryngoscopy, end-tidal CO_2 measurement, and bilaterally equal breath sounds. Additional confirmatory tests include chest radiograph and fiberoptic bronchoscopy. After endotracheal intubation, controlled mechanical ventilation is required in the setting of neuromuscular blockade (see Chapter 89).

Children with full stomach precautions may require **rapid sequence induction** . Before performing a rapid sequence induction, preoxygenation with 100% oxygen for 2-5 min increases alveolar oxygen content and provides an extra margin of safety if intubation is difficult. Rapid sequence induction involves concurrent administration of hypnotic and NMBAs. Assisted ventilation before or after drug administration is avoided due to the risk of gastric distention, regurgitation, and aspiration. After administering a sedative and NMBA, the Sellick maneuver (cricoid pressure) is performed by applying firm pressure in a posterior direction, against the cricoid cartilage. This displaces the cricoid cartilage into the esophagus, forming an artificial sphincter to prevent reflux of the gastroesophageal contents. Cricoid pressure should be maintained until correct ETT placement is verified by positive end-tidal CO_2 and bilateral breath sounds.

The major risk of rapid sequence induction is intubation failure. In this situation the child is paralyzed without a protected airway, and ventilation may be hazardous or impossible. Only experienced airway specialists should undertake rapid sequence induction. It should be avoided in patients with a history of failed endotracheal intubation or features (micrognathia) associated with difficult intubation. Under these circumstances, bronchoscopic awake intubation may be indicated.

Complications During Induction

During induction of anesthesia the transition between full wakefulness to unconsciousness is fraught with potential complications, including laryngospasm, bronchospasm, vomiting, and aspiration. Concerns for vomiting and aspiration dictate adherence to preanesthetic fasting guidelines and may be an indication for rapid sequence anesthetic induction.

During induction of anesthesia, especially with inhalational anesthetics, a period of excitement may occur. This period is associated with heightened airway reflexes, which can lead to coughing, gagging, laryngospasm, and bronchospasm. **Laryngospasm** is the reflex closure of the larynx, which prevents spontaneous or assisted ventilation. The child may make violent inspiratory efforts against a closed glottis, generating significantly negative intrathoracic pressure. This may affect cardiovascular function and cause postobstructive pulmonary edema. Laryngospasm can be prolonged, and hypoxia may ensue. Laryngospasm occurs in up to 2% of all anesthetic inductions in children <9 yr old and is much less common in older patients. Laryngospasm occurs twice as frequently in children with active or recent upper respiratory tract infection. A history of tobacco exposure increases the likelihood of laryngospasm significantly.

Laryngospasm can be relieved by increasing the depth of anesthesia, either intravenously or through inhalation (although with the glottis closed, further administration of inhalational anesthesia is not possible). Neuromuscular blockade relieves laryngospasm, and an acute situation may be an indication for succinylcholine administration. Continuous positive airway pressure administration may be beneficial in alleviating laryngospasm. Laryngospasm may also occur during emergence from anesthesia because airway tone is increased during the transition to wakefulness.

Bronchospasm may result from increased airway reactivity during the hyperexcitable stage of induction, or secondary to histamine release induced by anesthetic agents. Endotracheal intubation may provoke bronchospasm, especially in asthmatic patients, which may be associated with life-threatening hypoxemia and inability to ventilate. Alternative airway management strategies such as laryngeal mask should be considered when appropriate in children with severe reactive airway disease. The use of histamine-releasing anesthetic agents has been associated with severe bronchospasm, and in rare instances cardiorespiratory failure. Environmental tobacco smoke is another risk factor.

Hypoxemia during induction may be secondary to reduced functional residual capacity, atelectasis, and ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. Volatile anesthetics blunt hypoxic pulmonary vasoconstriction further contributing to $\dot{V}/\dot{Q}$ abnormalities. **Hypersecretion** may result in airway obstruction and should managed with antisialogues, such as glycopyrrolate and atropine. The newer inhalation agents are less potent secretagogues, and the routine use of atropine premedication is much less common, but often indicated when ketamine is used.

Hemodynamic complications may also develop during induction of anesthesia. **Hypotension** is common and may be exaggerated patients with hypervolemia, decreased myocardial function, or CHD. Inhalational anesthetics sensitize the myocardium to circulating catecholamines, and induction and excitement are associated with a hypercatecholaminergic state.

Maintenance of Anesthesia

Maintenance of anesthesia is the period between induction and emergence. The child should be unaware of pain, unresponsive to painful stimuli, and physiologically supported. Anesthesia is typically maintained with a volatile anesthetic (e.g., isoflurane, sevoflurane) supplemented with opioid-based analgesia. IV hypnotic agents (e.g., dexmedetomidine, benzodiazepines) may be administered to augment hypnosis and amnesia. Choice of ventilatory strategy (spontaneous, assisted, or controlled) varies according to procedure type and patient condition (see Chapter 89). Surgical trauma may result in hypothermia and hypovolemia due to blood loss and significant fluid shifts (third spacing). Management of these physiologic disturbances is the responsibility of the anesthesiologist during maintenance.

Temperature Management

Thermoregulation is critical during anesthesia. The absence of movement and inhibition of shivering reduce thermogenesis. Mechanisms of heat loss during anesthesia include convection, radiation, evaporation, and conduction. Although temperature sensing may remain normal, the autonomic response to hypothermia is reduced. Anesthetic agents cause vasoparesis, which further impairs thermoregulation and increases heat loss. In newborns, inhalational anesthetics inhibit nonshivering thermogenesis from brown fat, increasing the risk for hypothermia. Humidification and warming of inspired gases is required. Additional warming devices, such as forced-air warming blankets and radiant warmers, should also be used.

Fluid Management

Most anesthetics produce vasodilation and increase venous capacitance, effectively reducing myocardial preload. Surgical bleeding and insensible/third space fluid losses further contribute to intravascular volume depletion. Volume expansion with isotonic salt-containing solutions (normal saline, lactated Ringer, Plasmalyte) may be required to maintain cardiac output and organ perfusion. Increased renin-angiotensin-aldosterone axis activation and antidiuretic hormone (ADH) secretion further complicate fluid regulation.

Intraoperative fluid management must account for (1) deficits acquired during preoperative fasting, (2) maintenance fluid requirements, (3) surgical blood loss, and (4) insensible fluid loss. Infants should receive glucose-containing isotonic fluid to prevent perioperative hypoglycemia. Table 74.9 is a guideline for determining fluid deficits and maintenance requirements in the OR. For longer procedures, fluid deficits should be replaced with isotonic fluid over the 1st 3 hr of intraoperative management. Deficits are generally calculated as the number of hours of fasting status multiplied by the hourly maintenance rate for the child. Half the deficit is replaced during the 1st hr and half during the subsequent 2 hr. If hypotension or tachycardia persists in the early stages of anesthesia, more rapid replacement of the fluid deficit may be indicated.

Table 74.9

Intraoperative Pediatric Fluid Replacement

INFUSION RATE	PATIENT WEIGHT
4 mL/kg/hr	1-10 kg
2 mL/kg/hr	10-20 kg
1 mL/kg/hr	per kg >20 kg
Example: 22 kg child requires (4 × 10) + (2 × 10) + (1 × 2) = 62 mL/hr	

Third space interstitial fluid losses should be replaced with isotonic salt solutions. For smaller operations, such as herniorrhaphy, pyloromyotomy, and minor procedures, fluid replacement at 3-5 mL/kg/hr is indicated for insensible losses. Complex abdominal or thoracic procedures with large insensible losses may require an additional 8-10 mL/kg/hr of IV fluid replacement. Crystalloid solution is indicated for blood loss as a 3 : 1 ratio. Allogenic blood products should be replaced as a 1 : 1 ratio. Colloid (albumin) administration also decreases the amount of crystalloid replacement needed for blood loss. During large-volume transfusions, active fluid warming should be performed to prevent hypothermia. With major surgery and resultant SIRS, capillary integrity is lost and third space losses are common. Failure to replace fluid loss and restore intravascular volume may lead to shock.

Perioperative **hypoglycemia** may result from preoperative fasting, most often in neonates or in children with metabolic disorders. In neonates, perioperative glucose monitoring is indicated and glucose replacement is frequently required. In older children with normal nutritional status, isotonic salt solutions without glucose are adequate. In patients receiving total parenteral alimentation containing high glucose concentrations (>10%), continuous glucose administration should be ensured to avoid rebound hypoglycemia.

Postprocedural care includes supervision of emergence and recovery from anesthesia and surgery. **Emergence** describes the transition period between the anesthetized state and consciousness. During emergence, patients experience decreased anesthetic effect and increased physiologic and psychological responses to painful stimuli (e.g., reactive autonomic tone, excitement, anxiety). Inhalational anesthetic agents are rapidly excreted during ventilation, and muscle relaxants can be reversed; however, the effects of opioids, benzodiazepines, and IV hypnotics may be prolonged. Normal physiologic functions such as spontaneous ventilation resume, and hemodynamic function improves. Before leaving the OR after routine elective procedures, the child should be conscious with intact airway reflexes and a patent airway. The effects of muscle relaxants should be reversed. Ideally, emergence should be as brief as possible, with maintenance of analgesia and anxiolysis and restoration of cardiorespiratory function. However, critically ill patients scheduled for ICU admission may require postoperative endotracheal intubation and mechanical ventilation. In these patients, deeper levels of sedation and analgesia should be maintained after the procedure.

During emergence, it is essential to assess whether **residual neuromuscular blockade** (NMB) exists. If weakness or respiratory depression is observed in the postoperative phase, prolonged NMB should be considered. *Reversal of residual NMB is standard anesthetic practice.* With the virtual abandonment of succinylcholine, only nondepolarizing NMBAs are routinely used for intubation. The termination of NMB depends on metabolism and elution away from the neuromuscular junction. Classically, nondepolarizing muscle relaxants are reversed by increasing the acetylcholine concentration at the neuromuscular junction with acetylcholine esterase inhibitors (neostigmine, edrophonium), which work through competitive antagonism. Vagolytic agents (e.g., atropine, glycopyrrolate) must be co-administered to prevent bradycardia. This process, even for the shortest-acting muscle relaxant, rocuronium, can take several minutes. An intubating dose of rocuronium to rapidly induce paralysis in emergency situations may not spontaneously reverse for 20 min or longer (compared with about 3 min for succinylcholine). The effects of long-acting, nondepolarizing NMBAs (vecuronium, pancuronium) are invariably reversed. Residual NMB is common despite reversal with these agents. **Sugammadex** is an alternative reversal agent that has a very low rate of residual NMB. Its mechanism of action involves noncompetitive antagonism through encapsulation of neuromuscular agents.

Postanesthesia Care Unit

In the postanesthesia care unit (PACU), the child is observed until there is adequate recovery from anesthesia and sedation. Achievement of spontaneous breathing, adequate pulse oximetry saturation (> 95%), and hemodynamic stability are key recovery end-points. The child should be arousable, responsive, and oriented before discharge from the PACU. The amount of time spent in the PACU varies based on disposition (transfer to acute care or ICU, transfer to day surgery postrecovery unit, or discharge to home). Parents should be permitted to comfort their children in the PACU. Discharge from the PACU depends on the child's overall functional status—not merely the physiologic end-points, but also the adequate provision of analgesia and control of postoperative nausea and vomiting. Various scoring systems have been used for determining readiness for discharge from the PACU (Table 74.10).

Table 74.10

Postanesthesia Recovery Scores

ALDRETE RECOVERY SCORE	**>9 REQUIRED FOR DISCHARGE**
ACTIVITY—VOLUNTARILY OR ON COMMAND	
Moves 4 extremities	2
Moves 2 extremities	1
No motion	0
BREATHING	
Deep breath, cough, cry	2
Dyspnea or shallow breathing	1
Apnea	0
BLOOD PRESSURE	
Within 20% of preanesthetic value	2
Within 20–50% of preanesthetic value	1

>50% outside preanesthetic value	0
COLOR	
Pink	2
Pale, blotchy, dusky	1
Cyanotic	0
CONSCIOUSNESS	
Fully aware, responds	2
Arouses to stimulus	1
Unresponsive	0
STEWARD RECOVERY SCORE	**6 REQUIRED FOR DISCHARGE**
ACTIVITY	
Moves limbs purposefully	2
Nonpurposeful movement	1
Still	0
CONSCIOUSNESS	
Awake	2
Responsive	1
Unresponsive	0
AIRWAY	
Coughing on command or crying	2
Maintaining patent airway	1
Requires airway maintenance	0

Postanesthetic Complications

Respiratory insufficiency following general anesthesia is common. Prolonged emergence from anesthesia and respiratory depression may be caused by the residual effects of opioids, hypnotic agents, or NMBAs. Pain may also cause significant hypoventilation, especially after thoracic or abdominal surgery. Delayed emergence from anesthesia may result from retention of inhaled anesthetics worsened by hypoventilation. Hypothermia, especially in neonates, delays metabolism and excretion of anesthetics and prolongs NMB. Hypoventilation after surgery is associated with the development of **atelectasis** . Microatelectasis may lead to postoperative infections. When airway obstruction is present, maintenance of airway patency may necessitate oropharyngeal or nasopharyngeal airway placement. In the setting of profound respiratory depression, endotracheal intubation and mechanical ventilation may be indicated.

Opioid reversal with naloxone may be indicated in rare instances when excessive **opioid effect** is suspected. However, naloxone reverses both the respiratory depressant and the analgesic effects of opioids. Following naloxone reversal, a somnolent child with respiratory depression may experience increased pain. Opioid reversal requires bedside attention by the physician to monitor the child's behavioral, hemodynamic, and respiratory status. Importantly, naloxone is shorter-acting than most opioid analgesics, which may result in re-narcotization.

Postoperative stridor occurs in up to 2% of all pediatric patients. The use of appropriately sized ETTs and assurance of an air leak <30 cm H_2 O pressure decreases the risk of airway trauma or edema. A history of stridor increases the likelihood of postoperative complications. Stridor may be severe enough after extubation to require reintubation. Racemic epinephrine aerosols and dexamethasone are effective therapies; their use requires prolonged observation because of the potential for rebound stridor. Stridor in infants suggests the need for overnight observation.

Cardiovascular complications are less frequently encountered in the PACU. Volume expansion may be required to maintain adequate cardiac output, peripheral perfusion, and urine output. Large-volume fluid resuscitation (>30 mL/kg) in the postoperative period may be an indication of evolving shock physiology, and sources of hypovolemia (e.g., occult bleeding) or myocardial dysfunction (e.g., tamponade, pneumothorax) should be considered.

Emergence delirium immediately after anesthesia is noted in 5–10% of children and is more common in those 3-9 yr old. Manifestations include restlessness, combativeness, disorientation, and inconsolability. Almost all anesthetic agents have been linked to the development of delirium, especially newer volatile anesthetic agents (e.g., sevoflurane, desflurane). Potential postoperative complications, such as hypoglycemia and hypoxemia, should also be ruled out. Occasionally, it is necessary to provide additional sedation (e.g., propofol, dexmedetomidine, benzodiazepines) although these agents prolong postanesthesia recovery time and may not effectively reduce delirium.

Awareness During Anesthesia

A fundamental aim of anesthesia is to prevent recall by inducing hypnosis and amnesia. In adults, certain anesthetic techniques and surgical procedures have been associated with recall during anesthesia. The long-term sequelae of recall in children are unknown. Continuous cerebral bispectral index (BIS) electroencephalographic monitoring has been used to assess intraoperative awareness. Unfortunately, pediatric studies have not confirmed the usefulness of BIS monitoring as a means of determining anesthetic depth. Existing data do not support the routine use of BIS monitoring during pediatric anesthesia. Volatile anesthetic agents reliably produce dose-dependent hypnotic and amnestic effects and remain a mainstay of general anesthesia.

Postoperative Nausea and Vomiting

Following general anesthesia, 40–50% of children may experience postoperative nausea and vomiting (PONV) that generally lasts for several hours. This complication prolongs recovery room times and requires significant nursing attention. The etiology is not completely understood but is likely multifactorial related to the emetic effects of anesthetics, pain, and surgical stress. Opioid analgesics may provoke nausea and vomiting. Importantly, preoperative fasting does not decrease the incidence of PONV. Indeed, hydration and glucose supplementation appear to be important factors in decreasing PONV. Multimodal analgesia with nonopioid agents (e.g., acetaminophen, ibuprofen, ketorolac) and regional or local anesthesia may decrease PONV. The serotonin antagonist ondansetron is an effective treatment of PONV. Ondansetron prophylaxis is also recommended for patients at increased risk of PONV, such as after eye and otolaryngology surgery. Serotonin antagonists are contraindicated in children taking serotonin reuptake inhibitors for migraine headaches. Dexamethasone may also be used for the treatment of PONV.

Thermoregulation and Malignant Hyperthermia

Following anesthesia, thermoregulation remains abnormal for several hours. **Hypothermia** , especially in neonates, may to cardiorespiratory depression and prolongation of the effect of opioids and NMBAs. Although hypothermia has deleterious effects, active rewarming should be performed cautiously to avoid hyperthermia and cutaneous burns. Postoperative shivering is common and may occur in the absence of hypothermia. **Hyperthermia** , with temperatures in excess of 39°C (102.2°F), is of concern in the postoperative period. When high fevers occur within hours of the use of an inhalational anesthetic, especially if succinylcholine was used, malignant hyperthermia must be ruled out.

Malignant hyperthermia (MH) is a hypermetabolic syndrome triggered by volatile anesthetic agents and succinylcholine. The onset of MH may be acute, fulminant, and lethal without appropriate interventions. The disease is genetically heterogeneous, with >10 genes contributing to susceptibility, but typically displays an autosomal dominant inheritance pattern. A family history of death or febrile reactions during anesthesia should alert the anesthesiologist to its potential. Mutations within the gene encoding for the ryanodine receptor (the calcium channel of the sarcoplasmic reticulum) predispose to MH susceptibility and have been identified in 20–40% of humans with MH. Certain **myopathies**

are associated with the risk of MH, including Duchenne muscular dystrophy, central core disease, and King Denborough syndrome.

The pathophysiology of MH involves uncontrolled intracellular calcium release from skeletal muscle sarcolemma, resulting in prolonged muscle contraction, adenosine triphosphate (ATP) depletion, and muscle cell death. Myolysis results in the release of myoglobin, creatine phosphokinase (CPK), and potassium into the blood. The clinical course of MH is characterized by rapid onset of high fever (>38.5°C), muscle rigidity, acidosis (metabolic and respiratory), high end-tidal CO_2 , and multiorgan dysfunction. Death may ensue secondary to hemodynamic collapse from shock and cardiac dysrhythmias. Signs of MH generally occur within the 1st 2 hr of anesthesia, but (rarely) can occur up to 24 hr later.

Aggressive therapy involves discontinuation of all inhalational anesthetics, correction of the metabolic acidosis, and treatment with the muscle relaxant dantrolene. IV dantrolene (2.5 mg/kg as initial dose) should be initiated when MH is suspected. The need for repeat doses, up to a maximum of 10 mg/kg, is indicated for persistent fever, muscle rigidity, acidosis, and tachycardia. Once symptoms are controlled, the patient should be observed for at least 24 hr, because recrudescence may occur. The MH mortality rate was once >70% and is now <5% with standardized treatment algorithms. A MH cart with sufficient supplies of dantrolene should be present at every site where pediatric anesthesia is provided.

Certain phenomena suggest an increased risk of MH. Masseter spasm during induction, with rigid clenching of the masseter muscles and an inability to open the mouth, may signal MH susceptibility. Acute myoglobinuria associated with an MH-triggering agent is another clue. The child may not be hypermetabolic or febrile, but may have dark urine, high CPK levels, and risk of myoglobin-induced renal tubular damage. The finding of dark urine after administration of an anesthetic requires further investigation, including measurement electrolytes on CPK. Prevention of MH in susceptible patients requires the avoidance of triggering agents, which include inhalational anesthetics and succinylcholine. IV anesthesia and nitrous-opioid techniques are safe. MH-safe anesthesia machines devoid of trace concentrations of volatile anesthetic vapors should be used. Dantrolene prophylaxis is not recommended because MH is rapidly treatable and the drug causes respiratory depression and muscle weakness. For a child in whom MH is suspected, the MH hotline, 1-800-MHHYPER (1-800-644-9737), should be used to notify the Malignant Hyperthermia Association of the United

States (MHAUS). MHAUS registers susceptible patients and provides diagnostic and therapeutic information. Preanesthesia susceptibility testing includes genetic analysis of the ryanodine receptor gene, muscle biopsies, in vitro contraction studies, and possibly measurement of muscle CO_2 production in response to intramuscular caffeine.

Mediastinal Masses

Children with anterior mediastinal masses such as lymphomas, teratomas, and other primary mediastinal tumors are at serious risk for cardiorespiratory failure during anesthesia. Even mild sedation may result in airway compromise, inability to ventilate, cardiac tamponade, vascular obstruction, and circulatory collapse. These patients generally require surgical tissue diagnosis before treatment is initiated. Significant compression of vital structures can occur with seemingly mild symptoms. Tachypnea, orthopnea, wheezing, and avoidance of prone or supine positions are significant indications of serious risk. Echocardiographic or CT evidence of pericardial tamponade, right ventricular compression, or compression of the pulmonary artery suggests severe risk. Biopsy with light sedation under local anesthesia may be indicated. When anesthesia is required, preservation of spontaneous ventilation is critical during induction of anesthesia. Rigid bronchoscopy may be used to assist with ventilation in the setting of external airway compression Provisions to provide mechanical circulatory support (cardiopulmonary bypass) should also be available. In high-risk children, consideration should be given to initiating treatment with corticosteroids, radiation therapy, and chemotherapy before obtaining a tissue diagnosis.

Postoperative Apnea

Neonates and infants are at increased risk for the development of postoperative apnea after exposure to potent hypnotic and analgesic medications. Both central and obstructive apnea may occur. Postanesthetic apnea is most common within the 1st 12 hr, although apnea has been reported in premature infants up to 48 hr later. The risk of apnea is inversely proportional to postconceptual age at surgery and is highest in premature neonates <44 wk postconceptual age. This risk is minimal by the time premature infants have reached 60 wk postconceptual age. Theophyllines do not reliably decrease the incidence of postoperative apnea and are not routinely used. When surgery is required within the 1st mo of life, overnight observation and monitoring are indicated. In term infants >44 wk postconceptual age, management should include observation and monitoring for 6 hr with at least 1 sleep-wake-feed cycle without hypoxia, bradycardia, or supplemental oxygen. Premature infants <56 wk postconceptual age require observation for 12 hr after anesthesia.

Postoperative Pain Management

Postprocedural pain management should ensure adequate analgesia and anxiolysis (see Chapter 76). Preoperative education focusing on pain management through development of skills designed to decrease anticipatory anxiety and participation in treatment planning can be helpful for children and families. Pediatric pain management relies on multimodal therapy, including opioid and nonopioid analgesics. Nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, IV acetaminophen, opioids, and regional analgesia all have roles in postoperative pain management. Repeated evaluation is critical to effective pain management. Adjunctive therapy, such as pet therapy, may also decrease the need for potent analgesics postoperatively.

Patient-controlled analgesia (PCA) and **parent/nurse-controlled analgesia (PNCA)** are widely accepted postoperative pain regimens. PCA/PNCA provide a low-dose continuous (basal) infusion of opioid with intermittent (bolus) supplements as needed. The practitioner must determine the basal rate, bolus dose, lockout interval, and acceptable number of bolus doses per hour. PCA/PNCA safety requires appropriate medication dosing and assumes that patients are unlikely to overdose because somnolence will limit repeated self-administration. In young children, use of the *pain button* (for pain relief) may be more difficult to ensure, although children as young as 5 yr have been able to use PNCA successfully. In older children and adolescents, PCA is a standard modality of postoperative pain management.

Regional Anesthesia

Regional anesthesia is the use of anesthetics to block the conduction of afferent neural impulses to the central nervous system. Forms of regional anesthesia include local anesthesia, peripheral nerve blocks, nerve plexus blocks, and neuraxial (epidural and subarachnoid/spinal) blocks. Anesthetics may be administered as a single injection or as a continuous infusion. Regional anesthesia may be used for both intraoperative and postoperative analgesia. It has been linked to shortened recovery times and hospital stays in children. A major benefit of regional anesthesia is lesser central cardiorespiratory depressant effects. Injection of local anesthetics (e.g., lidocaine, bupivacaine) into the affected area may provide procedural analgesia lasting for hours to days. Wound infiltration with local anesthetics at the conclusion of surgery may also decrease early postoperative pain.

Neuraxial (epidural, spinal) analgesia is common in pediatric practice. The epidural space lies between the dura and the pia and arachnoid membranes, an area through which all nerve roots pass. Caudal epidural analgesia is placed through the sacral hiatus, inferior to the distal end of the spinal cord. This site is often used for pelvic and lower-limb anesthesia during urologic and orthopedic surgery in infants and toddlers. A single dose of caudal epidural anesthesia may provide hours of pain relief, and a continuous infusion may provide effective pain relief for hours to days. The epidural injection of opioids can provide analgesia for 12-24 hr and is a potential supplement to postoperative analgesia. Longer-acting local anesthetics (e.g., bupivacaine, ropivacaine) combined with an opioid (e.g., fentanyl, preservative-free morphine) are typically used in single-injection and continuous epidural therapy. It is also possible to provide epidural PCA with a continuous infusion pump and the patient's ability to self-administer analgesia as needed. Epidural analgesia can also provide pain relief in patients with chronic pain or pain caused by advanced malignant conditions.

Complications of neuraxial anesthesia include cephalad spread of blockade with respiratory depression, paralysis of respiratory muscles, and brainstem depression. Common complications of neuraxial analgesia are paresthesias and, if opioids are used, pruritus, nausea, and vomiting. Neuraxial opioid use necessitates antipruritic and antiemetic therapy. Infection and epidural hematoma are extremely rare. Neuraxial opioids, especially when administered intrathecally, may cause respiratory depression and require postoperative monitoring.

74.1

Anesthetic Neurotoxicity

John P. Scott

Keywords

general anesthesia
neurodevelopment
neurotoxicity
apoptosis

Laboratory animal studies have suggested a link between anesthetic exposure at an early age and neurotoxicity in developing brains. Existing nonclinical data implicate *N* -methyl-D -aspartate and γ-aminobutyric acid (GABA) pathways in apoptosis and neuronal cell death. Both histopathologic changes and adverse neurodevelopmental outcomes have been associated with exposure to both inhalational and IV anesthetics, including isoflurane, sevoflurane, ketamine, benzodiazepines, and propofol. Animal studies were initially performed in nonprimates (rodents), and controversy remains concerning experimental design (dose, duration of treatment, species differences). However, work in nonhuman primates has also shown an increased incidence of adverse neurodevelopmental outcomes after prolonged and/or multiple exposures to volatile anesthetics.

Human studies of anesthesia-induced neurotoxicity have yielded conflicting results. Further complicating the situation are other potential triggers for adverse neurodevelopmental outcomes, including comorbidities, surgical trauma, and perioperative cardiorespiratory status. Multiple population-based epidemiologic studies have suggested a potential association between anesthetic exposure and adverse neurodevelopmental outcomes following multiple or prolonged anesthetic exposures. Large-scale European and Canadian cohort studies utilizing national registries have revealed subtle differences in standardized psychometric testing of early school-aged children after exposure to general anesthesia. Interestingly, other studies in children have failed to yield similar results. The Pediatric Anesthesia and Neurodevelopmental Assessment (PANDA), a multicenter matched-sibling control study, revealed no association between brief anesthetic exposure for inguinal hernia repair and aptitude on psychometric testing. Similarly, the General Anaesthesia and Awake-Regional Anaesthesia in Infancy (GAS) study, a prospective multicenter randomized controlled trial comparing general and neuraxial spinal anesthesia in infants for hernia repair, *did not* demonstrate any significant differences in neurodevelopment at 2 yr of age between groups. The primary outcome of the GAS study is neurodevelopment at 5 yr of age, and these results have not yet been made available. Importantly, studies have not shown an association between adverse neurodevelopmental outcomes and anesthetic exposure <3 hr.

Alternatives to general anesthesia for many procedures in young children do not exist. Regional anesthetic techniques and narcotic-based anesthetics may gain popularity. Dexmedetomidine may also have some neuroprotective properties. Currently, there is insufficient data to make conclusions regarding the safety of one anesthetic approach over another. Ultimately, the potential for neurotoxicity must be balanced against the necessity of providing adequate anesthesia for children presenting for surgery.

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CHAPTER 75

Procedural Sedation

John P. Scott

See also Chapters 74 and 76 .

Sedation describes the continuum between wakefulness and general anesthesia (see Table 74.7). Many of the same drugs used to induce general anesthesia may be used to provide sedation (see Table 74.8). Analogous to the provision of anesthesia, performance of procedural sedation requires a comprehensive presedation evaluation, intraprocedural monitoring, and postsedation recovery care. The term **conscious sedation** refers to a condition in which a patient is sleepy, comfortable, and cooperative but maintains airway-protective and ventilatory reflexes. Depending on the choice of pharmacotherapy, sedation may not provide analgesia. Sedation that is sufficient to obtund painful responses describes deep sedation. **Deep sedation** is a state of unarousability to voice and is accompanied by suppression of reflex responses.

Pediatric procedural sedation requires vigilance and knowledge to ensure safety and is governed by the same guidelines as anesthesia care (Table 75.1). Adherence to guidelines for appropriate monitoring and management of sedation in children is imperative. Sedative doses that cause minimal sedation in one patient may produce complete unconsciousness and apnea in another. Anxiolysis or light sedation with chloral hydrate, benzodiazepines, and dexmedetomidine is often sufficient for nonpainful procedures. The use of dexmedetomidine for procedural sedation is safe; recovery time can be prolonged and success variable. For painful procedures (e.g., bone marrow aspiration), the combination of hypnosis and analgesia is required. The addition of opioids to sedation regimens increases the risk of respiratory insufficiency. Short-acting anesthetics (e.g., propofol, methohexital, remifentanil) provide effective procedural sedation, but their use carries a higher likelihood of inadvertent induction of general anesthesia. Use of these medications requires the presence of an anesthesiologist and/or specially trained, experienced, credentialed, and qualified physicians.

Table 75.1

Systematic Approach to Sedation in Children

Comprehensive medical history and organ system assessment, anticipating underlying medical problems that predispose the patient to anesthetic complications
Careful physical examination focused on the cardiorespiratory system and airway
Appropriate fasting
Informed consent
Pediatric drug dosing (mg/kg)
Appropriately sized equipment
Documentation of vital signs and condition on a time-based record
Rapid response (“code”) team to respond to emergencies with “crash cart”
Fully equipped and staffed recovery area
Discharge criteria documenting recovery from sedation

Many pediatric subspecialists provide sedation and anesthesia care for children. The use of anesthetic agents is not limited to anesthesiologists, but anesthesiology departments are obligated to help develop, manage, and oversee sedation services. Together, hospitals and providers, including anesthesiologists, share responsibility for the oversight and credentialing of individuals administering sedation and anesthesia.

The elements of a safe pediatric procedural sedation system include the following:

- Clearly defined knowledge and skill sets
- Adequate prerequisite training
- Credentialing of providers
- Maintenance of certification
- Ensuring that sedation sites meet recognized standards

◆ Continuous quality improvement

Table 75.2 provides an approach to proper language to help the child cope with procedural pain.

Table 75.2

Suggested Language for Parents and Health-Care Providers

LANGUAGE TO AVOID	LANGUAGE TO USE
You will be fine; there is nothing to worry about. (reassurance)	What did you do in school today? (distraction)
This is going to hurt/this won't hurt. (vague; negative focus)	It might feel like a pinch. (sensory information)
The nurse is going to take some blood. (vague information)	First, the nurse will clean your arm, you will feel the cold alcohol pad, and next … (sensory and procedural information)
You are acting like a baby. (criticism)	Let's get your mind off of it; tell me about that film … (distraction)
It will feel like a bee sting. (negative focus)	Tell me how it feels. (information)
The procedure will last as long as … (negative focus)	The procedure will be shorter than … (television program or other familiar time for child) (procedural information; positive focus)
The medicine will burn. (negative focus)	Some children say they feel a warm feeling. (sensory information; positive focus)
Tell me when you are ready. (too much control)	When I count to three, blow the feeling away from your body. (coaching to cope; distraction-limited control)
I am sorry. (apologizing)	You are being very brave. (praise; encouragement)
Don't cry. (negative focus)	That was hard; I am proud of you. (praise)
It is over. (negative focus)	You did a great job doing the deep breathing, holding still … (labeled praise)

Adapted from Krauss BS, Calligaris L, Green SM, Barbi E: Current concepts in management of pain in children in the emergency department, *Lancet* 387:83–92, 2016.

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CHAPTER 76

Pediatric Pain Management

Lonnie K. Zeltzer, Elliot J. Krane, Rona L. Levy

Pain is both a sensory and an emotional experience. When unrecognized and undertreated, pain extracts a significant physiologic, biochemical, and psychological toll on both the child and the family. Many disease processes and most interventional diagnostic or treatment procedures in pediatrics are associated with pain. Similarly, traumatic, developmental, cognitive, psychological, and social experiences can also trigger and maintain chronic pain.

Definition and Categories of Pain

The International Association for the Study of Pain (IASP) defines **pain** as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” The important elements to emphasize in this definition are (1) pain encompasses both peripheral physiologic and central neural components and (2) pain may or may not be associated with ongoing tissue damage. The experience of pain lies primarily in the strength and patterning of central neural connectivity (Fig. 76.1). While immediate upstream neural activation can originate from inflammatory, structural, or biochemical events, processes not only in the periphery of the body but also in the spinal cord and the brain influence the intensity and duration of pain. Similarly, central neural processes in the brain are associated with the location, intensity, and distress associated with pain. Chronic pain can develop when the upstream neural signaling continues to activate central neural circuits, such as with continued peripheral inflammatory or structural pain-associated processes.

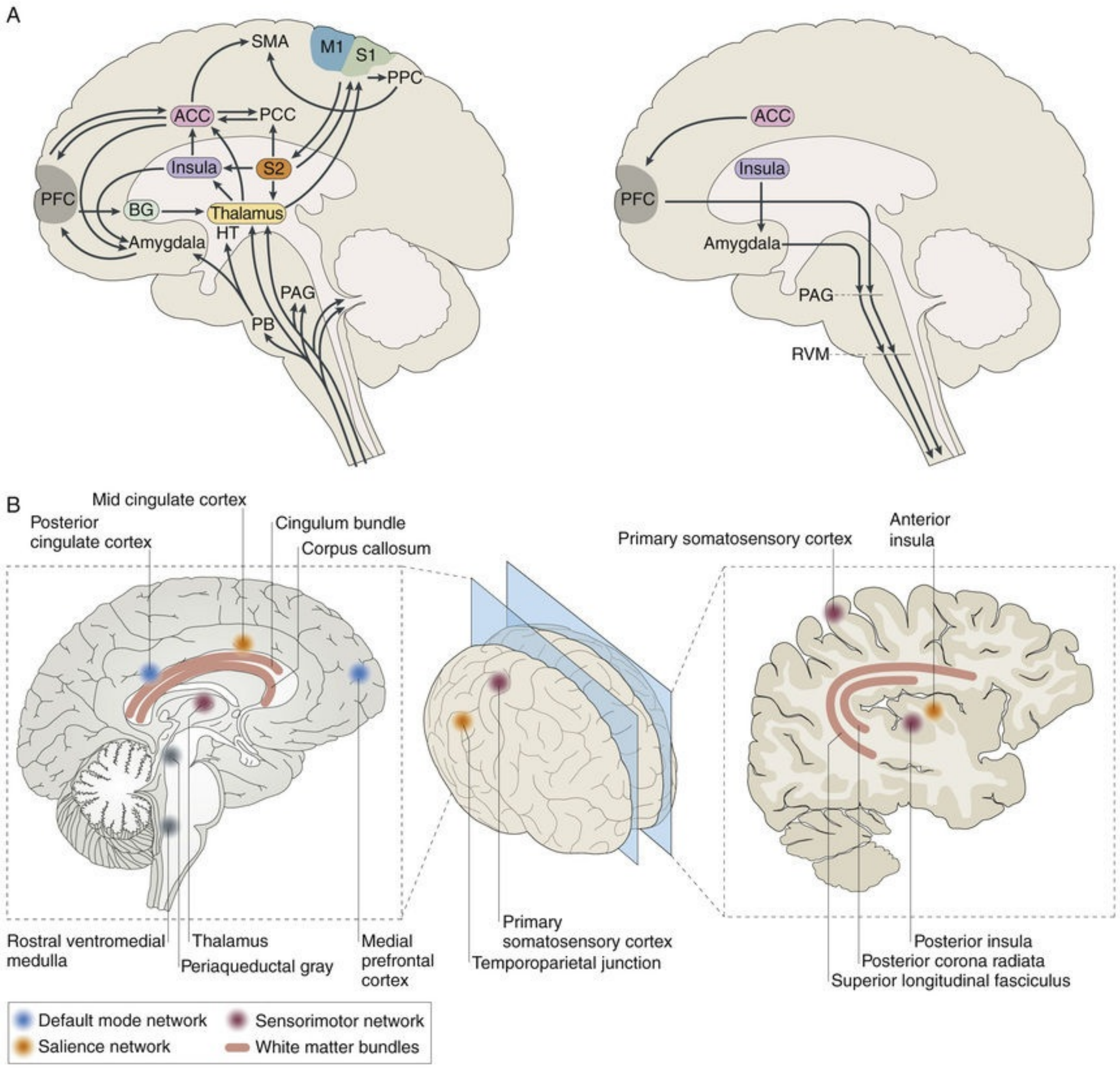
A
SMA
M1
S1
PPC
ACC
PCC
Insula
S2
PFC
BG
Thalamus
HT
Amygdala
PAG
PB
ACC
Insula
PFC
Amygdala
PAG
RVM
B
Mid cingulate cortex
Posterior cingulate cortex
Cingulum bundle
Corpus callosum
Primary somatosensory cortex
Anterior insula
Rostral ventromedial medulla
Thalamus
Periaqueductal gray
Medial prefrontal cortex
Primary somatosensory cortex
Temporoparietal junction
Posterior insula
Posterior corona radiata
Superior longitudinal fasciculus
● Default mode network
● Sensorimotor network
● Salience network
▬ White matter bundles

FIG. 76.1 **Brain pathways, regions, and networks involved in acute and chronic pain. ACC, Anterior cingulate cortex; PCC, posterior cingulate cortex; BG, basal ganglia; HT, hypothalamus; PAG, periaqueductal gray; PB, parabrachial nuclei; PFC, prefrontal cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; RVM, rostral ventromedial medulla. (*A, left panel* , From Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: Human brain mechanisms of pain perception and regulation in health and disease, *Eur J Pain* 9:463–484, 2005; *A, right panel* , from Schweinhardt P, Bushnell MC: Pain imaging in health and disease—how far have we come? *J Clin Invest* 120:3788–3797, 2010; *B,* from Davis KD, Flor H, Greely HT, et al: Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations, *Nat Rev Neurol* 13:624–638, 2017.)**

Often, however, pediatricians face the most difficult problems when either acute pain becomes chronic or chronic pain develops and is maintained without a definable infectious, inflammatory, metabolic, or structural cause. When no “cause” can be found, patients are often referred to mental health specialists, or the cause for the pain is labeled as “stress.” Children read this message as, “The doctor thinks I am faking pain or am crazy." Parents see their child suffering and often seek care elsewhere, with the child undergoing numerous tests, procedures, medication trials, and visits and many physicians looking for the cause of the pain so it can be "fixed." Meanwhile, the child may be missing school, social, and physical activities and developing poor sleep habits with increasing fatigue.

It is recognized that chronic pain, in the absence of a specific identified structural, biochemical, or inflammatory cause, develops through the initiation, maintenance, and strength of central neural connectivity patterns, the *connectome* of the child's brain (see Chapter 147). That is, what is now called "centrally mediated pain" derives from neural connectivity patterns in the brain that include centers involved in autonomic nervous system control, memory, and other cognitive centers, as well as emotional centers of the brain. In pediatrics, birth history and child development overlay these central patterns that contribute to the development of chronic pain. A child with high-functioning autism spectrum disorder (ASD) may perseverate on a pain symptom (e.g., headache) in the same way the child might perseverate on an idea or point of view (e.g., the parents may never "win" an argument with their child). Parents may understand the concept of a "sticky nervous system" as the perpetuator of the continued pain in such a child. This model of brain connectivity patterns or "top-down" mediators of chronic pain is important, since it explains how psychological and other nonpharmacologic interventions work to reduce pain and suffering. Science has come a long way since the model of pain as "psychological" or "physical." The current model of pain also includes the impact of the gut microbiome in altering central neural processes in relation to the development and maintenance of pain.

Table 76.1 specifies important pain categories typically treated (somatic, visceral, and neuropathic) and defines the elements and characteristics of **nociception,** the peripheral physiologic aspect of pain perception. Nociception refers to how specialized fibers (largely but not exclusively the small, unmyelinated A-delta and C fibers) in the peripheral nervous system transmit nerve impulses (usually transmitting signals originating from peripheral mechano- and chemoreceptors) through synapses in the spinal cord's dorsal horn through (but not exclusively through) the spinothalamic tracts to the brain's higher centers, where the development of neural connectivity patterns creates the experience of pain.

Table 76.1

Pain Categories and Characteristics

PAIN CATEGORY	DEFINITION AND EXAMPLES	CHARACTERISTICS
Somatic	Pain resulting from injury to or inflammation of tissues (e.g., skin, muscle, tendons, bone, joints, fascia, vasculature) *Examples:* burns, lacerations, fractures, infections, inflammatory conditions	In skin and superficial structures: sharp, pulsatile, well localized In deep somatic structures: dull, aching, pulsatile, not well localized
Visceral	Pain resulting from injury to or inflammation of viscera *Examples:* angina, hepatitic distention, bowel distention or hypermobility, pancreatitis	Aching and cramping; nonpulsatile; poorly localized (e.g., appendiceal pain perceived around umbilicus) or referred to distant locations (e.g., angina perceived in shoulder)
Neuropathic	Pain resulting from injury to, inflammation of, or dysfunction of the peripheral or central nervous system *Examples:* complex regional pain syndrome (CRPS), phantom limb pain, Guillain-Barré syndrome, sciatica	Spontaneous; burning; lancinating or shooting; dysesthesias (pins and needles, electrical sensations); hyperalgesia (amplification of noxious stimuli); hyperpathia (widespread pain in response to a discrete noxious stimulus); allodynia (pain in response to nonpainful stimulation); pain may be perceived distal or proximal to site of injury, usually corresponding to innervation pathways (e.g., sciatica)

Assessment and Measurement of Pain in Children

Assessing pain entails much more than merely quantifying it. Whenever feasible, the physician should ask the patient about the character, location, quality, duration, frequency, and intensity of the pain. Some children may not report pain because of fears (often well founded) of talking to strangers, disappointing or bothering others, receiving an injection if they report pain, returning to the hospital if they admit to pain, and other negative reactions. For infants and nonverbal children, their parents, pediatricians, nurses, and other caregivers are constantly challenged to interpret whether the child's distressed behaviors represent pain, fear, hunger, or a range of other perceptions or emotions. Similarly, lack of normal interest in play without behavioral distress signals can be manifestations of pain. Therapeutic trials of comfort measures (cuddling, feeding) and analgesic medication may be helpful in clarifying the triggers of the behaviors.

Behavior and physiologic signs are useful but can be misleading. A toddler may scream and grimace during an ear examination because of fear rather than pain. Conversely, children with inadequately relieved persistent pain from cancer, sickle cell disease, trauma, or surgery may withdraw from their surroundings and appear very quiet, leading observers to conclude falsely that these children are comfortable or sedated or, for adolescent patients, are “drug seeking.” In these situations, increased dosing of analgesics may make the child become more, not less, interactive and alert. Similarly, neonates and young infants may close their eyes, furrow their brows, and clench their fists in response to pain. Adequate analgesia is often associated with eye opening and increased involvement in surroundings. A child who is experiencing significant chronic pain may play normally as a way to distract attention away from pain. This coping behavior is sometimes misinterpreted as evidence of the child's “faking” or exaggerating pain at other times.

Age-Specific and Developmentally Specific Measures

Because infants, young children, and nonverbal children cannot express the quantity of pain they experience, several pain scales have been devised in an attempt to quantify pain in these populations (Fig. 76.2 and Table 76.2).

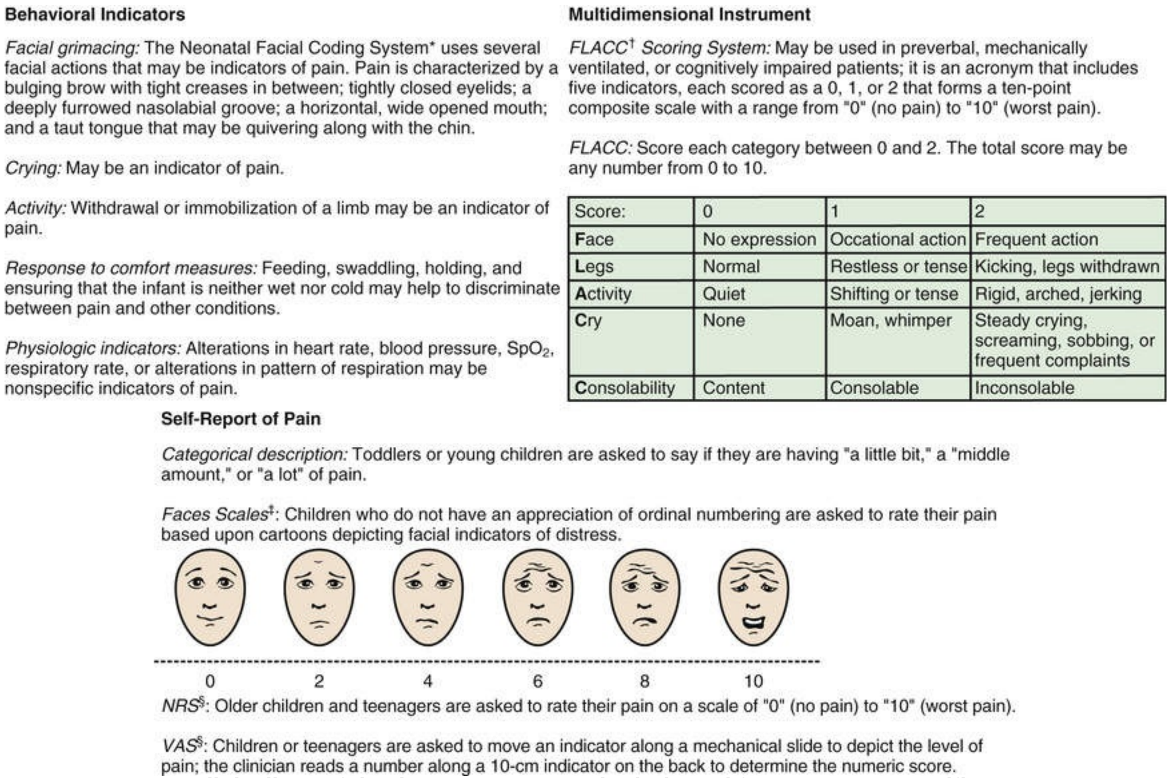

Behavioral Indicators

Facial grimacing: The Neonatal Facial Coding System* uses several facial actions that may be indicators of pain. Pain is characterized by a bulging brow with tight creases in between; tightly closed eyelids; a deeply furrowed nasolabial groove; a horizontal, wide opened mouth; and a taut tongue that may be quivering along with the chin.

Crying: May be an indicator of pain.

Activity: Withdrawal or immobilization of a limb may be an indicator of pain.

Response to comfort measures: Feeding, swaddling, holding, and ensuring that the infant is neither wet nor cold may help to discriminate between pain and other conditions.

Physiologic indicators: Alterations in heart rate, blood pressure, SpO_2, respiratory rate, or alterations in pattern of respiration may be nonspecific indicators of pain.

Multidimensional Instrument

FLACC[†] *Scoring System:* May be used in preverbal, mechanically ventilated, or cognitively impaired patients; it is an acronym that includes five indicators, each scored as a 0, 1, or 2 that forms a ten-point composite scale with a range from "0" (no pain) to "10" (worst pain).

FLACC: Score each category between 0 and 2. The total score may be any number from 0 to 10.

Score:	0	1	2
Face	No expression	Occational action	Frequent action
Legs	Normal	Restless or tense	Kicking, legs withdrawn
Activity	Quiet	Shifting or tense	Rigid, arched, jerking
Cry	None	Moan, whimper	Steady crying, screaming, sobbing, or frequent complaints
Consolability	Content	Consolable	Inconsolable

Self-Report of Pain

Categorical description: Toddlers or young children are asked to say if they are having "a little bit," a "middle amount," or "a lot" of pain.

Faces Scales[‡]: Children who do not have an appreciation of ordinal numbering are asked to rate their pain based upon cartoons depicting facial indicators of distress.

NRS[§]: Older children and teenagers are asked to rate their pain on a scale of "0" (no pain) to "10" (worst pain).

VAS[§]: Children or teenagers are asked to move an indicator along a mechanical slide to depict the level of pain; the clinician reads a number along a 10-cm indicator on the back to determine the numeric score.

FIG. 76.2 **Clinically useful pain assessment tools. (Adapted from Burg FD, Ingelfinger JR, Polin RA, et al, editors: *Current pediatric therapy,* ed 18, Philadelphia, 2006, Saunders/Elsevier, p 16; and Hicks CL, von Baeyer CL, Spafford P, et al: The Faces Pain Scale—revised: toward a common metric in pediatric pain measurement, *Pain* 93:173–183, 2001.)**

Table 76.2

Pain Measurement Tools

NAME	FEATURES	AGE RANGE	ADVANTAGES	VALIDATION AND USES	LIMITATIONS
Visual Analog Scale (VAS)	Horizontal 10-cm line; subject marks a spot on the line between anchors of “no pain” (or neutral face) and “most pain imaginable” (or sad face)	6-8 yr and older	Good psychometric properties; validated for research purposes	Acute pain Surgical pain Chronic pain	Cannot be used in younger children or in those with cognitive limitations Requires language skills and numerical processing; upper anchor of “most pain” requires an experiential reference point

					that is lacking in many children.
Likert Scale	Integers from 0-10, inclusive, corresponding to a range from no pain to most pain	6-8 yr and older	Good psychometric properties; validated for research purposes	Acute pain Surgical pain Chronic pain	Same as for VAS.
Faces Scales (e.g., FACES-R, Wong-Baker, Oucher, Bieri, McGrath scales)	Subjects rate their pain by identifying with line drawings of faces, or photos of children	4 yr and older	Can be used at younger ages than VAS and Likert	Acute pain Surgical pain	Choice of “no pain” face affects responses (neutral vs smiling); not culturally universal.
Behavioral or combined behavioral-physiologic scales (e.g., FLACC, N-PASS, CHEOPS, OPS, FACS, NIPS)	Scoring of observed behaviors (e.g., facial expression, limb movement) ± heart rate and blood pressure	Some work for any ages; some work for specific age-groups, including preterm infants	May be used in both infants and nonverbal children	FLACC, N-PASS: Acute pain Surgical pain	Nonspecific; overrates pain in toddlers and preschool children; underrates persistent pain; some measures are convenient, but others require videotaping and complex processing; vital sign changes unrelated to pain can occur and may affect total score.
Autonomic measures (e.g., heart rate, blood pressure, heart rate spectral analyses)	Scores changes in heart rate, blood pressure, or measures of heart rate variability (e.g., “vagal tone”)	All ages	Can be used at all ages; useful for patients receiving mechanical ventilation		Nonspecific; vital sign changes unrelated to pain may occur, and may artifactually increase or decrease score.
Hormonal-metabolic measures	Plasma or salivary sampling of “stress” hormones (e.g., cortisol, epinephrine)	All ages	Can be used at all ages		Nonspecific; changes unrelated to pain can occur; inconvenient; cannot provide “real-time” information; standard normal values not available for every age bracket.

The Newborn and Infant

There are several behavioral distress scales for the infant and young child, mostly emphasizing the patient's facial expressions, crying, and body movement. Facial expression measures appear most useful and specific in neonates. Autonomic and vital signs can indicate pain, but because they are nonspecific, they may reflect other processes, including fever, hypoxemia, and cardiac or renal dysfunction (Table 76.3).

Table 76.3

Signs and Symptoms of Pain in Infants and Young Children

Physiologic Changes

- Increase in heart rate, respiratory rate, blood pressure, muscle tone
- Oxygen desaturation
- Sweating
- Flushing
- Pallor

Behavioral Changes

- Change in facial expression (grimacing, furrowing of the brow, nasal flaring, deep nasolabial groove, curving of the tongue, quivering of the chin)
- Finger clenching
- Thrashing of limbs
- Writhing
- Back arching
- Head banging
- Poor feeding
- Sleep disturbance
- Pseudoparalysis

From Krauss BS, Calligaris L, Green SM, Barbi E: Current concepts in management of pain in children in the emergency department, *Lancet* 387:83–92, 2016.

The Older Child

Children age 3-7 yr become increasingly articulate in describing the intensity, location, and quality of pain. Pain is occasionally referred to adjacent areas;

referral of hip pain to the thigh or area above the knee is common in this age range. Self-report measures for children this age include using drawings, pictures of faces, or graded color intensities. Children ≥8 yr can usually use verbal numerical rating scales or visual analog pain scales (VAS) accurately (Fig. 76.2). Verbal numerical ratings are preferred and considered the gold standard; valid and reliable ratings can be obtained from children ≥8 yr. The numerical rating scale (NRS) consists of numbers from 0-10, in which 0 represents no pain and 10 represents very severe pain. There is debate about the label for the highest pain rating, but the current agreement is *not* to use the phrase “worst pain possible,” because children can always imagine a greater pain. In the United States, regularly documented pain assessments are required for hospitalized children and children attending outpatient hospital clinics and emergency departments (EDs). Pain scores do not always correlate with changes in heart rate or blood pressure.

The Cognitively Impaired Child

Measuring pain in cognitively impaired children remains a challenge. Understanding pain expression and experience in this population is important, because behaviors may be misinterpreted as indicating that cognitively impaired children are more insensitive to pain than cognitively competent children. Children with trisomy 21 may express pain less precisely and more slowly than the general population. Pain in children with ASD may be difficult to assess because these children may be both *hyposensitive* and *hypersensitive* to many different types of sensory stimuli, and they may have limited communication abilities. Although self-reports of pain can be elicited from some children who are cognitively impaired, observational measures have better validation among these children. The **Noncommunicating Child's Pain Checklist—Postoperative Version** is recommended for children up to 18 yr. Maladaptive behaviors and reduction in function may also indicate pain. Children with severe cognitive impairments experience pain frequently, mostly not because of accidental injury. Children with the fewest abilities experience the most pain.

Conceptual Framework for Treatment of Pediatric Pain

A number of models have been developed to understand the various factors that influence children's pain. Many of these theories focus on factors that explain the interindividual variability in pain perception and the chronicity and impairment experienced with pain. Central to these models are interrelationships among biologic, cognitive, affective, and social factors that influence children's pain and disability, commonly referred to as “biopsychosocial models” of pain. **Biologic** factors include the child's physical health, central nervous system (CNS) factors (pain processing), sex, pubertal status, and genetic factors. Individual child **cognitive and affective** factors related to perception of pain are anxiety, fear, negative affect, pain behaviors, and functional disability, whereas **social** factors include such areas as culture, socioeconomic status, school environment, social and peer interactions, and parental and family factors. For children, **developmental** factors need to be considered, such as cognitive and motor development, birth history, and epigenetic factors (the interaction in development between genetic and environmental factors).

A framework that considers the interplay of biologic, psychological, and social factors is useful for understanding pediatric pain and to guide pain assessment and the delivery of pain prevention and management. Many simple interventions designed to promote relaxation and patient control can work either alone or synergistically with pain medications for relief of pain and related distress. Moreover, psychological interventions are often coupled with physical therapy interventions to assist in the management of disabling chronic pain.

Pharmacologic Treatment of Pain

The pharmacokinetics and pharmacodynamics of analgesics vary with age; drug responses in infants and young children differ from those in older children and adults. The elimination half-life of most analgesics is prolonged in neonates and young infants because of their immature hepatic enzyme systems and glomerular filtration. Clearance of analgesics may also be variable in young infants and children. Renal blood flow, glomerular filtration, and tubular secretion increase dramatically in the 1st few weeks, approaching adult values by 3-5 mo of age. Renal clearance of analgesics is often greater in toddlers and preschool-aged children than in adults, whereas in premature infants, clearance is reduced. Age-related differences in body composition and protein binding also exist. Total body water as a fraction of body weight is greater in neonates than in children or adults. Tissues with high perfusion, such as the brain and heart, account for a larger proportion of body mass in neonates than do other tissues, such as muscle and fat. Because of decreased serum concentrations of albumin and α_1 -acid glycoprotein, neonates have reduced protein binding of some drugs, resulting in higher amounts of free, unbound, pharmacologically active drug.

Acetaminophen, Aspirin, Nonsteroidal Antiinflammatory, and Coxib Drugs

Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) have replaced aspirin as the most commonly used antipyretics and oral, nonopioid analgesics (Table 76.4).

Table 76.4

Commonly Used Nonopioid Medications

MEDICATION	DOSAGE	COMMENT(S)
Acetaminophen	10-15 mg/kg PO q4h 10 mg/kg IV q4h 15 mg/kg IV q6h 10 mg/kg IV q6h (<2 yr) 20-30 mg/kg/PR q4h 40 mg/kg/PR q6-8h *Maximum daily dosing:* 90 mg/kg/24 hr (children) 60 mg/kg/24 hr (<2 yr) 30-45 mg/kg/24 hr (neonates)	Minimal antiinflammatory action; no antiplatelet or adverse gastric effects; overdosing can produce fulminant hepatic failure.
Aspirin	10-15 mg/kg PO q4h *Maximum daily dosing:* 120 mg/kg/24 hr (children)	Antiinflammatory; prolonged antiplatelet effects; may cause gastritis; associated with Reye syndrome.
Ibuprofen	8-10 mg/kg PO q6h 10 mg/kg IV q4-6h to maximum of 400 mg *Maximum daily dose:* 2400 mg	Antiinflammatory; transient antiplatelet effects; may cause gastritis; extensive pediatric safety experience.
Naproxen	5-7 mg/kg PO q8-12h	Antiinflammatory; transient antiplatelet effects; may cause gastritis; more prolonged duration than that of ibuprofen.
Ketorolac	Loading dose 0.5 mg/kg, then 0.25-0.3 mg/kg IV q6h to a maximum of 5 days; maximum dose 60 mg loading with maximum dosing of 30 mg q6h	Antiinflammatory; reversible antiplatelet effects; may cause gastritis; useful for short-term situations in which oral dosing is not feasible.
Diclofenac sodium	2-3 mg/kg/day divided in 2 or 3 doses	Antiinflammatory; reversible antiplatelet effects; lower risk of gastritis and ulceration compared with other NSAIDs.
Choline magnesium	10-20 mg/kg PO q8-12h	Weak antiinflammatory; lower risk of bleeding and gastritis than with conventional NSAIDs.

salicylate		
Celecoxib	3-6 mg/kg PO q12-24h	Antiinflammatory; no or minimal antiplatelet or gastric effects; cross-reactivity with sulfa allergies.
Nortriptyline, amitriptyline, desipramine	0.1-0.5 mg/kg PO qhs Larger doses may be divided bid.	For neuropathic pain; facilitates sleep; may enhance opioid effect; may be useful in sickle cell pain; risk of dysrhythmia in prolonged QTc syndrome; may cause fatal dysrhythmia in overdose; FDA states agents may enhance suicidal ideation; little or no antidepression or antianxiety effects at lower dosages.
Gabapentin	100 mg bid or tid titrated to up to 3600 mg/24 hr	For neuropathic pain; associated with sedation, dizziness, ataxia, headache, and behavioral changes.
Quetiapine, risperidone, chlorpromazine, haloperidol	Quetiapine: 6.25 or 12.5 mg PO qd (hs); may use q6hr prn acute agitation with pain. Escalate dose to 25 mg/dose if needed. Risperidone: useful for PDD spectrum or tic disorder and chronic pain; 0.25-1 mg (in 0.25 mg increments) qd or bid; see PDR for other dosing.	Useful when arousal is amplifying pain; often used when patient first starting SSRI and then weaned after at least 2 wk; check for normal QTc before initiating; side effects include extrapyramidal reactions (diphenhydramine may be used to treat) and sedation; in high doses, can lower the seizure threshold.
Venlafaxine, duloxetine	Venlafaxine: start 37.5 mg daily as the XR formulation and titrate up monthly to effective dose, 2-4 mg/kg. Duloxetine: start 20 mg daily and titrate upward to effective dose, 1-1.5 mg/kg.	SNRIs with both clinically significant antidepression and antianxiety effects as well as analgesic effects.
Fluoxetine	10-20 mg PO qd (usually in morning)	SSRI for children with anxiety disorders in which arousal amplifies sensory signaling; useful in PDD spectrum disorders in very low doses; best to use in conjunction with psychiatric evaluation.
Sucrose solution via pacifier or gloved finger	*Preterm infants* (gestational age): 28 wk: 0.2 mL swabbed into mouth 28-32 wk: 0.2-2 mL, depending on suck/swallow >32 wk: 2 mL *Term infants:* 1.5-2 mL PO over 2 min	Allow 2 min before starting procedure; analgesia may last up to 8 min; the dose may be repeated once.

FDA, U.S. Food and Drug Administration; IV, intravenously; NSAIDs, nonsteroidal antiinflammatory drugs; PDD, pervasive developmental disorder; PDR, *Physicians' Desk Reference* ; PO, orally; PR, rectally; QTc, corrected QT interval on an electrocardiogram; SSRI, selective serotonin reuptake inhibitor.

Acetaminophen , a generally safe, nonopioid analgesic and antipyretic, has the advantage of intravenous (IV), rectal, and oral routes of administration.

Acetaminophen is not associated with the gastrointestinal (GI) or antiplatelet effects of aspirin and NSAIDs, making it a particularly useful drug in patients with cancer. Unlike aspirin and NSAIDs, acetaminophen has only mild antiinflammatory action.

Acetaminophen toxicity can result from a large single dose or cumulative excessive dosing over days or weeks (see Chapter 77). A single massive overdose overwhelms the normal glucuronidation and sulfation metabolic pathways in the liver, whereas long-term overdosing exhausts supplies of the sulfhydryl donor glutathione, leading to alternative cytochrome P-450 (CYP)–catalyzed oxidative metabolism and the production of the hepatotoxic metabolite *N* -acetyl-*p* -benzoquinone imine (NAPQI). Toxicity manifests as fulminant hepatic necrosis and failure in infants, children, and adults. Drug biotransformation processes are immature in neonates, very active in young children, and somewhat less active in adults. Young children are more resistant to acetaminophen-induced hepatotoxicity than are adults as a result of metabolic differences; sulfation predominates over glucuronidation in young children, leading to a reduction in NAPQI production.

Aspirin is indicated for certain rheumatologic conditions and for inhibition of platelet adhesiveness, as in the treatment of Kawasaki disease. Concerns about Reye syndrome have resulted in a substantial decline in pediatric aspirin use.

The **NSAIDs** are used widely to treat pain and fever in children. NSAIDs are nonselective cyclooxygenase (COX) inhibitors, that is, drugs that nonselectively block the activity of both COX-1 (found in gastric mucosa and platelets) and COX-2 (active in inflammatory pathways and cortical renal blood flow regulation) enzymes that synthesize prostaglandins. In children with juvenile idiopathic arthritis, ibuprofen and aspirin are equally effective, but ibuprofen is associated with fewer side effects and better drug adherence. NSAIDs and coxibs used adjunctively in surgical patients reduce opioid requirements (and therefore opioid side effects) by as much as 35–40%. Although NSAIDs can be useful postoperatively, they should be used as an adjunct to, not as a substitute for, opioids in patients with acute, moderate to severe pain.

Ketorolac, an IV NSAID, is useful in treating moderate to severe acute pain in patients who are unable or unwilling to swallow oral NSAIDs. U.S. Food and Drug Administration (FDA) recommendations limit ketorolac to 5 consecutive days of administration. IV ibuprofen (Caldolor) is FDA approved for the management of pain and fever in infants and children >6 mo of age. Adverse effects of NSAIDs are uncommon but may be serious when they occur, including inhibition of bone growth and healing; gastritis with pain and bleeding; decreased renal blood flow that may reduce glomerular filtration and enhance sodium reabsorption, in some cases leading to tubular necrosis; hepatic dysfunction and liver failure; inhibition of platelet function; and an increased incidence of cardiovascular events in patients predisposed to stroke and myocardial infarction. Although the overall incidence of bleeding is very low, gastric bleeding is the most common cause of mortality related to this class of analgesics. NSAIDs should not be used in the child with a bleeding diathesis or at risk for bleeding or when surgical hemostasis is a concern, such as after tonsillectomy. The drug class is usually not used in the setting of bone healing, except perhaps in the 1st few days after surgery. Renal injury from short-term use of ibuprofen in euvolemic children is quite rare; the risk is increased by hypovolemia or cardiac dysfunction. The safety of both ibuprofen and acetaminophen for short-term use is well established (see Table 76.4).

Coxib drugs available in the United States are limited to oral celecoxib, whereas in Europe and elsewhere parenteral parecoxib and oral rofecoxib are available. Parecoxib was not FDA approved, whereas rofecoxib was approved and withdrawn from marketing due to concern of enhanced risk of heart attack and stroke in high-risk adults, which has subsequently been found to be associated with all the coxibs and all the NSAID drugs as well. The coxib drugs are selective COX-2 enzyme inhibitors; therefore they are effective antiinflammatory and analgesic molecules that generally do not result in platelet inhibition or bleeding, or in gastric inflammation or ulceration, findings that may be seen with the nonselective COX inhibitors in the NSAID class. However, coxib drugs do inhibit regulation of cortical renal blood flow, and therefore carry the same risk of renal toxicity and acute tubular necrosis, particularly in the setting of low cardiac output states or dehydration. Celecoxib is therefore an appropriate primary or adjunctive analgesic to use in children after surgery, children with gastric mucosal pathology, or oncology patients in whom concern for hemostasis contraindicates conventional NSAIDs.

Opioids

Opioids are analgesic substances either derived from the opium poppy (**opiates**) or synthesized to have a similar chemical structure and mechanism of action (**opioids**). The older, pejorative term “narcotics” (narcotic analgesics) should not be used for these agents because it connotes criminality and lacks pharmacologic descriptive specificity. Opioids are administered for moderate and severe pain, such as acute postoperative pain, sickle cell crisis pain, and cancer pain. Opioids can be administered by the oral, rectal, oral transmucosal, transdermal, intranasal, IV, epidural, intrathecal, subcutaneous (SC), or intramuscular (IM) route. Regardless of route of administration, the site of action is at mu (μ) opioid receptors in the peripheral nervous system, spinal cord, brainstem, and higher CNS centers. Historically, infants and young children have been underdosed with opioids because of concern about significant respiratory side effects. Once thought to represent infants' particular sensitivity, the opioids' respiratory depressant effects are now known to result from infants' lower metabolic clearance of opioids and higher blood levels with frequent dosing. With proper understanding of the pharmacokinetic and pharmacodynamics of opioids, children can receive effective relief of pain and suffering with a good margin of safety, regardless of pharmacokinetic maturity, age, or size (Tables 76.5 to 76.8).

Table 76.5

Practical Aspects of Prescribing Opioids

- Morphine, hydromorphone, or fentanyl is regarded as 1st choice for severe pain.
- Dosing should be titrated and individualized. There is no “right” dose for everyone.
- The right dose is the dose that relieves pain with a good margin of safety.
- Dosing should be more cautious in infants, in patients with coexisting diseases that increase risk or impair drug clearance, and with concomitant administration of sedatives.
- Hydromorphone is metabolized by CYP2D6 and fentanyl by CYP3A4, and to some extent 2D6; drugs that compete for 2D6 enzyme will raise blood levels and increase risk of respiratory depression.
- Morphine is metabolized by glucuronidation to an active metabolite, morphine-6-glucuronide, which accumulates and causes CNS toxicity in renal impairment.
- Anticipate and treat peripheral side effects, including constipation, nausea, and itching.
- Give doses at sufficient frequency to prevent the return of severe pain before the next dose.

- Use a drug delivery method, such as patient-controlled anesthesia or continuous infusions, that avoids the need for “prn” decision-making.
- With opioid dosing for >1 wk, taper gradually to avoid abstinence syndrome.
- When converting between parenteral and oral opioid doses, use appropriate potency ratios (see Table 76.6).
- *Tolerance* refers to decreasing drug effect with continued administration of a drug. Over time a patient will need higher dosing to achieve the same clinical effect; however, tolerance to sedation and respiratory depression develop more rapidly than tolerance to analgesia. Thus, with higher doses, patients do not experience oversedation or respiratory depression.
- *Dependence* refers to the need for continued drug dosing to prevent abstinence syndrome when a drug is abruptly discontinued, or its dose reduced. Abstinence syndrome is characterized by irritability, agitation, autonomic arousal, nasal congestion, piloerection, diarrhea, jitteriness, and yawning; it is produced by administration of potent opioids for >5-7 days.
- *Addiction*, a psychiatric pathology, refers to psychological craving, compulsive drug-seeking behavior, and drug use despite medical harm. Addiction has strong genetic and environmental determinants. Opioid therapy will not lead to addiction in nonsusceptible individuals, and opioid underdosing does not prevent addiction; it may in fact increase drug-seeking behavior for relief of pain (e.g., watching the clock), referred to as “pseudoaddiction.”

Table 76.6

Pediatric Dosage Guidelines for Opioid Analgesics

DRUG	EQUI-ANALGESIC DOSES		PARENTERAL DOSING		IV:PO DOSE RATIO	ORAL DOSING	
	IV	Oral	<50 kg	>50 kg		<50 kg	>50 kg
Fentanyl	10 µg	100 µg	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	Oral transmucosal: 1 : 10 Transdermal: 1 : 1	Oral transmucosal: 10 µg/kg Transdermal: 12.5-50 µg/hr	Transderm patches available; patch reac steady sta 24 hr and should be changed c

Hydrocodone	N/A	1.5 mg	N/A	N/A	N/A	0.15 mg/kg	10 mg
Hydromorphone	0.2 mg	0.6 mg	0.01 mg q2-4h 0.002 mg/kg/hr	0.01 mg q2-4h 0.002 mg/kg/hr	1 : 3	0.04-0.08 mg/kg q3-4h	2-4 mg q
Meperidine	10 mg	30 mg	0.5 mg/kg q2-4h	0.5 mg/kg q2-4h	1 : 4	2-3 mg/kg q3-4h	100-150 q3-4h
Methadone	1 mg	2 mg	0.1 mg/kg q8-24h	0.1 mg/kg q8-24h	1 : 2	0.2 mg/kg q8-12h PO; available as liquid or tablet	2.5 mg TI

Morphine	1 mg	3 mg	0.05 mg/kg q2-4h 0.01-0.03 mg/kg/hr	*Bolus:* 5-8 mg q2-4h	1 : 3	Immediate release: 0.3 mg/kg q3-4h Sustained release*:* 20-35 kg: 10-15 mg q8-12h 35-50 kg: 15-30 mg q8-12h	Imme releas 15-20 q3-4h Sustai releas 30-90 q8-12
Oxycodone	N/A	3 mg	N/A	N/A	N/A	0.1-0.2 mg q3-4h; available in liquid (1 mg/mL)	Imme releas 10 mg Sustai releas 10-12 mg q8 12h

N/A, not available.

Table 76.7

Management of Opioid-Induced Adverse Effects

Respiratory	*Naloxone:* 0.01-0.02 mg/kg up to a full reversal dose of 0.1 mg/kg. May be given IV, IM,

depression	SC, or via ET. The full reversal dose should initially be used for apnea in opioid-naive patients. In opioid-tolerant patients, a reduced dose should be given and titrated up slowly to treat symptoms but prevent acute withdrawal. Ventilation may need to be supported during this process. Dose may be repeated every 2 min to a total of 10 mg. Adult maximum dose is 2 mg/dose. Give with caution to patients who are receiving long-term opioid therapy, as it may precipitate acute withdrawal. Duration of effect is 1-4 hr; therefore close observation for re-narcotization is essential to prevent re-narcotization.
Excessive sedation without evidence of respiratory depression	*Methylphenidate* * *:* 0.3 mg/kg per dose PO (typically 10-20 mg/dose to a teenager) before breakfast and lunch. Do not administer to patients receiving clonidine, because dysrhythmias may develop. *Dextroamphetamine* : 2.5-10 mg on awakening and at noon. Not for use in young children or in patients with cardiovascular disease or hypertension. *Modafinil:* Pediatric dose not established. May be useful in selected patients. Typical adult dose: 50-200 mg/day. Change opioid or decrease the dose.
Nausea and vomiting	*Metoclopramide* † *:* 0.15 mg/kg IV up to 10 mg/dose q6-12h for 24 hr. *Trimethobenzamide:* PO or PR if weight <15 kg, 100 mg q6h; if >15 kg, 200 mg q6h. (*Note:* Suppository contains benzocaine 2%.) Not for use in newborn infants or premature infants. 5-HT_3 receptor blockers: *Ondansetron:* 0.15 mg/kg up to 8 mg IV q6-8h not to exceed 32 mg/day (also available as a sublingual tablet). *Granisetron:* 10 to 20 µg/kg IV q12-24h. *Prochlorperazine* * (Compazine): >2 yr or >20 kg, 0.1 mg/kg per dose q8h IM or PO up to 10 mg/dose. Change opioid.
Pruritus	*Hydroxyzine* : 0.5 mg/kg PO q6h. *Nalbuphine:* 0.1 mg/kg IV q6h for pruritus caused by intraaxial opioids, especially fentanyl. Administer slowly over 15-20 min. May cause acute reversal of systemic µ-receptor effects and leave κ-agonism intact. *Naloxone:* 0.003 to 0.1 mg/kg/hr IV infusion (titrate up to decrease pruritus and reduce infusion if pain increases). *Ondansetron:* 0.05 to 0.1 mg/kg IV or PO q8h. *Cyproheptadine* † *:* 0.1-0.2 mg/kg PO q8-12h. Maximum dose 12 mg. Change opioid.
Constipation	Encourage water consumption, high-fiber diet, and vegetable fiber. *Bulk laxatives:* Metamucil, Maltsupex. *Lubricants:* Mineral oil 15-30 mL PO qd as needed (not for use in infants because of aspiration risk). *Surfactants:* Sodium docusate (Colace): <3 yr: 10 mg PO q8h 3-6 yr: 15 mg PO q8h 6-12 yr: 50 mg PO q8h >12 yr: 100 mg PO q8h *Stimulants:* Bisacodyl suppository (Dulcolax): <2 yr: 5 mg PR qhs >2 yr: 10 mg PR qhs *Senna syrup* (218 mg/5 mL): >3 yr: 5 mL qhs. *Enema:* Fleet hypertonic phosphate enema (older children; risk of hyperphosphatemia). *Electrolytic/osmotic:* Milk of magnesia; for severe impaction: polyethylene glycol

	(GoLYTELY, MiraLax). Methylnaltrexone is an opioid antagonist that works in the colon and does not cross the blood-brain barrier to reverse analgesia; given as subcutaneous injection every day or every other day (0.15 mg/kg) and is effective in producing stool in 30-60 min in most patients.
Urinary retention	Straight catheterization, indwelling catheter.

[*] Avoid in patients taking monoamine oxidase inhibitors.

[†] May be associated with extrapyramidal side effects, which may be more often seen in children than in adults.

ET, Endotracheal tube; IV, intravenously; IM, intramuscularly; PO, orally; PR, rectally; SC, subcutaneously.

Modified from Burg FD, Ingelfinger JR, Polin RA, et al, editors: *Current pediatric therapy,* ed 18, Philadelphia, 2006, Saunders/Elsevier, p 16.

Table 76.8

Equianalgesic Doses and Half-Life ($T_{1/2\beta}$) of Some Commonly Used Opioids

OPIOID	IM/IV DOSE (mg)	ORAL DOSE (mg)	$T_{1/2\beta}$ (hr)
Morphine	10	30	2-3
Meperidine	100	400	3-4
Oxycodone	15	20-30	2-3
Fentanyl	0.15-0.2	—	3-5
Alfentanil	0.75-1.5	—	1-2
Sufentanil	0.02	—	2-3
Diamorphine	5	60	0.5[*]
Methadone	10	10-15	15-40
Hydromorphone	1.5	7.5	3-4
Tramadol [†]	100	100	5-7
Buprenorphine	0.4	0.8 (sublingual)	3-5
Pentazocine	60	150	3-5
Nalbuphine	10-20	—	2-4
Butorphanol	2	—	2-3

[*] Rapidly hydrolyzed to morphine.

[†] Only part of its analgesic action results from action on μ-opioid receptors.

NOTES:

- Published reports vary in the suggested doses considered to be equianalgesic to morphine. Therefore, titration to clinical response in each patient is necessary.
- Suggested doses are the results of single-dose studies

only. Therefore, use of the data to calculate total daily dose requirements and repeated or continuous doses may not be appropriate.

- There may be incomplete cross-tolerance between these drugs. In patients who have been receiving one opioid for a prolonged period, it is usually necessary to use a dose lower than the expected equianalgesic dose when changing to another opioid, and to titrate to effect.

Modified from Macintyre PE, Ready LB: *Acute pain management: a practical guide,* ed 2, Philadelphia, 2001, Saunders, p 19.

Opioids act by mimicking the actions of endogenous opioid peptides, binding to receptors in the brain, brainstem, spinal cord, and to a lesser extent in the peripheral nervous system, and thus leading to inhibition of nociception. Opioids also bind to μ receptors in the pleasure centers of the midbrain, particularly in genetically susceptible individuals, a factor responsible for the euphoric effect in some individuals as well as the predilection to psychological dependence and addictive behavior. Opioids also have dose-dependent respiratory depressant effects when interacting with the μ-opioid receptors in the respiratory centers of the brainstem, depressing ventilator drive and blunting ventilatory responses to both hypoxia and hypercarbia. These respiratory depressant effects are increased with co-administration of other sedating drugs, particularly benzodiazepines or barbiturates.

Optimal use of opioids requires proactive and anticipatory management of side effects (see Table 76.7). Common side effects include sedation, constipation, nausea, vomiting, urinary retention, and pruritus. Tolerance usually develops to the side effect of **nausea** , which typically subsides with long-term dosing, but nausea may require treatment with antiemetics, such as a phenothiazine, butyrophenones, antihistamines, or a serotonin receptor antagonist such as ondansetron or granisetron. Pruritus and other complications during patient-controlled analgesia with opioids may be effectively managed by low-dose IV naloxone.

The most common, troubling, but treatable side effect is **constipation** . Patients who take opioids for chronic pain for long periods predictably develop tolerance to the sedative and analgesic effects of opioids over time, but tolerance to constipation does not occur, and constipation remains a troublesome and distressing problem in almost all patients with long-term opioid administration. Stool softeners and stimulant laxatives should be administered to most patients receiving opioids for more than a few days. Osmotic and bulk laxatives are less effective, usually producing more distention and discomfort. A peripherally acting opiate µ-receptor antagonist, **methylnaltrexone,** promptly and effectively reverses opioid-induced constipation in patients with chronic pain who are receiving opioids daily. Methylnaltrexone is approved for use as either an injectable or oral formulation, but only the SC injection is commercially available, which most children will object to receiving. Naldemedine and naloxegol are other agents with actions similar to methylnaltrexone. A novel laxative, **lubiprostone** , is a colonic chloride channel inhibitor that impairs water reabsorption in the colon and is very effective for opioid-induced constipation.

Media and government attention the "opioid epidemic" has reasonably led to scrutiny of the prescription of opioids to children, and recent FDA approval of opioid formulations for children has raised alarm and criticism by some vocal critics of the use of opioids for medical purposes. Thus, one of the potent barriers to effective management of pain with opioids is the fear of addiction held by many prescribing pediatricians and parents alike. Pediatricians should understand the phenomena of tolerance, dependence, withdrawal, and addiction (see Table 76.5). **Opioid addiction** is the result of the complex interplay of genetic predisposition, psychiatric pathology, and social forces, including poverty, joblessness, hopelessness, and despair. The dramatic increase in the amount of opioid abuse and overdoses and opioid-related deaths since 2001 has been largely restricted to the adult white population age 30-55 yr, not in children or adolescents. A longitudinal study of children and adolescents treated for medical reasons with opioids found that there was no increased risk of the development of substance abuse, at least until their mid-20s. Other epidemiologic studies have shown a negligible increase in opioid overdoses and deaths in the black and Latino populations, but rather a relationship to the unemployment rate. Thus the rational short- or even long-term use of opioids in children does not lead to a predilection for or risk of addiction in a child not otherwise at risk because of genetic background, race, or social milieu.

It is equally important for pediatricians to realize that even patients with recognized substance abuse diagnoses are entitled to effective analgesic management, which often includes the use of opioids. If legitimate concerns exist about addiction in a patient, safe effective opioid pain management is often best managed by specialists in pain management and addiction medicine. Table 76.9 outlines the U.S. Centers for Disease Control and Prevention (CDC) opioid recommendations for **chronic pain** (primarily in adults).

Table 76.9

CDC Recommendations for Prescribing Opioids for Chronic Pain Outside of Active Cancer, Palliative, and End-of-Life Care

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or

carefully justify a decision to titrate dosage to ≥90 MME/day.

6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required); see full guideline for evidence ratings.

From Dowell D, Haegerich TM, Chou R: CDC guideline for prescribing opioids for chronic pain—United States, 2016, *MMWR* 65(1):1–49, 2016.

There is no longer a reason to administer opioids by IM injection. Continuous IV infusion of opioids is an effective option that permits more constant plasma concentrations and clinical effects than intermittent IV bolus dosing, without the pain associated with IM injection. The most common approach in pediatric centers is to administer a low-dose basal opioid infusion, while permitting patients to use a **patient-controlled analgesia (PCA)** device to titrate the dosage above the infusion (Fig. 76.3) (see Chapter 74). Compared with children given intermittent IM morphine, children using PCA reported better pain scores. PCA has several other advantages: (1) dosing can be adjusted to account for individual pharmacokinetic and pharmacodynamic variation and for changing pain intensity during the day; (2) psychologically the patient is more in control, actively coping with the pain; (3) overall opioid consumption tends to be lower; (4) therefore fewer side effects occur; and (5) patient satisfaction is generally much higher. Children as young as 5-6 yr can effectively use PCA. The device can also be activated by parents or nurses, known as **PCA-by-proxy (PCA-P),** which produces analgesia in a safe, effective manner for children who cannot activate the PCA demand button themselves because they are too young or intellectually or physically impaired. PCA overdoses have occurred when well-meaning, inadequately instructed parents pushed the PCA button in medically complicated situations, with or without the use of PCA-P, highlighting the need for patient and family education, use of protocols, and adequate nursing supervision.

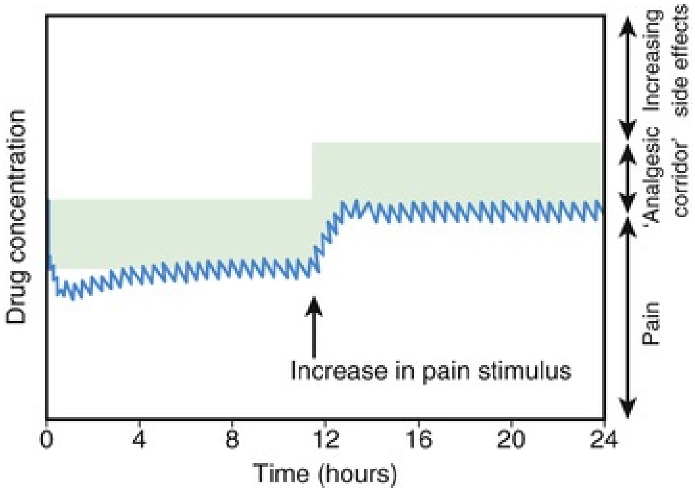

FIG. 76.3 Patient-controlled analgesia is more likely to keep blood concentrations of opioid within the "analgesic corridor" and allows rapid titration if there is an increase in pain stimulus requiring higher blood levels of opioid to maintain the analgesia. (From Burg FD, Ingelfinger JR, Polin RA, et al, editors: *Current pediatric therapy,* ed 18. Philadelphia, 2006, Saunders/Elsevier, p 16.)

Because of the high risk of adverse side effects (respiratory depression), the FDA has issued contraindications for the pediatric use of codeine and tramadol (Table 76.10).

Table 76.10

Summary of FDA Recommendations

- Use of codeine to treat pain or cough in children <12 yr old is contraindicated.
- Use of tramadol to treat pain in children <12 yr old is contraindicated.
- Use of tramadol for treatment of pain after tonsillectomy or adenoidectomy in patients <18 yr old is contraindicated. (Codeine was already contraindicated in such patients).
- Use of codeine or tramadol in children 12-18 yr old who are obese or who have an increased risk of serious breathing problems, such as those with obstructive sleep apnea or severe lung disease, is not recommended.
- Use of codeine or tramadol in breastfeeding women should be avoided.

From The Medical Letter: FDA warns against use of codeine and tramadol in children and breastfeeding women, *Med Lett* 59(1521):86–88, 2017.

Local Anesthetics

Local anesthetics are widely used in children for topical application, cutaneous infiltration, peripheral nerve block, neuraxial blocks (intrathecal or epidural infusions), and IV infusions (Table 76.11) (see Chapter 74). Local anesthetics can be used with excellent safety and effectiveness. Local anesthetics interfere with neural transmission by blocking neuronal sodium channels. Excessive systemic dosing can cause seizures, CNS depression, and (by cardiac and arteriolar sodium channel blockade) hypotension, arrhythmias, cardiac depression, and cardiovascular collapse. Local anesthetics therefore require a strict maximum dosing schedule. Pediatricians should be aware of the need to calculate these doses and adhere to guidelines.

Table 76.11

Topical Pharmacologic Management of Acute Pain in Children

DRUG	DOSE	NOTES
INTACT SKIN		
Lidocaine 2·5% and prilocaine 2·5% (EMLA cream)	<3 mo old or <5 kg: 1 g 3–12 mo and >5 kg: 2 g 1–6 yr and >10 kg: 10 g 7–12 yr and >20 kg: 20 g	60 min is needed to achieve maximum effect; cover cream with an occlusive dressing
Lidocaine 70 mg and tetracaine 70 mg (Synera patch)	Age ≥3 yr: apply patch	20–30 min needed to achieve maximum effect
Tetracaine 4% (Ametop)	>1 mo and <5 yr: apply 1 tube of gel (1 g) >5 yr: apply up to 5 tubes of gel (5 g)	30 min before venipuncture 45 min before intravenous cannulation
WOUNDS		
Lidocaine, epinephrine, tetracaine (LET) solution or gel*	Age ≥1 yr: apply to wound	20 min needed for maximum effect

* Also referred to as ALA on the basis of alternative names for the constituents: adrenaline, lignocaine, amethocaine. These mixtures are locally made by hospital formularies, with a common formula being lidocaine 4% plus epinephrine 0·1% plus tetracaine 0·5%. The cocaine-based formulation was historically avoided on wounds of digits, ears, penis, nose, mucous membranes, close to the eye, or deep wounds involving bone, cartilage, tendon, or vessels. The lidocaine-based formulation can be used in such settings.

Adapted from Krauss BS, Calligaris L, Green SM, Barbi E: Current concepts in management of pain in children in the emergency department, *Lancet* 387:83–92, 2016.

Topical local anesthetic preparations do not generally result in measurable systemic blood levels and can reduce pain in diverse circumstances: suturing of lacerations, placement of peripheral IV catheters, lumbar punctures, and accessing indwelling central venous ports. The application of tetracaine, epinephrine, and cocaine results in good anesthesia for suturing wounds but should not be used on mucous membranes. Combinations of tetracaine with phenylephrine and lidocaine-epinephrine-tetracaine are equally as effective, eliminating the need to use a controlled substance (cocaine). EMLA, a topical eutectic mixture of lidocaine and prilocaine used to anesthetize intact skin, is frequently applied for venipuncture, lumbar puncture, and other needle procedures. A 5% lidocaine cream (Elemax) is also effective as a topical anesthetic.

Lidocaine is the most commonly used local anesthetic for cutaneous infiltration. Maximum safe doses of lidocaine are 5 mg/kg without epinephrine and 7 mg/kg with epinephrine. Although concentrated solutions (2%) are commonly available from hospital pharmacies, more dilute solutions (0.25% and 0.5%) are equally as effective as 1–2% solutions. The diluted solutions cause less burning discomfort on injection and permit use of larger volumes without achieving toxic doses. In the surgical setting, cutaneous infiltration is more often performed with bupivacaine 0.25% or ropivacaine 0.2% because of the much longer duration of effect; maximum dosage of these long-acting amide anesthetics is 2-3 mg/kg and 3-4 mg/kg, respectively.

Neuropathic pain may respond well to the local application of a lidocaine topical patch (Lidoderm) for 12 hr/day (Table 76.12). Peripheral and central neuropathic pain also may respond to IV lidocaine infusions, which may be used in hospital settings for refractory pain, complex regional pain syndromes, and pain associated with malignancies or the therapy of malignancies, such as oral mucositis following bone marrow transplantation. In these patients, 1-2 mg/kg/hr should be administered, and the infusion titrated to achieve a blood lidocaine level in the 2-5 µg/mL range, with use of twice-daily therapeutic blood monitoring. Table 76.13 outlines approaches to central neuropathic pain.

Table 76.12

Examples of Neuropathic Pain Syndromes

Peripheral Nervous System Focal and Multifocal Lesions

Postherpetic neuralgia
Cranial neuralgias (e.g., trigeminal neuralgia, glossopharyngeal neuralgia)
Diabetic mononeuropathy
Nerve entrapment syndromes
Plexopathy from malignancy or irradiation
    Phantom limb pain
Posttraumatic neuralgia (e.g., nerve root compression, after thoracotomy)
    Ischemic neuropathy
Complex regional pain syndrome types 1 and 2
Erythromelalgia

Peripheral Nervous System Generalized Polyneuropathies

Metabolic/nutritional: Diabetes mellitus, pellagra, beriberi, multiple nutritional deficiency, hypothyroidism
Toxic: Alcohol-, platinum-, or taxane-based chemotherapy, isoniazid, antiretroviral drugs
Infective/autoimmune: HIV, acute inflammatory polyneuropathy (Guillain-Barré syndrome), neuroborreliosis (Bannwarth syndrome)
Hereditary: Fabry disease
Malignancy: Carcinomatosis
Others: Idiopathic small-fiber neuropathy, erythromelalgia

Central Nervous System Lesions

Spinal cord injury
Prolapsed disc
Stroke (brain infarction, spinal infarction)
Multiple sclerosis
Surgical lesions (e.g., rhizotomy, cordotomy)
Complex neuropathic disorders
Complex regional pain syndrome types 1 and 2

Adapted from Freynhagen R, Bennett MI: Diagnosis and management of neuropathic pain, *BMJ* 339:b3002, 2009.

Table 76.13

Treatment Recommendations for Central Neuropathic Pain Adapted From Current Evidence-Based Literature

MEDICATION CLASS/DRUG	RECOMMENDED STAGE OF TREATMENT
ANTIDEPRESSANTS	
Tricyclics (e.g., amitriptyline, nortriptyline)	1st or 2nd
Serotonin and norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine)	1st or 2nd
ANTICONVULSANTS	
Pregabalin	1st or 2nd
Gabapentin	1st or 2nd
Lamotrigine	2nd or 3rd (in pain after stroke)
Valproate	3rd
OPIOIDS *	
Levorphanol	
MISCELLANEOUS	
Cannabinoids	2nd (in multiple sclerosis)
Mexiletine	3rd

* 2nd or 3rd treatment stage (no specification).

Adapted from Freynhagen R, Bennett MI: Diagnosis and management of neuropathic pain, *BMJ* 339:b3002, 2009.

Unconventional Medications in Pediatric Pain

Unconventional analgesic medication refers to a wide number of drugs developed for other indications but found to have analgesic properties. These drugs include some antidepressants, antiepileptic drugs, and neurotropic drugs.

The unconventional analgesics are generally used to manage neuropathic pain conditions, migraine disorders, fibromyalgia syndrome, and some forms of functional chronic abdominal pain syndromes. These agents also are used as components of multimodal analgesia in the management of surgical, somatic, and musculoskeletal pain. Fig. 76.4 presents a decision-making tree to help the physician select the appropriate analgesic category for various types of pain.

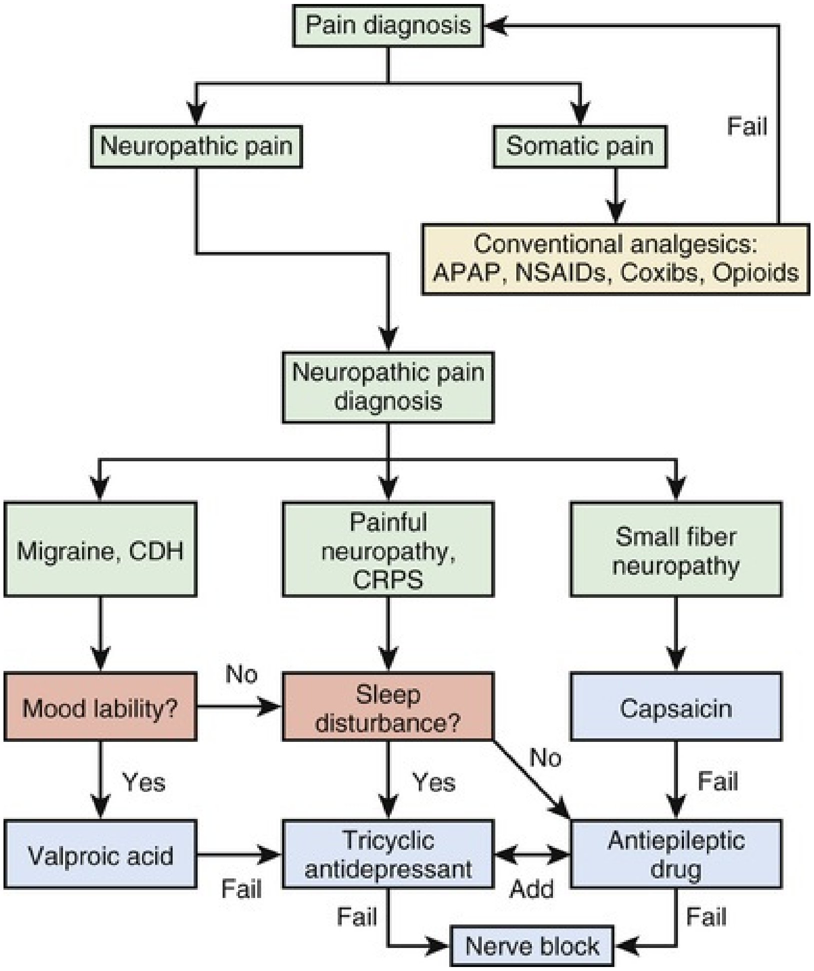
Pain diagnosis
Neuropathic pain
Somatic pain
Fail
Conventional analgesics: APAP, NSAIDs, Coxibs, Opioids
Neuropathic pain diagnosis
Migraine, CDH
Painful neuropathy, CRPS
Small fiber neuropathy
Mood lability?
No
Sleep disturbance?
Capsaicin
Yes
Yes
No
Fail
Valproic acid
Tricyclic antidepressant
Antiepileptic drug
Fail
Add
Fail
Fail
Nerve block

FIG. 76.4 **Decision tree for selection of conventional and nonconventional analgesics. APAP, Acetaminophen; CDH, chronic daily headaches; CRPS, complex regional pain syndromes; NSAIDs, nonsteroidal antiinflammatory drugs.**

Although several unconventional analgesics are FDA approved for analgesic use, none is approved for use in youths with acute or chronic pain. Thus, these drugs should be used with caution, with a focus on mitigating pain to allow a child to participate effectively in therapies and return to normal activity as soon as possible. The use of psychotropic medications should be guided by the principles applied to pharmacologic treatment of any symptom or disease. Target symptoms should be identified, and medication side effects monitored. To determine dosing regimens, the physician should consider the child's weight and the effects that the medical condition and other medications, such as psychotropic drugs, may have on the child's metabolism. When available, therapeutic blood level monitoring should be performed. Side effects should be addressed in detail with both parent and child, and specific instructions given for responding to possible adverse events. Directly addressing concerns about addiction, dependence, and tolerance may be necessary to decrease treatment-related anxiety and improve medication adherence.

Antidepressant Medications

Antidepressants are useful in adults with chronic pain, including neuropathic pain, headaches, and rheumatoid arthritis, independent of their effects on depressive disorders. Antidepressants' analgesic mechanism of action is inhibition of norepinephrine reuptake in the CNS. In children, because clinical trials have been limited, the practitioner should use antidepressants cautiously to treat chronic pain or associated depressive or anxiety symptoms. The FDA has issued a “black box warning,” its strongest warning, to inform the public of a small but significant increase in suicidal thoughts and attempts in children and adolescents receiving antidepressants. A meta-analysis of studies involving children and adolescents receiving antidepressants indicated that no suicides had been completed. The pediatrician should address this issue with parents of patients being treated with antidepressants and should develop monitoring plans consistent with current FDA recommendations.

Tricyclic antidepressants (TCAs) have been studied most in children with chronic pain and found to be effective in pain relief for symptoms that include neuropathic pain, functional abdominal pain, and migraine. TCA efficacy may be based on inhibition of the neurochemical pathways involved in norepinephrine and serotonin reuptake and interference with other neurochemicals involved in the perception or neural conduction of pain. Because sedation is the most common side effect, TCAs are also effective in treating the sleep disorders that frequently accompany pediatric pain. Biotransformation of TCAs is extensive in healthy children. Typically, TCAs are administered only at bedtime. Alternatively, the patient can be started on a bedtime dose of a TCA, which may be able to then be titrated to a daily divided dose, with the larger dose given at bedtime. The reader should note that pain symptoms usually remit at lower doses than those recommended or required for the treatment of mood disorders. Most children and adolescents do not require more than 0.25-0.5 mg/kg of amitriptyline or nortriptyline once daily at bedtime.

Attention should also be paid to hepatic microsomal enzyme metabolism, because CYP2D6 inhibitors, such as cimetidine and quinidine, can increase levels of TCAs. Anticholinergic side effects, which are less common in children than adults, may remit over time. Constipation, orthostatic hypotension, and dental caries from dry mouth should be addressed by emphasizing the importance of hydration and oral hygiene. Other side effects include weight gain, mild bone marrow suppression, and liver dysfunction. Some practitioners recommend monitoring complete blood count (CBC) and liver function values at baseline and periodically during therapy. TCA blood levels can be obtained as well, but therapeutic blood monitoring generally should occur individually, particularly if adherence, overdose, or sudden change in mental status is an issue.

All TCAs inhibit cardiac conduction pathways and prolong the QT interval. Sudden cardiac death has been reported in children taking TCAs, principally desipramine, probably related to QTc prolongation. There is no general agreement for monitoring the electrophysiologic effects of these drugs, but it is prudent to obtain a careful personal and family history focusing on cardiac arrhythmias, heart disease, and syncope before the initiation of treatment. If personal or family history is positive for any of these conditions, a baseline electrocardiogram (ECG) should be obtained, with care taken to ensure that the QTc is <445 msec. We recommend that if the dose of amitriptyline or nortriptyline is increased beyond 0.25-0.5 mg/kg/day, an ECG should be performed for each dosing increase. With TCAs, as with other antidepressants, physical dependence and a known discontinuation syndrome can occur. The *discontinuation syndrome* includes agitation, sleep disturbances, appetite changes, and GI symptoms. These medications should be tapered slowly to assist in distinguishing among symptoms that indicate rebound, withdrawal, or the need for continuing the medication.

Selective serotonin reuptake inhibitors (SSRIs) have minimal efficacy in the treatment of a variety of pain syndromes in adults. SSRIs are very useful when symptoms of depression or anxiety disorders are present and cannot be addressed adequately by nonpharmacologic means. Escitalopram (Lexapro), fluoxetine (Prozac), and sertraline (Zoloft) have been approved by the FDA for use in children and adolescents. SSRIs have a significantly milder side effect profile than TCAs (most side effects are transient), and they have no anticholinergic side effects. Chief side effects include GI symptoms, headaches, agitation, insomnia, sexual dysfunction, and anxiety. Rarely, hyponatremia, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH), may occur. Interactions with other medications that have serotonergic effects (tramadol, trazodone, tryptophan, and triptan migraine medication) may also occur in theory. When these medications are used in combination, many sources state there may be increased likelihood that a life-threatening **serotonergic syndrome** may occur, with associated symptoms of myoclonus, hyperreflexia, autonomic instability, muscle rigidity, and delirium (see Chapter 77). In fact, serotonin syndrome has never been reported in adults or children with triptans taken for headache disorder and SSRIs. There is also a **discontinuation syndrome** associated with shorter-acting SSRIs (e.g., paroxetine), which includes dizziness, lethargy, paresthesias, irritability, and vivid dreams. Dosages of medications should be tapered slowly over several weeks.

The **selective serotonin-norepinephrine reuptake inhibitors (SNRIs)** duloxetine and venlafaxine have demonstrated significant efficacy with chronic neuropathic and other pain syndromes because they inhibit both serotonin and norepinephrine reuptake, and they may directly block associated pain receptors as well. Venlafaxine has no pain indication labeling. Duloxetine is FDA approved for managing neuropathic pain (specifically, diabetic neuropathy) and fibromyalgia syndrome and for use in children as young as 7 yr. A significant advantage of SNRIs over TCAs when used for headache prophylaxis or neuropathic pain is that they have therapeutic effects on mood and anxiety at dosages effective for pain control.

Because both SSRIs and SNRIs have fewer anticholinergic side effects than TCAs, adherence to them is better than in psychiatric populations taking TCAs. Side effects of both types of drugs include GI symptoms, hyperhidrosis, dizziness, and agitation, but these effects generally wane over time. Hypertension and orthostatic hypotension may occur; in addition, the patient's blood pressure should be closely followed, and appropriate hydration should be stressed. Note that whereas appetite stimulation and weight gain are associated with all TCAs, duloxetine is often associated with weight loss, frequently a desirable side effect, especially in weight-conscious adolescent females.

All antidepressants, including the TCAs, SSRIs and SNRIs, are thought to have the potential to increase the risk of suicidal ideation and the risk of suicide in patients. The FDA states, “All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.” However, the FDA also notes, “Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.”

Antiepileptic Drugs

Anticonvulsants, such as gabapentin, carbamazepine, and valproic acid, are believed to relieve chronic pain by blocking sodium (valproate and the gabapentanoids) or calcium (carbamazepine and oxcarbazepine) channels at the cellular neuronal level, thereby suppressing spontaneous electrical activity and restoring the normal threshold to depolarization of hypersensitive nociceptive neurons, without affecting normal nerve conduction. These medications are particularly useful in patients with mood disorders who have neuropathic pain. In adults, the FDA has approved carbamazepine for trigeminal neuralgia, valproate for migraine prophylaxis, and pregabalin for neuropathic pain complicating diabetes, for zoster, and for management of fibromyalgia. Anticonvulsant medications generally have GI side effects in addition to sedation, anemia, ataxia, rash, and hepatotoxicity. Carbamazepine and oxcarbazepine are also associated with Stevens-Johnson syndrome.

Liver function and CBC should be monitored at the start of therapy and periodically with antiepileptic drugs (AEDs). Carbamazepine and valproic acid have narrow therapeutic windows and variability in therapeutic blood medication levels, as well as many drug-drug interactions, and may cause liver disease and renal impairment. Drug levels should be measured with each dose increase and periodically thereafter. Carbamazepine, in particular, causes autoinduction of hepatic microsomal enzymes, which can further complicate obtaining a therapeutic medication level. Female patients should have pregnancy testing before taking valproate, and those who are sexually active must be cautioned to use effective contraception, because neural tube defects are associated with carbamazepine.

Less toxic AEDs have supplanted the use of valproate and carbamazepine in patients with pain. These newer agents have their own, sometimes troubling, side effect profiles, but they are much less toxic than their predecessors and do not require monitoring of liver or bone marrow function or blood levels. Furthermore, they are also far less lethal in accidental or deliberate overdose.

Gabapentin , the most widely prescribed AED for the management of pain disorders, demonstrates efficacy in treating children with chronic pain, particularly neuropathic pain, and is playing an increasing role in the management of routine surgical pain. Gabapentin has proved effective in treating chronic headache disorders and many neuropathic pain syndromes, including complex regional pain syndromes, chemotherapy-induced neuropathy, postherpetic neuralgia, and diabetic neuropathy in both children and adults. This agent has a relatively benign side effect profile and no drug interactions. Side effects include somnolence, dizziness, and ataxia. Children occasionally demonstrate side effects not reported in adults, such as impulsive or oppositional behavior, agitation, and occasionally depression. These side effects do not seem to be dose related.

Pregabalin works by similar mechanisms as gabapentin but has a better side effect profile. Both gabapentin and pregabalin undergo virtually no hepatic metabolism, with no significant drug-drug interactions, a concern in patients with chronic pain, who frequently take multiple medications—for both the pain and the underlying medical condition associated with the pain. However, because both AEDs depend on renal function for clearance, doses must be adjusted in the presence of renal dysfunction.

Topiramate also demonstrates greater success than traditional anticonvulsants in treating trigeminal neuralgia in adults and in migraine prophylaxis. Topiramate therapy results more frequently in cognitive dysfunction and short-term memory loss than gabapentin or pregabalin, and these neurocognitive effects are particularly problematic for school-aged children. The pediatrician should also be aware that topiramate is associated with weight loss, whereas other anticonvulsants are typically associated with significant weight gain. This side effect is particularly valuable in weight-conscious adolescents, whereas in the anorexic cancer patient, a TCA would be preferable to induce appetite and weight gain.

Benzodiazepines

Children and adolescents with chronic pain may have comorbid psychological conditions, such as depressed mood, sleep disturbances, and anxiety disorders, including generalized anxiety disorder, separation anxiety, posttraumatic stress disorder (PTSD), and panic attacks. Pervasive developmental disorders are common in this population. Psychological factors affect a youth's ability to cope with a pain disorder. A *conditioned response* to pain may be to feel out of control and increase anxiety and pain, and conversely, *anticipatory anxiety* related to pain will inhibit activities and recovery. Feelings of helplessness sensitize the child to increasing amounts of pain, leading the child to perseverate on pain, think catastrophically, and feel hopeless. Changes in children's normal routines, with a negative impact on participation in valued activities, may further promote hopelessness, resulting in increased pain experiences and development of a depressive disorder.

Benzodiazepines are anxiolytic medications that also have muscle relaxant effects. They are particularly appropriate in acute situations as valuable adjuncts to the management of pain in the hospital setting, because they inhibit painful muscle spasms in surgical patients, but more importantly because they suppress the anxiety that virtually every hospitalized child experiences, anxiety that interferes with restorative sleep and amplifies the child's perception of pain. Benzodiazepines are useful to calm children with anxiety and anticipatory anxiety about planned, painful procedures.

Because dependence, tolerance, and withdrawal may occur with prolonged use, benzodiazepines are generally not recommended for the routine management of *chronic pain* . Further, the risk of respiratory depression when benzodiazepines are combined with opioid therapy has contributed to the increasing number of opioid-related deaths in the United States since 2001. In concert with psychotherapy, however, benzodiazepines help control anxiety symptoms that amplify the perception of pain.

Infrequently, benzodiazepines may cause behavioral disinhibition, psychosis-like behaviors, or, in large doses, respiratory depression. When dosing these medications, the pediatrician should consider that many benzodiazepines are metabolized by the cytochrome P-450 microsomal enzyme system. This issue may be less significant with lorazepam and oxazepam, which undergo first-pass hepatic conjugation. Side effects common to benzodiazepines include sedation, ataxia, anemia, increased bronchial secretions, and depressed mood. If a benzodiazepine is administered for more than several consecutive days, the dosage should be slowly tapered over 2 or more weeks; if therapy is abruptly discontinued, autonomic instability, delirium, agitation, seizures, and profound insomnia may occur. The child psychiatric literature cites concerns that the use of benzodiazepines during hospitalization for serious disease (e.g., organ transplantation, prolonged intensive care unit [ICU] stay) might increase the risk for development of PTSD or increase PTSD symptomatology by reducing orientation used in coping with stress. Thus, other anxiolytics, such as atypical antipsychotics, are often recommended.

Antipsychotics and Major Sedatives

Low doses of antipsychotic medications are often used to address the more severe anxiety, agitation, and behavioral decompensation sometimes associated with severe pain. The use of these medications is controversial because associated adverse events may be severe and irreversible. Typical antipsychotics used in the past, including thioridazine (Mellaril), haloperidol (Haldol), and chlorpromazine (Thorazine), are associated with a decreased seizure threshold, dystonia, agranulocytosis, weight gain, cardiac conduction disturbances, tardive dyskinesia, orthostatic hypotension, hepatic dysfunction, and life-threatening laryngeal dystonia. These side effects are generally less severe with atypical antipsychotics. Because these effects may still occur, the pediatrician should obtain a baseline ECG, liver function values, and CBC analysis, and if possible obtain a child psychiatry consultation. If the pediatrician is using typical antipsychotics, an inventory of movement disturbances, such as the Abnormal Involuntary Movement Scale (AIMS) test, should be performed at baseline and at every follow-up visit, because movement disorders can worsen with abrupt withdrawal of medications or can become irreversible.

Atypical antipsychotics are generally associated with less severe side effect profiles, particularly dyskinesias and dystonias. Use of olanzapine (Zyprexa), which is particularly helpful with insomnia and severe anxiety, requires assessing and monitoring blood levels of glucose, cholesterol, and triglyceride; olanzapine's side effects may include diabetes, hypercholesterolemia, or significant weight gain. The anticholinergic side effects associated with quetiapine (Seroquel) warrant frequent monitoring of blood pressure. Risperidone at doses >6 mg may cause side effects similar to those of typical antipsychotics. Clozapine (Clozaril), which causes increased incidence of life-threatening agranulocytosis, should generally be avoided as a treatment for children and adolescents with chronic pain. Aripiprazole (Abilify) has been used for severe anxiety and/or for treatment-resistant depression. All antipsychotics are associated with the rare, but potentially lethal **neuroleptic malignant syndrome** , which includes severe autonomic instability, muscular rigidity, hyperthermia, catatonia, and altered mental status.

Other Pain Control Medications

Alpha-adrenergic receptor agonists such as clonidine are typically used as antihypertensive agents. However, they are often helpful as both anxiolytics and sleep-onset agents in the anxious hospitalized child. The α-agonists also have central effects on pain reduction. **Clonidine** can be given orally or transdermally, if the child's blood pressure permits. In the ICU, IV **dexmedetomidine** , an α-agonist sedating agent, can be used for the anxious, medically unstable child. Weaning off the dexmedetomidine can often be accomplished with a transition to clonidine. **Propranolol** is a β-blocking agent typically used for the child with autonomic instability and for thalamic storm. There are reports that a β-blocker can enhance depression in a child who already has a major depressive disorder, and discussion with a child psychiatrist can be helpful in decisions about using propranolol if needed. Both clonidine and propranolol have been found useful for the agitated child with ASD. Another α-agonist, **guanfacine** , is more likely to be used during the day for the child with ASD because it is less sedating than clonidine. Despite research on the impact of clonidine on chronic pain, no data are available to determine if guanfacine is as effective in reducing pain. Lastly, **ketamine** , a blocker of *N* -methyl-D -aspartate (NMDA) receptors, has been used for intractable pain in hospitalized children and in outpatients with severe sickle cell disease–related chronic pain, as well as others in palliative care for whom opioids are not sufficient to reduce pain. Since ketamine can have central hallucinatory effects, such children should be monitored closely.

Nonpharmacologic Treatment of Pain

Numerous psychological and physical treatments for relieving pain, fear, and anxiety as well as enhancing functioning have excellent safety profiles and proven effectiveness and should always be considered for incorporation into pediatric pain treatment (Fig. 76.5). In acute and procedural pain, nonpharmacologic strategies have long been used to help reduce distress in children undergoing medical procedures and surgery. Many of these methods aim to help children shift attention from pain and alter pain perception (e.g., distraction, hypnosis, imagery). Similarly, in the treatment of chronic pain, several strategies, often falling under the umbrella category of **cognitive-behavioral therapies (CBTs)** , have been shown to reduce pain and improve functioning and quality of life. CBT was developed with the goal of modifying social/environmental and behavioral factors that may exacerbate the child's experience of pain and pain-related disability. Several decades of research is available on CBTs for pediatric chronic pain. Meta-analyses of randomized controlled trials (RCTs) of CBT interventions have found large positive effects of psychological intervention on reductions in pain and/or its deleterious effects in children with headache, abdominal pain, and fibromyalgia, with relative or comparative effectiveness of different interventions examined in areas such as headache and abdominal pain in children. Biofeedback and relaxation therapies have been found to have superior effects to pharmacologic treatments in reducing headache pain in children and adolescents. Similarly, for recurrent abdominal pain, positive effects for CBT were found relative to attention-control conditions and pharmaceutical, botanical, and dietary interventions (which had very weak evidence). Positive results have even resulted from very brief (3 sessions) and remotely delivered (telephone or internet) therapies, with outcomes lasting as long as 12 mo after intervention.

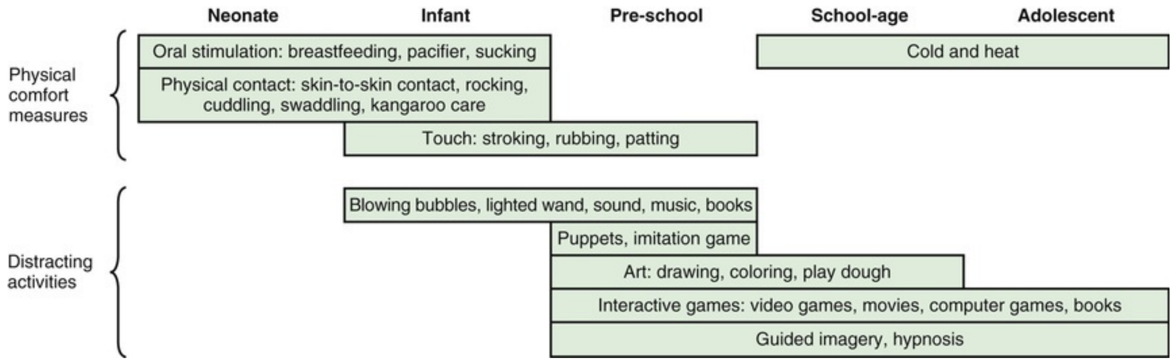
Neonate
Infant
Pre-school
School-age
Adolescent
Physical comfort measures
Oral stimulation: breastfeeding, pacifier, sucking
Physical contact: skin-to-skin contact, rocking, cuddling, swaddling, kangaroo care
Touch: stroking, rubbing, patting
Cold and heat
Distracting activities
Blowing bubbles, lighted wand, sound, music, books
Puppets, imitation game
Art: drawing, coloring, play dough
Interactive games: video games, movies, computer games, books
Guided imagery, hypnosis

FIG. 76.5 Nonpharmacologic interventions for pediatric pain. (From Krauss BS, Calligaris L, Green SM, Barbi E: Current concepts in management of pain in children in the emergency department, *Lancet* 387:83–92, 2016).

When deciding how to incorporate nonpharmacologic techniques to treat pain, the practitioner should (1) conduct a thorough assessment of individual, social, and environmental factors that may be contributing to the patient's pain and functioning limitations; (2) based on this assessment, decide whether nonpharmacologic techniques alone may be sufficient as a beginning to treatment, or if these treatments should be integrated with appropriate analgesics; (3) give children (and family members) developmentally and situationally appropriate information as to the rationale for treatment selection, and what to expect, given the child's medical condition, procedures, and treatments; (4) include patients and their families in decision making to ensure an appropriate treatment choice and to optimize adherence to treatment protocols; and (5) above all, develop a communication plan among the different **care providers** , typically with the pediatrician as the case manager, so that the messages to the child and parent are consistent and the modes of therapy are organized into an integrative team approach. Finally, it is important to recognize that in addition to pain, other psychological disorders (e.g., anxiety disorders, major depression) may impact the presenting pain complaint and may need to be identified and addressed as part of, or separate from, the pain management plan. Individual psychotherapy or psychiatric intervention may be warranted to adequately treat a comorbid disorder.

CBT strategies refer to a range of techniques that teach children (and their caregivers) how to manage pain by learning new ways to think about the pain and how to change behaviors associated with the pain. Strategies focusing on **cognitions** are typically aimed at enhancing parents' and children's confidence and self-efficacy to handle pain and decrease fear of pain. In addition, pain coping skills may shift the child's attentional focus away from pain and painful stimuli.

The goals of those strategies focusing on **behavior** change are to modify (1) contingencies in the child's environment, such as teaching parents how to respond to pain behaviors in ways that encourage wellness, rather than illness behaviors; (2) the ways parents model reactions to pain or discomfort; (3) child and parent coping techniques when psychosocial distress or problems in social relations exist; and (4) the child's behavioral reactions to situations, such as relaxation and exposure to previously avoided activities. Common examples of these strategies are discussed next. Whereas comprehensive CBTs are typically conducted by trained mental health specialists over several sessions, some basic CBT strategies can be briefly and easily introduced by practitioners into most medical settings. If more in-depth CBT treatment is needed, a referral to a qualified mental health specialist with CBT skills would be warranted.

Parent and family education and/or **psychotherapy** , particularly within cognitive-behavioral family approaches, is one treatment modality through which these goals are accomplished, and thus has been shown to be effective for treating chronic pain. Parents can learn to cope with their own distress and to understand pain mechanisms and appropriate treatment of pain. Key components include teaching parents to alter family patterns that may inadvertently exacerbate pain through developing behavior plans. Parents are taught to create plans for the child to manage the child's own symptoms and increase independent functioning. Often, adult caregivers (e.g., parents, teachers) need only guidance on developing a behavioral incentive plan to help the child return to school, gradually increase attendance, and receive tutoring, after a prolonged, pain-related absence. *Suggested sample brief strategy:* Ask caregivers how they react to the child's pain complaints; assess whether they encourage wellness activities or give attention and “rewards” primarily when the child says he or she does not feel well; and suggest that caregivers respond to the child in ways that encourage wellness both when complaining and not complaining.

Relaxation training is often employed to promote muscle relaxation and reduction of anxiety, which often accompanies and increases pain. Relaxation training, along with distraction and biofeedback, are treatments often included in CBT, but also are discussed in the literature without mention of CBT.

Controlled breathing and **progressive muscle relaxation** are commonly used relaxation techniques taught to preschool-age and older children. *Suggested sample brief strategy:* Ask the child (or instruct the caregiver to do so) to practice the following and use if pain is coming on: focus on the breath, and pretend to be blowing up a big balloon, while pursing the lips and exhaling slowly. This is one way to help induce controlled breathing.

Distraction can be used to help a child of any age shift attention away from pain and onto other activities. Common attention sustainers in the environment include bubbles, music, video games, television, the telephone, conversation, school, and play. Asking children to tell stories, asking parents to read to the child, and even mutual storytelling can be helpful distracters. Being involved with social, school, physical, or other activities helps the child in chronic pain to regain function. *Suggested sample brief strategy:* Encourage the child (or instruct the caregiver to do so) to shift attention away from the pain by continuing to engage in other activities and/or think of something else.

Biofeedback involves controlled breathing, relaxation, or hypnotic techniques with a mechanical device that provides visual or auditory feedback to the child when the desired action is approximated. Common targets of actions include muscle tension, peripheral skin temperature through peripheral vasodilation, and anal control through rectal muscle contraction and relaxation. Biofeedback also enhances the child's sense of mastery and control, especially for the child who needs more “proof” of change than that generated through hypnotherapy alone.

Hypnotherapy has also been used in the treatment of chronic pain in children, although the evidence for its effectiveness has not been as extensively studied as CBT. Hypnotherapy helps a child focus on an imaginative experience that is comforting, safe, fun, or intriguing. Hypnotherapy captures the child's attention, alters his or her sensory experiences, reduces distress, reframes pain experiences, creates time distortions, helps the child dissociate from the pain, and enhances feelings of mastery and self-control. Children with chronic pain can use *metaphor,* for example, imagining they have overcome something feared because of pain in real life. As the child increases mastery of imagined experiences, the enhanced sense of control can be used during actual pain rehabilitation. Hypnotherapy is best for children of school age or older.

Nonpharmacologic treatments of pain may also be applied to other treatment needs. A child who learns relaxation to reduce distress from lumbar punctures in cancer treatment may also apply this skill to other stressful medical and nonmedical situations, such as stressors caused by school.

Yoga is intended to achieve balance in mind, body, and spirit. **Therapeutic yoga** can be helpful in treating chronic pain; improving mood, energy, and sleep; and reducing anxiety. Yoga involves a series of *asanas* (body poses) oriented to the specific medical condition or symptoms. Some forms of yoga use poses within a movement flow and format. *Iyengar* yoga is unique in its use of props, such as blankets, bolsters, blocks, and belts, to support the body while the child assumes more healing poses. Yoga promotes a sense of energy, relaxation, strength, balance, and flexibility and, over time, enhances a sense of mastery and control. Within a yoga practice, the child may learn certain types of breathing *(pranayama)* for added benefit. With a focus on body postures or in types of *flow* yoga, the child learns mindfulness or being present and in the moment. By focusing on body and breath, the child can develop strategies to avoid ruminating about the past or worrying about the future.

Mindfulness meditation involves a focus on the present, “in-the-moment” experience using a variety of strategies. Many studies in adults report the value of meditation for chronic pain states as well as for anxiety and depression. These strategies help children learn how to be mindful and in the present, with enhanced parasympathetic control. Many mindfulness smartphone applications are geared to children of different ages, as well as books for parents on how to help their children achieve a mindful state to enhance relaxation (see Susan Kaiser-Greenland's book). Although there are different schools of mindfulness, such as *Vipassana* (insight-oriented meditation often using a focus on the breath) and *transcendental* meditation (in which the child learns the use of a silent mantra to facilitate acquiring a deeper inner calmness), the goal is to help the child learn strategies that enhance self-competence in reducing stress and enhancing a state of well-being.

Massage therapy involves the therapist's touching and applying varied degrees of pressure on the child's muscles. Massage is very useful for children with chronic pain and especially helpful for those with myofascial pain. There are several types of massage, including craniosacral therapy. For young children, it can be helpful to have parents learn and perform brief massage on their children before bedtime. Massage therapy likely will not be helpful to or tolerated by the child with sensory sensitivity and sensory aversion.

Physical therapy can be especially useful for children with chronic, musculoskeletal pain and for those deconditioned from inactivity. Exercise appears specifically to benefit muscle functioning, circulation, and posture, also improving body image, body mechanics, sleep, and mood. The physical therapist and the child can develop a graded exercise plan for enhancing the child's overall function and for the child to continue at home. Recent research indicates that physical therapy affects central neurobiologic mechanisms that enhance “top-down” pain control.

Acupuncture involves the placement of needles at specific acupuncture points along a *meridian* , or energy field, after the acupuncturist has made a diagnosis of excess or deficiency energy in that meridian as the primary cause of the pain. Acupuncture is a feasible, popular part of a pain management plan for children with chronic pain. Acupuncture alleviates chronic nausea, fatigue, and several chronic pain states, including migraine and chronic daily headaches, abdominal pain, and myofascial pain. Acupuncture also has efficacy in adults with myofascial pain, primary dysmenorrhea, sickle cell crisis pain, and sore throat pain. The acupuncturist must relate well to children so that the experience is not traumatic, because added stress would undo the benefits gained.

Transcutaneous electrical nerve stimulation (TENS) is the use of a battery-operated tool worn on the body to send electrical impulses into the body at certain frequencies set by the machine. TENS is believed to be safe and can be tried for many forms of localized pain. Children often find TENS helpful and effective.

Music therapy and **art therapy** can be especially helpful for young and nonverbal children who would otherwise have trouble with traditional talk psychotherapies. Also, many creative children can more easily express fears and negative emotions through creative expression and, with the therapist's help, learn about themselves in the process. There is also increasing research on the impact of art and music therapy on altering central neural circuits that maintain and enhance pain.

Dance, movement, and pet therapies , and **aromatherapy** have also been used and may be helpful, but these have not been as well studied in children for pain control as have other complementary therapies. Often, clinical experience helps guide the pediatrician in the benefits of these therapies with individual patients. For example, pet therapy is gaining favor in hospitals and in stress reduction for sick children. Pets often can become self-regulators for the child with ASD, although the neurobiologic mechanisms are not yet understood.

Invasive Interventions for Treating Pain

Interventional neuraxial and peripheral nerve blocks provide intraoperative anesthesia, postoperative analgesia (see Chapter 74), and treatment of acute pain (e.g., long-bone fracture, acute pancreatitis) and contribute to the management of chronic pain such as headache, abdominal pain, complex regional pain syndrome (CRPS), and cancer pain. Interventional procedures are often used in the treatment of nonmalignant chronic pain in children in some centers and are described here so that the pediatrician will understand the different types of procedures available to children but rarely described in pediatric texts. Interventional procedures may be useful in some children who have specific types of chronic pain, but their use in children (as widely practiced in adult pain clinics) generally is not recommended because the pediatric research is insufficient. Therefore the data are largely extrapolated from the adult population. In children with CRPS receiving multiple focal blocks at an adult pain center, the first block may work “wonders,” but the pain-free intervals between blocks may become shorter, until the blocks are no longer effective, and the CRPS pain spreads, including to the sites of the blocks. This does not mean that no block should be recommend in children, but that blocks should be used judiciously and in conjunction with other biopsychosocial treatments.

Regional anesthesia provides several benefits. As an alternative to or in augmentation of opioid-based pain control, regional anesthesia minimizes opioid requirements and therefore opioid side effects, such as nausea, vomiting, somnolence, respiratory depression, pruritus, constipation, and physical dependence. It generally provides better-quality pain relief than systemic medication because it interrupts nociceptive pathways and more profoundly inhibits endocrine stress responses. Regional anesthesia also results in earlier ambulation in recovering surgical patients, helps prevent atelectasis in the patient with chest pain, and usually results in earlier discharge from the hospital.

Theoretically, the interruption of nociceptive pathways in the periphery by regional anesthetics will prevent, or reverse, the process of amplification of pain signals induced by nociception (e.g., CNS wind-up, glial cell activation). For postoperative pain, effective regional anesthesia reduces the risks of acute pain evolving to chronic pain. Regional anesthesia is considered safe and effective if performed by trained staff with the proper instruments and equipment. Most frequently, nerve blocks are performed by an anesthesiologist or pain management physician; a few are easily performed by a nonanesthesiologist with appropriate training.

Head and Neck Blocks

Primary pain syndromes of the head, such as trigeminal neuralgia, are distinctly unusual in the pediatric population, and few surgical procedures in the head and neck are amenable to regional anesthesia. Pain following tonsillectomies is not amenable to nerve blockade, and neurosurgical incisional pain is usually mitigated by local infiltration of local anesthetic into the wound margins by the surgeon. Headache disorders, very common in the pediatric age-group, often respond well to regional anesthesia of the greater occipital nerve (2nd cervical, C2), which provides sensation to much of the cranial structures, from the upper cervical region, the occiput to the apex of the head, or even to the hairline. The greater occipital nerve can be blocked medial to the occipital artery, which can usually be identified at the occipital ridge midway between the occipital prominence and the mastoid process by palpation, Doppler sound amplification, or visually by high-frequency ultrasound. The short-term and especially long-lasting effects of nerve blocks for chronic headaches in children have not been documented by research. Studies are needed to determine which children with which types of headaches will benefit most from occipital nerve blocks.

Upper-Extremity Blocks

The brachial plexus block controls pain of the upper extremity. This block also protects the extremity from movement, reduces arterial spasm, and blocks sympathetic tone of the upper extremity. The brachial plexus, responsible for cutaneous and motor innervation of the upper extremity, is an arrangement of nerve fibers originating from spinal nerves C5 through 1st thoracic (T1), extending from the neck into the axilla, arm, and hand. The brachial plexus innervates the entire upper limb, except for the trapezius muscle and an area of skin near the axilla. If pain is located proximal to the elbow, the brachial plexus may be blocked above the clavicle (roots and trunks); if the pain is located distal to the elbow, the brachial plexus may be blocked at the axilla (cords and nerves). The block may be given as a single injection with a long-acting anesthetic (bupivacaine or ropivacaine, sometimes augmented with clonidine or dexamethasone to prolong block duration and intensity) to provide up to 12 hr of analgesia, or by a percutaneous catheter attached to a pump that can provide continuous analgesia over days or even weeks.

Trunk and Abdominal Visceral Blocks

Trunk blocks provide somatic and visceral analgesia and anesthesia for pain or surgery of the thorax and abdominal area. Sympathetic, motor, and sensory blockade may be obtained. These blocks are often used in combination to provide optimal relief. Intercostal and paravertebral blocks may be beneficial in patients for whom a thoracic epidural injection or catheter is contraindicated (e.g., patient with coagulopathy). Respiratory function is maintained, and the side effects of opioid therapy are eliminated.

The intercostal, paravertebral, rectus sheath, and transverse abdominal plane blocks are most useful for pediatric chest and somatic abdominal pain. The celiac plexus and splanchnic nerve block is most useful for abdominal visceral pain, such as caused by malignancy or pancreatitis. These blocks are best performed by an experienced anesthesiologist, pain physician, or interventional radiologist using ultrasound or CT imaging guidance.

The **intercostal block** is used to block the intercostal nerves, the anterior rami of the thoracic nerves from T1 to T11. These nerves lie inferior to each rib, between the inner and innermost intercostal muscles with their corresponding vein and artery, where they can be blocked, generally posterior to the posterior axillary line. Ultrasound imaging of the intercostal nerves helps avoid injury to intercostal vessels or insertion of the needle through the pleura, which may result in pneumothorax.

The **paravertebral block** , an alternative to intercostal nerve block or epidural analgesia, is useful for pain associated with thoracotomy or with unilateral abdominal surgery, such as nephrectomy or splenectomy. Essentially this block results in multiple intercostal blocks with a single injection. The thoracic paravertebral space, lateral to the vertebral column, contains the sympathetic chain, rami communicantes, dorsal and ventral roots of the spinal nerves, and dorsal root ganglion. Because it is a continuous space, local anesthetic injection will provide sensory, motor, and sympathetic blockade to several dermatomes. The paravertebral block may be performed as a single injection or, for a very prolonged effect, as a continuous infusion over several days or weeks via a catheter. This block is best performed by an anesthesiologist or interventional pain physician under ultrasound guidance.

Ilioinguinal and iliohypogastric nerve blocks are indicated with surgery for inguinal hernia repair, hydrocele, or orchiopexy repair, as well as for chronic pain subsequent to these procedures. The 1st lumbar (L1) nerve divides into the iliohypogastric and ilioinguinal nerves, which emerge from the lateral border of the psoas major muscle. The iliohypogastric nerve supplies the suprapubic area as it pierces the transversus abdominis muscle and runs deep to the internal oblique muscle. The ilioinguinal nerve supplies the upper medial thigh and superior inguinal region as it also pierces the transversus abdominis muscle and runs across the inguinal canal. Ultrasound guidance has made this nerve block almost always successful.

The **celiac plexus block** is indicated for surgery or pain of the pancreas and upper abdominal viscera. The celiac plexus, located on each side of the L1 vertebral body, contains 1-5 ganglia. The aorta lies posterior, the pancreas anterior, and the inferior vena cava lateral to these nerves. The celiac plexus receives sympathetic fibers from the greater, lesser, and least splanchnic nerves, as well as from parasympathetic fibers from the vagus nerve. Autonomic fibers from the liver, gallbladder, pancreas, stomach, spleen, kidneys, intestines, and adrenal glands originate from the celiac plexus. This block is best performed with CT guidance to provide direct visualization of the appropriate landmarks, avoid vascular and visceral structures, and confirm correct needle placement. The close proximity of structures such as the aorta and vena cava make this a technical procedure best performed by an anesthesiologist, interventional pain physician, or interventional radiologist.

Lower-Extremity Blocks

Lumbar plexus and sciatic nerve blocks provide pain control for painful conditions or surgical procedures of the lower extremities, with the benefit of providing analgesia to only one extremity while preserving motor and sensory function of the other. The lumbosacral plexus is an arrangement of nerve fibers originating from spinal nerves L2-L4 and S1-S3. The lumbar plexus arises from

L2-L4 and forms the lateral femoral cutaneous, femoral, and obturator nerves. These nerves supply the muscles and sensation of the upper leg, with a sensory branch of the femoral nerve (saphenous nerve) extending below the knee to innervate the medial aspect of the foreleg, ankle, and foot. The sacral plexus arises from L4-S3 and divides into the major branches of the sciatic, tibial, and common peroneal nerves. These nerves in turn supply the posterior thigh, lower leg, and foot. Unlike the brachial plexus block, blockade of the entire lower extremity requires >1 injection because the lumbosacral sheath is not accessible. Separate injections are necessary for the posterior (sciatic) and anterior (lumbar plexus) branches, and the injections can be performed at any of several levels during the course of the nerve, as is clinically expedient. The lumbar plexus can be blocked in the back, resulting in analgesia of the femoral, lateral femoral cutaneous, and obturator nerves. Alternatively, any of these 3 nerves can be individually anesthetized, depending on the location of the pain. Similarly, the sciatic nerve can be anesthetized proximally as it emerges from the pelvis or more distally in the posterior thigh, or its major branches (tibial and peroneal nerves) can be individually anesthetized. These nerve blocks are generally best performed by an anesthesiologist, pain physician, or radiologist.

Sympathetic Blocks

Sympathetic blocks were once thought to be useful in the diagnosis and treatment of sympathetically mediated pain, CRPS, and other neuropathic pain conditions, but more recently, large meta-analyses have shown their utility to be minimal. The peripheral sympathetic trunk is formed by the branches of the thoracic and lumbar spinal segments, and it extends from the base of the skull to the coccyx. The sympathetic chain, which consists of separate ganglia containing nerves and autonomic fibers with separate plexuses, can be differentially blocked. These separate plexuses include the stellate ganglion in the lower neck and upper thorax, the celiac plexus in the abdomen, the 2nd lumbar plexus for the lower extremities, and the ganglion impar for the pelvis. When blocks of these plexuses are performed, sympathectomy is obtained without attendant motor or sensory anesthesia.

The **stellate ganglion block** is indicated for pain in the face or upper extremity as well as for CRPS, phantom limb pain, amputation stump pain, or circulatory insufficiency of the upper extremities. The stellate ganglion arises from spinal nerves C7-T1 and lies anterior to the 1st rib. It contains ganglionic fibers to the head and upper extremities. Structures in close proximity include the subclavian and vertebral arteries anteriorly, the recurrent laryngeal nerve, and the phrenic nerve. Chassaignac tubercle, the transverse process of the C6 vertebral body superior to the stellate ganglion, is a useful and easily palpable landmark for the block, but radiographic or ultrasound imaging is used more often than surface anatomy and palpation.

The lumbar sympathetic block addresses pain in the lower extremity, CRPS, phantom limb pain, amputation stump pain, and pain from circulatory insufficiency. The lumbar sympathetic chain contains ganglionic fibers to the pelvis and lower extremities. It lies along the anterolateral surface of the lumbar vertebral bodies and is most often injected between the L2 and L4 vertebral bodies.

The analgesia produced by peripheral sympathetic blocks usually outlives the duration of the local anesthetic, often persisting for weeks or indefinitely. If analgesia is transient, the blocks may be performed with catheter insertion for continuous local anesthesia of the sympathetic chain over days or weeks. Because precise, radiographically guided placement of the needle and/or catheter is required for safety and success, sympathetic blocks are generally best performed by an anesthesiologist, interventional pain physician, or interventional radiologist.

Epidural Anesthesia (Thoracic, Lumbar, and Caudal)

Epidural anesthesia and analgesia are indicated for pain below the clavicles, management of regional pain syndromes, cancer pain unresponsive to systemic opioids, and pain limited by opioid side effects.

The 3 layers of the spinal meninges—dura mater (outer), arachnoid mater (middle), and pia mater (inner)—envelop the spinal neural tissue. The subarachnoid space contains cerebrospinal fluid between the arachnoid mater and pia mater. The epidural space extends from the foramen magnum to the sacral hiatus and contains fat, lymphatics, blood vessels, and the spinal nerves as they leave the spinal cord. The epidural space separates the dura mater from the periosteum of the surrounding vertebral bodies. In children the fat in the epidural space is not as dense as in adults, predisposing to greater spread of the local anesthetic from the site of injection.

Epidural local anesthetics block both sensory and sympathetic fibers, and if the local anesthetic is of sufficient concentration, they also block motor fibers. Mild hypotension may occur, although it is unusual in children <8 yr. Epidural local anesthetics high in the thoracic spine may also anesthetize the sympathetic nerves to the heart (the cardiac accelerator fibers), producing bradycardia. In addition to using local anesthetics, it is routine to use opioids and α-agonists as adjunctive medications in the epidural space. Clonidine and opioids have been well studied and shown not to be neurotoxic. Other drugs (neostigmine, ketamine, diazepam) also are analgesic in the epidural space, but neurotoxicity studies have not established their safety. These agents have their primary site of action in the spinal cord, to which they diffuse from their epidural depot. Side effects of epidural opioid administration include delayed respiratory depression, particularly when hydrophilic opioids such as morphine are used. The risk of this effect requires that children receiving epidural opioids by intermittent injection or continuous infusion be monitored by continuous pulse oximetry and nursing observation, particularly during the 1st 24 hr of therapy or after significant dose escalations. Respiratory depression occurring after the 1st 24 hr of epidural opioid administration is distinctly unusual.

Epidural clonidine (an α_2 -agonist with µ-opioid analgesic properties) is associated with minimal risk and side effects. Although product labeling indicates use only in children with severe cancer pain, clonidine is frequently used for routine postoperative pain as well as pain syndromes such as CRPS. Mild sedation is the most common side effect of epidural clonidine, and it is not associated with respiratory depression.

Because performing epidural blockade is technical and may result in spinal cord injury, it is best done by an anesthesiologist or pain physician skilled in the technique. Caution is advised in the use of epidural anesthesia/analgesia for CRPS in children because no published RCTs have shown these procedures superior to a combination of less invasive physical and psychological therapy with or without neuropathic pain-focused medications.

Intrathecal Analgesia

Intrathecal catheters infused with opioids, clonidine, ziconotide (derived from a marine neurotoxin produced by the cone snail), and local anesthetics are occasionally applicable in pediatric patients with intractable pain from cancer or other conditions. Typically, intrathecal catheters are attached to an implanted electronic pump containing a drug reservoir sufficient for several months of dosing. The technique is technical and best performed by an experienced pain management physician.

Nerve Ablation and Destruction

In some cases, pain remains refractory despite maximal reliance on oral and IV medications and nerve blockade. In these patients, temporary (pulsed radiofrequency ablation) or permanent (neurolytic) destruction of one or more nerves may be performed. The techniques should be carefully weighed against the consideration of permanent nerve destruction in a growing child with decades of life ahead. On the other hand, when pain is severe in life-limiting disease processes, the long-term considerations are less concerning, and these techniques should be discussed with a skilled pain management specialist.

Considerations for Special Pediatric Populations

Pain Perception and Effects of Pain on Newborns and Infants

Pain has a number of sources in the newborn period, including acute pain (diagnostic and therapeutic procedures, minor surgery, monitoring), continuous pain (pain from thermal/chemical burns, postsurgical and inflammatory pain), and chronic or disease-related pain (repeated heelsticks, indwelling catheters, necrotizing enterocolitis, nerve injury, chronic conditions, thrombophlebitis). The most common sources of pain in healthy infants are acute procedures, such as heel lances, surgical procedures, and in boys, circumcision.

Many procedures are performed for premature infants in the neonatal intensive care unit (NICU). In the 1st wk of life, approximately 94% of preterm infants <28 wk gestational age are mechanically ventilated. Other procedures are heelsticks (most common) and airway suctioning. Few of these procedures are preceded by any type of analgesia. Repeated handling and acute pain episodes sensitize the neonate to increased reactivity and stress responses to subsequent procedures. Typical stress responses include increases in heart rate, respiratory rate, blood pressure, and intracranial pressure. Cardiac vagal tone, transcutaneous oxygen saturation, carbon dioxide levels, and peripheral blood flow are decreased. Autonomic signs include changes in skin color, vomiting, gagging, hiccupping, diaphoresis, dilated pupils, and palmar and forehead sweating.

Untreated pain in the newborn has serious short- and long-term consequences. There has been a shift in most NICUs to more liberal use of opioids. Nonetheless, **morphine** , the traditional gold standard of analgesia for acute pain, may not be effective and may have adverse long-term consequences. No differences have been found in the incidence of severe intraventricular hemorrhage or in the mortality rate when infants receiving morphine are compared with the placebo group, and there are no changes in assessed pain from tracheal suctioning in ventilated infants receiving morphine compared with those receiving a placebo infusion. Morphine may not alleviate acute pain in ventilated preterm neonates, although there are few data on the effects of morphine and fentanyl in nonventilated newborns. The lack of opioid effects for acute pain in neonates may result from immaturity of opioid receptors; acute pain may cause the uncoupling of μ-opioid receptors in the forebrain. Repetitive acute pain may create central neural changes in the newborn that may have long-term consequences for later pain vulnerability, cognitive effects, and opioid tolerance. Most neonatologists use opioids in painful situations. Sucrose and pacifiers are also being used in the NICU. The effects of **sucrose** (sweet taste) are believed to be opioid mediated because they are reversed with naloxone; stress and pain relief are integrated through the endogenous opioid system. Sucrose, with or without a pacifier, may be effective for acute pain and stress control. Other nonpharmacologic strategies for stress and pain control include infant care by an individual primary nurse, tactile-kinesthetic stimuli (massage), “kangaroo care,” and soothing sensorial saturation.

Children With Cancer Pain

The World Health Organization (WHO) proposed an analgesic therapy model for cancer pain known as the *analgesic ladder* (Table 76.14). Designed to guide therapy in the Third World, this ladder consists of a hierarchy of oral pharmacologic interventions intended to treat pain of increasing magnitude. The hierarchy ignores modalities such as the use of nonconventional analgesics and interventional pain procedures, which are within the capability of physicians to prescribe in developed countries. Nevertheless, because oral medications are simple and efficacious, especially for home use, the ladder presents a framework for rationally using them before applying other drugs and techniques of drug administration.

Table 76.14

World Health Organization Analgesic Ladder for Cancer Pain

Step 1

Patients who present with mild to moderate pain should be treated with a nonopioid.

Step 2

Patients who present with moderate to severe pain or for whom the step 1 regimen fails should be treated with an oral opioid for moderate pain combined with a nonopioid analgesic.

Step 3

Patients who present with very severe pain or for whom the step 2 regimen fails should be treated with an opioid used for severe pain, with or without a nonopioid analgesic.

Oral medications are the first line of analgesic treatment. Because NSAIDs affect platelet adhesiveness, they are typically not used. Opioid therapy is the preferred approach for moderate or severe pain. Nonopioid analgesics are used for mild pain, a weak opioid is added for moderate pain, and strong opioids are administered for more severe pain. Adjuvant analgesics can be added, and side effects and comorbid symptoms are actively managed. Determining the type and sources of the pain will help develop an effective analgesic plan. Certain treatments, such as the chemotherapeutic agent vincristine, are associated with neuropathic pain. Such pain might require anticonvulsants or TCAs. Organ-stretching pain from tumor growth within an organ might require strong opioids and/or radiation therapy if the tumor is radiosensitive. Organ obstruction, such as intestinal obstruction, should be diagnosed to relieve or bypass the obstruction.

It is important to consider both pharmacologic and nonpharmacologic strategies (e.g., CBT, family/parent support) to treat pain in children with cancer.

Children With Pain Associated With Advanced Disease

Patients with advanced diseases, including cancer, acquired immunodeficiency syndrome (AIDS), neurodegenerative disorders, and cystic fibrosis, need palliative care approaches that focus on optimal quality of life. Nonpharmacologic and pharmacologic management of pain and other distressing symptoms is a key component. *Palliative care* should be offered to all children with serious diseases, whether or not the diseases are potentially curable or long life expectancy is predicted. Examples include young children diagnosed with acute lymphoblastic leukemia (>90% posttreatment life expectancy) and children undergoing organ transplantation. Palliative care in pediatrics connotes treatment that focuses on symptom reduction, quality of life, and good family and clinical team communication. It is not only for patients in hospice care or those at the end of life. Differences in the progression of underlying illness, associated distressing symptoms, and common emotional responses in these conditions should shape individual treatment plans. For end-of-life care, >90% of children and adolescents with cancer can be made comfortable by standard escalation of opioids according to the WHO protocol. A small subgroup (5%) has enormous opioid dose escalation to >100 times the standard morphine or other opiate infusion rate. Most of these patients have spread of solid tumors to the spinal cord, roots, or plexus, and signs of neuropathic pain are evident. **Methadone** given orally is often used in palliative care, not only end-of-life care, because of its long half-life and its targets at both opioid and NMDA receptors.

The type of pain experienced by the patient (neuropathic, myofascial) should determine the need for adjunctive agents. Complementary measures, such as massage, hypnotherapy, and spiritual care, must also be offered in palliative care. Although the oral route of opioid administration should be encouraged, especially to facilitate care at home if possible, some children are unable to take oral opioids. Transdermal and sublingual routes, as well as IV infusion with PCA, are likely next choices. Small, portable infusion pumps are convenient for home use. If venous access is limited, a useful alternative is to administer opioids (especially morphine or hydromorphone, but not methadone or meperidine) through continuous SC infusion, with or without a bolus option. A small (e.g., 22-gauge) cannula is placed under the skin and secured on the thorax, abdomen, or thigh. Sites may be changed every 3-7 days, as needed. As noted, alternative routes for opioids include the transdermal and oral transmucosal routes. These latter routes are preferred over IV and SC drug delivery when the patient is being treated at home.

Chronic and Recurrent Pain Syndromes

Chronic pain is defined as recurrent or persistent pain lasting longer than the normal tissue healing time, 3-6 mo. Children may experience pain related to injury (e.g., burns) or to a chronic or underlying disease process (e.g., cancer, arthritis), or pain can also be the chronic condition itself (e.g., CRPS, fibromyalgia, functional abdominal pain) (see Chapter 147). During childhood, abdominal, musculoskeletal, and headache pain are the most frequently occurring conditions. However, definitions of chronic pain do not take into account standard criteria for assessing particular pain symptoms or for evaluating the intensity or impact of pain, and therefore includes individuals with varying symptoms and experiences. Consequently, in epidemiologic surveys, prevalence estimates vary widely. Overall prevalence rates for different childhood pains range from 4–88%. For example, an average of 13.5–31.8% of adolescents in a community sample reported having weekly abdominal, headache, or musculoskeletal pains. Most epidemiologic studies report prevalence and do not report the *severity* or impact of the pain. Research indicates that only a subset of children and adolescents with chronic pain (approximately 5%) experience moderate to severe disability, and this likely better represents the estimated population for whom help is needed to treat pain and associated problems.

Neuropathic Pain Syndromes

Neuropathic pain is caused by abnormal excitability in the peripheral or central nervous system that may persist after an injury heals or inflammation subsides. The pain, which can be acute or chronic, is typically described as burning or stabbing and may be associated with cutaneous hypersensitivity (allodynia), distortion of sensation (dysesthesia), and amplification of noxious sensations (hyperalgesia and hyperpathia). Neuropathic pain conditions may be responsible for >35% of referrals to chronic pain clinics, conditions that typically include posttraumatic and postsurgical peripheral nerve injuries, phantom pain after amputation, pain after spinal cord injury, and pain caused by metabolic neuropathies. Patients with neuropathic pain typically respond poorly to opioids. Evidence supports the efficacy of antidepressants (nortriptyline, amitriptyline, venlafaxine, duloxetine) and anticonvulsants (gabapentin, pregabalin, oxcarbazepine) for treatment of neuropathic pain (see Tables 76.12 and 76.13).

Complex regional pain syndrome , formerly known as “reflex sympathetic dystrophy” (RSD), is well described in the pediatric population. **CRPS type 1** is a syndrome of neuropathic pain that typically follows an antecedent and usually minor injury or surgery to an extremity without identifiable nerve injury. It is often seen in oncology patients as a complication of their malignancy, IV infiltrations in the periphery, or surgery. The syndrome of CRPS type 1 includes severe spontaneous neuropathic pain, hyperpathia, hyperalgesia, severe cutaneous allodynia to touch and cold, changes in blood flow (typically extremity cyanosis), and increased sweating. In more advanced cases, symptoms include dystrophic changes of the hair, nails, and skin, immobility of the extremity (dystonia), and muscle atrophy. In the most advanced cases, symptoms include ankylosis of the joints of the extremity. Specific causal factors in CRPS type 1 in both children and adults remain elusive, although coincidental events may be noted. **CRPS type 2** , formerly referred to as “causalgia,” is less common and describes a very similar constellation of symptoms but is associated with a known nerve injury. CRPS type 2 pain may be restricted to the distribution of the injured nerve or too much of the involved limb in a stocking-glove distribution, whereas CRPS type 1 is generally seen in a stocking-glove distribution and by definition is not limited to a peripheral nerve or dermatomal distribution of signs and symptoms.

Treatment of CRPS in children has been extrapolated from that in adults, with some evidence for efficacy of physical therapy, CBT, nerve blocks, antidepressants, AEDs, and other related drugs. All experts in pediatric pain management agree on the value of aggressive physical therapy. Some centers provide aggressive therapy without the use of pharmacologic agents or interventional nerve blocks. Unfortunately, recurrent episodes of CRPS may be seen in up to 50% of patients, particularly adolescent females. Physical therapy can be extraordinarily painful for children to endure; it is tolerated only by the most stoic and motivated patients. If children have difficulty enduring the pain, there is a well-established role for pharmacologic agents with or without peripheral or central neuraxial nerve blocks to render the affected limb sufficiently analgesic so that physical therapy can be tolerated. Pharmacologic interventions include the use of AEDs such as gabapentin and/or TCAs such as amitriptyline (see Fig. 76.4). Although there is clear evidence of a peripheral inflammatory component of CRPS, with release of cytokines and other inflammatory mediators from the peripheral nervous system in the affected limb, the use of antiinflammatory agents has been disappointing. Common nerve block techniques include IV regional anesthetics, epidural analgesia, and peripheral nerve blocks. In extreme and refractory cases, more invasive strategies have been reported, including surgical sympathectomy and spinal cord stimulation.

Although an array of treatments has some benefit, the mainstay of treatment remains **physical therapy** emphasizing desensitization, strengthening, and functional improvement. Additionally, pharmacologic agents and psychological and complementary therapies are important components of a treatment plan. Invasive techniques, although not curative, can be helpful if they permit the performance of frequent and aggressive physical therapy that cannot be carried out otherwise. A good biopsychosocial evaluation will help determine the orientation of the treatment components. There are insufficient data to indicate the superior value of interventional blocks, such as epidural anesthesia, in children with CRPS over physical and psychological interventions, with or without pharmacologic support.

Myofascial Pain Disorders and Fibromyalgia

Myofascial pain disorders are associated with tender points in the affected muscles as well as with muscle spasms (tight muscles). Treatment is targeted at relaxing the affected muscles through physical therapy, Iyengar yoga, massage, and acupuncture. Rarely are pharmacologic muscle relaxants helpful other than for creating tiredness at night for sleep. Dry needling or injections of local anesthetic into the tender points has been advocated, but the data do not support this as a standard treatment. Similarly, although botulinum toxin injections may be used, no data support this practice in children. Often, poor body postures, repetitive use of a body part not accustomed to that movement, or carrying heavy backpacks initiates pain. When it becomes widespread with multiple tender points, the diagnosis may be made of *juvenile fibromyalgia,* which may or may not continue to subsequently become adult fibromyalgia. Likely there are different subtypes of widespread pain syndromes, and physical therapy is a key component of treatment. Psychological interventions may play an important role to assist the child in resuming normal activities and to manage any psychological comorbidities. Any pain rehabilitation plan should enhance return to full function. Because there is a high incidence of chronic pain in parents of children presenting with a chronic pain condition, especially fibromyalgia, attention to parent and family factors is important. Parent training may entail teaching the parent to model more appropriate pain coping behaviors and to recognize the child's independent attempts to manage pain and function adaptively. Parents may also need referrals to obtain appropriate pain management for their own pain condition.

Pregabalin and duloxetine are FDA approved for management of fibromyalgia in adults, but no clinical studies have confirmed their effectiveness in children and adolescents. One recent large study in adolescents with fibromyalgia found that CBT and physical therapy were superior to typical pharmacologic agents used in adults.

Erythromelalgia

Erythromelalgia in children is generally primary, whereas in adults it may be either primary or secondary to malignancy or other hematologic disorders, such as polycythemia vera. Patients with erythromelalgia exhibit red, warm, hyperperfused distal limbs. The disorder is usually bilateral and may involve either or both the hands and feet. Patients perceive burning pain and typically seek relief by immersing the affected extremities in ice water, sometimes so often and for so long so that skin pathology results. **Primary erythromelalgia** is caused by a genetic mutation (autosomal dominant) in the gene for the NaV1.7 neuronal sodium channel on peripheral C nociceptive fibers, resulting in their spontaneous depolarization, and thus continuous burning pain. The most common mutation identified is in the *SCN9A* gene, although there are several mutations that affect the NaV1.7 channel. Interestingly, another mutation in the NaV1.7 channel results in a rare but devastating genetic condition, the congenital indifference to pain.

It is easy to distinguish erythromelalgia (or related syndromes) from CRPS. The limb afflicted with CRPS is typically cold and cyanotic, the disease is typically unilateral, and children with CRPS have cold allodynia, making immersion in cold water exquisitely painful. In erythromelalgia, ice water immersion is analgesic, the condition is bilateral and symmetric, and it is associated with hyperperfusion of the distal extremity. The evaluation of hyperperfused limbs with burning pain should include genetic testing for **Fabry disease** and screening for hematologic malignancies, with diagnosis of primary erythromelalgia being one of exclusion. At present, few clinical laboratories are Clinical Laboratory Improvement Amendments (CLIA) certified to perform the DNA analysis required to identify the common NaV1.7 mutations.

The definitive treatment of Fabry disease includes enzyme replacement as disease-modifying treatment and administration of neuropathic pain medications such as gabapentin, although the success of antineuropathic pain drugs in small-fiber neuropathies has not been impressive. The treatment of erythromelalgia is much more problematic. Antineuropathic pain medications (AEDs, TCAs) are typically prescribed but rarely helpful (see Fig. 76.4). Although one might predict that sodium channel–blocking AEDs might be effective in this sodium channelopathy, oxcarbazepine has not proved to be a particularly effective modality. The pain responds well to regional anesthetic nerve blocks, but it returns immediately when the effects of the nerve block resolve. In contrast, in other neuropathic syndromes, the analgesia usually (and inexplicably) persists well after the resolution of the pharmacologic nerve block. Aspirin and even nitroprusside infusions have been anecdotally reported to be of benefit with secondary erythromelalgia, but have not been reported to be helpful in children with primary erythromelalgia. Case reports in adults and clinical experience in children suggest that periodic treatment with high-dose **capsaicin cream** is effective in alleviating the burning pain and disability of erythromelalgia. Capsaicin (essence of chili pepper) cream is a vanilloid receptor (TRPV1) agonist that depletes small-fiber peripheral nerve endings of the neurotransmitter substance P, an important neurotransmitter in the generation and transmission of nociceptive impulses. Once depleted, these nerve endings are no longer capable of generating spontaneous pain until the receptors regenerate, a process that takes many months.

Other Chronic Pain Conditions in Children

A variety of genetic and other medical/surgical conditions are often associated with chronic pain. Examples include Fabry disease, Chiari/syringomyelia, epidermolysis bullosa, juvenile idiopathic arthritis, porphyria, mitochondrial disorders, degenerative neurologic diseases, cerebral palsy, ASD, intestinal pseudoobstruction, inflammatory bowel disease, chronic migraine/daily headaches, and irritable bowel disease. In many cases, treating the underlying disease, such as enzyme replacement in Fabry disease and in other lysosomal disorders, will reduce what otherwise might be progression of symptoms, but may not totally reduce pain and suffering, and other modalities will be needed. Finally, pain that persists and is not well treated can lead to central sensitization and widespread pain, such as seen in children with one pain source who develop fibromyalgia.

Managing Complex Chronic Pain Problems

Some patients with chronic pain have a prolonged course of evaluation in attempts to find what is expected as the singular “cause” of the pain and thus also undergo many failed treatments (see Chapter 147). Parents worry that the doctors have not yet discovered the cause that may be serious and life threatening, and children often feel not believed, that they are faking their pain, or are “crazy.” There may be no identifiable or diagnosable condition, and families may seek opinions from multiple treatment facilities in an attempt to find help for their suffering child. For some children, what may have begun as an acute injury or infectious event may result in a chronic pain syndrome, with changes in the neurobiology of the pain-signaling system.

In the context of disabling chronic pain, it is very important for the pediatrician to avoid overmedication because this can exacerbate associated disability, maintain an open mind and reassess the diagnosis if the clinical presentation changes, and understand and communicate to the family that pain has a biologic basis (likely related to neural signaling and neurotransmitter dysregulation), and that the pain is naturally distressing to the child and family. All patients and families should receive a simple explanation of pain physiology that helps them understand the importance of (1) functional rehabilitation to normalize pain signaling, (2) the low risk of causing further injury with systematic increases in normal functioning, and (3) the likely failure of treatment if pain is managed as if it were acute. Because it is counterintuitive for most people to move a part of the body that hurts, many patients with chronic pain have atrophy or contractures of a painful extremity from disuse. Associated increases in worry and anxiety may exacerbate pain and leave the body even more vulnerable to further illness, injury, and disability. Pain can have a significant impact on many areas of normal functioning and routines for children, and school absenteeism and related consequences of missed schooling are often significant problems. Appropriate assessment and evaluation of the child with chronic pain and the family is the critical 1st step necessary in developing a treatment plan. For example, a high–academically functioning child might have an acute injury that leads to chronic pain and significant school absenteeism. While many downstream contributors to pain and disability maintenance can accumulate the more school that is missed, often previously unrecognized focal learning disabilities may become the increasing trigger for a downhill cascade of pain, disability, and school absenteeism. Even for the child with outstanding grades, it may be helpful to learn about the amount of time spent on each subject. As certain subjects become more complicated, such as math, the child with a previously unrecognized math learning disability may be spending hours on math homework each night, even with good grades in math. In this case the acute illness or injury becomes the “final straw” that breaks down the child's coping and turns the acute pain into a chronic problem.

Interdisciplinary pediatric pain programs have become the standard of care for treating complex chronic pain problems in youth. Although available in many parts of the United States, Canada, Europe, Australia, and New Zealand, the overall number of programs is still small. Therefore, many children and adolescents with chronic pain will be unable to receive specialized pain treatment in their local communities. In recognition of the severity and complexity of pain and disability for some children, different settings and treatment delivery models for providing pain care have been explored. One option is inpatient and day hospital treatment programs, which often address barriers to access to outpatient treatment and coordination of care. In addition, these programs provide an intensive treatment option for children who do not make adequate progress in outpatient treatment or who are severely disabled by pain. Early programs developed in the 1990s focused on CRPS treatment through intensive inpatient rehabilitation and exercise-based programs. Later programs expanded to other clinical populations and broadened the treatment focus to incorporate a range of rehabilitation and psychological therapies delivered both individually and in groups. The typical length of inpatient admissions for children with chronic pain in such programs is 3-4 wk, and emerging evidence suggests benefit from these programs. A major problem that limits such care for children with complex chronic disabling pain is the long waiting list for entry into these still relatively few programs, as well as obtaining insurance approval. Additional more widespread models of care are needed.

Another intervention delivery option is *remote management,* referring to pain interventions utilized outside the clinic/hospital setting to reach children in their homes or communities. Interventions are typically delivered using some form of technology, such as the internet, or may rely on other media, such as telephone counseling or written self-help materials. Typically, remote management of pain includes monitoring, counseling, and delivery of behavioral and CBT interventions. Internet interventions have received the most research attention to date, with published examples of several different pediatric chronic pain conditions with promising findings for pain reduction. *Telemedicine,* while in widespread use clinically for many pediatric health conditions, has not yet been formally evaluated in pediatric pain. Within any community, the pediatrician will need to locate appropriate referral sources for patients with complex chronic pain. However, while psychological interventions can be delivered through these telemedicine strategies, the pediatrician is still relied on to obtain the needed biopsychosocial history, complete a thorough physical examination, and provide the pharmacologic management as needed. The pediatrician also communicates with the family to help the child and family understand the pain and how the different pharmacologic and nonpharmacologic treatments will enhance function and alter the long-term neural processes underlying pain.

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CHAPTER 77

Poisoning

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Poisoning is the leading cause of injury-related death in the United States, surpassing that from motor vehicle crashes. Most these deaths are unintentional (i.e., not suicide). In adolescents, poisoning is the 3rd leading cause of injury-related death. Of the >2 million human poisoning exposures reported annually to the National Poison Data Systems (NPDS) of the American Association of Poison Control Centers (AAPCC), approximately 50% occur in children <6 yr old, with the highest number of exposures occurring in 1 and 2 yr olds. Almost all these exposures are unintentional and reflect the propensity for young children to put virtually anything in their mouth. Fortunately, children <6 yr old account for <2% of all poisoning fatalities reported to NPDS.

More than 90% of toxic exposures in children occur in the home, and most involve a single substance. Ingestion accounts for the majority of exposures, with a minority occurring by the dermal, inhalational, and ophthalmic routes. Approximately 40% of cases involve nondrug substances, such as cosmetics, personal care items, cleaning solutions, plants, and foreign bodies. Pharmaceutical preparations account for the remainder of exposures, and analgesics, topical preparations, vitamins, and antihistamines are the most commonly reported categories.

The majority of poisoning exposures in children <6 yr old can be managed without direct medical intervention beyond a call to the regional **poison control center (PCC)** . This is because the product involved is not inherently toxic or the quantity of the material is not sufficient to produce clinically relevant toxic effects. However, a number of substances can be highly toxic to toddlers in small doses (Table 77.1). In 2015, carbon monoxide (CO), batteries, and analgesics (mainly opioids) were the leading causes of poison-related fatalities in young children (<6 yr). In addition, stimulants/street drugs, cardiovascular (CV) drugs, and aliphatic hydrocarbons were significant causes of mortality.

Table 77.1

Common Agents Potentially Toxic to Young Children (<6 yr) in Small Doses*

SUBSTANCE	TOXICITY
Aliphatic hydrocarbons (e.g., gasoline, kerosene, lamp oil)	Acute lung injury
Antimalarials (chloroquine, quinine)	Seizures, dysrhythmias
Benzocaine	Methemoglobinemia
β-Adrenergic receptor blockers †	Bradycardia, hypotension
Calcium channel blockers	Bradycardia, hypotension, hyperglycemia
Camphor	Seizures
Caustics (pH <2 or >12)	Airway, esophageal and gastric burns
Clonidine	Lethargy, bradycardia, hypotension
Diphenoxylate and atropine (Lomotil)	CNS depression, respiratory depression
Hypoglycemics, oral (sulfonylureas and meglitinides)	Hypoglycemia, seizures
Laundry detergent packets (pods)	Airway issues, respiratory distress, altered mental status
Lindane	Seizures
Monoamine oxidase inhibitors	Hypertension followed by delayed cardiovascular collapse
Methyl salicylate	Tachypnea, metabolic acidosis, seizures
Opioids (especially methadone, buprenorphine)	CNS depression, respiratory depression
Organophosphate pesticides	Cholinergic crisis
Phenothiazines (especially chlorpromazine, thioridazine)	Seizures, dysrhythmias
Theophylline	Seizures, dysrhythmias
Tricyclic antidepressants	CNS depression, seizures, dysrhythmias, hypotension

* ”Small dose” typically implies 1 or 2 pills or 5 mL.

† Lipid-soluble β-blockers (e.g., propranolol) are more toxic than water-soluble β-blockers (e.g., atenolol).

CNS, Central nervous system.

Poison prevention education should be an integral part of all well-child visits, starting at the 6 mo visit. Counseling parents and other caregivers about potential poisoning risks, poison-proofing a child's environment, and actions in the event of an ingestion diminishes the likelihood of serious morbidity or mortality. Poison prevention education materials are available from the American Academy of Pediatrics (AAP) and regional PCCs. Through a U.S. network of PCCs, anyone at any time can contact a regional poison center by calling the toll-free number **1-800-222-1222** . Parents should be encouraged to share this number with grandparents, relatives, babysitters, and any other caregivers.

Product safety measures, poison prevention education, early recognition of exposures, and around-the-clock access to regionally based PCCs all contribute to the favorable exposure outcomes in young children. Poisoning exposures in children 6-12 yr are much less common, involving only approximately 10% of all reported pediatric exposures. A 2nd peak in pediatric exposures occurs in adolescence. Exposures in the adolescent age-group are primarily intentional (suicide or abuse or misuse of substances) and thus often result in more severe toxicity (see Chapter 140). Families should be informed and given anticipatory guidance that nonprescription and prescription medications, and even household products (e.g., inhalants), are common sources of adolescent exposures. Although adolescents (age 13-19 yr) account for only about 12% of exposures, they constituted a much larger proportion of deaths. Of the 90 poison-related pediatric deaths in 2015 reported to NPDS, 58 were adolescents (5% of all fatalities called in to poison centers). Pediatricians should be aware of the signs of drug abuse or suicidal ideation in adolescents and should aggressively intervene (see Chapter 40).

Prevention

Deaths caused by unintentional poisoning among younger children have decreased dramatically over the past 2 decades, particularly among children <5 yr old. In 1970, when the U.S. Poison Packaging Prevention Act was passed, 226 poisoning deaths of children <5 yr old occurred, compared with only 24 in 2015. Poisoning prevention demonstrates the effectiveness of passive strategies, including the use of child-resistant packaging and limited doses per container. Difficulty using child-resistant containers by adults is an important cause of poisoning in young children today. In 18.5% of households in which poisoning occurred in children <5 yr old, the child-resistant closure was replaced, and 65% of the packaging used did not work properly. Almost 20% of ingestions occur from drugs belonging to grandparents, who have difficulty using traditional child-resistant containers and often put their medications in pill organizers that are not childproof.

Even though there has been success in preventing poisoning in young children, there has been a remarkable rise in adolescent poison-related death over the past 20 years. This has mirrored the increasing rate of antidepressant prescriptions written by healthcare providers and the epidemic increase in opioid-related fatalities.

Approach to the Poisoned Patient

The initial approach to the patient with a witnessed or suspected poisoning should be no different than that in any other sick child, starting with stabilization and rapid assessment of the airway, breathing, circulation (pulse, blood pressure), and mental state, including Glasgow Coma Scale score and laryngeal reflexes (see Chapters 80 and 81). In any patient with altered mental status, a serum dextrose concentration should be obtained early, and naloxone administration should be considered. A targeted history and physical examination serves as the foundation for a thoughtful differential diagnosis, which can then be further refined through laboratory testing and other diagnostic studies.

History

Obtaining an accurate problem-oriented history is of paramount importance. *Intentional* poisonings (suicide attempts, drug abuse/misuse) are typically more severe than unintentional, exploratory ingestions. In patients without a witnessed exposure, historical features such as age of the child (toddler or adolescent), acute onset of symptoms without prodrome, multisystem organ dysfunction, or high levels of household stress should suggest a possible diagnosis of poisoning. In patients with a witnessed exposure, determining exactly what the child was exposed to and the circumstances surrounding the exposure is crucial to initiating directed therapy quickly. For household and workplace products, names (brand, generic, chemical) and specific ingredients, along with their concentrations, can often be obtained from the labels. PCC specialists can also help to identify possible ingredients and review the potential toxicities of each component. Poison center specialists can also help identify pills based on markings, shape, and color. If referred to the hospital for evaluation, parents should be instructed to bring the products, pills, and/or containers with them to assist with identifying and quantifying the exposure. If a child is found with an unknown pill, a list of all medications in the child's environment, including medications that grandparents, parents, siblings, caregivers, or other visitors might have brought into the house, must be obtained. In the case of an unknown exposure, clarifying where the child was found (e.g., garage, kitchen, laundry room, bathroom, backyard, workplace) can help to generate a list of potential toxins.

Next, it is important to clarify the *timing* of the ingestion and to obtain some estimate of how much of the substance was ingested. It is better to overestimate the amount ingested to prepare for the worst-case scenario. Counting pills or measuring the remaining volume of a liquid ingested can sometimes be useful in generating estimates. For inhalational, ocular, or dermal exposures, the concentration of the agent and the length of contact time with the material should be determined, if possible.

Symptoms

Obtaining a description of symptoms experienced after ingestion, including their timing of onset relative to the time of ingestion and their progression, can generate a list of potential toxins and help anticipate the severity of the ingestion. Coupled with physical exam findings, reported symptoms assist practitioners in identifying **toxidromes,** or recognized poisoning syndromes, suggestive of toxicity from specific substances or classes of substances (Tables 77.2 to 77.4).

Table 77.2

Selected Historical and Physical Findings in Poisoning

SIGN	TOXIN
ODOR	
Bitter almonds	Cyanide
Acetone	Isopropyl alcohol, methanol, paraldehyde, salicylates
Rotten eggs	Hydrogen sulfide, sulfur dioxide, methyl mercaptans (additive to natural gas)
Wintergreen	Methyl salicylate
Garlic	Arsenic, thallium, organophosphates, selenium
OCULAR SIGNS	
Miosis	Opioids (except propoxyphene, meperidine, and pentazocine), organophosphates and other cholinergics, clonidine, phenothiazines, sedative-hypnotics, olanzapine
Mydriasis	Anticholinergics (e.g., antihistamines, TCAs, atropine), sympathomimetics (cocaine, amphetamines, PCP), post–anoxic encephalopathy, opiate withdrawal, cathinones, MDMA
Nystagmus	Anticonvulsants, sedative-hypnotics, alcohols, PCP, ketamine, dextromethorphan
Lacrimation	Organophosphates, irritant gas or vapors
Retinal hyperemia	Methanol
CUTANEOUS SIGNS	
Diaphoresis	Cholinergics (organophosphates), sympathomimetics, withdrawal syndromes
Alopecia	Thallium, arsenic
Erythema	Boric acid, elemental mercury, cyanide, carbon monoxide, disulfiram, scombroid, anticholinergics, vancomycin
Cyanosis (unresponsive to oxygen)	Methemoglobinemia (e.g., benzocaine, dapsone, nitrites, phenazopyridine), amiodarone, silver
ORAL SIGNS	
Salivation	Organophosphates, salicylates, corrosives, ketamine, PCP, strychnine

Oral burns	Corrosives, oxalate-containing plants
Gum lines	Lead, mercury, arsenic, bismuth
GASTROINTESTINAL SIGNS	
Diarrhea	Antimicrobials, arsenic, iron, boric acid, cholinergics, colchicine, opioid withdrawal
Hematemesis	Arsenic, iron, caustics, NSAIDs, salicylates
Constipation	Lead
CARDIAC SIGNS	
Tachycardia	Sympathomimetics, anticholinergics, antidepressants, antipsychotics, methylxanthines (theophylline, caffeine), salicylates, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), withdrawal (ethanol, sedatives, clonidine, opioids), serotonin syndrome, neuroleptic malignant syndrome, MDMA, cathinones
Bradycardia	β-Blockers, calcium channel blockers, digoxin, clonidine, organophosphates, opioids, sedative-hypnotics
Hypertension	Sympathomimetics, anticholinergics, monoamine oxidase inhibitors, serotonin syndrome, neuroleptic malignant syndrome, clonidine withdrawal
Hypotension	β-Blockers, calcium channel blockers, cyclic antidepressants, iron, antipsychotics, barbiturates, clonidine, opioids, arsenic, amatoxin mushrooms, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), snake envenomation
RESPIRATORY SIGNS	
Depressed respirations	Opioids, sedative-hypnotics, alcohol, clonidine, barbiturates
Tachypnea	Salicylates, sympathomimetics, caffeine, metabolic acidosis, carbon monoxide, hydrocarbon aspiration
CENTRAL NERVOUS SYSTEM SIGNS	
Ataxia	Alcohols, anticonvulsants, sedative-hypnotics, lithium, dextromethorphan, carbon monoxide, inhalants
Coma	Opioids, sedative-hypnotics, anticonvulsants, antidepressants, antipsychotics, ethanol, anticholinergics, clonidine, GHB, alcohols, salicylates, barbiturates
Seizures	Sympathomimetics, anticholinergics, antidepressants (especially TCAs, bupropion, venlafaxine), cholinergics (organophosphates), isoniazid, camphor, lindane, salicylates, lead, nicotine, tramadol, water hemlock, withdrawal
Delirium/psychosis	Sympathomimetics, anticholinergics, LSD, PCP, hallucinogens, lithium, dextromethorphan, steroids, withdrawal, MDMA, cathinones
Peripheral neuropathy	Lead, arsenic, mercury, organophosphates, nicotine

GHB, γ-Hydroxybutyrate; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine (Ecstasy); NSAIDs, nonsteroidal antiinflammatory drugs; PCP, phencyclidine; TCAs, tricyclic antidepressants.

Table 77.3

Recognizable Poison Syndromes (“Toxidromes”)

TOXIDROME	**SIGNS**						**POSSI TOXIN**
	Vital Signs	**Mental Status**	**Pupils**	**Skin**	**Bowel Sounds**	**Other**	
Sympathomimetic	Hypertension, tachycardia, hyperthermia	Agitation, psychosis, delirium, violence	Dilated	Diaphoretic	Normal to increased		Amphe cocaine bath sal (cathinc

							ADHD medica
Anticholinergic	Hypertension, tachycardia, hyperthermia	Agitated, delirium, coma, seizures	Dilated	Dry, hot	Diminished	Ileus urinary retention	Antihis TCAs, jimson
Cholinergic	Bradycardia, BP, and temp typically normal	Confusion, coma, fasciculations	Small	Diaphoretic	Hyperactive	Diarrhea, urination, bronchorrhea, bronchospasm, emesis, lacrimation, salivation	Organo (insecti nerve a carbam (physos neostig pyridos Alzhei medica myasth treatme
Opioids	Respiratory depression bradycardia, hypotension, hypothermia	Depression, coma, euphoria	Pinpoint	Normal	Normal to decreased		Methad bupren morphi oxycod heroin,
Sedative-hypnotics	Respiratory depression, HR normal to decreased, BP normal to decreased, temp normal to decreased	Somnolence, coma	Small or normal	Normal	Normal		Barbitu benzodi ethanol
Serotonin syndrome (similar findings with neuroleptic malignant syndrome)	Hyperthermia, tachycardia, hypertension or hypotension (autonomic instability)	Agitation, confusion, coma	Dilated	Diaphoretic	Increased	Neuromuscular hyperexcitability: clonus, hyperreflexia (lower > upper extremities)	SSRIs, MAOIs tramad meperi dextron
Salicylates	Tachypnea, hyperpnea, tachycardia, hyperthermia	Agitation, confusion, coma	Normal	Diaphoretic	Normal	Nausea, vomiting, tinnitus, ABGs with primary respiratory alkalosis and primary metabolic acidosis; tinnitus or difficulty hearing	Aspirin aspirin- product salicyla
Withdrawal (sedative-hypnotic)	Tachycardia, tachypnea, hyperthermia	Agitation, tremor, seizure, hallucinosis, delirium tremens	Dilated	Diaphoretic	Increased		Lack of ethanol benzodi barbitu GHB, excessi flumaze

Withdrawal (opioid)	Tachycardia	Restlessness, anxiety	Dilated	diaphoretic	Hyperactive	Nausea, vomiting, diarrhea	Lack of opioids excessi naloxor

ABGs, Arterial blood gases; ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; GHB, γ-hydroxybutyrate; HR, heart rate; MAOIs, monoamine oxidase inhibitors; PCP, phencyclidine; SSRIs, selective serotonin reuptake inhibitors; temp, temperature; TCAs, tricyclic antidepressants.

Table 77.4

Mini-Toxidromes

TOXIDROME	SYMPTOMS AND SIGNS	EXAMPLES
α_1 -Adrenergic receptor antagonists	CNS depression, tachycardia, miosis	Chlorpromazine, quetiapine, clozapine, olanzapine, risperidone
α_2 -Adrenergic receptor agonist	CNS depression, bradycardia, hypertension (early), hypotension (late), miosis	Clonidine, oxymetazoline, tetrahydrozoline, tizanidine, dexmedetomidine
Clonus/myoclonus	CNS depression, myoclonic jerks, clonus, hyperreflexia	Carisoprodol, lithium, serotonergic agents, bismuth, organic lead, organic mercury, serotonin or neuroleptic malignant syndrome
Sodium channel blockers	CNS toxicity, wide QRS	Cyclic antidepressants and structurally related agents, propoxyphene, quinidine/quinine, amantadine, antihistamines, bupropion, cocaine
Potassium channel blockers	CNS toxicity, long QT interval	Antipsychotics, methadone, phenothiazines
Cathinones, synthetic cannabinoids	Hyperthermia, tachycardia, delirium, agitation, mydriases	See Chapter 140 .

CNS, Central nervous system.

From Ruha AM, Levine M: Central nervous system toxicity. *Emerg Med Clin North Am* 32(1):205–221, 2014, p 208.

Past Medical and Developmental History

Underlying diseases can make a child more susceptible to the effects of a toxin. Concurrent drug therapy can also increase toxicity because certain drugs may interact with the toxin. A history of psychiatric illness can make patients more prone to substance abuse, misuse, intentional ingestions, and polypharmacy complications. Pregnancy is a common precipitating factor in adolescent suicide attempts and can influence both evaluation of the patient and subsequent treatment. A developmental history is important to ensure that the exposure history provided is appropriate for the child's developmental stage (e.g., report of

6 mo old picking up a large container of laundry detergent and drinking it should indicate urgent need for treatment, or indicate a severe condition, or “red flag”).

Social History

Understanding the child's social environment helps to identify potential sources of exposures (caregivers, visitors, grandparents, recent parties or social gatherings) and social circumstances (new baby, parent's illness, financial stress) that might have contributed to the ingestion (suicide or unintentional). Unfortunately, some poisonings occur in the setting of serious neglect or intentional abuse.

Physical Examination

A targeted physical examination is important to identifying the potential toxin and assessing the severity of the exposure. Initial efforts should be directed toward assessing and stabilizing the airway, breathing, circulation, and mental status. Once the airway is secure and the patient is stable from a cardiopulmonary standpoint, a more extensive physical exam can help to identify characteristic findings of specific toxins or classes of toxins.

In the poisoned patient, key features of the physical exam are vital signs, mental status, pupils (size, reactivity), nystagmus, skin, bowel sounds, and muscle tone. These findings might suggest a toxidrome, which can then guide the differential diagnosis and management.

Laboratory Evaluation

A basic chemistry panel (electrolytes, renal function, glucose) is necessary for all poisoned or potentially poisoned patients. Any patient with acidosis (low serum bicarbonate level on serum chemistry panel) must have an anion gap calculated because of the more specific differential diagnoses associated with an elevated **anion gap metabolic acidosis** (Table 77.5). Patients with a known overdose of acetaminophen should have liver transaminases (ALT, AST) assessed, as well as an international normalized ratio (INR). A serum creatinine kinase level is indicated on any patient with a prolonged “down time” to evaluate for **rhabdomyolysis** . Serum osmolality is only helpful as a surrogate marker for a toxic alcohol exposure if a serum concentration of the alcohol cannot be obtained in a reasonable time frame. A urine pregnancy test is mandatory for all postpubertal female patients. Based on the clinical presentation and the presumed poison, additional lab tests may also be helpful. Acetaminophen is a widely available medication and a commonly detected co-ingestant with the potential for severe toxicity. There is an effective antidote to acetaminophen poisoning that is time dependent. Given that patients might initially be asymptomatic and might not report or be aware of acetaminophen ingestion, an acetaminophen level should be checked in all patients who present after an intentional exposure or ingestion.

Table 77.5

Laboratory Clues in Toxicologic Diagnosis

Anion Gap Metabolic Acidosis (Mnemonic = Mudpiles Cat)

M ethanol, metformin
U remia
D iabetic ketoacidosis
P ropylene glycol
I soniazid, iron, massive ibuprofen
L actic acidosis
E thylene glycol
S alicylates
C ellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide)
A lcoholic ketoacidosis
T ylenol (clinical significance depends upon presence or absence of liver injury)

Elevated Osmolar Gap

Alcohols: ethanol, isopropyl, methanol, ethylene glycol

Hypoglycemia (Mnemonic = Hobbies)

H ypoglycemics, oral: sulfonylureas, meglitinides
O ther: quinine, unripe ackee fruit
B eta **B** lockers

I nsulin
E thanol
S alicylates (late)

Hyperglycemia

Salicylates (early)
Calcium channel blockers
Caffeine

Hypocalcemia

Ethylene glycol
Fluoride

Rhabdomyolysis

Neuroleptic malignant syndrome, serotonin syndrome
Statins
Mushrooms (*Tricholoma equestre*)
Any toxin causing prolonged immobilization (e.g., opioids, antipsychotics) or excessive muscle activity or seizures (e.g., sympathomimetics)

Radiopaque Substance on Kub (Mnemonic = Chipped)

C hloral hydrate, calcium carbonate
H eavy metals (lead, zinc, barium, arsenic, lithium, bismuth)
I ron
P henothiazines
P lay-Doh, potassium chloride
E nteric-coated pills
D ental amalgam, drug packets

KUB, Kidney-ureter-bladder radiograph.

For select intoxications (e.g., salicylates, some anticonvulsants, acetaminophen, iron, digoxin, methanol, ethanol, lithium, ethylene glycol, theophylline, CO, lead), quantitative **blood concentrations** are integral to confirming the diagnosis and formulating a treatment plan. However, for most exposures, quantitative measurement is not readily available and is not likely to alter management. All intoxicant levels must be interpreted in conjunction with the history. For example, a methanol level of 20 mg/dL 1 hr after ingestion may be nontoxic, whereas a similar level 24 hr after ingestion implies a significant poisoning. In general, patients with multiple or chronic exposures to a drug or other chemical will be more symptomatic at lower drug levels than those with a single exposure.

Both the rapid urine drug-of-abuse screens and the more comprehensive drug screens vary widely in their ability to detect toxins and generally add little information to the clinical assessment. This is particularly true if the agent is known and the patient's symptoms are consistent with that agent. If a drug screen is ordered, it is important to know that the components screened for, and the lower limits of detection, vary from laboratory to laboratory. In addition, the interpretation of most drug screens is hampered by many false-positive and false-negative results. Many opiate toxicology screens poorly detect hydrocodone, and do not detect the fully synthetic opioids at all (e.g., methadone, buprenorphine, fentanyl). Several common benzodiazepines may not be detected, as may not synthetic cannabinoids or “bath salts.” The amphetamine screen, on the other hand, is typically overly sensitive and often is triggered by prescription amphetamines and some over-the-counter cold preparations. As such, the urine drug-of-abuse screen is typically of limited utility for medical clearance, but may serve a useful function for psychiatrists in their evaluation of the adolescent patient. Besides its psychiatric usefulness, urine drug-of-abuse screens are potentially helpful in patients with altered mental status of unknown etiology, persistent unexplained tachycardia, and acute myocardial ischemia or stroke at a young age. These screens can also be useful in the assessment of a neglected or abused child. Consultation with a medical toxicologist can be helpful in interpreting drug screens and directing which specific drug levels or other lab analyses might aid in patient management.

In the case of a neglected or allegedly abused child, a positive toxicology screen can add substantial weight to a claim of abuse or neglect. In these cases and any case with medicolegal implications, any positive screen *mus* t be confirmed with gas chromatography/mass spectroscopy, which is considered the gold standard measurement for legal purposes.

Additional Diagnostic Testing

An electrocardiogram (ECG) is a quick and noninvasive bedside test that can yield important clues to diagnosis and prognosis. Particular attention should be paid to the ECG intervals (Table 77.6). A widened QRS interval, putting the patient at risk for monomorphic ventricular tachycardia, suggests blockade of fast sodium channels. A widened QTc interval suggests effects at the potassium rectifier channels and portends a risk of torsades de pointes (polymorphic ventricular tachycardia).

Table 77.6

Electrocardiographic Findings in Poisoning

Pr Interval Prolongation

Digoxin
Lithium

QRS Prolongation

Tricyclic antidepressants
Diphenhydramine
Carbamazepine
Cardiac glycosides
Chloroquine, hydroxychloroquine
Cocaine
Lamotrigine
Quinidine, quinine, procainamide, disopyramide
Phenothiazines
Propoxyphene
Propranolol
Bupropion, venlafaxine (rare)

QTc Prolongation*

Amiodarone
Antipsychotics (typical and atypical)
Arsenic
Cisapride
Citalopram
Clarithromycin, erythromycin
Disopyramide, dofetilide, ibutilide
Fluconazole, ketoconazole, itraconazole
Methadone
Pentamidine
Phenothiazines
Sotalol

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* This is a select list of important toxins, other medications are also associated with QTc prolongation.

Chest radiography may reveal signs of pneumonitis (e.g., hydrocarbon aspiration), noncardiogenic pulmonary edema (e.g., salicylate toxicity), or a foreign body. Abdominal radiography is most helpful in screening for the presence of lead paint chips or other foreign bodies. It may detect a *bezoar* (concretion), demonstrate radiopaque tablets, or reveal drug packets in a “body packer.” Further diagnostic testing is based on the differential diagnosis and pattern of presentation.

Principles of Management

The principles of management of the poisoned patient are supportive care, decontamination, directed therapy (antidotes, ILE), and enhanced elimination. Few patients meet criteria for all these interventions, although clinicians should consider each option in every poisoned patient so as not to miss a potentially lifesaving intervention. Antidotes are available for relatively few poisons (Tables 77.7 and 77.8), thus emphasizing the importance of meticulous supportive care and close clinical monitoring.

Table 77.7

Common Antidotes for Poisoning

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Acetaminophen	*N* -Acetylcysteine (Mucomyst)	140 mg/kg loading, followed by 70 mg/kg q4h	PO	Vomiting (patient-tailored regimens are the norm)
	N -Acetylcysteine (Acetadote)	150 mg/kg over 1 hr, followed by 50 mg/kg over 4 hr, followed by 100 mg/kg over 16 hr	IV	Anaphylactoid reactions (most commonly seen with loading dose) (Higher doses of the infusion are often recommended depending on acetaminophen level or degree of injury)
Anticholinergics	Physostigmine	0.02 mg/kg over 5 min; may repeat q5-10 min to 2 mg max	IV/IM	Bradycardia, seizures, bronchospasm *Note:* Do not use if conduction delays on ECG.
Benzodiazepines	Flumazenil	0.2 mg over 30 sec; if response is inadequate, repeat q1min to 1 mg max	IV	Agitation, seizures from precipitated withdrawal (doses over 1 mg) **Do not use for unknown or polypharmacy ingestions.**
β-Blockers	Glucagon	0.15 mg/kg bolus followed by infusion of 0.05-0.15 mg/kg/hr	IV	Vomiting, relative lack of efficacy
Calcium channel blockers	Insulin	1 unit/kg bolus followed by infusion of 0.5-1 unit/kg/hr	IV	Hypoglycemia Follow serum potassium and glucose closely.
	Calcium salts	Dose depends on the specific calcium salt	IV	
Carbon monoxide	Oxygen	100% FIO_2 by non-rebreather mask (or ET if intubated)	Inhalation	Some patients may benefit from hyperbaric oxygen (see text).
Cyanide	Hydroxocobalamin (Cyanokit)	70 mg/kg (adults: 5 g) given over 15 min	IV	Flushing/erythema, nausea, rash, chromaturia, hypertension, headache
Digitalis	Digoxin-specific Fab antibodies (Digibind, DigiFab)	1 vial binds 0.6 mg of digitalis glycoside; #vials = digitalis level × weight in kg/100	IV	Allergic reactions (rare), return of condition being treated with digitalis glycoside
Ethylene glycol, methanol	Fomepizole	15 mg/kg load; 10 mg/kg q12h × 4 doses; 15 mg/kg q12h until ethylene glycol level is <20 mg/dL	IV	Infuse slowly over 30 min. If fomepizole is not available, can treat with oral ethanol (80 proof)
Iron	Deferoxamine	Infusion of 5-15 mg/kg/hr (max: 6 g/24 hr)	IV	Hypotension (minimized by avoiding rapid infusion rates)
Isoniazid (INH)	Pyridoxine	Empirical dosing: 70 mg/kg (max	IV	May also be used for *Gyromitra* mushroom ingestions

		dose = 5 g) If ingested dose is known: 1 g per gram of INH		
Lead and other heavy metals (e.g., arsenic, inorganic mercury)	BAL (dimercaprol)	3-5 mg/kg/dose q4h, for the 1st day; subsequent dosing depends on the toxin	Deep IM	Local injection site pain and sterile abscess, vomiting, fever, salivation, nephrotoxicity *Caution:* prepared in peanut oil; contraindicated in patients with peanut allergy
	Calcium disodium EDTA	35-50 mg/kg/day × 5 days; may be given as a continuous infusion or 2 divided doses/day	IV	Vomiting, fever, hypertension, arthralgias, allergic reactions, local inflammation, nephrotoxicity (maintain adequate hydration; follow UA and renal function)
	Dimercaptosuccinic acid (succimer, DMSA, Chemet)	10 mg/kg/dose q8h × 5 days, then 10 mg/kg q12h × 14 days	PO	Vomiting, hepatic transaminase elevation, rash
Methemoglobinemia	Methylene blue, 1% solution	0.1-0.2 mL/kg (1-2 mg/kg) over 5-10 min; may be repeated q30-60 min	IV	Vomiting, headache, dizziness, blue discoloration of urine
Opioids	Naloxone	1 mg if patient not likely to be addicted. 0.04-0.4 mg if possibly addicted; repeated as needed; may need continuous infusion	IV, intranasal, IO, IM, nebulized	Acute withdrawal symptoms if given to addicted patients May also be useful for clonidine ingestions (typically at higher doses)
Organophosphates	Atropine	0.05-0.1 mg/kg repeated q5-10 min as needed	IV/ET	Tachycardia, dry mouth, blurred vision, urinary retention
	Pralidoxime (2-PAM)	25-50 mg/kg over 5-10 min (max: 200 mg/min); can be repeated after 1-2 hr, then q10-12h as needed	IV/IM	Nausea, dizziness, headache, tachycardia, muscle rigidity, bronchospasm (rapid administration)
Salicylates	Sodium bicarbonate	Bolus 1-2 mEq/kg followed by continuous infusion	IV	Follow potassium closely and replace as necessary. Goal urine pH: 7.5-8.0
Sulfonylureas	Octreotide and dextrose	1-2 µg/kg/dose (adults 50-100 µg) q6-8h	IV/SC	
Tricyclic antidepressants	Sodium bicarbonate	Bolus 1-2 mEq/kg; repeated bolus dosing as needed to keep QRS <110 msec	IV	Indications: QRS widening (≥110 msec), hemodynamic instability; follow potassium.

BAL, British antilewisite; DMSA, dimercaptosuccinic acid; ECG, electrocardiogram; FIO_2, fraction of inspired oxygen; EDTA, ethylenediaminetetraacetic acid; ET, endotracheal tube; IO, intraosseous; max, maximum; UA, urinalysis.

Table 77.8

Other Antidotes

ANTIDOTES	TOXIN OR POISON
Latrodectus antivenin	Black widow spider
Botulinum antitoxin	Botulinum toxin
Diphenhydramine and/or benztropine	Dystonic reactions
Calcium salts	Fluoride, calcium channel blockers
Protamine	Heparin
Folinic acid	Methotrexate, trimethoprim, pyrimethamine
Crotalidae-specific Fab antibodies	Rattlesnake envenomation
Sodium bicarbonate	Sodium channel blockade (tricyclic antidepressants, type 1 antiarrhythmics)

Poison control center personnel are specifically trained to provide expertise in the management of poisoning exposures. Parents should be instructed to call the poison control center (**1-800-222-1222**) for any concerning exposure. PCC specialists can assist parents in assessing the potential toxicity and severity of the exposure. They can further determine which children can be safely monitored at home and which children should be referred to the emergency department for further evaluation and care. Although up to one third of calls to PCCs involve hospitalized patients, and 90% of all calls for exposures in children <6 yr old are managed at home. The AAPCC has generated consensus statements for out-of-hospital management of common ingestions (e.g., acetaminophen, iron, calcium channel blockers) that serve to guide poison center recommendations.

Supportive Care

Careful attention is paid first to the “ABCs” of airway, breathing, and circulation; there should be a low threshold to aggressively manage the airway of a poisoned patient because of the patient's propensity to quickly become comatose. In fact, endotracheal intubation is often the only significant intervention needed in many poisoned patients. An important caveat is the tachypneic patient with a clear lung examination and normal oxygen saturation. This should alert the clinician to the likelihood that the patient is compensating for an acidemia. Paralyzing such a patient and underventilating might prove fatal. If intubation is absolutely necessary for airway protection or a tiring patient, a good rule of thumb is to match the ventilatory settings to the patient's preintubation minute ventilation.

Hypotensive patients often are not hypovolemic but are poisoned, and aggressive fluid resuscitation may lead to fluid overload. If hypotension persists after 1 or 2 standard boluses of crystalloid, infusion of a direct-acting vasopressor, such as norepinephrine or epinephrine, is preferred. Dysrhythmias are managed in the standard manner, except for those caused by agents that block fast sodium channels of the heart, for which boluses of sodium bicarbonate are given.

Seizures should primarily be managed with agents that potentiate the γ-aminobutyric acid (GABA) complex, such as benzodiazepines or barbiturates. The goal of supportive therapy is to support the patient's vital functions until the patient can eliminate the toxin. Patients with an elevated creatine phosphokinase (CPK) should be aggressively hydrated with crystalloid, with a goal urine output of 1-2 mL/kg/hr and close monitoring of CPK trend.

Decontamination

The majority of poisonings in children are from ingestion, although exposures can also occur by inhalational, dermal, and ocular routes. The goal of decontamination is to minimize absorption of the toxic substance. The specific method employed depends on the properties of the toxin itself and the route of exposure. Regardless of the decontamination method used, the efficacy of the intervention decreases with increasing time since exposure. *Decontamination should not be routinely employed for every poisoned patient.* Instead, careful decisions regarding the utility of decontamination should be made for each patient and should include consideration of the toxicity and pharmacologic properties of the exposure, route of the exposure, time since the exposure, and risks vs benefits of the decontamination method.

Dermal and ocular decontamination begins with removal of any contaminated clothing and particulate matter, followed by flushing of the affected area with tepid water or normal saline (NS). Treating clinicians should wear proper protective gear when performing irrigation. Flushing for a minimum of 10-20 min is recommended for most exposures, although some chemicals (e.g., alkaline corrosives) require much longer periods of flushing. Dermal decontamination, especially after exposure to adherent or lipophilic (e.g., organophosphates) agents, should include thorough cleansing with soap and water. Water should *not* be used for decontamination after exposure to highly reactive agents, such as elemental sodium, phosphorus, calcium oxide, and titanium tetrachloride. After an inhalational exposure, decontamination involves moving the patient to fresh air and administering supplemental oxygen if indicated.

Gastrointestinal (GI) decontamination strategies are most likely to be effective in the 1 or 2 hours after an acute ingestion . GI absorption may be delayed after ingestion of agents that slow GI motility (anticholinergic medications, opioids), massive amounts of pills, sustained-release (SR) preparations, and agents that can form pharmacologic bezoars (e.g., enteric-coated salicylates). GI decontamination more than 2 hr after ingestion may be considered in patients who ingest toxic substances with these properties. However, even rapid institution of GI decontamination with activated charcoal will, at best, bind only approximately 30% of the ingested substance. GI decontamination should never supplant excellent supportive care and should not be employed in an unstable or persistently vomiting patient. Described methods of GI decontamination include induced emesis with ipecac, gastric lavage, cathartics, activated charcoal, and whole-bowel irrigation (WBI). *Of these, only activated charcoal and WBI are of potential benefit.*

Syrup of Ipecac

Syrup of ipecac contains 2 emetic alkaloids that work in both the central nervous system (CNS) and locally in the GI tract to produce vomiting. Many studies have failed to document a significant clinical impact from the use of ipecac and have documented multiple adverse events from its use. The AAP, the American Academy of Clinical Toxicology (AACT), and the AAPCC have all published statements in favor of *abandoning the use of ipecac*.

Gastric Lavage

Gastric lavage involves placing a large tube orally into the stomach to aspirate contents, followed by flushing with aliquots of fluid, usually water or NS. Although gastric lavage was used routinely for many years, objective data do not document or support clinically relevant efficacy. This is particularly true in children, in whom only small-bore tubes can be used. Lavage is time-consuming and painful and can induce bradycardia through a vagal response to tube placement. It can delay administration of more definitive treatment (activated charcoal) and under the best circumstances, only removes a fraction of gastric contents. *Thus, in most clinical scenarios, the use of gastric lavage is no longer* *recommended.*

Single-Dose Activated Charcoal

Activated charcoal is a potentially useful method of GI decontamination. Charcoal is "activated" by heating to extreme temperatures, creating an extensive network of pores that provides a very large adsorptive surface area that many (but not all) toxins will bind to, preventing absorption from the GI tract. Charged molecules (i.e., heavy metals, lithium, iron) and liquids do not bind well to activated charcoal (Table 77.9). *Charcoal is most likely to be effective when given within 1 hr of ingestion.* Administration should also be avoided after ingestion of a caustic substance, as it can impede subsequent endoscopic evaluation. A repeat dose of activated charcoal may be warranted in the cases of ingestion of an extended-release product or, more frequently, with a significant salicylate poisoning as a result of its delayed and erratic absorption pattern.

Table 77.9

Substances Poorly Adsorbed by Activated Charcoal

- Alcohols
- Caustics: alkalis and acids
- Cyanide
- Heavy metals (e.g., lead)
- Hydrocarbons
- Iron
- Lithium

The dose of activated charcoal, with or without sorbitol, is 1 g/kg in children or 50-100 g in adolescents and adults. Before administering charcoal, one *must* ensure that the patient's airway is intact or protected and that the patient has a benign abdominal examination. In the awake, uncooperative adolescent or child who refuses to drink the activated charcoal, there is little utility and potential morbidity associated with forcing activated charcoal down a nasogastric (NG) tube, and such practice should be avoided. In young children, practitioners can attempt to improve palatability by adding flavorings (chocolate or cherry syrup) or giving the mixture over ice cream. Approximately 20% of children vomit after receiving a dose of charcoal, emphasizing the importance of an intact airway and avoiding administration of charcoal after ingestion of substances that are particularly toxic when aspirated (e.g., hydrocarbons). If charcoal is given through a gastric tube in an intubated patient, placement of the tube should be carefully confirmed before activated charcoal is given. Instillation of charcoal directly into the lungs can have disastrous effects. Constipation is another common side effect of activated charcoal, and in rare cases, bowel perforation has been reported.

Cathartics (sorbitol, magnesium sulfate, magnesium citrate) have been used in conjunction with activated charcoal to prevent constipation and accelerate evacuation of the charcoal-toxin complex. There are no data demonstrating their value and numerous reports of adverse effects from cathartics, such as dehydration and electrolyte imbalance.

Whole-Bowel Irrigation

Whole-bowel irrigation (WBI) involves instilling large volumes (35 mL/kg/hr in children or 1-2 L/hr in adolescents) of a polyethylene glycol electrolyte solution (e.g., GoLYTELY) to “wash out” the entire GI tract. This technique may have some success for the ingestion of SR preparations, substances not well adsorbed by charcoal (e.g., lithium, iron), transdermal patches, foreign bodies, and drug packets. In children, WBI is most frequently administered to decontaminate the gut of a child whose abdominal radiograph demonstrates multiple lead paint chips. Careful attention should be paid to assessment of the airway and abdominal exam before initiating WBI. WBI should never be given to a patient with signs of obstruction or ileus or with a compromised airway. Given the rate of administration and volume needed to flush the system, WBI is typically administered by NG tube. WBI is continued until the rectal effluent is clear. If the WBI is for a child with ingested paint chips, the end-point will be clearing of the chips from the bowel based on repeat radiographs. Complications of WBI include vomiting, abdominal pain, and abdominal distention. Bezoar formation might respond to WBI but may also require endoscopy or surgery.

Directed Therapy

Antidotal Therapy

Antidotes are available for relatively few toxins (Tables 77.7 and 77.8), but early and appropriate use of an antidote is a key element in managing the poisoned patient.

Intralipid Emulsion Therapy

Intralipid emulsion (ILE) therapy is a potentially lifesaving intervention. ILE therapy sequesters fat-soluble drugs, decreasing their impact at target organs. It also enhances cardiac function by supplying an alternative energy source to a depressed myocardium and acting on calcium channels in the heart, increasing myocardial calcium and thus cardiac function. Intralipid is most effective as a reversal agent for toxicity from inadvertent intravenous (IV) injection of bupivacaine. Using the same 20% Intralipid used for total parenteral nutrition (TPN), a bolus dose of 1.5 mL/kg is given over 3 min, followed by an infusion of 0.25 mL/kg/min until recovery or until a total of 10 mL/kg has been infused. *Lipophilic drugs,* those in which the logarithm of the coefficient describing the partition between 2 solvents (hydrophobic phase and hydrophilic phase) is >2, have the most potential to be bound by ILE. These include, but are not limited to, calcium channel blockers (verapamil, diltiazem), bupropion, and tricyclic antidepressants.

Enhanced Elimination

Enhancing elimination results in increased clearance of a poison that has already been absorbed. It is only useful for a few toxins and in these cases is a potentially lifesaving intervention. Methods of enhanced elimination include urinary alkalinization, hemodialysis, and multidose activated charcoal.

Urinary Alkalinization

Urinary alkalinization enhances the elimination of drugs that are weak acids by forming charged molecules, which then become trapped in the renal tubules. Charged molecules, being polar and hydrophilic, do not easily cross cellular membranes, thus they remain in the renal tubules and are excreted. Urinary alkalinization is accomplished by a continuous infusion of sodium bicarbonate–containing IV fluids, with a goal urine pH of 7.5-8. Alkalinization of the urine is most useful in managing salicylate and methotrexate toxicity. Complications of urinary alkalinization include electrolyte derangements (e.g., hypokalemia, hypocalcemia), fluid overload, and excessive serum alkalinization. Serum pH should be closely monitored and not exceed a pH >7.55. Patients typically unable to tolerate the volumes required for alkalinization are those with heart failure, kidney failure, pulmonary edema, or cerebral edema.

Hemodialysis

Few drugs or toxins are removed by dialysis in amounts sufficient to justify the risks and difficulty of dialysis. Toxins amenable to dialysis have the following properties: low volume of distribution (<1 L/kg) with a high degree of water solubility, low molecular weight, and low degree of protein binding. Hemodialysis may be useful for toxicity from methanol, ethylene glycol, salicylates, theophylline, bromide, lithium, and valproic acid. Hemodialysis is also used to correct severe electrolyte disturbances and acid-base derangements resulting from the ingestion (e.g., severe metformin-associated lactic acidosis).

Multidose Activated Charcoal

Whereas single-dose activated charcoal is used as a method of decontamination, multidose activated charcoal (**MDAC**) can help to enhance the elimination of certain toxins. MDAC is typically given as 0.5 g/kg every 4-6 hr (for 4 doses). MDAC enhances elimination by 2 proposed mechanisms: interruption of enterohepatic recirculation and “GI dialysis.” The concept of GI dialysis involves using the intestinal mucosa as a dialysis membrane and pulling toxins from the bloodstream back into the intraluminal space, where they are adsorbed to the charcoal. The AACT/European Association of Poisons Centres and Clinical Toxicologists position statement recommends MDAC in managing significant ingestions of carbamazepine, dapsone, phenobarbital, quinine, and theophylline. As with single-dose activated charcoal, contraindications to use of MDAC include an unprotected airway and a concerning abdominal examination (e.g., ileus, distention, peritoneal signs). Thus the airway and abdominal exam *should be assessed before each dose.* A cathartic (e.g., sorbitol) may be given with the 1st dose, but it should not be used with subsequent doses because of the risk of dehydration and electrolyte derangements. Although MDAC reduces the serum level of an intoxicant quicker than without MDAC, it has not been shown to have a significant impact on outcome.

Select Compounds in Pediatric Poisoning

See other chapters for herbal medicines (Chapter 78), drugs of abuse (Chapter 140), and environmental health hazards (Chapters 735-741).

Pharmaceuticals

Analgesics

Acetaminophen.

Acetaminophen (APAP) is the most widely used analgesic and antipyretic in pediatrics, available in multiple formulations, strengths, and combinations. Consequently, APAP is commonly available in the home, where it can be unintentionally ingested by young children, taken in an intentional overdose by adolescents and adults, or inappropriately dosed in all ages. In the United States, APAP toxicity remains the most common cause of acute liver failure and is the leading cause of intentional poisoning death.

Pathophysiology.

APAP toxicity results from the formation of a highly reactive intermediate metabolite, *N* -acetyl-*p* -benzoquinone imine (NAPQI). In therapeutic use, only a small percentage of a dose (approximately 5%) is metabolized by the hepatic cytochrome P450 enzyme CYP2E1 to NAPQI, which is then immediately joined with glutathione to form a nontoxic mercapturic acid conjugate. In overdose, glutathione stores are overwhelmed, and free NAPQI is able to combine with hepatic macromolecules to produce hepatocellular necrosis. The single acute toxic dose of APAP is generally considered to be >200 mg/kg in children and >7.5-10 g in adolescents and adults. Repeated administration of APAP at supratherapeutic doses (>90 mg/kg/day for consecutive days) can lead to hepatic injury or failure in some children, especially in the setting of fever, dehydration, poor nutrition, and other conditions that serve to reduce glutathione stores.

Any child with a history of acute ingestion of >200 mg/kg (unusual in children <6 yr) or with an acute intentional ingestion of any amount should be referred to a healthcare facility for clinical assessment and measurement of a serum APAP level.

Clinical and Laboratory Manifestations.

Classically, 4 general stages of APAP toxicity have been described (Table 77.10). The initial signs are nonspecific (i.e., nausea and vomiting) and may not be present. Thus the diagnosis of APAP toxicity cannot be based on clinical symptoms alone, but instead requires consideration of the combination of the patient's history, symptoms, and laboratory findings.

Table 77.10

Classic Stages in Clinical Course of Acetaminophen Toxicity

STAGE	TIME AFTER INGESTION	CHARACTERISTICS
I	0.5-24 hr	Anorexia, vomiting, malaise Lab tests typically normal, except for acetaminophen level
II	24-48 hr	Resolution of earlier symptoms; right upper quadrant abdominal pain and tenderness; elevated hepatic transaminases (aspartate > alanine), INR
III	3-5 days	Peak transaminase elevations; development of liver failure, multi organ-system failure, death *or* recovery begins
IV	4 days to 2 wk	Resolution of liver function abnormalities Clinical recovery precedes histologic recovery

If a toxic ingestion is suspected, a serum APAP level should be measured 4 hr after the reported time of ingestion. For patients who present to medical care more than 4 hr after ingestion, a stat APAP level should be obtained. *APAP levels obtained <4 hr after ingestion, unless "nondetectable," are difficult to interpret and cannot be used to estimate the potential for toxicity.* Other important baseline lab tests include hepatic transaminases, renal function tests, and coagulation parameters.

Treatment.

When considering the treatment of a patient poisoned or potentially poisoned with APAP, and after assessment of the ABCs, it is helpful to place the patient into one of the following four categories.

1 Prophylactic.

By definition, these patients have a normal aspartate transaminase (AST). If the APAP level is known and the ingestion is within 24 hr of the level being drawn, treatment decisions are based on where the level falls on the Rumack-Matthew nomogram (Fig. 77.1). Any patient with a serum APAP level in the possible or probable hepatotoxicity range per the nomogram should be treated with *N* -acetylcysteine (NAC). This nomogram is only intended for use in patients who present within 24 hr of a single *acute* APAP ingestion with a known time of ingestion. If treatment is recommended, they should receive NAC as either oral

Mucomyst or IV Acetadote for 24 or 21 hr, respectively. Repeat AST and APAP concentration drawn toward the end of that interval should be obtained. If the AST remains normal and the APAP becomes nondetectable, treatment may be discontinued. If the AST becomes elevated, the patient moves into the next category of treatment (injury). If APAP is still present, treatment should be continued until the level is nondetectable. In the case of a patient with a documented APAP level, normal AST, and an unknown time of ingestion, treatment should ensue until the level is nondetectable, with normal transaminases.

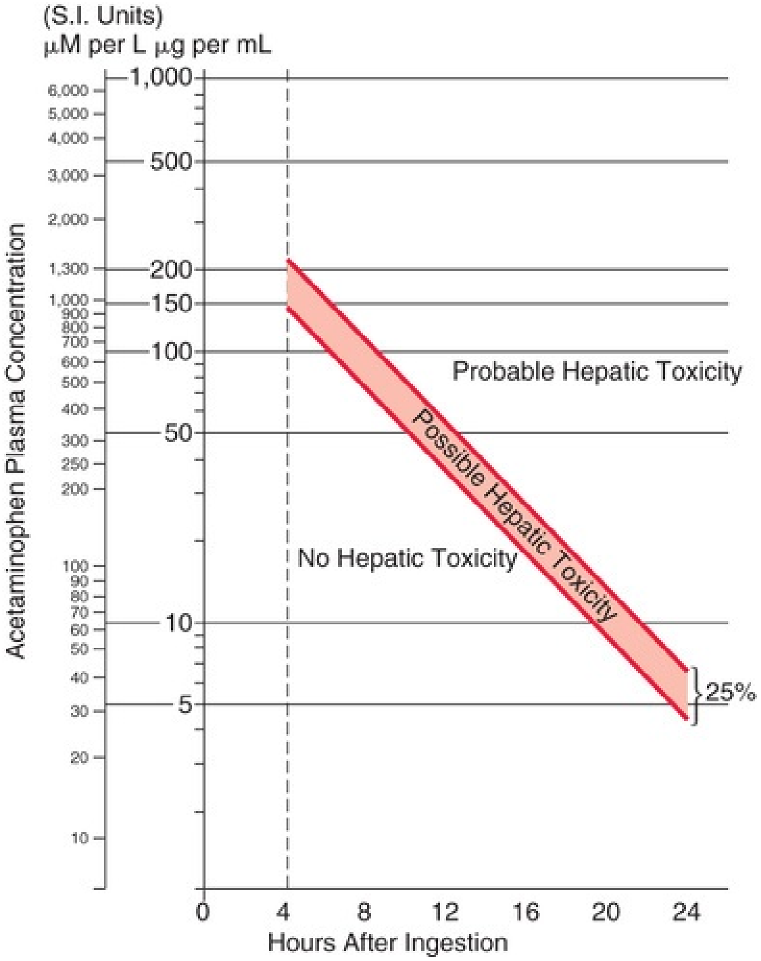

FIG. 77.1 Rumack-Matthew nomogram for acetaminophen poisoning, a semilogarithmic plot of plasma acetaminophen concentrations vs time. ***Cautions for the use of this chart:*** The time coordinates refer to time after ingestion; serum concentrations obtained before 4 hr are not interpretable; and the graph should be used only in relation to a single acute ingestion with a known time of ingestion. This nomogram is not useful for chronic exposures or unknown time of ingestion and should be used with caution in the setting of co-ingestants that that slow gastrointestinal motility. The ***lower solid line*** is typically used in the United States to

define toxicity and direct treatment, whereas the *upper line* is generally used in Europe. (From Rumack BH, Hess AJ, editors: *Poisindex* , Denver, 1995, Micromedix. Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity, *Pediatrics* 55:871–876, 1975.)

The importance of instituting therapy with either IV or oral NAC *no later than 8 hr from the time of ingestion* cannot be overemphasized. No patient, regardless of the size of the ingestion, who receives NAC within 8 hr of overdose should die from liver failure. The longer from the 8 hr mark the initiation of therapy is delayed, the greater the risk of acute liver failure. Any patient presenting close to or beyond the 8 hr mark after an APAP overdose should be empirically started on NAC pending laboratory results.

2 Hepatic Injury.

These patients are exhibiting evidence of hepatocellular necrosis, manifested first as elevated liver transaminases (usually AST first, then alanine transaminase [ALT]), followed by a rise in the INR. Any patient in this category requires therapy with NAC (IV or oral). When to discontinue therapy in the clinically well patient remains controversial, but in general the transaminases and INR have peaked and fallen significantly “toward” normal (they do not need to be normal). Most patients' liver enzymes will peak 3 or 4 days after their ingestion.

3 Acute Liver Failure.

The King's College criteria are used to determine which patients should be referred for consideration of liver transplant. These criteria include acidemia (serum pH <7.3) after adequate fluid resuscitation, coagulopathy (INR >6), renal dysfunction (creatinine >3.4 mg/dL), and grade III or IV hepatic encephalopathy (see Chapter 391). A serum lactic acid >3 mmol/L (after IV fluids) adds to both sensitivity and specificity of the criteria to predict death without liver transplant. The degree of transaminase elevation does not factor in to this decision-making process.

4 Repeated Supratherapeutic Ingestion.

APAP is particularly prone to unintentional overdose through the ingestion of multiple medications containing the drug or simply because people assume it to be safe at any dose. Ingestion of amounts significantly greater than the recommended daily dose for several days or more puts one at risk for liver injury. Because the Rumack-Matthew nomogram is not helpful in this scenario, a conservative approach is taken. In the asymptomatic patient, if the AST is normal and the APAP is <10 μg/mL, no therapy is indicated. A normal AST and an elevated APAP warrants NAC dosing for at least long enough for the drug to metabolize while the AST remains normal. An elevated AST puts the patient in the "hepatic injury" category previously described. A patient presenting with symptoms (i.e., right upper quadrant pain, vomiting, jaundice) should be empirically started on NAC pending lab results.

NAC is available in oral and IV forms, and both are considered equally efficacious (see Table 77.7 for the dosing regimens of the oral vs IV form). The IV form is used in patients with intractable vomiting, those with evidence of hepatic failure, and pregnant patients. Oral NAC has an unpleasant taste and smell and can be mixed in soft drink or fruit juice or given by NG tube to improve tolerability of the oral regimen. Administration of IV NAC (as a standard 3% solution to avoid administering excess free water, typically in 5% dextrose), especially the initial loading dose, is associated in some patients with the development of anaphylactoid reactions (non–immunoglobulin E mediated). These reactions are typically managed by stopping the infusion; treating with diphenhydramine, albuterol, and/or epinephrine as indicated; and restarting the infusion at a slower rate once symptoms have resolved. IV NAC is also associated with mild elevation in measured INR (range: 1.2-1.5) because of laboratory interference. IV dosing, however, delivers less medication to the liver compared with the oral regimen. As a result, many toxicologists now recommend higher doses of the IV formulation in patients with large overdoses. Transaminases, synthetic function, and renal function should be followed daily while the patient is being treated with NAC. Patients with worsening hepatic function or clinical status might benefit from more frequent lab monitoring. A patient-tailored approach is now the norm for when to stop NAC therapy, for deciding whom to refer for transplantation evaluation, and often for the dose of IV NAC in patients with either very high APAP levels or signs of injury. Consultation with the regional PCC and medical toxicologist can help streamline the care of these patients, ultimately shortening their length of stay with potentially improved outcomes.

Salicylates.

The incidence of salicylate poisoning in young children has declined dramatically since APAP and ibuprofen replaced aspirin as the most commonly used analgesics and antipyretics in pediatrics. However, salicylates remain widely available, not only in aspirin-containing products but also in antidiarrheal medications, topical agents (e.g., keratolytics, sports creams), oil of wintergreen, and some herbal products. Oil of wintergreen contains 5 g of salicylate in 1 teaspoon (5 mL), meaning ingestion of very small volumes of this product has the potential to cause severe toxicity.

Pathophysiology.

Salicylates lead to toxicity by interacting with a wide array of physiologic processes, including direct stimulation of the respiratory center, uncoupling of oxidative phosphorylation, inhibition of the tricarboxylic acid cycle, and stimulation of glycolysis and gluconeogenesis. The acute toxic dose of salicylates is generally considered to be >150 mg/kg. More significant toxicity is seen after ingestions of >300 mg/kg, and severe, potentially fatal, toxicity is described after ingestions of >500 mg/kg.

Clinical and Laboratory Manifestations.

Salicylate ingestions are classified as acute or chronic, and acute toxicity is much more common in pediatric patients. Early signs of acute salicylism include nausea, vomiting, diaphoresis, and tinnitus. Moderate salicylate toxicity can manifest as tachypnea and hyperpnea, tachycardia, and altered mental status. The tachycardia largely results from marked insensible losses from vomiting, tachypnea, diaphoresis, and uncoupling of oxidative phosphorylation. Thus, careful attention should be paid to volume status and early volume resuscitation in the significantly poisoned patient. Signs of severe salicylate toxicity include mild hyperthermia, coma, and seizures. Chronic salicylism can have a more insidious presentation, and patients can show marked toxicity (e.g. altered mental status, noncardiogenic pulmonary edema, acidemia) at significantly lower salicylate levels than in acute toxicity.

Classically, laboratory values from a patient poisoned with salicylates reveal a primary respiratory alkalosis and a primary, elevated anion gap metabolic acidosis. Early in the course of acute salicylism, respiratory alkalosis dominates and the patient is alkalemic. As the respiratory stimulation diminishes, the patient will move toward acidemia. Hyperglycemia (early) and hypoglycemia (late) have been described. Abnormal coagulation studies and acute kidney injury may be seen but are not common.

Serial serum salicylate levels should be closely monitored (every 2-4 hr initially) until they are consistently downtrending. Salicylate absorption in overdose is unpredictable and erratic, especially with an enteric-coated product, and levels can rapidly increase into the highly toxic range, even many hours after the ingestion. The Done nomogram is of poor value and should not be used. Serum and urine pH and electrolytes should be followed closely. An APAP level should be checked in any patient who intentionally overdoses on salicylates, because APAP is a common co-ingestant, and people often confuse or combine their nonprescription analgesic medications. Salicylate toxicity can cause a noncardiogenic pulmonary edema, especially in chronic overdose; consequently, a chest radiograph is recommended in any patient in respiratory distress.

Treatment.

For the patient who presents soon after an acute ingestion, initial treatment should include gastric decontamination with activated charcoal. Salicylate pills occasionally form bezoars, which should be suspected if serum salicylate concentrations continue to rise many hours after ingestion or are persistently elevated despite appropriate management. Gastric decontamination is typically not useful after chronic exposure.

Initial therapy focuses on aggressive volume resuscitation and prompt initiation of sodium bicarbonate therapy in the symptomatic patient, even before obtaining serum salicylate levels. Therapeutic salicylate levels are 10-20 mg/dL, and levels >25 or 30 mg/dL warrant treatment.

The primary mode of therapy for salicylate toxicity is **urinary alkalinization** . Urinary alkalinization enhances the elimination of salicylates by converting salicylate to its ionized form, “trapping” it in the renal tubules, thus enhancing elimination. In addition, maintaining an alkalemic serum pH decreases CNS penetration of salicylates because charged particles are less able to cross the blood-brain barrier. Alkalinization is achieved by administration of a sodium bicarbonate infusion at approximately 2 times maintenance fluid rates. *The goals of therapy include a urine pH of 7.5-8, a serum pH of 7.45-7.55, and decreasing serum salicylate levels.* In general, in the presence of an acidosis, an aspirin-poisoned patient's status can be directly related to the patient's serum pH: the lower the pH, the greater the relative amount of salicylate in the uncharged, nonpolar form and the greater the penetration of the blood-brain barrier by the drug. Careful attention should also be paid to serial potassium levels in any patient on a bicarbonate infusion, since potassium will be driven intracellularly and hypokalemia impairs alkalinization of the urine. For these reasons, potassium is often added to the bicarbonate drip. Repeat doses of charcoal may be beneficial because of the often delayed and erratic absorption of aspirin.

Parenteral glucose should be provided to any salicylate-poisoned patients with altered mental status because they may have CNS hypoglycemia (i.e., neuroglycopenia) not seen in a peripheral serum glucose test.

In patients with severe toxicity, hemodialysis may be required. Indications for dialysis include severe acid-base abnormalities (specifically severe acidosis and acidemia), a rising salicylate level (despite adequate decontamination and properly alkalinized urine), pulmonary edema, cerebral edema, seizures, and renal failure. Serum salicylate concentrations alone are not a clear indicator of the need for dialysis and should always be interpreted along with the clinical status of the patient.

Ibuprofen and Other Nonsteroidal Antiinflammatory Drugs (NSAIDs).

Ibuprofen and other NSAIDs are often involved in unintentional and intentional overdoses because of their widespread availability and common use as analgesics and antipyretics. Fortunately, serious effects after acute NSAID overdose are rare because of their wide therapeutic index.

Pathophysiology.

NSAIDs inhibit prostaglandin synthesis by reversibly inhibiting the activity of cyclooxygenase (COX), the primary enzyme responsible for the biosynthesis of prostaglandins. In therapeutic use, side effects include GI irritation, reduced renal blood flow, and platelet dysfunction. To minimize these side effects, NSAID analogs have been developed that are more specific for the inducible form of COX (the COX-2 isoform) than the constitutive form, COX-1. However, overdose of the more selective COX-2 inhibitors (e.g., celecoxib [Celebrex]) is treated the same as overdose of nonspecific COX inhibitors (e.g., ibuprofen) because at higher doses, COX-2–selective agents lose their COX inhibitory selectivity.

Ibuprofen, the primary NSAID used in pediatrics, is well tolerated, even in overdose. In children, acute doses of <200 mg/kg rarely cause toxicity, but ingestions of >400 mg/kg can produce more serious effects, including altered mental status and metabolic acidosis.

Clinical and Laboratory Manifestations.

Symptoms usually develop within 4-6 hr of ingestion and resolve within 24 hr. If toxicity does develop, it is typically manifested as nausea, vomiting, and abdominal pain. Although GI bleeding and ulcers have been described with chronic use, they are rare in the setting of acute ingestion. After massive ingestions, patients can develop marked CNS depression, anion gap metabolic acidosis, renal insufficiency, and (rarely) respiratory depression. Seizures have also been described, especially after overdose of mefenamic acid. Specific drug levels are not readily available, nor do they inform management decisions. Renal function studies, acid-base balance, complete blood count (CBC), and coagulation parameters should be monitored after very large ingestions. Co-ingestants, especially APAP, should be ruled out after any intentional ingestion.

Treatment.

Supportive care, including use of antiemetics and acid blockade as indicated, is the primary therapy for NSAID toxicity. Decontamination with activated charcoal should be considered if a patient presents within 1-2 hr of a potentially toxic ingestion. There is no specific antidote for this class of drugs. Given the high degree of protein binding and excretion pattern of NSAIDs, none of the modalities used to enhance elimination is particularly useful in managing these overdoses. Unlike in patients with salicylate toxicity, urinary alkalinization is not helpful for NSAID toxicity. Patients who develop significant clinical signs of toxicity should be admitted to the hospital for ongoing supportive care and monitoring. Patients who remain asymptomatic for 4-6 hr after ingestion may be considered medically cleared.

Prescription Opioids.

Opioids are a frequently abused class of medications in both IV and oral forms. The opioid epidemic gripping the United States and other countries is discussed in Chapter 140 . Two specific oral opioids, buprenorphine and methadone, merit mention because of potential life-threatening toxicity in toddlers with ingestion of even 1 pill. Both agents are used in managing opioid dependence, although **buprenorphine** is the drug of choice. **Methadone** is also widely used in the treatment of chronic pain, meaning multiday prescriptions can be filled. Both drugs are readily available for illicit purchase and potential abuse. Both drugs are of great potential toxicity to a toddler, especially buprenorphine because of its long half-life and high potency.

Pathophysiology.

Methadone is a lipophilic synthetic opioid with potent agonist effects at μ-opioid receptors, leading to both its desired analgesic effects and undesired side effects, including sedation, respiratory depression, and impaired GI motility. Methadone is thought to cause QTc interval prolongation through interactions with the human ether-a-go-go–related gene (hERG)-encoded potassium rectifier channel. Its duration of effect for pain control averages only about 8 hr, whereas the dangerous side effects can occur up to 24 hr from the last dose and longer after overdose. Methadone has an average half-life >25 hr, which may be extended to >50 hr in overdose.

Suboxone is a combination of buprenorphine, a potent opioid with partial agonism at μ-opioid receptors and weak antagonism at κ-opioid receptors, and naloxone. Naloxone has poor oral bioavailability but is included in the formulation to discourage diversion for IV use, during which it can precipitate withdrawal. Suboxone is formulated for buccal or sublingual administration; consequently, toddlers can absorb significant amounts of drug even by sucking on a tablet. Buprenorphine has an average half-life of 37 hr.

Clinical and Laboratory Manifestations.

In children, methadone and buprenorphine ingestions can manifest with the classic opioid toxidrome of respiratory depression, sedation, and miosis. Signs of more severe toxicity can include bradycardia, hypotension, and hypothermia. Even in therapeutic use, methadone is associated with a prolonged QTc interval and risk of torsades de pointes. Accordingly, an ECG should be part of the initial evaluation after ingestion of methadone or any unknown opioid. Neither drug is detected on routine urine opiate screens, although some centers have added a separate urine methadone screen. Levels of both drugs can be measured, although this is rarely done clinically and is seldom helpful in the acute setting. An exception may be in the cases involving concerns about neglect or abuse, at which point urine for gas chromatography/mass spectroscopy, the legal gold standard, should be sent to confirm and document the presence of the drug.

Treatment.

Patients with significant respiratory depression or CNS depression should be treated with the opioid antidote **naloxone** (see Table 77.7). In pediatric patients who are not chronically taking opioids, the full reversal dose of 1-2 mg should be used. In contrast, opioid-dependent patients should be treated with smaller initial doses (0.04-0.4 mg), which can then be repeated as needed to achieve the desired clinical response, avoiding abrupt induction of withdrawal. Because the half-life of methadone and buprenorphine is much longer than that of naloxone, patients can require multiple doses of naloxone. These patients may benefit from a continuous infusion of naloxone, typically started at two thirds of the reversal dose per hour and titrated to maintain an adequate respiratory rate and level of consciousness. Patients who have ingested methadone should be placed on a cardiac monitor and have serial ECGs to monitor for the development of a prolonged QTc interval. If a patient does develop a prolonged QTc, management includes close cardiac monitoring, repletion of electrolytes (potassium, calcium, and magnesium), and having a defibrillator readily available should the patient develop torsades de pointes.

Given the potential for clinically significant and prolonged toxicity, any toddler who has ingested methadone, even if asymptomatic, should be admitted to the hospital for at least 24 hr of monitoring. Some experts advocate a similar approach to management of buprenorphine ingestions, even in the asymptomatic patient. All such cases should be discussed with a PCC or medical toxicologist before determining disposition.

Cardiovascular Medications

β-Adrenergic Receptor Blockers.

β-Blockers competitively inhibit the action of catecholamines at the β-adrenergic receptor. Therapeutically, β-blockers are used for a variety of conditions, including hypertension, coronary artery disease, tachydysrhythmias, anxiety disorders, migraines, essential tremor, and hyperthyroidism. Because of its lipophilicity and blockade of fast sodium channels, **propranolol** is considered to be the most toxic member of the β-blocker class. Overdoses of water-soluble β-blockers (e.g., atenolol) are associated with milder symptoms.

Pathophysiology.

In overdose, β-blockers decrease chronotropy and inotropy in addition to slowing conduction through atrioventricular nodal tissue. Clinically, these effects are manifested as bradycardia, hypotension, and heart block. Patients with reactive airways disease can experience bronchospasm as a result of blockade of β_2 -mediated bronchodilation. β_2 -Blockers interfere with glycogenolysis and gluconeogenesis, which can sometimes lead to hypoglycemia, especially in patients with poor glycogen stores (e.g., toddlers).

Clinical and Laboratory Manifestations.

Toxicity typically develops within 6 hr of ingestion, although it may be delayed after ingestion of sotalol or slow-release (SR) preparations. The most common features of severe poisoning are bradycardia and hypotension. Lipophilic agents, including propranolol, can enter the CNS and cause altered mental status, coma, and seizures. Overdose of β-blockers with membrane-stabilizing properties (e.g., propranolol) can cause QRS interval widening and ventricular dysrhythmias.

Evaluation after β-blocker overdose should include an ECG, frequent reassessments of hemodynamic status, and blood glucose. Serum levels of β-blockers are not readily available for routine clinical use and are not useful in management of the poisoned patient.

Treatment.

In addition to supportive care and GI decontamination as indicated, **glucagon** is theoretically the preferred antidote of choice for β-blocker toxicity (see Table 77.7). Glucagon stimulates adenyl cyclase and increases levels of cyclic adenosine monophosphate (cAMP) independent of the β-receptor. Glucagon is typically given as a bolus and, if this is effective, followed by a continuous infusion. In practice, glucagon is often only marginally effective, limited by its proemetic effects, especially at the high doses typically required. Other potentially useful interventions include calcium, vasopressors, and high-dose insulin. Seizures are managed with benzodiazepines, and QRS widening should be treated with sodium bicarbonate. Children who ingest 1 or 2 water-soluble β-blockers are unlikely to develop toxicity and can typically be discharged to home if they remain asymptomatic over a 6 hr observation period. Children who ingest SR products, highly lipid-soluble agents, and sotalol can require longer periods of observation before safe discharge. Any symptomatic child should be admitted for ongoing monitoring and directed therapy.

Calcium Channel Blockers.

Calcium channel blockers (CCBs) are used for a variety of therapeutic indications and have the potential to cause severe toxicity, even after exploratory ingestions. Specific agents include verapamil, diltiazem, and the dihydropyridines (e.g., amlodipine, nifedipine). Of these, diltiazem and verapamil are the most dangerous in overdose because of their higher lipophilicity and direct cardiac suppressant effects.

Pathophysiology.

CCBs antagonize L -type calcium channels, inhibiting calcium influx into myocardial and vascular smooth muscle cells. Verapamil works primarily by slowing inotropy and chronotropy and has no effect on systemic vascular resistance (SVR). Diltiazem has effects both on the heart and the peripheral vasculature. The dihydropyridines exclusively diminish SVR. Verapamil and diltiazem can significantly diminish myocardial contractility and conduction, with diltiazem also lowering SVR. By contrast, dihydropyridines will decrease the SVR, leading to vasodilation and reflex tachycardia, although this receptor selectivity may be lost after a large overdose. Because the same L -type calcium channels blocked by CCBs are also on the pancreatic islet cells, any patient significantly poisoned with a CCB usually is hyperglycemic.

Clinical and Laboratory Manifestations.

The onset of symptoms typically is soon after ingestion, although it may be delayed with ingestions of SR products. Overdoses of CCBs lead to hypotension, accompanied by bradycardia, normal heart rate, or even tachycardia, depending on the agent. A common feature of CCB overdose is the patient exhibiting profound hypotension with preserved consciousness.

Initial evaluation should include an ECG, continuous and careful hemodynamic monitoring, and rapid measurement of serum glucose levels. Both the absolute degree of hyperglycemia and the percentage increase in serum glucose have been correlated with the severity of CCB toxicity in adults. The development of hyperglycemia can even precede the development of hemodynamic instability. Blood levels of CCBs are not readily available and are not useful in guiding therapy.

Treatment.

Once initial supportive care has been instituted, GI decontamination should begin with activated charcoal as appropriate. WBI may be beneficial in a stable patient after ingestion of an SR product. Calcium channel blockade in the smooth muscles of the GI tract can lead to greatly diminished motility; thus any form of GI decontamination should be undertaken with careful attention to serial abdominal tests.

Calcium salts, administered through a peripheral IV line as calcium gluconate or a central line as calcium chloride, help to overcome blocked calcium channels. **High-dose insulin euglycemia therapy** is considered the antidote of choice for CCB toxicity. An initial bolus of 1 unit/kg of regular insulin is followed by an infusion at 0.5-1 unit/kg/hr (see Table 77.7). The main mechanism of high-dose insulin euglycemia is to improve the metabolic efficiency of a poisoned heart that is in need of carbohydrates for energy (instead of the usual free fatty acids), but has minimal circulating insulin. Blood glucose levels should be closely monitored, and supplemental glucose may be given to maintain euglycemia, although this is rarely necessary in the severely poisoned patient.

Additional therapies include judicious IV fluid boluses and vasopressors (often in very high doses). Cardiac pacing is rarely of value. Lipid emulsion therapy (discussed earlier) is a potentially lifesaving intervention, especially for patients poisoned with the more lipid-soluble CCBs, verapamil and diltiazem. In extreme cases an intraaortic balloon pump or extracorporeal membrane oxygenation (ECMO) are potential rescue devices. Given the potential for profound and sometimes delayed toxicity in toddlers after ingestion of 1 or 2 CCB tablets, hospital admission and 12-24 hr of monitoring for all of these patients is strongly recommended.

Clonidine.

Although originally intended for use as an antihypertensive, the number of clonidine prescriptions in the pediatric population has greatly increased because of its reported efficacy in the management of attention-deficit/hyperactivity disorder (ADHD), tic disorders, and other behavioral disorders. With this increased use has come a significant rise in pediatric ingestions and therapeutic misadventures. Clonidine is available in pill and transdermal patch forms.

Pathophysiology.

Clonidine, along with the closely related agent **guanfacine** , is a centrally acting α_2 -adrenergic receptor agonist with a very narrow therapeutic index. Agonism at central α_2 receptors decreases sympathetic outflow, producing lethargy, bradycardia, hypotension, and apnea. Toxicity can develop after ingestion of only 1 pill or after sucking on or swallowing a discarded transdermal patch. Even a “used” transdermal patch might contain as much as one-third to one-half the original amount of drug.

Clinical and Laboratory Manifestations.

The most common clinical manifestations of clonidine toxicity are lethargy, miosis, and bradycardia. Hypotension, respiratory depression, and apnea may be seen in severe cases. Very early after ingestion, patients may be hypertensive in the setting of agonism at peripheral α-receptors and resulting vasoconstriction. Symptoms develop relatively soon after ingestion and typically resolve within 24 hr. Serum clonidine concentrations are not readily available and are of no clinical value in the acute setting. Although signs of clinical toxicity are common after clonidine overdose, death from clonidine alone is extremely unusual.

Treatment.

Given the potential for significant toxicity, most young children warrant referral to a healthcare facility for evaluation after unintentional ingestions of clonidine. Gastric decontamination is usually of minimal value because of the small quantities ingested and the rapid onset of serious symptoms. Aggressive supportive care is imperative and is the cornerstone of management. Naloxone, often in high doses, has shown variable efficacy in treating clonidine toxicity. Other potentially useful therapies include atropine, IV fluid boluses, and vasopressors. Symptomatic children should be admitted to the hospital for close cardiovascular and neurologic monitoring. Also, in a patient receiving chronic clonidine or guanfacine therapy, rapid discontinuation of the drug, or even missing 1 or 2 doses, could lead to potentially dangerous elevations in blood pressure.

Digoxin.

Digoxin is a cardiac glycoside extracted from the leaves of *Digitalis lanata* . Other natural sources of cardiac glycosides include *Digitalis purpura* (foxglove), *Nerium oleander* (oleander), *Convallaria majalis* (lily of the valley), Siberian ginseng, and the *Bufo marinus* toad. Therapeutically, digoxin is used in the management of heart failure and some supraventricular tachydysrhythmias. Acute overdose can occur in the setting of dosing errors (especially in younger children), unintentional or intentional medication ingestion, or exposure to plant material containing digitalis glycosides. Regarding exposure to such plants, toxicity is unusual unless the poison is concentrated in the form of a tea. Chronic toxicity can result from alteration of the digoxin dose, alteration in digoxin clearance as a result of renal impairment, or drug interactions.

Pathophysiology.

Digoxin blocks the sodium-potassium adenosine triphosphatase (Na^+ ,K^+ -ATPase) pump, leading to intracellular loss of K^+ and gain of Na^+ and calcium (Ca^{2+}). This resulting rise in Ca^{2+} available to the contractile myocardium improves inotropy. An increase in myocardial automaticity leads to subsequent atrial, nodal, and ventricular ectopy. Digoxin also affects nodal conduction, leading to a prolonged refractory period, decreased sinus node firing, and slowed conduction through the atrioventricular node. Impaired Na^+ /K^+ exchange results in dangerously high levels of serum K^+ . Overall, digoxin overdose manifests as a combination of slowed or blocked conduction and increased ectopy.

Clinical and Laboratory Manifestations.

Nausea and vomiting are common initial symptoms of acute digoxin toxicity, manifesting within 6 hr of overdose. Cardiovascular manifestations include bradycardia, heart block, and a wide variety of dysrhythmias. CNS manifestations consist of lethargy, confusion, and weakness. Chronic toxicity is more insidious and may also manifest as altered mental status and visual disturbances (rare).

Initial assessment should include an ECG, serum digoxin level, serum potassium, and kidney function tests. The serum digoxin level should be assessed at least 6 hr after ingestion and carefully interpreted in the setting of clinical symptoms, because the digoxin level alone does not entirely reflect the severity of intoxication. In acute ingestions, serum potassium is an independent marker of morbidity and mortality, with levels >5.5 mEq/L predicting poor outcomes. In chronic toxicity, serum K^+ concentration is less useful as a prognostic marker and may be altered from concomitant use of diuretics.

Digoxin has a very narrow therapeutic index. Therapeutic plasma digoxin concentrations are 0.5-2.0 ng/mL; a level >2 ng/mL is considered toxic and >6 ng/mL is considered potentially fatal (in chronic poisonings). As with all serum levels of intoxicants, one must be careful to interpret the number in the context of the scenario of the poisoning and the status of the patient. An acutely poisoned patient may have a very high serum level and minimal to no symptoms, whereas a patient with a chronic or acute on chronic poisoning will usually be sicker with a lower serum level.

Numerous drug interactions affect plasma digoxin concentrations. Medications known to increase serum digoxin concentrations include the macrolides, erythromycin and clarithromycin, spironolactone, verapamil, amiodarone, and itraconazole.

Treatment.

Initial treatment includes good general supportive care and gastric decontamination with activated charcoal if the ingestion was recent. An antidote for digoxin, digoxin-specific antibody fragments (Fab: Digibind or DigiFab) is available (see Table 77.7). Fab fragments bind free digoxin in both the intravascular and the interstitial spaces to form a pharmacologically inactive complex that is subsequently eliminated renally. Indications for Fab fragments include life-threatening dysrhythmias, K^+ value >5-5.5 mEq/L, serum digoxin level >15 ng/mL at any time or >10 ng/mL 6 hr after ingestion, clinically significant hypotension or other CV instability, altered mental state, and renal failure. Atropine is potentially useful in managing symptomatic bradycardia. Although dogma states that patients on digoxin with severe hyperkalemia and QRS widening on the ECG should not receive calcium salts, this has not been supported in the literature. Once stabilized, consultation with a cardiologist is recommended in the management of patients receiving chronic digoxin therapy, because administration of Fab fragments can lead to recurrence of the patient's underlying dysrhythmias or dysfunction.

Iron.

Historically, iron was a common cause of childhood poisoning deaths. However, preventive measures such as childproof packaging have significantly decreased the rates of serious iron toxicity in young children. Iron-containing products remain widely available, with the most potentially toxic being adult iron preparations and prenatal vitamins. The severity of an exposure is related to the amount of *elemental iron* ingested. Ferrous sulfate contains 20% elemental iron, ferrous gluconate 12%, and ferrous fumarate 33%. Multivitamin preparations and children's vitamins rarely contain enough elemental iron to cause significant toxicity. Furthermore, nonionic forms of iron, carbonyl iron and iron polysaccharide also do not cause significant toxicity.

Pathophysiology.

Iron is directly corrosive to the GI mucosa, leading to hematemesis, melena, ulceration, infarction, and potential perforation. Early iron-induced hypotension is caused by massive volume losses, increased permeability of capillary membranes, and vasodilation mediated by free iron. Iron accumulates in tissues, including the Kupffer cells of the liver and myocardial cells, leading to hepatotoxicity, coagulopathy, and cardiac dysfunction. Metabolic acidosis develops in the setting of hypotension, hypovolemia, and iron's direct interference with oxidative phosphorylation and the Krebs cycle. Pediatric patients who ingest >40 mg/kg of elemental iron should be referred to medical care for evaluation, although moderate to severe toxicity is typically seen with ingestions >60 mg/kg.

Clinical and Laboratory Manifestations.

Iron toxicity is described in 5 often-overlapping stages. The **1st stage** , 30 min to 6 hr after ingestion, consists of profuse vomiting and diarrhea (often bloody), abdominal pain, and significant volume losses leading to potential hypovolemic shock. Patients who do not develop GI symptoms within 6 hr of ingestion are unlikely to develop serious toxicity. The **2nd stage** , 6-24 hr after ingestion, is often referred to as the “quiescent phase” since the GI symptoms typically have resolved. However, careful clinical examination can reveal subtle signs of hypoperfusion, including tachycardia, pallor, and fatigue. During the **3rd stage** , 12-36 hr after ingestion, patients develop multisystem organ failure, shock, hepatic and cardiac dysfunction, acute lung injury, and profound metabolic acidosis. Death usually occurs during the 3rd stage. The **4th stage** (hepatic) results in fulminant liver failure and coagulopathy about 2-5 days after ingestion. The **5th stage** , 4-6 wk after ingestion, is marked by formation of strictures and signs of GI obstruction.

Symptomatic patients and patients with a large exposure by history should have serum iron levels drawn 4-6 hr after ingestion. Serum iron concentrations of <500 µg/dL 4-8 hr after ingestion suggest a low risk of significant toxicity, whereas concentrations of >500 µg/dL indicate that significant toxicity is likely. Additional laboratory evaluation in the ill patient should include arterial or venous blood gas, CBC, serum glucose level, liver transaminases, and coagulation parameters. Careful attention should be paid to the patient's hemodynamic status. An abdominal radiograph might reveal the presence of iron tablets, although not all formulations of iron are radiopaque.

Treatment.

Close clinical monitoring, combined with aggressive supportive and symptomatic care, is essential to the management of iron poisoning. Activated charcoal does not adsorb iron, and WBI remains the decontamination strategy of choice. **Deferoxamine** , a specific chelator of iron, is the antidote for moderate to severe iron intoxication (see Table 77.7). Indications for deferoxamine treatment include a serum iron concentration >500 µg/dL or moderate to severe symptoms of toxicity (e.g., acidosis), regardless of serum iron concentration. Deferoxamine is preferably given by continuous IV infusion at 15 mg/kg/hr. Hypotension is a common side effect of deferoxamine infusion and is managed by slowing the rate of the infusion and administering fluids and vasopressors as needed. Prolonged deferoxamine infusion (>24 hr) has been associated with pulmonary toxicity (acute respiratory distress syndrome, ARDS) and *Yersinia* sepsis. The deferoxamine-iron complex can color the urine reddish (“vin rosé”), although the degree of this coloration should not guide therapy. Deferoxamine is typically continued until clinical symptoms and acidosis resolve. Consultation with a PCC or medical toxicologist can yield guidelines for discontinuing deferoxamine.

Oral Hypoglycemics

Oral medications used in the management of type 2 diabetes include sulfonylureas, biguanides (e.g., metformin), thiazolidinediones, and meglitinides. Of these, only the sulfonylureas and meglitinides have the potential to cause profound hypoglycemia in both diabetic and nondiabetic patients. These classes of medications are widely prescribed and thus readily available for both unintentional and intentional exposures. In toddlers, ingestion of a single sulfonylurea tablet can lead to significant toxicity.

Pathophysiology.

Sulfonylureas work primarily by enhancing endogenous insulin secretion. In binding to the sulfonylurea receptor, these drugs induce closure of K^+ channels, leading to membrane depolarization, opening of Ca^{2+} channels, and stimulation of Ca^{2+} -mediated insulin release. Even in therapeutic use, the duration of hypoglycemic action can last up to 24 hr.

Clinical and Laboratory Manifestations.

Hypoglycemia and symptoms associated with hypoglycemia are the primary clinical manifestations of sulfonylurea toxicity. These signs and symptoms can include diaphoresis, tachycardia, lethargy, irritability, coma, seizures, and even focal neurologic findings. As with other hyperinsulinemic states, sulfonylurea overdoses are associated with a nonketotic hypoglycemia. In the majority of patients, hypoglycemia develops within 6 hr of ingestion but can be delayed up to 16-18 hr after ingestion. Toddlers are particularly susceptible to hypoglycemia during an overnight fast.

Treatment.

Patients with symptomatic hypoglycemia should be promptly treated with dextrose. In patients with mild symptoms, oral dextrose may be sufficient. However, patients with severe symptoms or profound hypoglycemia should be treated with a bolus of IV dextrose. Continuous dextrose infusions and repeated IV dextrose boluses should be avoided if possible, because this can stimulate further insulin release and lead to recurrent and prolonged hypoglycemia. Instead, the preferred antidote for persistent (i.e., requiring ≥2 doses of IV dextrose) sulfonylurea toxicity is **octreotide** (see Table 77.7). Octreotide is a somatostatin analog that inhibits insulin release. Octreotide is given intravenously (IV) or subcutaneously (SC), typically in doses of 1-2 µg/kg (50-100 µg in teens or adults) every 6-8 hr.

Given the potential for significant hypoglycemia, toddlers with witnessed or suspected sulfonylurea ingestions should be admitted to the hospital for serial glucose measurements for at least 12 hr, including an overnight fast. Patients of any age who develop hypoglycemia are also candidates for admission given the prolonged duration of hypoglycemic activity. Prophylactic IV dextrose infusions are not recommended because they can mask the symptoms of toxicity and stimulate further insulin secretion. Patients who require IV dextrose and/or octreotide should be monitored until they can demonstrate euglycemia for at least 8 hr off all therapy.

With the increasing numbers of adolescents with type 2 diabetes, pediatricians should be familiar with the toxic effects of **metformin** as well. Although metformin does not cause hypoglycemia, its association with lactic acidosis is well documented (metformin-associated lactic acidosis, MALA). This state typically arises after a large overdose in which the agent interferes with the liver's ability to clear lactic acid. Dangerously high serum lactate levels can result, leading to hemodynamic instability. Hemodialysis is usually the best option for patients with severe MALA.

Psychiatric Medications: Antidepressants

Selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, paroxetine, citalopram) are the most commonly prescribed class of antidepressants. This trend largely results from their wide therapeutic index and more favorable side effect profile compared with older agents such as tricyclic antidepressants (TCAs; amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, imipramine) and monoamine oxidase inhibitors (MAOIs). Other agents include the serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine) and atypical antidepressants (e.g., bupropion).

Tricyclic Antidepressants.

Although now prescribed less often for depression, TCAs remain in use for a variety of other conditions, including chronic pain syndromes, enuresis, ADHD, and obsessive-compulsive disorder. TCAs can cause significant toxicity in children, even with ingestion of 1 or 2 pills (10-20 mg/kg).

Pathophysiology.

TCAs achieve their desired antidepressant effects primarily through blockade of norepinephrine and serotonin reuptake. TCAs have complex interactions with other receptor types. Antagonism at muscarinic acetylcholine receptors leads to clinical features of the anticholinergic toxidrome. Antagonism at peripheral α-receptors leads to hypotension and syncope. Key to the toxicity of TCAs is their ability to block fast sodium channels, leading to impaired cardiac conduction and arrhythmias.

Clinical and Laboratory Manifestations.

Cardiovascular and CNS symptoms dominate the clinical presentation of TCA toxicity. Symptoms typically develop within 1-2 hr of ingestion, and serious toxicity usually manifests within 6 hr of ingestion. Patients can have an extremely rapid progression from mild symptoms to life-threatening dysrhythmias. Patients often develop features of the **anticholinergic toxidrome** , including delirium, mydriasis, dry mucous membranes, tachycardia, hyperthermia, urinary retention, and slow GI motility. CNS toxicity can include lethargy, coma, myoclonic jerks, and seizures. Sinus tachycardia is the most common cardiovascular manifestation of toxicity; however, patients can also develop widening of the QRS complex, premature ventricular contractions, and ventricular dysrhythmias. Refractory hypotension is a poor prognostic indicator and is the most common cause of death in TCA overdose.

An ECG is a readily available bedside test that can help determine the diagnosis and prognosis of the TCA-poisoned patient (Fig. 77.2 ; see Table 77.6). A QRS duration >100 msec identifies patients who are at risk for seizures and cardiac arrhythmias. An R wave in lead aVR of ≥3 mm is also an independent predictor of toxicity. Both ECG parameters are superior to measured serum TCA concentrations for identifying patients at risk for serious toxicity, and obtaining levels is rarely helpful in management of the acutely ill patient.

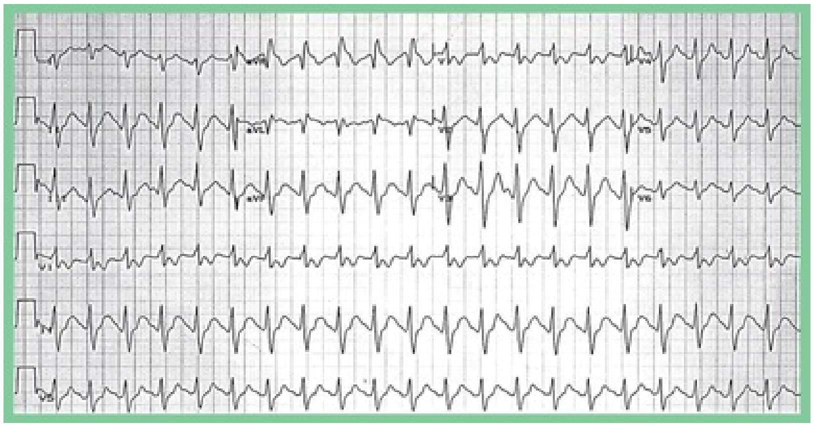

FIG. 77.2 **Electrocardiographic findings in tricyclic antidepressant toxicity. Note the tachycardia, widened QRS interval (144 msec), and prominent R wave in lead aVR. These findings are consistent with blockade of fast sodium channels.**

Treatment.

Initial attention should be directed to supporting vital functions, including airway and ventilation as needed. Gastric decontamination can be accomplished with activated charcoal in appropriate patients. Treating clinicians should obtain an ECG as soon as possible and follow serial ECGs to monitor for progression of toxicity. The 4 primary effects described next are seen at the bedside.

1 Altered Mental State.

TCA-poisoned patients can become deeply comatose relatively quickly, so careful and prompt attention to the airway and placement of an endotracheal tube is of paramount importance. The airway should be secured before any GI decontamination efforts.

2 Widened QRS on ECG.

TCAs, as well as with other agents (e.g., diphenhydramine, cocaine), will block the fast Na^+ channels on the myocardial cells, slowing the upstroke of the QRS complex. Because the effect on Na^+ channels is greatest within the 1st 6 hr, frequent ECGs (i.e., every 20-30 min) during this period are important. As the QRS approaches 160 msec, the risk of the patient developing monomorphic ventricular tachycardia rises to 30%. Sodium, usually in the form of sodium bicarbonate, is the antidote of choice. *Indications for sodium bicarbonate include a QRS duration ≥110 msec, ventricular dysrhythmias, and hypotension* . Multiple bolus doses of sodium bicarbonate, 1-2 mEq/kg each, may be needed to narrow the QRS to <110 msec. Some prefer then to place the patient on an infusion of sodium bicarbonate, but this may not be necessary if the QRS is carefully monitored after the initial doses and repeat bolus dosing is provided as needed during the 1st 6-12 hr. Hypertonic (3%) saline and/or lipid emulsion therapy may be beneficial in refractory cases.

3 Hypotension.

A direct-acting vasopressor such as norepinephrine or epinephrine is the agent of choice. Boluses of IV crystalloid fluids should be used with caution to prevent fluid overload.

4 Seizures.

Likely a result of the anticholinergic effects of TCAs, seizures are relatively common, typically brief, and should be treated with agents targeting the GABA-receptor complex in the brain. Benzodiazepines are the agent of choice.

Asymptomatic children should receive appropriate decontamination and have continuous cardiac monitoring and serial ECGs for at least 6 hr after exposure. If any manifestations of toxicity develop, the child should be admitted to a monitored setting. Children who remain completely asymptomatic with normal serial ECGs may be candidates for discharge after that monitoring period.

Selective Serotonin Reuptake Inhibitors.

In overdose, SSRIs are considerably less toxic than TCAs. SSRIs are unlikely to cause significant toxicity in exploratory ingestions. Some data suggest that initiating SSRI therapy is associated with an increased risk of suicidal ideation and behavior (see Chapter 40).

Pathophysiology.

SSRIs selectively block the reuptake of serotonin in the CNS. In contrast to TCAs and atypical antidepressants, SSRIs do not directly interact with other receptor types.

Clinical and Laboratory Manifestations.

In overdose, the principal manifestations of toxicity are sedation and tachycardia. Cardiac conduction abnormalities (primarily QTc prolongation) and seizures have been described in significant overdoses, especially after ingestions of citalopram. An ECG should be part of the initial assessment after SSRI ingestion. Serum creatine kinase (CK) levels are almost always elevated in a patient with clinically significant **serotonin syndrome** . Although seen more often after therapeutic use or overdose of several serotonergic agents in combination, the serotonin syndrome has also been described in ingestion of SSRIs alone (Table 77.11). Clinically, serotonin syndrome describes a spectrum of altered mental status, autonomic instability, fever, and neuromuscular hyperactivity (hyperreflexia, tremors, clonus in lower extremities > upper extremities). One or all of these signs may be present to varying degrees.

Table 77.11

Drugs Associated With the Serotonin Syndrome

DRUG TYPE	DRUGS
Selective serotonin reuptake inhibitors	Sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram
Antidepressant drugs	Trazodone, nefazodone, buspirone, clomipramine, venlafaxine
Monoamine oxidase inhibitors	Phenelzine, moclobemide, clorgyline, isocarboxazid
Anticonvulsants	Valproate
Analgesics	Meperidine, fentanyl, tramadol, pentazocine
Antiemetic agents	Ondansetron, granisetron, metoclopramide
Antimigraine drugs	Sumatriptan
Bariatric medications	Sibutramine
Antibiotics	Linezolid (a monoamine oxidase inhibitor), ritonavir (through inhibition of cytochrome P450 enzyme isoform 3A4)
Nonprescription	Dextromethorphan

cough and cold remedies	
Drugs of abuse	Methylenedioxymethamphetamine (MDMA, “Ecstasy”), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine (“foxy methoxy”), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products	Tryptophan, *Hypericum perforatum* (St. John's wort), *Panax ginseng* (ginseng)
Other	Lithium

From Boyer EW, Shannon M: The serotonin syndrome, *N Engl J Med* 352:1112–1120, 2005.

Treatment.

Initial management includes a careful assessment for signs and symptoms of serotonin syndrome and an ECG. Most patients simply require supportive care and observation until their mental status improves and tachycardia, if present, resolves. Management of serotonin syndrome is directed by the severity of symptoms; possible therapeutic interventions include benzodiazepines in mild cases and intubation, sedation, and paralysis in patients with severe manifestations (e.g., significant hyperthermia). Because agonism at the 5-HT$_{2A}$ serotonin receptor is thought to be primarily responsible for the development of serotonin syndrome, use of the 5-HT$_{2A}$ receptor antagonist cyproheptadine may also be helpful. Cyproheptadine is only available in an oral form.

Atypical Antidepressants.

The atypical antidepressant class includes agents such as venlafaxine and duloxetine (SNRIs), bupropion (dopamine, norepinephrine, and some serotonin reuptake blockade), and trazodone (serotonin reuptake blockade and peripheral α-receptor antagonism). The variable receptor affinities of these agents lead to some distinctions in their clinical manifestations and management.

Clinical and Laboratory Manifestations.

In overdose, **venlafaxine** and other SNRIs have been associated with cardiac conduction defects, including QRS and QTc prolongation, and seizures. **Bupropion** warrants special consideration because it is one of the most common etiologies of toxicant-induced seizures in the United States. After ingestion of SR or extended-release (ER) preparations, seizures can occur as late as 18-20 hr after ingestion. In addition, bupropion can cause tachycardia, agitation, and QRS and QTc prolongation. These cardiac effects are thought to result from a reduction in cardiac intracellular coupling caused by inhibition at gap junctions in the heart. Mortality results from not only status epilepticus but also the cardiac conduction disturbances causing ventricular tachycardia. Bupropion is of growing concern with the rising popularity of the drug, especially in the ER formulation. In addition to sedation and signs of serotonin excess, trazodone overdose may be associated with hypotension from blockade of peripheral α-receptors.

Treatment.

Management is directed to clinical signs and symptoms. QRS and QTc interval prolongation after bupropion poisoning is typically resistant to the standard treatments of sodium bicarbonate and magnesium. Seizures are often brief and self-limited but can be treated with benzodiazepines if necessary. A patient poisoned with bupropion who shows unstable hemodynamics with prolonged ECG intervals or persistent seizure activity should receive Intralipid emulsion therapy. Because of the potential for delayed seizures, asymptomatic patients who have ingested an SR preparation of bupropion should be admitted to a monitored setting for at least 20-24 hr. Trazodone-associated hypotension typically responds to fluids, though it can require vasopressors in extreme cases.

Monoamine Oxidase Inhibitors.

Although now rarely used therapeutically, MAOIs remain important agents given their potential for serious and delayed toxicity. Ingestions of only 1 or 2 pills (6 mg/kg) are associated with toxicity in children. Clinical manifestations initially include hypertension, hyperthermia, tachycardia, muscle rigidity, and seizures, followed up to 24 hr later by hemodynamic instability and CV collapse. *Any child who ingests a MAOI should be admitted to a monitored setting for at least 24 hr, regardless of symptoms.* Management includes blood pressure control, cooling and benzodiazepines for hyperthermia, serial monitoring of CK and renal function, and fluid and vasopressor therapy for hemodynamic instability.

Psychiatric Medications: Antipsychotics

Clinicians are increasingly prescribing antipsychotic medications in the pediatric population. Antipsychotics are usually classified as either typical or atypical. In general, typical agents are associated with more side effects and toxicity than the atypical agents.

Pathophysiology.

Typical or “traditional” antipsychotics (haloperidol, droperidol, thioridazine, chlorpromazine, fluphenazine) are characterized by their antagonism at D_2 dopamine receptors. In therapeutic use, these agents are associated with extrapyramidal symptoms, tardive dyskinesia, and development of the **neuroleptic malignant syndrome (NMS)** . The *atypical* agents (aripiprazole, clozapine, quetiapine, risperidone, ziprasidone) were developed with relatively less dopamine (D_2 -receptor) antagonism in the nigrostriatum in an effort to avoid these side effects and improve their efficacy in managing the “negative” symptoms of schizophrenia. Instead, these agents have complex and varied interactions with multiple receptor types, including α-receptors, serotonin receptors, muscarinic acetylcholine receptors, and histamine receptors.

Clinical and Laboratory Manifestations.

Typical antipsychotic toxicity usually includes sedation, tachycardia, and QTc prolongation. Patients can present with acute dystonia, akathisia, and NMS, although these are seen less frequently in acute overdoses than in therapeutic use. The phenothiazines (e.g., thioridazine) can cause widening of the QRS interval from blockade of fast sodium channels. Clinically, NMS can be difficult to distinguish from serotonin syndrome.

Although the presentation of atypical antipsychotic toxicity can vary based on the receptor affinities of the specific agent, sedation, tachycardia, and QTc prolongation are common. Peripheral α-receptor blockade (e.g., with quetiapine) is associated with hypotension. In therapeutic use, clozapine is associated with agranulocytosis.

Diagnostic testing should include an ECG. Patients with hyperthermia or muscle rigidity should have a serum CK level sent to monitor for possible rhabdomyolysis. Antipsychotic levels are not readily available and are not helpful in managing acute poisoning.

Management.

Initial management involves assessing and supporting vital functions. In some patients, CNS depression may be so profound as to require intubation for airway control. Acute dystonia is treated with diphenhydramine and benztropine. Management of NMS includes conscientious supportive care, IV fluids, cooling, benzodiazepines, and bromocriptine or dantrolene in severe cases. QTc prolongation is managed with repletion of electrolytes (especially calcium, magnesium, and potassium), continuous cardiac monitoring, prevention of bradycardia (overdrive pacing, isoproterenol, atropine), and defibrillation if the patient develops torsades de pointes. Seizures typically are well controlled with benzodiazepines. Hypotension usually responds to boluses of IV fluids, although vasopressor therapy is necessary in some patients.

Household Products

Caustics

Caustics include acids and alkalis as well as a few common oxidizing agents (see Chapter 353). Strong acids and alkalis can produce severe injury even in small-volume ingestions.

Pathophysiology.

Alkalis produce a *liquefaction necrosis*, allowing further tissue penetration of the toxin and setting the stage for possible perforation. **Acids** produce a *coagulative necrosis,* which limits further tissue penetration, although perforation can still occur. The severity of the corrosive injury depends on the pH and concentration of the product as well as the length of contact time with the product. Agents with a pH of <2 or >12 are most likely to produce significant injury.

Clinical Manifestations.

Ingestion of caustic materials can produce injury to the oral mucosa, posterior pharynx, vocal cords, esophagus, and stomach. Patients can have significant esophageal injury even in the absence of visible oral burns. Symptoms include pain, drooling, vomiting, abdominal pain, and difficulty swallowing or refusal to swallow. Laryngeal injury can manifest as stridor and respiratory distress, necessitating intubation. In the most severe cases, patients can present in shock after perforation of a hollow viscus. Circumferential burns of the esophagus are likely to cause strictures when they heal, which can require repeated dilation or surgical correction and long-term follow-up for neoplastic changes in adulthood. Caustics on the skin or in the eye can cause significant tissue damage.

Treatment.

Initial treatment of caustic exposures includes thorough removal of the product from the skin or eye by flushing with water. *Emesis and lavage are contraindicated* . Activated charcoal should not be used because it does not bind these agents and can predispose the patient to vomiting and subsequent aspiration. Stridor or other signs of respiratory distress should alert the provider to the need for a thorough evaluation of the airway for potential intubation or surgical airway management. Endoscopy can be performed within 12-24 hr of ingestion for prognostic and diagnostic purposes in symptomatic patients or those with suspected injury on the basis of history and known characteristics of the ingested product. Endoscopy's role is purely diagnostic. Whether the risks of the procedure are justified is debatable. Expectant management with a period of nothing by mouth (NPO) and proton pump inhibitor therapy is likely appropriate for the majority of patients *without* airway burns or signs of mediastinitis or peritonitis. Endoscopy is contraindicated in such patients, who instead require immediate surgical consultation. Corticosteroids or prophylactic antibiotics are not beneficial.

Pesticides

Cholinesterase-Inhibiting Insecticides.

The most commonly used insecticides in agriculture are **organophosphates** and **carbamates** ; both are inhibitors of cholinesterase enzymes: acetylcholinesterase (AChE), pseudocholinesterase, and erythrocyte AChE. Most pediatric poisonings occur as the result of unintentional exposure to insecticides in and around the home or farm. The chemical warfare weapons known as “nerve agents” are also organophosphate compounds with a similar mechanism of action but much greater potency.

Pathophysiology.

Organophosphates and carbamates produce toxicity by binding to and inhibiting AChE, preventing the degradation of acetylcholine (ACh) and resulting in its accumulation at nerve synapses. If left untreated, organophosphates form an irreversible bond to AChE, permanently inactivating the enzyme. This process, called *aging* , occurs over a variable time period depending on the characteristics of the specific organophosphate. A period of weeks to months is required to regenerate inactivated enzymes. In contrast, carbamates form a temporary bond to the enzymes, typically allowing reactivation of AChE within 24 hr.

Clinical and Laboratory Manifestations.

Clinical manifestations of organophosphate and carbamate toxicity relate to ACh accumulation at peripheral nicotinic and muscarinic synapses and in the CNS. Symptoms of carbamate toxicity are usually less severe than those seen with organophosphates. A commonly used mnemonic for the symptoms of cholinergic excess at muscarinic receptors is **DUMBBELS** : diarrhea/defecation, urination, miosis, bronchorrhea/bronchospasm, bradycardia, emesis, lacrimation, and salivation. Nicotinic signs and symptoms include muscle weakness, fasciculation, tremors, hypoventilation (diaphragm weakness), hypertension, tachycardia, and dysrhythmias. Severe manifestations include coma, seizures, shock, arrhythmias, and respiratory failure.

Diagnosis of poisoning is based primarily on history and physical exam findings. Red blood cell cholinesterase and pseudocholinesterase activity levels can be measured in the laboratory. These are only helpful when compared to the patient's known baseline. As such, these assessments are typically limited to farmworkers undergoing ongoing occupational surveillance.

Treatment.

Basic decontamination should be performed, including washing all exposed skin with soap and water and immediately removing all exposed clothing. Activated charcoal is unlikely to be of benefit because these are liquids that are rapidly absorbed. Basic supportive care should be provided, including fluid and electrolyte replacement, intubation, and ventilation if necessary. The use of succinylcholine for rapid sequence intubation should be avoided because the same cholinesterase enzymes that are poisoned metabolize this neuromuscular blocking agent, leading to prolonged paralysis.

Two antidotes are useful in treating cholinesterase inhibitor poisoning: atropine and pralidoxime (see Table 77.7). **Atropine** , which antagonizes the muscarinic ACh receptor, is useful for both organophosphate and carbamate intoxication. Often, large doses of atropine must be administered by intermittent bolus or continuous infusion to control symptoms. Atropine dosing is primarily targeted to drying the respiratory secretions. **Pralidoxime** breaks the bond between the organophosphate and the enzyme, reactivating AChE. Pralidoxime is only effective if it is used before the bond ages and becomes permanent. Pralidoxime is not necessary for carbamate poisonings because the bond between the insecticide and the enzyme degrades spontaneously.

Without treatment, symptoms of organophosphate poisoning can persist for weeks, requiring continuous supportive care. Even with treatment, some patients develop a delayed polyneuropathy and a range of chronic neuropsychiatric symptoms.

Pyrethrins and Pyrethroids.

Pyrethrins are derived from the chrysanthemum flower and along with pyrethroids, synthetic derivatives, are the most commonly used pesticides in the home. Although >1,000 pyrethrins and pyrethroids exist, <20 are available in the United States, with **permethrin** being the most common. Exposure to these compounds occurs by inhalation, dermal absorption, or ingestion. Ingestion is the predominant route and typically occurs by eating contaminated foods. Permethrin is also a prescribed medication for the treatment of scabies and lice.

Pathophysiology.

Pyrethrins and pyrethroids prolong the open state of the voltage-gated Na^+ channel conduction, which is the main mechanism resulting in its pesticide activity. Pyrethrins have minimal toxicity in mammals because of rapid metabolism, higher affinity for the insect Na^+ channel, and decreased activity at higher temperatures seen in warm-blooded animals. Since pyrethroids were specifically manufactured to be more stable in the environment, they have a higher likelihood of toxicity.

Clinical and Laboratory Manifestations.

Pyrethrin exposures can lead to allergic reactions ranging from dermatitis to urticaria to anaphylaxis. Acute exposure can result in headache, nausea, dizziness, tremors, ataxia, choreoathetosis, loss of consciousness, and seizures. The severity of the symptoms depends on the magnitude of the exposure. Reports of acute lung injury have also occurred after pyrethroid exposures, although this is likely from the other components of the insecticide, such as surfactants and solvents. Paresthesias limited to the cutaneous exposure area can also occur following a dermal exposure. Chronic exposures have not been shown to result in any clinical manifestations. Although one can test for urinary pyrethroid metabolites, this is only useful for monitoring occupational exposure and has no role for the acute exposure.

Treatment.

Initial treatment should focus on decontamination, which involves removing all clothing and irrigation of exposed areas. Allergic reactions are treated the same as for antihistamines and corticosteroids. Systemic toxicity should be treated with excellent supportive care, using benzodiazepines for tremors and seizures.

Hydrocarbons

Hydrocarbons include a wide array of chemical substances found in thousands of commercial products. Specific characteristics of each product determine whether exposure will produce systemic toxicity, local toxicity, both, or neither. Nevertheless, aspiration of even small amounts of certain hydrocarbons can lead to serious, potentially life-threatening toxicity.

Pathophysiology.

The most important manifestation of hydrocarbon toxicity is *aspiration pneumonitis* through inactivation of the type II pneumocytes and resulting in surfactant deficiency (see Chapter 425). Aspiration usually occurs during coughing and gagging at the time of ingestion or vomiting after the attempted ingestion of an aliphatic hydrocarbon. The propensity of a hydrocarbon to cause aspiration pneumonitis is inversely proportional to its viscosity, and directly proportional to its volatility. Compounds with low viscosity and high volatility, such as mineral spirits, naphtha, kerosene, gasoline, and lamp oil, spread rapidly across surfaces and cover large areas of the lungs when aspirated. Only small quantities (<1 mL) of such chemicals need be aspirated to produce significant injury. Pneumonitis does not result from dermal absorption of hydrocarbons or from ingestion in the absence of aspiration. Gasoline and kerosene are poorly absorbed, but they often cause considerable irritation of the GI mucosa as they pass through the intestines.

Certain hydrocarbons have unique toxicities and can cause symptoms after ingestion, inhalation, or dermal exposures. Several chlorinated solvents, most notably carbon tetrachloride, can produce hepatic toxicity. **Methylene chloride** , found in some paint removers, is metabolized to carbon monoxide. **Benzene** is known to cause cancer, most often acute myelogenous leukemia, after long-term exposure. Nitrobenzene, aniline, and related compounds can produce methemoglobinemia. A number of **volatile** hydrocarbons, including toluene, propellants, refrigerants, and volatile nitrites, are frequently abused by inhalation. Some of these substances, principally the **halogenated** hydrocarbons (which contain a chlorine, bromine, or fluorine), can sensitize the myocardium to the effects of endogenous catecholamines. This can result in dysrhythmias and "sudden sniffing death." Chronic abuse of these agents can lead to cerebral atrophy, neuropsychologic changes, peripheral neuropathy, and kidney disease (see Chapter 140).

Clinical and Laboratory Manifestations.

Transient, mild CNS depression is common after hydrocarbon ingestion or inhalation. Aspiration is characterized by coughing, which usually is the 1st clinical finding. Chest radiographs may initially be normal, but they often show abnormalities within 6 hr of exposure in patients who have aspirated. Respiratory symptoms can remain mild or progress rapidly to acute respiratory distress syndrome (ARDS) and respiratory failure. Fever and leukocytosis are common accompanying signs in patients with pneumonitis and do not necessarily imply bacterial superinfection. Chest radiographs can remain abnormal long after the patient is clinically normal. Pneumatoceles can appear on the chest radiograph 2-3 wk after exposure.

After inhalational exposures to halogenated hydrocarbons, patients can present with ventricular dysrhythmias, often refractory to conventional management. Recurrent inhalation of the aromatic hydrocarbon **toluene** can lead to a type IV renal tubular acidosis.

Treatment.

Emesis and lavage are contraindicated given the risk of aspiration . Activated charcoal is not useful because it does not bind the common hydrocarbons and can also induce vomiting. If hydrocarbon-induced pneumonitis develops, respiratory treatment is supportive (see Chapter 425). Neither corticosteroids nor prophylactic antibiotics have shown any clear benefit. Standard mechanical ventilation, high-frequency ventilation, and extracorporeal membrane oxygenation (ECMO) have all been used to manage the respiratory failure and ARDS associated with severe hydrocarbon-induced pneumonitis.

Patients with dysrhythmias in the setting of halogenated hydrocarbon inhalation should be treated with β-blockers (usually esmolol) to block the effects of endogenous catecholamines on the sensitized myocardium.

Toxic Alcohols

Methanol is found in windshield washer fluids, deicers, paint removers, fuel additives, liquid fuel canisters, and industrial solvents. **Ethylene glycol** is found in antifreeze. Unintentional ingestion is the most common exposure in children, and small-volume ingestions of concentrated products can theoretically cause toxicity. The pathophysiology, acid-base derangements, and treatment of both chemicals are similar, although they differ in their primary end-organ toxicity. In both cases the metabolites of the parent compounds are responsible for the serious clinical effects that can follow exposure.

Isopropyl alcohol (rubbing alcohol), found in hand sanitizers, causes intoxication similar to that associated with ethanol but can also cause a hemorrhagic gastritis and myocardial depression in massive ingestions. Unlike ethylene glycol and methanol, isopropyl alcohol is metabolized to a ketone and does not cause a metabolic acidosis. Management is similar to that of ethanol ingestions (see Chapter 140) and is not further discussed here.

Methanol

Pathophysiology.

Methanol is oxidized in the liver by alcohol dehydrogenase to formaldehyde, which is further oxidized to formic acid by aldehyde dehydrogenase. Toxicity is caused primarily by formic acid, which inhibits mitochondrial respiration.

Clinical and Laboratory Manifestations.

Drowsiness, mild inebriation, nausea, and vomiting develop early after methanol ingestion. The onset of serious effects, including profound metabolic acidosis and visual disturbances, is often delayed up to 12-24 hr as the parent methanol undergoes metabolism to its toxic metabolites. This metabolism is further slowed if *ethanol* has also been ingested, since the liver will preferentially metabolize ethanol. Visual disturbances include blurred or cloudy vision, constricted visual fields, decreased acuity, and the “feeling of being in a snowstorm” and appear only after acidosis is well established. These visual defects may be reversible if treated early, but untreated can lead to permanent blindness. On examination, dilated pupils, retinal edema, and optic disc hyperemia may be noted. Initially, patients have an elevated osmolar gap, then develop an anion gap metabolic acidosis as the parent compound is metabolized to formic acid.

In young children, determining if a significant exposure has occurred is usually difficult based on history. Methanol blood levels are available at some laboratories and should be sent after a concerning exposure. If methanol blood levels are not readily available, estimation of an osmolar gap may be used as a surrogate marker, but a normal osmolar gap does not rule out ingestion of any alcohol. Serum osmolality is measured by the freezing-point depression method and compared with a calculated serum osmolarity.

Treatment.

Treatment is as discussed for ethylene glycol toxicity.

Ethylene Glycol

Pathophysiology.

Ethylene glycol is oxidized by alcohol dehydrogenase in the liver to glycolaldehyde, which is further converted to glycolic acid by aldehyde dehydrogenase. Glycolic acid is responsible for the metabolic acidosis and is further metabolized to glyoxylic and then to oxalic acid. Oxalic acid combines with serum and tissue calcium, forming calcium oxalate crystals that deposit throughout the body, especially in the renal parenchyma, leading to acute tubular necrosis.

Clinical and Laboratory Manifestations.

Early symptoms include nausea, vomiting, CNS depression, and inebriation. Delayed manifestations include an anion gap metabolic acidosis, hypocalcemia, and acute kidney injury. Even later, patients can develop cranial nerve palsies.

Both ethylene glycol and methanol can produce profound, life threatening metabolic acidosis and acidemia, with measured serum bicarbonates that may even be nondetectable. The onset of the acidosis is delayed up to 4-12 hr after ethylene glycol ingestion and may be delayed further with any concomitant ingestion of ethanol. Ethylene glycol blood concentrations are technically difficult to perform and are available only at some larger reference laboratories. In the absence of readily available ethylene glycol concentrations, calculation of the osmolar gap may be helpful as a surrogate marker.

Examination of the urine with a Wood lamp is neither sensitive nor specific for ethylene glycol ingestion. The earliest sign on a urinalysis of ethylene glycol poisoning is usually hematuria. Calcium oxalate crystals can be seen on urine microscopy but might not be evident early after exposure. Electrolytes (including calcium), acid-base status, kidney function, and ECG should be closely monitored in poisoned patients.

Treatment.

Because methanol and ethylene glycol are rapidly absorbed, gastric decontamination is generally not of value. The classic antidote for methanol and ethylene glycol poisoning was ethanol, a preferential substrate for alcohol dehydrogenase, thus preventing the metabolism of parent compounds to toxic metabolites. **Fomepizole** , a potent competitive inhibitor of alcohol dehydrogenase, has almost entirely replaced ethanol because of its ease of administration, lack of CNS and metabolic effects, and overall excellent patient tolerability profile (see Table 77.7). A serum concentration must be interpreted along with the time removed from exposure. A patient with a methanol level of 20 mg/dL 24 hr after exposure had a much larger dose than a patient with the same level only 1 hr after ingestion. Classic indications for fomepizole include ethylene glycol or methanol level >20 mg/dL (assuming no ethanol is present), history of potentially toxic ingestion (e.g., any intentional overdose), or history of ingestion with evidence of acidosis. There are few disadvantages to giving the initial dose of fomepizole to patients with a concerning history of ingestion or lab findings, and given the dosing schedule of fomepizole (every 12 hr), this strategy buys the clinician time to confirm or exclude the diagnosis before giving a 2nd dose. Adjunctive therapy includes folate (methanol toxicity), pyridoxine (ethylene glycol toxicity), and sodium bicarbonate infusion for both (if acidemic). If a child has had an unintentional exposure and the alcohol level cannot be obtained, a reasonable approach is to follow serum chemistries every 4 hr until 12 hr after the exposure. If the bicarbonate level on the chemistry panel does not fall in that period, a toxic exposure is unlikely (assuming no ethanol is present).

Hemodialysis effectively removes ethylene glycol, methanol, and their metabolites (except calcium oxalate) and corrects acid-base and electrolyte disturbances. Fomepizole should be given both before and immediately after dialysis. Indications for dialysis include a methanol level >50 mg/dL, acidosis, severe electrolyte disturbances, and renal failure. However, in the absence of acidosis and kidney failure, even massive ethylene glycol ingestions have been managed without dialysis. Methanol, however, because its elimination in the setting of alcohol dehydrogenase inhibition is prolonged, often warrants dialysis to remove the parent compound. Therapy (fomepizole and/or dialysis) should be continued until ethylene glycol and methanol levels are <20 mg/dL. While the visual effects from methanol poisoning are usually permanent, the kidney injury from ethylene glycol injury is not. Patients requiring hemodialysis after ethylene glycol poisoning will almost always recover complete renal function within 2-6 wk. Consultation with a PCC, medical toxicologist, and nephrologist may be helpful in managing toxic alcohol ingestions.

Plants

Exposure to plants, both inside the home and outside in backyards and fields, is one of the most common causes of unintentional poisoning in children. Fortunately, the majority of ingestions of plant parts (leaves, seeds, flowers) result in either no toxicity or mild, self-limiting effects. However, ingestion of certain plants can lead to serious toxicity (Table 77.12).

Table 77.12

Commonly Ingested Plants With Significant Toxic Potential

PLANT	SYMPTOMS	MANAGEMENT
Autumn crocus (*Colchicum autumnale*)	Vomiting Diarrhea Initial leukocytosis followed by bone marrow failure Multisystem organ failure	Activated charcoal decontamination Aggressive fluid resuscitation and supportive care
Belladonna alkaloids: jimson weed (*Datura stramonium*) Belladonna (“deadly nightshade”; *Atropa belladonna*)	Anticholinergic toxidrome Seizures	Supportive care, benzodiazepines Consider physostigmine if patient is a threat to self or others; only use if no conduction delays on ECG
Cardiac glycoside–containing plants (foxglove, lily of the valley, oleander, yellow oleander, etc)	Nausea Vomiting Bradycardia Dysrhythmias (AV block, ventricular ectopy) Hyperkalemia	Digoxin-specific Fab fragments
Jequirity bean and other abrin-containing species (e.g., rosary pea, precatory bean)	Oral pain Vomiting Diarrhea Shock Hemolysis Renal failure	Supportive care, including aggressive volume resuscitation and correction of electrolyte abnormalities
Monkshood (*Aconitum* species)	Numbness and tingling of lips/tongue Vomiting Bradycardia	Atropine for bradycardia Supportive care
Oxalate-containing plants: *Philodendron, Dieffenbachia, Colocasia*	Local tissue injury Oral pain	Supportive care, pain control

(“elephant ear”)	Vomiting	
Poison hemlock *(Conium maculatum)*	Vomiting Agitation followed by CNS depression Paralysis Respiratory failure	Supportive care
Pokeweed	Hemorrhagic gastroenteritis Burning of mouth and throat	Supportive care
Rhododendron	Vomiting Diarrhea Bradycardia	Atropine for symptomatic bradycardia Supportive care
Tobacco	Vomiting Agitation Diaphoresis Fasciculations Seizures	Supportive care
Water hemlock (*Cicuta* species)	Abdominal pain Vomiting Delirium Seizures	Supportive care, including benzodiazepines for seizures
Yew (*Taxus* species)	GI symptoms QRS widening Hypotension CV collapse	Supportive care Atropine for bradycardia Sodium bicarbonate does not appear to be effective

AV, Atrioventricular; CNS, central nervous system; CV, cardiovascular; ECG, electrocardiogram; Fab, fragment, antigen binding; GI, gastrointestinal.

The potential toxicity of a particular plant is highly variable, depending on the part of the plant involved (flowers are generally less toxic than the root or seed), the time of year, growing conditions, and the route of exposure. Assessment of the potential severity after an exposure is also complicated by the difficulty in properly identifying the plant. Many plants are known by several common names, which can vary among communities. Poison control centers have access to professionals who can assist in properly identifying plants. They also are well versed in the common poisonous plants in their service area and the seasons when they are more abundant. For these reasons, consultation with the local PCC may be very helpful in the management of these ingestions.

For potentially toxic plant ingestions, consider decontamination with activated charcoal in patients who present within 1-2 hr of ingestion; otherwise, treatment is primarily supportive and based on symptoms. The most common manifestation of toxicity after plant ingestion is GI upset, which can be managed with antiemetics and fluid and electrolyte support. Table 77.12 outlines management strategies for a few specific toxicities.

Toxic Gases

Carbon Monoxide

Although many industrial and naturally occurring gases pose a health risk by inhalation, the most common gas involved in pediatric exposures is carbon monoxide. CO is a colorless, odorless gas produced during the combustion of any carbon-containing fuel; the less efficient the combustion, the greater the amount of CO produced. Wood-burning stoves, kerosene heaters, old furnaces, hot-water heaters, closed-space fires, and automobiles are a few of the potential sources of CO.

Pathophysiology.

CO binds to hemoglobin with an affinity >200 times that of oxygen, forming carboxyhemoglobin (HbCO). In doing so, CO displaces oxygen and creates a conformational change in hemoglobin that impairs the delivery of oxygen to the tissues, leading to tissue hypoxia. HbCO levels are not well correlated with clinical signs of toxicity, likely because CO interacts with multiple proteins in addition to hemoglobin. CO binds to cytochrome oxidase, disrupting cellular respiration. CO displaces nitric oxide (NO) from proteins, allowing NO to bind with free radicals to form the toxic metabolite peroxynitrite, leading to lipid peroxidation and cellular damage. NO is also a potent vasodilator, in part responsible for clinical symptoms such as headache, syncope, and hypotension.

Clinical and Laboratory Manifestations.

Early symptoms are nonspecific and include headache, malaise, nausea, and vomiting. These symptoms are often misdiagnosed as indicating flu or food poisoning. At higher exposure levels, patients can develop mental status changes, confusion, ataxia, syncope, tachycardia, and tachypnea. Severe poisoning is manifested by coma, seizures, myocardial ischemia, acidosis, cardiovascular collapse, and potentially death. Physical examination should focus on the cardiovascular and neurologic systems because these are the most detrimentally effected by CO. Emergency department evaluation should include arterial or venous blood gas analysis with HbCO determined by CO-oximetry, CK level in severely poisoned patients, pregnancy test, and ECG in any patient with cardiac symptoms.

Treatment.

Prevention of CO poisoning is paramount and should involve educational initiatives and the use of home CO detectors. Treatment of CO poisoning focuses on the administration of 100% oxygen to enhance elimination of CO. In ambient air the average half-life of HbCO is 4-6 hr. This is dramatically reduced to 60-90 min by providing 100% oxygen at normal atmospheric pressures by non-rebreather face mask. Severely poisoned patients might benefit from **hyperbaric oxygen (HBO)** , which decreases the half-life of HbCO to 20-30 min and is thought also to decrease the risk of delayed neurologic sequelae. Although the clinical benefits and referral guidelines for HBO therapy remain controversial, frequently cited indications include syncope, coma, seizure, altered mental status, acute coronary syndrome, HbCO level >25%, abnormal cerebellar examination, and pregnancy. Consultation with a PCC, medical toxicologist, or HBO facility can assist clinicians in determining which patients could benefit from HBO therapy. Sequelae of CO poisoning include persistent and delayed cognitive and cerebellar effects. HBO advocates believe that the risk of such sequelae is minimized through the delivery of 100% oxygen at 3 atm of pressure. Patients typically receive oxygen, by non-rebreather mask or hyperbaric chamber, for 6-24 hr.

Hydrogen Cyanide

Pathophysiology.

Cyanide inhibits cytochrome-*c* oxidase, part of the electron transport chain, interrupting cellular respiration and leading to profound tissue hypoxia. Patients may be exposed to hydrogen cyanide (HCN) gas in the workplace (manufacturing of synthetic fibers, nitriles, and plastics) or by smoke inhalation in a closed-space fire.

Clinical and Laboratory Manifestations.

Onset of symptoms is rapid after a significant exposure. Clinical manifestations of toxicity include headache, agitation/confusion, sudden loss of consciousness, tachycardia, cardiac dysrhythmias, and metabolic acidosis. Cyanide levels can be measured in whole blood but are not readily available at most institutions. A severe lactic acidosis (lactate >10 mmol/L) in fire victims suggests cyanide toxicity. Impaired oxygen extraction by tissues is implied by elevated mixed-venous oxyhemoglobin saturation, another laboratory finding suggesting cyanide toxicity.

Treatment.

Treatment includes removal from the source of exposure, rapid administration of high concentrations of oxygen, and antidotal therapy. The cyanide antidote kit (no longer manufactured) includes nitrites (amyl nitrite and sodium nitrite) used to produce methemoglobin, which then reacts with cyanide to form cyanomethemoglobin. The 3rd part of the kit is sodium thiosulfate, given to hasten the metabolism of cyanomethemoglobin to hemoglobin and the less toxic thiocyanate. In patients for whom induction of methemoglobinemia could produce more risk than benefit, the sodium thiosulfate component of the kit may be given alone.

The U.S. Food and Drug Administration (FDA) has approved **hydroxocobalamin** for use in known or suspected cyanide poisoning (see Table 77.7). This antidote reacts with cyanide to form the nontoxic cyanocobalamin (vitamin B_{12}), which is then excreted in urine. Side effects of hydroxocobalamin include red discoloration of the skin and urine, transient hypertension, and interference with colorimetric lab assays. *Hydroxocobalamin has an overall safety profile that appears superior to that of the cyanide antidote kit and thus is the preferred antidote for cyanide poisoning.*

Miscellaneous Toxic Agents Found in the Home

Nicotine-Containing Products

Nicotine poisoning has become increasingly common with the recent advent of vaporizer (“vaping”) and e-cigarette devices. Although there are many nicotine-containing products (patches, gums, snuff, chewing tobacco, sprays, lozenges), tobacco cigarettes remain the main source of exposure. Prescription medications (varenicline and cytisine) are available that are partial nicotine receptor agonists. For children, some of the most concerning exposures are from the bottles of liquid nicotine used to refill vaping and e-cigarette devices. These bottles typically do not have childproof caps and contain a large amount of concentrated nicotine.

Pathophysiology.

Nicotine acts on nicotinic ACh receptors in the nervous system, neuromuscular junctions, and adrenal medulla, stimulating neurotransmitter release. Nicotine's effects on the dopaminergic reward pathway play a significant role in its addictive properties. The effects of nicotine are dose dependent; at lower doses it primarily acts on the brain, causing stimulation. At higher doses, nicotine overstimulates receptors, leading to inhibition and resulting in neuromuscular and nervous system blockade.

Clinical and Laboratory Manifestations.

Clinical effects of nicotine also depend on the dose. At low doses typically achieved through smoking, nicotine results in cognitive and mood enhancement, increased energy, and appetite suppression. At higher doses, significant toxicity follows a biphasic pattern, where cholinergic stimulation symptoms predominate and are later followed by inhibition. The first signs of nicotine poisoning are nausea, vomiting, diarrhea, and often muscle fasciculations. Tachycardia and hypertension occur initially, although in severe poisoning these progress to bradycardia, hypotension, coma, and respiratory muscle failure, which typically leads to death if not treated. Serum and urinary levels of nicotine and its metabolite cotinine can be obtained, but these rarely are available in real time and therefore have little effect on diagnosis and management.

Treatment.

Treatment of nicotine poisoning focuses on maximizing symptomatic and supportive care. Aggressive airway management should be the priority, especially in severe poisonings, because death usually occurs from respiratory muscle paralysis. IV fluids with escalation to vasopressors should be used for hypotension. Seizures should be managed with benzodiazepines, barbiturates, or propofol.

Single-Use Detergent Sacs

Commonly known as laundry “pods” for clothing, these products resemble candy to many children. When bitten into, a relatively large dose of concentrated detergent is expelled under pressure onto the posterior pharynx and vocal cords. This can lead to stridor and other signs of respiratory distress. Occasionally, and for unknown reasons, these children may also develop altered mental status. Supportive care with attention to any airway and breathing issues is warranted. Admission to the hospital is often indicated. Importantly, these are not considered caustic ingestions; the pH of these products is in the neutral zone. As such, upper GI endoscopy is rarely indicated. Curiously, laundry detergent drank from a bottle is rarely of significant concern.

Electric Dishwasher Detergent

Especially when in the form of crystals, these products are highly alkaline (pH >13), and exposure by ingestion can cause significant burns to the vocal cords and GI tract. Admission for expectant management or upper GI endoscopy is usually indicated.

Magnets

Most foreign body ingestions pass through the GI tract once known to have passed into the stomach. However, ingestion of ≥2 magnets (unless very weak refrigerator-style magnets) cause concern for bowel obstruction and perforation. Admission for attempted retrieval by endoscopy or clearance by WBI should be considered.

Batteries

Any disk or button-style battery lodged in the esophagus or airway should be considered a true emergency warranting immediate referral to an endoscopist for removal. These batteries can cause necrosis of the tissues in which they are lodged by continued electrical discharge and leaking of their contents (the former is likely the primary method of injury). Mucosal contact for even 2 hr might induce necrosis. Once past the lower esophageal sphincter, button or even larger batteries (e.g., AA, AAA) can usually be allowed to pass through the GI tract with close follow-up.

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CHAPTER 78

Complementary Therapies and Integrative Medicine

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Integrative medicine focuses on promoting physical, mental, emotional, spiritual, social, and educational well-being in the context of a medical home in a healthy family and community. The foundations of integrative medicine are health-promoting practices such as optimal nutrition and dietary supplements to prevent deficiencies, avoidance of addictive substances (e.g., nicotine, illicit drugs), physical activity, adequate sleep, a healthy environment, and supportive social relationships. Evidence-based **complementary therapies** such as dietary supplements, massage, chiropractic, other forms of bodywork, yoga, meditation practices, hypnosis, guided imagery, biofeedback, and acupuncture may also be used. Although prayer and healing rituals are sometimes included under the rubric of complementary and integrative therapies, they are not covered in this chapter.

Not including multivitamins and mineral supplements such as iron and calcium, an estimated 10–40% of healthy children and >50% of children with chronic conditions use integrative medicine in the United States. The prevalence could be even higher because these treatments usually occur without disclosure to the children's primary care physician. Common therapies include dietary supplements, deep breathing, guided imagery, mediation, biofeedback, hypnosis, yoga, acupuncture, massage, and aromatherapy.

Use of complementary therapies is most common among youth with chronic, incurable, or recurrent conditions such as cancer, depression and other mental health conditions, asthma, autism, headaches, abdominal pain, and other chronic painful conditions. Children's hospitals and pediatric subspecialty programs are increasingly offering integrative medicine strategies alongside traditional medicine, as part of the care of children in both inpatient and outpatient settings.

In a 2014 survey the American Pain Society identified 48 pediatric chronic pain clinics, with most offering some type of integrative medicine or behavioral health strategies with conventional medicine. For example, integrative therapies are increasingly being used in pediatric chronic pain clinics to treat functional bowel disorders. Recent reviews include supplements (e.g., ginger, peppermint oil) and mind-body techniques (e.g., hypnotherapy, biofeedback, acupuncture/acupressure) with traditional medical management for these common pediatric conditions.

Dietary Supplements

Under the 1994 U.S. Dietary Supplement Health and Education Act, a **dietary supplement** is a product taken by mouth that contains a *dietary ingredient* intended to supplement the diet. These may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glands, and metabolites. Dietary supplements are the most frequently used complementary therapies for children and adolescents (Table 78.1). Some uses are common and recommended, such as vitamin D supplements for breastfed infants and probiotics to prevent antibiotic-associated diarrhea, whereas other uses are more controversial, such as using herbal products to treat otitis media.

Table 78.1

Commonly Used Dietary Supplements in Pediatrics

PRODUCT	**USES**
VITAMINS	
B_2 (riboflavin)	Migraine headache prophylaxis
B_6 (pyridoxine)	Pyridoxine-dependent epilepsy; neuropathy; nausea associated with pregnancy
B_9 (folate)	Prevention of neural tube defects
D	Prevention of rickets; treatment of vitamin D deficiencies
Multivitamins	General health promotion
MINERALS	
Iodine (salt)	Prevent goiter and mental retardation
Iron	Prevent and treat iron-deficiency anemia
Magnesium	Constipation, asthma, migraine prevention
Zinc	Diarrhea in nutrient-poor populations
HERBS	
Aloe vera	Mild burns
Chamomile	Mild sedative, dyspepsia
Echinacea	Prevention of upper respiratory infections

Ginger	Nausea
Lavender (aromatherapy)	Mild sedative
Peppermint	Irritable bowel syndrome
Tea tree oil	Antibacterial (acne remedies), pediculicide (lice)
OTHER	
Melatonin	Insomnia
Omega-3 fatty acids	ADHD, allergies, inflammation, anxiety and mood disorders
Probiotics	Antibiotic-associated diarrhea; *Clostridium difficile* –associated diarrhea; constipation; irritable bowel syndrome; pouchitis; inflammatory bowel disorders

ADHD, Attention-deficit/hyperactivity disorder.

In the United States, dietary supplements do not undergo the same stringent evaluation and postmarketing surveillance as prescription medications. Although they may not claim to prevent or treat specific medical conditions, product labels may make *structure-function* claims. For example, a label may claim that a product “promotes a healthy immune system,” but it may not claim to cure the common cold.

According to the 2012 National Health Interview Survey, 5% of U.S. children used non-vitamin/mineral dietary supplements. (e.g., fish oil, melatonin, prebiotics, probiotics) Use of dietary supplements is most common among children whose families have higher income and education and whose parents use supplements, among older children, and among those with chronic conditions.

Despite this widespread use, many patients and their parents who use dietary supplements do not talk with their physician about their use. Several guidelines have called for more complete dietary supplement history taking by healthcare professionals. The Joint Commission recommends that clinicians routinely ask patients about their use of dietary supplements and include this information as part of the medication reconciliation process.

Dietary Supplement Safety

Dietary supplements may have safety issues in children, but toxicity is much less common with nonprescription dietary supplements than with prescription medications (Table 78.2). Toxicity depends on dose, use of other therapies, and the child's underlying medical condition. Current use of a dietary supplement (e.g., ephedra for weight loss) may not reflect its traditional use (e.g., ephedra as a component of a traditional Chinese medicine tea in small doses to improve allergic or respiratory symptoms). Moreover, herbs that are apparently safe for most adults may be more hazardous in specific conditions (e.g., newborns, patients with impaired renal or hepatic function), under special circumstances (e.g., after organ transplantation or other surgery), or when combined with prescription medications. Some natural products are toxic in and of themselves. Even when a product is safe when used correctly, it can cause mild or severe toxicity when used incorrectly. For example, although peppermint is a commonly used and usually benign gastrointestinal spasmolytic included in after-dinner mints, it can exacerbate gastroesophageal reflux.

Table 78.2

Clinical Toxicity of Selected Herbs

COMMON NAME	BOTANICAL NAME	THERAPEUTIC USES	POTENTIAL TOXICITY
Aconite (monkshood, wolfsbane)	*Aconitum* spp.	Sedative, analgesic, antihypertensive	Cardiac arrhythmias
Aloe	*Aloe* spp.	Burns, skin diseases	Nephritis, GI upset
Betel nut	*Areca catechu*	Mood elevation	Bronchoconstriction, oral cancers
Bloodroot	*Sanguinaria canadensis*	Emetic, cathartic, eczema	GI upset, vertigo, visual disturbances
Chaparral (greasewood)	*Larrea tridentata*	Aging, free radical scavenging	Hepatitis
Compound Q	*Trichosanthes kirilowii*	Anthelmintic, cathartic	Diarrhea, hypoglycemia, CNS toxicity
Dandelion	*Taraxacum officinale*	Diuretic, heartburn remedy	Anaphylaxis
Figwort (xuan shen)	*Scrophularia* spp.	Antiinflammatory, antibacterial	Cardiac stimulation
Ginseng	*Panax quinquefolium*	Antihypertensive, aphrodisiac, stimulant, mood elevation, digestive aid	Ginseng abuse syndrome
Goldenseal	*Hydrastis canadensis*	Digestive aid, mucolytic, anti-infective	Uterine, cardiac stimulation; GI upset, leukopenia
Hellebore	*Veratrum* spp.	Antihypertensive	Vomiting, bradycardia, hypotension
Hyssop	*Hyssopus officinalis*	Asthma, mucolytic	Seizures
Juniper	*Juniperus communis*	Hallucinogen	GI upset, seizures, renal injury, hypotension, bradycardia
Kava kava	*Piper methysticum*	Sedative	Inebriation
Kombucha		Stimulant	Metabolic acidosis, hepatotoxicity, death
Licorice	*Glycyrrhiza* spp.	Indigestion	Mineralocorticoid effects
Lily of the valley	*Convallaria* spp.	Cardiotonic	GI (nausea, vomiting), cardiac arrhythmias
Linn (willow)	*Salix caprea*	Purgative	Hemolysis with glucose-6-phosphate dehydrogenase

			deficiency
Lobelia (Indian tobacco)	*Lobelia* spp.	Stimulant	Nicotine intoxication
Ma Huang	*Ephedra sinica*	Stimulant	Sympathetic crisis, especially with monamine oxidase inhibitors
Mandrake	*Mandragora officinarum*	Hallucinogen	Anticholinergic syndrome
Mormon tea	*Ephedra nevadensis*	Stimulant, asthma, antipyretic	Hypertension, sympathomimetic
Nutmeg	*Myristica fragrans*	Hallucinogen, abortifacient	Hallucinations, GI upset
Oleander	*Nerium oleander*	Cardiac stimulant	Cardiac arrhythmias
Passionflower	*Passiflora caeruliea*	Hallucinogen	Hallucinations, seizures, hypotension
Periwinkle	*Vinca* spp.	Antiinflammatory, diabetes	Alopecia, seizures, hepatotoxicity
Pokeweed	*Phytolacca* spp.	Arthritis, chronic pain	GI upset, seizures, death
Sabah	*Sauropus androgynus*	Weight loss, vision	Pulmonary injury
Sage	*Salvia* spp.	CNS stimulant	Seizures
Snakeroot	*Rauwolfia serpentina*	Sedative, antihypertensive	Bradycardia, coma
Squill	*Urginea maritima*	Arthritis, cardiac stimulant	Seizures, arrhythmias, death
Thorn apple (jimsonweed)	*Datura stramonium*	Hallucinations	Anticholinergic
Tonka bean	*Dipteryx odorata*	Anticoagulant	Bleeding diathesis
Valerian root	*Valeriana* spp.	Sedative	Sedation, obtundation
Wild (squirting) cucumber	*Ecballium elaterium*	Constipation, antiinflammatory, rheumatic disease	Airway obstruction
Wormwood (mugwort)	*Artemisia* spp.	Stimulant, hallucinogen	Hallucinations, seizures, uterine stimulation
Yohimbine	*Corynanthe yohimbe*	Aphrodisiac, stimulant	Hypertension, sympathetic crisis

CNS, Central nervous system; GI, gastrointestinal.

From Kingston RL, Foley C: Herbal, traditional, and alternative medicines. In *Haddad and Winchester's clinical management of poisoning and drug overdose,* ed 4, Philadelphia, 2007, Saunders/Elsevier, p 1081.

Although there are good manufacturing practices for dietary supplements in the United States, dietary supplement labels might not accurately reflect the contents or concentrations of ingredients. Because of natural variability, variations of 10-1,000–fold have been reported for several popular herbs, even across lots produced by the same manufacturer. Herbal products may be contaminated with pesticides, microbial agents or products, or the wrong herb misidentified during harvesting. Products from developing countries (e.g., Ayurvedic products from South Asia) might contain toxic levels of mercury, cadmium, arsenic, or lead, either from unintentional contamination during manufacturing or from intentional additions by producers who believe that these metals have therapeutic value. Approximately 30–40% of Asian patent medicines include potent pharmaceuticals, such as analgesics, antibiotics, hypoglycemic agents, or corticosteroids; typically the labels for these products are not written in English and do not note the inclusion of pharmaceutical agents. Even conventional mineral supplements, such as calcium, have been contaminated with lead or had significant problems with product variability.

Many families use supplements concurrently with medications, posing hazards of interactions (Table 78.3). Using the same principles of drug-drug interactions can help determine if a supplement-drug interaction is a concern. For example, St. John's wort induces CYP3A4 activity of the cytochrome P450 enzyme system and thus can enhance elimination of most drugs that use this pathway, including digoxin, cyclosporine, protease inhibitors, oral contraceptives, and numerous antibiotics, leading to subtherapeutic serum levels.

Table 78.3

Common Herbal Dietary Supplement (HDS)–Drug Interactions

HDS	DRUGS	POTENTIAL CONSEQUENCES/REACTIONS
Aloe vera	Glibenclamide (glyburide)	↑ Oral aloe vera gel can cause additive glycemic-lowering effects when taken concurrently with a hypoglycemic agent.
Bitter orange	Phenelzine	↑ Risk of hypertensive crisis
Garlic	Ritonavir	↓ Effect of ritonavir
	Saquinavir	↓ Effect of saquinavir
Licorice	Warfarin	↑ Risk of bleeding
Grapefruit	Calcium channel blockers	Grapefruit juice has been found to increase bioavailability of certain drugs by inhibition of cytochrome P450 (CYP) 3A4 isozyme in liver and gut wall.
Melatonin	Zolpidem	↑ Sedative effects
Valerian	Alprazolam, phenobarbital	↑ Central nervous system depression
Goldenseal	Inhibition of CYP2D6 and CYP3A4	May affect approximately 50% of common pharmaceutical agents
St. John's wort	Cyclosporine, tacrolimus, warfarin, protease inhibitors, digoxin, theophylline, venlafaxine, oral contraceptives	May decrease drug effectiveness

↓, Decreasing; ↑, increasing.

Dietary Supplement Efficacy

Evidence about the effectiveness of dietary supplements to prevent or treat pediatric problems is mixed, depending on the product used and condition treated. Some herbal products may be helpful adjunctive treatments for common childhood problems; some herbs have proved helpful for colic (fennel and the combination of chamomile, fennel, vervain, licorice, and balm mint), nausea (ginger), irritable bowel syndrome (peppermint), and diarrhea (probiotics).

Massage and Chiropractic

Massage is usually provided at home by parents and in clinical settings by professional massage therapists, physical therapists, and nurses. **Infant massage** is routinely provided in many neonatal intensive care units to promote growth and development in preterm infants. Massage also has been demonstrated to be beneficial for pediatric patients with asthma, insomnia, colic, cystic fibrosis, or juvenile arthritis and patients undergoing cancer therapy. **Massage therapy** is generally safe. Professional massage practice is regulated by state government and may be in the form of a license, registration, or certification. More than 40 states license massage therapists, with licensure being the strictest form of regulation, making it illegal for any nonlicensed professional to practice massage therapy.

Chiropractic healthcare deals with the diagnosis, treatment, and prevention of disorders of the neuromusculoskeletal system and their effects on general health. Currently, >60,000 chiropractors have licensure in the United States, with licensure in all 50 states. Most medical insurance companies cover chiropractic funding. Children and families seek chiropractic care for common childhood conditions such as asthma, infantile colic, nocturnal enuresis, constipation, and headache. A recent consensus update on chiropractic care in children overall found limited support in a small number of high-quality studies for effectiveness of chiropractic care for such common childhood conditions. With respect to safety, the evidence is also limited; however, published cases of serious adverse events in infants and children receiving chiropractic care are rare. If children and families are seeking chiropractic care, it is appropriately done in collaboration with the child's pediatric primary care provider to ensure patient safety.

Mind-Body Therapies

Mind-body therapies such as slow, deep breathing, meditation, guided imagery, biofeedback, hypnosis, tai chi, and yoga are also frequently used complementary therapies in pediatrics. These practices can be learned informally through books, YouTube videos, compact discs, digital video discs, smartphone apps, or classes, as well as in therapeutic sessions with health professionals, such as psychologists and social workers (Table 78.4). Substantial research suggests that such practices can aid in reducing anxiety, insomnia, and stress-related conditions, including migraine headaches and functional abdominal pain. These therapies can also help patients struggling with chronic pain.

Table 78.4

Commonly Used Mind-Body Practices in Pediatrics

PRACTICE	USES
Biofeedback	Preventing migraine headaches; reducing stress and anxiety; encopresis/constipation treatment; treatment of stress incontinence; neurofeedback is experimental for ADHD.
Deep breathing	Relaxation; stress management
Guided imagery	Stress management; anxiety reduction; pain relief
Hypnosis	Correcting habit disorders; preventing headaches; managing pain
Meditation	Stress management; improving concentration
Tai chi	Improving balance, coordination, concentration, and discipline
Yoga	Improving balance, coordination, and concentration

ADHD, Attention-deficit/hyperactivity disorder.

Acupuncture

Modern acupuncture incorporates treatment traditions from China, Japan, Korea, France, and other countries. In the United States, acupuncturists are licensed to practice in 45 states. Acupuncture can be delivered to pediatric patients in hospital and clinic settings to treat a variety of ailments. Acupuncture is particularly useful for children experiencing pain, and acupuncture services are offered alongside conventional medicine and psychology by >50% of North American academic pediatric chronic pain programs. The technique that has undergone most scientific study involves penetrating the skin with thin, solid, metallic needles manipulated by hand or by electrical stimulation. Variants include rubbing (**shiatsu**), heat (**moxibustion**), lasers, magnets, pressure (**acupressure**), or electrical currents.

Although pediatric patients may be averse to needles, when approached in a developmentally appropriate way by an acupuncturist trained in pediatrics, children are often amenable to acupuncture and report that it is helpful. Acupuncture can offer significant benefits in the treatment of recurrent headache, anxiety, back and other types of pain, depression, abdominal pain, and nausea. As with any needle therapy, infections and bleeding are rare but can occur, and more serious complications, such as pneumothorax, occur in <1 in 30,000 treatments.

Cannabis

Because marijuana has been legalized in many states for both recreational (adult) use and medical use, caregivers and families have inquired about the potential health benefits of cannabis for both children and adults. At this time, no pediatric studies support any health benefit of cannabis for children. Furthermore, significant safety concerns remain, since detrimental effects of marijuana on the developing brain have been documented.

It is important to note that in some children with severe refractory **epilepsy** , oral **cannabidiol** , a nonpsychoactive component in marijuana, has provided improvement in seizure control. On a case-by-case basis, this is a reasonable consideration for families facing this rare and difficult challenge, and additional research is required in this area, especially since the purity and regulation of marijuana and its commercially available component products are variable. Most of the recent pediatric literature on cannabis describes an increase in accidental ingestions in young children, presumably in association with the increase in products now available for adult use; this is an additional safety risk for pediatricians to consider.

Internet Resources

American Academy of Pediatrics Section on Integrative Medicine: http://www2.aap.org/sections/chim/default.cfm .

Academic Consortium Integrative Medicine and Health: http://www.imconsortium.org/ .

National Institutes of Health, National Center for Complementary and Integrative Health: https://nccih.nih.gov/ .

American Pain Society; pediatric chronic pain programs by state: http://americanpainsociety.org/uploads/get-involved/PediatricPainClinicList_Update_2.10.15.pdf .

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PART VIII

Emergency Medicine and Critical Care

OUTLINE

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Chapter 80 Triage of the Acutely Ill Child
Chapter 81 Pediatric Emergencies and Resuscitation
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CHAPTER 79

Emergency Medical Services for Children

Joseph L. Wright, Steven E. Krug

The overwhelming majority of the 27 million children who present annually for emergency care in the United States are seen at community hospital emergency departments (EDs). Visits to children's hospital EDs account for just 10% of initial emergency care encounters. This distribution suggests that the greatest opportunity to optimize care for acutely ill or injured pediatric patients, on a population basis, occurs broadly as part of a systems-based approach to emergency services, an approach that incorporates the unique needs of children at every level. Conceptually, emergency medical services for children are characterized by an integrated, continuum-of-care model (Fig. 79.1). The model is designed such that patient care flows seamlessly from the primary care medical home through transport and on to hospital-based definitive care. It includes the following 5 principal domains of activity:

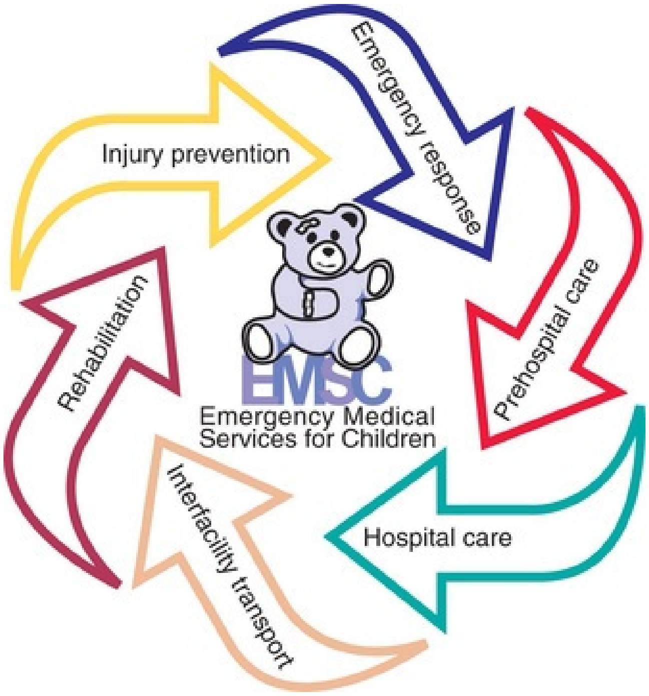
Injury prevention
Emergency response
Prehospital care
Hospital care
Interfacility transport
Rehabilitation
EMSC
Emergency Medical Services for Children

FIG. 79.1 **The emergency medical services for children (EMSC) continuum of care. Seriously ill and injured children interface with a large number of healthcare personnel as they move through the EMSC system.**

1. Prevention, primary and secondary
2. Out-of-hospital care, both emergency response and prehospital transport
3. Hospital-based care: ED and inpatient, including critical care
4. Interfacility transport, as necessary, for definitive or pediatric medical and surgical subspecialty care (see Chapter 79.1)
5. Rehabilitation

The federal **Emergency Medical Services for Children (EMSC)** program of the Health Resources and Services Administration's Maternal and Child Health Bureau has stewarded improvements in the care of children in the context of the continuum-of-care model. The programmatic mission of the EMSC program is as follows:

◆ To ensure state-of-the-art emergency medical care for ill or injured children and adolescents of all ages.

◆ To ensure that pediatric services are well integrated into an emergency medical services (EMS) system and backed by optimal resources.

◆ To ensure that the entire spectrum of emergency services—including primary prevention of illness and injury, acute care, and rehabilitation—is provided to infants, children, adolescents, and young adults.

Primary Care Physician and Office Preparedness

The primary care physician (PCP) has multiple important roles in the EMS system. Through anticipatory guidance, the PCP can help shape the attitudes, knowledge, and behaviors of parent and child, with the primary goal of preventing acute medical events, such as injury and status asthmaticus. The point-of-care initiation for many acute problems is often the PCP office. From the standpoint of personnel, equipment, training, and protocols, the PCP office setting must be adequately prepared to initially manage acute and emergency exacerbations of common pediatric conditions, such as respiratory distress and seizures. Furthermore, on rare occasion, the PCP office environment may be confronted with a child in clinical extremis who requires resuscitative intervention and stabilization. It is therefore incumbent on the PCP not only to ensure access to EMS, that is, 911 system activation, but also to ensure that there is adequate, on-site psychomotor skill preparation to deal with such an emergency. **Office preparedness** requires training and continuing education for staff members, protocols for emergency intervention, ready availability of appropriate resuscitation drugs and equipment, and knowledge of local EMS resources and ED capabilities. PCPs can also play a pivotal role in informing and advocating for pediatric emergency and disaster readiness in local EMS agencies, schools and childcare programs, and community hospitals; this is particularly important in rural communities.

Staff Training and Continuing Education

It is a reasonable expectation that all office staff, including receptionists and medical assistants, be trained in cardiopulmonary resuscitation (CPR) with their certification maintained annually. Nurses and physicians should also have training in a systematic approach to pediatric resuscitation. Core knowledge may be obtained through standardized courses in **advanced life support (ALS)** offered by national medical associations and professional organizations. Frequent practice and timely recertification is important for knowledge retention and skill maintenance. Examples include the Pediatric Advanced Life Support (PALS) and Pediatric Emergency Assessment, Recognition and Stabilization (PEARS) courses sponsored by the American Heart Association (AHA), the Advanced Pediatric Life Support (APLS) course sponsored by the American Academy of Pediatrics (AAP) and American College of Emergency Physicians (ACEP), and the Emergency Nurses Pediatric Course (ENPC) sponsored by the Emergency Nurses Association (ENA).

Protocols

Standardized protocols for telephone triage of seriously ill or injured children are essential. When a child's clinical status is in question and prehospital care is available, ambulance transport in the care of trained personnel is always preferable to transport by other means (e.g., private vehicle). This obviates the potentially serious medical consequences of relying on unskilled and distraught parents without the ability to provide even **basic life support (BLS)** measures to an unstable child during transport to an ED. Practitioners can work with their local pediatric emergency care resource center (e.g., children's hospital, academic medical center, trauma center) to develop and maintain written protocols for office-based management of a range of conditions, including anaphylaxis, cardiopulmonary arrest, head trauma, ingestions, shock, status asthmaticus, status epilepticus, and upper airway obstruction. Regular practice using mock code scenarios improves office-based practitioner and office staff confidence and self-efficacy in managing these problems.

Resuscitation Equipment

Availability of necessary equipment is a vital part of an emergency response. Every physician's office should have essential resuscitation equipment and medications packaged in a pediatric resuscitation cart or kit (Table 79.1). This cart or kit should be checked on a regular basis and kept in an accessible location known to all office staff. Outdated medication, a laryngoscope with a failed light source, or an empty oxygen tank represents a potential catastrophe in a resuscitation scenario. Such an incident can be easily avoided if an equipment checklist and regular maintenance schedule are implemented. A pediatric kit that includes posters, laminated cards, or a color-coded length-based resuscitation tape specifying emergency drug doses and equipment size are invaluable in avoiding critical therapeutic errors during resuscitation.

Table 79.1

Recommended Drugs and Equipment for Pediatric Office Emergencies

DRUGS/EQUIPMENT	PRIORITY
DRUGS	
Oxygen	E
Albuterol for inhalation	E
Epinephrine (1 : 1,000 [1 mg/mL])	E
Activated charcoal	S
Antibiotics	S
Anticonvulsants (diazepam/lorazepam)	S
Corticosteroids (parenteral/oral)	S
Dextrose (25%)	S
Diphenhydramine (parenteral, 50 mg/mL)	S
Epinephrine (1 : 10,000 [0.1 mg/mL])	S
Atropine sulfate (0.1 mg/mL)	S
Naloxone (0.4 mg/mL)	S
Sodium bicarbonate (4.2%)	S
INTRAVENOUS FLUIDS	
Normal saline (0.9 NS) *or* lactated Ringer solution (500 mL bags)	S
5% dextrose, 0.45 NS (500 mL bags)	S
EQUIPMENT FOR AIRWAY MANAGEMENT	
Oxygen and delivery system	E
Bag-valve-mask (450 mL and 1,000 mL)	E
Clear oxygen masks, breather and non-rebreather, with reservoirs (infant, child, adult)	E
Suction device, tonsil tip, bulb syringe	E
Nebulizer (or metered-dose inhaler with spacer/mask)	E
Oropharyngeal airways (sizes 00-5)	E
Pulse oximeter	E
Nasopharyngeal airways (sizes 12-30F)	S
Magill forceps (pediatric, adult)	S
Suction catheters (sizes 5-16F and Yankauer suction tip)	S
Nasogastric tubes (sizes 6-14F)	S
Laryngoscope handle (pediatric, adult) with extra batteries, bulbs	S
Laryngoscope blades (straight 0-2; curved 2-3)	S
Endotracheal tubes (uncuffed 2.5-5.5; cuffed 6.0-8.0)	S
Stylets (pediatric, adult)	S

Esophageal intubation detector or end-tidal carbon dioxide detector	S
EQUIPMENT FOR VASCULAR ACCESS AND FLUID MANAGEMENT	
Butterfly needles (19-25 gauge)	S
Catheter-over-needle device (14-24 gauge)	S
Arm boards, tape, tourniquet	S
Intraosseous needles (16 and 18 gauge)	S
Intravenous tubing, micro-drip	S
MISCELLANEOUS EQUIPMENT AND SUPPLIES	
Color-coded tape or preprinted drug doses	E
Cardiac arrest board/backboard	E
Sphygmomanometer (infant, child, adult, thigh cuffs)	E
Splints, sterile dressings	E
Automated external defibrillator with pediatric capabilities	S
Spot glucose test	S
Stiff neck collars (small/large)	S
Heating source (overhead warmer/infrared lamp)	S

E, Essential; S, strongly suggested.

From Frush K, American Academy of Pediatrics, Committee on Pediatric Emergency Medicine: Policy statement-preparation for emergencies in the offices of pediatricians and pediatric primary care providers, *Pediatrics* 120:200–212, 2007. Reaffirmed *Pediatrics* 128:e748, 2011.

To facilitate emergency response when a child needs rapid intervention in the office, all personnel should have designated roles. Organizing a “code team” within the office ensures that necessary equipment is made available to the physician in charge, that an appropriate medical record detailing all interventions and the child's response is generated, and that the 911 call for EMS response or a transport team is made in a timely fashion.

Transport

Once the child has been stabilized, a decision must be made on how best to transport a child to a facility capable of providing definitive care. If a child has required airway or cardiovascular support, has altered mental state or unstable vital signs, or has significant potential to deteriorate en route, it is not appropriate to send the child via privately owned vehicle, regardless of proximity to a hospital. Even when an ambulance is called, it is the PCP's responsibility to initiate essential life support measures and to attempt to stabilize the child before transport.

In metropolitan centers with numerous public and private ambulance agencies, the PCP must be knowledgeable about the level of service provided by each. The availability of BLS vs ALS services, the configuration of the transport team, and pediatric expertise vary greatly among agencies and across jurisdictions. BLS services provide basic support of airway, breathing, and circulation, whereas

ALS units are capable of providing resuscitation drugs and procedural interventions as well. Some communities may have only BLS services available, whereas others may have a 2-tiered system, providing both BLS and ALS. It may be appropriate to consider **medical air transport** when definitive or specialized care is not available within an immediate community or when ground transport times are prolonged. In that case, initial transport via ground to an appropriate helicopter landing zone or a local hospital for interval stabilization may be undertaken, pending arrival of the air transport team. Independent of whether a child is to be transported by air or ground, copies of the pertinent medical records and any imaging or laboratory studies should be sent with the patient, and a call made to the physicians at the receiving facility to alert them to the referral and any treatments administered. Such notification is not merely a courtesy; direct physician-to-physician communication is essential to ensure adequate transmission of patient care information, to allow mobilization of necessary resources in the ED, and to redirect the transport if the emergency physician believes that the child would be more optimally treated at a facility with specialized services.

Pediatric Prehospital Care

Prehospital care refers to emergency assistance rendered by trained emergency medical personnel before a child reaches a treating medical facility. The goals of prehospital care are to further minimize systemic insult or injury through a series of well-defined and appropriate interventions and to embrace principles that ensure patient safety. Most U.S. communities have a formalized EMS system; the organizational structure and nature of emergency medical response depend greatly on local demographics and population base. EMS may be provided by volunteers or career professionals working in a fire department–based or independent 3rd service response system. Key points to recognize in negotiation of the juncture between the community physician and the local EMS system include access to the system, provider capability, and destination determination.

Access to the EMS System

Virtually all Americans have access to the 911 telephone service that provides direct access to a dispatcher who coordinates police, fire, and EMS responses. Some communities have an enhanced telephone 911 system, in which the location of the caller is automatically provided to the dispatcher, permitting emergency response even if the caller, such as a young child, cannot give an address. The extent of medical training for these dispatchers varies among communities, as do the protocols by which they assign an emergency response level (BLS vs ALS). In some smaller communities, no coordinated dispatch exists, and emergency medical calls are handled by the local law enforcement agency.

When activating the 911 system, the physician must make clear to the dispatcher the nature of the medical emergency and the condition of the child. In many communities, emergency medical dispatchers are trained to ask a series of questions per protocol that determines the appropriate level of provider to be sent.

Provider Capability

There are many levels of training for prehospital EMS providers, ranging from individuals capable of providing only first aid to those trained and licensed to provide ALS. All EMS personnel, whether basic *emergency medical technicians* (EMTs) or paramedics, receive some training in pediatric emergencies; however, pediatric cases constitute approximately 10% of all EMS transports.

First responders may be law enforcement officers or firefighters, who are dispatched to provide emergency medical assistance, or bystanders. Public safety personnel have a minimum of 40 hr of training in first aid and CPR. Their role is to provide rapid response and stabilization pending the arrival of more highly trained personnel. In some smaller communities, this may be the only prehospital emergency medical response available.

In the United States the bulk of emergency medical response is provided by EMTs, who may be volunteers or paid professionals. Basic EMTs may staff an ambulance after undergoing a training program of approximately 100 hr. They are licensed to provide BLS services but may receive further training in some jurisdictions to expand their scope of practice to include intravenous catheter placement and fluid administration, management of airway adjuncts, and use of an automated external defibrillator (AED).

Paramedics, or EMT-Ps, represent the highest level of EMT response, with medical training and supervised field experience of approximately 1,000 hr. Paramedic skills include advanced airway management, including endotracheal intubation; placement of peripheral, central, or intraosseous lines; intravenous administration of drugs; administration of nebulized aerosols; needle thoracostomy; and cardioversion and defibrillation. These professionals provide ALS services, functioning out of an ambulance equipped as a mobile intensive care unit (ICU). In the joint policy statement *Equipment for Ground Ambulances* , the AAP, ACEP, American College of Surgeons Committee on Trauma, EMSC, ENA, National Association of EMS Physicians, and National Association of EMS Officials have published guideline standards for essential ambulance equipment, medications, and supplies necessary to provide BLS and ALS care across the age spectrum. This essential equipment list represents one of the reference standards that the federal EMSC program has adopted as a performance measure for state-level operational readiness to care for children in an EMS system.

Both basic EMTs and paramedics function under the delegated licensing authority of a supervisory EMS medical director. This physician oversight of prehospital practice is broadly characterized under the umbrella term *medical control.* **Direct** , or **online** , **medical control** refers to medical direction either at the scene or in real time via voice or video transmission. **Indirect** , or **offline** , **medical control** refers to the administering of medical direction before and after the provision of care. Offline activities, such as provider education and training, protocol development, and medical leadership of quality assurance/quality improvement programs, represent areas in need of greater pediatric input. As a measure of the degree to which EMSC permanence is being established in state EMS systems, the federal EMSC program has required demonstration of participation in online and offline medical direction activities for pediatric patients and the presence of an EMSC advisory committee at the state level. These advisory bodies are well positioned to support EMS agencies in their pediatric readiness as well as provide a forum for the active engagement of pediatric care experts at a system level.

Destination Determination

The destination to which a pediatric patient is transported may be defined by parental preference, provider preference, or jurisdictional protocol, which is typically predicated on field assessment of anatomic and physiologic criteria and, in the case of trauma, mechanism of injury. In communities served by an organized trauma or regionalized EMS system that incorporates pediatric designation based on objectively verified hospital capabilities, seriously ill or injured children may be triaged by protocol to the highest-level center reachable within a reasonable amount of time. The mantra is to deliver the child to the *right care in the right time* , even if it requires bypassing closer hospitals. An exception is the child in full cardiorespiratory arrest, for whom expeditious transport to the nearest facility is always warranted.

Regionalization in the context of EMS is defined as a geographically organized system of services that ensures access to care at a level appropriate to patient needs while maintaining efficient use of available resources. This system concept is especially germane in the care of children, given the relative scarcity of facilities capable of managing the full range and scope of pediatric conditions (Fig. 79.2). Regionalized systems of care coordinated with emergency medical dispatch, field triage, and EMS transport have demonstrated efficacy in improving outcomes for **pediatric trauma** patients, especially for younger children and for children with isolated head injury. Emerging evidence also suggests a similar benefit conferred to children in **shock** identified in the field who are preferentially transported to hospital EDs with documented pediatric ALS capability. The existence of statewide or regional standardized systems that formally recognize hospitals able to stabilize and/or manage pediatric medical emergencies is another federal EMSC performance measure against which operational capacity to provide optimal pediatric emergency care in the United States is currently being evaluated.

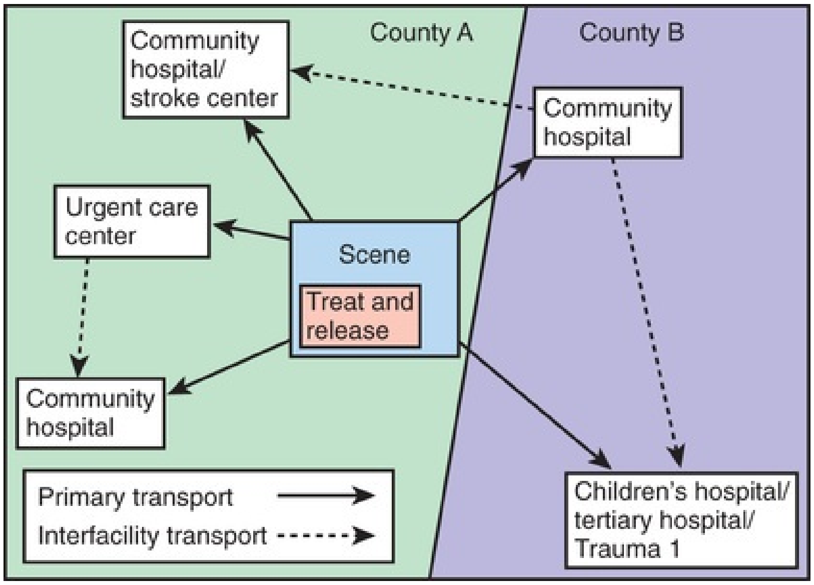
County A
County B
Community hospital/ stroke center
Community hospital
Urgent care center
Scene
Treat and release
Community hospital
Children's hospital/ tertiary hospital/ Trauma 1
Primary transport
Interfacility transport

FIG. 79.2 Transport options within a coordinated, regionalized emergency medical

services system model. The objective is to ensure access to definitive care at a level appropriate to meet patient needs. *Solid arrows,* Primary transport; *dotted arrows* , interfacility transport. (Adapted from Institute of Medicine, Committee on the Future of Emergency Care in the U.S. Health System: *Hospital-based emergency care: at the breaking point* , Washington, DC, 2006, National Academies Press.)

In communities that do not have a hospital with the equipment and personnel resources to provide definitive pediatric inpatient care, **interfacility transport** of a child to a regional center should be undertaken after initial stabilization (see Chapter 79.1).

The Emergency Department

The ability of hospital EDs to respond to the emergency care of children varies and depends on a number of factors in addition to availability of equipment and supplies. Training, awareness, and experience of the staff as well as access to pediatricians and medical and surgical subspecialists also play a key role. The majority of children who require emergency care are evaluated in community hospitals by physicians, nurses, and other healthcare providers with variable degrees of pediatric training and experience. Although children account for approximately 25% of all ED visits, only a fraction of these encounters represent true emergencies. Because the volume of critical pediatric cases is low, emergency physicians and nurses working in lower-volume community hospital EDs often have limited opportunity to reinforce their knowledge and skills in the assessment of ill or injured children and in pediatric resuscitation. Indeed, 50% of U.S. hospital EDs provide care for <10 children per day. General pediatricians from the community or pediatric hospitalists may be consulted when a seriously ill or injured child presents to the ED, and they should have a structured approach to the initial evaluation and treatment of an unstable child of any age, regardless of the underlying diagnosis. *Early recognition of life-threatening abnormalities in oxygenation, ventilation, perfusion, and central nervous system function and rapid intervention to correct those abnormalities are key to successful resuscitation and stabilization of the pediatric patient.*

The **National Pediatric Readiness Project (NPRP)** , a 2013–2014 survey of pediatric readiness in U.S. EDs, found higher readiness levels (as measured by compliance with published guidelines) in larger-volume EDs and in hospitals with a physician and/or nurse pediatric emergency care coordinator. Further information about the NPRP, including data by state, may be found on the website of the EMSC Innovation and Improvement Center, https://emscimprovement.center/ .

Baseline readiness standards must be met by all EDs that care for children, to ensure that children receive the best emergency care possible. Specific recommendations on equipment, supplies, and medications for the ED are listed and updates available on the AAP website. Table 79.2 lists sample policies, procedures, and protocols specifically addressing the needs of children in the ED.

Table 79.2

Guidelines for Pediatric-Specific Policies, Procedures, and Protocols for the Emergency Department (ED)

Illness and injury triage
Pediatric patient assessment and reassessment
Documentation of pediatric vital signs, abnormal vital signs, and actions to be taken for abnormal vital signs
Immunization assessment and management of the underimmunized patient
Sedation and analgesia for procedures, including medical imaging
Consent (including situations in which a parent is not immediately available)
Social and mental health issues
Physical or chemical restraint of patients
Child maltreatment (physical and sexual abuse, sexual assault, and neglect) mandated reporting criteria, requirements, and processes
Death of the child in the ED
Do-not-resuscitate orders
Family-centered care, including:

1. Involving families in patient care decision-making and in medication safety processes.
2. Family presence during all aspects of emergency care, including resuscitation.
3. Education of the patient, family, and regular caregivers.
4. Discharge planning and instruction.
5. Bereavement counseling.

Communication with patient's medical home or primary healthcare provider

Medical imaging policies that address age- or weight-appropriate dosing for children receiving studies that impart ionizing radiation, consistent with ALARA (as low as reasonably achievable) principles

All-hazard disaster preparedness plan that addresses the following pediatric issues:

  a. Availability of medications, vaccines, equipment, and appropriately trained providers for children in disasters.
  b. Pediatric surge capacity for both injured and noninjured children.
  c. Decontamination, isolation, and quarantine of families and children of all ages.
  d. A plan that minimizes parent-child separation and includes system tracking of pediatric patients, allowing for the timely reunification of separated children with their families.
  e. Access to specific medical and mental health therapies, as well as social services, for children in the event of a disaster.
  f. Disaster drills, which should include a pediatric mass casualty incident at least every 2 yr.
  g. Care of children with special healthcare needs.
  h. A plan that includes evacuation of pediatric units and pediatric specialty units.

Adapted from Gausche-Hill M, Krug SE, American Academy of Pediatrics Committee on Pediatric Emergency Medicine; American College of Emergency Physicians Pediatric Committee; Emergency Nurses Association Pediatric Committee: Joint policy statement—guidelines for care of children in the emergency department, *Pediatrics* 124:1233–1243, 2009. Reaffirmed *Pediatrics* 132:e281, 2013.

The way the family supports the child during a crisis, and consequently how the family is supported in the ED when caring for the child, are critical to patient recovery, family satisfaction, and mitigation of behavioral and mental health impact. Commitment to patient- and family-centered care in the ED ensures that the patient and family experience guides the practice of culturally sensitive care and promotes patient dignity, comfort, and autonomy. In the ED setting, particular issues, such as family presence, deserve specific attention. Surveys of parents have indicated that most want to be with their child during invasive procedures and even during resuscitation. Allowing their presence has been shown to reduce parental and patient anxiety and does not interfere with procedure performance. Patient- and family-centered care practices are also strongly associated with improved care quality and patient safety.

Disaster Preparedness

Throughout a catastrophic event, natural or human-made, several unique factors place children at disproportionate, increased risk. During an average workday, an estimated 69 million U.S. children are separated from their families, in schools and childcare centers, where mass casualty events can easily occur. This separation adds the additional challenge of safe and timely reunification of children with family during or after an incident. Furthermore, in the event of a biologic, chemical, or radionuclear attack, unique anatomic, developmental, and physiologic features make children especially vulnerable to absorption, ingestion, or inhalation of toxic agents and related morbidity and mortality.

Similar to day-to-day emergency readiness for ill and injured children, pediatric disaster preparedness requires advance considerations of the unique vulnerabilities and needs of children within planning, and exercises, at local, state, regional and even national levels. Pediatric planning considerations include training of first responders and other care providers, patient triage, decontamination, surge capacity and capability, medical countermeasures (medications, vaccines, equipment, supplies), evacuation, transport, sheltering, and family reunification. Planning for children should occur at all levels of the healthcare system, including the medical home, urgent care centers, EMS, acute care hospitals, pediatric tertiary hospitals, alternate care facilities, and rehabilitation services. While the NPRP noted meaningful progress in day-to-day emergency readiness, no improvement was found in disaster preparations, with less than half of U.S. hospitals having a disaster plan addressing the needs of children. Beyond acute medical treatment needs, pediatric planning must also consider the typically broad mental and behavioral health impact disasters have on children and families. Pediatric plans must also be in place for locations where children congregate, such as schools and childcare.

At the local, state, or regional level, healthcare coalitions have been identified as an optimal forum for disaster planning; core participants should include local or state public health departments, emergency management authorities, EMS agencies, and hospitals. Many other key stakeholder groups should be involved in coalition planning, such as healthcare professional organizations. To ensure that the needs of children are effectively considered, it has been recommended that disaster planning at all levels include pediatric subject matter experts. Pediatricians are an obvious source for this expertise and are also uniquely positioned to educate families about emergency readiness, particularly families with special needs children. The presence of an intact medical home during a public health emergency, and after a disaster has occurred, will contribute enormously toward response, recovery, and community resiliency. Lastly, community practice and healthcare system readiness and resiliency begin with *personal readiness planning* engaged by healthcare providers and support staff.

The AAP's Children and Disasters website* contains toolkits, checklists and other resources pertinent to pediatric readiness within the community, schools, the medical home, and hospitals; educational materials are also available for families. Reliable information and excellent disaster readiness resources may also located on the websites of the EMSC Innovation and Improvement Center (https://emscimprovement.center), U.S. Centers for Disease Control and Prevention (https://emergency.cdc.gov), U.S. Department of Health and Human Services (https://www.phe.gov/preparedness/Pages/default.aspx), and U.S. Federal Emergency Management Agency (https://www.fema.gov).

79.1

Interfacility Transport of the Seriously Ill or Injured Pediatric Patient

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Keywords

air ambulance
family-centered care
medical control physician
pediatric transport medicine
telemedicine

Patients often seek treatment at facilities that lack sufficient expertise to treat their conditions, necessitating transfer to more appropriate specialty centers. This is especially pronounced in pediatrics. Emergency medical services (EMS) providers or parents usually take children to local emergency departments (EDs) first, where their conditions and physiologic stabilities are assessed. Although bringing a child directly to the local ED may be proper logistically, local EDs can be less than ideal for pediatric emergencies. Children account for 27% of all ED visits, but only 6% of EDs have all the necessary supplies for pediatric emergencies. Also, general EDs are less likely to have pediatric expertise or policies in place for the care of children. Outcomes for critically ill children treated in pediatric intensive care units (PICUs) are better than for those treated in adult ICUs. When pediatric critical care is required, transport to a regional PICU is indicated. In addition, often the type of subspecialty care needed (e.g., pediatric orthopedics) is available only at the pediatric center.

Pediatric transport medicine consists of the interfacility transfer of infants, children, and adolescents from community facilities to pediatric centers that can provide the needed level of expertise. Transport is performed by professionals proficient in pediatric transport using age-equipped ground, rotorcraft, or fixed-wing ambulances. Pediatric transport medicine is a multidisciplinary field comprising pediatric critical care and **pediatric emergency medicine** (PEM) physicians (and, sometimes for very young infants, neonatologists); nurses, respiratory therapists, and paramedics with advanced training for pediatric transport; and communications specialists. The goal is to deliver quality pediatric care to the region's children, while optimizing the use of regional resources. For the individual child, the aim is to stabilize and, when appropriate, begin treating as soon as possible—that is, at the local ED and during transport, well before arrival at the referral center.

Models for pediatric transport services vary depending on the needs and available resources in a geographic region, but all should have certain basic components: a network of community hospitals and regional pediatric centers; an established communications and dispatch system that easily facilitates transfer to the pediatric center; ground and/or air ambulances; medical and nursing leadership from pediatric critical care or PEM (or neonatology); experienced pediatric **medical control physicians (MCPs)** ; a multidisciplinary team of pediatric transport professionals specially trained to provide the appropriate level of care required during transport; operational and clinical policies and procedures that guarantee safe, state-of-the-art, and timely pediatric critical care transport; and a database for quality and performance assessment.

Communications and Dispatch Center

Communications are one of the most vital components of a regional transport system. Treating a critically ill or injured child is generally an uncommon event for most community physicians. Therefore, they need to know *whom* , *how* , and *when* to call for assistance in the stabilization and transfer of a pediatric patient. The communications and dispatch center provides a single telephone number for such calls.

The communications and dispatch center coordinates communications among the outlying facility, receiving unit, MCP, transport team, and other consultants. This center may be part of a hospital unit (e.g., ED, PICU), self-contained in a single institution (e.g., Emergency Communications and Information Center), or based offsite as a freestanding center coordinating communications and dispatch for multiple transport programs.

Staffing varies depending on the type of center. On-duty nurses or physicians may receive calls at unit-based models with low volumes. In contrast, dedicated communications specialists usually staff self-contained or freestanding centers, which tend to be busier. The communications specialist has numerous responsibilities, including answering the referring physician's call promptly; documenting essential patient demographic information; arranging for immediate consultation with the MCP; dispatching the transport team to the referring facility expeditiously; updating the referring facility with any changes in the arrival time; and coordinating medical control and other necessary transport-related calls. The transport team must be equipped with a cellular telephone or radio for immediate contact with the receiving and referring facilities. Furthermore, with advances in technology and wireless communication systems, **telemedicine** —either *interactive* (synchronous) or *store and forward* (asynchronous)—is being used during pediatric transport; certain programs have incorporated it into their routine transport operations.

Medical Control Physician

The MCP is involved in the clinical care and safe transport of the patient from the time of referral through arrival at the receiving hospital unit. The MCP's oversight increases once the transport team arrives at the referring facility. The MCP should have expertise in pediatric critical care or PEM (or sometimes neonatology). Besides having the knowledge required to stabilize a critically ill or injured child, the MCP must be familiar with the transport environment; the transport team members’ resources and capabilities; the program's policies and procedures; and the region's geography, medical resources, and regulations regarding interhospital transport. The MCP must possess good interpersonal and communication skills and must be able to maintain collegiality with the referring hospital's staff during a potentially difficult and stressful situation.

Once a transport call is received, the MCP must be immediately available to confer with the referring physician. Although the MCP may have other responsibilities, these transport responsibilities take priority in order to avoid undue delays when transferring a critically ill child. Often the MCP recommends further testing or therapeutic interventions that can be delivered by the referring hospital before the transport team arrives. The MCP may seek additional guidance from other specialists, as necessary. Because the child's condition may change rapidly, the MCP must remain ready to give additional advice. All conversations and recommendations regarding the care of the patient should be documented. Some centers record these conversations.

After discussion with the referring physician—and when warranted, with the transport staff—the MCP determines the best team composition and vehicle for transport. The MCP usually does not accompany the team but remains available, by phone or radio (and sometimes through telemedicine), to supervise care.

Transport Team

Transport team composition varies among programs—and sometimes within an individual program. The team's composition is based on a variety of factors, including the child's age; the severity of the illness or injury; the distance to the referring facility; the transport vehicle used; the team members’ advanced practice scope and abilities; the referrer's (reasonable or unreasonable) insistence that a physician be present; the program's historical professional makeup; and the region's staffing regulations. Team members are generally physicians, nurse practitioners, nurses, respiratory therapists, and paramedics who have expertise in pediatric critical care, PEM, or neonatology (in some cases), as well as advanced education and training in those cognitive and procedural areas important for pediatric critical care transport. There is a lower incidence of transport-related morbidity for critically ill and injured children transported by pediatric specialty teams than for those transported by generalist teams. Nevertheless, in-transit critical events occur in almost 1 in 8 pediatric critical care transports.

Various scoring systems have been developed to predict the need for a physician during transport. It seems that a team member's training, experience, and skill in treating critically ill patients are more important considerations than that team member's professional degree. Team members must understand basic pediatric pathophysiology and collectively must be able to assess and monitor a critically ill or injured child; manage the airway and provide respiratory support; obtain vascular access; perform point-of-care testing; and administer medications typically used in pediatric critical care transport. They must be familiar with the physiologic alterations as well as practical difficulties of the transport environment and, importantly, must be comfortable working in an out-of-hospital setting. Physicians are less often deployed on transport teams in part because of the advanced training that other healthcare professionals on the transport team receive.

The transport team should have a designated team leader who, in addition to the team leader's many other responsibilities, interacts with the MCP during the transport. Once the team arrives at the referring facility, the team should reassess the child's condition, review all of the pertinent diagnostic studies and therapies, and discuss the situation with the referring staff and parents. If the patient's condition has changed significantly, the team leader may need to contact the MCP for additional advice. Otherwise, the team leader should generally notify the MCP before starting to bring the child to the receiving facility. Any care delivered by the team during transport should be documented, and copies of all medical records—including laboratory data, radiographs, and scans—should accompany the child to the pediatric center. The receiving unit must be updated prior to arrival so it can finalize preparations for the patient.

Ground vs Air Ambulance

Transport vehicle options include ground, rotorcraft, and fixed-wing ambulances. Vehicle selection depends on the child's emergency needs; transport team's capabilities; any out-of-ordinary staffing or equipment requirements (e.g., for extracorporeal membrane oxygenation, inhaled nitric oxide or heliox); referring facility's abilities; distance; terrain; traffic patterns; ground or air ambulance availability; helicopter landing pad or airport access; weather conditions; and expense.

The transport vehicle must be equipped with electrical power, oxygen, and suction and must have sufficient space for the equipment and supplies that the team brings along—stretcher or isolette, monitor, ventilator, oxygen tank(s), medication pack(s), infusion pumps, and more. Compared with helicopters, ambulances are more spacious and able to carry more weight, so they can accommodate larger teams and more equipment. Another advantage of ground ambulance transport is the ability to stop en route if the patient's condition deteriorates; this may facilitate the performance of certain interventions, such as intubation.

An airplane may be able to fly to an area when distance (>150 miles), altitude, or weather precludes helicopter use. However, the use of an airplane necessitates several ambulance transfers, with their attendant delays and potential complications. There also are delays when the plane must fly from a remote base to the program's jurisdiction.

Transport Physiology

When possible, the transport team tries to provide the same care during transport as the patient would receive in the specialty center. This can be difficult, however, because of limitations in personnel, equipment, and space, as well as other environmental challenges.

The team and child are subjected to variable intensities of background noise and vibration while traveling in the vehicle cabin. **Noise** can impair the team's ability to auscultate breath sounds and heart sounds or accurately measure the blood pressure manually—another reason for monitoring vital signs mechanically and relying on other assessment modalities, such as the level of mentation, skin color, and capillary refill. For rotor transports in particular, the crew and patient should wear helmets or headphones (or another wearable noise attenuator, such as MiniMuffs, Natus Medical, San Carlos, CA) to mitigate noise. **Motion** and **vibration** are additional transport hazards and can lead to increased metabolic rate, shortness of breath, and fatigue in the patient, as well as motion sickness in the patient and staff.

On fixed-wing or certain rotary-wing transports, the patient may suffer adverse physiologic effects from **altitude** . With increasing altitude, the barometric (atmospheric) pressure decreases and gas expands to occupy a greater volume due to decreased pressure exerted on it. Therefore, as barometric pressure drops with altitude, the partial pressures of inspired oxygen (PiO_2) and, consequently, arterial oxygen (PaO_2) decrease, as does the arterial oxygen-hemoglobin saturation (SpO_2). For example, at 8,000 feet—an elevation at which unpressurized airplanes may fly, as well as the effective cabin altitude for many pressurized airplanes flying at 35,000 to 40,000 feet—the barometric pressure, PiO_2 , PaO_2 , and SpO_2 fall to 565 mm Hg, 118 mm Hg, 61 mm Hg, an 93%, respectively. In comparison, the barometric pressure, PiO_2 , PaO_2 , and Sp $_2$ are 760 mm Hg, 159 mm Hg, 95 mm Hg, and 100% at sea level. Although healthy individuals usually tolerate these changes well, patients with respiratory insufficiency, pulmonary hypertension, significant blood loss, or shock may decompensate and should receive supplemental oxygen and/or have the cabin pressured at sea level.

Gases expand 10–15% at the few-thousand feet where helicopters typically fly, and approximately 30% at 8,000 feet. Gases within the body itself also expand as the altitude increases. The degree of gas expansion must be considered during transport via air of any patient with a pneumocephalus, pneumothorax, bowel obstruction, or another condition involving entrapped gas. Before transport, a pneumothorax should be decompressed and a nasogastric tube inserted for ileus.

Safety

Safety is of paramount importance and mandates constant vigilance by everyone involved. Accident rates for pediatric air and ground transport are estimated at approximately 1 in 1,000 transports. The team should routinely attend pilot briefs, as well as perform safety inspections of the vehicles and equipment, aided by checklists. When in doubt, the MCP should solicit input from the staff about whether to transport via air or ground ambulance or to employ lights and sirens, decisions that cannot be taken lightly. The pilot's or driver's judgment as to the safety of proceeding during inclement weather or with a mechanical problem must not be overruled.

Organizations such as the Federal Aviation Administration (FAA) and the National Transportation Safety Board (NTSB), play a role in ensuring safe interfacility transport. The **Commission on Accreditation of Medical Transport Systems (CAMTS)** is an independent, peer-review organization established in 1990 in response to the number of air medical accidents in the 1980s. CAMTS, through voluntary participation, audits and accredits fixed-wing, rotary-wing, and ground interfacility medical transport services.

Family-Centered Care

Family-centered care represents a philosophy that respects the important role that family members play in a child's care. It recognizes family members and healthcare providers as partners in caring for the child. Family presence during transport is beneficial because it provides support to children in stressful situations and assists healthcare providers in delivering care to patients with complex and chronic medical problems.

As care is transitioned from the referring hospital, it is the transport team's responsibility to maintain family-centered care. The team meets with family members to explain the transport process, help obtain consent, and discuss anticipated management. When possible, the transport team should attempt to accommodate a family member's presence onboard. However, the family member and child may need to be separated when the child is critically ill and rapid transport is essential, or in case of space or weight limitations in the air or ground ambulance. In these situations, it is important that family members have a clear understanding of how the child will be cared for during the separation.

Referring Hospital Responsibilities

Transfer of a child to another facility requires written documentation by the referring physician of the need and reasons for transfer, including a statement that the risks and benefits, as well as any alternatives, have been discussed with the parents. Informed consent should be obtained from the parent/legal guardian before transfer.

Federal law under the Emergency Medical Treatment and Active Labor Act (EMTALA), part of the Consolidated Omnibus Budget Reconciliation Act (COBRA), imposes specific requirements that a patient presenting to an ED be given a medical screening examination without regard to ability to pay. If on examination an emergency medical condition is found, the hospital is required to stabilize the patient or to transfer the patient to another facility if unable to stabilize the patient or if requested by the patient. The primary requirement is that the referring physician must certify that the medical risks of transfer are outweighed by its potential benefits. The receiving hospital must agree to accept the patient if it has the space and staff to provide the necessary level of care. The transferring hospital is responsible for arranging for the transfer and ensuring that it is performed by qualified medical personnel with appropriate equipment. The transferring hospital must also send copies of the patient's medical records and test results, even those that become available after the transfer is complete.

Some referring hospitals have entered into transfer agreements with specialty centers to facilitate the smooth and safe transfer of pediatric patients. Having prepared forms for all the above purposes also aids in the transfer process.

Each hospital needs to review its facility's guidelines; if established guidelines do not exist, the Emergency Medical Services for Children National Resource Center in partnership with the Emergency Nurses Association and the Society of Trauma Nurses has developed the “Inter Facility Transfer Tool Kit for the Pediatric Patient” (www.pediatricreadiness.org). This tool kit includes the essentials for comprehensively and safely transferring the pediatric patient to the most appropriate level of care in a timely manner.

Educational Outreach

Besides safe and rapid transport, regional pediatric transport programs (and their specialty centers) have an obligation to provide educational opportunities to community healthcare providers so that these providers can acquire the necessary skills to evaluate and stabilize a critically ill or injured child until the transport team arrives. These learning activities may include transport case reviews; lectures on pediatric acute care topics; resuscitation and related programs such as the Pediatric Advanced Life Support (PALS) course, Advanced Pediatric Life Support (APLS) course, Pediatric Education for Prehospital Professionals (PEPP) course, and S.T.A.B.L.E. (sugar and safe care, temperature, airway, blood pressure, lab work, emotional support) program; and rotations through the specialty center's pediatric ED and PICU. These activities also help cement relationships with the referring facility's staff.

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79.2

Outcomes and Risk Adjustment of Pediatric Emergency Medical Services

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Keywords

calibration
discrimination
PRISA II
PRISM
RePEAT
risk adjustment

Health services research has documented wide variation in the likelihood that patients receive quality, evidence-based healthcare, and this can negatively impact the health of children and youth (see Chapter 2). The complexities of delivering high-quality healthcare are magnified in the emergency department

(ED). Patients are in crisis, EDs are often overcrowded, patient–physician relationships are based on brief interactions, and the varieties of complaints and diagnoses are immense. Practitioners want to know whether the system is working well, and whether local performance is good compared with a recognized benchmark or standard. Physicians can make their practice better only if they can make the appropriate measurements. However, no two places of practice are the same, so besides assessing raw outcomes (e.g., times, mortality, patient satisfaction), practitioners also need to make some adjustment for severity of illness, case mix, or risk of morbidity (e.g., one ED's practice and cases may differ significantly from a theoretical standard being used as a benchmark for “best practice”).

Outcome Measures in Emergency Medical Services for Children

Pediatric emergency medical systems must support the development of national standards for emergency care performance measurement. The *Donabedian structure-process-outcome model* has set the framework for most contemporary quality measurement and improvement activities. **Structural** elements provide indirect quality-of-care measures related to a physical setting and resources. **Process** indicators provide a measure of the quality of care and services by evaluating the method or process by which care is delivered, including both technical and interpersonal components. **Outcome** elements describe valued results related to lengthening life, relieving pain, reducing disabilities, and satisfying the consumer.

A true *outcome-based* approach describes observable measures such as mortality, risk of organ system failure, and disability. An alternative approach is a *resource-based* outcome measure with a definition related to the level of care required. Children who are more ill, in general, require more resources. Thus, resource use across groups of patients reflects relative **severity of illness** in the groups, provided clinicians have a similar approach to practice. Examples of resource-based outcomes include need for hospital admission (ED disposition), ED length-of-stay, costs, and diagnostic and therapeutic interventions performed in the ED. This approach, certainly provides a measurement of activity, but child healthcare providers do not really know whether the patient receiving the therapeutic interventions or resources actually needed them (i.e., data may also reflect physician behavior or [lack of] experience). Therefore, some other assessment is needed that incorporates information on *how sick* the patient is, or their specific diagnosis.

Table 79.3 provides a list of outcome measures for pediatric ED care developed by **Emergency Medical Services for Children Innovation and Improvement Cente** r supported by the Health Resources and Services Administration of the U.S. Department of Health and Human Services.

Table 79.3

Stakeholder-Endorsed Outcome Measures for Pediatric Emergency Care

- Overall patient satisfaction with ED visit—nurses
- Overall patient satisfaction with ED visit—physicians
- Parent/caregiver understanding of ED discharge instructions
- ED length of stay for patients <18 yr of age
- Percentage of patients <18 yr of age left without being seen (LWBS)
- Effective pediatric procedural sedation
- Acute fracture patients with documented reduction in pain within 90 min of ED arrival
- Improvement in asthma severity score for patients with acute exacerbations
- ED revisit within 48 hr resulting in admission
- Medication error rates
- Global sentinel never events
- Unplanned return visit within 72 hr for the same/related asthma exacerbation
- Failure to achieve seizure control within 30 min of ED arrival
- Return visits within 48 hr resulting in admission for all urgent and emergency patients

Risk Adjustment

The purpose of measuring outcomes in the ED is to evaluate **performance** and therefore to offer EDs and other components of the healthcare system the opportunity to make effective improvements over time, using a benchmark within and between units. When making comparisons over time, one must ensure that patient-related attributes (e.g., age, preexisting conditions associated with outcome of interest, severity of illness) has not changed; otherwise one may be looking at changes in demography and case mix rather than any change in performance. The approach is to make some form of *risk adjustment* to *level the playing field* , so that comparison of outcomes is as fair and meaningful as possible. Because children present to EDs with illnesses of varying acuity, severity is inextricably linked to outcomes. Severity typifies the concept of *risk* —the higher the severity, the higher the risk of a given outcome. Without risk adjustment, EDs with sicker patients may appear to have poorer outcomes.

In the population of children admitted to a pediatric intensive care unit (PICU), 2 models, the **Pediatric Risk of Mortality** (PRISM) and **Pediatric Index of Mortality** (PIM),– have been developed and validated against the outcome of death during PICU admission and, in the case of PRISM IV, against functional outcome. These models or prediction algorithms, use a composite of a priori known high- or low-risk diagnoses, as well as acute physiology measurements taken around the time of presentation. In PRISM IV the data collection is from 2 hr before to 4 hr after admission, or the 1st 4 hr of care. The main concept is that deranged physiology reflects underlying severity of illness; the other features of the patient (e.g., age, diagnoses, postintervention status) modify the relationship between physiologic status and risk and enable accurate and reliable estimates of mortality and morbidity risks. Importantly, in the PRISM methodology, physiologic status is not conflated with therapies (e.g., mechanical ventilation) used at presentation (i.e., in the initial window for assessment). Historically, the measure used after the initial window of assessment with its laboratory and clinical evaluation was a period of intervention in the PICU, lasting a median of 2 days, and then discharge survival. However, the mortality rate in many U.S. PICUs is now <2.5%, and thus the need for algorithms that also include development of morbidity, now approximately 5%. The PRISM IV methodology has been validated using a *trichotomous* outcome (i.e., death, new morbidity, no new morbidity) at hospital discharge.

The previous approach is not well suited for the population presenting to the ED. Interventions may have already occurred in the prehospital setting, or physiology may have stabilized. Mortality rate is very low, and the other outcome measures may reflect what happens on the PICU or during hospital ward care. A number of disease-specific acuity scoring systems are available for use in the ED population, predominantly for those involved in trauma (e.g., Injury Severity Score, Trauma Score, Pediatric Trauma Score).

Risk Adjustment Tools in the ED

In the ED the choice of a risk adjustment tool depends on the outcomes of interest. Two general risk adjustment tools have been developed specifically for PEM, the second-generation Pediatric Risk of Admission (PRISA II) score and the Revised Pediatric Emergency Assessment Tool (RePEAT).

Pediatric Risk of Admission II

PRISA II uses components of acute and chronic medical history and physiology to determine the probability of hospitalization. The outcome measure of interest is *mandatory hospital admission* (admissions utilizing therapies best delivered as an inpatient). Table 79.4 lists the patient-related attributes contributing to the PRISA II risk adjustment score. Analytic models, including the PRISA II score, have good **calibration** (how well the probabilities predicted from the model correlated with the observed outcomes in the population) and **discrimination** (the ability to categorize subjects correctly into the categories of interest) with respect to mandatory hospital admission. Construct validity of the PRISA score has been demonstrated by measuring rates of the secondary outcomes: mandatory admission, PICU admission, and mortality. As the probability of hospital admission rises, the proportion of patients with these increasing care requirements also increases. This finding supports the use of the PRISA II score as a measure of severity of illness. PRISA II has also been used to demonstrate racial/ethnic differences in severity-adjusted hospitalization rates. One study demonstrated that teaching hospitals had higher-than-expected severity-adjusted admission rates than nonteaching hospitals.

Table 79.4

Elements of the PRISA II Score

- Age <90 days
- Minor injury
- Abdominal pain in an adolescent

- Immunodeficiency
- Indwelling medical device
- Controller asthma medication
- Referral status
- Temperature
- Decreased mental status
- Low systolic blood pressure (<70 neonates and infants; <83 children; <100 adolescents)
- High diastolic blood pressure (>59 neonates and infants; >70 children; >90 adolescents)
- Low serum bicarbonate value (<20 mEq/L)
- High potassium value (>4.9 mEq/L)
- High blood urea nitrogen value (>80 mg/dL)
- High white blood cell count (>20,000/mm^3)
- Oxygen therapy other than during inhaled bronchodilator treatments
- Low bicarbonate and high potassium values

Revised Pediatric Emergency Assessment Tool

RePEAT uses a limited set of data collected at the time of ED triage to model severity of illness as reflected by the level of care provided in the ED, for example, routine assessment (clinical examination only ± nonprescription medicine) vs specific ED care (ED diagnostics and/or therapeutics) vs hospital admission. It is assumed that patients needing a higher level of care have a higher severity of illness. Table 79.5 lists the patient-related attributes contributing to the RePEAT risk adjustment score. Analytic models such as RePEAT have good calibration and discrimination with respect to predicting ED care and hospital admission. Furthermore, analytic models that compare costs and ED length of stay between EDs are improved by adjustment for severity of illness using the RePEAT score. RePEAT is a reasonable objective marker of severity of illness that could be used in the administrative process comparing outcomes between EDs.

Table 79.5

Elements of the RePEAT Score

- Age
- Chief complaint
- Triage category
- Current use of prescription medications
- Arrival via EMS (ground/air)
- Heart rate
- Respiratory rate
- Temperature

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79.3

Principles Applicable to the Developing World

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Keywords

access
burns
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drowning
ETAT
IMCI guidelines
out-of-hospital care
pediatric emergency medicine
prehospital care
traffic-related injury
triage

The maturity of **pediatric emergency medicine** (PEM) in any given area depends on the healthcare priorities and resources of that geographic or physical setting. The places in which emergency care takes place range from the community (for those with no access to organized medical care) to state-of-the-art pediatric EDs in populated centers. The scope ranges from care of the individual patient to the management of populations of children involved in large-scale disasters. Barriers to quality care are different in each situation and in each part of the world, with the implication for the astute international PEM practitioner that solutions must be targeted to the local context of healthcare within a given environment.

Continuum-of-Care Model

This Emergency Medical Services for Children (EMSC) framework can also be applied to discussion of emergency care for children on a global level (see Chapter 79). With medical infrastructures that may not be consistent or well organized, or that have been weakened by civil strife, natural disasters, or economic loss, the focus of child health in the developing world has mostly been on prevention and acute care.

Prevention

Infectious Diseases

International child health has focused mainly on reducing preventable childhood illnesses, primarily through immunizations. Enormous advances have been realized in measles, neonatal tetanus, and polio reduction; wild-type smallpox was eradicated in 1978. Although there are advocates for providing primary care interventions (e.g., vaccinations) in the ED, the role of the PEM practitioner in this area of prevention has been limited.

Injuries

Injuries are a leading cause of childhood morbidity and mortality. Unintentional injuries constitute 90% of injury mortality to children 5-19 yr old and are the cause of 9% of the world's mortality (see Chapter 13). Intentional injuries, which remain underrecognized and underreported, make a smaller but significant contribution. Unintentional injuries cause more than 2,000 childhood deaths daily, or 950,000 annually worldwide. The burden of these deaths is borne disproportionately by children in middle- and lower-income countries, where >95% of all injury deaths occur. For each of these deaths, many more children are permanently disabled, and an even larger number are treated and released without permanent sequelae.

The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) have outlined several proven injury prevention strategies, of which child health practitioners in the global community must be aware. The top 3 causes of injury mortality are traffic-related injuries, burns, and drowning. There are 7 specific effective strategies for reducing **traffic-related injuries** : a minimum drinking age, appropriate child restraints and seatbelts, helmets for motorcycle and bicycle riders, reduced vehicle speeds around schools and residential areas, running lights on motorcycles, graduated licensing for drivers, and separation of different types of road users. There is insufficient evidence to demonstrate that school-based programs on drunk driving, increased pedestrian visibility, or designated driver programs are effective. Although these strategies have proved effective, the data are based on U.S. research and may not be generalizable to other countries. It may be difficult to reduce vehicle speeds around schools when there is insufficient infrastructure for street signs. Alternatively, lack of separation of car and bus traffic from bicyclists and pedestrians contributes to unsafe and dangerous road conditions. This is more of a problem in lower- and middle-income countries, where bicycles and motorized 2-wheel vehicles are used to carry children as well as goods, while the drivers negotiate among rapidly moving vehicles. With rising income, these countries have seen increases in both the number of cars and the number of 2-wheeled vehicles, with a corresponding increase in the number of related injuries.

For reducing **drowning deaths** , strategies that have proven effective focus on creating barriers between children and water hazards, such as covering wells, buckets, and other standing sources of water, and placing high fences around pools (see Chapter 91). **Burns** have been addressed by advocating for installation of smoke detectors and lowering the temperature of water from water heaters (see Chapter 92).

Out-of-Hospital Care

Out-of-hospital care comprises access to emergency services, prehospital care, and interfacility transport of patients. Morbidity and mortality arise from delayed or limited access to emergency care, lack of prehospital care, transport without proper monitoring or trained personnel, or delayed transport to a higher level of care. *Safe transport of seriously ill children* is a neglected global health issue. An emergency response system must address the following links in the patient's care: a communication system with prompt activation of EMS, the correct assessment and initial treatment of the patient, and the rapid transport to definitive care.

Access to Care

When a child is injured or ill, a parent or caretaker must be able to access help and activate EMS. Many countries worldwide have dedicated emergency numbers to rapidly dispatch medical, police, or fire services. The simple 112 emergency number has been adopted and is being phased in throughout the European Union (EU) member states, to access medical, fire, and police services, in addition to secondary regional emergency access numbers. The universal U.S. emergency number system 911 today covers the large majority of the country (98%) and has enhanced features of automatically linking the phone number to an address. However, there remain limitations to universal access resulting from absence of phones in some households, unclear addresses in rural areas, and insufficient reach of the emergency system.

In the majority of low- and middle-income countries, no such universal emergency numbers have been established, requiring access by direct dialing to an ambulance, if such private services exist. In most low- and middle-income countries, the family must bring the ill or injured child to the health facility for stabilization and treatment. For this to occur, families must overcome financial and geographic barriers, which can result in delayed presentation for care. This delay predictably increases the acuity of the illness or injury and associated complications and decreases the likelihood of full recovery and survival.

Prehospital Care

In regions with maturing EMS systems, there must be adequately trained personnel to stabilize and transport the child to a medical facility. The quality and level of training of such prehospital personnel vary tremendously among countries and within regions of the same country. In urban areas, there is a greater concentration of medical care and therefore a greater opportunity to have strong prehospital training. In most of Asia and sub-Saharan Africa, trained personnel are used primarily to transfer patients between health facilities, not from the initial site of illness or injury. In most high-income countries, medical services are dispatched to the patient.

In the French model, Service d'Aide Médicale Urgente (SAMU), a physician, often an emergency medicine specialist, will review calls for acuity and can dispatch a physician-led team by ambulance to go to the patient's home to assess, stabilize, and initiate treatment. This Franco-German system is used in other countries, including many in Latin America and Europe. There are no clear data on the cost-effectiveness and patient outcomes associated with delivery of patients to the nearest facility vs bringing hospital resources to the patient.

Around the world, the effort to establish standardized approaches to prehospital care exists primarily in the form of courses to educate EMS and hospital personnel in the emergency management of patients. For trauma care, the WHO manuals *Prehospital Trauma Care Systems* and *Guidelines for Essential Trauma Care* both focus on guidelines for prehospital and trauma care systems that are affordable and sustainable. The AAP course Pediatric Education for Prehospital Professionals is a dynamic, modularized teaching tool designed to provide specific pediatric prehospital education that can be adapted to any EMS system. Table 79.6 describes additional prehospital resources.

Table 79.6

Pediatric Emergency Care Resources

Prehospital

Advanced Medical Life Support (AMLS)

Newest course developed by the National Association of Emergency Medical Technicians (NAEMT) to provide more clinical teaching and reasoning around emergent medical problems. Course is open to physicians, nurses EMTs and paramedics.

www.naemt.org/education/amls/amls.aspx

Prehospital Trauma Life Support

Available in 33 countries, PHTLS is the leading continuing education program for prehospital emergency trauma care.

www.phtls.org

International Trauma Life Support

Training course for prehospital trauma care.

www.itrauma.org

Pediatric Education for Prehospital Professionals (PEPP)

Curriculum designed specifically to teach prehospital professionals how to assess and manage ill or injured children.

www.peppsite.org

Hospital Care

Pocket Book of Hospital Care for Children

WHO publication providing guidelines for the management of common illnesses with limited resources; incorporates both the Emergency Triage Assessment and Treatment (ETAT) and Integrated Management of Childhood Illness (IMCI) guidelines.

www.who.int/maternal_child_adolescent/documents/9241546700/en/index.

AFEM Handbook of Acute and Emergency Care

Management strategies based on available resources. It leads providers through a rapid, systematic, and integrated approach to stabilization and resuscitation of patients stratified to 3 resource levels: where there are no available resources, where there are minimal resources, and where there are full resources.

Available for purchase online.

Where There Is No Doctor: A Village Health Handbook

Healthcare manual for health workers, clinicians, and others involved in primary healthcare delivery and health promotion programs around the world. Available for purchase or as a free download.

www.hesperian.org

International Federation for Emergency Medicine

2012 International Standards of Care for Children in Emergency Departments.

https://www.ifem.cc/wp-content/uploads/2016/07/International-Standards-for-Children-in-Emergency-Departments-V2.0-June-2014-1.pdf

Humanitarian Emergencies

CHILDisaster Network

Registry for those with education and experience in humanitarian emergencies to volunteer their time when needed in a disaster.

www.aap.org/disaster

The Sphere Project

Downloadable modules on disaster preparedness.

www.sphereproject.org

Management of Complex Humanitarian Emergencies: Focus on Children and Families

Training course offered by the Children in Disasters Project, sponsored by the Rainbow Center for Global Child Health (RCGCH) in Cleveland, OH. Held in early June annually.

Manual for the Health Care of Children in Humanitarian Emergencies

WHO publication that provides comprehensive guidance on childcare in emergencies; includes information on care of traumatic injuries and mental health emergencies.

www.who.int/child_adolescent_health/documents/9789241596879/en/index

Access to Academic Publications Relevant to PEM

PEMdatabase.org

A website devoted to pediatric emergency medicine (PEM). Contains links to conferences, evidence-based medicine reviews, research networks, and professional organizations.

www.pemdatabase.org

HINARI Access to Research Initiative

Program established by WHO and others to enable developing countries to gain access to one of the world's largest collections of biomedical and health literature.

www.who.int/hinari/en

Involvement

ACEP Ambassador Program

Provides the names of U.S.-boarded emergency medicine physicians who can provide advice and information on issues pertaining to the progress and status of emergency medicine in their assigned countries.

www.acep.org/content.aspx?id=25138

Section on International Emergency Medicine, American College of Emergency Physicians

This group maintains a list of international organizations and clinical opportunities, many of which involve emergency care of children.

http://www.acep.org/_InternationalSection/International-Emergency-Medicine-Related-Resources/

Section of International Child Health, American Academy of Pediatrics

Lists non-U.S. clinical opportunities, many of which involve emergency care.

http://www2.aap.org/sections/ich/working_overseas.htm

Organizations Involved in International PEM Activities

U.S. Agency for International Development (USAID)
Government agency providing U.S. economic and humanitarian assistance worldwide.
www.usaid.gov
World Health Organization (WHO)
Publication catalog, media resources, health articles, and current health news.
www.who.int/topics/child_health/en
United Nations Children's Fund (UNICEF)
Organization dedicated to providing lifesaving assistance to children affected by disasters and to protecting their rights in any circumstances; formerly United Nations International Children's Emergency Fund.
www.unicef.org
Safe Kids Worldwide
The first and only international nonprofit organization dedicated solely to preventing unintentional childhood injury.
www.safekids.org

Although most middle- and high-income countries have a system of trained EMS workers, low-income countries lack this advanced tier of emergency care. In these countries, commercial drivers, volunteers, and willing bystanders provide the first line of care. Training a cadre of first responders can rely on existing networks of aid or can be drawn from specific populations, such as students, soldiers, or public servants. Training needs to emphasize basic lifesaving and limb-saving interventions, including how to stop bleeding and support breathing, access advanced care, and splint broken limbs. In Ghana, for example, taxi drivers participated in a first-aid course that relied heavily on demonstration and practice rather than knowledge transfer through didactic sessions. Taxi drivers were selected because they already provided much of the transport for injured patients, either voluntarily or for pay by the family. Two years after the course, external evaluators favorably rated the quality of their care compared with untrained drivers. In rural areas, such first responders become vital in providing emergency interventions when more definitive care is distant. Thus a system of trained first responders forms the foundation of an effective prehospital system.

Methods of Transport

In many low-income countries, there is no means of transport other than the family's motorized or other type of transport. Health centers may only have 1 vehicle for transport to a higher-level facility. This vehicle may also be used for outreach primary care services, such as offering immunizations and collecting drugs and equipment from a central supply location, and sometimes, improperly for personal reasons by local officials or politicians. In large cities, taxis and auto rickshaws are frequently used because they are rapidly available, well disseminated, and able to pass around traffic jams. Where organized prehospital systems exist, different types of vehicles are adapted for emergency transportation, from fully equipped ambulances to basic transport with trained personnel. The WHO recommends identifying transport vehicles in advance, choosing vehicles that can be repaired and maintained locally, and equipping the vehicles according to recognized standards. Therefore the provision of available and appropriately staffed and equipped transport vehicles is crucial to the realization of recommended emergency care plans.

Hospital-Based Care

Once a child has reached a medical facility for the care of an injury or illness, adequate emergency services must be available. In many countries the ED serves only as a triage area where patients are distinguished by their likely disease process and directed for admission to the corresponding unit within the hospital. Strengthening emergency services includes seeing the ED as a unit where definitive treatment can be provided to the ill and injured child. Critically ill children must receive not only prompt care but also correct care. Such expedience and accuracy are ensured by implementation of an effective triage system, moving the sickest patients to immediate care and standardizing the initial care of emergency conditions.

Triage

Children requiring emergency care frequently are not promptly recognized. Too often, children presenting to EDs are treated on a first-come first-served basis, in an approach that creates long waiting times for critically ill children, a contributor to unnecessary mortality. Medical facilities need to adopt an efficient and effective triage system to respond rapidly to the needs of patients and to assign the appropriate amount of resources. To this end, WHO has developed a course entitled **Emergency Triage Assessment and Treatment (ETAT)** . This course teaches to triage patients on arrival as having emergency, priority, or nonurgent signs and to provide emergency treatment for life-threatening conditions. ETAT emphasizes the evaluation of a patient's **ABCD status** to identify emergency situations—the patency of the airway (A), the quality of breathing (B), the quality of circulation and presence of coma or convulsions (C), and the presence of severe dehydration (D).

One of the benefits of the ETAT guidelines is that they can be adapted to centers with limited resources and are applicable to areas with high morbidity and mortality from meningitis, dehydration, malaria, respiratory illness, and malnutrition. Another benefit is that the care algorithms are based on limited diagnostic studies, that is, hemoglobin measurement, blood smear for malaria, and bedside blood glucose testing. Widely accepted triage assessment guidelines are teachable to emergency care staff, and their adoption can provide better organization within a healthcare center. At the Queen Elizabeth Central Hospital in Blantyre, Malawi, for example, the institution of triage and rapid treatment in its emergency care center led to a 50% decrease in the mortality of children within 24 hr of presentation to the hospital, with a further 50% decrease as implementation and practice of triaging patients have continued.

Beyond triage, education on overall emergency center organization is a low-resource intervention that can obviate some of the obstacles to quality care delivery. Additionally, the arrangement of short-stay areas (hydration and infusion rooms) can lessen the burden on inpatient units.

Pediatric-Specific Emergency Centers

Anecdotally, most countries have developed at least 1 pediatric-capable center, usually as part of an academic medical center. The emergency services in these centers are variable, but certainly can be a starting point from which to build overall improvement in pediatric emergency care.

Practitioners

Throughout the world, nurses, paramedics, and nonspecialist physicians provide most of the care to acutely ill or injured children. The majority of sick children attend local clinics or district or central hospitals, where financial and human resources are not always matched to the potential acuity of presenting patient complaints. Nominal supervision is provided to staff attending these patients. Pediatric EDs located in tertiary hospitals are often staffed by training physicians with little or no supervision from faculty, who themselves may have limited exposure to or training in PEM. General hospitals lack dedicated pediatric staff; guidelines as to which patients should be moved to a higher level of care are often not standardized and depend on local influences and/or cultural beliefs about health and illness.

Clinical Guidelines

The **Integrated Management of Childhood Illnesses (IMCI)** guidelines were developed by the WHO and UNICEF to provide assistance in the initial triage and management of the presenting signs and symptoms of the major killers of children <5 yr old in first-level health facilities (e.g., clinics, health centers, outpatient departments of hospitals). The flow charts within each chapter of the IMCI manuals allow easy accessibility to materials that can enhance education and outreach to less experienced health workers.

Evaluations in various countries of the implementation of IMCI guidelines have shown improvements in health worker performance and quality of care, as well as decreases in delay in treatment and mortality of the under-5 population. These guidelines also dramatically reduce the cost of healthcare. The WHO website provides all the necessary implementation tools, including course manuals and evaluation tools.

The International Federation of Emergency Medicine developed standards to improve emergency care globally. These standards are not just aimed at dedicated EDs, but at any setting where emergency care takes place, regardless of the providers or the resources available. At the same time, however, the existence of the standards allows sites to advocate for improved resources dedicated to expertise in the various aspects of providing quality emergency care for children. The standards address design of care spaces, child- and family-centered care, assessment of ill and injured children, staff training and competencies, quality and safety, and disaster response.

Trauma

Morbidity and mortality from trauma are among the most prevalent problems for children worldwide. Trauma care presents the challenge of sequential, often simple, interventions that must be performed in a timely manner to limit the severity of the outcome. However, with lack of specific training, signs and symptoms of pediatric trauma may go unrecognized or may be underappreciated.

Trauma courses such as Advanced Trauma Life Support (ATLS) are educational tools that can be disseminated to improve the quality of care at emergency centers worldwide. For low-resource settings, WHO has developed the Integrated Management for Emergency and Essential Surgical Care toolkit, which provides clear directions and reasoning for the initial care of injured patients. Not expressly addressed in the ATLS course is specific concern about **child abuse** as the cause of trauma. This is an area of pediatric care that many countries do not yet address comprehensively in their medical training, their law enforcement, or their judicial systems. The epidemiologic need for reliable trauma registries is great, as is the need to identify personnel with trauma management skill sets and dedicated trauma centers to serve as higher-level referral sites.

Equipment

Pediatric emergency equipment guidelines are available for a variety of settings where acutely ill and injured children would present. Although these equipment guidelines may represent minimum supplies to treat the widest variety of pediatric emergencies, the roles of substitution and improvisation often provide for equivalent function of recommended supplies.

Inpatient Services

After the initial stabilization, children requiring ongoing care are admitted to the hospital. The quality of inpatient services varies greatly depending on institutional and provider experience, comfort with pediatric conditions, and the resources available to treat them. WHO has produced the *Pocket Book of Hospital Care for Children*, which is based on IMCI guidelines and focuses on inpatient management of high-morbidity/high-mortality illnesses common in developing countries.

Humanitarian Disasters

Children are a vulnerable population who experience disproportionate suffering during humanitarian emergencies, either natural (earthquakes, tsunamis, hurricanes, floods, droughts) or manmade (armed conflicts, terrorist attacks). The under-5 population is especially susceptible to infectious diseases, malnutrition, and trauma following disasters. The **Rainbow Center for Global**

Child Health at the Case Western Reserve University School of Medicine offers a training course, *Management of Humanitarian Emergencies: Focus on Children and Families*, to educate and train health professionals, relief workers, and policymakers to recognize and address the unique needs of children affected by manmade and natural disasters worldwide. AAP also maintains a CHILD disaster Network, which acts as an electronic database of child health professionals with education and experience in humanitarian emergencies. Nongovernmental organizations can access the database to solicit practitioners to aid in disaster response.

The WHO *Manual for the Health Care of Children in Humanitarian Emergencies* is based on IMCI guidelines and addresses the emergency care of children in disaster situations where hospital facilities and resources are not immediately available. It goes beyond the IMCI guidelines by discussing initial assessment and management of trauma, burns, and poisonings. Preexisting IMCI guidelines assumed a functioning health system that facilitated the referral of children, which may not be available in all emergency situations. This manual also includes the initial management of severe conditions, such as injuries, burns, neonatal illness, and psychosocial problems, which are considered high priority in acute care settings.

Exchange and Dissemination of Information

The WHO established the **HINARI** (Health InterNetwork Access to Research Initiative) program to allow free or reduced-cost access to more than 6,200 journal publications. This internet access is made available to the 108 countries with gross national income per capita <$3,500. For middle-income countries not meeting the financial eligibility, internet access continues to be a barrier, and resources may be limited to out-of-date textbooks and journals.

Another valuable tool is the website pemdatabase.org . This nonproprietary site was started as an online resource for PEM practitioners. It contains links to PEM abstracts and articles, evidence-based reviews, pediatric resuscitation websites, and relevant journals, as well as PEM conferences and professional organizations.

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CHAPTER 80

Triage of the Acutely Ill Child

Anna K. Weiss, Frances B. Balamuth

Identifying the acutely ill child in the ambulatory setting is a challenge. Children presenting to pediatricians' offices, urgent care practices, and emergency departments (EDs) may have a range of illnesses from simple viral infections to life-threatening emergencies. Although most children in this setting will have a benign course of illness, it is incumbent on the pediatric practitioner to quickly and accurately discern which children are likely to deteriorate from potentially serious or life-threatening disease. When assessing an acutely ill child, practitioners must remember that the early signs of severe illness may be subtle.

Assessment of Vital Signs

Assessment of vital signs is critical in all pediatric visits for acute illness, including temperature, heart rate, respiratory rate, and blood pressure. Normal vital signs vary with age. Although there have been increasing efforts to build evidence-based vital sign cutoffs for different age-groups, most institutions use nonempirically derived cutoffs such as those in Pediatric Advanced Life Support (PALS). **Tachycardia** is common in children presenting for acute care and can result from benign (fever, pain, dehydration) to life-threatening (septic shock, hemorrhage) conditions. An abnormal heart rate should prompt a full history and physical examination, as described later, and careful *reassessment* (often multiple times) after the presumed cause is identified and treated. The vast majority of children will improve after initiation of simple interventions such as antipyretics or analgesia. Tachycardia that persists after fever, pain, and dehydration have been treated *must* be evaluated further, particularly if the child appears ill or has deficit in perfusion or altered mental state.

Tachypnea is also common and has many causes, including fever, respiratory conditions (bronchiolitis, asthma, pneumonia), cardiac disease (e.g., heart failure), and metabolic acidosis (shock, poisoning, diabetic ketoacidosis). Similar to tachycardia, tachypnea often resolves with antipyretics in febrile children, and should be reassessed to ensure resolution once fever has been managed. In cases where bronchiolitis and asthma have been ruled out, persistent tachypnea and fever can be a sign of pneumonia, even in the absence of focal lung findings on examination. Consider evaluation for metabolic acidosis in cases of significant tachypnea without apparent pulmonary or cardiac causes. **Apnea** is a sign of respiratory failure and should be *treated emergently with bag-valve-mask ventilation and immediate ED evaluation.*

Hypotension is rare in children, and when present, it is a sign of critical illness. Children with hypotension should be evaluated in an ED. Hypotension is evidence of decompensated circulatory shock and can result from severe dehydration, sepsis, hemorrhage, neurogenic spinal shock, or cardiogenic shock.

Pulse oximetry (oxygen-hemoglobin saturation, Spo_2) should be assessed in children with respiratory or cardiac illness/compromise and also in children with underlying abnormalities of oxygenation. Healthy children have Spo_2 >95%. The practitioner should consider evaluating for any underlying respiratory or cardiac causes in children with Spo_2 <93–95%. For children with underlying abnormalities, the child's baseline Spo_2 should be assessed and alterations from that baseline should be investigated further.

The combination of bradycardia, hypertension, and altered breathing known as **Cushing triad** can be a sign of life-threatening increased intracranial pressure (ICP) and should be evaluated in an ED. Anisocoria and a 6th cranial nerve palsy are other signs of increased ICP. **Toxidromes** should also be considered in children with abnormal combinations of vital signs (see Chapter 77).

History

A thorough history is paramount to identifying patients whose condition will require prompt intervention. Obtaining an accurate history from young patients is challenging, particularly with preverbal or very anxious children who are unable or unwilling to localize the source of their discomfort. In such instances, parents or caretakers often provide the most important information, and their perceptions of the child's course of illness must be carefully considered. Pediatricians should be guided by the patient's chief complaint to ask *open-*

ended questions that help distinguish between benign and potentially life-threatening disease entities. The most common complaints leading to acute care visits among children include fever, headache and altered mental status, trauma, abdominal pain and vomiting, respiratory distress, and chest pain. Table 80.1 describes signs and symptoms that should prompt immediate transfer to an ED or, if already in the ED, initiation of rapid intervention.

Table 80.1

History and Examination Findings That Should Prompt Immediate Intervention and/or Transfer to Emergency Department

HISTORY AND EXAM FINDINGS	**RISK FACTORS**
RED FLAGS FOR RESPIRATORY FAILURE	
Tachycardia Tachypnea Cyanosis Apnea Brief resolved unexplained event (BRUE) with cyanosis or change in tone Suspected button-battery ingestion Foreign body aspiration with respiratory distress Respiratory distress with hypoxemia and/or altered mental status	Tracheostomy Ventilator dependence History of critical airway
RED FLAGS FOR CIRCULATORY FAILURE	
Tachycardia Tachypnea Cyanosis Apnea Petechial or purpuric rashes Erythroderma Peritonitis Bilious emesis Posttonsillectomy or postadenoidectomy with bleeding Extremity trauma with neurovascular deficits	Oncology (or other immunosuppressed) patients Bone marrow or solid-organ transplants Sickle cell (or otherwise asplenic) patients Infants <56 days old Cardiac patient with change from baseline pulse oximetry Bleeding disorder with trauma
RED FLAGS FOR NEUROLOGIC FAILURE	
Tachycardia Bradycardia-hypertension Double vision Unequal pupils Apnea Frequent or prolonged seizure(s) Focal neurologic deficit(s) Acute onset of severe headache Suicidal or homicidal ideation, psychosis	Ventriculoperitoneal shunt Diabetes or metabolic disease with altered mental status Hypoxic-ischemic encephalopathy Clotting disorder with neurologic change(s)

Adapted from Farah MM, Tay Y, Lavelle J. A general approach to ill and injured children. In Shaw KN, Bachur RG, editors: *Fleischer and Ludwig's textbook of pediatric emergency medicine,* Philadelphia, 2015, LWW.

Fever is the most common reason for a sick-child visit. Most cases of fever are the result of self-limited viral infection. However, pediatricians need to be aware of the age-dependent potential for serious bacterial infections, such as urinary tract infection (UTI), sepsis, meningitis, pneumonia, acute abdominal infection, and osteoarticular infection.

During the 1st 2 mo of life, the neonate is at risk for sepsis caused by pathogens that are uncommon in older children. These organisms include group B streptococcus, *Escherichia coli* , *Listeria monocytogenes* , and herpes simplex virus (HSV). In neonates, the history must include untreated maternal obstetric information and the patient's birth history. Risk factors for sepsis include untreated maternal group B streptococcus colonization, prematurity, chorioamnionitis, and prolonged rupture of membranes. If there is a maternal history of sexually transmitted infections (STIs) during the pregnancy, the differential diagnosis must be expanded to include those pathogens. Septic infants can present with lethargy, poor feeding, grunting respirations, and cool or mottled extremities, in addition to fever (or hypothermia). Febrile infants in the 1st 1-2 mo of life should be evaluated broadly for infection, including sampling blood, urine, and cerebrospinal fluid (CSF).

When the infant matures beyond 2 mo of age and receives their 1st set of vaccinations, serious bacterial infections become less common. Evaluation to rule out serious infection is an important part of treating the febrile older child. Children with fever should have a full set of vital signs, history, and physical examination to ensure that critical illness is absent and to identify any focal source. Red flags for **septic shock** include hypotension, poor perfusion, altered mental status, or the presence of purpuric or erythrodermic rash. Red flags for **meningitis** include severe headache, meningismus, and altered mental state. The presence of any of these signs should prompt emergency evaluation in the ED or rapid treatment if the patient is already in the ED.

Additional focal findings to consider include evaluation for acute otitis media, pharyngitis, pneumonia, abdominal infections (bacterial enteritis, appendicitis), skin and soft tissue infections, septic arthritis, and osteomyelitis. Occult UTI should be considered if 3 of the following risk factors are present: age <1 yr, fever >39°C, fever >48 hr, and no focal source of fever. Pneumonia should be considered in the presence of tachypnea, hypoxia, or focal findings on chest examination. Bacteremia is rare in the post–pneumococcal and *Haemophilus influenzae* vaccine era but should be considered if staphylococcal infection or meningococcemia is suspected, as well as in unvaccinated children or children with signs of septic shock. In addition to infection, inflammatory conditions to consider include juvenile idiopathic arthritis and Kawasaki disease. The diagnosis of **Kawasaki disease** should be considered if the patient meets the diagnostic criteria for this illness although some patients may have an atypical or incomplete presentation (see Chapter 191).

For patients presenting in an **altered mental state** , the pediatrician should inquire about any symptoms, such as fever or headache. Screening questions should explore feeding changes, medications in the household, ill contacts, and the possibility of trauma. Parents will often describe a febrile child as lethargic, but further questioning will reveal a tired-appearing child who interacts appropriately when no longer febrile. The child who appears ill only when febrile must be differentiated from the lethargic patient who presents with suspected sepsis or meningitis, and from the child whose altered behavior is secondary to an intracranial emergency or seizure. Infants with meningitis, sepsis, or cardiac defects may have a history of irritability, being inconsolable, poor feeders, grunting breathing, seizures, poor urine output, and/or color changes such as pallor, mottling, or cyanosis. Patients with poisoning or inborn error of metabolism can also present with lethargy, poor feeding, unusual odors, seizures, and vomiting. Nonaccidental **trauma** should always be considered in a lethargic infant, particularly in the absence of additional signs or symptoms. In infants and young toddlers, rapidly growing head circumference or bulging anterior fontanel may signal increased ICP. Older children may present with altered mental state as a result of meningitis/encephalitis, trauma, or ingestions. School-age children and adolescents with meningitis may have a history of fever and neck pain; other associated symptoms may include rash, headache, photophobia, or vomiting. Children with ingestions can present with other abnormal neurologic symptoms, such as ataxia, slurred speech, and seizures, or with characteristic constellations of vital sign changes and other physical findings consistent with certain toxidromes.

In patients with **headache** , ask questions about the chronicity of the headache and any accompanying symptoms. Headaches that occur on arising in the morning, are worse when lying flat, or are accompanied by vomiting are concerning for increased ICP. Similarly, headache accompanied by focal neurologic deficit should be referred to an ED for urgent head imaging. While migraine headaches in teenagers are similar in presentation to those in adults (unilateral, throbbing, accompanied by an aura), pediatric practitioners should be aware that migraines in prepubertal children may have a nonclassic presentation and may be bilateral and not accompanied by aura, photophobia, or phonophobia.

Parents may interpret a variety of symptoms as **respiratory distress** , and care must be taken to distinguish normal and benign respiratory patterns from true respiratory distress. Tachypnea secondary to fever is a common source of parental anxiety, and parents of newborn infants are sometimes alarmed by the presence of periodic breathing. Parents should be questioned about their child's other symptoms, such as fever, limitation of neck movement, drooling, choking, and the presence of stridor or wheezing. A history of apnea or cyanosis warrants further investigation. Practitioners should also remember that tachypnea in a child without evidence of true respiratory distress may be evidence of compensation for shock or metabolic acidosis, both of which will require rapid treatment. Although wheezing is often secondary to bronchospasm, it can also be caused by cardiac disease or congenital airway anomalies such as vascular rings. Parents may interpret true **stridor** as noisy breathing or wheezing. Stridor is most frequently caused by upper airway obstruction such as croup. However, anatomic abnormalities such as laryngeal webs, laryngomalacia, subglottic stenosis, and paralyzed vocal cords also cause stridor. Toddlers who present with breathing difficulty after a coughing or choking episode should be evaluated for **foreign body aspiration** . In these cases, practitioners must ask about the possibility of button-battery ingestion, as this constitutes a true medical emergency that warrants immediate endoscopic removal or transfer to a facility that can perform the procedure. In toxic-appearing children with stridor, the pediatrician should consider epiglottitis, bacterial tracheitis, or a rapidly expanding retropharyngeal abscess. The incidence of epiglottitis has greatly declined with the advent of the *H. influenzae* type b (Hib) vaccine, but it remains a possibility in the unimmunized or partially immunized patient. Children with retropharyngeal abscesses may also present with drooling and limitation of neck movement (especially hyperextension) after a recent upper respiratory infection or penetrating mouth injury.

Abdominal pain is a very common complaint in the ambulatory setting and can herald either acute intraabdominal or pelvic pathology, or it can be a subtler sign of systemic illness. Both relatively benign (e.g., streptococcal infection, UTI, pneumonia) and severe abdominal (e.g., appendicitis) or systemic (e.g., diabetic ketoacidosis) illness can present with abdominal pain, and questions to the patient and parent should include whether there is an extraabdominal source of discomfort. Questions should include details about pain onset and location; presence of accompanying symptoms, such as fever, abdominal distention; and changes in feeding, urination, and stooling patterns. Care should be taken to elicit a history of peritonitis or obstruction, including worsening pain with abrupt movements and persistent or bilious vomiting.

In neonates, a tender abdomen with or without bilious emesis should raise concern for the presence of a small bowel obstruction (volvulus). These infants appear ill and may have a history of decreased stooling. Pediatricians should be wary of neonates with abdominal tenderness and bloody stools, because 10% of cases of necrotizing enterocolitis occur in term infants. Infants with milk protein intolerance can also present with bloody stools, but these infants appear well and do not have abdominal tenderness. In older patients the differential diagnosis for emergency causes of abdominal pain expands to include intussusception and appendicitis. Patients with intussusception present in a variety of ways, ranging from colicky abdominal pain but otherwise well between episodes to being lethargic or in shock. The diagnosis of appendicitis in the child younger than 3 yr is extremely difficult because children in this age-group cannot localize pain well. In adolescent females with abdominal pain, practitioners must obtain a menstrual and sexual history, because acute lower abdominal pain may be caused by adnexal pathology, including ovarian torsion or ectopic pregnancy.

For patients with **vomiting** , pediatricians should ask if they have experienced bilious or blood-stained emesis, abdominal distention or constipation, weight changes, and diarrhea or bloody stools. An infant with bilious emesis and abdominal distention may have intestinal obstruction (as with midgut volvulus or Hirschsprung disease), whereas an infant who appears immediately hungry after nonbilious projectile vomiting may have pyloric stenosis. In an older child, vomiting may be caused by peritonitis or obstruction, as well as by systemic illnesses, including diabetic ketoacidosis, ingestion, or trauma. Patients with headache and vomiting raise the concern for increased ICP and should be questioned about neurologic changes, meningismus, and fever.

Practitioners should also obtain a thorough account of the child's **past medical history** . It is important to be aware of any underlying chronic problems that might predispose the child to recurring infections or a serious acute illness. Children with sickle cell anemia, indwelling central venous access devices, or immune compromise are at increased risk for bacteremia and sepsis. Similarly, children with prior surgery, including ventriculoperitoneal shunt placement or intraabdominal procedures, can develop complications from their previous surgeries.

Physical Examination

Observation is important when evaluating the acutely ill child. Most observational data that the pediatrician gathers should focus on assessing the child's response to stimuli. Does the child awaken easily? Does the child smile and interact with the parent, or with the examiner? Evaluating these responses requires knowledge of normal child development and an understanding of the manner in which normal responses are elicited, depending on the child's age.

During the physical examination, the pediatric practitioner seeks evidence of illness. The portions of the exam that require the child to be most cooperative are completed first. Initially, it is best to seat the child on the parent's lap; the older child may be seated on the examination table. It is also important to assess the child's willingness to move, as well as ease of movement. It is reassuring to see the child moving about on the parent's lap with ease and without discomfort. *Vital signs are often overlooked but are invaluable in assessing ill children.* The presence of tachycardia out of proportion to fever and the presence of tachypnea and blood pressure abnormalities raise the suspicion for more serious illness. The respiratory evaluation includes determining respiratory rate, noting the presence or absence of hypoxia by SpO_2, and noting any evidence of inspiratory stridor, expiratory wheezing, grunting, coughing, or increased work of breathing (e.g., retractions, nasal flaring, accessory muscle use). The **skin** should be carefully examined for rashes. Frequently, viral infections cause an exanthem, and many of these eruptions are diagnostic, such as the reticulated rash and slapped-cheek appearance of parvovirus infections and the stereotypical appearance of hand-foot-and-mouth disease caused by coxsackieviruses, as well as measles, chickenpox, and roseola. The skin examination may also yield evidence of more serious infections, including petechiae and purpura associated with bacteremia and erythroderma associated with a toxin-producing systemic infection. Cutaneous perfusion should be assessed by warmth and capillary refill time. The extremities may then be evaluated not only for ease of movement but also for the presence of swelling, warmth, tenderness, or alterations in perfusion. Such abnormalities may indicate focal infections (e.g., cellulitis, bone/joint infection) or vascular changes (e.g., arterial or venous thromboembolus).

When an infant is seated and is least perturbed, the examiner should assess the anterior fontanel to determine whether it is depressed, flat, or bulging. While the child is calm and cooperative, the **eyes** should be examined to identify features that might indicate an infectious or neurologic process. Often, viral infections result in watery discharge or redness of the bulbar conjunctivae. Bacterial infection, if superficial, results in purulent drainage; if the infection is more deep-seated, tenderness, swelling, and redness of the tissues surrounding the eye may be present, as well as proptosis, altered visual acuity, and impaired extraocular movement. Abnormalities in pupillary response or extraocular movements may also be indicators of cranial nerve abnormalities and if new, are indications for head imaging.

During this initial portion of the physical examination, when the child is most comfortable (and therefore most likely to be quiet), the **heart and lungs** are auscultated. It is important to assess the adequacy of air entry into the lungs, the equality of breath sounds, and any evidence of adventitial breath sounds, especially wheezes, rales, or rhonchi. The coarse sound of air moving through a congested nasal passage is frequently transmitted to the lungs. The examiner can become attuned to these coarse sounds by placing the stethoscope near the child's nose and then compensating for this sound as the chest is auscultated. The cardiac examination is next; findings such as pericardial friction rubs, loud murmurs, and distant heart sounds may indicate cardiac inflammation or infection. In the neonate, murmurs may herald congenital heart disease, especially in the presence of cyanosis, unequal extremity pulses, or a differential in upper- vs lower-extremity blood pressures. A complete cardiac exam should also look for displacement of the PMI (point of maximal impulse) and the presence of jugular venous distention or facial plethora.

The components of the physical examination that are more bothersome to the child are completed last. This is best done with the patient on the examination table. Initially, the **neck** is examined to assess for areas of swelling, redness, or tenderness, as may be seen in cervical adenitis. Resistance to neck movement should prompt evaluation for signs of meningeal irritation or retropharyngeal abscess. During examination of the **abdomen** , the diaper, if present, is removed. The abdomen is inspected for distention. Auscultation is performed to assess adequacy of bowel sounds, followed by palpation. Every attempt should be made to quiet a fussing child during this part of the exam; if this is not possible, practitioners should note that increased crying as the abdomen is palpated may indicate tenderness, especially if this finding is focally reproducible. In addition to focal tenderness, palpation may elicit involuntary guarding or rebound tenderness (including tenderness to percussion); these findings indicate peritoneal irritation, as seen in appendicitis. During palpation of the abdomen, practitioners should look for signs of hepatomegaly or splenomegaly. When palpating the bottom-most edge of the liver or spleen, examiners should begin in the pelvis and work upward toward the ribs, because severe organomegaly can be missed if the examiner begins palpating in the mid-abdomen. The **inguinal area and genitals** are then examined. One should assess the inguinal area for hernias. Care should be taken to examine the testicles of boys with abdominal pain; testicular trauma, testicular torsion, and epididymitis all may present with abdominal discomfort. A unilateral swollen or painful testicle with an absent cremasteric reflex on the affected side is concerning for testicular torsion and should be referred for emergent ultrasound and urologic consultation. After the genital exam, the child is then placed in the prone position, and abnormalities of the **back** are sought. The spine and costovertebral angle areas are percussed to elicit any tenderness; such findings may be indicative of vertebral osteomyelitis or diskitis and pyelonephritis, respectively.

Examining the **ears and throat** completes the physical examination. These are usually the most bothersome parts of the examination for the child, and parents frequently can be helpful in minimizing head movement. During the oropharyngeal examination, it is important to document the presence of enanthemas; these may be seen in many infectious processes, such as stomatitis caused by herpes or enteroviruses. This portion of the examination is also important in documenting inflammation or exudates on the tonsils, which may indicate viral or bacterial infection. Findings such as trismus or unilateral tonsillar swelling are concerning for peritonsillar abscess and for infections in the para- and retropharyngeal spaces; such cases should be referred for specialist ear, nose, and throat evaluation and imaging of the neck.

Repeating portions of the assessment may be indicated. If the child cried continuously during the initial clinical evaluation, the examiner may not be certain whether the crying was caused by the high fever, stranger anxiety, or pain, or is indicative of a serious or localizing illness. Constant crying also makes portions of the physical examination, such as auscultation of the chest, more difficult. Before a repeat assessment is performed, efforts to make the child as comfortable as possible are indicated. In young infants, **persistent irritability** , even when the examiner is absent from the room, is concerning for meningitis, encephalitis, or other causes of meningeal irritation (e.g., intracranial injury from nonaccidental trauma). When faced with a truly inconsolable infant, practitioners should have a low threshold to obtain head imaging and/or perform lumbar puncture, as the clinical scenario dictates.

Management

Most patients who present to the pediatrician's office with an acute illness will not require acute stabilization. However, the pediatrician needs to be prepared to evaluate and begin resuscitation for the seriously ill or unstable child. Outpatient pediatric offices and urgent care facilities should be stocked with appropriate equipment necessary to stabilize an acutely ill child. Maintenance of that equipment and ongoing training of the office staff in its use is required, and every effort should be made to ensure that pediatric clinicians are PALS certified (see Chapter 81).

The evaluation of the potentially unstable child must begin with assessment of the ABCs—airway, breathing, and circulation. When assessing the **airway** , chest rise should be evaluated and evidence of increased work of breathing sought. The examiner should ensure that the trachea is midline and should listen carefully for evidence of air exchange at the level of the extrathoracic airway. If the airway is patent and no signs of obstruction are present, the patient is allowed to assume a position of comfort. If the child shows signs of airway obstruction, repositioning of the head with the chin-lift maneuver may alleviate the obstruction. An oral or nasal airway may be necessary in patients in whom airway patency cannot be maintained. These devices are not well tolerated in conscious patients because they may induce gagging or vomiting; instead, they are most often used to facilitate effective bag-valve-mask ventilation in semiconscious or unconscious children. Once airway patency has been established, the adequacy of **breathing** should be evaluated. Slow respiratory rates or cyanosis may signal impending respiratory failure. If the airway is patent but the child's respiratory effort is inadequate, positive pressure ventilation via bag-valve-mask support should be initiated. Oxygen should be administered to all seriously ill or hypoxic children via nasal cannula or face mask. Auscultation of the lung fields should assess for air entry, symmetry of breath sounds, and presence of adventitious breath sounds such as crackles or wheezes. Bronchodilator therapy can be initiated to alleviate bronchospasm. Racemic epinephrine is indicated for stridor at rest in a patient with croup. Once airway and breathing have been addressed, **circulation** must be evaluated. Symptoms of *shock* include tachycardia, cool extremities, delayed capillary refill time, mottled or pale skin, and effortless tachypnea. In children, hypotension is a late finding in shock and indicates that significant decompensation has already taken place. Vascular access is necessary for volume resuscitation in patients with impaired circulation, and an intraosseous line should be considered early if there is any difficulty in obtaining vascular access for a patient requiring resuscitation. Each time an intervention is performed, the clinician should **reassess the patient** to determine whether interventions have been successful and whether additional care is needed.

Disposition

The majority of children evaluated in the office or urgent care setting for an acute illness can be managed as an **outpatient** . These patients should have a reassuring physical examination, stable vital signs, and an adequate follow-up plan before being sent home. A mildly dehydrated patient can be discharged home for a trial of oral rehydration. Patients with respiratory illness who exhibit signs of mild respiratory distress may be monitored at home, with a repeat examination scheduled the next day. Depending on the child's condition, the comfort of the parents, and the relationship of the family with the physician, telephone follow-up may be all that is necessary. When no specific diagnosis has been established at the first outpatient visit, a follow-up examination may yield the diagnosis and can provide reassurance for both the caregiver and the practitioner that a child's severity of illness has not progressed.

However, if it is deemed that the child needs a higher level of care, it is the pediatrician's responsibility to decide what method of transfer is appropriate. Physicians may be reluctant to call for help because of a misperception that emergency 911 services should be activated only for ongoing resuscitation. Emergency medical services (EMS) transport should be initiated for any child who is physiologically unstable (e.g., with severe respiratory distress, hypoxia, signs of shock, or altered mental state). If the family's ability to comply promptly with recommendation for ED evaluation is in question, this patient also should be transported by EMS. Some physicians and families may defer calling EMS because of the perception that a parent can reach the hospital faster by private motor vehicle. Although rapidity of transport should be considered, the need for further interventions during transport and the risk of clinical decompensation are other important factors in the decision to activate EMS. Ultimately, the legal responsibility for choosing an appropriate level of transport for a patient lies with the referring physician, until responsibility of care is officially transferred to another medical provider.

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CHAPTER 81

Pediatric Emergencies and Resuscitation

Mary E. Hartman, Ira M. Cheifetz

Injuries are the leading cause of death in American children and young adults and account for more childhood deaths than all other causes combined (see Chapter 13). Rapid, effective bystander cardiopulmonary resuscitation (CPR) for children is associated with survival rates as high as 70%, with good neurologic outcome. However, bystander CPR is still provided for <50% of children who experience cardiac arrest outside medical settings. This failing has led to long-term survival rates of <40%, often with a poor neurologic outcome.

Approach to the Emergency Evaluation of a Child

The first response to a pediatric emergency of any cause is a systematic, rapid **general assessment** of the scene and the child to identify immediate threats to the child, care providers, or others. If an emergency is identified, the emergency response system (emergency medical services, EMS) should be activated immediately. Care providers should then proceed through **primary** , **secondary** , and **tertiary** assessments as allowed by the child's condition, safety of the scene, and resources available. This standardized approach provides organization to what might otherwise be a confusing or chaotic situation and reinforces an organized thought process for care providers. If at any point in these assessments the caregiver identifies a life-threatening problem, the assessment is halted and lifesaving interventions are initiated. Further assessment and intervention should be delayed until other caregivers arrive or the condition is successfully treated or stabilized.

General Assessment

On arrival at the scene of a compromised child, a caregiver's first task is a quick survey of the scene itself. Is the rescuer or child in imminent danger because of circumstances at the scene (e.g., fire, high-voltage electricity)? If so, can the child be safely extricated to a safe location for assessment and treatment? Can the child be safely moved with the appropriate precautions (i.e., cervical spine protection), if indicated? A rescuer is expected to proceed only if these important safety conditions have been met.

Once the caregiver and patient's safety has been ensured, the caregiver performs a rapid **visual survey** of the child, assessing the child's **general appearance** and **cardiopulmonary function** . This action should be only a few seconds and include assessment of (1) general appearance, determining color, tone, alertness, and responsiveness; (2) adequacy of breathing, distinguishing between normal, comfortable respirations and respiratory distress or apnea; and (3) adequacy of circulation, identifying cyanosis, pallor, or mottling. A child found unresponsive from an *unwitnessed* collapse should be approached with a gentle touch and the verbal question, “Are you OK?” If there is no response, the caregiver should immediately shout for help and send someone to activate the emergency response system and locate an **automated external defibrillator (AED)** . Figs. 81.1 and 81.2 present basic life support (BLS) pediatric cardiac arrest algorithms for 1 rescuer and 2 or more rescuers, respectively. The provider should then determine whether the child is breathing and, if not, provide 2 rescue breaths. If the child is breathing adequately, the circulation is quickly assessed. Any child with heart rate <60 beats/min or without a pulse requires immediate CPR. If the caregiver *witnesses* the sudden collapse of a child, the caregiver should have a higher suspicion for a sudden cardiac event. In this case, rapid deployment of an AED is crucial. Any interruptions in care of the child to activate EMS and locate the nearest AED should be very brief. If >1 caregiver is present, someone should always remain with the child and provide initial care or stabilization (see Fig. 81.2).

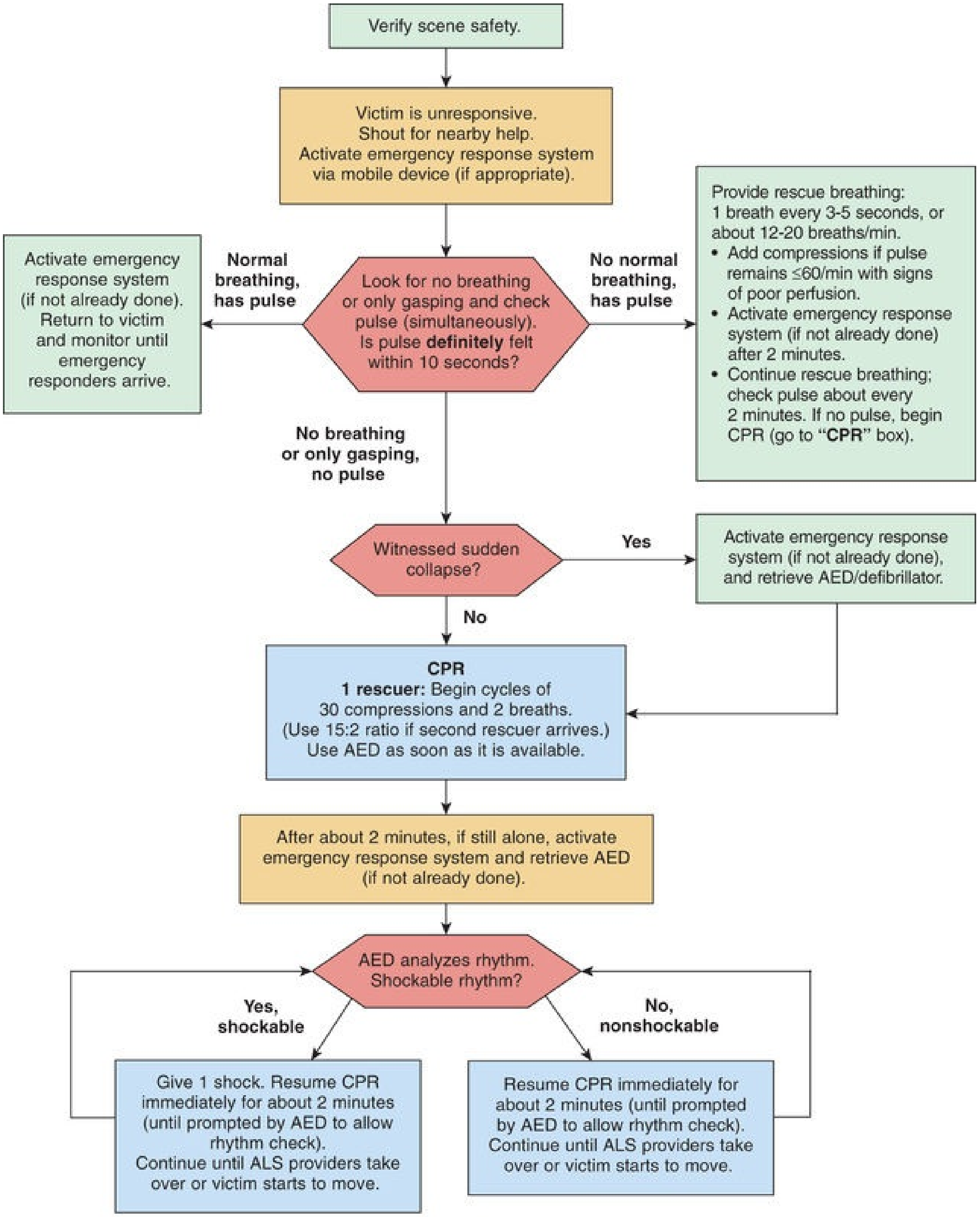
Verify scene safety.
Victim is unresponsive. Shout for nearby help. Activate emergency response system via mobile device (if appropriate).
Look for no breathing or only gasping and check pulse (simultaneously). Is pulse **definitely** felt within 10 seconds?
Normal breathing, has pulse
Activate emergency response system (if not already done). Return to victim and monitor until emergency responders arrive.
No normal breathing, has pulse
Provide rescue breathing: 1 breath every 3-5 seconds, or about 12-20 breaths/min.
• Add compressions if pulse remains ≤60/min with signs of poor perfusion.
• Activate emergency response system (if not already done) after 2 minutes.
• Continue rescue breathing; check pulse about every 2 minutes. If no pulse, begin CPR (go to "**CPR**" box).
No breathing or only gasping, no pulse
Witnessed sudden collapse?
Yes
Activate emergency response system (if not already done), and retrieve AED/defibrillator.
No
CPR
1 rescuer: Begin cycles of 30 compressions and 2 breaths. (Use 15:2 ratio if second rescuer arrives.) Use AED as soon as it is available.
After about 2 minutes, if still alone, activate emergency response system and retrieve AED (if not already done).
AED analyzes rhythm. Shockable rhythm?
Yes, shockable
Give 1 shock. Resume CPR immediately for about 2 minutes (until prompted by AED to allow rhythm check). Continue until ALS providers take over or victim starts to move.
No, nonshockable
Resume CPR immediately for about 2 minutes (until prompted by AED to allow rhythm check). Continue until ALS providers take over or victim starts to move.

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FIG. 81.1 Basic life support (BLS) healthcare provider: pediatric cardiac arrest algorithm for the single rescuer—2015 update. AED, Automated external defibrillator; ALS, advanced life support; CPR, cardiopulmonary resuscitation. (From Atkins DL, Berger S, Duff JP, et al: Part 11. Pediatric basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation 132[Suppl 2]:S519–S525, 2015, Fig 1, p S521.)

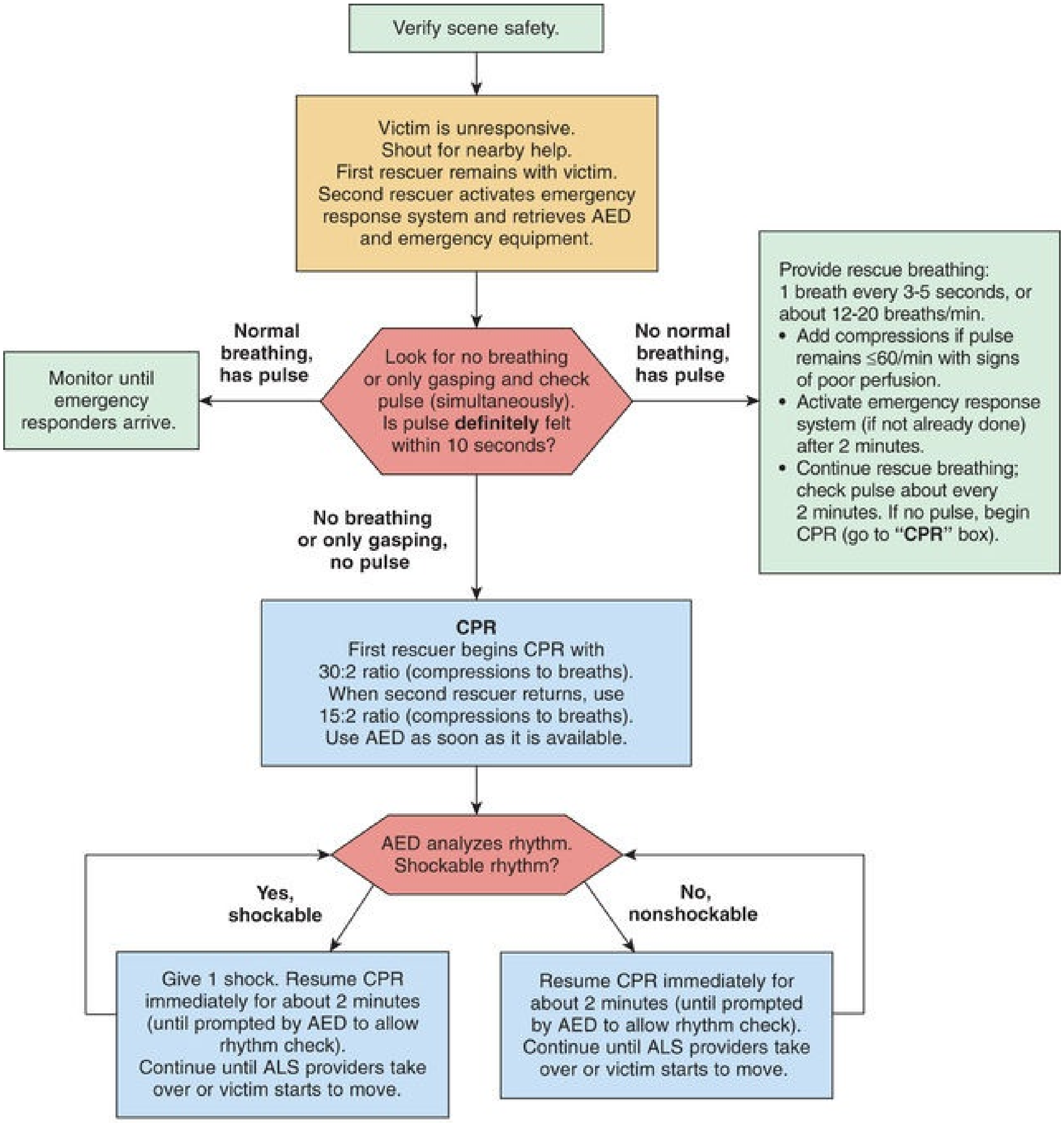

Verify scene safety.

Victim is unresponsive.
Shout for nearby help.
First rescuer remains with victim.
Second rescuer activates emergency response system and retrieves AED and emergency equipment.

Look for no breathing or only gasping and check pulse (simultaneously).
Is pulse **definitely** felt within 10 seconds?

Normal breathing, has pulse

Monitor until emergency responders arrive.

No normal breathing, has pulse

Provide rescue breathing:
1 breath every 3-5 seconds, or about 12-20 breaths/min.
- Add compressions if pulse remains ≤60/min with signs of poor perfusion.
- Activate emergency response system (if not already done) after 2 minutes.
- Continue rescue breathing; check pulse about every 2 minutes. If no pulse, begin CPR (go to "**CPR**" box).

No breathing or only gasping, no pulse

CPR
First rescuer begins CPR with 30:2 ratio (compressions to breaths).
When second rescuer returns, use 15:2 ratio (compressions to breaths).
Use AED as soon as it is available.

AED analyzes rhythm.
Shockable rhythm?

Yes, shockable

Give 1 shock. Resume CPR immediately for about 2 minutes (until prompted by AED to allow rhythm check).
Continue until ALS providers take over or victim starts to move.

No, nonshockable

Resume CPR immediately for about 2 minutes (until prompted by AED to allow rhythm check).
Continue until ALS providers take over or victim starts to move.

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FIG. 81.2 Basic life support (BLS) healthcare provider pediatric cardiac arrest algorithm for 2 or more rescuers—2015 update. AED, Automated external defibrillator; ALS, advanced life support; CPR, cardiopulmonary resuscitation. (From Atkins DL, Berger S, Duff JP, et al: Part 11. Pediatric basic life support and cardiopulmonary resuscitation quality: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation 132[Suppl 2]:S519–S525, 2015, Fig 2, p S522.)

Primary Assessment

Once the emergency response system has been activated and the child is determined not to need CPR, the caregiver should proceed with a primary assessment that includes a brief, **hands-on assessment** of cardiopulmonary and neurologic function and stability. This assessment includes a limited physical examination, evaluation of vital signs, and measurement of pulse oximetry if available. The American Heart Association, in its Pediatric Advanced Life Support (PALS) curriculum, supports the structured format of **airway, breathing, circulation, disability, exposure (ABCDE)** . The goal of the primary assessment is to obtain a focused, systems-based assessment of the child's injuries or abnormalities, so that resuscitative efforts can be directed to these areas; if the caregiver identifies a life-threatening abnormality, further evaluation is postponed until appropriate corrective action has been taken.

The exam and vital sign data can be interpreted only if the caregiver has a thorough understanding of normal values. In pediatrics, normal respiratory rate, heart rate, and blood pressure have age-specific norms (Table 81.1). These ranges can be difficult to remember, especially if used infrequently. However, several standard principals apply: (1) a child's respiratory rate should not be >60 breaths/min for a sustained period; (2) normal heart rate is 2-3 times normal respiratory rate for age; and (3) a simple guide for pediatric blood pressure is that the lower limit of systolic blood pressure should be ≥60 mm Hg for neonates; ≥70 mm Hg for 1 mo-1 yr olds; ≥70 mm Hg + (2 × age) for 1-10 yr olds; and ≥90 mm Hg for any child older than 10 yr.

Table 81.1

Normal Vital Signs According to Age

AGE	HEART RATE (beats/min)	BLOOD PRESSURE (mm Hg)	RESPIRATORY RATE (breaths/min)
Premature	120-170[*]	55-75/35-45[†]	40-70[‡]
0-3 mo	100-150[*]	65-85/45-55	35-55
3-6 mo	90-120	70-90/50-65	30-45
6-12 mo	80-120	80-100/55-65	25-40
1-3 yr	70-110	90-105/55-70	20-30
3-6 yr	65-110	95-110/60-75	20-25
6-12 yr	60-95	100-120/60-75	14-22
12+ yr	55-85	110-135/65-85	12-18

[*] In sleep, infant heart rates may drop significantly lower, but if perfusion is maintained, no intervention is required.

[†] A blood pressure cuff should cover approximately two thirds of the arm; too small a cuff yields

spuriously high pressure readings, and too large a cuff yields spuriously low pressure readings. Values are systolic/diastolic.

‡ Many premature infants require mechanical ventilatory support, making their spontaneous respiratory rate less relevant.

Airway and Breathing

The most common precipitating event for cardiac instability in infants and children is respiratory insufficiency . Therefore, rapid assessment of respiratory failure and immediate restoration of adequate ventilation and oxygenation remain the first priority in the resuscitation of a child. Using a systematic approach, the caregiver should first assess whether the child's airway is patent and maintainable. A healthy, **patent** airway is unobstructed, allowing normal respiration without noise or effort. A **maintainable** airway is one that is either already patent or can be made patent with a simple maneuver. To assess airway patency, the provider should look for breathing movements in the child's chest and abdomen, listen for breath sounds, and feel the movement of air at the child's mouth and nose. Abnormal breathing sounds (e.g., snoring or stridor), increased work of breathing, and apnea are all findings potentially consistent with airway obstruction. If there is evidence of airway obstruction, maneuvers to relieve the obstruction should be instituted before the caregiver proceeds to evaluate the child's breathing.

Assessment of breathing includes evaluation of the child's respiratory rate, respiratory effort, abnormal sounds, and pulse oximetry. Normal breathing appears comfortable, is quiet, and occurs at an age-appropriate rate. Abnormal respiratory rates include apnea and rates that are either too slow (bradypnea) or too fast (tachypnea). *Bradypnea and irregular respiratory patterns require urgent attention because they are often signs of impending respiratory failure and/or apnea.* Signs of increased respiratory effort include nasal flaring, grunting, chest or neck muscle retractions, head bobbing, and seesaw respirations. Hemoglobin oxygen desaturation, as measured by pulse oximetry, often accompanies parenchymal lung disease apnea or airway obstruction. However, providers should keep in mind that adequate perfusion is required to produce a reliable oxygen saturation (SO_2) measurement. A child with low SO_2 is a child in distress. **Central cyanosis** is a sign of severe hypoxia and indicates an emergent need for oxygen supplementation and respiratory support.

Circulation

Cardiovascular function is assessed by evaluation of skin color and temperature, heart rate, heart rhythm, pulses, capillary refill time, and blood pressure. In nonhospital settings, much of the important information can be obtained without measuring the blood pressure; lack of blood pressure data should not prevent the provider for determining adequacy of circulation or implementing a lifesaving response. Mottling, pallor, delayed capillary refill, cyanosis, poor pulses, and cool extremities are all signs of diminished perfusion and compromised cardiac output. **Tachycardia** is the earliest and most reliable sign of shock but is itself fairly nonspecific and should be correlated with other components of the exam, such as weakness, threadiness, and absence of pulses. An age-specific approach to pulse assessment will yield best results.

Disability

In the setting of a pediatric emergency, *disability* refers to a child's neurologic function in terms of the level of consciousness and cortical function. Standard evaluation of a child's neurologic condition can be done quickly with an assessment of pupillary response to light (if one is available) and use of either of the standard scores used in pediatrics: the Alert, Verbal, Pain, Unresponsive (AVPU) Pediatric Response Scale and the Glasgow Coma Scale (GCS). The causes of decreased level of consciousness in children are numerous and include conditions as diverse as respiratory failure with hypoxia or hypercarbia, hypoglycemia, poisonings or drug overdose, trauma, seizures, infection, and shock. *Most often, an ill or injured child has an altered level of consciousness because of respiratory compromise, circulatory compromise, or both.* Any child with a depressed level of consciousness should be immediately assessed for abnormalities in cardiorespiratory status.

Alert, Verbal, Pain, Unresponsive Pediatric Response Scale.

The AVPU scoring system is used to determine a child's level of consciousness and cerebral cortex function (Table 81.2). Unlike the GCS, the AVPU scale is not developmentally dependent—a child does not have to understand spoken language or follow commands, merely respond to a stimulus. The child is scored according to the amount of stimulus required to obtain a response, from *alert* (no stimulus, the child is already awake and interactive) to *unresponsive* (child does not respond to any stimulus).

Table 81.2

AVPU Neurologic Assessment

A	The child is awake, alert, and interactive with parents and care providers.
V	The child responds only if the care provider or parents call the child's name or speak loudly.
P	The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger.
U	The child is unresponsive to all stimuli.

A, Alert; V, verbal, P, pain, U, unresponsive.

From Ralston M, Hazinski MF, Zaritsky AL, et al, editors: *Pediatric advanced life support course guide and PALS provider manual: provider manual,* Dallas, 2007, American Heart Association.

Glasgow Coma Scale.

Although it has not been systematically validated as a prognostic scoring system for infants and young children as it has in adults, GCS is frequently used in the assessment of pediatric patients with an altered level of consciousness. The GCS is the most widely used method of evaluating a child's neurologic function and has 3 components. Individual scores for eye opening, verbal response, and motor response are added together, with a maximum of 15 points (Table 81.3). Patients with a GCS score ≤8 require aggressive management, generally including stabilization of the airway and breathing with endotracheal intubation and mechanical ventilation, respectively, and if indicated, placement of an intracranial pressure monitoring device. The **Full Outline of Unresponsiveness** (FOUR) score is another useful assessment and monitoring tool (see Table 85.1).

Table 81.3

Glasgow Coma Scale

EYE OPENING (TOTAL POSSIBLE POINTS 4)			
Spontaneous	4		
To voice	3		
To pain	2		
None	1		
VERBAL RESPONSE (TOTAL POSSIBLE POINTS 5)			
Older Children		**Infants and Young Children**	
Oriented	5	Appropriate words; smiles, fixes, and follows	5
Confused	4	Consolable crying	4
Inappropriate	3	Persistently irritable	3
Incomprehensible	2	Restless, agitated	2
None	1	None	1

MOTOR RESPONSE (TOTAL POSSIBLE POINTS 6)			
Obeys	6		
Localizes pain	5		
Withdraws	4		
Flexion	3		
Extension	2		
None	1		

Adapted from Teasdale G, Jennett B: Assessment of coma and impaired consciousness: a practical scale, *Lancet* 2:81–84, 1974.

Exposure

Exposure is the final component of the pediatric primary assessment. This component of the exam is reached only after the child's airway, breathing, and circulation have been assessed and determined to be stable or have been stabilized through simple interventions. In this setting, *exposure* stands for the dual responsibility of the provider to both expose the child to assess for previously unidentified injures and consider prolonged exposure in a cold environment as a possible cause of hypothermia and cardiopulmonary instability. The provider should undress the child (as is feasible and reasonable) to perform a focused physical exam, assessing for burns, bruising, bleeding, joint laxity, and fractures. If possible, the provider should assess the child's temperature. All maneuvers should be performed with careful maintenance of cervical spine precautions.

Secondary Assessment

For healthcare providers in community or outpatient settings, transfer of care of a child to emergency or hospital personnel may occur before a full secondary assessment is possible. However, before the child is removed from the scene and separated from witnesses or family, a brief history should be obtained for medical providers at the accepting facility. The components of a secondary assessment include a **focused history** and **focused physical examination.**

The history should be targeted to information that could explain cardiorespiratory or neurologic dysfunction and should take the form of a **SAMPLE history** : signs/symptoms, allergies, medications, past medical history, timing of last meal, and events leading to this situation. Medical personnel not engaged in resuscitative efforts can be dispatched to elicit history from witnesses or relatives. The physical examination during the secondary assessment is a thorough head-to-toe exam, although the severity of the child's illness or injury could necessitate curtailing portions of the exam or postponing nonessential elements until a later time.

Tertiary Assessment

The tertiary assessment occurs in a hospital setting, where ancillary laboratory and radiographic assessments contribute to a thorough understanding of the child's condition. A basic blood chemistry profile, complete blood count, liver function tests, coagulation studies, and arterial blood gas analyses give fairly broad (but somewhat nonspecific) estimates of renal function, acid-base balance, cardiorespiratory function, and presence or absence of shock. Chest radiographs can be useful to evaluate both the heart and lungs, although more detailed estimates of heart function and cardiac output can be made with **echocardiography** . Arterial and central venous catheters can be placed to monitor arterial and central venous pressure.

Recognition and Treatment of Respiratory Distress and Failure

The goals of initial management of respiratory distress or failure are to rapidly stabilize the child's airway and breathing and to identify the cause of the problem so that further therapeutic efforts can be appropriately directed.

Airway Obstruction

Children <5 yr old are particularly susceptible to foreign body aspiration and choking. Liquids are the most common cause of choking in infants, whereas small objects and food (e.g., grapes, nuts, hot dogs, candy) are the most common source of foreign bodies in the airways of toddlers and older children. A history consistent with foreign body aspiration is considered diagnostic. Any child in the proper setting with the sudden onset of choking, stridor, or wheezing has foreign body aspiration until proven otherwise.

Airway obstruction is treated with a sequential approach, starting with the head-tilt/chin-lift maneuver to open and support the airway, followed by inspection for a foreign body, and finger-sweep clearance or suctioning if one is visualized (Fig. 81.3). *Blind suctioning or finger sweeps of the mouth are not recommended.* A nasopharyngeal airway or oropharyngeal airway can be inserted for airway support, if indicated. A conscious child suspected of having a partial foreign body obstruction should be permitted to cough spontaneously until coughing is no longer effective, respiratory distress and stridor increase, or the child becomes unconscious.

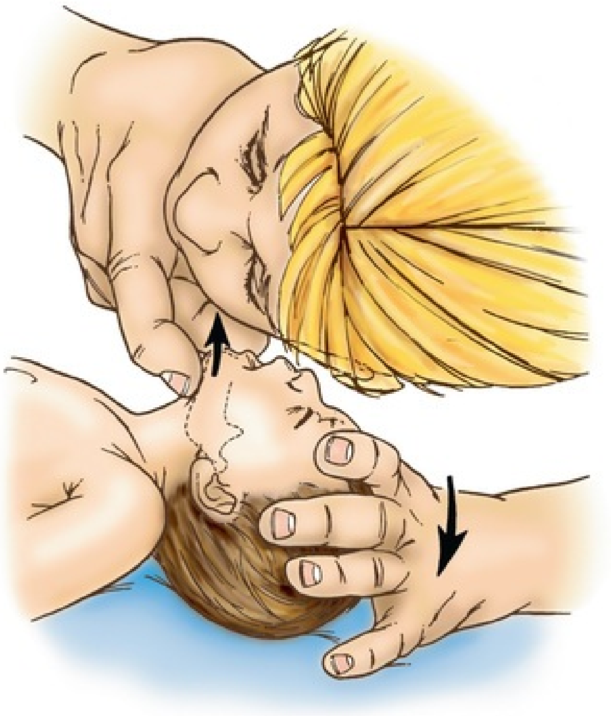

FIG. 81.3 **Opening the airway with the head-tilt/chin-lift maneuver. One hand is used to tilt the head, extending the neck. The index finger of the rescuer's other hand lifts the mandible outward by lifting the chin. Head-tilt should not be performed if a cervical spine injury is suspected. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, *JAMA* 268:2251–2261, 1992.)**

If the child becomes unconscious, the child should be gently placed on the ground, supine. The provider should then open the airway with the head-tilt/chin-lift maneuver and attempt mouth-to-mouth ventilation (Figs. 81.4 and 81.5). If ventilation is unsuccessful, the airway is repositioned and ventilation attempted again. If there is still no chest rise, attempts to remove a foreign body are indicated. In an infant <1 yr old, a combination of 5 back blows and 5 chest thrusts is administered (Fig. 81.6). After each cycle of back blows and chest thrusts, the child's mouth should be visually inspected for the presence of the foreign body. If identified within finger's reach, it should be removed with a gentle finger sweep. If no foreign body is visual, ventilation is again attempted. If this is unsuccessful, the head is repositioned and ventilation attempted again. If there is still no chest rise, the series of back blows and chest thrusts is repeated.

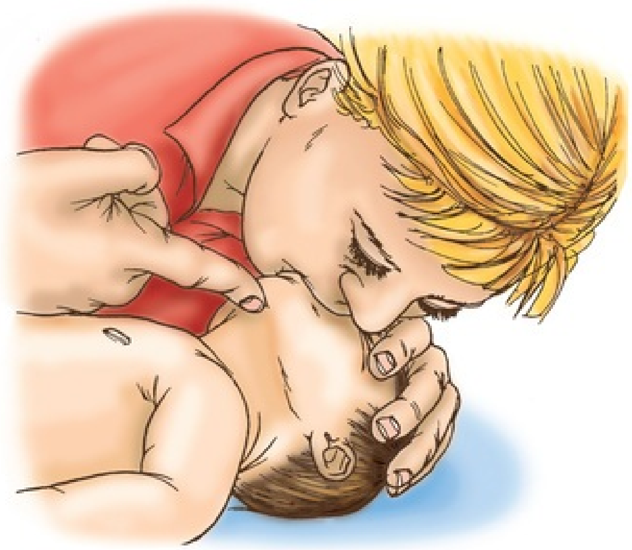

FIG. 81.4 **Rescue breathing in an infant. The rescuer's mouth covers the infant's nose and mouth, creating a seal. One hand performs the head-tilt while the other hand lifts the infant's jaw. Avoid head-tilt if the infant has sustained head or neck trauma. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, *JAMA* 268:2251–2261, 1992.)**

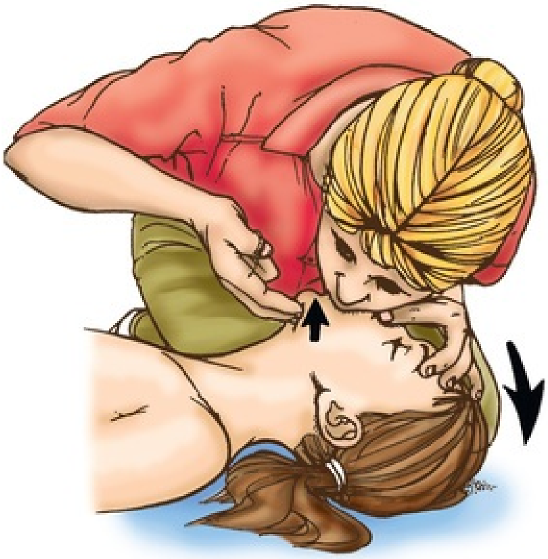

FIG. 81.5 Rescue breathing in a child. The rescuer's mouth covers the child's mouth, creating a mouth-to-mouth seal. One hand maintains the head-tilt; the thumb and forefinger of the same hand are used to pinch the child's nose. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, *JAMA* 268:2251–2261, 1992.)

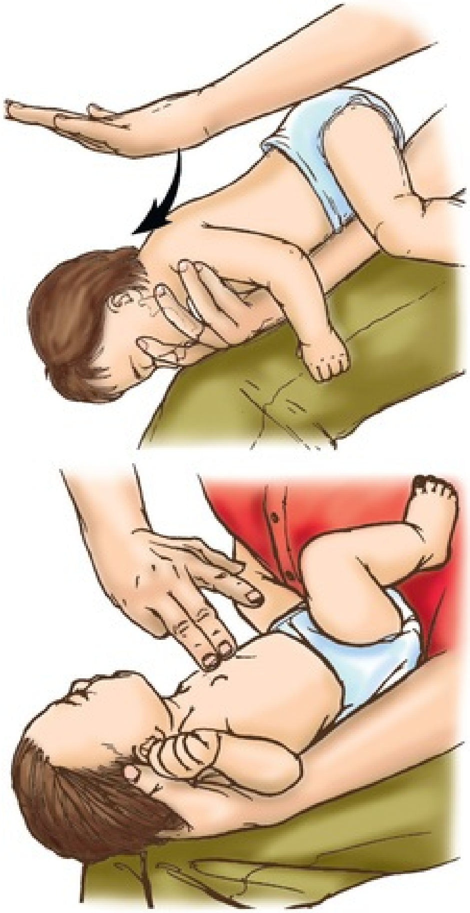

FIG. 81.6 Back blows *(top)* and chest thrusts *(bottom)* to relieve foreign body airway obstruction in the infant. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, *JAMA* 268:2251–2261, 1992.)

For a conscious child >1 yr old, providers should give a series of 5 abdominal thrusts (**Heimlich maneuver**) with the child standing or sitting (Fig. 81.7); this should occur with the child lying down if unconscious (Fig. 81.8). After the abdominal thrusts, the airway is examined for a foreign body, which should be removed if visualized. If no foreign body is seen, the head is repositioned and ventilation attempted. If unsuccessful, the head is repositioned and ventilation attempted again. If these efforts are unsuccessful, the Heimlich sequence is repeated.

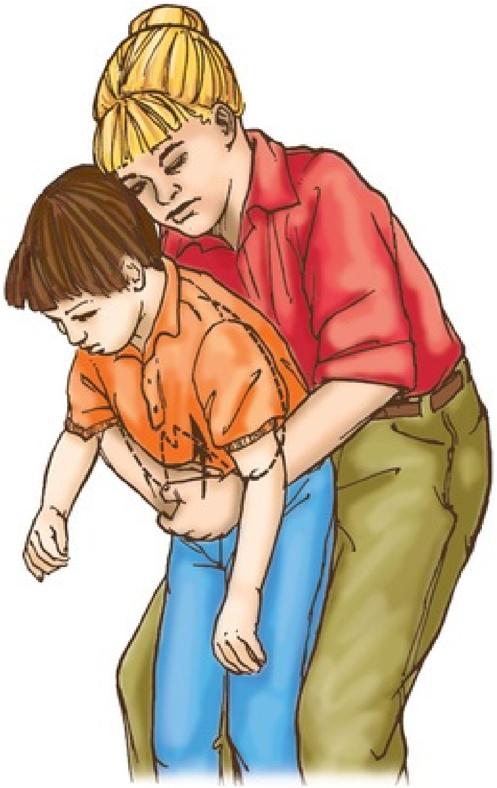

FIG. 81.7 Abdominal thrusts with the victim standing or sitting (conscious). (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, *JAMA* 268:2251–2261, 1992.)

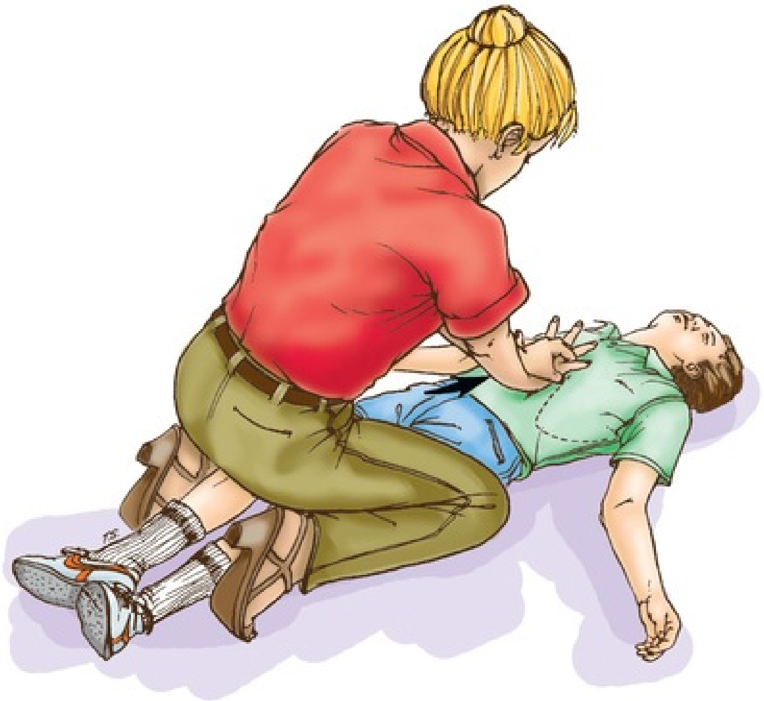

FIG. 81.8 Abdominal thrusts with victim lying (conscious or unconscious). (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, *JAMA* 268:2251–2261, 1992.)

Airway Narrowing

Airway obstruction can also be caused by airway narrowing, in both the upper and lower airways. *Upper airway obstruction* refers to narrowing of the extrathoracic portion of the airway, including the oropharynx, larynx, and trachea. In the upper airways, narrowing is most often caused by airway **edema** (e.g., croup or anaphylaxis). Lower airway disease affects all intrathoracic airways, notably the bronchi and bronchioles. In the lower airways, **bronchiolitis** and acute **asthma** exacerbations are the major contributors to intrathoracic airway obstruction in children, causing airway narrowing through a combination of airway swelling, mucus production, and circumferential smooth muscle constriction of smaller airways.

Airway support for these processes is dictated by both the underlying condition and the clinical severity of the problem. In cases of mild upper airway obstruction, the child has minimally elevated work of breathing (evidenced by tachypnea and few to mild retractions). Stridor, if present at all, should be audible with only coughing or activity. Children with these findings can be supported with supplemental oxygen as needed. In cases with moderate obstruction, in which the child has a higher work of breathing and more pronounced stridor, nebulized racemic **epinephrine** and oral or intravenous (IV) **dexamethasone** can be added. **Heliox** (combined helium-oxygen therapy) administration may also be considered. Children with severe upper airway obstruction have marked intercostal retractions, prominent stridor, and decreased air entry on auscultation of the lung fields. Most children with significant airway obstruction are also hypoxic, and many appear dyspneic and agitated. A child in severe distress needs to be closely observed because the signs of impending respiratory failure may be initially confused with improvement. Stridor becomes quieter and intercostal retractions less prominent when a child's respiratory effort begins to diminish. The child in respiratory failure can be distinguished from one who is improving by evidence of poor air movement on auscultation and lethargy or decreased level of consciousness from hypercarbia, hypoxia, or both. When **anaphylaxis** is suspected as the cause for upper airway edema, providers should administer an intramuscular (IM) or IV dose of epinephrine as needed (see Chapter 174). No matter the cause, any child in impending respiratory failure should be prepared for endotracheal intubation and respiratory support. Prompt notification of providers trained in airway management is essential.

In cases of *lower airway obstruction* , therapies are targeted to both relieving the obstruction and reducing the child's work of breathing. Inhaled **bronchodilators** , such as albuterol, augmented by oral or IV corticosteroids, remain the mainstay of therapy in settings of mild to moderate acute distress caused by lower airway obstruction (e.g., **asthma**). Children with more significant obstruction appear dyspneic, with tachypnea, retractions, and easily audible wheezing. In these cases, the addition of an anticholinergic agent, such as nebulized ipratropium bromide, or a smooth muscle relaxant, such as magnesium sulfate, may provide further relief, although the evidence for these measures remains controversial (see Chapter 169). Supplemental oxygen and IV fluid hydration can also be useful adjuncts. As in cases of upper airway obstruction, impending respiratory failure in children with lower airway obstruction can be insidious. When diagnosed early in a school-age child who is cooperative, respiratory failure can be averted through judicious use of noninvasive support, including heated, high-flow nasal cannula (HFNC) therapy, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or heliox therapy. Endotracheal intubation should be performed only by skilled providers, preferably in a hospital setting, because there is a high risk of cardiorespiratory compromise in patients with lower airway obstruction during the procedure.

Parenchymal Lung Disease

Parenchymal lung disease includes a heterogeneous list of conditions, such as pneumonia, acute respiratory distress syndrome (ARDS), pneumonitis, bronchiolitis, bronchopulmonary dysplasia, cystic fibrosis, and pulmonary edema. The commonalities of these conditions are their effects on the small airways and alveoli, including inflammation and exudation leading to consolidation of lung tissue, decreased gas exchange, and increased work of breathing. Clinical management of these conditions includes specific treatment as indicated (e.g., antibiotics for bacterial pneumonia) and supportive care in the form of supplemental oxygen, noninvasive respiratory support (with HFNC, CPAP, or BiPAP), or invasive mechanical ventilation.

Advanced Airway Management Techniques

Bag-Valve-Mask Positive Pressure Ventilation

Rescue breathing with a bag-valve-mask apparatus can be as effective as endotracheal intubation and safer when the provider is inexperienced with intubation. Bag-valve-mask ventilation itself requires training to ensure that the provider is competent to select the correct mask size, open the child's airway, form a tight seal between the mask and the child's face, deliver effective ventilation, and assess the effectiveness of the ventilation. An appropriately sized mask is one that fits over the child's mouth and nose but does not extend below the chin or over the eyes (Fig. 81.9). An adequate seal is best achieved through a combination “C-E” grip on the mask, in which the thumb and index finger form the letter “C” on top of the mask, pressing the mask downward onto the child's face, and the remaining 3 fingers form an “E” grip under the child's mandible, holding the jaw forward and extending the head up toward the mask. Using this method, the care provider can secure the mask to the child's face with one hand and use the other hand to compress the ventilation bag (Fig. 81.10).

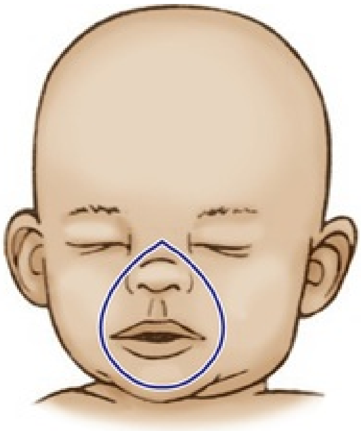

Correct
Covers mouth, nose, and chin but not eyes

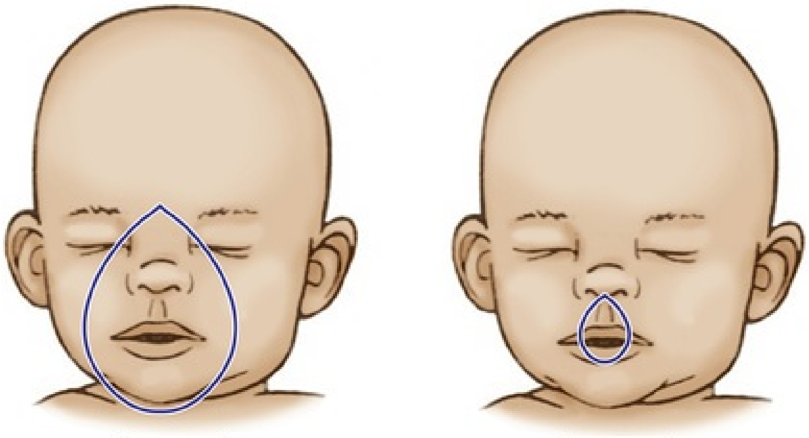

Incorrect
Too large: covers eyes and extends over chin

Incorrect
Too small: does not cover nose and mouth well

FIG. 81.9 Appropriate sizing technique for pediatric bag-valve-mask apparatus. (From American Academy of Pediatrics and the American Heart Association; Kattwinkel J (ed): *Textbook of Neonatal Resuscitation,* ed 6. Elk Grove, IL: American Academy of Pediatrics, 2011. Fig 3-17.)

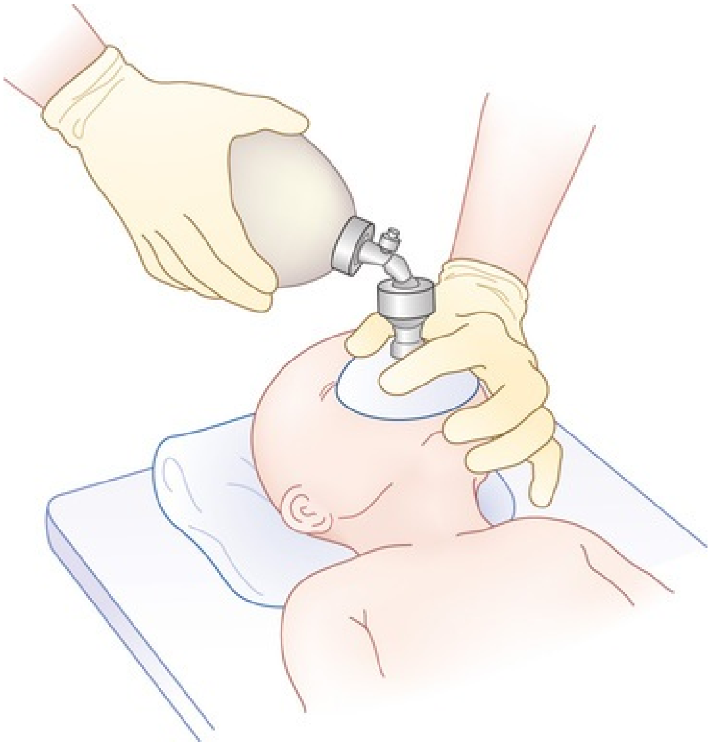

FIG. 81.10 “C-E” grip to secure bag-valve-mask to a child's face with appropriate seal.

The provider may have to move the head and neck through a range of positions to find the one that best maintains airway patency and allows maximal ventilation. In infants and young children, optimal ventilation is often provided when the child's head is in the neutral sniffing position without hyperextension of the head (Fig. 81.11). Poor chest rise and persistently low S_{O_2} values indicate inadequate ventilation. In this setting the care provider should recheck the mask's seal on the child's face, reposition the child's head, and consider suctioning the airway, if indicated. If these maneuvers do not restore ventilation, the provider should consider noninvasive or invasive respiratory support (i.e., endotracheal intubation) as clinically indicated.

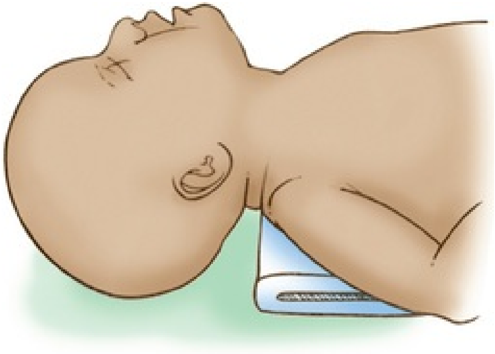

FIG. 81.11 Appropriate head position for bag-valve-mask ventilation. (From American Academy of Pediatrics and the American Heart Association; Kattwinkel J (ed): *Textbook of Neonatal Resuscitation,* ed 6. Elk Grove, IL: American Academy of Pediatrics, 2011. Fig 3-19.)

Endotracheal Intubation

A child generally requires intubation when at least one of these conditions exists: (1) the child is unable to maintain airway patency or protect the airway against aspiration (as occurs in settings of neurologic compromise); (2) the child is failing to maintain adequate oxygenation; (3) the child is failing to control blood carbon dioxide levels and maintain safe acid-base balance; (4) sedation and/or paralysis is required for a procedure; and (5) care providers anticipate a deteriorating course that will eventually lead to any of the first 4 conditions. It should be noted that in centers *experienced in noninvasive respiratory support* , a trial of HFNC, CPAP, and/or BiPAP may be indicated based on the specific clinical scenario.

There are few *absolute contraindications* to tracheal intubation, but experts generally agree that in settings of known complete airway obstruction, endotracheal intubation should be avoided, and emergency cricothyroidotomy performed instead. Another important consideration is to ensure that caregivers provide appropriate cervical spine (C-spine) protection during the intubation procedure when neck or spinal cord injury is suspected.

The most important phase of the intubation procedure is the preprocedural preparation, when the provider ensures all the equipment and staff needed for safe intubation are present and functioning. An easy pneumonic for this is **SOAP MM** : *suction* (Yankauer suction catheter attached to wall suction); *oxygen* (both preoxygenation of the patient and devices needed to deliver oxygen, such as a bag-valve-mask); *airway* (appropriately sized endotracheal tube and laryngoscope); *people* (all those needed during and immediately after the procedure, including respiratory therapists and nurses); *monitor* (SO_2, heart rate, blood pressure, capnography); and *medications* (sedation and often neuromuscular blockade to allow the provider(s) to control the airway). A simple formula for selecting the appropriately sized endotracheal tube (ETT) is:

$$\text{Uncuffed ETT size (in mm)} = \left(\frac{\text{age in years}}{4}\right) + 4$$

Cuffed ETTs should generally be 0.5 mm smaller. Providers should always have a range of ETTs available given the heterogeneity of patients and airway size.

Analgesia is recommended to reduce metabolic stress, discomfort, and anxiety during intubation. Pretreatment with a sedative, an analgesic, and possibly a muscle relaxant is recommended unless the situation is emergent (i.e., apnea, asystole, unresponsiveness) and the administration of drugs would cause an unacceptable delay.

Because many intubations in critically ill children are emergency procedures, caregivers should be prepared for **rapid sequence intubation** (RSI) (Fig. 81.12 and Table 81.4). The goals of RSI are to induce anesthesia and paralysis and to complete intubation quickly. This approach minimizes elevations of intracranial pressure and blood pressure that may accompany intubation in awake or lightly sedated patients. Because the stomach generally cannot be emptied before RSI, the **Sellick maneuver** (downward pressure on the cricoid cartilage to compress the esophagus against the vertebral column) should be used to prevent aspiration of gastric contents.

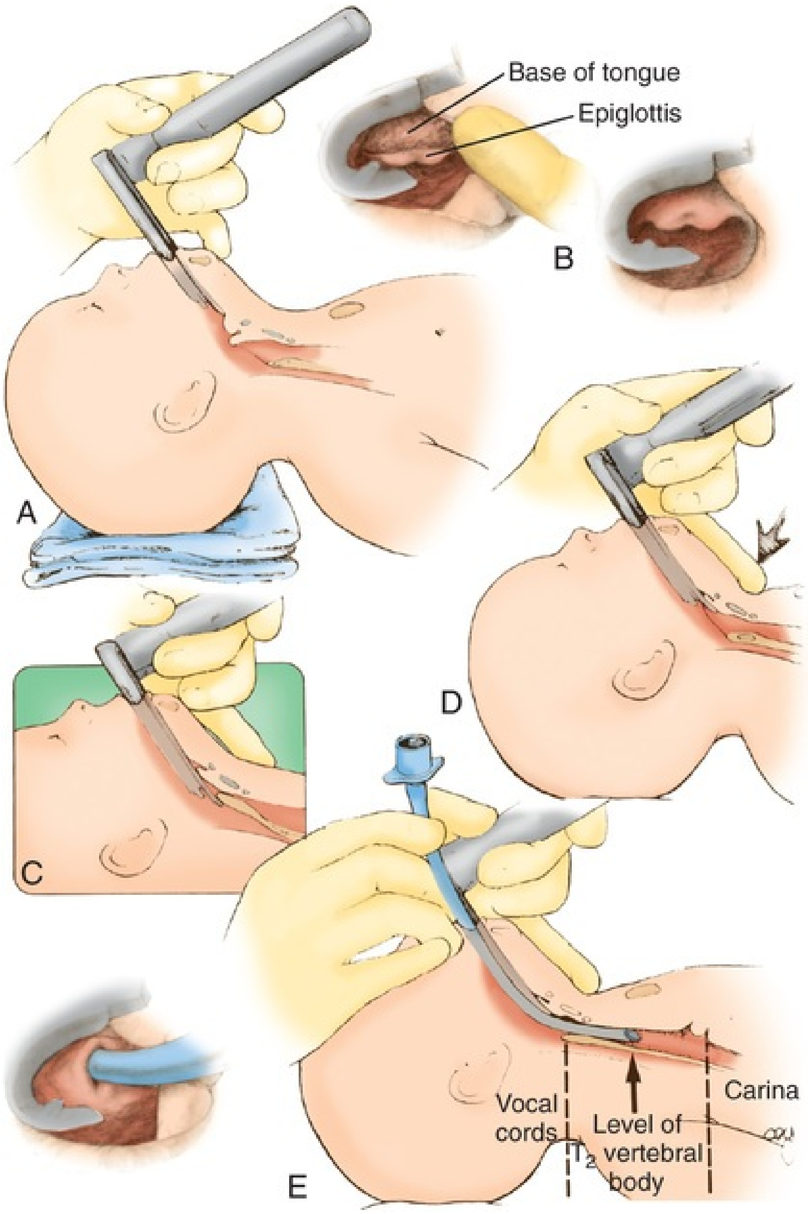
Base of tongue
Epiglottis
B
A
D
C
Vocal cords
Level of T_2 vertebral body
Carina
E

FIG. 81.12 **A-E,** Intubation technique. (From Fleisher G, Ludwig S: *Textbook of pediatric emergency medicine,* Baltimore, 1983, Williams & Wilkins, p. 1250.)

Table 81.4

Rapid Sequence Intubation

STEP	PROCEDURE	COMMENT/EXPLANATION
1	Obtain a brief history and perform an	Rule out drug allergies; examine the airway anatomy (e.g., micrognathia, cleft palate).

	assessment.	
2	Assemble equipment, medications, etc.	ETT: select the proper size for the age and weight of the child. Laryngoscope blades: a variety of Miller and the Macintosh blades.
3	Preoxygenate the patient.	With bag/mask, nasal cannula, hood or blow-by.
4	Position the patient.	Patient supine; neck is extended moderately to the “sniffing” position.
5	Premedicate the patient with lidocaine, atropine.	Lidocaine minimizes the ICP rise with intubation and can be applied topically to the airway mucosa for local anesthesia.
		Atropine helps blunt the bradycardia associated with upper airway manipulation and reduces airway secretions.
6	Perform a Sellick maneuver.	Pressure on the cricoid cartilage, to occlude the esophagus and prevent regurgitation or aspiration.
7	Induce sedation and analgesia.	**Sedatives**
		Midazolam (0.1 mg/kg): onset ~1 min; elimination in 30-40 min.
		Ketamine (2 mg/kg, may repeat as clinically indicated): onset 1-2 min; elimination in 30-40 min. May cause hallucinations if used alone; can cause higher ICP, mucous secretions, increased vital signs, and bronchodilation.
		Analgesics
		Fentanyl (3-5 µg/kg, may repeat as clinically indicated): onset ~1 min; elimination in 20-30 min. Rapid administration risks “tight chest” response, with no effective ventilation. Effects wear off in 20-30 min.
		Morphine (0.05-0.1 mg/kg dose): may last 30-60 min; may lead to hypotension in hypovolemic patients.
8	Administer muscle relaxants.	**Option 1:** Rocuronium (1 mg/kg): rapid onset and short duration. Other nondepolarizing agents include vecuronium and pancuronium, both dosed at 0.1 mg/kg.
		Option 2: Succinylcholine dose is 1-2 mg/kg; causes initial contraction of muscles, then relaxation. This depolarization can, however, increase ICP and blood pressure. Onset of paralysis in 30-40 sec; duration is 5-10 min. Pretreat with a small dose of a nondepolarizing paralytic agent, with intent of diminishing the depolarizing effect of succinylcholine.
9	Perform endotracheal intubation.	Performed by trained personnel.
10	Secure the tube, and verify position with radiograph.	ETT secured with tape to the cheeks and upper lip or to an adhesive patch applied to the skin near the mouth.
11	Begin mechanical ventilation.	Verify tube placement before ventilating with positive pressure; if an ETT is in 1 bronchus, barotraumas may occur.

ETT, Endotracheal tube; ICP, intracranial pressure.

Once the patient is intubated, proper ETT placement should be assessed by auscultation of breath sounds, evidence of symmetric chest rise, and analysis of exhaled carbon dioxide (CO_2) by a colorimetric device placed within the respiratory tubing near the ETT or a device that directly measures CO_2 elimination (capnogram or capnograph). Chest radiography is necessary to confirm appropriate tube position.

Recognition and Management of Shock

In simple terms, shock occurs when oxygen and nutrient delivery to the tissues is inadequate to meet metabolic demands (see Chapter 88). The definition of shock *does not* include hypotension, and it is important for care providers to understand that **shock does not begin when blood pressure drops; it merely worsens and becomes more difficult (refractory) to treat once blood pressure is abnormal.**

Early *compensated* shock, whereby oxygen delivery is mostly preserved through compensatory mechanisms, is defined by the presence of normal blood pressure. When compensatory mechanisms fail, the shock progresses to *decompensated* shock, as defined by hypotension and organ dysfunction. In *irreversible* shock, organ failure progresses and death ensues.

Shock is also often described according to the underlying pathophysiology, which dictates the appropriate therapeutic response. **Hypovolemic shock** is the most common type of shock in children worldwide, usually related to fluid losses from severe diarrhea. Hemorrhage is a cause of hypovolemic shock after trauma or intestinal hemorrhage. When hypovolemia occurs because of third spacing of intravascular fluids into the extravascular compartment, the shock is described as **distributive shock** . The most common causes of distributive shock are sepsis, anaphylaxis, and burn injuries, in which release of inflammatory cytokines causes massive capillary leak of fluid and proteins, leading to low oncotic pressure and intravascular volume. In settings of profound myocardial dysfunction, a child has tissue hypoperfusion from **cardiogenic shock** . The most common causes of cardiogenic shock are myocarditis, cardiomyopathy, and congenital heart disease, generally in the postoperative setting. **Obstructive shock** occurs when cardiac output is lowered by obstruction of blood flow to the body, as occurs when a ductus arteriosus closes in a child with ductus-dependent systemic blood flow, pericardial tamponade, tension pneumothorax, or massive pulmonary embolism.

The evaluation of a child in shock should proceed as described in the preceding sections on primary, secondary, and tertiary assessments. If the child presents in a hospital setting, providers should generally place a central venous line to provide secure venous access and an arterial line to permit continuous blood pressure monitoring and a more thorough laboratory assessment of organ systems, including studies of renal and liver function, acid-base balance and presence of lactic acidosis, hypoxemia and/or hypercapnia, and evidence of coagulopathy or disseminated intravascular coagulation. Chest radiography and echocardiography may also be useful. Respiratory and cardiovascular support should be provided as clinically indicated.

The treatment of shock focuses on the modifiable determinants of oxygen delivery while reducing the imbalance between oxygen supply and demand. A multipronged approach is recommended consisting of optimizing the arterial oxygen content of the blood, improving the volume and distribution of cardiac output, correcting metabolic derangements, and reducing oxygen demand. Blood oxygen content is maximized when hemoglobin values are normal and 100% of available hemoglobin is saturated with oxygen. Transfusion may be considered in the presence of hemorrhagic or distributive shock, in which crystalloid volume resuscitation has led to hemodilution and anemia. Appropriate SO_2 may be achieved by simple maneuvers, such as oxygen administration by nasal cannula or face mask; supportive measures (e.g., HFNC, CPAP, BiPAP) or invasive mechanical ventilation may be necessary. Therapies to increase cardiac output should be selected on the basis of the underlying pathophysiology. For hypovolemic and distributive shock, aggressive volume resuscitation, guided by arterial and central venous pressures, is the mainstay of therapy. In obstructive shock, relief of the obstruction is critical. The ductus arteriosus can often be reopened with prostaglandin administration and tamponade physiology relieved with appropriate drainage.

Recognition of Bradyarrhythmias and Tachyarrhythmias

In the advanced life support (ALS) setting, arrhythmias are most usefully classified according to the observed heart rate (i.e., slow or fast) and its effect on perfusion (i.e., adequate or poor). If, in the primary survey, a caregiver finds a child with an abnormal heart rate plus poor perfusion and/or altered mental status, the rhythm is inadequate no matter its rate. In those settings the child is diagnosed with shock, and further evaluation is generally halted until appropriate resuscitation has been initiated.

Bradyarrhythmias

By definition, a child is *bradycardic* when the heart rate is slower than the normal range for age (see Table 81.1). Sinus bradycardia can be a harmless incidental finding in an otherwise healthy person and not usually associated with cardiac compromise. A relative bradycardia occurs when the heart rate is too slow for a child's activity level or metabolic needs. A clinically significant bradycardia occurs when the heart rate is slow and there are signs of systemic hypoperfusion (i.e., pallor, altered mental status, hypotension, acidosis). Symptomatic bradycardia occurs most often in the setting of hypoxia but can also be caused by hypoglycemia, hypocalcemia, other electrolyte abnormalities, hypothermia, heart block, and intracranial hypertension. Bradyarrhythmias are often the most common *prearrest* rhythms in young children.

Initial management of symptomatic bradycardia includes support or opening of the airway and confirming or establishing adequate So_2 and ventilation (Fig. 81.13). After breathing has been secured, the child should be reassessed for continued bradycardia and poor perfusion. If cardiac compromise was solely the result of respiratory insufficiency, support of the child's airway and breathing may have been sufficient to restore normal hemodynamics. If respiratory support does not correct the perfusion abnormalities, further care is based on the quality of perfusion and degree of bradycardia. *A heart rate <60 beats/min with poor perfusion is an indication to begin chest compressions.* If the bradycardia persists, vascular access should be obtained; resuscitative epinephrine should be administered, and it should be repeated every 3-5 min for persistent symptomatic bradycardia. If increased vagal tone (e.g., in the setting of head injury with increased intracranial pressure) or primary atrioventricular block is suspected, atropine can also be given. For cases of refractory bradycardia, cardiac pacing should be considered. During the resuscitation of a child with bradycardia, providers should assess and treat factors known to cause bradycardia, referred to collectively as the **6 Hs** —hypoxia, hypovolemia, hydrogen ions (acidosis), hypokalemia or hyperkalemia, hypoglycemia, and hypothermia—and **5 Ts** —toxins, tamponade, tension pneumothorax, thrombosis (in either the pulmonary or cardiac circulations), and trauma (causing hypovolemia, intracranial hypertension, cardiac compromise or tamponade) (Table 81.5).

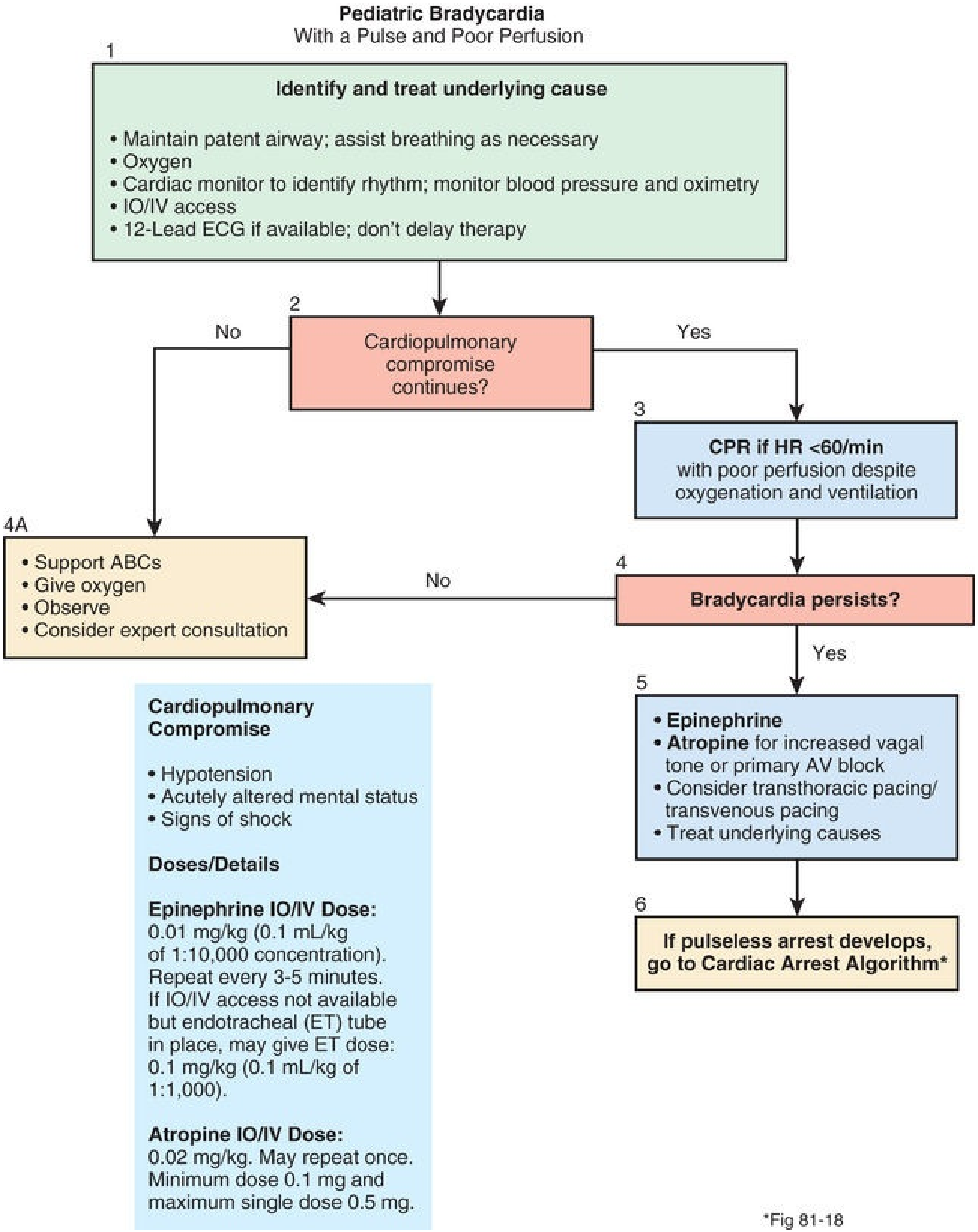
Pediatric Bradycardia
With a Pulse and Poor Perfusion
1
Identify and treat underlying cause
• Maintain patent airway; assist breathing as necessary
• Oxygen
• Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
• IO/IV access
• 12-Lead ECG if available; don't delay therapy
2
Cardiopulmonary compromise continues?
No
Yes
3
CPR if HR <60/min
with poor perfusion despite oxygenation and ventilation
4A
• Support ABCs
• Give oxygen
• Observe
• Consider expert consultation
No
4
Bradycardia persists?
Yes
5
• Epinephrine
• Atropine for increased vagal tone or primary AV block
• Consider transthoracic pacing/ transvenous pacing
• Treat underlying causes
6
If pulseless arrest develops, go to Cardiac Arrest Algorithm*
Cardiopulmonary Compromise
• Hypotension
• Acutely altered mental status
• Signs of shock
Doses/Details
Epinephrine IO/IV Dose:
0.01 mg/kg (0.1 mL/kg of 1:10,000 concentration). Repeat every 3-5 minutes. If IO/IV access not available but endotracheal (ET) tube in place, may give ET dose: 0.1 mg/kg (0.1 mL/kg of 1:1,000).
Atropine IO/IV Dose:
0.02 mg/kg. May repeat once. Minimum dose 0.1 mg and maximum single dose 0.5 mg.
*Fig 81-18

FIG. 81.13 Pediatric advanced life support bradycardia algorithm. ABCs, Airway, breathing, and circulation; AV, atrioventricular (conductor); ECG, electrocardiogram; HR, heart rate; IO/IV, intraosseous/intravenous. (From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14, *Circulation* 122[Suppl 3]:S876–S908, 2010, Fig. 2, p. S887.)

Table 81.5

Potentially Treatable Conditions Associated With Cardiac Arrest

CONDITION	COMMON CLINICAL SETTINGS	CORRECTIVE ACTIONS
Acidosis	Preexisting acidosis, diabetes, diarrhea, drugs and toxins, prolonged resuscitation, renal disease, and shock	Reassess the adequacy of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement. Hyperventilate. Consider intravenous bicarbonate if pH <7.2 after above actions have been taken.
Cardiac tamponade	Hemorrhagic diathesis, cancer, pericarditis, trauma, after cardiac surgery, and after myocardial infarction	Administer fluids; obtain bedside echocardiogram, if available. Perform pericardiocentesis; immediate surgical intervention is appropriate if pericardiocentesis is unhelpful but cardiac tamponade is known or highly suspected.
Hypothermia	Alcohol abuse, burns, central nervous system disease, debilitated patient, drowning, drugs and toxins, endocrine disease, history of exposure, homelessness, extensive skin disease, spinal cord disease, and trauma	If hypothermia is severe (temperature <30°C [86°F]), limit initial shocks for ventricular fibrillation or pulseless ventricular tachycardia to 3; initiate active internal rewarming and cardiopulmonary support. If hypothermia is moderate (temperature 30-34°C [86-93.2°F]), proceed with resuscitation (space medications at longer intervals than usual), passively rewarm child, and actively rewarm truncal body areas.
Hypovolemia, hemorrhage, anemia	Major burns, diabetes, gastrointestinal losses, hemorrhage, hemorrhagic diathesis, cancer, pregnancy, shock, and trauma	Administer fluids. Transfuse packed red blood cells if hemorrhage or profound anemia is present. Thoracotomy is appropriate when a patient has cardiac arrest from penetrating trauma and a cardiac rhythm and the duration of cardiopulmonary resuscitation before thoracotomy is <10 min.
Hypoxia	Consider in all patients with cardiac arrest.	Reassess the technical quality of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement.
Hypomagnesemia	Alcohol abuse, burns, diabetic ketoacidosis, severe diarrhea, diuretics, and drugs (e.g., cisplatin, cyclosporine, pentamidine)	Administer 1-2 g magnesium sulfate intravenously over 2 min.
Poisoning	Alcohol abuse, bizarre or puzzling behavioral or metabolic presentation, classic toxicologic syndrome, occupational or industrial exposure, and psychiatric disease	Consult a toxicologist for emergency advice on resuscitation and definitive care, including an appropriate antidote. Prolonged resuscitation efforts may be appropriate; immediate cardiopulmonary bypass should be considered, if available.
Hyperkalemia	Metabolic acidosis, excessive administration of potassium, drugs and toxins, vigorous exercise, hemolysis, renal disease, rhabdomyolysis, tumor lysis syndrome, and	If hyperkalemia is identified or strongly suspected, treat* with all the following: 10% calcium chloride (5-10 mL by slow IV push; do not use if hyperkalemia is secondary to digitalis poisoning), glucose and insulin (50 mL of 50% dextrose in water and 10 units of regular insulin IV), sodium bicarbonate (50 mmol IV; most effective if concomitant

	clinically significant tissue injury	metabolic acidosis is present), and albuterol (15-20 mg nebulized or 0.5 mg by IV infusion).
Hypokalemia	Alcohol abuse, diabetes, use of diuretics, drugs and toxins, profound gastrointestinal losses, hypomagnesemia	If profound hypokalemia (<2.0-2.5 mmol of potassium) is accompanied by cardiac arrest, initiate urgent IV replacement (2 mmol/min IV for 10-15 mmol);* then reassess.
Pulmonary embolism	Hospitalized patient, recent surgical procedure, peripartum, known risk factors for venous thromboembolism, history of venous thromboembolism, or prearrest presentation consistent with a diagnosis of acute pulmonary embolism	Administer fluids; augment with vasopressors as necessary. Confirm the diagnosis, if possible; consider immediate cardiopulmonary bypass to maintain patient's viability. Consider definitive care (e.g., thrombolytic therapy, embolectomy by interventional radiology or surgery).
Tension pneumothorax	Placement of a central catheter, mechanical ventilation, pulmonary disease (including asthma, chronic obstructive pulmonary disease, and necrotizing pneumonia), thoracentesis, and trauma	Needle decompression, followed by chest tube insertion.

* Adult dose. Adjust for size of child. See Table 81.6 .

From Eisenbery MS, Mengert TJ: Cardiac resuscitation, *N Engl J Med* 344:1304–1313, 2001.

Tachyarrhythmias

Tachyarrhythmias represent a wide variety of rhythm disturbances of atrial and ventricular origin (see Chapter 462). Sinus tachycardia is a normal physiologic response to the body's need for increased cardiac output or oxygen delivery, as occurs with fever, exercise, or stress. It can also occur in more pathologic states, such as hypovolemia, anemia, pain, anxiety, and metabolic stress. Tachyarrhythmias that do not originate in the sinus node are often categorized as *narrow complex rhythms* (i.e., originating in the atrium, such as atrial flutter or supraventricular tachycardia, SVT) and *wide complex rhythms* (i.e., rhythms of ventricular origin, such as ventricular tachycardia).

The initial management of tachycardia includes confirmation that the child has an adequate airway and life-sustaining breathing and circulation (Fig. 81.14). For children with persistent symptoms, further treatment is based on whether the QRS complex of the electrocardiogram (ECG) is narrow (≤0.09 sec) or wide (>0.09 sec). For narrow complex tachycardia, providers must distinguish between sinus tachycardia and SVT. In **sinus tachycardia** , (a) the history and onset are consistent with a known cause of tachycardia, such as fever or dehydration, and (b) P waves are consistently present, are of normal morphology, and occur at a rate that varies somewhat. In **supraventricular tachycardia** , (a) onset is often abrupt without prodrome, and (b) P waves are absent or polymorphic, and when present, their rate is often fairly steady at or above 220 beats/min. For children with SVT and good perfusion, vagal maneuvers can be attempted. When SVT is associated with poor perfusion, providers should rapidly move to convert the child's heart rhythm back to sinus rhythm. If the child already has IV access, adenosine can be given via IV access with rapid push. Adenosine has an extremely short half-life, so a proximal IV line is best, and the adenosine should be set up with a 3-way stopcock so it can be given and immediately flushed into the circulation. If the child does not have IV access, or adenosine does not successfully convert the heart rhythm back to sinus rhythm, then **synchronized cardioversion** , using 0.5-1.0 joule (J)/kg, should be performed. In cases of wide complex tachycardia, providers should generally move immediately to cardioversion and increase the dose to 2 J/kg if 1 J/kg is not effective. As with cases of bradycardia, providers should review the 6 Hs and 5 Ts to identify factors that might be contributing to the tachycardia (see Table 81.5).

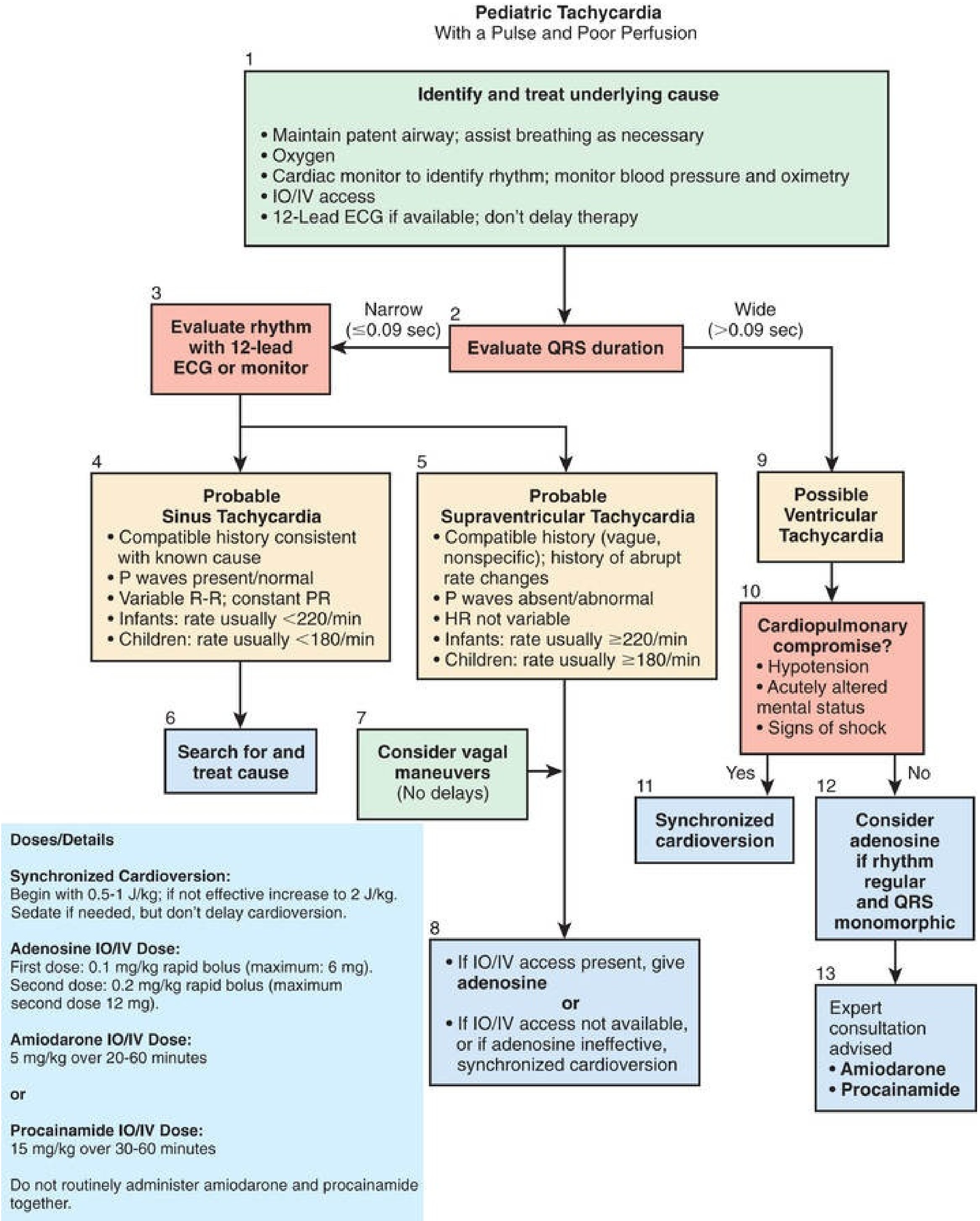
Pediatric Tachycardia
With a Pulse and Poor Perfusion
1
Identify and treat underlying cause
• Maintain patent airway; assist breathing as necessary
• Oxygen
• Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
• IO/IV access
• 12-Lead ECG if available; don't delay therapy
2
Evaluate QRS duration
Narrow (≤0.09 sec)
Wide (>0.09 sec)
3
Evaluate rhythm with 12-lead ECG or monitor
4
Probable Sinus Tachycardia
• Compatible history consistent with known cause
• P waves present/normal
• Variable R-R; constant PR
• Infants: rate usually <220/min
• Children: rate usually <180/min
5
Probable Supraventricular Tachycardia
• Compatible history (vague, nonspecific); history of abrupt rate changes
• P waves absent/abnormal
• HR not variable
• Infants: rate usually ≥220/min
• Children: rate usually ≥180/min
9
Possible Ventricular Tachycardia
10
Cardiopulmonary compromise?
• Hypotension
• Acutely altered mental status
• Signs of shock
Yes
No
6
Search for and treat cause
7
Consider vagal maneuvers (No delays)
11
Synchronized cardioversion
12
Consider adenosine if rhythm regular and QRS monomorphic
8
• If IO/IV access present, give adenosine
or
• If IO/IV access not available, or if adenosine ineffective, synchronized cardioversion
13
Expert consultation advised
• Amiodarone
• Procainamide
Doses/Details
Synchronized Cardioversion:
Begin with 0.5-1 J/kg; if not effective increase to 2 J/kg. Sedate if needed, but don't delay cardioversion.
Adenosine IO/IV Dose:
First dose: 0.1 mg/kg rapid bolus (maximum: 6 mg).
Second dose: 0.2 mg/kg rapid bolus (maximum second dose 12 mg).
Amiodarone IO/IV Dose:
5 mg/kg over 20-60 minutes
or
Procainamide IO/IV Dose:
15 mg/kg over 30-60 minutes
Do not routinely administer amiodarone and procainamide together.

FIG. 81.14 Pediatric advanced life support tachycardia algorithm. AV, Atrioventricular (conductor); ECG, electrocardiogram; HR, heart rate; IO/IV, intraosseous/intravenous. (From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 14, *Circulation* 122[Suppl 3]:S876–S908, 2010, Fig 3, p S888.)

Recognition and Management of Cardiac Arrest

Cardiac arrest occurs when the heart fails as an effective pump and blood flow ceases. Outwardly, the patient in cardiac arrest presents as unresponsive and apneic with no palpable pulse. Internally, the cessation of nutrient flow causes progressive tissue ischemia and organ dysfunction. If not rapidly reversed, cardiac arrest leads to progressive deterioration in brain, heart, and other organ function, such that resuscitation and recovery are no longer possible.

Pediatric cardiac arrest is rarely caused by a sudden coronary event or arrhythmia. Instead, cardiac arrest in children is most often the end result of progressive organ and tissue ischemia, caused by tissue hypoxia, acidosis, and nutrient depletion at the end stages of respiratory deterioration, shock, or heart failure. Therefore, **the most important treatment of cardiac arrest is anticipation and prevention. Intervening when a child manifests respiratory distress or early stages of shock can prevent deterioration to full arrest** . When sudden cardiac arrest does occur, it is often associated with an arrhythmia, specifically ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). In sudden events such as these, the key to successful resuscitation is early recognition of the arrhythmia and prompt treatment with high-quality CPR *and* defibrillation.

The principle behind high-quality CPR is that adequate chest compressions—those that circulate blood around the body with a good pulse pressure—are the most important component of CPR. The caregiver providing chest compressions should **push hard, push fast, allow for complete chest recoil, and minimize interruptions** . Ideally, chest compressions should be interrupted only for a rhythm check or delivery of a defibrillating shock. Providers should refer to the most recent American Heart Association (AHA) guidelines for pediatric BLS and ALS (eccguidelines.heart.org).

Cardiac arrest is recognized from general and primary survey findings consistent with a pale or cyanotic child who is unresponsive, apneic, and pulseless. Even experienced providers have a relatively high error rate when asked to determine presence or absence of pulse in a child. Therefore, any child found unresponsive and apneic can be presumed to be in cardiac arrest, and a rescuer should respond accordingly. **A lone rescuer for an *unwitnessed* pediatric cardiac arrest in an outpatient setting should treat the arrest as**

asphyxial in nature, immediately initiate CPR, and activate the emergency response system via a mobile phone (if available). If a mobile phone is not immediately available, the rescuer should perform initial rescue breaths and 2 min of chest compressions and ventilations before leaving the child to activate the emergency response system. For an in-hospital arrest, the provider should call for help and have a team member activate the emergency response system while beginning CPR. **A lone rescuer in an outpatient setting who *witnesses* a child's sudden collapse should treat the arrest as a primary arrhythmia, should immediately activate the EMS system, and obtain an AED.** On returning to the child, the rescuer should confirm pulselessness, turn on the AED, place the leads on the child's chest, and follow the defibrillator's voice commands.

The initial step in CPR for a child of any age is to restore ventilation and oxygenation as quickly as possible. On confirmation of unresponsiveness, apnea, and/or pulselessness, resuscitation should follow current AHA Basic Life Support (BLS), (or Advanced Cardiac Life Support, ACLS) guidelines, as appropriate (eccguidelines.heart.org).

If a person is pulseless, chest compressions should be initiated. Chest compressions in infants <1 yr old may be performed by placing 2 thumbs on the midsternum with the hands encircling the thorax or by placing 2 fingers over the midsternum and compressing (Figs. 81.15 and 81.16). For children >1 yr old, the care provider should perform chest compressions over the lower half of the sternum with the heel of 1 hand, or with 2 hands as used for adult resuscitation (Fig. 81.17). In all cases, care should be taken to avoid compression of the xiphoid and the ribs. When feasible, a cardiac resuscitation board should be placed under the child's back to maximize the efficiency of compressions. CPR and rescue breathing should be performed based on current AHA BLS/ACLS guidelines.

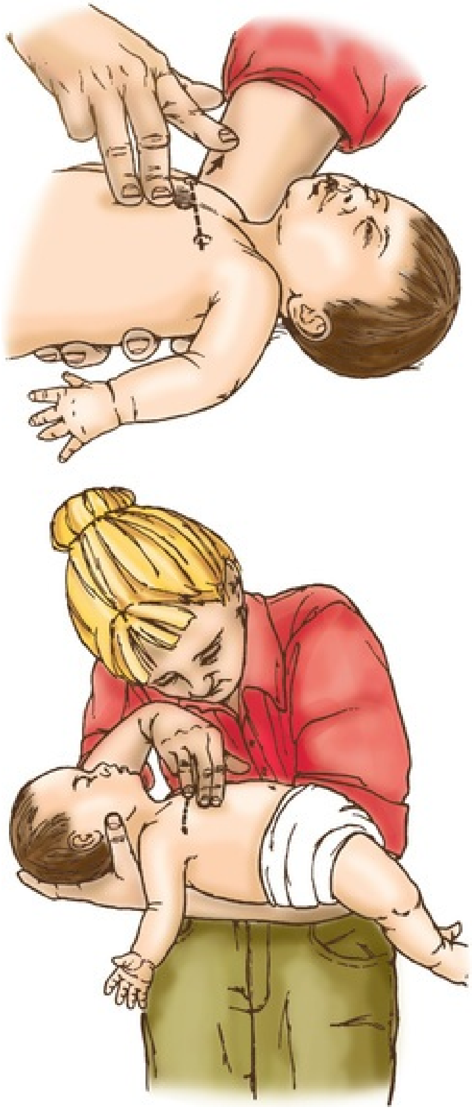

FIG. 81.15 Cardiac compressions. *Top,* The infant is supine on the palm of the rescuer's hand. *Bottom,* Performing CPR while carrying an infant or small child. Note that the head is kept level with the torso. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, *JAMA* 268:2251–2261, 1992.)

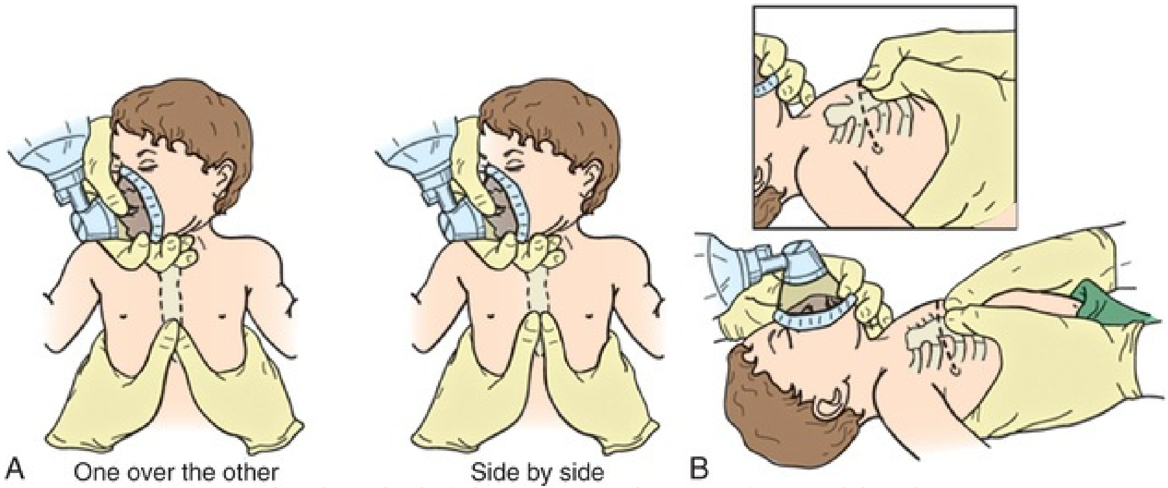

FIG. 81.16 Thumb method of chest compressions. A, Infant receiving chest compressions with thumb 1 fingerbreadth below the nipple line and hands encircling chest. B, Hand position for chest encirclement technique for external chest compressions in neonates. Thumbs are side by side over the lower third of the sternum. In the small newborn, thumbs may need to be superimposed *(inset)* . Gloves should be worn during resuscitation. (From Fleisher GR, Ludwig S, editors: *Textbook of pediatric emergency medicine,* Philadelphia, 2010, Wolters Kluwer/Lippincott Williams & Wilkins Health, Fig 2.2.)

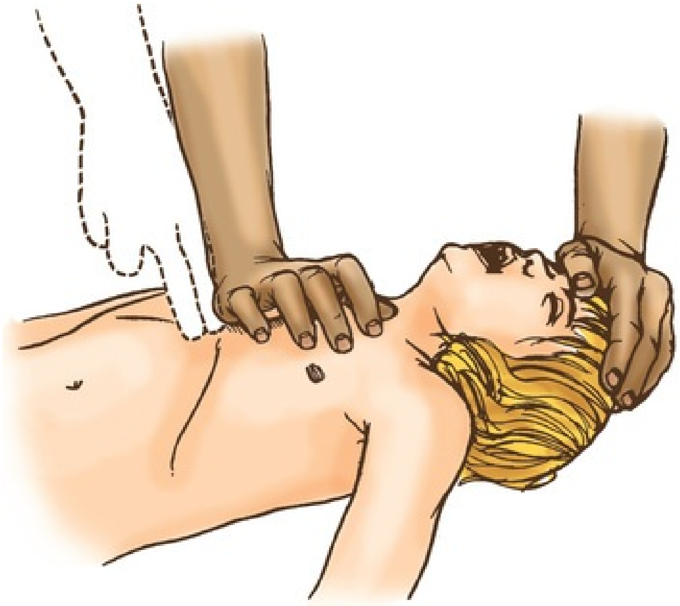

FIG. 81.17 Locating the hand position for chest compression in a child. Note that the rescuer's other hand is used to maintain the head position to facilitate ventilation. (From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support, *JAMA* 268:2251–2261, 1992.)

The goal of CPR is to reestablish spontaneous circulation at a level that is compatible with survival. If resuscitative efforts do not succeed in reestablishing life-sustaining breathing and circulation, the medical team must decide whether continued efforts are warranted or whether the resuscitation should be stopped. If EMS care is en route, bringing the potential for further escalation in care, such as endotracheal intubation, vascular access, and medications, CPR should be continued as long as possible or deemed reasonable by the rescuers.

In the in-hospital setting, the ECG should dictate further resuscitative efforts. For children without a pulse and in asystole or electromechanical dissociation (**pulseless electrical activity** , PEA), providers should continue rescue breathing and CPR, obtain vascular access, and administer emergency IV epinephrine (Fig. 81.18). For continued asystole or PEA, epinephrine can be repeated every 3-5 min. Patient history, physical exam findings, and laboratory evaluation should be used to elicit correctable causes of arrest (e.g., 6 Hs, 5 Ts; see Table 81.5). CPR should be continued after epinephrine administration, to circulate the drug through the body. After 5 cycles of CPR, providers should reassess the child for the presence of a pulse or a change in the ECG rhythm that would necessitate a different response.

Pediatric Cardiac Arrest

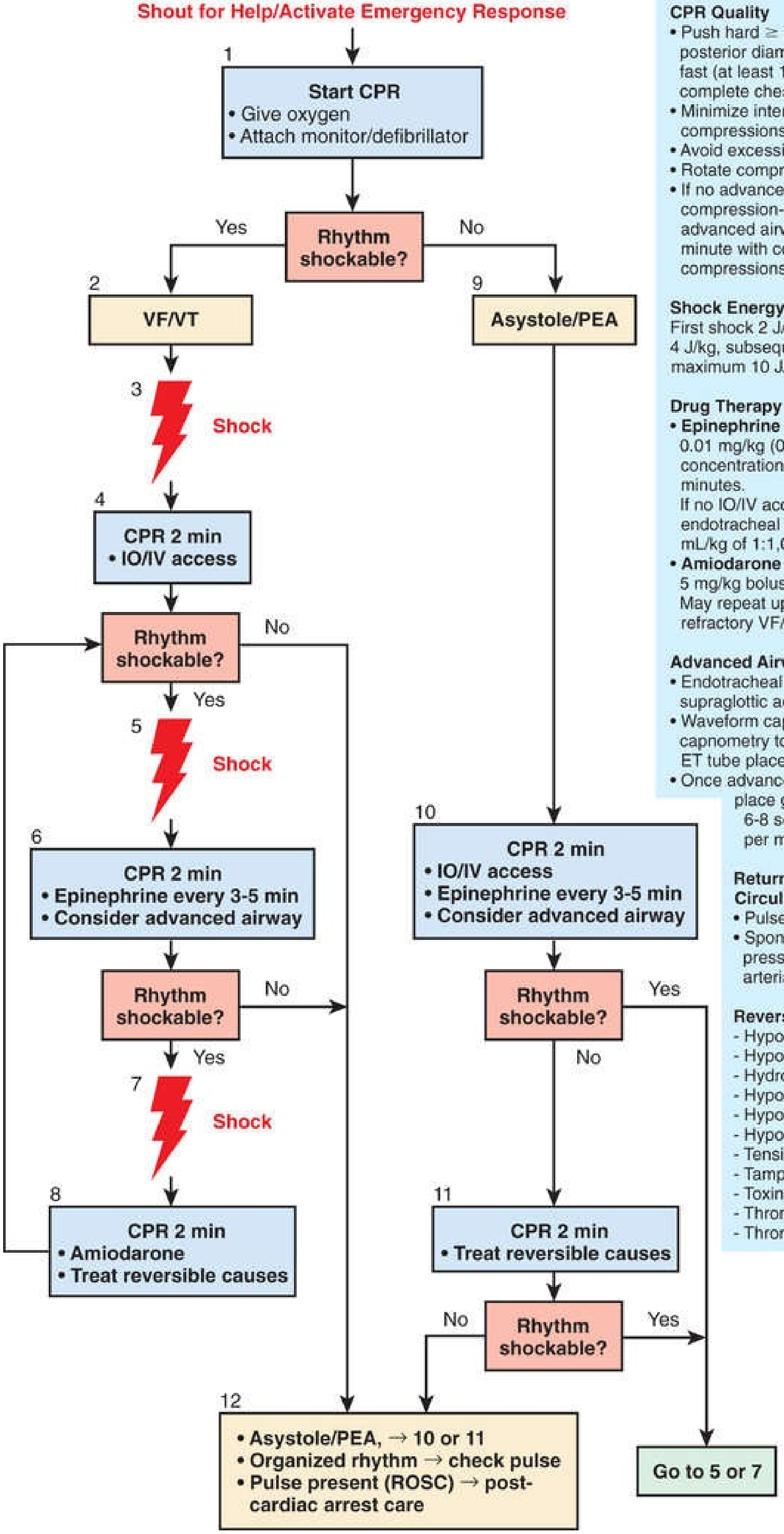
Shout for Help/Activate Emergency Response
1
Start CPR
• Give oxygen
• Attach monitor/defibrillator
Rhythm shockable?
Yes
No
2
VF/VT
9
Asystole/PEA
3
Shock
4
CPR 2 min
• IO/IV access
Rhythm shockable?
No
Yes
5
Shock
6
CPR 2 min
• Epinephrine every 3-5 min
• Consider advanced airway
Rhythm shockable?
No
Yes
7
Shock
8
CPR 2 min
• Amiodarone
• Treat reversible causes
10
CPR 2 min
• IO/IV access
• Epinephrine every 3-5 min
• Consider advanced airway
Rhythm shockable?
Yes
No
11
CPR 2 min
• Treat reversible causes
Rhythm shockable?
No
Yes
12
• Asystole/PEA, → 10 or 11
• Organized rhythm → check pulse
• Pulse present (ROSC) → post-cardiac arrest care
Go to 5 or 7

Doses/Details

CPR Quality

- Push hard ≥ 1/3 of anterior-posterior diameter of chest) and fast (at least 100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 15:2 compression-ventilation ratio. If advanced airway, 8-10 breaths per minute with continuous chest compressions

Shock Energy for Defibrillation

First shock 2 J/kg, second shock 4 J/kg, subsequent shocks ≥ 4 J/kg, maximum 10 J/kg or adult dose.

Drug Therapy

- **Epinephrine IO/IV Dose:** 0.01 mg/kg (0.1 mL/kg of 1:10,000 concentration). Repeat every 3-5 minutes.
  If no IO/IV access, may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of 1:1,000 concentration).
- **Amiodarone IO/IV Dose:** 5 mg/kg bolus during cardiac arrest May repeat up to 2 times for refractory VF/pulseless VT.

Advanced Airway

- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement.
- Once advanced airway in place give 1 breath every 6-8 seconds (8-10 breaths per minute)

Return of Spontaneous Circulation (ROSC)

- Pulse and blood pressure
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible Causes

- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypoglycemia
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary

FIG. 81.18 Pediatric advanced life support pulseless arrest algorithm. CPR, Cardiopulmonary resuscitation; IO/IV, intraosseous/intravenous; PEA, pulseless electrical activity; VF/VT, ventricular fibrillation/tachycardia. (From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 14, *Circulation* 122[Suppl 3]:S876–S908, 2010, Fig 1, p S885.)

For those children with pulseless VT or VF, emergency defibrillation is indicated (Fig. 81.18). Providers should apply the pads to the child's bare chest and back and follow the verbal instructions given by the AED. For younger children, a defibrillator (if available) set to the dose of 2 J/kg should be used. Ideally, the AED used in a child ≤8 yr of age should be equipped with an attenuated adult dose or should be designed for children; if neither device is available, a standard adult AED should be used. CPR should be immediately restarted after defibrillation. Emergency dose epinephrine can also be administered with another 5 cycles of CPR to ensure its circulation throughout the child's body. If the ECG rhythm continues to show VF or VT, defibrillation can be alternated with epinephrine. For refractory VF or VT, an IV antiarrhythmic, such as lidocaine or amiodarone, can be given (Tables 81.6 and 81.7). Some adult studies have suggested that a combination of epinephrine, vasopressin, and methylprednisolone improves intact survival after CPR.

Table 81.6

Medications for Pediatric Resuscitation and Arrhythmias

MEDICATION	DOSE	REMARKS
Adenosine	0.1 mg/kg (max: 6 mg)	Monitor ECG.
	Repeat: 0.2 mg/kg (max: 12 mg)	Rapid IV/IO bolus.
Amiodarone	5 mg/kg IV/IO; repeat up to 15 mg/kg	Monitor ECG and blood pressure.
	Max: 300 mg	Adjust administration rate to urgency (give more slowly when perfusing rhythm is present).
		Use caution when administering with other drugs that prolong QT interval (consider expert consultation).
Atropine	0.02 mg/kg IV/IO	Higher doses may be used with organophosphate poisoning.
	0.03 mg/kg ETT*	
	Repeat once if needed	
	Minimum dose: 0.1 mg	
	Minimum single dose:	
	Child, 0.5 mg	
	Adolescent, 1 mg	
Calcium chloride (10%)	20 mg/kg IV/IO (0.2 mL/kg)	Slowly
		Adult dose: 5-10 mL

Epinephrine	0.01 mg/kg (0.1 mL/kg 1 : 10,000) IV/IO 0.1 mg/kg (0.1 mL/kg 1 : 1,000) ETT* Max dose: 1 mg IV/IO; 10 mg ET	May repeat every 3-5 min
Glucose	0.5-1 g/kg IV/IO	D10W: 5-10 mL/kg D25W: 2-4 mL/kg D50W: 1-2 mL/kg
Lidocaine	Bolus: 1 mg/kg IV/IO Max dose: 100 mg Infusion: 20-50 µg/kg/min ETT* : 2-3 mg	
Magnesium sulfate	25-50 mg/kg IV/IO over 10-20 min; faster in torsades de pointes Max dose: 2 g	
Naloxone	<5 yr or ≤20 kg: 0.1 mg/kg IV/IO/ETT* ≥5 yr or >20 kg: 2 mg IV/IO/ETT*	Use lower doses to reverse respiratory depression associated with therapeutic opioid administration (1-15 µg/kg).
Procainamide	15 mg/kg IV/IO over 30-60 min	Monitor EGG and blood pressure.
	Adult dose: 20 mg/min IV infusion up to total max dose of 17 mg/kg	Use caution when administering with other drugs that prolong QT interval (consider expert consultation).
Sodium bicarbonate	1 mEq/kg/dose IV/IO slowly	After adequate ventilation

* Flush with 5 mL of normal saline and follow with 5 ventilations.

ECG, Electrocardiogram; ETT, endotracheal tube; IO, intraosseous; IV, intravenous.

From ECC Committee, Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, *Circulation* 112:IV1–203, 2005.

Table 81.7

Medications to Maintain Cardiac Output and for Postresuscitation Stabilization*

MEDICATION	DOSE RANGE	COMMENT
Inamrinone	0.75-1 mg/kg IV/IO over 5 min; may repeat 2×; then: 2-20 µg/kg/min	Inodilator
Dobutamine	2-20 µg/kg/min IV/IO	Inotrope; vasodilator
Dopamine	2-20 µg/kg/min IV/IO in low doses; pressor in higher doses	Inotrope; chronotrope; renal and splanchnic vasodilator
Epinephrine	0.1-1 µg/kg/min IV/IO	Inotrope; chronotrope; vasodilator in low doses; vasopressor in higher doses
Milrinone	50-75 µg/kg IV/IO over 10-60 min then 0.5-0.75 µg/kg/min	Inodilator
Norepinephrine	0.1-2 µg/kg/min	Inotrope; vasopressor
Sodium nitroprusside	1-8 µg/kg/min	Vasodilator; prepare only in D5W

* Alternative formula for calculating an infusion: Infusion rate (mL/hr) = [weight (kg) × dose (µg/kg/min) × 60 (min/hr)]/concentration µg/mL).

D5W, 5% Dextrose in water; IO, intraosseous; IV, intravenous.

From ECC Committee, Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, *Circulation* 112:IV1–IV203, 2005.

Traditionally, continuing CPR >20 min in children with in-hospital cardiac arrest has been considered futile. With current practice for CPR, survival for in-hospital cardiac arrest is approximately 40% for CPR duration <15 min, compared with approximately 12% for CPR lasting >35 min. Survivors had a favorable neurologic outcome in 70% with a CPR duration <15 min, compared with 60% for those requiring resuscitation for >35 min.

Vascular Access

Venous Access

Veins suitable for cannulation are numerous, but there is considerable anatomic variation from patient to patient. In the upper extremities, the *median antecubital vein* , located in the antecubital fossa, is often the largest and easiest to access (Fig. 81.19). Many veins on the dorsum of the hand are also suitable for cannulation because they are often large and easily located, and their cannulation is generally well tolerated. The *cephalic vein* is usually cannulated at the wrist, along the forearm, or at the elbow. The *median vein* of the forearm is also suitable as it lies along a flat surface of the forearm. In the lower extremity, the *great saphenous vein* , located just anterior to the medial malleolus, is accessible in most patients. The dorsum of the foot usually has a large vein in the midline, passing across the ankle joint, but catheters are difficult to maintain in this vein because dorsiflexion tends to dislodge them. A 2nd large vein on the lateral side of the foot, running in the horizontal plane, usually 1-2 cm dorsal to the lower margin of the foot, is preferable (Fig. 81.20). The most notable scalp veins are the *superficial temporal* (just anterior to the ear) and *posterior auricular* (just behind the ear).

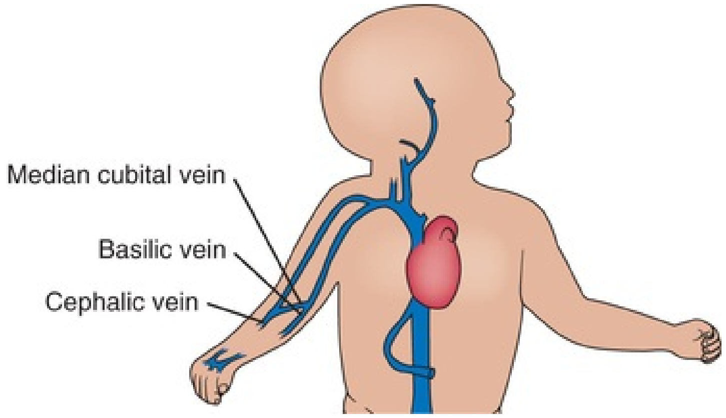
Median cubital vein
Basilic vein
Cephalic vein

FIG. 81.19 Veins of the upper extremity. (From Roberts JR, Hedges JR, editors: *Clinical procedures in emergency medicine,* ed 4, Philadelphia, 2004, Saunders.)

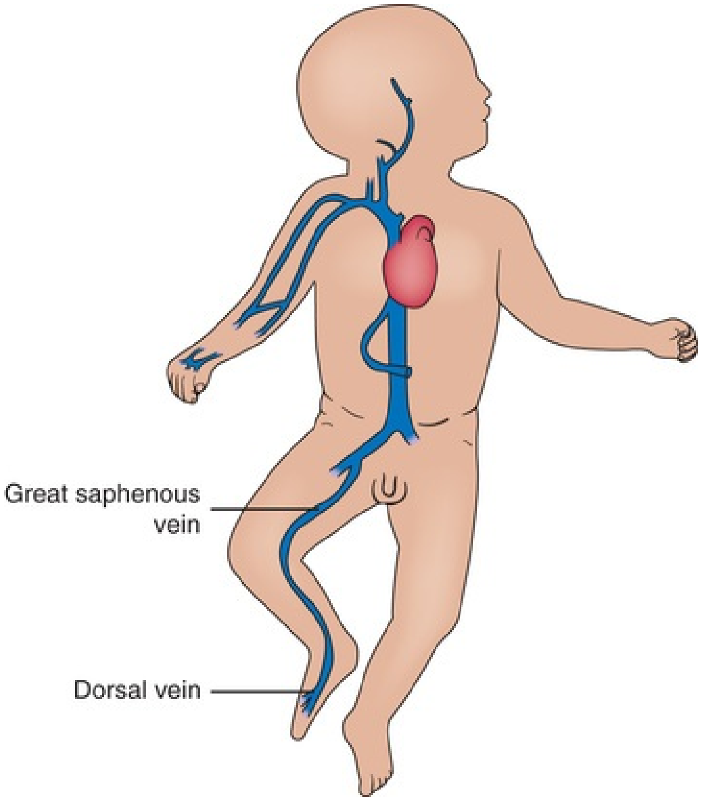
Great saphenous vein
Dorsal vein

FIG. 81.20 Veins of the lower extremity. (From Roberts JR, Hedges JR, editors: *Clinical procedures in emergency medicine,* ed 4, Philadelphia, 2004, Saunders.)

Deeper and larger central veins can provide more reliable, larger-bore access for medications, nutritive solutions, and blood sampling than peripheral venous lines. They may be reached by percutaneous cannulation or surgical exposure. In infants and young children, the *femoral vein* is often the easiest to access and cannulate, but the *internal jugular* and *subclavian* veins may also be used (Figs. 81.21 and 81.22). Because of its proximity to the median nerve, the brachial vein is not often recommended for cannulation.

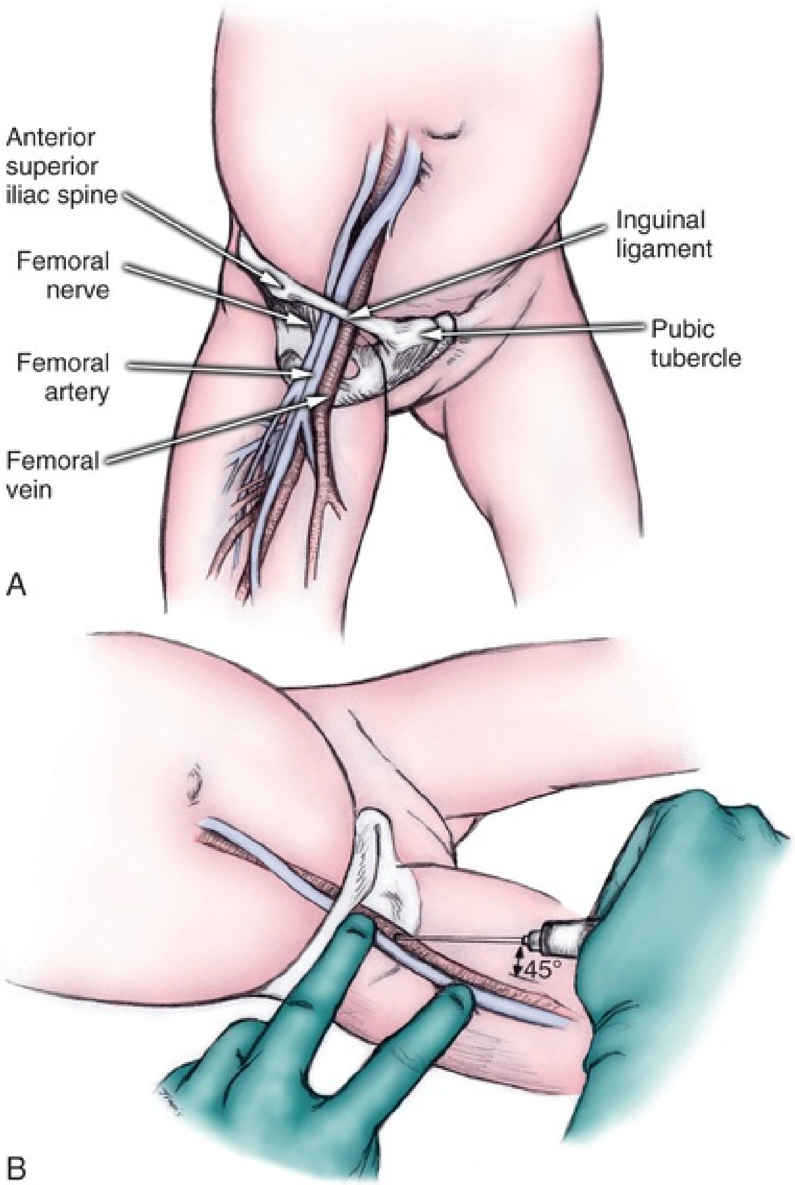
Anterior superior iliac spine
Femoral nerve
Femoral artery
Femoral vein
Inguinal ligament
Pubic tubercle
A
45°
B

FIG. 81.21 **Femoral vein approach. Remember the mnemonic NAVEL for nerve, artery, vein, empty space, and lymphatics. (From Putigna F, Solenberger R: *Central venous access* . http://emedicine.medscape.com/article/940865-overview .)**

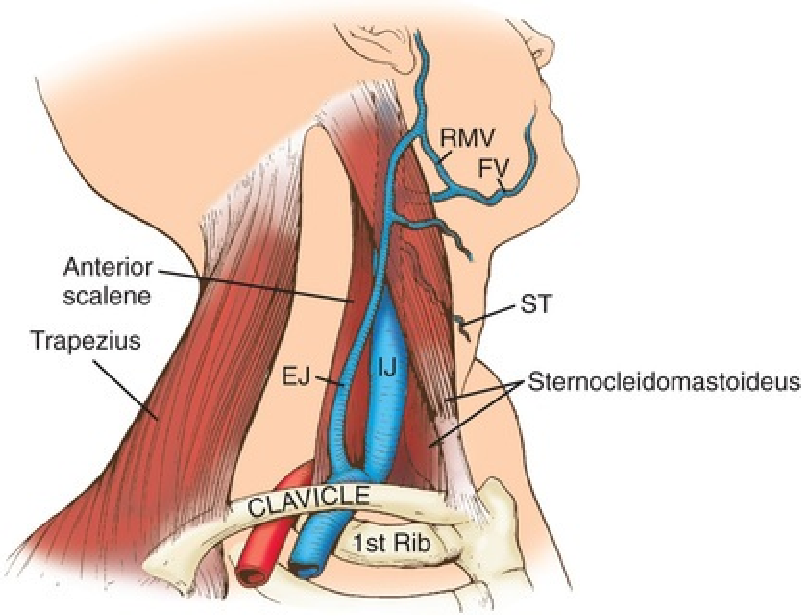

FIG. 81.22 Internal and external jugular veins. EJ, External jugular vein; FV, facial vein; IJ, internal jugular vein; RMV, retromandibular vein; ST, superior thyroid vein. The 2 heads of the sternocleidomastoideus are indicated by the *lines* . (From Mathers LW, Smith DW, Frankel L: Anatomic considerations in placement of central venous catheters, *Clin Anat* 5:89, 1992. Reprinted by permission of Wiley-Liss.)

Intraosseous Access

Intraosseous (IO) needles (for intramedullary venous plexus access) are special rigid, large-bore needles. IO cannulation is recommended for patients in whom IV access proves difficult or unattainable, even in older children. If venous access is not available within approximately 1 min in a child with cardiopulmonary arrest, an IO needle should be placed in the anterior proximal tibia (with care taken to avoid traversing the epiphyseal plate). The needle should penetrate the anterior layer of compact bone, and its tip is advanced into the spongy interior of the bone (Fig. 81.23). Commercially available IO kits frequently include drills that obviate the complications of needle placement associated with manual placement. All medications, blood products, and fluids may be administered through the IO route, including medications required for emergency resuscitation. Complications are uncommon but may include osteomyelitis with prolonged infusions and tibial fracture.

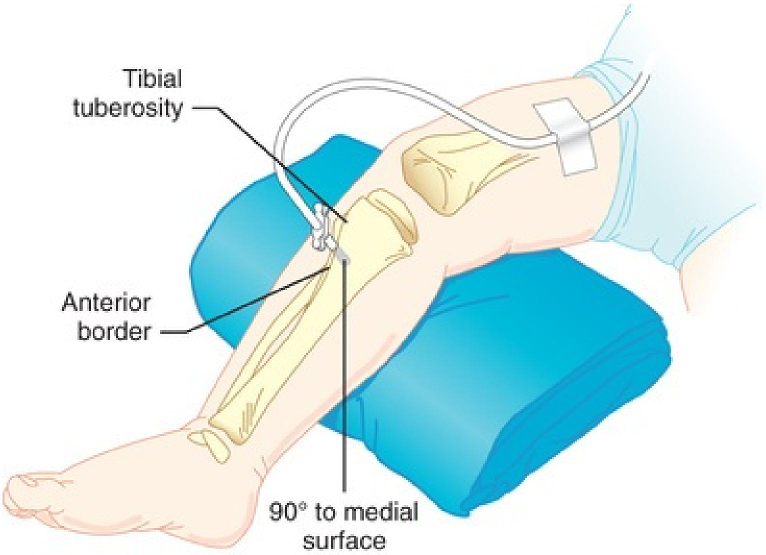

FIG. 81.23 Intraosseous cannulation technique. (From Zwass MS, Gregory GA: Pediatric and neonatal intensive care. In Miller RD, Eriksson LI, Fleisher LA, et al, editors: *Miller's anesthesia,* ed 7, Philadelphia, 2009, Churchill Livingstone, Fig 84-1.)

If IV and IO routes are unavailable in an intubated patient, medication can be given through the ETT (epinephrine, atropine, naloxone, vasopressin).

Arterial Access

Arterial access is indicated when care providers need frequent blood sampling, particularly to assess adequacy of oxygenation, ventilation, or acid-base balance, and/or continuous blood pressure monitoring. The *radial artery* , the most commonly cannulated artery, lies on the lateral side of the anterior wrist, just medial to the styloid process of the radius (Fig. 81.24). The ulnar artery, just lateral to the tendon of the flexor carpi ulnaris, is used less often because of its proximity to the ulnar nerve. Useful sites in the lower extremity, particularly in neonates and infants, are the *dorsalis pedis artery* , on the dorsum of the foot between the tendons of the tibialis anterior and the extensor hallucis longus, and the *posterior tibial artery* , posterior to the medial malleolus. Arterial catheters require special care for insertion and subsequent management.

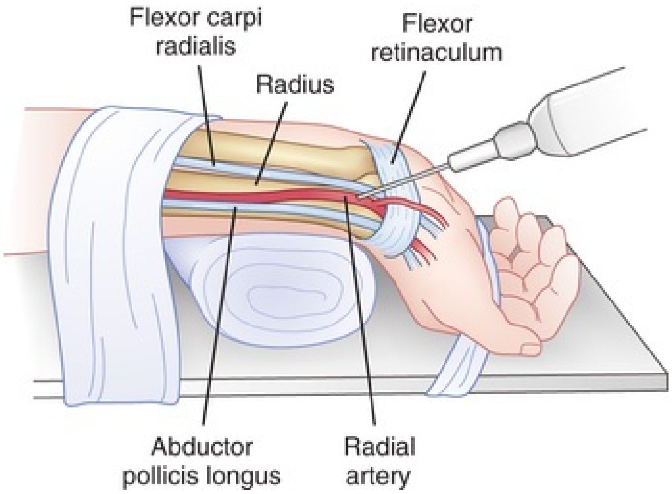

FIG. 81.24 Radial artery anatomy and cannulation.

Nonvascular Emergency Procedures

Thoracentesis and Chest Tube Placement

Thoracentesis is the placement of a needle or catheter into the pleural space to evacuate fluid, blood, or air. Most insertions are performed in one of the intercostal spaces between the 4th and 9th ribs in the plane of the midaxillary line. After appropriate systemic and local anesthesia/sedation is performed as clinically indicated, a skin incision is made, and dissection through the chest wall is accomplished in layers with use of blunt dissection techniques. The needle (and later the chest tube) that enters the pleural space should penetrate the intercostal space by passing over the superior edge of the lower rib, because there are larger vessels along the inferior edge of the rib. Ideally, the chest tube should lie *anterior* in the pleural space for air accumulation and *posterior* for fluid accumulation. A radiograph must be obtained to verify chest tube placement and evacuation of the pleural space.

Pericardiocentesis

When fluid, blood, or gas accumulates in the pericardial sac, the heart may become compressed and may be unable to fill/empty with normal volumes of blood, leading to diminished cardiac output. The cardinal signs of such a restrictive pericardial effusion are tachycardia, hypotension generally with a narrowed pulse pressure, and decreased So_2. Pericardiocentesis includes needle aspiration of the pericardial sac, often followed by the placement of a catheter for continuous drainage. As with thoracentesis, chest radiography should be done to confirm catheter location as well as evaluate for any complications, such as pneumothorax or hemothorax. Pericardiocentesis may be performed with echocardiography.

Postresuscitation Care

After successful resuscitation, close observation in an intensive care unit, where the child can receive ongoing multiorgan system assessments and support, is critical. Optimal postresuscitation care includes ongoing support of cardiovascular and respiratory system function as needed and the identification and treatment of other organ system dysfunction that may have contributed to (or resulted from) the child's cardiopulmonary instability. Good postresuscitation intensive care also includes supportive services for the child's parents, siblings, family, and friends.

Induced hypothermia (32-34°C [89.6-91.4°F] versus targeted temperature 36.8°C (98.2°F) (range, 36-37.5°C [96.8-99.5°F]) for about 48 hr) has *not* been shown to improve survival and neurologic function in pediatric survivors of CPR. However, *hyperthermia must be avoided.* **Hypoxic-ischemic encephalopathy** with subsequent development of seizures, intellectual impairment, and spasticity, is a serious and common complication of cardiac arrest. In addition, *hyperglycemia and hypoglycemia should be avoided.*

Postresuscitation management generally has 2 phases. First, the providers must assess the child's airway and breathing and support oxygenation and ventilation as indicated. If the child has ongoing respiratory failure and has been supported with bag-valve-mask ventilation until this time, the providers should now move forward with intubation. Once the child is intubated, mechanical ventilation must be established and respiratory assessments performed, such as chest radiography and arterial blood gas analysis. The child's circulatory system must also be assessed and supported as needed. Continuous arterial blood pressure monitoring can help the provider determine the need for, and response to, inotropic and chronotropic medications (see Table 81.7). Once the ABCs have been managed, providers can move on to full organ system assessments. A systematic approach should be used, with a full physical exam and laboratory evaluation to reveal the child's respiratory, cardiovascular, neurologic, gastrointestinal, renal, and hematologic system function.

Communication with the patients' family is an essential element of postresuscitation care. The family should be thoroughly briefed on the elements of the resuscitation performed, the child's condition, and ongoing medical concerns, uncertainties, or issues by the *most senior provider available* . This provider should be available to answer the family's questions, clarify information, and provide comfort. Other support staff, including social workers and chaplains, should be contacted, as the family wishes, to provide additional support and comfort. For situations in which the resuscitation is ongoing and the child is not expected to survive, it is recommended that the provider make every effort possible to have the family present at the bedside, if they wish. Family presence during CPR or other emergency resuscitative efforts, even if the child dies, is associated with a more positive medical experience than if they are excluded. In situations where the child is critically ill but stable, the family should be brought to the bedside as soon as the healthcare team deems it safe and appropriate (see Chapter 7).

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CHAPTER 82

Acute Care of Multiple Trauma

Cindy Ganis Roskind, Howard I. Pryor II, Bruce L. Klein

Epidemiology

Injury is a leading cause of death and disability in children throughout the world (see Chapter 13). Deaths represent only a small fraction of the total trauma burden. Approximately 140,000 children were treated in U.S. trauma centers in 2016 for serious injury. Many survivors of trauma have permanent or temporary functional limitations. Motor vehicle–related injuries and falls rank among the top 15 causes of disability-adjusted life years in children worldwide.

Trauma is frequently classified according to the number of significantly injured body parts (≥1), the severity of injury (mild, moderate, or severe), and the mechanism of injury (blunt or penetrating). In childhood, blunt trauma predominates, accounting for the majority of injuries. In adolescence, penetrating trauma increases in frequency, accounting for approximately 15% of injuries, and penetrating trauma secondary to a firearm is associated with a high case fatality rate of 11%.

Regionalization and Trauma Teams

Mortality and morbidity rates have decreased in geographic regions with comprehensive, coordinated trauma systems. Treatment at designated trauma centers is associated with decreased mortality. At the scene of injury, paramedics should administer necessary advanced life support and perform **triage** (Fig. 82.1). It is usually preferable to bypass local hospitals and rapidly transport a seriously injured child directly to a pediatric trauma center (or a trauma center with pediatric commitment). *Children have lower mortality rates, lower complication rates, and less operative interventions after severe blunt trauma* *when they are treated in designated pediatric trauma centers or in hospitals with pediatric intensive care units.*

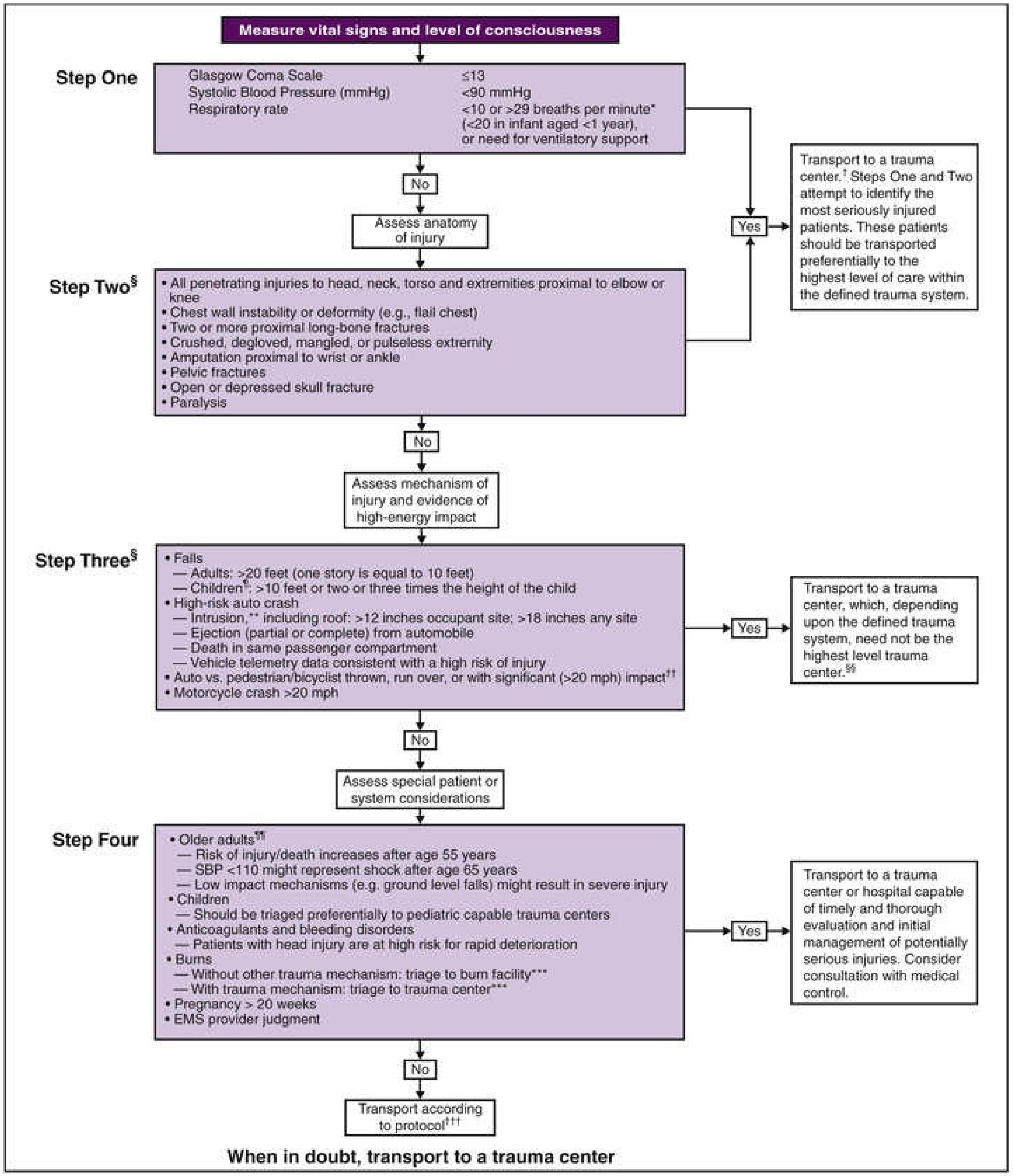
Measure vital signs and level of consciousness
Step One
Glasgow Coma Scale ≤13
Systolic Blood Pressure (mmHg) <90 mmHg
Respiratory rate <10 or >29 breaths per minute* (<20 in infant aged <1 year), or need for ventilatory support
No
Assess anatomy of injury
Step Two§
• All penetrating injuries to head, neck, torso and extremities proximal to elbow or knee
• Chest wall instability or deformity (e.g., flail chest)
• Two or more proximal long-bone fractures
• Crushed, degloved, mangled, or pulseless extremity
• Amputation proximal to wrist or ankle
• Pelvic fractures
• Open or depressed skull fracture
• Paralysis
Yes
Transport to a trauma center.† Steps One and Two attempt to identify the most seriously injured patients. These patients should be transported preferentially to the highest level of care within the defined trauma system.
No
Assess mechanism of injury and evidence of high-energy impact
Step Three§
• Falls
— Adults: >20 feet (one story is equal to 10 feet)
— Children¶: >10 feet or two or three times the height of the child
• High-risk auto crash
— Intrusion,** including roof: >12 inches occupant site; >18 inches any site
— Ejection (partial or complete) from automobile
— Death in same passenger compartment
— Vehicle telemetry data consistent with a high risk of injury
• Auto vs. pedestrian/bicyclist thrown, run over, or with significant (>20 mph) impact††
• Motorcycle crash >20 mph
Yes
Transport to a trauma center, which, depending upon the defined trauma system, need not be the highest level trauma center.§§
No
Assess special patient or system considerations
Step Four
• Older adults¶¶
— Risk of injury/death increases after age 55 years
— SBP <110 might represent shock after age 65 years
— Low impact mechanisms (e.g. ground level falls) might result in severe injury
• Children
— Should be triaged preferentially to pediatric capable trauma centers
• Anticoagulants and bleeding disorders
— Patients with head injury are at high risk for rapid deterioration
• Burns
— Without other trauma mechanism: triage to burn facility***
— With trauma mechanism: triage to trauma center***
• Pregnancy > 20 weeks
• EMS provider judgment
Yes
Transport to a trauma center or hospital capable of timely and thorough evaluation and initial management of potentially serious injuries. Consider consultation with medical control.
No
Transport according to protocol†††
When in doubt, transport to a trauma center

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[*] The upper limit of respiratory rate in infants is >29 breaths per minute to maintain a higher level of overtriage for infants.

[†] Trauma centers are designated Level I-IV. A Level I center has the greatest amount of resources and personnel for care of the injured patient and provides regional leadership in education, research, and prevention programs. A Level II facility offers similar resources to a Level I facility, possibly differing only in continuous availability of certain subspecialties or sufficient prevention, education, and research activities for Level I designation; Level II facilities are not required to be resident or fellow education centers. A Level III center is capable of assessment, resuscitation, and emergency surgery, with severely injured patients being transferred to a Level I or II facility. A Level IV trauma center is capable of providing 24-hour physician coverage, resuscitation, and stabilization to injured patients before transfer to a facility that provides a higher level of trauma care.

[§] Any injury noted in Step Two or mechanism identified in Step Three triggers a "yes" response.

[¶] Age <15 years.

[**] Intrusion refers to interior compartment intrusion, as opposed to deformation which refers to exterior damage.

[††] Includes pedestrians or bicyclists thrown or run over by a motor vehicle or those with estimated impact >20 mph with a motor vehicle.

[§§] Local or regional protocols should be used to determine the most appropriate level of trauma center within the defined trauma system; need not be the highest-level trauma center.

[¶¶] Age >55 years.

[***] Patients with both burns and concomitant trauma for whom the burn injury poses the greatest risk for morbidity and mortality should be transferred to a burn center. If the nonburn trauma presents a greater immediate risk, the patient may be stabilized in a trauma center and then transferred to a burn center.

[†††] Patients who do not meet any of the triage criteria in Steps One through Four should be transported to the most appropriate medical facility as outlined in local EMS protocols.

FIG. 82.1 Guidelines for field triage of injured patients—United States, 2011. (From Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, *MMWR* 61:6, 2012.)

When the receiving emergency department (ED) is notified before the child's arrival, the trauma team should also be mobilized in advance. Each member has defined tasks. A senior surgeon (surgical coordinator) or, sometimes initially, an emergency physician leads the team. Team compositions vary somewhat from hospital to hospital; Fig. 82.2 shows the model used at The Johns Hopkins Hospital Bloomberg Children's Center (Baltimore, MD). Consultants, especially neurosurgeons and orthopedic surgeons, must be promptly available; and the operating room staff should be alerted.

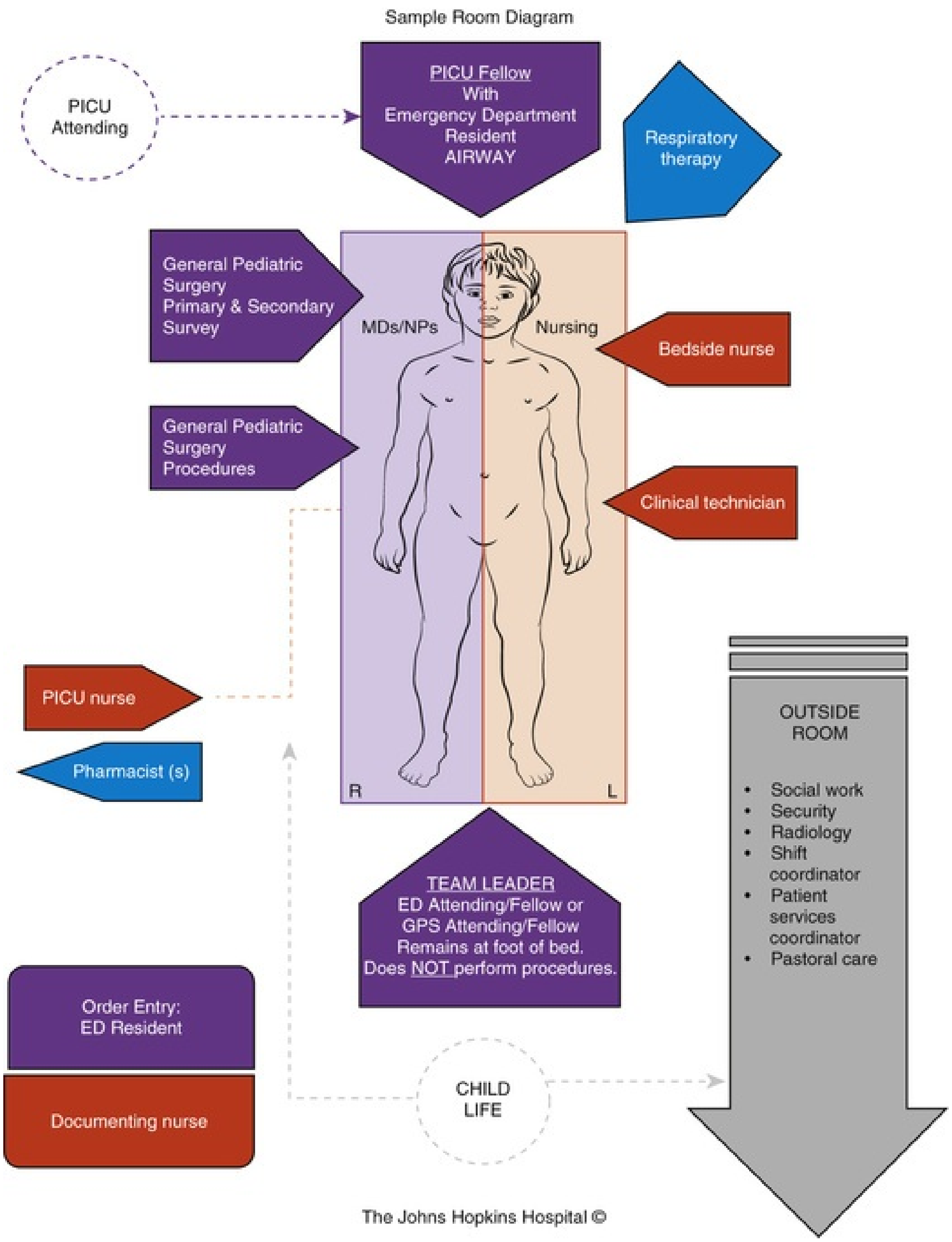
Sample Room Diagram
PICU Attending
PICU Fellow With Emergency Department Resident AIRWAY
Respiratory therapy
General Pediatric Surgery Primary & Secondary Survey
MDs/NPs
Nursing
Bedside nurse
General Pediatric Surgery Procedures
Clinical technician
PICU nurse
Pharmacist (s)
R
L
OUTSIDE ROOM
• Social work
• Security
• Radiology
• Shift coordinator
• Patient services coordinator
• Pastoral care
TEAM LEADER ED Attending/Fellow or GPS Attending/Fellow Remains at foot of bed. Does NOT perform procedures.
Order Entry: ED Resident
Documenting nurse
CHILD LIFE
The Johns Hopkins Hospital ©

FIG. 82.2 **Staff in the ED trauma bay at The Johns Hopkins Hospital Bloomberg Children's Center. ED, emergency department; NP, nurse practitioner; GPS, general pediatric surgery; PICU, pediatric intensive care unit; PSC, patient services coordinator. (Courtesy The Johns Hopkins Hospital, Baltimore, Maryland.)**

Physiologic status, anatomic locations, and/or mechanism of injury are used for field triage as well as to determine whether to activate the trauma team. More importance should be placed on physiologic compromise and less on mechanism of injury. Scoring scales such as the Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), Pediatric Trauma Score (Table 82.1), and Revised Trauma

Score use these parameters to predict patient outcome. The AIS and ISS are used together. First, the AIS is used numerically to score injuries—as 1 minor, 2 moderate, 3 serious, 4 severe, 5 critical, or 6 probably lethal—in each of 6 ISS body regions: head/neck, face, thorax, abdomen and pelvic contents, extremities and bony pelvis, and external. The ISS is the sum of the squares of the highest 3 AIS region scores.

Table 82.1

Pediatric Trauma Score*

COMPONENT	**+2**	**+1**	**−1**
Size	≥20 kg	10-20 kg	<10 kg
Airway	Normal	Maintainable	Unmaintainable
Systolic BP	≥90 mm Hg	50-90 mm Hg	<50 mm Hg
CNS	Awake	Obtunded/LOC	Coma/decerebrate
Open wound	None	Minor	Major/penetrating
Skeletal	None	Closed fracture	Open/multiple fractures
Sum total points			

[*] Children with a Pediatric Trauma Score ≤6 are at increased risk of mortality as well as morbidity.

BP, Blood pressure; CNS, central nervous system; LOC, loss of consciousness.

From Tepas JJ 3rd, Mollitt DL, Talbert JL, et al: The Pediatric Trauma Score as a predictor of injury severity in the injured child, *J Pediatr Surg* 22:14–18, 1987 (Table 1, p 15).

Primary Survey

During the primary survey, the physician quickly assesses and treats any life-threatening injuries. The principal causes of death shortly after trauma are airway obstruction, respiratory insufficiency, shock from hemorrhage, and central nervous system (CNS) injury. The primary survey addresses the **ABCDEs** : Airway, Breathing, Circulation, neurologic Deficit, and Exposure of the patient and control of the Environment.

Airway/Cervical Spine

Optimizing oxygenation and ventilation, while protecting the cervical spine (C-spine) from potential further injury, is of paramount importance. Initially, C-spine injury should be suspected in any child sustaining multiple, blunt trauma. Although C-spine injuries occur less often in children than adults, children are at risk for such injuries because of their relatively large heads in proportion to the rest of their body, which augment flexion-extension forces, and weak neck muscles, which predispose them to ligament injuries. To prevent additional spinal injury, paramedics have traditionally been taught to immobilize the cervical (and thoracic and lumbar) spine in neutral position with a stiff collar, head blocks, tape or cloth placed across the forehead, torso, and thighs to restrain the child, and a rigid backboard.

Airway obstruction manifests as snoring, gurgling, hoarseness, stridor, and/or diminished breath sounds (even with apparently good respiratory effort). Children are more likely than adults to have airway obstruction because of their smaller oral and nasal cavities, proportionately larger tongues and more tonsillar and adenoidal tissue, higher and more anterior glottic opening, and narrower larynx and trachea. Obstruction is common in patients with severe head injuries, partly because of decreased muscle tone, which allows the tongue to fall posteriorly and occlude the airway. With trauma, obstruction can also result from fractures of the mandible or facial bones, secretions such as blood or vomit, crush injuries of the larynx or trachea, and foreign body aspiration.

If it is necessary to open the airway, a jaw thrust without head tilt is recommended. This procedure minimizes cervical spine motion. In an unconscious child, an oropharyngeal airway may be inserted to prevent posterior displacement of the mandibular tissues. A semiconscious child will gag with an oropharyngeal airway but may tolerate a nasopharyngeal airway. A nasopharyngeal airway is contraindicated when there is a possibility of cribriform plate fracture. If these maneuvers plus suctioning do not clear the airway, oral endotracheal intubation is indicated. When endotracheal intubation proves difficult, a laryngeal mask airway can be used as a temporary alternative. A laryngeal mask airway consists of a tube with an inflatable cuff that rests above the larynx and thus does not require placement of the tube into the trachea. Video-assisted laryngoscopy or the use of a bougie can also be helpful in the management of a difficult airway. Emergency cricothyrotomy is needed in <1% of trauma victims.

Breathing

The physician assesses breathing by counting the respiratory rate; visualizing chest wall motion for symmetry, expansion, and accessory muscle use; and auscultating breath sounds in both axillae. Continuous waveform capnography monitoring should also be used as an adjunct; however, it is less reliable in patients with shock. In addition to looking visually for cyanosis, pulse oximetry is standard. If ventilation is inadequate, bag-valve-mask ventilation with 100% oxygen must be initiated immediately, followed by endotracheal intubation. End-expiratory carbon dioxide (CO_2) detectors or capnography help verify accurate tube placement.

Head trauma is the most common cause of respiratory insufficiency. An unconscious child with severe head injury may have a variety of breathing abnormalities, including Cheyne-Stokes respiration, slow irregular breaths, and apnea.

Although less common than a pulmonary contusion, tension pneumothorax and massive hemothorax are immediately life threatening (Tables 82.2 and 82.3). **Tension pneumothorax** occurs when air accumulates under pressure in the pleural space. The adjacent lung is compacted, the mediastinum is pushed toward the opposite hemithorax, and the heart, great vessels, and contralateral lung are compressed or kinked (see Chapter 439). Both ventilation and cardiac output are impaired. Characteristic findings include cyanosis, tachypnea, retractions, asymmetric chest rise, contralateral tracheal deviation, diminished breath sounds on the ipsilateral (more than contralateral) side, and signs of shock. Needle thoracentesis, followed by thoracostomy tube insertion, is diagnostic and lifesaving. **Hemothorax** results from injury to the intercostal vessels, lungs, heart, or great vessels. When ventilation is adequate, fluid resuscitation should begin before evacuation, because a large amount of blood may drain through the chest tube, resulting in shock.

Table 82.2

Differential Diagnosis of Immediately Life-Threatening Cardiopulmonary Injuries

	TENSION PNEUMOTHORAX	MASSIVE HEMOTHORAX	CARDIAC TAMPONADE
Breath sounds	Ipsilaterally decreased more than contralaterally	Ipsilaterally decreased	Normal
Percussion note	Hyperresonant	Dull	Normal
Tracheal location	Contralaterally shifted	Midline or shifted	Midline
Neck veins	Distended	Flat	Distended
Heart tones	Normal	Normal	Muffled

Modified from Cooper A, Foltin GL: Thoracic trauma. In Barkin RM, editor: *Pediatric emergency medicine* , ed 2, St Louis, 1997, Mosby, p 325.

Table 82.3

Life-Threatening Chest Injuries

Tension Pneumothorax

- One-way valve leak from the lung parenchyma or tracheobronchial tree
- Lung collapse with mediastinal and tracheal shift to the side opposite the leak
- Compromises venous return and decreases ventilation of the other lung
- Clinically, manifests as respiratory distress, unilateral absence of breath sounds, tracheal deviation, distended neck veins, tympany to percussion of the involved side, and cyanosis
- Relieve first with needle aspiration, then with chest tube drainage

Open Pneumothorax (Sucking Chest Wound)

- Effect on ventilation depends on size

Major Flail Chest

- Usually caused by blunt injury resulting in multiple rib fractures
- Loss of bone stability of the thoracic cage
- Major disruption of synchronous chest wall motion
- Mechanical ventilation and positive end-expiratory pressure required

Massive Hemothorax

- Must be drained with a large-bore tube
- Initiate drainage only with concurrent vascular volume replacement

Cardiac Tamponade

Beck's triad:

1. Decreased or muffled heart sounds
2. Jugular venous distention
3. Hypotension (with narrow pulse pressure)

Must be drained

Modified from Krug SE: The acutely ill or injured child. In Behrman RE, Kliegman RM, editors: *Nelson essentials of pediatrics* , ed 4, Philadelphia, 2002, Saunders, p 97.

Circulation

Signs of **shock** include tachycardia; weak pulse; delayed capillary refill; cool, mottled, pale skin; and altered mental state (see Chapter 88). The most common type of shock in trauma is *hypovolemic* shock caused by hemorrhage. *Cardiac tamponade*, which is a form of obstructive shock, may be suspected clinically or diagnosed by **focused assessment with sonography in trauma (FAST)** examination or echocardiography. Cardiac tamponade is best managed by thoracotomy or pericardial window, although pericardiocentesis may be necessary as a temporizing maneuver (see Table 82.3).

Early in shock, blood pressure remains normal because of compensatory increases in heart rate and peripheral vascular resistance (Table 82.4). Some individuals can lose up to 30% of blood volume before blood pressure declines. It is important to note that 25% of blood volume equals 20 mL/kg, which is only 200 mL in a 10 kg child. Losses >40% of blood volume cause severe hypotension that, if prolonged, may become irreversible. Direct pressure should be applied to control external hemorrhage. When direct pressure does not control hemorrhage, a tourniquet should be applied to a proximal pressure point. Blind clamping of bleeding vessels, which risks damaging adjacent structures, is not advisable.

Table 82.4

Systemic Responses to Blood Loss in Pediatric Patients

SYSTEM	MILD BLOOD LOSS (<30%)	MODERATE BLOOD LOSS (30–45%)	SEVERE BLOOD LOSS (>45%)
Cardiovascular	Increased heart rate; weak, thready	Markedly increased heart rate; weak, thready central pulses;	Tachycardia followed by bradycardia; central pulses very weak or absent;

	peripheral pulses; normal systolic blood pressure; normal pulse pressure	peripheral pulses absent; low normal systolic blood pressure; narrowed pulse pressure	peripheral pulses absent; hypotension; narrowed pulse pressure (or undetectable diastolic blood pressure).
Central nervous	Anxiety; irritability; confusion	Lethargy; dulled response to pain	Coma
Skin	Cool, mottled; capillary refill prolonged	Cyanotic; capillary refill markedly prolonged	Pale and cold
Urine output	Low to very low	Minimal	None

Adapted from American College of Surgeons Committee on Trauma: *Advanced trauma life support for doctors: student course manual,* ed 9, Chicago, 2012, American College of Surgeons.

Cannulating a larger vein, such as an antecubital vein, is usually the quickest way to achieve intravenous (IV) access. A short, large-bore catheter offers less resistance to flow, allowing for more rapid fluid administration. Ideally, a 2nd catheter should be placed within the first few minutes of resuscitation in a severely injured child. If IV access is not rapidly obtainable, an intraosseous (IO) needle should be inserted; all medications and fluids can be administered intraosseously. Other alternatives are central venous access using the Seldinger technique (e.g., in the femoral vein) and, rarely, surgical cutdown (e.g., in saphenous vein). Ultrasonography should be used to facilitate central venous catheter placement, if possible.

Traditionally, fluids are administered aggressively early in hemorrhagic shock to reverse and prevent further clinical deterioration. Isotonic crystalloid solution, such as lactated Ringer injection or normal saline (20 mL/kg), should be infused rapidly. When necessary, repeated crystalloid boluses may be given. Most children are stabilized with administration of crystalloid solution alone. However, if the patient remains in shock after boluses totaling 40-60 mL/kg of crystalloid, packed red blood cells should be transfused. Massive transfusion protocols (including fresh-frozen plasma) should be initiated early to prevent coagulopathy. When shock persists despite these measures, surgery to stop internal hemorrhage is usually indicated. Although literature is emerging regarding the benefits of permissive hypotension, hemostatic resuscitation, and damage control surgery for adult trauma patients, currently there are no pediatric data.

Neurologic Deficit

Neurologic status is briefly assessed by determining the level of consciousness and evaluating pupil size and reactivity. The level of consciousness can be classified using the mnemonic **AVPU** : Alert, responsive to Verbal commands, responsive to Painful stimuli, or Unresponsive.

At least 75% of pediatric blunt trauma deaths are accounted for by head injuries. Primary direct cerebral injury occurs within seconds of the event and is irreversible. Secondary injury is caused by subsequent anoxia or ischemia. *The goal is to minimize secondary injury by ensuring adequate oxygenation, ventilation, and perfusion, and maintaining normal cerebral perfusion pressure.* A child with severe neurologic impairment—i.e., with a Glasgow Coma Scale (GCS; see Chapter 85) score of ≤8—should undergo endotracheal intubation and supportive mechanical ventilation.

Signs of **increased intracranial pressure** (ICP), including progressive neurologic deterioration and evidence of transtentorial herniation, must be treated immediately (see Chapter 85). Hyperventilation lowers the arterial partial pressure of carbon dioxide (Pa_{CO_2}), resulting in cerebral vasoconstriction, reduced cerebral blood flow, and decreased ICP. Brief hyperventilation remains an immediate option for patients with acute increases in ICP. Prophylactic hyperventilation, or vigorous or prolonged hyperventilation, is not recommended, because the consequent vasoconstriction may excessively decrease cerebral perfusion and oxygenation. Mannitol lowers ICP and may improve survival. Because mannitol induces an osmotic diuresis, it can exacerbate hypovolemia and must be used cautiously. Hypertonic saline may be a more useful agent for control of increased ICP in patients with severe head injury. Neurosurgical consultation is mandatory. If signs of increased ICP persist, the neurosurgeon must decide whether to operate emergently.

Exposure and Environmental Control

All clothing should be cut away to reveal any injuries. Cutting is quickest and minimizes unnecessary patient movement. Children often arrive in the ED mildly hypothermic because of their higher body surface area-to-mass ratios. They can be warmed with use of radiant heat as well as heated blankets and IV fluids.

Secondary Survey

During the secondary survey, the physician completes a detailed, head-to-toe physical examination.

Head Trauma

A GCS or Pediatric GCS score (see Chapter 85) should be assigned to every child with significant head trauma. This scale assesses eye opening and motor and verbal responses. In the Pediatric GCS, the verbal score is modified for age. The GCS helps categorize neurologic disability, and serial measurements identify improvement or deterioration over time. Patients with low scores 6-24 hr after injuries have poorer prognosis.

In the ED, cranial CT scanning of the head without a contrast agent has become standard to determine the type of injury in patients with concerning findings. Diffuse cerebral injury with edema is a common and serious finding on CT scan in severely brain-injured children. Focal hemorrhagic lesions (e.g., epidural hematoma) that can be evacuated occur less often but may require immediate neurosurgical intervention (Fig. 82.3).

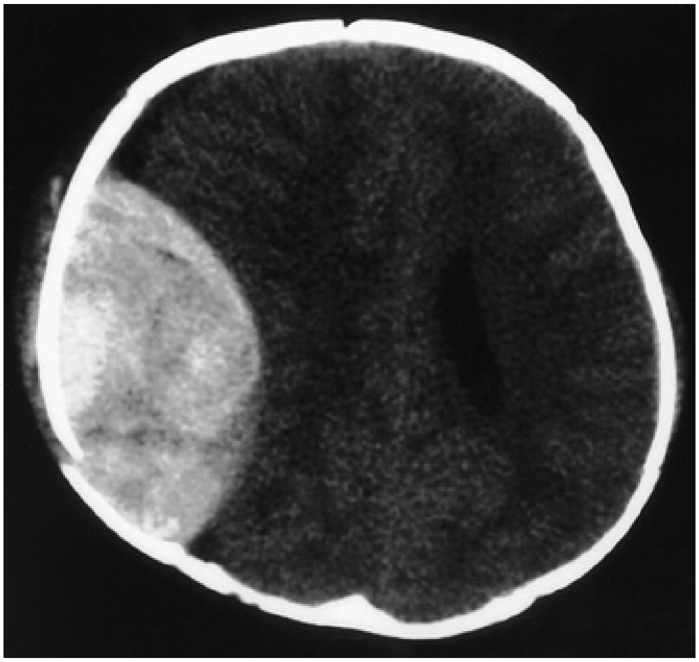

FIG. 82.3 **Epidural hematoma. CT head scan from 7 mo old girl who, according to the history provided, did not wake up for her nightly feeding and began vomiting in the morning. The mother's boyfriend reported that the infant had fallen from a chair the previous day. The CT scan shows a large epidural hematoma on the right and marked shift of the midline from right to left. The right lateral ventricle is compressed as a result of the mass effect, and the left lateral ventricle is slightly prominent. The infant underwent emergency surgical evacuation of the epidural hematoma and recovered uneventfully. (From O'Neill JA Jr: *Principles of pediatric surgery,* ed 2, St Louis, 2003, Mosby, p 191.)**

Monitoring of ICP should be strongly considered for children with severe brain injury, particularly for those with a GCS score of ≤8 and abnormal head CT findings (see Chapter 85). One advantage of an intraventricular catheter over an intraparenchymal device is that cerebrospinal fluid can be drained to treat acute increases in ICP. Hypoxia, hypercarbia, hypotension, and hyperthermia must be aggressively managed to prevent secondary brain injury. Cerebral perfusion pressure (i.e., the difference between mean arterial blood pressure and mean ICP) should be maintained >40 mm Hg, at least (and an even higher minimum, >50 mm Hg, especially for older children).

A child with a severe brain injury must be treated aggressively in the ED because it is difficult to predict the long-term neurologic outcome.

Cervical Spine Trauma

Cervical spine injuries occur in <3% of children with blunt trauma—with the risk being substantially higher in those with GCS scores ≤8—but they are associated with significant mortality and morbidity. Bony injuries occur mainly from C1 to C4 in children younger than 8 yr. In older children, they occur equally in the upper and lower cervical spine. The mortality rate is significantly higher in patients with upper C-spine injuries. **Spinal cord injury without radiographic abnormalities (SCIWORA***)* on plain films or CT may be present. Patients with SCIWORA have neurologic symptoms, and spinal cord abnormalities are nearly always noted on MRI. Approximately 30% of all patients with C-spine injuries have permanent neurologic deficits.

Evaluation begins with a detailed history and neurologic examination. Identifying the mechanism of injury helps in estimating the likelihood of a C-spine injury. Both the patient and the paramedic should be asked whether any neurologic symptoms or signs, such as weakness or abnormal sensation, were present before arrival in the ED. In a child with neurologic symptoms and normal findings on C-spine plain radiographs and CT scan, SCIWORA must be considered.

Whenever the history, physical examination, or mechanism of injury suggests a C-spine injury, radiographs should be obtained after initial resuscitation. The **National Emergency X-Radiography Utilization Study (NEXUS)** cervical spine rule helps identify low-risk patients who may not require radiographs (Table 82.5). The standard series of plain radiographs includes lateral, anteroposterior (AP), and odontoid views. Some centers use cervical spine CT as the primary diagnostic tool, particularly in patients with abnormal GCS scores and/or significant injury mechanisms, recognizing that CT is more sensitive in detecting bony injury than plain radiographs. CT is also helpful if an odontoid fracture is suspected, because young children typically do not cooperate enough to obtain an open-mouth (odontoid) radiographic view. Use of cervical spine CT scan must be balanced with the knowledge that CT exposes thyroid tissue to 90-200 times the amount of radiation from plain films. MRI is indicated in a child with suspected SCIWORA and in the evaluation of children who remain obtunded.

Table 82.5

National Emergency X-Radiography Utilization Study (NEXUS) to Rule Out Cervical Spine Injury Following Blunt Trauma

If ***none*** *of the following is present, the patient is at very low risk for clinically significant cervical spine injury:*

Midline cervical tenderness
Evidence of intoxication
Altered level of alertness
Focal neurologic deficit
Distracting painful injury

Data from Hoffman JR, Mower WR, Wolfson AB, et al: Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma, *N Engl J Med* 343:94–99, 2000; and Viccellio P, Simon H, Pressman BD, et al: A prospective multicenter study of cervical spine injury in children, *Pediatrics* 108:e20, 2001.

Rapid diagnosis of spinal cord injury is essential. Initiating high-dose IV methylprednisolone within 8 hr of spinal cord injury has been reported to improve motor outcome, but this treatment has become controversial.

Thoracic Trauma

Pulmonary contusions occur frequently in young children with blunt chest trauma. A child's chest wall is relatively pliable; therefore, less force is absorbed by the rib cage, and more is transmitted to the lungs. Respiratory distress may be noted initially or may develop during the 1st 24 hr after injury.

Rib fractures result from significant external force. They are noted in patients with more severe injuries and are associated with a higher mortality rate. Flail chest, which is caused by multiple rib fractures, is rare in children. Table 82.6 lists indications for operative management in thoracic trauma. (See Table 82.2 for the differential diagnosis of immediately life-threatening cardiopulmonary injuries.)

Table 82.6

Indications for Operation in Thoracic Trauma

Thoracotomy Immediately or Shortly After Injury

- Massive continuing pneumothorax or large air leak from tracheobronchial injury (cannot expand lung and ventilate)
- Cardiac tamponade
- Open pneumothorax
- Esophageal injury
- Aortic or other vascular injury
- Acute rupture of the diaphragm

Delayed Thoracotomy

- Chronic rupture of the diaphragm
- Clotted hemothorax
- Persistent chylothorax
- Traumatic intracardiac defects
- Evacuation of large foreign bodies
- Chronic atelectasis from traumatic bronchial stenosis

Modified from O'Neill JA Jr: *Principles of pediatric surgery*, ed 2, St Louis, 2003, Mosby, p 157.

Abdominal Trauma

Liver and spleen contusions, hematomas, and lacerations account for the majority of intraabdominal injuries from blunt trauma. The kidneys, pancreas, and duodenum are relatively spared because of their retroperitoneal location. Pancreatic and duodenal injuries are more common after a bicycle handlebar impact or a direct blow to the abdomen.

Although a thorough examination for intraabdominal injuries is essential, achieving it often proves difficult. Misleading findings can result from gastric distention after crying or in an uncooperative toddler. Calm reassurance, distraction, and gentle, persistent palpation help with the examination. Important findings include distention, bruises, and tenderness. Specific symptoms and signs give insight into the mechanism of injury and the potential for particular injuries. Pain in the left shoulder may signify splenic trauma. A lap belt mark across the abdomen raises concern for bowel or mesentery injury. The presence of certain other injuries, such as lumbar spinal fractures and femur fractures, increases the likelihood of intraabdominal injury.

An abdominal (and pelvic) CT scan with IV contrast medium enhancement rapidly identifies structural abnormalities and is the preferred study in a stable child. Negative abdominal CT scan has been shown to have a negative predictive value (NPV) of 99.6%. It has excellent sensitivity and specificity for splenic (Fig. 82.4), hepatic (Fig. 82.5), and renal injuries, but is less sensitive for diaphragmatic, pancreatic, or intestinal injuries. Small amounts of free fluid or air or a mesenteric hematoma may be the only sign of an intestinal injury. Administration of an oral contrast agent is not routinely recommended for all abdominal CT scans, but it sometimes aids in identifying an intestinal, especially a duodenal, injury.

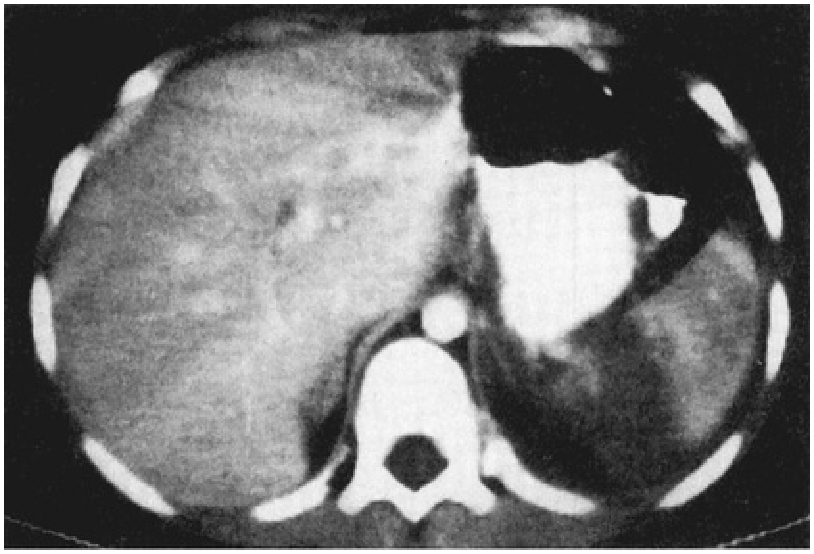

FIG. 82.4 Splenic rupture. CT scan with intravenous and gastrointestinal contrast enhancement shows an isolated splenic rupture that resulted from blunt trauma. This injury responded to nonoperative management, as do most splenic injuries. (From O'Neill JA Jr: *Principles of pediatric surgery,* ed 2, St Louis, 2003, Mosby, p 166.)

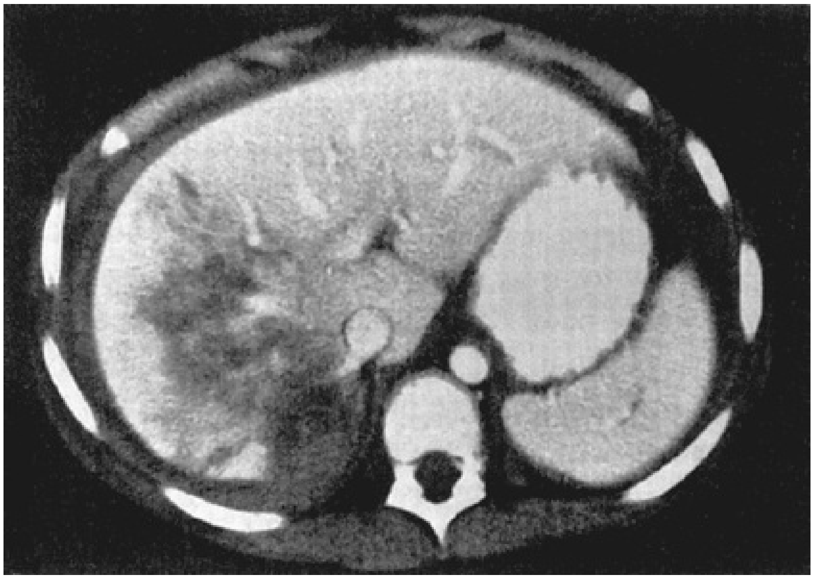

FIG. 82.5 Liver injury. CT scan performed after severe blunt injury of the abdomen shows a bursting injury of the liver. The patient was stable, and no operative intervention was required. The decision to perform surgery should be based on the patient's physiologic stability. (From O'Neill JA Jr: *Principles of pediatric surgery,* ed 2, St Louis, 2003, Mosby, p 168.)

Although the **FAST** examination helps detect hemoperitoneum, the variably low sensitivity of this test in children suggests that it should not be used alone to exclude intraabdominal injury in patients with a moderate to high pretest probability for injury. A positive FAST exam for hemoperitoneum requires further investigation. Serial FAST exams over time (by a skilled ultrasonographer) may be used to rule out injury in need of intervention. The FAST exam is most clinically useful in patients who have blunt trauma and are hemodynamically unstable or in patients who require operative intervention for nonabdominal injuries, because in these cases the performance of a CT scan may not be feasible.

Nonoperative treatment has become standard for hemodynamically stable children with splenic, hepatic, and renal injuries from blunt trauma. The majority of such children can be treated nonsurgically. In addition to avoiding perioperative complications, nonoperative treatment decreases the need for blood transfusions and shortens hospital stay. When laparotomy is indicated, splenic repair is preferable to splenectomy.

Pelvic Trauma

Pelvic fractures in children are much less common than in adults, occurring in approximately 4% of children with more severe blunt trauma. Pelvic fractures are typically caused by high forces (e.g., high-speed motor vehicle crashes or pedestrian impacts) and are often associated with intraabdominal and/or vascular injuries. The pelvis itself forms a ring, and high-force impacts can lead to disruption of this ring. When the ring is disrupted in >1 location, such as the symphysis pubis and the sacroiliac joint, the ring can become unstable and displaced, potentially injuring large pelvic vessels and leading to massive blood loss. Catheter-directed embolization to control bleeding, performed by an interventional radiologist, may be required.

The pelvis should be assessed for stability by means of compression-distraction maneuvers. If instability is noted, immediate external fixation with a pelvis-stabilizing device or a sheet should be applied and orthopedic consultation sought. A trauma patient with a potential pelvic fracture should receive an AP pelvic radiograph in the trauma bay, or a CT scan, if there is high suspicion of injury. Children *without* a high-risk clinical finding (i.e., GCS <14; abdominal pain or tenderness; pelvic tenderness, laceration, ecchymosis, or abrasion; gross hematuria or >20 red blood cells/high-power field on urinalysis; or femur fracture) or a high-risk mechanism of injury (i.e., unrestrained motor vehicle collision, motor vehicle collision with ejection, motor vehicle collision rollover, auto vs pedestrian, or auto vs bicycle), however, are unlikely to have pelvic fractures.

Lower Genitourinary Trauma

The perineum should be inspected and the stability of the bones of the pelvis assessed. Urethral injuries are more common in males. Findings suggestive of urethral injury include scrotal or labial ecchymosis, blood at the urethral meatus, gross hematuria, and a superiorly positioned prostate on rectal examination (in an adolescent male). Certain pelvic fractures also increase the risk for potential genitourinary injury. Any of these findings is a contraindication to urethral catheter insertion and warrants consultation with a urologist. Retrograde urethrocystogram and CT scan of the pelvis and abdomen are used to determine the extent of injury.

Extremity Trauma

Thorough examination of the extremities is essential because extremity fractures are among the most frequently overlooked injuries in children with multiple trauma. All limbs should be inspected for deformity, swelling, and bruises; palpated for tenderness; and assessed for active and passive range of motion, sensory function, and perfusion.

Before radiographs are obtained, suspected fractures and dislocations should be immobilized and an analgesic administered. Splinting a femur fracture helps alleviate pain and may decrease blood loss. An orthopedic surgeon should be consulted immediately to evaluate children with compartment syndrome, neurovascular compromise, open fracture, or most traumatic amputations.

Radiologic and Laboratory Evaluation

Most authorities recommend ordering multiple laboratory tests (e.g., complete blood cell count, electrolytes, glucose, blood urea nitrogen, creatinine, liver function tests, amylase, lipase, lactate, blood gas, prothrombin and partial thromboplastin times, type and cross-match, urinalysis) and x-ray films (e.g., lateral C-spine, AP chest, AP pelvis) in the ED. One benefit of standardizing the evaluation of patients with major trauma is that fewer decisions need to be made on an individual basis, possibly expediting ED management. Some of these studies have prognostic importance. A large base deficit is associated with a higher mortality rate, and elevated lactate values correlate with poor prognosis.

There are some limitations in standard tests. The lateral cervical spine radiograph can miss clinically significant injuries. Hemoglobin and hematocrit values provide baseline values in the ED, but they may not have yet equilibrated after a hemorrhage. Abnormal liver function test results or elevated serum amylase and lipase values may be noted in patients with significant abdominal trauma, but most patients with significant trauma to the abdomen already have clinical indications for CT scanning or surgery. The majority of previously healthy children have normal coagulation profiles; these may become abnormal after major head trauma. Although routine urinalysis or dipstick urine testing for blood has been recommended for children, other data suggest that this evaluation may be unnecessary in patients without gross hematuria, hypotension, or other associated abdominal injuries.

Clinical prediction rules that combine patient history with physical examination findings have been developed to identify those at low risk of injury for whom specific radiographic and laboratory studies may not be necessary. The NEXUS C-spine rule is a sensitive, easily applicable rule that was validated for adults and children, although there were fewer young patients studied (see Table 82.5). Several clinical prediction rules have been developed to identify children at low risk of traumatic brain injury (Table 82.7). Another clinical prediction rule has been developed to identify children at very low risk of clinically important intraabdominal injuries following blunt trauma (Table 82.8). Although this rule has an NPV of 99.9%, it needs to be externally validated before widespread implementation.

Table 82.7

Prediction Rule for Identification of Children at Very Low Risk of Clinically Important Brain Injuries After Head Trauma

*Children <2 yr old are at very low risk of clinically important traumatic brain injury if they have **none** of the following:*

Severe mechanism of injury
History of LOC >5 sec
GCS ≤14 or other signs of altered mental status

Not acting normally per parent
Palpable skull fracture
Occipital/parietal/temporal scalp hematoma

Children 2-18 yr old are at very low risk of clinically important traumatic brain injury if they have ***none*** *of the following:*

Severe mechanism of injury
History of LOC
History of vomiting
GCS ≤14 or other signs of altered mental status
Severe headache in the ED
Signs of basilar skull fracture

ED, Emergency department; GCS, Glasgow Coma Scale score; LOC, loss of consciousness.

Modified from Kuppermann N, Holmes JF, Dayan PS, et al: Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study, *Lancet* 374:1160–1170, 2009.

Table 82.8

Prediction Rule for Identification of Children at Very Low Risk of Clinically Important Intraabdominal Injuries After Blunt Trauma

If ***none*** *of the following is present, the patient is at very low risk for clinically significant intraabdominal injury:*

Glasgow Coma Scale score <14
Vomiting
Evidence of thoracic wall trauma
Decreased breath sounds
Evidence of abdominal wall trauma or seatbelt sign
Abdominal pain
Abdominal tenderness

Modified from Holmes JF, Lillis K, Monroe D, et al: Identifying children at very low risk of clinically important blunt abdominal injuries, *Ann Emerg Med*

62:107–116, e2, 2013.

Psychological and Social Support

Serious multisystem trauma may result in significant long-term psychological and social difficulties for the child and family, particularly when there is a major head injury. Like adults, children are at risk for depressive symptoms and posttraumatic stress disorder. Caregivers face persistent stress and have been noted to have more psychological symptoms. Psychological and social support, during the resuscitation period and afterward, is extremely important. Parents often prefer to be offered the choice to be present during resuscitations. A member of the resuscitation team should be made responsible for answering the family's questions and supporting them in the trauma room.

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CHAPTER 83

Spinal Cord Injuries in Children

Mark R. Proctor

See also Chapter 729 .

Compared with adults, spine and spinal cord injuries are rare in children, particularly young children, because of both anatomic differences and etiologies of injury. The main mechanisms of injury to the spine are motor vehicle crashes, falls, sports, and violence, which affect young children less often (see Chapter 82).

Several anatomic differences affect the pediatric spine. The head of a young child is larger relative to body mass than in adults, and the neck muscles are still underdeveloped, which places the fulcrum of movement higher in the spine. Therefore, children <9 yr old have a higher percentage of injuries in the upper cervical spine than older children and adults. The spine of a small child also is very mobile, with pliable bones and ligaments, so fractures of the spine are exceedingly rare. However, this increased mobility is not always a positive feature. Transfer of energy leading to spinal distortion may not affect the structural integrity of the bones and ligaments of the spine but can still lead to significant injuries of the spinal cord. This phenomenon of **spinal cord injury without radiographic abnormalities (SCIWORA)** is more common in children than adults. The term is relatively outdated, since almost all injuries are detectable by MRI, but is still clinically useful when referring to spinal cord injuries evaluated by plain radiographs or CT. There seem to be 2 distinct forms of SCIWORA. The **infantile** form involves severe injury of the cervical or thoracic spinal cord; these patients have a poor chance of complete recovery. In older children and adolescents, SCIWORA is more likely to be a less severe injury, with a high likelihood of complete recovery over time. The **adolescent** form, also called *transient neurapraxia* , is assumed to be a spinal cord concussion or mild contusion, as opposed to the severe spinal cord injury related to the mobility of the spine in small children.

Although the mechanisms of spinal cord injury in children include birth trauma, falls, and child abuse, the major cause of morbidity and mortality across all ages remains **motor vehicle injuries** . Adolescents incur spinal cord injuries with epidemiology similar to that of adults, including significant male predominance and a high likelihood of fracture dislocations of the lower cervical spine or thoracolumbar region. In infants and children <5 yr old, fractures and mechanical disruption of spinal elements are more likely to occur in the upper cervical spine between the occiput and C3, for the reasons previously discussed.

Clinical Manifestations

One in 3 patients with significant trauma to the spine and spinal cord will have a concomitant severe head injury, which makes early diagnosis challenging. For these patients, clinical evaluation may be difficult. Patients with a potential spine injury need to be maintained in a protective environment, such as a collar, until the spine can be cleared by clinical and/or radiographic means. A careful neurologic examination is necessary for infants with suspected spinal cord injuries. Complete spinal cord injury will lead to **spinal shock** with early areflexia (see Chapter 729). Severe cervical spinal cord (C-spine) injuries will usually lead to paradoxical respiration in patients who are breathing spontaneously. **Paradoxical respiration** occurs when the diaphragm, which is innervated by the phrenic nerves with contributions from C3, C4, and C5, is functioning normally, but the intercostal musculature innervated by the thoracic spinal cord is paralyzed. In this situation, inspiration fails to expand of the chest wall but distends the abdomen. Other complications during the acute (2-48 hr) phase include autonomic dysfunction (brady- and tachyarrhythmias, orthostatic hypotension, hypertension), temperature instability, thromboembolism, dysphagia, and bowel/bladder dysfunction.

The *mildest* injury to the spinal cord is **transient quadriparesis** evident for seconds or minutes with complete recovery in 24 hr. This injury follows a concussion of the cord and is most frequently seen in adolescent athletes. If their imaging is normal, these children can generally return to normal activities after a period of rest from days to weeks, depending on the initial severity, similar to cerebral concussion management.

Significant spinal cord injury in the cervical region is characterized by: flaccid quadriparesis, loss of sphincter function, and a sensory level corresponding to the level of injury. An injury at the high cervical level (C1-C2) can cause respiratory arrest and death in the absence of ventilatory support. Injuries in the *thoracic* region are generally the result of fracture dislocations. They may produce paraplegia when at T10 or above, or the **conus medullaris syndrome** if at the T12-L1 level. This includes a loss of urinary and rectal sphincter control, flaccid weakness, and sensory disturbances of the legs. A **central cord lesion** may result from contusion and hemorrhage in the center of the spinal cord. It typically involves the upper extremities to a greater degree than the legs, because the motor fibers to the cervical and thoracic region are more centrally located in the spinal cord. There are lower motor neuron signs in the upper extremities and upper motor neuron signs in the legs, bladder dysfunction, and loss of sensation caudal to the lesion. There may be considerable recovery, particularly in the lower extremities, although sequelae are common (see Chapter 729).

Clearing the Cervical Spine in Children

The management of children following major trauma is challenging. For older children, the clearance is similar to a lucid adult, and the NEXUS (National Emergency X-Radiography Utilization Study) criteria are appropriate (see Chapter 82 , Table 82.5). Clearing the cervical spine in younger and uncooperative children involves similar issues as in adults with an altered level of consciousness. Small children generally have a difficult-to-assess physical examination, and it is difficult to determine if they have cervical pain. Plain radiography remains a mainstay for assessing the spine because it is easy to obtain. There has been increasing emphasis on MRI for evaluation of potential C-spine instability, but in small children MRI requires sedation and in most centers the presence of an anesthesiologist (Fig. 83.1). CT scan is another important study with high sensitivity and specificity, but the risk of radiation exposure must be considered.

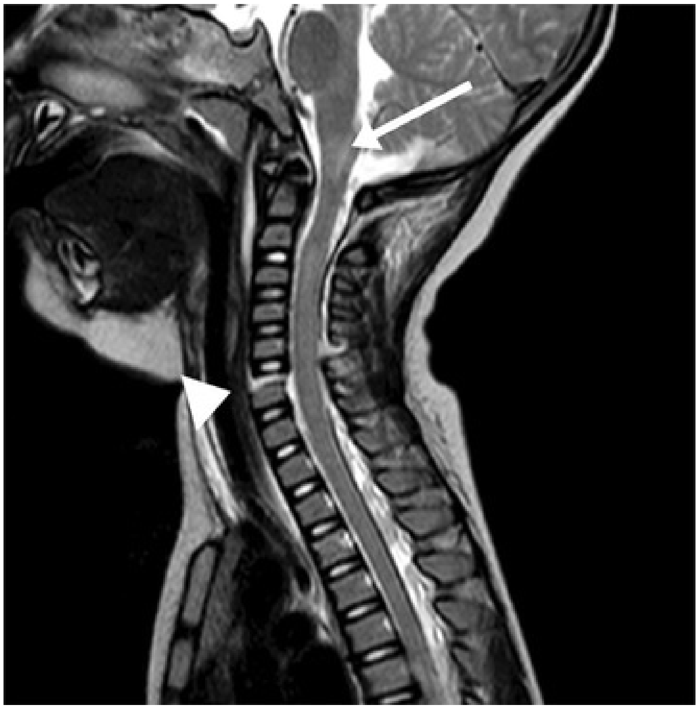

FIG. 83.1 T2-weighted MRI performed the day after the accident showed cervical spinal cord swelling combined with high signal intensity (C1-C3) (*arrow*) and dislocation of C5-C6 (*arrowhead*). (From Inoue K, Kumada T, Fujii T, Kimura N: Progressive cervical spinal cord atrophy after a traffic accident, *J Pediatr* 180:287, 2017, Fig 1, p 287.)

Treatment

The cervical spine should be immobilized in the field by the emergency medical technicians. In cases of acute spinal cord injury, weak data suggest the acute infusion of a bolus of high-dose (30 mg/kg) methylprednisolone, followed by a 23 hr infusion (5.4 mg/kg/hr). The data for this treatment are controversial and have not been tested specifically in children; *many centers no longer use it routinely* . Maintenance of euvolemia and normotension are very important, and vasopressors might be needed if the sympathetic nervous system has been compromised.

Surgical management of spinal injuries must be tailored to the patient's age but can be a crucial step in management. Any compression of the spinal cord must be surgically relieved to afford the best chance of a favorable outcome. In addition, spinal cord injury can be worsened by instability, so surgical stabilization can prevent further injury (Fig. 83.2). In general, younger children have a higher healing capacity for bones and ligaments, and external immobilization might be considered for injuries that require surgery in older children and adults. However, some injuries are highly unstable and always require surgery. **Occipitocervical dislocation** is one such highly unstable injury, and early surgery with fusion from the occiput to C2 or C3 should be performed, even in very young children. Fixation of the subaxial spine must be tailored to the size of the pedicles and other osseous structures of the developing axial skeleton.

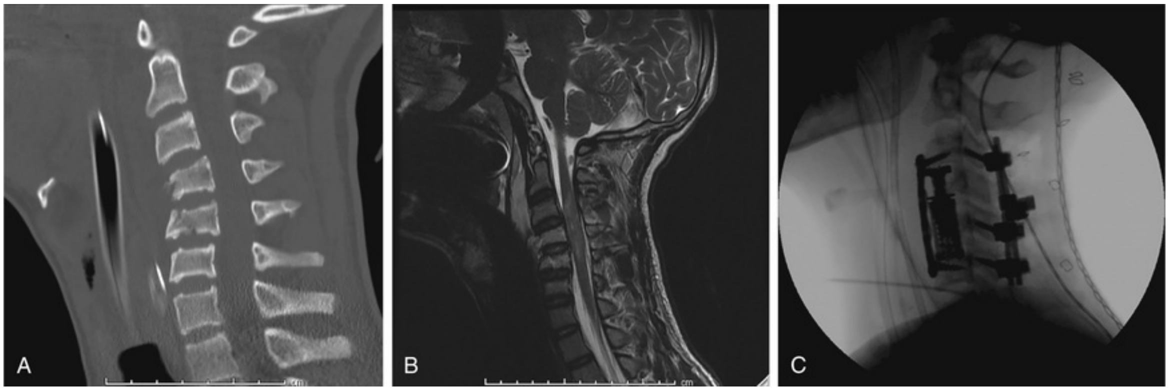

FIG. 83.2 A 15 yr old hockey player suffered acute paraplegia after his head struck the boards during a hockey game. **A,** CT scan shows compression fractures of C4 and C5. **B,** MRI shows severe spinal cord contusion. **C,** Because of the need to decompress the spinal cord and stabilize the spine, anterior and posterior surgery was performed. No meaningful recovery was obtained.

Prevention

The most important aspect of the care of spinal cord injuries in children is injury prevention. Use of appropriate child restraints in automobiles is the most important precaution. In older children and adolescents, rules against “spear tackling” in American football and the *Feet First, First Time* aimed at adolescents diving into swimming pools and natural water areas are important ways to help prevent severe cervical spinal cord injuries. Safe driving practices, such as using safety belts, avoiding distracted driving, and following the speed limit, can have substantial beneficial effects on injury rates.

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CHAPTER 84

Care of Abrasions and Minor Lacerations

Joanna S. Cohen, Bruce L. Klein

Lacerations and Cuts

Lacerations are tears of the skin caused by blunt or shearing forces. A **cut** (or a *stab*), in contrast, is an injury inflicted by a sharp object. Although distinguishing between the two can be important for forensic purposes, their evaluation and management are similar. In this chapter, lacerations include cuts and stabs.

Epidemiology

More than half of the 12 million wounds treated annually in U.S. emergency departments (EDs) are lacerations. Approximately 30% occur in children younger than 18 yr. Approximately 2% of pediatric office visits are related to wound management.

Evaluation

The history should include the mechanism of injury, the amount of force, and the time the injury occurred. The mechanism helps determine whether there may be foreign material in the wound, which would increase the risk for infection. Particularly in children, it is essential to determine whether the injury was inflicted intentionally. *If nonaccidental trauma is suspected, child protective services should be notified.* The type of force causing the laceration also influences the risk of infection, because a significant crush injury is more likely to become infected than a shearing one. **Blunt injury** , such as bumping the head, is a common cause of lacerations in children and is less likely to become infected. Theoretically, the amount of bacteria in the wound should increase exponentially with the time from injury to repair; however, the length of time that results in a clinically significant increase in wound infection is unclear. Older wounds may require delayed primary closure or healing by secondary intention. The patient or parent should be asked about any special host factors that may predispose to infection or impede healing, such as diabetes, malnutrition, obesity, and corticosteroid therapy, as well as immunization status, with particular attention to tetanus administration.

On examination, the clinician should note the size and depth of the wound, as well as any associated vascular, neurologic, tendon, or other tissue injury. The laceration's location also is important with regard to both the risk for infection and the cosmetic outcome. Compared with lacerations in adults, those in children occur more often on the face and scalp and less often on the upper extremities. Because the face and scalp are more vascular, wounds located there are less likely to become infected. Lacerations overlying joints are more likely to develop wider scars as a result of tension during healing.

Treatment

The goals of treatment are to establish hemostasis, minimize the risk of infection, restore skin and underlying tissue integrity, and produce the most functionally and cosmetically acceptable result possible. Complications of wounds, including infection, hypertrophic scar formation, and functional limitation occur in approximately 8% of children.

Any significant bleeding must be controlled, usually with external pressure, before a thorough evaluation of the wound can occur. If there is a skin flap, it should be returned to its original position before application of pressure. Infrequently, a tourniquet may need to be applied if bleeding cannot be controlled with direct pressure. Clothing over the injury should be removed to minimize wound contamination. Jewelry encircling an injured extremity should be removed to prevent the jewelry from forming a constricting band when the extremity swells.

It is best to administer a **local anesthetic** early, before exploration and more meticulous cleansing of the wound. This anesthetic can be applied topically (e.g., lidocaine, epinephrine, and tetracaine gel) or infiltrated locally or as a regional nerve block (e.g., lidocaine or bupivacaine), depending on the location of the laceration and the complexity of the repair. Buffering the acidic lidocaine with sodium bicarbonate can reduce pain during injection. Sometimes, nonpharmacologic or additional pharmacologic methods of analgesia and anxiolysis are required for a young, frightened, or uncooperative child. The wound should be examined under proper light to enable identification of foreign bodies or damage to vessels, nerves, or tendons.

Many lacerations, especially heavily contaminated ones, benefit from **irrigation** , with either water or sterile saline, to reduce the risk of infection. It is important to recognize that many traumatic lacerations treated in the ED, or office, are only minimally contaminated, containing $<10^2$ bacterial colonies. In fact, in one of the few human studies on irrigation, irrigation did not decrease the infection rate of *minimally* contaminated scalp or facial lacerations in patients who presented to an ED within 6 hr of injury. Higher-pressure irrigation may actually increase tissue damage, making the wound and adjacent tissue more susceptible to infection and delaying healing. These caveats notwithstanding, irrigation has benefits, although which technique to use—that is, which device, what size syringe, what size needle, which solution, how much volume, how much pressure—remains to be determined. These features may vary for different types of lacerations. In heavily contaminated wounds, the benefit of higher-pressure irrigation likely outweighs the harm of tissue damage. For heavily contaminated lacerations, a typical recommendation is to use a 35-65 mL syringe attached to a plastic splatter shield, or a 19-gauge needle if a splatter shield is unavailable, and to irrigate with approximately 100 mL of solution per centimeter of wound. Conversely, for relatively clean wounds, lower-pressure irrigation minimizes tissue damage, which may be more important for outcome than any decrease in bacterial clearance that may ensue. Debridement of devitalized tissue with higher-pressure irrigation, scrubbing, or surgical excision can also be necessary in certain cases, such as crush injuries.

Most lacerations seen in the pediatric ED or office should be closed primarily. Contraindications exist to **primary closure** (e.g., certain bite wounds; see Chapter 743). Although it is accepted that the time from injury to repair should be as brief as possible to minimize the risk of infection, there is no universally accepted guideline as to what length of time is too long for primary wound closure. Also, this length of time varies for different types of lacerations. A prudent recommendation is that higher-risk wounds should be closed within 6 hr at most after the injury but that some low-risk wounds (e.g., clean facial lacerations) may be closed as late as 12-24 hr.

Many lacerations can be closed with simple, interrupted, 4-0, 5-0, or 6-0, **nonabsorbable sutures** . For certain lacerations, absorbable sutures for external skin closure are not necessarily inferior to nonabsorbable sutures, and may provide cost and time savings, as well as avoiding having to remove them, an unpleasant procedure in a young child. For lacerations under tension, horizontal or vertical mattress sutures, which provide added strength and may evert the wound edges better, can be used instead. For lacerations in cosmetically significant areas, a **running intradermal stitch** may produce a less conspicuous, more aesthetic scar than simple or mattress skin sutures, which can leave unattractive track marks. Deeper lacerations may need repair with an absorbable dermal and/or fascial layer. Other complex lacerations, such as those involving the ear, eyelid, nose, lip, tongue, genitalia, or fingertip, sometimes require more advanced techniques as well as subspecialty consultation.

Staples, topical skin adhesives, and surgical tape are acceptable alternatives to sutures, depending on the laceration's location and the healthcare provider's preference. **Staples** are particularly useful for scalp lacerations, where the scar's appearance tends to be less important. Topical **skin adhesives** (octyl cyanoacrylates or butyl cyanoacrylates) are ideal for linear, relatively superficial lacerations with easily approximated edges that are not under tension. Adhesives are particularly useful for lacerations located in areas where suture track marks are especially undesirable, or in situations where resources are constrained.

Maintaining a warm, moist, wound environment following repair accelerates wound healing without increasing the risk of infection. A topical antimicrobial ointment (e.g., bacitracin or bacitracin, neomycin, and polymyxin B combination) and conventional gauze dressing provide such an environment and reduce the infection rate. Compared with conventional dressings, **occlusive dressings** (hydrocolloids, hydrogels, polyurethane films) may be better at accelerating healing, reducing infection, and decreasing pain but are more expensive. Occlusive dressings that adhere (hydrocolloids or polyurethane films) are impractical for lacerations with protruding sutures. If the laceration overlies or is near a joint, **splinting** helps limit mobility and can speed healing and minimize dehiscence.

For most routine lacerations that are repaired early and meticulously, prophylactic systemic antibiotics are unnecessary because they do not decrease the rate of infection. **Antibiotic prophylaxis** is or may be indicated for human and many animal bites, for open fractures and joints, and for grossly contaminated wounds, as well as for wounds in patients who are immunosuppressed or have prosthetic devices. *Tetanus prophylaxis should be administered, if indicated,* according to U.S. Centers for Disease Control and Prevention guidelines (see Chapter 238).

Abrasions

An **abrasion** is a scrape to the epidermis, and sometimes the dermis, that is usually caused by friction of the skin against a rough surface. *Road rash* is a colloquial term for abrasions that result from friction of the skin against pavement. Motor vehicle collisions with pedestrians and cycling accidents are common causes of road rash in children. Road rash can be extensive, involving multiple areas on the body. These abrasions also can be deep, and they often contain embedded debris. A *rug burn* is an abrasion sustained by sliding across a carpet. Some abrasions display specific patterns and are called **imprint abrasions** . *Ligature marks* are a type of imprint abrasion caused by a rope or cord that has been tied around a part of the body and has rubbed against the skin. These injuries should alert the clinician to the likelihood of nonaccidental (including self-inflicted) trauma.

Treatment

All abrasions should be cleansed thoroughly and any debris or foreign material removed. If debris is not removed, abnormal skin pigmentation, known as **posttraumatic tattooing** , can occur and can be difficult to treat. A nonadherent occlusive dressing or a topical antibiotic and conventional dressing should be applied. *Tetanus prophylaxis should be administered, if indicated* (see Chapter 238). Large and/or deep abrasions that have not healed in a few weeks require consultation with a plastic surgeon for more advanced care.

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CHAPTER 85

Neurologic Emergencies and Stabilization

Patrick M. Kochanek, Michael J. Bell

Neurocritical Care Principles

The brain has high metabolic demands, which are further increased during growth and development. Preservation of nutrient supply to the brain is the mainstay of care for children with evolving brain injuries. *Intracranial dynamics* describes the physics of the interactions of the contents—brain parenchyma, blood (arterial, venous, capillary), and cerebrospinal fluid (CSF)—within the cranium. Normally, brain parenchyma accounts for up to 85% of the contents of the cranial vault, and the remaining portion is divided between CSF and blood. The brain resides in a relatively rigid cranial vault, and cranial compliance decreases with age as the skull ossification centers gradually replace cartilage with bone. The **intracranial pressure (ICP)** is derived from the volume of its components and the bony compliance. The **perfusion pressure** of the brain (cerebral perfusion pressure, CPP) is equal to the pressure of blood entering the cranium (mean arterial pressure, MAP) minus the ICP, in most cases.

Increases in intracranial volume can result from swelling, masses, or increases in blood and CSF volumes. As these volumes increase, compensatory mechanisms decrease ICP by (1) decreasing CSF volume (CSF is displaced into the spinal canal or absorbed by arachnoid villi), (2) decreasing cerebral blood volume (venous blood return to the thorax is augmented), and/or (3) increasing cranial volume (sutures pathologically expand or bone is remodeled). Once compensatory mechanisms are exhausted (the increase in cranial volume is too large), small increases in volume lead to large increases in ICP, or intracranial hypertension (Fig. 85.1). As ICP continues to increase, brain ischemia can occur as CPP falls. Further increases in ICP can ultimately displace the brain downward into the foramen magnum—a process called **cerebral herniation,** which can become irreversible in minutes and may lead to severe disability or death; Fig. 85.2 notes other sites of brain herniation.

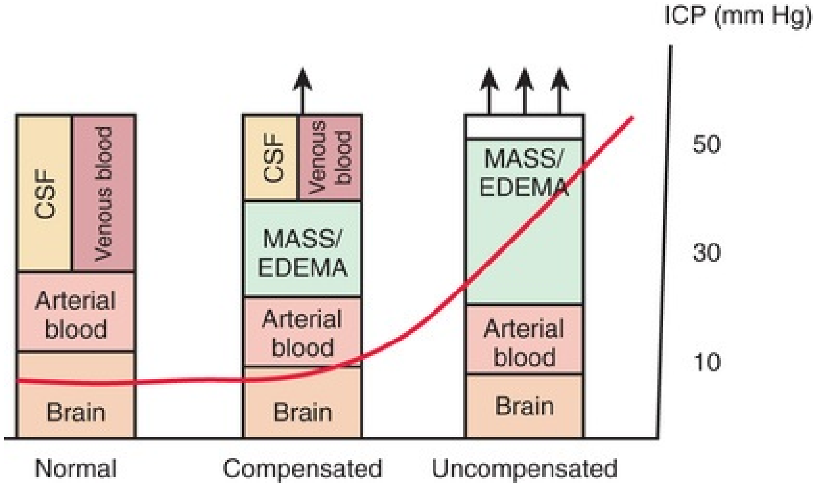
ICP (mm Hg)
50
30
10
CSF
Venous blood
Arterial blood
Brain
CSF
Venous blood
MASS/ EDEMA
Arterial blood
Brain
MASS/ EDEMA
Arterial blood
Brain
Normal
Compensated
Uncompensated

FIG. 85.1 The Munro-Kellie doctrine describes intracranial dynamics in the setting of an expanding mass lesion (i.e., hemorrhage, tumor) or brain edema. In the normal state, the brain parenchyma, arterial blood, cerebrospinal fluid (CSF), and venous blood occupy the cranial vault at a low pressure, generally <10 mm Hg. With an expanding mass lesion or brain edema, initially there is a compensated state as a result of reduced CSF and venous blood volumes, and intracranial pressure (ICP) remains low. Further expansion of the lesion, however, leads to an uncompensated state when compensatory mechanisms are exhausted, and intracranial hypertension results.

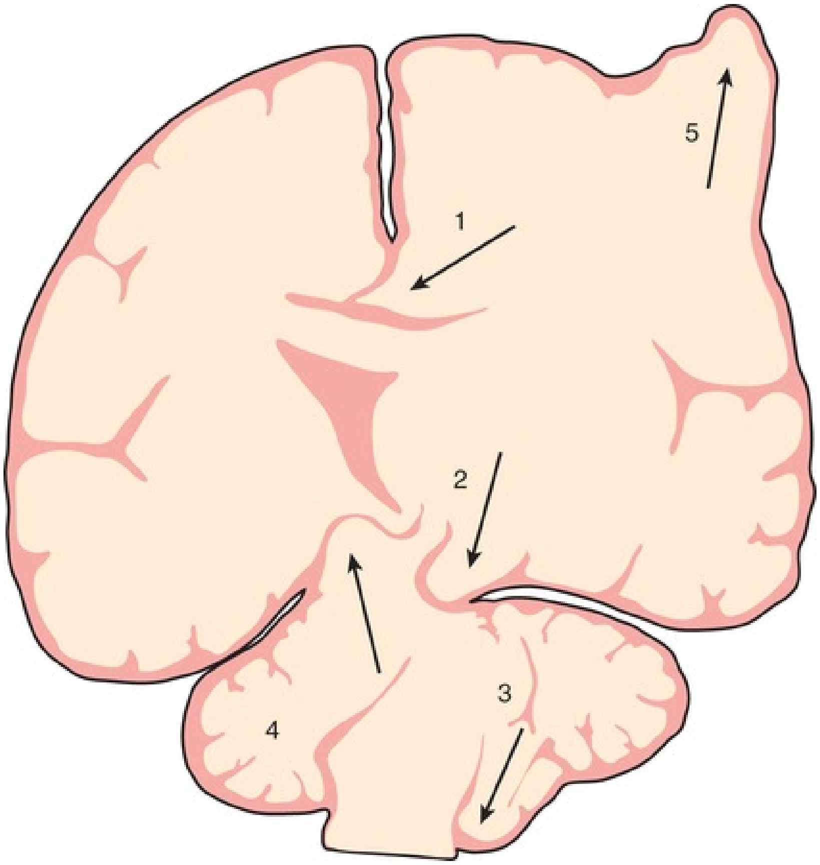

FIG. 85.2 Different forms of brain herniation. *1,* Cingulate. *2,* Uncal. *3,* Cerebellar tonsillar. *4,* Upward cerebellar. *5,* Transcalvarial. (From Fishman RA: *Cerebrospinal fluid in diseases of the nervous system,* Philadelphia, 1980, Saunders.)

Oxygen and glucose are required by brain cells for normal functioning, and these nutrients must be constantly supplied by cerebral blood flow (CBF). Normally, CBF is constant over a wide range of blood pressures (i.e., blood pressure autoregulation of CBF) via actions mainly within the cerebral arterioles. Cerebral arterioles are maximally dilated at lower blood pressures and maximally constricted at higher pressures so that CBF does not vary during normal fluctuations (Fig. 85.3). Above the upper limit of autoregulation, breakthrough dilation occurs, which if severe can produce hypertensive encephalopathy. Acid-base balance of the CSF, often reflected by acute changes in arterial partial pressure of carbon dioxide (Pa_{CO_2}), body/brain temperature, glucose utilization, blood viscosity, and other vasoactive mediators (i.e., adenosine, nitric oxide), can also affect the cerebral vasculature.

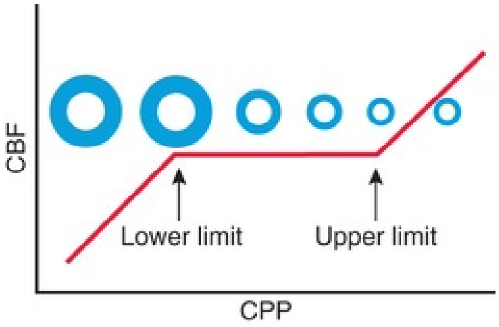

FIG. 85.3 **Schematic of the relationship between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP). The diameter of a representative cerebral arteriole is also shown across the center of the *y* axis to facilitate understanding of the vascular response across CPP that underlies blood pressure autoregulation of CBF. CPP is generally defined as the mean arterial pressure (MAP) minus the intracranial pressure (ICP). At normal values for ICP, this generally represents MAP. Thus, normally, CBF is kept constant between the lower limit and upper limit of autoregulation; in normal adults, these values are approximately 50 mm Hg and 150 mm Hg, respectively. In children, the upper limit of autoregulation is likely proportionally lower than the adult value relative to normal MAP for age. However, according to the work of Vavilala et al. (2003) , lower-limit values are surprisingly similar in infants and older children. Thus, infants and young children may have less reserve for adequate CPP.**

Knowledge of these concepts is instrumental to preventing secondary brain injury. Increases in CSF pH that occur because of inadvertent hyperventilation (which decreases $\mathrm{Pa{CO}}_2$) can produce cerebral ischemia. Hyperthermia-mediated increases in cerebral metabolic demands may damage vulnerable brain regions after injury. Hypoglycemia can produce neuronal death when CBF fails to compensate. Prolonged seizures can lead to permanent injuries if hypoxemia occurs from loss of airway control.

Attention to detail and constant reassessment are paramount in managing children with critical neurologic insults. Among the most valuable tools for serial, objective assessment of neurologic condition is the **Glasgow Coma Scale (GCS)** (see Chapter 81 , Table 81.3). Originally developed for use in comatose adults, the GCS is also valuable in pediatrics. Modifications to the GCS have been made for nonverbal children and are available for infants and toddlers. Serial assessments of the GCS score along with a focused neurologic examination are invaluable to detection of injuries before permanent damage occurs in the vulnerable brain. The **full outline of unresponsiveness (FOUR)** score is a modification of the GCS, with eye and motor response, but eliminates the verbal response and adds 2 functional assessments of the brainstem (pupil, corneal, and cough reflexes) and respiratory patterns (Table 85.1).

Table 85.1

Commonly Used Coma Scores

POINTS	**DESCRIPTION**
GLASGOW COMA SCALE (GCS) SCORE	
Eye Opening	
1	Does not open eyes
2	Opens eyes in response to noxious stimuli
3	Opens eyes in response to voice
4	Opens eyes spontaneously
Verbal Output	
1	Makes no sounds
2	Makes incomprehensible sounds
3	Utters inappropriate words
4	Confused and disoriented
5	Speaks normally and oriented
Motor Response (Best)	
1	Makes no movements
2	Extension to painful stimuli
3	Abnormal flexion to painful stimuli
4	Flexion/withdrawal to painful stimuli
5	Localized to painful stimuli
6	Obeys commands
FULL OUTLINE OF UNRESPONSIVENESS (FOUR) SCORE	
Eye Response	
4	Eyelids open or opened, tracking, or blinking to command
3	Eyelids open but not tracking
2	Eyelids closed but open to loud voice
1	Eyelids closed but open to pain
0	Eyelids remain closed with pain
Motor Response	
4	Thumbs-up, fist, or “peace” sign
3	Localizing to pain
2	Flexion response to pain
1	Extension response to pain
0	No response to pain or generalized myoclonus status
Brainstem Reflexes	
4	Pupil and corneal reflexes present
3	One pupil wide and fixed
2	Pupil or corneal reflexes absent
1	Pupil and corneal reflexes absent
0	Absent pupil, corneal, and cough reflex
Respiration	
4	Not intubated, regular breathing pattern
3	Not intubated, Cheyne-Stokes breathing pattern
2	Not intubated, irregular breathing
1	Breathes above ventilatory rate
0	Breathes at ventilator rate or apnea

Adapted from Edlow JA, Rabinstein A, Traub SJ, Wijdicks EFM: Diagnosis of reversible causes of coma, *Lancet* 384:2064-2076, 2014.

The most studied monitoring device in clinical practice is the **ICP monitor** .

Monitoring is accomplished by inserting a catheter-transducer either into the cerebral ventricle or into brain parenchyma (i.e., externalized ventricular drain and parenchymal transducer, respectively). ICP-directed therapies are standard of care in traumatic brain injury (TBI) and are used in other conditions, such as intracranial hemorrhage, some cases of encephalopathy, meningitis, and encephalitis. Other devices being used include catheters that measure brain tissue oxygen concentration, external probes that noninvasively assess brain oxygenation by absorbance of near-infrared light (i.e., near-infrared spectroscopy), monitors of brain electrical activity (continuous electroencephalography [EEG] or somatosensory, visual, or auditory evoked potentials), and CBF monitors (transcranial Doppler, xenon CT, perfusion MRI, or tissue probes). In the severe TBI guidelines, brain tissue oxygen concentration monitoring received level III support and thus may be considered.

Traumatic Brain Injury

Etiology and Epidemiology

Mechanisms of TBI include motor vehicle crashes, falls, assaults, and abusive head trauma. Most TBIs in children are from closed-head injuries (Fig. 85.4). TBI is an important pediatric public health problem, with approximately 37,000 cases resulting in the death of >7,000 children annually in the United States.

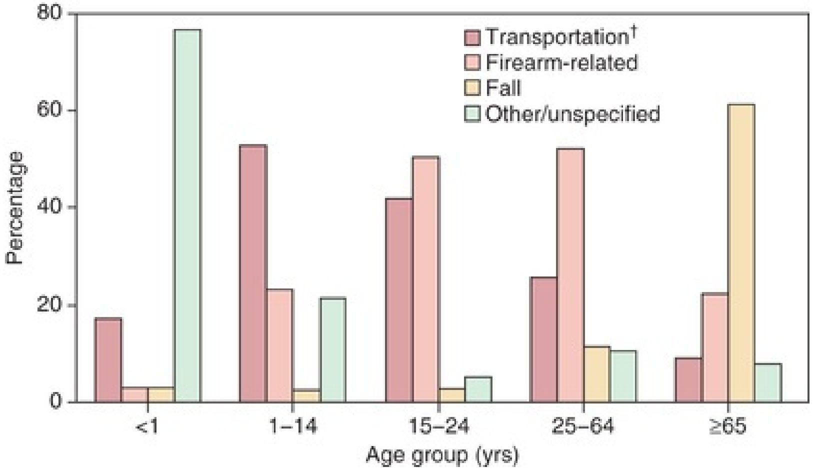

FIG. 85.4 Percentage of traumatic brain injury (TBI)–related deaths* by underlying cause and age group—United States, 2013. *TBI-related deaths were identified using the *International Classification of Diseases, Tenth Revision,* underlying cause of death codes of *U01–*U03, V01–Y36, Y85–Y87, or Y89 with a multiple cause of death code of

S01.0–S01.9, S02.0, S02.1, S02.3, S02.7–S02.9, S04.0, S06.0–S06.9, S07.0, S07.1, S07.8, S07.9, S09.7–S09.9, T01.0, T02.0, T04.0, T06.0, T90.1, T90.2, T90.4, T90.5, T90.8, or T90.9, for a total of 54,185 deaths in 2013 for all ages. † Transportation includes all modes, such as motor vehicle, motorcycle, pedal cycle, pedestrian, other land transport, railway, watercraft, and aircraft. The causes of injury that result in TBI-related deaths vary by age-group. In 2013, 77% of the TBI-related deaths among infants <1 yr old were from causes other than transportation, firearms, or falls and primarily resulted from assault and maltreatment. Transportation accounted for 53% of the TBI-related deaths among children 1-14 yr. Firearm-related injuries accounted for 50% and 52% of the TBI-related deaths for persons 15-24 and 25-64 yr, respectively. Most of the firearm-related TBI deaths in these 2 age-groups were suicides (62% and 83%, respectively). The majority (61%) of TBI-related deaths for those aged ≥65 yr resulted from falls. (From National Vital Statistics System mortality data. http://www.cdc.gov/nchs/deaths.htm . Additional information on TBI available at http://www.cdc.gov/traumaticbraininjury/ . The Lancet: The burden of traumatic brain injury in children, *Lancet* 391:813, 2018.)

Pathology

Epidural, subdural, and parenchymal intracranial hemorrhages can result. Injury to gray or white matter is also commonly seen and includes focal cerebral contusions, diffuse cerebral swelling, axonal injury, and injury to the cerebellum or brainstem. Patients with severe TBI often have multiple findings; diffuse and potentially delayed cerebral swelling is common.

Pathogenesis

TBI results in primary and secondary injury. Primary injury from the impact produces irreversible tissue disruption. In contrast, 2 types of secondary injury are targets of neurointensive care. First, some of the ultimate damage seen in the injured brain evolves over hours or days, and the underlying mechanisms involved (e.g., edema, apoptosis, secondary axotomy) are therapeutic targets. Second, the injured brain is vulnerable to additional insults because injury disrupts normal autoregulatory defense mechanisms; disruption of autoregulation of CBF can lead to ischemia from hypotension that would otherwise be tolerated by the uninjured brain.

Clinical Manifestations

The hallmark of **severe TBI** is coma (**GCS score 3-8**). Often, coma is seen immediately after the injury and is sustained. In some cases, such as with an epidural hematoma, a child may be alert on presentation but may deteriorate after a period of hours. A similar picture can be seen in children with diffuse swelling, in whom a “talk-and-die” scenario has been described. Clinicians should also not be lulled into underappreciating the potential for deterioration of a child with **moderate TBI** (**GCS score 9-12**) with a significant contusion, because progressive swelling can potentially lead to devastating complications. In the comatose child with severe TBI, the second key clinical manifestation is the development of *intracranial hypertension* . The development of increased ICP with impending herniation may be heralded by new-onset or worsening headache, depressed level of consciousness, vital sign changes (hypertension, bradycardia, irregular respirations), and signs of 6th (lateral rectus palsy) or 3rd (anisocoria [dilated pupil], ptosis, down-and-out position of globe as a result of rectus muscle palsies) cranial nerve compression. Increased ICP is managed with continuous ICP monitoring, as well as monitoring for clinical signs of increased ICP or impending herniation. The development of brain swelling is progressive. Significantly raised ICP (>20 mm Hg) can occur early after severe TBI, but peak ICP generally is seen at 48-72 hr. Need for ICP-directed therapy may persist for longer than a week. A few children have coma without increased ICP, resulting from axonal injury or brainstem injury. *In addition to head trauma, it is critical to identify potential cervical spine injury* (see Chapter 83).

Laboratory Findings

Cranial CT should be obtained immediately after resuscitation and cardiopulmonary stabilization (Figs. 85.5 to 85.11). In some cases, MRI can be diagnostic (Fig. 85.12). Generally, other laboratory findings are normal in isolated TBI, although occasionally coagulopathy or the development of the syndrome of inappropriate antidiuretic hormone (SIADH) secretion or, rarely, cerebral salt wasting (CSW) is seen. In the setting of TBI with polytrauma, other injuries can result in laboratory and radiographic abnormalities, and a **full trauma survey** is important in all patients with severe TBI (see Chapter 82).

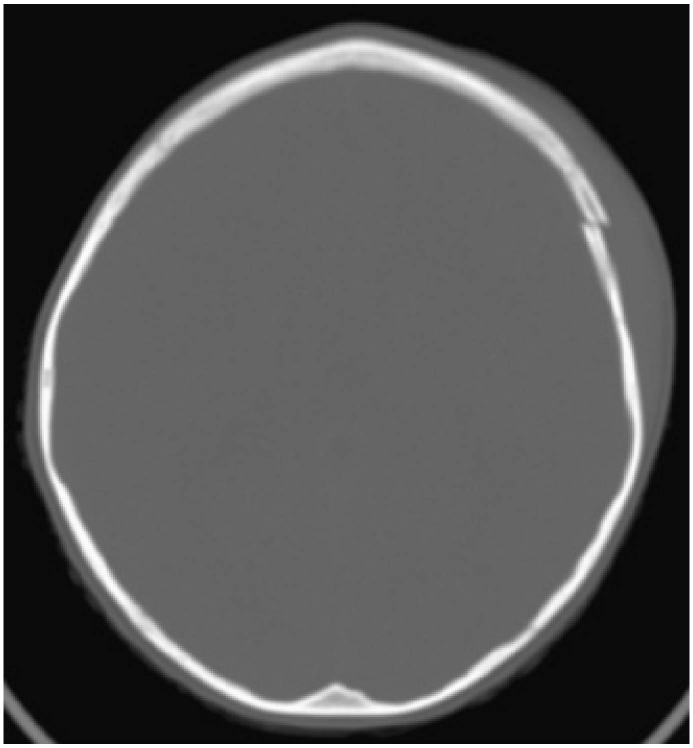

FIG. 85.5 Skull fracture. Mildly displaced skull fracture seen on CT imaging (bone window view) in a 4 yr old child who fell and hit her head on a curb.

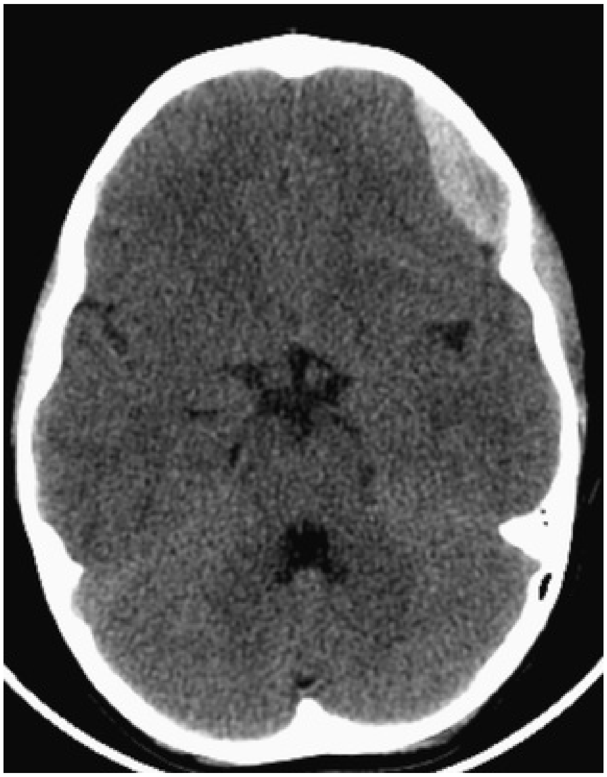

FIG. 85.6 Epidural hematoma. Left frontal epidural hematoma observed on CT imaging in a 12 yr old child who fell off his bike onto concrete surface.

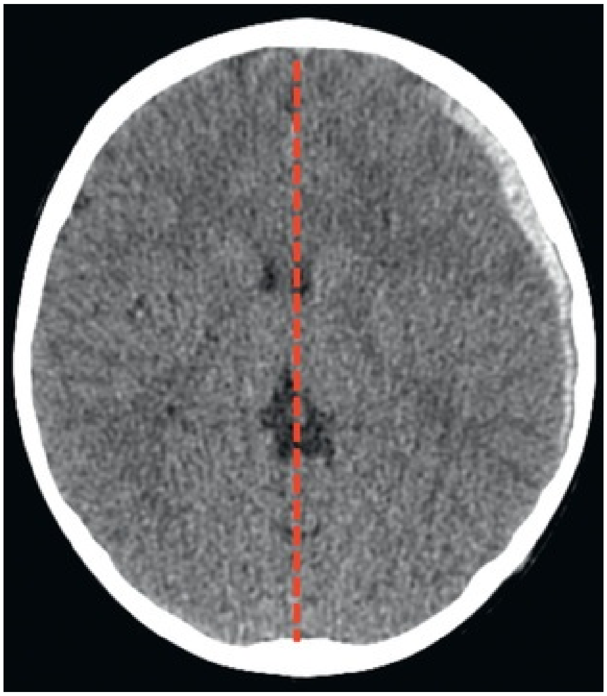

FIG. 85.7 Subdural hematoma. Left subdural hematoma observed on CT imaging in a 10 yr old child after motor vehicle crash. Note effacement of the left lateral ventricle and midline shift (see *dotted line* for midline reference).

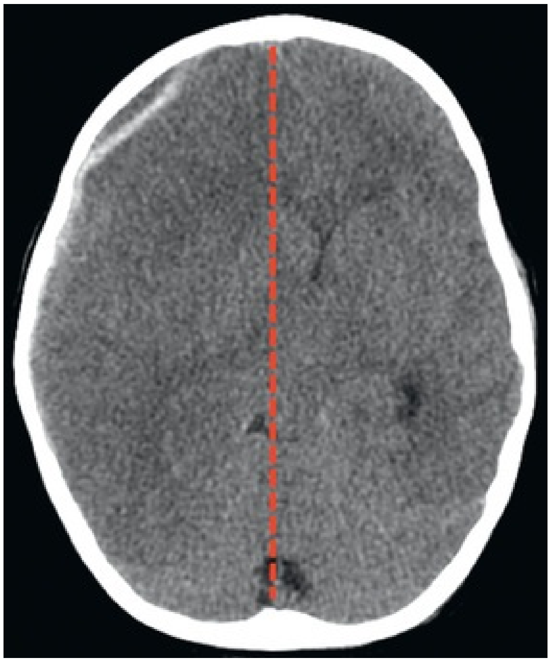

FIG. 85.8 Subdural hematoma. Hyperacute right frontal subdural hematoma observed on CT imaging in a 5 yr old child after motor vehicle crash. Note that the hyperacute aspect of the subdural hematoma is dark on CT imaging in the early stage after injury. Also, there is marked midline shift of intracranial contents, with both lateral ventricles displaced into the left side of the skull (*dotted line* for midline reference).

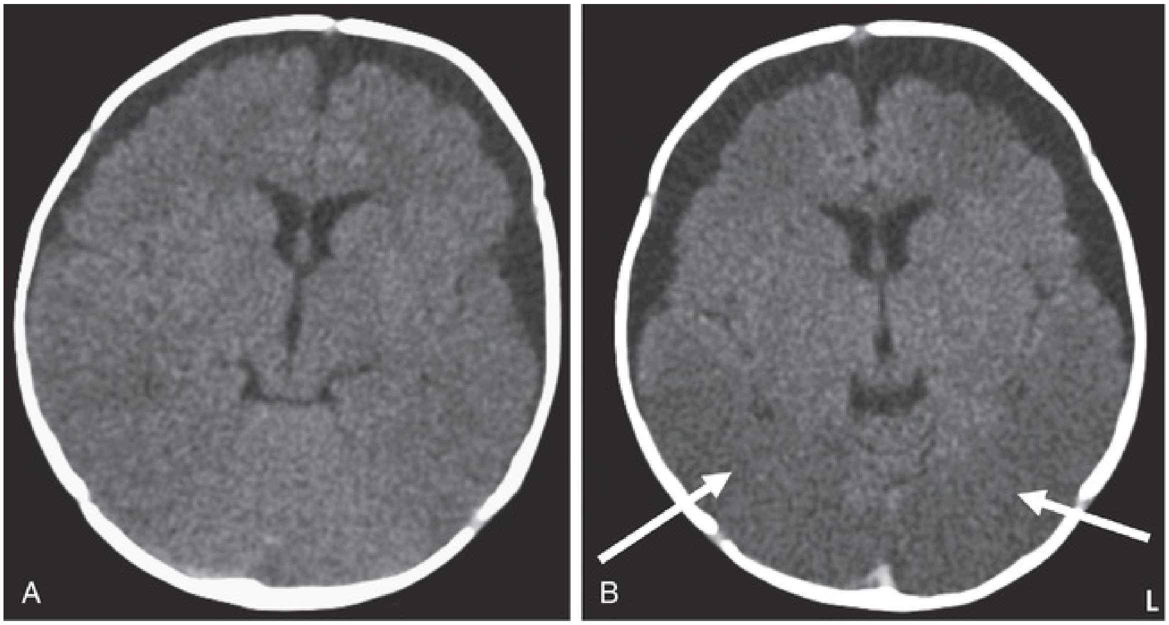

FIG. 85.9 Subdural hematoma. A, In a 3 mo old child who suffered from abusive head trauma, initial CT imaging demonstrates chronic subdural hematoma bilaterally. B, Three days after hospitalization, the subdural hematomas are slightly larger, but infarctions are noted in the posterior areas of brain parenchyma (*arrows*).

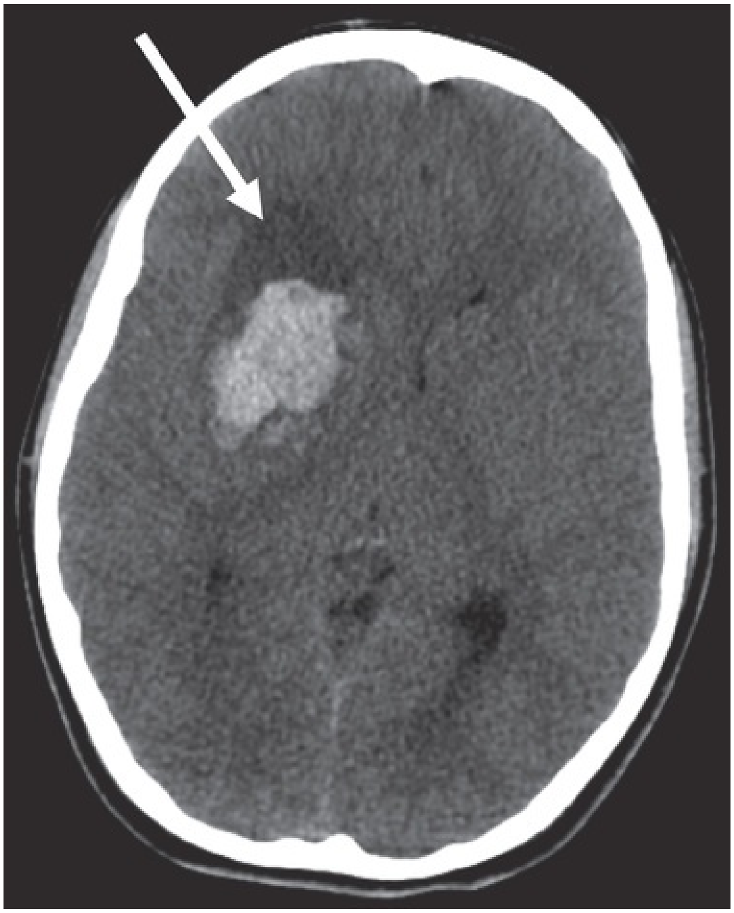

FIG. 85.10 Hemorrhage and edema. In a 16 yr old child who fell from his dirt bike, CT imaging demonstrates intraparenchymal hemorrhage and significant surrounding edema (*arrow*).

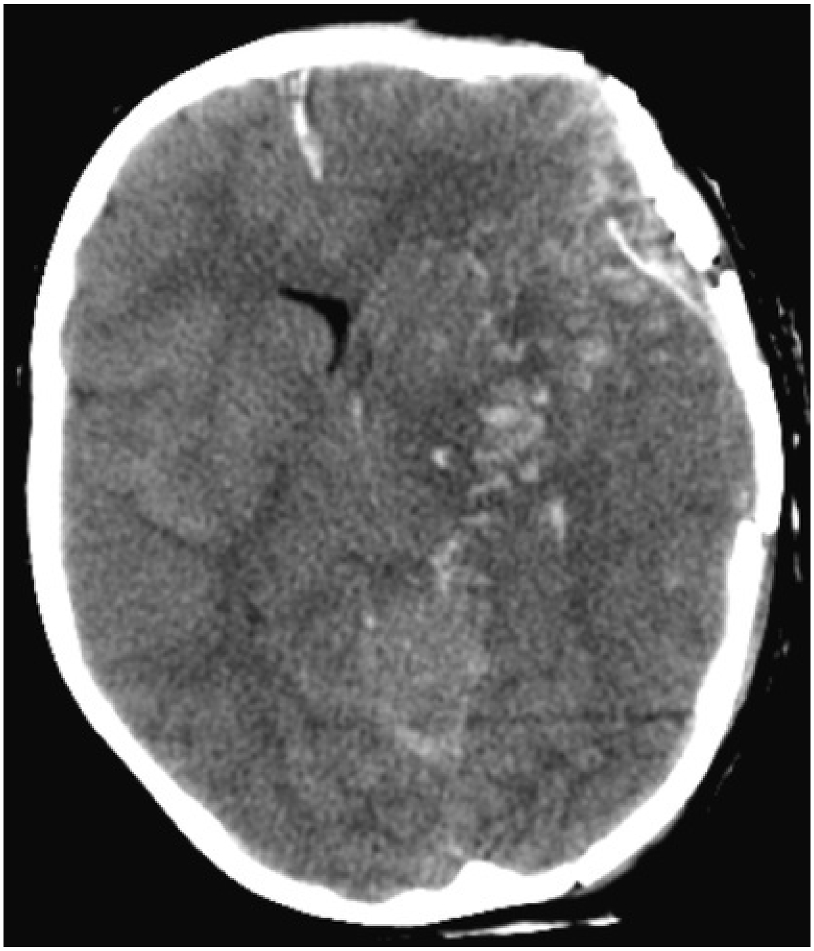

FIG. 85.11 Skull fractures and hemorrhage. An 11 yr old child was hit in the head by a horse, and CT imaging demonstrates multiple, comminuted skull fractures with fragments of bone within the brain parenchyma, multifocal areas of intraparenchymal hemorrhage, and obliteration of the left lateral ventricle.

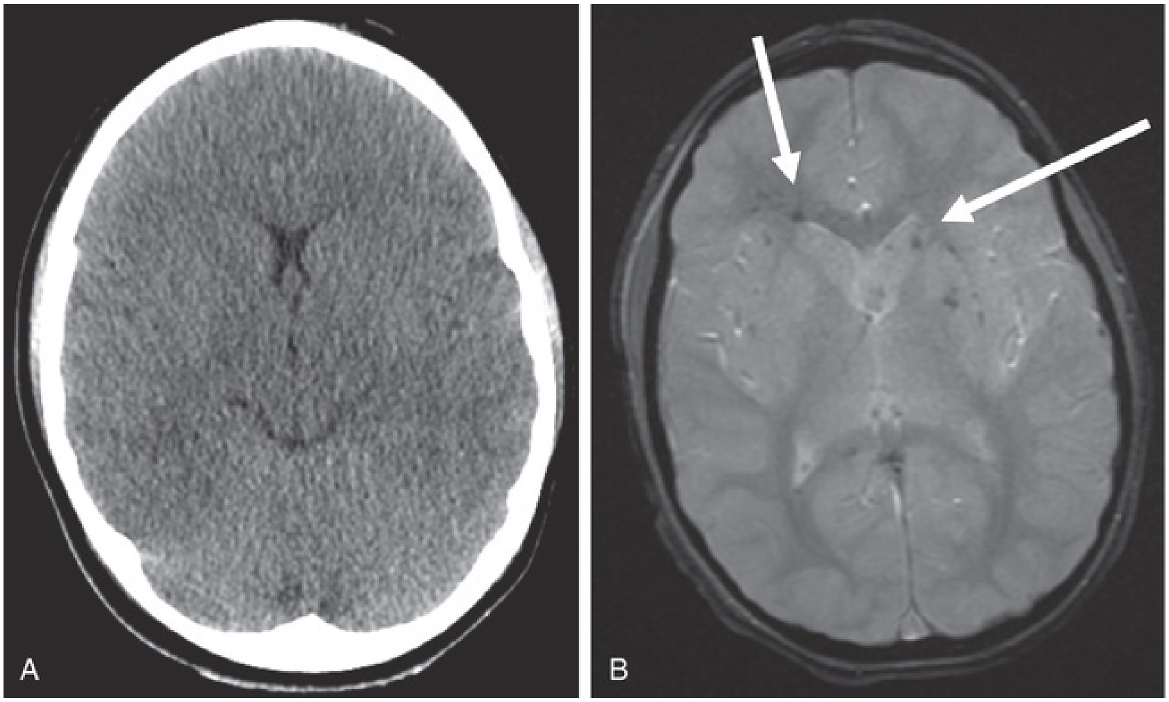

FIG. 85.12 Hemorrhages and axonal injury. A, In a 6 yr old child who was hit by a car while riding his bike, initial CT imaging demonstrated no obvious abnormality. B, However, immediate MRI demonstrates multiple areas of punctate hemorrhages (lucencies) consistent with diffuse axonal injury (*arrows*).

Diagnosis and Differential Diagnosis

In severe TBI the diagnosis is generally obvious from the history and clinical presentation. Occasionally, TBI severity can be overestimated because of concurrent alcohol or drug intoxication. The diagnosis of TBI can be problematic in cases of **abusive head trauma** or following an anoxic event such as drowning or smoke inhalation.

Treatment

Infants and children with severe or moderate TBI (GCS score 3-8 or 9-12, respectively) receive intensive care unit (ICU) monitoring. Evidence-based guidelines for management of severe TBI have been published (Fig. 85.13). This approach to ICP-directed therapy is also reasonable for other conditions in which ICP is monitored. Care involves a multidisciplinary team comprising pediatric caregivers from neurologic surgery, critical care medicine, surgery, and rehabilitation and is directed at preventing secondary insults and managing increased ICP. Initial stabilization of infants and children with severe TBI includes rapid sequence tracheal intubation with spine precautions along with maintenance of normal extracerebral hemodynamics, including blood gas values (PaO_2, $PaCO_2$), MAP, and temperature. Intravenous (IV) fluid boluses may be required to treat hypotension. Euvolemia is the target, and hypotonic fluids must be rigorously avoided; *normal saline is the fluid of choice* . Vasopressors may be needed as guided by monitoring of central venous pressure, with avoidance of both fluid overload and exacerbation of brain edema. A trauma survey should be performed. Once stabilized, the patient should be taken for CT scanning to rule out the need for emergency neurosurgical intervention. If surgery is not required, an ICP monitor should be inserted to guide the treatment of intracranial hypertension.

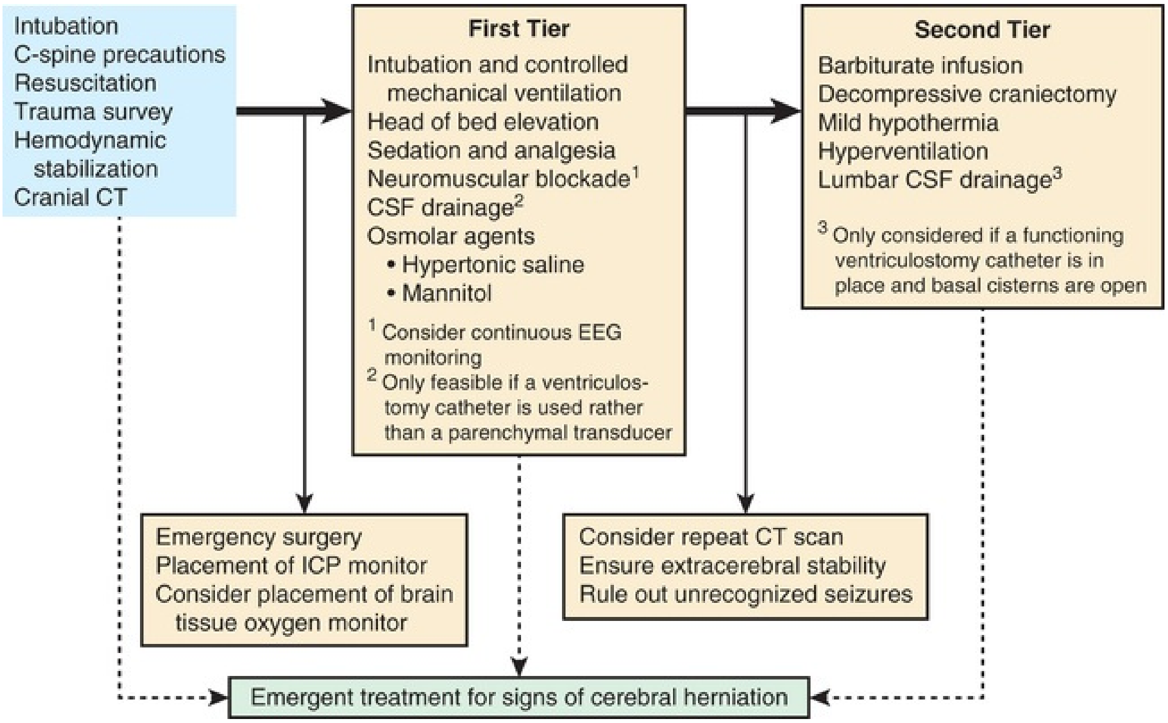
Intubation
C-spine precautions
Resuscitation
Trauma survey
Hemodynamic stabilization
Cranial CT
First Tier
Intubation and controlled mechanical ventilation
Head of bed elevation
Sedation and analgesia
Neuromuscular blockade[1]
CSF drainage[2]
Osmolar agents
• Hypertonic saline
• Mannitol
[1] Consider continuous EEG monitoring
[2] Only feasible if a ventriculostomy catheter is used rather than a parenchymal transducer
Second Tier
Barbiturate infusion
Decompressive craniectomy
Mild hypothermia
Hyperventilation
Lumbar CSF drainage[3]
[3] Only considered if a functioning ventriculostomy catheter is in place and basal cisterns are open
Emergency surgery
Placement of ICP monitor
Consider placement of brain tissue oxygen monitor
Consider repeat CT scan
Ensure extracerebral stability
Rule out unrecognized seizures
Emergent treatment for signs of cerebral herniation

FIG. 85.13 Schematic outlining the approach to management of a child with severe traumatic brain injury (TBI). This schematic is specifically presented for severe TBI, for which the experience with intracranial pressure (ICP)–directed therapy is greatest. Nevertheless, the general approach provided here is relevant to the management of intracranial hypertension in other conditions for which evidence-based data on ICP monitoring and ICP-directed therapy are lacking. The ICP and CPP targets are discussed in the text. (Based on 2012 guidelines for the management of severe TBI, along with minor modifications from later literature.)

During stabilization or at any time during the treatment course, patients can present with signs and symptoms of *cerebral herniation* (pupillary dilation, systemic hypertension, bradycardia, extensor posturing). Because herniation and its devastating consequences can sometimes be reversed if promptly addressed, it should be treated as a *medical emergency* , with use of hyperventilation, with a fraction of inspired oxygen of 1.0, and intubating doses of either thiopental or pentobarbital and either mannitol (0.25-1.0 g/kg IV) or hypertonic saline (3% solution, 5-10 mL/kg IV).

Intracranial pressure should be maintained at <20 mm Hg . Age-dependent cerebral perfusion pressure targets are approximately 50 mm Hg for children 2-6 yr old; 55 mm Hg for those 7-10 yr old; and 65 mm Hg for those 11-16 yr old. **First-tier** therapy includes elevation of the head of the bed, ensuring midline positioning of the head, controlled mechanical ventilation, and analgesia and sedation (i.e., narcotics and benzodiazepines). If neuromuscular blockade is needed, it may be desirable to monitor EEG continuously because status epilepticus can occur; this complication will not be recognized in a paralyzed patient and is associated with increased ICP and unfavorable outcome. If a ventricular rather than parenchymal catheter is used to monitor ICP, therapeutic CSF drainage is available and can be provided either continuously (often targeting an ICP >5 mm Hg) or intermittently in response to ICP spikes, generally >20 mm Hg. Other first-tier therapies include the osmolar agents **hypertonic saline** (often given as a continuous infusion of 3% saline at 0.1-1.0 mL/kg/hr) and **mannitol** (0.25-1.0 g/kg IV over 20 min), given in response to ICP spikes >20 mm Hg or with a fixed (every 4-6 hr) dosing interval. Use of hypertonic saline is more common and has stronger literature support than mannitol, although both are used; these 2 agents can be used concurrently. It is recommended to avoid serum osmolality >320 mOsm/L. A Foley urinary catheter should be placed to monitor urine output.

If increased ICP remains refractory to treatment, careful reassessment of the patient is needed to rule out unrecognized hypercarbia, hypoxemia, fever, hypotension, hypoglycemia, pain, and seizures. Repeat imaging should be considered to rule out a surgical lesion. Guidelines-based **second-tier** therapies for refractory raised ICP are available, but evidence favoring a given second-tier therapy is limited. In some centers, surgical decompressive **craniectomy** is used for refractory traumatic intracranial hypertension. Others use a **pentobarbital infusion** , with a loading dose of 5-10 mg/kg over 30 min followed by 5 mg/kg every hour for 3 doses and then maintenance with an infusion of 1 mg/kg/hr. Careful blood pressure monitoring is required because of the possibility of drug-induced hypotension and the frequent need for support with fluids and pressors.

Mild hypothermia (32-34°C [89.6-93.2°F]) in an attempt to control refractory ICP may be induced and maintained by means of surface cooling. Hypothermia for increased ICP after traumatic brain injury remains controversial for pediatric and adult patients. **Hyperthermia** *must* be avoided and if present should be treated aggressively. Sedation and neuromuscular blockade are used to prevent shivering, and rewarming should be slow, no faster than 1°C (1.8°F) every 4-6 hr. Hypotension should be prevented during rewarming. Refractory raised ICP can also be treated with hyperventilation ($\mathrm{Pa{\scriptstyle CO}}_2$ 25-30 mm Hg). Combinations of these second-tier therapies are often required.

Supportive Care

Euvolemia should be maintained, and isotonic fluids are recommended throughout the ICU stay. SIADH and CSW can develop and are important to differentiate, because management of SIADH is fluid restriction and that of CSW is sodium replacement. Severe hyperglycemia (blood glucose level >200 mg/dL) should be avoided and treated. The blood glucose level should be monitored frequently. Early nutrition with enteral feedings is advocated. Corticosteroids should generally not be used unless adrenal insufficiency is documented. Tracheal suctioning can exacerbate raised ICP. Timing of the use of analgesics or sedatives around suctioning events and use of tracheal or IV lidocaine can be helpful. Seizures are common after severe acute TBI. Early posttraumatic seizures (within 1 wk) will complicate management of TBI and are often difficult to treat. Anticonvulsant prophylaxis with fosphenytoin, carbamazepine, or levetiracetam is a common treatment option. Late posttraumatic seizures (≥7 days after TBI) and, if recurrent, late posttraumatic epilepsy are *not* prevented by prophylactic anticonvulsants, whereas early posttraumatic seizures are prevented by initiating anticonvulsants soon after TBI. Antifibrinolytic agents (tranexamic acid) reduce hemorrhage size, as well as the development of new focal ischemic cerebral lesions, and improve survival in adults with severe TBI.

Prognosis

Mortality rates for children with severe TBI who reach the pediatric ICU range between 10% and 30%. Ability to control ICP is related to patient survival, and the extent of cranial and systemic injuries correlates with quality of life. Motor and cognitive sequelae resulting from severe TBI generally benefit from rehabilitation to minimize long-term disabilities. Recovery from TBI may take months to achieve. Physical therapy, and in some centers methylphenidate or amantadine, helps with motor and behavioral recovery. Pituitary insufficiency may be an uncommon but significant complication of severe TBI.

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CHAPTER 86

Brain Death

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Brain death is the irreversible cessation of all functions of the entire brain, including the brainstem. It is also known as **death by neurologic criteria** and is legally accepted as death in the United States.

Epidemiology

In children, brain death usually develops after traumatic brain injury (TBI, including brain injury from nonaccidental trauma) or asphyxial injury. Pathogenesis is multifactorial, with the end result being irreversible loss of brain and brainstem function.

Clinical Manifestations and Diagnosis

Current guidelines do not apply to preterm infants <37 wk gestational age (Fig. 86.1).

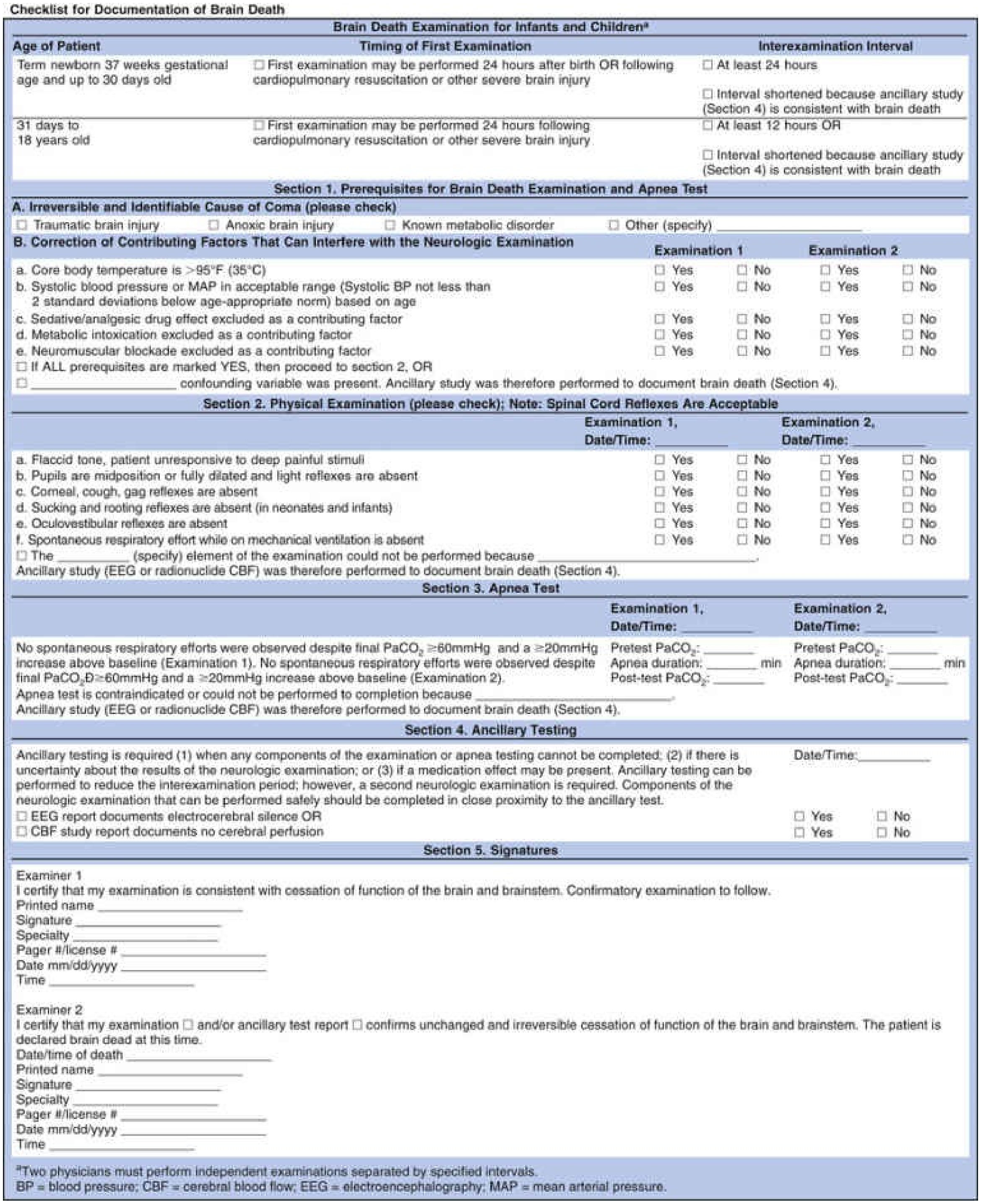

Checklist for Documentation of Brain Death

Brain Death Examination for Infants and Children[a]

Age of Patient	Timing of First Examination	Interexamination Interval
Term newborn 37 weeks gestational age and up to 30 days old	☐ First examination may be performed 24 hours after birth OR following cardiopulmonary resuscitation or other severe brain injury	☐ At least 24 hours ☐ Interval shortened because ancillary study (Section 4) is consistent with brain death
31 days to 18 years old	☐ First examination may be performed 24 hours following cardiopulmonary resuscitation or other severe brain injury	☐ At least 12 hours OR ☐ Interval shortened because ancillary study (Section 4) is consistent with brain death

Section 1. Prerequisites for Brain Death Examination and Apnea Test

A. Irreversible and Identifiable Cause of Coma (please check)

☐ Traumatic brain injury ☐ Anoxic brain injury ☐ Known metabolic disorder ☐ Other (specify) ______________

B. Correction of Contributing Factors That Can Interfere with the Neurologic Examination	Examination 1		Examination 2	
a. Core body temperature is >95°F (35°C)	☐ Yes	☐ No	☐ Yes	☐ No
b. Systolic blood pressure or MAP in acceptable range (Systolic BP not less than 2 standard deviations below age-appropriate norm) based on age	☐ Yes	☐ No	☐ Yes	☐ No
c. Sedative/analgesic drug effect excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No
d. Metabolic intoxication excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No
e. Neuromuscular blockade excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No

☐ If ALL prerequisites are marked YES, then proceed to section 2, OR

☐ ______________ confounding variable was present. Ancillary study was therefore performed to document brain death (Section 4).

Section 2. Physical Examination (please check); Note: Spinal Cord Reflexes Are Acceptable

	Examination 1, Date/Time: ________		Examination 2, Date/Time: ________	
a. Flaccid tone, patient unresponsive to deep painful stimuli	☐ Yes	☐ No	☐ Yes	☐ No
b. Pupils are midposition or fully dilated and light reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
c. Corneal, cough, gag reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
d. Sucking and rooting reflexes are absent (in neonates and infants)	☐ Yes	☐ No	☐ Yes	☐ No
e. Oculovestibular reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
f. Spontaneous respiratory effort while on mechanical ventilation is absent	☐ Yes	☐ No	☐ Yes	☐ No

☐ The ________ (specify) element of the examination could not be performed because ____________________.
Ancillary study (EEG or radionuclide CBF) was therefore performed to document brain death (Section 4).

Section 3. Apnea Test

	Examination 1, Date/Time: ________	Examination 2, Date/Time: ________
No spontaneous respiratory efforts were observed despite final $PaCO_2 \geq 60$mmHg and a ≥20mmHg increase above baseline (Examination 1). No spontaneous respiratory efforts were observed despite final $PaCO_2$Đ≥60mmHg and a ≥20mmHg increase above baseline (Examination 2).	Pretest $PaCO_2$: ______ Apnea duration: ______ min Post-test $PaCO_2$: ______	Pretest $PaCO_2$: ______ Apnea duration: ______ min Post-test $PaCO_2$: ______

Apnea test is contraindicated or could not be performed to completion because ____________________.
Ancillary study (EEG or radionuclide CBF) was therefore performed to document brain death (Section 4).

Section 4. Ancillary Testing

Ancillary testing is required (1) when any components of the examination or apnea testing cannot be completed; (2) if there is uncertainty about the results of the neurologic examination; or (3) if a medication effect may be present. Ancillary testing can be performed to reduce the interexamination period; however, a second neurologic examination is required. Components of the neurologic examination that can be performed safely should be completed in close proximity to the ancillary test.

Date/Time:________

☐ EEG report documents electrocerebral silence OR	☐ Yes	☐ No
☐ CBF study report documents no cerebral perfusion	☐ Yes	☐ No

Section 5. Signatures

Examiner 1
I certify that my examination is consistent with cessation of function of the brain and brainstem. Confirmatory examination to follow.
Printed name ______________
Signature ______________
Specialty ______________
Pager #/license # ______________
Date mm/dd/yyyy ______________
Time ______________

Examiner 2
I certify that my examination ☐ and/or ancillary test report ☐ confirms unchanged and irreversible cessation of function of the brain and brainstem. The patient is declared brain dead at this time.
Date/time of death ______________
Printed name ______________
Signature ______________
Specialty ______________
Pager #/license # ______________
Date mm/dd/yyyy ______________
Time ______________

[a] Two physicians must perform independent examinations separated by specified intervals.
BP = blood pressure; CBF = cerebral blood flow; EEG = electroencephalography; MAP = mean arterial pressure.

FIG. 86.1 Checklist for documentation of brain death. (From Nakagawa TA, Ashwal S, Mathur M, et al. Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations—executive summary, Ann Neurol 71:573–585, 2012, Table 2.).

Brain death is determined by clinical assessment. Although ancillary tests such as electroencephalography (EEG) and cerebral blood flow (CBF) studies are sometimes used to assist in making the diagnosis, repeated clinical examination is the standard for diagnosis. The 3 components for determining brain death are demonstration of coexisting **irreversible coma with a known cause** , **absence of brainstem reflexes** , and **apnea** .

Before a determination of brain death may be made, it is of utmost importance that the cause of the coma be determined using the history, any radiology, and laboratory data, to rule out a reversible condition. *Potentially reversible causes of coma* include metabolic disorders, toxins, sedative drugs, paralytic agents, hypothermia, hypoxia, hypotension/shock, recent cardiopulmonary resuscitation (CPR), hypo-/hyperglycemia, hypo-/hypernatremia, hypercalcemia, hypermagnesemia, nonconvulsive status epilepticus, hypothyroidism, hypocortisolism, hypercarbia, liver or renal failure, sepsis, meningitis, encephalitis, subarachnoid hemorrhage, and surgically remediable brainstem lesions. Confounding factors must be corrected before initiation of brain death assessment.

Coma

The state of coma requires that the patient be unresponsive, even to noxious stimuli. Any purposeful motor response, such as localization, does not constitute coma. Likewise, any posturing (decerebrate or decorticate) is not consistent with coma, and therefore not consistent with brain death. The presence of spinal cord reflexes—even complex reflexes—does not preclude the diagnosis of brain death.

Brainstem Reflexes

Brainstem reflexes must be absent. Table 86.1 lists the brainstem reflexes to be tested, the brainstem location of each reflex, and the result of each test that is consistent with a diagnosis of brain death.

Table 86.1

Brainstem Reflex Testing to Determine Brain Death

BRAINSTEM REFLEX	AREA TESTED	HOW TO PERFORM EXAM	EXPLANATION OF RESULTS
Pupillary light	Cranial	Shine a light into the eyes	Midposition (4-6 mm) or fully dilated pupils

reflex	nerves (CNs) II and III, midbrain	while closely observing pupillary size.	that are not reactive to light are consistent with brain death. Pinpoint pupils, even if nonreactive, suggest intact function of the Edinger-Westphal nucleus in the midbrain and are therefore *not* consistent with brain death.
Oculocephalic reflex (doll's eyes reflex)	CNs III, VI, and VIII; midbrain; pons	Manually rotate the patient's head side to side and closely watch the position of the eyes. Should not be performed in a patient with a cervical spine injury.	In the intact patient, the eyes remain fixed on a distant spot, as if maintaining eye contact with that spot. In an exam consistent with brain death, the eyes move in concert with the patient's head movement.
Corneal reflex	CNs III, V, and VII; pons	Touch the patient's cornea with a cotton swab.	In the intact patient, the touch results in eyelid closure, and the eye may rotate upward. In an exam consistent with brain death, there is no response.
Oculovestibular reflex	CNs III, IV, VI, and VIII; pons; midbrain	Irrigate the tympanic membrane with iced water or saline and look for eye movement.	Absence of eye movement is consistent with brain death.
Gag and cough reflex	CNs IX and X, medulla	Touch the posterior pharynx with a tongue depressor or a cotton-tipped swab to stimulate a gag. Advance a suction catheter through the endotracheal tube to the carina to stimulate a cough.	Absence of both a cough and a gag is consistent with brain death.

Apnea

Apnea is the absence of respiratory effort in response to an adequate stimulus. An arterial partial pressure of carbon dioxide (Pa_{CO_2}) value ≥60 mm Hg *and* >20 mm Hg above baseline is a sufficient stimulus. Apnea is clinically confirmed through the apnea test. Because the apnea test has the potential to destabilize the patient, it is performed only if the 1st 2 criteria for brain death (irreversible coma and absence of brainstem reflexes) are already confirmed.

The **apnea test** assesses the function of the medulla in driving ventilation. It is performed by first ensuring appropriate hemodynamics and temperature (>35°C) and the absence of apnea-producing drug effects or significant metabolic derangements. The patient is then preoxygenated with 100% oxygen for approximately 10 min, and ventilation is adjusted to achieve a Pa_{CO_2} of approximately 40 mm Hg. A baseline arterial blood gas (ABG) result documents the starting values. During the test, oxygenation can be maintained with 100% oxygen via a T -piece attached to the endotracheal tube or via a resuscitation bag such as a Mapleson device. Throughout the test, the child's hemodynamics and pulse oximetry oxygen-hemoglobin saturation (Spo_2) are monitored while the physician observes for respiratory efforts. An ABG sample is obtained approximately 10 min into the test and every 5 min thereafter until the target $Paco_2$ is surpassed; ventilatory support is resumed at that time. If at any point during the test the patient becomes hypoxic (Spo_2 <85%) or hypotensive, the tes is aborted and ventilatory support resumed. Absence of respiratory efforts with a $Paco_2$ ≥60 mm Hg and >20 mm Hg above baseline is consistent with brain death.

Observation Periods

To determine brain death in the United States, the findings must remain consistent for 2 examinations performed by different attending physicians (apnea testing may be performed by the same physician) separated by an observation period. The 1st exam determines that the child has met the criteria for brain death, whereas the 2nd exam confirms brain death based on an unchanged and irreversible condition. Recommended observation periods are 24 hr for neonates from 37 wk gestation to term infants 30 days old, and 12 hr for infants and children >30 days old. An observation period of 24-48 hr before initiation of brain death assessment is recommended after CPR or severe acute brain injury.

Ancillary Studies

Ancillary studies are not required for the diagnosis of brain death unless the clinical examination including the apnea test cannot be safely or reliably completed. Examples include cervical spinal cord injury, presence of high therapeutic or supratherapeutic levels of sedative medications, or hemodynamic instability or Spo_2 desaturation during an apnea test. Ancillary studies may also be used to shorten the recommended observation period. In this case, 2 complete clinical examinations, including apnea test, should be carried out and documented along with the ancillary study. Ancillary studies are no substitute for the neurologic examination.

The 2 most widely used ancillary tests are EEG and radionuclide CBF studies. A valid **electroencephalogram** to support suspected brain death must be performed according to the American EEG Society standards and technical requirements, under conditions of normothermia and appropriate hemodynamics, and in the absence of drug levels sufficient to suppress the EEG response. An EEG that demonstrates **electrocerebral silence** over a 30 min recording time under these conditions supports the diagnosis of brain death. Advantages of this study are its wide availability and low risk. Disadvantages include potential confounders, such as artifact in the tracing and the presence of suppressing levels of drugs such as barbiturates.

A **radionuclide cerebral blood flow study** consists of intravenous (IV) injection of a radiopharmaceutical agent followed by imaging of the brain to look for cerebral uptake. As with EEG, nuclear medicine scans are widely available and low risk. Unlike EEG, radionuclide CBF studies are not affected by drug levels. A study that shows absence of uptake in the brain demonstrates absence of CBF and is supportive of brain death. Four-vessel intracranial contrast angiography was previously used as the definitive ancillary test, but practical technical difficulties and risks have led to the use of nuclear medicine scans instead.

Interpretation of both EEG and radionuclide CBF studies should be done by appropriately trained and qualified individuals. If the studies show electrical activity or presence of CBF, brain death cannot be declared. A 24 hr waiting period is recommended before repeating the clinical examination or ancillary study.

Documentation

Documentation is an important aspect of diagnosing brain death. Complete documentation should include statements of the following:

1. Etiology and irreversibility of the coma.
2. Absence of confounding factors: hypothermia, hypotension, hypoxia, significant metabolic derangement, and significant drug levels.
3. Absence of motor response to noxious stimulation.
4. Absence of brainstem reflexes: pupillary light reflex, oculocephalic/oculovestibular reflex, corneal reflex, cough reflex, and

gag reflex.

5. Absence of respiratory effort in response to an adequate stimulus; ABG values should be documented at the start and end of the apnea test.

Supportive Care

Following a diagnosis of brain death, supportive care may continue for hours to days as the family makes decisions about potential organ donation and comes to terms with the diagnosis. A diagnosis of brain death may not be accepted by the family for personal, religious, or cultural reasons. It is important for care providers to be patient and supportive of the family dealing with this difficult situation.

Objections to the Idea of Brain Death

Although the concept of brain death is widely accepted and very useful in facilitating organ transplantation, it is not accepted by all. Several countries do not recognize brain death, and some individuals, both medical personnel and laypeople, object to the idea of brain death.

It has been pointed out that some patients who meet brain death criteria continue to show evidence of *integrative functioning,* such as control over free-water homeostasis (absence of diabetes insipidus), control of temperature regulation, capacity for growth and wound healing, and variability of heart rate and blood pressure in response to stimulus. Along with scientific arguments, there are also philosophical arguments about what constitutes death and whether a person who lacks function of the brain, but not of the body, is truly dead.

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CHAPTER 87

Syncope

Aarti S. Dalal, George F. Van Hare

Syncope is defined as a sudden transient loss of consciousness with inability to maintain postural tone. The most common cause of syncope in the normal pediatric population is **neurocardiogenic syncope** (vasovagal syncope, fainting). **Vasovagal syncope** is classically associated with a prodrome that includes diaphoresis, warmth, pallor, or feeling lightheaded and is often triggered by a specific event or situation such as pain, medical procedures, or emotional distress (Table 87.1). This type of syncope is characterized by hypotension and bradycardia. Approximately 30–50% of children will have had a **fainting** episode before 18 yr of age.

Table 87.1

Noncardiac Causes of Syncope

- Reflex vasodepressor syncope
    - Neurocardiogenic (vasovagal)
    - Emotion (seeing blood)
    - Pain (needle phobia)
- Miscellaneous situational reflex
    - Tussive
    - Sneeze
    - Exercise, after exercise
    - Swallowing
    - Stretching
    - Defecation
    - Micturition
    - Hair grooming

  - Valsalva (increased intrathoracic pressure)
  - Trumpet playing
  - Weightlifting
  - Breath-holding spells
- Systemic illness
  - Hypoglycemia
  - Anemia
  - Infection
  - Hypovolemia, dehydration
  - Adrenal insufficiency
  - Narcolepsy, cataplexy
  - Pulmonary embolism
  - Pheochromocytoma
  - Mastocytosis
  - Ruptured ectopic pregnancy
- Central nervous system
  - Seizure (atonic, absence, myoclonic-astatic)
  - Stroke, transient ischemic attack
  - Subarachnoid hemorrhage
- Dysautonomia
- Myotonic dystrophy
- Kearns-Sayre syndrome
- Friedreich ataxia
- Basilar artery migraine
- Drug effects
  - β-Blocking agents
  - Vasodilating agents
  - Opiates
  - Sedatives
  - Drugs prolonging QT interval
  - Diuretics
  - Anticonvulsant agents
  - Antihistamines
  - Antidepressant agents
  - Anxiolytic agents
  - Drugs of abuse
  - Insulin, oral hypoglycemic agents

    - Carbon monoxide
- Other etiologies
    - Carotid sinus sensitivity
    - Subclavian steal
    - Panic attack, anxiety
    - Conversion disorder

Most patients with a vasovagal syncope episode will have prodromal features followed by loss of motor tone. Once in a horizontal position, consciousness returns rapidly, in 1-2 min; some patients may have 30 sec of tonic-clonic motor activities, which should not be confused with a **seizure** (Table 87.2). Syncope must also be distinguished from **vertigo** and **ataxia** (Table 87.3).

Table 87.2

Comparison of Clinical Features of Syncope and Seizures

FEATURES	SYNCOPE	SEIZURES
Relation to posture	Common	No
Time of day	Diurnal	Diurnal or nocturnal
Precipitating factors	Emotion, injury, pain, crowds, heat, exercise, fear, dehydration, coughing, micturition	Sleep loss, drug/alcohol withdrawal
Skin color	Pallor	Cyanosis or normal
Diaphoresis	Common	Rare
Aura or premonitory symptoms	Long	Brief
Convulsion	Rare, brief	Common
Other abnormal movements	Minor twitching	Rhythmic jerks
Injury	Rare	Common (with convulsive seizures)
Urinary incontinence	Rare	Common
Tongue biting	No	Can occur with convulsive seizures
Postictal confusion	Rare	Common
Postictal headache	No	Common
Focal neurologic signs	No	Occasional
Cardiovascular signs	Common (cardiac syncope)	No
Abnormal findings on EEG	Rare (generalized slowing may occur during the event)	Common

From Bruni J: Episodic impairment of consciousness. In Daroff RB, Jankovic JM, Mazziotta JC, Pomeroy SL, editors: *Bradley's neurology in clinical practice,* ed 7, Philadelphia, 2016, Elsevier.

Table 87.3

Syncope and Dizziness

	VERTIGO	PRESYNCOPE	DISEQUILIBRIUM	LIGHTHEADEDNESS
Patient complaint	"My head is spinning." "The room is whirling."	"I feel I might pass out." "I feel faint." "I feel like blacking out."	"I feel unsteady." "My balance is off."	"I feel dizzy." "I feel disconnected, drugged."
Associated features	Motion, swaying, spinning, nystagmus	Syncope: loss of postural tone, brief loss of consciousness Situational	Poor balance No vertigo or ataxia	Anxiety, hyperventilation, paresthesias, respiratory alkalosis, panic attacks
Usual cause	Vestibular disorders	Impaired cerebral perfusion	Sensory and/or central neurologic dysfunction	Anxiety and/or depressive disorders
Key differential diagnoses	Peripheral (labyrinthine-cochlear) vs central neurologic disorder	Neurocardiogenic (vagal) vs cardiac syncope vs neuropsychiatric syncope	Sensory deficit vs central neurologic disease	Anxiety/depression vs hyperventilation vs medication effects

From Cohen G: Syncope and dizziness. In *Nelson pediatric symptom-based diagnosis,* Philadelphia, 2018, Elsevier (Table 6.1, p 84).

Although this type of syncope is very common in adolescence and has an excellent prognosis, other causes for loss of consciousness are more dangerous; thus syncope may be the first sign of more serious conditions (Table 87.4). Indeed, the occurrence of syncope may well be the pediatrician's best opportunity to diagnose a life-threatening condition before the patient subsequently succumbs. The task of the clinician, therefore, is not only to counsel the family and the patient concerning the common form, but also to rule out a number of important life-threatening cardiac problems.

Table 87.4

Life-Threatening Cardiac Causes as Risk With Syncope

- Long QT syndromes (congenital and drug induced)
- Short QT syndromes
- Cardiomyopathies
    - Hypertrophic cardiomyopathy
    - Dilated cardiomyopathy
    - Arrhythmogenic right ventricular dysplasia
- Brugada syndrome

Catecholaminergic polymorphic ventricular tachycardia
Myocarditis
Lyme myocarditis
Chagas disease
Wolff-Parkinson-White syndrome
Coronary artery anomalies
Late postoperative arrhythmias
Adult congenital heart patients
Congenital or acquired complete atrioventricular block
Aortic, mitral, or pulmonic valve stenosis
Primary pulmonary hypertension
Eisenmenger syndrome
Dissecting aortic aneurysm (Marfan syndrome)
Cardiac tumor
Pacemaker malfunction
Takotsubo cardiomyopathy

Mechanisms

Syncope by whatever mechanism is caused by a lack of adequate cerebral blood flow with loss of consciousness and inability to remain upright.

Primary **cardiac causes** of syncope (Table 87.4) include arrhythmias such as long QT syndrome (LQTS), Wolff-Parkinson-White syndrome (particularly with atrial fibrillation), ventricular tachycardia (VT), and occasionally supraventricular tachycardia (see Chapter 462). VT may be associated with hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy, repaired congenital heart disease, or a genetic cause such as catecholaminergic polymorphous ventricular tachycardia (CPVT). Other arrhythmias that may lead to syncope are bradyarrhythmias such as sinus node dysfunction and high-grade second- or third-degree atrioventricular (AV) block. Patients with congenital complete AV block may present with syncope. Syncope may also be caused by cardiac obstructive lesions, such as critical aortic stenosis, or coronary artery anomalies, such as an aberrant left coronary artery arising from the right sinus of Valsalva. Patients with primary pulmonary hypertension or Eisenmenger syndrome may experience syncope. In all the obstructive forms of syncope, exercise increases the likelihood of an episode because the obstruction interferes with the ability of the heart to increased cardiac output in response to exercise.

Noncardiac causes of loss of consciousness include epilepsy, as well as basilar artery migraine, hysterical syncope, and pseudoseizures (see Table 87.1). Occasionally, patients with narcolepsy may present with syncope. Hypoglycemia and hyperventilation may also present as syncope.

Evaluation

The most important goal in the evaluation of the new patient with syncope is to diagnose life-threatening causes of syncope so that these causes can be managed. Many patients presenting with sudden cardiac arrest caused by conditions such as LQTS will have previously experienced an episode of syncope, so the presentation with syncope is an opportunity to prevent sudden death.

The most important tool in evaluation is a careful **history** . The characteristics of cardiac syncope differ significantly from the prodrome seen in neurocardiogenic syncope (Table 87.5). Several red flags can be identified that should lead the clinician to suspect that the mechanism is a life-threatening cardiac cause rather than simple fainting (Table 87.6). The occurrence during exercise suggests an arrhythmia or coronary obstruction. Injury because of an episode of syncope indicates sudden occurrence with a lack of adequate prodromal symptoms and suggests an arrhythmia. The occurrence of syncope while recumbent would be quite unusual in a patient with neurocardiogenic syncope and therefore suggests a cardiac or neurologic cause. Occasionally, a patient with syncope caused by a tachyarrhythmia will report the sensation of a racing heart before the event, but this is unusual.

Table 87.5

Differentiating Features for Causes of Syncope

NEUROCARDIOGENIC
Symptoms after prolonged motionless standing, sudden unexpected pain, fear, or unpleasant sight, sound, or smell; pallor Syncope in a well-trained athlete *after* exertion (without heart disease) Situational syncope during or immediately after micturition, cough, swallowing, or defecation Syncope with throat or facial pain (glossopharyngeal or trigeminal neuralgia)
ORGANIC HEART DISEASE (PRIMARY ARRHYTHMIA, OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY, PULMONARY HYPERTENSION)
Brief sudden loss of consciousness, no prodrome, history of heart disease Syncope while sitting or supine Syncope with exertion History of palpitations

Family history of sudden death
NEUROLOGIC
Seizures: preceding aura, post event symptoms lasting > 5 min (includes postictal state of decreased level of consciousness, confusion, headache or paralysis) Migraine: syncope associated with antecedent headaches with or without aura
OTHER VASCULAR
Carotid sinus: syncope with head rotation or pressure on the carotid sinus (as in tumors, shaving, tight collars) Orthostatic hypotension: syncope immediately on standing especially after prolonged bed rest
DRUG INDUCED
Patient is taking a medication that may lead to long QT syndrome, orthostasis, or bradycardia
PSYCHIATRIC ILLNESS
Frequent syncope, somatic complaints, no heart disease

From Cohen G: Syncope and dizziness. In Kliegman RM, Lye PS, Bordini BJ, et al, editors: Nelson pediatric symptom-based diagnosis. Philadelphia, 2018, Elsevier, Table 6.4.

Table 87.6

Red Flags in Evaluation of Patients With Syncope

- Syncope with activity or exercise or supine
- Syncope not associated with prolonged standing
- Syncope precipitated by loud noise or extreme emotion
- Absence of presyncope or lightheadedness
- Family history of syncope, drowning, sudden death, familial ventricular arrhythmia syndromes,* cardiomyopathy
- Syncope requiring CPR
- Injury with syncope
- Anemia
- Other cardiac symptoms
- Chest pain
- Dyspnea
- Palpitations
- History of cardiac surgery
- History of Kawasaki disease
- Implanted pacemaker
- Abnormal physical examination
    - Murmur
    - Gallop rhythm
    - Loud and single second heart sound
    - Systolic click

Increased apical impulse (tachycardia)
Irregular rhythm
Hypo- or hypertension
Clubbing
Cyanosis

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[*] Long QT syndrome, Brugada syndrome, catecholamine polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia.

A careful family history is essential in evaluation of syncope. Specifically, if there are first-degree relatives with inherited syndromes, such as a LQTS or HCM, this should lead to more specific evaluation of the patient. Also, if relatives died suddenly at a young age without a clear and convincing cause, inherited cardiac arrhythmias or cardiomyopathies should also be suspected.

Patients with a history of heart disease, especially cardiac repair, may have causes that are specific to their repair. Sinus node dysfunction is common after the Senning or Mustard procedure for transposition of the great vessels. VT may be seen after repair of tetralogy of Fallot. A patient with a history of septal defect repair should be evaluated for the late occurrence of AV block, and patients with an implanted pacemaker should be evaluated for pacemaker lead failure.

The physical examination may also offer clues (Table 87.6). Patients with HCM may have a prominent cardiac impulse and/or an ejection murmur, as will patients with aortic stenosis. The patient with primary pulmonary hypertension will have a loud and single second heart sound and may also have an ejection click and the murmur of pulmonary insufficiency. Scars from prior cardiac surgery and pacemaker implantation would be evident.

All patients presenting with a first episode of syncope *must* have an electrocardiogram obtained, looking primarily for QT interval prolongation, preexcitation, ventricular hypertrophy, T-wave abnormalities, and conduction abnormalities. Other tests that may be needed depending on the results of the initial evaluation may include echocardiography, exercise testing, cardiac MRI, or 24 hr Holter monitoring. In patients for whom there is a strong suspicion of a paroxysmal arrhythmia, an implantable loop recorder may be the most effective means of diagnosis. Additional tests to look for anemia, hypoglycemia, drugs of abuse, and other etiologies noted in Table 87.1 will be determined by the history and physical examination.

Treatment

Therapy for vasovagal syncope includes avoiding triggering events (if possible), fluid and salt supplementation, and if needed, midodrine (see Chapter 87.1 , Table 87.7). Immediately after the event, the patient should remain supine until symptoms abate to avoid recurrence.

Table 87.7

First-Line Medications in Treatment of Postural Tachycardia Syndrome (POTS)

DRUG	MECHANISM OF ACTION	SIDE EFFECTS	TREATMENT GUIDELINES
Fludrocortisone	Low dose: sensitizes α receptors Higher doses: mineralocorticoid effect	Peripheral edema, headache, irritability, hypokalemia, hypomagnesemia, acne	Monitor basic metabolic panel and magnesium.
Midodrine	α_1 -Agonist; produces vasoconstriction	Scalp tingling, urinary retention, goose bumps, headache, supine hypertension	Monitor supine blood pressure 30-60 min after dose.
Metoprolol succinate/tartrate	β-Blocker	Worsening of asthma, dizziness, fatigue	Use with caution in asthma. If fatigue is severe, use at bedtime.
Propranolol	Nonselective β-blocker	Bradycardia, gastrointestinal symptoms, lightheadedness, sleepiness, hypotension, syncope	Use with caution in diabetes and asthma.
Pyridostigmine	Peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine in autonomic ganglia and at peripheral muscarinic receptors	Symptoms of excessive cholinergic activity (diarrhea, urinary incontinence, salivation)	Very useful if patient has POTS and constipation. Use with caution in asthma. Contraindicated in urinary or bowel obstruction.

Treatment for cardiac causes of syncope will be determined by the diagnosis. If a reentrant tachycardia (AVNRT, AVRT) is found, then a catheter ablation is indicated. If bradycardia from AV block was the cause of the syncope, a pacemaker may be warranted. Patients with syncope from medically refractory malignant arrhythmias, as may be seen in HCM, LQTS, arrhythmogenic cardiomyopathy, or CPVT, require an implantable cardioverter-defibrillator. Patients with structural heart disease (valvular disease or coronary artery anomalies) should be referred for surgery.

87.1

Postural Tachycardia Syndrome

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Keywords

orthostatic hypotension
POTS
reflex syncope

Several complex and interrelated mechanisms allow humans to stand despite the pull of gravity on the cerebral circulation. In the supine posture, most blood sits in the thoracic cavity, with 25–30% of total volume in the splanchnic vasculature. When an adult stands up, about 500 mL of blood shifts to the lower extremities and to the splanchnic vasculature. The decrease in hydrostatic pressure in the carotid sinuses produces vasoconstriction in the peripheral vessels mediated by sympathetic outflow, as well as in the splanchnic vasculature. This action is mediated by norepinephrine, adenosine triphosphate (ATP), and neuropeptide Y. The muscles in the legs and gluteal area work as a pump when the individual is upright and during exercise, to help return the blood to the heart.

Understanding postural tachycardia syndrome (**POTS**), or postural orthostatic tachycardia syndrome, requires an understanding of other orthostatic conditions.

Many adolescents have lightheadedness or tunnel vision in the first few seconds of assuming the upright posture. This phenomenon, termed **initial orthostatic hypotension (IOH)** , can lead to *syncope* , but usually is very short, perhaps 30-60 sec, and occurs primarily with active standing, not passive upright tilt. Blood pressure (BP) may drop 30% of baseline at 10-20 sec of standing and may be associated with tachycardia. BP returns to baseline in 30-60 sec, whereas heart rate (HR) typically returns to a new, higher value above the baseline when supine. Because of its transient rapidity, IOH escapes detection with standard BP machines and requires beat-to-beat monitoring of BP and HR. The clinical diagnosis requires a careful history. The symptoms usually happen after prolonged recumbence and when the individual stands. The person complains of lightheadedness and “blacking out” or tunnel vision 5-10 sec after standing.

In contrast to IOH, **orthostatic hypotension (OH)** is defined as a *sustained* decrease in the systolic BP of >20 mm Hg or diastolic BP >10 mm Hg in the 1st 3 min of upright tilt. This 2nd type of orthostatic disorder rarely occurs in children. The patient frequently has no orthostatic symptoms while upright despite very low pressures (Fig. 87.1). This distinguishes OH from POTS, which *requires* symptoms while upright. A 3rd orthostatic disorder, **reflex syncope** (i.e., vasovagal or neurally mediated), is defined as relatively sudden change in autonomic nervous system activity that leads to a sudden decrease in BP, HR, and cerebral perfusion (Fig. 87.2).

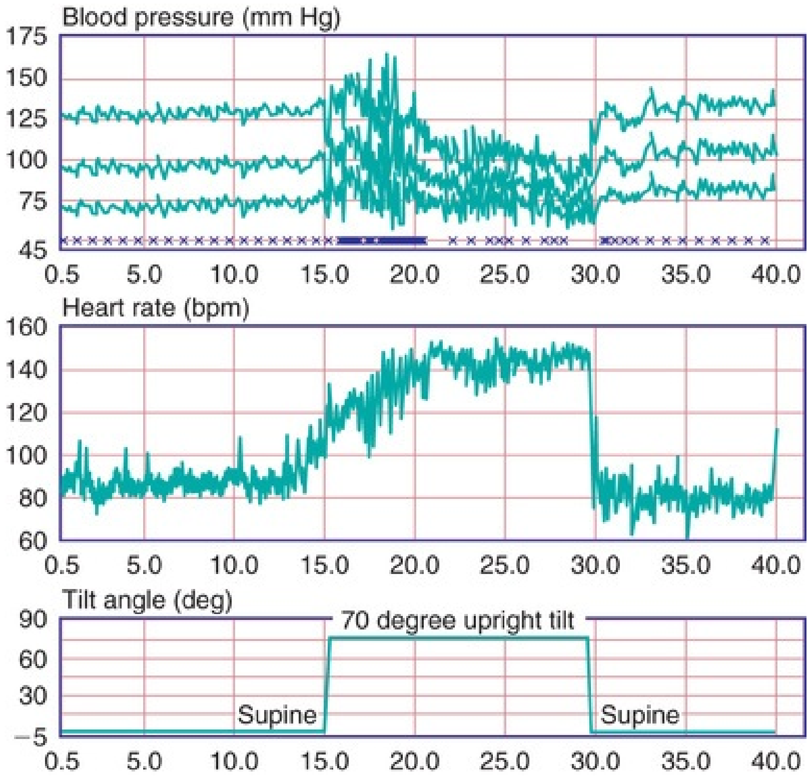

FIG. 87.1 **Example of orthostatic hypotension.**

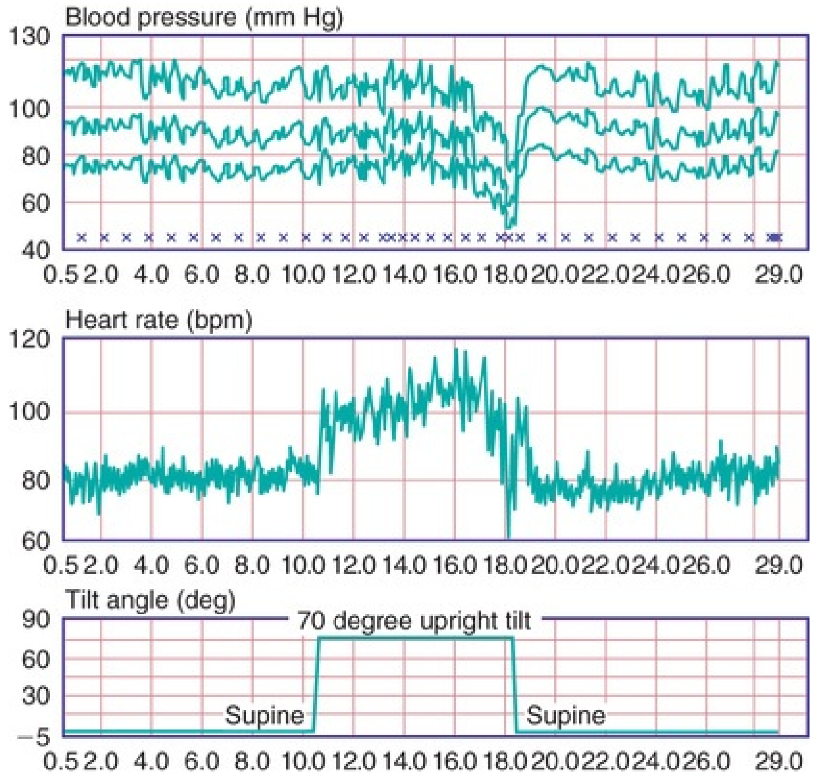

FIG. 87.2 **Example of neurally mediated syncope.**

In children, POTS is defined as a syndrome characterized by HR increase of >40 beats/min during the 1st 10 min of upright tilt test without associated hypotension, (>30 beats/min if >19 yr old) while replicating orthostatic symptoms that occur when upright (Fig. 87.3). Improvement of symptoms in the supine position is expected. The diagnosis of POTS also requires *daily* orthostatic symptoms. In patients with POTS, the larger decline in cardiac stroke volume appears to be the primary trigger for the tachycardia, which may result from various pathophysiologic mechanisms, such as the following:

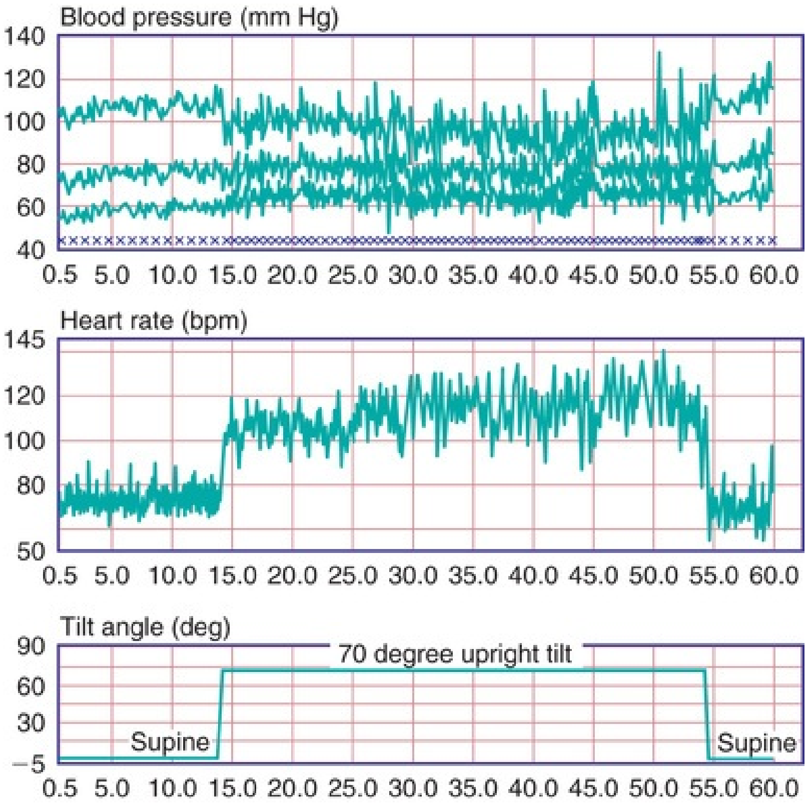

FIG. 87.3 **Example of postural tachycardia syndrome.**

◆ **Neuropathic** POTS, an autonomic neuropathy impairing sympathetic venoconstriction in the lower extremities or splanchnic circulation, decreasing stroke volume, and consequently resulting in a tachycardia

◆ **Hypovolemic** POTS, a common contributor, often related to decreased aldosterone with reduced renin activity, resulting in a tachycardia caused by decrease blood volume

◆ **Hyperadrenergic** POTS, with norepinephrine levels rising 3-4–fold in the standing position (norepinephrine normally doubles on standing), which may occur in norepinephrine transporter deficiency or strong stimulation of central baroreflex responses

◆ **Autoimmune** POTS, typically assumed based on a postviral chronology, but seldom proven; such a form may or may not exist. The antiganglionic antibody is almost never elevated in these patients. Nonetheless, a group of patients report that intravenous immune globulin (IVIG) is helpful to them. Whether they benefit from the increase in intravascular volume or an actual immune effect is unknown.

Some patients have orthostatic symptoms while upright but do not meet criteria for syncope, OH, or POTS. This group has **orthostatic intolerance otherwise not specified (OI-NOS)** .

Clinical Presentation

The symptoms that intrinsically relate to POTS are those that are replicated during upright tilt testing or standing. Many other symptoms also occur in patients with POTS, fitting the description of comorbid conditions, but not reproduced while upright. A patient may have nausea while upright associated with lightheadedness and has a diagnosis of POTS. Another patient may complain of nausea on awakening and have POTS, but has no nausea while upright. In the former patient the nausea is a symptom of POTS itself, whereas in the latter nausea is an associated condition. The symptoms that often directly relate to POTS include lightheadedness, orthostatic nausea, sometimes orthostatic headaches, fatigue, tunnel vision, and brain fog. About 20–30% of pediatric patients with POTS will also have syncope (Fig. 87.4). Other comorbid conditions frequently occur in these patients but are not caused by POTS (i.e., not an orthostatic phenomenon). These comorbidities include (1) sleep issues, usually delayed onset of sleep, frequent awakening, and not feeling refreshed in the morning; (2) aches in different parts of the body; (3) abdominal pain; (4) headaches and migraines; (5) nausea and vomiting; and (6) Raynaud like symptoms and other, less frequent problems (e.g., urinary symptoms).

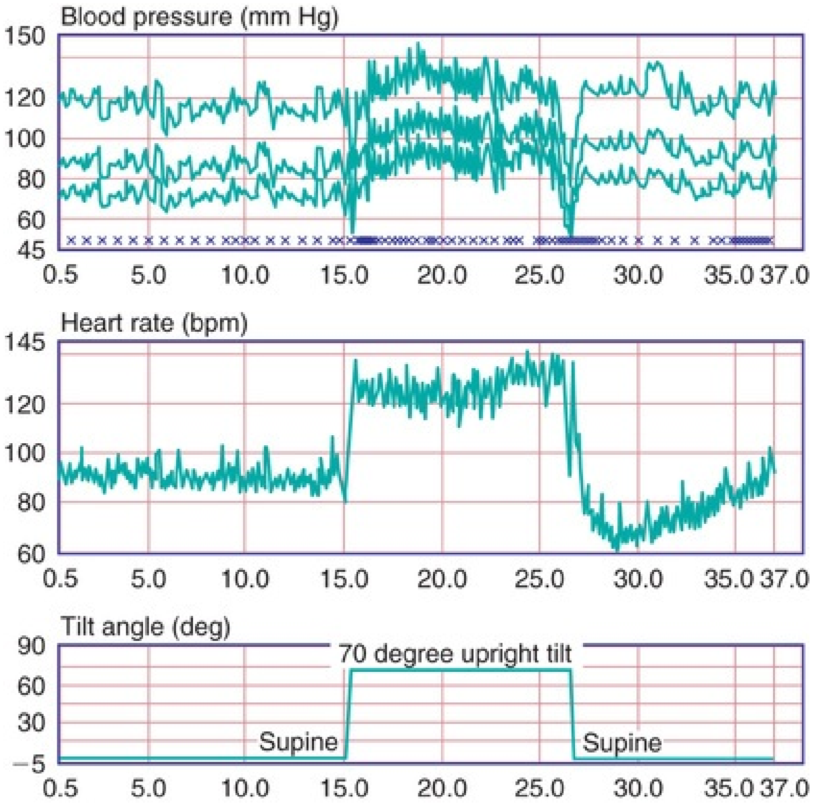

FIG. 87.4 **Example of postural tachycardia syndrome (POTS) followed by a neurally mediated syncope.**

The association of upper gastrointestinal (GI) symptoms and POTS are well described. Nausea, early satiety, and bloating are described in association with POTS. Such GI symptoms relate mechanistically to POTS only when they occur in the upright position. Many patients with POTS have comorbid GI symptom that are not a consequence of the orthostatic challenge. Therefore, only the GI symptoms replicated during tilt testing will improve with treatment aimed at orthostasis. Patients with POTS have changes in the electrical activity of the stomach while upright, which may explain the upright GI symptoms; they usually do not have delayed gastric emptying. The emptying is either normal or accelerated, implying that the cause of nausea is not gastroparesis.

Patients with **hypermobility Ehlers-Danlos syndrome** (h-EDS) may have POTS. Typically, such individuals have more migraine and syncope. Joint hypermobility itself in *adults* is associated with more autonomic complaints such as syncope, presyncope, palpitations, chest discomfort, fatigue, and heat intolerance. Those with hypermobility have more frequent positive tilt tests than healthy controls. Interestingly, in children, joint hypermobility does not influence the number of comorbidities or autonomic disorders. Similarly, those with pediatric chronic overlapping pain conditions with or without POTS have the same comorbidities, suggesting that neither POTS nor hypermobility are drivers of the comorbidities or the chronic overlapping pain condition, but rather another associated disorder (Chapter 147).

Diagnosis

Orthostatic intolerance is clinically diagnosed by detailed history attending specifically to symptoms as they relate to body position. Dizziness that begins in the supine position cannot be a manifestation of orthostatic intolerance. Furthermore, those symptoms that do develop while upright should improve or resolve when supine. Importantly, the history should include a detailed description of current physical exercise habits, with frequency, type, and endurance. One should also assess sleep, diet (mainly evaluating intake of salt), fluid intake, and other comorbidities. The physical examination is also important and should include a cardiac and neurologic evaluation with supine and standing BP and HR. Examination of the extremities may provide information about venous pooling, such as mild edema or reddish purple discoloration when sitting or standing. Cold, clammy hands can signify excess sympathetic activity.

To diagnose POTS the patient needs to undergo a *head-up tilt test for at least 10 min* . It is important to have the patient supine for at least 20 min before the tilt test. POTS can also be assessed by a standing test, measuring BP and HR at 1, 3, 5, and 10 min standing, but to have a reliable test similar to the tilt test, the patient needs to be supine for 1 hr before standing. The HR increase with active standing is typically less than with tilt, because the lower-extremity muscle pump is less active in tilt. The diagnosis of POTS requires replication of the day-to-day symptoms while upright, not just the increased HR while upright. A small but significant proportion of healthy teenagers in school will have an increased HR that may be diagnosed as POTS but will not have associated symptoms.

Other tests may include electrocardiogram, echocardiogram, and Holter monitor when there is concern of a primary cardiac cause of tachycardia, or if there is a need to determine if symptoms correlate with tachycardia (see Chapter 87). Supine and standing plasma catecholamines help confirm the diagnosis of POTS, as one expects to see either the normal doubling of norepinephrine levels from supine to standing, or a tripling with hyperadrenergic POTS. Beyond tilt table testing, autonomic testing will also include cardiac response to deep breathing (checking cardiac parasympathetic function), Valsalva maneuver (checking cardiac sympathetic and parasympathetic functions and vasomotor sympathetic function), and quantitative axon reflex sudomotor test (to assess for an autonomic neuropathy and vasomotor sympathetic dysfunction).

Additional studies depend on the clinical symptoms and include morning cortisol (to rule out Addison disease) and hypo- or hyperthyroid studies if the patient has unusually severe fatigue or is not responsive to usual treatment. Serum tryptase and urine methylhistamine are tested if mast cell activation disorder is suspected, based on a history of flushing during the spells. If an autoimmune cause for the POTS is a concern, antibodies such as voltage-gated potassium channel and acetylcholine receptor antibodies could be checked, but this etiology for POTS is being questioned. Patients rarely (<5 in 1000) benefit from IVIG; if this mechanism is really causing POTS, such patients will experience peak benefit at about 10 days after the infusion, rather than immediately, which may simply reflect increasing intravascular volume. If the patient has hypertension, plasma and urine metanephrines should be measured to test for a pheochromocytoma. In addition, if symptoms are associated with perimenstrual timing, an assessment of sex hormone axis is helpful, with occult polycystic ovarian syndrome or low testosterone levels sometimes present.

Management

The core of POTS management is **nonpharmacologic** . Medications will be of little benefit without these measures being undertaken first. The best measure for treating POTS is a regular **aerobic exercise** program. Given the combination of orthostatic symptoms and severe deconditioning found in most patients, the exercise program must be introduced in a slow, progressive manner. Patients with POTS typically have moderate to severe exercise intolerance, and compared with sedentary healthy controls, have decreased peak oxygen uptake. After 3 mo of exercise, POTS patients have an increase in cardiac mass and size, blood volume, and peak oxygen uptake, as reflected in a better exercise performance. The tachycardia in POTS is caused by a decrease in stroke volume and not an intrinsic circulatory problem. An exercise program should start with water exercises combined with recumbent aerobic activities (recumbent bike or rowing machine). Slowly increase the exercise time to 45 min at least 5 times per week. When tolerance increases, patients can advance to more upright aerobic activities. These aerobic activities need to be combined with light core- and limb-strengthening exercises.

Exercise usually cannot be performed without simultaneous expansion of the intravascular volume. To this end, encourage teenagers to drink >80 oz of fluids daily and to add 2 g of salt to usual diet in both the morning and the early afternoon. **Salt supplementation** increases plasma and blood volume, improves orthostatic tolerance, and decreases baroreflex sensitivity. Salt also reduces nitric oxide production, resulting in less vasodilation. Trial and error of different salt formulation can help to identify the best method for each individual patient. Salt tablets are simple and inexpensive but may make some people nauseous. An alternative is simply to obtain empty capsules on the internet and fill them with table salt. A “0” size capsule contains about 400 mg of salt.

The content of sodium in the body determines the extracellular fluid volume that in turn dictates orthostatic tolerance. Patients with POTS who have lower urinary sodium excretion have more symptoms than those with higher urinary sodium (> 123 mmol/24 hr), and they often respond less well to salt supplementation. Those with severe orthostatic symptoms either in the morning or before sports should drink 16 oz of plain water, which is known to increase sympathetic response mainly in individuals with baroreflex dysregulation. The effect starts soon after drinking the water and lasts for about 1 hr. Compression garments may also be useful. These can be thigh or waist high; the waist-high compression garments may not be tolerated.

Medications can be added when the nonpharmacologic interventions are not insufficient (). Different centers use different strategies, and there is no single correct evidence-based approach. Table 87.3 addresses first-line medications that primary care physicians could use; only the most common side effects are included.

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CHAPTER 88

Shock

David A. Turner, Ira M. Cheifetz

Shock is an acute process characterized by the body's inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues. Insufficient oxygen at the tissue level is unable to support normal aerobic cellular metabolism, resulting in a shift to less efficient anaerobic metabolism. As shock progresses, increases in tissue oxygen extraction are unable to compensate for this deficiency in oxygen delivery, leading to progressive clinical deterioration and lactic acidosis. If inadequate tissue perfusion persists, adverse vascular, inflammatory, metabolic, cellular, endocrine, and systemic responses worsen physiologic instability.

Compensation for inadequate oxygen delivery involves a complex set of responses that attempt to preserve oxygenation of the vital organs (i.e., brain, heart, kidneys, liver) at the expense of other organs (i.e., skin, gastrointestinal tract, muscles). Of importance, the brain is especially sensitive to periods of poor oxygen supply given its lack of capacity for anaerobic metabolism. Initially, shock is often well compensated, but it may rapidly progress to an *uncompensated* state requiring more aggressive therapies to achieve clinical recovery. The combination of a continued presence of an inciting trigger and the body's exaggerated and potentially harmful neurohumoral, inflammatory, and cellular responses lead to the progression of shock. Irrespective of the underlying cause of shock, the specific pattern of response, pathophysiology, clinical manifestations, and treatment may vary significantly depending on the specific etiology (which may be unknown), the clinical circumstances, and an individual patient's biologic response to the shock state. Untreated shock causes irreversible tissue and organ injury (i.e., *irreversible shock*) and, ultimately, death.

Epidemiology

Shock occurs in approximately 2% of all hospitalized infants, children, and adults in developed countries, and the mortality rate varies substantially depending on the etiology and clinical circumstances. Of patients who do not survive, most do not die in the acute hypotensive phase of shock, but rather as a result of associated complications and **multiple-organ dysfunction syndrome (MODS).** MODS is defined as any alteration of organ function that requires medical support for maintenance, and the presence of MODS in patients with shock substantially increases the probability of death. In pediatrics, educational efforts and the utilization of standardized management guidelines that emphasize early recognition and intervention along with the rapid transfer of critically ill patients to a pediatric intensive care unit (PICU) have led to decreases in the mortality rate for shock (Figs. 88.1 and 88.2).

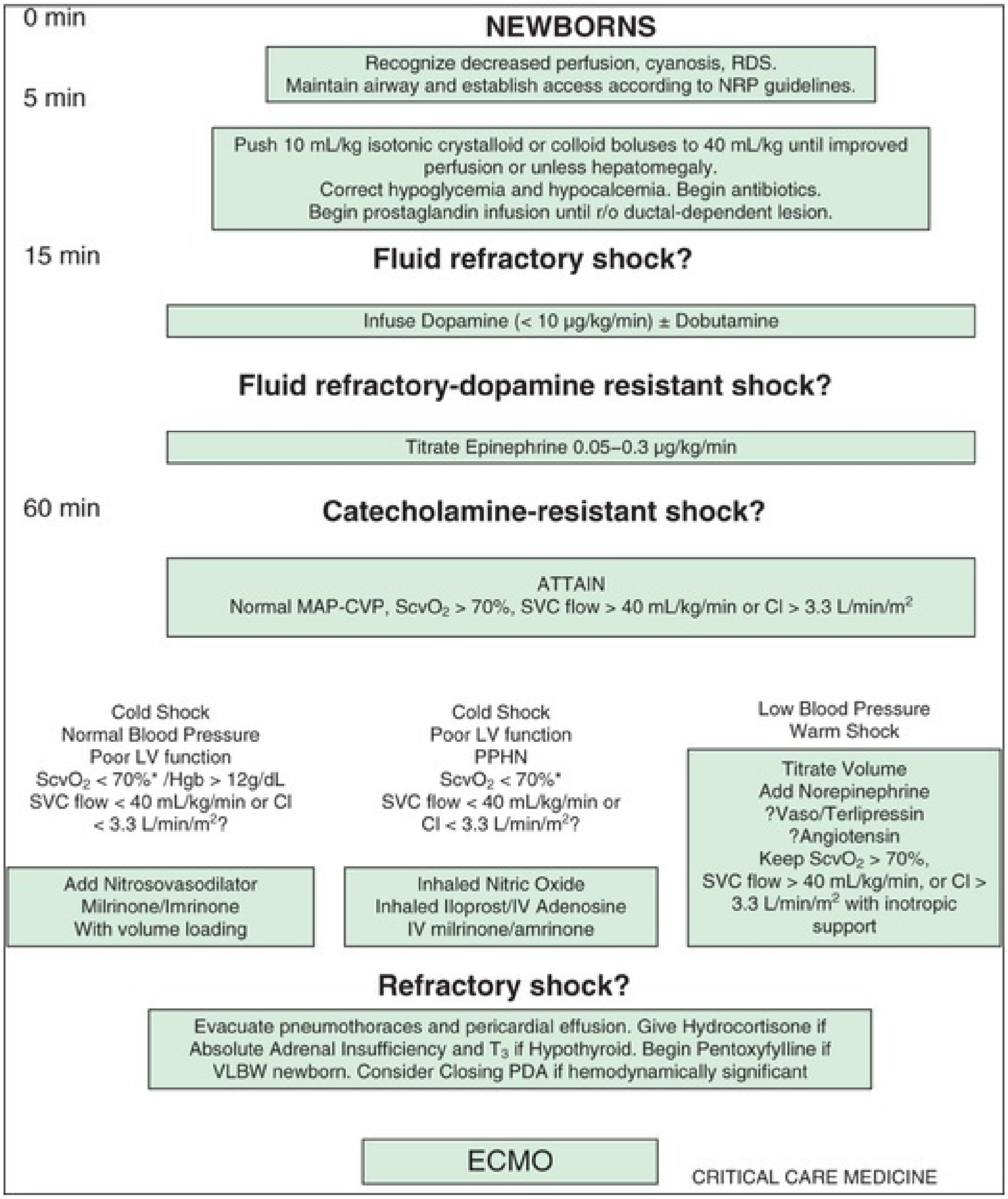
0 min
NEWBORNS
Recognize decreased perfusion, cyanosis, RDS.
Maintain airway and establish access according to NRP guidelines.
5 min
Push 10 mL/kg isotonic crystalloid or colloid boluses to 40 mL/kg until improved perfusion or unless hepatomegaly.
Correct hypoglycemia and hypocalcemia. Begin antibiotics.
Begin prostaglandin infusion until r/o ductal-dependent lesion.
15 min
Fluid refractory shock?
Infuse Dopamine (< 10 μg/kg/min) ± Dobutamine
Fluid refractory-dopamine resistant shock?
Titrate Epinephrine 0.05–0.3 μg/kg/min
60 min
Catecholamine-resistant shock?
ATTAIN
Normal MAP-CVP, $ScvO_2$ > 70%, SVC flow > 40 mL/kg/min or CI > 3.3 L/min/m^2
Cold Shock
Normal Blood Pressure
Poor LV function
$ScvO_2$ < 70%* /Hgb > 12g/dL
SVC flow < 40 mL/kg/min or CI < 3.3 L/min/m^2?
Cold Shock
Poor LV function
PPHN
$ScvO_2$ < 70%*
SVC flow < 40 mL/kg/min or CI < 3.3 L/min/m^2?
Low Blood Pressure
Warm Shock
Titrate Volume
Add Norepinephrine
?Vaso/Terlipressin
?Angiotensin
Keep $ScvO_2$ > 70%,
SVC flow > 40 mL/kg/min, or CI > 3.3 L/min/m^2 with inotropic support
Add Nitrosovasodilator
Milrinone/Imrinone
With volume loading
Inhaled Nitric Oxide
Inhaled Iloprost/IV Adenosine
IV milrinone/amrinone
Refractory shock?
Evacuate pneumothoraces and pericardial effusion. Give Hydrocortisone if Absolute Adrenal Insufficiency and T_3 if Hypothyroid. Begin Pentoxyfylline if VLBW newborn. Consider Closing PDA if hemodynamically significant
ECMO
CRITICAL CARE MEDICINE

FIG. 88.1 **American College of Critical Care Medicine algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in *newborns* . Proceed to next step if shock persists. (1) First-hour goals—restore and maintain heart rate thresholds, capillary refill ≤ 2 sec, and normal blood pressure in the 1st hr. (2) Subsequent ICU goals—restore normal perfusion pressure (mean arterial pressure – central venous pressure), preductal and postductal oxygen saturation difference < 5%, and either $ScvO_2$ > 70% (*except congenital heart patients with mixing lesions), superior vena cava flow > 40 mL/kg/min, or cardiac index > 3.3 L/min/m^2 in NICU. (From Davis AL, Carcillo JA, Aneja RK, et al: American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock, *Crit Care Med* 45:1061–1093, 2017, Fig 4.)**

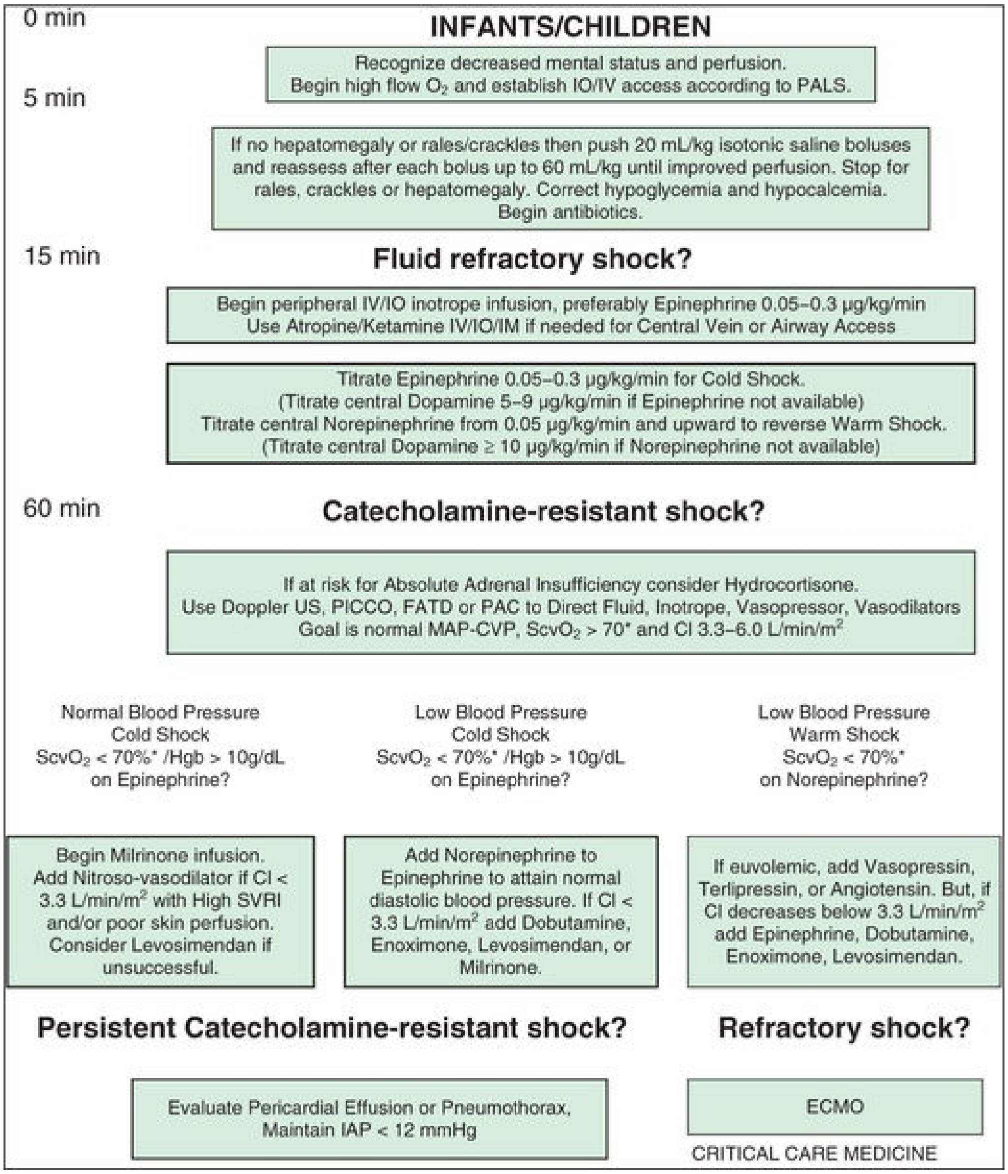

Recognize decreased mental status and perfusion. Begin high flow O_2 and establish IO/IV access according to PALS.

If no hepatomegaly or rales/crackles then push 20 mL/kg isotonic saline boluses and reassess after each bolus up to 60 mL/kg until improved perfusion. Stop for rales, crackles or hepatomegaly. Correct hypoglycemia and hypocalcemia. Begin antibiotics.

Fluid refractory shock?

Begin peripheral IV/IO inotrope infusion, preferably Epinephrine 0.05–0.3 μg/kg/min Use Atropine/Ketamine IV/IO/IM if needed for Central Vein or Airway Access

Titrate Epinephrine 0.05–0.3 μg/kg/min for Cold Shock. (Titrate central Dopamine 5–9 μg/kg/min if Epinephrine not available) Titrate central Norepinephrine from 0.05 μg/kg/min and upward to reverse Warm Shock. (Titrate central Dopamine ≥ 10 μg/kg/min if Norepinephrine not available)

Catecholamine-resistant shock?

If at risk for Absolute Adrenal Insufficiency consider Hydrocortisone. Use Doppler US, PICCO, FATD or PAC to Direct Fluid, Inotrope, Vasopressor, Vasodilators Goal is normal MAP-CVP, $ScvO_2 > 70^*$ and CI 3.3–6.0 L/min/m^2

Normal Blood Pressure Cold Shock $ScvO_2 < 70\%^*$ /Hgb > 10g/dL on Epinephrine?

Low Blood Pressure Cold Shock $ScvO_2 < 70\%^*$ /Hgb > 10g/dL on Epinephrine?

Low Blood Pressure Warm Shock $ScvO_2 < 70\%^*$ on Norepinephrine?

Begin Milrinone infusion. Add Nitroso-vasodilator if CI < 3.3 L/min/m^2 with High SVRI and/or poor skin perfusion. Consider Levosimendan if unsuccessful.

Add Norepinephrine to Epinephrine to attain normal diastolic blood pressure. If CI < 3.3 L/min/m^2 add Dobutamine, Enoximone, Levosimendan, or Milrinone.

If euvolemic, add Vasopressin, Terlipressin, or Angiotensin. But, if CI decreases below 3.3 L/min/m^2 add Epinephrine, Dobutamine, Enoximone, Levosimendan.

Persistent Catecholamine-resistant shock?

Refractory shock?

Evaluate Pericardial Effusion or Pneumothorax, Maintain IAP < 12 mmHg

ECMO

FIG. 88.2 **American College of Critical Care Medicine algorithm for time-sensitive, goal-directed stepwise management of hemodynamic support in *infants and children* . Proceed to next step if shock persists. (1) First-hour goals—restore and maintain heart rate thresholds, capillary refill ≤ 2 sec, and normal blood pressure in the 1st hr/emergency department. (2) Subsequent ICU goals—if shock not reversed, proceed to restore and maintain normal perfusion pressure (MAP – CVP) for age, $ScvO_2 > 70\%$ (*except congenital heart patients with mixing lesions), and cardiac index > 3.3 and < 6.0 L/min/m^2 in PICU. (From Davis AL, Carcillo JA, Aneja RK, et al: American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock, *Crit Care Med* 45:1061–1093, 2017, Fig 2.)**

Types of Shock

Shock classification systems generally define 5 major types of shock:

hypovolemic, cardiogenic, distributive, obstructive, and septic (Table 88.1). **Hypovolemic shock** , the most common cause of shock in children worldwide, is most frequently caused by diarrhea, vomiting, or hemorrhage. **Cardiogenic shock** is seen in patients with congenital heart disease (before or after surgery, including heart transplantation) or those with congenital or acquired cardiomyopathies, including acute myocarditis. **Obstructive shock** stems from any lesion that creates a mechanical barrier that impedes adequate cardiac output, which includes pericardial tamponade, tension pneumothorax, pulmonary embolism, and ductus-dependent congenital heart lesions. **Distributive shock** is caused by inadequate vasomotor tone, which leads to capillary leak and maldistribution of fluid into the interstitium. **Septic shock** is often discussed synonymously with distributive shock, but the septic process usually involves a more complex interaction of distributive, hypovolemic, and cardiogenic shock.

Table 88.1

Types of Shock

HYPOVOLEMIC	CARDIOGENIC	DISTRIBUTIVE	SEPTIC	OBSTRUCTIVE
Decreased preload secondary to internal or external losses	Cardiac pump failure secondary to poor myocardial function	Abnormalities of vasomotor tone from loss of venous and arterial capacitance	Encompasses multiple forms of shock Hypovolemic: third spacing of fluids into the extracellular, interstitial space Distributive: early shock with decreased afterload Cardiogenic: depression of myocardial function by endotoxins	Decreased cardiac output secondary to direct impediment to right- or left-sided heart outflow or restriction of all cardiac chambers
POTENTIAL ETIOLOGIES				
Blood loss: hemorrhage Plasma loss: burns, nephrotic syndrome Water/electrolyte loss: vomiting, diarrhea	Congenital heart disease Cardiomyopathies: infectious or acquired, dilated or restrictive Ischemia Arrhythmias	Anaphylaxis Neurologic: loss of sympathetic vascular tone secondary to spinal cord or brainstem injury Drugs	Bacterial Viral Fungal (immunocompromised patients are at increased risk)	Tension pneumothorax Pericardial tamponade Pulmonary embolism Anterior mediastinal masses Critical coarctation of aorta

Pathophysiology

An initial insult triggers shock, leading to inadequate oxygen delivery to organs and tissues. Compensatory mechanisms attempt to maintain blood pressure (BP) by increasing cardiac output and systemic vascular resistance (SVR). The body also attempts to optimize oxygen delivery to the tissues by increasing oxygen extraction and redistributing blood flow to the brain, heart, and kidneys at the expense of the skin and gastrointestinal (GI) tract. These responses lead to an initial state of **compensated shock** in which BP is maintained. If treatment is not initiated or is inadequate during this period, **decompensated shock** develops, with hypotension and tissue damage that may lead to **multisystem organ dysfunction** and, ultimately, death (Tables 88.2 and 88.3).

Table 88.2

Criteria for Organ Dysfunction

ORGAN SYSTEM	**CRITERIA FOR DYSFUNCTION**
Cardiovascular	Despite administration of isotonic intravenous fluid bolus ≥60 mL/kg in 1 hr: decrease in BP (hypotension) systolic BP <90 mm Hg, mean arterial pressure <70 mm Hg, <5th percentile for age, or systolic BP <2 SD below normal for age *or* Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) *or* Two of the following: Unexplained metabolic acidosis: base deficit >5.0 mEq/L Increased arterial lactate: >1 mmol/L or >2× upper limit of normal Oliguria: urine output <0.5 mL/kg/hr Prolonged capillary refill: >5 sec Core-to-peripheral temperature gap: >3°C (5.4°F)
Respiratory	PaO_2 /FIO_2 ratio <300 in absence of cyanotic heart disease or preexisting lung disease *or* $PaCO_2$ >65 torr or 20 mm Hg over baseline $PaCO_2$ *or* Need for >50% FIO_2 to maintain saturation ≥92% *or* Need for nonelective invasive or noninvasive mechanical ventilation
Neurologic	GCS score ≤11 *or* Acute change in mental status with decrease in GCS score ≥3 points from abnormal baseline
Hematologic	Platelet count <100,000/mm^3 or decline of 50% in platelet count from highest value recorded over last 3 days (for patients with chronic hematologic or oncologic disorders) *or* INR >1.5 *or* Activated prothrombin time >60 sec
Renal	Serum creatinine >0.5 mg/dL, ≥2× upper limit of normal for age, or 2-fold increase in baseline creatinine value

Hepatic	Total bilirubin ≥4 mg/dL (not applicable for newborn) Alanine transaminase level 2× upper limit of normal for age

BP, Blood pressure; FIO_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; INR, international normalized ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, partial pressure arterial oxygen; SD, standard deviations.

Table 88.3

Signs of Decreased Perfusion

ORGAN SYSTEM	↓ PERFUSION	↓↓ PERFUSION	↓↓↓ PERFUSION
Central nervous system	—	Restless, apathetic, anxious	Agitated/confused, stuporous, coma
Respiration	—	↑ Ventilation	↑↑ Ventilation
Metabolism	—	Compensated metabolic acidemia	Uncompensated metabolic acidemia
Gut	—	↓ Motility	Ileus
Kidney	↓ Urine volume	Oliguria (<0.5 mL/kg/hr)	Oliguria/anuria
	↑ Urinary specific gravity		
Skin	Delayed capillary refill	Cool extremities	Mottled, cyanotic, cold extremities
Cardiovascular system	↑ Heart rate	↑↑ Heart rate	↑↑ Heart rate
		↓ Peripheral pulses	↓ Blood pressure, central pulses only

In the early phases of shock, multiple compensatory physiologic mechanisms act to maintain BP and preserve tissue perfusion and oxygen delivery. Cardiovascular effects include increases in heart rate (HR), stroke volume, and vascular smooth muscle tone, which are regulated through sympathetic nervous system activation and neurohormonal responses. Respiratory compensation involves greater carbon dioxide (CO_2) elimination in response to the metabolic acidosis and increased CO_2 production from poor tissue perfusion. Renal excretion of hydrogen ions (H^+) and retention of bicarbonate (HCO_3^-) also increase in an effort to maintain normal body pH (see Chapter 68.7). Maintenance of intravascular volume is facilitated via sodium regulation through the renin-angiotensin-aldosterone and atrial natriuretic factor axes, cortisol and catecholamine synthesis and release, and antidiuretic hormone secretion. Despite these compensatory mechanisms, the underlying shock and host response lead to vascular endothelial cell injury and significant leakage of intravascular fluids into the interstitial extracellular space.

Another important aspect of the initial pathophysiology of shock is the impact on cardiac output. All forms of shock affect cardiac output through several mechanisms, with changes in HR, preload, afterload, and myocardial contractility occurring separately or in combination (Table 88.4). **Hypovolemic shock** is characterized primarily by fluid loss and decreased preload. Tachycardia and an increase in SVR are the initial compensatory responses to maintain cardiac output and systemic BP. Without adequate volume replacement, hypotension develops, followed by tissue ischemia and further clinical deterioration. When there is preexisting low plasma oncotic pressure (caused by nephrotic syndrome, malnutrition, hepatic dysfunction, acute severe burns, etc.), even further volume loss and exacerbation of shock may result from endothelial breakdown and worsening capillary leak.

Table 88.4

Pathophysiology of Shock

Extracorporeal Fluid Loss

Hypovolemic shock may be a result of direct blood loss through hemorrhage or abnormal loss of body fluids (diarrhea, vomiting, burns, diabetes mellitus or insipidus, nephrosis).

Lowering Plasma Oncotic Forces

Hypovolemic shock may also result from hypoproteinemia (liver injury, or as a progressive complication of increased capillary permeability).

Abnormal Vasodilation

Distributive shock (neurogenic, anaphylaxis, or septic shock) occurs when there is loss of vascular tone—venous, arterial, or both (sympathetic blockade, local substances affecting permeability, acidosis, drug effects, spinal cord transection).

Increased Vascular Permeability

Sepsis may change the capillary permeability in the absence of any change in capillary hydrostatic pressure (endotoxins from sepsis, excess histamine release in anaphylaxis).

Cardiac Dysfunction

Peripheral hypoperfusion may result from any condition that affects the heart's ability to pump blood efficiently (ischemia, acidosis, drugs, constrictive pericarditis, pancreatitis, sepsis).

In contrast, the underlying pathophysiologic mechanism leading to **distributive shock** is a state of abnormal vasodilation and decreased SVR. Sepsis, hypoxia, poisoning, anaphylaxis, spinal cord injury, or mitochondrial dysfunction can cause *vasodilatory shock* (Fig. 88.3). The lowering of SVR is accompanied initially by a maldistribution of blood flow away from vital organs and a compensatory increase in cardiac output. This process leads to significant decreases in both preload and afterload. Therapies for distributive shock must address both these problems simultaneously.

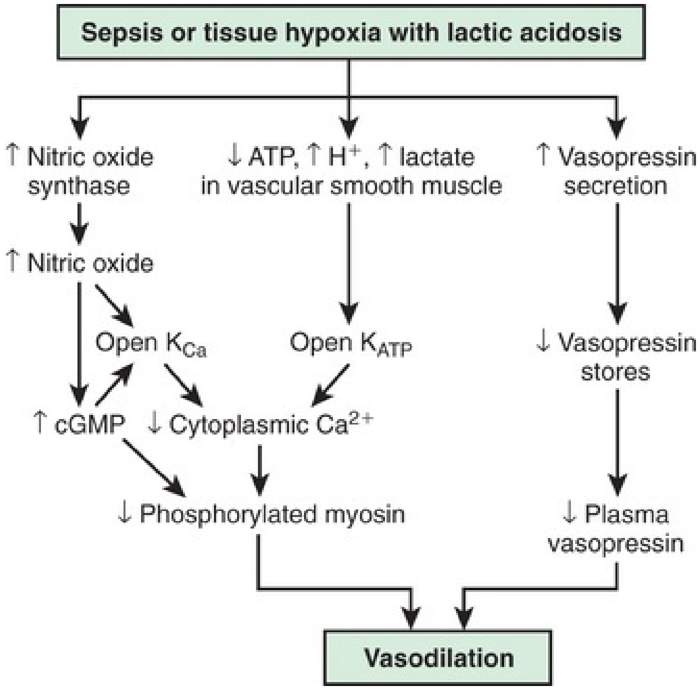
Sepsis or tissue hypoxia with lactic acidosis
↑ Nitric oxide synthase
↓ ATP, ↑ H⁺, ↑ lactate in vascular smooth muscle
↑ Vasopressin secretion
↑ Nitric oxide
Open K_Ca
Open K_ATP
↓ Vasopressin stores
↑ cGMP
↓ Cytoplasmic Ca²⁺
↓ Phosphorylated myosin
↓ Plasma vasopressin
Vasodilation

FIG. 88.3 **Mechanisms of vasodilatory shock. Septic shock and states of prolonged shock causing tissue hypoxia with lactic acidosis increase nitric oxide synthesis, activate the adenosine triphosphate (ATP)–sensitive and calcium-regulated potassium channels (K_{ATP} and K_{Ca} , respectively) in vascular smooth muscle, and lead to depletion of vasopressin. cGMP, Cyclic guanosine monophosphate. (From Landry DW, Oliver JA:**

The pathogenesis of vasodilatory shock, *N Engl J Med* 345:588.595, 2001.)

Cardiogenic shock may be seen in patients with myocarditis, cardiomyopathy, arrhythmias and congenital heart disease (generally following cardiac surgery) (see Chapter 461). In these patients, myocardial contractility is affected, leading to systolic and/or diastolic dysfunction. The later phases of all forms of shock frequently have a negative impact on the myocardium, leading to development of a cardiogenic component to the initial shock state.

Septic shock is generally a unique combination of distributive, hypovolemic, and cardiogenic shock. Hypovolemia from intravascular fluid losses occurs through capillary leak. Cardiogenic shock results from the myocardial-depressant effects of sepsis, and distributive shock is the result of decreased SVR. The degree to which a patient exhibits each of these responses varies, but there are frequently alterations in preload, afterload, and myocardial contractility.

In septic shock, it is important to distinguish between the inciting infection and the host inflammatory response. Normally, host immunity prevents the development of sepsis through activation of the reticular endothelial system along with the cellular and humoral immune systems. This host immune response produces an *inflammatory cascade* of toxic mediators, including hormones, cytokines, and enzymes. If this inflammatory cascade is uncontrolled, derangement of the microcirculatory system leads to subsequent organ and cellular dysfunction.

The **systemic inflammatory response syndrome** (**SIRS**) is an inflammatory cascade that is initiated by the host response to an infectious or noninfectious trigger (Table 88.5). This inflammatory cascade is triggered when the host defense system does not adequately recognize and/or eliminate the triggering event. The inflammatory cascade initiated by shock can lead to hypovolemia, cardiac and vascular failure, acute respiratory distress syndrome (ARDS), insulin resistance, decreased cytochrome P450 activity (decreased steroid synthesis), coagulopathy, and unresolved or secondary infection. Tumor necrosis factor (TNF) and other inflammatory mediators increase vascular permeability, causing diffuse capillary leak, decreased vascular tone, and an imbalance between perfusion and metabolic demands of the tissues. TNF and interleukin (IL)-1 stimulate the release of proinflammatory and antiinflammatory mediators, causing fever and vasodilation. Proinflammatory mediators include IL-6, IL-12, interferon-γ, and macrophage migration inhibitory factor; antiinflammatory cytokines include IL-10, transforming growth factor-β, and IL-4. Arachidonic acid metabolites lead to the development of fever, tachypnea, ventilation-perfusion abnormalities, and lactic acidosis. Nitric oxide (NO), released from the endothelium or inflammatory cells, is a major contributor to hypotension. Myocardial depression is caused directly by myocardial-depressant factors, TNF, and some interleukins and is further depressed by depleted catecholamines, increased β-endorphin, and production of myocardial NO.

Table 88.5

Differential Diagnosis of Systemic Inflammatory Response Syndrome (SIRS)

Infection

Bacteremia or meningitis (*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis*, group A streptococcus, *Staphylococcus aureus*)
Viral illness (influenza, enteroviruses, hemorrhagic fever group, herpes simplex virus, respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus)
Encephalitis (arboviruses, enteroviruses, herpes simplex virus)
Rickettsiae (Rocky Mountain spotted fever, *Ehrlichia,* Q fever)
Syphilis
Vaccine reaction (pertussis, influenza, measles)
Toxin-mediated reaction (toxic shock, staphylococcal scalded skin syndrome)

Cardiopulmonary

Pneumonia (bacteria, virus, mycobacteria, fungi, allergic reaction)
Pulmonary emboli
Heart failure
Arrhythmia
Pericarditis
Myocarditis

Metabolic-Endocrine

Adrenal insufficiency (adrenogenital syndrome, Addison disease, corticosteroid withdrawal)
Electrolyte disturbances (hypo- or hypernatremia; hypo- or hypercalcemia)
Diabetes insipidus
Diabetes mellitus
Inborn errors of metabolism (organic acidosis, urea cycle, carnitine deficiency, mitochondrial disorders)
Hypoglycemia
Reye syndrome

Gastrointestinal

Gastroenteritis with dehydration
Volvulus
Intussusception
Appendicitis
Peritonitis (spontaneous, associated with perforation or peritoneal dialysis)
Necrotizing enterocolitis
Hepatitis
Hemorrhage
Pancreatitis

Hematologic

Anemia (sickle cell disease, blood loss, nutritional)
Methemoglobinemia
Splenic sequestration crisis
Leukemia or lymphoma
Hemophagocytic syndromes

Neurologic

Intoxication (drugs, carbon monoxide, intentional or accidental overdose)

Intracranial hemorrhage
Infant botulism
Trauma (child abuse, accidental)
Guillain-Barré syndrome
Myasthenia gravis

Other

Anaphylaxis (food, drug, insect sting)
Hemolytic-uremic syndrome
Kawasaki disease
Erythema multiforme
Hemorrhagic shock–encephalopathy syndrome
Poisoning
Toxic envenomation
Macrophage activation syndrome
Idiopathic systemic capillary leak (Clarkson) syndrome

The inflammatory cascade is initiated by toxins or superantigens through macrophage binding or lymphocyte activation (Fig. 88.4). The vascular endothelium is both a target of tissue injury and a source of mediators that may cause further injury. Biochemical responses include the production of arachidonic acid metabolites, release of myocardial-depressant factors and endogenous opiates, activation of the complement system, and production and release of other mediators, which may be proinflammatory or antiinflammatory. The balance among these mediator groups for an individual patient contributes to the progression (and resolution) of disease and affects the prognosis.

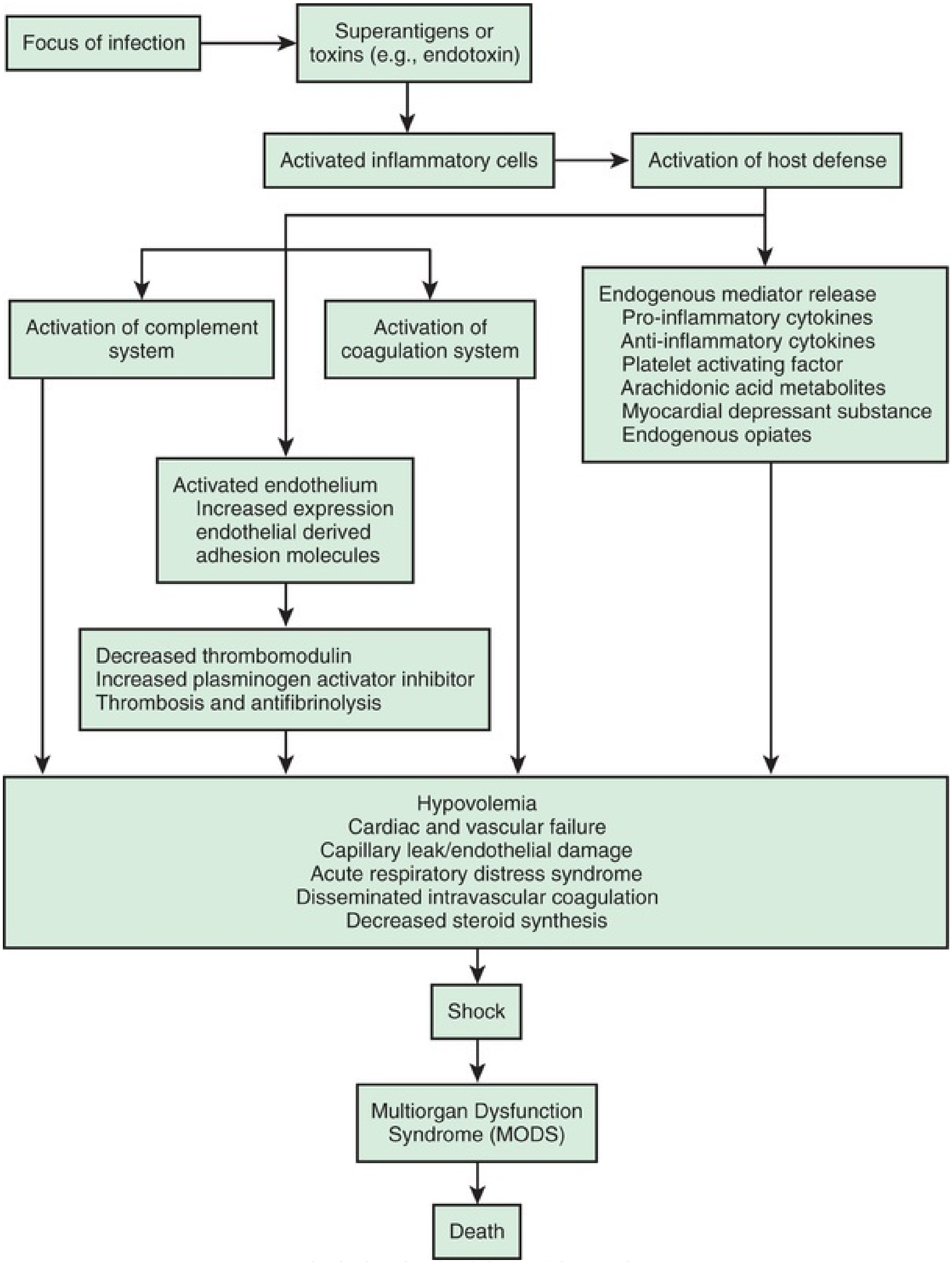
Focus of infection
Superantigens or toxins (e.g., endotoxin)
Activated inflammatory cells
Activation of host defense
Activation of complement system
Activation of coagulation system
Endogenous mediator release
Pro-inflammatory cytokines
Anti-inflammatory cytokines
Platelet activating factor
Arachidonic acid metabolites
Myocardial depressant substance
Endogenous opiates
Activated endothelium
Increased expression endothelial derived adhesion molecules
Decreased thrombomodulin
Increased plasminogen activator inhibitor
Thrombosis and antifibrinolysis
Hypovolemia
Cardiac and vascular failure
Capillary leak/endothelial damage
Acute respiratory distress syndrome
Disseminated intravascular coagulation
Decreased steroid synthesis
Shock
Multiorgan Dysfunction Syndrome (MODS)
Death

FIG. 88.4 Hypothetical pathophysiology of the septic process.

Clinical Manifestations

Table 88.1 shows a classification system for shock. Categorization is important, but there may be significant overlap among these groups, especially in septic shock. The clinical presentation of shock depends in part on the underlying etiology, but if unrecognized and untreated, all forms of shock follow a common and untoward progression of clinical signs and pathophysiologic changes that may ultimately lead to irreversible organ injury and death.

Shock may initially manifest as only tachycardia, with or without tachypnea. Progression leads to decreased urine output, poor peripheral perfusion, respiratory distress or failure, alteration of mental status, and low BP (see Table 88.3). A significant misconception is that shock occurs only with low BP; hypotension is often a late finding and is not a criterion for the diagnosis of shock because of a complex set of compensatory mechanisms that attempt to preserve BP and peripheral perfusion. Hypotension reflects an advanced state of decompensated shock and is associated with increased morbidity and mortality.

Hypovolemic shock often manifests initially as orthostatic hypotension and is associated with dry mucous membranes, dry axillae, poor skin turgor, and decreased urine output. Depending on the degree of dehydration, the patient with hypovolemic shock may present with either normal or slightly cool distal extremities, and pulses may be normal, decreased, or absent depending on disease severity. The presenting signs of **cardiogenic shock** are tachypnea, cool extremities, delayed capillary filling time, poor peripheral and/or central pulses, declining mental status, and decreased urine output caused by the combination of decreased cardiac output and compensatory peripheral vasoconstriction (see Chapter 469.1). **Obstructive shock** often also manifests as inadequate cardiac output because of a physical restriction of forward blood flow, and the acute presentation may quickly progress to cardiac arrest. **Distributive shock** manifests initially as peripheral vasodilation and increased but inadequate cardiac output.

Regardless of etiology, uncompensated shock, with hypotension, high SVR, decreased cardiac output, respiratory failure, obtundation, and oliguria, occurs late in the progression of disease. Table 88.6 lists the hemodynamic findings in various shock states. Additional clinical findings in shock include cutaneous lesions such as petechiae, diffuse erythema, ecchymoses, ecthyma gangrenosum, and peripheral gangrene. Jaundice can be present either as a sign of infection or as a result of MODS.

Table 88.6

Hemodynamic Variables in Different Shock States

TYPE OF SHOCK	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE	MEAN ARTERIAL PRESSURE	CAPILLARY WEDGE PRESSURE	CENTRAL VENOUS PRESSURE
Hypovolemic	↓	↑	↔ or ↓	↓↓↓	↓↓↓
Cardiogenic[*]					
Systolic	↓↓	↑↑↑	↔ or ↓	↑↑	↑↑
Diastolic	↔	↑↑	↔	↑↑	↑
Obstructive	↓	↑	↔ or ↓	↑↑ [†]	↑↑ [†]
Distributive	↑↑	↓↓↓	↔ or ↓	↔ or ↓	↔ or ↓
Septic					
Early	↑↑↑	↓↓↓	↔ or ↓ [‡]	↓	↓
Late	↓↓	↓↓	↓↓	↑	↑ or ↔

[*] Systolic or diastolic dysfunction.

[†] Wedge pressure, central venous pressure, and pulmonary artery diastolic pressures are equal.

[‡] Wide pulse pressure.

Sepsis is defined as SIRS resulting from a suspected or proven infectious etiology. The clinical spectrum of sepsis begins when a *systemic* (e.g., bacteremia, rickettsial disease, fungemia, viremia) or *localized* (e.g., meningitis, pneumonia, pyelonephritis, peritonitis, necrotizing fasciitis) infection progresses from sepsis to **severe sepsis** (i.e., presence of sepsis combined with organ dysfunction). Further clinical deterioration leads to **septic shock** (severe sepsis plus the persistence of hypoperfusion or hypotension despite adequate fluid resuscitation or a requirement for vasoactive agents), MODS, and possibly death (Table 88.7). This is a complex spectrum of clinical problems that is a leading cause of mortality in children worldwide. Mortality can be mitigated and outcomes improved with early recognition and treatment.

Table 88.7

International Consensus Definitions for Pediatric Sepsis

Infection

Suspected or proven infection or a clinical syndrome associated with high probability of infection.

Systemic Inflammatory Response Syndrome (SIRS)

Two of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count:

1. Core temperature >38.5°C (101.3°F) or <36°C (96.8°F) (rectal, bladder, oral, or central catheter)
2. Tachycardia:

   Mean heart rate >2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli

   or

   Unexplained persistent elevation over 0.5-4 hr

   or

   In children <1 yr old, persistent bradycardia over 0.5 hr (mean heart rate <10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease)
3. Respiratory rate >2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia
4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils

Sepsis

SIRS plus a suspected or proven infection

Severe Sepsis

Sepsis plus 1 of the following:

1. Cardiovascular organ dysfunction, defined as:

   Despite >40 mL/kg of isotonic intravenous fluid in 1 hr:

   - Hypotension <5th percentile for age or systolic blood pressure <2 SD below normal for age

   or

   - Need for vasoactive drug to maintain blood pressure

   or

   Two of the following:

   - Unexplained metabolic acidosis: base deficit >5 mEq/L

- Increased arterial lactate: >2 times upper limit of normal
- Oliguria: urine output <0.5 mL/kg/hr
- Prolonged capillary refill: >5 sec
- Core-to-peripheral temperature gap: >3°C (5.4°F)

2. Acute respiratory distress syndrome (ARDS), as defined by the presence of a PaO_2/FIO_2 ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left-sided heart failure.

or

Sepsis plus ≥2 organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic).

Septic Shock

Sepsis plus cardiovascular organ dysfunction as defined above.

Multiple-Organ Dysfunction Syndrome (MODS)

Presence of altered organ function such that homeostasis cannot be maintained without medical intervention.

FIO_2, Fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; SD, standard deviations.

Although **septic shock** is primarily distributive in nature, multiple other elements of pathophysiology are represented in this disease process. The initial signs and symptoms of sepsis include alterations in temperature regulation (hyperthermia or hypothermia), tachycardia, and tachypnea. In the early stages (hyperdynamic phase, low SVR, or *warm* shock), cardiac output increases to maintain adequate oxygen delivery and meet the greater metabolic demands of the organs and tissues. As septic shock progresses, cardiac output falls in response to the effects of numerous inflammatory mediators, leading to a compensatory elevation in SVR and the development of *cold* shock.

Diagnosis

Shock is a clinical diagnosis based on a thorough history and physical examination (see Tables 88.2 and 88.3). Septic shock has a specific consensus conference definition (see Table 88.7). In cases of suspected septic shock, an infectious etiology should be sought through culture of clinically appropriate specimens and prompt initiation of empirical antimicrobial therapy based on patient age, underlying disease, and geographic location, recognizing that time is necessary for incubation of cultures, and results often are not positive. Additional evidence for identifying an infectious etiology as the cause of SIRS includes physical examination findings, imaging, presence of white blood cells in normally sterile body fluids, and suggestive rashes such as petechiae and purpura. Affected children should be admitted to a PICU or other highly monitored environment as indicated by clinical status and the resources of the medical facility. These patients necessitate continuous monitoring, with a combination of noninvasive (e.g., pulse oximetry, capnography, near-infrared spectroscopy) and invasive (e.g., central venous pressure, arterial BP) techniques as clinically indicated.

Laboratory Findings

Laboratory findings often include evidence of hematologic abnormalities and electrolyte disturbances. Hematologic abnormalities may include thrombocytopenia, prolonged prothrombin and partial thromboplastin times, reduced serum fibrinogen level, elevation of fibrin split products, and anemia. Elevated neutrophil counts and increased immature forms (i.e., bands, myelocytes, promyelocytes), vacuolation of neutrophils, toxic granulations, and Döhle bodies can be seen with infection. Neutropenia or leukopenia may be an ominous sign of overwhelming sepsis.

Glucose dysregulation, a common stress response, may manifest as hyperglycemia or hypoglycemia. Other electrolyte abnormalities are hypocalcemia, hypoalbuminemia, and metabolic acidosis. Renal and/or hepatic function may also be abnormal. Patients with ARDS or pneumonia have impairment of oxygenation (decreased partial pressure of arterial oxygen [$Pa{O_2}$]) as well as of ventilation (increased arterial partial pressure of carbon dioxide [$Pa{CO_2}$]) in the later stages of lung injury (see Chapter 89).

The hallmark of *uncompensated* shock is an imbalance between oxygen delivery ($D{O_2}$) and oxygen consumption ($V{O_2}$). Oxygen delivery normally exceeds oxygen consumption by threefold. The oxygen extraction ratio is approximately 25%, thus producing a normal mixed venous oxygen saturation (SvO_2) of approximately 75%. A falling SvO_2 value, as measured by cooximetry reflects an increasing oxygen extraction ratio and documents a decrease in oxygen delivery relative to consumption. This increase in oxygen extraction by the end organs is an attempt to maintain adequate oxygen delivery at the cellular level. This state is manifested clinically by increased lactic acid production (e.g., high anion gap, metabolic acidosis) caused by anaerobic metabolism and a compensatory increase in tissue oxygen extraction. The gold standard measurement of SvO_2 is from a pulmonary arterial catheter, but measurements from this location are often not clinically feasible. Sites such as the right ventricle, right atrium, superior vena cava ($SvCO_2$), or inferior vena cava can be as surrogate measures of mixed venous blood to follow the adequacy of oxygen delivery and effectiveness of therapeutic interventions. *Elevated blood lactate levels reflect poor tissue oxygen delivery noted in all forms of shock.*

Treatment

Initial Management

Early recognition and prompt intervention are extremely important in the management of all forms of shock (Tables 88.8 to 88.12 ; see Figs. 88.1 and 88.2). *The vital sign targets and dose recommendations in Tables 88.9 to 88.12 should be adjusted to pediatric-size patients.* Baseline mortality is much lower in pediatric shock than in adult shock, and further improvements in mortality are associated with early interventions (see Fig. 81.1). The initial assessment and treatment of the pediatric shock patient should include stabilization of airway, breathing, and circulation as established by the American Heart Association's pediatric advanced life support and neonatal advanced life support guidelines (see Chapter 81). Depending on the severity of shock, further airway intervention, including intubation and mechanical ventilation, may be necessary to lessen the work of breathing and decrease the body's overall metabolic demands.

Table 88.8

Goal-Directed Therapy of Organ System Dysfunction in

Shock

SYSTEM	DISORDERS	GOALS	THERAPIES
Respiratory	Acute respiratory distress syndrome	Prevent/treat: hypoxia and respiratory acidosis	Oxygen Noninvasive ventilation
	Respiratory muscle fatigue Central apnea	Prevent barotrauma Decrease work of breathing	Early endotracheal intubation and mechanical ventilation
			Positive end-expiratory pressure (PEEP) Permissive hypercapnia High-frequency ventilation Extracorporeal membrane oxygenation (ECMO)
Renal	Prerenal failure Renal failure	Prevent/treat: hypovolemia, hypervolemia, hyperkalemia, metabolic acidosis, hypernatremia/hyponatremia, and hypertension Monitor serum electrolytes	Judicious fluid resuscitation Establishment of normal urine output and blood pressure for age Furosemide (Lasix) Dialysis, ultrafiltration, hemofiltration
Hematologic	Coagulopathy (disseminated intravascular coagulation)	Prevent/treat: bleeding	Vitamin K Fresh-frozen plasma Platelets
	Thrombosis	Prevent/treat: abnormal clotting	Heparinization
Gastrointestinal	Stress ulcers Ileus	Prevent/treat: gastric bleeding Avoid aspiration, abdominal distention	Histamine H_2 -receptor–blocking agents or proton pump inhibitors Nasogastric tube
	Bacterial translocation	Avoid mucosal atrophy	Early enteral feedings
Endocrine	Adrenal insufficiency, primary or secondary to chronic steroid therapy	Prevent/treat: adrenal crisis	Stress-dose steroids in patients previously given steroids Physiologic dose for presumed primary insufficiency in sepsis
Metabolic	Metabolic acidosis	Correct etiology Normalize pH	Treatment of hypovolemia (fluids), poor cardiac function (fluids, inotropic agents) Improvement of renal acid excretion Low-dose (0.5-2.0 mEq/kg) sodium bicarbonate if patient is not showing response, pH <7.1, and ventilation (CO_2 elimination) is adequate

Table 88.9

Recommendations for Shock: Initial Resuscitation and Infection Issues—Adults

Initial Resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). Goals during the 1st 6 hr of resuscitation:
    a. Central venous pressure 8-12 mm Hg
    b. Mean arterial pressure (MAP) ≥65 mm Hg
    c. Urine output ≥0.5 mL kg^{-1} hr
    d. Central venous (superior vena cava) or mixed venous oxygen saturation: 70% or 65%, respectively
2. In patients with elevated lactate levels, targeting resuscitation to normalize lactate as rapidly as possible.

Screening for Sepsis and Performance Improvement

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy.
2. Hospital-based performance improvement efforts in severe sepsis.

Diagnosis

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (>45 min) in the start of antimicrobial(s). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) should be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hr) inserted.
2. Use of the 1,3 β-D -glucan assay, mannan and antimannan antibody assays, if available, and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection.

Antimicrobial Therapy

1. Administration of effective intravenous antimicrobials within the 1st hr of

recognition of septic shock and severe sepsis without septic shock as the goal of therapy.

2a. Initial empirical antiinfective therapy of 1 or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis.

2b. Antimicrobial regimen should be reassessed daily for potential deescalation.

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empirical antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection.

4a. Combination empirical therapy for neutropenic patients with severe sepsis and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp.

    For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended-spectrum β-lactam and either an aminoglycoside or a fluoroquinolone is for *Pseudomonas aeruginosa* bacteremia. A combination of β-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections.

4b. Empirical combination therapy should not be administered for more than 3-5 days. Deescalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.

5. Duration of therapy typically 7-10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus* , some fungal and viral infections, or immunodeficiencies (e.g., neutropenia).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin.

7. Antimicrobial agents should *not* be used in patients with severe inflammatory states determined to be of noninfectious cause.

Source Control

1. A specific anatomic diagnosis of infection requiring consideration for

emergent source control should be sought and diagnosed or excluded as rapidly as possible, and intervention undertaken for source control within the 1st 12 hr after the diagnosis is made, if feasible.
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred.
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, these should be removed promptly after other vascular access has been established.

Infection Prevention

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; this infection control measure can then be instituted in healthcare settings and regions where this methodology is found to be effective.

1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012, *Crit Care Med* 41(2):580–637, 2013 (Table 5, p 589).

Table 88.10

Surviving Sepsis Campaign: Care Bundles

To be completed within 3 hr:

1. Measure lactate level.
2. Obtain blood cultures before administration of antibiotics.
3. Administer broad-spectrum antibiotics.
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L.

To completed within 6 hr:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg.
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
    Measure central venous pressure (CVP).*
    Measure central venous oxygen saturation ($ScvO_2$).*
7. Remeasure lactate if initial lactate was elevated.*

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[*] Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $ScvO_2$ of ≥70%, and normalization of lactate.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving Sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 41(2):580–637, 2013 (Fig 1, p 591).

Table 88.11

Recommendations for Shock: Hemodynamic Support and Adjunctive Therapy—Adults

Fluid Therapy of Severe Sepsis

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock.
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock.
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids.
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia, to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients.
5. Fluid challenge technique be applied in which fluid administration is continued as long as there is hemodynamic improvement either based on

dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables.

Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg.
2. Norepinephrine as the first-choice vasopressor.
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure.
4. Vasopressin 0.03 units/min can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage.
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension, and vasopressin doses >0.03-0.04 units/min should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).
6. Dopamine as an alternative vasopressor agent to NE only in highly selected patients (e.g., with low risk of tachyarrhythmias and absolute or relative bradycardia).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) NE is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target.
8. Low-dose dopamine should not be used for renal protection.
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available.

Inotropic Therapy

1. A trial of dobutamine infusion up to 20 µg/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.
2. Not using a strategy to increase cardiac index to predetermined

supranormal levels.

Corticosteroids

1. Not using intravenous hydrocortisone to treat adult septic shock patients, if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In the event this is not achievable, we suggest IV hydrocortisone alone at a dose of 200 mg/day.
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone.
3. In treated patients, hydrocortisone tapered when vasopressors are no longer required.
4. Corticosteroids should *not* be administered for the treatment of sepsis in the absence of shock.
5. When hydrocortisone is given, use continuous flow.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving Sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012, *Crit Care Med* 41(2):580–637, 2013 (Table 6, p 596).

Table 88.12

Recommendations for Shock: Special Considerations in Pediatric Patients

Initial Resuscitation

1. For respiratory distress and hypoxemia, start with face mask oxygen or, if needed and available, high-flow nasal cannula oxygen or nasopharyngeal CPAP (NP CPAP). For improved circulation, peripheral intravenous access or intraosseous access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required, cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation.
2. Initial therapeutic end-points of resuscitation of septic shock: capillary refill of ≤2 sec, normal blood pressure for age, normal pulses with no

differential between peripheral and central pulses, warm extremities, urine output >1 mL kg^{-1} hr^{-1} , and normal mental status. Scv_{O_2} saturation ≥70% and cardiac index between 3.3 and 6.0 L/min/m^2 should be targeted thereafter.
3. Follow American College of Critical Care Medicine–Pediatric Advanced Life Support (ACCM-PALS) guidelines for the management of septic shock.
4. Evaluate for and reverse pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock.

Antibiotics and Source Control

1. Empirical antibiotics should be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible, but this should not delay administration of antibiotics. The empirical drug choice should be changed as epidemic and endemic ecologies dictate (e.g., H1N1, methicillin-resistant *Staphylococcus aureus* [MRSA], chloroquine-resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia).
2. Clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension.
3. Early and aggressive source control.
4. *Clostridium difficile* colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease.

Fluid Resuscitation

1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystalloids or albumin with boluses of up to 20 mL/kg crystalloids (or albumin equivalent) over 5-10 min, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales present, inotropic support should be implemented, not fluid resuscitation. In

nonhypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises), blood transfusion is considered superior to crystalloid or albumin bolus.

Inotropes, Vasopressors, and Vasodilators

1. Begin peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation.
2. Patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure should be given vasodilator therapies in addition to inotropes.

Extracorporeal Membrane Oxygenation

1. Consider ECMO for refractory pediatric septic shock and respiratory failure.

Corticosteroids

1. Timely hydrocortisone therapy in children with fluid-refractory, catecholamine-resistant shock and suspected or proven absolute (classic) adrenal insufficiency.

Protein C and Activated Protein Concentrate

No recommendations (no longer available).

Blood Products and Plasma Therapies

1. Similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (<70%), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia, a lower target (>7.0 g/dL) can be considered reasonable.
2. Similar platelet transfusion targets in children as in adults.

3. Use plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura.

Mechanical Ventilation

1. Lung-protective strategies during mechanical ventilation.

Sedation, Analgesia, and Drug Toxicities

1. We recommend use of sedation with a sedation goal in critically ill, mechanically ventilated patients with sepsis.
2. Monitor drug toxicity lab results because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events.

Glycemic Control

1. Control hyperglycemia using a similar target as in adults (≤180 mg/dL). Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant.

Diuretics and Renal Replacement Therapy

1. Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful, use continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent >10% total body weight fluid overload.

Deep Vein Thrombosis (DVT) Prophylaxis

No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.

Stress Ulcer (SU) Prophylaxis

No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis.

Nutrition

1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

CPAP, Continuous positive airway pressure.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving Sepsis campaign: *I* nternational guidelines for management of severe sepsis and septic shock: 2012, *Crit Care Med* 41(2):580–637, 2013 (Table 9, p 614).

Given the predominance of sepsis and hypovolemia as the most common causes of shock in the pediatric population, most therapeutic regimens are based on guidelines established in these settings. Immediately following establishment of intravenous (IV) or intraosseous (IO) access, aggressive, early goal-directed therapy should be initiated unless there are significant concerns for cardiogenic shock as an underlying pathophysiology. Rapid IV administration of 20 mL/kg isotonic fluid should be initiated to reverse the shock state. This bolus should be repeated quickly up to 60-80 mL/kg; it is not unusual for severely affected patients to require this volume within the 1st 3 hr of treatment.

Rapid fluid resuscitation totaling 60-80 mL/kg or more is associated with improved survival without an increased incidence of pulmonary edema. Fluid resuscitation in increments of 20 mL/kg should be titrated to normalize HR (according to age-based HRs), urine output (to 1 mL/kg/hr), capillary refill time (to <2 sec), and mental status. If shock remains refractory following 60-80 mL/kg of volume resuscitation, vasopressor therapy (e.g., norepinephrine, epinephrine) should be instituted while additional fluids are administered. Pediatric guidelines for septic shock unresponsive to fluid resuscitation suggest epinephrine (Fig. 88.2) or dopamine (Fig. 88.1), whereas adult guidelines recommend norepinephrine.

Fluid resuscitation may sometimes require as much as 200 mL/kg or greater. It must be stressed that hypotension is often a late and ominous finding, and BP normalization alone is not a reliable end-point for assessing the effectiveness of resuscitation. Although the type of fluid (crystalloid vs colloid) is an area of ongoing debate, fluid resuscitation (usually crystalloid) in the 1st hr is unquestionably essential to survival in septic shock, regardless of the fluid type administered.

Additional Early Considerations

In **septic shock** specifically, early (*within 1 hr*) administration of broad-spectrum antimicrobial agents is associated with a reduction in mortality. The choice of antimicrobial agents depends on the predisposing risk factors and the clinical situation. Bacterial resistance patterns in the community and/or hospital should be considered in the selection of optimal antimicrobial therapy. Neonates should be treated with ampicillin plus cefepime and/or gentamicin. Acyclovir should be added if herpes simplex virus is suspected clinically. In infants and children, community-acquired infections with *Neisseria meningitidis* can initially be treated empirically with a third-generation cephalosporin (e.g., ceftriaxone, cefepime), as can *Haemophilus influenzae* infections. The prevalence of resistant *Streptococcus pneumoniae* requires the addition of vancomycin. Suspicion of community- or hospital-acquired, methicillin-resistant *Staphylococcus aureus* (MRSA) infection warrants coverage with vancomycin, depending on local resistance patterns. If an intraabdominal process is suspected, anaerobic coverage should be included with an agent such as metronidazole, clindamycin, or piperacillin-tazobactam.

Nosocomial sepsis should generally be treated with at least a third- or fourth-generation cephalosporin or a penicillin with an extended gram-negative spectrum (e.g., piperacillin-tazobactam). An aminoglycoside should be added as the clinical situation warrants. Vancomycin should be added to the regimen if the patient has an indwelling medical device (see Chapter 206), if gram-positive cocci are isolated from the blood, if MRSA infection is suspected, or as empirical coverage for *S. pneumoniae* in a patient with meningitis. Empirical coverage for fungal infections should be considered for selected immunocompromised patients (see Chapter 205). It should be noted that these are broad, generalized recommendations that must be tailored to the individual clinical scenario and to the local resistance patterns of the community and hospital.

Distributive shock that is not secondary to sepsis is caused by a primary abnormality in vascular tone. Cardiac output in affected patients is usually maintained and may initially be supranormal. These patients may benefit temporarily from volume resuscitation, but the early initiation of a vasoconstrictive agent to increase SVR is an important element of clinical care. Patients with spinal cord injury and spinal shock may benefit from either phenylephrine or vasopressin to increase SVR; epinephrine is the treatment of choice for patients with anaphylaxis (Table 88.13). Epinephrine has peripheral α-adrenergic as well as inotropic effects that may improve the myocardial depression seen with anaphylaxis and its associated inflammatory response (see Chapter 174).

Table 88.13

Cardiovascular Drug Treatment of Shock

DRUG	EFFECT(S)	DOSING RANGE	COMMENT(S)
Dopamine	↑ Cardiac contractility Significant peripheral vasoconstriction at >10 μg/kg/min	3-20 μg/kg/min	↑ Risk of arrhythmias at high doses
Epinephrine	↑ Heart rate and ↑ cardiac contractility Potent vasoconstrictor	0.05-3.0 μg/kg/min	May ↓ renal perfusion at high doses ↑ Myocardial O_2 consumption Risk of arrhythmia at high doses
Dobutamine	↑ Cardiac contractility Peripheral vasodilator	1-10 μg/kg/min	—
Norepinephrine	Potent vasoconstriction No significant effect on cardiac contractility	0.05-1.5 μg/kg/min	↑ Blood pressure secondary to ↑ systemic vascular resistance ↑ Left ventricular afterload
Phenylephrine	Potent vasoconstriction	0.5-2.0 μg/kg/min	Can cause sudden hypertension ↑ O_2 consumption

Patients with **cardiogenic shock** have poor cardiac output secondary to systolic and/or diastolic myocardial depression, often with a compensatory elevation in SVR. These patients may show poor response to fluid resuscitation and may decompensate quickly when fluids are administered. Smaller boluses of fluid (5-10 mL/kg) should be given in cardiogenic shock to replace deficits and maintain preload. In any patient with shock whose clinical status deteriorates with fluid resuscitation, a cardiogenic etiology should be considered, and further administration of IV fluids should be provided judiciously. Early initiation of myocardial support with epinephrine or dopamine to improve cardiac output is important in this context, and early consideration should be given to administration of an inodilator, such as milrinone.

Despite adequate cardiac output with the support of inotropic agents, a high SVR with poor peripheral perfusion and acidosis may persist in cardiogenic shock. Therefore, if not already started, milrinone therapy may improve systolic function and decrease SVR without causing a significant increase in HR. Furthermore, this agent has the added benefit of enhancing diastolic relaxation. Dobutamine or other vasodilating agents, such as nitroprusside, may also be considered in this setting (Table 88.14). Titration of these agents should target clinical end-points, including increased urine output, improved peripheral perfusion, resolution of acidosis, and normalization of mental status. Even though they may be beneficial in other forms of shock, agents that improve BP by increasing SVR, such as norepinephrine and vasopressin, should generally be avoided in patients with cardiogenic shock. These agents may cause further decompensation and potentially precipitate cardiac arrest as a result of the increased afterload and additional work imposed on the myocardium. The combination of inotropic and vasoactive agents must be tailored to the pathophysiology of the individual patient with close and frequent reassessment of the patient's cardiovascular status.

Table 88.14

Vasodilators/Afterload Reducers in Treatment of Shock

DRUG	EFFECT(S)	DOSING RANGE	COMMENT(S)
Nitroprusside	Vasodilator (mainly arterial)	0.5-4.0 μg/kg/min	Rapid effect Risk of cyanide toxicity with prolonged use (>96 hr)
Nitroglycerin	Vasodilator (mainly venous)	1-20 μg/kg/min	Rapid effect Risk of increased intracranial pressure
Prostaglandin E_1	Vasodilator Maintains an open ductus arteriosus in the newborn with ductal-dependent congenital heart disease	0.01-0.2 μg/kg/min	Can lead to hypotension Risk of apnea
Milrinone	Increased cardiac contractility	Load 50 μg/kg over 15 min	Phosphodiesterase inhibitor—slows cyclic adenosine monophosphate breakdown
	Improves cardiac diastolic function Peripheral vasodilation	0.5-1.0 μg/kg/min	

For patients with **obstructive shock** , fluid resuscitation may be briefly temporizing in maintaining cardiac output, but the primary insult must be immediately addressed. Examples of lifesaving therapeutic interventions for such patients are pericardiocentesis for pericardial effusion, pleurocentesis or chest tube placement for pneumothorax, thrombectomy/thrombolysis for pulmonary embolism, and the initiation of a prostaglandin infusion for ductus-dependent cardiac lesions. There is often a *last-drop phenomenon* associated with some obstructive lesions, in that small additional amounts of intravascular volume depletion may lead to a rapid deterioration, including cardiac arrest, if the obstructive lesion is not corrected.

Regardless of the etiology of shock, metabolic status should be meticulously maintained (see Table 88.8). Electrolyte levels should be monitored closely and corrected as needed. Hypoglycemia is common and should be promptly treated. Neonates and infants in particular may have profound glucose dysregulation in association with shock. Glucose levels should be checked routinely and treated appropriately, especially early in the course of illness. Hypocalcemia, which may contribute to myocardial dysfunction, should be treated with a goal of normalizing the ionized calcium concentration. There is no evidence that supranormal calcium levels benefit the myocardium, and hypercalcemia may be associated with increased myocardial toxicity.

Adrenal function is another important consideration in shock, and hydrocortisone replacement may be beneficial. Up to 50% of critically ill patients may have absolute or relative adrenal insufficiency. Patients at risk for adrenal insufficiency include those with congenial adrenal hypoplasia, abnormalities of the hypothalamic-pituitary axis, and recent therapy with corticosteroids (including those with asthma, rheumatic diseases, malignancies, and inflammatory bowel disease). These patients are at high risk for adrenal dysfunction and should receive stress doses of hydrocortisone. *Corticosteroids may also be considered in patients with shock that is unresponsive to fluid resuscitation and catecholamines.* Although a subset of pediatric septic shock patients may benefit from treatment with hydrocortisone, currently available pediatric data do not demonstrate an overall survival benefit in patients with shock treated with hydrocortisone. Determination of baseline cortisol levels before corticosteroid administration may be beneficial in guiding therapy, although this approach remains controversial.

Considerations for Continued Therapy

After the 1st hr of therapy and attempts at early reversal of shock, focus on goal-directed end-points should continue in an intensive care setting (see Figs. 88.1 and 88.2 and Table 88.8). Clinical end-points serve as global markers for organ perfusion and oxygenation. Laboratory parameters such as SvO_2 (or $ScvO_2$), serum lactate concentration, cardiac index, and hemoglobin serve as adjunctive measures of tissue oxygen delivery. Hemoglobin should be generally maintained at 10 g/dL, SvO_2 (or $ScvO_2$) >70%, and cardiac index at 3.3-6.0 L/min/m^2 to optimize oxygen delivery in the acute phase of shock. It is important to note that cardiac index is rarely monitored in the clinical setting because of the limited use of pulmonary artery catheters and lack of accurate noninvasive cardiac output monitors for infants and children. Blood lactate levels and calculation of base deficit from arterial blood gas values are very useful markers for the adequacy of oxygen delivery. These traditional markers are indicators of global oxygen utilization and delivery. There is increasing use of measures of local tissue oxygenation, including near-infrared spectroscopy of the cerebrum, flank, or abdomen.

Respiratory support should be used as clinically appropriate. When shock leads to ARDS requiring mechanical ventilation, lung-protective strategies to keep plateau pressure <30 cm H_2O and maintain tidal volume at 6 mL/kg have been shown to improve mortality in adult patients (see Chapter 89). These data are extrapolated to pediatric patients because of the lack of definitive pediatric studies in this area. Additionally, after the initial shock state has been reversed, data demonstrate that judicious fluid administration, renal replacement therapy, and fluid removal may also be useful in children with anuria or oliguria and fluid overload (see Chapter 550). Other interventions include correction of coagulopathy with fresh-frozen plasma or cryoprecipitate and platelet transfusions as necessary, especially in the presence of active bleeding.

If shock remains refractory despite maximal therapeutic interventions, mechanical support with **extracorporeal membrane oxygenation** (ECMO) or a **ventricular assist device** (VAD) may be indicated. ECMO may be lifesaving in cases of refractory shock regardless of underlying etiology. Similarly, a VAD may be indicated for refractory cardiogenic shock in the setting of cardiomyopathy or recent cardiac surgery. Systemic anticoagulation, which is required while patients are receiving mechanical support, may be difficult, given the significant coagulopathy often encountered in refractory shock, especially when the underlying etiology is sepsis. Mechanical support in refractory shock poses substantial risks but can improve survival in specific populations of

patients.

Prognosis

In septic shock, mortality rates are as low as 3% in previously healthy children and 6–9% in children with chronic illness (compared with 25–30% in adults). With early recognition and therapy, the mortality rate for pediatric shock continues to improve, but shock and MODS remain one of the leading causes of death in infants and children. The risk of death involves a complex interaction of factors, including the underlying etiology, presence of chronic illness, host immune response, and timing of recognition and therapy.

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CHAPTER 89

Respiratory Distress and Failure

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The term *respiratory distress* is used to indicate signs and symptoms of abnormal respiratory pattern. A child with nasal flaring, tachypnea, chest wall retractions, stridor, grunting, dyspnea, and wheezing has respiratory distress. Taken together, the magnitude of these findings is used to judge clinical severity. Nasal flaring is nonspecific, but the other signs are useful in localizing the site of pathology (see Chapter 400). *Respiratory failure* is defined as inability of the lungs to provide sufficient oxygen (hypoxic respiratory failure) or remove carbon dioxide (ventilator failure) to meet metabolic demands. Therefore, whereas respiratory distress is determined by a clinical impression, the diagnosis of respiratory failure is indicated by inadequacy of oxygenation or of ventilation, or both. Respiratory distress can occur in patients without respiratory disease, and respiratory failure can occur in patients without respiratory distress.

Respiratory Distress

A careful physical examination must be performed when managing a child in respiratory distress. **Nasal flaring** , although nonspecific, is an extremely important sign of distress in infants. It may indicate discomfort, pain, fatigue, or breathing difficulty. The state of **responsiveness** is another crucial sign. Lethargy, disinterest in surroundings, and poor cry are suggestive of exhaustion, hypercarbia, and impending respiratory failure. Abnormalities of the rate and depth of **breathing** can occur with both pulmonary and nonpulmonary causes of respiratory distress. In diseases of decreased lung compliance, such as pneumonia and pulmonary edema, breathing is characteristically rapid and shallow (decreased tidal volume). In obstructive airway diseases, such as asthma and laryngotracheitis, breathing is deep with increased tidal volume, but less rapid. Rapid and deep breathing without other respiratory signs should alert the physician to possible nonpulmonary or nonthoracic causes of respiratory distress, such as response to metabolic acidosis (e.g., diabetic ketoacidosis, renal tubular acidosis) or stimulation of the respiratory center (e.g., encephalitis, ingestion of central nervous system stimulants). Chest wall, suprasternal, and subcostal **retractions** are manifestations of increased inspiratory effort, weak chest wall, or both. Inspiratory **stridor** indicates airway obstruction above the thoracic inlet, whereas expiratory wheezing results from airway obstruction below the thoracic inlet. **Grunting** is most commonly heard in diseases with decreased functional residual capacity (e.g., pneumonia, pulmonary edema) and peripheral airway obstruction (e.g., bronchiolitis).

Respiratory Disease Manifesting as Respiratory Distress

Clinical examination is important in localizing the site of pathology (see Chapter 400). Extrathoracic airway obstruction occurs anywhere above the thoracic inlet. Inspiratory stridor, suprasternal, chest wall, and subcostal retractions; and prolongation of inspiration are hallmarks of extrathoracic airway obstruction. By comparison, features of intrathoracic airway obstruction are prolongation of expiration and expiratory wheezing. Typical manifestations of alveolar interstitial pathology are rapid, shallow respirations, chest wall retractions, and grunting. The site of pathology can be localized and the differential diagnosis established on the basis of the clinical signs and symptoms (Tables 89.1 and 89.2).

Table 89.1

Typical Localizing Signs for Pulmonary Pathology

SITE OF PATHOLOGY	RESPIRATORY RATE	RETRACTIONS	AUDIBLE SOUNDS
Extrathoracic airway	↑	↑↑↑↑	Stridor
Intrathoracic extrapulmonary	↑	↑↑	Wheezing
Intrathoracic intrapulmonary	↑↑	↑↑	Wheezing
Alveolar interstitial	↑↑↑	↑↑↑	Grunting

Table 89.2

Examples of Anatomic Sites of Lesions Causing

Respiratory Failure

LUNG	**RESPIRATORY PUMP**
CENTRAL AIRWAY OBSTRUCTION	**THORACIC CAGE**
Choanal atresia Tonsilloadenoidal hypertrophy Retropharyngeal/peritonsillar abscess Laryngomalacia Epiglottitis Vocal cord paralysis Laryngotracheitis Subglottic stenosis Vascular ring/pulmonary sling Mediastinal mass Foreign body aspiration Obstructive sleep apnea	Kyphoscoliosis Diaphragmatic hernia Flail chest Eventration of diaphragm Asphyxiating thoracic dystrophy Prune-belly syndrome Dermatomyositis Abdominal distention
PERIPHERAL AIRWAY OBSTRUCTION	**BRAINSTEM**
Asthma Bronchiolitis Foreign body aspiration Aspiration pneumonia Cystic fibrosis α_1 -Antitrypsin deficiency	Arnold-Chiari malformation Central hypoventilation syndrome CNS depressants Trauma Increased intracranial pressure CNS infections
ALVEOLAR-INTERSTITIAL DISEASE	**SPINAL CORD**
Lobar pneumonia ARDS, hyaline membrane disease Interstitial pneumonia Hydrocarbon pneumonia Pulmonary hemorrhage/hemosiderosis	Trauma Transverse myelitis Spinal muscular atrophy Poliomyelitis Tumor/abscess Acute flaccid myelitis
	NEUROMUSCULAR
	Phrenic nerve injury Birth trauma Infant botulism Guillain-Barré syndrome Muscular dystrophy Myasthenia gravis Organophosphate poisoning

ARDS, Acute respiratory distress syndrome; CNS, central nervous system.

Respiratory Distress Without Respiratory Disease

Although respiratory distress most frequently results from diseases of lungs, airways, and chest wall, pathology in other organ systems can manifest as respiratory distress and lead to misdiagnosis and inappropriate management (Table 89.3). Respiratory distress resulting from heart failure or diabetic ketoacidosis may be misdiagnosed as asthma and improperly treated with albuterol, resulting in worsened hemodynamic state or ketoacidosis. Careful history and physical examination provide essential clues in avoiding misdiagnosis.

Table 89.3

Nonpulmonary Causes of Respiratory Distress

SYSTEM	EXAMPLE(S)	MECHANISM(S)
Cardiovascular	Left-to-right shunt Congestive heart failure Cardiogenic shock	↑ Pulmonary blood/water content Metabolic acidosis Baroreceptor stimulation
Central nervous	Increased intracranial pressure Encephalitis Neurogenic pulmonary edema Toxic encephalopathy	Stimulation of brainstem respiratory centers
Metabolic	Diabetic ketoacidosis Organic acidemia Hyperammonemia	Stimulation of central and peripheral chemoreceptors
Renal	Renal tubular acidosis	Stimulation of central and peripheral chemoreceptors
	Hypertension	Left ventricular dysfunction → increased pulmonary blood/water content
Sepsis	Toxic shock syndrome Meningococcemia	Cytokine stimulation of respiratory centers Baroreceptor stimulation from shock Metabolic acidosis

Cardiovascular Disease Manifesting as Respiratory Distress

A child with cardiovascular pathology may present with respiratory distress caused by either *decreased lung compliance* or *cardiogenic shock* (Table 89.4). Diseases that result in increased pulmonary arterial blood flow (e.g., left-to-right shunts) or increased pulmonary venous pressure (e.g., left ventricular dysfunction from hypertension or myocarditis, obstructed total anomalous pulmonary venous return) cause an increase in pulmonary capillary pressure and transudation of fluid into the pulmonary interstitium and alveoli. The increased pulmonary blood and water content lead to decreased lung compliance and result in rapid shallow breathing.

Table 89.4

Cardiovascular Pathology Manifesting as

Respiratory Distress

- I. **Decreased lung compliance**
  - A. Left-to-right shunts
    - 1. Ventricular septal defect, atrial septal defect, patent ductus arteriosus, atrioventricular canal, truncus arteriosus
    - 2. Cerebral or hepatic arteriovenous fistula
  - B. Ventricular failure
    - 1. Left heart obstructive lesions
      - a. Aortic stenosis
      - b. Coarctation of the aorta
      - c. Mitral stenosis
      - d. Interrupted aortic arch
      - e. Hypoplastic left heart syndrome
    - 2. Myocardial infarction
      - a. Anomalous left coronary artery arising from the pulmonary artery
    - 3. Hypertension
      - a. Acute glomerulonephritis
    - 4. Inflammatory/infectious
      - a. Myocarditis
      - b. Pericardial effusion
    - 5. Idiopathic
      - a. Dilated cardiomyopathy
      - b. Hypertrophic obstructive cardiomyopathy
  - C. Pulmonary venous obstruction
    - 1. Total anomalous pulmonary venous return with obstruction
    - 2. Cor triatriatum
- II. **Shock resulting in metabolic acidosis**
  - A. Left heart obstructive lesions
  - B. Acute ventricular failure
    - 1. Myocarditis, myocardial infarction

It is important to recognize that interstitial lung edema cannot only manifest as alveolar fluid, but as small airway obstruction as well. **Wheezing** as a sign of congestive cardiac disease is common in infants and young children and should be recognized. Patients with cardiac lesions, resulting in low cardiac output, often present in shock. For example, obstructive lesions of left side of the heart and acquired or congenital cardiomyopathy result in decreased perfusion and metabolic acidosis, as well as respiratory distress because of chemoreceptor and baroreceptor stimulation. The likelihood of a particular cardiovascular illness manifesting as respiratory distress depends on age at presentation (Table 89.5).

Table 89.5

Typical Chronology of Heart Disease Presentation in Children

AGE	MECHANISM	DISEASE
Newborn (1-10 days)	↑ Arteriovenous pressure difference	Arteriovenous fistula (brain, liver)
	Ductal closure	Single ventricle lesions or severe ventricular outflow obstruction
	Independent pulmonary and systemic blood flow	Transposition of the great arteries
	Pulmonary venous obstruction	Total anomalous pulmonary venous return (TAPVR)
Young infant (1-6 mo)	↓ Pulmonary vascular resistance	Left-to-right shunt
	↓ Pulmonary artery pressure	Anomalous left coronary artery to the pulmonary artery
Any age	Rate disturbance	Tachy- or bradyarrhythmias
	Infection	Myocarditis, pericarditis
	Abnormal cardiac myocytes	Cardiomyopathy
	Excess afterload	hypertension

Neurologic Disease Manifesting as Respiratory Distress

Central nervous system (CNS) dysfunction can lead to alterations in respiratory patterns and manifest as respiratory distress. Increased intracranial pressure (ICP) may manifest as respiratory distress. Early rise in intracranial pressure (ICP) results in stimulation of respiratory centers, leading to increases in the rate (**tachypnea**) and depth (**hyperpnea**) of respiration. The resultant decrease in arterial blood partial pressure of carbon dioxide (Pa_{CO_2}) and elevation of cerebrospinal fluid (CSF) pH lead to cerebral vasoconstriction and amelioration of intracranial hypertension. Stereotypical respiratory patterns are associated with dysfunction at multiple levels of the brain. Cerebral hemisphere and midbrain lesions result in hyperpnea as well as tachypnea. In such situations, arterial blood gas (ABG) measurements typically show respiratory alkalosis without hypoxemia. Pathology affecting the pons and medulla manifests as irregular breathing patterns such as **apneustic breathing** (prolonged inspiration with brief expiratory periods), **Cheyne-Stokes breathing** (alternate periods of rapid and slow breathing), and irregular, ineffective breathing or apnea (Table 89.6). Along with respiratory changes, other manifestations of CNS dysfunction and increased ICP may be present, such as focal neurologic signs, pupillary changes, hypertension, and bradycardia (see Chapter 85). Occasionally, severe CNS dysfunction can result in **neurogenic pulmonary edema** and respiratory distress, which may follow excessive sympathetic discharge resulting in increased pulmonary venous hydrostatic pressure as well as increased pulmonary capillary permeability. **Central neurogenic hyperventilation** is characteristically observed in CNS involvement by illnesses such as urea cycle defects and encephalitis. **Bradycardia** and **apnea** may be caused by CNS-depressant medications, poisoning, prolonged hypoxia, trauma, or infection (see Table 89.2).

Table 89.6

Respiratory Patterns in Neurologic Disease

INJURY	PATTERN[*]	COMMENTS
Normal	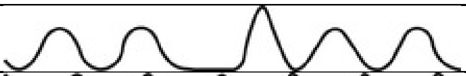	Variable V_T with normal respiratory pauses and sighs
Cortex	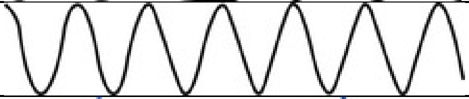	Hyperpnea and tachypnea
Midbrain	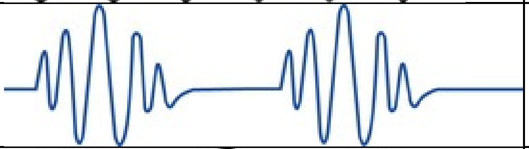	*Cheyne-Stokes breathing* : Gradually increasing and decreasing V_T
Pons	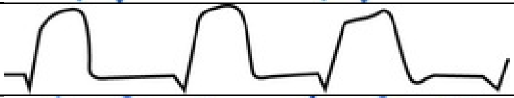	*Apneustic breathing* : Prolonged inspiration followed by prolonged expiration
Medulla and pons	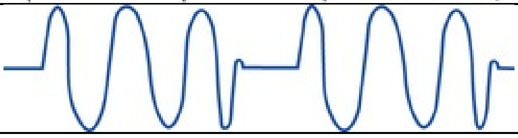	*Biot's breathing* : Rapid and irregular respirations with pauses

[*] Lung volume vs time.

VT , Tidal volume.

Toxic Metabolic States Manifesting as Respiratory Distress

Direct stimulation of respiratory centers resulting in respiratory alkalosis is encountered in intoxication involving agents such as salicylates and theophylline. Similarly, intoxication with general CNS stimulants, such as cocaine and amphetamines, may result in increased respiration. Presence of endogenous and exogenous toxins, such as organic acidemias, ingestion of methanol and ethylene glycol, and late stages of salicylism, cause metabolic acidosis and compensatory hyperventilation, which can manifest as respiratory distress. ABG measurements show decreased pH and compensatory hypocarbia with normal oxygenation. Metabolic disorders causing hyperammonemia, on the other hand, cause respiratory alkalosis (decreased $PaCO_2$ with increased pH) because ammonia stimulates the respiratory centers. Carbon monoxide and cyanide poisoning or methemoglobinemia may produce respiratory distress.

Other Nonpulmonary Entities Manifesting as Respiratory Distress

Sepsis and **septic shock** may cause an acute respiratory distress syndrome (ARDS) with hypovolemic stimulation of baroreceptors, cytokine stimulation of respiratory centers, and lactic acidosis. Other indirect causes of lung injury include systemic inflammatory conditions, trauma, transfusion-related acute lung injury, and pancreatitis. Similarly, renal disease may manifest as respiratory distress by causing metabolic acidosis (e.g., renal tubular acidosis or renal failure) or hypertensive left ventricular failure and fluid overload.

Respiratory Failure

Respiratory failure occurs when oxygenation and ventilation are insufficient to meet the metabolic demands of the body. Respiratory failure may result from an abnormality in (1) lung and airways, (2) chest wall and muscles of breathing, or (3) central and peripheral chemoreceptors. Clinical manifestations depend largely on the site of pathology. Although respiratory failure is traditionally defined as respiratory dysfunction resulting in arterial partial pressure of oxygen (PaO_2) <60 mm Hg when breathing room air and $PaCO_2$ >50 mm Hg resulting in acidosis, the patient's general state, respiratory effort, and potential for impending exhaustion are more important indicators than ABG values.

The Berlin definition of ARDS was once used to describe pediatric patients with ARDS, even though the pathophysiology is different between children and adults. The current pediatric definition differs in chest imaging findings, definition of oxygenation, consideration of both noninvasive and invasive mechanical ventilation, and consideration of special populations (Table 89.7 and Fig. 89.1).

Table 89.7

Pediatric Acute Respiratory Distress Syndrome (PARDS) Definition

	BERLIN DEFINITION	PARDS
Age	Adults and children	Excludes patients with perinatal-related lung disease
Timing	Within 1 wk of known clinical insult or new or worsening respiratory symptoms	Within 1 wk of a known clinical insult
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema, even if no risk factor present.	Respiratory failure not fully explained by cardiac failure or fluid overload
Chest imaging [a]	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. (Illustrative clinical cases and chest radiographs have been provided.)	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease
Oxygenation [b]		
Mild	200 mm Hg < $\mathrm{PaO_2/FIO_2} \leq 300$ mm Hg with PEEP, or CPAP ≥5 cm H_2O [c]	Noninvasive mechanical ventilation: PARDS (No severity stratification) Full face-mask bilevel ventilation or CPAP >5 cm H_2O [e] PF ratio <300 SF ratio <264 [d] Invasive mechanical ventilation [f]: Mild: 4 < OI <8, or 5 < OSI <7.5 [d] Moderate: 8 < OI <16, or 7.5 < OSI <12.3 [d] Severe: OI >16, or OSI >12.3 [d]
Moderate	100 mm Hg < $\mathrm{PaO_2/FIO_2} \leq 200$ mm Hg with PEEP ≥5 cm H_2O	
Severe	$\mathrm{PaO_2/FIO_2} < 100$ mm Hg with PEEP ≥5 cm H_2O	

[a] Chest radiograph or CT scan in Berlin criteria only.

[b] If altitude is >1,000 m, the correction factor should be calculated as follows: $\mathrm{PaO_2/FIO_2} \times$ Barometric pressure/760.

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

[d] Use $\mathrm{PAO_2}$-based metric when available. If $\mathrm{PaO_2}$ not available, wean $\mathrm{FIO_2}$ to maintain $\mathrm{SpO_2}$ <97% to calculate OSI or SF ratio.

[e] For nonintubated patients treated with supplemental oxygen or nasal modes of noninvasive ventilation, refer to reference below for “At Risk Criteria.”

[f] ARDS severity groups stratified by OI or OSI should not be applied to children with chronic lung disease who normally receive invasive mechanical ventilation or children with cyanotic heart disease.

In addition to the above, the Pediatric Acute Lung Injury Consensus Conference Group added definitions for special populations, including cyanotic heart disease, chronic lung disease, and left ventricular function.

CPAP, Continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure. OI, oxygenation index; OSI, oxygen saturation index.

Adapted from Pediatric Acute Lung Injury Consensus Conference Group, Pediatric Acute Respiratory Distress Syndrome: Consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference, Pediatr Crit Care Med 16;428–439, 2015.

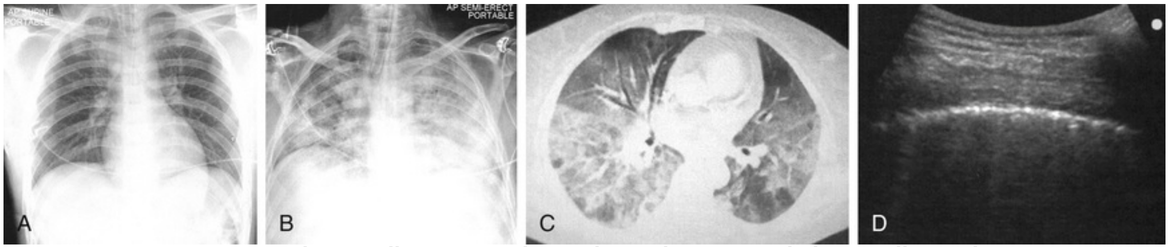

FIG. 89.1 **Acute respiratory distress syndrome (ARDS). A, Normal chest radiograph. B, Chest radiograph demonstrating bilateral alveolar infiltrates consistent with ARDS. (C, Chest CT showing bilateral pneumonitis and consolidation with air bronchograms consistent with ARDS, D, Lung ultrasonogram illustrating smooth pleural line, absence of horizontal A lines, and presence of vertical B lines suggestive of ARDS. (Modified from MacSweeney R, McAuley DF: Acute respiratory distress syndrome, *Lancet* 388:2416–2430, 2016, Fig 3.)**

Pathophysiology

Respiratory failure can be classified into *hypoxic* respiratory failure (failure of oxygenation) and *hypercarbic* respiratory failure (failure of ventilation). Systemic venous (pulmonary arterial) blood is arterialized after equilibration with alveolar gas in the pulmonary capillaries and is carried back to the heart by pulmonary veins. The ABG is influenced by the composition of inspired gas, effectiveness of alveolar ventilation, pulmonary capillary perfusion, and diffusion capacity of the alveolar capillary membrane. Abnormality in any of these steps can result in respiratory failure. **Hypoxic respiratory failure** results from intrapulmonary shunting and venous admixture or insufficient diffusion of oxygen from alveoli into pulmonary capillaries. This physiology can be caused by small airways obstruction, increased barriers to diffusion (e.g., interstitial edema, fibrosis), and conditions in which alveoli are collapsed or filled with fluid (e.g., ARDS, pneumonia, atelectasis, pulmonary edema). In most cases, hypoxic respiratory failure is associated with decreased functional residual capacity and can be managed by lung volume recruitment with positive pressure ventilation. **Hypercarbic respiratory failure** is caused by decreased minute ventilation (i.e., tidal volume multiplied by respiratory rate). This physiology can result from centrally mediated disorders of respiratory drive, increased dead space ventilation, or obstructive airways disease. *Hypoxic and hypercarbic respiratory failure may coexist as a combined failure of oxygenation and ventilation.*

Ventilation-Perfusion Mismatch

For exchange of O_2 and CO_2 to occur, alveolar gas must be exposed to blood in pulmonary capillaries. Both ventilation and perfusion are lower in nondependent areas of the lung and higher in dependent areas. The difference in perfusion ($\dot{Q}$) is greater than the difference in ventilation ($\dot{V}$). Perfusion in excess of ventilation results in incomplete arterialization of systemic venous (pulmonary arterial) blood and is referred to as **venous admixture** . Perfusion of unventilated areas is referred to as **intrapulmonary shunting** of systemic venous blood to systemic arterial circulation. Conversely, ventilation that is in excess of perfusion is wasted; that is, it does not contribute to gas exchange and is referred to as **dead space ventilation** . Dead space ventilation results in return of greater amounts of atmospheric gas (which has not participated in gas exchange and has negligible CO_2) back to the atmosphere during exhalation. The respiratory dead space is divided into the anatomic dead space and the alveolar dead space. The *anatomic dead space* includes the conducting airways from the nasopharynx to the terminal bronchioles, ends at the alveoli, and has no contact with the pulmonary capillary bed. The *alveolar dead space* refers to areas of the lung where alveoli are ventilated but not perfused. Under normal conditions, this physiology usually occurs in West zone I, where alveolar pressure is greater than pulmonary capillary pressure. Under clinical conditions, this physiology may result from dynamic hyperinflation, high levels of positive end-expiratory pressure (PEEP), or large tidal volume in ventilated patients. Additionally, decreased pulmonary artery perfusion from pulmonary embolism or decreased cardiac output and hypovolemia can result in alveolar dead space. The end result is a decrease in mixed expired CO_2 ($PECO_2$) and an increase in the $PaCO_2$ – $PECO_2$ gradient. Dea space as a fraction of tidal volume (VD /VT) is calculated as:

$$(PaCO_2 - PECO_2) \div PaCO_2$$

Normal VD /VT is approximately 0.33. Venous admixture and intrapulmonary shunting predominantly affect oxygenation, resulting in a alveolar oxygen (PAO_2) to PaO_2 (A-aO_2) gradient without elevation in $PaCO_2$. This physiology is caused by greater ventilation of perfused areas, which is sufficient to normalize $PaCO_2$ but not PaO_2 because of their respective dissociation curves. The relative straight-line relationship of the hemoglobin-CO_2 dissociation allows for averaging of capillary PCO_2 ($PcCO_2$) from hyperventilated and hypoventilated areas. Because the association between oxygen tension and hemoglobin saturation plateaus with increasing PaO_2, the decreased hemoglobin-O_2 saturation in poorly ventilated areas cannot be compensated for by well-ventilated areas where hemoglobin-O_2 saturation has already reached near-maximum. This physiology results in decreased arterial oxyhemoglobin saturation (SaO_2) and PaO_2. Elevation of $PaCO_2$ in such situations is indicative of coincident alveolar hypoventilation. Examples of diseases leading to venous admixture include asthma and aspiration pneumonia, and those of intrapulmonary shunt include lobar pneumonia and ARDS.

Diffusion

Even if ventilation and perfusion are matched, gas exchange requires diffusion across the interstitial space between alveoli and pulmonary capillaries. Under normal conditions, there is sufficient time for the pulmonary capillary blood to equilibrate with alveolar gas across the interstitial space. When the interstitial space is filled with inflammatory cells or fluid, diffusion is impaired. Because the diffusion capacity of CO_2 is 20 times greater than that of O_2, diffusion defects manifest as hypoxemia rather than hypercarbia. Even with the administration of 100% oxygen, PAO_2 increases to approximately 660 mm Hg from 100 mm Hg at sea level, and the concentration gradient for diffusion of O_2 is increased by only 6.6 times. Therefore, with diffusion defects, lethal hypoxemia will set in before clinically significant CO_2 retention results. In fact, in such situations, Pa_{CO_2} is often decreased because of the hyperventilation that accompanies hypoxemia. Presence of hypercarbia in diseases that impair diffusion is indicative of alveolar hypoventilation from coexisting airway obstruction, exhaustion, or CNS depression. Examples of disease that impair diffusion are interstitial pneumonia, ARDS, scleroderma, and pulmonary lymphangiectasia.

Monitoring a Child in Respiratory Distress and Respiratory Failure

Clinical Examination

It cannot be overemphasized that clinical observation is the most important component of monitoring. The presence and magnitude of abnormal clinical findings, their progression with time, and their temporal relation to therapeutic interventions serve as guides to diagnosis and management (see Chapter 400). As much as possible, the child with respiratory distress or failure should be observed in the position of greatest comfort and in the least threatening environment.

Pulse oximetry is the most commonly used technique to monitor oxygenation. Noninvasive and safe, it is the standard of care in bedside monitoring of children during transport, procedural sedation, surgery, and critical illness. It indirectly measures arterial hemoglobin-O_2 saturation by differentiating oxyhemoglobin from deoxygenated hemoglobin using their respective light absorption at wavelengths of 660 nm (red) and 940 nm (infrared). A pulsatile circulation is required to enable detection of oxygenated blood entering the capillary bed. Percentage of arterial oxyhemoglobin is reported as Sa_{O_2} ; however, the correct description is *oxyhemoglobin saturation as measured by pulse oximetry* (Sp_{O_2}). Such precision is needed because Sp_{O_2} may not always reflect Sa_{O_2} . It is important to be familiar with the hemoglobin-O_2 dissociation curve (see Chapter 400) to estimate Pa_{O_2} at a given oxyhemoglobin saturation. Because of the shape of the hemoglobin-O_2 dissociation curve, changes in Pa_{O_2} above 70 mm Hg are not readily identified by pulse oximetry. Also, at the same Pa_{O_2} , there may be significant change in Sp_{O_2} at a different blood pH value. In most situations, Sp_{O_2} >95% is a reasonable goal, especially in emergency care. In some adult studies of ARDS, the recommended saturation is 94–96% to avoid oxygen toxicity. There are exceptions, such as in patients with single-ventricle cardiac lesions, in whom the pulmonary and systemic circulations are receiving blood flow from the same ventricle (e.g., after Norwood procedure for hypoplastic left heart syndrome), or with large left-to-right shunts (e.g., ventricular septal defect, patent ductus arteriosus). In these types of pathophysiologic situations, a lower SpO_2 is desired to avoid excessive blood flow to the lungs and pulmonary edema from the pulmonary vasodilatory effects of oxygen, in the patient with a single ventricle, diverting blood flow away from the systemic circulation. Because most commercially available pulse oximeters recognize all types of hemoglobin as either oxyhemoglobin or deoxygenated hemoglobin, they provide inaccurate information in the presence of carboxyhemoglobin and methemoglobin. In carbon monoxide poisoning, **carboxyhemoglobin** absorbs light in the same (red) wavelength as oxyhemoglobin, leading to overestimation of oxygen saturation. **Methemoglobin** absorbs light in both the oxygenated and deoxygenated wavelengths, which can cause either an overestimation or underestimation of oxygen saturation. Data suggest that increasing methemoglobin concentrations tend to drive SpO_2 toward 85%, no matter the actual percent of oxyhemoglobin. At lower methemoglobin levels, the pulse oximetry reading is falsely low, whereas high levels lead to a falsely high pulse oximetry reading. Newer pulse oximeters may have the ability to distinguish dyshemoglobinemias and to prevent false readings, but these are not currently in widespread use. It should be recognized that dangerous levels of hypercarbia may exist in patients with ventilatory failure, who have satisfactory SpO_2 if they are receiving supplementa oxygen. Pulse oximetry should not be the only monitoring method in patients with primary ventilatory failure, such as neuromuscular weakness and CNS depression. It is also unreliable in patients with poor perfusion and poor pulsatile flow to the extremities. Despite these limitations, pulse oximetry is a noninvasive, easily applicable, and effective means of evaluating the percentage of oxyhemoglobin in most patients.

Volumetric capnography (end-tidal CO_2 [$PetCO_2$] measurement) is helpful in non-invasively determining the effectiveness of ventilation and pulmonary circulation. The $PetCO_2$ can be used to determine the alveolar dead space fraction and is calculated as follows: [($PaCO_2$ − $PetCO_2$)/$PaCO_2$]. Changes in the alveola dead space fraction usually correlate well with changes in the gradient of $PaCO_2$

and $PetCO_2$ ($PaCO_2 – PetCO_2$). Thus a change in $PaCO_2 – PetCO_2$ can be used as an index of changes in alveolar dead space. In healthy children the gradient is smaller than in adults and is usually <3 mm Hg. Diseases resulting in increased alveolar dead space (e.g., dynamic hyperinflation) or decreased pulmonary blood flow (e.g., pulmonary embolism, low cardiac output) lead to decreases in $PetCO_2$ and an increase in $PaCO_2 – PetCO_2$. $PetCO_2$ alone may overestimate adequacy of ventilation.

Blood Gas Abnormalities

Arterial blood gas analysis offers valuable assistance in diagnosis, monitoring, and management of a child in respiratory distress and failure. Because of technical difficulties in obtaining an arterial sample in children, a *capillary blood gas* (CBG) sample is most often obtained in emergency situations. A properly arterialized CBG sample obtained by warming the digit and obtaining free-flowing blood is acceptable. The blood sample needs to be processed without delay. CBG provides a good estimate of $PaCO_2$ and arterial pH, but less so for PaO_2. In patients who mainly require monitoring of ventilation (especially those whose oxygenation is being monitored with pulse oximetry) a *venous blood gas* sample provides reliable estimate of arterial pH and $PaCO_2$ values, provided tissue perfusion is reasonably adequate. Venous PCO_2 ($PvCO_2$) is approximately 6 mm Hg higher and pH approximately 0.03 lower than the arterial values. PvO_2 has a poor correlation with PaO_2. Mixed venous O_2 saturation obtained from a central venous catheter in the right atrium is an excellent marker of the balance between oxygen delivery and oxygen consumption. In patients with a constant arterial O_2 content and O_2 consumption, mixed venous O_2 saturation offers valuable information about cardiac output.

Blood gas analysis is important not only for determining the adequacy of oxygenation and ventilation but also for determining site of respiratory pathology and planning treatment (see Chapter 400). Briefly, in the presence of pure alveolar hypoventilation (e.g., airway obstruction above carina, decreased CO_2 responsiveness, neuromuscular weakness), the blood gas will show respiratory acidosis with an elevated $PaCO_2$ but a relative sparing of oxygenation $V/\dot{Q}$ mismatch (peripheral airway obstruction, bronchopneumonia) will be reflected in increasing hypoxemia and variable levels of $PaCO_2$ (low, normal, high) depending on severity of disease. Intrapulmonary right-to-left shunting and diffusion defects (alveolar-interstitial diseases such as pulmonary edema, ARDS) will be associated with a large A-aO_2 gradient and hypoxemia with relative sparing of CO_2 elimination, unless there is coincident fatigue or CNS depression.

Acid-Base Abnormalities

It is crucial to analyze the magnitude and appropriateness of changes in pH, $PaCO_2$, and bicarbonate concentration ($[HCO_3^-]$) because they provide useful clues to the underlying pathophysiology and presence of more than 1 disorder. To do so, it is useful to assume baseline values of pH 7.40, $PaCO_2$ 40 mm Hg, and $[HCO_3^-]$ 24 mEq/L. Newborns have lower renal threshold for bicarbonate and therefore have slightly different baseline values of pH 7.38, $PaCO_2$ 35 mm Hg, and $[HCO_3^-]$ 20 mEq/L.

Metabolic Acidosis With Respiratory Compensation

Patients with metabolic acidosis have decreased pH resulting from decreased serum $[HCO_3^-]$. Chemoreceptor stimulation results in hyperventilation and respiratory compensation that may clinically manifest as respiratory distress. Normal compensation does not completely correct the pH but rather minimizes a change in pH that would otherwise occur without compensation. The adequacy of respiratory compensation is judged by the extent of the decline in $PaCO_2$ in response to the decline in $[HCO_3^-]$ or pH. A normal compensation for metabolic acidosis results in a fall in $PaCO_2$ by 1.2 mm Hg for every 1 mEq/L fall in $[HCO_3^-]$. The most commonly used method to analyze the adequacy of respiratory compensation is Winter's formula:

$$PaCO_2 = ([HCO_3^-] \times 1.5) + 8 \pm 2$$

A quick method is to look at the last 2 digits of pH (provided it is not <7.10), which should be within 2 mm Hg of $PaCO_2$. For example, pH 7.27, $PaCO_2$ 26 mm Hg, and $[HCO_3^-]$ 12 mEq/L represents metabolic acidosis with a normal respiratory compensation response. On the other hand, pH 7.15, Pa_{CO_2} 30 mm Hg, and $[HCO_3^-]$ 10 mEq/L constitutes metabolic acidosis with inadequate respiratory compensation. The reasons for inadequate compensation include decreased CO_2 responsiveness (e.g., narcotic poisoning, cerebral edema), abnormalities of lungs and airways, or neuromuscular weakness. A decrease in Pa_{CO_2} that is greater than what could be expected as a normal compensatory response to metabolic acidosis is indicative of a mixed disorder. A pH 7.20, Pa_{CO_2} 15 mm Hg, and $[HCO_3^-]$ 7.5 mEq/L represents metabolic acidosis with a concomitant respiratory alkalosis because the decline in Pa_{CO_2} is greater than what can be expected as normal compensation. Combination of metabolic acidosis and respiratory alkalosis is often encountered in serious conditions such as cardiogenic shock (e.g., anxiety, stimulation of baroreceptors), sepsis, or toxic-metabolic states (e.g., salicylates, organic acidemia).

Respiratory Acidosis With Metabolic Compensation

Patients with respiratory acidosis have decreased pH as a result of elevated Pa_{CO_2}. An acute increase in Pa_{CO_2} of 10 mm Hg results in a decrease in pH by 0.08. Thus a child with severe status asthmaticus and a Pa_{CO_2} of 60 mm Hg will have blood pH of approximately 7.24. Chronically elevated (>3-5 days) Pa_{CO_2} is accompanied by renal compensation and increase in serum $[HCO_3^-]$, limiting the fall in pH to 0.03 for every 10 mm Hg rise in Pa_{CO_2}. Thus an infant with bronchopulmonary dysplasia who has a basal Pa_{CO_2} of 60 mm Hg will have blood pH of approximately 7.34. These findings are helpful in distinguishing acute from chronic changes in Pa_{CO_2}. Also, for a given level of CO_2 accumulation, a decrease in pH that is greater than expected is indicative of concomitant metabolic acidosis, and a decline in pH that is less than expected is caused by accompanying metabolic alkalosis.

Assessment of Oxygenation and Ventilation Deficits

For standardizing management, following clinical progress, and determining prognosis for patients with defects in oxygenation or ventilation, the following indicators have been proposed, each with its strengths and limitations:

A-aO$_2$ gradient is calculated by the subtraction, PAO$_2$ − PaO$_2$. For the comparison to be valid, both values must be taken at the same time and with the same fraction of oxygen in the inspired gas (FIO$_2$).

PaO$_2$/FIO$_2$ ratio (P/F) is calculated by dividing PaO$_2$ by FIO$_2$. In hypoxic respiratory failure, a PaO$_2$/FIO$_2$ value <300 mm Hg is consistent with acute lung injury, and a value <200 mm Hg is consistent with ARDS. Although the intent is to measure $V/\dot{Q}$ mismatch, intrapulmonary shunt, and diffusion defect, the status of alveolar hypoventilation could have a significant impact on PaO$_2$/FIO$_2$.

SpO$_2$/FIO$_2$ ratio is a surrogate measure of oxygenation when PaO$_2$ is not available. It is calculated by dividing the pulse oximeter saturation by the FIO$_2$. P/F ratios of 200 mm Hg and 300 mm Hg correlate approximately with S/F ratios of 235 and 315 respectively. This relationship is most valid for SpO$_2$ values between 80% and 97%.

PaO$_2$/PAO$_2$ ratio is determined by dividing PaO$_2$ by PAO$_2$. The level of alveolar ventilation is accounted for in the calculation of PaO$_2$. Therefore, PaO$_2$/PAO$_2$ is more indicative of $V/\dot{Q}$ mismatch and alveolar capillary integrity.

Oxygenation index (OI) is aimed at standardizing oxygenation to the level of therapeutic interventions, such as mean airway pressure (MAP) and FIO$_2$ used during mechanical ventilation, which are directed toward improving oxygenation. None of the indicators of oxygenation mentioned above takes into account the degree of positive pressure respiratory support.

$$\mathrm{OI} = (\mathrm{MAP} \times \mathrm{FIO_2} \times 100) \div \mathrm{PaO_2}$$

The limitation of OI is that level of ventilation is not accounted for in the assessment.

Ventilation index (VI) is aimed at standardizing alveolar ventilation to the level of therapeutic interventions, such as peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and ventilator rate ([R) directed toward lowering PaCO$_2$.

$$VI = [R \times (PIP - PEEP) \times PaCO_2] \div 1000$$

Management

The goal of management for respiratory distress and respiratory failure is to ensure a patent airway and provide necessary support for adequate oxygenation of the blood and removal of CO_2 . Compared with hypercapnia, **hypoxemia** is a life-threatening condition; therefore initial therapy for respiratory failure should be aimed at ensuring adequate oxygenation.

Oxygen Administration

Supplemental oxygen administration is the least invasive and most easily tolerated therapy for hypoxemic respiratory failure. **Nasal cannula** oxygen provides low levels of oxygen supplementation and is easy to administer. Oxygen is humidified in a bubble humidifier and delivered via nasal prongs inserted in to the nares. In children, a flow rate <5 L/min is most often used because of increasing nasal irritation with higher flow rates. A common formula for an estimation of the FIO_2 during use of a nasal cannula in older children and adults follows:

$$FIO_2 \text{ (as percentage)} = 21\% + [(\text{Nasal cannula flow (L/min)} \times 3)]$$

The typical FIO_2 value (expressed as percentage rather than fraction of 1) using this method is between 23% and 40%, although the FIO_2 varies according to the size of the child, the respiratory rate, and the volume of air moved with each breath. In a young child, because typical nasal cannula flow rates are a greater percentage of total minute ventilation, significantly higher FIO_2 may be provided. Alternately, a **simple mask** may be used, which consists of a mask with open side ports and a valveless oxygen source. Variable amounts of room air are entrained through the ports and around the side of the mask, depending on the fit, size, and minute volume of the child. Oxygen flow rates vary from 5-10 L/min, yielding typical FIO_2 values (expressed as percentage rather than fraction of 1) between 30% and 65%. If more precise delivery of oxygen is desired, other mask devices should be used.

A **Venturi mask** provides preset FIO_2 through a mask and reservoir system by entraining precise flow rates of room air into the reservoir along with high-flow oxygen. The adapter at the end of each mask reservoir determines the flow rate of entrained room air and the subsequent FIO_2 . (Adapters provide FIO_2 of 0.30-0.50.) Oxygen flow rates of 5-10 L/min are recommended to achieve the desired FIO_2 and to prevent rebreathing. Partial rebreather and non-rebreather masks use a reservoir bag attached to a mask to provide higher FIO_2 . **Partial rebreather masks** have 2 open exhalation ports and contain a valveless oxygen reservoir bag. Some exhaled gas can mix with reservoir gas, although most exhaled gas exits the mask via the exhalation ports. Through these same ports, room air is entrained, and the partial rebreather mask can provide FIO_2 up to 0.60, for as long as oxygen flow is adequate to keep the bag from collapsing (typically 10-15 L/ min). As with nasal cannulas, smaller children with smaller tidal volumes entrain less room air, and their Fio_2 values will be higher. **Non-rebreather masks** include 2 one-way valves, 1 between the oxygen reservoir bag and the mask and the other on 1 of the 2 exhalation ports. This arrangement minimizes mixing of exhaled and fresh gas and entrainment of room air during inspiration. The 2nd exhalation port has no valve, a safeguard to allow some room air to enter the mask in the event of disconnection from the oxygen source. A non-rebreather mask can provide FIO_2 up to 0.95. The use of a non-rebreather mask in conjunction with an oxygen blender allows delivery of FIO_2 between 0.50 and 0.95 (Table 89.8). When supplemental oxygen alone is inadequate to improve oxygenation, or when ventilation problems coexist, additional therapies may be necessary.

Table 89.8

Approximate Oxygen Delivery According to Device and Flow Rates in Infants and Older Children*

DEVICE	FLOW (L/min)	FIO_2 DELIVERED
Nasal cannula	0.1-6	0.21-0.4
Simple face mask	5-10	0.4-0.6
Partial rebreather	6-15	0.55-0.7
Non-rebreather	6-15	0.7-0.95
Venturi mask	5-10	0.25-0.5

Hood/tent	7-12	0.21-1.0
High-flow systems	1-40	0.21-1.0

[*] Individual delivery varies and depends on the patient's size, respiratory rate, and volume moved with every breath.

Airway Adjuncts

Maintenance of a patent airway is a critical step in maintaining adequate oxygenation and ventilation. Artificial pharyngeal airways may be useful in patients with oropharyngeal or nasopharyngeal airway obstruction and in those with neuromuscular weakness in whom inherent extrathoracic airway resistance contributes to respiratory compromise. An **oropharyngeal airway** is a stiff plastic spacer with grooves along each side that can be placed in the mouth to run from the teeth along the tongue to its base just above the vallecula. The spacer prevents the tongue from opposing the posterior pharynx and occluding the airway. Because the tip sits at the base of the tongue, it is usually not tolerated by patients who are awake or whose gag reflex is strong. The **nasopharyngeal airway** , or *nasal trumpet* , is a flexible tube that can be inserted into the nose to run from the nasal opening along the top of the hard and soft palate with the tip ending in the hypopharynx. It is useful in bypassing obstruction from enlarged adenoids or from contact of the soft palate with the posterior nasopharynx. Because it is inserted past the adenoids, a nasopharyngeal airway should be used with caution in patients with bleeding tendencies.

Inhaled Gases

Helium-oxygen mixture (heliox) is useful in overcoming airway obstruction and improving ventilation. Helium is much less dense and slightly more viscous than nitrogen. When substituted for nitrogen, helium helps maintain laminar flow across an obstructed airway, decreases airway resistance, and improves ventilation. It is especially helpful in diseases of large airways obstruction in which turbulent airflow is more common, such as acute laryngotracheobronchitis, subglottic stenosis, and vascular ring. It is also used in patients with severe status asthmaticus. To be effective, helium should be administered in concentrations of at least 60%, so associated hypoxemia may limit its use in patients requiring >40% oxygen.

Inhaled nitric oxide (iNO) is a powerful inhaled pulmonary vasodilator. Its use may improve pulmonary blood flow and $\dot{V}/\dot{Q}$ mismatch in patients with diseases that elevate pulmonary vascular resistance, such as occurs in persistent pulmonary hypertension of the newborn, primary pulmonary hypertension, and secondary pulmonary hypertension as a result of chronic excess pulmonary blood flow (e.g., ventriculoseptal defect) or collagen vascular diseases. iNO is administered in doses ranging from 5 to 20 parts per million of inspired gas. Although administration of iNO to unintubated patients is possible, it is usually administered to patients undergoing mechanical ventilation via an endotracheal tube, because of the need for precision in iNO dosing.

Positive Pressure Respiratory Support

Noninvasive positive pressure respiratory support is useful in treating both hypoxemic and hypoventilatory respiratory failure. Positive airway pressure helps with aeration of partially atelectatic or filled alveoli, prevention of alveolar collapse at end-exhalation, and increase in functional residual capacity (FRC). These actions improve pulmonary compliance and hypoxemia, as well as decrease intrapulmonary shunt. In addition, positive pressure ventilation is useful in preventing collapse of extrathoracic airways by maintaining positive airway pressure during inspiration. Improving compliance and overcoming airway resistance also improves tidal volume and therefore ventilation. A **high-flow nasal cannula** delivers gas flow at 4-16 L/min and up to 60 L/min, with newer systems for older children and adolescents, capable of providing significant **continuous positive airway pressure (CPAP)** . In this setting, the amount of CPAP provided is not quantifiable and varies with each patient, depending on the percentage of total inspiratory flow that is delivered from the cannula, airway anatomy, and degree of mouth breathing. In small children the relative amount of CPAP for a given flow is usually greater than in older children and may provide significant positive pressure. The F_{IO_2} can be adjusted by provision of gas flow through an oxygen blender. Another benefit of a high-flow nasal cannula system is the washout of CO_2 from the nasopharynx, which decreases rebreathing of CO_2 and dead space ventilation. When delivering high-flow air or oxygen, adequate humidification is essential, by using a separate heated humidification chamber. CPAP can also be provided through snugly fitting nasal prongs or a tight-fitting face mask attached to a mechanical ventilator or other positive pressure device. Noninvasive CPAP is most useful in diseases of mildly decreased lung compliance and low FRC, such as atelectasis and pneumonia. Patients with diseases of extrathoracic airway obstruction, in which extrathoracic negative airway pressures during inspiration lead to airway narrowing (e.g., laryngotracheitis, obstructive sleep apnea, postextubation airway edema), may also benefit from CPAP. Potential risks include nasal irritation, hyperinflation from excessive CPAP in smaller patients, and abdominal distention from swallowed air.

Noninvasive positive airway pressure ventilation (NIPPV) provides positive airway pressure during exhalation, and bilevel modes can apply additional positive pressure during inspiration (see Chapter 89.1).

Endotracheal Intubation and Mechanical Ventilation

When hypoxemia or significant hypoventilation persists despite the interventions already described, endotracheal intubation and mechanical ventilation are indicated. Additional indications for intubation include maintaining airway patency in patients who have the potential for airway compromise, such as those with actual or potential neurologic deterioration, and in patients with hemodynamic instability.

Proper monitoring is essential to ensuring a safe and successful endotracheal intubation. Pulse oximetry, heart rate, and blood pressure monitoring are mandatory and should be forgone only in situations calling for emergency intubation. All necessary equipment, including bag-mask ventilation device, laryngoscope, endotracheal tube (ETT) with stylet, and suction equipment, must be available and working properly before the procedure of intubation. The proper internal diameter (ID) for the ETT can be estimated using the following formula:

$$\mathrm{ID} = (\mathrm{Age}\ [\mathrm{yr}]/4) + 4$$

Table 89.9 provides average values for age, size, and depth of insertion for tracheal tubes. Preoxygenation of the patient with high $F\mathrm{IO}_2$ is essential and will allow maximum procedure time before the onset of hypoxemia. Although intubation can be accomplished without sedation and pharmacologic paralysis in selected patients, the physiologic benefits of these measures to the patient as well as to the facilitation of the intubation usually far outweigh the risks. Administration of a sedative and analgesic followed by a paralytic agent is a common pharmacologic regimen for facilitating intubation. In fact, sedation and paralysis with neuromuscular blocking agents should be considered standard unless contraindicated. The particular type and dose of each agent often depends on the underlying disease and clinician preference. Table 89.10 lists commonly used agents. *Dexmedetomidine* has been a standard sedating agent for maintenance during mechanical ventilation. An alternative to this pharmacologic approach is **rapid sequence intubation** , used when endotracheal intubation is urgent, or the patient is suspected of having a full stomach and at increased risk of aspiration (see Chapter 81).

Table 89.9

Average Size and Depth Dimensions for Tracheal Tubes

PATIENT AGE	INTERNAL DIAMETER (mm)	OROTRACHEAL DEPTH (cm)	NASOTRACHEAL DEPTH (cm)
Premature	2.0-3.0	8-9	9-10
Full-term neonate	3.0-3.5	10	11
6 mo	4.0	11	13
12-24 mo	4.5	13-14	16-17
4 yr	5.0	15	17-18
6 yr	5.5	17	19-20
8 yr	6.0	19	21-22
10 yr	6.5	20	22-23
12 yr	7.0	21	23-24
14 yr	7.5	22	24-25
Adult	8.0-9.0	23-25	25-28

Table 89.10

Medications Commonly Used for Intubation

DRUG	DOSE	ONSET (min)	DURATION (min)	COMMENTS
SEDATIVES/ANESTHETICS				
Midazolam	0.1 mg/kg IV	3-5	60-120	Amnesia Respiratory depression
Lorazepam	0.1 mg/kg IV	3-5	120-240	Amnesia Respiratory depression
Ketamine	1-2 mg/kg IV 4-6 mg/kg IM	2-3	10-15	↑ HR, BP, and ICP Bronchodilation
Propofol	1-3 mg/kg IV	0.5-2	10-15	↓ BP Apnea
Thiopental	4-7 mg/kg IV	0.5-1	5-10	↓ BP Apnea

ANALGESICS				
Fentanyl	2-5 µg/kg IV	3-5	30-90	Respiratory depression Chest wall rigidity
Morphine	0.1 mg/kg IV	5-15	120-240	↓ BP Respiratory depression
NEUROMUSCULAR BLOCKING AGENTS				
Vecuronium	0.1 mg/kg IV	2-3	30-75	↑ HR Renal elimination
Rocuronium	0.6-1.2 mg/kg IV 1 mg/kg IM	5-15	15-60	↑ HR Renal elimination
Cisatracurium	0.1 mg/kg IV	2-3	25-30	Histamine release Nonrenal elimination

BP, Blood pressure; HR, heart rate; ICP, intracranial pressure; IM, intramuscularly; IV, intravenously.

Once adequate sedation and/or paralysis have been achieved, ventilation should be assisted with a **bag-mask device** . After optimal preoxygenation, intubation can be performed. The clinician uses the dominant hand to open the patient's mouth and insert the laryngoscope blade gently along the tongue to its base. The airway opening can be visualized by applying lift up-and-away from the clinician, along the axis of the laryngoscope handle. When a *straight* (Miller) laryngoscope blade is used to visualize the glottis, the tip of the blade lifts the epiglottis anteriorly. When a *curved* (Macintosh) blade is used to visualize the glottis, the tip of the blade should be advanced into the vallecula and then lifted. Secretions often obscure visualizations at this step and should be suctioned clear. Once clear visualization of the vocal cords is accomplished, the ETT can be placed through the vocal cords. Rapid confirmation of ETT placement is essential and should be assessed by as many of the following steps as possible: presence of PetCO_2 determined by a monitor attached in-line with ETT; auscultation of both lung fields as well as the epigastrium for equal breath sounds; and, good air movement and evaluation of the abdomen for increasing distention. Adequate, bilateral chest expansion and misting inside the ETT with each breath confirm proper tube placement. An increasing heart rate, if heart rate has decreased during the attempt, and a rising or normal SpO_2 reading are suggestive of successful tube placement. Preoxygenation may significantly delay any drop in SpO_2 with improper tube placement, leading to a significant delay in its recognition. Confirmation of exhaled PetCO_2 is mandatory, using a disposable colorimetric CO_2 detector or with capnography. In situations of very low pulmonary perfusion, such as cardiac arrest, PetCO_2 may not be detected. A chest radiograph should also be obtained to confirm proper placement of the ETT, which should lie with the tip about halfway between the glottis and the carina (see Chapter 81).

Transient Manual Ventilation in Immediate Preintubation and Postintubation Periods

Establishment of supportive ventilation via bag-mask or bag-ETT is required before transport of the patient to a setting of continued critical care. The technique of manual ventilation should take into account the underlying pathology. Mechanical ventilation of patients with diseases characterized by low FRC (e.g., pneumonia, pulmonary edema, ARDS) should include the application of PEEP to prevent alveolar derecruitment. Lung volume recruitment can be accomplished with a PEEP valve on a self-inflating ventilation bag or by careful manipulation of exhaust gas using an anesthesia bag. Such diseases are also characterized by a short time constant for lung deflation and therefore are best managed with relatively small tidal volumes and high ventilation rates.

In contrast, diseases characterized by airway obstruction have prolonged deflation time constants and are therefore best managed with relatively slow rates and high tidal volumes.

89.1

Mechanical Ventilation

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Keywords

atelectrauma
auto-PEEP
barotrauma
biotrauma

functional residual capacity
mechanical ventilation
noninvasive positive pressure ventilation
recruitment
tidal recruitment
tidal volume
volutrauma

The decision to institute support with mechanical ventilation is based mainly on the need to assist lung function; supporting left ventricular (LV) performance and treating intracranial hypertension are additional indications. Although there are no absolute criteria for derangement of gas exchange, Pa_{O_2} <60 mm Hg while breathing >60% oxygen, Pa_{CO_2} >60 mm Hg, and pH <7.25 are often reasons to initiate mechanical ventilation. Clinical impressions of fatigue and impending exhaustion are also indications for ventilatory support, even in the presence of adequate gas exchange. Positive pressure ventilation is a powerful means of decreasing LV afterload, and it is used for this purpose in patients with cardiogenic shock resulting from LV dysfunction. Mechanical ventilation is also used in patients whose breathing is unreliable (e.g., unconscious patients, those with neuromuscular dysfunction) and when deliberate hyperventilation is desired, such as in patients with intracranial hypertension.

Mechanical ventilation is not intended to normalize gas exchange, nor is it a cure. The goals are to maintain sufficient oxygenation and ventilation to ensure tissue viability until the disease process that has compromised the patient's lung function has resolved, while minimizing any complications. Thus, Pa_{O_2} , Pa_{CO_2} and pH levels are maintained in ranges that provide a safe environment for the patient, while protecting the lungs from damage caused by oxygen toxicity, pressure (**barotrauma**), tidal volume overdistention (**volutrauma**), **atelectrauma** , and cytokine release (**biotrauma**) (Figs. 89.2 and 89.3).

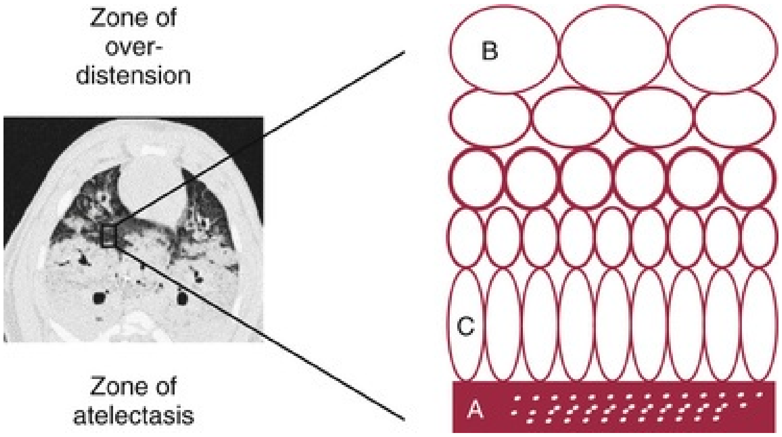
Zone of over-distension
B
C
Zone of atelectasis
A

FIG. 89.2 Atelectrauma. The interface between collapsed and consolidated lung *(A)* and overdistended lung units *(B)* is heterogeneous and unstable. Depending on ambient conditions, this region is prone to cyclic recruitment and derecruitment and localized asymmetric stretch of lung units *(C)* immediately apposed to regions of collapsed lung. (From Pinhu L, Whitehead T, Evans T, et al: Ventilator-associated lung injury, *Lancet* 361:332–340, 2003.)

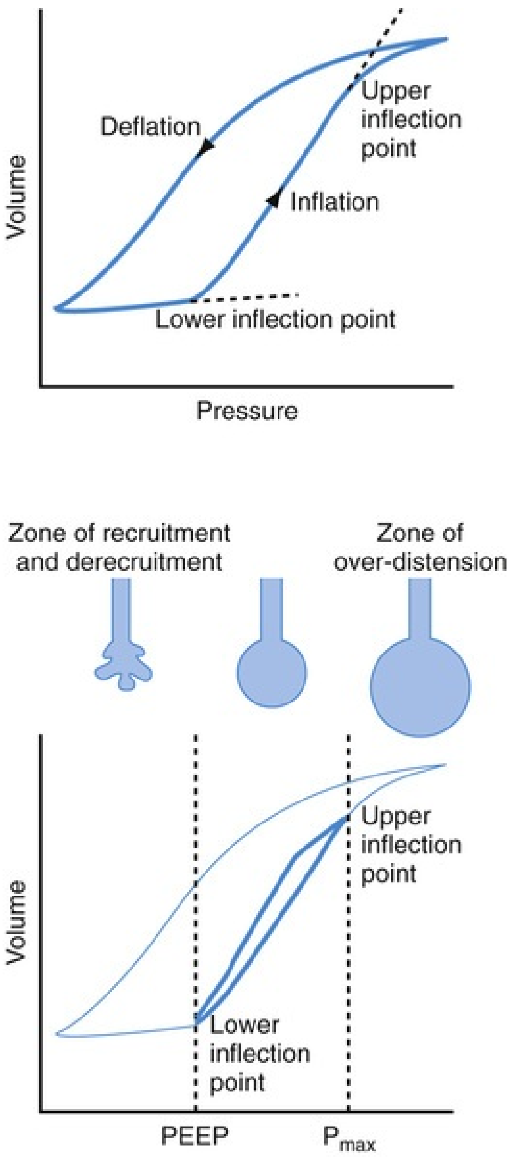
Deflation
Upper
inflection
point
Inflation
Volume
Lower inflection point
Pressure
Zone of recruitment
and derecruitment
Zone of
over-distension
Volume
Upper
inflection
point
Lower
inflection
point
PEEP
P_{max}

FIG. 89.3 Pulmonary pressure-volume relation in a patient with acute lung injury. Top, The lower inflection point is typically 12-18 cm H_2O, and the upper inflection point 26-32 cm H_2O. Bottom, Specific protective ventilation strategies require that positive end-expiratory pressure (PEEP) is set just above the lower inflection point and the pressure limit (P_{max}) just below the upper inflection point. Thus the lung is ventilated in the safe zone between the zone of recruitment and derecruitment and the zone of overdistention, and both high-volume and low-volume injuries are avoided. (From Pinhu L, Whitehead T, Evans T, et al: Ventilator-associated lung injury, *Lancet* 361:332–340, 2003.)

Basic Concepts of Ventilator Management

Equation of Motion

A pressure gradient is required for air to move from one place to another. During natural spontaneous ventilation, inspiration results from generation of negative intrapleural pressure from contraction of the diaphragm and intercostal muscles, drawing air from the atmosphere across the airways into the alveoli. During mechanical ventilation, inspiration results from positive pressure created by compressed gases through the ventilator, which pushes air across the airways into alveoli. In both spontaneous and mechanical ventilation, exhalation results from alveolar pressure generated by the elastic recoil of the lung and the chest wall. Pressure necessary to move a given amount of air into the lung is determined by 2 factors: lung and chest wall elastance and airway resistance. Fig. 89.4 describes the relationship in pressure gradient, compliance, and resistance. *Elastance* —defined as the change in pressure (ΔP) divided by the change in volume (ΔV)—refers to the property of a substance to oppose deformation. It is opposite of *compliance* (ΔV ÷ ΔP), the property of a substance to allow distention or lengthening when subjected to pressure. Compliance (C) is therefore expressed as 1/elastance.

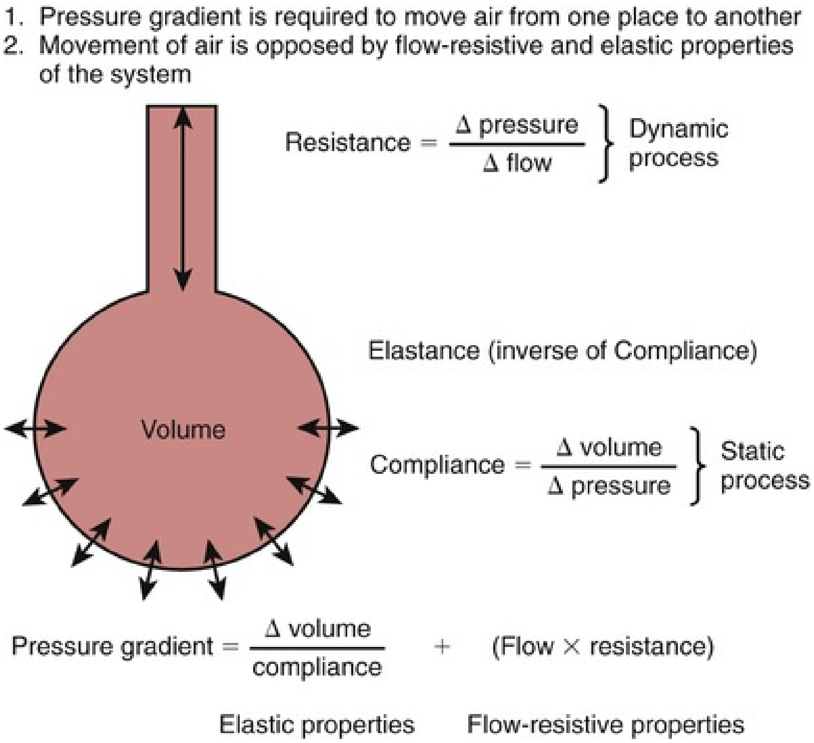
1. Pressure gradient is required to move air from one place to another
2. Movement of air is opposed by flow-resistive and elastic properties of the system
Resistance = Δ pressure / Δ flow
Dynamic process
Elastance (inverse of Compliance)
Volume
Compliance = Δ volume / Δ pressure
Static process
Pressure gradient = Δ volume / compliance + (Flow × resistance)
Elastic properties
Flow-resistive properties

FIG. 89.4 **Equation of motion. A pressure gradient is required to move air from one**

place to another. In the lungs, the required pressure gradient must overcome the lung and chest wall elastance (static component) and the flow-resistive properties (dynamic component). The static component is increased in alveolar interstitial diseases and stiff chest wall, whereas the dynamic component is increased with airway obstruction.

The pressure needed to overcome tissue elastance is measured in conditions in which there is no flow (at end-inspiration and end-expiration) and is therefore a reflection of static conditions in the lung. It is influenced by tidal volume (V_T) and compliance ($P = \Delta V \div C$). It is increased with high V_T and low compliance. This pressure gradient is used to calculate the static compliance of the respiratory system (C_{STAT}).

Resistance (R) refers to the opposition to generation of flow. It is measured as the amount of pressure needed to generate a unit of flow ($\Delta P \div \Delta$Flow). Pressure needed to overcome airway resistance is calculated as flow multiplied by resistance. Because this pressure is needed only when the flow is occurring through the airways, it is referred to as the *dynamic component* . Pressure to overcome flow-resistive properties is measured when there is maximum flow and is therefore under dynamic conditions. It is increased in conditions with greater airway resistance and flow rate. Flow rate depends on the time allowed for inspiration and expiration. At higher respiratory rates, there is less time available for each inspiration and expiration, necessitating higher flows; therefore higher pressure is required to overcome flow-resistive properties. The pressure gradient necessary to move air from one place to another is the sum of pressure needed to overcome the elastic and flow-resistive properties of the lung. This pressure gradient is taken into account to calculate the dynamic compliance of the respiratory system (C_{DYN}). The difference in change in pressure between static conditions and dynamic conditions is attributable to airway resistance.

Functional Residual Capacity

During inspiration, oxygen-enriched gas enters alveoli. During exhalation, oxygen continues to be removed by the pulmonary capillary circulation. FRC is the volume of gas left in the alveoli at end-expiration. It is the only source of gas available for gas exchange during exhalation. In diseases with decreased FRC (e.g., ARDS, pulmonary edema), P_{AO_2} declines sharply throughout expiration, resulting in hypoxemia. Two ventilator strategies used to improve oxygenation in such situations are the application of PEEP and increasing the *inspiratory time* (T_I) (Fig. 89.5). PEEP increases FRC, whereas a longer T_I allows longer exposure of pulmonary capillary blood to a higher concentration of O_2 during inspiration. (See also Chapter 400 .)

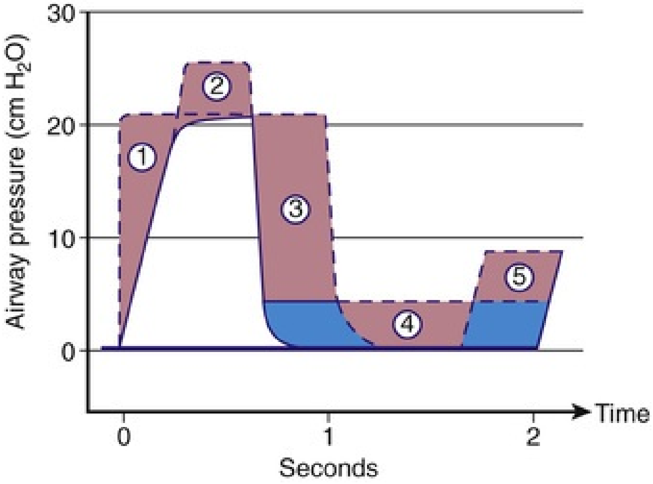

FIG. 89.5 **Five different ways to increase mean airway pressure.** ***(1)*** **Increase the respiratory flow rate, producing a square wave inspiratory pattern;** ***(2)*** **increase the peak inspiratory pressure;** ***(3)*** **reverse the inspiratory-expiratory ratio or prolong the inspiratory time without changing the rate;** ***(4)*** **increase positive end-expiratory pressure; and** ***(5)*** **increase the ventilatory rate by reducing the expiratory time without changing the inspiratory time. (From Harris TR, Wood BR: Physiologic principles. In Goldsmith JP, Karotkin EH, editors:** ***Assisted ventilation of the neonate,*** **ed 3, Philadelphia, 1996, Saunders.)**

Time Constant

At the beginning of inspiration, the atmospheric pressure is higher than the pressure in the alveoli, resulting in movement of air into the alveoli. During mechanical ventilation, the ventilator circuit serves as the patient's atmosphere. As alveoli expand with air, the alveolar pressure rises throughout inspiration until it equilibrates with the ventilator pressure, at which time airflow ceases. Expiration starts when the ventilator pressure falls below the alveolar pressure. Alveolar pressure decreases throughout expiration until it reaches the ventilator pressure, at which time no further egress of air from the alveoli occurs. If inspiration or expiration is terminated before pressure equilibration between alveoli and the ventilator is allowed to occur, alveolar expansion during inspiration or alveolar emptying during expiration is incomplete. Incomplete inspiration results in delivery of decreased V_T , whereas incomplete expiration is associated with air trapping and the presence of residual PEEP in the alveoli that is greater than the ventilator pressure, referred to as **auto-PEEP** . Some time is required for pressure equilibration to occur between alveoli and the atmosphere, which is reflected in the *time constant* (TC). It takes 3 TCs for 95% (and 5 TCs for 99%) of pressure equilibration to occur. The TC depends on compliance (C) and resistance (R), and their relationship is depicted in Fig. 89.6 . TC is calculated as compliance multiplied by resistance (C × R) and is measured in seconds.

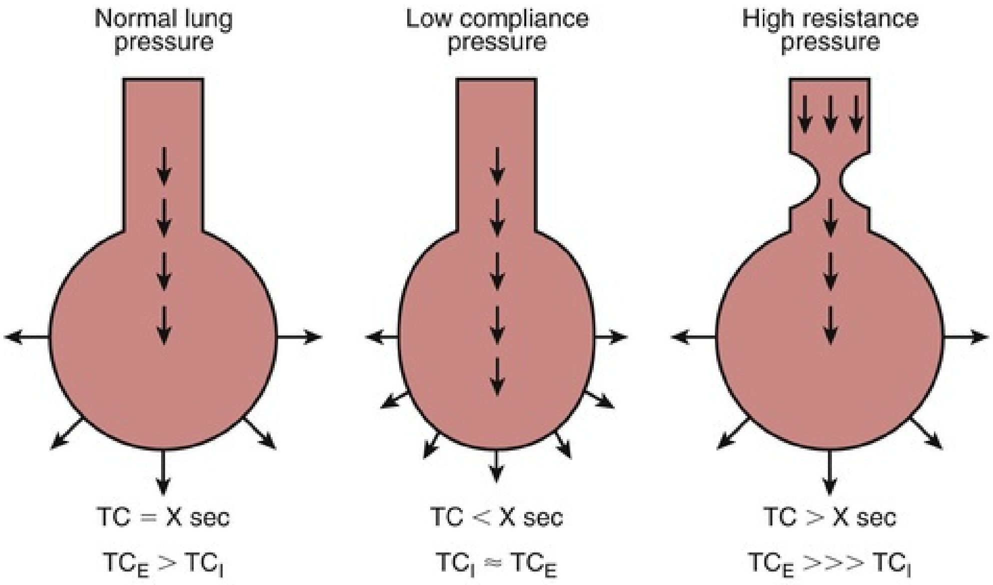

FIG. 89.6 **Time constant (TC). A certain amount of time is necessary for pressure equilibration (and therefore completion of delivery of gas) to occur between proximal airway and alveoli. TC, a reflection of time required for pressure equilibration, is a product of compliance and resistance. In diseases of decreased lung compliance, less time is needed for pressure equilibration to occur, whereas in diseases of increased airway resistance, more time is required. Expiratory TC is increased much more than inspiratory TC in obstructive airway diseases, because airway narrowing is exaggerated during expiration.**

Diseases with decreased compliance (increased elastance) are characterized by high elastic recoil pressure, which results in more rapid equilibration of alveolar and ventilator pressures, thereby decreasing TC. Diseases with increased airway resistance are associated with slower flow rates, require longer time for movement of air from one place to another, and therefore have increased TC. Airways expand during inspiration and narrow during expiration. Therefore, expiratory time constant (TC_E) is longer than inspiratory time constant (TC_I). In intrathoracic airway obstruction (e.g., asthma, bronchiolitis, aspiration syndromes), airway narrowing is much more pronounced during expiration.

Therefore, although both TC_E and TC_I are prolonged in such diseases, TC_E is much more prolonged than TC_I . Patients with such diseases therefore are best ventilated with slower rates, higher V_T , and longer expiratory time than inspiratory time. In diseases characterized by decreased compliance, both TC_E and TC_I are short; however, the TC_E is closer to TC_I than in normal lungs because of the stiffer alveoli recoil with greater force. Patients with these diseases are best ventilated with small V_T to prevent ventilator-induced lung injury and with a relatively longer inspiratory time in each breath to improve oxygenation.

Critical Opening Pressure

Collapsed or atelectatic alveoli require a considerable amount of pressure to open. Once open, the alveoli require relatively less pressure for continued expansion. The process of opening atelectatic alveoli is called **recruitment** . In a normal lung, alveoli remain open at end-expiration, and therefore the lung requires relatively less pressure to receive its V_T . In a disease process in which the alveoli collapse at end-expiration (e.g., ARDS), a substantial amount of pressure is required to open the alveoli during inspiration. This pressure causes ventilator-induced lung injury by 2 mechanisms: *barotrauma* at the terminal airway–alveolar junction and *volutrauma* as a result of overdistention of alveoli that are already open (see Figs. 89.2 and 89.3). Although a pulmonary parenchymal disease process is rarely uniform, and each of the millions of alveoli may have its own mechanical characteristics, a composite volume-pressure relationship could be conceptualized for the whole lung (Fig. 89.7).

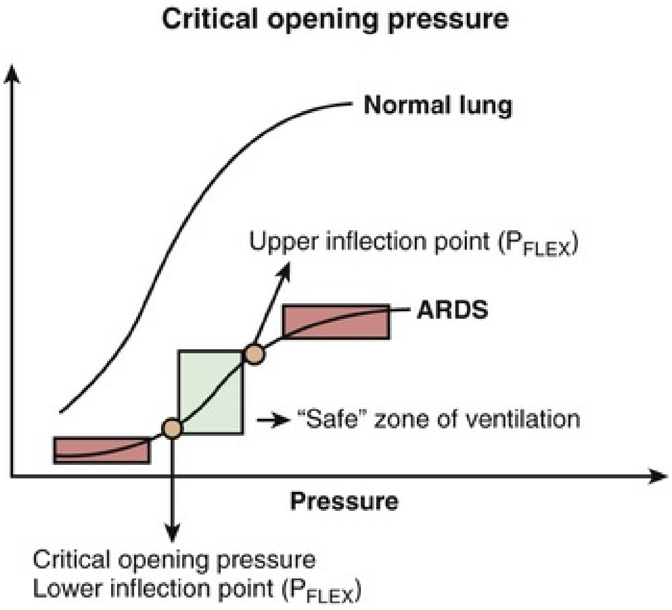

FIG. 89.7 **Volume-pressure relationship in normal lung and in acute respiratory distress syndrome. In ARDS, atelectatic alveoli require a considerable amount of pressure to open. Critical opening pressure, also referred to as lower P_{FLEX} , is the airway pressure above which further alveolar expansion occurs with relatively less pressure. Upper P_{FLEX} is the airway pressure above which further increase in pressure results in less alveolar expansion; this is the area of alveolar overdistention. Keeping tidal volume between upper and lower P_{FLEX} values is considered less injurious to the lung.**

In these situations, the lower and upper portions of the curve are relatively horizontal, and the middle portion is more vertical. At the beginning of inspiration, atelectatic alveoli are being recruited, requiring high pressure for a relatively small increase in volume. Once they are recruited, further increase in volume requires relatively less pressure. The pressure at which most alveoli are open is called *critical opening pressure* ; this point is also referred to as the *lower inflection point* (lower P_{FLEX}). After the lower P_{FLEX} , greater volume can be delivered for relatively less pressure until the upper P_{FLEX} is reached, at which the volume-pressure curve again becomes relatively horizontal. The goal of mechanical ventilation in alveolar interstitial pathology is to deliver a VT between the lower and upper inflection points, the so-called safe zone of ventilation. If VT is delivered with a change in inflation pressure that includes the lower P_{FLEX} , alveoli are likely to open *and* close during every breath, a process termed **tidal recruitment** that is injurious to the lung, especially at the terminal airway–alveolar junction. If VT is delivered with a change of pressure that includes the upper P_{FLEX} , overdistention of alveoli is likely to occur, resulting in volutrauma and barotrauma. Keeping tidal ventilation between the upper and lower P_{FLEX} values is accomplished by maintaining a level of PEEP to produce baseline alveolar recruitment and delivering a relatively small (6 mL/kg) V_T . Called “open lung” strategy, this approach has proved to be beneficial in alveolar interstitial diseases such as ARDS.

Mechanical ventilation may be delivered either noninvasively with a patient-machine interface other than an ETT or invasively after endotracheal intubation.

Noninvasive Mechanical Ventilation

Delivering positive pressure mechanical respiratory support without the use of endotracheal intubation is called noninvasive positive pressure ventilation (**NIPPV**). This type of respiratory support has been increasingly used in the pediatric intensive care setting.

The most common techniques applied are continuous positive airway pressure (**CPAP**) or biphasic (inspiratory and expiratory) positive airway pressure (**BiPAP**). A variety of devices with increasing sophistication has been developed in recent years, and different interfaces are available, such as nasal prongs, nasal and full-face masks, as well as helmets. Especially in the pediatric population a comfortable interface is critical for the successful application of NIPPV. NIPPV has been successfully used in acute and chronic hypoxic and/or hypercarbic respiratory failure. Indications range from acute lower airway obstruction such as asthma or acute upper airway obstruction including postextubation airway swelling, to parenchymal lung diseases such as pneumonia and ARDS. Acute and chronic respiratory failure, from neuromuscular weakness and chest wall deformities, has been the classic indication for its use. NIPPV can also be used to help prevent reintubation after prolonged mechanical ventilation.

BiPAP provides positive airway pressure during exhalation and additional positive pressure during inspiration. These pressures can be adjusted independently to suit individual needs and comfort, and a respiratory rate can be delivered. The additional positive pressure during inspiration helps improve alveolar ventilation in low compliance and obstructive lung disease. During exhalation, expiratory positive airway pressure can decrease the effects of airway closure by raising intraluminal pressure and ameliorating intrathoracic airway collapse. During inspiration, inspiratory positive airway pressure can unload inspiratory muscle work.

These mechanics may explain many of the physiological benefits of NIPPV including an increase in lung compliance and FRC, a decrease of dynamic airway narrowing (“stenting” of the airway), augmentation of VT and alveolar ventilation, and decreased work of breathing. Physiologic benefits of NIPPV in obstructive (e.g., asthma) and restrictive (e.g., ARDS) lung disease are schematically presented in Figs. 89.8 and 89.9 . Additional benefits result from improving cardiopulmonary interactions, especially LV afterload reduction, thereby improving cardiac output in patients with acute or chronic LV dysfunction.

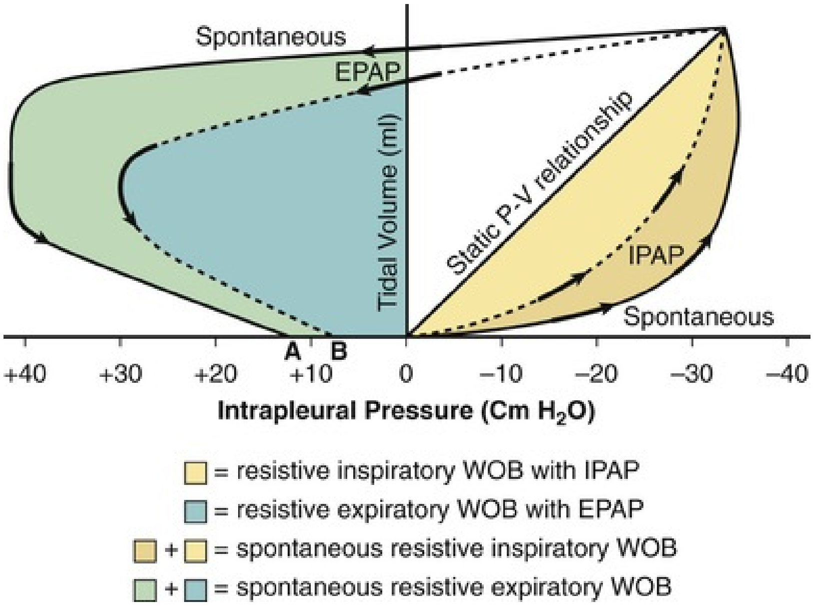
Spontaneous
EPAP
Tidal Volume (ml)
Static P-V relationship
IPAP
Spontaneous
A
B
+40
+30
+20
+10
0
−10
−20
−30
−40
Intrapleural Pressure (Cm H_2O)
🟨 = resistive inspiratory WOB with IPAP
🟦 = resistive expiratory WOB with EPAP
🟧 + 🟨 = spontaneous resistive inspiratory WOB
🟩 + 🟦 = spontaneous resistive expiratory WOB

FIG. 89.8 **Work of breathing (WOB) in status asthmaticus with and without noninvasive positive pressure ventilation. In the expiratory limb of the respiratory cycle, the equal pressure point is displaced distally, causing airways to begin to close at a higher lung volume (increased closing capacity), leading to dynamic hyperinflation, and auto–positive end-expiratory pressure (auto-PEEP) *(A).* Application of expiratory positive airway pressure (EPAP) stents the airways, reducing intrathoracic airway collapse, dynamic hyperinflation, auto-PEEP *(B),* and WOB. In the inspiratory limb, the patient needs to generate less negative pressure to initiate inspiration because of lower auto-PEEP. Inspiratory muscles are further unloaded by inspiratory positive airway pressure (IPAP) throughout inspiration for the given tidal volume. Both expiratory and inspiratory WOB are thus reduced by application of noninvasive positive pressure ventilation. P-V, Pressure-volume. (From Sarnaik AA, Sarnaik AP: Noninvasive ventilation in pediatric status asthmaticus: sound physiologic rationale but is it really safe, effective, and cost-efficient? *Pediatr Crit Care Med* 13:484–485, 2012.)**

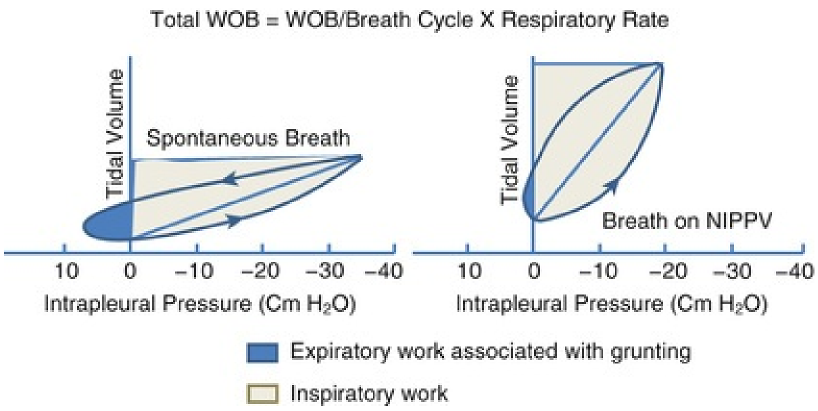

FIG. 89.9 **Beneficial physiologic pulmonary effects of noninvasive positive pressure ventilation (NIPPV) in restrictive lung disease (e.g., ARDS). Left, Without NIPPV, the slope of pressure-volume relationship is flatter, resulting in lower tidal volume for a given inflation pressure and necessitating in increased respiratory rate to maintain required minute alveolar ventilation. Start of inspiration is at a lower lung volume, indicating decreased functional residual capacity (FRC). Expiration is active toward the end as a result of grunting aimed at increasing FRC. Right, On institution of NIPPV, the slope of pressure-volume relationship is increased, resulting in greater tidal volume for a given inflation pressure, with a subsequent decrease in respiratory rate and inspiratory work of breathing (WOB). FRC is increased because of expiratory positive airway pressure (EPAP), resulting in improved oxygenation and decreased expiratory work associated with grunting.**

NIPPV is usually well tolerated and safer than invasive mechanical ventilation. Airway trauma from endotracheal intubation can be avoided, and less sedation is required. Breaks can be given for the application of oral medications and clearance of respiratory secretions, and selected stable patients can be fed by mouth. The number of nosocomial infections, ventilator-associated pneumonia, and ventilator-induced lung injury is expected to decrease as well. In addition, aerosol therapy driven by NIPPV, appears to be more effective.

Complications of NIPPV may include upper airway mucosal irritation, pulmonary hyperinflation with resulting interstitial emphysema and pneumothorax, abdominal distention, aspiration, and feeding intolerance. Patients initiated on NIPPV need close cardiorespiratory monitoring because the respiratory failure may progress, leading to the need for endotracheal intubation.

Some authorities have suggested independent predictors of NIPPV failure. Patients with more severe respiratory distress and those who do not show improvement of respiratory indices (i.e., respiratory rate, reduction in F_{IO_2}) within 2 hr of initiation are more likely to fail. Underlying severe systemic diseases such as sepsis, multiorgan dysfunction, and malignancies are less likely to respond favorably to NIPPV. Absolute contraindications include loss of airway reflexes, acute severe neurologic insults, cardiorespiratory arrest, and severe hemodynamic instability. Patients with mid-face abnormalities or facial trauma and burns should not be considered as candidates for NIPPV. Other contraindications include the immediate postoperative period after facial and upper airway surgery, recent gastrointestinal surgery, or patients with bowel obstruction and vomiting. Patients who are severely agitated and confused should not be initiated on NIPPV. NIPPV has been shown to decrease intubation rates, as well as reintubation rates, and is increasingly used to treat acute or chronic respiratory failure in pediatric patients.

Invasive Mechanical Ventilation

Mechanical ventilation involves considering the four phases of the respiratory cycle: (1) initiation of respiration and a variable that is controlled, often referred to as *mode* ; (2) inspiratory phase characteristics, which determine the duration of inspiration and how the pressure or volume is delivered; (3) termination of inspiration, often referred to as *cycle* ; and (4) expiratory phase characteristics. Ideally, mechanical ventilation should not completely take over the work of breathing, but rather should assist the patient's own respiratory effort. In the absence of any patient effort, respiratory muscle deconditioning may occur, making weaning from mechanical ventilation more difficult.

Initiation of Inspiration and the Control Variable (Mode)

The initiation of inspiration may be set to occur at a predetermined rate and interval regardless of patient effort, or it could be timed in response to patient effort. Once inspiration is initiated, the ventilator breath either is controlled entirely by the ventilator (*control mode*) or supports the patient's inspiratory effort to a predetermined inspiratory volume or pressure target (*support mode*). Advances in technology allow for greater patient-ventilator synchrony to occur. The ventilator may be set to be *triggered* by the signal it receives as a result of patient effort. This feature may be in the form of lowering of either pressure (*pressure trigger*) or airflow (*flow trigger*) in the ventilator circuit generated by the patient's inspiratory effort. If no such signal is received because of lack of patient effort, the ventilator delivers a breath at an interval selected by the operator.

Control Modes

Intermittent Mandatory Ventilation Mode.

In intermittent mandatory ventilation (**IMV**), the inspiration is initiated at a set frequency with a timing mechanism independent of patient effort. In between machine-delivered breaths, the patient can breathe spontaneously from a fresh source of gas. IMV allows for adjustment of ventilator support according to the patient's needs, making it useful in the weaning process. Lack of synchrony between machine-delivered breaths and patient efforts may result in ineffective ventilation and patient discomfort, especially when IMV is delivered at a high rate. In such cases the patient may require sedation and pharmacologic neuromuscular blockade for efficient delivery of V_T . To obviate this problem, **synchronized** IMV (**SIMV**) is used, whereby the machine-delivered breaths are triggered by the patient's inspiratory efforts (Fig. 89.10). In between the machine-delivered breaths, a fresh source of gas is available for spontaneous patient breaths. In the absence of patient effort, the patient receives a backup rate, as in IMV mode. Even with SIMV, ventilator-patient asynchrony can occur, because V_T , inflation pressure, and inspiratory time are determined by the ventilator alone.

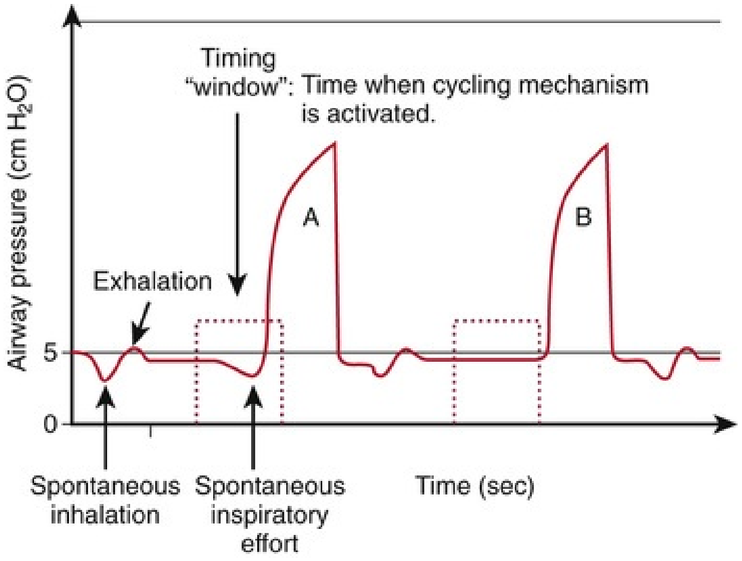

FIG. 89.10 Synchronized intermittent mandatory ventilation. At set intervals, the ventilator's timing circuit becomes activated and a timing "window" appears *(dotted line area)* . If the patient initiates a breath in the timing window, the ventilator delivers a mandatory breath *(A)* . If no spontaneous effort occurs, the ventilator delivers a mandatory breath at a fixed time after the timing window *(B)* . (From Banner MJ,

Gallagher TJ: Respiratory failure in the adult: ventilatory support. In Kirby RR, Smith RA, Desautels DA, editors: *Mechanical ventilation* , New York, 1985, Churchill Livingstone.)

Assist-Control Mode.

In assist-control (AC) mode, every patient breath is triggered by pressure or flow generated by patient inspiratory effort and “assisted” with either preselected inspiratory pressure or volume. The rate of respirations is therefore determined by the patient's inherent rate. A backup total (patient and ventilator) obligatory rate is set to deliver a minimum number of breaths. On AC mode, with a backup rate of 20 breaths/min and a patient's inherent rate of 15 breaths/min; the ventilator will assist all the patient's breaths, and the patient will receive 5 additional breaths/min. On the other hand, a patient with an inherent rate of 25 breaths/min will receive all 25 breaths assisted. Although useful in some patients, the AC mode cannot be used in the weaning process, which involves gradual decrease in ventilator support.

Control Variable

Once initiated, either the VT or the pressure delivered by the machine can be controlled. The machine-delivered breath is thus referred to as either volume controlled or pressure controlled (Table 89.11). With **volume-controlled ventilation (VCV)** , machine-delivered volume is the primary control, and the inflation pressure generated depends on the respiratory system's compliance and resistance. Changes in respiratory system compliance and resistance are therefore easily detected from changes observed in inflation pressure. In **pressure-controlled ventilation (PCV)** the pressure change above the baseline is the primary control, and the Vt delivered to the lungs depends on the respiratory system's C and R. Changes in respiratory system C and R do not affect inflation pressure and may therefore go undetected unless the exhaled Vt is monitored.

Table 89.11

Characteristics of Pressure-Controlled and Volume-Controlled Methods of Ventilation

	PRESSURE-CONTROLLED VENTILATION	VOLUME-CONTROLLED VENTILATION
Control setting(s)	Inflation pressure	Tidal volume

	Inspiratory time Rise time	Flow rate Inspiratory flow pattern (constant vs decelerating)
Machine-delivered volume	Depends on respiratory system compliance and resistance	Constant
Inflation pressure	Constant	Depends on respiratory system compliance and resistance
Endotracheal tube leak	Somewhat compensated	Leaked volume part of tidal volume
Distribution of ventilation	More uniform in lungs with varying time constant units	Less uniform in lungs with varying time constant units
Patient comfort	Possibly compromised	Possibly enhanced
Weaning	Inflation pressure adjustment required to deliver desired tidal volume	Tidal volume remains constant; inflation pressure automatically weaned

VCV and PCV have their own advantages and disadvantages (Table 89.11). Generally speaking, PCV is more efficient than VCV in terms of amount of V_T delivered for a given inflation pressure during ventilation of a lung that has nonuniform TC, as in asthma. In VCV, relatively less-obstructed airways are likely to receive more of the machine-delivered volume throughout inspiration than relatively more-obstructed airways with longer TC (Fig. 89.11 *A*). This situation would result in uneven ventilation, higher peak inspiratory pressure (PIP), and a decrease in C_{DYN} . In PCV, because of a constant inflation pressure that is held throughout inspiration, relatively less-obstructed lung units with shorter TC would achieve pressure equilibration earlier during inspiration than the relatively more-obstructed areas. Thus, units with shorter TCs would attain their final volume earlier in inspiration, and those with longer TCs would continue to receive additional volume later in inspiration (Fig. 89.11 *B*). This situation would result in more even distribution of inspired gas, delivery of more V_T for the same inflation pressure, and improved C_{DYN} compared with VCV.

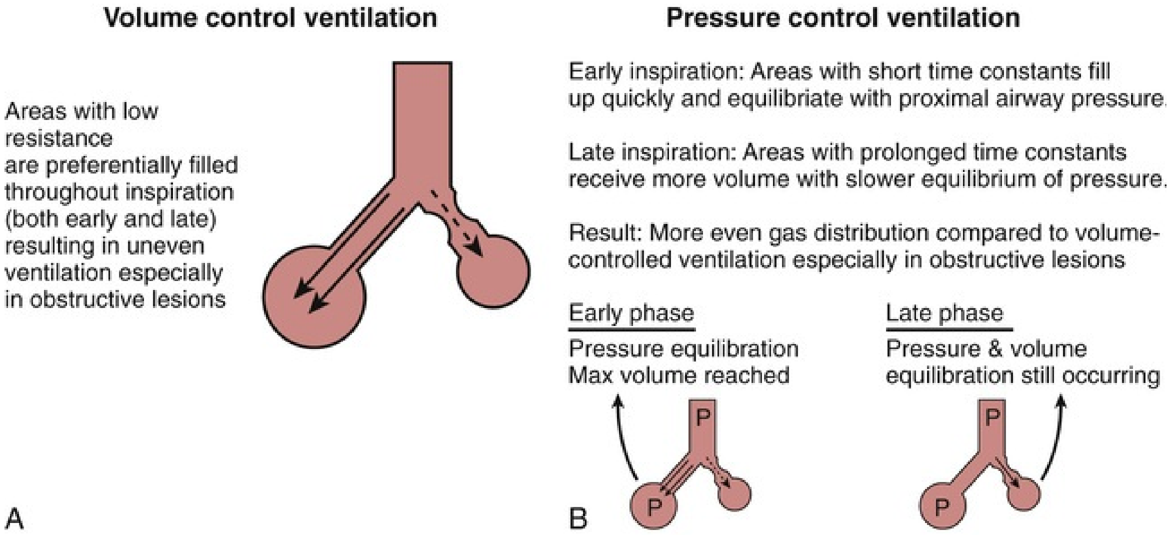
Volume control ventilation
Areas with low resistance are preferentially filled throughout inspiration (both early and late) resulting in uneven ventilation especially in obstructive lesions
A
Pressure control ventilation
Early inspiration: Areas with short time constants fill up quickly and equilibriate with proximal airway pressure.
Late inspiration: Areas with prolonged time constants receive more volume with slower equilibrium of pressure.
Result: More even gas distribution compared to volume-controlled ventilation especially in obstructive lesions
Early phase
Pressure equilibration
Max volume reached
Late phase
Pressure & volume equilibration still occurring
P
P
P
P
B

FIG. 89.11 **A,** In volume-controlled ventilation (VCV), tidal volume (VT) is delivered to the less-obstructed areas throughout inspiration. Obstructed areas of the lung therefore receive a lower proportion of VT , resulting in uneven ventilation. **B,** In pressure-controlled ventilation (PCV), less-obstructed areas equilibrate with inflation pressure and therefore receive most of their VT early during inspiration. More-obstructed areas, with prolonged time constants, require longer time for pressure equilibration and therefore continue to receive a portion of their VT later during inspiration. The entire VT is more evenly distributed than with volume-cycled ventilation.

Pressure-regulated volume control (PRVC) combines the advantages of VCV and PCV. In this mode, the VT and TI are controlled as primary variables, but the ventilator determines the amount of pressure needed to deliver the desired VT . Inflation pressure is thus adjusted to deliver the prescribed VT over the TI , depending on the patient's respiratory C and R.

Support Modes

Pressure-support ventilation (PSV) and **volume-support ventilation (VSV)** are designed to support the patient's spontaneous respirations. With PSV, initiation of inspiration is triggered by the patient's spontaneous breath, which is then "supported" by a rapid rise in ventilator pressure to a preselected level. The inspiration is continued until the inspiratory flow rate falls to a set level (generally 25% of peak flow rate) as the patient's lungs fill up. Thus, TI is controlled by the patient's own efforts. PSV can be combined with SIMV so that any breath above the SIMV rate is supported by PSV. Allowing the patient to control as much of the rate, VT , and inspiratory time as possible is considered a gentler form of mechanical ventilation than SIMV, in which the VT (or inflation pressure) and TI are preset. PSV as the sole source of mechanical ventilator support is often not adequate for patients with severe lung disease. However, PSV is especially useful in patients being weaned and in those who require mechanical ventilation for relatively minor lung disease or for neuromuscular weakness.

VSV is similar to PSV, in that all the spontaneous breaths are supported. In VSV, inspiratory pressure to support spontaneous breaths is adjusted to guarantee a preset VT . If there is a change in respiratory mechanics or patient effort, the inspiratory pressure to support the breath initiated by patient effort is automatically adjusted to deliver the set VT .

Inspiratory Phase Characteristics

TI , inspiratory flow waveform, and pressure rise time can be adjusted in the inspiratory phase to suit the patient's respiratory mechanics.

In PCV the duration of TI is directly set in seconds. In VCV the TI can be adjusted by adjusting the inspiratory flow (volume/time). The choice of TI value depends on the respiratory rate, which determines the total duration of each breath, and on the estimation of inspiratory and expiratory TCs. Decreasing the flow rate delivery increases TI , and vice versa. With an increase in TI , the pulmonary capillary blood is exposed to a higher level of PAO$_2$ for a longer time. This feature is beneficial in diseases with decreased FRC, such as ARDS and pulmonary edema. An increase in TI also increases VT without increasing inflation pressure in PCV if inspiratory flow is still occurring at end-expiration. It must be recognized that at a given ventilator rate, an increase in TI decreases expiratory time (TE). Therefore, any strategy that employs an increase in the inspiratory component of the respiratory cycle should ensure that the decreased TE is still sufficient for complete exhalation.

Inspiratory flow waveform can be adjusted in VCV mode as either a constant flow (square waveform) or a decelerating flow (descending ramp waveform). With a square waveform, flow is held constant throughout inspiration. In a descending ramp waveform, flow is maximal at the start of inspiration and declines throughout its duration. It is debatable which flow pattern is better for a given disease.

In PCV and PSV, the prescribed PIP is reached through delivery of airflow. *Pressure rise time* reflects the time required for the ventilator to reach PIP and can be adjusted by control of flow at the beginning of the inspiratory phase. The inspiratory flow rise time is adjusted to provide comfort for a patient who is awake and also to prevent an extremely rapid rise in inspiratory pressure, which might result in barotrauma.

Termination of Inspiration (Cycle)

The 2 most commonly used inspiratory terminating mechanisms in control modes are time-cycled and volume-cycled. With a **time-cycled** mechanical breath, inspiration is terminated after a preselected TI has elapsed, whereas with **volume-cycled** breath the inspiration ends after a preselected volume has been delivered by the machine into the ventilator circuit. A time-cycled breath is almost always pressure-limited, with the PIP held constant for the duration of inspiration. A volume-cycled breath can be pressure-limited as a safety mechanism to avoid barotrauma. The inspiration-terminating mechanism is set somewhat differently in support modes. In PSV the inspiration is set to end after the inspiratory flow decreases below a certain percentage (usually 25%) of peak inspiratory flow. This happens when the patient no longer desires to receive additional VT . Such a breath can be termed **flow-cycled** . In VSV the inspiration is terminated when the patient has received the desired VT .

Expiratory Phase Maneuvers

The most useful expiratory phase maneuver is the application of PEEP, which is applied to both the control breath and the assisted breath. The most important clinical benefits of PEEP are to recruit atelectatic alveoli and to increase FRC in patients with alveolar-interstitial diseases and thereby improve oxygenation. There is growing recognition that even a brief disconnection from a ventilator, and therefore having zero end-expiratory pressure (ZEEP), can result in significant alveolar **derecruitment** and decline in oxygenation. In patients with obstructive lesions in which insufficient exhalation results in air trapping and auto-PEEP, extrinsic PEEP (that applied through a mechanical device) can prevent airway closure during expiration and improve ventilation. Other salutary effects of PEEP include redistribution of extravascular lung water away from gas-exchanging areas, improved V̇/Q̇ relationship, and stabilization of the chest wall. The effect of PEEP on lung C is variable, depending on the level of PEEP provided and the patient's pulmonary mechanics. By shifting the VT ventilation to a more favorable part of the pressure-volume curve, PEEP may recruit more alveoli, delay airway closure, and improve lung C. Excessive PEEP, on the other hand, may lead to overdistention of alveoli and reduced C. The effect of PEEP in individual patients can be ascertained by measuring exhaled V_T and calculating C_{DYN} . Other deleterious effects of PEEP include decreased venous return, increased pulmonary vascular resistance, and decreased cardiac output.

Additional Ventilatory Modalities

Airway Pressure Release Ventilation

Airway pressure release ventilation (**APRV**) improves oxygenation in patients with severe hypoxemic respiratory failure resulting from alveolar-interstitial disease. This modality applies a CPAP, designated $CPAP_{HIGH}$, to recruit and maintain FRC with brief intermittent release phases of $CPAP_{LOW}$ to allow alveolar gas to escape. $CPAP_{HIGH}$ is analogous to PIP, and $CPAP_{LOW}$ is similar to setting PEEP. In contrast to the patient receiving conventional mechanical ventilation, a patient receiving APRV spends the majority of time in the $CPAP_{HIGH}$ phase, which may last as long as 3-5 sec with a brief (0.3-0.5 sec) time in the $CPAP_{LOW}$ phase. These atypically long T_I s are tolerated because of a floating expiratory valve in the ventilator circuit that permits spontaneous breathing during $CPAP_{HIGH}$ phase. Therefore, even if the $CPAP_{HIGH}$ phase can be considered “inspiratory” and the $CPAP_{LOW}$ phase “expiratory” in regard to the ventilator, the patient is able to breathe spontaneously during both these phases. The longer ventilator T_I recruits lung units, and the ability to breathe spontaneously during this phase allows distribution of gas flow to atelectatic lung regions. The outcome benefit of APRV in pediatric hypoxemic respiratory failure has not been proved.

High-Frequency Ventilation

Mechanical ventilation at supraphysiologic rates and low V_T , known as high-frequency ventilation (**HFV**), improves gas exchange in a select group of patients who show no response to traditional ventilatory modalities. The mechanism of alveolar ventilation in HFV is very different from that in conventional ventilation, in that HFV is less dependent on V_T and more dependent on asymmetric velocities and convective dispersion of inspired gas.

Patients with severe persistent hypoxic failure are most likely to benefit from HFV. HFV is also helpful in patients with bronchopleural fistula and persistent air leaks. The main tenet of HFV is to recruit lung volume with a high MAP and produce smaller fluctuations in alveolar pressure during inspiration and expiration, thus maintaining a satisfactory FRC and reducing alveolar stretch. The 2 most investigated techniques of HFV are HFO and HFJV.

The most commonly used HFV modality is **high-frequency oscillation (HFO)** , which employs a mechanism to generate to-and-fro air movement. Additional air is drawn in (entrained) through a parallel circuit via a Venturi effect. Air is pushed in during inspiration and actively sucked out during expiration. The main determinants of oxygenation are FIO_2 and MAP, whereas ventilation is determined by changes in pressure (amplitude) from the MAP. Commonly used respiratory frequency varies from 5 Hz (300 breaths/min) in adults and older children, to 6-8 Hz (360-480 breaths/min) in young children, 8-10 Hz (480-600 breaths/min) in infants, and 10-12 Hz (600-720 breaths/min) in newborn and premature infants.

In **high-frequency jet ventilation (HFJV)** , a high-frequency interrupter is interposed between a high-pressure gas source and a small cannula that is incorporated in the ETT. The cannula propels tiny amounts of gas (jets) at high velocity and high frequency through the ETT. An additional amount of gas is entrained from a parallel circuit. Unlike in HFO, expiration occurs passively in HFJV as a result of elastic recoil of the lung and the chest wall. PEEP is set through the parallel circuit by a conventional ventilator in line. Respiratory rate is generally set at 420 breaths/min. Major determinants of oxygenation are Fio_2 and PEEP, and the major determinant of ventilation is PIP.

Conventional Ventilator Settings

Fraction of Inspired Oxygen

The shape of the hemoglobin-O_2 dissociation curve dictates that oxygen content in the blood is not linearly related to PaO_2 . A PaO_2 value that results in an oxyhemoglobin saturation of 94% is reasonable in most situations, because a higher PaO_2 would cause minimal increase in arterial oxygen content, and a modest (10 mm Hg) drop in PaO_2 would result in minimal decrease in oxyhemoglobin saturation. In most cases, a PaO_2 value of 70-75 mm Hg is a reasonable goal. F_{IO_2} values that are higher than those necessary to attain oxyhemoglobin saturations of approximately 95% expose the patient to unnecessary oxygen toxicity. Whenever possible, F_{IO_2} values should be decreased to a level ≤0.40 as long as oxyhemoglobin saturation remains ≥95%.

Mode

The choice of mode of ventilation depends on how much ventilator-patient interaction is desired and the disease entity that is being treated. SIMV or AC is chosen as the control mode; PCV, VCV, or PRVC as the variable that is to be controlled; and pressure support and volume support are the choices for support modes.

Tidal Volume and Rate

As previously discussed, alveolar ventilation, the chief determinant of Pa_{CO_2}, is calculated using V_T, respiratory rate, and V_D. A change in V_T results in a corresponding change in alveolar ventilation without affecting V_D-ventilation. A change in respiratory rate will affect alveolar ventilation as well as the V_D-ventilation. Choice of V_T and rate depends on the TC. In a patient with relatively normal lungs, an age-appropriate ventilator rate and a V_T of 7-10 mL/kg would be appropriate initial settings. Diseases associated with decreased TC (decreased static compliance; e.g., ARDS, pneumonia, pulmonary edema) are best treated with small (6 mL/kg) V_T and relatively rapid rates (e.g., 25-40 breaths/min). Diseases associated with prolonged TCs (increased airway resistance; e.g., asthma, bronchiolitis) are best treated with relatively slow rates and higher (10-12 mL/kg) V_T. In PCV the delivered V_T depends on the C and R of the patient's respiratory system and needs to be monitored to ensure the appropriate amount for a given situation. An inflation pressure of 15-35 cm H_2O is sufficient for most patients, but it may need adjustment, depending on the volume of exhaled V_T. It should be emphasized that achieving a *normal* Pa_{CO_2} value is not a goal of mechanical ventilation. Mild hypercapnia (permissive hypercapnia) should be acceptable, especially when one is attempting to limit injurious inflation pressures or V_Ts.

Inspiratory Time and Expiratory Time

TI and TE are adjusted by setting inspiratory flow rate in VCV and by setting the precise TI in PCV. Increasing the TI results in increased MAP, improved oxygenation in diseases with decreased FRC, and better distribution of VT in obstructive lung disease. Sufficient expiratory time must be provided to ensure adequate emptying of the alveoli.

Positive End-Expiratory Pressure

The best level of PEEP depends on the disease entity that is being treated, and it may change in the same patient from time to time. Decisions are often based on the PaO_2/FIO_2 ratio and the measurement of C_{DYN}.

Patient-Ventilator Asynchrony

Patient-ventilator asynchrony occurs when the patient's respiratory pattern does not match that of the ventilator. This can occur during all phases of respiration. Adverse effects of patient-ventilator asynchrony include wasted effort, ineffective delivery of desired VT , excessive generation of intrathoracic pressure resulting in barotrauma and adverse effects on cardiac output, increased work of breathing, and patient discomfort. Although several mechanisms exist to facilitate patient-ventilator asynchrony, a certain amount of asynchrony is inevitable unless the patient is pharmacologically sedated and paralyzed.

Triggering the Ventilator

The patient must be able to trigger the ventilator without excessive effort. Ventilators can be pressure-triggered or flow-triggered. With **pressure triggering** , the inspiratory valve opens and flow is delivered when a set negative pressure is generated within the patient-ventilator circuit during inspiration. The amount of pressure required to trigger an inspiration depends on the pressure trigger sensitivity. In **flow triggering** the ventilator provides a base flow of gas through the ventilator-patient circuit. When a flow sensor on the expiratory limb of the patient-ventilator circuit detects a decrease in flow as a result of the patient's inspiratory effort, the inspiratory valve opens and a ventilator breath is delivered. The degree of change in flow required to trigger an inspiration depends on the flow trigger sensitivity. Flow triggering is considered to be more comfortable, primarily because the patient receives some flow before triggering the ventilator, in contrast to pressure triggering, in which no flow is provided until the ventilator breath is triggered. Increasing the trigger sensitivity by decreasing the change in either pressure or flow needed to trigger an inspiration decreases the work of breathing. However, reducing the required pressure or flow excessively could result in accidental triggering and unwanted breaths by turbulence, caused by condensation in the ventilator circuit, ETT air leaks, or cardiac oscillations.

Selection of Appropriate Inspiratory Time

The duration of T_I should match the patient's own inspiratory phase. If T_I is too long, the patient's drive to exhale may begin before the ventilator breath has cycled off. When this occurs, exhalation occurs against inspiratory flow and a closed exhalation valve, resulting in increased work of breathing, excessive rise in intrathoracic pressure, and discomfort. If T_I is too short, the patient may be still inhaling without respirator support. In general terms, T_I is usually initiated at 0.5-0.7 sec for neonates, 0.8-1 sec in older children, and 1-1.2 sec for adolescents and adults. Adjustments need to be made through individual patient observations and according to the type of lung disease present. In patients with severe lung disease (both obstructive and restrictive), unnatural T_I and T_E values may have to be selected, as discussed earlier. In such situations, adequate analgesia, sedation, and in extreme cases neuromuscular blockade may be needed.

Selection of Inspiratory Flow Pattern

In VCV, inappropriate flow may be another source of patient-ventilator dyssynchrony. After initiation of inspiration, if the set amount of flow is inadequate to meet patient demand, a state of **flow starvation** occurs, resulting in excessive work of breathing and discomfort. Such patients may require a decelerating inspiratory flow pattern, in which a higher flow is provided in the beginning of inspiration and less toward the end as the lungs fill up. On the other hand, such a pattern may be uncomfortable for a patient who desires more gradual alveolar filling. The selection of inspiratory flow pattern should be based on the individual patient's respiratory mechanics. In PCV and PSV, the inspiratory rise time determines the manner in which the airway pressure is raised and V_T delivered. Considerations for choosing the appropriate rise time in

PCV and PSV are similar to those for choosing the inspiratory flow pattern in VCV.

Use of Support Modes

A conscious patient should be allowed to have spontaneous breaths that are supported by either PSV or VSV. This approach minimizes the mandatory breaths generated by the ventilator that are beyond the patient's control to modulate. Therefore, continued assessments should be made to determine whether the patient is able to maintain ventilatory requirements more in support modes and less in control modes.

Use of Sedation and Pharmacologic Neuromuscular Blockade

Having a conscious but comfortable patient is a desirable goal during mechanical ventilation. Spontaneous breaths with good muscle tone and presence of cough are important for adequate clearance of tracheobronchial secretions. The patient's ability to indicate distress is also important in identifying and preventing potential injurious factors. In certain situations, management of patient-ventilator asynchrony assumes much greater importance when the asynchrony is causing unacceptable derangement of gas exchange and ventilator-induced lung injury. Both alveolar interstitial lung pathology and obstructive airway diseases may necessitate unnatural and uncomfortable settings for respiratory rate, T_I , and inflation pressures. In such patients, deep sedation is often necessary; dexmedetomidine, benzodiazepines, and opiates are the agents most commonly used for this purpose. In extreme situations, pharmacologic neuromuscular blockade with a nondepolarizing agent, such as vecuronium, is required to abolish any patient effort and respiratory muscle tone. When such pharmacologic paralysis is used, deep sedation must be ensured so that the patient does not sense pain and discomfort. Pharmacologic sedation and paralysis can ensure total control of the patient's ventilation by mechanical means and may result in lifesaving improvement in gas exchange with reduction in inflation pressures. However, long-term use of such agents may be associated with undesirable consequences and higher morbidity. The risk of inadequate tracheobronchial secretions and atelectasis is potentially greater. Long-term use of pharmacologic sedation may be associated with chemical dependency and withdrawal manifestations, and prolonged neuromuscular blockade is associated with neuromyopathy in critically ill patients. The benefits of sedation and pharmacologic paralysis therefore should be carefully balanced with the risks, and periodic assessments should be made to determine the need for their continuation.

Cardiopulmonary Interactions

Mechanical ventilation can have salutary as well as adverse effects on cardiac performance. By decreasing oxygen consumption necessary for work of breathing, oxygen supply to vital organs is improved. Positive pressure breathing decreases LV afterload, thus enhancing stroke volume and cardiac output in patients with failing myocardium (e.g., myocarditis). On the other hand, the decreased systemic venous return may further compromise stroke volume in hypovolemic patients. Such patients will require intravascular fluid loading. Also, an increase in pulmonary vascular resistance (PVR) caused by positive intrathoracic pressure may result in further decompensation of a poorly performing right ventricle. PVR is at its lowest value at an optimum FRC. When FRC is too low or too high, PVR (and therefore the right ventricular afterload) is increased. Both desirable and undesirable effects of cardiopulmonary interactions may coexist and require ongoing assessment and necessary interventions (Table 89.12).

Table 89.12

Suggested Mechanical Ventilation Strategies in Various Clinical Situations

SITUATION	DISEASE	STRATEGY
Low compliance, normal resistance	ARDS	PCV, APRV, HFO, HFJV
Normal compliance, high resistance	Asthma	PVC, PRVC
Normal compliance, normal resistance, for weaning	Head trauma, drug overdose, subglottic stenosis	VCV

APRV, Airway pressure release ventilation; ARDS, acute respiratory distress syndrome; HFO, high-frequency oscillation; HFJV, high-frequency jet ventilation; PCV, pressure-controlled ventilation; PRVC, pressure-regulated volume control; VCV, volume-controlled ventilation.

Monitoring Respiratory Mechanics

Exhaled Tidal Volume

Exhaled tidal volume (VTE) is measured by a pneumotachometer in the ventilator circuit during exhalation. In VCV, part of the machine-delivered volume may leak out during inspiration and therefore never reach the patient. Measurement of VTE more accurately describes the VT that is contributing to the patient's alveolar ventilation. In PCV the VTE depends on the patient's respiratory system compliance and resistance and therefore offers valuable diagnostic clues. A decrease in VTE during PCV is indicative of either decrease in compliance or increase in resistance and is helpful in directing the clinician to appropriate investigation and management. An increase in VTE is indicative of improvement and may require weaning of inflation pressures to adjust the VTE .

Peak Inspiratory Pressure

In VCV and PRVC, the PIP is the secondary variable determined by the patient's respiratory system compliance and resistance. An increase in PIP in these modes is indicative of decreased C (e.g., atelectasis, pulmonary edema, pneumothorax) or increased R (e.g., bronchospasm, obstructed ET). During VCV and PRVC, decreasing the respiratory rate or prolonging the TI will result in a lower PIP in patients with prolonged TCs because more time will be available for alveoli to fill. In such patients, a decrease in PIP suggests increased C or decreased R of the respiratory system.

Respiratory System Dynamic Compliance and Static Compliance

The changes in PIP during VCV and PRVC, and in VTE during PCV, are determined by C_{DYN} of the respiratory system (lung and chest wall). C_{DYN} is calculated as follows:

$$C_{DYN} = \mathrm{VTE} \div (\mathrm{PIP} - \mathrm{PEEP})$$

C_{DYN} takes into account both the flow-resistive and the elastic properties of the respiratory system. Changes in C_{DYN} can be used to assess effects of different levels of PEEP as tidal ventilation is shifted along the slope of the volume-pressure curve (see Fig. 89.7). An increase in PEEP in alveolar-interstitial diseases (increased elastance), resulting in an increase in C_{DYN} suggests alveolar recruitment, whereas a decrease in C_{DYN} may indicate overdistention. Similarly, in obstructive diseases (increased R), adjustment in PEEP levels to ameliorate airway collapse during exhalation can be guided by monitoring C_{DYN} . To assess only the elastic recoil of the lung, measurement of C_{STAT} when there is no airflow is required. This measurement is performed by using an inspiratory hold maneuver with the patient under neuromuscular blockade and observing pressure-time and flow-time waveforms (Fig. 89.12). During this maneuver, inspiratory flow ceases while the expiratory valve continues to remain closed, thus allowing pressure to equilibrate throughout the ventilator circuit and the patient's lungs. This pressure, referred to as the *plateau pressure* (P_{plat}), reflects alveolar pressure. C_{STAT} is calculated as follows:

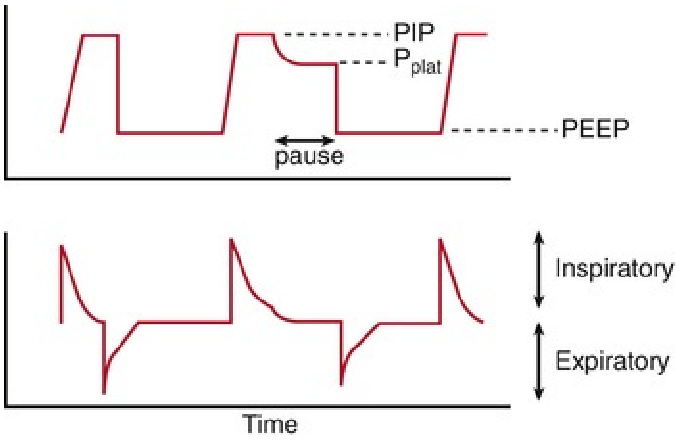

FIG. 89.12 Alveolar pressure is best determined by measurement of plateau pressure (P_{plat}). Inspiration is paused for an extended period, and alveolar gas pressure is allowed to equilibrate with the ventilator circuit pressure. Airway pressure at the end of the inspiratory pause is P_{plat} . The difference between peak inspiratory pressure (PIP) and P_{plat} is meant to overcome flow-resistive properties of the lung, whereas P_{plat} reflects the pressure needed to overcome elastic properties of lung and chest wall. PEEP, Positive end-expiratory pressure.

$$C_{STAT} = VTE \div (P_{plat} - PEEP)$$

The difference between C_{DYN} and C_{STAT} is attributable to airway resistance. This difference is minimal in alveolar-interstitial diseases but substantial in airway obstruction.

Assessment of Auto-PEEP

Auto-PEEP is assessed with the use of an expiratory pause maneuver in which inspiration is delayed and alveolar pressure is allowed to equilibrate with the airway. In diseases with airway obstruction, insufficient alveolar emptying may occur if exhalation time is not adequate. The alveolar pressure in excess of the set PEEP at the completion of the expiratory pause is measured as auto-PEEP or intrinsic PEEP. Auto-PEEP can have adverse effects on ventilation and hemodynamic status. It can be managed by decreasing the respiratory rate or T_I and thus allowing longer time for exhalation. Auto-PEEP may also be managed by increasing the set PEEP (*extrinsic* PEEP), thereby delaying airway closure during exhalation and improving alveolar emptying.

Assessment of Dead Space Ventilation

Positive pressure ventilation and application of PEEP may result in a decrease in venous return, cardiac output, and therefore pulmonary perfusion as well. Ventilation of poorly perfused alveoli results in dead space ventilation, which does not contribute to gas exchange. The V_D/V_T fraction can be calculated (see Chapter 89). Normal V_D/V_T is 0.33. Increased V_D/V_T is indicative of poorly perfused alveoli. Patients with increased V_D/V_T may require intravascular volume infusion or other means of augmenting the cardiac output to improve pulmonary perfusion. The V_D/V_T fraction is calculated and displayed by commercially available capnographs, which measure endotracheal P_{ETCO_2} continuously.

Ventilator-Induced Lung Injury

As with most medical therapies, mechanical ventilation can be harmful. Pathophysiology of ventilator-induced lung injury can be multifactorial. Large lung volumes and high pressures delivered with increased frequency cause cyclic strain, which may lead to disruption of the tight junctions between the alveolar epithelial and capillary endothelial cells, with intracapillary blebs resulting in alveolar and interstitial edema. This **biotrauma** may cause the release of proinflammatory cytokines that further injure the lung and travel in the blood outside the lung, leading to multiorgan failure. Evidence shows that in patients with ARDS, avoidance of $V_T \geq 10$ mL/kg and $P_{plat} \geq 30$ cm H_2O limits diffuse alveolar damage.

Atelectrauma is shear stress on the alveolar walls caused by cyclic opening and closing of the alveoli. PEEP can be used to prevent collapse and keep alveoli open. It is important that alveolar units are neither overdistended nor collapsed. Careful adjustments of PEEP may also permit the clinician to wean a patient from a high F_{IO_2}, another potential source of lung injury (**oxytrauma**). Although most patients receive an F_{IO_2} of 1.00 during endotracheal intubation and at the beginning of mechanical ventilation, increasing PEEP to recruit alveoli without overdistention should be quickly instituted to improve oxygenation and permit weaning of the F_{IO_2}. Although the F_{IO_2} value below which there is no risk of oxygen toxicity is unknown, most clinicians aim for a value <0.6. Regional mechanics may play a role in lung injury.

Ventilator-Associated Pneumonia

The pathophysiology of ventilator-associated pneumonia (VAP) is multifactorial. Aspiration of oral and/or gastric secretions, colonization of ETTs, and suppression of cough reflexes with sedation all play a role. New-onset fever and leukocytosis accompanied by demonstration of an infiltrative process on chest radiography are consistent with a diagnosis of VAP. This complication can lead to worsened gas exchange, increased duration of ventilation, and even death. Elevation of the head of the bed to 30 degrees after initiation of mechanical ventilation and use of a protocol for oral decontamination during mechanical ventilation are 2 means of reducing the risk for VAP. The most effective strategy to minimize any of the aforementioned complications is regular assessment of extubation readiness and liberation from mechanical ventilation as soon as clinically possible.

Weaning

Weaning from mechanical ventilation should be considered as a patient's respiratory insufficiency begins to improve. Most pediatricians favor gradual weaning from ventilator support. With SIMV, the ventilator rate is slowly reduced, allowing the patient's spontaneous breaths (typically assisted with pressure or volume support) to assume a larger proportion of the minute ventilation. When the ventilator rate is low (<5 breaths/min) such that its contribution to minute ventilation is minimal, assessment of extubation readiness is performed. An alternative method of gradual weaning is transition to PSV. In this mode, no ventilator rate is set, allowing all triggered breaths to be assisted with pressure support. The clinician reduces the pressure support slowly to a low value (<5-10 cm H_2O), at which point assessment of extubation readiness is performed. During either technique, weaning should be halted if tachypnea, increased work of breathing, hypoxemia, hypercapnia, acidosis, diaphoresis, tachycardia, or hypotension occurs.

The most objective means of assessing extubation readiness is a **spontaneous breathing trial (SBT)** . Before performance of an SBT, a patient should be awake with intact airway reflexes, capable of handling oropharyngeal secretions, and with stable hemodynamic status. In addition, gas exchange should be adequate, defined as Pa_{O_2} >60 mm Hg while receiving F_{IO_2} <0.4 and PEEP ≤5 cm H_2O. If these criteria are present, a patient should be started on CPAP with minimal or no pressure support (≤5 cm H_2O). If this SBT is tolerated with no episodes of respiratory or cardiovascular decompensation, successful extubation is likely.

Some neonates and small children cannot be calmed or consoled long enough to complete the SBT. In this situation, extubation readiness must be assessed on a low level of ventilator support. Data suggest a low risk of extubation failure if the patient is comfortable and has stable hemodynamic status, with adequate gas exchange and spontaneous V_T >6.5 mL/kg, while receiving <20% of total minute ventilation from the ventilator. Certain patient populations are at increased risk for extubation failure, such as young infants, children mechanically ventilated for >7 days, and patients with chronic respiratory or neurologic conditions. These children often benefit from transition to a noninvasive form of positive pressure ventilation (e.g., high-flow nasal cannula, CPAP, or BiPAP) delivered via nasal prongs or face mask to increase the odds of successful extubation.

The likelihood of **postextubation upper airway obstruction** , the most common cause of extubation failure in children, cannot be predicted on the basis of an SBT result or bedside measurements of physiologic variables. Traumatic endotracheal intubation and subglottic swelling from ETT irritation, especially in patients who exhibit agitation while receiving mechanical ventilation, are common causes of airway narrowing after extubation. Administration of intravenous corticosteroids (dexamethasone, 0.5 mg/kg every 6 hr for 4 doses before extubation) has been shown to minimize the incidence of postextubation airway obstruction. In patients in whom postextubation airway obstruction develops, the need for reintubation may be obviated by administration of nebulized racemic epinephrine and heliox.

89.2

Long-Term Mechanical Ventilation

See Chapter 446.4 .

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CHAPTER 90

Altitude-Associated Illness in Children (Acute Mountain Sickness)

Christian A. Otto

High-altitude illness represents a spectrum of clinical entities with neurologic and pulmonary manifestations that overlap in their presentations and share common elements of pathophysiology. **Acute mountain sickness (AMS)** is the relatively benign and self-limited presentation, whereas **high-altitude pulmonary edema (HAPE)** and **high-altitude cerebral edema (HACE)** have potentially life-threatening manifestations.

Often overlooked by travelers as high-altitude destinations are cities such as La Paz, Bolivia (3,700 meters, approximately 12,100 feet), Lhasa, Tibet (3,600 m, ~11,800 ft), Cusco, Peru (3,400 m, ~11,200 ft), and Quito, Ecuador (2,850 m, ~9,350 ft), which reside at an elevation where altitude illness is likely to develop. In 2014, >15 million people visited Lhasa, a 6-fold increase over 8 yr since the opening of the Qinghai-Tibet Railway. In the western United States, 35 million people visit alpine resorts each year. Over 40% of those who stay above 3,300 m (~11,000 ft) have been found to suffer from AMS. In Colorado alone, approximately 150,000 children <12 yr old visit the mountains annually on ski holidays with their families. In 2014, AMS symptoms were severe enough to result in 1,350 visits to emergency departments (EDs) throughout Colorado. Because of the increasing family travel to high altitude, thousands of children are likely to develop AMS symptoms.

Etiology

The altitude threshold where clinical illness may begin to occur is 1,500 m (~4,900 ft). At this altitude a mild impairment in oxygen transport begins, although altitude illness is relatively rare until higher elevations are reached. Children with underlying medical problems that impair oxygen transport may be predisposed to developing altitude illness at these lower levels. At *moderate high altitude,* 2,500-3,500 m (~8,000-11,500 ft), arterial oxygen saturation (SaO_2) is generally well maintained; however, mild tissue hypoxia may occur as a result of low arterial oxygen partial pressure (PaO_2), and altitude illness becomes common after rapid ascent above 2,500 m (~8,200 ft). This is the altitude range that most people visit and the elevation of many popular U.S. ski resorts and thus the most common range to find the greatest number of altitude illness cases. *Very high altitude,* 3,500-5,500 m (~11,500-18,000 ft), is associated with the most serious altitude illness; SaO_2 falls below 90%, on the steep portion of the oxyhemoglobin dissociation curve, and marked desaturation may occur with relatively small increases in altitude. At these heights, severe hypoxemia is seen with sleep, exercise, and illness. HAPE and HACE are most common in this environment. *Extreme high altitude,* above 5,500 m (~18,000 ft), generally results in severe altitude illness during acute ascent without supplemental oxygen. Acclimatization at intermediate altitudes is required to reach extreme altitudes. Complete acclimatization is not possible, and long visits result in progressive deterioration.

General Effects of Hypobaric Hypoxia

The partial pressure of oxygen (PO_2) in the atmosphere decreases logarithmically as geographic altitude rises, but oxygen remains a constant 20.93% of the barometric pressure. SaO_2 falls with increasing altitude, eventually triggering central chemoreceptor responses to produce hyperventilation in an attempt to normalize SaO_2; relative hypoventilation exacerbates the hypoxemia of high-altitude exposure. During sleep, periodic breathing associated with high-altitude exposure may result in periods of apnea, causing further arterial oxygen desaturation. Fluid homeostasis often shifts at altitude, resulting in a generalized fluid retention and redistribution into intracellular and interstitial spaces, manifested by peripheral edema, decreased urine output, and impaired gas exchange.

Acclimatization

Gradual ascents allowing for acclimatization over several weeks have allowed successful summiting of many of the world's highest peaks without supplemental oxygen. Without this gradual approach, rapid exposure to extreme altitude results in loss of consciousness and asphyxia in minutes. Children acclimatize as well as, if not better than, adults when comparing heart rate and SaO_2 of 7-9 yr olds to their parents during a slow ascent.

Some of the responses to hypoxia are mediated at the molecular level by *hypoxia-inducible factor* (HIF). This transcriptional activator orchestrates the expression of hundreds of genes in response to both acute and chronic hypoxic conditions. Acclimatization begins at the altitude that causes SaO_2 to fall below sea-level values. Most healthy, unacclimatized visitors to high altitude will not experience a significant drop in SaO_2 (<90%) until they reach elevations above 2,500 m (~8,200 ft). Children with preexisting conditions that reduce oxygen transport may have altitude intolerance and hypoxic stress at lower levels. Of particular importance are both acute and chronic cardiac and respiratory illnesses. An individual's inherent ability to acclimatize is also important. Previous successful acclimatization may be predictive of future responses for adults in similar conditions but may not be the case for children. Some acclimatize easily without developing clinical symptoms; others may transiently develop AMS during acclimatization; and a few have marked reactions to altitude exposure, fail to acclimatize, and develop severe altitude illness.

The most important response to acute hypoxia is an increase in minute ventilation. Peripheral chemoreceptors in the carotid bodies respond to hypoxia by signaling the respiratory control center in the medulla to increase ventilation. This decreases alveolar carbon dioxide partial pressure ($PACO_2$), resulting in a corresponding increase of PAO_2 and arterial oxygenation. This increased ventilation, known as the **hypoxic ventilatory response (HVR)** , varies in magnitude among individuals, may be genetically predetermined, and is related to the ability to acclimatize. Changes in the HVR and the onset of AMS with ascent to high altitude have been found to be remarkably similar between children and their fathers. Additional research has demonstrated that familial clustering of AMS accounts for up to 50% of the variability of AMS onset among children. A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE, whereas a strong HVR enhances acclimatization. As ventilation increases, a respiratory alkalosis occurs, exerting negative feedback on central respiratory control and limiting further ventilation increase. The kidneys excrete bicarbonate in an effort to compensate for the alkalosis. As the pH normalizes, ventilation rises slowly, reaching a maximum after 4-7 days. *This process is enhanced by acetazolamide, which induces a bicarbonate diuresis.*

Increased sympathetic activity and catecholamine release on ascent result in elevation of heart rate, blood pressure, cardiac output, and venous tone. Except at extreme altitudes, acclimatization results in the resting heart rate gradually returning to near sea-level values. *Resting relative tachycardia is evidence of poor acclimatization.*

Hematopoietic acclimatization consists of an increase in hemoglobin (Hb) and red blood cells (RBCs) and in 2,3-diphosphoglycerate (DPG). After acute ascent, an early increase of up to 15% occurs in Hb concentration primarily from fluid shifting into the extravascular space. Acclimatization leads to an increase in plasma volume and total blood volume. Erythropoietin is secreted in a HIF-mediated response to hypoxemia within hours of ascent, stimulating the production of new RBCs, which begin to appear in the circulation in 4 or 5 days. Hypoxemia also increases 2,3-DPG, resulting in a rightward shift of the oxyhemoglobin dissociation curve, favoring release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the curve caused by the respiratory alkalosis from hyperventilation. The result is a net null change in the oxyhemoglobin dissociation curve and an increase in O_2 -Hb binding in the lung, raising Sa_{O_2} . Climbers at extreme altitude respond with marked hyperventilation, alkalosis, and a leftward shift that favors oxygen loading in a hypoxic environment and increases Sa_{O_2} .

Acute Mountain Sickness

Epidemiology and Risk Factors

The incidence of high-altitude illness depends on several variables, including the rate of ascent, previous altitude exposure, and individual genetic susceptibility. Sleeping altitude, final altitude reached, and duration of stay at altitude are also clear risk factors for AMS development. AMS is very common with **rapid ascent** . Climbers around the world who ascend quickly (1 or 2 days) from sea level to altitudes of about 4,300-6100 m (14,000-20,000 ft) have a very high incidence of AMS (27–83%). The rapid ascent profile associated with air travel to high-altitude locations also results in high AMS attack rates. Trekkers who fly into the Khumbu region to explore the Mt. Everest area have a higher incidence of AMS (47%) compared with those who walk (23%). Skiers who visit resorts in the western United States from sea level generally fly or drive to the region but sleep at relatively moderate altitudes (2,000-3,000 m, 6,300-9,700 ft). Among this population, AMS occurs in approximately 25%.

Children have the same incidence of AMS as adults. Individual (genetic) susceptibility for the development of AMS plays a significant role in risk assessment. Most individuals with a previous history of AMS after acute ascent are likely to experience similar symptoms with repeated visits to altitude. Gender does not affect the incidence of AMS.

Pathophysiology

The symptoms of AMS develop several hours after arrival at high altitude, whereas the development of HAPE and HACE generally requires several days of altitude exposure. Because hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness, but rather the initiating factor.

The clinical manifestations of AMS/HACE are primarily the result of central nervous system (CNS) dysfunction caused by hemodynamic mechanical factors and biochemical mediators of permeability. The CNS vasodilatory response to hypoxemia causes an increase in cerebral blood flow and volume. Significant elevation of brain volume is observed in moderate to severe AMS and HACE but has not been demonstrated in mild AMS. Hypoxic alteration of CNS vascular autoregulation and hypertension from exercise may increase pressure transmission to the brain's capillary beds, resulting in transcapillary leakage and vasogenic edema. HIF-mediated vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation may increase permeability. Both mechanical and biochemical activation of the trigeminovascular system have been proposed as the cause of **high-altitude headache** , the primary symptom of AMS. Vasogenic edema has been implicated in severe AMS and HACE, but MRI reveals signal changes in persons with and without clinical AMS. It has been well established that adults can have changes in cognitive function with acute exposure to high altitude. Investigation of cognitive dysfunction in healthy, lowlander European children found significant impairment in verbal short-term memory, episodic memory, and executive functions 24 hr after arrival at 3,450 m (11,400 ft). These impairments were attributed to hypoxia-induced dysfunction of the cerebral white matter. The neuropsychological changes were found to be reversible, since cognitive function returned to baseline on reevaluation 3 mo after returning to sea level.

Many of the responses to hypoxia and altitude exposure occur in both individuals who develop symptoms and those who remain free of AMS. To address the discrepancy in symptomatic illness, the “tight fit” hypothesis was proposed. This theory suggests that the development of AMS/HACE is the result of a lack of intracranial space to accommodate increasing volume from brain swelling and edema that develop at altitude. The adequacy of the intracranial and intraspinal space to buffer changes in brain and cerebrospinal fluid (CSF) volume is the central concept. Buffering occurs as the intracranial CSF is displaced by the foramen magnum into the space available in the spinal canal, followed by increased CSF absorption and decreased CSF production. Individuals with less CSF buffering capacity have less compliance and are hypothesized to become more symptomatic (develop AMS).

Prevention

A comprehensive approach to travel to high altitude with children should focus on 3 phases: planning the ascent and assessment of risk, recognition and management of altitude-associated illness, and follow-up of any illness relative to future travel or diagnostic testing necessary.

Planning for travel to high altitude with children should consider rate of ascent, formulation of an emergency plan for communication and evacuation, and availability of medical care at the high-altitude destination. The availability of medical care and evacuation from altitude will influence the degree of personal preparation necessary. *Slow ascent with time for acclimatization is the best prevention for all forms of altitude illness* . Residing for a few days at moderate altitudes (2,000-3,100 m, 6,600-10,200 ft) followed by graded ascent before arriving at high altitude. One extra night of acclimatization (at the same sleeping altitude) should be taken for every 1,000 m (~3,300 ft) gained. Rapid ascent by air may be avoidable through alternate routes or alternate means of transportation. Exposure to hypobaric hypoxia (reduced barometric pressure with maintained O_2 of 20.9%) decreases end-tidal CO_2 and AMS score, while increasing SaO_2 and exercise endurance on exposure to higher altitude. Staying over in Denver, Colorado, for 1 or 2 days before traveling to higher alpine destinations is an example of such a strategy and has been an effective technique of acclimatization; it has the advantage of reducing the likelihood of developing AMS, HACE, or HAPE. A similar trend in preacclimatization was found with preexposure to *normobaric* hypoxia (maintained barometric pressure with O_2 <20.9%) using commercially available low-O_2 tents or hypoxia breathing masks, although not as effective as preacclimatization with *hypobaric* hypoxia. Slow, gradual ascent is another effective means of acclimatization. The altitude at which someone sleeps is considered more important than the highest altitude reached during waking hours. Guidelines recommend that *above 3,000 m (~9,800 ft), one should not increase sleeping elevation by >500 m (1,600 ft) per day and should include a rest day every 3-4 days with no ascent to a higher sleeping elevation.* Acclimatization and slow ascent are by far the best ways to avoid AMS. The first few days at altitude, individuals should limit their activity and maintain adequate hydration.

Medical risk assessment encompasses consideration of age, previous altitude-associated illness, and possible predisposing circumstances to altitude illness. Very young infants (<4-6 wk) may not have completed the postnatal circulatory transition and may be more vulnerable to altitude-associated desaturation with periodic breathing, right-to-left shunting across the foramen ovale, and hypoxic pulmonary vasoconstriction. Infants who required supplemental oxygen during the neonatal period, especially for pulmonary hypertension, may be at risk for hypoxemia with prolonged altitude exposure. History and physical examination are useful to identify conditions predisposing to HAPE, including recent viral infections, cardiac malformations, or obstructive sleep apnea. Children are known to have greater pulmonary vascular reactivity than adults. Thus, respiratory illnesses such as otitis media, pneumonia, or bronchiolitis that cause release of inflammatory mediators will increase capillary permeability; although normally tolerated at sea level, when superimposed on hypoxia at high elevations, it may predispose children to serious altitude illness. If a child has had a recent upper or lower respiratory infection or otitis media, careful consideration should be given to rapid ascent above 2,000 m (~6,600 ft).

Children with chronic lung disease (e.g., cystic fibrosis, bronchopulmonary dysplasia) and obstructive sleep apnea (OSA) are at increased risk of hypoxia at altitude and development of HAPE. Therefore they should undergo S_{O_2} monitoring during altitude travel. Similarly, children with cardiac lesions involving an increase in pulmonary blood flow or pulmonary hypertension are at greater risk of developing HAPE. Children with trisomy 21 have increased pulmonary vascular reactivity and a higher risk of pulmonary hypertension, and are also more likely to have OSA and hypoventilation. *Children with sickle cell anemia who live at sea level should reconsider travel to altitude, or else ascend carefully because sickle cell crisis may occur at as low as 1,500 m (~5,000 ft).* Those with sickle cell trait may become symptomatic at altitudes above 2,500 m (~8,200 ft).

Acetazolamide is commonly prescribed as prophylaxis against AMS because of its ability to stimulate respiration and increase alveolar and arterial oxygenation. It acts as a carbonic anhydrase inhibitor that induces a renal bicarbonate diuresis, causing a metabolic acidosis that increases ventilation and arterial oxygenation. However, prophylactic pharmacologic therapy with acetazolamide in children is generally not recommended because preacclimatization with slow ascent achieves the same effect. Exceptions include children with previous susceptibility to AMS and an unavoidably rapid ascent, such as flying to La Paz, Bolivia (3,700 m, 12,100 ft), or Cusco, Peru (3,400 m, 11,200 ft), from sea level. The pediatric dose of acetazolamide is 2.5 mg/kg (maximum, 125 mg/dose) every 12 hr (Table 90.1). In adults, it is recommended that prophylaxis begin 24 hr before arriving at altitude and be continued for 48 hr at altitude, or until the final destination high altitude is reached. The respiratory stimulation caused by acetazolamide also improves sleep by eradicating periodic breathing. Side effects are common and include paresthesias, polyuria, lightheadedness, dry mouth, and metallic taste with carbonated beverages. Acetazolamide is a nonbacteriostatic sulfonamide drug, so a history of anaphylactic reaction to sulfa medications is a contraindication to its use. Acetazolamide should be avoided in breastfeeding mothers and pregnant women. **Dexamethasone** is another agent that has been used for AMS prophylaxis in the adult population. However, it should not be used for prophylaxis in children because of the potential for side effects; pancreatitis, pseudotumor cerebri, and interference with normal growth. Low-risk children should not need medications for prophylaxis and should use gradual ascent to prevent illness.

Table 90.1

Medications for Treatment of Altitude-Associated Illness in Children (No Studies in Children for High-Altitude Indications)

MEDICATION	CLASSIFICATION	INDICATION	DOSE AND ROUTE	ADVERSE EFFECTS
Acetazolamide	Carbonic anhydrase inhibitor	AMS prevention[*]	2.5 mg/kg PO every 12 hr; max 125 mg/dose	Collateral effects include paresthesias and taste alteration
		AMS treatment	2.5 mg/kg PO every 12 hr; max 250 mg/dose	
Dexamethasone	Steroid	AMS prevention [†]		Risk of adverse effects precludes prophylactic use
		AMS HACE treatment [‡]	0.15 mg/kg PO/IM/IV every 6 hr; max 4 mg/dose	Hypertension, gastrointestinal hemorrhage, pancreatitis, growth inhibition
Nifedipine	Calcium channel blocker	HAPE treatment (small children) [§]	0.5 mg/kg PO every 4-8 hr; max 20 mg/dose	Hypotension
		HAPE treatment (>60 kg) [§]	30 mg SR PO every 12 hr or 20 mg SR PO every 8 hr	
		Reentry HAPE prevention	Same dose as HAPE treatment	
Sildenafil	Phosphodiesterase-5 inhibitor	HAPE [¶]	0.5 mg/kg/dose PO every 4-8 hr; max 50 mg/dose every 8 hr	

[*] AMS prophylaxis is not routinely recommended in children. It is indicated when rapid ascent profile is unavoidable or with previous altitude illness in child about to undergo similar ascent profile. Doses as low as 1.25 mg/kg every 12 hr have been successful in some children.

[†] Use not warranted due to risk of adverse effects. Use slow, graded ascent or acetazolamide.

[‡] Oxygen and descent are the treatment of choice for severe AMS. If acetazolamide is not tolerated, dexamethasone may be used. Oxygen, descent, and dexamethasone should be used in HACE.

[§] In emergency settings where oxygen and descent are not an option, nifedipine is indicated.

[¶] In emergency settings where oxygen and descent are not an option, if nifedipine is not well tolerated, sildenafil may provide an alternative.

AMS, Acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema, IM, intramuscularly; IV, intravenously; PO, orally; SR, sustained release.

Diagnosis

AMS is easily identified in older children and adolescents using the **Self-Report Lake Louise AMS Scoring System** . The criteria require that the individual be in the setting of a recent gain in altitude, be at the new altitude for at least several hours, and report a headache *plus* at least 1 of the following symptoms: gastrointestinal (GI) upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness or lightheadedness, or difficulty sleeping. Shortness of breath on exertion may also be a part of the clinical picture, although if occurring at rest, the presence of HAPE should be considered in the absence of other causes. The headache may vary from mild to severe; anorexia and nausea, with or without vomiting, are common. Sleep disturbance caused by periodic breathing is common in all visitors to high altitudes but is exacerbated in the setting of AMS. All the symptoms of AMS can range in severity from mild to incapacitating. Symptoms develop within a few hours after ascent and generally reach maximum severity between 24 and 48 hr, followed by gradual resolution. Most adults become symptom free by the 3rd or 4th day. The vague nature of this presentation has resulted in many misdiagnoses and morbidity among adults. In the setting of recent altitude exposure, these symptoms warrant a presumptive diagnosis of AMS and limitation of further ascent. Any evidence of CNS dysfunction, such as mild ataxia or altered mentation, is early evidence of HACE.

In nonverbal young children and infants, recognition of AMS symptoms is more challenging. AMS is often a diagnosis of exclusion and is characterized by nonspecific signs: fussiness, lack of playfulness, anorexia, nausea, vomiting, and disordered sleep. In most cases of AMS in nonverbal young children and infants, all these symptoms are present. *Fussiness* is defined as a state of irritability that is not easily explained by a cause, such as tiredness, wet diaper, hunger, teething, or pain from an injury. Fussy behavior may include crying, restlessness, or muscular tension. Decreased playfulness may be profound. Alterations of appetite may progress to frank vomiting. Sleep disturbance can manifest with either increased or decreased sleep compared to normal patterns. Most often, decreased sleep and the inability to nap are noted.

The **Children's Lake Louise Score (CLLS)** has been successfully tested in preverbal children <4 yr old by parents briefed on the use of the scoring system. The CLLS combines a score for the amount and intensity of unexplained fussiness with a symptom score of how well the child has eaten, played, and slept in the past 24 hr. Evaluating for headache is done by asking if the head hurts or by using a “faces” pain scale. GI symptoms are evaluated by asking children if they are “hungry” rather than trying to evaluate their appetite. A combined score of ≥7 is indicative of AMS (Fig. 90.1). Many of the symptoms manifested by AMS in children may also result from the disruption of normal routine with travel. A change in environment, sleeping accommodation, or eating options can result in a fussy child. The threshold scores for AMS diagnostic criteria are modified to account for these baseline variations. Supplemental oxygen may serve as a diagnostic aid; 2-4 L/min by nasal cannula (27–33% O_2) for 15-20 min should significantly improve headache and other symptoms.

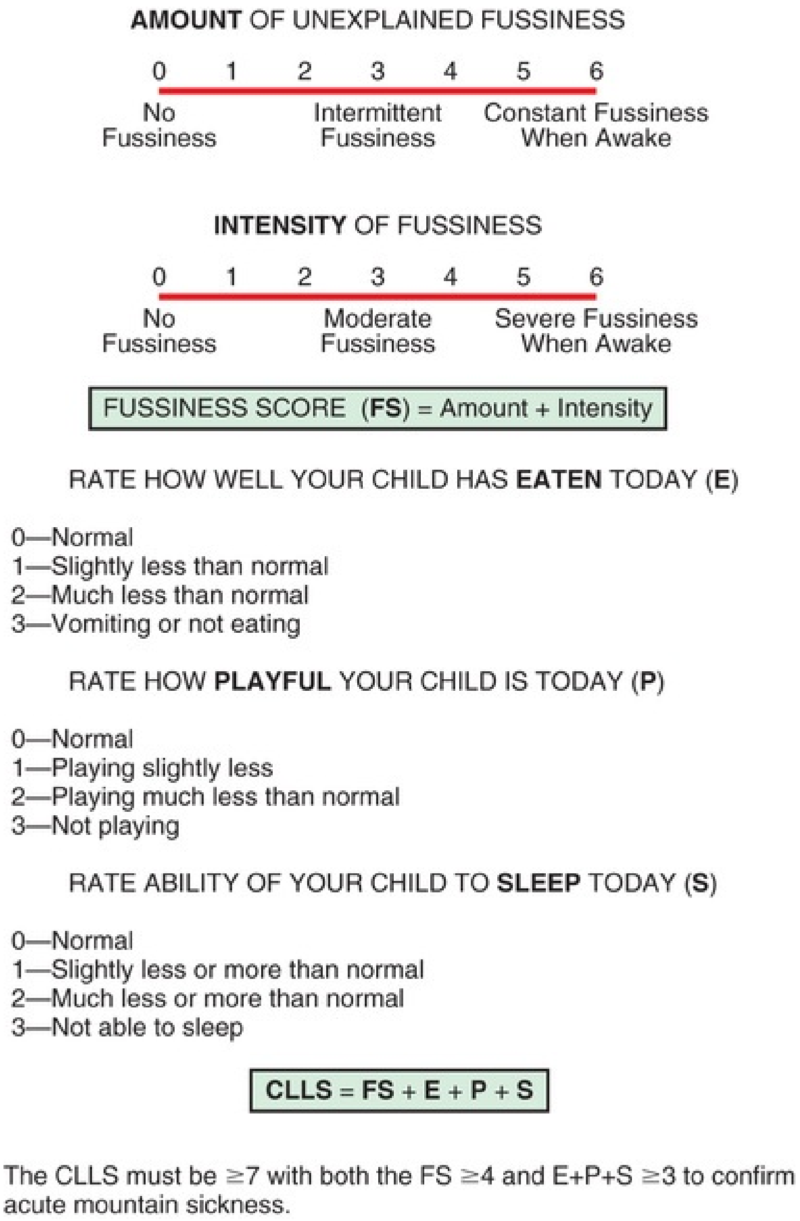

AMOUNT OF UNEXPLAINED FUSSINESS

0 1 2 3 4 5 6

No Fussiness — Intermittent Fussiness — Constant Fussiness When Awake

INTENSITY OF FUSSINESS

0 1 2 3 4 5 6

No Fussiness — Moderate Fussiness — Severe Fussiness When Awake

FUSSINESS SCORE (**FS**) = Amount + Intensity

RATE HOW WELL YOUR CHILD HAS **EATEN** TODAY (**E**)

0—Normal
1—Slightly less than normal
2—Much less than normal
3—Vomiting or not eating

RATE HOW **PLAYFUL** YOUR CHILD IS TODAY (**P**)

0—Normal
1—Playing slightly less
2—Playing much less than normal
3—Not playing

RATE ABILITY OF YOUR CHILD TO **SLEEP** TODAY (**S**)

0—Normal
1—Slightly less or more than normal
2—Much less or more than normal
3—Not able to sleep

CLLS = FS + E + P + S

The CLLS must be ≥7 with both the FS ≥4 and E+P+S ≥3 to confirm acute mountain sickness.

FIG. 90.1 Children's Lake Louise Score (CLLS). ***Fussiness*** **is defined as a state of irritability that is not easily explained by a cause, such as tiredness, hunger, teething, or pain from an injury. Fussy behavior may include crying, restlessness, or muscular tension. Please rate your child's typical fussy behavior** ***during the last 24 hr*** **without the benefit of your intervention.**

If symptoms occur >2 days after arrival at altitude and headache and dyspnea at rest are absent, and if the child fails to improve with supplemental oxygen, an alternative diagnosis should be sought. It must be emphasized that altered mental status, neurologic abnormalities, breathing difficulty, or cyanosis are *not* part of uncomplicated AMS. **Any of these signs warrants immediate medical attention.** If serious bacterial illness, a surgical condition, or another problem meriting specific intervention is suspected in a child, descent to lower altitude is recommended to eliminate the confounding variable of altitude illness.

Periodic Breathing

Periodic breathing at altitude is common at all ages during sleep, resulting in brief, repeated episodes of oxyhemoglobin desaturation. Prepubertal children (9-12 yr old) have similar nighttime oxygen desaturation as their parents but have somewhat more stable breathing patterns with less periodicity. Periodic breathing is not a sign of AMS, but the exacerbation of hypoxia during sleep plays a role in AMS development. Newborn infants normally have periodicity in their respiratory pattern, which is increased by high-altitude exposure and sleep. $\mathrm{Sa}_{\mathrm{O}_2}$ of awake neonates born in Colorado at 3,100 m ranges from 88–91%. During sleep with increased periodic breathing, $\mathrm{Sa}_{\mathrm{O}_2}$ may drop to 81% during the 1st wk of life. The amount and magnitude of respiratory periodicity decrease as the child matures, and $\mathrm{Sa}_{\mathrm{O}_2}$ during sleep increases to 86% after 2 mo. A stable, mature pattern is usually reached by 6 mo of age. Preterm babies may demonstrate marked periodicity with prolonged desaturation as a result of their immaturity. Acute ascent with a child born preterm is best delayed until maturity, when normal pulmonary function and respiratory drive can be demonstrated. Parents of normal healthy babies may become distressed by the marked periodic breathing pattern in their child after ascent to moderate altitude. Clinicians can reassure parents that this is generally not a precursor of true apnea; however, desaturation can occur with periodic breathing in sleep, especially at higher altitudes.

Management

The management of AMS must include strict adherence to the principle that further ascent to a higher sleeping altitude is contraindicated after the symptoms of altitude illness occur. Halting ascent or activity to allow further acclimatization may reverse the symptoms. However, the ascent exacerbates the underlying pathologic processes and may lead to disastrous results. Stopping further ascent and waiting for acclimatization treats most AMS in 1-4 days. Mild cases of AMS may be treated without descent if monitoring by a reliable caregiver is available. Conservative treatment may be provided, including rest, analgesics for headache, and antiemetics for nausea. Ibuprofen and acetaminophen are useful for the treatment of high-altitude headache; for nausea and vomiting, ondansetron dissolving tablets may be used.

More moderate symptoms may require acetazolamide and/or oxygen when conservative measures have proved inadequate. Oxygen is effective in the treatment of moderate AMS, titrated to maintain Sao_2 >94%. Although no studies have formally assessed its use in pediatric patients, anecdotal reports have demonstrated efficacy of acetazolamide in treating mild AMS in this population. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention after 48 hr mandates descent. Descent (500-1,000 m, ~1,600-3,300 ft) is effective treatment for all forms of altitude illness and should be tailored to the individual response. *The presence of neurologic abnormalities (ataxia or altered mentation) or evidence of pulmonary edema (dyspnea at rest) mandates descent because these signs indicate a progression of AMS to severe altitude illness.*

High-Altitude Cerebral Edema

The incidence of HACE is very low and practically unheard of below 4,000 m (~13,100 ft), but it is rapidly fatal if unrecognized. Generally seen in adults with prolonged stays above 4,000 m, HACE is usually associated with concurrent AMS or HAPE but can occur on its own.

HACE is regarded as the extreme expression of the same pathophysiology underlying AMS. The etiology is believed to be secondary to increased cerebral blood flow leading to increased intracranial pressure (ICP). Cerebral venous congestion caused by compression and/or elevated central venous pressure may be an underappreciated mechanism of the increased ICP. In patients with HACE, MRI reveals white matter changes consistent with vasogenic edema that correlate with symptoms; evidence of cytotoxic edema has also been described.

HACE is frequently preceded by AMS, but it is differentiated from severe AMS by the presence of **neurologic signs** , most often ataxia and altered mental status, including confusion, progressive decrease in responsiveness, and eventually coma. Less common signs are focal cranial nerve palsies, motor and sensory deficits, and seizures. The CT scan is consistent with edema and increased ICP. MRI shows a high T2 signal in the white matter, specifically in the splenium of the corpus callosum, with diffusion-weighted technique.

Descent remains the most effective treatment for HACE. If available, supplemental oxygen is useful, especially when descent is not possible or delayed. Portable hyperbaric treatment is beneficial, but its use should not delay descent. Dexamethasone should be administered at a dose of 0.15 mg/kg orally every 6 hr. The few children reported with mild cases of HACE have recovered with dexamethasone and descent.

High-Altitude Pulmonary Edema

Epidemiology and Risk Factors

HAPE is a **noncardiogenic pulmonary edema** caused by intense pulmonary vasoconstriction and subsequent high capillary pressure, secondary to hypoxia, resulting in altered permeability of the alveolocapillary membrane and the extravasation of intravascular fluid into the extravascular space of the lung. *HAPE is the deadliest of the high-altitude illnesses* ; its reported incidence is 0.5%, without an underlying predisposition, and typically requires recent ascent above 3,000 m. The development of HAPE depends on genetic factors typically affecting pulmonary vasoreactivity, rate of ascent, altitude achieved, and time spent at that altitude. Among children, HAPE occurs in 2 distinct settings. **Type I** HAPE (or simply HAPE) occurs in a child who resides at low altitude who travels to high altitude. **Type II** HAPE (also termed **reentry** or **reascent** HAPE) affects children who reside at high altitude but become ill on their return home after descent to lower altitudes. HAPE may also occur in children who develop acute respiratory illnesses that exacerbate hypoxia at high altitude. Fatal outcomes of HAPE in children have been reported. Most mild and moderate cases resolve without difficulty; however, if unrecognized and untreated, rapid progression to death can occur, especially when infection or cardiac conditions complicate the illness.

HAPE affects male and female children more equally than adults, among whom the observed male predominance appears to result from strenuous sport activities and military assignments. The occurrence and even the pathophysiology of HAPE may vary by population and genetic background. Individuals of Tibetan ancestry, resident on the Himalayan plateau and having minimal admixture with other populations, represent the extreme of adaptation to high altitude and rarely experience HAPE. Other native populations residing at high altitude, such as Andeans, do not appear to be protected from HAPE, and certain populations may have genetic polymorphisms associated with pulmonary edema.

A number of conditions may predispose a child to HAPE (Table 90.2). Preexisting viral respiratory infections have been linked to HAPE, especially in children. Cardiorespiratory conditions associated with pulmonary hypertension, such as atrial and ventricular septal defects, pulmonary vein stenosis, congenital absence of a pulmonary artery, and OSA, also predispose to HAPE. Down syndrome is a risk factor for HAPE development, as are previously repaired congenital heart defects and the presence of hypoplastic lungs. Undiagnosed structural cardiopulmonary abnormalities may result in severe hypoxia and/or altitude illness once ascent occurs.

Table 90.2

Conditions Associated With Increased Risk of High-Altitude Pulmonary Edema (HAPE)

Environmental

- Ascent above 2,500 m (~8,200 ft)
- Rapid rate of ascent (generally >1,000 m [~3,300 ft] per day)
- Cold exposure

Cardiac

- Anomalies causing increased pulmonary blood flow or increased pulmonary artery pressure
- Ventricular septal defect, atrial septal defect, patent foramen ovale, patent ductus arteriosus
- Anomalous pulmonary venous return or pulmonary vein stenosis
- Unilateral absent pulmonary artery or isolated pulmonary artery of ductal origin
- Coarctation of the aorta
- Congestive heart failure

Pulmonary

- Chronic lung disease
  - Bronchopulmonary dysplasia
  - Pulmonary hypoplasia
  - Supplemental oxygen requirement at sea level
- Pulmonary hypertension
- Perinatal respiratory distress
  - Persistent pulmonary hypertension of the newborn
  - Perinatal asphyxia or depression
- Sleep apnea

Infectious

- Upper respiratory tract infection
- Bronchitis/bronchiolitis
- Pneumonitis
- Otitis media

Pharmacologic

- Any medication causing central nervous system and respiratory depression
- Alcohol
- Sympathomimetics

Systemic

- Down syndrome (trisomy 21)
- History of premature birth or low birthweight

Pathophysiology

Alveolar hypoxia results in vasoconstriction of pulmonary arterioles just proximal to the alveolar capillary bed. Hypoxic pulmonary vasoconstriction is a normal physiologic response to optimize ventilation/perfusion (V̇/Q̇) matching by redistributing regional pulmonary blood flow to areas of highest ventilation, thereby optimizing arterial oxygenation. Under conditions that result in widespread alveolar hypoxia, extensive pulmonary vasoconstriction will lead to significant elevations in pulmonary arterial pressure; uneven pulmonary vasoconstriction can result in localized overperfusion, increased capillary pressures, distention, and leakage in the remaining vessels. This explains the patchy and heterogeneous edema that is classically observed in HAPE. The combination of pulmonary hypertension and uneven pulmonary vasoconstriction appears to be necessary in the pathogenesis of HAPE. Children and adolescents acutely exposed to high-altitude hypoxia demonstrated pulmonary hypertension, with increases in pulmonary artery pressure inversely related to age. Once the vascular leak occurs and alveolar fluid accumulates, a defect in transepithelial sodium transport impairs the clearance of alveolar fluid and contributes to HAPE.

Diagnosis

The diagnosis of HAPE is based on clinical findings and their evolution in the context of recent ascent from lower elevation. There is no single diagnostic test or constellation of laboratory findings. Symptoms usually develop within 24-96 hr, with onset of symptoms the 1st or 2nd night at altitude, when hypoxia may be exacerbated during sleep. HAPE generally is not observed beyond 5 days after ascent to altitude (unless additional ascent occurs) because pulmonary vascular remodeling and acclimatization have taken place. The minimum criteria to diagnose HAPE include recent exposure to altitude, dyspnea at rest, radiographic evidence of alveolar infiltrates, and near-complete resolution of both clinical and radiographic signs within 48 hr after descent or institution of oxygen therapy. Portable ultrasound is useful to diagnose HAPE through the finding of *comet tails* , artifacts created by microreflections of the ultrasound beam within interlobular septa thickened by interstitial and alveolar edema.

Frequently, patients first exhibit general malaise that may progress to more specific signs of dyspnea at rest, then cardiopulmonary distress. In preverbal toddlers and infants, HAPE may manifest as worsening respiratory distress over 1-2 days, pallor, depressed consciousness, increased fussiness, decreased playfulness, crying, decreased appetite, poor sleep, and sometimes vomiting. Young children may show agitation and general debility. Older children and adolescents may complain of headache and orthopnea and present with cough, dyspnea not relieved by rest or out of proportion to effort, and production of frothy, rust-colored sputum. Physical exam findings include tachypnea, cyanosis, elevated jugular venous pressure, and diffuse crackles on lung auscultation. Dyspnea at rest, orthopnea, cyanosis, tachycardia, and chest pain herald worsening compromise, which may advance within hours to production of pink-tinged sputum.

Findings on physical examination frequently are less severe than the patient's chest radiograph and hypoxemia on pulse oximetry would predict. Children often appear pale, with or without visible cyanosis. Low-grade fever (<38.5°C [101.3°F]) is common, and respiratory rate is generally increased. Auscultation typically reveals rales, usually greater in the right lung than the left on presentation. Chest radiograph reveals diffuse interstitial changes typical of noncardiogenic pulmonary edema, with central interstitial edema associated with peribronchial cuffing, poorly defined vessels, enlargement of the pulmonary artery silhouette with dilation of more peripheral pulmonary arteries, and patchy air space consolidation; Kerley lines may be present. In severe cases, air space consolidation may become confluent and involve the entire lung (Fig. 90.2). Often the right lung shows more radiographic changes of edema than the left. Cardiomegaly is an uncommon finding, but enlargement of the pulmonary artery is a frequent finding. Significant arterial oxygen desaturation, as measured by pulse oximetry, is a consistent finding, with SpO_2 frequently below 75%. A complete blood count often reveals a leukocytosis with a left shift of the granulocyte series.

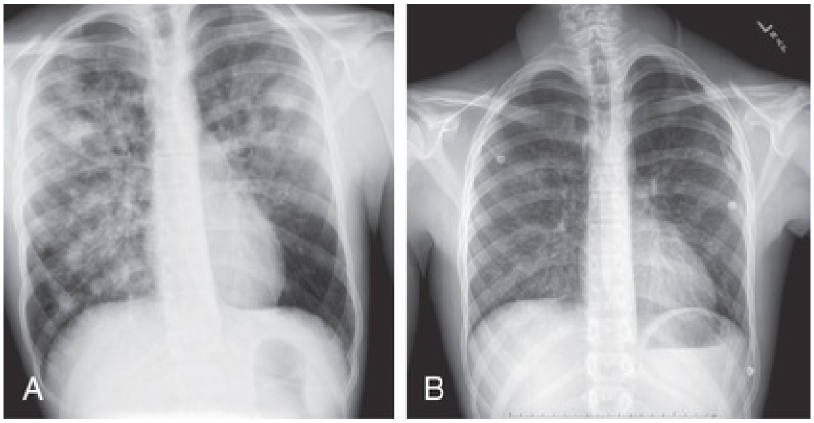

FIG. 90.2 **Acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE). A healthy 15 yr old boy flew from Buffalo, NY, to Denver, CO, and immediately drove with his school group from the airport to a ski resort at 9,300 ft in the Rocky Mountains. The following day he felt dizzy and complained of headache. Symptoms of headache**

and dizziness continued along with emesis daily for 2 days. A snowboarding coach brought the patient to the local emergency facility the next day because of dyspnea, cough, headache, emesis, and fatigue. Pulse oximetry showed an arterial oxygen saturation of 51%. Chest radiograph showed diffuse pulmonary edema (A). The patient was transported to Denver (5,280 ft) by ambulance with 15 L/min oxygen via a non-rebreathing mask. SaO_2 improved with descent and was 94% on arrival at the Children's Hospital Colorado emergency department. Breath sounds remained coarse, and the patient was tachycardic and tachypneic. Oxygen flow was weaned to 1 L/min shortly after admission. Two days after presentation, lung exam was improved, without crackles. Repeat chest radiograph showed clearing of edema pattern (B). The patient maintained adequate SaO_2 without supplemental oxygen and was discharged. (Courtesy of the Department of Radiology, Children's Hospital of Colorado.)

The **differential diagnosis** of HAPE includes pneumonia, bronchitis/bronchiolitis, asthma, and other forms of cardiogenic and noncardiogenic pulmonary edema, as well as pulmonary embolism. HAPE is most frequently misdiagnosed as pneumonia or a viral respiratory illness, especially when suspicion of altitude-associated pathology is not appropriately high. The presenting signs of cough, dyspnea, and orthopnea, followed by sputum production, can easily be misinterpreted as pneumonia, an impression reinforced by the frequent low-grade fever. Respiratory viral infections increase the risk of developing HAPE, which may lead to further confusion in diagnosis.

Complications of HAPE in children often relate to underlying, sometimes undiagnosed, cardiopulmonary pathology or coexisting viral infections that potentiate the severity of pulmonary edema and pulmonary hypertension. Acute altitude exposure in such circumstances may lead to severe presentations that progress rapidly to extreme hypoxemia or cardiac failure and death. Children with trisomy 21, with or without structural cardiac anomalies, show increased susceptibility to HAPE and rapid symptom progression. Neonatal respiratory distress with pulmonary hypertension has been linked to exaggerated hypoxic pulmonary vasoreactivity in early adulthood and thereby a theoretical predisposition to HAPE. Other conditions related to pulmonary overcirculation, small cross-sectional area of the pulmonary vascular bed, obstruction to pulmonary venous return, or left-sided obstruction potentiate HAPE. Inflammatory processes, such as viral infection, predispose to HAPE and may worsen hypoxemia.

Management

Descent with supplemental oxygen is the treatment of choice for HAPE in children. Unlike AMS, HAPE does not respond to rest and oxygen alone. When feasible, or in the absence of medical care, rapid descent of at least 1,000 m

(~3,300 ft) usually results in rapid recovery. As with all altitude illness, the magnitude of the descent is tailored to the resolution of symptoms. Those affected should exert themselves as little as possible on descent and prevent exposure to cold, to avoid exacerbation of pulmonary artery pressure and pulmonary edema. Oxygen and bed rest without descent can be safe and effective treatment for mild HAPE in children where careful medical observation is available. Mild HAPE in children and young adults at 3,750 m (~12,300 ft) has been treated with bed rest alone, although clinical recovery may be slower than with supplemental oxygen therapy.

Supplemental oxygen at altitude is administered at 2-6 L/min by nasal cannula for 48-72 hr to maintain an SaO_2 of at least 90%. Oxygen flow can be weaned with improvement in symptoms and SaO_2; at flow rates <2-4 L/min, children may be sufficiently stable and comfortable to continue treatment at home under family monitoring. Most children experience complete resolution of mild HAPE within 24-72 hr of oxygen therapy when treated at the altitude of symptom onset.

Pharmacotherapy for pediatric HAPE is rarely needed since oxygen and descent are so effective. However, in emergency situations without the option of descent or oxygen, pharmacotherapy should be considered for treatment of HAPE. In adults, nifedipine, a calcium channel blocker, is the preferred drug. Although its use has not been studied in children for treatment of HAPE, **nifedipine** is indicated for treatment of pulmonary hypertension. Extrapolated dosing for children is 0.5 mg/kg orally every 4-8 hr and titrated to response (maximum, 10 mg/dose). Liquid-filled capsules of nifedipine (10 mg/0.34 mL) can be punctured to obtain doses for children <20 kg. Patients should be monitored for hypotension during nifedipine administration. Alternatively, diltiazem can be given at 0.5-1.0 mg/kg/dose every 8 hr in tablet form or compounded oral suspension (12 mg/mL). Phosphodiesterase-5 inhibitors reduce pulmonary pressure at high altitude in adults through vasodilation and may be used if a calcium channel blocker is not available or poorly tolerated. However, concurrent use of multiple pulmonary vasodilators is not recommended. Pulmonary hypertension guidelines for children cite level I evidence for sildenafil in treatment of pulmonary hypertension.

β-Adrenergic agonists upregulate the clearance of alveolar fluid through transepithelial sodium transport and therefore could have a positive effect on HAPE. A single randomized controlled study in adults susceptible to HAPE exposed to very high altitude found that those receiving inhaled salmeterol had a 50% decreased incidence of HAPE compared to those who received placebo.

Prevention of pulmonary edema using salmeterol was not associated with a decrease in pulmonary pressure, underscoring the clearance of alveolar fluid and improved hypoxia, which is believed to have accounted for the improved AMS score in these patients compared with the placebo group.

Special Considerations

Reentry HAPE

Children residing at high altitude may also experience HAPE of the type termed *reentry* or *reascent* HAPE. Reentry HAPE occurs on reascent to the altitude of residence after a sojourn to low altitude. Most cases occur after several days at lower altitude, and probability of recurrence may justify pharmacologic prophylaxis.

Travel With Young Infants

Newborn infants retain some of the circulatory characteristics of recent fetal life, and these can pose a unique risk for altitude exposure. The fetal circulation has high pulmonary resistance, low pulmonary blood flow, and both intra- and extracardiac shunts that optimize oxygenation through the placenta rather than the fetal lungs. After birth, a transition begins that closes fetal shunts and establishes normal pulmonary circulation and oxygen transport. *Exposure to marked hypoxia (3,000-5,000 m) can result in reversion to fetal shunting patterns despite the absence of a placenta.* Therefore, prolonged exposure to high altitude should be avoided for infants <6 mo old who normally live at low altitude, or whose gestation occurred at low altitude. Normal infants at sea level complete these changes in 4-6 wk, although for infants born at moderate or high altitude, changes may last ≥3 mo. Travel to high altitude with young infants is generally safe after 4-6 wk, when circulatory changes have occurred, breastfeeding is established, and congenital abnormalities may have been detected. Infants between 6 wk and 1 yr of age may have a higher incidence of pulmonary hypertension with hypoxia, patent ductus arteriosus (PDA), and patent foramen ovale (PFO) with prolonged exposure to high altitudes. Hypoxic exposure induces medial hypertrophy of pulmonary arteries and pulmonary arterioles, together with dilation of the pulmonary trunk and impressive hypertrophy and dilation of the right ventricle.

Infants residing at an altitude above 2,400 m (~8,000 ft) are at an increased risk of **sudden infant death syndrome (SIDS)** , possibly from greater hypoxia. Altitude may be an independent risk factor for SIDS. Similar to low altitude, infants should be placed on their backs for sleeping, and parents should be counseled on the potential elevated risk of SIDS at altitude.

Sickle Trait and Sickle Cell Disease

Children with sickle cell disease or sickle trait should avoid travel to altitude, because hypoxemia may trigger sickling and painful crises, including splenic crises. Up to 20% of pediatric patients with sickle cell and sickle-thalassemia disease may experience a vasoocclusive crisis at moderate altitude. Although the majority of children with sickle trait remain asymptomatic, children can experience splenic ischemia or infarction, with severe left upper quadrant pain.

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CHAPTER 91

Drowning and Submersion Injury

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Drowning is one of the leading causes of childhood morbidity and mortality in the world. Prevention is the most important step to reducing the impact of drowning injury, followed by early initiation of cardiopulmonary resuscitation (CPR) at the scene.

Etiology

Children are at risk of drowning when they are exposed to a water hazard in their environment. The World Congress of Drowning definition of drowning is “the process of experiencing respiratory impairment from submersion/immersion in liquid.” The term *drowning* does not imply the final outcome—death or survival; the outcome should be denoted as *fatal* or *nonfatal* drowning. Use of this terminology should improve consistency in reporting and research; the use of confusing descriptive terms such as “near,” “wet,” “dry,” “secondary,” “silent,” “passive,” and “active” should be abandoned. The injury following a drowning event is *hypoxia* .

Epidemiology

From 2005 to 2014, an average 3,536 people per year were victims of **fatal drowning** , and an estimated 6,776 persons per year were treated in U.S. hospital emergency departments (EDs) for **nonfatal drowning** . Compared with other types of injuries, drowning has one of the highest case fatality rates and is in the top-10 causes of death related to unintentional injuries for all pediatric age-groups. From 2010 to 2015, the highest drowning death rates were seen in children age 1-4 yr and 15-19 yr (crude rates of 2.56 and 1.2 per 100,000, respectively). In children age 1-4 yr, drowning was the number-one cause of death from *unintentional injury* in the United States in 2014. Pediatric hospitalization rates associated with drowning ranged from 4.7 to 2.4 per 100,000 between 1993 and 2008. Rates of fatal drowning hospitalization declined from 0.5 to 0.3 deaths per 100,000 during the same period. Morbidity following nonfatal drowning is poorly studied.

The risk of drowning and the circumstances leading to it vary by age (Fig. 91.1). Drowning risk also relates to other host factors, including male gender, alcohol use, a history of seizures, and swimming lessons. Environmental risk factors include exposure to water and varying supervision. These factors are embedded in the context of geography, climate, socioeconomic status, and culture.

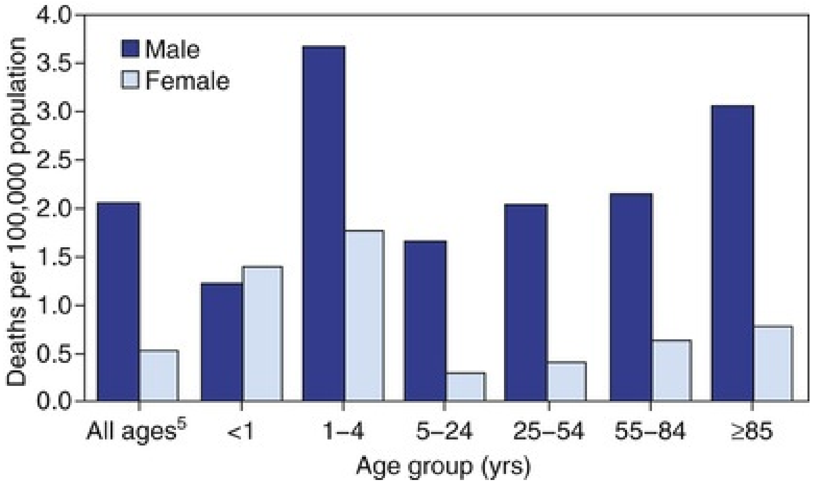

FIG. 91.1 Death rates from unintentional drowning* by age-group and sex—United States,[†] 2011. A total of 3,961 deaths from unintentional drowning were reported in the United States in 2011; the overall death rate for males was 2.05 per 100,000 population, almost 4 times the rate for females (0.52). In each age-group except for infants (i.e., those age <1 yr), the drowning death rate was higher for males. Males age 1-4 yr had the highest rate (3.67); for males and females, death rates increased with age after age 5-24 yr. *Unintentional drowning as the underlying cause of death includes codes for accidental drowning and submersion (W65-74), watercraft causing drowning and submersion (V90), and water-transport–related drowning and submersion without accident to watercraft (V92) in the *International Classification of Diseases, 10th Revision* . [†] U.S. residents only. [§] Includes decedents whose ages were not reported. (From National Vital Statistics System: Mortality public use data file for 2011. http://www.cdc.gov/nchs/data_access/vitalstatsonline.htm .)

Children <1 Yr Old

Most (71%) drowning deaths in children younger than 1 yr occur in the **bathtub** , when an infant is left alone or with an older sibling. Infant tub seats or rings may exacerbate the risk by giving caregivers a false sense of security that the child is safe in the tub. The next major risk to children <1 yr is the large (5-gallon) household bucket, implicated in 16% of infant drowning deaths. These buckets are approximately 30 cm (1 ft) tall and designed not to tip over when half-full. The average 9 mo old child tends to be top-heavy and thus can easily fall headfirst into a half-full bucket, become stuck, and drown within minutes.

Children 1-4 Yr Old

Drowning rates are consistently highest in 1-4 yr old children, likely because of their curious but unaware nature, coupled with the rapid progression of their physical capabilities. From 1999 to 2015, U.S. rates are highest in the southern regions, in some areas as high as 3.8 per 100,000. A common factor in many of these deaths is a lapse in adult supervision, often reportedly <5 min. Most U.S. drownings occur in residential **swimming pools** . Usually, the child is in the child's own home, and the caregiver does not expect the child to be near the pool.

In rural areas, children 1-4 yr old often drown in irrigation ditches or nearby ponds and rivers. The circumstances are similar to those noted previously, in a body of water that is near the house. Drowning is one of the leading causes of *farm injury–related deaths* in children.

School-Age Children

School-age children are at increased risk of drowning in natural bodies of water such as lakes, ponds, rivers, and canals. Although swimming pools account for most nonfatal drownings across all ages, **natural waterways** account for a higher death rate in children 10-19 yr old. Unlike for preschool children, swimming or boating activities are important factors in drowning injuries in school-age children.

Adolescents

The 2nd major peak in drowning death rates occurs in older adolescents, age 15-19 yr. Almost 90% drown in open water. In this age-group particularly, striking disparities in drowning deaths exist in gender and race. From 1999 to 2015, adolescent males fatally drowned at a rate of 2.4/100,000 compared to 0.3/100,000 in adolescent females. The gender disparity may likely be related to males' greater risk-taking behavior, greater alcohol use, less perception about risks associated with drowning, and greater confidence in their swimming ability than females.

Dangerous underwater breath-holding behaviors (DUBBs) are often performed by experienced healthy swimmers or fitness enthusiasts (hypoxic training) or when teenagers hold breath-holding contests during horseplay. DUBBs have been primarily reported in regulated swimming facilities. Behaviors include intentional hyperventilation before submersion, static apnea, and extended periods of underwater distance swimming or breathhold intervals. Swimmers are found motionless and submerged; resuscitation is often unsuccessful.

There is also significant racial disparity seen across drowning rates and causes. In 2015, as in previous years, drowning rates for black males age 15-19 yr were double those for white males of the same age. Non-Caucasian children are 4 times more likely to have a nonfatal drowning across all age-groups through 19 yr old. Black children are more likely to drown in unguarded public or apartment pools; white children are more likely to drown in private residential pools. Hispanic and foreign-born children have lower rates of drowning than their white counterparts. Those with private insurance have lower rates of nonfatal drowning. Other factors include differences in exposure to swimming lessons, cultural attitudes, and fears about swimming, as well as experience around water, all of which may contribute to overall drowning risk.

Underlying Conditions

Several underlying medical conditions are associated with drowning at all ages. A number of studies have found an increased risk, up to 19-fold, in individuals with **epilepsy** . Drowning risk for children with seizures is greatest in bathtubs and swimming pools. Cardiac etiologies, including arrhythmias, myocarditis, and prolonged QT syndromes, have been found in some children who die suddenly in the water, particularly in those with a family history of syncope, cardiac arrest, prior drowning, or QT prolongation. Some children with long QT syndrome are misdiagnosed as having seizures (see Chapter 462.5).

Drowning may also be an **intentional injury** . A history of the event that changes or is inconsistent with the child's developmental stage is the key to recognition of intentional drowning. Physical examination and other physical injuries rarely provide clues. **Child abuse** is more often recognized in bathtub-related drownings. **Suicide** usually occurs in lone swimmers in open water.

Alcohol Use

The use of alcohol and drugs greatly increases the risk of drowning. Of teenagers and adults who die, up to 70% are associated with alcohol use. Alcohol can impair judgment, leading to riskier behavior, decreased balance and coordination, and blunted ability to self-rescue. Furthermore, an intoxicated adult may provide less effective supervision of children around water.

Sports and Recreation

Most U.S. drowning deaths occur during recreational activities. Drowning is the leading cause of *noncardiac sports-related deaths* . Surveys confirm that alcohol use is common during water recreation, as is not using a personal flotation device (PFD) during boating activities. In 2015 the U.S. Coast Guard reported that 85% of those who drowned in boating accidents were not wearing a PFD.

Global Impact of Drowning

Drowning injury is the 3rd leading cause of unintentional death worldwide, with the majority (90%) of fatalities occurring in low- and middle-income countries. More than half of the global drowning occurs in the World Health Organization (WHO) Western Pacific and Southeast Asia regions. Global drowning rates are vastly underestimated, since many drowning deaths in this region go unreported, and many immediate fatalities are unrecognized. In addition, these data exclude any cases of drowning as the result of intentional harm or assault, accidents of watercraft or water transport, and drowning related to forces of nature or cataclysmic storms, which usually claim large numbers of lives per incident; thus, true numbers of fatal drowning are likely much higher.

Some patterns of pediatric drowning are similar in all countries. By most accounts, the highest rates are seen in males and in children 1-4 yr old.

Whereas bathtubs and places of recreation (i.e., pools, spas) are significant locations for drowning in U.S. children, these are virtually unreported locations for drownings in developing countries. Instead, the predominant locations are near or around the home, involving bodies of water used for activities of daily living. These include water-collecting systems, ponds, ditches, creeks, and watering holes. In tropical areas, death rates increase during monsoon season, when ditches and holes rapidly fill with rain, and are highest during daylight hours, when caregivers are busy with daily chores.

Drowning during natural disasters such as **storms** and **floods** is important in all areas of the world. The largest numbers of reported flood-related deaths occur in developing nations; most are drownings that occur during the storm surge. In the United States and much of Europe, advances in weather monitoring and warning systems have reduced such deaths. U.S. flooding incidents, including hurricanes Katrina and Sandy, showed that drowning caused the most deaths, particularly when people became trapped in their vehicles, were unable or refused to evacuate homes, or attempted to rescue others.

Pathophysiology

Drowning victims drown silently and do not signal distress or call for help. Vocalization is precluded by efforts to achieve maximal lung volume to keep the head above the water or by aspiration leading to **laryngospasm** . Young children can struggle for only 10-20 sec and adolescents for 30-60 sec before final submersion. A swimmer in distress is vertical in the water, pumping the arms up and down. This splashing or efforts to breathe are often misconstrued by nearby persons as merely playing in the water, until the victim sinks.

Anoxic-Ischemic Injury

After experimental submersion, a conscious animal initially panics, trying to surface. During this stage, small amounts of water enter the hypopharynx, triggering laryngospasm. There is a progressive decrease in arterial blood oxyhemoglobin saturation (SaO_2), and the animal soon loses consciousness from hypoxia. Profound hypoxia and medullary depression lead to terminal apnea. At the same time, the cardiovascular response leads to progressively decreasing cardiac output and oxygen delivery to other organs. By 3-4 min, myocardial hypoxia leads to abrupt circulatory failure. Ineffective cardiac contractions with electrical activity may occur briefly, without effective perfusion (**pulseless electrical activity**). With early initiation of CPR, spontaneous circulation may initially be successfully restored. The extent of the global **hypoxic-ischemic injury** determines the final outcome and becomes more evident over subsequent hours.

With modern intensive care, the cardiorespiratory effects of resuscitated drowning victims are usually manageable and are less often the cause of death than irreversible hypoxic-ischemic central nervous system (CNS) injury (see Chapter 85). CNS injury is the most common cause of mortality and long-term morbidity. Although the duration of anoxia before irreversible CNS injury begins is uncertain, it is probably on the order of 3-5 min. Submersions <5 min are associated with a favorable prognosis, whereas those >25 min are generally fatal.

Several hours after cardiopulmonary arrest, **cerebral edema** may occur, although the mechanism is not entirely clear. Severe cerebral edema can elevate intracranial pressure (ICP), contributing to further ischemia; intracranial hypertension is an ominous sign of profound CNS damage.

All other organs and tissues may exhibit signs of hypoxic-ischemic injury. In the lung, damage to the pulmonary vascular endothelium can lead to **acute respiratory distress syndrome** (see Chapter 89). Aspiration may also compound pulmonary injury. Myocardial dysfunction (so-called stunning), arterial hypotension, decreased cardiac output, arrhythmias, and cardiac infarction may also occur. Acute kidney injury, cortical necrosis, and renal failure are common complications of major hypoxic-ischemic events (see Chapter 550.1). Vascular endothelial injury may initiate disseminated intravascular coagulation, hemolysis, and thrombocytopenia. Many factors contribute to gastrointestinal damage; bloody diarrhea with mucosal sloughing may be seen and often portends a fatal injury. Serum levels of hepatic transaminases and pancreatic enzymes are often acutely increased. Violation of normal mucosal protective barriers predisposes the victim to bacteremia and sepsis.

Pulmonary Injury

Pulmonary aspiration occurs in many drowning victims, but the amount of aspirated fluid is usually small (see Chapter 425). Aspirated water does not obstruct airways and is readily moved into the pulmonary circulation with positive pressure ventilation. More importantly, it can wash out surfactant and cause alveolar instability, ventilation-perfusion mismatch, and intrapulmonary shunting. In humans, aspiration of small amounts (1-3 mL/kg) can lead to marked hypoxemia and a 10–40% reduction in lung compliance. The composition of aspirated material can also affect the patient's clinical course: Gastric contents, pathogenic organisms, toxic chemicals, and other foreign matter can injure the lung or cause airway obstruction. Clinical management is not significantly different in saltwater and freshwater aspirations, because most victims do not aspirate enough fluid volume to make a clinical difference.

Cold Water Injury

Drowning should be differentiated from cold water **immersion** injuries, in which the victim remains afloat, keeping the head above water without respiratory impairment in cold waters. The definition of cold water varies from <15 to 20°C (<59 to 68°F).

Heat loss through conduction and convection is more efficient in water than in air. Children are at increased risk for **hypothermia** because of their relatively high ratio of body surface area (BSA) to mass, decreased subcutaneous fat, and limited thermogenic capacity. Hypothermia can develop because of prolonged surface contact with cold water during immersion, while the airway is above water, or with submersion. Body temperature may also continue to fall because of cold air, wet clothes, hypoxia, and hospital transport. Hypothermia in pediatric drowning victims may be observed even after drowning in relatively warm water and in warm climates.

Immersion in cold water has immediate respiratory and cardiovascular effects. Victims experience **cold water shock** , a dynamic series of cardiorespiratory physiologic responses that can cause drowning. In adults, immersion in icy water results in intense involuntary reflex hyperventilation and to a decrease in breath-holding ability to <10 sec, which leads to fluid aspiration. Severe bradycardia, the *diving reflex* , occurs in adults but is transient and rapidly followed by supraventricular and ectopic tachycardia and hypertension. There is *no evidence* that the diving reflex has any protective effect.

Even after surviving the chaotic minutes of cold water shock, after an additional 5-10 min of cold water immersion, the victim can become incapacitated. Cooling of large and small muscles disables the victim's ability to grab hold, swim, or perform other self-rescue maneuvers. Depending on water and air temperature, insulation, BSA, thermogenic capacity, physical condition, swimming efforts, or high-water flow rates, heat loss with continued immersion can significantly decrease core temperature to hypothermic levels within 30-60 min.

The symptoms and severity of hypothermia are categorized based on body temperature. The victim with mild hypothermia has a temperature of 34-36°C (93.2-96.8°F) with intact thermogenic mechanisms (shivering and nonshivering thermogenesis, vasoconstriction) and active movements. Compensatory mechanisms usually attempt to restore normothermia at body temperatures >32°C (89.6°F). Lower core temperatures lead to impaired cognition, coordination, and muscle strength and with it, less ability to self-rescue. Thermoregulation may fail and spontaneous rewarming will not occur. With moderate hypothermia (30 to <34°C [86 to <93.2°F]), loss of consciousness leads to water aspiration. Progressive bradycardia, impaired myocardial contractility, and loss of vasomotor tone contribute to inadequate perfusion, hypotension, and possible shock. At body temperatures <28°C (82.4°F), extreme bradycardia is usually present with decreases in cardiac output, and the propensity for spontaneous ventricular fibrillation or asystole is high. Central respiratory center depression with moderate to severe hypothermia results in hypoventilation and eventual apnea. A deep coma, with fixed and dilated pupils and absence of reflexes at very low body temperatures (<25-29°C [77-84.2°F]), may give the false appearance of death.

If the cooling process is quick—and cardiac output lasts long enough for sufficient heat loss to occur before the onset of severe hypoxia—the brain can cool to a level that may be considered in the *neuroprotective* range, approximately 33°C (91.4°F) in controlled, experimental conditions. However, if submersion leading to drowning occurs before development of a neuroprotective level of hypothermia, severe anoxia devastates tissue organs. The theoretical benefits, implications, and consequences of hypothermia in drowning victims are areas of controversy. Known adverse effects are associated with hypothermia, and these must be balanced against the potential benefits observed in experimental data. One should clearly differentiate among **controlled hypothermia** , such as that used in the operating room before the onset of hypoxia or ischemia; **accidental hypothermia** , such as occurs in drowning, which is uncontrolled and variable, with onset during or shortly after hypoxia-ischemia; and **therapeutic hypothermia** , involving the purposeful and controlled lowering and maintenance of body (or brain) temperature after a hypoxic-ischemic event.

In drowning victims with uncontrolled accidental hypothermia associated with icy water submersion, there are a few case reports of good neurologic recovery after prolonged (10-150 min) cardiopulmonary arrest. Almost all these rare survivors have been in freezing water (<5°C [41°F]) and had core body temperatures <30°C (86°F), often much lower. Presumably, very rapid and sufficiently deep hypothermia developed in these fortunate survivors before irreversible hypoxic-ischemic injury occurred.

Most often, hypothermia is a poor prognostic sign, and a neuroprotective effect has not been demonstrated A 2014 study from Washington State found that submersion duration <6 min is most strongly related to good outcome, not water temperature. In another study of comatose drowning patients admitted to pediatric intensive care unit (PICU), 65% of hypothermic patients (body temperature <35°C [95°F]) died, compared with a 27% observed mortality rate in nonhypothermic victims. Similarly, in Finland (where the median water temperature was 16°C [60.9°F]) and in the United States, a beneficial effect of drowning-associated hypothermia was not seen in pediatric submersion victims; submersion duration <10 min was most strongly related to good outcome, not water temperature.

Management

Duration of submersion, speed of the rescue, effectiveness of resuscitative efforts, and clinical course determine the outcome in submersion victims. Two groups may be identified on the basis of responsiveness at the scene. The **first group** consists of children who require minimal resuscitation at the scene and quickly regain spontaneous respiration and consciousness. They have good outcomes and minimal complications. These victims should be transported from the scene to the ED for further evaluation and observation. The **second group** comprises children in cardiac arrest who require aggressive or prolonged resuscitation and have a high risk of multiple–organ system complications, major neurologic morbidity, or death. Compared with cardiac arrest from other causes, cardiac arrest from drowning has a higher survival rate.

Initial management of drowning victims requires coordinated and experienced prehospital care following the ABCs (airway, breathing, circulation) of emergency resuscitation. CPR of drowning victims must include providing ventilation. Children with severe hypoxic injury and symptoms often remain comatose and lack brainstem reflexes despite the restoration of oxygenation and circulation. Subsequent ED and PICU care often involve advanced life support (ALS) strategies and management of multiorgan dysfunction with discussions about end-of-life care.

Initial Evaluation and Resuscitation

See Chapter 81 .

Once a submersion has occurred, immediate institution of CPR efforts at the scene is imperative. The goal is to reverse the anoxia from submersion and limit secondary hypoxic injury after submersion. Every minute that passes without the reestablishment of adequate breathing and circulation dramatically decreases the possibility of a good outcome. When safe for the victim and the rescuer, institution of in-water resuscitation for nonbreathing victims by trained personnel may improve the likelihood of survival. Victims usually need to be extricated from the water as quickly as possible so that effective CPR can be provided. Common themes in children who have good recovery are a short duration of event and initiation of CPR as soon as possible, before arrival of emergency medical services.

Initial resuscitation must focus on rapidly restoring oxygenation, ventilation, and adequate circulation. The airway should be clear of vomitus and foreign material, which may cause obstruction or aspiration. Abdominal thrusts should not be used for fluid removal, because many victims have a distended abdomen from swallowed water; abdominal thrusts may increase the risk of regurgitation and aspiration. In cases of suspected airway foreign body, chest compressions or back blows are preferable maneuvers.

The cervical spine should be protected in anyone with potential traumatic neck injury (see Chapters 82 and 85). Cervical spine injury is a rare concomitant injury in drowning; only approximately 0.5% of submersion victims have C-spine injuries, and history of the event and victim's age should guide suspicion of C-spine injury. Drowning victims with C-spine injury are usually preteens or teenagers whose drowning event involved diving, a motor vehicle crash, a fall from a height, a water sport accident, child abuse, or other clinical signs of serious traumatic injury. In such cases, the neck should be maintained in a neutral position and protected with a well-fitting cervical collar. Patients rescued from unknown circumstances may also warrant C-spine precautions. In low-impact submersions, spinal injuries are exceedingly rare, and routine spinal immobilization is not warranted.

If the victim has ineffective respiration or apnea, ventilatory support must be initiated immediately. Mouth-to-mouth or mouth-to-nose breathing by trained bystanders often restores spontaneous ventilation. As soon as it is available, supplemental oxygen should be administered to all victims. Positive pressure bag-mask ventilation with 100% inspired oxygen should be instituted in patients with respiratory insufficiency. If apnea, cyanosis, hypoventilation, or labored respiration persists, trained personnel should perform endotracheal intubation as soon as possible. Intubation is also indicated to protect the airway in patients with depressed mental status or hemodynamic instability. Hypoxia must be corrected rapidly to optimize the chance of recovery.

Concurrent with securing of airway control, oxygenation, and ventilation, the child's cardiovascular status must be evaluated and treated according to the usual resuscitation guidelines and protocols. Heart rate and rhythm, blood pressure, temperature, and end-organ perfusion require urgent assessment. CPR should be instituted immediately in pulseless, bradycardic, or severely hypotensive victims. Continuous monitoring of the electrocardiogram (ECG) allows appropriate diagnosis and treatment of arrhythmias. Slow capillary refill, cool extremities, and altered mental status are potential indicators of shock (see Chapter 88).

Recognition and treatment of hypothermia are the unique aspects of cardiac resuscitation in the drowning victim. Core temperature must be evaluated, especially in children, because moderate to severe hypothermia can depress myocardial function and cause arrhythmias. Wet clothing should be removed to prevent ongoing heat losses, although in the hemodynamically stable patient, rewarming should be initiated in the controlled environment of the receiving ED or PICU. Unstable patients (i.e., arrhythmias) should be warmed to 34°C (93.2°F), taking care not to overheat. Trials are investigating if therapeutic hypothermia might be helpful, or if avoiding hyperthermia is the key element to long-term neurologic survival.

Often, intravenous (IV) fluids and vasoactive medications are required to improve circulation and perfusion. Vascular access should be established as quickly as possible for the administration of fluids or pressors. Intraosseous catheter placement is a potentially lifesaving vascular access technique that avoids the delay usually associated with multiple attempts to establish IV access in critically ill children. Epinephrine is usually the initial drug of choice in victims with bradyasystolic cardiopulmonary arrest (IV dose is 0.01 mg/kg using the 1 : 10,000 [0.1 mg/mL] solution given every 3-5 min, as needed). Epinephrine can be given intratracheally (endotracheal tube dose is 0.1-0.2 mg/kg of 1 : 1,000 [1 mg/mL] solution) if no IV access is available. An intravascular bolus of lactated Ringer solution or 0.9% normal saline (10-20 mL/kg) is often used to augment preload; repeated doses may be necessary. Hypotonic or glucose-containing solutions should not be used for intravascular volume administration of drowning victims.

Hospital-Based Evaluation and Treatment

Most pediatric drowning victims should be observed for at least 6-8 hr, even if they are asymptomatic on presentation to the ED. At a minimum, serial monitoring of vital signs (respiratory rate, heart rate, blood pressure, and temperature) and oxygenation by pulse oximetry, repeated pulmonary examination, and neurologic assessment should be performed in all drowning victims. Other studies may also be warranted, depending on the specific circumstances (possible abuse or neglect, traumatic injuries, or suspected intoxication). Almost half of asymptomatic or minimally symptomatic alert children (those who do not require ALS in the prehospital setting or who have an initial ED **Glasgow Coma Scale [GCS]** score of ≥13) experience some level of respiratory distress or hypoxemia progressing to pulmonary edema, usually during the 1st 4-8 hr after submersion. Most alert children with early respiratory symptoms respond to oxygen and, despite abnormal initial radiographs, become asymptomatic with a return of normal room-air pulse oximetry oxyhemoglobin saturation ($\mathrm{Sp}_{\mathrm{O}_2}$) and pulmonary examination by 4-6 hr. Subsequent delayed respiratory deterioration is extremely unlikely in such children. Selected low-risk patients who are alert and asymptomatic with normal physical findings and oxygenation levels may be considered for discharge after 6-8 hr of observation if appropriate follow-up can be ensured.

Cardiorespiratory Management

For children who are not in cardiac arrest, the level of respiratory support should be appropriate to the patient's condition and is a continuation of prehospital management. Frequent assessments are required to ensure that adequate oxygenation, ventilation, and airway control are maintained (see Chapter 89). Hypercapnia should generally be avoided in potentially brain-injured children. Patients with actual or potential hypoventilation or markedly elevated work of breathing should receive mechanical ventilation to avoid hypercapnia and decrease the energy expenditures of labored respiration.

Measures to stabilize cardiovascular status should also continue. Conditions contributing to myocardial insufficiency include hypoxic-ischemic injury, ongoing hypoxia, hypothermia, acidosis, high airway pressures during mechanical ventilation, alterations of intravascular volume, and electrolyte disorders. Heart failure, shock, arrhythmias, or cardiac arrest may occur. Continuous ECG monitoring is mandatory for recognition and treatment of arrhythmias (see Chapter 462).

The provision of adequate oxygenation and ventilation is a prerequisite to improving myocardial function. Fluid resuscitation and inotropic agents are often necessary to improve heart function and restore tissue perfusion (see Chapter 81). Increasing preload with IV fluids may be beneficial through improvements in stroke volume and cardiac output. Overzealous fluid administration, however, especially in the presence of poor myocardial function, can worsen pulmonary edema.

For patients with persistent cardiopulmonary arrest on arrival in the ED after *non–icy water* drowning, the decision to withhold or stop resuscitative efforts can be addressed by review of the history and the response to treatment. Because there are reports of good outcome following ongoing CPR in the ED, most drowning victims should be treated aggressively on presentation. However, for children who do not show ready response to aggressive resuscitative efforts, the need for prolonged ongoing CPR after non–icy water submersion almost invariably predicts death or persistent vegetative state. Consequently, in most cases, discontinuation of CPR in the ED is probably warranted for victims of non–icy water submersion who do not respond to resuscitation within 25-30 min. Final decisions regarding whether and when to discontinue resuscitative efforts must be individualized, with the understanding that the possibility of good outcome is generally very low with protracted resuscitation efforts.

Neurologic Management

Drowning victims who present to the hospital awake and alert usually have normal neurologic outcomes. In comatose victims, irreversible CNS injury is highly likely. The most critical and effective neurologic intensive care measures after drowning are rapid restoration and maintenance of adequate oxygenation, ventilation, and perfusion. Core body temperature and glucose management may also be important modulators of neurologic injury after hypoxia-ischemia.

Comatose drowning patients are at risk for intracranial hypertension. There is little evidence that ICP monitoring and therapy to reduce intracranial hypertension improve outcomes for drowning victims. Patients with elevated

ICP usually have poor outcomes—either death or persistent vegetative state. Children with normal ICP can also have poor outcomes, although less frequently. Conventional neurologic intensive care therapies, such as fluid restriction, hyperventilation, and administration of muscle relaxants, osmotic agents, diuretics, barbiturates, and corticosteroids, have not been shown to benefit the drowning victim, either individually or in combination. There is some evidence that these therapies may reduce overall mortality but increase the number of survivors with severe neurologic morbidity.

Seizures after hypoxic brain injury are common, although detection is often difficult in the ICU because these patients are frequently sedated, thus masking clinical signs. Continuous electroencephalographic (EEG) monitoring in critically ill patients revealed a 13% incidence of seizures, 92% of which were exclusively nonconvulsive. However, EEG monitoring has only limited value in the management of drowning victims, except to detect seizures or as an adjunct in the clinical evaluation of brain death (see Chapter 86). Seizures should be treated if possible to stabilize cerebral oxygen use, although benefits are inconclusive. Fosphenytoin or phenytoin (loading dose of 10-20 mg of phenytoin equivalents/kg, followed by maintenance dosing with 5-8 mg of phenytoin equivalents/kg/day in 2-3 divided doses; levels should be monitored) may be considered as an anticonvulsant; it may have some neuroprotective effects and may mitigate neurogenic pulmonary edema. Benzodiazepines, barbiturates, and other anticonvulsants may also have some role in seizure therapy, although no conclusive studies have shown improved neurologic outcome.

With optimal management, many initially comatose children can have impressive neurologic improvement, but usually do so within the 1st 24-72 hr. Unfortunately, half of deeply comatose drowning victims admitted to the PICU die of their hypoxic brain injury or survive with severe neurologic damage. Many children become brain dead. Deeply comatose drowning victims who do not show substantial improvement on neurologic examination after 24-72 hr and whose coma cannot be otherwise explained should be seriously considered for limitation or withdrawal of support.

Other Management Issues

A few drowning victims may have traumatic injury (see Chapter 82), especially if their drowning event involved participation in high-energy water sports such as personal watercraft, boating, diving, or surfing. A high index of suspicion for such injury is required. *Spinal precautions should be maintained in victims with altered mental status and suspected traumatic injury.* Significant anemia suggests trauma and internal hemorrhage.

Hypoxic-ischemic injury can have multiple systemic effects, although protracted organ dysfunction is uncommon in the absence of severe CNS injury. Hyperglycemia is associated with a poor outcome in critically ill pediatric drowning victims. Its etiology is unclear, but hyperglycemia is possibly a stress response. Glucose control in patients after drowning should be focused on avoiding hypoglycemia, hyperglycemia, and wide or rapid fluctuations in serum glucose, to prevent further harm.

Manifestations of acute kidney injury may be seen after hypoxic-ischemic injury (see Chapter 550). Diuretics, fluid restriction, and dialysis are occasionally needed to treat fluid overload or electrolyte disturbances; renal function usually normalizes in survivors. **Rhabdomyolysis** after drowning has been reported.

Profuse bloody diarrhea and mucosal sloughing usually portend a grim prognosis; conservative management includes bowel rest, nasogastric suction, and gastric pH neutralization. Nutritional support for most drowning victims is usually not difficult, because the majority of children either die or recover quickly and resume a normal diet within a few days. Enteral tube feeding or parenteral nutrition is occasionally indicated in children who do not recover quickly.

Hyperthermia after drowning or other types of brain injury may increase the risk of mortality and exacerbate hypoxic-ischemic CNS damage. Almost half of drowning victims have a fever during the 1st 48 hr after submersion. Hyperthermia is usually not caused by infection and resolves without antibiotics in approximately 80% of patients. Generally, prophylactic antibiotics are not recommended. However, there is general consensus that fever or hyperthermia (core body temperature >37.5°C [99.5°F]) in comatose drowning victims resuscitated from cardiac arrest should be prevented at all times in the acute recovery period (at least the 1st 24-48 hr).

Psychiatric and psychosocial sequelae in the family of a pediatric drowning victim are common. Grief, guilt, and anger are typical among family members, including siblings. Divorce rates increase within a few years of the injury, and parents often report difficulties with employment or substance abuse. Friends and family may blame the parents for the event. Professional counseling, pastoral care, or social work referral should be initiated for drowning victims and their families.

Hypothermia Management

Attention to core body temperature starts in the field and continues during transport and in the hospital. The goal is to prevent or treat moderate or severe hypothermia. Damp clothing should be removed from all drowning victims. Rewarming measures are generally categorized as passive, active external, or active internal (see Chapter 93). **Passive rewarming measures** can be applied in the prehospital or hospital setting and include the provision of dry blankets, a warm environment, and protection from further heat loss. These should be instituted as soon as possible for hypothermic drowning victims who have not had a cardiac arrest.

Full CPR with chest compressions is indicated for hypothermic victims if no pulse can be found or if narrow complex QRS activity is absent on ECG (see Chapters 81 and 93). When core body temperature is <30°C (86°F), resuscitative efforts should proceed according to the American Heart Association guidelines for CPR, but IV medications may be given at a lower frequency in moderate hypothermia because of decreased drug clearance. When ventricular fibrillation is present in severely hypothermic victims (core temperature <30°C [86°F]), defibrillation should be initiated but may not be effective until the core temperature is ≥30°C (86°F), at which time successful defibrillation may be more likely.

Significant controversy surrounds the discontinuation of prolonged resuscitative efforts in hypothermic drowning victims. Body temperature should be taken into account before resuscitative efforts are terminated. Other considerations include whether the victim may have been immersed before submerged, whether water was icy, or the cooling was very rapid with fast-flowing cold water. Victims with profound hypothermia may appear clinically dead, but full neurologic recovery is possible, although rare. Attempts at lifesaving resuscitation should not be withheld based on initial clinical presentation unless the victim is obviously dead (dependent lividity or rigor mortis). Rewarming efforts should usually be continued until the temperature is 32-34°C (89.6-93.2°F); if the victim continues to have no effective cardiac rhythm and remains unresponsive to aggressive CPR, resuscitative efforts can be discontinued.

Complete rewarming is not indicated for all arrest victims before resuscitative efforts are abandoned. Discontinuing resuscitation in victims of non–icy water submersion who remain asystolic despite 30 min of CPR is probably warranted. Physicians must use their individual clinical judgment about deciding to stop resuscitative efforts, taking into account the unique circumstances of each incident.

Once a drowning victim has undergone successful CPR after a cardiac arrest, temperature management should be carefully considered and body temperature continuously monitored. In victims in whom resuscitation duration was brief and who are awake soon after resuscitation, attempts to restore and maintain normothermia are warranted. Careful monitoring is necessary to prevent unrecognized worsening hypothermia, which can have untoward consequences.

For drowning victims who remain comatose after successful CPR, more contentious issues include rewarming of hypothermic patients and controlled application of therapeutic hypothermia. Although there is no evidence basis or opinion consensus, many investigators cautiously recommend that hypothermic drowning victims who remain unresponsive because of hypoxic-ischemic encephalopathy after restoration of adequate spontaneous circulation should not be actively rewarmed to normal body temperatures. Active rewarming should be limited to victims with core body temperatures <32°C (89.6°F), but temperatures 32-37.5°C (89.6-99.5°F) should be allowed without further rewarming efforts.

More controversial is the **induction of therapeutic hypothermia** in drowning victims who remain comatose because of hypoxic-ischemic encephalopathy after CPR for cardiac arrest. *A specific recommendation for therapeutic hypothermia, especially in children, is not yet generally accepted.* The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (2002) did not recommend therapeutic hypothermia in drowned children resuscitated after cardiopulmonary arrest, citing insufficient evidence and older studies demonstrating a potential deleterious effect in pediatric drowning victims. Several subsequent studies evaluating extracorporeal membrane circulation, rewarming, and therapeutic hypothermia in pediatric and adult drowning patients have shown no significant improvement in neurologic outcome or mortality.

The Therapeutic Hypothermia After Out-of-Hospital Pediatric Cardiac Arrest (THAPCA) randomized controlled trial (RCT) investigators analyzed post hoc the findings of *targeted temperature management* (TTM) in pediatric comatose survivors of out-of-hospital cardiac arrest due to drowning. Drowning comprised 28% of the landmark pediatric TTM (33°C vs 36.8°C) RCT, and the authors’ principal observation is that targeting hypothermia, compared with targeting normothermia, did not result in better survival.

Prognosis

The outcomes for drowning victims are remarkably bimodal: The great majority of victims either have a good outcome (intact or mild neurologic sequelae) or a poor outcome (severe neurologic sequelae, persistent vegetative state, or death), with very few exhibiting intermediate neurologic injury at hospital discharge. Subsequent evaluation of good outcome survivors may identify significant persistent cognitive deficits. Of hospitalized pediatric drowning victims, 15% die and as many as 20% survive with severe permanent neurologic damage.

Strong predictors of outcome are based on the incident and response to treatment at the scene. Intact survival or mild neurologic impairment has been seen in 91% of children with submersion duration <5 min and in 87% with resuscitation duration <10 min. Children with normal sinus rhythm, reactive pupils, or neurologic responsiveness at the scene virtually always had good outcomes (99%). Poor outcome is highly likely in patients with deep coma, apnea, absence of papillary responses, and hyperglycemia in the ED, with submersion durations >10 min, and with failure of response to CPR given for 25 min. In one comprehensive case series, all children with *resuscitation durations* >25 min either died or had severe neurologic morbidity, and all victims with *submersion durations* >25 min died. Long-term health-related quality of life and school performance in those who had received either bystander- or emergency medical service personnel–initiated CPR was high if their submersion duration was <5 min. Higher morbidity, mortality, and lower quality of life were reported in patients with >10 min submersion duration. In several studies of pediatric drowning, submersion duration was the best predictor of outcome, and water temperature was not. However, there are rare case reports of intact recovery following non–icy water drowning with longer submersion or resuscitation duration.

The GCS score has some limited utility in predicting recovery. Children with a score ≥6 on hospital admission generally have a good outcome, whereas those with a score ≤5 have a much higher probability of poor neurologic outcome. Occasionally, children with a GCS score of 3 or 4 in the ED have complete recovery. Improvement in the GCS score during the 1st several hr of hospitalization may indicate a better prognosis. Overall, early GCS assessments fail to adequately distinguish children who will survive intact from those with major neurologic injury.

Neurologic examination and progression during the 1st 24-72 hr are the best prognosticators of long-term CNS outcome. Children who regain consciousness within 48-72 hr, even after prolonged resuscitation, are unlikely to have serious neurologic sequelae. On the contrary, several studies have shown that patients with minimal improvement during this initial period rarely show significant subsequent neurologic recovery despite aggressive resuscitation efforts and remain in a persistent vegetative state or die. Laboratory and technologic methods to improve prognostication have not yet proved superior to neurologic examination. Serial neurologic evaluations after CPR should be performed over the ensuing 48-72 hr, with consideration given to limitation or withdrawal of support in patients who do not have significant neurologic recovery, even though this may occur before absolute prognostic certainty is achieved.

Prevention

The most effective way to decrease the injury burden of drowning is prevention. Drowning is a multifaceted problem, but several evidence-based preventive strategies are effective. The pediatrician has a prime opportunity to identify and inform families at risk of these strategies through anticipatory guidance. Advocacy should focus on anticipatory guidance regarding the appropriate supervision of children, access to swim lessons, presence of lifeguards, barriers to swimming pools, and use of personal floatation devices (PFDs). A family-centered approach to anticipatory guidance for water safety helps explore and identify the water hazards that each family is exposed to in their environment. The practitioner can then discuss the best tools and strategies for prevention that are relevant for the family. It is important to identify the risk both in and around the home and in other locations they may frequent, often when vacationing, such as vacation or relatives' homes. For some families the focus may be on bathtubs and bucket safety; for others, home pools or hot tubs may be the major hazards. If the family recreates near or on open water, they also need to learn about safety around boats and open water. In a rural environment, water collection systems and natural bodies of water may pose great risk.

Parents must build layers of water protection around their children. Table 91.1 provides an approach to the hazards and preventive strategies relevant to the most common sources of water involved in childhood drowning. A common preventive strategy for exposure to all water types and all ages is ensuring **appropriate supervision** . Pediatricians should define for parents what constitutes appropriate supervision at the various developmental levels of childhood. Many parents either underestimate the importance of adequate supervision or are simply unaware of the risks associated with water. Even parents who say that constant supervision is necessary will often admit to brief lapses while their child is alone near water. Parents also overestimate the supervisory abilities of older siblings; many bathtub drownings occur when an infant or toddler is left with a child <5 yr old.

Table 91.1

Approach to Prevention Strategies for Drowning

	HOME	RECREATION	NEIGHBORHOOD
Water hazards	Swimming pools Ponds Bathtubs Large buckets	Playing in water-swimming, wading Playing near water Being on water—boating	Irrigation ditches Watering holes Water drainage
Common risks	Lapse in supervision Unexpected toddler exposure Delayed discovery of child Reliance on water wings or pool toys Reliance on sibling or bath seat for bathing supervision	Lapse in supervision Change in weather Unfamiliarity with or change(s) in water conditions: Steep drop-off Current/tide Low temperature Alcohol use Peer pressure	Lapse in supervision, particularly when caregiver is socializing Risky behavior when with peers
Prevention strategies	Recognize hazards and risks. Provide constant adult supervision around water. Install 4-sided, isolation fencing of pools. Install rescue equipment and phone at poolside. Learn swimming and water survival skills. Avoid bath; instead shower, if a child/teen with seizure disorder. Learn first aid and CPR.	Provide constant adult supervision. Swim in lifeguarded areas. Know when and how to wear U.S. Coast Guard–approved PFDs. Avoid alcohol and other drugs. Learn swimming and water survival skills. Teach children about water safety. Be aware of current weather and water conditions. Learn first aid and CPR.	Identify hazardous bodies of water. Prevent access to water with barriers. Provide fenced-in “safe area” for water recreation. Provide lifeguarded swim sites. Provide access to low-cost swim/water survival lessons.

CPR, Cardiopulmonary resuscitation; PFDs, personal floatation devices.

Supervision of infants and young children means that a responsible adult should be with the child every moment. The caregiver must be alert, must not be consuming alcohol or other drugs or socializing, and must be attentive and focused entirely on watching the child. Even a brief moment of inattention, such as to answer a phone, get a drink, or hold a conversation, can have tragic consequences. If the child does not swim, *touch supervision* is required, meaning that the caregiver should be within arm's reach at all times. Adolescents require active adult supervision and avoidance of alcohol or drug use during water activities.

Learning to swim offers another layer of protection. Children may start swim lessons at an early age that are developmentally appropriate and aimed at the individual child's readiness and skill level. Swim lessons are beneficial and provide some level of protection to young children. A study from Bangladesh, where drowning accounts for 20% of all deaths in children ages 1-4 yr, showed that swim lessons and water safety curricula are cost-effective and led to a decrease in mortality from drowning. As with any other water safety intervention, parents need to know that swimming lessons and acquisition of swim skills cannot be solely relied on to prevent drowning. *No child can be drown-proof.* A supervising caretaker should be aware of where and how to get help and know how to safely rescue a child in trouble. Because only those trained in water rescue can safely attempt it, families should be encouraged to swim in designated areas only when and where a lifeguard is on duty.

Children and adolescents should never swim alone regardless of their swimming abilities. Even as they become more independent and participate in recreational activities without their parents, they should be encouraged to seek areas that are watched by **lifeguards** . In 2015, lifeguards rescued 940,000 Americans from drowning, and they probably prevent millions more drownings through verbal warnings and prompt interventions when needed. It is important to emphasize that even if the child is considered a strong swimmer, the ability to swim in a pool does not translate to being safe in open water, where water temperature, currents, and underwater obstacles can present additional and unfamiliar challenges. For swimmers, supervision by lifeguards reduces drowning risk, because lifeguards monitor risk behaviors and are trained in the difficult and potentially dangerous task of rescuing drowning victims.

Two of the preventive strategies listed in Table 91.1 deserve special mention. The most vigorously evaluated and effective drowning intervention applies to swimming pools. **Isolation fencing** that surrounds a pool with a secure, self-locking gate could prevent up to 75% of swimming pool–related drowning. Guidelines for appropriate fencing, provided by the U.S. Consumer Product

Safety Commission, are very specific; they were developed through testing of active toddlers in a gymnastics program on their ability to climb barriers of different materials and heights, and recent studies show them to be effective in preventing drowning in young children. In families who have a pool on their property, caregivers often erroneously believe that if a child falls into the water, there will be a loud noise or splash to alert them. Unfortunately, these events are usually silent, delaying timely rescue. This finding highlights the need for a fence that separates the pool from the house, not just surrounds the entire property.

The use of U.S. Coast Guard–approved **lifejackets or PFDs** should be advised with all families spending time around open water, not just those who consider themselves boaters. This issue is also particularly important for families who will participate in aquatic activities on a vacation. A PFD should be chosen with respect to the weight of the child and the proposed activity. Young children should wear PFDs that will float their head up. Parents should be urged to wear PFDs as well, since their use of PFDs is associated with greater use by their children. Toys such as water wings and "floaties" should not be relied on as drowning prevention measures.

Effective preventive efforts must also consider **cultural practices** . Different ethnic groups may have certain attitudes, beliefs, dress, or other customs that may affect their water safety. The higher drowning risk of minority children needs to be addressed by community-based prevention programs.

In addition to anticipatory guidance, pediatricians can play an active role in drowning prevention by participating in advocacy efforts to improve legislation for pool fencing, PFD use, and alcohol consumption in various water activities. Several counties in the United States, Australia, and New Zealand have laws requiring isolation fencing for pools. Their effectiveness has been limited by a lack of enforcement. Similarly, all states have boating-under-the-influence laws but, similarly, rarely enforce them. Furthermore, efforts at the community level may be needed to ensure the availability of swimming lessons for underserved populations and lifeguarded swim areas.

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CHAPTER 92

Burn Injuries

Alia Y. Antoon

Burns are a leading cause of *unintentional injury* in children, second only to motor vehicle crashes. There has been a decline in the incidence of burn injury requiring medical care that has coincided with a stronger focus on burn treatment and prevention, increased fire and burn prevention education, greater availability of regional treatment centers, widespread use of smoke detectors, greater regulation of consumer products and occupational safety, and societal changes such as reductions in smoking and alcohol abuse.

Epidemiology

Approximately 2 million people in the United States require medical care for burn injuries each year. Approximately 50% of these patients are younger than 5 yr, with an average age of 32 mo. The principal cause of the burn is scald; one of the causes of **scald burn** is heating liquids in the microwave. The leading cause of burn in children 5-14 yr old is **flame injury** . In children 5-10 yr old, burns are usually a result of match play, whereas for older children, it is usually a result of gasoline ignition. **Fires** are a major cause of mortality in children, accounting for up to 34% of fatal injuries in those <16 yr old.

Scald burns account for 85% of total injuries and are most prevalent in children <4 yr old. Although the incidence of hot water scalding has been reduced by legislation requiring new water heaters to be preset at 48.9°C (120°F), scald injury remains the leading cause of hospitalization for burns. *Steam inhalation* used as a home remedy to treat respiratory infections is another potential cause of burns. Flame burns account for 13%; the remaining are electrical and chemical burns. **Clothing ignition** events have declined since passage of the Federal Flammable Fabric Act requiring sleepwear to be flame-retardant; however, the U.S. Consumer Product Safety Commission has voted to relax the existing children's sleepwear flammability standard. *Polyester* is the fabric most resistant to ignition by small flame source. Polyester does burn deeply as it melts, but it self-extinguishes when the flame source is removed. *Cotton,* on the other hand, continues to burn after the flame source has been removed, resulting in large, deep burns. Polyester melts downward, sparing the face and respiratory tract; cotton burns upward toward the face. Pellet stove, glass front stoves, and flat top stoves are becoming frequent sources of hand burns in children. Approximately 18% of burns are the result of **child abuse** (usually scalds), making it important to assess the pattern and site of injury and their consistency with the patient history (see Chapter 16). **Friction burns** from treadmills are also a problem. Hands are the most commonly injured sites, with deep 2nd-degree friction injury sometimes associated with fractures of the fingers. *Anoxia,* not the actual burn, is a major cause of morbidity and mortality in house fires.

Review of the history usually shows a common pattern: scald burns to the side of the face, neck, and arm if liquid is pulled from a table or stove; burns in the pant leg area if clothing ignites; burns in a splash pattern from cooking; and burns on the palm of the hand from contact with a hot stove. However, **glove or stocking burns** of the hands and feet; single-area deep burns on the trunk, buttocks, or back; and small, full-thickness burns (e.g., cigarette burns) in young children should raise the suspicion of child abuse.

Burn care involves a range of activities: prevention, acute care and resuscitation, wound management, pain relief, reconstruction, rehabilitation, and psychosocial adjustment. Children with massive burns require early and appropriate psychological and social support as well as resuscitation. Surgical debridement, wound closure, and rehabilitative efforts should be instituted concurrently to promote optimal rehabilitation. In order to maximize survival, the clinical approach includes aggressive surgical removal of devitalized tissue, infection control, and judicious use of antibiotics; life support with endotracheal intubation and mechanical ventilation; and use of early nutrition. Children who have sustained burn injuries differ in appearance from their peers, necessitating supportive efforts for reentry to school and social and sporting activities.

Prevention

The aim of burn prevention is a continuing reduction in the number of serious burn injuries (Table 92.1). Effective first aid and triage can decrease both the extent (area) and the severity (depth) of injuries. The use of flame-retardant clothing and smoke detectors, control of hot water temperature (thermostat settings) to 48.9°C (120°F) within buildings, and prohibition of cigarette smoking have been partially successful in reducing the incidence of burn injuries. Treatment of children with significant burn injuries in dedicated burn centers facilitates medically effective care, improves survival, and leads to greater cost efficiency. Survival of at least 80% of patients with burns of 90% of the body surface area (BSA) is possible; the overall survival rate of children with burns of all sizes is 99%. Death is more likely in children with irreversible anoxic brain injury sustained at the time of the burn. It is well known that burns occur in predictable patterns. Sources of burns include, by season:

Table 92.1

Burn Prophylaxis

Prevent Fires

Install and use smoke detectors.
Control the hot water thermostat; in public buildings, maximum water temperature should be 48.9°C (120°F).
Keep fire, matches, and lighters out of the reach of children.
Avoid cigarette smoking, especially in bed.
Do not leave lit candles unattended.
Use flame retardant–treated clothing.
Use caution when cooking, especially with oil.
Keep cloth items off heaters.

Prevent Injury

Roll, but do not run, if clothing catches fire; wrap in a blanket.
Practice escape procedures.
Crawl beneath smoke if a fire occurs indoors.
Use educational materials.*

[*] National Fire Protection Association pamphlets and videos.

Winter :

- Glass front fireplaces/pellet stoves and radiators increase hand burns.
- Treadmill injuries as more people exercise inside—child imitates adults or young child touches belt.

Summer :

- Fireworks, sparkler—temperatures reach 537.8°C (1,000°F).
- Burn contact with hot grill; hand/feet burn from hot embers.
- Lawnmowers

Spring/Fall :

- Burning leaves
- Gasoline burns
- Tap water scalds are essentially preventable through a combination of behavioral and environmental changes.

Pediatricians can play a major role in preventing the most common burns by educating parents and healthcare providers. Simple, effective, efficient, and cost-effective preventive measures include the use of appropriate clothing and smoke detectors and the planning of routes for emergency exit from the home. The National Fire Protection Association (NFPA) recommends replacing smoke detector batteries annually and the smoke detector alarm every 10 yr (or earlier, if indicated on the device). Child neglect and abuse must be seriously considered when the history of the injury and the distribution of the burn do not match.

Acute Care, Resuscitation, and Assessment

Indications for Admission

Burns covering >10% of total body surface area (BSA), burns associated with smoke inhalation, burns resulting from high-tension (voltage) electrical injuries, and burns associated with suspected child abuse or neglect should be treated as emergencies and the child hospitalized (Table 92.2). Small 1st- and 2nd-degree burns of the hands, feet, face, perineum, and joint surfaces also require admission if close follow-up care is difficult to provide. Children who have been in enclosed-space fires and those who have face and neck burns should be hospitalized for at least 24 hr for observation for signs of central nervous system (CNS) effects of anoxia from carbon monoxide (CO) poisoning and pulmonary effects from smoke inhalation.

Table 92.2

Indications for Hospitalization for Burns

Burns affecting >10% of BSA
Burns >10–20% of BSA in adolescent/adult
3rd-degree burns
Electrical burns caused by high-tension wires or lightning
Chemical burns
Inhalation injury, regardless of the amount of BSA burned
Inadequate home or social environment
Suspected child abuse or neglect
Burns to the face, hands, feet, perineum, genitals, or major joints
Burns in patients with preexisting medical conditions that may complicate the acute recovery phase
Associated injuries (fractures)
Pregnancy

BSA, Body surface area.

First Aid Measures

Acute care should include the following measures:

1. Extinguish flames by rolling the child on the ground; cover the child with a blanket, coat, or carpet.
2. After determining that the airway is patent, remove smoldering clothing or clothing saturated with hot liquid. Jewelry, particularly rings and bracelets, should be removed or cut away to prevent constriction and vascular compromise during the edema phase in the first 24-72 hr after burn injury.
3. In cases of **chemical injury** , brush off any remaining chemical, if

powdered or solid; then use copious irrigation or wash the affected area with water. Call the local poison control center for the neutralizing agent to treat a chemical ingestion.

4. Cover the burned area with clean, dry sheeting and apply cold (not iced) wet compresses to small injuries. Significant large-burn injury (>15% of BSA) decreases body temperature control and contraindicates the use of cold compresses.
5. If the burn is caused by **hot tar** , use mineral oil to remove the tar.
6. Administer analgesic medications.

Emergency Care

Supportive measures are as follows (Table 92.3 and Table 92.4)

Table 92.3

Acute Treatment of Burns

First aid, including washing of wounds and removal of devitalized tissue
Fluid resuscitation
Provision of energy requirements
Control of pain
Prevention of infection—early excision and grafting
Prevention of excessive metabolic expenditures
Control of bacterial wound flora
Use of biologic and synthetic dressings to close the wound

Table 92.4

Four Phases of Burn Care, With Physiologic Changes and Objectives

PHASE AND TIMING	PHYSIOLOGIC CHANGES	OBJECTIVES
1 : Initial evaluation and resuscitation, 0 to 72 hr	Massive capillary leak and burn shock	Accurate fluid resuscitation and thorough evaluation
2 : Initial wound excision and biologic closure, days 1-7	Hyperdynamic and catabolic state with high risk of infection	Accurately identify and remove all full-thickness wounds and achieve biologic closure
3 : Definitive wound closure, day 7 to week 6	Continued catabolic state and risk of nonwound septic events	Replace temporary with definitive covers, and close small complex wounds
4 : Rehabilitation,	Waning catabolic state	Initially to maintain range of motion and reduce

reconstruction, and reintegration, day 1 through discharge	and recovering strength	edema; subsequently to strengthen and facilitate return to home, work, and school

From Sheridan RL: Burns, including inflammation injury. In Vincent JL, Abraham E, Moore FA, et al, editors: *Textbook of critical care,* ed 7, Philadelphia, 2017, Elsevier (Table 168-1, p. 1173).

1. Rapidly review the cardiovascular and pulmonary status and document preexisting or physiologic lesions (asthma, congenital heart disease, renal or hepatic disease).
2. Ensure and maintain an adequate airway, and provide humidified oxygen by mask or endotracheal intubation (Fig. 92.1). The latter may be needed in children who have facial burns or a burn sustained in an enclosed space, before facial or laryngeal edema becomes evident. If hypoxia or CO poisoning is suspected, 100% oxygen should be used (see Chapters 81 and 89).

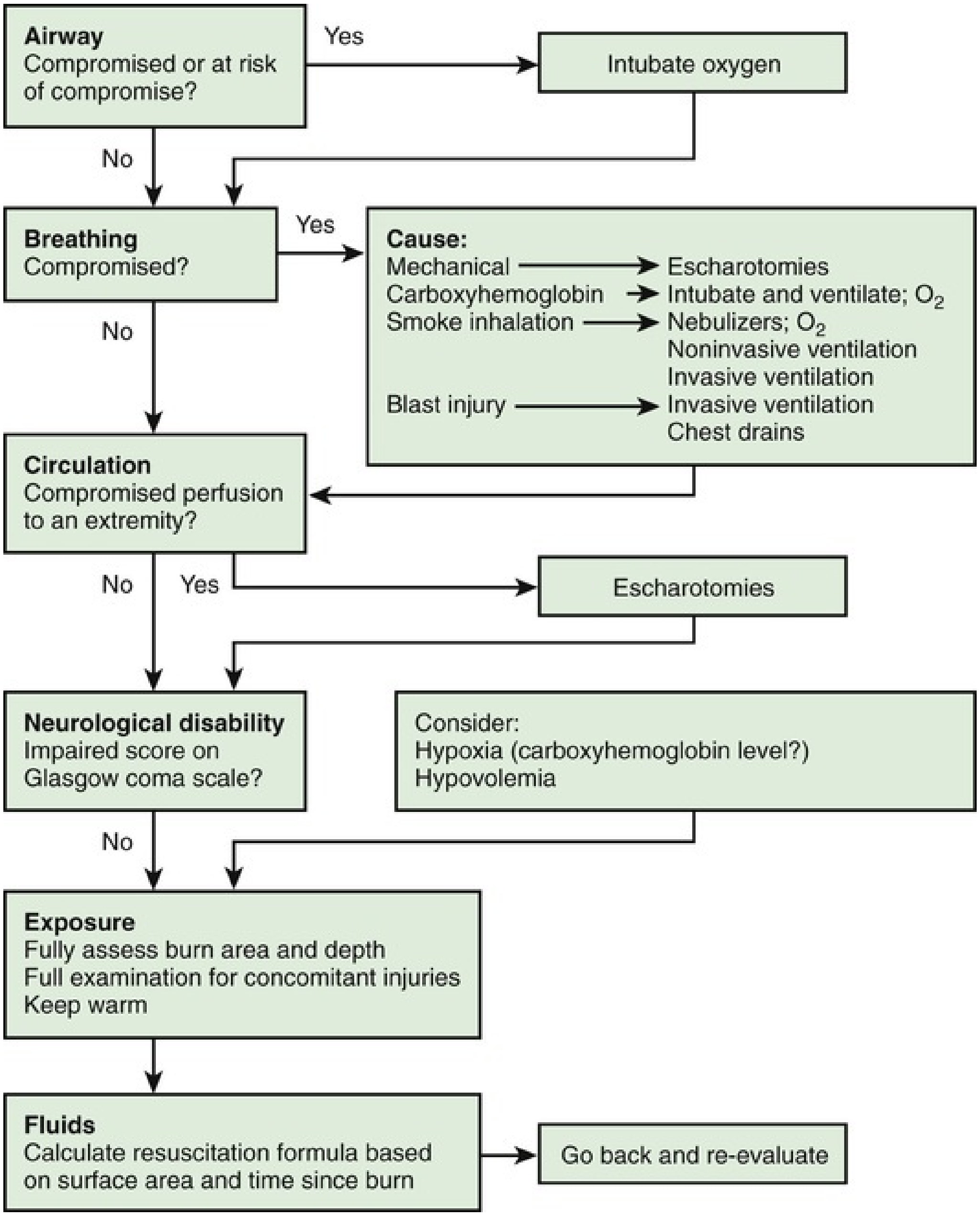
Airway
Compromised or at risk of compromise?
Yes
Intubate oxygen
No
Breathing
Compromised?
Yes
Cause:
Mechanical
Escharotomies
Carboxyhemoglobin
Intubate and ventilate; O_2
Smoke inhalation
Nebulizers; O_2
Noninvasive ventilation
Invasive ventilation
Blast injury
Invasive ventilation
Chest drains
No
Circulation
Compromised perfusion to an extremity?
No
Yes
Escharotomies
Neurological disability
Impaired score on Glasgow coma scale?
Consider:
Hypoxia (carboxyhemoglobin level?)
Hypovolemia
No
Exposure
Fully assess burn area and depth
Full examination for concomitant injuries
Keep warm
Fluids
Calculate resuscitation formula based on surface area and time since burn
Go back and re-evaluate

FIG. 92.1 **Algorithm for primary survey of a major burn injury.** (From Hettiaratchy S, Papini R: Initial management of a major burn. I. Overview, *BMJ* 328:1555–1557, 2004.)

3. Children with burns >15% of BSA require intravenous (IV) fluid resuscitation to maintain adequate perfusion. In an emergency situation if IV access is unattainable, an intraosseous line should be placed. When inserting central lines to provide high-volume fluid, special attention should be paid to use a very-small-caliber catheter in small children to avoid injury to the vascular lining, which may predispose to formation of clots. All inhalation injuries, regardless of the extent of BSA burn, require venous access to control fluid intake. All high-tension and

electrical injuries require venous access to ensure forced alkaline diuresis in case of muscle injury to avoid myoglobinuric renal damage. Lactated Ringer solution, 10-20 mL/kg/hr (normal saline may be used if lactated Ringer solution is not available), is initially infused until proper fluid replacement can be calculated. Consultation with a specialized burn unit should be made to coordinate fluid therapy, the type of fluid, the preferred formula for calculation, and preferences for the use of colloid agents, particularly if transfer to a burn center is anticipated.

4. Evaluate the child for associated injuries, which are common in patients with a history of high-tension electrical burn, especially if there has also been a fall from a height. Injuries to the spine, bones, and thoracic or intraabdominal organs may occur (see Chapter 82). Cervical spine precautions should be observed until this injury is ruled out. There is a very high risk of cardiac abnormalities, including ventricular tachycardia and ventricular fibrillation, resulting from conductivity of the high electric voltage. Cardiopulmonary resuscitation (CPR) should be instituted promptly at the scene and cardiac monitoring started on the patient's arrival at the emergency department (ED) (see Chapter 81).
5. Children with burns of >15% of BSA should not receive oral fluids (initially) because gastric distention may develop. These children require insertion of a nasogastric tube in the ED to prevent aspiration.
6. A Foley catheter should be inserted into the bladder to monitor urine output in all children who require IV fluid resuscitation.
7. All wounds should be wrapped with sterile dressings until it is decided whether to treat the patient on an outpatient basis or refer to an appropriate facility.
8. A CO measurement (carboxyhemoglobin [HbCO]) should be obtained for fire victims and 100% oxygen administered until the result is known.
9. Review child immunization. Burns <10% BSA do not require tetanus prevention, whereas burns >10% need tetanus immunization. Use diphtheria, tetanus toxoids, and acellular pertussis (DTaP) for tetanus prophylaxis for children <11 yr old, and use tetanus, diphtheria, and pertussis (TdaP) for children >11 yr old (see Chapter 238).

Classification of Burns

Proper triage and treatment of burn injury require assessment of the extent and depth of the injury (Table 92.5 and Fig. 92.2). **1st-degree burns** involve only the epidermis and are characterized by swelling, erythema, and pain (similar to mild sunburn). Tissue damage is usually minimal, and there is no blistering. Pain resolves in 48-72 hr; in a small percentage of patients, the damaged epithelium peels off, leaving no residual scars.

Table 92.5

Categories of Burn Depth

	1ST-DEGREE BURN	2ND-DEGREE, OR PARTIAL-THICKNESS, BURN	3RD-DEGREE, OR FULL-THICKNESS, BURN
Surface appearance	Dry, no blisters Minimal or no edema Erythematous Blanches, bleeds	Moist blebs, blisters Underlying tissue is mottled pink and white, with fair capillary refill Bleeds	Dry, leathery eschar Mixed white, waxy, khaki, mahogany, soot-stained No blanching or bleeding
Pain	Very painful	Very painful	Insensate
Histologic depth	Epidermal layers only	Epidermis, papillary, and reticular layers of dermis May include domes of subcutaneous layers	Down to and may include fat, subcutaneous tissue, fascia, muscle, and bone
Healing time	2-5 days with no scarring	Superficial: 5-21 days with no grafting Deep partial: 21-35 days with no infection; if infected, converts to full-thickness burn	Large areas require grafting, but small areas may heal from the edges after weeks

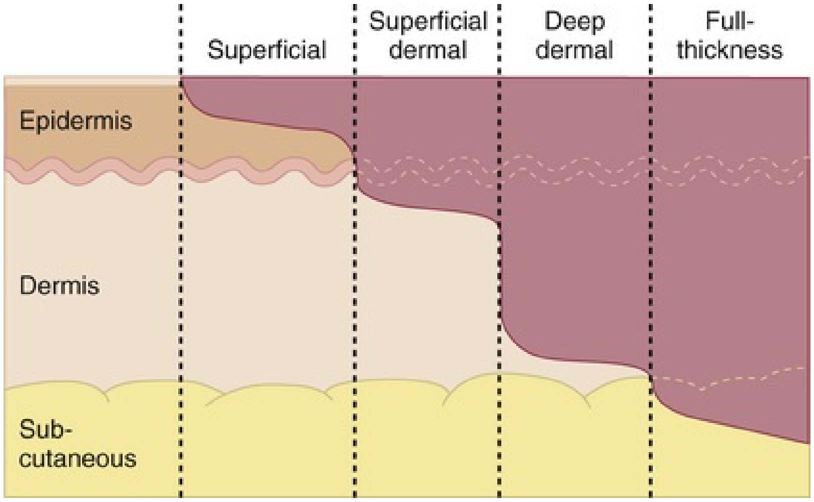

FIG. 92.2 Diagram of different burn depths. (From Hettiaratchy S, Papini R: Initial

management of a major burn. II. Assessment and resuscitation, *BMJ* 329:101–103, 2004.)

A **2nd-degree burn** involves injury to the entire epidermis and a variable portion of the dermal layer (vesicle and blister formation are characteristic). A *superficial* 2nd-degree burn is extremely painful because many remaining viable nerve endings are exposed. Superficial 2nd-degree burns heal in 7-14 days as the epithelium regenerates in the absence of infection. *Mid-level to deep* 2nd-degree burns also heal spontaneously if wounds are kept clean and infection free. Pain is less with these burns than in more superficial burns because fewer nerve endings remain viable. Fluid losses and metabolic effects of deep dermal (2nd-degree) burns are essentially the same as those of 3rd-degree burns.

Full-thickness, or **3rd-degree, burns** involve destruction of the entire epidermis and dermis, leaving no residual epidermal cells to repopulate the damaged area. The wound cannot epithelialize and can heal only by wound contraction or skin grafting. The absence of painful sensation and capillary filling demonstrates the loss of nerve and capillary elements.

Technologies are being used to help accurately determine the depth of burns. Laser *Doppler imaging* can be used from 48 hr to 5 days after the burn. It produces a color map of the affected tissue; *yellow* indicates second-degree burns, reflecting the presence of capillaries, arterioles, and venules, and *blue* reflects very low or absence of blood flow, which indicates third-degree burns. Its accuracy is up to 95%, and with accurate assessment, the proper treatment can be applied without delay. Doppler imaging can be used in both outpatients and inpatients.

Another technology called *reflectance confocal microscopy* (RCM), can be combined with *optical coherence tomography* (OCT) to visualize tissue morphology at the subcellular level. It determines if the cells are damaged and enables detection of skin morphologic changes up to 1 mm in depth. It provides accurate determination of the depth of the burn, allowing for the appropriate treatment.

Estimation of Body Surface Area for a Burn

Appropriate burn charts for different childhood age-groups should be used to accurately estimate the extent of BSA burned. The volume of fluid needed in resuscitation is calculated from the estimation of the extent and depth of burn surface. Mortality and morbidity also depend on the extent and depth of the burn. The variable growth rate of the head and extremities throughout childhood makes it necessary to use BSA charts, such as that modified by Lund and Brower or the chart used at the Shriners Hospital for Children in Boston (Fig. 92.3). The **rule of nines** used in adults may be used only in children >14 yr old or as a rough estimate to institute therapy before transfer to a burn center. In small burns, <10% of BSA, the **rule of palm** may be used, especially in outpatient settings; the area from the wrist crease to the finger crease (the palm) in the child equals 1% of the child's BSA.

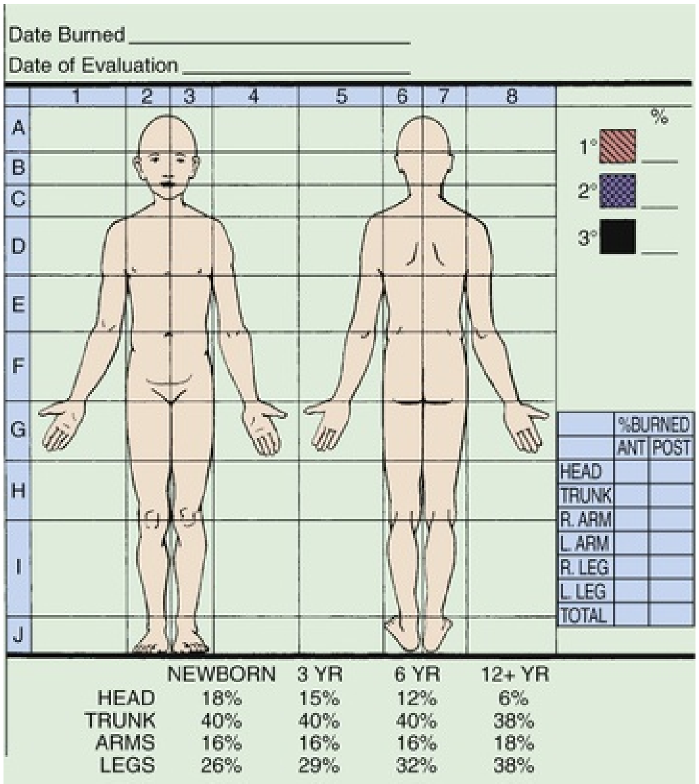

	%BURNED	
	ANT	POST
HEAD		
TRUNK		
R. ARM		
L. ARM		
R. LEG		
L. LEG		
TOTAL		

	NEWBORN	3 YR	6 YR	12+ YR
HEAD	18%	15%	12%	6%
TRUNK	40%	40%	40%	38%
ARMS	16%	16%	16%	18%
LEGS	26%	29%	32%	38%

FIG. 92.3 Chart to determine developmentally related percentage of body surface area affected by burn injury. ANT, Anterior; POST, posterior; R., right; L., left. (Courtesy of Shriners Hospital for Crippled Children, Burn Institute, Boston Unit.)

Treatment

Outpatient Management of Minor Burns

A patient with 1st- and 2nd-degree burns of <10% BSA may be treated on an outpatient basis unless family support is judged inadequate or there are issues of child neglect or abuse. These outpatients do not require a tetanus booster (unless not fully immunized) or prophylactic penicillin therapy. Blisters should be left intact and dressed with *bacitracin* or *silver sulfadiazine* cream (Silvadene). Dressings should be changed once daily, after the wound is washed with lukewarm water to remove any cream left from the previous application. Very small wounds, especially those on the face, may be treated with bacitracin ointment and left open. **Debridement** of the devitalized skin is indicated when the blisters rupture. A variety of wound dressings and wound membranes (e.g., AQUACEL Ag dressing [ConvaTec USA, Skillman, NJ] in soft felt-like material impregnated with silver ion) may be applied to 2nd-degree burns and wrapped with a dry sterile dressing. Similar wound membranes provide pain control, prevent wound desiccation, and reduce wound colonization (Table 92.6). These dressings are usually kept on for 7-10 days but are checked twice a week.

Table 92.6

Select Common Wound Membranes for Burns

MEMBRANE	CHARACTERISTIC(S)
Porcine xenograft	Adheres to coagulum Excellent pain control
Biobrane	Bilaminate Fibrovascular in growth into inner layer
Acticoat	Nonadherent dressing that delivers silver
AQUACEL Ag	Absorptive hydrofiber that delivers silver
Various semipermeable membranes	Provide vapor and bacterial barrier
Various hydrocolloid dressings	Provide vapor and bacterial barrier Absorb exudates
Various impregnated gauzes	Provide barrier while allowing drainage

Burns to the palm with large blisters usually heal beneath the blisters; they should receive close follow-up on an outpatient basis. The great majority of superficial burns heal in 10-20 days. Deep 2nd-degree burns take longer to heal and may benefit from enzymatic debridement ointment (collagenase) applied daily on the wound, which aids in the removal of the dead tissue. These ointments should not be applied to the face, to avoid the risk of getting into the eyes.

The depth of scald injuries is difficult to assess early; conservative treatment is appropriate initially, with the depth of the area involved determined before grafting is attempted (Fig. 92.4). This approach obviates the risk of anesthesia and unnecessary grafting.

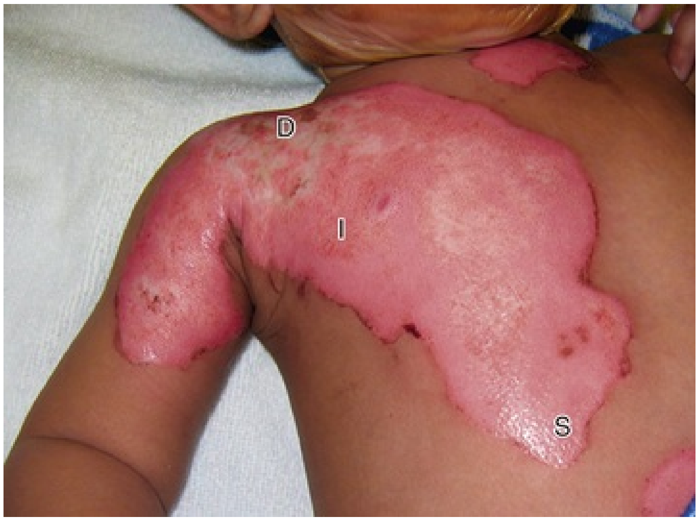

FIG. 92.4 Tea scald over the chest and shoulder of a child showing heterogeneity of burn depth. D, Deep; I, intermediate; S, superficial. (From Enoch S, Roshan A, Shah M: Emergency and early management of burns and scalds, *BMJ* 338:937–941, 2009.)

Fluid Resuscitation

Fluid resuscitation should begin soon after the injury has occurred, in the ED before transferring to a burn center. For most children, the *Parkland formula* is an appropriate starting guideline for fluid resuscitation (4 mL lactated Ringer solution/kg/% BSA burned). Half the fluid is given over the 1st 8 hr, calculated from the time of onset of injury; the remaining fluid is given at an even rate over the next 16 hr. The rate of infusion is adjusted according to the patient's response to therapy. Pulse and blood pressure should return to normal, and an adequate urine output (>1 mL/kg/hr in children; 0.5-1.0 mL/kg/hr in adolescents) should be accomplished by varying the IV infusion rate. Vital signs, acid-base balance, and mental status reflect the adequacy of resuscitation. Because of interstitial edema and sequestration of fluid in muscle cells, patients may gain up to 20% over baseline (preburn) body weight. Patients with burns of 30% BSA require a large venous access (central venous line) to deliver the fluid required over the critical 1st 24 hr. Patients with burns of >60% BSA may require a multilumen central venous catheter; these patients are best cared for in a specialized burn unit. In addition to fluid resuscitation, children should receive standard maintenance fluids (see Chapter 69).

During the 2nd 24 hr after the burn, patients begin to reabsorb edema fluid and to experience diuresis. Half the 1st day's fluid requirement is infused as lactated Ringer solution in 5% dextrose. Children <5 yr old may require the addition of 5% dextrose in the 1st 24 hr of resuscitation. Controversy surrounds whether *colloid* should be provided in the early period of burn resuscitation. One preference is to use colloid replacement concurrently if the burn is >85% of total BSA. Colloid is usually instituted 8-24 hr after the burn injury. In children <12 mo old, sodium tolerance is limited; the volume and sodium concentration of the resuscitation solution should be decreased if the urinary sodium level is rising. The adequacy of resuscitation should be constantly assessed by means of vital signs as well as urine output, blood gas, hematocrit, and serum protein measurements. Some patients require arterial and central venous lines, particularly those undergoing multiple excision and grafting procedures, as needed, for monitoring and replacement purposes. Central venous pressure monitoring may be indicated to assess circulation in patients with hemodynamic or cardiopulmonary instability. Femoral vein cannulation is a safe access for fluid resuscitation, especially in infants and children. Burn patients who require frequent blood gas monitoring benefit from radial or femoral arterial catheterization.

Oral supplementation may start as early as 48 hr after the burn. Milk formula, artificial feedings, homogenized milk, or soy-based products can be given by bolus or constant infusion through a nasogastric or small bowel feeding tube. As oral fluids are tolerated, IV fluids are decreased proportionately in an effort to keep the total fluid intake constant, particularly if pulmonary dysfunction is present.

A **5% albumin infusion** may be used to maintain the serum albumin levels at a desired 2 g/dL. The following rates are effective: for burns of 30–50% of total BSA, 0.3 mL of 5% albumin/kg/% BSA burn is infused over 24 hr; for burns of 50–70% of total BSA, 0.4 mL/kg/% BSA burn is infused over 24 hr; and for burns of 70–100% of total BSA, 0.5 mL/kg/% BSA burn is infused over 24 hr. **Infusion of packed red blood cells** is recommended if the hematocrit falls to <24% (hemoglobin = 8 g/dL). Some authorities recommend treatment for hematocrit <30% or hemoglobin <10 g/dL in patients with systemic infection, hemoglobinopathy, cardiopulmonary disease, anticipated (or ongoing) blood loss, and if repeated excision and grafting of full-thickness burns are needed.

Fresh-frozen plasma (FFP) is indicated if clinical and laboratory assessment shows a deficiency of clotting factors, a prothrombin level >1.5 times control, or a partial thromboplastin time >1.2 times control in children who are bleeding or are scheduled for an invasive procedure or a grafting procedure that could result in an estimated blood loss of more than half of blood volume. FFP may be used for volume resuscitation within 72 hr of injury in patients <2 yr old with burns >20% BSA and associated inhalation injury.

Sodium supplementation may be required for children with burns of >20% BSA if 0.5% silver nitrate solution is used as the topical antibacterial burn dressing. Sodium losses with silver nitrate therapy are regularly as high as 350 mEq/m^2 burn surface area. Oral sodium chloride supplement of 4 g/m^2 burn area/24 hr is usually well tolerated, divided into 4-6 equal doses to avoid osmotic diarrhea. The aim is to maintain serum sodium levels >130 mEq/L and urinary sodium concentration >30 mEq/L. Young children <5 yr are especially susceptible to hyponatremic and cerebral edema. IV **potassium supplementation** is supplied to maintain a serum potassium level >3 mEq/dL. Potassium losses may be significantly increased when 0.5% silver nitrate solution is used as the topical antibacterial agent or when aminoglycoside, diuretic, or amphotericin therapy is required.

Prevention of Infection and Surgical Management of the Burn Wound

Controversy surrounds the use of **prophylactic penicillin** for all patients hospitalized with acute burn injury and the periodic **replacement of central venous catheters** to prevent infection. In some units, a 5-day course of penicillin therapy is used for all patients with acute burns; standard-dose crystalline penicillin is given orally or intravenously in 4 divided doses. *Erythromycin* may be used as an alternative in penicillin-allergic children. Other units have discontinued prophylactic use of penicillin therapy without an increase in the infection rate. Similarly, there is conflicting evidence as to whether relocation of the IV catheter every 48-72 hr decreases or increases the incidence of catheter-related sepsis. Some recommend that the central venous catheter be replaced and relocated every 5-7 days, even if the site is not inflamed and there is no suspicion of catheter-related sepsis.

Mortality related to burn injury is associated not with the toxic effect of thermally injured skin, but with the metabolic and bacterial consequences of a large open wound, reduction of the patient's host resistance, and malnutrition. These abnormalities set the stage for life-threatening bacterial infection originating from the burn wound. Wound treatment and prevention of wound infection also promote early healing and improve aesthetic and functional outcomes. Topical treatment of the burn wound with 0.5% silver nitrate solution, silver sulfadiazine cream, or mafenide acetate (Sulfamylon) cream or topical solution at a concentration of 2.5–5% to be used for wounds with multidrug–resistant bacteria aims at prevention of infection (Table 92.7). These 3 agents have tissue-penetrating capacity. Regardless of the choice of topical antimicrobial agent, it is essential that all 3rd-degree burn tissue be fully excised before bacterial colonization occurs, and that the area is grafted as early as possible to prevent deep wound sepsis. Children with a burn of >30% BSA should be housed in a bacteria-controlled nursing unit to prevent cross-contamination and to provide a temperature- and humidity-controlled environment to minimize hypermetabolism.

Table 92.7

Topical Agents Used for Burns

AGENT	EFFECTIVENESS	EASE OF USE
Silver sulfadiazine cream (Silvadene)	Good penetration	Changed once daily
		Residue *must* be washed off with each dressing change
Mafenide acetate cream* (Sulfamylon)	Broad spectrum, including *Pseudomonas*	Closed dressings Changed twice daily
	Rapid and deep wound penetration	Residue *must* be washed off with each dressing changed
0.5% Silver nitrate solution	Bacteriostatic	Closed bulky dressing soaked every 2 hr and changed once daily
	Broad spectrum, including some fungi	
	Superficial penetration	
AQUACEL Ag	Dressing impregnated with silver	Applied directly to 2nd-degree burn; occlusive dressing kept for 10 days

* Mafenide acetate solution at concentrations of 2.5% or 5% for use on heavily colonized, multidrug-resistant organisms to be used for 5 days only.

Deep 3rd-degree burns of >10% BSA benefit from early excision and grafting. To improve outcome, sequential excision and grafting of 3rd-degree and deep 2nd-degree burns is required in children with large burns. Prompt excision with immediate wound closure is achieved with **autografts** , which are often meshed to increase the efficiency of coverings. Alternatives for wound closure, such as allografts, xenografts, and Integra (Integra LifeSciences, York, PA) and other synthetic skin coverings (bilaminate membrane composed of a porous lattice of crosslinked chondroitin-6-sulfate engineered to induce neovascularization as it is biodegraded), may be important for wound coverage in patients with extensive injury to limit fluid, electrolyte, and protein losses and to reduce pain and minimize temperature loss. Epidermal cultured cells (autologous keratinocytes) are a costly alternative and are not always successful. An experienced burn team can safely perform early-stage or total excision while burn fluid resuscitation continues. Important keys to success are: (1) accurate preoperative and intraoperative determination of burn depth; (2) the choice of excision area and appropriate timing; (3) control of intraoperative blood loss; (4) specific instrumentation; (5) the choice and use of perioperative antibiotics; and (6) the type of wound coverage chosen. This process can accomplish early wound coverage without the use of recombinant human growth hormone.

Nutritional Support

Supporting the increased energy requirements of a patient with a burn is a high priority. The burn injury produces a hypermetabolic response characterized by both protein and fat catabolism. Depending on the time lapse since the burn, children with a burn of 40% of total BSA require basal energy expenditure (oxygen consumption) approximately 50–100% higher than predicted for their age. Early excision and grafting can decrease the energy requirement. Pain, anxiety, and immobilization increase the physiologic demands. Additional energy expenditure is caused by cold stress if environmental humidity and temperature are not controlled; this is especially true in young infants, in whom the large BSA:mass ratio allows proportionately greater heat loss than in adolescents and adults. Providing environmental temperatures of 28-33°C (82.4-91.4°F), adequate covering during transport, and liberal use of analgesics and anxiolytics can decrease caloric demands. Special units to control ambient temperature and humidity may be necessary for children with large surface area burns. Appropriate sleep intervals are necessary and should be part of the regimen. Sepsis increases metabolic rates, and early enteral nutrition, initially with high-carbohydrate, high-protein caloric support (1,800 kcal/m^2 /24 hr maintenance plus 2,200 kcal/m^2 of burn/24 hr) reduces metabolic stress.

The objective of **caloric supplementation** programs is to maintain body weight and minimize weight loss by meeting metabolic demands. This reduces the loss of lean body mass. Calories are provided at approximately 1.5 times the basal metabolic rate, with 3-4 g/kg of protein/day. The focus of nutritional therapy is to support and compensate for the metabolic needs. Multivitamins, particularly the B vitamin group, vitamin C, vitamin A, and zinc, are also necessary.

Alimentation should be started as soon as is practical, both enterally and parenterally, to meet all the caloric needs and keep the gastrointestinal (GI) tract active and intact after the resuscitative phase. Patients with burns of >40% of total BSA need a flexible nasogastric or small bowel feeding tube to facilitate continuous delivery of calories without the risk of aspiration. To decrease the risk of infectious complications, parenteral nutrition is discontinued as soon as is practical, after delivery of sufficient enteral calories are established. Continuous GI feeding is essential, even if feeding is interrupted, causing frequent visits to the operating room, until full grafting takes place. The use of anabolic agents (growth hormone, oxandrolone, low-dose insulin) or anticatabolic agents (propranolol) remains controversial, although β-blocking agents may reduce metabolic stress. Burn centers caring for large burns (>50% BSA, 3rd-degree) in patients who might be malnourished have used the anabolic steroid *oxandrolone,* at a dose of 0.1-0.2 mg/kg/day orally, to promote better protein synthesis while the nutritional support by nasogastric feeding and IV hyperalimentation continues.

Topical Therapy

Topical therapy is widely used and is effective against most burn wound pathogens (see Table 92.7). A number of topical agents are used: 0.5% silver nitrate solution, sulfacetamide acetate cream or solution, silver sulfadiazine cream, and Accuzyme ointment or AQUACEL Ag^+ . Accuzyme is an enzymatic debridement agent and may cause a stinging feeling for 15 min after application. Preferences vary among burn units. Each topical agent has advantages and disadvantages in application, comfort, and bacteriostatic spectrum. *Mafenide acetate* is a very effective broad-spectrum agent with the ability to diffuse through the burn eschar; it is the treatment of choice for injury to cartilaginous surface, such as the ear. Mafenide acetate solution at a concentration of 5% is useful for the treatment of burn wounds that are heavily colonized with multidrug-resistant bacteria (use should be limited to 5 days). The carbonic anhydrase inhibition activity of mafenide acetate may cause acid-base imbalance if large surface areas are treated, and adverse reactions to the sulfur-containing agents may produce transient **leukopenia** . This latter reaction is mostly noted with the use of silver sulfadiazine cream when applied over large surface areas in children <5 yr old. This phenomenon is transient, self-limiting, and reversible. No sulfa-containing agent should be used if the child has a history of sulfa allergies.

Inhalational Injury

Inhalational injury is serious in the infant and child, particularly if preexisting pulmonary conditions are present (see Chapter 89). Inhalation injury should be suspected in a patient confined to a closed space (building), with a history of an explosion or a decreased level of consciousness, or with evidence of carbon deposits in the oropharynx or nose, singed facial hair, and carbonaceous sputum. Mortality estimates vary, depending on the criteria for diagnosis, but are 45–60% in adults; exact figures are not available in children. Evaluation aims at early identification of inhalation airway injuries, which may result from (1) direct heat (greater problems with steam burns); (2) acute asphyxia; (3) CO poisoning; and (4) toxic fumes, including cyanides from combustible plastics. Sulfur and nitrogen oxides and alkalis formed during the combustion of synthetic fabrics produce corrosive chemicals that may erode mucosa and cause significant tissue sloughing. Exposure to smoke may cause degradation of surfactant and decrease its production, resulting in atelectasis. Inhalation injury and burn injury are synergistic, and the combined effect can increase morbidity and mortality.

The pulmonary complications of burns and inhalation can be divided into 3 syndromes that have distinct clinical manifestations and temporal patterns:

1. Early complications include CO and/or cyanide poisoning, airway obstruction, and pulmonary edema.
2. Acute respiratory distress syndrome (ARDS) usually becomes clinically evident later, at 24-48 hr, although it can occur even later (see Chapter 89).
3. Late complications (days to weeks) include pneumonia and pulmonary emboli.

Inhalation injury should be assessed from the evidence of obvious injury (swelling or carbonaceous material in the nasal passages), wheezing, crackles or poor air entry, and laboratory determinations of HbCO and arterial blood gases.

Treatment is initially focused on establishing and maintaining a patent airway through prompt and early nasotracheal or orotracheal intubation and adequate ventilation and oxygenation. **Wheezing** is common, and β-agonist aerosols or inhaled corticosteroids are useful. Aggressive pulmonary toilet and chest physiotherapy are necessary in patients with prolonged nasotracheal intubation or in the rare patient with a tracheotomy. An endotracheal tube can be maintained for months without the need for tracheostomy. If tracheotomy must be performed, it should be delayed until burns at and near the site have healed, and then it should be performed electively, with the child under anesthesia with optimal tracheal positioning and hemostasis. In children with inhalation injury or burns of the face and neck, upper airway obstruction can develop rapidly; endotracheal intubation becomes a lifesaving intervention. Extubation should be delayed until the patient meets the accepted criteria for maintaining the airway.

Signs of CNS injury from hypoxemia caused by asphyxia or **carbon monoxide poisoning** vary from irritability to depression. CO poisoning may be *mild* (<20% HbCO), with slight dyspnea, headache, nausea, and decreased visual acuity and higher cerebral functions; *moderate* (20–40% HbCO), with irritability, agitation, nausea, dimness of vision, impaired judgment, and rapid fatigue; or *severe* (40–60% HbCO), producing confusion, hallucination, ataxia, collapse, acidosis, and coma. Measurement of HbCO is important for diagnosis and treatment. The PaO_2 value may be normal and the HbCO saturation values misleading because HbCO is not detected by the usual tests of oxygen saturation. CO poisoning is assumed until the tests are performed, and it is treated with 100% oxygen. Significant CO poisoning requires hyperbaric oxygen therapy (see Chapter 77). **Cyanide poisoning** should be suspected if a metabolic acidosis persists despite adequate fluid resuscitation, and in environments containing synthetic polymers. Unless specifically suspected, most burn centers do not routinely screen for cyanide poisoning.

Patients with severe inhalation injury or with other causes of respiratory deterioration that lead to ARDS who do not improve with conventional pressure-controlled ventilation (progressive oxygenation failure, as manifested by oxygen saturation <90% while receiving FIO_2 of 0.9-1.0 and positive end-expiratory pressure of at least 12.5 cm H_2O) may benefit from high-frequency ventilation or nitric oxide inhalation treatment. Nitric oxide usually is administered through the ventilator at 5 parts per million (ppm) and increased to 30 ppm. This method of therapy reduces the need for extracorporeal membrane oxygenation (see

Chapter 89).

Pain Relief and Psychologic Adjustment

See Chapter 76 .

It is important to provide adequate analgesia, anxiolytics, and psychologic support to reduce early metabolic stress, decrease the potential for posttraumatic stress disorder (PTSD), and allow future stabilization as well as physical and psychologic rehabilitation. Patients and family members require team support to work through the grieving process and accept long-term changes in appearance.

Children with burn injury show frequent and wide fluctuations in pain intensity. Appreciation of pain depends on the depth of the burn; the stage of healing; the patient's age, stage of emotional development, and cognition; the experience and efficiency of the treating team; the use of analgesics and other drugs; the patient's pain threshold; and interpersonal and cultural factors. From the onset of treatment, **preemptive pain control** during dressing changes is crucial. The use of a variety of nonpharmacologic interventions as well as pharmacologic agents must be reviewed throughout the treatment period. Opiate analgesia, prescribed in an adequate dose and timed to cover dressing changes, is essential to comfort management. A supportive person who is consistently present and knows the patient profile can integrate and encourage patient participation in burn care. The problem of *undermedication* is most prevalent in adolescents, in whom fear of drug dependence may inappropriately influence treatment. A related problem is that the child's specific pain experience may be misinterpreted; for anxious patients, those who are confused and alone, or those with preexisting emotional disorders, even small wounds may illicit intense pain. Anxiolytic medication added to the analgesic is usually helpful and has more than a synergistic effect. Equal attention is necessary to decrease stress in the intubated patient. Other modalities of pain and anxiety relief (**relaxation techniques**) can decrease the physiologic stress response.

Oral *morphine sulfate* (immediate release) is recommended at a consistent schedule at a dose of 0.3-0.6 mg/kg every 4-6 hr initially and until wound cover is accomplished. Morphine sulfate IV bolus is administered at a dose of 0.05-0.1 mg/kg (maximum, 2-5 mg) every 2 hr. Morphine sulfate rectal suppositories may be useful at a dose of 0.3-0.6 mg/kg every 4 hr when oral administration is not possible. The use of *codeine* preparation should be limited to children >6 yr old because of the ultrarapid metabolizers of codeine into morphine. For anxiety, *lorazepam* is given on a consistent schedule, 0.05-0.1 mg/kg/dose every 6-8 hr. To control pain during a procedure (dressing change or debridement), oral morphine, (0.3-0.6 mg/kg) is given 1-2 hr before the procedure, supplemented by a morphine IV bolus (0.05-0.1 mg/kg) given immediately before the procedure. Lorazepam, 0.04 mg/kg, is given orally or intravenously, if necessary, for anxiety before the procedure. *Midazolam* is also very useful for conscious sedation at a dose of 0.01-0.02 mg/kg for nonintubated patients and 0.05-0.1 mg/kg for intubated patients, as an IV infusion or bolus, and may be repeated in 10 min. During the process of weaning from analgesics, the dose of oral opiates is reduced by 25% over 1-3 days, sometimes with the addition of acetaminophen as opiates are tapered. When weaning off antianxiety medications, the approach involves reducing the dose of benzodiazepines, at 25–50% per dose, daily over 1-3 days. *Risperidone*, up to 2.5 mg/day, is being used in children with severe burns.

For ventilated patients, pain control is accomplished by using morphine sulfate intermittently as an IV bolus at 0.05-0.1 mg/kg every 2 hr. Doses may need to be increased gradually, and some children may need continuous infusion; a starting dose of 0.05 mg/kg/hr as an infusion is increased gradually as the need of the child changes. Naloxone is rarely needed but should be immediately available to reverse the effect of morphine, if necessary; if needed for an airway crisis, it should be given in a dose of 0.1 mg/kg up to a total of 2 mg, either intramuscularly or intravenously. For patients undergoing assisted respiration who require treatment of anxiety, midazolam is used as an intermittent IV bolus (0.04 mg/kg by slow push every 4-6 hr) or as a continuous infusion. For intubated patients, opiates do not need to be discontinued during the process of weaning from the ventilator. Benzodiazepine should be reduced to approximately half the dose over 24-72 hr before extubation; too-rapid weaning from a benzodiazepine can lead to seizures.

There is a growing use of *psychotropic medication* in the care of children with burns, including prescription of selective serotonin reuptake inhibitors as antidepressants, the use of haloperidol as a neuroleptic in the critical care setting, and the treatment of PTSD with benzodiazepines. Conscious sedation using ketamine or propofol may be used for major dressing changes.

Reconstruction and Rehabilitation

To ensure maximum cosmetic and functional outcome, occupational and physical therapy must begin on the day of admission, continue throughout hospitalization, and for some patients, continue after discharge. Physical rehabilitation involves body and limb positioning, splinting, exercises (active and passive movement), assistance with activities of daily living, and gradual ambulation. These measures maintain adequate joint and muscle activity with as normal a range of movement as possible after healing or reconstruction. **Pressure therapy** is necessary to reduce hypertrophic scar formation; a variety of prefabricated and custom-made garments are available for use in different body areas. These custom-made garments deliver consistent pressure on scarred areas, shorten the time of scar maturation, and decrease scar thickness, redness, and associated itching. Continued adjustments to scarred areas (scar release, grafting, rearrangement) and multiple minor cosmetic surgical procedures are necessary to optimize long-term function and improve appearance. Replacement of areas of alopecia and scarring has been achieved with the use of tissue-expander techniques. The use of ultrapulse laser for reduction of scarring is an adjunct in scar management.

School Reentry and Long-Term Outcome

It is best for the child to return to school immediately after discharge. Occasionally, a child may need to attend a few half-days (because of rehabilitation needs). It is important for the child to return to the normal routine of attending school and being with peers. Planning for a return to home and school often requires a **school reentry program** that is individualized to each child's needs. For a school-age child, planning for the return to school occurs simultaneously with planning for discharge. The hospital schoolteacher contacts the local school and plans the program with the school faculty, nurses, social workers, recreational/child-life therapists, and rehabilitation therapists. This team should work with students and staff to ease anxiety, answer questions, and provide information. Burns and scars evoke fears in those who are not familiar with this type of injury and can result in a tendency to withdraw from or reject the burned child. A school reentry program should be appropriate to a child's development and changing educational needs.

Major advances have made it possible to save the lives of children with massive burns. Although some children have had lingering physical difficulties, most have a satisfactory quality of life. The comprehensive burn care that includes experienced multidisciplinary aftercare plays an important role in recovery. Table 92.8 lists the long-term disabilities and complications of burns.

Table 92.8

Common Long-Term Complications and Disabilities in Patients With Burn Injuries

Complications Affecting the Skin and Soft Tissue

- Hypertrophic scars
- Susceptibility to minor trauma
- Dry skin
- Contractures
- Itching and neuropathic pain
- Alopecia
- Chronic open wounds
- Skin cancers

Orthopedic Disabilities

- Amputations
- Contractures
- Heterotopic ossification
- Temporary reduction in bone density

Metabolic Disabilities

- Heat sensitivity
- Obesity

Psychiatric and Neurologic Disabilities

- Sleep disorders
- Adjustment disorders
- Posttraumatic stress disorder
- Depression

Body image issues
Neuropathy and neuropathic pain
Long-term neurologic effects of carbon monoxide poisoning
Anoxic brain injury

Long-Term Complications of Critical Care

Deep vein thrombosis, venous insufficiency, or varicose veins
Tracheal stenosis, vocal cord disorders, or swallowing disorders
Renal or adrenal dysfunction
Hepatobiliary or pancreatic disease
Cardiovascular disease
Reactive airway disease or bronchial polyposis

Preexisting Disabilities That Contributed to the Injuries

Risk-taking behavior
Untreated or poorly treated psychiatric disorder

Modified from Sheridan RL, Schultz JT, Ryan CM, et al: Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 6-2004: a 35-year-old woman with extensive, deep burns from a nightclub fire, *N Engl J Med* 350:810–821, 2004.

Electrical Burns

There are 3 types of electrical burns: extension cord (minor), high-tension wire, and lightning. **Minor electrical burns** usually occur as a result of biting on an extension cord. These injuries produce localized burns to the mouth, which usually involve the portions of the upper and lower lips that come in contact with the extension cord. The injury may involve or spare the corners of the mouth. Because these are *nonconductive* injuries (do not extend beyond the site of injury), hospital admission is not necessary, and care is focused on the area of the injury visible in the mouth, ensuring it is low voltage and does not cause entry or exit wounds or cardiac issues. Treatment with topical antibiotic creams is sufficient until the patient is seen in a burn unit outpatient department or by a plastic surgeon.

A more serious category of electrical burn is the **high-tension electrical wire burn** , for which children must be admitted for observation, regardless of the extent of the surface area burn. Deep muscle injury is typical and cannot be readily assessed initially. These injuries result from high voltage (>1,000 V) and occur particularly at high-voltage installations, such as electric power stations or railroads; children climb an electric pole and touch an electric box out of curiosity or accidentally touch a high-tension electrical wire. Such injuries have a mortality rate of 3–15% for children who arrive at the hospital for treatment. Survivors have a high rate of morbidity, including major limb amputations. Points of entry of current through the skin and the exit site show characteristic features consistent with current density and heat. The majority of entrance wounds involve the upper extremity, with small exit wounds in the lower extremity. The electrical path, from entrance to exit, takes the shortest distance between the 2 points and may produce injury in any organ or tissue in the path of the current. Multiple exit wounds in some patients attest to the possibility of several electrical pathways in the body, placing virtually any structure in the body at risk (Table 92.9). Damage to the abdominal viscera, thoracic structures, and the nervous system (confusion, coma, paralysis) in areas remote from obvious extremity injury occurs and must be sought, particularly in injuries with multiple current pathways or those in which the victim falls from a high pole. Sometimes an *ignition* occurs and results in concurrent flame burn and clothing fire. **Cardiac abnormalities** , manifested as ventricular fibrillation or cardiac arrest, are common; patients with high-tension electrical injury need an initial electrocardiogram and cardiac monitoring until they are stable and have been fully assessed. Higher-risk patients have abnormal electrocardiographic findings and a history of loss of consciousness. Renal damage from **deep muscle necrosis** and subsequent myoglobinuria is another complication; such patients need forced alkaline diuresis to minimize renal damage. Soft tissue (muscle) injury of an extremity may produce a **compartment syndrome** . Aggressive removal of all dead and devitalized tissue, even with the risk of functional loss, remains the key to effective management of the electrically damaged extremity. Early debridement facilitates early closure of the wound. Damaged major vessels must be isolated and buried in a viable muscle to prevent exposure. Survival depends on immediate intensive care; functional result depends on long-term care and delayed reconstructive surgery.

Table 92.9

Electrical Injury: Clinical Considerations

SYSTEM	CLINICAL MANIFESTATIONS	MANAGEMENT
General	—	Extricate the patient. Perform ABCs of resuscitation; immobilize the spine.
		Obtain history: voltage, type of current.
		Obtain complete blood count with platelets, electrolytes, BUN, creatinine, and glucose.
Cardiac	Dysrhythmias: asystole, ventricular fibrillation, sinus tachycardia, sinus bradycardia, premature atrial contractions, premature ventricular contractions, conduction defects, atrial fibrillation, ST-T wave changes	Treat dysrhythmias. Provide cardiac monitor, electrocardiogram, and radiographs with suspected thoracic injury.
		Perform creatinine phosphokinase with isoenzyme measurements if indicated.
Pulmonary	Respiratory arrest, acute respiratory distress, aspiration syndrome	Protect and maintain the airway.
		Provide mechanical ventilation if indicated, chest radiograph, and arterial blood gas levels.
Renal	Acute kidney injury, myoglobinuria	Provide aggressive fluid management unless central nervous system injury is present.
		Maintain adequate urine output, >1 mL/kg/hr.
		Consider central venous or pulmonary artery pressure monitoring.
		Measure urine myoglobin; perform urinalysis; measure BUN, creatinine.
Neurologic	Immediate: loss of consciousness, motor paralysis, visual disturbances, amnesia, agitation; intracranial hematoma	Treat seizures. Provide fluid restriction if indicated.
	Secondary: pain, paraplegia, brachial plexus injury, syndrome of inappropriate antidiuretic hormone secretion, autonomic disturbances, cerebral edema	Consider spine radiographs and MRI, especially cervical.
	Delayed: paralysis, seizures, headache, peripheral neuropathy	Perform CT or MRI scan of the brain if indicated.
Cutaneous/oral	Oral commissure burns, tongue and dental injuries; skin burns resulting from ignition of clothes, entrance and exit burns, and arc burns	Search for the entrance and exit wounds. Treat cutaneous burns; determine patient's

		tetanus status.
		Obtain consultation for plastic surgery of ear, nose, and throat, if indicated.
	Electrical burns to mouth could include oral commissures and lips; low-voltage electrical burns secondary to high conductivity of saliva	Ensure no entry or exit wounds and no cardiac involvement. Confirm all injuries are localized. Management is observation until eschar sloughs off and granulation tissue fills in. Obtain plastic surgeon evaluation after first healing, usually with scar formation.
Abdominal	Viscus perforation and solid-organ damage; ileus; abdominal injury rare without visible abdominal burns	Place nasogastric tube if patient has airway compromise or ileus.
		Obtain serum ALT, AST, amylase, BUN, and creatinine measurements and CT scans as indicated.
Musculoskeletal	Compartment syndrome from subcutaneous necrosis limb edema and deep burns	Monitor patient for possible compartment syndrome.
	Long-bone fractures, spine injuries	Obtain radiographs and orthopedic/general surgery consultations as indicated.
Ocular	Visual changes, optic neuritis, cataracts, extraocular muscle paresis	Obtain an ophthalmology consultation as indicated.

AST, Aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen.

Adapted from Hall ML, Sills RM: Electrical and lightning injuries. In Barkin RM, editor: *Pediatric emergency medicine,* St Louis, 1997, Mosby, p 484.

Lightning burns occur when a high-voltage current directly strikes a person (most dangerous) or when the current strikes the ground or an adjacent (in-contact) object. A *step voltage burn* is observed when lightning strikes the ground and travels up one leg and down the other (the path of least resistance). Lightning burns depend on the current path, the type of clothing worn, the presence of metal, and cutaneous moisture. Entry, exit, and path lesions are possible; the prognosis is poorest for lesions of the head or legs. Internal organ injury along the path is common and does not relate to the severity of the cutaneous burn. Linear burns, usually 1st or 2nd degree, are in the locations where sweat is present. *Feathering,* or an arborescent pattern, is characteristic of lightning injury. Lightning may ignite clothing or produce serious cutaneous burns from heated metal in the clothing. Internal complications of lightning burns include cardiac arrest caused by asystole, transient hypertension, premature ventricular contractions, ventricular fibrillation, and myocardial ischemia. Most severe cardiac complications resolve if the patient is supported with CPR (see Chapter 81). CNS complications include cerebral edema, hemorrhage, seizures, mood changes, depression, and paralysis of the lower extremities. Rhabdomyolysis and myoglobinuria (with possible renal failure) also occur. Ocular manifestations include vitreous hemorrhage, iridocyclitis, retinal tearing, or retinal detachment.

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Useful Links

www.ameriburn.org .
www.cpsc.gov .
www.safekids.org .

CHAPTER 93

Cold Injuries

Alia Y. Antoon

The involvement of children and youth in snowmobiling, mountain climbing, winter hiking, and skiing places them at risk for cold injury. Cold injury may produce either local tissue damage, with the injury pattern depending on exposure to *damp cold* (frostnip, immersion foot, or trench foot), *dry cold* (which leads to local frostbite), or generalized systemic effects (hypothermia).

Pathophysiology

Ice crystals may form between or within cells, interfering with the sodium pump, and may lead to rupture of cell membranes. Further damage may result from clumping of red blood cells or platelets, causing microembolism or thrombosis. Blood may be shunted away from an affected area by secondary neurovascular responses to the cold injury; this shunting often further damages an injured part while improving perfusion of other tissues. The spectrum of injury ranges from mild to severe and reflects the result of structural and functional disturbance in small blood vessels, nerves, and skin.

Etiology

Body heat may be lost by *conduction* from wet clothing or contact with metal or other solid conducting objects, *convection* from wind chill, *evaporation*, or *radiation* . Susceptibility to cold injury may be increased by dehydration, alcohol or drug use, impaired consciousness, exhaustion, hunger, anemia, impaired circulation from cardiovascular disease, and sepsis; very young or older persons also are more susceptible. Certain medications may contribute to hypothermia, whereas others may cause reduced metabolism or clearance during hypothermia (Table 93.1).

Table 93.1

Drugs Displaying Reduced Metabolism or Clearance in Hypothermia

Atropine
Digoxin
Fentanyl
Gentamicin
Lidocaine
Phenobarbital
Procaine
Propranolol
Sulfanilamide (AVC cream)
Succinylcholine
D -Tubocurarine

Adapted from Bope ET, Kellerman RD, editors: *Conn's current therapy 2014* , Philadelphia, 2014, Elsevier/Saunders (Box 3, p 1135).

Hypothermia occurs when the body can no longer sustain normal core temperature by physiologic mechanisms, such as vasoconstriction, shivering, muscle contraction, and nonshivering thermogenesis. When shivering ceases, the body is unable to maintain its core temperature; when the body core temperature falls to <35°C (95°F), the syndrome of hypothermia occurs. Wind chill, wet or inadequate clothing, and other factors increase local injury and may cause dangerous hypothermia, even in the presence of an ambient temperature that is not <17-20°C (50-60°F).

Clinical Manifestations

Frostnip

Frostnip results in the presence of firm, cold, white areas on the face, ears, or extremities. Blistering and peeling may occur over the next 24-72 hr, occasionally leaving mildly increased hypersensitivity to cold for days or weeks. Treatment consists of warming the area with an unaffected hand or a warm object before the lesion reaches a stage of stinging or aching and before numbness supervenes. Rewarming in a water bath (40-42.2°C [104-108°F]) is effective.

Immersion Foot (Trench Foot)

Immersion foot occurs in cold weather when the feet remain in damp or wet, poorly ventilated boots. The feet become cold, numb, pale, edematous, and clammy. Tissue maceration and infection are likely, and prolonged autonomic disturbance is common. This autonomic disturbance leads to increased sweating, pain, and hypersensitivity to temperature changes, which may persist for years. Treatment includes drying the foot, gentle rewarming and nonsteroidal antiinflammatory drugs (NSAIDs) for pain. Prevention consists of using well-fitting, insulated, waterproof, nonconstricting footwear. Once damage has occurred, patients must choose clothing and footwear that are more appropriate, dry, and well fitting. The disturbance in skin integrity is managed by keeping the affected area dry and well ventilated and by preventing or treating infection. Only supportive measures are possible for control of autonomic symptoms.

Frostbite

With frostbite, initial stinging or aching of the skin progresses to cold, hard, white anesthetic and numb areas. Clear or hemorrhagic vesicles may develop over the exposed areas. On rewarming, the area becomes blotchy, itchy, and often red, swollen, and painful. The injury spectrum ranges from complete normality to extensive tissue damage, even gangrene, if early relief is not obtained.

Treatment consists of warming the damaged area. It is important not to cause further damage by attempting to rub the area with ice or snow. The area may be warmed against an unaffected hand, the abdomen, or an axilla during transfer of the patient to a facility where more rapid warming with a warm (and not hot) water bath is possible. If the skin becomes painful and swelling occurs, NSAIDs are helpful, and an analgesic agent is necessary. Freeze and rethawing cycles are most likely to cause permanent tissue injury, and it may be necessary to delay definitive warming and apply only mild measures if the patient is required to walk on the damaged feet en route to definitive treatment. In the hospital the affected area should be immersed in warm water (approximately 42°C [107.6°F]), with care taken not to burn the anesthetized skin. Broken vesicles may be debrided, but intact vesicles should be left alone. Vasodilating agents, such as prazosin and phenoxybenzamine, may be helpful. Use of anticoagulants (e.g., heparin, dextran) has had equivocal results; results of chemical and surgical sympathectomy have also been equivocal. Oxygen is of help only at high altitudes. Meticulous local care, prevention of infection, and keeping the rewarmed area dry, open, and sterile provide optimal results.

Recovery can be complete, and prolonged observation with conservative therapy is justified before any excision or amputation of tissue is considered. Analgesia and maintenance of good nutrition are necessary throughout the prolonged waiting period.

Hypothermia

Hypothermia may occur in winter sports when injury, equipment failure, or exhaustion decreases the level of exertion, particularly if sufficient attention is not paid to wind chill. Immersion in frozen bodies of water and wet wind chill rapidly produce hypothermia. As the core temperature of the body falls, insidious onset of extreme lethargy, fatigue, incoordination, and apathy occurs, followed by mental confusion, clumsiness, irritability, hallucinations, and finally, bradycardia. A number of medical conditions, such as cardiac disease, diabetes mellitus, hypoglycemia, sepsis, β-blocking agent overdose, and substance abuse, may need to be considered in a differential diagnosis. The decrease in rectal temperature to <34°C (93°F) is the most helpful diagnostic feature. Hypothermia associated with drowning is discussed in Chapter 91 .

Prevention is a high priority. Of extreme importance for those who participate in winter sports is wearing layers of warm clothing, gloves, socks within insulated boots that do not impede circulation, and a warm head covering, as well as application of adequate waterproofing and protection against the wind. Thirty percent of heat loss for infants occurs from the head. Ample food and fluid must be provided during exercise. Those who participate in sports should be alert to the presence of cold or numbing of body parts, particularly the nose, ears, and extremities, and they should review methods to produce local warming and know to seek shelter if they detect symptoms of local cold injury.

Application of petrolatum (Vaseline) to the nose and ears helps protect against frostbite.

Treatment at the scene aims at prevention of further heat loss and early transport to adequate shelter (Table 93.2). Dry clothing should be provided as soon as practical, and transport should be undertaken if the victim has a pulse. If no pulse is detected at the initial review, cardiopulmonary resuscitation is indicated (Fig. 93.1) (see Chapter 81). During transfer, jarring and sudden motion should be avoided because of the risk of ventricular arrhythmia. It is often difficult to attain a normal sinus rhythm during hypothermia.

Table 93.2

Management of Hypothermia

History and Physical Examination

Gentle handling of the patient to prevent arrhythmias
ABCDE: cardiopulmonary resuscitation for ventricular fibrillation and asystole
Underlying disease diagnosis and treatment
Vital signs, pulse oximetry, electrocardiogram
Wet or cold clothing removed and patient placed in warm environment

Laboratory Tests

Arterial blood gas analysis corrected for temperature
Electrolytes, BUN, creatinine, Ca, Mg, P
CBC with differential, PT/PTT, fibrinogen
Glucose, amylase/lipase
Liver function tests
Additional lab tests, if appropriate, such as toxicology screen

Passive Rewarming

≥32°C (89.6°F) in patients who are capable of spontaneous thermogenesis

Active Rewarming

<32°C (89.6°F), cardiovascular instability, patients at risk for developing hypothermia
Close monitoring for core-temperature afterdrop
Acute: external and/or core rewarming
Chronic (<32°C [89.6°F] for >24 hr): core rewarming
Extracorporeal membrane oxygenation
Availability of rapid deployment

ABCDE, *A* irway and possibly *a* ntibiotics, *b* reathing, *c* irculation, *d* isability or neurologic and possible *d* extrose, *e* xtracorporeal support if all else fails; BUN, blood urea nitrogen; Ca, calcium; CBC, complete blood count; Mg, magnesium; P, phosphorus; PT, prothrombin time; PTT, partial thromboplastin time.

Adapted from Burg FD, Ingelfinger JR, Polin RA, Gershon AA, editors: *Current pediatric therapy*, ed 18, Philadelphia, 2006, Saunders/Elsevier (Table 4, p 174).

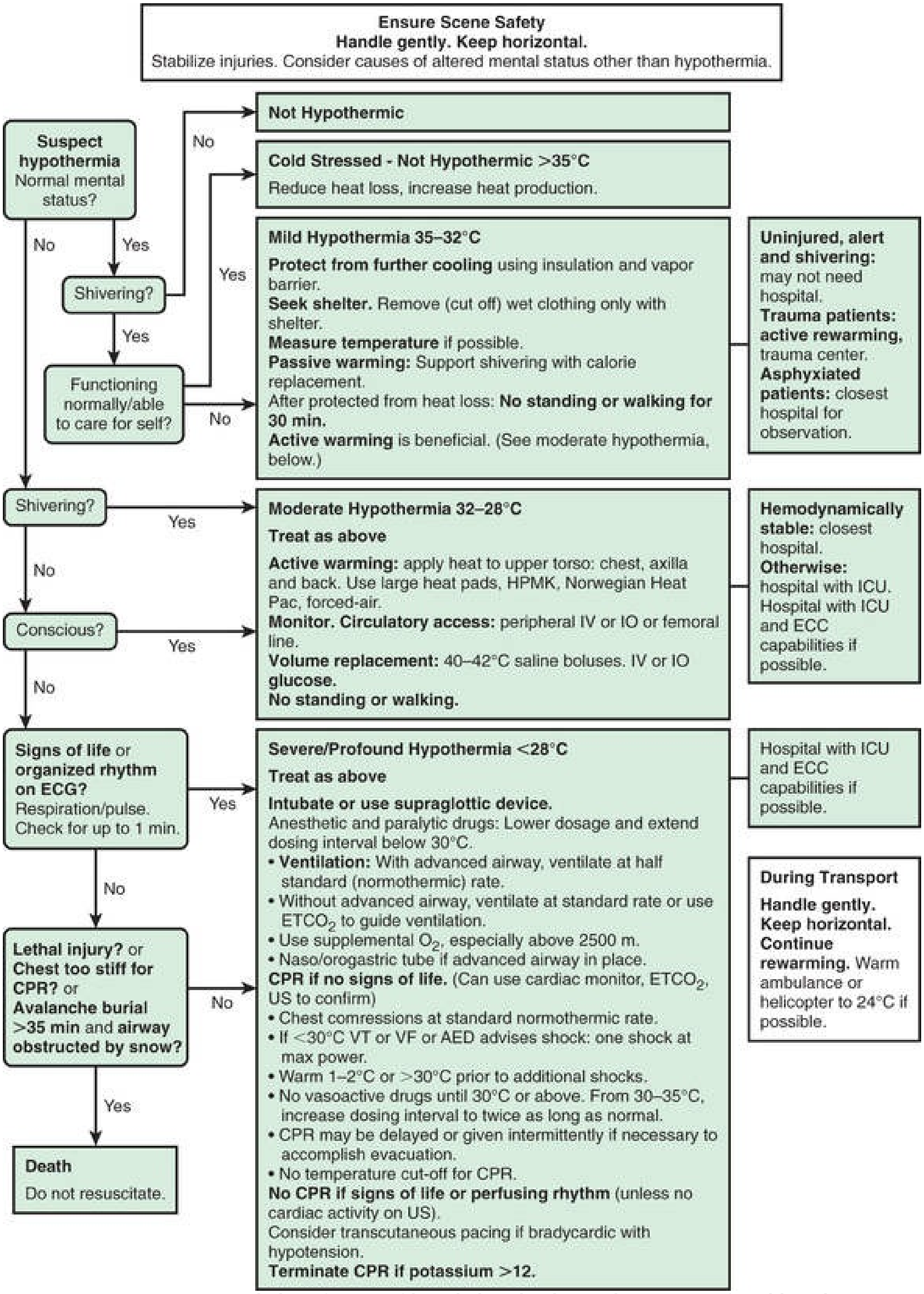
Suspect hypothermia
Normal mental status?
No
Yes
Shivering?
No
Yes
Functioning normally/able to care for self?
Yes
No
Shivering?
Yes
No
Conscious?
Yes
No
Signs of life or organized rhythm on ECG?
Respiration/pulse. Check for up to 1 min.
Yes
No
Lethal injury? or Chest too stiff for CPR? or Avalanche burial >35 min and airway obstructed by snow?
No
Yes
Death
Do not resuscitate.

Ensure Scene Safety
Handle gently. Keep horizontal.
Stabilize injuries. Consider causes of altered mental status other than hypothermia.

Not Hypothermic

Cold Stressed - Not Hypothermic >35°C
Reduce heat loss, increase heat production.

Mild Hypothermia 35–32°C
Protect from further cooling using insulation and vapor barrier.
Seek shelter. Remove (cut off) wet clothing only with shelter.
Measure temperature if possible.
Passive warming: Support shivering with calorie replacement.
After protected from heat loss: **No standing or walking for 30 min.**
Active warming is beneficial. (See moderate hypothermia, below.)

Uninjured, alert and shivering: may not need hospital.
Trauma patients: active rewarming, trauma center.
Asphyxiated patients: closest hospital for observation.

Moderate Hypothermia 32–28°C
Treat as above
Active warming: apply heat to upper torso: chest, axilla and back. Use large heat pads, HPMK, Norwegian Heat Pac, forced-air.
Monitor. Circulatory access: peripheral IV or IO or femoral line.
Volume replacement: 40–42°C saline boluses. IV or IO **glucose.**
No standing or walking.

Hemodynamically stable: closest hospital.
Otherwise: hospital with ICU. Hospital with ICU and ECC capabilities if possible.

Severe/Profound Hypothermia <28°C
Treat as above
Intubate or use supraglottic device.
Anesthetic and paralytic drugs: Lower dosage and extend dosing interval below 30°C.
- **Ventilation:** With advanced airway, ventilate at half standard (normothermic) rate.
- Without advanced airway, ventilate at standard rate or use $ETCO_2$ to guide ventilation.
- Use supplemental O_2, especially above 2500 m.
- Naso/orogastric tube if advanced airway in place.

CPR if no signs of life. (Can use cardiac monitor, $ETCO_2$, US to confirm)
- Chest comressions at standard normothermic rate.
- If <30°C VT or VF or AED advises shock: one shock at max power.
- Warm 1–2°C or >30°C prior to additional shocks.
- No vasoactive drugs until 30°C or above. From 30–35°C, increase dosing interval to twice as long as normal.
- CPR may be delayed or given intermittently if necessary to accomplish evacuation.
- No temperature cut-off for CPR.

No CPR if signs of life or perfusing rhythm (unless no cardiac activity on US).
Consider transcutaneous pacing if bradycardic with hypotension.
Terminate CPR if potassium >12.

Hospital with ICU and ECC capabilities if possible.

During Transport
Handle gently. Keep horizontal. Continue rewarming. Warm ambulance or helicopter to 24°C if possible.

FIG. 93.1 **Recommendations for out-of-hospital evaluation and treatment of accidental hypothermia. AED, Automatic external defibrillator; CPR, cardiopulmonary resuscitation; ECC, extracorporeal circulation; ECG, electrocardiogram; $ETCO_2$, end-tidal carbon dioxide; HPMK, Hypothermia Prevention Management Kit; ICU, intensive**

care unit; IO, intraosseous; IV, intravenous; US, ultrasound; VF, ventricular fibrillation; VT, ventricular tachycardia. (From Zafren K, Giesbrecht GG, Danzl DF, et al: Wilderness Medical Society practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia: 2014 update, *Wilderness Environ Med* 25:S66–S85, 2014, Fig 2.)

If the patient is conscious, mild muscle activity should be encouraged and a warm drink offered. If the patient is unconscious, external warming should be undertaken initially with use of blankets and a sleeping bag; wrapping the patient in blankets or sleeping bag with a warm companion may increase the efficiency of warming. On arrival at a treatment center, while a warming bath of 45-48°C (113-118°F) water is prepared, the patient should be warmed through inhalation of warm, moist air or oxygen or with heating pads or thermal blankets. Monitoring of serum chemistry values and an electrocardiogram are necessary until the core temperature rises to >35°C (95°F) and can be stabilized. Control of fluid balance, pH, blood pressure, and arterial partial pressure of oxygen ($Pa{O_2}$) is necessary in the early phases of the warming period and resuscitation. In severe hypothermia, there may be a combined respiratory and metabolic acidosis. Hypothermia may falsely elevate pH; nonetheless, most authorities recommend warming the arterial blood gas specimen to 37°C (98.6°F) before analysis and regarding the result as one from a normothermic patient. In patients with marked abnormalities, warming measures, such as gastric or colonic irrigation with warm saline or peritoneal dialysis, may be considered, but the effectiveness of these measures in treating hypothermia is unknown. In accidental *deep hypothermia* (core temperature 28°C [82.4°F]) with circulatory arrest, rewarming with cardiopulmonary bypass may be lifesaving for previously healthy young individuals. If rewarming is not successful despite appropriate measures, one should suspect infection, drug overdose, endocrine disorders, or a futile resuscitation.

Chilblain (Pernio)

Chilblain (pernio) is a form of cold injury in which erythematous, vesicular, or ulcerative lesions occur. The lesions are presumed to be of vascular or vasoconstrictive origin. They are often itchy, may be painful, and result in swelling and scabbing. The lesions are most often found on the ears, the tips of the fingers and toes, and exposed areas of the legs. The lesions last for 1-2 wk but may persist for longer. Treatment consists of prophylaxis: avoiding prolonged chilling and protecting potentially susceptible areas with a cap, gloves, and stockings. Prazosin and phenoxybenzamine may be helpful in improving circulation if this is a recurrent problem. For significant itching, local corticosteroid preparations may be helpful.

Familial chilblain lupus , an autosomal dominant variant of lupus, is caused by mutations in the *TREX1*, *SAMHD1*, and *STING* genes. Patients develop cold-induced erythematous peripheral skin lesions and also manifest systemic disease typical of lupus (Chapter 183). In addition, fever and arthralgias may be present. Those with the *STING* mutation may develop a necrotizing acral vasculitis.

Cold-Induced Fat Necrosis (Panniculitis)

A common, usually benign injury, cold-induced fat necrosis occurs on exposure to cold air, snow, or ice and manifests in exposed (or less often covered) surfaces as red (or less often purple to blue) macular, papular, or nodular lesions. Treatment is with NSAIDs. The lesions may last 10 days to 3 wk but may persist for longer. Severe coagulopathy may be associated with poor outcome in some severe cold injuries, thus meriting anticoagulation therapy (see Chapter 680.1).

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PART IX
Human Genetics

OUTLINE

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CHAPTER 94

Integration of Genetics Into Pediatric Practice

Brendan Lee

Genetic testing involves analyzing genetic material to obtain information related to a person's health status using chromosomal (cytogenetic) analysis (see Chapter 98) or DNA-based testing.

Diagnostic Testing

Diagnostic genetic testing helps explain a set of signs and symptoms of a disease. The list of disorders for which specific genetic tests are available is extensive. The website http://www.ncbi.nlm.nih.gov/gtr/ provides a database of available tests that is provider driven, so claims are not validated by the site's host, the National Institutes of Health (NIH).

Single-gene disorders can be tested by at least 3 different approaches: linkage analysis (though this is now rarely used), array comparative genomic hybridization (**aCGH**), and direct mutation analysis, usually by DNA sequencing (Table 94.1). Linkage analysis is used if the responsible gene is mapped but not yet identified, or if it is impractical to find specific mutations, usually because of the large size and larger number of different mutations in some genes. Array CGH can be used to detect large, multigene deletions or duplications (**copy number variations**). In addition, with increasing resolution, single-gene or smaller intragenic deletions or duplications can be detected by aCGH, although it is important to note that coverage of each gene may vary from different providers. *Direct DNA mutation analysis is preferred and is possible with the availability of the complete human genome sequence.* An emerging feature is the increasing recognition of oligogenic disease where more than one disease gene contributes to a complex, or “blended,” phenotype. The ability to sequence hundreds to thousands of genes at once has provided insight into this added layer of complexity in disease pathogenesis.

Table 94.1

Approaches for Genetic Testing

TYPE OF MUTATION TESTING	RESOLUTION	ADVANTAGES	DISADVANTAGES	SAMPLE REQUIREMENTS
Linkage analysis	Depends on location of polymorphic markers near putative disease gene	Possible when specific disease-causing genetic mutation is not identifiable or found	Can give only diagnostic probability based on likelihood of genetic recombination between presumed DNA mutation and polymorphic markers	Requires multiple family members with documented mendelian pattern of inheritance within family
Array comparative genomic hybridization (aCGH)	Several hundred base pairs to several hundreds of kilobases	Able to detect small deletion or duplications within 1 or more genes	Can miss small deletions or insertions depending on resolution of the array used	Single patient sample sufficient, but having sample from biological parents can help with interpretation
Direct DNA-based testing (e.g., DNA sequencing)	Single–base-pair changes	High specificity if previously described deleterious mutation is found	Can miss deletion or duplication of a segment of gene	Single patient sample sufficient, but having sample from biological parents can help with interpretation

Linkage testing involves tracking a genetic trait through a family using closely linked polymorphic markers as a surrogate for the trait (Fig. 94.1). It requires testing an extended family and is vulnerable to several pitfalls, such as genetic recombination, genetic heterogeneity, and incorrect diagnosis in the proband. **Genetic recombination** occurs between any pair of loci, the frequency being proportional to the distance between them. This problem can be ameliorated by using very closely linked markers and, if possible, using markers that flank the specific gene. **Genetic heterogeneity** can be problematic for a linkage-based test if there are multiple distinct genomic loci that can cause the same phenotype, resulting in the risk that the locus tested for is not the one responsible for disease in the family. **Incorrect diagnosis** in the proband also leads to tracking the wrong gene. Linkage testing remains useful for several genetic conditions, but it is increasingly being superseded by the availability of direct DNA sequencing of either single genes or of the whole collection of genes that encode all proteins. It is critically important that genetic counseling be provided to the family to explain the complexities of interpretation of test results.

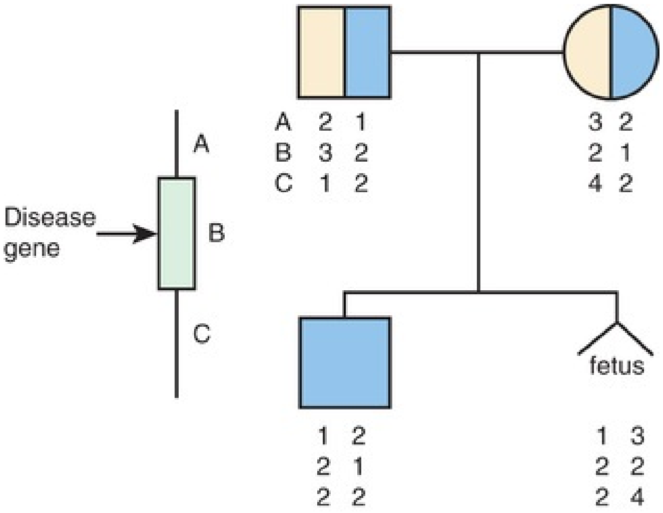

FIG. 94.1 **Use of linkage analysis in prenatal diagnosis of an autosomal recessive disorder. Both parents are carriers, and they have 1 affected son. The numbers below the symbols indicate alleles at 3 polymorphic loci: A, B, and C. Locus B resides within the disease gene. The affected son inherited the 1-2-2 chromosome from his father and the 2-1-2 chromosome from his mother. The fetus has inherited the same chromosome from the father, but the 3-2-4 chromosome from the mother and therefore is most likely to be a carrier.**

Array comparative genomic hybridization can detect copy number variation in a patient's DNA by comparing it to a standard control DNA (see Chapter 98). In so doing, aCGH provides a level of genetic resolution between that available with DNA sequencing and that available with chromosome analysis. Whereas earlier technologies could only identify large deletions or duplications that might encompass multiple genes, aCGH can resolve deletions or duplications of several kilobases within 1 gene. In theory, this approach can detect deletion and duplication mutations that would be missed by either chromosome analysis or direct mutation testing by DNA sequencing. However, because the specific resolution and coverage of different aCGH platforms can vary tremendously for different gene regions, the sensitivity for detecting deletions and duplications can vary for different diseases and laboratories. The highest resolution is what would be detection of on average deletion or duplication at the single exon level.

Direct DNA-based mutation testing avoids the pitfalls of linkage testing by detecting the specific gene mutation (i.e., sequence change). The specific approach used is customized to the biology of the gene being tested. In some disorders, 1 or a few distinct mutations occur in all affected individuals. This is the case in sickle cell anemia, in which the same single-base substitution occurs in everyone with the disorder. In other conditions, many possible mutations may account for the disorder in different individuals. In cystic fibrosis, for example, >1,000 distinct mutations have been found in the *CFTR* gene. Mutation analysis is challenging because no single technique can detect all possible mutations. However, with the completion of the human genome sequence and high-throughput DNA sequencing technology, the approach of choice is to directly sequence DNA that is generated by **polymerase chain reaction (PCR)** amplification of DNA isolated from peripheral blood white blood cells. The limitation of this approach is that only DNA that is amplified is sequenced, and usually this is restricted to the *coding* or *exonic* regions of a gene. Because mutations sometimes occur in the *noncoding intronic* regions, failure to detect a mutation does not exclude the diagnosis. Whole *genome* sequencing should identify mutations in the noncoding regions. In addition, genes in a deleted region will not be detected. Although DNA sequencing can be highly specific, it is not completely sensitive because of practical limitations of what is commercially available. Gene sequencing techniques may not be able to identify diseases caused by triplet repeat sequences; specific tests are needed.

The most useful development in clinical DNA diagnosis is application of **next-generation sequencing** technology to testing panels of genes that target disease symptoms (e.g., seizures, ataxia syndromes) or the whole exome (**whole exome sequencing [WES])** . Soon, whole genome sequencing (WGS), where both coding and noncoding sequences are identified, will provide even more information, although initial clinical interpretation will still be limited to the coding sequences of the approximately 20,000 human genes, the so-called digital exome, as it is extracted electronically from the whole genome data. The challenge is not so much the generation of DNA sequence, but the interpretation of enormous genetic variation within a single sample. Direct sequencing of tens to hundreds of genes in next-generation sequencing panels offer a potentially higher sensitivity because the “depth” of read is higher without complicating high discovery rate of **variants of unknown sequences (VUS)** . WES and WGS also offer the potential for identifying new disease-gene associations as well as phenotypes caused by more than one disease gene (i.e., oligogenic phenotypes).

An important ethical consideration is the reporting of *incidental findings,* whether medically actionable or not medically actionable in a patient. WES and WGS may identify mutations that cause aminoglycoside-sensitive hearing loss, which would be medically actionable. At the same time, the discovery of apolipoprotein E variants in a child that increase Alzheimer disease risk susceptibility may not be medically actionable. Therefore, counseling for patients undergoing these tests is important so that only wanted results are reported back to the patient. Guidelines are currently evolving for reporting of incidental findings for WES by the American College of Medical Genetics (www.acmg.net). Practice varies among institutions and recommendations vary among international genetic organizations about the approach for revealing incidental findings from WES/WGS to patients; many leave the choice up to the patient and family. Most require revealing to the patient and/or family significant diseases (actionable) with a specific and successful treatment or prevention strategy (Table 94.2).

Table 94.2

Variants That Are Incidental Findings Are Assigned to 1 of 4 Categories

Childhood onset	Medically actionable*
Childhood onset	Not medically actionable †
Adult onset	Medically actionable*
Adult onset	Not medically actionable †

* “Medically actionable” refers to a variant in a gene in which knowledge of the particular variant will affect medical decision-making, such as initiation of a treatment or family planning.

† “Not medically actionable” refers to variants that increase the individual's risk for a disease in which no treatment is proven to significantly change medical decision-making.

From Bick D, Dimmock D: Whole exome and whole genome sequencing. *Curr Opin Pediatr* 23:594–600, 2011.

Genetic testing is interpreted by 3 factors: analytic validity, clinical validity, and clinical utility. **Analytical validity** is test accuracy: Does the test correctly detect the presence or absence of mutation? Most genetic tests have a very high analytical validity, assuming that human error, such as sample mix-up, has not occurred. Human errors are possible, and unlike most medical tests, a genetic test is unlikely to be repeated, because it is assumed that the result will not change over time. Therefore, human errors can go undetected for long periods of time. However, it may be reinterpreted over time as our knowledge base of what are disease-causing mutations and genes increases over time.

Clinical validity is the degree to which the test correctly predicts presence or absence of disease. False-positive and false-negative test results can occur.

False-positive results are more likely for predictive tests than for diagnostic tests. An important contributing factor is **nonpenetrance** : an individual with an at-risk genotype might not clinically express the condition. Another factor is the finding of a **genetic variant of unknown significance** (VUS). Detection of a base sequence variation in an affected patient does not prove that it is the cause of the patient's disorder. In WES there may be more than 30,000 VUS; in WGS there may be more than 3,000,000 VUS. Various lines of evidence are used to establish pathogenicity. These include finding the variant only in affected individuals, inferring that the variant alters the function of the gene product, determining whether the amino acid altered by the mutation is conserved in evolution, and determining whether the mutation segregates with disease in the family. In some cases, it is possible to be certain whether the variant is pathogenic or incidental, but in other cases it might be impossible to definitively assign causality with 100% confidence.

False-negative results reflect an inability to detect a mutation in an affected patient. This occurs principally in disorders where genetic heterogeneity—**allelic** (different mutations occur in 1 causative gene) or **locus** (>1 gene can cause a disease) heterogeneity—is the rule. It is difficult to detect all possible mutations within a gene, because mutations can be varied in location within the gene and in the type of mutation. Direct sequencing may miss gene deletions or rearrangements (i.e. structural variants), and mutations may be found within noncoding sequences such as introns or the promoter; a negative DNA test does not necessarily exclude a diagnosis.

Clinical utility is the degree to which the results of a test guide clinical management. For genetic testing, clinical utility includes establishing a diagnosis that obviates the need for additional workup or guiding surveillance or treatment. Test results may also be used as a basis for genetic counseling. For some disorders, genetic testing is possible, but the test results do not add to the clinical assessment. If the diagnosis and genetic implications are already clear, it might not be necessary to pursue genetic testing.

Predictive Testing

Predictive genetic testing involves performing a test in a person who is at risk for developing a genetic disorder (**presymptomatic**), usually on the basis of family history, yet who does not manifest signs or symptoms. This is usually done for disorders that display age-dependent penetrance; the likelihood of manifesting signs and symptoms increases with age, as in cancer or Huntington disease.

A major caution with predictive testing is that the presence of a gene mutation does not necessarily mean that the disease will develop. Many of the disorders with age-dependent penetrance display *incomplete penetrance* . A person who inherits a mutation might never develop signs of the disorder. There is concern that a positive DNA test could result in stigmatization of the person and might not provide information that will guide medical management. Stigmatization might include psychological stress, but it could also include discrimination, including denial of health, life, or disability insurance, or employment (see Chapter 95).

It is generally agreed that predictive genetic tests should be performed for children only if the results of the test will benefit the medical management of the child. Otherwise, the test should be deferred until the child has an understanding of the risks and benefits of testing and can provide informed consent. Individual states offer varying degrees of protection from discrimination on the basis of genetic testing. A major milestone in the prevention of genetic discrimination was the passage of the **Genetic Information Nondiscrimination Act** (GINA) in 2008, which is a U.S. federal law that prohibits discrimination in health coverage or employment based on genetic information; *it does not* protect against refusal of life insurance.

Predispositional Testing

It is expected that genetic tests will become available that will predict risk of disease. Common disorders are multifactorial in etiology; many different genes may contribute to risk of any specific condition (see Chapter 99). Most of the genetic variants that have been found to correlate with risk of a common disease add small increments of relative risk, probably in most cases too little to guide management. It is possible that further discovery of genes that contribute to common disorders will reveal examples of variants that convey more significant levels of risk. It is also possible that testing several genes together will provide more information about risk than any individual gene variant would confer.

The rationale for predispositional testing is that the results would lead to strategies aimed at risk reduction as part of a *personalized approach* to healthcare maintenance. This might include avoidance of environmental exposures that would increase risk of disease (cigarette smoking and α_1 -

antitrypsin deficiency), medical surveillance (familial breast cancer and mammography), or in some cases, pharmacologic treatment (statins and hypercholesterolemia). The value of predispositional testing will need to be critically appraised through outcomes studies as these tests are developed.

Pharmacogenetic Testing

Polymorphisms in drug metabolism genes can result in distinctive patterns of drug absorption, metabolism, excretion, or effectiveness (see Chapters 72 and 99). Knowledge of individual genotypes will guide pharmacologic therapy, allowing customization of choice of drug and dosage to avoid toxicity and provide a therapeutic response. An example is testing for polymorphisms within the methylenetetrahydrofolate reductase (*MTHFR*) gene for susceptibility of potentially increased toxicity to methotrexate antimetabolite therapy for acute lymphoblastic leukemia.

94.1

Genetic Counseling

Brendan Lee, Pilar L. Magoulas

Genetic counseling is a communication process in which the genetic contribution to health, specific risks of transmission of a trait, and options to manage the condition are explained to individuals and their family members (Table 94.3). Genetic counselors are specialized healthcare providers trained in the psychosocial aspects of counseling and the science of medical genetics who may serve as members of medical teams in many different specialties. The genetic counselor is expected to present information in a neutral, nondirective manner while providing resources and psychosocial support to the individual and family to cope with decisions that are made.

Table 94.3

Indications for Genetic Counseling

- Advanced parental age
    - Maternal age ≥35 yr
    - Paternal age ≥40 yr
- Previous child with or family history of:
    - Congenital abnormality
    - Dysmorphology
    - Intellectual disability
    - Isolated birth defect
    - Metabolic disorder
    - Chromosome abnormality
    - Single-gene disorder
- Adult-onset genetic disease (presymptomatic testing)
    - Cancer
    - Huntington disease
- Pharmacogenomics
- Consanguinity
- Teratogen exposure (occupational, abuse)
- Repeated pregnancy loss or infertility
- Pregnancy screening abnormality
    - Maternal serum α-fetoprotein
- Maternal 1st-trimester screen
    - Maternal triple or quad screen or variant of this test
    - Fetal ultrasonography
- Noninvasive prenatal testing (NIPT)
    - Fetal karyotype
- Heterozygote screening based on ethnic risk
    - Sickle cell anemia
    - Tay-Sachs, Canavan, and Gaucher diseases
    - Thalassemias
- Universal carrier screening panels
- Follow-up to abnormal neonatal genetic testing
- Prior to whole genome or exome sequencing
- Prior to preimplantation genetic testing

Genetic counseling has evolved from a model of care that was developed in the context of prenatal diagnosis and pediatrics into a multidisciplinary approach to medicine that factors into all aspects of healthcare (Table 94.3). In the prenatal setting, a common indication for genetic counseling is to assess risk of occurrence or recurrence of having a child with a genetic condition and to discuss management or treatment options that might be available before, during, or after the pregnancy, such as preimplantation genetic diagnosis, prenatal diagnosis or fetal intervention, and perinatal management. In pediatrics and adult genetics practices, the goals of genetic counseling are to help establish a diagnosis in an individual, provide longitudinal care and psychosocial support to the family, and discuss the genetic basis and inheritance of the condition as it relates to immediate and distant family members.

The genetic counseling role has expanded, particularly with advances in understanding the genetics of adult-onset or common and rare disease therapeutics. In the former context, genetic counseling has a major role in risk assessment for cancer, especially breast, ovarian, or colon cancer, for which well-defined risk models and genetic tests are available to assess risk to an individual. In the latter, the genetic counselor may discuss developments in rare disease therapeutics and make appropriate referral for medical therapies.

Talking to Families

The type of information provided to a family depends on the urgency of the situation, the need to make decisions, and the need to collect additional information. There are 4 situations in which genetic counseling plays a particularly important role in this process.

The 1st situation is the **prenatal diagnosis** of a congenital anomaly or genetic disease. The need for information is urgent because a family must often make time-sensitive decisions about treatment and management options, such as fetal intervention or continuation of a pregnancy in the context of fetal anomalies. Risks to the mother must also be considered. The 2nd type of situation occurs when a child is born with a life-threatening **congenital anomaly** or suspected **genetic disease** . Decisions must be made immediately with regard to how much support should be provided for the child and whether certain types of therapy should be attempted. The 3rd situation arises when there are concerns about a **genetic condition** affecting one later in life. For example, this may occur in an adolescent or young adult with a family history of an adult-onset genetic disorder (e.g., Huntington disease, hereditary breast/ovarian cancer), in an individual with a suspected yet undiagnosed genetic condition, or if a couple with a personal or family history of a genetic condition (or a carrier) is planning a family. In these situations it is often necessary to have several meetings with a family to discuss possible testing, screening, and management options. Urgency is not as much of an issue as being sure that they have as much information and as many options as are available. The 4th situation is **genetic counseling** before genome sequencing, where the family is given options of what they want reported back to them (actionable/nonactionable incidental findings vs a specific diagnosis).

Genetic Counseling

Providing accurate information to families requires the following:

- Taking a careful family history and constructing a pedigree that lists the patient's relatives (including miscarriages, abortions, stillbirths, deceased persons) with their sex, age, ethnicity, and state of health, up to and including third-degree relatives.
- Gathering information from hospital records about the affected individual and, in some cases, about other family members.
- Documenting prenatal, pregnancy, and delivery histories.
- Reviewing the latest available medical, laboratory, and genetic information concerning the disorder.
- Performing a careful physical examination of the affected individual (photographs, measurements) and of apparently unaffected individuals in the family

(this is usually performed by a physician rather than a genetic counselor).

◆ Establishing or confirming the diagnosis by the diagnostic tests available.

◆ Giving the family information about support groups and local and national resources.

◆ Providing new information to the family as it becomes available (a mechanism for updating needs to be established).

Counseling sessions must include the specific condition, knowledge of the diagnosis of the particular condition, natural history of the condition, genetic aspects of the condition and risk of recurrence, prenatal diagnosis and reproductive options, therapies and referrals, support groups, and nondirective counseling.

Specific Condition or Conditions

If a specific diagnosis is made and confirmed, this should be discussed with the family and information provided in writing. Often, however, the disorder fits into a spectrum (e.g., one of many types of arthrogryposis) or the diagnosis is clinical rather than laboratory based. In these situations the family needs to understand the limits of present knowledge, and that additional research will probably lead to better information in the future.

Knowledge of the Diagnosis of the Particular Condition

Although it is not always possible to make an exact diagnosis, having a diagnosis *as accurate as possible* is important. Estimates of recurrence risk for various family members depend on an accurate diagnosis, that considers the likelihood that a particular finding is isolated, associated with a syndrome, or nonsyndromic (e.g., isolated cleft lip and palate). When a specific diagnosis cannot be made (as in many cases of multiple congenital anomalies), the various possibilities in the differential diagnosis should be discussed with the family and empirical information provided. If available, specific diagnostic tests should be discussed. Often, empirical recurrence risks can be given even without a specific laboratory-based diagnosis. At the same time, even negative laboratory testing can further modify this risk.

Natural History of the Condition

It is important to discuss the natural history of the specific genetic disorder in the family. Affected persons and their families have questions regarding the prognosis and potential management or therapy that can be answered only with knowledge of the natural history. If there are other possible diagnoses, their natural history may also be discussed. If the disorder is associated with a spectrum of clinical outcomes or complications, the range of possible outcomes and variability of the condition, as well as treatment and referral to the appropriate specialist, should be addressed.

Genetic Aspects of the Condition and Recurrence Risk

The genetic aspects and risk of recurrence are important because all family members should be informed of their reproductive choices. The genetic basis of the disorder can be explained with visual aids (e.g., diagrams of chromosomes and inheritance patterns). It is important to provide accurate occurrence and recurrence risks for various members of the family, including unaffected individuals. If a definite diagnosis cannot be made, it is necessary to use empirical recurrence risks. Genetic counseling gives patients the necessary information to understand the various options and to make their own informed decisions regarding pregnancy, adoption, artificial insemination, prenatal diagnosis, screening, carrier detection, or termination of pregnancy. It may be necessary to have more than one counseling session.

Prenatal Diagnosis and Prevention

Many different methods of prenatal diagnosis are available, depending on the specific genetic disorder (see Chapter 115). The use of ultrasonography allows prenatal screening of anatomic abnormalities such as congenital heart defects. Amniocentesis and chorionic villus sampling are used to obtain fetal tissue for analysis of chromosomal abnormalities, biochemical disorders, and DNA studies. Maternal blood or serum sampling is used for some types of screening, including noninvasive prenatal screening by direct analysis of fetal DNA fragments found in maternal blood. This has gained widespread use for screening of conditions such as trisomy 21. In addition, this source of cell free fetal DNA has also been used clinically for DNA sequencing for dominant de novo conditions in the fetus that may occur with increased frequency with increasing paternal age. In the research arena, intact fetal cells can also be retrieved from maternal blood (though this is not yet readily available compared to free fetal DNA) for testing, and this may potentially offer higher resolution testing including whole exome or whole genome testing. Importantly, current tests of fetal DNA from maternal blood should be considered screening tests, and invasive testing like amniocentesis or chorionic villus sampling should be considered for confirmatory diagnostic testing.

Therapies and Referral

A number of genetic disorders require the care of multiple specialists. Many genetic conditions now have diagnosis and management guidelines to aid in the treatment and management of these complex patients. Prevention of known complications is a priority, so close follow-up with the necessary specialists involved in the child's care is essential to identify any potentially concerning issues early. The psychological adjustment of the family might also require specific intervention. Some challenges may involve when to discuss the diagnosis of a chronic disease with the patient, siblings, and other family members or friends. The decision to do so should always involve the parents and an assessment of the maturity and capacity of the child or adolescent.

Alternative medicines or nontraditional therapies are often brought to attention by parents after exhaustive internet searches. Such treatments should not necessarily be dismissed out of hand because the physician and genetic counselor should serve as an important resource for helping parents navigate the maze of nonstandard treatments. Instead, the relative merits of treatments should be framed in the context of cost and benefit, scientific rationale, evidence from controlled and observational studies, the placebo effect, safety of the treatment, and the gaps in our own scientific knowledge base.

Support Groups

A large number of community and online lay support groups have been formed to provide information and to fund research on specific genetic and nongenetic conditions. An important part of genetic counseling is to give information about these groups to patients and to suggest a contact person for the families. Many groups have established websites with very helpful information. With the rise of social media and its ability to connect families with rare syndromes from around the world, it is important to stress to families that their individual disease course will be unique.

Follow-up

Families should be encouraged to continue to ask questions and keep up with new information about the specific disorder. New developments often influence the diagnosis and therapy of specific genetic disorders. Lay support groups are a good source of new information.

Nondirective Counseling

Genetic counseling is usually nondirective; choices about reproduction are left to the family to decide what is right for them. The role of the counselor (physician, genetic counselor, nurse, medical geneticist) is to provide information in understandable terms and outline the range of options available.

94.2

Management and Treatment of Genetic Disorders

Brendan Lee, Nicola Brunetti-Pierri

Genetic conditions are often chronic disorders; few are amenable to curative therapies, although there has been a rapid increase in the number available in recent years. All patients and families should be provided information about the disorder, genetic counseling, anticipatory guidance, and appropriate medical surveillance. Surgical management is available for many conditions that are associated with congenital anomalies or predisposition to tumors.

Resources for patients include the National Organization of Rare Disorders (www.rarediseases.org), the Genetic Alliance (www.geneticalliance.org), the National Library of Medicine (www.nlm.nih.gov/medlineplus/geneticdisorders.html), and a large number of disease-specific websites. A current listing of federally and privately funded clinical trials, including many for genetic diseases, is available at www.ClinicalTrials.gov .

Specific medical therapies for genetic disorders can be classified into physiologic and replacement therapies. Another approach corrects protein misfolding induced by missense mutations through use of small molecules that specifically bind to mutant proteins stabilizing their conformation, thereby preventing early degradation and allowing proper cellular trafficking and localization. This strategy has found successful applications for therapy of cystic fibrosis caused by specific *CFTR* mutations, including the F508del (see Chapter 432).

Physiologic Therapies

Physiologic therapies attempt to ameliorate the phenotype of a genetic disorder by modifying the physiology of the affected individual. The underlying defect itself is not altered by treatment. Physiologic therapies are used in the treatment of **inborn errors of metabolism** (see Chapter 102). These include dietary manipulation, such as avoiding phenylalanine by persons with phenylketonuria; coenzyme supplementation for some patients with methylmalonic acidemia and mitochondrial diseases; stimulation of alternative pathways to excrete ammonia for those with urea cycle disorders; phototherapy to increase excretion of neurotoxic unconjugated bilirubin in Crigler-Najjar syndrome; bisphosphonate treatment for those with osteogenesis imperfecta to reduce bone fractures; and avoiding cigarette smoking by persons with α_1 -antitrypsin deficiency or specific foods and drugs by persons with glucose-6-phosphate dehydrogenase deficiency or acute intermittent porphyria. Physiologic treatments can be highly effective, but they usually need to be maintained for a lifetime because they do not affect the underlying genetic disorder. Many of these treatments are most effective when begun early in life, before irreversible damage has occurred. This is the rationale for comprehensive newborn screening for inborn errors of metabolism.

Many physiologic therapies use small-molecule pharmaceuticals (e.g., to remove ammonia in those with urea cycle disorders). **Pharmacologic treatments** directly target a defective cellular pathway that is altered by an abnormal or a missing gene product. However, there are relatively few such therapies. One example is the inhibition of an enzyme reaction that is upstream of the deficient enzyme, to prevent accumulation of the toxic metabolites, such as the nitisinone (NTBC) for therapy of tyrosinemia type I. A similar approach focuses on partially reducing the synthesis of the substrate of the mutant enzyme or its precursors in lysosomal storage disorders (see Chapter 104.4).

Replacement Therapies

Replacement therapies include replacement of a missing metabolite, an enzyme, an organ, or even a specific gene.

Enzyme Replacement

Enzyme replacement therapy is a component of the treatment of cystic fibrosis to manage intestinal malabsorption. Pancreatic enzymes are easily administered orally, because they must be delivered to the gastrointestinal tract. Recombinant alkaline phosphatase coupled to bone targeting motif is available for intravenous therapy of hypophosphatasia, a skeletal disorder caused by alkaline-phosphatase deficiency.

Enzyme replacement strategies are effective for several lysosomal storage disorders. Enzymes are targeted for the lysosome by modification with mannose-6-phosphate, which binds to a specific receptor. This receptor is also present on the cell surface, so lysosomal enzymes with exposed mannose-6-phosphate residues can be infused into the blood and are taken into cells and transported to lysosomes. Enzyme replacement therapies are available for Gaucher disease and Fabry disease, some mucopolysaccharidoses (MPS I, II, IVA, VI), acid lipase deficiency, and Pompe disease, and are being tested for MPS IIIA, MPS VII, metachromatic leukodystrophy, α-mannosidosis, Niemann-Pick disease type B, and neuronal ceroid lipofuscinosis, late infantile (CLN2). Other examples include enzyme replacement therapy for hypophosphatasia.

One complication of enzyme replacement therapy is antibody response to the infused recombinant enzyme. The magnitude of this response is not always predictable and varies depending on the enzyme preparation and the disease. In most cases, the patient's antibody response does not affect the treatment's efficacy (e.g., Gaucher disease), but in other situations it may be a significant hurdle (e.g., Pompe disease and phenylketonuria).

Transplantation

Cell transplantation and **organ transplantation** are potentially effective approaches to replacement of a defective gene. Aside from transplantation to replace damaged tissues, transplantation of stem cells, liver, or bone marrow is also used for several diseases, mainly inborn errors of metabolism, and hematologic or immunologic disorders. A successful transplant is essentially curative, although there may be significant risks and side effects (see Chapters 161-165). Cell and tissue transplantation is effective in many clinical scenarios, but there is always short-term morbidity, often associated with either surgical (liver) or preparative (bone marrow) regimens, and long-term morbidity related to chronic immunosuppression and graft failure. Bone marrow transplantation is the best example of stem cell therapy, but much effort also is focused on identifying, characterizing, expanding, and using other tissue stem cells for regenerative therapies.

Alternatively, research has focused on replacing a defective gene (**gene therapy**). In theory, if one can target the specific tissue that has a deficiency in the gene or gene product, this can offer a less invasive means of achieving a cure for a genetic disorder. Ultimately, gene therapy depends on the unique interaction of the disease pathophysiology, which is specific to the patient, and the gene delivery vehicle.

Gene-transfer vehicles include viral and nonviral vectors administered through ex vivo or in vivo approaches. In ex vivo approaches the patient's cells are removed and after gene correction are infused into the patient. An example of this is the FDA approved CAR-T cell therapy for non-Hodgkin lymphoma. In the in vivo approaches the gene therapy vector is directly injected into the body by either systemic (e.g., intravenous) or localized (e.g., intramuscular, intracerebral, intraocular) injections. Most human clinical trials have used viral vectors because of their efficiency of tissue transduction. In some diseases, such as X-linked and adenosine deaminase–deficient severe combined immunodeficiency, chronic granulomatous disease, and Wiskott-Aldrich syndrome, clinical gene therapy is a viable and effective option (see Chapter 152.1). Ex vivo gene transfer of hematopoietic stem cells can now be considered at least as effective to allogenic hematopoietic stem cells transplantation in presymptomatic patients with X-linked adrenoleukodystrophy and metachromatic leukodystrophy. In vivo gene therapy is also promising for Leber congenital amaurosis by intraocular delivery, lipoprotein lipase deficiency by intramuscular injections, and hemophilia B by systemic intravenous injection. The first ever human in vivo gene therapy was recently approved in the United States by the FDA for treatment of a specific RPE65-deficient form of retinitis pigmentosa using adenoassociated virus (AAV)-mediated expression of the normal RPE65 gene via intraretinal injection.

Gene editing with direct correction of a pathologic mutation is a possible approach to genetic therapy. **CRISPR/Cas9** (clustered regularly interspaced short palindromic repeats/CRISPR-associated system) is a mechanism that permits permanent gene modification of genes in cells. CRISPR genes are bacterial DNA sequences used as a defense mechanism to destroy DNA from viral infections. Combined with related Cas nuclease proteins, the foreign RNA or DNA is recognized, excised, and digested. In gene editing, a complex of the nuclease enzyme and a complementary RNA sequence recognizes the base sequence in the mutated gene. Once bound to the targeted sequence, the nuclease excises both strands and inserts the corrected (nonmutated) sequence. The CRISPR system has corrected the gene defect in a mouse model of Duchenne muscular dystrophy and reduced the tumor burden in explanted human prostate cancer cells in mice. CRISPR-edited T cells can be modified to target and kill tumor cells. CRISPR/Cas9 has been employed to correct the mutation in *MYBPC3* (hypertrophic cardiomyopathy) in an experimental human embryo model. Clinical trials are now in progress applying this approach in somatic tissue. Currently, germline and/or embryonic gene editing studies in humans have not been approved.

Prevention of genetic disease has been accomplished by **preimplantation genetic diagnosis** . This procedure requires in vitro fertilization and single–embryo cell genetic testing of the known families' mutation and is performed with PCR amplification of the affected gene. To avoid recurrent disease, only the unaffected embryos are used for implantation.

In addition, mitochondrial DNA mutations may be avoided by using **mitochondrial replacement therapies** . In one technique the mutation carrier mother's nuclear DNA is removed from the unfertilized oocyte and transferred to the unaffected mitochondrial donor oocyte (minus that cell's nuclear DNA). In another approach the pronucleus from the mutation-carrier mother's fertilized oocyte is transferred to the unaffected mitochondrial donor's fertilized oocyte (minus the pronucleus).

These different and promising methodologies have many technical and ethical considerations that are being discussed by medical, ethical, legal, and policymaking organizations.

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CHAPTER 95

The Genetic Approach in Pediatric Medicine

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Since the completion of the Human Genome Project, we have seen an unprecedented expansion in our understanding of how human health is impacted by variations in genomic sequence and **epigenetic** , non-sequence-based, changes that affect gene expression. This period has also seen the development and implementation of new clinical tests that have made it easier for physicians to detect such changes. In addition, there has been a dramatic increase in the availability of information about the genetic aspects of pediatric diseases, particularly on the internet (Table 95.1).

Table 95.1

Useful Internet Genetic Reference Sites

RESOURCE	WEB ADDRESS
National Center for Biotechnology Information. A general reference maintained by the National Library of Medicine.	www.ncbi.nlm.nih.gov
Online Mendelian Inheritance in Man. A useful resource for clinicians containing information on all known mendelian disorders and >12,000 genes. Information focuses on the relationship between phenotype and genotype.	www.ncbi.nlm.nih.gov/omim
Genetic Testing Registry. A resource that provides information on individual genes, genetic tests, clinical laboratories, and medical conditions. This resource also provides access to GeneReviews, a collection of expert-authored reviews on a variety of genetic disorders.	www.ncbi.nlm.nih.gov/gtr/
Genetics Home Reference. A resource that provides consumer-friendly information about the effects of genetic variations on human health.	www.ghr.nlm.nih.gov
National Human Genome Research Institute. A resource for information about human genetics and ethical issues.	www.genome.gov
Human Gene Mutation Database. A searchable index of all described mutations in human genes with phenotypes and references.	www.hgmd.cf.ac.uk
DECIPHER. A database designed to aid physicians in determining the potential consequences of chromosomal deletions and duplications.	http://decipher.sanger.ac.uk

Database of Genomic Variants. A database of chromosomal alterations seen in normal controls.	http://dgv.tcag.ca/dgv/app/home
Gene Letter . An online magazine of genetics.	www.geneletter.com
American Society of Human Genetics	www.ashg.org
American College of Medical Genetics	www.acmg.net

The Burden of Genetic Disorders in Childhood

Medical problems associated with genetic disorders can appear at any age, with the most obvious and serious problems typically manifesting in childhood. It has been estimated that 53/1,000 children and young adults can be expected to have diseases with an important genetic component. If congenital anomalies are included, the rate increases to 79/1,000. In 1978 it was estimated that just over half of admissions to pediatric hospitals were for a genetically determined condition. By 1996, because of changes in healthcare delivery and a greater understanding of the genetic basis of many disorders, that percentage rose to 71%, in one large pediatric hospital in the United States, with 96% of chronic disorders leading to admission having an obvious genetic component or being influenced by genetic susceptibility.

Major categories of genetic disorders include single-gene, genomic, chromosomal, and multifactorial conditions.

Individually, each **single-gene disorder** is rare, but collectively they represent an important contribution to childhood disease. The hallmark of a single-gene disorder is that the phenotype is overwhelmingly determined by changes that affect an individual gene. The phenotypes associated with single-gene disorders can vary from one patient to another based on the severity of the change affecting the gene and additional modifications caused by genetic, environmental, and stochastic factors. This feature of genetic disease is termed **variable expressivity** . Common single-gene disorders include sickle cell anemia and cystic fibrosis. Some identifiable syndromes and diseases can be caused by more than one gene (e.g., Noonan syndrome by *RAF1*, *NF1*, *NRAS*, *PTPN11*, *SOS1*, *SOS2*, *KRAS*, *BRAF*, *SOC2*, *LZTR1*, and *RIT1*). In addition, mutations affecting a single gene may produce different phenotypes (e.g., *SCN5A* and Brugada syndrome, long QT syndrome 3, dilated cardiomyopathy, familial atrial fibrillation, and congenital sick sinus syndrome).

Single-gene disorders tend to occur when changes in a gene have a profound effect on the *quantity* of the gene product produced, either too much or too little, or the *function* of the gene product, either a loss of function or a harmful gain of function. Single-gene disorders can be caused by de novo sequence changes that are not found in the unaffected parents of the affected individual, or they may be caused by inherited changes. When a single-gene disorder is known to be caused by changes in only 1 gene, or a small number of individual genes, searching for deleterious changes is most often performed by directly sequencing that gene and, in some cases, looking for small deletions and/or duplications. When multiple genes can cause a particular disorder, it is sometimes more efficient and cost-effective to screen large numbers of disease-causing genes using a disease-specific panel that takes advantage of next-generation sequencing technology than to screen genes individually. When such panels are not available, or when the diagnosis is in question, physicians may consider screening the protein-coding regions of all genes by **whole exome sequencing (WES)** on a clinical basis. In many circumstances, WES is less expensive than sequencing multiple individual genes. In the future, **whole genome sequencing** , in which an individual's entire genome is sequenced, may become a valid clinical option as the cost of such tests fall and our ability to interpret the clinical consequences of the thousands of changes identified in such tests improves (see Chapter 94).

The risk of having a child with a particular single-gene disorder can vary from one population to another. In some cases, this is the result of a **founder effect** , in which a specific change affecting a disease-causing gene becomes relatively common in a population derived from a small number of founders. This high frequency is maintained when there is relatively little interbreeding with persons outside that population because of social, religious, or physical barriers. This is the case for Tay-Sachs disease in Ashkenazi Jews and French Canadians. Other changes may be subject to **positive selection** when found in the heterozygous carrier state. In this case, individuals who carry a single copy of a genetic change (**heterozygotes**) have a survival advantage over noncarriers. This can occur even when individuals who inherit 2 copies of the change (**homozygotes**) have severe medical problems. This type of positive selection is evident among individuals in sub-Saharan Africa who carry a single copy of a hemoglobin mutation that confers relative resistance to malaria but causes sickle cell anemia in homozygotes.

Genomic disorders are a group of diseases caused by alterations in the genome, including **deletions** (copy number loss), **duplications** (copy number gain), **inversions** (altered orientation of a genomic region), and **chromosomal**

rearrangements (altered location of a genomic region). **Contiguous gene disorders** are caused by changes that affect 2 or more genes that contribute to the clinical phenotype and are located near one other on a chromosome. DiGeorge syndrome, which is caused by deletions of genes located on chromosome 22q11, is a common example. Some genomic disorders are associated with distinctive phenotypes whose pattern can be recognized clinically. Other genomic disorders do not have a distinctive pattern of anomalies but can cause developmental delay, cognitive impairment, structural birth defects, abnormal growth patterns, and changes in physical appearance. **Fluorescent in situ hybridization (FISH)** can provide information about the copy number and location of a specific genomic region. **Array-based copy number detection assays** can be used to screen for chromosomal deletions (large and small) and duplications across the genome, but do not provide information about the orientation or location of genomic regions. A **chromosome analysis (karyotype**) can detect relatively large chromosomal deletions and duplications and can also be useful in identifying inversions and chromosomal rearrangements even when they are **copy number neutral** changes that do not result in a deletion or duplication of genomic material.

Deletions, duplications, and chromosomal rearrangements that affect whole chromosomes, or large portions of a chromosome, are typically referred to as **chromosomal disorders** . One of the most common chromosomal disorders is Down syndrome, most often associated with the presence of an extra copy, or **trisomy** , of an entire chromosome 21. When all or a part of a chromosome is missing, the disorder is referred to as **monosomy** . **Translocations** are a type of chromosomal rearrangement in which a genomic region from one chromosome is transferred to a different location on the same chromosome or on a different (nonhomologous) chromosome. Translocations can be *balanced,* meaning that no genetic material has been lost or gained, or they can be *unbalanced,* in which some genetic material has been deleted or duplicated.

In some cases, only a portion of cells that make up a person's body are affected by a single-gene defect, a genomic disorder, or a chromosomal defect. This is referred to as **mosaicism** and indicates that the individual's body is made up of 2 or more distinct cell populations.

Polygenic disorders are caused by the cumulative effects of changes or variations in more than 1 gene. **Multifactorial** disorders are caused by the cumulative effects of changes or variations in multiple genes and/or the combined effects of both genetic and environmental factors. Spina bifida and isolated cleft lip or palate are common birth defects that display multifactorial inheritance patterns. Multifactorial inheritance is seen in many common pediatric disorders, such as asthma and diabetes mellitus. These traits can cluster in families but do not have a mendelian pattern of inheritance (see Chapter 97). In these cases the genetic changes or variations that are contributing to a particular disorder are often unknown, and genetic counseling is based on empirical data.

The Changing Paradigm of Genetics in Medicine

Genetic testing is increasingly available for a wide variety of both rare and relatively common genetic disorders. Genetic testing is typically used in pediatric medicine to resolve uncertainty regarding the underlying etiology of a child's medical problems and provides a basis for improved genetic counseling and possibly a specific therapy. Even in cases where a specific treatment is not available, identifying a genetic cause can aid physicians in providing individuals and family with accurate prognostic and recurrence risk information and usually helps to relieve unfounded feelings of guilt and stem the tide of misdirected blame.

Genetic tests will ultimately come to underlie a high proportion of medical decisions and will be seamlessly incorporated into routine medical care. Although most genetic testing is presently aimed at identifying or confirming a diagnosis, in the future, genetic testing may find wider application as a means of determining if an individual is predisposed to develop a particular disease. Another area in which genetic testing could make a significant impact is on individualized drug treatment. It has long been known that genetic variation in the enzymes involved in drug metabolism underlies differences in the therapeutic effect and toxicity of some drugs. As the genetic changes that underlie these variations are identified, new genetic tests are being developed that allow physicians to tailor treatments based on individual variations in drug metabolism, responsiveness, and susceptibility to toxicity (see Chapter 72). It is likely that the expansion of such testing will depend, at least in part, on the extent to which such tests can be linked to strategies to prevent disease or improve outcome (see Chapter 94). As such links are made, we will enter into a new era of personalized medical treatment.

Long-standing and highly successful carrier screening programs have existed for disorders such as Tay-Sachs disease and many other rare, single-gene disorders that are prevalent in specific populations. Couples are usually offered screening for a variety of conditions, in part based on ancestry (Tay-Sachs disease, hemoglobinopathies, cystic fibrosis). Couples found to be at increased risk for such disorders can be offered preconception or prenatal testing aimed at detecting specific disease-causing mutations.

Prenatal screening is routinely offered for chromosomal disorders such as trisomy 13, trisomy 18, and Down syndrome. An increasing number of pregnancies affected by these and other genetic disorders are being recognized by noninvasive screening tests targeting fetal cell-free DNA in maternal blood and by fetal ultrasound. When genetic disorders are suspected, chorionic villus sampling at 10-12 wk of gestation or amniocentesis at 16-18 wk of gestation can provide material for genetic testing. When a couple are at risk for a specific genetic defect, **preimplantation genetic diagnosis** can sometimes be used to select unaffected early embryos, which are then implanted as part of an in vitro fertilization procedure.

Although prenatally obtained genetic material can be used to identify single-gene disorders, genomic disorders, and chromosomal anomalies, the information obtained on any pregnancy depends on the tests that are ordered. It is important that physicians select the most appropriate prenatal tests, and that couples understand the limitations of these tests. No amount of genetic testing can guarantee the birth of a healthy child.

Specific treatments are not available for the majority of genetic disorders, although some important exceptions exist (Chapter 94). **Inborn errors of metabolism** were the first genetic disorders to be recognized, and many are amenable to treatment by dietary manipulation (see Chapter 102). These conditions result from genetically determined deficiency of specific enzymes, leading to the buildup of toxic substrates and/or deficiency of critical end products.

Individual metabolic disorders tend to be very rare, but their combined impact on the pediatric population is significant. Tandem mass spectrometry has made it relatively inexpensive to screen for a large number of these disorders in the newborn period. Use of this technology not only dramatically increases the number of metabolic disorders identified within a population, but also allows treatment to be initiated at a much earlier stage in development.

Another area showing progress in genetic therapies is the treatment of

lysosomal storage disorders (see Chapter 104.4). These metabolic diseases are caused by defects in lysosomal function. *Lysosomes* are cellular organelles that contain specific digestive enzymes. Some of these disorders that were characterized by early lethal or intractable chronic illness can now be treated using specially modified enzymes administered by intravenous infusion. These enzymes are taken up by cells and incorporated into lysosomes. Conditions such as Gaucher disease and Fabry disease are routinely treated using **enzyme replacement** , and similar therapies are being developed for other lysosomal disorders.

Therapeutic advances are also being made in the treatment of nonmetabolic genetic disorders. Improvements in surgical techniques and intensive care medicine are extending the survival of children with life-threatening birth defects such as congenital diaphragmatic hernia and severe cardiac defects. In many cases the life expectancy of children with debilitating genetic disorders is also increasing. For example, in cystic fibrosis, improvements in nutrition and the management of chronic pulmonary disease allow an increasing percentage of affected patients to survive into adulthood, creating a need to transition care from pediatric to adult providers.

Gene replacement therapies have long been anticipated and are starting to show some benefit (see Chapter 94). Stem cell–based therapies have also been touted as a potential treatment for a number of intractable disorders, but clear evidence that such therapies are effective has yet to materialize.

Ethics Issues

As with all medical care, genetic testing, diagnosis, and treatment should be performed *confidentially* . Nothing is as personal as one's genetic information, and all efforts should be made to avoid any stigma for the patient. Many people worry that results of genetic testing will put them, or their child, at risk for genetic discrimination. **Genetic discrimination** occurs when people are treated unfairly because of a difference in their DNA that suggests they have a genetic disorder or they are at an increased risk of developing a certain disease. In the United States the Genetic Information Nondiscrimination Act of 2008 protects individuals from genetic discrimination at the hands of health insurers and employers, but does not extend protection against discrimination from providers of life, disability, or long-term care insurance.

As in all medical decision-making, the decisions about genetic testing should be based on a careful evaluation of the potential benefits and risks. In the pediatric setting, these decisions may be more difficult because physicians and parents are often called on to make decisions for a child who cannot directly participate in discussions about testing. Molecular diagnostic tests are often used to diagnose malformation syndromes, cognitive delay, or other disabilities in which there is a clear benefit to the child. In other cases, such as genetic testing for susceptibility to adult-onset diseases, it is appropriate to wait until the child or adolescent is mature enough to weigh the potential risks and benefits and make his or her own decisions about genetic testing.

Policies regarding genetic testing of children have been developed collaboratively by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG; *Pediatrics* 131[3]:620–622, 2013). These recommendations are outlined next.

General Recommendations

1. Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child.
2. Genetic testing is best offered in the context of genetic counseling. Genetic counseling can be performed by clinical geneticists, genetic counselors, or any other health care provider with appropriate training and expertise. AAP and ACMG support the expansion of educational opportunities in human genomics and genetics for medical students, residents, and practicing pediatric primary care providers.

Diagnostic Testing

3. In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally, and when appropriate, the assent of the child should be obtained.
4. When performed for therapeutic purposes, pharmacogenetic testing of children is acceptable, with permission of parents or guardians and, when appropriate, the child's assent. If a pharmacogenetic test result carries implications beyond drug targeting or dose responsiveness, the broader implications should be discussed before testing.

Newborn Screening

5. AAP and ACMG support the mandatory offering of newborn screening for all children. After education and counseling about the substantial

benefits of newborn screening, its remote risks, and the next steps in the event of a positive screening result, parents should have the option of refusing the procedure, and an informed refusal should be respected.

Carrier Testing

6. AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood. The AAP and ACMG advise against school-based testing or screening programs, because the school environment is unlikely to be conducive to voluntary participation, thoughtful consent, privacy, confidentiality, or appropriate counseling about test results.
7. For pregnant adolescents or for adolescents considering reproduction, genetic testing and screening should be offered as clinically indicated, and the risks and benefits should be explained clearly.

Predictive Genetic Testing

8. Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained.
9. Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and the parents concur in their interest in predictive testing.
10. For ethical and legal reasons, healthcare providers should be cautious about providing predictive genetic testing to minors without the involvement of their parents or guardians, even if a minor is mature. Results of such tests may have significant medical, psychological, and social implications, not only for the minor but also for other family members.

Histocompatibility Testing

11. Tissue compatibility testing of minors of all ages is permissible to benefit immediate family members but should be conducted only after thorough exploration of the psychosocial, emotional, and physical implications of the minor serving as a potential stem cell donor. A donor advocate or similar mechanism should be in place from the outset to avert coercion and safeguard the interests of the child.

Adoption

12. The rationale for genetic testing of children in biological families should apply for adopted children and children awaiting placement for adoption. If a child has a known genetic risk, prospective adoptive parents must be made aware of this possibility. In rare cases, it may be in a child's best interest to undergo predictive genetic testing for a known risk before adoption, to ensure the child's placement with a family capable of and willing to accept the child's potential medical and developmental challenges. In the absence of such indications, genetic testing should not be performed as a condition of adoption.

Disclosure

13. At the time of genetic testing, parents or guardians should be encouraged to inform their child of the test results at an appropriate age. Parents or guardians should be advised that, under most circumstances, a request by a mature adolescent for test results should be honored.
14. Results from genetic testing of a child may have implications for the parents and other family members. Healthcare providers have an obligation to inform parents and the child, when appropriate, about these potential implications. Healthcare providers should encourage patients and families to share this information and offer to help explain the results to the extended family or refer them for genetic counseling.
15. Misattributed paternity, use of donor gametes, adoption, or other questions about family relationships may be uncovered “incidentally” whenever genetic testing is performed, particularly when testing multiple family members. This risk should be discussed, and a plan about disclosure or nondisclosure should be in place before testing.

Direct-to-Consumer Testing

16. AAP and ACMG strongly discourage the use of direct-to-consumer and home-kit genetic testing of children because of the lack of oversight on test content, accuracy, and interpretation.

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CHAPTER 96

The Human Genome

Daryl A. Scott, Brendan Lee

The human genome has approximately 20,000 genes that encode the wide variety of proteins found in the human body. Reproductive or germline cells contain 1 copy (N) of this genetic complement and are **haploid** , whereas somatic (nongermline) cells contain 2 complete copies (2N) and are **diploid** . Genes are organized into long segments of deoxyribonucleic acid (**DNA**), which, during cell division, are compacted into intricate structures together with proteins to form chromosomes. Each somatic cell has 46 chromosomes: 22 pairs of **autosomes** , or nonsex chromosomes, and 1 pair of **sex chromosomes** (XY in a male, XX in a female). Germ cells (ova or sperm) contain 22 autosomes and 1 sex chromosome, for a total of 23. At fertilization, the full diploid chromosome complement of 46 is again realized in the embryo.

Most of the genetic material is contained in the cell's nucleus. The mitochondria (the cell's energy-producing organelles) contain their own unique genome. The **mitochondrial chromosome** consists of a double-stranded circular piece of DNA, which contains 16,568 base pairs (bp) of DNA and is present in multiple copies per cell. The proteins that occupy the mitochondria are produced either in the mitochondria, using information contained in the mitochondrial genome, or are produced outside of the mitochondria, using information contained in the nuclear genome, and then transported into the organelle. Sperm do not usually contribute mitochondria to the developing embryo, so all mitochondria are maternally derived, and a child's mitochondrial genetic makeup derives exclusively from the child's biological mother (see Chapter 106).

Fundamentals of Molecular Genetics

DNA consists of a pair of chains of a sugar-phosphate backbone linked by pyrimidine and purine bases to form a **double helix** (Fig. 96.1). The sugar in DNA is deoxyribose. The pyrimidines are cytosine (C) and thymine (T); the purines are guanine (G) and adenine (A). The bases are linked by hydrogen bonds such that A always pairs with T and G with C. Each strand of the double helix has polarity, with a free phosphate at one end (5′) and an unbonded hydroxyl on the sugar at the other end (3′). The 2 strands are oriented in opposite polarity in the double helix.

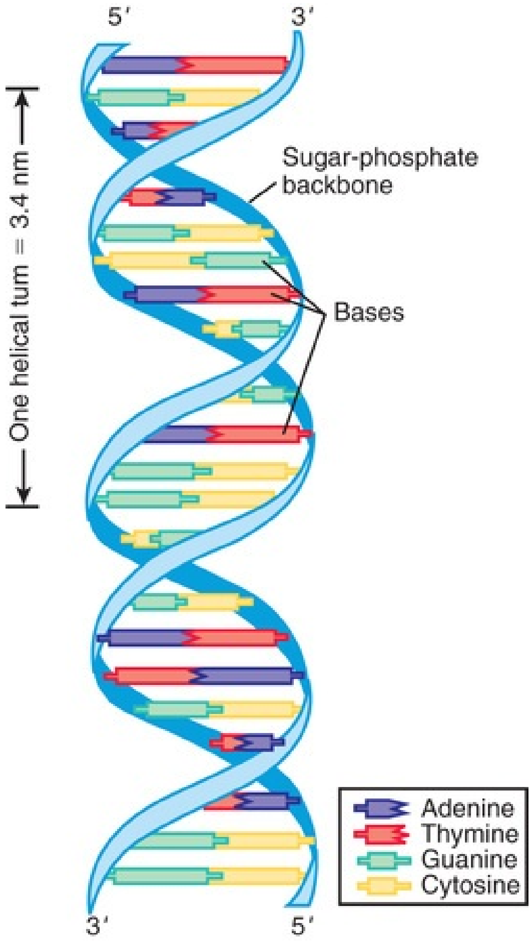

FIG. 96.1 DNA double helix, with sugar-phosphate backbone and nitrogenous bases. (From Jorde LB, Carey JC, Bamshad MJ, et al, editors: *Medical genetics* , ed 2, St Louis, 1999, Mosby, p 8.)

The replication of DNA follows the pairing of bases in the parent DNA strand. The original 2 strands unwind by breaking the hydrogen bonds between base pairs. Free nucleotides, consisting of a base attached to a sugar-phosphate chain, form new hydrogen bonds with their complementary bases on the parent strand;

new phosphodiester bonds are created by enzymes called **DNA polymerases.** Replication of chromosomes begins simultaneously at multiple sites, forming replication bubbles that expand bidirectionally until the entire DNA molecule (chromosome) is replicated. Errors in DNA replication, or mutations induced by environmental mutagens such as irradiation or chemicals, are detected and potentially corrected by DNA repair systems.

The central tenet of molecular genetics is that information encoded in DNA, predominantly located in the cell nucleus, is transcribed into **messenger** ribonucleic acid (**mRNA**), which is then transported to the cytoplasm, where it is translated into protein. A prototypical gene consists of a regulatory region, segments called **exons** that encode the amino acid sequence of a protein, and intervening segments called **introns** (Fig. 96.2).

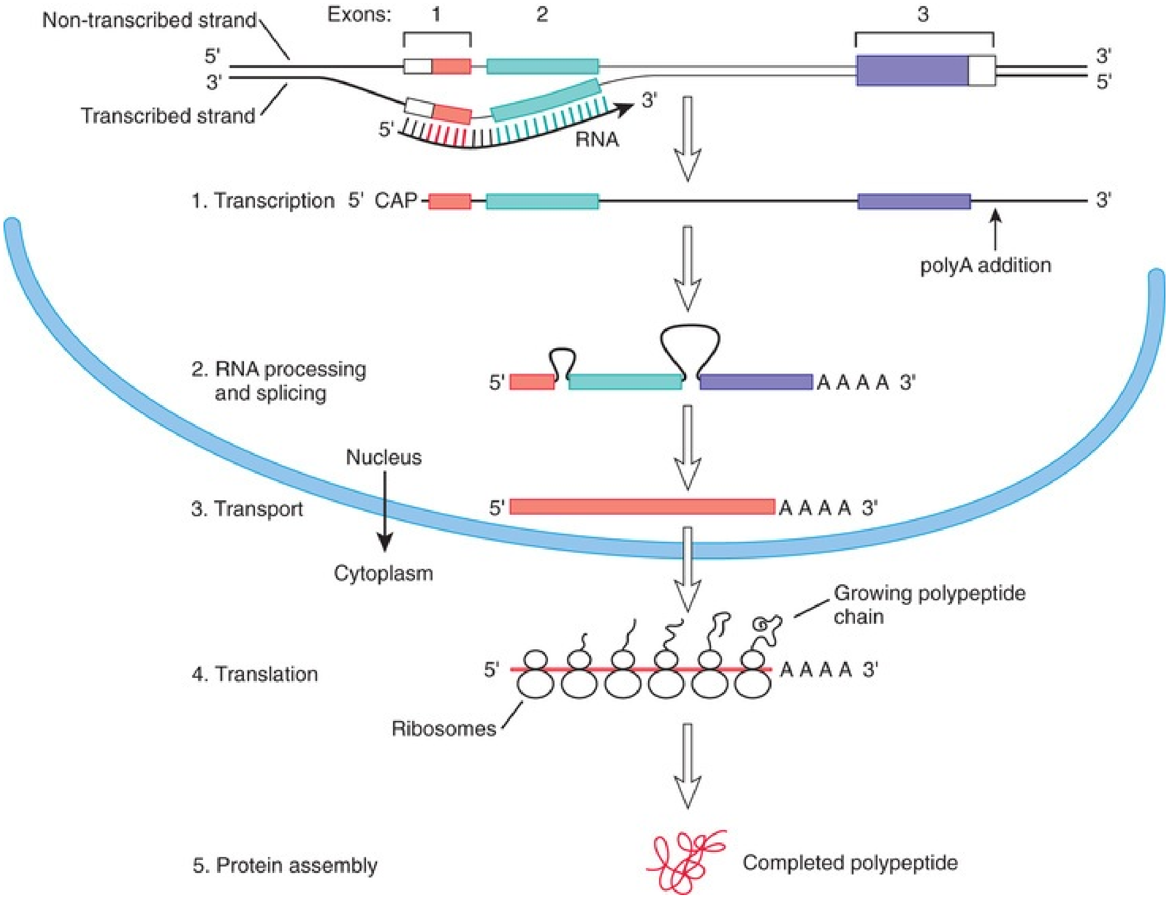
Non-transcribed strand
Exons: 1 2 3
5'
3'
3'
5'
Transcribed strand
5'
3'
RNA
1. Transcription 5' CAP
3'
polyA addition
2. RNA processing and splicing
5'
A A A A 3'
Nucleus
3. Transport
5'
A A A A 3'
Cytoplasm
Growing polypeptide chain
4. Translation
5'
A A A A 3'
Ribosomes
5. Protein assembly
Completed polypeptide

FIG. 96.2 Flow of information from DNA to RNA to protein for a hypothetical gene with 3 exons and 2 introns. Within the exons, *colored regions* indicate coding sequences. Steps include transcription, RNA processing and splicing, RNA transport from the nucleus to the cytoplasm, translation, and protein assembly. (From Nussbaum RL, McInnis RR, Willard HF, Hamosh A, editors: *Thompson & Thompson genetics in medicine,* ed 7, Philadelphia, 2007, Saunders/Elsevier, p 31.)

Transcription is initiated by attachment of ribonucleic acid (**RNA**) polymerase to the promoter site upstream of the beginning of the coding sequence. Specific proteins bind to the region to repress or activate transcription by opening up the **chromatin** , which is a complex of DNA and histone proteins. It is the action of these regulatory proteins (**transcription factors**) that determines, in large part, when a gene is turned on or off. Some genes are also turned on and off by methylation of cytosine bases that are adjacent to guanine bases (**cytosine-phosphate-guanine bases, CpGs**). Methylation is an example of an **epigenetic** change, meaning a change that can affect gene expression, and possibly the characteristics of a cell or organism, but that *does not* involve a change in the underlying genetic sequence. Gene regulation is flexible and responsive, with genes being turned on or off during development and in response to internal and external environmental conditions and stimuli.

Transcription proceeds through the entire length of the gene in a 5′ to 3′ direction to form an mRNA transcript whose sequence is complementary to that of one of the DNA strands. RNA, like DNA, is a sugar-phosphate chain with pyrimidines and purines. In RNA the sugar is ribose, and uracil replaces the thymine found in DNA. A “cap” consisting of 7-methylguanosine is added to the 5′ end of the RNA in a 5′-5′ bond and, for most transcripts, several hundred adenine bases are enzymatically added to the 3′ end after transcription.

mRNA processing occurs in the nucleus and consists of excision of the introns and splicing together of the exons. Specific sequences at the start and end of introns mark the sites where the splicing machinery will act on the transcript. In some cases, there may be tissue-specific patterns to splicing, so that the same primary transcript can produce multiple distinct proteins.

The processed transcript is next exported to the cytoplasm, where it binds to ribosomes, which are complexes of protein and **ribosomal** RNA (**rRNA**). The genetic code is then read in triplets of bases, each triplet corresponding with a specific amino acid or providing a signal that terminates **translation** . The triplet codons are recognized by **transfer** RNAs (**tRNAs**) that include complementary anticodons and bind the corresponding amino acid, delivering it to the growing peptide. New amino acids are enzymatically attached to the peptide. Each time an amino acid is added, the ribosome moves 1 triplet codon step along the mRNA. Eventually a **stop codon** is reached, at which point translation ends and the peptide is released. In some proteins, there are **posttranslational modifications** , such as attachment of sugars (**glycosylation**); the protein is then delivered to its destination within or outside the cell by trafficking mechanisms that recognize portions of the peptide.

Another mechanism of genetic regulation is **noncoding** RNAs, which are RNAs transcribed from DNA but not translated into proteins. Noncoding RNAs function in mediating splicing, the processing of coding RNAs in the nucleus, and the translation of coding mRNAs in ribosomes. The roles of *large* noncoding RNAs (>200 bp) and *short* noncoding RNAs (<200 bp) extend beyond these processes to impact a diverse set of biologic functions, including the regulation of gene expression. For example, **micro** RNAs (**miRNAs**) are a class of small RNAs that control gene expression in the cell by directly targeting specific sets of coding RNAs by direct RNA–RNA binding. This RNA–RNA interaction can lead to degradation of the target-coding RNA or inhibition of translation of the protein specified by that coding RNA. miRNAs, in general, target and regulate several hundred mRNAs.

Genetic Variation

The process of producing protein from a gene is subject to disruption at multiple levels because of alterations in the coding sequence (Fig. 96.3). Changes in the regulatory region can lead to altered gene expression, including increased or decreased rates of transcription, failure of gene activation, or activation of the gene at inappropriate times or in inappropriate cells. Changes in the coding sequence can lead to **substitution** of one amino acid for another (**missense variant** or **nonsynonymous variant**) or creation of a stop codon in the place of an amino acid codon. Overall, missense or nonsense variants are the most common (56% of variants); small deletions or insertions represent approximately 24% of variants (Table 96.1). Some single-base changes do not affect the amino acid (**silent** , **wobble** , or **synonymous variants**), because there may be several triplet codons that correspond to a single amino acid. Amino acid substitutions can have a profound effect on protein function if the chemical properties of the substituted amino acid are markedly different from the usual one. Other substitutions can have a subtle or no effect on protein function, particularly if the substituted amino acid is chemically similar to the original one.

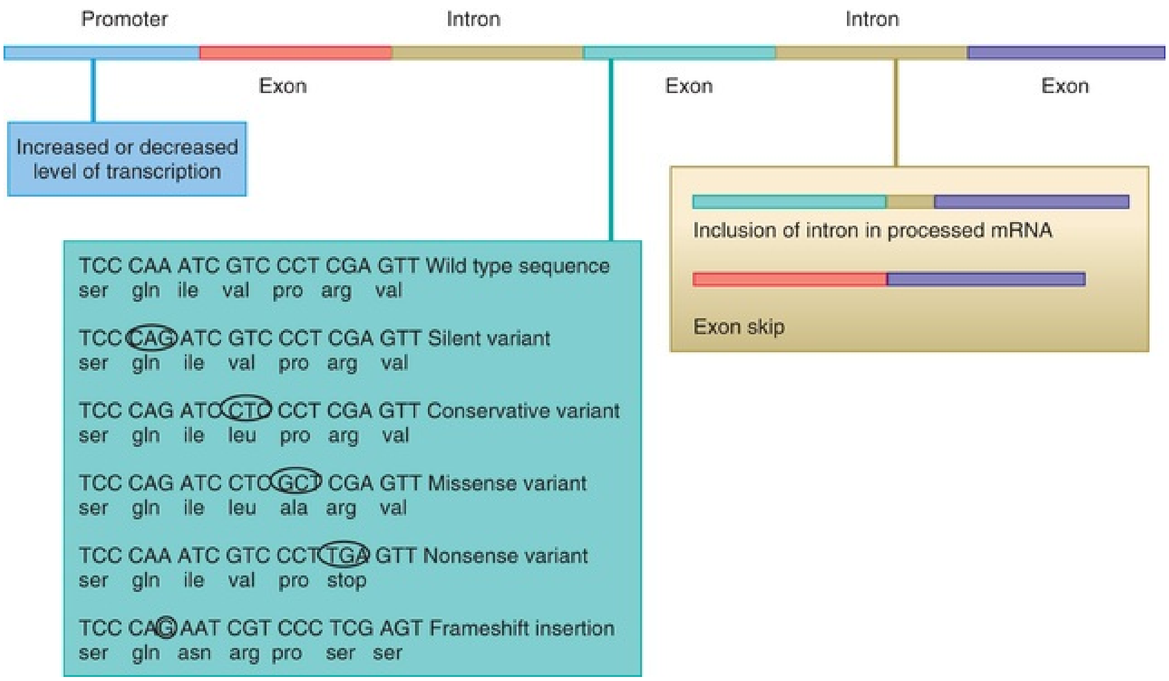
Promoter
Intron
Intron
Exon
Exon
Exon
Increased or decreased level of transcription
TCC CAA ATC GTC CCT CGA GTT Wild type sequence
ser gln ile val pro arg val
TCC CAG ATC GTC CCT CGA GTT Silent variant
ser gln ile val pro arg val
TCC CAG ATC CTC CCT CGA GTT Conservative variant
ser gln ile leu pro arg val
TCC CAG ATC CTC GCT CGA GTT Missense variant
ser gln ile leu ala arg val
TCC CAA ATC GTC CCT TGA GTT Nonsense variant
ser gln ile val pro stop
TCC CAG AAT CGT CCC TCG AGT Frameshift insertion
ser gln asn arg pro ser ser
Inclusion of intron in processed mRNA
Exon skip

FIG. 96.3 Various types of intragenic sequence variants. Promoter variants alter rate of transcription or disrupt gene regulation. Base changes within exons can have various effects, as shown. Variants within introns can lead to inclusion of some intronic sequence in the final processed mRNA, or it can lead to exon skipping.

Table 96.1

Main Classes, Groups, and Types of Sequence Variants and Their Effects on Protein Products

CLASS	GROUP	TYPE	EFFECT ON PROTEIN PRODUCT
Substitution	Synonymous	Silent*	Same amino acid
	Nonsynonymous	Missense*	Altered amino acid—may affect protein function or stability
		Nonsense*	Stop codon—loss of function or expression from degradation of mRNA
		Splice site	Aberrant splicing—exon skipping or intron retention
		Promoter	Altered gene expression
Deletion	Multiple of 3 (codon)		In-frame deletion of 1 or more amino acid(s)—may affect protein function or stability
	Not multiple of 3	Frameshift	Likely to result in premature termination with loss of function or expression
	Large deletion	Partial gene deletion	May result in premature termination with loss of function or expression
		Whole gene deletion	Loss of expression
Insertion	Multiple of 3 (codon)		In-frame insertion of 1 or more amino acid(s)—may affect protein function or stability
	Not multiple of 3	Frameshift	Likely to result in premature termination with loss of

			function or expression
	Large insertion	Partial gene duplication	May result in premature termination with loss of function or expression
		Whole gene duplication	May have an effect because of increased gene dosage
	Expansion of trinucleotide repeat	Dynamic mutation	Altered gene expression or altered protein stability or function

[*] Some have been shown to cause aberrant splicing.

From Turnpenny P, Ellard S (Editors): *Emery's elements of medical genetics,* ed 14, Philadelphia, 2012, Elsevier/Churchill Livingstone, p 23.

Genetic changes can also include **insertions** or **deletions** . Insertions or deletions of a nonintegral multiple of 3 bases into the coding sequence leads to a **frameshift,** altering the grouping of bases into triplets. This leads to translation of an incorrect amino acid sequence and often a premature stop to translation. Insertion or deletion of an integral multiple of 3 bases into the coding sequence will insert or delete a corresponding number of amino acids from the protein, leading to **in-frame** alterations that maintain the amino acid sequence outside the deleted or duplicated amino acids. Larger-scale insertions or deletions can disrupt a coding sequence or result in complete deletion of an entire gene or group of genes.

Pathogenic variants usually can be classified as causing a loss of function or a gain of function. **Loss-of-function variants** cause a reduction in the level of protein function as a result of decreased expression or production of a protein that does not work as efficiently. In some cases, loss of protein function from 1 gene is sufficient to cause disease. **Haploinsufficiency** describes the situation in which maintenance of a normal phenotype requires the proteins produced by both copies of a gene, and a 50% decrease in gene function results in an abnormal phenotype. Thus, haploinsufficient phenotypes are, by definition, dominantly inherited. Loss-of-function variants can also have a dominant negative effect when the abnormal protein product actively interferes with the function of the normal protein product. Both these situations lead to diseases inherited in a dominant fashion. In other cases, loss-of-function variants must be present in both copies of a gene before an abnormal phenotype results. This situation typically results in diseases inherited in a recessive fashion (see Chapter 97).

Gain-of-function variants typically cause dominantly inherited diseases. These variants can result in production of a protein molecule with an increased ability to perform a normal function or can confer a novel property on the protein. The gain-of-function variant in **achondroplasia** , the most common of the disproportionate, short-limbed short stature disorders, exemplifies the enhanced function of a normal protein. Achondroplasia results from a mutation in the fibroblast growth factor (FGF) receptor 3 gene (*FGFR3*), which leads to activation of the receptor, even in the absence of FGF. In **sickle cell disease** an amino acid is substituted into the hemoglobin molecule and has little effect on the ability of the protein to transport oxygen. However, sickle hemoglobin chains have a novel property. Unlike normal hemoglobin, sickle hemoglobin chains aggregate under conditions of deoxygenation, forming fibers that deform the red cells.

Other gain-of-function mutations result in overexpression or inappropriate expression of a gene product. Many cancer-causing genes (**oncogenes**) are normal regulators of cellular proliferation during development. However, expression of these genes in adult life and/or in cells in which they usually are not expressed can result in neoplasia.

In some cases, changes in gene expression are caused by changes in the number of copies of a gene that are present in the genome (Fig. 96.4). Although some **copy number variations** are common and do not appear to cause or predispose to disease, others are clearly disease causing. **Charcot-Marie-Tooth disease type 1A** , the most common inherited form of chronic peripheral neuropathy of childhood, is caused by duplications of the gene for peripheral myelin protein 22, resulting in overexpression as a result of the existence of 3 active copies of this gene (see Chapter 631.1). Deletions of this same gene leaving only 1 active copy are responsible for a different disorder, hereditary neuropathy with liability to pressure palsies.

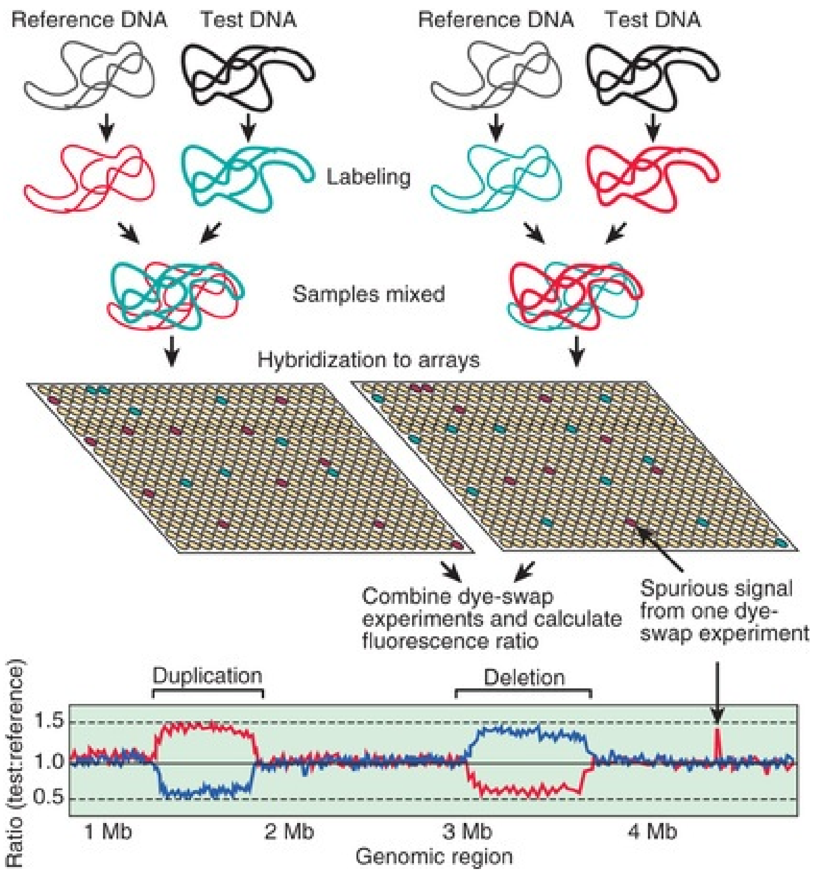
Reference DNA
Test DNA
Reference DNA
Test DNA
Labeling
Samples mixed
Hybridization to arrays
Combine dye-swap experiments and calculate fluorescence ratio
Spurious signal from one dye-swap experiment
Duplication
Deletion
Ratio (test:reference)
1.5
1.0
0.5
1 Mb
2 Mb
3 Mb
4 Mb
Genomic region

FIG. 96.4 **Array comparative genomic hybridization. Test and reference DNA samples are differentially labeled, mixed, and passed over a target array of probes (e.g., bacterial artificial chromosome clones or oligonucleotides) containing DNA fragments from across the whole human genome. The experiment is often repeated with reversal of the test and reference dyes to detect dye effects or identify spurious signals. DNA samples hybridize with their corresponding probe, and the ratio of fluorescence from each probe (test:reference) is used to detect regions that vary in copy number between the test and the reference sample (*red line,* original hybridization; *blue line,* dye-swapped hybridization). Equal copy number for both the test and the reference DNA is identified by equal binding, resulting in a ratio of 1 : 1. Duplication in a genomic region of the test sample is identified by an increased ratio, and a deletion is identified by a decreased ratio, but a deletion in the test sample is indistinguishable from a duplication in the reference sample. These ratios are usually converted to log2 scale for further analysis. (Adapted from Feuk L, Carson AR, Scherer SW: Structural variation in the human genome, *Nat Rev Genet* 7:85–97, 2006, with permission from *Nature Reviews Genetics.*)**

Deletions and duplications can vary in their extent and can involve several genes, even when they are not visible on a traditional chromosome analysis. Such changes are commonly called **microdeletions** and **microduplications** . When deletion or duplication of 2 or more genes in the same chromosomal region each play a role in the resulting clinical features, the condition can also be referred to as a **contiguous gene disorder** .

In some cases the recognition of a specific constellation of features leads the clinician to suspect a specific microdeletion or microduplication syndrome. Examples of such disorders include Smith-Magenis, DiGeorge, and Williams syndromes. In other cases the clinician may be alerted to this possibility by an unusually diverse array of clinical features in one patient or the presence of unusual features in a person with a known condition. Because of the close physical proximity of a series of genes, different deletions involving the short arm of the X chromosome can produce individuals with various combinations of ichthyosis, Kallmann syndrome, ocular albinism, intellectual disability, chondrodysplasia punctata, and short stature.

DNA rearrangements can also take place in **somatic cells** (cells that do not go on to produce ova or sperm). Rearrangements that occur in **lymphoid** cells are required for the formation of functional immunoglobulin in B cells and antigen-recognizing receptors on T cells. Large segments of DNA, which code for the variable and the constant regions of either immunoglobulin or the T-cell receptor (TCR), are physically joined at a specific stage in the development of an immunocompetent lymphocyte. These rearrangements take place during development of the lymphoid cell lineage in humans and result in the extensive diversity of immunoglobulin and TCR molecules. Because of this postgermline DNA rearrangement, no 2 individuals, not even identical twins, are really identical, because mature lymphocytes from each will have undergone random DNA rearrangements at these loci.

Studies of the human genome sequence reveal that any 2 individuals differ in about 1 base in 1,000. Some of these differences are silent; some result in changes that explain phenotypic differences (hair or eye color, physical appearance); some have medical significance, causing single-gene disorders such as sickle cell anemia or explaining susceptibility to common pediatric disorders such as asthma. Genetic variants in a single gene that occur at a frequency of >1% in a population are often referred to as **polymorphisms** . These variations may be silent or subtle or may have significant phenotypic effects.

Genotype-Phenotype Correlations in Genetic Disease

The term **genotype** is used to signify the internally coded, heritable information of an individual and can also be used to refer to which particular alternative version (**allele**) of a gene is present at a specific location (**locus**) on a chromosome. A **phenotype** is the observed structural, biochemical, and physiologic characteristics of an individual, determined by the genotype, and can also refer to the observed structural and functional effects of a variant allele at a specific locus. Many sequence variants result in predictable phenotypes. In these cases, physicians can predict clinical outcomes and plan appropriate treatment strategies based on a patient's genotype. Increasingly, there is phenotypic expansion where multiple alleles (variants) within a gene can be associated with often diverse and distinct clinical presentations.

The **long QT syndrome** exemplifies a disorder with predictable associations between a patient's genotype and his or her phenotype (see Chapter 462.5). Long QT syndrome is genetically heterogeneous, meaning that pathogenic variants in several different genes can cause the same disorder. The risk for cardiac events (syncope, aborted cardiac arrest, or sudden death) is higher in patients with long QT syndrome involving the *KCNQ1* gene (63%) or *KCNH2* (46%) than in those with pathogenic variants in *SCN5A* (18%). In addition, those with *KCNQ1* variants experience most of their episodes during exercise and rarely during rest or sleep. In contrast, individuals with pathogenic variants in *KCNH2* and *SCN5A* are more likely to have episodes during sleep or rest and rarely during exercise. Therefore, variants in specific genes (genotype) are correlated with specific manifestations (phenotype) of long QT syndrome. These types of relationships are commonly referred to as *genotype-phenotype correlations.*

Pathogenic variants in the fibrillin-1 gene associated with **Marfan syndrome** represent another example of predictable genotype-phenotype correlations (see Chapter 722). Marfan syndrome is characterized by the combination of skeletal, ocular, and aortic manifestations, with the most devastating outcome being aortic root dissection and sudden death. The fibrillin-1 gene consists of 65 exons, and mutations have been found in almost all these. The location of the mutation within the gene (genotype) might play a significant role in determining the severity of the condition (phenotype). Neonatal Marfan syndrome is caused by mutations in exons 24-27 and in exons 31 and 32, whereas milder forms are caused by mutations in exons 59-65 and in exons 37 and 41.

Genotype-phenotype correlations have also been observed in some complications of **cystic fibrosis** (CF; see Chapter 432). Although pulmonary disease is the major cause of morbidity and mortality, CF is a multisystem disorder that affects not only the epithelia of the respiratory tract but also the exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands. CF is caused by pathologic variants in the CF transmembrane conductance regulator (*CFTR*) gene; >1,600 different pathogenic variants have been identified. The most common is a deletion of 3 nucleotides that removes the amino acid phenylalanine (F) at the 508th position on the protein (ΔF508 variant), which accounts for approximately 70% of all pathogenic CF variants and is associated with severe disease. The best genotype-phenotype correlations in CF are seen in the context of pancreatic function, with most common mutations being classified as either *pancreatic sufficient* or *pancreatic insufficient.* Persons with pancreatic sufficiency usually have either 1 or 2 pancreatic-sufficient alleles, indicating that pancreatic-sufficient alleles are dominant. In contrast, the genotype-phenotype correlation in pulmonary disease is much weaker, and persons with identical genotypes have wide variations in the severity of their pulmonary disease. This finding may be accounted for in part by genetic modifiers or environmental factors.

In many disorders the effects of variants on phenotype can be modified by changes in the other allele of the same gene, by changes in specific **modifier genes** , and/or by variations in a number of unspecified genes (**genetic background**). When sickle cell anemia is co-inherited with the gene for hereditary persistence of fetal hemoglobin, the sickle cell phenotypic expression is less severe. Modifier genes in CF can influence the development of congenital meconium ileus, or colonization with *Pseudomonas aeruginosa.* Modifier genes can also affect the manifestations of Hirschsprung disease, neurofibromatosis type 2, craniosynostosis, and congenital adrenal hyperplasia. The combination of genetic variants producing glucose-6-phosphate dehydrogenase deficiency and longer versions of the TATAA element in the uridine diphosphate–glucuronosyltransferase gene promoter exacerbates neonatal physiologic hyperbilirubinemia.

Human Genome Project

A rudimentary genetic map can be made using genetic linkage, which is based on the principle that alleles at 2 genetic loci that are located near each other segregate together in a family unless they are separated by genetic **recombination** . The frequency of recombination between the loci can be used to estimate the physical distance between points. Some of the first maps of the human genome were linkage maps based on a set of polymorphic genetic loci located along the entire human genome. Linkage analysis is still used to map the location of genetic changes responsible for phenotypic traits and genetic disorders that are inherited in a mendelian fashion.

In contrast to linkage maps, which are based on recombination frequencies, physical maps rely on overlapping DNA fragments to determine the location of loci with respect to one another. Several strategies can be used to create physical maps of a chromosomal region. In one strategy, segments of the region of interest with lengths from hundreds or thousands to a few million base pairs are isolated and placed in microorganisms such as bacteria or yeast. Common regions contained in different organisms can then be identified and this information used to piece together a map composed of overlapping DNA pieces, each contained in a different microorganism. The pieces contained in each organism can then be sequenced to obtain the DNA sequence of the entire region. An alternative strategy involves breaking the entire genome into random fragments, sequencing the fragments, and then using a computer to order the fragments based on overlapping segments. This whole genome approach in combination with new next-generation sequencing technologies has resulted in a dramatic reduction in the cost of sequencing an individual's entire genome.

Analysis of the human genome has produced some surprising results. The number of genes appears to be about 20,000. This is fewer than had been expected and is in the same range as many simpler organisms. *The number of protein products encoded by the genome is greater than the number of genes.* This is a result of the presence of alternative promoter regions, alternative splicing, and posttranslational modifications, which can allow a single gene to encode a number of protein products.

It is also apparent that most of the human genome does not encode protein, with <5% being transcribed and translated, although a much larger percentage may be transcribed without translation. Many transcribed sequences are not translated but represent genes that encode RNAs that serve a regulatory role. A large fraction of the genome consists of repeated sequences that are interspersed among the genes. Some of these are transposable genetic elements that can move from place to place in the genome. Others are static elements that were expanded and dispersed in the past during human evolution. Other repeated sequences might play a structural role. There are also regions of genomic duplications. Such duplications are substrate for evolution, allowing genetic motifs to be copied and modified to serve new roles in the cell. Duplications can also play a role in chromosomal rearrangement, permitting nonhomologous chromosome segments to pair during meiosis and exchange material. This is another source of evolutionary change and a potential source of chromosomal instability leading to congenital anomalies or cancer. Low copy repeats also play an important role in causing genomic disorders. When low copy repeats flank unique genomic segments, these regions can be duplicated or deleted through a process known as *nonallelic homologous recombination.*

Availability of the entire human genomic sequence permits the study of large groups of genes, looking for patterns of gene expression or genome alteration. Microarrays permit the expression of thousands of genes to be analyzed on a small glass chip. Increasingly, studies of gene expression are being performed using next generation sequencing techniques to obtain information about all of the RNA transcripts in a tissue sample. In some cases the patterns of gene expression provide signatures for particular disease states, such as cancer, or change in response to therapy (Fig. 96.5).

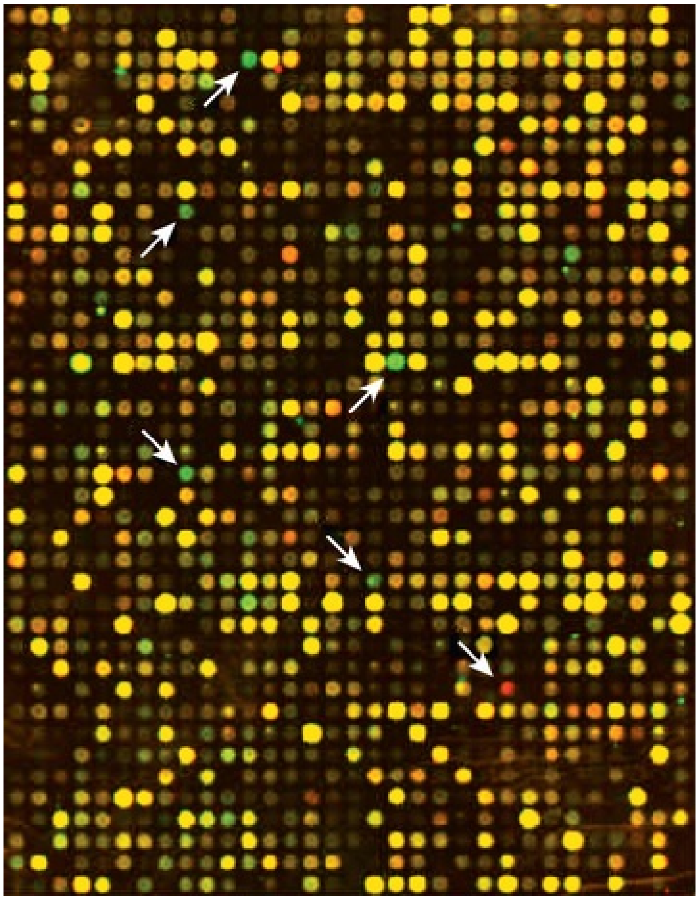

FIG. 96.5 **Microarray containing 36,000 oligonucleotides. The microarray was exposed to RNA from normal fibroblasts (labeled in *red* ; see *arrows*) and fibroblasts from a**

patient with Niemann-Pick disease, type C (labeled *green*). *Arrows* point to regions in which there was a strong hybridization signal with either normal or disease RNA. This microarray was used to search for genes that are highly expressed in the fibroblasts of patients. (From Jorde LB, Carey JC, Bamshad MJ, et al, editors: *Medical genetics* , ed 3, St Louis, 2006, Mosby, p 116.)

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CHAPTER 97

Patterns of Genetic Transmission

Daryl A. Scott, Brendan Lee

Family History and Pedigree Notation

The family history remains the most important screening tool for pediatricians in identifying a patient's risk for developing a wide range of diseases, from multifactorial conditions such as diabetes and attention-deficit/hyperactivity disorder, to single-gene disorders such as sickle cell anemia and cystic fibrosis. Through a detailed family history, the physician can often ascertain the mode of genetic transmission and the risks to family members. Because not all familial clustering of disease is caused by genetic factors, a family history can also identify common environmental and behavioral factors that influence the occurrence of disease. The main goal of the family history is to identify genetic susceptibility, and the cornerstone of the family history is a systematic and standardized pedigree.

A **pedigree** provides a graphic depiction of a family's structure and medical history. It is important when taking a pedigree to be systematic and use standard symbols and configurations so that anyone can read and understand the information (Figs. 97.1 to 97.4). In the pediatric setting, the **proband** is typically the child or adolescent who is being evaluated. The proband is designated in the pedigree by an arrow.

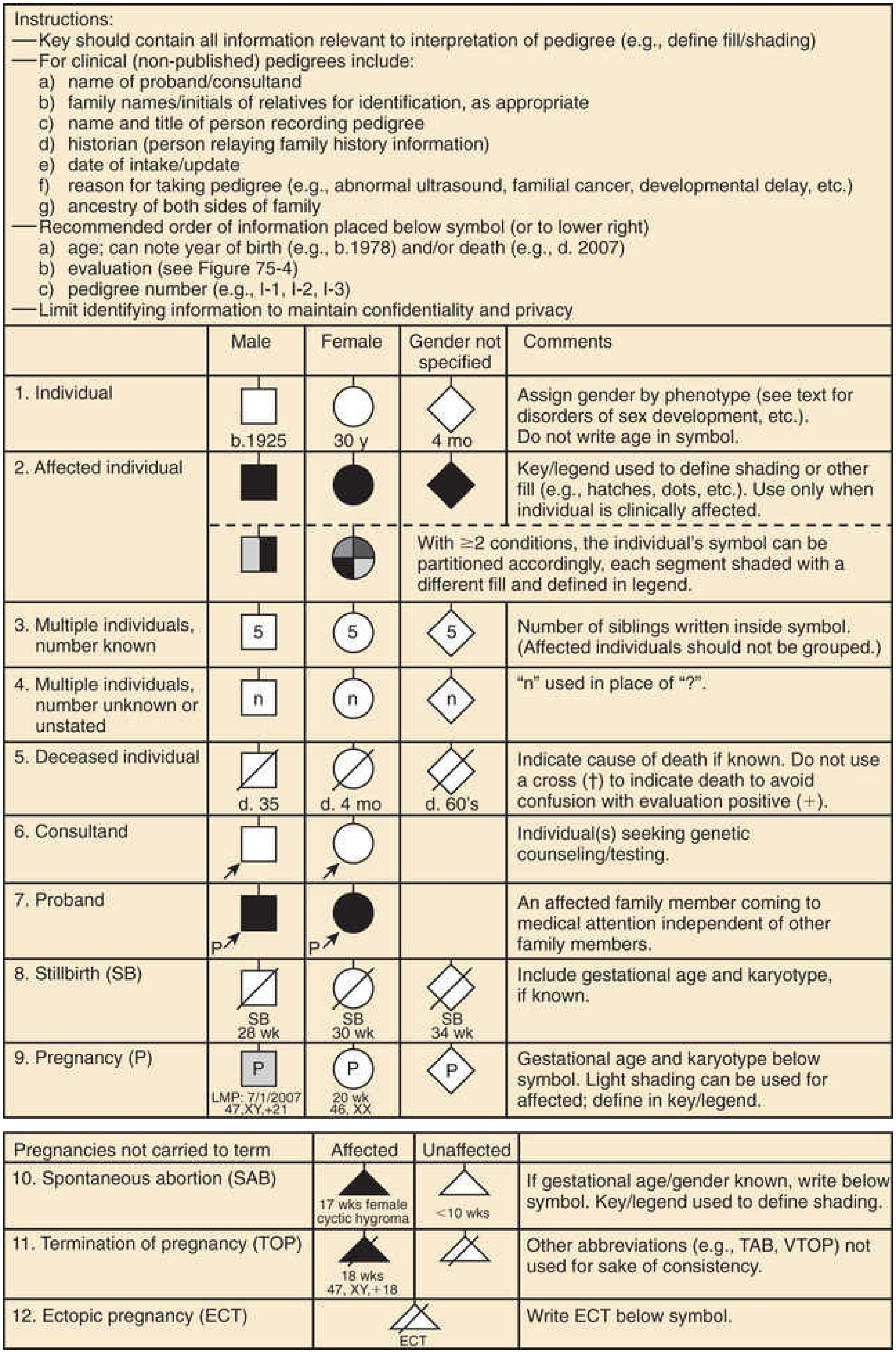

Instructions:
- Key should contain all information relevant to interpretation of pedigree (e.g., define fill/shading)
- For clinical (non-published) pedigrees include:
  - a) name of proband/consultand
  - b) family names/initials of relatives for identification, as appropriate
  - c) name and title of person recording pedigree
  - d) historian (person relaying family history information)
  - e) date of intake/update
  - f) reason for taking pedigree (e.g., abnormal ultrasound, familial cancer, developmental delay, etc.)
  - g) ancestry of both sides of family
- Recommended order of information placed below symbol (or to lower right)
  - a) age; can note year of birth (e.g., b.1978) and/or death (e.g., d. 2007)
  - b) evaluation (see Figure 75-4)
  - c) pedigree number (e.g., I-1, I-2, I-3)
- Limit identifying information to maintain confidentiality and privacy

	Male	Female	Gender not specified	Comments
1. Individual	□ b.1925	○ 30 y	◇ 4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.
2. Affected individual	■	●	◆	Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.
	◧	◕	With ≥2 conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.	
3. Multiple individuals, number known	5	5	5	Number of siblings written inside symbol. (Affected individuals should not be grouped.)
4. Multiple individuals, number unknown or unstated	n	n	n	"n" used in place of "?".
5. Deceased individual	⧄ d. 35	⊘ d. 4 mo	◇ d. 60's	Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).
6. Consultand	↗□	↗○		Individual(s) seeking genetic counseling/testing.
7. Proband	P↗■	P↗●		An affected family member coming to medical attention independent of other family members.
8. Stillbirth (SB)	⧄ SB 28 wk	⊘ SB 30 wk	◇ SB 34 wk	Include gestational age and karyotype, if known.
9. Pregnancy (P)	P LMP: 7/1/2007 47,XY,+21	P 20 wk 46, XX	P	Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.

Pregnancies not carried to term	Affected	Unaffected	
10. Spontaneous abortion (SAB)	▲ 17 wks female cyctic hygroma	△ <10 wks	If gestational age/gender known, write below symbol. Key/legend used to define shading.
11. Termination of pregnancy (TOP)	▲ 18 wks 47, XY,+18	△	Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.
12. Ectopic pregnancy (ECT)	△ ECT		Write ECT below symbol.

FIG. 97.1 Common pedigree symbols, definitions, and abbreviations. (From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, *J Genet Couns* 17:424–433, 2008.)

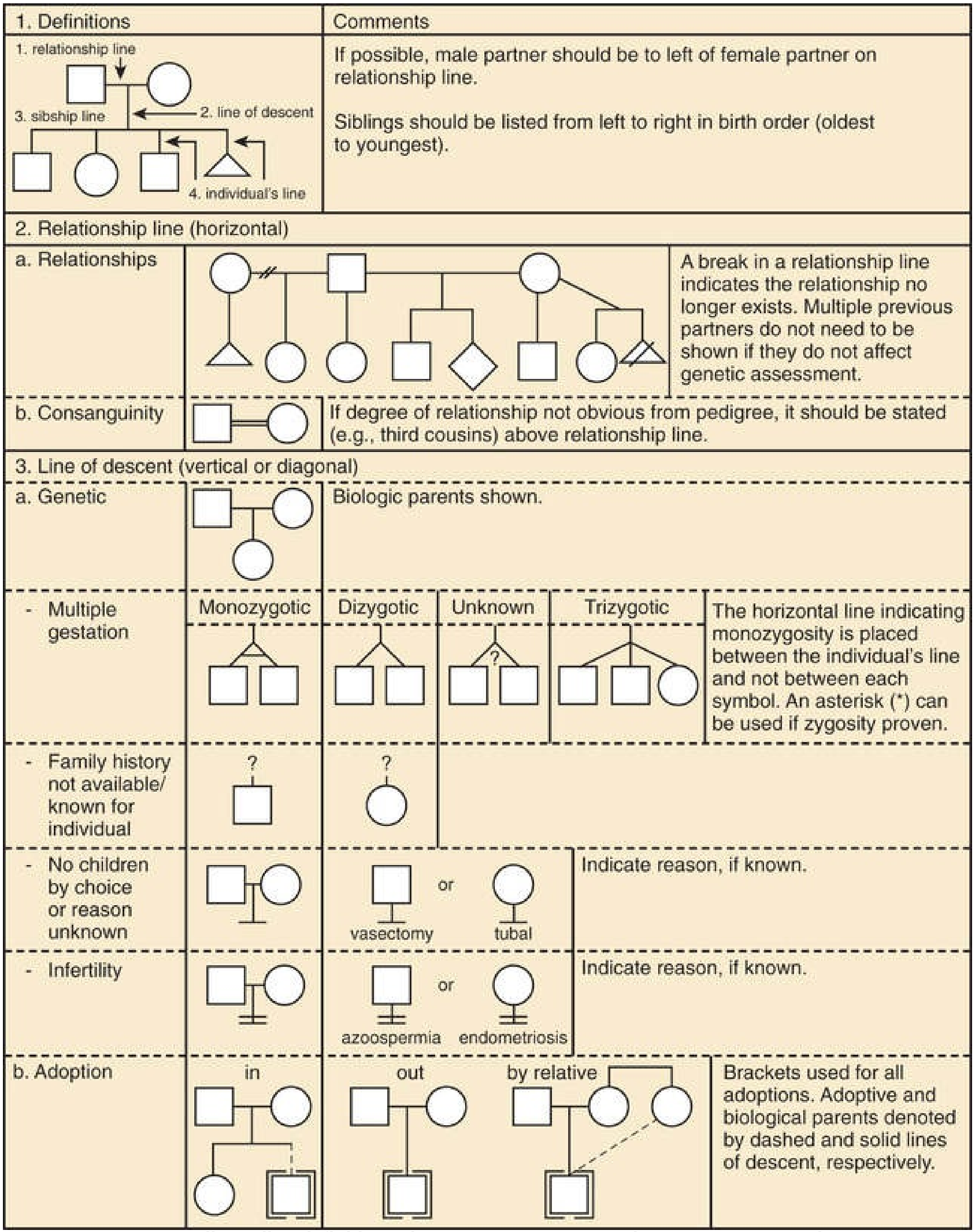
1. Definitions
Comments
1. relationship line
2. line of descent
3. sibship line
4. individual's line
2. Relationship line (horizontal)
a. Relationships
b. Consanguinity
3. Line of descent (vertical or diagonal)
a. Genetic
- Multiple gestation
Monozygotic
Dizygotic
Unknown
Trizygotic
?
- Family history not available/ known for individual
?
?
- No children by choice or reason unknown
or
vasectomy
tubal
- Infertility
or
azoospermia
endometriosis
b. Adoption
in
out
by relative

If possible, male partner should be to left of female partner on relationship line.

Siblings should be listed from left to right in birth order (oldest to youngest).

A break in a relationship line indicates the relationship no longer exists. Multiple previous partners do not need to be shown if they do not affect genetic assessment.

If degree of relationship not obvious from pedigree, it should be stated (e.g., third cousins) above relationship line.

Biologic parents shown.

The horizontal line indicating monozygosity is placed between the individual's line and not between each symbol. An asterisk (*) can be used if zygosity proven.

Indicate reason, if known.

Indicate reason, if known.

Brackets used for all adoptions. Adoptive and biological parents denoted by dashed and solid lines of descent, respectively.

FIG. 97.2 Pedigree line definitions. (From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, *J Genet Couns* 17:424–433, 2008.)

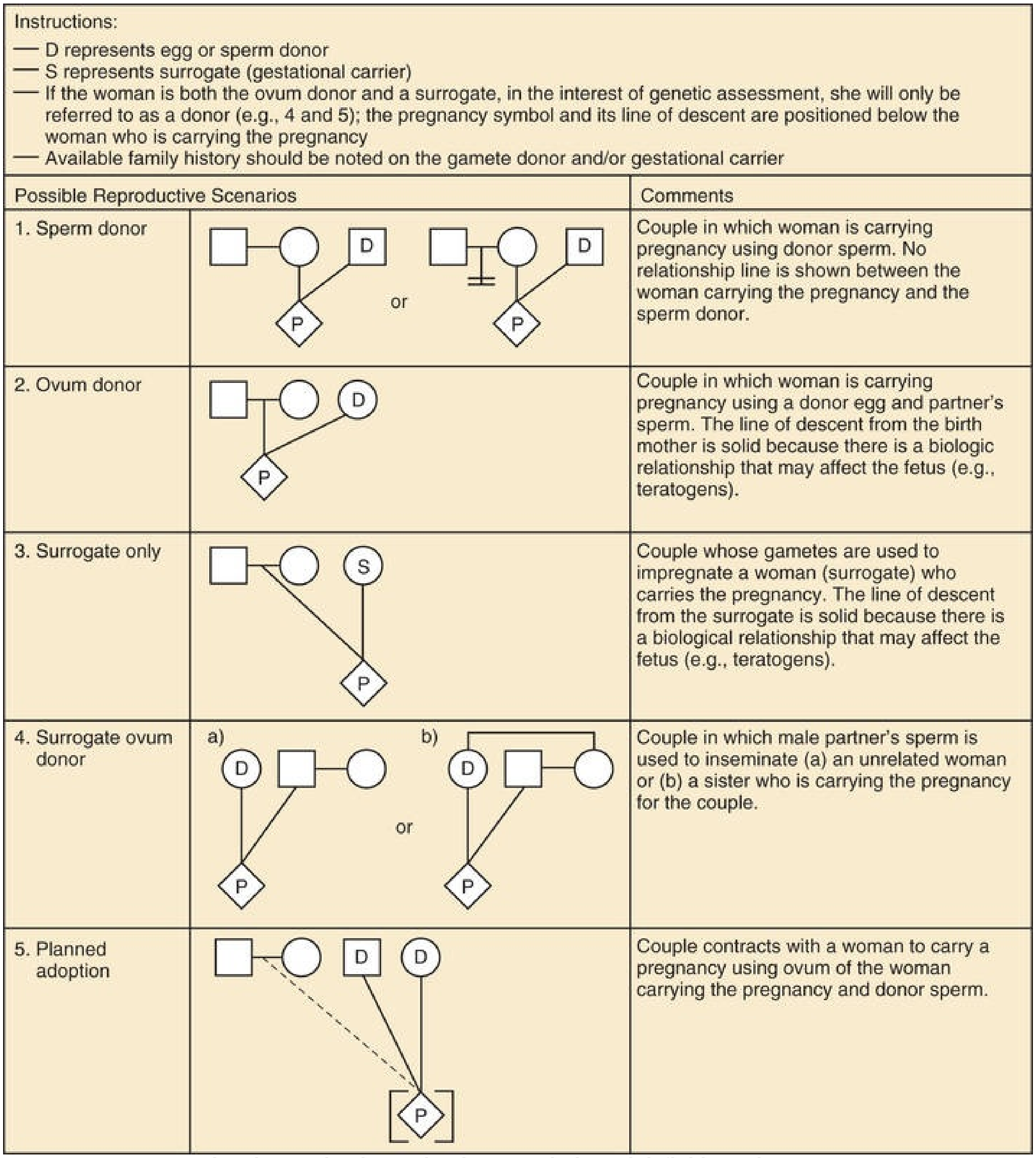

Instructions:

- D represents egg or sperm donor
- S represents surrogate (gestational carrier)
- If the woman is both the ovum donor and a surrogate, in the interest of genetic assessment, she will only be referred to as a donor (e.g., 4 and 5); the pregnancy symbol and its line of descent are positioned below the woman who is carrying the pregnancy
- Available family history should be noted on the gamete donor and/or gestational carrier

Possible Reproductive Scenarios		Comments
1. Sperm donor		Couple in which woman is carrying pregnancy using donor sperm. No relationship line is shown between the woman carrying the pregnancy and the sperm donor.
2. Ovum donor		Couple in which woman is carrying pregnancy using a donor egg and partner's sperm. The line of descent from the birth mother is solid because there is a biologic relationship that may affect the fetus (e.g., teratogens).
3. Surrogate only		Couple whose gametes are used to impregnate a woman (surrogate) who carries the pregnancy. The line of descent from the surrogate is solid because there is a biological relationship that may affect the fetus (e.g., teratogens).
4. Surrogate ovum donor		Couple in which male partner's sperm is used to inseminate (a) an unrelated woman or (b) a sister who is carrying the pregnancy for the couple.
5. Planned adoption		Couple contracts with a woman to carry a pregnancy using ovum of the woman carrying the pregnancy and donor sperm.

FIG. 97.3 **Assisted reproductive technology symbols and definitions. (From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, *J Genet Couns* 17:424–433, 2008.)**

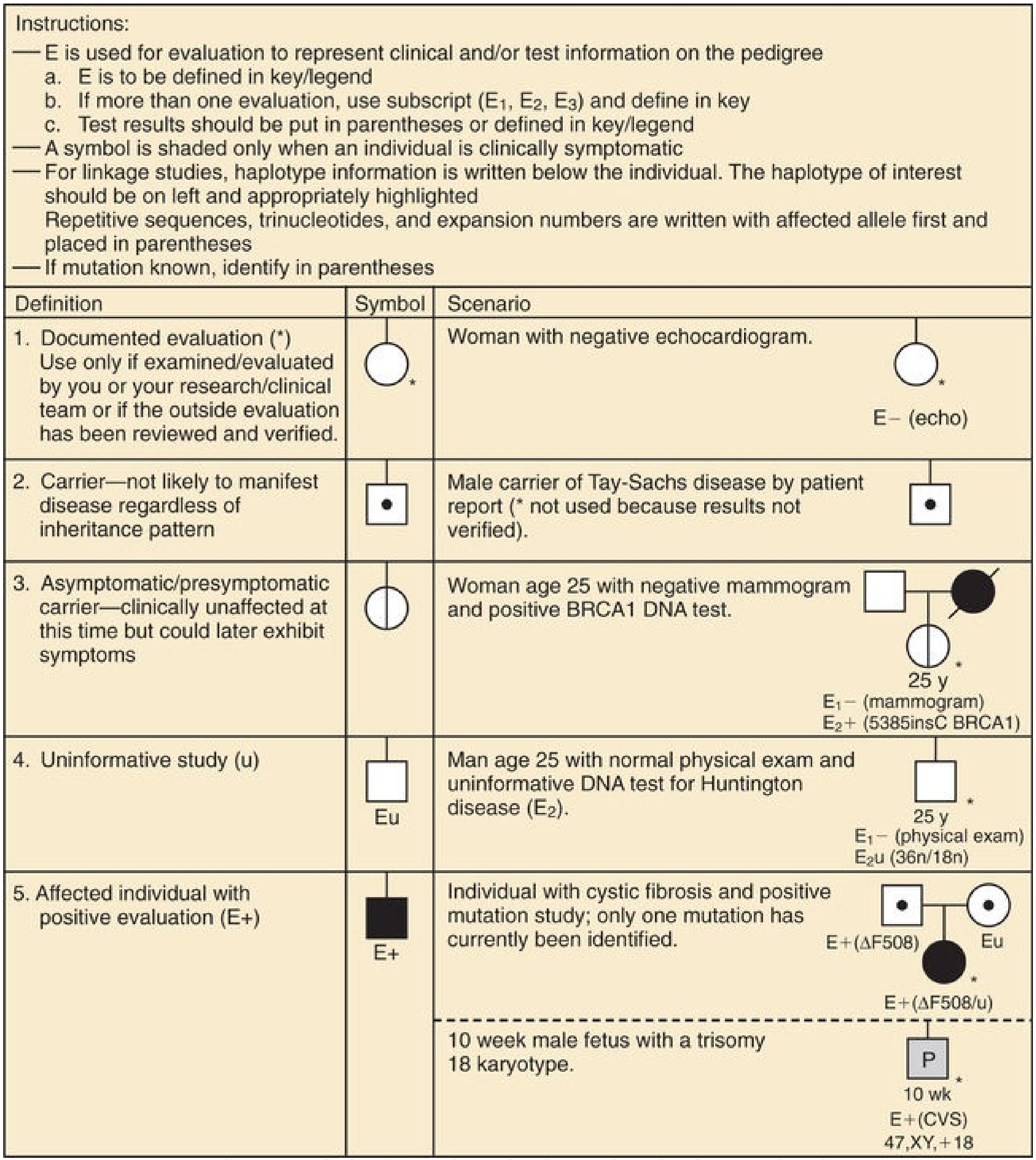

Instructions:

— E is used for evaluation to represent clinical and/or test information on the pedigree
  a. E is to be defined in key/legend
  b. If more than one evaluation, use subscript (E_1, E_2, E_3) and define in key
  c. Test results should be put in parentheses or defined in key/legend
— A symbol is shaded only when an individual is clinically symptomatic
— For linkage studies, haplotype information is written below the individual. The haplotype of interest should be on left and appropriately highlighted
  Repetitive sequences, trinucleotides, and expansion numbers are written with affected allele first and placed in parentheses
— If mutation known, identify in parentheses

Definition	Symbol	Scenario
1. Documented evaluation (*) Use only if examined/evaluated by you or your research/clinical team or if the outside evaluation has been reviewed and verified.	*	Woman with negative echocardiogram. * E− (echo)
2. Carrier—not likely to manifest disease regardless of inheritance pattern		Male carrier of Tay-Sachs disease by patient report (* not used because results not verified).
3. Asymptomatic/presymptomatic carrier—clinically unaffected at this time but could later exhibit symptoms		Woman age 25 with negative mammogram and positive BRCA1 DNA test. * 25 y E_1− (mammogram) E_2+ (5385insC BRCA1)
4. Uninformative study (u)	Eu	Man age 25 with normal physical exam and uninformative DNA test for Huntington disease (E_2). * 25 y E_1− (physical exam) E_2u (36n/18n)
5. Affected individual with positive evaluation (E+)	E+	Individual with cystic fibrosis and positive mutation study; only one mutation has currently been identified. E+(ΔF508) Eu * E+(ΔF508/u)
		10 week male fetus with a trisomy 18 karyotype. P * 10 wk E+(CVS) 47,XY,+18

FIG. 97.4 **Pedigree symbols of genetic evaluation and testing information. (From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors, *J Genet Couns* 17:424–433, 2008.)**

A 3 to 4–generation pedigree should be obtained for every new patient as an initial screen for genetic disorders segregating within the family. The pedigree can provide clues to the inheritance pattern of these disorders and can aid the clinician in determining the risk to the proband and other family members. The closer the relationship of the proband to the person in the family with the genetic disorder, the greater is the shared genetic complement. **First-degree** relatives, such as a parent, full sibling, or child, share one-half their genetic information on average; first cousins share one-eighth. Sometimes the person providing the family history may mention a distant relative who is affected with a genetic disorder. In such cases a more extensive pedigree may be needed to identify the risk to other family members. For example, a history of a distant maternally related cousin with intellectual disability caused by fragile X syndrome can still place a male proband at an elevated risk for this disorder.

Mendelian Inheritance

There are 3 classic forms of genetic inheritance: **autosomal dominant, autosomal recessive,** and **X-linked** . These are referred to as **mendelian inheritance** forms, after Gregor Mendel, the 19th-century monk whose experiments led to the laws of **segregation of characteristics, dominance,** and **independent assortment** . These remain the foundation of single-gene inheritance.

Autosomal Dominant Inheritance

Autosomal dominant inheritance is determined by the presence of one abnormal gene on one of the **autosomes** (chromosomes 1-22). Autosomal genes exist in pairs, with each parent contributing 1 copy. In an autosomal dominant trait, a change in 1 of the paired genes affects the phenotype of an individual, even though the other copy of the gene is functioning correctly. A **phenotype** can refer to a physical manifestation, a behavioral characteristic, or a difference detectable only through laboratory tests.

The pedigree for autosomal dominant disorders demonstrates certain characteristics. These disorders show a **vertical transmission** (parent-to-child) pattern and can appear in multiple generations. In Fig. 97.5 , this is illustrated by individual I.1 passing on the changed gene to II.2 and II.5. An affected individual has a 50% (1 in 2) chance of passing on the deleterious gene in *each* pregnancy and, therefore, of having a child affected by the disorder. This is referred to as the **recurrence risk** for the disorder. Unaffected individuals (family members who do not manifest the trait and do not harbor a copy of the deleterious gene) do not pass the disorder to their children. Males and females are equally affected.

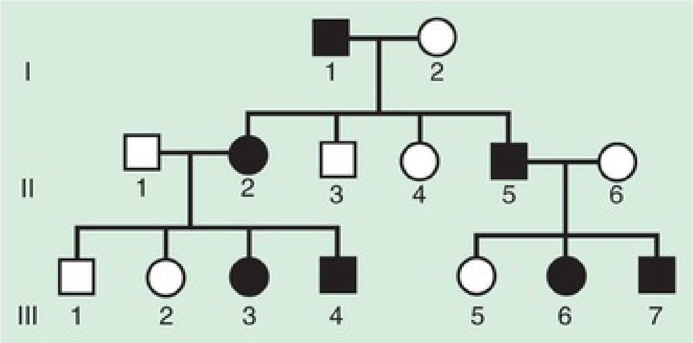

FIG. 97.5 **Autosomal dominant pedigree. Pedigree showing typical inheritance of a form of achondroplasia *(FGFR3)* inherited as an autosomal dominant trait. *Black,* Affected patients.**

Although not a characteristic per se, the finding of male-to-male transmission essentially confirms autosomal dominant inheritance. Vertical transmission can also be seen with X-linked traits. However, because a father passes on his Y chromosome to a son, male-to-male transmission cannot be seen with an X-linked trait. Therefore, male-to-male transmission eliminates X-linked inheritance as a possible explanation. Although male-to-male transmission can occur with Y-linked genes as well, there are very few **Y-linked** disorders, compared with thousands having the autosomal dominant inheritance pattern.

Although parent-to-child transmission is a characteristic of autosomal dominant inheritance, many patients with an autosomal dominant disorder have no history of an affected family member, for several possible reasons. First, the patient may have the disorder due to a **de novo** (new) mutation that occurred in the DNA of the egg or sperm that formed that individual. Second, many autosomal dominant conditions demonstrate **incomplete penetrance** , meaning that not all individuals who carry the mutation have phenotypic manifestations. In a pedigree this can appear as a **skipped generation** , in which an unaffected individual links 2 affected persons (Fig. 97.6). There are many potential reasons that a disorder might exhibit incomplete penetrance, including the effect of modifier genes, environmental factors, gender, and age. Third, individuals with the same autosomal dominant variant can manifest the disorder to different degrees. This is termed **variable expression** and is a characteristic of many autosomal dominant disorders. Fourth, some spontaneous genetic mutations occur not in the egg or sperm that forms a child, but rather in a *cell* in the developing embryo. Such events are referred to as **somatic mutations** , and because not all cells are affected, the change is said to be **mosaic** . The phenotype caused by a somatic mutation can vary but is usually milder than if all cells were affected by the mutation. In **germline mosaicism** the mutation occurs in cells that populate the germline that produces eggs or sperm. An individual who is germline mosaic might not have any manifestations of the disorder but may produce multiple eggs or sperm that are affected by the mutation.

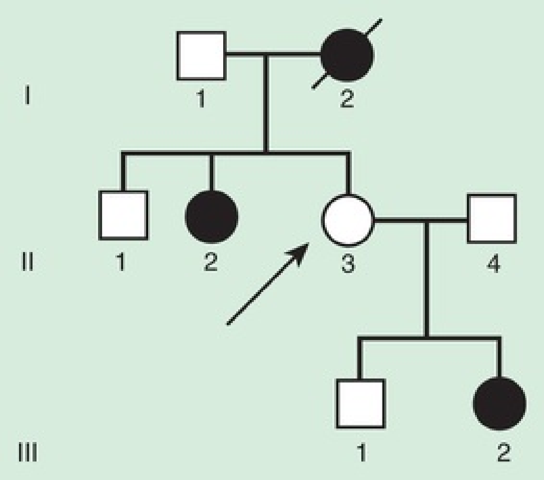

FIG. 97.6 **Incomplete penetrance. This family segregates a familial cancer syndrome, familial adenomatous polyposis. Individual II.3 is an obligate carrier, but there are no findings to suggest the disorder. This disorder is nonpenetrant in this individual. *Black,* Affected patients.**

Autosomal Recessive Inheritance

Autosomal recessive inheritance requires deleterious variants in both copies of a gene to cause disease. Examples include cystic fibrosis and sickle cell disease. Autosomal recessive disorders are characterized by **horizontal transmission** , the observation of multiple affected members of a kindred in the same generation, but no affected family members in other generations (Fig. 97.7). They are associated with a recurrence risk of 25% for carrier parents who have had a previous affected child. Male and female offspring are equally likely to be affected, although some traits exhibit differential expression between sexes. The offspring of consanguineous parents are at increased risk for rare, autosomal recessive traits due to the increased chance that that both parents may carry a gene affected by a deleterious mutation that they inherited from a common ancestor. **Consanguinity** between parents of a child with a suspected genetic disorder implies, but certainly does not prove, autosomal recessive inheritance. Although consanguineous unions are uncommon in Western society, in other parts of the world (southern India, Japan, and the Middle East) as high as 50% of all children may be conceived in consanguineous unions. The risk of a genetic disorder for the offspring of a first-cousin union (6–8%) is about double the risk in the general population (3–4%).

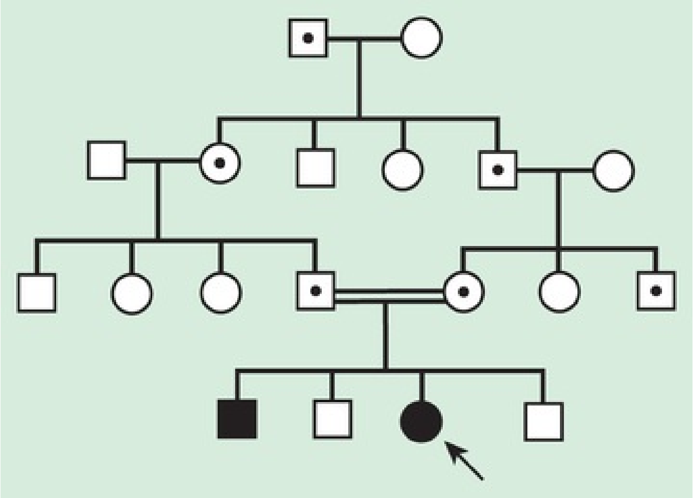

FIG. 97.7 **Autosomal recessive pedigree with parental consanguinity. *Central dot,* Carriers; *Black,* Affected patients.**

Every individual probably has several rare, deleterious recessive pathogenic sequence variants. Because most pathogenic variants carried in the general population occur at a very low frequency, it does not make economic sense to screen the entire population in order to identify the small number of persons who carry these variants. As a result, these variants typically remain undetected unless an affected child is born to a couple who both carry pathogenic variants affecting the same gene.

However, in some **genetic isolates** (small populations isolated by geography, religion, culture, or language), certain rare recessive pathogenic variants are much more common than in the general population. Even though there may be no known consanguinity, couples from these genetic isolates have a greater chance of sharing pathogenic alleles inherited from a common ancestor. Screening programs have been developed among some such groups to detect persons who carry common disease-causing variants and therefore are at increased risk for having affected children. A variety of autosomal recessive conditions are more common among Ashkenazi Jews than in the general population. Couples of Ashkenazi Jewish ancestry should be offered prenatal or preconception screening for Gaucher disease type 1 (carrier rate 1 : 14), cystic fibrosis (1 : 25), Tay-Sachs disease (1 : 25), familial dysautonomia (1 : 30), Canavan disease (1 : 40), glycogen storage disease type 1A (1 : 71), maple syrup urine disease (1 : 81), Fanconi anemia type C (1 : 89), Niemann-Pick disease type A (1 : 90), Bloom syndrome (1 : 100), mucolipidosis IV (1 : 120), and possibly neonatal familial hyperinsulinemic hypoglycemia.

The prevalence of carriers of certain autosomal recessive variants in some larger populations is unusually high. In such cases, **heterozygote advantage** is postulated. The carrier frequencies of sickle cell disease in the African population and of cystic fibrosis in the northern European population are much higher than would be expected from the rate of new mutations. In these populations, heterozygous carriers may have had an advantage in terms of survival and reproduction over noncarriers. In sickle cell disease the carrier state is thought to confer some resistance to malaria; in cystic fibrosis the carrier state has been postulated to confer resistance to cholera or enteropathogenic *Escherichia coli* infections. Population-based **carrier screening** for cystic fibrosis is recommended for persons of northern European and Ashkenazi Jewish ancestry; population-based screening for sickle cell disease is recommended for persons of African ancestry.

If the frequency of an autosomal recessive disease is known, the frequency of the heterozygote or carrier state can be calculated from the **Hardy-Weinberg formula:**

$$p^2 + 2pq + q^2 = 1$$

where *p* is the frequency of one of a pair of alleles and *q* is the frequency of the other. For example, if the frequency of cystic fibrosis among white Americans is 1 in 2,500 (p^2), then the frequency of the heterozygote (2pq) can be calculated: If $p^2 = 1/2{,}500$, then $p = 1/50$ and $q = 49/50$; $2pq = 2 \times (1/50) \times (49/50) = 98/2500$, or 3.92%.

Pseudodominant Inheritance

Pseudodominant inheritance refers to the observation of apparent dominant (parent to child) transmission of a known autosomal recessive disorder (Fig. 97.8). This occurs when a homozygous affected individual has a partner who is a heterozygous carrier. This is most likely to occur for relatively common recessive traits within a population, such as sickle cell anemia or nonsyndromic autosomal recessive hearing loss caused by deleterious mutations in the *GJB2* , the gene that encodes connexin 26.

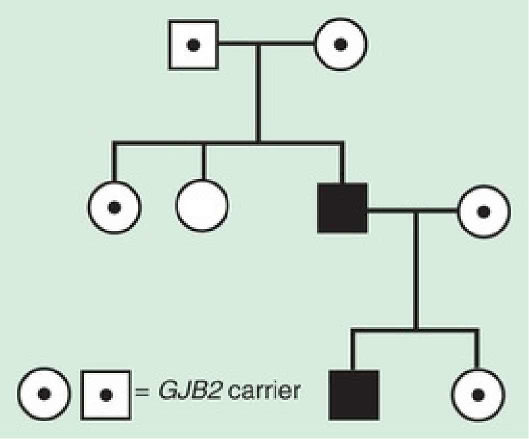

FIG. 97.8 **Pseudodominant inheritance. *Black,* Affected (deaf); *central dot* shows carrier who is asymptomatic (unaffected).**

X-Linked Inheritance

X-linked inheritance describes the inheritance pattern of most disorders caused by deleterious changes in genes located on the X chromosome (Fig. 97.9). In X-liked disorders, males are more commonly affected than females. Female carriers of these disorders are generally unaffected, or if affected, they are affected more mildly than males. In each pregnancy, female carriers have a 25% chance of having an affected son, a 25% chance of having a carrier daughter, and a 50% chance of having a child that does not inherit the mutated X-linked gene. Since affected males pass their X chromosome to all their daughters and their Y chromosome to all their sons, they have a 50% chance of having an unaffected son that does not carry the disease gene and a 50% chance of having a daughter who is a carrier. Male-to-male transmission excludes X-linked inheritance but is seen with autosomal dominant and Y-linked inheritance.

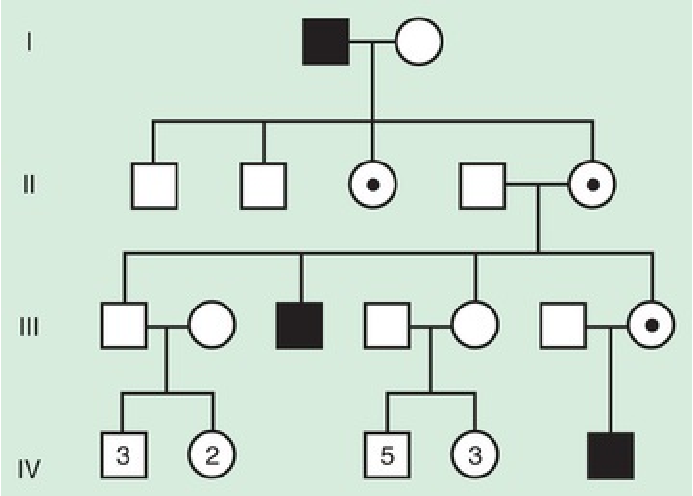

FIG. 97.9 Pedigree demonstrating X-linked recessive inheritance. *Central dot,* Carriers; *Black,* Affected patients.

A female occasionally exhibits signs of an X-linked trait similar to a male. This occurs rarely from homozygosity for an X-linked trait or the presence of a sex chromosome abnormality (45,X or 46,XY female) or skewed or nonrandom X-inactivation. **X chromosome inactivation** occurs early in development and involves the random and irreversible inactivation of most genes on one X chromosome in female cells (Fig. 97.10). In some cases, a preponderance of cells inactivates the same X chromosome, resulting in phenotypic expression of an X-linked pathogenic variant if it resides on the active chromosome. This can occur because of chance, selection against cells that have inactivated the X chromosome carrying the normal gene, or an X chromosome abnormality that results in inactivation of the X chromosome carrying the normal gene.

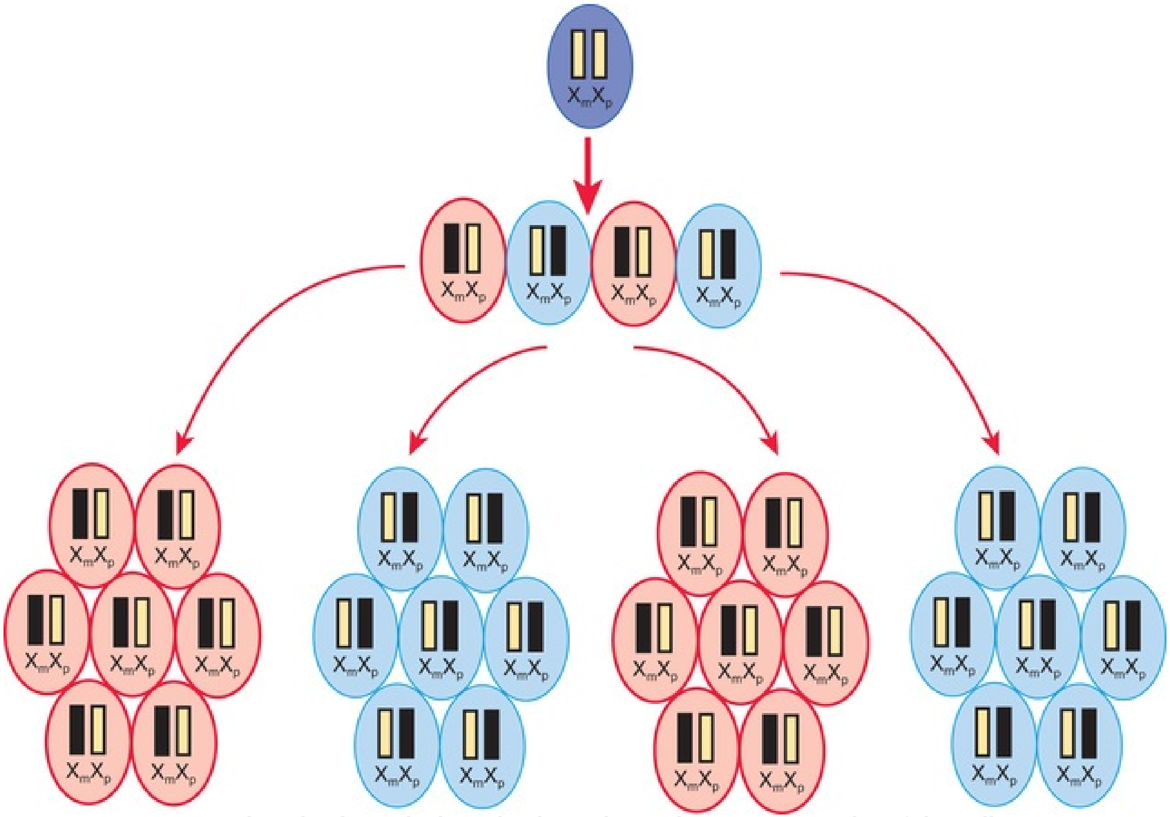
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FIG. 97.10 X-inactivation. *Black* marks the active X chromosome. Color of the cell represents its active X chromosome is paternally (X_p , *blue*) or maternally (X_m , *pink*) derived.

In some X-linked disorders, both **hemizygous** males and heterozygous females who carry an affected X–linked gene have similar phenotypic manifestations. In these cases, an affected male will have a 50% chance of having an affected daughter and a 50% chance of having an unaffected son in each pregnancy, whereas half the male and female offspring of an affected woman will be affected (Fig. 97.11). Some X-linked conditions are lethal in a high percentage of males, such as **incontinentia pigmenti** (see Chapter 614.7). In such cases the pedigree typically shows only affected females and an overall female/male ratio of 2 : 1, with an increased number of miscarriages (Fig. 97.12).

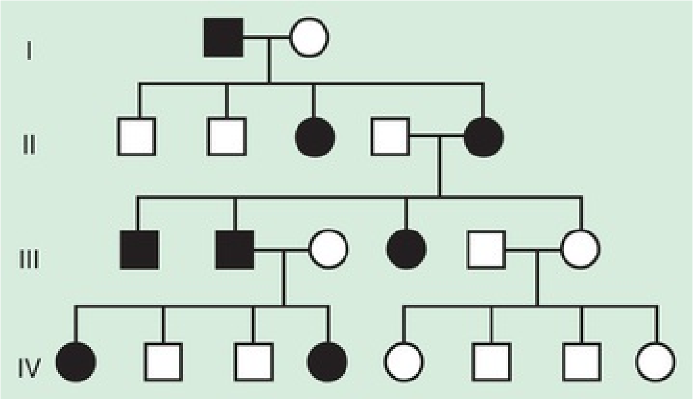

FIG. 97.11 Pedigree pattern demonstrating X-linked dominant inheritance. *Black,* Affected patients. Note there is no father-to-son transmission in this situation, and hemizygosity (i.e., X-linked gene in a male) is not lethal. In some X-linked dominant conditions, X-linked males have a more severe phenotype and might not survive. In that case, only females manifest the disease (see Fig. 97.12).

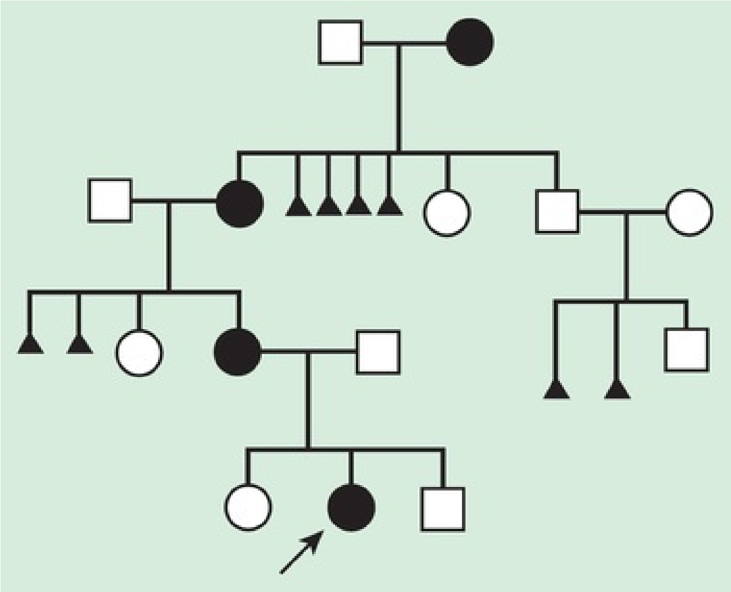

FIG. 97.12 Pedigree of an X-linked dominant disorder with male lethality, such as incontinentia pigmenti. *Black,* Affected patients.

Y-Linked Inheritance

There are few Y-linked traits. These demonstrate *only* male-to-male transmission, and only males are affected (Fig. 97.13). Most Y-linked genes are related to male sex determination and reproduction and are associated with infertility. Therefore, it is rare to see familial transmission of a Y-linked disorder. However, advances in assisted reproductive technologies might make it possible to have familial transmission of male infertility.

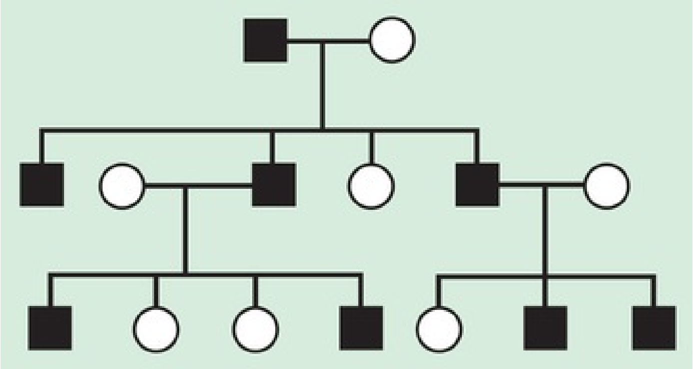

FIG. 97.13 Y-linked inheritance. *Black,* Affected patients.

Inheritance Associated With Pseudoautosomal Regions

Of special note are the pseudoautosomal regions on the X and Y chromosomes. Since these regions are made up of homologous sequences of nucleotides, genes that are located in these regions are present in equal numbers among both males and females. *SHOX* is one of the best-characterized disease genes located in these regions. Heterozygous *SHOX* mutations cause **Leri-Weil dyschondrosteosis** , a rare skeletal dysplasia that involves bilateral bowing of the forearms with dislocations of the ulna at the wrist and generalized short stature. Homozygous *SHOX* mutations cause the much more severe **Langer mesomelic dwarfism** .

Digenic Inheritance

Digenic inheritance explains the occurrence of **retinitis pigmentosa (RP)** in children of parents who each carry a pathogenic variant in a different RP-associated gene (Fig. 97.14). Both parents have normal vision, as would be expected, but their offspring who are **double heterozygotes** —having inherited both mutations—develop RP. Digenic pedigrees can exhibit characteristics of both autosomal dominant (vertical transmission) and autosomal recessive inheritance (1 in 4 recurrence risk). A couple in which the 2 unaffected partners are carriers for mutation in 2 different RP-associated genes that show digenic inheritance have a 1 in 4 risk of having an affected child, similar to what is seen in autosomal recessive inheritance. However, their affected children, and affected children in subsequent generations, have a 1 in 4 risk of transmitting both mutations to their offspring, who would be affected (vertical transmission).

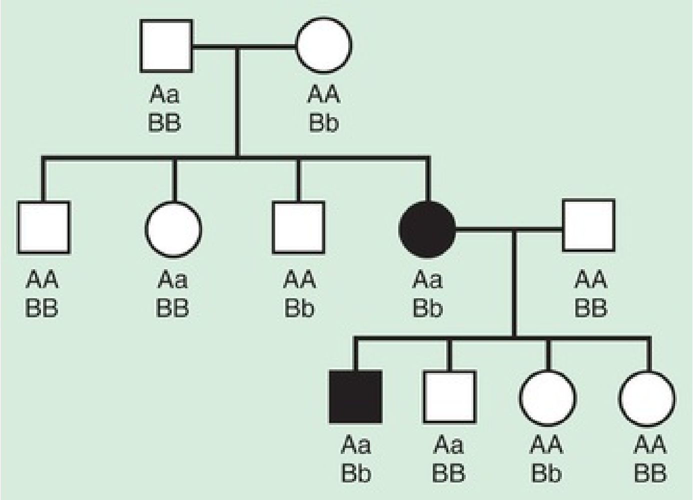

FIG. 97.14 **Digenic pedigree. Here, the disease alleles are *a* and *b* and they reside on distinct genetic loci or genes. For a person to have the disease, heterozygosity for mutant alleles in both genes (A/a; B/b) is required. *Black,* Affected patients.**

Pseudogenetic Inheritance and Familial Clustering

Sometimes nongenetic reasons for the occurrence of a particular disease in multiple family members can produce a pattern that mimics genetic transmission. These nongenetic factors can include identifiable environmental factors, teratogenic exposures, or as yet undetermined or undefined factors. Examples of identifiable factors might include multiple siblings in a family having asthma because of exposure to cigarette smoke from their parents or having failure to thrive, developmental delay, and unusual facial appearance caused by exposure to alcohol during pregnancy.

In some cases the disease is sufficiently common in the general population that some familial clustering occurs simply by chance. Breast cancer affects 11% of all women, and it is possible that several women in a family will develop breast cancer even in the absence of a genetic predisposition. However, hereditary breast cancer associated with mutations in *BRCA1* and *BRCA2* should be suspected in any individual who has a personal history of breast cancer with onset before age 50, early-onset breast and ovarian cancer at any age, bilateral or multifocal breast cancer, a family history of breast cancer or breast and ovarian cancer consistent with autosomal dominant inheritance, or a personal or family history of male breast cancer.

Nonetheless, such clustering within families may be caused by as yet undefined genetic factors or unidentified pathogenic sequence variants (nuclear or mitochondrial).

Nontraditional Inheritance

Some genetic disorders are inherited in a manner that does not follow classical mendelian patterns. Nontraditional inheritance is seen in mitochondrial disorders, triplet repeat expansion diseases, and imprinting defects.

Mitochondrial Inheritance

An individual's mitochondrial genome is entirely derived from the mother because sperm contain relatively few mitochondria, and these are degradated after fertilization. It follows that **mitochondrial inheritance** is essentially **maternal inheritance** . A woman with a mitochondrial genetic disorder can have affected offspring of either sex, but an affected father cannot pass on the disease to his offspring (Fig. 97.15). Mitochondrial DNA mutations are often deletions or point mutations; overall, 1 person in 400 has a maternally inherited pathogenic mitochondrial DNA mutation (see Chapter 106). In individual families, mitochondrial inheritance may be difficult to distinguish from autosomal dominant or X-linked inheritance, but in many cases, the sex of the transmitting and nontransmitting parents can suggest a mitochondrial basis (Table 97.1).

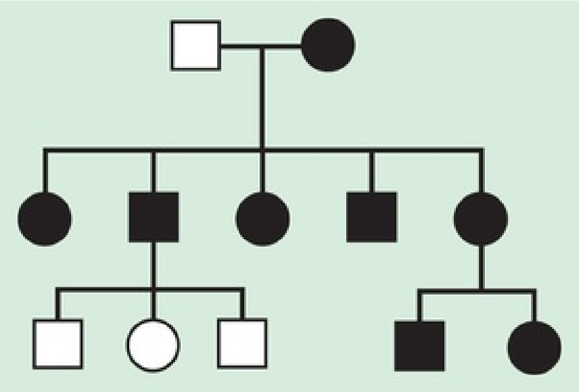

FIG. 97.15 Pedigree of a mitochondrial disorder, exhibiting maternal inheritance. *Black,* Affected patients.

Table 97.1

Representative Examples of Disorders Caused by Mutations in Mitochondrial DNA and Their Inheritance

DISEASE	PHENOTYPE	MOST FREQUENT MUTATION IN mtDNA MOLECULE	HOMOPLASMY vs HETEROPLASMY	INHERITANCE
Leber hereditary optic neuropathy	Rapid optic nerve atrophy, leading to blindness in young adult life; sex bias approximately 50% males with visual loss, only 10% females	Substitution p.Arg340His in *ND1* gene of complex I of electron transport chain; other complex I missense mutations	Homoplasmic (usually)	Maternal
NARP, Leigh disease	*N* europathy, *a* taxia, *r* etinitis *p* igmentosa, developmental delay, intellectual disability lactic academia	Point mutations in ATPase subunit 6 gene	Heteroplasmic	Maternal
MELAS	*M* itochondrial *e* ncephalomyopathy, *l* actic *a* cidosis, and *s* trokelike episodes; may manifest only as diabetes mellitus or deafness	Point mutation in tRNA^{Leu}	Heteroplasmic	Maternal
MERRF	*M* yoclonic *e* pilepsy, *r* agged *r* ed *f* ibers in muscle, ataxia, sensorineural deafness	Point mutation in tRNA^{Lys}	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics	m.1555A>G mutation in 12S rRNA	Homoplasmic	Maternal
	Nonsyndromic sensorineural deafness	m.7445A>G mutation in 12S rRNA	Homoplasmic	Maternal
Chronic	Progressive weakness of	The common MELAS	Heteroplasmic	Maternal if point

progressive external ophthalmoplegia (CPEO)	extraocular muscles, cardiomyopathy, ptosis, heart block, ataxia, retinal pigmentation, diabetes	point mutation in $tRNA^{Lys}$; large deletions similar to KSS		mutations
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis	Large deletions	Heteroplasmic	Sporadic, somatic mutations
Kearns-Sayre syndrome (KSS)	PEO of early onset with heart block, retinal pigmentation	5-kb large deletion	Heteroplasmic	Sporadic, somatic mutations

mtDNA, Mitochondrial DNA; rRNA, ribosomal RNA; tRNA, transfer RNA.

From Nussbaum RL, McInnes RR, Willard HF, editors: *Thompson & Thompson genetics in medicine,* ed 6, Philadelphia, 2001, Saunders, p 246.

The mitochondria are the cell's suppliers of energy, and it is not surprising that the organs that are most affected by the presence of abnormal mitochondria are those that have the greatest energy requirements, such as the brain, muscle, heart, and liver (see Chapters 105.4 , 388 , 616.2 , and 629.4) (Fig. 97.16). Common manifestations include developmental delay, seizures, cardiac dysfunction, decreased muscle strength and tone, and hearing and vision problems.

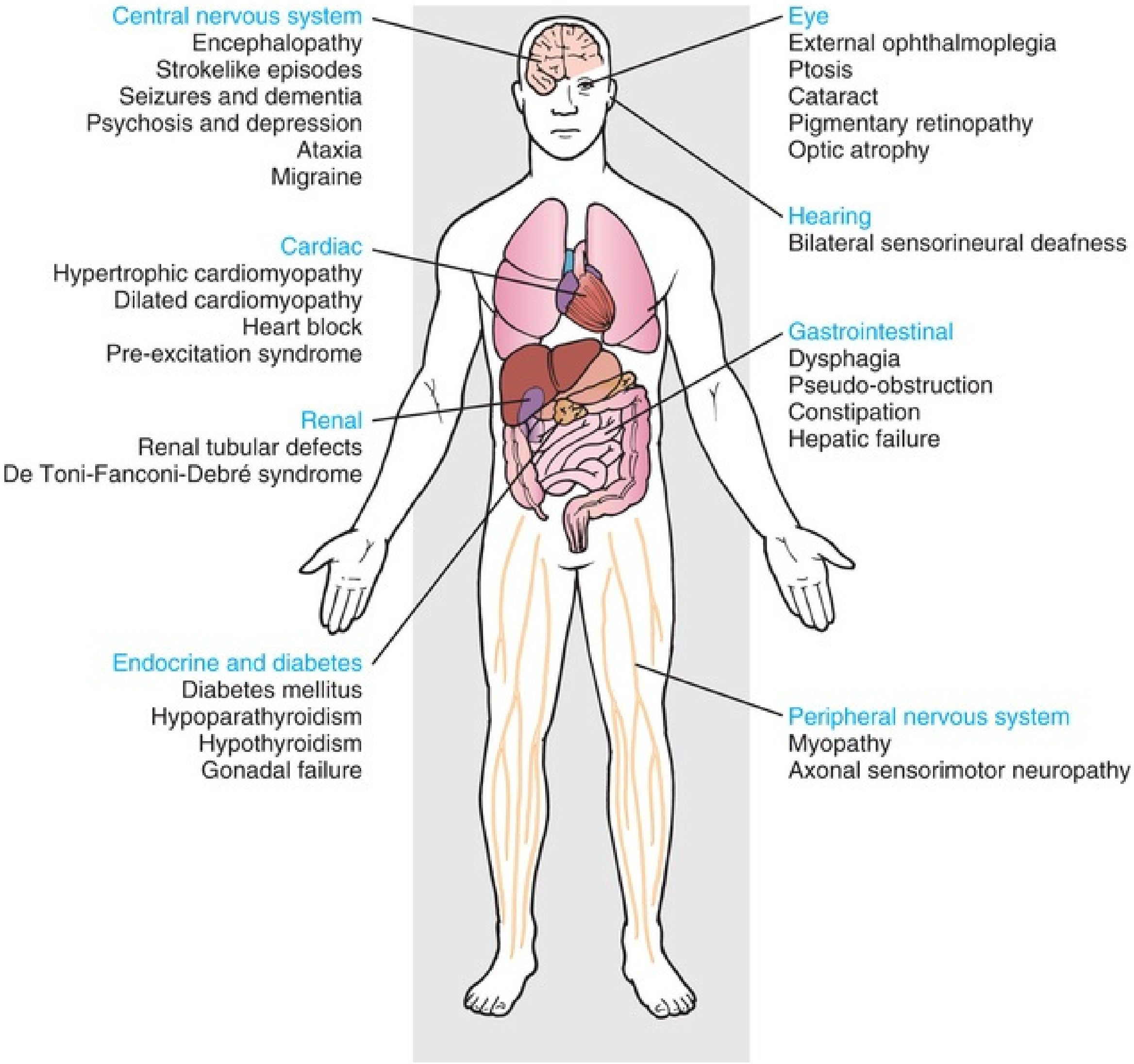
Central nervous system
Encephalopathy
Strokelike episodes
Seizures and dementia
Psychosis and depression
Ataxia
Migraine
Cardiac
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Heart block
Pre-excitation syndrome
Renal
Renal tubular defects
De Toni-Fanconi-Debré syndrome
Endocrine and diabetes
Diabetes mellitus
Hypoparathyroidism
Hypothyroidism
Gonadal failure
Eye
External ophthalmoplegia
Ptosis
Cataract
Pigmentary retinopathy
Optic atrophy
Hearing
Bilateral sensorineural deafness
Gastrointestinal
Dysphagia
Pseudo-obstruction
Constipation
Hepatic failure
Peripheral nervous system
Myopathy
Axonal sensorimotor neuropathy

FIG. 97.16 The range of affected tissues and clinical phenotypes associated with mutations in mitochondrial DNA (mtDNA). (Modified from Chinnery PF, Turnbull DM: Mitochondrial DNA and disease, *Lancet* 345:SI17–SI21, 1999.)

Mitochondrial diseases can be highly variable in clinical manifestation. This is partly because cells can contain multiple mitochondria, each bearing several copies of the mitochondrial genome. Thus a cell can have a mixture of normal and abnormal mitochondrial genomes, which is referred to as **heteroplasmy** . In contrast, **homoplasmy** refers a state in which all copies of the mitochondrial genome carry the same sequence variant. Unequal segregation of mitochondria carrying normal and abnormal genomes and replicative advantage can result in varying degrees of heteroplasmy in the cells of an affected individual, including the individual ova of an affected female. Because of this, a mother may be asymptomatic yet have children who are severely affected. The level of heteroplasmy at which disease symptoms typically appear can also vary based on the type of mitochondrial variant. Detection of mitochondrial genome variants can require sampling of the affected tissue for DNA analysis. In some tissues, such as blood, testing for mitochondrial DNA variants may be inadequate because the variant may be found primarily in affected tissues such as muscle (Fig. 97.17).

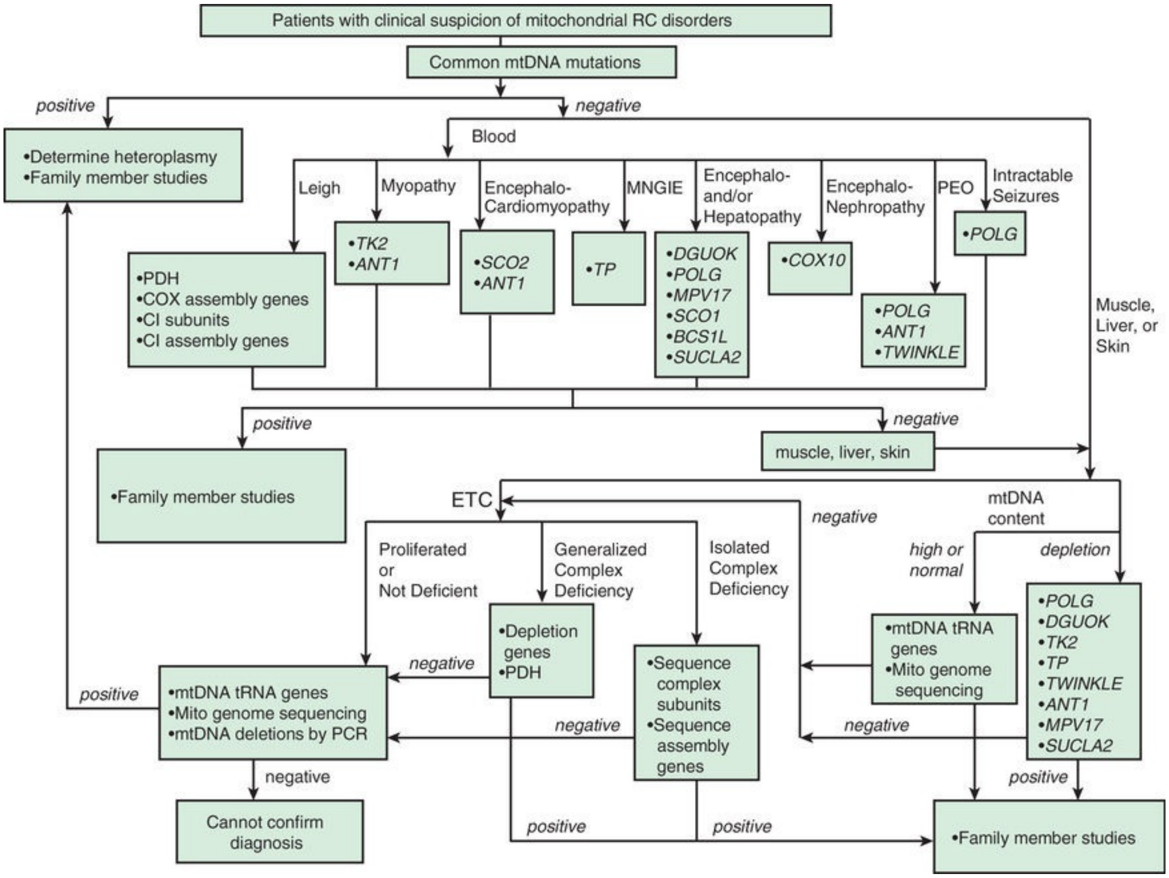
Patients with clinical suspicion of mitochondrial RC disorders
Common mtDNA mutations
positive
negative
•Determine heteroplasmy
•Family member studies
Blood
Leigh
Myopathy
Encephalo-Cardiomyopathy
MNGIE
Encephalo- and/or Hepatopathy
Encephalo-Nephropathy
PEO
Intractable Seizures
•PDH
•COX assembly genes
•CI subunits
•CI assembly genes
•TK2
•ANT1
•SCO2
•ANT1
•TP
•DGUOK
•POLG
•MPV17
•SCO1
•BCS1L
•SUCLA2
•COX10
•POLG
•ANT1
•TWINKLE
•POLG
Muscle, Liver, or Skin
positive
negative
•Family member studies
muscle, liver, skin
ETC
negative
mtDNA content
Proliferated or Not Deficient
Generalized Complex Deficiency
Isolated Complex Deficiency
high or normal
depletion
•Depletion genes
•PDH
•Sequence complex subunits
•Sequence assembly genes
•mtDNA tRNA genes
•Mito genome sequencing
•POLG
•DGUOK
•TK2
•TP
•TWINKLE
•ANT1
•MPV17
•SUCLA2
negative
positive
•mtDNA tRNA genes
•Mito genome sequencing
•mtDNA deletions by PCR
negative
negative
negative
positive
Cannot confirm diagnosis
positive
positive
•Family member studies

FIG. 97.17 Clinical algorithm for genetic diagnostic testing of mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) genes in patients suspected of mitochondrial disorders (Baylor College of Medicine, Mitochondrial Diagnostics Laboratory). RC, Respiratory chain; MNGIE, mitochondrial neurogastrointestinal encephalopathy; PEO, progressive external ophthalmoplegia; PDH, pyruvate dehydrogenase; CI, respiratory complex I; ETC, electron transport chain; PCR, polymerase chain reaction. (From Haas RH, Parikh S, Falk MJ, et al: The in-depth evaluation of suspected mitochondrial disease, *Mol Genet Metab* 94:16–37, 2008.)

Growth and differentiation factor 15 (GDF-15) and blood lactate levels are screening tests for mitochondrial disorders.

Triplet Repeat Expansion Disorders

Triplet repeat expansion disorders are distinguished by the special dynamic nature of the disease-causing variant. Triplet repeat expansion disorders include fragile X syndrome, myotonic dystrophy, Huntington disease, and spinocerebellar ataxias (Table 97.2 and Fig. 97.18). These disorders are caused by expansion in the number of 3-bp repeats. The fragile X gene, *FMR1*, normally has 5-40 CGG triplets. An error in replication can result in expansion of that number to a level in the gray zone between 41 and 58 repeats, or to a level referred to as **premutation** , which comprises 59-200 repeats. Some premutation carriers, more often males, develop fragile X–associated tremor/ataxia syndrome (FXTAS) as adults. Female premutation carriers are at risk for fragile X–associated primary ovarian insufficiency (*FXPOI*). Persons with a premutation are also at risk for having the repeat expand further in subsequent meiosis, thus crossing into the range of a **full mutation** (>200 repeats) in offspring. With this number of repeats, the *FMR1* gene becomes hypermethylated, and protein production is lost.

Table 97.2

Diseases Associated With Polynucleotide Repeat Expansions

DISEASE	DESCRIPTION	REPEAT SEQUENCE	NORMAL RANGE	ABNORMAL RANGE	PARENT IN WHOM EXPANSION USUALLY OCCURS	LOCATIO OF EXPANSI
CATEGORY 1						
Huntington disease	Loss of motor control, dementia, affective disorder	CAG	6-34	36-100 or more	More often through father	Exon
Spinal and bulbar muscular atrophy	Adult-onset motor-neuron disease associated with androgen insensitivity	CAG	11-34	40-62	More often through father	Exon
Spinocerebellar ataxia type 1	Progressive ataxia, dysarthria,	CAG	6-39	41-81	More often through father	Exon

	dysmetria					
Spinocerebellar ataxia type 2	Progressive ataxia, dysarthria	CAG	15-29	35-59	—	Exon
Spinocerebellar ataxia type 3 (Machado-Joseph disease)	Dystonia, distal muscular atrophy, ataxia, external ophthalmoplegia	CAG	13-36	68-79	More often through father	Exon
Spinocerebellar ataxia type 6	Progressive ataxia, dysarthria, nystagmus	CAG	4-16	21-27	—	Exon
Spinocerebellar ataxia type 7	Progressive ataxia, dysarthria, retinal degeneration	CAG	7-35	38-200	More often through father	—
Spinocerebellar ataxia type 17	Progressive ataxia, dementia, bradykinesia, dysmetria	CAG	29-42	47-55	—	Exon
Dentatorubral-pallidoluysian atrophy/Haw River syndrome	Cerebellar atrophy, ataxia, myoclonic epilepsy, choreoathetosis, dementia	CAG	7-25	49-88	More often through father	Exon
CATEGORY 2						
Pseudoachondroplasia, multiple epiphyseal dysplasia	Short stature, joint laxity, degenerative joint disease	GAC	5	6-7	—	Exon
Oculopharyngeal muscular dystrophy	Proximal limb weakness, dysphagia, ptosis	GCG	6	7-13	—	Exon
Cleidocranial dysplasia	Short stature, open skull sutures with bulging calvaria, clavicular hypoplasia, shortened fingers, dental anomalies	GCG, GCT, GCA	17	27 (expansion observed in 1 family)	—	Exon
Synpolydactyly	Polydactyly and syndactyly	GCG, GCT, GCA	15	22-25	—	Exon
CATEGORY 3						
Myotonic dystrophy (DM1; chromosome 19)	Muscle loss, cardiac arrhythmia, cataracts, frontal balding	CTG	5-37	100 to several thousand	Either parent, but expansion to congenital form through mother	3′ untransla region
Myotonic dystrophy (DM2; chromosome 3)	Muscle loss, cardiac arrhythmia,	CCTG	<75	75-11,000	—	3′ untransla region

	cataracts, frontal balding					
Friedreich ataxia	Progressive limb ataxia, dysarthria, hypertrophic cardiomyopathy, pyramidal weakness in legs	GAA	7-2	200-900 or more	Autosomal recessive inheritance, so disease alleles are inherited from both parents	Intron
Fragile X syndrome (FRAXA)	Intellectual impairment, large ears and jaws, macroorchidism in males	CGG	6-52	200-2,000 or more	Exclusively through mother	5′ untransla region
Fragile site (FRAXE)	Mild intellectual impairment	GCC	6-35	>200	More often through mother	5′ untransla region
Spinocerebellar ataxia type 8	Adult-onset ataxia, dysarthria, nystagmus	CTG	16-37	107-127	More often through mother	3′ untransla region
Spinocerebellar ataxia type 10	Ataxia and seizures	ATTCT	12-16	800-4,500	More often through father	Intron
Spinocerebellar ataxia type 12	Ataxia, eye movement disorders; variable age at onset	CAG	7-28	66-78	—	5′ untransla region
Progressive myoclonic epilepsy type 1	Juvenile-onset convulsions, myoclonus, dementia	12-bp repeat motif	2-3	30-75	Autosomal recessive inheritance, so transmitted by both parents	5′ untransla region

From Jorde LB, Carey JC, Bamshad MJ, et al: *Medical genetics* , ed 3, St Louis, 2006, Mosby, p 82.

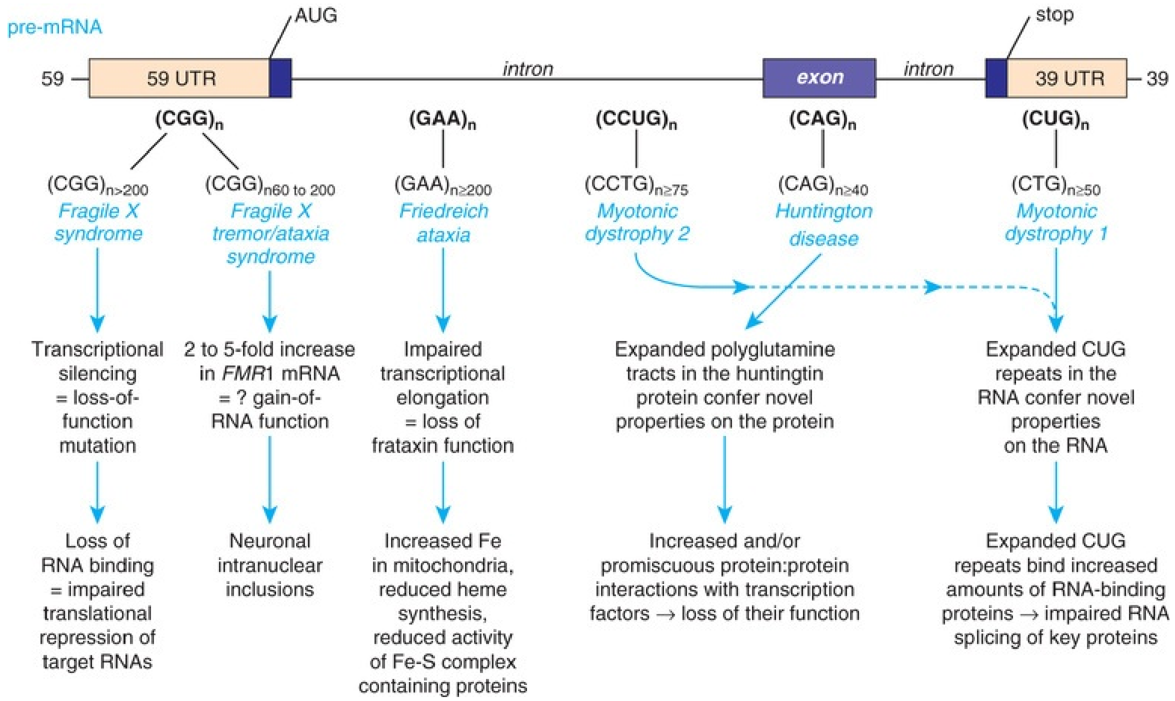
pre-mRNA
AUG
stop
59
59 UTR
intron
exon
intron
39 UTR
39
(CGG)n
(GAA)n
(CCUG)n
(CAG)n
(CUG)n
(CGG)n>200
Fragile X syndrome
(CGG)n60 to 200
Fragile X tremor/ataxia syndrome
(GAA)n≥200
Friedreich ataxia
(CCTG)n≥75
Myotonic dystrophy 2
(CAG)n≥40
Huntington disease
(CTG)n≥50
Myotonic dystrophy 1
Transcriptional silencing = loss-of-function mutation
2 to 5-fold increase in FMR1 mRNA = ? gain-of-RNA function
Impaired transcriptional elongation = loss of frataxin function
Expanded polyglutamine tracts in the huntingtin protein confer novel properties on the protein
Expanded CUG repeats in the RNA confer novel properties on the RNA
Loss of RNA binding = impaired translational repression of target RNAs
Neuronal intranuclear inclusions
Increased Fe in mitochondria, reduced heme synthesis, reduced activity of Fe-S complex containing proteins
Increased and/or promiscuous protein:protein interactions with transcription factors → loss of their function
Expanded CUG repeats bind increased amounts of RNA-binding proteins → impaired RNA splicing of key proteins

FIG. 97.18 The locations of the trinucleotide repeat expansions and the sequence of each trinucleotide in 5 representative trinucleotide repeat diseases, shown on a schematic of a generic pre–messenger RNA (mRNA). The minimal number of repeats in the DNA sequence of the affected gene associated with the disease is also indicated, as well as the effect of the expansion on the mutant RNA or protein. (From Nussbaum RL, McInnes RR, Willard HF, editors: *Thompson & Thompson genetics in medicine,* ed 8, Philadelphia, 2016, Elsevier; based partly on an unpublished figure of John A. Phillips III, Vanderbilt University.)

Some triplet expansions associated with other genes can cause disease through a mechanism other than decreased protein production. In Huntington disease the expansion causes the gene product to have a new, toxic effect on the neurons of the basal ganglia. For most triplet repeat disorders, there is a clinical correlation to the size of the expansion, with a greater expansion causing more severe symptoms and having an earlier age of disease onset. The observation of increasing severity of disease and early age at onset in subsequent generations is termed **genetic anticipation** and is a defining characteristic of many triplet repeat expansion disorders (Fig. 97.19).

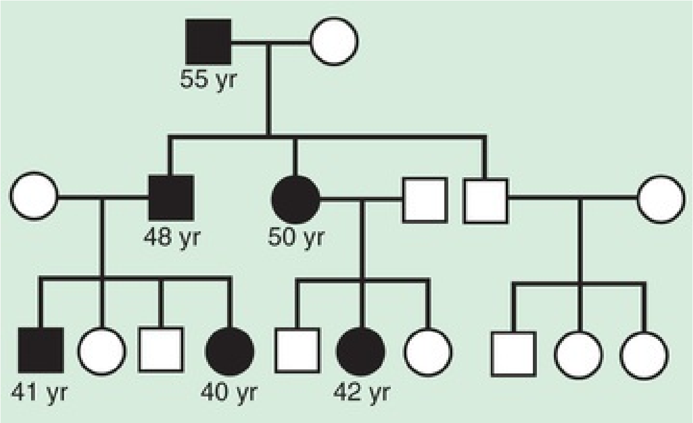

FIG. 97.19 Myotonic dystrophy pedigree illustrating genetic anticipation. In this case the age at onset for family members affected with an autosomal dominant disease is lower in more recent generations. *Black,* Affected patients.

Genetic Imprinting

The 2 copies of most autosomal genes are functionally equivalent. However, in some cases, only 1 copy of a gene is transcribed and the 2nd copy is silenced. This gene silencing is typically associated with methylation of DNA, which is an **epigenetic** modification, meaning it does not change the nucleotide sequence of the DNA (Fig. 97.20). In **imprinting** , gene expression depends on the parent of origin of the chromosome (see Chapter 98.8). Imprinting disorders result from an imbalance of active copies of a given gene, which can occur for several reasons. Prader-Willi and Angelman syndromes, two distinct disorders associated with developmental impairment, are illustrative. Both can be caused by microdeletions of chromosome 15q11-12. The microdeletion in **Prader-Willi syndrome** is always on the paternally derived chromosome 15, whereas in **Angelman syndrome** it is on the maternal copy. *UBE3A* is the gene responsible for Angelman syndrome. The paternal copy of *UBE3A* is transcriptionally silenced in the brain, and the maternal copy continues to be transcribed. If an individual has a maternal deletion, an insufficient amount of UBE3A protein is produced in the brain, resulting in the neurologic deficits seen in Angelman syndrome.

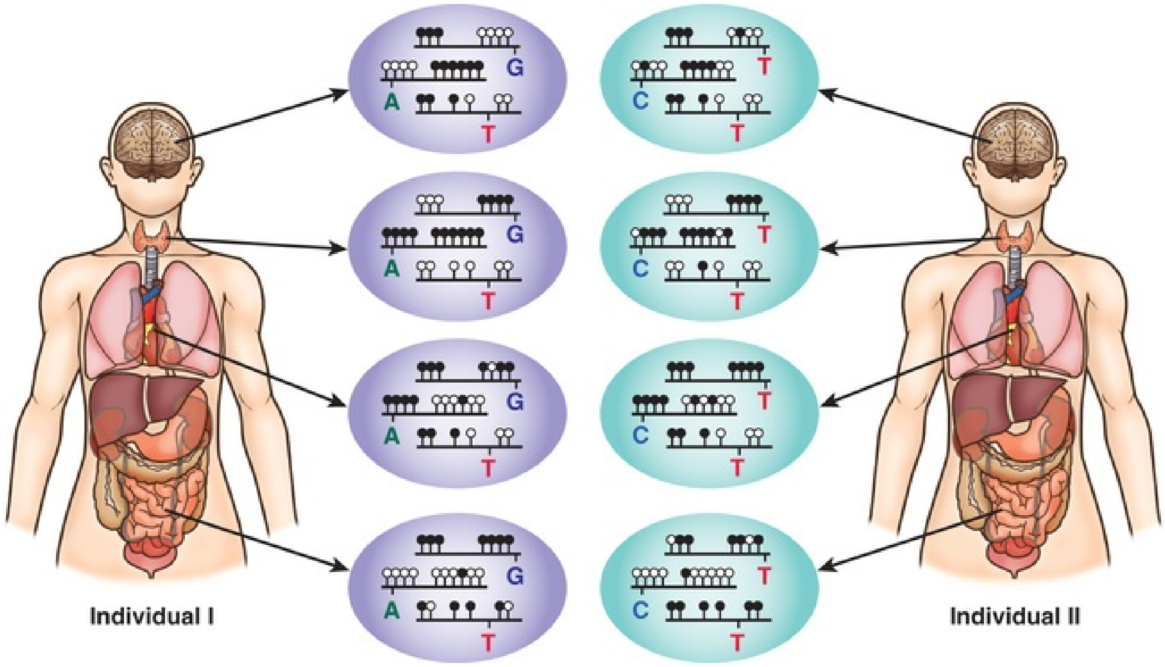

FIG. 97.20 **Tissue-specific DNA methylation and epigenetic heterogeneity among individuals. A subset of the DNA methylation patterns within a cell is characteristic of that cell type. Cell type–specific and tissue-specific DNA methylation patterns are illustrated by organ-to-organ variations in the clusters of methylated CpGs (cytosine-phosphate-guanine bases) within the same individual. Despite overall consistency in tissue-specific DNA methylation patterns, variations in these patterns exist among different individuals. Methylated CpGs are indicated by a *filled circle* and unmethylated CpGs by an *open circle* . Single nucleotide polymorphisms (SNPs) are indicated by the corresponding base. (Redrawn from Brena RM, Huang THM, Plass C: Toward a human epigenome, *Nat Genet* 38:1359–1360, 2006.)**

Uniparental disomy (UPD) , the rare occurrence of a child inheriting both copies of a chromosome from the same parent, is another genetic mechanism that can cause Prader-Willi and Angelman syndromes. Inheriting both chromosomes 15 from the mother is functionally the same as deletion of the paternal 15q12 and results in Prader-Willi syndrome. Approximately 30% of cases of Prader-Willi syndrome are caused by maternal UPD15, whereas paternal UPD15 accounts for only 3% of Angelman syndrome (see Chapter 98.8).

A mutation in an imprinted gene is another cause. Pathologic variants in *UBE3A* account for almost 11% of patients with Angelman syndrome and also result in familial transmission. The most uncommon cause is a mutation in the imprinting center, which results in an inability to correctly imprint *UBE3A* . In a woman, inability to reset the imprinting on her paternally inherited chromosome 15 imprint results in a 50% risk of passing on an incorrectly methylated copy of *UBE3A* to a child, who would then develop Angelman syndrome.

Besides 15q12, other imprinted regions of clinical interest include the short arm of chromosome 11, where the genes for Beckwith-Wiedemann syndrome and nesidioblastosis map, and the long arm of chromosome 7 with maternal UPD of 7q, which has been associated with some cases of idiopathic short stature and Russell-Silver syndrome.

Imprinting of a gene can occur during gametogenesis or early embryonic development (reprogramming). Genes can become inactive or active by various mechanisms including DNA methylation or demethylation or histone acetylation or deacetylation, with different patterns of (de)methylation noted on paternal or maternal imprintable chromosome regions. Some genes demonstrate tissue-specific imprinting (see Fig. 97.20). Several studies suggest a small but significantly increased incidence of imprinting disorders, specifically Beckwith-Wiedemann and Angelman syndrome, associated with assisted reproductive technologies such as in vitro fertilization and intracytoplasmic sperm injection. However, the overall incidence of these disorders in children conceived using assisted reproductive technologies is likely to be <1%.

Multifactorial and Polygenic Inheritance

Multifactorial inheritance refers to traits that are caused by a combination of inherited, environmental, and stochastic factors (Fig. 97.21). Multifactorial traits differ from **polygenic inheritance** , which refers to traits that result from the additive effects of multiple genes. Multifactorial traits segregate within families but do not exhibit a consistent or recognizable inheritance pattern. Characteristics include the following:

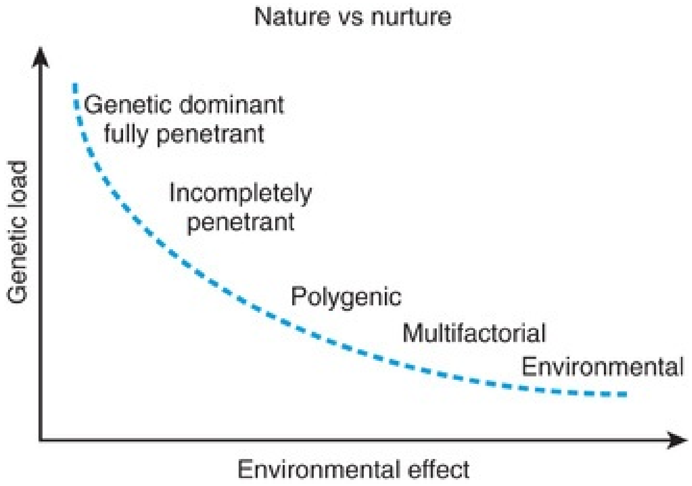

FIG. 97.21 The progressive decrease in the genetic load contributing to

the development of a disease creates a smooth transition in the distribution of illnesses on an etiologic diagram. In theory, no diseases are completely free from the influence of both genetic and environmental factors. (From Bomprezzi R, Kovanen PE, Martin R: New approaches to investigating heterogeneity in complex traits, *J Med Genet* 40:553–559, 2003. Reproduced with permission from the BMJ Publishing Group.)

◆ There is a similar rate of recurrence among all first-degree relatives (parents, siblings, offspring of affected child). It is unusual to find a substantial increase in risk for relatives related more distantly than second degree to the index case.

◆ The risk of recurrence is related to the incidence of the disease.

◆ Some disorders have a sex predilection, as indicated by an unequal male:female incidence. Pyloric stenosis, for example, is more common in males, whereas congenital dislocation of the hips is more common in females. With an altered sex ratio, the risk is higher for the relatives of an index case whose gender is less often affected than relatives of an index case of the more frequently affected gender. For example, the risk to the son of an affected female with infantile pyloric stenosis is 18%, compared with the 5% risk for the son of an affected male. An affected female presumably has a greater genetic susceptibility, which she can then pass on to her offspring.

◆ The likelihood that both identical twins will be affected with the same malformation is <100% but much greater than the chance that both members of a nonidentical twin pair will be affected. This contrasts with the pattern seen in mendelian inheritance, in which identical twins almost always share fully penetrant genetic disorders.

◆ The risk of recurrence is increased when multiple family members are affected. A simple example is that the risk of recurrence for unilateral cleft lip and palate is 4% for a couple with 1 affected child and increases to 9% with 2 affected children. It is sometimes difficult to distinguish between a multifactorial and mendelian etiology in families with multiple affected individuals.

◆ The risk of recurrence may be greater when the disorder is more severe. For example, an infant who has long-segment Hirschsprung disease has a greater chance of having an affected sibling than the infant who has short-segment Hirschsprung disease.

There are two types of multifactorial traits. One exhibits continuous variation, with “normal” individuals falling within a statistical range—often defined as having a value 2 standard deviations (SDs) above and/or below the mean—and “abnormals” falling outside that range. Examples include such traits as intelligence, blood pressure, height, and head circumference. For many of these traits, offspring values can be estimated based on a modified average of their parental values, with nutritional and environmental factors playing an important role.

With other multifactorial traits, the distinction between normal and abnormal is based on the presence or absence of a particular trait. Examples include pyloric stenosis, neural tube defects, congenital heart defects, and cleft lip and cleft palate. Such traits follow a **threshold model** (see Fig. 97.15). A distribution of liability because of genetic and nongenetic factors is postulated in the population. Individuals who exceed a threshold liability develop the trait, and those below the threshold do not.

The balance between genetic and environmental factors is demonstrated by neural tube defects. Genetic factors are implicated by the increased recurrence risk for parents of an affected child compared with the general population, yet the recurrence risk is about 3%, less than what would be expected if the trait was caused by a single, fully penetrant mutation. The role of nongenetic environmental factors is shown by the recurrence risk decreasing up to 87% if the mother-to-be takes 4 mg of folic acid daily starting 3 mo before conception.

Many adult-onset diseases behave as if caused by multifactorial inheritance. Diabetes, coronary artery disease, and schizophrenia are examples.

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CHAPTER 98

Cytogenetics

Carlos A. Bacino, Brendan Lee

Clinical cytogenetics is the study of chromosomes: their structure, function, inheritance, and abnormalities. Chromosome abnormalities are very common and occur in approximately 1–2% of live births, 5% of stillbirths, and 50% of early fetal losses in the 1st trimester of pregnancy (Table 98.1). Chromosome abnormalities are more common among individuals with intellectual disability and play a significant role in the development of some neoplasias.

Table 98.1

Incidence of Chromosomal Abnormalities in Newborn Surveys

TYPE OF ABNORMALITY	NUMBER	APPROXIMATE INCIDENCE
SEX CHROMOSOME ANEUPLOIDY		
Males (43,612 newborns)		
47,XXY	45	1/1,000*
47,XYY	45	1/1,000
Other X or Y aneuploidy	32	1/1,350
Total	**122**	**1/360 male births**
Females (24,547 newborns)		
45,X	6	1/4,000
47,XXX	27	1/900
Other X aneuploidy	9	1/2,700
Total	**42**	**1/580 female births**
AUTOSOMAL ANEUPLOIDY (68,159 NEWBORNS)		
Trisomy 21	82	1/830
Trisomy 18	9	1/7,500
Trisomy 13	3	1/22,700
Other aneuploidy	2	1/34,000
Total	**96**	**1/700 live births**
STRUCTURAL ABNORMALITIES (68,159 NEWBORNS)		
Balanced Rearrangements		
Robertsonian	62	1/1,100

Other	77	1/885
Unbalanced Rearrangements		
Robertsonian	5	1/13,600
Other	38	1/1,800
Total	**182**	**1/375 live births**
All chromosome abnormalities	**442**	**1/154 live births**

[*] Recent studies show the prevalence is currently 1:580.

Data from Hsu LYF: Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A, editor: *Genetic disorders and the fetus* , ed 4, Baltimore, 1998, Johns Hopkins University Press, pp 179–248.

Chromosome analyses are indicated in persons presenting with multiple congenital anomalies, dysmorphic features, and/or intellectual disability. The specific indications for studies include advanced maternal age (>35 yr), multiple abnormalities on fetal ultrasound (prenatal testing), multiple congenital anomalies, unexplained growth restriction in the fetus, postnatal problems in growth and development, ambiguous genitalia, unexplained intellectual disability with or without associated anatomic abnormalities, primary amenorrhea or infertility, recurrent miscarriages (≥3) or prior history of stillbirths and neonatal deaths, a first-degree relative with a known or suspected structural chromosome abnormality, clinical findings consistent with a known anomaly, some malignancies, and chromosome breakage syndromes (e.g., Bloom syndrome, Fanconi anemia).

98.1

Methods of Chromosome Analysis

Carlos A. Bacino, Brendan Lee

Cytogenetic studies are usually performed on peripheral blood lymphocytes, although cultured fibroblasts obtained from a skin biopsy may also be used. Prenatal (fetal) chromosome studies are performed with cells obtained from the amniotic fluid (amniocytes), chorionic villus tissue, and fetal blood or, in the case of preimplantation diagnosis, by analysis of a *blastomere* (cleavage stage) biopsy, polar body biopsy, or blastocyst biopsy. Cytogenetic studies of bone marrow have an important role in tumor surveillance, particularly among patients with leukemia. These are useful to determine induction of remission and success of therapy or in some cases the occurrence of relapses.

Chromosome anomalies include abnormalities of number and structure and are the result of errors during cell division. There are 2 types of cell division: mitosis, which occurs in most somatic cells, and meiosis, which is limited to the germ cells. In **mitosis,** 2 genetically identical daughter cells are produced from a single parent cell. DNA duplication has already occurred during **interphase** in the S phase of the cell cycle (DNA synthesis). Therefore, at the beginning of mitosis the chromosomes consist of 2 double DNA strands joined together at the centromere, known as *sister chromatids.* Mitosis can be divided into 4 stages: prophase, metaphase, anaphase, and telophase. **Prophase** is characterized by condensation of the DNA. Also during prophase, the nuclear membrane and the nucleolus disappear and the mitotic spindle forms. In **metaphase** the chromosomes are maximally compacted and are clearly visible as distinct structures. The chromosomes align at the center of the cell, and spindle fibers connect to the centromere of each chromosome and extend to centrioles at the 2 poles of the mitotic figure. In **anaphase** the chromosomes divide along their longitudinal axes to form 2 daughter chromatids, which then migrate to opposite poles of the cell. **Telophase** is characterized by formation of 2 new nuclear membranes and nucleoli, duplication of the centrioles, and cytoplasmic cleavage to form the 2 daughter cells.

Meiosis begins in the female oocyte during fetal life and is completed years to decades later. In males it begins in a particular spermatogonial cell sometime between adolescence and adult life and is completed in a few days. Meiosis is preceded by DNA replication so that at the outset, each of the 46 chromosomes consists of 2 chromatids. In meiosis, a **diploid cell** (2n = 46 chromosomes) divides to form **4 haploid cells** (n = 23 chromosomes). Meiosis consists of 2 major rounds of cell division. In **meiosis I** , each of the homologous chromosomes pair precisely so that **genetic recombination** , involving exchange between 2 DNA strands (**crossing over**), can occur. This results in reshuffling of the genetic information for the recombined chromosomes and allows further genetic diversity. Each daughter cell then receives 1 of each of the 23 homologous chromosomes. In oogenesis, one of the daughter cells receives most of the cytoplasm and becomes the egg, whereas the other smaller cell becomes the first polar body. **Meiosis II** is similar to a mitotic division but without a preceding round of DNA duplication (replication). Each of the 23 chromosomes divides longitudinally, and the homologous chromatids migrate to opposite poles of the cell. This produces 4 spermatogonia in males, or an egg cell and a 2nd polar body in females, each with a haploid (n = 23) set of chromosomes. Consequently, meiosis fulfills 2 crucial roles: It reduces the chromosome number from diploid (46) to haploid (23) so that on fertilization a diploid number is restored, and it allows genetic recombination.

Two common errors of cell division may occur during meiosis or mitosis, and either can result in an abnormal number of chromosomes. The 1st error is **nondisjunction** , in which 2 chromosomes fail to separate during meiosis and thus migrate together into one of the new cells, producing 1 cell with 2 copies of the chromosome and another with no copy. The 2nd error is **anaphase lag** , in which a chromatid or chromosome is lost during mitosis because it fails to move quickly enough during anaphase to become incorporated into 1 of the new daughter cells (Fig. 98.1).

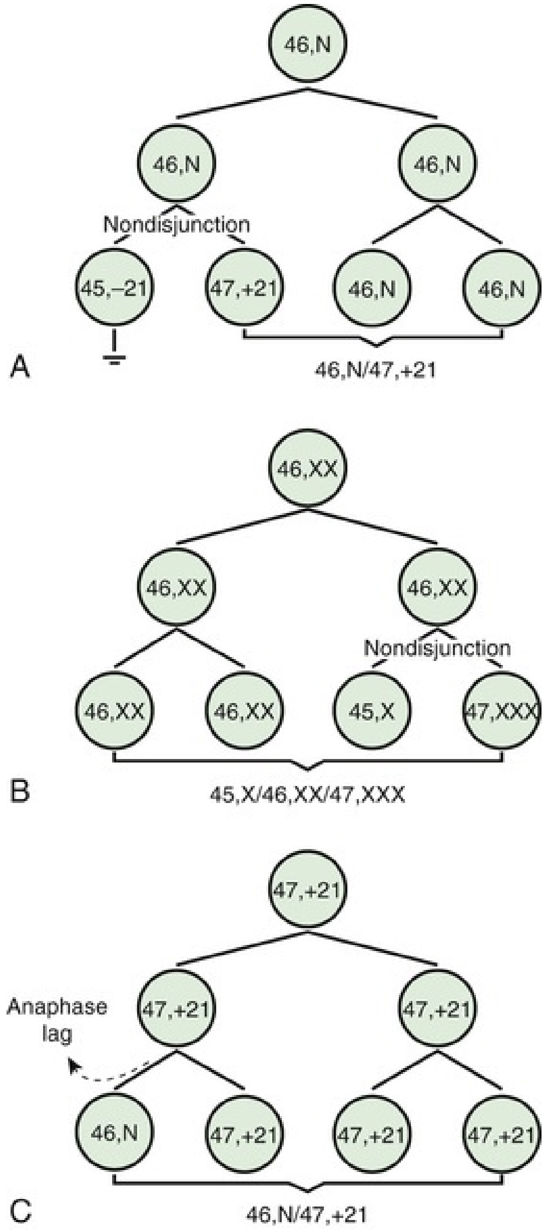
46,N
46,N
46,N
Nondisjunction
45,–21
47,+21
46,N
46,N
A
46,N/47,+21
46,XX
46,XX
46,XX
Nondisjunction
46,XX
46,XX
45,X
47,XXX
B
45,X/46,XX/47,XXX
47,+21
Anaphase lag
47,+21
47,+21
46,N
47,+21
47,+21
47,+21
C
46,N/47,+21

FIG. 98.1 **Generation of mosaicism. A, Postzygotic nondisjunction in an initially normal conceptus. In this example, 1 cell line (monosomic 21) is subsequently lost, with the final karyotype 46,N/47,+21. B, Postzygotic nondisjunction in an initially 46,XX conceptus, resulting in 45,X/46,XX/47,XXX mosaicism. C, Postzygotic anaphase lag in an initially 47,+21 conceptus. (From Gardner RJM, Sutherland GR. *Chromosome abnormalities and genetic counseling,* ed 3 New York, 2003, Oxford University Press, p 33, Figure 43.1. By permission of Oxford University Press, Inc, www.oup.com .)**

For chromosome analysis, cells are cultured (for varying periods depending on cell type), with or without stimulation, and then artificially arrested in mitosis during metaphase (or prometaphase), later subjected to a hypotonic solution to allow disruption of the nuclear cell membrane and proper dispersion of the chromosomes for analysis, fixed, banded, and finally stained. The most commonly used banding and staining method is the **GTG banding** (G-bands trypsin Giemsa), also known as **G banding** , which produces a unique combination of dark (G-positive) and light (G-negative) bands that permits recognition of all individual 23 chromosome pairs for analysis.

Metaphase chromosome spreads are first evaluated microscopically, and then their images are photographed or captured by a video camera and stored on a computer for later analysis. Humans have 46 chromosomes or 23 pairs, which are classified as *autosomes* for chromosomes 1-22, and the *sex chromosomes* , often referred as *sex complement* : XX for females and XY for males. The homologous chromosomes from a metaphase spread can then be paired and arranged systematically to assemble a karyotype according to well-defined standard conventions such as those established by International System for Human Cytogenetic Nomenclature (ISCN), with chromosome 1 being the largest and 22 the smallest. According to nomenclature, the description of the karyotype includes the total number of chromosomes followed by the sex chromosome constitution. A normal karyotype is 46,XX for females and 46,XY for males (Fig. 98.2). Abnormalities are noted after the sex chromosome complement.

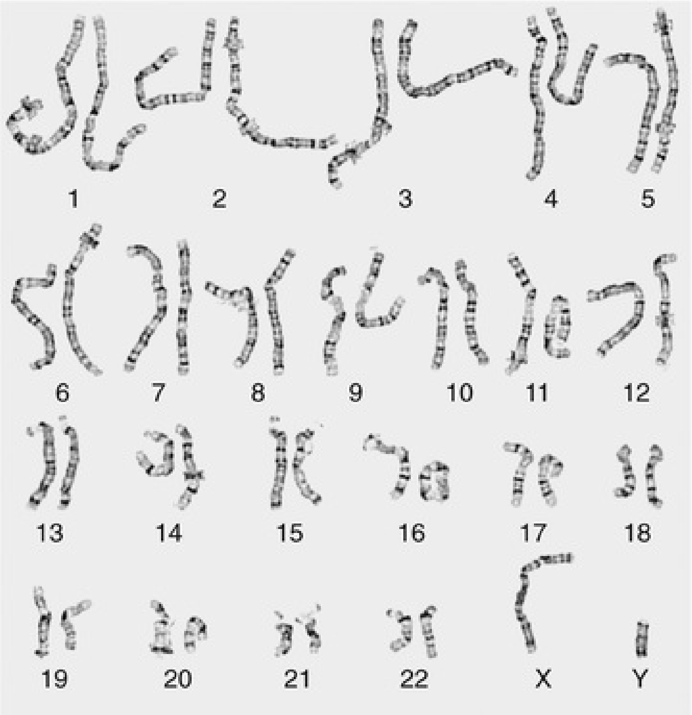

FIG. 98.2 **Karyotype of a normal male at the 550-600 band level. The longer the chromosomes are captured at metaphase or sometimes prometaphase, the more bands that can be visualized.**

Although the internationally accepted system for human chromosome classification relies largely on the length and banding pattern of each chromosome, the position of the centromere relative to the ends of the chromosome also is a useful distinguishing feature (Fig. 98.3). The centromere divides the chromosome in 2, with the short arm designated the **p arm** and the long arm designated the **q arm** . A plus or minus sign before the number of a chromosome indicates that there is an extra or missing chromosome, respectively. Table 98.2 lists some of the abbreviations used for the descriptions of chromosomes and their abnormalities. A metaphase chromosome spread usually shows 450-550 bands. Prophase and prometaphase chromosomes are longer, are less condensed, and often show 550-850 bands. High-resolution analysis may detect small chromosome abnormalities although has been mostly replaced by chromosome microarray studies (array CGH or aCGH).

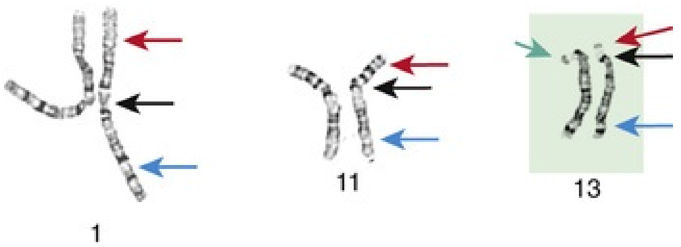

FIG. 98.3 Example of different chromosome types according to the position of the centromere. On the *left* is a chromosome 1 pair with the centromere equidistant from the short and long arm (also known as *metacentric*). In the center is a chromosome 11 pair that is submetacentric. On the *right* is a chromosome 13 pair that is an example of an acrocentric chromosome. Acrocentric chromosomes contain a very small short arm, stalks, and satellite DNA. The *black arrow* indicates the position of the centromere. The *blue arrow* shows the long arm of a chromosome. The *red arrow* shows the short arm of a chromosome. The *green arrow* highlights the satellite region, which is made of DNA repeats. The *light area* between the short arm and the satellite is known as the *stalk.*

Table 98.2

Some Abbreviations Used for Description of Chromosomes and Their Abnormalities

ABBREV	MEANING	EXAMPLE	CONDITION
XX	Female	46,XX	Normal female karyotype
XY	Male	46,XY	Normal male karyotype
[##]	Number [#]	46,XY[12]/47,XXY[10]	Number of cells in each clone, typically inside brackets

	of cells		Mosaicism in Klinefelter syndrome with 12 normal cells and 10 cells with an extra X chromosome
cen	Centromere		
del	Deletion	46,XY,del(5p)	Male with deletion of chromosome 5 short arm
der	Derivative	46,XX,der(2),t(2p12;7q13)	Female with a structurally rearranged chromosome 2 that resulted from a translocation between chromosomes 2 (short arm) and 7 (long arm)
dup	Duplication	46,XY,dup(15)(q11-q13)	Male with interstitial duplication in the long arm of chromosome 15 in the Prader-Willi/Angelman syndrome region
ins	Insertion	46,XY,ins(3)(p13q21q26)	Male with an insertion within chromosome 3
			A piece between q21q26 has reinserted on p13
inv	Inversion	46,XY,inv(2)(p21q31)	Male with pericentric inversion of chromosome 2 with breakpoints at bands p21 and q31
ish	Metaphase FISH	46,XX.ish del(7)(q11.23q11.23)	Female with deletion in the Williams syndrome region detected by in situ hybridization
nuc ish	Interphase FISH	nuc ish(DXZ1 × 3)	Interphase in situ hybridization showing 3 signals for the X chromosome centromeric region
mar	Marker	47,XY,+mar	Male with extra, unidentified chromosome material
mos	Mosaic	mos 45,X[14]/46,XX[16]	Turner syndrome mosaicism (analysis of 30 cells showed that 14 cells were 45,X and 16 cells were 46,XX)
p	Short arm	46,XY,del(5)(p12)	Male with a deletion on the short arm of chromosome 5, band p12 (short nomenclature)
q	Long arm	46,XY,del(5)(q14)	Male with a deletion on the long arm of chromosome 5, band 14
r	Ring chromosome	46,X,r(X)(p21q27)	Female with 1 normal X chromosome and a ring X chromosome
t	Translocation	t(2;8)(q33;q24.1)	Interchange of material between chromosomes 2 and 8 with breakpoints at bands 2q33 and 8q24.1
ter	Terminal	46,XY,del(5)(p12-pter)	Male with a deletion of chromosome 5 between p12 and the end of the short arm (long nomenclature)
/	Slash	45,X/46,XY	Separate lines or clones Mosaicism for monosomy X and a male cell line
+	Gain of	47,XX,+21	Female with trisomy 21
−	Loss of	45,XY,−21	Male with monosomy 21

Molecular techniques (e.g., FISH, CMA, aCGH) have filled a significant void for the diagnosing cryptic chromosomal abnormalities. These techniques identify subtle abnormalities that are often below the resolution of standard cytogenetic studies. **Fluorescence in situ hybridization (FISH)** is used to identify the presence, absence, or rearrangement of *specific* DNA segments and is performed with gene- or region-specific DNA probes. Several FISH probes are used in the clinical setting: unique sequence or single-copy probes, repetitive-sequence probes (alpha satellites in the pericentromeric regions), and multiple-copy probes (chromosome specific or painting) (Fig. 98.4*A* and *B*). FISH involves using a unique, known DNA sequence or probe labeled with a fluorescent dye that is complementary to the studied region of disease interest. The labeled probe is exposed to the DNA on a microscope slide, typically metaphase or interphase chromosomal DNA. When the probe pairs with its complementary DNA sequence, it can then be visualized by fluorescence microscopy (Fig. 98.5). In metaphase chromosome spreads, the exact chromosomal location of each probe copy can be documented, and often the *number of copies* (deletions, duplications) of the DNA sequence as well. When the interrogated segments (as in genomic duplications) are close together, only interphase cells can accurately determine the presence of 2 or more copies or signals since in metaphase cells, some duplications might falsely appear as a single signal.

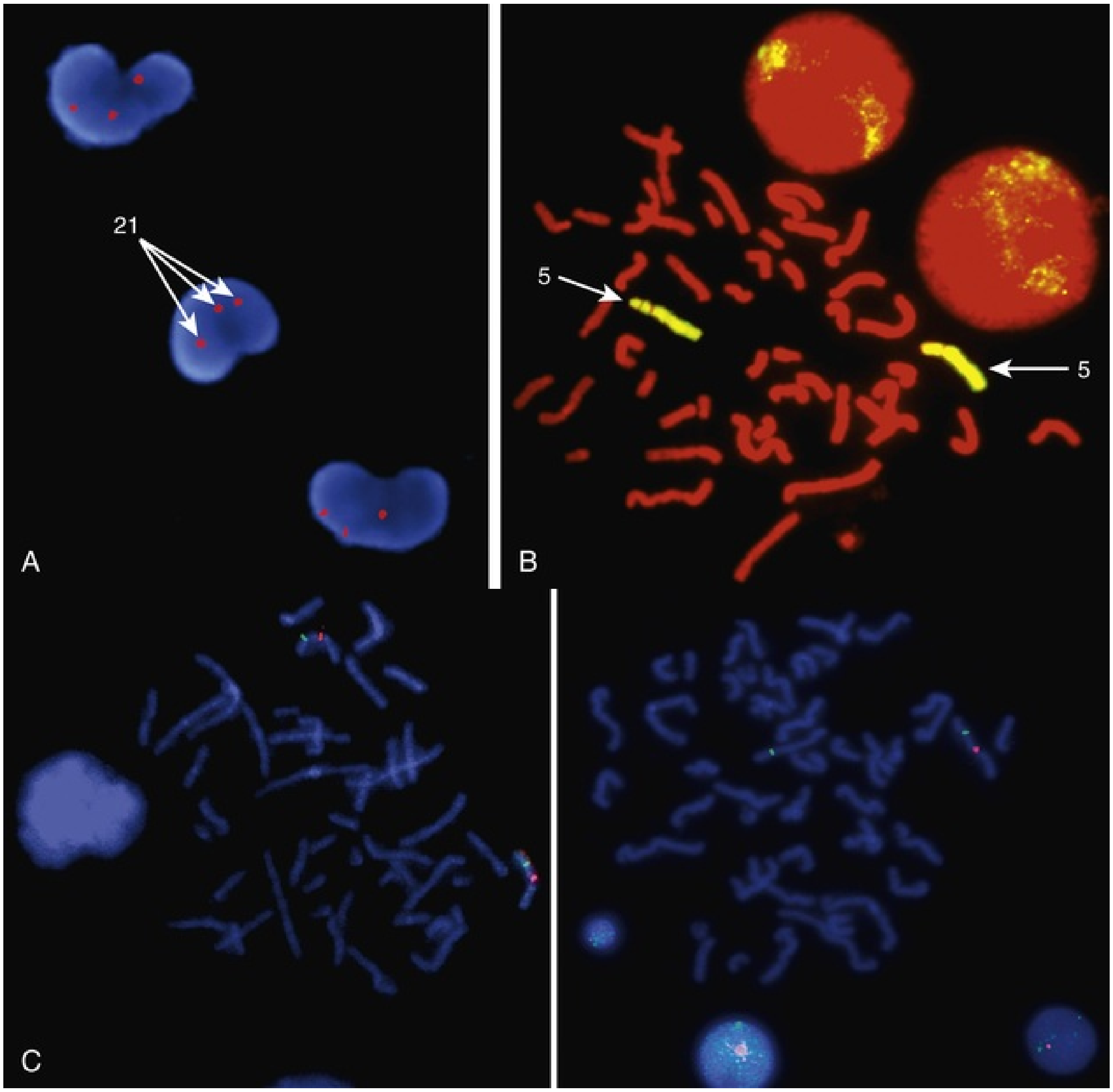

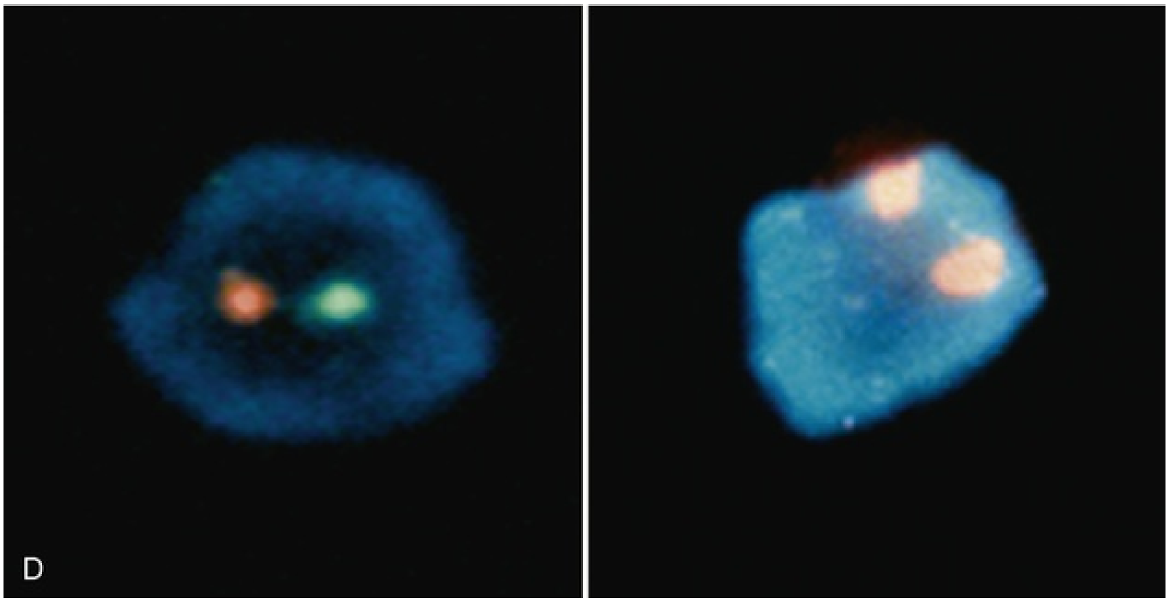

FIG. 98.4 **A,** FISH analysis of interphase peripheral blood cells from a patient with Down syndrome using a chromosome 21–specific probe. The 3 red signals mark the presence of 3 chromosomes 21. **B,** FISH analysis of a metaphase chromosome spread from a clinically normal individual using a whole chromosome paint specific for chromosome 5. Both chromosomes 5 are completely labeled *(yellow)* along their entire length. **C,** FISH on metaphase cells using a unique sequence probe that hybridizes to the elastin gene on chromosome 7q11.23, inside the Williams syndrome critical region. The elastin probe is labeled in *red* , and a control probe on chromosome 7 is labeled in *green* . The *left* image shows normal hybridization to chromosome 7, with 2 signals for the elastin region and 2 for the control probe. The *right* image shows a normal chromosome on the right with control and elastin signals, and a deleted chromosome 7 on the left, evidenced by a single signal for the control probe. This image corresponds to a patient with a Williams syndrome region deletion. **D,** FISH in interphase cells using DNA probes that hybridize to repetitive α-satellite sequences in the pericentromeric region for the sex chromosomes. *Left,* interphase cells with 2 signals, 1 labeled in *red* for the X chromosome and *green* for the Y chromosome, consistent with a normal male chromosome complement. *Right,* interphase cell showing 2 *red* signals for the X chromosome, compatible with a normal female chromosome complement.

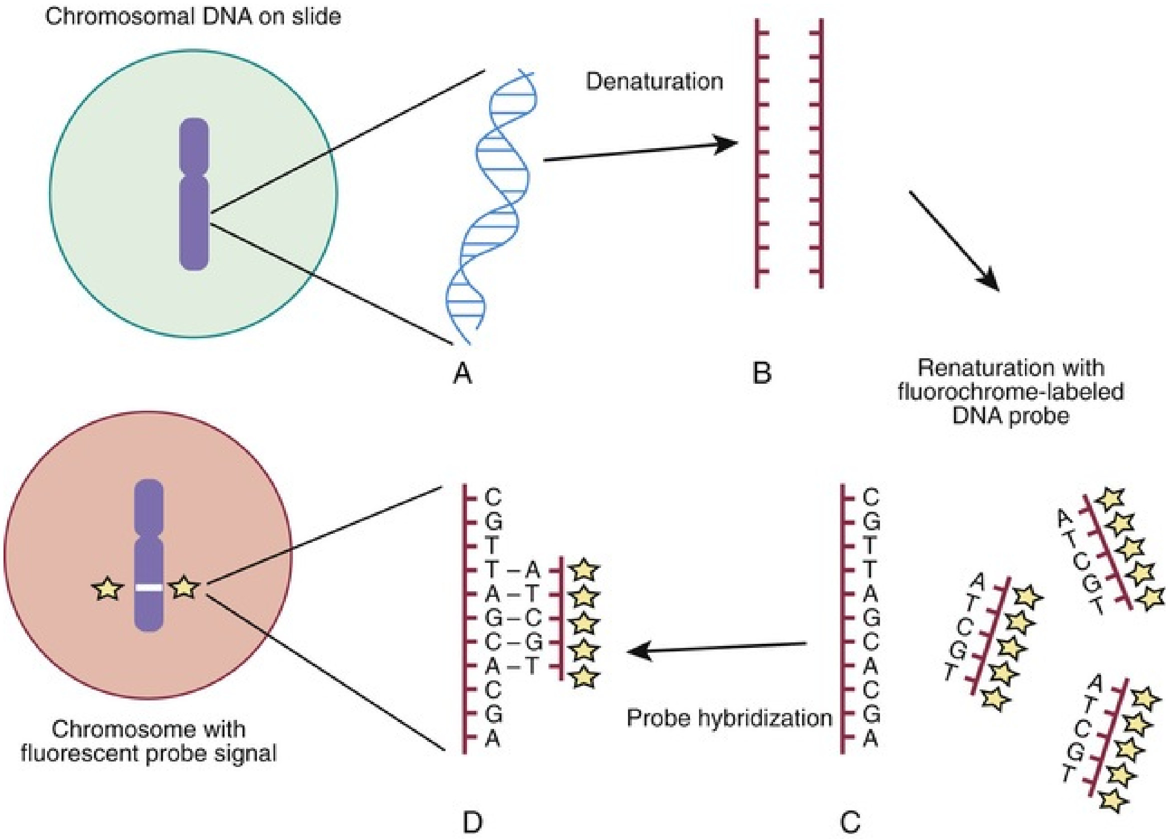
Chromosomal DNA on slide
Denaturation
A
B
Renaturation with fluorochrome-labeled DNA probe
Chromosome with fluorescent probe signal
C G T T A G C A C G A
T – A
A – T
G – C
C – G
A – T
Probe hybridization
C G T T A G C A C G A
A T C G T
A T C G T
A T C G T
D
C

FIG. 98.5 FISH involves denaturation of double-stranded DNA as present in metaphase chromosomes or interphase nuclei on cytogenetic slide preparations (**A**) into single-stranded DNA (**B**). The slide-bound (in situ) DNA is then renatured or reannealed in the presence of excess copies of a single-stranded, fluorochrome-labeled DNA base-pair sequence or probe (**C**). The probe anneals or "hybridizes" to sites of complementary DNA sequence (**D**) within the chromosomal genome. Probe signal is visualized and imaged on the chromosome by fluorescent microscopy. (From Lin RL, Cherry AM, Bangs CD, et al: FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In Hyme HE, Greydanus D, editors: *Genetic disorders in adolescents: state of the art reviews. Adolescent medicine,* Philadelphia, 2002, Hanley and Belfus, pp. 305–313.)

Chromosome rearrangements <5 million bp (5 Mbp) cannot be detected by conventional cytogenetic techniques. FISH was initially used to detect deletions as small as 50-200 kb of DNA and facilitated the early clinical characterization of a number of **microdeletion syndromes** . Some FISH probes hybridize to repetitive sequences located in the pericentromeric regions. Pericentromeric probes are still widely used for the rapid identification of certain trisomies in interphase cells of blood smears, or even in the rapid analysis of prenatal samples from cells obtained through amniocentesis. Such probes are available for chromosomes 13, 18, and 21 and for the sex pair X and Y (see Fig. 98.4*C* and *D*). With regard to the detection of genomic disorders, FISH is no longer the first line of testing, and its role has also mostly changed to the confirmation of microarray findings. In summary, FISH is reserved for (1) confirmation studies of abnormalities detected by CMA, (2) rapid prenatal screening on interphase amniotic fluid cells, and (3) interphase blood smear for sex assignment of newborns who present with ambiguous genitalia.

Array comparative genomic hybridization (aCGH) and **chromosomal microarray (CMA)** are molecular-based techniques that involve differentially labeling the patient's DNA with a fluorescent dye (green fluorophore) and a normal reference DNA with a red fluorophore (Fig. 98.6). Oligonucleotides (short DNA segments) encompassing the entire genome are spotted onto a slide or **microarray** grid. Equal amounts of the 2-label DNA samples are mixed, and the green:red fluorescence ratio is measured along each tested area. Regions of amplification of the patient's DNA display an excess of green fluorescence, and regions of loss show excess red fluorescence. If the patient's and the control DNA are equally represented, the green:red ratio is 1 : 1, and the tested regions appear yellow (see Chapter 96 , Fig. 96.5). The detection is currently possible at the single-exon resolution level, depending on the arrays used. In the near future, copy number detections may further evolve to be detected by next generation sequencing in the context of whole *genome* sequencing.

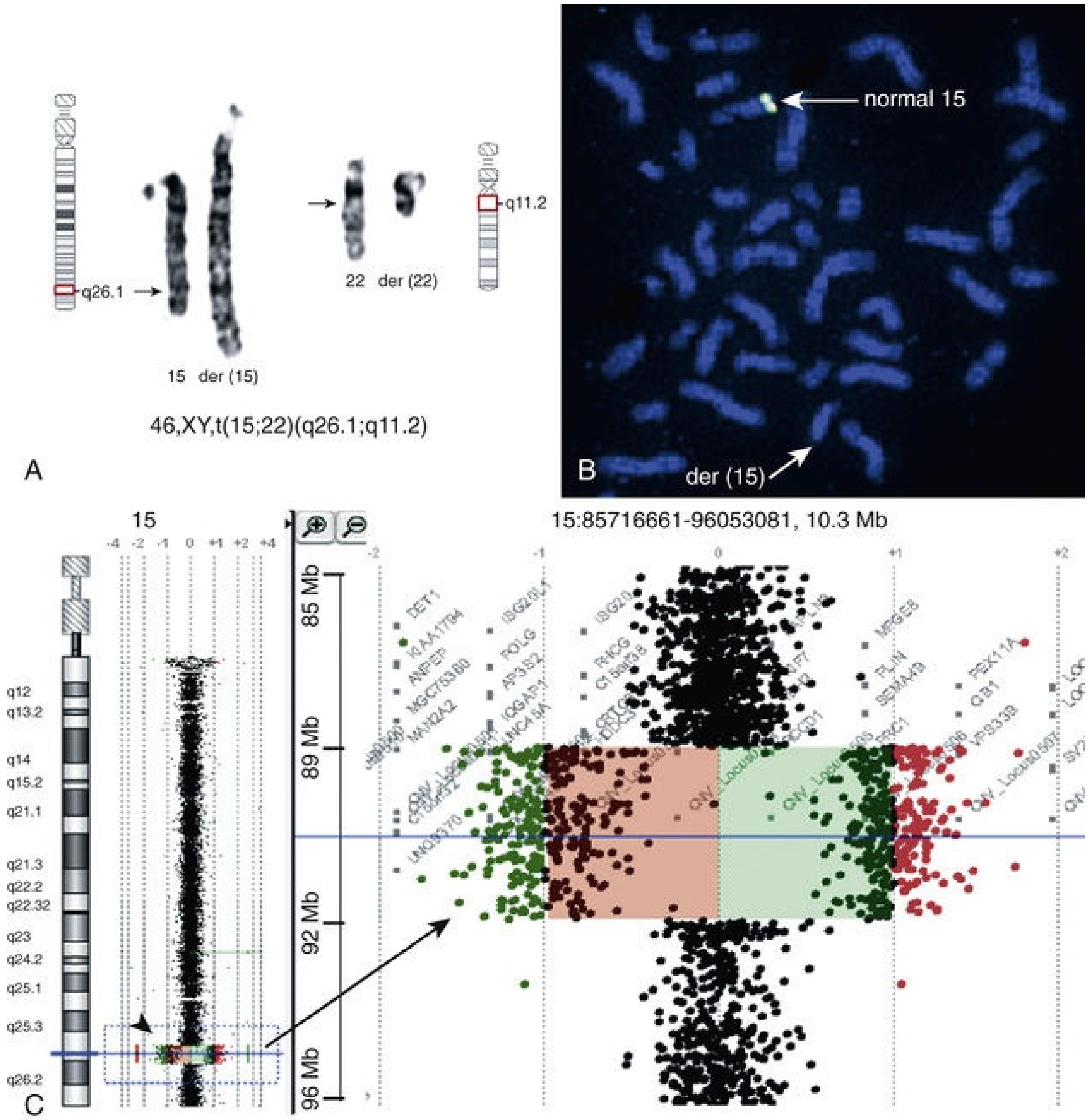
q26.1
15 der (15)
22 der (22)
q11.2
46,XY,t(15;22)(q26.1;q11.2)
A
normal 15
der (15)
B
15
-4 -2 -1 0 +1 +2 +4
q12
q13.2
q14
q15.2
q21.1
q21.3
q22.2
q22.32
q23
q24.2
q25.1
q25.3
q26.2
C
15:85716661-96053081, 10.3 Mb
-2
-1
0
+1
+2
85 Mb
89 Mb
92 Mb
96 Mb

FIG. 98.6 Example of a cryptic microdeletion at a translocation breakpoint of an apparently balanced translocation in a patient with developmental delay (dd) and growth defect. A, Partial karyotype shows t(15;22)(q26.1;q11.2). B, FISH with clones 2O19 *(green)* and 354M14 *(red)* at 15q26.1; *arrows* indicate signals only present on the normal chromosome 15, suggesting a deletion on the der(15). C, Two-color aCGH with dye swap with 244 K oligo probes; *arrowhead* indicates a 3.3-Mbp deletion at chromosome 15q26.1-q26.2, *arrow* points to the close-up view of the deletion. (From Li MM, Andersson HC: Clinical application of microarray-based molecular cytogenetics: an emerging new era of genomic medicine, *J Pediatr* 155:311–317, 2009, with permission of the authors and publisher.)

The many advantages of aCGH include its ability to test all critical disease-causing regions in the genome at once, detect duplications and deletions not currently recognized as recurrent disease-causing regions probed by FISH, and detect single-gene and contiguous gene deletion syndromes. Also, aCGH does not always require cell culture to generate sufficient DNA, which may be important in the context of prenatal testing because of timing. Limitations of aCGH are that it does not detect balanced translocations or inversions and may not detect low levels of chromosomal mosaicism. Among different types of aCGH, some are more targeted than others. **Targeted aCGH** can be an efficient way to detect clinically known cryptic chromosomal aberrations, which are typically associated with known disease phenotypes. **Whole genome arrays** target the entire genome and allow better and denser coverage in evenly spaced genomic regions. Its disadvantage is that interpretation of deletions or duplications may be difficult if it involves areas not previously known to be involved in disease.

A frequently used array in the clinical setting is the **single nucleotide polymorphism (SNP)** . SNPs are polymorphic variations between 2 nucleotides, and when analyzed in massive parallel fashion, they can provide valuable clinical information. Several million SNPs normally occur in the human genome. SNP arrays can help with the detection of **uniparental disomies** (i.e., genetic information derived from only 1 parent), as well as consanguinity in the family. Many arrays currently used in clinical practice combine the use of oligonucleotides for the detection of **copy number variations** in conjunction with SNPs. There are many copy number variations causing deletion or duplication in the human genome. Thus, most detected genetic abnormalities, unless associated with well-known clinical phenotypes, require *parental investigations* because a detected copy number variation that is inherited could be benign or an incidental polymorphic variant. A **de novo** abnormality (i.e., one found only in the child and not the parents) is often more significant if it is associated with an abnormal phenotype found only in the child, and if it involves genes with important functions.

aCGH is a very valuable technology alone or when combined with FISH and conventional chromosome studies (Fig. 98.7).

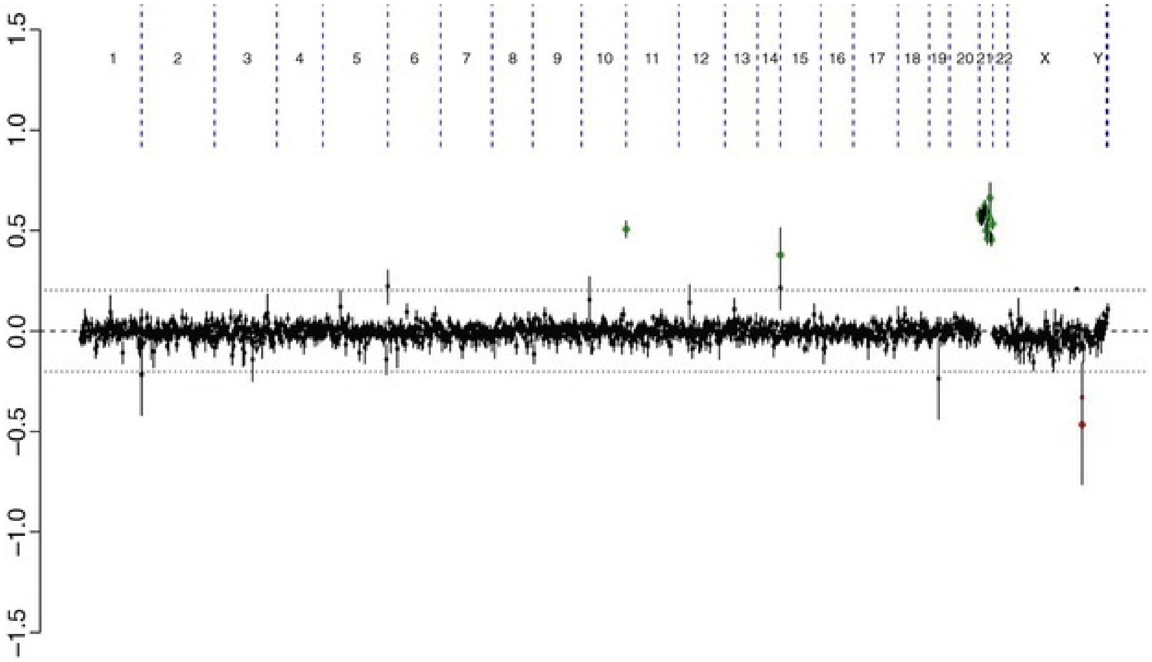

FIG. 98.7 aCGH in a female patient with Down syndrome. Each *black dot* represents a piece of DNA segment specific for different chromosome location. Most of the dots displayed between the 0.0 and 0.2 axis are considered within normal range. Exceptions are often a result of polymorphic variations. A group of dots colored in *green* clusters on chromosome 21 and above 0.5. These represent a *gain* in copy number of DNA segments for chromosome 21, as seen in Down syndrome and consistent with trisomy 21.

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98.2

Down Syndrome and Other Abnormalities of Chromosome Number

Brendan Lee

Aneuploidy and Polyploidy

Human cells contain a multiple of 23 chromosomes (n = 23). A haploid cell (n) has 23 chromosomes (typically in the ovum or sperm). If a cell's chromosomes are an exact multiple of 23 (46, 69, 92 in humans), those cells are referred to as **euploid** . **Polyploid** cells are euploid cells with more than the normal **diploid** number of 46 (2n) chromosomes: 3n, 4n. Polyploid conceptions are usually not viable, but the presence of mosaicism with a karyotypically normal cell line can allow survival. **Mosaicism** is an abnormality defined as the presence of 2 or more cell lines in a single individual. **Polyploidy** is a common abnormality seen in 1st-trimester pregnancy losses. **Triploid cells** are those with 3 haploid sets of chromosomes (3n) and are only viable in a mosaic form. Triploid infants can be liveborn but do not survive long. Triploidy is often the result of fertilization of an egg by 2 sperm (dispermy). Failure of 1 of the meiotic divisions, resulting in a diploid egg or sperm, can also result in triploidy. The phenotype of a triploid conception depends on the origin of the extra chromosome set. If the extra set is of **paternal** origin, it results in a partial *hydatidiform mole* (excessive placental growth) with poor embryonic development, but triploid conceptions that have an extra set of **maternal** chromosomes results in severe embryonic restriction with a small, fibrotic placenta (insufficient placental development) that is typically spontaneously aborted.

Abnormal cells that do not contain a multiple of haploid number of chromosomes are termed **aneuploid** cells. **Aneuploidy** is the most common and clinically significant type of human chromosome abnormality, occurring in at least 3–4% of all clinically recognized pregnancies. **Monosomies** occur when only 1, instead of the normal 2, of a given chromosome is present in an otherwise diploid cell. In humans, most autosomal monosomies appear to be lethal early in development, and survival is possible in **mosaic forms** or by means of chromosome rescue (restoration of the normal number by duplication of single monosomic chromosome). An exception to this rule is monosomy for the X chromosome (45,X), seen in Turner syndrome; the majority of 45,X conceptuses are believed to be lost early in pregnancy for as yet unexplained reasons.

The most common cause of aneuploidy is **nondisjunction** , the failure of chromosomes to disjoin normally during meiosis (see Fig. 98.1). Nondisjunction can occur during meiosis I or II or during mitosis, although maternal meiosis I is the most common nondisjunction in aneuploidies (e.g., Down syndrome, trisomy 18). After meiotic nondisjunction, the resulting gamete either lacks a chromosome or has 2 copies instead of 1 normal copy, resulting in a monosomic or trisomic zygote, respectively.

Trisomy is characterized by the presence of 3 chromosomes, instead of the normal 2, of any particular chromosome. Trisomy is the most common form of aneuploidy. Trisomy can occur in all cells or it may be mosaic. Most individuals with a trisomy exhibit a consistent and specific phenotype depending on the chromosome involved.

FISH is a technique that can be used for rapid diagnosis in the prenatal detection of common fetal aneuploidies, including chromosomes 13, 18, and 21, as well as sex chromosomes (see Fig. 98.4*C* and *D*). Direct detection of fetal cell-free DNA from maternal plasma for fetal trisomy is a safe and highly effective screening test for fetal aneuploidy. The most common numerical abnormalities in liveborn children include trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), and sex chromosomal aneuploidies: Turner syndrome (usually 45,X), Klinefelter syndrome (47,XXY), 47,XXX, and 47,XYY. By far the most common type of trisomy in liveborn infants is trisomy 21 (47,XX,+21 or 47,XY,+21) (see Table 98.1). Trisomy 18 and trisomy 13 are relatively less common and are associated with a characteristic set of congenital anomalies and severe intellectual disability (Table 98.3). The occurrence of trisomy 21 and other trisomies increases with advanced maternal age (≥35 yr). Because of this increased risk, women who are ≥35 yr old at delivery should be offered genetic counseling and prenatal diagnosis (including serum screening, ultrasonography, and cell-free fetal DNA detection, amniocentesis, or chorionic villus sampling; see Chapter 115).

Table 98.3

Chromosomal Trisomies and Their Clinical Findings

SYNDROME	INCIDENCE	CLINICAL MANIFESTATIONS
Trisomy 13, Patau syndrome	1/10,000 births	Cleft lip often midline; flexed fingers with postaxial polydactyly; ocular hypotelorism, bulbous nose; low-set, malformed ears; microcephaly; cerebral malformation, especially holoprosencephaly; microphthalmia, cardiac malformations; scalp defects; hypoplastic or absent ribs; visceral and genital anomalies
		Early lethality in most cases, with a median survival of 12 days; ~80% die by 1 year; 10-year survival ~13%. Survivors have significant neurodevelopmental delay.
Trisomy 18, Edwards syndrome	1/6,000 births	Low birthweight, closed fists with index finger overlapping the 3rd digit and the 5th digit overlapping the 4th, narrow hips with limited abduction, short sternum, rocker-bottom feet, microcephaly, prominent occiput, micrognathia, cardiac and renal malformations, intellectual disability
		~88% of children die in the 1st year; 10-year survival ~10%. Survivors have significant neurodevelopmental delay.
Trisomy 8, mosaicism	1/20,000 births	Long face; high, prominent forehead; wide, upturned nose, thick, everted lower lip; microretrognathia; low-set ears; high-arched, sometimes cleft, palate; osteoarticular anomalies common (camptodactyly of 2nd-5th digits, small patella); deep plantar and palmar creases; moderate intellectual disability

Down Syndrome

Trisomy 21 is the most common genetic etiology of moderate intellectual disability. The incidence of Down syndrome in live births is approximately 1 in 733; the incidence at conception is more than twice that rate; the difference is accounted for by early pregnancy losses. In addition to cognitive impairment, Down syndrome is associated with congenital anomalies and characteristic dysmorphic features (Figs. 98.8 and 98.9 and Table 98.4). Although there is variability in the clinical features, the constellation of phenotypic features is fairly consistent and permits clinical recognition of trisomy 21. Affected individuals are more prone to congenital heart defects (50%) such as atrioventricular septal defects, ventricular septal defects, isolated secundum atrial septal defects, patent ductus arteriosus, and tetralogy of Fallot. Pulmonary complications include recurrent respiratory infections, sleep-disordered breathing, laryngo- and tracheobronchochomalacia, tracheal bronchus, pulmonary hypertension, and asthma. Congenital and acquired gastrointestinal anomalies (celiac disease) and hypothyroidism are common (Table 98.5). Other abnormalities include megakaryoblastic leukemia, immune dysfunction, diabetes mellitus, seizures, alopecia, juvenile idiopathic arthritis, and problems with hearing and vision. Alzheimer disease–like dementia is a known complication that occurs as early as the 4th decade and has an incidence 2-3 times higher than sporadic Alzheimer disease. Most males with Down syndrome are sterile, but some females have been able to reproduce, with a 50% chance of having trisomy 21 pregnancies. Two genes (*DYRK1A, DSCR1*) in the putative critical region of chromosome 21 may be targets for therapy.

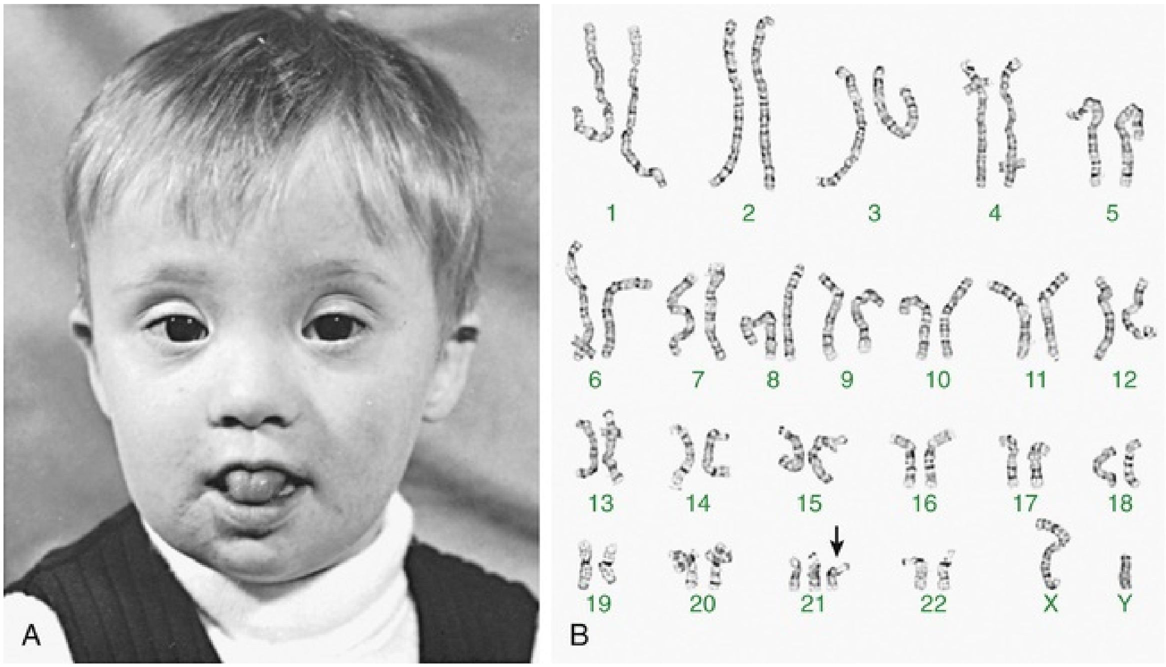
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FIG. 98.8 **A,** Face of a child with Down syndrome. **B,** Karyotype of a male with trisomy 21 as seen in Down syndrome. This karyotype reveals 47 chromosomes instead of 46, with an extra chromosome in pair 21.

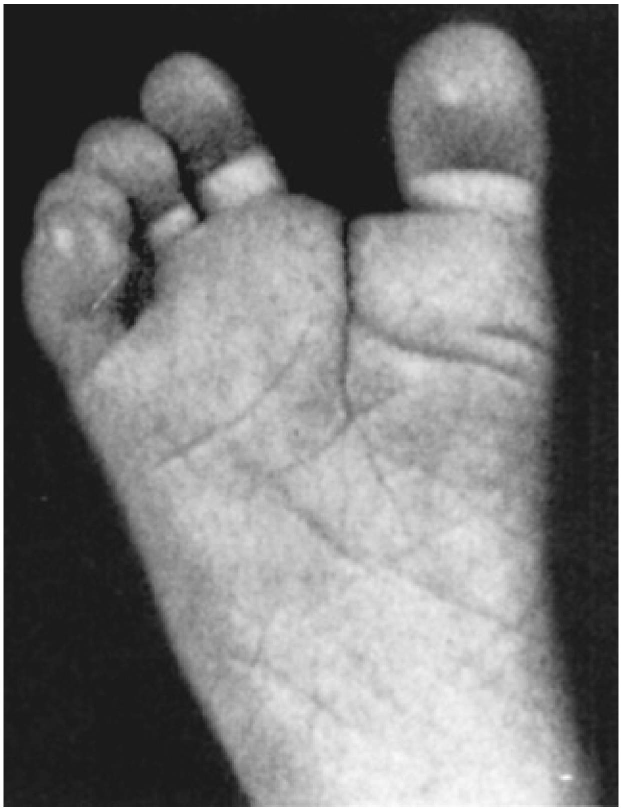

FIG. 98.9 Prehensile foot in a 1 mo old child with Down syndrome. (From Wiedemann HR, Kunze J, Dibbern H: *Atlas of clinical syndromes: a visual guide to diagnosis,* ed 3, St Louis, 1989, Mosby.)

Table 98.4

Clinical Features of Down Syndrome in the Neonatal Period

Central Nervous System

Hypotonia*
Developmental delay
Poor Moro reflex*

Craniofacial

Brachycephaly with flat occiput
Flat face*

Upward slanted palpebral fissures*
Epicanthal folds
Speckled irises (Brushfield spots)
Three fontanels
Delayed fontanel closure
Frontal sinus and midfacial hypoplasia
Mild microcephaly
Short, hard palate
Small nose, flat nasal bridge
Protruding tongue, open mouth
Small dysplastic ears*

Cardiovascular

Endocardial Cushing defects
Ventricular septal defect
Atrial septal defect
Patent ductus arteriosus
Aberrant subclavian artery
Pulmonary hypertension

Musculoskeletal

Joint hyperflexibility*
Short neck, redundant skin*
Short metacarpals and phalanges
Short 5th digit with clinodactyly*
Single transverse palmar creases*
Wide gap between 1st and 2nd toes
Pelvic dysplasia*
Short sternum
Two sternal manubrium ossification centers

Gastrointestinal

Duodenal atresia

Annular pancreas
Tracheoesophageal fistula
Hirschsprung disease
Imperforate anus
Neonatal cholestasis

Cutaneous

Cutis marmorata

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[*] Hall's criteria to aid in diagnosis.

Table 98.5

Additional Features of Down Syndrome That Can Develop or Become Symptomatic With Time

Neuropsychiatric

Developmental delay
Seizures
Autism spectrum disorders
Behavioral disorders (disruptive)
Depression
Alzheimer disease

Sensory

Congenital or acquired hearing loss
Serous otitis media
Refractive errors (myopia)
Congenital or acquired cataracts
Nystagmus
Strabismus

Glaucoma
Blocked tear ducts

Cardiopulmonary

Acquired mitral, tricuspid, or aortic valve regurgitation
Endocarditis
Obstructive sleep apnea

Musculoskeletal

Atlantoaxial instability
Hip dysplasia
Slipped capital femoral epiphyses
Avascular hip necrosis
Recurrent joint dislocations (shoulder, knee, elbow, thumb)

Endocrine

Congenital or acquired hypothyroidism
Diabetes mellitus
Infertility
Obesity
Hyperthyroidism

Hematologic

Transient myeloproliferative syndrome
Acute lymphocytic leukemia
Acute myelogenous leukemia

Gastrointestinal

Celiac disease
Delayed tooth eruption

Respiratory
Obstructed sleep apnea
Frequent infections (sinusitis, nasopharyngitis, pneumonia)

Cutaneous

Hyperkeratosis
Seborrhea
Xerosis
Perigenital folliculitis

Developmental delay is universal (Tables 98.6 and 98.7 and Fig. 98.10). Cognitive impairment does not uniformly affect all areas of development. Social development is often relatively spared, but autism spectrum disorder can occur. Children with Down syndrome have considerable difficulty using expressive language. Understanding the individual developmental strengths and challenges is necessary to maximize the educational process. Persons with Down syndrome often benefit from programs aimed at cognitive training, stimulation, development, and education. Children with Down syndrome also benefit from anticipatory guidance, which establishes the protocol for screening, evaluation, and care for patients with genetic syndromes and chronic disorders (Table 98.8). Up to 15% of children with Down syndrome have misalignment of the 1st cervical vertebra (C1), which places them at risk for spinal cord injury with neck hyperextension or extreme flexion. Special Olympics recommends sports participation and training but requires x-ray examination (full extension and flexion views) of the neck before participation in sports that may result in hyperextension or radical flexion or pressure on the neck or upper spine. Such sports include diving starts in swimming, butterfly stroke, diving, pentathlon, high jump, equestrian sports, gymnastics, football, soccer, alpine skinning, and warm-up exercises placing stress on the head and neck. If atlantoaxial instability is diagnosed, Special Olympics will permit participation if the parents or guardians request so and only after obtaining written certification from a physician and acknowledgment of the risks by the parent or guardian.

Table 98.6

Developmental Milestones

Milestone	CHILDREN WITH DOWN SYNDROME		UNAFFECTED CHILDREN	
	Average (mo)	Range (mo)	Average (mo)	Range (mo)
Smiling	2	1.5-3	1	1.5-3
Rolling over	6	2-12	5	2-10
Sitting	9	6-18	7	5-9
Crawling	11	7-21	8	6-11
Creeping	13	8-25	10	7-13
Standing	10	10-32	11	8-16
Walking	20	12-45	13	8-18
Talking, words	14	9-30	10	6-14
Talking, sentences	24	18-46	21	14-32

From Levine MD, Carey WB, Crocker AC, editors: *Developmental-behavioral pediatrics,* ed 2, Philadelphia, 1992, Saunders.

Table 98.7

Self-Help Skills

Skill	DOWN SYNDROME CHILDREN		UNAFFECTED CHILDREN	
	Average (mo)	Range (mo)	Average (mo)	Range (mo)
EATING				
Finger feeding	12	8-28	8	6-16
Using spoon/fork	20	12-40	13	8-20
TOILET TRAINING				
Bladder	48	20-95	32	18-60
Bowel	42	28-90	29	16-48
DRESSING				
Undressing	40	29-72	32	22-42
Putting clothes on	58	38-98	47	34-58

From Levine MD, Carey WB, Crocker AC, editors: *Developmental-behavioral pediatrics,* ed 2, Philadelphia, 1992, Saunders.

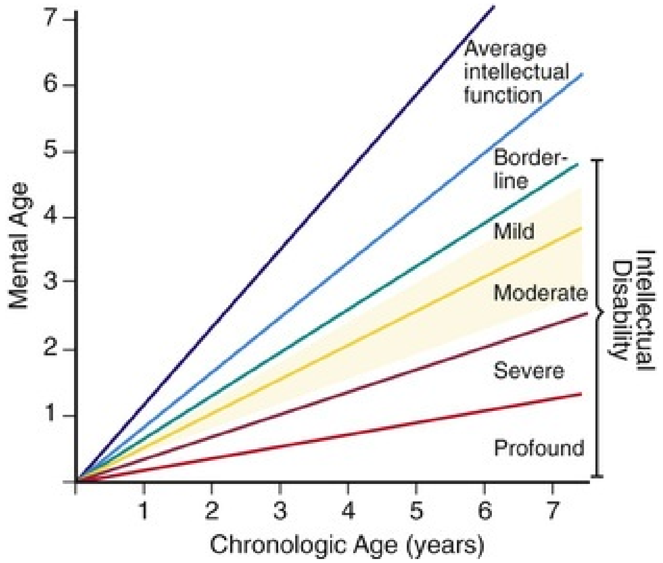

FIG. 98.10 The area shaded in *yellow* denotes the range of intellectual function of the majority of children with Down syndrome. (From Levine MD, Carey WB, Crocker AC, editors: *Developmental-behavioral pediatrics,* ed 2, Philadelphia, 1992, Saunders, p 226.)

Table 98.8

Health Supervision for Children With Down Syndrome

CONDITION	TIME TO SCREEN	COMMENT
Congenital heart disease	Birth; by pediatric cardiologist	50% risk of congenital heart disease; increased risk for pulmonary hypertension
	Young adult for acquired valve disease	
Strabismus, cataracts, nystagmus	Birth or by 6 mo; by pediatric ophthalmologist	Cataracts occur in 15%, refractive errors in 50%
	Check vision annually	
Hearing impairment or loss	Birth or by 3 mo with auditory brainstem response or otoacoustic emission testing; check hearing q6mo up to 3 yr if tympanic membrane is not visualized; **annually thereafter**	Risk for congenital hearing loss plus 50–70% risk of serous otitis media
Constipation	Birth	Increased risk for Hirschsprung disease
Celiac disease	At 2 yr or with symptoms	Screen with IgA and tissue transglutaminase antibodies
Hematologic disease	At birth and in adolescence or if symptoms develop	Increased risk for neonatal polycythemia (18%), leukemoid reaction, leukemia (<1%)
Hypothyroidism	Birth; repeat at 6-12 mo and **annually**	Congenital (1%) and acquired (5%)
Growth and development	At each visit	Discuss school placement options
	Use Down syndrome growth curves	Proper diet to avoid obesity
Obstructive sleep apnea	Start at ~1 yr and at each visit	Monitor for snoring, restless sleep

Atlantoaxial subluxation or instability (incidence 10–30%)	At each visit by history and physical exam	Special Olympics recommendations are to screen for high-risk sports, e.g., diving, swimming, contact sports
	Radiographs at 3-5 yr or when planning to participate in contact sports	
	Radiographs indicated wherever neurologic symptoms are present even if transient (neck pain, torticollis, gait disturbances, weakness)	
	Many are asymptomatic	
Gynecologic care	Adolescent girls	Menstruation and contraception issues
Recurrent infections	When present	Check IgG subclass and IgA levels
Psychiatric, behavioral disorders	At each visit	Depression, anxiety, obsessive-compulsive disorder, schizophrenia seem in 10–17%
		Autism spectrum disorder in 5–10%
		Early-onset Alzheimer disease

IgA, Immunoglobulin A; IgG, immunoglobulin G.

Data from Committee on Genetics: Health supervision for children with Down syndrome, *Pediatrics* 107:442–449, 2001; and Baum RA, Spader M, Nash PL, et al: Primary care of children and adolescents with Down syndrome: an update, *Curr Probl Pediatr Adolesc Health Care* 38:235–268, 2008.

Compared with the general population, children with Down syndrome are at increased risk for behavior problems; psychiatric comorbidity is an estimated 18–38% in this population. Common behavioral difficulties that occur in children with Down syndrome include inattentiveness, stubbornness, and a need for routine and sameness. Aggression and self-injurious behavior are less common in this population than other children with similar degrees of intellectual disability from other etiologies. All these behaviors can respond to educational, behavioral, or pharmacologic interventions.

The life expectancy for children with Down syndrome is reduced and is approximately 50-55 yr. Little prospective information about the secondary medical problems of adults with Down syndrome is known. Retrospective studies have shown premature aging and an increased risk of Alzheimer disease in adults with Down syndrome. These studies have also shown unexpected negative (protective) associations between Down syndrome and comorbidities. Persons with Down syndrome have fewer-than-expected deaths caused by solid tumors and ischemic heart disease. This same study reported increased risk of adult deaths from congenital heart disease, seizures, and leukemia. In one large study, leukemias accounted for 60% of all cancers in people with Down syndrome and 97% of all cancers in children with Down syndrome. There was decreased risk of solid tumors in all age-groups with Down syndrome, including neuroblastomas and nephroblastomas in children and epithelial tumors in adults.

Most adults with Down syndrome are able to perform activities of daily living. However, most have difficulty with complex financial, legal, or medical decisions, and a guardian may be appointed.

The risk of having a child with trisomy 21 is highest in women who conceive after age 35 yr. Even though younger women have a lower risk, they represent half of all mothers with babies with Down syndrome because of their higher overall birth rate. *All women should be offered screening for Down syndrome* in their 2nd trimester by means of 4 maternal serum tests (free β-human chorionic gonadotropin [β-hCG], unconjugated estriol, inhibin, and α-fetoprotein). This is known as the *quad screen;* it can detect up to 80% of Down syndrome pregnancies vs 70% in the triple screen. Both tests have a 5% false-positive rate. There is a method of screening during the 1st trimester using fetal nuchal translucency (NT) thickness that can be done alone or in conjunction with maternal serum β-hCG and pregnancy-associated plasma protein-A (PAPP-A). In the 1st trimester, NT alone can detect ≤70% of Down syndrome pregnancies, but with β-hCG and PAPP-A, the detection rate increases to 87%. If both 1st- and 2nd-trimester screens are combined using NT and biochemical profiles (integrated screen), the detection rate increases to 95%. If only 1st-trimester quad screening is done, maternal serum α-fetoprotein (which is decreased in affected pregnancies) is recommended as a 2nd-trimester follow-up.

Detection of cell-free fetal DNA in maternal plasma is also diagnostic and replacing conventional 1st- and 2nd-trimester screens. The noninvasive detection of fetal trisomy 21 by analyzing cell-free fetal DNA in maternal serum is an important advance in prenatal diagnosis of Down syndrome. Next-generation DNA sequencing has reduced the cost of this procedure, which has a high degree of accuracy (98% detection rate) and applicability. The prenatal screens are also useful for other trisomies, although the detection rates may be different from those given for Down syndrome. Current tests can detect microdeletions including 22q11.2 deletion syndrome, Angelman syndrome, Prader Willi syndrome deletion, cri du chat syndrome, Williams syndrome, and 1p36.3 deletion syndrome. Importantly, especially for microdeletions, cell-free noninvasive prenatal testing (NIPT) should be considered primarily for screening tests and follow-up invasive testing (e.g., amniocentesis) pursued for definitive diagnosis.

In approximately 95% of the cases of Down syndrome, there are 3 copies of chromosome 21. The origin of the supernumerary chromosome 21 is maternal in

97% of the cases as a result of errors in meiosis. The majority of these occur in maternal meiosis I (90%). Approximately 1% of persons with trisomy 21 are mosaics, with some cells having 46 chromosomes, and another 4% have a **translocation** that involves chromosome 21. The majority of translocations in Down syndrome are fusions at the centromere between chromosomes 13, 14, 15, 21, and 22, known as *robertsonian translocations.* The translocations can be de novo or inherited. Very rarely is Down syndrome diagnosed in a patient with only a part of the long arm of chromosome 21 in triplicate (**partial trisomy**). Isochromosomes and ring chromosomes are other rarer causes of trisomy 21. Down syndrome patients without a visible chromosome abnormality are the least common. It is not possible to distinguish the phenotypes of persons with full trisomy 21 and those with a translocation. Representative genes on chromosome 21 and their potential effects on development are noted in Table 98.9 . Patients who are mosaic tend to have a milder phenotype.

Table 98.9

Genes Localized to Chromosome 21 That May Affect Brain Development, Neuronal Loss, and Alzheimer-Type Neuropathology

SYMBOL	NAME	POSSIBLE EFFECT IN DOWN SYNDROME	FUNCTION
SIM2	Single-minded homolog 2	Brain development	Required for synchronized cell division and establishment of proper cell lineage
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Brain development	Expressed during neuroblast proliferation Believed important homolog in regulating cell-cycle kinetics during cell division
GART	Phosphoribosylglycinamide formyltransferase Phosphoribosylglycinamide synthetase Phosphoribosylaminoimidazole synthetase	Brain development	Expressed during prenatal development of the cerebellum
PCP4	Purkinje cell protein 4	Brain development	Function unknown but found exclusively in the brain and most abundantly in the cerebellum
DSCAM	Down syndrome cell adhesion molecule	Brain development and possible candidate gene for congenital heart	Expressed in all molecule regions of the brain and believed to have a role in axonal outgrowth during development of the nervous system

		disease	
GRIK1	Glutamate receptor, ionotropic kainite1	Neuronal loss	Function unknown, found in the cortex in fetal and early postnatal life and in adult primates, most concentrated in pyramidal cells in the cortex
APP	Amyloid beta (A4) precursor protein (protease nexin-II, Alzheimer disease)	Alzheimer type neuropathy	Seems to be involved in plasticity, neurite outgrowth, and neuroprotection
S100B	S100 calcium binding protein β (neural)	Alzheimer type neuropathy	Stimulates glial formation
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis, adult)	Accelerated aging?	Scavenges free superoxide molecules in the cell and might accelerate aging by producing hydrogen peroxide and oxygen

Chromosome analysis is indicated in every person suspected of having Down syndrome. If a translocation is identified, parental chromosome studies must be performed to determine whether one of the parents is a translocation carrier, which carries a high recurrence risk for having another affected child. That parent might also have other family members at risk. Translocation (21;21) carriers have a 100% recurrence risk for a chromosomally abnormal child, and other robertsonian translocations, such as t(14;21), have a 5–7% recurrence risk when transmitted by females. Genomic dosage imbalance contributes through direct and indirect pathways to the Down syndrome phenotype and its phenotypic variation.

Tables 98.10 and 98.11 provide more information on other aneuploidies and partial autosomal aneuploidies (Figs. 98.11 to 98.14).

Table 98.10

Other Rare Aneuploidies and Partial Autosomal Aneuploidies

DISORDER	KARYOTYPE	CLINICAL MANIFESTATIONS
Trisomy 8	47,XX/XY,+8	Growth and mental deficiency are variable.
		The majority of patients are mosaics.
		Deep palmar and plantar furrows are characteristic.
		Joint contractures
Trisomy 9	47,XX/XY,+9	The majority of patients are mosaics.
		Clinical features include craniofacial (high forehead, microphthalmia, low-set malformed ears, bulbous nose) and skeletal (joint contractures) malformations and heart defects (60%).
Trisomy 16	47,XX/XY,+16	The most commonly observed autosomal aneuploidy in spontaneous abortion; the recurrence risk is negligible.
Tetrasomy 12p	46,XX[12]/46,XX,+i(12p)[8] (mosaicism for an	Known as Pallister-Killian syndrome
		Sparse anterior scalp hair (more so temporal region), eyebrows, and eyelashes; prominent forehead; chubby cheeks; long philtrum with thin

isochromosome 12p)	upper lip and cupid-bow configuration; polydactyly; streaks of hyper- and hypopigmentation

Table 98.11

Findings That May Be Present in Trisomy 13 and Trisomy 18

TRISOMY 13	**TRISOMY 18**
HEAD AND FACE	
Scalp defects (e.g., cutis aplasia) Microphthalmia, corneal abnormalities Cleft lip and palate in 60–80% of cases Microcephaly Microphthalmia Sloping forehead Holoprosencephaly (arrhinencephaly) Capillary hemangiomas Deafness	Small and premature appearance Tight palpebral fissures Narrow nose and hypoplastic nasal alae Narrow bifrontal diameter Prominent occiput Micrognathia Cleft lip or palate Microcephaly
CHEST	
Congenital heart disease (e.g., VSD, PDA, ASD) in 80% of cases Thin posterior ribs (missing ribs)	Congenital heart disease (e.g., VSD, PDA, ASD) Short sternum, small nipples
EXTREMITIES	
Overlapping of fingers and toes (clinodactyly) Polydactyly Hypoplastic nails, hyperconvex nails	Limited hip abduction Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist Rocker-bottom feet Hypoplastic nails
GENERAL	
Severe developmental delays and prenatal and postnatal growth restriction Renal abnormalities Survival (see Table 98.3)	Severe developmental delays and prenatal and postnatal growth restriction Premature birth, polyhydramnios Inguinal or abdominal hernias Survival (see Table 98.3)

ASD, Atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

From Behrman RE, Kliegman RM: *Nelson essentials of pediatrics,* ed 4, Philadelphia, 2002, Saunders, p 142.

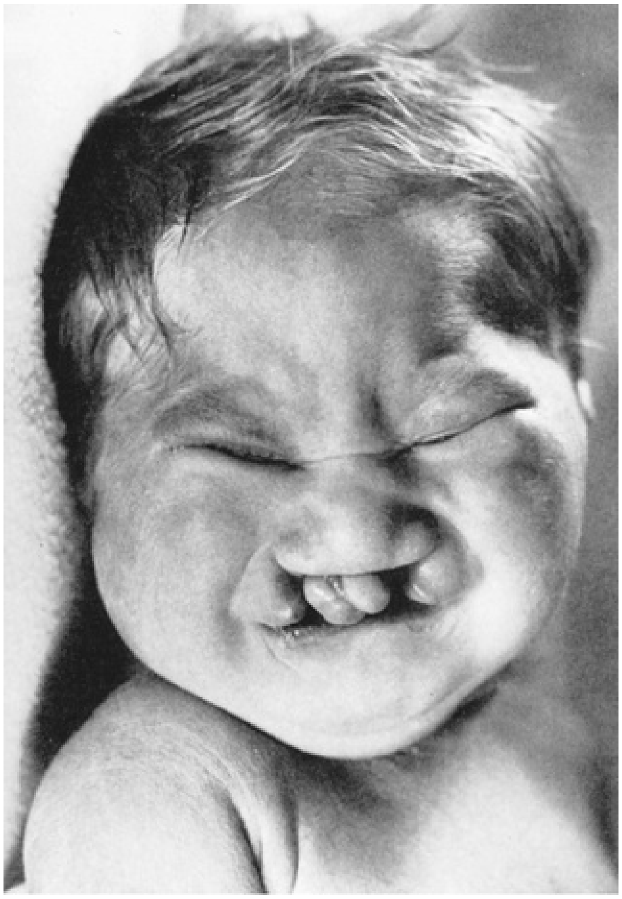

FIG. 98.11 Facial appearance of a child with trisomy 13. (From Wiedemann HR, Kunze J, Dibbern H: *Atlas of clinical syndromes: a visual guide to diagnosis,* ed 3, St Louis, 1989, Mosby.)

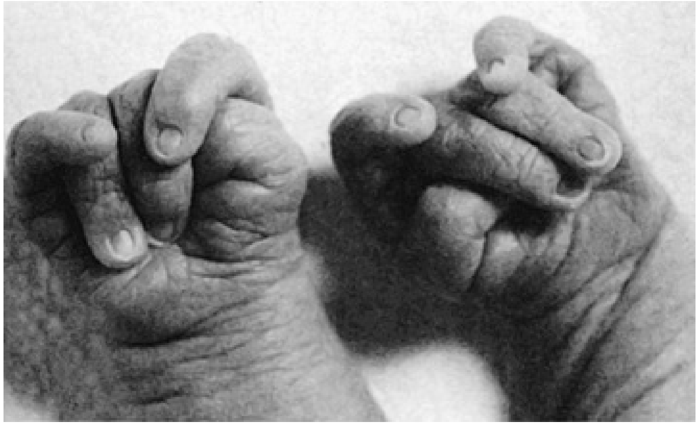

FIG. 98.12 Trisomy 18: overlapping fingers and hypoplastic nails. (From Wiedemann HR, Kunze J, Dibbern H: *Atlas of clinical syndromes: a visual guide to diagnosis,* ed 3, St Louis, 1989, Mosby.)

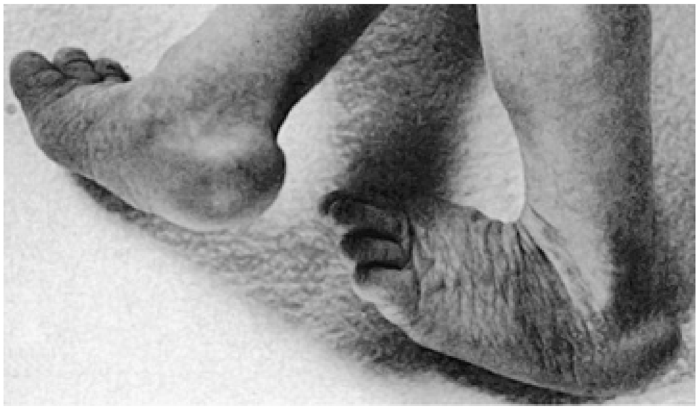

FIG. 98.13 Trisomy 18: rocker-bottom feet (protruding calcanei). (From Wiedemann HR, Kunze J, Dibbern H: *Atlas of clinical syndromes: a visual guide to diagnosis,* ed 3, St Louis, 1989, Mosby.)

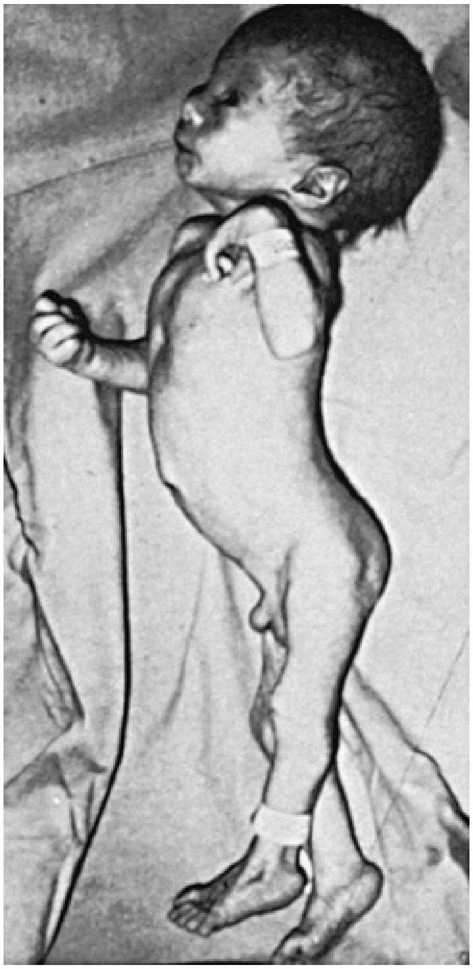

FIG. 98.14 Male infant with trisomy 18 at age 4 days. Note prominent occiput, micrognathia, low-set ears, short sternum, narrow pelvis, prominent calcaneus, and flexion abnormalities of the fingers.

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98.3

Abnormalities of Chromosome Structure

Translocations

Translocations, which involve the transfer of material from one chromosome to another, occur with a frequency of 1 in 500 liveborn human infants. They may be inherited from a carrier parent or appear de novo, with no other affected family member. Translocations are usually reciprocal or robertsonian, involving 2 chromosomes (Fig. 98.15).

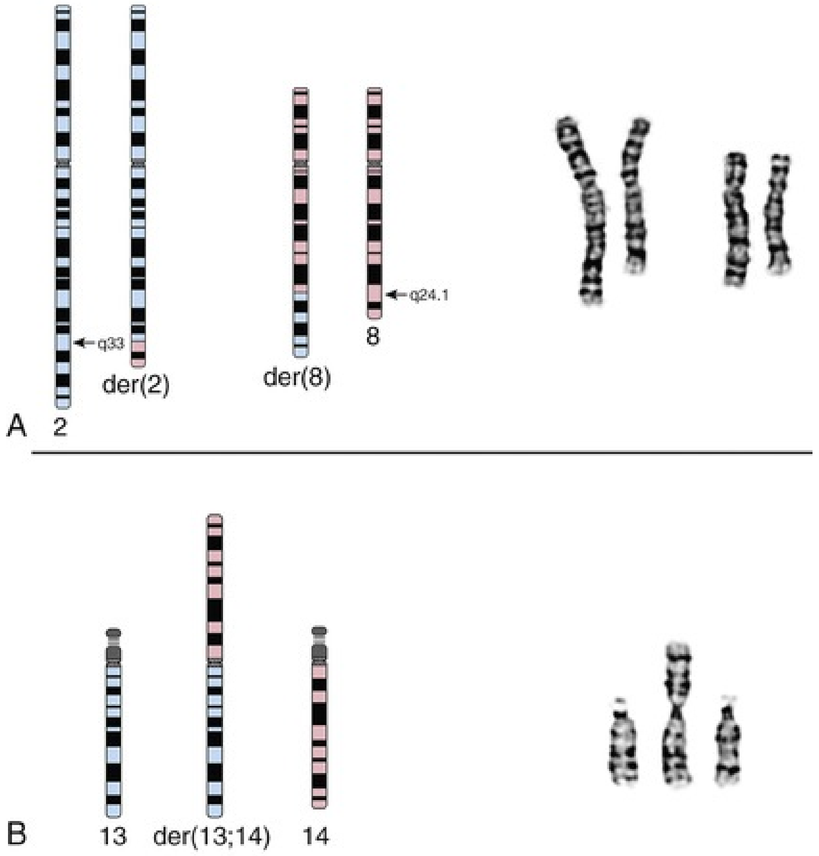

FIG. 98.15 **A,** Schematic diagram *(left)* and partial G-banded karyotype *(right)* of a reciprocal translocation between chromosome 2 *(blue)* and chromosome 8 *(pink).* The breakpoints are on the long *(q)* arm of both chromosomes at bands 2q33 and 8q24.1, with the reciprocal exchange of material between the derivative *(der)* chromosomes 2 and 8. This translocation is balanced, with no net gain or loss of material. The nomenclature for this exchange is t(2;8)(q33:q24.1). **B,** Schematic diagram

(left) and partial G-banded karyotype *(right)* of a robertsonian translocation between chromosomes 13 *(blue)* and 14 *(pink).* The breakpoints are at the centromere (band q10) of both chromosomes, with fusion of the long arms into a single derivative chromosome and loss of the short *(p)* arm material. The nomenclature for this exchange is der(13;14)(q10;q10).

Reciprocal translocations are the result of breaks in nonhomologous chromosomes, with reciprocal exchange of the broken segments. Carriers of a reciprocal translocation are usually phenotypically normal but are at an increased risk for miscarriage caused by transmission of unbalanced reciprocal translocations and for bearing chromosomally abnormal offspring. Unbalanced translocations are the result of abnormalities in the segregation or crossover of the translocation carrier chromosomes in the germ cells.

Robertsonian translocations involve 2 acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22) that fuse near the centromeric region with a subsequent loss of the short arms. Because the short arms of all 5 pairs of acrocentric chromosomes have multiple copies of genes encoding for ribosomal RNA, loss of the short arm of 2 acrocentric chromosomes has no deleterious effect. The resulting karyotype has only 45 chromosomes, including the translocated chromosome, which consists of the long arms of the 2 fused chromosomes. Carriers of robertsonian translocations are usually phenotypically normal. However, they are at increased risk for miscarriage and unbalanced translocations in phenotypically abnormal offspring.

In some rare instances, translocations can involve 3 or more chromosomes, as seen in complex rearrangements. Another, less common type is the insertional translocation. **Insertional translocations** result from a piece of chromosome material that breaks away and later is reinserted inside the same chromosome at a different site or inserted in another chromosome.

Inversions

An inversion requires that a single chromosome break at 2 points; the broken piece is then inverted and joined into the same chromosome. Inversions occur in 1 in 100 live births. There are 2 types of inversions: pericentric and paracentric. In **pericentric inversions** the breaks are in the 2 opposite arms of the chromosome and include the centromere. They are usually discovered because they change the position of the centromere. The breaks in **paracentric inversions** occur in only 1 arm. Carriers of inversions are usually phenotypically normal, but they are at increased risk for miscarriages, typically in paracentric inversions, and chromosomally abnormal offspring in pericentric inversions.

Deletions and Duplications

Deletions involve loss of chromosome material and, depending on their location, can be classified as **terminal** (at the end of chromosomes) or **interstitial** (within the arms of a chromosome). They may be isolated or may occur along with a duplication of another chromosome segment. The latter typically occurs in unbalanced reciprocal chromosomal translocation secondary to abnormal crossover or segregation in a translocation or inversion carrier.

A carrier of a deletion is monosomic for the genetic information of the missing segment. Deletions are usually associated with intellectual disability and malformations. The most commonly observed deletions in routine chromosome preparations include 1p−, 4p−, 5p−, 9p−, 11p−, 13q−, 18p−, 18q−, and 21q− (Table 98.12 and Fig. 98.16), all distal or terminal deletions of the short or the long arms of chromosomes. Deletions may be observed in routine chromosome preparations, and deletions and translocations larger than 5-10 Mbp are usually visible microscopically.

Table 98.12

Common Deletions and Their Clinical Manifestations

DELETION	CLINICAL ABNORMALITIES
4p−	Wolf-Hirschhorn syndrome. The main features are a typical “Greek helmet” facies secondary to ocular hypertelorism, prominent glabella, and frontal bossing; microcephaly, dolichocephaly, hypoplasia of the orbits, ptosis, strabismus, nystagmus, bilateral epicanthic folds, cleft lip and palate, beaked nose with prominent bridge, hypospadias, cardiac malformations, and intellectual disability.
5p−	Cri du chat syndrome. The main features are hypotonia, short stature, characteristic shrill cry in the first few weeks of life (also called cat's cry syndrome), microcephaly with protruding metopic suture, hypertelorism, bilateral epicanthic folds, high arched palate, wide and flat nasal bridge, and intellectual disability.
9p−	The main features are craniofacial dysmorphic features with trigonocephaly, slanted palpebral fissures, discrete exophthalmos secondary to supraorbital hypoplasia, arched eyebrows, flat and wide nasal bridge, short neck with low hairline, genital anomalies, long fingers and toes with extra flexion creases, cardiac malformations, and intellectual disability.
13q−	The main features are low birthweight, failure to thrive, microcephaly, and severe intellectual disability. Facial features include high, wide nasal bridge; hypertelorism; ptosis; and micrognathia. Ocular malformations are common (retinoblastoma). The hands have hypoplastic or absent thumbs and syndactyly.
18p−	A few patients (15%) are severely affected and have cephalic and ocular malformations: holoprosencephaly, cleft lip and palate, ptosis, epicanthal folds, and varying degrees of intellectual

	disability. Most (80%) have only minor malformations and mild intellectual disability.
18q−	The main features are growth deficiency and hypotonia with a “froglike” position with the legs flexed, externally rotated, and in hyperabduction. The face is characteristic, with depressed midface and apparent protrusion of the mandible, deep-set eyes, short upper lip, and everted lower lip (“carplike” mouth); antihelix of the ears is very prominent. Varying degrees of intellectual disability and belligerent personality are present. Myelination abnormalities occur in the central nervous system.

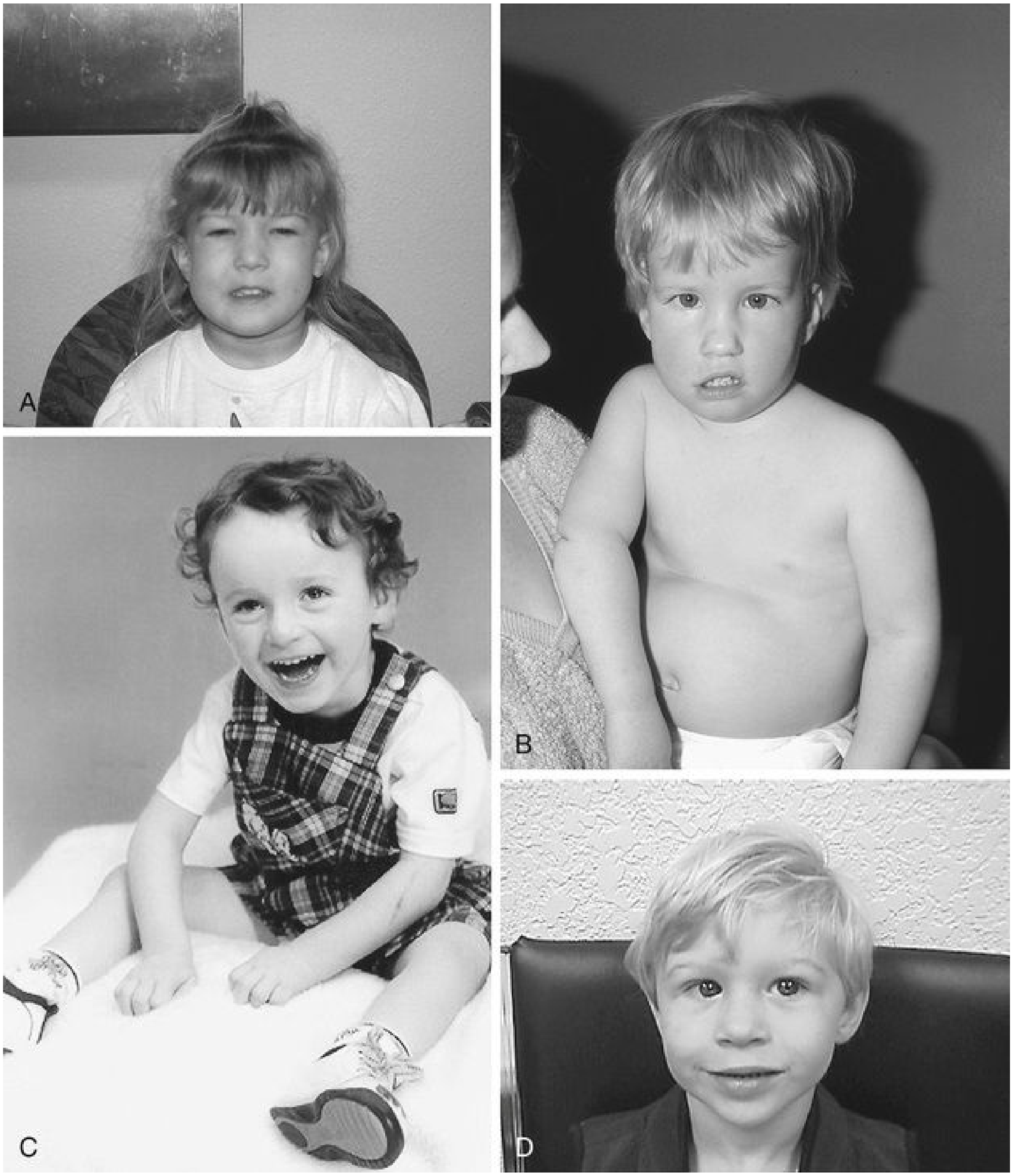

FIG. 98.16 **A,** Child with velocardiofacial syndrome (deletion 22q11.2). **B,** Child with Prader-Willi syndrome (deletion 15q11-13). **C,** Child with Angelman syndrome (deletion 15q11-13). **D,** Child with Williams syndrome (deletion 7q11.23). (From Lin RL, Cherry AM, Bangs CD, et al: FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In Hyme HE, Greydanus D, editors: *Genetic disorders in adolescents: state of the art reviews. Adolescent medicine,* Philadelphia, 2002, Hanley and Belfus, pp 305–313.)

High-resolution banding techniques, FISH, and molecular studies such as aCGH can reveal deletions that are too small to be seen in ordinary or routine chromosome spreads (see Fig. 98.7). **Microdeletions** involve loss of small chromosome regions, the largest of which are detectable only with prophase chromosome studies and molecular methods. For submicroscopic deletions, the missing piece can only be detected using molecular methodologies such as DNA-based studies (e.g., aCGH, FISH). The presence of extra genetic material from the same chromosome is referred to as **duplication** . Duplications can also be sporadic or result from abnormal segregation in translocation or inversion carriers.

Microdeletions and microduplications usually involve regions that include several genes, so the affected individuals can have a distinctive phenotype depending on the number of genes involved. When such a deletion involves more than a single gene, the condition is referred to as a **contiguous gene deletion syndrome** (Table 98.13). With the advent of clinically available aCGH, a large number of duplications, most of them microduplications, have been uncovered. Many of those **microduplication syndromes** are the reciprocal duplications of the known deletions or microdeletion counterparts and have distinctive clinical features (Table 98.14).

Table 98.13

Microdeletion and Contiguous Gene Syndromes and Their Clinical Manifestations

DELETION	SYNDROME	CLINICAL MANIFESTATIONS
1p36	1p deletion	Growth restriction, dysmorphic features with midface hypoplasia, straight thin eyebrows, pointy chin, sensorineural hearing loss, progressive cardiomyopathy, hypothyroidism, seizures, intellectual disability
5q35	Sotos (50% are deletions of *NSD1* gene in Asians but only 6% in whites)	Overgrowth, macrocephaly, prominent forehead, prominence of extraaxial fluid spaces on brain imaging, large hands and feet, hypotonia, clumsiness, mental disabilities
6p25	Axenfeld-Rieger	Axenfeld-Rieger malformation, hearing loss, congenital heart defects, dental anomalies, developmental delays, facial dysmorphism

7q11.23	Williams	Round face with full cheeks and lips, long philtrum, stellate pattern in iris, strabismus, supravalvular aortic stenosis and other cardiac malformations, varying degrees of intellectual disability, friendly personality
8p11	8p11	Kallmann syndrome type 2 (hypogonadotropic hypogonadism and anosmia), spherocytosis (deletions of ankyrin 1), multiple congenital anomalies, intellectual disability
8q24.1-q24.13	Langer-Giedion or trichorhinophalangeal type II	Sparse hair, multiple cone-shaped epiphyses, multiple cartilaginous exostoses, bulbous nasal tip, thickened alar cartilage, upturned nares, prominent philtrum, large protruding ears, mild intellectual disability
9q22	Gorlin	Multiple basal cell carcinomas, odontogenic keratocysts, palmoplantar pits, calcification falx cerebri
9q34	9q34 deletion	Distinct face with synophrys, anteverted nares, tented upper lip, protruding tongue, midface hypoplasia, conotruncal heart defects, intellectual disability
10p12-p13	DiGeorge type 2	Many of the DiGeorge type 1 and velocardiofacial type 1 features (conotruncal defects, immunodeficiency, hypoparathyroidism, dysmorphic features)
11p11.2	Potocki-Shaffer	Multiple exostoses, parietal foramina, craniosynostosis, facial dysmorphism, syndactyly, intellectual disability
11p13	WAGR	Hypernephroma (*W*ilms tumor), *a*niridia, male *g*enital hypoplasia of varying degrees, *g*onadoblastoma, long face, upward-slanting palpebral fissures, ptosis, beaked nose, low-set poorly formed auricles, intellectual disability (*r*etardation)
11q24.1-11qter	Jacobsen	Growth restriction, intellectual disability, cardiac and digit anomalies, thrombocytopenia
15q11-q13 (paternal)	Prader-Willi	Severe hypotonia and feeding difficulties at birth, voracious appetite and obesity in infancy, short stature (responsive to growth hormone), small hands and feet, hypogonadism, intellectual disability
15q11-q13 (maternal)	Angelman	Hypotonia, feeding difficulties, gastroesophageal reflux, fair hair and skin, midface hypoplasia, prognathism, seizures, tremors, ataxia, sleep disturbances, inappropriate laughter, poor or absent speech, severe intellectual disability
16p13.3	Rubinstein-Taybi	Microcephaly, ptosis, beaked nose with low-lying philtrum, broad thumbs and large toes, intellectual disability
17p11.2	Smith-Magenis	Brachycephaly, midfacial hypoplasia, prognathism, myopia, cleft palate, short stature, severe behavioral problems, intellectual disability
17p13.3	Miller-Dieker	Microcephaly, lissencephaly, pachygyria, narrow forehead, hypoplastic male external genitals, growth restriction, seizures, profound intellectual disability
20p12	Alagille	Bile duct paucity with cholestasis; heart defects, particularly pulmonary artery stenosis; ocular abnormalities (posterior embryotoxon); skeletal defects such as butterfly vertebrae; long nose
22q11.2	Velocardiofacial-DiGeorge	Conotruncal cardiac anomalies, cleft palate, velopharyngeal incompetence, hypoplasia or agenesis of thymus and parathyroid glands, hypocalcemia, hypoplasia of auricle, learning disabilities, psychiatric disorders
22q13.3 deletion		Hypotonia, developmental delay, normal or accelerated growth, severe expressive language deficits, autistic behavior
Xp21.2-p21.3		Duchenne muscular dystrophy, retinitis pigmentosa, adrenal hypoplasia, intellectual disability, glycerol kinase deficiency
Xp22.2-p22.3		Ichthyosis, Kallmann syndrome, intellectual disability, chondrodysplasia punctata
Xp22.3	MLS	*M*icrophthalmia, *l*inear *s*kin defects, poikiloderma, congenital heart defects, seizures, intellectual disability

Table 98.14

Microduplications and Their Clinical Manifestations

DUPLICATION CHROMOSOME REGION	DISEASE REGION	CLINICAL FEATURES
1q21.1		Macrocephaly, DD, learning disabilities
3q29		Mild to moderate MR, microcephaly
7q11.23	Williams syndrome	DD and severe expressive language disorder, autistic features, subtle dysmorphisms
15q13.3	Prader-Willi/Angelman syndrome	DD, MR, autistic features in duplications of maternal origin
15q24		Growth restriction, DD, microcephaly, digital anomalies, hypospadias, connective tissue abnormalities
16p11.2		FTT, severe DD, short stature, GH deficiency, dysmorphic features
17p11.2	Potocki-Lupski syndrome	Hypotonia, cardiovascular anomalies, FTT, DD, verbal apraxia, autism, anxiety
17q21.31		Severe DD, microcephaly, short and broad digits, dysmorphic features
22q11.2	Velocardiofacial-DiGeorge syndrome	Cardiovascular defects, velopharyngeal insufficiency
Xq28	*MECP2* gene (Rett syndrome)	In males: infantile hypotonia, immune deficiency, dysmorphic features, DD, speech delay, autistic behavior, regression in childhood

DD, Developmental delay; ID, intellectual disability; FTT, failure to thrive; GH, growth hormone; MR, mental retardation.

Subtelomeric regions are often involved in chromosome rearrangements that cannot be visualized using routine cytogenetics. *Telomeres*, which are the distal ends of the chromosomes, are gene-rich regions. The distal structure of the telomeres is essentially common to all chromosomes, but proximal to these are unique regions known as *subtelomeres,* which typically are involved in deletions and other chromosome rearrangements. Small subtelomeric deletions, duplications, or rearrangements (translocations, inversions) may be relatively common in children with nonspecific intellectual disability and minor anomalies. Subtelomeric rearrangements have been found in 3–7% of children with moderate to severe intellectual disability and 0.5% of those with mild intellectual disability and can be detected by aCGH studies.

Telomere mutations and length abnormalities have also been associated with dyskeratosis congenita and other aplastic anemia syndromes, as well as pulmonary or hepatic fibrosis. Both the subtelomeric rearrangements and the microdeletion and microduplication syndromes are typically diagnosed by molecular techniques such as aCGH and multiple ligation-dependent primer amplification studies. Recent studies show that aCGH can detect 14–18% of abnormalities in patients who previously had normal chromosome studies.

Insertions

Insertions occur when a piece of a chromosome broken at 2 points is incorporated into a break in another part of a chromosome. A total of 3 breakpoints are then required, and they can occur between 2 or within 1 chromosome. A form of nonreciprocal translocation, insertions are rare. Insertion carriers are at risk of having offspring with deletions or duplications of the inserted segment.

Isochromosomes

Isochromosomes consist of 2 copies of the same chromosome arm joined through a single centromere and forming mirror images of one another. The most commonly reported autosomal isochromosomes tend to involve chromosomes with small arms. Some of the more common chromosome arms involved in this formation include 5p, 8p, 9p, 12p, 18p, and 18q. There is also a common isochromosome abnormality seen in long arm of the X chromosome and associated with Turner syndrome. Individuals who have 1 isochromosome X within 46 chromosomes are monosomic for genes in the lost short arm and trisomic for the genes present in the long arm of the X chromosome.

Marker and Ring Chromosomes

Marker chromosomes are rare and are usually chromosome fragments that are too small to be identified by conventional cytogenetics; they usually occur in addition to the normal 46 chromosomes. Most are sporadic (70%); mosaicism is often (50%) noted because of the mitotic instability of the marker chromosome. The incidence in newborn infants is 1 in 3,300, and the incidence in persons with intellectual disability is 1 in 300. The associated phenotype ranges from normal to severely abnormal, depending on the amount of chromosome material and number of genes included in the fragment.

Ring chromosomes, which are found for all human chromosomes, are rare. A ring chromosome is formed when both ends of a chromosome are deleted and the ends are then joined to form a ring. Depending on the amount of chromosome material that is lacking or in excess (if the ring is in addition to the normal chromosomes), a patient with a ring chromosome can appear normal or nearly normal or can have intellectual disability and multiple congenital anomalies.

Marker and ring chromosomes can be found in the cells of solid tumors of children the cells of whose organs do not contain this additional chromosomal material.

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Abnormalities of Chromosome Structure

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98.4

Sex Chromosome Aneuploidy

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About 1 in 400 males and 1 in 650 females have some form of sex chromosome abnormality. Considered together, sex chromosome abnormalities are the most common chromosome abnormalities seen in liveborn infants, children, and adults. Sex chromosome abnormalities can be either structural or numerical and can be present in all cells or in a mosaic form. Those affected with these abnormalities might have few or no physical or developmental problems (Table 98.15).

Table 98.15

Sex Chromosome Abnormalities

DISORDER	KARYOTYPE	APPROXIMATE INCIDENCE
Klinefelter syndrome	47,XXY	1/580 males
	48,XXXY	1/50,000-1/80,000 male births
	Other (48,XXYY; 49,XXXYY; mosaics)	
XYY syndrome	47,XYY	1/800-1,000 males
Other X or Y chromosome abnormalities		1/1,500 males
XX males	46,XX	1/20,000 males
Turner syndrome	45,X	1/2,500-1/5,000 females
	Variants and mosaics	
Trisomy X	47,XXX	1/1,000 females
	48,XXXX and 49,XXXXX	Rare
Other X chromosome abnormalities		1/3,000 females
XY females	46,XY	1/20,000 females

Turner Syndrome

Turner syndrome is a condition characterized by complete or partial monosomy of the X chromosome and defined by a combination of phenotypic features (Table 98.16). Half the patients with Turner syndrome have a 45,X chromosome complement. The other half exhibit mosaicism and varied structural abnormalities of the X or Y chromosome. Maternal age is not a predisposing factor for children with 45,X. Turner syndrome occurs in approximately 1 in 5,000 female live births. In 75% of patients, the lost sex chromosome is of paternal origin (whether an X or a Y). 45,X is one of the chromosome abnormalities most often associated with spontaneous abortion. It has been estimated that 95–99% of 45,X conceptions are miscarried.

Table 98.16

Signs Associated With Turner Syndrome

- Short stature
- Congenital lymphedema
- Horseshoe kidneys
- Patella dislocation
- Increased carrying angle of elbow (cubitus valgus)
- Madelung deformity (chondrodysplasia of distal radial epiphysis)
- Congenital hip dislocation
- Scoliosis
- Widespread nipples
- Shield chest
- Redundant nuchal skin (in utero cystic hygroma)
- Low posterior hairline
- Coarctation of aorta
- Bicuspid aortic valve
- Cardiac conduction abnormalities
- Hypoplastic left heart syndrome and other left-sided heart abnormalities
- Gonadal dysgenesis (infertility, primary amenorrhea)
- Gonadoblastoma (increased risk if Y chromosome material is present)
- Learning disabilities (nonverbal perceptual motor and visuospatial skills) (in 70%)
- Developmental delay (in 10%)
- Social awkwardness
- Hypothyroidism (acquired in 15–30%)
- Type 2 diabetes mellitus (insulin resistance)

Strabismus
Cataracts
Red-green color blindness (as in males)
Recurrent otitis media
Sensorineural hearing loss
Inflammatory bowel disease
Celiac disease (increased incidence)

Clinical findings in the newborns can include small size for gestational age, webbing of the neck, protruding ears, and lymphedema of the hands and feet, although many newborns are phenotypically normal (Fig. 98.17). Older children and adults have short stature and exhibit variable dysmorphic features. Congenital heart defects (40%) and structural renal anomalies (60%) are common. The most common heart defects are bicuspid aortic valves, coarctation of the aorta, aortic stenosis, and mitral valve prolapse. The gonads are generally streaks of fibrous tissue (**gonadal dysgenesis**). There is primary amenorrhea and lack of secondary sex characteristics. These children should receive regular endocrinologic testing (see Chapter 604). Most patients tend to be of normal intelligence, but intellectual disability is seen in up to 6% of affected children. They are also at increased risk for behavioral problems and deficiencies in spatial and motor perception. Guidelines for health supervision for children with Turner syndrome are published by the American Academy of Pediatrics (AAP) and include pubertal induction, as well as treatment with growth hormone and oxandrolone.

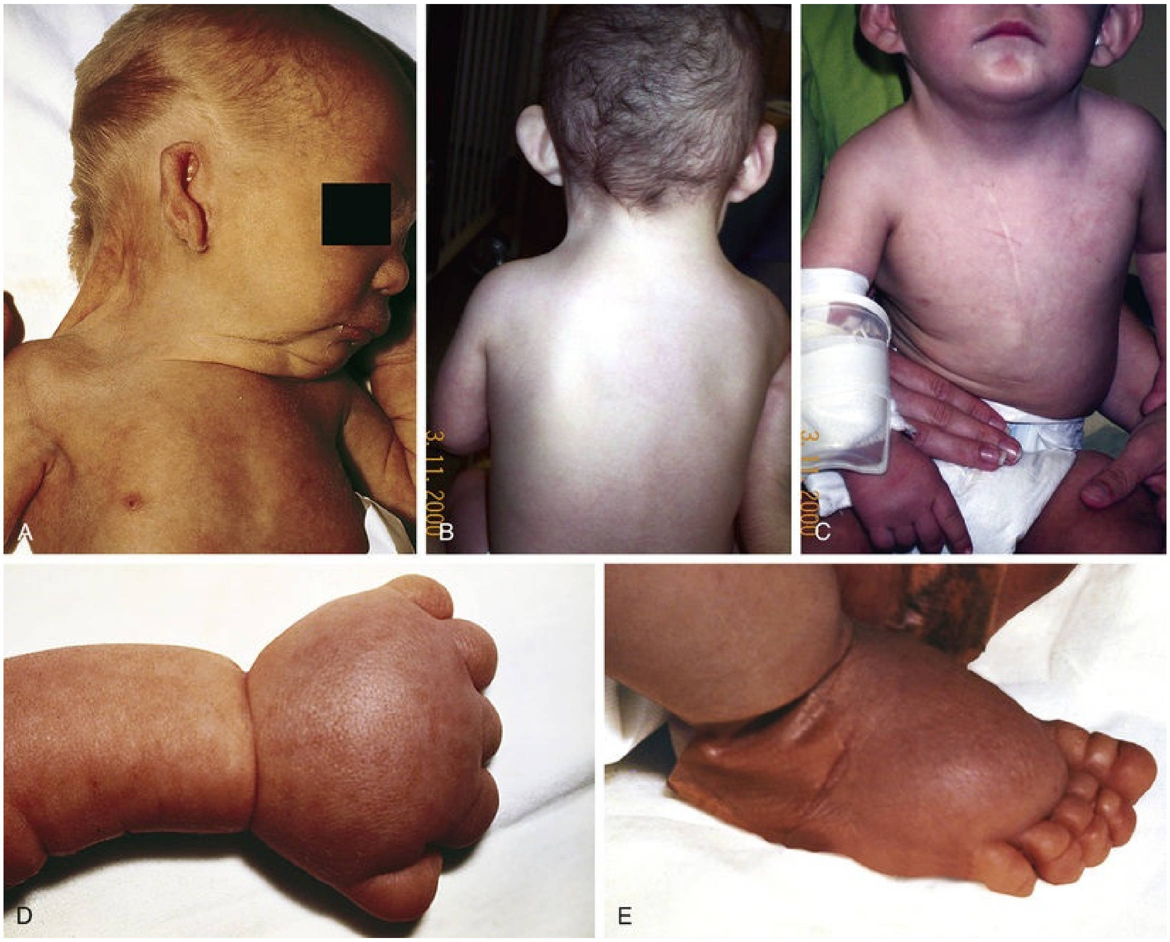

FIG. 98.17 Physical manifestations associated with turner syndrome. A, This newborn shows a webbed neck with low hairline, shield chest with widespread nipples, abnormal ears, and micrognathia. B, The low-set posterior hairline can be better appreciated in this older child, who also has protruding ears. C, In this frontal view, mild webbing of the neck and small, widely spaced nipples are evident, along with a midline scar from prior cardiac surgery. The ears are low set and prominent, protruding forward. D and E, The newborn shown in A also has prominent lymphedema of the hands and feet. (From Madan-Khetarpal S, Arnold G: Genetic disorders and dysmorphic conditions. In Zitelli BJ, McIntire SC, Nowalk AJ, editors: *Zitelli and Davis' atlas of pediatric physical diagnosis,* ed 6, Philadelphia, 2012, Elsevier, Fig 1.25.)

Patients with **45,X/46,XY mosaicism** can have Turner syndrome, although this form of mosaicism can also be associated with male pseudohermaphroditism, male or female genitalia in association with mixed gonadal dysgenesis, or a normal male phenotype. This variant is estimated to represent approximately 6% of patients with mosaic Turner syndrome. Some of the patients with Turner syndrome phenotype and a Y cell line exhibit masculinization. Phenotypic females with 45,X/46,XY mosaicism have a 15–30% risk of developing **gonadoblastoma** . The risk for the patients with a male phenotype and external testes is not so high, but tumor surveillance is nevertheless recommended. AAP has recommended the use of FISH analysis to look for Y chromosome mosaicism in all 45,X patients. If Y chromosome material is identified, laparoscopic gonadectomy is recommended.

Noonan syndrome shares many clinical features with Turner syndrome and was formerly called *pseudo-Turner syndrome* , although it is an autosomal dominant disorder resulting from mutations in several genes involved in the RAS-MAPK (mitogen-activated protein kinase) pathway. The most common of these is *PTPN11* (50%), which encodes a protein-tyrosine phosphatase (SHP-2) on chromosome 12q24.1. Other genes include *SOS1* in 10–13%, *RAF1* in 3–17%, *RITI* in 5%, *KRAS* <5%, *BRAF* <2%, *MAP2K* <2%, and *NRAS* (only few reported families). Overlapping phenotypes are seen in LEOPARD (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness) syndrome, cardiofaciocutaneous (CFC) syndrome, and Costello syndrome; these are Noonan-related disorders. Features common to Noonan syndrome include short stature, low posterior hairline, shield chest, congenital heart disease, and a short or webbed neck (Table 98.17). In contrast to Turner syndrome, Noonan syndrome affects both sexes and has a different pattern of congenital heart disease, typically involving right-sided lesions.

Table 98.17

Signs Associated With Noonan Syndrome

Short stature
Failure to thrive (best to use Noonan growth curve)
Tall forehead
Epicanthal folds
Ptosis
Blue-green irises
Hypertelorism
Low nasal bridge, upturned nose
Downward-slanting palpebral fissures
Myopia
Nystagmus
Low-set and posteriorly rotated auricles
Dental malocclusion
Low posterior hairline
Short, webbed neck (excessive nuchal skin), cystic hygroma

Shield chest
Pectus carinatum superiorly
Scoliosis
Pigmented villonodular synovitis (polyarticular)
Cubitus valgus
Pulmonary valve stenosis (dysplastic valve)
Hypertrophic cardiomyopathy
Atrial septal defect, ventricular septal defect
Lymphedema
Nevi, lentigines, café au lait spots
Cryptorchidism
Small penis
Delayed puberty
Bleeding disorders, including thrombocytopenia and coagulation factor deficiencies
Leukemia, myeloproliferative disorders, other malignancies
Cognitive delay (*KRAS* mutation)

Klinefelter Syndrome

Persons with Klinefelter syndrome are phenotypically male; this syndrome is the most common cause of hypogonadism and infertility in males and the most common sex chromosome aneuploidy in humans (see Chapter 601). Eighty percent of children with Klinefelter syndrome have a male karyotype with an extra chromosome X-47,XXY. The remaining 20% have multiple sex chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY), mosaicism (46,XY/47,XXY), or structurally abnormal X chromosomes; the greater the aneuploidy, the more severe the mental impairment and dysmorphism. Early studies showed a birth prevalence of approximately 1 in 1,000 males, but more recent studies suggest that the prevalence of 47,XXY appears has increased to approximately 1 in 580 liveborn males; the reasons for this are still unknown but hypothesized to be the result of environmental factors acting in spermatogenesis. Errors in paternal nondisjunction in meiosis I account for half the cases.

Puberty commences at the normal age, but the testes remain small. Patients develop secondary sex characters late, and 50% ultimately develop gynecomastia. They have taller stature. Because many patients with Klinefelter syndrome are phenotypically normal until puberty, the syndrome often goes undiagnosed until they reach adulthood, when their infertility leads to identification. Patients with 46,XY/47,XXY have a better prognosis for testicular function. Their intelligence shows variability and ranges from above to below average. Persons with Klinefelter syndrome can show behavioral problems, learning disabilities, and deficits in language. Problems with self-esteem often occur in adolescents and adults. Substance abuse, depression, and anxiety have been reported in adolescents with Klinefelter syndrome. Those who have higher X chromosome counts show impaired cognition. It has been estimated that each additional X chromosome reduces the IQ by 10-15 points, when comparing these individuals with typical siblings. The main effect is seen in language skills and social domains.

47,XYY

The incidence of 47,XYY is approximately 1 in 800-1,000 males, with many cases remaining undiagnosed, because most affected individuals have a normal appearance and normal fertility. The extra Y is the result of nondisjunction at paternal meiosis II. Those with this abnormality have normal intelligence but are at risk for learning disabilities. Behavioral abnormalities, including hyperactive behavior, pervasive developmental disorder, and aggressive behavior, have been reported. Early reports that assigned stigmata of criminality to this disorder have long been disproved.

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98.5

Fragile Chromosome Sites

Carlos A. Bacino, Brendan Lee

Fragile sites are regions of chromosomes that show a tendency for separation, breakage, or attenuation under particular growth conditions. They visually appear as a gap in the staining in chromosome studies. At least 120 chromosomal loci, many of them heritable, have been identified as fragile sites in the human genome (see Table 97.2).

A clinically significant fragile site is on the distal long arm of chromosome Xq27.3 associated with the **fragile X syndrome** . Fragile X syndrome accounts for 3% of males with intellectual disability. There is another fragile site on the X chromosome (FRAXE on Xq28) that has also been implicated in mild intellectual disability. The FRA11B (11q23.3) breakpoints are associated with **Jacobsen syndrome** (condition caused by deletion of the distal long arm of chromosome 11). Fragile sites can also play a role in tumorigenesis. In fragile X syndrome the CGG repeat expansion silences the gene producing **fragile X mental retardation protein (FMRP)** that regulates the translation of multiple mRNAs to specific proteins, thus affecting synaptic function. FMRP deficiency upregulates the metabotropic glutamate receptor (mGluR) 5 pathway. FMRP deficiency also alters the expression of matrix metalloproteinase (MMP) 9.

The main clinical manifestations of fragile X syndrome in affected males are intellectual disability, autistic behavior, postpubertal macroorchidism, hyperextensible finger joints, and characteristic facial features (Table 98.18). The facial features, which include a long face, large ears, and a prominent square jaw, become more obvious with age. Females affected with fragile X show varying degrees of intellectual disability and/or learning disabilities. Diagnosis of fragile X syndrome is possible by DNA testing that shows an expansion of a triplet DNA repeat inside the *FMR1* gene on the X chromosome >200 repeats. The expansion involves an area of the gene that contains a variable number of trinucleotide (CGG) repeats (typically <50 in unaffected individuals). The larger the triplet repeat expansion, the more significant is the intellectual disability. In cases where the expansion is large, females can also manifest different degrees of intellectual disability. Males with premutation triple repeat expansions (55-200 repeats) have been found to have an adult, late-onset, progressive neurodegenerative disorder known as **fragile X–associated tremor/ataxia syndrome** . Females with premutation triple repeat expansions are at high risk for developing premature ovarian failure (POF).

Table 98.18

Clinical Features of Full and Premutation *FMR1* Alleles

DISORDER	PHENOTYPE		ONSET	PENETRANCE
	Cognitive or Behavioral	Clinical and Imaging Signs		
FULL MUTATION (>200 repeats)				
FXS	Developmental delay: mean IQ = 42 in M; IQ is higher if significant residual FMRP is produced (e.g., females and mosaic males or unmethylated full mutations) Autism 20–30% ADHD 80% Anxiety 70–100%	Hypothalamic dysfunction: macroorchidism, 40%[*] Facial features, 60%,[*] large cupped ears, elongated face, high arched palate Connective tissue abnormalities: mitral valve prolapse, scoliosis, joint laxity, flat feet Others: seizures (20%), recurrent otitis media (60%), strabismus (8–30%)	Neonate	M 100%
PREMUTATION (55-200 repeats)				
Female reproductive symptoms		POF (<40 yr)	Adult/childhood	F 20% [†]
		Early menopause (<45 yr)		F 30% [†]
FXTAS	Cognitive decline, dementia, apathy, disinhibition, irritability, depression	Gait ataxia, intention tremor, parkinsonism, neuropathy, autonomic dysfunction	>50 yr	M 33% [‡] F unknown
Neurodevelopmental disorder	ADHD, autism, or developmental delay	Mild features of FXS	Childhood	8% (1/13)[*]

[*] Frequency of those signs in prepubertal boys; one third of boys with FXS are without classic facial features. Macroorchidism is present in 90% of men.

[†] Maximum penetrance reported for allele size approximately 80-90 CGG repeats.

[‡] Penetrance is correlated with age and repeat size.

ADHD, Attention-deficit/hyperactivity disorder; F, female; FMRP, fragile X mental retardation protein; FXS, fragile X syndrome; FXTAS, fragile X–associated tremor/ataxia syndrome; M, male; POF, premature ovarian failure.

From Jacquemont S, Hagerman RJ, Hagerman PJ, et al: Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMRI, *Lancet Neurol* 6:45–55, 2007, Table 1.

Table 98.19 outlines therapy of the diverse neuropsychiatric manifestations associated with fragile X syndrome. Inhibitors of mGluR (overexpressed in fragile X) are undergoing clinical trials. In preliminary trials, minocycline (lowers MMP-9) has resulted in short-term improvements in anxiety, mood, and the clinical Global Impression Scale.

Table 98.19

Therapy for *FMR1* -Related Disorders

DISORDER	SYMPTOM	THERAPY AND INTERVENTIONS	FUTURE POTENTIAL THERAPY
FULL MUTATION			
FXS[*]	ADHD	Stimulants	mGluR5 antagonists
	Anxiety, hyperarousal, aggressive outbursts	SSRIs, atypical antipsychotics, occupational therapy, behavioral therapy, counseling	mGluR5 antagonists
	Seizures	Carbamazepine, valproic acid	mGluR5 antagonists
	Cognitive deficit	Occupational therapy, speech therapy, special education support	mGluR5 antagonists
PREMUTATION			
POF	Premature ovarian failure	Reproductive counseling, egg donation	Cryopreservation of ovarian tissue
		Hormone replacement therapy	
FXTAS [†]	Intention tremor	β-Blockers	
	Parkinsonism	Carbidopa/levodopa	
	Cognitive decline, dementia	Acetylcholinesterase inhibitors	
	Anxiety, apathy, disinhibition, irritability, depression	Venlafaxine, SSRIs	
	Neuropathic pain	Gabapentin	

[*] These data are based on a survey in 2 large referral centers. Drugs for anxiety were more frequently prescribed than those for neurologic signs.

[†] There have been no controlled studies to assess drugs for FXTAS. These data were collected through a questionnaire study (n = 56).

ADHD, Attention-deficit/hyperactivity disorder; FXS, fragile-X syndrome; FXTAS, fragile X–associated tremor/ataxia syndrome; POF, premature ovarian failure; SSRIs, selective serotonin reuptake inhibitors.

From Jacquemont S, Hagerman RJ, Hagerman PJ, et al: Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMRI, *Lancet Neurol* 2006:45–55, 2007, Table 2.

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98.6

Mosaicism

Carlos A. Bacino, Brendan Lee

Mosaicism describes an individual or tissue that contains ≥2 different cell lines typically derived from a single zygote and the result of mitotic nondisjunction (see Fig. 98.1). Study of placental tissue from chorionic villus samples collected at or before the 10th wk of gestation has shown that ≥2% of all conceptions are mosaic for a chromosome abnormality. With the exception of chromosomes 13, 18, and 21, complete autosomal trisomies are usually nonviable; the presence of a normal cell line might allow these other trisomic conceptions to survive to term. Depending on the point at which the new cell line arises during early embryogenesis, mosaicism may be present in some tissues but not in others. **Germline mosaicism** , which refers to the presence of mosaicism in the germ cells of the gonad, may be associated with an increased risk for recurrence of an affected child if the germ cells are affected with a chromosomal abnormality or with a specific gene mutation.

Pallister-Killian Syndrome

Pallister-Killian syndrome is characterized by coarse facies (prominent full cheeks), abnormal ear lobes, localized alopecia (sparse hair in the temporal regions), pigmentary skin anomalies, diaphragmatic hernia, cardiovascular anomalies, supernumerary nipples, seizures, and profound intellectual disability. The syndrome is caused by mosaicism for an isochromosome 12p. The presence of the isochromosome 12p in cells gives 4 functional copies for the short arm of chromosome 12 in the affected cells. The isochromosome 12p is preferentially cultured from fibroblasts that can be readily obtained from a skin punch biopsy and is seldom present in lymphocytes. The abnormalities seen in affected persons probably reflect the presence of abnormal cells during early embryogenesis.

Hypomelanosis of Ito

Hypomelanosis of Ito is characterized by unilateral or bilateral macular hypo- or hyperpigmented whorls, streaks, and patches (see Chapter 672). Sometimes these pigmentary defects follow the lines of Blaschko. Hair and tooth anomalies are common. Abnormalities of the eyes, musculoskeletal system (growth asymmetry, syndactyly, polydactyly, clinodactyly), and central nervous system (microcephaly, seizures, intellectual disability) may also be present. Patients with hypomelanosis of Ito might have two genetically distinct cell lines. The mosaic chromosome anomalies that have been observed involve both autosomes and sex chromosomes and have been demonstrated in about 50% of clinically affected patients. The mosaicism might not be visible in lymphocyte-derived chromosome studies; it is more likely to be found when chromosomes are analyzed from skin fibroblasts. The distinct cell lines might not always be caused by observable chromosomal anomalies but might result from single-gene mutations or other mechanisms.

98.7

Chromosome Instability Syndromes

Carlos A. Bacino, Brendan Lee

Chromosome instability syndromes, formerly known as *chromosome breakage syndromes,* are characterized by an increased risk of malignancy and specific phenotypes. They display autosomal recessive inheritance and have an increased frequency of chromosome breakage and/or rearrangement, either spontaneous or induced. Chromosome instability syndromes result from specific defects in DNA repair, cell cycle control, and apoptosis. The resulting chromosomal instability leads to the increased risk of developing neoplasms. The classic chromosome instability syndromes are Fanconi anemia, ataxia telangiectasia, Nijmegen syndrome, ICF (immunodeficiency, centromere instability, facial anomalies) syndrome, Roberts syndrome, Werner syndrome, and Bloom syndrome.

98.8

Uniparental Disomy and Imprinting

Carlos A. Bacino, Brendan Lee

Uniparental Disomy

Uniparental disomy (**UPD**) occurs when both chromosomes of a pair or areas from one chromosome in any individual have been inherited from a single parent. UPD can be of 2 types: uniparental isodisomy or uniparental heterodisomy. **Uniparental isodisomy** means that both chromosomes or chromosomal regions are identical (typically the result of monosomy rescue by duplication). **Uniparental heterodisomy** means that the 2 chromosomes are different members of a pair, both of which were still inherited from 1 parent. This results from a trisomy that is later reduced to disomy, leaving 2 copies from 1 parent. The phenotypic result of UPD varies according to the chromosome involved, the parent who contributed the chromosomes, and whether it is isodisomy or heterodisomy. Three types of phenotypic effects are seen in UPD: those related to imprinted genes (i.e., the absence of a gene that is normally expressed only when inherited from a parent of a specific sex), those related to the uncovering of autosomal recessive disorders, and those related to a vestigial aneuploidy producing mosaicism (see Chapter 97).

In uniparental isodisomy, both chromosomes or regions (and thus the genes) in the pair are identical. This is particularly important when the parent is a carrier of an autosomal recessive disorder. If the offspring of a carrier parent has UPD with isodisomy for a chromosome that carries an abnormal gene, the abnormal gene will be present in 2 copies, and the phenotype will be that of the autosomal recessive disorder; the child has an autosomal recessive disorder even though only 1 parent is a carrier of that recessive disorder. It is estimated that all humans carry approximately 20 abnormal autosomal recessive genes. Some autosomal recessive disorders, such as spinal muscular atrophy, cystic fibrosis, cartilage-hair hypoplasia, α- and β-thalassemias, and Bloom syndrome, have been reported in cases of UPD. The possibility of uniparental isodisomy should also be considered when a person is affected with >1 recessive disorder because the abnormal genes for both disorders could be carried on the same isodisomic chromosome. Uniparental isodisomy is a *rare* cause of recessively inherited disorders. Uniparental isodisomies can also be detected by SNP microarrays.

Maternal UPD involving chromosomes 2, 7, 14, and 15 and **paternal UPD** involving chromosomes 6, 11, 15, and 20 are associated with phenotypic abnormalities of growth and behavior. UPD of maternal chromosome 7 is associated with a phenotype similar to Russell-Silver syndrome with intrauterine growth restriction. These phenotypic effects may be related to imprinting (see later) (Fig. 98.18).

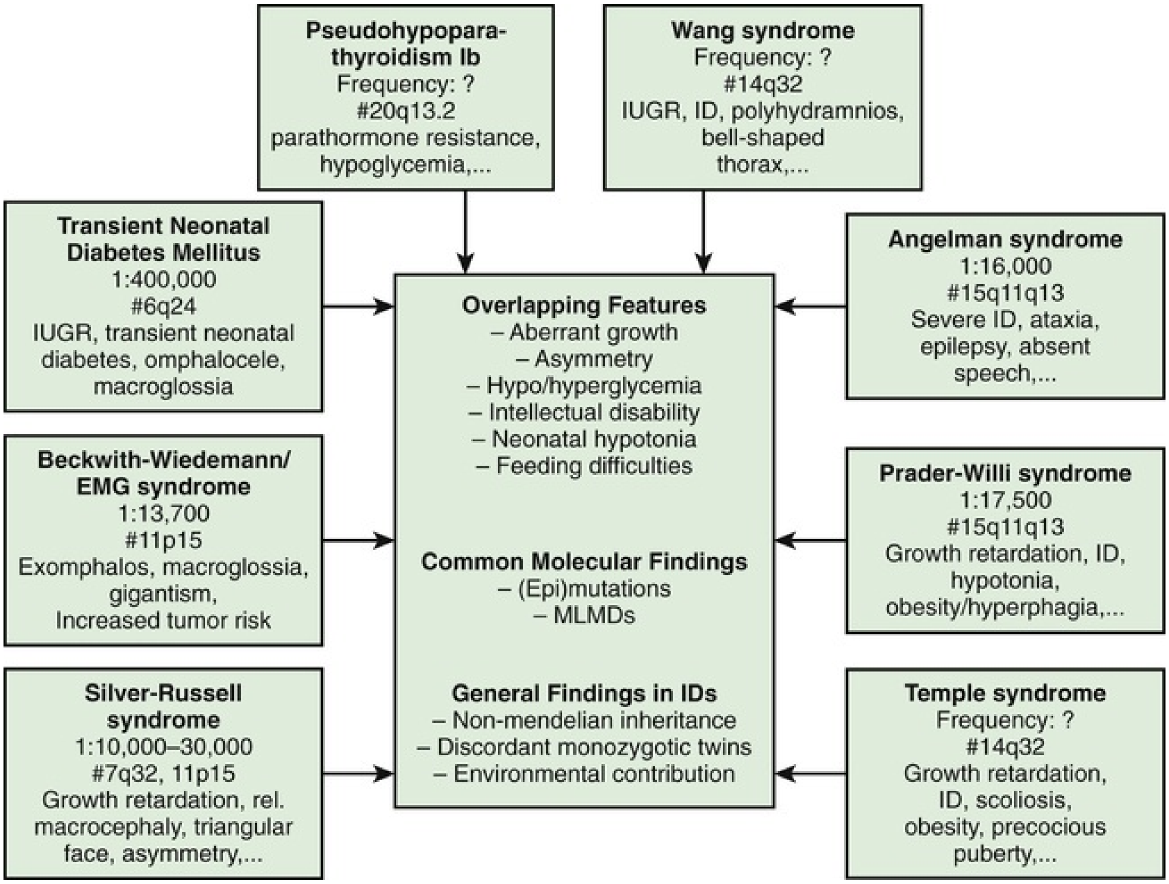

Pseudohypopara-thyroidism Ib
Frequency: ?
#20q13.2
parathormone resistance, hypoglycemia,...
Wang syndrome
Frequency: ?
#14q32
IUGR, ID, polyhydramnios, bell-shaped thorax,...
Transient Neonatal Diabetes Mellitus
1:400,000
#6q24
IUGR, transient neonatal diabetes, omphalocele, macroglossia
Overlapping Features
– Aberrant growth
– Asymmetry
– Hypo/hyperglycemia
– Intellectual disability
– Neonatal hypotonia
– Feeding difficulties
Angelman syndrome
1:16,000
#15q11q13
Severe ID, ataxia, epilepsy, absent speech,...
Beckwith-Wiedemann/ EMG syndrome
1:13,700
#11p15
Exomphalos, macroglossia, gigantism,
Increased tumor risk
Common Molecular Findings
– (Epi)mutations
– MLMDs
Prader-Willi syndrome
1:17,500
#15q11q13
Growth retardation, ID, hypotonia, obesity/hyperphagia,...
Silver-Russell syndrome
1:10,000–30,000
#7q32, 11p15
Growth retardation, rel. macrocephaly, triangular face, asymmetry,...
General Findings in IDs
– Non-mendelian inheritance
– Discordant monozygotic twins
– Environmental contribution
Temple syndrome
Frequency: ?
#14q32
Growth retardation, ID, scoliosis, obesity, precocious puberty,...

FIG. 98.18 Overview of the common clinical and molecular findings in the 8 known imprinting disorders, including specific features, frequencies, and major chromosomal localization. #6q24, Chromosome 6q24; EMG, exomphalos-macroglossia-gigantism; IUGR, intrauterine growth restriction; ID, intellectual disability; MLMDs, multilocus methylation defects. (From Eggermann T, Elbracht M, Schröder C, et al: Congenital imprinting disorders: a novel mechanism linking seemingly unrelated disorders, *J Pediatr* 163:1204, 2013).

UPD for chromosome 15 is seen in some cases of Prader-Willi syndrome and Angelman syndrome. In **Prader-Willi syndrome** , approximately 25–29% of cases have maternal UPD (missing the paternal chromosome 15) (Fig. 98.19). In **Angelman syndrome** , paternal UPD of chromosome 15 is rarer and is observed in approximately 5% of the cases (missing the maternal chromosome 15). The phenotype for Prader-Willi syndrome and Angelman syndrome in cases of UPD is thought to result from the lack of the functional contribution from a particular parent of chromosome 15. In Prader-Willi syndrome the paternal contribution is missing, and the maternal contribution is missing in Angelman syndrome. Prader-Willi syndrome may be caused by paternal deficiency of HB11-85 small nucleolar RNAs (snoRNAs). These findings suggest that there are differences in function of certain regions of chromosome 15, depending on whether it is inherited from the mother or from the father. Angelman syndrome is caused by absence of a maternally contributed gene known as *UBE3A* and can be the result of maternal deletion, maternal *UBE3A* mutation, paternal UPD, and abnormalities in the maternal imprinting center on chromosome 15q11-13 region.

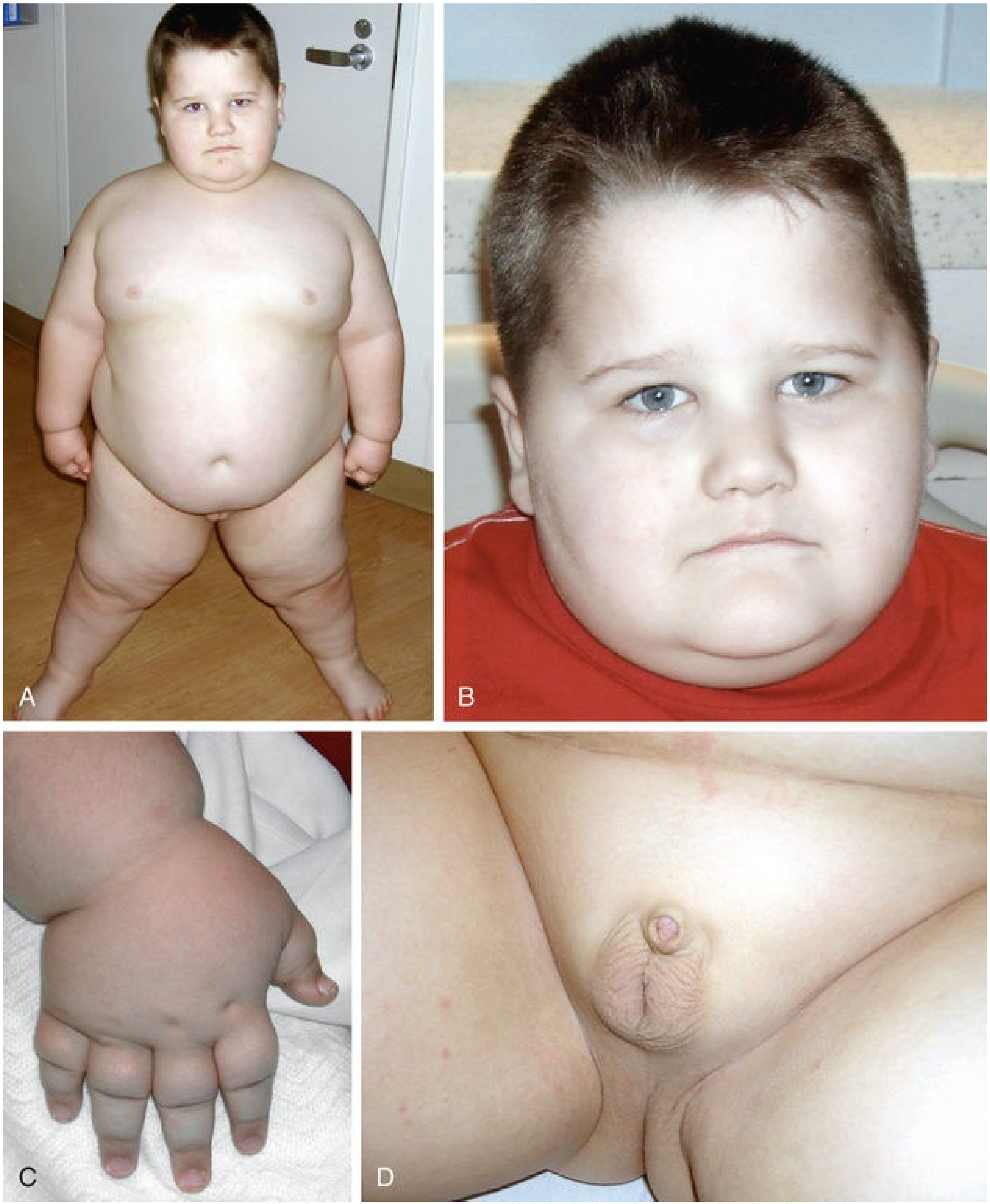

FIG. 98.19 Prader-Willi phenotype. A and B, Individual showing morbid obesity with facial features as shown. C, Upper extremities are notable for small hands relative to body size. D, External genitalia after laparoscopic orchiopexy at 13 mo. Parental informed consent, as approved by the Baylor College of Medicine Institutional Review Board, was obtained to publish the photographs. (From Sahoo T, del Gaudio D, German JR, et al: Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster, *Nat Genet* 40:719–721, 2008.)

UPD most frequently arises when a pregnancy starts off as a **trisomic**

conception followed by **trisomy rescue.** Because most trisomies are lethal, the fetus can only survive if a cell line loses 1 of the extra chromosomes to revert to the disomic state. One third of the time, the disomic cell line is uniparental. This is the typical mechanism for Prader-Willi syndrome, and it is often associated with advanced maternal age. The embryo starts off as trisomy 15 secondary to maternal meiosis I nondisjunction, followed by random loss of the paternal chromosome. In this case the disomic cell line becomes the more viable one and outgrows the trisomic cell line. When mosaic trisomy is found at prenatal diagnosis, care should be taken to determine whether UPD has resulted and whether the chromosome involved is one of the disomies known to be associated with phenotypic abnormalities. There must always be concern that some residual cells that are trisomic are present in some tissues, leading to malformations or dysfunction. The presence of aggregates of trisomic cells might account for the spectrum of abnormalities seen in persons with UPD.

Imprinting

Traditional genetics for many years has suggested that most genes are equally expressed when inherited from maternal vs paternal lineages. The only exception to this rule were genes on the X chromosome that are subject to inactivation, and the immunoglobulin genes subject to allelic exclusion, a phenomenon that results in monoallelic expression of a particular immunoglobulin chain by switching expression of parental alleles on and off. Genomic imprinting occurs when the phenotypic expression of a gene depends on the parent of origin for certain genes or in some cases entire chromosome regions. Whether the genetic material is expressed or not depends on the sex of the parent from whom it was derived. Genomic imprinting can be suspected in some cases on the basis of a pedigree. In these pedigrees the disease is always transmitted from one sex and could be passed on silently for several generations by the opposite sex (Figs. 98.20 and 98.21). Imprinting probably occurs in many different parts of the human genome and is thought to be particularly important in gene expression related to development, growth, cancer, and even behavior; >60 genes have been classified as imprintable. Imprinting disorders may arise from UPD, deletions or duplications, epigenetic aberrant methylation patterns, or point mutations in a specific gene.

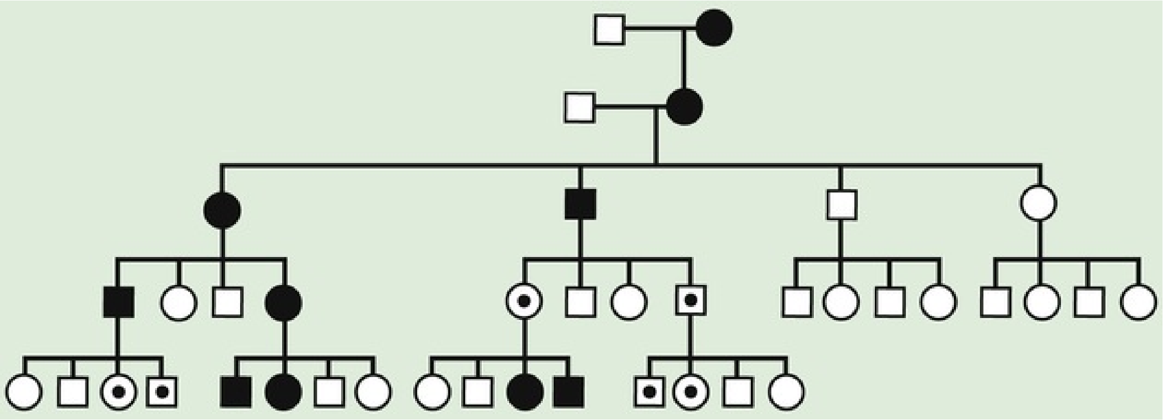

FIG. 98.20 In this hypothetical pedigree suggestive of imprinting, phenotypic effects occur only when the mutated gene is transmitted from the mother, but not when it is transmitted from the father, that is, maternal deficiency. Equal numbers of males and females can be affected and not affected phenotypically in each generation. A nonmanifesting transmitter gives a clue to the sex of the parent who passes the expressed genetic information; that is, in maternal deficiency disorders (also termed *paternal imprinting*), there are "skipped" nonmanifesting females. This is theoretical, because in most clinical scenarios of maternal deficiency, such as Angelman syndrome, affected persons do not reproduce.

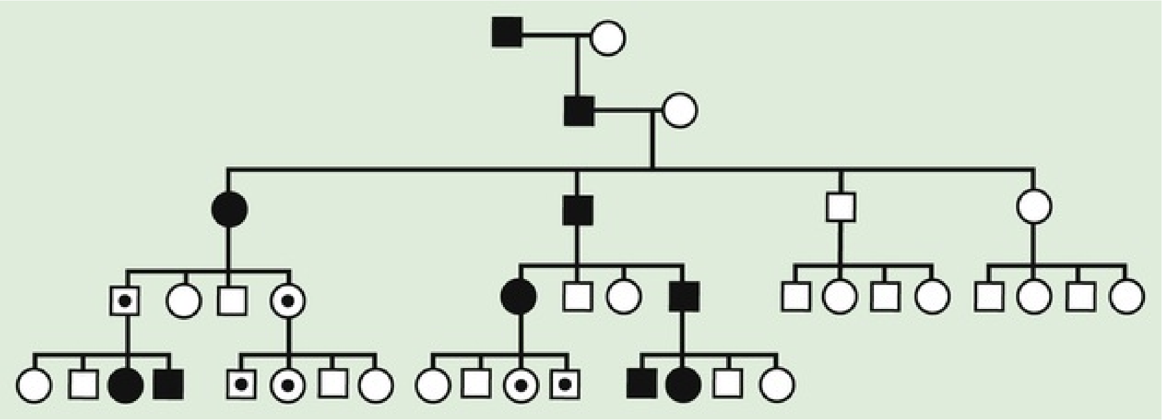

FIG. 98.21 In theoretical pedigrees suggestive of paternal deficiency (maternal imprinting), phenotypic effects occur only when the mutated gene is transmitted from the father, but not when transmitted from the mother. Equal numbers of males and females can be affected and not affected phenotypically in each generation. In a theoretical situation, a nonmanifesting transmitter gives a clue to the sex of the parent who passes on the expressed genetic information; that is, in paternal deficiency (also known as *maternal imprinting*), there are "skipped" nonmanifesting males. In real-life clinical cases of Prader-Willi syndrome, affected persons do not reproduce.

A classic example of imprinting disorder is seen in Prader-Willi syndrome and Angelman syndrome, 2 very different clinical conditions. These syndromes are usually associated with deletion of the same region in the proximal long arm of chromosome 15. A deletion on the paternally derived chromosome causes Prader-Willi syndrome, in which the maternally derived copy is still intact, but some of the imprinted genes within this region normally remain silent. Prader-Willi syndrome can be diagnosed clinically (Table 98.20) and confirmed with genetic testing. Additional clinical features and issues of weight gain are noted in Table 98.21 . The weight gain is difficult to control, but treatment with growth hormone has resulted in improvements in height, lean body mass, decreased adipose tissue, and improvement in cognitive function.

Table 98.20

Consensus Diagnostic Criteria for Prader-Willi Syndrome

	MAJOR CRITERIA (1 point each)	MINOR CRITERIA (1/2 point each)
1	Neonatal/infantile hypotonia	Decreased fetal movement and infantile lethargy
2	Feeding problems and failure to thrive as an infant	Typical behavior problems
3	Weight gain at 1-6 yr; obesity; hyperphagia	Sleep apnea
4	Characteristic dysmorphic facial features	Short stature for family by 15 yr
5	Small genitalia; pubertal delay and insufficiency	Hypopigmentation for the family
6	Developmental delay/intellectual disability	Small hands and feet for height
7		Narrow hands, straight ulnar border
8		Esotropia, myopia
9		Thick, viscous saliva
10		Speech articulation defects
11		Skin picking

Data from Cassidy SB, Schwartz S, Miller JL, Driscoll DJ: Prader-Willi syndrome, *Genet Med* 14(1):15, 2012, Table 2.

Table 98.21

Nutritional Phases in Prader-Willi Syndrome

PHASE	MEDIAN AGES	CLINICAL CHARACTERISTICS
0	Prenatal to birth	Decreased fetal movements and lower birthweight than siblings
1a	0-9 mo	Hypotonia with difficulty feeding and decreased appetite
1b	9-25 mo	Improved feeding and appetite and growing appropriately
2a	2.1-4.5 yr	Weight increasing without appetite increase or excess calories
2b	4.5-8 yr	Increased appetite and calories, but can feel full
3	8 yr to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

Modified from Miller JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome.

Am J Med Genet A 155A:1040–1049, 2011.

A maternal deletion of the same region as in Prader-Willi syndrome causes Angelman syndrome, leaving intact the paternal copy that in this case has genes that are also normally silent. In other situations, UPD can lead to the same diagnosis (Table 98.22). Many other disorders are associated with this type of parent-of-origin effect, as in some cases of Beckwith-Wiedemann syndrome, Russell-Silver syndrome, and neonatal diabetes.

Table 98.22

Molecular Mechanisms Causing Prader-Willi and Angelman Syndromes

	PRADER-WILLI SYNDROME	ANGELMAN SYNDROME
15q11-q13 deletion	~70% (paternal)	~70% (maternal)
Uniparental disomy	~30% (maternal)	~5% (paternal)
Single-gene mutation	None detected	E6-AP ubiquitin-protein ligase (11% of total but mostly in familial cases)
Imprinting center mutation	5%	1%
Unidentified	<1%	10–15%

Data from Nicholls RD, Knepper JL: Genome organization, function and imprinting in Prader-Willi and Angelman syndromes, *Annu Rev Genomics Hum Genet* 2:153–175, 2001; and Horsthemke B, Buiting K: Imprinting defects on human chromosome 15, *Cytogenet Genome Res* 113:292–299, 2006.

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CHAPTER 99

Genetics of Common Disorders

Bret L. Bostwick, Brendan Lee

Common pediatric diseases are usually multifactorial. The combination of many genes and environmental factors contribute to a complex sequence of events leading to disease. The complexity of the combination of contributing factors increases the challenge of finding genetic variants that cause disease. Genetic tools include the completed human genome sequence, public databases of genetic variants, and the human haplotype map. In addition to public genetic databases, dramatic reduction in the cost of genotyping and DNA sequencing has allowed very large numbers of genetic variants to be efficiently tested in large numbers of patients. Most of these studies focus on common variants (those with frequencies >5%). Technologies for DNA sequencing are allowing whole exome sequencing in many individuals at very low cost. This technology is being used to investigate the role of rare coding sequence variants in common diseases. The incorporation of these tools into large, well-designed population studies is the field of **genetic epidemiology** . Many new methods for analyzing genetic data have been developed, stimulating a renaissance in applied population genetics.

99.1

Major Genetic Approaches to the Study of Common Pediatric Disorders

Millions of genetic variants are present in every person. Many of these variants have no impact on health, while others have a measureable influence. Sometimes, single-gene mutations consistently cause a disease, as with cystic fibrosis and sickle cell anemia. Other types of genetic variation, however, can contribute much less to the emergence of specific medical conditions, and these are best conceptualized as *modifiers* of disease risk. Fig. 99.1 demonstrates the relationship between variant frequency and the relative medical impact of the allele. The spectrum of variant impact is logarithmic, ranging widely from a slightly increased risk of illness to predetermined fully expressed disease. Studies aimed at discovering rare variants with outsized health effects only require small sample populations to achieve statistical significance, while those studying common variants require much larger sample sizes because of the small anticipated impact of each variant.

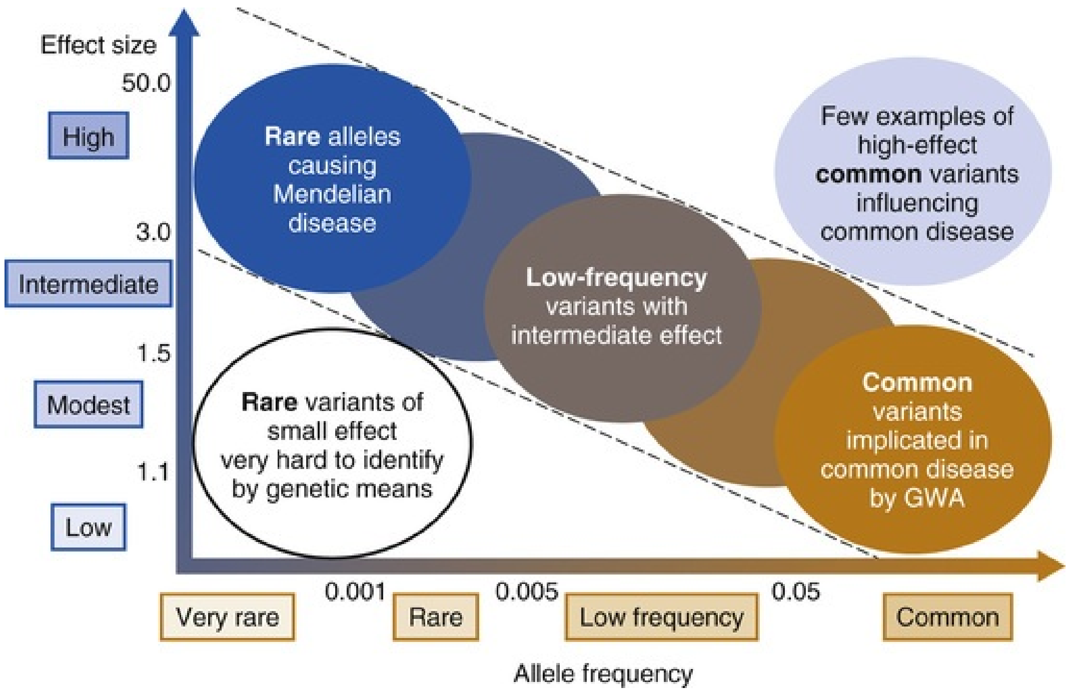
Effect size
50.0
High
3.0
Intermediate
1.5
Modest
1.1
Low
Rare alleles causing Mendelian disease
Few examples of high-effect common variants influencing common disease
Low-frequency variants with intermediate effect
Common variants implicated in common disease by GWA
Rare variants of small effect very hard to identify by genetic means
Very rare
0.001
Rare
0.005
Low frequency
0.05
Common
Allele frequency

FIG. 99.1 Relationship between allele frequency and relative strength of genetic effect. Alleles with large effect tend to be very rare but can be studied with a small sample size because of the relative ease of allele detection when medical impact is high. Common variants tend to have a modest or low effect on health, requiring large datasets to visualize statistically small effects. The vast majority of disease-associated alleles

identified to date have the characteristics shown within the *diagonal dotted lines.* GWA, Genome-wide association. (Adapted from McCarthy MI, Abecasis GR, Cardon LR, et al: Genome-wide association studies for complex traits: consensus, uncertainty and challenges, *Nat Rev Genet* 9:356–369, 2008.)

The cumulative risk of many common variants determines genetic susceptibility. For common conditions, the genetic predisposition alone is not sufficient to cause disease. Everyone inherits a different degree of disease vulnerability, which is then augmented by exposure to certain environmental factors. Fig. 99.2 shows a model for the contribution of common genetic variants to individual health. One of the goals in medical genetics is to identify the genes that contribute to initial genetic susceptibility and to help prevent the occurrence of disease, either by avoiding inciting environmental factors or by instituting interventions that reduce risk. For persons who cross the threshold of disease, the goal is to better understand the pathogenesis in the hope that this will suggest better approaches to treatment. Common genetic variation can also influence response to medications and the risk of adverse drug reactions (see Chapter 72) and augment the health impacts of environmental toxins.

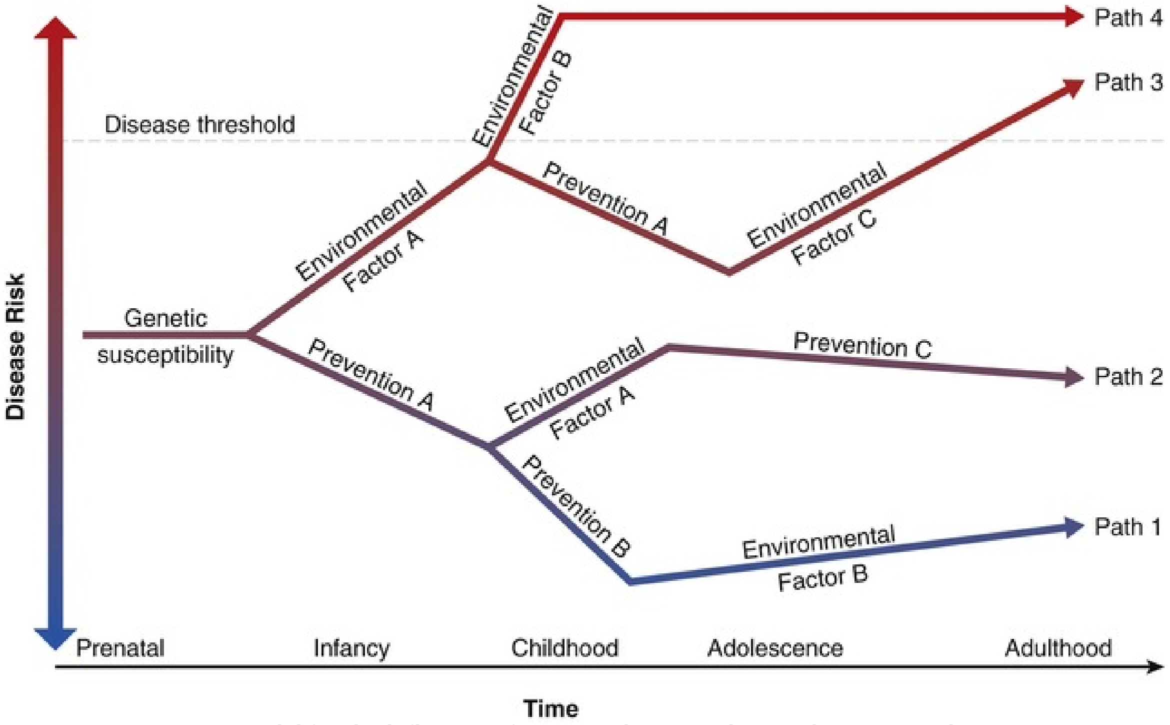
Disease Risk
Disease threshold
Genetic susceptibility
Environmental Factor A
Prevention A
Environmental Factor B
Prevention A
Environmental Factor C
Environmental Factor A
Prevention C
Prevention B
Environmental Factor B
Path 4
Path 3
Path 2
Path 1
Prenatal
Infancy
Childhood
Adolescence
Adulthood
Time

FIG. 99.2 Model for the influence of gene-environment interaction on genetic susceptibility to common diseases. Everyone inherits common variants that determine initial genetic liability for disease risk. For multifactorial disorders, the initial genetic susceptibility is insufficient to produce disease on its own. Over time, exposure to environmental factors increases the likelihood of a disease state. Identifying the gene

variants responsible for risk can lead to prevention strategies or treatments.

Complex traits may be inherently difficult to study if the precision of clinical diagnosis (phenotype) is problematic, as often occurs with neurobehavioral traits. A starting point in the genetic analysis of a complex trait is to obtain evidence in support of a genetic contribution and to estimate the relative strength of genetic and environmental factors. Complex traits typically exhibit familial clustering but are not transmitted in a regular pattern as is autosomal dominant or recessive inheritance. Complex traits often show variation among different ethnic or racial groups, possibly reflecting the differences in gene variants among these groups.

Assessing the potential genetic contribution begins by determining whether the trait is seen among related individuals more often than in the general population. A common measure of **familiality** is the first-degree relative risk (usually designated by the symbol λ_s), which is equal to the ratio of the prevalence rate in siblings and/or parents to the prevalence rate in the general population. The λ_s for type 1 diabetes is about 15. The relative strength of genetic and nongenetic risk factors can be estimated by variance components analysis. The **heritability** of a trait is the estimate of the fraction of the total variance contributed by genetic factors (Fig. 99.3).

$$\overset{\text{Phenotypic variance}}{V_P} = \overset{\text{Genetic variance}}{V_G} + \overset{\text{Environmental variance}}{V_E} + \overset{\text{Measurement variance}}{V_M}$$

$$\underset{\text{Heritability}}{h^2 = V_G / V_P}$$

FIG. 99.3 Heritability concept. The phenotypic variance of a particular trait can be partitioned between the contributions of the genetic variance, environmental variance, and measurement variance. This is usually empirically determined. Heritability is defined by the proportion of the phenotypic variance that is accounted for by the genetic variance. One can estimate the heritability from correlation of a quantitative trait between relatives.

A minority of cases of common diseases such as diabetes may be caused by single-gene mutations (mendelian inheritance), chromosomal disorders, and other genomic disorders. These *less common* causes of the disease can often provide important insight into the most important molecular pathways involved. Chromosomal regions with genes that might contribute to disease susceptibility could theoretically be located with **linkage mapping** , which locates regions of DNA that are inherited in families with the specific disease. In practical terms, however, this has become quite difficult for most complex traits either because of a dearth of families or because the effect of individual genetic loci is weak.

Genetic **association studies** are more powerful in identifying common gene variants (>5% in the population) that confer increased risk of disease, but they fail if the disease-causing gene variants are relatively rare. Detection of the modest effect of each variant and interactions with environmental factors requires well-powered studies that often include thousands of individuals. A number of parallel approaches for analyzing the aggregate effects of rare variants in genes have also been developed. Such rare variant association methods also seem to require large sample sizes because the gene effects have also proved to be relatively weak.

Linkage mapping and association studies require markers along the DNA that can be ascertained, or **genotyped** , with large-scale, high-throughput laboratory techniques. Markers that are typically used are in the forms of microsatellites and **single nucleotide polymorphisms** (**SNPs** ; Fig. 99.4). A sample of the same region of genome from 50 people will reveal that approximately 1 in every 200 bases varies from the more common form. Although most SNPs lack any obvious function, a few alter the amino acid sequence of the protein or affect regulation of gene expression. Some of these functional alterations directly affect susceptibility to disease. A complex clinical **phenotype** can be defined by the presence or absence of a disease as a **dichotomous trait** , or by selection of a clinically meaningful variable such as serum glucose in type 2 diabetes, which is a continuous or **quantitative trait** .

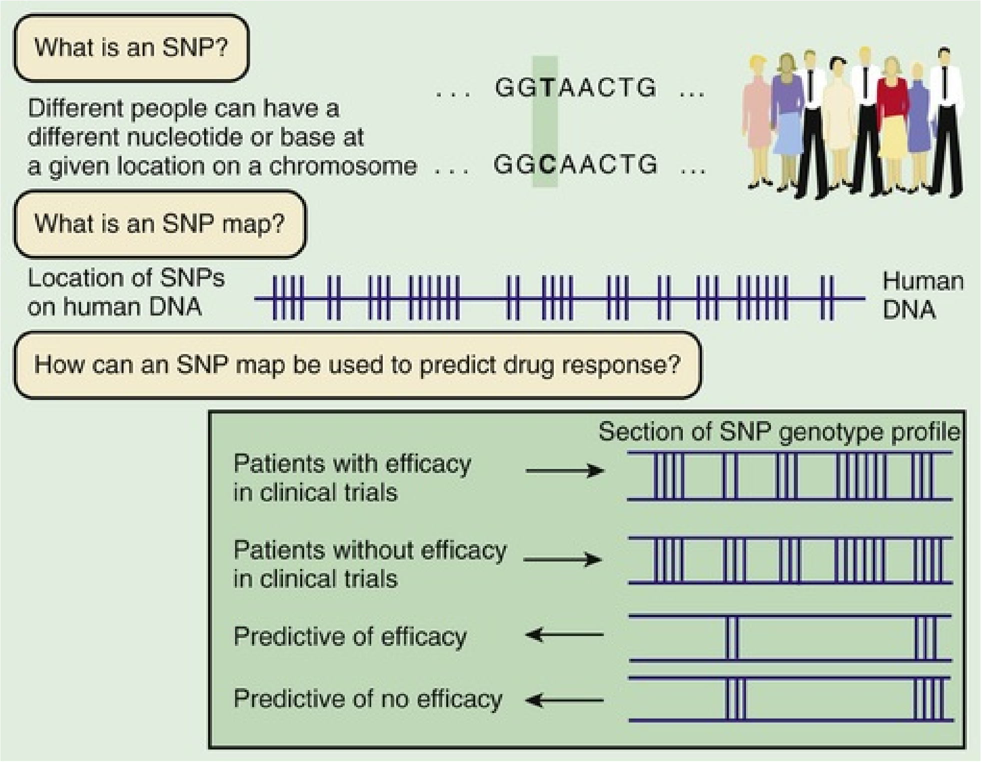
What is an SNP?
Different people can have a different nucleotide or base at a given location on a chromosome
. . . GGTAACTG . . .
. . . GGCAACTG . . .
What is an SNP map?
Location of SNPs on human DNA
Human DNA
How can an SNP map be used to predict drug response?
Section of SNP genotype profile
Patients with efficacy in clinical trials
Patients without efficacy in clinical trials
Predictive of efficacy
Predictive of no efficacy

FIG. 99.4 **Different combinations of SNPs are found in different individuals. The locations of these SNPs can be pinpointed on maps of human genes. Subsequently, they can be used to create profiles that are associated with difference in response to a drug, such as efficacy and nonefficacy. (Adapted from Roses A: Pharmacogenetics and the practice of medicine, *Nature* 405:857–865, 2000. Copyright 2000. Reprinted by permission of Macmillan Publishers Ltd.)**

Although it might not be possible to define subgroups of patients in advance based on common disease mechanisms, the more uniform the phenotype, the more likely that a genetic study will be successful. **Locus heterogeneity** refers to the situation in which a trait results from the independent action of more than 1 gene. **Allelic heterogeneity** indicates that more than 1 variant in a particular gene can contribute to disease risk. The development of a trait or disease from a nongenetic mechanism results in a **phenocopy** . These 3 factors often contribute to the difficulty in identifying individual disease susceptibility genes, because they reduce the effective size of the study population.

A person bearing any variant or **allele** (inherited unit, DNA segment, or chromosome) in a gene has a certain probability of being affected with a specific gene variant–associated disease. This is called the **penetrance** . Some diseases manifest signs only later in life (age-related penetrance), which could lead to misclassifying children who actually have the disease-producing gene as unaffected. Single-gene disorders are typically caused by mutations with relatively high penetrance, but some common variants have very low penetrance because their overall contribution to the disease is small. Many such common variants can contribute to disease risk for a complex trait. Normal human height is influenced by >400 genes.

Ideally, important environmental exposures should be measured and accounted for in a population because there may be a dependent interaction between the environmental factor and specific genetic variant. An example is the likely requirement for a viral infection preceding onset of type 1 diabetes. Although **gene-environment interactions** are strongly suspected to play an important role in common diseases, it is difficult to identify and measure them. Very large studies with uniform collection of information about environmental exposures are rare. Methods, such as genome-wide analysis of DNA methylation, may show evidence of environmental effects—so-called developmental programming (see Chapter 100). This information might be used to discover and validate gene-environment interactions.

Linkage Mapping

Linkage studies were used in the past to isolate genes that cause rare genetic syndromes; modified methods have been used to identify chromosomal regions linked to more common diseases. Linkage studies involve tagging segments of a person's genome with markers that allow identification of segments that have been inherited through the family along with disease. The markers are typically **microsatellites** or SNPs that define and help to distinguish which type of an allele any person carries. **Genotype** refers to the combination of alleles at a locus in a diploid organism**.** Linkage analyses of common diseases have shown inconsistent results. Factors such as heterogeneity, pleiotropy, variable expressivity, and reduced penetrance, in addition to variability in environmental exposures, weaken the power of linkage studies in complex traits.

Genetic Association

For multifactorial common diseases, association analyses may be used to identify causally important genes. There are two types of association study: **direct association** , in which the causal variant itself is tested to see whether its presence correlates with disease, and **indirect association** , in which markers that are physically close to the biologically important variant are used as proxies. The correlation of markers with other genetic variants in a small region of the genome is called **linkage disequilibrium** . Indirect association is enabled by the construction of a detailed genetic map in 3 reference populations (Europeans, Asians, West Africans) through the International HapMap Project. SNPs that tag most of the genome have been identified and can be genotyped at low cost using specially designed microarrays.

Three basic study designs are used for association testing. In a case control design, the frequency of an allele in the affected group is compared with the unaffected group. In a family-based control design, parents or siblings of an affected individual are used as the controls. In a cohort design, large numbers of people are ascertained and then followed for the onset of any number of diseases. The cohort analysis is very expensive, and there are few true cohort studies.

Family-based control study designs are somewhat attractive for pediatric diseases because it is usually possible to enroll parents. These studies solve a major problem in testing for association because the parents are perfectly matched for genetic background. When parents are collected, the statistical test used for these studies is called the **transmission disequilibrium test** . TDT compares the transmitted genotype with the inferred nontransmitted genotype. The success of all association analysis depends on the design of a well-powered study and an accurately measured trait to avoid phenotypic misclassification. In large, population-based studies, confounding by ethnicity or **population stratification** could distort results. Some genetic variants are more common in people from a particular ethnic group, which could cause an apparent association of a variant with a disease, when the disease rate happens to be higher in that group. This association would not be a true association between an allele and a disease, because the association would be confounded by genetic background. The family-based tests using the TDT are immune to population stratification. However, TDT and related study designs are inherently less efficient than case control studies. Newer methods for measuring subtle mismatching between cases and controls using many thousands of markers routinely genotyped in genome-wide association studies allow researchers to account for this effect.

Association studies should be a powerful tool to find genetic variation that confers risk to an individual; the effect of any 1 genetic variant will be a very small contribution to the complex disease pathway. Genetic variants have been found that implicate a novel gene in a process, motivating more in-depth research into systems that will affect disease outcome. Associations such as the *APOE* ε4 variant with an increased risk of Alzheimer disease are noted by many studies. Many published association results are not reproducible; insufficient power and stratification might account for the inconsistencies. As of late 2016, 2,650 studies and 29,954 unique SNP-trait associations have been catalogued (https://www.ebi.ac.uk/gwas/).

Low-cost methods for sequencing the complete exomes *and* genomes of individuals will allow a more comprehensive evaluation of the full range of genetic variants involved in common diseases. Rare genetic variants, including small insertions or deletions, could turn out to be extremely important in explaining the impact of genetic factors in important pediatric diseases such as autism, cardiovascular malformations, and other birth defects. Common traits such as obesity, diabetes, and autoimmune diseases might also be affected by rare variants. In common severe disorders such as intellectual disability and complex heart malformations, de novo mutations (i.e., mutations not present in either parent) are known to play an important role.

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CHAPTER 100

Epigenome-Wide Association Studies and Disease

John M. Greally

Pediatricians are asked to consider the possibility that certain conditions involve epigenetic mechanisms. The assumption is that **epigenetic** processes, generally defined as regulatory control of gene expression, are capable of overriding information encoded in the DNA sequence to increase or decrease the risk of a disease. Despite powerful genomic assays to test these regulators of gene expression, it has proved difficult to provide clear answers about how epigenetic mechanistic insights could improve patient care. Clarifying the fundamental concepts and definitions that underlie proposed epigenetic contributions to phenotypes should lead to valuable insights into their role in human health.

Epigenetic Mechanisms of Disease: Viable Yellow Mouse Model

The back-translated meaning of **epigenetics** (*epi,* above, upon; *genetic,* DNA sequence) implies that information encoded in the DNA sequence may be modifiable in some way by higher-order information that regulates the levels of activity of specific genes. Such a concept is attractive when trying to understand why monozygotic twins, who have identical DNA sequences, are sometimes discordant for certain heritable diseases, such as Alzheimer disease and type 1 diabetes mellitus. Genetic predisposition that fails to account fully for the development of a disease (or other) phenotype has been called “missing heritability,” a gap that epigenetic regulatory processes have been proposed to fill. Furthermore, because the environment influences the risk of certain disorders by modifying an underlying genetic predisposition, environmental stimuli may act through epigenetic regulatory processes of gene expression.

The most compelling evidence for the epigenetic, higher-level regulation of genes and predisposition to disease was the viable yellow mouse model (Fig. 100.1). This mouse was found to have a mutation involving an endogenous retrovirus, a component of the genome that can replicate itself and move to a new location. In the case of the viable yellow mouse, the endogenous retrovirus was the type called an **intracisternal A particle (IAP)** , which inserted upstream from a gene called *a* (*nonagouti*). The *nonagouti* gene encodes agouti-signaling protein precursor, which binds to and has a negative effect on melanocortin receptors. When it stimulates melanocytes in hair follicles, it causes the production of the yellow pheomelanin pigment rather than black eumelanin. Without the upstream IAP element, *nonagouti* would normally switch on for a very short burst of activity and stimulate a limited amount of yellow pigment production. The presence of the active IAP element upstream was found to create a new, constitutively active start site for the *nonagouti* gene, leading to the hair being produced with pheomelanin throughout its length, and a distinctive yellow fur phenotype. Because the agouti-signaling protein precursor is also expressed in other cell types, the extra activity of the *nonagouti* gene driven by the IAP element caused the yellow mice to become obese (due to actions on adipocytes), creating a syndrome comparable to human type 2 diabetes mellitus in these animals.

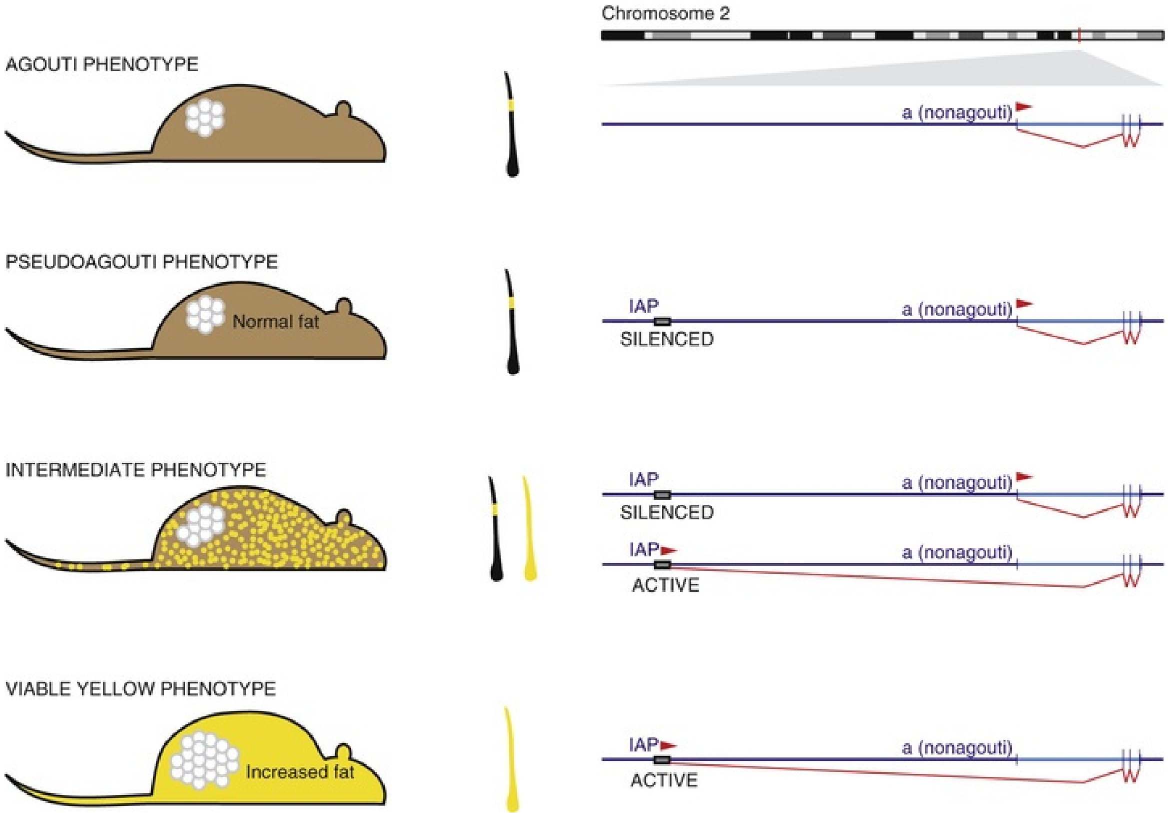
Chromosome 2
AGOUTI PHENOTYPE
a (nonagouti)
PSEUDOAGOUTI PHENOTYPE
Normal fat
IAP
SILENCED
a (nonagouti)
INTERMEDIATE PHENOTYPE
IAP
SILENCED
a (nonagouti)
IAP
ACTIVE
a (nonagouti)
VIABLE YELLOW PHENOTYPE
Increased fat
IAP
ACTIVE
a (nonagouti)

FIG. 100.1 The viable yellow mouse model of epigenetic modification of disease risk. The wild-type strain is depicted at the *top* ; the brown coat color is caused by a band of yellow pheomelanin within the shaft of the otherwise black hair, resulting from a pulse of expression during hair growth from the *a* (*nonagouti*) gene on chromosome 2. The lower examples represent what happens when the intracisternal A particle (IAP) transposable element inserts upstream from the *nonagouti* gene. These mice can be indistinguishable from wild-type mice when the IAP element is completely silenced (pseudoagouti phenotype), or the IAP element can be active in every cell (*bottom*), driving continuous transcription of the *nonagouti* gene and causing pheomelanin to be expressed throughout the growth of the hair, causing the yellow color of the fur (viable yellow phenotype). These mice are also obese because of the effect of agouti-signaling protein on adipocytes. When some cells express and others silence the IAP element, an intermediate fur phenotype, often described as “mottled,” is generated, accompanied by a less pronounced obesity. This demonstrates how the same genetic mutation (the IAP insertion) is variable in its association with a phenotype, depending on differences in transcriptional regulation at a specific locus in the genome.

These mice became an intriguing model of a potential epigenetic role in disease risk because of the unexpected observation that pups from the same litter, all containing the same IAP insertion mutation, differed strikingly in their amount of yellow fur and associated adult obesity. Some of the mice had so little yellow fur that they had no visible evidence of having a mutation at all. The IAP element in these littermates was active in the cells of the yellow mice, as expected, but had undergone **silencing** in the mice with the brown fur. The inactive IAP element was distinctive for having acquired **DNA methylation** , the modification of cytosines located immediately before guanines (CG or CpG dinucleotides) to 5-methylcytosine. Methylation of cytosines at CG dinucleotides is the default state throughout the genome, but it is usually absent at the sites regulating expression of nearby genes, so its acquisition at these sites indicates that the gene has undergone silencing. This suggested that an influence on how genes are expressed overrode innate genetic susceptibility, modifying the risk of acquiring a disease. Further, researchers modified the diets of mothers pregnant with a litter of pups with the IAP insertion by supplementing **folic acid** , a single-carbon donor that increased the availability of a cofactor needed for DNA methylation. The outcome was a higher proportion of pups born with DNA methylation and inactivation of the IAP mutation (Fig. 100.2).

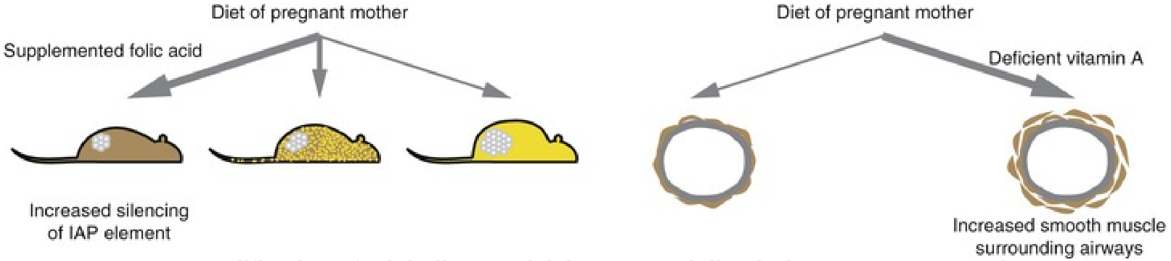

FIG. 100.2 Modification of adult disease risk by maternal diet during pregnancy. On the *left* is the pseudoagouti, intermediate, and viable yellow phenotypes associated with differences in silencing of the IAP element inserted upstream from the *nonagouti* gene. Increasing the amount of folic acid in the mother's diet during pregnancy is associated with an increased proportion of pups born with pseudoagouti and intermediate phenotypes, as well as less obesity during adulthood. On the *right* is the effect of vitamin A deficiency in the pregnant mother's diet during lung formation in the offspring. The lack of vitamin A during development is associated with the accumulation of smooth muscle (brown) around the airways and increased airway resistance during adulthood. The vitamin A deficiency results in a lack of retinoic acid in the developing embryos, leading to changes in gene expression regulation that alter cell fates and cause more smooth muscle cells to form. Both examples represent how dietary influences during pregnancy alter decisions made by cells during development, acting through regulation of gene expression, and predispose to adult diseases.

Therefore, a reason for the variability in whether the mice developed the yellow fur and obesity could be influences during pregnancy, such as maternal diet. This supported suggestions that intrauterine stresses were associated with increased risks of certain adult conditions, such as cardiovascular, renal, and metabolic diseases. This field of study is often known as the **Developmental Origins of Health and Disease (DOHaD)** , which asks how someone's cells remember an intrauterine stress years or decades later. The viable yellow mouse model suggested that such memory could be mediated by regulators of gene expression and influenced by environmental factors such as maternal diet during pregnancy.

Epigenetics and Regulation of Gene Expression

Two examples of gene regulation provide a model for locking in a regulatory pattern early in development and maintaining it indefinitely thereafter. The first is **X chromosome inactivation** . Because males have only 1 X chromosome, it does not undergo inactivation. However, a person with 2 X chromosomes will inactivate 1, a person with trisomy for the X chromosome will inactivate 2, and so on. The result is that males and females have 1 active X chromosome per cell, despite starting with different numbers of X chromosomes, a process referred to as **dosage compensation** .

X chromosome inactivation is generally a random event, choosing the maternal X for inactivation in half the cells of the body and the paternal X in the other half. The inactivation occurs very early during development, when the blastocyst is implanting itself into the uterine wall. However, once established in this small number of pluripotent cells, the inactivation persists in all the cells of the individual throughout life.

The other relevant model of gene regulation is **genomic imprinting** (see Chapter 97). Gene activation in a specific cell type usually switches on the copies present on both the paternal and the maternal chromosomes. However, an **imprinted locus** is distinctive because only the copy on the *paternal* chromosome is switched on for some imprinted genes, while other imprinted genes are distinctive for only switching on the maternal copy. The timing of this inactivation event is even earlier than X chromosome inactivation, occurring during the formation of the male or female gametes. Again, these patterns of inactivation persist throughout life into old age.

Evolution of the Term “Epigenetics”

Because the 2 previous examples both involved a gene regulation event (silencing) that occurred early in development and was maintained into adulthood, they were described as “epigenetic,” emphasizing how a cell retains a memory of past regulatory processes. This highlights that epigenetics has long been held to have a 2nd property, mediating cellular memory.

In the 1950s, Nanney interpreted the epigenetic landscape to define epigenetics as the property of a cell to remember past events. In the 1970s, Riggs and Holliday both noted that DNA methylation patterns could be propagated from parent to daughter cells, potentially providing a molecular mechanism of cellular memory, and described this as an “epigenetic property.” When DNA methylation was found to be a feature of the alleles silenced during X chromosome inactivation and genomic imprinting, this appeared to confirm the idea of a “heritable molecular mark” being involved in remembering a past silencing event during development, leading DNA methylation to be described as an “epigenetic regulator.” When the active and silenced alleles at X inactivated or imprinted loci were further studied, differences in chromatin states and long noncoding RNAs were found to distinguish the chromosomes, suggesting that they helped to mediate the long-term silencing at these loci.

There have been attempts to test whether chromatin states are heritable through cell division in the same way as DNA methylation. Despite the evidence for their heritability being less compelling, the field has tended to be *inclusive* rather than exclusive in labeling transcriptional regulators as epigenetic, but needed to redefine epigenetics as *epi* (above, upon) and *genetics* (DNA sequence), the back-translated definition. This definition is not only dissociated from the original ideas of cell fates and cellular memory, but now also encompasses all transcriptional regulatory processes. Because of the broadened definition of epigenetics, an experiment testing for differences in cellular memory is no different in design from an experiment testing for differences in transcriptional regulation, which may or may not mediate cellular memory.

Pediatric Diseases Involving Epigenetic Processes

Prime examples of epigenetics are those involving imprinted loci, exemplified by the Prader-Willi and Angelman syndromes (see Chapter 97). Each of these syndromes may be caused by the same deletion on chromosome 15, distinguished by the deletion occurring on the *paternal* chromosome 15 causing **Prader-Willi syndrome** and the *maternal* chromosome 15 causing **Angelman syndrome** . There are imprinted genes located within the 15q11-q13 region, some of which are expressed only on the paternal chromosome, some only on the maternal chromosome. When an individual is missing the region on the paternally inherited chromosome, the person still has a copy of the gene on the remaining maternal chromosome, but if it is silenced by imprinting, the individual effectively has *no functional copy* of the gene, leading to the Prader-

Willi phenotype. The converse happens for Angelman syndrome; a deletion of the maternal chromosome leaves a silenced copy of the gene on the paternal chromosome.

Although deletions cause these syndromes in the majority of affected individuals, a subset results from **uniparental disomy (UPD)** , in which there are 2 intact chromosomes 15, but both are inherited from *1 parent* . Maternal UPD has the same effect as a paternal deletion in that there is no contribution of a paternally inherited chromosome, causing Prader-Willi syndrome, with paternal UPD causing Angelman syndrome. UPD is thought to start with trisomy for that chromosome, with a 2nd event occurring early in development in which 1 of the 3 chromosomes is lost, occasionally leaving 2 chromosomes derived from the same parent. In a further, very small proportion of individuals, mutations within the 15q11-q13 region seem to affect the imprinted domain as a whole.

Prader-Willi and Angelman syndromes occur because of **genetic mutations** : large deletions, nondisjunction events leading to whole chromosomal gains or losses, or smaller DNA mutations. These mutations reveal the underlying pattern of genomic imprinting, a distinctive organization of gene regulation at chromosome 15q11-q13 that reflects a memory of the gamete of origin of each chromosome, described as epigenetic. What is *not* occurring in these individuals is an alteration of the normal epigenetic regulation of the locus, as exemplified by the yellow agouti mice. To find examples of altered epigenetic regulation associated with disease, researchers take advantage of assays that studied DNA methylation patterns throughout the genome. If we had never known about the IAP element insertion in the yellow agouti mice, for example, the locus would have revealed itself by having distinctive DNA methylation in the yellow, obese animals compared with the brown, lean, genetically identical littermates. This approach, referred to as an **epigenome-wide association study (EWAS)** , was initially applied to study individuals who had intrauterine perturbations, environmental exposures, or various types of cancer, to look for cellular reprogramming events.

Epigenome-Wide Association Studies: DNA Methylation

Because of the availability of genome-wide assays and its demonstrated heritability through mitosis, DNA methylation has been the primary focus for studies attempting to link altered epigenetic regulation with disease phenotypes. The *genome-wide association study* (GWAS) template was used for EWAS, but instead of linking variability in DNA sequences, the EWAS links variability in DNA methylation with the presence of a phenotype.

Interpretation of EWAS is more complex than foreseen partly because DNA methylation in a sample of cells reflects not only its reprogramming in these cells but also other influences. For example, if a sample of cells contains more than 1 subtype (each subtype of cells in the body has distinctive DNA methylation patterns), a change in proportion of *cell subtypes* between individuals will cause a change in the pattern of DNA methylation, at the loci where differences in DNA methylation distinguish the cell subtypes. In this way, DNA methylation changes can be found in an EWAS without any individual cells having altered their DNA methylation.

Another major influence, accounting for an estimated 22–80% of DNA methylation variation between individuals, is DNA sequence variability. Epigenetic regulation is defined as a level of information above that of DNA sequence, but the reciprocal influence of DNA sequence *variation* on DNA methylation is substantial. The typical EWAS to date has not taken genetic variation into account when interpreting its results, again suggesting misinterpretation of DNA methylation changes as reflective of reprogramming of cells, when in fact the differences in DNA methylation may reflect *sequence differences* in the individuals studied.

The typical design of an EWAS is cross-sectional: comparing a group of individuals with a condition against a group without the condition; by the time these people are studied, they have already developed the disorder of interest. This makes the study vulnerable to the effects of *reverse causation* , in which the condition studied alters DNA methylation, rather than reprogramming of DNA methylation causing the condition. This has been shown to occur in peripheral blood leukocytes in individuals with high body mass index. The results of all EWAS to date therefore should be interpreted with caution.

Cell Fate Variability as Model for Epigenetics and Disease

A universally held belief is that 1 or more cell types in the body undergo a change in the regulation of gene expression, a type of cellular reprogramming that alters the properties of the cell to contribute to the disease. However, another model to consider is a reprogramming occurring earlier, during cell fate decision-making, and changing the repertoire of cells in the organ in such a way that it predisposes to disease.

Studies are guided by a mouse model characterized by maternal **vitamin A deficiency** during pregnancy. Vitamin A is the dietary precursor of **retinoic acid** , which binds to a retinoic acid receptor that then finds its way to specific locations in the genome to regulate the expression of groups of genes. When vitamin A was restricted in the diet of pregnant female mice from embryonic days 9.5-14.5, the period when most lung formation occurs, the mice were born with increased amounts of smooth muscle around the airways, later in their lives shown to be associated with increased airway resistance. The mice were thus showing a component of the reactive airways disease (asthma) phenotype caused solely by a micronutrient deficiency during fetal life (see Fig. 100.2). The change in a cell fate decision to alter the proportion of 1 or more cell types in the mature organ is a strikingly attractive mechanism for DOHaD and highly consistent with the original definition of epigenetic events based on cell fate decisions, but it is not considered the outcome of interest in current EWAS.

The same model can be considered for the epigenetic response to toxins, in particular **endocrine disruptors** , defined by their interaction with the endocrine system, for which links with epigenetic regulatory processes have been frequently sought. One interesting class of endocrine-disrupting chemical is the *organotins*, biocides used in different types of manufacturing. The organotin tributyltin was found to cause obesity and to direct tissue stem cells preferentially toward the production of adipocytes, signaling through a transcriptional pathway involving PPAR gamma. Again, this is not an outcome generally sought in a typical EWAS at present, but it represents a perturbation acting to change cell fate through transcriptional regulatory mechanisms and leading to an altered repertoire of cells in the exposed individual.

Epigenetic Disease and Therapeutic Interventions

The question arises whether interventions can ameliorate or reverse a disease phenotype when it is caused by epigenetic processes. In cancer, involving somatic mutations that can target various mediators of transcriptional regulation, numerous therapeutic avenues have emerged that show promise. An interesting noncancer example is the genetic condition called **Kabuki syndrome** , which is caused by mutations in either a histone methyltransferase (*KMT2D*) or a histone demethylase (*KDM6A*) gene, each of which has a role in creating accessible chromatin to allow genes to be expressed appropriately (Fig. 100.3 and Table 100.1). With the idea that increasing the amount of histone acetylation could help to compensate for the inappropriate histone methylation, mice with Kabuki syndrome were placed on a ketogenic diet, which increases the amount of β-hydroxybutyrate, an endogenous inhibitor of histone deacetylases. Mice on this diet showed improved neurogenesis and memory, suggesting that such an intervention in children with Kabuki syndrome may also have beneficial effects.

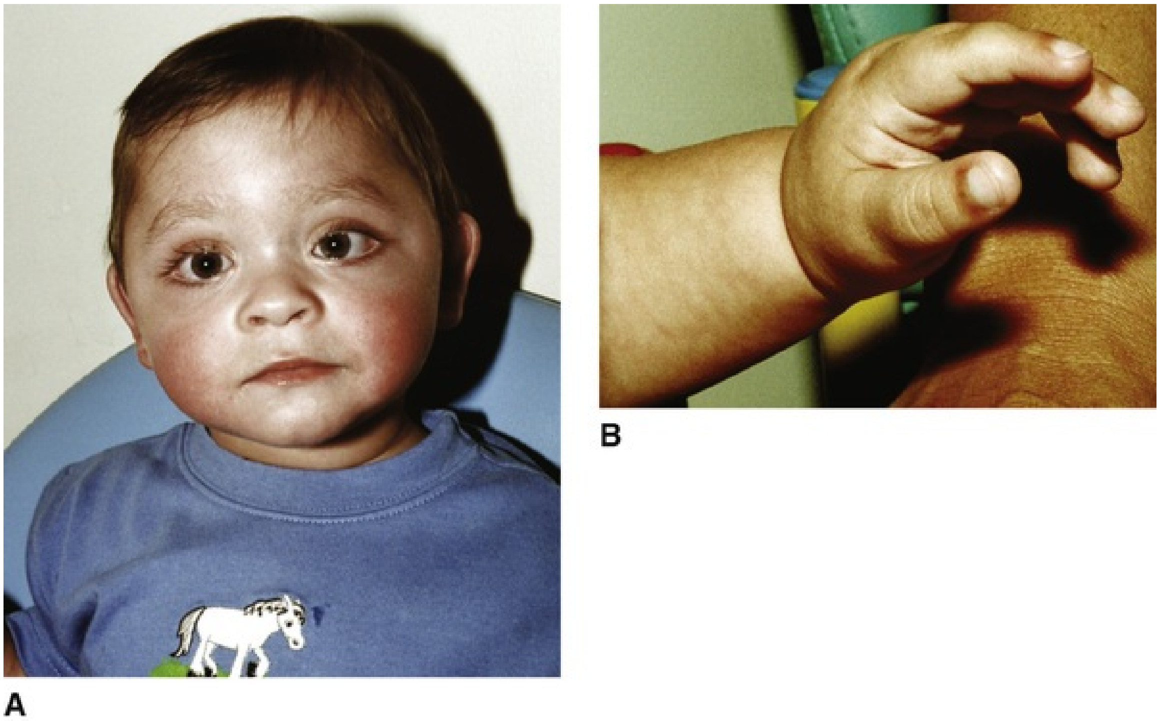

FIG. 100.3 Kabuki syndrome in 18 mo old boy. A, Long palpebral fissures and eversion of lateral portion of lower eyelids. B, Prominent fingertip pads. (From Jones, KL, Jones MC, Del Campo, M, editors: Smith's recognizable patterns of human malformation, ed 7, Philadelphia, 2013, Elsevier, p 158.)

Table 100.1

Clinical Manifestations of Kabuki Syndrome

Facial

Long palpebral tissues and eversions of lateral third of lower eyelids
Ptosis
Broad, arched eyebrows with sparse hair on lateral third
Long eyelashes
Blue sclerae
Protuberant ears
Short nasal columella (depressed nasal tip)

Neurodevelopmental

Hypotonia
Developmental delay (IQ about 60; >80 in 10%)
Low birthweight
Postnatal growth deficiency
Microcephaly
Seizures
Autism

Extremity/Skeletal

Short, incurved 5th finger
Brachydactyly
Kyphosis
Joint hyperextensibility
Persistent fetal fingertip pads
Hypoplastic finger nails

Cardiovascular

Multiple forms of congenital heart disease

Other

Nonimmune hydrops
Hypothyroidism
Precocious puberty
Delayed puberty
Lymphatic malformations
Feeding difficulties

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CHAPTER 101

Genetic Approaches to Rare and Undiagnosed Diseases

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Rare and novel disorders often present in childhood and represent a diagnostic challenge that can be addressed using advanced genetic techniques. In the United States, **rare disorders** are defined as those affecting <200,000 people (about 1 in 1,500 persons), but no single definition has been agreed on internationally.

Scope of Genetic Disease

An estimated 8000 rare disorders are recognized, and the existence of approximately 23,000 human genes suggests that many more genetic diseases will be discovered in the future. Potential reasons patients may remain undiagnosed despite extensive prior investigation include:

- The genetic variant had not previously been associated with the disease phenotype.
- There is genetic *pleiotropy* (same gene but different variant producing a different phenotype).
- There is genetic *heterogeneity* (different genes producing similar phenotype).
- Presentation is known but atypical features for a known disease.

◆ Multiple diseases are contributing to the presenting set of disease features.

◆ Somatic mosaicism

NIH Undiagnosed Diseases Program

One approach toward investigating undiagnosed diseases was taken by the National Institutes of Health (NIH) Undiagnosed Diseases Program (**UDP**), which was expanded to a nationwide Undiagnosed Diseases Network (UDN). For the >4,000 patient applications to the UDP, prior investigations are recounted in a summary letter from the referring clinician and documented with medical records that include photos, videos, imaging, and histologic slides of biopsy material. Specialty consultants review the records, and the UDP directors determine the next steps. Accepted patients come to the NIH Clinical Center for a week-long inpatient admission. Approximately half the patients with undiagnosed diseases have neurologic disease; cardiovascular, rheumatology, immunology, and pulmonary problems are also common. Approximately 40% of accepted patients are children, who often have congenital anomalies and neurologic disorders.

Clinical Evaluation

Patients remain without a definitive diagnosis after an extensive workup in part because every individual has a unique genetic and environmental background, and diseases have variable expression. Undiagnosed conditions include those never before seen, unusual presentations of otherwise recognizable conditions, and combinations of conditions that obfuscate each other's identities. A thorough clinical investigation allows the clinician to broaden the differential diagnosis through research, consultation, and clinical testing. Extensive phenotyping, imaging, and other tests provide better documentation of the presentation and allow for association with diseases not yet discovered, genetic variants, and patient cohorts.

A complete history anchors the data and includes prenatal and neonatal findings, developmental milestones, growth pattern, onset and progression of symptoms and signs, precipitating influences, response to medications, and a pedigree to determine which family members are possibly affected. Pertinent physical findings include dysmorphisms, organomegaly, neurologic impairment, bone involvement, and dermatologic findings. Because many rare and novel disorders are *multisystemic*, consultants play a critical role in every diagnostic evaluation. Typical studies performed to address possible diagnoses are listed in Table 101.1 ; neurodevelopmental or neurodegenerative phenotypes require even more extensive studies (Table 101.2).

Table 101.1

Initial Studies to Generate New Diagnostic Hypotheses

TEST	RELATED DISORDERS/DISORDER GROUPS
Electrolytes, lactate, pyruvate	Energy metabolism defects, including mitochondrial disorders
Plasma amino acids	Renal disorders, amino acid disorders
Urine organic acids	Renal disorders, organic acid disorders, energy metabolism disorders, vitamin deficiencies
Aldolase, creatine phosphokinase	Muscle disorders
Carnitine (free, total, acyl, panel)	Fatty acid oxidation disorders, carnitine metabolism disorders
Cerebrospinal fluid (CSF) analysis	Neurotransmitter disorders, inborn errors of metabolism, select disorders that may present only in the CSF
Brain MRI/magnetic resonance spectroscopy	Structural and morphologic clues to disorders affecting central nervous system
Mass spectrometry to detect *N* - and *O* -linked proteoglycan abnormalities	Congenital disorders of glycosylation
Lysosomal enzyme testing	Lysosomal storage diseases
White cell and skin electron microscopy	Lysosomal storage diseases; neuronal lipofuscinoses
Pathologic evaluation of affected tissues with special stains, DNA hybridization	Any
Echocardiogram, electrocardiogram	Structural and functional abnormalities of the heart
Nerve conduction velocity, electromyogram	Dysfunction of anterior horn cells, nerves, neuromuscular junction, or muscle
Fibroblast cell line	Any
Single nucleotide polymorphism, exome/genome/karyotype	Any
Erythrocyte sedimentation rate, C-reactive protein	Inflammatory disorders

Table 101.2

Diagnostic Evaluation of the Neurologically Impaired Child

Consultations

- Genetics/genetic counseling
- Neurology

Ophthalmology
Endocrinology
Immunology
Rheumatology
Dermatology
Cardiology
Neuropsychology
Nutrition
Rehabilitative medicine
    Physical therapy
    Occupational therapy
    Speech therapy

Procedures

Swallow study for aspiration
Abdominal ultrasound (hepatosplenomegaly)
Skeletal survey (dysostosis)
Bone density scan (nonambulatory or growth failure patients)
Bone age
Electroencephalogram, evoked responses, electroretinogram (ERG)
Muscle biopsy for electron transport chain function, histology, immunohistochemistry
Neuropsychometric testing
Nerve biopsy

Laboratory Evaluations

Complete blood count with differential and peripheral smear
Comprehensive metabolic panel
Prothrombin time/partial thromboplastin time (for anesthesia sedation)
Thyroid-stimulating hormone, thyroxine
Vitamins A and E, 1,25-dihydroxyvitamin D
Lactate, pyruvate
Ammonia
Amino acids (plasma and urine)

Organic acids (urine)
Acylcarnitine profile
Total and free carnitine
Lysosomal enzyme analysis in leukocytes/fibroblasts
White blood cell coenzyme Q
Purines and pyrimidines (urine)
α-Glucosidase (plasma and urine)
Peroxisomal panel
Oxysterols
Methylmalonic acid and homocysteine (plasma)
Copper/ceruloplasmin
Transferrin isoelectric focusing
N - and *O* -glycans (plasma)
Oligosaccharides and free glycans (urine)
Glycosaminoglycans (urine)

Additional Testing if Clinically Indicated

Electron microscopy of white blood cell buffy coat for inclusion bodies
Electron microscopy of skin biopsy for evidence of storage
Stool for ova and parasites, occult blood, fecal fat, or fecal calprotectin
Autoimmune antibodies
Vaccine response titers
C3/C4
Quantitative immunoglobulins
T-cell subsets
Conjunctival or salivary gland biopsy

Research Specimens

Cerebrospinal fluid
Serum
Plasma
Skin biopsy for fibroblasts and/or melanocytes
Isolated DNA/RNA
Urine

Studies Under Sedation

3T MRI/magnetic resonance spectroscopy of brain (and spine if indicated)
Skin biopsy
Ophthalmologic exam
Brainstem auditory evoked response
Electroretinogram
Lumbar puncture for biopterin, neopterin, neurotransmitters, folate, and inflammatory markers
Dental exam
Large blood draws
Catheterization for urine
Any part of the physical exam difficult to do in an awake child, including dysmorphology measurements and genital and rectal exam
Electromyography and nerve conduction studies

An inpatient admission allows for close interaction among experts in different fields, informs the evaluation of complex cases, and often leads to new disease discovery. In the last situation, other family members require evaluation to ascertain whether they are affected with the disorder.

Commercial Genetic Studies

Once **phenotyping** is complete, a list of candidate genetic disorders can be compiled. Laboratory testing is available for an increasingly large number of molecular disorders. Examples of genetic panels include those for X-linked cognitive impairment, hereditary spastic paraplegia, spastic paraplegia and gait disorders, spinocerebellar ataxias, dystonias, and mitochondrial disorders. Some of these are expensive and may exceed the cost of **exome sequencing** . On the other hand, exome and genome sequencing are not useful for detecting diseases caused by many types of genetic disorder, including from DNA repeats. In addition, exome sequencing may provide less certainty for excluding genetic diseases than a disease-specific test panel.

Single Nucleotide Polymorphism Arrays

Single nucleotide polymorphism (**SNP**) arrays and next-generation sequencing (NGS) provide valuable genome-wide structural information. The human genome's 3.2 billion bases include many that are **polymorphic,** customarily defined as differing between any 2 people >1% of the time. In most human populations, about 4 million differences exist between any 2 unrelated individuals (about 1 polymorphism for every 1,000 bases in the genome on average). Within a single ethnic population, about 1 common SNP occurs per 3,000-7,000 bases, where *common* means a >10% chance that the base will differ between 2 unrelated people. Approximately 1 million of these common SNPs can be included on a DNA hybridization array and examined simultaneously, revealing copy number variants, mosaicism, and regions of identity by descent. These results complement NGS results; one example is the pairing of sequence variants detected by exome or genome sequencing with *trans* -oriented deletions detected by SNP assay.

Exome Sequencing

Technical advances have allowed for massive, inexpensive DNA sequencing, making it feasible to determine the sequence of the coding regions of almost all the human genes. Because this involves 1.9% of the 3.2 billion bases in the human genome, exome sequences comprise approximately 60,000,000 bases. Using current technology, clinical exome sequencing adequately sequences >80% of known genes and >90% of genes that have been associated with human disease. The average exome sequencing produces about 35,000 bases (0.06%) that differ from the “reference” sequence and from any other unrelated human sequence of the same ethnic group. These variants include some laboratory and computational errors. In practice, most variants are inconsequential polymorphisms and minor polynucleotide repeats that occur near intron/exon boundaries. However, each of the 35,000 variants of unknown significance is a *potential* disease-causing variant, yet only 1 (or 2 for compound heterozygous recessive cases) is *the* disease-causing mutation for a monogenic disorder (with perhaps 2 or 3 additional loci modifying severity). The clinician and bioinformatician must reduce the number of candidate variants to a tractable number, which is challenging. For instance, a variant causing an adult-onset disease may look just as damaging as a different variant causing congenital-onset disease. However, the likelihood of the presence of the associated diseases is much different in an adult vs a child.

Certain rules are used to separate *likely-interesting variants* from likely-uninteresting variants. For example, variants that segregate in a family consistent with a given inheritance model (e.g., dominant or recessive) are retained, while those that segregate in an inconsistent manner are set aside. This segregation filter requires careful clinical data collection and experimental design, since it depends on correct assignment of affected vs unaffected statuses in the family and collection of sequencing data for family members besides the proband.

A 2nd technique used to evaluate sequence variants is **pathogenicity assessment** . Bioinformaticians estimate the likelihood that a given DNA sequence variant will have biologic consequences (e.g., change protein function or gene expression). Factors such as nucleotide conservation and differences in coded amino acids are used to create a pathogenicity estimate, or score. Various software programs take different, often overlapping, approaches. PolyPhen-2, SIFT, and MutationTaster rate the pathogenicity of amino acid changes. Computer modeling programs such as CADD, Eigen, and M-CAP, trained on model genetic changes that are already validated, predict effects on gene expression of noncoding variants. These filters are very powerful because of large population datasets that are publically available, including the 1000Genomes project, ExAC, and the UK's 10K genome project. In the next 1 or 2 yr, datasets with genome populations in the 100,000 to 1 million range (e.g., GnomAD database) will further improve these filters and provide better subpopulation frequencies. Ultimately, a multiethnic, graph theory-based alignment should allow successful filtering of variants in currently incomplete genomic regions such as the HLA region. Overall, computational pathogenicity assessment has false-positive and false-negative rates of 10–20%.

Some filters compare variants to databases that contain previously measured or asserted properties of variants found in human populations, such as population frequency information (e.g., ExAC), or curated evidence for association with human disease (e.g., CLINVAR). The latter, while potentially useful, is quite incomplete for many genes, but this is improving. One common pitfall of database-derived filters is an inaccurate designation of certain variants as rare. This typically happens when the database is missing information from human populations in whom the variant is seen more often than in the included populations.

Several points need to be considered when employing genome-scale sequencing for clinical diagnostics. **Positive predictive value** gives the likelihood that a positive test is a true positive. This is higher in a population in whom a disease is common and lower in a population in whom the disease is rare. A person being tested with exome sequencing will show no clinical signs or symptoms of most of the genetic diseases for which the exome sequencing tests. Therefore, many apparently positive findings will be *false positives*, variants associated with phenotypes that do not match the person being tested.

Individual vs family studies are relevant because family data allow for the proband's variants to be substantially filtered. This advantage must be weighed against the financial costs of studying families vs individuals. Furthermore, family studies are useless if an affected person is called unaffected, or vice versa. Therefore, *phenotyping family members is critical.* For later-onset conditions, younger siblings may not be suitable for inclusion in an exome sequencing study unless their affected status can be determined unambiguously. Datasets with large numbers of young individuals may have many pathologic variants that cause disease in elderly persons and are inappropriate for filtering variants in late-onset adult diseases or for prenatal counseling about late-onset disease inheritance risks.

Data revisiting policies must be addressed. Genome-scale sequencing generates data for many genes besides those involved in the current diagnostic effort; these data may be useful in the future care of the patient. Some unreported mutated genes, not currently associated with disease, may be implicated in the future as disease risk factors or even as protective factors. In the current testing environment, time-limited data reuse policies and storage and reuse fees are increasingly common. In fact, the storage of data is now becoming more expensive than the cost of re-generating the data.

Early discussion with a genetic specialist is critical. Genetic counseling should be sought before an exome sequencing study is sent. Proper consent for exome sequencing studies is an involved process, including discussions of disease risk factors, unrelated medical conditions, carrier states, and cancer susceptibility. Consented individuals should be asked which types of results they would like to receive.

Anticipating findings that are difficult to use clinically is an important part of counseling. Variants of unknown significance (VUS) are problematic, and genome-scale sequencing amplifies the problem by including variable numbers of results that are difficult to use for medical decision-making. Discussing such variants with families can be challenging; counseling families about the likelihood of receiving this type of result before testing is performed can help the family to cope when the report is returned (see Chapter 94).

When used as a gene panel, exome sequencing rules *in* but does not rule *out* . An exome study is a cost-effective way to test many genes simultaneously, but coverage of any given exon varies. Therefore, exome studies cannot always exclude **variants** in a panel of genes. With careful analysis involving laboratory validation performed on many similarly processed individuals, the exome coverage of any given gene can be assessed. However, commercial/clinical testing facilities may be unwilling to perform such an analysis when a large set of genes needs to be considered. Therefore, a gene panel can be useful when the index of suspicion is high for a disorder caused by a large group of genes. Cerebellar ataxia and hereditary spastic paraplegia are examples (see Chapters 615.1 and 631).

Providing information to the testing facility improves the chance of diagnosis. Exome sequencing interpretation benefits substantially from the incorporation of an accurate and detailed phenotype. The more clinical information provided to the testing lab, the more specific and useful will be the clinical report.

The role of whole *genome* sequencing (WGS) is not yet defined in clinical practice but remains a consideration when *exome* sequencing yields no diagnosis. The fundamental issue is whether the VUS findings in an exome will be more meaningful than any additional variants discovered by WGS, rather than a clinical conclusion that there is no germline genetic/molecular cause for the undiagnosed patient. WGS tools have less confidence because of net lower coverage, take more time to process, and generate variants in noncoding regions of the genome that are much more difficult to filter and interpret.

Gene Function Studies

Despite filtering for frequency and predicted deleteriousness, a variant identified by exome or genome sequencing cannot be interpreted as the cause of an individual's disease unless it has been previously demonstrated to cause a disease with a similar phenotype. To prove causality, medical genetics relies on **association** (the recurrence of mutations within a gene among individuals with a similar phenotype). For rare diseases, there may be too few affected patients to demonstrate a statistically significant association, and other evidence from phenotype ontologies, metabolomics, glycomics, proteomics, and lipidomics may be required. In addition, models (e.g., mice, zebrafish, fruit flies, yeast, cultured cells) can be developed to recapitulate the disease. The variant in question can also be linked to a biologic process or pathway that is known to cause a similar phenotype when disturbed. Finally, standardized and correlated phenotypic and genomic data are deposited into a database to identify other individuals with a similar phenotype and mutations in the same gene.

Physicians may apply their past biases to a group of variants that could be disease causing, but this is often misleading. A standardized computational approach is preferable. For example, the Human Phenotype Ontology standardizes the description of a disease and, because the descriptors have been mapped to other human diseases and to mutant model organisms, identifies possible candidate genes and genetic networks for causing the disease. Similarly, untargeted laboratory screening tests provide an unbiased survey of patient cellular biology and physiology and a more informed prioritization of candidate variants.

The ultimate proof of causality is to ameliorate the disease process by correcting the genetic defect; this might be demonstrable in a model system that recapitulates the human disease. Alternatively, a search for other patients with a similar phenotype and mutations in the same gene can be performed using public databases established using strict statistical and biologic standards.

Pediatric Issues

Of the UDP's 1st 500 pediatric applications, >10% had more than 1 family member (usually a sibling) similarly affected. The age distribution had peaks at 4-5 yr (reflecting patients with congenital disorders) and at 16-18 yr (representing disorders with symptom onset at early school age). Most applicants had been on a diagnostic odyssey for >5 yr. Of the 200 pediatric cases accepted, 25% received a diagnosis; half were obtained using conventional diagnostic methods, including clinical suspicion, biochemical testing with molecular confirmation, or radiographic interpretation. Otherwise, SNP analysis and NGS yielded the diagnosis; all involved rare diseases.

Pediatric medical records require attention to what has and what has not been completed previously. The electronic medical record is an important tool, but “copy forward” functions can perpetuate errors, such as reports of normal testing when in fact the test was recommended or ordered but not performed. Repetitive copying also fosters sloppiness in critical thinking, failure to take an adequate history, and missing the nuances of symptom progression. A history and physical examination should be performed anew and all prior testing results confirmed through copies of original laboratory reports.

Prolonged and painful procedures should be performed under sedation, but the risks associated with sedation must be weighed against the value of information and samples obtained.

Considerations for Families of Undiagnosed Children

When a child comes to a genetics clinic for evaluation, the parents ask these questions:

- What does my child have? (diagnosis)
- Why did it happen? (etiology/inheritance)
- What will happen in the future? (natural history; prognosis)
- Is there a treatment? (therapy)
- Could the same thing happen to other family members? (recurrence risk)

The answers all require an accurate diagnosis. The lack of a diagnosis makes both the family and the physician uncomfortable, raises suspicion among relatives and acquaintances, and creates feelings of guilt about not having worked hard enough to obtain a diagnosis. Families often consult more and more specialists, becoming frustrated with the lack of coordination among providers. Families should save copies of every test and every visit from each institution in a binder for travel among institutions. A 2- to 3-page narrative summarizing the child's history, medications, list of healthcare providers with contact information, main medical issues, level of functioning on well days and sick days, and interventions that worked in the past can be invaluable in an emergency room setting. An electronic copy is easily updated. Parents can always be the best advocates for their child, particularly an undiagnosed child.

Recommendations to parents of an undiagnosed child are similar to those that apply to any child with chronic illness:

◆ Organize copies of all records, especially original reports from “send-out” laboratories.

◆ Carry an updated emergency letter.

◆ Establish a medical home even if you obtain many second opinions.

◆ Find a physiatrist (rehabilitation medicine physician) to coordinate rehabilitative care.

◆ Strongly advocate with the school system for needed services (see Chapter 48), using a legal advocate if necessary;

◆ Explore parent support groups for unknown disorders (Syndromes Without a Name, National Organization for Rare Disorders).

◆ Periodically check with providers (especially geneticists) for new diagnoses reported in the medical literature.

◆ Carve out time for yourselves as caregivers by engaging extended family members or respite care services.

◆ Work at supporting and being attentive to well children in the family.

◆ For the dying child, consider an autopsy to establish a diagnosis, especially when there is a possibility of future pregnancies.

The Diagnostic Spectrum

Rare and new genetic disorders can present at any age; a gene's “severe” mutations may manifest early in life while “mild” mutations present later. Diagnoses of known disorders can have very different bases, such as the extent of recognition of a clinical entity, a molecular confirmation, or biochemical evidence. Some variants identified by SNP and exome sequencing analyses may represent new diseases.

One example of the use of these technologies to discover a new diagnosis involves 2 brothers whose parents were first cousins. The brothers had an early-onset spastic ataxia-neuropathy syndrome, with lower-extremity spasticity, peripheral neuropathy, ptosis, oculomotor apraxia, dystonia, cerebellar atrophy, and progressive myoclonic epilepsy. A homozygous missense mutation (c.1847G>A; p.Y616C) in *AFG3L2* , which encodes a subunit of a mitochondrial protease, was identified by exome sequencing. The AFG3L2 protein can bind to another AFG3L2 molecule or to paraplegin. UDP collaborators in Germany used a yeast model system to demonstrate that the patients' mutation affects the specific amino acid involved in the formation of both these complexes. As a result, the brothers exhibited the signs and symptoms of a known AFG3L2 defect, autosomal dominant spinocerebellar ataxia type 28 (SCA28), and also deficits attributable to a paraplegin defect, hereditary spastic paraplegia type 7 (SPG7). Other features of a mitochondrial disorder (oculomotor apraxia, extrapyramidal dysfunction, myoclonic epilepsy) were also present. The 2 brothers represent the 1st such cases in the world and expand the phenotype of AFG3L2 disease.

A 2nd example involves 2 siblings ages 5 and 10 yr with hypotonia, developmental delays, facial dysmorphisms, hearing loss, nystagmus, seizures, and atrophy on brain MRI. In this case the leading clue was biochemical in nature, and genetic analysis confirmed the diagnosis. Urine thin-layer chromatography for oligosaccharides identified a strong band determined by mass spectrometry to consist of a tetrasaccharide containing 3 glucoses and 1 mannose. This suggested a defect of glucosidase I, the 1st enzyme involved in endoplasmic reticulum trimming of *N* -linked glycoproteins from a high-mannose to a complex form. Mutation analysis confirmed compound heterozygous variants in the glucosidase I gene, establishing the diagnosis of congenital disorder of glycosylation IIb. The 2 siblings were the 2nd and 3rd patients in the world with this disorder.

Occasionally an autosomal dominant disorder, typically presenting in adulthood, can manifest as a completely different and more severe disorder when pathologic variants in the same gene are inherited from each parent; the child is a *compound heterozygote*. This was the case in a 3 yr old child who inherited 2 variants in *GARS*, the gene causing autosomal dominant Charcot-Marie-Tooth disease (CMT) 2D. The child had severe intrauterine and postnatal growth retardation, microcephaly, developmental delay, optic nerve atrophy and retinal pigment changes, as well as an atrial septal defect. Neither parent was symptomatic at the time the child was evaluated; the parents had normal electromyography and nerve conduction studies. This case emphasizes the need to consent families before any genetic testing as to the possibility of receiving unexpected results in additional family members. In this case, genetic counseling was expanded to include possible CMT2D in the parents.

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PART X

Metabolic Disorders

OUTLINE

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CHAPTER 102

An Approach to Inborn Errors of Metabolism

Oleg A. Shchelochkov, Charles P. Venditti

Many childhood conditions are caused by single-gene mutations that encode specific proteins. These mutations can change primary protein structure or the amount of protein synthesized. The function of a protein, whether it is an enzyme, receptor, transport vehicle, membrane component, transcriptional co-regulator, or structural element, may be compromised or abolished. Hereditary diseases that disrupt normal biochemical processes are termed **inborn errors of metabolism** or **inherited metabolic diseases** .

Most genetic changes are clinically inconsequential and represent *benign* variants. However, pathogenic variants produce diseases that range in severity of presentation and time of onset. Severe metabolic disorders usually become clinically apparent in the newborn period or shortly thereafter, whereas milder forms may present later in childhood and even in adulthood. With some exceptions, the presenting symptoms of most metabolic conditions lack the specificity to enable a definitive diagnosis without further evaluation. The combination of *low specificity* of presenting symptoms and *low prevalence* of metabolic disorders makes determination of the diagnosis difficult. Progressive symptoms, the lack of plausible non-genetic diagnosis after detailed evaluation, history of overlapping symptoms in patient's relatives, or consanguinity should alert a pediatrician to seek a consultation with a geneticist and consider metabolic testing early in the evaluation.

Correct diagnosis is often only the beginning of a long medical journey for most families affected by metabolic conditions (see Chapter 95). Although each inherited metabolic disorder is individually rare, improved diagnosis and increasing survival of patients with metabolic conditions virtually ensure that a pediatrician will encounter and provide care to affected patients. Pediatricians can play a critical role in establishing the continuity of care, managing some aspects of treatment, fostering adherence, and delivering routine pediatric interventions such as immunizations, referrals to specialists, and elements of genetic counseling (see Chapter 94.1).

The greater awareness of metabolic conditions, wider availability of biochemical laboratories, global metabolomic analysis, and routine application of exome sequencing dramatically increased the detection rate of the known disorders and contributed to the discovery of new metabolic disorders. Nonetheless, collection and analysis of family history remains a critical screening test that a healthcare provider can use to identify an infant or child at risk for a metabolic disorder. The identification of consanguinity or a particular ethnic background with an unusually high incidence of inborn errors of metabolism can be important to direct further studies. For example, tyrosinemia type 1 is more common among French-Canadians of Quebec, maple syrup urine disease is seen with higher frequency in the U.S. Amish population, and Canavan disease in patients of the Ashkenazi Jewish ancestry.

Newborn Screening

The individual rarity of inborn errors of metabolism, the importance of early diagnosis, and the ensuing genetic counseling ramifications make a strong argument for the universal screening all newborn infants. **Tandem mass spectrometry** of metabolites and **digital microfluidics analysis** of enzyme activities form the foundation of newborn screening today. Both methods require a few drops of blood to be placed on a filter paper and delivered to a central laboratory for assay. Many genetic conditions can be identified by these methods, and the list of disorders continues to grow (Tables 102.1 and 102.2). Pediatricians need to be aware of the general screening procedure and limitations of screening. As a screening method, a positive result may require a repeat newborn screen or confirmatory testing to secure the diagnosis. Time required to return the results vary from country to country and even within states in the same country. Some metabolic conditions can be severe enough to cause clinical manifestations before the results of the newborn screening become available. Conversely, diagnostic metabolites in milder forms of screened disorders may not reach a set threshold to trigger secondary studies, thus leading to a negative newborn screen results and delayed diagnosis. *Therefore, negative newborn screening in a patient with symptoms suggestive of a metabolic disorder* *warrants a referral to genetics center for further evaluation.*

Table 102.1

Disorders Recommended by the American College of Medical Genetics Task Force for Inclusion in Newborn Screening (“Primary Disorders”)*

Disorders of Organic Acid Metabolism

Isovaleric acidemia
Glutaric aciduria type I
3-Hydroxy-3-methylglutaric aciduria
Multiple carboxylase deficiency
Methylmalonic acidemia (methylmalonyl-CoA mutase deficiency)
Methylmalonic acidemia (*cbl* A and *cbl* B defects)
Propionic acidemia
3-Methylcrotonyl-CoA carboxylase deficiency
β-Ketothiolase deficiency

Disorders of Fatty Acid Metabolism

Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-hydroxy-acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake defect

Disorders of Amino Acid Metabolism

Phenylketonuria
Maple syrup urine disease
Homocystinuria
Citrullinemia type 1
Argininosuccinic acidemia

Tyrosinemia type I

Hemoglobinopathies

Sickle cell anemia (hemoglobin SS disease)
Hemoglobin S/β-thalassemia
Hemoglobin S/C disease

Other Disorders

Congenital hypothyroidism
Biotinidase deficiency
Congenital adrenal hyperplasia
Galactosemia
Hearing loss
Cystic fibrosis
Severe combined immunodeficiency (SCID) [†]
Critical congenital heart disease [†]

cbl A, Cobalamin A defect; *cbl* B, cobalamin B defect; CoA, coenzyme A.

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[*] As of November 2014, there is state-to-state variation in newborn screening; a list of the disorders that are screened for by each state is available at http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf .

[†] The inclusion of SCID and critical congenital heart disease received support of the American College of Medical Genetics and Genomics.

Table 102.2

Secondary Conditions Recommended by American College of Medical Genetics[*] Task Force for Inclusion in Newborn Screening

Organic Acid Metabolism Disorders

Methylmalonic acidemia (*cbl* C and *cbl* D defects)
Malonic acidemia
2-Methyl-3-hydroxybutyric aciduria
Isobutyryl-CoA dehydrogenase deficiency
2-Methylbutyryl-CoA dehydrogenase deficiency
3-Methylglutaconic aciduria

Fatty Acid Oxidation Disorders

Short-chain acyl-CoA dehydrogenase deficiency
Glutaric acidemia type 2
Medium/short-chain 3-hydroxy-acyl-CoA dehydrogenase deficiency
Medium-chain ketoacyl-CoA thiolase deficiency
Carnitine palmitoyltransferase IA deficiency
Carnitine palmitoyltransferase II deficiency
Carnitine:acylcarnitine translocase deficiency
Dienoyl-CoA reductase deficiency

Amino Acid Metabolism Disorders

Hyperphenylalaninemia, benign (not classic phenylketonuria)
Tyrosinemia type II
Tyrosinemia type III
Defects of biopterin cofactor biosynthesis
Defects of biopterin cofactor regeneration
Argininemia
Hypermethioninemia
Citrullinemia type II (citrin deficiency)

Hemoglobinopathies

Hemoglobin variants (including hemoglobin E)

Others

Galactose epimerase deficiency
Galactokinase deficiency

cbl C, Cobalamin C defect; *cbl* D, cobalamin D defect; CoA, coenzyme A.

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[*] The American College of Medical Genetics Newborn Screening Expert Group (May 2006) recommended reporting, in addition to the primary disorders, 25 disorders (“secondary targets”) that can be detected through screening but that do not meet the criteria for primary disorders (https://www.acmg.net/resources/policies/nbs/NBS_Main_Report_01.pdf).

Universal newborn screening may also identify mild forms of inherited metabolic conditions, some of which may never cause clinical manifestations in the lifetime of the individual. For example, short-chain acyl-CoA dehydrogenase deficiency has been identified with unexpectedly high frequency in screening programs using tandem mass spectrometry, but most of these children have remained asymptomatic. This highlights the need for an ongoing evaluation of metabolite cutoff values and approaches to confirmatory testing to maximize the diagnostic yield and minimize potential psychosocial and economic implications of such findings. Premature infants represent a special patient population in whom the incidence of false-positive or false-negative test results can be especially high.

With the advent of genetic therapy for spinal muscular atrophy (SMA) and enzyme replacement therapy for some lysosomal storage diseases (e.g., Pompe disease, Fabry disease, Gaucher disease, and mucopolysaccharidosis type 1), pilot newborn screening programs have demonstrated initial success in identifying SMA or lysosomal storage disorders, often before severe symptoms develop.

Clinical Manifestations of Genetic Metabolic Diseases

Physicians and other healthcare providers who care for children should familiarize themselves with early manifestations of genetic metabolic disorders, because (1) severe forms of some of these conditions may cause symptoms before the results of screening studies become available, and (2) the current screening methods, although quite extensive, identify a small number of all inherited metabolic conditions. In the newborn period, the clinical findings are usually nonspecific and similar to those seen in infants with sepsis. A genetic disorder of metabolism should be considered in the differential diagnosis of a severely ill newborn infant, and special studies should be undertaken if the index of suspicion is high (Fig. 102.1).

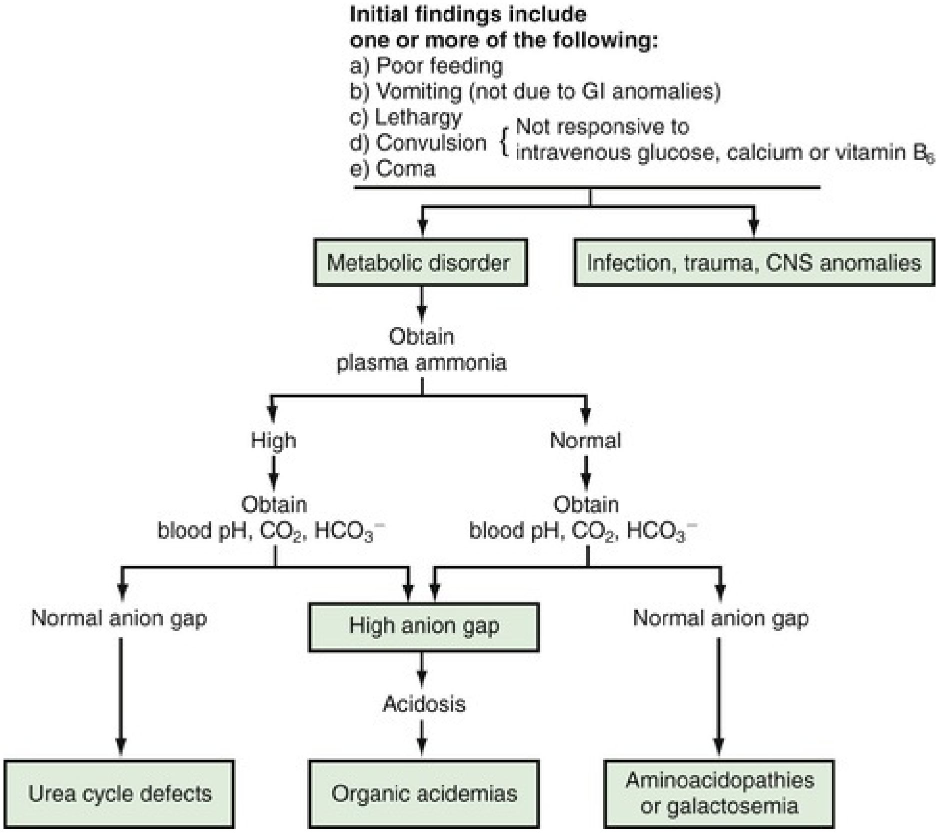
Initial findings include
one or more of the following:
a) Poor feeding
b) Vomiting (not due to GI anomalies)
c) Lethargy
d) Convulsion
e) Coma
Not responsive to intravenous glucose, calcium or vitamin B6
Metabolic disorder
Infection, trauma, CNS anomalies
Obtain plasma ammonia
High
Normal
Obtain blood pH, CO2, HCO3−
Obtain blood pH, CO2, HCO3−
Normal anion gap
High anion gap
Normal anion gap
Acidosis
Urea cycle defects
Organic acidemias
Aminoacidopathies or galactosemia

FIG. 102.1 **Initial clinical approach to a full-term newborn infant with a suspected genetic metabolic disorder. This schema is a guide to elucidate some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases affected by disorders or intermediate metabolism. CNS, Central nervous system; GI, gastrointestinal; HCO_3^- , bicarbonate.**

Signs and symptoms such as lethargy, hypotonia, hypothermia, convulsions (Table 102.3), poor feeding, and vomiting may develop as early as a few hours after birth. Occasionally, vomiting may be severe enough to suggest the diagnosis of pyloric stenosis, which is usually not present, although it may occur simultaneously in such infants. Lethargy, poor feeding, seizures, and coma may also be seen in infants with hypoglycemia (Table 102.4) (see Chapters 111 and 127), hypocalcemia (Chapters 64 and 589), and hyperammonemia (Table 102.5) (Chapter 103). Measurements of blood concentrations of glucose and calcium and response to intravenous injection of glucose or calcium help establish these diagnoses. Every organ system can be affected by metabolic disorders. However, *physical examination* usually reveals nonspecific findings; most signs are related to the central nervous system such as opisthotonus in the case of maple syrup urine disease (MSUD). Hepatomegaly is a common finding in a variety of inborn errors of metabolism (Table 102.6). Cardiomyopathy (Table 102.7), dysmorphology (Table 102.8), and fetal hydrops (Table 102.9) are additional potential manifestations of a metabolic disorder (Table 102.10). Occasionally, a peculiar odor may offer an invaluable aid to the diagnosis (Table 102.11).

Table 102.3

Select Inborn Errors of Metabolism Associated With Neurologic and Laboratory Manifestations in Neonates

DETERIORATION IN CONSCIOUSNESS
Metabolic Acidosis
Organic acidemias
Disorders of pyruvate metabolism
Fatty acid oxidation defects
Fructose-1,6-bisphosphatase deficiency
Glycogen storage diseases
Mitochondrial respiratory chain defects
Disorders of ketone metabolism
***Hypoglycemia* ***
Fatty acid oxidation defects
Disorders of gluconeogenesis
Disorders of fructose and galactose metabolism
Glycogen storage diseases
Disorders of ketogenesis
Organic acidemias
Hyperinsulinemic hypoglycemias
Mitochondrial respiratory chain defects
Neonatal intrahepatic cholestasis caused by citrin deficiency

Pyruvate carboxylase deficiency
Carbonic anhydrase VA deficiency
Hyperammonemia [**]
Urea cycle disorders
Organic acidemias
Fatty acid oxidation disorders
Disorders of pyruvate metabolism
GLUD1 -related hyperinsulinemic hypoglycemia
Carbonic anhydrase VA deficiency
SEIZURES AND HYPOTONIA
Antiquitin deficiency (pyridoxine-dependent epilepsy)
Pyridoxamine 5'-phosphate oxidase (PNPO) deficiency (pyridoxal phosphate-responsive epilepsy)
Folate metabolism disorders
Multiple carboxylase deficiency (holocarboxylase synthetase deficiency and biotinidase deficiency)
Urea cycle disorders
Organic acidemias
Fatty acid oxidation disorders
Disorders of creatine biosynthesis and transport
Disorders of neurotransmitter metabolism
Molybdenum cofactor deficiency and sulfite oxidase deficiency
Serine deficiency disorders
Glycine encephalopathy
Asparagine synthetase deficiency
Mitochondrial respiratory chain defects
Zellweger spectrum disorders
Congenital disorders of glycosylation
Purine and pyrimidine metabolism defects
NEONATAL APNEA
Glycine encephalopathy
Asparagine synthetase deficiency
Urea cycle disorders
Organic acidemias
Disorders of pyruvate metabolism
Fatty acid oxidation defects
Mitochondrial respiratory chain defects

[*] Refer to Table 102.4 for more details on the metabolic disorders associated with neonatal hypoglycemia.

** Refer to Table 102.5 for more details on the differential diagnosis of neonatal and infantile hyperammonemia.

Modified from El-Hattab AW: Inborn errors of metabolism, Clin Perinatol 42:413-439, 2015 (Box 1, p 415).

Table 102.4

Select Inborn Errors of Metabolism Associated With Neonatal Hypoglycemia

CATEGORY OF DISORDERS	DISORDERS
Fatty acid oxidation disorders	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase Ia deficiency Carnitine palmitoyltransferase II deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/trifunctional protein deficiency Medium-chain acyl-CoA dehydrogenase deficiency Very-long-chain acyl-CoA dehydrogenase deficiency Multiple acyl-CoA dehydrogenase deficiency
Disorders of gluconeogenesis	Fructose-1,6-diphosphatase deficiency Phosphoenolpyruvate carboxykinase deficiency
Disorders of fructose and galactose metabolism	Hereditary fructose intolerance Classic galactosemia
Glycogen storage diseases (GSD)	GSD type Ia (glucose-6-phosphatase deficiency) GSD type Ib (impaired glucose-6-phosphate exchanger) GSD type III (glycogen debrancher enzyme deficiency) GSD type VI (liver glycogen phosphorylase deficiency) GSD type IX (phosphorylase kinase deficiencies)
Disorders of ketogenesis	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency
Organic acidemias	Propionic acidemia Methylmalonic acidemia Isovaleric acidemia Maple syrup urine disease Multiple carboxylase deficiency (holocarboxylase synthetase deficiency and biotinidase deficiency)
Hyperinsulinemic hypoglycemia	*HADH* -related disorder (3-alpha-hydroxyacyl-CoA dehydrogenase deficiency) *GLUD1* -related disorder (hyperammonemia-hyperinsulinism syndrome, HIHA)
Other	Mitochondrial respiratory chain defects Neonatal intrahepatic cholestasis caused by citrin deficiency Pyruvate carboxylase deficiency Carbonic anhydrase VA deficiency

Modified from Zinn AB: Inborn errors of metabolism. In *Fanaroff & Martin's neonatal-perinatal medicine: diseases of the fetus and infant,* ed 10, vol 2, Philadelphia, 2015, Elsevier (Table 99.17, p 1605).

Table 102.5

Differential Diagnosis of Hyperammonemia

INBORN ERRORS OF METABOLISM
Urea Cycle Enzyme Defects
N-acetylglutamate synthase (NAGS) deficiency
Carbamoyl phosphate synthetase 1 (CPS1) deficiency
Ornithine transcarbamylase (OTC) deficiency
Argininosuccinate synthetase (ASS) deficiency (citrullinemia type 1)
Argininosuccinate lyase (ASL) deficiency (argininosuccinic aciduria)
Arginase 1 deficiency
Transport and Synthesis Defects of Urea Cycle Intermediates
Hyperornithinemia-hyperammonemia-homocitrullinemia (HHH syndrome)
Citrullinemia type 2 caused by citrin deficiency
Lysinuric protein intolerance
Ornithine aminotransferase deficiency
Carbonic anhydrase VA deficiency
Organic Acidemias
Propionic acidemia
MUT **-**related methylmalonic acidemia and cobalamin metabolism disorders
Isovaleric acidemia
Fatty Acid Oxidation Disorders
Long-chain fatty acid oxidation defects
Systemic primary carnitine deficiency
Other
Pyruvate carboxylase deficiency
GLUD1 **-**related hyperinsulinemic hypoglycemia
Neonatal iron overload disorders (e.g. hereditary hemochromatoses)
ACQUIRED DISORDERS
Transient Hyperammonemia of the Newborn
Diseases of the Liver and Biliary Tract
Liver failure
Biliary atresia
Severe Systemic Neonatal Illness
Neonates sepsis
Heart failure
Medications

Valproic acid

Cyclophosphamide

5-Pentanoic acid

Asparaginase

Other

Reye syndrome

ANATOMIC VARIANTS

Vascular bypass of the liver (e.g. a portosystemic anastomosis)

TECHNICAL

Inappropriate sample collection (e.g., capillary blood or prolonged placement of a tourniquet)

Sample not immediately analyzed

Modified from El-Hattab AW: Inborn errors of metabolism, Clin Perinatol 42:413-439, 2015 (Box 8, p 428).

Table 102.6

Select Metabolic Disorders Associated With Hepatic Dysfunction

CATEGORY OF DISORDERS	DISORDERS
Disorders of amino acid metabolism	Tyrosinemia type I Citrullinemia type II caused by citrin deficiency Disorders of methionine metabolism Urea cycle disorders
Biliary tract disorders and disorder of bile acid synthesis	See Chapter 383
Disorders of fructose and galactose metabolism	Hereditary fructose intolerance Classic galactosemia Epimerase deficiency galactosemia
Congenital disorders of glycosylation	Multiple types
Fatty acid oxidation disorders	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase Ia deficiency Carnitine palmitoyltransferase II deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/trifunctional protein deficiency Very-long-chain acyl-CoA dehydrogenase deficiency Multiple acyl-CoA dehydrogenase deficiency
Glycogen storage disorders (GSD)	GSD type III (glycogen debrancher enzyme deficiency) GSD type IV (glycogen branching enzyme deficiency) GSD type VI (liver glycogen phosphorylase deficiency)
Peroxisomal disorders	Zellweger spectrum disorders Disorders of peroxisomal β-oxidation
Mitochondrial respiratory chain (RC) defects	*Mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) defects* Specific single nucleotide pathogenic variants in mtDNA Large-scale mtDNA re-arrangements (Pearson syndrome)

	Disorders of mitochondrial translation (e.g., tRNA^{Glu}) Disorder of protein synthesis of RC complexes Disorders affected the assembly or stabilization of RC complexes (e.g., *BCS1L*) Disorders of cofactor biosynthesis (e.g. coenzyme Q10) Disorders of mitochondrial transport and dynamics mtDNA depletion syndromes (e.g., *DGUOK, MPV17, POLG, SUCLG1*)
Lysosomal storage disorders	Niemann-Pick disease type C
Other	α_1 -Antitrypsin deficiency

Modified from Zinn AB: Inborn errors of metabolism. In Fanaroff & Martin's neonatal-perinatal medicine: diseases of the fetus and infant, ed 10, vol 2, Philadelphia, 2015, Elsevier (Table 99.5, p 1579).

Table 102.7

Select Metabolic Disorders Associated With Cardiomyopathy

CATEGORY OF DISORDERS	**DISORDERS**
Organic acidemias	Propionic acidemia Cobalamin C deficiency 3-methylglutaconic acidurias (e.g., Barth syndrome and DCMA syndrome)
Lysosomal storage disorders	Sphingolipidoses (e.g., Fabry disease) Oligosaccharidoses and mucolipidoses (e.g., I-cell disease) Mucopolysaccharidoses
Glycogen storage disorders (GSD)	GSD type II (Pompe disease) GSD type III (glycogen debrancher enzyme deficiency) *PRKAG2* -related disorders (includes lethal congenital glycogen storage disease of heart)
Congenital disorders of glycosylation	Multiple types
Fatty acid oxidation disorders	Carnitine-acylcarnitine translocase deficiency Carnitine palmitoyltransferase II deficiency Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency/trifunctional protein deficiency *ACAD9* -related disorder (mitochondrial acyl-CoA dehydrogenase deficiency) Multiple acyl-CoA dehydrogenase deficiency (includes glutaric aciduria type 2) Very-long-chain acyl-CoA dehydrogenase deficiency Systemic primary carnitine deficiency
Mitochondrial respiratory chain (RC) defects	*Mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) defects* Specific single nucleotide pathogenic variants in mtDNA Large-scale mtDNA deletions Disorders of mitochondrial translation (e.g., tRNA^{Leu}) Disorders of protein synthesis of RC complexes (e.g., *MT-ATP6* , *MT-ATP8* , *NDUFS2, NDUFV2, SDHA, SCO2, COX10, COX15*) Disorders affecting the assembly or stabilization of RC complexes (e.g., *TMEM70*) Disorders of cofactor biosynthesis (e.g. coenzyme Q10) Disorders of mitochondrial transport and dynamics (e.g., *SLC25A3*) mtDNA depletion syndromes (e.g., *SUCLG1*)

Other	Danon disease

Modified from Zinn AB: Inborn errors of metabolism. In Fanaroff & Martin's neonatal-perinatal medicine: diseases of the fetus and infant, ed 10, vol 2, Philadelphia, 2015, Elsevier (Table 99.4, p 1576).

Table 102.8

Select Inborn Errors of Metabolism Associated With Dysmorphic Features

CATEGORY OF DISORDERS	DISORDERS
Congenital disorders of glycosylation	N-Glycosylation disorders (e.g., PMM2-CDG and ALG3-CDG) O-Glycosylation disorders (e.g., Walker-Warburg syndrome)
Disorders of cholesterol biosynthesis	Smith-Lemli-Opitz syndrome Desmosterolosis Lathosterolosis *EBP* -related disorder (includes Conradi-Hunermann syndrome)
Lysosomal storage disorders	Sphingolipidoses Oligosaccharidoses and mucolipidoses Mucopolysaccharidoses
Organic acidurias	Multiple acyl-CoA dehydrogenase deficiency (includes glutaric aciduria type 2) Mevalonic aciduria*
Peroxisomal disorders	Zellweger spectrum disorders Disorders of peroxisomal β-oxidation
Other	Pyruvate dehydrogenase complex deficiency

* Mevalonic aciduria has been classified as an organic acidemia based on the method used for its diagnosis, but it can also be classified as a peroxisomal single-enzyme disorder or as a defect in cholesterol biosynthesis because of its intracellular location and function, respectively.

Modified from Zinn AB: Inborn errors of metabolism. In Fanaroff & Martin's neonatal-perinatal medicine: diseases of the fetus and infant, ed 10, vol 2, Philadelphia, 2015, Elsevier (Table 99.8, p 1583).

Table 102.9

Select Inborn Errors of Metabolism Associated With Hydrops Fetalis

Lysosomal storage disorders
Mucopolysaccharidoses types I, IVA, and VII
Sphingolipidoses (e.g., Gaucher disease, Farber disease, Niemann-Pick disease A, GM_1 gangliosidosis, multiple sulfatase deficiency)
Lipid storage diseases (Wolman and Niemann-Pick disease C)
Oligosaccharidoses (e.g., sialidosis type I)
Mucolipidoses (e.g., I-cell disease)
Zellweger spectrum disorders

Glycogen storage disease type IV

Congenital disorders of glycosylation

Mitochondrial respiratory chain defects

Transaldolase deficiency

Modified and adapted from El-Hattab AW: Inborn errors of metabolism, Clin Perinatol 42:413-439, 2015 (Box 6, p 417).

Table 102.10

Pathognomonic Clinical Findings Associated With Inborn Errors of Metabolism (Select Examples)

FINDINGS	DISORDERS
Hepatomegaly	Disorders of fructose and galactose metabolism (e.g., classic galactosemia and hereditary fructose intolerance) Glycogen storage diseases Disorders of gluconeogenesis Disorders of fatty acid oxidation and transport Mitochondrial respiratory chain defects Tyrosinemia type 1 Urea cycle disorders Zellweger spectrum disorders Niemann-Pick disease type C Congenital disorders of glycosylation
Hepatosplenomegaly	Mucopolysaccharidoses Niemann-Pick disease types A, B, and C Sphingolipidoses (e.g., GM_1 gangliosidosis or Gaucher disease) Wolman disease Farber disease (acid ceramidase deficiency)
Macrocephaly	Glutaric acidemia type 1 Canavan disease
Microcephaly	Mitochondrial respiratory chain defects Disorders of intracellular cobalamin metabolism (e.g., *cbl* C deficiency)
Coarse facial features	Mucopolysaccharidoses Oligosaccharidoses and mucolipidoses (e.g., α-mannosidosis) Sphingolipidoses (e.g., GM_1 gangliosidosis) Galactosialidosis
Macroglossia	Glycogen storage disease type II (Pompe disease) Mucopolysaccharidoses Oligosaccharidoses and mucolipidoses Sphingolipidoses Galactosialidosis
Dystonia or extrapyramidal signs	Gaucher disease type 2 Glutaric acidemia type 1 Methylmalonic acidemia Propionic acidemia

	Krabbe disease Crigler–Najjar syndrome Disorders of neurotransmitter metabolism Pyruvate dehydrogenase complex deficiency
Macular “cherry-red spot”	GM$_1$ gangliosidosis Tay-Sachs disease (GM$_2$ gangliosidosis) Farber disease (acid ceramidase deficiency) Galactosialidosis Niemann-Pick disease type A Sialidosis Multiple sulfatase deficiency
“Bull eye” maculopathy	*cbl* C deficiency (combined methylmalonic acidemia and homocystinuria, type C)
Retinitis pigmentosa	Mitochondrial respiratory chain defects Peroxisomal disorders Abetalipoproteinemia
Optic nerve atrophy or hypoplasia	Pyruvate dehydrogenase complex deficiency Mitochondrial respiratory chain defects Peroxisomal disorders Propionic acidemia *MUT* -related methylmalonic acidemia and cobalamin metabolism disorders
Corneal clouding or opacities	Mucolipidoses Mucopolysaccharidoses Steroid sulfatase deficiency Tyrosinemia type II Cystinosis
Cataracts	Disorders of galactose metabolism (e.g., classic galactosemia) Congenital disorders of glycosylation Mitochondrial respiratory chain (RC) defects Peroxisomal disorders Lowe oculocerebrorenal syndrome
Dislocated lens	Cystathionine β-synthase deficiency Molybdenum cofactor deficiency and sulfite oxidase deficiency
Skeletal dysplasias and dysostosis multiplex	Oligosaccharidoses and mucolipidoses Mucopolysaccharidoses Sphingolipidoses Galactosialidosis Peroxisomal disorders Disorders of cholesterol biosynthesis Congenital disorders of glycosylation
Thick skin	Oligosaccharidoses and mucolipidoses Mucopolysaccharidoses Sphingolipidoses
Desquamating, eczematous, or vesiculobullous skin lesions	Acrodermatitis enteropathica Essential amino acid deficiencies in organic acidemias Hartnup disorder Multiple carboxylase deficiency (holocarboxylase synthetase deficiency and biotinidase deficiency) Porphyrias
Ichthyosis	Gaucher disease type 2 Steroid sulfatase deficiency Refsum disease *ELOVL4* -related disorder Serine deficiency disorders

Alopecia	Multiple carboxylase deficiency (holocarboxylase synthetase deficiency and biotinidase deficiency)
Steely or kinky hair	Menkes disease
Trichorrhexis nodosa	Argininosuccinic aciduria (ASL deficiency)
Persistent diarrhea	Glucose-galactose malabsorption Congenital lactase deficiency Congenital chloride diarrhea Sucrase-isomaltase deficiency Acrodermatitis enteropathica Abetalipoproteinemia Congenital folate malabsorption Wolman disease Lysinuric protein intolerance Classic galactosemia

Modified from Cederbaum S: Introduction to metabolic and biochemical genetic diseases. In Gleason CA, Juul SE, editors: Avery's diseases of the newborn, ed 10, Philadelphia, 2018, Elsevier (Table 21.1, p 227).

Table 102.11

Inborn Errors of Amino Acid Metabolism Associated With Peculiar Odor

INBORN ERROR OF METABOLISM	URINE ODOR
Isovaleric acidemia Glutaric acidemia (type II)	Sweaty feet, acrid
Maple syrup urine disease	Maple syrup, burnt sugar
Multiple carboxylase deficiency 3-Methylcrotonyl-CoA carboxylase deficiency 3-Hydroxy-3-methylglutaric aciduria	Cat urine
Phenylketonuria	Mousey or musty
Trimethylaminuria Dimethylglycine dehydrogenase deficiency	Rotten fish
Tyrosinemia type 1	Boiled cabbage, rancid butter
Hypermethioninemia	Boiled cabbage
Cystinuria Tyrosinemia type I	Sulfur
Hawkinsinuria	“Swimming pool”
Oasthouse urine disease	Hops-like

In an increasing number of patients, a metabolic condition may be recognized months or years after birth. This is more typical in patients carrying milder autosomal recessive pathogenic variants, in mitochondrial disorders, in females affected by X-linked recessive conditions, and specific metabolic conditions that usually present later in life. *Clinical manifestations*, such as intellectual disability, motor deficits, developmental regression, seizures, psychosis, cardiomyopathy, myopathy, organomegaly, and recurrent emesis, in patients beyond the neonatal period should suggest an inherited metabolic disease (Table

102.12). There may be an episodic or intermittent pattern, with episodes of acute clinical manifestations separated by periods of seemingly disease-free states. The episodes are usually triggered by stress or nonspecific catabolic stress such as an infection. The child may die during one of these acute attacks. An inborn error of metabolism should be considered in any child with 1 or more of the following manifestations: unexplained developmental delay; intellectual disability; developmental regression; motor deficits or adventitious movements (e.g., dystonia, choreoathetosis, ataxia); seizures; catatonia; unusual odor (particularly during an acute illness); intermittent episodes of unexplained vomiting, acidosis, mental deterioration, psychosis, or coma; hepatomegaly; renal stones; renal dysfunction, especially Fanconi syndrome or renal tubular acidosis; muscle weakness; and cardiomyopathy (Table 102.12).

Table 102.12

Clinical Findings That Should Prompt a Metabolic Workup

Family history	Sibling(s) who died from unexplained causes or exhibit overlapping symptoms Ethnic groups with high prevalence of metabolic disorders Consanguinity
Perinatal history	Intrauterine growth retardation, sepsis-like presentation in the neonatal period, nonimmune fetal hydrops
Growth	Postnatal failure to thrive, microcephaly, macrocephaly, short stature
Central and peripheral nervous systems	Progressive encephalopathy, lethargy, coma, intractable seizures, developmental delay, developmental regression, intellectual disability, autism spectrum disorder, hypotonia, spasticity, dystonia, strokes, ataxia, psychosis, intracranial calcifications, white matter disease, peripheral neuropathy
Respiratory system	Hyperventilation, apnea
Cardiovascular system	Cardiac failure with or without cardiomyopathy, arrhythmia
Musculoskeletal system	Rhabdomyolysis, myopathy Osteopenia, early-onset osteoporosis, skeletal dysplasia, epiphyseal abnormalities, bone crises
Eye	Retinitis pigmentosa, macular dystrophy, cataracts, corneal opacities, nystagmus, cherry-red spot
Hearing	Sensorineural hearing loss
Gastrointestinal system	Hepatomegaly, splenomegaly, liver failure, Reye syndrome, cholestasis, cirrhosis, chronic diarrhea, vomiting, acute pancreatitis
Kidney	Renal dysfunction, renal stones
Hematological system	Anemia, leukopenia, thrombocytopenia, pancytopenia, hemolytic-uremic syndrome
Skin	Hair abnormality, alopecia, lipodystrophy, recalcitrant eczema

Diagnosis usually requires a variety of specific *laboratory studies.* Plasma amino acid analysis, plasma acylcarnitine profile, total and free carnitine profile, and urine organic acid assay, while not exhaustive in their diagnostic scope, are useful as initial screening tests to evaluate for a suspected inborn error of metabolism. Measurements of plasma ammonia, lactate, bicarbonate, and pH are readily available in hospitals and very helpful initially in differentiating major causes of genetic metabolic disorders (Table 102.13 ; see Fig. 102.1). Elevation of blood ammonia is usually caused by defects of urea cycle enzymes, organic acidemias, and disorders of fatty acid oxidation. Infants with elevated blood ammonia levels from urea cycle defects tend to have normal serum pH and bicarbonate values; without measurement of blood ammonia, they may remain undiagnosed and succumb to their disease. In organic acidemias, elevated plasma ammonia is accompanied by severe acidosis caused by accumulation of organic acids, ketone bodies, and lactate in body fluids.

Table 102.13

Laboratory Findings That Should Prompt a Metabolic Workup

Hyperammonemia
Metabolic acidosis
Lactic acidosis
Ketosis
Hypoglycemia
Liver dysfunction
Pancytopenia

When blood ammonia, pH, and bicarbonate values are normal, other aminoacidopathies (e.g. hyperglycinemia) or galactosemia should be considered. Galactosemic infants may also manifest cataracts, hepatomegaly, ascites, and jaundice.

Treatment

The majority of patients with genetic disorders of metabolism respond to one or more of the following treatments:

1. Special diets play an important role in the treatment of affected children.

Dietary changes should be tailored to the pathophysiology of the condition and vary greatly among disorders.

2. Hemodialysis for expeditious removal of accumulated noxious compounds. This is a very effective modality for treatment of the acute phase of the condition.
3. Catabolic states in patients at risk for metabolic crisis can be treated with fluids containing dextrose and electrolytes.
4. Administration of the deficient metabolite.
5. Administration of the cofactor or coenzyme to maximize the residual enzyme activity.
6. Activation of alternate pathways to reduce the noxious compounds accumulated because of the genetic mutation.
7. Administration of the deficient enzyme.
8. Bone marrow transplantation.
9. Liver and kidney transplantation.

The organ transplantation modalities may offer the best treatment modality to stabilize a metabolic patient and improve quality of life. To date, replacement of the mutant gene with a normal copy using gene therapy has been successful in only a few diseases.

Treatment of genetic disorders of metabolism is complex and requires medical and technical expertise. The therapeutic regimen often needs to be tailored to the individual patient because of large phenotypic variations in the severity of the disease, even within a single family. Providing education and support for the family is the key to successful long-term therapy. Even in patients with poor prognoses, every effort should be made to establish correct diagnoses premortem. Effective treatment is best achieved by a team of specialists—metabolic genetics specialist, nutritionist, neurologist, and psychologist—in a major medical center.

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CHAPTER 103

Defects in Metabolism of Amino Acids

103.1

Phenylalanine

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Keywords

phenylalanine
phenylketonuria
PKU
hyperphenylalaninemia
phenylalanine hydroxylase
tetrahydrobiopterin
BH4

Phenylalanine is an essential amino acid. Dietary phenylalanine not utilized for protein synthesis is normally degraded by way of the tyrosine pathway (Fig. 103.1). Deficiency of the enzyme **phenylalanine hydroxylase (PAH)** or of its cofactor **tetrahydrobiopterin (BH_4)** causes accumulation of phenylalanine in body fluids and in the brain.

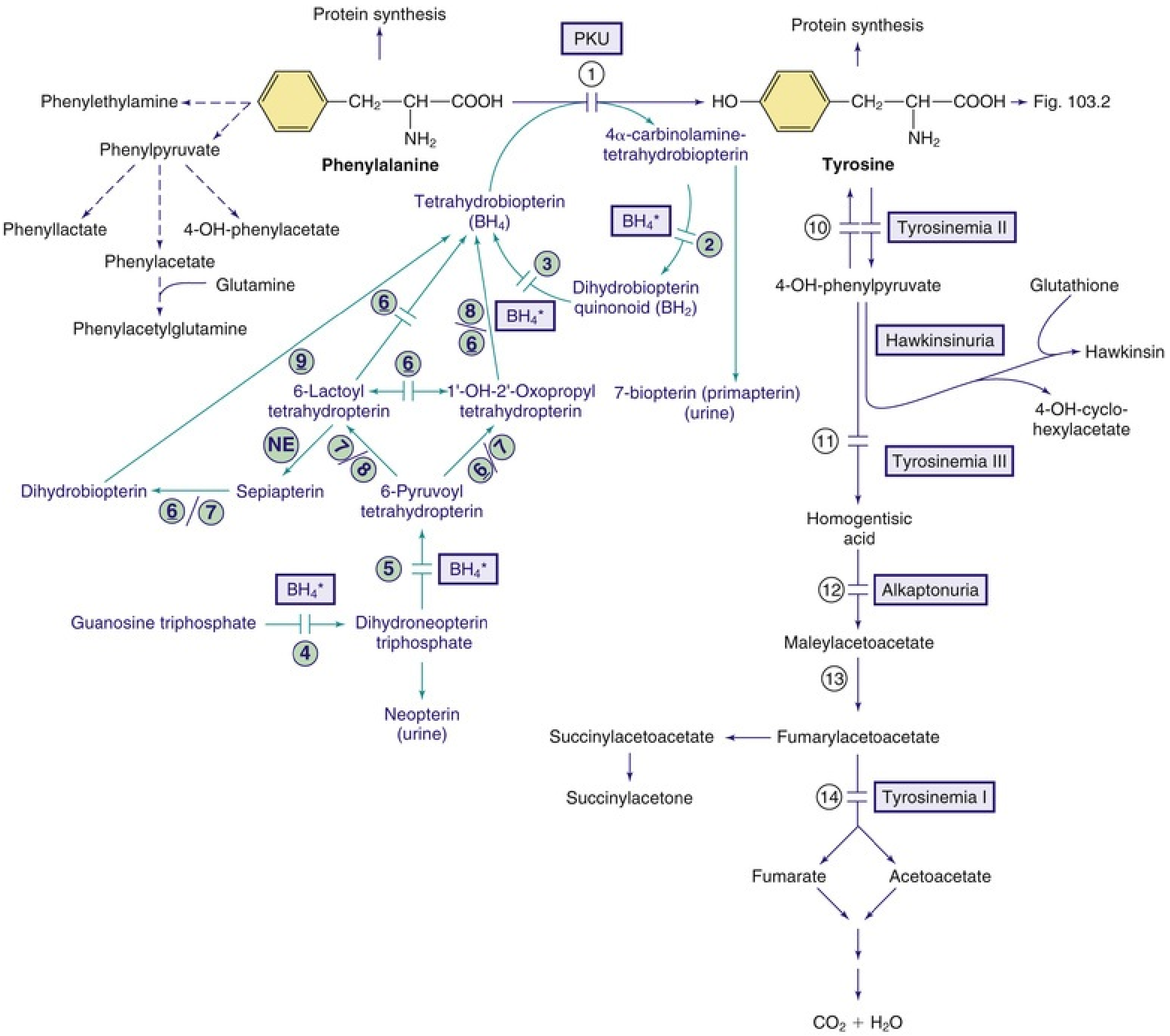
Protein synthesis
PKU
①
Protein synthesis
Phenylethylamine
CH$_2$—CH—COOH
NH$_2$
Phenylalanine
HO
CH$_2$—CH—COOH
NH$_2$
Tyrosine
Fig. 103.2
Phenylpyruvate
4α-carbinolamine-tetrahydrobiopterin
Phenyllactate
4-OH-phenylacetate
Phenylacetate
Glutamine
Phenylacetylglutamine
Tetrahydrobiopterin (BH$_4$)
BH$_4$*
2
3
Dihydrobiopterin quinonoid (BH$_2$)
⑩
Tyrosinemia II
4-OH-phenylpyruvate
Glutathione
Hawkinsinuria
Hawkinsin
6
8
BH$_4$*
6
9
6
6-Lactoyl tetrahydropterin
1'-OH-2'-Oxopropyl tetrahydropterin
7-biopterin (primapterin) (urine)
4-OH-cyclo-hexylacetate
⑪
Tyrosinemia III
NE
7
8
7
6
Dihydrobiopterin
Sepiapterin
6-Pyruvoyl tetrahydropterin
6/7
Homogentisic acid
5
BH$_4$*
BH$_4$*
⑫
Alkaptonuria
Guanosine triphosphate
Dihydroneopterin triphosphate
4
Maleylacetoacetate
⑬
Neopterin (urine)
Succinylacetoacetate
Fumarylacetoacetate
Succinylacetone
⑭
Tyrosinemia I
Fumarate
Acetoacetate
CO$_2$ + H$_2$O

FIG. 103.1 Pathways of phenylalanine and tyrosine metabolism. Enzyme defects causing genetic conditions are depicted as *horizontal bars* crossing the reaction arrow(s). Pathways for synthesis of cofactor BH_4 are shown in *purple.* BH_4 * refers to defects of BH_4 metabolism that affect the phenylalanine, tyrosine, and tryptophan hydroxylases (see Figs. 103.2 and 103.5). PKU, Phenylketonuria; NE, nonenzymatic. Enzymes: *(1)* Phenylalanine hydroxylase, *(2)* pterin-carbinolamine dehydratase, *(3)* dihydrobiopterin reductase, *(4)* guanosine triphosphate (GTP) cyclohydrolase, *(5)* 6-pyruvoyltetrahydropterin synthase, *(6)* sepiapterin reductase, *(7)* carbonyl reductase, *(8)* aldolase reductase, *(9)* dihydrofolate reductase, *(10)* tyrosine aminotransferase, *(11)* 4-hydroxyphenylpyruvate dioxygenase, *(12)* homogentisic acid dioxygenase, *(13)* maleylacetoacetate isomerase, *(14)* fumarylacetoacetate hydrolase.

Elevations of phenylalanine in the plasma depend on the degree of enzyme deficiency. In patients with **severe PAH deficiency** (previously referred to as *classic phenylketonuria*), plasma phenylalanine levels on unrestricted diet usually exceed 20 mg/dL (>1,200 µmol/L). Patients with milder PAH pathogenic variants have plasma phenylalanine levels between 10 mg/dL (600 µmol/L) and 20 mg/dL (1,200 µmol/L). Levels between 2 and 10 mg/dL (120-600 µmol/L) on unrestricted diet are observed in patients with **mild hyperphenylalaninemia** . In affected infants with plasma concentrations >20 mg/dL, excess phenylalanine is metabolized to phenylketones (phenylpyruvate and phenylacetate; see Fig. 103.1) that are excreted in the urine, giving rise to the term *phenylketonuria* (PKU).

These metabolites have no known role in pathogenesis of central nervous system (CNS) damage in PKU patients; their presence in the body fluids simply signifies the severity of the condition. The **brain** is the main organ damaged by PKU, but the exact mechanism of injury remains elusive. Both toxic levels of phenylalanine and insufficient tyrosine may play a role. Phenylalanine hydroxylase converts phenylalanine to **tyrosine** , which is necessary for the production of neurotransmitters such as epinephrine, norepinephrine, and dopamine (Fig. 103.2). If the degree of enzymatic block is severe, tyrosine becomes an essential amino acid and may be deficient if intake is not adequate. On the other hand, observations that lower concentration of phenylalanine in plasma and brain tissue are associated with improved neurobehavioral outcomes support the view that toxic levels of phenylalanine are key to the mechanisms of the disease. High blood levels of phenylalanine can saturate the transport system across the blood-brain barrier and cause inhibition of the cerebral uptake of other large neutral amino acids such as branched-chain amino acids, tyrosine, and tryptophan, impairing brain protein synthesis.

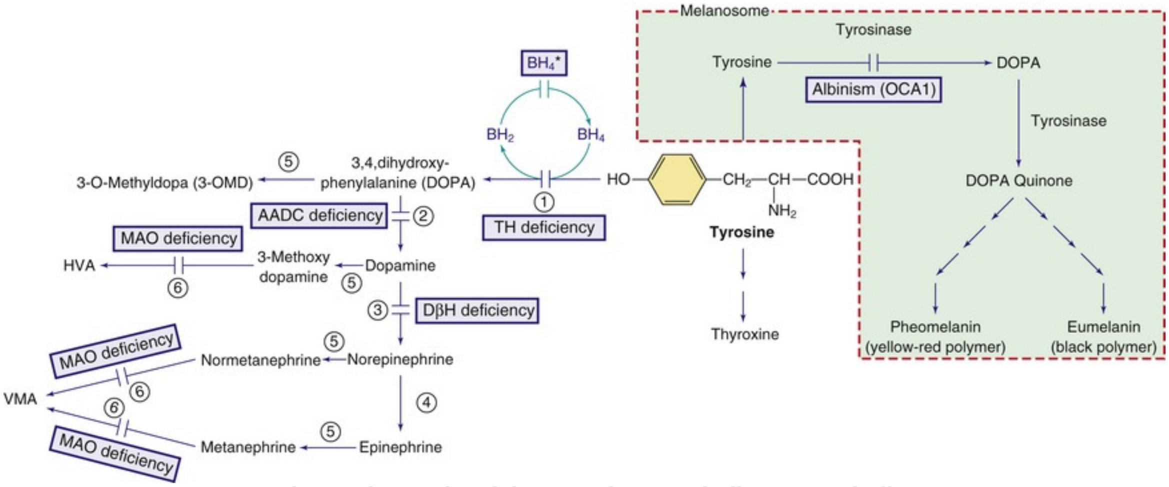
Melanosome
Tyrosinase
Tyrosine
DOPA
Albinism (OCA1)
Tyrosinase
DOPA Quinone
Pheomelanin
(yellow-red polymer)
Eumelanin
(black polymer)
BH4*
BH2
BH4
HO
CH2—CH—COOH
NH2
Tyrosine
Thyroxine
①
TH deficiency
3,4,dihydroxy-
phenylalanine (DOPA)
⑤
3-O-Methyldopa (3-OMD)
AADC deficiency
②
MAO deficiency
HVA
⑥
3-Methoxy
dopamine
Dopamine
⑤
③
DβH deficiency
⑤
MAO deficiency
Normetanephrine
Norepinephrine
⑥
VMA
⑥
④
⑤
MAO deficiency
Metanephrine
Epinephrine

FIG. 103.2 Other pathways involving tyrosine metabolism. BH$_4$ * indicates hyperphenylalaninemia caused by tetrahydrobiopterin (BH$_4$) deficiency (see Fig. 103.1). HVA, Homovanillic acid; VMA, vanillylmandelic acid. Enzymes: *(1)* Tyrosine hydroxylase (TH), *(2)* aromatic L -amino acid decarboxylase (AADC), *(3)* dopamine β-hydroxylase (DβH), *(4)* phenylethanolamine-*N* -methyltransferase (PNMT), *(5)* catechol *O* -methyltransferase (COMT), *(6)* monoamine oxidase (MAO).

Severe Phenylalanine Hydroxylase Deficiency (Classic Phenylketonuria)

Elevations of plasma phenylalanine >20 mg/dL (>1,200 µmol/L), if untreated, invariably result in the development of signs and symptoms of classic PKU, except in uncommon and unpredictable cases.

Clinical Manifestations

The affected infant appears normal at birth. Profound intellectual disability develops gradually if the infant remains untreated. Cognitive delay may not be evident for the 1st few months. In untreated patients, 50–70% will have an IQ below 35, and 88–90% will have an IQ below 65. Only 2–5% of untreated patients may have normal intelligence. Vomiting, sometimes severe enough to be misdiagnosed as pyloric stenosis, may be an early symptom. Older untreated children become hyperactive with autistic behaviors, including purposeless hand movements, rhythmic rocking, and athetosis.

Untreated and undertreated infants are lighter in their complexion than unaffected siblings. Some may have a seborrheic or eczematoid rash, which is usually mild and disappears as the child grows older. These children have an odor of phenylacetic acid, which has been described as musty or “mousey.” Neurologic signs include seizures (approximately 25%), spasticity, hyperreflexia, and tremors; >50% have electroencephalographic (EEG) abnormalities. Microcephaly, prominent maxillae with widely spaced teeth, enamel hypoplasia, and growth retardation are other common findings in untreated children. Low bone mineral density and osteopenia have been reported in affected individuals of all ages. Although inadequate intake of natural proteins seems to be the major culprit, the exact pathogenesis of this sequela remains unclear. Long-term care of patients with PKU is best achieved by a team of experienced professionals (metabolic specialist, nutritionist, and psychologist) in a regional treatment center. The clinical manifestations of classic PKU are rarely seen in countries where neonatal screening programs for the detection of PKU are in effect.

Non-PKU Hyperphenylalaninemia

In any screening program for PKU, a group of infants will be identified in whom initial plasma concentrations of phenylalanine are above normal (i.e., >2 mg/dL, or 120 µmol/L) but <20 mg/dL (1,200 µmol/L). These infants typically do not excrete phenylketones. Patients with non-PKU hyperphenylalaninemia may still require dietary therapy, depending on their untreated plasma phenylalanine level. Attempts have been made to classify these patients in different subgroups depending on the degree of hyperphenylalaninemia, but such a practice has little clinical or therapeutic advantage. The possibility of deficiency of BH_4 should be investigated in all infants with the milder forms of hyperphenylalaninemia.

Diagnosis

Because of the gradual and nonspecific nature of early clinical symptoms such as vomiting, developmental delay, or eczematoid rash, hyperphenylalaninemia is usually diagnosed through newborn screening in all developed countries. In infants with positive screening results, diagnosis should be confirmed by quantitative measurement of plasma phenylalanine concentration. Identification and measurement of phenylketones in the urine has no place in any screening program. In countries and places where such programs are not in effect, identification of phenylketones in the urine by ferric chloride may offer a simple test for diagnosis of infants with developmental and neurologic abnormalities. Once the diagnosis of hyperphenylalaninemia is established, additional studies for BH_4 metabolism should be performed to rule out BH_4 deficiency as the cause of hyperphenylalaninemia.

Neonatal Screening for Hyperphenylalaninemia

Effective and relatively inexpensive methods for mass screening of newborn infants are used in the United States and many other countries. A few drops of blood, which are placed on a filter paper and mailed to a central laboratory, are used for assay. The screening method of choice uses **tandem mass spectrometry** , which identifies all forms of hyperphenylalaninemia with a low false-positive rate and excellent accuracy and precision. The addition of the phenylalanine:tyrosine molar ratio has further reduced the number of false-positive results. Diagnosis must be confirmed by measurement of plasma phenylalanine concentration. Blood phenylalanine in affected infants with PKU may rise to diagnostic levels as early as 4 hr after birth, even in the absence of protein feeding. It is recommended that the blood for screening be obtained in the 1st 24-48 hr of life after feeding protein to reduce the possibility of false-negative results, especially in the milder forms of the condition.

Treatment

The mainstay of treatment of PKU is a *low-phenylalanine diet* . The general consensus is to start diet treatment immediately in patients with blood phenylalanine levels >10 mg/dL (600 µmol/L). It is generally accepted that infants with persistent (more than a few days) plasma levels of phenylalanine ≥6 mg/dL (360 µmol/L) should also be treated with a phenylalanine-restricted diet similar to that in classic PKU. The goal of therapy is to reduce phenylalanine levels in the plasma and brain. Formulas free of, or low in, phenylalanine are commercially available. The diet should be started as soon as the diagnosis is established. Because phenylalanine is not synthesized endogenously, the diet should provide phenylalanine to prevent phenylalanine deficiency. Dietary phenylalanine tolerance is determined based on age and severity of the PAH deficiency. **Phenylalanine deficiency** is manifested by lethargy, failure to thrive, anorexia, anemia, rashes, diarrhea, and even death. Further, tyrosine becomes an essential amino acid in this disorder, and its adequate intake must be ensured. Special food items low in phenylalanine are commercially available for dietary treatment of affected children and adults.

There is no firm consensus concerning optimal levels of blood phenylalanine in affected patients either across different countries or among treatment centers in the United States. The current recommendation is to maintain blood phenylalanine levels between 2 and 6 mg/dL (120-360 µmol/L) throughout life. Discontinuation of therapy, even in adulthood, may cause deterioration of IQ and cognitive performance. Lifelong adherence to a low-phenylalanine diet is extremely difficult. Patients who maintain good control as children but discontinue the phenylalanine-restricted diet as teenagers or adults may experience significant difficulties with executive function, concentration, emotional liability, and depression. Executive dysfunction may also occur in early-treated children despite diet treatment.

Given the difficulty of maintaining a strict low-phenylalanine diet, there are continuing attempts to find other modalities for treatment of these patients. Administration of **large neutral amino acids** (LNAAs) is another approach to dietary therapy. LNAAs (tyrosine, tryptophan, leucine, isoleucine, valine, methionine, histidine, and phenylalanine) share the same transporter protein (LNAA type 1 or LAT-1) for transit through the intestinal cell membrane and blood-brain barrier (BBB). Binding of LNAAs to the transporter protein is a competitive process. The rationale for use of LNAA is that these molecules compete with phenylalanine for transport across the BBB; therefore, large concentrations of other LNAAs in the intestinal lumen and in the blood reduce the uptake of phenylalanine into bloodstream and the brain. Large, controlled clinical trials are necessary to establish the efficacy of this treatment.

Oral administration of BH_4 , the cofactor for PAH, may result in reduction of plasma levels of phenylalanine in some patients with PAH deficiency. Plasma levels of phenylalanine in these patients may decrease enough to allow for considerable modification of their dietary restriction. In very rare cases the diet may be discontinued because the phenylalanine levels remain under 6 mg/dL (360 µmol/L). The response to BH_4 cannot be predicted consistently based on the genotype alone, especially in compound heterozygous patients. **Sapropterin dihydrochloride** , a synthetic form of BH_4 , which acts as a cofactor in patients with residual PAH activity, is approved by the U.S. Food and Drug Administration (FDA) to reduce phenylalanine levels in PKU. A sustained decrease of plasma phenylalanine by at least 30% is consistent with sapropterin responsiveness. Injectable PEGylated recombinant phenylalanine ammonia lyase is in development.

Pregnancy in Women With PAH Deficiency (Maternal Phenylketonuria)

Pregnant women with PAH deficiency who are not on a phenylalanine-restricted diet have a very high risk of having offspring with intellectual disability, microcephaly, growth retardation, congenital malformations, and congenital heart disease. These complications are directly correlated with elevated maternal blood phenylalanine levels during pregnancy. Prospective mothers who have been treated for PAH deficiency should be maintained on a phenylalanine-restricted diet before and during pregnancy. The best observed outcomes occur when strict control of maternal blood phenylalanine concentration is instituted before pregnancy. Plasma phenylalanine levels >6 mg/dL (360 µmol/L) after conception are associated with increased incidence of intrauterine growth restriction and congenital malformations, as well as lower IQ. However, there is strong evidence that phenylalanine control instituted after conception results in improved outcomes. The currently recommended phenylalanine concentration is

2-6 mg/dL (120-360 µmol/L) throughout the pregnancy, although some expert groups advocate plasma phenylalanine levels <4 mg/dL (<240 µmol/L). All women with PAH deficiency who are of childbearing age should be counseled properly regarding the risk of congenital anomalies in their offspring.

Hyperphenylalaninemia Caused by Deficiency of the Cofactor Tetrahydrobiopterin

In 1-3% of infants with hyperphenylalaninemia, the defect resides in one of the enzymes necessary for production or recycling of the cofactor BH_4 (see Fig. 103.1). If these infants are misdiagnosed as having PKU, they may deteriorate neurologically despite adequate control of plasma phenylalanine. BH_4 is synthesized from guanosine triphosphate (GTP) through several enzymatic reactions (see Fig. 103.1). In addition to acting as a cofactor for PAH, BH_4 is also a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, which are involved in the biosynthesis of dopamine (see Fig. 103.2) and serotonin (see Fig. 103.5), respectively. Therefore, patients with hyperphenylalaninemia resulting from BH_4 deficiency also manifest neurologic findings related to deficiencies of these neurotransmitters. Four enzyme deficiencies leading to defective BH_4 formation cause hyperphenylalaninemia with concomitant deficiencies of dopamine and serotonin: autosomal recessive GTP cyclohydrolase I deficiency, 6-pyruvoyl-tetrahydropterin synthase deficiency, dihydropteridine reductase deficiency, and pterin-4-α-carbinolamine dehydratase deficiency. More than half the reported patients have had a deficiency of 6-pyruvoyl-tetrahydropterin synthase. Autosomal dominant forms of GTP cyclohydrolase I deficiency and sepiapterin reductase deficiency result in deficiencies of neurotransmitters without hyperphenylalaninemia (see Chapter 103.11).

Clinical Manifestations

Infants with cofactor BH_4 deficiency are identified during screening programs for PKU because of evidence of hyperphenylalaninemia. Plasma phenylalanine levels may be as high as those in classic PKU or may be in the milder range.

However, the clinical manifestations of the neurotransmitter disorders differ greatly from those of PKU. Neurologic symptoms of the neurotransmitter disorders often manifest in the 1st few months of life and include extrapyramidal signs (choreoathetotic or dystonic limb movements, axial and truncal hypotonia, hypokinesia), feeding difficulties, and autonomic abnormalities. Intellectual disability, seizures, hypersalivation, and swallowing difficulties are also seen. The symptoms are usually progressive and often have a marked diurnal fluctuation. Prognosis and outcome strongly depend on the age at diagnosis and at introduction of treatment, but also on the specific nature of the pathogenic variant and resulting enzyme defect.

Diagnosis

Despite the low incidence of BH_4 synthesis defects, all newborns with hyperphenylalaninemia detected through newborn screening *must* be screened for BH_4 synthesis defects. BH_4 deficiency and the responsible enzyme defect may be diagnosed by several studies.

Measurement of Neopterin and Biopterin.

Neopterin (oxidative product of dihydroneopterin triphosphate) and biopterin (oxidative product of dihydrobiopterin and BH_4) are measured in body fluids, especially urine (see Fig. 103.1). In patients with GTP cyclohydrolase I deficiency, urinary excretion of both neopterin and biopterin is very low. In patients with 6-pyruvoyl-tetrahydropterin synthase deficiency, there is a marked elevation of neopterin excretion and a concomitant decrease in biopterin excretion. In patients with dihydropteridine reductase deficiency, the excretion of neopterin and biopterin is elevated. Excretion of biopterin increases in this enzyme deficiency because the quinonoid dihydrobiopterin cannot be recycled back to BH_4 . Patients with pterin-4-α-carbinolamine dehydratase deficiency excrete 7-biopterin (an unusual isomer of biopterin) in their urine.

Cerebrospinal Fluid Studies.

Examination of cerebrospinal fluid (CSF) may reveal decreased levels of dopamine and serotonin metabolites (see Chapter 103.11).

BH_4 Loading Test.

An oral dose of BH_4 (20 mg/kg) normalizes plasma phenylalanine and phenylalanine:tyrosine ratio in patients with BH_4 deficiency within 4-12 hr. The blood phenylalanine should be elevated (>400 µmol/L) to enable interpretation of the results. This may be achieved by discontinuing diet therapy for 2 days before the test or by administering a loading dose of phenylalanine (100 mg/kg) 3 hr before the test. In BH_4 -responsive PKU caused by PAH deficiency, blood phenylalanine levels may decrease during the BH_4 loading test, but increase later even with BH_4 supplementation. Patients who demonstrate phenylalanine levels within normal range over at least 1 wk without a phenylalanine-restricted diet can continue BH_4 supplementation as the sole treatment for the hyperphenylalaninemia. However, it is imperative that plasma phenylalanine levels be monitored prospectively to ensure that phenylalanine levels remain within the normal range.

Molecular Testing.

Sequencing and deletion/duplication analysis are clinically available and play an increasingly more important role in confirming the biochemical diagnosis.

Enzyme Assay.

The activity of dihydropteridine reductase can be measured in the dry blood spots on the filter paper used for screening purposes. 6-Pyruvoyl-tetrahydropterin synthase activity can be measured in the liver, fibroblasts, and erythrocytes. Pterin-4-α-carbinolamine dehydratase activity can be measured in the liver and fibroblasts. GTP cyclohydrolase I activity can be measured in the liver and in cytokine (interferon-γ)–stimulated mononuclear cells or fibroblasts (the enzyme activity is normally very low in unstimulated cells).

Treatment

The goals of therapy are to correct hyperphenylalaninemia and to restore neurotransmitter deficiencies in the CNS. The control of hyperphenylalaninemia is important in patients with cofactor deficiency, because high levels of phenylalanine cause intellectual disability and interfere with the transport of neurotransmitter precursors (tyrosine and tryptophan) into the brain. Plasma phenylalanine should be maintained as close to normal as possible (<6 mg/dL or

<360 µmol/L). This can be achieved by oral supplementation of BH_4 (5-20 mg/kg/day). Sapropterin dihydrochloride, the synthetic form of BH_4, is commercially available but expensive.

Lifelong supplementation with neurotransmitter precursors such as L -dopa and 5-hydroxytryptophan, along with carbidopa to inhibit degradation of L -dopa before it enters the CNS, is necessary in most of these patients even when treatment with BH_4 normalizes plasma levels of phenylalanine. BH_4 does not readily enter the brain to restore neurotransmitter production. To minimize untoward side effects (especially L -dopa–induced dyskinesia), the treatment should be started with low doses of L -dopa/carbidopa and 5-hydroxytryptophan and should be gradually adjusted based on response to therapy and clinical improvement for each individual patient. Supplementation with folinic acid is also recommended in patients with dihydropteridine reductase deficiency. Unfortunately, attempting to normalize neurotransmitter levels using neurotransmitter precursors usually does not fully resolve the neurologic symptoms, because of the inability to attain normal levels of BH_4 in the brain. Patients often demonstrate intellectual disability, fluctuating abnormalities of tone, eye movement abnormalities, poor balance and coordination, decreased ability to ambulate, and seizures despite supplementation with neurotransmitter precursors.

Hyperprolactinemia occurs in patients with BH_4 deficiency and may be the result of hypothalamic dopamine deficiency. Measurement of serum prolactin levels may be a convenient method for monitoring adequacy of neurotransmitter replacement in affected patients.

Some drugs, such as trimethoprim/sulfamethoxazole, methotrexate, and other antileukemic agents, are known to inhibit dihydropteridine reductase enzyme activity and should be used with great caution in patients with BH_4 deficiency.

Genetics and Prevalence

All defects causing hyperphenylalaninemia are inherited as autosomal recessive traits. The prevalence of PKU in the United States is estimated at 1 in 14,000 to 1 in 20,000 live births. The prevalence of non-PKU hyperphenylalaninemia is estimated at 1 in 50,000 live births. The condition is more common in whites and Native Americans and less prevalent in blacks, Hispanics, and Asians.

The gene for PAH is located on chromosome 12q23.2, and many disease-causing mutations have been identified in different families. Most patients are compound heterozygotes for 2 different mutant alleles. The gene for 6-pyruvoyl-tetrahydropterin synthase *(PTS)* , the most common cause of BH_4 deficiency, resides on chromosome 11q23.1, the gene for dihydropteridine reductase *(QDPR)* is located on chromosome 4p15.32, and those of pterin-4-α-carbinolamine dehydratase *(PCBD1)* and GTP cyclohydrolase I *(GCH1)* are on 10q22.1 and 14q22.2, respectively. Prenatal diagnosis is possible if causative mutations are known.

Tetrahydrobiopterin Defects Without Hyperphenylalaninemia

See Chapter 103.11 .

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103.2

Tyrosine

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Keywords

tyrosine
hypertyrosinemia
fumarylacetoacetate hydrolase
tyrosine aminotransferase
4-hydroxyphenylpyruvate dioxygenase
4-HPPD
tyrosinemia type I
tyrosinemia type II
tyrosinemia type III
hepatorenal tyrosinemia
succinylacetone
Richner-Hanhart syndrome
oculocutaneous tyrosinemia
FAH
TAT
HPD
nitisinone

NTBC
hawkinsin
hawkinsinuria
transient tyrosinemia of the newborn
alkaptonuria
homogentisic acid
homogentisate 1,2-dioxygenase
HGD
albinism
oculocutaneous albinism
tyrosinase
TYR
ocular albinism
GPR143
Nettleship-Falls ocular albinism
Hermansky-Pudlak syndrome
HSP
Chédiak-Higashi syndrome
LYST
Griscelli syndrome
Vici syndrome
MAPBP-interacting protein deficiency
localized albinism
piebaldism
KIT
SNAI2
Waardenburg syndrome
PAX3
MITF
SOX10
EDN3
EDNRB

Tyrosine is derived from ingested proteins or is synthesized endogenously from phenylalanine. It is used for protein synthesis and is a precursor of dopamine, norepinephrine, epinephrine, melanin, and thyroxine. Excess tyrosine is metabolized to carbon dioxide and water (see Fig. 103.1). Hereditary causes of hypertyrosinemia include deficiencies of the enzymes fumarylacetoacetate hydrolase (**FAH**), tyrosine aminotransferase, and 4-hydroxyphenylpyruvate dioxygenase (**4-HPPD**). **Acquired hypertyrosinemia** may occur in severe hepatocellular dysfunction (liver failure), scurvy (vitamin C is the cofactor for 4-HPPD), and hyperthyroidism. Hypertyrosinemia is common in blood samples obtained soon after eating and in premature infants.

Tyrosinemia Type I (Fumarylacetoacetate Hydrolase Deficiency, Hepatorenal Tyrosinemia)

Tyrosinemia type I is a severe multisystemic disease caused by FAH deficiency. Liver, kidney, and nerve damage is likely caused by metabolites of tyrosine degradation, especially fumarylacetoacetate and succinylacetone.

Clinical Manifestations and Natural History

Without treatment, affected infants appear normal at birth and develop symptoms in the 1st yr of life. Most patients present between 2 and 6 mo of age but rarely may become symptomatic in the 1st mo or appear healthy beyond the 1st yr of life. Earlier presentation confers poorer prognosis. The 1-yr mortality of untreated children, which is approximately 60% in infants developing symptoms before 2 mo of age, decreases to 4% in infants who become symptomatic after 6 mo.

An acute **hepatic crisis** typically heralds the onset of the disease and is usually precipitated by an intercurrent illness that produces a catabolic state. Fever, irritability, vomiting, hemorrhage, hepatomegaly, jaundice, elevated levels of serum transaminases, hypoglycemia, and neuropathy are common. An odor resembling boiled cabbage may be present, resulting from increased methionine metabolites. Hepatic crises may progress to liver failure and death. Between the crises, varying degrees of failure to thrive, hepatomegaly, and coagulation abnormalities often persist. Cirrhosis and eventually hepatocellular carcinoma occur with increasing age.

Episodes of acute **peripheral neuropathy** resembling acute porphyria occur in approximately 40% of affected children. These crises, often triggered by a minor infection, are characterized by severe pain, often in the legs, associated with extensor hypertonia of the neck and trunk, vomiting, paralytic ileus, and occasionally self-induced injuries of the tongue or buccal mucosa. Marked weakness occurs in about 30% of episodes, which may lead to respiratory failure requiring mechanical ventilation. Crises typically last 1-7 days, but recuperation from paralytic crises can require weeks to months.

Renal involvement is manifested as a Fanconi-like syndrome with hyperphosphaturia, hypophosphatemia, normal–anion gap metabolic acidosis, and vitamin D–resistant rickets. Nephromegaly and nephrocalcinosis may be present on ultrasound examination. Glomerular failure may occur in adolescents and older patients.

Hypertrophic cardiomyopathy and hyperinsulinism are seen in some infants.

Laboratory Findings

Elevated levels of succinylacetone in serum and urine are diagnostic for tyrosinemia type I (see Fig. 103.1). Succinylacetone levels may fall below the diagnostic threshold in patients treated with nitisinone. In untreated patients, the blood level of α-fetoprotein is increased, often greatly, and liver-synthesized coagulation factors are decreased in most patients. Increased levels of α-fetoprotein are present in the cord blood of affected infants, indicating intrauterine liver damage. Serum transaminase levels are often increased, with marked increases possible during acute hepatic episodes. Serum concentration of bilirubin is usually normal but can be increased with liver failure. Plasma tyrosine levels are usually elevated at diagnosis, but this is a nonspecific finding and depends on dietary intake. Plasma levels of other amino acids, particularly methionine, may also be elevated in patients with liver damage. Hyperphosphaturia, hypophosphatemia, and generalized aminoaciduria may occur. The urinary level of 5-aminolevulinic acid (also known as delta aminolevulinic acid) is elevated because of inhibition of 5-aminolevulinate dehydratase by succinylacetone (see Fig. 110.1).

Diagnosis is usually established by demonstration of elevated levels of succinylacetone in urine or blood. Neonatal screening for hypertyrosinemia using tyrosine alone detects only a fraction of patients with tyrosinemia type I. Succinylacetone, which is assayed by many neonatal screening programs, has higher sensitivity and specificity than tyrosine and is the preferred metabolite for screening. Tyrosinemia type I should be differentiated from other causes of hepatitis and hepatic failure in infants, including galactosemia, hereditary fructose intolerance, neonatal iron storage disease, giant cell hepatitis, and citrullinemia type II (see Chapter 103.12).

Treatment and Outcome

A diet low in phenylalanine and tyrosine can slow but does not halt the progression of the condition. The treatment of choice is **nitisinone** (NTBC), which inhibits 4-HPPD and reduces the flux of tyrosine metabolites to FAH, thus decreasing the production of the offending compounds, fumarylacetoacetate and succinylacetone (see Fig. 103.1). The dose of nitisinone is titrated to the lowest, most effective dose (usually targeting the blood range of 20-40 µmol/L) to suppress production of succinylacetone while maintaining plasma tyrosine level <400 µmol/L (7.2 mg/dL). This treatment prevents acute hepatic and neurologic crises. Although nitisinone greatly slows disease progression, some pretreatment liver damage is not reversible. Therefore, patients must be followed for development of *cirrhosis* or *hepatocellular carcinoma* . On imaging, the presence of even a single liver nodule usually indicates underlying cirrhosis. Most liver nodules in tyrosinemic patients are benign, but current imaging techniques do not accurately distinguish all malignant nodules. For patients with severe liver failure not responding to nitisinone, liver transplantation is an effective therapy, which can also alleviate the risk of hepatocellular carcinoma. The impact of nitisinone treatment on the need for liver transplantation is still under study, but the greatest effect is in patients treated early, such as children detected by neonatal screening, prior to developing clinical symptoms. In early-treated patients, nitisinone has greatly reduced the need for liver transplantation. Because nitisinone treatment increases plasma tyrosine, a low-tyrosine, low-phenylalanine diet is recommended. Rarely, nitisinone-treated patients develop corneal crystals, presumably of tyrosine, which are reversible by strict dietary compliance. This finding, combined with observations of developmental delay in some patients with tyrosinemia type II who chronically have elevated tyrosine levels, suggest that a diet low in phenylalanine and tyrosine should be continued in patients treated with nitisinone. The dietary treatment of patients with tyrosine and phenylalanine restriction necessitates surveillance of growth and development by ensuring adequate intakes of amino acids and other nutrients.

Genetics and Prevalence

Tyrosinemia type I is inherited as an autosomal recessive trait. The *FAH* gene maps to chromosome 15q25.1. DNA analysis is useful for molecular prenatal diagnosis if the familial pathogenic variants are known and for carrier testing in groups at risk for specific mutations, such as French-Canadians from the Saguenay-Lac Saint-Jean region of Quebec. The prevalence of the condition is estimated to be 1 in 1,846 live births in the Saguenay-Lac Saint-Jean region and approximately 1 in 100,000 live births worldwide. Prenatal screening can be performed by measurement of succinylacetone in amniotic fluid. Prenatal diagnosis is possible using DNA analysis of amniocytes or of chorionic villi, if the familial pathogenic variants are known.

Tyrosinemia Type II (Tyrosine Aminotransferase Deficiency, Richner-Hanhart Syndrome, Oculocutaneous Tyrosinemia)

Tyrosinemia type II is a rare autosomal recessive disorder caused by deficiency of cytosolic tyrosine aminotransferase and results in palmar and plantar hyperkeratosis, herpetiform corneal ulcers, and intellectual disability (see Fig. 103.1). *Ocular manifestations* , which may occur as early as 6 mo of age, include excessive tearing, redness, pain, and photophobia. Corneal lesions are presumed to be caused by tyrosine deposition. In contrast to herpetic ulcers, corneal lesions in tyrosinemia type II stain poorly with fluorescein and often are bilateral. *Skin lesions* , which may develop later in life, include painful, nonpruritic hyperkeratotic plaques on the soles, palms, and fingertips. Intellectual disability, which occurs in approximately 50% of patients, is usually mild to moderate. The contribution of consanguinity in this rare disorder is incompletely understood.

The principal **laboratory finding** in untreated patients is marked hypertyrosinemia, >500 µmol/L and may reach 1,100-2,750 µmol/L. Surprisingly, 4-hydroxyphenylpyruvic acid and its metabolites are also elevated in urine despite being downstream from the metabolic block (see Fig. 103.1). This is hypothesized to occur via the action of other transaminases in the presence of high tyrosine concentrations, producing 4-hydroxyphenylpyruvic acid in mitochondria, where it cannot be further degraded. In contrast to tyrosinemia type I, liver and kidney function are normal, as are serum concentrations of other amino acids and succinylacetone. Tyrosinemia type II is caused by tyrosine aminotransferase *(TAT)* gene pathogenic variants, causing deficiency of cytosolic TAT activity in liver. *TAT* maps to chromosome 16q22.

Diagnosis of type II tyrosinemia is established by assay of plasma tyrosine concentration in patients with suggestive findings. Molecular diagnosis is possible. Assay of liver TAT requires a liver biopsy and is rarely indicated.

Treatment with a diet low in tyrosine and phenylalanine aiming to achieve plasma tyrosine levels <500 µmol/L improves skin and eye manifestations. The claim that intellectual disability may be prevented by early diet therapy is reasonable and is consistent with some case reports.

Tyrosinemia Type III (Primary Deficiency of 4-Hydroxyphenylpyruvate Dioxygenase)

Only a few patients with tyrosinemia type III have been reported. Most were detected by amino acid chromatography performed for various neurologic findings; therefore ascertainment bias likely confounds our current understanding of this disorder. Apparently, asymptomatic infants with 4-HPPD deficiency have been identified by neonatal screening for hypertyrosinemia. Age at presentation has been from 1-17 mo. In symptomatic patients, developmental delay, seizures, intermittent ataxia, and self-injurious behavior have been reported. Liver and renal abnormalities are absent.

The role of 4-HPPD deficiency in the disease mechanisms needs further study. The **diagnosis** is suspected in children with sustained moderate increases in plasma levels of tyrosine (typically 350-700 µmol/L on a normal diet) and the presence of 4-hydroxyphenylpyruvic acid and its metabolites 4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids in urine. Diagnosis may be refined by demonstrating the presence of pathogenic variants in the *HPD* gene encoding 4-HPPD, or rarely by demonstrating a low activity of 4-HPPD enzyme; the latter requires a liver biopsy and is not usually indicated.

Given the possible association with neurologic abnormalities, dietary reduction of plasma tyrosine levels is prudent. It is also logical to attempt a trial of vitamin C, the cofactor for 4-HPPD. The condition is inherited as an autosomal recessive trait.

Hawkinsinuria

A missense variant c.722A>G (p.Asn241Ser) in *HPD* encoding 4-HPPD results in the uncoupling of normal oxidization of 4-hydroxyphenylpyruvate to homogentisic acid and premature release of quinolacetic acid. The abnormal enzyme, incapable of normally oxidizing 4-hydroxyphenylpyruvate to homogentisic acid, forms an intermediate that reacts with glutathione to form the unusual organic acid **hawkinsin** ([2-L -cystein-*S* -yl-1,4-dihydroxycyclohex-5-en-1-yl]acetic acid), named after the first affected family (see Fig. 103.1). As a result, secondary glutathione deficiency may ensue. Hawkinsinuria is inherited as an autosomal dominant trait. In one patient, compound heterozygosity for hawkinsuria and tyrosinemia type III alleles produced only biochemical features of hawkinsuria.

The clinical course of this rare disorder is incompletely understood. Individuals with hawkinsinuria may be symptomatic only during infancy. The symptoms usually appear in the 1st few months of life, typically after weaning from breastfeeding and with the introduction of a high-protein diet. Severe metabolic acidosis, ketosis, failure to thrive, anemia, mild hepatomegaly, renal tubular acidosis, and an unusual odor are reported manifestations of this disorder. Neurocognitive development is usually normal.

Symptomatic infants and asymptomatic affected children and adults excrete hawkinsin, 4-hydroxyphenylpyruvic acid, and its metabolites (4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids), 4-hydroxycyclohexylacetic acid and 5-oxoproline (from secondary glutathione deficiency) in their urine. The plasma tyrosine level, which is moderately elevated in the symptomatic infants, may become normal in the asymptomatic affected individuals.

Treatment consists of a low-protein diet during infancy. Breastfeeding is encouraged. Avoidance of protein overrestriction is important because some patients may present with failure to thrive. Successful long-term use of *N* -acetyl-L -cysteine to treat secondary glutathione deficiency has been reported. A trial with vitamin C is recommended. The abnormal enzyme is susceptible to inhibition by nitisinone. Clinical studies showing the efficacy of this agent in symptomatic infants are lacking at this time, and the indications for its use are not known.

Transient Tyrosinemia of the Newborn

In a small number of newborn infants, plasma tyrosine may be as high as 3,300 µmol/L during the 1st 2 wk of life. Most affected infants are premature and are receiving a high-protein diet. Transient tyrosinemia is thought to result from delayed maturation of 4-HPPD (see Fig. 103.1). Lethargy, poor feeding, and decreased motor activity are noted in some patients. Most are asymptomatic and are identified by a high blood phenylalanine or tyrosine level on routine screening. Laboratory findings include marked elevation of plasma tyrosine with a moderate increase in plasma phenylalanine. The finding of hypertyrosinemia differentiates this condition from PKU. 4-Hydroxyphenylpyruvic acid and its metabolites are present in the urine. Hypertyrosinemia usually resolves spontaneously in the 1st 2 mo of life. It can be corrected by reducing dietary protein to below 2 g/kg/24 hr and by administering vitamin C. Mild intellectual deficits have been reported in some infants who had this condition, but the causal relationship to hypertyrosinemia is not conclusively established.

Alkaptonuria

Alkaptonuria is a rare (approximately 1 in 250,000 live births) autosomal recessive disorder caused by a deficiency of homogentisate 1,2-dioxigenase.Large amounts of homogentisic acid are formed (see Fig. 103.1), which are excreted in urine or deposited in tissues.

The main **clinical manifestations** of alkaptonuria consist of ochronosis and arthritis in adulthood. The only sign in children is blackening of the urine on standing, caused by oxidation and polymerization of homogentisic acid. A history of gray- or black-stained diapers should suggest the diagnosis. This sign may never be noted; thus diagnosis is often delayed until adulthood. *Ochronosis,* which is seen clinically as dark spots on the sclera or ear cartilage, results from the accumulation of the black polymer of homogentisic acid. *Arthritis* is another result of this deposition and can be disabling with advancing age. It involves the spine and large joints (shoulders, hips, and knees) and is usually more severe in males. As with rheumatoid arthritis, the alkaptonuric arthritis has acute exacerbations, but the radiologic findings are typical of osteoarthritis, with characteristic narrowing of the joint spaces and calcification of the intervertebral disks. High incidence of heart disease (mitral and aortic valvulitis, calcification of heart valves, myocardial infarction) has been reported.

The **diagnosis** is confirmed by finding massive excretion of homogentisic acid on urine organic acid testing. Tyrosine levels are normal. The enzyme is expressed only in the liver and kidneys.

Treatment of the arthritis is symptomatic. Nitisinone efficiently reduces homogentisic acid production in alkaptonuria. If presymptomatic individuals are detected, treatment with nitisinone, combined with a phenylalanine- and tyrosine-restricted diet, seems reasonable, although no experience is available regarding long-term efficacy.

The gene for homogentisate 1,2-dioxygenase *(HGD)* maps to chromosome 3q13.3. Alkaptonuria is most common in the Dominican Republic and Slovakia.

Tyrosine Hydroxylase Deficiency

See Chapter 103.11 .

Albinism

See also Chapters 640 and 672 .

Albinism is caused by deficiency of **melanin** , the main pigment of the skin and eye (Table 103.1). Melanin is synthesized by melanocytes from tyrosine in a membrane-bound intracellular organelle, the melanosome. Melanocytes originate from the embryonic neural crest and migrate to the skin, eyes (choroid and iris), hair follicles, and inner ear. The melanin in the eye is confined to the iris stromal and retinal pigment epithelia, whereas in skin and hair follicles, it is secreted into the epidermis and hair shaft. Albinism can be caused by deficiencies of melanin synthesis, by some hereditary defects of melanosomes, or by disorders of melanocyte migration. Neither the biosynthetic pathway of melanin nor many facets of melanocyte cell biology are completely elucidated (see Fig. 103.2). The end products are 2 pigments: *pheomelanin,* which is a yellow-red pigment, and *eumelanin,* a brown-black pigment.

Table 103.1

Classification of Major Causes of Albinism

TYPE	GENE	CHROMOSOME
OCULOCUTANEOUS ALBINISM (OCA)		
OCA1 (tyrosinase deficient)	*TYR*	11q14-q21

OCA1A (severe deficiency)	*TYR*	11q14-q21
OCA1B (mild deficiency)[*]	*TYR*	11q14-q21
OCA2 (tyrosinase positive) [†]	*OCA2*	15q12-q13
OCA3 (Rufous, red OCA)	*TYRP1* [‡]	9p23
OCA4	*SLC45A2*	5p13.3
Hermansky-Pudlak syndrome	*HPS1-9*	Different chromosomes
Chédiak-Higashi syndrome	*LYST*	1q42.1
OCULAR ALBINISM (OA)		
OA1 (Nettleship-Falls type)	*OA*	Xp22.3
LOCALIZED ALBINISM		
Piebaldism	*KIT*	4q12
Waardenburg syndrome (WS1-WS4)	See text	See text

[*] This includes Amish, minimal pigment, yellow albinism, and platinum and temperature-sensitive variants.

[†] Includes brown OCA.

[‡] Tyrosinase-related protein 1.

Clinically, primary albinism can be *generalized* or *localized.* Primary generalized albinism can be *ocular* or *oculocutaneous.* Some syndromes feature albinism in association with platelet, immunologic, or neurologic dysfunction. In generalized oculocutaneous albinism, hypopigmentation can be either complete or partial. Individuals with complete albinism do not develop either generalized (tanning) or localized (pigmented nevi) skin pigmentation.

The **diagnosis** of albinism is usually evident, but for some white children whose families are particularly light-skinned, normal variation may be a diagnostic consideration. Unlike patients with albinism, normal fair-skinned children progressively develop pigmentation with age, do not exhibit the eye manifestations of albinism, and have pigmentary development similar to other family members. The clinical diagnosis of oculocutaneous albinism, as opposed to other types of cutaneous hypopigmentation, requires the presence of characteristic eye findings.

The **ocular manifestations** of albinism include hypopigmentation of iris and retina with foveal hypoplasia, along with reduced visual acuity, refractive errors, nystagmus, alternating strabismus, and iris transillumination (diffuse reddish hue of iris produced during ophthalmoscopic or slit-lamp examination of eye). There is also an abnormality in routing of the optic fibers at the chiasm. Unlike in pigmented individuals, in patients with albinism the majority of the nerve fibers from the temporal side of the retina cross to the contralateral hemisphere of the brain. This results in lack of binocular (stereoscopic) vision and depth perception and in repeated switching of vision from eye to eye, causing alternating strabismus. This abnormality also causes a characteristic pattern of visual evoked potentials. These findings are highly specific for albinism and can be used to enable the clinical diagnosis. Regular ophthalmologic follow-up is recommended for patients with oculocutaneous albinism. Correction of refractive errors can maximize visual function. Usually, the alternating strabismus does not result in amblyopia and does not require surgery.

Patients with albinism should be counseled to avoid ultraviolet (UV) radiation by wearing protective long-sleeved clothing and by using sunscreens with a sun protection factor (SPF) rating >30. Melanin is also present in the cochlea. Albino individuals may be more susceptible to ototoxic agents such as gentamicin.

Oculocutaneous albinism is inherited as autosomal recessive trait. Many clinical forms of albinism have been identified. Some of the seemingly distinct clinical forms are caused by different pathogenic variants of the same gene. Several genes located on different chromosomes are involved in melanogenesis (see Table 103.1). Attempts to differentiate types of albinism based on the mode of inheritance, tyrosinase activity, or extent of hypopigmentation have failed to yield a comprehensive classification. The classification outlined next is based on the distribution of albinism in the body and the affected genes.

Genetic analysis is clinically available for most albinism genes (see Table 103.1). Molecular diagnosis is of little use therapeutically in isolated albinism but can be helpful for precise genetic counseling of families.

Oculocutaneous (Generalized) Albinism

Lack of pigment is generalized, affecting skin, hair, and eyes. At least 4 genetically distinct forms of oculocutaneous albinism (**OCA**) have been identified: OCA_1 , OCA_2 , OCA_3 , and OCA_4 . The lack of pigment is complete in patients with OCA_1 A; the other types may not be clinically distinguishable from one another. All affected individuals have ocular manifestations of albinism. All forms are inherited as autosomal recessive traits.

OCA_1 (Tyrosinase-Deficient Albinism)

The defect in patients with OCA_1 resides in the tyrosinase gene, *TYR* , located on chromosome 11q14.3. Many mutant alleles have been identified. Most affected individuals are compound heterozygotes. A clinical clue to the diagnosis of OCA_1 is complete lack of pigment at birth. The condition can be subdivided to OCA_1 A and OCA_1 B, based on enzyme activity and difference in clinical manifestations as a function of age.

OCA_1 A (Tyrosinase-Negative OCA)

In patients with OCA_1 A, the most severe form of OCA, both *TYR* alleles have pathogenic variants that completely inactivate tyrosinase. Clinically, lack of pigment in the skin (milky white), hair (white hair), and eyes (red-gray irides) is evident at birth and remains unchanged throughout life. They do not tan and do not develop pigmented nevi or freckles.

OCA_1 B

Patients with OCA_1 B have *TYR* gene pathogenic variants that preserve some residual activity. Clinically, they completely lack pigment at birth, but with age become light blond with light-blue or hazel eyes. They develop pigmented nevi and freckles, and they may tan. OCA_1 B patients, depending on the degree of pigmentation, were once subdivided into different groups and thought to be genetically distinct.

OCA_2 (Tyrosinase-Positive OCA)

OCA_2 is the *most common form of generalized OCA*, particularly in patients of African ancestry. Clinically, the phenotype is highly variable; most patients demonstrate some pigmentation of the skin and eyes at birth and continue to accumulate pigment throughout life. The hair is yellow at birth and may darken with age. They have pigmented nevi and freckles, and some may tan. They may be clinically indistinguishable from OCA_1 B patients. Individuals with $OCA_{2,}$ however, have normal tyrosinase activity in hair bulbs. The defect is in the *OCA2* gene, which is an orthologue of the *p* (pink-eyed dilution) gene in the mouse. This gene produces the P protein, a melanosome membrane protein. Patients with **Prader-Willi** and **Angelman** syndromes caused by microdeletion of chromosome 15q12 that includes the *OCA2* gene have mild pigmentary deficiency (see Chapter 98.8).

OCA_3 (Rufous Albinism)

This form has been identified predominantly in Africans, African-Americans, and natives of New Guinea. Patients with OCA_3 can make pheomelanin but not eumelanin. Patients have reddish hair and reddish brown skin as adults. The skin color is peculiar to this form. In young persons the coloration may resemble that of OCA_2 . The pathogenic variant is in the tyrosinase-related protein 1 *(TYRP1)* gene (located on chromosome 9p23), the function of which is not well-understood.

OCA_4

Similar manifestations to OCA_2 (both in the skin and the eyes) have been observed in OCA_4 patients (mostly from Japan) with pathogenic variants in the *SLC45A2* (previously called *MATP*) gene (located on chromosome 5p13.2).

Ocular Albinism

Patients with ocular albinism (**OA**) present in the 1st months of life with nystagmus, hypopigmentation of iris and fundus, foveal hypoplasia, and decreased visual acuity. Electron microscopy demonstrates characteristic macromelanosomes in skin biopsies or hair root specimens. Most patients affected by ocular albinism have ocular albinism type 1 (**OA_1**), an X-linked disorder caused by pathogenic variants in the *GPR143* gene. A rare form of OA with late-onset sensorineural deafness and apparent autosomal dominant inheritance has also been reported.

Ocular Albinism Type 1 (Nettleship-Falls Ocular Albinism)

OA_1 is an X-linked disorder characterized by congenital nystagmus, reduced pigmentation of ocular structures, and visual impairment in affected males. Heterozygous females may present with segments of abnormal retinal pigmentations. Infrequently, depending on the pattern of X chromosome inactivation, heterozygous females may also present with severe manifestations, including nystagmus, iris and foveal hypopigmentation, foveal hypoplasia, and reduced visual acuity. In families with darker skin complexion, mild skin hypopigmentation can be seen. The diagnosis of OA_1 is suspected in males with features of albinism in the eye, normal to mildly reduced skin pigmentation, and a family history suggestive of an X-linked transmission. It is a nonprogressive disorder, and the eye findings often improve with age. In patients who are the first of their families to be affected, genetic analysis of the *GPR143* gene

(Xp22.2) helps confirm the diagnosis.

Syndromic Forms of Generalized Albinism

Hermansky-Pudlak Syndrome

This group of autosomal recessive disorders is caused by pathogenic variants of 1 of 9 different genes located on different chromosomes, *HPS1* to *HPS9* . Hermansky-Pudlak syndrome (**HPS**) is suspected in patients with albinism and a bleeding diathesis with inflammatory bowel disease (IBD) or pulmonary fibrosis. Disease subtype can be established with molecular studies (see Chapter 511).

The *HPS* genes are necessary for normal structure and function of lysosome-derived organelles, including melanosomes and platelet dense bodies. Patients have a tyrosinase-positive OCA of variable severity associated with platelet dysfunction (caused by the absence of platelet dense bodies). A ceroid-like material accumulates in tissues. HPS is panethnic. However, taking into account patients' ancestry can help develop a cost-effective testing strategy. HPS is prevalent in two regions of Puerto Rico (**type 1** in the northwest and **type 3** in the central regions as a result of different founder effects). The cutaneous and ocular symptoms of albinism are present. Patients can develop epistaxis, postsurgical bleeding, or abundant menses. Bleeding time is prolonged, but platelet count is normal. Major complications include progressive pulmonary fibrosis in young adults and Crohn-like IBD in adolescents and young adults. Kidney failure and cardiomyopathy have been reported. Neutropenia has been described in HPS **type 2** . Treatment is symptomatic.

Chédiak-Higashi Syndrome

Patients with this rare autosomal recessive condition have OCA of variable severity and susceptibility to infection (see Chapter 156). Bacterial infections of skin and upper respiratory tract are common. Giant peroxidase-positive lysosomal granules can be seen in granulocytes in a blood smear. Patients have a reduced number of melanosomes, which are abnormally large (macromelanosomes). The bleeding tendency is typically mild. If treatment is not successful, children can reach a stage of the disease known as the **accelerated phase** , which is a major, life-threatening complication of Chédiak-Higashi syndrome. It is caused by macrophage activation resulting in hemophagocytic lymphohistiocytosis, and systemic manifestations include fever, lymphadenopathy, hepatosplenomegaly, cytopenia, and elevated plasma ferritin level. Patients surviving childhood may develop cerebellar atrophy, peripheral neuropathy, and cognitive delay. Pathogenic variants in the *LYST* gene on chromosome 1q42.3 are the only known cause of this syndrome. Hematopoietic stem cell transplantation offers an effective approach to control immunodeficiency and hematologic abnormalities as well as prevent development of the accelerated phase.

Other Disorders Featuring Generalized Albinism

Hypopigmentation is a feature of other syndromes, some with abnormalities of lysosomal biogenesis or melanosome biology. **Griscelli syndrome** patients have silver-gray hair, pigmentary dilution of skin, and melanosomal clumping in hair shafts and the center of melanocytes, with intellectual disability or macrophage activation with hemophagocytosis in different subtypes. **Vici syndrome** patients have combined immunodeficiency, intellectual disability, agenesis of the corpus callosum, cataracts, and cleft lip/palate. Patients with **MAPBP-interacting protein deficiency** have short stature, recurrent infections, neutropenia.

Localized Albinism

Localized albinism refers to localized patches of hypopigmentation of skin and hair, which may be evident at birth or develop with time. These conditions are caused by abnormal migration of melanocytes during embryonic development.

Piebaldism

Piebaldism is an autosomal dominant inherited condition in which the individual is usually born with a white forelock. The underlying skin is depigmented and devoid of melanocytes. In addition, there are usually white macules on the face, trunk, and extremities. Pathogenic variants in the *KIT* and *SNAI2* genes have been shown in affected patients.

Waardenburg Syndrome

In Waardenburg syndrome, a white forelock is often associated with lateral displacement of inner canthi of the eyes, broad nasal bridge, heterochromia of irides, and sensorineural deafness. This condition is inherited as an autosomal dominant trait; 4 major types have been identified. Patients with Waardenburg syndrome type 1 (**WS1** , the *most common form*) have all the previous clinical findings, including lateral displacement of inner canthi. The condition is caused by pathogenic variants (>90%) in the *PAX3* gene. Patients with Waardenburg syndrome type 2 (**WS2**) have the clinical findings of WS1 except for the lateral displacement of inner canthi. Genetically, this is a heterogeneous condition caused by pathogenic variants in several genes, including *MITF* , *SOX10* , and *SNAI2* . Patients with Waardenburg syndrome type 3 (**WS3**) have all the findings seen in individuals with WS1 plus hypoplasia and contractures of the upper limbs. It is caused by heterozygous or homozygous pathogenic variants of *PAX3* gene. Waardenburg syndrome type 4 (**WS4**), associated with **Hirschsprung disease** , is genetically heterogeneous; pathogenic variants in different genes (*EDN3*, *EDNRB*, or *SOX10*) have been identified in different patients.

Other causes of **localized hypopigmentation** include vitiligo and hypomelanosis of Ito (see Chapter 672).

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103.3

Methionine

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Keywords

methionine
homocysteine
homocystine
homocystinuria
homocysteinemia
methylcobalamin
cystathionine β-synthase deficiency
CBS
cbl C
cbl D
cbl E *cbl* G
cbl F
cbl J
cbl X
methionine synthase reductase
methionine synthase
methylmalonic acidemia
methylenetetrahydrofolate reductase deficiency
MTHFR deficiency
MTHFR polymorphism
hypermethioninemia
methionine adenosyltransferase deficiency
MAT I
MAT III
Mudd disease
MAT1A
MAT2A
S -adenosylmethionine
S -adenosylhomocysteine
cystathionine
glycine *N* -methyltransferase deficiency
GNMT
S -adenosylhomocysteine hydrolase deficiency
SAHH

AHCY
cystathioninemia
cystathioninuria
cystathionine γ-lyase
CTH

The usual pathway for catabolism of methionine, an essential amino acid, produces S-*adenosylmethionine*, which serves as a methyl group donor for methylation of a variety of compounds in the body, and *cysteine*, which is formed through a series of reactions collectively called *trans-sulfuration* (Fig. 103.3).

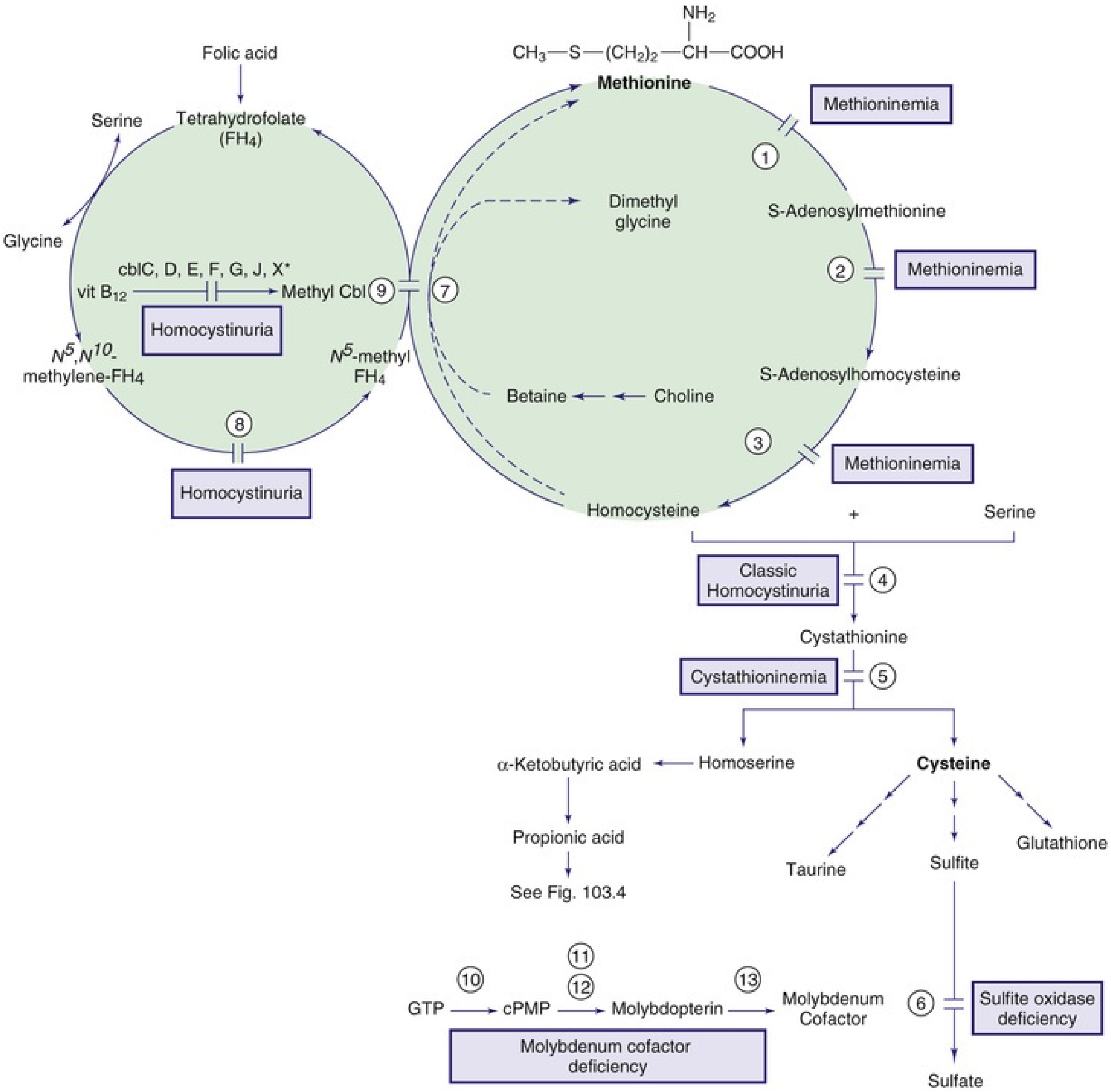
NH2
CH3—S—(CH2)2—CH—COOH
Methionine
Folic acid
Tetrahydrofolate (FH4)
Serine
Glycine
cblC, D, E, F, G, J, X*
vit B12
Methyl Cbl
Homocystinuria
N5,N10-methylene-FH4
N5-methyl FH4
8
Homocystinuria
9
7
Dimethyl glycine
Betaine
Choline
Homocysteine
1
Methioninemia
S-Adenosylmethionine
2
Methioninemia
S-Adenosylhomocysteine
3
Methioninemia
+
Serine
Classic Homocystinuria
4
Cystathionine
Cystathioninemia
5
α-Ketobutyric acid
Homoserine
Cysteine
Propionic acid
See Fig. 103.4
Taurine
Sulfite
Glutathione
GTP
10
cPMP
11
12
Molybdopterin
13
Molybdenum Cofactor
Molybdenum cofactor deficiency
6
Sulfite oxidase deficiency
Sulfate

FIG. 103.3 **Pathways in the metabolism of sulfur-containing amino acids. Enzymes: *(1)* Methionine adenosyltransferase (MAT I/III), *(2)* glycine *N* -methyltransferase, *(3) S* -adenosylhomocysteine hydrolase, *(4)* cystathionine synthase, *(5)* cystathionase, *(6)* sulfite oxidase, *(7)* betaine homocysteine methyltransferase, *(8)* methylene tetrahydrofolate reductase, *(9)* methionine synthase (cblG), *(10)* molybdenum cofactor biosynthesis protein 1, *(11)* molybdopterin synthase, *(12)* adenylyltransferase and sulfurtransferase (*MOCS3*), *(13)* gephyrin. GTP, Guanosine triphosphate; cPMP, cyclic pyranopterin monophosphate. *Defects in cblC, D, F, J, X result in methylmalonic acidemia and homocystinuria.**

Homocystinuria (Homocystinemia)

Normally, most *homocysteine*, an intermediate compound of methionine degradation, is remethylated to methionine. This methionine-sparing reaction is catalyzed by the enzyme methionine synthase, which requires a metabolite of folic acid (5-methyltetrahydrofolate) as a methyl donor and a metabolite of vitamin B_{12} (methylcobalamin) as a cofactor (see Fig. 103.3). In healthy individuals, most plasma homocysteine is either protein-bound or exists as disulfides. Three major forms of homocystinemia and homocystinuria have been identified.

Homocystinuria Caused by Cystathionine β-Synthase Deficiency (Classic Homocystinuria)

This is the most common inborn error of methionine metabolism. Approximately 40% of affected patients respond to high doses of vitamin B_6 and usually have milder clinical manifestations than those who are unresponsive to vitamin B_6 therapy. These patients possess some residual enzyme activity.

Infants with classic homocystinuria appear normal at birth. **Clinical manifestations** during infancy are nonspecific and may include failure to thrive and developmental delay. Without newborn screening, the diagnosis can be delayed and is usually made after 3 yr of age, when subluxation of the ocular lens (*ectopia lentis*) occurs. This causes severe myopia and iridodonesis (quivering of the iris). Astigmatism, glaucoma, staphyloma, cataracts, retinal detachment, and optic atrophy may develop later in life. Progressive intellectual disability is common. Normal intelligence has been reported. In an international survey of >600 patients, IQ scores ranged from 10-135. Higher IQ scores are seen in vitamin B_6 –responsive patients. Psychiatric and behavioral disorders have been observed in more than 50% of affected patients. Seizures are seen in approximately 20% of untreated patients. Affected individuals with homocystinuria manifest skeletal abnormalities resembling those of Marfan syndrome (see Chapter 722): tall with elongated limbs and arachnodactyly. Scoliosis, pectus excavatum or pectus carinatum, genu valgum, pes cavus, high-arched palate, and crowding of the teeth are typically seen. These children usually have fair complexions, blue eyes, and a peculiar malar flush. Generalized osteoporosis, especially of the spine, is the main x-ray finding. Thromboembolic episodes involving both large and small vessels, especially those of the brain, are common and may occur at any age. Optic atrophy, paralysis, cor pulmonale, and severe hypertension (from renal infarcts) are among the serious consequences of thromboembolism, which is likely caused by elevated homocysteine levels leading to abnormal angiogenesis and inhibition of fibrinolytic activity. The risk of thromboembolism increases after surgical procedures. Spontaneous pneumothorax and acute pancreatitis are rare complications.

Elevations of both methionine and homocystine (or homocysteine) in body fluids are the diagnostic **laboratory findings** . Freshly voided urine should be tested for homocystine because this compound is unstable and may disappear after prolonged storage. Cysteine is low or absent in plasma. Total plasma homocysteine is the preferred analyte for management of classic homocystinuria. Free plasma homocysteine may normalize or remain normal when total plasma homocysteine is lowered. The diagnosis may be established by molecular analysis of cystathionine β-synthase *(CBS)* or by assay of the enzyme in cultured fibroblasts, phytohemagglutinin-stimulated lymphocytes, or liver biopsy specimens.

Treatment with high doses of vitamin B_6 (100-500 mg/24 hr) causes dramatic improvement in patients who are responsive to this therapy. The degree of response to vitamin B_6 treatment may vary across families. Some patients may not respond because of folate depletion; a patient should not be considered unresponsive to vitamin B_6 until folic acid (1-5 mg/24 hr) has been added to the treatment regimen. For patients who are unresponsive to vitamin B_6 , restriction of methionine intake in conjunction with cysteine supplementation is also recommended. The need for dietary restriction and its extent remains controversial in patients with vitamin B_6 –responsive form. In some patients with this form, addition of betaine may obviate the need for any dietary restriction. *Betaine* (trimethylglycine, 6 g/24 hr for adults or 200-250 mg/kg/day for children) lowers homocysteine levels in body fluids by remethylating homocysteine to methionine (see Fig. 103.3), which may result in elevation of plasma methionine levels. This treatment has produced clinical improvement (preventing vascular events) in patients who are unresponsive to vitamin B_6 therapy. Cerebral edema has occurred in a patient with vitamin B_6 –nonresponsive homocystinuria and dietary noncompliance during betaine therapy.

More than 100 pregnancies in women with classic homocystinuria have been reported with favorable outcomes for both mothers and infants. The majority of infants were full-term and normal. Postpartum thromboembolic events occurred in a few mothers.

The screening of newborn infants for classic homocystinuria has been performed worldwide, with an estimated prevalence of 1 in 200,000 to 1 in 350,000 live births, although it can be more common in some parts of the world (e.g., 1 : 1,800 in Qatar). Early treatment of patients identified by screening has produced favorable results. The mean IQ of patients with vitamin B_6 –unresponsive form treated in early infancy was in the normal range. Dislocation of the lens seemed to be prevented in some patients.

Classic homocystinuria is inherited as an autosomal recessive trait. The gene for cystathionine β-synthase *(CBS)* is located on chromosome 21q22.3. Prenatal diagnosis is feasible by DNA analysis or by performing an enzyme assay of cultured amniotic cells. Most affected patients are compound heterozygotes for 2 different alleles. Heterozygous carriers are asymptomatic.

Homocystinuria Caused by Defects in Methylcobalamin Formation

Methylcobalamin is the cofactor for the enzyme methionine synthase, which catalyzes remethylation of homocysteine to methionine. At least 7 distinct defects in the intracellular metabolism of cobalamin may interfere with the formation of methylcobalamin. (To better understand the metabolism of cobalamin, see Methylmalonic Acidemia in Chapter 103.6 and Figs. 103.3 and 103.4 .) The 7 defects are designated as *cbl* C, *cbl* D (including *cbl* D variant 1), *cbl* E (methionine synthase reductase), *cbl* G (methionine synthase), *cbl* F, *cbl* J, and *cbl* X. Patients with *cbl* C, *cbl* D, *cbl* F, *cbl* J, and *cbl* X defects have **methylmalonic acidemia** in addition to homocystinuria, because the formation of both adenosylcobalamin and methylcobalamin is impaired.

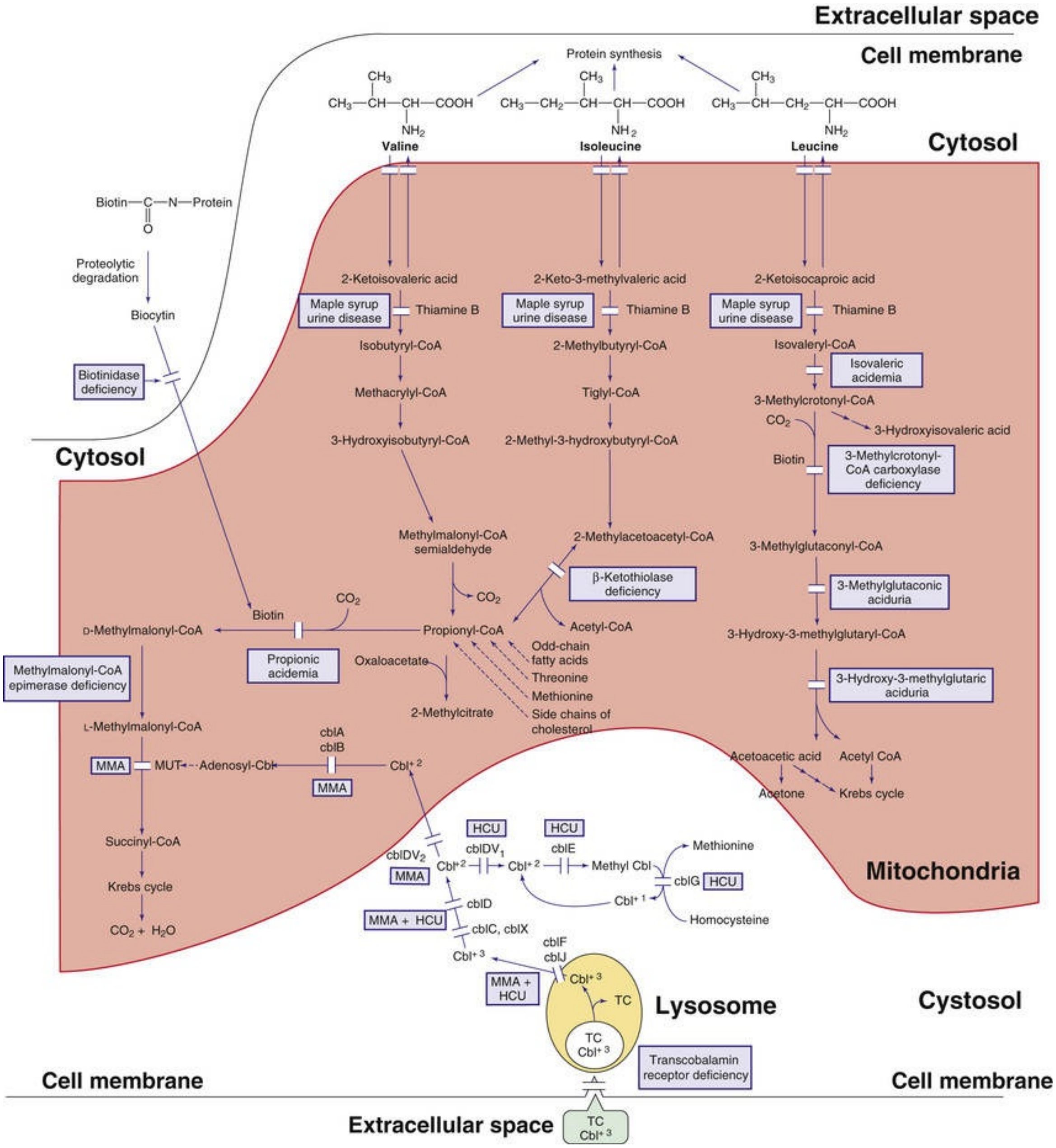
Extracellular space
Cell membrane
Protein synthesis
Valine
Isoleucine
Leucine
Cytosol
Biotin—C—N—Protein
Proteolytic degradation
Biocytin
Biotinidase deficiency
2-Ketoisovaleric acid
2-Keto-3-methylvaleric acid
2-Ketoisocaproic acid
Maple syrup urine disease
Thiamine B
Isobutyryl-CoA
2-Methylbutyryl-CoA
Isovaleryl-CoA
Isovaleric acidemia
Methacrylyl-CoA
Tiglyl-CoA
3-Methylcrotonyl-CoA
CO2
3-Hydroxyisovaleric acid
3-Hydroxyisobutyryl-CoA
2-Methyl-3-hydroxybutyryl-CoA
Biotin
3-Methylcrotonyl-CoA carboxylase deficiency
Cytosol
Methylmalonyl-CoA semialdehyde
2-Methylacetoacetyl-CoA
3-Methylglutaconyl-CoA
β-Ketothiolase deficiency
3-Methylglutaconic aciduria
CO2
Biotin
D-Methylmalonyl-CoA
Propionyl-CoA
Acetyl-CoA
3-Hydroxy-3-methylglutaryl-CoA
Methylmalonyl-CoA epimerase deficiency
Propionic acidemia
Oxaloacetate
Odd-chain fatty acids
Threonine
Methionine
Side chains of cholesterol
3-Hydroxy-3-methylglutaric aciduria
2-Methylcitrate
L-Methylmalonyl-CoA
cblA
cblB
MMA
MUT
Adenosyl-Cbl
Cbl+2
Acetoacetic acid
Acetyl CoA
Acetone
Krebs cycle
Succinyl-CoA
HCU
cblDV2
cblDV1
cblE
Methionine
Methyl Cbl
cblG
Mitochondria
Krebs cycle
Cbl+1
cblD
MMA + HCU
cblC, cblX
Homocysteine
CO2 + H2O
Cbl+3
cblF
cblJ
MMA + HCU
TC
Lysosome
Cystosol
TC Cbl+3
Transcobalamin receptor deficiency
Cell membrane
Extracellular space

FIG. 103.4 **Pathways in the metabolism of the branched-chain amino acids, biotin, and vitamin B_{12} (cobalamin). Adenosyl Cbl, Adenosylcobalamin; Cbl, cobalamin; *cbl* , defect in metabolism of cobalamin; *cbl* DV1, *cbl* D variant 1; *cbl* DV2, *cbl* D variant 2; HCU, homocystinuria; methyl Cbl, methylcobalamin; MMA, methylmalonic acidemia; MUT, mutase; OHCbl, hydroxycobalamin; TC, transcobalamin; TCR, transcobalamin receptor. See text for the name of the enzymes.**

Patients with *cbl* E, *cbl* G, and *cbl* D variant 1 defects are unable to form methylcobalamin and develop homocystinuria without methylmalonic acidemia (Fig. 103.4). The clinical manifestations are similar in patients with these 3 defects. Nonspecific symptoms such as vomiting, poor feeding, failure to thrive, lethargy, hypotonia, seizures, and developmental delay may occur in the 1st few months of life. Late-onset forms of these disorders may present with neurocognitive defects, psychosis, and peripheral neuropathy. **Laboratory findings** include megaloblastic anemia, hyperhomocysteinemia, homocystinuria, and hypomethioninemia. The absence of hypermethioninemia differentiates these conditions from cystathionine β-synthase deficiency (see earlier). Renal artery thrombosis, hemolytic uremic syndrome, pulmonary hypertension, and optic nerve atrophy have been reported in some patients with these defects.

Diagnosis is established by DNA testing or by complementation studies performed in cultured fibroblasts. Prenatal diagnosis has been accomplished by studies in amniotic cell cultures. *cbl* E, *cbl* G, and *cbl* D variant 1 deficiencies are inherited as autosomal recessive traits. The gene for *cbl* E is *MTRR* , encoding methionine synthase reductase (located on chromosome 5p15.31). The gene for *cbl* G is *MTR* , encoding methionine synthase (located on chromosome 1q43). The *cbl* D variant 1 deficiency is caused by pathogenic variants affecting the C-terminal of the *MMADHC* gene (located on chromosome 2q23.2).

Treatment with vitamin B_{12} in the form of high-dose hydroxycobalamin helps improve the clinical and biochemical findings. Results vary among both diseases and sibships.

Homocystinuria Caused by Deficiency of Methylenetetrahydrofolate Reductase (MTHFR Deficiency)

This enzyme reduces 5,10-methylenetetrahydrofolate to form 5-methyltetrahydrofolate, which provides the methyl group needed for remethylation of homocysteine to methionine (see Fig. 103.3). The severity of the enzyme defect and the clinical manifestations vary considerably in different families. **Clinical findings** vary from apnea, seizure, microcephaly, coma, and death to developmental delay, ataxia, motor abnormalities, peripheral neuropathy, and psychiatric manifestations. Thromboembolism has also been observed. Exposure to the anesthetic nitrous oxide (which inhibits methionine synthase) in patients with MTHFR deficiency may result in neurologic deterioration and death.

Laboratory findings include moderate homocystinemia and homocystinuria. The methionine concentration is low or low-normal. This finding helps differentiate this condition from classic homocystinuria caused by cystathionine β-synthase deficiency. The diagnosis may be confirmed by molecular analysis of *MTHFR* or by the enzyme assay in cultured fibroblasts or leukocytes.

MTHFR deficiency should be differentiated from **mild hyperhomocysteinemia** due to two common polymorphisms in the *MTHFR* gene. Two "thermolabile" polymorphisms have been extensively studied, c.665C>T (p.Ala222Val, previously referred to as c.677C>T) and c.1286A>C (p.Glu429Ala, formerly referred to as c.1298A>C). These polymorphisms may minimally affect levels of plasma total homocysteine in some patients and are often confounded by dietary folate deficiency. Both polymorphisms have been studied as possible risk factors for a wide variety of medical conditions, including birth defects, autism, vascular disease, stroke, pregnancy loss, cancer, and response to chemotherapy. Population-based studies revealed a surprisingly high prevalence of homozygosity for these polymorphisms in the general population: up to 10–15% of the North American Caucasians and >25% in some Hispanics. It is hypothesized that fortification of flour with folate may have decreased the strength of associations observed in the past. To date, the best data support a role for the c.665C>T polymorphism (formerly c. 677C>T) as a risk factor for neural tube defects. Although a clinical test for this polymorphism is widely available, recent meta-analyses have not supported the association between the *MTHFR* polymorphism and risk for venous thromboembolism or between mild hyperhomocysteinemia and an increased risk for coronary heart disease.

The condition is inherited as an autosomal recessive trait. The **diagnosis** can be confirmed by *MTHFR* gene analysis. Prenatal diagnosis can be achieved by molecular analysis of *MTHFR* of the known familial pathogenic variants or by measuring MTHFR enzyme activity in cultured chorionic villus cells or amniocytes.

Treatment of MTHFR deficiency with a combination of folic acid, vitamin B_6 , vitamin B_{12} , methionine supplementation, and betaine has been tried. Of these, early treatment with betaine appears to have the most beneficial effect.

Hypermethioninemia

Primary (Genetic) Hypermethioninemia

Elevation of plasma level of methionine occurs in several genetic conditions.

Classic Homocystinuria.

See earlier discussion.

Hepatic Methionine Adenosyltransferase (MAT I/MAT III) Deficiency (Mudd Disease).

This enzyme, which has 2 isoforms, MAT I (tetrameric) and MAT III (dimeric), is encoded by a single gene (*MAT1A* on chromosome 10q22.3) and is involved in the 1st step of methionine catabolism (see Fig. 103.3). Another structurally similar enzyme, MAT II, is encoded by a different gene (*MAT2A* on chromosome 2p11.2) and is expressed predominantly in nonhepatic tissues (kidney, brain, lymphocytes). Deficiency of MAT I/MAT III causes hypermethioninemia. In severe deficiency, total plasma homocysteine can also be elevated. The majority of these patients have been diagnosed in the neonatal period through screening for homocystinuria. Most affected individuals have residual enzyme activity and remain asymptomatic throughout life despite persistent hypermethioninemia. Some complain of an unusual odor to their breath, likely caused by accumulation of dimethylsulfide. A few patients with complete enzyme deficiency have had neurologic abnormalities related to demyelination (intellectual disability, dystonia, dyspraxia).

Laboratory studies reveal markedly elevated levels of plasma methionine with a normal or low level of *S* -adenosylmethionine and normal concentrations of *S* -adenosylhomocysteine and homocysteine. These findings help differentiate MAT I/MAT III deficiency from other causes of hypermethioninemia.

No uniformly accepted therapeutic regimen has yet emerged. Although no specific treatment is used in most patients, long-term follow-up to monitor for neurologic and liver abnormalities should be considered. Diets low in methionine result in lowering of plasma methionine, but the advisability of such diets has been questioned since lowering the plasma methionine level causes further lowering of *S* -adenosylmethionine in the body. Supplementation with *S* -adenosylmethionine in conjunction with a low-methionine diet seems prudent, but no large clinical experience is yet available. Normal pregnancies producing normal offspring have been reported in mothers with MAT I/MAT III *(MAT1A)* deficiency. The condition is inherited as an autosomal recessive trait, although pathogenic variant p.R264H in *MAT1A* appears to disrupt protein dimerization and may result in mild hypermethioninemia even in heterozygous patients.

Glycine *N* -Methyltransferase Deficiency.

Glycine *N* -methyltransferase mediates catabolism of *S* -adenosylmethionine to *S* -adenosylhomocysteine (see Fig. 103.3). A few patients with deficiency of this enzyme have been reported to date. Clinically, patients were asymptomatic except for mild hepatomegaly and elevated serum levels of transaminases. Other laboratory findings included hypermethioninemia and very high levels of serum *S* -adenosylmethionine. No specific treatment has yet been identified. The condition is inherited as an autosomal recessive trait; the gene *GNMT* is on chromosome 6p21.1.

S -Adenosylhomocysteine Hydrolase (SAHH) Deficiency.

Deficiency of SAHH (see Fig. 103.3) has been described infrequently. Intellectual disability, severe hypotonia, and progressive liver dysfunction were common clinical findings. Laboratory studies included elevated levels of serum creatine kinase, hypoalbuminemia (associated with fetal hydrops in one family), hypoprothrombinemia and greatly elevated levels of serum *S* -adenosylhomocysteine with moderate elevations of plasma methionine and *S* -adenosylmethionine. Marked elevation in *S* -adenosylhomocysteine has been thought to cause inhibition of methyltransferases, including those involved in the synthesis of creatine (see Fig. 103.10) and choline, resulting in their deficiencies. MRI of the brain can reveal delayed myelination of the white matter. The diagnosis can be achieved by the *AHCY* gene analysis (chromosome 20q11.22) or by biochemical assay of red blood cells, cultured skin fibroblasts, or liver biopsy. Treatment with a low-methionine diet has been used, but its long-term effectiveness has not been established.

Tyrosinemia Type I.

See Chapter 103.2 .

Citrin Deficiency.

See Chapter 103.12 .

Acquired (Nongenetic) Hypermethioninemia

Hypermethioninemia occurs in premature and some full-term infants receiving high-protein diets, in whom it may represent delayed maturation of the enzyme

MAT. Lowering the protein intake usually resolves the abnormality. It is also commonly found in patients with various forms of liver disease.

Primary Cystathioninemia (Cystathioninuria)

Cystathionase (cystathionine γ-lyase) deficiency results in massive cystathioninuria and mild to moderate cystathioninemia. Deficiency of this enzyme is inherited as an autosomal recessive trait, with an estimated prevalence of 1 in 14,000 live births. A wide variety of clinical manifestations have been reported. Lack of a consistent clinical picture and the presence of cystathioninuria in a number of individuals free of clinical findings suggest that cystathionase deficiency may be of no clinical significance. Many reported cases are responsive to oral administration of large doses of vitamin B_6 (≥100 mg/24 hr). When cystathioninuria is discovered in a patient, vitamin B_6 treatment can be tried, but its beneficial effect has not been established. The gene encoding for cystathionase *(CTH)* is located on chromosome 1p31.1. The disorder is inherited as an autosomal recessive trait.

Primary cystathioninuria needs to be differentiated from secondary cystathioninuria, which can occur in patients with vitamin B_6 or B_{12} deficiency, liver disease (particularly damage caused by galactosemia), thyrotoxicosis, hepatoblastoma, neuroblastoma, ganglioblastoma, or defects in remethylation of homocysteine.

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103.4

Cysteine and Cystine

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Keywords

cysteine
cystine
sulfite oxidase deficiency
SUOX
molybdenum cofactor deficiency
MOCS1
MOCS2
GPHN
xanthine dehydrogenase
aldehyde oxidase
antiquitin
α-aminoadipic semialdehyde
P6C
pyridoxal-5-phosphate
cyclic pyranopterin monophosphate
cPMP

Cysteine is a sulfur-containing amino acid that is synthesized from methionine (see Fig. 103.3). Oxidation of cysteine forms *cystine,* a poorly soluble dimer. The most common genetic disorders of cysteine and cystine metabolism are cystinuria (see Chapter 562) and cystinosis (see Chapter 547.3).

Sulfite Oxidase Deficiency and Molybdenum Cofactor Deficiency

In the last step in cysteine metabolism, sulfite is oxidized to sulfate by sulfite oxidase, and the sulfate is excreted in the urine (see Fig. 103.3). Sulfite oxidase is encoded by *SUOX* (located on chromosome 12q13.2). This enzyme requires a molybdenum-pterin complex termed *molybdenum cofactor.* This cofactor is also necessary for the function of 2 other enzymes in humans: xanthine dehydrogenase (which oxidizes xanthine and hypoxanthine to uric acid) and aldehyde oxidase (involved in oxidizing a number of natural compounds and drugs). Three enzymes, encoded by 3 different genes (*MOCS1* , *MOCS2,* and

GPHN, mapped to chromosomes 6p21.2, 5q11.2, and 14q23.3, respectively), are involved in the synthesis of the cofactor. Deficiency of any of the 3 enzymes causes cofactor deficiency with similar phenotypes. Most patients, who were originally diagnosed as having **sulfite oxidase deficiency** , have been shown to have **molybdenum cofactor deficiency** . Sulfite oxidase deficiency and molybdenum cofactor deficiency are inherited as autosomal recessive traits.

The enzyme and cofactor deficiencies produce overlapping **clinical manifestations** . Refusal to feed, vomiting, an exaggerated startle reaction, severe intractable seizures (tonic, clonic, myoclonic), cortical atrophy with subcortical multicystic lesions, and severe developmental delay may develop within a few weeks after birth. The biochemical diagnosis should be considered in infants presenting with neonatal seizures and neonates with symptoms reminiscent of hypoxic-ischemic encephalopathy. Bilateral dislocation of ocular lenses is a common finding in patients who survive the neonatal period. The intractable seizures seen in this condition are in part a consequence of secondary vitamin B_6 dependency. The accumulation of sulfites in body fluids in this condition causes the inhibition of *antiquitin* enzyme, which is necessary for conversion of α-amino adipic semialdehyde to α-aminoadipic acid; the resultant accumulation of α-aminoadipic semialdehyde and its cyclic form, P6C, causes the inactivation of pyridoxal-5-phosphate (active form of vitamin B_6) and thus the vitamin B_6 –dependent epilepsy (see also Chapter 103.14).

Affected children excrete large amounts of sulfite, thiosulfate, *S* -sulfocysteine, xanthine, and hypoxanthine in the urine. Urinary and serum levels of uric acid and urinary concentration of sulfate are diminished. Fresh urine should be used for screening purposes and for quantitative measurements of sulfite, because oxidation of sulfite to sulfate at room temperature may produce false-negative results. Increased concentrations of α-aminoadipic semialdehyde and P6C are present in the cerebrospinal fluid, plasma, and urine.

Diagnosis is confirmed by measurement of sulfite oxidase and molybdenum cofactor in fibroblasts and liver biopsies, respectively or by DNA studies. Prenatal diagnosis is possible by performing an assay of sulfite oxidase activity in cultured amniotic cells, in samples of chorionic villi or by DNA studies. The prevalence of these deficiencies in the general population is not known, but likely is very low.

No effective treatment is available. Large doses of vitamin B_6 (5-100 mg/kg) result in alleviation of seizures but do not seem to alter the devastating neurologic outcome. Most children die in the 1st 2 yr of life. Patients with molybdenum cofactor deficiency caused by pathogenic variants in *MOCS1* have benefited from supplementation using intravenous **cyclic pyranopterin monophosphate** (cPMP), which is undergoing a multicenter clinical trial.

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2012;130:e1716–e1719.

103.5

Tryptophan

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Keywords

tryptophan
niacin
nicotinamide
serotonin
B0AT1
SLC6A19

Tryptophan is an essential amino acid and a precursor for nicotinic acid (niacin) and serotonin (Fig. 103.5). The genetic disorders of metabolism of serotonin, one of the major neurotransmitters, are discussed in Chapter 103.11 .

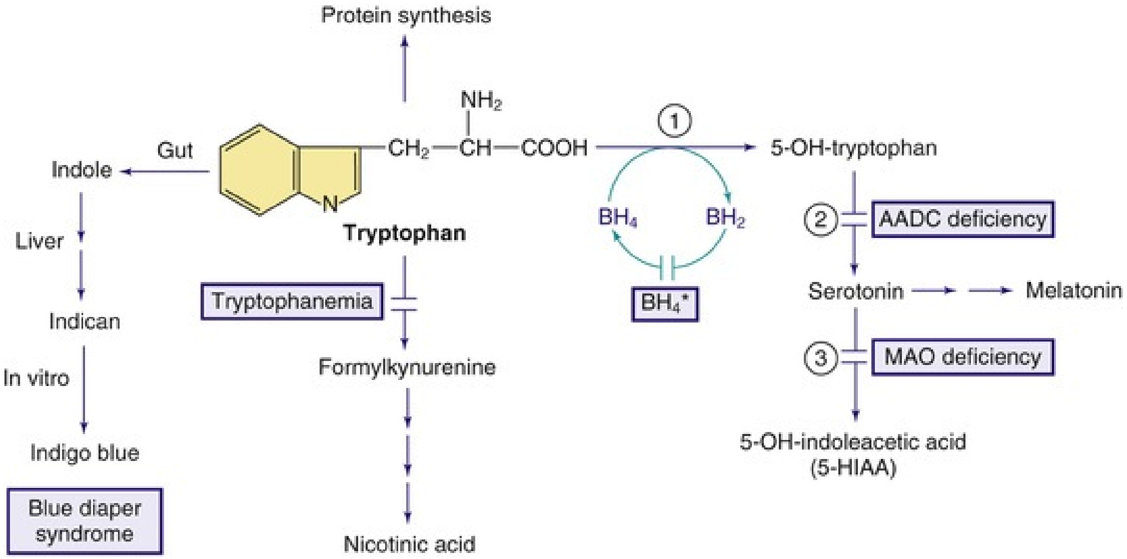
Protein synthesis
Gut
Indole
Liver
Indican
In vitro
Indigo blue
Blue diaper syndrome
NH2
CH2—CH—COOH
N
Tryptophan
Tryptophanemia
Formylkynurenine
Nicotinic acid
1
BH4
BH2
BH4*
5-OH-tryptophan
2
AADC deficiency
Serotonin
Melatonin
3
MAO deficiency
5-OH-indoleacetic acid
(5-HIAA)

FIG. 103.5 Pathways in the metabolism of tryptophan. BH_4 * indicates hyperphenylalaninemia caused by tetrahydrobiopterin deficiency (see Fig. 103.1). Enzymes: *(1)* Tryptophan hydroxylase, *(2)* aromatic L -amino acid decarboxylase (AADC), *(3)* monoamine oxidase (MAO).

Hartnup Disorder

In the autosomal recessive Hartnup disorder, named after the 1st affected family, a defect occurs in the transport of monoamino-monocarboxylic amino acids (neutral amino acids), including tryptophan, by the intestinal mucosa and renal tubules. The transporter protein for these amino acids (**B^0 AT1**) is encoded by the *SLC6A19* gene (located on chromosome 5p15.33). Most children with Hartnup defect remain asymptomatic. Patients show significant variability in presentation, likely related to the nutritional factors, environment, and genetic heterogeneity (e.g., 2 proteins, TMEM27 and ACE2, that interact with B^0 AT1). Decreased intestinal absorption of tryptophan in conjunction with its increased renal loss can lead to reduced availability of tryptophan for niacin synthesis. **Tryptophan deficiency** can be accentuated by malabsorption such as celiac disease. The major clinical manifestation in the rare symptomatic patient is **cutaneous photosensitivity** . The skin becomes rough and red after moderate exposure to the sun, and with greater exposure, a *pellagra-like rash* may develop. The rash may be pruritic, and a chronic eczema may develop. The skin changes have been reported in affected infants as young as 10 days of age. Some patients may have intermittent ataxia manifested as an unsteady, wide-based gait. The ataxia may last a few days and can respond to niacin supplementation.

Cognitive development is usually normal. Episodic psychiatric manifestations such as irritability, emotional instability, depression, and suicidal tendencies, have been observed; these changes are usually associated with bouts of ataxia. Short stature and atrophic glossitis are seen in some patients.

Most children diagnosed with Hartnup disorder by neonatal screening have remained asymptomatic. This indicates that other factors are also involved in pathogenesis of the clinical condition.

The main laboratory finding is **aminoaciduria** , which is restricted to neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine). Urinary excretion of proline, hydroxyproline, and arginine remains normal. This finding helps differentiate Hartnup disorder from other causes of generalized aminoaciduria, such as Fanconi syndrome. Plasma concentrations of neutral amino acids are normal or mildly decreased. This seemingly unexpected finding reflects compensatory mechanisms required to maintain normal transport and utilization of amino acids. The indole derivatives (especially indican) may be found in large amounts in some patients, resulting from bacterial breakdown of unabsorbed tryptophan in the intestines.

Diagnosis of Hartnup disorder is established by the intermittent nature of symptoms and characteristic findings on the urine amino acid analysis. If necessary, the diagnosis can be confirmed molecularly by *SLC6A19* gene analysis.

Treatment with nicotinic acid or nicotinamide (50-300 mg/24 hr) and a high-protein diet results in a favorable response in symptomatic patients with Hartnup disorder. Because of the intermittent nature of the clinical manifestations, the efficacy of these treatments is difficult to evaluate. The prevalence of Hartnup disorder is estimated to be 1 in 20,000 to 1 in 55,000 live births. Normal outcome for both mother and fetus has been reported in several affected women.

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103.6

Isoleucine, Leucine, Valine, and Related Organic Acidemias

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Keywords

isoleucine
leucine
valine
branched-chain amino acid dehydrogenase
BCKDH
maple syrup urine disease
MSUD
leucinosis
BCKDHA
BCKDHB
DBT
branched-chain ketoacid dehydrogenase kinase deficiency
BCKDK
branched-chain amino acid transporter deficiency
LAT1
SLC7A5
SLC3A2
isovaleric acidemia
isovalerylglycine
IVA
isovaleryl-CoA dehydrogenase

isovalerylcarnitine
C5
IVD
multiple carboxylase deficiencies
holocarboxylase synthetase deficiency
HLCS
biotinidase deficiency
biotinidase
BTD
3-methylcrotonyl-CoA carboxylase deficiency
3-MCC
MCCC1
MCCC2
hydroxyisovalerylcarnitine
C5-OH
3-hydroxyisovaleric acid
3-methylglutaconic acidurias
3-MGA
3-methylglutaconyl-CoA hydratase deficiency
AUH
Barth syndrome
TAZ
Costeff syndrome
OPA3
MEGDEL syndrome
SERAC1
TMEM70 -related disorder
TMEM70
DCMA syndrome
DNAJC19
β-ketothiolase deficiency
3-oxothiolase deficiency
mitochondrial acetoacetyl-CoA thiolase deficiency
T2 deficiency
ACAT1
cytosolic acetoacetyl-CoA thiolase deficiency
mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency

3HMG-CoA synthase
HMGCS2
3-hydroxy-3-methylglutaryl-CoA lyase deficiency
3-hydroxy-3-methylglutaric aciduria
3-HMG-CoA lyase
HMGCL
succinyl-CoA:3-oxoacid-CoA transferase deficiency
SCOT deficiency
OXCT1
mevalonate kinase deficiency
MVK
mevalonic aciduria
hyperimmunoglobulinemia D syndrome
propionic acidemia
propionyl-CoA carboxylase deficiency
PCCA
PCCB
propionylcarnitine
C3-carnitine
methylmalonic acidemia
methylmalonyl-CoA mutase
C4DC-carnitine
C4-DC
methylmalonic acid
MUT
hydroxocobalamin
methylcobalamin
adenosylcobalamin
haptocorrin
transcobalamin II
transcobalamin receptor
TCBLR
CD320
LMBRD1
cbl F
ABCD4
cbl J

MMACHC
cbl C
MMADHC
cbl D
MMAB
cbl B
MMAA
cbl A
methionine synthase reductase
MTRR
cbl E
for methionine synthase
MTR
cbl G
HCFC1
cbl X
combined malonic and methylmalonic aciduria
CMAMMA
ACSF3 -related disorder

The early steps in the degradation of the branched-chain amino acids (BCAAs)—isoleucine, leucine, and valine—are similar (see Fig. 103.4). Under catabolic conditions, BCAAs in the muscle tissue undergo a reversible reaction of transamination catalyzed by BCAA transaminase. α-Ketoacids formed by this reaction then undergo an oxidative decarboxylation step mediated by branched-chain α-ketoacid dehydrogenase (**BCKDH**) complex. The deficiency of BCKDH results in maple syrup urine disease, whereas the deficiency of enzymes mediating more distal steps results in accumulation of enzyme-specific organic acids excreted in the urine, thus giving those inborn errors of metabolism the eponyms **organic acidemias** and **organic acidurias** . These disorders typically cause metabolic acidosis, which usually occurs in the 1st few days of life. Although most of the clinical findings are nonspecific, some manifestations may provide important clues to the nature of the enzyme deficiency. Fig. 103.6 presents an approach to infants suspected of having an organic acidemia. The diagnosis is usually established by identifying and measuring specific organic acids in body fluids (blood, urine), identifying pathogenic variants in a respective gene, and enzyme assay.

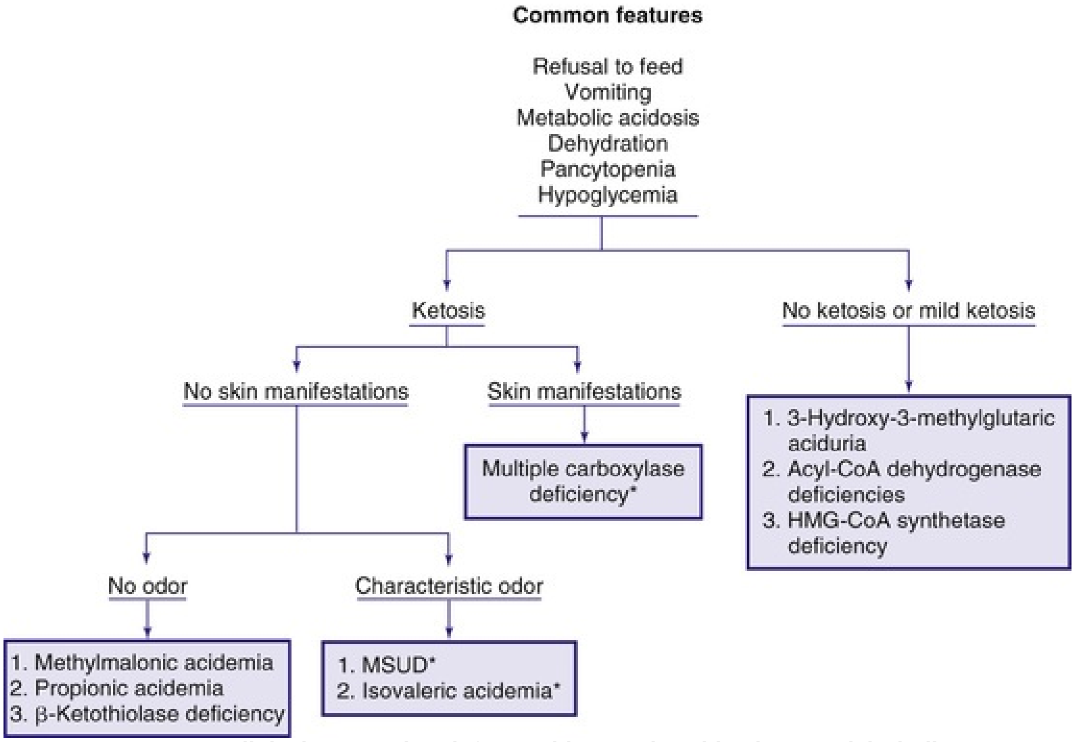
Common features
Refusal to feed
Vomiting
Metabolic acidosis
Dehydration
Pancytopenia
Hypoglycemia
Ketosis
No ketosis or mild ketosis
No skin manifestations
Skin manifestations
Multiple carboxylase deficiency*
1. 3-Hydroxy-3-methylglutaric aciduria
2. Acyl-CoA dehydrogenase deficiencies
3. HMG-CoA synthetase deficiency
No odor
Characteristic odor
1. Methylmalonic acidemia
2. Propionic acidemia
3. β-Ketothiolase deficiency
1. MSUD*
2. Isovaleric acidemia*

FIG. 103.6 **Clinical approach to infants with organic acidemia. *Asterisks* indicate disorders in which patients have a characteristic odor (see text and Table 103.2). MSUD, Maple syrup urine disease.**

Organic acidemias are *not* limited to defects in the catabolic pathways of BCAAs. Disorders causing accumulation of other organic acids include those derived from lysine (see Chapter 103.14), disorders of γ-glutamyl cycle (see Chapter 103.11), those associated with lactic acid (see Chapter 105), and dicarboxylic acidemias associated with defective fatty acid degradation (see Chapter 104.1).

Maple Syrup Urine Disease

Decarboxylation of leucine, isoleucine, and valine is accomplished by a complex enzyme system (BCKDH) using thiamine (vitamin B_1) pyrophosphate as a coenzyme. This mitochondrial enzyme consists of 4 subunits: $E_{1\alpha}$, $E_{1\beta}$, E_2 , and E_3 . The E_3 subunit is shared with 2 other dehydrogenases, pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Deficiency of any of these subunits causes maple syrup urine disease (**MSUD**) (see Fig. 103.4), a disorder named after the sweet odor of maple syrup found in body fluids, especially urine. Clinical conditions caused by defects in $E_{1\alpha}$, $E_{1\beta}$, E_2 and E_3 are designated as MSUD type IA, type IB, type 2, and type 3, respectively. This classification, however, is not very helpful clinically because the severity of clinical manifestations does not correlate with, or correspond specifically to, any single enzyme subunit. An affected infant with type 1A defect can have clinical manifestations ranging from relatively mild to very severe. A more useful classification, based on clinical findings and response to thiamine administration, delineates 5 phenotypes of MSUD.

Classic Maple Syrup Urine Disease

Classic MSUD has the **most severe** clinical manifestations. The BCKDH complex activity in this group varies between 0% and 2% of controls. Patients with uncontrolled or poorly controlled disease develop signs of acute encephalopathy. The mechanisms underlying this life-threatening complication are complex, but leucine and its derivative, α-ketoisocaproic acid, appear to be the key factors underlying acute encephalopathy. Elevated leucine competitively inhibits the uptake of other amino acids by the large neutral amino acid (LNAA) transporter. Once taken up by the brain tissue, leucine is metabolized by BCAA aminotransferase to α-ketoisocaproic acid, which leads to the disrupted metabolism of neurotransmitters and amino acids (glutamate, GABA, glutamine, alanine, and aspartate). α-Ketoisocaproic acid can reversibly inhibit oxidative phosphorylation and result in cerebral lactic acidosis. Collectively, these processes are detrimental to the normal function of neurons and glia, clinically manifesting as encephalopathy and brain edema and referred to as **leucinosis** . Affected infants who appear healthy at birth develop poor feeding and vomiting in the 1st days of life. Lethargy and coma may ensue within a few days. Physical examination reveals hypertonicity and muscular rigidity with severe opisthotonos. Periods of hypertonicity may alternate with bouts of flaccidity manifested as repetitive movements of the extremities (“boxing” and “bicycling”). Neurologic findings are often mistakenly thought to be caused by generalized sepsis and meningitis. Cerebral edema may be present; convulsions occur in most infants, and hypoglycemia is common. In contrast to most hypoglycemic states, correction of the blood glucose concentration does not improve the clinical condition. Aside from the blood glucose, routine laboratory findings are usually unremarkable, except for varying degrees of ketoacidosis. If left untreated, death can occur in the 1st few weeks or months of life.

Diagnosis is often suspected because of the peculiar odor of maple syrup in urine, sweat, and cerumen. It is usually confirmed by amino acid analysis showing marked elevations in plasma levels of leucine, isoleucine, valine, and alloisoleucine (a stereoisomer of isoleucine not normally found in blood) and depressed level of alanine. Leucine levels are usually higher than those of the other 3 amino acids. Urine contains high levels of leucine, isoleucine, and valine and their respective ketoacids. These ketoacids may be detected qualitatively by adding a few drops of 2,4-dinitrophenylhydrazine reagent (0.1% in 0.1N HCl) to the urine; a yellow precipitate of 2,4-dinitrophenylhydrazone is formed in a positive test. Neuroimaging during the acute state may show cerebral edema, which is most prominent in the cerebellum, dorsal brainstem, cerebral peduncle, and internal capsule. After recovery from the acute state and with advancing age, hypomyelination and cerebral atrophy may be seen in neuroimaging of the brain.

Treatment of the acute state is aimed at hydration and rapid removal of the BCAAs and their metabolites from the tissues and body fluids. Uptake of leucine by the brain and accumulation of the downstream metabolite, α-ketoisocaproic acid, appear to be the key metabolic events underlying MSUD encephalopathy. Therefore, strategies of MSUD management focus on decreasing plasma leucine to control acute and chronic manifestations of the disease.

Because renal clearance of leucine is poor, hydration alone may not produce a rapid improvement. *Hemodialysis* is the most effective mode of therapy in critically ill infants and should be instituted promptly; significant decreases in plasma levels of leucine, isoleucine, and valine are usually seen within 24 hr. Sufficient calories and nutrients should be provided intravenously or orally as soon as possible to reverse patient's catabolic state. Cerebral edema, if present, may require treatment with mannitol, diuretics (e.g., furosemide), or hypertonic saline. Counterintuitively, supplementation with isoleucine and valine is also needed to control plasma leucine level in MSUD patients. Judiciously administered isoleucine and valine will compete with leucine for the LNAA transporter at the blood-brain barrier and thus decrease leucine entry into the central nervous system (CNS) and help in the prevention and treatment of leucine encephalopathy.

Treatment after recovery from the acute state requires a diet low in BCAAs. Synthetic formulas devoid of leucine, isoleucine, and valine are available commercially. Because these amino acids cannot be synthesized endogenously, age-appropriate amounts of BCAAs should be provided in the diet in the form of complete protein. To avoid essential amino acid deficiencies, the amount should be titrated carefully by performing frequent analyses of the plasma amino acids, with close attention to plasma isoleucine, leucine, and valine levels. A clinical condition resembling **acrodermatitis enteropathica** (see Chapter 691) occurs in affected infants whose plasma isoleucine or valine become *very low* ; addition of isoleucine or valine, respectively, to the diet will hasten the recovery of skin rash. Patients with MSUD need to remain on the diet for the rest of their lives. Liver transplantation has been performed in patients with classic MSUD, with promising results.

The long-term prognosis of affected children remains guarded. Severe ketoacidosis, cerebral edema, and death may occur during any stressful situation such as infection or surgery, especially in mid-childhood. Cognitive and other neurologic deficits are common sequelae.

Intermediate (Mild) Maple Syrup Urine Disease

Children with intermediate MSUD develop milder disease after the neonatal period. Clinical manifestations are insidious and limited to the CNS. Patients have mild to moderate intellectual disability with or without seizures. They have the odor of maple syrup and excrete moderate amounts of the BCAAs and their ketoacid derivatives in the urine. Plasma concentrations of leucine, isoleucine, and valine are moderately increased whereas those of lactate and pyruvate tend to be normal. These children are commonly diagnosed during an intercurrent illness, when signs and symptoms of classic MSUD may occur. The dehydrogenase activity is 3–40% of controls. Because patients with thiamine-responsive MSUD usually have manifestations similar to the mild form, a trial of thiamine therapy is recommended. Diet therapy, similar to that of classic MSUD, is needed.

Intermittent Maple Syrup Urine Disease

In intermittent MSUD, seemingly normal children develop vomiting, odor of maple syrup, ataxia, lethargy, and coma during any stress or catabolic state such as infection or surgery. During these attacks, laboratory findings are indistinguishable from those of the classic form, and death may occur. Treatment of the acute attack of intermittent MSUD is similar to that of the classic form. After recovery, although a normal diet can be tolerated, a low-BCAA diet is recommended. The BCKDH activity in patients with the intermittent form is higher than in the classic form and may reach 40% of the control activity.

Thiamine-Responsive Maple Syrup Urine Disease

Some children with mild or intermediate forms of MSUD who are treated with high doses of thiamine have dramatic clinical and biochemical improvement. Although some respond to treatment with thiamine at 10 mg/24 hr, others may require as much as 100 mg/24 hr for at least 3 wk before a favorable response is observed. These patients also require BCAA-restricted diets. The enzymatic activity in these patients can be up to 40% of normal.

Maple Syrup Urine Disease Caused by Deficiency of E_3 Subunit (MSUD Type 3)

Although sometimes referred to as “maple syrup urine disease type 3,” this very rare disorder leads to clinical and biochemical abnormalities that encompass a wide range of mitochondrial reactions. E_3 subunit, dihydrolipoamide dehydrogenase, is a component of the BCKDH complex, pyruvate dehydrogenase complex, and α-ketoglutarate dehydrogenase complex. Pathogenic variants in dihydrolipoamide dehydrogenase cause lactic acidosis, elevated pyruvate, as well as signs and symptoms similar to intermediate MSUD. Progressive neurologic impairment manifested by hypotonia and developmental delay occurs after 2 mo of age. Abnormal movements progress to ataxia or Leigh syndrome. Death may occur in early childhood.

Laboratory findings include persistent lactic acidosis with high levels of plasma pyruvate and alanine. Plasma BCAA concentrations are moderately increased. Patients excrete large amounts of lactate, pyruvate, α-ketoglutarate, and the 3 branched-chain ketoacids in their urine.

No effective treatment is available. BCAA-restricted diets and treatment with high doses of thiamine, biotin, and lipoic acid have been ineffective.

Genetics and Prevalence of Maple Syrup Urine Disease

All forms of MSUD are inherited as an autosomal recessive trait. The gene for each subunit resides on different chromosomes. The gene for $E_{1\alpha}$ *(BCKDHA)* is on chromosome 19q13.2; that for $E_{1\beta}$ *(BCKDHB)* is on chromosome 6q14.1; the gene for E_2 (*DBT*) is on chromosome 1p21.2; and that for E_3 *(DLD)* is on chromosome 7q31.1. Genotype-phenotype correlations are difficult to establish and are usually imprecise. The exception is thiamine-responsive MSUD, shown to be caused by pathogenic variants in *DBT* . Most patients are compound heterozygotes inheriting 2 different pathogenic alleles. Pathogenic variants in *BCKDHA* (45%) and *BCKDHB* (35%) account for approximately 80% of cases. Pathogenic variants in *DBT* are responsible for 20% of MSUD cases.

The prevalence is estimated at 1 in 185,000 live births. Classic MSUD is more prevalent in the Old Order Mennonites in the United States, at an estimated 1 in 380 live births. Affected patients in this population are homozygous for a specific pathogenic variant (c.1312T>A) in *BCKDHA* -encoding $E_{1\alpha}$ subunit.

Early detection of MSUD is feasible by universal newborn screening. In most cases, however, especially those with classic MSUD, the infant may be quite sick by the time screening results become available (see Chapter 102). Prenatal diagnosis has been accomplished by enzyme assay of the cultured amniocytes, cultured chorionic villus tissue, or direct assay of samples of the chorionic villi and by identification of the known pathogenic variants in the affected gene.

Several successful pregnancies have occurred in women with different forms of MSUD. The teratogenic potential of leucine during pregnancy is unknown. Tight control of isoleucine, leucine, and valine before and during the pregnancy is important to minimize the risk of metabolic decompensation and to optimize fetal nutrition. Mothers affected by MSUD require close monitoring and meticulous management of nutrition, electrolytes, and fluids in the postpartum period.

Branched-Chain α-Ketoacid Dehydrogenase Kinase Deficiency

A defect in the regulation of branched-chain α-ketoacid dehydrogenase (BCKDH) by BCKDH kinase (BCKDK), the enzyme responsible for the phosphorylation-mediated inactivation of the BCKDH complex, causes the *reverse* biochemical phenotype of MSUD. Pathogenic variants in *BCKDK* decrease the negative regulation by the kinase, resulting in uncontrolled degradation and depletion of isoleucine, leucine, and valine in plasma and brain. Patients with BCKDK deficiency present with low plasma concentrations of isoleucine, leucine, and valine associated with autism, intellectual impairment, fine motor coordination problems, and seizures.

Branched-Chain Amino Acid Transporter Deficiency

Isoleucine, leucine, and valine are transported across the BBB mainly by the heterodimeric LNAA transporter LAT1 encoded by *SLC7A5* . A defect in LAT1 caused by pathogenic variants in *SLC7A5* results in low brain concentrations of isoleucine, leucine, and valine. Patients with this defect may present clinically similar to BCKDK-deficient patients, with autism, microcephaly, gross motor delays, and in some cases, seizures.

Isovaleric Acidemia

Isovaleric acidemia (**IVA**) is caused by deficiency of isovaleryl–coenzyme A (CoA) dehydrogenase (see Fig. 103.4). Decreased or lost activity of isovaleryl-CoA dehydrogenase results in impaired leucine degradation. Accumulating derivatives of isovaleric acid, isovalerylcarnitine, isovalerylglycine, and 3-hydroxyisovaleric acid can be detected in body fluids and thus enable the biochemical diagnosis and screening. Clinically, the course of IVA is highly variable, ranging from essentially asymptomatic to severe. Introduction of newborn screening and proactive management of IVA changed its outlook and the clinical course. Older siblings of symptomatic newborn infants have been reported with identical genotype and biochemical abnormalities but without clinical manifestations, suggesting that presymptomatic detection of affected patients on the newborn screen can improve clinical outcomes.

Patients with severe IVA can present with vomiting, severe acidosis, hyperammonemia, hypoglycemia, hypocalcemia, and bone marrow suppression in the infantile period. Lethargy, convulsions, and coma may ensue, and death may occur if proper therapy is not initiated. Vomiting may be severe enough to suggest pyloric stenosis. The characteristic odor of *sweaty feet* or *rancid-cheese* may be present. Infants who survive this acute episode are at risk to develop episodes of metabolic decompensation later in life. In the mild form without treatment, typical clinical manifestations of severe IVA (vomiting, lethargy, acidosis or coma) may not appear until the child is a few months or a few years old. Acute episodes of metabolic decompensation may occur during a catabolic state, such as infection, dehydration, surgery, or high-protein intake. Acute episodes may be mistaken for diabetic ketoacidosis. Some patients may experience acute and recurrent episodes of pancreatitis.

Laboratory findings during the acute attacks include ketoacidosis, neutropenia, thrombocytopenia, and occasionally pancytopenia. Hypocalcemia, hypoglycemia, and moderate to severe hyperammonemia may be present in some patients. Increases in plasma ammonia may suggest a defect in the urea cycle (see Chapter 103.12). In urea cycle defects, however, the infant usually shows no significant ketoacidosis (see Fig. 103.6).

Diagnosis is established by demonstrating marked elevations of isovaleric acid metabolites (isovalerylglycine, 3-hydroxyisovaleric acid) in body fluids, especially urine. The main compound in plasma is isovalerylcarnitine (C5-carnitine). C5-carnitine can be measured in dried blood spots, thus enabling universal newborn screen using tandem mass spectrometry. The diagnosis can be confirmed by molecular analysis of the *IVD* gene. In some patients with equivocal results, measurement of the enzyme activity in cultured skin fibroblasts may be necessary.

Treatment of the acute attack is aimed at hydration, reversal of the catabolic state (by providing adequate calories orally or intravenously), correction of metabolic acidosis, and facilitation of the isovaleric acid excretion. L -Carnitine (100 mg/kg/24 hr orally) also increases removal of isovaleric acid by forming isovalerylcarnitine, which is excreted in the urine. Because isovalerylglycine has a high urinary clearance, some centers recommend glycine supplementation (250 mg/kg/24 hr) to enhance the formation of isovalerylglycine. Temporary restriction of protein intake (<24 hr) may be beneficial in some cases. In patients with significant hyperammonemia (blood ammonia >200 µmol/L), measures that reduce blood ammonia should be employed (see Chapter 103.12). Renal replacement therapy may be needed if the previously described measures fail to produce significant clinical and biochemical improvement. Long-term management of IVA patients requires restriction of protein according to age-appropriate intake (recommended dietary allowance of protein). Patients benefit from carnitine supplementation with or without glycine. Normal development can be achieved with early and proper treatment.

Prenatal diagnosis can be accomplished by enzyme assay in cultured amniocytes, or if causative mutations are known, by the *IVD* gene analysis. Successful pregnancies with favorable outcomes have been reported. Universal newborn screening of IVA is used in the United States and other countries (see

Chapter 102). IVA is caused by autosomal recessive pathogenic variants in *IVD* . The prevalence of IVA is estimated from 1 in 62,500 (in parts of Germany) to 1 in 250,000 live births (in the United States).

Multiple Carboxylase Deficiencies (Defects of Biotin Cycle)

Biotin is a water-soluble vitamin that is a cofactor for all 4 carboxylase enzymes in humans: pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase. The latter 2 are involved in the catabolic pathways of leucine, isoleucine, and valine (see Fig. 103.4).

Most of the dietary biotin is bound to proteins. Free biotin is generated in the intestine by the action of digestive enzymes, by intestinal bacteria, and perhaps by biotinidase. **Biotinidase** , which is found in serum and most tissues, is also essential for the recycling of biotin in the body by releasing it from the apoenzymes (carboxylases; see Fig. 103.4). Free biotin must form a covalent bond with the apocarboxylases to produce the activated enzyme (holocarboxylase). This binding is catalyzed by holocarboxylase synthetase. Deficiencies in this enzyme activity or in biotinidase result in malfunction of all the carboxylases and in organic acidemias.

Holocarboxylase Synthetase Deficiency

Infants with this rare autosomal recessive disorder become symptomatic in the 1st few weeks of life. Symptoms may appear as early as a few hours after birth to as late as 8 yr of age. Clinically, shortly after birth, the affected infant develops breathing difficulties (tachypnea and apnea). Feeding problems, vomiting, and hypotonia are also usually present. If the condition remains untreated, *generalized erythematous rash with exfoliation and alopecia* , failure to thrive, irritability, seizures, lethargy, and even coma may occur. Developmental delay is common. Immune deficiency manifests with susceptibility to infection. Urine may have a peculiar odor, which has been described “tomcat urine.” The rash, when present, helps differentiate this condition from other organic acidemias (see Fig. 103.6).

Laboratory findings include metabolic acidosis, ketosis, hyperammonemia, and the presence of a variety of organic acids (lactic acid, 3-methylcrotonic acid, 3-methylcrotonylglycine, tiglylglycine, 3-OH-propionic acid, methylcitric acid, and 3-hydroxyisovaleric acid) in body fluids. **Diagnosis** is confirmed by identification of pathogenic variants in *HLCS* or by the enzyme assay in lymphocytes or cultured fibroblasts. Most pathogenic variants cause the enzyme to have an increased K_m (Michaelis-Menten dissociation constant) for biotin; the enzyme activity in such patients can be restored by the administration of large doses of biotin. Newborn screening can identify holocarboxylase synthetase–deficient infants by detecting elevated C5-OH-carnitine on tandem mass spectrometry. In these infants, biotinidase enzymatic assay would be normal.

Treatment with biotin (10-20 mg/day orally) usually results in an improvement in clinical manifestations and biochemical abnormalities. Early diagnosis and treatment are critical to prevent irreversible neurologic damage. In some patients, however, complete resolution may not be achieved even with large doses (up to 60 mg/day) of biotin.

The gene for holocarboxylase synthetase *(HLCS)* is located on chromosome 21q22.13. **Prenatal diagnosis** can be accomplished by prenatal molecular analysis of the known pathogenic variants in *HLCS* or by assaying enzyme activity in cultured amniotic cells. Pregnant mothers who had previous offspring with holocarboxylase synthetase deficiency have been treated with biotin late in pregnancy. Affected infants were normal at birth, but the efficacy of prenatal treatment remains unclear.

Biotinidase Deficiency

Impaired biotinidase activity results in biotin deficiency. Affected infants may develop clinical manifestations similar to those seen in infants with holocarboxylase synthetase deficiency. Unlike the latter, however, symptoms tend to appear later, when the child is several months or years old. The delay in onset of symptoms presumably results from the presence of free biotin derived from the mother or the diet. Clinical manifestations are mostly confined to skin and the nervous system. Atopic or seborrheic dermatitis, candidiasis, alopecia, ataxia, seizures (usually myoclonic), hypotonia, developmental delay, optic nerve atrophy, sensorineural hearing loss, and immunodeficiency resulting from impaired T-cell function may occur. A small number of children with *intractable seborrheic dermatitis* and *partial* (15–30% activity) biotinidase deficiency, in whom the dermatitis resolved with biotin therapy, have been reported; these children were otherwise asymptomatic. Asymptomatic children and adults with this enzyme deficiency have been identified in screening programs. Most of these individuals have been shown to have partial biotinidase deficiency. With universal newborn screening leading to early identification and treatment of the affected patients, the clinical disease is predicted to become extinct.

Laboratory findings and the pattern of organic acids in body fluids resemble those associated with holocarboxylase synthetase deficiency (see above). **Diagnosis** can be established by measurement of the enzyme activity in the serum or by the identification of the mutant gene. **Treatment** with free biotin (5-20 mg/day) results in a dramatic clinical and biochemical improvement. Treatment with biotin is also suggested for individuals with partial biotinidase deficiency. The prevalence of this autosomal recessive trait is estimated at 1 in 60,000 live births. The gene for biotinidase *(BTD)* is located on chromosome 3p25.1. **Prenatal diagnosis** is possible by identification of the known pathogenic variants in *BTD*, or less frequently by the measurement of the enzyme activity in the amniotic cells, although in practice, a prenatal approach is rarely used.

Multiple Carboxylase Deficiency Caused by Acquired Biotin Deficiency

Acquired deficiency of biotin may occur in infants receiving total parenteral nutrition without added biotin, in patients with prolonged use of antiepileptic drugs (phenobarbital, phenytoin, primidone, carbamazepine), and in children with short bowel syndrome or chronic diarrhea who are receiving formulas low in biotin. Excessive ingestion of raw eggs may also cause biotin deficiency because the protein avidin in egg white binds biotin, decreasing its absorption. Infants with biotin deficiency may develop dermatitis, alopecia, and candidal skin infections. This condition readily responds to treatment with oral biotin.

3-Methylcrotonyl-CoA Carboxylase Deficiency

This enzyme is 1 of the 4 carboxylases requiring biotin as a cofactor (see Fig. 103.4). An isolated deficiency of this enzyme must be differentiated from disorders of biotin metabolism (multiple carboxylase deficiency), which causes diminished activity of all 4 carboxylases (see earlier). 3-Methylcrotonyl-CoA carboxylase (3-MCC) is a heteromeric enzyme consisting of α (biotin containing) and β subunits, encoded by genes *MCCC1* and *MCCC2* , respectively. 3-MCC deficiency can be detected in the newborn period by identifying elevated 3-hydroxyisovalerylcarnitine (C5-OH) in dried blood spots. Universal newborn screening using tandem mass spectrometry has identified an unexpectedly high number of infants with 3-MCC deficiency, with prevalence ranging from 1 : 2,400 to 1 : 68,000.

Clinical manifestations are highly variable, ranging from completely asymptomatic adults (including mothers of affected newborn infants), to children presenting with developmental delay without episodes of metabolic decompensation, to patients with seizures, hyperammonemia, and metabolic acidosis. In severe 3-MCC deficiency the affected infant who has been seemingly normal develops an acute episode of vomiting, hypotonia, lethargy, and convulsions after a minor infection, in some cases progressing to life-threatening complications (e.g., Reye syndrome, coma). In patients prone to developing these symptoms, the onset is usually between 3 wk and 3 yr of age. Among infants identified through newborn screening, 85–90% of children remain apparently asymptomatic. The reason for differences in outcomes is unknown. None of the symptoms reported so far could be clearly attributed to the degree of enzyme deficiency.

Laboratory findings during acute episodes include mild to moderate metabolic acidosis, ketosis, hypoglycemia, hyperammonemia, and elevated serum transaminase levels. Large amounts of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine are found in the urine. Urinary excretion of 3-methylcrotonic acid is not usually increased in this condition because the accumulated 3-methylcrotonyl-CoA is converted to 3-hydroxyisovaleric acid. Plasma acylcarnitine profile shows elevated 3-hydroxyisovalerylcarnitine (C5-OH). Severe secondary carnitine deficiency is common. 3-MCC deficiency should be differentiated biochemically from multiple carboxylase deficiency (see earlier), in which, in addition to 3-hydroxyisovaleric acid, lactic acid and metabolites of propionic acid are also present. **Diagnosis** may be confirmed by molecular analysis or by measurement of the enzyme activity in cultured fibroblasts. Documentation of normal activities of other carboxylases is necessary to rule out multiple carboxylase deficiency.

Treatment of acute episodes is similar to that of isovaleric acidemia (see earlier). Hydration and measures to correct hypoglycemia and severe metabolic acidosis by infusing glucose and sodium bicarbonate should be instituted promptly. Secondary carnitine deficiency, seen in up to 50% of patients, can be corrected with L-carnitine supplementation. For symptomatic patients, some centers recommend keeping protein intake at the recommended dietary allowance in conjunction with the oral administration of L-carnitine and the proactive management of catabolic states. Normal growth and development are expected in most patients.

3-MCC deficiency is an autosomal recessive condition. The gene for α-subunit *(MCCC1)* is located on chromosome 3q27.1, and that for the β-subunit *(MCCC2)* is mapped to chromosome 5q13.2. Pathogenic variants in either of these genes result in the enzyme deficiency with overlapping clinical features.

3-Methylglutaconic Acidurias

The 3-methylglutaconic acidurias are a heterogeneous group of metabolic disorders characterized by excessive excretion of 3-methylglutaconic acid in the urine (Table 103.2). Other metabolites found in 3-methylglutaconic aciduria patients may include 3-methylglutaric acid and 3-hydroxyisovaleric acid. Current classification distinguishes primary and secondary forms. **Primary** 3-methylglutaconic aciduria is caused by the deficiency of mitochondrial 3-methylglutaconyl-CoA hydratase (see Fig. 103.4), formerly *3-methylglutaconic aciduria type I* . **Secondary** 3-methylglutaconic aciduria can be further classified based on the underlying mechanism (e.g., defective phospholipid remodeling vs dysfunction of mitochondrial membrane) or the known molecular cause. Known secondary 3-methylglutaconic aciduria includes *TAZ* -related syndrome (**Barth syndrome**), *OPA3* -related 3-methylglutaconic aciduria (**Costeff syndrome**), *SERAC1* -related syndrome (**MEGDEL syndrome**), *TMEM70* -related syndrome, and *DNAJC19* -related syndrome (**DCMA syndrome**).

Table 103.2

3-Methylglutaconic Acidurias

GROUP	DISORDER	GENE (CHROMOSOME)	PREVIOUS CLASSIFICATION	DISEASE MECHANISM	CLINICAL DESCRIPT
Primary 3-methylglutaconic aciduria	3-Methylglutaconyl-CoA hydratase deficiency	*AUH* (9q22.31)	Type I	Enzyme deficiency in the leucine degradation pathway	Depending o variable pres is seen rangi younger asymptomati patients to ol

					patients with progressive leukoenceph
Secondary 3-methylglutaconic acidurias	Barth syndrome	*TAZ* (Xq28)	Type II	Defective phospholipid remodeling	X-linked inh cardiomyopa endocardial fibroelastosi proximal my failure to thr neutropenia, dysmorphic
	Costeff syndrome	*OPA3* (19q13.32)	Type III	Mitochondrial membrane dysfunction	Progressive nerve atroph chorea, spast paraparesis, cognitive impairment
	MEGDEL syndrome	*SERAC1* (6q25.3)	Type IV	Defective phospholipid remodeling	Progressive deafness, dy spasticity, ba ganglia chan
	TMEM70 -related disorder	*TMEM70* (8q21.11)	Type IV	Mitochondrial membrane dysfunction	Developmen delay, failure thrive, metab decompensat microcephal cardiomyopa dysmorphic
	3-Methylglutaconic aciduria, not otherwise specified	Unknown	Type IV	Unknown	Variable pres
	DCMA syndrome	*DNAJC19* (3q26.33)	Type V	Mitochondrial membrane dysfunction	Cardiomyop ataxia, optic atrophy, failu thrive

Significant and persistent 3-methylglutaconic aciduria with negative molecular evaluation for known genetic causes represents a heterogeneous group called 3-methylglutaconic aciduria **not otherwise specified** awaiting further molecular characterization. Primary and secondary 3-methylglutaconic aciduria should be distinguished from mild and transient urinary elevations of 3-methylglutaconic acid seen in patients affected by other metabolic disorders, such as mitochondrial disorders of diverse etiology.

3-Methylglutaconyl-CoA Hydratase Deficiency

Two main clinical forms of 3-methylglutaconyl-CoA hydratase deficiency have been described (see Fig. 103.4). In the **childhood** form, nonspecific neurodevelopmental findings such as speech delay or regression, choreoathetoid movements, optic nerve atrophy, and mild psychomotor delay may be present. Metabolic acidosis may occur during a catabolic state. In the **adulthood** form, affected individuals may remain asymptomatic until the 2nd or 3rd decade of life, when a clinical picture of *slowly progressing leukoencephalopathy* with optic nerve atrophy, dysarthria, ataxia, spasticity, and dementia occurs. Brain MRI typically shows white matter abnormalities, which may precede the appearance of clinical symptoms by years. Asymptomatic pediatric and adult patients have also been reported. Patients excrete large amounts of 3-methylglutaconic acid and moderate amounts of 3-hydroxyisovaleric and 3-methylglutaric acids in urine. **Treatment** with L -carnitine may help some patients. The effectiveness of a low-leucine diet has not been established. The condition is inherited as an autosomal recessive trait. The gene for the hydratase enzyme *(AUH)* is mapped to chromosome 9q22.31.

Barth Syndrome (*TAZ* -Related Disorder)

This X-linked condition is caused by deficiency of *tafazzin* , a mitochondrial protein, encoded by *TAZ* gene. This enzyme is necessary for remodeling of immature cardiolipin into its mature form. *Cardiolipin,* a mitochondrial phospholipid, is critical for the integrity of inner mitochondrial membrane. **Clinical manifestations** of Barth syndrome, which usually occur in the 1st yr of life in a male infant, include cardiomyopathy, hypotonia, growth retardation, hypoglycemia, and mild to severe neutropenia. The onset of clinical manifestations may be as late as adulthood, but most affected individuals become symptomatic by adolescence. If patients survive infancy, relative improvement may occur with advancing age. Cognitive development is usually normal, although delayed motor function and learning disabilities are possible.

Laboratory findings include mild to moderate increases in urinary excretion of 3-methylglutaconic, 3-methylglutaric, and 2-ethylhydracrylic acids. Unlike primary 3-methylglutaconic aciduria (type I), urinary excretion of 3-hydroxyisovaleric acid is not elevated. The activity of the enzyme 3-methylglutaconyl-CoA hydratase is normal. *Neutropenia is a common finding* . Lactic acidosis, hypoglycemia, low serum cholesterol concentration, low prealbumin, and abnormal mitochondrial ultrastructure have been shown in some patients. Total cardiolipin and subclasses of cardiolipin are very low in skin fibroblast cultures from these patients. The monolysocardiolipin/cardiolipin ratio in cultured fibroblast may be useful for establishing the diagnosis in patients with negative or equivocal molecular results. Because of its nonspecific presentation, the condition could be underdiagnosed and underreported.

The condition is inherited as an *X-linked* recessive trait. The gene *(TAZ)* has been mapped to chromosome Xq28. The modest 3-methylglutaconic aciduria seen in Barth syndrome is thought to be related to the defect in mitochondrial membrane, causing the leakage of this organic acid. *Specific treatment is not available*. Patients with an unsatisfactory response to medical management of cardiomyopathy may benefit from cardiac transplantation. Daily aspirin to reduce the risk of strokes has been described.

OPA3 -Related 3-Methylglutaconic Aciduria (Costeff Syndrome)

Clinical manifestations in patients with Costeff syndrome include early-onset optic nerve atrophy and later development of choreoathetoid movements, spasticity, ataxia, dysarthria, and cognitive impairment. Patients excrete moderate amounts of 3-methylglutaconic and 3-methylglutaric acids. Activity of the enzyme 3-methylglutaconyl-CoA hydratase is normal. The condition is inherited as an autosomal recessive trait. The gene for this condition *(OPA3)* is mapped to chromosome 19q13.32. Pathogenic variants in *OPA3* are thought to cause electron transport chain dysfunction. Treatment is supportive.

Disorders Formerly Described as 3-Methylglutaconic Aciduria Type IV

3-Methylglutaconic aciduria type IV represents a group of disorders with diverse genetic etiology. Two disorders in this group have been linked to specific molecular etiology, while other conditions are still awaiting the discovery of their underlying molecular defect.

MEGDEL syndrome (3-*me* thyl*g* lutaconic aciduria with *d* eafness, *e* ncephalopathy and *L* eigh-like) is an autosomal recessive disorder caused by deleterious mutations in *SERAC1* on chromosome 6q25.3. Affected patients experience progressive deafness, dystonia, spasticity and basal ganglia injury similar to patients with Leigh syndrome. Treatment is symptomatic.

***TMEM70* -related disorder** is also inherited in an autosomal recessive fashion. Pathogenic variants in *TMEM70* result in the mitochondrial complex V deficiency, although the exact mechanism of disease is unknown. Clinical manifestations include developmental delay, developmental regression, Reye syndrome–like episodes, intellectual disability, failure to thrive, microcephaly, cardiomyopathy, and dysmorphic findings. Patients are prone to metabolic decompensation, characterized by hyperammonemia (up to 900 µmol/L) and lactic acidosis, which are more common in the 1st yr of life. **Acute hyperammonemic** episodes are treated with intravenous glucose, lipid emulsion, ammonia-scavenging drugs, and occasionally require hemodialysis. Long-term therapy that has been described includes L -carnitine, coenzyme Q_{10} , and bicarbonate substitution (e.g., citric acid/sodium citrate). Patients require interval echocardiographic and electrocardiographic (ECG) monitoring to enable early diagnosis and management of cardiomyopathy.

DCMA Syndrome (*DNAJC19* -Related Syndrome, 3-Methylglutaconic Aciduria Type V)

DCMA syndrome (*d* ilated *c* ardio*m* yopathy with *a* taxia) is a novel autosomal recessive disorder identified in patients of the Canadian Dariusleut Hutterite ancestry living in The Great Plains of North America. As the disorder's abbreviated name suggests, affected individuals present with dilated cardiomyopathy, long QTc interval, and CNS involvement. Neurologic symptoms include intellectual disability, cerebellar involvement, and optic atrophy. Growth is affected in all patients. Intrauterine growth restriction is seen in up to 50% of patients. Cryptorchidism and hypospadias are frequent findings in affected boys. Urine organic acid assay reveals increased 3-methylglutaconic acid and 3-methylglutaric acid. Pathogenic variants in *DNAJC19* (3q26.33) are the underlying cause of DCMA syndrome. Treatment is symptomatic. Interval echocardiography and ECG can prospectively identify patients requiring treatment of cardiomyopathy and long QTc interval.

β-Ketothiolase (3-Oxothiolase) Deficiency (Mitochondrial Acetoacetyl-CoA Thiolase [T_2] Deficiency)

This reversible mitochondrial enzyme is involved in the final steps of isoleucine catabolism and in ketolysis. In the isoleucine catabolic pathway, the enzyme cleaves 2-methylacetoacetyl-CoA into propionyl-CoA and acetyl-CoA (see Fig. 103.4). In the fatty acid oxidation pathway, the enzyme generates 2 moles of acetyl-CoA from 1 mole of acetoacetyl-CoA (Fig. 103.7). The same enzyme synthesizes 2-methyacetoacetate-CoA and acetoacetyl-CoA in the reverse direction. The hallmark of this disorder is **ketoacidosis** , often triggered by infections, prolonged fasting, and large protein load. The mechanism of ketosis in this condition is incompletely understood, because in this enzyme deficiency one expects impaired ketone formation (Fig. 103.7). It is postulated that excess acetoacetyl-CoA produced from other sources can be used as a substrate for 3-hydroxy-3-methylglutaryl-CoA synthesis in the liver.

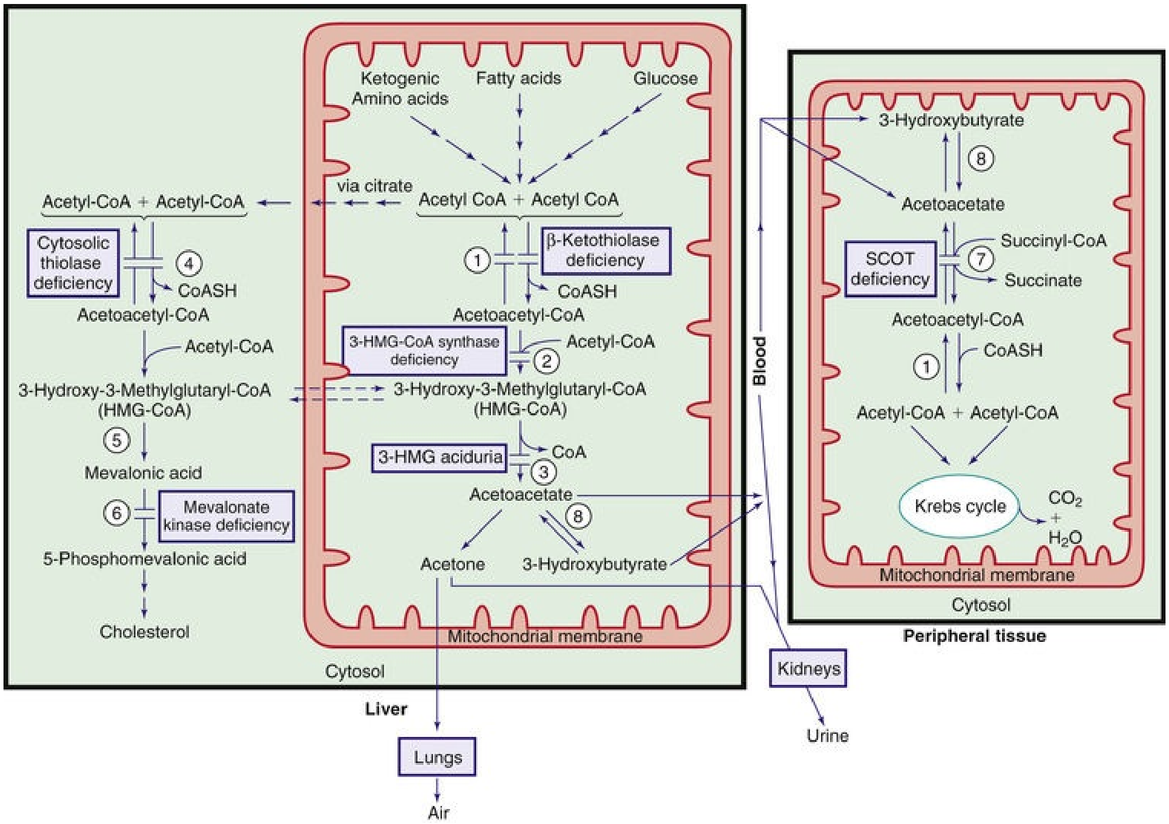
Ketogenic Amino acids
Fatty acids
Glucose
via citrate
Acetyl-CoA + Acetyl-CoA
Acetyl CoA + Acetyl CoA
Cytosolic thiolase deficiency
4
CoASH
Acetoacetyl-CoA
Acetyl-CoA
3-Hydroxy-3-Methylglutaryl-CoA (HMG-CoA)
5
Mevalonic acid
6
Mevalonate kinase deficiency
5-Phosphomevalonic acid
Cholesterol
1
β-Ketothiolase deficiency
CoASH
Acetoacetyl-CoA
3-HMG-CoA synthase deficiency
Acetyl-CoA
2
3-Hydroxy-3-Methylglutaryl-CoA (HMG-CoA)
3-HMG aciduria
CoA
3
Acetoacetate
8
Acetone
3-Hydroxybutyrate
Mitochondrial membrane
Cytosol
Liver
Lungs
Air
Blood
Kidneys
Urine
3-Hydroxybutyrate
8
Acetoacetate
SCOT deficiency
Succinyl-CoA
7
Succinate
Acetoacetyl-CoA
CoASH
1
Acetyl-CoA + Acetyl-CoA
Krebs cycle
CO₂ + H₂O
Mitochondrial membrane
Cytosol
Peripheral tissue

FIG. 103.7 Formation (liver) and metabolism (peripheral tissues) of ketone bodies and cholesterol synthesis. Enzymes: *(1)* Mitochondrial acetoacetyl CoA thiolase, *(2)* HMG-CoA synthase, *(3)* HMG-CoA lyase, *(4)* cytosolic acetoacetyl-CoA thiolase, *(5)* HMG-CoA reductase, *(6)* mevalonic kinase, *(7)* succinyl CoA:3-ketoacid CoA transferase (SCOT), *(8)* 3-hydroxybutyrate dehydrogenase.

Clinical manifestations are quite variable, ranging from mild cases showing normal development to severe episodes of acidosis starting in the 1st yr of life causing severe cognitive impairment. Unless identified on the newborn screening, affected children present with intermittent episodes of unexplained ketoacidosis. These episodes usually occur after an intercurrent infection and typically respond promptly to intravenous fluids and bicarbonate therapy. Mild to moderate hyperammonemia may also be present during attacks. Both hypoglycemia and hyperglycemia have been reported in isolated cases. The child may be completely asymptomatic between episodes and may tolerate a normal protein diet. Cognitive development is normal in most children. The episodes may be misdiagnosed as salicylate poisoning because of the similarity of the clinical findings and the interference of elevated blood levels of acetoacetate with the colorimetric assay for salicylate.

Laboratory findings during the acute attack include ketoacidosis, and hyperammonemia. Findings of ketones in the urine and hyperglycemia may be interpreted as diabetic ketoacidosis, and the high index of suspicion is needed to identify this metabolic disorder. Urine organic acid assay can provide clues leading to correct diagnosis. Urine contains large amounts of 2-methylacetoacetate and its decarboxylated products butanone, 2-methyl-3-hydroxybutyrate, and tiglylglycine. Lower concentrations of urinary metabolites can be seen when patients are stable. Mild hyperglycinemia may also be present. Plasma acylcarnitine profile show elevations of C5 : 1 and C5-OH carnitines, although these metabolites can normalize in between catabolic episodes. Minimal elevations of C5 : 1 and C5-OH carnitines can result in false-negative results on the newborn screening of affected infants who were clinically well at the time of blood collection. The clinical and biochemical findings should be differentiated from those seen with propionic and methylmalonic acidemias (see later).

Treatment of acute episodes includes hydration. Recalcitrant metabolic acidosis can be severe enough to require infusion of bicarbonate. A 10% glucose solution with the appropriate electrolytes is used to suppress protein catabolism, lipolysis, and ketogenesis. Restriction of protein intake to age-appropriate physiologic requirements is recommended for long-term therapy. Oral L-carnitine (50-100 mg/kg/24 hr) is also recommended to prevent possible secondary carnitine deficiency. Long-term prognosis for achieving normal quality of life seems very favorable. Successful pregnancy with a normal outcome has been reported.

β-Ketothiolase deficiency is inherited as an autosomal recessive trait and may be more prevalent than previously appreciated. The gene *(ACAT1)* for this enzyme is located on chromosome 11q22.3. **Diagnosis** may be confirmed by molecular analysis of the *ACAT1* gene or using enzyme assay of leukocytes or cultured fibroblasts.

Cytosolic Acetoacetyl-CoA Thiolase Deficiency

This enzyme catalyzes the cytosolic production of acetoacetyl-CoA from two moles of acetyl-CoA (see Fig. 103.7). Cytosolic acetoacetyl-CoA is the precursor of hepatic cholesterol synthesis. Cytosolic acetoacetyl-CoA thiolase should be differentiated from the mitochondrial thiolase (see earlier and Fig. 103.4). Clinical manifestations in patients with this very rare enzyme deficiency have been incompletely characterized. Patients may present with severe progressive developmental delay, hypotonia, and choreoathetoid movements in the 1st few months of life. Laboratory findings are nonspecific; elevated levels of lactate, pyruvate, acetoacetate, and 3-hydroxybutyrate may be found in blood and urine. One patient had normal levels of acetoacetate and 3-hydroxybutyrate. Diagnosis can be aided by demonstrating a deficiency in cytosolic thiolase activity in liver biopsy or in cultured fibroblasts or by DNA analysis. No effective treatment has been described, although a low-fat diet helped to diminish ketosis in one patient.

Mitochondrial 3-Hydroxy-3-Methylglutaryl-CoA Synthase Deficiency

This enzyme catalyzes synthesis of 3-hydroxy-3-methylglutaryl (HMG)-CoA from acetoacetyl-CoA and acetyl-CoA in the mitochondria. This is a critical step in ketone body synthesis in the liver (see Fig. 103.7). A few patients with deficiency of this enzyme have been reported. The principal clinical syndrome is hypoketotic hypoglycemia triggered by physiologic stress, such as infections or fasting. Age at presentation has ranged from infancy to 6 yr. Children tend to be asymptomatic before these episodes and with appropriate management can remain stable after the recovery (except for mild hepatomegaly with fatty infiltration). Future episodes can be prevented by avoiding prolonged fasting during ensuing intercurrent illnesses. Hepatomegaly is a consistent physical finding in these patients. **Laboratory findings** include hypoglycemia, acidosis with mild or no ketosis, elevated levels in liver function tests, and massive dicarboxylic aciduria. The clinical and laboratory findings may be confused with fatty acid metabolism defects (see Chapter 104.1). In contrast to the latter, in patients with HMG-CoA synthase deficiency the blood concentrations of acylcarnitine conjugates are negative for acylcarnitine findings characteristic of fatty acid oxidation disorders. Treatment of the secondary carnitine deficiency with L -carnitine supplementation can result in elevated plasma acetylcarnitine (C2-carnitine), likely reflecting intracellular accumulation of acetyl-CoA. A controlled fasting study can produce the clinical and biochemical abnormalities.

Treatment consists of provision of adequate calories and avoidance of prolonged periods of fasting. No dietary protein restriction was needed.

The condition is inherited as an autosomal recessive trait. The gene *(HMGCS2)* for this enzyme is located on chromosome 1p12. The condition should be considered in any child with fasting hypoketotic hypoglycemia and may be more common than appreciated.

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (3-Hydroxy-3-Methylglutaric Aciduria)

3-HMG-CoA lyase (see Fig. 103.4) catalyzes the conversion of 3-HMG-CoA to acetoacetate and is a rate-limiting enzyme for ketogenesis (see Fig. 103.7). The deficiency of this enzyme is a rare disorder seen with increased frequency in Saudi Arabia, the Iberian Peninsula, and in Brazil in patients of Portuguese ancestry. Clinically, approximately 30% develop symptoms in the 1st few days of life, and >60% of patients become symptomatic between 3 and 11 mo of age. Infrequently, patients may remain asymptomatic until adolescence. With the addition of 3-HMG-CoA lyase deficiency to the newborn screening using C5-OH-carnitine, many infants are identified presymptomatically in the newborn period. Similar to 3-HMG-CoA synthase deficiency, patients affected by 3-HMG-CoA lyase deficiency may present with acute hypoketotic hypoglycemia. Episodes of vomiting, severe hypoglycemia, hypotonia, acidosis with mild or no ketosis, and dehydration may rapidly lead to lethargy, ataxia, and coma. These episodes often occur during a catabolic state such as prolonged fasting or an intercurrent infection. Hepatomegaly is common. These manifestations may be mistaken for Reye syndrome or fatty acid oxidation defects such as medium-chain acyl-CoA dehydrogenase deficiency. Long-term complications can include dilated cardiomyopathy, hepatic steatosis, and pancreatitis. Development can be normal, but intellectual disability and seizures with abnormalities in the white matter seen on MRI have been observed in patients after prolonged episodes of hypoglycemia.

Laboratory findings include hypoglycemia, moderate to severe hyperammonemia, and acidosis. There is mild or no ketosis (see Fig. 103.7). Urinary excretion of 3-hydroxy-3-methylglutaric acid and other proximal intermediate metabolites of leucine catabolism (3-methylglutaric acid, 3-methylglutaconic acid, and 3-hydroxyisovaleric acid) is markedly increased, causing the urine to smell like *cat urine* . Glutaric and dicarboxylic acids may also be increased in urine during acute attacks. Secondary carnitine deficiency is common. The condition is inherited as an autosomal recessive trait. 3-HMG-CoA lyase is encoded by gene *HMGCL* . **Diagnosis** may be confirmed by molecular analysis of *HMGCL* or by enzyme assay in cultured fibroblasts, leukocytes, or liver specimens. Prenatal diagnosis is possible by molecular DNA analysis if the familial pathogenic variants are known or by enzymatic assay of the cultured amniocytes or a chorionic villi biopsy.

Treatment of acute episodes includes hydration, infusion of glucose to control hypoglycemia, provision of adequate calories, and administration of bicarbonate to correct acidosis. Hyperammonemia should be treated promptly (see Chapter 103.12). Renal replacement therapy may be required in patients with severe recalcitrant hyperammonemia. Restriction of protein and fat intake is recommended for long-term management. Oral administration of L -carnitine (50-100 mg/kg/24 hr) prevents secondary carnitine deficiency. Prolonged fasting should be avoided.

Succinyl-CoA:3-Oxoacid-CoA Transferase Deficiency

Succinyl-CoA:3-oxoacid-CoA transferase (**SCOT**) deficiency and β-ketothiolase deficiency collectively are referred to as **ketone utilization disorders.** SCOT participates in the conversion of ketone bodies (acetoacetate and 3-hydroxybutyrate) generated in liver mitochondria into *acetoacetyl-CoA in* *the nonhepatic tissues* (see Fig. 103.7). A deficiency of this enzyme results in the accumulation of ketone bodies, ketoacidosis, increased utilization of glucose, and hypoglycemia. During fasting, patients tend to have a proportional elevation of plasma free fatty acids. More than 30 patients with SCOT deficiency have been reported to date. The condition may not be rare because many cases may be mild and may remain undiagnosed. SCOT deficiency can be distinguished from β-ketothiolase deficiency by the absence of 2-methylacetoacetate, 2-methyl-3-hydroxybutyrate, and tiglylglycine, characteristic of the latter disorder. Plasma acylcarnitine profile tends to show no specific abnormalities.

A common clinical presentation is an acute episode of severe ketoacidosis in an infant who had been growing and developing normally. About half the patients become symptomatic in the 1st wk of life, and practically all become symptomatic before 2 yr of age. The acute episode is often precipitated by a catabolic state triggered by an infection or prolonged fasting. Without treatment, the ketoacidotic episode can result in death. A chronic subclinical ketosis may persist between the attacks. Development is usually normal, although severe and recurrent episodes of ketoacidosis and hypoglycemia can predispose patients to neurocognitive impairment.

Laboratory findings during the acute episode are nonspecific and include metabolic acidosis and ketonuria with high levels of acetoacetate and 3-hydroxybutyrate in blood and urine. No other organic acids are found in the blood or in the urine. Blood glucose levels are usually normal, but hypoglycemia has been reported in some affected newborn infants with severe ketoacidosis. Plasma amino acids and plasma acylcarnitine profile are usually normal. Severe SCOT deficiency can be accompanied by ketosis even when patients are clinically stable. This condition should be considered in any infant with unexplained bouts of ketoacidosis. **Diagnosis** can be established by molecular analysis of *OXCT1* or by demonstrating a deficiency of enzyme activity in cultured fibroblasts. The condition is inherited as an autosomal recessive trait.

Treatment of acute episodes consists of rehydration with solutions containing dextrose, correction of acidosis, and the provision of a diet adequate in calories. Long-term treatment should include high-carbohydrate diet and avoidance of prolonged fasting and administration of dextrose before anticipated or during established catabolic states.

Mevalonate Kinase Deficiency

Mevalonic acid, an intermediate metabolite of cholesterol synthesis, is converted to 5-phosphomevalonic acid by the action of the enzyme mevalonate kinase (MVK) (see Fig. 103.7). Based on clinical manifestations and degree of enzyme deficiency, 2 conditions have been recognized: mevalonic aciduria and hyperimmunoglobulinemia D syndrome. Both disorders are accompanied by recurrent fever, gastrointestinal symptoms, mucocutaneous manifestations, and lymphadenopathy. Patients with mevalonic aciduria also show growth retardation and nervous system involvement. In practice, the 2 disorders represent the 2 ends of the spectrum.

Mevalonic Aciduria

Clinical manifestations include failure to thrive, growth retardation, intellectual disability, hypotonia, ataxia, myopathy, hepatosplenomegaly, cataracts, and facial dysmorphisms (dolichocephaly, frontal bossing, low-set ears, downward slanting of eyes, long eyelashes). Most patients experience recurrent crises characterized by fever, vomiting, diarrhea, hepatosplenomegaly, arthralgia, lymphadenopathy, edema, and morbilliform rash. These episodes typically last 2-7 days and recur up to 25 times a year. Death may occur during these crises.

Laboratory findings include marked elevation of mevalonic acid in urine; the concentration of urinary mevalonic acid ranges between 500 and 56,000 mmol/mol of creatinine (normal: <0.3 mmol/mol of creatinine). Plasma levels of mevalonic acid are also greatly increased (as high as 540 µmol/L; normal: <0.04 µmol/L). Mevalonic acid levels tend to correlate with the severity of the condition and increase during crises. Serum cholesterol concentration is normal or mildly decreased. Serum concentration of creatine kinase can be greatly increased. Inflammatory markers are elevated during the crises. Brain MRI may reveal progressive atrophy of the cerebellum.

Diagnosis may be confirmed by DNA analysis or by assaying the MVK activity in lymphocytes or cultured fibroblasts. The enzyme activity in this form of the condition is below the detection level. **Treatment** with high doses of prednisone helps in the acute crises, but due to side effects, it is not routinely used long term. *Etanercept* (tumor necrosis factor inhibitor) and *anakinra* (interleukin-1 receptor antagonist) have shown to be effective in bringing significant clinical improvement. The condition is inherited as an autosomal recessive trait. **Prenatal diagnosis** is possible by identifying known familiar pathogenic variants in *MVK*, by measurement of mevalonic acid in the amniotic fluid, or by assaying the enzyme activity in cultured amniocytes or chorionic villi samples. The gene (*MVK*) for the enzyme is on chromosome 12q24.11.

Hyperimmunoglobulinemia D Syndrome (Hyperimmunoglobulinemia D and Periodic Fever Syndrome)

Some pathogenic variants of mevalonic kinase gene *(MVK)* cause milder enzyme deficiency and produce the clinical picture of periodic fever with hyperimmunoglobulinemia D. These patients have periodic bouts of fever associated with abdominal pain, vomiting, diarrhea, arthralgia, arthritis, hepatosplenomegaly, lymphadenopathy, and morbilliform rash (even petechiae and purpura), which usually start before 1 yr of age. The attacks can be triggered by vaccination, minor trauma, or stress and can occur every 1-2 mo, lasting 2-7 days. Patients are free of symptoms between acute attacks. The diagnostic laboratory finding is elevation of serum immunoglobulin D (IgD). IgA is also elevated in 80% of patients. During acute attacks, leukocytosis, increased C-reactive protein, and mild mevalonic aciduria may be present. High concentrations of serum IgD help differentiate this condition from familial Mediterranean fever. See Chapter 188 for treatment recommendations.

Propionic Acidemia (Propionyl-CoA Carboxylase Deficiency)

Propionic acid is an intermediate metabolite of isoleucine, valine, threonine, methionine, odd-chain fatty acids, and side chains of cholesterol. Normally, propionic acid in the form of propionyl-CoA undergoes carboxylation to D -methylmalonyl-CoA, catalyzed by the mitochondrial enzyme propionyl-CoA carboxylase. This enzyme requires biotin as a cofactor; thus the disorders of biotin metabolism, among other findings, can also result in elevation of propionic acid metabolites (see Fig. 103.4). Propionyl-CoA carboxylase is a multimeric enzyme composed of 2 nonidentical subunits, α and β, encoded by 2 genes, *PCCA* and *PCCB* , respectively. Pathogenic variants in propionyl-CoA carboxylase result in the disorder called propionic acidemia.

Clinical findings of propionic acidemia are not specific to this disorder only.

In the severe form, patients develop symptoms in the 1st few days of life. Poor feeding, vomiting, hypotonia, lethargy, dehydration, a sepsis-like picture, and clinical signs of severe ketoacidosis progress rapidly to coma and death. Seizures occur in approximately 30% of affected infants. If an infant survives the first attack, similar episodes of metabolic decompensation may occur during an intercurrent infection, trauma, surgery, prolonged fasting, severe constipation, or after ingestion of a high-protein diet. Moderate to severe intellectual disability and neurologic manifestations reflective of extrapyramidal (dystonia, choreoathetosis, tremor) and pyramidal (paraplegia) dysfunction are common sequelae in the survivors. Neuroimaging shows that these abnormalities, which often occur after an episode of metabolic decompensation, are the result of damage to the basal ganglia, especially to the globus pallidus. This phenomenon has been referred to as **metabolic stroke** . This is the main cause of neurologic sequelae seen in the surviving affected children. Additional long-term complications include failure to thrive, optic nerve atrophy, pancreatitis, cardiomyopathy, and osteopenia.

In the *milder* form, episodes of metabolic decompensation are less frequent, but these children are still at risk to develop intellectual disability, seizures, long QTc interval, and severe cardiomyopathy. Universal newborn screening can identify propionic acidemia by detecting elevated propionylcarnitine (C3) in dried blood spots. However, in patients with the mild form of propionic acidemia, propionylcarnitine could remain below the cutoff value set by the screening laboratory, resulting in a false-negative result. Therefore, physicians should maintain a high index of suspicion for this disorder and follow up with a biochemical evaluation of infants and children presenting with unexplained ketosis or metabolic acidosis.

Laboratory findings during the acute attack include various degrees of metabolic acidosis, often with a large anion gap, ketosis, ketonuria, hypoglycemia, anemia, neutropenia, and thrombocytopenia. Moderate to severe hyperammonemia is common; plasma ammonia concentrations usually correlate with the severity of the disease. In contrast to other causes of hyperammonemia, plasma concentration of glutamine tends to be within normal limits or decreased. Presence of severe metabolic acidosis and normal to reduced plasma glutamine help differentiate propionic academia from hyperammonemia caused by urea cycle defects. Measurement of plasma ammonia is especially helpful in planning therapeutic strategy during episodes of exacerbation in a patient whose diagnosis has been established. Mechanisms of hyperammonemia in propionic acidemia are not well understood but are likely related to the perturbed biochemical and pH environment of the mitochondrial matrix, where the proximal part of urea cycle resides. **Glycine** concentration can be elevated in all body fluids (blood, urine, CSF) and possibly are the result of the inhibited glycine cleavage system in the hepatic mitochondria (Fig. 103.8). Glycine elevation has also been observed in patients with methylmalonic acidemia. These disorders were collectively referred to as *ketotic hyperglycinemia* in the past before the specific enzyme deficiencies were elucidated. Mild to moderate increase in blood lactate and lysine may also be present in these patients. Concentrations of propionylcarnitine, 3-hydroxypropionic acid, and methylcitric acid (presumably formed through condensation of propionyl-CoA with oxaloacetic acid) are greatly elevated in the plasma and urine of infants with propionic acidemia. Propionylglycine and other intermediate metabolites of branched-chain amino acid catabolism, such as tiglylglycine, can also be found in urine. Moderate elevations in blood levels of glycine, and previously mentioned organic acids can persist between the acute attacks. Brain imaging may reveal cerebral atrophy, delayed myelination, and abnormalities in the globus pallidus and other parts of the basal ganglia.

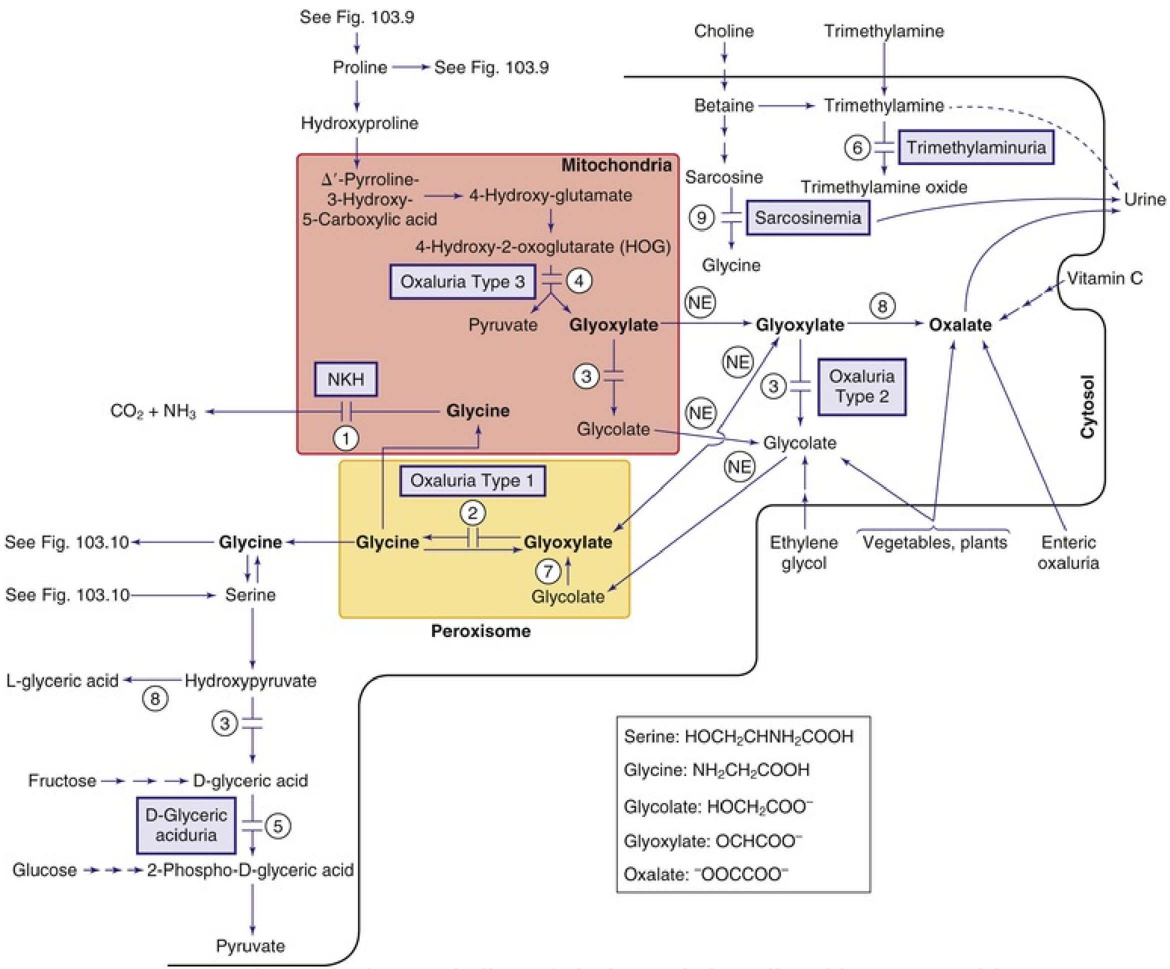
See Fig. 103.9
Proline
See Fig. 103.9
Hydroxyproline
Mitochondria
Δ′-Pyrroline-3-Hydroxy-5-Carboxylic acid
4-Hydroxy-glutamate
4-Hydroxy-2-oxoglutarate (HOG)
Oxaluria Type 3
4
Pyruvate
Glyoxylate
NKH
3
CO₂ + NH₃
Glycine
1
Glycolate
Oxaluria Type 1
2
See Fig. 103.10
Glycine
Glycine
Glyoxylate
7
See Fig. 103.10
Serine
Glycolate
Peroxisome
L-glyceric acid
Hydroxypyruvate
8
3
Fructose
D-glyceric acid
D-Glyceric aciduria
5
Glucose
2-Phospho-D-glyceric acid
Pyruvate
Choline
Trimethylamine
Betaine
Trimethylamine
6
Trimethylaminuria
Sarcosine
Trimethylamine oxide
9
Sarcosinemia
Urine
Glycine
Vitamin C
NE
Glyoxylate
8
Oxalate
NE
3
Oxaluria Type 2
NE
Glycolate
NE
Cytosol
Ethylene glycol
Vegetables, plants
Enteric oxaluria
Serine: HOCH₂CHNH₂COOH
Glycine: NH₂CH₂COOH
Glycolate: HOCH₂COO⁻
Glyoxylate: OCHCOO⁻
Oxalate: ⁻OOCCOO⁻

FIG. 103.8 Pathways in the metabolism of glycine and glyoxylic acid. Enzymes: *(1)* Glycine cleavage system, *(2)* alanine:glyoxylate aminotransferase, *(3)* glyoxylic reductase/hydroxypyruvate reductase (GR/HRP), *(4)* hydroxyoxoglutarate aldolase 1 (HOGA1), *(5)* glycerate kinase, (*6)* trimethylamine oxidase, *(7)* glycolate oxidase (D - amino acid oxidase), *(8)* lactate dehydrogenase, *(9)* sarcosine dehydrogenase. NE, Nonenzymatic; NKH, nonketotic hyperglycinemia.

The **diagnosis** of propionic acidemia should be differentiated from multiple carboxylase deficiencies (see earlier and Fig. 103.6). In addition to propionic acid metabolites, infants with the latter condition excrete large amounts of lactic acid, 3-methylcrotonylglycine, and 3-hydroxyisovaleric acid. The presence of hyperammonemia may suggest a genetic defect in the urea cycle enzymes. Infants with defects in the urea cycle are usually *not* acidotic (see Fig. 103.1) and have elevated levels of plasma glutamine. The definitive diagnosis of propionic acidemia can be established through molecular analysis of *PCCA* and *PCCB* or by measuring the enzyme activity in leukocytes or cultured fibroblasts.

Treatment of acute episodes of metabolic decompensation includes hydration with solutions containing glucose, correction of acidosis, and amelioration of the catabolic state by provision of adequate calories through enteral or parenteral hyperalimentation. A brief restriction of protein intake, no more than 24 hr, is often necessary. Depending on the clinical status, gradual reintroduction of protein is recommended. If enteral feedings cannot be tolerated after 48 hours of protein restriction, parenteral nutrition should be instituted to achieve the age-specific recommended dietary protein intake. Patients unable to tolerate the recommended dietary allowance of protein can receive specialized medical foods free of isoleucine, valine, threonine, and methionine. The composition and the amount of protein vary among patients. The metabolic diet composition can be adjusted by monitoring growth and plasma amino acids drawn 3-4 hr after the typical feeding. Some patients may benefit from the suppression of propionogenic gut microflora. This can be achieved by oral antibiotics such as oral neomycin or metronidazole. Prolonged use of metronidazole should be avoided because it has been associated with reversible peripheral neuropathy and increased QTc interval. The risk of QTc prolongation can be problematic in propionic acidemia patients, who are at risk for cardiomyopathy and long QT interval. Baseline and interval electrocardiograms (ECGs) are recommended before and after initiation of the metronidazole therapy. Patients may benefit from management of constipation.

Patients with propionic acidemia often develop secondary carnitine deficiency, presumably as a result of the urinary loss of propionylcarnitine. Administration of L -carnitine (50-100 mg/kg/24 hr orally or intravenously) helps restore free carnitine in blood. In patients with concomitant hyperammonemia, measures to reduce blood ammonia should be employed (see Chapter 103.12). Very ill patients with severe acidosis and hyperammonemia require hemodialysis to remove ammonia and other toxic compounds rapidly and efficiently. *N* -carbamoylglutamate (carglumic acid) and nitrogen scavengers (sodium benzoate, sodium phenylacetate, sodium phenylbutyrate) can aid in the treatment of acute hyperammonemia. Although no infant with propionic acidemia has been found to be responsive to biotin, this compound should be administered (10 mg/24 hr orally) to all infants during the first attack and until the diagnosis is established and multiple carboxylase deficiency ruled out.

Long-term treatment consists of a low-protein diet meeting age-specific recommended dietary allowance and administration of L -carnitine (50-100 mg/kg/24 hr orally). Some centers manage mild cases of propionic acidemia without medical foods, opting for only restricting the protein intake to recommended dietary allowance. Patients unable to tolerate the recommended dietary intake of protein may require medical foods free of propionate precursors (isoleucine, valine, methionine, and threonine). Excessive use of medical foods while restricting natural-source protein may cause a deficiency of the essential amino acids, especially isoleucine and valine, which may cause a condition resembling **acrodermatitis enteropathica** (see Chapter 691). Overrestriction of methionine, especially in the 1st years of life, may contribute to the reduced brain growth and microcephaly. To avoid this problem, natural proteins should comprise most of the dietary protein. Some patients may require bicarbonate substitution (e.g., citric acid/sodium citrate) to correct chronic acidosis. The concentration of plasma ammonia usually normalizes between attacks, although some patients may experience mild chronic hyperammonemia. Acute attacks triggered by infections, fasting, trauma, stress, constipation, or dietary indiscretions should be treated promptly and aggressively. Close monitoring of plasma ammonia, plasma amino acids obtained 3-4 hr after the last typical meal (especially isoleucine, leucine, valine, threonine, and methionine), and growth parameters is necessary to ensure the diet is appropriate. Orthotopic liver transplantation is used in clinically unstable patients experiencing recurrent hyperammonemia, frequent metabolic decompensations, and poor growth. Liver transplantation does not cure propionic acidemia, and lifelong dietary management and proactive management during periods of significant metabolic stress are recommended.

Long-term **prognosis** is guarded. Death may occur during an acute attack. Normal psychomotor development is possible in the mild form identified through newborn screening. Children identified clinically may manifest some degree of permanent neurodevelopmental deficit, such as tremor, dystonia, chorea, and spasticity despite adequate therapy. These neurologic findings may be the sequelae of a metabolic stroke occurring during an acute decompensation. Long QTc interval as well as cardiomyopathy with potential progression to heart failure, fatal arrhythmias, and death may develop in older affected children despite adequate metabolic control. Acute pancreatitis is a common and severe complication in propionic acidemia. Osteoporosis can predispose to fractures, which can occur even after minimal mechanical stress.

Prenatal diagnosis can be achieved by identification of the known familial pathogenic variants in *PCCA* or *PCCB* or by measuring the enzyme activity in cultured amniotic cells or in samples of uncultured chorionic villi.

Propionic acidemia is inherited as an autosomal recessive trait and has a worldwide prevalence of 1 : 105,000 to 1 : 250,000 live births. It is more prevalent in Greenlandic Inuits (1 : 1,000) and in some Saudi Arabian tribes (1 :

2,000 to 1 : 5,000 live births). The gene for the α-subunit *(PCCA)* is located on chromosome 13q32.3 and that of the β-subunit *(PCCB)* is mapped to chromosome 3q22.3. Pathogenic variants in either gene result in similar clinical and biochemical manifestations. Although pregnancies with normal outcomes have been reported, the perinatal period poses special risks to females with propionic acidemia because of hyperemesis gravidarum, worsening cardiomyopathy, changing protein requirements, and risk of metabolic decompensation.

Isolated Methylmalonic Acidemias

Methylmalonic acidemias are a group of metabolic disorders of diverse etiology characterized by impaired conversion of methylmalonyl-CoA into succinyl-CoA. Propionyl-CoA derived from catabolism of isoleucine, valine, threonine, methionine, side chain of cholesterol, and odd-chain fatty acids is catalyzed by propionyl-CoA carboxylase to form D -methylmalonyl-CoA. Methylmalonyl-CoA epimerase then converts D -methylmalonyl-CoA to its enantiomer L -methylmalonyl-CoA. **Methylmalonyl-CoA epimerase deficiency** is a rare disorder associated with persistent elevations of propionate-related metabolites and methylmalonic acid. It may present with metabolic acidosis, ketosis, but known patients appear more clinically stable than those with severe forms of methylmalonic acidemia.

In the next biochemical step, L -methylmalonyl-CoA is converted to succinyl-CoA by methylmalonyl-CoA mutase (see Fig. 103.4). The latter enzyme requires adenosylcobalamin, a metabolite of vitamin B_{12} , as a coenzyme. Deficiency of either the mutase or its coenzyme results in the accumulation of methylmalonic acid and its precursors in body fluids. Two biochemical forms of methylmalonyl-CoA mutase deficiencies have been identified. These are designated mut^0 , referring to no detectable enzyme activity, and mut^- , indicating residual, although insufficient, mutase activity. Patients with methylmalonic acidemia due to deficiency of the mutase apoenzyme (mut^0) are not responsive to hydroxocobalamin therapy.

In the remaining methylmalonic acidemia patients, the defect resides in the formation of adenosylcobalamin from dietary vitamin B_{12} . The absorption of dietary vitamin B_{12} in the terminal ileum requires *intrinsic factor,* a glycoprotein secreted by the gastric parietal cells. It is transported in the blood by haptocorrin and transcobalamin II. The transcobalamin II–cobalamin complex (TCII-Cbl) is recognized by a specific receptor on the cell membrane (transcobalamin receptor encoded by *CD320*) and enters the cell by endocytosis. In the lysosome, TCII-Cbl is hydrolyzed, and, with the participation of LMBRD1 (*cbl* F) and ABCD4 (*cbl* J), free cobalamin is released into the cytosol (see Fig. 103.4). Pathogenic variants in either *LMBRD1* or *ABCD4* genes result in impaired release of cobalamin from lysosomes. In the cytoplasm, cobalamin binds to the MMACHC protein (see *cbl* C later), which removes a moiety attached to cobalt in the cobalamin molecule and reduces the cobalt from oxidation state +3 (cob[III]alamin) to +2 (cob[II]alamin). It then enters the mitochondria, where it is catalyzed by MMAB (*cbl* B) and MMAA (*cbl* A) to form adenosylcobalamin, a coenzyme for methylmalonyl-CoA mutase. The other arm of the pathway directs cytosolic cobalamin toward methionine synthase reductase (*cbl* E), which forms methylcobalamin, acting as a coenzyme for methionine synthase (*cbl* G, see Fig. 103.3). The MMADHC protein (see *cbl* D) appears to play a role in determining whether cobalamin enters the mitochondria or remains in the cytoplasm.

The uptake of TCII-Cbl by cells is impaired in individuals with pathogenic variants affecting transcobalamin receptor *(CD320)*, which is located on the cell surface. Individuals homozygous for pathogenic variants in the *CD320* gene encoding the transcobalamin receptor may have mild elevations of methylmalonic acid in blood and urine. These patients can be identified by the newborn screen based on the elevated propionylcarnitine (C3). In **transcobalamin receptor deficiency** , methylmalonic acid levels and plasma propionylcarnitine tend to normalize in the 1st yr of life. It is not clear whether there is a long-term clinical phenotype associated with this defect.

Nine different defects in the intracellular metabolism of cobalamin have been identified. These are designated *cbl* A through *cbl* G, *cbl* J, and *cbl* X, where *cbl* stands for a defect in any step of cobalamin metabolism. The *cbl* A, *cbl* B, and *cbl* D variant 2 defects cause methylmalonic acidemia *alone* . In patients with *cbl* C, classic *cbl* D, *cbl* F, *cbl* J, and *cbl* X defects, synthesis of both adenosylcobalamin and methylcobalamin is impaired, resulting in *combined* methylmalonic acidemia and homocystinuria. The *cbl* D variant 1, *cbl* E, and the *cbl* G defects affect only the synthesis of methylcobalamin, resulting in homocystinuria without methylmalonic aciduria (see Chapter 103.3).

Biochemical manifestations of patients with isolated methylmalonic acidemia caused by *mut* ^{0} , *mut* $^{-}$, *cbl* A, *cbl* B, and *cblD* variant 2 overlap. The wide variations in severity of clinical course range from very sick newborn infants to apparently asymptomatic adults. In **severe** forms, lethargy, feeding problems, vomiting, a sepsis-like picture, tachypnea (from metabolic ketoacidosis), and hypotonia may develop in the 1st few days of life and may progress to hyperammonemic encephalopathy, coma, and death if left untreated. Infants who survive the first attack may go on to develop similar acute metabolic episodes during a catabolic state such as infection or prolonged fasting or after ingestion of a high-protein diet. In certain situations, such acute events can cause a sudden injury of the basal ganglia (movement centers in CNS), a metabolic stroke, resulting in a debilitating movement disorder. Between the acute attacks, the patient usually continues to exhibit hypotonia and feeding problems with failure to thrive, while other complications of the disease occur with age, including recurrent episodes of pancreatitis, bone marrow suppression, osteopenia, and optic nerve atrophy. Chronic renal failure and tubulointerstitial nephritis necessitating renal transplant have been reported in older patients. Renal complications are more severe in patients with the *mut* ^{0} and severe *cbl* B forms of methylmalonic acidemia. In milder forms, patients may present later in life with hypotonia, failure to thrive, and developmental delay. Neurocognitive development of patients with mild methylmalonic acidemia may remain within the normal range.

The episodic nature of the condition and its biochemical abnormalities in some patients may be confused with those of *ethylene glycol* (antifreeze) ingestion. The peak of propionate in a blood sample from an infant with methylmalonic acidemia has been mistaken for ethylene glycol when the sample was assayed by gas chromatography without mass spectrometry.

Laboratory findings include ketosis, metabolic acidosis, hyperglycinemia, hyperammonemia, hypoglycemia, anemia, neutropenia, thrombocytopenia, and the presence of large quantities of methylmalonic acid in body fluids (see Fig. 103.6). Metabolites of propionic acid (3-hydroxypropionate and methylcitrate) are also found in the urine. Plasma acylcarnitine profile reveals elevated propionylcarnitine (C3) and methylmalonylcarnitine (C4DC). Hyperammonemia in methylmalonic acidemia may be confused with a urea cycle disorder. However, patients with defects in urea cycle enzymes are typically not acidotic and tend to have high plasma glutamine (see Fig. 103.12). The reason for hyperammonemia is not well understood, but it is likely related to the inhibition of proximal urea cycle in the mitochondrial matrix.

Diagnosis can be confirmed by identifying pathogenic variants in the causal gene, by measuring propionate incorporation with complementation analysis in cultured fibroblasts, and by measuring the specific activity of the mutase enzyme in biopsies or cell extracts.

Treatment of acute attacks is similar to propionic acidemia. Long-term treatment consists of administration of a low-protein diet limited to the recommended dietary allowance, L -carnitine (50-100 mg/kg/24 hr orally). Patients with severe forms of methylmalonic acidemia may require protein diet modifications similar to those prescribed for patients with propionic acidemia. Patients with isolated methylmalonic acidemia caused by defects in the intracellular metabolism of cobalamin (*cbl* A, *cblD* variant 2, and some patients with *cbl* B) respond to parenteral hydroxocobalamin. Chronic bicarbonate replacement therapy is usually required to correct chronic acidosis. Plasma ammonia tends to normalize between the attacks, and chronic treatment of hyperammonemia is rarely needed. Stressful situations that may trigger acute attacks (infection, prolonged fasting, trauma, surgeries, high-protein meals) should be treated promptly.

Inadequate oral intake secondary to poor appetite, protein overrestriction, or essential amino acid deficiencies are common complications in long-term management of these patients. Consequently, enteral feeding through gastrostomy is often recommended early in the course of treatment. Close monitoring of blood pH, essential amino acid levels, blood and urinary concentrations of methylmalonate, and growth parameters is required to ensure the nutritional prescription meets patient's metabolic demands. In addition, frequent monitoring of kidney function, vision, hearing, and bone mineral density are necessary for early recognition and management of chronic complications. Glutathione deficiency responsive to treatment with ascorbate has been described.

Liver, kidney, and combined liver-kidney transplantations have been attempted in an increasing number of affected patients. Liver and liver-kidney transplantation can alleviate but not eliminate the metabolic abnormalities. Liver and liver-kidney transplants do not provide complete protection against the occurrence of metabolic stroke. Kidney transplantation alone can restore the renal function but results in only minor improvement of the clinical stability of patients.

Prognosis depends on the severity of symptoms and the occurrence of complications. In general, patients with complete deficiency of mutase apoenzyme (*mut* ^{0}) and severe forms of *cbl* B deficiency have the least favorable prognosis, and those with *mut*$^{-}$ and *cbl* A defects have a better outcome.

Methylmalonic acidemia can be identified on the universal newborn screening by measuring propionylcarnitine (C3) using tandem mass spectrometry. The prevalence of all forms of methylmalonic aciduria is estimated at 1 : 50,000 to 1 : 100,000 live births. All defects causing isolated methylmalonic acidemia are inherited as autosomal recessive traits. The gene for the mutase *(MUT)* is on the short arm of chromosome 6p12.3. Neonates with methylmalonic acidemia and severe diabetes caused by β-cell agenesis, who have paternal uniparental isodisomy of chromosome 6, have been reported. Pathogenic variants in the genes for *cbl* A (*MMAA,* on chromosome 4q31.21), *cbl* B (*MMAB,* on chromosome 12q24.11), and all forms of *cbl* D (*MMADHC,* on chromosome 2q23.2) have been identified in affected patients. The previously described *cbl* H group is identical to *cbl* D variant 2.

Combined Methylmalonic Aciduria and Homocystinuria (*cbl* C, *cbl* D, *cbl* F, *cbl* J, and *cbl* X Defects)

Combined methylmalonic acidemia and homocystinuria caused by *cbl* C deficiency is the most common type of intracellular cobalamin (vitamin B_{12}) biosynthesis defects. Deficiency of *cbl* C is as common as methylmalonyl-CoA mutase deficiency. The other disorders (*cbl* D, *cbl* F, *cbl* J, *cbl* X) are much rarer (see Figs. 103.3 and 103.4). Neurologic findings are prominent in patients with *cbl* C, *cbl* D and *cbl* X defects. Most patients with the *cbl* C defect present in the 1st mo of life because of failure to thrive, lethargy, poor feeding, developmental delay, nystagmus and seizures. Hyperammonemia may be seen infrequently, while hyperglycinemia is not present, unlike in isolated *mut* -type methylmalonic acidemia. Intrauterine growth restriction and microcephaly suggest that *cbl* C can manifest prenatally in some affected infants. Late-onset patients with sudden development of dementia and myelopathy have been reported, even with presentation in adulthood. Megaloblastic anemia is a common finding in patients with *cbl* C defect. Mild to moderate increases in concentrations of methylmalonic acid and significant elevations in total plasma homocysteine are found in blood. Unlike classic homocystinuria, in untreated *cbl* C patients plasma methionine is low to normal. Retinal abnormalities (e.g., bull's eye maculopathy) resulting in severe progressive vision loss are common and can be seen as early as 3 mo of age, even in prospectively identified and well-treated patients. **Thrombotic microangiopathy** can present as hemolytic uremic syndrome, pulmonary hypertension, and cor pulmonale. Hydrocephalus, and non-compaction cardiomyopathy have been reported as complications in patients with *cbl* C defect.

Similar to *cblC* patients, males with *cbl* X have elevations of both total plasma homocysteine and methylmalonic acid, but they tend to have milder elevations of these metabolites. Unlike *cbl* C-deficient patients, who tend to respond to treatment, *cbl* X-deficient patients experience failure to thrive, severe developmental delay, and intractable epilepsy despite aggressive treatment.

Clinical findings in *cbl* F deficiency are quite variable. Patients may present with poor feeding, growth and developmental delay, and persistent stomatitis manifesting in the 1st mo of life. Delay in diagnosis and treatment can be accompanied by hyperpigmentation of skin, developmental delay, intellectual disability, and short stature. Vitamin B_{12} malabsorption and low plasma vitamin B_{12} has been noted in patients with *cbl* F defect. Clinical manifestations of *cbl* J defect show significant overlap with those of the *cbl* F deficiency. Dysmorphic features and congenital heart disease have been reported in some patients with *cbl* F and *cbl* J defects.

Experience with **treatment** of patients with *cbl* C, *cbl* D, *cbl* F, *cblJ,* and *cbl* X defects is limited. Large doses of hydroxocobalamin (up to 0.3 mg/kg/day) in conjunction with betaine (up to 250 mg/kg/day) produce biochemical improvement with variable clinical effect. Patients with *cbl* F and *cbl* J deficiency typically show favorable biochemical and clinical response to smaller hydroxocobalamin doses (1 mg once weekly to 1 mg daily parenterally). Folic or folinic acid supplementation is recommended. Dietary methionine deficiency should be avoided.

The *cbl* C disorder is caused by pathogenic variants in the *MMACHC* gene (on chromosome 1p34.1). A frameshift variant (c.271dupA) is seen in up to 40% of *MMACHC* alleles and is associated with a less favorable clinical outcome. The *cbl* D disorder is caused by pathogenic variants in the *MMADHC* gene (on chromosome 2q23.2). Pathogenic variants resulting in *cbl* D variant 1 (causing only homocystinuria) affect the C-terminal domain of the gene product; those resulting in *cbl* D variant 2 (causing only methylmalonic aciduria) affect the N-terminus. Patients with classic *cbl* D, with both homocystinuria and methylmalonic acidemia, have pathogenic variants resulting in decreased protein expression. The *cbl* F disorder is caused by pathogenic variants in the *LMBRD1* gene (on chromosome 6q13) encoding a lysosomal membrane protein. The *cbl* J disorder is associated with pathogenic variants in the *ABCD4* gene (on chromosome 14q24.3), encoding an adenosine triphosphate–binding cassette protein localized to the lysosomal membrane. The *cbl* X disorder is caused by pathogenic variants in the *HCFC1* gene on the X chromosome (Xq28), which encodes a transcription factor that appears to be essential for expression of the *MMACHC* gene. This is the only X-linked disorder in the B_{12} intracellular metabolism pathway.

Isolated Homocystinuria

Patients with *cbl* D variant 1, *cbl* E, and *cbl* G deficiency present with isolated homocystinuria without methylmalonic acidemia (see Chapter 103.3 , Homocystinuria Caused by Defects in Methylcobalamin Formation).

Combined Malonic and Methylmalonic Aciduria (*ACSF3* -Related Disorder)

C ombined *m* alonic and *m* ethyl*m* alonic *a* ciduria (**CMAMMA**) is a rare autosomal recessive disorder resulting from pathogenic variants in *ACSF3* . ACSF3 is a putative acyl-CoA synthetase required for the conversion of malonic and methylmalonic acids to their CoA derivatives in the mitochondrial matrix. The disorder can be suspected based on the presence of elevated malonic and methylmalonic acids in urine and plasma. It is distinguished from malonyl-CoA decarboxylase, because methylmalonic acid is about 5-fold greater than malonic acid in the urine. Plasma propionylcarnitine (C3-carnitine) in CMAMMA patients is normal, so universal newborn screening programs using C3-carnitine in blood spots to screen for methylmalonic acidemia would not detect this condition. The clinical phenotype is incompletely understood. Young patients identified prospectively in infancy through urine-based newborn screening were reported to be asymptomatic, but the long-term outcome in this cohort awaits further characterization. Older patients ascertained clinically have highly variable presentations, including metabolic crises, failure to thrive, seizures, memory problems, optic nerve or spinal cord atrophy, and progressive neurodegeneration. Treatment of CMAMMA is supportive and includes avoidance of an excessively high-protein diet. Vitamin B_{12} supplementation does not appear to lower malonic and methylmalonic metabolites in body fluids.

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103.7

Glycine

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Glycine is a nonessential amino acid synthesized mainly from serine and threonine. Structurally, it is the simplest amino acid. Glycine is involved in many reactions in the body, especially in the nervous system, where it functions as a neurotransmitter (excitatory in the cortex, inhibitory in the brainstem and the spinal cord; see Chapter 103.11). Its main catabolic pathway requires the *glycine cleavage system,* a pyridoxal phosphate–dependent, mitochondrial enzyme complex that converts glycine to carbon dioxide and ammonia and transfers α-carbon to tetrahydrofolate (see Fig. 103.8). The glycine cleavage system is composed of 4 proteins: P protein (glycine decarboxylase), H protein, T protein, and L protein, which are encoded by 4 different genes.

Hypoglycinemia

Defects in the biosynthetic pathway of serine (see Chapter 103.8) cause deficiency of glycine in addition to that of serine in body fluids, especially in the cerebrospinal fluid (CSF). Isolated primary deficiency of glycine has not been reported.

Hyperglycinemia

Elevated levels of glycine in body fluids occur in propionic acidemia, methylmalonic acidemia, isovaleric acidemia, and β-ketothiolase deficiency, which are collectively referred to as *ketotic hyperglycinemia* because of the coexistence of acidosis and ketosis. The pathogenesis of hyperglycinemia in these disorders is not fully understood, but inhibition of the glycine cleavage enzyme system by the various organic acids has been shown to occur in some of these patients. The term **nonketotic hyperglycinemia (NKH)** is reserved for the clinical condition caused by the genetic deficiency of the glycine cleavage enzyme system (see Fig. 103.8). In this condition, hyperglycinemia is present without ketosis.

Nonketotic Hyperglycinemia (Glycine Encephalopathy)

Four forms of NKH have been identified: neonatal, infantile, late onset, and transient.

Neonatal Nonketotic Hyperglycinemia

This is the most common form of NKH. Clinical manifestations develop in the 1st few days of life (between 6 hr and 8 days after birth). Poor feeding, failure to suck, lethargy, and profound hypotonia may progress rapidly to a deep coma, apnea, and death. Convulsions, especially myoclonic seizures and hiccups, are common.

Laboratory findings reveal moderate to severe hyperglycinemia (as high as 8 times normal) and hyperglycinuria. The unequivocal elevation of glycine concentration in CSF (15-30 times normal) and the high ratio of glycine concentration in CSF to that in plasma (a value >0.08, normal <0.02) are diagnostic of NKH. Affected patients' blood pH is usually normal, and urine assay is negative for organic acids. CSF serine levels can be low.

Approximately 30% of NKH infants die despite supportive therapy. Those who survive develop profound psychomotor retardation and intractable seizure disorders (myoclonic and/or grand mal seizures). Hydrocephalus, requiring shunting, and pulmonary hypertension have been noted in some survivors. In some patients the hyperglycemia is transient.

Infantile Nonketotic Hyperglycinemia

These previously normal infants develop signs and symptoms of neonatal NKH after 6 mo of age. Seizures and hypotonia are the common presenting signs. Infantile NKH appears to be a milder form of neonatal NKH; infants usually survive, and intellectual disability is not as profound as in the neonatal form.

Laboratory findings in patients with infantile NKH are identical to those seen in neonatal NKH.

Late-Onset Nonketotic Hyperglycinemia

Clinical manifestations of this atypical form of NKH include progressive spastic diplegia, optic nerve atrophy, and choreoathetotic movements. Age of onset has been between 2 and 33 yr. Symptoms of delirium, chorea, and vertical gaze palsy may occur episodically in some patients during an intercurrent infection. Mental development is usually normal, but mild cognitive impairment and infrequent seizures have been reported in some patients.

Laboratory findings in late-onset NKH are similar but not as pronounced as in neonatal NKH.

All forms of NKH should be differentiated from *ketotic* hyperglycinemia, pyridox(am)ine phosphate oxidase (PNPO) deficiency, ingestion of valproic acid, and transient glycine encephalopathy. Valproic acid can moderately increase blood, CSF, and urinary concentrations of glycine. Repeat assays after discontinuation of the drug will help establish the diagnosis.

Transient Nonketotic Hyperglycinemia

Most clinical and laboratory manifestations of transient NKH are indistinguishable from those of the neonatal form. By 2-8 wk of age, however, a complete clinical recovery may occur, and the elevated glycine levels in plasma and CSF normalize after the patient stops a glycine-lowering medication. Some of these patients develop normally with no neurologic sequelae, but intellectual disability has been noted in others. The etiology of this condition is not known, but it is thought to be a consequence of immaturity of the enzyme system.

Diagnosis and Treatment

Diagnosis of NKH can be suspected based on the findings of elevated glycine in plasma or CSF and the abnormal CSF/plasma ratio of glycine. The diagnosis is confirmed using molecular analysis of the NKH-related genes. Rarely, assay of the enzyme in liver or brain specimens is necessary to establish the diagnosis. Enzyme activity in the neonatal form is close to zero, whereas in the other forms, some residual activity is present. In most patients with neonatal NKH, the enzyme defect resides in the P protein (75%); defects in the T protein account for approximately 20% of cases, whereas <1% are caused by pathogenic variants in the H protein.

No effective treatment is known. Exchange transfusion, dietary restriction of glycine, and administration of sodium benzoate or folate have not altered the neurologic outcome in severe forms of NKH. Patients with attenuated NKH may experience clinical improvement from enteral sodium benzoate. Drugs that counteract the effect of glycine on neuronal cells, such as dextromethorphan and felbamate, have shown some beneficial effects in patients with the mild forms of the condition.

NKH is inherited as an autosomal recessive trait. The prevalence is not known, but high frequency of the disorder has been noted in northern Finland (1 in 12,000 live births) suggesting that this disorder is likely underdiagnosed. The gene for P protein *(GLDC)* is on chromosome 9p24.1. The gene encoding T protein *(AMT)* is on chromosome 3p21.31 and that for H protein *(GCSH)* is mapped to chromosome 16q23.2. The L protein gene *(DLD)* on chromosome 7q31.7 encodes dihydrolipoamide dehydrogenase, the E3 component of α-ketoacid dehydrogenase complexes and is discussed in Chapter 103.6 (Valine, Leucine, Isoleucine, and Related Organic Acidemias). **Prenatal diagnosis** has been accomplished by identification of the known familial pathogenic variants in the affected gene or by performing an assay of the enzyme activity in chorionic villus biopsy specimens.

Sarcosinemia

Increased concentrations of sarcosine (*N* -methylglycine) are observed in both blood and urine, but no consistent clinical picture has been attributed to sarcosinemia. This autosomal recessive metabolic condition is caused by a defect in sarcosine dehydrogenase, the enzyme that converts sarcosine to glycine (see Fig. 103.8). The gene for this enzyme (*SARDH*) is on chromosome 9q34.2.

Primary Trimethylaminuria

Trimethylamine is normally produced in the intestine from the breakdown of dietary choline and trimethylamine oxide by bacteria. Egg yolk and liver are the main sources of choline, and fish is the major source of trimethylamine oxide. Trimethylamine is absorbed and oxidized in the liver by trimethylamine oxidase (flavin-containing monooxygenases) to trimethylamine oxide, which is odorless and excreted in the urine (see Fig. 103.8). Deficiency of this enzyme results in massive excretion of trimethylamine in urine. There is a body odor that resembles that of a fish, which may have significant social and psychosocial ramifications. Transient symptomatic trimethylaminuria can occur in normal individuals following ingestion of large quantities of the above mentioned foods. **Treatment** with oral activated charcoal, short courses of oral metronidazole, neomycin, or lactulose cause temporary reduction in the body odor. Restriction of fish, eggs, liver, and other sources of choline (e.g., nuts, grains) in the diet significantly reduces the odor. Topical use of acidic soaps (pH 5.5) can also help control the odor. The gene for trimethylamine oxidase (*FMO3*) has been mapped to chromosome 1q24.3.

Hyperoxaluria and Oxalosis

Normally, oxalic acid is derived mostly from oxidation of glyoxylic acid and, to a lesser degree, from oxidation of ascorbic acid (see Fig. 103.8). Glyoxylic acid is formed from oxidation of glycolic acid and glycine in the peroxisomes, and catabolism of **hydroxyproline** in the mitochondria (Fig. 103.9). Vegetables and foods containing oxalic acid, such as spinach, rhubarb, and almond milk, are the main *exogenous* sources of glycolic and oxalic acids; most of glyoxylic and oxalic acids are produced endogenously. Normally, a major portion of glyoxylate produced in the body is shuttled to peroxisomes, where it is converted to glycine by the action of the enzyme alanine:glyoxylate transaminase. Deficiency of this enzyme causes hyperoxaluria **type 1** . Most of the remaining glyoxylate in the cytosol is reduced to glycolate by the action of the enzyme glyoxylate reductase/hydroxypyruvate reductase. Deficiency of this enzyme causes hyperoxaluria **type 2** . These 2 pathways protect the body from excessive production of oxalic acid (see Fig. 103.8). Any glyoxylate that cannot be disposed of through these pathways is readily converted to oxalic acid by the action of the enzyme lactate dehydrogenase (LDH). Oxalic acid cannot be further metabolized in humans and is excreted in the urine as oxalates. Calcium oxalate is relatively insoluble in water and precipitates in tissues (kidneys and joints) if its concentration increases in the body.

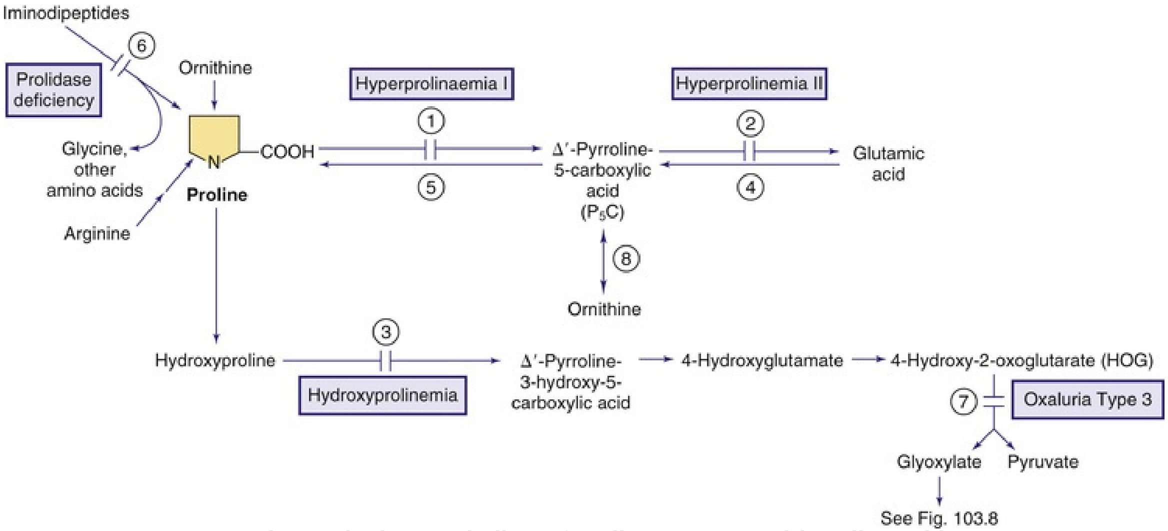
Iminodipeptides
⑥
Prolidase deficiency
Ornithine
Hyperprolinaemia I
Hyperprolinemia II
①
②
Glycine, other amino acids
N
COOH
Proline
Δ′-Pyrroline-5-carboxylic acid (P₅C)
Glutamic acid
⑤
④
Arginine
⑧
Ornithine
③
Hydroxyproline
Hydroxyprolinemia
Δ′-Pyrroline-3-hydroxy-5-carboxylic acid
4-Hydroxyglutamate
4-Hydroxy-2-oxoglutarate (HOG)
⑦
Oxaluria Type 3
Glyoxylate
Pyruvate
See Fig. 103.8

FIG. 103.9 **Pathways in the metabolism of proline. Enzymes: *(1)* Proline oxidase (dehydrogenase), *(2)* Δ^1 -pyrroline-5-carboxylic acid (P5C) dehydrogenase, *(3)* hydroxyproline oxidase, *(4)* Δ^1 -pyrroline-5-carboxylic acid (P5C) synthase, *(5)* Δ^1 -pyrroline-5-carboxylic acid (P5C) reductase, *(6)* prolidase, *(7)* 4-hydroxyoxoglutarate aldolase 1 (HOGA1), *(8)* ornithine aminotransferase.**

Secondary hyperoxaluria has been observed in pyridoxine deficiency (cofactor for alanine:glyoxylate transaminase), in patients with inflammatory bowel disease, extensive resection of small bowel, or jejunoileal bypass (*enteric* *hyperoxaluria*), after ingestion of ethylene glycol or high doses of vitamin C, and after administration of the anesthetic agent methoxyflurane (which oxidizes directly to oxalic acid). Acute, fatal hyperoxaluria may develop after ingestion of plants with high oxalic acid content (e.g., sorrel) or intentional ingestion of oxalic acid. Precipitation of calcium oxalate in tissues causes hypocalcemia, liver necrosis, renal failure, cardiac arrhythmia, and death. The lethal dose of oxalic acid is estimated at 5-30 g.

Primary hyperoxaluria is a group of disorders in which large amounts of oxalates accumulate in the body. Three types of primary hyperoxaluria have been identified to date. The term **oxalosis** refers to deposition of calcium oxalate in parenchymal tissues.

Primary Hyperoxaluria Type 1

This rare condition (prevalence of 1 : 120,000 live births in Europe) is the most common form of primary hyperoxaluria. It is caused by deficiency of the peroxisomal enzyme alanine:glyoxylate transaminase, which is expressed only in the liver peroxisomes and requires pyridoxine (vitamin B_6) as a cofactor. In the absence of this enzyme, glyoxylic acid, which cannot be converted to glycine, is transferred to the cytosol, where it is oxidized to oxalic acid (see earlier and Fig. 103.8).

The age of presentation varies widely, from neonatal period to late adulthood. The majority of patients become symptomatic in late childhood or early adolescence. In about 20% of cases, symptoms develop before 1 yr of age. The initial clinical manifestations are related to renal stones and nephrocalcinosis. Renal colic and asymptomatic hematuria lead to a gradual deterioration of renal function, manifested by growth retardation and uremia. If the disorder is left untreated, most patients die before 20 yr of age from renal failure. Other frequent manifestations of the disease include failure to thrive, short stature, arterial calcifications, arrhythmia, heart failure, hypothyroidism, and skin nodules. Acute arthritis is a rare manifestation and may be misdiagnosed as gout because uric acid is usually elevated in patients with type 1 hyperoxaluria. Crystalline retinopathy and optic neuropathy causing visual loss have occurred in a few patients.

A marked increase in urinary excretion of oxalate (normal excretion: 10-50 mg/24 hr) is the most important laboratory finding. The presence of oxalate crystals in urinary sediment is rarely helpful for diagnosis because such crystals can also be seen in normal individuals. Urinary excretion of glycolic acid and glyoxylic acid is increased in most but not all patients. Diagnosis can be confirmed by identification of pathogenic variants in the *AGXT* gene or by performing an enzymatic assay in liver specimens.

Treatment focuses on the reduction of oxalic acid production and on increasing calcium oxalate disposal. Patients with primary hyperoxaluria type 1 should receive a 3-mo trial of pyridoxine treatment to establish pyridoxine responsiveness. In up to 30% of patients (e.g., homozygous for pathogenic variant c.508G>A in *AGXT*), administration of large doses of pyridoxine reduces plasma level and urinary excretion of oxalate. To increase calcium oxalate disposal and prevent nephrolithiasis, high oral fluid intake (2-3 L/m^2 /24 hr while controlling for fluid balance), urine alkalinization, phosphate supplementation, monitoring of vitamin C and vitamin D intake, and avoidance of drugs that increase urinary calcium excretion (e.g., loop diuretics) are recommended. Urinary stones should be managed by experienced urologists because excessive surgical trauma may contribute to renal dysfunction. Renal function replacement strategies (e.g., hemodialysis) are used in some patients (e.g., to bridge patients to transplant or when transplant is not a viable option).

Organ **transplantation** has emerged as the most definitive treatment. The decision to undergo kidney, liver, or liver-kidney transplant is complex and may vary from one medical center to another. Except for older patients with pyridoxine-responsive form of disease, renal transplantation for patients in renal failure may not improve the outcome, because oxalosis will recur in the transplanted kidney. Combined liver-kidney transplants have resulted in a significant decrease in plasma and urinary oxalate and thus may be the most effective treatment strategy in this disorder, particularly in children.

The condition is inherited as an autosomal recessive trait. The gene for this enzyme *(AGXT)* is mapped to chromosome 2q37.3. The most common pathogenic variant in patients with high residual enzyme activity (c.508G>A, p.Gly170Arg) results in mistargeting of the enzyme to the mitochondria instead of the peroxisomes and loss of in vivo function. **Prenatal diagnosis** has been achieved by DNA analysis of chorionic villus samples or by the measurement of fetal hepatic enzyme activity obtained by needle biopsy.

Primary Hyperoxaluria Type 2 (l-Glyceric Aciduria)

This rare condition is caused by a deficiency of the glyoxylate reductase–hydroxypyruvate reductase enzyme complex (see Fig. 103.8). A deficiency in the activity of this complex results in an accumulation of two intermediate metabolites, hydroxypyruvate (the ketoacid derivative of serine) and glyoxylic acid. Both these compounds are further metabolized by LDH to L -glyceric acid and oxalic acid, respectively. A high prevalence of this disorder is reported in the Saulteaux-Ojibway Indians of Manitoba.

Primary hyperoxaluria type 2 results in the deposition of calcium oxalate in the renal parenchyma and urinary tract. Renal stones presenting with renal colic and hematuria may develop before age 2 yr. Renal failure is less common in this condition than in primary hyperoxaluria type 1.

Urinary testing reveals large amounts of L -glyceric acid in addition to high levels of oxalate. Urinary L -glyceric acid is considered a pathognomonic finding in primary hyperoxaluria type 2. Urinary excretion of glycolic acid and glyoxylic acid is not increased. The presence of L -glyceric acid without increased levels of glycolic and glyoxylic acids in urine differentiates this type from type 1 hyperoxaluria. Diagnosis can be confirmed by molecular analysis of *GRHPR* (9p13.2) or by the enzyme assay in liver biopsy.

Principles of therapy are similar to those in primary hyperoxaluria type 1. Renal transplant is used in some patients; no experience with kidney-liver transplantation is available at this time.

Primary Hyperoxaluria Type 3

Approximately 10% of patients with primary hyperoxaluria have deficiency of 4-hydroxy-2-oxoglutarate aldolase 1 (HOGA1), the underlying cause of hyperoxaluria type 3. The enzyme is encoded by *HOGA1* mapped to chromosome 10q24.2. This mitochondrial enzyme catalyzes the final step in the metabolic pathway of hydroxyproline generating pyruvate and glyoxylate from 4-hydroxy-2-oxoglutarate (HOG; see Figs. 103.8 and 103.9). In vitro studies show inhibition of glyoxylate reductase–hydroxypyruvate reductase enzyme activity by high concentration of HOG that accumulates in patients with hyperoxaluria type 3. This inhibition results in a biochemical phenotype similar to hyperoxaluria type 2 (see Fig. 103.8).

Patients with primary hyperoxaluria type 3 usually presented with calcium oxalate kidney stones in early childhood, but asymptomatic older siblings were also identified. Gradually, renal function may decline, infrequently resulting in end-stage renal disease. Increased levels of HOG in urine, serum, and liver biopsy samples of these patients is the distinguishing feature of this disorder. **Treatment** involves high oral fluid intake, management of oral citrate or phosphate intake to prevent calcium oxalate renal stone formation, and avoidance of dehydration to prevent acute kidney injury. In severe forms of this disorder, dialysis and transplantation may be required to address the end-stage renal disease.

Creatine Deficiency Disorders

Creatine is synthesized mainly in the liver, pancreas, and kidneys and to a lesser degree in the brain from arginine and glycine and is transported to muscles and the brain, where there is high activity of the enzyme creatine kinase (Fig. 103.10). Phosphorylation and dephosphorylation of creatine in conjunction with adenosine triphosphate and diphosphate provide high-energy phosphate transfer reactions in these organs. Creatine is nonenzymatically metabolized to creatinine at a constant daily rate and is excreted in the urine. Three genetic conditions are known to cause creatine deficiency in the brain and other tissues. Two enzymes, arginine:glycine amidinotransferase (**AGAT**) and guanidinoacetate methyltransferase (**GAMT** ; Fig. 103.10), are involved in the biosynthesis of creatine. Both conditions may respond to creatine supplementation, especially when the treatment is started in early age. The 3rd condition, an X-linked inherited defect, is caused by deficiency of the creatinine transporter (CRTR) protein mediating uptake of creatine by brain and muscle.

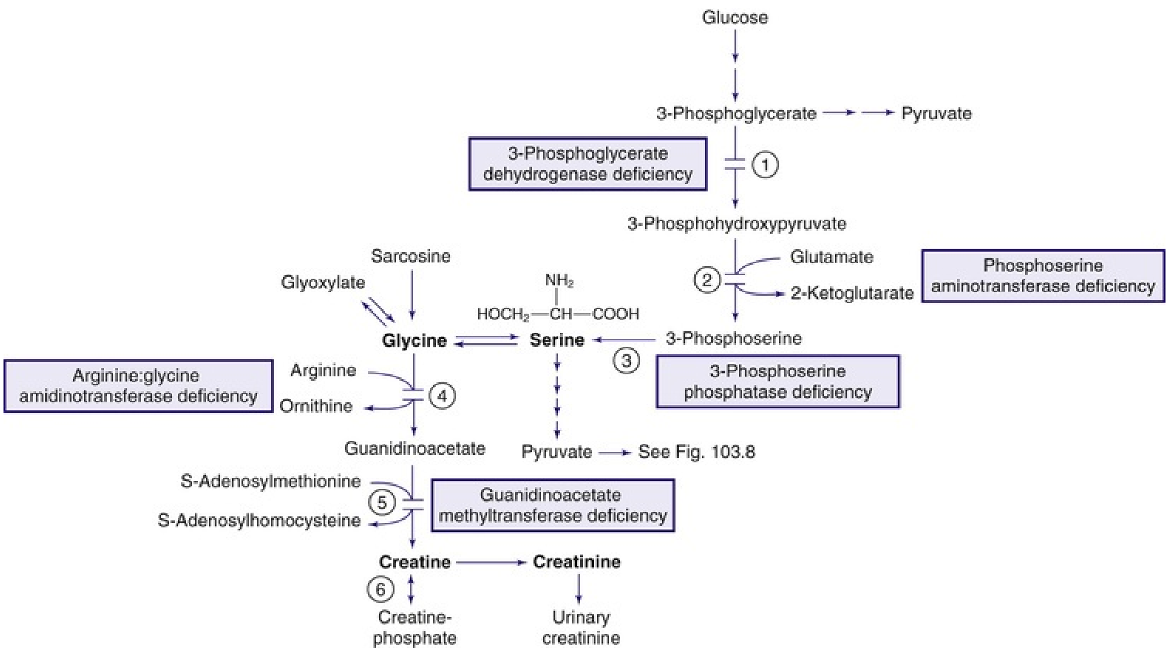
Glucose
3-Phosphoglycerate
Pyruvate
3-Phosphoglycerate dehydrogenase deficiency
①
3-Phosphohydroxypyruvate
Glutamate
②
2-Ketoglutarate
Phosphoserine aminotransferase deficiency
Sarcosine
Glyoxylate
NH2
HOCH2—CH—COOH
Glycine
Serine
3-Phosphoserine
③
3-Phosphoserine phosphatase deficiency
Arginine:glycine amidinotransferase deficiency
Arginine
Ornithine
④
Guanidinoacetate
Pyruvate
See Fig. 103.8
S-Adenosylmethionine
⑤
S-Adenosylhomocysteine
Guanidinoacetate methyltransferase deficiency
Creatine
Creatinine
⑥
Creatine-phosphate
Urinary creatinine

FIG. 103.10 **Biosynthesis of serine and creatine. Enzymes: *(1)* 3-Phosphoglycerate dehydrogenase, *(2)* 3-phosphoserine aminotransferase, *(3)* 3-phosphoserine phosphatase, *(4)* arginine:glycine amidinotransferase (AGAT), *(5)* guanidinoacetate methyltransferase (GAMT), *(6)* creatine kinase.**

Clinical manifestations of the 3 defects overlap, relate to the brain and muscle, and may appear in the 1st few wk or mo of life. Developmental delay, intellectual disability, speech delay, psychiatric symptoms (autism and psychosis), hypotonia, ataxia, and seizures are common findings. Dystonic movements have been documented in GAMT and CRTR deficiency.

Laboratory findings include decreased creatine in plasma in patients with AGAT and GAMT defects. Plasma creatinine level alone is insufficient to diagnose these disorders. Secondary to impaired reabsorption of creatine in kidneys, the urinary ratio of creatine to creatinine is increased in male patients with a CRTR defect but can also be mildly elevated in female carriers. Marked elevations of guanidinoacetate in blood, urine, and especially in CSF, are diagnostic of GAMT defects. In contrast, low levels of guanidinoacetate can be found in body fluids in the AGAT defect. Absence of creatine and creatine phosphate (in all 3 defects) and high levels of guanidinoacetate (in GAMT defect) can be demonstrated in the brain by magnetic resonance spectroscopy (MRS). Brain MRI may show signal hyperintensity in the globus pallidus. Diagnosis of AGAT deficiency or GAMT deficiency may be confirmed by DNA analysis or by measuring of enzymatic activity in cultured fibroblasts (GAMT) or lymphoblasts (AGAT). Diagnosis of CRTR deficiency can be confirmed by DNA analysis or a creatine uptake assay in fibroblasts.

The outcomes of **treatment** are age-dependent and best with treatment started in the neonatal period or presymptomatically. In AGAT-deficient patients, oral creatine monohydrate (up to 400-800 mg/kg/24 hr) may improve muscle weakness in most and neurocognitive outcomes in some patients. In GAMT-deficient patients, supplementation with oral creatine monohydrate (up to 400-800 mg/kg/24 hr), ornithine (up to 400-800 mg/kg/24 hr), and dietary arginine restriction may result in improved muscle tone and neurocognitive development and may alleviate seizures. In CRTR-deficient patients, administration of creatine and its precursors (arginine and glycine) does not restore creatine in the brain, but some patients may experience improvements of seizures and neurocognitive outcomes.

AGAT and GAMT defects are inherited as autosomal recessive traits. The gene for AGAT *(GATM)* is on chromosome 15q21.1 and that for GAMT *(GAMT)* is on chromosome 19p13.3. CRTR is an X-linked disorder and the gene *(SLC6A8)* is on Xq28. CRTR defect is the most common cause of creatine deficiency, accounting for up to 1–2% of males with intellectual disability of unknown cause.

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103.8

Serine Deficiency Disorders (Serine Biosynthesis and Transport Defects)

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Keywords

serine
phosphoglycerate dehydrogenase
PHGDH
PGDH
phosphoserine aminotransferase
PSAT
PSAT1
3-phosphoserine phosphatase
PSP
Neu-Laxova syndrome
serine transporter
ASCT1
SLC1A4

Serine is a nonessential amino acid supplied through dietary sources and through its endogenous synthesis, mainly from glucose and glycine. The endogenous production of serine comprises an important portion of the daily requirement of this amino acid, especially in the synaptic junctions where it contributes to the metabolism of phospholipids as well as D -serine and glycine, both involved in neurotransmission (see Chapter 103.11). Consequently, deficiency of any of the enzymes involved in the biosynthesis of serine or its transport causes neurologic manifestations. The clinical spectrum of serine deficiency disorders is wide and varies from Neu-Laxova syndrome on the severe end of spectrum to epilepsy and developmental delay on the milder end. Affected patients respond favorably to oral supplementation with serine and glycine provided that the treatment is initiated very early in life. Figs. 103.8 and 103.10 show the metabolic pathway for synthesis and catabolism of serine.

3-Phosphoglycerate Dehydrogenase Deficiency

3-Phosphoglycerate dehydrogenase (**PHGDH**) deficiency has a broad range of symptoms and ages of presentation. **Neu-Laxova syndrome type 1** is the most severe manifestation and presents prenatally with intrauterine growth restriction and congenital anomalies, including dysmorphic facial features, microcephaly, CNS malformations, limb deformities, and ichthyosis. Most patients with this form are stillborn or have early neonatal mortality. Infantile-onset PHGDH deficiency presents with feeding problems, failure to thrive, vomiting, irritability, intractable seizures, severe developmental delay, and hypertonia progressing to spastic quadriplegia. Nystagmus, cataracts, hypogonadism, and megaloblastic anemia have been observed in some affected infants. Patients with a milder form of this disorder experience cognitive impairment, behavioral problems, sensorineural polyneuropathy, and childhood-onset seizures.

Laboratory findings include low fasting levels of serine and glycine in plasma and very low levels of serine and glycine in CSF. No abnormal organic acid metabolite is found in the urine. MRI of the brain shows cerebral atrophy with enlarged ventricles, significant attenuation of white matter, and impaired myelination. **Diagnosis** can be confirmed by DNA analysis or by measurement of the enzyme activity in cultured fibroblasts. **Treatment** with high doses of serine (200-700 mg/kg/24 hr orally) and glycine (200-300 mg/kg/24 hr) normalizes the serine levels in the blood and CSF. When started postnatally, this treatment may improve seizures, spasticity, and brain myelination. One case report suggests that developmental delay may be prevented if the treatment commences in the 1st days of life or prenatally.

The condition is inherited as an autosomal recessive trait. The gene for 3-phosphoglycerate dehydrogenase enzyme *(PHGDH)* has been mapped to chromosome 1p12. If familial pathogenic variants are known, molecular **prenatal diagnosis** is possible. Administration of serine to the mother carrying an affected fetus was associated with stabilization of the fetal head circumference, as evidenced by ultrasound. Treatment with supplemental serine has continued postnatally; the patient remained normal neurologically at 4 yr of age. The favorable response of this condition to a relatively straightforward treatment makes this diagnosis an important consideration in any child with microcephaly and neurologic defects such as psychomotor delay or a seizure disorder. Measurements of serine and glycine in the CSF are critical for diagnosis because mild decreases of these amino acids in the plasma can be easily overlooked.

Phosphoserine Aminotransferase Deficiency

Phosphoserine aminotransferase 1 (**PSAT1**) catalyzes conversion of 3-phosphohydroxypyruvate to 3-phosphoserine (see Fig. 103.10). Deficiency of this enzyme may present in the neonatal period with poor feeding, cyanotic episodes, and irritability and may progress to intractable, multifocal seizures and microcephaly. Brain imaging may reveal generalized cerebral and cerebellar atrophy. Laboratory studies done on postprandial plasma samples may reveal normal or mildly decreased levels of serine and glycine. Serine and glycine levels are usually more depressed on the CSF amino acid analysis. **Treatment** with serine and glycine as outlined earlier may result in clinical improvement. The condition is inherited as an autosomal recessive trait, and the gene *(PSAT1)* is mapped to chromosome 9q21.2.

3-Phosphoserine Phosphatase

Deficiency

3-Phosphoserine phosphatase catalyzes the final step in the L -serine synthesis converting 3-phosphoserine to L -serine. Deficiency of this enzyme results in a rare disorder with clinical and biochemical findings indistinguishable from the PHGDH and PSAT1 deficiencies. The disorder is caused by autosomal recessive pathogenic variants in *PSPH* mapped to chromosome 7p11.2.

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103.9

Proline

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Keywords

proline
hydroxyproline
hyperprolinemia
hyperprolinemia type 1
proline oxidase
PRODH
hyperprolinemia type 2
aldehyde dehydrogenase 4
ALDH4A1
pyrroline-5-carboxylate
P5C
prolidase
prolidase deficiency
PEPD
De novo proline synthesis
pyrroline-5-carboxylate synthase
P5C synthase
ALDH18A1
pyrroline-5-carboxylate reductase
PYCR1
de Barsy syndrome

Proline is a nonessential amino acid synthesized endogenously from glutamic acid, ornithine, and arginine (see Fig. 103.9). Proline and hydroxyproline are found in high concentrations in collagen. Normally, neither of these amino acids is found in large quantities in urine. Excretion of proline and hydroxyproline as *iminopeptides* (dipeptides and tripeptides containing proline or hydroxyproline) is increased in disorders of accelerated collagen turnover, such as rickets or hyperparathyroidism. Proline is also found in synapses, where it can interact with glycine and glutamate receptors (see Chapter 103.11). The catabolic pathway of proline and hydroxyproline produces glyoxylic acid, which can be further metabolized to glycine or oxalic acid (see Fig. 103.8).

Accumulation of proline in tissues is associated with disorders of hyperprolinemia type 1 and hyperprolinemia type 2. Reduced de novo synthesis of proline causes syndromes manifesting with **cutis laxa** (see Fig. 678.8) with **progeroid features** or **spastic paraplegia** . Two types of primary hyperprolinemia have been described.

Hyperprolinemia Type I

This rare autosomal recessive condition is caused by deficiency of proline oxidase (proline dehydrogenase; see Fig. 103.9). Most patients with hyperprolinemia type 1 appear asymptomatic, although some may present with intellectual disability, seizures, and behavioral problems. Hyperprolinemia may also be a risk factor for autism spectrum disorders and schizophrenia. The nature of such wide phenotypic range in this biochemical condition has not been elucidated. The gene encoding proline oxidase *(PRODH)* is mapped to 22q11.2 and is located within the critical region for the **velocardiofacial syndrome** . Laboratory studies reveal high concentrations of proline in plasma, urine, and CSF. Increased urinary excretion of hydroxyproline and glycine is also present, which could be related to saturation of the shared tubular reabsorption mechanism due to massive prolinuria.

No effective treatment has yet emerged. Restriction of dietary proline causes modest improvement in plasma proline with no proven clinical benefit.

Hyperprolinemia Type II

This is a rare autosomal recessive condition caused by the deficiency of Δ^1 -pyrroline-5-carboxylate dehydrogenase (aldehyde dehydrogenase 4; see Fig.

103.9). Intellectual disability and seizures (usually precipitated by an intercurrent infection) have been reported in affected children, but asymptomatic patients have also been described. The cause for such disparate clinical outcomes is incompletely understood. The gene encoding P5C dehydrogenase *(ALDH4A1)* is mapped to chromosome 1p36.13.

Laboratory studies reveal increased concentrations of proline and Δ^1 -pyrroline-5-carboxylic acid (P5C) in blood, urine, and CSF. The presence of P5C differentiates this condition from hyperprolinemia type I. Increased level of P5C in body fluids, especially in the CNS, appears to antagonize vitamin B_6 and lead to vitamin B_6 dependency (see Chapter 103.14). Vitamin B_6 dependency may be the main cause of seizures and neurologic findings in this condition and may explain the variability in clinical manifestations in different patients. **Treatment** with high doses of vitamin B_6 is recommended.

Prolidase Deficiency

During collagen degradation, imidodipeptides are formed and are normally cleaved by tissue prolidase. Deficiency of prolidase, which is inherited as an autosomal recessive trait, results in the accumulation of imidodipeptides in body fluids. Age at onset varies from 6 mo to the 3rd decade of life.

The **clinical manifestations** of this rare condition also vary and include recurrent, severe, and painful skin ulcers, which are typically on hands and legs. Other skin lesions that may precede ulcers by several years may include a scaly erythematous maculopapular rash, purpura, and telangiectasia. Most ulcers become infected. Healing of the ulcers may take months. Other findings include developmental delays, intellectual disability, organomegaly, anemia, thrombocytopenia, and immune dysfunction resulting in increased susceptibility to infections (recurrent otitis media, sinusitis, respiratory infection, splenomegaly). Some patients may have craniofacial abnormalities such as ptosis, ocular proptosis, hypertelorism, small beaked nose, and prominent cranial sutures. Asymptomatic cases have also been reported. Increased incidence of systemic lupus erythematosus has been noted in children. High levels of urinary excretion of imidodipeptides are diagnostic. The gene for prolidase *(PEPD)* has been mapped to chromosome 19q13.11. The diagnosis can be confirmed using DNA analysis. Enzyme assay may be performed in erythrocytes or cultured skin fibroblasts.

Treatment of prolidase deficiency is supportive. Infectious complications can be fatal and warrant close and proactive antibiotic management. Oral supplementation with proline, ascorbic acid, and manganese and topical proline and glycine have not been found to be consistently effective in all patients.

Disorders of De Novo Proline Synthesis

De novo synthesis of proline and ornithine from glutamate appears to be critical in the normal biology of connective tissue and to maintain urea cycle in a repleted state. Correspondingly, clinical manifestations of these disorders encompass connective tissue abnormalities, nervous system abnormalities, and variable biochemical abnormalities reflecting urea cycle dysfunction. This section summarizes clinical and laboratory findings associated with the deficient function of Δ^1 -pyrroline-5-carboxylate (P5C) synthase (see Fig. 103.9) encoded by *ALDH18A1* (mapped to 10q24.1) and PSC reductase encoded by *PYCR1* (mapped to 17q25.3).

Deficient activity of P5C synthase has been associated with several phenotypes, including **de Barsy syndrome** , characterized by cataracts, growth retardation, intellectual disability, a prematurely aged appearance (progeroid features), and cutis laxa. Some patients may show pyramidal signs. Skin biopsy may reveal decreased size of elastic fibers and collagen abnormalities. Brain imaging studies show cortical atrophy, ventriculomegaly, and reduced creatine. Laboratory findings include reduced levels of proline, ornithine, citrulline, and arginine as well as mild fasting hyperammonemia. Patients may show only intermittent abnormalities of plasma amino acids, likely related to the time of blood sampling in relation to the last meal. Interestingly, both autosomal recessive and autosomal dominant forms of inheritance have been described. The diagnosis can be suspected in a patient presenting with cutis laxa, developmental delay, mild hyperammonemia, and amino acid abnormalities. The diagnosis can be confirmed using molecular DNA analysis or using the glutamine loading test on skin fibroblasts. Treatment is supportive, although supplementation with citrulline or arginine to address hyperammonemia and cerebral creatine depletion have been proposed.

Deleterious mutations in *PYCR1* result in the abnormal function of the mitochondrial Δ^1 -pyrroline-5-carboxylate reductase, which catalyzes the last step in the synthesis of proline from P5C. The most consistent finding in patients carrying proven pathogenic variants in *PYCR1* include triangular facies, cutis laxa (**de Barsy–like syndrome**), joint hypermobility, wrinkled skin, gerodermia osteodysplastica, and progeroid features. Skin biopsy reveals reduction of the elastic fibers and infiltration with inflammatory cells. Some patients may have epilepsy, developmental delays, intellectual disability, cataracts, osteopenia, and failure to thrive. However, many of the affected families are consanguineous, thus confounding the phenotype. Of note, plasma amino acid analysis typically reveals no specific abnormalities. The diagnosis depends on the recognition of the skin findings and can be confirmed using molecular DNA analysis. Available pedigrees of families affected by *PYCR1* -related disorder supports the autosomal recessive mode of inheritance.

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103.10

Glutamic Acid

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Keywords

glutamic acid
glutamate
γ-glutamylcysteinylglycine
glutathione
γ-glutamyl cycle
glutathione synthetase
GSSD
5-oxoprolinase
OPLAH
glutamate-cysteine ligase
γ-glutamylcysteine synthetase
GCLC
γ-glutamyl transpeptidase
GGT
glutathionemia
hemolytic anemia
5-oxoproline
5-oxoprolinemia

high–anion gap metabolic acidosis
5-oxoprolinuria
secondary 5-oxoprolinuria

Glutamic acid and its amide derivative glutamine have a wide range of functions in the body. *Glutamate* plays numerous biologic roles, functioning as a neurotransmitter, an intermediate compound in many fundamental biochemical reactions, and a precursor of an inhibitory neurotransmitter γ-aminobutyric acid (GABA) (see Chapter 103.11). Another major product of glutamate is *glutathione* (γ-glutamylcysteinylglycine). This ubiquitous tripeptide, with its function as the major antioxidant in the body, is synthesized and degraded through a complex cycle called the γ-glutamyl cycle (Fig. 103.11). Because of its free sulfhydryl (–SH) group and its abundance in the cell, glutathione protects other sulfhydryl-containing compounds (e.g., enzymes, coenzyme A) from oxidation. It is also involved in the detoxification of peroxides, including hydrogen peroxide, and in keeping the intracellular milieu in a reduced state. In addition, glutathione participates in amino acid transport across the cell membrane through the γ-glutamyl cycle.

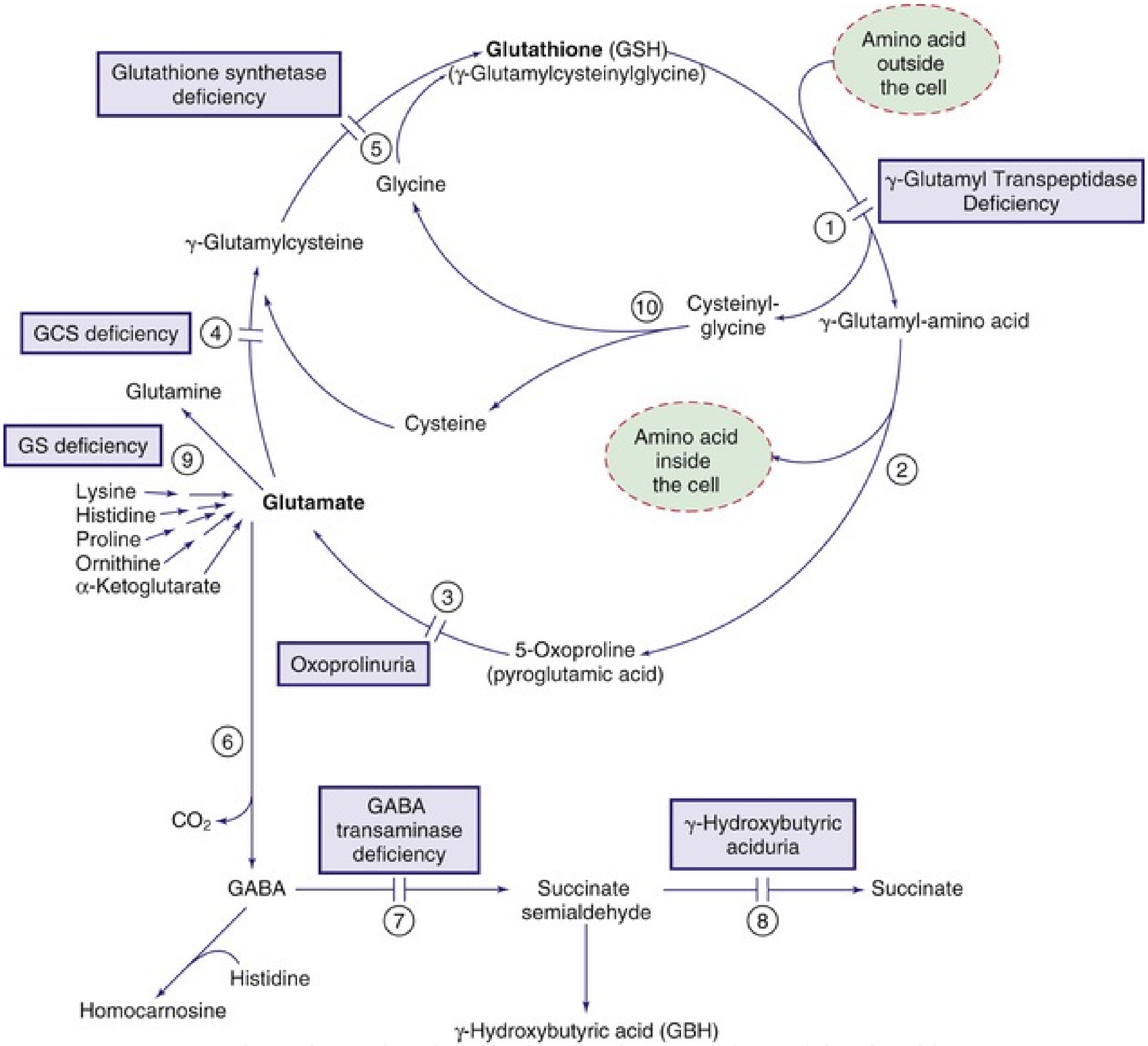
Glutathione (GSH)
(γ-Glutamylcysteinylglycine)
Amino acid outside the cell
Glutathione synthetase deficiency
⑤
Glycine
γ-Glutamyl Transpeptidase Deficiency
①
γ-Glutamylcysteine
⑩
Cysteinyl-glycine
γ-Glutamyl-amino acid
GCS deficiency
④
Glutamine
Cysteine
Amino acid inside the cell
GS deficiency
⑨
②
Lysine
Histidine
Proline
Ornithine
α-Ketoglutarate
Glutamate
③
Oxoprolinuria
5-Oxoproline
(pyroglutamic acid)
⑥
CO_2
GABA transaminase deficiency
γ-Hydroxybutyric aciduria
GABA
⑦
Succinate semialdehyde
⑧
Succinate
Histidine
Homocarnosine
γ-Hydroxybutyric acid (GBH)

FIG. 103.11 **The γ-glutamyl cycle and related pathways. Defects of the glutathione (GSH) synthesis and degradation are noted. Enzymes: *(1)* γ-Glutamyl transpeptidase (GGT), *(2)* γ-glutamyl cyclotransferase, *(3)* 5-oxoprolinase, *(4)* γ-glutamyl-cysteine synthetase, *(5)* glutathione synthetase, *(6)* glutamate decarboxylase, *(7)* γ-aminobutyric acid (GABA) transaminase, *(8)* succinate-semialdehyde dehydrogenase, *(9)* glutamine synthetase, *(10)* dipeptidase.**

One of the biochemical manifestations of γ-glutamyl cycle deficiency is increased urinary excretion of 5-oxoproline, which could be the result of both genetic and non-genetic causes. 5-Oxoprolinemia should be routinely considered in the differential diagnosis of **high–anion gap metabolic acidosis** (HAGMA). Two metabolic disorders can present with massive 5-oxoprolinuria: **glutathione synthetase deficiency** and **5-oxoprolinase deficiency** (Fig. 103.11). However, a more common clinical scenario is a transient and mild urinary elevation of 5-oxoproline in urine that can be seen in a variety of metabolic and acquired conditions, such as exposure to acetaminophen and some hydrolyzed-protein formulas, severe burns, Stevens-Johnson syndrome, homocystinuria, urea cycle defects, and tyrosinemia type I.

Glutathione Synthetase Deficiency

Three forms of this rare condition have been reported. In the **mild form** , enzyme deficiency causes glutathione deficiency only in erythrocytes. These patients present with hemolytic anemia without chronic metabolic acidosis and demonstrate high residual activity of glutathione synthetase on enzymatic testing. A **moderate form** has also been observed in which the hemolytic anemia is associated with variable degrees of metabolic acidosis and 5-oxoprolinuria. Its **severe form** is distinguished by presence of hemolytic anemia accompanied by severe acidosis, massive 5-oxoprolinuria, and neurologic manifestations.

Glutathione Synthetase Deficiency, Severe and Moderate Forms

Affected newborn infants with this rare condition usually develop acute symptoms of metabolic acidosis, jaundice, and mild to moderate hemolytic anemia in the 1st few days of life. Chronic acidosis continues after recovery. Similar episodes of life-threatening acidosis may occur during an infection (e.g., gastroenteritis) or after a surgical procedure. Progressive neurologic damage develops with age, manifested by intellectual disability, spastic tetraparesis, ataxia, tremor, dysarthria, and seizures. Susceptibility to infections, presumably because of granulocyte dysfunction, is observed in some patients. Patients with the moderate form of glutathione synthetase deficiency have milder acidosis and less 5-oxoprolinuria than is seen in the severe form, with no neurologic manifestations.

Laboratory findings include metabolic acidosis, mild to moderate degrees of hemolytic anemia, and 5-oxoprolinuria. High concentrations of 5-oxoproline are also found in blood. The urinary and blood levels of 5-oxoproline is less pronounced in patients with moderate form of the condition. The glutathione content of erythrocytes is markedly decreased. Increased synthesis of 5-oxoproline in this disorder is thought to be the result of the conversion of γ-glutamylcysteine to 5-oxoproline by the enzyme γ-glutamyl cyclotransferase (see Fig. 103.11). γ-Glutamylcysteine production increases greatly because the normal inhibitory effect of glutathione on the γ-glutamylcysteine synthetase enzyme is removed.

Treatment of acute attack includes hydration, correction of acidosis (by infusion of sodium bicarbonate), and measures to correct anemia and hyperbilirubinemia. Chronic administration of alkali is usually needed indefinitely. Supplementation with vitamin C, vitamin E, and selenium is recommended. Drugs and oxidants known to cause hemolysis and stressful catabolic states should be avoided. Oral administration of glutathione analogs has been tried with variable success.

Prenatal diagnosis can be achieved by the measurement of 5-oxoproline in amniotic fluid, by enzyme analysis in cultured amniocytes or chronic villus samples, or by DNA analysis. Successful pregnancy in an affected female (moderate form) has been reported, with favorable outcomes for both mother and infant.

Glutathione Synthetase Deficiency, Mild Form

The mild form has been reported in only a few patients. Mild to moderate hemolytic anemia has been the only clinical finding. Splenomegaly has been reported in some patients. Cognitive development is normal. Chronic metabolic acidosis typically is not seen. Some patients can have increased concentrations of 5-oxoproline in the urine. Pathogenic variants in the gene for this enzyme *(GSSD)* appear to decrease the half-life of the enzyme, which causes an increased rate of protein turnover without affecting its catalytic function. The expedited rate of enzyme turnover caused by these pathogenic variants is of little or no consequence for tissues with protein synthetic capability. However, inability of mature erythrocytes to synthesize protein results in glutathione deficiency in the erythrocytes. **Treatment** is that of hemolytic anemia and avoidance of drugs and oxidants that can trigger the hemolytic process.

All forms of glutathione synthetase deficiency are inherited as an autosomal recessive trait. *GSSD* is located on chromosome 20q11.22. **Diagnosis** can be confirmed by DNA analysis or enzyme activity in erythrocytes or skin fibroblasts.

5-Oxoprolinase Deficiency

More than 20 patients with 5-oxoprolinuria (4-10 g/day) caused by 5-oxoprolinase (see Fig. 103.11) deficiency have been described. No specific clinical picture has yet emerged; completely asymptomatic affected individuals have also been identified. It is therefore not clear whether 5-oxoprolinase deficiency is of any clinical consequence. *No treatment is currently recommended.* The gene for the enzyme *(OPLAH)* is on chromosome 8q24.3.

γ-Glutamylcysteine Synthetase Deficiency (Glutamate-Cysteine Ligase Deficiency)

Only a few patients with this enzyme deficiency have been reported. The most consistent clinical manifestation has been mild chronic hemolytic anemia. Acute attacks of hemolysis have occurred after exposure to sulfonamides. Peripheral neuropathy and progressive spinocerebellar degeneration have been noted in 2 siblings in adulthood. Laboratory findings of chronic hemolytic anemia were present in all patients. Generalized aminoaciduria is also present because the γ-glutamyl cycle is involved in amino acid transport in cells (see Fig. 103.11). **Treatment** should focus on the management of hemolytic anemia and avoidance of drugs and oxidants that may trigger the hemolytic process. The condition is inherited as an autosomal recessive trait; the gene *(GCLC)* is mapped to chromosome 6p12.1.

γ-Glutamyl Transpeptidase Deficiency (Glutathionemia)

γ-Glutamyl transpeptidase (GGT) is present in any cell that has secretory or absorptive functions. It is especially abundant in the kidneys, pancreas, intestines, and liver. The enzyme is also present in the bile. Measurement of GGT in the blood is frequently performed to evaluate liver and bile duct diseases.

GGT deficiency causes elevation in glutathione concentrations in body fluids, but the cellular levels remain normal (see Fig. 103.11). Because only a few patients with GGT deficiency have been reported, the scope of clinical manifestations has not yet been defined. Mild to moderate intellectual disability and severe behavioral problems were observed in 3 patients. However, 1 of 2 sisters with this condition had normal intelligence as an adult, and the other had

Prader-Willi syndrome.

Laboratory findings include marked elevations in urinary concentrations of glutathione (up to 1 g/day), γ-glutamylcysteine, and cysteine. None of the reported patients has had generalized aminoaciduria, a finding that would have been expected to occur in this enzyme deficiency (see Fig. 103.11).

Diagnosis can be confirmed by measurement of the enzyme activity in leukocytes or cultured skin fibroblasts. *No effective treatment has been proposed.* The condition is inherited as an apparent autosomal recessive trait. γ-Glutamyl transpeptidases represent a large family of enzymes encoded by at least 7 genes.

Genetic Disorders of Metabolism of γ-Aminobutyric Acid

See Chapter 103.11 .

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103.11

Genetic Disorders of Neurotransmitters

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Keywords

neurotransmitters
tyrosine hydroxylase deficiency
autosomal recessive Segawa syndrome
aromatic L -amino acid decarboxylase deficiency
AADC
GTP cyclohydrolase 1 deficiency
GCH1
autosomal dominant Segawa syndrome
BH_4 deficiency
hyperphenylalaninemia
sepiapterin reductase deficiency
SPR
dopamine β-hydroxylase deficiency
DBH
monoamine oxidase deficiency
monoamine oxidase A deficiency
MAOA
MAOB
γ-aminobutyric acid transaminase deficiency
ABAT
succinic semialdehyde dehydrogenase deficiency
γ-hydroxybutyric aciduria
SSADH
ALDH5A1
dopamine transporter protein deficiency

SLC6A3
dopamine-serotonin vesicular transporter disease
vesicular monoamine transporter deficiency
SLC18A2
vesicular monoamine transporter 2
VMAT2
hyperprolinemia

Neurotransmitters are chemical substances released from the axonal end of excited neurons at the synaptic junctions; they mediate initiation and amplification or inhibition of neural impulses. A number of amino acids and their metabolites comprise the bulk of neurotransmitters. Pathogenic variants in genes responsible for the synthesis, transport, or degradation of these substances may cause conditions that manifest neurologic and/or psychiatric abnormalities (Table 103.3). Previously, children affected by disorders of neurotransmitters have been given syndromic diagnoses such as cerebral palsy, epilepsy, parkinsonism, dystonia, or autism. Diagnosis, in most cases, requires specialized laboratory studies of the cerebrospinal fluid (CSF), because some of the neurotransmitters generated in the central nervous system (CNS), dopamine and serotonin, do not cross the blood-brain barrier, and their abnormal concentrations are not detected in the serum or urine. A growing number of these conditions are being identified; diseases once thought to be rare are now diagnosed with increasing frequency.

Table 103.3

Genetic Disorders of Neurotransmitters in Children

TRANSMITTER	SYNTHESIS DEFECTS	DEGRADATION DEFECTS
MONOAMINES		
Dopamine	TH deficiency	MAO deficiency
Serotonin and dopamine	AADC deficiency	MAO deficiency
	BH_4 deficiency With and without hyperphenylalaninemia	
Norepinephrine	DβH deficiency	MAO deficiency
GABA	?	GABA transaminase deficiency GHB aciduria
Histamine	HDC deficiency	?
TRANSPORTER PROTEINS		

Dopamine transporter	DAT deficiency	?
Vesicular monoamine transporter	VMAT2 deficiency	?
AMINO ACIDS		
Proline	?	Hyperprolinemia
Serine	3-PGD, PSAT, PSPH deficiencies	?
Glycine	3-PDG, PSAT deficiencies	NKH

AADC, Aromatic L -amino acid decarboxylase; BH_4 , tetrahydrobiopterin; DAT, dopamine transporter; DβH, dopamine β-hydroxylase; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyric acid; HDC, histidine decarboxylase; hyperphe, hyperphenylalaninemia; MAO, monoamine oxidase; NKH, nonketotic hyperglycinemia; 3-PGD, 3-phosphoglycerate dehydrogenase; PSAT, phosphoserine aminotransferase; PSPH, 3-Phosphoserine Phosphatase Deficiency; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter 2.

Tyrosine Hydroxylase Deficiency (Infantile Parkinsonism, Autosomal Recessive Dopa-Responsive Dystonia, Autosomal Recessive Segawa Syndrome)

Tyrosine hydroxylase catalyzes the formation of L -dopa from tyrosine. Deficiency of this enzyme results in deficiencies of dopamine and norepinephrine (see Fig. 103.2). The differential diagnosis includes a wide range of inherited dystonias, including autosomal dominant dystonia caused by GTP cyclohydrolase 1 deficiency.

Clinical manifestations range from mild to very severe. In general, 2 phenotypes have been recognized. In the **mild** form (dopa-responsive dystonia, or **type A**), symptoms of unilateral limb dystonia causing gait incoordination and postural tremor occur in childhood and worsen with age if the condition remains untreated. Diurnal variation of symptoms (worse at the end of the day) may be present. Cognitive development is usually normal.

In the **severe** form of tyrosine hydroxylase deficiency (infantile parkinsonism, infantile encephalopathy, or **type B**), the clinical manifestations occur at birth or shortly thereafter and include microcephaly, developmental delay, involuntary movements of the limbs with spasticity, dystonia, ptosis, expressionless face, oculogyric crises (upward eye-rolling movements), and autonomic dysfunction (temperature instability, excessive sweating, hypoglycemia, salivation, tremor, gastrointestinal reflux, constipation). Brisk reflexes, myoclonus, athetosis, and distal chorea may be present. The patient with the severe form usually shows incomplete response to treatment with L -dopa and is prone to developing L -dopa–induced dyskinesia as a side effect.

Laboratory findings include reduced levels of dopamine and its metabolite homovanillic acid (HVA) and normal concentrations of tetrahydrobiopterin (BH_4), neopterin, and 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) in the CSF. Serum prolactin levels are usually elevated. These findings are not diagnostic of the condition; diagnosis should be established by molecular gene analysis.

Treatment with L -dopa/carbidopa results in significant clinical improvement in most patients, but the severe forms are invariably associated with L -dopa–induced dyskinesias. To minimize the side effects of therapy, the treatment should be started with a low dose and increased very slowly, if needed. Other therapeutic interventions include anticholinergics, serotonergic agents, and monoamine oxidase (MAO) B inhibitors, including amantadine, biperiden, and selegiline. Bilateral subthalamic nucleus deep brain stimulation has shown clinical efficacy in one case. Tyrosine hydroxylase deficiency is inherited as an autosomal-recessive trait. Molecular testing for pathogenic variants in the *TH* gene is available clinically.

Aromatic l-Amino Acid Decarboxylase Deficiency

Aromatic L -amino acid decarboxylase (AADC) is a vitamin B_6 –dependent enzyme that catalyzes the decarboxylation of both 5-hydroxytryptophan to form serotonin (see Fig. 103.5) and L -dopa to generate dopamine, (see Fig. 103.2). **Clinical manifestations** are related to reduced availability of dopamine and serotonin. Poor feeding, lethargy, hypotension, hypothermia, oculogyric crises, and ptosis have been observed in affected neonates. Clinical findings in infants and older children include developmental delay, truncal hypotonia with hypertonia of limbs, oculogyric crises, extrapyramidal movements (choreoathetosis, dystonia, myoclonus), and autonomic abnormalities (sweating, salivation, irritability, temperature instability, hypotension). Symptoms may have a diurnal variation, becoming worse by the end of the day.

Laboratory findings include decreased concentrations of dopamine and serotonin and their metabolites (HVA, 5-HIAA, norepinephrine, vanillylmandelic acid [VMA]) and increased levels of 5-hydroxytryptophan, L -dopa, and its metabolite (3-*O* -methyldopa) in body fluids, especially in CSF. Elevated serum concentrations of prolactin (a result of dopamine deficiency) have also been observed. MRI of the brain reveals cerebral atrophy with degenerative changes in the white matter. A urine screening program, focused on 3-*O* -methyl-dopa and VMA, has demonstrated diagnostic promise in high-disease prevalence populations.

Treatment with neurotransmitter precursors has produced limited clinical improvement. Dopamine and serotonin have no therapeutic value because of their inability to cross the blood-brain barrier. Dopamine agonists (L -dopa/carbidopa, bromocriptine), MAO inhibitors (tranylcypromine), serotonergic agents and high doses of pyridoxine, a cofactor for AADC enzyme, have been tried. Pyridoxine supplementation in patients harboring the p.S250F variant in AADC may be beneficial. The recent demonstration of CNS-directed gene therapy with an adeno-associated viral vector has shown benefit in some patients. Preimplantation genetic diagnosis after in vitro fertilization has been achieved in the high-prevalence Taiwanese population. The gene encoding AADC (*DDC*) is on chromosome 7p12.1. The condition is inherited as an autosomal recessive trait.

Tetrahydrobiopterin Deficiency

See Chapter 103.1 .

BH_4 is the cofactor for phenylalanine hydroxylase (see Fig. 103.1), tyrosine hydroxylase (see Fig. 103.2), tryptophan hydroxylase (see Fig. 103.5), and nitric oxide synthase. It is synthesized from GTP in many tissues (see Fig. 103.1). Deficiencies of enzymes involved in the biosynthesis of BH_4 result in inadequate production of this cofactor, which causes deficiencies of monoamine neurotransmitters with or without concomitant hyperphenylalaninemia.

Tetrahydrobiopterin Deficiency With Hyperphenylalaninemia

See Chapter 103.1 .

Tetrahydrobiopterin Deficiency Without Hyperphenylalaninemia

GTP Cyclohydrolase 1 Deficiency (Hereditary Progressive Dystonia, Autosomal Dominant Dopa-Responsive Dystonia, Autosomal Dominant Segawa Syndrome)

This form of dystonia, caused by guanosine triphosphate (GTP) cyclohydrolase 1 deficiency, is inherited as an autosomal dominant trait and is more common in females than males (4 : 1 ratio) (see Chapter 615.4). **Clinical manifestations** usually start in early childhood with tremor and dystonia of the lower limbs (**toe gait**), which may spread to all extremities within a few years. Torticollis, dystonia of the arms, and poor coordination may precede dystonia of the lower limbs. Early development is generally normal. Symptoms have an impressive diurnal variation, becoming worse by the end of the day and improving with sleep. Autonomic instability is not uncommon. Parkinsonism may also be present or develop with advancing age. Late presentation in adult life has also been reported, associated with **action dystonia** ("writer's cramp"), torticollis, or generalized rigid hypertonia with tremor but without postural dystonia. Additionally, limited data on adults suggest symptoms related to serotonin deficiency (sleep disturbance, cognitive impairment, impulsivity).

Laboratory findings show reduced levels of BH_4 and neopterin in the CSF without hyperphenylalaninemia (see Chapter 103.1). Dopamine and its metabolite (HVA) may also be reduced in CSF. The serotonergic pathway is less affected by this enzyme deficiency; thus concentrations of serotonin and its metabolites are usually normal. Plasma phenylalanine is normal, but an oral phenylalanine loading test (100 mg/kg) produces an abnormally high plasma phenylalanine level with an elevated phenylalanine/tyrosine ratio. The ratio, obtained at the 2-3 hr after the load, in combination with urine neopterin level, has optimal diagnostic specificity and sensitivity. The existence of asymptomatic carriers indicates that other factors or genes may play a role in pathogenesis. The asymptomatic carrier may be identified by the phenylalanine loading test. **Diagnosis** may be confirmed by reduced levels of BH_4 and neopterin in CSF, measurement of the enzyme activity, and molecular genetic analysis (see Chapter 103.1). Clinically, the condition should be differentiated from other causes of dystonias and childhood parkinsonism, especially tyrosine hydroxylase, sepiapterin reductase, and aromatic amino acid decarboxylase deficiencies.

Treatment with L -dopa/carbidopa usually produces dramatic clinical improvement. Oral administration of BH_4 is also effective but is rarely used. The gene for GTP cyclohydroxylase 1 (*GCH1*) is located on chromosome 14q22.2.

Sepiapterin Reductase Deficiency

Sepiapterin reductase is involved in conversion of 6-pyruvoyl-tetrahydropterin to BH_4 . It also participates in the salvage pathway of BH_4 synthesis (see Fig. 103.1). Sepiapterin reductase deficiency results in accumulation of 6-lactoyl-tetrahydropterin, which can be converted to sepiapterin nonenzymatically. The majority of sepiapterin is metabolized to BH_4 through the salvage pathway in peripheral tissues (see Fig. 103.1), but because of the low activity of dihydrofolate reductase in brain, the amount of BH_4 remains insufficient for proper synthesis of dopamine and serotonin. This explains the absence of hyperphenylalaninemia and the often-delayed diagnosis.

Clinical manifestations usually appear within a few months of life. Cardinal manifestations include paroxysmal stiffening, oculogyric crises, and hypotonia. Additional findings include motor and language delays, weakness, limb hypertonia, dystonia, hyperreflexia, and early-onset parkinsonism. The symptoms usually have a diurnal variation. Misdiagnosis as cerebral palsy is common and a wide variability of symptoms have been reported. **Diagnosis** is established by measurement of CSF neurotransmitters and pterin metabolites, which reveal decreased dopamine, HVA, norepinephrine, and 5-HIAA and marked elevations of sepiapterin and dihydrobiopterin. The serum concentration of prolactin may be elevated. The phenylalanine loading test may have diagnostic utility. Diagnosis may be confirmed by molecular genetic analysis or enzyme assay in fibroblasts. **Treatment** with slowly increasing doses of L-dopa/carbidopa and 5-hydroxytryptophan usually produces dramatic clinical improvement. The condition is inherited as an autosomal recessive trait; the gene *SPR* encoding sepiapterin reductase is located on chromosome 2p13.2.

Dopamine β-Hydroxylase Deficiency

Dopamine β-hydroxylase catalyzes the conversion of dopamine to norepinephrine (see Fig. 103.2). The deficiency of this enzyme results in reduced or absent synthesis of norepinephrine, leading to dysregulation of the sympathetic function. Infants and children may present with difficulty opening eyes, ptosis, hypotension, hypothermia, hypoglycemia, and nasal stuffiness. Adult patients may present with profound deficits of autonomic regulation, resulting in severe orthostatic hypotension, and sexual dysfunction in males. Presyncopal symptomatology includes dizziness, blurred vision, dyspnea, nuchal discomfort, and chest pain; olfactory function remains relatively intact. The **diagnosis** can be aided by performing autonomic function testing (measurement of the sinus arrhythmia ratio, blood pressure studies during controlled hyperventilation, Valsalva maneuver, cold pressor, handgrip exercise). **Laboratory findings** include decreased or absent norepinephrine and epinephrine and their metabolites, with elevated levels of dopamine and its metabolite (HVA), in plasma, CSF, and urine. Elevated plasma dopamine may be pathognomonic for this disease. MRI of the brain shows decreased brain volume, consistent with the neurotrophic role of norepinephrine. **Treatment** with L -dihydroxyphenylserine, which is converted to norepinephrine directly in vivo by the action of AADC, leads to significant improvement in orthostatic hypotension and normalizes noradrenaline and its metabolites. The condition is inherited as an autosomal recessive trait; the gene *(DBH)* encoding dopamine β-hydroxylase resides on chromosome 9q34.2.

Monoamine Oxidase a Deficiency

Human genome encodes 2 monoamine oxidase (MAO) isoenzymes: MAO A and MAO B. Both enzymes catalyze oxidative deamination of most biogenic amines in the body, including serotonin (see Fig. 103.5), norepinephrine, epinephrine, and dopamine (see Fig. 103.2). The genes for both isoenzymes are on the X chromosome (Xp11.3), residing in close proximity. A deletion of both genes can also encompass a neighboring gene, *NDP,* resulting in a contiguous deletion syndrome, which can present as an atypical **Norrie disease** (see Chapter 640). Male patients with MAO A deficiency manifest borderline intellectual deficiency and impaired impulse control. The consequences of the isolated MAO B deficiency are incompletely understood. Combined MAO A and B deficiency causes severe intellectual disability and behavioral problems and can be associated with pronounced laboratory abnormalities (e.g., 4-6–fold serotonin elevation in physiologic fluids, elevated *O* -methylated amine metabolites, and reduced deamination products [VMA, HVA]). Dietary intervention (low tyramine, phenylethylamine, and L -dopa/dopamine intake) did not improve patients' blood serotonin levels. Inheritance of MAO deficiency is X-linked. **Treatment** of MAO A deficiency is supportive.

Disorders of γ-Aminobutyric Acid (GABA) Metabolism

GABA is the main inhibitory neurotransmitter synthesized in the synapses through decarboxylation of glutamic acid by glutamate decarboxylase (GAD). The same pathway is responsible for production of GABA in other organs, especially the kidneys and the β-cells of the pancreas. GAD enzyme requires pyridoxine (vitamin B_6) as cofactor. Two GAD enzymes, GAD1 (GAD_{67}) and GAD2 (GAD_{65}) have been identified. **GAD1** is the main enzyme in the brain, and **GAD2** is the major enzyme in the β-cells. Antibodies against GAD_{65} and GAD_{67} have been implicated in the development of type 1 diabetes and **stiff-person syndrome** , respectively. GABA is catabolized to succinic acid by 2 enzymes, GABA transaminase and succinic semialdehyde dehydrogenase (SSADH) (see Fig. 103.11).

γ-Aminobutyric Acid Transaminase Deficiency

Clinical manifestations in the 2 index infant siblings included severe psychomotor retardation, hypotonia, hyperreflexia, lethargy, refractory seizures, and increased linear growth likely related to GABA-mediated increased secretion of growth hormone. Increased concentrations of GABA and β-alanine were found in CSF (see Fig. 103.11). Evidence of leukodystrophy was noted in the postmortem examination of the brain. A 3rd patient showed severe psychomotor retardation, recurrent episodic lethargy, and intractable seizures with comparable CSF metabolite abnormalities to those of the index probands. GABA transaminase deficiency is demonstrated in brain and lymphocytes. **Treatment** is symptomatic. Intervention with vitamin B_6 , the cofactor for the enzyme, was without therapeutic benefit. The gene *(ABAT)*, maps to chromosome 16p13.2; the condition is inherited as an autosomal recessive trait.

Succinic Semialdehyde Dehydrogenase

Deficiency (γ-Hydroxybutyric Aciduria)

Clinical manifestations of SSADH deficiency usually begin in infancy with developmental delays with a disproportionate deficit in expressive language, hypotonia, and ataxia; seizures occur in approximately 50% of patients (see Fig. 103.11). Many patients also carry the diagnosis of **autism spectrum disorder** . Neuropsychiatric comorbidity (especially oppositional defiance, obsession-compulsion, and hyperactivity) can be disabling, particularly in adolescents and adults. Abnormal EEG findings include background slowing and generalized spike-wave paroxysms, with variable lateralization in hemispheric onset and voltage predominance. Photosensitivity and electrographic status epilepticus of sleep have been reported in combination with difficulties in sleep maintenance and excessive daytime somnolence. MRI of the brain shows an increased T2-weighted hyperintensity involving the globus pallidi, cerebellar dentate nuclei, and subthalamic nuclei, usually in a bilaterally symmetric distribution.

The biochemical hallmark, γ-hydroxybutyric acid (GHB), is elevated in physiologic fluids (CSF, plasma, urine) in all patients. Increased concentrations of GABA are also found in CSF. Heightened diagnostic suspicion evolves through documentation of elevated urinary GHB, and confirmation is achieved by molecular genetic testing.

Treatment remains elusive; vigabatrin (GABA-transaminase inhibitor) has been employed empirically, with mixed outcomes, and there is concern with its use as it further elevates CNS GABA in an already hyper-GABAergic disorder. Additionally, vigabatrin can cause constriction of the visual field and long-term use is contraindicated.

The gene for SSADH *(ALDH5A1)* is located on chromosome 6p22, and inheritance follows an autosomal-recessive pattern. **Prenatal diagnosis** has been achieved by measurement of GHB in the amniotic fluid, assay of the enzyme activity in the amniocytes, chorionic villus sampling, or DNA analysis.

Defects in Neurotransmitter Transporter Proteins

More than 20 different proteins are involved in transporting different neurotransmitters across the neuronal membranes. The main function of most of these transporters is to remove the excess neurotransmitters from the synaptic junction back into the presynaptic neurons (reuptake). This recycling process not only regulates the precise effect of neurotransmitters at the synaptic junction, but also resupplies the presynaptic neurons with neurotransmitters for future use. A few transporter proteins are involved in shuttling neurotransmitters from the neuronal cytoplasm across the membrane of synaptic vesicles for storage (vesicular transporters). On neuronal stimulation, these vesicles release a bolus of neurotransmitters through exocytosis. As expected, pathogenic variants in transporter proteins interfere with the proper reuptake and storage of neurotransmitters and may result in clinical manifestations similar to those seen in deficiencies of neurotransmitters metabolism. Several conditions caused by pathogenic variants of neurotransmitter protein transporters have been described, including dopamine transporter protein deficiency and dopamine-serotonin vesicular transporter disease.

Dopamine Transporter Protein Deficiency

This transporter protein is involved in reuptake of dopamine by the presynaptic neurons, and its deficiency causes depletion of dopamine and thus a dopamine deficiency state. Dopamine transporter protein (DAT) is encoded by *SLC6A3* gene on chromosome 5p15.33. Pathogenic variants of this gene has been reported in 13 children. These children presented with symptoms of infantile **parkinsonism-dystonia syndrome** . Irritability and feeding difficulties started shortly after birth and progressed to hypotonia, lack of head control, parkinsonism, dystonia, and global developmental delay by early infancy. Brain MRI usually shows no abnormalities.

CSF examination revealed elevation of HVA and normal level of 5-HIAAs. The urinary level of HVA and serum concentration of prolactin were increased. Diagnosis was established by demonstrating the loss-of-function mutation in the *SLC6A3* gene. *No effective treatment* has been identified; L -dopa/carbidopa did not result in improvements in clinical or biochemical parameters.

Dopamine-Serotonin Vesicular Transporter Disease (Vesicular Monoamine Transporter Deficiency)

This autosomal recessive condition, described in 8 children from a consanguineous Saudi Arabian family, is caused by a pathogenic variant in the

SLC18A2 gene. This gene encodes the vesicular monoamine transporter 2 (VMAT2), which is involved in transporting dopamine and serotonin from the cytoplasm into the synaptic storage vesicles located in the axonal terminals of the presynaptic neurons. Most affected children presented in the 1st yr of life with symptoms consistent with deficiencies of dopamine (hypotonia progressing into dystonia, parkinsonism, oculogyric crises), serotonin (sleep and psychiatric disturbances), and norepinephrine-epinephrine (excessive sweating, tremors, temperature instability, postural hypotension, ptosis). Neurocognitive delays become apparent in the 1st yr of life. No diurnal variation of the symptoms was noted. Brain imaging studies were within normal limits. Changes in the levels of CNS neurotransmitters and their metabolites have been inconsistent.

The phenotype resembles that seen in AADC and BH_4 deficiencies (see earlier). Diagnosis requires molecular analysis of *SLC18A2* (located on chromosome 10q25.3). **Treatment** with L -dopa/carbidopa caused exacerbation of symptoms, whereas pramipexole, a dopamine receptor agonist, resulted in a promising clinical response.

Histidine Decarboxylase Deficiency

Decarboxylation of histidine by histidine decarboxylase produces histamine, which functions as a neurotransmitter in the brain. Deficiency of this enzyme (expressed mainly in the posterior hypothalamus) results in deficiency of histamine in the CNS and in one family caused an autosomal dominant form of Tourette syndrome (see Chapter 103.13).

Hyperprolinemia

Intellectual disability and seizures are common findings in most patients with hyperprolinemia types I and II. Patients with **type I** hyperprolinemia typically show a benign clinical course but could have an increased risk of developing schizophrenia. The contribution of increased concentration of proline to the mechanisms of schizophrenia, however, remains unclear. The neurologic abnormalities observed in hyperprolinemia **type II** are mainly caused by development of vitamin B_6 dependency in this condition (see Chapter 103.9). Dietary intervention in hyperprolinemias type I and II is neither feasible nor recommended.

3-Phosphoglycerate Dehydrogenase Deficiency

See Chapter 103.8 .

Phosphoserine Aminotransferase Deficiency

See Chapter 103.8 .

Nonketotic Hyperglycinemia

See Chapter 103.7 .

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103.12

Urea Cycle and Hyperammonemia (Arginine, Citrulline, Ornithine)

Keywords

urea cycle disorder
hyperammonemia
carbamoyl phosphate synthetase 1
CPS1
ornithine transcarbamylase
OTC
argininosuccinate synthetase 1
classic citrullinemia
ASS1
citrin
citrin deficiency
SLC25A13
neonatal intrahepatic cholestasis
argininosuccinate lyase
argininosuccinic aciduria
ASL
arginase 1
hyperargininemia
argininemia
ARG1
N -acetylglutamate
NAG
N -acetylglutamate synthetase
NAGS
sodium benzoate
sodium phenylacetate
sodium phenylbutyrate
Ammonul
ariginine
citrulline
orotate

orotic acid
argininosuccinate
argininosuccinic acid
acrodermatitis enteropathica
valproic acid
valproate
transient hyperammonemia of the newborn
THAN
disorders of ornithine metabolism
gyrate atrophy of the retina and choroid
ornithine aminotransferase
OAT
hyperammonemia-hyperornithinemia-homocitrullinemia syndrome
hyperammonemia-hyperornithinemia-homocitrullinuria syndrome
HHH syndrome
SLC25A15
congenital glutamine deficiency
glutamine synthetase
GLUL

Catabolism of amino acids results in the production of free ammonia, which in high concentration is toxic to the CNS. Mammals detoxify ammonia to urea through a series of reactions known as the **urea cycle** (Fig. 103.12), which is composed of 5 enzymes: carbamoyl phosphate synthetase 1 (**CPS1**), ornithine transcarbamylase (**OTC**), argininosuccinate synthetase (**ASS**), argininosuccinate lyase (**ASL**), and arginase 1. A 6th enzyme, *N* -acetylglutamate (NAG) synthetase (**NAGS**), catalyzes synthesis of NAG, which is an obligatory activator (effector) of the CPS1 enzyme. Individual deficiencies of these enzymes have been observed and, with an overall estimated prevalence of 1 in 35,000 live births, they are the most common genetic causes of hyperammonemia in infants.

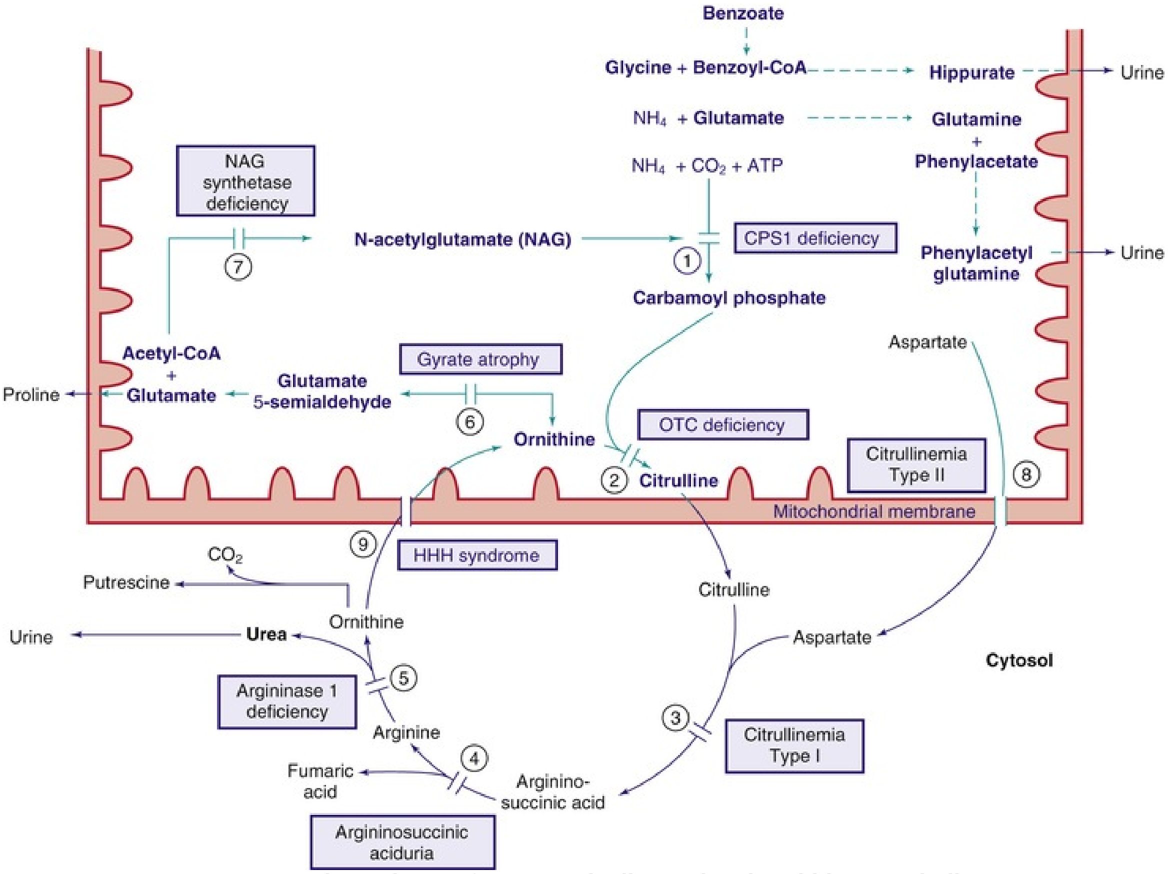
Benzoate
Glycine + Benzoyl-CoA
Hippurate
Urine
NH4 + Glutamate
Glutamine
+
Phenylacetate
NH4 + CO2 + ATP
NAG synthetase deficiency
N-acetylglutamate (NAG)
CPS1 deficiency
1
7
Phenylacetyl glutamine
Urine
Carbamoyl phosphate
Aspartate
Acetyl-CoA
+
Glutamate
Gyrate atrophy
Proline
Glutamate 5-semialdehyde
6
Ornithine
OTC deficiency
Citrullinemia Type II
8
2
Citrulline
Mitochondrial membrane
9
HHH syndrome
CO2
Putrescine
Citrulline
Ornithine
Urine
Urea
Aspartate
Cytosol
5
Argininase 1 deficiency
3
Citrullinemia Type I
Arginine
4
Fumaric acid
Arginino-succinic acid
Argininosuccinic aciduria

FIG. 103.12 Urea cycle: pathways for ammonia disposal and ornithine metabolism. Reactions occurring in the mitochondria are depicted in *purple.* Reactions shown with *interrupted arrows* are the alternate pathways for the disposal of ammonia. Enzymes: *(1)* Carbamyol phosphate synthetase type 1 (CPS1), *(2)* ornithine transcarbamylase (OTC), *(3)* argininosuccinate synthetase (ASS), *(4)* Argininosuccinate lyase (ASL), *(5)* arginase 1, *(6)* ornithine aminotransferase, *(7) N* -acetylglutamate (NAG) synthetase, *(8)* citrin, *(9)* ornithine transporter (ORNT1). HHH syndrome, Hyperammonemia-hyperornithinemia-homocitrullinemia.

Genetic Causes of Hyperammonemia

Hyperammonemia, sometimes severe, occurs in inborn errors of metabolism other than the urea cycle defects (Table 103.4 ; see also Table 102.5). The mechanisms of hyperammonemia in some of these conditions are diverse and include accumulation of toxic metabolites (e.g., organic acids), impaired transport of urea cycle intermediates (e.g., HHH syndrome), or depletion of urea cycle intermediates (e.g., lysinuric protein intolerance), leading to compromised function of the urea cycle.

Table 103.4

Inborn Errors of Metabolism Causing Hyperammonemia

- Deficiencies of the urea cycle enzymes
    - Carbamyl phosphate synthetase 1
    - Ornithine transcarbamylase
    - Argininosuccinate synthetase
    - Argininosuccinate lyase
    - Arginase 1
    - *N* -acetylglutamate synthetase
- Organic acidemias
    - Propionic acidemia
    - Methylmalonic acidemia
    - Isovaleric acidemia
    - β-Ketothiolase deficiency
    - Multiple carboxylase deficiencies
    - Medium-chain fatty acid acyl-CoA dehydrogenase deficiency
    - Glutaric acidemia type I
    - 3-Hydroxy-3-methylglutaric aciduria
- Lysinuric protein intolerance
- Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome
- Transient hyperammonemia of the newborn
- Congenital hyperinsulinism with hyperammonemia

Clinical Manifestations of Hyperammonemia

In the **neonatal period** , symptoms and signs are mostly related to brain dysfunction and are similar regardless of the cause of the hyperammonemia. The affected infant appears normal at birth but becomes symptomatic following the introduction of dietary protein. Refusal to eat, vomiting, tachypnea, and lethargy can quickly progress to a deep coma. Seizures are common. Physical examination may reveal hepatomegaly in addition to obtundation. Hyperammonemia can trigger increased intracranial pressure that may be manifested by a bulging fontanelle and dilated pupils.

In **infants and older children** , acute hyperammonemia is manifested by vomiting and neurologic abnormalities such as ataxia, confusion, agitation, irritability, combativeness, and psychosis. These manifestations may alternate with periods of lethargy and somnolence that may progress to coma.

Routine laboratory studies show no specific findings when hyperammonemia is caused by defects of the urea cycle enzymes. Blood urea nitrogen is usually low in these patients. Some patients may initially present with unexplained elevated serum alanine transaminase (ALT) and aspartate transaminase (AST) and even meet the criteria for acute liver failure. In infants with organic acidemias, hyperammonemia is commonly associated with severe *acidosis* as well as *ketonuria* . Newborn infants with hyperammonemia are often misdiagnosed as having sepsis; they may succumb without a correct diagnosis. Neuroimaging may reveal cerebral edema. Autopsy may reveal microvesicular steatosis, mild cholestasis, and fibrosis of the liver. Thus, because of the nonspecific presentation or urea cycle disorders, it is imperative to measure plasma ammonia levels in any ill infant with severe sepsis, unexplained liver dysfunction, recurrent emesis, or progressive encephalopathy.

Diagnosis

The main criterion for diagnosis is hyperammonemia. Each clinical laboratory should establish its own normal values for blood ammonia. Normal newborn values are higher than those of the older child or adult. Levels as high as 100 µmol/L can occur in healthy term infants. An ill infant usually manifests a blood ammonia level >150 µmol/L. Fig. 103.13 illustrates an approach to the differential diagnosis of hyperammonemia in the newborn infant. Careful inspection of individual plasma amino acids usually reveals abnormalities that may help the diagnosis. In patients with deficiencies of CPS1, OTC, or NAGS, frequent findings include elevations in plasma glutamine and alanine with concurrent decrements in citrulline and arginine. These disorders cannot be differentiated from one another by the plasma amino acid levels alone. A marked increase in urinary orotic acid in patients with OTC deficiency helps differentiate this defect from CPS1 deficiency. Differentiation between the CPS1 deficiency and the NAGS deficiency may require an assay of the respective enzymes or molecular analysis of the relevant genes. Clinical improvement occurring after oral administration of carbamylglutamate, however, may suggest NAGS deficiency. Patients with a deficiency of ASS, ASL, or arginase 1 have marked increases in the plasma levels of citrulline, argininosuccinic acid, or arginine, respectively. The combination of hyperammonemia and marked hypercitrullinemia or argininosuccinic acidemia is virtually pathognomonic for these disorders. Children with urea cycle defects often self-select a low-protein, high-carbohydrate diet, especially those with late-onset disease or symptomatic females with partial OTC deficiency.

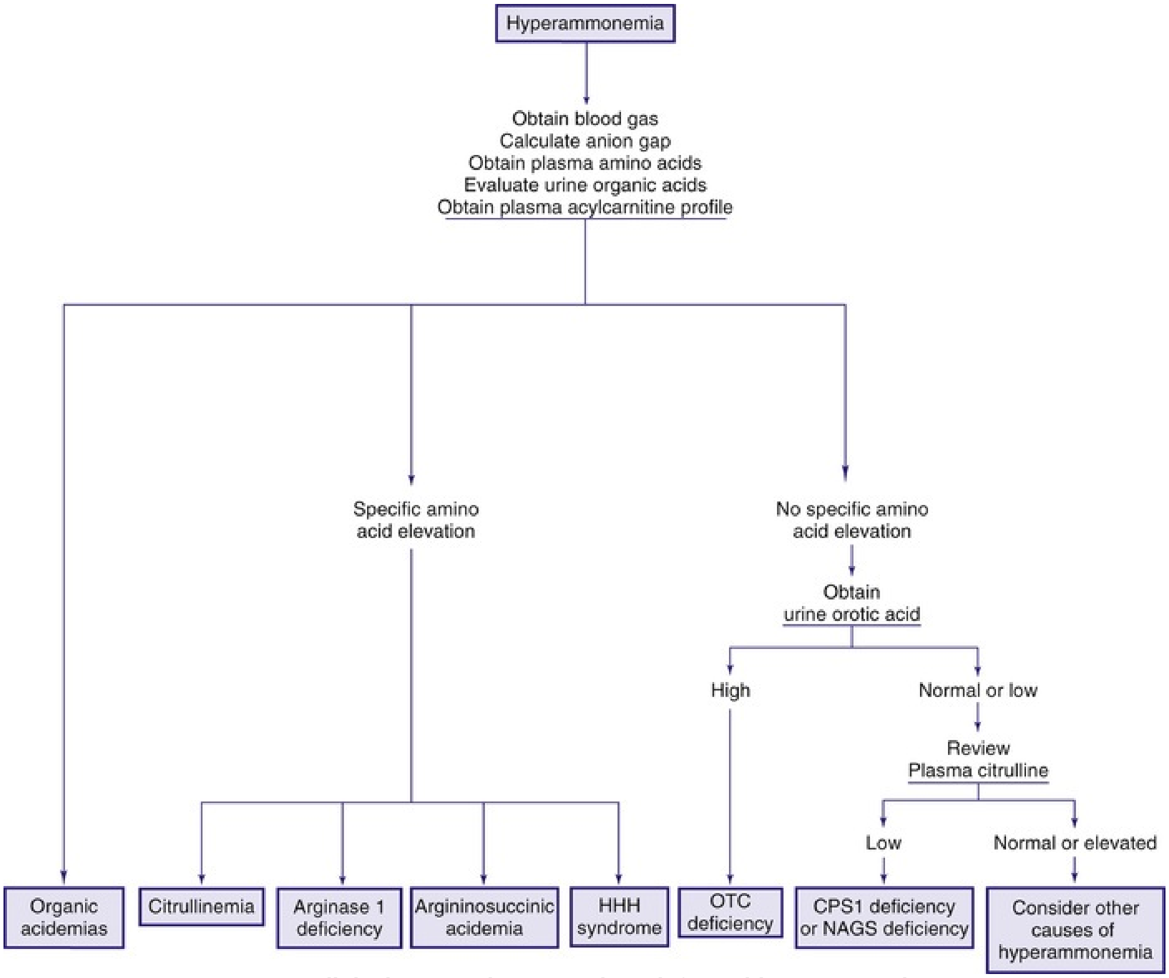
Hyperammonemia
Obtain blood gas
Calculate anion gap
Obtain plasma amino acids
Evaluate urine organic acids
Obtain plasma acylcarnitine profile
Specific amino acid elevation
No specific amino acid elevation
Obtain urine orotic acid
High
Normal or low
Review Plasma citrulline
Low
Normal or elevated
Organic acidemias
Citrullinemia
Arginase 1 deficiency
Argininosuccinic acidemia
HHH syndrome
OTC deficiency
CPS1 deficiency or NAGS deficiency
Consider other causes of hyperammonemia

FIG. 103.13 Clinical approach to a newborn infant with symptomatic hyperammonemia. CPS1, Carbamoyl phosphate synthetase 1; HHH syndrome, hyperornithinemia-hyperammonemia-homocitrullinemia; NAGS, *N* -acetylglutamate synthetase; OTC, ornithine carbamoyltransferase.

Mass screening of newborn infants identifies patients with ASS, ASL, and arginase 1 deficiencies.

Treatment of Acute Hyperammonemia

Clinical outcome depends mainly on the severity and the duration of hyperammonemia. Serious neurologic sequelae are likely in newborns with severe elevations in blood ammonia (>300 µmol/L) for more than 12 hr. Thus, acute hyperammonemia should be treated promptly and vigorously. The goal of therapy is to lower the concentration of ammonia. This is accomplished by (1) removal of ammonia from the body in a form other than urea and (2) minimizing endogenous protein breakdown and favoring endogenous protein synthesis by providing adequate calories and essential amino acids (Table 103.5). Fluid, electrolytes, glucose (10–15%), and lipids (1-2 g/kg/24 hr) should be infused intravenously, together with minimal amounts of protein (0.25 g/kg/24 hr), preferably including essential amino acids. Oral feeding with a low-protein formula (0.5-1.0 g/kg/24 hr) through a nasogastric tube should be started as soon as sufficient improvement is seen.

Table 103.5

Treatment of Acute Hyperammonemia in an Infant

1. Provide adequate calories, fluid, and electrolytes intravenously (10% glucose, NaCl* and intravenous lipids 1 g/kg/24 hr). Add minimal amounts of protein preferably as a mixture of essential amino acids (0.25 g/kg/24 hr) during the 1st 24 hr of therapy.
2. Give priming doses of the following compounds:
   (To be added to 20 mL/kg of 10% glucose and infused within 1-2 hr)
   - Sodium benzoate 250 mg/kg †
   - Sodium phenylacetate 250 mg/kg †
   - Arginine hydrochloride 200-600 mg/kg as a 10% solution
3. Continue infusion of sodium benzoate † (250-500 mg/kg/24 hr), sodium phenylacetate † (250-500 mg/kg/24 hr), and arginine (200-600 mg/kg/24 hr ‡) following the above priming doses. These compounds should be added to the daily intravenous fluid.
4. Initiate peritoneal dialysis or hemodialysis if above treatment fails to produce an appreciable decrease in plasma ammonia.

[*] The concentration of sodium chloride should be calculated to be 0.45–0.9%, including the amount of the sodium in the drugs.

[†] Sodium from these drugs should be included as part of the daily sodium requirement.

[‡] The higher dose is recommended in the treatment of patients with citrullinemia and argininosuccinic aciduria. Arginine is not recommended in patients with arginase deficiency and in those whose hyperammonemia is secondary to organic acidemia. Sodium benzoate and sodium phenylacetate should be used with caution in patients with organic acidemias.

Because the kidneys clear ammonia poorly, its removal from the body must be expedited by formation of compounds with a high renal clearance. An important advance in the treatment of hyperammonemia has been the introduction of **acylation therapy** by using an exogenous organic acid that is acylated endogenously with nonessential amino acids to form a nontoxic compound with high renal clearance. The main organic acids used for this purpose are sodium salts of benzoic acid and phenylacetic acid. **Benzoate** forms hippurate with endogenous glycine in the liver (see Fig. 103.12). Each mole of benzoate removes 1 mole of ammonia as glycine. **Phenylacetate** conjugates with glutamine to form phenylacetylglutamine, which is readily excreted in the urine. One mole of phenylacetate removes 2 moles of ammonia as glutamine from the body (see Fig. 103.12). Sodium phenylbutyrate, metabolized to phenylacetate, is the primary oral formulation. For intravenous (IV) use, a combined formulation of benzoate and phenylacetate (Ammonul) is commercially available.

Another valuable therapeutic adjunct is IV infusion of **arginine** , which is effective in all patients (except those with arginase deficiency). Arginine administration supplies the urea cycle with ornithine (see Fig. 103.12). In patients with citrullinemia, 1 mole of arginine reacts with 1 mole of ammonia (as carbamoyl phosphate) to form citrulline. In patients with argininosuccinic acidemia, 2 moles of ammonia (as carbamoyl phosphate and aspartate) react with arginine to form argininosuccinic acid. Citrulline and argininosuccinate are less toxic than ammonia and more readily excreted by the kidneys. In patients with CPS1 or OTC deficiencies arginine administration is indicated because this amino acid is not produced in sufficient amounts to enable endogenous protein synthesis. For enteral therapy, patients with OTC deficiency benefit from supplementation with *citrulline* (200 mg/kg/24 hr) because 1 mole of citrulline reacts with 1 mole of ammonia (through aspartic acid) to form arginine. Administration of arginine or citrulline is contraindicated in patients with **arginase deficiency** , a rare condition in which the usual presenting clinical picture is spastic diplegia rather than hyperammonemia. Arginine therapy is of no benefit if hyperammonemia is secondary to an organic acidemia. In a newborn infant with an initial episode of hyperammonemia, arginine should be used until the diagnosis is established (see Table 103.5).

Benzoate, phenylacetate, and arginine may be administered together for maximal therapeutic effect. A priming dose of these compounds is followed by continuous infusion until recovery from the acute state occurs. Both benzoate and phenylacetate are usually supplied as concentrated solutions and should be properly diluted (1–2% solution) for IV use. The recommended therapeutic doses of both compounds deliver a substantial amount of sodium to the patient; this amount should be included in calculation of the daily sodiumn requirement. Benzoate and phenylacetate (or the combined formulation, Ammonul) should be used with caution in newborn infants with hyperbilirubinemia because they may displace bilirubin from albumin; however, there are no documented cases of kernicterus (see Chapter 123.4) reported in neonates with hyperammonemia who have received such therapies. In infants at risk, it is advisable to reduce bilirubin to a safe level while considering IV administration of benzoate or phenylacetate.

If the initial ammonia level is <500 µmol/L, and if the foregoing therapies fail within 4-6 hr to produce any appreciable change in the blood ammonia level, **hemodialysis** should be used. For patients presenting with an ammonia level >500 µmol/L, extracorporeal detoxification is the initial method of ammonia removal. Exchange transfusion has little effect on reducing total body ammonia. It should be used only if dialysis cannot be employed promptly or when the patient is a newborn infant with hyperbilirubinemia (see earlier). Hemodialysis dramatically lowers blood ammonia within a few hours, but if it is unavailable or technically unfeasible, peritoneal dialysis may be used as an alternative. When hyperammonemia is caused by an organic acidemia and hemodialysis is not available, peritoneal dialysis can be used to remove both the offending organic acid and ammonia.

Oral administration of **neomycin** limits growth of intestinal bacteria that can produce ammonia. However, this modality is of limited use in patients (e.g., affected neonates) in whom reduction of hyperammonemia is an urgent priority.

Oral **lactulose** acidifies the intestinal lumen, thereby reducing the diffusion of ammonia across the intestinal epithelium. This agent is of limited applicability in newborns, who have a high risk of acidemia and dehydration.

There has been interest in the use of **cooling** as a therapeutic adjunct in newborn infants with metabolic encephalopathy such as that caused by hyperammonemia. Clinical studies are in progress to evaluate the efficacy of this approach. There may be considerable lag between the normalization of ammonia level and an improvement in the patient's neurologic status. Several days may be needed before the infant becomes fully alert.

Long-Term Therapy

Once the infant is alert, therapy should be tailored to the underlying cause of the hyperammonemia. In general, all patients, regardless of the enzymatic defect, require protein restriction limited to age-adjusted recommended dietary allowance (RDA). In pediatric patients with defects in the urea cycle, chronic administration of sodium benzoate (250 mg/kg/24 hr), sodium phenylbutyrate (250-500 mg/kg/24 hr), and arginine (200-400 mg/kg/24 hr) or citrulline (in patients with OTC deficiency, 200-400 mg/kg/24 hr) is effective in maintaining blood ammonia levels within the normal range (shown doses are for patients who weigh <20 kg). Arginine and citrulline are contraindicated in patients with argininemia. Patients who have difficulty taking sodium phenylbutyrate can receive a trial of glycerol phenylbutyrate. This compound conceals the offensive odor of sodium phenylbutyrate and may help with patient adherence. Glycerol phenylbutyrate is not yet approved for use in children <2 months of age. Benzoate and phenylacetate may lower carnitine levels, but clinical signs of carnitine deficiency or benefit from carnitine supplementation have not yet been demonstrated. These compounds have been used during pregnancy without obvious teratogenic effect. However, experience is still limited, and appropriate caution should be exercised.

Growth parameters, especially head circumference, and nutritional indices (blood albumin, prealbumin, pH, electrolytes, amino acids, zinc, selenium) should be followed closely. Long-term care of these patients is best achieved by a team of experienced professionals (pediatrician, nutritionist, child neurologist, metabolic geneticist). Skin lesions resembling **acrodermatitis enteropathica** (see Chapter 691) have been noted in a few patients with different types of urea cycle defects, presumably from deficiency of essential amino acids, caused by overzealous dietary protein restriction. Catabolic states (infections, fasting) that may trigger hyperammonemia should be avoided. They must be treated vigorously if they occur. It is important that all children with urea cycle defects avoid valproic acid because this drug can elevate blood ammonia even in some healthy individuals. In patients with CPS1, OTC, or ASS deficiency, acute hyperammonemic attacks may be precipitated by valproate administration.

Carbamoyl Phosphate Synthetase 1 and *N* -Acetylglutamate Synthase Deficiencies

Deficiencies of these 2 enzymes produce similar clinical and biochemical manifestations (see Figs. 103.12 and 103.13). There is a wide variation in severity of symptoms and in the age at presentation. In near-complete enzymatic deficiency, symptoms appear during the 1st few days or even hours of life with signs and symptoms of hyperammonemia (refusal to eat, vomiting, lethargy, convulsion, coma). Increased intracranial pressure is frequent. Late forms (as late as the 4th decade of life) may present as an acute bout of hyperammonemia (lethargy, headache, seizures, psychosis) in a seemingly normal individual. Coma and death may occur during these episodes (a previously asymptomatic 26-yr-old female died from hyperammonemia during childbirth). Diagnostic confusion with migraine is common. Intermediate forms with intellectual disability and chronic subclinical hyperammonemia interspersed with bouts of acute hyperammonemia have also been observed.

Laboratory findings include hyperammonemia. The plasma amino acid analysis typically shows a marked increase of glutamine and alanine with relatively low levels of citrulline and arginine. These are nondiagnostic changes that occur in hyperammonemia of diverse cause. Urinary orotic acid is usually low or may be absent (see Fig. 103.13).

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are previously outlined (see Table 103.5). Patients with NAGS deficiency benefit from oral administration of carbamylglutamate. It is therefore important to differentiate between CPS1 and NAGS deficiencies by gene sequencing. Deficiency of NAGS is rare in North America.

CPS1 and NAGS deficiencies are inherited as an autosomal recessive trait; the

CPS1 enzyme is normally present in liver and intestine. The gene *(CPS1)* is mapped to chromosome 2q34. The prevalence of the condition is approximately 1 : 1,300,000. The gene for NAG synthetase *(NAGS)* is located on chromosome 17q21.31. Neither of these conditions is identified by the mass screening of the newborn infants.

Ornithine Transcarbamylase Deficiency

In this X-linked disorder, the hemizygous males are more severely affected than heterozygous females (see Figs. 103.12 and 103.13). The heterozygous females may have a mild form of the disease, but the majority (approximately 75%) remain asymptomatic, although investigations indicate subtle neurologic defects even in women without a frank history of hyperammonemia. Ornithine transcarbamylase (OTC) deficiency is the most common form of all the urea cycle disorders, comprising approximately 40% of cases of urea cycle disorders.

Clinical manifestations in a male newborn are usually those of **severe** hyperammonemia (see earlier) occurring in the 1st few days of life. **Mild forms** , such as in some heterozygous females, characteristically have episodic manifestations, which may occur at any age (usually after infancy). Episodes of hyperammonemia, manifested by vomiting and neurologic abnormalities (e.g., ataxia, mental confusion, agitation, combativeness, frank psychosis), are separated by periods of wellness. These episodes usually occur after ingestion of a high-protein diet or as a result of a catabolic state such as infection. Hyperammonemic coma, cerebral edema, and death may occur during one of these attacks. Cognitive development may proceed normally. Mild to moderate intellectual disability, however, is common. Gallstones have been seen in the survivors; the mechanism remains unclear.

The major **laboratory finding** during the acute attack is hyperammonemia accompanied by marked elevations of plasma concentrations of glutamine and alanine with low levels of citrulline and arginine. The blood level of urea is usually low. A marked increase in the urinary excretion of orotic acid differentiates this condition from CPS1 deficiency (see Fig. 103.13). Orotate may precipitate in urine as pink-colored gravel or stones. In the **mild form** , these laboratory abnormalities may revert to normal between attacks. This form should be differentiated from all the episodic conditions of childhood. In particular, patients with lysinuric protein intolerance (see Chapter 103.14) may demonstrate some features of OTC deficiency, but the former can be differentiated by increased urinary excretion of lysine, ornithine, and arginine and elevated blood concentrations of citrulline.

The **diagnosis** is most conveniently confirmed by gene analysis. As many as 20% of affected patients demonstrate a normal sequence, perhaps because the pathogenic variant involves copy number variants and pathogenic variants involving introns or a promoter region. Copy number variants can be evaluated using a chromosomal microarray, and if positive, a contiguous gene deletion should be considered. If the molecular diagnostic approach is negative, a liver biopsy may be indicated. Prenatal diagnosis is feasible by analysis of DNA in amniocytes or chorionic villus samples. Increase in urinary excretion of orotidine after an allopurinol loading test can identify female carriers. Mild cerebral dysfunction may be present in asymptomatic female carriers. The importance of a detailed family history should be emphasized. A history of migraine or protein aversion is common in maternal female relatives of the proband. Indeed, careful scrutiny of the family history may reveal a pattern of unexplained deaths in male newborns in the maternal lineage.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are previously outlined. For enteral use, citrulline is used in place of arginine in patients with OTC deficiency. Liver transplantation is a successful treatment for patients with severe OTC deficiency.

The gene for OTC has been mapped to the X chromosome (Xp21.1). Many disease-causing pathogenic variants (>300) have been identified. The prevalence of OTC deficiency is 1 : 56,000-1 : 77,000 live births. Genotype and the resulting degree of enzyme deficiency determine severity of the phenotype in most cases. Mothers of affected infants are expected to be carriers of the mutant gene unless a de novo pathogenic variant has occurred. A mother who gave birth to 2 affected male offspring was found to have a normal genotype, suggesting that gonadal mosaicism can be seen in some families. This condition is not identified by the mass screening of newborn infants.

Citrullinemia

Two clinically and genetically distinct forms of citrullinemia have been identified. The classic form (**type I**) is caused by the deficiency of the ASS enzyme. Citrullinemia **type II** is caused by the deficiency of a mitochondrial transport protein named *citrin* . (See Figs. 103.12 and 103.13 .)

Citrullinemia Type I (Argininosuccinate Synthetase Deficiency, Classic Citrullinemia)

This condition is caused by the deficiency of ASS (see Fig. 103.12) and has variable clinical manifestations depending on the degree of the enzyme deficiency. Two major forms of the condition have been identified. The **severe** or **neonatal form** , which is most common, appears in the 1st few days of life with signs and symptoms of hyperammonemia (see earlier). In the **subacute or mild form** , clinical findings such as failure to thrive, frequent vomiting, developmental delay, and dry, brittle hair appear gradually after 1 yr of age. Acute hyperammonemia, triggered by an intercurrent catabolic state, may bring the diagnosis to light.

Laboratory findings are similar to those found in patients with OTC deficiency, except that the plasma citrulline concentration is greatly elevated (50-100 times normal) (see Fig. 103.13). Urinary excretion of orotic acid is moderately increased; crystalluria may also occur as a result of precipitation of orotates. The diagnosis is confirmed by DNA analysis or less frequently by assay of enzyme activity in cultured fibroblasts. Prenatal diagnosis is feasible with enzyme assay in cultured amniotic cells or by DNA analysis of cells obtained from chorionic villus biopsy.

Treatment of acute hyperammonemic attacks and long-term therapy are outlined earlier (see Table 103.5). Plasma concentration of citrulline remains elevated at all times and may increase further after administration of arginine. Patients can do well on a protein-restricted diet in conjunction with sodium benzoate, phenylbutyrate, and arginine therapy. Mild to moderate cognitive impairment is a common sequela, even in a well-treated patient.

Citrullinemia is inherited as an autosomal recessive trait. The gene *(ASS1)* is located on chromosome 9q34.11. The majority of patients are compound heterozygotes for 2 different alleles. The prevalence of the condition is 1 : 250,000 live births. The recent introduction of neonatal screening for urea cycle defects has shown that some affected patients are ostensibly asymptomatic even with ingestion of a regular diet. Long-term follow-up is needed to be certain that these individuals do not sustain neurologic sequelae.

Citrin Deficiency (Citrullinemia Type II)

Citrin (aspartate-glutamate carrier protein) is a mitochondrial transporter encoded by a gene *(SLC25A13)* located on chromosome 7q21.3. One of this protein's functions is to transport aspartate from mitochondria into cytoplasm and replenish the cytosolic aspartate pool required for converting citrulline to argininosuccinic acid (see Fig. 103.12). If aspartate is unavailable to the cytoplasmic component of the urea cycle, urea will not be formed at a normal rate, and citrulline will accumulate. ASS activity is diminished in the liver of these patients, but no pathogenic variant in the *ASS1* gene has been found. It is postulated that citrin deficiency interferes with translation of messenger RNA for ASS enzyme in the liver. The condition initially was reported in Japan, but non-Japanese patients have also been identified. Two clinical forms of citrin deficiency have been described.

Neonatal Intrahepatic Cholestasis (Citrullinemia Type II, Neonatal Form)

Clinical and laboratory manifestations, which usually start before 1 yr of age, include cholestatic jaundice with mild to moderate direct (conjugated) hyperbilirubinemia, marked hypoproteinemia, clotting dysfunction (increased prothrombin time and partial thromboplastin time), and increased serum γ-glutamyltransferase and alkaline phosphatase activities; liver transaminases are usually normal. Plasma concentrations of ammonia and citrulline are usually normal, but moderate elevations have been reported. There may be increases in plasma concentrations of methionine, tyrosine, alanine, and threonine. Elevated levels of serum galactose have been found, even though the enzymes of galactose metabolism are normal. The reason for hypergalactosemia is not known. Marked elevation in the serum level of α-fetoprotein is also present. These findings resemble those of tyrosinemia type I, but unlike the latter condition, urinary excretion of succinylacetone is not elevated (see Chapter 103.2). Liver biopsy shows fatty infiltration, cholestasis with dilated canaliculi, and a moderate degree of fibrosis. The condition is usually self-limiting, and the majority of infants recover spontaneously by 1 yr of age with supportive and symptomatic treatment. Hepatic failure requiring liver transplantation has occurred in a few cases. Although the condition is commonly seen in Japan, the diagnosis should be considered in any case of unexplained neonatal hepatitis with cholestasis. Data on the long-term prognosis and the natural history of the condition are limited; development into the adult form of the condition after several years of seemingly asymptomatic hiatus has been observed.

Citrullinemia Type II, Adult Form (Adult-Onset Citrullinemia; Citrullinemia Type II, Mild Form)

This form of citrullinemia type II starts acutely in a previously apparently normal individual and manifests with neuropsychiatric symptoms such as disorientation, delirium, delusion, aberrant behavior, tremors, and frank psychosis. Moderate degrees of hyperammonemia and hypercitrullinemia are present. The age at onset is usually between 20 and 40 yr (range: 11 to >100 yr). Patients who recover from the 1st episode may have recurrent attacks. Pancreatitis, hyperlipidemia, and hepatoma are major complications among the survivors. Medical **treatment** has been mostly ineffective for prevention of future attacks. Diet enriched for protein and lipids helps restore cytosolic aspartate pool and stimulate ureagenesis. Indeed, some have speculated that the administration of large amounts of glucose might even prove deleterious, because the citrin transporter is important to the glycolytic pathway. Although liver transplantation appears to be effective in preventing future episodes of hyperammonemia, enteral supplementation with arginine, pyruvate, and medium-chain triglycerides can be tried first to improve hyperammonemic episodes and growth.

Several disease-causing mutations of the gene have been identified in affected Japanese and non-Japanese families. Although the frequency of homozygosity is relatively high in Japan (1 : 20,000 people), the clinical condition has a frequency of only 1 : 100,000 to 1 : 230,000. This indicates that a substantial number of homozygous individuals remain asymptomatic.

Argininosuccinate Lyase Deficiency (Argininosuccinic Aciduria)

The severity of the clinical and biochemical manifestations varies considerably (see Figs. 103.12 and 103.13). In severe form of ASL deficiency, signs and symptoms of severe hyperammonemia (see earlier) develop in the 1st few days of life, and without treatment, mortality can be high. Clinical course of ASL deficiency in patients who survive the initial acute episode can be characterized by intellectual disability, failure to thrive, hypertension, gallstones, liver fibrosis, and hepatomegaly. A common finding in untreated patients is dry and brittle hair (**trichorrhexis nodosa**). Acute attacks of severe hyperammonemia may occur during a catabolic state.

Laboratory findings include hyperammonemia, moderate elevations in liver enzymes, nonspecific increases in plasma levels of glutamine and alanine, a moderate increase in plasma levels of citrulline (less than in citrullinemia), and marked increase in the concentration of argininosuccinic acid in plasma, urine, and CSF. The CSF levels are usually higher than those in plasma. The enzyme is normally present in erythrocytes, the liver, and cultured fibroblasts. **Prenatal diagnosis** is possible by measurement of the enzyme activity in cultured amniotic cells or by identification of pathogenic variants in the *ASL* gene. Argininosuccinic acid is also elevated in the amniotic fluid of affected fetuses.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier in this chapter. Intellectual disability, persistent hepatomegaly with mild increases in liver enzymes, and bleeding tendencies as a result of abnormal clotting factors are common sequelae. This deficiency is inherited as an autosomal recessive trait with a prevalence of about 1 in 220,000 live births. The gene *(ASL)* is located on chromosome 7q11.21. Early detection is achieved through mass screening of newborn infants.

Arginase 1 Deficiency (Hyperargininemia)

This defect is inherited as an autosomal recessive trait (see Figs. 103.12 and 103.13). There are 2 genetically distinct arginases in humans. One is cytosolic (ARG1) and is expressed in the liver and erythrocytes, and the other (ARG2) is found in renal and brain mitochondria. The gene for ARG1, the enzyme that is deficient in patients with arginase 1 deficiency, is mapped to chromosome 6q23.2. The role of the mitochondrial enzyme is not well understood; its activity increases in patients with argininemia but has no protective effect.

Clinical manifestations of this rare distal urea cycle disorder are somewhat different from those of other urea cycle enzyme defects, although acute neonatal form with intractable seizures, cerebral edema, and death has also been reported. The onset arginase 1 deficiency often is insidious; the infant can remain asymptomatic in the 1st few mo or yr of life. A **progressive spastic diplegia** with scissoring of the lower extremities, choreoathetotic movements, loss of developmental milestones, and failure to thrive in a previously normal infant may suggest a degenerative disease of the CNS. Some children were treated for years as cases of cerebral palsy before their arginase 1 deficiency was confirmed.

Intellectual disability is progressive; seizures are common, but episodes of severe hyperammonemia are not as frequent as in the more proximal urea cycle defects. Hepatomegaly may be present.

Laboratory findings include marked elevations of arginine in plasma and CSF (see Fig. 103.13). Urinary orotic acid can be increased. Determination of amino acids in plasma is a critical step in the diagnosis of argininemia. The guanidino compounds (α-keto-guanidinovaleric acid and α-keto-argininic acid) are markedly increased in urine. The diagnosis is confirmed by assaying arginase activity in erythrocytes or by the identification of the mutant gene.

Treatment consists of a low-protein diet providing the RDA. The composition of the diet and the daily intake of protein should be monitored by frequent plasma amino acid determinations. Sodium benzoate or sodium phenylbutyrate are also effective in controlling hyperammonemia and lowering plasma arginine levels. Intellectual disability is a common sequela of the condition. One patient developed type 1 diabetes by 9 yr of age while his argininemia was under good control. Liver transplantation has produced promising results, but experience with long-term outcome is limited. Early detection is feasible through mass screening of newborn infants.

Transient Hyperammonemia of the Newborn

The blood concentration of ammonia in full-term infants may be as high as 100 µmol/L, or 2-3 times greater than that of the older child or adult. Blood levels approach the adult normal values after a few weeks of life (see Fig. 103.13).

Severe transient hyperammonemia is observed in some newborn infants. The majority of affected infants are premature and have mild respiratory distress syndrome. Hyperammonemic coma may develop within 2-3 days of life, and the infant may succumb to the disease if treatment is not started immediately. Laboratory studies reveal marked hyperammonemia (plasma ammonia as high as 4,000 µmol/L) with moderate increases in plasma levels of glutamine and alanine. Plasma concentrations of urea cycle intermediate amino acids are usually normal except for citrulline, which may be moderately elevated. The cause of the disorder is unknown. Urea cycle enzyme activities are normal. **Treatment** of hyperammonemia should be initiated promptly and continued vigorously. Recovery without sequelae is common, and hyperammonemia does not recur even with a normal protein diet.

Disorders of Ornithine Metabolism

Ornithine, a key intermediate of the urea cycle, is not incorporated into natural proteins. Rather, it is generated in the cytosol from arginine and must be transported into mitochondria, where it becomes a substrate for the reaction catalyzed by OTC that forms citrulline. Excess ornithine is catabolized by 2 enzymes, ornithine aminotransferase, which is a mitochondrial enzyme converting ornithine to a proline precursor, and ornithine decarboxylase, which resides in the cytosol and converts ornithine to putrescine (see Fig. 103.12). Two genetic disorders feature **hyperornithinemia** : gyrate atrophy of the retina and hyperammonemia-hyperornithinemia-homocitrullinemia syndrome.

Gyrate Atrophy of the Retina and Choroid

This rare, autosomal recessive disorder is caused by deficiency of ornithine aminotransferase (see Fig. 103.12). Approximately 30% of the reported cases are from Finland. Clinical manifestations may include hyperammonemia in the 1st mo of life in some patients. Findings that define the phenotype of ornithine aminotransferase deficiency include night blindness, myopia, loss of peripheral vision, and posterior subcapsular cataracts. These eye changes start between 5 and 10 yr of age and progress to complete blindness by the 4th decade of life. Atrophic lesions in the retina resemble cerebral gyri. These patients usually have normal intelligence. Besides the characteristic 10-20–fold increase in plasma levels of ornithine (400-1,400 µmol/L), plasma levels of glutamate, glutamine, lysine, creatine, and creatinine can be moderately decreased. Some patients respond partially to high doses of pyridoxine. An arginine-restricted diet in conjunction with supplemental lysine, proline, and creatine has been successful in reducing plasma ornithine concentration and has produced some clinical improvement. The gene for ornithine aminotransferase *(OAT)* is mapped to chromosome 10q26.13. Many (at least 60) pathogenic variants have been identified in different families.

Hyperammonemia-Hyperornithinemia-Homocitrullinemia Syndrome

In this rare autosomal recessive disorder the defect is in the transport system of ornithine from the cytosol into the mitochondria, resulting in accumulation of ornithine in the cytosol and a depletion of this amino acid in mitochondria. The former causes hyperornithinemia, and the latter results in disruption of the urea cycle and hyperammonemia (see Fig. 103.12). Homocitrulline is presumably formed from the reaction of mitochondrial carbamoyl phosphate with lysine, which can become a substrate for the OTC reaction when ornithine is deficient. Clinical manifestations of hyperammonemia may develop shortly after birth or may be delayed until adulthood. Acute episodes of hyperammonemia manifest as refusal to feed, vomiting, and lethargy; coma may occur during infancy. Progressive neurologic signs, such as lower limb weakness, increased deep tendon reflexes, spasticity, clonus, seizures, and varying degrees of psychomotor retardation may develop if the condition remains undiagnosed. No clinical ocular findings have been observed in these patients. Laboratory findings reveal marked increases in plasma levels of ornithine and homocitrulline in addition to hyperammonemia (see Fig. 103.13). Acute episodes of hyperammonemia should be treated promptly (see earlier). Restriction of protein intake improves hyperammonemia. Oral supplementation with arginine (or citrulline) has produced clinical improvement in some patients. The gene for this disorder *(SLC25A15)* is located on chromosome 13q14.11.

Congenital Glutamine Deficiency

Glutamine is synthesized endogenously from glutamate and ammonia by a ubiquitous enzyme, glutamine synthetase (see Fig. 103.11). Glutamine is known to be involved in several important functions, including detoxification of ammonia. Deficiency of this enzyme, resulting in glutamine deficiency, has been reported in 3 infants from 3 unrelated families. All affected infants manifested multiorgan involvement, including significant brain malformations (abnormal gyrations, hypomyelination), facial abnormalities (broad nasal root, low-set ears), hypotonia and seizures at birth. Two of the patients died from multiorgan failure (respiratory and heart failure) in the neonatal period. One child was alive at 3 yr of age with severe developmental delay. Glutamine was absent in plasma, urine, and CSF, but plasma levels of glutamic acid were normal. Genetic defects of this enzyme underline the critical role of glutamine in embryogenesis, especially for normal brain development. The condition is inherited as an autosomal recessive trait; the gene for glutamine synthetase *(GLUL)* is mapped to chromosome 1q25.3.

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103.13

Histidine

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Keywords

histidine
L -histidine decarboxylase
urocanic acid

Histidine is degraded through the urocanic acid pathway to glutamic acid. Several genetic biochemical aberrations involving the degradative pathway of histidine have been reported, but the clinical significance of elevated histidine levels has not been established.

Decarboxylation of histidine by histidine decarboxylase produces histamine. Deficiency of this enzyme has been implicated in the familial form of **Tourette syndrome** (see Chapter 103.11).

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103.14

Lysine

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Keywords

lysine
saccharopine
hyperlysinemia-saccharopinuria
antiquitin
ALDH7A1
pyridoxine-dependent epilepsy
α-aminoadipic semialdehyde dehydrogenase deficiency
pyridoxal 5′-phosphate
pyridoxine 5′-phosphate oxidase deficiency
PNPO deficiency
PNPO
piperideine-6-carboxylic acid
P6C
hypophosphatasia
glutaric acid
glutarylcarnitine
3-OH-glutaric acid
glutaric aciduria type 1
glutaryl-CoA dehydrogenase deficiency
GCDH
lysinuric protein intolerance
SLC7A7

Lysine is catabolized through 2 pathways. In the 1st pathway, lysine is condensed with α-ketoglutaric acid to form saccharopine. Saccharopine is then catabolized to α-aminoadipic semialdehyde and glutamic acid. These 1st 2 steps are catalyzed by α-aminoadipic semialdehyde synthase, which has 2 activities: lysine-ketoglutarate reductase and saccharopine dehydrogenase (Fig. 103.14). In the 2nd pathway, lysine is first transaminated and then condensed to its cyclic forms, pipecolic acid and piperideine-6-carboxylic acid (**P6C**). P6C and its linear form, α-aminoadipic semialdehyde, are oxidized to α-aminoadipic acid by the enzyme **antiquitin** . This is the major pathway for D -lysine in the body and for the L -lysine in the brain.

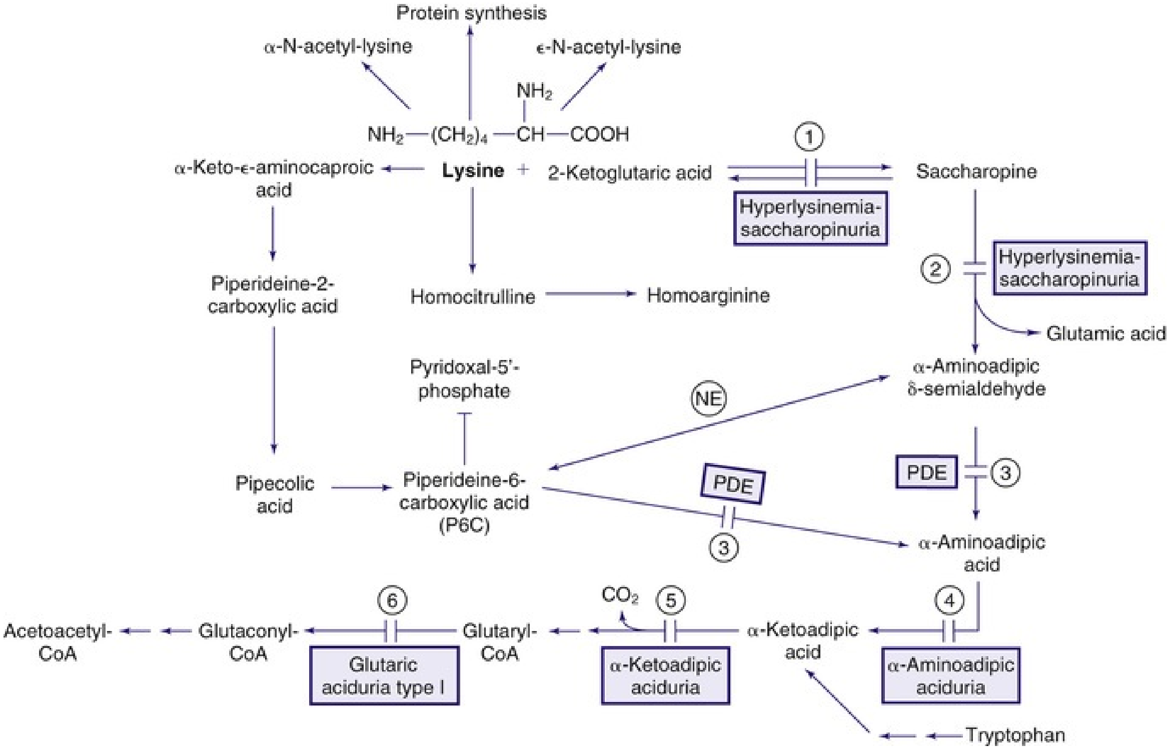
Protein synthesis
α-N-acetyl-lysine
ε-N-acetyl-lysine
NH2
NH2—(CH2)4—CH—COOH
①
α-Keto-ε-aminocaproic acid
Lysine + 2-Ketoglutaric acid
Saccharopine
Hyperlysinemia-saccharopinuria
②
Hyperlysinemia-saccharopinuria
Piperideine-2-carboxylic acid
Homocitrulline
Homoarginine
Glutamic acid
Pyridoxal-5'-phosphate
NE
α-Aminoadipic δ-semialdehyde
PDE
③
Pipecolic acid
Piperideine-6-carboxylic acid (P6C)
PDE
③
α-Aminoadipic acid
⑥
CO2
⑤
④
Acetoacetyl-CoA
Glutaconyl-CoA
Glutaryl-CoA
α-Ketoadipic acid
Glutaric aciduria type I
α-Ketoadipic aciduria
α-Aminoadipic aciduria
Tryptophan

FIG. 103.14 Pathways in the metabolism of lysine. Enzymes: *(1)* Lysine ketoglutarate reductase, *(2)* saccharopine dehydrogenase, *(3)* α-aminoadipic semialdehyde/piperidine-6-carboxylic acid (P6C) dehydrogenase (antiquitin), *(4)* α-aminoadipic acid transferase, *(5)* α-ketoadipic acid dehydrogenase, *(6)* glutaryl-CoA-dehydrogenase. NE, Nonenzymatic; PDE, pyridoxine-dependent epilepsy.

Hyperlysinemia-saccharopinuria and **α-aminoadipic-α-ketoadipic acidemia** are biochemical conditions caused by inborn errors of lysine degradation. Individuals with these conditions are usually asymptomatic.

Pyridoxine (Vitamin B_6)–Dependent

Epilepsy

Pyridoxal 5′-phosphate (**P5P**), the active form of pyridoxine, is the cofactor for many enzymes including those involved in the metabolism of neurotransmitters. Intracellular P5P deficiency in the brain may result in a seizure disorder that is refractory to common anticonvulsant agents but is responsive to high doses of pyridoxine. These pyridoxine-responsive phenotypes are seen in the following genetic metabolic conditions:

Antiquitin (α-Aminoadipic Semialdehyde Dehydrogenase) Deficiency

This is the most common cause of pyridoxine-dependent epilepsy. Deficiency of antiquitin results in accumulation of P6C in brain tissue (see Fig. 103.14); P6C reacts with P5P and renders it inactive. Large doses of pyridoxine are therefore needed to overcome this inactivation. The condition is inherited as an autosomal recessive trait; the gene for antiquitin *(ALDH7A1)* is on chromosome 5q31.

Pyridox(am)ine 5′-Phosphate Oxidase (PNPO) Deficiency

PNPO deficiency clinically overlaps with antiquitin deficiency. PNPO-deficient patients often present with neonatal-onset seizures, developmental delays, spastic tetraplegia, and nonspecific findings on brain imaging (delayed myelination, cerebral atrophy, and abnormal signals in basal ganglia). Developmental regression, optic disc pallor, and retinopathy have been reported infrequently. Plasma and CSF amino acid analysis may reveal elevated glycine, prompting evaluation for nonketotic hyperglycinemia (see Chapter 103.7) and lead to a delay in initiating treatment with P5P. CSF neurotransmitter assay revealed inconsistent changes in the levels of 3-*O* -methyldopa, homovanillic acid, and 5-hydroxyindoleacetic acid. Normal CSF level of P5P was reported in one patient, suggesting that a therapeutic trial with P5P and molecular analysis may be a prudent strategy in some patients irrespective of the CSF studies. The lowest effective dose of P5P should be used to avoid toxicity. The disorder is caused by autosomal recessive pathogenic variants in *PNPO* .

Sulfite Oxidase Deficiency and Molybdenum Cofactor Deficiency

In this rare condition (see Chapter 103.4), accumulation of sulfites causes inhibition of enzymatic activity of antiquitin and accumulation of P6C, which in turn causes inactivation of P5P and vitamin B_6 dependency.

Hyperprolinemia Type II

In this condition, accumulation of Δ1-pyrroline-5-carboxylate (P5C) in brain tissue causes inactivation of P5P, leading to pyridoxine dependency (see Chapter 103.9 and Fig. 103.9).

Hypophosphatasia

Pyridoxal-5′-phosphate is the main circulating form of pyridoxine. Alkaline phosphatase (ALP) is required for dephosphorylation of P5P to generate free pyridoxine, which is the only form of vitamin B_6 that can cross the blood-brain barrier and enter the brain cells. Pyridoxine is rephosphorylated intracellularly to form P5P. In the infantile form of hypophosphatasia, P5P cannot be dephosphorylated to free pyridoxine because of marked deficiency of tissue-nonspecific ALP. This results in deficiency of pyridoxine in the brain and pyridoxine-dependent epilepsy (see Chapters 611 and 724).

The main **clinical manifestation** of pyridoxine-dependent epilepsy caused by antiquitin deficiency is generalized seizures, which usually occur in the first days of life and are unresponsive to conventional anticonvulsant therapies. Some mothers of affected fetuses report abnormal intrauterine fluttering movements. The seizures are usually tonic-clonic in nature but can be almost any type. Other manifestations such as dystonia, respiratory distress, and abdominal distention with vomiting, hepatomegaly, hypoglycemia and hypothermia may be present. Learning problems and speech delay are common sequelae. Late-onset forms of the condition (as late as 5 years of age) have been reported. Consequently, a trial with vitamin B_6 is recommended in any infant with intractable convulsions (see Chapters 611.04 and 611.06).

Laboratory findings show increased concentrations of α-aminoadipic semialdehyde and pipecolic acid in the CSF, plasma, and urine. EEG abnormalities may normalize after treatment. Neuroimaging may be normal but cerebellar and cerebral atrophy, periventricular hyperintensity, intracerebral hemorrhage, and hydrocephalus have been reported.

Treatment with vitamin B_6 (50-100 mg/day) usually results in a dramatic improvement of both seizures and the EEG abnormalities. High doses of pyridoxine can result in peripheral neuropathy, and doses >500 mg/day should be avoided. The pyridoxine dependency and thus the therapy are lifelong. The therapeutic benefit of a lysine-restricted diet is being evaluated.

Glutaric Aciduria Type 1 (Glutaryl-CoA Dehydrogenase Deficiency)

Glutaric acid is an intermediate in the degradation of lysine (see Fig. 103.14), hydroxylysine, and tryptophan. Glutaric aciduria **type 1** , a disorder caused by a deficiency of glutaryl-CoA dehydrogenase, should be differentiated from glutaric aciduria **type 2** , a distinct clinical and biochemical disorder caused by defects in the mitochondrial electron transport chain (see Chapter 104.1).

Clinical Manifestations

Macrocephaly is a common but nonspecific finding in patients with glutaric aciduria type 1. It develops in the 1st yr of life but can also be present at birth and precede the onset of neurologic manifestations. Some affected infants may also show subtle neurologic symptoms, such as delayed onset of motor milestones, irritability, and feeding problems, during this seemingly asymptomatic period. The onset of the condition is usually heralded by **acute encephalopathic findings** , such as loss of normal developmental milestones (head control, rolling over, or sitting), seizures, generalized rigidity, opisthotonos, choreoathetosis, and dystonia caused by acute striatal injury. These symptoms may occur suddenly in an apparently normal infant after a minor infection. Brain imaging reveals increased extraaxial (particularly frontal) fluid with stretched bridging veins, striatal lesions, dilated lateral ventricles, cortical atrophy (mainly in frontotemporal region), and fibrosis. Recovery from the 1st attack usually occurs slowly, but some residual neurologic abnormalities may persist, especially dystonia and choreoathetosis. Without treatment, additional acute attacks resembling the first can occur during subsequent episodes of intercurrent infections or catabolic states. In some patients these signs and symptoms may develop gradually in the 1st few yr of life. Hypotonia and choreoathetosis may gradually progress into rigidity and dystonia (**insidious form**). Acute episodes of metabolic decompensation with vomiting, ketosis, seizures, and coma also occur in this form after infection or other catabolic states. Without treatment, death may occur in the 1st decade of life during one of these episodes. Affected infants are prone to development of subdural hematoma and retinal hemorrhage following minor falls and head traumas. This can be misdiagnosed as child abuse. The intellectual abilities usually remain relatively normal in most patients.

Laboratory Findings

During acute episodes, mild to moderate metabolic acidosis and ketosis may occur. Hypoglycemia, hyperammonemia, and elevations of serum transaminases are seen in some patients. High concentrations of glutaric acid are usually found in urine, blood, and CSF. 3-Hydroxyglutaric acid may also be present in the body fluids. Acylcarnitine profile shows elevated glutarylcarnitine (C5-DC) in blood and urine. Plasma concentrations of amino acids are usually within normal limits. Laboratory findings may be unremarkable between attacks. Glutaric aciduria type 1 can be identified on the newborn screen by measuring glutarylcarnitine levels in blood spots. The sensitivity of this screening method depends on the cutoff value used by a newborn screen program, and some patients can be missed. For example, it can happen in a subset of patients with glutaric aciduria type 1 who may present with normal plasma and urinary levels of glutaric acid and variably elevated plasma glutarylcarnitine. This type of glutaric aciduria type 1 referred to as a “low-excretor” phenotype carries the same risk of developing brain injury as in a “high-excretor” phenotype. In some low-excreting patients, glutaric acid is elevated only in CSF. Urinary glutarylcarnitine appears to be a more sensitive screening method to identify affected low-excreting patients. In any child with progressive dystonia and dyskinesia, activity of the enzyme glutaryl-CoA dehydrogenase and molecular analysis of *GCDH* should be performed.

Treatment

Patients require lysine- and tryptophan-restricted diet while meeting physiologic requirements for protein, micronutrients, and vitamins. Increased dietary arginine may decrease cellular uptake of lysine and decrease the endogenous formation of glutaryl-CoA. Patients should be routinely evaluated for lysine and tryptophan deficiency by monitoring plasma amino acids and growth. L -Carnitine supplementation (50-100 mg/kg/24 hr orally) is recommended in all cases. Emergency treatment during acute illness, including temporary cessation of protein intake for 24 hr, replacement of lost calories using carbohydrates or lipids, IV L -carnitine, IV dextrose, prompt treatment of infection, and control of fever, is critical to decreasing the risk of striatal injury. All patients should be provided with an emergency letter describing the underlying diagnosis, recommended evaluation, and treatment. Early diagnosis through newborn screening with prevention and aggressive treatment of intercurrent catabolic states (infections) can help minimize striatal injury and ensure a more favorable prognosis. Patients with movement disorder and spasticity may require treatment with baclofen, diazepam, trihexyphenidyl, and injectable botulinum toxin A.

Glutaric aciduria type 1 is inherited as an autosomal recessive trait. The prevalence is estimated at 1 : 100,000 live births worldwide. The condition is more prevalent in some ethnic populations (Canadian Oji-Cree Indians, Irish Travelers, black South Africans, Swedes, and the Old Order Amish population in the United States). The gene for glutaryl-CoA dehydrogenase *(GCDH)* is located on chromosome 19p13.2. Molecular analysis of *GCDH* can aid in identifying patients with a low-excretor phenotype associated with specific pathogenic variants (e.g., p.M405V, p.V400M, p.R227P). High prevalence of known pathogenic variants in specific ethnic populations can enable a cost-effective molecular evaluation and counseling.

Prenatal diagnosis can be accomplished by demonstrating increased concentrations of glutaric acid in amniotic fluid, by assay of the enzyme activity in amniocytes or chorionic villus samples, or by identification of the known pathogenic variants in *GCDH* .

Lysinuric Protein Intolerance (Familial Protein Intolerance)

This rare autosomal recessive disorder is caused by a defect in the transport of the cationic amino acids lysine, ornithine, and arginine in both intestine and kidneys. Deficiency of the transporter protein (Y+L amino acid transporter 1) in this condition causes multisystem manifestations, which start initially with gastrointestinal (GI) symptoms. The transport defect in this condition resides in the basolateral (antiluminal) membrane of enterocytes and renal tubular epithelia. This explains the observation that cationic amino acids are unable to cross these cells even when administered as dipeptides. Lysine in the form of dipeptide crosses the luminal membrane of the enterocytes but hydrolyzes to free lysine molecules in the cytoplasm. Free lysine, unable to cross the basolateral membrane of the cells, diffuses back into the lumen.

Refusal to feed, nausea, aversion to protein, vomiting, and mild diarrhea, which may result in failure to thrive, wasting, and hypotonia, may be seen shortly after birth. Breastfed infants usually remain asymptomatic until soon after weaning, possibly because of the low-protein content of breast milk. Episodes of hyperammonemia may occur after ingestion of a high-protein meal. Mild to moderate hepatosplenomegaly, osteoporosis, sparse brittle hair, thin extremities with moderate centripetal adiposity, and growth retardation are common physical findings in patients whose condition has remained undiagnosed. Neurocognitive status is usually normal, but moderate intellectual disability has been observed in some patients.

Progressive interstitial pneumonitis with bouts of acute exacerbation often occurs in these patients. This usually progresses to severe alveolar proteinosis. Clinical manifestations include progressive exertional dyspnea, fatigue, cough, diminished breath sound, and inspiratory rales; cyanosis may develop in older patients. Some patients have remained undiagnosed until the appearance of pulmonary manifestations. Radiographic evidence of pulmonary fibrosis has been observed in up to 65% of patients without clinical manifestations of pulmonary involvement.

Renal involvement is manifested initially by proteinuria, hematuria, and elevation of serum creatinine, which may progress to end-stage renal failure. Renal tubular involvement with laboratory findings of renal Fanconi syndrome may also be present. Renal biopsy reveals pathologic findings consistent with glomerulonephritis and tubulointerstitial nephritis. Hematologic findings of anemia, leukopenia, thrombocytopenia, and elevated ferritin may also be present. A condition resembling hemophagocytic lymphohistiocytosis/macrophage activation syndrome has also been reported. Immunologic abnormalities (impaired lymphocyte function, abnormalities in immune globulins, hypocomplementemia) and acute pancreatitis are frequent features of lysinuric protein intolerance.

Laboratory findings may reveal hyperammonemia and an elevated concentration of urinary orotic acid, which develop after high-protein feeding. Plasma concentrations of lysine, arginine, and ornithine are usually mildly decreased, but urinary levels of these amino acids, especially lysine, are greatly increased. The pathogenesis of hyperammonemia is likely related to the depletion of urea cycle intermediates caused by poor absorption and the increased renal loss of ornithine and arginine. Plasma concentrations of alanine, glutamine, serine, glycine, and proline are usually increased. Anemia, increased serum levels of ferritin, lactate dehydrogenase (LDH), thyroxine-binding globulin, hypercholesterolemia, and hypertriglyceridemia are common findings. This condition should be differentiated from hyperammonemia caused by urea cycle defects (see Chapter 103.12), especially in heterozygous females with OTC deficiency, in whom increased urinary excretion of lysine, ornithine, and arginine is not seen.

Treatment with a low-protein diet providing the RDA of protein and supplemented with oral citrulline (50-100 mg/kg/day) can produce biochemical and clinical improvements. Episodes of hyperammonemia should be treated promptly (see Chapter 103.12). Supplementation with lysine (10-30 mg/kg/day) given in small and frequent doses helps improve plasma levels. The dose of lysine should be titrated down if patients develop abdominal pain and diarrhea. Treatment with high doses of prednisone has been effective in the management of acute pulmonary complications in some patients. **Bronchopulmonary lavage** is the treatment of choice for patients with alveolar proteinosis. The condition is more prevalent in Finland and Japan, where the prevalence is 1 : 60,000 and 1 : 57,000 live births, respectively.

The gene for lysinuric protein intolerance *(SLC7A7)* is mapped to chromosome 14q11.2. Pregnancies in affected mothers have been complicated by anemia, thrombocytopenia, toxemia, and bleeding, but offspring have been normal.

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103.15

N -Acetylaspartic Acid (Canavan Disease)

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Keywords

Canavan disease
atypical Canavan disease
N -acetylaspartic acid
NAA
ASPA
aspartoacylase
recombinant adeno-associated viruses
rAAVs
blood-brain barrier
leukodystrophy
progressive macrocephaly

N -Acetylaspartic acid (**NAA**), a derivative of aspartic acid, is synthesized in the brain and is found in a high concentration similar to glutamic acid. Studies suggest that NAA has multiple functions, such as serving as an acetate reservoir for myelin synthesis and being an organic osmolyte that helps regulate cerebral osmolality. However, the complete function of NAA is not yet fully understood. **Aspartoacylase** cleaves the *N* -acetyl group from NAA. Deficiency of aspartoacylase leads to **Canavan disease** , a severe **leukodystrophy** characterized by excessive excretion of NAA and spongy degeneration of the white matter of the brain. Canavan disease is an autosomal recessive disorder and is more prevalent in individuals of Ashkenazi Jewish descent than in other ethnic groups. The defective gene for Canavan disease *(ASPA)* is located on chromosome 17, and genetic testing can be offered for patients, family members, and at-risk populations.

Etiology and Pathology

The deficiency of the enzyme aspartoacylase leads to NAA accumulation in the brain, especially in white matter, and massive urinary excretion of this compound. Excessive amounts of NAA are also present in the blood and CSF. Brain biopsies of patients with Canavan disease show spongy degeneration of the myelin fibers, astrocytic swelling, and elongated mitochondria. There is striking vacuolization and astrocytic swelling in white matter. Electron microscopy reveals distorted mitochondria. As the disease progresses, the ventricles enlarge because of cerebral atrophy.

Clinical Manifestations

The severity of Canavan disease covers a wide spectrum. Infants usually appear normal at birth and may not manifest symptoms of the disease until 3-6 mo of age, when they develop **progressive macrocephaly** , severe hypotonia, persistent head lag, and delayed milestones. As the disease progresses, there is spasticity, joint stiffness, and contractures. Optic atrophy and seizures develop. Feeding difficulties, poor weight gain, and gastroesophageal reflux may occur in the 1st yr of life; swallowing deteriorates, and nasogastric feeding or permanent gastrostomy may be required. In the past, most patients died in the 1st decade of life, but with the advances in medical technology and improved supportive care, now they often survive to the 2nd or 3rd decade.

Atypical Canavan Disease

Juvenile or **mild** Canavan disease is less common than **infantile** Canavan disease and is most prevalent in non-Ashkenazi Jews. Affected patients with juvenile Canavan disease usually present with mild speech and motor delay and may have **retinitis pigmentosa** . The other typical features of Canavan disease are usually not present. These children have moderately increased urinary excretion of NAA, which suggests Canavan disease. Brain MRI demonstrates increased signal intensity in the basal ganglia rather than global white matter disease, sometimes leading to confusion with mitochondrial disease.

Diagnosis

In a typical patient with Canavan disease, CT scan and MRI reveal diffuse white matter degeneration, primarily in the cerebral hemispheres, with less involvement of the cerebellum and brainstem (Fig. 103.15). Repeated evaluations may be required. MRS performed at the time of MRI can be done to show the high peak of NAA, suggesting Canavan disease. The diagnosis can also be established by finding elevated amounts of NAA in the urine or blood. NAA is found only in trace amounts (24 ±16 µmol/mmol creatinine) in the urine of unaffected individuals, whereas in patients with Canavan disease its concentration is in the range of 1,440 ±873 µmol/mmol creatinine. High levels of NAA can also be detected in plasma, CSF, and brain tissue. Aspartoacylase in fibroblasts is often used to confirm the diagnosis but is not necessary. The activity of aspartoacylase in the fibroblasts of obligate carriers is half or less the activity found in normal individuals. Genotyping of patients with Canavan disease should always be done and will show mutations of *ASPA* . The differential diagnosis of Canavan disease should include **Alexander disease** , which is another leukodystrophy associated with macrocephaly. Alexander disease is caused by a defect in the synthesis of glial fibrillary acidic protein, and the diagnosis can be ruled out by molecular diagnosis on blood lymphocytes.

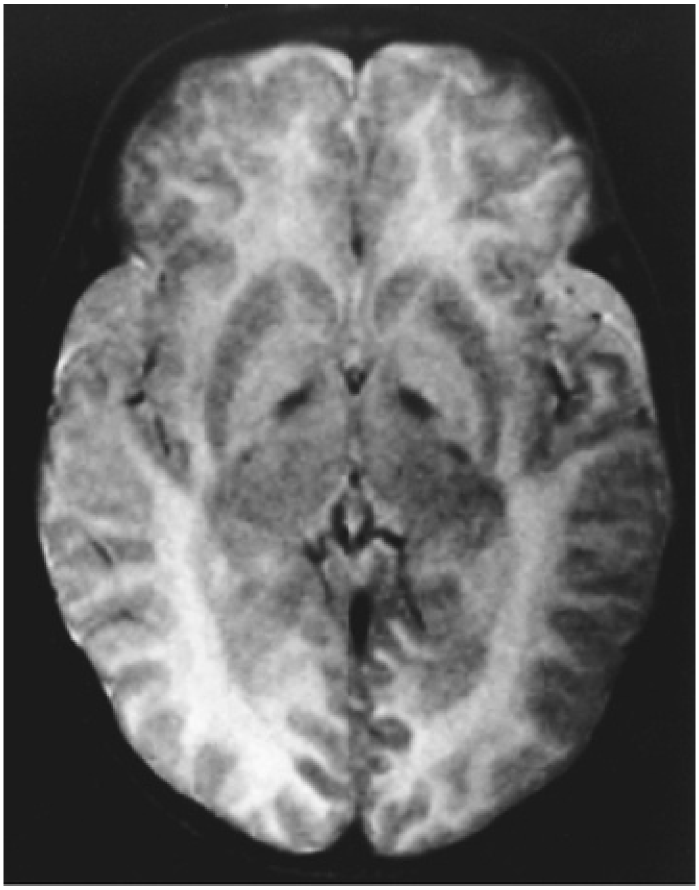

FIG. 103.15 Axial T-weighted MRI of a 2 yr old patient with Canavan disease. Extensive thickening of the white matter is seen.

There are 2 predominant pathogenic variants leading to Canavan disease in the Ashkenazi Jewish population. The first is an amino acid substitution (E285A) in which glutamic acid is substituted for alanine. This mutation is the most frequent and encompasses 83% of 100 mutant alleles examined in Ashkenazi Jewish patients. The 2nd common pathogenic variant is a change from tyrosine to a nonsense mutation, leading to a stop in the coding sequence (Y231X). This accounts for 13% of mutant alleles. In the non-Jewish population, more diverse pathogenic variants have been observed, and the 2 variants common in Jewish people are rare. A different mutation (A305E), the substitution of alanine for glutamic acid, accounts for 40% of 62 mutant alleles in non-Jewish patients. More than 50 pathogenic variants are described in the non-Jewish population. With Canavan disease, it is important to obtain a molecular diagnosis because this will lead to accurate counseling and prenatal guidance for the family. If the mutations are not known, **prenatal diagnosis** relies on the NAA level in the amniotic fluid. In Ashkenazi Jewish patients, the carrier frequency can be as high as 1 : 40, which is close to that of Tay-Sachs disease. Carrier screening for Canavan disease is available for Jewish individuals. Genotype phenotype correlation and aspartoacylase expression show that expression studies may aid in understanding the disease.

Patients with juvenile or mild forms of Canavan disease have been compound heterozygotes with a mild pathogenic variant on one allele and a severe variant on the other allele. Mild variants include p.Tyr288Cys and p.Arg71His.

Treatment and Prevention

No specific treatment is currently available. Recent studies of gene therapy using recombinant adeno-associated viruses (**rAAVs**) have shown some positive results in rescuing knockout mice but have yet to be tested in humans. Feeding problems and seizures should be treated on an individual basis. Genetic counseling, carrier testing, and prenatal diagnosis are the only methods of prevention. Gene therapy attempts in children with Canavan disease have shown lack of long-term adverse events, some decrease in the brain elevation of *N* -acetylaspartic acid, improved seizure frequency, and stabilization of overall clinical status.

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CHAPTER 104

Defects in Metabolism of Lipids

104.1

Disorders of Mitochondrial Fatty Acid β-Oxidation

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Keywords

fatty acid oxidation defects
carnitine cycle
newborn screening
hypoglycemia
medium-chain acyl-CoA dehydrogenase deficiency
liver disease
cardiomyopathy
rhabdomyolysis
fasting intolerance
mitochondrial metabolism
Reye syndrome

Mitochondrial β-oxidation of fatty acids is an essential energy-producing pathway. It is particularly important during prolonged periods of starvation and during periods of reduced caloric intake caused by gastrointestinal illness or increased energy expenditure during febrile illness. Under these conditions, the body switches from using predominantly *carbohydrate* to predominantly *fat* as its major fuel. Fatty acids are also important fuels for exercising skeletal muscle and are the preferred substrate for normal cardiac metabolism. In these tissues, fatty acids are completely oxidized to carbon dioxide and water. The end products of hepatic fatty acid oxidation are the ketone bodies β-*hydroxybutyrate* and *acetoacetate*. These cannot be oxidized by the liver but are exported to serve as important fuels in peripheral tissues, particularly the brain, where ketone bodies can partially substitute for glucose during periods of fasting.

Genetic defects have been identified in almost all the known steps in the fatty acid oxidation pathway; all are recessively inherited (Table 104.1).

Table 104.1

Mitochondrial Fatty Acid Oxidation Disorders—Clinical and Biochemical Features

ENZYME DEFICIENCY	GENE	CLINICAL PHENOTYPE	LABORATORY FINDINGS
Carnitine transporter	*OCTN2* *SLC22A5*	Cardiomyopathy, skeletal myopathy, liver disease, sudden death, endocardial fibroelastosis, prenatal and newborn screening diagnosis reported	↓ Total and free carnitine, normal acylcarnitines, acylglycine, and organic acids
Long-chain fatty acid transporter	*FATP1-6*	Rare, acute liver failure in childhood requiring liver transplantation	↓ intracellular C_{14} -C_{18} fatty acids, ↓ fatty acid oxidation
Carnitine palmitoyl transferase-I	*CPT-IA*	Liver failure, renal tubulopathy, and sudden death. Prenatal and newborn screening diagnosis reported, maternal preeclampsia, HELLP syndrome association described in a few patients.	Normal or ↑ free carnitine, normal acylcarnitines, acylglycine, and organic acids
Carnitine acylcarnitine translocase	*CACT* *SLC25A20*	Chronic progressive liver failure, persistent ↑ NH_3 , hypertrophic cardiomyopathy. Newborn screening diagnosis reported.	Normal or ↓ free carnitine, abnormal acylcarnitine profile
Carnitine palmitoyl transferase-II	*CPT-II*	Early and late onset types. Liver failure, encephalopathy, skeletal myopathy, cardiomyopathy, renal cystic changes, newborn screening diagnosis reported. Adult form with acute rhabdomyolysis, myoglobinuria.	Normal or ↓ free carnitine, abnormal acylcarnitine profile
Short-chain acyl-CoA dehydrogenase	*SCAD* *ACADS*	Clinical phenotype unclear. Many individuals appear to be normal. Others have a variety of inconsistent signs and symptoms. Subset may have severe manifestations of unclear relationship to biochemical defects. Newborn screening diagnosis reported; significance	Normal or ↓ free carnitine, elevated urine ethylmalonic acid, inconsistently abnormal acylcarnitine profile

		being questioned.	
Medium-chain acyl-CoA dehydrogenase	*MCAD* *ACADM*	Hypoglycemia, hepatic encephalopathy, sudden death. Newborn screening diagnosis possible, maternal preeclampsia, HELLP syndrome association described rarely, possible long Qt interval.	Normal or ↓ free carnitine, ↑ plasma acylglycine, plasma C_6-C_{10} free fatty acids, ↑ C_8-C_{10} acyl-carnitine
Very long-chain acyl-CoA dehydrogenase	*VLCAD* *ACADVL*	Dilated cardiomyopathy, arrhythmias, hypoglycemia, and hepatic steatosis. Late-onset, stress-induced rhabdomyolysis, episodic myopathy. Prenatal and newborn screening diagnosis possible.	Normal or ↓ free carnitine, ↑ plasma $C_{14:1}$, C_{14} acylcarnitine, ↑ plasma C_{10}-C_{16} free fatty acids
ETF dehydrogenase*	*ETF-DH*	Nonketotic fasting hypoglycemia, congenital anomalies, milder forms of liver disease, cardiomyopathy, and skeletal myopathy. Newborn screening diagnosis reported.	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
ETF-α*	*α-ETF*	Nonketotic fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy also described. Newborn screening diagnosis reported.	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
ETF-β*	*β-ETF*	Fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy also described. Newborn screening diagnosis reported.	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
Short-chain L-3-hydroxyacyl-CoA dehydrogenase	*SCHAD* *HAD1*	Hyperinsulinemic hypoglycemia, cardiomyopathy, myopathy. Newborn screening diagnosis reported.	Normal or ↓ free carnitine, elevated free fatty acids, inconsistently abnormal urine organic acid, ↑ 3-OH glutarate, ↑ plasma C_4-OH acylcarnitine
Long-chain L-3-hydroxyacyl-CoA dehydrogenase	*LCHAD* *HADH-A*	Newborn screening diagnosis reported, maternal preeclampsia, HELLP syndrome, and AFLP association described frequently. See also MTP below for clinical manifestations.	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ C_{16}-OH and C_{18}-OH carnitines
MTP	*HADH-A*, *HADH-B*	Severe cardiac and skeletal myopathy, hypoglycemia, acidosis, hyper NH_3, sudden death, elevated liver enzymes, retinopathy. Maternal preeclampsia, HELLP syndrome, and AFLP association described frequently.	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ C_{16}-OH and C_{18}-OH carnitines
Long-chain 3-ketoacyl-CoA thiolase	*LKAT* *HADH-B*	Severe neonatal presentation, hypoglycemia, acidosis, ↑ creatine kinase, cardiomyopathy, neuropathy, and early death	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ 2-*trans*, 4-*cis*-decadienoylcarnitine
Short-chain 2,3-enoyl-CoA hydratase	*ECHS1*	Leigh disease, lactic acidosis, seizures, cystic degeneration of white matter, microcephaly, metabolic acidosis, extrapyramidal dystonia, dilated cardiomyopathy	Abnormal organic acids, 2-methacrylglycine, 2-methyl-2,3 dihydroxybutyrate, also S-(2-carboxypropyl)cysteine, S-(2-carboxyethyl) cysteamine. Acylcarnitine shows ↑ C4OH (inconsistently).
2,4-Dienoyl-CoA reductase	*DECR1*	Only 1 patient described, hypotonia in the newborn, mainly severe skeletal myopathy	Normal or ↓ free carnitine, ↑ acyl:free carnitine ratio,

		and respiratory failure. Hypoglycemia rare.	normal urine organic acids and acylglycines
HMG CoA synthetase	*HMGCS2*	Hypoketosis and hypoglycemia, rarely myopathy	↑ total plasma fatty acids, enzyme studies in biopsied liver may be diagnostic, genetic testing preferred
HMG CoA lyase	*HMGCL*	Hypoketosis and hypoglycemia, rarely myopathy	Normal free carnitine, ↑ C_5 -OH, and methylglutarylcarnitine, enzymes studies in fibroblasts may be diagnostic
Monocarboxylate transporter 1 (MCT1)	*SLC16A1*	Severe fasting induced ketoacidosis, rarely hypoglycemia	Profound ketoacidosis; no specific biomarkers yet identified

[*] Also known as glutaric acidemia type II or multiple acyl-CoA dehydrogenase defect (MADD).

AFLP, Acute fatty liver of pregnancy; CoA, coenzyme A; ETF, electron transport flavoprotein; HELLP, hemolysis, elevated liver enzymes, low platelets; MTP, mitochondrial trifunctional protein; NH_3 , ammonia.

From Shekhawat PS, Matern D, Strauss AW: Fetal fatty oxidation disorders, their effect on maternal health and neonatal outcome: impact of expanded newborn screening on their diagnosis and management, *Pediatr Res* 57:78R–84R, 2005.

Clinical manifestations characteristically involve tissues with a high β-oxidation flux, including liver, skeletal, and cardiac muscle. The most common presentation is an acute episode of life-threatening coma, hepatic encephalopathy, and hypoglycemia induced by a period of fasting resulting from defective hepatic ketogenesis. Other manifestations may include chronic cardiomyopathy and muscle weakness or exercise-induced acute rhabdomyolysis. The fatty acid oxidation defects can often be asymptomatic during periods when there is no fasting stress or increased energy demand. Acutely presenting disease may be misdiagnosed as **Reye syndrome** or, if fatal, as **sudden unexpected infant death** . Fatty acid oxidation disorders are easily overlooked because the only specific clue to the diagnosis may be the finding of inappropriately low concentrations of plasma or urinary ketones in an infant who has hypoglycemia, unless specialized metabolic testing is performed. Genetic defects in ketone body utilization may also be overlooked because ketonemia is an expected finding with fasting hypoglycemia. In some circumstances, clinical manifestations appear to arise from toxic effects of fatty acid metabolites rather than inadequate energy production. These circumstances include certain long-chain fatty acid oxidation disorders (deficiencies of long-chain 3-hydroxyacyl dehydrogenase [**LCHAD**], carnitine palmitoyltransferase-IA [**CPT-IA**], or mitochondrial trifunctional protein [**MTP** ; also known as TFP]) in which the presence of a homozygous affected fetus increases the risk of a life-threatening illness in the heterozygote mother, resulting in **acute fatty liver of pregnancy** (AFLP) or **preeclampsia with HELLP** (hemolysis, elevated liver enzymes, low platelets) syndrome. The mechanism of these obstetric complications is likely accumulation of toxic intermediates. Malformations of the brain and kidneys have been described in severe deficiencies of electron transfer flavoprotein (**ETF**), ETF dehydrogenase (**ETF-DH**), and carnitine palmitoyltransferase-II (**CPT-II**), which might reflect in utero toxicity of fatty acid metabolites or a developmental role for these enzymes. Progressive retinal degeneration, peripheral neuropathy, and chronic progressive liver disease have been identified in LCHAD and MTP deficiency. Newborn screening programs using tandem mass spectrometry detect characteristic plasma acylcarnitine profiles in most of these disorders, allowing early and presymptomatic diagnosis. Screening programs have demonstrated that all the fatty acid oxidation disorders combined are among the most common inborn errors of metabolism, at least in predominantly Caucasian populations.

Figs. 104.1 and 104.2 outline the steps involved in the oxidation of a typical long-chain fatty acid. In the *carnitine cycle* , long-chain fatty acids are transported across the barrier of the inner mitochondrial membrane as acylcarnitine esters. (Medium-chain fatty acids, which are commonly provided as medium-chain triglyceride supplementation in infants who are failing to thrive, can bypass the carnitine cycle and enter the mitochondrial β-oxidation cycle directly.) Within the mitochondria, successive turns of the 4-step *β-oxidation cycle* convert the **coenzyme A (CoA)** –activated fatty acids to acetyl-CoA units. Two or 3 different specific isoenzymes are needed for each of these β-oxidation steps to accommodate the different chain-length fatty acyl-CoA species. The electrons generated in the first β-oxidation step (acyl-CoA dehydrogenase) are carried by the *electron transfer pathway* to the *electron transport chain* at the level of coenzyme Q for adenosine triphosphate production; while electrons generated from the 3rd step (3-hydroxyacyl-CoA dehydrogenase) enter the *electron transport chain* at the level of complex 1. Most of the acetyl-CoA generated from fatty acid β-oxidation in the liver flows through the *pathway of ketogenesis* to form β-hydroxybutyrate and acetoacetate, whereas in muscle and heart the fatty acids are completely oxidized to CO_2 and water.

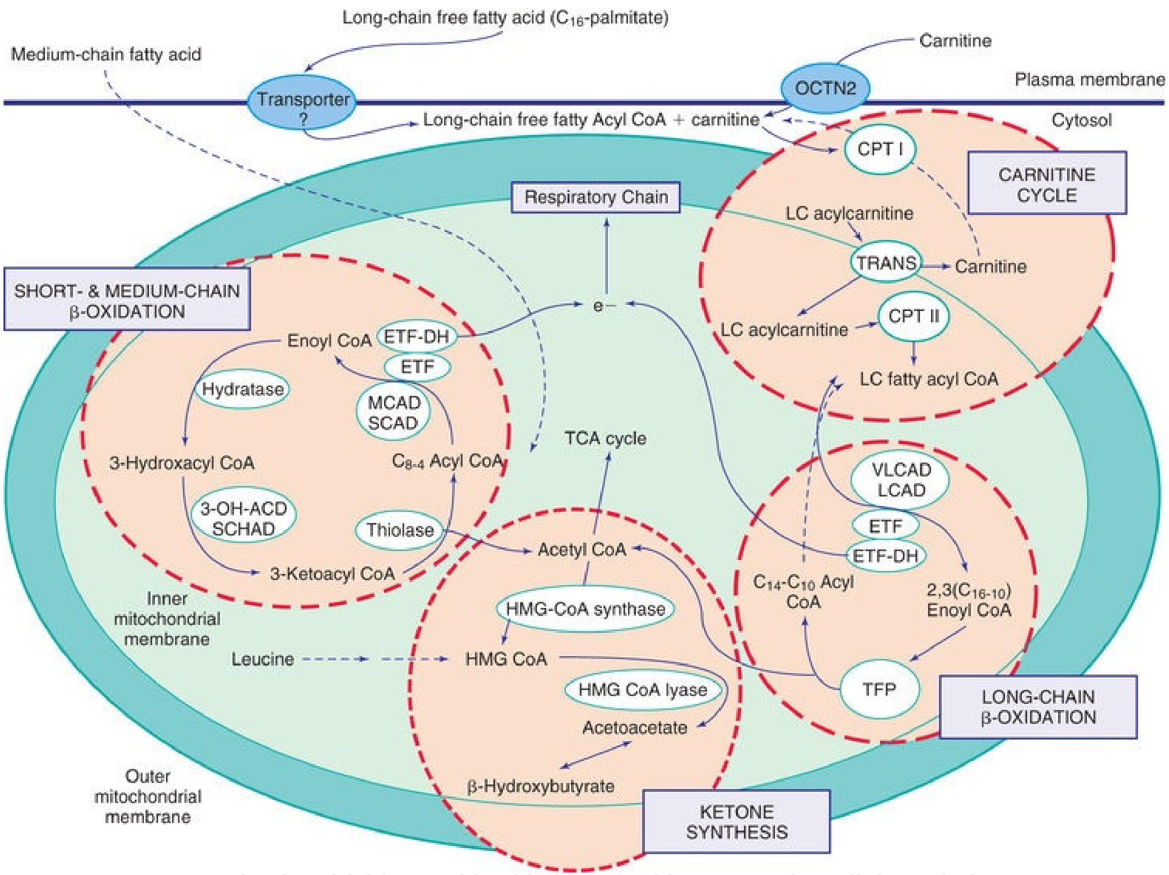
Long-chain free fatty acid (C16-palmitate)
Medium-chain fatty acid
Carnitine
Plasma membrane
Transporter ?
OCTN2
Long-chain free fatty Acyl CoA + carnitine
Cytosol
CPT I
CARNITINE CYCLE
Respiratory Chain
LC acylcarnitine
TRANS
Carnitine
SHORT- & MEDIUM-CHAIN β-OXIDATION
e−
LC acylcarnitine
CPT II
Enoyl CoA
ETF-DH
ETF
LC fatty acyl CoA
Hydratase
MCAD SCAD
TCA cycle
3-Hydroxacyl CoA
C8-4 Acyl CoA
VLCAD LCAD
3-OH-ACD SCHAD
Thiolase
ETF
Acetyl CoA
ETF-DH
3-Ketoacyl CoA
C14-C10 Acyl CoA
2,3(C16-10) Enoyl CoA
Inner mitochondrial membrane
HMG-CoA synthase
Leucine
HMG CoA
TFP
LONG-CHAIN β-OXIDATION
HMG CoA lyase
Acetoacetate
Outer mitochondrial membrane
β-Hydroxybutyrate
KETONE SYNTHESIS

FIG. 104.1 **Mitochondrial fatty acid oxidation. Carnitine enters the cell through the action of the organic cation/carnitine transporter (OCTN2). Palmitate, a typical 16-carbon long-chain fatty acid, is transported across the plasma membrane and can be activated to form a long-chain (LC) fatty acyl coenzyme A (CoA). It then enters into the carnitine cycle, where it is transesterified by carnitine palmitoyltransferase-I (CPT-I), translocated across the inner mitochondrial membrane by carnitine/acylcarnitine translocase (TRANS), and then reconverted into a long-chain fatty acyl-CoA by carnitine palmitoyltransferase-II (CPT-II) to undergo β-oxidation. Very-long-chain acyl-CoA dehydrogenase (VLCAD/LCAD) leads to the production of $(C_{16} -C_{10})$ 2,3-enoyl CoA. Mitochondrial trifunctional protein (MTP) contains the activities of enoyl CoA hydratase (hydratase), 3-OH-hydroxyacyl-CoA dehydrogenase (3-OH-ACD), and β-ketothiolase (thiolase). Acetyl-CoA, reduced form of flavin adenine dinucleotide (FADH), and reduced form of nicotinamide adenine dinucleotide (NADH) are produced. Medium- and short-chain fatty acids (C8-4) can enter the mitochondrial matrix independent of the carnitine cycle. Medium-chain acyl-CoA dehydrogenase (MCAD), short-chain acyl-CoA dehydrogenase (SCAD), and short-chain hydroxy acyl-CoA dehydrogenase (SCHAD) are required. Acetyl-CoA can then enter the Krebs (TCA) cycle. Electrons are transported from FADH to the respiratory chain via the electron transfer flavoprotein (ETF) and the electron transfer flavoprotein dehydrogenase (ETF-DH). NADH enters the electron transport chain through complex I. In liver, acetyl-CoA can be converted into hydroxymethylglutaryl (HMG) CoA by β-hydroxy-β-methylglutaryl-CoA synthase (HMG CoA synthase) and then the ketone body acetoacetate by the action of β-hydroxy-β-methylglutaryl-CoA lyase (HMG-CoA lyase).**

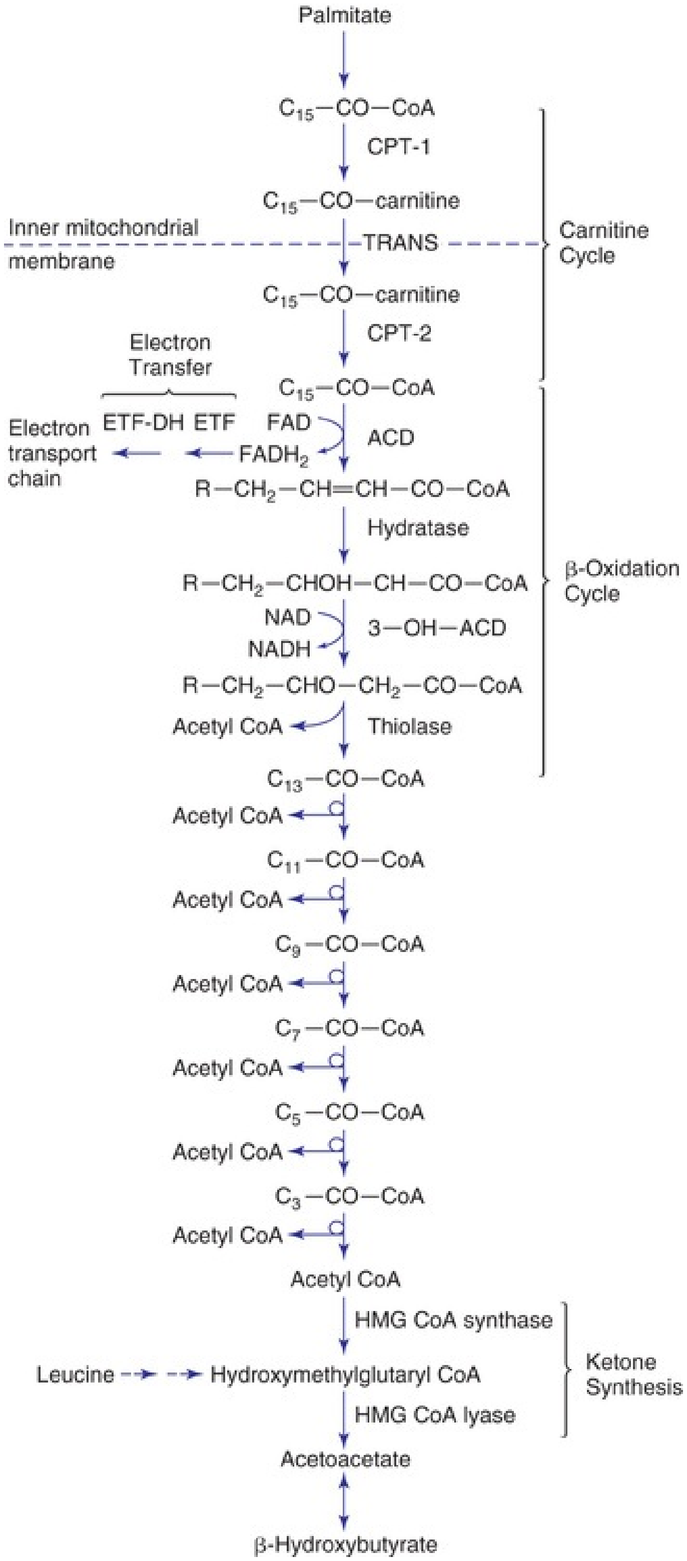
Palmitate
$C_{15}-CO-CoA$
CPT-1
$C_{15}-CO-carnitine$
Inner mitochondrial membrane
TRANS
Carnitine Cycle
$C_{15}-CO-carnitine$
CPT-2
Electron Transfer
$C_{15}-CO-CoA$
Electron transport chain
ETF-DH
ETF
FAD
$FADH_2$
ACD
$R-CH_2-CH=CH-CO-CoA$
Hydratase
$R-CH_2-CHOH-CH-CO-CoA$
β-Oxidation Cycle
NAD
NADH
3-OH-ACD
$R-CH_2-CHO-CH_2-CO-CoA$
Acetyl CoA
Thiolase
$C_{13}-CO-CoA$
Acetyl CoA
$C_{11}-CO-CoA$
Acetyl CoA
$C_9-CO-CoA$
Acetyl CoA
$C_7-CO-CoA$
Acetyl CoA
$C_5-CO-CoA$
Acetyl CoA
$C_3-CO-CoA$
Acetyl CoA
Acetyl CoA
HMG CoA synthase
Leucine
Hydroxymethylglutaryl CoA
Ketone Synthesis
HMG CoA lyase
Acetoacetate
β-Hydroxybutyrate

FIG. 104.2 **Pathway of mitochondrial oxidation of palmitate, a typical 16-carbon long-chain fatty acid. Enzyme steps include carnitine palmitoyltransferase (CPT) 1 and 2, carnitine/acylcarnitine translocase (TRANS), electron transfer flavoprotein (ETF), ETF dehydrogenase (ETF-DH), acyl-CoA dehydrogenase (ACD), enoyl CoA hydratase (hydratase), 3-hydroxy-acyl-CoA dehydrogenase (3-OH-ACD), β-ketothiolase (thiolase),**

β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase, and lyase.

Defects in the β-Oxidation Cycle

Medium-Chain Acyl-CoA Dehydrogenase Deficiency

Medium-chain acyl-CoA dehydrogenase (**MCAD**) deficiency is the most common fatty acid oxidation disorder. The disorder shows a strong founder effect; most patients have a northwestern European ancestry, and the majority of these patients are homozygous for a single common MCAD missense mutation, an A-G transition at cDNA position 985 (c.985A>G) that changes a lysine to glutamic acid at residue 329 (p.K329E).

Clinical Manifestations

Previously undiagnosed affected patients usually present in the 1st 3 mo to 5 yr of life with episodes of acute illness triggered by prolonged fasting (>12-16 hr). Signs and symptoms include vomiting and lethargy, which rapidly progress to coma or seizures and cardiorespiratory collapse. Sudden unexpected infant death may occur. The liver may be slightly enlarged with fat deposition. Attacks are rare until the infant is beyond the 1st few mo of life, presumably because of more frequent feedings at a younger age. Affected older infants are at higher risk of illness as they begin to fast through the night or are exposed to fasting stress during an intercurrent childhood illness. Presentation in the 1st days of life with neonatal hypoglycemia has been reported in newborns who were fasted inadvertently or were being breastfed. Diagnosis of MCAD has occasionally been documented in previously healthy teenage and adult individuals, indicating that even patients who have been asymptomatic in infancy are still at risk for metabolic decompensation if exposed to sufficient periods of fasting. An unknown number of patients may remain asymptomatic. Prior to routine newborn screening testing, as many as 25% of MCAD-deficient patients died or suffered severe brain damage from their first episode. Most patients are now diagnosed in the newborn period by **blood spot acylcarnitine screening** , allowing the initiation of early treatment and prevention of many of the severe signs and symptoms. In some reports, newborns with MCAD deficiency presented acutely before newborn screening results were obtained; neonates who are exclusively breastfed are at higher risk because of early poor caloric intake.

Laboratory Findings

During acute episodes, hypoglycemia is usually present. Plasma and urinary ketone concentrations are inappropriately low (**hypoketotic hypoglycemia**). Because of the hypoketonemia, there is little or no metabolic acidosis, which is expected to be present in many children with hypoglycemia. Liver function tests (LFTs) are abnormal, with elevations of liver enzymes (alanine transaminase, aspartate transaminase), elevated blood ammonia, and prolonged prothrombin and partial thromboplastin times. Liver biopsy at times of acute illness shows microvesicular or macrovesicular steatosis from triglyceride accumulation. During fasting stress or acute illness, urinary organic acid profiles by gas chromatography/mass spectrometry show inappropriately low concentrations of ketones and elevated levels of medium-chain dicarboxylic acids (adipic, suberic, and sebacic acids) that derive from microsomal and peroxisomal omega oxidation of accumulated medium-chain fatty acids. Plasma and tissue concentrations of total carnitine are reduced to 25–50% of normal, and the fraction of total esterified carnitine is increased. This pattern of **secondary carnitine deficiency** is seen in most fatty acid oxidation defects and reflects competition between increased acylcarnitine levels and free carnitine for transport at the renal tubular plasma membrane. Significant exceptions to this rule are the plasma membrane carnitine transporter, CPT-IA, and β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase deficiencies, which do not manifest secondary carnitine deficiency.

Diagnostic metabolite patterns for MCAD deficiency include increased plasma $C_{6:0}$, $C_{8:0}$, $C_{10:0}$, and $C_{10:1}$ acylcarnitine species and increased urinary acylglycines, including hexanoylglycine, suberylglycine, and 3-phenylpropionylglycine. Newborn screening, which almost all babies born in the United States receive, can detect presymptomatic MCAD deficiency based on these abnormal acylcarnitines in filter paper blood spots. The diagnosis can be confirmed by finding the common A985G mutation or sequencing the *MCAD* gene. A 2nd common variant, T199C, has been detected in infants identified by newborn screening. Interestingly, this allele has not been seen to date in symptomatic MCAD patients; it may represent a milder mutation.

Treatment

Acute illnesses should be promptly treated with intravenous (IV) fluids containing 10% dextrose to correct or prevent hypoglycemia and to suppress lipolysis as rapidly as possible (see Chapter 111). Chronic therapy consists of avoiding fasting. This usually requires simply adjusting the diet to ensure that overnight fasting periods are limited to <10-12 hr. Restricting dietary fat or treatment with carnitine is controversial. The need for active therapeutic intervention for individuals with the T199C variant has not yet been established.

Prognosis

Up to 25% of unrecognized patients may die during their first attack of illness. There is frequently a history of a previous sibling death that is presumed to be from an unrecognized MCAD deficiency. Some patients may sustain permanent brain injury during an attack of profound hypoglycemia. For survivors without brain damage, the prognosis is excellent because progressive cognitive impairment or cardiomyopathy does not occur in MCAD deficiency. Fasting tolerance improves with age, and the risk of illness decreases. Because as many as 35% of affected patients have never had an episode, testing of siblings of affected patients is important to detect asymptomatic family members.

Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency

Very-long-chain acyl-CoA dehydrogenase (**VLCAD**) deficiency is the second most commonly diagnosed disorder of fatty acid oxidation. It was originally termed “long-chain acyl-CoA dehydrogenase deficiency” before the existence of the inner mitochondrial membrane-bound VLCAD was known. *All patients previously diagnosed as having long-chain acyl-CoA dehydrogenase deficiency have* VLCAD *gene defects.* Patients with VLCAD deficiency have no ability to oxidize physiologic long-chain fatty acids and are usually more severely affected than those with MCAD deficiency, who have a milder oxidative defect. VLCAD deficiency presents earlier in infancy and has more chronic problems with muscle weakness or episodes of muscle pain and rhabdomyolysis. Cardiomyopathy may be present during acute attacks provoked by fasting. The left ventricle may be hypertrophic or dilated and may show poor contractility on echocardiography. Sudden unexpected death has occurred in several patients, but most who survive the initial episode show improvement, including normalization of cardiac function. Other physical and routine laboratory features are similar to those of MCAD deficiency, including secondary carnitine deficiency. The urinary organic acid profile shows a nonketotic dicarboxylic aciduria with increased levels of $C_{6\text{-}12}$ dicarboxylic acids. Diagnosis may be suggested by an abnormal acylcarnitine profile with plasma or blood spot $C_{14:0,\ 14:1,\ 14:2}$ acylcarnitine species. However, the specific diagnosis requires mutational analysis of the *VLCAD* gene. Treatment is based primarily on avoidance of fasts for >10-12 hr. Continuous intragastric feeding is useful in some patients.

Short-Chain Acyl-CoA Dehydrogenase Deficiency

A small number of patients with 2 null mutations in the short-chain acyl-CoA dehydrogenase *(SCAD)* gene have been described with variable phenotype. Most individuals classified as being SCAD deficient actually have polymorphic DNA changes in the *SCAD* gene; for example, 2 common polymorphisms are G185S and R147W, which are homozygously present in 7% of the population. Some investigators argue that these variants may be susceptibility factors, which require a 2nd, as yet unknown, genetic mutation to express a clinical phenotype; many other investigators believe that SCAD deficiency is a harmless biochemical condition. This autosomal recessive disorder presents with neonatal hypoglycemia and may have normal levels of ketone bodies. The diagnosis is indicated by elevated levels of butyrylcarnitine (C4-carnitine) on newborn blood spots or plasma and increased excretion of urinary ethylmalonic acid and butyrylglycine. These metabolic abnormalities are most pronounced in patients with null mutations and are variably present in patients who are homozygous for the common polymorphisms.

The need for treatment in SCAD deficiency has not yet been established. It has been proposed that long-term evaluation of asymptomatic individuals is necessary to determine whether this is or is not a real disease. Most individuals with SCAD deficiency remain asymptomatic throughout life, but there may be a subset of individuals with **severe manifestations** , including dysmorphic facial features, feeding difficulties/failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizures, hypotonia, dystonia, and myopathy.

Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase/Mitochondrial Trifunctional Protein Deficiency

The LCHAD enzyme is part of the MTP, which also contains 2 other steps in β-oxidation: long-chain 2,3-enoyl CoA hydratase and long-chain β-ketothiolase. MTP is a hetero-octameric protein composed of 4 α and 4 β chains derived from distinct contiguous genes sharing a common promoter region. In some patients, only the LCHAD activity of the MTP is affected (**LCHAD deficiency**), whereas others have deficiencies of all 3 activities (**MTP deficiency**).

Clinical manifestations include attacks of acute hypoketotic hypoglycemia similar to MCAD deficiency; however, patients often show evidence of more severe disease, including cardiomyopathy, muscle cramps and weakness, and abnormal liver function (cholestasis). Toxic effects of fatty acid metabolites may produce pigmented retinopathy leading to blindness, progressive liver failure, peripheral neuropathy, and rhabdomyolysis. Life-threatening obstetric complications (AFLP, HELLP syndrome) have been observed in heterozygous mothers carrying homozygous fetuses affected with LCHAD/MTP deficiency. Sudden unexpected infant death may occur. The **diagnosis** is indicated by elevated levels of blood spot or plasma 3-hydroxy acylcarnitines of chain lengths C_{16} -C_{18} . Urinary organic acid profile in patients may show increased levels of 3-hydroxydicarboxylic acids of chain lengths C_6 -C_{14} . Secondary carnitine deficiency is common. A common mutation in the α subunit, E474Q, is seen in more than 60% of LCHAD-deficient patients. This mutation in the fetus is especially associated with the obstetric complications, but other mutations in either subunit may also be linked to maternal illness.

Treatment is similar to that for MCAD or VLCAD deficiency; that is, avoiding fasting stress. Some investigators have suggested that dietary supplements with medium-chain triglyceride oil to bypass the defect in long-chain fatty acid oxidation and docosahexaenoic acid (for protection against the retinal changes) may be useful. Liver transplantation has been attempted in patients with severe liver failure, but does not ameliorate the metabolic abnormalities or prevent the myopathic or retinal complications.

Short-Chain 3-Hydroxyacyl-CoA Dehydrogenase

Deficiency

Only 14 patients with proven mutations of short-chain 3-hydroxyacyl-CoA dehydrogenase (**SCHAD**) have been reported. Most cases with recessive mutations of the *SCHAD* gene have presented with episodes of hypoketotic hypoglycemia that was caused by hyperinsulinism. In contrast to those with other forms of fatty acid oxidation disorders, these patients required specific therapy with diazoxide for hyperinsulinism to avoid recurrent hypoglycemia. A single patient with compound heterozygous mutations presented with fulminant hepatic failure at age 10 mo. The SCHAD protein has a nonenzymatic function in which it directly interacts with glutamate dehydrogenase (GDH) to inhibit its activity. In the absence of SCHAD protein, this inhibition is removed, leading to upregulation of GDH enzyme activity, a recognized cause of hyperinsulinism usually from activating mutations of the *GDH* gene. Severe deficiency of SCHAD protein often presents predominantly as protein-sensitive hypoglycemia rather than as fasting hypoglycemia. It appears that if SCHAD protein is present, inhibition of GDH is maintained even when there is no SCHAD enzyme activity; these patients may present with a more traditional fatty acid oxidation defect. Specific metabolic markers for SCHAD deficiency include elevated plasma C4-hydroxy acylcarnitine and urine 3-hydroxyglutaric acid. Successful newborn screening for SCHAD deficiency has been recorded, but the sensitivity of the process has not yet been established.

Treatment of SCHAD-deficient patients with hyperinsulinism is with diazoxide. There is insufficient experience with the nonhyperinsulinemic form of SCHAD deficiency at present to recommend treatment modalities, but prevention of fasting seems advisable.

Short-Chain 2,3-Enoyl-CoA Hydratase Deficiency

This disorder, resulting from mutations in the *ECHS1* gene, has only recently been defined. Many patients were identified through exome sequencing, and currently there are approximately 20 cases in the literature. The disorder affects a shared pathway of short-chain fatty acid and valine metabolism. The clinical phenotypes are more characteristic of mitochondrial disorders of pyruvate metabolism with predominantly a Leigh-like disease (see Chapter 616.2) with profound and often-fatal lactic acidosis. Currently, no treatment modalities or specific biomarkers have been established. Several patients were found to excrete increased levels of methacrylylglycine, a highly reactive and potentially toxic intermediate; 2-methyl-2.3 dihydroxybutyrate; *S* -(2-carboxypropyl) cysteine; and *S* -(2-carboxpropyl) cysteamine.

Defects in the Carnitine Cycle

Plasma Membrane Carnitine Transport Defect (Primary Carnitine Deficiency)

Primary carnitine deficiency is the only genetic defect in which carnitine deficiency is the cause, rather than the consequence, of impaired fatty acid oxidation. The most common presentation is progressive **cardiomyopathy** with or without **skeletal muscle weakness** beginning at age 1-4 yr. A smaller number of patients may present with fasting hypoketotic hypoglycemia in the 1st yr of life, before the cardiomyopathy becomes symptomatic. The underlying defect involves the plasma membrane sodium gradient–dependent carnitine transporter that is present in heart, muscle, and kidney. This transporter is responsible both for maintaining intracellular carnitine concentrations 20-50–fold higher than plasma concentrations and for renal conservation of carnitine.

Diagnosis of the carnitine transporter defect is aided by patients having extremely reduced carnitine levels in plasma and muscle (1–2% of normal). Heterozygote parents have plasma carnitine levels approximately 50% of normal. Fasting ketogenesis may be normal because liver carnitine transport is normal, but it may become impaired if dietary carnitine intake is interrupted. The fasting urinary organic acid profile may show a hypoketotic dicarboxylic aciduria pattern if hepatic fatty acid oxidation is impaired, but is otherwise unremarkable. The defect in carnitine transport can be demonstrated clinically by the severe reduction in renal carnitine threshold or by in vitro assay of carnitine uptake using cultured fibroblasts or lymphoblasts. Mutations in the organic cation/carnitine transporter *(OCTN2)* underlie this disorder. **Treatment** with pharmacologic doses of oral carnitine (100-200 mg/kg/day) is highly effective in correcting the cardiomyopathy and muscle weakness, as well as any impairment in fasting ketogenesis. Muscle total carnitine concentrations remain <5% of normal on treatment.

Carnitine Palmitoyltransferase-IA Deficiency

Several dozen infants and children have been described with a deficiency of the liver and kidney CPT-I isozyme (CPT-IA). **Clinical manifestations** include fasting-induced hypoketotic hypoglycemia, occasionally with extremely abnormal LFTs and rarely with renal tubular acidosis. The heart and skeletal muscle are not involved because the muscle isozyme is unaffected. Fasting urinary organic acid profiles sometimes show a hypoketotic C_6 -C_{12} dicarboxylic aciduria but may be normal. Plasma acylcarnitine analysis demonstrates mostly free carnitine with very little acylated carnitine. This observation has been used to identify CPT-IA deficiency on newborn screening by tandem mass spectrometry. CPT-IA deficiency is the only fatty acid oxidation disorder in which plasma total carnitine levels may be elevated, often to 150–200% of normal. This phenomenon is explained by the absence of inhibitory effects of long-chain acylcarnitines on the renal tubular carnitine transporter in CPT-IA deficiency. The enzyme defect can be demonstrated in cultured fibroblasts or lymphoblasts. CPT-IA deficiency in the fetus has been associated in a single case report with AFLP in the mother. A common variant in the *CPTIA* gene (c.1436C>t, p.P479L) has been identified in individuals of Inuit background in the United States, Canada, and Greenland. This variant is associated with an increased risk for sudden infant death syndrome (SIDS) in the Inuit population. The variant can be detected by newborn screening; enzyme activity is reduced by 80%, and regulation by malonyl-CoA is lost. It has not been established whether CPT-IA (c.1436C>t, p.P479L) is a pathologic enzyme variant or an adaptation to ancient Inuit high-fat diets. **Treatment** for the severe form of CPT-IA deficiency that is found in non-Inuit populations is similar to that for MCAD deficiency, with avoidance of situations where fasting ketogenesis is necessary. The need for treatment of the Inuit variant has not yet been determined.

Carnitine:Acylcarnitine Translocase Deficiency

This defect of the inner mitochondrial membrane carrier protein for long-chain acylcarnitines blocks the entry of long-chain fatty acids into the mitochondria for oxidation. The clinical phenotype of this disorder is characterized by a severe and generalized impairment of fatty acid oxidation. Most newborn patients present with attacks of fasting-induced hypoglycemia, hyperammonemia, and cardiorespiratory collapse. All symptomatic newborns have had evidence of cardiomyopathy and muscle weakness. Several patients with a partial translocase deficiency and milder disease without cardiac involvement have also been identified. No distinctive urinary or plasma organic acids are noted, although increased levels of plasma long-chain acylcarnitines of chain lengths C_{16} -C_{18} are reported. **Diagnosis** can be confirmed using genetic analysis. Functional carnitine:acylcarnitine translocase activity can be measured in cultured fibroblasts or lymphoblasts. **Treatment** is similar to that of other long-chain fatty acid oxidation disorders.

Carnitine Palmitoyltransferase-II Deficiency

Three forms of CPT-II deficiency have been described. A **severe neonatal lethal** presentation associated with a profound enzyme deficiency and early death has been reported in several newborns in association with dysplastic kidneys, cerebral malformations, and mild facial anomalies. A milder defect is associated with an **adult presentation** of episodic rhabdomyolysis. The first episode usually does not occur until late childhood or early adulthood. Attacks are frequently precipitated by prolonged exercise. There is aching muscle pain and myoglobinuria that may be severe enough to cause renal failure. Serum levels of creatine kinase are elevated to 5,000-100,000 units/L. Hypoglycemia has not been described, but fasting may contribute to attacks of myoglobinuria. Muscle biopsy shows increased deposition of neutral fat. This adult myopathic presentation of CPT-II deficiency is associated with a common mutation, c.338C>T, p.S113L. This mutation produces a heat-labile protein that is unstable to increased muscle temperature during exercise resulting in the myopathic presentation. The 3rd, **intermediate form** of CPT-II deficiency presents in infancy or early childhood with fasting-induced hepatic failure, cardiomyopathy, and skeletal myopathy with hypoketotic hypoglycemia, but is not associated with the severe developmental changes seen in the neonatal lethal presentation. This pattern of illness is similar to that seen in VLCAD deficiency, and management is identical.

Diagnosis of all forms of CPT-II deficiency can be made by a combination of molecular genetic analysis and demonstrating deficient enzyme activity in muscle or other tissues and in cultured fibroblasts.

Defects in the Electron Transfer Pathway

Electron Transfer Flavoprotein and Electron

Transfer Flavoprotein Dehydrogenase Deficiencies (Glutaric Acidemia Type 2, Multiple Acyl-CoA Dehydrogenation Defects)

ETF and ETF-DH function to transfer electrons into the mitochondrial electron transport chain from dehydrogenation reactions catalyzed by VLCAD, MCAD, and SCAD, as well as by glutaryl-CoA dehydrogenase and 4 enzymes involved in branched-chain amino acid (BCAA) oxidation. Deficiencies of ETF or ETF-DH produce illness that combines the features of impaired fatty acid oxidation and impaired oxidation of several amino acids. Complete deficiencies of either protein are associated with severe illness in the newborn period, characterized by acidosis, hypoketotic hypoglycemia, coma, hypotonia, cardiomyopathy, and an unusual odor of sweaty feet caused by isovaleryl-CoA dehydrogenase inhibition. Some affected neonates have had congenital facial dysmorphism and polycystic kidneys similar to that seen in severe CPT-II deficiency, which suggests that toxic effects of accumulated metabolites may occur in utero.

Diagnosis can be made from the newborn blood spot acylcarnitine profile and urinary organic acids; both tests show abnormalities corresponding to blocks in the oxidation of fatty acids (ethylmalonate and C_6 -C_{10} dicarboxylic acids), lysine (glutarate), and BCAAs (isovaleryl-, isobutyryl-, and α-methylbutyryl-glycine). The diagnosis can be confirmed by genetic testing for ETF (2 genes, A and B) and ETF dehydrogenase. Most severely affected infants do not survive the neonatal period.

Partial deficiencies of ETF and ETF-DH produce a disorder that may mimic MCAD deficiency or other milder fatty acid oxidation defects. These patients have attacks of fasting hypoketotic coma. The urinary organic acid profile reveals primarily elevations of dicarboxylic acids and ethylmalonate, derived from short-chain fatty acid intermediates. Secondary carnitine deficiency is present. Some patients with mild forms of ETF/ETF-DH deficiency may benefit from treatment with high doses of *riboflavin,* a precursor of the various flavoproteins involved in electron transfer.

Defects in the Ketone Synthesis Pathway

The final steps in production of ketones from mitochondrial fatty acid β-oxidation convert acetyl-CoA to acetoacetate through 2 enzymes of the HMG-

CoA pathway (Fig. 104.2).

β-Hydroxy-β-Methylglutaryl-CoA Synthase Deficiency

See Chapter 103.6 .

HMG-CoA synthase is the rate-limiting step in the conversion of acetyl-CoA derived from fatty acid β-oxidation in the liver to ketones. Several patients with this defect have been identified. The presentation is one of fasting hypoketotic hypoglycemia without evidence of impaired cardiac or skeletal muscle function. Urinary organic acid profile shows only a nonspecific hypoketotic dicarboxylic aciduria. Plasma and tissue carnitine levels are normal, in contrast to all the other disorders of fatty acid oxidation. A separate synthase enzyme, present in cytosol for cholesterol biosynthesis, is not affected. The HMG-CoA synthase defect is expressed only in the liver (and kidney) and cannot be demonstrated in cultured fibroblasts. The **diagnosis** can be made by genetic mutation analysis. *Avoiding fasting is usually a successful treatment.*

β-Hydroxy-β-Methylglutaryl-CoA Lyase Deficiency (3 Hydroxy-3-Methylgutaric Aciduria)

See Chapter 103.6 .

Defects in Ketone Body Utilization

The ketone bodies, β-hydroxybutyrate and acetoacetate, are the end products of hepatic fatty acid oxidation and are important metabolic fuels for the brain during fasting. Three defects in utilization of ketones in brain and other peripheral tissues present as episodes of **hyperketotic coma** , with or without hypoglycemia.

Monocarboxylate Transporter-1 Deficiency

About 10 patients have been described with recurrent episodes of potentially lethal ketoacidosis, with or without hypoglycemia, caused by deficiency of monocarboxylate transporter 1 (MCT1), a plasma membrane carrier encoded by

SLC16A1 that is required to transport ketones into tissues from plasma. Although the first cases identified were homozygous for inactivating mutations of *MCT1*, heterozygous carriers can also be affected. Affected patients developed severe ketoacidosis provoked by fasting or infections in their 1st years of life; hypoglycemia was not always present. The differential includes ketotic hypoglycemia associated with milder forms of glycogen storage disease, such as phosphorylase or phosphorylase kinase deficiency (see Chapter 105). **Treatment** for acute episodes includes IV dextrose to suppress lipolysis and inhibit ongoing ketogenesis. Long-term treatment includes avoidance of prolonged fasting stress. The **diagnosis** can be suspected by unusually severe ketosis and delayed suppression of ketones after starting treatment with dextrose. There are no specific metabolic markers or newborn screening methods. The diagnosis can be established by genetic sequencing of *SLC16A1* .

Succinyl-CoA:3-Ketoacid-CoA Transferase Deficiency

See Chapter 103.6 .

Several patients with succinyl-CoA:3-ketoacid-CoA transferase (**SCOT**) deficiency have been reported. The characteristic presentation is an infant with recurrent episodes of severe ketoacidosis induced by fasting. Plasma acylcarnitine and urine organic acid abnormalities do not distinguish SCOT deficiency from other causes of ketoacidosis. **Treatment** of episodes requires infusion of glucose and large amounts of bicarbonate until metabolically stable. Patients usually exhibit inappropriate hyperketonemia even between episodes of illness. SCOT is responsible for activating acetoacetate in peripheral tissues, using succinyl CoA as a donor to form acetoacetyl-CoA. Deficient enzyme activity can be demonstrated in the brain, muscle, and fibroblasts from affected patients. The gene has been cloned, and numerous mutations have been characterized.

β-Ketothiolase Deficiency

See Chapter 103.6 .

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104.2

Disorders of Very-Long-Chain Fatty Acids and Other Peroxisomal Functions

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Keywords

very-long-chain fatty acids
VLCFAs
peroxisome
Zellweger syndrome
adrenoleukodystrophy

Peroxisomal Disorders

Disorders of very-long-chain fatty acids (VLCFAs) fall within the broader group of peroxisomal diseases. The **peroxisomal diseases** are genetically determined disorders caused either by the failure to form or maintain the peroxisome or by a defect in the function of a single protein that is normally located in this organelle. These disorders cause serious disability in childhood and occur more frequently and present a wider range of phenotypes than recognized in the past. Many, but not all, peroxisomal disorders are associated with elevations of VLCFAs. This discussion addresses the broader group of peroxisomal disorders with a focus on pediatric presentations.

Etiology

Peroxisomal disorders are subdivided into two major categories (Table 104.2). In the **peroxisomal biogenesis disorders (PBDs)** the basic defect is the failure to import 1 or more proteins into the organelle. In the other group, defects affect a single peroxisomal protein (**single-enzyme defects**). The *peroxisome* is present in all cells except mature erythrocytes and is a subcellular organelle surrounded by a single membrane; >50 peroxisomal enzymes are identified. Some enzymes are involved in production and decomposition of hydrogen peroxide and others in lipid and amino acid metabolism. Most peroxisomal enzymes are first synthesized in their mature form on free polyribosomes and enter the cytoplasm. Proteins that are destined for the peroxisome contain specific **peroxisome targeting sequences** (PTSs). Most peroxisomal matrix proteins contain **PTS1** , a 3-amino acid sequence at the carboxyl terminus. **PTS2** is an aminoterminal sequence that is critical for the import of enzymes involved in plasmalogen and branched-chain fatty acid metabolism. Import of proteins involves a complex series of reactions that involves at least 23 distinct proteins. These proteins, referred to as *peroxins*, are encoded by *PEX* genes.

Table 104.2

Classification of Peroxisomal Disorders

PEROXISOMAL BIOGENESIS DISORDERS	SINGLE-ENZYME DEFECTS
Zellweger spectrum disorder	X-linked adrenoleukodystrophy Acyl-CoA oxidase deficiency Bifunctional enzyme deficiency 2-Methylacyl-CoA racemase deficiency DHAP acyltransferase deficiency Alkyl-DHAP synthase deficiency Adult Refsum disease
Zellweger syndrome Neonatal adrenoleukodystrophy (ALD) Infantile Refsum disease	
Rhizomelic chondrodysplasia punctata (RCDP) and other *PEX7* conditions	

Epidemiology

Except for X-linked **adrenoleukodystrophy (ALD)** , all the peroxisomal disorders listed in Table 104.2 are **autosomal recessive diseases** . ALD is the most common peroxisomal disorder, with an estimated incidence of 1 in 17,000 live births. The combined incidence of the other peroxisomal disorders is estimated to be 1 in 50,000 live births, although with broader newborn screening it is expected that the actual incidences of all of the disorders of very-long-chain fatty acids will be more accurately established.

Pathology

Absence or reduction in the number of peroxisomes is pathognomonic for disorders of peroxisome biogenesis. In most disorders, membranous sacs contain peroxisomal integral membrane proteins, which lack the normal complement of matrix proteins; these are peroxisome “ghosts.” Pathologic changes are observed in most organs and include profound and characteristic defects in neuronal migration, micronodular cirrhosis of the liver, renal cysts, chondrodysplasia punctata, sensorineural hearing loss, retinopathy, congenital heart disease, and dysmorphic features.

Pathogenesis

All pathologic changes likely are secondary to the peroxisome defect. Multiple peroxisomal enzymes fail to function in the PBDs (Table 104.3). The enzymes that are diminished or absent are synthesized but are degraded abnormally fast because they may be unprotected outside the peroxisome. It is not clear how defective peroxisome functions lead to the widespread pathologic manifestations.

Table 104.3

Abnormal Laboratory Findings Common to Zellweger Spectrum Disorders

Peroxisomes absent to reduced in number
Catalase in cytosol
Deficient synthesis and reduced tissue levels of plasmalogens
Defective oxidation and abnormal accumulation of very-long-chain fatty acids
Deficient oxidation and age-dependent accumulation of phytanic acid
Defects in certain steps of bile acid formation and accumulation of bile acid intermediates
Defects in oxidation and accumulation of L -pipecolic acid
Increased urinary excretion of dicarboxylic acids

Mutations in 12 different *PEX* genes have been identified in PBDs. The pattern and severity of pathologic features vary with the nature of the import defects and the degree of import impairment. These gene defects lead to disorders that were named before their relationship to the peroxisome was recognized, namely, Zellweger syndrome, neonatal ALD, infantile Refsum disease, and rhizomelic chondrodysplasia punctata (**RCDP**). The first 3 disorders are considered to form a *clinical continuum* , with Zellweger syndrome the most severe, infantile Refsum disease the least severe, and neonatal ALD intermediate. They can be caused by mutations in any of the 11 genes involved in peroxisome assembly. The specific gene defects cannot be distinguished by clinical features. The clinical severity varies with the degree to which protein import is impaired. Mutations that abolish import completely are often associated with the Zellweger syndrome phenotype, whereas a missense mutation, in which some degree of import function is retained, leads to the somewhat milder phenotypes. A defect in *PEX7*, which involves the import of proteins that utilize PTS2, is associated with RCDP. *PEX7* defects that leave import partially intact are associated with milder phenotypes, some of which resemble classic (adult) Refsum disease.

The genetic disorders that involve single peroxisomal enzymes usually have clinical manifestations that are more restricted and relate to the single biochemical defect. The primary adrenal insufficiency of ALD is caused by accumulation of VLCFAs in the adrenal cortex, and the peripheral neuropathy in adult Refsum disease is caused by the accumulation of phytanic acid in Schwann cells and myelin.

Zellweger Spectrum Disorder

Newborn infants with **Zellweger syndrome** show striking and consistent recognizable abnormalities. Of central diagnostic importance are the typical facial appearance (high forehead, unslanting palpebral fissures, hypoplastic supraorbital ridges, and epicanthal folds; Fig. 104.3), severe weakness and hypotonia, neonatal seizures, and eye abnormalities. Because of the hypotonia and craniofacial appearance, Down syndrome may be suspected. Infants with Zellweger syndrome rarely live more than a few months. More than 90% show postnatal growth failure. Table 104.4 lists the main clinical abnormalities.

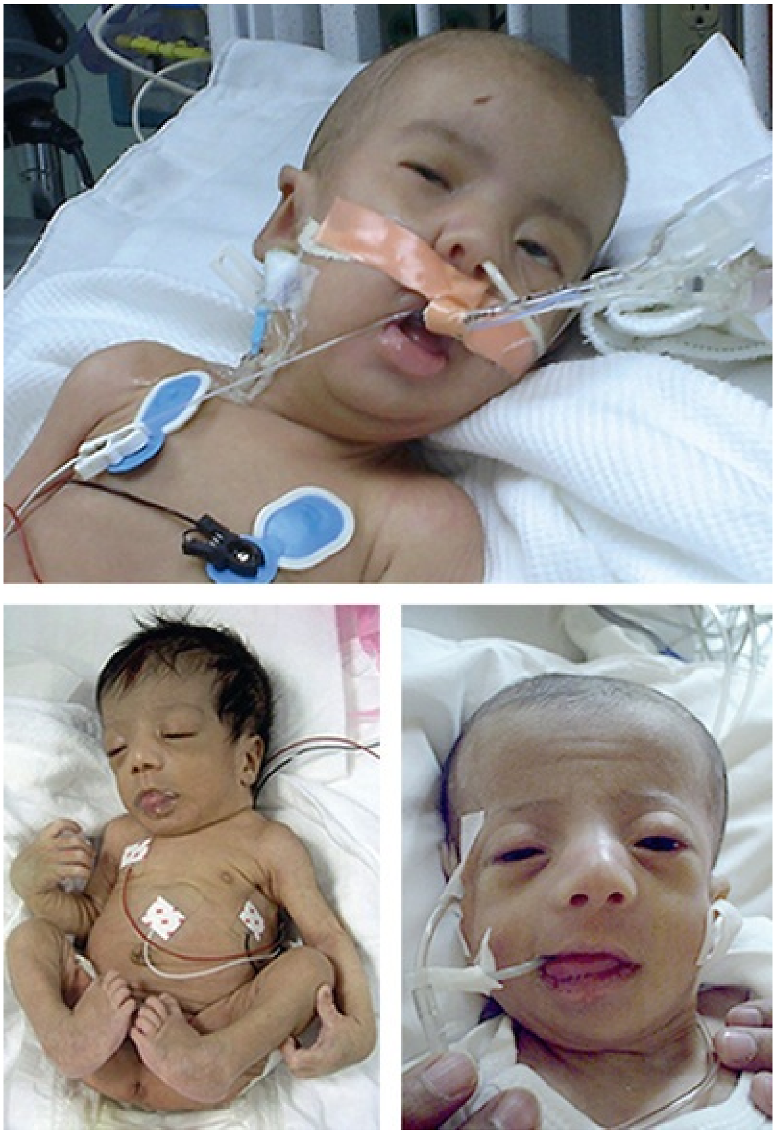

FIG. 104.3 Zellweger syndrome. Three affected neonates. Note the hypotonia, high forehead with shallow supraorbital ridges, anteverted nares, and mild micrognathia, as well as the talipes equinovarus and contractures at the knees. (From Shaheen R, Al-Dirbashi OY, Al-Hassnan ZN, et al: Clinical, biochemical and molecular characterization of peroxisomal diseases in Arabs, *Clin Genet* 79(1):60–70, 2011.)

Table 104.4

Main Clinical Abnormalities in Zellweger Syndrome

ABNORMAL FEATURE	PATIENTS IN WHOM THE FEATURE WAS PRESENT	
	Number	%
High forehead	58	97
Flat occiput	13	81
Large fontanelle(s), wide sutures	55	96

Shallow orbital ridges	33	100
Low/broad nasal bridge	23	100
Epicanthus	33	92
High-arched palate	35	95
External ear deformity	39	97
Micrognathia	18	100
Redundant skin fold of neck	13	100
Brushfield spots	5	83
Cataract/cloudy cornea	30	86
Glaucoma	7	58
Abnormal retinal pigmentation	6	40
Optic disc pallor	17	74
Severe hypotonia	94	99
Abnormal Moro response	26	100
Hyporeflexia or areflexia	56	98
Poor sucking	74	96
Gavage feeding	26	100
Epileptic seizures	56	92
Psychomotor retardation	45	100
Impaired hearing	9	40
Nystagmus	30	81

From Heymans HAS: Cerebro-hepato-renal (Zellweger) syndrome: clinical and biochemical consequences of peroxisomal dysfunctions, Thesis, University of Amsterdam, 1984.

Patients with **neonatal ALD** show fewer, less prominent craniofacial features. Neonatal seizures occur frequently. Some degree of psychomotor developmental delay is present; function remains in the range of severe intellectual disability, and development may regress after 3-5 yr of age, probably from a progressive leukodystrophy. Hepatomegaly, impaired liver function, pigmentary degeneration of the retina, and severely impaired hearing are invariably present. Adrenocortical function is usually impaired and may require adrenal hormone replacement. Chondrodysplasia punctata and renal cysts are absent.

Patients with **infantile Refsum disease** have survived to adulthood. They can walk, although gait may be ataxic and broad based. Cognitive function is generally impaired, but accurate assessment is limited, usually by the presence of both vision and hearing impairment. Almost all have some degree of sensorineural hearing loss and pigmentary degeneration of the retina. They have moderately dysmorphic features that may include epicanthal folds, a flat nose bridge, and low-set ears. Early hypotonia and hepatomegaly with impaired function are common. Levels of plasma cholesterol and high-density and low-density lipoprotein are often moderately reduced. Chondrodysplasia punctata and renal cortical cysts are absent. Postmortem study in infantile Refsum disease reveals micronodular liver cirrhosis and small, hypoplastic adrenals. The brain shows no malformations, except for severe hypoplasia of the cerebellar granule layer and ectopic locations of the Purkinje cells in the molecular layer. The mode of inheritance is autosomal recessive.

Some patients with PBDs have milder and atypical phenotypes. They may present with peripheral neuropathy or with retinopathy, impaired vision, or cataracts in childhood, adolescence, or adulthood and have been diagnosed to have **Charcot-Marie-Tooth disease** or **Usher syndrome** . Some patients have survived to the fifth decade. Defects in *PEX7*, which most frequently lead to the RCDP phenotype, may also lead to a milder phenotype with clinical manifestations similar to those of adult Refsum disease.

Rhizomelic Chondrodysplasia Punctata

RCDP is characterized by the presence of stippled foci of calcification within the hyaline cartilage and is associated with dwarfing, cataracts (72%), and multiple malformations caused by contractures. Vertebral bodies have a coronal cleft filled by cartilage that is a result of an embryonic arrest. Disproportionate short stature affects the proximal parts of the extremities (Fig. 104.4*A*). Radiologic abnormalities consist of shortening of the proximal limb bones, metaphyseal cupping, and disturbed ossification (Fig. 104.4*B*). Height, weight, and head circumference are less than the 3rd percentile, and these children have a severe intellectual disability. Skin changes such as those observed in **ichthyosiform erythroderma** are present in approximately 25% of patients.

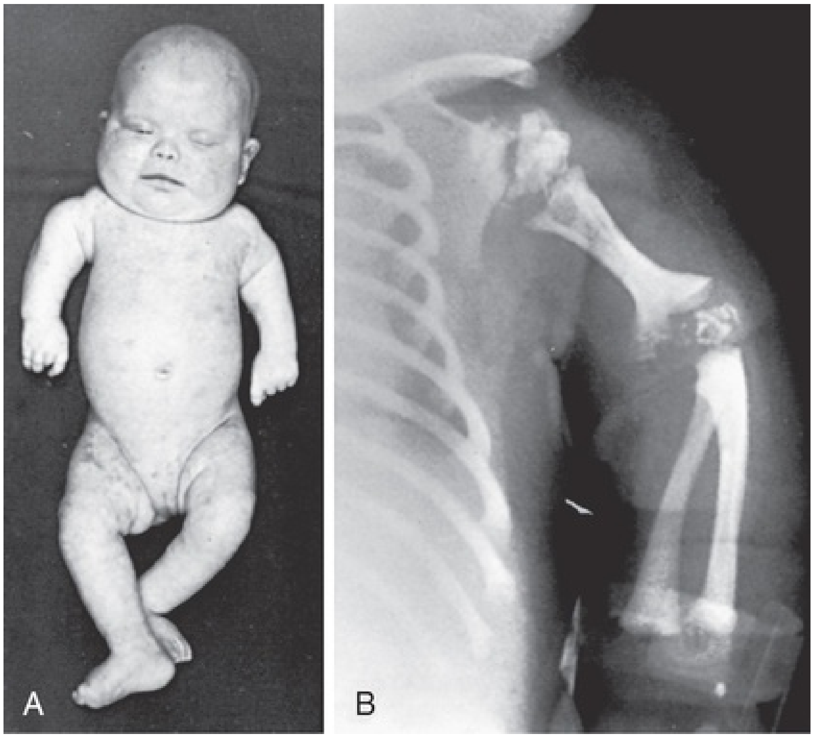

FIG. 104.4 **A,** Newborn infant with rhizomelic chondrodysplasia punctata. Note the severe shortening of the proximal limbs, the depressed bridge of the nose, hypertelorism, and widespread scaling skin lesions. **B,** Note the marked shortening of the humerus and epiphyseal stippling at the shoulder and elbow joints. (Courtesy of John P. Dorst, MD.)

Isolated Defects of Peroxisomal Fatty Acid Oxidation

In the group of single-enzyme defects, acyl-CoA oxidase and bifunctional enzyme deficiency involve a single enzymatic step in peroxisomal fatty acid oxidation. **Defects of bifunctional enzyme** are common and are found in approximately 15% of patients who are initially suspected of having Zellweger spectrum disorder. Patients with isolated **acyl-CoA oxidase deficiency** have a somewhat milder phenotype that resembles, and comes to attention because of the development of, an early childhood leukodystrophy.

Isolated Defects of Plasmalogen Synthesis

Plasmalogens are lipids in which the first carbon of glycerol is linked to an alcohol rather than a fatty acid. They are synthesized through a complex series of reactions, the first 2 steps of which are catalyzed by the peroxisomal enzymes dihydroxyacetone phosphate alkyl transferase (DHAPT) and synthase. Deficiency of either of these enzymes leads to a phenotype that is clinically indistinguishable from the peroxisomal import disorder RCDP. This latter disorder is caused by a defect in *PEX7*, the receptor for PTS2. RCDP shares the severe deficiency of plasmalogens with these single-enzyme disorders but also has defects of phytanic oxidation. The fact that these single genetic disorders are associated with the full phenotype of RCDP suggests that a deficiency of plasmalogens is sufficient to produce it.

Adult (Classic) Refsum Disease

The defective enzyme (phytanoyl-CoA hydroxylase) is localized to the peroxisome. The manifestation of Refsum disease includes impaired vision from retinitis pigmentosa, anosmia, ichthyosis, peripheral neuropathy, ataxia, and occasionally cardiac arrhythmias. In contrast to infantile Refsum disease, cognitive function is normal, and there are no congenital malformations. Refsum disease often does not manifest until young adulthood, but visual disturbances such as night blindness, ichthyosis, and peripheral neuropathy may already be present in childhood and adolescence. Early diagnosis is important because institution of a phytanic acid–restricted diet can reverse the peripheral neuropathy and prevent the progression of the visual and central nervous system (CNS) manifestations. The adult Refsum disease phenotype may also be caused by defects in *PEX7*.

2-Methylacyl-CoA Racemase Deficiency (AMACR)

This disorder is caused by an enzyme defect that leads to the accumulation of the branched-chain fatty acids (phytanic and pristanic acid) and bile acids. Individuals present with typically an adult-onset peripheral neuropathy and may also have pigmentary degeneration of the retina.

Laboratory Findings

Diagnosis of a peroxisomal disorder often follows from a biochemical determination of an abnormality and then is confirmed through further genetic testing.

The biochemical characterization of peroxisomal disorders uses the generally available testing listed in Table 104.5 . Measurement of plasma VLCFA levels is the most common assay. It must be emphasized that although plasma VLCFA levels are elevated in many patients with peroxisomal disorders, this is not always the case. The most important exception is RCDP, in which VLCFA levels are normal, but plasma phytanic acid levels are increased and red blood cell (RBC) plasmalogen levels are reduced. In other peroxisomal disorders, the biochemical abnormalities are still more restricted. Therefore, a panel of tests is recommended and includes plasma levels of VLCFAs and phytanic, pristanic, and pipecolic acids and RBC levels of plasmalogens. Tandem mass spectrometry techniques also permit convenient quantitation of bile acids in plasma and urine. This panel of tests can be performed on very small amounts of venous blood and permits detection of most peroxisomal disorders. Furthermore, normal results make the presence of the typical peroxisomal disorder unlikely. Biochemical findings combined with the clinical presentation are often sufficient to arrive at a clinical diagnosis. *Methods using dried blood spots of filter paper have been developed and are being incorporated into newborn screening assays.*

Table 104.5

Diagnostic Biochemical Abnormalities in Peroxisomal Disorders

DISORDER	VLCFA	PHYTANIC ACID	PRISTANIC ACID	PLASMALOGENS
ZSD	↑↑	↑[*]	↑[*]	↓
RCDP	Nl	↑	Nl	↓↓
ALD	↑	Nl	Nl	Nl
ACoX	↑	Nl	Nl	Nl
Bifunctional enzyme deficiency	↑	↑	↑	Nl
AMACR	Nl	↑	↑	Nl
Refsum disease	Nl	↑	↑	Nl

[*] Phytanic acid and pristanic acid accumulation is age dependent, and normal (Nl) levels may be seen in infants and young children.

VLCFA, Very-long-chain fatty acids; ZSD, Zellweger spectrum disorder; RCDP, rhizomelic chondroplasia punctata; ALD, adrenoleukodystrophy; ACoX, acyl-CoA oxidase deficiency; AMACR, 2-methylacyl-CoA racemase deficiency.

The next step in diagnosis is generally to proceed to molecular DNA diagnosis, and many clinical laboratories provide a peroxisomal panel using next-generation technology. In some circumstances the diagnosis has been revealed through whole exome sequencing and the pathogenic nature of the alteration then confirmed through biochemical means.

Definition of the molecular defect in the *proband* is essential for carrier detection and speeds **prenatal diagnosis** . Characterization of the mutation may be of prognostic value in patients with *PEX1* defects. This defect is present in approximately 60% of PBD patients, and about half the *PEX1* defects have the

G843D allele, which is associated with a significantly milder phenotype than found in other mutations.

Diagnosis

Several noninvasive laboratory tests permit precise and early diagnosis of peroxisomal disorders (see Table 104.5). The challenge in PBDs is to differentiate them from the large variety of other conditions that can cause hypotonia, seizures, failure to thrive, or dysmorphic features. Experienced clinicians readily recognize classic Zellweger syndrome by its clinical manifestations. However, more mildly affected PBD patients often do not show the full clinical spectrum of disease and may be identifiable only by laboratory assays. Clinical features that warrant diagnostic assay include intellectual disability; weakness and hypotonia; dysmorphic features; neonatal seizures; retinopathy, glaucoma, or cataracts; hearing deficits; enlarged liver and impaired liver function; and chondrodysplasia punctata. The presence of 1 or more of these abnormalities increases the likelihood of this diagnosis. Atypical milder forms presenting as peripheral neuropathy have also been described.

Some patients with the isolated defects of peroxisomal fatty acid oxidation resemble those with Zellweger spectrum disorder and can be detected by the demonstration of abnormally high levels of VLCFAs.

Patients with RCDP must be distinguished from patients with other causes of chondrodysplasia punctata. RCDP is suspected clinically because of the shortness of limbs, developmental delays, and ichthyosis. The most decisive laboratory test is the demonstration of abnormally low plasmalogen levels in RBCs and an alteration in *PEX7* .

Complications

Patients with Zellweger syndrome have multiple disabilities involving muscle tone, swallowing, cardiac abnormalities, liver disease, and seizures. These conditions are treated symptomatically, but the prognosis is poor, and most patients succumb in the 1st yr of life. Similarly, individuals with RCDP have multiple systemic and neurologic issues. In addition, they may develop quadriparesis from compression at the base of the brain.

Treatment

The most effective therapy is the dietary treatment of adult Refsum disease with a phytanic acid–restricted diet. However, this only applies to this specific condition.

For patients with the somewhat milder variants of the peroxisome import disorders, success has been achieved with multidisciplinary early intervention, including physical and occupational therapy, hearing aids or cochlear implants, augmentative and alternative communication, nutrition, and support for the families. Although most patients continue to function in the impaired range, some make significant gains in self-help skills, and several are in stable condition in their teens or even early 20s.

Attempts to mitigate some of the secondary biochemical abnormalities include the oral administration of docosahexaenoic acid (DHA). DHA level is greatly reduced in patients with disorders of peroxisome biogenesis, and this therapy normalizes DHA plasma levels. Although there were anecdotal reports of clinical improvement with DHA therapy, a randomized placebo-controlled study failed to find benefit.

Genetic Counseling

All the discussed peroxisomal disorders can be diagnosed prenatally. Prenatal testing using chorionic villi sampling or amniocentesis will usually rely on genetic testing when the alteration is known, but biochemical measurements may be made using the same tests as described for postnatal diagnosis (see Table 104.5). Because of the 25% recurrence risk, couples with an affected child should be advised about the availability of prenatal diagnosis.

Adrenoleukodystrophy

ALD is an X-linked disorder associated with the accumulation of saturated VLCFAs and a progressive dysfunction of the adrenal cortex and nervous system. It is the most common peroxisomal disorder.

Etiology

The key biochemical abnormality in ALD is the tissue accumulation of saturated VLCFAs, with a carbon chain length of 24 or more. Excess hexacosanoic acid ($C_{26:0}$) is the most striking and characteristic feature. This accumulation of fatty acids is caused by genetically deficient peroxisomal degradation of fatty acid. The defective gene *(ABCD1)* codes for a peroxisomal membrane protein (ALDP, the ALD protein). Many alterations in *ABCD1* have been determined to be pathogenic, with over half these being private or unique to the kindred. A curated database of mutations is maintained (www.x-ald.nl). The mechanism by which the ALDP defect leads to VLCFA accumulation appears to be a disruption of transport of saturated fatty acids into the peroxisome, with resultant continued elongation of progressively longer fatty acids.

Epidemiology

The minimum incidence of ALD in males is 1 in 21,000, and the combined incidence of ALD males and heterozygous females in the general population is estimated to be 1 in 17,000. All races are affected. The various phenotypes often occur in members of the same kindred. Increased implementation of newborn screening in the United States and other countries is expected to improve the accuracy of these incidence estimates.

Pathology

Characteristic lamellar cytoplasmic inclusions can be demonstrated on electron microscopy in adrenocortical cells, testicular Leydig cells, and nervous system macrophages. These inclusions probably consist of cholesterol esterified with VLCFA. They are most prominent in cells of the zona fasciculata of the adrenal cortex, which at first are distended with lipid and later atrophy.

The nervous system displays 2 types of ALD lesions. In the severe cerebral form, demyelination is associated with an inflammatory response manifested by the accumulation of perivascular lymphocytes that is most intense in the involved region. In the slowly progressive adult form, **adrenomyeloneuropathy** , the main finding is a distal axonopathy that affects the long tracts in the spinal cord. In this form the inflammatory response is mild or absent.

Pathogenesis

The adrenal dysfunction is probably a direct consequence of the accumulation of VLCFAs. The cells in the adrenal zona fasciculata are distended with abnormal lipids. Cholesterol esterified with VLCFA is relatively resistant to adrenocorticotropic hormone (ACTH)–stimulated cholesterol ester hydrolases, and this limits the capacity to convert cholesterol to active steroids. In addition, $C_{26:0}$ excess increases the viscosity of the plasma membrane, which may interfere with receptor and other cellular functions.

There is no correlation between the neurologic phenotype and the nature of the mutation or the severity of the biochemical defect as assessed by plasma VLCFA levels or between the degree of adrenal involvement and nervous system involvement. The severity of the illness and rate of progression correlate with the intensity of the **inflammatory response** . The inflammatory response may be partially cytokine mediated and may involve an autoimmune response triggered in an unknown way by the excess of VLCFAs. Mitochondrial damage and oxidative stress also appear to contribute. Approximately half the patients do not experience the inflammatory response; this difference is not understood.

Clinical Manifestations

There are 5 relatively distinct ALD phenotypes, 3 of which are present in childhood with symptoms and signs. In all the phenotypes, development is usually normal in the 1st 3-4 yr of life.

In the **childhood cerebral form** of ALD, symptoms most often are first noted between ages 4 and 8 yr. The most common initial manifestations are hyperactivity, inattention, and worsening school performance in a child who had previously been a good student. *Auditory discrimination* is often impaired, although tone perception is preserved. This may be evidenced by difficulty in using the telephone and greatly impaired performance on intelligence tests in items that are presented verbally. Spatial orientation is often impaired. Other initial symptoms are disturbances of vision, ataxia, poor handwriting, seizures, and strabismus. Visual disturbances are often caused by involvement of the parietooccipital cortex rather than eye or optic tract abnormalities, which leads to variable and seemingly inconsistent visual capacity. Seizures occur in nearly all patients and may represent the first manifestation of the disease. Some patients present with increased intracranial pressure. Impaired cortisol response to ACTH stimulation is present in 85% of patients, and mild hyperpigmentation is noted. In most patients with this phenotype, adrenal dysfunction is recognized only after the condition is diagnosed because of the cerebral symptoms. Cerebral childhood ALD tends to progress rapidly with increasing spasticity and paralysis, visual and hearing loss, and loss of ability to speak or swallow. The mean interval between the first neurologic symptom and an apparently vegetative state is 1.9 yr. Patients may continue in this apparently vegetative state for ≥10 yr.

Adolescent ALD designates patients who experience neurologic symptoms between ages 10 and 21 yr. The manifestations resemble those of childhood cerebral ALD except that progression is slower. Approximately 10% of patients present acutely with status epilepticus, adrenal crisis, acute encephalopathy, or coma.

Adrenomyeloneuropathy first manifests in late adolescence or adulthood as a progressive paraparesis caused by long tract degeneration in the spinal cord. Approximately half the affected men also have involvement of the cerebral white matter.

The **Addison-only** phenotype is an important condition. Of male patients with Addison disease, 25% may have the biochemical defect of ALD. Many of these patients have intact neurologic systems, whereas others have subtle neurologic signs. Many acquire adrenomyeloneuropathy in adulthood.

The term **asymptomatic ALD** is applied to persons who have the biochemical defect of ALD but are free of neurologic or endocrinal disturbances. Almost all persons with the gene defect eventually become neurologically symptomatic.

Approximately 50% of female heterozygotes acquire a syndrome that resembles adrenomyeloneuropathy but is milder and of later onset. Adrenal insufficiency and cerebral disease are rare.

Cases of typical ALD have occurred in relatives of those with adrenomyeloneuropathy. One of the most difficult problems in the management of ALD is the common observation that affected individuals in the same family may have quite different clinical courses. For example, in one family, an affected boy may have severe classic ALD culminating in death by age 10 yr, and another brother will have the later-onset adrenomyeloneuropathy.

Laboratory and Radiographic Findings

The most specific and important laboratory finding is the demonstration of abnormally high levels of VLCFAs in plasma, RBCs, or cultured skin fibroblasts. Positive results are obtained in all male patients with ALD and in approximately 85% of female carriers of ALD. Mutation analysis is the most reliable method for the identification of carriers. Simply finding a variation in *ABCD1* is not adequate for making the diagnosis of ALD. It must be shown to segregate with elevated VLCFA levels.

Neuroimaging

Patients with childhood cerebral or adolescent ALD have characteristic white matter lesions on MRI. In 80% of patients the lesions are symmetric and involve the splenium of the corpus callosum and periventricular white matter in the posterior parietal and occipital lobes. Many will show a garland of contrast enhancement adjacent and anterior to the posterior hypodense lesions (Fig. 104.5). This zone corresponds to the zones of intense perivascular lymphocytic infiltration where the blood-brain barrier breaks down. In 10–15% of patients, the initial lesions are frontal. Unilateral lesions that produce a mass effect suggestive of a brain tumor may occur rarely. MRI provides a clearer delineation of normal and abnormal white matter than does CT and is the preferred imaging modality.

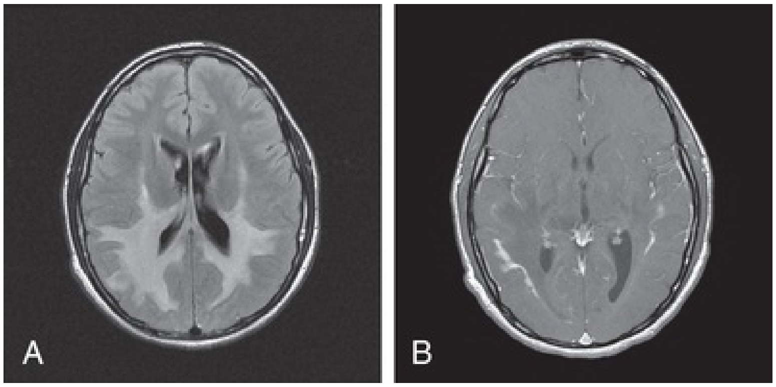

FIG. 104.5 **Characteristic MRI findings in cerebral adrenoleukodystrophy. A, Symmetric T2-weighted MRI abnormalities involve the posterior white matter, including the corpus callosum. B, Contrast administration reveals a garland of enhancement.**

Impaired Adrenal Function

More than 85% of patients with the childhood form of ALD have elevated levels of ACTH in plasma and a subnormal rise of cortisol levels in plasma after IV injection of 250 µg of ACTH (Cortrosyn).

Diagnosis and Differential Diagnosis

Diagnosis of asymptomatic males has become available by newborn screening that has been added to the recommended uniform screening panel. After diagnosis, confirmatory testing and genetic counseling should be provided. Males then enter a program of surveillance for adrenal insufficiency and early detection of potential cerebral disease. Females identified through these programs should also have confirmatory testing, genetic counseling for the family, and screening of other at-risk males. Females do not generally require any other monitoring in childhood.

The earliest manifestations of childhood cerebral ALD are difficult to distinguish from the more common attention-deficit disorders or learning disabilities of school-age children. Rapid progression, signs of dementia, or difficulty in auditory discrimination suggest ALD. Even in early stages, neuroimaging shows abnormal changes. Other leukodystrophies or multiple sclerosis may sometimes mimic these radiographic findings, although early ALD has more of a predilection for the posterior brain than its mimics. Definitive diagnosis depends on demonstration of VLCFA excess, which occurs only in ALD and the other peroxisomal disorders.

Cerebral forms of ALD, especially if asymmetric, may be misdiagnosed as gliomas or other mass lesion. Individuals have received brain biopsy and rarely other therapies before the correct diagnosis was made. Measurement of VLCFAs in plasma is the most reliable differentiating test.

Adolescent or adult cerebral ALD can be confused with psychiatric disorders, dementing disorders, multiple sclerosis, or epilepsy. The first clue to the diagnosis of ALD may be the demonstration of characteristic white matter lesions by neuroimaging; VLCFA assays are confirmatory.

ALD *cannot* be distinguished clinically from other forms of Addison disease; it is recommended that assays of VLCFA levels be performed in all male patients with Addison disease. ALD patients *do not* usually have antibodies to adrenal tissue in their plasma.

Complications

An avoidable complication is the occurrence of **adrenal insufficiency** . The most difficult neurologic problems are those related to bed rest, contracture, coma, and swallowing disturbances. Other complications involve behavioral disturbances and injuries associated with defects of spatial orientation, impaired vision and hearing, and seizures.

Treatment

Corticosteroid replacement for adrenal insufficiency or adrenocortical hypofunction is effective. It may be lifesaving and may increase general strength and well-being, but it does not alter the course of the neurologic disability.

Bone Marrow Transplantation

Bone marrow transplantation (BMT) or hematopoietic stem cell therapy benefits patients who show early evidence of the inflammatory demyelination characteristic of the rapidly progressive neurologic disability in boys and adolescents with the cerebral ALD phenotype. BMT carries risk, and patients must be evaluated and selected with care. The mechanism of the beneficial effect is incompletely understood. Bone marrow–derived cells do express ALDP, the protein that is deficient in ALD; approximately 50% of brain microglial cells are bone marrow derived. The favorable effect may be caused by modification of the brain inflammatory response. Follow-up of boys and adolescents who had early cerebral involvement has shown stabilization. On the other hand, BMT does not arrest the course in those who already had severe brain involvement and may accelerate disease progression under these circumstances. The ALD MRI score and the use of performance measures on IQ testing have shown some predictive ability for boys likely to benefit from this procedure. Transplant is not recommended in patients with performance IQ significantly <80. Unfortunately, in more than half the patients who are diagnosed because of neurologic symptoms, the illness is so advanced at diagnosis that they are not candidates for transplant.

Consideration of BMT is most relevant in neurologically asymptomatic or mildly involved patients. Screening at-risk relatives of symptomatic patients identifies these patients most frequently. Screening by measurement of plasma VLCFA levels in patients with Addison disease may also identify candidates for BMT. Because of its risk (10–20% mortality) and because up to 50% of untreated patients with ALD do not develop inflammatory brain demyelination, transplant is not recommended in patients who are free of demonstrable brain involvement on MRI. MRI is also of key importance for the crucial decision of whether transplant should be performed. MRI abnormalities precede clinically evident neurologic or neuropsychologic abnormalities. The brain MRI should be monitored at 6 mo intervals in neurologically asymptomatic boys and adolescents age 3-15 yr. If the MRI is normal, BMT is not indicated. If brain

MRI abnormalities develop, the boy should be evaluated by a center familiar with transplant for ALD. This should include MRI, neurologic, and neuropsychologic evaluations. It is not known whether BMT has a favorable effect on the noninflammatory spinal cord involvement in adults with the adrenomyeloneuropathy phenotype.

Lorenzo's Oil Therapy

Lorenzo's oil (4 : 1 mixture of glyceryl trioleate and glyceryl trierucate) combined with a dietary regimen has been under investigation to prevent the development of various aspects of ALD. The compound does lower plasma levels of VLCFAs, but despite early enthusiasm, clinical trials have been equivocal. Lorenzo's oil has not been shown to alter disease progression in males with cerebral disease. Whether it or another agent that lowers VLCFA levels has disease-modifying effects is as yet uncertain.

Supportive Therapy

The progressive behavioral and neurologic disturbances associated with the childhood form of ALD are extremely difficult for the family. ALD patients require the establishment of a comprehensive management program and partnership among the family, physician, visiting nursing staff, school authorities, and counselors. In addition, parent support groups (e.g., United Leukodystrophy Foundation) are often helpful. Communication with school authorities is important because under the provisions of Public Law 94-142, children with ALD qualify for special services as “other health impaired” or “multi-handicapped.” Depending on the rate of progression of the disease, special needs might range from relatively low-level resource services within a regular school program to home- and hospital-based teaching programs for children who are not mobile.

Management challenges vary with the stage of the illness. The early stages are characterized by subtle changes in affect, behavior, and attention span. Counseling and communication with school authorities are of prime importance. Changes in the sleep–wake cycle can be benefited by the judicious use of nighttime sleep medications.

As the leukodystrophy progresses, the modulation of muscle tone and support of bulbar muscular function are major concerns. **Baclofen** in gradually increasing doses (5 mg twice a day to 25 mg 4 times a day) is an effective pharmacologic agent for the treatment of acute episodic painful muscle spasms. Other agents may also be used, with care taken to monitor the occurrence of side effects and drug interactions. As the leukodystrophy progresses, bulbar muscular control is lost. Although initially this can be managed by changing the diet to soft and pureed foods, most patients eventually require a gastrostomy tube. At least 30% of patients have focal or generalized seizures that usually readily respond to standard anticonvulsant medications.

Genetic Counseling and Prevention

Genetic counseling and appropriate monitoring are of crucial importance. Extended-family screening should be offered to all at-risk relatives of symptomatic patients; one program led to the identification of >250 asymptomatic affected males and 1,200 women heterozygous for ALD. The plasma assay permits reliable identification of affected males in whom plasma VLCFA levels are increased already on the day of birth. Identification of asymptomatic males permits institution of steroid replacement therapy when appropriate and prevents adrenal crisis, which may be fatal. Monitoring of brain MRI also permits identification of patients who are candidates for BMT at a stage when this procedure has the greatest chance of success. Plasma VLCFA assay is recommended in all male patients with Addison disease. ALD has been shown to be the cause of adrenal insufficiency in >25% of boys with Addison disease of unknown cause. Identification of women heterozygous for ALD is more difficult than that of affected males. Plasma VLCFA levels are normal in 15–20% of heterozygous women, and failure to note this has led to serious errors in genetic counseling. DNA analysis permits accurate identification of carriers, provided that the mutation has been defined in a family member, and this is the procedure recommended for the identification of heterozygous women.

Prenatal diagnosis of affected male fetuses can be achieved by determination of the known mutation or by the measurement of VLCFA levels in cultured amniocytes or chorionic villus cells. Whenever a new patient with ALD is identified, a detailed pedigree should be constructed and efforts made to identify all at-risk female carriers and affected males. These investigations should be accompanied by careful and sympathetic attention to social, emotional, and ethical issues during counseling.

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104.3

Disorders of Lipoprotein Metabolism and Transport

Lee A. Pyles, William A. Neal

Keywords

cholesterol
familial hyperlipidemia
cholesterol screening
sitosterolemia
Smith-Lemli-Opitz syndrome
lipid
statin
PCSK-9
PCSK-9 inhibitor
ezetimibe
hypertriglyceridemia
chylomicronemia

Epidemiology of Blood Lipids and Cardiovascular Disease

There is a strong association between average intake of saturated fats, plasma cholesterol, and mortality from coronary heart disease (CHD). Of all common chronic diseases, none is so clearly influenced by both environmental *and* genetic factors as CHD. This multifactorial disorder is strongly associated with increasing age and male gender, although it is increasingly apparent that heart disease is underrecognized in women. Tobacco use confers a 2-fold higher lifetime risk. Sedentary activity and high intake of processed sugars leading to adiposity increase risk through differences in the plasma levels of atherogenic lipoproteins. Family history reflects the combined influence of lifestyle and genetic predisposition to early heart disease. Risk of premature heart disease associated with positive family history is 1.7 times higher than in families with no such history.

Atherosclerosis begins during childhood. The Johns Hopkins Precursors Study demonstrated that white male medical students with blood cholesterol levels in the lowest quartile showed only a 10% incidence of CHD 3 decades later, whereas those in the highest quartile had a 40% incidence. The Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated a significant relationship between the weight of the abdominal fat pad and the extent of atherosclerosis found at autopsy on individuals 15-34 yr of age. The Bogalusa Heart Study of more than 3,000 black and white children and adolescents has provided the most comprehensive longitudinal data relating the presence and severity of CHD risk factors with semiquantifiable severity of atherosclerosis. Coronary atherosclerosis was present in 8.5% of military autopsies performed following combat or unintentional injuries.

The *fetal origins hypothesis* is based on the observation that infants born with low birthweight have a higher incidence of heart disease as adults. Epidemiologic studies support the idea that prenatal and early postnatal conditions may affect adult health status. Children who are large for gestational age at birth and exposed to an intrauterine environment of either diabetes or maternal obesity are at increased risk of eventually developing the **metabolic syndrome** (insulin resistance, type II diabetes, obesity, CHD). Breastfeeding preterm infants confers a long-term cardioprotective benefit 13-16 yr later. Those adolescents who were breastfed as infants had lower C-reactive protein (CRP) concentrations and a 14% lower low-density lipoprotein (LDL)/high-density lipoprotein (HDL) ratio than formula-fed infants. The impact of early nutrition and other lifestyle variables on gene expression, *epigenetics* , is one mechanism by which adult metabolism and body composition may be determined.

Secondary causes of hyperlipidemia may be the result of drugs (cyclosporine, corticosteroids, isotretinoin, protease inhibitors, alcohol, thiazide diuretics, β-blocking agents, valproate); or various diseases (nephrotic syndrome, hypothyroidism, Cushing syndrome, anorexia nervosa, obstructive jaundice). Psychotropic medications, including second-generation antipsychotics such as olanzapine, are associated with dyslipidemia, obesity, and insulin resistance.

Blood Lipids and Atherogenesis

Numerous epidemiologic studies demonstrate the association of hypercholesterolemia, referring to elevated total and LDL blood cholesterol, with atherosclerotic disease. The ability to measure subcomponents within classes of lipid particles, as well as markers of inflammation, have further elucidated the process of atherogenesis and plaque rupture leading to acute coronary syndromes. Atherosclerosis affects primarily the coronary arteries but may also involve the aorta, arteries of the lower extremities, and carotid arteries.

The early stage of development of atherosclerosis is thought to begin with vascular endothelial dysfunction and intima-media thickness, which has been shown to occur in preadolescent children with risk factors such as obesity or familial hypercholesterolemia. The complex process of penetrating the intimal lining of the vessel may result from a variety of insults, including the presence of highly toxic oxidized LDL particles. Lymphocytes and monocytes penetrate the damaged endothelial lining, where they become macrophages laden with LDL lipids and then become foam cells. Such accumulation is counterbalanced by HDL particles capable of removing lipid deposits from the vessel wall. Fundamental to plaque formation is an inflammatory process (elevated CRP) involving macrophages and the arterial wall. The deposition of lipid within the subendothelial lining of the arterial wall appears macroscopically as fatty streaks, which may to some degree be reversible. A later stage of plaque development involves disruption of arterial smooth muscle cells stimulated by the release of tissue cytokines and growth factors. The *atheroma* is composed of a core of fatty substance separated from the lumen by collagen and smooth muscle (Fig. 104.6). Growth of the atherosclerotic plaque may result in ischemia of the tissue supplied by the artery. Chronic inflammation within the atheroma results in plaque instability and subsequent rupture. Platelet adherence leads to clot formation at the site of rupture, resulting in myocardial infarction (MI) or a cerebrovascular accident (CVA), depending on the site of thrombosis or thromboembolism.

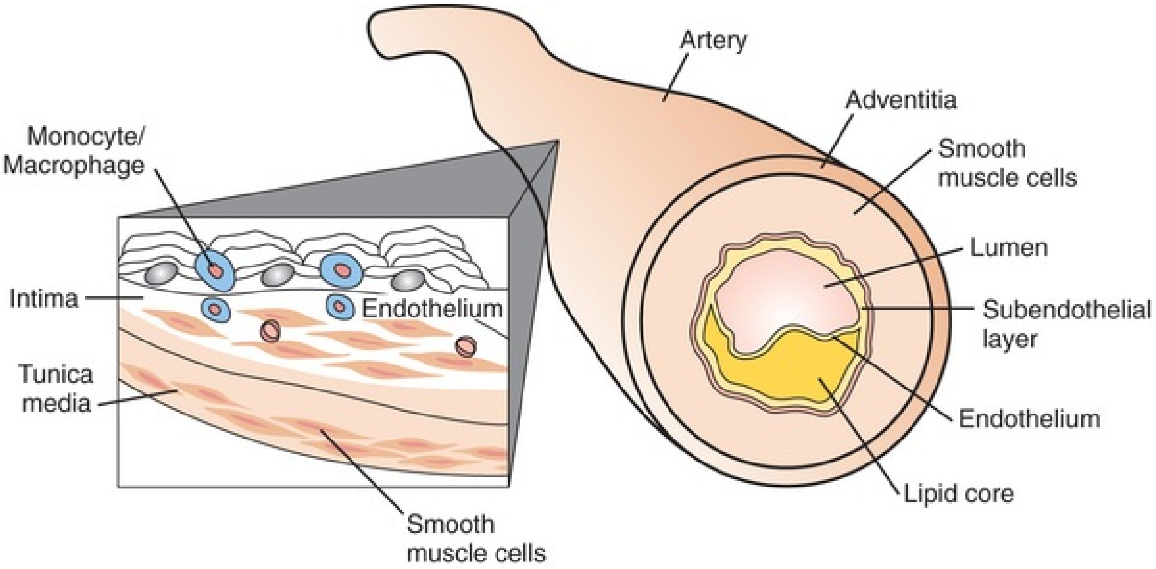
Artery
Adventitia
Smooth muscle cells
Lumen
Subendothelial layer
Endothelium
Lipid core
Monocyte/ Macrophage
Intima
Endothelium
Tunica media
Smooth muscle cells

FIG. 104.6 The early stage of development of atherosclerosis begins with penetration of the intimal lining of the vessel by inflammatory cells. Deposition of lipid within the subendothelial lining of the arterial wall eventually leads to disruption of smooth muscle cells to form an atheromatous lipid core that impinges on the lumen. Chronic inflammation leads to plaque instability, setting the stage for plaque rupture and complete occlusion of the vessel lumen by clot formation.

Plasma Lipoprotein Metabolism and Transport

Abnormalities of lipoprotein metabolism are associated with diabetes mellitus and premature atherosclerosis. *Lipoproteins* are soluble complexes of lipids and proteins that effect transport of fat absorbed from the diet, or synthesis by the liver and adipose tissues, for utilization and storage. Dietary fat is transported from the small intestine as chylomicrons. Lipids synthesized by the liver as very-low-density lipoproteins (VLDLs) are catabolized to intermediate-density lipoproteins (IDLs) and LDLs. HDL is fundamentally involved in VLDL and chylomicron metabolism and cholesterol transport. Nonesterified free fatty acids are metabolically active lipids derived from lipolysis of triglycerides stored in adipose tissue and bound to albumin for circulation in the plasma (Fig. 104.7).

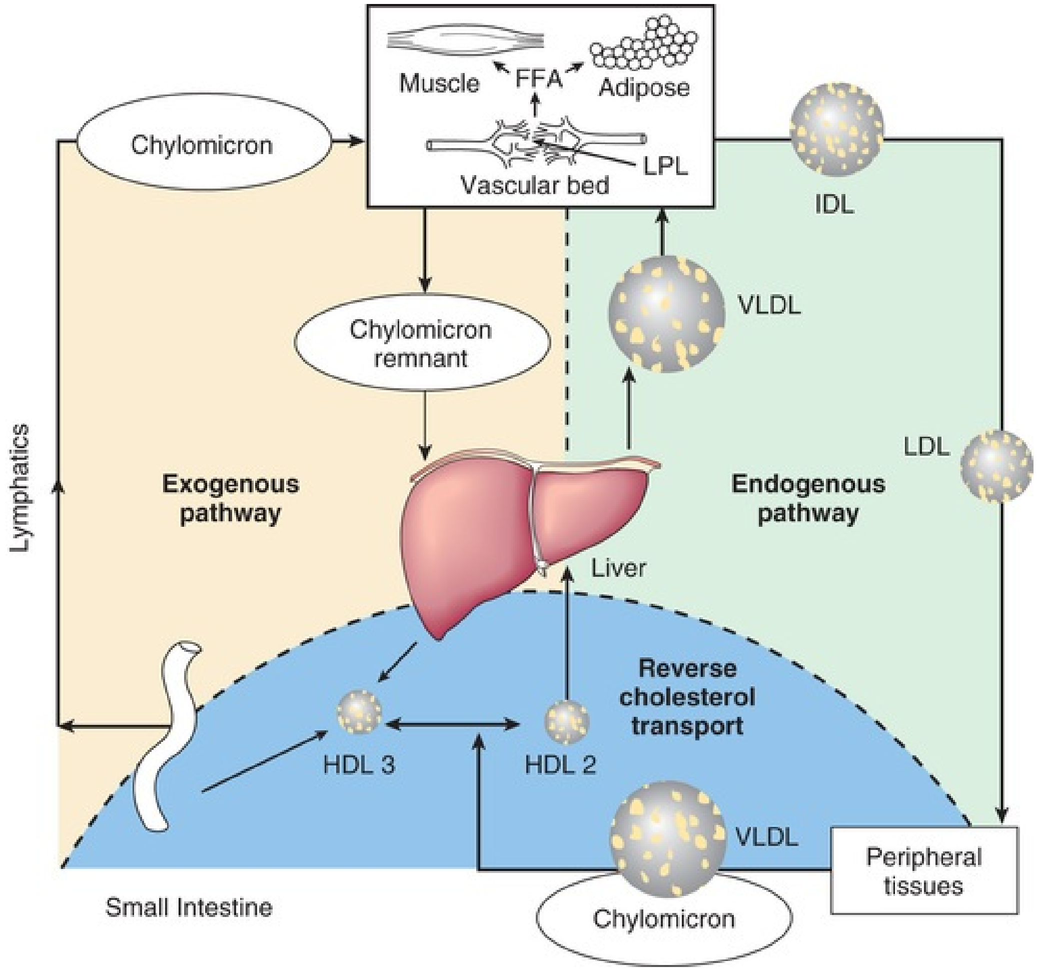
Muscle
FFA
Adipose
Chylomicron
LPL
Vascular bed
IDL
VLDL
Chylomicron remnant
LDL
Lymphatics
Exogenous pathway
Endogenous pathway
Liver
Reverse cholesterol transport
HDL 3
HDL 2
VLDL
Peripheral tissues
Small Intestine
Chylomicron

FIG. 104.7 The exogenous, endogenous, and reverse cholesterol pathways. The exogenous pathway transports dietary fat from the small intestine as chylomicrons to the periphery and the liver. The endogenous pathway denotes the secretion of very-low-density lipoprotein (VLDL) from the liver and its catabolism to intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL). Triglycerides are hydrolyzed from the VLDL particle by the action of lipoprotein lipase (LPL) in the vascular bed, yielding free fatty acids (FFA) for utilization and storage in muscle and adipose tissue. High-density lipoprotein (HDL) metabolism is responsible for the transport of excess cholesterol from the peripheral tissues back to the liver for excretion in the bile. Nascent HDL-3 particles derived from the liver and small intestine are esterified to more mature HDL-2 particles by enzyme-mediated movement of chylomicron and VLDL into the HDL core, which is removed from the circulation by endocytosis.

Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins (Fig. 104.8). The density of the several classes of lipoproteins is inversely proportional to the ratio of lipid to protein, which is generally denser (Fig. 104.9). Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins.

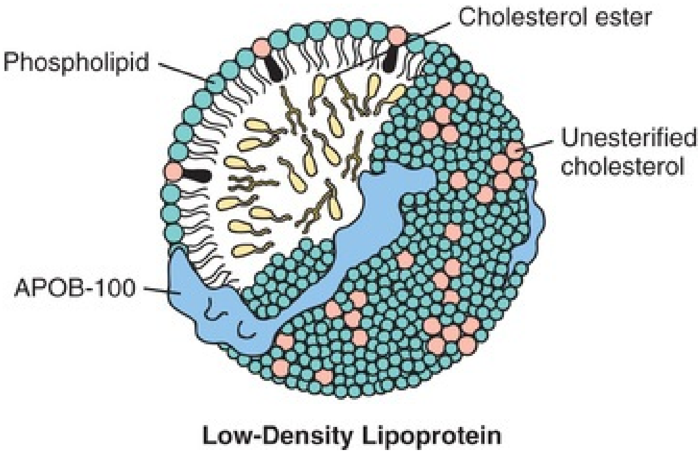

FIG. 104.8 **Schematic of low-density lipoprotein. Lipoprotein consists of a central core of cholesteryl esters, surrounded by phospholipids, cholesterol, and protein.**

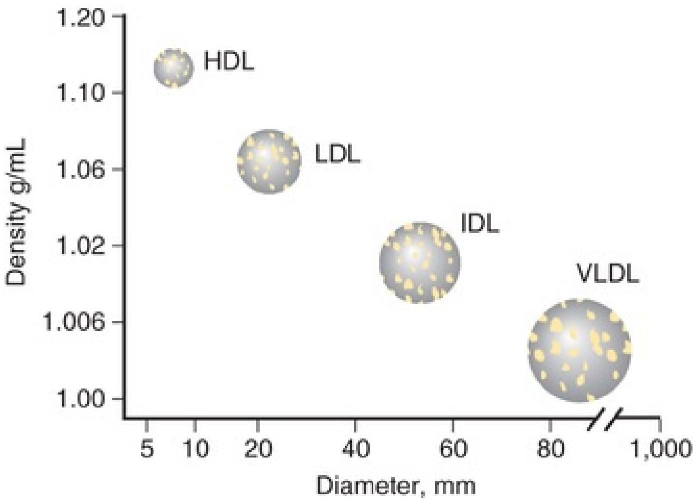

FIG. 104.9 The density of the several classes of lipoprotein is inversely proportional to the ratio of lipid to protein. As lipid is less dense than protein, the more lipid contained in the particle increases its size and decreases its density. HDL, High-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; VLDL, very-low-density lipoprotein.

Constituent proteins known as *apolipoproteins* are responsible for a variety of metabolic functions in addition to their structural role, including as cofactors or inhibitors of enzymatic pathways and mediators of lipoprotein binding to cell surface receptors (Table 104.6). **ApoA** is the major apolipoprotein (Apo) of HDL. **ApoB** is present in LDL, VLDL, IDL, and chylomicrons. ApoB-100 is derived from the liver, whereas apoB-48 comes from the small intestine. ApoC-I, C-II, and C-III are small peptides important in triglyceride metabolism. Loss of function and disruptive mutations of the *APOC3* gene are associated with low levels of triglycerides and a reduced risk of ischemic CHD. Likewise, **apoE** , which is present in VLDL, HDL, chylomicrons, and chylomicron remnants, plays an important role in the clearance of triglycerides.

Table 104.6

Characteristics of the Major Lipoproteins

LIPOPROTEIN	SOURCE	SIZE (nm)	DENSITY (g/mL)	COMPOSITION		
				Protein (%)	Lipid (%)	Apolipoproteins
Chylomicrons	Intestine	80-1,200	<0.95	1-2	98-99	C-I, C-II, C-III, E, A-I, A-II, A-IV, B-48
Chylomicron remnants	Chylomicrons	40-150	<1.0006	6-8	92-94	B-48, E
VLDL	Liver, intestine	30-80	0.95-1.006	7-10	90-93	B-100, C-I, C-II, C-III
IDL	VLDL	25-35	1.006-1.019	11	89	B-100, E
LDL	VLDL	18-25	1.019-1.063	21	79	B-100
HDL	Liver, intestine VLDL, chylomicrons	5-20	1.125-1.210	32-57	43-68	A-I, A-II, A-IV C-I, C-II, C-III D, E

HDL, High-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; VLDL, very-low-density lipoproteins.

Transport of Exogenous (Dietary) Lipids

All dietary fat except medium-chain triglycerides is efficiently carried into the circulation by way of lymphatic drainage from the intestinal mucosa. Triglyceride and cholesteryl esters combine with apoA and apoB-48 in the intestinal mucosa to form chylomicrons, which are carried into the peripheral circulation via the lymphatic system. HDL particles contribute apoC-II to the chylomicrons, required for the activation of *lipoprotein lipase* (LPL) within the capillary endothelium of adipose, heart, and skeletal muscle tissue. Free fatty acids are oxidized, esterified for storage as triglycerides, or released into the circulation bound to albumin for transport to the liver. After hydrolysis of the triglyceride core from the chylomicron, apoC particles are recirculated back to HDL. The subsequent contribution of apoE from HDL to the remnant chylomicron facilitates binding of the particle to hepatic LDL receptor (LDL-R). Within the hepatocyte, the chylomicron remnant may be incorporated into membranes, resecreted as lipoprotein back into the circulation, or secreted as bile acids. Normally, all dietary fat is disposed of within 8 hr after the last meal, an exception being individuals with a disorder of chylomicron metabolism. **Postprandial hyperlipidemia** is a risk factor for atherosclerosis. Abnormal transport of chylomicrons and their remnants may result in their absorption into the blood vessel wall as foam cells, caused by the ingestion of cholesteryl esters by macrophages, the earliest stage in the development of fatty streaks.

Transport of Endogenous Lipids From the Liver

The formation and secretion of VLDL from the liver and its catabolism to IDL and LDL particles describe the endogenous lipoprotein pathway. Fatty acids used in the hepatic formation of VLDL are derived primarily by uptake from the circulation. VLDL appears to be transported from the liver as rapidly as it is synthesized, and it consists of triglycerides, cholesteryl esters, phospholipids, and apoB-100. Nascent particles of VLDL secreted into the circulation combine with apoC and apoE. The size of the VLDL particle is determined by the amount of triglyceride present, progressively shrinking in size as triglyceride is hydrolyzed by the action of LPL, yielding free fatty acids for utilization or storage in muscle and adipose tissue. Hydrolysis of approximately 80% of the triglyceride present in VLDL particles produces IDL particles containing an equal amount of cholesterol and triglyceride. The remaining remnant IDL is converted to LDL for delivery to peripheral tissues or to the liver. ApoE is attached to the remnant IDL particle to allow binding to the cell and subsequent incorporation into the lysosome. Individuals with deficiency of either apoE2 or hepatic triglyceride lipase accumulate IDL in the plasma.

LDL particles account for approximately 70% of the plasma cholesterol in normal individuals. LDL receptors are present on the surfaces of nearly all cells. Most LDL is taken up by the liver, and the rest is transported to peripheral tissues such as the adrenal glands and gonads for steroid synthesis. Dyslipidemia is greatly influenced by LDL-R activity. The efficiency with which VLDL is converted into LDL is also important in lipid homeostasis. The normal newborn LDL level of 50 mg/dL is probably adequate for steroid synthesis throughout the life cycle.

High-Density Lipoprotein and Reverse Cholesterol Transport

Because hepatic secretion of lipid particles into the bile is the only mechanism by which cholesterol can be removed from the body, transport of excess cholesterol from the peripheral cells is a vitally important function of HDL. HDL is heavily laden with apoA-I–containing lipoproteins, which is nonatherogenic, in contrast to B lipoproteins. Cholesterol-poor nascent HDL particles secreted by the liver and small intestine are esterified to more mature HDL-2 particles by the action of the enzyme lecithin-cholesterol acyltransferase (**LCAT**), which facilitates movement of chylomicrons and VLDL into the HDL core. HDL-2 may transfer cholesteryl esters back to apoB lipoproteins mediated by cholesteryl ester transfer protein (CETP), or the cholesterol-rich particle may be removed from the plasma by endocytosis, completing reverse cholesterol transport. Low HDL may be genetic (deficiency of apoA-I) or secondary to increased plasma triglyceride.

LCAT deficiency results in diminished maturation of HDL particles, affecting their ability to do reverse cholesterol transport. This reduces its protective effect on atherosclerosis. There are rare reports, however, of less-than-expected severity of atherosclerosis despite low HDL secondary to LCAT deficiency, suggesting that the relationship may, for unknown reasons, be variable.

Hyperlipoproteinemias

Hypercholesterolemia

See Table 104.7 .

Table 104.7

Hyperlipoproteinemias

DISORDER	LIPOPROTEINS ELEVATED	CLINICAL FINDINGS	GENETICS	ESTIMATED INCIDENCE
Familial hypercholesterolemia	LDL	Tendon xanthomas, CHD	AD	1 in 500
Familial defective ApoB-100	LDL	Tendon xanthomas, CHD	AD	1 in 1,000
Autosomal recessive hypercholesterolemia	LDL	Tendon xanthomas, CHD	AR	<1 in 1,000,000
Sitosterolemia	LDL	Tendon xanthomas, CHD	AR	<1 in 1,000,000
Polygenic hypercholesterolemia	LDL	CHD		1 in 30?
Familial combined hyperlipidemia	LDL, TG	CHD	AD	1 in 200

Familial dysbetalipoproteinemia	LDL, TG	Tuberoeruptive xanthomas, peripheral vascular disease	AD	1 in 10,000
Familial chylomicronemia (Frederickson type I)	TG ↑↑	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	1 in 1,000,000
Familial hypertriglyceridemia (Frederickson type IV)	TG ↑	±CHD	AD	1 in 500
Familial hypertriglyceridemia (Frederickson type V)	TG ↑↑	Xanthomas ± CHD	AD	—
Familial hepatic lipase deficiency	VLDL	CHD	AR	<1 in 1,000,000

AD, Autosomal dominant; AR, autosomal recessive; CHD, coronary heart disease; LDL, low-density lipoproteins, TG, triglycerides; VLDL, very-low-density lipoproteins.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a monogenic autosomal co-dominant disorder characterized by strikingly elevated LDL cholesterol (LDL-C), premature cardiovascular disease (CVD), and tendon xanthomas. In the past, FH referred to defects of LDL-R activity. The etiology of this lipoprotein abnormality also includes defects in the genes for apoB (as well as PCSK-9). Of the almost 1200 mutations described, some result in failure of synthesis of the LDL-R (receptor negative), and others cause defective binding or release at the lipoprotein-receptor interface. Receptor-negative mutations result in more severe phenotypes than receptor-defective mutations.

Homozygous Familial Hypercholesterolemia

FH homozygotes inherit 2 abnormal LDL receptor genes, resulting in markedly elevated plasma cholesterol levels ranging between 500 and 1,200 mg/dL. Triglyceride levels are normal to mildly elevated, and HDL levels may be slightly decreased. The condition occurs in 1 in 500,000 persons. Receptor-negative patients have <2% normal LDL-R activity, whereas those who are receptor defective may have as much as 25% normal activity and a better prognosis.

The prognosis is poor regardless of the specific LDL-R aberration. Severe atherosclerosis involving the aortic root and coronary arteries is present by early to middle childhood. These children usually present with **xanthomas** , which may cause thickening of the Achilles tendon or extensor tendons of the hands, or cutaneous lesions on the hands, elbows, knees, or buttocks (Figs. 104.10 to 104.12). Corneal arcus may be present. Family history is informative because premature heart disease is strongly prevalent among relatives of both parents.

The diagnosis may be confirmed genetically or by measuring LDL-R activity in cultured skin fibroblasts. Phenotypic expression of the disease may also be assessed by measuring receptor activity on the surface of lymphocytes by using cell-sorting techniques.

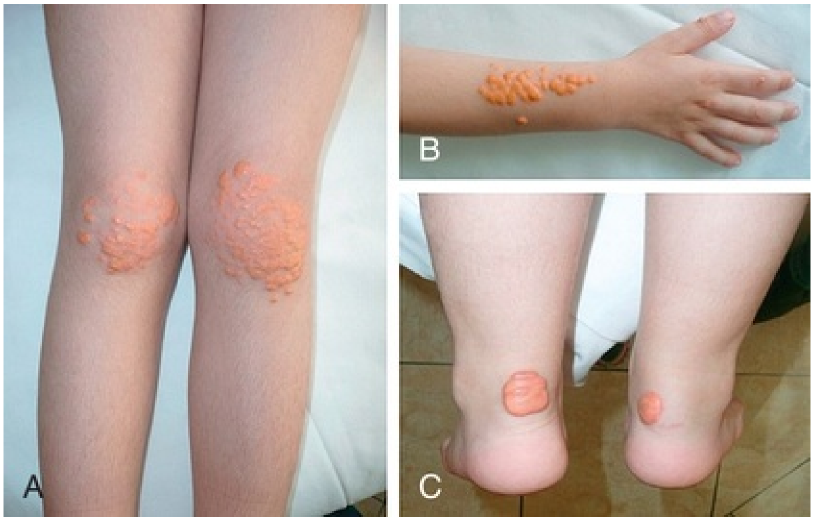

FIG. 104.10 **Homozygous familial hypercholesterolemia. Tendon xanthomas in a 5 yr old male with homozygous FH noted at the knee (A), wrist (B), and Achilles (C). (Modified from Macchiaiolo M, Gagliardi MG, Toscano A, et al: Homozygous familial hypercholesterolaemia, *Lancet* 379:1330, 2012.)**

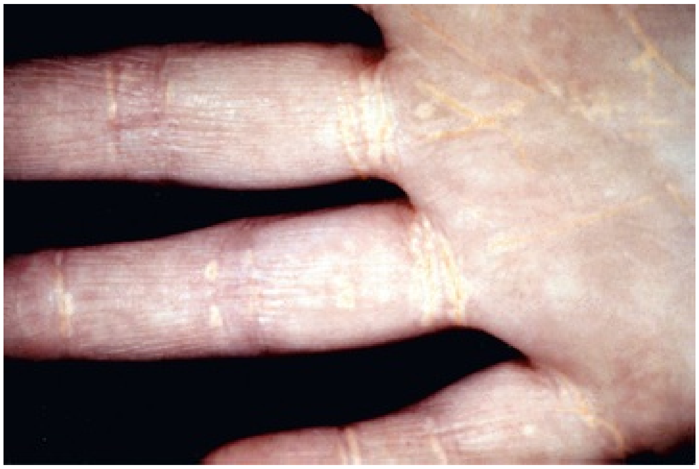

FIG. 104.11 Striate palmar xanthomata. (From Durrington P: Dyslipidaemia, *Lancet* 362:717–731, 2003.)

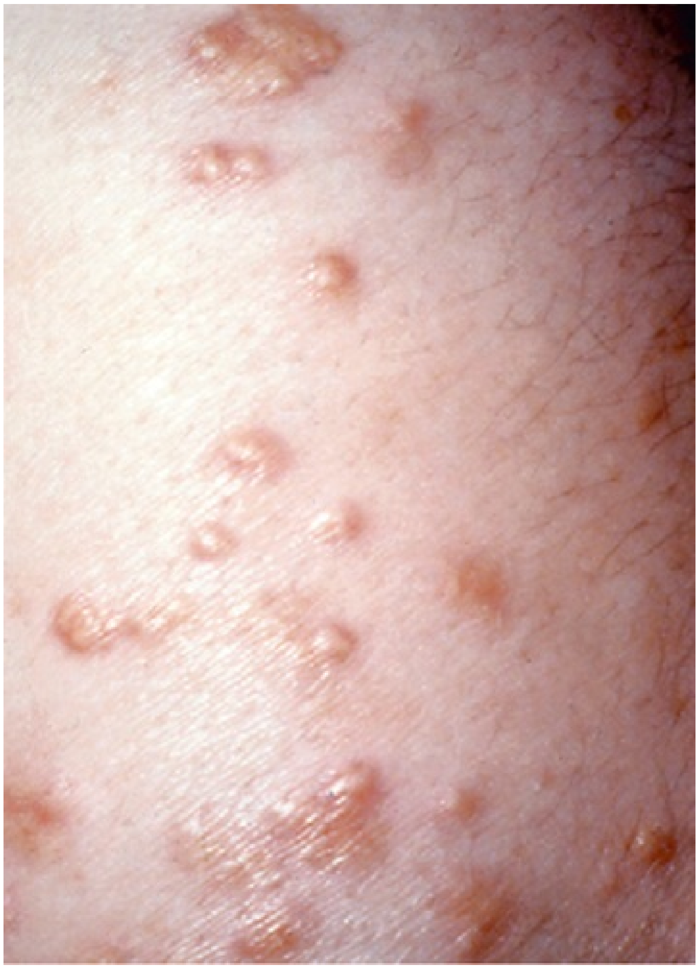

FIG. 104.12 Eruptive xanthomata on extensor surface of forearm. (From Durrington P: Dyslipidaemia, *Lancet* 362:717–731, 2003.)

Untreated homozygous patients rarely survive to adulthood. Symptoms of coronary insufficiency may occur; sudden death is common. LDL apheresis to remove LDL particles selectively from the circulation is recommended for many children because it slows the progression of atherosclerosis. Liver transplantation is also successful in decreasing LDL-C levels, but complications related to immunosuppression are common. HMG-CoA reductase inhibitors may be modestly effective depending on the specific class of LDL-R defect present. Combination therapy with *ezetimibe*, selectively blocking cholesterol adsorption in the gut, usually results in further decline in LDL levels; it has largely replaced the use of bile acid sequestrants. Early clinical trials using microsomal triglyceride transfer protein inhibition with *lomitapide* (oral agent) resulted in a significant reduction in all apoB lipoproteins, including LDL, but hepatic fat deposition as a side effect limits consideration of this pharmacologic approach.

Mipomersen (subcutaneous injection), an antisense oligonucleotide that binds to the sequence that encodes apolipoprotein B, reduces the synthesis of apoB and thus also VLDL and LDL; LDL cholesterol levels may decline approximately 25% with this treatment. Adverse effects include flulike symptoms, hepatic steatosis, and cirrhosis.

Heterozygous Familial Hypercholesterolemia

Heterozygous FH is the most common single-gene mutations associated with acute coronary syndromes and atherosclerotic CHD in adults. Its prevalence is approximately 1 in 250 individuals worldwide, but the frequency may be greater in select populations, such as French Canadians, Afrikaners, and Christian Lebanese, as a result of the founder effect of unique new mutations. The founder effect noted in Ashkenazi Jews can be traced through gene disequilibrium analysis to an initial mutation in Lithuania in the 1400s.

Heart disease accounts for more than half of all deaths in Western society. The pathogenesis of CHD is both environmental and genetic, and the complex interrelationship determines the phenotypic expression of disease.

Because heterozygous FH is a co-dominant condition with nearly full penetrance, 50% of first-degree relatives of affected individuals will have the disease, as will 25% of second-degree relatives. An estimated 20 million people have FH worldwide. Symptoms of CHD usually occur at the mean age of 45-48 yr in males and a decade later in females. Genetic testing of individuals who fulfill clinical criteria for the diagnosis of heterozygous FH is variably positive dependent on the population under investigation, including pediatric vs adult participants.

The World Health Organization (WHO) has targeted FH for individualized intervention strategies because of its large effect on morbidity and mortality. A relatively small percentage of the population accounts for a disproportionately high share of the burden of CVD. The clinical expression of the disease is straightforward, and treatment is effective.

One cannot overemphasize the importance of family history for suspecting the possibility of FH, especially given the 3% cholesterol screening rate for children in primary care offices. American Academy of Pediatrics (AAP) and National Heart, Lung, and Blood Institute (NHLBI) guidelines advocate for universal screening for cholesterol in childhood, but with poor acceptance and disagreement. There is an increased interest in genetic testing for persons with suspected FH because of variability in phenotype based on genotype. In fact, the risk of CHD in individuals with FH can be up to 20 times greater than in the general population.

Plasma levels of LDL-C do not allow unequivocal diagnosis of FH heterozygotes, but values are generally twice normal for age because of 1 absent or dysfunctional allele. The U.S. MED-PED *(Make Early Diagnosis–Prevent Early Death)* Program has formulated diagnostic criteria. Similar criteria with minor variations exist in the United Kingdom (Simon Broome criteria) and Holland (Dutch Lipid Clinic Network criteria). Within well-defined FH families, the diagnosis is reliably established according to LDL cutoff points. More stringent criteria are required to establish the diagnosis in previously undiagnosed families, requiring strong evidence of an autosomal inheritance pattern and higher LDL cutoff points. At a total cholesterol level of 310 mg/dL, only 4% of adults in the general population would have FH, whereas 95% of adults who were first-degree relatives of known cases would have the disease. The mathematical probability of FH in MED-PED, verified by molecular genetics, is derived from a U.S. population cohort and may not be applicable to other countries.

Very high cholesterol levels in children should prompt extensive screening of adult first- and second-degree relatives (“reverse cascade” cholesterol screening). In the general population, a child younger than age 18 yr with total plasma cholesterol of 270 mg/dL and/or LDL-C of 200 mg/dL has an 88% chance of having FH (Table 104.8). *Formal clinical diagnosis of FH is based on the presence of 2 or more family members having elevated LDL-C levels* (the 95th percentile LDL-C level cutoff points for children vary with age and are lower than for adults; see Table 104.9). Thus the criteria for probable FH in a child whose first-degree relative has known FH require only modest elevation of total cholesterol to 220 mg/dL (LDL-C 160 mg/dL; Table 104.8). The challenge of childhood FH diagnosis is heightened by the lack of clinical stigmata such as xanthomata that are employed in the Simon Broome and Dutch Lipid Clinic Network schema and highlights the shift toward genetic diagnosis.

Table 104.8

Percentage of Youths Younger than Age 18 Yr Expected to Have Familial Hypercholesterolemia (FH) According to Cholesterol Levels and Closest Relative With FH

TOTAL CHOL (mg/dL)	**LDL CHOL (mg/dL)**	**PERCENTAGE WITH FH AT THAT LEVEL**			
		Degree of Relative			**General Population**
		First	**Second**	**Third**	
180	122	7.2	2.4	0.9	0.01
190	130	13.5	5.0	2.2	0.03
200	138	26.4	10.7	4.9	0.07
210	147	48.1	23.6	11.7	0.19
220	155	73.1	47.5	27.9	0.54
230	164	90.0	75.0	56.2	1.8
240	172	97.1	93.7	82.8	6.3
250	181	99.3	97.6	95.3	22.2
260	190	99.9	99.5	99.0	57.6
270	200	100.0	99.9	99.8	88.0
280	210	100.0	100.0	100.0	97.8
290	220	100.0	100.0	100.0	99.6
300	230	100.0	100.0	100.0	99.9
310	240	100.0	100.0	100.0	100.0

Chol, Cholesterol; LDL, low-density lipoprotein.

From Williams RR, Hunt SC, Schumacher MC, et al: Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics, *Am J Cardiol* 72:171–176, 1993.

Table 104.9

Plasma Cholesterol and Triglyceride Levels in Childhood and Adolescence: Means and Percentiles

	TOTAL TRIGLYCERIDE (mg/dL)					**TOTAL CHOLESTEROL (mg/dL)**					**LDL CHOLESTEROL (mg/dL)**					**HDL CHO (mg/dL)***	
	5th	**Mean**	**75th**	**90th**	**95th**	**5th**	**Mean**	**75th**	**90th**	**95th**	**5th**	**Mean**	**75th**	**90th**	**95th**	**5th**	**10th**
Cord	14	34	—	—	84	42	68	—	—	103	17	29	—	—	50	13	—
1-4 YR																	
Male	29	56	68	85	99	114	155	170	190	203	—	—	—	—	—	—	—
Female	34	64	74	95	112	112	156	173	188	200	—	—	—	—	—	—	—
5-9 YR																	
Male	28	52	58	70	85	125	155	168	183	189	63	93	103	117	129	38	42
Female	32	64	74	103	126	131	164	176	190	197	68	100	115	125	140	36	38
10-14 YR																	
Male	33	63	74	94	111	124	160	173	188	202	64	97	109	122	132	37	40
Female	39	72	85	104	120	125	160	171	191	205	68	97	110	126	136	37	40
15-19 YR																	
Male	38	78	88	125	143	118	153	168	183	191	62	94	109	123	130	30	34
Female	36	73	85	112	126	118	159	176	198	207	59	96	111	29	137	35	38

[*] Note that different percentiles are listed for high-density lipoprotein (HDL) cholesterol. LDL, Low-density lipoprotein.

Data for cord blood from Strong W: Atherosclerosis: its pediatric roots. In Kaplan N, Stamler J, editors: *Prevention of coronary heart disease* , Philadelphia, 1983, Saunders. Data for children 1-

4 yr from Tables 6, 7, 20, and 21, and all other data from Tables 24, 25, 32, 33, 36, and 37 in *Lipid research clinics population studies data book* , Vol 1, “The prevalence study,” NIH Pub No 80-1527, Washington, DC, 1980, National Institutes of Health.

Treatment of children with FH should begin with a rather rigorous low-fat diet. Diet alone is rarely sufficient for decreasing blood cholesterol levels to acceptable levels (LDL-C <130 mg/dL). Ezetimibe blocks cholesterol adsorption in the gastrointestinal (GI) tract and has a low risk of side effects. Data suggest that ezetimibe will lower total cholesterol by 20-30 mg/dL. *HMG-CoA reductase inhibitors (statins) are the drug of choice for treatment of FH because of their remarkable effectiveness and acceptable risk profile.* There is sufficient clinical experience with this class of drugs in children over age 10 yr to document that they are as effective in children as in adults, and the risks of elevated hepatic enzymes and myositis are no greater than in adults. Another class of drugs, the proprotein convertase subtilisin/kexin type 9 (**PCSK-9**) inhibitors, are monoclonal antibodies (mAbs) that block the action of PCSK-9 to downregulate the LDL-R. These agents boost LDL-R levels and result in a marked decrease in plasma LDL-C levels. PCSK-9 inhibitors have a role in adults intolerant of statins and those with subtherapeutic statin effect. Use in children is experimental.

Familial Defective ApoB-100

Familial defective apoB-100 is an autosomal dominant condition that is indistinguishable from heterozygous FH. LDL cholesterol levels are increased, triglycerides are normal, adults often develop tendon xanthomas, and premature CHD occurs. Familial defective apoB-100 is caused by mutation in the receptor-binding region of apoB-100, the ligand of the LDL receptor, with an estimated frequency of 1 in 700 people in Western cultures. It is usually caused by substitution of glutamine for arginine in position 3500 in apoB-100, which results in reduced ability of the LDL-R to bind LDL-C, thus impairing its removal from the circulation. Specialized laboratory testing can distinguish familial defective apoB-100 from FH, but this is not necessary, except in research settings, because treatment is the same.

Autosomal Recessive Hypercholesterolemia

This rare condition, caused by a defect in LDL-R–mediated endocytosis in the liver, clinically presents with severe hypercholesterolemia at levels intermediate between those found in homozygous and heterozygous FH. It is disproportionately present among Sardinians and is modestly responsive to treatment with HMG-CoA reductase inhibitors.

Sitosterolemia

A rare autosomal recessive condition characterized by excessive intestinal adsorption of plant sterols, sitosterolemia is caused by mutations in the adenosine triphosphate (ATP)–binding cassette transporter system (*ABCG5* or *ABCG8*), which is responsible for limiting adsorption of plant sterols in the small intestine and promotes biliary excretion of the small amounts adsorbed. Plasma cholesterol levels may be severely elevated, resulting in tendon xanthomas and premature atherosclerosis. Other features include hemolytic anemia, macrothrombocytopenia (large platelets, reduced number), and hemorrhage. Diagnosis can be confirmed by measuring elevated plasma sitosterol levels. Treatment with HMG-CoA reductase inhibitors is not effective, but cholesterol adsorption inhibitors, such as ezetimibe, and bile acid sequestrants are effective.

Polygenic Hypercholesterolemia

Primary elevation in LDL-C among children and adults is most often polygenic; the small effects of many genes are impacted by environmental influences (diet). Plasma cholesterol levels are modestly elevated; triglyceride levels are normal. Polygenic hypercholesterolemia aggregates in families sharing a common lifestyle but does not follow predictable hereditary patterns found in single-gene lipoprotein defects. Treatment of children with polygenic hypercholesterolemia is directed toward adoption of a healthy lifestyle: reduced total and saturated fat consumption and at least 1 hr of physical activity daily. Cholesterol-lowering medication is rarely necessary.

Hypercholesterolemia With Hypertriglyceridemia

Familial Combined Hyperlipidemia

This autosomal dominant condition is characterized by moderate elevation in plasma LDL-C and triglycerides and reduced plasma HDL-C. Familial combined hyperlipidemia (FCHL) is the most common primary lipid disorder, affecting approximately 1 in 200 people. Family history of premature heart disease is typically positive; the formal diagnosis requires that at least 2 first-degree relatives have evidence of 1 of 3 variants of dyslipidemia: (1) >90th percentile plasma LDL-C; (2) >90th percentile LDL-C and triglycerides; and (3) >90th percentile triglycerides. Individuals switch from one phenotype to another. Xanthomas are not a feature of FCHL. Elevated plasma apoB levels with increased small, dense LDL particles support the diagnosis.

Children and adults with FCHL have coexisting adiposity, hypertension, and hyperinsulinemia, suggesting the presence of the **metabolic syndrome** . Formal diagnosis in adults, as defined by the National Cholesterol Education Program (**NCEP**) Adult Treatment Panel III, identifies 6 major components: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance with or without impaired glucose tolerance, evidence of vascular inflammation, and prothrombotic state. An estimated 30% of overweight adults fulfill criteria for the diagnosis of metabolic syndrome, including 65% of those with FCHL. Hispanics and South Asians from the Indian subcontinent are especially susceptible. *There is no official definition of metabolic syndrome for children.* Absolute cutoffs for diagnosis in children do not account for continuous variables in aging, sexual maturation, and race/ethnicity.

FCHL and type 2 diabetes share many features of the metabolic syndrome, suggesting that they are less distinct entities than originally conceptualized. Genetic association studies reveal evidence for a common genetic background. The resultant metabolic overlap is associated with ectopic fat accumulation and insulin resistance. The mechanisms associating visceral adiposity with the metabolic syndrome and type 2 diabetes are not fully understood. A plausible unifying principle is that obesity causes endoplasmic reticulum stress, leading to suppression of insulin receptor signaling and thus insulin resistance and heightened inflammatory response. How this relates to atherogenesis is unclear. It is assumed that hypercholesterolemia and, with less certainty, hypertriglyceridemia confer risk for CVD in patients with FCHL. When features of the metabolic syndrome are included in logistic models, shared etiologic features such as increased visceral adiposity become apparent. Visceral adiposity increases with age, and its importance in children as a risk factor for heart disease and diabetes is limited by the relative paucity of data. Although longitudinal measurement of waist circumference and the presence of intraabdominal fat as determined by MRI is being conducted in the research setting, body mass index (BMI) remains the surrogate for adiposity in the pediatric clinical setting.

The metabolic syndrome is a dramatic illustration of the interaction of genetics and the environment. Genetic susceptibility is essential as an explanation for premature heart disease in individuals with FCHL. Unhealthy lifestyle, poor diet, and physical inactivity contribute to obesity and attendant features of the metabolic syndrome.

The cornerstone of management is lifestyle modification . This includes a diet low in saturated fats, *trans* fats, and cholesterol, as well as reduced consumption of processed sugars. Increased dietary intake of fruits and vegetables is important, as is 1 hr of moderate physical activity daily. Compliance among children and their parents is often a problem, but small incremental steps are more likely to succeed than aggressive weight loss strategies. It is very important that the child's caregivers participate in the process. Plasma triglyceride levels are usually quite responsive to dietary restriction, especially reduction in the amount of sweetened drinks consumed. Blood cholesterol levels may decrease by 10–15%, but if LDL-C remains >160 mg/dL, drug therapy should be considered.

Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

Familial dysbetalipoproteinemia (FDBL) is caused by mutations in the gene for apoE, which when exposed to environmental influences (e.g., high-fat high-caloric diet, excessive alcohol intake) results in a mixed type of hyperlipidemia. Patients tend to have elevated plasma cholesterol and triglycerides to a relatively similar degree. HDL-C is typically normal, in contrast to other causes of hypertriglyceridemia associated with low HDL. This rare disorder affects approximately 1 in 10,000 persons. ApoE mediates removal of chylomicron and VLDL remnants from the circulation by binding to hepatic surface receptors. The polymorphic *APOE* gene expresses in 3 isoforms: *apoE3, apoE2,* and *apoE4. E4* is the “normal” allele present in the majority of the population. The *apoE2* isoform has lower affinity for the LDL receptor, and its frequency is approximately 7%. Approximately 1% of the population is homozygous for *apoE2/E2,* the most common mutation associated with FDBL, but only a minority expresses the disease. Expression requires precipitating illnesses such as diabetes, obesity, renal disease, or hypothyroidism. Individuals homozygous for *apoE4/E4* are at risk for late-onset Alzheimer disease and dementia from repeated sports-related head injuries.

Most patients with FDBL present in adulthood with distinctive xanthomas. Tuberoeruptive xanthomas resemble small, grapelike clusters on the knees, buttocks, and elbows. Prominent orange-yellow discoloration of the creases of the hands (palmar xanthomas) is also typically present. Atherosclerosis, often presenting with peripheral vascular disease, usually occurs in the 4th or 5th decade. Children may present with a less distinctive rash and generally have precipitating illnesses.

The diagnosis of FDBL is established by lipoprotein electrophoresis, which demonstrates a broad beta band containing remnant lipoproteins. Direct measurement of VLDL by ultracentrifugation can be performed in specialized lipid laboratories. A VLDL/total triglyceride ratio >0.30 supports the diagnosis. *APOE* genotyping for *apoE2* homozygosity can be performed, confirming the diagnosis in the presence of the distinctive physical findings. A negative result does not necessarily rule out the disease as other mutations in *APOE* may cause even more serious manifestations.

Pharmacologic treatment of FDBL is necessary to decrease the likelihood of symptomatic atherosclerosis in adults. HMG-CoA reductase inhibitors, nicotinic acid, and fibrates are all effective. FDBL is quite responsive to recommended dietary restriction.

Hypertriglyceridemias

The familial disorders of triglyceride-rich lipoproteins include both common and rare variants of the **Frederickson classification** system. These include familial chylomicronemia (type I), familial hypertriglyceridemia (type IV), and the more severe combined hypertriglyceridemia and chylomicronemia (type V). Hepatic lipase deficiency also results in a similar combined hyperlipidemia.

Familial Chylomicronemia (Type I Hyperlipidemia)

This rare single-gene defect, like FH, is caused by mutations affecting clearance of apoB-containing lipoproteins. Deficiency or absence of LPL or its cofactor apoC-II, which facilitates lipolysis by LPL, causes severe elevation of triglyceride-rich plasma chylomicrons. HDL-C levels are decreased. Clearance of these particles is greatly delayed, so the plasma is noted to have a turbid appearance even after prolonged fasting (Fig. 104.13). Chylomicronemia caused by LPL deficiency is associated with modest elevation in triglycerides, whereas this is not the case when the cause is deficient or absent apoC-II. Both are autosomal recessive conditions with a frequency of approximately 1 in 1 million population. The disease usually presents during childhood with acute pancreatitis. Eruptive xanthomas on the arms, knees, and buttocks may be present, and there may be hepatosplenomegaly. The diagnosis is established by assaying triglyceride lipolytic activity. **Treatment** of chylomicronemia is by vigorous dietary fat restriction supplemented by fat-soluble vitamins. Medium-chain triglycerides that are adsorbed into the portal venous system may augment total fat intake, and administration of fish oils may also be beneficial.

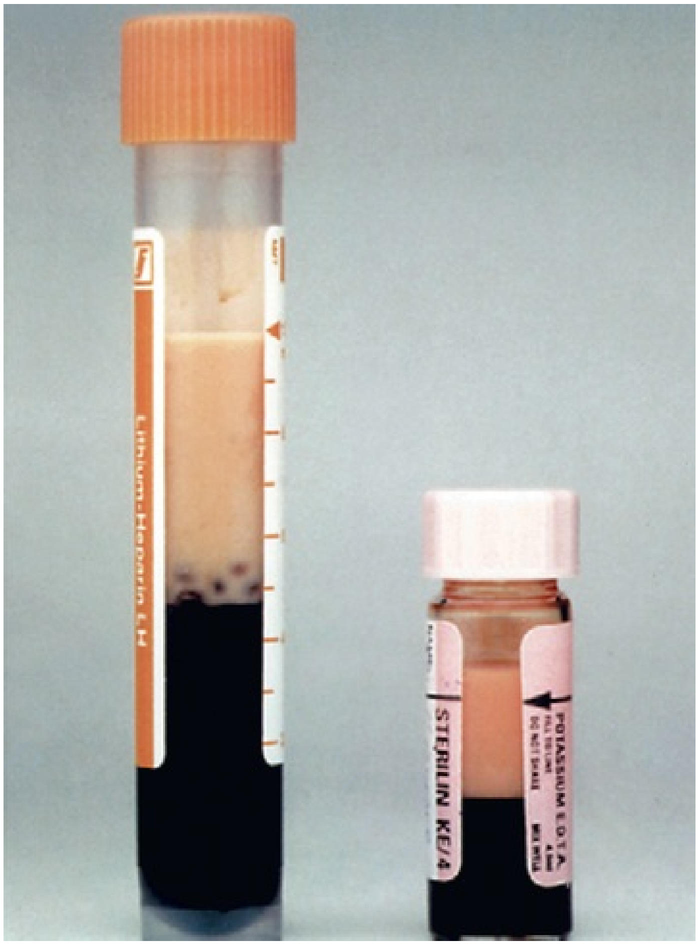

FIG. 104.13 Milky plasma from patient with acute abdominal pain. (From Durrington P: Dyslipidaemia, *Lancet* 362:717–731, 2003.)

Familial Hypertriglyceridemia (Type IV Hyperlipidemia)

Familial hypertriglyceridemia (FHTG) is an autosomal dominant disorder of unknown etiology that occurs in approximately 1 in 500 individuals. It is characterized by elevation of plasma triglycerides >90th percentile (250-1,000 mg/dL range), often accompanied by slight elevation in plasma cholesterol and low HDL. FHTG does not usually manifest until adulthood, although it is expressed in approximately 20% of affected children. In contrast to FCHL, FHTG is not thought to be highly atherogenic. It is most likely caused by defective breakdown of VLDL, or less often by overproduction of this class of lipoproteins.

The diagnosis should include the presence of at least 1 first-degree relative with hypertriglyceridemia. FHTG should be distinguished from FCHL and FDBL, which require more vigorous treatment to prevent coronary or peripheral vascular disease. The differentiation is usually possible on clinical grounds, in that lower LDL-C levels accompany FHTG, but measurement of normal apoB levels in FHTG may be helpful in ambiguous situations.

A more severe hypertriglyceridemia characterized by increased levels of chylomicrons as well as VLDL particles (Frederickson **type V**) may occasionally be encountered. Triglyceride levels are often >1,000 mg/dL. The disease is rarely seen in children. In contrast to chylomicronemia (Frederickson **type I**), LPL or apoC-II deficiency is not present. These patients often develop eruptive xanthomas in adulthood, whereas **type IV** hypertriglyceridemia individuals do not. Acute pancreatitis may be the presenting illness. As with other hypertriglyceridemias, excessive alcohol consumption and estrogen therapy can exacerbate the disease.

Secondary causes of *transient hypertriglyceridemia* should be ruled out before making a diagnosis of FHTG. A diet high in simple sugars and carbohydrates or excessive alcohol consumption, as well as estrogen therapy, may exacerbate hypertriglyceridemia. Adolescents and adults should be questioned about excessive consumption of soda and other sweetened drinks, as it is common to encounter people who drink supersized drinks or multiple 12 oz cans of sweetened drinks daily. Cessation of this practice often results in dramatic fall in triglyceride levels as well as weight among those who are obese. HDL-C levels will tend to rise as BMI stabilizes.

Pediatric diseases associated with hyperlipidemia include hypothyroidism, nephrotic syndrome, biliary atresia, glycogen storage disease, Niemann-Pick disease, Tay-Sachs disease, systemic lupus erythematosus, hepatitis, and anorexia nervosa (Table 104.10). Certain medications exacerbate hyperlipidemia, including isotretinoin (Accutane), thiazide diuretics, second-generation antipsychotic agents, oral contraceptives, corticosteroids, β blockers, immunosuppressants, and protease inhibitors used in HIV treatment.

Table 104.10

Secondary Causes of Hyperlipidemia

Hypercholesterolemia

Hypothyroidism
Nephrotic syndrome
Cholestasis
Anorexia nervosa
Drugs: progesterone, thiazides, carbamazepine (Tegretol), cyclosporine

Hypertriglyceridemia

Obesity
Type 2 diabetes
Alcohol
Renal failure
Sepsis
Stress
Cushing syndrome
Pregnancy
Hepatitis
AIDS, protease inhibitors
Drugs: anabolic steroids, β-blockers, estrogen, thiazides

Reduced High-Density Lipoprotein

Smoking
Obesity
Type 2 diabetes
Malnutrition
Drugs: β-blockers, anabolic steroids

Treatment of hypertriglyceridemia in children rarely requires medication unless levels >1,000 mg/dL persist after dietary restriction of fats, sugars, and carbohydrates, accompanied by increased physical activity. In such patients the aim is to prevent episodes of pancreatitis. The common use of fibrates (fenofibric acid) and niacin in adults with hypertriglyceridemia is not recommended in children. HMG-CoA reductase inhibitors are variably effective in lowering triglyceride levels, and there is considerably more experience documenting the safety and efficacy of this class of lipid-lowering medications in children. In adults, the U.S. Food and Drug Administration (FDA) has approved prescription (Lovaza, Vascepa) and nonprescription fish oils as adjuncts to diet in the treatment of severe hypertriglyceridemias.

Hepatic Lipase Deficiency

Hepatic lipase deficiency is a very rare autosomal recessive condition causing elevation in both plasma cholesterol and triglycerides. Hepatic lipase hydrolyzes triglycerides and phospholipids in VLDL remnants and IDL, preventing their conversion to LDL. HDL-C levels tend to be increased rather than decreased, suggesting the diagnosis. Laboratory confirmation is established by measuring hepatic lipase activity in heparinized plasma.

Disorders of High-Density Lipoprotein Metabolism

Primary Hypoalphalipoproteinemia

Isolated low HDL cholesterol is a familial condition that often follows a pattern suggestive of autosomal dominant inheritance but may occur independent of family history. It is the most common disorder of HDL metabolism. It is defined as HDL-C <10th percentile for gender and age with normal plasma triglycerides and LDL-C. Whether it is associated with more rapid atherosclerosis is uncertain. Primary hypoalphalipoproteinemia appears to be related to a reduction in apoA-I synthesis and increased catabolism of HDL. Secondary causes of low HDL-C, such as the metabolic syndrome, and rare diseases such as LCAT deficiency and Tangier disease must be ruled out.

Familial Hyperalphalipoproteinemia

This is an unusual condition conferring decreased risk for CHD among family members. Plasma levels of HDL-C exceed 80 mg/dL.

Familial Apolipoprotein A-I Deficiency

Mutations in the *apoA-I* gene may result in complete absence of plasma HDL. Nascent HDL is produced in the liver and small intestine. Free cholesterol from peripheral cells is esterified by LCAT, enabling formation of mature HDL particles. ApoA-I is required for normal enzymatic functioning of LCAT. The resultant accumulation of free cholesterol in the circulation eventually leads to corneal opacities, planar xanthomas, and premature atherosclerosis. Some patients, however, may have mutations of *apoA-I* that result in very rapid catabolism of the protein not associated with atherogenesis, despite HDL-C levels in the 15-30 mg/dL range.

Tangier Disease

This autosomal co-dominant disease is associated with HDL-C levels <5 mg/dL. It is caused by mutations in ABCA1, a protein that facilitates the binding of cellular cholesterol to apoA-I. This results in free cholesterol accumulation in the reticuloendothelial system, manifested by tonsillar hypertrophy of a distinctive orange color and hepatosplenomegaly. Intermittent peripheral neuropathy may occur from cholesterol accumulation in Schwann cells. Diagnosis should be suspected in children with enlarged orange tonsils and extremely low HDL-C levels.

Familial Lecithin–Cholesterol Acyltransferase (LCAT) Deficiency

Mutations affecting LCAT interfere with the esterification of cholesterol, thereby preventing formation of mature HDL particles. This is associated with rapid catabolism of apoA-I. Free circulating cholesterol in the plasma is greatly increased, which leads to corneal opacities and HDL-C levels <10 mg/dL. Partial LCAT deficiency is known as “fish-eye” disease. Complete deficiency causes hemolytic anemia and progressive renal insufficiency early in adulthood. This rare disease is not thought to cause premature atherosclerosis. Laboratory confirmation is based on demonstration of decreased cholesterol esterification in the plasma.

Cholesteryl Ester Transfer Protein Deficiency

Mutations involving the *CETP* gene are localized to chromosome 16y21. Cholesteryl ester transfer protein (CETP) facilitates the transfer of lipoproteins from mature HDL to and from VLDL and chylomicron particles, thus ultimately regulating the rate of cholesterol transport to the liver for excretion in the bile. About half of mature HDL-2 particles are directly removed from the circulation by HDL receptors on the surface of the liver. The other half of cholesteryl esters in the core of HDL exchange with triglycerides in the core of apoB lipoproteins (VLDL, IDL, LDL) for transport to the liver. Homozygous deficiency of CETP has been observed in subsets of the Japanese population with extremely high HDL-C levels (>150 mg/dL).

Conditions Associated With Low Cholesterol

Disorders of apoB-containing lipoproteins and intracellular cholesterol metabolism are associated with low plasma cholesterol.

Abetalipoproteinemia

This rare autosomal recessive disease is caused by mutations in the gene encoding microsomal triglyceride transfer protein necessary for the transfer of lipids to nascent chylomicrons in the small intestine and VLDL in the liver. This results in absence of chylomicrons, VLDL, LDL, and apoB and very low levels of plasma cholesterol and triglycerides. Fat malabsorption, diarrhea, and failure to thrive present in early childhood. Spinocerebellar degeneration, secondary to vitamin E deficiency, manifests in loss of deep tendon reflexes progressing to ataxia and lower-extremity spasticity by adulthood. Patients with abetalipoproteinemia also acquire a progressive pigmented retinopathy associated with decreased night and color vision and eventual blindness. The neurologic symptoms and retinopathy may be mistaken for **Friedreich ataxia** . Differentiation from Friedreich ataxia is suggested by the presence of malabsorption and acanthocytosis on peripheral blood smear in abetalipoproteinemia. Many of the clinical manifestations of the disease are a result of malabsorption of fat-soluble vitamins, such as vitamins E, A, and K. *Early treatment with supplemental vitamins, especially E, may significantly slow the development of neurologic sequelae.* Vitamin E is normally transported from the small intestine to the liver by chylomicrons, where it is dependent on the endogenous VLDL pathway for delivery into the circulation and peripheral tissues. Parents of children with abetalipoproteinemia have normal blood lipid and apoB levels.

Familial Hypobetalipoproteinemia

Familial homozygous hypobetalipoproteinemia is associated with symptoms very similar to those of abetalipoproteinemia, but the inheritance pattern is autosomal co-dominant. The disease is caused by mutations in the gene encoding apoB-100 synthesis. It is distinguishable from abetalipoproteinemia in that heterozygous parents of probands have plasma LDL-C and apoB levels less than half normal. There are no symptoms or sequelae associated with the heterozygous condition.

The selective inability to secrete apoB-48 from the small intestine results in a condition resembling abetalipoproteinemia or homozygous hypobetalipoproteinemia. Sometimes referred to as **Anderson disease** , the failure of chylomicron absorption causes steatorrhea and fat-soluble vitamin deficiency. The blood level of apoB-100, derived from normal hepatocyte secretion, is normal in this condition.

Smith-Lemli-Opitz Syndrome

Patients with Smith-Lemli-Opitz syndrome (**SLOS**) often have multiple congenital anomalies and developmental delay caused by low plasma cholesterol and accumulated precursors (Tables 104.11 and 104.12) (see Chapter 606.2). Family pedigree analysis has revealed its autosomal recessive inheritance pattern. Mutations in the *DHCR7* (7-dehydrocholesterol-Δ7 reductase) gene result in deficiency of the microsomal enzyme DHCR7, which is necessary to complete the final step in cholesterol synthesis. It is not known why defects in cholesterol synthesis result in congenital malformations, but since cholesterol is a major component of myelin and a contributor to signal transduction in the developing nervous system, neurodevelopment is severely impaired. The incidence of SLOS is estimated to be 1 in 20,000-60,000 births among whites, with a somewhat higher frequency in Hispanics and lower incidence in individuals of African descent.

Table 104.11

Major Clinical Characteristics of Smith-Lemli-Opitz Syndrome: Frequent Anomalies (>50% of Patients)

Craniofacial

Microcephaly
Blepharoptosis
Anteverted nares
Retromicrognathia
Low-set, posteriorly rotated ears
Midline cleft palate
Broad maxillary alveolar ridges
Cataracts (<50%)

Skeletal Anomalies

Syndactyly of toes II/III
Postaxial polydactyly (<50%)
Equinovarus deformity (<50%)

Genital Anomalies

Hypospadias
Cryptorchidism
Sexual ambiguity (<50%)

Development

Prenatal and postnatal growth retardation
Feeding problems
Mental impairment
Behavioral abnormalities

From Haas D, Kelley RI, Hoffmann GF: Inherited disorders of cholesterol biosynthesis, *Neuropediatrics* 32:113–122, 2001.

Table 104.12

Characteristic Malformations of Internal Organs in Severely Affected Smith-Lemli-Opitz Patients

Central Nervous System

Frontal lobe hypoplasia
Enlarged ventricles
Agenesis of corpus callosum
Cerebellar hypoplasia
Holoprosencephaly

Cardiovascular

Atrioventricular canal
Secundum atrial septal defect
Patent ductus arteriosus
Membranous ventricular septal defect

Urinary Tract

Renal hypoplasia or aplasia
Renal cortical cysts
Hydronephrosis
Ureteral duplication

Gastrointestinal

Hirschsprung disease
Pyloric stenosis
Refractory dysmotility
Cholestatic and noncholestatic progressive liver disease

Pulmonary

Pulmonary hypoplasia
Abnormal lobation

Endocrine	
	Adrenal insufficiency

From Haas D, Kelley RI, Hoffmann GF: Inherited disorders of cholesterol biosynthesis, *Neuropediatrics* 32:113–122, 2001.

Spontaneous abortion of SLOS fetuses may occur. **Type II** SLOS often leads to death by the end of the neonatal period. Survival is unlikely when the plasma cholesterol level is <20 mg/dL. Laboratory measurement should be performed by gas chromatography, because standard techniques for lipoprotein assay include measurement of cholesterol precursors, which may yield a false-positive result. Milder cases may not present until late childhood. Phenotypic variance ranges from microcephaly, cardiac and brain malformation, and multiorgan system failure to only subtle dysmorphic features and mild developmental delay. **Treatment** includes supplemental dietary cholesterol (egg yolk) and HMG-CoA reductase inhibition to prevent the synthesis of toxic precursors proximal to the enzymatic block.

Disorders of Intracellular Cholesterol Metabolism

Cerebrotendinous Xanthomatosis

This autosomal recessive disorder presents clinically in late adolescence with tendon xanthomas, cataracts, and progressive neurodegeneration. It is caused by tissue accumulation of bile acid intermediates shunted into cholestanol, resulting from mutations in the gene for sterol 27-hydroxylase. This enzyme is necessary for normal mitochondrial synthesis of bile acids in the liver. Early treatment with chenodeoxycholic acid reduces cholesterol levels and prevents the development of symptoms.

Wolman Disease and Cholesterol Ester Storage Disease

These autosomal recessive disorders are caused by lack of lysosomal acid lipase. After LDL cholesterol is incorporated into the cell by endocytosis, it is delivered to lysosomes, where it is hydrolyzed by lysosomal lipase. Failure of hydrolysis because of complete absence of the enzyme causes accumulation of cholesteryl esters within the cells. Hepatosplenomegaly, steatorrhea, and failure to thrive occur during early infancy, leading to death by age 1 yr. In cholesterol ester storage disease, a less severe form than Wolman disease, there is low but detectable acid lipase activity (see Chapter 104.4).

Niemann-Pick Disease Type C

This disorder of intracellular cholesterol transport is characterized by accumulation of cholesterol and sphingomyelin in the CNS and reticuloendothelial system. Death from this autosomal recessive neurologic disease usually occurs by adolescence (see Chapter 104.4).

Lipoprotein Patterns in Children and Adolescents

Derived primarily from the Lipid Research Clinics Population Studies, Table 104.9 shows the distribution of lipoprotein levels in American youth at various ages. Total plasma cholesterol rises rapidly from a mean of 68 mg/dL at birth to a level approximately twice that by the end of the neonatal period. A very gradual rise in total cholesterol level occurs until puberty, when the mean level reaches 160 mg/dL. Total cholesterol falls transiently during puberty, in males because of a small decrease in HDL-C, and in females secondary to a slight fall in LDL-C. Blood cholesterol levels track reasonably well as individuals age.

High blood cholesterol tends to aggregate in families, a reflection of genetic and environmental influences.

Acceptable total cholesterol among children and adolescents is <170 mg/dL; borderline is 170-199 mg/dL; and high >200 mg/dL. Acceptable LDL-C is <110 mg/dL; borderline 110-129 mg/dL; and high >130 mg/dL. HDL-C should be >40 mg/dL.

Blood Cholesterol Screening

The AAP began recommending a universal approach for cholesterol screening to all children in 2011. *A lipid profile should be checked for all children between ages 9 and 11 yr and then another between ages 17 and 21 yr*, because cholesterol levels may vary after puberty. However, if a child would have met the selective criteria from the previous risk-based guidelines (premature coronary artery disease in parent or grandparent, parent with cholesterol >240 mg/dL), screening can occur as early as age 2 yr. Data also suggest that obtaining a *nonfasting* lipid profile can be just as useful in detecting severe genetic dyslipidemias as a fasting lipid profile, and thus can be used as first-line screening in children. Fasting lipid profiles may also be used depending on parental, child, and clinician preference, especially if there is concern for hypertriglyceridemia, since triglycerides are affected more by fasting status. Abnormal lipid panels should be repeated, and especially when the concern is the triglycerides, the 2nd panel should be obtained ≥2 wk later in the fasted state. Treatment other than lifestyle modification is not initiated based on a single lipid panel determination.

Risk Assessment and Treatment of Hyperlipidemia

The NCEP recommends a population-based approach toward healthy lifestyle applicable to all children, and an individualized approach directed at those children at high risk (Fig. 104.14). The important focus on maintenance of a healthy lifestyle rather than aggressive weight reduction is recommended by the AAP.

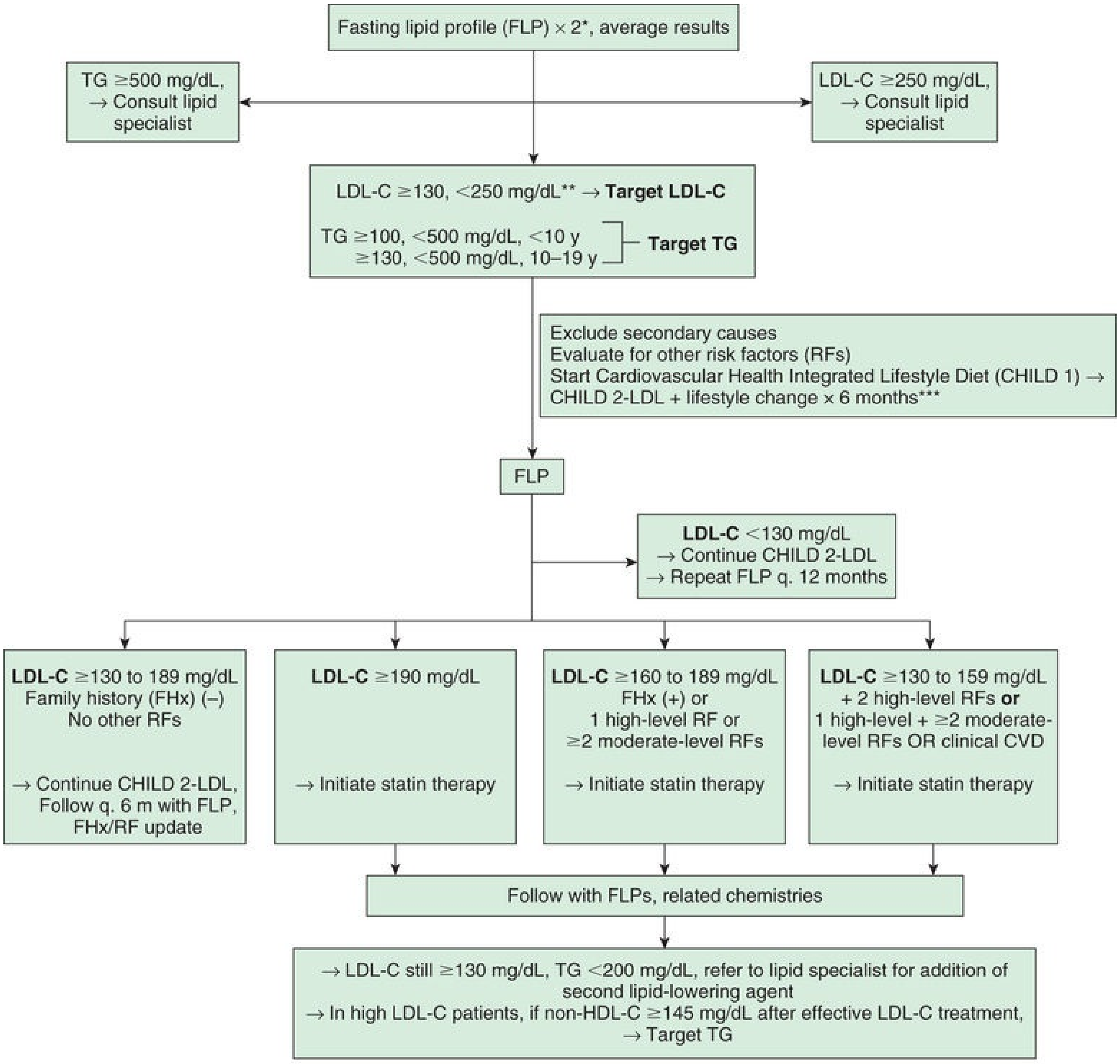
Fasting lipid profile (FLP) × 2*, average results
TG ≥500 mg/dL, → Consult lipid specialist
LDL-C ≥250 mg/dL, → Consult lipid specialist
LDL-C ≥130, <250 mg/dL** → Target LDL-C
TG ≥100, <500 mg/dL, <10 y
≥130, <500 mg/dL, 10–19 y
Target TG
Exclude secondary causes
Evaluate for other risk factors (RFs)
Start Cardiovascular Health Integrated Lifestyle Diet (CHILD 1) → CHILD 2-LDL + lifestyle change × 6 months***
FLP
LDL-C <130 mg/dL → Continue CHILD 2-LDL → Repeat FLP q. 12 months
LDL-C ≥130 to 189 mg/dL Family history (FHx) (–) No other RFs → Continue CHILD 2-LDL, Follow q. 6 m with FLP, FHx/RF update
LDL-C ≥190 mg/dL → Initiate statin therapy
LDL-C ≥160 to 189 mg/dL FHx (+) or 1 high-level RF or ≥2 moderate-level RFs → Initiate statin therapy
LDL-C ≥130 to 159 mg/dL + 2 high-level RFs or 1 high-level + ≥2 moderate-level RFs OR clinical CVD → Initiate statin therapy
Follow with FLPs, related chemistries
→ LDL-C still ≥130 mg/dL, TG <200 mg/dL, refer to lipid specialist for addition of second lipid-lowering agent
→ In high LDL-C patients, if non-HDL-C ≥145 mg/dL after effective LDL-C treatment, → Target TG

* Obtain FLPs at least 2 weeks but no more than 3 months apart.

** Use of drug therapy is limited to children ≥10 y with defined risk profiles.

*** In a child with LDL-C >190 mg/dL and other RFs, trial of CHILD 2-LDL may be abbreviated.

FIG. 104.14 Dyslipidemia treatment algorithm: Target LDL-C (low-density lipoprotein cholesterol). Note: Values given are in mg/dL. To convert to SI units, divide results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non-HDL-C by 38.6; for triglycerides (TG), divide by 88.6. (From US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. NIH Publication No. 12-7486A, Oct 2012, Fig 9-1.)

All children with dyslipidemias are stratified according to the presence of high-level or moderate-level risk factors to determine their ultimate treatment. **High-level risk factors** are defined as hypertension requiring drug therapy (blood pressure ≥99th percentile + 5 mm Hg), current cigarette smoker, BMI at the ≥97th percentile, presence of type 1 or type 2 diabetes mellitus, chronic kidney disease, postorthoptic heart transplant, and/or Kawasaki disease with current aneurysms. **Moderate-level risk factors** are defined as hypertension that does not require drug therapy, BMI at the ≥95th percentile but <97th percentile, HDL-C <40 mg/dL, Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease, HIV infection, and/or presence of nephrotic syndrome.

The initial treatment for dyslipidemia in a child always begins with a 6-mo trial of lifestyle modification, namely, improvements in dietary and physical activity patterns. Being overweight confers special risk of CVD because of the strong association with the insulin resistance syndrome (metabolic syndrome). Although there is no standardized definition of metabolic syndrome defined for youth, it is likely that half of all severely obese children are insulin resistant. Data from the CARDIAC project noted that 49% of 5th grade children with the hyperpigmented rash, acanthosis nigricans, had 3 or more factors for the insulin resistance syndrome when using the definition classically used for adults, including evidence of insulin resistance, hypertension, HDL-C <40 mg/dL, and triglycerides >150 mg/dL, in addition to obesity.

The Cardiovascular Health Integrated Lifestyle Diet-1 (**CHILD-1**) diet is the first level of dietary change to be recommended for all children with dyslipidemias. The CHILD-1 diet is specially designed for children with risk factors for coronary artery disease and focuses on limiting dietary cholesterol to 300 mg/day, limiting sugary drink consumption, using reduced-fat/skim milk, avoiding foods high in *trans* -type fats, limiting foods high in sodium, and encouraging consumption of foods high in fiber. Specific recommendations depend on the child's age.

The use of the Cardiovascular Health Integrated Lifestyle Diet-2 (**CHILD-2**) diet is recommended if the CHILD-1 diet alone is unsuccessful. Although similar in many aspects to the CHILD-1 diet, the CHILD-2 diet is geared toward a specific dyslipidemia type; the **CHILD-2 LDL** diet is recommended for children with elevated LDL levels and the **CHILD-2 TG** diet for those presenting with elevated triglycerides. The basic recommendations of calorie consumption for the CHILD-2 diet are as follows: only 25–30% of calories from fat, ≤7% of calories from saturated fat, 10% of calories from monounsaturated fat, and <200 mg/day of cholesterol. If the CHILD-2 LDL diet is recommended, the use of plant sterols and water-soluble fiber is emphasized. If the CHILD-2 TG diet is recommended, the increasing consumption of omega-3 fatty acids and complex rather than simple carbohydrates is emphasized.

If followed, these dietary recommendations will provide adequate calories for optimal growth and development without promoting obesity. Compliance on the part of children and their caregivers is challenging. Children learn eating habits from their parents. Successful adoption of a healthier lifestyle is much more likely to occur if meals and snacks in the home are applicable to the entire family rather than an individual child. A regular time for meals together as a family is desirable. Grandparents and other nonparental caregivers sometimes need to be reminded not to indulge the child who is on a restricted diet. Additionally, the rise in obesity is prompting some school districts to restrict sweetened drink availability and offer more nutritious cafeteria selections.

Changes in physical activity habits are also an important part of the initial lifestyle modification. The National Association for Sport and Physical Education recommends that children should accumulate at least 60 min of age-appropriate physical activity on most days of the week. Extended periods (≥2 hr) of daytime inactivity are discouraged, as is >2 hr of television and other forms of screen time.

Pharmacologic Therapy.

See Tables 104.13 and 104.14 .

Table 104.13

Drugs Used for the Treatment of Hyperlipidemia

DRUG	MECHANISM OF ACTION	INDICATION	STARTING DOSE
HMG-CoA reductase inhibitors (statins)	↓ Cholesterol and VLDL synthesis	Elevated LDL	5-80 mg every night at bedtime
	↑ Hepatic LDL receptors		
Bile acid sequestrants:	↑ Bile and excretion	Elevated LDL	
Cholestyramine			4-32 g daily
Colestipol			5-40 g daily
Nicotinic acid	↓ Hepatic VLDL synthesis	Elevated LDL	100-2,000 mg 3 times daily
		Elevated TG	
Fibric acid derivatives:	↑ LPL	Elevated TG	600 mg twice daily
Gemfibrozil	↓ VLDL		
Fish oils	↓ VLDL production	Elevated TG	3-10 g daily
Cholesterol absorption inhibitors:			
Ezetimibe	↓ Intestinal absorption cholesterol	Elevated LDL	10 mg daily

LDL, Low-density lipoprotein(s); LPL, lipoprotein lipase; TG, triglycerides; VLDL, very-low-density lipoprotein.

Table 104.14

Adverse Effects of Cholesterol-Lowering Drugs

Statins

Myalgia, myositis, transaminase elevations, hepatic dysfunction, increased risk of diabetes mellitus
Rare: Rhabdomyolysis, hemorrhagic stroke

Ezetimibe

Diarrhea, arthralgia, rhabdomyolysis, hepatitis, pancreatitis, thrombocytopenia

Pcsk9 Inhibitors

Nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection site reactions, rash, allergic skin reactions, cognitive effects, antidrug antibodies

Bile Acid Sequestrants

Constipation, heartburn, nausea, eructation, bloating
Adverse effects are more common with colestipol and cholestyramine and may diminish over time.

Fibric Acid Derivatives

Gastrointestinal (GI) disturbances, cholelithiasis, hepatitis, myositis

Niacin

Skin flushing, pruritus, GI disturbances, blurred vision, fatigue, glucose intolerance, hyperuricemia, hepatic toxicity, exacerbation of peptic ulcers
Adverse effects, especially flushing, occur more frequently with immediate-release products.
Rare: Dry eyes, hyperpigmentation

Fish Oil

Eructation, dyspepsia, unpleasant aftertaste

From *The Medical Letter:* Lipid-lowering drugs, *Med Lett* 58:133-140, 2016 (Table 2, p 136).

Pharmacologic therapy with cholesterol-lowering medication is the cornerstone of therapy for children who fail to respond to 6 mo of rigorous lifestyle modification. Drug therapy should be considered when 1 of the following conditions are met (also shown in Fig. 104.14):

- LDL cholesterol remains >190 mg/dL
- LDL cholesterol remains >160 mg/dL with presence of 1 high-level risk factor *and/or* at least 2 moderate-level risk factors
- LDL cholesterol remains >130 mg/dL with presence of at least 2 high-level risk factors, 1 high-level risk factor, *and* at least 2 moderate-level risk factors, *or* evidence of coronary artery disease (CAD)

HMG-CoA reductase inhibitors, also known as “statins” are remarkably effective in lowering LDL cholesterol levels and reducing plaque inflammation, thereby reducing the likelihood of a sudden coronary event in an at-risk adult within weeks of starting the medication. As a class, they work by blocking the intrahepatic biosynthesis of cholesterol, thereby stimulating the production of more LDL receptors on the cell surface and facilitating the uptake of LDL-C from the bloodstream. The NCEP Adult Treatment Panel advocates aggressive lowering of LDL to <70 mg/dL in individuals with known CAD. This information is relevant because a child who fulfills criteria for consideration of cholesterol-lowering medication will almost always have inherited the condition from one of the child's parents. Not infrequently, when providing care for the child, questions arise about screening and treatment of parents or grandparents. Statins are equally effective in children, capable of lowering LDL-C levels by 50% when necessary. They are considered first-line therapy for children who meet criteria for pharmacologic therapy. They also will affect a modest reduction in triglycerides and an inconsistent increase in HDL-C. Their side effect profile, mainly liver dysfunction and rarely rhabdomyolysis with secondary renal failure, should be taken into consideration before prescribing the drug. However, there has been no evidence that complications are any more frequent in children than adults, and skeletal muscle discomfort seems to be somewhat less of a problem. Drug interactions may occur as well, so careful attention should be paid to a child's active prescriptions to avoid potentiation of the side effects. Children should have liver enzymes monitored regularly, and creatine phosphokinase measured if muscle aches or weakness occurs. Liver (muscle) enzymes may be allowed to rise 3-fold before discontinuing the drug. There is a suggested link between the use of statins and increased risk of developing type 2 diabetes mellitus in adults, but these results have not been replicated in children. Sex hormones have been measured in children receiving statins and are unchanged. It should be reemphasized that children with modest elevations in cholesterol, such as that seen in polygenic hypercholesterolemia, are not, as a rule, candidates for statins because of their side effect profile and the childhood response to lifestyle modifications. Statins should be started at the lowest effective dose and allowed at least 8 wk to achieve their peak effect. If LDL levels are not at goal, which in children who are treated is generally established to be <130 mg, the medication may be titrated upward with careful monitoring of side effects.

Other cholesterol-lowering medications, such as nicotinic acid and fibrates, have been used far less often in children than bile acid sequestrants and statins. Nicotinic acid and fibrates have been used selectively in children with marked hypertriglyceridemia (>500 mg/dL) at risk for acute pancreatitis, though dietary restriction of complex sugars (stressing elimination of sugar-sweetened beverages) and carbohydrates will usually result in significant lowering of triglyceride levels. Current guidelines recommend treatment of LDL-C as the initial priority and after LDL levels are at goal, then if triglycerides remain between 200 and 499 mg/dL and non-HDL cholesterol ≥145 mg/dL, pharmacologic treatment to reduce triglyceride levels is indicated. Omega-3 fatty acid supplementation, available in both over-the-counter and prescription form, is a safe and useful treatment thought to reduce triglyceride levels by decreasing the hepatic synthesis of triglycerides. LDL-C levels in adults of about 70 mg/dL were recently associated with coronary artery atheromatous plaque reduction and reversal of CAD. Knowledge in this area will continue to evolve.

Ezetimibe has proved to be useful in the pediatric population because of its efficacy and low side effect profile. Ezetimibe reduces plasma LDL-C by blocking sterol absorption in enterocytes. The drug is marketed as an adjunct to statins when adults are not achieving sufficient blood lipid lowering with statins alone. Sufficient reports documenting its effectiveness without side effects support recommending ezetimibe instead of a statin when moderate hypercholesterolemia is encountered, or apprehension from parents makes using a statin difficult.

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104.4

Lipidoses (Lysosomal Storage Disorders)

Margaret M. McGovern, Robert J. Desnick

Keywords

Lipidoses
Sphingolipids
GM1 gangliosidosis
GM2 gangliosidosis
Gaucher disease
Fabry disease
Niemann Pick disease
Schindler disease
Metachromatic leukodystrophy
Farber disease
Wolman disease

Multiple sulfatase deficiency
Krabbe disease

The lysosomal lipid storage diseases are diverse disorders, each caused by an inherited deficiency of a specific lysosomal hydrolase leading to the intralysosomal accumulation of the enzyme's particular substrate (Tables 104.15 and 104.16). Except for Wolman disease and cholesterol ester storage disease, the lipid substrates share a common structure that includes a ceramide backbone (2-*N* -acylsphingosine) from which the various sphingolipids are derived by substitution of hexoses, phosphorylcholine, or 1 or more sialic acid residues on the terminal hydroxyl group of the ceramide molecule. The pathway of sphingolipid metabolism in nervous tissue (Fig. 104.15) and in visceral organs (Fig. 104.16) is known; each catabolic step, with the exception of the catabolism of lactosylceramide, has a genetically determined metabolic defect and a resultant disease. Because **sphingolipids** are essential components of all cell membranes, the inability to degrade these substances and their subsequent accumulation results in the physiologic and morphologic alterations and characteristic clinical manifestations of the lipid storage disorders (Table 104.15). Progressive lysosomal accumulation of glycosphingolipids in the CNS leads to neurodegeneration, whereas storage in visceral cells can lead to organomegaly, skeletal abnormalities, pulmonary infiltration, and other manifestations. The storage of a substrate in a specific tissue depends on its normal distribution in the body.

Table 104.15

Clinical Findings in Lysosomal Storage Diseases

NOMENCLATURE	ENZYME DEFECT	HYDROPS FETALIS	COARSE FACIAL FEATURES DYSOSTOSIS MULTIPLEX	HEPATOSPLEN
MUCOLIPIDOSES				
Mucolipidoses II, I-cell disease	*N* -Acetylglucosaminylphosphotransferase	(+)	++	+
Mucolipidosis III, pseudo-Hurler	*N* -Acetylglucosaminylphosphotransferase	−	+	(+)
Mucolipidosis IV	Unknown	−	−	+
SPHINGOLIPIDOSES				
Fabry disease	α-Galactosidase	−	−	−
Farber disease	Acid ceramidase	−	−	(+)

Galactosialidosis	β-Galactosidase and sialidase	(+)	++	++
GM$_1$ gangliosidosis	β-Galactosidase	(+)	++	+
GM$_2$ gangliosidosis (Tay-Sachs, Sandhoff disease)	β-Hexosaminidases A and B	−	−	(+)
Gaucher type I	Glucocerebrosidase	−	−	++
Gaucher type II	Glucocerebrosidase	(+)	−	++
Gaucher type III	Glucocerebrosidase	(+)	−	+
Niemann-Pick type A	Acid Sphingomyelinase	(+)	−	++
Niemann-Pick type B	Acid Sphingomyelinase	−	−	++
Metachromatic leukodystrophy	Arylsulfatase A	−	−	−
Krabbe disease	β-Galactocerebrosidase	−	−	−
LIPID STORAGE DISORDERS				
Niemann-Pick type C	Intracellular cholesterol transport	−	−	(+)
Wolman disease	Lysosomal acid lipase	(+)	−	+
Ceroid lipofuscinosis, infantile (Santavuori-Haltia)	Palmitoyl-protein thioesterase (CLN1)	−	−	−
Ceroid lipofuscinosis, late infantile (Jansky-Bielschowsky)	Pepstatin-insensitive peptidase (CLN2); variants in Finland (CLN5), Turkey (CLN7), and Italy (CLN6)	−	−	−
Ceroid lipofuscinosis, juvenile (Spielmeyer-Vogt)	CLN3, membrane protein	−	−	−
Ceroid lipofuscinosis, adult (Kufs, Parry)	CLN4, probably heterogeneous	(+)	−	−
OLIGOSACCHARIDOSES				
Aspartylglucosaminuria	Aspartylglucosylaminase	−	+	(+)
Fucosidosis	α-Fucosidase	−	++	(+)
α-Mannosidosis	α-Mannosidase	−	++	+
β-Mannosidosis	β-Mannosidase	−	+	(+)
Schindler disease	α-*N* -Acetylgalactosaminidase	−	−	−
Sialidosis I	Sialidase	(+)	−	−
Sialidosis II	Sialidase	(+)	++	+

++, Prominent; +, often present; (+), inconstant or occurring later in the disease course; –, not present.

Modified from Hoffmann GF, Nyhan WL, Zschoke J, et al: *Storage disorders in inherited metabolic diseases* , Philadelphia, 2002, Lippincott Williams & Wilkins, pp 346–351.

Table 104.16

Lysosomal Storage Disorders in the Newborn Period: Genetic and Clinical Characteristics of Neonatal Presentation

DISORDER	ONSET	FACIES	NEUROLOGIC FINDINGS	DISTINCTIVE FEATURES	EYE FINDINGS	DEFECT

Niemann–Pick A disease	Early infancy	Frontal bossing	Difficulty feeding, apathy, deafness, blindness, hypotonia	Brownish-yellow skin, xanthomas	Cherry-red spot (50%)	Sphingomye deficiency
Niemann–Pick C disease	Birth–3 months	Normal	Developmental delay, vertical gaze paralysis, hypotonia, later spasticity	–	–	Abnormal cholesterol esterification
Gaucher disease type 2	In utero–6 months	Normal	Poor suck and swallow, weak cry, squint, trismus, strabismus, opsoclonus, hypertonic, later flaccidity	Congenital ichthyosis, collodion skin	–	Glucocerebr deficiency
Krabbe disease	3–6 months	Normal	Irritability, tonic spasms with light or noise stimulation, seizures, hypertonia, later flaccidity	Increased CSF protein level	Optic atrophy	Galactocereb deficiency
GM1 gangliosidosis	Birth	Coarse	Poor suck, weak cry, lethargy, exaggerated startle, blindness, hypotonia, later spasticity	Gingival hypertrophy, edema, rashes	Cherry-red spot (50%)	β-Galactosid deficiency
Farber disease type I	2 weeks–4 months	Normal	Progressive psychomotor impairment, seizures, decreased reflexes, hypotonia	Joint swelling with nodules, hoarseness, lung disease, contractures, fever, granulomas, dysphagia, vomiting, increased CSF protein level	Grayish opacification surrounding retina in some patients, subtle cherry-red spot	Lysosomal a ceramidase
Farber disease types II and III	Birth–9 months (≤20 months)	Normal	—	Joint swelling with nodules, hoarseness	Normal macula, corneal opacities	—
Farber disease type IV (neonatal)	Birth	Normal	Nodules not consistent findings	Corneal opacities (1/3)	—	—
Congenital sialidosis	In utero–birth	Cognitive, edema	Intellectual impairment, hypotonia	Neonatal ascites, inguinal hernias, renal disease	Corneal clouding	Neuraminida deficiency

Galactosialidosis	In utero–birth	Coarse	Intellectual impairment, occasional deafness, hypotonia	Ascites, edema, inguinal hernias, renal disease, telangiectasias	Cherry-red spot, corneal clouding	Absence of a protective pr that safeguar neuraminidas β-galactosida premature degradation
Wolman disease	First weeks of life	Normal	Cognitive deterioration	Vomiting, diarrhea, steatorrhea, abdominal distention, failure to thrive, anemia, adrenal calcifications	—	Lysosomal a lipase deficie
Infantile sialic acid storage disease	In utero–birth	Coarse, dysmorphic	Intellectual impairment, hypotonia	Ascites, anemia, diarrhea, failure to thrive	—	Defective tra of sialic acid the lysosome
I-cell disease	In utero–birth	Coarse	Intellectual impairment, deafness	Gingival hyperplasia, restricted joint mobility, hernias	Corneal clouding	Lysosomal e lack mannos phosphate recognition r and fail to er lysosome (phosphotrar deficiency, 3 complex [α2
Mucolipidosis type IV	Birth–3 months	Normal	Intellectual impairment, hypotonia	—	Severe corneal clouding, retinal degeneration, blindness	Unknown; sc patients with deficiency of ganglioside s
Mucopolysaccharidosis type VII	In utero–childhood	Variable coarseness	Mild to severe intellectual impairment	Hernias	Variable corneal clouding	β-Glucuronic deficiency

Modified from Thomas JA, Lam C, Berry GT: Lysosomal storage, peroxisomal, and glycosylation disorders and Smith-Lemli-Opitz syndrome presenting in the neonate. In Gleason CA, Juul SE, editors: Avery's diseases of the newborn, ed 10, Philadelphia, 2018, Elsevier, Table 23.1.

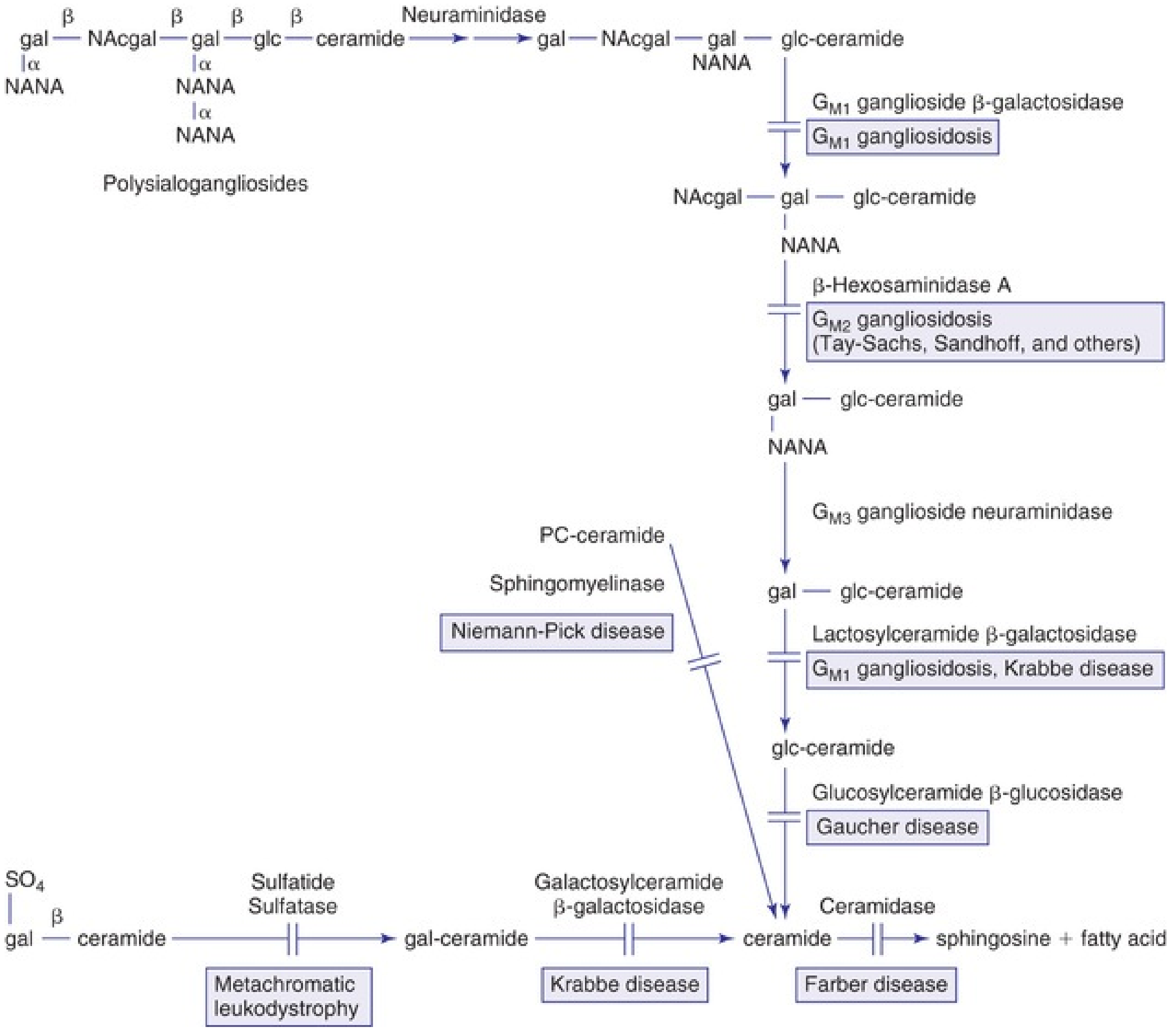

gal β NAcgal β gal β glc β ceramide
α NANA
α NANA
α NANA
Polysialogangliosides
Neuraminidase
gal — NAcgal — gal — glc-ceramide
NANA
G_{M1} ganglioside β-galactosidase
G_{M1} gangliosidosis
NAcgal — gal — glc-ceramide
NANA
β-Hexosaminidase A
G_{M2} gangliosidosis (Tay-Sachs, Sandhoff, and others)
gal — glc-ceramide
NANA
G_{M3} ganglioside neuraminidase
gal — glc-ceramide
Lactosylceramide β-galactosidase
G_{M1} gangliosidosis, Krabbe disease
glc-ceramide
Glucosylceramide β-glucosidase
Gaucher disease
PC-ceramide
Sphingomyelinase
Niemann-Pick disease
SO_4
gal β ceramide
Sulfatide Sulfatase
Metachromatic leukodystrophy
gal-ceramide
Galactosylceramide β-galactosidase
Krabbe disease
ceramide
Ceramidase
Farber disease
sphingosine + fatty acid

FIG. 104.15 **Pathways in the metabolism of sphingolipids found in nervous tissues. The name of the enzyme catalyzing each reaction is given with the name of the substrate that it hydrolyzes. Inborn errors are depicted as *bars* crossing the reaction arrows, and the name of the associated defect or defects is given in the nearest *box.* The gangliosides are named according to the nomenclature of Svennerholm. Anomeric configurations are given only at the largest starting compound. Gal, Galactose; glc, glucose; NAcgal, *N* -acetylgalactosamine; NANA, *N* -acetylneuraminic acid; PC, phosphorylcholine.**

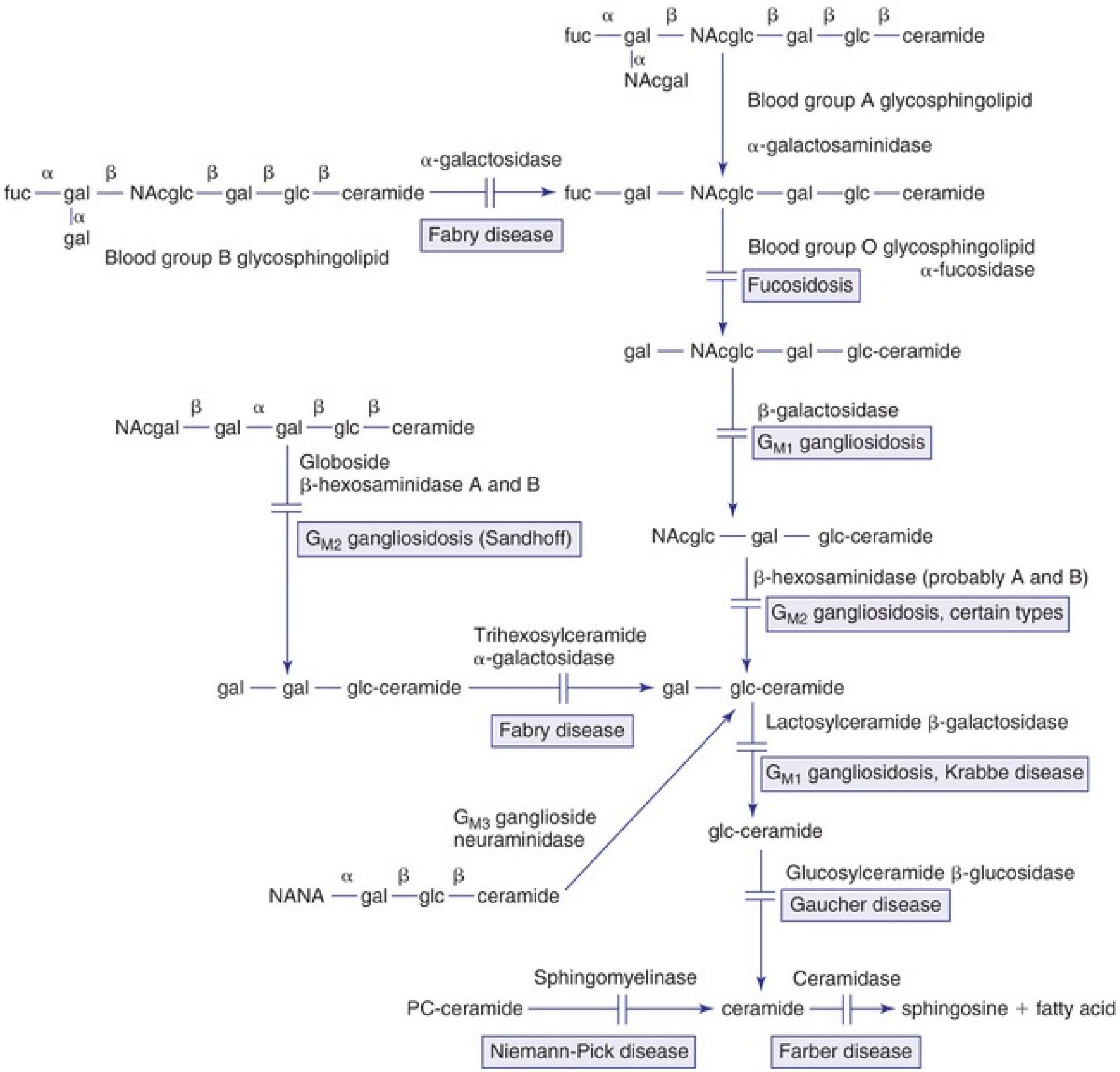
fuc —α— gal —β— NAcglc —β— gal —β— glc —β— ceramide
|α NAcgal
Blood group A glycosphingolipid
α-galactosaminidase
fuc —α— gal —β— NAcglc —β— gal —β— glc —β— ceramide
|α gal
Blood group B glycosphingolipid
α-galactosidase
Fabry disease
fuc — gal — NAcglc — gal — glc — ceramide
Blood group O glycosphingolipid
α-fucosidase
Fucosidosis
gal — NAcglc — gal — glc-ceramide
β-galactosidase
GM1 gangliosidosis
NAcgal —β— gal —α— gal —β— glc —β— ceramide
Globoside
β-hexosaminidase A and B
GM2 gangliosidosis (Sandhoff)
NAcglc — gal — glc-ceramide
β-hexosaminidase (probably A and B)
GM2 gangliosidosis, certain types
Trihexosylceramide
α-galactosidase
gal — gal — glc-ceramide
Fabry disease
gal — glc-ceramide
Lactosylceramide β-galactosidase
GM1 gangliosidosis, Krabbe disease
GM3 ganglioside
neuraminidase
NANA —α— gal —β— glc —β— ceramide
glc-ceramide
Glucosylceramide β-glucosidase
Gaucher disease
Sphingomyelinase
PC-ceramide
ceramide
Ceramidase
sphingosine + fatty acid
Niemann-Pick disease
Farber disease

FIG. 104.16 Pathways in the degradation of sphingolipids found in visceral organs and red or white blood cells. See also the legend for Fig. 104.15 . Fuc, Fucose; NAcglc, *N* -acetylglucosamine.

Diagnostic assays for the identification of affected individuals rely on the measurement of the specific enzymatic activity, typically in isolated leukocytes. Fig. 104.17 shows an approach to differentiating these disorders. For most, carrier identification and prenatal diagnosis are available; a specific diagnosis is essential to permit genetic counseling. Neonatal screening using dried blood spots and performing enzyme assays and mutational analysis for Gaucher, Pompe, Fabry, and Niemann-Pick diseases are undergoing pilot studies, and the FDA has approved the *Seeker System* for detection of Gaucher and Fabry diseases. The characterization of the genes that encode the specific enzymes required for sphingolipid metabolism permit the development of therapeutic options, such as recombinant enzyme replacement therapy, as well as the potential of cell or gene therapy. Identification of specific disease-causing mutations improves diagnosis, prenatal detection, and carrier identification. For several disorders (Gaucher, Fabry, Niemann-Pick types A and B), it has been possible to make genotype-phenotype correlations that predict disease severity and allow more precise genetic counseling. Inheritance is autosomal recessive except for X-linked Fabry disease.

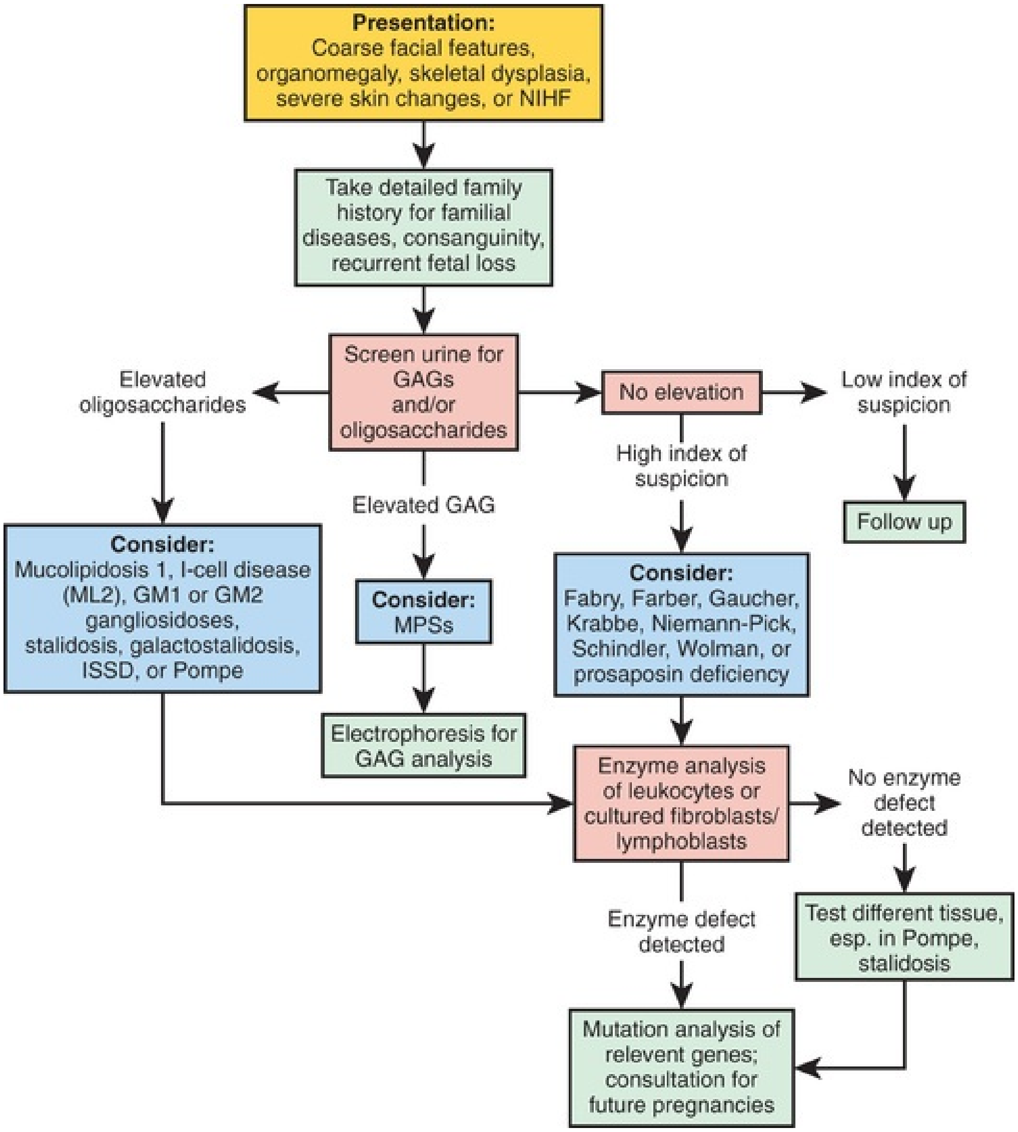
Presentation:
Coarse facial features, organomegaly, skeletal dysplasia, severe skin changes, or NIHF
Take detailed family history for familial diseases, consanguinity, recurrent fetal loss
Screen urine for GAGs and/or oligosaccharides
Elevated oligosaccharides
No elevation
Low index of suspicion
High index of suspicion
Follow up
Elevated GAG
Consider:
Mucolipidosis 1, I-cell disease (ML2), GM1 or GM2 gangliosidoses, stalidosis, galactostalidosis, ISSD, or Pompe
Consider:
MPSs
Consider:
Fabry, Farber, Gaucher, Krabbe, Niemann-Pick, Schindler, Wolman, or prosaposin deficiency
Electrophoresis for GAG analysis
Enzyme analysis of leukocytes or cultured fibroblasts/ lymphoblasts
No enzyme defect detected
Test different tissue, esp. in Pompe, stalidosis
Enzyme defect detected
Mutation analysis of relevent genes; consultation for future pregnancies

FIG. 104.17 Algorithm of the clinical evaluation recommended for an infant with a suspected lysosomal storage disease. GAGs, Glycosaminoglycans; ISSD, infantile sialic acid storage disease; NIHF, nonimmune hydrops fetalis. (From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal

storage disorders in the newborn, *Pediatrics* 123:1191–1207, 2009.)

GM_1 Gangliosidosis

GM_1 gangliosidosis most frequently presents in early infancy but has been described in patients with juvenile- and adult-onset subtypes. Inherited as an autosomal recessive trait, each subtype results from a different gene mutation that leads to the deficient activity of β-galactosidase, a lysosomal enzyme encoded by a gene on chromosome 3 (3p21.33). Although the disorder is characterized by the pathologic accumulation of GM_1 gangliosides in the lysosomes of both neural and visceral cells, GM_1 ganglioside accumulation is most marked in the brain. In addition, keratin sulfate, a mucopolysaccharide, accumulates in liver and is excreted in the urine of patients with GM_1 gangliosidosis. The β-galactosidase gene has been isolated and sequenced; mutations causing the disease subtypes have been identified.

The clinical manifestations of the **infantile** form of GM_1 gangliosidosis may be evident in the newborn as hepatosplenomegaly, edema, and skin eruptions (**angiokeratoma**). It most frequently presents in the 1st 6 mo of life with developmental delay followed by progressive psychomotor retardation and the onset of tonic-clonic seizures. Typical facies is characterized by low-set ears, frontal bossing, a depressed nasal bridge, and an abnormally long philtrum. Up to 50% of patients have a macular cherry-red spot. Hepatosplenomegaly and skeletal abnormalities are present, such as those of the mucopolysaccharidoses, including anterior beaking of the vertebrae, enlargement of the sella turcica, and thickening of the calvarium. By the end of the 1st yr of life, most patients are blind and deaf, with severe neurologic impairment characterized by decerebrate rigidity. Death usually occurs by 3-4 yr of age. The **juvenile-onset** form of GM_1 gangliosidosis is clinically distinct, with a variable age at onset. Affected patients present primarily with neurologic symptoms, including ataxia, dysarthria, intellectual disability, and spasticity. Deterioration is slow; patients may survive through the 4th decade of life. These patients lack the visceral involvement, facial abnormalities, and skeletal features seen in type 1 disease. Adult-onset patients have been described who present with gait and speech abnormalities, dystonia and mild skeletal abnormalities. *There is no specific treatment* for either form of GM_1 gangliosidosis.

The diagnosis of GM_1 gangliosidosis should be suspected in infants with typical clinical features and is confirmed by the demonstration of the deficiency of β-galactosidase activity in peripheral leukocytes. Other disorders that share some of the features of the GM_1 gangliosidoses include Hurler disease (mucopolysaccharidosis type I), I-cell disease, and Niemann-Pick disease type A, each of which can be distinguished by the demonstration of their specific enzymatic deficiencies. Carriers of the disorder are detected by the measurement of the enzymatic activity in peripheral leukocytes or by identifying the specific gene mutations; prenatal diagnosis is accomplished by determination of the enzymatic activity in cultured amniocytes or chorionic villi or identification of the specific disease-causing mutations. Only supportive therapy is available for patients with GM_1 gangliosidosis. However, studies in mice with GM_1 gangliosidosis have demonstrated that oral *N* -octyl-4-epi-β-valienamine (NOEV), which stabilizes the mutant enzyme protein produced by the affected animals, crossed the brain and improved neurologic deterioration, suggesting that this approach may be useful in human study.

The GM_2 Gangliosidoses

The GM_2 gangliosidoses include Tay-Sachs disease and Sandhoff disease; each results from deficiency of β-hexosaminidase activity and lysosomal accumulation of GM_2 gangliosides, particularly in the CNS. Both disorders have been classified into infantile-, juvenile-, and adult-onset forms based on the age at onset and clinical features. β-Hexosaminidase occurs as 2 isozymes: β-hexosaminidase A, which is composed of 1 α and 1 β subunit, and β-hexosaminidase B, which has 2 β subunits. B-Hexosaminidase A deficiency results from mutations in the α subunit and causes Tay-Sachs disease, whereas mutations in the β subunit result in the deficiency of both β-hexosaminidases A and B and cause Sandhoff disease. Both are autosomal recessive traits, with Tay-Sachs disease being more common in the Ashkenazi Jewish population, in whom the carrier frequency is approximately 1 in 25.

More than 50 mutations have been identified; most are associated with the infantile forms of disease. Three mutations account for >98% of mutant alleles among Ashkenazi Jewish carriers of Tay-Sachs disease, including one allele associated with the adult-onset form. Mutations that cause the subacute or adult-onset forms result in enzyme proteins with residual enzymatic activities, the levels of which correlate with the severity of the disease.

Patients with the infantile form of **Tay-Sachs disease** have clinical manifestations in infancy such as loss of motor skills, increased startle reaction, and macular pallor and retinal cherry-red spots (see Table 104.15). Affected infants usually develop normally until 4-5 mo of age, when decreased eye contact and an exaggerated startle response to noise (**hyperacusis**) are noted. **Macrocephaly** , not associated with hydrocephalus, may develop. In the 2nd yr of life, seizures develop, which may be refractory to anticonvulsant therapy. Neurodegeneration is relentless, with death occurring by age 4 or 5 yr. The juvenile- and later-onset forms initially present with ataxia and dysarthria and may not be associated with a macular cherry-red spot.

The clinical manifestations of **Sandhoff disease** are similar to those of Tay-Sachs disease. Infants with Sandhoff disease have hepatosplenomegaly, cardiac involvement, and mild bony abnormalities. The **juvenile** form of this disorder presents as ataxia, dysarthria, and mental deterioration, but without visceral enlargement or a macular cherry-red spot. *No treatment is available* for Tay-Sachs disease or Sandhoff disease, although experimental approaches are being evaluated.

The diagnosis of **infantile** Tay-Sachs disease and Sandhoff disease is usually suspected in an infant with neurologic features and a cherry-red spot. Definitive diagnosis is made by determination of β-hexosaminidase A and B activities in peripheral leukocytes. The 2 disorders are distinguished by the enzymatic assay, because in Tay-Sachs disease only the β-hexosaminidase A isozyme is deficient, whereas in Sandhoff disease both the β-hexosaminidase A and B isozymes are deficient. At-risk pregnancies for both disorders can be prenatally diagnosed by determining the enzyme levels in fetal cells obtained by amniocentesis or chorionic villus sampling. Identification of carriers in families is also possible by β-hexosaminidases A and B determination. Indeed, for Tay-Sachs disease, carrier screening of all couples in which at least 1 member is of Ashkenazi Jewish descent is recommended before the initiation of pregnancy to identify couples at risk. These studies can be conducted by the determination of the level of β-hexosaminidase A activity in peripheral leukocytes or plasma. Molecular studies to identify the exact molecular defect in enzymatically identified carriers should also be performed to permit more specific identification of carriers in the family and to allow prenatal diagnosis in at-risk couples by both enzymatic and genotype determinations. The incidence of Tay-Sachs disease has been greatly reduced since the introduction of carrier screening programs in the Ashkenazi

Jewish population. Newborn screening may be possible by measuring specific glycosphingolipid markers or the relevant enzymatic activities in dried blood spots.

Gaucher Disease

Gaucher disease is a multisystemic lipidosis characterized by hematologic abnormalities, organomegaly, and skeletal involvement, the latter usually manifesting as bone pain and pathologic fractures (see Table 104.15). It is one of the most common lysosomal storage diseases and the most prevalent genetic defect among Ashkenazi Jews. There are 3 clinical subtypes, delineated by the absence or presence and progression of neurologic manifestations: **type 1** , or the adult, nonneuronopathic form; **type 2** , the infantile or acute neuronopathic form; and **type 3** , the juvenile or subacute neuronopathic form. All are autosomal recessive traits. Type 1, which accounts for 99% of cases, has a striking predilection for Ashkenazi Jews, with an incidence of approximately 1 in 1,000 live births and a carrier frequency of approximately 1 in 18 adults.

Gaucher disease results from the deficient activity of the lysosomal hydrolase, acid β-glucosidase, which is encoded by a gene located on chromosome 1q21-q31. The enzymatic defect results in the accumulation of undegraded glycolipid substrates, particularly glucosylceramide, in cells of the reticuloendothelial system (RES). This progressive deposition results in infiltration of the bone marrow, progressive hepatosplenomegaly, and skeletal complications. Four mutations—N370S, L444P, 84insG, and IVS2+2—account for approximately 95% of mutant alleles among Ashkenazi Jewish patients, permitting screening for this disorder in this population. Genotype-phenotype correlations have been noted, providing the molecular basis for the clinical heterogeneity seen in Gaucher disease type 1. Patients who are homozygous for the N370S mutation tend to have a later onset of clinical manifestations, with a more indolent course than patients with 1 copy of N370S and another common allele.

Clinical manifestations of **type 1 Gaucher disease** have a variable age at onset, from early childhood to late adulthood, with most symptomatic patients presenting by adolescence. At presentation, patients may have bruising from thrombocytopenia, chronic fatigue secondary to anemia, hepatomegaly with or without elevated LFT results, splenomegaly, and bone pain. Occasional patients have pulmonary involvement at presentation. Patients presenting in the 1st decade frequently are not Jewish and have growth retardation and a more malignant course. Other patients may be discovered fortuitously during evaluation for other conditions or as part of routine examinations; these patients may have a milder or even a benign course. In symptomatic patients, splenomegaly is progressive and can become massive. Most patients develop radiologic evidence of skeletal involvement, including an Erlenmeyer flask deformity of the distal femur. Clinically apparent bony involvement, which occurs in most patients, can present as bone pain, a pseudoosteomyelitis pattern, or pathologic fractures. Lytic lesions can develop in the long bones, including the femur, ribs, and pelvis; osteosclerosis may be evident at an early age. Bone crises with severe pain and swelling can occur. Bleeding secondary to thrombocytopenia may manifest as epistaxis or bruising and is frequently overlooked until other symptoms become apparent. With the exception of the severely growth-retarded child, who may experience developmental delay secondary to the effects of chronic disease, development and intelligence are normal.

The pathologic hallmark of Gaucher disease is the Gaucher cell in the RES, particularly in the bone marrow (Fig. 104.18). These cells, which are 20-100 µm in diameter, have a characteristic wrinkled-paper appearance resulting from the presence of intracytoplasmic substrate inclusions. The cytoplasm of the Gaucher cell reacts strongly positive with the periodic acid–Schiff (PAS) stain. The presence of this cell in bone marrow and tissue specimens is highly suggestive of Gaucher disease, although it also may be found in patients with granulocytic leukemia and myeloma.

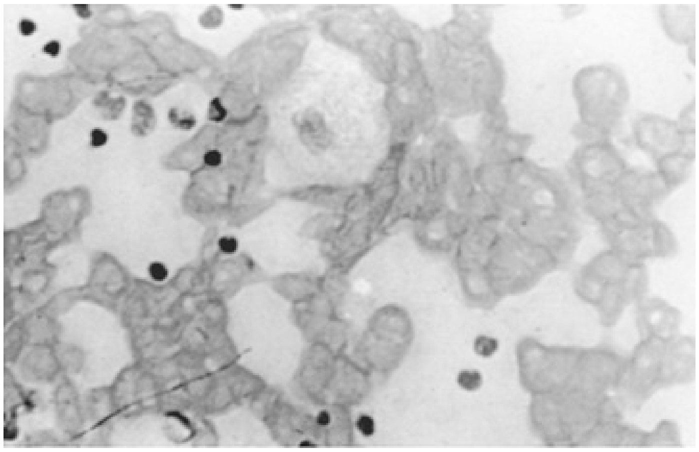

FIG. 104.18 Cells from the spleen of a patient with Gaucher disease. A characteristic spleen cell is shown engorged with glucocerebroside.

Gaucher disease type 2 is a rare form and does not have an ethnic predilection. It is characterized by a rapid neurodegenerative course with extensive visceral involvement and death early in life. It presents in infancy with increased tone, strabismus, and organomegaly. Failure to thrive and stridor caused by laryngospasm are typical. After a several-year period of psychomotor regression, death typically occurs secondary to respiratory compromise. **Gaucher disease type 3** presents with clinical manifestations that are intermediate to those seen in types 1 and 2, with presentation in childhood and death by age 10-15 yr. It has a predilection for the Swedish Norrbottnian population, in whom the incidence is approximately 1 in 50,000. Neurologic involvement is present. Type 3 disease is further classified as types 3a and 3b based on the extent of neurologic involvement and whether there is progressive myotonia and dementia (**type 3a**) or isolated supranuclear gaze palsy (**type 3b**).

Gaucher disease should be considered in the differential diagnosis of patients with unexplained organomegaly, who bruise easily, who have bone pain, or who have a combination of these conditions. Bone marrow examination usually reveals the presence of Gaucher cells. All suspected diagnoses should be confirmed by determination of the acid β-glucosidase activity in isolated leukocytes or cultured fibroblasts, as well as by identification of their specific acid β-glucosidase gene mutations. In Ashkenazi Jewish individuals the identification of carriers can be achieved best by molecular testing for the common Ashkenazi mutations. Testing should be offered to all family members, keeping in mind that heterogeneity, even among members of the same kindred, can be so great that nonsymptomatic affected individuals may be diagnosed. **Prenatal diagnosis** is available by determination of enzyme activity and/or the specific family mutations in chorionic villi or cultured amniotic fluid cells.

Treatment of patients with Gaucher disease type 1 includes enzyme replacement therapy (ERT). The efficacy of ERT with mannose-terminated recombinant human acid β-glucosidase (*imiglucerase* [Cerezyme, Genzyme]), *velaglucerase alfa* [VPRIV, Shire HGT]), or *taliglucerase alfa* (Uplyso, Protalix Biotherapeutics) is the standard of care for the treatment of patients with type 1 disease. Most symptoms (organomegaly, hematologic indices, bone pain) are reversed by ERT (60 IU/kg) administered by IV infusion every other week, and the bone involvement can be stabilized or improved. Although ERT does not alter the neurologic progression of patients with Gaucher disease types 2 and 3, it has been used in selected patients as a palliative measure, particularly in type 3 patients with severe visceral involvement. Alternative treatment with oral substrate reduction agents designed to decrease the synthesis of glucosylceramide by chemical inhibition of glucosylceramide synthase include *miglustat* (Zavesca, Actelion), although its efficacy on hematologic parameters is not as great as ERT. A 2nd, more effective substrate inhibitor, *eliglustat* (Cerdelga, Sanofi-Genzyme), has demonstrated significant efficacy versus placebo and is not inferior to imiglucerase making this an alternative first-line oral treatment for patients with type 1 disease. A small number of patients have undergone bone marrow transplantation (BMT), which is curative but is associated with significant morbidity and mortality from the procedure, limiting the selection of appropriate candidates.

Niemann-Pick Disease

The original description of Niemann-Pick disease (NPD) was what is now known as **type A** NPD, a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, and a rapidly progressive neurodegenerative course that leads to death by 2-3 yr of age. **Type B** disease is a nonneuronopathic form observed in children and adults. **Type C** disease is a neuronopathic form that results from defective cholesterol transport. All subtypes are inherited as autosomal recessive traits and display variable clinical features (see Table 104.15).

NPD types A and B result from the deficient activity of **acid sphingomyelinase (ASM)** , a lysosomal enzyme encoded by a gene on chromosome 11 (11p15.1-p15.4). The enzymatic defect results in the pathologic accumulation of *sphingomyelin*, a ceramide phospholipid, and other lipids in the monocyte-macrophage system, the primary pathologic site. The progressive deposition of sphingomyelin in the CNS results in the neurodegenerative course seen in type A and in nonneural tissue in the systemic disease manifestations of type B, including progressive lung disease in some patients. A variety of mutations in the acid sphingomyelinase gene that cause types A and B NPD have been identified.

The **clinical manifestations** and course of type A NPD are uniform and characterized by a normal appearance at birth followed by hepatosplenomegaly, moderate lymphadenopathy, and psychomotor retardation evident by 6 mo of age. Over time, the loss of motor function and the deterioration of intellectual capabilities are progressively debilitating; spasticity and rigidity develop; and death occurs by 3 yr of age. In contrast to the stereotyped type A phenotype, the clinical presentation and course of patients with type B disease are more variable. Most are diagnosed in infancy or childhood when enlargement of the liver or spleen, or both, is detected during a routine physical examination. At diagnosis, type B NPD patients usually have evidence of mild pulmonary involvement, usually detected as a diffuse reticular or finely nodular infiltration on the chest radiograph. Pulmonary symptoms may present in adults. In most patients, hepatosplenomegaly is particularly prominent in childhood, but with increasing linear growth, the abdominal protuberance decreases and becomes less conspicuous. In mildly affected patients the splenomegaly may not be noted until adulthood, and disease manifestations may be minimal.

Severely affected patients may have liver involvement leading to life-threatening cirrhosis, portal hypertension, and ascites. Clinically significant pancytopenia caused by secondary hypersplenism may require partial or complete splenectomy; this should be avoided if possible because splenectomy frequently causes progression of pulmonary disease, which can be life threatening. In general, type B patients do not have neurologic involvement and have a normal IQ. Some patients with type B disease have cherry-red maculae or haloes and subtle neurologic symptoms (peripheral neuropathy). In some type B patients, decreased pulmonary diffusion caused by alveolar infiltration becomes evident in late childhood or early adulthood and progresses with age. Severely affected individuals may experience significant pulmonary compromise by 15-20 yr of age. Such patients have low oxygen tension (Po_2) values and dyspnea on exertion. Life-threatening bronchopneumonia may occur, and cor pulmonale has been described.

Type C NPD patients often present with prolonged neonatal jaundice, appear normal for 1-2 yr, and then experience a slowly progressive and variable neurodegenerative course. Their hepatosplenomegaly is less severe than that of patients with types A or B NPD, and they may survive into adulthood. The underlying biochemical defect in type C patients is an abnormality in cholesterol transport, leading to the accumulation of sphingomyelin and cholesterol in their lysosomes and a secondary partial reduction in ASM activity (see Chapter 104.3).

In type B NPD patients, splenomegaly is usually the first manifestation detected. The splenic enlargement is noted in early childhood; in very mild disease the enlargement may be subtle and detection delayed until adolescence or adulthood. The presence of the characteristic NPD cells in bone marrow aspirates supports the diagnosis of type B NPD. Patients with type C NPD, however, also have extensive infiltration of NPD cells in the bone marrow, and thus all suspected cases should be evaluated enzymatically to confirm the clinical diagnosis by measuring the ASM activity level in peripheral leukocytes. Patients with types A and B NPD have greatly decreased ASM levels (1–10%), whereas patients with type C NPD have normal or somewhat decreased ASM activities. The enzymatic identification of NPD carriers is problematic. For families in whom the specific molecular lesion has been identified, however, family members can be accurately tested for heterozygote status by DNA analysis. **Prenatal diagnosis** of types A and B NPD can be made reliably by the measurement of ASM activity in cultured amniocytes or chorionic villi; molecular analysis of fetal cells to identify the specific *ASM* mutations can provide the specific diagnosis or serve as a confirmatory test. The clinical diagnosis of type C NPD can be supported by filipin stain positivity in cultured fibroblasts and identification of a specific mutation in the *NPC1* or *NPC2* gene.

There is no specific treatment for NPD. Orthotopic liver transplantation in an infant with type A disease and cord blood transplantation in several type B NPD patients have been attempted with little or no success. BMT in a small number of type B NPD patients has been successful in reducing the spleen and liver volumes, the sphingomyelin content of the liver, the number of Niemann-Pick cells in the marrow, and radiologically detected infiltration of the lungs. In one patient, liver biopsies taken up to 33 mo after transplant showed only a moderate reduction in stored sphingomyelin. ERT with recombinant human ASM is currently in clinical trials for the treatment of type B patients. A 26-wk phase 1b study in adult patients with NPD type B established initial proof of concept in this patient group, and a phase 1/2 clinical trial in pediatric patients and a phase 2/3 trial in adult patients with ASM deficiency are ongoing. Clinical trials of miglustat have been performed, and the drug has been approved in Europe for the treatment of type C disease. Treatment of type A disease by BMT has not been successful, presumably because of the severe neurologic involvement.

Fabry Disease

Fabry disease is an X-linked inborn error of glycosphingolipid metabolism caused by the absent or extremely deficient activity of α-galactosidase A (α-gal A). There are 2 major phenotypes. Affected males with the **classic** phenotype present in childhood with angiokeratomas (telangiectatic skin lesions), hypohidrosis, corneal and lenticular opacities, and painful acroparesthesias. With advancing age, they develop kidney failure, heart disease, and stroke (see Table 104.15). This classic phenotype is caused by the absent activity of the α-gal A and has an estimated prevalence of approximately 1 in 40,000 males. The **later-onset** phenotype occurs in affected males with residual α-gal A activity and presents in the 4th to 8th decades with cardiac disease and renal failure. This phenotype is more prevalent than the classic phenotype. Heterozygous females for the classic phenotype can be asymptomatic or as severely affected as the males, the variability a result of random X-chromosomal inactivation. The enzyme deficiency results from mutations in the α-gal A gene located on the long arm of the X chromosome (Xq22). The enzymatic defect leads to the systemic accumulation of neutral glycosphingolipids, primarily globotriaosylceramide, particularly in the plasma and lysosomes of vascular endothelial and smooth muscle cells, cardiac myocytes, and renal podocytes. The progressive vascular glycosphingolipid deposition in classically affected males results in small-vessel occlusion and ischemia, leading to the major disease manifestations. The complementary DNA (cDNA) and genomic sequences encoding α-gal A have been characterized, and >900 different mutations in the α-gal A gene are responsible for this lysosomal storage disease.

The **angiokeratomas** usually occur in childhood and may lead to early diagnosis (Fig. 104.19). They increase in size and number with age and range from barely visible to several millimeters in diameter. The lesions are punctate, dark red to blue-black, and flat or slightly raised. They do not blanch with pressure, and the larger ones may show a slight hyperkeratosis. Characteristically, the lesions are densest between the umbilicus and knees, in the “bathing trunk area,” but may occur anywhere, including the oral mucosa. The hips, thighs, buttocks, umbilicus, lower abdomen, scrotum, and glans penis are common sites, and there is a tendency toward symmetry. Variants without skin lesions have been described. Sweating is usually decreased or absent. Corneal opacities and characteristic lenticular lesions, observed under slit-lamp examination, are present in affected males, as well as in approximately 90% of heterozygotes from families with the classic phenotype. Conjunctival and retinal vascular tortuosity is common and results from the systemic vascular involvement.

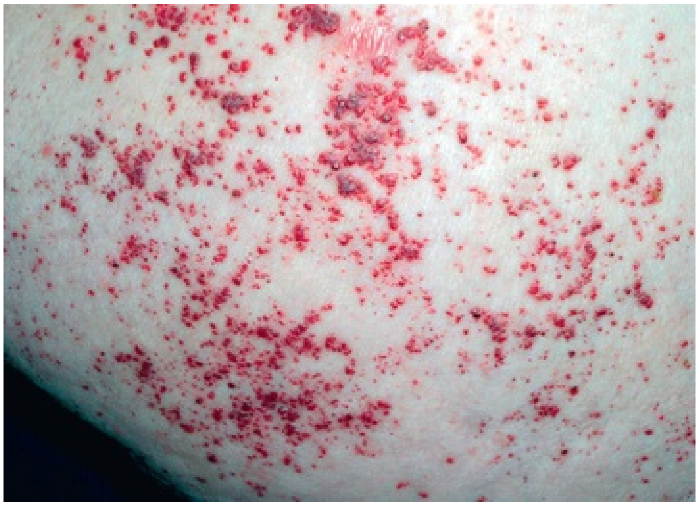

FIG. 104.19 Typical angiokeratomas. Angiokeratomas are quite large and easily recognizable, but if only a few lesions exist or they are restricted only to the genitalia or umbilical regions, they can be easily missed. (From Zarate VA, Hopkin RJ: Fabry's disease, *Lancet* 372:1427, 2008.)

Pain is the most debilitating symptom in childhood and adolescence. **Fabry crises,** lasting from hours to several days, consist of agonizing, burning pain in the hands, feet, and proximal extremities and are usually associated with exercise, fatigue, fever, or a combination of these factors. These painful acroparesthesias usually become less frequent in the 3rd and 4th decades, although in some men these may become more frequent and severe. Attacks of abdominal or flank pain may simulate appendicitis or renal colic. Pain may suggest other diagnoses (Table 104.17).

Table 104.17

Common Misdiagnoses for Fabry Disease

Growing pains Chronic overlapping pain syndrome Irritable bowel syndrome Malingering Systemic lupus erythematous Rheumatic fever Fibromyalgia Dermatomyositis Raynaud phenomenon Raynaud syndrome	Polyphyria Guillain-Barre syndrome Hereditary neuropathy Uremic neuropathy Diabetic neuropathy Polyneuropathy C1 esterase deficiency TNF receptor-associated periodic syndrome (TRAPS) Joint and recurrent fever syndromes (juvenile idiopathic arthritis, familial Mediterranean fever)	Erythromelalgia Meniere disease Coronary heart disease Complex regional pain syndromes Multiple sclerosis Osler disease Appendicitis Metabolic bone disease (rickets, uremia, scurvy)

Adapted from Sivley MD: Fabry disease: a review of ophthalmic and systemic manifestations. Optometry Vision Sci 90(2)e63-e78, 2013 (Table 2, p e71).

The major morbid symptoms in classically affected males result from the progressive involvement of the vascular system. Early in the course of the classic phenotype, casts, RBCs, and lipid inclusions with characteristic birefringent “Maltese crosses” appear in the urinary sediment. Proteinuria, isosthenuria, and gradual deterioration of renal function and development of azotemia occur in the 2nd to 4th decades in the classic phenotype and in the 4th to 8th decades in the later-onset form. Cardiovascular findings may include arrhythmias, hypertrophic cardiomyopathy, and heart failure. Mitral insufficiency is the most common valvular lesion. Cerebrovascular manifestations, including transient ischemic attack (TIA) and stroke (CVA), result secondary to cardiac arrhythmias as well as multifocal small-vessel involvement, other features may include chronic bronchitis and dyspnea, lymphedema of the legs without hypoproteinemia, episodic diarrhea, osteoporosis, impaired growth, and delayed puberty. Death most often results from renal failure, cardiac disease, or stroke. Before hemodialysis or renal transplantation, the mean age at death for affected men was about 40 yr. Patients with the later-onset phenotype with residual α-gal A activity have cardiac and/or renal disease. The cardiac manifestations include hypertrophy of the left ventricular wall and interventricular septum, and electrocardiographic abnormalities consistent with cardiomyopathy. Hypertrophic cardiomyopathy may lead to ventricular tachycardia as a cause of death.

The **diagnosis** of Fabry disease in classically affected males is most readily made from the history of painful acroparesthesias, hypohidrosis, the presence of the characteristic skin lesions, and the observation of the corneal opacities and lenticular lesions. The disorder is often misdiagnosed as rheumatic fever, erythromelalgia, or neurosis. The skin lesions must be differentiated from the benign angiokeratomas of the scrotum (**Fordyce disease**) or from angiokeratoma circumscriptum. Angiokeratomas identical to those of Fabry disease have been reported in fucosidosis, aspartylglycosaminuria, late-onset GM_1 gangliosidosis, galactosialidosis, α-*N* -acetylgalactosaminidase deficiency, and sialidosis. Later-onset patients have been identified among patients on hemodialysis and patients with hypertrophic cardiomyopathy or who had cryptogenic strokes. Later-onset patients lack the early classic manifestations previously described. The diagnosis of classic and later-onset Fabry disease is confirmed biochemically by the demonstration of greatly decreased α-gal A activity in plasma, isolated leukocytes, or cultured fibroblasts or lymphoblasts. The specific α-gal A mutation can be determined by gene sequencing.

Heterozygous females from classic families may have corneal opacities, isolated skin lesions, and intermediate activities of α-gal A in plasma or cells. Rare female heterozygotes may have manifestations as severe as those in affected males. Asymptomatic at-risk females in classic and later-onset families affected by Fabry disease, however, should be optimally diagnosed by the direct analysis of their family's specific mutation. Prenatal detection of affected males can be accomplished by demonstrating deficient α-gal A activity and the family's specific gene mutation in chorionic villi obtained in the 1st trimester or in cultured amniocytes obtained by amniocentesis in the 2nd trimester of pregnancy. Fabry disease can be detected by newborn screening, and pilot studies have been conducted in Europe, Asia, and North America.

Treatment for Fabry disease may include the use of phenytoin and carbamazepine to decrease the frequency and severity of the chronic acroparesthesias and the periodic crises of excruciating pain. Renal transplantation and long-term hemodialysis are lifesaving procedures for patients with renal failure.

Enzyme replacement therapy (ERT) for Fabry patients using recombinant human α-gal A preparations produced in Chinese hamster ovary cells (*agalsidase beta*, Fabrazyme, Genzyme) and in human fibrosarcoma cells (*agalsidase alfa*, Replagal, Shire HGT) is available. Both Fabrazyme and Replagal were approved by the European Medicines Agency in the European Union, but only Fabrazyme is approved by the U.S. FDA. The effectiveness of ERT with Fabrazyme has been demonstrated in stabilization of renal disease, regression of hypertrophic cardiomyopathy, reduction of pain, and improvement in quality of life. Because most classically affected males produce no enzyme protein, these patients can produce immunoglobulin G (IgG) antibodies in response to the infused enzyme, which does not reduce the effectiveness of substrate clearance unless the antibody titer is very high. Treatment of classically affected males should begin in childhood.

Fucosidosis

Fucosidosis is a rare autosomal recessive disorder caused by the deficient activity of α-fucosidase and the accumulation of fucose-containing glycosphingolipids, glycoproteins, and oligosaccharides in the lysosomes of the liver, brain, and other organs (see Table 104.15). The α-fucosidase gene is on chromosome 1 (1p24), and specific mutations are known. Although the disorder is panethnic, most reported patients are from Italy and the United States. There is wide variability in the clinical phenotype, with the most severely affected patients presenting in the 1st yr of life with developmental delay and somatic features similar to those of the mucopolysaccharidoses. These features include frontal bossing, hepatosplenomegaly, coarse facial features, and macroglossia. The CNS storage results in a relentless neurodegenerative course, with death in childhood. Patients with milder disease have angiokeratomas and longer survival. *No specific therapy exists for fucosidosis.* The disorder can be diagnosed by the demonstration of deficient α-fucosidase activity in peripheral leukocytes or cultured fibroblasts. Carrier identification and prenatal diagnosis are possible by determination of the enzymatic activity or the specific family mutations.

Schindler Disease

This autosomal recessive neurodegenerative disorder results from the deficient activity of α-*N* -acetylgalactosaminidase and the accumulation of asialoglycopeptides and sialyloligosaccharides (see Table 104.15). The gene for the enzyme is located on chromosome 22 (22q11). Schindler disease is clinically heterogeneous, and 2 major phenotypes have been identified. **Type I** disease is an infantile-onset neuroaxonal dystrophy. Affected infants have normal development for the 1st 9-15 mo of life followed by a rapid neurodegenerative course that results in severe psychomotor retardation, cortical blindness, and frequent myoclonic seizures. **Type II** disease is characterized by a variable age at onset, mild intellectual disability, and angiokeratomas. *There is no specific therapy* for either form of the disorder. The diagnosis is by demonstration of the enzymatic deficiency in leukocytes or cultured skin fibroblasts or specific gene mutations.

Metachromatic Leukodystrophy

This autosomal recessive white matter disease is caused by a deficiency of **arylsulfatase A (ASA)** , which is required for the hydrolysis of sulfated glycosphingolipids. Another form of metachromatic leukodystrophy (**MLD**) is caused by a deficiency of a sphingolipid activator protein (SAP1), which is required for the formation of the substrate-enzyme complex. The deficiency of this enzymatic activity results in the white matter storage of sulfated glycosphingolipids, which leads to demyelination and a neurodegenerative course. The *ASA* gene is on chromosome 22 (22q13.31qter); specific mutations tend to fall into 2 groups that correlate with disease severity.

The **clinical manifestations** of the **late-infantile** form of MLD, which is most common, usually present between 12 and 18 mo of age as irritability, inability to walk, and hyperextension of the knee, causing genu recurvatum. The clinical progression of the disease relates to the pathologic involvement of both central and peripheral nervous systems, giving a mixture of upper and lower motor neuron and cognitive and psychiatric signs. Deep tendon reflexes are diminished or absent. Gradual muscle wasting, weakness, and hypotonia become evident and lead to a debilitated state. As the disease progresses, nystagmus, myoclonic seizures, optic atrophy, and quadriparesis appear, with death in the 1st decade of life (see Table 104.15). The **juvenile** form of MLD has a more indolent course, with onset that may occur as late as 20 yr of age. This form of the disease presents with gait disturbances, mental deterioration, urinary incontinence, and emotional difficulties. The **adult** form, which presents after the 2nd decade, is similar to the juvenile form in its clinical manifestations, although emotional difficulties and psychosis are more prominent features. Dementia, seizures, diminished reflexes, and optic atrophy also occur in both juvenile and adult forms. The pathologic hallmark of MLD is the *deposition of metachromatic bodies,* which stain strongly positive with PAS and Alcian blue, in the white matter of the brain. Neuronal inclusions may be seen in the midbrain, pons, medulla, retina, and spinal cord; demyelination occurs in the peripheral nervous system. The **diagnosis** of MLD should be suspected in patients with the clinical features of leukodystrophy. Decreased nerve conduction velocities, increased cerebrospinal fluid protein, metachromatic deposits in sampled segments of sural nerve, and metachromatic granules in urinary sediment are all suggestive of MLD. Confirmation of the diagnosis is based on the demonstration of the reduced activity of ASA in leukocytes or cultured skin fibroblasts. SAP deficiency is diagnosed by measuring the concentration of SAP1 in cultured fibroblasts using a specific antibody to the protein. The diagnosis, identification of carriers, and prenatal diagnosis are available for both forms of MLD by detection of the causative mutations in the *ASA* or *SAP* genes.

Unrelated-donor umbilical cord blood transplantation has been undertaken in some pediatric patients with MLD. A longitudinal study of 6 patients with late-infantile onset and 14 with juvenile onset revealed that motor deficits present at the time of transplant did not improve, and that neurologic symptoms continued to progress in those with late-infantile presentation. In contrast, in juvenile patients the brainstem auditory evoked responses, visual evoked potentials, electroencephalogram, and/or peripheral nerve conduction velocities stabilized or improved. Therefore, consideration of umbilical cord blood transplantation for children with presymptomatic late-infantile MLD or minimally symptomatic juvenile MLD may be indicated. Clinical trials of a recombinant human arylsulfatase A (rhARSA) enzyme (Metazym, Shire HGT) demonstrated its safety in children with late-infantile MLD, but a lack of efficacy. A multicenter phase I/II clinical trial to evaluate the safety and efficacy of rhARSA administered intrathecally is ongoing.

Multiple-Sulfatase Deficiency

This autosomal recessive disorder results from the enzymatic deficiency of at least 9 sulfatases, including arylsulfatases A, B, and C and iduronate-2-sulfatase. The specific defect is an enzyme in the C-α-formylglycine–generating system (the gene for which is located at 3p26), which introduces a common posttranslational modification in all the affected sulfatases and explains the occurrence of these multiple enzyme defects. Because of the deficiency of these enzymes, sulfatides, mucopolysaccharides, steroid sulfates, and gangliosides accumulate in the cerebral cortex and visceral tissues, resulting in a clinical phenotype with features of a **leukodystrophy** as well as those of the **mucopolysaccharidoses** . Severe ichthyosis may also occur. Carrier testing and prenatal diagnosis can be done by measurement of the enzymatic activities or the specific gene defects. *There is no specific treatment for multiple sulfatase deficiency* other than supportive care.

Krabbe Disease

Also called *globoid cell leukodystrophy,* Krabbe disease is an autosomal recessive fatal disorder of infancy. It results from the deficient activity of **galactocerebrosidase** and the white matter accumulation of **galactosylceramide**

, which is normally found almost exclusively in the myelin sheath. Both peripheral and central myelin is affected, resulting in spasticity and cognitive impairment coupled with deceptively normal or even absent deep tendon reflexes. The galactocerebrosidase gene is on chromosome 14 (14q31), and specific disease-causing mutations are known. The **infantile** form of Krabbe disease is rapidly progressive, and patients present in early infancy with irritability, seizures, and hypertonia (see Table 104.15). Optic atrophy is evident in the 1st yr of life, and mental development is severely impaired. As the disease progresses, optic atrophy and severe developmental delay become apparent; affected children exhibit opisthotonos and die before 3 yr of age. A **late-infantile** form of Krabbe presents after age 2 yr. Affected individuals have a course similar to that of the early-infantile form.

The **diagnosis** of Krabbe disease relies on the demonstration of the specific enzymatic deficiency in white blood cells or cultured skin fibroblasts. Causative gene mutations have been identified. Carrier identification and prenatal diagnosis are available. The development of methods to measure galactocerebrosidase activity on dried blood spots has led to the inclusion of Krabbe disease in the newborn screening programs of some states. **Treatment** of infants with Krabbe disease with umbilical cord blood transplantation has been reported in prenatally identified asymptomatic newborns and symptomatic infants. Transplanted infants appear to develop neurologic manifestations at a slower rate but succumb to a neurologic demise.

Farber Disease

This rare autosomal recessive disorder results from the deficiency of the lysosomal enzyme acid ceramidase and the accumulation of ceramide in various tissues, especially the joints. Symptoms can begin in the 1st yr of life with painful joint swelling and nodule formation (Fig. 104.20), which is sometimes diagnosed as **rheumatoid arthritis** . As the disease progresses, nodule or granulomatous formation on the vocal cords can lead to hoarseness and breathing difficulties; failure to thrive is common. In some patients, moderate CNS dysfunction is present (see Table 104.15). Patients may die of recurrent pneumonias in their teens. *There is currently no specific therapy.* The **diagnosis** of Farber disease should be suspected in patients who have nodule formation over the joints but no other findings of rheumatoid arthritis. In such patients, acid ceramidase activity should be determined in cultured skin fibroblasts or peripheral leukocytes. Various disease-causing mutations have been identified in the acid ceramidase gene. Carrier detection and prenatal diagnosis are available.

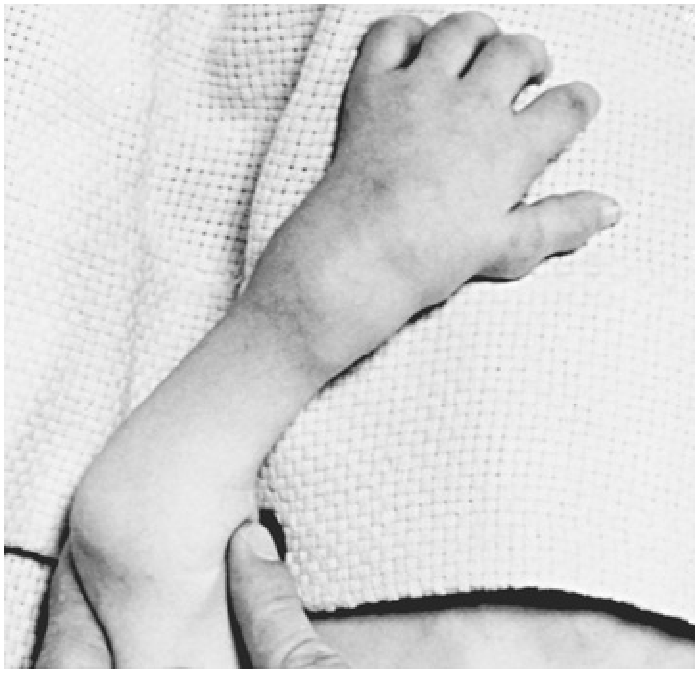

FIG. 104.20 Forearm of an 18 mo old girl with Farber disease. Note the painful joint swelling and the nodule formation. The infant was suspected of having rheumatoid arthritis.

Wolman Disease and Cholesterol Ester Storage Disease

These autosomal recessive lysosomal storage diseases result from deficiency of **lysosomal acid lipase (LAL)** and accumulation of cholesterol esters and triglycerides in histiocytic foam cells of most visceral organs. The *LAL* gene is on chromosome 10 (10q24-q25). **Wolman disease** is the more severe clinical phenotype and is a fatal disorder of infancy. Clinical features become apparent in the 1st weeks of life and include failure to thrive, relentless vomiting, abdominal distention, steatorrhea, and hepatosplenomegaly (see Table 104.15). There usually is hyperlipidemia. Hepatic dysfunction and fibrosis may occur. **Calcification of the adrenal glands** occurs in about 50% of patients. Death usually occurs within the 1st 6 mo of life.

Cholesterol ester storage disease is less severe than Wolman disease and may not be diagnosed until adulthood. Hepatomegaly can be the only detectable abnormality, but affected individuals are at significant risk for premature cirrhosis and atherosclerosis. Adrenal calcification can occur in patients with severe early onset.

Diagnosis and carrier identification are based on measuring LAL activity in peripheral leukocytes or cultured skin fibroblasts. Disease-causing mutations have been identified in the *LAL* gene. Prenatal diagnosis depends on measuring decreased enzyme levels or identifying specific mutations in cultured chorionic villi or amniocytes. Pharmacologic agents to suppress cholesterol synthesis, in combination with cholestyramine and diet modification, have been used in patients, but with little to no clinical benefit. *Sebelipase alfa* (Kanuma, Alexion) is a recombinant form of LAL approved by the FDA in 2015. In a clinical study, 67% of infants with LAL deficiency survived beyond 12 mo of age, compared with 0% of untreated infants in a historical cohort, all of whom died by 8 mo. In a study of 66 pediatric and adult patients with cholesteryl ester storage disease, those treated with Kanuma had demonstrated significant reductions in serum alanine transaminase (ALT) levels and liver fat and improvements in LDL-C, triglycerides, and HDL-C, compared to placebo-treated patients (see Chapter 104.3).

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104.5

Mucolipidoses

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Keywords

I cell disease
mucolipidosis

I-cell disease (mucolipidosis II [ML-II]) and **pseudo-Hurler polydystrophy (mucolipidosis III [ML-III])** are rare autosomal recessive disorders that share some clinical features with Hurler syndrome (see Chapter 107). These diseases result from the abnormal targeting of newly synthesized lysosomal enzymes that normally have phosphorylated mannose residues for binding to the mannose-6-phosphate receptors that transport the enzymes to the lysosomes. These mannose-6-phosphate residues are synthesized in a 2-step reaction that occurs in the Golgi apparatus and is mediated by 2 enzymatic activities. The enzyme that catalyzes the first step, the lysosomal enzyme *N* -acetylglucosamine-1-phosphotransferase, is defective in both ML-II and ML-III, which are allelic disorders resulting from mutations in the GlcNAc-phosphotransferase α/β-subunits precursor gene *(GNPTAB).* This enzyme deficiency results in abnormal targeting of the lysosomal enzymes, which are consequently secreted into the extracellular matrix. Because the lysosomal enzymes require the acidic environment of the lysosome to function, patients with this defect accumulate a variety of different substrates because of the intracellular deficiency of most lysosomal enzymes. The **diagnosis** of ML-II and ML-III can be made by the determination of the serum lysosomal enzymatic activities, which are markedly elevated, or by the demonstration of their reduced enzymatic activity levels in cultured skin fibroblasts. Direct measurement of the phosphotransferase activity is possible as well. **Prenatal diagnosis** is available for both disorders by measurement of lysosomal enzymatic activities in amniocytes or chorionic villus cells. Carrier identification is available for both disorders by measurement of enzymatic activities using cultured skin fibroblasts or by mutation analysis of the causative gene. Neonatal screening by tandem mass spectroscopy may detect I-cell disease.

I-Cell Disease

I-cell disease, or ML-II, shares many of the clinical manifestations of Hurler syndrome (see Chapter 107), although there is no mucopolysacchariduria, and the presentation is earlier (see Table 104.15). Some patients have clinical features evident at birth, including coarse facial features, craniofacial abnormalities, restricted joint movement, and hypotonia. Nonimmune hydrops may be present in the fetus. The remainder of patients present in the 1st yr with severe psychomotor retardation, coarse facial features, and skeletal manifestations that include kyphoscoliosis and a lumbar gibbus. Patients may also have congenital dislocation of the hips, inguinal hernias, and gingival hypertrophy. Progressive, severe psychomotor impairment leads to death in early childhood. *No treatment is available for I-cell disease.*

Pseudo-Hurler Polydystrophy

Pseudo-Hurler polydystrophy, or ML-III, is a less severe disorder than I-cell disease, with later onset and survival to adulthood reported. Affected children may present around age 4 or 5 yr with joint stiffness and short stature. Progressive destruction of the hip joints and moderate dysostosis multiplex are evident. Radiographic evidence of low iliac wings, flattening of the proximal femoral epiphyses with valgus deformity of the femoral head, and hypoplasia of the anterior third of the lumbar vertebrae are characteristic findings. Ophthalmic findings include corneal clouding, retinopathy, and astigmatism; visual complaints are uncommon (see Table 104.15). Some patients have learning disabilities or intellectual disability. **Treatment** , which should include orthopedic care, is symptomatic.

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CHAPTER 105

Defects in Metabolism of Carbohydrates

Priya S. Kishnani, Yuan-Tsong Chen

Carbohydrate synthesis and degradation provide the energy required for most metabolic processes. The important carbohydrates include 3 monosaccharides—glucose, galactose, and fructose—and a polysaccharide, glycogen. Fig. 105.1 shows the relevant biochemical pathways of these carbohydrates. **Glucose** is the principal substrate of energy metabolism, continuously available through dietary intake, gluconeogenesis (glucose made de novo from amino acids, primarily alanine), and glycogenolysis (breakdown of glycogen). Metabolism of glucose generates adenosine triphosphate (ATP) via glycolysis (conversion of glucose or glycogen to pyruvate), mitochondrial oxidative phosphorylation (conversion of pyruvate to carbon dioxide and water), or both. Dietary sources of glucose come from polysaccharides, primarily starch, and the disaccharides lactose, maltose, and sucrose. However, oral intake of glucose is intermittent and unreliable. Gluconeogenesis contributes to maintaining euglycemia (normal levels of glucose in the blood), but this process requires time. Hepatic glycogenolysis provides the rapid release of glucose, and is the most significant factor in maintaining euglycemia. **Glycogen** is also the primary stored energy source in muscle, providing glucose for muscle activity during exercise. Galactose and fructose are monosaccharides that provide fuel for cellular metabolism, though their role is less significant than that of glucose. **Galactose** is derived from lactose (galactose + glucose), which is found in milk and milk products. Galactose is an important energy source in infants, but it is first metabolized to glucose. Galactose (exogenous or endogenously synthesized from glucose) is also an important component of certain glycolipids, glycoproteins, and glycosaminoglycans. The dietary sources of **fructose** are sucrose (fructose + glucose, sorbitol) and fructose itself, which is found in fruits, vegetables, and honey.

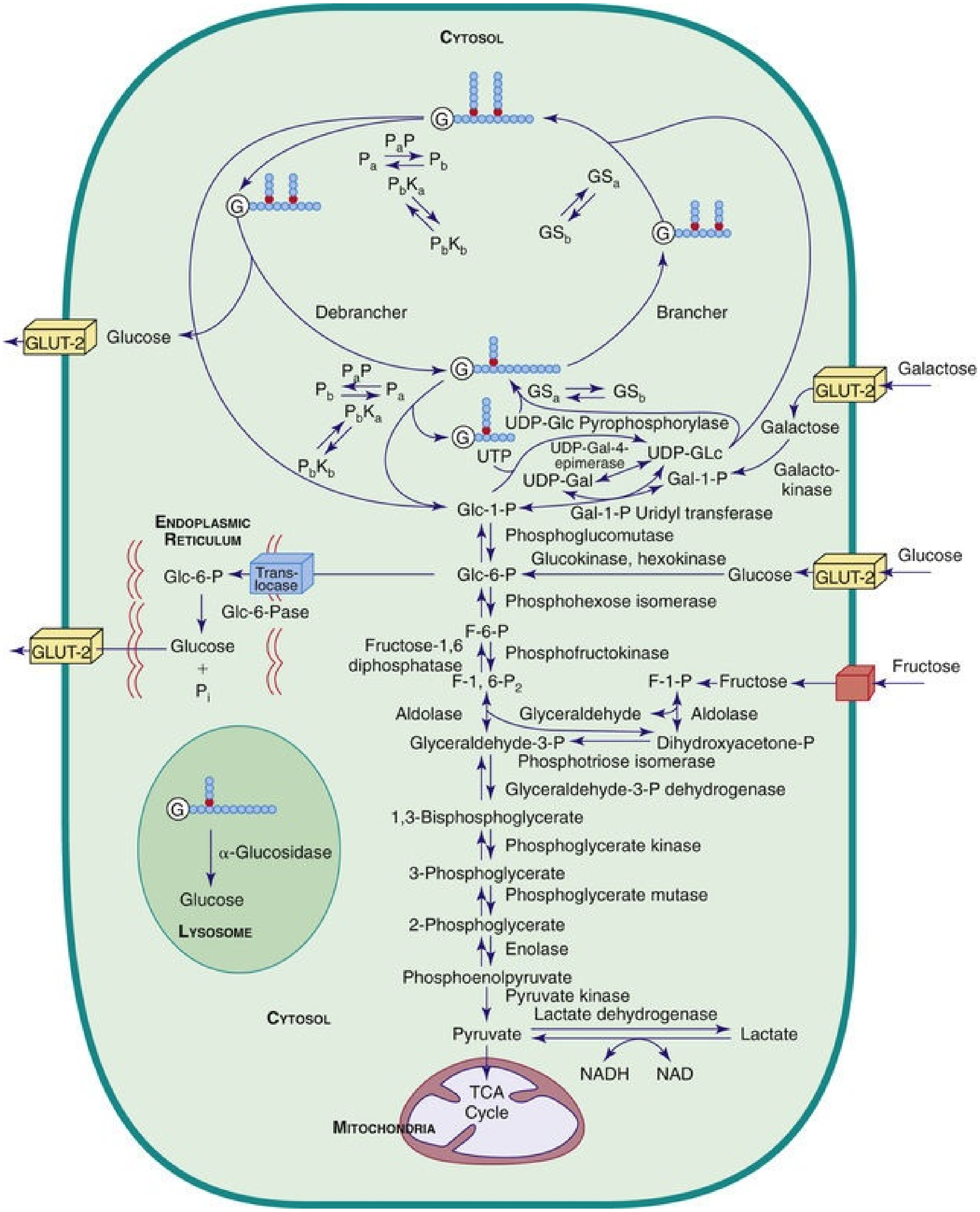
CYTOSOL
G
P_aP
P_a
P_b
P_bK_a
P_bK_b
GS_a
GS_b
Debrancher
Brancher
GLUT-2
Glucose
Galactose
P_aP
P_b
P_a
P_bK_a
P_bK_b
GS_a
GS_b
UDP-Glc Pyrophosphorylase
UTP
UDP-Gal-4-epimerase
UDP-GLc
UDP-Gal
Gal-1-P
Galacto-kinase
Glc-1-P
Gal-1-P Uridyl transferase
ENDOPLASMIC RETICULUM
Phosphoglucomutase
Glucokinase, hexokinase
Glc-6-P
Trans-locase
Glc-6-Pase
Phosphohexose isomerase
F-6-P
Fructose-1,6 diphosphatase
Phosphofructokinase
$F\text{-}1,6\text{-}P_2$
F-1-P
Fructose
Aldolase
Glyceraldehyde
Glyceraldehyde-3-P
Dihydroxyacetone-P
Phosphotriose isomerase
Glyceraldehyde-3-P dehydrogenase
1,3-Bisphosphoglycerate
Phosphoglycerate kinase
3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
Enolase
Phosphoenolpyruvate
Pyruvate kinase
Lactate dehydrogenase
Pyruvate
Lactate
NADH
NAD
+
P_i
α-Glucosidase
LYSOSOME
TCA Cycle
MITOCHONDRIA

FIG. 105.1 Pathway related to glycogen storage diseases and galactose and fructose disorders. G, Glycogen, the primer for glycogen synthesis; GLUT-2, glucose transporter 2; GSa, active glycogen synthase; GSb, inactive glycogen synthase; NAD/NADH, nicotinamide adenine dinucleotide; Pa, active phosphorylase; PaP, phosphorylase a

phosphatase; Pb, inactive phosphorylase; PbKa, active phosphorylase b kinase; PbKb, inactive phosphorylase b kinase; UDP, uridine diphosphate. (Adapted from Beaudet AR: Glycogen storage disease. In Harrison TR, Isselbacher KJ, editors: *Harrison's principles of internal medicine,* ed 13, New York, 1994, McGraw-Hill. Reproduced with permission of The McGraw-Hill Companies.)

Defects in glycogen metabolism typically cause an accumulation of glycogen in the tissues, thus the name **glycogen storage disease** (Table 105.1). Defects in gluconeogenesis or the glycolytic pathway, including galactose and fructose metabolism, do not result in an accumulation of glycogen (Table 105.1). The defects in pyruvate metabolism in the pathway of the conversion of pyruvate to carbon dioxide and water via mitochondrial oxidative phosphorylation are more often associated with **lactic acidosis** and some tissue glycogen accumulation.

Table 105.1

Features of the Disorders of Carbohydrate Metabolism

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
LIVER GLYCOGENOSES			
Type/Common Name			
Ia/Von Gierke	Glucose-6-phosphatase	Growth retardation, hepatomegaly, hypoglycemia; elevated blood lactate, cholesterol, triglyceride, and uric acid levels	Common, severe hypoglycemia Adulthood: hepatic adenomas and carcinoma, osteoporosis, pulmonary hypertension, and renal failure
Ib	Glucose-6-phosphate translocase	Same as type Ia, with additional findings of neutropenia, periodontal disease, inflammatory bowel disease	10% of type Ia
IIIa/Cori or Forbes	Liver and muscle debrancher deficiency (amylo-1,6-glucosidase)	Childhood: hepatomegaly, growth retardation, muscle weakness, hypoglycemia, hyperlipidemia, elevated transaminase levels Adult form: muscle atrophy and weakness, peripheral neuropathy, liver cirrhosis and failure, risk for hepatocellular carcinoma	Common, intermediate severity of hypoglycemia Muscle weakness may progress to need for ambulation assistance such as wheelchair.
IIIb	Liver debrancher deficiency; normal muscle enzyme activity	Liver symptoms same as in type IIIa; no muscle symptoms	15% of type III
IV/Andersen	Branching enzyme	Childhood: failure to thrive, hypotonia, hepatomegaly, splenomegaly, progressive cirrhosis (death usually before	Rare neuromuscular variants exist

		5th yr), elevated transaminase levels; a subset does not have progression of liver disease Adult form: isolated myopathy, central and peripheral nervous system involvement	
VI/Hers	Liver phosphorylase	Hepatomegaly, typically mild hypoglycemia, hyperlipidemia, and ketosis	Often underdiagnosed, severe presentation also known
IX/phosphorylase kinase (PhK) deficiency			Common, X-linked, typically less severe than autosomal forms; clinical variability within and between subtypes; severe cases being recognized across different subtypes
IX (*PHKA2* variant)	Liver PhK	Hypoglycemia, hyperketosis hepatomegaly, chronic liver disease, hyperlipidemia, elevated liver enzymes, growth retardation	X-linked
IX (*PHKB* variant)	Liver and muscle PhK	Hepatomegaly, growth retardation	Autosomal recessive
IX (*PHKG2* variant)	Liver PhK	More severe than IXa; marked hepatomegaly, recurrent hypoglycemia, liver cirrhosis	Autosomal recessive
Glycogen synthase deficiency	Glycogen synthase	Early morning drowsiness and fatigue, fasting hypoglycemia, and ketosis, no hepatomegaly	Decreased liver glycogen store
XI/Fanconi-Bickel syndrome	Glucose transporter 2 (GLUT-2)	Failure to thrive, rickets, hepatorenomegaly, proximal renal tubular dysfunction, impaired glucose and galactose utilization	GLUT-2 expressed in liver, kidney, pancreas, and intestine
MUSCLE GLYCOGENOSES			
Type/Common Name			
IX (*PHKA1* variant)	Muscle PhK	Exercise intolerance, cramps, myalgia, myoglobinuria; no hepatomegaly	X-linked or autosomal recessive
II/Pompe infantile	Acid α-glucosidase (acid maltase)	Cardiomegaly, hypotonia, hepatomegaly; onset: birth to 6 mo	Common, cardiorespiratory failure leading to death by age 1-2 yr; minimal to no residual enzyme activity
II/Late-onset Pompe (juvenile and adult)	Acid α-glucosidase (acid maltase)	Myopathy, variable cardiomyopathy, respiratory insufficiency; onset: childhood to adulthood	Residual enzyme activity
Danon disease	Lysosome-associated membrane protein 2 (LAMP2)	Hypertrophic cardiomyopathy, heart failure	Rare, X-linked
PRKAG2 deficiency	Adenosine monophosphate (AMP)–activated protein kinase γ	Hypertrophic cardiomyopathy. Congenital fetal form is rapidly fatal; myopathy, myalgia, seizures	Autosomal dominant
V/McArdle	Myophosphorylase	Exercise intolerance, muscle cramps, myoglobinuria, “second	Common, male predominance

		wind" phenomenon	
VII/Tarui	Phosphofructokinase	Exercise intolerance, muscle cramps, compensatory hemolytic anemia, myoglobinuria	Prevalent in Japanese and Ashkenazi Jews
Late-onset polyglucosan body myopathy	Glycogenin-1	Adult-onset proximal muscle weakness, nervous system involvement uncommon	Autosomal recessive, rare
Phosphoglycerate kinase deficiency	Phosphoglycerate kinase	As with type V	Rare, X-linked
Phosphoglycerate mutase deficiency	M subunit of phosphoglycerate mutase	As with type V	Rare, majority of patients are African American
Lactate dehydrogenase deficiency	M subunit of lactate dehydrogenase	As with type V	Rare
GALACTOSE DISORDERS			
Galactosemia with transferase deficiency	Galactose-1-phosphate uridyltransferase	Vomiting, hepatomegaly, cataracts, aminoaciduria, failure to thrive	Black patients tend to have milder symptoms
Galactokinase deficiency	Galactokinase	Cataracts	Benign
Generalized uridine diphosphate galactose-4-epimerase deficiency	Uridine diphosphate galactose-4-epimerase	Similar to transferase deficiency with additional findings of hypotonia and nerve deafness	A benign variant also exists
FRUCTOSE DISORDERS			
Essential fructosuria	Fructokinase	Urine reducing substance	Benign
	Fructose-1-phosphate aldolase	Acute: vomiting, sweating, lethargy	
Hereditary fructose intolerance		Chronic: failure to thrive, hepatic failure	Prognosis good with fructose restriction
DISORDERS OF GLUCONEOGENESIS			
Fructose-1,6-diphosphatase deficiency	Fructose-1,6-diphosphatase	Episodic hypoglycemia, apnea, acidosis	Good prognosis, avoid fasting
Phosphoenolpyruvate carboxykinase deficiency	Phosphoenolpyruvate carboxykinase	Hypoglycemia, hepatomegaly, hypotonia, failure to thrive	Rare
DISORDERS OF PYRUVATE METABOLISM			
Pyruvate dehydrogenase complex defect	Pyruvate dehydrogenase	Severe fatal neonatal to mild late onset, lactic acidosis, psychomotor retardation, failure to thrive	Most commonly caused by $E_{1\alpha}$ subunit, defect X-linked
Pyruvate carboxylase deficiency	Pyruvate carboxylase	Same as above	Rare, autosomal recessive
Respiratory chain defects (oxidative phosphorylation disease)	Complexes I-V, many mitochondrial DNA mutations	Heterogeneous with multisystem involvement	Mitochondrial inheritance
DISORDERS IN PENTOSE METABOLISM			
Pentosuria	L-Xylulose reductase	Urine-reducing substance	Benign
Transaldolase deficiency	Transaldolase	Liver cirrhosis and failure, cardiomyopathy	Autosomal recessive
Ribose-5-phosphate	Ribose-5-phosphate	Progressive leukoencephalopathy	

isomerase deficiency	isomerase	and peripheral neuropathy	

105.1

Glycogen Storage Diseases

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Keywords

glycogen
liver glycogen
hepatomegaly
myopathy
hypoglycemia
ketosis
enzyme replacement therapy

The disorders of glycogen metabolism, the glycogen storage diseases (**GSDs**), result from deficiencies of various enzymes or transport proteins in the pathways of glycogen metabolism (see Fig. 105.1). Glycogen found in these disorders is abnormal in quantity, quality, or both. GSDs are categorized by numerical type in accordance with the chronological order in which these enzymatic defects were identified. This numerical classification is still widely used, at least up to number VII. The GSDs can also be classified by organ involvement into liver and muscle glycogenoses (see Table 105.1).

There are more than 12 forms of GSDs. Glucose-6-phosphatase deficiency (type I), lysosomal acid α-glucosidase deficiency (type II), debrancher deficiency (type III), and liver phosphorylase kinase deficiency (type IX) are the most common of those that typically present in early childhood; myophosphorylase deficiency (type V, McArdle disease) is the most common in adolescents and adults. The cumulative frequency of all forms of GSD is approximately 1 in 20,000 live births.

Liver Glycogenoses

The GSDs that principally affect the liver include glucose-6-phosphatase deficiency (**type I**), debranching enzyme deficiency (**type III**), branching enzyme deficiency (**type IV**), liver phosphorylase deficiency (**type VI**), phosphorylase kinase deficiency (**type IX** , formerly GSD VIa), glycogen synthase deficiency (**type 0**), and glucose transporter-2 defect. Because hepatic carbohydrate metabolism is responsible for plasma glucose homeostasis, this group of disorders typically causes fasting hypoglycemia and hepatomegaly. Some (types III, IV, IX) can be associated with liver cirrhosis. Other organs can also be involved and may manifest as renal dysfunction in type I, myopathy (skeletal and/or cardiomyopathy) in types III and IV, as well as in some rare forms of phosphorylase kinase deficiency, and neurologic involvement in types III (peripheral nerves) and IV (diffuse central and peripheral nervous system dysfunction).

Type I Glycogen Storage Disease (Glucose-6-Phosphatase or Translocase Deficiency, Von Gierke Disease)

Type I GSD is caused by the absence or deficiency of **glucose-6-phosphatase** activity in the liver, kidney, and intestinal mucosa. It has 2 subtypes: **type Ia** , in which the defective enzyme is glucose-6-phosphatase, and **type Ib** , in which the defective enzyme is a **translocase** that transports glucose-6-phosphate across the microsomal membrane. Deficiency of the enzymes in both type Ia and type Ib lead to inadequate hepatic conversion of glucose-6-phosphate to glucose through normal glycogenolysis and gluconeogenesis, resulting in fasting hypoglycemia.

Type I GSD is an autosomal recessive disorder. The gene for glucose-6-phosphatase *(G6PC)* is located on chromosome 17q21; the gene for translocase *(SLC37A4)* is on chromosome 11q23. Common pathogenic variants have been identified. Carrier detection and prenatal diagnosis are possible with DNA-based methodologies.

Clinical Manifestations

Patients with type I GSD may present in the neonatal period with hypoglycemia and lactic acidosis but more often present at 3-4 mo of age with hepatomegaly, hypoglycemic seizures, or both. Affected children often have a **doll-like face** with fat cheeks, relatively thin extremities, short stature, and a protuberant abdomen that is a consequence of massive hepatomegaly. The kidneys are also enlarged, whereas the spleen and heart are not involved.

The biochemical characteristics of type I GSD are *hypoglycemia, lactic acidosis, hyperuricemia,* and *hyperlipidemia*. Hypoglycemia and lactic acidosis can develop after a short fast. Hyperuricemia is present in young children; it rarely progresses to symptomatic gout before puberty. Despite marked hepatomegaly, the liver transaminase levels are usually normal or only slightly elevated. Intermittent diarrhea may occur in GSD I. In patients with GSD Ib, the loss of mucosal barrier function as a result of inflammation, which is likely related to the disturbed neutrophil function, seems to be the main cause of diarrhea. Easy bruising and epistaxis are common and are associated with a **prolonged bleeding time** as a result of impaired platelet aggregation and adhesion.

The plasma may be “milky” in appearance due to strikingly elevated triglyceride levels. Cholesterol and phospholipids are also elevated, but less prominently. The lipid abnormality resembles type IV hyperlipidemia and is characterized by increased levels of very-low-density lipoprotein, low-density lipoprotein, and a unique apolipoprotein profile consisting of increased levels of apolipoproteins B, C, and E, with relatively normal or reduced levels of apolipoproteins A and D. The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and fat. The lipid vacuoles are particularly large and prominent. There is no associated liver fibrosis.

Although type I GSD affects mainly the liver, multiple organ systems are involved. **Delayed puberty** is often seen. Females can have ultrasound findings consistent with **polycystic ovaries** even though other features of polycystic ovary syndrome (acne, hirsutism) are not seen. Nonetheless, fertility appears to be normal, as evidenced in several reports of successful pregnancy in women with GSD I. Increased bleeding during menstrual cycles, including life-threatening menorrhagia, has been reported and could be related to the impaired platelet aggregation. Symptoms of gout usually start around puberty from long-term hyperuricemia. There is an increased risk of **pancreatitis,** secondary to the lipid abnormalities. The dyslipidemia, together with elevated erythrocyte aggregation, could predispose these patients to atherosclerosis, but premature atherosclerosis has not yet been clearly documented except for rare cases. Impaired platelet aggregation and increased antioxidative defense to prevent lipid peroxidation may function as a protective mechanism to help reduce the risk of atherosclerosis. Frequent fractures and radiographic evidence of **osteopenia** are common; bone mineral content is reduced, even in prepubertal patients.

By the 2nd or 3rd decade of life, some patients with type I GSD develop **hepatic adenomas** that can hemorrhage and turn malignant in some cases. **Pulmonary hypertension** has been seen in some long-term survivors of the disease. Iron-refractory anemia and an increased prevalence of thyroid autoimmunity are also being recognized.

Renal disease is another late complication, and most patients with type I GSD >20 yr of age have proteinuria. Many also have hypertension, renal stones, nephrocalcinosis, and altered creatinine clearance. Glomerular hyperfiltration, increased renal plasma flow, and microalbuminuria are often found in the early stages of renal dysfunction and can occur before the onset of proteinuria. In younger patients, hyperfiltration and hyperperfusion may be the only signs of renal abnormalities. With the advancement of renal disease, focal segmental glomerulosclerosis and interstitial fibrosis become evident. In some patients, renal function has deteriorated and progressed to failure, requiring dialysis and transplantation. Other renal abnormalities include amyloidosis, a Fanconi-like syndrome, hypocitraturia, hypercalciuria, and a distal renal tubular acidification defect.

Patients with GSD Ib can have additional features of recurrent bacterial infections from **neutropenia** and impaired neutrophil function. Oral involvement including recurrent mucosal ulceration, gingivitis, and rapidly progressive periodontal disease may occur in type Ib. Intestinal mucosa ulceration culminating in GSD enterocolitis is also common. Type 1b is also associated with a chronic inflammatory bowel disease (IBD)–like picture involving the colon that may be associated with neutropenia and/or neutrophil dysfunction; it may resemble ulcerative colitis or Crohn disease.

Diagnosis

The clinical presentation and laboratory findings of hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia lead to a suspected diagnosis of type I GSD. Neutropenia is noted in GSD Ib patients, typically before 1 yr of age. Neutropenia has also been noted in some patients with GSD Ia, especially those with the p.G188A variant. Administration of glucagon or epinephrine leads to a negligible increase, if any, in blood glucose levels, but the lactate level rises significantly. Before the availability of genetic testing, a definitive diagnosis required a liver biopsy. Gene-based variant analysis by single-gene sequencing or gene panels provides a noninvasive way to diagnose most patients with GSD types Ia and Ib.

Treatment

Treatment focuses on maintaining normal blood glucose levels and is achieved by continuous nasogastric (NG) infusion of glucose or oral administration of uncooked cornstarch. In infancy, overnight NG drip feeding may be needed to maintain normoglycemia. NG feedings can consist of an elemental enteral formula or only glucose or a glucose polymer to provide sufficient glucose to maintain euglycemia. During the day, frequent feedings with high-carbohydrate content are typically sufficient.

Uncooked cornstarch acts as a slow-release form of glucose and can be introduced at a dose of 1.6 g/kg every 4 hr for children <2 yr of age. The response of young children is variable. For older children, the cornstarch regimen can be changed to every 6 hr at a dose of 1.6-2.5 g/kg body weight and can be given orally as a liquid. Newer starch products, such as extended-release waxy maize starch, are thought to be longer acting, better tolerated, and more palatable. Medium-chain triglyceride (MCT) supplementation improves metabolic control, leading to improved growth in children. Since fructose and galactose cannot be converted directly to glucose in GSD type I, these sugars should be restricted in the diet. Sucrose (table sugar, cane sugar, other ingredients), fructose (fruit, juice, high-fructose corn syrup), lactose (dairy foods), and sorbitol should be avoided or limited. As a result of these dietary restrictions, vitamins and minerals such as calcium and vitamin D may be deficient, and supplementation is required to prevent nutritional deficiencies.

Dietary therapy improves hyperuricemia, hyperlipidemia, and renal function, slowing the development of renal failure. This therapy fails, however, to normalize blood uric acid and lipid levels completely in some individuals, despite good metabolic control, especially after puberty. The control of hyperuricemia can be further augmented by the use of allopurinol, a xanthine oxidase inhibitor. The hyperlipidemia can be reduced with lipid-lowering drugs such as β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrate (see Chapter 104). **Microalbuminuria** , an early indicator of renal dysfunction in type I disease, is treated with angiotensin-converting enzyme (ACE) inhibitors. Citrate supplements can be beneficial for patients with hypocitraturia by preventing or ameliorating nephrocalcinosis and development of urinary calculi. Thiazide diuretics increase renal reabsorption of filtered calcium and decrease urinary calcium excretion, thereby preventing hypercalciuria and nephrocalcinosis. Growth hormone (GH) should be used with extreme caution and limited to only those with a documented GH deficiency. Even in those patients, there should be close monitoring of metabolic parameters and for the presence of adenomas.

In patients with type Ib GSD, granulocyte and granulocyte-macrophage colony-stimulating factors are successful in correcting the neutropenia, decreasing the number and severity of bacterial infections, and improving the chronic IBD. The minimum effective dose should be used because side effects are noted on these agents, including splenomegaly, hypersplenism, and bone pain. Bone marrow transplantation has been reported to correct the neutropenia of type Ib GSD.

Orthotopic liver transplantation is a potential cure of type I GSD, especially for patients with liver malignancy, multiple liver adenomas, metabolic derangements refractory to medical management, and liver failure. However, this should be considered as a last resort because of the inherent short- and long-term complications. Large adenomas (>2 cm) that are rapidly increasing in size and/or number may necessitate partial hepatic resection. Smaller adenomas (<2 cm) may be treated with percutaneous ethanol injection or transcatheter arterial embolization. Recurrence of liver adenomas is a challenge and may potentiate malignant transformation in these patients, ultimately requiring a liver transplant.

Before any surgical procedure, the bleeding status must be evaluated and good metabolic control established. Prolonged bleeding times can be normalized by the use of intensive intravenous (IV) glucose infusion for 24-48 hr before surgery. DDAVP (1-deamino-8-D -arginine vasopressin) can reduce bleeding complications, but it should be used with caution because of the risk of fluid overload and hyponatremia when administered as an IV infusion. Lactated Ringer solution should be avoided because it contains lactate and no glucose. Glucose levels should be maintained in the normal range throughout surgery with the use of 10% dextrose. Overall, metabolic control is assessed by growth, improvement, and correction of the metabolic abnormalities, such as elevated lactate, glucose, triglyceride, cholesterol, and uric acid levels.

Prognosis

Previously, type I GSD was associated with a high mortality at a young age, and even for those who survived, the prognosis was guarded. Inadequate metabolic control during childhood can lead to long-term complications in adults. Clinical outcomes have improved dramatically with early diagnosis and effective treatment. However, serious complications such as renal disease and formation of hepatic adenomas with potential risk for malignant transformation persist. The ability to identify transformation to hepatocellular carcinoma in the liver adenomas remains a challenge: α-fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels often remain normal in the setting of hepatocellular carcinoma.

Type III Glycogen Storage Disease (Debrancher Deficiency, Limit Dextrinosis)

Type III GSD is caused by deficient activity of the **glycogen debranching enzyme** . Debranching enzyme, together with phosphorylase, is responsible for complete degradation of glycogen. When debranching enzyme is defective, glycogen breakdown is incomplete, resulting in the accumulation of an abnormal glycogen with short outer-branch chains, which resemble *limit dextrin.* Symptoms of glycogen debranching enzyme deficiency include hepatomegaly, hypoglycemia, short stature, variable skeletal myopathy, and variable cardiomyopathy. GSD **type IIIa** usually involves both liver and muscle, whereas in **type IIIb** , seen in approximately 15% of patients, the disease appears to involve only liver.

Type III GSD is an autosomal recessive disease that has been reported in many different ethnic groups. The frequency is relatively high in Sephardic Jews from North Africa, inhabitants of the Faroe Islands, and in Inuits. The gene for debranching enzyme *(AGL)* is located on chromosome 1p21. More than 130 different pathogenic variants have been identified; 2 pathogenic variants in exon 3, c.18_19delGA (previously described as c.17_18delAG) and p.Gln6X, are specifically associated with glycogenosis IIIb. Carrier detection and prenatal diagnosis are possible using DNA-based methodologies.

Clinical Manifestations

In infancy and childhood, GSD type III may be indistinguishable from type I

GSD because of overlapping features such as hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation (Fig. 105.2). Splenomegaly may be present, but the kidneys are typically not affected. Hepatomegaly in most patients with type III GSD improves with age; however, liver fibrosis, cirrhosis progressing to liver failure, and hepatocellular carcinoma (HCC) are noted in many in late adulthood. Hepatic adenomas occur less often in individuals with GSD III than those with GSD I. The relationship between hepatic adenomas and malignancy in GSD III remains unclear. AFP and CEA levels are not good predictors of the presence of hepatocellular adenomas or malignant transformation. A single case of malignant transformation at the site of adenomas has been noted.

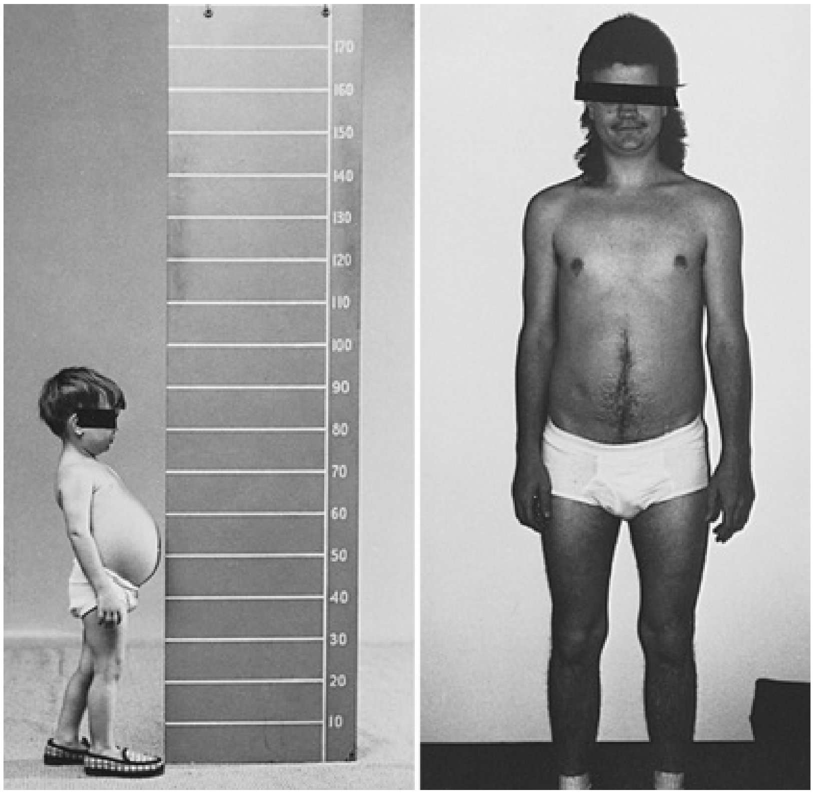

FIG. 105.2 **Growth and development in a patient with type IIIb glycogen storage disease. The patient has debrancher deficiency in the liver but normal activity in muscle. As a child, he had hepatomegaly, hypoglycemia, and growth retardation. After puberty, he no longer had hepatomegaly or hypoglycemia, and his final adult height is normal. He had no muscle weakness or atrophy; this is in contrast to type IIIa patients, in whom a progressive myopathy is seen in adulthood.**

In patients with GSD type IIIa, the **muscle weakness** is slowly progressive and associated with wasting. The weakness is less remarkable in childhood but can become severe after the 3rd or 4th decade of life. Low bone mineral density in patients with GSD III put them at an increased risk of potential fractures. Myopathy does not follow any particular pattern of involvement; both proximal and distal muscles are involved. Electromyography reveals a widespread myopathy; nerve conduction studies are often abnormal.

Although overt cardiac dysfunction is rare, ventricular hypertrophy is a frequent finding. **Cardiac pathology** has shown diffuse involvement of various cardiac structures, including vacuolation of myocytes, atrioventricular conduction, and hyperplasia of smooth muscles. Life-threatening arrhythmia and the need for heart transplant have been reported in some GSD III patients. Hepatic symptoms in some patients may be so mild that the diagnosis is not made until adulthood, when the patients show symptoms and signs of neuromuscular disease.

The initial diagnosis has been confused with Charcot-Marie-Tooth disease (see Chapter 631.1). Polycystic ovaries are noted; some patients can develop hirsutism, irregular menstrual cycles, and other features of polycystic ovarian syndrome. Fertility does not appear to be affected; successful pregnancies have been reported.

Hypoglycemia and hyperlipidemia are common. In contrast to type I GSD, elevation of liver transaminase levels and fasting ketosis are prominent, but blood lactate and uric acid concentrations are usually normal. Glucagon administration 2 hr after a carbohydrate meal provokes a normal increase in blood glucose; after an overnight fast, however, glucagon may provoke no change in blood glucose level. Serum creatine kinase levels can be useful to identify patients with muscle involvement, although normal levels do not rule out muscle enzyme deficiency.

Diagnosis

The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and the presence of fibrous septa. The fibrosis and the paucity of fat distinguish type III glycogenosis from type I. The fibrosis, which ranges from minimal periportal fibrosis to micronodular cirrhosis, appears in most cases to be nonprogressive. Overt cirrhosis has been seen in some patients with GSD III.

Patients with myopathy and liver symptoms have a generalized enzyme defect (type IIIa). The deficient enzyme activity can be demonstrated not only in liver and muscle, but also in other tissues such as heart, erythrocytes, and cultured fibroblasts. Patients with hepatic symptoms without clinical or laboratory evidence of myopathy have debranching enzyme deficiency only in the liver, with enzyme activity retained in the muscle (type IIIb). Before the availability of genetic testing, a definitive diagnosis required enzyme assay in liver, muscle, or both. Gene sequencing now allows for diagnosis and subtype assignment in the majority of patients.

Treatment

The mainstay of treatment of GSD III is dietary management, as in GSD I, although it is less demanding. Patients do not need to restrict dietary intake of fructose and galactose, although simple sugars should be avoided to prevent sudden spikes in blood glucose levels. Hypoglycemia is treated with small, frequent meals high in complex carbohydrates, such as cornstarch supplements or nocturnal gastric drip feedings. Additionally, a high-protein diet during the daytime as well as overnight protein enteral infusion is effective in preventing hypoglycemia. The exogenous protein can be used as a substrate for gluconeogenesis which helps to meet energy needs and prevent endogenous protein breakdown. Protein in the diet also reduces the overall starch requirement. Overtreatment with cornstarch should be avoided as it can result in excessive glycogen buildup, which is detrimental and can lead to excessive weight gain. MCT supplementation is being considered as an alternative source of energy. There is no satisfactory treatment for the progressive myopathy other than recommending a high-protein diet and a submaximal exercise program. Close monitoring with abdominal MRI is needed to detect progression of liver fibrosis to cirrhosis and further to HCC. Liver transplantation has been performed in GSD III patients with progressive cirrhosis and/or HCC. There are reports of cardiac transplant in GSD III patients with end stage cardiac disease.

Type IV Glycogen Storage Disease (Branching Enzyme Deficiency, Amylopectinosis, Polyglucosan Disease, or Andersen Disease)

Type IV GSD is caused by the deficiency of **branching enzyme** activity, which results in the accumulation of an abnormal glycogen with poor solubility. The disease is also known as *amylopectinosis* because the abnormal glycogen has fewer branch points, more α 1-4 linked glucose units, and longer outer chains, resulting in a structure resembling amylopectin. Accumulation of polyglucosan, which is positive on periodic acid–Schiff (PAS) and partially resistant to diastase digestion, is seen in all tissues of patients, but to different degrees.

Type IV GSD is an autosomal recessive disorder. The glycogen branching enzyme *(GBE)* gene is located on chromosome 3p21. More than 20 pathogenic variants responsible for type IV GSD have been identified, and their characterization in individual patients can be useful in predicting clinical outcome. The nearly complete absence of GBE activity with null variants has been associated with perinatal death and fatal neonatal hypotonia. Residual GBE enzyme activity >5% and presence of at least 1 missense variant are associated with a nonlethal hepatic cirrhosis phenotype and, in some situations, a lack of progressive liver disease.

Clinical Manifestations

There is a high degree of clinical variability associated with type IV GSD. The most common and classic form is characterized by progressive cirrhosis of the liver and manifests in the 1st 18 mo of life as hepatosplenomegaly and failure to thrive. Cirrhosis may present with portal hypertension, ascites, and esophageal varices and may progress to liver failure, usually leading to death by 5 yr of age. Rare patients survive without progression of liver disease; they have a milder hepatic form and do not require a liver transplant. Extrahepatic involvement in some patients with GSD IV consists of musculoskeletal involvement, particularly cardiac and skeletal muscles, as well as central nervous system (CNS) involvement.

A **neuromuscular** form of type IV GSD has been reported, with 4 main variants recognized based on age at presentation. The **perinatal** form is characterized by a *fetal akinesia deformation sequence* (FADS) and death in the perinatal period. The **congenital** form presents at birth with severe hypotonia, muscle atrophy, and neuronal involvement, with death in the neonatal period; some patients have cardiomyopathy. The **childhood** form presents primarily with myopathy or cardiomyopathy. The **adult** form, *adult polyglucosan body disease* (APBD), presents as an isolated myopathy or with diffuse CNS and peripheral nervous system dysfunction, accompanied by accumulation of polyglucosan material in the nervous system. Symptoms of neuronal involvement include peripheral neuropathy, neurogenic bladder, and leukodystrophy, as well as mild cognitive decline in some patients. For APBD, a leukocyte or nerve biopsy is needed to establish the diagnosis because branching enzyme deficiency is limited to those tissues.

Diagnosis

Deposition of amylopectin-like materials can be demonstrated in liver, heart, muscle, skin, intestine, brain, spinal cord, and peripheral nerve in type IV GSD. Liver histology shows micronodular cirrhosis and faintly stained basophilic inclusions in the hepatocytes. The inclusions are composed of coarsely clumped, stored material that is PAS positive and partially resistant to diastase digestion. Electron microscopy (EM) shows, in addition to the conventional α and β glycogen particles, accumulation of the fibrillar aggregations that are typical of amylopectin. The distinct staining properties of the cytoplasmic inclusions, as well as EM findings, could be diagnostic. However, polysaccharides with histologic features reminiscent of type IV disease, but without enzymatic correlation, have been observed. The definitive diagnosis rests on the demonstration of the deficient branching enzyme activity in liver, muscle, cultured skin fibroblasts, or leukocytes, or on the identification of pathogenic variants in the *GBE* gene. Prenatal diagnosis is possible by measuring enzyme activity in cultured amniocytes, chorionic villi, or DNA-based methodologies.

Treatment

There is no specific treatment for type IV GSD. Nervous system involvement, such as gait problems and bladder involvement, requires supportive, symptomatic management. Unlike patients with the other liver GSDs (I, III, VI, IX), those with GSD IV do not have hypoglycemia, which is only seen when there is overt liver cirrhosis. Liver transplantation has been performed for patients with progressive liver disease, but patients must be carefully selected as this is a multisystem disease, and in some patients, extrahepatic involvement may manifest after transplant. The long-term success of liver transplantation is unknown. Individuals with significant diffuse reticuloendothelial involvement may have greater risk for morbidity and mortality, which may impact the success rate for liver transplant.

Type VI Glycogen Storage Disease (Liver Phosphorylase Deficiency, Hers Disease)

Type VI GSD is caused by deficiency of **liver glycogen phosphorylase** .

Relatively few patients are documented, likely because of underreporting of this disease. Patients usually present with hepatomegaly and growth retardation in early childhood. Hypoglycemia, hyperlipidemia, and hyperketosis are of variable severity. Ketotic hypoglycemia may present after overnight or prolonged fasting. Lactic acid and uric acid levels are normal. Type VI GSD presents within a broad spectrum of involvement, some with a more severe clinical presentation. Patients with severe hepatomegaly, recurrent severe hypoglycemia, hyperketosis, and postprandial lactic acidosis have been reported. Focal nodular hyperplasia of liver and hepatocellular adenoma with malignant transformation into carcinoma is reported in some patients. While cardiac muscle was thought to be unaffected, recently mild cardiomyopathy has been reported in a patient with GSD VI.

Treatment is symptomatic and aims to prevent hypoglycemia while ensuring adequate nutrition. A high-carbohydrate, high-protein diet and frequent feeding are effective in preventing hypoglycemia. Blood glucose and ketones should be monitored routinely, especially during periods of increased activity/illness. Long-term follow-up of these patients is needed to expand the understanding of the natural history of this disorder.

GSD VI is an autosomal recessive disease. **Diagnosis** can be confirmed through molecular testing of the liver phosphorylase gene *(PYGL),* which is found on chromosome 14q21-22 and has 20 exons. Many pathogenic variants are known in this gene; a splice-site variant in intron 13 has been identified in the Mennonite population. A liver biopsy showing elevated glycogen content and decreased hepatic phosphorylase enzyme activity can also be used to make a diagnosis. However, with the availability of DNA analysis and next-generation sequencing panels, liver biopsies are considered unnecessary.

Type IX Glycogen Storage Disease (Phosphorylase Kinase Deficiency)

Type IX GSD represents a heterogeneous group of glycogenoses. It results from deficiency of the enzyme **phosphorylase kinase** (PhK), which is involved in the rate-limiting step of glycogenolysis. This enzyme has 4 subunits (α, β, γ, δ), each encoded by different genes on different chromosomes and differentially expressed in various tissues. Pathogenic variants in the *PHKA1* gene cause muscle PhK deficiency; pathogenic variants in the *PHKA2* and *PHKG2* genes cause liver PhK deficiency; pathogenic variants in the *PHKB* gene cause PhK deficiency in liver and muscle. Pathogenic variants in the *PHKG1* gene have not been identified. Defects in subunits α, β, and γ are responsible for liver presentation.

Clinical manifestations of liver PhK deficiency are usually recognizable within the 1st 2 yr of life and include short stature and abdominal distention from moderate to marked hepatomegaly. The clinical severity of liver PhK deficiency varies considerably. Hyperketotic hypoglycemia, if present, can be mild but may be severe in some cases. Ketosis may occur even when glucose levels are normal. Some children may have mild delays in gross motor development and hypotonia. It is becoming increasingly clear that GSD IX is not a benign condition. Severe phenotypes are reported, with liver fibrosis progressing to cirrhosis and HCC, particularly in patients with *PHKG2* variants. Progressive splenomegaly and portal hypertension are reported secondary to cirrhosis. Mild cardiomyopathy has been reported in a patient with GSD IX *(PHKB variant).* Cognitive and speech delays have been reported in a few individuals, but it is not clear whether these delays are caused by PhK deficiency or coincidental. Renal tubular acidosis has been reported in rare cases. Unlike in GSD I, lactic acidosis, bleeding tendency, and loose bowel movements are not characteristic. Although growth is retarded during childhood, normal height and complete sexual development are eventually achieved. As with debrancher deficiency, abdominal distention and hepatomegaly usually decrease with age and may disappear by adolescence. Most adults with liver PhK deficiency are asymptomatic, although further long-term studies are needed to fully assess the impact of this disorder in adults.

Phenotypic variability within each subtype is being uncovered with the availability of molecular testing. The incidence of all subtypes of PhK deficiency is approximately 1 : 100,000 live births.

X-Linked Liver Phosphorylase Kinase Deficiency (From *PHKA2* Variants)

X-linked liver PhK deficiency is one of the most common forms of liver glycogenosis in males. In addition to liver, enzyme activity can also be deficient in erythrocytes, leukocytes, and fibroblasts; it is normal in muscle. Typically, a 1-5 yr old boy presents with growth retardation, an incidental finding of hepatomegaly, and a slight delay in motor development. Cholesterol, triglycerides, and liver enzymes are mildly elevated. Ketosis may occur after fasting. Lactate and uric acid levels are normal. Hypoglycemia is typically mild, if present, but can be severe. The response in blood glucose to glucagon is normal. Hepatomegaly and abnormal blood chemistries gradually improve and can normalize with age. Most adults achieve a normal final height and are usually asymptomatic despite a persistent PhK deficiency. It is increasingly being recognized that this disorder is not benign as previously thought, and there are patients with severe disease and long-term hepatic sequelae. In rare cases, liver fibrosis can occur and progress to cirrhosis.

Liver histology shows glycogen-distended hepatocytes, steatosis, and potentially mild periportal fibrosis. The accumulated glycogen (β particles, rosette form) has a frayed or burst appearance and is less compact than the glycogen seen in type I or III GSD. Fibrous septal formation and low-grade inflammatory changes may be seen.

The gene for the common liver isoform of the PhK α subunit, *PHKA2,* is located on the X chromosome (αL at Xp22.2). Mutations in the *PHKA2* gene account for 75% of all PhK cases. X-linked liver PhK deficiency is further subdivided into 2 biochemical subtypes: XLG1, with measurable deficiency of PhK activity in both blood cells and liver, and XLG2, with normal in vitro PhK activity in blood cells and variable activity in liver. It is suspected that XLG2 may be caused by missense variants that affect enzyme regulation, whereas nonsense variants affecting the amount of protein result in XLG1. Female carriers are unaffected.

Autosomal Liver and Muscle Phosphorylase Kinase Deficiency (From *PHKB* Variants)

PhK deficiency in liver and blood cells with an autosomal recessive mode of inheritance has been reported. Similar to the X-linked form, chief symptoms in early childhood include hepatomegaly and growth retardation. Some patients also exhibit muscle hypotonia. In a few cases where enzyme activity has been measured, reduced PhK activity has been demonstrated in muscle. Mutations are found in *PHKB* (chromosome 16q12-q13), which encodes the β subunit, and result in liver and muscle PhK deficiency. Several nonsense variants, a single-base insertion, a splice-site mutation, and a large intragenic mutation have been identified. In addition, a missense variant was discovered in an atypical patient with normal blood cell PhK activity.

Autosomal Liver Phosphorylase Kinase Deficiency (From *PHKG2* Variants)

This form of PhK deficiency is caused by pathogenic variants in the testis/liver isoform (TL) of the γ subunit gene *(PHKG2)*. In contrast to X-linked PhK deficiency, patients with variants in *PHKG2* typically have more severe phenotypes, with recurrent hypoglycemia, prominent hepatomegaly, significant liver fibrosis, and progressive cirrhosis. Liver involvement may present with cholestasis, bile duct proliferation, esophageal varices, and splenomegaly. Other reported presentations include delayed motor milestones, muscle weakness, and renal tubular damage. The spectrum of involvement continues to evolve as more cases are recognized. *PHKG2* maps to chromosome 16p12.1-p11.2; many pathogenic variants are known for this gene.

Phosphorylase Kinase Deficiency Limited to Heart

These patients have been reported with **cardiomyopathy** in infancy and rapidly progress to heart failure and death. Recent studies have shown that this is not a case of cardiac-specific primary PhK deficiency as suspected previously, but rather linked to the γ_2 subunit of adenosine monophosphate (AMP)–activated protein kinase (see later). The γ_2 subunit is encoded by the *PRKAG2* gene.

Diagnosis

PhK deficiency may be diagnosed by demonstration of the enzymatic defect in affected tissues. PhK can be measured in leukocytes and erythrocytes, but because the enzyme has many isozymes, the diagnosis can be easily missed without studies of liver, muscle, or heart. Individuals with liver PhK deficiency also usually have elevated transaminases, mildly elevated triglycerides and cholesterol, normal uric acid and lactic acid concentrations, and normal glucagon responses. Gene sequencing is used for diagnostic confirmation and subtyping of GSD IX.

The *PHKA2* gene encoding the α subunit is most frequently involved, followed by the *PHKB* gene encoding the β subunit. Variants in the *PHKG2* gene underlying γ-subunit deficiency are typically associated with severe liver involvement with recurrent hypoglycemia and liver fibrosis.

Treatment and Prognosis

The treatment for liver PhK deficiency is symptomatic. It includes a diet high in complex carbohydrates and proteins and small, frequent feedings to prevent hypoglycemia. Cornstarch can be administered with symptom-dependent dosage and timing (0.6-2.5 g/kg every 6 hr). Oral intake of glucose, if tolerated, should be used to treat hypoglycemia. If not, IV glucose should be given.

Prognosis for the X-linked and certain autosomal forms is typically good; however, long term complications are being recognized. Patients with mutations in the γ subunit typically have a more severe clinical course with progressive liver disease. Liver involvement needs to be monitored in all patients with GSD IX by periodic imaging (abdominal ultrasound or MRI every 6-12 mo) and serial hepatic function tests.

Liver Glycogen Synthase Deficiency

Liver glycogen synthase deficiency type 0 (**GSD 0**) is caused by deficiency of **hepatic glycogen synthase** (GYS2) activity, leading to a marked decrease of glycogen stored in the liver. The gene *GYS2* is located at 12p12.2. Several pathogenic variants have been identified in patients with GSD 0. The disease appears to be rare in humans, and in the true sense, this is not a type of GSD because the deficiency of the enzyme leads to decreased glycogen stores. Patients present in infancy with early-morning (prebreakfast) drowsiness, pallor, emesis, and fatigue and sometimes convulsions associated with hypoglycemia and hyperketonemia. Blood lactate and alanine levels are low, and there is no hyperlipidemia or hepatomegaly. Prolonged *hyperglycemia* , glycosuria, lactic acidosis, and hyperalaninemia, with normal insulin levels after administration of glucose or a meal, suggest a deficiency of glycogen synthase. Definitive diagnosis may be by a liver biopsy to measure the enzyme activity or identification of pathogenic variants in *GYS2* .

Treatment consists of frequent meals, rich in protein and nighttime supplementation with uncooked cornstarch to prevent hypoglycemia and hyperketonemia. Most children with GSD 0 are cognitively and developmentally normal. Short stature and osteopenia are common features. The **prognosis** seems good for patients who survive to adulthood, including resolution of hypoglycemia, except during pregnancy.

Hepatic Glycogenosis With Renal Fanconi Syndrome (Fanconi-Bickel Syndrome)

Fanconi-Bickel Syndrome is a rare autosomal recessive disorder is caused by defects in the facilitative glucose transporter 2 (GLUT-2), which transports glucose in and out of hepatocytes, pancreatic β cells, and the basolateral membranes of intestinal and renal epithelial cells. The disease is characterized by proximal renal tubular dysfunction, impaired glucose and galactose utilization, and accumulation of glycogen in liver and kidney.

The affected child typically presents in the 1st yr of life with failure to thrive, rickets, and a protuberant abdomen from hepatomegaly and nephromegaly. The disease may be confused with GSD I because a Fanconi-like syndrome can also develop in type I patients. Adults typically present with short stature, dwarfism, and excess fat in the abdomen and shoulders. Patients are more susceptible to fractures because of early-onset generalized osteopenia. In addition, intestinal malabsorption and diarrhea may occur.

Laboratory findings include glucosuria, phosphaturia, generalized aminoaciduria, bicarbonate wasting, hypophosphatemia, increased serum alkaline phosphatase levels, and radiologic findings of rickets. Mild fasting hypoglycemia and hyperlipidemia may be present. Liver transaminase, plasma lactate, and uric acid levels are usually normal. Oral galactose or glucose tolerance tests show intolerance, which could be explained by the functional loss of GLUT-2 preventing liver uptake of these sugars. Tissue biopsy results show marked accumulation of glycogen in hepatocytes and proximal renal tubular cells, presumably from the altered glucose transport out of these organs. Diffuse glomerular mesangial expansion along with glomerular hyperfiltration and microalbuminuria similar to nephropathy in GSD Ia and diabetes have been reported.

This condition is rare, and 70% of patients with Fanconi-Bickel syndrome have consanguineous parents. Most patients have homozygous pathogenic variants; some patients are compound heterozygotes. The majority of variants detected thus far predict a premature termination of translation. The resulting loss of the C-terminal end of the GLUT-2 protein predicts a nonfunctioning glucose transporter with an inward-facing substrate-binding site.

There is no specific treatment. Symptom-dependent treatment with phosphate and bicarbonate can result in growth improvement. Growth may also improve with symptomatic replacement of water, electrolytes, and vitamin D; restriction of galactose intake; and a diet similar to that used for diabetes mellitus, with small, frequent meals and adequate caloric intake.

Muscle Glycogenoses

The role of glycogen in muscle is to provide substrates for the generation of ATP for muscle contraction. The muscle GSDs are broadly divided into 2 groups. The first group is characterized by hypertrophic cardiomyopathy, progressive skeletal muscle weakness and atrophy, or both, and includes deficiencies of **acid α-glucosidase** , a lysosomal glycogen-degrading enzyme (**type II** GSD), lysosomal-associated membrane protein 2 (**LAMP2**), and AMP-activated protein kinase γ_2 (**PRKAG2**). The 2nd group comprises muscle energy disorders characterized by muscle pain, exercise intolerance, myoglobinuria, and susceptibility to fatigue. This group includes myophosphorylase deficiency (McArdle disease, **type V** GSD) and deficiencies of phosphofructokinase (**type VII**), phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, and muscle-specific phosphorylase kinase. Some of these latter enzyme deficiencies can also be associated with *compensated hemolysis* , suggesting a more generalized defect in glucose metabolism.

Type II Glycogen Storage Disease (Lysosomal Acid α-1,4-Glucosidase Deficiency, Pompe Disease)

Pompe disease, also referred to as GSD type II or **acid maltase deficiency** , is caused by a deficiency of acid α-1,4-glucosidase (acid maltase), an enzyme responsible for the degradation of glycogen in lysosomes. This enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, predominantly affecting cardiac, skeletal, and smooth muscle cells. In Pompe disease, glycogen typically accumulates within lysosomes, as opposed to its accumulation in cytoplasm in the other glycogenoses. However, as the disease progresses, lysosomal rupture and leakage lead to the presence of cytoplasmic glycogen as well.

Pompe disease is an autosomal recessive disorder. The incidence was thought to be approximately 1 in 40,000 live births in Caucasians and 1 in 18,000 live births in Han Chinese. Newborn screening for Pompe disease in the United States suggests that the prevalence is much higher than previously thought (between 1 in 9,132 and 1 in 24,188). The gene for acid α-glucosidase *(GAA)* is on chromosome 17q25.2. More than 500 pathogenic variants have been identified that could be helpful in delineating the phenotypes. A splice-site variant (IVS1-13T → G; c.-32-13T>G) is commonly seen in late-onset Caucasian

patients.

Clinical Manifestations

Pompe disease is broadly classified into infantile and late-onset forms. **Infantile Pompe disease** (IPD) is uniformly lethal without enzyme replacement therapy (ERT) with *alglucosidase alfa.* Affected infants present in the 1st day to weeks of life with hypotonia, generalized muscle weakness with a *floppy infant* appearance, neuropathic bulbar weakness, feeding difficulties, macroglossia, hepatomegaly, and hypertrophic cardiomyopathy, which if untreated leads to death from cardiorespiratory failure or respiratory infection, usually by 1 yr of age.

Late-onset Pompe disease (LOPD; juvenile-, childhood-, and adult-onset disease) is characterized by proximal limb girdle muscle weakness and early involvement of respiratory muscles, especially the diaphragm. Cardiac involvement ranges from cardiac rhythm disturbances to cardiomyopathy and a less severe, short-term prognosis. Symptoms related to progressive dysfunction of skeletal muscles can start as early as within 1 yr of age to as late as the 6th decade of life. The clinical picture is dominated by slowly progressive proximal muscle weakness with truncal involvement and greater involvement of the lower limbs than the upper limbs. The pelvic girdle, paraspinal muscles, and diaphragm are the muscle groups most seriously affected in patients with LOPD. Other symptoms may include lingual weakness, ptosis, and dilation of blood vessels (e.g., basilar artery, ascending aorta). With disease progression, patients become confined to a wheelchair and require artificial ventilation. The initial symptoms in some patients may be respiratory insufficiency manifested by somnolence, morning headache, orthopnea, and exertional dyspnea, which eventually lead to sleep-disordered breathing and respiratory failure. Respiratory failure is the cause of significant morbidity and mortality in LOPD. Basilar artery aneurysms with rupture also contribute to mortality in some cases. Small-fiber neuropathy presenting as painful paresthesia has been identified in some LOPD patients. Gastrointestinal disturbances such as postprandial bloating, dysphagia, early satiety, diarrhea, chronic constipation, and irritable bowel disease have been reported. Genitourinary tract involvement is not uncommon and may present as bladder and bowel incontinence, weak urine stream or dribbling. If untreated, the age of death varies from early childhood to late adulthood, depending on the rate of disease progression and the extent of respiratory muscle involvement. With the advent of ERT, a new natural history is emerging for both survivors of infantile and LOPD.

Laboratory Findings

These include elevated levels of serum creatine kinase (CK), aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH). Urine glucose tetrasaccharide, a glycogen breakdown metabolite, is a reliable biomarker for disease severity and treatment response. In the infantile form a chest x-ray film showing massive cardiomegaly is frequently the first symptom detected. **Electrocardiographic findings** include a high-voltage QRS complex, Wolff-Parkinson-White (WPW) syndrome, and a shortened PR interval. Echocardiography reveals thickening of both ventricles and/or the intraventricular septum and/or left ventricular outflow tract obstruction. Muscle biopsy shows the presence of vacuoles that stain positively for glycogen; acid phosphatase is increased, presumably from a compensatory increase of lysosomal enzymes. EM reveals glycogen accumulation within a membranous sac and in the cytoplasm. Electromyography reveals myopathic features with excessive electrical irritability of muscle fibers and pseudomyotonic discharges. Serum CK is not always elevated in adult patients. Depending on the muscle sampled or tested, the muscle histologic appearance and electromyography may not be abnormal.

Some patients with infantile Pompe disease who had peripheral nerve biopsies demonstrated glycogen accumulation in the neurons and Schwann cells.

Diagnosis

Diagnosis of Pompe disease can be made by enzyme assay in dried blood spots, leukocytes, blood mononuclear cells, muscle, or cultured skin fibroblasts demonstrating deficient acid α-glucosidase activity. Gene sequencing showing 2 pathogenic variants in the *GAA* gene is confirmatory. The enzyme assay should be done in a laboratory with experience using maltose, glycogen, or 4-methylumbelliferyl-α-ᴅ -glucopyranoside (4MUG) as a substrate. The infantile form has a more severe enzyme deficiency than the late-onset forms. Detection of percent residual enzyme activity is captured in skin fibroblasts and muscle. Blood-based assays, especially dried blood spots, have the advantage of a rapid turnaround time and are being increasingly used as the first-line tissue to make a diagnosis. A muscle biopsy is often done with suspected muscle disease and a broad differential; it yields faster results and provides additional information about glycogen content and site of glycogen storage within and outside the lysosomes of muscle cells. However, a normal muscle biopsy *does not* exclude a diagnosis of Pompe disease. Late-onset patients show variability in glycogen accumulation in different muscles and within muscle fibers; muscle histology and glycogen content can vary depending on the site of muscle biopsy. There is also a high risk from anesthesia in infantile patients. An electrocardiogram can be helpful in making the diagnosis in suspected cases of the infantile form and should be done for patients suspected of having Pompe disease before any procedure requiring anesthesia, including muscle biopsy, is performed. Urinary glucose tetrasaccharides can be elevated in the urine of affected patients, and levels are extremely high in infantile patients. Availability of next-generation sequencing panels and whole exome sequencing allows for identification of additional patients with Pompe disease, especially when the diagnosis is ambiguous. **Prenatal diagnosis** using amniocytes or chorionic villi is available.

Treatment

Enzyme replacement therapy with recombinant human acid α-glucosidase (alglucosidase alfa) is available for treatment of Pompe disease. Recombinant acid α-glucosidase is capable of preventing deterioration or reversing abnormal cardiac and skeletal muscle functions (Fig. 105.3). ERT should be initiated as soon as possible across the disease spectrum, especially for babies with the infantile form, because the disease is rapidly progressive. Infants who are negative for cross-reacting immunologic material (CRIM) develop a high-titer antibody against the infused enzyme and respond to the ERT less favorably. Treatment using immunomodulating agents such as methotrexate, rituximab, and intravenous immune globulin (IVIG) have demonstrated efficacy in preventing the development of an immune response to ERT and immune tolerance. Nocturnal ventilatory support, when indicated, should be used; it has been shown to improve the quality of life and is particularly beneficial during a period of respiratory decompensation.

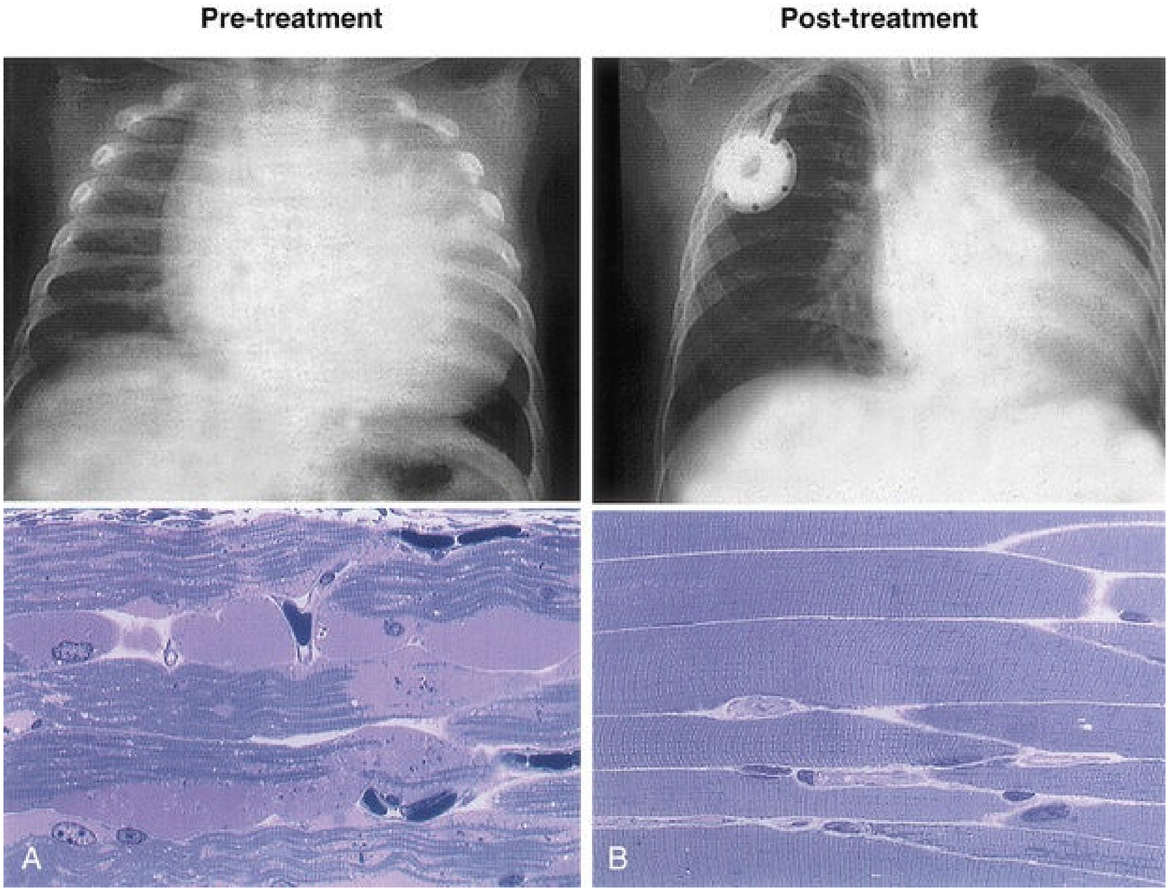

FIG. 105.3 Chest radiograph and muscle histology findings of an infantile-onset Pompe disease patient before (**A**) and after (**B**) enzyme replacement therapy. Note the decrease in heart size and muscle glycogen with the therapy. (Modified from Amalfitano A, Bengur AR, Morse RP, et al: Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial, *Genet Med* 3:132–138, 2001.)

In addition to ERT, other adjunctive therapies have demonstrated benefit in Pompe patients. For patients with the late-onset disease, a high-protein diet may be beneficial. Respiratory muscle strength training has demonstrated improvements in respiratory parameters when combined with ERT. Submaximal exercise regimens are of assistance to improve muscle strength, pain, and fatigue. Other approaches are under clinical development to improve the safety and efficacy of enzyme delivery to affected tissues. These include use of chaperone molecules to enhance rhGAA delivery, and neoGAA, which is a second-generation ERT with a high number of mannose-6-phosphate (M6P) tags that enhances M6P receptor targeting and enzyme uptake. Gene therapy studies to correct the endogenous enzyme production pathways have shown promise.

Early diagnosis and treatment are necessary for optimal outcomes. Newborn screening using blood-based assays in Taiwan has resulted in early identification of Pompe cases and thus improved disease outcomes through the early initiation of ERT.

Glycogen Storage Diseases Mimicking Hypertrophic Cardiomyopathy (Danon Disease)

Danon disease is caused by pathogenic variants in the *LAMP2* gene, which leads to a deficiency of **lysosomal-associated membrane protein 2** (LAMP2). This leads to accumulation of glycogen in the heart and skeletal muscle, which presents primarily with hypertrophic cardiomyopathy and skeletal muscle weakness. Danon disease can be distinguished from the usual causes of hypertrophic cardiomyopathy (defects in sarcomere-protein genes) by their electrophysiologic abnormalities, particularly ventricular preexcitation and conduction defects. Patients present with cardiac symptoms, including chest pain, palpitations, syncope, and cardiac arrest, usually between ages 8 and 15 yr. Other clinical manifestations in Danon disease include peripheral pigmentary retinopathy, lens changes, and abnormal electroretinograms. This disorder is inherited in an X-linked dominant pattern. Diagnosis can be done by genetic testing for the *LAMP2* gene. The prognosis for LAMP2 deficiency is poor, with progressive end-stage heart failure early in adulthood. **Treatment** is directed toward management of symptoms in affected individuals, including management of cardiomyopathy, correction of arrhythmias, and physical therapy for muscle weakness. Cardiac transplantation has been tried successfully in some patients.

Adenosine Monophosphate–Activated Protein Kinase γ_2 Deficiency (PRKAG2 Deficiency)

AMP-activated protein kinase γ_2 (PRKAG2) deficiency is caused by pathogenic variants in the *PRKAG2* gene mapped to chromosome 7q36. *PRKAG2* is required for the synthesis of the enzyme AMP-activated protein kinase (AMPK), which regulates cellular pathways involved in ATP metabolism. Common presentations include hypertrophic cardiomyopathy and electrophysiologic abnormalities such as WPW syndrome, atrial fibrillation, and progressive atrioventricular block. Cardiac involvement is variable and includes supraventricular tachycardia, sinus bradycardia, left ventricular dysfunction, and even sudden cardiac death in some cases. In addition to cardiac involvement, there is a broad spectrum of phenotypic presentations including myalgia, myopathy, and seizures. Cardiomyopathy caused by *PRKAG2* variants usually allows for long-term survival, although a rare congenital form presenting in early infancy is associated with a rapidly fatal course. Cardiomyopathy in PRKAG2 syndrome often mimics that in other conditions, especially Pompe disease, and should be considered as a differential diagnosis in infants presenting with severe hypertrophic cardiomyopathy. **Treatment** is primarily symptomatic, including management of cardiac failure and correction of conduction defects.

Muscle Glycogen Synthase Deficiency

This GSD results from muscle glycogen synthase (**glycogen synthase I** , GYS1) deficiency. The gene GYS1 has been localized to chromosome 19q13.3. In the true sense, this is not a type of GSD because the deficiency of the enzyme leads to decreased glycogen stores. The disease is extremely rare and has been reported in 3 children of consanguineous parents of Syrian origin. Muscle biopsies showed lack of glycogen, predominantly oxidative fibers, and mitochondrial proliferation. Glucose tolerance was normal. Molecular study revealed a homozygous stop mutation (R462→ter) in the muscle glycogen synthase gene. The phenotype was variable in the 3 siblings and ranged from sudden cardiac arrest, muscle fatigability, hypertrophic cardiomyopathy, an abnormal heart rate, and hypotension while exercising, to mildly impaired cardiac function at rest.

Late-Onset Polyglucosan Body Myopathy (From *GYG1* Variants)

Late-onset polyglucosan body myopathy is an autosomal recessive, slowly progressive skeletal myopathy caused by pathogenic variants in the *GYG1* gene blocking **glycogenin-1** biosynthesis. There is a reduced or complete absence of glyogenin-1, which is a precursor necessary for glycogen formation. Polyglucosan accumulation in skeletal muscles causes adult-onset proximal muscle weakness, prominently affecting hip and shoulder girdles. Cardiac involvement is not seen. Compared with GSD IV–APBD, nervous system involvement is uncommon, although polyglucosan deposition is seen in both disorders. *GYG1* is mapped to chromosome 3q24. Muscle biopsies show PAS-positive storage material in 30–40% of muscle fibers. EM reveals the typical polyglucosan structure, consisting of ovoid form composed of partly filamentous material.

Type V Glycogen Storage Disease (Muscle Phosphorylase Deficiency, McArdle Disease)

GSD type V is caused by deficiency of **myophosphorylase** activity. Lack of this enzyme limits muscle ATP generation by glycogenolysis, resulting in muscle glycogen accumulation, and is the prototype of muscle energy disorders. A deficiency of myophosphorylase impairs the cleavage of glucosyl molecules from the straight chain of glycogen.

Clinical Manifestations

Symptoms usually first develop in late childhood or in the 2nd decade of life. Clinical heterogeneity is uncommon, but cases suggesting otherwise have been documented. Studies have shown that McArdle disease can manifest in individuals as old as 74, as well as in infancy in a fatal, early-onset form characterized by hypotonia, generalized muscle weakness, and respiratory complication. Symptoms are generally characterized by exercise intolerance with muscle cramps and pain. Symptoms are precipitated by 2 types of activity: brief, high-intensity exercise, such as sprinting or carrying heavy loads, and less intense but sustained activity, such as climbing stairs or walking uphill. Most patients can perform moderate exercise, such as walking on level ground, for long periods. Many patients experience a characteristic “second wind” phenomenon, with relief of muscle pain and fatigue after a brief period of rest. As a result of the underlying myopathy, these patients may be at risk for statin-induced myopathy and rhabdomyolysis. While patients typically experience episodic muscle pain and cramping from exercise, 35% of patients with McArdle disease report permanent pain that has a serious impact on sleep and other activities. Studies also suggest that there may also be a link between GSD V and variable cognitive impairment.

Approximately 50% of patients report burgundy-colored urine after exercise as a result of exercise-induced **myoglobinuria** secondary to **rhabdomyolysis** . Excessive myoglobinuria after intense exercise may precipitate acute renal failure.

Lab findings show elevated levels of serum CK at rest, which further increases after exercise. Exercise also elevates the levels of blood ammonia, inosine, hypoxanthine, and uric acid, which may be attributed to accelerated recycling of muscle purine nucleotides caused by insufficient ATP production. Type V GSD is an autosomal recessive disorder. The gene for muscle phosphorylase *(PYGM)* has been mapped to chromosome 11q13.

Diagnosis

The standard diagnosis for GSD V includes a muscle biopsy to measure glycogen content as well as enzyme and sequencing of *PYGM* . An ischemic exercise test offers a rapid diagnostic screening for patients with a metabolic myopathy. Lack of an increase in blood lactate levels and exaggerated blood ammonia elevations indicate muscle glycogenosis and suggest a defect in the conversion of muscle glycogen or glucose to lactate. The abnormal ischemic exercise response is *not limited* to type V GSD. Other muscle defects in glycogenolysis or glycolysis produce similar results (deficiencies of muscle phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, or LDH). An ischemic exercise test was once used to be a rapid diagnostic screening for suspected patients but was associated with severe complications and false-positive results. A nonischemic forearm exercise test with high sensitivity that is easy to perform and cost-effective has been determined to be indicative of muscle glycogenosis. However, as with the ischemic test, it cannot differentiate between abnormal exercise responses due to type V disease versus other defects in glycogenolysis or glycolysis or debranching enzyme (noted when the test is done after fasting).

The diagnosis is confirmed by molecular genetic testing of PYGM. A common nonsense variant, p.R49X in exon 1, is found in 90% of Caucasian patients, and a deletion of a single codon in exon 17 is found in 61% of Japanese patients. The p.R49X variant represents 55% of alleles in Spanish patients, whereas the p.W797R variant represents 14% and the p.G204S 9% of pathogenic alleles in the Spanish population. There seems to be an association between clinical severity of GSD V and presence of the D allele of the ACE insertion/deletion polymorphism. This may help explain the spectrum of phenotypic variability manifested in this disorder.

Treatment

Avoidance of strenuous exercise prevents the symptoms; regular and moderate exercise is recommended to improve exercise capacity. Glucose or sucrose given before exercise or injection of glucagon can greatly improve tolerance in these patients. A high-protein diet may increase muscle endurance, and low-dose creatine supplement has been shown to improve muscle function in some patients. The clinical response to creatine is dose dependent; muscle pain may increase on high doses of creatine supplementation. Vitamin B_6 supplementation reduces exercise intolerance and muscle cramps. Longevity is not generally affected.

Type VII Glycogen Storage Disease (Muscle Phosphofructokinase Deficiency, Tarui Disease)

Type VII GSD is caused by pathogenic variants in the *PFKM* gene, located on chromosome 12q13.1, which results in a deficiency of **muscle phosphofructokinase** enzyme. This enzyme is a key regulatory enzyme of glycolysis and is necessary for the ATP-dependent conversion of fructose-6-phosphate to fructose-1,6-diphosphate. Phosphofructokinase is composed of 3 isoenzyme subunits according to the tissue type and are encoded by different genes: (*PFKM* [M: muscle], *PFKL* [L: liver], and *PFKP* [P: platelet]). Skeletal muscle has only the M subunit, whereas red blood cells (RBCs) express a hybrid of L and M forms. In type VII GSD the M isoenzyme is defective, resulting in complete deficiency of enzyme activity in muscle and a partial deficiency in RBCs.

Type VII GSD is an autosomal recessive disorder with increased prevalence in individuals of Japanese ancestry and Ashkenazi Jews. A splicing defect and a nucleotide deletion in *PFKM* account for 95% of pathogenic variants in Ashkenazi Jews. Diagnosis based on molecular testing for the common variants is thus possible in this population.

Clinical Manifestations

Although the clinical picture is similar to that of type V GSD, the following features of type VII GSD are distinctive:

1. Exercise intolerance, which usually commences in childhood, is more severe than in type V disease and may be associated with nausea,

vomiting, and severe muscle pain; vigorous exercise causes severe muscle cramps and myoglobinuria.

2. Compensatory hemolysis occurs, as indicated by an increased level of serum bilirubin and an elevated reticulocyte count.
3. Hyperuricemia is common and exaggerated by muscle exercise to a greater degree than that observed in type V or III GSD.
4. An abnormal polysaccharide is present in muscle fibers; it is PAS positive but resistant to diastase digestion.
5. Exercise intolerance is especially worse after carbohydrate-rich meals because the ingested glucose prevents lipolysis, thereby depriving muscle of fatty acid and ketone substrates. This is in contrast to patients with type V disease, who can metabolize blood borne glucose derived from either endogenous liver glycogenolysis or exogenous glucose; indeed, glucose infusion improves exercise tolerance in type V patients.
6. The “second wind” phenomenon is absent because of the inability to break down blood glucose.

Several rare type VII variants occur. One variant presents in infancy with hypotonia and limb weakness and proceeds to a rapidly progressive myopathy that leads to death by 4 yr of age. A 2nd variant occurs in infancy and results in congenital myopathy and arthrogryposis with a fatal outcome. A 3rd variant presents in infancy with hypotonia, mild developmental delay, and seizures. An additional presentation is *hereditary nonspherocytic hemolytic anemia* . Although these patients do not experience muscle symptoms, it remains unclear whether these symptoms will develop later in life. One variant presents in adults and is characterized by a slowly progressive, fixed muscle weakness rather than cramps and myoglobinuria. It may also cause mitral valve thickening from glycogen buildup.

Diagnosis

To establish a diagnosis, a biochemical or histochemical demonstration of the enzymatic defect in the muscle is required. The absence of the M isoenzyme of phosphofructokinase can also be demonstrated in muscle, blood cells, and fibroblasts. Gene sequencing can identify pathogenic variants for the phosphofructokinase gene.

Treatment

There is no specific treatment. Strenuous exercise should be avoided to prevent acute episodes of muscle cramps and myoglobinuria. Consuming simple carbohydrates before strenuous exercise may benefit by improving exercise tolerance. A ketogenic diet has been reported to show clinical improvement in a patient with infantile GSD VII. Drugs such as statins should be avoided. Precautionary measures should be taken to avoid hyperthermia while undergoing anesthesia. Carbohydrate meals and glucose infusions have demonstrated worsening symptoms because of the body's inability to utilize glucose. The administered glucose tends to lower the levels of fatty acids in the blood, a primary source of muscle fuel.

Muscle-Specific Phosphorylase Kinase Deficiency (From *PHKA1* Variants)

A few cases of PhK deficiency restricted to muscle are known. Patients, both male and female, present either with muscle cramps and myoglobinuria with exercise or with progressive muscle weakness and atrophy. PhK activity is decreased in muscle but normal in liver and blood cells. There is no hepatomegaly or cardiomegaly. This is inherited in an X-linked or autosomal recessive manner. The gene for the muscle-specific form α subunit (αM) is located at Xq12. Pathogenic variants of the gene have been found in some male patients with this disorder. The gene for muscle γ subunit (γM, *PHKG1*) is on chromosome 7p12. No pathogenic variants in this gene have been reported so far.

Other Muscle Glycogenoses With Muscle Energy Impairment

Six additional defects in enzymes—phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, fructose-1,6-bisphosphate aldolase A, muscle pyruvate kinase, and β-enolase in the pathway of the terminal glycolysis—cause symptoms and signs of muscle energy impairment similar to those of types V and VII GSD. The failure of blood lactate to increase in response to exercise is a useful diagnostic test and can be used to differentiate muscle glycogenoses from disorders of lipid metabolism, such as carnitine palmitoyltransferase II deficiency and very-long-chain acyl-CoA dehydrogenase deficiency, which also cause muscle cramps and myoglobinuria. Muscle glycogen levels can be normal in the disorders affecting terminal glycolysis, and assaying the muscle enzyme activity is needed to make a definitive diagnosis. There is no specific treatment (see preceding Treatment section).

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105.2

Defects in Galactose Metabolism

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Keywords

galactose
lactose
galactosemia
transferase

galactokinase
epimerase
reducing substance

Milk and dairy products contain **lactose** , the major dietary source of galactose. The metabolism of galactose produces fuel for cellular metabolism through its conversion to glucose-1-phosphate (see Table 105.1). Galactose also plays an important role in the formation of galactosides, which include glycoproteins, glycolipids, and glycosaminoglycans. **Galactosemia** denotes the elevated level of galactose in the blood and is found in 3 distinct inborn errors of galactose metabolism in 1 of the following enzymes: galactose-1-phosphate uridyl transferase, galactokinase, and uridine diphosphate galactose-4-epimerase. The term galactosemia, although adequate for the deficiencies in any of these disorders, generally designates the *transferase* deficiency.

Galactose-1-Phosphate Uridyl Transferase Deficiency Galactosemia

Two forms of the deficiency exist: infants with complete or near-complete deficiency of the enzyme (classic galactosemia) and those with partial transferase deficiency. **Classic galactosemia** is a serious disease with onset of symptoms typically by the 2nd half of the 1st wk of life. The incidence is predicted to be 1 in 60,000 live births. The newborn infant receives high amounts of lactose (up to 40% in breast milk and certain formulas), which consists of equal parts of glucose and galactose. Without the transferase enzyme, the infant is unable to metabolize galactose-1-phosphate, the accumulation of which results in injury to kidney, liver, and brain. This injury may begin prenatally in the affected fetus by transplacental galactose derived from the diet of the heterozygous mother or by endogenous production of galactose in the fetus.

Clinical Manifestations

The diagnosis of uridyl transferase deficiency should be considered in newborn or young infants with any of the following features within a few days or weeks after birth: jaundice, hepatomegaly, vomiting, hypoglycemia, seizures, lethargy, irritability, feeding difficulties, poor weight gain or failure to regain birthweight, and aminoaciduria. Untreated children may show nuclear cataracts, vitreous hemorrhage, hepatic failure, cirrhosis, ascites, splenomegaly, or intellectual disability. Patients with galactosemia are at increased risk for *Escherichia coli* neonatal sepsis; the onset of sepsis often precedes the diagnosis of galactosemia. Pseudotumor cerebri can occur and cause a bulging fontanel. Complete withdrawal of lactose from the diet results in improvement of the acute symptoms. If untreated, death from liver and kidney failure and sepsis may follow within days. When the diagnosis is not made at birth, damage to the liver (cirrhosis) and brain (intellectual disability) becomes increasingly severe and irreversible.

Partial transferase deficiency is generally asymptomatic. It is more common than classic galactosemia and is diagnosed in newborn screening because of moderately elevated blood galactose and/or low transferase activity. Galactosemia should be considered for the newborn or young infant who is not thriving or who has any of the preceding findings. Light and electron microscopy of hepatic tissue reveals fatty infiltration, the formation of pseudoacini, and eventual macronodular cirrhosis. These changes are consistent with a metabolic disease but do not indicate the precise enzymatic defect.

Diagnosis

The *initial* diagnosis of galactosemia is done by demonstration of a **reducing substance** in several urine specimens collected while the patient is on a diet containing human milk, cow's milk, or any other formula containing lactose. The reducing substance detected in urine by Clinitest (e.g., glucose, galactose) can be identified by chromatography or an enzymatic test specific for galactose. Galactose can be detected in urine, provided the milk feeding was within the last few hours and the child is not vomiting excessively. Clinistix urine test results are usually negative because the test relies on the action of glucose oxidase, which is specific for glucose but is nonreactive with galactose. Amino acids may be detected in urine since they are excreted together with glucose because of a proximal renal tubular syndrome. Since galactose is injurious to persons with galactosemia, diagnostic challenge tests dependent on administering galactose orally or intravenously should not be used. *Direct enzyme assay using erythrocytes establishes the diagnosis.* The clinician needs to confirm that the patient did not receive a blood transfusion before the collection of the blood sample, because a diagnosis could be missed. A novel method utilizes nonradioactive ultraviolet (UV) light and high-performance liquid chromatography (HPLC) to accurately detect levels of galactose-1-phosphate uridyl transferase in erythrocytes.

Genetics

Transferase deficiency is an autosomal recessive disorder. Based on newborn screening in the United States, the frequency of the disease is approximately 1 in 47,000 live births. There are several enzymatic variants of galactosemia. The *Duarte variant,* a single– amino acid substitution (p.N314D), has diminished RBC enzyme activity (50% of normal), but usually is of no clinical significance. This variant is the most common, with a carrier frequency of 12% in the general population. Those who are heterozygous for the Duarte variant of galactosemia typically have 25% of normal galactose activity, few symptoms, elevated metabolites, and no need for intervention. Other similar variants expressing little enzyme activity typically require no intervention. Some black patients have milder symptoms despite the absence of measurable transferase activity in erythrocytes; these patients retain 10% enzyme activity in liver and intestinal mucosa, whereas most white patients have no detectable activity in any of these tissues. More than 230 identifiable pathogenic variants have been associated with transferase deficiency. In blacks, 62% of alleles are represented by the p.S135L variant, a variant that is responsible for a milder disease course. In the white population, 70% of alleles are represented by the p.Q188R and p.K285N missense variants and are associated with severe disease. Carrier testing and prenatal diagnosis can be performed by direct enzyme analysis of amniocytes or chorionic villi; testing can also be DNA based.

Treatment and Prognosis

With the availability of newborn screening for galactosemia, it is possible to identify and treat patients earlier than before. All galactose-containing foods should be removed from the diet on initial suspicion of galactosemia. Various non–lactose-containing milk substitutes are available (casein hydrolysates, soybean-based formula). Elimination of galactose from the diet along with adequate calcium supplementation reverses growth failure and renal and hepatic dysfunction. Cataracts regress, and most patients have no impairment of vision.

Early diagnosis and treatment have improved the prognosis of galactosemia. On long-term follow-up, however, patients still manifest ovarian failure with primary or secondary amenorrhea, decreased bone mineral density, developmental delay, and learning disabilities that increase in severity with age. *Hypergonadotropic hypogonadism* is reported in 80% to >90% of female patients with classic galactosemia. Although most women with classic galactosemia are infertile when they reach childbearing age, a small number have given birth. Most patients manifest speech disorders, whereas a smaller number demonstrate poor growth and impaired motor function and balance (with or without overt ataxia). The relative control of galactose-1-phosphate levels does not always correlate with long-term outcome, leading to the belief that other factors, such as elevated galactitol, decreased uridine diphosphate galactose (a donor for galactolipids and proteins), and endogenous galactose production may be responsible.

Galactokinase Deficiency

The deficient enzyme is **galactokinase** , which normally catalyzes the phosphorylation of galactose. The principal metabolites accumulated are galactose and galactitol. Two genes are reported to encode galactokinase: *GK1* on chromosome 17q24 and *GK2* on chromosome 15. **Cataracts** are usually the sole manifestation of galactokinase deficiency; pseudotumor cerebri is a rare complication. The affected infant is otherwise asymptomatic. Heterozygous carriers may be at risk for presenile cataracts. Lab findings show an increased concentration of blood galactose levels, provided the infant has been fed a lactose-containing formula. The diagnosis is made by demonstrating an absence of galactokinase activity in erythrocytes or fibroblasts. Transferase activity is normal. Treatment is dietary restriction of galactose.

Uridine Diphosphate Galactose-4-Epimerase Deficiency

There are 2 distinct forms of **epimerase** deficiency. The first is a **benign** form that is diagnosed incidentally through newborn screening programs. Affected individuals are asymptomatic because the enzyme deficiency is limited to leukocytes and erythrocytes. This form does not require treatment. The second variety is **severe** because the epimerase deficiency is more generalized. Clinical manifestations resemble transferase deficiency, with the additional symptoms of hypotonia and nerve deafness. Clinical symptoms improve with restriction of galactose in diet. Although the severe form of galactosemia is rare, it must be considered in a symptomatic patient with measurable galactose-1-phosphate who has normal transferase activity. The abnormally accumulated metabolites are similar to those in transferase deficiency; however, there is also an increase in cellular uridine diphosphate (UDP) galactose. Diagnosis is confirmed by the assay of epimerase in erythrocytes.

Patients with the severe form of epimerase deficiency cannot synthesize UDP galactose from UDP glucose and are galactose dependent. Because galactose is an essential component of many nervous system structural proteins, patients are placed on a galactose-restricted diet rather than a galactose-free diet.

Infants with the mild form of epimerase deficiency have not required treatment. It is advisable to follow urine specimens for reducing substances and exclude aminoaciduria within a few weeks of diagnosis while the infant is still on lactose-containing formula.

The gene for UDP galactose-4-epimerase *(GALE)* is located on chromosome 1 at 1p36. Carrier detection is possible by measurement of epimerase activity in the erythrocytes. **Prenatal diagnosis** for the severe form of epimerase deficiency can be done using an enzyme assay of cultured amniotic fluid cells.

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105.3

Defects in Fructose Metabolism

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Keywords

fructose
fructosuria
hereditary fructose intolerance
fructokinase
aldolase
hypoglycemia

Two inborn errors are known in the specialized pathway of fructose metabolism: benign or essential fructosuria and hereditary fructose intolerance. Fructose-1,6-bisphosphatase deficiency, although strictly speaking not a defect of the specialized fructose pathway, is discussed in Chapter 105.4 .

Deficiency of Fructokinase (Essential or Benign Fructosuria)

Deficiency of fructokinase is not associated with any clinical manifestations. **Fructosuria** is an accidental finding usually made because the asymptomatic patient's urine contains a reducing substance. No treatment is necessary, and the prognosis is excellent. Inheritance is autosomal recessive with an incidence of 1 in 120,000 live births. The gene encoding fructokinase (*KHK)* is located on chromosome 2p23.3.

Fructokinase catalyzes the first step of metabolism of dietary fructose: conversion of fructose to fructose-1-phosphate (see Fig. 105.1). Without this enzyme, ingested fructose is not metabolized; its level is increased in the blood, and it is excreted in urine because practically no renal threshold exists for fructose. Clinitest results reveal the urinary reducing substance, which can be identified as fructose by chromatography.

Deficiency of Fructose-1,6-Bisphosphate Aldolase (Aldolase B, Hereditary Fructose Intolerance)

Deficiency of fructose-1,6-bisphosphate aldolase (**aldolase-B**) is a severe condition of infants caused by a deficiency of aldolase B activity in the liver, kidney, and intestine. This enzyme catalyzes the hydrolysis of fructose-1,6-bisphosphate into triose phosphate and glyceraldehyde phosphate. The same enzyme also hydrolyzes fructose-1-phosphate. In the absence of enzyme activity, there is a rapid accumulation of fructose-1-phosphate, which presents with severe symptoms when fructose-containing food is ingested.

Epidemiology and Genetics

The exact incidence of **hereditary fructose intolerance (HFI)** is unknown but is estimated to be as high as 1 in every 26,000 live births. HFI is inherited in an autosomal recessive manner. The *ALDOB* gene is mapped to chromosome 9q22.3. At least 40 pathogenic variants causing HFI are known. The most common pathogenic variant identified in northern Europeans is a single missense variant, a G→C transversion in exon 5 resulting in the normal alanine at position 149 being replaced by proline. This variant, along with 2 other missense variants (p.A174D and p.N334K), account for 80–85% of HFI in Europe and the United States. Diagnosis of HFI can be made by direct DNA analysis for the common variants and phosphorus magnetic resonance spectroscopy.

Clinical Manifestations

Affected individuals remain asymptomatic until fructose or sucrose (table sugar) is introduced in diet (usually from fruit, fruit juice, or sweetened cereal). Signs and symptoms typically manifest in infancy when foods or formulas containing these sugars are introduced. Certain patients are very sensitive to fructose, whereas others can tolerate moderate intakes (up to 250 mg/kg/day). The average intake of fructose in Western societies is 1-2 g/kg/day. Early clinical manifestations resemble galactosemia and include jaundice, hepatomegaly, vomiting, lethargy, irritability, and convulsions. There may also be a higher incidence of *celiac disease* in HFI patients (>10%) than in the general population (1–3%). As they grow older, patients usually develop an aversion to fructose-containing foods due to associated symptoms of nausea, vomiting, and abdominal pain.

Characteristic lab findings include lactic acidosis, hypophosphatemia, hyperuricemia, and hypermagnesemia. A prolonged clotting time, hypoalbuminemia, elevation of bilirubin and transaminase levels, and proximal tubular dysfunction are also seen. Acute fructose ingestion produces symptomatic hypoglycemia; the higher the intake, the more severe the clinical picture. Chronic ingestion results in failure to thrive and hepatic disease. If the intake of fructose persists, hypoglycemic episodes recur, leading to progressive renal and hepatic failure and eventually death.

Diagnosis

The presence of a reducing substance in urine during an acute episode raises the possibility of HFI. Oral fructose challenge is *no longer* considered a diagnostic approach because of high risk to the patient, who can become acutely ill after the test. Definitive diagnosis is made by demonstration of 2 pathogenic variants in *ALDOB* on molecular genetic testing. A common pathogenic variant (substitution of *Pro* for *Ala* at position 149) accounts for 53% of HFI alleles worldwide. An alternative is to show deficient hepatic fructose 1-phosphate aldolase (aldolase B) activity on liver biopsy.

Treatment

Acute episodes are managed symptomatically by correcting hypoglycemia with IV glucose (dextrose) administration, providing supportive treatment of hepatic insufficiency, and correcting metabolic acidosis. Complete elimination of fructose usually rapidly reverses symptoms and results in normalization of related metabolic disturbances. The cornerstone of long-term treatment is the complete restriction of all sources of sucrose, fructose, and sorbitol from the diet. It may be difficult because these sugars are widely used additives, found even in most medicinal preparations. With treatment, liver and kidney dysfunction improves, and catch-up in growth is common. Intellectual development is usually unimpaired. As the patient matures, symptoms become milder even after fructose ingestion; the long-term prognosis is good. Because of voluntary dietary avoidance of sucrose, affected patients have few dental caries. Care should be taken to avoid fructose-containing IV fluids during hospitalizations.

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105.4

Defects in Intermediary Carbohydrate Metabolism Associated With Lactic Acidosis

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Keywords

pyruvate
lactic acidosis
lactate
biotin
mitochondria
respiratory chain
Leigh disease
oxidation, retinopathy

Lactic acidosis (**type B3**) occurs with defects of carbohydrate metabolism that interfere with the conversion of pyruvate to glucose via the pathway of gluconeogenesis or to carbon dioxide and water via the mitochondrial enzymes of the Krebs cycle. Fig. 105.4 depicts the relevant metabolic pathways. Type I GSD, fructose-1,6-diphosphatase deficiency, and phosphoenolpyruvate carboxylase deficiency are disorders of gluconeogenesis associated with lactic acidosis. Pyruvate dehydrogenase complex deficiency, respiratory chain defects, and pyruvate carboxylase deficiency are disorders in the pathway of pyruvate metabolism causing lactic acidosis. Lactic acidosis (type B3) can also occur in defects of fatty acid oxidation, organic acidurias (see Chapters 103.6 , 103.10 , and 104.1), or biotin utilization diseases (type B3) (Table 105.2). These disorders are easily distinguishable by the presence of abnormal acyl carnitine profiles, amino acids in the blood, and unusual organic acids in the urine. Blood lactate, pyruvate, and acyl carnitine profiles, and the presence of these unusual urine organic acids should be determined in infants and children with unexplained acidosis, especially if there is an increase of anion gap.

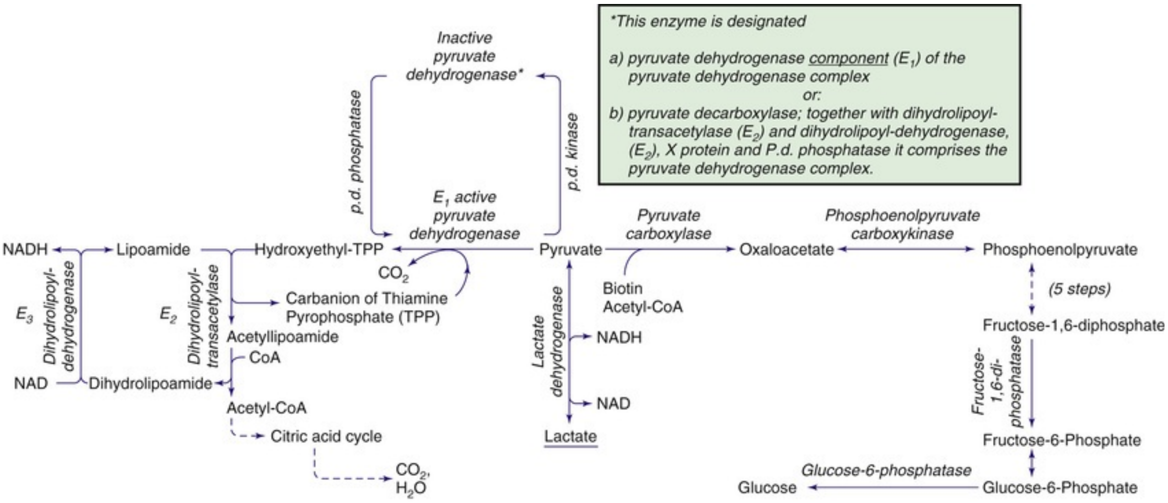
*This enzyme is designated
a) pyruvate dehydrogenase component (E_1) of the pyruvate dehydrogenase complex
or:
b) pyruvate decarboxylase; together with dihydrolipoyl-transacetylase (E_2) and dihydrolipoyl-dehydrogenase, (E_3), X protein and P.d. phosphatase it comprises the pyruvate dehydrogenase complex.
Inactive pyruvate dehydrogenase*
p.d. phosphatase
p.d. kinase
E_1 active pyruvate dehydrogenase
NADH
Lipoamide
Hydroxyethyl-TPP
Pyruvate
Pyruvate carboxylase
Oxaloacetate
Phosphoenolpyruvate carboxykinase
Phosphoenolpyruvate
E_3
Dihydrolipoyl-dehydrogenase
E_2
Dihydrolipoyl-transacetylase
CO_2
Carbanion of Thiamine Pyrophosphate (TPP)
Acetyllipoamide
CoA
NAD
Dihydrolipoamide
Acetyl-CoA
Citric acid cycle
CO_2, H_2O
Biotin
Acetyl-CoA
Lactate dehydrogenase
NADH
NAD
Lactate
(5 steps)
Fructose-1,6-diphosphate
Fructose-1,6-di-phosphatase
Fructose-6-Phosphate
Glucose-6-phosphatase
Glucose
Glucose-6-Phosphate

FIG. 105.4 Enzymatic reactions of carbohydrate metabolism, deficiencies of which can give rise to lactic acidosis, pyruvate elevations, or hypoglycemia. The pyruvate dehydrogenase complex comprises, in addition to E_1, E_2, and E_3, an extra lipoate-containing protein (not shown), called protein X, and pyruvate dehydrogenase phosphatase.

Table 105.2

Causes of Type B Lactic Acidosis

Type B1—Underlying Diseases

Renal failure
Hepatic failure
Diabetes mellitus
Malignancy
Systemic inflammatory response syndrome
Human immunodeficiency virus

Type B2—Drugs and Toxins

Acetaminophen
Alcohols—ethanol, methanol, diethylene glycol, isopropanol, and propylene glycol
Antiretroviral nucleoside analogs—zidovudine, didanosine, and lamivudine
β-Adrenergic agonists—epinephrine, ritodrine, and terbutaline
Biguanides—phenformin and metformin

Cocaine, methamphetamine
Cyanogenic compounds—cyanide, aliphatic nitriles, and nitroprusside
Diethyl ether
Fluorouracil
Halothane
Iron
Isoniazid
Linezolid
Nalidixic acid
Niacin
Propopol
Salicylates
Strychnine
Sugars and sugar alcohols—fructose, sorbitol, and xylitol
Sulfasalazine
Total parenteral nutrition
Valproic acid
Vitamin deficiencies—thiamine and biotin

Type B3—Inborn Errors of Metabolism

Glucose-6-phosphatase deficiency (von Gierke disease)
Fructose-1,6-diphosphatase deficiency
Phosphoenolpyruvate carboxykinase deficiency
Pyruvate carboxylase deficiency
Pyruvate dehydrogenase complex (PDHC) deficiency
Krebs cycle defects
Methylmalonic aciduria and other organic acidemias
Kearns-Sayre syndrome
Pearson syndrome
Barth syndrome
Mitochondrial DNA depletion syndromes
Nuclear DNA respiratory chain defects
Mitochondrial DNA respiratory defects
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
Myoclonic epilepsy with ragged red fibers (MERRF)

Adapted from Vernon C, LeTourneau JL: Lactic acidosis: recognition, kinetics, and associated prognosis, Crit Care Clin 26:255–283, 2010 (Box 1, p 264).

Lactic acidosis unrelated to an enzymatic defect occurs in hypoxemia (**type A** lactic acidosis). In this case, as well as in defects in the respiratory chain, the serum pyruvate concentration may remain normal (<1.0 mg/dL, with increased lactate:pyruvate ratio), whereas pyruvate is usually increased when lactic acidosis results from an enzymatic defect in gluconeogenesis or pyruvate dehydrogenase complex (both lactate and pyruvate are increased, and the ratio is normal). Lactate and pyruvate should be measured in the same blood specimen and on multiple blood specimens obtained when the patient is symptomatic because lactic acidosis can be intermittent. Fig. 105.5 is an algorithm for the differential diagnosis of lactic acidosis. Lactic acidosis is also noted with various underlying diseases (**type B1**) and drugs or toxins (**type B2**) (Table 105.2).

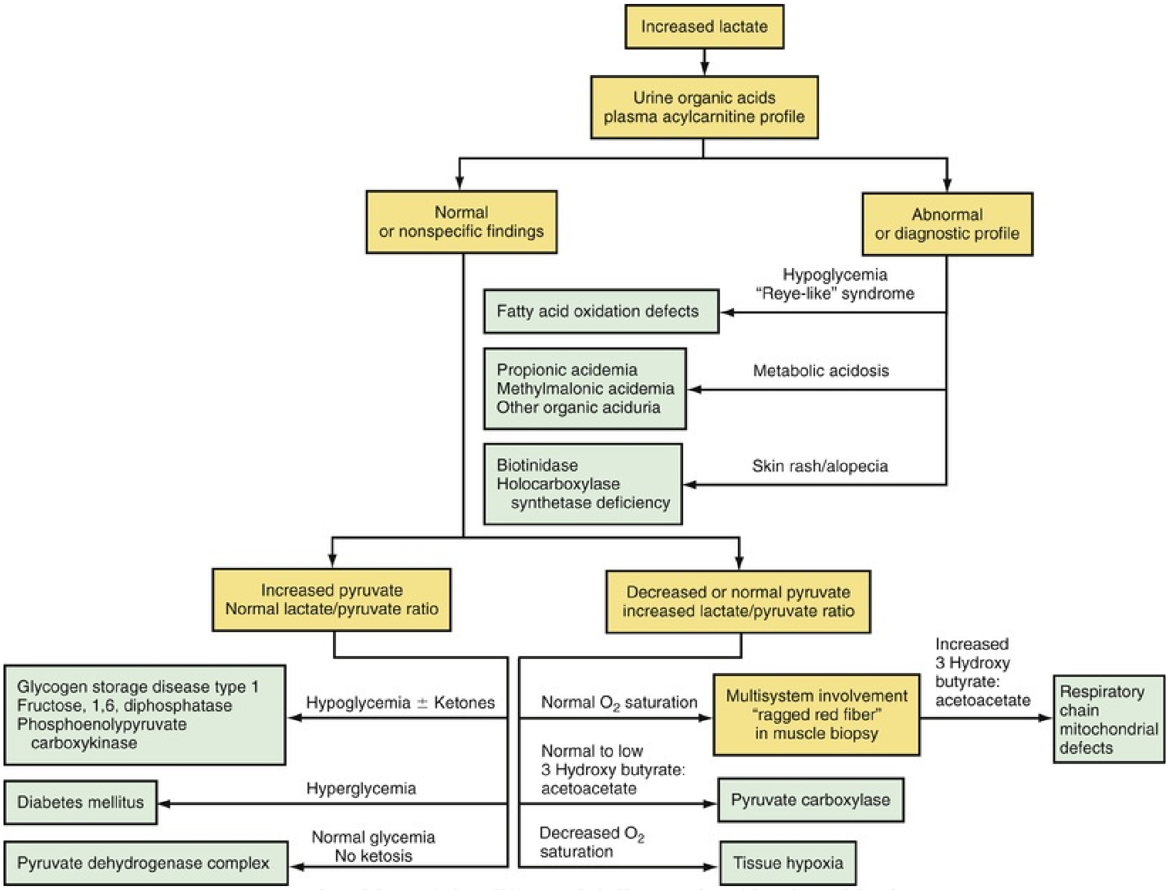
Increased lactate
Urine organic acids
plasma acylcarnitine profile
Normal
or nonspecific findings
Abnormal
or diagnostic profile
Hypoglycemia
"Reye-like" syndrome
Fatty acid oxidation defects
Metabolic acidosis
Propionic acidemia
Methylmalonic acidemia
Other organic aciduria
Skin rash/alopecia
Biotinidase
Holocarboxylase
synthetase deficiency
Increased pyruvate
Normal lactate/pyruvate ratio
Decreased or normal pyruvate
increased lactate/pyruvate ratio
Hypoglycemia ± Ketones
Glycogen storage disease type 1
Fructose, 1,6, diphosphatase
Phosphoenolypyruvate
carboxykinase
Hyperglycemia
Diabetes mellitus
Normal glycemia
No ketosis
Pyruvate dehydrogenase complex
Normal O_2 saturation
Multisystem involvement
"ragged red fiber"
in muscle biopsy
Increased
3 Hydroxy
butyrate:
acetoacetate
Respiratory
chain
mitochondrial
defects
Normal to low
3 Hydroxy butyrate:
acetoacetate
Pyruvate carboxylase
Decreased O_2
saturation
Tissue hypoxia

FIG. 105.5 Algorithm of the differential diagnosis of lactic acidosis.

Disorders of Gluconeogenesis

Deficiency of Glucose-6-Phosphatase (Type I Glycogen Storage Disease)

Type I GSD is the only glycogenosis associated with significant **lactic acidosis** . The chronic metabolic acidosis predisposes these patients to osteopenia; after prolonged fasting, the acidosis associated with hypoglycemia is a life-threatening condition (see Chapter 105.1).

Fructose-1,6-Diphosphatase Deficiency

Fructose-1,6-diphosphatase deficiency impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose. Hypoglycemia occurs when glycogen reserves are limited or exhausted. The **clinical manifestations** are characterized by life-threatening episodes of acidosis, hypoglycemia, hyperventilation, convulsions, and coma. In about half the cases, the deficiency presents in the 1st wk of life. In infants and small children, episodes are triggered by febrile infections and gastroenteritis if oral food intake decreases. The frequency of the attacks decreases with age. Laboratory findings include low blood glucose, high lactate and uric acid levels, and metabolic acidosis. In contrast to HFI, there is usually no aversion to sweets; renal tubular and liver function is normal.

The **diagnosis** is established by demonstrating an enzyme deficiency in either liver or intestinal biopsy. The enzyme defect can also be demonstrated in leukocytes in some cases. The gene coding for fructose-1,6-diphosphatase *(FBP1)* is located on chromosome 9q22; pathogenic variants are characterized, making carrier detection and prenatal diagnosis possible. **Treatment** of acute attacks consists of correction of hypoglycemia and acidosis by IV glucose infusion; the response is usually rapid. Avoidance of fasting, aggressive management of infections, and restriction of fructose and sucrose from the diet can prevent further episodes. For long-term prevention of hypoglycemia, a slowly released carbohydrate such as cornstarch is useful. Patients who survive childhood develop normally.

Phosphoenolpyruvate Carboxykinase Deficiency

Phosphoenolpyruvate carboxykinase (**PEPCK**) is a key enzyme in gluconeogenesis. It catalyzes the conversion of oxaloacetate to phosphoenolpyruvate (see Fig. 105.4). PEPCK deficiency is both a mitochondrial enzyme deficiency and a cytosolic enzyme deficiency, encoded by 2 distinct genes.

PEPCK deficiency has been reported in only a few cases. The clinical features are heterogeneous, with hypoglycemia, lactic acidemia, hepatomegaly, hypotonia, developmental delay, and failure to thrive as the major manifestations. There may be multisystem involvement, with neuromuscular deficits, hepatocellular damage, renal dysfunction, and cardiomyopathy. The **diagnosis** is based on the reduced activity of PEPCK in liver, fibroblasts, or lymphocytes. Fibroblasts and lymphocytes are not suitable for diagnosing the cytosolic form of PEPCK deficiency because these tissues possess only mitochondrial PEPCK. To avoid hypoglycemia, patients should receive **treatment** with slow-release carbohydrates such as cornstarch, and fasting should be avoided.

Disorders of Pyruvate Metabolism

Pyruvate is formed from glucose and other monosaccharides, from lactate, and from alanine. It is metabolized through 4 main enzyme systems: lactate dehydrogenase, alanine transaminase, pyruvate carboxylase, and pyruvate dehydrogenase complex. Deficiency of the M subunit of LDH causes exercise intolerance and myoglobinuria (see Chapter 105.1).

Pyruvate Dehydrogenase Complex Deficiency

After entering the mitochondria, pyruvate is converted into acetyl-CoA by the pyruvate dehydrogenase complex (**PDHC**), which catalyzes the oxidation of pyruvate to acetyl-CoA, which then enters the tricarboxylic acid cycle for ATP production. The complex comprises 5 components: **E_1** , an α-ketoacid decarboxylase; **E_2** , a dihydrolipoyl transacylase; **E_3** , a dihydrolipoyl dehydrogenase; **protein X** , an extra lipoate-containing protein; and pyruvate dehydrogenase phosphatase. The most common is a defect in the E_1 (see Fig. 105.4).

Deficiency of the PDHC is the most common of the disorders leading to lactic acidemia and CNS dysfunction. The CNS dysfunction occurs because the brain obtains its energy primarily from oxidation of glucose. Brain acetyl-CoA is synthesized almost exclusively from pyruvate.

The E_1 defects are caused by pathogenic variants in the gene coding for E_1 α subunit, which is X-linked dominant. Although X-linked, its deficiency is a problem in both male and female patients, despite only one E_1 α allele in females carrying a variant.

Clinical Manifestations

PDHC deficiency has a wide spectrum of presentations, from the most severe neonatal presentation to a mild late-onset form. The **neonatal onset** is associated with lethal lactic acidosis, white matter cystic lesions, agenesis of the corpus callosum, and the most severe enzyme deficiency. **Infantile onset** can be lethal or associated with psychomotor delay and chronic lactic acidosis, cystic lesions in the brainstem and basal ganglia, and pathologic features resembling **Leigh disease** (see later and Chapter 616.2). Neurologic symptoms in PDHC can be categorized into 2 groups: abnormal brain development, seen in both males and females, and brain lesions and epilepsy, seen in male patients only. Older children, usually boys, may have less acidosis, have greater enzyme activity, and manifest ataxia with high-carbohydrate diets. Intelligence may be normal. Patients of all ages may have facial dysmorphology, features similar to those of fetal alcohol syndrome.

The **E_2** and **protein X–lipoate** defects are rare and result in severe psychomotor retardation. The **E_3 lipoamide dehydrogenase** defect leads to deficient activity not only in the PDHC, but also in the α-ketoglutarate and branched-chain ketoacid dehydrogenase complexes. This deficiency is more common in the Ashkenazi Jewish population. The reactive oxygen species generated by the pathogenic variants responsible for lipoamide dehydrogenase deficiency may in fact explain certain disease characteristics and suggest the utility of antioxidant therapy. **Pyruvate dehydrogenase phosphatase** deficiency has also been reported. These other PDHC defects have clinical manifestations within the variable spectrum associated with PDHC deficiency caused by E_1 deficiency.

Treatment

The general prognosis is poor, except in rare patients in whom variants are associated with altered affinity for thiamine pyrophosphate, who may respond to thiamine supplementation. Because carbohydrates can aggravate lactic acidosis, a ketogenic diet is recommended. The diet has been found to lower the blood lactate level; the long-term benefit to patient outcome is unclear. A potential treatment strategy is to maintain any residual PDHC in its active form by oral administration of **dichloroacetate** , an inhibitor of E_1 kinase. Beneficial effects of controlling postprandial lactic acidosis have been shown in some patients. Young children with congenital acidosis generally tolerate dichloroacetate well, but continued exposure is associated with peripheral neuropathy, a condition that could be attributable to the drug or the disease.

Deficiency of Pyruvate Carboxylase

Pyruvate carboxylase is a mitochondrial, biotin-containing enzyme essential in the process of gluconeogenesis; it catalyzes the conversion of pyruvate to oxaloacetate. The enzyme is also essential for Krebs cycle function as a provider of oxaloacetate and is involved in lipogenesis and formation of nonessential amino acids. **Clinical manifestations** of this deficiency have varied from neonatal severe lactic acidosis accompanied by hyperammonemia, citrullinemia, and hyperlysinemia (**type B**) to late-onset mild to moderate lactic acidosis and developmental delay (**type A**). In both types, patients who survived usually had severe psychomotor retardation with seizures, spasticity, and microcephaly. Some patients have pathologic changes in the brainstem and basal ganglia that resemble **Leigh disease** . The clinical severity appears to correlate with the level of the residual enzyme activity. A “benign” form of pyruvate carboxylase deficiency has also been described, characterized by recurrent attacks of lactic acidosis and mild neurologic deficits (**type C**). Laboratory findings are characterized by elevated levels of blood lactate, pyruvate, alanine, and ketonuria. In the case of type B, blood ammonia, citrulline, and lysine levels are also elevated, which might suggest a primary defect of the urea cycle. The mechanism is likely caused by depletion of oxaloacetate, which leads to reduced levels of aspartate, a substrate for argininosuccinate synthase in the urea cycle (see Chapter 103.12). The gene for pyruvate carboxylase (*PC)* is located on chromosome 11q13.4-q13.5, and about 15 pathogenic variants have been identified.

Treatment consists of avoidance of fasting and eating a carbohydrate meal before bedtime. During acute episodes of lactic acidosis, patients should receive continuous IV glucose. Aspartate and citrate supplements restore the metabolic abnormalities; whether this treatment can prevent the neurologic deficits is not known. Liver transplantation has been attempted; its benefit remains unknown. **Diagnosis** of pyruvate carboxylase deficiency is made by the measurement of enzyme activity in liver or cultured skin fibroblasts and must be differentiated from holocarboxylase synthase or biotinidase deficiency.

Deficiency of Pyruvate Carboxylase Secondary to Deficiency of Holocarboxylase Synthase or Biotinidase

Deficiency of either holocarboxylase synthase (**HCS**) or biotinidase, which are enzymes of biotin metabolism, result in multiple-carboxylase deficiency (pyruvate carboxylase and other biotin-requiring carboxylases and metabolic reactions) and in **clinical manifestations** associated with the respective deficiencies, as well as rash, lactic acidosis, and alopecia (see Chapter 103.6). The course of HCS or biotinidase deficiency can be protracted, with intermittent exacerbation of chronic lactic acidosis, failure to thrive, seizures, and hypotonia leading to spasticity, lethargy, coma, and death. Auditory and optic nerve dysfunction can lead to deafness and blindness, respectively. Late-onset milder forms have also been reported. Laboratory findings include metabolic acidosis and abnormal organic acids in the urine. In HCS deficiency, biotin concentrations in plasma and urine are normal. **Diagnosis** can be made in skin fibroblasts or lymphocytes by assay for HCS activity, and in the case of biotinidase, in the serum by a screening blood spot.

Treatment consists of biotin supplementation, 5-20 mg/day, and is generally effective if treatment is started before the development of brain damage. Patients identified through newborn screening and treated with biotin have remained asymptomatic.

Both enzyme deficiencies are autosomal recessive disorders. The incidence of HCS deficiency is approximately 1 in 87,000 live births. *HCS* and biotinidase *(BTD)* are located on chromosome 21q22 and 3p25, respectively. Ethnic-specific pathogenic variants in the *HCS* gene have been identified. Two common pathogenic variants (del7/ins3 and p.R538C) in the *BTD* account for 52% of all pathogenic alleles in symptomatic patients with biotinidase deficiency.

Mitochondrial Respiratory Chain Defects (Oxidative Phosphorylation Disease)

The mitochondrial respiratory chain catalyzes the oxidation of fuel molecules and transfers the electrons to molecular oxygen with concomitant energy transduction into adenosine triphosphate (**oxidative phosphorylation**) (see Chapter 106). The respiratory chain produces ATP from adenosine diphosphate and inorganic phosphate utilizing the energy from electrons transferred from nicotinamide adenine dinucleotide (NADH) or flavin adenine dinucleotide and includes 5 specific complexes (I: NADH–coenzyme Q reductase; II: succinate–coenzyme Q reductase; III: coenzyme QH_2 cytochrome-*c* reductase; IV: cytochrome-*c* oxidase; V: ATP synthase). Each complex is composed of 4-35 individual proteins and, with the exception of complex II (which is encoded solely by nuclear genes), is encoded by nuclear or mitochondrial DNA (inherited only from the mother by mitochondrial inheritance). Defects in any of these complexes or assembly systems produce chronic lactic acidosis, presumably because of a change of the reduction-oxidation state with increased concentrations of NADH (see Table 105.3).

In contrast to PDHC or pyruvate carboxylase deficiency, skeletal muscle and heart are usually involved in the respiratory chain disorders. On muscle biopsy, **ragged red fibers** indicating mitochondrial proliferation are very suggestive when present (see Fig. 105.5). Because of the ubiquitous nature of oxidative phosphorylation, a defect of the mitochondrial respiratory chain accounts for a vast array of clinical manifestations and should be considered in patients in all age-groups presenting with multisystem involvement. Some deficiencies resemble **Leigh disease** , whereas others cause infantile myopathies such as **MELAS** (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), **MERRF** (myoclonic epilepsy and ragged red fibers), and **Kearns-Sayre syndrome** (external ophthalmoplegia, acidosis, retinal degeneration, heart block, myopathy, and high cerebrospinal fluid protein) (Table 105.3) (see Chapters 616.2 and 629.4). There is a higher incidence of psychiatric disorders in adults with a primary oxidative phosphorylation disease than in the general population. Elevated serum growth and differentiation factor (GDF)-15 levels help screen for mitochondrial disorders.

Table 105.3

Clinical and Genetic Heterogeneity of Disorders Related to Mutations in Mitochondrial DNA*

SYMPTOMS, SIGNS, AND FINDINGS	**LARGE DELETIONS IN MITOCHONDRIAL DNA**			**MUTATION IN TRANSFER RNA**		**MUTATION IN RIBOSOMAL RNA**	**MUTATION IN MESSENGER RNA**		
	KSS	**PEO**	**PS**	**MERRF**	**MELAS**	**AID**	**NARP**	**MILS**	**LHON**
CENTRAL NERVOUS SYSTEM									
Seizures	−	−	−	+++	+	−	−	+	−
Ataxia	+	−	−	+	+		+	±	−
Myoclonus	−	−	−	+	±	−	−	−	−
Psychomotor retardation	−	−	−	−	−	−	−	+	−
Psychomotor regression	+	−	−	±	+	−	−	−	−
Hemiparesis and hemianopia	−	−	−	−	+++	−	−	−	−
Cortical blindness	−	−	−	−	+	−	−	−	−
Migraine-like headaches	−	−	−	−	+	−	−	−	−
Dystonia	−	−	−	−	+	−	−	+	±
PERIPHERAL NERVOUS SYSTEM									
Peripheral neuropathy	±	−	−	±	±	−	+	−	−
MUSCLE									
Weakness and exercise intolerance	+	+++	−	+	+	−	+	+	−
Ophthalmoplegia	+	+	±	−	−	−	−	−	−
Ptosis		+	−	−	−	−	−	−	−
EYE									
Pigmentary retinopathy	+	−	−	−	−	−	+	±	−
Optic atrophy	−	−	−	−	−	−	±	±	
BLOOD									
Sideroblastic anemia	±	−	+	−	−	−	−	−	−
ENDOCRINE SYSTEM									
Diabetes mellitus	±	−	−	−	±	−	−	−	−
Short stature	+	−	−	+	+	−	−	−	−
Hypoparathyroidism	±	−	−	−	−	−	−	−	−
HEART									
Conduction disorder	+	−	−	−	±	−	−	−	±
Cardiomyopathy	±	−	−	−	±	+	−	±	−
GASTROINTESTINAL SYSTEM									
Exocrine pancreatic dysfunction	±	−	+	−	−	−	−	−	−
Intestinal pseudoobstruction	−	−	−	−	+	−	−	−	−
EAR, NOSE, AND THROAT									
Sensorineural hearing loss	±	−	−	+	+	+	±	−	−
KIDNEY									

Fanconi syndrome		−	±	−	±	−	−	−	−
LABORATORY FINDINGS									
Lactic acidosis	+	±	+	+	+	±	±	±	−
Ragged-red fibers on muscle biopsy	+	+	±	+	+	−	−	−	−
MODE OF INHERITANCE									
Maternal	−	−	−	+	+	−	+	+	+
Sporadic	+	+	+	−	−	−	−	−	−

[*] Characteristic constellations of symptoms and signs are in **bold** .

+, Presence of a symptom, sign, or finding; −, absence of a symptom, sign, or finding; ±, possible presence of a symptom, sign, or finding; AID, aminoglycoside-induced deafness; KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; MILS, maternally inherited Leigh syndrome; NARP, neuropathy, ataxia, and retinitis pigmentosa; PEO, progressive external ophthalmoplegia; PS, Pearson syndrome.

From DiMauro S, Schon EA: Mitochondrial respiratory-chain diseases, *N Engl J Med* 348:2656–2668, 2003. Copyright 2003 Massachusetts Medical Society. All rights reserved.

Diagnosis requires demonstration of abnormalities of oxidative phosphorylation enzyme complex activities in tissues or of mitochondrial DNA or a nuclear gene coding for mitochondrial functions, or both (Fig. 105.6). Muscle histology, including EM, can detect ragged red fibers and other abnormalities typical of mitochondrial myopathies. Analysis of oxidative phosphorylation complexes I-IV from intact mitochondria isolated from fresh skeletal muscle is the most sensitive assay for mitochondrial disorders; however, electron transport chain testing of flash-frozen muscle provides an alternative approach when fresh muscle testing is not available. Next-generation sequencing of mitochondrial DNA and panels of nuclear genes provides a noninvasive alternative to diagnosis. Specific criteria may assist in making a diagnosis (Table 105.4). Table 105.5 lists clues to the diagnosis of mitochondrial diseases.

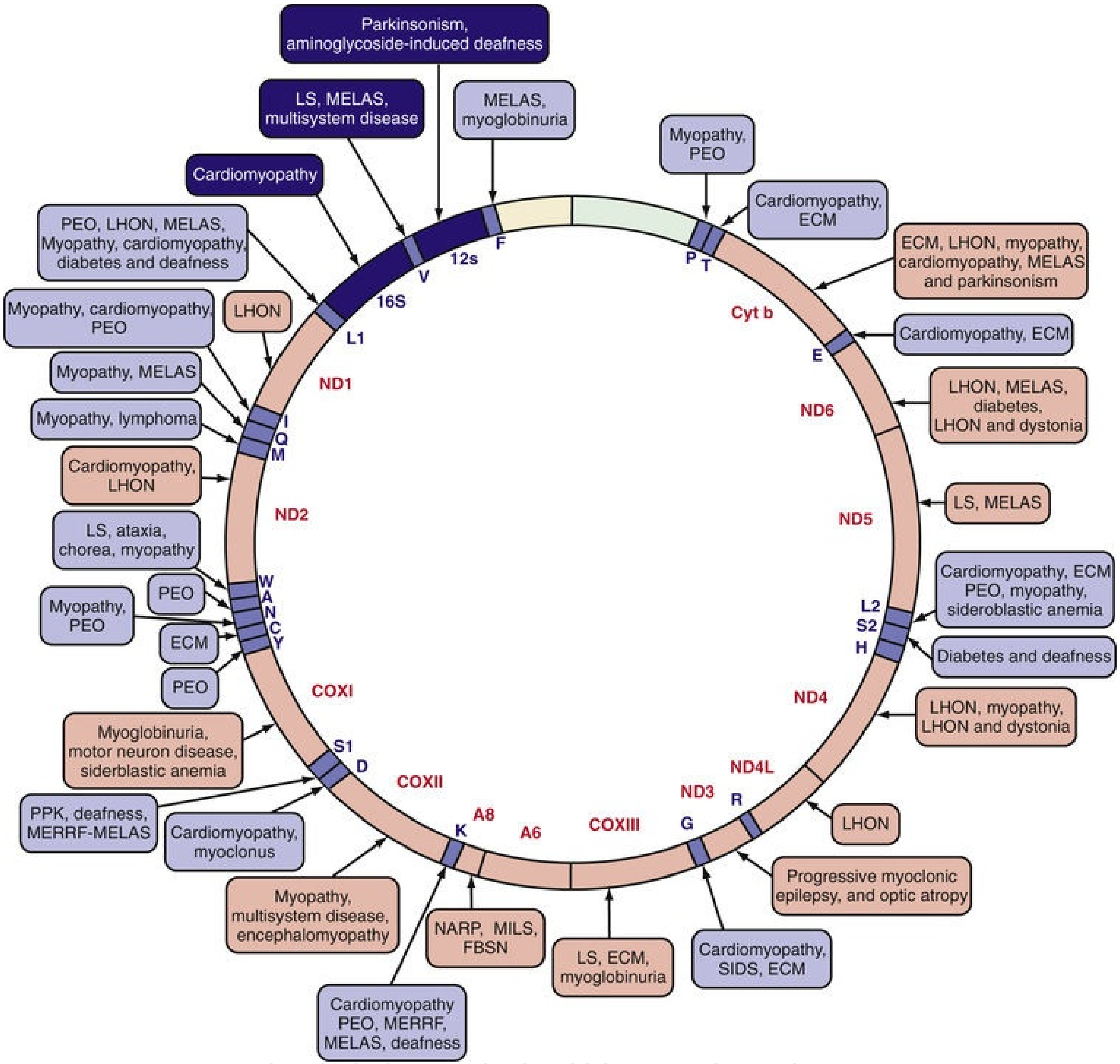
Parkinsonism, aminoglycoside-induced deafness
LS, MELAS, multisystem disease
MELAS, myoglobinuria
Cardiomyopathy
Myopathy, PEO
Cardiomyopathy, ECM
PEO, LHON, MELAS, Myopathy, cardiomyopathy, diabetes and deafness
ECM, LHON, myopathy, cardiomyopathy, MELAS and parkinsonism
Myopathy, cardiomyopathy, PEO
LHON
Cardiomyopathy, ECM
Myopathy, MELAS
LHON, MELAS, diabetes, LHON and dystonia
Myopathy, lymphoma
Cardiomyopathy, LHON
LS, MELAS
LS, ataxia, chorea, myopathy
PEO
Cardiomyopathy, ECM PEO, myopathy, sideroblastic anemia
Myopathy, PEO
ECM
Diabetes and deafness
PEO
LHON, myopathy, LHON and dystonia
Myoglobinuria, motor neuron disease, siderblastic anemia
PPK, deafness, MERRF-MELAS
Cardiomyopathy, myoclonus
LHON
Progressive myoclonic epilepsy, and optic atropy
Myopathy, multisystem disease, encephalomyopathy
NARP, MILS, FBSN
LS, ECM, myoglobinuria
Cardiomyopathy, SIDS, ECM
Cardiomyopathy PEO, MERRF, MELAS, deafness
F
12s
V
16S
L1
P
T
Cyt b
E
ND6
ND1
I
Q
M
ND2
ND5
W
A
N
C
Y
L2
S2
H
COXI
ND4
S1
D
COXII
ND4L
ND3
R
A8
K
A6
COXIII
G

FIG. 105.6 Mutations in the human mitochondrial genome that are known to cause disease. Disorders that are frequently or prominently associated with mutations in a particular gene are shown in bold . Diseases caused by mutations that impair mitochondrial protein synthesis are shown in *blue.* Diseases caused by mutations in protein-coding genes are shown in *red.* ECM, Encephalomyopathy; FBSN, familial bilateral striatal necrosis; LHON, Leber hereditary optic neuropathy; LS, Leigh syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; MILS, maternally inherited Leigh syndrome; NARP, neuropathy, ataxia, and retinitis pigmentosa; PEO, progressive external ophthalmoplegia; PPK, palmoplantar keratoderma; SIDS, sudden infant death syndrome. (From DiMauro S, Schon EA: Mitochondrial respiratory-chain diseases, *N Engl J Med* 348:2656–2668, 2003. Copyright 2003 Massachusetts Medical Society. All rights reserved.)

Table 105.4

Mitochondrial Disease Criteria (Simplified Version for Bedside Use)*

I. CLINICAL SIGNS AND SYMPTOMS, 1 POINT/SYMPTOM (max. 4 points)				
A. Muscular Presentation (max. 2 points)	**B. CNS Presentation (max. 2 points)**	**C. Multisystem Disease (max. 3 points)**	**II. Metabolic/Imaging Studies (max. 4 points)**	**III. Morphology (max. 4 points)**
Ophthalmoplegia [†]	Developmental delay	Hematology	Elevated lactate [†]	Ragged red/blue fibers [‡]
Facies myopathica	Loss of skills	GI tract	Elevated L/P ratio	COX-negative fibers [‡]
Exercise intolerance	Stroke-like episode	Endocrine/growth	Elevated alanine [†]	Reduced COX staining [‡]
Muscle weakness	Migraine	Heart	Elevated CSF lactate [†]	Reduced SDH staining
Rhabdomyolysis	Seizures	Kidney	Elevated CSF protein	SDH positive blood vessels [†]
Abnormal EMG	Myoclonus	Vision	Elevated CSF alanine [†]	Abnormal mitochondria/EM [†]
	Cortical blindness	Hearing	Urinary TA excretion [†]	
	Pyramidal signs	Neuropathy	Ethylmalonic aciduria	
	Extrapyramidal signs	Recurrent/familial	Stroke-like picture/MRI	
	Brainstem involvement		Leigh syndrome/MRI [†]	
			Elevated lactate/MRS	

[*] Score 1: mitochondrial disorder unlikely; score 2 to 4: possible mitochondrial disorder; score 5 to 7: probable mitochondrial disorder; score 8 to 12: definite mitochondrial disorder.

[†] This specific symptom scores 2 points.

[‡] This symptom in a higher percentage scores 4 points.

GI, gastrointestinal; L/P, lactate/pyruvate; COX, cytochrome C oxidase; SDH, succinate dehydrogenase; EM, electron microscopy; EMG, electromyography; TA, tricarbon acid.

From Morava E, van den Heuvel L, Hol F, et al: Mitochondrial disease criteria – diagnostic applications in children. Neurology 67:1823-1826, 2006, p 1824.

Table 105.5

Clues to the Diagnosis of Mitochondrial Disease

Neurologic

Cerebral stroke-like lesions in a nonvascular pattern
Basal ganglia disease
Encephalopathy: recurrent or with low/moderate dosing of valproate

Neurodegeneration
Epilepsia partialis continua
Myoclonus
Ataxia
MRI findings consistent with Leigh disease
Characteristic MRS peaks
Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
Succinate peak at 2.4 ppm

Cardiovascular

Hypertrophic cardiomyopathy with rhythm disturbance
Unexplained heart block in a child
Cardiomyopathy with lactic acidosis (>5 mM)
Dilated cardiomyopathy with muscle weakness
Wolff-Parkinson-White arrhythmia

Ophthalmologic

Retinal degeneration with signs of night blindness, color vision deficits, decreased visual acuity, or pigmentary retinopathy
Ophthalmoplegia/paresis
Fluctuating, dysconjugate eye movements
Ptosis
Sudden- or insidious-onset optic neuropathy/atrophy

Gastroenterologic

Unexplained or valproate-induced liver failure
Severe dysmotility
Pseudoobstructive episodes

Other

A newborn, infant, or young child with unexplained hypotonia, weakness,

failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
Exercise intolerance that is not in proportion to weakness
Hypersensitivity to general anesthesia
Episodes of acute rhabdomyolysis
Elevated GDF-15 level

MRI, Magnetic resonance imaging, MRS, magnetic resonance spectroscopy; GDF, growth and differentiation factor.

From Haas RH, Parikh S, Falk MJ, et al: Mitochondrial disease: a practical approach for primary care physicians, *Pediatrics* 120:1326–1333, 2007 (Table 1, p 1327).

The majority of mitochondrial disorders are caused by nuclear genes involved in mitochondrial function, and >300 genes have been included in nuclear gene panels for mitochondrial disorder diagnosis. However, pathogenic variants can be identified in 50% or fewer of patients diagnosed clinically with a mitochondrial disorder. An important consideration is that many genetic and multifactorial conditions have been associated with defects in 1 or more of the 4 complexes assayed in mitochondrial oxidative phosphorylation testing. These latter conditions feature so-called secondary mitochondrial dysfunction, because the conditions are not considered to be mitochondrial disorders per se.

Treatment remains largely symptomatic and does not significantly alter the outcome of disease. Some patients appear to respond to cofactor supplements, typically coenzyme Q_{10} ± L -carnitine at pharmacologic doses. The addition of creatine monohydrate and α-lipoic acid supplementation may add a significant benefit. EPI-743 is a parobenzoquinone like agent that has protective activity against oxidative injury; it is a promising agent in the treatment of mitochondrial disorders, including Leigh syndrome.

Leigh Disease (Subacute Necrotizing Encephalomyelopathy)

Leigh disease is a heterogeneous neurologic disease characterized by demyelination, gliosis, necrosis, relative neuronal sparing, and capillary proliferation in specific brain regions (see Chapter 616.2). Patients with Leigh disease frequently present with feeding and swallowing problems, failure to thrive, and developmental delay. The presentation is highly variable and may include seizures, altered consciousness, pericardial effusion, and dilated cardiomyopathy. **Diagnosis** is usually confirmed by radiologic or pathologic evidence of symmetric lesions affecting the basal ganglia, brainstem, and subthalamic nuclei. Patients with Leigh disease have defects in several enzyme complexes. Dysfunction in cytochrome-*c* oxidase (complex IV) is the most commonly reported defect, followed by NADH–coenzyme Q reductase (complex I), PDHC, and pyruvate carboxylase (see Chapter 106). Pathogenic variants in the nuclear *SURF1* gene, which encodes a factor involved in the biogenesis of cytochrome-*c* oxidase and mitochondrial DNA variants in the adenosine triphosphatase 6 coding region, have been reported in patients with Leigh disease in association with complex IV deficiency. The most common mitochondrial DNA variant in Leigh disease is the T8993G variant in *MT-ATP6* . The **prognosis** for Leigh syndrome is poor. In a study of 14 cases, there were 7 fatalities before age 1.5 yr.

Lactic acidosis, hypoglycemia, and encephalopathy have also been reported in patients with thiamine transporter deficiency and with pyridoxine-dependent epilepsy. Both disorders should improve by the provision of thiamine and pyridoxine, respectively.

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105.5

Defects in Pentose Metabolism

Priya S. Kishnani, Yuan-Tsong Chen

Keywords

- hexose monophosphate
- pentosuria
- xylulose
- transaldolase
- ribose
- urine reducing substance

Approximately 90% of glucose metabolism in the body is via the glycolytic pathway, with the remaining 10% via the hexose monophosphate pathway. The hexose monophosphate shunt leads to formation of pentoses, as well as providing NADH. One of the metabolites is ribose-5-phosphate, which is used in the biosynthesis of ribonucleotides and deoxyribonucleotides. Through the transketolase and transaldolase reactions, the pentose phosphates can be converted back to fructose-6-phosphate and glucose-6-phosphate.

Essential Pentosuria

Essential pentosuria is a benign disorder encountered principally in Ashkenazi Jews and is an autosomal recessive trait. The urine contains **L -xylulose** , which is excreted in increased amounts because of a block in the conversion of L -xylulose to xylitol as a result of **xylitol dehydrogenase deficiency** . The condition is usually discovered accidentally in a urine test for reducing substances. No treatment is required.

Transaldolase Deficiency

Few patients have reported symptoms that include liver cirrhosis, hepatosplenomegaly, severe neonatal hepatopathy, and cardiomyopathy. Biochemical abnormalities revealed elevated levels of arabitol, ribitol, and erythritol in the urine. Erythronic acid has been identified by urine nuclear magnetic resonance spectroscopy as another hallmark metabolite. Enzyme assay in the lymphoblasts and fibroblasts demonstrated low transaldolase activity, which was confirmed by pathogenic variants in the transaldolase gene. In addition, measurement of transaldolase activity in fibroblasts, lymphoblasts, or liver tissue, as well as assessing urinary concentrations of polyols, also can be used to confirm the diagnosis.

Ribose-5-Phosphate Isomerase Deficiency

Only one case of this disorder has been reported. The affected male had psychomotor delay from early in life and developed epilepsy at 4 yr of age. Thereafter, a slow neurologic regression developed, with prominent cerebellar ataxia, some spasticity, optic atrophy, and a mild sensorimotor neuropathy. MRI of the brain at ages 11 and 14 yr showed extensive abnormalities of the cerebral white matter. Proton magnetic resonance spectroscopy (MRS) of the brain revealed elevated levels of ribitol and D -arabitol. These pentitols were also increased in urine and plasma similar to the patient found in transaldolase deficiency. Enzyme assays in cultured fibroblasts showed deficient **ribose-5-phosphate isomerase** activity, which was confirmed by a molecular study. These results, combined with a study of ribose-5-phosphate isomerase–deficient mice, demonstrated that the specific genetic pairing of a null allele with an allele coding for a form of the enzyme that is only partly active, allowing for cell type–dependent expression deficits, is a contributing factor to the rarity of the disease. Ribose-5-phosphate isomerase deficiency may represent an example of a single-gene disease that appears seldom because of its complex molecular etiology.

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105.6

Disorders of Glycoprotein Degradation and Structure

Margaret M. McGovern, Robert J. Desnick

The disorders of glycoprotein degradation and structure include several lysosomal storage diseases that result from defects in glycoprotein degradation, and the congenital disorders of glycosylation (see Chapter 105.7). *Glycoproteins* are macromolecules composed of oligosaccharide chains linked to a peptide backbone. They are synthesized by 2 pathways: the glycosyltransferase pathway, which synthesizes oligosaccharides linked *O* -glycosidically to serine or threonine residues; and the dolichol, lipid-linked pathway, which synthesizes oligosaccharides linked *N* -glycosidically to asparagine.

The **glycoprotein lysosomal storage diseases** result from the deficiency of the enzymes that normally participate in the degradation of oligosaccharides and include sialidosis, galactosialidosis, aspartylglucosaminuria, and α-mannosidosis. In some instances the underlying abnormality that leads to glycoprotein accumulation also results in abnormal degradation of other classes of macromolecules that contain similar oligosaccharide linkages, such as certain glycolipids and proteoglycans. In these cases the underlying enzymatic deficiency results in the accumulation of both glycoproteins and *glycolipids*. The classification of these types of disorders as *lipidoses* or *glycoproteinoses* depends on the nature of the predominantly stored substance. In general, the glycoprotein disorders are characterized by autosomal recessive inheritance and a progressive disease course with clinical features that resemble those seen in the mucopolysaccharidoses.

Sialidosis and Galactosialidosis

Sialidosis is an autosomal recessive disorder that results from the primary deficiency of neuraminidase because of mutations in the gene (*NEU1*) that encodes this protein, located on chromosome 6p21.33. In contrast, **galactosialidosis** is caused by the deficiency of 2 lysosomal enzymes—neuraminidase and β-galactosidase. The loss of these enzymatic activities results from mutations in a single gene, *CTSA*, located on chromosome 20q13.12, that encodes the protective protein cathepsin A, which functions to stabilize these enzymatic activities. Neuraminidase normally cleaves terminal sialyl linkages of several oligosaccharides and glycoproteins. Its deficiency results in the accumulation of oligosaccharides, and the urinary excretion of sialic acid terminal oligosaccharides and sialylglycopeptides. Examination of tissues from affected individuals reveals pathologic storage of substrate in many tissues, including liver, bone marrow, and brain.

The clinical phenotype associated with neuraminidase deficiency is variable and includes **type I** sialidosis, which usually presents in the 2nd decade of life with myoclonus and cherry-red spots in the macula. These patients typically present secondary to gait disturbances, myoclonus, or visual complaints. In contrast, **type II** sialidosis occurs at several ages of onset (congenital, infantile, and juvenile), depending on the severity of the gene mutation. The **congenital** and **infantile** forms result from isolated neuraminidase deficiency, whereas the **juvenile** form results from both neuraminidase and β-galactosidase deficiency.

The congenital type II disease is characterized by hydrops fetalis, neonatal ascites, hepatosplenomegaly, stippling of the epiphyses, periosteal cloaking, and stillbirth or death in infancy. The type II infantile form presents in the 1st yr of life with dysostosis multiplex, moderate global developmental delays, visceromegaly, corneal clouding, cherry-red maculae, and seizures. The juvenile type II form of sialidosis, which is sometimes designated *galactosialidosis*, has a variable age of onset ranging from infancy to adulthood. In infancy, the phenotype is similar to that of GM_1 gangliosidosis, with edema, ascites, skeletal dysplasia, and cherry-red spots. Patients with later-onset disease have dysostosis multiplex, visceromegaly, intellectual disability, dysmorphism, corneal clouding, progressive neurologic deterioration, and cherry-red spots.

No specific therapy exists for any form of the disease, although studies in animal models have demonstrated improvement in the phenotype after bone marrow transplantation. The **diagnosis** of sialidosis and galactosialidosis is achieved by the demonstration of the specific enzymatic deficiency or by mutations in the responsible gene. **Prenatal diagnosis** using cultured amniotic cells or chorionic villi is available by demonstrating the enzyme defect and/or specific gene mutations.

Aspartylglucosaminuria

This is a rare autosomal recessive lysosomal storage disorder, except in Finland, where the carrier frequency is estimated at 1 in 36 adults, the high frequency due to a *founder* gene. The disorder results from the deficient activity of **aspartylglycosaminidase** and the subsequent accumulation of aspartylglycosamine, particularly in the liver, spleen, and thyroid. The gene for the enzyme *(AGA)* has been localized to chromosome 4q32-33, and the DNA and gene have been isolated and sequenced. In the Finnish population, a single *AGA* mutation encoding p.C163S accounts for most mutant alleles, whereas outside of Finland, a large number of private mutations have been described.

Affected individuals with aspartylglucosaminuria typically present in the 1st yr of life with recurrent infections, diarrhea, and umbilical hernias. Coarsening of the facies and short stature usually develop later. Other features include joint laxity, macroglossia, hoarse voice, crystal-like lens opacities, hypotonia, and spasticity. Psychomotor development is usually near normal until age 5 yr, when a decline is noted. Behavioral abnormalities are typically seen, and IQ values in affected adults are usually<40 (severe intellectual disability). Survival to adulthood is common, with most early deaths attributable to pneumonia or other pulmonary causes. Definitive **diagnosis** requires demonstration of markedly deficient aspartylglucosaminidase in peripheral blood leukocytes, and/or the specific *AGA* mutation(s). Several patients have undergone allogeneic bone marrow transplants, but this approach has not proved effective, and *no specific treatment is available*. **Prenatal diagnosis** is available by the determination of aspartylglucosaminidase deficiency and/or the specific *AGA* mutations in cultured amniocytes or chorionic villi.

α-Mannosidosis

This autosomal recessive disorder results from the deficient activity of **α-mannosidase** and the accumulation of mannose-rich compounds. The gene *MAN2B1* encoding the enzyme has been localized to chromosome 19p13.2-q12, and the cDNA and gene sequence have been determined. To date >140 gene mutations have been reported. Affected patients display clinical heterogeneity. There is a severe infantile form, or **type I** disease, and a milder juvenile variant, **type II** disease. All patients have psychomotor retardation, facial coarsening, and dysostosis multiplex. The **infantile** form of the disorder, however, is characterized by more rapid cognitive deterioration, with death occurring between ages 3 and 10 yr. Patients with the infantile form also have more severe skeletal involvement and hepatosplenomegaly. The **juvenile** disorder is characterized by onset of symptoms in early childhood or adolescence, with milder somatic features and survival to adulthood. Hearing loss, destructive synovitis, pancytopenia, and spastic paraplegia have been reported in type II patients. The **diagnosis** is made by the demonstration of the marked deficiency of α-mannosidase activity in white blood cells or cultured fibroblasts. Clinical trials of ERT with recombinant human α-mannosidase are underway. **Prenatal diagnosis** can be made by demonstrating the enzyme defect and/or the specific gene mutations in cultured amniocytes or chorionic villi.

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105.7

Congenital Disorders of Glycosylation

Eva Morava, Peter Witters

Keywords

glycosylation
deglycosylation
glycans
transferrin isoelectric focusing
TIEF
cerebro-ocular dysplasia–muscular dystrophy

phosphomannomutase-2 deficiency
PMM2-CDG
mannosephosphoisomerase deficiency
MPI-CDG
mannose therapy
glucosyltransferase-1 deficiency
ALG6-CDG
UDP-GlcNAc:Dol-P-GlcNAc-P transferase deficiency
DPAGT1-CDG
muscle-eye-brain disease
hyperphosphatasia
PIGA-CDG
steroid 5α-reductase deficiency
SRD5A3-CDG
cutis laxa
Golgi-α_{1-2} mannosidase-1 deficiency
MAN1B1-CDG
phosphoglucomutase-1 deficiency
PGM1-CDG
D -galactose
Golgi homeostasis
manganese transporter defect
SLC39A8-CDG
N -glycanase-1 deficiency
NGLY1

Glycosylation is the complex multistep metabolic process of adding (oligo)saccharides to proteins and lipids. The classification of **disorders of hypoglycosylation** is based on biochemical structures: (1) defects in protein *N* -linked glycosylation, (2) defects in protein *O* -linked glycosylation, (3) defects in glycosphingolipid and in glycosylphosphatidylinositol-anchor glycosylation, and (4) defects in multiple glycosylation pathways and in other pathways (Fig. 105.7). No disorders are known to result from abnormal *C* -linked glycosylation. Congenital disorders of glycosylation are labeled based on their genetic defect *(CDG)* .

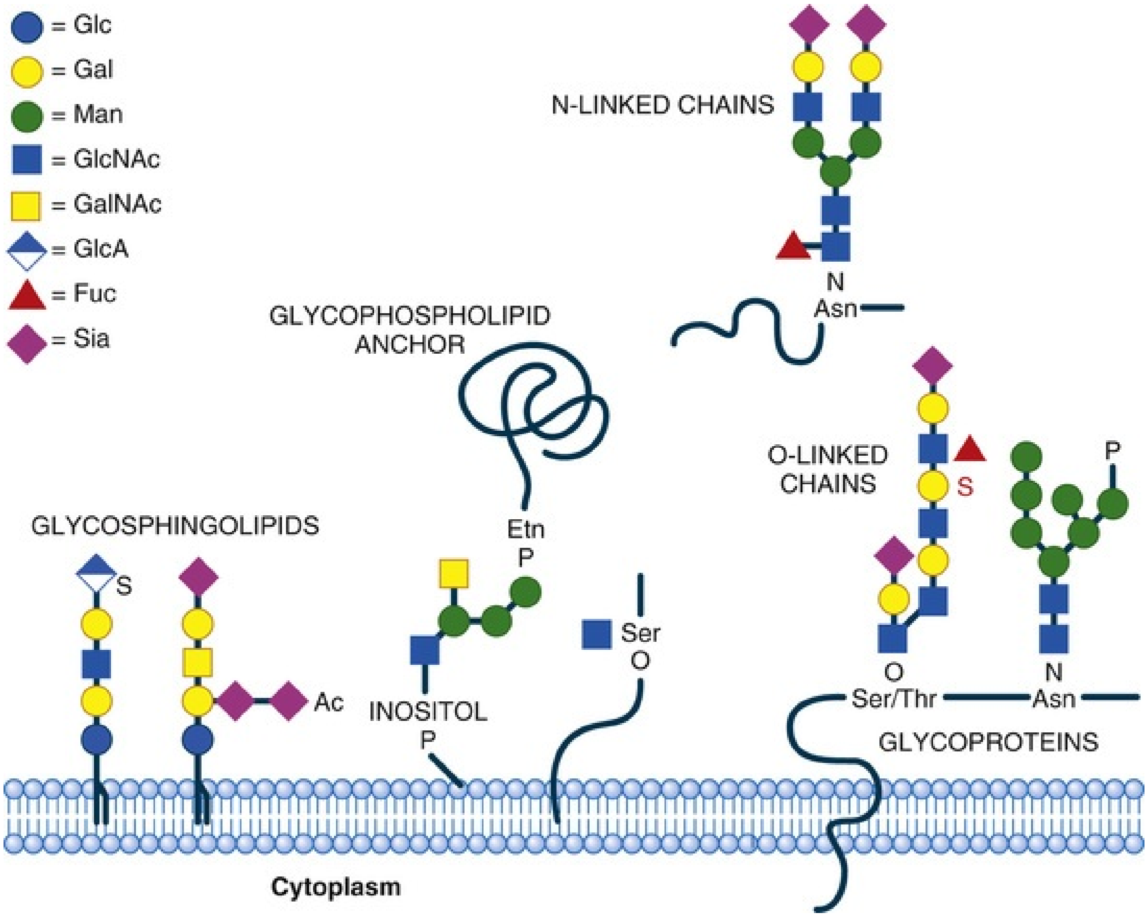
= Glc
= Gal
= Man
= GlcNAc
= GalNAc
= GlcA
= Fuc
= Sia
N-LINKED CHAINS
N
Asn
GLYCOPHOSPHOLIPID ANCHOR
O-LINKED CHAINS
S
P
GLYCOSPHINGOLIPIDS
S
Ac
Etn
P
INOSITOL
P
Ser
O
O
Ser/Thr
N
Asn
GLYCOPROTEINS
Cytoplasm

FIG. 105.7 Schematic of different types of glycosylation. ***Left to right,*** Glycosphingolipids, glycophospholipid anchor (GPI anchor), ***O*** -linked membrane protein glycosylation, ***N*** -linked membrane glycosylation, and secretory ***N*** -linked glycan.

Protein glycosylation is an essential pathway. Most functional proteins are glycosylated, including serum proteins (e.g., transferrin, ceruloplasmin, TBG), hormones (e.g., TSH, FSH, FH, ACTH, IGFBP3), and clotting and anticoagulation factors (e.g., factors IX and XI, antithrombin). Membrane proteins are also highly glycosylated. Important intracellular glycoproteins include enzymes such as glycosyltransferases or lysosomal enzymes.

N **-glycans** are linked to the amide group of asparagine. They are synthetized in a complicated process throughout the cytoplasm, endoplasmic reticulum (ER), and Golgi complex, starting with sugar activation and nucleotide sugar synthesis, then oligosaccharide assembly, and finally glycan processing (Fig. 105.8). The majority of the pediatric disorders are *N* -glycosylation disorders. ***O*** **-glycans** are linked to the hydroxyl group of serine or threonine. These diverse glycoproteins are mostly formed in the Golgi complex; their defects can involve xylosylation, fucosylation, mannosylation, or other modifications. An important focus is *O* -

mannosylation defects because of their relevance for dystroglycanopathies.

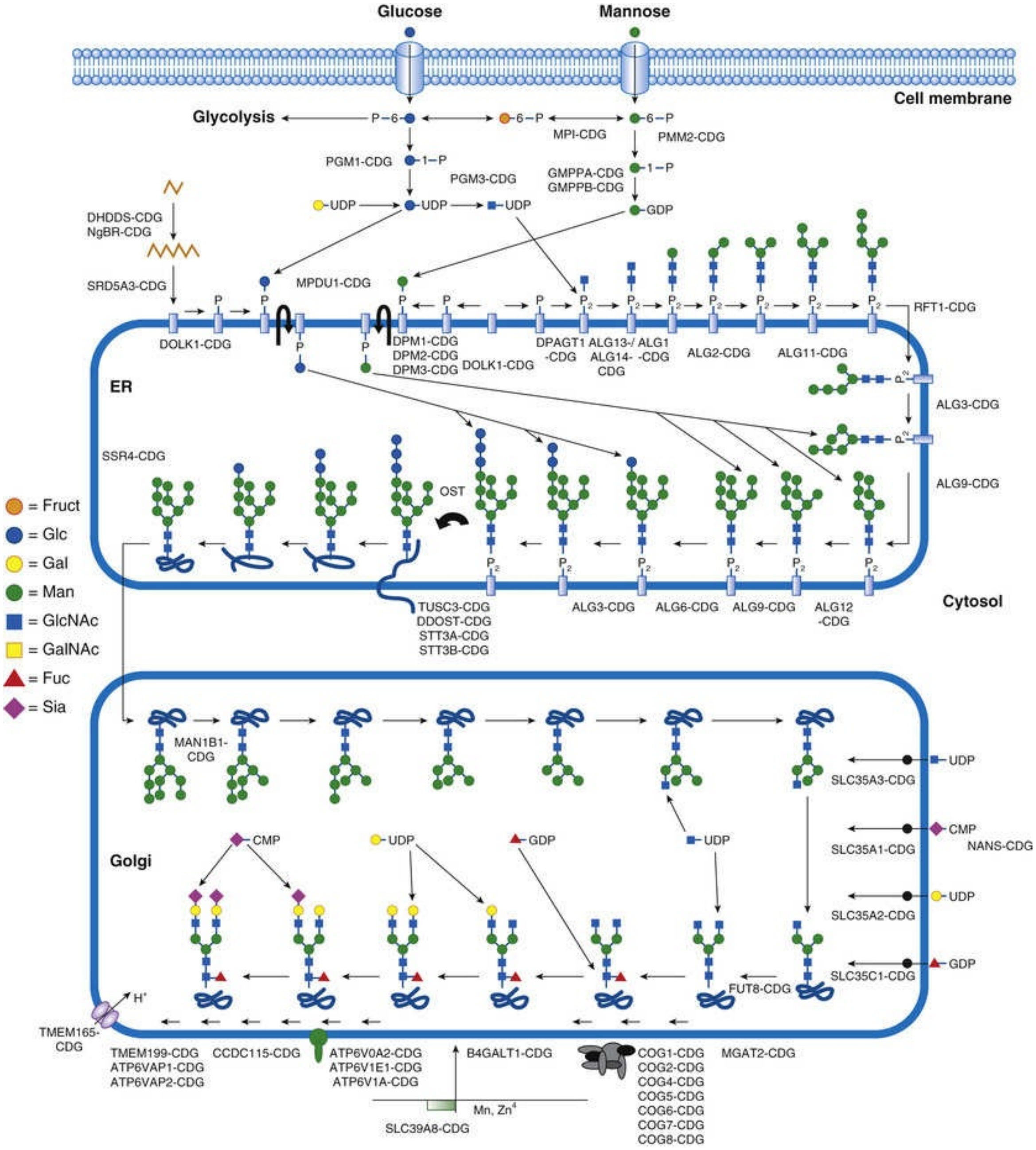
Glucose
Mannose
Cell membrane
Glycolysis
P–6–
6–P
–6–P
MPI-CDG
PMM2-CDG
PGM1-CDG
1–P
PGM3-CDG
GMPPA-CDG
GMPPB-CDG
–1–P
UDP
UDP
UDP
GDP
DHDDS-CDG
NgBR-CDG
SRD5A3-CDG
MPDU1-CDG
P
P
P
P_2
RFT1-CDG
DOLK1-CDG
DPM1-CDG
DPM2-CDG
DPM3-CDG
DOLK1-CDG
DPAGT1 -CDG
ALG13-/ ALG14- CDG
ALG1 -CDG
ALG2-CDG
ALG11-CDG
ER
ALG3-CDG
ALG9-CDG
SSR4-CDG
OST
= Fruct
= Glc
= Gal
= Man
= GlcNAc
= GalNAc
= Fuc
= Sia
TUSC3-CDG
DDOST-CDG
STT3A-CDG
STT3B-CDG
ALG3-CDG
ALG6-CDG
ALG9-CDG
ALG12 -CDG
Cytosol
MAN1B1-CDG
UDP
SLC35A3-CDG
CMP
SLC35A1-CDG
NANS-CDG
UDP
SLC35A2-CDG
GDP
SLC35C1-CDG
Golgi
CMP
UDP
GDP
UDP
FUT8-CDG
H^+
TMEM165-CDG
TMEM199-CDG
ATP6VAP1-CDG
ATP6VAP2-CDG
CCDC115-CDG
ATP6V0A2-CDG
ATP6V1E1-CDG
ATP6V1A-CDG
B4GALT1-CDG
COG1-CDG
COG2-CDG
COG4-CDG
COG5-CDG
COG6-CDG
COG7-CDG
COG8-CDG
MGAT2-CDG
Mn, Zn^+
SLC39A8-CDG

FIG. 105.8 **Overview of different cell compartments involved in *N* -linked protein glycosylation. Activation of nucleotide sugars in the cytoplasm is followed by step-by-step dolichol-linked synthesis of glycans associated with the endoplasmic reticulum. Transfer of the glycan from the lipid arm to the protein is followed by transport to the Golgi for further modifications.**

Lipid glycosylation is an essential process for the synthesis of ceramide and ganglioside synthesis. **Glycosylphosphatidylinositols** (GPIs) are very special glycolipids that link various proteins to the plasma membrane, as complex lipid-sugar anchors (GPI anchors, see Fig. 105.7).

Congenital disorders of glycosylation (CDG) are predominantly multisystem diseases, caused by >140 different genetic defects in glycoprotein and glycolipid glycan synthesis. This rapidly growing group is one of the newest and largest metabolic disorder groups. Most patients described with CDG have *N* -glycosylation defects, followed by the fastest-growing group of CDGs, involving multiple glycosylation pathways and dolicholphosphate synthesis. Smaller groups are *O* -glycosylation disorders and disorders of glycosylphosphatidylinositol. The “oldest” CDG is PMM2-CDG, in which the genetic defect leads to the loss of **phosphomannomutase 2** (PMM2), the enzyme that catalyzes the conversion of mannose-6-phosphate into mannose-1-phosphate. The majority of CDGs have an autosomal recessive inheritance. Only 2 *N* -linked CDGs are autosomal dominant, GANAB-CDG and PRKCSH-CDG. The dominantly inherited *O* -linked CDGs include EXT1/EXT2-CDG, POFUT1-CDG, and POGLUT1-CDG. X-linked CDGs include ALG13-CDG, SSR4-CDG, PIGA-CDG, SLC35A2-CDG, ATP6AP2-CDG and ATP6AP1-CDG.

Some CDGs are lethal; 20% of PMM2-CDG patients die in the 1st 2 yr of life. Some patients, however, stabilize throughout young adulthood. Almost any clinical phenotype can be present in a patient with CDG. It can affect any organ or organ system and most often includes the central nervous system (CNS). The most common clinical features include developmental and speech delay, seizures, ataxia, spasticity, peripheral neuropathy, hypotonia, strabismus, abnormal fat distribution, visual loss, cardiomyopathy, feeding difficulties, liver dysfunction, endocrine abnormalities, bleeding diathesis, and thrombosis (Fig. 105.9 and Table 105.6). Single-organ presentations are rare in CDGs (e.g., TUSC3-CDG and ST3GAL3-CDG: brain; DHDDS-CDG: retina; ALG14-CDG: neuromuscular junction; POFUT1-CDG and POGLUT1-CDG: skin; SEC23B-CDG: red cell lineage; EXT1/EXT2-CDG: cartilage; TMEM199-CDG: liver). Many CDGs are recognizable syndromes. CDG should be considered in any patient with a developmental disability or an unexplained clinical condition, especially in multisystem disease with neurologic involvement.

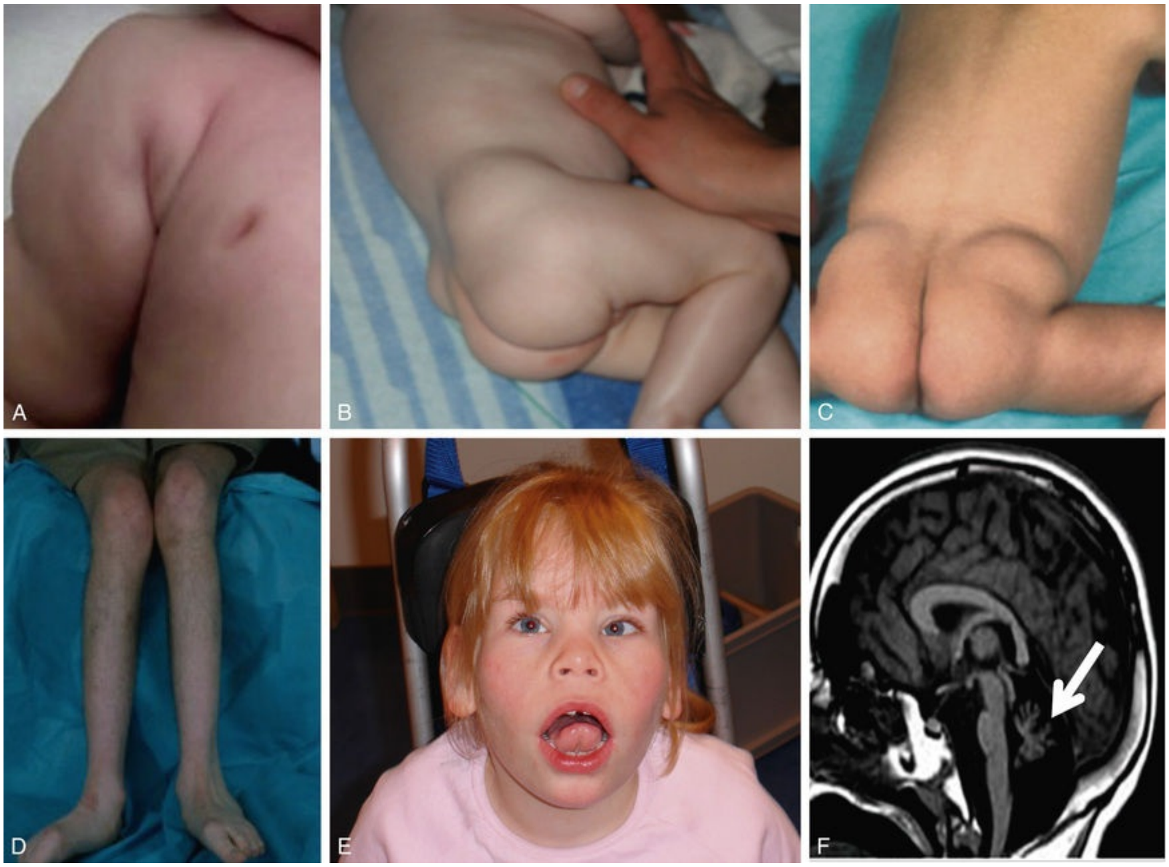

FIG. 105.9 Patients with phosphomannomutase-2 deficiency (PMM2-CDG) and recognizable clinical features. A, Inverted nipples. B and C, Abnormal fat distribution. D, Muscle atrophy caused by peripheral neuropathy after puberty. E, Characteristic facial features with strabismus, short nose, anteverted nares, long philtrum, and large ears. F, MRI of brain with T1-weighted sagittal image showing cerebellar vermis hypoplasia *(arrow)* and brain atrophy.

Table 105.6

Clinical and Laboratory Features in Common Congenital Disorders of Glycosylation (CDGs), with Clinically Recognizable Phenotype and Abnormal Glycosylation, Detectable by Serum Transferrin Isoform Analysis (TIEF)

DEFECTIVE GENE	MOST FREQUENT CLINICAL FEATURES	SUGGESTIVE FEATURES	LABORATORY ABNORMALITIES	OTHER BIOCHEMICAL ANOMALIES
PMM2	Strabismus, nystagmus, smooth philtrum, large ears, vomiting, diarrhea, FTT, axial hypotonia, cerebellar vermis hypoplasia, ataxia, psychomotor disability,	Inverted nipples and/or abnormal fat pads, stroke-like episodes	Elevated serum transaminases, hypoalbuminemia, decreased factor IX, XI and AT activity, low serum	Type 1 serum TIEF, decreased PMM activity in leukocytes and fibroblasts

	seizures, spasticity, neuropathy, pigmentary retinitis		ceruloplasmin and TBG levels	
PMI	Cholestasis, hepatomegaly, feeding difficulties, recurrent vomiting, chronic diarrhea, ascites, recurrent thrombosis, gastrointestinal bleeding	Hyperinsulinism, protein losing enteropathy Normal intelligence and absence of neurologic features	Elevated transaminases, hypoalbuminemia, hypoglycemia, decreased factor IX, XI, and AT-III activity	Type 1 serum TIEF, decreased PMI activity in leukocytes and fibroblasts
ALG6	Hypotonia, muscle weakness, seizures, ataxia, intellectual disability, behavioral abnormalities	(Distal limb malformations)	Elevated serum transaminases; hypoalbuminemia; decreased factor IX, XI, and AT activity; low serum IgG level	Type 1 serum TIEF, abnormal LLO results in fibroblasts
DPAGT1	Microcephaly, brain malformations, hypotonia, severe psychomotor disability, seizures, spasticity, proximal weakness, failure to thrive, joint contractures	Congenital myasthenia phenotype In multisystem phenotype: cataract	Decreased AT, protein C, and protein S activity; increased creatine kinase; hypoalbuminemia; normal creatine kinase in myasthenia	Type 1 serum TIEF
SRD5A3	Developmental delay, hypotonia, ataxia, cerebellar vermis hypoplasia, intellectual disability, speech delay, visual loss	Congenital cataract, retinal and iridic coloboma, glaucoma, optic nerve dysplasia, ichthyosis	Low anticoagulation factors (AT, protein C, and protein S activity), increased serum transaminases	Type 1 serum TIEF *but reported false-negative TIEF*
ATP6V0A2	Generalized cutis laxa, hypotonia, strabismus, characteristic facial features, joint laxity, seizures, motor and language developmental delay, spontaneous improvement of cutis laxa by aging	Cobblestone-like brain dysgenesis	Mild coagulation abnormalities, increased serum transaminase levels	Type 2 serum TIEF *but reported false-negative TIEF* Abnormal apoC-III IEF, characteristic MALDI TOF profile (Note abnormal skin histology)
ATP6V1A and ATP6V1E1		Cardiovascular anomalies	Mild coagulation abnormalities and increased serum transaminase levels, hypercholesterolemia	
PGM1	Pierre Robin sequence, cholestasis, short stature, dilated cardiomyopathy,	Cleft palate, hyperinsulinism, normal intelligence	Hypoglycemia, increased serum transaminase levels, decreased AT	Mixed type 1/ 2 serum TIEF, decreased fibroblast PGM1 activity
MAN1B1	Developmental delay, speech delay, intellectual disability, muscle weakness	Obesity, autistic features, inverted nipples, characteristic face	Increased serum transaminase levels, low AT	Type 2 serum TIEF, abnormal apoC-III IEF, diagnostic MALDI TOF profile
TMEM199	Cholestasis, hepatomegaly,	Normal intelligence	Decreased serum	Type 2 serum

CCDC115	liver steatosis, liver fibrosis, liver failure, spontaneous bleedings, motor developmental delay	Hepatomegaly	ceruloplasmin, increased serum transaminase levels, hypercholesterolemia, high AP	TIEF, abnormal apoC-III IEF, characteristic MALDI TOF profile
ATP6AP1 and ATP6AP2		Immune deficiency		
SLC39A8	Seizures, hypsarrhythmia, hypotonia, developmental and speech delay, FTT	Dwarfism, craniosynostosis, rhizomelia, Leigh disease	Decreased serum manganese, high serum transaminases, abnormal coagulation	Type 2 serum TIEF, abnormal apoC-III, characteristic MALDI TOF profile

AP, Alkaline phosphatase; AT, antithrombin; apoC-III: apolipoprotein C-III; FTT, failure to thrive; LLO, lipid-linked oligosaccharides; MALDI-TOF, matrix-assisted laser desorption/ionization time of flight; TBG, thyroxine-binding globulin; TIEF, transferrin isoelectric focusing.

There are also **congenital disorders of deglycosylation** , including known lysosomal disorders and a severe neurologic condition caused by defective *N* -glycanase function (*NGLY1* defect).

Laboratory evaluations in most *N* -linked CDGs rely on a primary screening method called serum **transferrin isoelectric focusing (TIEF)** . Transferrin isoforms, which are hyposialylated (missing terminal sialic acid residues), show different cathodal shifts depending on either missing glycan chains or truncated glycans. A **type 1 pattern** suggests an early metabolic defect in the cytosolic-ER–related glycan synthesis and assembly. A **type 2 pattern** suggests Golgi-related glycan-processing defects (Fig. 105.10).

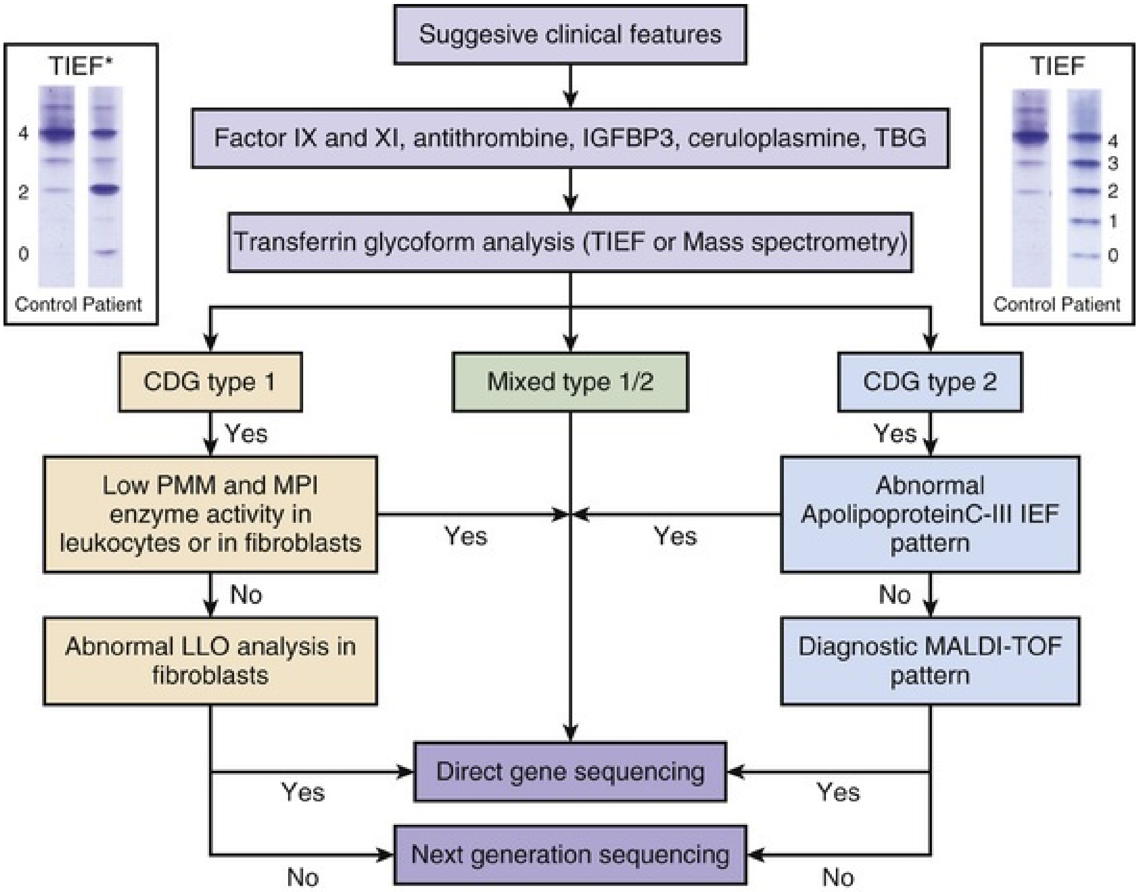
TIEF*
4
2
0
Control Patient
Suggesive clinical features
Factor IX and XI, antithrombine, IGFBP3, ceruloplasmine, TBG
Transferrin glycoform analysis (TIEF or Mass spectrometry)
TIEF
4
3
2
1
0
Control Patient
CDG type 1
Mixed type 1/2
CDG type 2
Yes
Yes
Low PMM and MPI enzyme activity in leukocytes or in fibroblasts
Yes
Yes
Abnormal ApolipoproteinC-III IEF pattern
No
No
Abnormal LLO analysis in fibroblasts
Diagnostic MALDI-TOF pattern
Direct gene sequencing
Yes
Yes
Next generation sequencing
No
No

FIG. 105.10 Diagnostic flow chart of glycosylation disorders affecting N-linked glycosylation. *Instead of TIEF, mass spectrometry methods can be used as well. IGFBP3, Insulin-like growth factor–binding protein 3; TBG, thyroxine-binding globulin; CDG, congenital disorders of glycosylation; PMM, phosphomannomutase; MPI, mannosephosphoisomerase, LLO, lipid-linked oligosaccharides; TIEF, transferrin isoelectric focusing; IEF, isoelectric focusing; MALDI-TOF, matrix-assisted laser desorption/ionization time of flight.

Isoelectric focusing of apolipoprotein C-III (**IEF apoC-III)** , a serum mucine type *O* -glycosylated protein, can detect some *O* -glycosylation disorders (combined *N* - and *O* -linked glycosylation defects). Mass spectrometry in serum for type 1 defects is highly sensitive for mild glycosylation abnormalities. Glycomics by matrix-assisted laser desorption/ionization time of flight (**MALDI-TOF**) can be diagnostic in specific types of CDG (mostly Golgi related with a type 2 pattern). Dolichol-linked glycan or lipid-linked oligosaccharide (LLO) analysis is a complicated but sensitive method to detect ER-related *N* -glycan assembly (CDG type 1) defects in patient fibroblasts. GPI-anchor defects can be suspected based on *recurrent elevation of alkaline phosphatase levels* in blood.

Dystroglycanopathies can be confirmed based on abnormal immunohistochemistry in muscle biopsy. Fluorescence-activated cell sorting (**FACS**) analysis of the membrane-anchored markers CD16 and CD24 in leukocytes is highly suggestive for a GPI-anchor abnormality, especially when alkaline phosphatase in blood is significantly elevated. Enzyme analysis in blood is only available for a few, more common CDGs (PMM2-CDG, MPI-CDG, PGM1-CDG); it is more reliable in fibroblasts.

With an abnormal TIEF pattern result or clinical suspicion of any type of CDG, most metabolic centers use a direct *CDG* gene panel analysis or next-generation sequencing (NGS; whole exome sequencing) (see Fig. 105.10).

Congenital Disorders of Protein *N* -Glycosylation

Phosphomannomutase-2 Deficiency (PMM2-CDG)

Clinical Manifestations

PMM2-CDG is the most common and easily recognizable CDG. Most patients have alternating strabismus, characteristic facial features (short nose, long philtrum, large ears) (Fig. 105.9*E*), inverted nipples and/or abnormal fat pads (Fig. 105.9*A* -*C*), feeding difficulties, axial hypotonia, and decreased reflexes, already in the 1st few mo of life. Nystagmus (caused by pontocerebellar and vermis hypoplasia; Fig. 105.9*F*) is also common. Psychomotor disability is present in most patients, but normal intellectual development has been described in a few patients. Most patients develop a multisystem disease, and <25% show an isolated neurologic phenotype without other organ involvement, normal endocrine regulation, and no coagulopathy. The neurologic involvement is quite diverse, with ataxia, seizures, spasticity, and peripheral neuropathy (Fig. 105.9*D*) the most common features. Dystonia, stroke-like episodes, and proximal myopathy can also occur. PMM2-CDG is not a progressive disease, but certain features, when present, typically appear at different ages during the disease. From birth, pericardial fluid collection, cardiomyopathy, or chronic vomiting/diarrhea can occur; after 7 yr, retinitis pigmentosa and cataract; and after puberty, scoliosis, neuropathy, and recurrent thrombotic events. Liver function anomalies are mild, and only a few patients develop cholestasis or liver fibrosis. Most patients have a hypergonadotropic hypogonadism; no successful pregnancies have been reported. Intellectual disability can be mild to severe; speech development is frequently delayed and can even be absent. Autistic behavior is common, although patients usually have a cheerful personality.

Pathophysiology

Phosphomannomutase 2 catalyzes the conversion of mannose-6-phosphate to mannose-1-phosphate, essential for the formation of activated mannose units used in the synthesis of the growing glycan chain in the ER. Hypoglycosylation leads to abnormal function affecting many essential glycoproteins, such as coagulation and anticoagulation factors, endocrine regulation, transport proteins, liver function, and immune, membrane, and receptor proteins.

Diagnosis

The primary screening method for PMM2-CDG is serum transferrin glycoform analysis, which is most frequently performed by TIEF. Intact transferrin has 4 negatively charged sialic acid residues (tetrasialotransferrin). Transferrin glycoforms, missing terminal sialic acid residues, show different cathodal shifts, less abundant tetrasialotransferrin, increased disialotransferrin, and some a-sialotransferrin (see Fig. 105.10). This is the so-called type 1 pattern, suggestive of a defect in glycan assembly in the cytosol-ER. Transferrin isoforms are also detectable by mass spectrometry. Certain other disorders can cause a *false-positive* transferrin isoform pattern, including galactosemia, hereditary fructose intolerance, and excessive alcohol use. PMM enzyme analysis is available in leukocytes and fibroblasts.

The presence of elevated serum transaminases, hypoalbuminemia, decreased factor IX and XI and antithrombin activity, or low ceruloplasmin or thyroxine-binding globulin (TBG) level is highly suggestive of CDG, including the most common type, PMM2-CDG.

PMM2-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The most frequent pathogenic variant (c.422G>A; R141H) is present in 75% of patients of Caucasian origin. The exact incidence of PMM2-CDG is not known, but it is estimated to be as high as 1 in 40,000-80,000 in Europe. Prenatal diagnosis is only reliable by genetic testing.

Treatment

The therapy in PMM2-CDG relies on supportive treatment. Even with the best treatment, mortality is about 20% in the 1st 2 yr of life, mostly from cardiac or kidney involvement and severe infections. Current recommended therapy includes adequate nutrition, diet or tube feeding if needed, cardiac support, hormone supplements, physical and occupational therapy, speech therapy, seizure management, and strabismus surgery. Therapeutic developments include targeted mannose-phosphate treatment, and chaperone therapy; these are only in preclinical trial phases.

Mannosephosphoisomerase Deficiency (MPI-CDG)

Clinical Manifestations

MPI deficiency is a recognizable and treatable CDG. Most patients show early symptoms of liver disease (cholestasis, elevated transaminases) and feeding difficulties, with recurrent vomiting and chronic diarrhea, most frequently with protein-losing enteropathy. Life-threatening episodes might appear as early as the 1st few mo of life with recurrent thrombosis and severe gastrointestinal bleeding because of severe coagulation abnormalities. Hypoglycemia is usually caused by hyperinsulinism. Hypoalbuminemia can be severe; patients might develop visible abdominal distention from a combination of ascites and hepatomegaly. Patients with MPI-CDG have no other organ involvement, and the CNS is not affected. There are no dysmorphic features. The liver disease frequently progresses to fibrosis or cirrhosis.

Pathophysiology

Mannosephosphoisomerase (MPI) catalyzes the conversion of fructose-6-phosphate to mannose-6-phosphate, 1 step before PMM2, therefore blocking the formation of activated mannose units (GDP mannose) for oligosaccharide synthesis. Hypoglycosylation leads to abnormal glycoprotein function the same as in PMM2-CDG, especially coagulation and anticoagulation factors, liver function, and hormone receptors.

Diagnosis

The primary screening method in a suspected MPI-CDG patient is serum transferrin isoform analysis by TIEF (see Fig. 105.10) or MS analysis. MPI deficiency leads to a type 1 pattern, as seen in PMM2 deficiency. MPI enzyme analysis is available in leukocytes and fibroblasts. The presence of elevated serum transaminases, hypoalbuminemia, decreased factor IX and XI and antithrombin activity, hyperinsulinism, and nonketotic hypoglycemia are highly suggestive for MPI-CDG.

MPI-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The exact incidence of MPI-CDG is not known, but it is estimated at 1 : 800 000 in Europe. Prenatal diagnosis is only reliable by genetic testing. Although this is a rare CDG, early diagnosis is imperative because it is treatable.

Treatment

MPI-CDG is the first CDG type treatable by dietary therapy. Mannose therapy is clinically effective by both IV and oral supplementation of 1 g/kg/day divided into 3-4 doses. A known side effect is hemolysis. The treatment uses an alternative pathway: mannose can be phosphorylated by hexokinases to mannose 6-phosphate, bypassing the MPI defect. The clinical symptoms improve rapidly, but liver function might further deteriorate. Liver fibrosis and cirrhosis might necessitate liver transplantation, which will resolve the metabolic disease. The oldest patient known with MPI-CDG has survived into her late 30s.

Glucosyltransferase-1 Deficiency (ALG6-CDG)

Clinical Manifestations

ALG6-CDG is the 2nd most common CDG. Most patients have hypotonia, muscle weakness, seizures, and ataxia. To date, no patient with ALG6-CDG has normal intelligence. Speech delay and nystagmus are common neurologic signs. Brachydactyly, skeletal abnormalities, and transverse limb defects have been observed. Strabismus and characteristic facial dysmorphism are rare (hypertelorism, oval face, short nose). Inverted nipples and/or abnormal fat pads are exceptional in ALG6-CDG.

The most severe ALG6-CDG patients show a multisystem phenotype in the 1st few mo of life, including severe infections, protein-losing enteropathy, hypoalbuminemia, anemia, and failure to thrive. Autistic behavior and mood changes have been observed in several patients. The oldest patient to date is almost 45 yr.

Pathophysiology

The metabolic problem is caused by defective binding of the 1st of 3 glucoses to the lipid-linked oligosaccharide in the ER. This glucose binding is essential for attachment of the oligosaccharyltransferase enzyme complex to the newly built oligosaccharide chain and the ability to transfer it to the protein. This leads to protein hypoglycosylation and abnormal glycoprotein function similar to PMM2-CDG and MPI-CDG. Laboratory abnormalities are also similar, including abnormalities in coagulation and anticoagulation factors, liver function, thyroid hormones, and immunoglobulins (IgG).

Diagnosis

The primary screening method in a suspected ALG6-CDG patient is serum transferrin glycoform analysis by TIEF or MS analysis. ALG6 deficiency leads to a type 1 pattern (see Fig. 105.10), as seen in PMM2 and MPI deficiency. There is no available enzyme analysis, although lipid-linked oligosaccharides could be evaluated in patient fibroblasts.

ALG6-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The most common mutations are p.A333V and p.I299Del. Prenatal diagnosis is only reliable by genetic testing. The exact incidence of ALG6-CDG is not known.

Treatment

The current therapy in ALG6-CDG relies on supportive treatment. Mortality is about 10% in the 1st years of life, mostly from protein-losing enteropathy and severe infections.

UDP-GlcNAc:Dol-P-GlcNAc-P Transferase Deficiency (DPAGT1-CDG)

Clinical Manifestations

DPAGT1 deficiency is a recognizable and potentially treatable CDG. About one third of patients show the **congenital myasthenia** phenotype, indistinguishable from other genetic congenital myasthenias. Creatine kinase (CK) levels are normal. These patients have a relatively good prognosis, especially with early myasthenia therapy. The other patients show a multisystem phenotype with microcephaly, brain malformations, hypotonia, severe psychomotor disability, seizures, spasticity, failure to thrive, joint contractures, and cataracts.

Pathophysiology

DPAGT1 defect leads to very early arrest of glycan synthesis outside the ER membrane, by slowing down the addition of the 2nd GlcNAc sugar to the phosphorylated dolichol arm. Abnormal receptor glycosylation in the *neuromuscular junction* leads to myasthenia. Hypoglycosylation in the multisystem type leads to abnormal glycoprotein function similar to that in PMM2-CDG, especially involving the anticoagulation factors, and interestingly leading to high serum CK (in contrast to the congenital myasthenia phenotype) and hypoalbuminemia.

Diagnosis

The primary screening method is serum transferrin glycoform analysis or MS analysis. Most patients show a type 1 pattern (see Fig. 105.10), but patients with the congenital myasthenia phenotype can show normal screening. There is no clinically available enzyme analysis.

DPAGT1-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The exact incidence is not known. Prenatal diagnosis is only reliable by genetic testing. Because of the false-negative TIEF results in several patients with the myasthenic phenotype, congenital myasthenia panel testing is suggested in suspected cases, especially for determining the potential therapy.

Treatment

The congenital myasthenia phenotype is frequently treatable by high-dose pyridostigmine, eventually enhanced with salbutamol. In the multisystem phenotype of DPAGT1-CDG, treatment is supportive.

Congenital Disorders of Protein *O* -Glycosylation

Cerebro-Ocular Dysplasia–Muscular Dystrophy and Muscle-Eye-Brain Disease

Spectrum (POMT1-CDG, POMT2-CDG, POMGNT1-CDG)

From isolated muscular dystrophy to **Walker Warburg syndrome** , this group of *O* -linked glycosylation disorders presents with severe muscle weakness, congenital eye malformations, and neuronal migration defects. Pachygyria, cobblestone dysgenesis, hydrocephalus, polymicrogyria, heterotopias, and corpus callosum agenesis are variably present. Eye malformations include anophthalmia, microphthalmia, congenital cataract, or colobomas. **Congenital muscular dystrophy** is associated with significant CK level elevations. There is severe psychomotor disability.

The underlying metabolic defect is the abnormal synthesis of the *O*-mannosylglycan core, which is essential for the proper glycosylation of α-dystroglycan. The α-dystroglycan is heavily *O* -glycosylated with mannose residues and is expressed in both muscle and brain. Defective mannosylation of α-dystroglycan leads to muscle degeneration and migration defects. Muscle biopsy shows abnormal α-dystroglycan staining on immunohistochemistry.

Transferrin isoelectric focusing is normal in patients with isolated *O* -mannosylation defects. There is also no clinically available enzyme analysis. **Diagnosis** is based on histology (muscle biopsy) and genetic analysis.

POMT1-CDG, POMT2-CDG, POMGNT1-CDG are the most common autosomal recessive α-dystroglycanopathies. Additional gene defects occur in the pathway; *POMK*, *FKTN*, *FKRP*, *LARGE*, *B4GAT1*, *TMEM5*, and *ISPD* have been described in association with human disease. The exact incidence of α-dystroglycanopathies is not known.

In α-dystroglycanopathies the **treatment** is supportive.

Defects in Lipid Glycosylation and in Glycosylphosphatidylinositol Anchor Biosynthesis

Hyperphosphatasia–Intellectual Disability Syndromes: PIGA Deficiency (PIGA-CDG)

This clinically recognizable syndrome is an epilepsy syndrome with intellectual disability, hypotonia, dysmorphic facial features, skin anomalies, congenital brain malformations, and behavioral abnormalities, including autism. Other organ malformations, including cardiac and renal defects, have also been reported. (Note that *somatic* mutations with *PIGA* defect can also lead to paroxysmal nocturnal hemoglobinuria.)

N -acetylglucosamine (GlcNAc) cannot be efficiently transferred to phosphatidylinositol for glycophosphatidylinositol synthesis. Abnormal anchoring of alkaline phosphatase leads to hyperphosphatasemia in blood and loss of specific surface antigens on blood cells.

Transferrin isoform analysis is normal in GPI-anchor defects. FACS analysis of the membrane-anchored markers CD16 and CD24 in leukocytes is highly suggestive for a GPI-anchor abnormality, especially in association with increased levels of serum alkaline phosphatase. Mutation analysis confirms the defect.

PIGA-CDG is X-linked. The exact incidence is not known. A similar phenotype has been described in *PIGO, PIGV, PIGY, PIG*, *PGAP2*, and *PGAP3* defects.

In PIGA-CDG the **treatment** is supportive.

Defects in Multiple Glycosylation Pathways and in Other Pathways, Including Dolicholphosphate Biosynthesis Defects

Steroid 5α-Reductase Deficiency (SRD5A3-CDG)

Clinical Manifestations

SRD5A3 deficiency is a clinically recognizable CDG, originally described as a multiple–congenital malformation syndrome. About 20 patients have been diagnosed at different ages, including one at 45 yr. Patients have hypotonia, ataxia, and eye abnormalities, including congenital cataract, retinal and iridic colobomas, glaucoma, optic nerve dysplasia, and visual loss. Cerebellar vermis hypoplasia can be variable. Intellectual disability has been described in all affected patients thus far. About one third of patients have severe *congenital ichthyosis* . Hypertrichosis and dysmorphic facial features are common, including squared face, high forehead, large ears, and coarsening. Some children with SRD5A3-CDG have a severe autism spectrum disorder. Skeletal abnormalities (scoliosis) and cardiac malformations are less common.

Pathophysiology

SRD5A3 deficiency leads to abnormal dolichol synthesis affecting early glycan synthesis outside the ER membrane and affects *O* -mannosylation and GPI-anchor synthesis. Hypoglycosylation affects anticoagulation factors and leads to increased serum transaminases.

Diagnosis

The primary screening method in a suspected SRD5A3-CDG patient is serum transferrin glycoform analysis or MS analysis. Most patients show a type 1 pattern (see Fig. 105.10), but several false-negative cases have been described. There is no clinically available enzyme analysis.

SRD5A3-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The exact incidence is not known.

Treatment

In SRD5A3-CDG the treatment is supportive.

Autosomal Recessive Cutis Laxa Type 2 (ARCL-2A or ATP6V0A2-CDG, ATP6V1A-CDG and ATP6V1E1-CDG)

Clinical Manifestations

ATP6V02-CDG is a multiple-malformation syndrome originally described as *cutis laxa syndrome* and recently discovered to be a combined *N* - and *O* -linked glycosylation disorder. Patients show generalized cutis laxa with inelastic, sagging skin at birth, hypotonia, strabismus, myopia, characteristic facial features, and joint laxity. The facial features include hypertelorism, short nose, long philtrum, down-slanting palpebral fissures with sagging eyelids, and sagging cheeks. Cardiovascular involvement is rare, and there is variable CNS involvement. Seizures and motor and language developmental disability are common, but normal intelligence has been described as well. Sensorineural hearing loss is sometimes observed. Some patients have vermis hypoplasia, and several children have been described with cobblestone like dysgenesis and partial pachygyria on brain MRI. Skeletal abnormalities and short stature are common, as well as late-closing fontanels, and/or brachydactyly and scoliosis. There is frequently enamel dysplasia. The skin features spontaneously improve with age. **ATP6V1A-CDG** and **ATP6V1E1-CDG** show a highly overlapping phenotype with associated cardiovascular symptoms and hypercholesterolemia.

Pathophysiology

ATP6V0A2 is a membrane subunit of the proton pump of the vesicular adenosine triphosphatase (V-ATPase) complex. Abnormal function of the V-ATPase complex alters the pH gradient in the secretory pathway and affects the maturation and transport of several glycosyltransferases and elastic fibers (e.g., elastin). ATP6V1A and ATP6V1E1 are other complex subunits affecting ATP6V0A2 function and cause secondary ATPase deficiency. Both *N* - and *O* -linked glycosylation are affected. There are mild coagulation abnormalities and high serum transaminase levels in some patients.

Diagnosis

The primary screening method in a suspected ATP6V0A2-CDG patient is serum transferrin glycoform analysis or MS analysis. Most patients show a type 2 pattern (see Fig. 105.10), but false-negative cases have been described before age 6 wk. Apolipoprotein III-C (apoC-III) is a mucin-type secretory glycoprotein that is only *O* -glycosylated. ApoC-III IEF shows a hypoglycosylation pattern in patients, even when the TIEF is falsely negative. Skin biopsy in patients show classic histologic changes of cutis laxa with diminished, short, abnormal, and fuzzy elastic fibers.

ATP6V0A2-CDG is autosomal recessive. Genetic testing is mostly performed by direct sequencing. The exact incidence is not known. *ATP6V1A* and *ATP6V1E1* defects have been recently described.

Treatment

In autosomal recessive cutis laxa type 2, the treatment is supportive. There is continuous and spontaneous improvement of skin symptoms throughout the disease course, especially in ATP6V0A2-CDG.

Golgi-$\alpha_{1\text{-}2}$ Mannosidase-1 Deficiency (MAN1B1-CDG)

Clinical Manifestations

MAN1B1 defect was originally described as an intellectual disability syndrome in association with dysmorphic features. Additional patients were recognized with psychomotor disability, muscle hypotonia, and inverted nipples in association with truncal obesity. The degree of intellectual disability is quite variable. Autistic behaviors, eating disorders, and aggressive behavior are frequent features. More than 30 patients have been reported.

Pathophysiology

MAN1B1 codes for a Golgi mannosidase, which is essential for the final “trimming” of mannose units during the glycan processing in the Golgi. Hypermannosylation leads to abnormal, truncated glycans and CDG-II. The glycosylation abnormality in serum is relatively mild. Increased serum transaminases and abnormal coagulation are uncommon.

Diagnosis

Most patients show a mild type 2 pattern by TIEF, but false-negative cases have been described. MALDI-TOF analysis shows characteristic, hybrid glycans in serum. In suspected cases, direct sequence analysis is recommended, even if the TIEF is normal.

MAN1B1-CDG is autosomal recessive. The exact incidence is unknown; several adult patients are known.

Treatment

Only supportive treatment is available.

Phosphoglucomutase-1 Deficiency (PGM1-CDG)

Clinical Manifestations

PGM1-CDG is a disorder presenting with midline malformations (cleft palate, Pierre Robin sequence, bifid uvula), liver dysfunction, hypoglycemia, and short stature in almost all patients. *Hypoglycemia* is usually caused by hyperinsulinism in the 1st years of life. It can resolve with aging; ketotic hypoglycemia has also been observed. Cholestasis, liver fibrosis, and even cirrhosis have been described in a few patients. About one third of patients also show proximal muscle weakness and dilated cardiomyopathy; the latter led to mortality in at least 7 reported cases. Other malformations, including cardiac and skeletal anomalies, have also been described. Wound healing is frequently abnormal, and there is a very high risk for bleeding during surgery. Intelligence is normal.

Pathophysiology

Phosphoglucomutase 1 (PGM1) is an essential enzyme for glycogenolysis and glycolysis. It also provides substrates for nucleotide sugars needed for normal glycosylation. PGM1 regulates the bidirectional conversion of glucose-1-phosphate and glucose-6-phosphate. During fasting it leads to a glycogenosis-like phenotype (also called GSD XIV, MIM 614921). PGM1-CDG affects both the ER- and Golgi-related glycosylation and causes a mixed type 1/type 2 hypoglycosylation pattern. Abnormal serum proteins include coagulation and anticoagulation factors, insulin-like growth factor–binding protein 3 (IGFBP3), TBG, and thyroid-stimulating hormone (TSH), in addition to serum transaminases, hypoglycemia, and elevated CK.

Diagnosis

The primary screening method in a suspected PGM1-CDG is serum transferrin glycoform analysis or MS analysis. Patients show a mixed type 1/type 2 pattern.

PGM1-CDG is autosomal recessive. It is among the relatively common CDGs; >40 patients have been described. Enzyme testing is possible in blood, but is more reliable in fibroblasts. Direct sequencing is available for testing.

Treatment

PGM1-CDG seems to be the 2nd treatable CDG besides MPI-CDG. D-Galactose is hypothesized to restore the balance in the availability of different nucleotide sugars. Adding 1 g/kg/day D-galactose for a few weeks to the diet improves glycosylation significantly, although the TIEF pattern does not fully normalize. This treatment improves liver transaminases and antithrombin levels and in some patients the hormonal status. The effect of D-galactose on hypoglycemic episodes and the myopathy is not yet clear. Larger, long-term dietary trials are ongoing.

Disorders of Golgi Homeostasis: TMEM199-, CCDC115-, ATP6AP2-CDG, and ATP6AP1-CDG

Clinical Manifestations

These 4 disorders are clinically and biochemically indistinguishable. They have been described with liver function anomalies, cholestasis, fibrosis, and cirrhosis with liver failure, necessitating liver transplantation in a few patients. The phenotype resembles **Wilson disease** , especially because of low serum ceruloplasmin and copper levels, but there is no Kayser-Fleischer ring. In CCDC115-CDG there are frequently also neurologic features. The intellectual outcome is variable. Additional abnormalities include hypercholesterolemia and elevated alkaline phosphatase. In ATP6AP1-CDG there is also immunologic involvement.

Pathophysiology

TMEM199-, CCDC115-, ATP6AP1-CDG, and ATP6AP2-CDG are important for Golgi homeostasis. The exact pathologic mechanism is not yet known, but it is hypothesized that the secondary Golgi dysfunction affects and delays the normal glycosylation process.

Diagnosis

The primary screening method in a patient with suspected PGM1-CDG is serum transferrin glycoform analysis or MS analysis. Patients show a type 2 pattern (see Fig. 105.10). ApoC-III IEF is abnormal. Glycomics results by MALDI-TOF analysis are characteristic but cannot discriminate between the 3 defects. Final diagnosis requires mutation analysis.

TMEM199-CDG and CCDC115-CDG are autosomal recessive, whereas ATP6AP1-CDG, and ATP6AP2-CDG are X-linked.

Treatment

Treatment is supportive; 2 patients successfully underwent liver transplantation.

Manganese Transporter Defect: SLC39A8-CDG

Clinical Manifestations

This intriguing disorder was originally described as a neurologic disease with hypotonia, seizures (hypsarrhythmia), and developmental disability. Some of the later-described patients had severe *skeletal dysplasia* with rhizomelic chondrodysplasia, craniosynostosis, and dwarfism. Mitochondrial dysfunction (Leigh disease, cerebral lactic acidemia, dystonia) may also be present.

Pathophysiology

SLC39A8 is a membrane transporter, responsible for the manganese (Mn) transmembrane transport. SLC39A8 deficiency affects all Mn-dependent enzymes and therefore different parts of the metabolism. Since several glycosyltransferases (e.g. β-1,4-galactosyltransferase) are Mn dependent, a secondary Golgi glycosylation occurs with a type 2 glycosylation defect. Low serum Mn levels are suggestive but not always present in patients.

Diagnosis

The primary screening method in a suspected SLC39A8-CDG is serum transferrin glycoform analysis or MS analysis. Patients show a type 2 pattern (see Fig. 105.10). MALDI-TOF analysis is suggestive, but not discriminative. Final diagnosis requires mutation analysis.

SLC39A8-CDG is an autosomal recessive disease. Its incidence is unknown.

Treatment

Besides supportive treatment, a few patients showed biochemical and clinical improvement (better seizure control) with oral D -galactose (1-3 g/kg/day) therapy.

Congenital Disorders of Deglycosylation

N-Glycanase 1 Deficiency (*NGLY1* Defect)

Clinical Manifestations

Patients with NGLY1 deficiency do have a glycosylation disorder, but not from the deficient synthesis; rather, it is caused by deficient breakdown of glycoproteins. The phenotype comprises severe CNS involvement, microcephaly, intellectual disability, seizures, neuropathy, movement disorders, and hypotonia. The presence of *alacrimia* , hypolacrimia, or chalazion is highly suggestive for the diagnosis, but not all patients have problems with tearing. Other features include failure to thrive, intrauterine growth restriction, and liver involvement. Some patients have a recognizable oval face with a short nose, flat profile, and hypertelorism. Masklike face also occurs, imitating the phenotype of mitochondrial disorders, especially when serum lactic acid levels are also elevated.

Pathophysiology

N -glycanase is responsible for the deglycosylation of misfolded *N* -linked glycoproteins. The enzyme is essential for cutting off the glycans before the proteins are degraded in the ER. The increased abundance of misfolded *N* -glycans increases ER stress, which has been suggested as a possible reason for lactate elevation in several patients. Serum transaminase and α-fetoprotein levels are also frequently increased.

Diagnosis

Serum transferrin isoform analysis shows a normal pattern. Final diagnosis requires mutation analysis.

NGLY1-CDG is an autosomal recessive disease. The most common mutation is c.1201A>T/p.R401X. The exact incidence of the condition is unknown, but >20 patients have been reported in a few years since the discovery of the disease.

Treatment

Only supportive treatment is available for the patient with NGLY1 deficiency.

Therapeutic Summary

Most CDGs are only treatable with supportive therapy. The initially discovered oral mannose treatment in MPI-CDG (1 g/kg/day) has proved to be efficient for coagulation problems and protein-losing enteropathy but cannot prevent liver fibrosis in all patients. Liver transplantation in MPI-CDG has been successful in a few patients. Oral D-galactose in PGM1-CDG (1g/kg/day) improves serum transaminases and coagulation, and has a positive effect on endocrine function, but cannot restore glycosylation fully. Seizure frequency improved in patients with SLC39A8-CDG receiving oral D -galactose treatment (1 g/kg/day) and oral Mn intake. The congenital myasthenic syndrome in DPAGT1-CDG, GFPT1-CDG and GMPPB-CDG has been successfully treated with high dose of cholinesterase inhibitors. Several CDG have been positively controlled by transplantation; including DOLK-CDG (DK1-CDG; heart transplantation) PGM3-CDG (hematopoietic stem cell transplantation), CCDC155-CDG (liver transplantation).

Additional CDG treatment options are available for disorders not described in this chapter. Patients with CAD-CDG show significant clinical improvement on receiving oral uridine therapy, especially with seizure control. Two children with SLC35C1-CDG–defective immune function improved on oral fucose therapy. GNE-CDG patients showed significant improvement in muscle strength on *N* -acetylmannoseamin therapy. Several dietary trials are currently ongoing in different CDG.

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CHAPTER 106

Mitochondrial Disease Diagnosis

Marni J. Falk

See also Chapter 105.4 .

Overview of Mitochondrial Disease

Mitochondrial diseases are multisystemic energy failure states with extensive clinical and genetic heterogeneity. Their common basis is best understood through recognition that mitochondria function as biologic “fuel cells” or “batteries,” producing chemical energy in the form of adenosine triphosphate (ATP) by aerobic metabolism of nutrient-derived reducing equivalents, through the integrated function of the 5-complex mitochondrial **respiratory chain (RC)** (Fig. 106.1). Mitochondria also play other essential roles that can be variably disrupted in disease states, such as regulating calcium homeostasis, diverse aspects of intermediary nutrient metabolism, nucleotide metabolism, and oxidative stress. Primary mitochondrial disease results from deficient RC function, which can be caused by mutations in genes that encode RC subunits, assembly factors or cofactors, components of mitochondrial DNA (mtDNA) metabolism and maintenance, or a host of other basic metabolic processes ongoing within mitochondria. Approximately 1,500 proteins exist within the mitochondrial proteome of different tissues, with variants in more than 350 unique genes across both the nuclear and the mitochondrial genomes already implicated as causal in human mitochondrial disease.

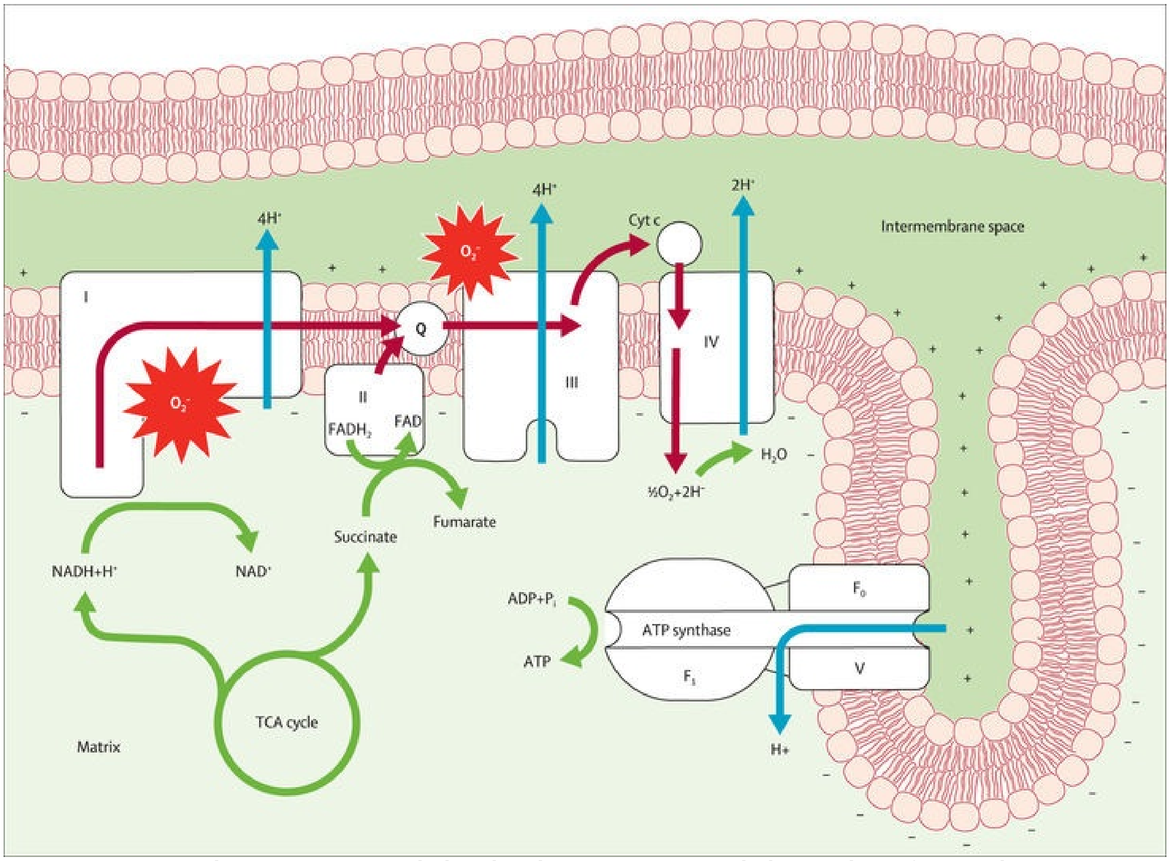

FIG. 106.1 **Electron transport chain. The electron transport chain consists of 4 protein complexes (I-IV) coupled to a 5th (V), unlinked complex, ATP synthase. Together, these 5 complexes are known as the respiratory chain and are the site where oxidative phosporylation (OXPHOS) occurs to generate energy. The transport chain accepts electrons from NADH (complex I) or $FADH_2$ (complex II) that have been produced by glycolysis, the formation of acetyl–coenzyme A, and the TCA cycle *(green arrows).* Electrons flow from one complex to another *(red arrows)* because of the redox potential of each complex and lose a small amount of energy as they move through the chain. Three of the 4 complexes act as pumps, driven by electron flow, moving H^+ ions from the matrix to the intermembrane space *(blue arrows)* . This pumping builds a concentration gradient and creates an electrochemical force that is used by ATP synthase to produce ATP. Under normal conditions, this machinery provides almost all (90%) of the ATP in a cell. However, a small proportion of electrons escape the electron transport chain even under normal conditions and can react with oxygen and complexes I and III to form superoxide ($O_2{}^-$). ADP, Adenosine diphosphate; ATP, adenosine triphosphate; Cyt c, cytochrome *c* ; Q, coenzyme Q; NADH, nicotinamide dinucleotide; Pi, inorganic phosphate; TCA, tricarboxylic acid cycle; FADH2, 1,5-dihydro-flavin adenine dinucleotide. (Adapted from Hagberg H, Mallard C, Rousset CI, Thornton C: Mitochondria: hub of injury responses in the developing brain, *Lancet Neurol* 13(2):217–232, 2014.)**

Collectively recognized as the most common group of inherited metabolic diseases, **primary** (genetic-based) mitochondrial disease has a combined minimal prevalence of 1 in 4,300 individuals across all ages. In addition, **secondary** mitochondrial dysfunction is broadly implicated in the pathogenesis of a host of complex diseases, ranging from metabolic syndrome to ischemia-reperfusion injury after stroke, to neurodegenerative diseases. Failure of high-energy demand organs in mitochondrial diseases may clinically present as severe neurodevelopmental, cardiac, myopathic, renal, hepatic, endocrine, immune, gastrointestinal, hearing, and vision disabilities, as well as global metabolic instability with lactic acidosis (Fig. 106.2) (see Tables 105.2 and 105.3). In most mitochondrial disorders, the phenotype may vary depending on the patient's age or the specific gene or genetic variant. Particularly common mitochondrial disease clinical syndromes that present in children include Leigh syndrome (for which there are more than 90 causal genes), mtDNA depletion syndrome (MDS, for which there are dozens of causal genes), mtDNA deletion syndromes (Pearson, Kearns Sayre), primary lactic acidosis, and pyruvate dehydrogenase deficiency. Common clinical features in children present in at least 90 percent of patients include fatigue, exercise intolerance, weakness, gastrointestinal problems, ataxia, and developmental delay. Thus, mitochondrial diseases present to and must be considered by clinicians across every medical specialty.

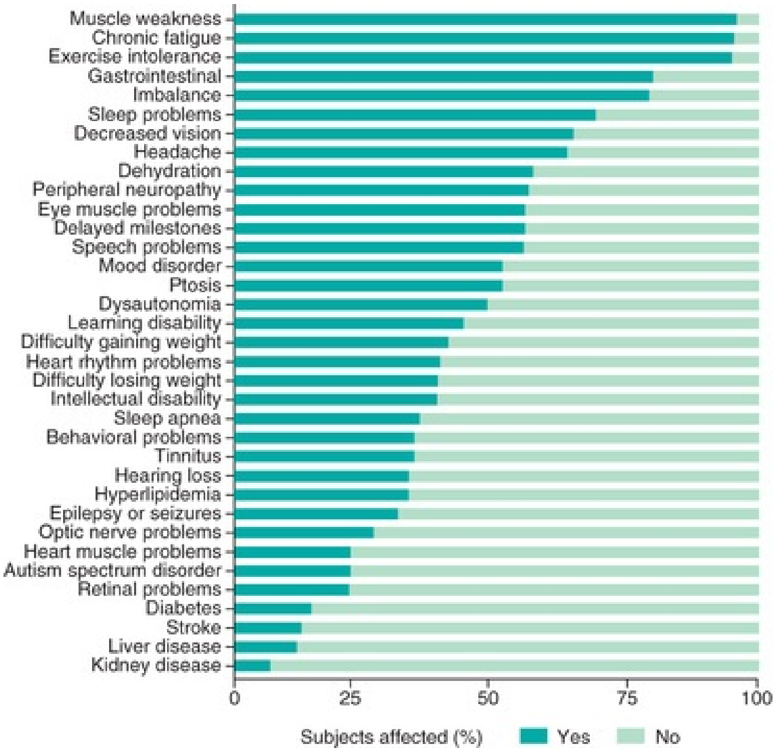

FIG. 106.2 Mitochondrial disease subject cohort, experienced symptoms. Frequency of experienced symptoms as reported by the RDCRN self-reported cohort revealed muscle weakness, chronic fatigue, exercise

intolerance, imbalance, and gastrointestinal problems to be the top 5 common symptoms. (Modified from Zolkipli-Cunningham Z, Xiao R, Stoddart A, et al: Mitochondrial disease patient motivations and barriers to participate in clinical trials. PLoS ONE 13(5):e0197513 [Fig. 2].)

Patients with suspected mitochondrial disease may frequently experience a *diagnostic odyssey* , both clinically and genetically. Their extensive phenotypic heterogeneity without a common biomarker (GDF-15 may be one screening test that may be elevated in some mitochondrial myopathies particularly involving mtDNA deletions or depletion, along with lactic acidosis) presents a challenge to the readily available and accurate **clinical diagnosis** of mitochondrial disorders in many medical settings. Similarly, their extensive genetic heterogeneity involving known etiologies in >300 nuclear genes and all 37 mitochondrial DNA (mtDNA) genes, with likely dozens to hundreds more causative nuclear disease genes awaiting discovery, can make the accurate **genetic diagnosis** of an individual patient challenging. The diagnostic uncertainty can be further compounded by poor genotype-phenotype correlations and variable clinical presentations of individual gene disorders, high locus heterogeneity (i.e., multiple different causal disease genes) for similar clinical phenotypes, incomplete penetrance for some gene disorders, variable life stressors or environmental exposures that may exacerbate a given child's disease, and the unique biologic aspects of maternal inheritance for the subset of mitochondrial diseases caused by mtDNA gene mutations.

When to Suspect Mitochondrial Disease

Because of failure in the ability to generate cellular energy, mitochondrial diseases can involve any organ system at any age (see Fig. 106.2). Mitochondrial disease should be suspected when classic symptoms are present or if unexplained symptoms occur in 3 or more apparently unrelated organs. Individuals may present with a vast array of symptoms, including fatigue, muscle weakness, exercise intolerance, metabolic strokes, seizures, cardiomyopathy, arrhythmias, developmental or cognitive disabilities, autism, diabetes mellitus, other endocrinopathies (adrenal, thyroid), dysautonomia, and autoimmune disorders, as well as impairment of hearing, vision, growth, liver, gastrointestinal (GI), or kidney function. Although individuals may have just one or a few symptoms and a fluctuating disease course in terms of symptom severity, most patients with primary mitochondrial disease tend to develop *progressive* symptoms over time. A study of patients with mitochondrial diseases showed an average of 16 different clinically significant symptoms per patient, with a range of 7-35. When considering the diagnosis, it is helpful to recognize that most symptoms of mitochondrial disease involve *functional,* rather than structural, problems.

When mitochondrial disease is considered in the differential diagnosis, it is often helpful to obtain several **laboratory screening** studies for common biochemical features of mitochondrial disease and overlapping disorders, both at baseline and if unrevealing, during an acute illness or period of decompensation. Blood-based metabolic screening studies include comprehensive chemistry panel, complete blood count with differential, plasma amino acid quantitative analysis, carnitine analysis (total, free, acyl-carnitine profile), ammonia, creatine kinase, and testing for common secondary manifestations of mitochondrial disease (e.g., thyroid screen, lipoprotein profile, hemoglobin A_{1c}). Urine-based metabolic screening studies include urinalysis, urine organic acid quantitative analysis, and urine amino acid quantitative analysis. Consideration should also be given for screening for congenital disorders of glycosylation or vitamin deficiencies, which may have overlapping clinical features in some cases with mitochondrial disease. Lactic acidemia is neither highly sensitive nor specific for primary mitochondrial disease, but laboratory findings suggestive of primary mitochondrial disease include elevations of blood lactate, pyruvate, lactate:pyruvate ratio, alanine, ratios of alanine to lysine (>3) and alanine to sum of phenylalanine and tyrosine (>4), and anion gap. Biochemical alterations further suggestive of mitochondrial disease may include secondary impairment of fatty acid oxidation with elevation of dicarboxylic acids on acyl-carnitine profile, increased branched-chain amino acids and proline on plasma amino acid analysis, increased tricarboxylic acid cycle intermediates and lactate excretion on urine organic acid analysis, and generalized aminoaciduria on urine amino acid analysis. Growth and differentiation factor 15 (**GDF-15**) may be a useful screening test for mitochondrial depletion based myopathies.

Similarly, when mitochondrial disease is considered in the differential diagnosis, obtaining additional **clinical evaluations** to carefully phenotype the patient for prevalent or highly morbid and potentially modifiable features of mitochondrial disease is important. Because many individuals with mitochondrial disease develop problems with their *vision* (reduced visual acuity not correctable with glasses, photophobia or nyctalopia with reduced peripheral vision associated with retinal disease or optic atrophy, ophthalmoplegia, ptosis), *hearing* (high-frequency sensorineural hearing loss), and *heart* (arrhythmia, conduction block, cardiomyopathy), carefully evaluating for involvement of these high-energy systems is indicated. **Neurologic** evaluation is essential because many mitochondrial disease patients experience a range of *central* (metabolic stroke in cortical or deep gray matter including basal ganglia, midbrain, and/or brainstem, white matter changes, seizures, ataxia, movement disorder, migraine, cognitive changes), *peripheral* (axonal sensorimotor neuropathy), or *autonomic* nervous system dysfunction; brain imaging (MRI), spectroscopy (MRS), and on occasion electromyogram or nerve conduction velocity (EMG/NCV) studies can be helpful to support the diagnosis. Formal **exercise physiology** evaluation can also be useful to quantify and advise patients on their exercise capacity and safety, with some specific features (e.g., reduced $V\text{O}_2$ maximal capacity) suggestive of quantifiable mitochondrial dysfunction. **Sleep** study may be useful for individuals with sleep dysfunction because sleep disorders may mimic mitochondrial disease symptoms, and sleep problems are common and potentially treatable in mitochondrial disease. **Gastrointestinal** symptoms are common and underrecognized in mitochondrial disease patients, usually involving dysmotility of any portion of the GI tract with reflux, swallowing dysfunction, delayed gastric emptying, feeding and/or growth problems, pseudoobstruction, malabsorption, and constipation. **Endocrine** abnormalities are also common but underappreciated in many patients, including pituitary, adrenal, thyroid, and pancreatic dysfunction. Such careful phenotyping of patients with suspected mitochondrial disease can thus provide reassurance that the common, and potentially treatable, clinical aspects of mitochondrial disease are not present although they may develop over time, or conversely if identified, increase diagnostic suspicion and direct further diagnostic evaluation.

Mitochondrial Disease Inheritance

Primary mitochondrial disease may result from variants in either nuclear genes or mtDNA genes, which may be inherited from a parent or occur de novo in an affected individual. Thus, all *mendelian* (autosomal recessive, autosomal dominant, X-linked) or *maternal* (mtDNA) inheritance patterns can be consistent with mitochondrial diseases (Table 106.1). Obtaining a detailed, three-generation pedigree is important to potentially highlight the specific inheritance pattern in a given family. Individuals with inherited mtDNA disorders may report family members related through their maternal lineage (both males and females may be affected, but only affected individuals will be connected through the female germline), with a range of functional problems in different organs, such as migraines, fatigue, exercise intolerance, stroke, diabetes mellitus, thyroid dysfunction, irritable bowel spectrum, mood disorder, or vision and hearing problems. Inherited X-linked disorders typically present with symptoms only, or more severely, in males related through unaffected or minimally affected females. **Autosomal recessive** disorders are common in pediatric mitochondrial disease, particularly in consanguineous pedigrees, where a rare variant in the general population becomes enriched and passed down through both maternal and paternal lineages to become homozygous in the affected proband and also affect multiple individuals in a given generation without having affected individuals in earlier generations. **Autosomal dominant** variants may occur de novo or are passed on from either parent to their child, although many disorders may have reduced penetrance, which may make the genetic disorder appear to skip a generation. Identifying a likely inheritance pattern through pedigree analysis can inform accurate interpretation of large-scale genetic diagnostic evaluations, such as multigene sequencing and deletion/duplication analysis panels and exome or genome sequencing. Establishing a correct genetic diagnosis for mitochondrial disease in an affected individual is essential to enable reliable recurrence risk counseling and testing options in a given family, whether in a future pregnancy by chorionic villus sampling (CVS, typically performed at 10-12 weeks' gestation) or amniocentesis (typically performed at 16-20 weeks' gestation) or in the in vitro fertilization (IVF) setting with preimplantation genetic diagnosis (PGD) for a specific disease-causing variant.

Table 106.1

Major Molecular Categories of Mitochondrial Genes

COMPONENT	CAUSAL GENOME	GENE MUTATION EFFECTS	DISEASE EXAMPLES
Electron transport chain enzyme subunits	Nuclear or mtDNA	Decreased functioning of electron transport chain complex	Complex I deficiency Complex II deficiency
Electron transport chain assembly factors	Nuclear	Decreased assembly of electron transport chain enzyme complex	Complex III deficiency Complex IV deficiency Complex V

			deficiency
Electron transport chain cofactors	Nuclear	Decreased functioning of electron transport chain	Coenzyme Q10 deficiency Iron sulfur cluster defect Lipoyltransferase deficiency
mtDNA translation	Nuclear or mtDNA	Decreased translation of protein-coding mitochondrial DNA genes leading to decreased functioning of electron transport chain enzymes	Combined oxidative phosphorylation complexes deficiency
mtDNA maintenance	Nuclear	Increased errors in mitochondrial DNA leading to increased presence of point mutations and deletions, resulting in decreased translation of electron transport chain subunits	Mitochondrial DNA depletion syndromes Mitochondrial DNA multiple deletion disorders
Mitochondrial membrane fission and fusion	Nuclear	Increased mtDNA point mutations and deletions; clumped and fragmented mitochondria	*OPA1* -related conditions *MFN2* -related conditions

From McCormick EM, Muraresku CC, Falk MJ: Mitochondrial genomics: a complex field now coming of age. *Curr Genet Med Rep* 6:52–61, 2018 (Table 1, p. 57).

Special mention is warranted to consider the unique aspects of *maternal inheritance* that typify mtDNA disorders. More than 300 disease-causing mtDNA variants have been identified, with extensive variation in disease manifestations and features. Most disease-causing variants are present in only a portion of an individual's mtDNA genomes, a concept known as **heteroplasmy** . For heteroplasmic mtDNA variants, the precise mutation level (percent) can vary between an individual's different tissues and can change over time, with symptom severity corresponding to different threshold mutation levels that can be difficult to define and that typically vary between organs. An individual's mtDNA genome background set of fixed sequence variants, known as a **haplogroup** , can also influence the penetrance or severity of a mtDNA disease. When a novel or rare mtDNA variant is identified in a given individual, it may be useful to use highly sensitive sequencing methods to test the levels of that mutation (which may be accurate to detect 1% mutation levels) in their different tissues (blood, urine, buccal, skin cells, muscle), as well as tissues from their mother or maternal relatives, to accurately determine whether it may be causal of disease in that family. Research-based functional testing may also be necessary to characterize fully the effects of a newly recognized mtDNA variant. When it is not known whether an mtDNA variant is maternally inherited or occurs de novo, the recurrence risk to future offspring of their asymptomatic parent is empirically estimated at 1 in 25 (4%), although the empirical recurrence risk rises to 1 in 2 (50%) when the mother is symptomatic.

Diagnostic Testing for Mitochondrial Disease

The diagnosis of mitochondrial disease relies foremost on genetic testing (genomic analysis), with biochemical screens useful in blood or urine and invasive tissue testing often seen as secondary, or sometimes not required at all (Fig. 106.3).

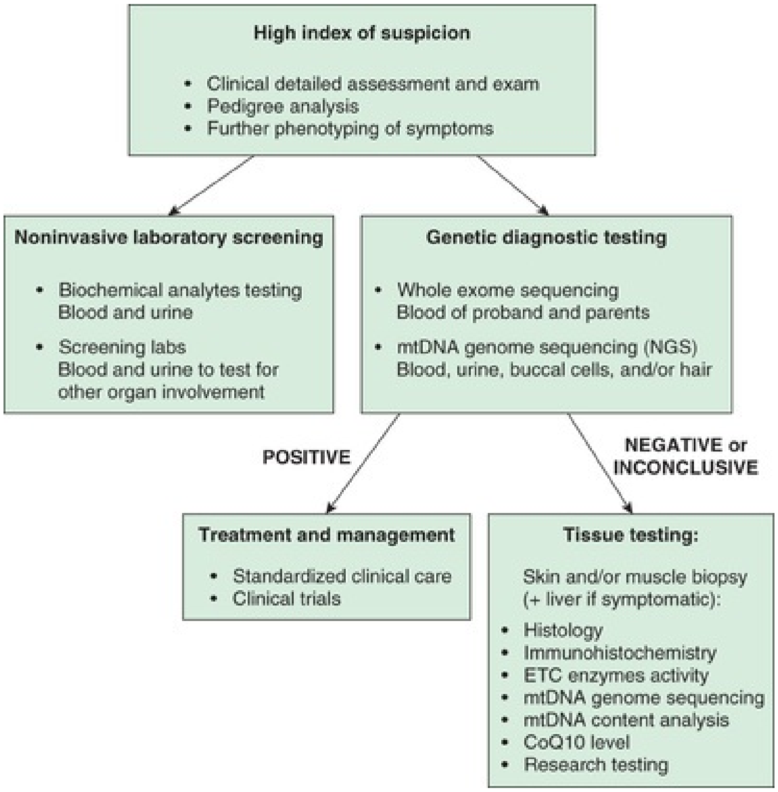
High index of suspicion
Clinical detailed assessment and exam
Pedigree analysis
Further phenotyping of symptoms
Noninvasive laboratory screening
Biochemical analytes testing Blood and urine
Screening labs Blood and urine to test for other organ involvement
Genetic diagnostic testing
Whole exome sequencing Blood of proband and parents
mtDNA genome sequencing (NGS) Blood, urine, buccal cells, and/or hair
POSITIVE
NEGATIVE or INCONCLUSIVE
Treatment and management
Standardized clinical care
Clinical trials
Tissue testing:
Skin and/or muscle biopsy (+ liver if symptomatic):
Histology
Immunohistochemistry
ETC enzymes activity
mtDNA genome sequencing
mtDNA content analysis
CoQ10 level
Research testing

FIG. 106.3 Diagnostic algorithm for suspected mitochondrial disease. (From Muraresku CC, McCormick EM, Flak MJ: Mitochondrial disease: advances in clinical diagnosis, management, therapeutic development, and preventative strategies. *Curr Genet Med Rep* 6:62–72, 2018.)

When the clinical evaluation—medical history; detailed review of systems; careful physical, neurologic, and dysmorphic examinations; pedigree-, blood-, and urine-based biochemical screening studies; and additional phenotyping clinical evaluations—is suggestive of mitochondrial disease, a range of clinical diagnostic testing options can be pursued. Absent a known molecular etiology in an affected family member, first-line genetic diagnostic testing may involve a focused panel of hundreds to thousands of known nuclear genes and the mtDNA genome using **next-generation sequencing** (NGS) methodologies that will detect both single-nucleotide variants and larger-scale gene deletions and duplications. If such testing is unrevealing, clinically based **whole exome sequencing** (WES) may be pursued. The standard of care is moving to pursue initial diagnostic testing by WES, which is more comprehensive for genes known not only to cause mitochondrial disease, but also to cause all human genetic diseases. The rationale for this evolution in diagnostic testing approach includes the following factors:

1. An increasingly similar cost and turnaround-time for panel-based and WES-based massively parallel NGS studies.
2. The common genetic diagnostic laboratory practice of generating WES data for all tests ordered, but only evaluating and reporting variants in specific gene subsets when panel-based testing is requested, leaving the remaining genes uninterpreted.
3. The mtDNA genome sequence is often included at no extra cost when clinical WES is ordered in blood, but may need to be repeated in a symptomatic tissue (e.g., muscle, liver) to detect heteroplasmic mtDNA variants that may not be present in blood.
4. The utility of performing concurrent proband and both parental sample sequencing *(trio-based testing),* as usually pursued with WES but not panel-based testing, thereby allowing concurrent segregation analysis of a suspected pathogenic variants as well as ready identification of de novo dominant variants in the proband.
5. The improved diagnostic yield of exome relative to panel-based testing increasingly being reported by clinical diagnostic laboratories, given the highly heterogeneous nature of mitochondrial disease, rapid rate of change in the recognition of *new* gene diagnoses making prior established gene panels obsolete, and the extensive phenotypic overlap with non-mitochondrial diseases.
6. The ability to utilize WES raw data (either on a research basis or for reanalysis at a later date by the clinical diagnostic laboratory) to highlight and/or identify “novel” gene disorders not previously

recognized or associated with human disease.

A mitochondrial disease community resource to centrally curate all mitochondrial disease, gene, and variant knowledge across both genomes is publicly accessible at www.mseqdr.org . Exome sequencing including mtDNA is estimated to identify the definitive genetic etiology for mitochondrial disease in at least 60% of patients in whom it is strongly suspected, reducing the diagnostic odyssey in many patients from decades or years to months.

Tissue-based diagnostic testing has decreased in frequency as a front-line test in all patients with suspected mitochondrial disease, although it still has clinical utility in some cases. These include (1) in the setting of rapidly deteriorating clinical status when genetic testing results may not be available in a timely fashion; (2) when a variant of uncertain significance identified on genomic testing has unclear biochemical consequences; and (3) when uninformative genomic sequencing in blood in an individual with myopathy or muscle symptoms raises concern for other disease processes that may be evident on histology, electron microscopy, immunohistochemistry or enzymatic tissue testing. In addition, some mitochondrial diseases are only evident by tissue-based diagnostic testing. These include mtDNA deletion disorders (typically involving several-thousand nucleotides) not present in blood that cause chronic **progressive external ophthalmoplegia** (CPEO) or **Kearns-Sayre syndrome** (KSS) spectrum disorder, as well as different tissue (muscle or liver)-specific mtDNA depletion disorders (e.g., reduced mtDNA tissue content) that confirm a mitochondrial pathophysiology in a given patient and highlight a likely underlying nuclear gene cause for their disease, since mtDNA maintenance requires a host of nuclear-encoded proteins. Muscle analysis for integrated RC oxidative phosphorylation capacity assessment requires analysis of a fresh muscle biopsy only available at a very limited number of sites worldwide, whereas **electron transport chain enzyme** activity analyses are the accepted gold standard to evaluate for mitochondrial dysfunction in a previously frozen tissue sample, often shipped elsewhere for diagnostic analysis. Skin biopsies are useful to establish fibroblast cell lines in which these same studies of mitochondrial function can be clinically performed. If detected, abnormalities can be revealing of a specific type of mitochondrial disorder, although not all mitochondrial diseases may be expressed or detectable in skin analysis. Thus, if fibroblast testing is unrevealing, more invasive tissue studies may subsequently need to be pursued. Fibroblast cell lines, and occasionally blood-based lymphoblastoid cell lines, also provide a minimally invasive cell source to allow other clinical enzymatic analyses to be performed, as well as novel disease gene validation and research-based therapeutic modeling.

Treatment Principles for Mitochondrial Disease

Effective therapies for both primary and secondary mitochondrial diseases are lacking, because little has been known about the biochemical and physiologic abnormalities that contribute to their diverse clinical manifestations. Clinical complexity and imprecisely defined or understood biochemical phenotypes of different mitochondrial disease subtypes have made it difficult for clinicians to effectively apply or monitor targeted therapies for RC disease. *Mitochondrial cocktails* of vitamins and supplements variably include vitamins (B_1 , B_2 , C), antioxidants (CoQ_{10} , lipoic acid, vitamin E), and metabolic modifiers (creatine, L -carnitine, L -arginine, folinic acid). Although the efficacy, toxicity, and optimal dose of these drugs are not known and have not been objectively assessed in human RC disease patients, they continue to be empirically prescribed in hopes of enhancing residual RC enzymatic function or quenching toxic metabolites theorized to accumulate in RC dysfunction, and because of patient-based reports of improved well-being. However, provision of these therapies has often adopted a one-size-fits-all approach, ignoring the inherent variation in primary mitochondrial disease subtypes, the tissue-specific manifestations, and the major pathogenic factors, such as the predominant downstream metabolic and signaling alterations that occur in different disease subclasses.

Although no cure or U.S. Food and Drug Administration (FDA)–approved therapy yet exists for any mitochondrial disease, improved molecular delineation has enabled selected therapies to advance from the theoretical, empirical, and largely ineffective stage to a promising horizon of rational, personalized, and effective interventions. An increasing number of mitochondrial disease diagnoses have interventions involving the initiation or avoidance of specific medications (corticosteroids, valproic acid, phenytoin, barbiturates, propofol for prolonged duration beyond 30-60 min, certain anesthetics, statins, β-blocking agents, amiodarone, nucleoside reverse transcriptase inhibitors), provision of cofactors or diets, and screening regimens for progressive clinical involvement of modifiable manifestations. General therapies for **Leigh syndrome** such as L -arginine and citrulline may prevent or reverse neurodevelopmental sequelae from a metabolic stroke. Nutritional therapies in these disorders are tailored to specific disease genes, such as thiamine and biotin for *SLC19A3* disease, ubiquinol for *PDSS2* (CoQ_{10} deficiency) disease, and thiamine and the ketogenic diet for *PDHA1* (pyruvate dehydrogenase) deficiency. Establishing the precise molecular diagnosis can further be lifesaving by avoiding fasting and mitochondrial-toxic medicines or general anesthetics in specific mitochondrial disease subsets, improving recurrence risk counseling and prevention, enabling targeted screening for reported medical complications, and in some cases providing necessary cofactors or vitamins that may not otherwise have been considered. In addition, reproductive methodologies emerging in some countries for mitochondrial disease prevention, such as **mitochondrial replacement technologies** (MRTs), are only appropriate to consider in the setting of known pathogenic, inherited mtDNA variants. Finally, the ability to molecularly identify primary mitochondrial disease patients has enabled the design of an increasing number of clinical treatment trials now being planned or underway for a diverse range of symptoms that occur in primary mitochondrial diseases (see www.clinicaltrials.gov).

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CHAPTER 107

Mucopolysaccharidoses

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Mucopolysaccharidoses are hereditary, progressive diseases caused by mutations of genes coding for lysosomal enzymes needed to degrade glycosaminoglycans (acid mucopolysaccharides). *Glycosaminoglycans* (GAGs) are long-chain complex carbohydrates composed of uronic acids, amino sugars, and neutral sugars. The major GAGs are chondroitin-4-sulfate, chondroitin-6-sulfate, heparan sulfate, dermatan sulfate, keratan sulfate, and hyaluronan. These substances are synthesized and, with the exception of hyaluronan, linked to proteins to form *proteoglycans,* major constituents of the ground substance of connective tissue and of nuclear and cell membranes. Degradation of proteoglycans starts with the proteolytic removal of the protein core, followed by the stepwise degradation of the GAG moiety. Failure of this degradation because of absent or grossly reduced activity of mutated lysosomal enzymes results in the intralysosomal accumulation of GAG fragments (Fig. 107.1). Distended lysosomes accumulate in the cell, interfere with cell function, and lead to characteristic patterns of clinical, radiologic, and biochemical abnormalities (Table 107.1 and Fig. 107.2). Within these patterns, specific diseases can be recognized that evolve from the intracellular accumulation of different degradation products (Table 107.2). As a general rule, the impaired degradation of heparan sulfate is more closely associated with **mental deficiency** , and that of dermatan, chondroitin, and keratan sulfate with **mesenchymal abnormalities** . Variable expression within a given entity results from allelic mutations and varying residual activity of mutated enzymes. For instance, allelic mutations of the gene encoding L -iduronidase may result in severe **Hurler disease** (Hurler syndrome) with early death or in mild **Scheie disease** (Scheie syndrome) manifesting only with limited joint mobility, mild skeletal abnormalities, and corneal opacities.

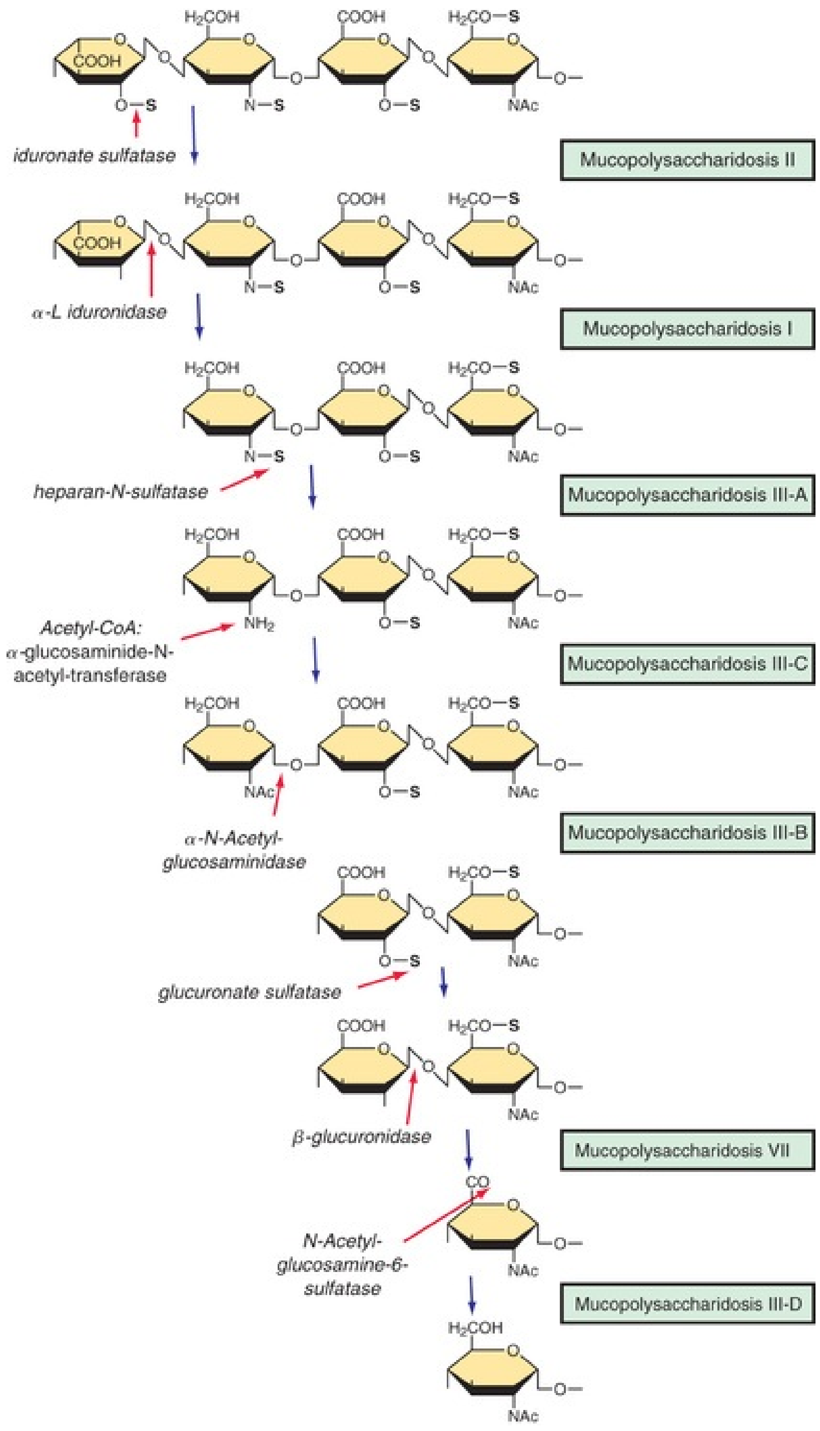
H2COH
COOH
H2CO—S
COOH
O—S
N—S
O—S
NAc
iduronate sulfatase
Mucopolysaccharidosis II
α-L iduronidase
Mucopolysaccharidosis I
heparan-N-sulfatase
Mucopolysaccharidosis III-A
NH2
Acetyl-CoA:
α-glucosaminide-N-
acetyl-transferase
Mucopolysaccharidosis III-C
α-N-Acetyl-
glucosaminidase
Mucopolysaccharidosis III-B
glucuronate sulfatase
β-glucuronidase
Mucopolysaccharidosis VII
CO
N-Acetyl-
glucosamine-6-
sulfatase
Mucopolysaccharidosis III-D

FIG. 107.1 Degradation of heparan sulfate and mucopolysaccharidoses resulting from the deficiency of individual enzymes. Some of the enzymes are also involved in the degradation of other glycosaminoglycans (not shown).

Table 107.1

Recognition Pattern of Mucopolysaccharidoses

MANIFESTATIONS	MUCOPOLYSACCHARIDOSIS (MPS) TYPE						
	I-H	I-S	II	III	IV	VI	VII
Intellectual disability	+	−	±	+	−	−	±
Coarse facial features	+	(+)	+	+	−	+	±
Corneal clouding	+	+	−	−	(+)	+	±
Visceromegaly	+	(+)	+	(+)	−	+	+
Short stature	+	(+)	+	−	+	+	+
Joint contractures	+	+	+	−	−	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	−	+	+
Mucopolysacchariduria	+	+	+	+	+	+	+

I-H, Hurler syndrome; I-S, Scheie syndrome; II, Hunter syndrome; III, Sanfilippo syndrome; IV, Morquio syndrome; VI, Maroteaux-Lamy syndrome; VII, Sly syndrome.

+, Presence of manifestation, −, absence of manifestation; ±, possible presence of manifestation; (+), mild manifestation.

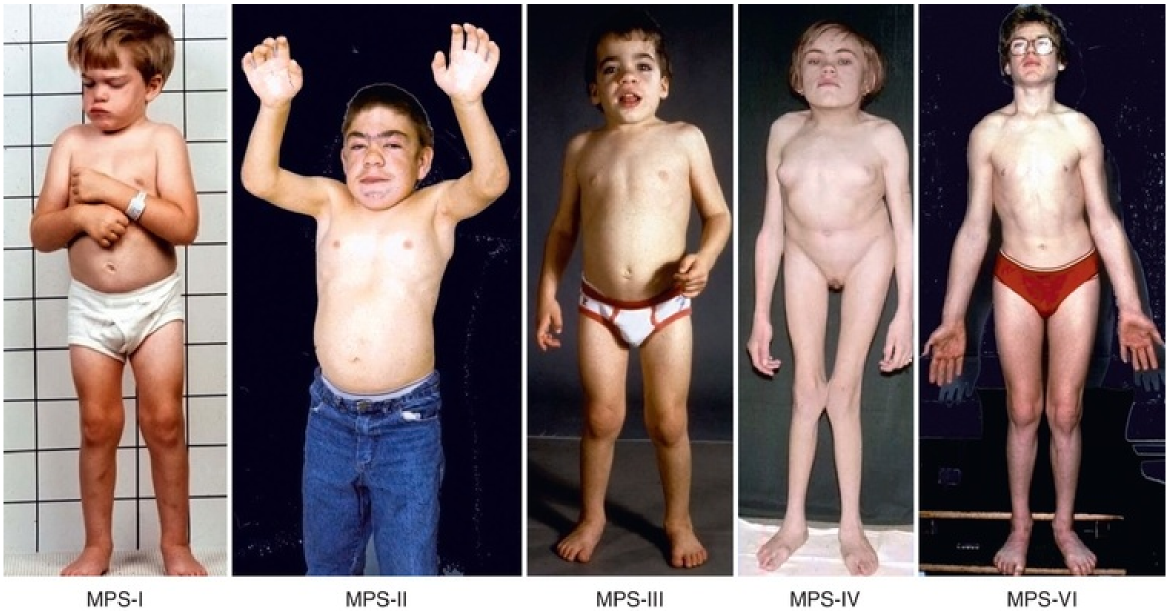

FIG. 107.2 Patients with various types of mucopolysaccharidoses. MPS-I: Hurler syndrome, age 3 yr; MPS-II: Hunter syndrome, 12 yr; MPS-III: Sanfilippo syndrome, 4 yr; MPS-IV: Morquio syndrome, 10 yr; MPS-VI: Maroteaux-Lamy syndrome, 15 yr.

Table 107.2

Mucopolysaccharidoses: Clinical, Molecular, and Biochemical Aspects

MPS TYPE	EPONYM	INHERITANCE	GENE CHROMOSOME	MAIN CLINICAL FEATURES	DEFECTIVE ENZYME	ASSA
I-H	(Pfaundler-) Hurler	AR	*IDUA* 4p16.3	Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 yr	α-L -iduronidase	L, F, Ac, C
I-S	Scheie	AR	*IDUA* 4p16.4	Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood	α-L -iduronidase	L, F, Ac, C
I-HS	Hurler-Scheie	AR	*IDUA* 4p16.4	Phenotype intermediate between I-H and I-S	α-L -iduronidase	L, F, Ac, C
II	Hunter	XLR	*IDS* Xq27.3-28	Severe course: similar to I-H but clear corneas Mild course: less pronounced features, later manifestation, survival to adulthood with mild or without mental deficiency	Iduronate sulfate sulfatase	S, F, Af, A Cv
IIIA	Sanfilippo A	AR	*SGSH* 17q25.3	Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas Survival to adulthood possible	Heparan-S-sulfamidase	L, F, Ac, C
IIIB	Sanfilippo B	AR	*NAGLU* 17q21		*N* -Acetyl-α-D -glucosaminidase	S, F, Ac, C
IIIC	Sanfilippo C	AR	*HGSNAT* 8p11.21		Acetyl-CoA-glucosaminide *N* -acetyltransferase	F, Ac
IIID	Sanfilippo D	AR	*GNS* 12q14		*N* -Acetylglucosamine–6-sulfate sulfatase	F, Ac
IVA	Morquio A	AR	*GALNS* 16q24.3	Short-trunk dwarfism, fine corneal opacities,	*N* -Acetylgalactosamine-6-sulfate sulfatase	L, F, Ac

				characteristic bone dysplasia; final height <125 cm		
IVB	Morquio B	AR	*GLB1* 3p21.33	Same as IVA, but milder; adult height >120 cm	β-Galactosidase	L, F, Ac, C
VI	Maroteaux-Lamy	AR	*ARSB* 5q11-q13	Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate, and severe expression in different families	*N* -Acetylgalactosamine-α-4-sulfate sulfatase (arylsulfatase B)	L, F, Ac
VII	Sly	AR	*GUSB* 7q21.11	Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes	β-Glucuronidase	S, F, Ac, C
IX	Hyaluronidase deficiency	AR	*HYAL1* 3p21.3	Periarticular masses, no Hurler phenotype	Hyaluronidase 1	S
MPSPS	MPS plus syndrome	AR	*VPS33A*	Mild Hurler phenotype, cognitive deficiency, organomegaly, skeletal dysplasia, pancytopenia, renal insufficiency, optic atrophy, early death	No lysosomal enzyme deficiency	

AR, Autosomal recessive; XLR, X-linked recessive; L, Leukocytes; S, serum; F, cultured fibroblasts; Ac, cultured amniotic cells; Af, amniotic fluid; Cv, chorionic villus sampling; MIM, Mendelian Inheritance in Man Catalogue.

Mucopolysaccharidoses are autosomal recessive disorders, with the exception of **Hunter disease** (Hunter syndrome), which is X-linked recessive. Their birth prevalence varies between 1.2 per 100,000 births (United States) and 16.9 per 100,000 births (Saudi Arabia). In the United States the most common subtype is MPS-III, followed by MPS-I and MPS-II.

Disease Entities

Mucopolysaccharidosis I

Mucopolysaccharidosis I (MPS-I) is caused by mutations of the *IUA* gene on chromosome 4p16.3 encoding α-L -iduronidase. Mutation analysis has revealed 2 major alleles, W402X and Q70X, which account for more than half the MPS-I alleles in the white population. The mutations that introduce stop codons with ensuing absence of functional enzyme (null alleles), and in homozygosity or compound heterozygosity, give rise to Hurler syndrome. Other mutations occur in only one or a few individuals.

Deficiency of α-L -iduronidase results in a wide range of clinical involvement, from severe Hurler syndrome to mild Scheie syndrome, which are ends of a broad clinical spectrum. Homozygous nonsense mutations result in severe forms of MPS-I, whereas missense mutations are more likely to preserve some residual enzyme activity associated with a milder form of the syndrome.

Hurler Syndrome

The Hurler form of MPS-I (**MPS I-H**) is a severe, progressive disorder with involvement of multiple organs and tissues that results in premature death, usually by 10 yr of age. An infant with Hurler syndrome appears normal at birth, but inguinal hernias and failed neonatal hearing tests may be early signs. Diagnosis is usually made at 6-24 mo, with evidence of hepatosplenomegaly, coarse facial features, corneal clouding, large tongue, enlarged head circumference, joint stiffness, short stature, and skeletal dysplasia. Acute cardiomyopathy has been found in some infants <1 yr. Most patients have recurrent upper respiratory tract and ear infections, noisy breathing, and persistent copious nasal discharge. Valvular heart disease, notably with incompetence of the mitral and aortic valves, regularly develops, and narrowing of the coronary arteries occurs. Obstructive airway disease, especially during sleep, may necessitate tracheotomy. Obstructive airway disease, respiratory infection, and cardiac complications are the common causes of death (Table 107.3).

Table 107.3

Analysis of Symptom Frequency in Patients With MPS-I ≤2 Yr of Age

SYMPTOMS/COMPLICATIONS	PERCENTAGE OF PATIENTS WITH SYMPTOM
Coarse facies	98
Valvular disease	95
Corneal clouding	90
Hepatomegaly	84

Upper airway obstruction → OSA	82
Kyphosis gibbus	75
Joint contractures	72
Hernia	70
Dysostosis multiplex	70
Cognitive impairment	60
Enlarged tongue	60
Splenomegaly	60
Eustachian tube obstruction → otitis media	55
Hip dysplasia	42
Genu valgum	38
Reactive airway disease	37
Scoliosis	35
Carpal tunnel syndrome	25
Pes cavus	18
Glaucoma	10
Heart failure	3
Cor pulmonale	2

OSA, Obstructive sleep apnea.

From Clarke LA, Atherton AM, Burton BK, et al: Mucopolysaccharidosis type I newborn screening: best practices for diagnosis and management, *J Pediatr* 182:363–370, 2017 (Table 1, p 364).

Most children with Hurler syndrome acquire only limited language skills because of intellectual disability, combined conductive and neurosensory hearing loss, and an enlarged tongue. Progressive ventricular enlargement with increased intracranial pressure caused by communicating hydrocephalus also occurs. Corneal clouding, glaucoma, and retinal degeneration are common. Radiographs show a characteristic skeletal dysplasia known as **dysostosis multiplex** (Figs. 107.3 and 107.4). The earliest radiographic signs are thick ribs and ovoid vertebral bodies. Skeletal abnormalities (in addition to those shown in the figures) include enlarged, coarsely trabeculated diaphyses of the long bones with irregular metaphyses and epiphyses. With disease progression, macrocephaly develops with thickened calvarium, premature closure of lambdoid and sagittal sutures, shallow orbits, enlarged J -shaped sella, and abnormal spacing of teeth with dentigerous cysts.

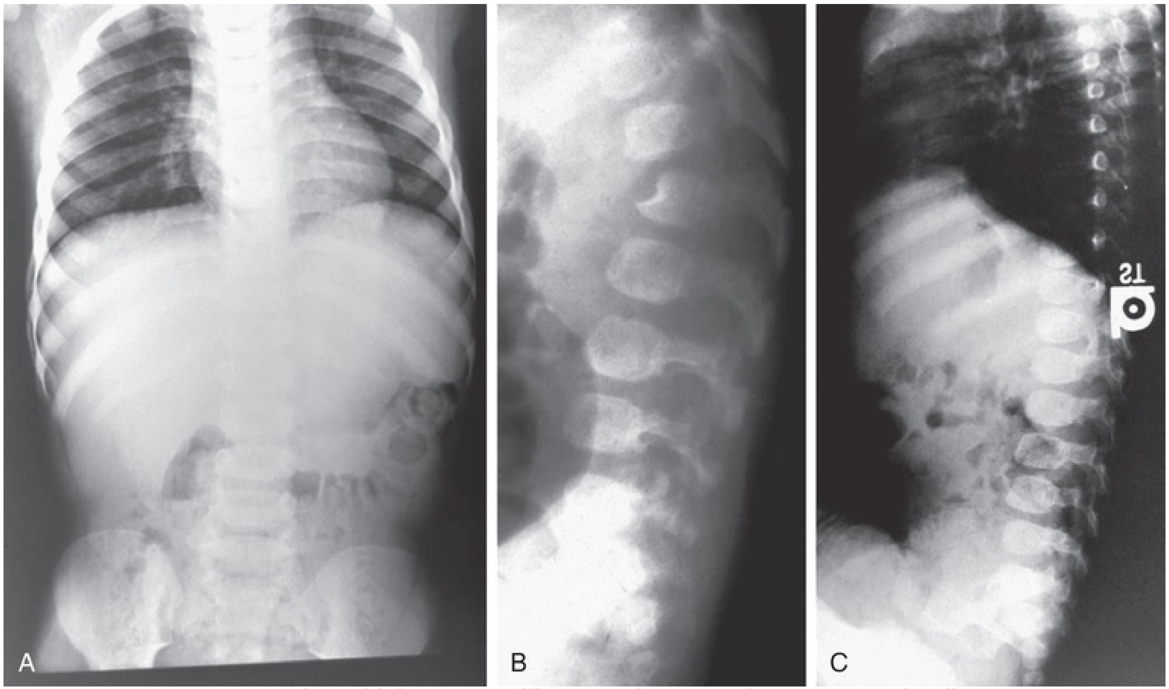

FIG. 107.3 Dysostosis multiplex. A, Sanfilippo syndrome, patient age 4 yr; the ribs are wide. B, Sanfilippo syndrome, age 4 yr; immature, ovoid configuration of the vertebral bodies. C, Hurler syndrome, age 18 mo; anterosuperior hypoplasia of 1st lumbar vertebra (L1) resulting in hook-shaped appearance.

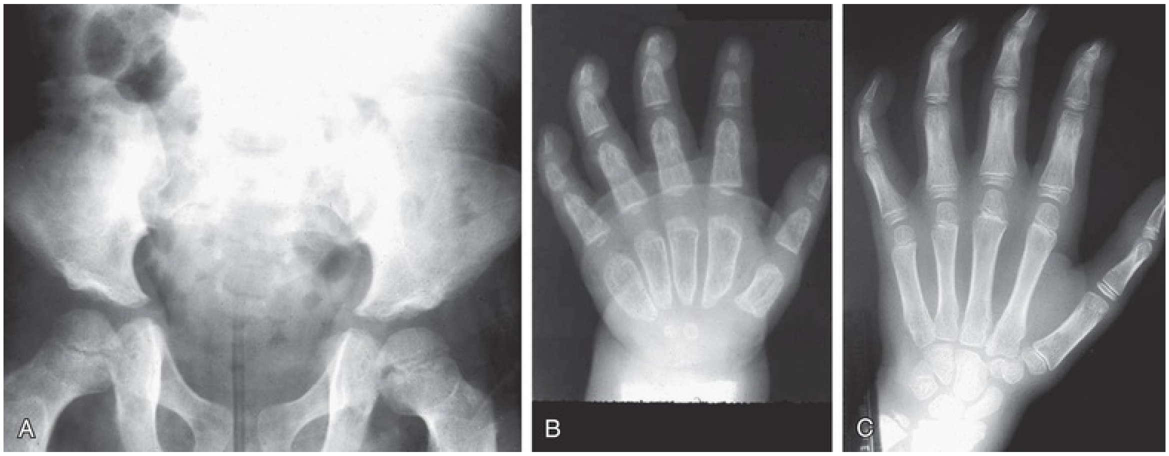

FIG. 107.4 Dysostosis multiplex. A, Mucopolysaccharidosis I-H, patient age 10 yr. The inferior portions of the ilia are hypoplastic, with resulting iliac flare and shallow acetabular fossae. The femoral necks are in valgus position. B, MPS I-H, age 4 yr. Metacarpals and phalanges are abnormally short, wide, and deformed with proximal pointing of the metacarpals and bullet-shaped phalanges. Bone trabeculation is coarse, and the cortices are thin. C, MPS I-S, age 13 yr. The carpal bones are small, leading to a V -shaped configuration of the digits. The short, tubular bones are well modeled. Flexion of the middle and distal phalanges II-V is caused by joint contractures.

Hurler-Scheie Syndrome

The clinical phenotype of the Hurler-Scheie form of MPS-I (**MPS I-H/S**) is *intermediate* between Hurler and Scheie syndromes and is characterized by progressive somatic involvement, including dysostosis multiplex with little or no intellectual dysfunction. The onset of symptoms is usually observed between 3 and 8 yr of age. Survival to adulthood is common. Cardiac involvement and upper airway obstruction contribute to clinical morbidity. Some patients have spondylolisthesis, which may cause cord compression.

Scheie Syndrome

The Scheie form of MPS-I (**MPS I-S**) is a comparatively mild disorder characterized by joint stiffness, aortic valve disease, corneal clouding, and mild dysostosis multiplex. Onset of significant symptoms is usually after age 5 yr, with diagnosis made between 10 and 20 yr. Patients with Scheie syndrome have normal intelligence and stature but have significant joint and ocular involvement. A carpal tunnel syndrome often develops. Ophthalmic features include corneal clouding, glaucoma, and retinal degeneration. Obstructive airway disease, causing sleep apnea, develops in some patients, necessitating tracheotomy. Aortic valve disease is common and has required valve replacement in some patients.

Mucopolysaccharidosis II

Hunter syndrome (MPS-II) is an X-linked disorder caused by the deficiency of iduronate 2-sulfatase. The *IDS* gene is mapped to Xq28. Point mutations of *IDS* have been detected in about 80% of patients with MPS-II. Major deletions or rearrangements of *IDS* have been found in the rest, and these are usually associated with a more severe clinical phenotype. As an X-linked recessive disorder, Hunter syndrome manifests almost exclusively in males. However, it has been observed in females, because of skewed inactivation of the X-chromosome carrying the normal gene.

Marked molecular heterogeneity explains the wide clinical spectrum of Hunter syndrome. Patients with severe MPS-II have features similar to those of Hurler syndrome, except for the lack of corneal clouding and the somewhat slower progression of somatic and central nervous system (CNS) deterioration. Coarse facial features, short stature, dysostosis multiplex, joint stiffness, and intellectual disability manifest between 2 and 4 yr of age. Grouped skin papules are present in some patients. Extensive mongolian spots have been observed in African and Asian patients and may be an early marker of the disease. Gastrointestinal (GI) storage may produce chronic diarrhea. Communicating hydrocephalus and spastic paraplegia may result from thickened meninges. In severely affected patients, extensive, slowly progressive neurologic involvement precedes death, which usually occurs at age 10-15 yr.

Patients with the mild form have a near-normal or normal life span, minimal CNS involvement, and slow progression of somatic deterioration with preservation of cognitive function in adult life. Survival to ages 65 and 87 yr has been reported, and some patients have had children. Somatic features are Hurler-like but milder with a greatly reduced rate of progression. Adult height may exceed 150 cm (60 inches). Airway involvement, valvular cardiac disease, hearing impairment, carpal tunnel syndrome, and joint stiffness are common and can result in significant loss of function in both the mild and severe forms.

Mucopolysaccharidosis III

Sanfilippo syndrome (MPS-III) is a genetically heterogeneous but clinically similar group of 4 recognized types (IIIA-IIID). Each type is caused by a different enzyme deficiency involved in the degradation of heparan sulfate (see Fig. 107.1). Genes encoding these enzymes are listed in Table 107.2 .

Sanfilippo syndrome is characterized by slowly progressive, severe CNS degeneration with mild somatic disease. Onset of clinical features usually occurs at age 2–6 yr in a child who previously appeared normal. Presenting features include delayed cognitive development, hyperactivity with aggressive behavior, coarse hair, hirsutism, sleep disorders, and mild hepatosplenomegaly. Delay in diagnosis of MPS-III is common because of the mild physical features, hyperactivity, and slowly progressive neurologic disease. Severe neurologic deterioration occurs in most patients by age 6-10 yr, accompanied by rapid deterioration of social and adaptive skills. Severe behavior problems are common, such as sleep disturbance, uncontrolled hyperactivity, temper tantrums, destructive behavior, and physical aggression. Profound intellectual disability and behavior problems often occur in patients with normal physical strength, making management particularly difficult.

Mucopolysaccharidosis IV

Morquio syndrome (MPS-IV) is caused by a deficiency of *N* -acetylgalactosamine-6-sulfatase (**MPS-IVA**) or of β-galactosidase (**MPS-IVB**). Both result in the defective degradation of keratan sulfate. The gene encoding *N* -acetylgalactosamine-6-sulfatase is *GALNS* on chromosome 16q24.3, and the gene encoding β-galactosidase is *GLB1* on chromosome 3p21.33. β-Galactosidase catalyzes GM_1 ganglioside in addition to endohydrolysis of keratan sulfate, and most mutations of *GLB1* result in generalized **gangliosidosis** , a spectrum of neurodegenerative disorders associated with dysostosis multiplex. A W273L mutation of the *GLB1* gene, either in the homozygous state or as part of compound heterozygosity, usually results in Morquio B syndrome.

Both types of Morquio syndrome are characterized by short-trunk dwarfism, a skeletal dysplasia that is distinct from other mucopolysaccharidoses, and preservation of intelligence. MPS-IVA is usually more severe than MPS-IVB, with adult height of <125 cm (50 inches) and >150 cm, respectively. However, there is considerable variability of expression in both subtypes. The appearance of genu valgum, kyphosis, growth retardation with short trunk and neck, and waddling gait with a tendency to fall are early symptoms of MPS-IV. Extraskeletal manifestations include mild corneal clouding, small teeth with abnormally thin enamel, frequent caries formation, and occasionally hepatomegaly and cardiac valvular lesions. Instability of the odontoid process and ligamentous laxity are invariably present and can result in life-threatening atlantoaxial instability and dislocation. Thickened anterior extradural tissue contributes to spinal cord compression. Regular neurologic assessment and radiologic imaging are imperative. Surgery to stabilize the upper cervical spine, usually by posterior spinal fusion, before the development of cervical myelopathy, can be lifesaving.

Mucopolysaccharidosis VI

Maroteaux-Lamy syndrome (MPS-VI) is caused by mutations of the *ARSB* gene on chromosome 5q11-13 encoding *N* -acetylgalactosamine-4-sulfatase (arylsulfatase B). It is characterized by severe to mild somatic involvement, as seen in MPS-I, but with preservation of intelligence. The somatic involvement of the severe form of MPS-IV is characterized by corneal clouding, coarse facial features, joint stiffness, valvular heart disease, communicating hydrocephalus, and dysostosis multiplex. In the severe form, growth can be normal for the 1st few years of life but seems to virtually stop after age 6-8 yr. The mild to intermediate forms of Maroteaux-Lamy syndrome can be easily confused with Scheie syndrome. Spinal cord compression from thickening of the dura in the upper cervical canal with resultant myelopathy is common in patients with MPS-VI.

Mucopolysaccharidosis VII

Sly syndrome (MPS-VII) is caused by mutations of the *GUSB* gene located on chromosome 7q21.11. Mutations result in a deficiency of ß-glucuronidase, intracellular storage of GAG fragments, and extensive clinical involvement. The most severe form presents as lethal **nonimmune fetal hydrops** and may be detected in utero by ultrasound. Some severely affected newborns survive for months and have, or develop, signs of lysosomal storage disease, including thick skin, visceromegaly, and dysostosis multiplex. Less severe forms of MPS-VII present during the 1st years of life with features of MPS-I but slower progression. Corneal clouding varies. Patients with manifestation after 4 yr of life have skeletal abnormalities of dysostosis multiplex but normal intelligence and usually clear corneas. They may be found incidentally on the basis of a blood smear that shows coarse granulocytic inclusions.

Mucopolysaccharidosis IX

MPS-IX is caused by a mutation in the *HYAL1* gene on chromosome 3p21.2-21.2 encoding 1 of 3 hyaluronidases. Clinical findings in the only known patient, a 14 yr old girl, were bilateral nodular soft tissue periarticular masses, lysosomal storage of GAGs in histiocytes, mildly dysmorphic craniofacial features, short stature, normal joint movement, and normal intelligence. Small erosions in both acetabula were the only radiographic findings.

Mucopolysaccharidosis Plus Syndrome

Coarse facial features, organomegaly, joint contractures, dysostosis multiplex, cognitive deficiency, increased mucopolysacchariduria, and massive intracellular accumulation of heparin sulfate were found in 13 children in Northeastern Siberia and 2 Turkish children. Further findings were optic atrophy, intracerebral calcifications, pancytopenia, and renal insufficiency. Most patients died within the 1st 2 yr of life from cardiorespiratory failure.

Lysosomal enzyme activities were normal in children with MPS plus syndrome. This autosomal recessive multisystem disorder is caused by homozygous mutations of *VPS33A* encoding a protein involved in lysosomal fusion processes.

Diagnosis and Differential Diagnosis

Clinical suspicion of a MPS justifies a skeletal survey. Radiographs of chest, spine, pelvis, and hands may show signs of dysostosis multiplex. The next diagnostic step is to assay the urinary excretion of GAGs. Semiquantitative spot tests for increased urinary GAG excretion are quick, inexpensive, and useful for initial evaluation but are subject to both false-positive and false-negative results. Quantitative analysis of single GAG and/or oligosaccharides by mass spectrometry detection tests reveals type-specific profiles in urine, serum, plasma, and dried blood spots.

Any individual with a suspected MPS disorder based on clinical features, radiographic results, or urinary GAG screening tests should have a definitive diagnosis established by **enzyme assay** . Serum, leukocytes, or cultured fibroblasts are used as the tissue source for measuring lysosomal enzymes (see Table 107.2).

Molecular analysis is typically performed using appropriate gene panels. In many cases the type and location of the mutation are related to the future course of the disease and thus have a predictive value. The specific mutation is also needed if **prenatal diagnosis** on fetal cells from a subsequent pregnancy is considered. Carrier testing in Hunter syndrome, an X-linked disorder, requires analysis of *IDS* once the specific mutation or chromosome arrangement in the family is known. Prenatal molecular analysis must be offered in a male fetus of a proven female carrier of the *IDS* gene. His risk to be affected is 50%. In a female fetus the risk is small, but not zero, as a result of skewed maternal X-chromosome inactivation.

Newborn screening for mucopolysaccharidoses is available from dried blood spots and is essential for their early detection and therapeutic intervention.

Mucolipidoses and **oligosaccharidoses** manifest with the same clinical and radiographic features as mucopolysaccharidoses. In these conditions the urinary excretion of GAGs is not elevated. Hurler-like facial features, joint contractures, dysostosis multiplex, and elevated urinary GAG excretion differentiate the mucopolysaccharidoses from other neurodegenerative and dwarfing conditions.

Treatment

Hematopoietic stem cell transplantation has resulted in significant clinical improvement of somatic disease in patients with MPS I, II, and VI (Table 107.4). Clinical effects are increased life expectancy with resolution or improvement of growth, hepatosplenomegaly, joint stiffness, facial appearance, skin changes, obstructive sleep apnea, heart disease, communicating hydrocephalus, and hearing loss. Enzyme activity in serum and urinary GAG excretion normalize. This is true for MPS I-H, II, and III. Patients with MPS-I who have undergone transplantation before 9 mo of age may show normal cognitive development. Transplantation before 24 mo and with a baseline mental development index >70 have improved long-term outcome. Transplantation does not significantly improve the neuropsychological outcome of MPS patients with impaired cognition at transplantation. Early transplantation in the MPS-II patient may have the same effect. Transplantation in the MPS-VI patient stabilizes or improves cardiac manifestations, posture, and joint mobility. Stem cell transplantation does not correct skeletal or ocular anomalies.

Table 107.4

Therapies Aimed at Proximate Causes of Mucopolysaccharidoses

MPS TYPE	HEMATOPOIETIC STEM CELL TRANSPLANTATION	ENZYME REPLACEMENT THERAPY	REMARKS
I	Yes	Laronidase (Aldurazyme)	Developmental trajectory dependent on time of transplantation. Little effect on connective tissue manifestations. Enzyme replacement immediately after diagnosis.
II	Yes	Idursulfase (Elaprase)	
III	No	No	Experimental intrathecal application of recombinant heparin-*N* -sulfatase in MPS-IIIA.
IV	Yes	Elosulfase (Vimizim)	Improved daily activities. No effect on growth or skeletal dysplasia.
VI	Yes	Galsulfase (Naglazyme)	Improved daily activities. Improved growth. No effect on skeletal dysplasia.
VII	Yes	rhGUS	Phase 3 study by Ultragenyx, 2016. Limited experience because of rarity of condition.

Enzyme replacement therapy (ERT) using recombinant α-L -iduronidase has been approved for patients with MPS-I (Table 107.4). It reduces organomegaly and ameliorates rate of growth, improves joint mobility, and reduces the number of episodes of sleep apnea and urinary GAG excretion. The enzyme does not cross the blood-brain barrier and does not prevent deterioration of neurocognitive function. Consequently, ERT is appropriate for patients with mild CNS involvement or to stabilize extraneural manifestations in young patients before stem cell transplantation. Recombinant iduronate-2-sulfatase is the treatment of choice for MPS-II to ameliorate nonneural manifestations. ERT with recombinant human *GALNS* improves physical endurance, respiratory function, and daily living activity of patients with MPS-IV. Similar effects produce recombinant *N* -acetylgalactosamine-4-sulfatase in patients with MPS-VI.

Symptomatic therapy focuses on respiratory and cardiovascular complications, hearing loss, carpal tunnel syndrome, spinal cord compression, hydrocephalus, and other problems (Table 107.5). The multisystem involvement and progressive nature of MPS syndromes usually requires the complex care provided by medical centers.

Table 107.5

Symptomatic Management of Mucopolysaccharidoses

PROBLEM	PREDOMINANTLY IN	MANAGEMENT
NEUROLOGIC		
Hydrocephalus	MPS I, II, VI, VII	Funduscopy, CT scan Ventriculoperitoneal shunting
Chronic headaches	All	
Behavioral disturbance	MPS-III	Behavioral medication, sometimes CT scan, ventriculoperitoneal shunting
Disturbed sleep–wake cycle	MPS-III	Melatonin
Seizures	MPS I, II, III	EEG, anticonvulsants
Atlantoaxial instability	MPS IV	Cervical MRI, upper cervical fusion
Spinal cord compression	All	Laminectomy, dural excision
OPHTHALMOLOGIC		
Corneal opacity	MPS I, VI, VII	Corneal transplant
Glaucoma	MPS I, VI, VII	Medication, surgery
Retinal degeneration	MPS I, II	Night-light
EARS, AIRWAYS		
Recurrent otitis media	MPS I, II, VI, VII	Ventilating tubes
Impaired hearing	All except MPS-IV	Audiometry, hearing aids
Obstruction	All except MPS-III	Adenotomy, tonsillectomy, bronchodilator therapy, CPAP at night,

		laser excision of tracheal lesions, tracheotomy
CARDIAC		
Cardiac valve disease	MPS I, II, VI, VII	Endocarditis prevention, valve replacement
Coronary insufficiency	MPS I, II, VI, VII	Medical therapy
Arrhythmias	MPS I, II, VI, VII	Antiarrhythmic medication, pacemaker
ORAL, GASTROINTESTINAL		
Hypertrophic gums, poor teeth	MPS I, II, VI, VII	Dental care
Chronic diarrhea	MPS-II	Diet modification, loperamide
MUSCULOSKELETAL		
Joint stiffness	All except MPS IV	Physical therapy
Weakness	All	Physical therapy, wheelchair
Gross long-bone malalignment	All	Corrective osteotomies
Carpal tunnel syndrome	MPS I, II, VI, VII	Electromyography, surgical decompression
ANESTHESIA	All except III	Avoid atlantoaxial dislocation; use angulated video intubation laryngoscope and small endotracheal tubes.

CT, Computed tomography; CPAP, continuous positive airway pressure; EEG, electroencephalogram; MRI, magnetic resonance imaging.

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CHAPTER 108

Disorders of Purine and Pyrimidine Metabolism

James C. Harris

The inherited disorders of purine and pyrimidine metabolism cover a broad spectrum of illnesses with various presentations. These include hyperuricemia, acute renal failure, renal stones, gout, unexplained neurologic deficits (seizures, muscle weakness, choreoathetoid and dystonic movements), intellectual and developmental disabilities, acrofacial dysostosis, compulsive self-injury and aggression, autistic-like behavior, unexplained anemia, failure to thrive, susceptibility to recurrent infection (immune deficiency), and deafness. When identified, all family members should be screened.

Purines and pyrimidines form the basis of *nucleotides* and *nucleic acids* (DNA and RNA) and thus are involved in all biologic processes. Metabolically active nucleotides are formed from heterocyclic nitrogen-containing purine bases (guanine and adenine) and pyrimidine bases (cytosine, uridine, and thymine): all cells require a balanced supply of nucleotides for growth and survival. Purines provide the primary source of cellular energy through adenosine triphosphate (ATP) and the basic coenzymes (nicotinamide adenine dinucleotide and its reduced form) for metabolic regulation and play a major role in signal transduction (guanosine triphosphate [GTP], cyclic adenosine monophosphate, cyclic guanosine monophosphate). Fig. 108.1 shows the early steps in the biosynthesis of the purine ring. Purines are primarily produced from endogenous sources, and in usual circumstances, dietary purines have a small role. The end product of purine metabolism in humans is uric acid (2,6,8-trioxypurine).

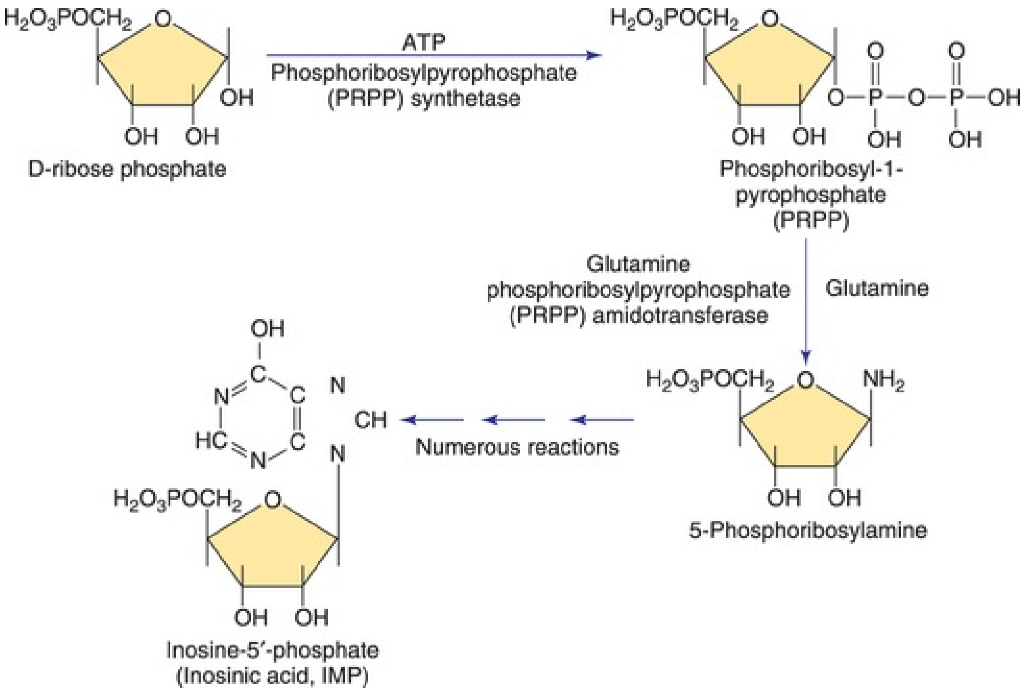
H2O3POCH2
OH
OH OH
D-ribose phosphate
ATP
Phosphoribosylpyrophosphate
(PRPP) synthetase
Phosphoribosyl-1-
pyrophosphate
(PRPP)
Glutamine
phosphoribosylpyrophosphate
(PRPP) amidotransferase
Glutamine
NH2
5-Phosphoribosylamine
Numerous reactions
CH
Inosine-5′-phosphate
(Inosinic acid, IMP)

FIG. 108.1 Early steps in the biosynthesis of the purine ring.

Uric acid is not a specific disease marker, so the cause of its elevation must be determined. The serum level of uric acid present at any time depends on the size of the purine nucleotide pool, which is derived from de novo purine synthesis, catabolism of tissue nucleic acids, and increased turnover of preformed purines. Uric acid is poorly soluble and must be excreted continuously to avoid toxic accumulation in the body. Baseline serum uric acid is established by the balancing of activity between secretory and absorptive urate transporters in both kidney and intestine. Urate secretion and absorption are mediated by separate, opposing groups of transporters. The majority of the genes involved in the variation in uric acid blood level encode urate transporters or associated regulatory proteins.

Thus the fraction of uric acid excreted by the kidney is the result of a complex interplay between secretion and reabsorption by specific and nonspecific uric acid transporters in the proximal tubule, and this sets the level of uric acid in the plasma. Because renal tubule excretion is greater in children than in adults, serum uric acid levels are a less reliable indicator of uric acid production in children than in adults, and therefore measurement of the level in urine may be required to determine excessive production. Clearance of a smaller portion of uric acid is through the gastrointestinal (GI) tract (biliary and intestinal secretion). Because of poor solubility of uric acid under normal circumstances, uric acid is near the maximal tolerable limits, and small alterations in production or solubility or changes in secretion may lead to hyperuricemia and can result in precipitation monosodium urate crystals in extremities (e.g., fingers or toes), which defines **clinical gout** . In renal insufficiency, urate excretion is increased by residual nephrons and the GI tract. Increased production of uric acid is found in malignancy, Reye syndrome, Down syndrome, psoriasis, sickle cell anemia, cyanotic congenital heart disease, pancreatic enzyme replacement, glycogen storage disease (types I, III, IV, and V), hereditary fructose intolerance, and acyl-coenzyme A dehydrogenase deficiency.

The metabolism of both purines and pyrimidines can be divided into biosynthetic, salvage, and catabolic pathways. The first, the de novo pathway, involves a multistep biosynthesis of phosphorylated ring structures from precursors such as CO_2 , glycine, and glutamine. Purine and pyrimidine nucleotides are produced from ribose-5-phosphate or carbamyl phosphate, respectively. The second, a single-step salvage pathway, recovers purine bases and pyrimidine nucleosides derived from either dietary intake or the catabolic pathway (Figs. 108.2 and 108.3). In the de novo pathway, the nucleosides guanosine, adenosine, cytidine, uridine, and thymidine are formed by the addition of ribose-1-phosphate to the purine bases guanine or adenine and to the pyrimidine bases cytosine, uracil, and thymine, respectively. The phosphorylation of these nucleosides produces monophosphate, diphosphate, and triphosphate nucleotides, as well as the deoxy-nucleotides that are utilized for DNA formation. Under usual circumstances, the salvage pathway predominates over the biosynthetic pathway because nucleotide salvage saves energy for cells. Only a small fraction of the nucleotides turned over by the body each day are degraded and excreted. Synthesis of nucleotides is most active in tissues with high rates of cellular turnover, such as gut epithelium, skin, and bone marrow. The third pathway is catabolism. The end product of the catabolic pathway of the purines in humans is uric acid, whereas catabolism of pyrimidines produces citric acid cycle intermediates.

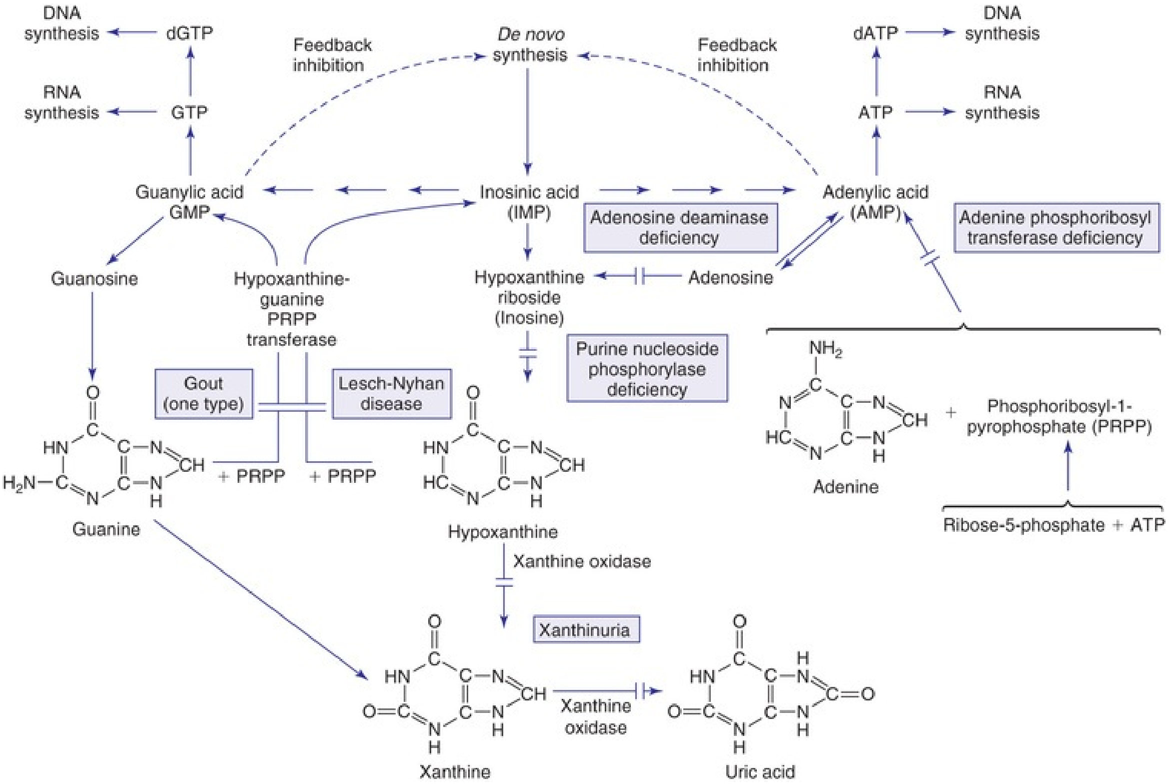
DNA synthesis
dGTP
RNA synthesis
GTP
Feedback inhibition
De novo synthesis
Feedback inhibition
dATP
DNA synthesis
ATP
RNA synthesis
Guanylic acid GMP
Inosinic acid (IMP)
Adenylic acid (AMP)
Adenosine deaminase deficiency
Adenine phosphoribosyl transferase deficiency
Guanosine
Hypoxanthine-guanine PRPP transferase
Hypoxanthine riboside (Inosine)
Adenosine
Purine nucleoside phosphorylase deficiency
Gout (one type)
Lesch-Nyhan disease
Guanine
+ PRPP
+ PRPP
Hypoxanthine
Adenine
Phosphoribosyl-1-pyrophosphate (PRPP)
Ribose-5-phosphate + ATP
Xanthine oxidase
Xanthinuria
Xanthine
Xanthine oxidase
Uric acid

FIG. 108.2 Pathways in purine metabolism and salvage.

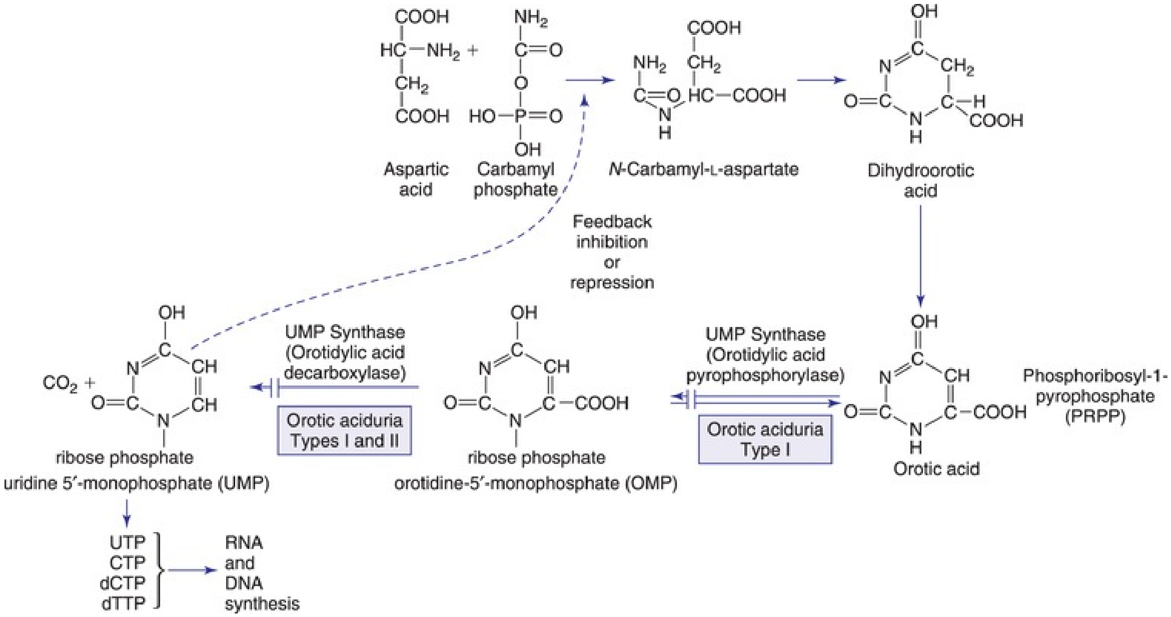
Aspartic acid
Carbamyl phosphate
N-Carbamyl-L-aspartate
Dihydroorotic acid
Feedback inhibition or repression
CO_2 +
UMP Synthase (Orotidylic acid decarboxylase)
Orotic aciduria Types I and II
UMP Synthase (Orotidylic acid pyrophosphorylase)
Orotic aciduria Type I
Phosphoribosyl-1-pyrophosphate (PRPP)
Orotic acid
ribose phosphate
uridine 5′-monophosphate (UMP)
ribose phosphate
orotidine-5′-monophosphate (OMP)
UTP
CTP
dCTP
dTTP
RNA and DNA synthesis

FIG. 108.3 Pathways in pyrimidine biosynthesis.

Inborn errors in the **synthesis of purine nucleotides** comprise the phosphoribosylpyrophosphate synthetase spectrum of disorders, including deficiency and superactivity, adenylosuccinate lyase deficiency, and 5-amino-4-imizolecarboxamide (AICA) riboside deficiency (AICA-ribosiduria). Disorders resulting from abnormalities in **purine catabolism** comprise muscle adenosine monophosphate (AMP) deaminase deficiency, adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, and xanthine oxidoreductase deficiency. Disorders resulting from the **purine salvage** pathway include hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency and adenine phosphoribosyltransferase (APRT) deficiency.

Hereditary orotic aciduria (uridine monophosphate synthase deficiency) is an inborn error of **pyrimidine synthesis** that leads to an excessive excretion of orotic acid in urine. Dihydrorotate dehydrogenase deficiency (Miller syndrome), also a disorder of de novo pyrimidine synthesis, paradoxically may lead to orotic aciduria. Other pyrimidine disorders lead to abnormalities in **pyrimidine catabolism** , including dihydropyrimidine dehydrogenase (DPD) deficiency, dihydropyrimidinase (DPH) deficiency, β-ureidopropionase deficiency, pyrimidine 5′-nucleotidase deficiency, and thymidine phosphorylase deficiency. A disorder resulting from the **pyrimidine salvage** is thymidine kinase-2 deficiency.

Gout

Gout presents with hyperuricemia, uric acid nephrolithiasis, and acute inflammatory arthritis. **Gouty arthritis** is caused by monosodium urate crystal deposits that result in inflammation in joints and surrounding tissues. The presentation is most commonly monoarticular, typically in the metatarsophalangeal joint of the big toe. *Tophi*, deposits of monosodium urate crystals, may occur over points of insertion of tendons at the elbows, knees, and feet or over the helix of the ears. **Primary gout** usually occurs in middle-aged males and results mainly from decreased renal excretion of uric acid, or purine overconsumption, or high intake of alcohol or fructose, or a combination of these factors. Gout occurs in any condition that leads to reduced clearance of uric acid: during therapy for malignancy or with dehydration, lactic acidosis, ketoacidosis, starvation, diuretic therapy, and renal failure. Excessive purine, alcohol, or fructose ingestion may increase uric acid levels. The biochemical etiology of gout is unknown for most patients, and it is considered to have a basis in genetic polymorphisms, predominantly in uric acid transporters. Purine overproduction is a rare cause of primary gout and is associated with several genetic disorders discussed later. **Secondary gout** is either the result of another disorder with rapid tissue breakdown or cellular turnover, leading to increased production or decreased excretion of uric acid, or the result of some types of drug treatment; for example, diuretics cause plasma volume reduction and can precipitate a gouty attack.

Gout resulting from **endogenous purine overproduction** is associated with hereditary disorders of 3 different enzymes that result in hyperuricemia. These include the HPRT deficiency spectrum (ranging from severe deficiency or Lesch-Nyhan syndrome to partial HPRT deficiency), 2 forms of superactivity of PP-ribose-P synthetase, and glycogen storage disease type I (glucose-6-phosphatase deficiency). In the first 2 disorders, the basis of hyperuricemia is purine nucleotide and uric acid overproduction, whereas in the 3rd disorder it is both excessive uric acid production and diminished renal excretion of urate. Glycogen storage disease types III, V, and VII are associated with exercise-induced hyperuricemia, the consequence of rapid ATP utilization and failure to regenerate it effectively during exercise (see Chapter 105.1).

Juvenile gout results from purine underexcretion. The earlier terminology *juvenile hyperuricemic nephropathy* has been replaced by the newer term (autosomal dominant) *tubulointerstitial kidney disease* (ADTKD). The term **ADTKD-UMOD** *(uromodulin-associated kidney disease)* is used for medullary cystic kidney disease type 2 and maps to chromosome 16p11.2. It results from uromodulin mutations. Other genes classified as forms of familial juvenile hyperuricemic nephropathy include those for renin and hepatic nuclear factor-1β. Unlike the 3 inherited purine disorders that are X-linked and the recessively inherited glycogen storage disease, these are autosomal dominant conditions. Familial juvenile hyperuricemic nephropathy is associated with a reduced fractional excretion of uric acid. Although it typically presents from puberty up to the 3rd decade, it has been reported in early childhood. It is characterized by early onset, hyperuricemia, gout, familial renal disease, and low urate clearance relative to glomerular filtration rate. It occurs in both males and females and is frequently associated with a rapid decline in renal function that may lead to death unless diagnosed and treated early. Once familial juvenile hyperuricemic nephropathy is recognized, presymptomatic detection is of critical importance to identify asymptomatic family members with hyperuricemia and to begin treatment, when indicated, to prevent nephropathy.

Genetics

Familial juvenile hyperuricemic nephropathy-2 (HNFJ2; 613092) is caused by mutation in the renin gene (*REN* ; 179820) on chromosome 1q32. HNFJ3 (614227) has been mapped to chromosome 2p22.1-p21. ADTKD involves mutations of the mucin *(MUC1)* gene. The mutation of uromodulin has been traced to chromosome 16.

Treatment

Treatment of hyperuricemia involves the combination of allopurinol or febuxostat (xanthine oxidase inhibitors) to decrease uric acid production, probenecid to increase uric acid clearance in those with normal renal function, and increased fluid intake to reduce the concentration of uric acid. A low-purine diet, weight reduction, and reduced alcohol and fructose intake (fructose both reduces urate clearance and accelerates ATP breakdown to uric acid) are recommended.

Abnormalities in Purine Salvage

Hypoxanthine-Guanine Phosphoribosyltransferase (HPRT) Deficiency

Lesch-Nyhan disease (LND) is a rare X-linked disorder of purine metabolism that results from HPRT deficiency. This enzyme is normally present in each cell in the body, but its highest concentration is in the brain, especially in the basal ganglia. Clinical manifestations include hyperuricemia, intellectual disability, dystonic movement disorder that may be accompanied by choreoathetosis and spasticity, dysarthric speech, and compulsive self-biting, usually beginning with the eruption of teeth.

There is a spectrum of severity for the clinical presentations. HPRT levels are related to the extent of motor symptoms, to the presence or absence of self-injury, and possibly to the level of cognitive function. Purine overproduction is present. The majority of individuals with classic LND have low or undetectable levels of the HPRT enzyme. Partial deficiency in HPRT (**Kelley-Seegmiller syndrome**) with >1.5–2.0% enzyme is associated with purine overproduction and variable neurologic dysfunction (neurologic HPRT deficiency). HPRT deficiency with activity levels >8% of normal still shows purine (and uric acid) overproduction but apparently normal cerebral functioning (HPRT-related hyperuricemia), although cognitive deficits may occur. Qualitatively similar cognitive deficit profiles have been reported in both LND and variant cases. Variants produced scores intermediate between those of patients with LND and normal controls on almost every neuropsychological measure tested.

Genetics

The *HPRT* gene has been localized to the long arm of the X chromosome (q26-q27). The complete amino acid sequence for HPRT is known and is encoded by the *HPRT1* gene (approximately 44 kb; 9 exons). The disorder appears in males; occurrence in females is extremely rare and ascribed to nonrandom inactivation of the normal X chromosome. Absence of HPRT activity results in a failure to salvage hypoxanthine, which is degraded to uric acid. Failure to consume phosphoribosylpyrophosphate in the salvage reaction results in an increase in this metabolite, which drives de novo purine synthesis, leading to the overproduction of uric acid. Excessive uric acid production manifests as gout, necessitating specific drug treatment (allopurinol). Because of the enzyme deficiency, hypoxanthine accumulates in the cerebrospinal fluid (CSF), but uric acid does not; uric acid is not produced in the brain and does not cross the blood-brain barrier. The behavior disorder is not caused by hyperuricemia or excess hypoxanthine because patients with partial HPRT deficiency, the variants with hyperuricemia, do not self-injure, and infants with isolated hyperuricemia from birth do not develop self-injurious behavior.

The prevalence of the classic LND has been estimated at 1 in 100,000 to 1 in 380,000 persons based on the number of known cases in the United States. The incidence of partial variants is not known. Those with the classic syndrome rarely survive the 3rd decade because of renal or respiratory compromise. The life span may be normal for patients with partial HPRT deficiency without severe renal involvement.

Pathology

No specific brain abnormality is documented after detailed histopathology and electron microscopy of affected brain regions. MRI has documented reductions in the volume of basal ganglia nuclei. Abnormalities in neurotransmitter metabolism have been identified in 3 autopsied cases. All 3 patients had very low HPRT levels (<1% in striatal tissue and 1–2% of control in thalamus cortex). There was a functional loss of 65–90% of the nigrostriatal and mesolimbic dopamine terminals, although the cells of origin in the substantia nigra did not show dopamine reduction. The brain regions primarily involved were the caudate nucleus, putamen, and nucleus accumbens. It is proposed that the neurochemical changes may be linked to functional abnormalities, possibly resulting from a diminution of arborization or branching of dendrites rather than cell loss. A neurotransmitter abnormality is demonstrated by changes in CSF neurotransmitters and their metabolites and is confirmed by positron emission tomography (PET) scans of dopamine function. In vivo reductions in the presynaptic dopamine transporter have been documented in the caudate and putamen of 6 individuals.

The mechanism whereby HPRT leads to the neurologic and behavioral symptoms is unknown. However, both hypoxanthine and guanine metabolism are affected, and GTP and adenosine have substantial effects on neural tissues. The functional link between purine nucleotides and the dopamine system is through salvage of guanine by HPRT to form GTP; this is essential for GTP cyclohydrolase activity, the first step in the synthesis of pterins and dopamine. In a controlled study that sought correlations between HPRT and GPRT and behavior, GPRT was more highly correlated than HPRT on 13 of 14 measures of the clinical phenotype; these included severity of dystonia, cognitive impairment, and behavioral abnormalities. These findings suggest that loss of guanine recycling might be more closely linked to the LND/LNV phenotype than loss of hypoxanthine recycling. Moreover, patients with inherited GTP cyclohydrolase deficiency show clinical features in common with LND.

Dopamine reduction in brain is documented in HPRT-deficient strains of mutant mice. Dopamine binding to its receptor results in either an activation (D1 receptor) or an inhibition (D2 receptor) of adenylcyclase. Both receptor effects are mediated by G proteins (GTP-binding proteins) dependent on guanine diphosphate in the guanine diphosphate/GTP exchange for cellular activation. Dopamine and adenosine systems are also linked through the role of adenosine as a neuroprotective agent in preventing neurotoxicity. Adenosine derives from AMP, which depends on hypoxanthine salvage in the brain by HPRT. Adenosine agonists mimic the biochemical and behavioral actions of dopamine antagonists, whereas adenosine receptor antagonists act as functional dopamine agonists. LND can thus be seen as arising ultimately from nucleotide depletion specifically in the brain, which relies on the HPRT salvage pathway, leading to dopamine and adenosine depletions.

Clinical Manifestations

At birth, infants with LND have no apparent neurologic dysfunction. After several months, developmental delay and neurologic signs become apparent. Before age 4 mo, hypotonic, recurrent vomiting, and difficulty with secretions may be noted. By 8-12 mo, extrapyramidal signs appear, primarily dystonic movements. In some patients, spasticity may become apparent at this time; in others it becomes apparent later in life.

Cognitive function is usually reported to be in the mild to moderate range of intellectual disability, although some individuals test in the low-normal range. Because test scores may be influenced by difficulty in testing caused by movement disorder and dysarthric speech, overall intelligence may be underestimated.

The age of onset of self-injury may be as early as 1 yr and occasionally as late as the teens. Self-injury occurs, although all sensory modalities, including pain, are intact. The **self-injurious behavior** (SIB) usually begins with self-biting, although other SIB patterns emerge with time. Most characteristically, the fingers, mouth, and buccal mucosa are mutilated. Self-biting is intense and causes tissue damage and may result in the amputation of fingers and substantial loss of tissue around the lips. Extraction of primary teeth may be required. The biting pattern can be asymmetric, with preferential mutilation of the left or right side of the body. The type of behavior is different from that seen in other intellectual disability syndromes involving self-injury. Self-hitting and head-banging are the most common initial presentations in *other* syndromes. The intensity of SIB generally requires that the patient be restrained. When restraints are removed, the patient with LND may appear terrified, and stereotypically place a finger in the mouth. The patient may ask for restraints to prevent elbow movement; when the restraints are placed, or replaced, he may appear relaxed and cheerful. Dysarthric speech may cause interpersonal communication problems; however, the higher-functioning children can express themselves fully and participate in verbal therapy.

The self-mutilation presents as a compulsive behavior that the child tries to control but frequently is unable to resist. Older individuals may enlist the help of others and notify them when they are comfortable enough to have restraints removed. In some cases the behavior may lead to deliberate self-harm. The LND patient may also show compulsive aggression and inflict injury to others through pinching, grabbing, or hitting or by using verbal forms of aggression. Afterward he may apologize, stating that this behavior was out of his control. Other maladaptive behaviors include head- or limb-banging, eye-poking, and psychogenic vomiting.

Diagnosis

The presence of **dystonia** along with self-mutilation of the mouth and fingers suggests LND. With partial HPRT deficiency, recognition is linked to either hyperuricemia alone or hyperuricemia and a dystonic movement disorder. Serum levels of uric acid that exceed 4-5 mg uric acid/dL and a urine uric acid:creatinine ratio of ≥3-4 : 1 are highly suggestive of HPRT deficiency, particularly when associated with neurologic symptoms. The definitive diagnosis requires an analysis of the HPRT enzyme. This is assayed in an erythrocyte lysate. Individuals with classic LND have near 0% enzyme activity, and those with partial variants show values between 1.5% and 60%. The intact cell HPRT assay in skin fibroblasts offers a good correlation between enzyme activity and severity of disease. Molecular techniques are used for gene sequencing and identification of carriers.

Differential diagnosis includes other causes of infantile hypotonia and dystonia. Children with LND are often initially *incorrectly* diagnosed as having athetoid cerebral palsy. When a diagnosis of cerebral palsy is suspected in an infant with a normal prenatal, perinatal, and postnatal course, LND should be considered. Partial HPRT deficiency may be associated with acute renal failure in infancy; therefore clinical awareness of partial HPRT deficiency is of particular importance. The simplest test to exclude LND or partial deficiency is the urinary uric acid:creatinine ratio.

An understanding of the molecular disorder has led to effective drug treatment for uric acid accumulation and arthritic tophi, renal stones, and neuropathy. However, reduction in uric acid alone does not influence the neurologic and behavioral aspects of LND. Despite treatment from birth for uric acid elevation, behavioral and neurologic symptoms are unaffected. The most significant complications of LND are renal failure and self-mutilation.

Treatment

Medical management of LND focuses on prevention of renal failure by pharmacologic treatment of hyperuricemia, with high fluid intake along with alkalization and allopurinol (or more often febuxostat). A low-purine diet and reduced fructose intake are desirable.

Allopurinol treatment must be monitored because urinary oxypurine excretion with all overproduction disorders is sensitive to allopurinol, resulting in an increased urine concentration of xanthine, which is extremely insoluble. Self-mutilation is reduced through behavior management and the use of restraints and/or removal of teeth. Pharmacologic approaches to decrease anxiety and spasticity with medication have mixed results. Drug therapy focuses on symptomatic management of anticipatory anxiety, mood stabilization, and reduction of self-injurious behavior. Although there is no standard drug treatment, diazepam may be helpful for anxiety symptoms, risperidone for aggressive behavior, and carbamazepine or gabapentin for mood stabilization. Each of these medications may reduce SIB by helping to reduce anxiety and stabilize mood. *S* -adenosylmethionine (**SAMe**), which is thought to act by countering nucleotide depletion in the brain, has been reported specifically to reduce the rate of self-injury in some cases. Animal studies have suggested that D1-dopamine receptor antagonists such as ecopipam may suppress SIB. Despite limited data, the drug appears to reduce SIB in most patients, suggesting further study to establish an appropriate dosing regimen and assess toxicity.

Several patients have received **bone marrow transplantation** (BMT), based on the hypothesis that the central nervous system (CNS) damage is produced by a circulating toxin. There is no evidence that BMT is a beneficial treatment approach; it remains an experimental and potentially dangerous therapy. Two patients received partial exchange transfusions every 2 mo for 3-4 yr. Erythrocyte HPRT activity was 10–70% of normal during this period, but no reduction of neurologic or behavioral symptoms was apparent. Successful preimplantation genetic diagnosis and in vitro fertilization for LND has been reported with the birth of an unaffected male infant.

Both the motivation for self-injury and its biologic basis must be addressed in treatment programs. However, behavioral techniques alone, using operant conditioning approaches, have not proved to be an adequate general treatment. Although **behavioral procedures** have had some selective success in reducing self-injury, difficulty with generalization outside the experimental setting limits this approach, and patients under stress may revert to their previous SIB. Behavioral approaches may also focus on reducing SIB through treatment of phobic anxiety associated with being unrestrained. The most common techniques are systematic desensitization, extinction, and differential reinforcement of other (competing) behavior. Stress management has been recommended to assist patients to develop more effective coping mechanisms. Individuals with LND do not respond to contingent electric shock or similar aversive behavioral measures. An increase in self-injury may be observed when aversive methods are used.

Restraint (day and night) and dental procedures are common means to prevent self-injury. The time in restraints is linked to the age of onset of self-injury. Children with LND can participate in making decisions regarding restraints and the type of restraints. The time in restraints may potentially be reduced with systematic behavior treatment programs. Many patients have teeth extracted to prevent self-injury. Others use a protective mouth guard designed by a dentist. Most parents suggest that stress reduction and awareness of the patient's needs are the most effective in reducing self-injury. Positive behavioral techniques of reinforcing appropriate behavior are rated effective by almost half the families.

Deep brain stimulation to the anteroventral internal globus pallidus is a procedure that has successfully treated self-injury and lessened dystonia in several case reports.

Adenine Phosphoribosyltransferase Deficiency (Dihydroxyadeninuria)

APRT, a purine salvage enzyme, catalyzes the synthesis of AMP from adenine and 5-phosphoribosyl-1-pyrophosphate (PP-ribose-P). The absence of this enzyme results in the cellular accumulation of adenine and it being oxidized as an alternative substrate by xanthine dehydrogenase to form **2,8-dihydroxyadenine** , which is extremely insoluble. APRT deficiency is present from birth, becoming apparent as early as 5 mo and as late as the 7th decade.

Genetics

The disorder is an autosomal recessive trait with considerable clinical heterogeneity. The *APRT* gene is located on chromosome 16q (16q24.3) and encompasses 2.8 kb of genomic DNA.

Clinical Manifestations

These include urinary calculus formation with crystalluria, urinary tract infections, hematuria, renal colic, dysuria, and acute renal failure. Brownish spots on the infant's diaper or yellow-brown crystals in the urine suggest the diagnosis. The 2,8-dihydroxyadenine is cleared efficiently by the kidneys and so does not accumulate in plasma, but precipitates readily in the renal lumen.

Laboratory Findings

Urinary levels of adenine, 8-hydroxyadenine, and 2,8-dihydroxyadenine are elevated, whereas plasma uric acid is normal. The deficiency may be complete (**type I**) or partial (**type II**); the partial deficiency is reported in Japan. The diagnosis is made based on the level of residual enzyme in erythrocyte lysates. The renal calculi, composed of 2,8-dihydroxyadenine, are radiolucent, soft, and easily crushed. These stones are not distinguishable from uric acid stones by routine tests but require high-performance liquid chromatography (HPLC), ultraviolet (UV) light, infrared light, mass spectrometry, x-ray crystallography, or capillary electrophoresis for diagnosis, particularly to distinguish from stones in HPRT deficiency.

Treatment

Treatment includes high fluid intake, dietary purine restriction, and allopurinol, which inhibits the conversion of adenine to its metabolites and prevents further stone formation. Alkalinization of the urine is to be avoided, because unlike that of uric acid, the solubility of 2,8-dihydroxyadenine does not increase up to pH 9. **Shock wave lithotripsy** has been reported to be successful. The **prognosis** depends on renal function at diagnosis. Early treatment is critical in the prevention of stones because severe renal insufficiency may accompany late recognition.

Disorders Linked to Purine Nucleotide Synthesis

Phosphoribosylpyrophosphate Synthetase Superactivity and Deficiency

Phosphoribosylpyrophosphate (**PRPP**) is a substrate involved in the synthesis of essentially all nucleotides and important in the regulation of the de novo pathways of purine and pyrimidine nucleotide synthesis. The synthetase enzyme (**PRPS**) produces PRPP from ribose-5-phosphate and ATP (see Figs. 108.1 and 108.2). PRPP is the first intermediary compound in the de novo synthesis of purine nucleotides that lead to the formation of inosine monophosphate, then to ATP and GTP.

Genetic disorders of this enzyme affect only the PRPS-1 isoform; PRPS-2 mutations have not been described. PRPS-1 disorders are all X-linked and are divided into "superactivity," which occurs as 2 phenotypes (infantile or early childhood onset, and a milder form with late-juvenile or early-adult onset), and "deficiency," which is a spectrum disorder that is distinguished clinically according to severity as 3 disorders: Arts syndrome, Charcot-Marie-Tooth disease X-linked-5, and X-linked deafness-2.

Superactivity of the enzyme results in an increased generation of PRPP in dividing cells. Because PRPP aminotransferase, the first enzyme of the purine de novo pathway, is not physiologically saturated by PRPP, the synthesis of purine nucleotides increases, and consequently the production of uric acid is increased. PRPP synthetase superactivity is one of the few hereditary disorders in which the activity of an enzyme is enhanced. The infantile or early childhood form of PRPS-1 superactivity has severe neurologic consequences accompanied by uric acid overproduction, whereas individuals with the late-juvenile or early-adult presentation are neurologically normal but still have uric acid overproduction.

Deficiency of PRPS-1 produces depleted purine nucleotide synthesis in tissues dependent on PRPS-1, which includes brain as well as other neural tissues and lung.

Genetics

Three distinct complementary DNAs for PRPS have been cloned and sequenced. Two forms, PRPS-1 and PRPS-2, are X-linked to Xq22-q24 and Xp22.2-p.22.3 (escapes X inactivation), respectively, and are widely expressed. The 3rd locus maps to human chromosome 7 and appears to be transcribed only in the testes. PRPS-1 defects are thus inherited as X-linked traits and present with varying degrees of severity. The **late-onset** form of superactivity arises from increased transcription of normal messenger RNA; the cause of this has not been discovered. The **early-onset** form of superactivity arises from mutations affecting allosteric regulation of the protein that controls feedback inhibition by inorganic phosphate and dinucleotides. At the same time, these mutations destabilize the protein, so that in slow or nonreplicating cells, such as neurons and red blood cells (RBCs), the enzyme becomes inactive. In contrast, the deficiency phenotypes of PRPS-1 are produced by mutations directly affecting enzyme function, usually in the substrate binding site. Even though the defect is X-linked, it should be considered in a child or young adult of either sex with hyperuricemia and/or hyperuricosuria and normal HPRT activity in lysed RBCs.

Clinical Manifestations

Affected hemizygous males with early-onset superactivity show signs of uric acid overproduction that are apparent in infancy or early childhood, as well as psychomotor delay and sensorineural deafness. Hypotonia, ataxia, and autistic-like behavior have been described. Heterozygous female carriers may also develop gout and hearing impairment. The late-onset type is found in males who show only hyperuricemia and hyperuricosuria, but no neurologic signs. The mildest form of PRPS-1 deficiency manifests as progressive postlingual hearing loss in **X-linked deafness-2** (DFN2). More severe mutations constitute the **Charcot-Marie-Tooth disease X-linked-5** phenotype, which includes peripheral neuropathy, hearing impairment, and optic atrophy. The most severe PRPS-1 mutations occur in patients with **Arts syndrome** , who also have central neuropathy and an impaired immune system. Females appear to be unaffected, but hemizygous males have usually not survived beyond the 1st decade, typically succumbing to lung disease. SAMe therapy has prolonged survival, although the neurologic deficits, including the deafness, do not appear to be responsive.

A mechanism for the neurologic symptoms is not yet known, but it can be hypothesized that nucleotide depletion is present in neural tissues, including the brain. Abnormalities of hearing and vision are typical of PRPS-1 deficiency, where the absence of this enzyme presumably compromises these highly energy-dependent neural functions. The high transcript level of PRPS-1 in lung and bone marrow also suggests that its absence may be causal for the recurrent lung infections that characterize Arts syndrome.

Laboratory Findings

For PRPS-1 “superactivity” (both juvenile and adult presentations), serum uric acid may be grossly raised and the urinary excretion of uric acid increased. For PRPS “deficiency,” uric acid is normal, not low, probably because PRPS-2 provides the major uric acid–forming activity in liver and other major organs.

Diagnosis requires that PRPS-1 activity be measured in erythrocytes and cultured fibroblasts. The adult superactivity disorder must be differentiated from partial HPRT deficiency involving the salvage pathway, which also presents with mild or absent neurologic traits accompanied by hyperuricemia.

Treatment

Treatment of PRPS deficiency, specifically Arts syndrome, has involved mainly experimental therapy with SAMe, as a dietary supplement to correct the depletion of purines. Dietary purines are usually not absorbed into the body but are degraded to uric acid by the gut. SAMe supplementation (beginning at 20 mg/kg/day orally) has been effective in greatly reducing the acute hospitalization episodes of 2 brothers with Arts syndrome, over a period of 10 yr. Treatment of PRPS superactivity is aimed at controlling the hyperuricemia with allopurinol, which inhibits xanthine oxidase, the last enzyme of the purine catabolic pathway. Uric acid production is reduced and is replaced by hypoxanthine, which is more soluble, and xanthine. The initial dose of allopurinol is 10-20 mg/kg/24 hr in children and is adjusted to maintain normal uric acid levels in plasma. The risk of xanthine stone formation is similar to that described for LND. A low-purine diet (free of organ meats, dried beans, and sardines), high fluid intake, and alkalinization of the urine to establish a urinary pH of 6.0-6.5 are necessary. These measures control the hyperuricemia and urate nephropathy but do not affect the neurologic symptoms. There is no known treatment for the neurologic complications.

Adenylosuccinase Lyase Deficiency (Succinylpurinuria)

Adenylosuccinase lyase deficiency is an inherited deficiency of de novo purine synthesis in humans. Adenylosuccinase lyase is an enzyme that catalyzes 2 pathways in de novo synthesis and purine nucleotide recycling. These are the conversion of succinylaminoimidazole carboxamide ribotide (SAICAr) into aminoimidazole carboxamide ribotide (AICAR) in the de novo synthesis of purine nucleotides and the conversion of adenylosuccinate (S-AMP) into AMP, the 2nd step in the conversion of inosine monophosphate (IMP) into AMP, in the purine nucleotide cycle. Adenylosuccinase lyase deficiency results in the accumulation in urine, CSF, and to a smaller extent in plasma, of SAICAr and succinyladenosine (S-Ado), the dephosphorylated derivatives of SAICAr and S-AMP, respectively.

Genetics

Succinylpurinuria is an autosomal recessive disorder; the gene has been mapped to chromosome 22q13.1-q13.2, and approximately 50 gene mutations have been identified. Laboratory investigations show grossly raised succinylpurines in urine and CSF, which are normally undetectable.

Clinical Manifestations

The fatal **neonatal** form presents with lethal encephalopathy. Clinical manifestations include varying degrees of psychomotor retardation, generally accompanied by a seizure disorder and autistic-like behaviors (poor eye contact and repetitive behaviors). Neonatal seizures and a severe infantile epileptic encephalopathy are often the first manifestations of this disorder. Others demonstrate moderate to severe intellectual disability, sometimes associated with growth retardation and muscle hypotonia. One female tested in the mild range of intellectual disability. The form of adenylosuccinase lyase deficiency with profound intellectual disability has been designated **type I** and the variant case with mild intellectual disability **type II** . Other patients have an intermediate clinical symptom pattern with moderately delayed psychomotor development, seizures, stereotypies, and agitation.

Pathology

CT and MRI of the brain may show hypotrophy or hypoplasia of the cerebellum, particularly the vermis. It is proposed that rather than being caused by purine nucleotide depletion, the symptoms are from the neurotoxic effects of accumulating succinylpurines. The S-Ado: SAICAr ratio has been linked to phenotype severity, suggesting that SAICAr is the more toxic compound and that S-Ado might be neuroprotective.

The laboratory diagnosis is based on the presence in urine and CSF of SAICAr and S-Ado, both normally undetectable.

Treatment

No successful treatment has been demonstrated for adenylosuccinase lyase deficiency. SAMe supplementation therapy was tested for 6 mo for an infant diagnosed in the early postnatal period, but no amelioration of symptoms was noted, providing further evidence that the disorder arises from nucleotide toxicity rather than depletion. Prenatal diagnosis has been reported. Systematic screening is suggested in infants and children with unexplained psychomotor retardation or seizure disorder.

Aminoimidazole Carboxamide Ribotide (AICAR) Transformylase/Inosine Monophosphate (IMP) Cyclohydrolase Deficiency

AICA riboside is the dephosphorylated product of AICAR, also termed *ZMP*. Along with its di- and triphosphates, ZMP accumulates in RBCs and fibrocytes in inherited deficiency of the bifunctional enzyme AICAR transformylase/IMP cyclohydrolase (**ATIC**), which catalyzes the conversion of AICAR to formyl-AICAR.

Genetics

This inborn error of purine biosynthesis is caused by a mutation of the *ATIC* gene effecting AICAR transformylase activity. In a single reported case, AICAR transformylase was profoundly deficient, whereas the IMP cyclohydrolase level was 40% of normal.

Clinical Features

The disorder is described in a female infant with profound intellectual disability, epilepsy, dysmorphic features (prominent forehead and metopic suture, brachycephaly, wide mouth with thin upper lip, low-set ears, and prominent clitoris because of fused labia minora), and congenital blindness.

Laboratory Findings

Urinary screening with the Bratton-Marshall test to detect AICA resulted in the identification of this disorder. The transformylase was found to be deficient in fibroblasts, confirming diagnosis of ATIC deficiency.

Treatment

No successful treatment is described.

Disorders Resulting From Abnormalities in Purine Catabolism

Myoadenylate Deaminase Deficiency (Muscle Adenosine Monophosphate Deaminase Deficiency)

Myoadenylate deaminase is a muscle-specific isoenzyme of AMP deaminase that is active in skeletal muscle. During exercise, the deamination of AMP leads to increased levels of IMP and ammonia in proportion to the work performed by the muscle. Two forms of myoadenylate deaminase deficiency are known: an inherited (**primary**) form that may be asymptomatic or associated with cramps or myalgia with exercise, and a **secondary** form that may be associated with other neuromuscular or rheumatologic disorders.

Clinical Manifestations

Clinical manifestations are typically isolated muscle weakness, fatigue, myalgias following moderate to vigorous exercise, or cramps. Myalgia may be associated with an increased serum creatine kinase level and detectable electromyelographic abnormalities. Muscle wasting or histologic changes on biopsy are absent. The age of onset may be as early 8 mo, with approximately 25% of cases recognized between 2 and 12 yr. The enzyme defect has been identified in asymptomatic family members. Secondary forms of muscle AMP deaminase deficiency have been identified in Werdnig-Hoffmann disease, Kugelberg-Welander syndrome, polyneuropathies, and amyotrophic lateral sclerosis (see Chapter 630.2). The metabolic disorder involves the purine nucleotide cycle. As shown in Fig. 108.2 , the enzymes involved in this cycle are AMP deaminase, S-AMP synthetase, and S-AMP lyase. It is proposed that muscle dysfunction in AMP deaminase deficiency results from impaired energy production during muscle contraction. It is unclear how individuals may carry the deficit and be asymptomatic. In addition to muscle dysfunction, a mutation of liver AMP deaminase has been proposed as a cause of primary gout, leading to overproduction of uric acid.

Genetics

The inherited form of the disorder is an autosomal recessive trait. *AMPD1,* the gene responsible for encoding muscle AMP deaminase, is located on the short arm of chromosome 1 (1p13-21). Population studies reveal that a mutant allele is found at high frequency in white populations, but alternative splicing of the gene can result in removal of the mutation and normal enzyme function. As a result, the disorder is usually screened by performing the forearm ischemic exercise test. The elevation of venous plasma ammonia following exercise that is seen in unaffected individuals is *absent* in AMP deaminase deficiency.

Laboratory Findings

The final diagnosis is made by histochemical or biochemical assays of a muscle biopsy. The primary form is distinguished by the finding of enzyme levels <2% with little or no immunoprecipitable enzyme. Affected individuals are advised to exercise with caution to prevent rhabdomyolysis and myoglobinuria.

Treatment

Although there are no documented fully effective treatments for myoadenylate deaminase deficiency, it has been proposed that enhancing the rate of replenishment of the ATP pool might be beneficial. Using this rationale, treatment with **ribose** (2-60 g/24 hr orally in divided doses) or **xylitol** , which is converted to ribose, has been reported to improve endurance and muscle strength in some patients, but is ineffective in others. Genetic approaches may be feasible in the future for inherited cases, whereas treatment of the underlying condition is essential in secondary cases.

Adenosine Deaminase Deficiency

See Chapter 152.1 .

Purine Nucleoside Phosphorylase Deficiency

See Chapter 152.2 .

Xanthine Oxidoreductase Deficiency (Hereditary Xanthinuria/Molybdenum Cofactor Deficiency)

Xanthine oxidoreductase (XOR) is the catalytic enzyme in the final step of the purine catabolic pathway and oxidizes hypoxanthine to xanthine and xanthine to uric acid. Because XOR exists in 2 forms, xanthine dehydrogenase and xanthine oxidase, the deficiency is also referred to as **xanthine dehydrogenase/xanthine oxidase deficiency** . Xanthine, the immediate precursor of uric acid, is less soluble than uric acid in urine, and deficiency of the enzyme results in xanthinuria. XOR deficiency may occur in isolated form (**xanthinuria type 1**), in a combined form involving XOR and aldehyde oxidase deficiencies (**xanthinuria type II**), or multiple deficiencies of XOR, aldehyde oxidase, and sulfite oxidase (**molybdenum cofactor deficiency**). All 3 forms result in an almost total replacement of uric acid by hypoxanthine and xanthine in urine, while plasma uric acid is very low or undetectable.

Patients with the isolated form can be asymptomatic or can have mild symptoms; renal stones, often not visible on radiography, are a risk for renal damage and may appear at any age, when patients may present with loin pain or renal insufficiency. For type II xanthinuria the clinical presentation is similar to type I, but patients also have aldehyde oxidase deficiency, which has no known clinical attributes. Molybdenum cofactor deficiency arises from inherited deficiency of molybdenum cofactor synthase, which affects all 3 molybdoenzymes; as with isolated sulfite oxidase deficiency, it usually presents with neonatal feeding problems, neonatal seizures, increased or decreased muscle tone, ocular lens dislocation, severe intellectual disability, and death in early childhood. Milder cases have presented with lens dislocation only.

Genetics

The inheritance of all 3 types of xanthinuria is complex and autosomal recessive. Type I results from mutations in the human *XDH* gene located on chromosome 2p22. Type II xanthinuria arises from mutations in the molybdenum cofactor sulfurase gene located on chromosome 18q12.2; this enzyme completes the synthesis of the molybdenum cofactor, which is essential for the activity of both XOR and aldehyde oxidase. Type III xanthinuria (XOR, aldehyde oxidase, and sulfite oxidase deficiencies) can arise from functional mutations in any of 3 genes: *MOCS1* (encoding 2 enzymes for synthesis of the precursor via a bicistronic transcript), *MOCS2* (encoding molybdopterin synthase), or *GPHN* (encoding gephyrin), located at 6p21.2, 5q11.2, and 14q23.3, respectively.

Laboratory Findings

Diagnosis is made initially by measuring plasma and/or urinary concentrations of uric acid. Plasma uric acid is very low or absent (<1 mg/dL). Urinary uric acid is reduced, being replaced by xanthine and hypoxanthine. Type II patients can be distinguished by the absence in urine of methyl-2-pyridone-carboxamide, the product of nicotinamide (niacin) breakdown by aldehyde oxidase. Alternately, type II patients can be distinguished from type I by their inability to oxidize a test dose of allopurinol to oxypurinol via aldehyde oxidase. Molybdenum cofactor deficiency is distinguished by an additional excessive urinary excretion of sulfite and other sulfur-containing metabolites such as sulfocysteine.

Enzyme assay of XOR is not usually offered because it requires jejunal or liver biopsy, because these are the only human tissues that contain appreciable amounts of the enzyme. Sulfite oxidase and the molybdenum cofactor synthase can be measured in liver and fibroblasts. Molecular genetic analysis can be used to confirm diagnosis by searching for functional mutations among the 3 groups of genes.

Treatment

Although isolated deficiency is generally benign, treatment with a diet of low purines and low fructose (which reduces ATP breakdown to xanthine) with increased fluid intake is recommended. Allopurinol is not recommended. The prognosis for molybdenum cofactor deficiency has previously been very poor, but trials of cyclic pyranopterin monophosphate are promising in patients with a defect in the *MOCS1* gene.

Disorders of Pyrimidine Metabolism

The pyrimidines are the building blocks of DNA and RNA and involved in the formation of active intermediates in carbohydrate and phospholipid metabolism (e.g., uridine diphosphate glucose, cytidine diphosphate choline), glucuronidation in detoxification processes (uridine diphosphate), and glycosylation of proteins and lipids.

The essential precursor for pyrimidine biosynthesis is carbamyl-phosphate, which is shared with the urea cycle. Consequently, proximal blockages of the urea cycle results in carbamyl-phosphate overflowing into the pyrimidine pathway. Pyrimidine synthesis differs from that of purines in that the single pyrimidine ring is first assembled to form orotic acid and then linked to ribose phosphate to form the central pyrimidine nucleotide *uridine monophosphate* (UMP). The pyrimidine bases, uracil and thymine, are catabolized in 4 steps (see Fig. 108.3). Eight disorders of pyrimidine metabolism are reviewed. Purine catabolism has an easily measurable end-point in uric acid; however, there is no equivalent compound in pyrimidine catabolism. Disorders of de novo pyrimidine synthesis include hereditary **orotic aciduria** and dihydroorotate dehydrogenase deficiency (**Miller syndrome**). **Thymidine kinase deficiency** is part of pyrimidine salvage, and the other disorders involve overactivity (in one syndrome) or defects in the pyrimidine degradation pathway. Pyrimidine disorders may present as anemia, neuropathologies, acrofacial dysostosis, or multisystem mitochondrial disorders. The first 3 steps of the degradation pathways for thymine and uracil, respectively, make use of the same enzymes (DPD, DPH, and UP). These 3 steps result in the conversion of uracil into β-alanine. There is increasing evidence that pyrimidines play an important role in the regulation of the nervous system. Reduced production of the neurotransmitter function of β-alanine is hypothesized to produce clinical symptoms. Clinically, pyrimidine disorders may be overlooked because they are rare and their symptoms are not highly specific; however, they should be considered as possible causes of anemia and neurologic disease and are a contraindication for treatment of cancer patients with certain pyrimidine analogs.

Uridine Monophosphate Synthase Type 1 Deficiency (Hereditary Orotic Aciduria)

Hereditary orotic aciduria is a disorder of pyrimidine synthesis associated with deficient activity of the last 2 steps of the de novo pyrimidine synthetic pathway: orotate phosphoribosyltransferase and orotidine-5′-monophosphate decarboxylase (ODC). The activities of these 2 steps reside in separate domains of a bifunctional protein, UMP synthase. This catalyzes the 2-step conversion of orotic acid to UMP via orotidine monophosphate. Hereditary orotic aciduria (UMP synthase deficiency) results in the excessive accumulation of orotic acid.

Genetics

UMP synthase deficiency is inherited as an autosomal recessive disorder, with both functional domains encoded on a single gene, *UMPS*, located on the long arm of chromosome 3 (3q13). Theoretically, random mutations in the gene should have equal chances of producing either orotate phosphoribosyltransferase or ODC deficiency, but there has been only a single case of ODC deficiency reported. Genetic metabolic defects that involve 4 of the 6 enzymes associated with the urea cycle may also result in orotic aciduria, secondary to PPRP depletion resulting from a substantial increased flux through the pyrimidine synthesis pathway.

Clinical Manifestations

Patients with hereditary orotic aciduria (UMP synthase type 1 deficiency) have a macrocytic hypochromic megaloblastic anemia unresponsive to usual therapy (iron, folic acid, vitamin B_{12}) and may develop leukopenia. Onset is usually in 1st months of life. Untreated, this disorder can lead to intellectual disability, failure to thrive, cardiac disease, strabismus, crystalluria, and occasional ureteric obstruction. Renal function is generally normal. Heterozygotes may have mild orotic aciduria but are not otherwise affected. The clinical features are thought to be related to pyrimidine nucleotide depletion. Metabolites derived from several pharmacologic agents (e.g., 5-azauridine, allopurinol) can produce secondary orotic aciduria and orotidinuria by specifically inhibiting the ODC step of UMP synthase. Orotic aciduria may also occur in association with parenteral nutrition, essential amino acid deficiency, and Reye syndrome.

Laboratory Findings

The enzymatic defect may be demonstrated in liver, lymphoblasts, erythrocytes, leukocytes, and cultured skin fibroblasts. A carrier detection test is available, as is prenatal diagnosis.

Treatment

The administration of **uridine** in doses of 50-300 mg/kg/day has led to clinical improvement and reduction in orotic acid excretion in UMP synthase type 1 deficiency. Lifelong treatment is required. Uracil is ineffective because, unlike purines, pyrimidine salvage occurs at the nucleoside (uridine) level. The long-term prognosis in uncomplicated cases is good; however, congenital malformations and other associated features may adversely affect outcome.

Dihydroorotate Dehydrogenase Deficiency

(Miller Syndrome)

Miller syndrome was the first mendelian disorder whose molecular basis was identified by whole exome sequencing and shown to correlate with mutations in dihydroorotate dehydrogenase *(DHODH)* . The enzyme DHODH is associated with the mitochondrial electron transport chain and is required for de novo pyrimidine synthesis, catalyzing the oxidation of DHO to orotic acid.

Clinical Manifestations

Miller syndrome is a recognizable **acrofacial dysostosis syndrome** with a combination of craniofacial and limb anomalies. It includes micrognathia, orofacial clefts, malar hypoplasia, aplasia of the medial lower-lid eyelashes, cleft lip/palate, coloboma of the lower eyelid, and cup-shaped ears, combined with postaxial limb deformities, hypoplasia of the limbs with or without ulnar and fibular hypoplasia, and supernumerary nipples. Many of these features are similar to **Treacher Collins syndrome** (see Chapter 337).

Laboratory Findings

Assays of disease-associated *DHODH* alleles predict affected individuals have a deficiency of de novo pyrimidine synthesis, but with significant residual function.

Treatment

Theoretically, dietary supplementation with orotic acid or uridine should bypass the metabolic block. However, because the main effects occur in utero, it is unlikely that the phenotypic abnormality could be corrected.

Dihydropyrimidine Dehydrogenase Deficiency (Thymine-Uraciluria, Pyrimidinuria)

DPD catalyzes the initial and rate-limiting step in the degradation of the pyrimidine bases uracil and thymine. DPD has been identified in most tissues, with the highest activity being in lymphocytes.

Genetics

DPD deficiency is an autosomal recessive disorder, with the *DPYD* gene mapping to chromosome 1p22, with at least 32 polymorphisms detected. It is estimated that the frequency of heterozygosity may be as high as 3%.

Clinical Manifestations

Children may have seizure disorder, intellectual disability and motor delay. Less common features are growth retardation, microcephaly, autistic-like behavior, and ocular anomalies. Others may have milder neurologic symptoms and language disorder. Unaffected individuals have been reported, suggesting possible secondary gene effects. Most patients have an initial period of normal psychomotor development, followed by subsequent developmental delays. Symptoms may be linked to altered uracil, thymine, or β-alanine homeostasis. Because β-alanine is a structural analog of γ-aminobutyric acid and glycine, it has been proposed that it may affect inhibitory neurotransmission. DPD is the initial and rate-limiting enzyme in the inactivation of the antineoplastic drug 5-fluorouracil (5-FU), being responsible for 80% of its catabolism. Patients with partial DPD deficiency are at risk for developing a severe 5-FU–associated toxicity. In adult patients, neurotoxicity (headache, somnolence, visual illusions, memory impairment) linked to pyrimidinemia after 5-FU treatment for cancer is reported in previously healthy individuals.

Laboratory Findings

DPD deficiency is characterized by a variable phenotype and diagnosed by the gross accumulation of thymine and uracil in urine (**thymine-uraciluria**), plasma, and CSF. Uric acid levels have been reported to be normal. Prenatal diagnosis has been reported.

Treatment

There is no established treatment for this disorder, although patients with seizures do respond to anticonvulsant medications. *DPYD* genetic variants associated with partial or complete DPD activity and occurring with relatively high frequency in populations are potentially useful predictive markers of patient response to 5-FU chemotherapy.

Dihydropyrimidinase Deficiency (Dihydropyrimidinuria)

DPH is the 2nd enzyme in the 3-step degradation pathway of uracil and thymine. DPH deficiency is characterized by increased urinary excretion of dihydrouracil and dihydrothymine (**dihydropyrimidinuria**), as well as uracil and thymine. Similar to DPD deficiency, there is a variable clinical phenotype.

Genetics

This is an autosomal recessive disorder, with the *DPYS* gene mapped to chromosome 8q22. One study found no significant difference in residual activity between mutations observed in symptomatic and asymptomatic individuals, again similar to DPD deficiency. Population prevalence in a Japanese sample was 0.1%.

Clinical Manifestations

Clinical manifestations are similar to DPD deficiency, which is evidence that defects in these sequential steps produce a common disorder. Symptoms in 3 unrelated affected cases included seizures with dysmorphic features and developmental delay in 2 patients. However, 3 unrelated infants and 2 adult asymptomatic cases were identified in a screening program for pyrimidine degradation disorders in Japan and were asymptomatic despite the accumulation of pyrimidine degradation products in body fluids.

Laboratory Findings

Organic acid screening may identify increased amounts of uracil and thymine in urine. Oral loading tests with uracil, dihydrouracil, thymine, and dihydrothymine have been used to detect carriers of DPH deficiency. In symptomatic cases, treatment with β-alanine has been attempted with equivocal results. A single case of increased sensitivity to 5-FU has been reported.

Deficiency of β-Ureidopropionase (*N* -Carbamyl-β-Amino Aciduria)

The pyrimidine bases uracil and thymine are degraded via the consecutive action of 3 enzymes to β-alanine and β-aminoisobutyric acid, respectively. The 3rd enzyme in the pathway is **ureidopropionase (UP)** , and its deficiency leads to *N* -carbamyl-β-amino aciduria. 3-Ureidopropionic acid (3-UPA) acts as an endogenous neurotoxin through inhibition of mitochondrial energy metabolism, resulting in the initiation of secondary, energy-dependent excitotoxic mechanisms.

Genetics

Fluorescence in situ hybridization (FISH) localized the human β-ureidopropionase gene, *UPB1*, to 22q11.2.

Clinical Manifestations

These include muscular hypotonia, dystonic movements, seizures, and severe developmental delay. Some individuals with UP deficiency and no neurologic problems have been reported.

Laboratory Findings

Neuropathology involves both gray and white matter. UP deficiency leads to pathologic accumulation of 3-UPA in body fluids. Urinary analysis in a reported case showed elevated levels of *N* -carbamyl-β-alanine and *N* -carbamyl-β-aminoisobutyric acid (ureidoisobutyric acid). The enzyme is expressed only in the liver, and no activity of β-ureidopropionase is detected in a liver biopsy.

Treatment

There is no known treatment for UP deficiency.

Pyrimidine 5′-Nucleotidase Deficiency

Erythrocyte maturation is accompanied by RNA degradation and the release of mononucleotides. Pyrimidine 5′-nucleotidase is the first degradative enzyme of the pyrimidine salvage cycle and catalyzes the hydrolysis of pyrimidine 5′-nucleotides to the corresponding nucleosides. Enzyme deficiency results in the accumulation of high levels of cytidine and uridine nucleotides in the erythrocytes, which in turn results in hemolysis. Deficiency of pyrimidine 5′-nucleotidase may be at least in part compensated in vivo by other nucleotidases or perhaps other nucleotide metabolic pathways.

Genetics

This is an autosomal recessive disorder involving the gene *NT5C3A* on chromosome 7 (7p15).

Clinical Manifestations

Affected patients with pyrimidine 5′-nucleotidase deficiency clinically present with a defect restricted to erythrocytes and characterized by nonspherocytic hemolytic anemia with basophilic stippling. Other characteristic features include splenomegaly, increased indirect bilirubin, and hemoglobinuria. **Lead** is a powerful inhibitor of pyrimidine 5′-nucleotidase, and assessment of lead levels should be included whenever hemolytic anemia, pyrimidine 5′-nucleotidase deficiency, and basophilic stippling are found together.

Laboratory Findings

Diagnosis requires assay of erythrocyte UMP hydrolysis to form uridine and inorganic phosphate. The enzyme defect should be suspected in patients with nonspherocytic hemolytic anemia with basophilic stippling. The anemia is usually moderate, and transfusions are rarely necessary.

Treatment

There is no specific treatment. Splenectomy has not proved to be effective. Lead-induced acquired pyrimidine 5′ nucleotidase deficiency is treatable, unlike the congenital deficiency.

Overactive Cytosolic 5′-Nucleotidase (Pyrimidine Nucleotide Depletion)

Pyrimidine nucleotide depletion and overactive cytosolic 5′-nucleotidase, may lead to a neurodevelopmental disorder. Four unrelated patients showed 6-10–fold elevation in the activity of pyrimidine 5′-nucleotidase in fibroblasts with both purine and pyrimidine substrates. Investigation in cultured fibroblasts derived from these patients showed normal incorporation of purine bases into nucleotides but decreased incorporation of uridine and orotic acid.

Clinical Manifestations

These include developmental delay, seizures, ataxia, recurrent infections, severe language deficit, hyperactivity, short attention span, and aggressive behavior appearing within the 1st few years of life. Affected patients show electroencephalogram abnormalities. Metabolic testing is normal except for persistent hypouricosuria. It is proposed that increased catabolic activity and decreased pyrimidine salvage cause a deficiency of pyrimidine nucleotides.

Treatment

Treatment is with oral uridine based on compensating for the increased nucleotide catabolism. All reported patients treated with uridine showed improved speech and behavior, decreased seizure activity with discontinuation of seizure medications, and decreased infections.

Thymidine Phosphorylase Deficiency (Mitochondrial Neurogastrointestinal Encephalomyopathy)

Thymidine phosphorylase catalyzes the catabolism of thymidine to thymine. This enzyme is also known as *platelet-derived endothelial cell growth factor* because of its angiogenic properties, or *gliostatin*, indicating its inhibitory effects on glial cell proliferation. It has been implicated in mitochondrial nucleoside metabolism. Plasma thymidine level is increased more than 20-fold in patients compared to controls. Loss of function of thymidine phosphorylase causes **mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)** , which is inherited as a single autosomal recessive disorder, causing mitochondrial DNA depletion and instability. In MNGIE, loss of thymidine phosphorylase activity causes toxic accumulations of the nucleosides thymidine and deoxyuridine, which are phosphorylated to the corresponding nucleoside triphosphate in the mitochondrion, leading to mitochondrial deoxynucleoside triphosphate pool imbalances and aberrant mitochondrial DNA replication.

Genetics

The *TYMP* gene encoding thymidine phosphorylase has been identified as the *MNGIE* gene and is mapped to chromosome 22q13.32-qter, but the protein is imported into mitochondria.

Clinical Manifestations

Clinical manifestations of MNGIE usually begin in adolescence and young adulthood and include ptosis, progressive external ophthalmoparesis, GI dysmotility (pseudoobstruction) and malabsorption, cachexia, peripheral neuropathy, skeletal muscle myopathy, and leukoencephalopathy.

Laboratory Findings

Muscle biopsies typically reveal mitochondrial abnormalities. Screening is performed by detection of grossly raised thymidine and deoxyuridine in urine and plasma, which are normally absent. Confirmation of the diagnosis can be made by assay of thymidine phosphorylase activity in peripheral leukocytes. Molecular genetic analysis will show functional mutations in the *TYMP* gene. Increased thymidine and/or deoxyuridine nucleotides may cause mitochondrial nucleotide pool imbalance, resulting in mitochondrial DNA alterations, in particular DNA depletion.

Treatment

Supportive treatment is indicated. There is no established therapy for MNGIE; bone marrow transplantation has been performed on several patients, but no improvement in symptoms or disease progression has been reported. Allogeneic hematopoietic stem cell transplantation to restore thymidine phosphorylase activity and eliminate toxic metabolites is a potential therapy for MNGIE.

Thymidine Kinase 2 Deficiency

Thymidine kinase 2 (TK2) is a key enzyme for the pyrimidine salvage pathway to provide precursor nucleotide for mitochondrial DNA. TK2 deficiency causes tissue-specific depletion of mitochondrial DNA. TK2 normally phosphorylates thymidine and deoxycytidine.

Genetics

The TK2 gene is located on chromosome 16q 22; the deficiency is inherited in an autosomal recessive manner.

Clinical Manifestations

Affected individuals with TK2 deficiency have severe myopathy and depletion of muscular mitochondrial DNA in infancy.

Treatment

No specific treatment is available. Supportive treatment is indicated.

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CHAPTER 109

Hutchinson-Gilford Progeria Syndrome (Progeria)

Leslie B. Gordon

Hutchinson-Gilford progeria syndrome (HGPS), or progeria, is a rare, fatal, autosomal dominant segmental premature aging disease. With an estimated incidence of 1 in 4 million live births and prevalence of 1 in 20 million living individuals, there are an estimated total of 400 children living with progeria in 2018 worldwide. There is no gender, ethnic, or regional bias.

Progeria is caused by a single-base mutation in the *LMNA* gene, which results in the production of a mutant lamin A protein called **progerin** . Lamin A is an intermediate filament inner nuclear membrane protein found in most differentiated cells of the body. Without progerin-specific treatment, children with progeria develop **premature progressive atherosclerosis** and die of heart failure, usually between ages 5 and 20 yr. Progerin is found in increased concentration in skin and the vascular wall of normal older individuals compared to younger individuals, suggesting a role in normal aging.

Clinical Manifestations

Children develop the appearance of accelerated aging, but both clinical and biologic overlaps with aging are segmental, or partial. Physical appearance changes dramatically each year that they age (Fig. 109.1). The descriptions discussed next are roughly in order of clinical appearance.

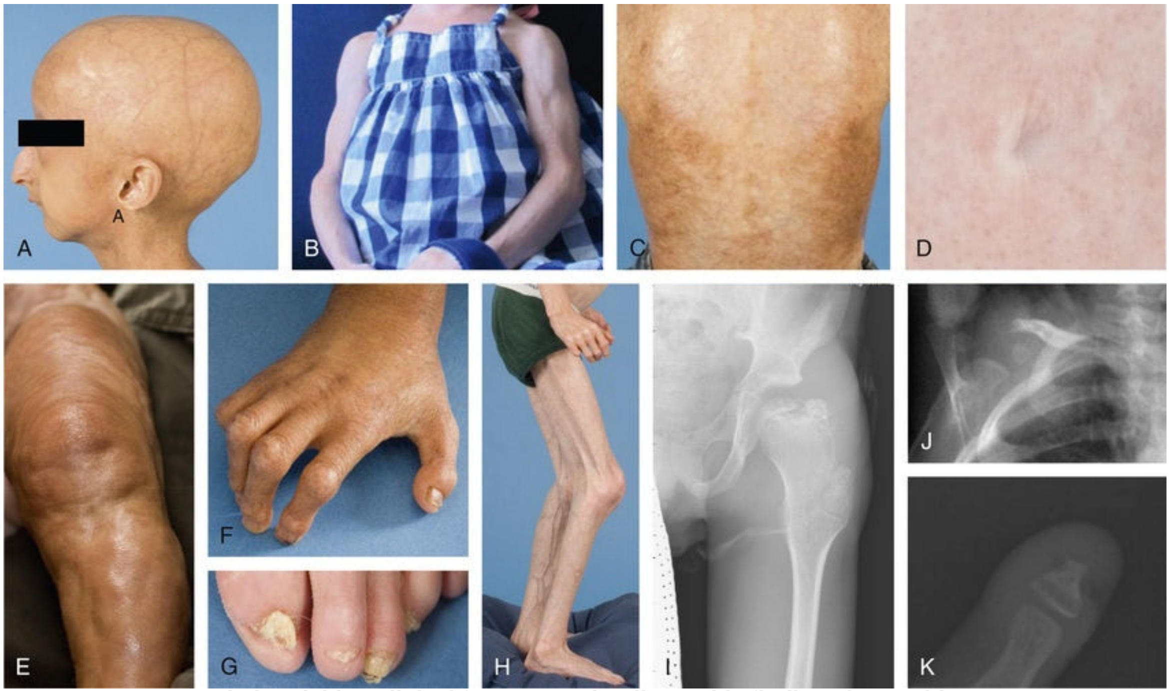

FIG. 109.1 Distinguishing clinical features and radiographic findings in Hutchinson-Gilford progeria syndrome. A, Alopecia, prominent scalp veins, narrowed nasal bridge, retrognathia; B, generalized lipoatrophy leaves muscular prominence; C, skin tightening and mottling; D, flat umbilicus with scarred-over appearance; E, skin bulging; F, digital joint contractures; G, nail dystrophy with spooning; H, knee joint contractures, lipodystrophy; I, coxa valga of the hip; J, clavicular osteolysis; K, acroosteolysis in a thumb. (Photos courtesy of The Progeria Research Foundation and Boston Children's Hospital.)

Dermatologic Changes

Skin findings are often apparent as initial signs of progeria. These are variable in severity and include areas of discoloration, stippled pigmentation, tightened areas that can restrict movement, and areas of the trunk or legs where small (1-2 cm), soft, bulging skin is present. Although usually born with normal hair presence, cranial hair is lost within the first few years, leaving soft, downy, sparse immature hair on the scalp, no eyebrows, and scant eyelashes. Nail dystrophy occurs later in life.

Failure to Thrive

Children with progeria experience apparently normal fetal and early postnatal development. Between several months and 1 yr of age, abnormalities in growth and body composition are readily apparent. Severe failure to thrive ensues, heralding generalized lipoatrophy, with apparent wasting of limbs, circumoral cyanosis, and prominent veins around the scalp, neck, and trunk. The mean weight percentile is usually normal at birth, but decreases to below the 3rd percentile despite adequate caloric intake for normal growth and normal resting energy expenditure. A review of 35 children showed an average weight increase of only 0.44 kg/yr, beginning at 24 mo of age and persisting through life. There is interpatient variation in weight gain, but the projected weight gain over time in individual patients is constant, linear, and very predictable; this sharply contrasts with the parabolic growth pattern for normal age- and gender-matched children. Children reach an average final height of approximately 1 meter and weight of approximately 15 kg. Head circumference is normal. The weight deficit is more pronounced than the height deficit and, associated with the loss of subcutaneous fat, results in the emaciated appearance characteristic of progeria. Clinical problems caused by the lack of subcutaneous fat include sensitivity to cold temperatures and foot discomfort caused by lack of fat cushioning. Overt diabetes is very unusual in progeria, but about 30–40% of children have insulin resistance.

Ocular Abnormalities

Ophthalmic signs and symptoms are caused in part by tightened skin and a paucity of subcutaneous fat around the eyes. Children often experience hyperopia and signs of ocular surface disease from nocturnal lagophthalmos and exposure keratopathy, which in turn may lead to corneal ulceration and scarring. Some degree of photophobia is common. Most patients have relatively good acuity; however, advanced ophthalmic disease can be associated with reduced acuity. *Children with progeria should have an ophthalmic evaluation at diagnosis and at least yearly thereafter.* Aggressive ocular surface lubrication is recommended, including the use of tape tarsorrhaphy at night.

Craniofacial and Dental Phenotypes

Children develop craniofacial disproportion, with micrognathia and retrognathia caused by mandibular hypoplasia. Typical oral and dental manifestations include hypodontia, delayed tooth eruption, severe dental crowding, ogival palatal arch, ankyloglossia, presence of median sagittal palatal fissure, and generalized gingival recession. Eruption may be delayed for many months, and primary teeth may persist for the duration of life. Secondary teeth are present but may or may not erupt. They sometimes erupt on the lingual and palatal surfaces of the mandibular and maxillary alveolar ridges, rather than in place of the primary incisors. In some, but not all cases, extracting primary teeth promotes movement of secondary teeth into place.

Bone and Cartilaginous Abnormalities

Development of bone structure and bone density represents a unique skeletal dysplasia that is not based in malnutrition. Acroosteolysis of the distal phalanges, distal clavicular resorption, and thin, tapered ribs are early signs of progeria (as early as 3 mo of age). *Facial disproportion a narrowed nasal bridge and retrognathia makes intubation extremely difficult, and fiberoptic intubation is recommended.* A pyriform chest structure and small clavicles can lead to reducible glenohumeral joint instability. Growth of the spine and bony pelvis are normal. However, dysplastic growth of the femoral head and neck axis result in coxa valgus (i.e., straightening of the femoral head-neck axis >125 degrees) and coxa magna, where the diameter of the femoral head is disproportionately large for the acetabulum, resulting in hip instability. The resulting hip dysplasia can be progressive and may result in osteoarthritis, avascular necrosis, hip dislocation, and inability to bear weight. Other changes to the appendicular skeleton include flaring of the humeral and femoral metaphyses and constriction of the radial neck. Growth plate morphology is generally normal but can be variable within a single radiograph. The appearance of ossification centers used to define bone age is normal. Bone structure assessed by peripheral quantitative computed tomography (pQCT) of the radius demonstrates distinct and severe abnormalities in bone structural geometry, consistent with progeria representing a *skeletal dysplasia.* Areal bone mineral density (aBMD) *z* scores measured by dual-energy X-ray absorptiometry (DXA) adjusted for height-age, and true (volumetric) BMD assessed by pQCT are normal to mildly reduced, refuting the assumption that patients with progeria are osteoporotic. Fracture rates in progeria are normal and not associated with fragility fractures observed in other pediatric metabolic bone diseases, such as osteogenesis imperfecta.

Contractures in multiple joints (e.g., fingers, elbows, hips, knees, ankles) may be present at birth and may progress with age because of changes in the laxity of the surrounding soft tissue structures (joint capsule, ligament, skin). Along with irregularities in the congruency of articulating joint surfaces, these changes serve to limit joint motion and affect the pattern of gait. Physical therapy is recommended routinely and throughout life to maximize joint function.

Hearing

Low-tone conductive hearing loss is pervasive in progeria and indicative of a stiff tympanic membrane and/or deficits in the middle ear bony and ligamentous structures. Overall, this does not affect ability to hear the usual spoken tones, but preferential classroom seating is recommended, with annual hearing examinations.

Cardiovascular Disease

Approximately 80% of progeria deaths are caused by heart failure, possibly precipitated by events such as superimposed respiratory infection or surgical intervention. Progeria is a **primary vasculopathy** characterized by pervasive accelerated vascular stiffening, followed by large- and small-vessel occlusive disease from atherosclerotic plaque formation, with valvular and cardiac insufficiency in later years. Hypertension, angina, cardiomegaly, metabolic syndrome, and congestive heart failure are common end-stage events**.**

A study of transthoracic echocardiography in treatment-naïve patients revealed diastolic left ventricular dysfunction associated with age-related decline in lateral and septal early (E′) diastolic tissue Doppler velocity *z* scores and an increase in the ratio of mitral inflow (E) to lateral and septal E’ velocity *z* scores. Other echocardiographic findings included left ventricular hypertrophy, left ventricular systolic dysfunction, and mitral or aortic valve disease. These tend to appear later in life. Routine carotid ultrasound for plaque monitoring, carotid-femoral pulse wave velocity (PWV_{cf}) measures for vascular stiffening, and echocardiography are recommended.

Cerebrovascular Arteriopathy and Stroke

Cerebral infarction may occur while the child exhibits a normal electrocardiogram. The earliest incidence of stroke occurred at age 0.4 yr. More often strokes occur in the later years. Over the life span, MRI evidence of infarction can be found in 60% of progeria patients, with half of these clinically silent. Both large- and small-vessel disease is found; collateral vessel formation is extensive. Carotid artery blockages are well documented, but infarction can occur even in their absence. A propensity for strokes and an underlying stiff vasculature make maintaining adequate blood pressure through hydration (habitually drinking well) a priority in progeria patients; special care should be taken when considering maintenance of consistent blood pressure during general anesthesia, airplane trips, and hot weather. In addition, 15% of deaths in children with progeria occur from head injury or trauma, including subdural hematoma. This implies an underlying susceptibility to subdural hematoma.

Sexual Development

Females with progeria can develop Tanner Stage II secondary sexual characteristics, including signs of early breast development and sparse pubic hair. They do not achieve Tanner Stage III. Despite minimal to no physical signs of pubertal development and minimal body fat, over half of females experience spontaneous menarche at a median age of 14 yr. Those experiencing menarche vs nonmenstruating females have similar body mass indices, percentage body fat, and serum leptin levels, all of which are vastly below the healthy adolescent population. If bleeding becomes severe, the complete blood count may be decreased, and an oral contraceptive may be used to decrease bleeding severity. Secondary sexual characteristics in males have not been studied. There are no documented cases of reproductive capacity in females or males with progeria.

Normally Functioning Systems

Liver, kidney, thyroid, immune, gastrointestinal, and neurologic systems (other than stroke related) remain intact. Intellect is normal for age, possibly in part from downregulation of progerin expression in the brain by a brain-specific micro-RNA, miRNA-9.

Laboratory Findings

The most consistent laboratory findings are low serum leptin below detectable levels (>90%) and insulin resistance (60%). Platelet count is often moderately high. High-density lipoprotein (HDL) cholesterol and adiponectin concentrations decrease with increasing age to values significantly below normal. Otherwise, lipid panels, high-sensitivity C-reactive protein, blood chemistries, liver and kidney function tests, endocrine test, and coagulation tests are generally normal.

Molecular Pathogenesis

Mutations in the *LMNA* gene cause progeria. The normal *LMNA/C* gene encodes the proteins lamins A and C, of which only lamin A is associated with human diseases. The lamin proteins are the principal proteins of the nuclear lamina, a complex molecular interface located between the inner membrane of the nuclear envelope and chromatin. The integrity of the lamina is central to many cellular functions, creating and maintaining structural integrity of the nuclear scaffold, DNA replication, RNA transcription, organization of the nucleus, nuclear pore assembly, chromatin function, cell cycling, senescence, and apoptosis.

Progeria is almost always a sporadic autosomal dominant disease. There are 2 documented sibling occurrences, both presumably stemming from parental mosaicism, where 1 phenotypically normal parent has germline mosaicism. It is caused by the accelerated use of an alternative, internal splice site that results in the deletion of 150 base pairs in the 3′ portion of exon 11 of the *LMNA* gene. In about 90% of cases, this results from a single C to T transition at nucleotide 1824 that is silent (Gly608Gly) but optimizes an internal splice site within exon 11. The remaining 10% of cases possess 1 of several single-base mutations within the intron 11 splice donor site, thus reducing specificity for this site and altering the splicing balance in favor of the internal splice. Subsequent to all these mutations, translation followed by posttranslational processing of the altered mRNA produces progerin, a shortened abnormal lamin A protein with a 50–amino acid deletion near its C-terminal end. An understanding of the posttranslational processing pathway and how it is altered to create progerin has led to a number of treatment prospects for the disease (Fig. 109.2).

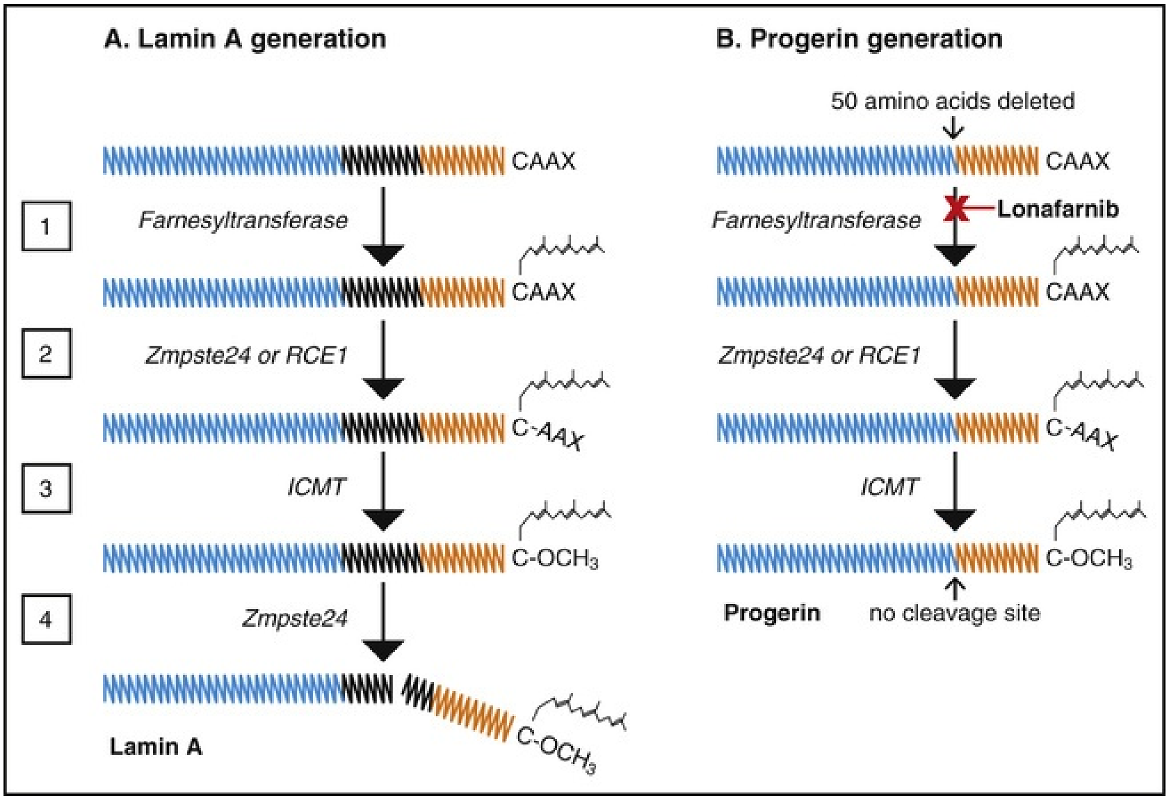

FIG. 109.2 **Posttranslational processing pathways producing lamin A and progerin, including the target site for lonafarnib. A, Prelamin A polypeptide chain, showing its central α-helical rod domain and C-terminal −CAAX box, representing cysteine (C), aliphatic amino acids (AA), and any amino acid (X). The α-helical rod domain is divided into segments that assist in displaying the progerin defect. Posttranslational processing consists of 4 steps: *1,* a farnesyl group is attached to the cysteine residue of the −CAAX box by farnesyltransferase; *2,* the last 3 residues are proteolytically cleaved by the zinc metalloprotease Zmpste24 or Ras-converting enzyme (RCE1); *3,* carboxy-methylation by isoprenyl-cysteine carboxyl methyltransferase (ICMT); and *4,* the terminal 15 C-terminal residues, including the farnesylated and carboxymethylated cysteine, are cleaved off by Zmpste24. B, A 50–amino acid deletion in prelamin A (represented by black segment of the lamin A rod) is the result of a mutation that activates a cryptic splice site within exon 11 of the *LMNA* gene. This deletion leaves progerin without an attachment site for the last processing step—cleavage of the farnesylation and carboxymethylated terminal 15 amino acid residues. Thus, progerin remains farnesylated and intercalated within the inner nuclear membrane, where it causes much of its cellular damage.**

Both lamin A and progerin possess a methylated farnesyl side group attached during posttranslational processing. This is a lipophilic moiety that facilitates intercalation of proteins into the inner nuclear membrane, where most of the lamin and progerin functions are performed. For normal lamin A, loss of the methylated farnesyl anchor releases prelamin from the nuclear membrane, rendering it soluble for autophagic degradation. However, progerin retains its farnesyl moiety. It remains anchored to the membrane, binding other proteins, causing blebbing of the nucleus, disrupting mitosis, and altering gene expression. Progerin also retains a methyl moiety.

Disease in progeria is produced by a dominant negative mechanism; *the action of progerin*, not the diminution of lamin A, causes the disease phenotype. The severity of disease is determined in part by progerin levels, which are regulated by the particular mutation, tissue type, or other factors influencing use of the internal splice site.

Diagnosis and Differential Diagnosis

Overall, the constellation of small body habitus, bone, hair, subcutaneous fat, and skin changes results in the marked physical resemblance among patients with progeria (Fig. 109.3). For this reason, clinical diagnosis can be achieved or excluded with relative confidence even at young ages, even though there have been a few cases of low–progerin-expressing patients with extremely mild signs. Clinical suspicion should be followed by *LMNA* genetic sequence testing. The disorders that resemble progeria are those grouped as the senile-like syndromes and include Wiedmann-Rautenstrauch syndrome, Werner syndrome, Cockayne syndrome, Rothmund-Thomson syndrome, restrictive dermopathy, and Nestor-Guillermo progeria syndrome (Table 109.1). Patients often fall under none of these diagnoses and represent ultra-rare, unnamed progeroid laminopathies that carry either non–progerin-producing mutations in *LMNA* or the lamin-associated enzyme *(ZMPSTE24)* , or progeroid syndromes without lamin-associated mutations.

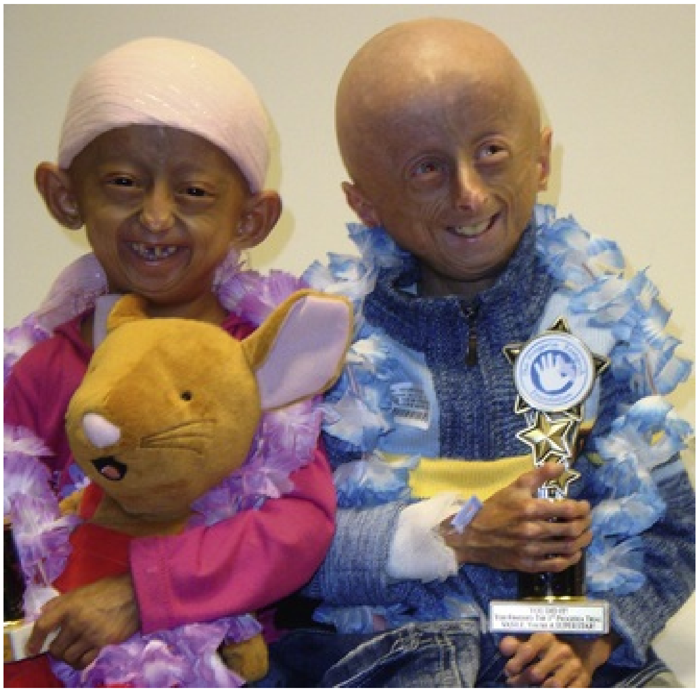

FIG. 109.3 Unrelated 7 yr old female and 10 yr old male with progeria. Appearance is remarkably similar between patients. (Photograph courtesy of The Progeria Research Foundation)

Table 109.1

Features of Hutchinson-Gilford Progeria Syndrome and Other Disorders With Overlapping Features

	HUTCHINSON-GILFORD PROGERIA SYNDROME	**WIEDEMANN-RAUTENSTRAUCH SYNDROME**	**WERNER SYNDROME**	**COCKAYNE SYNDROME**	**ROTHMUND-THOMPSON SYNDROME**	**R D**
Causative gene(s)	*LMNA*	Unknown	*WRN* , *LMNA*	*CSA (ERCC8)* *CSB (ERCC6)*	*RECQL4*	*Z* *L*
Inheritance	Autosomal Dominant	Unknown, likely recessive	Recessive	Recessive	Recessive	R
Onset	Infancy	Newborn	Young adult	Newborn/infancy	Infancy	N
Growth retardation	Postnatal	Intrauterine	Onset after puberty	Postnatal	Postnatal	Ir
Hair loss	+ Total	+ Scalp patchy	+ Scalp, sparse, graying	−	+ Diffuse	+
Skin abnormalities	+	+	+	+	+	+
Subcutaneous	+	+	+	+	−	−

fat loss						
Skin calcification	+ Rarely	−	+	−	−	−
Short stature	+	+	+	+	+	+
Coxa valga	+	−	−	−	−	−
Acroosteolysis	+	+	+	−	−	−
Mandibular dysplasia	+	+	−	−	−	+
Osteopenia	+ Mild	+	+	−	+	+
Vasculopathy	+	−	+	+	−	−
Heart failure	+	−	+	−	−	−
Strokes	+	−	−	−	−	−
Insulin Resistance	+	−	+ Rarely	−	−	−
Diabetes	−	−	+	−	−	−
Hypogonadism	+	−	+	+	+	−
Dental abnormality	+	+	+	+	+	+
Voice abnormality	+	−	+	−	−	−
Hearing loss	+	−	−	+	−	−
Joint contractures	+	−	−	−	−	+
Hyperkeratosis	−	−	+	−	+	−
Cataracts	−	−	+	+	+	−
Tumor predisposition	−	−	+	−	+	−
Intellectual disability	−	+	−	+	−	−
Neurologic disorder	−	+	+ Mild	+	−	−

Adapted from Hegele RA: Drawing the line in Progeria syndromes, *Lancet* 362;416–417, 2003.

Treatment and Prognosis

Children with progeria develop a severe premature form of atherosclerosis. Prior to death, cardiac decline with left-sided hypertrophy, valvular insufficiency, and pulmonary edema develop; neurovascular decline with transient ischemic attacks (TIAs), strokes, and occasionally seizures can result in significant morbidity. Death occurs generally between ages 5 and 20 yr, with a median life span of 14.5 yr, resulting from heart failure, sometimes with superimposed respiratory infection (approximately 80%); from head injury or trauma, including subdural hematoma (approximately 15%); and rarely from stroke (1–3%) or complications from anesthesia during surgery (1–3%).

Growth hormone , 0.05 mg/kg/day subcutaneously, has resulted in increased rate of weight gain and overall size, but still well below that seen in normal children. Low-dose aspirin therapy is recommended at 2 mg/kg/day, as an extension of what is known about decreasing cardiovascular risk in the general at-risk adult population. It is not known whether growth hormone or low-dose aspirin has any effect on morbidity or mortality.

Several clinical treatment trials have been based on medications that target the posttranslational pathway of progerin (see Fig. 109.2). Inhibiting posttranslational progerin farnesylation is aimed at preventing this disease-causing protein from anchoring to the nuclear membrane, where it carries out much of its damage. A prospective single-arm clinical trial was conducted with the farnesyltransferase inhibitor **lonafarnib** (NCT00425607). Lonafarnib was well tolerated; the most common side effects were diarrhea, nausea, and loss of appetite, which generally improved with time. Subgroups of patients experienced increased rate of weight gain, decreased vascular stiffness measured by decreased PWV_{cf} and carotid artery echodensity, improved left ventricular diastolic function, increased radial bone structural rigidity, improved sensorineural hearing, and early evidence of decreased headache, TIA, and stroke rates. Dermatologic, dental, joint contracture, insulin resistance, lipodystrophy, BMD, and joint contractures were unaffected by drug treatment. A lonafarnib extension study was initiated, which added 30 children to the study. Children treated with lonafarnib demonstrated an increase in estimated survival over untreated children with progeria.

A clinical trial that added *pravastatin* (FDA approved to lower cholesterol) and *zoledronate* (FDA approved for osteoporosis) to the lonafarnib regimen was similarly aimed at inhibiting progerin farnesylation (NCT00916747), but results showed no detected improvements in clinical status over lonafarnib monotherapy. An ongoing clinical trial adding *everolimus* (FDA-approved mTOR inhibitor) to the lonafarnib regimen is aimed at accelerating autophagy of progerin, thus theoretically reducing its accumulation and cellular damage (NCT02579044). Results of this study are forthcoming.

Patient Resources

The **Progeria Research Foundation** (www.progeriaresearch.org) maintains an international progeria patient registry, provides a diagnostics program and complete patient care manual, and coordinates clinical treatment trials. It funds preclinical and clinical research to define the molecular basis of the disorder and to discover treatments and a cure. The Foundation website is an excellent source of current information on progeria for families of children with the disorder, their physicians, and interested scientists. Additional resources include the National Human Genome Research Institute (www.genome.gov/11007255/), National Center for Biotechnology Information Genereviews (www.ncbi.nlm.nih.gov/books/NBK1121/), and National Center for Advancing Translational Sciences (www.rarediseases.info.nih.gov/diseases/7467/progeria).

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CHAPTER 110

The Porphyrias

Manisha Balwani, Robert J. Desnick, Karl E. Anderson

Porphyrias are metabolic diseases resulting from altered activities of specific enzymes of the heme biosynthetic pathway. These enzymes are most active in bone marrow and liver. **Erythropoietic porphyrias** , in which overproduction of heme pathway intermediates occurs primarily in bone marrow erythroid cells, usually present at birth or in early childhood with *cutaneous photosensitivity,* or in the case of congenital erythropoietic porphyria, even in utero as nonimmune hydrops. Erythropoietic protoporphyria is the most common porphyria in children and of most interest to pediatricians. Most porphyrias are *hepatic,* with overproduction and initial accumulation of porphyrin precursors or porphyrins in the liver. Activation of hepatic porphyrias is very rare during childhood, reflecting the distinct hepatic regulatory mechanisms for heme biosynthesis that are influenced by pubertal development. Homozygous forms of the hepatic porphyrias may manifest clinically before puberty. Children who are heterozygous for inherited hepatic porphyrias may present with nonspecific and unrelated symptoms, and parents often request advice about long-term prognosis and express concerns about drugs that may exacerbate these conditions.

The DNA sequences and chromosomal locations are established for the genes of the enzymes in this pathway, and multiple disease-related mutations have been found for each porphyria. However, benign variants identified by gene sequencing can be misleading. The inherited porphyrias display autosomal dominant, autosomal recessive, or X-linked inheritance. Although initial diagnosis of porphyria by biochemical methods remains essential, it is especially important to confirm the diagnosis by demonstrating a specific pathogenic gene mutation(s).

The Heme Biosynthetic Pathway

Heme is required for a variety of hemoproteins, such as hemoglobin, myoglobin, respiratory cytochromes, and cytochrome P450 enzymes (CYPs). It is believed that the 8 enzymes in the pathway for heme biosynthesis are active in all tissues. Hemoglobin synthesis in erythroid precursor cells accounts for approximately 85% of daily heme synthesis in humans. Hepatocytes account for most of the rest, primarily for synthesis of CYPs, which are especially abundant in the liver endoplasmic reticulum, and turn over more rapidly than many other hemoproteins, such as the mitochondrial respiratory cytochromes. Pathway intermediates are the porphyrin precursors **δ-aminolevulinic acid** (**ALA** , also known as 5-aminolevulinic acid) and **porphobilinogen (PBG)** , as well as porphyrins (mostly in their reduced forms, known as **porphyrinogens**) (Fig. 110.1). These intermediates do not accumulate in significant amounts under normal conditions or have important physiologic functions.

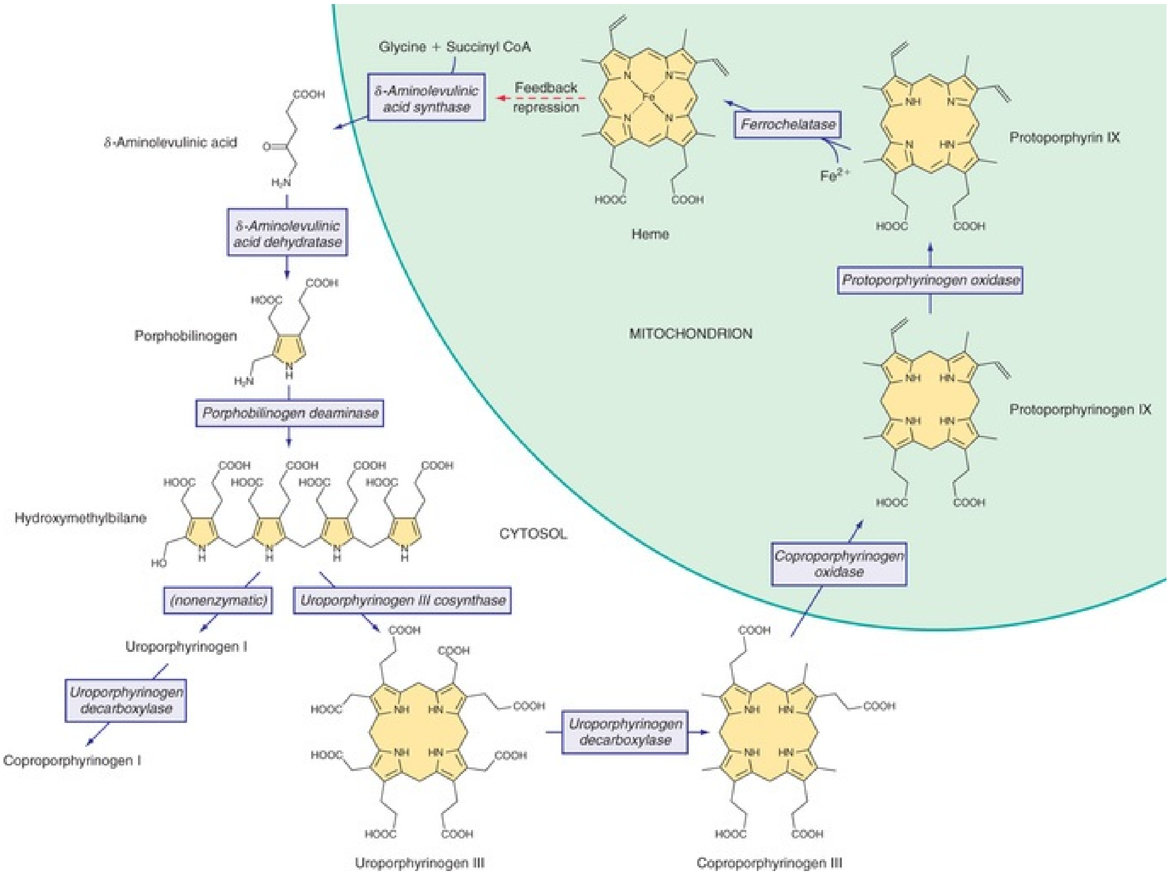

Glycine + Succinyl CoA
δ-Aminolevulinic acid synthase
Feedback repression
Heme
Ferrochelatase
Fe2+
Protoporphyrin IX
COOH
δ-Aminolevulinic acid
O
H2N
δ-Aminolevulinic acid dehydratase
Protoporphyrinogen oxidase
HOOC
Porphobilinogen
MITOCHONDRION
Protoporphyrinogen IX
Porphobilinogen deaminase
Hydroxymethylbilane
HO
CYTOSOL
Coproporphyrinogen oxidase
(nonenzymatic)
Uroporphyrinogen III cosynthase
Uroporphyrinogen I
Uroporphyrinogen decarboxylase
Coproporphyrinogen I
Uroporphyrinogen decarboxylase
Uroporphyrinogen III
Coproporphyrinogen III

FIG. 110.1 **Enzymes and intermediates of the heme biosynthetic pathway. The pathway is regulated in the liver by the end product, heme, mainly by feedback repression**

(dashed arrow) .

Altered activity of each enzyme in the pathway has been associated with a specific type of porphyria (Table 110.1). The first enzyme, ALA synthase (ALAS), occurs in 2 forms. An erythroid specific form, ALAS2, is deficient in X-linked sideroblastic anemia, as a result of mutations of the *ALAS2* gene on chromosome Xp11.2. Gain-of-function mutations of *ALAS2* caused by deletions in the last exon cause X-linked protoporphyria (**XLP**), which is phenotypically identical to erythropoietic protoporphyria.

Table 110.1

The Human Porphyrias: Mutations, Time of Presentation, and Tissue- and Symptom-Based Classifications

DISEASE	ENZYME	INHERITANCE	PRESENTATION	Classification*			
				H	E	A/N	C
X-Linked protoporphyria (XLP)	*δ-Aminolevulinate synthase 2 (ALAS2)*	X-linked	Childhood		X		X
δ-Aminolevulinic acid dehydratase porphyria (ADP)	*δ-Aminolevulinic acid dehydratase (ALAD)*	Autosomal recessive	Mostly post puberty	X	X*	X	
Acute intermittent porphyria (AIP)	*Porphobilinogen deaminase (PBGD)*	Autosomal dominant	Post puberty	X		X	
Homozygous AIP		Homozygous dominant	Childhood	X	X	X	
Congenital erythropoietic porphyria (CEP)	*Uroporphyrinogen III synthase (UROS)*	Autosomal recessive	In utero or infancy		X		X
Porphyria cutanea tarda (PCT) type 1	*Uroporphyrinogen decarboxylase (UROD)*	Sporadic	Adults	X			X
PCT type 2 †		Autosomal dominant	Adults	X			X
PCT type 3		Unknown	Adults	X			X
Hepatoerythropoietic porphyria (HEP)		Homozygous dominant	Childhood	X	X*		X
Hereditary coproporphyria (HCP)	*Coproporphyrinogen oxidase (CPOX)*	Autosomal dominant	Post puberty	X		X	X
Homozygous HCP		Homozygous dominant	Childhood	X	X	X	X
Variegate porphyria (VP)	*Protoporphyrinogen oxidase (PPOX)*	Autosomal dominant	Post puberty	X		X	X
Homozygous VP		Homozygous dominant	Childhood	X	X	X	X
Erythropoietic protoporphyria (EPP)	*Ferrochelatase (FECH)*	Autosomal recessive (most commonly heteroallelic with hypomorphic allele)	Childhood		X		X

[*] Classification abbreviations: H, Hepatic; E, Erythropoietic; A/N, Acute/Neurologic; C, Cutaneous.

[†] PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT.

ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.

Regulation of heme synthesis differs in the 2 major heme-forming tissues. Liver heme biosynthesis is primary controlled by the ubiquitous form of ALAS (ALAS1). Synthesis of ALAS1 in liver is regulated by a “free” heme pool (see Fig. 110.1), which can be augmented by newly synthesized heme or by existing heme released from hemoproteins and destined for breakdown to biliverdin by heme oxygenase.

In the erythron, novel regulatory mechanisms allow for the production of the very large amounts of heme needed for hemoglobin synthesis. The response to stimuli for hemoglobin synthesis occurs during cell differentiation, leading to an increase in cell number. Also, unlike the liver, heme has a stimulatory role in hemoglobin formation, and the stimulation of heme synthesis in erythroid cells is accompanied by increases not only in ALAS2, but also by sequential induction of other heme biosynthetic enzymes. Separate erythroid-specific and nonerythroid or “housekeeping” transcripts are known for the first 4 enzymes in the pathway. The separate forms of ALAS are encoded by genes on different chromosomes, but for each of the other three, erythroid and nonerythroid transcripts are transcribed by alternative promoters in the same gene. Heme also regulates the rate of its synthesis in erythroid cells by controlling the transport of iron into reticulocytes.

Intermediates of the heme biosynthetic pathway are efficiently converted to heme and, normally, only small amounts of the intermediates are excreted. Some may undergo chemical modifications before excretion. Whereas the porphyrin precursors ALA and PBG are colorless, nonfluorescent, and largely excreted unchanged in urine, PBG may degrade to colored products such as the brownish pigment called *porphobilin* or spontaneously polymerize to uroporphyrins. Porphyrins are red in color and display bright-red fluorescence when exposed to long-wavelength ultraviolet (UV) light. Porphyrinogens are the reduced form of porphyrins, and are colorless and nonfluorescent, but are readily autoxidized to the corresponding porphyrins when they accumulate or are outside the cell. Only the type III isomers of uroporphyrinogen and coproporphyrinogen are converted to heme (see Fig. 110.1).

ALA and PBG are excreted in urine. Excretion of porphyrins and porphyrinogens in urine or bile is determined by the number of carboxyl groups. Those with many carboxyl groups, such as *uroporphyrin* (octacarboxyl porphyrin) and *heptacarboxyl porphyrin*, are water soluble and readily excreted in urine. Those with fewer carboxyl groups, such as *protoporphyrin* (dicarboxyl porphyrin), are not water soluble and are excreted in bile and feces. *Coproporphyrin* (tetracarboxyl porphyrin) is excreted partly in urine and partly in bile. Because coproporphyrin I is more readily excreted in bile than coproporphyrin III, impaired hepatobiliary function may increase total urinary coproporphyrin excretion and the ratio of these isomers.

Classification and Diagnosis of Porphyrias

Two useful classification schemes reflect either the underlying pathophysiology or the clinical features of porphyrias (see Table 110.1). In **hepatic porphyrias** and **erythropoietic porphyrias** the source of excess production of porphyrin precursors and porphyrins is the liver and bone marrow, respectively. **Acute porphyrias** cause neurologic symptoms that are associated with increases of one or both of the porphyrin precursors, ALA and PBG. In the **cutaneous porphyrias,** photosensitivity results from transport of porphyrins in blood from the liver or bone marrow to the skin. **Dual porphyria** refers to the very rare cases of porphyria with deficiencies of 2 different heme pathway enzymes.

Porphyria cutanea tarda (**PCT**), acute intermittent porphyria (**AIP**), and erythropoietic protoporphyria (**EPP**) are the 3 most common porphyrias, in that order, considering all age-groups, and are very different in clinical presentation, precipitating factors, methods of diagnosis, and effective therapy (Table 110.2). Two less common acute porphyrias, hereditary coproporphyria (**HCP**) and variegate porphyria (**VP**), can also cause blistering photosensitivity (see Table 110.1). Congenital erythropoietic porphyria (**CEP**) causes more severe blistering lesions, often with secondary infection and mutilation. EPP and XLP have the same phenotype and are distinct from the other cutaneous porphyrias in causing nonblistering photosensitivity that occurs acutely after sun exposure. EPP is also the most common porphyria to become manifest before puberty.

Table 110.2

Three Most Common Human Porphyrias and Major

Features

	PRESENTING SYMPTOMS	EXACERBATING FACTORS	MOST IMPORTANT SCREENING TESTS	TREATMENT
Acute intermittent porphyria	Neurologic, adult onset	Drugs (mostly P450 inducers), progesterone, dietary restriction	Urinary porphobilinogen	Hemin, glucose
Porphyria cutanea tarda	Skin blistering and fragility (chronic), adult onset	Iron, alcohol, smoking, estrogens, hepatitis C, HIV, halogenated hydrocarbons	Plasma (or urine) porphyrins	Phlebotomy, low-dose hydroxychloroquine
Erythropoietic protoporphyria	Phototoxic pain and swelling (mostly acute), childhood onset		Total erythrocyte protoporphyrin with metal-free and zinc protoporphyrin	Sun protection

First-Line Laboratory Diagnostic Testing

A few sensitive and specific first-line laboratory tests should be obtained whenever symptoms or signs suggest the diagnosis of porphyria. If a first-line or screening test is significantly abnormal, more comprehensive testing should follow to establish the type of porphyria. Overuse of lab tests for screening can lead to unnecessary expense and even delay in diagnosis. In patients who present with a past diagnosis of porphyria, lab reports that were the basis for the original diagnosis must be reviewed, and if these were inadequate, further testing considered.

Acute porphyria should be suspected in patients with neurovisceral symptoms such as abdominal pain after puberty, when initial clinical evaluation does not suggest another cause. *Urinary PBG* and *total porphyrins* should be measured. Urinary PBG is virtually always increased during acute attacks of AIP, HCP, and VP and is not substantially increased in any other medical conditions. Therefore this measurement is both sensitive and specific. Results from spot (single void) urine specimens are highly informative because very substantial increases are expected during acute attacks of porphyria. A 24 hr collection can unnecessarily delay diagnosis. The same spot urine specimen should be saved for quantitative determination of PBG and total porphyrins (both expressed relative to creatinine) to confirm the qualitative PBG result. ALA is often measured as well, but is usually less elevated than PBG in AIP, HCP, and VP. In ALA dehydratase porphyria, urinary ALA and porphyrins, but not PBG, are greatly elevated. Urinary porphyrins may remain increased longer than porphyrin precursors in some cases of HCP and VP. Measurement of urinary porphyrins alone should be avoided for screening, however, because they are often increased in many disorders other than porphyrias, such as liver diseases, and misdiagnoses of porphyria can result from minimal increases in urinary porphyrins that have no diagnostic significance.

Blistering Cutaneous Porphyrias

Blistering skin lesions caused by porphyria are virtually always accompanied by increases in *total plasma* and *urinary porphyrins*. Porphyrins in plasma in VP are mostly covalently linked to plasma proteins and readily detected by a diagnostic peak in a fluorescence scanning method. The normal range for plasma porphyrins is somewhat increased in patients with end-stage renal disease.

Nonblistering Cutaneous Porphyria

Measurement of total erythrocyte protoporphyrin and, if the total amount is elevated, fractionation of protoporphyrin into its metal-free and zinc-chelated forms, is essential for diagnosis of EPP and XLP. Unfortunately, this is not offered by some major commercial laboratories. Results of zinc protoporphyrin measurements are often recorded (even in the same report) as both *protoporphyrin* and *free erythrocyte protoporphyrin* , with each calculated differently, based on past practices for screening for lead poisoning (which only increases zinc protoporphyrin). Thus the obsolete term *free protoporphyrin* does not mean metal-free protoporphyrin, because it was defined as iron-free protoporphyrin, and dates from before it was known that (except in protoporphyrias) protoporphyrin in erythrocytes is mostly zinc chelated. This unnecessary confusion makes diagnosis and reliable exclusion of protoporphyrias difficult. Total plasma porphyrins are elevated in most but not all cases of protoporphyria, so a normal level should not be relied on to exclude protoporphyria when total erythrocyte protoporphyrin is elevated.

Increases in erythrocyte total and zinc-chelated protoporphyrin occur in many other conditions, including iron deficiency, lead poisoning, hemolysis, anemia of chronic disease, and other erythrocyte disorders. Therefore the diagnosis of EPP must be confirmed by showing a predominant increase in metal-free protoporphyrin. In XLP, both free and zinc protoporphyrin are elevated.

Second-Line Testing

More extensive testing is well justified when a first-line test is positive. For example, a substantial increase in PBG may be caused by AIP, HCP, or VP, and these can be distinguished by measuring erythrocyte porphobilinogen deaminase, urinary porphyrins (using the same spot urine sample), fecal porphyrins, and plasma porphyrins. The various porphyrias that cause blistering skin lesions are differentiated by measuring porphyrins in urine, feces, and plasma. Confirmation at the gene level is important once the diagnosis is established by biochemical testing.

Testing for Subclinical Porphyria

It is often difficult to diagnose or rule out porphyria in patients who had suggestive symptoms months or years in the past, and in relatives of patients with acute porphyrias, because porphyrin precursors and porphyrins may be normal. More extensive testing and consultation with a specialist laboratory and physician may be needed. Before evaluating relatives, the diagnosis of porphyria should be firmly established in an index case, and the lab results reviewed to guide the choice of tests for the family members. The index case or another family member with confirmed porphyria should be retested if necessary. Identification of a disease-causing mutation in an index case greatly facilitates detection of additional gene carriers, because biochemical tests in latent carriers may be normal.

δ-Aminolevulinic Acid Dehydratase Deficient Porphyria

ALA dehydratase deficient porphyria (**ADP**) is sometimes termed *Doss porphyria* after the investigator who described the first cases. The term *plumboporphyria* emphasizes the similarity of this condition to lead poisoning, but incorrectly implies that it is caused by lead exposure.

Etiology

This porphyria results from a deficiency of ALA dehydratase (ALAD), which is inherited as an autosomal recessive trait. Only six cases have been confirmed by mutation analysis. The prevalence of heterozygous ALAD deficiency was estimated to be <1% in Germany and approximately 2% in Sweden.

Pathology and Pathogenesis

ALAD catalyzes the condensation of 2 molecules of ALA to form the pyrrole PBG (see Fig. 110.1). The enzyme is subject to inhibition by a number of exogenous and endogenous chemicals. ALAD is the principal lead-binding protein in erythrocytes, and lead can displace the zinc atoms of the enzyme. Inhibition of erythrocyte ALAD activity is a sensitive index of lead exposure.

Eleven abnormal ALAD alleles, most with point mutations, have been identified, some expressing partial activity, such that heme synthesis is partially preserved. The amount of residual enzyme activity may predict the phenotypic severity of this disease.

ADP is often classified as a hepatic porphyria, although the site of overproduction of ALA is not established. A patient with severe, early-onset disease underwent liver transplantation, without significant clinical or biochemical improvement, which might suggest that the excess intermediates did not originate in the liver. Excess urinary coproporphyrin III in ADP might originate from metabolism of ALA to porphyrinogens in a tissue other than the site of ALA overproduction. Administration of large doses of ALA to normal individuals also leads to substantial coproporphyrinuria. Increased erythrocyte protoporphyrin, as in all other homozygous porphyrias, may be explained by accumulation of earlier pathway intermediates in bone marrow erythroid cells during hemoglobin synthesis, followed by their transformation to protoporphyrin after hemoglobin synthesis is complete. Neurologic symptoms are attributed to neurotoxic effects of ALA, but this is unproven.

Clinical Manifestations

In most cases, symptoms resemble other acute porphyrias, including acute attacks of abdominal pain and peripheral neuropathy. Precipitating factors, such as exposure to harmful drugs, have not been evident in most cases. Four of the reported cases were adolescent males. A Swedish infant had more severe disease, with neurologic impairment and failure to thrive. A 63 yr old man in Belgium developed an acute motor polyneuropathy concurrently with a myeloproliferative disorder.

Laboratory Findings

Urinary ALA, coproporphyrin III, and erythrocyte zinc protoporphyrin are substantially increased. Urinary PBG is normal or slightly increased. Erythrocyte ALAD activity is markedly reduced, and both parents have approximately half-normal activity of this enzyme and normal urinary ALA.

Diagnosis and Differential Diagnosis

The other 3 acute porphyrias are characterized by substantial increases in both ALA and PBG. In contrast, ALA but not PBG is substantially increased in ADP. A marked deficiency of erythrocyte ALAD and half-normal activity in the parents support the diagnosis. Other causes of ALAD deficiency, such as **lead poisoning** , must be excluded. Succinylacetone accumulates in hereditary tyrosinemia type 1 and is structurally similar to ALA, inhibits ALAD, and can cause increased urinary excretion of ALA and clinical manifestations that resemble acute porphyria. Idiopathic acquired ALAD deficiency has been reported. Unlike lead poisoning, the deficient ALAD activity in ADP is not restored by the in vitro addition of sulfhydryl reagents such as dithiothreitol. Even if no other cause of ALAD deficiency is found, it is essential to confirm the diagnosis of ADP by molecular studies.

Treatment

Treatment experience with ADP is limited but is similar to other acute porphyrias. Glucose seems to have minimal effectiveness but may be tried for mild symptoms. **Hemin therapy** was apparently effective for acute attacks in male adolescents, and weekly infusions prevented attacks in 2 of these patients. Hemin was not effective either biochemically or clinically in the Swedish child with severe disease, and it produced a biochemical response but no clinical improvement in the Belgian man with a late-onset form, who had a peripheral neuropathy but no acute attacks. Hemin is also effective in treating porphyria-like symptoms associated with hereditary tyrosinemia and can significantly reduce urinary ALA and coproporphyrin in lead poisoning. Avoidance of drugs that are harmful in other acute porphyrias is advisable. Liver transplantation was not effective in the child with severe disease.

Prognosis

The outlook is generally good in typical ADP cases, although recurrent attacks may occur. The course was unfavorable in the Swedish child with more severe disease and is uncertain in adults with late-onset disease associated with myeloproliferative disorders.

Prevention and Genetic Counseling

Heterozygous parents should be aware that subsequent children are at risk for ADP, as in any autosomal recessive disorder. Prenatal diagnosis is possible but has not been reported.

Acute Intermittent Porphyria

AIP is also termed *pyrroloporphyria, Swedish porphyria,* and *intermittent acute porphyria* and is the most common type of acute porphyria in most countries.

Etiology

AIP results from the deficient activity of the housekeeping form of **porphobilinogen deaminase (PBGD)** . This enzyme is also known as hydroxymethylbilane (HMB) synthase (the prior term, uroporphyrinogen I synthase, is obsolete). PBGD catalyzes the deamination and head-to-tail condensation of 4 PBG molecules to form the linear tetrapyrrole, HMB (also known as preuroporphyrinogen; see Fig. 110.1). A unique dipyrromethane cofactor binds the pyrrole intermediates at the catalytic site until 6 pyrroles (including the dipyrrole cofactor) are assembled in a linear fashion, after which the tetrapyrrole HMB is released. The apo-deaminase generates the dipyrrole cofactor to form the holodeaminase, and this occurs more readily from HMB than from PBG. Indeed, high concentrations of PBG may inhibit formation of the holodeaminase. The product HMB can cyclize nonenzymatically to form nonphysiologic uroporphyrinogen I, but in the presence of the next enzyme in the pathway is more rapidly cyclized to form uroporphyrinogen III.

Erythroid and housekeeping forms of the enzyme are encoded by a single gene on human chromosome 11 (11q24.1→q24.2), which contains 15 exons. The 2 isoenzymes are both monomeric proteins and differ only slightly in molecular weight (approximately 40 and 42 kDa), and result from alternative splicing of 2 distinct messenger RNA (mRNA) transcripts arising from 2 promoters. The housekeeping promoter functions in all cell types, including erythroid cells.

The pattern of inheritance of AIP is autosomal dominant, with very rare homozygous cases that present in childhood. More than 400 *PBGD* mutations, including missense, nonsense, and splicing mutations, and insertions and deletions have been identified in AIP and in many population groups, including blacks. Most mutations are found in only one or a few families. Because of founder effects, however, some are more common in certain geographic areas, such as northern Sweden (W198X), Holland (R116W), Argentina (G116R), Nova Scotia (R173W), and Switzerland (W283X). De novo mutations may be found in approximately 3% of cases. The nature of the *PBGD* mutation does not account for the severity of the clinical presentation, which varies greatly within families. **Chester porphyria** was initially described as a variant form of acute porphyria in a large English family but was found to be caused by a *PBGD* mutation.

Most mutations lead to approximately half-normal activity of the housekeeping and erythroid isozymes and half-normal amounts of their respective enzyme proteins in all tissues of heterozygotes. In approximately 5% of unrelated AIP patients, the housekeeping isozyme is deficient, but the erythroid-specific isozyme is normal. Mutations causing this variant are usually found within exon 1 or its 5′ splice donor site or initiation of translation codon.

Pathology and Pathogenesis

Induction of the rate-limiting hepatic enzyme ALAS1 is thought to underlie acute exacerbations of this and the other acute porphyrias. AIP remains latent (or asymptomatic) in the great majority of those who are heterozygous carriers of *PBGD* mutations, and this is almost always the case before puberty. In those with no history of acute symptoms, porphyrin precursor excretion is usually normal, suggesting that half-normal hepatic PBGD activity is sufficient unless hepatic ALAS1 activity is increased. Patients can also be asymptomatic with elevated levels of porphyrin precursors and are classified as *asymptomatic high excretors*. These patients may have a remote history of symptoms. Many factors that lead to clinical expression of AIP, including certain drugs and steroid hormones, have the capacity to induce hepatic ALAS1 and CYPs. When hepatic heme synthesis is increased, half-normal PBGD activity may become limiting, and ALA, PBG, and other heme pathway intermediates may accumulate. In addition, heme synthesis becomes impaired, and heme-mediated repression of hepatic ALAS1 is less effective.

It is not proved, however, that hepatic PBGD remains constant at approximately 50% of normal activity during exacerbations and remission of AIP, as in erythrocytes. An early report suggested that the enzyme activity is considerably less than half-normal in the liver during an acute attack. Hepatic PBGD activity might be reduced further once AIP becomes activated if, as suggested, excess PBG interferes with assembly of the dipyrromethane cofactor for this enzyme. It also seems likely that currently unknown genetic factors play a contributing role in, for example, patients who continue to have attacks even when known precipitants are avoided.

AIP is almost always latent before puberty and becomes active mostly in adult women, which suggests that endocrine factors, and especially adult levels of female steroid hormones, are important for clinical expression. Premenstrual attacks are probably the result of endogenous progesterone. Acute porphyrias are sometimes exacerbated by exogenous steroids, including oral contraceptive preparations containing progestins. Surprisingly, pregnancy is usually well tolerated, suggesting that beneficial metabolic changes may ameliorate the effects of high levels of progesterone.

Drugs that are unsafe in acute porphyrias (Table 110.3) include those having the capacity to induce hepatic ALAS1, which is closely associated with induction of CYPs. Some chemicals (e.g., griseofulvin) can increase heme turnover by promoting the destruction of specific CYPs to form an inhibitor (e.g., *N* -methyl protoporphyrin) of ferrochelatase (FECH, the final enzyme in the pathway). Sulfonamide antibiotics are harmful but apparently not inducers of hepatic heme synthesis. Ethanol and other alcohols are inducers of ALAS1 and some CYPs.

Table 110.3

Drugs Regarded as Unsafe and Safe in Acute Porphyrias

UNSAFE	**SAFE**
Barbiturates (all)	Narcotic analgesics
Sulfonamide antibiotics*	Aspirin
Meprobamate* (also mebutamate,* tybutamate*)	Acetaminophen (paracetamol)
Carisoprodol*	Phenothiazines
Glutethimide*	Penicillin and derivatives
Methyprylon	Streptomycin
Ethchlorvynol*	Glucocorticoids
Mephenytoin	Bromides
Phenytoin*	Insulin

Succinimides	Atropine
Carbamazepine[*]	Cimetidine
Clonazepam [‡]	Ranitidine [†]
Primidone[*]	Acetazolamide
Valproic acid[*]	Allopurinol
Pyrazolones (aminopyrine, antipyrine)	Amiloride
Griseofulvin[*]	Bethanidine
Ergots	Bumetanide
Metoclopramide[*] [‡]	Coumarins
Rifampin[*]	Fluoxetine
Pyrazinamide[*] [‡]	Gabapentin
Diclofenac[*] [‡]	Gentamicin
Fluconazole[*]	Guanethidine
Oral contraceptives	Ofloxacin
Progesterone and synthetic progestins[*]	Propranolol
Danazol[*]	Succinylcholine
Alcohol	Tetracycline
ACEIs (especially enalapril) [‡]	
Spironolactone	
CCBs (especially nifedipine) [‡]	
Ketoconazole	
Ketamine[*]	

[*] Porphyria has been listed as a contraindication, warning, precaution, or adverse effect in U.S. labeling for these drugs. Estrogens are also listed as harmful in porphyria but have been implicated as harmful in acute porphyrias, mostly based only on experience with estrogen-progestin combinations. Although estrogens can exacerbate porphyria cutanea tarda, there is little evidence they are harmful in the acute porphyrias.

[†] Porphyria has been listed as a precaution in U.S. labeling for this drug. However, this drug is regarded as safe by other sources.

[‡] These drugs have been classified as probably safe by some sources, but this is controversial, and they should be avoided.

This partial listing does not include all available information about drug safety in acute porphyrias. Other sources should be consulted for drugs not listed here.

ACEIs, Angiotensin-converting enzyme inhibitors; CCBs, calcium channel blockers.

Nutritional factors , principally reduced intake of calories and carbohydrates, as may occur with illness or attempts to lose weight, can increase porphyrin precursor excretion and induce attacks of porphyria. Increased carbohydrate intake may ameliorate attacks. Hepatic ALAS1 is modulated by the peroxisome proliferator-activated receptor-γ coactivator-1α, which is an important link between nutritional status and exacerbations of acute porphyria.

Other factors have been implicated. Chemicals in cigarette smoke, such as polycyclic aromatic hydrocarbons, can induce hepatic CYPs and heme synthesis.

A survey of AIP patients found an association between **smoking** and repeated porphyric attacks. Attacks may result from metabolic stress and impaired nutrition associated with major illness, infection, or surgery. Clinical observations suggest an additive effect of multiple predisposing factors, including drugs, endogenous hormones, nutritional factors, and smoking, are common.

Neurologic Mechanisms

The mechanism of neural damage in acute porphyrias is poorly understood. The most favored hypothesis at present is that 1 or more heme precursors, or perhaps a derivative, are neurotoxic. Increased ALA in AIP, HCP, VP, ADP, plumbism, and hereditary tyrosinemia type 1, which have similar neurologic manifestations, suggests that this substance or a derivative may be neuropathic. Porphyrins derived from ALA after its uptake into cells may have toxic potential. ALA can also interact with γ-aminobutyric acid (GABA) receptors. Severe AIP greatly improves after allogeneic liver transplantation. This experience and the demonstration that recipients of AIP livers develop porphyria support the hypothesis that heme precursors from the liver cause the neurologic manifestations.

Epidemiology

AIP occurs in all races and is the most common acute porphyria, with an estimated prevalence in most countries of 5 in 100,000. In Sweden, prevalence was estimated to be 7.7 in 100,000, including latent cases with normal porphyrin precursors. A much higher prevalence of 60-100 in 100,000 in northern Sweden is the result of a founder effect. The combined prevalence of AIP and VP in Finland is approximately 3.4 in 100,000. A survey of chronic psychiatric patients in the United States using an erythrocyte PBGD determination found a high prevalence (210 in 100,000) of PBGD deficiency, but a study in Mexico found a similar prevalence in psychiatric patients and controls. Population screening by erythrocyte PBGD activity or DNA analysis revealed a prevalence of 200 heterozygotes per 100,000 people in Finland, and 1 in approximately 1,675 (60 in 100,000) in France. Studies using exomic/genomic databases show that the estimated frequency of pathogenic mutations in the *HMBS* gene is 0.00056 (56 in 100,000) suggesting that the penetrance of this disorder may be as low as 1%, and that carriers of *PBGD* mutations that can cause AIP are much more common than previously believed.

Clinical Manifestations

Neurovisceral manifestations of acute porphyrias may appear any time after puberty, but rarely before (Table 110.4). Symptomatic childhood cases have been reported, but most were not adequately documented biochemically and confirmed by genetic testing. Abdominal pain is the most common presenting symptom in such cases, but seizures are common and may precede the diagnosis of AIP. Other manifestations reported in children include peripheral neuropathy, myalgias, hypertension, irritability, lethargy, and behavioral abnormalities. A population-based study in Sweden indicated that symptoms suggestive of porphyria may occur in heterozygotes during childhood, even, in contrast to adults, when urinary porphyria precursors are not elevated. This study did not compare the frequency of such nonspecific symptoms in a control group of children. Very rare cases of homozygous AIP present differently, with severe neurologic manifestations early in childhood.

Table 110.4

Common Presenting Symptoms and Signs of Acute Porphyria

SYMPTOMS AND SIGNS	FREQUENCY (%)	COMMENT
GASTROINTESTINAL		
Abdominal pain	85–95	Usually unremitting (for hours or longer) and poorly localized but can be cramping.
Vomiting	43–88	Neurologic in origin and rarely accompanied by peritoneal signs, fever, or leukocytosis.
Constipation	48–84	Nausea and vomiting often accompany abdominal pain. May be accompanied by bladder paresis.
Diarrhea	5–12	
NEUROLOGIC		
Pain in extremities, back	50–70	Pain may begin in the chest or back and move to the abdomen. Extremity pain chest, neck, or head indicates involvement of sensory nerves; objective sensory loss reported in 10–40% of cases.
Paresis	42–68	May occur early or late during a severe attack. Muscle weakness usually begins proximally rather than distally and more often in the upper than lower extremities.
Respiratory paralysis	9–20	Preceded by progressive peripheral motor neuropathy and paresis.
Mental	40–58	May range from minor behavioral changes to agitation, confusion,

symptoms		hallucinations, and depression.
Convulsions	10–20	A central neurologic manifestation of porphyria or caused by hyponatremia, which often results from syndrome of inappropriate antidiuretic hormone secretion or sodium depletion.
CARDIOVASCULAR		
Tachycardia	64–85	May warrant treatment to control rate, if symptomatic
Systemic arterial hypertension	36–55	May require treatment during acute attacks, and sometimes becomes chronic.

From Anderson KE, Bloomer JR, Bonkovsky HL, et al: Desnick recommendations for the diagnosis and treatment of the acute porphyrias, *Ann Intern Med* 142(6):439–450, 2005.

Acute attacks in adults are characterized by a constellation of nonspecific symptoms, which may become severe and life threatening. **Abdominal pain** occurs in 85–95% of AIP patients; is usually severe, steady, and poorly localized, but is sometimes cramping; and accompanied by signs of ileus, including abdominal distention and decreased bowel sounds. Nausea, vomiting, and constipation are common, but increased bowel sounds and diarrhea may occur. Bladder dysfunction may cause hesitancy and dysuria. **Tachycardia** , the most common physical sign, occurs in up to 80% of attacks. This is often accompanied by **hypertension** , restlessness, coarse or fine tremors, and excess sweating, which are attributed to sympathetic overactivity and increased catecholamines. Other common manifestations include mental symptoms; pain in the extremities, head, neck, or chest; muscle weakness; and sensory loss. Because all these manifestations are neurologic rather than inflammatory, there is little or no abdominal tenderness, fever, or leukocytosis.

Porphyric neuropathy is primarily motor and appears to result from axonal degeneration rather than demyelinization. Sensory involvement is indicated by pain in the extremities, which may be described as muscle or bone pain, and by numbness, paresthesias, and dysesthesias. Paresis may occur early in an attack but is more often a late manifestation in an attack that is not recognized and adequately treated. Rarely, severe neuropathy develops when there is little or no abdominal pain. Motor weakness most commonly begins in the proximal muscles of the upper extremities and then progresses to the lower extremities and the periphery. It is usually symmetric, but occasionally asymmetric or focal. Initially, tendon reflexes may be little affected or hyperactive and become decreased or absent. Cranial nerves, most often X and VII, may be affected, and blindness from involvement of the optic nerves or occipital lobes has been reported. More common central nervous system (CNS) manifestations include seizures, anxiety, insomnia, depression, disorientation, hallucinations, and paranoia. Seizures may result from hyponatremia, porphyria itself, or an unrelated cause. Chronic depression and other mental symptoms occur in some patients, but attribution to porphyria is often difficult.

Hyponatremia is common during acute attacks. Inappropriate antidiuretic hormone (ADH) secretion is often the most likely mechanism, but salt depletion from excess renal sodium loss, gastrointestinal (GI) loss, and poor intake have been suggested as causes of hyponatremia in some patients. Unexplained reductions in total blood and red blood cell volumes are sometimes found and increased ADH secretion might then be an appropriate physiologic response. Other electrolyte abnormalities may include hypomagnesemia and hypercalcemia.

The attack usually resolves within several days, unless treatment is delayed. Abdominal pain may resolve within a few hours and paresis within a few days. Even severe motor neuropathy can improve over months or several years, but may leave some residual weakness. Progression of neuropathy to respiratory paralysis and death seldom occurs with appropriate treatment and removal of harmful drugs. Sudden death may result from cardiac arrhythmia.

Laboratory Findings

Levels of ALA and PBG are substantially increased during acute attacks. These levels may decrease after an attack but usually remain increased unless the disease becomes asymptomatic for a prolonged period.

Porphyrins are also markedly increased, which accounts for reddish urine in AIP. These are predominantly uroporphyrins, which can form nonenzymatically from PBG. Because the increased urinary porphyrins in AIP are predominantly isomer III, however, their formation is likely to be largely enzymatic, which might occur if excess ALA produced in the liver enters cells in other tissues and is then converted to porphyrins by the heme biosynthetic pathway. Porphobilin, a degradation product of PBG, and dipyrrylmethenes appear to account for brownish urinary discoloration. Total fecal porphyrins and plasma porphyrins are normal or slightly increased in AIP. Erythrocyte protoporphyrin may be somewhat increased in patients with manifest AIP.

Erythrocyte PBGD activity is approximately half-normal in most patients with AIP. The normal range is wide and overlaps with the range for AIP heterozygotes. Some *PBGD* gene mutations cause the enzyme to be deficient only in nonerythroid tissues. PBGD activity is also highly dependent on erythrocyte age, and an increase in erythropoiesis from concurrent illness in an

AIP patient may raise the activity into the normal range. Thus, PBGD activity alone is insufficient to make the diagnosis of AIP.

Diagnosis and Differential Diagnosis

An increased urinary PBG level establishes that a patient has 1 of the 3 most common acute porphyrias (see Table 110.2). Measuring PBG in serum is preferred when there is coexistent severe renal disease but is less sensitive when renal function is normal. Measurement of urinary ALA is less sensitive than PBG and also less specific, but will detect ADP, the 4th type of acute porphyria. Erythrocyte PBGD activity is decreased in most AIP patients and helps confirm the diagnosis in a patient with high PBG. A normal enzyme activity in erythrocytes does not exclude AIP.

Knowledge of the *PBGD* mutation in a family enables reliable identification of other gene carriers. Prenatal diagnosis can be performed by amniocentesis or chorionic villus sampling (CVP) in a fetus with a known *PBGD* mutation in the family. Prenatal diagnosis is typically not performed due to the low penetrance of the disorder and favorable prognosis with treatment.

Complications

AIP and other acute porphyrias are typically associated with mild abnormalities in liver function tests; some patients develop chronic liver disease. The risk of hepatocellular carcinoma is also increased, perhaps 60-70–fold after age 50, even in asymptomatic individuals who have increased porphyrins or porphyrin precursors. Few patients who developed this neoplasm had increases in serum α-fetoprotein. Patients with acute porphyrias, especially >50 yr old, should be screened at least yearly by ultrasound or an alternative imaging method.

The risk of chronic hypertension and impaired renal function is increased in these patients, most often with evidence of interstitial nephritis. A nephrotoxic effect of ALA may contribute. This may progress to severe renal failure and require renal transplantation.

Patients with recurrent attacks may develop **chronic neuropathic pain** , although this has not been well characterized. Referral to a neurologist is recommended for any patient with ongoing or residual neurologic symptoms. In addition, depression and anxiety are common in these patients.

Treatment

Hemin

Intravenous (IV) hemin is the treatment of choice for most *acute* attacks of porphyria. There is a favorable biochemical and clinical response to early treatment with hemin, but less rapid clinical improvement if treatment is delayed. It is no longer recommended that therapy with hemin for a severe attack be started only after an unsuccessful trial of IV glucose for several days. Mild attacks without severe manifestations, such as paresis, seizures, hyponatremia, or pain requiring opioids, may be treated with IV glucose. After IV administration, hemin binds to hemopexin and albumin in plasma and is taken up primarily in hepatocytes, where it augments the regulatory heme pool in hepatocytes, represses the synthesis of hepatic ALAS1, and dramatically reduces porphyrin precursor overproduction.

Hemin* is available for IV administration in the United States as *lyophilized hematin* (Panhematin, Recordati). Degradation products begin to form as soon as the lyophilized product is reconstituted with sterile water, and these are responsible for phlebitis at the site of infusion and a transient anticoagulant effect. Loss of venous access due to phlebitis is common after repeated administration. Stabilization of lyophilized hematin by reconstitution with 30% human albumin can prevent these adverse effects; this is recommended especially if a peripheral vein is used for the infusion. Uncommon side effects of hemin include fever, aching, malaise, hemolysis, anaphylaxis, and circulatory collapse. Heme arginate, a more stable hemin preparation, is available in Europe and South Africa.

Hemin treatment should be instituted only after a diagnosis of acute porphyria has been initially confirmed by a marked increase in urinary PBG. When prior documentation of the diagnosis is available for review, it is not essential to confirm an increase in PBG with every recurrent attack, if other causes of the symptoms are excluded clinically. The standard regimen of hemin for treatment of acute porphyric attacks is 3-4 mg/kg/day for 4 days. Lower doses have less effect on porphyrin precursor excretion and probably less clinical benefit.

General and Supportive Measures

Drugs that may exacerbate porphyrias (see Table 110.3) should be discontinued whenever possible, and other precipitating factors identified. Hospitalization is warranted, except for mild attacks; for treatment of severe pain, nausea, and vomiting; for administration of hemin and fluids; and for monitoring vital capacity, nutritional status, neurologic function, and electrolytes. Pain usually requires an opioid; there is low risk for addiction after recovery from the acute attack. Ondansetron or a phenothiazine such as chlorpromazine is needed for nausea, vomiting, anxiety, and restlessness. Low doses of short-acting benzodiazepines can be given for restlessness or insomnia. β-Adrenergic blocking agents may be useful during acute attacks to control tachycardia and hypertension but may be hazardous in patients with hypovolemia and incipient cardiac failure.

Carbohydrate Loading

The effects of carbohydrates on repressing hepatic ALAS1 and reducing porphyrin precursor excretion are weak compared to those of hemin. Therefore, carbohydrate loading is seldom beneficial except in mild attacks. Glucose polymer solutions by mouth are sometimes tolerated. At least 300 g of IV glucose, usually given as a 10% solution, has been recommended for adults hospitalized with attacks of porphyria. Amounts up to 500 g daily may be more effective, but large volumes may favor development of hyponatremia.

Other Therapies

Liver transplantation was effective in several patients with severe AIP. A group from the United Kingdom reported their experience with liver transplantation in 10 AIP patients with significantly impaired quality of life and recurrent attacks refractory to medical management. Patients had a complete biochemical and symptomatic resolution after transplantation; 2 patients succumbed to multiorgan failure. Liver transplantation was also successful in a U.S. patient with AIP and intractable symptoms who became unresponsive to hemin therapy; liver transplantation normalized porphyrin precursor excretion, and symptoms resolved. However, liver transplantation is a high-risk procedure and should be considered only as a last resort. Hepatocyte-targeted RNA interference (**RNAi**) therapy is being developed to reverse directly the extremely elevated hepatic ALAS1 mRNA in this disease. Preliminary results from clinical trials are promising.

Seizures and Other Complications

Seizures caused by hyponatremia or other electrolyte imbalances may not require prolonged treatment with anticonvulsant drugs, most of which have at least some potential for exacerbating acute porphyrias. Bromides, gabapentin, and probably vigabatrin are safe. Clonazepam may be less harmful than phenytoin or barbiturates. Control of hypertension is important and may help prevent chronic renal impairment, which can progress and require renal transplantation.

Safe and Unsafe Drugs

Patients often do well with avoidance of harmful drugs. Table 110.3 lists some drugs known or strongly suspected to be harmful or safe in the acute porphyrias. More extensive listings are available from the **European Porphyria Network** (www.porphyria-europe.com) and **American Porphyria Foundation** (www.porphyriafoundation.com), but some listings are controversial. Information regarding safety is lacking for many drugs, especially for those recently introduced.

Exogenous progestins, usually in combination with estrogens, can induce attacks of porphyria. Estrogens are seldom reported to be harmful when given alone. Synthetic steroids with an ethynyl substituent can cause a mechanism-based destruction of hepatic CYPs and should probably be avoided in patients with acute porphyria. Danazol is especially contraindicated.

Other Situations

Major surgery can be carried out safely in patients with acute porphyria, especially if barbiturates are avoided. Halothane has been recommended as an inhalation agent and propofol and midazolam as IV induction agents.

Pregnancy is usually well tolerated, which is surprising, because levels of progesterone, a potent inducer of hepatic ALAS1, are considerably increased during pregnancy. Some women do experience continuing attacks during pregnancy. This has sometimes been attributed to reduced caloric intake or metoclopramide, a drug sometimes used to treat hyperemesis gravidarum and considered harmful in acute porphyrias.

Diabetes mellitus and other endocrine conditions are not known to precipitate attacks of porphyria. In fact, the onset of diabetes mellitus and resulting high circulating glucose levels may decrease the frequency of attacks and lower porphyrin precursor levels in AIP.

Prognosis

The outlook for patients with acute porphyrias has improved greatly in the past several decades. In Finland, for example, 74% of patients with AIP or VP reported that they led normal lives, and <30% had recurrent attacks during several years of follow-up. In those presenting with acute symptoms, recurrent attacks were most likely within the next 1-3 yr. Moreover, only 6% of gene carriers who had never had attacks developed symptoms. The improved outlook may result from earlier detection, better treatment of acute attacks, and replacement of harmful drugs such as barbiturates and sulfonamides with safer drugs. However, some patients continue to have recurrent attacks, chronic pain, and other symptoms, even after avoiding known exacerbating factors.

Prevention

For prevention of attacks, it is important to identify multiple inciting factors and remove as many as possible. Drugs for concurrent medical conditions should be reviewed. Because dietary factors are often unapparent, consultation with a dietitian may be useful. A well-balanced diet that is somewhat high in carbohydrate (60–70% of total calories) and sufficient to maintain weight is recommended. There is little evidence that additional dietary carbohydrate helps further in preventing attacks, and it may lead to weight gain. Patients who wish to lose excess weight should do so gradually and when they are clinically stable. Rapid weight loss after bariatric surgery may exacerbate acute porphyrias. Iron deficiency, which can be detected by a low serum ferritin level, should be corrected.

Gonadotropin-releasing hormone (GnRH) analogs, which reversibly suppress ovulation, can be dramatically effective for preventing frequently recurring luteal phase attacks, but baseline and continuing gynecologic evaluation and bone mineral density measurements are important; transdermal estrogen or a bisphosphonate may be added to prevent bone loss. Hemin administered once or twice weekly can prevent frequent, noncyclic attacks of porphyria in some patients. Alternatively, single-dose hemin can be administered “on demand” at an outpatient infusion center to abort an attack and prevent hospitalization, if a patient can recognize early “prodromal” symptoms. Inpatient management is warranted, however, if advanced manifestations such as vomiting, paresis, or other neuropsychiatric symptoms have developed.

Genetic Counseling

A mutation identified in the index case can be sought in the child. Counseling should emphasize that the great majority of those who inherit a *PBGD* mutation never develop symptoms, and the prognosis of those who do is favorable. Therefore a normal, healthy life is expected, especially with avoidance of harmful drugs and other factors and prompt recognition and treatment of symptoms should they occur. Given the favorable outlook for most mutation carriers, even during pregnancy, having children is not precluded, and prenatal diagnosis of acute porphyrias is less important than it is for many other inherited diseases.

Congenital Erythropoietic Porphyria

Also termed *Günther disease*, this rare disease usually presents with photosensitivity shortly after birth or in utero as nonimmune hydrops.

Etiology

CEP is an autosomal recessive disease caused by a marked deficiency of uroporphyrinogen III synthase (UROS). Many *UROS* mutations have been identified among CEP families. Later-onset disease in adults is likely to be associated with myeloproliferative disorders and expansion of a clone of erythroblasts that carry a *UROS* mutation.

Pathology and Pathogenesis

UROS, which is extremely deficient in CEP, catalyzes inversion of pyrrole ring D of HMB and rapid cyclization of the linear tetrapyrrole to form uroporphyrinogen III. This enzyme is also termed *uroporphyrinogen III cosynthase*. The human enzyme is a monomer. The gene for the enzyme is found on chromosome 10q25.3→q26.3 and contains 10 exons. Erythroid and housekeeping transcripts are generated by alternative promoters but encode the same enzyme.

In CEP, HMB accumulates in erythroid cells during hemoglobin synthesis and cyclizes nonenzymatically to form uroporphyrinogen I, which is auto-oxidized to uroporphyrin I. Some of the uroporphyrinogen I that accumulates is metabolized to coproporphyrinogen I, which accumulates because it is not a substrate for coproporphyrinogen oxidase. Thus, both uroporphyrin I and coproporphyrin I accumulate in the bone marrow and are then found in circulating erythrocytes, plasma, urine, and feces.

A variety of *UROS* mutations have been identified in CEP, including missense and nonsense mutations, large and small deletions and insertions, splicing defects, and intronic branch point mutations. At least 4 mutations have been identified in the erythroid-specific promoter. Many patients inherited a different mutation from each parent, and most mutations have been detected in only one or a few families. An exception is a common mutation, C73R, which is at a mutational hot spot and was found in approximately 33% of alleles. One child with CEP had a *GATA1* mutation, with no *URO* S mutation. The CEP phenotype may be modulated by gain of function *ALAS2* mutations, which were first identified as causing XLP.

Genotype–phenotype correlations have been based on the in vitro expression of various CEP mutations and the severity of associated phenotypic manifestations. The C73R allele, which is associated with a severe phenotype in homozygotes or in patients heteroallelic for C73R and another mutation expressing little residual activity, resulted in <1% of normal enzyme activity. Patients with the C73R allele and heteroallelic for other mutations expressing more residual activity have milder disease.

Hemolysis is a common feature of CEP. Excess porphyrins in circulating erythrocytes cause cell damage, perhaps by a phototoxic mechanism, leading to both intravascular hemolysis and increased splenic clearance of erythrocytes. Also important is ineffective erythropoiesis, with intramedullary destruction of porphyrin-laden erythroid cells and breakdown of heme. Expansion of the bone marrow as a result of erythroid hyperplasia may contribute, along with vitamin D deficiency, to bone loss. Nutrient deficiencies sometimes cause erythroid hypoplasia. Despite the marked deficiency of UROS, heme production in the bone marrow is increased because of hemolysis and a compensatory increase in hemoglobin production. This occurs, however, at the expense of marked accumulation of HMB, which is converted to porphyrinogens and porphyrins.

Clinical Manifestations

In severe cases, CEP can cause fetal loss or may be recognized in utero as causing intrauterine hemolytic anemia and **nonimmune hydrops fetalis** . CEP may be associated with neonatal hyperbilirubinemia, and *phototherapy may unintentionally induce severe photosensitivity and scarring.*

The most characteristic presentation is reddish urine or pink staining of diapers by urine or meconium shortly after birth (Fig. 110.2). With sun exposure, severe blistering lesions appear on exposed areas of skin on the face and hands and have been termed *hydroa estivale* because they are more severe with greater sunlight exposure during summer (Fig. 110.3). Vesicles and bullae, as well as friability, hypertrichosis, scarring, thickening, and areas of hypopigmentation and hyperpigmentation are very similar to those seen in PCT but usually much more severe. Infection and scarring sometimes cause loss of facial features and fingers and damage to the cornea, ears, and nails. Porphyrins are deposited in dentin and bone in utero. Reddish brown teeth in normal light, an appearance termed **erythrodontia** , display reddish fluorescence under long-wave UV light (Fig. 110.4). Unaffected children born to a mother with CEP may have erythrodontia. Hemolysis and splenomegaly are common in CEP. Bone marrow compensation may be adequate, especially in milder cases. Patients with severe phenotypes, however, are often transfusion dependent. Splenomegaly may contribute to the anemia and cause leukopenia and thrombocytopenia, which may be complicated by significant bleeding. Neuropathic symptoms are absent, and there is no sensitivity to drugs, hormones, or carbohydrate restriction. The liver may be damaged by iron overload or viral hepatitis acquired from blood transfusions.

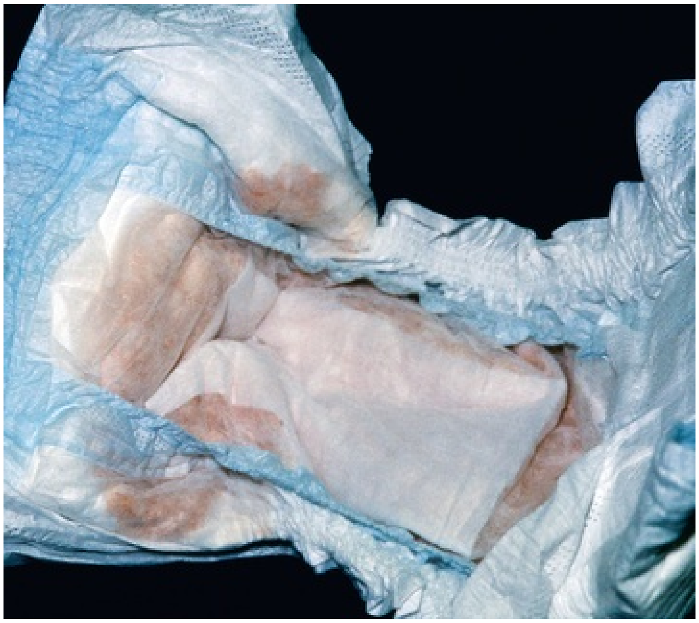

FIG. 110.2 Congenital erythropoietic porphyria (CEP). The diaper of a baby with CEP demonstrates the red color of urine. (From Paller AS, Macini AJ: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, Elsevier Saunders, p 517.)

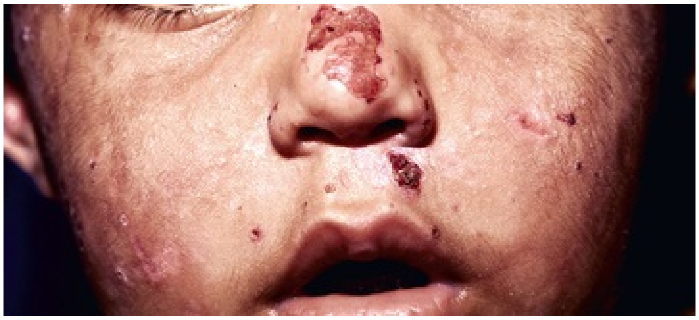

FIG. 110.3 Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas. (From Paller AS, Macini AJ: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, Elsevier Saunders, p 517.)

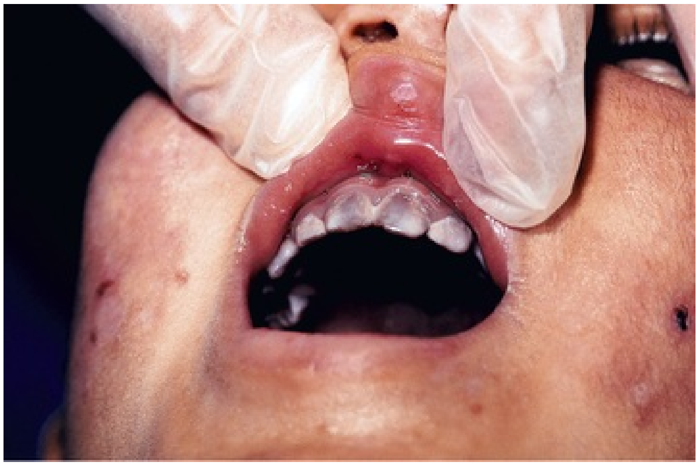

FIG. 110.4 Congenital erythropoietic porphyria. Brownish teeth that fluoresce under Wood lamp examination. (From Paller AS, Macini AJ: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, Elsevier Saunders, p 517.)

Milder cases of CEP with onset of symptoms in adult life and without erythrodontia may mimic PCT. These late-onset cases are likely to be associated with myeloproliferative disorders and expansion of a clone of cells carrying a *UROS* mutation.

Laboratory Findings

Urinary porphyrin excretion and circulating porphyrin levels in CEP are much higher than in almost all other porphyrias. Urinary porphyrin excretion can be as high as 50-100 mg daily and consists mostly of uroporphyrin I and coproporphyrin I. ALA and PBG are normal. Fecal porphyrins are greatly increased, with a predominance of coproporphyrin I.

Marked increases in erythrocyte porphyrins in CEP also consist mostly of uroporphyrin I and coproporphyrin I. These porphyrins are also increased in bone marrow, spleen, plasma, and to a lesser extent, liver. The porphyrin pattern in erythrocytes is influenced by rates of erythropoiesis and erythroid maturation. A predominance of protoporphyrin has been noted in some CEP patients, and in 1 such patient, uroporphyrin and coproporphyrin increased when erythropoiesis was stimulated by blood removal.

Diagnosis and Differential Diagnosis

The diagnosis of CEP should be documented by full characterization of porphyrin patterns and identification of the underlying mutations. In later-onset cases, an underlying myeloproliferative disorder and a *UROS* somatic mutation should be suspected and studied in detail.

The clinical picture in hepatoerythropoietic porphyria (HEP) may be very similar, but the porphyrin patterns in urine and feces in HEP resemble PCT. A predominant increase in erythrocyte protoporphyrin is unusual in CEP but is characteristic of HEP as well as rare homozygous cases of AIP, HCP, and VP. EPP and XLP are also distinguished by normal urinary porphyrins and by increases in erythrocyte metal-free protoporphyrin, whereas the increased protoporphyrin in other conditions is mostly complexed with zinc.

CEP should be suspected as a cause of nonimmune hydrops or hemolytic anemia in utero. With recognition of the disease at this stage, intrauterine transfusion can be considered, avoiding severe, scarring photosensitivity from phototherapy for hyperbilirubinemia after birth. Prenatal diagnosis is feasible by finding red-brown discoloration and increased porphyrins in amniotic fluid and measuring porphyrins in fetal erythrocytes and plasma. UROS activity can be measured in cultured amniotic fluid cells, or *UROS* mutations identified in chorionic villi or cultured amniotic cells.

Treatment

Protection from sunlight exposure, minimizing skin trauma, and prompt treatment of any cutaneous infections are essential in managing CEP. Sunscreen lotions and beta-carotene are sometimes beneficial. Transfusions to achieve a level of hemoglobin sufficient to suppress erythropoiesis significantly can be quite effective in reducing porphyrin levels and photosensitivity. Concurrent deferoxamine to reduce iron overload and hydroxyurea to suppress erythropoiesis further may provide additional benefit. Splenectomy reduces hemolysis and transfusion requirements in some patients. Oral charcoal may increase fecal loss of porphyrins but may contribute little in more severe cases. IV hemin may be somewhat effective but has not been extensively studied and seems unlikely to provide long-term benefit.

The most effective treatment is marrow stem cell transplantation in early childhood, which has greatly reduced porphyrin levels and photosensitivity and increased long-term survival.

Prognosis

The outlook is favorable in milder cases and in patients with more severe disease, especially after successful bone marrow or stem cell transplantation. Otherwise, prognosis relates to adherence to sunlight avoidance.

Prevention and Genetic Counseling

Genetic counseling is important for affected families because CEP can be recognized before birth, and a severe phenotype can often be predicted by identifying the nature of the *UROS* mutations.

Porphyria Cutanea Tarda

Porphyria cutanea tarda is the most common and readily treated human porphyria (see Table 110.2). It occurs in mid or late adult life and is rare in children. Previous terms include *symptomatic porphyria, PCT symptomatica,* and *idiosyncratic porphyria.* The underlying cause is a liver-specific, acquired deficiency of uroporphyrinogen decarboxylase (UROD) with contributions by several types of genetic and acquired susceptibility factors, including heterozygous *UROD* mutations in familial PCT. HEP, the homozygous form of familial PCT, usually has a more severe presentation in childhood, resembling CEP clinically.

Etiology

PCT is caused by a reduction of hepatic UROD activity to ≤20% of normal activity. An inhibitor of hepatic UROD has been characterized as a *uroporphomethene* , which is derived from partial oxidation of the enzyme substrate uroporphyrinogen. CYPs, such as CYP1A2, as well as iron, are involved in its formation (Fig. 110.5). Although enzyme activity is inhibited, the amount of hepatic enzyme protein measured immunochemically remains at its genetically determined level.

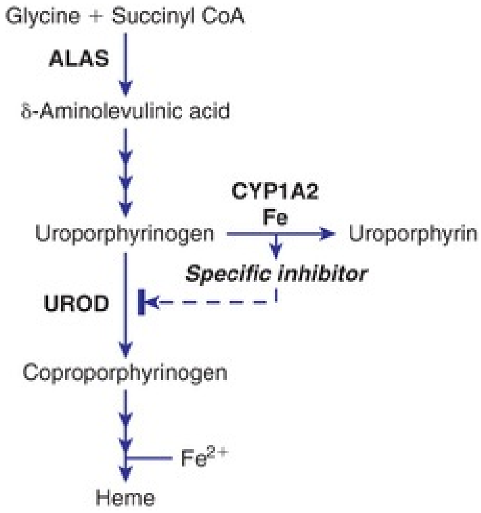

FIG. 110.5 Formation of a specific inhibitor of uroporphyrinogen decarboxylase in the liver in porphyria cutanea tarda. ALAS, δ-Aminolevulinic acid synthase; CYP1A2, cytochrome P450 1A2; UROD, uroporphyrinogen decarboxylase.

UROD catalyzes the decarboxylation of the 4 acetic acid side chains of uroporphyrinogen (an octacarboxyl porphyrinogen) to form coproporphyrinogen (a tetracarboxyl porphyrinogen). The enzyme reaction occurs in a sequential, clockwise fashion, with the intermediate formation of hepta-, hexa-, and pentacarboxyl porphyrinogens. Uroporphyrinogen III, as compared with other uroporphyrinogen isomers, is the preferred substrate. Human UROD is a dimer with the 2 active site clefts juxtaposed. The UROD gene is on chromosome 1p34 and contains 10 exons, with only 1 promoter. Therefore the gene is transcribed as a single mRNA in all tissues.

The majority of PCT patients (80%) have no *UROD* mutations and have sporadic (**type 1**) disease. Some are heterozygous for *UROD* mutations and have familial (**type 2**) PCT. Described mutations include missense, nonsense, and splice-site mutations; several small and large deletions; and small insertions, with only a few identified in more than 1 family. A few of these mutations may be located near the active site cleft, but most appear to involve regions with important structural roles. Being heterozygous for a *UROD* mutation is insufficient to cause PCT. Individuals with type 2 PCT are born with 50% of normal UROD activity, and later in life other susceptibility factors (as in type 1) lead to production of the uroporphomethene inhibitor and further reduction on hepatic UROD activity to <20% of normal. Because penetrance of the genetic trait is low, many patients with familial PCT have no family history of the disease.

Induction of hepatic ALAS1 is not a prominent feature in PCT, although alcohol may increase this enzyme slightly. Iron and estrogens are not potent inducers of ALAS1, and drugs that are potent inducers of ALAS1 and CYPs are much less frequently implicated in PCT than in acute porphyrias.

Blistering skin lesions result from porphyrins that are released from the liver. Sunlight exposure leads to generation of reactive oxygen species (ROS) in the skin, complement activation, and lysosomal damage.

Epidemiology

Differences in prevalence probably relate to geographic variations in susceptibility factors such as hepatitis C and ethanol use. The yearly incidence in the United Kingdom was estimated at 2-5 in 1 million in the general population, and the prevalence in the United States and Czechoslovakia was estimated at 1 in 25,000 and 1 in 5,000 in the general population, respectively. The disease was reported to be prevalent in the Bantus of South Africa in association with iron overload. PCT is more common in males, possibly because of greater alcohol intake, and in women it is usually associated with estrogen use.

A massive outbreak of PCT occurred in eastern Turkey in the 1950s. Wheat intended for planting and treated with hexachlorobenzene as a fungicide was consumed by many at a time of food shortage. Cases and small outbreaks of PCT after exposure to other chemicals including di- and trichlorophenols and 2,3,7,8-tetrachlorodibenzo-*p* -dioxin (TCDD, dioxin) have been reported. The manifestations improved in most cases when the exposure was stopped. There are reported cases of delayed onset many years after chemical exposure.

Pathology and Pathogenesis

Porphyria cutanea tarda is classified into 3 clinically similar types. Generation of a UROD inhibitor in the liver plays an important role in all 3 types. The 80% of patients with type 1 (**sporadic**) PCT have no *UROD* mutations, and UROD activity is normal in nonhepatic tissues such as erythrocytes. In type 2 (**familial**) PCT, a heterozygous *UROD* mutation results in a partial (approximately 50%) deficiency of UROD in all tissues from birth, and the disease becomes active in some heterozygotes after further reduction of hepatic UROD activity to ≤20% of normal. HEP results from inheritance of a *UROD* mutation from each parent and typically causes severe photosensitivity resembling CEP starting in early childhood. Some compound heterozygotes have developed symptoms in childhood more typical of PCT. **Type 3** is rare and describes PCT without a *UROD* mutation occurring in more than 1 family member. Another genetic basis, such as *HFE* mutations, may be identified in type 3.

CYPs, especially CYP1A2, can catalyze the oxidation of uroporphyrinogen to uroporphyrin. This uroporphyrinogen oxidase activity is enhanced by iron and leads to formation of a UROD inhibitor (see Fig. 110.5). CYP1a2 seems essential for development of uroporphyria in rodents, because experimental uroporphyria does not develop in *CYP1a2* knockout mice.

Susceptibility Factors

The following factors are implicated in the development of PCT, and these occur in various combinations in individual patients.

Iron

A normal or increased amount of iron in the liver is essential for developing PCT, and treatment by phlebotomy to reduce hepatic iron leads to remission. Serum ferritin levels are usually in the upper part of the normal range or moderately increased, and liver histology commonly shows increased iron staining. Prevalence of the C282Y mutation of the *HFE* gene, which is the major cause of hemochromatosis in people of northern European ancestry, is increased in both type 1 and type 2 PCT, and approximately 10% of patients are C282Y homozygotes. In southern Europe the H63D mutation is more prevalent. PCT may develop in patients with secondary iron overload. Reduced hepatic expression of the hormone hepcidin occurs in hemochromatosis and also in PCT, regardless of *HFE* genotype, which may explain hepatic siderosis in this condition.

Hepatitis C

Hepatitis C virus (HCV) infection is highly prevalent in PCT in most geographic locations; in the United States, for example, HCV is present in 56–74% of cases, which is similar to rates in southern Europe. Prevalence of hepatitis C in PCT is lower in northern Europe (<20%). Steatosis and oxidative stress in HCV infection may favor iron-mediated generation of ROS and a UROD inhibitor. Dysregulation of hepcidin occurs in hepatitis C and may lead to increased iron absorption.

Human Immunodeficiency Virus

Many reports suggest that HIV infection can contribute to the development of PCT, although less frequently than HCV.

Ethanol

The long-recognized association between alcohol and PCT may be explained by the generation of ROS, which may cause oxidative damage, mitochondrial injury, depletion of reduced glutathione and other antioxidant defenses, increased production of endotoxin, and activation of Kupffer cells. Also, alcohol may contribute to iron overload by impairing hepcidin production.

Smoking and Cytochrome P450 Enzymes

Smoking has not been extensively studied as a susceptibility factor but is often associated with alcohol use in PCT. It may act to induce hepatic CYPs and oxidative stress. Hepatic CYPs are thought to be important in oxidizing uroporphyrinogen and generating a UROD inhibitor (see Fig. 110.5). Genetic polymorphisms of *CYP1A2* and *CYP1A1* have been implicated in human PCT. The frequency of an inducible *CYP1A2* genotype was more common in PCT patients than in controls in several studies.

Antioxidant Status

Ascorbic acid deficiency contributes to uroporphyria in laboratory models and perhaps in human PCT. In one series, plasma ascorbate levels were substantially reduced in 84% of patients with PCT. Low levels of serum carotenoids were also described, further suggesting that oxidant stress in hepatocytes is important in PCT.

Estrogens

Use of estrogen-containing oral contraceptives (OCs) or postmenopausal estrogen replacement therapy is frequently associated with PCT (type 1 or 2) in women. PCT sometimes occurs during pregnancy, although it is not clear whether the risk is increased.

Clinical Manifestations

Cutaneous Manifestations

PCT is readily recognized by blistering and crusted skin lesions on the backs of the hands, which are the most sun-exposed areas of the body, and somewhat less often on the forearms, face, ears, neck, legs, and feet (Fig. 110.6). The fluid-filled vesicles usually rupture and become crusted or denuded areas, heal slowly, and are subject to infection. The skin on the backs of the hands is characteristically friable, and minor trauma may cause blisters or denudation of skin. Small white plaques, termed *milia,* may precede or follow vesicle formation. Facial hypertrichosis and hyperpigmentation are also common. Severe scarring and thickening of sun-exposed skin may resemble scleroderma. Skin biopsy findings include subepidermal blistering and deposition of periodic acid–Schiff-(PAS)–positive material around blood vessels and fine fibrillar material at the dermoepithelial junction, which may be related to excessive skin fragility. IgG, other immunoglobulins, and complement are also deposited at the dermoepithelial junction and around dermal blood vessels. The skin lesions and histologic changes are not specific for PCT. The same findings occur in VP and HCP and resemble those of CEP and HEP, but are usually less severe. PCT usually develops in mid or late adult life. Onset in early adult life may be seen in those with *UROD* or *HFE* mutations. Childhood onset is rare and may be associated with cancer chemotherapy and *UROD* mutations.

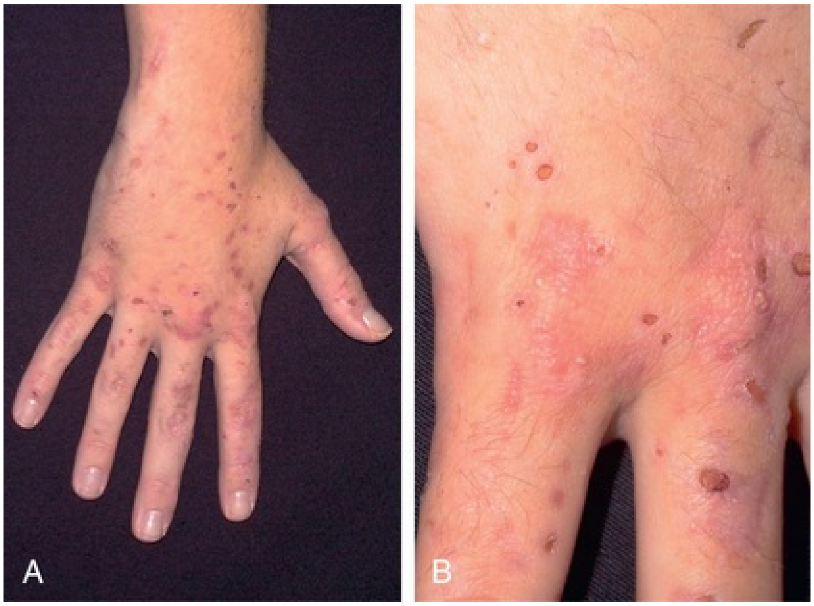

FIG. 110.6 **Porphyria cutanea tarda (PCT). A, Right hand of a patient with PCT, revealing numerous erosions and erythematous patches. B, Close-up of right hand. (From Horner**

ME, Alikhan A, Tintle S, et al: Cutaneous porphyrias. Part 1. Epidemiology, pathogenesis, presentation, diagnosis, and histopathology, *Int J Dermatol* 52:1464–1480, 2013, Fig 2, p 1470.)

Liver Abnormalities

PCT is almost always associated with nonspecific liver abnormalities, especially increased serum transaminases and γ-glutamyltranspeptidase, even in the absence of heavy alcohol intake or hepatitis C. Most histologic findings, such as necrosis, inflammation, increased iron, and increased fat, are nonspecific. Specific findings include red fluorescence of liver tissue, and fluorescent, birefringent, needle-like inclusions presumably consisting of porphyrins. Electron microscopy shows these inclusions are in lysosomes, and paracrystalline inclusions are found in mitochondria. Distorted lobular architecture and cirrhosis are more common with long-standing disease.

The risk of developing hepatocellular carcinoma is increased, with reported incidences ranging from 4–47% in PCT. These tumors seldom contain large amounts of porphyrins.

Other Features and Associations

Mild or moderate erythrocytosis in some adult patients is not well understood, but chronic lung disease from smoking may contribute. An earlier onset of symptoms may be noted in patients with genetic predisposing factors, such as an inherited partial deficiency of UROD or the C282Y/C282Y *HFE* genotype. Iron overload secondary to conditions such as myelofibrosis and end-stage renal disease (ESRD) may be associated with PCT. The disease can be especially severe in patients with ESRD because the lack of urinary excretion leads to much higher concentrations of porphyrins in plasma, and the excess porphyrins are poorly dialyzable. PCT occurs more frequently in patients with systemic lupus erythematosus and other immunologic disorders than would be expected by chance.

Laboratory Findings

Porphyrins accumulate in the liver mostly as the oxidized porphyrins rather than porphyrinogens in PCT, as indicated by the immediate *red fluorescence* observed in liver tissue. This develops over weeks or months before porphyrins appear in plasma and are transported to the skin, causing photosensitivity. In contrast to the acute hepatic porphyrias, only a very small increase in synthesis of heme pathway intermediates and little or no increase in hepatic ALAS1 are required to account for the excess porphyrins excreted in PCT.

Hepatic UROD deficiency leads to a complex pattern of excess porphyrins, which initially accumulate as porphyrinogens and then undergo nonenzymatic oxidation to the corresponding porphyrins (uro-, hepta-, hexa-, and pentacarboxyl porphyrins, and isocoproporphyrins). Uroporphyrin and heptacarboxyl porphyrin predominate in urine, with lesser amounts of coproporphyrin and penta- and hexacarboxyl porphyrin. A normally minor pathway is accentuated by UROD deficiency, whereby pentacarboxyl porphyrinogen is oxidized by coproporphyrinogen oxidase (CPOX; the next enzyme in the pathway), forming isocoproporphyrinogen, an atypical tetracarboxyl porphyrinogen. Relative to normal values, urinary porphyrins are increased to a greater extent than fecal porphyrins. However, the total amount of porphyrins excreted in feces in PCT exceeds that in urine, and total excretion of type III isomers (including isocoproporphyrins, which are mostly derived from the type III series) exceeds that of type I isomers. Perhaps because uroporphyrinogen III is the preferred substrate for UROD, more uroporphyrinogen I than III accumulates and is excreted as uroporphyrin I in PCT. Hepta- and hexacarboxyl porphyrin are mostly isomer III; and pentacarboxyl porphyrin and coproporphyrin are approximately equal mixtures of isomers I and III.

Diagnosis and Differential Diagnosis

Plasma porphyrins are always increased in clinically manifest PCT, and a total plasma porphyrin determination is useful for screening. A normal value rules out PCT and other porphyrias that produce blistering skin lesions. If increased, it is useful to determine the plasma fluorescence emission maximum at neutral pH, because a maximum near 619 nm is characteristic of PCT (as well as CEP and HCP) and importantly, excludes VP, which has a distinctly different fluorescence maximum. Increased urinary or plasma porphyrins, with a predominance of uroporphyrin and heptacarboxyl porphyrin, is confirmatory. Urine porphyrins are less useful for initial screening because nonspecific increases, especially of coproporphyrin, occur in liver disease and other medical conditions. Urinary ALA may be increased slightly, and PBG is normal. Mild cases of CEP can mimic PCT clinically, and this possibility is ruled out by finding normal or only mildly increased levels of erythrocyte porphyrins.

Familial (type 2) can be distinguished from sporadic (type 1) PCT by finding decreased erythrocyte UROD activity (in type 2), or more reliably by finding a disease-related *UROD* mutation. Type 3 is distinguished from type 1 only by occurrence of PCT in a relative. Biochemical findings in HEP are similar to those in PCT, but with an additional marked increase in erythrocyte zinc protoporphyrin.

Pseudoporphyria (also known as pseudo-PCT) presents with skin lesions that closely resemble PCT, but without significant increases in plasma porphyrins. A photosensitizing agent such as a nonsteroidal antiinflammatory drug (NSAID) is sometimes implicated. Both PCT and pseudoporphyria may occur in patients with ESRD.

Complications

Cutaneous blisters may rupture and become infected, sometimes leading to cellulitis. In more-severe disease in patients with ESRD, repeated infections can be mutilating, as in CEP. **Pseudoscleroderma** , with scarring, contraction, and calcification of skin and subcutaneous tissue, is a rare complication. Other complications include advanced liver disease and hepatocellular carcinoma.

Treatment

Two specific and effective forms of treatment, phlebotomy and low-dose hydroxychloroquine, are available. Susceptibility factors should be removed when possible. The diagnosis of PCT must be firmly established because conditions that produce identical cutaneous lesions do not respond to these treatments. Treatment can usually be started after demonstrating an increase in plasma total porphyrins and excluding VP by analysis of the fluorescence spectrum at neutral pH, while urine and fecal studies are still pending. Use of alcohol, estrogens (in women), and smoking should be stopped and patients tested for HCV, HIV, and *HFE* mutations. Susceptibility factors and degree of iron overload, as assessed by the serum ferritin concentration, can influence the choice of treatment.

Phlebotomy is considered standard therapy and is effective in both children and adults with PCT because it reduces hepatic iron content. Treatment is guided by plasma (or serum) ferritin and porphyrin levels. Hemoglobin or hematocrit levels should be followed to prevent symptomatic anemia. For adults, a unit of blood (450 mL) is removed at about 2 wk intervals until a target serum ferritin near the lower limit of normal (15 ng/mL) is achieved. A total of 6-8 phlebotomies is often sufficient in adults. After this, plasma porphyrin concentrations continue to fall from pretreatment levels (generally 10-25 µg/dL) to below the upper limit of normal (1 µg/dL), usually after several more weeks. This is followed by gradual clearing of skin lesions, sometimes including pseudoscleroderma. Liver function abnormalities may improve, and hepatic siderosis, needle-like inclusions, and red fluorescence of liver tissue will disappear. Although remission usually persists even if ferritin levels later return to normal, it is advisable to follow porphyrin levels and reinstitute phlebotomies if porphyrins begin to increase. Infusions of deferoxamine, an iron chelator, may be used when phlebotomy is contraindicated.

An alternative when phlebotomy is contraindicated or poorly tolerated is a low-dose regimen of **hydroxychloroquine** (or chloroquine). Normal doses of these 4-aminoquinoline antimalarials in PCT increase plasma and urinary porphyrin levels and increase photosensitivity, reflecting an outpouring of porphyrins from the liver. This is accompanied by acute hepatocellular damage, with fever, malaise, nausea, and increased serum transaminases, but is followed by complete remission of the porphyria. These adverse consequences of normal doses are largely avoided by a low-dose regimen (for adults, hydroxychloroquine 100 mg or chloroquine 125 mg, i.e., half a normal tablet, twice weekly), which can be continued until plasma or urine porphyrins are normalized. In young children, half the adult dose is recommended. There is at least some risk of retinopathy, which may be lower with hydroxychloroquine. The mechanism of action of 4-aminoquinolines in PCT is not known but is quite specific, because these drugs are not useful in other porphyrias. Recent studies indicate that low-dose hydroxychloroquine is as safe and effective as phlebotomy in adults with PCT.

In patients with PCT and hepatitis C, PCT should be treated first because this condition is more symptomatic and can be treated more quickly and effectively. Treatment of PCT by phlebotomy may not be possible once interferon-ribavirin treatment is complicated by anemia. Moreover, treatment of hepatitis C may be more effective after iron reduction. Whether direct-acting antiviral agents should be used initially for treating both hepatitis C and PCT is under investigation.

PCT in patients with ESRD is often more severe and difficult to treat. However, erythropoietin administration can correct anemia, mobilize iron, and support phlebotomy in many cases. Improvement after renal transplantation may be partly from resumption of endogenous erythropoietic production.

Liver imaging and a serum α-fetoprotein determination may be advisable in all PCT patients, perhaps at 6-12 mo intervals, for early detection of hepatocellular carcinoma. Finding low-erythrocyte UROD activity or a *UROD* mutation identifies those with an underlying genetic predisposition, which does not alter treatment but is useful for genetic counseling.

Prognosis

Porphyria cutanea tarda is the most readily treated form of porphyria, and complete remission is expected with treatment either by phlebotomy or low-dose hydroxychloroquine. There is little information on rates of recurrence and long-term outlook. Risk for hepatocellular carcinoma is increased, and some susceptibility factors such as hepatitis C can lead to complications even after PCT is in remission.

Prevention and Genetic Counseling

A heritable *UROD* mutation can usually be detected or excluded by measuring erythrocyte UROD activity, although DNA studies are more sensitive. Relatives of patients with *UROD* mutations have an increased risk for developing PCT and may have increased motivation to avoid adverse behaviors such as ethanol and tobacco use and exposures to HCV and HIV (although such counseling would be given to anyone). The finding of *HFE* mutations, and especially C282Y, should prompt screening of relatives, some of whom may be C282Y homozygotes and warrant lifelong monitoring of serum ferritin.

Hepatoerythropoietic Porphyria

HEP is the homozygous form of familial (type 2) PCT; it resembles CEP clinically. Excess porphyrins originate mostly from liver, with a pattern consistent with severe UROD deficiency. This rare disorder has no particular racial predominance.

Etiology

HEP is an autosomal recessive disorder, and most patients have inherited a different mutation from unrelated parents. In contrast to most mutations in familial PCT, most causing HEP are associated with expression of some residual enzyme activity. At least 1 genotype is associated with the predominant excretion of pentacarboxyl porphyrin.

Pathology and Pathogenesis

Excess porphyrins originate primarily from the liver in HEP, although the substantial increase in erythrocyte zinc protoporphyrin indicates that the heme biosynthetic pathway is also impaired in bone marrow erythroid cells. Apparently, porphyrinogens accumulate in the marrow while hemoglobin synthesis is most active and are metabolized to protoporphyrin after hemoglobin synthesis is complete. The cutaneous lesions are a result of photoactivation of porphyrins in skin, as in other cutaneous porphyrias.

Clinical Manifestations

As in CEP, this disease usually presents with blistering skin lesions, hypertrichosis, scarring, and red urine in infancy or childhood. *Sclerodermoid* skin changes are sometimes prominent. Unusually mild cases have been described. Concurrent conditions that affect liver function can alter disease severity; the disease manifested because of hepatitis A in a 2 yr old child and then improved with recovery of liver function.

Laboratory Findings

Biochemical findings resemble those in PCT, with accumulation and excretion of uroporphyrin, heptacarboxyl porphyrin, and isocoproporphyrin. In addition, erythrocyte zinc protoporphyrin is substantially increased.

Diagnosis and Differential Diagnosis

HEP is distinguished from CEP by increases in both uroporphyrin and heptacarboxyl porphyrin, and isocoproporphyrins. In CEP, the excess erythrocyte porphyrins are predominantly uroporphyrin I and coproporphyrin I rather than protoporphyrin. Blistering skin lesions are unusual in EPP, the excess erythrocyte protoporphyrin in that disease is metal free and not complexed with zinc, and urinary porphyrins are normal.

Treatment and Prognosis

Avoiding sunlight exposure is most important in managing HEP, as in CEP. Oral charcoal was helpful in a severe case associated with dyserythropoiesis. Phlebotomy has shown little or no benefit. The outlook depends on the severity of the enzyme deficiency and may be favorable if sunlight can be avoided.

Prevention and Genetic Counseling

As part of genetic counseling in affected families, it is feasible to diagnose HEP in utero, either by analysis of porphyrins in amniotic fluid or DNA studies.

Hereditary Coproporphyria

This autosomal dominant hepatic porphyria is caused by a deficiency of coproporphyrinogen oxidase (CPOX). The disease presents with acute attacks, as in AIP. Cutaneous photosensitivity may occur, but much less often than in VP. Rare homozygous cases present in childhood.

Etiology

A partial (50%) deficiency in CPOX activity has been found in all cells studied from patients with HCP. A much more profound deficiency is found in homozygous cases. Human CPOX is a homodimer composed of 39 kDa subunits and contains no metals or prosthetic groups. The enzyme requires molecular oxygen and is localized in the mitochondrial intermembrane space. A single active site on the enzyme catalyzes the oxidative decarboxylation of 2 of the 4 propionic acid groups of coproporphyrinogen III to form the 2 vinyl groups at positions 2 and 4, on rings A and B, respectively, of protoporphyrinogen IX. Most of the intermediate tricarboxyl porphyrinogen, termed *harderoporphyrinogen*, is not released before undergoing the 2nd decarboxylation to protoporphyrinogen IX. Coproporphyrinogen I is not a substrate for this enzyme.

The human *CPOX* gene contains 7 exons and is located on chromosome 3q12.1. A single promoter contains elements for both housekeeping and erythroid-specific expression. A variety of *CPOX* mutations have been described in HCP, with a predominance of missense mutations and no genotype-phenotype correlations. **Harderoporphyria** , an autosomal recessive biochemical variant form of HCP, is caused by *CPOX* mutations that impair substrate binding, leading to premature release of harderoporphyrinogen.

Epidemiology

HCP is less common than AIP and VP, but its prevalence has not been carefully estimated. There is no obvious racial predominance. Homozygous HCP is rare and presents during childhood. Harderoporphyria, a biochemically distinguishable variant of HCP, has been recognized in heteroallelic and homoallelic forms.

Pathology and Pathogenesis

Increased ALA and PBG during acute attacks of HCP may be explained by induction of ALAS1 and by the normally relatively low activity of PBGD in the liver. Hepatic ALAS1 is increased during acute attacks but is normal when the disease is latent and porphyrin precursor excretion is normal. Because coproporphyrinogen III concentration in the liver is probably less than the K_m for CPOX, the reaction rate is likely to be determined in part by substrate concentration. The substrate coproporphyrinogen appears to be lost more readily from the liver cell than, for example, uroporphyrinogen, especially when heme synthesis is stimulated. Coproporphyrin and coproporphyrinogen are both transported into bile and excreted in urine, and do not appear to accumulate in the liver in HCP.

Clinical Manifestations

Symptoms are identical to those of AIP except that attacks are generally milder, and cutaneous lesions that resemble those in PCT develop occasionally. Severe motor neuropathy and respiratory paralysis can occur. As in other acute porphyrias, HCP is almost always latent before puberty, and symptoms are most common in adult women. Attacks are precipitated by the same factors that cause attacks in AIP, including fasting, OCs, and hormone increases during the luteal phase of the menstrual cycle. Concomitant liver diseases may increase porphyrin retention and photosensitivity. The risk of hepatocellular carcinoma is increased, as in other acute porphyrias.

The clinical features of homozygous HCP or harderoporphyria begin in early childhood and include jaundice, hemolytic anemia, hepatosplenomegaly, and skin photosensitivity. These symptoms are generally quite distinct from those seen in heterozygotes. Hematologic features are particularly characteristic in harderoporphyria.

Laboratory Findings

The porphyrin precursors ALA and PBG are increased during acute attacks in HCP but may decrease more rapidly than in AIP. Marked increases in coproporphyrin III in urine and feces are more persistent in HCP. In homozygous cases, porphyrin excretion may be more increased and is accompanied by substantial increases in erythrocyte zinc protoporphyrin. Harderoporphyria is characterized by a marked increase in fecal excretion of harderoporphyrin (tricarboxyl porphyrin) as well as coproporphyrin. Plasma porphyrins are usually normal or only slightly increased.

Diagnosis and Differential Diagnosis

The diagnosis of HCP is readily established in patients with clinically manifest disease, although urinary ALA, PBG, and uroporphyrin may revert to normal more quickly than in AIP. Urinary coproporphyrin III is increased. Urinary porphyrins, especially coproporphyrin, can be increased in many medical conditions (e.g., liver disease), and small increases that are not diagnostically significant may lead to an incorrect diagnosis of HCP. Fecal porphyrins are mostly coproporphyrin (isomer III) in HCP, whereas in VP, coproporphyrin III and protoporphyrin are often increased approximately equally. Plasma porphyrins are usually normal in HCP and increased in VP.

The ratio of fecal coproporphyrin III to coproporphyrin I is especially sensitive for detecting latent heterozygotes (especially adults). Assays for CPOX, a mitochondrial enzyme, require cells such as lymphocytes and are not widely available. Identification of a *CPOX* mutation in an index case greatly facilitates screening family members.

Treatment and Prognosis

Acute attacks of HCP are treated as in AIP, which includes IV hemin and identifying and avoiding precipitating factors. Cholestyramine may be of some value for photosensitivity occurring with liver dysfunction. Phlebotomy and chloroquine are not effective. GnRH hormone analogs can be effective for prevention of cyclic attacks. The prognosis is generally better than in AIP.

Prevention and genetic counseling are the same as in other acute porphyrias.

Variegate Porphyria

This hepatic porphyria is caused by a deficiency of protoporphyrinogen oxidase (PPOX), which is inherited as an autosomal dominant trait. The disorder is termed *variegate* because it can present with neurologic or cutaneous manifestations, or both. Other terms have included *porphyria variegata, protocoproporphyria,* and *South African genetic porphyria*. Rare cases of homozygous VP are symptomatic in childhood.

Etiology

PPOX is approximately half normal in all cells studied in patients with VP. The enzyme is more markedly deficient in rare cases of homozygous VP, with approximately half-normal enzyme activity in parents.

Human PPOX is a homodimer that contains flavin adenine dinucleotide and is localized to the cytosolic side of the inner mitochondrial membrane. Membrane-binding domains may be docked onto human FECH, the next enzyme in the pathway, which is embedded in the opposite side of the membrane. PPOX catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX by the removal of 6 hydrogen atoms. The enzyme requires molecular oxygen. The substrate is readily oxidized nonenzymatically to protoporphyrin under aerobic conditions, or if exported into the cytosol. PPOX is highly specific for protoporphyrinogen IX and is inhibited by tetrapyrroles such as heme, biliverdin, and bilirubin and by certain herbicides that cause protoporphyrin to accumulate and induce phototoxicity in plants. Inhibition by bilirubin may account for decreased PPOX activity in Gilbert disease.

The human *PPOX* gene on chromosome 1q22-q23 consists of 1 noncoding and 12 coding exons. A single PPOX transcript is produced in a variety of tissues, but putative transcriptional element binding sequences may allow for erythroid-specific expression. Many *PPOX* mutations have been reported in VP families. A missense mutation, R59W, is prevalent in South Africa. No convincing genotype-phenotype correlations have been identified. Mutations in homozygous cases of VP are more likely to encode enzyme proteins with residual activity.

Epidemiology

VP is less common than AIP in most countries. The R59W mutation is highly prevalent in South African whites (3 in 1,000 in this population). This example of “genetic drift” or founder effect has been traced to a man or his wife who emigrated from Holland to South Africa in 1688. In Finland, prevalence is 1.3 in 100,000 people and is about as common as AIP.

Pathology and Pathogenesis

Acute attacks develop in a minority (approximately 25%) of heterozygotes for PPOX deficiency and are often attributable to drugs, steroids, and nutritional factors that play a role in other acute porphyrias. Protoporphyrinogen IX accumulates and undergoes autoxidation to protoporphyrin IX. Coproporphyrinogen III accumulates, perhaps as the result of a close functional association between PPOX in the inner mitochondrial membrane and CPOX in the intermembrane space. Liver porphyrin content is not increased. The increased porphyrin content in plasma consists of porphyrin-peptide conjugates, which may be formed from protoporphyrinogen. Increased ALA and PBG during acute attacks may be explained, as in HCP, by induction of ALAS1 by exacerbating factors, and by the normally relatively low activity of PBGD in liver. Furthermore, PBGD is inhibited by protoporphyrinogen, the substrate for PPOX.

Clinical Manifestations

Symptoms develop in some heterozygotes after puberty. Neurovisceral symptoms occurring as acute attacks are identical to AIP but are generally milder and less often fatal. Drugs, steroids, and nutritional alterations such as fasting, which are harmful in AIP, can also induce attacks of VP. Attacks occur equally in males and females, at least in South Africa. Cutaneous fragility, vesicles, bullae, hyperpigmentation, and hypertrichosis of sun-exposed areas are much more common than in HCP. They are likely to occur apart from and to be longer lasting than the neurovisceral symptoms. OCs can precipitate cutaneous manifestations. Acute attacks have become less common, and skin manifestations are more frequently the initial presentation; this may result from earlier diagnosis and counseling. The risk of hepatocellular carcinoma is increased.

Symptoms of homozygous VP begin in infancy or childhood. These children generally have severe photosensitivity, neurologic symptoms, seizures, developmental disturbances, and sometimes growth retardation, but they do not have acute attacks.

Laboratory Findings

Urinary ALA, PBG, and uroporphyrin are increased during acute attacks, but often less so than in AIP, and may be normal or only slightly increased during remission. Plasma porphyrins, urinary coproporphyrin III, and fecal coproporphyrin III and protoporphyrin are more persistently increased between attacks. Erythrocyte zinc protoporphyrin levels are greatly increased in homozygous VP and may be modestly increased in heterozygous cases.

Diagnosis and Differential Diagnosis

VP is readily distinguished biochemically from AIP and HCP, which also present with acute attacks and increases in PBG. Plasma porphyrin analysis is especially useful because the plasma porphyrins in VP are tightly protein bound, resulting in a characteristic fluorescence emission spectrum at neutral pH. Fecal porphyrins are increased, with approximately equal amounts of coproporphyrin III and protoporphyrin. Fluorometric detection of plasma porphyrins is more sensitive than stool porphyrin analysis in asymptomatic VP. PPOX assays using cells that contain mitochondria, such as lymphocytes, are sensitive for identifying asymptomatic carriers but are not widely available. Knowing the *PPOX* mutation in an index case enables the identification of relatives who carry the same mutation.

Treatment

Acute attacks are treated as in AIP. Hemin is beneficial for acute attacks but not for cutaneous symptoms. Light protection is important in patients with skin manifestations, using long-sleeved clothing, gloves, a broad-brimmed hat, and opaque sunscreen preparations. Exposure to short-wavelength UV light, which does not excite porphyrins, may increase skin pigmentation and provide some protection. Phlebotomy and chloroquine are not effective. Surprisingly, oral activated charcoal was reported to increase porphyrin levels and worsen skin manifestations.

Prognosis and Prevention

The outlook of patients with VP has improved, which may be attributed to improved treatment, earlier diagnosis, and detection of latent cases. Cyclic acute attacks in women can be prevented with a GnRH analog, as in AIP. A diagnosis of VP or any other acute porphyria should not lead to difficulty obtaining insurance, because the prognosis is usually good once the diagnosis is established.

Genetic counseling is the same as in other acute porphyrias.

Erythropoietic Protoporphyria and X-Linked Protoporphyria

These forms of protoporphyria are genetically distinct but have essentially the same phenotype. In EPP, an autosomal recessive disorder, protoporphyrin accumulates as the result of a marked deficiency of FECH, the last enzyme in the heme biosynthetic pathway, because of *FECH* mutations. EPP is sometimes termed *erythrohepatic protoporphyria*, although the liver does not contribute substantially to production of excess protoporphyrin in uncomplicated cases. XLP is the most recently described porphyria, in which gain-of-function *ALAS2* mutations leads to overproduction of ALA in the marrow, where it is metabolized to excess amounts of protoporphyrin.

Etiology

Ferrochelatase (FECH), the enzyme that is deficient in EPP, catalyzes the final step in heme synthesis, which is insertion of ferrous iron (Fe^{2+}) into protoporphyrin IX (see Fig. 110.1). The enzyme is also termed *heme synthetase* or *protoheme ferrolyase.* The human enzyme is a dimer, and each homodimer contains a [2Fe-2S] cluster, which may have a role in bridging homodimers. FECH is found in the mitochondrial inner membrane, where its active site faces the mitochondrial matrix. It may be associated with complex I of the mitochondrial electron transport chain, and the ferrous iron substrate may be produced on nicotinamide adenine dinucleotide oxidation. FECH is specific for the reduced form of iron but can utilize other metals, such as Zn^{2+} and Co^{2+} , and other dicarboxyl porphyrins. Accumulation of free protoporphyrin rather than zinc protoporphyrin in EPP indicates that formation of the latter is dependent on FECH activity in vivo.

The human *FECH* gene is located on chromosome 18q21.3, has a single promoter sequence, and contains 11 exons. Two mRNAs of 1.6 and 2.5 kb were described, which may be explained by the use of 2 alternative polyadenylation signals. The larger transcript is more abundant in murine erythroid cells, suggesting erythroid-specific regulation of FECH. A variety of *FECH* mutations have been reported in EPP, including missense, nonsense, and splicing mutations; small and large deletions; and an insertion.

The inheritance of 2 alleles associated with reduced FECH activity is required for disease expression. This is consistent with FECH activities as low as 15–25% of normal in EPP patients. In most patients, a pathogenic mutation on 1 *FECH* allele is combined with a common variant affecting the other allele. This common variant *FECH* allele (IVS3-48T>C) produces less-than-normal amounts of enzyme because it expresses an aberrantly spliced mRNA that is degraded by a nonsense-mediated RNA decay mechanism. The IVS3-48T > C *FECH* variant by itself does not cause disease, even when homozygous. In a few families, 2 severe *FECH* mutations have been found, without the IVS3-48T> C allele.

EPP with autosomal recessive inheritance occurs naturally in cattle and in mouse models.

XLP is associated with gain-of-function deletions in the last exon of *ALAS2* . These lesions delete the last 10-20 amino acids of the ALAS2 polypeptide and apparently make the enzyme more stable. Metal-free protoporphyrin predominates in erythrocytes in these cases, but because FECH activity is normal, the proportion of zinc protoporphyrin is greater than in classic EPP. XLP accounts for approximately 2% of cases with the EPP phenotype in Europe and approximately 10% of cases in North America.

EPP is sometimes associated with **myelodysplastic syndromes** and expansion of a clone of hematopoietic cells with deletion of 1 *FECH* allele or with other

FECH mutations. In such cases there is late onset of the disease.

Epidemiology

EPP is the most common porphyria to cause symptoms in children but is often not diagnosed until adult life. Overall it is the 3rd most common porphyria, although its prevalence is not precisely known (see Table 110.2). It is described mostly in white people but occurs in other races. The IVS3-48T>C splice variant is common in whites and Japanese but rare in Africans, which explains lower disease prevalence in populations of African origin.

Pathology and Pathogenesis

FECH is deficient in all tissues in EPP, but bone marrow reticulocytes are thought to be the primary source of the excess protoporphyrin, some of which enters plasma and circulates to the skin. Circulating erythrocytes are no longer synthesizing heme and hemoglobin, but they contain excess free protoporphyrin, which also contributes. In XLP caused by terminal deletions in exon 11 of *ALAS2* , all intermediates of the heme pathway are overproduced and ultimately accumulate in bone marrow erythroblasts as protoporphyrin. FECH is not deficient in XLP, so this enzyme chelates some of the excess protoporphyrin with zinc. An aberrantly spliced mitoferrin transcript, which limits iron transport into mitochondria, has also been described in XLP. The liver functions as an excretory organ rather than a major source for excess protoporphyrin. FECH deficiency in the skin and liver may be important, however, because tissue transplantation studies in mice suggest that skin photosensitivity and liver damage occur only when FECH is deficient in these tissues.

Patients with EPP and XLP are maximally sensitive to light in the 400 nm range, which corresponds to the so-called Soret band, the narrow peak absorption maximum that is characteristic for protoporphyrin and other porphyrins. Having absorbed light, porphyrins enter an excited energy state and release energy as fluorescence, singlet oxygen, and other ROS. Resulting tissue damage is accompanied by lipid peroxidation, oxidation of amino acids, cross linking of proteins in cell membranes, and damage to capillary endothelial cells. Such damage may be mediated by photoactivation of the complement system and release of histamine, kinins, and chemotactic factors. Repeated acute damage leads to thickening of the vessel walls and perivascular deposits from accumulation of serum components. Deposition of amorphous material containing immunoglobulin, complement components, glycoproteins, acid glycosaminoglycans, and lipids occurs around blood vessels in the upper dermis.

There is little evidence for impaired erythropoiesis or hemolysis in EPP. However, mild anemia with microcytosis, hypochromia, and reticulocytosis is common. Iron accumulation in erythroblasts and ring sideroblasts has been noted in bone marrow in some patients. Decreased transferrin saturation and low or low-normal serum ferritin suggest iron deficiency. Iron status should be carefully evaluated in EPP patients, keeping in mind that iron deficiency may lead to further increases in protoporphyrin and increase the risk for cholestasis. Poor response to oral iron supplements is described in EPP and is unexplained. Some patients report increased photosensitivity when given iron supplements, but whether this is from transient increases in porphyrins when iron deficiency is corrected and erythropoiesis increases is not known. Case reports suggest that iron supplementation decreases protoporphyrin and improves anemia, especially in patients with XLP.

Liver damage develops in a small proportion of EPP and XLP patients and is attributed to excess protoporphyrin, which is insoluble in water and excreted only by hepatic uptake, and biliary excretion is cholestatic. Some may be reabsorbed by the intestine and undergo enterohepatic circulation. With cholestasis the excess protoporphyrin that accumulates in the liver can form crystalline structures in hepatocytes and impair mitochondrial function.

Clinical Manifestations

Symptoms of cutaneous photosensitivity begin in childhood and consist of acute pain and itching often occurring within minutes of sunlight exposure and followed by redness and swelling with continued exposure (Fig. 110.7). Petechiae and purpuric lesions may be seen, but blisters are rare. Swelling may resemble angioneurotic edema and *solar urticaria*. Symptoms are usually worse in the spring and summer. Chronic changes may include lichenification, leathery pseudovesicles, labial grooving, and nail changes, but changes in pigmentation and pronounced scarring are unusual. Although physical findings in EPP and XLP may not be impressive, the symptoms significantly impair quality of life to a greater extent than in PCT or VP. An association between EPP caused by mutations affecting both FECH alleles and seasonal palmar keratoderma is unexplained. Neuropathy develops only in some patients with severe hepatic decompensation. XLP males have a more severe phenotype with higher protoporphyrin levels than most EPP patients. XLP females have a variable clinical presentation—some with no symptoms or mild symptoms and others with severe symptoms similar to XLP males. This variability in females is likely the result of random X-chromosome inactivation.

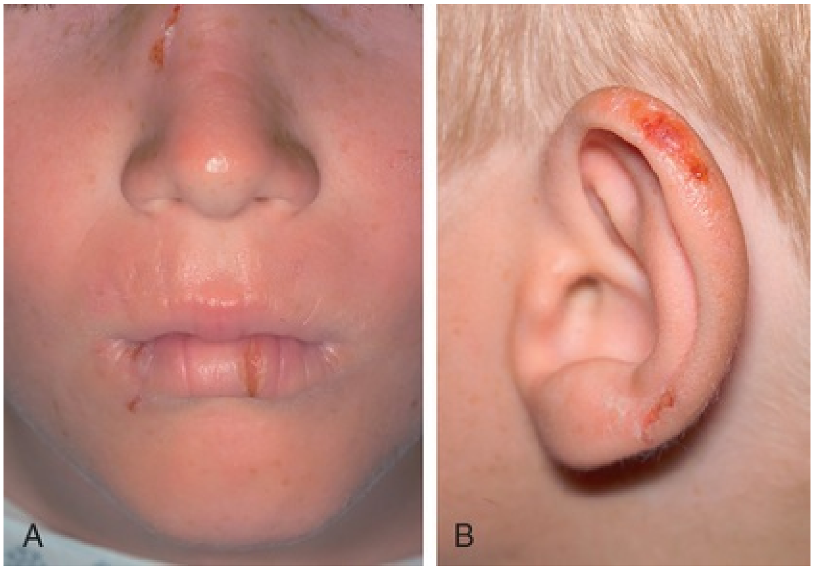

FIG. 110.7 Erythropoietic protoporphyria (EPP). A, Linear erosions of the lateral nasal bridge and lower lip in a patient with EPP. B, Erosions with crusting on the left helix of a patient with EPP. (From Horner ME, Alikhan A, Tintle S, et al: Cutaneous porphyrias. Part 1. epidemiology, pathogenesis, presentation, diagnosis, and histopathology, *Int J Dermatol* 52:1464–1480, 2013, Figs 7 and 8, p 1473.)

Unless hepatic or other complications develop, protoporphyrin levels and symptoms of photosensitivity remain remarkably stable for many years in most patients. Factors that exacerbate hepatic porphyrias play little or no role in EPP or XLP. Erythrocyte protoporphyrin levels may decrease and sunlight tolerance may improve during pregnancy, which is unexplained.

Laboratory Findings

Protoporphyrin is substantially increased in circulating erythrocytes in EPP and consists almost entirely of free protoporphyrin. In XLP, both zinc protoporphyrin and free protoporphyrin are increased, although the latter still predominates. Protoporphyrin is also increased in bone marrow, plasma, bile, and feces. Other porphyrins and porphyrin precursors are normal in uncomplicated EPP and XLP.

Diagnosis and Differential Diagnosis

A diagnosis of EPP is confirmed biochemically by finding a substantially elevated concentration of total erythrocyte protoporphyrin, which is predominantly (at least 85%) metal free and not complexed with zinc. In XLP, both free and zinc-complexed protoporphyrins are elevated. Erythrocyte total protoporphyrin levels are on average higher in XLP and more variable between individuals with EPP, possible reflecting differences in severity of the many reported *FECH* mutations. Erythrocyte zinc protoporphyrin concentration is increased with little increase in metal-free protoporphyrin in homozygous porphyrias (except CEP), iron deficiency, lead poisoning, anemia of chronic disease, hemolytic conditions, and many other erythrocytic disorders. Measurement of FECH activity requires cells containing mitochondria and is not widely available.

Plasma total porphyrin concentration is often less increased in EPP than in other cutaneous porphyrias and may be normal. Great care must be taken to avoid light exposure during sample processing, because plasma porphyrins in EPP are particularly subject to photodegradation. Urinary porphyrin precursors and porphyrins are not increased.

DNA studies are strongly recommended for confirming *FECH* or *ALAS2* mutations and for genetic counseling.

Life-threatening **protoporphyric hepatopathy** is characterized by greater increases in erythrocyte and plasma protoporphyrin levels, increased photosensitivity and either chronically abnormal liver function tests or rapidly progressive hepatic failure. Presumably this is heralded by increases above the patient's baseline erythrocyte and plasma porphyrin levels, but this has not been documented, because most such patients have not had adequate baseline determinations of porphyrin values. Increases in urinary porphyrins, especially coproporphyrin, in this setting are attributable to liver dysfunction.

Complications

There is an increased risk of biliary stones, which contain protoporphyrin and are sometimes symptomatic, requiring cholecystectomy. Protoporphyric hepatopathy occurs in <5% of protoporphyria patients, including children, and may be chronic or progress rapidly to death from liver failure. This liver disease is sometimes the major presenting feature of EPP. In XLP, liver disease may be more frequent, and in one report of 8 families, 17% of patients had overt liver dysfunction. Protoporphyric hepatopathy can cause acute upper abdominal pain suggesting biliary obstruction, and unnecessary laparotomy to exclude this possibility can be detrimental. Concurrent conditions that impair liver function, such as viral hepatitis, alcohol- or drug-induced liver disease, or OCs may contribute. Whether iron deficiency may contribute is unclear. Liver histology shows marked deposition of protoporphyrin as inclusions in liver cells and bile canaliculi. Patients with protoporphyric liver failure most often have *FECH* “null mutations” and the IVS3–48T>C hypoexpression allele, but some may have 2 severe mutant *FECH* alleles or XLP caused by *ALAS2* exon 11 deletions. The bone marrow is probably the major source of protoporphyrin, even in EPP patients with hepatic failure.

Treatment

Exposure to sunlight should be avoided, which is aided by wearing closely woven clothing. A systematic review of treatment options, including beta-carotene, oral cysteine, and vitamin C, showed no proven efficacy of these treatments. One report suggested that high doses of cimetidine were effective in reducing symptoms in 3 children with EPP, but no objective clinical evidence of efficacy was presented.

Measures to darken the skin may also be helpful. This may be accomplished by narrow-band UV-B phototherapy. Double-blind, placebo-controlled studies in the United States and Europe of **afamelanotide** , a synthetic analog of melanocyte-stimulating hormone, showed an increase in pain-free sun exposure and improved quality of life in patients with protoporphyria. This drug is approved for adult use in Europe and is pending U.S. Food and Drug Administration (FDA) approval, and studies in children are anticipated.

Drugs or hormone preparations that impair hepatic excretory function should be avoided, particularly in patients with liver dysfunction, and iron deficiency should be corrected if present, especially in XLP. Vitamin D supplementation and hepatitis A and B vaccination are recommended.

Treatment of protoporphyric hepatopathy must be individualized, and results are unpredictable. Ursodeoxycholic acid may be of some value in early stages. Cholestyramine or activated charcoal may interrupt the enterohepatic circulation of protoporphyrin, promote its fecal excretion, and reduce liver protoporphyrin content. Spontaneous resolution may occur, especially if another reversible cause of liver dysfunction, such as viral hepatitis or alcohol abuse, is contributing. In patients with severe hepatic decompensation, combined treatment with plasmapheresis, transfusion to correct anemia and suppress erythropoiesis, IV hemin to suppress erythroid and possibly hepatic protoporphyrin production, ursodeoxycholic acid, vitamin E, and cholestyramine may be beneficial and bridge patients to liver transplantation.

Motor neuropathy resembling that seen in acute porphyrias sometimes develops in protoporphyria patients with liver disease before or after transfusion or liver transplantation and is sometimes reversible. Artificial lights, such as operating room lights during liver transplantation or other surgery, may cause severe photosensitivity, with extensive burns of the skin and peritoneum and damage to circulating erythrocytes.

Although liver disease may recur in the transplanted liver as a result of continued bone marrow production of excess protoporphyrin, outcomes are comparable to transplantation for other types of liver disease. Bone marrow transplantation should also be considered after liver transplantation if a suitable donor is available.

Prognosis

Typical EPP patients have lifelong photosensitivity but can otherwise expect normal longevity. Protoporphyric liver disease is often life-threatening; however, the incidence is low.

Prevention and Genetic Counseling

Symptoms can be prevented by avoiding sunlight. Avoiding agents that may cause liver damage may help prevent liver complications. Opinions vary on the value of iron replacement, and this is currently under study.

DNA studies to identify *FECH* mutations, the common IVS3–48T>C *FECH* hypoexpression allele, or *ALAS2* exon 11 deletions are important for genetic counseling. When EPP is caused by a severe *FECH* mutation and the common IVS3–48T>C *FECH* allele, DNA studies in the spouse to determine the presence, or more likely the absence, of the hypoexpression allele can predict whether offspring are at risk for EPP. EPP may improve during pregnancy.

Dual Porphyria

An unusual pattern of porphyrin precursors and porphyrins may suggest mutations of 2 heme pathway enzymes, as documented in 2 patients. One presented with acute porphyria and had heterozygous mutations of both *CPOX* and *ALAD* . The other had symptoms of AIP and PCT and was reported to have both *HMBS* and *UROD* mutations. In other reported cases, 1 or both enzyme deficiencies were based on enzyme measurements.

Porphyria Resulting From Tumors

Very rarely, hepatocellular tumors contain and presumably produce excess porphyrins, but such cases have not been studied carefully. Hepatocellular carcinomas complicating PCT and acute hepatic porphyrias usually are not described as containing large amounts of porphyrins. Erythropoietic porphyrias can develop late in life from clonal expansion of erythroid cells containing a specific enzyme deficiency in patients who have developed myelodysplastic or myeloproliferative syndromes.

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[*] Hemin is the generic name for all heme preparations used for intravenous administration. Hemin is also a chemical term that refers to the oxidized (ferric) form of heme (iron protoporphyrin IX) and is usually isolated as hemin chloride. In alkaline solution, the chloride is replaced by the hydroxyl ion, forming hydroxyheme, or hematin.

CHAPTER 111

Hypoglycemia

Mark A. Sperling

Glucose has a central role in fuel economy and is a source of energy storage in the form of glycogen, fat, and protein (see Chapter 105). As an immediate source of energy, glucose provides 38 mol of adenosine triphosphate (ATP) per mole of glucose oxidized. Glucose is essential for energy metabolism in the brain, where it is usually the preferred substrate and where its utilization accounts for nearly all the brain's oxygen consumption. Cerebral transport of glucose is a GLUT-1, carrier-mediated, facilitated diffusion process that is dependent on blood glucose concentration and not regulated by insulin. Therefore, low concentrations of blood glucose result in cerebral glucopenia. Deficiency of brain glucose transporters can result in seizures because of low cerebral and cerebrospinal fluid (CSF) glucose concentrations *(hypoglycorrhachia)* despite normal blood glucose levels. To maintain the blood glucose concentration and prevent it from falling precipitously to levels that impair brain function, an elaborate regulatory system has evolved.

The defense against hypoglycemia includes the autonomic nervous system and hormones that act in concert to enhance glucose production through enzymatic modulation of glycogenolysis and gluconeogenesis, while simultaneously limiting peripheral glucose utilization, which conserves glucose for cerebral metabolism. Hypoglycemia represents a defect in one or several of the complex interactions that normally integrate glucose homeostasis during feeding and fasting. This process is particularly important for neonates, in whom there is an abrupt transition from intrauterine life, characterized by dependence on transplacental glucose supply, to extrauterine life, characterized ultimately by the autonomous ability to maintain euglycemia. Because prematurity or placental insufficiency may limit tissue nutrient deposits, and genetic abnormalities in enzymes or hormones may become evident in the neonate, hypoglycemia is common in the neonatal period.

Definition

In neonates, there is not always an obvious correlation between blood glucose concentration and the classic clinical manifestations of hypoglycemia. The absence of symptoms does not indicate that glucose concentration is normal and has not fallen to less than some optimal level for maintaining brain metabolism. There is evidence that hypoxemia and ischemia may potentiate the role of hypoglycemia in causing permanent brain sequelae. Consequently, the lower limit of accepted normality of the blood glucose level in newborn infants with associated illness that already impairs cerebral metabolism has not been determined (see Chapter 127). Because of concern for possible neurologic, intellectual, or psychologic sequelae in later life, most authorities recommend that any value of blood glucose <55 mg/dL in neonates be viewed with suspicion, investigated, and vigorously treated if there are symptoms or it persists or recurs after a meal. This is particularly applicable after the initial 2-3 hr of life, when glucose normally has reached its nadir; subsequently, blood glucose levels begin to rise and achieve values of 55-65 mg/dL or higher after 12-24 hr. By day 3 of life in normal full-term newborns, blood glucose averages approximately 65 mg/dL (range 65-100). Therefore, in otherwise normal, full-term infants after day 3 of life and in older infants and children, a whole blood glucose concentration <55 mg/dL (10–15% higher for serum or plasma) represents hypoglycemia, because counter-regulatory mechanisms are activated at these glucose concentrations. In older children an idealized definition of hypoglycemia is based on “Whipple's Triad”; a plasma glucose concentration less than 60 mg/dL, together with concurrent CNS- or catecholamine-based symptoms, and resolution of symptoms when glucose concentration is restored to normal by treatment with glucose.

Significance and Sequelae

Most of the endogenous hepatic glucose production in infants and young children, which occurs several hours after feeding and during fasting, can be accounted for by brain metabolism.

Because the brain grows most rapidly in the 1st yr of life, and the larger proportion of glucose turnover is used for brain metabolism, sustained or repetitive hypoglycemia in infants and children can retard brain development and function. *Transient isolated and asymptomatic hypoglycemia of short duration does not appear to be associated with these severe sequelae.* In the rapidly growing brain, glucose may also be a source of membrane lipids and, together with protein synthesis, can provide structural proteins and myelination important for normal brain maturation. Under conditions of severe and sustained hypoglycemia, these cerebral structural substrates may become degraded to energy-usable intermediates such as lactate, pyruvate, amino acids, and ketoacids, which can support brain metabolism at the expense of brain growth. The capacity of the newborn brain to take up and oxidize ketone bodies is about 5-fold greater than that of the adult brain. However, the capacity of the liver to produce ketone bodies is limited in the immediate newborn period, especially in the presence of **hyperinsulinism** , which acutely inhibits hepatic glucose output, lipolysis, and ketogenesis, thereby depriving the brain of any alternate fuel sources. Although the brain may metabolize ketones, these alternate fuels cannot completely replace glucose as an essential central nervous system (CNS) fuel. The deprivation of the brain's major energy source during hypoglycemia and particularly the limited availability of alternate fuel sources during hyperinsulinism have predictable adverse consequences on brain metabolism and growth: decreased brain oxygen consumption and increased breakdown of endogenous structural components, with destruction of functional membrane integrity.

The major long-term sequelae of **severe, prolonged hypoglycemia** are cognitive impairment, recurrent seizure activity, cerebral palsy, and autonomic dysregulation. Subtle effects on personality are also possible but have not been clearly defined. Permanent neurologic sequelae are present in 25–50% of patients <6 mo old with severe recurrent symptomatic hypoglycemia. These sequelae may be reflected in pathologic changes characterized by reduced myelination in cerebral white matter and atrophy of the cerebral cortex, reflected in enlargement of the sulci and thinning of the gyri of the brain. These sequelae also are more likely when alternative fuel sources are limited, as occurs with hyperinsulinism, when the episodes of hypoglycemia are repetitive or prolonged, or when they are compounded by hypoxia. There is no precise knowledge relating the duration or severity of hypoglycemia to subsequent neurologic development of children in a predictable manner. Although less common, hypoglycemia in older children may also produce long-term neurologic defects through neuronal death mediated, in part, by cerebral excitotoxins released during hypoglycemia.

Substrate, Enzyme, and Hormonal Integration of Glucose Homeostasis

In the Newborn

Under nonstressed conditions, fetal glucose is derived entirely from the mother through placental transfer. Therefore, fetal glucose concentration usually reflects, but is slightly lower than, maternal glucose levels. Catecholamine release, which occurs with fetal stress such as hypoxia, mobilizes fetal glucose and free fatty acids (FFAs) through β-adrenergic mechanisms, reflecting β-adrenergic activity in fetal liver and adipose tissue. Catecholamines may also inhibit fetal insulin and stimulate glucagon release.

The acute interruption of maternal glucose transfer to the fetus at delivery imposes an immediate need to mobilize endogenous glucose. Three related events facilitate this transition: changes in hormones, changes in their receptors, and changes in key enzyme activity. There is a 3-5–fold abrupt increase in glucagon concentration within minutes to hours of birth. The insulin level usually falls initially and remains in the basal range for several days, without demonstrating the usual brisk response to physiologic stimuli such as glucose. A dramatic surge in spontaneous catecholamine secretion is also characteristic. Epinephrine can also augment growth hormone (GH) secretion by α-adrenergic mechanisms; GH levels are markedly elevated at birth. In addition, cortisol levels are higher in the immediate newborn period in infants born vaginally than by cesarean birth, in part reflecting the stress of labor on fetal cortisol secretion. Acting in concert, these hormonal changes at birth mobilize glucose by glycogenolysis and gluconeogenesis, activate lipolysis, and promote ketogenesis. As a result of these processes, plasma glucose concentration stabilizes after a transient decrease immediately after birth; liver glycogen stores become rapidly depleted within hours of birth; and gluconeogenesis from alanine, a major gluconeogenic amino acid, can account for approximately 10% of glucose turnover in the human newborn infant by several hours of age. FFA concentrations also increase sharply in concert with the surges in glucagon and epinephrine, followed later by rises in ketone bodies. Glucose is thus partially spared for brain utilization while FFAs and ketones provide alternative fuel sources for muscle as well as essential gluconeogenic factors such as acetyl-coenzyme A (CoA) and the reduced form of nicotinamide adenine dinucleotide from hepatic fatty acid oxidation, which is required to drive gluconeogenesis.

In the early postnatal period, responses of the endocrine pancreas favor glucagon secretion so that blood glucose concentration can be maintained. These adaptive changes in hormone secretion are paralleled by similarly striking adaptive changes in hormone receptors. Key enzymes involved in glucose production also change dramatically in the perinatal period. Thus, there is a rapid fall in glycogen synthase activity and a sharp rise in phosphorylase activity after delivery. Similarly, the activity of the rate-limiting enzyme for gluconeogenesis, phosphoenolpyruvate carboxykinase, rises dramatically after birth, activated in part by the surge in glucagon and the fall in insulin. This framework can explain several causes of neonatal hypoglycemia based on inappropriate changes in hormone secretion and unavailability of adequate reserves of **substrates** in the form of hepatic glycogen, **muscle** as a source of amino acids for gluconeogenesis, and **lipid** stores for the release of fatty acids. In addition, appropriate activities of key enzymes governing glucose homeostasis are required (see Fig. 105.1).

In Older Infants and Children

Hypoglycemia in older infants and children is analogous to that of adults, in whom glucose homeostasis is maintained by glycogenolysis in the immediate postfeeding period and by gluconeogenesis several hours after meals. The liver of a 10 kg child contains 20-25 g of glycogen, which is sufficient to meet normal glucose requirements of 4-6 mg/kg/min for only 6-12 hr. Beyond this period, hepatic gluconeogenesis must be activated. Both glycogenolysis and gluconeogenesis depend on the metabolic pathway summarized in Fig. 105.1 . Defects in glycogenolysis or gluconeogenesis may not be manifested in infants until the frequent feeding at 3-4 hr intervals ceases and infants sleep through the night, a situation usually present by 3-6 mo of age. The source of gluconeogenic precursors is derived primarily from muscle protein. The muscle bulk of infants and small children is substantially smaller relative to body mass than that of adults, whereas glucose requirements per unit of body mass are greater in children. Therefore the ability to compensate for glucose deprivation by gluconeogenesis is more limited in infants and young children, as is the ability to withstand fasting for prolonged periods. The ability of muscle to generate *alanine,* the principal gluconeogenic amino acid, may also be limited. Thus, in normal young children, the blood glucose level falls after 24 hr of fasting, insulin concentrations fall appropriately to levels of <5 µU/mL, lipolysis and ketogenesis are activated, and ketones may appear in the urine.

The switch from glycogen synthesis during and immediately after meals to glycogen breakdown and later gluconeogenesis is governed by hormones, with insulin of central importance. After a meal, plasma insulin concentrations increase to peak levels of 5-10–fold greater than their normal baseline concentration of approximately 5-10 µU/mL, which serves to lower the blood glucose concentration through the activation of glycogen synthesis, enhancement of peripheral glucose uptake, and inhibition of glucose production. In addition, lipogenesis is stimulated, whereas lipolysis and ketogenesis are curtailed. During fasting, plasma insulin concentrations fall to ≤5 µU/mL, and together with the rise of counter-regulatory hormones, this fall in insulin results in activation of gluconeogenic pathways (see Fig. 105.1). Fasting glucose concentrations are maintained through the activation of glycogenolysis and gluconeogenesis, inhibition of glycogen synthesis, and activation of lipolysis and ketogenesis. It should be emphasized that a plasma insulin concentration of >5 µU/mL, in association with a blood glucose concentration of ≤55 mg/dL (2.8-3.0 mM), is abnormal, indicating a state of excessive insulin action, termed *hyperinsulinism,* caused by failure of the mechanisms that normally result in suppression of insulin secretion during fasting or hypoglycemia.

The hypoglycemic effects of insulin are opposed by the actions of several hormones whose concentration in plasma increases as blood glucose falls. These counter-regulatory hormones—glucagon, growth hormone, cortisol, and epinephrine—act synergistically and in concert to increase blood glucose concentrations by activating glycogenolytic enzymes (glucagon, epinephrine); inducing gluconeogenic enzymes (glucagon, cortisol); inhibiting glucose uptake by muscle (epinephrine, growth hormone, cortisol); mobilizing amino acids from muscle for gluconeogenesis (cortisol); activating lipolysis and thereby providing glycerol for gluconeogenesis and fatty acids for ketogenesis (epinephrine, cortisol, GH, glucagon); and inhibiting insulin release and promoting GH and glucagon secretion (epinephrine).

Congenital or acquired deficiency of any one of these hormones is uncommon but will result in hypoglycemia, which occurs when endogenous glucose production cannot be mobilized to meet energy needs in the postabsorptive state, that is, 4-6 hr in the newborn and 8-12 hr after meals or during fasting in an infant or child. Concurrent deficiency of several hormones (**hypopituitarism-ACTH-cortisol deficiency combined with GH deficiency**) may result in hypoglycemia that is more severe or appears earlier during fasting than that seen with isolated hormone deficiencies. Most of the causes of hypoglycemia in neonates, infants, and children reflect inappropriate adaptation to fasting as a result of (1) excess insulin action, (2) inadequate counter-regulatory hormone response primarily of cortisol and GH, (3) enzymatic defects in the mechanisms for glycogen storage and release, or (4) defects in gluconeogenesis.

Clinical Manifestations

See Chapter 127 .

Clinical features of hypoglycemia generally fall into 2 categories: (1) symptoms associated with the activation of the autonomic nervous system and epinephrine release, usually seen with a rapid decline in blood glucose concentration and (2) symptoms caused by decreased cerebral glucose utilization (**cerebral glucopenia**), usually associated with a slow decline in blood glucose level or prolonged hypoglycemia (Table 111.1). Although these classic symptoms occur in older children, the symptoms of hypoglycemia in newborns and infants may be subtler and include cyanosis, apnea, hypothermia, hypotonia, poor feeding, lethargy, and seizures, all reflecting the deprivation of glucose for normal brain activity. Some of these symptoms may be so mild that they are missed. Occasionally, hypoglycemia may be asymptomatic in the immediate newborn period. Newborns with hyperinsulinism are often large for gestational age (LGA), mimicking the features of the infant born to a mother with poorly controlled diabetes. Older infants with hyperinsulinism may eat excessively because of chronic hypoglycemia and become obese. In childhood, hypoglycemia may present as behavior problems, inattention, ravenous appetite, or seizures. It may be misdiagnosed as epilepsy, inebriation, personality disorders, headache, hysteria, and developmental delay. A blood glucose determination should always be performed in sick neonates, who should be vigorously treated if concentrations are <55 mg/dL. At any age, hypoglycemia should be considered a cause of an initial episode of convulsions or a sudden deterioration in psychobehavioral functioning or level of consciousness.

Table 111.1

Manifestations of Hypoglycemia in Childhood

Features Associated With Activation of Autonomic Nervous System and Epinephrine Release*

Anxiety [†]
Perspiration [†]
Palpitation (tachycardia) [†]
Pallor [‡]
Tremulousness [‡]
Weakness
Hunger
Nausea
Emesis

Features Associated With Cerebral Glucopenia

Headache [†]
Mental confusion [†]
Visual disturbances (↓ acuity, diplopia) [†]
Organic personality changes [†]
Inability to concentrate [†]
Dysarthria
Staring
Paresthesias
Dizziness
Amnesia
Ataxia, incoordination
Refusal to feed [‡]
Somnolence, lethargy [‡]
Seizures [‡]
Coma
Stroke, hemiplegia, aphasia
Decerebrate or decorticate posture

[*] Some of these features will be attenuated if the patient is receiving β-adrenergic blocking agents.

[†] Common.

[‡] Most common manifestations in the newborn.

Many neonates have asymptomatic (chemical) hypoglycemia. The incidence of symptomatic hypoglycemia is highest in small-for-gestational-age (SGA) infants (Fig. 111.1). The exact incidence of symptomatic hypoglycemia has been difficult to establish because many of the symptoms in neonates occur together with other conditions, such as infections, especially sepsis and meningitis; CNS anomalies, hemorrhage, or edema; hypocalcemia and hypomagnesemia; asphyxia; drug withdrawal; apnea of prematurity; congenital heart disease; or polycythemia.

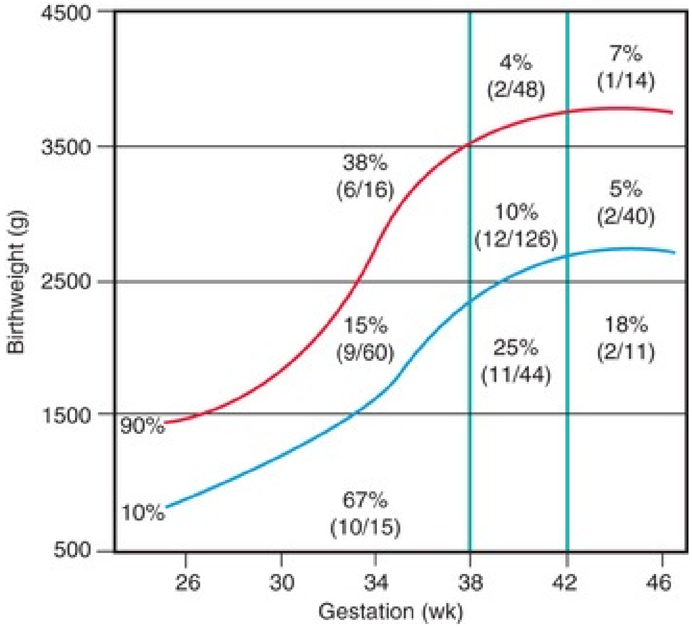

FIG. 111.1 Incidence of hypoglycemia by birthweight, gestational age, and intrauterine growth. (From Lubchenco LO, Bard H: Incidence of hypoglycemia in newborn infants classified by birthweight and gestational age, *Pediatrics* 47:831–838, 1971.)

The onset of symptoms in neonates varies from a few hours to a week after birth. In approximate order of frequency, symptoms include jitteriness or tremors, apathy, episodes of cyanosis, seizures, intermittent apneic spells or tachypnea, weak or high-pitched cry, limpness or lethargy, difficulty feeding (latching on), and eye rolling. Episodes of sweating, sudden pallor, hypothermia, and cardiac arrest and failure may also occur. Frequently, a clustering of episodic symptoms may be noted. Because these clinical manifestations may result from various causes, it is critical to measure serum glucose levels and determine whether symptoms disappear with the administration of sufficient glucose to raise the blood glucose to normal levels; if they do not, other diagnoses must be considered.

Classification of Hypoglycemia in Infants and Children

Classification is based on knowledge of the control of glucose homeostasis in infants and children (Table 111.2).

Table 111.2

Classification of Hypoglycemia in Infants and Children

Neonatal Transitional (Adaptive) Hypoglycemia

Associated With Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates

- Prematurity
- Small for gestational age
- Normal newborn

Transient Neonatal Hyperinsulinism

- Infant of diabetic mother
- Small for gestational age
- Discordant twin
- Birth asphyxia
- Infant of toxemic mother

Neonatal, Infantile, or Childhood Persistent Hypoglycemia

Hyperinsulinism

Recessive K_{ATP} channel HI
Recessive HADH (hydroxyl acyl-CoA dehydrogenase) mutation HI
Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI
Focal K_{ATP} channel HI
Dominant K_{ATP} channel HI
Atypical congenital hyperinsulinemia (no mutations in *ABCC8* or *KCN11* genes)
Dominant glucokinase HI
Dominant glutamate dehydrogenase HI (hyperinsulinism-hyperammonemia syndrome)
Dominant mutations in HNF-4A and HNF-1A (hepatocyte nuclear factors 4α and 1α) HI with monogenic diabetes of youth later in life
Dominant mutation in SLC16A1 (the pyruvate transporter)—exercise-induced hypoglycemia
Activating mutations in the calcium channel CACNA1D (permit calcium influx and thus unregulated insulin secretion)
Acquired or familial islet adenoma associated with mutations in *MEN1* gene
Beckwith-Wiedemann syndrome
Kabuki syndrome
Insulin administration (Munchausen syndrome by proxy)
Oral sulfonylurea drugs
Congenital disorders of glycosylation

Counter-Regulatory Hormone Deficiency

Panhypopituitarism
Isolated growth hormone deficiency
Adrenocorticotropic hormone deficiency
Addison disease (including congenital adrenal hypoplasia, adrenal leukodystrophy, triple A syndrome, ACTH receptor deficiency, and autoimmune disease complex)
Epinephrine deficiency

Glycogenolysis and Gluconeogenesis Disorders

Glucose-6-phosphatase deficiency (GSD Ia)
Glucose-6-phosphate translocase deficiency (GSD Ib)
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD III)
Liver phosphorylase deficiency (GSD VI)
Phosphorylase kinase deficiency (GSD IX)
Glycogen synthetase deficiency (GSD 0)
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
Galactosemia
Hereditary fructose intolerance

Lipolysis Disorders

Fatty Acid Oxidation Disorders

Carnitine transporter deficiency (primary carnitine deficiency)
Carnitine palmitoyltransferase-1 deficiency
Carnitine translocase deficiency
Carnitine palmitoyltransferase-2 deficiency
Secondary carnitine deficiencies
Very-long-, long-, medium-, short-chain acyl-CoA dehydrogenase deficiency

Other Etiologies

Substrate-Limited Causes

Ketotic hypoglycemia
Poisoning—drugs
Salicylates
Alcohol
Oral hypoglycemic agents
Insulin
Propranolol
Pentamidine
Quinine

Disopyramide
Ackee fruit (unripe)—hypoglycin
Litchi – associated toxin (toxic hypoglycemic syndrome).
Vacor (rat poison)
Trimethoprim-sulfamethoxazole (with renal failure)
L -Asparaginase and other antileukemic drugs

Liver Disease

Reye syndrome
Hepatitis
Cirrhosis
Hepatoma

Amino Acid and Organic Acid Disorders

Maple syrup urine disease
Propionic acidemia
Methylmalonic acidemia
Tyrosinosis
Glutaric aciduria
3-Hydroxy-3-methylglutaric aciduria

Systemic Disorders

Sepsis
Carcinoma/sarcoma (secreting—insulin-like growth factor II)
Heart failure
Malnutrition
Malabsorption
Antiinsulin receptor antibodies
Antiinsulin antibodies
Neonatal hyperviscosity
Renal failure
Diarrhea
Burns

Shock
Chiari malformation
Postsurgical complication
Pseudohypoglycemia (leukocytosis, polycythemia)
Excessive insulin therapy of insulin-dependent diabetes mellitus
Factitious disorder
Nissen fundoplication (dumping syndrome)
Falciparum malaria

GSD, Glycogen storage disease; HI, hyperinsulinemia; K_{ATP} , regulated potassium channel.

Neonatal, Transient, Small-for-Gestational-Age, and Premature Infants

The estimated incidence of symptomatic hypoglycemia in newborns is 1-3 in 1,000 live births. This incidence is increased several fold in certain high-risk neonatal groups (see Table 111.2 and Fig. 111.1). Premature and SGA infants are vulnerable to the development of hypoglycemia. The factors responsible for the high frequency of hypoglycemia in this group, as well as in other groups outlined in Table 111.2 , are related to the inadequate stores of liver glycogen, muscle protein, and body fat needed to sustain the substrates required to meet energy needs. These infants are small by virtue of prematurity or impaired placental transfer of nutrients. Their enzyme systems for gluconeogenesis may not be fully developed. **Transient hyperinsulinism** responsive to diazoxide has also been reported as contributing to hypoglycemia in asphyxiated, SGA, and premature newborn infants. This form of hyperinsulinism, associated with perinatal asphyxia, intrauterine growth restriction, maternal toxemia, and other perinatal stressors, is probably the most common cause of hyperinsulinemic hypoglycemia in neonates and may be quite severe. In most patients the condition resolves quickly, but it may persist to 7 mo of life or longer.

In contrast to deficiency of substrates or enzymes, the hormonal system appears to be functioning normally at birth in most low-risk neonates. Despite hypoglycemia, plasma concentrations of alanine, lactate, and pyruvate are higher, implying their diminished rate of utilization as substrates for gluconeogenesis. Infusion of alanine elicits further glucagon secretion but causes no significant rise in glucose. During the initial 24 hr of life, plasma concentrations of acetoacetate and β-hydroxybutyrate are lower in SGA infants than in full-term infants, implying diminished lipid stores, diminished fatty acid mobilization, impaired ketogenesis, or a combination of these conditions. Diminished lipid stores most likely occur because fat (triglyceride) feeding of newborns results in elevated plasma levels of glucose, ketones such as β-hydroxybutyrate, and FFAs. For infants with perinatal asphyxia and SGA newborns who have transient hyperinsulinism, the combination of hypoglycemia together with diminished concentrations of β-hydroxybutyrate and FFAs are the diagnostic hallmarks of hyperinsulinism.

The role of FFAs and their oxidation in stimulating neonatal gluconeogenesis is essential. The provision of FFAs as triglyceride feedings from formula or human milk together with gluconeogenic precursors may prevent the hypoglycemia that usually ensues after neonatal fasting. For these and other reasons, milk feedings are introduced early (at birth or within 2-4 hr) after delivery. In the hospital setting, when feeding is precluded by virtue of respiratory distress or other illness, or when feedings alone cannot maintain blood glucose concentrations at levels >55 mg/dL, intravenous (IV) glucose at a rate that supplies 4-8 mg/kg/min should be started. Infants with transient neonatal hypoglycemia can usually maintain the blood glucose level spontaneously after 2-3 days of life, but some require longer periods of support. In these latter infants, insulin values >5 µU/mL at the time of hypoglycemia should be treated with diazoxide.

Infants Born to Diabetic Mothers

See Chapter 127.1 .

Of the transient hyperinsulinemic states, infants born to diabetic mothers are the most common. Gestational diabetes affects approximately 2% of pregnant women, and 1 in 1,000 pregnant women have insulin-dependent diabetes. At birth, infants born to these mothers may be large and plethoric, and their body stores of glycogen, protein, and fat are replete.

Hypoglycemia in infants of diabetic mothers is mostly related to hyperinsulinemia and partly related to diminished glucagon secretion. Hypertrophy and hyperplasia of the islets is present, as is a brisk, biphasic, and typically mature insulin response to glucose; this brisk insulin response is absent in normal infants. Infants born to diabetic mothers also have a subnormal surge in plasma glucagon immediately after birth, subnormal glucagon secretion in response to stimuli, and initially, excessive sympathetic activity that may lead to adrenomedullary exhaustion, as reflected by decreased urinary excretion of epinephrine. The normal plasma hormonal pattern of low insulin, high glucagon, and high catecholamines is reversed to a pattern of high insulin, low glucagon, and low epinephrine. As a consequence of this abnormal hormonal profile, endogenous glucose production is significantly inhibited compared with that in normal infants, thus predisposing them to hypoglycemia.

Mothers whose diabetes has been well controlled during pregnancy, labor, and delivery generally have infants near normal size who are less likely to develop neonatal hypoglycemia and other complications formerly considered typical of such infants. In supplying exogenous glucose to these hypoglycemic infants, it is important to avoid hyperglycemia that evokes a prompt exuberant insulin release, which may result in **rebound hypoglycemia** . When needed, glucose should be provided at continuous infusion rates of 4-8 mg/kg/min, but the appropriate dose for each patient must be individually adjusted. During labor and delivery, maternal hyperglycemia should be avoided because it results in fetal hyperglycemia, which predisposes to hypoglycemia when the glucose supply is interrupted at birth. Hypoglycemia persisting beyond day 3 after birth or initially occurring after 1 wk of life requires an evaluation for the causes listed in Table 111.2 .

Infants born with **erythroblastosis fetalis** may also have hyperinsulinemia and share many physical features, such as large body size, with infants born to diabetic mothers. The cause of the hyperinsulinemia in infants with erythroblastosis is not clear.

Persistent or Recurrent Hypoglycemia in Infants and Children

Hyperinsulinism

Most children with hyperinsulinism that causes hypoglycemia present in the neonatal period or later in infancy. Hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy. Infants who have hyperinsulinism may be macrosomic at birth, reflecting the anabolic effects of insulin in utero. There is no history or biochemical evidence of maternal diabetes. The onset of symptoms is from birth to 18 mo of age, but occasionally it only becomes evident in older children.

Insulin concentrations are inappropriately elevated at the time of documented hypoglycemia; with nonhyperinsulinemic hypoglycemia, plasma insulin concentrations should be <5 µU/mL. In affected infants, plasma insulin concentrations at the time of hypoglycemia are usually >5 µU/mL. Some authorities set more stringent criteria, arguing that any value of insulin >2 µU/mL with hypoglycemia is abnormal. The insulin (µU/mL):glucose (mg/dL) ratio is typically >0.4; plasma insulin-like growth factor binding protein-1 (IGFBP-1), β-hydroxybutyrate, and FFA levels are low with hyperinsulinism. Rare instances of activating mutations in the insulin receptor signaling pathway have been reported where the clinical and biochemical features are similar to states of excessive insulin secretion, yet insulin concentrations are low to the point of being undetectable. Therefore, the preferred term is *hyperinsulinism* , to describe a state of increased insulin action. Macrosomic infants may present with hypoglycemia from the 1st days of life. Infants with lesser degrees of hyperinsulinism may manifest hypoglycemia only after the 1st few wk to mo, when the frequency of feedings has been decreased to permit the infant to sleep through the night, and hyperinsulinism prevents the mobilization of endogenous glucose. Increasing appetite and demands for feeding, wilting spells, jitteriness, and frank seizures are the most common presenting features.

Additional clues include the rapid development of fasting hypoglycemia within 4-8 hr of food deprivation, compared with other causes of hypoglycemia (Tables 111.3 and 111.4); the need for high rates of exogenous glucose infusion to prevent hypoglycemia, often at rates >10-15 mg/kg/min; the absence of ketonemia or acidosis; and elevated C-peptide or proinsulin levels at the time of hypoglycemia. The latter insulin-related products are absent in **factitious hypoglycemia** from exogenous administration of insulin as a form of child abuse (see Chapter 16.2). Hypoglycemia is invariably provoked by withholding feedings for several hours, permitting simultaneous measurement of glucose, insulin, ketones, and FFAs in the same sample at the time of clinically manifested hypoglycemia. This is termed the *critical sample.* The glycemic response to glucagon at the time of hypoglycemia reveals a brisk increment in glucose concentration of at least 40 mg/dL, which implies that glucose mobilization has been restrained by insulin but that glycogenolytic mechanisms are intact (Tables 111.5 to 111.7).

Table 111.3

Hypoglycemia in Infants and Children: Clinical and Laboratory Features

GROUP	AGE AT DIAGNOSIS (mo)	GLUCOSE[*] (mg/dL)	INSULIN (μU/mL)	FASTING TIME TO HYPOGLYCEMIA (hr)
Hyperinsulinemia (*N* = 12)				
Mean	7.4	23.1	22.4	2.1 [†]
SEM	2.0	2.7	3.2	0.6
Nonhyperinsulinemia (*N* = 16)				
Mean	41.8	36.1	5.8	18.2
SEM	7.3	2.4	0.9	2.9

[*] In hypoglycemia caused by hyperinsulinism β-hydroxybutyrate and free fatty acids are low compared with normal at same duration of fasting.

[†] Milder forms of hyperinsulinism may require up to 18 hr of fasting to provoke hypoglycemia.

SEM, Standard error of mean.

Adapted from Antunes JD, Geffner ME, Lippe BM, et al: Childhood hypoglycemia: differentiating hyperinsulinemic from nonhyperinsulinemic causes, *J Pediatr* 116:105–108, 1990.

Table 111.4

Correlation of Clinical Features With Molecular Defects in Persistent Hyperinsulinemic Hypoglycemia in Infancy

TYPE	MACROSOMIA	HYPOGLYCEMIA/HYPERINSULINEMIA	FAMILY HISTORY	MOLECULAR DEFECTS
Sporadic	Present at birth	Moderate/severe in 1st days to weeks of life	Negative	? *SUR1* /K_{IR} 6.2 mutations not alw identified in diffus hyperplasia

Autosomal recessive	Present at birth	Severe in 1st days to weeks of life	Positive	*SUR* /K_{IR} 6.2
Autosomal dominant	Unusual	Moderate onset usually >6 mo of age	Positive	Glucokinase (activating) Some cases ge unknown
Autosomal dominant	Unusual	Moderate onset usually >6 mo of age	Positive	Glutamate dehydrogenase (activating)
Beckwith-Wiedemann syndrome	Present at birth	Moderate, spontaneously resolves >6 mo of age	Negative	Duplicating/impri in chromosome 11p15.1
Congenital disorders of glycosylation	Not usual	Moderate/onset >3 mo of age	Negative	Phosphomannose isomerase deficien

Table 111.5

Analysis of Critical Blood Sample During Hypoglycemia and 30 Min After Glucagon*

Substrates

Glucose
Free fatty acids
Ketones
Lactate
Uric acid
Ammonia

Hormones

Insulin
Cortisol

Growth hormone
Thyroxine, thyroid-stimulating hormone
Insulin-like growth factor binding protein-1 [†]

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[*] Glucagon 0.5 mg with maximum of 1 mg IV or IM.

[†] Measure once only before or after glucagon administration. Rise in glucose of ≥40 mg/dL after glucagon given at the time of hypoglycemia strongly suggests a hyperinsulinemic state with adequate hepatic glycogen stores and intact glycogenolytic enzymes. If ammonia is elevated to 100-200 µM, consider activating mutation of glutamate dehydrogenase.

Table 111.6

Criteria for Diagnosing Hyperinsulinism Based on "Critical" Samples (Drawn at a Time of Fasting Hypoglycemia: Plasma Glucose <50 mg/dL)

1. Hyperinsulinemia (plasma insulin >2 µU/mL)*
2. Hypofatty acidemia (plasma free fatty acids <1.5 mmol/L)
3. Hypoketonemia (plasma β-hydroxybutyrate <2.0 mmol/L)
4. Inappropriate glycemic response to glucagon, 1 mg IV (change in glucose >40 mg/dL)

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[*] Depends on sensitivity of insulin assay.

From Stanley CA, Thomson PS, Finegold DN, et al: Hypoglycemia in infants and neonates. In Sperling MA, editor: *Pediatric endocrinology* , ed 2, Philadelphia, 2002, Saunders, pp 135–159.

Table 111.7

Diagnosis of Acute Hypoglycemia in Infants and Children

Acute Symptoms Present

1. Obtain blood sample before and 30 min after glucagon administration.
2. Obtain urine as soon as possible. Examine for ketones; if not present and hypoglycemia confirmed, suspect hyperinsulinemia or fatty acid oxidation defect; if present, suspect ketotic, hormone deficiency, inborn error of glycogen metabolism, or defective gluconeogenesis.
3. Measure glucose in the original blood sample. If hypoglycemia is confirmed, proceed with substrate-hormone measurement as in Table 111.5 .
4. If glycemic increment after glucagon exceeds 40 mg/dL above basal, suspect hyperinsulinemia.
5. If insulin level at time of confirmed hypoglycemia is >5 µU/mL, suspect endogenous hyperinsulinemia; if >100 µU/mL, suspect factitious hyperinsulinemia (exogenous insulin injection). Admit to hospital for supervised fast.
6. If cortisol is <10 µg/dL or growth hormone is <5 ng/mL, or both, suspect adrenal insufficiency or pituitary disease, or both. Admit to hospital for hormonal testing and neuroimaging.

History Suggestive: Acute Symptoms Not Present

1. Careful history for relation of symptoms to time and type of food intake, considering age of patient. Exclude possibility of alcohol or drug ingestion. Assess possibility of insulin injection, salt craving, growth velocity, or intracranial pathology.
2. Careful examination for hepatomegaly (glycogen storage disease; defect in gluconeogenesis); pigmentation (adrenal failure); stature and neurologic status (pituitary disease).
3. Admit to hospital for provocative testing:
    a. 24 hr fast under careful observation; when symptoms provoked, proceed with steps 1-4 as when acute symptoms present.
    b. Pituitary-adrenal function using arginine-insulin stimulation test if indicated.
4. Consider molecular diagnostic test before liver biopsy for histologic and enzyme determinations.

5. Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected (e.g., dumping syndrome).

The measurement of serum IGFBP-1 concentration may help diagnose hyperinsulinism. The secretion of IGFBP-1 is acutely inhibited by insulin action; IGFBP-1 concentrations are low during hyperinsulinism-induced hypoglycemia. In patients with spontaneous or fasting-induced hypoglycemia with a low insulin level (ketotic hypoglycemia, normal fasting), IGFBP-1 concentrations are significantly higher.

The differential diagnosis of endogenous hyperinsulinism includes **diffuse β-cell hyperplasia** or **focal β-cell microadenoma** . The distinction between these 2 major entities is important because the diffuse hyperplasia, if unresponsive to medical therapy, requires near-total pancreatectomy, despite which hypoglycemia may persist or diabetes mellitus may ensue later. Some, but not all, affected infants may respond to sirolimus. By contrast, focal adenomas diagnosed preoperatively or intraoperatively permit localized curative resection with subsequent normal glucose metabolism. Approximately 50% of the autosomal recessive or sporadic forms of neonatal/infantile hyperinsulinism are caused by focal microadenomas, which may be distinguished from the diffuse form by the pattern of insulin response to selective insulin secretagogues infused into an arterial branch supplying the pancreas, with sampling by the hepatic vein. However, these invasive and technically difficult procedures have been largely abandoned in favor of positron emission tomography (PET) using 18-fluoro-L -dopa. This technique can distinguish the diffuse form (uniform fluorescence throughout the pancreas) from the focal form (focal uptake of 18-fluoro-L -dopa and localized fluorescence) with an extremely high degree of reliability, success, specificity, and sensitivity (see Fig. 111.3).

Insulin-secreting **macroadenomas** are rare in childhood and may be diagnosed preoperatively by CT or MRI. The plasma levels of insulin alone, however, cannot distinguish the aforementioned entities. The diffuse or microadenomatous forms of islet cell hyperplasia represent a variety of genetic defects responsible for abnormalities in the endocrine pancreas, characterized by autonomous insulin secretion that is not appropriately reduced when blood glucose declines spontaneously or in response to provocative maneuvers such as fasting (see Tables 111.4 , 111.7 , and 111.8). Clinical, biochemical, and molecular genetic approaches permit classification of congenital hyperinsulinism, formerly termed *nesidioblastosis,* into distinct entities.

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) may be inherited or sporadic, is severe, and is caused by mutations that affect the regulation of the potassium channel intimately involved in insulin secretion by the pancreatic β cell (Fig. 111.2). Normally, glucose entry into the β cell is enabled by the non–insulin-responsive glucose transporter GLUT-2. On entry, glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase, enabling glucose metabolism to generate ATP. The rise in the molar ratio of ATP relative to adenosine diphosphate (ADP) closes the ATP-sensitive potassium channel in the cell membrane (K_{ATP} channel). This channel is composed of 2 subunits, the K_{IR} 6.2 channel, part of the family of inward-rectifier potassium channels, and a regulatory component in intimate association with K_{IR} 6.2 known as the *sulfonylurea receptor* (SUR1). Together, K_{IR} 6.2 and SUR1 constitute the potassium-sensitive ATP channel K_{ATP} . Normally, the K_{ATP} is open, but with the rise in ATP and closure of the channel, potassium accumulates intracellularly, causing depolarization of the membrane, opening of voltage-gated calcium channels, influx of calcium into the cytoplasm, and secretion of insulin by exocytosis. The genes for both SUR1 and K_{IR} 6.2 are located close together on the short arm of chromosome 11, the site of the insulin gene.

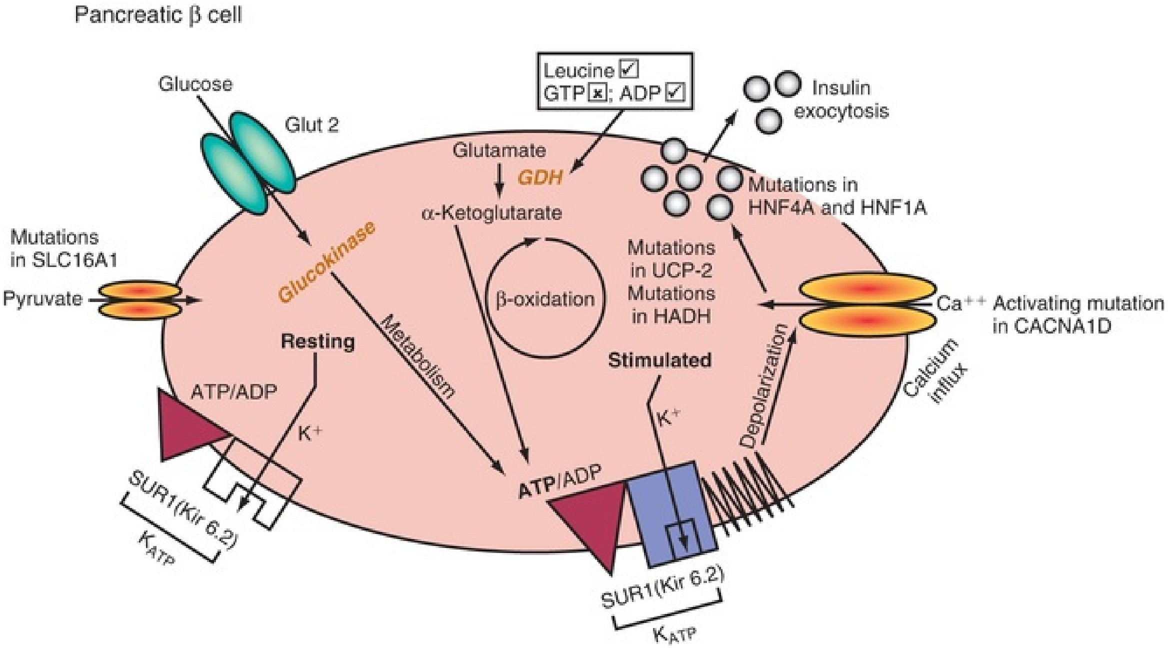
Pancreatic β cell
Glucose
Glut 2
Leucine ☑
GTP ☒; ADP ☑
Insulin exocytosis
Glutamate
GDH
α-Ketoglutarate
Mutations in HNF4A and HNF1A
Mutations in SLC16A1
Pyruvate
Glucokinase
β-oxidation
Mutations in UCP-2
Mutations in HADH
Ca++
Activating mutation in CACNA1D
Resting
Metabolism
Stimulated
Depolarization
Calcium influx
ATP/ADP
K+
SUR1(Kir 6.2)
KATP
ATP/ADP
K+
SUR1(Kir 6.2)
KATP

FIG. 111.2 **Schematic of the pancreatic cell with some important steps in insulin secretion. The membrane-spanning, adenosine triphosphate (ATP)–sensitive potassium**

(K^+) channel (K_{ATP}) consists of 2 subunits: the sulfonylurea receptor (SUR) and the inward rectifying K channel (K_{IR} 6.2). In the resting state, the ratio of ATP to adenosine diphosphate (ADP) maintains K_{ATP} in an open state, permitting efflux of intracellular K^+. When blood glucose concentration rises, its entry into the β cell is facilitated by the Glut-2 glucose transporter, a process not regulated by insulin. Within the β cell, glucose is converted to glucose-6-phosphate by the enzyme glucokinase and then undergoes metabolism to generate energy. The resultant increase in ATP relative to ADP closes K_{ATP}, preventing efflux of K^+, and the rise of intracellular K^+ depolarizes the cell membrane and opens a calcium (Ca^{2+}) channel. The intracellular rise in Ca^{2+} triggers insulin secretion via exocytosis. Sulfonylureas trigger insulin secretion by reacting with their receptor (SUR) to close K_{ATP}; diazoxide inhibits this process, whereas somatostatin, or its analog octreotide, inhibits insulin secretion by interfering with calcium influx. Genetic mutations in SUR1 or K_{IR} 6.2 that prevent K_{ATP} from being open tonically maintain inappropriate insulin secretion and are responsible for autosomal recessive forms of persistent hyperinsulinemic hypoglycemia of infancy (PHHI). One form of autosomal dominant PHHI is caused by an activating mutation in glucokinase. The amino acid leucine also triggers insulin secretion by closure of K_{ATP}. Metabolism of leucine is facilitated by the enzyme glutamate dehydrogenase (GDH), and overactivity of this enzyme in the pancreas leads to hyperinsulinemia with hypoglycemia, associated with hyperammonemia from overactivity of GDH in the liver. Mutations in the pyruvate channel SLC16A1 can cause ectopic expression in the β cell and permit pyruvate, accumulated during exercise, to induce insulin secretion and thus exercise-induced hypoglycemia. Mutations in the mitochondrial uncoupling protein 2 (UCP2) and hydroxyl acyl-CoA dehydrogenase (HADH) are associated with hyperinsulinism (HI) by mechanisms yet to be defined. Mutations in the transcription factors hepatocyte nuclear factors (HNF) 4α and 1α can be associated with neonatal macrosomia and HI, but progress to monogenic diabetes of youth (MODY) later in life. Activating mutations in the calcium channel CACNA1D permit calcium influx and hence unregulated insulin secretion at membrane voltages which normally exclude calcium flux. √, Stimulation; GTP, guanosine triphosphate; X, inhibition.

Inactivating mutations in the gene for SUR1 or, less often, K_{IR} 6.2 prevent the potassium channel from opening; it remains variably closed with constant depolarization and therefore constant inward flux of calcium. Thus, insulin secretion is continuous and not governed by the glucose concentration. A milder autosomal dominant form of these defects is also reported. Similarly, an **activating** mutation in the gene for glucokinase or for glutamate dehydrogenase enzyme activity increases substrate metabolism and results in closure of the potassium channel through overproduction of ATP, which causes hyperinsulinism. Genetic defects in fatty acid metabolism, in the insulin transcription factors HNF-4α and HNF-1α, and in the uncoupling protein UCP-2 of the mitochondrial gene complex also have been involved in hyperinsulinemic hypoglycemia. Most recently, an activating mutation in the calcium channel has been reported to permit flux of calcium into the β cell, resulting in excessive, dysregulated insulin secretion and hypoglycemia that responds to diazoxide. **Inactivating** mutations of the glucokinase gene or **activating** mutations of the ATP-regulated potassium channel, which prevent or limit closure of the channel, are responsible for inadequate insulin secretion and form the basis of some forms of maturity-onset diabetes of youth and neonatal diabetes mellitus (see Chapter

607).

The familial forms of PHHI are more common in certain populations, notably Arabic and Ashkenazi Jewish communities, where it may reach an incidence of approximately 1 in 2,500, compared with the sporadic rates in the general population of 1 in 50,000. These **autosomal recessive forms** of PHHI typically present in the immediate newborn period as macrosomic newborns with a weight frequently >4.0 kg and severe recurrent or persistent hypoglycemia manifesting in the initial hours or days of life. Glucose infusions as high as 15-20 mg/kg/min and frequent feedings fail to maintain euglycemia. **Diazoxide** , which acts by opening K_{ATP} channels, fails to control hypoglycemia adequately. Somatostatin (**octreotide**), which also opens K_{ATP} channels and inhibits calcium flux, may be partially effective in 50% of patients (see Fig. 111.2). Calcium channel–blocking agents have had inconsistent effects. When affected patients are unresponsive to these measures, **pancreatectomy** is strongly recommended to avoid the long-term neurologic sequelae of hypoglycemia. If surgery is undertaken, preoperative CT or MRI rarely reveals an isolated adenoma, which would then permit local resection. Intraoperative ultrasonography may identify a small impalpable adenoma, permitting local resection. Adenomas often present in late infancy or early childhood.

Distinguishing between **focal** and **diffuse** cases of **persistent hyperinsulinism** has been attempted in several ways. Preoperatively, transhepatic portal vein catheterization and selective pancreatic venous sampling to measure insulin may localize a focal lesion from the step-up in insulin concentration at a specific site. Selective catheterization of arterial branches supplying the pancreas, followed by infusion of a secretagogue such as calcium and portal vein sampling for insulin concentration (arterial stimulation–venous sampling) may localize a lesion. Both approaches are highly invasive, restricted to specialized centers, and not uniformly successful in distinguishing the focal from the diffuse forms. Thus these techniques are not recommended and have largely been abandoned. Fluorine 18 (^{18} F)–labeled L -dopa combined with PET scanning is a highly promising means to distinguish the focal from the diffuse lesions of hyperinsulinism unresponsive to medical management (Fig. 111.3). The gold standard remains intraoperative **histologic** characterization. Diffuse hyperinsulinism is characterized by large β cells with abnormally large nuclei, whereas focal adenomatous lesions display small and normal β-cell nuclei. Although *SUR1* mutations are present in both types, the focal lesions arise by a random loss of a maternally imprinted growth-inhibitory gene on maternal chromosome 11p, in association with paternal transmission of a mutated *SUR1* or K_{IR} 6.2 paternal chromosome 11p, expressing the insulin-like growth factor 2 *(IGF2)* gene. Thus the focal form represents a double hit–loss of maternal repressor and transmission of a paternal mutation that contains a growth-promoting gene. This is similar to what occurs in children with the hyperinsulinemic hypoglycemia seen in Beckwith-Wiedemann syndrome, as discussed later.

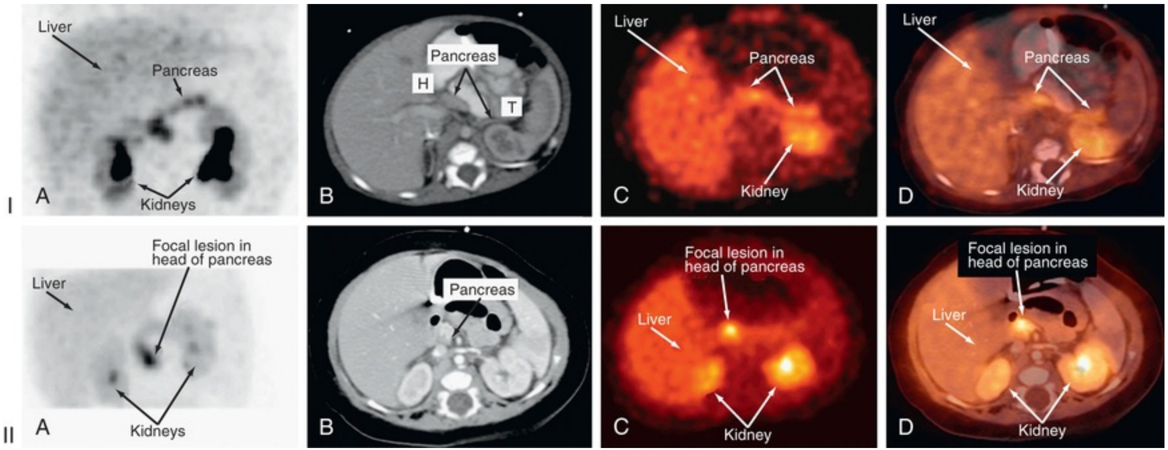
I
A
Liver
Pancreas
Kidneys
B
Pancreas
H
T
C
Liver
Pancreas
Kidney
D
Liver
Pancreas
Kidney
II
A
Focal lesion in head of pancreas
Liver
Kidneys
B
Pancreas
C
Focal lesion in head of pancreas
Liver
Kidney
D
Focal lesion in head of pancreas
Liver
Kidney

FIG. 111.3 Congenital hyperinsulinism. I Panels (*diffuse*): Fluorine 18 (^{18}F)-L -dopa positron emission tomography (PET) of patient with diffuse form of congenital hyperinsulinism. A, Diffuse uptake of ^{18}F-L -dopa is visualized throughout the pancreas. Transverse views show B, normal pancreatic tissue on abdominal CT; C, diffuse uptake of ^{18}F-L -dopa in pancreas; and D, confirmation of pancreatic uptake of ^{18}F-L -dopa with co-registration. H, Head of pancreas; T, tail of pancreas. II Panels (*focal*): ^{18}F-L -dopa PET of patient with focal form of congenital hyperinsulinism. A, Discrete area of increased ^{18}F-L -dopa uptake is visualized in the head of the pancreas. The intensity of this area is greater than that observed in the liver and neighboring normal pancreatic tissue. Transverse views show B, normal pancreatic tissue on abdominal CT; C, focal uptake of ^{18}F-L -dopa in pancreatic head; and D, confirmation of ^{18}F-L -dopa uptake in the pancreatic head with co-registration. (Courtesy of Dr. Olga Hardy, Children's Hospital of Philadelphia.)

Local excision of the focal adenomatous islet cell hyperplasia results in a cure with little or no recurrence. For the diffuse form, near-total resection of 85–90% of the pancreas is recommended. The near-total pancreatectomy required for the diffuse hyperplastic lesions, however, is often associated with persistent hypoglycemia or later development of hyperglycemia or frank, insulin-dependent diabetes mellitus.

Further resection of the remaining pancreas may occasionally be necessary if hypoglycemia recurs and cannot be controlled by medical measures, such as the use of octreotide or diazoxide.

Experienced pediatric surgeons in medical centers equipped to provide the necessary preoperative and postoperative care, diagnostic evaluation, and management should perform surgery. In some patients who have been managed medically, hyperinsulinism and hypoglycemia regress over months. If hypoglycemia first manifests between 3 and 6 mo of age or later, a therapeutic trial using medical approaches with diazoxide, octreotide, and frequent feedings can be attempted for up to 2-4 wk. Failure to maintain euglycemia without undesirable side effects from the drugs may prompt the need for surgery. Some success in suppressing insulin release and correcting hypoglycemia in patients with PHHI has been reported with the use of the long-acting somatostatin analog octreotide. Most cases of neonatal PHHI are sporadic; familial forms permit genetic counseling on the basis of anticipated autosomal recessive inheritance.

A 2nd form of familial PHHI suggests **autosomal dominant inheritance** . The clinical features tend to be less severe, and onset of hypoglycemia is most likely, but not exclusively, to occur beyond the immediate newborn period and usually beyond the period of weaning, at an average age at onset of 1 yr. At birth, macrosomia is rarely observed, and response to diazoxide is almost uniform. The initial presentation may be delayed and rarely may occur as late as 30 yr, unless provoked by fasting. The genetic basis for this autosomal dominant form has not been delineated; it is not always linked to K_{IR} 6.2/*SUR1*. The activating mutation in glucokinase is transmitted in an autosomal dominant manner. If a family history is present, genetic counseling for a 50% recurrence rate can be given for future offspring.

A 3rd form of persistent PHHI is associated with mild and asymptomatic **hyperammonemia** , usually as a sporadic occurrence, although dominant inheritance occurs. Presentation is more like the autosomal dominant form than the autosomal recessive form. Diet and diazoxide control symptoms, but pancreatectomy may be necessary in some patients. The association of hyperinsulinism and hyperammonemia is caused by an inherited or de novo gain-of-function mutation in the enzyme glutamate dehydrogenase. The resulting increase in glutamate oxidation in the pancreatic β cell raises the ATP concentration and thus the ATP/ADP ratio, which closes K_{ATP} , leading to membrane depolarization, calcium influx, and insulin secretion (see Fig. 111.2). In the liver the excessive oxidation of glutamate to β-ketoglutarate may generate ammonia and divert glutamate from being processed to *N* -acetylglutamate, an essential cofactor for removal of ammonia through the urea cycle by activation of the enzyme carbamoyl phosphate synthetase. The hyperammonemia is mild, with concentrations of 100-200 µM/L, and produces no CNS symptoms or consequences, as seen in other hyperammonemic states. Leucine, a potent amino acid for stimulating insulin secretion and implicated in **leucine-sensitive hypoglycemia** , acts by allosterically stimulating glutamate dehydrogenase. Thus, leucine-sensitive hypoglycemia may be a form of the hyperinsulinemia-hyperammonemia syndrome or a potentiation of mild disorders of the K_{ATP} channel; it need not always be associated with a modest increase in serum ammonia.

Hypoglycemia associated with hyperinsulinemia is also seen in approximately 50% of patients with **Beckwith-Wiedemann syndrome** (see Chapter 576). This syndrome is caused by an imprinting disorder (see Chapter 98.8) and characterized by omphalocele, gigantism, macroglossia, microcephaly, and visceromegaly (Fig. 111.4). Distinctive lateral earlobe fissures and facial nevus flammeus are present; hemihypertrophy occurs in many of these infants. Diffuse islet cell hyperplasia occurs in infants with hypoglycemia. The diagnostic and therapeutic approaches are the same as those discussed previously, although microcephaly and slowing of brain development may occur independent of hypoglycemia. Patients with Beckwith-Wiedemann syndrome may acquire tumors, including Wilms tumor, hepatoblastoma, adrenal carcinoma, gonadoblastoma, and rhabdomyosarcoma. This overgrowth syndrome is caused by mutations in the chromosome 11p15.5 region close to the genes for insulin, *SUR1*, K_{IR} 6.2, and *IGF2.* Duplications in this region and genetic imprinting from a defective or absent copy of the maternally derived gene are involved in the variable features and patterns of transmission. Hypoglycemia may resolve in weeks to months of medical therapy. Pancreatic resection may rarely be needed.

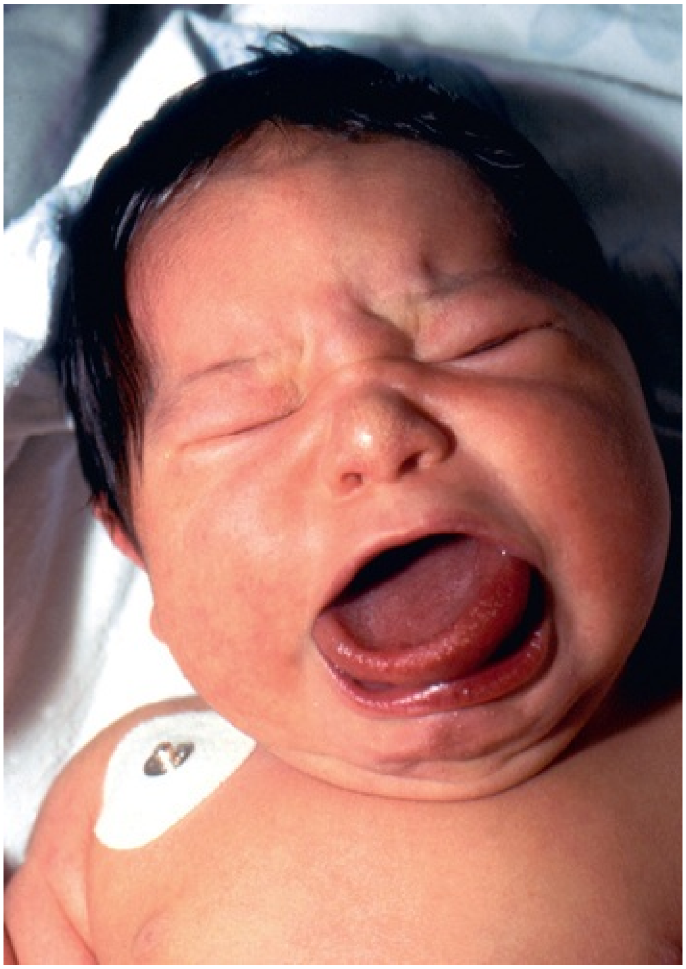

FIG. 111.4 Beckwith-Wiedemann syndrome. (Courtesy of Dr. Michael Cohen, Dalhousie University, Halifax, Nova Scotia. From Jones KL: *Smith's recognizable patterns of human malformation* , ed 6, Philadelphia, 2006, Saunders.)

Kabuki syndrome , caused by mutations in a methyltransferase or demethylase, is the 2nd most common syndromic form of hyperinsulinemic hypoglycemia of infancy (HHI) after Beckwith-Wiedemann Syndrome. Neonatal hypoglycemia with congenital hyperinsulinism occurs in about 70% of children with this syndrome; most are diazoxide responsive. Congenital hyperinsulinemia also is reported to occur in **Turner syndrome** . Activating mutations in *AKT2* and in PI3-kinase of the insulin signaling cascade have been reported in association with hypoketotic hypoglycemia and other metabolic features indicative of excessive insulin action, but insulin concentrations are subnormal as a result of negative feedback from the activated insulin receptor signal.

HHI is reported as a manifestation of 1 form of **congenital disorder of glycosylation** . Disorders of protein glycosylation usually present with neurologic symptoms but may also include liver dysfunction with hepatomegaly, intractable diarrhea, protein-losing enteropathy, and hypoglycemia (see Chapter 105.6). These disorders are often underdiagnosed. One entity associated with HHI is caused by phosphomannose isomerase deficiency, and clinical improvement followed supplemental treatment with oral mannose, 0.17 g/kg 6 times per day.

After the 1st 12 mo of life, hyperinsulinemic states are uncommon until islet cell adenomas reappear as a cause after the patient is several years of age. Hyperinsulinemia as a result of **islet cell adenoma** should be considered in any child ≥5 yr who presents with hypoglycemia. Islet cell adenomas do not “light up” during scanning with ^{18}F-labeled L -dopa. An islet cell adenoma in a child should arouse suspicion of the possibility of **multiple endocrine neoplasia type I** (Wermer syndrome), which involves mutations in the menin gene and may be associated with hyperparathyroidism and pituitary tumors. Tables 111.7 and 111.8 outline the diagnostic approach. In a newborn, fasting for only 6-8 hr (1 missed meal in a 3-4 hr feeding schedule) may be sufficient to provoke hypoglycemia, and this maneuver should be performed to exclude persistent forms of hypoglycemia before discharge from a neonatal unit. In older infants and children, fasting for up to 24-36 hr usually provokes hypoglycemia; coexisting hyperinsulinemia confirms the diagnosis, provided that factitious administration of insulin by the parents is excluded. Occasionally, provocative tests may be required. Exogenously administered insulin can be distinguished from endogenous insulin by simultaneous measurement of C-peptide concentration. If C-peptide levels are elevated, endogenous insulin secretion is responsible for the hypoglycemia; if C-peptide levels are low but insulin values are high, exogenous insulin has been administered, perhaps as a form of child abuse (see Chapter 16.2). Islet cell adenomas at this age are treated by surgical excision. Antibodies to insulin or the insulin receptor (**insulin mimetic action**) are also rarely associated with hypoglycemia. Some **tumors** produce IGFs, thereby provoking hypoglycemia by interacting with the insulin receptor. The astute clinician must also consider the possibility of deliberate or accidental ingestion of drugs such as a sulfonylurea or related compound that stimulates insulin secretion. In such cases, both insulin and C-peptide concentrations in blood will be elevated. Inadvertent substitution of an insulin secretagogue by a dispensing error should be considered in those taking medications who suddenly develop documented hypoglycemia.

Table 111.8

Clinical Manifestations and Differential Diagnosis in Childhood Hypoglycemia

CONDITION	HYPOGLYCEMIA	URINARY KETONES OR REDUCING SUGARS	HEPATOMEGALY	SERUM		EFFECT OF	
				Lipids	Uric Acid	Glucose	Insu
Normal	0	0	0	Normal	Normal	↓	↓
Hyperinsulinemia	Recurrent severe	0	0	Normal or ↑	Normal	↓↓	↑↑
Ketotic hypoglycemia	Severe with missed meals	Ketonuria +++	0	Normal	Normal	↓↓	↓
Fatty acid oxidation disorder	Severe with missed meals	Absent	0 to + Abnormal liver function test results	Abnormal	↑		Con
Hypopituitarism	Moderate with missed meals	Ketonuria ++		Normal	Normal	↓↓	↓
Adrenal insufficiency	Severe with missed meals	Ketonuria ++	0	Normal	Normal	↓↓	↓
Type 1 glycogen storage disease [1]	Severe with missed meals	Ketonuria +++ [2]	+++	↑↑	↑↑	↓↓	↓
Glycogen debrancher	Moderate with fasting	++	++	Normal	Normal	↓↓	↓
GLycogen phosphorylase	Mild-moderate	Ketonuria ++	+	Normal	Normal	↓	↓
Fructose-1,6-diphosphatase	Severe with fasting	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓
Galactosemia	After milk or milk products	0 Ketones;(s) +	+++	Normal	Normal	↓	↓
Fructose intolerance	After fructose	0 Ketones;(s) +	+++	Normal	Normal	↓	↓

[1] Glucose-6-phosphatase deficiency.

[2] Hepatomegaly may not be present in the newborn.

Details of each condition are discussed in the text.

0 absence of ketonuria or hepatomegaly; + mildly detected ketonuria or hepatomegaly; ++ moderately increased; +++ markedly increased; 0, Absence; ↑ or ↓ indicates, respectively, small increase or decrease; ↑↑ or ↓↓ indicates, respectively, large increase or decrease.

A rare form of hyperinsulinemic hypoglycemia has been reported after exercise. Whereas glucose and insulin remain unchanged in most people after moderate, short-term exercise, rare patients manifest severe hypoglycemia with hyperinsulinemia 15-50 min after the same standardized exercise. This form of **exercise-induced hyperinsulinism** is caused by abnormal responsiveness of β-cell insulin release to pyruvate generated during exercise. The gene responsible for this syndrome, *SLC16A1*, regulates a transporter (MCT1R) that controls the entry of pyruvate into cells. Dominant mutations in *SLC16A1* that increase the ectopic expression of MCTR1 in pancreatic β cells permit excessive entry of pyruvate into β cells and act to increase insulin secretion, with resultant hypoglycemia during exercise.

Hypoglycemia with so-called nesidioblastosis has also rarely been reported after **bariatric surgery** for obesity. The mechanism for this form of hyperinsulinemic hypoglycemia remains to be defined.

Infants and children with **Nissen fundoplication** , a relatively common procedure used to ameliorate gastroesophageal reflux, frequently have an associated "dumping" syndrome with hypoglycemia. Characteristic features include significant hyperglycemia of 200 mg/dL and up to 500 mg/dL 30 min postprandially, and severe hypoglycemia (average 32 mg/dL in one series) 1.5-3.0 hr later. The early hyperglycemia phase is associated with brisk and excessive insulin release that causes the rebound hypoglycemia. A role for exaggerated GLP1 secretion has been proposed and glucagon responses have been reported to be inappropriately low in some cases. However, the physiologic mechanisms are not always clearly understood, and attempted treatments not always effective; **acarbose** , an inhibitor of glucose absorption, was reported to be successful in one small series.

Endocrine Deficiencies

Hypoglycemia associated with endocrine deficiency is usually caused by adrenal cortisol insufficiency with or without associated growth hormone deficiency (see Chapters 573 and 593). In **panhypopituitarism** , isolated adrenocorticotropic hormone (ACTH) or GH deficiency, or combined ACTH and GH deficiency, the incidence of hypoglycemia is as high as 20%. In the newborn period, hypoglycemia may be the presenting feature of hypopituitarism; in males, a microphallus may provide a clue to a coexisting deficiency of gonadotropin. Newborns with hypopituitarism often have a form of hepatitis associated with **cholestatic jaundice** and hypoglycemia. The combination of hypoglycemia and cholestatic jaundice requires exclusion of hypopituitarism as a cause, as the jaundice resolves with replacement treatment of GH, cortisol, and thyroid as required. This constellation is often associated with the syndrome of **septooptic dysplasia.** When adrenal disease is severe, as in congenital adrenal hyperplasia caused by enzyme defects in cortisol synthesis, adrenal hemorrhage, or congenital adrenal hypoplasia, serum electrolyte disturbances with hyponatremia and hyperkalemia or disordered genital development may provide diagnostic clues (see Chapter 576). In older children, failure of growth should suggest GH deficiency. Hyperpigmentation, weakness, or salt craving may provide the clue to primary adrenal insufficiency (**Addison disease**), characterized by greatly increased ACTH levels or adrenal unresponsiveness to exogenous ACTH caused by a defect in the adrenal receptor for ACTH, congenital adrenal hypoplasia, adrenoleukodystrophy, or the Allgrove triple A syndrome. The frequent association of Addison disease in childhood with hypoparathyroidism (hypocalcemia), chronic mucocutaneous candidiasis, and other endocrinopathies that constitute the autoimmune polyendocrinopathy syndrome type 1 should be considered. Adrenoleukodystrophy and congenital adrenal hypoplasia are sex-linked conditions and should be considered in the differential diagnosis of primary Addison disease in male children (see Chapter 104.2).

Hypoglycemia in cortisol-GH deficiency may be caused by decreased gluconeogenic enzymes with cortisol deficiency, increased glucose utilization because of a lack of the antagonistic effects of GH on insulin action, or failure to supply endogenous gluconeogenic substrate in the form of alanine and lactate with compensatory breakdown of fat and generation of ketones. Deficiency of these hormones results in reduced gluconeogenic substrate, which resembles the syndrome of ketotic hypoglycemia. Investigation of a child with hypoglycemia therefore requires exclusion of ACTH-cortisol or GH deficiency and, if diagnosed, its appropriate replacement with cortisol or GH.

Epinephrine deficiency could theoretically be responsible for hypoglycemia. Urinary excretion of epinephrine has been decreased in some patients with spontaneous or insulin-induced hypoglycemia in whom absence of pallor and tachycardia were also noted. This suggests that failure of catecholamine release, as the result of a defect anywhere along the hypothalamic-autonomic-adrenomedullary axis, might be responsible for the hypoglycemia. This possibility has been challenged, however, because of the rarity of hypoglycemia in patients with bilateral adrenalectomy, provided that they receive adequate glucocorticoid replacement, and because diminished epinephrine excretion is found in normal patients with repeated insulin-induced hypoglycemia. Many of the patients described as having hypoglycemia with failure of epinephrine excretion fit the criteria for ketotic hypoglycemia (see next). Also, repetitive hypoglycemia leads to diminished cortisol plus epinephrine responses, as seen most often in insulin-treated diabetes mellitus and the syndrome of hypoglycemia unawareness, associated with autonomic failure.

Glucagon deficiency in infants or children may theoretically be associated with hypoglycemia but has never been documented.

Substrate-Limited Etiologies

Ketotic Hypoglycemia

Idiopathic ketotic hypoglycemia is the most common form of *childhood* hypoglycemia. This condition usually presents between ages 18 mo and 5 yr and remits spontaneously by 8-9 yr. Hypoglycemic episodes typically occur during periods of intercurrent illness when food intake is limited. The classic history is of a child who eats poorly or completely avoids the evening meal, is difficult to arouse from sleep the following morning and thus eats poorly again, and may have a seizure or may be comatose by mid-morning. Another common presentation occurs when parents sleep late, and the affected child is unable to eat breakfast, thus prolonging the overnight fast.

At the time of documented hypoglycemia, there is associated marked ketonuria and ketonemia; plasma insulin concentrations are appropriately low, ≤5 µU/mL, thus excluding hyperinsulinemia. A ketogenic-provocative diet, formerly a diagnostic test, is no longer used to establish the diagnosis because fasting alone provokes a hypoglycemic episode with ketonemia and ketonuria within 12-18 hr in susceptible individuals. Normal children of similar age can withstand fasting without hypoglycemia developing during the same period, although even normal children may acquire these features by 36 hr of fasting.

Children with ketotic hypoglycemia have plasma alanine concentrations that are markedly reduced in the basal state after an overnight fast and decline even further with prolonged fasting. **Alanine** , produced in muscle, is a major gluconeogenic precursor. Alanine is the only amino acid that is significantly lower in these children, and infusions of alanine (250 mg/kg) produce a rapid rise in plasma glucose without causing significant changes in blood lactate or pyruvate levels, indicating that the entire gluconeogenic pathway from the level of pyruvate is intact, but that there is a deficiency of substrate. Glycogenolytic pathways are also intact because glucagon induces a normal glycemic response in affected children in the fed state. The levels of hormones that counter hypoglycemia are appropriately elevated, and insulin is appropriately low.

The etiology of ketotic hypoglycemia may be a defect in any of the complex steps involved in protein catabolism, oxidative deamination of amino acids, transamination, alanine synthesis, or alanine efflux from muscle. Children with ketotic hypoglycemia are frequently smaller than age-matched controls and often have a history of transient neonatal hypoglycemia. Any decrease in muscle mass may compromise the supply of gluconeogenic substrate at a time when glucose demands per unit of body weight are already relatively high, thus predisposing the patient to the rapid development of hypoglycemia, with ketosis representing the attempt to switch to an alternative fuel supply. Children with ketotic hypoglycemia may represent the low end of the spectrum of children's capacity to tolerate fasting. Similar relative intolerance to fasting is present in normal children, who cannot maintain blood glucose after 30-36 hr of fasting, compared with the adult's capacity for prolonged fasting. Although the defect may be present at birth, it may not be evident until the child is stressed by more prolonged periods of calorie restriction. Moreover, the spontaneous remission observed in children at age 8-9 yr might be explained by the increase in muscle bulk with its resultant increase in supply of endogenous substrate and the relative decrease in glucose requirement per unit of body mass with increasing age.

In anticipation of spontaneous resolution of this syndrome, **treatment** of ketotic hypoglycemia consists of frequent feedings of a high-protein, high-carbohydrate diet. During intercurrent illnesses, parents should be taught to test the child's urine for the presence of ketones, the appearance of which precedes hypoglycemia by several hours. In the presence of ketonuria, liquids of high carbohydrate content should be offered to the child. If these cannot be tolerated, the child should be treated with IV glucose administration in a hospital.

Branched-Chain Ketonuria (Maple Syrup Urine Disease)

See Chapter 103.6 .

The hypoglycemic episodes were once attributed to high levels of leucine, but evidence indicates that interference with the production of alanine and its availability as a gluconeogenic substrate during calorie deprivation is responsible for hypoglycemia.

Glycogen Storage Disease

See Chapter 105.1 .

Glucose-6-Phosphatase Deficiency (Type I Glycogen Storage Disease)

Affected children usually display a remarkable tolerance to their chronic hypoglycemia; blood glucose values in the range of 20-50 mg/dL are not associated with the classic symptoms of hypoglycemia, possibly reflecting the adaptation of the CNS to ketone bodies and lactate as alternative fuels. Hepatomegaly and poor growth are consistent physical features. Hypoglycemia is associated with acidosis (HCO_3^- <18 mEq/L) and increased β-hydroxybutyrate and lactate; hyperuricemia also is frequently seen. Management is discussed in detail in Chapter 105.1 .

Amylo-1,6-Glucosidase Deficiency (Debrancher Enzyme Deficiency; Type III Glycogen Storage Disease)

See Chapter 105.1 .

Liver Phosphorylase Deficiency (Type VI Glycogen Storage Disease)

Low hepatic phosphorylase activity may result from a defect in any of the steps of activation; a variety of defects have been described. Hepatomegaly, excessive deposition of glycogen in liver, growth retardation, and occasional symptomatic hypoglycemia occur. A diet high in protein and reduced in carbohydrate usually prevents hypoglycemia.

Glycogen Synthetase Deficiency

The inability to synthesize glycogen is rare. Hypoglycemia and hyperketonemia occur after fasting because glycogen reserves are greatly decreased or absent. After feeding, however, hyperglycemia with glucosuria may occur because of the inability to assimilate some of the glucose load into glycogen. During fasting hypoglycemia, levels of the counter-regulatory hormones, including catecholamines, are appropriately elevated or normal, and insulin levels are appropriately low. The liver is not enlarged. Protein-rich feedings at frequent intervals result in dramatic clinical improvement, including growth velocity. Glycogen synthetase deficiency mimics the syndrome of **ketotic hypoglycemia** and should be considered in the differential diagnosis of that syndrome.

Disorders of Gluconeogenesis

Fructose-1,6-Diphosphatase Deficiency

See Chapter 105.3 .

A deficiency of this enzyme results in a block of gluconeogenesis from all possible precursors below the level of fructose-1,6-diphosphate. Infusion of these gluconeogenic precursors results in lactic acidosis without a rise in glucose; acute hypoglycemia may be provoked by inhibition of glycogenolysis. Glycogenolysis remains intact, and glucagon elicits a normal glycemic response in the fed, but not in the fasted, state. Accordingly, affected individuals have hypoglycemia only during caloric deprivation, as in fasting, or during intercurrent illness. As long as glycogen stores remain normal, hypoglycemia does not develop. In affected families, there may be a history of siblings with known hepatomegaly who died in infancy with unexplained metabolic acidosis.

Defects in Fatty Acid Oxidation

See Chapter 104.1 .

The important role of fatty acid oxidation in maintaining gluconeogenesis is underscored by examples of congenital or drug-induced defects in fatty acid metabolism that may be associated with fasting hypoglycemia.

Various congenital enzymatic deficiencies cause defective carnitine or fatty acid metabolism. A severe and relatively common form of fasting hypoglycemia with hepatomegaly, cardiomyopathy, and hypotonia occurs with long- and medium-chain fatty acid CoA dehydrogenase deficiency. Plasma carnitine levels are low, ketones are not present, but dicarboxylic aciduria is present in urine. Clinically, patients with **acyl-CoA dehydrogenase deficiency** present with a Reye-like syndrome (see Chapter 388), recurrent episodes of severe fasting hypoglycemic coma, and cardiorespiratory arrest (sudden infant death syndrome–like events). Severe hypoglycemia and metabolic acidosis without ketosis also occur in patients with multiple acyl-CoA dehydrogenase disorders. Hypotonia, seizures, and acrid odor are other clinical clues. Survival depends on whether the defects are severe or mild; diagnosis is established from studies of enzyme activity in liver biopsy tissue or in cultured fibroblasts from affected patients. Tandem mass spectrometry can be employed for blood samples, even those on filter paper, for screening of congenital inborn errors. Molecular diagnosis also is available for most entities. The frequency of acyl-CoA dehydrogenase deficiency is at least 1 in 10,000-15,000 births. Avoidance of fasting and supplementation with carnitine may be lifesaving in these patients, who generally present in infancy.

Interference with fatty acid metabolism also underlies the fasting hypoglycemia associated with Jamaican vomiting sickness, with atractyloside, and with the drug valproate. In **Jamaican vomiting sickness** the unripe ackee fruit contains a water-soluble toxin, *hypoglycin*, which produces vomiting, CNS depression, and severe hypoglycemia. The hypoglycemic activity of hypoglycin derives from its inhibition of gluconeogenesis secondary to its interference with the acyl-CoA and carnitine metabolism essential for the oxidation of long-chain fatty acids. The disease is almost totally confined to Jamaica, where ackee forms a staple of the diet for the poor population. The ripe ackee fruit no longer contains this toxin.

Atractyloside is a reagent that inhibits oxidative phosphorylation in mitochondria by preventing the translocation of adenine nucleotides, such as ATP, across the mitochondrial membrane. Atractyloside is a perhydrophenanthrenic glycoside derived from *Atractylis gummifera*. This plant is found in the Mediterranean basin; ingestion of this "thistle" is associated with hypoglycemia and a syndrome similar to Jamaican vomiting sickness. A similar illness noted in India, the **acute toxic encephalopathy-hypoglycemic syndrome**, may be caused by litchi consumption. Litchi contains hypoglycin A and/or methylenecyclopropylglycine, which may inhibit fatty acid oxidation or gluconeogenesis.

The anticonvulsant drug **valproate** is associated with side effects, predominantly in young infants, which include a Reye-like syndrome, low serum carnitine levels, and the potential for fasting hypoglycemia.

In all these conditions, hypoglycemia *is not associated with ketonemia and ketonuria.*

Acute Alcohol Intoxication

The liver metabolizes alcohol as a preferred fuel, and generation of reducing equivalents during the oxidation of ethanol alters the reduced form of nicotinamide adenine dinucleotide:nicotinamide adenine dinucleotide ratio, which is essential for certain gluconeogenic steps. As a result, gluconeogenesis is impaired and hypoglycemia may ensue if glycogen stores are depleted by starvation or by preexisting abnormalities in glycogen metabolism. In toddlers who have been unfed for some time, even the consumption of small quantities of alcohol can precipitate these events. The hypoglycemia promptly responds to IV glucose, which should always be considered in a child who presents initially with coma or seizure, after taking a blood sample to determine glucose concentration. The possibility that child ingested alcoholic drinks must also be considered if there was a preceding evening party. A careful history allows the diagnosis to be made and may avoid needless and expensive hospitalization and investigation.

Salicylate Intoxication

See Chapter 77 .

Both hyperglycemia and hypoglycemia occur in children with salicylate intoxication. Accelerated utilization of glucose, resulting from augmentation of insulin secretion by salicylates, and possible interference with gluconeogenesis may contribute to hypoglycemia. Infants are more susceptible than older children. Monitoring of blood glucose levels with appropriate glucose infusion in the event of hypoglycemia should form part of the therapeutic approach to salicylate intoxication in childhood. Ketosis may occur.

Phosphoenolpyruvate Carboxykinase Deficiency

Deficiency of the rate-limiting gluconeogenic enzyme phosphoenolpyruvate carboxykinase is associated with severe fasting hypoglycemia and variable onset after birth. Hypoglycemia may occur within 24 hr after birth, and defective gluconeogenesis from alanine can be documented in vivo. Liver, kidney, and myocardium demonstrate fatty infiltration, and atrophy of the optic nerve and visual cortex may occur. Hypoglycemia may be profound. Lactate and pyruvate levels in plasma have been normal, but a mild metabolic acidosis may be present. The fatty infiltration of various organs is caused by increased formation of acetyl-CoA, which becomes available for fatty acid synthesis. Diagnosis of this rare entity can be made with certainty only through appropriate enzymatic determinations in liver biopsy material or molecular diagnosis. Avoidance of periods of fasting through frequent feedings rich in carbohydrate should be helpful because glycogen synthesis and breakdown are intact.

Pyruvate Carboxylase Deficiency

See Chapter 105.4 .

Other Enzyme Defects

Galactosemia (Galactose-1-Phosphate Uridyl Transferase Deficiency)

See Chapter 105.2 .

Fructose Intolerance (Fructose-1-Phosphate Aldolase Deficiency)

See Chapter 105.3 .

Acute hypoglycemia is caused by fructose-1-phosphate aldolase deficiency, which inhibits glycogenolysis via the phosphorylase system and of gluconeogenesis at the level of fructose-1,6-diphosphate aldolase. Affected individuals usually learn spontaneously to eliminate fructose from their diet.

Defects in Glucose Transporters

GLUT-1 Deficiency

Rarely, infants with a seizure disorder are found to have low CSF glucose concentrations despite normal plasma glucose. Lactate concentrations in CSF are low, suggesting decreased glycolysis rather than bacterial infection, which causes low CSF glucose with high lactate. The erythrocyte glucose transporter (GLUT-1) is defective, suggesting a similar defect in the brain glucose transporter responsible for the clinical features. A ketogenic diet reduces the severity of seizures by supplying an alternate source of brain fuel that bypassed the defect in glucose transport.

GLUT-2 Deficiency

Children with hepatomegaly, galactose intolerance, and renal tubular dysfunction **(Fanconi-Bickel syndrome)** have a deficiency of GLUT-2 of plasma membranes. In addition to liver and kidney tubules, GLUT-2 is also expressed in pancreatic β cells. Thus the clinical manifestations reflect impaired glucose release from liver and defective tubular reabsorption of glucose plus phosphaturia and aminoaciduria**.**

Systemic Disorders

Several systemic disorders are associated with hypoglycemia in infants and children. **Neonatal sepsis** is often associated with hypoglycemia, possibly as a result of diminished caloric intake with impaired gluconeogenesis. Similar mechanisms may apply to the hypoglycemia found in severely malnourished infants or those with severe malabsorption. **Hyperviscosity** with a central hematocrit >65% is associated with hypoglycemia in at least 10–15% of affected infants. **Falciparum malaria** is associated with hyperinsulinemia and hypoglycemia. Heart and renal failure are also associated with hypoglycemia, but the mechanism is obscure.

Diagnosis and Differential Diagnosis

Table 111.8 and Fig. 111.5 list the pertinent clinical and biochemical findings in the common childhood disorders associated with hypoglycemia. A careful and detailed history is essential in every suspected or documented case of hypoglycemia (see Table 111.7). Specific points to note include age at onset, temporal relation to meals or caloric deprivation, and a family history of prior infants known to have had hypoglycemia or of unexplained infant deaths.

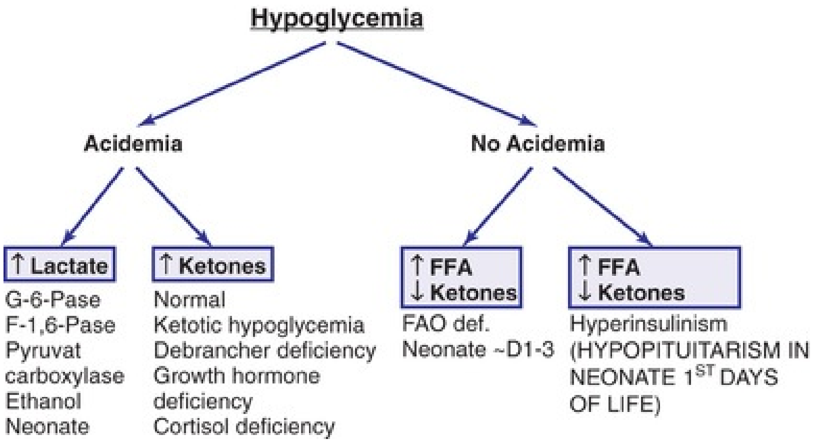
Hypoglycemia
Acidemia
No Acidemia
↑ Lactate
G-6-Pase
F-1,6-Pase
Pyruvat carboxylase
Ethanol
Neonate
↑ Ketones
Normal
Ketotic hypoglycemia
Debrancher deficiency
Growth hormone deficiency
Cortisol deficiency
↑ FFA
↓ Ketones
FAO def.
Neonate ~D1-3
↑ FFA
↓ Ketones
Hyperinsulinism
(HYPOPITUITARISM IN NEONATE 1ST DAYS OF LIFE)

FIG. 111.5 **Algorithm for diagnosis of hypoglycemia based on fasting fuel responses. FFA, Free fatty acids; F-1,6-Pase, fructose-1,6-diphosphatase; G-6-Pase, glucose-6-phosphatase; FAO def., fatty acid oxidation defects; D1-3, Days 1-3 of life.**

In the 1st week of life, most infants have the transient form of neonatal hypoglycemia either as a result of prematurity/intrauterine growth restriction or by virtue of being born to diabetic mothers. The absence of a history of maternal diabetes, but the presence of macrosomia and the characteristic large plethoric appearance of an infant of a diabetic mother, should arouse the possibility of hyperinsulinemic hypoglycemia of infancy, probably resulting from a K_{ATP} channel defect that is familial (autosomal recessive) or sporadic. Decreased β-hydroxybutyrate, low FFAs, and plasma insulin concentration >5 μU/mL or C-peptide >0.5 ng/mL in the presence of documented hypoglycemia confirm this diagnosis. The presence of hepatomegaly should arouse suspicion of an enzyme deficiency such as glucose-6-phosphatase in glycogen storage disease (GSD) I or other GSDs; if a non–glucose-reducing sugar is present in the urine (e.g., Clinitest positive but Clinistix negative), galactosemia is most likely. In males, the presence of a microphallus suggests the possibility of hypopituitarism, which also may be associated with cholestatic jaundice in both sexes; evidence of a midline facial defect such as cleft palate also suggests possible hypopituitarism as the cause of hypoglycemia from deficiency in GH and/or cortisol. A high index of suspicion and awareness of hypoglycemia as the cause for unusual behavior of any sick newborn should prompt a **bedside glucose determination** . However, because glucose meters have an accuracy of only ±20%, any blood glucose value <60 mg/dL *must be confirmed* by a formal laboratory measurement that is performed without delay on a blood sample preserved in a tube that prevents glycolysis, which can cause spurious low values.

After the newborn period, clues to the cause of persistent or recurrent hypoglycemia may be obtained through a careful history, physical examination, and initial laboratory findings. The temporal relation of the hypoglycemia to food intake may suggest that the defect is one of gluconeogenesis, if symptoms occur 6 hr or more after meals. If hypoglycemia occurs shortly after meals, **hyperinsulinism** should be suspected and confirmed or excluded via measurement of β-hydroxybutyrate, insulin, C-peptide, and FFAs in a sample in which blood glucose is <55 mg/dL. The autosomal dominant forms of hyperinsulinemic hypoglycemia need to be considered, with measurement of glucose, insulin, and ammonia and careful history for other affected family members of any age. Measurement of IGFBP-1 may be useful; it is low in states of hyperinsulinism and high in other forms of hypoglycemia. The presence of hepatomegaly suggests one of the **enzyme deficiencies** in glycogen breakdown or in gluconeogenesis, as outlined in Table 111.8 . The absence of ketonemia or ketonuria at the initial presentation strongly suggests hyperinsulinism or a defect in fatty acid oxidation. In most other causes of hypoglycemia, with the exception of galactosemia and fructose intolerance, ketonemia and ketonuria are present at the time of fasting hypoglycemia. During hypoglycemia, serum should be obtained for determination of substrates, especially glucose, β-hydroxybutyrate, lactate, and FFAs, as well as hormones, especially insulin, C-peptide, cortisol, ACTH, and GH, followed by repeated measurement of glucose after an intramuscular or IV injection of glucagon, as outlined in Table 111.7 . Table 111.8 summarizes the interpretation of the findings. Hypoglycemia with ketonuria in children between ages 18 mo and 5 yr is most likely to be **ketotic hypoglycemia** , especially if hepatomegaly is absent. The ingestion of a toxin, including alcohol or salicylate, can usually be excluded rapidly by the history. Inadvertent or deliberate drug ingestion and errors in dispensing medicines should also be considered. Factitious disorder (Munchausen) by proxy should be considered when parents or other caregivers have access to insulin or insulin secretagogues—high insulin concentrations in the sample with low concentrations of C-peptide confirm exogenous insulin administration. Deliberate or accidental ingestion of drugs that stimulate endogenous insulin secretion will result in both high insulin and C-peptide concentrations and may require specialized laboratory methods that identify the offending substance.

When the history is suggestive, but acute symptoms are not present, a 24 hr supervised fast can usually provoke hypoglycemia and resolve the question of hyperinsulinism or other conditions (see Table 111.8). Such a fast rarely needs to be extended to 36 hr, and only in older children. Such a fast is contraindicated if a fatty acid oxidation defect is suspected; other approaches such as mass tandem spectrometry or molecular diagnosis, or both, should be considered. Because adrenal insufficiency may mimic ketotic hypoglycemia, plasma cortisol and ACTH levels should be determined at the time of documented hypoglycemia; increased buccal or skin pigmentation may provide the clue to primary adrenal insufficiency with elevated ACTH (melanocyte-stimulating hormone) activity. Short stature or a decrease in the growth rate may provide the clue to pituitary insufficiency involving GH as well as ACTH. Definitive tests of pituitary-adrenal function, such as the arginine-insulin stimulation test for GH, IGF-1, IGFBP-1, and cortisol release, may be necessary.

In the presence of hepatomegaly and hypoglycemia, a presumptive diagnosis of the enzyme defect can often be made through the clinical manifestations, presence of hyperlipidemia, acidosis, hyperuricemia, response to glucagon in the fed and fasted states, and response to infusion of various appropriate precursors (see Table 111.7). Table 111.8 summarizes these clinical findings and investigative approaches. Definitive diagnosis of the GSD may require molecular diagnosis (see Chapter 105.1). Occasional patients with all the manifestations of GSD are found to have normal enzyme activity. These definitive studies require special expertise available only in certain institutions.

Treatment

The prevention of hypoglycemia and its resultant effects on CNS development are critically important in the newborn period. For neonates with hyperinsulinism not associated with maternal diabetes, subtotal or focal pancreatectomy may be needed, unless hypoglycemia can be readily controlled with long-term diazoxide, with somatostatin analogs (e.g., octreotide), or with sirolimus. Other novel approaches for treating hyperinsulinemic hypoglycemia are being investigated.

Treatment of **acute symptomatic** neonatal or infant hypoglycemia includes IV administration of 2 mL/kg of 10% dextrose in water (D10W), followed by a continuous infusion of glucose at 6-8 mg/kg/min, adjusting the rate to maintain blood glucose levels in the normal range. If hypoglycemic seizures are present, some recommend a 4 mL/kg bolus of D10W.

Treatment of asymptomatic hypoglycemia in at-risk infants usually includes enteral feedings rather than parenteral glucose. If symptoms develop or the hypoglycemia persists despite enteral feedings, IV glucose is indicated. Dextrose gel (40% at 400 mg/kg) administered into the mouth may be an alternative to enteral feedings if breast milk or if formula is not available.

The management of **persistent** neonatal or infantile hypoglycemia includes increasing the rate of IV glucose infusion to 10-15 mg/kg/min or more, if needed. This may require a central venous or umbilical venous catheter to administer a hypertonic 15–25% glucose solution. If hyperinsulinism is present, it should be medically managed initially with diazoxide and then somatostatin analogs. If hypoglycemia is unresponsive to IV glucose plus diazoxide (maximal doses up to 15 mg/kg/day) and somatostatin analogs, partial or near-total pancreatectomy should be considered. Such surgery should be performed in centers with the requisite facilities and trained staff experienced in the procedures. If possible, surgery should be preceded by ^{18}F-L-DOPA scanning to localize a lesion which can then provide guidance to the surgeon for curative resection before the operation is undertaken.

Oral **diazoxide** , 5-15 mg/kg/24 hr in divided doses twice daily, may reverse hyperinsulinemic hypoglycemia but may also produce hirsutism, edema, nausea, hyperuricemia, electrolyte disturbances, advanced bone age, IgG deficiency, and rarely, hypertension with prolonged use. The long-acting somatostatin analog **octreotide** may be helpful in controlling hyperinsulinism causing hypoglycemia in patients with islet cell disorders, including genetic mutations in K_{ATP} channel and islet cell adenoma. In neonates and young infants, **glucagon** given by continuous IV infusion at 5 µg/kg/hr, together with octreotide, 20-50 µg/kg/day subcutaneously every 6-12 hr, may maintain blood glucose, but generally these agents are used as a temporizing measure before partial or more complete pancreatectomy. Potential but unusual complications of octreotide include poor growth because of impaired GH release, pain at the injection site, vomiting, diarrhea, and hepatic dysfunction (hepatitis, cholelithiasis), and necrotizing enterocolitis; tachyphylaxis to the drug's effects is more common. Octreotide may be particularly useful for the treatment of refractory hypoglycemia despite subtotal pancreatectomy.

Total pancreatectomy is not optimal therapy because of the risks of surgery, permanent diabetes mellitus, and exocrine pancreatic insufficiency. Continued prolonged medical therapy without pancreatic resection, if hypoglycemia is controllable, is worthwhile because over time some children have a spontaneous resolution of the hyperinsulinism-induced hypoglycemia. This should be balanced against the risk of hypoglycemia-induced CNS injury and the toxicity of drugs.

Prognosis

The prognosis is good in asymptomatic neonates with hypoglycemia of short duration. Hypoglycemia recurs in 10–15% of infants after adequate treatment. Recurrence is more common if IV fluids are extravasated or discontinued too rapidly before oral feedings are well tolerated. Children who had transient neonatal hypoglycemia have an increased incidence of ketotic hypoglycemia later in life.

The prognosis for normal intellectual function must be guarded because prolonged, recurrent, and severe symptomatic hypoglycemia is associated with neurologic sequelae. Symptomatic infants with hypoglycemia, particularly low-birthweight infants, those with persistent hyperinsulinemic hypoglycemia, and severely hypoglycemic infants born to poorly controlled diabetic mothers, have a poorer prognosis for subsequent normal intellectual development than asymptomatic infants.

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PART XI

The Fetus and the Neonatal Infant

OUTLINE

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CHAPTER 112

Overview of Morbidity and Mortality

James M. Greenberg

Infant Mortality

The **infant mortality rate** is a metric used by public health agencies, policymakers, and governments to gauge the overall quality of pediatric and population health among a given population residing within geographically defined boundaries. The rate is stated as the number of infant deaths per 1,000 live births. Specific definitions support each variable. In the United States, an *infant death* is defined as mortality taking place from the time after delivery at any gestational age, up to the 1st birthday. No age correction is made to account for a premature birth. Each infant death is assigned to a geographic entity (e.g., county, state, country) on the basis of the mother's home address at the time of death. The definition of a *live birth* is typically based on the complete expulsion of the productions of conception from the uterus and 1 of 3 criteria: detection of cardiac activity (by auscultation or palpation of the umbilical cord stump), definite movement generated by voluntary muscle contraction, or any respiratory effort. It is important to note that this definition does not incorporate any gestational age cutoff.

The risk of mortality and major morbidity is particularly high around the time of birth (Fig. 112.1). Therefore, within the spectrum of infant mortality, certain subcategories are used in maternal and child health practice to focus on specific periods of high risk. The **perinatal period** is typically defined as the time from the 28th wk of pregnancy through the 7th postpartum day. The **neonatal period** spans the 1st 28 days of life and can be further subdivided into *early neonatal* (1st 7 days) and *late neonatal* (days 8-28) (Fig. 112.2). The primary causes of mortality shift as infancy progresses: during the perinatal and neonatal periods, **preterm birth** (Fig. 112.3) and **congenital malformations** predominate, whereas **unsafe sleep practices** accounts for the majority of deaths during the remainder of infancy. In developing countries with limited resources, preterm birth remains a concern, but other causes, such as infection, birth asphyxia, and complications of labor and delivery, add an additional burden (see Fig. 112.2).

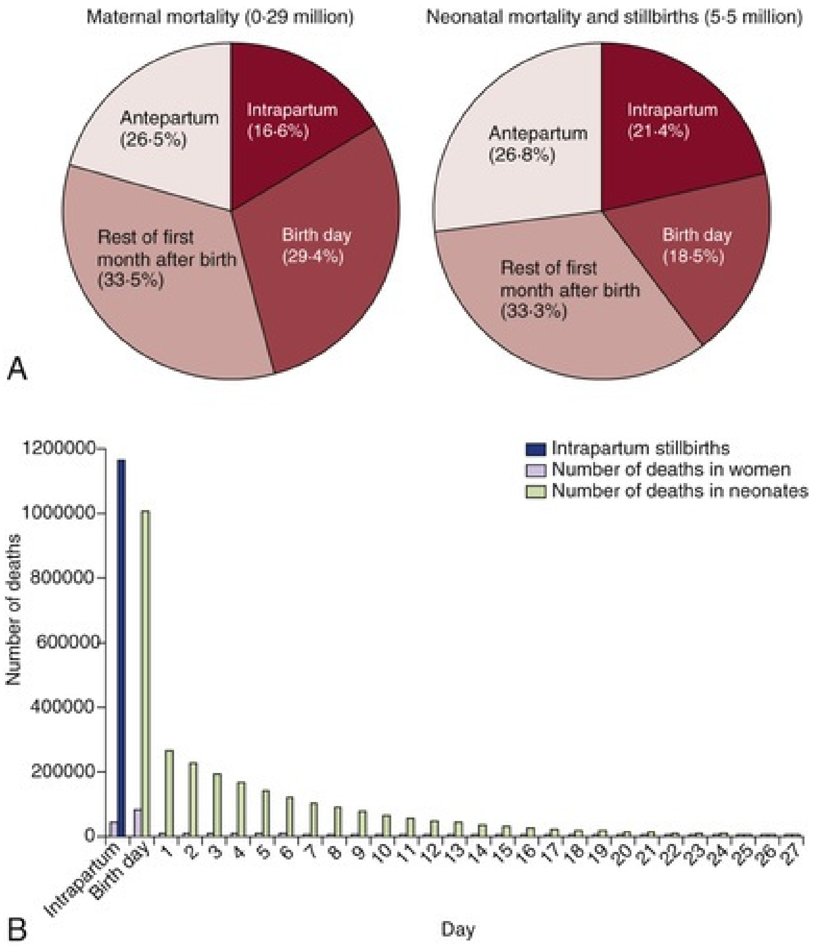

FIG. 112.1 **A,** Timing of death for women and their babies (third-trimester stillbirths and neonatal deaths) during pregnancy, birth, and the postnatal period. Includes all deaths of mothers and their babies from 28 wk of gestation up to 28 days of life. **B,** Number of deaths during labor and the 1st month after birth of women and their babies (intrapartum stillbirths and neonates). Insufficient data were available to accurately assign the day of death for the 1.4 million antepartum stillbirths and 63,000 maternal deaths occurring during the last trimester of pregnancy (before the onset of labor). (From Lawn JE, Blencowe H, Oza S, et al: Every newborn: progress, priorities, and potential beyond survival. Lancet 384:189–202, 2014, Fig 5.)

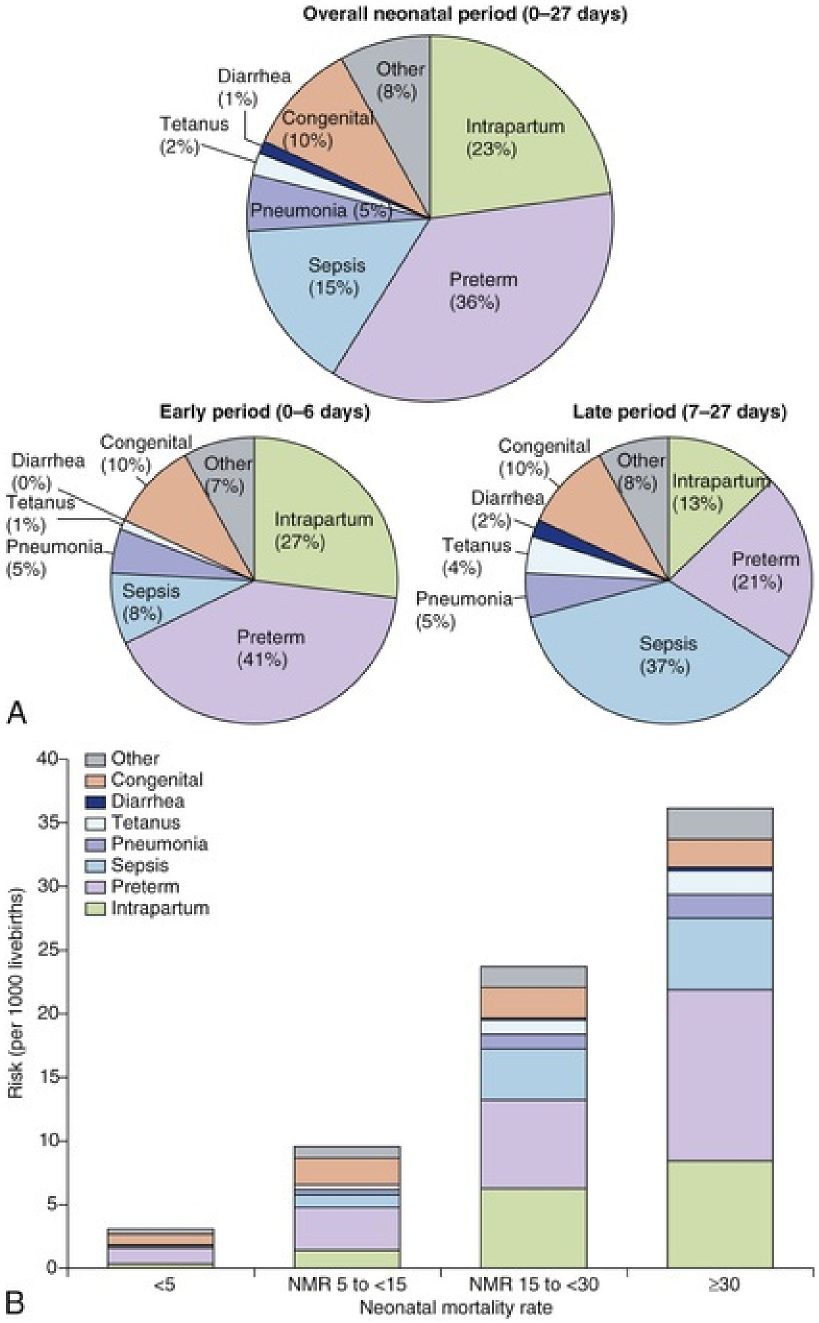

FIG. 112.2 **A,** Cause of death distribution for the neonatal period, and by the early (<7 days) and late (7–28 days) neonatal periods, for 194 countries in 2012. **B,** Variation in cause-specific neonatal mortality rates (NMRs) by level of NMR in 2012, showing risk difference by cause of death compared with the lowest mortality group (NMR <5). Data from Child Health Epidemiology Reference Group and World Health Organization (WHO) estimates for 194 countries for 2012. Estimates are based on multicause statistical models. In 2012, an additional estimated 196,000 deaths occurred in the postneonatal period from neonatal conditions (preterm birth, intrapartum related) and an estimated further 309,000 from term, small for gestational age. (From Lawn JE, Blencowe H, Oza S, et al: Every

newborn: progress, priorities, and potential beyond survival, Lancet 384:189–202, 2014, Fig 6.)

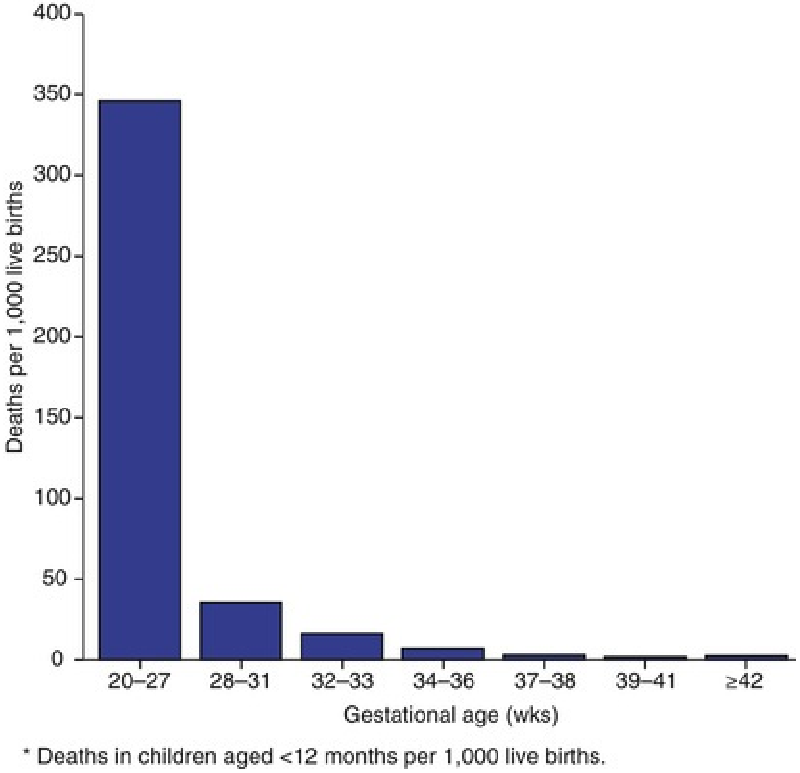

FIG. 112.3 Infant mortality rates by gestational age—United States, 2013. Deaths in children age <12 mo per 1,000 live births. (From Shapiro-Mendoza CK, Barfield WD, Henderson Z, et al: CDC Grand Rounds: Public health strategies to prevent preterm birth, MMWR 65(32):826–830, 2016, p 827.)

Rankings and Trends

Over the past century, infant mortality rates have declined in the United States and across most of the world. However, rates continue to differ worldwide (Fig. 112.4). In general, the highest rates are observed in low-resource, developing countries. However, the United States remains an anomaly among nations in the developed world. Table 112.1 shows infant mortality rates from a representative sample of developed countries. The rates are adjusted to exclude deaths before 24 wk gestation to account for potential variation in definitions of live births that might occur at the threshold of viability, to ensure comparability. Beginning in the 1980s, U.S. rates began to consistently exceed other developed nations; in 2015, U.S. infant mortality rates were >2-fold higher than in many developed countries. A wide range of infant mortality rates is also observed, with the highest rates in the Southeast United States and lower rates in the Upper Midwest, the Northeast, and the West Coast.

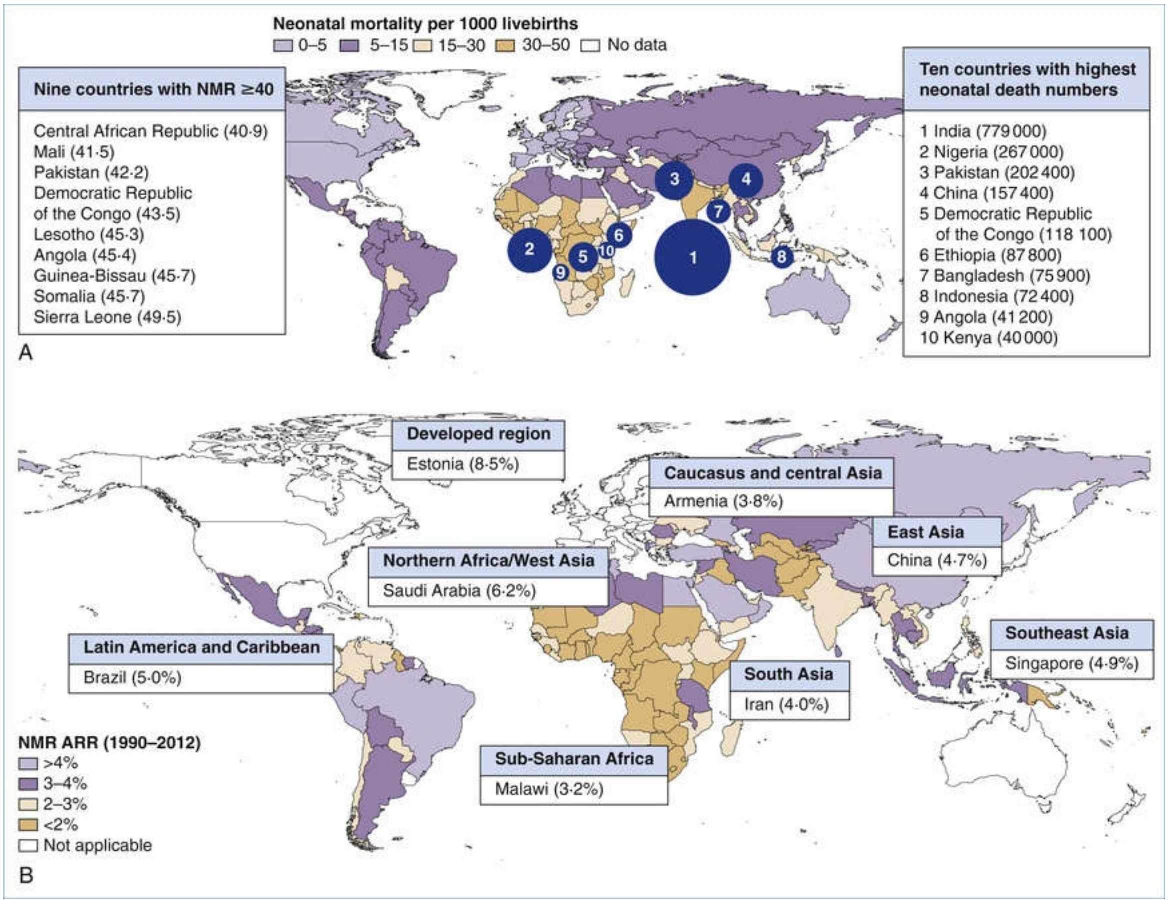
Neonatal mortality per 1000 livebirths
0–5
5–15
15–30
30–50
No data
Nine countries with NMR ≥40
Central African Republic (40·9)
Mali (41·5)
Pakistan (42·2)
Democratic Republic of the Congo (43·5)
Lesotho (45·3)
Angola (45·4)
Guinea-Bissau (45·7)
Somalia (45·7)
Sierra Leone (49·5)
Ten countries with highest neonatal death numbers
1 India (779 000)
2 Nigeria (267 000)
3 Pakistan (202 400)
4 China (157 400)
5 Democratic Republic of the Congo (118 100)
6 Ethiopia (87 800)
7 Bangladesh (75 900)
8 Indonesia (72 400)
9 Angola (41 200)
10 Kenya (40 000)
1
2
3
4
5
6
7
8
9
10
A
Developed region
Estonia (8·5%)
Caucasus and central Asia
Armenia (3·8%)
East Asia
China (4·7%)
Northern Africa/West Asia
Saudi Arabia (6·2%)
Southeast Asia
Singapore (4·9%)
Latin America and Caribbean
Brazil (5·0%)
South Asia
Iran (4·0%)
Sub-Saharan Africa
Malawi (3·2%)
NMR ARR (1990–2012)
>4%
3–4%
2–3%
<2%
Not applicable
B

FIG. 112.4 **A,** Variation among countries in neonatal mortality rate per 1,000 live births (NMR) in 2012. **B,** Variation in average annual rates of reduction (ARR) of NMR for all regions apart from developed regions, 1990–2012, showing the fastest-progressing country according to Millennium Development Goal region. Data from UN Interagency Group for Child Mortality Estimation estimates for NMR in 1990–2012. (From Lawn JE, Blencowe H, Oza S, et al: Every newborn: progress, priorities, and potential beyond survival, Lancet 384:189–202, 2014, Fig 2.)

Table 112.1

Infant Mortality Rate per 1,000 Live Births (IMR) for Select Developed Countries, 2010

COUNTRY	IMR
Finland	2.3
Japan	2.3
Greece	3.8
United Kingdom	4.2
United States	6.1

Data from the National Center for Health Statistics: *Natl Vital Stat Rep* 63(5):1, 2014 (Fig 1). https://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_05.pdf .

Major Causes of Infant Death

In the United States and Europe, most infant deaths fall into 1 of 3 major categories of causation: preterm birth, congenital malformations, and sleep related (e.g., SIDS). Infections, trauma, birth asphyxia, and injuries account for the remainder. The pattern differs in the developing world, where infections and asphyxia predominate. When considered based on the classification of infant cause of death by the *International Classification of Diseases, Tenth Revision* , congenital malformations are the leading cause, followed by disorders related to prematurity and low birthweight. Nonetheless, preterm birth rather than congenital malformations accounts for the majority of infant deaths in the United States, when deaths from unique complications of prematurity are included.

The U.S. preterm birth rate is substantially higher than in other developed countries and best explains elevated U.S. infant mortality rates. Worldwide, preterm birth rates display a tight concordance with infant mortality rates, providing further evidence for the importance of this linkage (Fig. 112.5). In the era of modern neonatal intensive care, most preterm birth deaths occur among the earliest gestational ages (<28 wk), and within the 1st few days of life, because of profound respiratory immaturity and insufficiency. The remaining preterm birth deaths result from morbidities associated with prematurity. Late preterm birth (35-36 wk gestation) is not a significant contributor to infant mortality.

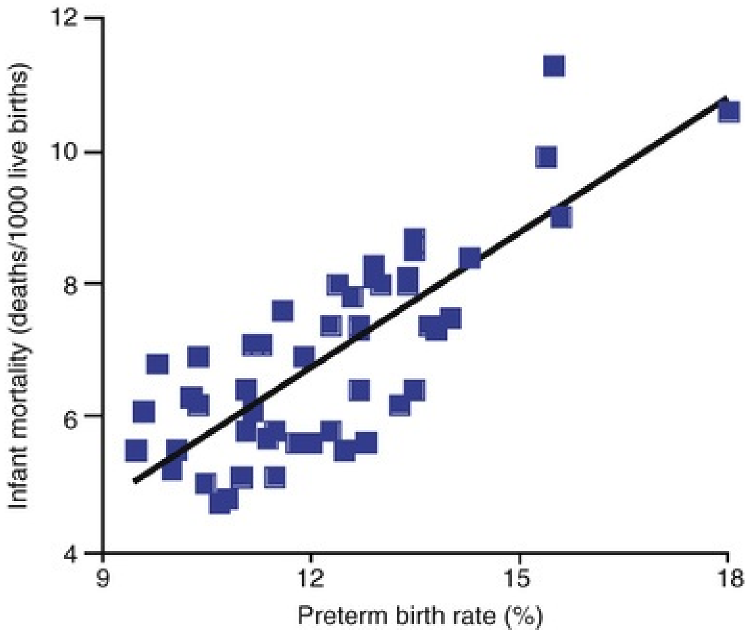

FIG. 112.5 Preterm birth as a function of infant mortality rates for 40 countries. (Data courtesy of L. Muglia, MD, PhD, Cincinnati Children's Research Foundation.)

International variation in live-birth registration practices may explain the elevated U.S. infant mortality. Although these technical explanations deserve further investigation, they should not be used to justify high U.S. infant mortality. In the United States, where live-birth registration practices are consistent, substantial variation in infant mortality and preterm birth rates implies *systemic* rather than technical explanations.

Racial Disparity and Infant Mortality

There is a significant disparity between infant mortality rates among U.S.-born white and black (African American) infants. This difference persists, even when socioeconomic status (SES) and educational levels are considered. The disparity is restricted to blacks; Hispanic populations in the United States tend to have infant mortality rates in line with the white population. Understanding this *Hispanic paradox* may provide insight into mechanisms driving the African American disparity. Interestingly, South Asian (Indian) populations in the United States may also have elevated infant mortality driven by low birthweight. Preterm birth and low birthweight are the key drivers of the black infant mortality disparity. Black preterm births rates are twice that of other U.S. racial and ethnic groups (Fig. 112.6), a gap that has persisted for decades. This is especially true for preterm birth rates at very low gestational ages, <28 wk, where mortality risks are high, even with the availability of modern neonatal intensive care units (NICUs). Racial disparities of mortality are not present among those receiving NICU care. Mechanistic explanations for the racial disparity remain elusive. Theories based on concepts of lifetime stress from experiences of racism or adverse life events are compelling (Chapter 2.1) However, studies focusing on stress and pregnancy outcomes fail to demonstrate clear mechanistic links.

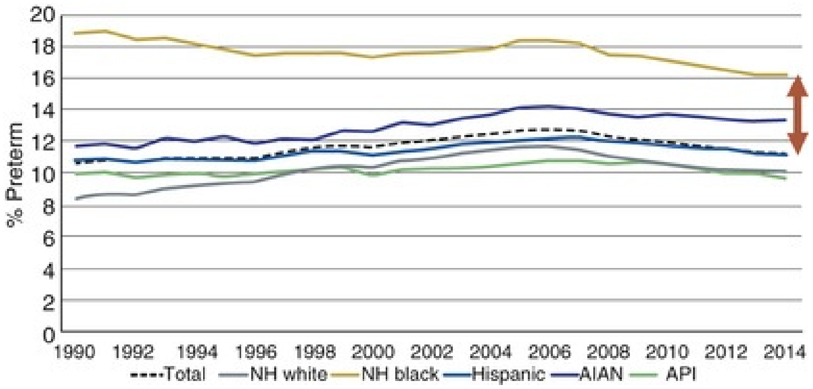

FIG. 112.6 The gap between black and white preterm birth rates in the United States has persisted for >3 decades. NH, Non-Hispanic; AIAN, American Indian/Alaskan Native; API, Asian/Pacific Islander. (Data from the National Center for Health Statistics.)

Congenital Malformations

Infant deaths from congenital malformations are the 2nd leading cause of infant death after premature birth. Many disorders reside in this category, with **congenital heart disease** the leading etiology. From a public health perspective, specific interventions can reduce the potential for certain congenital malformations, most notably periconceptional folic acid intake and appropriate vaccination programs to prevent diseases such as rubella during pregnancy. However, the mechanism of most congenital malformations remains poorly understood and therefore not yet amenable to population-based prevention strategies. In contrast to preterm birth, there is no discernible racial disparity for mortality caused by congenital malformations in the United States.

Sleep-Related Deaths (SUID, SIDS)

Sudden unexpected infant death (SUID) is a sudden and unexpected death during infancy. Following a thorough investigation of the death, SUID may be explained through mechanisms such as cosleeping and suffocation, or airway obstruction caused by soft objects or excessive bedding. **Sudden infant death syndrome (SIDS)** is a subcategory of SUID assigned to SUIDS that cannot be explained after a thorough investigation, including postmortem examination (see Chapter 402). SIDS represents a small fraction of all sleep-related deaths. With the advent of effective public health messaging, rates of sleep-related deaths in the United States have declined. However, a wide variation of rates is still observed across different geographic jurisdictions. SUID rates also display a racial disparity. The leading cause of infant death beyond the neonatal period is **unsafe infant sleep practices** .

Infant Mortality Reduction

Reduction of U.S. infant mortality is a challenging but attainable goal. Decreasing the preterm birth rate, especially extreme prematurity before 28 wk gestation, is an imperative. Improving our understanding of the biologic factors that control gestational duration and initiation of labor and delivery is key. Studies of intramuscular (but not vaginal) progesterone treatment during pregnancy for women known to be at elevated risk for a preterm birth have proved promising. However, the mechanism of action is not well understood, and the public health impact appears limited except perhaps for women with a previous preterm birth. Improving our understanding of how social determinants of health and health behavior influence birth outcomes is also important. **Smoking** during pregnancy is known to drive low birthweight, preterm birth, and elevated mortality. Improving interventions to eliminate smoking during pregnancy should reduce infant mortality. Understanding mechanistic links between the biology of parturition and the social and behavioral determinants of health is imperative.

Preterm Birth

Preterm birth is defined as a live birth occurring before the 37th wk of gestation. Comparison of preterm births between countries or other jurisdictions can be compromised by methods used to calculate gestational age. Three approaches are currently in use: **last menstrual period** (LMP), **obstetric estimate** (OE), and a **combined estimate** . The last defers to the LMP *unless* the value is missing from the vital record information or is extremely inconsistent with the recorded birthweight. In this circumstance (0.4% of record in 2013) the combined method uses the OE value. From a public health perspective, the OE offers superior validity. Since 2014 reports by federal agencies and stakeholder organizations (e.g., March of Dimes) use the OE to state preterm birth rates. The OE is typically a 1–2% lower preterm birth rate than the LMP or combined method. In 2016 the national preterm birth rate based on OE was 9.84%, compared to an 11.40% rate using the combined method.

The mortality and morbidity challenges encountered by a newborn delivered at 36 wk differ in severity from delivery at 25 wk. Subcategories of preterm birth corresponding to late (35-36 wk), moderate (32-34 wk), and early (<32 wk) acknowledge important differences in morbidity and mortality risk. From an infant mortality perspective, an additional subcategory of the early preterm population, *extreme preterm* births (<28 wk) has substantial importance, because >50% of all infant deaths occur in this population.

In addition to socioeconomic and racial factors, genetic variables may be associated with pregnancy duration and risk for preterm birth. Variants in *EBF1, EEFSEC, AGTR2, WNT4, ADCY5,* and *RAP2C* are reported to be associated with pregnancy length, whereas variants in *EBF1, EEFSEC,* and *AGTR2* loci are associated with preterm birth. In addition, 7 unrelated free RNA transcripts in maternal blood cells have been found to predict preterm delivery. These results are preliminary but may add specific targets for prevention of prematurity.

The Late Preterm Neonate

There is an important appreciation for the significance of late preterm delivery. Often these infants seem similar to their term counterparts, but epidemiologic data demonstrate that they are at significantly higher risk for apneic episodes, disorders of thermoregulation (e.g., hypothermia), hypoglycemia, respiratory distress, feeding difficulties, dehydration, and suspected sepsis. They are more likely to require NICU admission and experience an extended hospital stay. Late preterm neonates also appear to have a higher risk for longer-term neurologic problems, such as attention-deficit disorders and learning disabilities.

Late preterm deliveries may result from complications of pregnancy (e.g., chorioamnionitis, premature rupture of membranes) or maternal conditions (e.g., preeclampsia). Many are caused by elective delivery through induction of labor or scheduled cesarean birth during the late preterm period. As appreciation grew for an elevated morbidity and mortality risk in late preterm infants, a movement to eliminate elective deliveries before 39 wk gained national traction. The Ohio Perinatal Quality Collaborative initiated a statewide quality improvement initiative to eliminate elective deliveries before 39 wk of gestation through establishment of a multihospital learning network. Their work led to a material and sustained reduction of elective deliveries, with attendant reductions in neonatal morbidity and hospital length of stay.

The Moderate and Early Preterm Neonate

As gestational age at delivery declines, morbidity and mortality risks increase. With modern neonatal intensive care, the potential for survival at a given gestational age has improved. With that, the *threshold* gestational age for offering comprehensive neonatal intensive care has correspondingly declined. However, assigning a specific gestational age for threshold of viability remains a challenging problem. Current published data suggest minimal life-sustaining impact for neonatal intensive care offered before 22-23 wk gestation. However, covariables such as birthweight and perhaps exposure to antenatal steroids must be considered. Neonates born at extremely early gestational ages are at very high risk for morbidities carrying lifelong consequences. Major morbidities of prematurity contribute to infant mortality after the early neonatal period (e.g., BPD, IVH, NEC, PDA). All are more common in extremely premature infants, and when present, each can prolong NICU length of stay or may be listed as an immediate cause of death. Therefore, multidisciplinary decision-making with direct family participation is essential.

Preterm neonates at moderate and early gestational ages are at elevated risk for all the complications of late prematurity. Additional categories of morbidity that are absent or extremely rare in the late preterm and term populations also become much more common at earlier gestational ages (Table 112.2). These include adverse **neurodevelopmental** sequelae such as cerebral palsy, periventricular leukomalacia, intraventricular hemorrhage, hydrocephalus, visual impairment, and hearing impairment. Problems affecting other major organ systems include bronchopulmonary dysplasia, necrotizing enterocolitis, and patent ductus arteriosus. Early preterm infants are at the highest risk for these complications, which also tend to be more severe.

Table 112.2

Major Morbidities of the Neonate and Associated Etiologic Conditions

MORBIDITIES	EXAMPLES OF ETIOLOGY
CENTRAL NERVOUS SYSTEM	
Spastic diplegic/quadriplegic cerebral palsy	HIE, periventricular leukomalacia, undetermined factors
Choreoathetotic cerebral palsy	Kernicterus/bilirubin encephalopathy
Microcephaly	Intrauterine infections
Hydrocephalus	IVH, HIE, meningitis
Seizures	HIE, encephalopathies, hypoglycemia
Learning disorders, developmental delay	Prematurity, HIE, hypoglycemia, IVH
SENSATION—PERIPHERAL NEUROPATHIES	
Visual impairments	Retinopathy of prematurity, congenital viral infection
Strabismus	Opioid exposure, undetermined
Hearing impairment	HIE, bilirubin toxicity, drug toxicity (loop diuretics, aminoglycosides)
Speech delay	Prematurity, prolonged endotracheal intubation, hearing loss
Paralysis, paresis	Birth trauma (usually affected: phrenic nerve, brachial plexus, spinal cord)
RESPIRATORY SYSTEM	
Bronchopulmonary dysplasia	Prematurity, positive pressure ventilation, oxygen exposure
Subglottic stenosis	Prolonged endotracheal intubation
Sudden unexpected infant death	Prematurity, unsafe sleep conditions
Choanal stenosis, nasal septum injury	Prolonged nasotracheal intubation, nasal CPAP
CARDIOVASCULAR SYSTEM	
Cyanosis	Pulmonary hypertension, cor pulmonale, severe BPD
Heart failure	PDA, congenital heart defects with left-to-right shunting
GASTROINTESTINAL SYSTEM	
Short gut syndrome	NEC, malrotation with mid-gut volvulus, bowel atresia
Cholestatic liver disease	Injury from prolonged parenteral nutrition, sepsis, short gut syndrome
Failure to thrive	Short gut syndrome, BPD, cyanotic heart disease
Inguinal hernia	Preterm birth, male gender, positive pressure ventilation
MISCELLANEOUS	
Cutaneous scarring	Cutis aplasia, chest tube placement
Hypertension	Renal thrombi, prolonged umbilical artery catheterization, unknown

BPD, Bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; HIE, hypoxia-ischemic encephalopathy; IVH, intraventricular hemorrhage; NEC, necrotizing colitis; PDA, patent ductus arteriosus.

Intraventricular hemorrhage (IVH) occurs when the very fragile capillaries of the periventricular white matter and choroid plexus rupture. The typical pathophysiology is accumulation of blood in the lateral ventricles, which can lead to obstruction of cerebrospinal fluid circulation and ultimately hydrocephalus.

Bronchopulmonary dysplasia (BPD) is a complication of respiratory distress syndrome and prematurity leading to reactive airway disease, alveolar insufficiency, and in severe cases, pulmonary hypertension and death. BPD remains the most common morbidity of prematurity among NICU survivors. The most powerful predictor of BPD is gestational age: as gestational age decreases, the risk of BPD increases. Oxygen exposure and treatment with positive pressure ventilation also increase the risk of developing BPD at any gestational age.

Necrotizing enterocolitis (NEC) is a devastating inflammatory process that can occur anywhere in the lower gastrointestinal tract, most often at the distal ilium and ascending colon. In approximately 40% of patients, surgical exploration and resection of necrotic bowel is required, increasing potential for failure to thrive, malabsorption, and short bowel syndrome. Those at the lowest gestational ages are at the highest risk. Interestingly, preterm infants at the earliest gestational ages tend to develop NEC later in their hospital course than moderate or late preterm infants, suggesting a developmental window of susceptibility.

Patent ductus arteriosus (PDA) is a common finding in preterm neonates born before 28 wk. The ductus arteriosus must be patent during intrauterine life to sustain fetal circulation. Under normal physiologic conditions, the ductus undergoes functional closure within a few minutes of parturition. However, under conditions of marginal oxygenation and ventilation, ductal closure in preterm infants may be delayed. If ductal patency persists, it can promote pulmonary overcirculation, complicating the management of respiratory disease.

Low Birthweight, Intrauterine Growth Restriction, and Small for Gestational Age

Low birthweight (LBW) is classified as any live birth <2,500 g. The **very-low-birthweight (VLBW)** subcategory corresponds to <1,500 g. In general, LBW and VLBW infants are also preterm, although other intrauterine conditions discussed below also contribute. **Intrauterine growth restriction (IUGR)** refers to deficiency of fetal growth and an abnormal fetal growth trajectory. Etiologies of IUGR include certain congenital infections (e.g., rubella, cytomegalovirus), placental insufficiency, environmental factors (e.g., maternal smoking), and certain congenital conditions (e.g., aneuploidy). In contrast, **small-for-gestational-age (SGA)** neonates are constitutionally normal, without known genetic abnormalities or pathologic conditions. SGA and IUGR may occur at any gestational age. Birthweight and gestational age combine to predict mortality and morbidity risk at any gestational age. Healthcare providers can use an online mortality calculator developed by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network that incorporates gestational age and birthweight to assist with prenatal counseling for families anticipating a preterm delivery.

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CHAPTER 113

The Newborn Infant

Neera K. Goyal

See also Chapter 21 .

Although the neonatal period is a highly vulnerable time as infants complete the many physiologic adjustments required for extrauterine existence, this transition is uneventful for most full-term infants. Management of the newborn should focus on parental anticipatory guidance and early detection of conditions or complications that carry risk of morbidity or even death.

113.1

History in Neonatal Pediatrics

Neera K. Goyal

Assessment of the newborn should begin with a review of the maternal and family history, the pregnancy, and the delivery. Details of this history should include the following information, which will guide further evaluation and management in the newborn period:

◆ Demographic and social data (socioeconomic status, age, race, prenatal care utilization, substance use). Newborns whose mothers are young (<18 yr old) or who have concerns regarding housing, food insecurity, or access to healthcare may warrant evaluation by a social worker or case manager. Newborns exposed in utero to substances such as alcohol, cocaine, nicotine, caffeine, and opioids should be evaluated for associated symptoms (see Chapter 126).

◆ Maternal medical conditions (cardiopulmonary disorders, infectious diseases, genetic disorders, anemia, diabetes mellitus, current medications). Newborns of diabetic mothers warrant screening within the 1st 24 hr of life for severe hypoglycemia (see Chapter 127.1).

◆ Past medical illnesses in the mother and family, including previous siblings with a history of jaundice (see Chapter 123.3).

◆ Previous maternal reproductive problems: stillbirth, prematurity, blood group sensitization (see Chapter 124).

◆ Events occurring in the present pregnancy (prenatal laboratory and imaging results, preterm labor, fetal assessments, vaginal bleeding, acute illness, duration of rupture of membranes). Such information may prompt additional newborn testing, such as rapid plasma reagin (RPR) testing in the case of a positive maternal syphilis screen, or renal ultrasound imaging if fetal pyelectasis was detected prenatally.

◆ Description of the labor (duration, fetal presentation, fetal distress, fever) and delivery (cesarean section, anesthesia or sedation, use of forceps, Apgar scores, need for resuscitation). This information, combined with clinical assessment of the newborn, will determine risk for clinical deterioration and need for further monitoring and intervention.

113.2

Physical Examination of the Newborn Infant

Neera K. Goyal

Many physical and behavioral characteristics of a normal newborn infant are described in Chapter 21 .

The **initial examination** of a newborn infant should be performed as soon as possible after delivery. Temperature, pulse, respiratory rate, color, signs of respiratory distress, tone, activity, and level of consciousness of infants should be monitored frequently until stabilization. For high-risk deliveries, this examination should take place in the delivery room and should focus on congenital anomalies, maturation and growth, and pathophysiologic problems that may interfere with normal cardiopulmonary and metabolic adaptation to extrauterine life. Congenital anomalies of varying degrees of severity may be present in 3–5% of infants. After a stable delivery room course, a second and more detailed examination should be performed within 24 hr of birth.

If an infant remains in the hospital longer than 48 hr, repeat assessments should be performed throughout the hospital stay including a discharge examination within 24 hr of discharge. For a healthy infant, the mother should be present during this examination; even minor, seemingly insignificant anatomic variations may worry the parents and should be explained. The explanation must be careful and skillful so that otherwise unworried parents are not unduly alarmed. Infants should not be discharged from the hospital without a final examination because certain abnormalities, particularly cyanosis and heart murmurs, often appear or disappear in the immediate neonatal period; in addition, evidence of disease that has just been acquired may be noted. The pulse (normal: 120-160 beats/min), respiratory rate (normal: 30-60 breaths/min), temperature, weight, length, head circumference, and dimensions of any visible or palpable structural abnormality should be assessed. Blood pressure is determined if a neonate appears ill or has a heart murmur. Pulse oximetry should be performed to screen for critical congenital heart disease and is part of the routine screening for newborn infants.

Examining a newborn requires patience, gentleness, and procedural flexibility. Thus, if the infant is quiet and relaxed at the beginning of the examination, palpation of the abdomen or auscultation of the heart should be performed first, before other, more intrusive manipulations are attempted.

General Appearance

Physical activity may be decreased by the effects of illness or drugs; an infant may be either lying with the extremities motionless, to conserve energy for the effort of difficult breathing, or vigorously crying, with accompanying activity of the arms and legs. Both active and passive muscle tone and any unusual posture should be noted. Coarse, tremulous movements with ankle or jaw **myoclonus** are more common and less significant in newborn infants than at any other age. Such movements tend to occur when an infant is active, whereas convulsive twitching usually occurs in a quiet state. **Edema** may produce a superficial appearance of good nutrition. Pitting after applied pressure may or may not be noted, but the skin of the fingers and toes lacks the normal fine wrinkles when filled with fluid. Edema of the eyelids commonly results from irritation caused by the administration of silver nitrate. Generalized edema may occur with prematurity, hypoproteinemia secondary to severe erythroblastosis fetalis, nonimmune hydrops, congenital nephrosis, Hurler syndrome, and from unknown causes. Localized edema suggests a congenital malformation of the lymphatic system; when confined to one or more extremities of a female infant, it may be the initial sign of Turner syndrome (see Chapters 98 and 604).

Skin

Vasomotor instability and peripheral circulatory sluggishness are revealed by deep redness or purple lividity in a crying infant, whose color may darken profoundly with closure of the glottis preceding a vigorous cry, and by harmless cyanosis (**acrocyanosis**) of the hands and feet, especially when they are cool. Mottling, another example of general circulatory instability, may be associated with serious illness or related to a transient fluctuation in skin temperature. An extraordinary division of the body from the forehead to the pubis into red and pale halves is known as *harlequin color change* , a transient and harmless condition. Significant **cyanosis** may be masked by the pallor of circulatory failure or anemia; alternatively, the relatively high hemoglobin content of the 1st few days and the thin skin may combine to produce an appearance of cyanosis at a higher partial pressure of arterial oxygen (Pa_{O_2}) than in older children. Localized cyanosis is differentiated from *ecchymosis* by the momentary blanching pallor (with cyanosis) that occurs after pressure. The same maneuver also helps in demonstrating icterus. **Pallor** may be caused by anemia, asphyxia, shock, or edema. Early recognition of anemia may lead to a diagnosis of fetomaternal blood transfusion, erythroblastosis fetalis, subcapsular hematoma of the liver or spleen, subdural hemorrhage, or fetal-maternal or twin-twin transfusion. Without being anemic, postmature infants tend to have paler and thicker skin than term or premature infants. The ruddy appearance of plethora is seen with polycythemia.

The vernix and common transitory macular capillary hemangiomas of the eyelids and neck are described in Chapter 669 . Cavernous hemangiomas are deeper, blue masses that, if large, may trap platelets and produce disseminated intravascular coagulation or interfere with local organ function. Scattered petechiae may be seen on the presenting part (usually the scalp or face) after a difficult delivery. Slate-blue, well-demarcated areas of pigmentation called **mongolian spots** are seen over the buttocks, back, and sometimes other parts of the body in more than 50% of black, Native American, and Asian infants, and occasionally in white infants. These benign patches have no known anthropologic significance despite their name; they tend to disappear within the 1st year. The vernix, skin, and especially the cord may be stained brownish yellow if the amniotic fluid has been colored by the passage of meconium during or before birth.

The skin of premature infants is thin and delicate and tends to be deep red; in extremely premature infants, the skin appears almost gelatinous and translucent. Fine, soft, immature hair called **lanugo** frequently covers the scalp and brow and may also cover the face of premature infants. Lanugo has usually been lost or replaced by vellus hair in term infants. **Tufts of hair** over the lumbosacral spine suggest an underlying abnormality, such as occult spina bifida, a sinus tract, or a tumor. The nails are rudimentary in very premature infants, but they may protrude beyond the fingertips in infants born past term. Postterm infants may have a peeling, parchment-like skin (Fig. 113.1), a severe degree of which may mimic **ichthyosis congenita** (see Chapter 677).

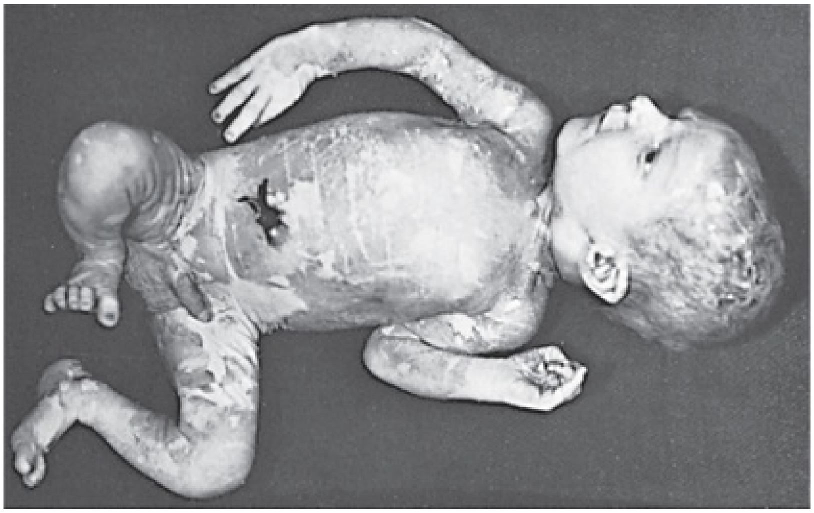

FIG. 113.1 **Infant with intrauterine growth restriction as a result of placental insufficiency. Note the long, thin appearance with peeling, parchment-like dry skin, alert expression, meconium staining of the skin, and long nails. (From Clifford S: *Advances in pediatrics,* vol 9, Chicago, 1962, Year Book.)**

In many neonates, small, white papules on an erythematous base develop 1-3 days after birth. This benign rash, **erythema toxicum** , persists for as long as 1 wk, contains eosinophils, and is usually distributed on the face, trunk, and extremities (see Chapter 666). **Pustular melanosis** , a benign lesion seen predominantly in black neonates, contains neutrophils and is present at birth as a vesiculopustular eruption around the chin, neck, back, extremities, and palms or soles; it lasts 2-3 days. Both lesions need to be distinguished from more dangerous vesicular eruptions such as herpes simplex (see Chapter 279) and staphylococcal disease of the skin (Chapter 208.1).

Amniotic bands may disrupt the skin, extremities (amputation, ring constriction, syndactyly), face (clefts), or trunk (abdominal or thoracic wall defects). Their cause is uncertain but may be related to amniotic membrane rupture or vascular compromise with fibrous band formation. Excessive skin fragility and extensibility with joint hypermobility suggest Ehlers-Danlos syndrome (see Chapter 679), Marfan syndrome (Chapter 722), congenital contractural arachnodactyly, and other disorders of collagen synthesis.

Skull

The skull may be molded, particularly if the infant is the first-born and if the head has been engaged in the pelvic canal for a considerable time. **Caput succedaneum** , caused by scalp pressure from the uterus, cervix, or pelvis, appears as a circular boggy area of edema with indistinct borders and often with overlying ecchymosis. A **cephalohematoma** presents as a well-circumscribed fluid-filled mass that does not cross suture lines. Unlike caput succedaneum, cephalohematoma is often not present at delivery but develops over the 1st few hr of life. Both cephalohematoma and caput succedaneum must be distinguished from a **subgaleal hemorrhage** , which is not restricted by the boundaries of the sutures and therefore is larger and more diffuse. Subgaleal hemorrhage requires prompt recognition because extensive bleeding may result in hypovolemic shock, with estimated mortality up to 20%. The head circumference of all newborns should be plotted on a growth chart to identify an excessively small head (**microcephaly**) or excessively large head (**megalencephaly**). The diagnostic differential for microcephaly is broad and includes underlying genetic disorders, congenital infection, and intrauterine drug exposure (see Chapter 609). Megalencephaly can suggest hydrocephaly, storage disease, achondroplasia, cerebral gigantism, neurocutaneous syndromes, or inborn errors of metabolism, or it may be familial. The suture lines and the size and fullness of the anterior and posterior fontanels should be determined digitally by palpation. The parietal bones tend to override the occipital and frontal bones. Premature fusion of sutures (**cranial synostosis**) is identified as a hard nonmovable ridge over the suture and an abnormally shaped skull. Great variation in the size of the **fontanels** exists at birth; if small, the anterior fontanel usually tends to enlarge during the 1st few mo after birth. The persistence of excessively large anterior (normal: 20 ±10 mm) and posterior fontanels has been associated with several disorders (Table 113.1). Persistently small fontanels suggest microcephaly, craniosynostosis, congenital hyperthyroidism, or wormian bones; presence of a 3rd fontanel suggests trisomy 21 but is seen in preterm infants. Soft areas (**craniotabes**) are occasionally found in the parietal bones at the vertex near the sagittal suture; they are more common in preterm infants and in infants who have been exposed to uterine compression. Although such soft areas are usually insignificant, their possible pathologic cause should be investigated if they persist. Soft areas in the occipital region suggest the irregular calcification and wormian bone formation associated with osteogenesis imperfecta, cleidocranial dysostosis, lacunar skull, cretinism, and occasionally Down syndrome.

Table 113.1

Disorders Associated with a Large Anterior Fontanel

Hypothyroidism
Achondroplasia
Apert syndrome
Cleidocranial dysostosis
Congenital rubella syndrome
Hallermann-Streiff syndrome
Hydrocephaly
Hypophosphatasia
Intrauterine growth restriction
Kenny syndrome
Osteogenesis imperfecta
Prematurity
Pyknodysostosis
Russell-Silver syndrome
Trisomies 13, 18, and 21
Vitamin D deficiency rickets

Atrophic or alopecic scalp areas may represent **aplasia cutis congenita** , which may be sporadic, or autosomal dominant, or associated with trisomy 13, chromosome 4 deletion, or Johanson-Blizzard syndrome. **Deformational plagiocephaly** may be the result of in utero positioning forces on the skull and manifests as an asymmetric skull and face with ear malalignment (see Chapter 610). It is associated with torticollis and vertex positioning. Depression of the skull (indentation, fracture, Ping-Pong ball deformity) is usually of prenatal onset and a result of prolonged focal pressure by the maternal pelvic bone.

Face

The general appearance of the face should be noted with regard to **dysmorphic features** , such as epicanthal folds, widely or narrowly spaced eyes, microphthalmos, asymmetry, long philtrum, and low-set ears, which are often associated with congenital syndromes. The face may be asymmetric as a result of a 7th nerve palsy, hypoplasia of the depressor muscle at the angle of the mouth, or an abnormal fetal posture (see Chapter 128); when the jaw has been held against a shoulder or an extremity during the intrauterine period, the mandible may deviate strikingly from the midline. Symmetric facial palsy suggests absence or hypoplasia of the 7th nerve nucleus (**Möbius syndrome**).

Eyes

The eyes often open spontaneously if the infant is held up and tipped gently forward and backward. This maneuver, a result of labyrinthine and neck reflexes, is more successful for inspecting the eyes than is forcing the lids apart. Conjunctival and retinal hemorrhages are usually benign. Retinal hemorrhages are more common with vacuum- or forceps-assisted deliveries than spontaneous vaginal delivery and least common after cesarean section. They are usually bilateral, intraretinal, and in the posterior pole. They resolve in most infants by 2 wk of age (85%) and in all infants by 4 wk. **Pupillary reflexes** are present after 28-30 wk of gestation. The iris should be inspected for colobomas and heterochromia. A cornea >1 cm in diameter in a term infant (with photophobia and tearing) or corneal clouding suggests congenital glaucoma and requires prompt ophthalmologic consultation. The presence of bilateral red reflexes suggests the absence of cataracts and intraocular pathology (see Chapter 637). **Leukokoria** (white pupillary reflex) suggests cataracts, tumor, chorioretinitis, retinopathy of prematurity, or a persistent hyperplastic primary vitreous and warrants an immediate ophthalmologic consultation (see Chapter 640).

Ears

Deformities of the pinnae are occasionally seen. Unilateral or bilateral preauricular skin tags occur frequently; if pedunculated, they can be tightly ligated at the base, resulting in dry gangrene and sloughing. The tympanic membrane, easily seen otoscopically through the short and straight external auditory canal, normally appears dull gray.

Nose

The nose may be slightly obstructed by mucus accumulated in the narrow nostrils. The nares should be symmetric and patent. Dislocation of the nasal cartilage from the vomerian groove results in asymmetric nares. Anatomic obstruction of the nasal passages secondary to unilateral or bilateral choanal atresia results in respiratory distress.

Mouth

A normal mouth may rarely have precocious dentition, with natal (present at birth) or neonatal (eruption after birth) teeth in the lower incisor position or aberrantly placed; these teeth are shed before the deciduous ones erupt (see Chapter 333). Alternatively, such teeth occur in Ellis–van Creveld, Hallermann-Streiff, and other syndromes. Extraction is not usually indicated. Premature eruption of deciduous teeth is even more unusual. The soft and hard palate should be inspected and palpated for a complete or submucosal cleft, and the contour noted if the arch is excessively high or the uvula is bifid. On the hard palate on either side of the raphe, there may be temporary accumulations of epithelial cells called **Epstein pearls** . Retention cysts of similar appearance may also be seen on the gums. Both disappear spontaneously, usually within a few weeks of birth. Clusters of small, white or yellow follicles or ulcers on erythematous bases may be found on the anterior tonsillar pillars, most frequently on the 2nd or 3rd day of life. Of unknown cause, they clear without treatment in 2-4 days.

Neonates do not have active salivation. The tongue appears relatively large; the frenulum may be short, but its shortness (**tongue-tie** or **ankyloglossia**) is rarely a reason for cutting it. If there are problems with feedings (breast or bottle) and the frenulum is short, frenulectomy (**frenotomy**) may be indicated. Frenotomy may reduce maternal nipple pain and improve breastfeeding scores more rapidly than no treatment, but over time, neonates not treated with frenotomy also have successful feeding. The sublingual mucous membrane occasionally forms a prominent fold. The cheeks have fullness on both the buccal and the external aspects as a result of the accumulation of fat in the sucking pads. These pads, as well as the labial tubercle on the upper lip (**sucking callus**), disappear when suckling ceases. A marble-sized buccal mass is usually caused by benign idiopathic fat necrosis.

The throat of a newborn infant is difficult to see because of the low arch of the palate; it should be clearly viewed because posterior palatal or uvular clefts are easy to miss. The tonsils are small.

Neck

The neck appears relatively short. Abnormalities are not common but include goiter, cystic hygroma, branchial cleft cysts, teratoma, hemangioma, and lesions of the sternocleidomastoid muscle that are presumably traumatic or caused by a fixed positioning in utero that produces either a hematoma or fibrosis, respectively. Congenital **torticollis** causes the head to turn toward and the face to turn away from the affected side (see Chapter 700.1). Plagiocephaly, facial asymmetry, and hemihypoplasia may develop if it is untreated (see Chapter 610). Redundant skin or webbing in a female infant suggests intrauterine lymphedema and Turner syndrome (see Chapters 98 and 604). Both clavicles should be palpated for fractures.

Chest

Breast hypertrophy is common, and milk may be present (but should not be expressed). Asymmetry, erythema, induration, and tenderness suggest mastitis or a breast abscess. Supernumerary nipples, inverted nipples, or widely spaced nipples with a shield-shaped chest may be seen; the last finding suggests Turner syndrome.

Lungs

Much can be learned by observing breathing. Normal variations in rate and rhythm are characteristic and fluctuate according to the infant's physical activity, the state of wakefulness, or the presence of crying. Because fluctuations are rapid, the **respiratory rate** should be counted for a full minute with the infant in the resting state, preferably asleep. Under these circumstances, the usual rate for normal term infants is 30-60 breaths/min; in premature infants the rate is higher and fluctuates more widely. A rate consistently >60 breaths/min during periods of regular breathing that persists for >1 hr after birth is an indication to rule out pulmonary, cardiac, or metabolic disease (acidosis) etiologies. Preterm infants may breathe with a Cheyne-Stokes rhythm, known as **periodic respiration** , or with complete irregularity. Irregular gasping, sometimes accompanied by spasmodic movements of the mouth and chin, strongly indicates serious impairment of the respiratory centers.

The breathing of newborn infants at rest is almost entirely *diaphragmatic*, so during inspiration, the soft front of the thorax is usually drawn inward while the abdomen protrudes. If the baby is quiet, relaxed, and with good color, this “paradoxical movement” does not necessarily signify insufficient ventilation. On the other hand, labored respiration with retractions is important evidence of respiratory distress syndrome, pneumonia, anomalies, or mechanical disturbance of the lungs. A weak, persistent or intermittent groaning, whining cry, or **grunting** during expiration can signify potentially serious cardiopulmonary disease or sepsis and warrants immediate attention. When benign, the grunting resolves 30-60 min after birth. Flaring of the alae nasi and retraction of the intercostal muscles and sternum are common signs of pulmonary pathology.

Normally, the breath sounds are *bronchovesicular.* Suspicion of pulmonary pathology because of diminished breath sounds, rhonchi, retractions, or cyanosis should always be verified with a chest radiograph.

Heart

Normal variation in the size and shape of the chest makes it difficult to estimate the size of the heart. The location of the heart should be determined to detect **dextrocardia** . The pulse is usually 110-140 beats/min at rest but may vary normally from 90 beats/min in relaxed sleep to 180 beats/min during activity. The still higher rate of supraventricular tachycardia (>220 beats/min) may be determined better with a cardiac monitor or electrocardiogram (ECG) than by auscultation. Preterm infants usually have a higher resting heart rate, up to about 160 beats/min, but may have a sudden onset of sinus bradycardia secondary to apnea. On both admission to and discharge from the nursery, the infant's pulses should be palpated in the upper and lower extremities to detect **coarctation of the aorta** . Transitory murmurs usually represent a closing ductus arteriosus. Although congenital heart disease (CHD) may not initially produce a murmur, a substantial portion of infants in whom persistent murmurs are detected during routine neonatal examination have underlying malformation. Routine screening for critical CHD using pulse oximetry is performed between 24 and 48 hr of life, which overall yields a sensitivity approaching 80% and specificity >99%. Pulse oximetry screening with SO_2 of ≥95% in the right hand or either foot and <3% difference between the right hand and foot is considered a normal screening test. Those with SO_2 <95% should be referred for evaluation and possible echocardiogram (see Chapter 452). Blood pressure (BP) measurements are indicated in the evaluation of ill-appearing infants and those in whom CHD is suspected. The oscillometric method is the easiest and most accurate noninvasive method available. Mean BP values vary by gestational age, however for all neonates, BP is expected to rise in the 1st 72 hr after birth (Fig. 113.2).

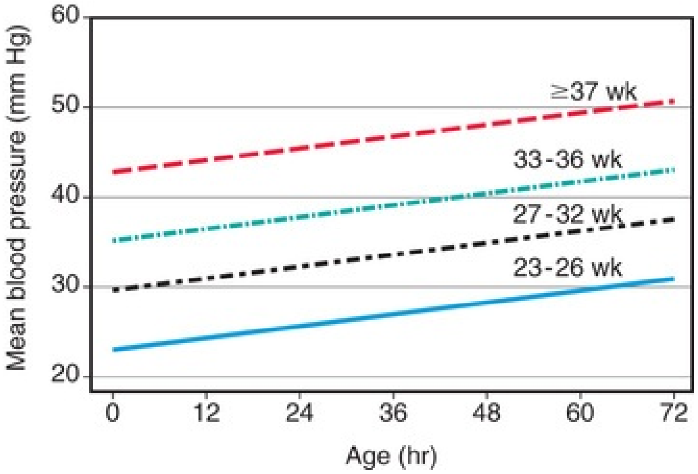

FIG. 113.2 **Nomogram for mean blood pressure (BP) in neonates with gestational ages of 23-43 wk. Derived from continuous arterial BP measurements obtained from 103 infants admitted to the neonatal intensive care unit. The graph shows the predicted mean BP of neonates of different gestational ages during the 1st 72 hr of life. Each line represents the lower limit of the 80% confidence interval (2-tail) of the mean BP for each gestational age-group; 90% of infants for each gestational age-group will be expected to have a mean BP value equal to or above the value indicated by the corresponding line, the lower limit of the confidence interval. (From Nuntnarumit P, Yang W, Bada-Ellzey SB: Blood pressure measurements in the newborn, *ClinPerinatol* 26:976–996, 1999.)**

Abdomen

The liver is usually palpable, sometimes as much as 2 cm below the rib margin. Less often, the tip of the spleen may be felt. The approximate size and location of each kidney can usually be determined on deep palpation. At no other period of life does the amount of air in the gastrointestinal tract vary so much, nor is it usually so great under normal circumstances. The intestinal tract is gasless at birth. Gas is swallowed soon after birth, and gas should normally be present in the rectum on radiograph by 24 hr of age. The abdominal wall is normally weak (especially in premature infants), and diastasis recti and umbilical hernias are common, particularly among black infants.

Unusual masses should be investigated immediately with ultrasonography. Renal pathology is the cause of most neonatal abdominal masses. **Cystic abdominal masses** include hydronephrosis, multicystic-dysplastic kidneys, adrenal hemorrhage, hydrometrocolpos, intestinal duplication, and choledochal, ovarian, omental, or pancreatic cysts. **Solid masses** include neuroblastoma, congenital mesoblastic nephroma, hepatoblastoma, and teratoma. A solid flank mass may be caused by **renal vein thrombosis** , which becomes clinically apparent with hematuria, hypertension, and thrombocytopenia. Renal vein thrombosis in infants is associated with polycythemia, dehydration, maternal diabetes, asphyxia, sepsis, nephrosis, and hypercoagulable states such as antithrombin III and protein C deficiency.

Abdominal distention at birth or shortly afterward suggests either obstruction or perforation of the gastrointestinal tract, often as a result of meconium ileus; later distention suggests lower bowel obstruction, sepsis, or peritonitis. A scaphoid abdomen in a newborn suggests diaphragmatic hernia. Abdominal wall defects produce an **omphalocele** when they occur through the umbilicus and gastroschisis when they occur lateral to the midline (see Chapter 125). Omphaloceles are associated with other anomalies and syndromes, such as Beckwith-Wiedemann, conjoined twins, trisomy 18, meningomyelocele, and imperforate anus. **Omphalitis** is an acute local inflammation of the periumbilical tissue that may extend to the abdominal wall, the peritoneum, the umbilical vein or portal vessels, or the liver and may result in later portal hypertension. The umbilical cord should have 2 arteries and 1 vein. A single umbilical artery is associated with an increased risk for an occult renal anomaly.

Genitals

The genitals and mammary glands normally respond to transplacentally acquired maternal hormones to produce enlargement and secretion of the breasts in both sexes and prominence of the genitals in females, often with considerable nonpurulent discharge. These transitory manifestations require no intervention.

An imperforate hymen or other causes of vaginal obstruction may result in **hydrometrocolpos** and a lower abdominal mass. A normal scrotum at term is relatively large; its size may be increased by the trauma of breech delivery or by a transitory **hydrocele** , which is distinguished from a hernia by palpation and transillumination. The testes should be in the scrotum or should be palpable in the canals in term infants. Black male infants usually have dark pigmentation of the scrotum before the rest of the skin assumes its permanent color. The scrotum may be ecchymotic from breech presentation or a retroperitoneal hemorrhage; it may contain meconium particles associated with meconium peritonitis.

The prepuce or foreskin of a newborn infant is normally tight and adherent to the penile glans at birth and cannot be retracted. The foreskin should separate naturally over several months. Severe **hypospadias** or **epispadias** should always suggest either that abnormal sex chromosomes are present (see Chapter 98) or that the infant is actually a masculinized female with an enlarged clitoris, because this finding may be the first evidence of adrenogenital syndrome (see Chapter 594). Erection of the penis is common and has no significance. Urine is usually passed during or immediately after birth; a period without voiding may normally follow. Most neonates void by 12 hr, and approximately 95% of preterm and term infants void within 24 hr.

Anus

Some passage of **meconium** usually occurs within the 1st 12 hr after birth; 99% of term infants and 95% of premature infants pass meconium within 48 hr of birth. Physical examination is usually sufficient for diagnosis of **imperforate anus** , if the anal opening is absent or incorrectly located. However, if there is a fistula to the skin, urethra or vagina, a newborn can pass meconium; in such cases, unless a careful exam is done, imperforate anus may not be suspected. Abdominal radiographs are used to confirm distal obstruction and to determine how low the rectum is. In females with imperforate anus, careful examination of the vestibule must be made to ensure separate openings of the urethra and vagina. All newborns with anorectal malformations warrant evaluation for possible associated cardiac, renal and spine anomalies.

The dimple or irregularity in skin fold often normally present in the sacrococcygeal midline may be mistaken for an actual or potential neurocutaneous sinus.

Extremities

During examination of the extremities, the effects of fetal posture (see Chapter 692) should be noted so that their cause and usual transitory nature can be explained to the mother. Such explanations are particularly important after breech presentations. A fracture or nerve injury associated with delivery can be detected more frequently by observation of the extremities in spontaneous or stimulated activity than by any other means. The hands and feet should be examined for polydactyly, syndactyly, and abnormal dermatoglyphic patterns such as a simian crease.

The hips of all infants should be examined with specific maneuvers to rule out congenital dislocation (see Chapter 698.1).

Neurologic Examination

See Chapter 21 .

In utero neuromuscular diseases associated with limited fetal motion produce a constellation of signs and symptoms that are independent of the specific disease. Severe positional deformations and contractures produce **arthrogryposis** . Other manifestations of fetal neuromuscular disease include breech presentation, polyhydramnios, failure to breathe at birth, pulmonary hypoplasia, dislocated hips, undescended testes, thin ribs, and clubfoot. Many congenital disorders manifest as hypotonia, hypertonia, or seizures.

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113.3

Routine Newborn Care

Neera K. Goyal

The initial steps of management for all newborns after delivery are to provide warmth, drying, and tactile stimulation, while simultaneously evaluating respiratory effort, heart rate, and color. Full-term, vigorous infants may initially be placed on the mother's abdomen after delivery, during which time **delayed clamping** of the umbilical cord (30-60 sec) is recommended to improve transitional circulation and increase neonatal red blood cell (RBC) volume. Clearing the mouth of secretions with gentle suction with a bulb syringe or soft catheter is indicated if there is an excessive (copious) amount of fluid in the mouth or nares. In resource-poor countries, gentle wiping of the face, nose, and mouth with a soft cloth may be equally effective as a bulb syringe. Spontaneously breathing neonates without distress require no assisted method to clear their airway.

The **Apgar score** is a practical method of systematically evaluating infants immediately after birth and is assessed at 1 and 5 min of life (Table 113.2). Most healthy infants who appear to be in satisfactory condition may remain in skin-to-skin contact with their mothers for immediate bonding and nursing. However, infants who fail to initiate or sustain respiratory effort after stimulation, those with a heart rate <100 beats/min, and those with persistent central cyanosis should be placed under warmers for prompt resuscitation and monitoring (see Chapter 121). Apgar scores should not be used to determine need for resuscitation or to guide steps of resuscitation. However, changes in Apgar scores at sequential time points after birth can reflect how well the infant is responding to resuscitation. If the 5 min score remains <7, additional scores should be assigned every 5 min for up to 20 min. In addition to fetal distress, a number of factors, including prematurity and drugs given to the mother during labor, can result in low Apgar scores (Table 113.3).

Table 113.2

Apgar Evaluation of Newborn Infants[*]

SIGN	**0**	**1**	**2**
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

[*] At 60 sec after complete birth of the infant (disregarding the cord and placenta), the 5 objective signs listed here are evaluated, and each is given a score of 0, 1, or 2. A total score of 10 indicates an infant in the best possible condition. An infant with a score of 0-3 requires immediate resuscitation.

Adapted from Apgar V: A proposal for a new method of evaluation of the newborn infant, *Curr Res Anesth Analg* 32:260–267, 1953.

Table 113.3

Factors Affecting the Apgar Score[*]

FALSE-POSITIVE RESULT [†]
Prematurity
Analgesics, narcotics, sedatives
Magnesium sulfate
Acute cerebral trauma
Precipitous delivery
Congenital myopathy
Congenital neuropathy
Spinal cord trauma
Central nervous system anomaly
Lung anomaly (diaphragmatic hernia)
Airway obstruction (choanal atresia)
Congenital pneumonia and sepsis
Previous episodes of fetal asphyxia (recovered)
Hemorrhage-hypovolemia
FALSE-NEGATIVE RESULT [‡]
Maternal acidosis
High fetal catecholamine levels
Some full-term infants

[*] Regardless of the etiology, a low Apgar score because of fetal asphyxia, immaturity, central nervous system depression, or airway obstruction identifies an infant needing immediate resuscitation.

[†] No fetal acidosis or hypoxia; low Apgar score.

[‡] Acidosis; normal Apgar score.

Maintenance of Body Heat

Newborn infants are at risk for heat loss and hypothermia for several reasons. Relative to body weight, the body surface area (BSA) of a newborn infant is approximately 3 times that of an adult. Generation of body heat depends in large part on body weight, but heat loss depends on BSA. In low-birthweight and preterm infants, the insulating layer of subcutaneous fat is thin. The estimated rate of heat loss in a newborn is approximately 4 times that of an adult. Under the usual delivery room conditions (20-25°C [68-77°F]), an infant's skin temperature falls approximately 0.3°C (0.54°F)/min, and deep body temperature decreases approximately 0.1°C (0.18°F)/min during the period immediately after delivery; these rates generally result in a cumulative loss of 2-3°C (3.6-5.4°F) in deep body temperature (corresponding to a heat loss of approximately 200 kcal/kg). The heat loss occurs by 4 mechanisms: **convection** of heat energy to the cooler surrounding air, **conduction** of heat to the colder materials touching the infant, **heat radiation** from the infant to other nearby cooler objects, and **evaporation** from skin and lungs.

Metabolic acidosis, hypoxemia, hypoglycemia, and increased renal excretion of water and solutes may develop in term infants exposed to cold after birth because of their effort to compensate for heat loss. Heat production is augmented by increasing the metabolic rate and oxygen consumption in part by releasing **norepinephrine** , which results in nonshivering thermogenesis through oxidation of fat, particularly brown fat. In addition, muscular activity may increase. Hypoglycemic or hypoxic infants cannot increase their oxygen consumption when exposed to a cold environment, and their central temperature decreases. After labor and vaginal delivery, many newborn infants have mild to moderate metabolic acidosis, for which they may compensate by hyperventilating, a response that is more difficult for infants with central nervous system (CNS) depression (asphyxia, drugs) and infants exposed to cold stress in the delivery room. Therefore, to reduce heat loss, it is desirable to ensure that infants are dried and either wrapped in blankets or placed with the mother or under radiant warmers. **Skin-to-skin contact** with the mother is the optimal method of maintaining temperature in the stable newborn. Because carrying out resuscitative measures on a covered infant or one enclosed in an incubator is difficult, a radiant heat source should be used to warm the baby during resuscitation.

Antiseptic Skin and Cord Care

Nursery personnel should use alcohol-based solutions or chlorhexidine or iodophor-containing antiseptic soaps for routine handwashing before caring for each infant. Rigid enforcement of hand-to-elbow washing for 2 min in the initial wash and 15-30 sec in subsequent washes is essential for staff and visitors entering the nursery. Careful removal of the amniotic fluid and blood from the skin shortly after birth may reduce the risk of infection with bloodborne agents. For the infant's first bath, the entire skin and cord should be cleansed with warm water or a mild nonmedicated soap solution and rinsed with water to reduce the incidence of skin and periumbilical colonization with pathogenic bacteria and subsequent infectious complications. Based on World Health Organization (WHO) recommendations, this should be delayed until 24 hr of life to allow full transition to extrauterine life with emphasis on maternal–infant bonding and early breastfeeding. To avoid heat loss, the infant should then be dried and wrapped in clean blankets.

Staphylococcus aureus remains the most frequent pathogenic bacteria to colonize the umbilical cord, although other common pathogens include group A and group B streptococci and gram-negative bacilli. Pathogenic bacteria may derive from the mother's birth canal or various bacterial sources, including the nonsterile hands of personnel attending the delivery. Topical chlorhexidine to the umbilical cord is recommended for infants born outside of birthing centers or hospital settings, and for those born in low-resource communities with high neonatal mortality rates. However, in high-resource countries the incidence of omphalitis is very low and the severity is mild, so **dry cord care** is recommended without the application of topical substances such as alcohol or chlorhexidine. Dry cord care involves leaving the umbilical cord exposed to air or loosely covered, cleaning it with soap and water if it becomes soiled. Colonization and infection of newborns from potentially pathogenic organisms can also be reduced through continuous rooming-in with their mother, which creates an environment conducive for colonization from less pathogenic bacteria acquired from the mother's flora.

Vernix is spontaneously shed within 2-3 days, much of it adhering to the clothing, which should be completely changed daily. The diaper should be checked before and after feeding and when the baby cries; it should be changed when wet or soiled. The perineal area can be cleaned with baby wipes or with mild soap and warm water. Meconium or feces should be cleansed from the buttocks with sterile cotton moistened with sterile water. The foreskin of a male infant should not be retracted.

Newborn Prophylaxis and Screening

Newborn assessment and vital sign monitoring may vary by hospital but generally decreases in frequency after the 1st 1-2 hr after birth. For well-appearing newborns, a reasonable interval between assessments is 4 hr during the 1st 2-3 days of life and 8 hr thereafter. The infant's temperature should be taken by axillary measurement, with a normal range of 36.5-37.4°C (97.7-99.3°F). Weighing at birth and daily thereafter is sufficient.

The eyes of all infants, including those of cesarean birth, must be protected against **gonococcal ophthalmia neonatorum** by application of a 1 cm ribbon of erythromycin (0.5%) or tetracycline (1.0%) sterile ophthalmic ointments in each lower conjunctival sac. This procedure may be delayed during the initial short-alert period after birth to promote bonding, but once applied, drops should not be rinsed out (see Chapters 219 and 253.3). A 1% silver nitrate solution is an acceptable alternative but leads to a transient chemical conjunctivitis in 10–20% of cases.

Although hemorrhage in newborn infants can be a result of factors other than vitamin K deficiency, an intramuscular (IM) injection of 0.5-1 mg of water-soluble vitamin K_1 (phytonadione) should be given to all infants shortly after birth to prevent **hemorrhagic disease of the newborn** (see Chapter 124.4). Oral vitamin K is *not* as effective as the parenteral dosage.

Hepatitis B immunization before discharge from the nursery is recommended for newborns with weight >2 kg, irrespective of maternal hepatitis status.

Neonatal screening is available for various genetic, metabolic, hematologic, and endocrine disorders. All states in the United States have adopted the recommendations of the **Advisory Committee on Heritable Disorders in Newborns and Children** , although the specific tests performed vary by state based in part to disease prevalence, detection rates, and costs (see Chapter 102). The most commonly identified disorders (and their rates) include hypothyroidism (52/100,000 births), cystic fibrosis (30/100,000), hemoglobinopathies (26/100,000), medium-chain acyl–coenzyme A dehydrogenase deficiency (6/100,000), galactosemia (5/100,000), phenylketonuria (5/100,000), and adrenal hyperplasia (5/100,000). To be effective in the timely identification and prompt management of treatable diseases, screening programs must include not only high-quality laboratory tests but also follow-up of infants with abnormal test results; education, counseling, and psychologic support for families; and prompt referral of the identified neonate for accurate diagnosis and appropriate treatment.

Hearing impairment , a serious morbidity that affects speech and language development, may be severe in 2/1,000 births and overall affects 5/1,000 births. Universal screening of infants is recommended to ensure early detection of hearing loss and appropriate, timely intervention. Parents of infants who fail screening should be counseled on the importance of screening results, reinforcing the need for prompt audiologic confirmation and emphasizing the potential for normal language development with prompt intervention.

Universal screening with pulse oximetry provides early detection of ductal dependent cyanotic congenital heart disease (see Chapter 452).

Universal screening for hyperbilirubinemia should include risk assessment in all infants with measurement of serum or transcutaneous bilirubin levels before hospital discharge (see Chapter 123.4 , Kernicterus).

Universal screening for congenital hip dysplasia with physical examination with the **Ortolani test** (sensation of the dislocated hip reducing) and **Barlow test** (unstable hip dislocating from the acetabulum) is recommended, but routine hip ultrasound is not indicated.

Screening for hypoglycemia is risk based and should be performed in infants who are small for gestational age, large for gestational age, born to mothers who have diabetes, preterm, or symptomatic (see Chapter 127.1).

For infants with suspected maternal chorioamnionitis, current clinical guidelines recommend laboratory screening for sepsis, including a blood culture, and at least 48 hr of broad-spectrum antibiotic therapy. However, evidence suggests a low incidence of sepsis among well-appearing, term neonates, and that frequent, reliable observation to detect early signs of sepsis, with or without laboratory studies, may be appropriate. (see Chapter 129).

Table 113.4 lists minimum criteria to be met before newborn discharge. A shortened hospital stay (<48 hr after delivery) may be reasonable for healthy, term newborns but is not always appropriate. Early discharge requires careful ambulatory follow-up at home (by a visiting nurse) or in the office within 48 hr of discharge.

Table 113.4

Criteria for Discharge of Healthy Term Newborns*

GENERAL
Normal vital signs including respiratory rate <60 breaths/min; axillary temperature 36.5°C-37.4°C (97.7°-99.3°F) in open crib
Physical examination reveals no abnormalities requiring continued hospitalization
Regular urination; stool × 1
At least 2 uneventful, successful feedings
No excessive bleeding 2 hr after circumcision
LABORATORY AND OTHER SCREENS
Maternal syphilis, hepatitis B surface antigen, and HIV status
Newborn hepatitis B vaccine administered or appointment for vaccination confirmed
Maternal tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) vaccination
Maternal influenza vaccination during flu season
Evaluation and monitoring for sepsis based on maternal risk factors including GBS colonization
Umbilical or newborn direct Coombs test and blood type if clinically indicated
Expanded newborn metabolic screening
Hearing screening
Screening for hypoglycemia based on infant risk factors
Pulse oximetry screening
Screening for hyperbilirubinemia, with management and follow-up as recommended based on level of jaundice
SOCIAL
Evidence of parental knowledge, ability, and confidence to care for the baby at home: Feeding Normal stool and urine output Cord, skin, and genital care Recognition of illness (jaundice, poor feeding, lethargy, fever, etc.) Infant safety (car seat, supine sleep position, etc.)
Availability of family and physician support (physician follow-up)
Assessment of family, environmental, and social risk factors: Substance abuse History of child abuse Domestic violence Mental illness Teen mother Homelessness Barriers to follow-up
Source of continuing medical care is identified.

* Refers to infants born between 37 and 42 wk of gestation after uncomplicated pregnancy, labor, and delivery.

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113.4

Circumcision

Neera K. Goyal

Male circumcision consists of the surgical removal of some, or all, of the foreskin from the penis, and is one of the most common procedures performed worldwide. Circumcision performed during the newborn period has considerably lower complication rates than when performed later in life. The procedure should only be performed in healthy newborns whose condition is stable. Those providing circumcision should be adequately trained in both sterile techniques and effective pain management to reduce risk of complications. The surgery includes dilation of the preputial orifice to visualize the glans, freeing the preputial epithelium from the epithelium of the glans, placement of the circumcision device (Gomco clamp, Plastibell, or Mogen clamp) to enhance hemostasis, and removal of foreskin. For pain management, topical 4% lidocaine (i.e., LMX4 cream), a dorsal penile nerve block, and a subcutaneous ring block are all effective options. Topical anesthetic creams may cause a higher incidence of skin irritation in low-birthweight infants; therefore penile nerve block techniques should be chosen for this group. Usually, the dorsal penile nerve block consists of injections of 0.4 mL of 1% lidocaine *without* epinephrine on both sides of the base of the penis. The subcutaneous **circumferential ring block** involves 0.8 mL of 1% lidocaine *without* epinephrine injected at the base or midshaft of the penis and may provide the most effective analgesia compared with other techniques. Nonpharmacologic techniques, such as positioning on a padded environment and use of sucrose pacifiers, are useful adjuncts to improve infant comfort during the procedure but are insufficient as sole therapies to prevent procedural and postprocedural pain.

Contraindications to this procedure include critically ill infants, those with blood dyscrasias, individuals who have a family history of bleeding disorders, and those who have congenital abnormalities (e.g., hypospadias), congenital chordee, or deficient shaft skin (e.g., penoscrotal fusion, congenital buried penis). In addition, it should be confirmed before the procedure that the newborn received IM vitamin K in accordance with standard practice of newborn care. Premature infants may undergo circumcision before discharge.

Preventive health benefits of elective circumcision for male newborns include significant reductions in the risk of urinary tract infection in the 1st year of life, heterosexual acquisition of HIV and transmission of other sexually transmitted infections (human papillomavirus, herpes simplex virus type 2, and syphilis), and penile cancer. Acute complications from circumcision in the United States and other high-resource countries are rare, including bleeding (0.08–0.18%), infection (0.06%), and penile injury (0.04%). More catastrophic injuries, including glans or penile amputation, are extremely rare and published as case reports only. Later complications can include excessive residual skin (incomplete circumcision), excessive skin removal, adhesions (natural and vascularized skin bridges), meatal stenosis, phimosis, and epithelial inclusion cysts.

Current evidence indicates while health benefits outweigh the risks of male circumcision, health benefits are not great enough to recommend routine circumcision for all male newborns. Therefore, physicians who counsel families about this decision should explain the potential benefits and risks, in a nonbiased manner, and ensure that parents understand that circumcision is an elective procedure. Ultimately, parents should decide whether circumcision is in the best interests of their male child, weighing the medical information in context of their own religious, ethical, and cultural beliefs and practices.

Regardless of whether or not the newborn is circumcised, parents should be instructed in the care of the penis at discharge from the newborn hospital stay. The circumcised penis should be washed gently each day with soap and water. As part of normal healing, the glans may appear raw or yellowish for 7-10 days. Gauze with petroleum jelly can be used to cover the area and should be changed with each urine and stool until the glans heals.

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113.5

Parent–Infant Bonding

Neera K. Goyal

See also Chapter 21 .

Normal infant development depends partly on a series of affectionate responses exchanged between a mother and her newborn infant that binds them psychologically and physiologically. This bonding is facilitated and reinforced by the emotional support of a loving family. The attachment process may be important in enabling some mothers to provide loving care during the neonatal period and subsequently during childhood. The power of this attachment is so great that it enables the mother and the father to make unusual sacrifices necessary for the day-to-day care of the infant, care night after night, giving feedings 24 hr a day, attending to crying, and so on. The sacrifices continue for many years as parents dedicate much of their lives to their children.

Parent–infant bonding is initiated before birth with the planning and confirmation of the pregnancy. Subsequently, there is a growing awareness of the baby as an individual, starting usually with the remarkably powerful event of quickening or sensation of fetal movements. After delivery and during the ensuing weeks, sensory (visual, auditory, olfactory) and physical contact between the mother and baby triggers various mutually rewarding and pleasurable interactions, such as the mother touching the infant's extremities and face with her fingertips and encompassing and gently massaging the infant's trunk with her hands. Touching an infant's cheek elicits responsive turning toward the mother's face or toward the breast with nuzzling and licking of the nipple, a powerful stimulus for prolactin secretion. An infant's initial quiet alert state provides the opportunity for eye-to-eye contact, which is particularly important in stimulating the loving and possessive feelings of many parents for their babies. An infant's crying elicits the maternal response of touching the infant and speaking in a soft, soothing, higher-toned voice.

Initial contact between the mother and infant should take place in the delivery room, and opportunities for extended intimate contact and breastfeeding should be provided within the 1st hours after birth. Delayed or abnormal maternal–infant bonding, as occurs because of prematurity, infant or maternal illness, birth defects, or family stress, may harm infant development and maternal caretaking ability. Hospital routines should be designed to encourage parent–infant contact. Rooming-in arrangements, care by parents, and family-centered care increase the opportunities for better parent–infant interaction.

Rooming-in and Breastfeeding

See Chapter 56 for full discussions of breastfeeding and formula feeding.

Ample evidence indicates that there are infant and maternal benefits to breastfeeding. One important hospital practice to encourage successful breastfeeding is rooming-in of newborns with their mothers. Therefore, it should be encouraged that term, healthy infants remain continuously in the mother's room whenever possible. To reduce the risk of **sudden infant death syndrome** , infants should be placed to sleep supine in a bassinet, preferably of clear plastic to allow for easy visibility and care. All professional care should be given to the infant in the bassinet, including the physical examination, clothing changes, temperature taking, skin cleansing, and other procedures that, if performed elsewhere, would establish a common contact point and possibly provide a channel for cross-infection. The clothing and bedding should be minimal, only enough needed for an infant's comfort; the room temperature should be kept at approximately 22-26°C (72-78°F).

Additional practices that encourage successful breastfeeding include antepartum education and encouragement, immediate postpartum mother–infant contact with suckling, demand feeding, inclusion of maternal partners in breastfeeding education, and support from experienced women. Nursing at first for least 5 min at each breast is reasonable, allows a baby to obtain most of the available breast contents, and provides effective stimulation for increasing the milk supply. Nursing episodes should then be extended according to the comfort and desire of the mother and infant. A confident and relaxed mother, supported by an encouraging home and hospital environment, is likely to nurse well. The **Baby-Friendly Hospital Initiative** , a global effort sponsored by WHO and the UN Children's Fund to promote breastfeeding, recommends 10 steps to successful breastfeeding (Table 113.5). When instituted together as a complete bundle, these practices can improve multiple outcomes, including breastfeeding initiation, duration of exclusive breastfeeding, and duration of overall breastfeeding. In the United States, however, the vast majority of newborns are still not delivered in Baby-Friendly hospitals that have implemented all 10 steps. Educating mothers during pregnancy and showing mothers how to breastfeed are the most widely implemented strategies, while establishment of written breastfeeding policies, restriction of formula access, and establishment of breastfeeding support groups after discharge are among the most challenging to implement.

Table 113.5

Ten Steps to Successful Breastfeeding

Every facility providing maternity services and care for newborn infants should accomplish the following:

1. Have a written feeding policy that is routinely communicated to staff and patients, comply with WHO restrictions on marketing of breast milk substitutes, and establish ongoing monitoring and data-management systems.
2. Ensure that staff have sufficient knowledge, competence, and skills to support breastfeeding.
3. Discuss the importance and management of breastfeeding with pregnant women and their families.
4. Facilitate immediate and uninterrupted skin-to-skin contact and help initiate breastfeeding as soon as possible after birth.
5. Support mothers to initiate and maintain breastfeeding and manage common difficulties.
6. Give newborn infants no food or drink other than breast milk unless *medically* indicated.
7. Practice rooming-in (allow mothers and infants to remain together) 24 hr a day.
8. Support mothers to recognize and respond to their infants' feeding cues.
9. Counsel mothers on the use and risks of feeding bottles, teats, and pacifiers.
10. Coordinate discharge to ensure timely access to ongoing support and care.

Adapted from Guideline: Protecting, promoting and supporting breastfeeding in facilities providing maternity and newborn services. Geneva, 2017, World Health Organization.

Drugs and Breastfeeding

Ideally, drugs of any type should be avoided in breastfeeding women, unless prescribed for specific medical conditions. Many mothers are advised to discontinue breastfeeding or avoid taking essential medications due to fears of adverse infant effects. However, such an approach may be inappropriate in many cases, as only a small proportion of medications are contraindicated when breastfeeding. When weighing risks and benefits, healthcare providers should consider the following factors in discussion with the family: maternal need for the medication, potential effects on lactation, extent of excretion into human milk, extent of oral absorption by the breastfeeding infant, potential adverse infant effects, proportion of feedings comprised of breast milk, and age of the infant. Although previous editions of this text sought to list medications potentially used during lactation and to describe their potential for infant harm, revisions to this text can no longer keep pace with rapidly changing information available via the internet, published studies, and new drug approvals. For up-to-date information on drug levels in human milk and infant serum, possible adverse effects on infant health and lactation, and recommendations for possible medication alternatives, providers should refer to LactMed (http://toxnet.nlm.nih.gov).

Among US women of childbearing age, illicit drug use and legal substance use or abuse is common, with >5% of pregnant women reporting active illicit drugs, >9% alcohol use, and >15% cigarette use. Multiple drug use is also common. For mothers desiring to breastfeed with a history of current or past illegal drug abuse or legal drug use or abuse, healthcare providers must carefully and thoughtfully weigh the documented benefits of human milk and breastfeeding against the risks associated with the substance that the infant may be exposed to during lactation. Most illicit drugs are found in human milk with varying degrees of oral bioavailability, and breastfeeding is generally contraindicated (Table 113.6). However, mothers with substance use disorders should be encouraged to breastfeed under the following circumstances: established engagement in substance abuse treatment (e.g., methadone or buprenorphine maintenance therapy) that includes counseling and social support; abstinence from drug use for 90 days before delivery, with maternal urine toxicology testing at delivery negative other than prescribed substances, ability to maintain sobriety demonstrated in an outpatient setting, and engagement and compliance with care.

Table 113.6

Drugs of Abuse and Adverse Infant Effects

CONTRAINDICATED
Amphetamines
Antineoplastic agents
Bromocriptine
Chloramphenicol
Clozapine
Cocaine
Cyclophosphamide
Doxorubicin
Ecstasy (MDMA)
Ergots
Gold salts
Heroin
Immunosuppressants
Methamphetamine
Phencyclidine (PCP)
Radiopharmaceuticals
Thiouracil
USE WITH CAUTION
Alcohol
Amiodarone
Anthraquinones (laxatives)
Aspirin (salicylates)
Atropine
β-Adrenergic blocking agents
Benzodiazepines
Birth control pills
Bromides
Cascara
Codeine
Dicumarol
Dihydrotachysterol
Domperidone
Estrogens
Hydrocodone
Lithium
Marijuana
Metoclopramide
Meperidine
Oxycodone
Phenobarbital[*]
Primidone
Reserpine
Salicylazosulfapyridine (sulfasalazine)

[*] Watch for sedation.

Contraindications to Breastfeeding

Medical contraindications to breastfeeding in the United States include infants with galactosemia, maple syrup urine disease, and phenylketonuria. Maternal conditions that contraindicate breastfeeding include infection with human T-cell lymphotropic virus types 1 and 2, active tuberculosis (until appropriately treated ≥2 wk and not considered contagious), herpesvirus infection on breast, use of or dependence on certain illicit drugs, and maternal treatment with some radioactive compounds (Table 113.7). Because clean water and affordable replacement feeding are available in the United States, it is recommended that HIV-infected mothers not breastfeed their infants regardless of maternal viral load and antiretroviral therapy. However, in resource-limited countries where diarrhea and pneumonia are significant causes of infant and child mortality, breastfeeding may not be contraindicated for HIV-positive mothers receiving antiretroviral therapy. Donor human milk, particularly that purchased online, may be contaminated with potential pathogens. Contamination is much less of a concern with pasteurized human milk obtained from a milk bank.

Table 113.7

Summary of Infectious Agents Detected in Milk and Newborn Disease

INFECTIOUS AGENT	DETECTED IN BREAST MILK?	BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?
BACTERIA			
Mastitis/*Staphylococcus aureus*	Yes	No	No, unless breast abscess present
Mycobacterium tuberculosis :			
Active disease	Yes	No	Yes, because of aerosol spread, or tuberculosis mastitis
Purified protein derivative skin test result positive, chest radiograph findings negative	No	No	No
Escherichia coli , other gram-negative rods	Yes, stored	Yes, stored	—
Group B streptococci	Yes	Yes	No*
Listeria monocytogenes	Yes	Yes	No*
Coxiella burnetii	Yes	Yes	No*
Syphilis	No	No	No †
VIRUSES			
HIV	Yes	Yes	Yes, developed countries
Cytomegalovirus:			
Term infant	Yes	Yes	No

Preterm infant	Yes	Yes	Evaluate on an individual basis
Hepatitis B virus	Yes, surface antigen	No	No, developed countries [‡]
Hepatitis C virus	Yes	No	No [§]
Hepatitis E virus	Yes	No	No
Human T-cell leukemia virus (HTLV)-1	Yes	Yes	Yes, developed countries
HTLV-2	Yes	Uncertain	Yes, developed countries
Herpes simplex virus	Yes	Yes	No, unless breast vesicles present
Rubella			
Wild type	Yes	Yes, rare	No
Vaccine	Yes	No	No
Varicella-zoster virus	Yes	No	No, cover active lesions [¶]
Epstein-Barr virus	Yes	No	No
Human herpesvirus (HHV)-6	No	No	No
HHV-7	Yes	No	No
West Nile virus	Possible	Possible	Unknown
Zika virus	Yes	No	No
PARASITES			
Toxoplasma gondii	Yes	Yes, 1 case	No

[*] Provided that the mother and child are taking appropriate antibiotics.

[†] Treat mother and child if active disease.

[‡] Immunize and immune globulin at birth.

[§] Provided that the mother is HIV seronegative. Mothers should be counseled that breast milk transmission of hepatitis C virus has not been documented, but is theoretically possible.

[¶] Provide appropriate antivaricella therapy or prophylaxis to newborn.

Adapted from Jones CA: Maternal transmission of infectious pathogens in breast milk, *J Paediatr Child Health* 37:576–582, 2001.

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CHAPTER 114

High-Risk Pregnancies

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The care of high-risk pregnancies should be coordinated with an experienced maternal-fetal medicine specialist.

In general, high-risk pregnancies are those that increase the likelihood of maternal complications, miscarriage, fetal death, preterm delivery, intrauterine growth restriction (IUGR), poor cardiopulmonary or metabolic transitioning at birth, fetal or neonatal disease, congenital malformations, or intellectual impairment and other handicaps (Table 114.1).There is no accepted comprehensive definition of what constitutes a *high-risk pregnancy* , therefore, specific epidemiologic data regarding the incidence/prevalence cannot be reliably reported. Some factors, such as ingestion of a teratogenic drug in the first trimester, are causally related to the risk, while others, such as polyhydramnios, are associations that alert a physician to determine the etiology and avoid the inherent risks associated with excessive amniotic fluid. Although assessing antepartum risk is important in reducing perinatal mortality and morbidity, some pregnancies become high risk only during labor and delivery; therefore careful monitoring is critical throughout the intrapartum course.

Table 114.1

Factors Associated With High-Risk Pregnancy

ECONOMIC
Poverty
Unemployment
Uninsured, underinsured
Poor access to prenatal care
CULTURAL/BEHAVIORAL
Low educational status
Poor healthcare attitudes

No care or inadequate prenatal care
Cigarette, alcohol, or illicit drug use
Age <20 or >40 yr
Unmarried
Short interpregnancy interval (<18 mo between pregnancies)
Lack of support group (husband, family, religion)
Stress (physical, psychologic)
Black race (preterm birth rates are 48% higher than for other women)
BIOLOGIC/GENETIC
Previous low-birthweight or preterm infant
Low weight for height
Poor weight gain during pregnancy
Short stature
Poor nutrition
Consanguinity
Intergenerational effects
Low maternal birthweight
Maternal obesity
Hereditary diseases (inborn error of metabolism)
REPRODUCTIVE
Previous cesarean birth
Previous infertility
Conception by reproductive technology
Prolonged gestation (>40 wk)
Prolonged labor
Previous infant with cerebral palsy, intellectual impairment, birth trauma, or congenital anomalies
Abnormal lie (breech)
Multiple gestations
Premature rupture of membranes
Infection (systemic, amniotic, extra-amniotic, cervical)
Preeclampsia or eclampsia
Uterine bleeding (abruptio placentae, placenta previa)
Parity (0 or >5 previous deliveries)
Uterine or cervical anomalies
Fetal disease
Abnormal fetal growth
Idiopathic premature labor
Iatrogenic prematurity
High or low levels of maternal serum α-fetoprotein
MEDICAL
Diabetes mellitus
Hypertension
Congenital heart disease
Autoimmune disease
Sickle cell anemia
Intercurrent surgery or trauma
Sexually transmitted infection
Maternal hypercoagulable states
Exposure to prescription medications
TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex) infection

Identifying high-risk pregnancies is important not only because it is the first step toward prevention but also because critical steps may often be taken to reduce the risks to the fetus or neonate if the physician is alerted to the specific condition early in pregnancy.

Genetic Factors

The occurrence of chromosomal abnormalities, congenital anomalies, inborn errors of metabolism, cognitive delay, or any familial disease in blood relatives increases the risk of the same condition in the infant. Because many parents recognize only obvious clinical manifestations of genetically determined diseases, specific inquiry should be made about any disease affecting one or more blood relatives. A high index of suspicion should be maintained to the possibility of autosomal recessive disorders in offspring of couples who are closely related (i.e., consanguinity).

Maternal Factors

The lowest neonatal mortality rate occurs in infants of mothers who receive adequate prenatal care and who are 20-30 yr of age. Pregnancies in both teenagers and women older than 40, particularly primiparous women, are at increased risk for IUGR, fetal distress, preeclampsia, and stillbirth. Advanced maternal age increases the risk of both chromosomal and nonchromosomal fetal malformations (Fig. 114.1).

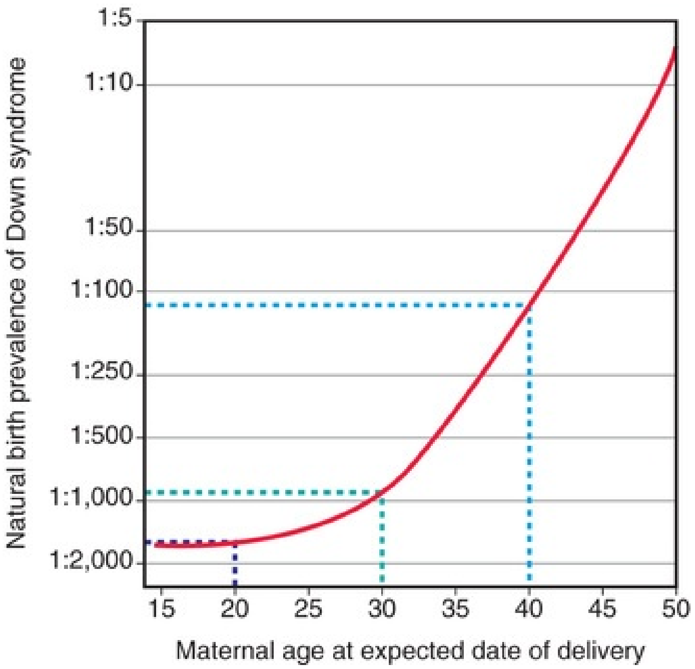

FIG. 114.1 **Natural birth prevalence of Down syndrome according to maternal age. (From Wald NJ, Leck I: *Antenatal and neonatal screening,* ed 2, Oxford, 2000, Oxford University Press.)**

Maternal illness (Table 114.2), multiple pregnancies (particularly those involving monochorionic twins), infections (Table 114.3), and certain drugs (see Chapter 115.4) increase the risk for the fetus. The use of assisted reproductive technology (e.g., ovulation induction, in vitro fertilization, intracytoplasmic sperm injection) increases the risk of prematurity, perinatal mortality, infant morbidity, low and very-low birthweight, imprinting disorders, and cerebral palsy. These risks are largely because of the increase in *multiple gestations* with such technology and the association with *prematurity* . The risks for *birth defects* are also increased with assisted reproductive technology, in part because of epigenetic effects on gene expression.

Table 114.2

Maternal Conditions Affecting the Fetus or Neonate

DISORDER	EFFECT(S)	MECHANISM(S)
Assisted reproductive technology	Beckwith-Wiedemann, Silver-Russel, Angelman syndromes	Altered imprinting
Autoantibody against folate receptors	Neural tube defects	Blockage of cellular uptake of folate
Cervical neoplasia	Preterm premature rupture of membranes, preterm birth	Associated with loop electrosurgical excision procedure or cone therapy

Cholestasis	Preterm delivery, intrauterine fetal demise	Unknown, possibly bile acid–induced fetal arrhythmia
Cyanotic heart disease	IUGR	Low fetal oxygen delivery
Diabetes mellitus:		
Mild	LGA, hypoglycemia	Fetal hyperglycemia: produces hyperinsulinemia; insulin promotes growth
Severe	Growth restriction	Vascular disease, placental insufficiency
Drug addiction	IUGR, neonatal withdrawal	Direct drug effect plus poor nutrition
Endemic goiter	Hypothyroidism	Iodine deficiency
Graves' disease	Transient neonatal thyrotoxicosis	Transplacental passage of IgG thyroid-stimulating antibody
Herpes gestationis (noninfectious)	Bullous rash, intrauterine fetal demise	Autoantibody similar to that in bullous pemphigoid
Hyperparathyroidism	Neonatal hypocalcemia	Maternal calcium crosses to fetus and suppresses fetal parathyroid gland
Hypertension	IUGR, intrauterine fetal demise	Placental insufficiency, fetal hypoxia
Idiopathic thrombocytopenic purpura	Thrombocytopenia	Nonspecific maternal platelet antibodies cross placenta
Isoimmune neutropenia or thrombocytopenia	Neutropenia or thrombocytopenia	Specific antifetus neutrophil or platelet antibody crosses placenta after sensitization of mother
Malignant melanoma	Placental or fetal tumor	Placental metastasis
Myasthenia gravis	Transient neonatal myasthenia	IgG antibody to acetylcholine receptor crosses placenta
Myotonic dystrophy	Neonatal myotonic dystrophy, congenital contractures, respiratory insufficiency	Genetic anticipation
NMDAR antibody encephalitis	Cortical dysplasia	Transplacental antibody
Obesity	LGA or IUGR, hypoglycemia	Unknown, similarities to diabetes
Phenylketonuria	Microcephaly, retardation	Elevated fetal phenylalanine values
Poor nutrition	IUGR, adult insulin resistance	Reduced fetal nutrients, nutritional programming
Preeclampsia, eclampsia	IUGR, thrombocytopenia, neutropenia, fetal demise	Uteroplacental insufficiency, fetal hypoxia, vasoconstriction
Renal transplantation	IUGR	Uteroplacental insufficiency
Rhesus or other blood group sensitization	Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice	IgG crosses placenta and is directed to fetal cells with antigen
Sickle cell anemia	Preterm birth, IUGR, stillbirth	Placental insufficiency via maternal sickling, producing fetal hypoxia
Systemic lupus erythematosus	Congenital heart block, rash, anemia, thrombocytopenia, neutropenia	Antibody directed to fetal heart, red and white blood cells, and platelets

IgG, Immunoglobulin G; LGA, large for gestational age; NMDAR, antibody to *N* -methyl-D -aspartate receptor; IUGR, intrauterine growth restriction.

Table 114.3

Maternal Infections Affecting the Fetus or Newborn

INFECTION	**MODE(S) OF**	**NEONATAL OUTCOME**

	TRANSMISSION	
BACTERIA		
Group B streptococcus	Ascending cervical	Sepsis, pneumonia
Escherichia coli	Ascending cervical	Sepsis, pneumonia
Listeria monocytogenes	Transplacental	Sepsis, pneumonia
Mycoplasma hominis	Ascending cervical	Pneumonia
Chlamydia trachomatis	Vaginal passage	Conjunctivitis, pneumonia
Syphilis	Transplacental, vaginal passage	Congenital syphilis
Neisseria gonorrhoeae	Vaginal passage	Ophthalmia (conjunctivitis), sepsis, meningitis
Mycobacterium tuberculosis	Transplacental	Prematurity, fetal demise, congenital tuberculosis
VIRUS		
Rubella	Transplacental	Congenital rubella
Cytomegalovirus	Transplacental, breast milk (rare)	Congenital cytomegalovirus or asymptomatic
HIV	Transplacental, vaginal passage, breast milk	Congenital or acquired immunodeficiency syndrome
Hepatitis B	Vaginal passage, transplacental, breast milk	Neonatal hepatitis, chronic hepatitis B surface antigen carrier state
Hepatitis C	Transplacental and vaginal passage	Rarely neonatal hepatitis, ~5% chronic carrier state possible
Herpes simplex type 2 or 1	Intrapartum exposure	Neonatal herpes simplex virus
		Neonatal encephalitis; disseminated viremia, or cutaneous infection
Varicella-zoster	Transplacental:	
	Early	Congenital anomalies
	Late	Neonatal varicella
Parvovirus	Transplacental	Fetal anemia, hydrops
Coxsackievirus B	Fecal-oral	Myocarditis, meningitis, hepatitis
Rubeola	Transplacental	Abortion, fetal measles
West Nile	Transplacental (rare) Possible perinatal	Uncertain, possible rash, encephalitis
Zika	Transplacental	Congenital microcephaly, intracranial calcifications, brain abnormalities, retinal lesions
Chikungunya	Transplacental (rare), perinatal	Neonatal encephalitis
Dengue	Transplacental, perinatal	Neonatal sepsis-like symptoms
PARASITES		
Toxoplasmosis	Transplacental	Congenital toxoplasmosis
Malaria	Transplacental	Abortion, prematurity, intrauterine growth restriction
FUNGI		
Candida	Ascending, cervical	Sepsis, pneumonia, rash

Preterm birth is common in high-risk pregnancies (see Chapter 117). Factors associated with prematurity (see Table 114.1) include multiple gestations as well as biologic markers such as cervical shortening, genital infection, presence of fetal fibronectin in cervicovaginal secretions, serum α-fetoprotein (AFP), and premature rupture of membranes (PROM). PROM occurs in 3% of all pregnancies in the United States and is a leading identifiable cause of prematurity.

The presence of **polyhydramnios** or **oligohydramnios** indicates high-risk pregnancies. Amniotic fluid volume is variable throughout pregnancy and progressively increases from 10 to 30 wk of gestation. On average, volume is typically <10 mL at 8 wk and increases to 630 and 770 mL at 22 and 28 wk, respectively. After 30 wk, the rate of increase slows and the volume remains fairly constant until 36-38 wk gestation. This is followed by a progressive decline, with an average volume of 515 mL at 41 wk of gestation. Polyhydramnios complicates 1–3%, and oligohydramnios 1–5%, of pregnancies; although the true incidence of amniotic fluid disorders is confounded by the lack of a uniform approach to diagnosis. The ultrasound (US) criteria for these diagnoses are based on either the *amniotic fluid index* (AFI) or a *deepest vertical pocket* (DVP). The AFI is determined by measuring the vertical dimension of amniotic fluid pockets in 4 quadrants and reporting the sum of these values. An index >24 cm suggests polyhydramnios, whereas an index <5 cm suggests oligohydramnios. The DVP method reports the deepest pocket of fluid identified with a value of 2-8 cm is considered normal.

Polyhydramnios is associated with preterm labor, abruptio placentae, maternal diabetes, multiple congenital anomalies, aneuploidy, and fetal neuromuscular dysfunction or obstruction of the gastrointestinal tract that interferes with reabsorption of the amniotic fluid that is normally swallowed by the fetus (Table 114.4). Increased fetal urination, as with congenital nephrotic syndrome, or edema formation, such as hydrops fetalis, is also associated with excessive amniotic fluid volume. US demonstrates the increased amniotic fluid surrounding the fetus and detects associated fetal anomalies, hydrops, pleural effusions, and ascites. **Idiopathic** polyhydramnios is the most common cause, affecting approximately 40% of patients. About 25% of these cases will demonstrate an abnormality in the postnatal period. Otherwise, approximately 33% of prenatally detected cases have an associated anomaly, and 25% are associated with maternal diabetes. Severe and symptomatic polyhydramnios may be managed by serial reduction amniocenteses. Treatment is indicated for acute maternal respiratory discomfort and threatened preterm labor, or to provide time for the administration of corticosteroids to enhance fetal lung maturity.

Table 114.4

Conditions Associated With Disorders of Amniotic Fluid Volume

OLIGOHYDRAMNIOS
Amniotic fluid leak/rupture of membranes
Intrauterine growth restriction
Fetal anomalies (particularly GU abnormalities)
Twin-twin transfusion (donor)
Fetal akinesia syndrome
Prune-belly syndrome
Pulmonary hypoplasia
Amnion nodosum
Indomethacin
Angiotensin-converting enzyme inhibitors or receptor antagonists
POLYHYDRAMNIOS
Congenital Anomalies
CNS abnormalities
Tracheoesophageal fistula
Intestinal atresia
Spina bifida
Cleft lip or palate
Cystic adenomatoid lung malformation
Diaphragmatic hernia
Syndromes
Achondroplasia
Klippel-Feil
Trisomy 18
Trisomy 21
TORCH*
Hydrops fetalis
Multiple congenital anomalies
Bartter
Other
Diabetes mellitus
Twin-twin transfusion (recipient)
Fetal anemia
Fetal heart failure
Polyuric renal disease (congenital nephrotic syndrome)
Neuromuscular diseases
Nonimmune hydrops
Chylothorax
Teratoma
Idiopathic

* Toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex.

CNS, Central nervous system; GU, genitourinary.

Oligohydramnios is associated with congenital anomalies; IUGR; severe renal, bladder, or urethral anomalies; and drugs that interfere with fetal urination (see Table 114.4). Oligohydramnios becomes most evident after 16-20 wk of gestation, when fetal urination is the major source of amniotic fluid. PROM is a common cause of oligohydramnios and must be ruled out if present, especially if a normal-sized bladder and kidneys are seen on fetal US. Oligohydramnios causes fetal compression abnormalities such as fetal distress/stillbirth from umbilical cord compression, clubfoot, spadelike hands, and a flattened nasal bridge. The most serious complication of chronic oligohydramnios is **pulmonary hypoplasia** , especially if present during the canalicular stage of fetal lung development, which occurs between 16 and 24 wk of gestation. The risk of umbilical cord compression during labor and delivery is increased in pregnancies complicated by oligohydramnios and may be alleviated by saline amnioinfusion via a transcervical intrauterine pressure catheter, which has been demonstrated to reduce the need for cesarean section and improve Apgar scores.

A pregnancy should be considered high risk when the uterus is inappropriately large or small. A uterus large for the estimated stage of gestation suggests the presence of multiple fetuses, polyhydramnios, or an excessively large infant. An inappropriately small uterus suggests oligohydramnios or poor fetal growth.

Mode of delivery is influenced by a complex interplay between maternal-fetal factors. Spontaneous vaginal delivery is always preferred when not otherwise contraindicated. Operative vaginal delivery with vacuum or forceps is a safe alternative to cesarean delivery in appropriately selected patients. The absolute rate of significant newborn injury from these procedures is low, with rates ranging from 1 in 650-850 for **intracranial hemorrhage** and 1 in 220-385 for **neurologic complications** . With some of these injuries, the *indication* for operative vaginal delivery is more likely to be associated with the injury than the procedure itself, and could not have been prevented with a cesarean birth.

Cesarean delivery is indicated for a wide variety of circumstances. Cesarean-born infants present problems that are often related to the unfavorable obstetric circumstance that necessitated the operation. In normal term pregnancies without indication of fetal distress, cesarean delivery carries a greater neonatal risk than delivery through the birth canal. Even when accounting for gestational age, any malformations, birthweight, and multiple gestations, infants born ≥34 wk of gestation via elective cesarean section have 2 times the mortality rate of babies born following a planned vaginal birth, even if cesarean delivery was ultimately required. They also are 1.4 times as likely to require neonatal intensive care unit (NICU) admission and 1.8 times as likely to require breathing support for >30 min after birth. Cesarean-born infants are also at increased risk for persistent **pulmonary hypertension of the newborn** . An elective cesarean birth should be delayed until ≥39 wk of gestation, assuming there is no indication for delivery earlier.

Obstetric anesthesia is a vital component of care on the labor and delivery unit. The most common form of anesthesia in this patient population is *regional* (i.e., epidural or spinal). From the fetal/neonatal standpoint, the most significant complication encountered with this procedure is acute maternal hypotension, which can significantly impair uteroplacental perfusion. Fetal heart rate (FHR) abnormalities are common in this circumstance and, rarely, require emergent cesarean delivery if not amenable to standard in utero resuscitative efforts. *Opioid analgesia* is sometimes used in women who are not candidates for regional anesthesia. This form of pain relief is best avoided as delivery approaches, to minimize risk of neonatal depression. To this end, when opioid use is necessary, it is best to prescribe regimens that have a very short half-life. It is essential that the pediatric team is present at the birth in women receiving opioid analgesia. Furthermore, the pediatricians must be alerted to the specific type of opioid used, because all these drugs cross the placenta and have varying neonatal pharmacokinetics. Some of the common regimens used and their respective neonatal half-life are listed in the referenced American College of Obstetricians and Gynecologists (ACOG) practice bulletin on obstetric anesthesia.

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CHAPTER 115

The Fetus

Kristen R. Suhrie, Sammy M. Tabbah

The major emphasis in fetal medicine involves (1) assessment of fetal growth and maturity, (2) evaluation of fetal well-being or distress, (3) assessment of the effects of maternal disease on the fetus, (4) evaluation of the effects of drugs administered to the mother on the fetus, and (5) identification and when possible treatment of fetal disease or anomalies.

One of the most important tools used to access fetal well-being is ultrasonography (ultrasound, US); it is both safe and reasonably accurate. Indications for antenatal US include estimation of gestational age (unknown dates, discrepancy between uterine size and dates, or suspected growth restriction), assessment of amniotic fluid volume, estimation of fetal weight and growth, determination of the location of the placenta and the number and position of fetuses, and identification of congenital anomalies. Fetal MRI is a more advanced imaging method that is thought to be safe to the fetus and neonate and is used for more advanced diagnostic and therapeutic planning (Fig. 115.1).

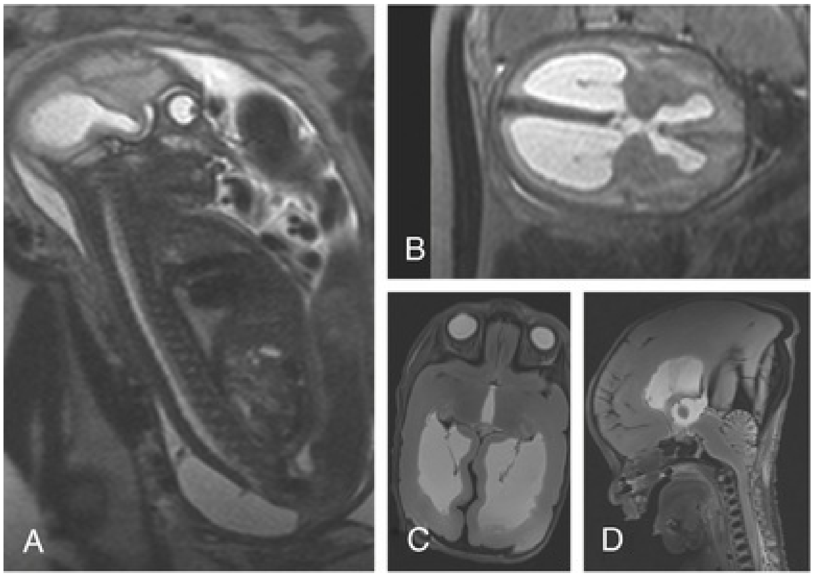

FIG. 115.1 MRI of fetal pathology. A, Fetus with sacral myelomeningocele at 30 wk gestation. B, Ventriculomegaly in the same fetus as in A. C, MRI can also be used for postmortem examination, here in a 33 wk old fetus, demonstrating ventriculomegaly with heterotopic foci in the ventricular walls. D, Chiari II malformation of the brainstem. (Courtesy of Filip Claus, Aalst, Belgium.)

115.1

Fetal Growth and Maturity

Kristen R. Suhrie, Sammy M. Tabbah

Fetal growth can be assessed by US as early as 6-8 wk of gestation by measurement of the crown-rump length. Accurate determination of gestational age can be achieved through the 1st half of pregnancy; however, first-trimester assessment by crown-rump length measurement is the most effective method of pregnancy dating. In the second trimester and beyond, a combination of biometric measures (i.e., biparietal diameter, head and abdominal circumference, femoral diaphysis length) is used for gestational age and growth assessment (Fig. 115.2). If a single US examination is performed, the most information can be obtained with a scan at 18-20 wk, when both gestational age and fetal anatomy can be evaluated. Serial scans assessing fetal growth are performed when risk factors for **fetal growth restriction (FGR)** are present. Two patterns of FGR have been identified: *symmetric* FGR, typically present early in pregnancy, and *asymmetric* FGR, typically occurring later in gestation. The most widely accepted definition of FGR in the United States is an **estimated fetal weight (EFW)** of less than the 10th percentile (Fig. 115.3). Some aspects of human fetal growth and development are summarized in Chapter 20 .

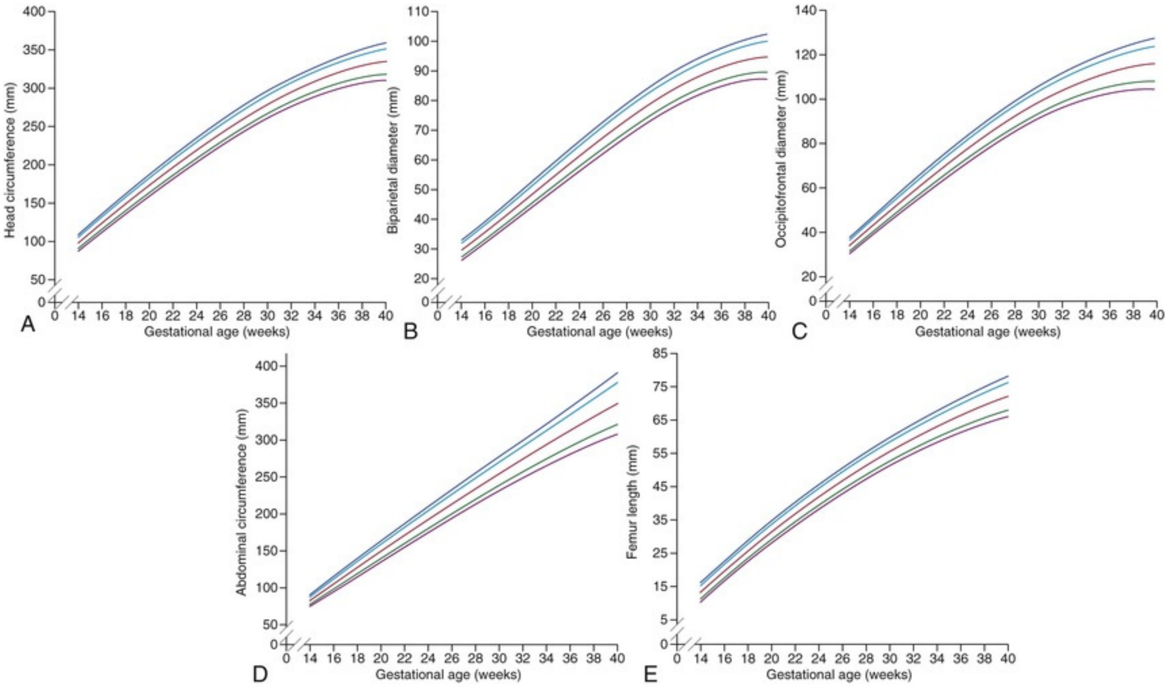

FIG. 115.2 Fetal measurements: 3rd, 10th, 50th, 90th, and 97th smoothed centile curves. A, Fetal head circumference; B, fetal biparietal diameter; C, fetal occipitofrontal diameter; D, fetal abdominal circumference; and E, fetal femur length measured by ultrasound (US) according to gestational age. (From Papageorghiou AT, Ohyma EO, Altman DG, et al: International standards for fetal growth based on serial US measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project, Lancet 384:869–878, 2014, Fig 3.)

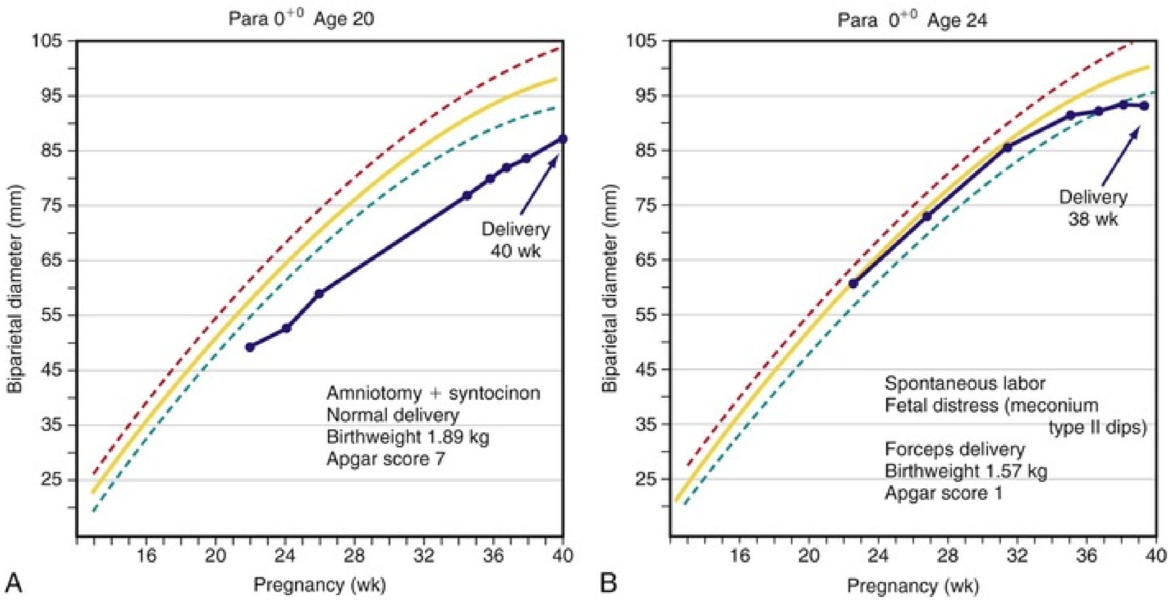

FIG. 115.3 **A,** Example of a “low-profile” growth restriction pattern in an uneventful pregnancy and labor. The baby cried at 1 min, and hypoglycemia did not develop. Birthweight was below the 5th percentile for gestational age. **B,** Example of a “late-flattening” growth restriction pattern. The mother had a typical history of preeclampsia, and the infant had intrapartum fetal distress, a low Apgar score, and postnatal hypoglycemia. Birthweight was below the 5th percentile for gestational age. (From Campbell S: Fetal growth, *Clin Obstet Gynecol* 1:41–65, 1974.)

Fetal maturity and dating are usually assessed by last menstrual period (LMP), assisted reproductive technology (ART)–derived gestational age, or US assessments. Dating by LMP assumes an accurate recall of the 1st day of LMP, a menstrual cycle that lasted 28 days, and ovulation occurring on the 14th day of the cycle, which would place the **estimated delivery date (EDD)** 280 days after LMP. Inaccuracies with any of these parameters can lead to an incorrectly assigned gestational age if the LMP is used for dating. Dating by ART is the most accurate method for assigning gestational age with EDD occurring 266 days after conception (when egg is fertilized by sperm). When US is used for dating, the most accurate assessment of gestational age is by first-trimester ($\leq 13\frac{6}{7}$ wk) US measurement of crown-rump length, which is accurate to within 5-7 days. In contrast, US dating in the second trimester is accurate to 10-14 days, and third trimester is only accurate to 21-30 days. Dating of a pregnancy is critical to determine when delivery should occur, if growth is appropriate during the pregnancy, and when testing and interventions should be offered. The earliest assessment of pregnancy dating should be used throughout the pregnancy unless methodologies used later in pregnancy are significantly different.

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115.2

Fetal Distress

Kristen R. Suhrie, Sammy M. Tabbah

Fetal compromise may occur during the antepartum or intrapartum period. It may be asymptomatic in the antenatal period but is often suspected by maternal perception of decreased fetal movement. **Antepartum fetal surveillance** is warranted for women at increased risk for fetal death, including those with a history of stillbirth, intrauterine growth restriction (IUGR), oligohydramnios or polyhydramnios, multiple gestation, rhesus sensitization, hypertensive disorders, diabetes mellitus or other chronic maternal disease, decreased fetal movement, preterm labor, preterm rupture of membranes (PROM), and postterm pregnancy. The predominant cause of antepartum fetal distress is uteroplacental insufficiency, which may manifest clinically as IUGR, fetal hypoxia, increased vascular resistance in fetal blood vessels (Figs. 115.4 and 115.5), and, when severe, mixed respiratory and metabolic (lactic) acidosis. The goal of antepartum fetal surveillance is to identify the fetus at risk of stillbirth such that appropriate interventions (i.e., delivery vs optimization of underlying maternal medical condition) can be implemented to allow for a healthy live-born infant. Table 115.1 lists methods for assessing fetal well-being.

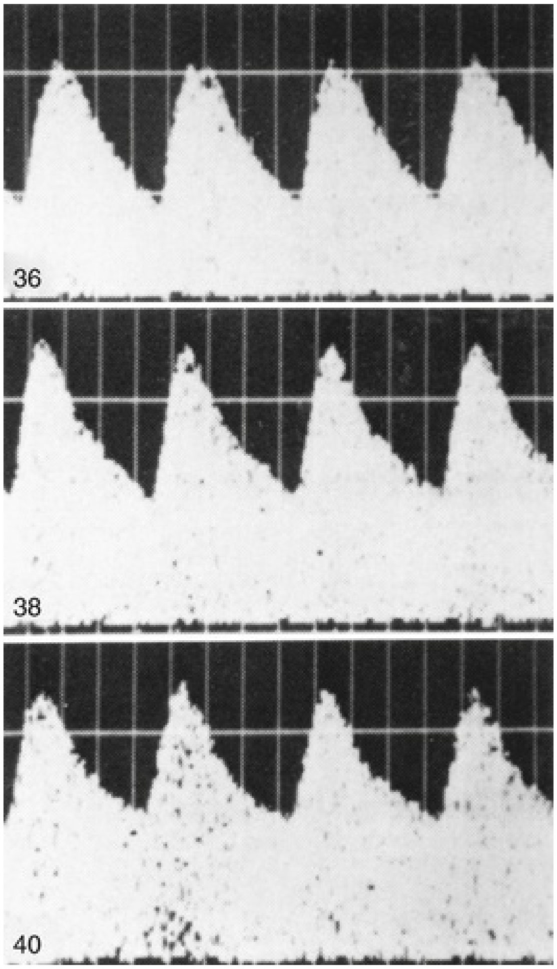

FIG. 115.4 Normal doppler velocity in sequential studies of fetal umbilical artery flow velocity waveforms from one normal pregnancy. Note the systolic peak flow with lower but constant heart flow during diastole. The systolic/diastolic ratio can be determined and, in normal pregnancies, is <3 after the 30th wk of gestation. The *numbers* indicate the weeks of gestation. (From Trudinger B: Doppler US assessment of blood flow. In Creasy RK, Resnik R, editors: *Maternal-fetal medicine: principles and practice,* ed 5, Philadelphia, 2004, Saunders.)

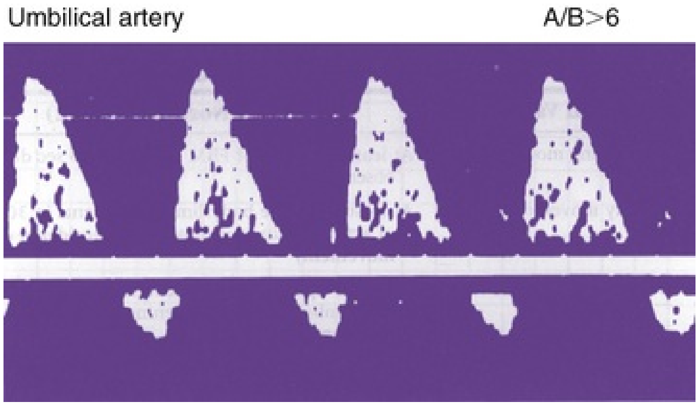

FIG. 115.5 Abnormal umbilical artery Doppler in which the diastolic component shows flow in a reverse direction. This finding occurs in severe intrauterine hypoxia and intrauterine growth restriction. (From Trudinger C: Doppler US assessment of blood flow. In Creasy RK, Resnik R, editors: *Maternal-fetal medicine: principles and practice,* ed 5, Philadelphia, 2004, Saunders.)

Table 115.1

Fetal Diagnosis and Assessment

METHOD	COMMENT(S) AND INDICATION(S)
IMAGING	
Ultrasound (real-time)	Biometry (growth), anomaly detection, number of fetuses, sites of calcification
	Biophysical profile
	Amniotic fluid volume, hydrops
Ultrasound (Doppler)	Velocimetry (blood flow velocity)
	Detection of increased vascular resistance in the umbilical artery secondary to placental insufficiency
	Detection of fetal anemia (MCA Doppler)
MRI	Defining of lesions before fetal surgery
	Better delineation of fetal CNS anatomy
FLUID ANALYSIS	
Amniocentesis	Karyotype or microarray (cytogenetics), biochemical enzyme analysis, molecular genetic DNA diagnosis, or α-fetoprotein determination
	Bacterial culture, pathogen antigen, or genome detection (PCR)
Cordocentesis (percutaneous umbilical blood sampling)	Detection of blood type, anemia, hemoglobinopathies, thrombocytopenia, polycythemia, acidosis, hypoxia, thrombocytopenia, IgM antibody response to infection
	Rapid karyotyping and molecular DNA genetic diagnosis
	Fetal therapy (see Table 115.5)
FETAL TISSUE ANALYSIS	
Chorionic villus biopsy	Cytogenetic and molecular DNA analysis, enzyme assays
Circulating fetal DNA	Noninvasive molecular DNA genetic analysis including microarray analysis and chromosome number (screening method)
MATERNAL SERUM α-FETOPROTEIN CONCENTRATION	
Elevated	Twins, neural tube defects (anencephaly, spina bifida), intestinal atresia, hepatitis,

	nephrosis, fetal demise, incorrect gestational age
Reduced	Trisomies, aneuploidy
MATERNAL CERVIX	
Fetal fibronectin	Indicates possible risk of preterm birth
Transvaginal cervical length	Short length suggests possible risk of preterm birth
Bacterial culture	Identifies risk of neonatal infection (group B streptococcus, *Neisseria gonorrhoeae, Chlamydia trachomatis*)
Amniotic fluid	Determination of premature rupture of membranes (PROM)
ANTEPARTUM BIOPHYSICAL MONITORING	
Nonstress test	Fetal distress; hypoxia
Biophysical profile and modified biophysical profile	Fetal distress; hypoxia
Intrapartum fetal heart rate monitoring	See Fig. 115.6

The most common noninvasive tests are the nonstress test (**NST**) and the biophysical profile (**BPP**). The NST monitors the presence of fetal heart rate (**FHR**) accelerations that follow fetal movement. A reactive (normal) NST result demonstrates 2 FHR accelerations of at least 15 beats/min above the baseline FHR lasting 15 sec during 20 min of monitoring. A nonreactive NST result suggests possible fetal compromise and requires further assessment with a BPP. Although the NST has a low false-negative rate, it does have a high false-positive rate, which is often remedied by the BPP. The full BPP assesses fetal breathing, body movement, tone, NST, and amniotic fluid volume. It effectively combines acute and chronic indicators of fetal well-being, which improves the predictive value of abnormal testing (Table 115.2). A score of 2 or 0 is given for each observation. A total score of 8-10 is reassuring; a score of 6 is equivocal, and retesting should be done in 12-24 hr; and a score of 4 or less warrants immediate evaluation and possible delivery. The BPP has good negative predictive value. The modified BPP consists of the combination of an US estimate of amniotic fluid volume (the amniotic fluid index) and the NST. When results of both are normal, fetal compromise is very unlikely. Signs of progressive compromise seen on Doppler US include reduced, absent, or reversed diastolic waveform velocity in the fetal aorta or umbilical artery (see Fig. 115.5 and Table 115.1). The umbilical vein and ductus venosus waveforms are also used to assess the degree of fetal compromise. Fetuses at highest risk of stillbirth often have combinations of abnormalities, such as growth restriction, oligohydramnios, reversed diastolic Doppler umbilical artery blood flow velocity, and a low BPP.

Table 115.2

Biophysical Profile Scoring: Technique and Interpretation

BIOPHYSICAL VARIABLE	NORMAL SCORE (2)	ABNORMAL SCORE (0)
Fetal breathing movements (FBMs)	At least 1 episode of FBM of at least 30 sec duration in 30 min observation	Absence of FBM or no episode ≥30 sec in 30 min
Gross body movement	At least 3 discrete body/limb movements in 30 min (episodes of active continuous movement considered a single movement)	2 or fewer episodes of body/limb movements in 30 min
Fetal tone	At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk Opening and closing of hand considered evidence of normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absence of fetal movement with the hand held in complete or partial deflection
Reactive fetal heart rate (FHR)	At least 2 episodes of FHR acceleration of ≥15 beats/min and at least 15 sec in duration associated with fetal movement in 30 min	Less than 2 episodes of acceleration of FHR or acceleration of <15 beats/min in 30 min
Quantitative amniotic fluid (AF) volume[*]	At least 1 pocket of AF that measures at least 2 cm in 2 perpendicular planes	Either no AF pockets or a pocket <2 cm in 2 perpendicular planes

[*] Modification of the criteria for reduced amniotic fluid from <1 cm to <2 cm would seem reasonable. Ultrasound is used for biophysical assessment of the fetus.

From Creasy RK, Resnik R, Iams JD, editors: *Maternal-fetal medicine: principles and practice,* ed 5, Philadelphia, 2004, Saunders.

Fetal compromise *during labor* may be detected by monitoring the FHR, uterine pressure, and fetal scalp blood pH (Fig. 115.6). **Continuous fetal heart rate monitoring** detects abnormal cardiac patterns by instruments that compute the beat-to-beat FHR from a fetal electrocardiographic signal. Signals are derived either from an electrode attached to the fetal presenting part, from an ultrasonic transducer placed on the maternal abdominal wall to detect continuous ultrasonic waves reflected from the contractions of the fetal heart, or from a phonotransducer placed on the mother's abdomen. Uterine contractions are recorded from an intrauterine pressure catheter or from an external tocotransducer applied to the maternal abdominal wall overlying the uterus. FHR patterns show various characteristics, some of which suggest fetal compromise. The baseline FHR is determined over 10 min devoid of accelerations or decelerations. Over the course of pregnancy, the normal baseline FHR gradually decreases from approximately 155 beats/min in early pregnancy to 135 beats/min at term. The normal range throughout pregnancy is 110-160 beats/min. **Tachycardia** (>160 beats/min) is associated with early fetal hypoxia, maternal fever, maternal hyperthyroidism, maternal β-sympathomimetic drug or atropine therapy, fetal anemia, infection, and some fetal arrhythmias. Arrhythmias do not generally occur with congenital heart disease and may resolve spontaneously at birth. **Fetal bradycardia** (<110 beats/min) may be normal (e.g., 105-110 beats/min) but may occur with fetal hypoxia, placental transfer of local anesthetic agents and β-adrenergic blocking agents, and occasionally, heart block with or without congenital heart disease.

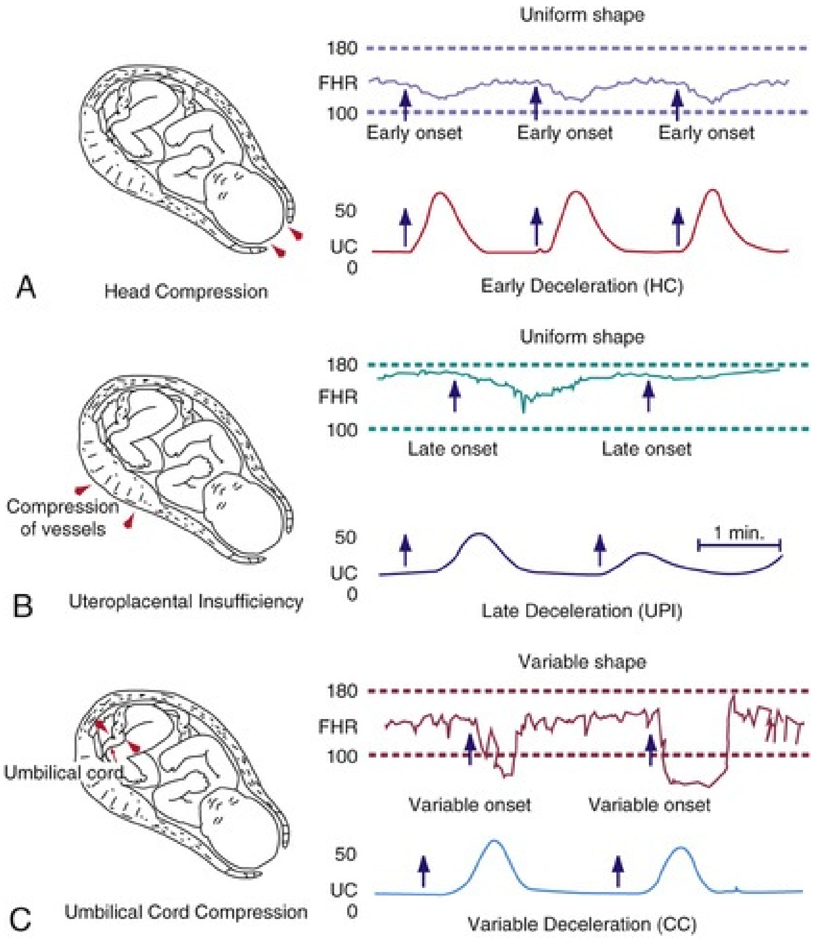
Uniform shape
180
FHR
100
Early onset
Early onset
Early onset
50
UC
0
A
Head Compression
Early Deceleration (HC)
Uniform shape
180
FHR
100
Late onset
Late onset
Compression of vessels
50
1 min.
UC
0
B
Uteroplacental Insufficiency
Late Deceleration (UPI)
Variable shape
180
FHR
100
Umbilical cord
Variable onset
Variable onset
50
UC
0
C
Umbilical Cord Compression
Variable Deceleration (CC)

FIG. 115.6 **Patterns of periodic fetal heart rate (FHR) deceleration. The tracing in A shows early deceleration occurring during the peak of uterine contractions as a result of pressure on the fetal head. B, Late deceleration caused by uteroplacental insufficiency. C, Variable deceleration as a result of umbilical cord compression. *Arrows* denote the time relationship between the onset of FHR changes and uterine contractions. (From Hon EH: *An atlas of fetal heart rate patterns,* New Haven, CT, 1968, Harty Press.)**

Normally, the baseline FHR is variable as a result of opposing forces from the fetal sympathetic and parasympathetic nervous systems. **Variability** is classified as follows: *absence of variability*, if an amplitude change is undetectable;

minimal variability, if amplitude range is ≤5 beats/min; *moderate* variability, if amplitude range is 6-25 beats/min; and *marked* variability, if amplitude range is >25 beats/min. Variability may be decreased or lost with fetal hypoxemia or the placental transfer of drugs such as atropine, diazepam, promethazine, magnesium sulfate, and most sedative and narcotic agents. Prematurity, the sleep state, and fetal tachycardia may also diminish beat-to-beat variability.

Accelerations or decelerations of the FHR in response to or independent of uterine contractions may also be monitored (see Fig. 115.6). An **acceleration** is an abrupt increase in FHR of ≥15 beats/min in ≥15 sec. The presence of accelerations or moderate variability reliably predicts the absence of fetal metabolic acidemia. However, their absence does not reliably predict fetal acidemia or hypoxemia. **Early decelerations** are a physiologic vagal response to uterine contractions, with resultant fetal head compression, and represent a repetitive pattern of gradual decrease and return of the FHR that is coincidental with the uterine contraction (Table 115.3). **Variable decelerations** are associated with umbilical cord compression and are characterized by a V or U shaped pattern, are abrupt in onset and resolution, and may occur with or without uterine contractions.

Table 115.3

Characteristics of Decelerations of Fetal Heart Rate (FHR)

LATE DECELERATION
Visually apparent, usually symmetric *gradual* decrease and return of the FHR associated with a uterine contraction. A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the nadir of the FHR. The decrease in FHR is calculated from the onset to the nadir of the deceleration. The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction. In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively.
EARLY DECELERATION
Visually apparent, usually symmetric *gradual* decrease and return of the FHR associated with a uterine contraction. A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the FHR nadir. The decrease in FHR is calculated from the onset to the nadir of the deceleration. The nadir of the deceleration occurs at the same time as the peak of the contraction. In most cases, the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively.
VARIABLE DECELERATION
Visually apparent, *abrupt* decrease in FHR. An *abrupt* FHR decrease is defined as duration <30 sec from the onset of the deceleration to the beginning of the FHR nadir of the deceleration. The decrease in FHR is calculated from the onset to the nadir of the deceleration.

The decrease in FHR is ≥15 beats/min, lasting ≥15 sec, and <2 min in duration. When variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions.

From Macones GA, Hankins GDV, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, *Obstet Gynecol* 112:661–666, 2008.

Late decelerations are associated with fetal hypoxemia and are characterized by onset after a uterine contraction is well established and persists into the interval following resolution of the contraction. The late deceleration pattern is usually associated with maternal hypotension or excessive uterine activity, but it may be a response to any maternal, placental, umbilical cord, or fetal factor that limits effective oxygenation of the fetus. The significance of late decelerations varies according to the underlying clinical context. They are most likely to be associated with true fetal hypoxemia/acidemia when they are recurrent and occur in conjunction with decreased or absent variability. Late decelerations represent a compensatory, chemoreceptor-mediated response to fetal hypoxemia. The transient decrease in FHR serves to increase ventricular preload during the peak of hypoxemia (i.e., at the crest of a uterine contraction). If fetal acidemia progresses, late decelerations may become less pronounced or absent, indicating severe hypoxic depression of myocardial function. Prompt delivery is indicated if late decelerations are unresponsive to oxygen supplementation, hydration, discontinuation of labor stimulation, and position changes. Approximately 10–15% of term fetuses have *terminal* (just before delivery) FHR decelerations that are usually benign if they last <10 min before delivery.

A 3-tier system has been developed by a panel of experts for interpretation of FHR tracings (Table 115.4). **Category I tracings** are normal and are strongly predictive of normal fetal acid-base status at the time of the observation. **Category II tracings** are not predictive of abnormal fetal status, but there is insufficient evidence to categorize them as category I or III; therefore further evaluation, surveillance, and reevaluation are indicated. **Category III tracings** are abnormal and predictive of abnormal fetal acid-base status at the time of observation. Category III tracings require prompt evaluation and efforts to resolve expeditiously the abnormal FHR as previously discussed for late decelerations.

Table 115.4

Three-Tier Fetal Heart Rate (FHR) Interpretation System

CATEGORY I
Category I FHR tracings include all the following: • Baseline rate: 110-160 beats/min • Baseline FHR variability: moderate • Late or variable decelerations: absent • Early decelerations: present or absent • Accelerations: present or absent
CATEGORY II
Category II FHR tracings include all FHR tracings not categorized as category I or category III. Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples of category II FHR tracings include any of the following:
Baseline Rate
• Bradycardia not accompanied by absence of baseline variability • Tachycardia
Baseline FHR Variability
• Minimal baseline variability • Absence of baseline variability not accompanied by recurrent decelerations • Marked baseline variability
Accelerations
• Absence of induced accelerations after fetal stimulation
Periodic or Episodic Decelerations
• Recurrent variable decelerations accompanied by minimal or moderate baseline variability • Prolonged deceleration, ≥2 min but <10 min • Recurrent late decelerations with moderate baseline variability • Variable decelerations with other characteristics, such as slow return to baseline, “overshoots,” and “shoulders”
CATEGORY III
Category III FHR tracings include either: • Absence of baseline FHR variability *or* Any of the following: • Recurrent late decelerations • Recurrent variable decelerations • Bradycardia • Sinusoidal pattern

Adapted from Macones GA, Hankins GDV, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, *Obstet Gynecol* 112:661–666, 2008.

Umbilical cord blood samples obtained at delivery are useful to document fetal acid-base status. Although the exact cord blood pH value that defines significant fetal acidemia is unknown, an umbilical artery pH <7.0 has been associated with greater need for resuscitation and a higher incidence of respiratory, gastrointestinal, cardiovascular, and neurologic complications. Nonetheless, in many cases, even when a low pH is detected, newborn infants are neurologically normal.

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115.3

Maternal Disease and the Fetus

Kristen R. Suhrie, Sammy M. Tabbah

Infectious Diseases

See Table 114.3 in Chapter 114 for a list of common maternal infectious diseases that impact the fetus and newborn.

Almost any maternal infection with severe systemic manifestations may result in miscarriage, stillbirth, or premature labor. Whether these results are a consequence of infection of the fetus or are secondary to maternal illness is not always clear. Another important factor to consider when dealing with infectious diseases in pregnancy is the timing of infection. In general, infections that occur earlier in the pregnancy (first or second trimester) are more likely to result in miscarriage or problems with organogenesis, such as the neuromigrational abnormalities seen in newborns with congenital CMV infections.

Cytomegalovirus (CMV) is the most common congenital infection, affecting 0.2–2.2% of all neonates (see Chapter 282). Perinatal transmission can occur at any time during the pregnancy; however, the most devastating sequelae occur with first-trimester infection. After a primary infection, 12–18% of neonates will have signs and symptoms at birth, and as many as 25% can develop long-term complications. The most common complication is **congenital hearing loss** . Severely affected infants have an associated 30% mortality, and 65–80% of survivors develop severe neurologic morbidity. A mother with a history of CMV may experience reactivation of the disease or may be infected with a different strain of the virus and transmit the infection to the fetus. Currently, there are no well-studied or validated antenatal therapies targeted toward decreasing disease severity or preventing congenital infection in the setting of primary maternal CMV infection. Preliminary data from some studies have demonstrated promise with drugs such as valganciclovir and CMV-specific hyperimmune globulin, but confirmatory data are lacking. For this reason, the American College of Obstetricians and Gynecologists (ACOG) does not recommend antenatal therapy for congenital CMV infection outside of an established research protocol.

Noninfectious Diseases (see Table 114.2)

Maternal diabetes increases the risk for neonatal hypoglycemia, hypocalcemia, respiratory distress syndrome and other respiratory problems, feeding difficulties, polycythemia, macrosomia, growth restriction, myocardial dysfunction, jaundice, and congenital malformations (see Chapter 127.1). There is an increased risk of uteroplacental insufficiency, polyhydramnios, and fetal demise in poorly controlled diabetic mothers. **Preeclampsia-eclampsia** , **chronic hypertension** , and **chronic renal disease** can result in IUGR, prematurity, and fetal death, all probably caused by diminished uteroplacental perfusion.

Uncontrolled maternal **hypothyroidism** or **hyperthyroidism** is responsible for relative infertility, spontaneous abortion, premature labor, and fetal death. Hypothyroidism in pregnant women (even if mild or asymptomatic) can adversely affect neurodevelopment of the child, especially if the newborn is found to have congenital hypothyroidism.

Maternal **immunologic diseases** such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis, and Graves disease, all of which are mediated by immunoglobulin G autoantibodies that can cross the placenta, frequently cause transient illness in the newborn. Maternal autoantibodies to the folate receptor are associated with neural tube defects (**NTDs**), whereas maternal immunologic sensitization to fetal antigens may be associated with neonatal alloimmune hepatitis and neonatal alloimmune thrombocytopenia (**NAIT**).

Untreated metabolic disorders such as maternal **phenylketonuria** (PKU) results in miscarriage, congenital cardiac malformations, and injury to the brain of a nonphenylketonuric heterozygous fetus. Women whose PKU is well controlled before conception can avoid these complications and have a normal newborn.

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115.4

Medication and Teratogen Exposure

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When an infant or child has a congenital malformation or is developmentally delayed, the parents often wrongly blame themselves and attribute the child's problems to events that occurred during pregnancy. Because benign infections occur, and several nonteratogenic drugs are often taken during many pregnancies, the pediatrician must evaluate the presumed viral infections and the drugs ingested to help parents understand their child's birth defect. The causes of approximately 40% of congenital malformations are unknown. Although only relatively few agents are recognized to be teratogenic in humans, new agents continue to be identified. An excellent internet-based resource known as **Reprotox** (reprotox.org) provides comprehensive and routinely updated summaries on drugs and other potentially teratogenic agents in pregnancy. Overall, only 10% of anomalies are caused by recognizable teratogens (see Chapter 128). The time of exposure that is most likely to cause injury is usually during organogenesis at <60 days of gestation. Specific agents produce predictable lesions. Some agents have a dose or *threshold* effect, below which no alterations in growth, function, or structure occur. Genetic variables such as the presence of specific enzymes may metabolize a benign agent into a more toxic, teratogenic form (e.g., phenytoin conversion to its epoxide). In many circumstances the same agent and dose may not consistently produce the lesion.

Reduced enzyme activity of the folate methylation pathway, particularly the formation of 5-methyltetrahydrofolate, may be responsible for NTDs or other birth defects. The common thermolabile mutation of 5,10-methylene tetrahydrofolate reductase may be one of the enzymes responsible. Folate supplementation for all pregnant women (by direct fortification of cereal grains, which is mandatory in the United States), and oral folic acid tablets taken during organogenesis may overcome this genetic enzyme defect, thus reducing the incidence of NTDs and perhaps other birth defects.

The U.S. Food and Drug Administration (FDA) classifies drugs into 5 pregnancy risk categories. **Category A** drugs pose no risk on the basis of evidence from controlled human studies. For **category B** drugs, either no risk has been shown in animal studies but no adequate studies have been done in humans, *or* some risk has been shown in animal studies but these results are not confirmed by human studies. For **category C** drugs, either definite risk has been shown in animal studies but no adequate human studies have been performed, *or* no data are available from either animal or human studies. **Category D** includes drugs with some risk but with a benefit that may exceed that risk for the treated life-threatening condition, such as streptomycin for tuberculosis. **Category X** is for drugs that are contraindicated in pregnancy on the basis of animal and human evidence and for which the risk exceeds the benefits.

The use of medications or herbal remedies during pregnancy is potentially harmful to the fetus. Consumption of medications occurs during the majority of pregnancies. The average mother has taken 4 drugs other than vitamins or iron during pregnancy. Almost 40% of pregnant women receive a drug for which human safety during pregnancy has not been established (category C pregnancy risk). Moreover, many women are exposed to potential reproductive toxins, such as occupational, environmental, or household chemicals, including solvents, pesticides, and hair products. The effects of drugs taken by the mother vary considerably, especially in relation to the time in pregnancy when they are taken and the fetal genotype for drug-metabolizing enzymes.

Miscarriage or **congenital malformations** result from the maternal ingestion of teratogenic drugs during the period of organogenesis. Maternal medications taken later, particularly during the last few weeks of gestation or during labor, tend to affect the function of specific organs or enzyme systems, and these adversely affect the neonate rather than the fetus (Tables 115.5 and 115.6). The effects of drugs may be evident immediately in the delivery room or later in the neonatal period, or they may be delayed even longer. The administration of diethylstilbestrol during pregnancy, for instance, increased the risk for vaginal adenocarcinoma in female offspring in the 2nd or 3rd decade of life.

Table 115.5

Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn

DRUG	EFFECT ON FETUS
Accutane (isotretinoin)	Facial-ear anomalies, heart disease, CNS anomalies
Alcohol	Congenital cardiac, CNS, limb anomalies; IUGR; developmental delay; attention deficits; autism
Aminopterin	Abortion, malformations
Amphetamines	Congenital heart disease, IUGR, withdrawal
ACE inhibitors, angiotensin receptor antagonists	Oligohydramnios, IUGR, renal failure, Potter-like syndrome
Azathioprine	Abortion
Busulfan (Myleran)	Stunted growth; corneal opacities; cleft palate; hypoplasia of ovaries, thyroid, and parathyroids
Carbamazepine	Spina bifida, possible neurodevelopmental delay
Carbimazole	Scalp defects, choanal atresia, esophageal atresia, developmental delay
Carbon monoxide	Cerebral atrophy, microcephaly, seizures
Chloroquine	Deafness
Chorionic villus sampling	Probably no effect, possibly limb reduction

Cigarette smoking	LBW for gestational age
Cocaine/crack	Microcephaly, LBW, IUGR, behavioral disturbances
Cyclophosphamide	Multiple malformations
Danazol	Virilization
17α-Ethinyl testosterone (Progestoral)	Masculinization of female fetus
Hyperthermia	Spina bifida
Infliximab	Possible increased risk of live vaccine associated disease in infant; neutropenia
Lithium	Ebstein anomaly, macrosomia
Lopinavir-ritonavir	Transient adrenal dysfunction
6-Mercaptopurine	Abortion
Methyl mercury	Minamata disease, microcephaly, deafness, blindness, mental retardation
Methyltestosterone	Masculinization of female fetus
Misoprostol	Arthrogryposis, cranial neuropathies (Möbius syndrome), equinovarus
Mycophenolate mofetil	Craniofacial, limb, cardiovascular, CNS anomalies
Norethindrone	Masculinization of female fetus
Penicillamine	Cutis laxa syndrome
Phenytoin	Congenital anomalies, IUGR, neuroblastoma, bleeding (vitamin K deficiency)
Polychlorinated biphenyls	Skin discoloration—thickening, desquamation, LBW, acne, developmental delay
Prednisone	Oral clefts
Progesterone	Masculinization of female fetus
Quinine	Abortion, thrombocytopenia, deafness
Selective serotonin reuptake inhibitors	Small increased risk of congenital anomalies, persistent pulmonary hypertension of newborn
Statins	IUGR, limb deficiencies, VACTERAL
Stilbestrol (diethylstilbestrol [DES])	Vaginal adenocarcinoma in adolescence
Streptomycin	Deafness
Tetracycline	Retarded skeletal growth, pigmentation of teeth, hypoplasia of enamel, cataract, limb malformations
Thalidomide	Phocomelia, deafness, other malformations
Toluene (solvent abuse)	Craniofacial abnormalities, prematurity, withdrawal symptoms, hypertonia
Topiramate	Cleft lip
Trimethadione and paramethadione	Abortion, multiple malformations, mental retardation
Valproate	CNS (spina bifida), facial and cardiac anomalies, limb defects, impaired neurologic function, autism spectrum disorder
Vitamin D	Supravalvular aortic stenosis, hypercalcemia
Warfarin (Coumadin)	Fetal bleeding and death, hypoplastic nasal structures

ACE, Angiotensin-converting enzyme; CNS, central nervous system; IUGR, intrauterine growth restriction; LBW, low birthweight; VACTERAL, vertebral, anal, cardiac, tracheoesophageal fistula, renal, arterial, limb.

Table 115.6

Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant*

Acebutolol—IUGR, hypotension, bradycardia

Acetazolamide—metabolic acidosis
Amiodarone—bradycardia, hypothyroidism
Anesthetic agents (volatile)—CNS depression
Adrenal corticosteroids—adrenocortical failure (rare)
Ammonium chloride—acidosis (clinically inapparent)
Aspirin—neonatal bleeding, prolonged gestation
Atenolol—IUGR, hypoglycemia
Baclofen—withdrawal
Blue cohosh herbal tea—neonatal heart failure
Bromides—rash, CNS depression, IUGR
Captopril, enalapril—transient anuric renal failure, oligohydramnios
Caudal-paracervical anesthesia with mepivacaine (accidental introduction of anesthetic into scalp of baby)—bradypnea, apnea, bradycardia, convulsions
Cholinergic agents (edrophonium, pyridostigmine)—transient muscle weakness
CNS depressants (narcotics, barbiturates, benzodiazepines) during labor—CNS depression, hypotonia
Cephalothin—positive direct Coombs test reaction
Dexamethasone—periventricular leukomalacia
Fluoxetine and other SSRIs—transient neonatal withdrawal, hypertonicity, minor anomalies, preterm birth, prolonged QT interval
Haloperidol—withdrawal
Hexamethonium bromide—paralytic ileus
Ibuprofen—oligohydramnios, pulmonary hypertension
Imipramine—withdrawal
Indomethacin—oliguria, oligohydramnios, intestinal perforation, pulmonary hypertension
Intravenous fluids during labor (e.g., salt-free solutions)—electrolyte disturbances, hyponatremia, hypoglycemia
Iodide (radioactive)—goiter
Iodides—goiter
Lead—reduced intellectual function
Magnesium sulfate—respiratory depression, meconium plug, hypotonia
Methimazole—goiter, hypothyroidism
Morphine and its derivatives (addiction)—withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)
Naphthalene—hemolytic anemia (in G6PD-deficient infants)
Nitrofurantoin—hemolytic anemia (in G6PD-deficient infants)
Oxytocin—hyperbilirubinemia, hyponatremia
Phenobarbital—bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation
Primaquine—hemolytic anemia (in G6PD-deficient infants)
Propranolol—hypoglycemia, bradycardia, apnea
Propylthiouracil—goiter, hypothyroidism
Pyridoxine—seizures
Reserpine—drowsiness, nasal congestion, poor temperature stability
Sulfonamides—interfere with protein binding of bilirubin; kernicterus at low levels of serum bilirubin, hemolysis with G6PD deficiency
Sulfonylurea agents—refractory hypoglycemia
Sympathomimetic (tocolytic β-agonist) agents—tachycardia
Thiazides—neonatal thrombocytopenia (rare)
Tumor necrosis factor blocking agents—neutropenia, possible increased risk of infection during 1st yr of life
Valproate—developmental delay
Zolpidem (Ambien)—low birthweight

[*] See also Table 115.5 .

CNS, Central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; SSRI, selective serotonin reuptake inhibitor.

Often the risk of controlling maternal disease must be balanced with the risk of possible complications in the fetus. Most women with epilepsy have normal fetuses. Nonetheless, several commonly used **antiepileptic drugs** are associated with congenital malformations. Infants exposed to valproic acid may have multiple anomalies, including NTDs, hypospadias, facial anomalies, cardiac anomalies, and limb defects. In addition, they have lower developmental index scores than unexposed infants and infants exposed to other common antiepileptic drugs.

Moderate or high alcohol intake (≥7 drinks/wk or ≥3 drinks on multiple occasions) is a risk for **fetal alcohol syndrome** . The exposed fetuses are at risk for growth failure, central nervous system abnormalities, cognitive defects, and behavioral problems. It must be emphasized, however, that there is no known dose-response threshold for fetal alcohol exposure; therefore pregnant women should be counseled toward complete abstinence. **Smoking** during pregnancy is associated with IUGR and facial clefts.

Chronic **heroin (opioid)** use throughout pregnancy is associated with an increased risk of fetal growth restriction, placental abruption, stillbirth, preterm birth, and intrauterine passage of meconium. Opiates readily cross the placenta; therefore these effects are postulated to be related to cyclic fetal opiate withdrawal. Furthermore, the lifestyle issues surrounding opioid abuse, including lack of or late entry into prenatal care, place the mother at higher risk of adverse pregnancy outcome. Therefore, opioid maintenance therapy with either methadone or buprenorphine is recommended for opioid-dependent pregnant women to prevent complications of illicit opioid use and narcotic withdrawal, encourage prenatal care and drug treatment, reduce criminal activity, and avoid risks to the patient of associating with a drug culture.

Neonatal abstinence syndrome (NAS) occurs in the setting of opioid maintenance treatment or illicit drug use; thus opiate maintenance therapy is not preventive in this regard. **Methadone** is considered first-line therapy for treatment of opioid dependence in pregnancy; **buprenorphine** is an acceptable alternative in the appropriately selected patient. There is no established, dose-response relationship between methadone or buprenorphine and risk/severity of NAS, so the lowest effective dose to eliminate maternal cravings/withdrawal is recommended. Methadone is associated with a lower birthweight than buprenorphine. Both medications have a similar rate of NAS requiring treatment (approximately 50%); however, the use of antenatal buprenorphine has been associated with significantly lower dosages of morphine to treat NAS and significantly shorter NAS-related hospital stays than methadone. For these reasons, buprenorphine may be preferred under certain circumstances.

The specific mechanism of action is known or postulated for very few teratogens. **Warfarin** , a vitamin K antagonist used for anticoagulation, prevents the carboxylation of γ-carboxyglutamic acid, which is a component of osteocalcin and other vitamin K–dependent bone proteins. The teratogenic effect of warfarin on developing cartilage, especially nasal cartilage, appears to be avoided if the pregnant woman's anticoagulation treatment is switched from warfarin to heparin for the period between weeks 6 and 12 of gestation. However, the risk of intracranial hemorrhage is maintained with exposure throughout pregnancy. For these reasons, **low-molecular-weight heparin** is the preferred anticoagulant when treating pregnant women.

Hypothyroidism in the fetus may be caused by maternal ingestion of an excessive amount of iodide or propylthiouracil; each interferes with the conversion of inorganic to organic iodides. Furthermore, there is an interaction between genetic factors and susceptibility to certain drugs or environmental toxins. Phenytoin teratogenesis, for example, may be mediated by genetic differences in the enzymatic production of epoxide metabolites. Polymorphisms of genes encoding enzymes that metabolize the polycyclic aromatic hydrocarbons in cigarette smoke influence the growth-restricting effects of smoking on the fetus.

Recognition of teratogenic potential from a variety of sources offers the opportunity to prevent related birth defects. If a pregnant woman is informed of the potentially harmful effects of alcohol, tobacco, and illicit drugs on her unborn infant, she may be motivated to avoid consumption of these substances during pregnancy. A woman with insulin-dependent diabetes mellitus may significantly decrease her risk for having a child with birth defects by achieving good control of her disease before conception. Lastly, in view of the limits of current knowledge regarding the fetal effects of maternal medication use, drugs and herbal agents should only be prescribed during pregnancy after carefully weighing the maternal benefit against the risk of fetal harm.

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115.5

Radiation

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See also Chapter 736 .

Accidental exposure of a pregnant woman to radiation is a common cause for anxiety about whether her fetus will have genetic abnormalities or birth defects. It is unlikely that exposure to diagnostic radiation will cause gene mutations; no increase in genetic abnormalities has been identified in the offspring exposed as unborn fetuses to the atomic bomb explosions in Japan in 1945.

A more realistic concern is whether the exposed human fetus will show birth defects or a higher incidence of malignancy. The background fetal radiation exposure in a given pregnancy is approximately 0.1 rad. The estimated radiation dose for most radiographs is <0.1 rad and for most CT scans <5 rad (maximum recommended radiation exposure in pregnancy). Imaging studies with high radiation exposure (e.g., CT scans) can be modified to ensure that radiation doses are kept as low as possible. Thus, single diagnostic studies do not result in radiation doses high enough to affect the embryo or fetus. Pregnancy termination should not be recommended only on the basis of diagnostic radiation exposure. Most of the evidence suggests that usual fetal radiation exposure does not increase the risk of childhood leukemia and other cancers; although some sources suggest that a 1-2 rad fetal radiation exposure may confer a 1.5-2–fold increased risk of childhood leukemia, which has a background risk of 1 in 3,000. Before implantation (0-2 wk postconception), radiation doses of 5-10 rad may result in miscarriage. At 2-8 wk gestation, doses in excess of 20 rad have been associated with congenital anomalies and fetal growth restriction. Severe intellectual disabilities can occur with exposures of ≥25 rad before 25 wk gestation. The available data suggest no harmful fetal effect of diagnostic MRI or US, which do not involve radiation.

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115.6

Intrauterine Diagnosis of Fetal Disease

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See Table 115.1 and Chapter 115.2 .

Diagnostic procedures are used to identify fetal diseases when direct fetal treatment is possible, to better direct neonatal care, when a decision is made to deliver a viable but premature infant to avoid intrauterine fetal demise, or when pregnancy termination is being considered. Fetal assessment is also indicated in a broader context when the family, medical, or reproductive history of the mother suggests the presence of a high-risk pregnancy or a high-risk fetus (see Chapters 114 and 115.3).

Various methods are used for identifying fetal disease (see Table 115.1). Fetal US imaging may detect fetal growth abnormalities (by previously outlined biometric measurements) or fetal malformations (Fig. 115.7). Serial determinations of growth velocity and the head-to-abdomen circumference ratio enhance the ability to detect IUGR. Real-time US may identify placental abnormalities (abruptio placentae, placenta previa) and fetal anomalies such as hydrocephalus, NTDs, duodenal atresia, diaphragmatic hernia, renal agenesis, bladder outlet obstruction, congenital heart disease, limb abnormalities, sacrococcygeal teratoma, cystic hygroma, omphalocele, gastroschisis, and hydrops (Table 115.7).

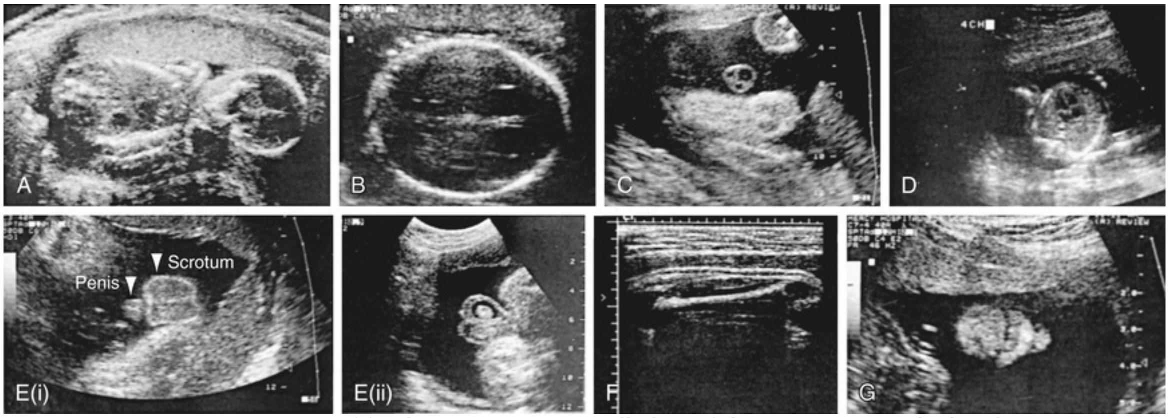

FIG. 115.7 **Assessment of fetal anatomy. A, Overall view of the uterus at 24 wk showing a longitudinal section of the fetus and an anterior placenta. B, Transverse section at the level of the lateral ventricle at 18 wk showing (*on the right*) prominent anterior horns of the lateral ventricles on either side of the midline echo of the falx. C, Cross section of the umbilical cord showing that the lumen of the umbilical vein is much wider than that of the 2 umbilical arteries. D, Four-chambered view of the heart at 18 wk with equal-sized atria. E(i), Normal male genitals near term. E(ii), Hydrocele outlining a testicle within the scrotum projecting into a normal-size pocket of amniotic fluid at 38 wk. Approximately 2% of male infants after birth have clinical evidence of a hydrocele that is often bilateral, not to be confused with subcutaneous edema occurring during vaginal breech birth. F, Section of a thigh near term showing thick subcutaneous tissue (4.6 mm between *markers*) above the femur of a fetus with macrosomia. G, Fetal face viewed from below, showing (*from right to left*) the nose, alveolar margin, and chin at 20 wk. (From Special investigative procedures. In Beischer NA, Mackay EV, Colditz PB, editors: *Obstetrics and the newborn,* ed 3, Philadelphia, 1997, Saunders.)**

Table 115.7

Significance of Fetal Ultrasonographic Anatomic Findings

PRENATAL OBSERVATION	DEFINITION	DIFFERENTIAL DIAGNOSIS	SIGNIFICANCE	POSTNATAL EVALUATION
Dilated cerebral ventricles	Ventriculomegaly ≥10 mm	Hydrocephalus Hydranencephaly Dandy-Walker cyst Agenesis of corpus callosum Volume loss	Transient isolated ventriculomegaly is common and usually benign. Persistent or progressive ventriculomegaly is more worrisome. Identify associated cranial and extracranial anomalies.	Serial head US or MRI Evaluate for extracranial anomalies.
Choroid plexus cysts	Size ~10 mm: unilateral or bilateral 1–3% incidence	Abnormal karyotype (trisomy 18, 21) Increased risk if AMA	Often isolated, benign; resolves by 24-28 wk. Fetus should be examined for other organ anomalies; if	Head US Examine for extracranial anomalies; karyotype if indicated.

			additional anomalies present, amniocentesis should be performed for karyotype.	
Nuchal fold thickening	≥6 mm at 15-20 wk	Cystic hygroma trisomy 21, 18 Turner syndrome (XO) Other genetic syndromes Normal (~25%)	~50% of affected fetuses have chromosome abnormalities. Amniocentesis for karyotype needed.	Evaluate for multiple organ malformations; karyotype if indicated.
Dilated renal pelvis	Pyelectasis ≥4 to 10 mm 0.6–1% incidence	Normal variant Uteropelvic junction obstruction Vesicoureteral reflux Posterior ureteral valves Entopic ureterocele Large-volume nonobstruction	Often “physiologic” and transient Reflux is common. If dilation is >10 mm or associated with caliectasis, pathologic cause should be considered. If large bladder present, posterior urethral valves and megacystis–microcolon hypoperistalsis syndrome should be considered.	Repeat ultrasonography on day 5 and at 1 mo; voiding cystourethrogram, prophylactic antibiotics
Echogenic bowel	0.6% incidence	CF, meconium peritonitis, trisomy 21 or 18, other chromosomal abnormalities cytomegalovirus, toxoplasmosis, GI obstruction, intrauterine bleeding (fetal swallowing of blood)	Often normal Consider CF, aneuploidy, and TORCH.	Sweat chloride and DNA testing Karyotype Surgery for obstruction Evaluation for TORCH
Stomach appearance	Small or absent or with double bubble	Upper GI obstruction (esophageal atresia) Double bubble signifies duodenal atresia Aneuploidy Polyhydramnios Stomach in chest signifies diaphragmatic hernia	Must also consider neurologic disorders that reduce swallowing. >30% with double bubble have trisomy 21.	Chromosomes; kidney, ureter, and bladder radiograph if indicated; upper GI series; neurologic evaluation

CF, Cystic fibrosis; CMV, cytomegalovirus; GI, gastrointestinal; TORCH, toxoplasmosis, other agents, rubella, CMV, herpes simplex syndrome; US, ultrasound.

Real-time US also facilitates performance of needle-guided procedures (i.e. cordocentesis) and the BPP by imaging fetal breathing, body movements, tone, and amniotic fluid volume (see Table 115.2). Doppler velocimetry assesses fetal arterial blood flow (vascular resistance) (see Figs. 115.4 and 115.5). Fetal MRI is used to better define abnormalities detected on US and to help with prognostication (see Fig. 115.1).

Amniocentesis , the transabdominal withdrawal of amniotic fluid during pregnancy for diagnostic purposes (see Table 115.1), is a common obstetric procedure. It is frequently performed to evaluate for infection. It is also done for genetic indications, usually between the 15th and 20th wk of gestation, with results available as soon as 24-48 hr for fluorescence in situ hybridization (FISH) testing and 2-3 wk for microarray testing. The most common indication for genetic amniocentesis is **advanced maternal age** ; the risk for chromosome abnormality at term at age 21 yr is 1 : 525, vs 1 : 6 at age 49 yr. ACOG recommends that all pregnant women be offered amniocentesis to evaluate further for an underlying genetic condition such as Down syndrome. Analysis of amniotic fluid may also help in identifying NTDs (elevation of α-fetoprotein [AFP] and presence of acetylcholinesterase). Additionally, families with a known genetic syndrome may be offered prenatal genetic testing from amniotic fluid or amniocytes obtained via amniocentesis or CVS.

Chorionic villus sampling (CVS) is performed in the first trimester, either transvaginally or transabdominally. The sample obtained is placental in origin, which can sometimes be problematic because aneuploidy may be present in the placenta and not the fetus, a condition known as **confined placental mosaicism** , which can give a false-positive rate as high as 3%. Furthermore, CVS may be associated with a slightly higher risk of fetal loss than amniocentesis.

Amniocentesis can be carried out with little discomfort to the mother. Procedure-related complications are relatively rare, and many can be avoided by using a US-guided approach. These risks include direct damage to the fetus, placental puncture and bleeding with secondary damage to the fetus, stimulation of uterine contraction and premature labor, chorioamnionitis, maternal sensitization to fetal blood, and pregnancy loss. Best available data indicate that the pregnancy loss rate associated with amniocentesis is 1 : 500-900 procedures. Amniocentesis is not recommended before 14 wk of gestation because this has been associated with a higher risk of pregnancy loss, ruptured membranes, and clubfoot.

Cordocentesis , or percutaneous umbilical blood sampling (PUBS), is used to diagnose fetal hematologic abnormalities, genetic disorders, infections, and fetal acidosis (see Table 115.1). Under direct US visualization, a long needle is passed into the umbilical vein at its entrance to the placenta or in a free loop of cord. Transfusion or administration of drugs can be performed through the umbilical vein (Table 115.8). The predominant indication for this procedure is for confirmation of fetal anemia (in Rh isoimmunization) or thrombocytopenia (NAIT), with subsequent transfusion of packed red blood cells or platelets into the umbilical venous circulation.

Table 115.8

Fetal Therapy

DISORDER	POSSIBLE TREATMENT
HEMATOLOGIC	
Anemia with hydrops (erythroblastosis fetalis)	Cordocentesis of umbilical vein with packed red blood cell transfusion
Isoimmune thrombocytopenia	Umbilical vein platelet transfusion, maternal IVIG
Autoimmune thrombocytopenia (ITP)	Maternal steroids and IVIG
METABOLIC/ENDOCRINE	
Maternal phenylketonuria (PKU)	Phenylalanine restriction
Fetal galactosemia	Galactose-free diet (?)
Multiple carboxylase deficiency	Biotin if responsive
Methylmalonic acidemia	Vitamin B_{12} if responsive
21-Hydroxylase deficiency	Dexamethasone if female fetus
Maternal diabetes mellitus	Tight insulin control during pregnancy, labor, and delivery
Fetal goiter	Maternal hyperthyroidism—maternal propylthiouracil
	Fetal hypothyroidism—intraamniotic thyroxine
Bartter syndrome	Maternal indomethacin may prevent nephrocalcinosis and postnatal sodium losses
FETAL DISTRESS	
Hypoxia	Maternal oxygen, position changes
Intrauterine growth restriction	Improve macronutrients and micronutrients if deficient, smoking cessation, treatment of maternal disease, antenatal fetal surveillance
Oligohydramnios, premature rupture of membranes with variable deceleration	Antenatal fetal surveillance
	Approach dependent on etiology
	Amnioinfusion (intrapartum)
Polyhydramnios	Antenatal fetal surveillance
	Approach dependent on etiology
	Amnioreduction if indicated,
Supraventricular tachycardia	Maternal digoxin,[*] flecainide, procainamide, amiodarone, quinidine
Lupus anticoagulant	Maternal aspirin and heparin
Meconium-stained fluid	Amnioinfusion
Congenital heart block	Dexamethasone, pacemaker (with hydrops)
Premature labor	Magnesium sulfate, nifedipine, indomethacin with antenatal corticosteroids (betamethasone)
RESPIRATORY	
Pulmonary immaturity	Betamethasone
Bilateral chylothorax—pleural effusions	Thoracentesis, pleuroamniotic shunt
CONGENITAL ABNORMALITIES [†]	
Neural tube defects	Folate, vitamins (prevention); fetal surgery [‡]

Posterior urethral valves, urethral atresia (lower urinary tract obstruction)	Percutaneous vesicoamniotic shunt
Cystic adenomatoid malformation (with hydrops)	Pleuroamniotic shunt or resection [‡]
Fetal neck masses	Secure an airway with EXIT procedure [‡]
INFECTIOUS DISEASE	
Group B streptococcus colonization	Ampicillin, penicillin
Chorioamnionitis	Antibiotics and delivery
Toxoplasmosis	Spiramycin, pyrimethamine, sulfadiazine, folic acid
Syphilis	Penicillin
Tuberculosis	Antituberculosis drugs
Lyme disease	Penicillin, ceftriaxone
Parvovirus	Intrauterine red blood cell transfusion for hydrops, severe anemia
Chlamydia trachomatis	Azithromycin
HIV-AIDS	Maternal and neonatal antiretroviral therapy (see Chapter 302)
Cytomegalovirus	No approved prenatal treatments
OTHER	
Nonimmune hydrops (anemia)	Umbilical vein packed red blood cell transfusion
Narcotic abstinence (withdrawal)	Maternal methadone maintenance
Sacrococcygeal teratoma (with hydrops)	In utero resection or catheter-directed vessel obliteration
Cardiac rhabdomyoma	Maternal sirolimus
Intrapericardial teratoma	Fetal surgery
CRISPR-Cas9 gene editing	Proof of concept in previable in vitro fertilized human embryos
Twin-twin transfusion syndrome	Repeated amniocentesis, yttrium-aluminum-garnet (YAG) laser photocoagulation of shared vessels
Twin reversed arterial perfusion (TRAP) syndrome	Cord occlusion, radiofrequency ablation
Multifetal gestation	Selective reduction
Neonatal hemochromatosis	Maternal IVIG
Aortic stenosis	In utero valvuloplasty

[*] Drug of choice (may require percutaneous umbilical cord sampling and umbilical vein administration if hydrops is present). Most drug therapy is given to the mother, with subsequent placental passage to the fetus.

[†] Detailed fetal ultrasonography is needed to detect other anomalies; karyotype is also indicated.

[‡] EXIT permits surgery and other procedures.

EXIT, Ex utero intrapartum treatment; IVIG, intravenous immune globulin; (?), possible but not proved efficacy.

Aneuploidy screening is offered to pregnant women in the first trimester or at midgestation to evaluate the risk for common aneuploidies such as Down syndrome (trisomy 21), trisomy 18, trisomy 13, and congenital malformations (e.g., abdominal wall or neural tube defects) known to cause elevations of various markers. A combination of these biochemical markers (including AFP, inhibin A, estriol, pregnancy-associated plasma protein A, β–human chorionic gonadotropin [hCG]) and US increases the positive predictive value (PPV) of these screening tests. Fetal DNA in maternal plasma and fetal cells circulating in maternal blood are potential noninvasive sources of material for prenatal genetic testing. This testing, however, is not diagnostic, and a positive test requires either amniocentesis or postnatal analysis to confirm the diagnosis. Nonetheless, fetal karyotyping by analysis of fetal DNA in maternal plasma is another screening test that is very sensitive for the detection of Down syndrome, with a higher PPV than any other prenatal screening test for Down syndrome. Currently, however, the use of this technology is only advocated in pregnancies deemed at high risk for aneuploidy.

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115.7

Treatment and Prevention of Fetal Disease

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See also Chapter 116 .

Management of a fetal disease depends on coordinated advances in diagnostic accuracy and knowledge of the disease's natural history; an understanding of fetal nutrition, pharmacology, immunology, and pathophysiology; the availability of specific active drugs that cross the placenta; and therapeutic procedures. Progress in providing specific treatments for accurately diagnosed diseases has improved with the advent of real-time ultrasonography, amniocentesis, and cordocentesis (see Tables 115.1 and 115.8).

The incidence of sensitization of Rh-negative women by Rh-positive fetuses has been reduced by prophylactic administration of Rh(D) immunoglobulin to mothers early in pregnancy and after each delivery or abortion, thus reducing the frequency of hemolytic disease in their subsequent offspring. **Fetal erythroblastosis** (see Chapter 124.2) may be accurately detected by fetal Doppler assessment of the peak systolic velocity of the middle cerebral artery and treated with intrauterine transfusions of packed Rh-negative blood cells via the intraperitoneal or, more often, intraumbilical vein approach.

Pharmacologic approaches to fetal immaturity mostly revolve around the administration of antenatal corticosteroids to the mother to promote fetal production of surfactant with a resultant decrease in the incidence of **respiratory distress syndrome** (see Chapter 122.3). Tocolytic agents have been demonstrated to prolong pregnancy to allow the administration of antenatal corticosteroids (48 hr); however, there is no proven benefit beyond this timeframe. Maternal administration of magnesium sulfate for fetal/neonatal neuroprotection is recommended in pregnancies deemed to be at risk of imminent delivery before 32 wk gestation in light of evidence demonstrating a reduction in frequency of cerebral palsy compared to those who did not receive this treatment.

Management of definitively diagnosed fetal genetic disease or congenital anomalies consists of multidisciplinary parental counseling. Rarely, high-dose **vitamin therapy** for a responsive inborn error of metabolism (e.g., biotin-dependent disorders) or fetal transfusion (with red blood cells or platelets) may be indicated. **Fetal surgery** is well-established treatment for certain conditions but remains a largely experimental approach to therapy for other conditions and is available only in a few, highly specialized perinatal centers (see Table 115.8 and Chapter 116). The nature of the defect and its consequences must be considered, as well as ethical implications for the fetus and the parents. **Termination of pregnancy** is also an option that should be discussed during the initial phases of counseling.

Folic acid supplementation decreases the incidence and recurrence of NTDs. Because the neural tube closes within the 1st 28 days of conception, periconceptional supplementation is needed for prevention. It is recommended that women without a prior history of a NTD ingest 400 µg/day of folic acid throughout their reproductive years. Women with a history of a prior pregnancy complicated by an NTD or a first-degree relative with an NTD should have preconceptional counseling and should ingest 4 mg/day of supplemental folic acid beginning at least 1 mo before conception. Fortification of cereal grain flour with folic acid is established policy in the United States and some other countries. The optimal concentration of folic acid in enriched grains is somewhat controversial. The incidence of NTD in the United States and other countries has decreased significantly since these public health initiatives were implemented. Use of some antiepileptic drugs (valproate, carbamazepine) during pregnancy is associated with an increased risk of NTD. Women taking these medications should ingest 1-5 mg of folic acid daily in the preconception period.

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CHAPTER 116

Fetal Intervention and Surgery

Paul S. Kingma

Numerous diagnoses have been evaluated for the possibility of fetal intervention (Tables 116.1 and 116.2). Some have proved beneficial to the developing infant, some have been abandoned, and some are still under investigation.

Table 116.1

Fetal Diagnoses Evaluated and Treated in Fetal Centers

Amniotic band syndrome (ABS)
Anomalies in monochorionic twins
Aortic stenosis
Arachnoid cyst
Bladder exstrophy
Bladder outlet obstruction
Bronchopulmonary sequestration (BPS)
Cervical teratoma
Cloaca
Cloaca exstrophy
Complete heart block
Congenital pulmonary airway malformation (CPAM)
Congenital diaphragmatic hernia (CDH)
Congenital high airway obstruction syndrome (CHAOS)
EXIT to airway procedure for CHAOS
Conjoined twins
Dandy-Walker malformation
Duodenal atresia
Encephalocele
Enteric duplicational atresia
Esophageal atresia
Gastroschisis
Hydrocephalus
Hydronephrosis
Hypoplastic left heart syndrome (HLHS)
Imperforate anus
Intraabdominal cyst
Lymphangioma

Mediastinal teratoma
Myelomeningocele, spina bifida
Neuroblastoma
Obstructive uropathy
Omphalocele
Pentalogy of Cantrell
Pericardial teratoma
Pleural effusions
Pulmonary agenesis
Pulmonary atresia with intact ventricular septum
Sacrococcygeal teratoma (SCT)
Twin reversed arterial perfusion (TRAP) sequence
Twin-twin transfusion syndrome (TTTS)
Vein of Galen aneurysm

EXIT, Ex utero intrapartum treatment.

Table 116.2

Indications and Rationales for in Utero Surgery on the Fetus, Placenta, Cord, or Membranes

FETAL SURGERY	PATHOPHYSIOLOGY	RATIONALE FOR IN UTERO INTERVENTION
SURGERY ON THE FETUS		
1. Congenital diaphragmatic hernia	Pulmonary hypoplasia and anatomic substrate for pulmonary hypertension	Reversal of pulmonary hypoplasia and reduced degree of pulmonary hypertension; repair of actual defect delayed until after birth
2. Lower urinary tract obstruction	Progressive renal damage due to obstructive uropathy Pulmonary hypoplasia due to oligohydramnios	Prevention of renal failure and pulmonary hypoplasia by anatomic correction or urinary deviation
3. Sacrococcygeal teratoma	High-output cardiac failure due to AV shunting and/or bleeding Direct anatomic effects of the tumoral mass Polyhydramnios-related preterm labor	Reduction of functional impact of tumor by ablation of tumor or (part of) its vasculature Reduction of anatomic effects by drainage of cysts or bladder Amnioreduction preventing obstetric complications
4. Thoracic space-occupying lesions	Pulmonary hypoplasia (space-occupying mass) Hydrops due to impaired venous return (mediastinal compression)	Creation of space for lung development Reversal of the process of cardiac failure
5. Neural tube defects	Damage to exposed neural tube Chronic CSF leak, leading to Arnold-Chiari malformation and hydrocephalus	Prevention of exposure of the spinal cord to amniotic fluid; restoration of CSF pressure correcting Arnold-Chiari malformation
6. Cardiac malformations	Critical lesions causing irreversible hypoplasia or damage to developing heart	Reversal of process by anatomic correction of restrictive pathology
SURGERY ON THE PLACENTA, CORD, OR MEMBRANES		
7. Chorioangioma	High-output cardiac failure due to AV	Reversal of process of cardiac failure

	shunting Effects of polyhydramnios	and hydrops fetoplacentalis by ablation or reduction of flow
8. Amniotic bands	Progressive constrictions causing irreversible neurologic or vascular damage	Prevention of amniotic band syndrome leading to deformities and function loss
9. Abnormal monochorionic twinning: twin-to-twin transfusion; fetus acardiacus, and discordant anomalies	Intertwin transfusion leading to oligopolyhydramnios sequence, hemodynamic changes; preterm labor, and rupture of membranes; in utero damage to brain, heart, or other organs In utero fetal death may cause damage to co-twin. Cardiac failure of pump twin and consequences of polyhydramnios Serious anomaly raising the question of termination of pregnancy Selective fetocide	Arrest of intertwin transfusion; prevention/reversal of cardiac failure and/or neurologic damage, including at in utero death; prolongation of gestation Selective fetocide to arrest parasitic relationship, to prevent consequences of in utero fetal death, and to avoid termination of entire pregnancy

AV, Arteriovenous; CSF, cerebrospinal fluid.

From Deprest J, Hodges R, Gratacos E, Lewi L: Invasive fetal therapy. In Creasy RK, Resnick R, Iams JD, et al, editors: *Creasy & Resnik's maternal-fetal medicine,* ed 7, Philadelphia, 2014, Elsevier (Table 35-1).

Fetal Therapy Ethics

With the development of advanced fetal ultrasound (US), fetal MRI, and fetal echocardiography, the ability to accurately diagnose fetal disease has improved substantially over the past 3 decades. There have also been advances in maternal anesthesia and tocolysis, reduction in maternal morbidity, development of fetal surgery–specific equipment, improved clinical expertise of the fetal care team, and construction of state–of-the-art fetal treatment centers. Fetal surgery remains controversial, however, and every discussion of fetal surgery must include a careful consideration of the ethical conflicts inherit to these procedures.

Unlike most surgical procedures, fetal surgery must consider 2 patients simultaneously, balancing the potential risks and benefits to the fetus with those to the mother during the current and future pregnancies. The **International Fetal Medicine and Surgery Society** (IFMSS) established a consensus statement on fetal surgery, as follows:

1. A fetal surgery candidate should be a singleton with no other abnormalities observed on level II ultrasound, karyotype (by amniocentesis), α-fetoprotein (AFP) level or viral cultures.
2. The disease process must not be so severe that the fetus cannot be saved

and also not so mild that the infant will do well with postnatal therapy.

3. The family must be fully counseled and understand the risks and benefits of fetal surgery, and they must agree to long-term follow-up to track efficacy of the fetal intervention.
4. A multidisciplinary team must concur that the disease process is fatal without intervention, that the family understands the risks and benefits, and that the fetal intervention is appropriate.

Obstructive Uropathy

Obstructive uropathy is most frequently caused by **posterior urethral valves** (PUV) but can be caused by a variety of other defects, including urethral atresia, persistent cloaca, caudal regression, and megacystis–microcolon–intestinal hypoperistalsis syndrome (see Chapters 555 and 556). Obstructive uropathy usually presents on fetal US with an enlarged bladder, bilateral hydroureteronephrosis, and oligohydramnios. Mild forms of obstructive uropathy may lead to minimal short- or long-term clinical sequelae. However, the lack of fetal urine output and resulting oligohydramnios or anhydramnios in more severe forms can cause significant **pulmonary hypoplasia** , which is associated with death shortly after delivery in >80% of infants. Pulmonary survivors are still subject to high mortality and chronic morbidity resulting from renal dysplasia, renal failure, and the need for chronic renal replacement therapy.

The primary objective of fetal intervention in fetuses with obstructive uropathy is *restoration of amniotic fluid volume to prevent pulmonary hypoplasia.* Although prevention of ongoing renal injury is also desired, the efficacy of fetal intervention in achieving this goal is uncertain. Several studies have attempted to use fetal urine evaluation to predict renal outcome in these patients, but the reliability of these markers has been disappointing due to the influence of gestational age on many of these markers. Therefore, fetal intervention for obstructive uropathy is currently limited to fetuses in whom the obstruction is sufficient to cause oligohydramnios or anhydramnios.

For fetuses who still have adequate renal function and are capable of producing urine, treatment options include vesicoamniotic shunting, valve ablation via cystoscopy, and vesicostomy. **Vesicoamniotic shunting** is the most common and involves percutaneous, US-guided placement of a double-pigtailed shunt from the fetal bladder to the amniotic space, allowing decompression of the obstructed bladder and restoration of the amniotic fluid volume (Fig. 116.1).

Although simple in concept, bladder decompression may not always occur, and many catheters will become dislodged as the fetus develops; a fetus typically requires 3 catheter replacements before completion of pregnancy. Vesicoamniotic shunting may improve perinatal survival, but at the expense of poor long-term renal function.

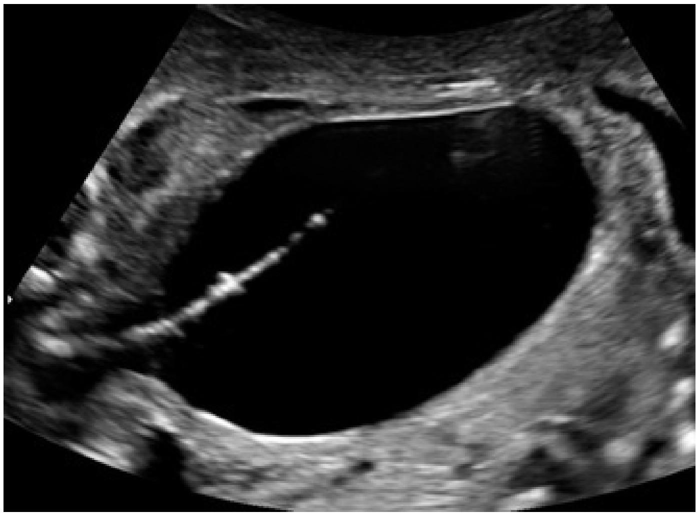

FIG. 116.1 Ultrasound image showing fetoscopic placement of a transurethral vesicoamniotic shunt in a patient with posterior urethral valves. (Courtesy of Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.)

Fetal cystoscopy is more technically challenging than vesicoamniotic shunt placement, more invasive, and requires more sedation, but this option holds some important advantages. Cystoscopy allows for direct visualization of the obstruction and does not require amnioinfusion. Moreover, when the obstruction is visualized and the diagnosis of PUV confirmed, the valves can be treated, restoring urine flow to the amniotic space and eliminating the need for repeated fetal interventions in most patients. Creation of a **vesicostomy** (direct opening from bladder through fetal abdominal wall) by open fetal surgery has improved perinatal survival (Fig. 116.2). However, the current dataset evaluating this approach is still limited, and direct comparisons to shunting suggest no significant difference between these interventions.

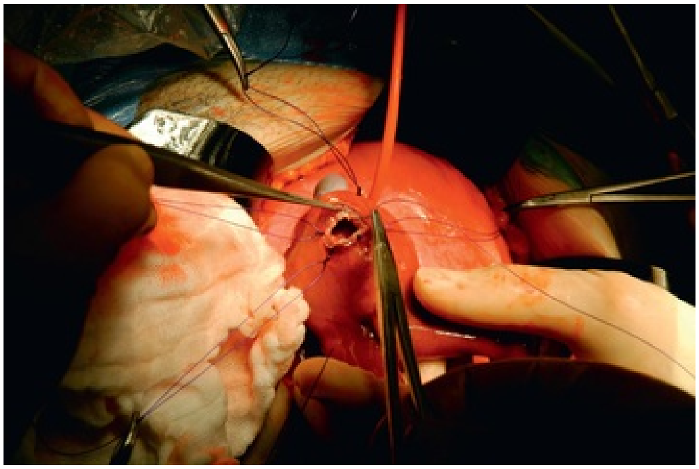

FIG. 116.2 Creation of a fetal vesicostomy. The uterine opening is stapled to prevent bleeding, and a catheter is inserted to replace amniotic fluid and maintain uterine volume. The fetus is positioned with the legs to the lower part of the field and the umbilical cord to the upper part of the field. A vesicostomy is created through the bladder and the abdominal wall to allow drainage of the obstructed bladder and restoration of amniotic fluid volume. (Courtesy of Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.)

Nonobstructive Renal Disease

Nonobstructive fetal renal disease can result from renal hypoplasia/dysplasia and from genetic disease such as autosomal recessive polycystic kidney disease. Similar to obstructive uropathy, fetal therapy is focused on restoring amniotic fluid volume in patients with oligohydramnios or anhydramnios. However, restoration of amniotic fluid volume in nonobstructive renal disease requires external sources of amniotic fluid. Current treatment options include serial percutaneous amnioinfusion and infusion of fluid by amnioport. **Serial amnioinfusions** are less invasive as a single procedure, but most pregnancies will require weekly infusions to maintain adequate amniotic fluid volume. Amnioinfusion through an **amnioport** involves open surgical placement of a catheter into the amniotic space that is connected to an ex utero subcutaneous port. This allows repeated fluid infusion into the amniotic space. The amnioport is more challenging and invasive as an individual procedure but provides more reliable access to the amniotic space for the duration of the pregnancy. Small studies suggest both these procedures improve pulmonary outcomes and perinatal survival in infants with renal disease, but these infants will require dialysis and then renal transplant when the infant is large enough (2-3 yr of age).

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (**CDH**) is a defect in the fetal diaphragm causing herniation of the abdominal contents into the thorax and inhibition of fetal lung growth (see Chapter 122.10). CDH occurs in 1 in 3,000 births and can range from mild to severe. In mild cases of CDH, surgical repair of the diaphragm is typically performed in the 1st few days of life. Lungs in these infants are smaller than normal at birth, but as they grow, these patients can lead normal, active lives. In the severe cases of CDH infants experience severe pulmonary hypoplasia and pulmonary hypertension, requiring extracorporeal membrane oxygenation (ECMO) in the perinatal period. Mortality is high in severely affected infants, and survivors often have long-term respiratory, feeding, and neurodevelopmental problems.

Early attempts at fetal intervention for CDH used **in utero** surgical correction of the diaphragm defect in severe CDH infants. Survival rates were poor, with most infants dying during or shortly after the fetal surgery. Since significant complications during this procedure involved reduction of the incarcerated liver, a follow-up study compared **postnatal** repair to in utero repair that was limited to infants without liver herniation in the chest. The fetal repair group had more premature delivery (32 vs 38 wk gestation) without an improvement in survival (75% fetal repair vs 86% postnatal repair). Therefore, attempts at in utero repair of CDH have been abandoned.

Occlusion of the fetal trachea causes lung growth, and this approach was capable of dramatically improving lung growth in animal models of pulmonary hypoplasia. Several groups explored the use of fetal tracheal occlusion in CDH. The fetal surgical team in Philadelphia evaluated both open fetal tracheal ligation and endoscopic tracheal occlusion with an inflatable balloon. Open fetal tracheal ligation was quickly abandoned, with most patients dying from either complications associated with the procedure or shortly after delivery from respiratory failure caused by the lack of alveolar type II cell maturation and surfactant production in the hyperexpanded lungs. Endoscopic balloon tracheal occlusion was eventually evaluated in a larger trial. Survival was better than open fetal tracheal ligation but still not improved over control patients. Development of **fetoscopic balloon tracheal occlusion** in CDH led to the multicenter prospective randomized Tracheal Occlusion to Accelerate Lung Growth (**TOTAL**) study. In this trial the balloon was inserted at 27-30 wk and removed at 34 wk. This timing is based on the hypothesis that tracheal occlusion will promote lung expansion while removal of the balloon before delivery will promote alveolar type II cell maturation. Initial data suggest that this approach is associated with a high incidence of preterm delivery but a significant increase in survival. The use of fetoscopic tracheal occlusion in CDH therapy is gaining popularity, but this approach in both severe and moderate CDH is still under investigation.

Congenital Pulmonary Airway Malformation

Congenital pulmonary airway malformation (**CPAM**), previously referred to as *congenital cystic adenomatoid malformation* (CCAM), is caused by abnormal branching and hamartomatous growth of the terminal respiratory structures that results in cystic and adenomatoid malformations (see Chapter 423). Although rare, these remain the most common congenital lung lesion. CPAMs usually arise between 5 and 22 wk of gestation and continue to increase in size until around the 26th wk of pregnancy. If large enough, CPAM can cause significant pulmonary hypoplasia and in severe cases, hydrops fetalis. The size of the CPAM is tracked by CPAM volume ratio (**CVR**), an index that compares the volume of the CPAM to the fetal head circumference. Most studies indicate >95% survival in CPAM patients with no hydrops and CVR <1.6, with a much lower survival and greater risk for hydrops in patients with a CVR >1.6. Without intervention, CPAM with hydrops is uniformly fatal.

Open fetal **resection** of CPAM was considered one of the first clearly beneficial fetal surgeries. A less invasive option in fetal patients with CPAM composed of a large, dominant cyst is the insertion of a thoracoamniotic shunt into the dominant cyst. This decreases CPAM size, allowing lung growth and reducing risk of hydrops. An alternative surgical approach involving resection of the CPAM at delivery while the infant remains on placental support via an **ex utero intrapartum therapy (EXIT)** procedure has also demonstrated improved survival in a select group of patients.

Patients (in utero) receiving corticosteroids experience improved survival compared with those receiving open fetal resection. Survival rates approach 100% in high-risk CPAM (CVR >1.6) treated with steroids before the onset of hydrops and 50% in patients who have developed hydrops. Therefore the current approach to fetal therapy for CPAM has been away from open fetal resection and toward single or multiple courses of antenatal corticosteroids in fetuses with CVR >1.6.

Myelomeningocele

Before the introduction of fetal repair of **myelomeningocele (MMC)** , fetal surgery was limited to diagnoses considered fatal for the fetus or infant without intervention. However, a growing body of data suggests that the neurologic outcome in MMC is directly related to progressive injury from ongoing damage to the exposed spinal cord during pregnancy (see Chapter 609.3). Controversy remained as to whether the maternal and fetal risks of fetal repair should be accepted when the goal was to reduce postnatal morbidity rather than to improve survival.

The observation in early studies that patients receiving open fetal MMC repair were less likely to require **ventriculoperitoneal (VP) shunt** prompted the prospective randomized trial of prenatal vs postnatal MMC management (MOMS) (Fig. 116.3). The study was closed to enrollment in 2010 after 183 patients were randomized and the data safety monitoring board determined a clear advantage for prenatal surgery. The MOMS trial demonstrated a significant reduction in the need for VP shunt in the fetal repair group (40% vs 82% in postnatal repair group). The fetal repair group had an improved composite score for mental development and motor function at 30 mo, but also an increased risk of preterm delivery and uterine dehiscence. The average gestational age at delivery in the fetal repair group was 34 wk, with 10% delivering at <30 wk, compared to 37 wk and no infants <30 wk in the postnatal repair group.

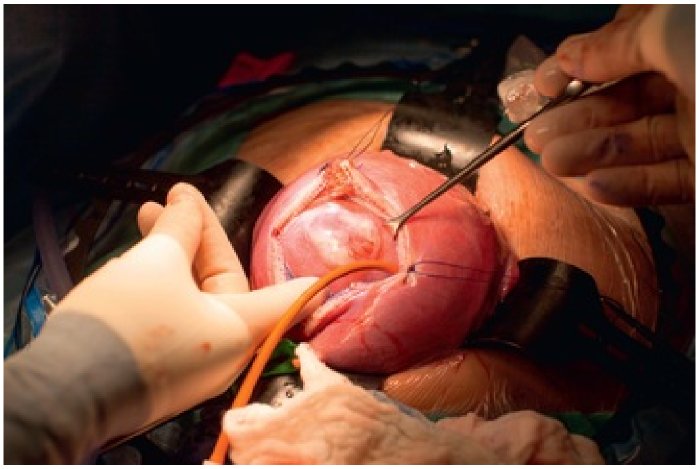

FIG. 116.3 Fetus during open repair of myelomeningocele. The uterine opening is stapled to prevent bleeding, and a catheter is inserted to replace amniotic fluid and maintain uterine volume. The myelomeningocele is exposed through the uterine opening and repaired. (Courtesy of Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.)

Open fetal repair of MMC has been an important advance but the risk of prematurity significantly decreases the benefit of this procedure. In theory, the less invasive fetoscopic MMC repair approach, which is being developed at a limited number of centers, should reduce maternal morbidity and prematurity rates associated with open fetal MMC repair (▶ Video 116.1).

Other Indications

Antenatal intervention for cardiac defects, such as aortic stenosis, pulmonic stenosis, and hypoplastic left heart syndrome (HLHS), have been used to dilate, with balloon valvuloplasty, stenotic valves (aortic stenosis) to prevent further development of HLHS (creating biventricular physiology) (Fig. 116.4) (see Chapter 458.10).

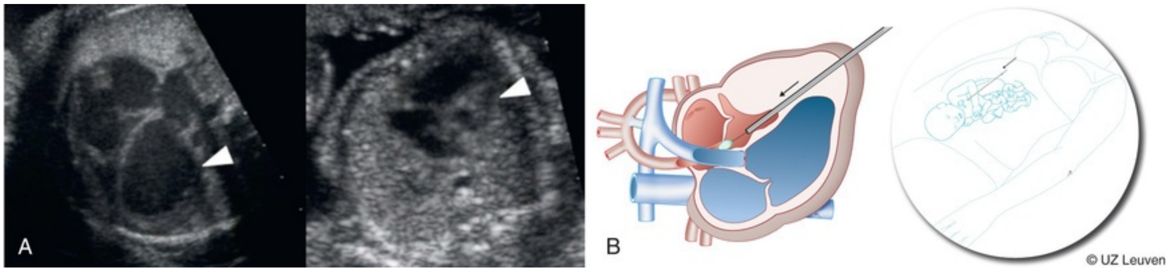

FIG. 116.4 **A,** Ultrasound image *(right panel)* is a cross section at the level of the fetal chest, demonstrating the 4-chamber view in a fetus with aortic

stenosis. Notice that the left ventricle *(arrowhead)* is dilated. Dilation occurs before the development of hypoplasia, which can be seen *(arrowhead)* in another fetus *(left panel)* . **B,** Schematic representation of percutaneous valvuloplasty, in this case of the left ventricular outlet tract. (**A,** From van Mieghem T, Baud D, Devlieger R, et al: Minimally invasive fetal therapy, *Best Pract Res Clin Obstet Gynaecol* 26:711–725, 2012; ***B,*** copyright © UZ Leuven, Leuven, Belgium.)

Laser therapy has been used to treat twin-twin transfusions syndrome (Chapter 117.1) and amniotic bands (Fig. 116.5).

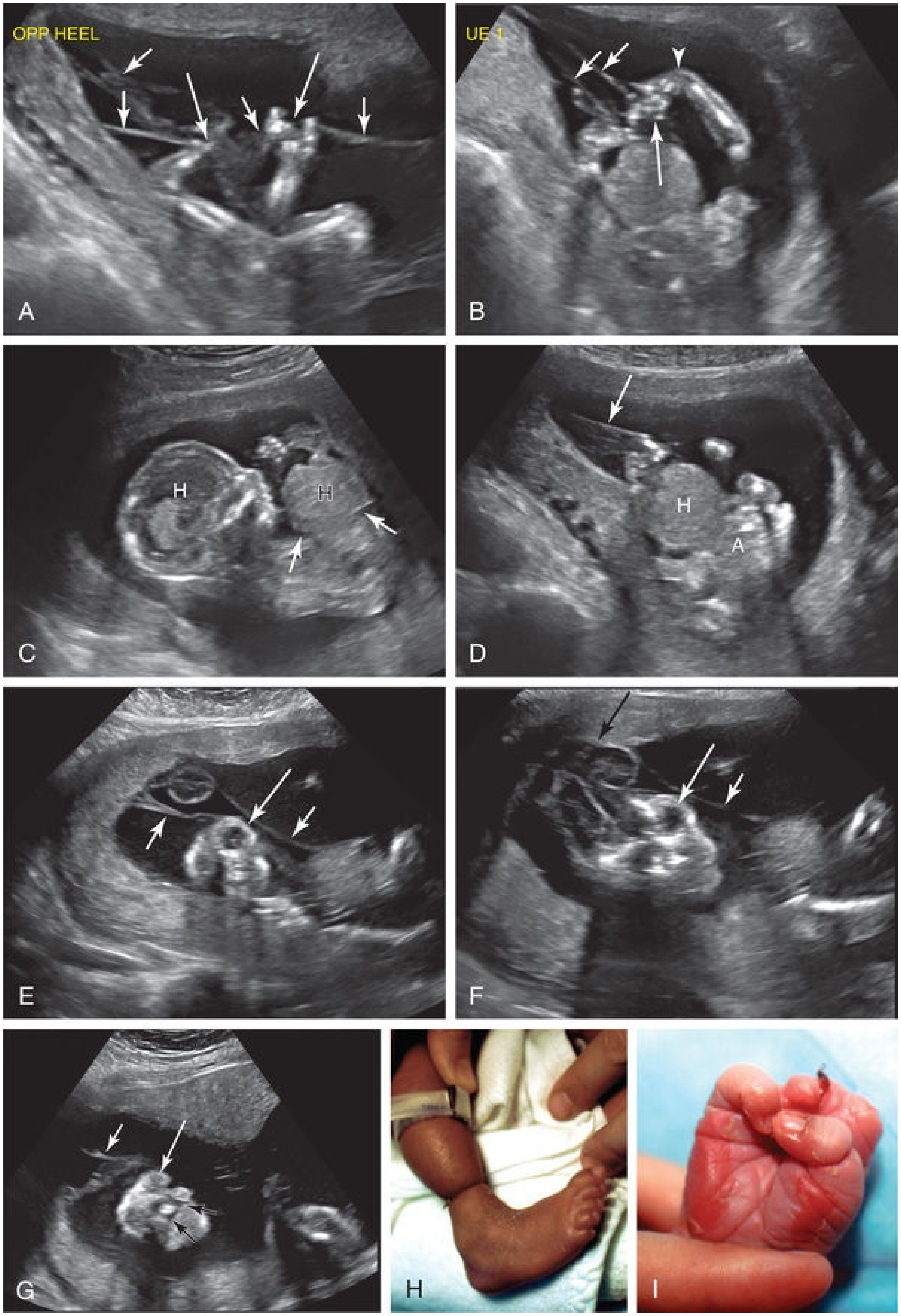
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FIG. 116.5 Amniotic band sequence in two different fetuses. A and B, Effects on the

extremities. Images of the limbs of a fetus with amniotic band sequence show multiple amniotic bands (*short arrows,* A and B), amputation of fingers and toes (*long arrows,* A and B), and a fixed deformity of the hand at the wrist (*arrowhead,* B). C and D, Effects on the thorax and abdomen of the same fetus as in A and B. Sagittal image (C) shows a thoracoabdominal wall defect *(arrows)* with a large amount of herniated abdominal and thoracic contents *(black H)* outside the body. *White H,* Head. D, Axial image of the fetal abdomen *(A)* confirms the presence of a large ventral abdominal hernia (H), in the setting of amniotic bands *(arrow).* E to G, Effects on craniofacial structures in a different fetus. E, Coronal image of face shows multiple amniotic bands *(short arrows)* and nonvisualization of the calvarium. This results in a craniofacial appearance that resembles anencephaly *(long arrow).* F, A large encephalocele *(black arrow)* is seen above the level of the orbits *(long white arrow)* in a different scan plane. An amniotic band *(short white arrow)* is also seen. G, Coronal image of anterior portion of face shows facial clefts *(black arrows)* due to amniotic bands. *Short white arrow,* Amniotic band; *long white arrow,* orbits. H, Band constricting the ankle, leading to deformational defects. I, Pseudosyndactyly, amputation and disruption of finger morphogenesis. (A-G, From Hertzberg BS, Middleton WD: Ultrasound: the requisites, ed 3, Philadelphia, 2016, Elsevier, Fig 19-22; H and I, From Jones KL, Smith DW, Hall BD, et al. A pattern of craniofacial and limb defects secondary to aberrant tissue bands. *J Pediatr* 84:90–95:1974.)

Fetal Centers

The value of fetal centers extends beyond fetal surgery. Often, families will present to a fetal center with a newly discovered diagnosis and little understanding of what the diagnosis means for their baby. **Prenatal counseling** by the fetal team can provide comfort to the family by helping them understand the diagnosis and treatment options and by developing a management plan that may include fetal surgery. Some plans may call for enhanced monitoring of the fetus and mother, followed by complex deliveries involving multidisciplinary delivery teams and specialized equipment, as required for EXIT to ECMO, EXIT to airway, EXIT to tumor resection, delivery to cardiac catheterization, and procedures on placental support. Other plans may focus on postnatal therapy.

Not all severely affected fetuses have available therapies in utero or after birth. In these lethal situations, fetal care planning will provide support for the family and a plan for delivery room or nursery palliative care (Table 116.3) (see Chapter 7).

Table 116.3

Selection of Patients for Fetal Repair

LEVEL OF CERTAINTY	DIAGNOSIS
DIAGNOSTIC CERTAINTY/PROGNOSTIC CERTAINTY	
Genetic problems	Trisomy 13, 15, or 18
	Triploidy

Central nervous system abnormalities	Anencephaly/acrania
	Holoprosencephaly
	Large encephaloceles
Heart problems	Acardia
	Inoperable heart anomalies
Kidney problems	Potter syndrome/renal agenesis
	Multicystic/dysplastic kidneys
	Polycystic kidney disease
DIAGNOSTIC UNCERTAINTY/PROGNOSTIC CERTAINTY	
Genetic problems	Thanatophoric dwarfism or lethal forms of osteogenesis imperfecta
Early oligo/anhydramnios and pulmonary hypoplasia	Potter syndrome with unknown etiology
Central nervous system abnormalities	Hydranencephaly
	Congenital severe hydrocephalus with absent or minimal brain growth
Prematurity	<23 wk gestation
PROGNOSTIC UNCERTAINTY/BEST INTEREST	
Genetic problems	Errors of metabolism that are expected to be lethal even with available therapy
Mid oligo/anhydramnios	Renal failure requiring dialysis
Central nervous system abnormalities	Complex or severe cases of meningomyelocele
	Neurodegenerative diseases, such as spinal muscular atrophy
Heart problems	Some cases of hypoplastic left heart syndrome
	Pentalogy of Cantrell (ectopia cordis)
Other structural anomalies	Some cases of giant omphalocele
	Severe congenital diaphragmatic hernia with hypoplastic lungs
	Idiopathic nonimmune hydrops
	Inoperable conjoined twins
	Multiple severe anomalies
Prematurity	23-24 wk gestation

From Leuthner SR: Fetal palliative care, *Clin Perinatol* 31:649–665, 2004 (Table 1, p 652).

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CHAPTER 117

The High-Risk Infant

Jennifer M. Brady, Maria E. Barnes-Davis, Brenda B. Poindexter

The term *high-risk infant* designates an infant at greater risk for neonatal morbidity and mortality; many factors can contribute to an infant being high risk (Table 117.1). High-risk infants are categorized into 4 main groups: the preterm infant, infants with special health care needs or dependence on technology, infants at risk because of family issues, and infants with anticipated early death.

Table 117.1

Factors in Considering Infants as High Risk for Morbidity or Mortality in the Neonatal Period

MATERNAL DEMOGRAPHIC/SOCIAL FACTORS
Maternal age <16 yr or >40 yr
Illicit drug, alcohol, cigarette use
Poverty
Unmarried
Emotional or physical stress
MATERNAL MEDICAL HISTORY
Genetic disorders
Diabetes mellitus
Hypertension
Asymptomatic bacteriuria
Rheumatologic illness (systemic lupus erythematosus)
Immune-mediated diseases (IgG crossing placenta)
Long-term medication (see Chapters 115.4 and 115.5)
PREVIOUS PREGNANCY
Intrauterine fetal demise
Neonatal death
Prematurity
Intrauterine growth restriction
Congenital malformation
Incompetent cervix
Blood group sensitization, neonatal jaundice
Neonatal thrombocytopenia
Hydrops

Inborn errors of metabolism

PRESENT PREGNANCY

Vaginal bleeding (abruptio placentae, placenta previa)
Sexually transmitted infections (colonization: herpes simplex, group B streptococcus, chlamydia, syphilis, hepatitis B, HIV)
Multiple gestation
Preeclampsia
Premature rupture of membranes
Short interpregnancy time
Poly-/oligohydramnios
Acute medical or surgical illness
Inadequate prenatal care
Familial or acquired hypercoagulable states
Abnormal fetal ultrasonographic findings
Treatment of infertility

LABOR AND DELIVERY

Premature labor (<37 wk)
Postdates pregnancy (≥42 wk)
Fetal distress
Immature lecithin/sphingomyelin ratio; absence of phosphatidylglycerol
Breech presentation
Meconium-stained fluid
Nuchal cord
Cesarean delivery
Forceps delivery
Apgar score <4 at 5 min

NEONATE

Birthweight <2,500 g or >4,000 g
Birth <37 wk or ≥42 wk of gestation
Small or large for gestational age
Respiratory distress, cyanosis
Congenital malformation
Pallor, plethora, petechiae

All high-risk infants require closer evaluation and/or treatment by experienced physicians and nurses. This often starts at delivery and continues through a neonatal intensive care unit (NICU) stay (see Chapter 121). Regionalized care for infants is based on the acuity of care that can be provided at hospitals with different levels of care and whether transport should be undertaken (see Chapter 118). It is important to note that additional care does not stop at time of NICU discharge, and that many high-risk infants also benefit from additional resources and follow-up after discharge from the hospital (see Chapter 117.5).

Approximately 15 million infants are born preterm (before 37 wk gestational age) each year worldwide, accounting for approximately 1 in every 10 babies born, and the overwhelming majority of high-risk infants. The World Health Organization (WHO) defines infants born before 28 wk gestational age as *extremely preterm* infants, infants born between 28 and $31\frac{6}{7}$ wk as *very preterm*, and infants born between 32 and $36\frac{6}{7}$ weeks as *moderate to late preterm* infants.

Risk of both morbidity and mortality increases with earlier gestational age. Gestational age, birthweight, and gender are all important factors that impact neonatal mortality (Fig. 117.1). The **highest risk** of neonatal and infant mortality occurs in infants with birthweight <1,000 g and/or with gestational age <28 wk. The **lowest risk** of neonatal mortality occurs in infants with birthweight of 3,000-4,000 g and a gestational age of 39-41 wk. As birthweight increases from 400 to 3,000 g and gestational age increases from 23 to 39 wk, a logarithmic decrease in neonatal mortality occurs. Once birthweight exceeds 4000 g and/or gestational age exceeds 42 wk, the incidence of neonatal morbidities and mortality increases.

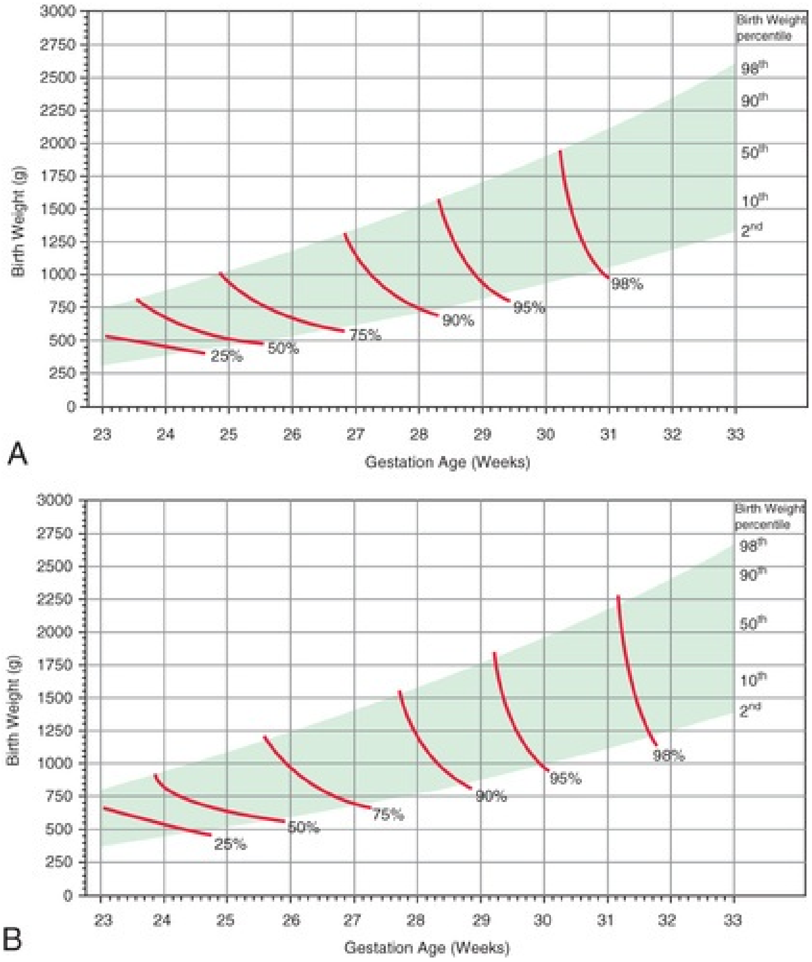

FIG. 117.1 Contour plot of predicted survival according to gestational age, birthweight, and gender. A, Female. B, Male. The contour lines join combinations of gestational age and birthweight of equal estimated probability of survival. Birthweight percentiles are shown for information. Data based on singleton infants born in the United Kingdom between January 2008 and December 2010 who survived to NICU admission. (From Manktelow BN, Seaton SE, Fields DJ, et al: Population-based estimates of in-unit

survival for very preterm infants, *Pediatrics* 131:e425–e432, 2013, Fig 2.)

117.1

Multiple-Gestation Pregnancies

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Keywords

acardiac fetus
chimeric
conjoined twins
diamnionic
dichorionic
dizygotic
endoparasitic twins
exoparasitic twins
fission theory
fusion theory
monoamniotic
monochorionic
monozygotic
superfecundation
superfetation
TRAP
TTTS
twin reversed arterial perfusion syndrome
twin-twin transfusion syndrome

Monozygotic vs Dizygotic Twins

Identifying twins as **monozygotic** or **dizygotic** is useful in determining the relative influence of heredity and environment on human development and disease. The previous assumption that twins not of the same sex are dizygotic can no longer be held as true. Sex discordance, placentation, and determination of amnionicity and chorionicity are not reliable ways of determining zygosity. Detailed blood typing, gene analysis, or tissue (human leukocyte antigen) typing can be used for zygosity testing (an exception being blood typing in cases of **chimeric** twins, where one or both twins contain distinct cell lines from multiple zygotes). Physical and cognitive differences may still exist between monozygotic twins because of other factors. The in utero environment may have been different. Additionally, differences may exist in the mitochondrial genome, in posttranslational gene product modification, and in the epigenetic modification of nuclear genes in response to environmental factors.

Examination of the Placenta

If the placentas are separate, twins are **dichorionic** , but not necessarily dizygotic. One third of monozygotic twins are **dichorionic** and **diamnionic.** An apparently single placenta may be present with either monozygotic or dizygotic twins, but inspection of a dizygotic placenta usually reveals that each twin has a separate chorion that crosses the placenta between the attachments of the cords and 2 amnions. Separate or fused dichorionic placentas may be disproportionate in size. The fetus attached to the smaller placenta or the smaller portion of the placenta is usually smaller than its twin or is malformed. **Monochorionic** twins are usually **diamnionic** , and the placenta is usually a single mass.

Incidence

The incidence of **spontaneous twinning** is highest among blacks and East Indians, followed by northern European whites, and is lowest in the Asian races. Differences in the incidence of twins worldwide mainly involve dizygotic twins. The incidence of monozygotic twins (3-5 per 1,000) is unaffected by racial or familial factors. Until recently, monozygotic twinning rates remained stable across continents and cultures. In 2014 the U.S. final natality report recorded a twin rate of 33.9 per 1,000 live births, which was a new high for the nation.

Increases in monozygotic and dizygotic twinning have been associated with advanced maternal age (AMA) and the use of assisted reproductive technologies (ART). The rate of triplets and higher-order multiple births is 113.5 per 100,000 live births in the United States and continues to decline. The use of single-embryo transfer in ART has decreased the numbers of triplet births and higher-order multiples. However, a doubling of **monozygotic** twinning and an increase in atypical twinning have been reported. The incidence of **dizygotic** multifetal gestation is also increasing, attributed to treatment of infertility with ovarian stimulants (clomiphene, gonadotropins).

Etiology

Polyovular pregnancies are more frequent beyond the 2nd pregnancy, in older women, and in families with a history of dizygotic twins. They may result from simultaneous maturation of multiple ovarian follicles, but follicles containing 2 ova have also been described as a genetic trait leading to twin pregnancies. Twin-prone women have higher levels of gonadotropin. Polyovular pregnancies occur in many women treated for infertility.

The occurrence of monozygotic twins appears to be independent of heritable factors. The etiology of monozygotic twinning is unknown, but there are 2 prevailing theories. In the classic **fission theory** , twinning results from the splitting of a single conceptus, with the timing of splitting resulting in differing amnionicity and chorionicity (i.e., the earlier the fission occurs, the more likely the twins are to be diamniotic dichorionic) (Fig. 117.2). However, this theory fails to account for several forms of atypical twinning, including the occurrence of **diamniotic dichorionic monozygotic** twinning after single-embryo transfer in the late blastocyst state, phenotypically-discordant monozygotic twins, and asymmetrically attached conjoined twins. An alternate **fusion theory** of twinning has been proposed to account for this discrepancy, in which the inner cell masses of trophectoderm fuse after the initial 2-cell splitting stage (Fig. 117.3).

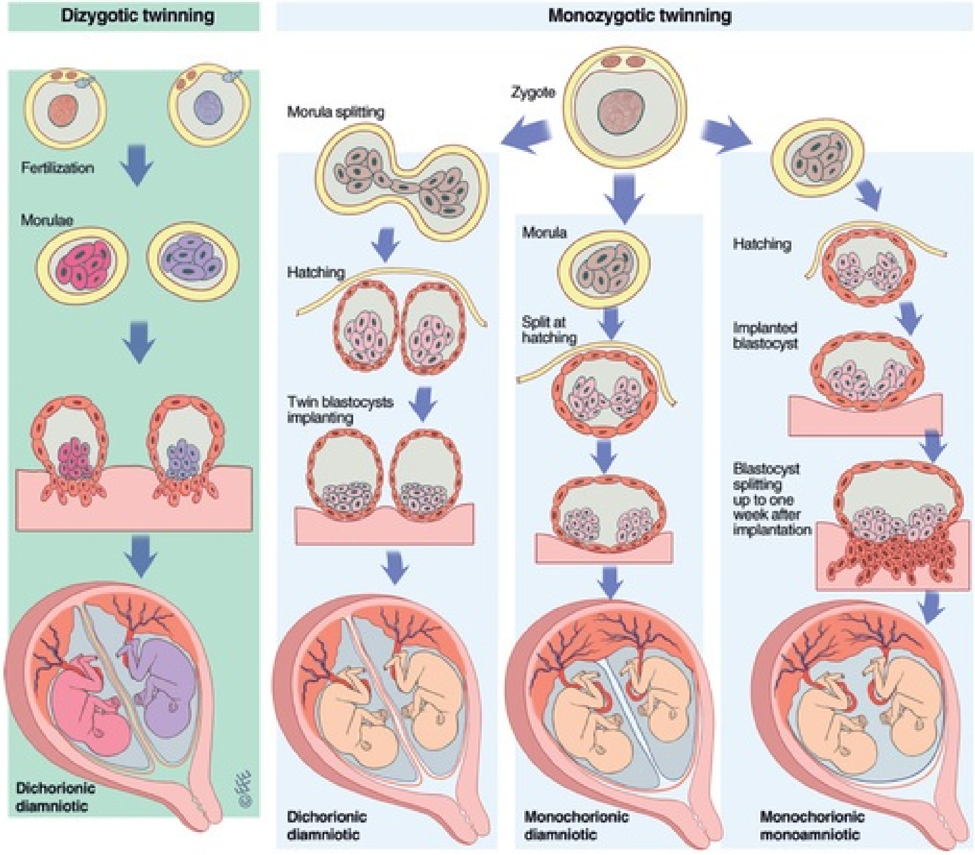
Dizygotic twinning
Monozygotic twinning
Fertilization
Morulae
Dichorionic
diamniotic
Zygote
Morula splitting
Hatching
Twin blastocysts
implanting
Dichorionic
diamniotic
Morula
Split at
hatching
Monochorionic
diamniotic
Hatching
Implanted
blastocyst
Blastocyst
splitting
up to one
week after
implantation
Monochorionic
monoamniotic

FIG. 117.2 Classical fission theory of twinning. *Dizygotic twins* result from 2 distinct fertilization events, with dichorionic diamniotic twins each developing to become a genetically distinct individual. *Monozygotic twins* result from postzygotic splitting of the product of a single fertilization event. Splitting on days 1-3 (up to the morula stage) results in dichorionic diamniotic twins, on days 3-8 (during which blastocyst hatching occurs) in monochorionic diamniotic twins, on days 8-13 in monochorionic monoamniotic twins. (Illustration copyright © LeventEfe, CMI. www.leventefe.com.au .)

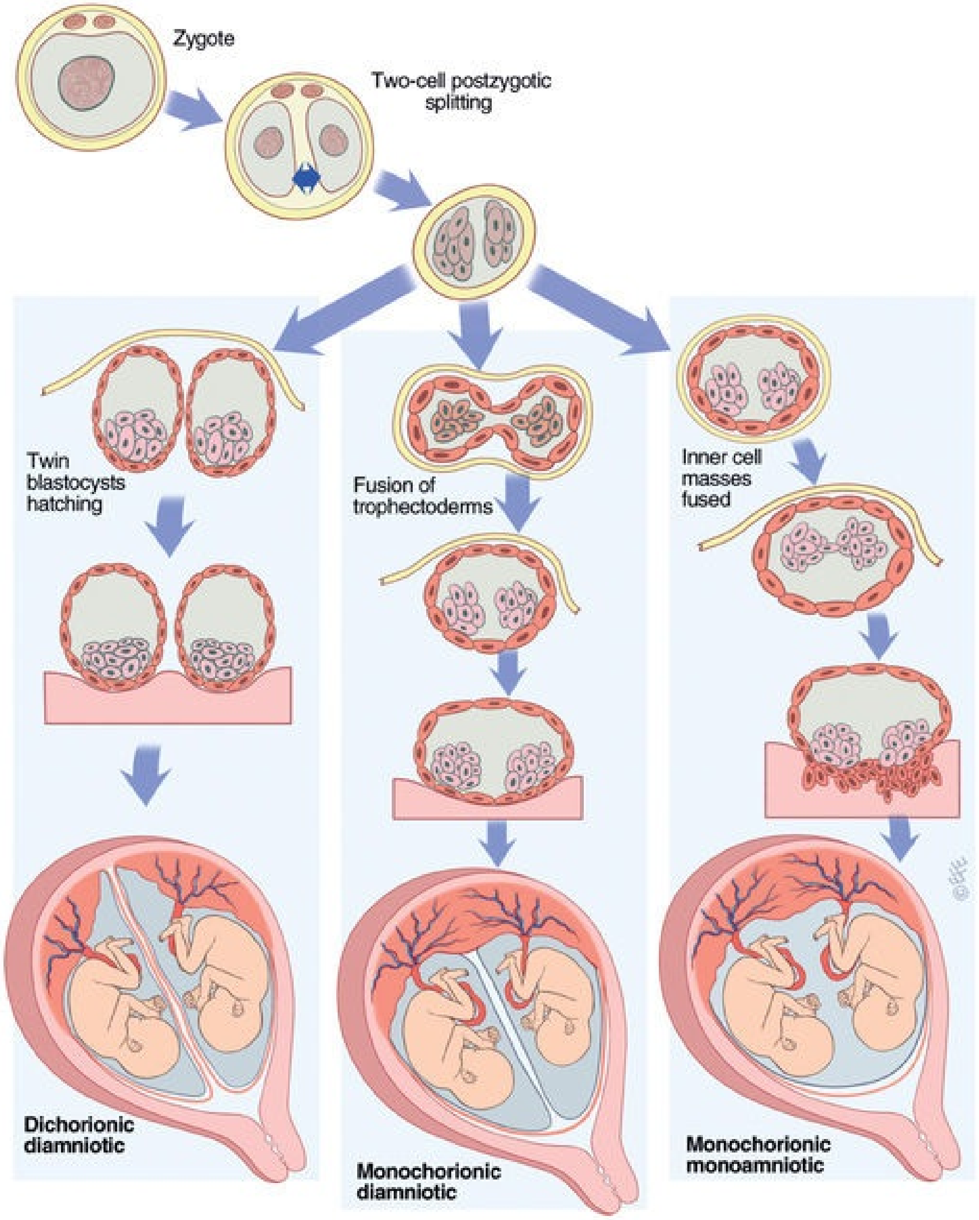
Zygote
Two-cell postzygotic splitting
Twin blastocysts hatching
Fusion of trophectoderms
Inner cell masses fused
Dichorionic diamniotic
Monochorionic diamniotic
Monochorionic monoamniotic

FIG. 117.3 Fusion theory of monozygotic twinning. Splitting occurs at the postzygotic 2-cell stage, with each cell forming a distinct individual. If twin blastocysts hatch from the zona pellucida together, dichorionic diamniotic twins will result. If the 2 trophectoderms fuse before hatching and the inner cells masses are separated within the shared trophectoderm, monochorionic diamniotic twins will result. If the inner cell masses are fused and separated later, monochorionic monoamniotic twins will result. (Illustration copyright © LeventEfe, CMI. www.leventefe.com.au .)

Atypical Twinning

Conjoined twins (1 in 50,000 pregnancies and 1 in 250,000 live births) are obligate **monozygotes** . Theoretically, they result from later fission of a single zygote (10-14 days) or from fusion of 2 zygotes (as proposed for asymmetrically attached conjoined twins). The majority of conjoined twins are female. The prognosis for symmetrically conjoined twins depends on the possibility of surgical separation, which in turn depends on the extent to which vital organs are shared. The site of connections varies: thoracoomphalopagus (28% of conjoined twins), thoracopagus (18%), omphalopagus (10%), craniopagus (6%), and incomplete duplication (10%). The term *parasitic twin* has historically been used to describe the smaller and less completely developed member of a pair of conjoined twins; this *parasitic* twin has typically had embryonic demise but remains vascularized by the surviving *independent* twin (the **autocyte**). For asymmetrically attached conjoined twins in whom one twin is dependent on the cardiovascular system of the intact autocyte (**exoparasitic twins** , 1 in 1 million live births) survival of the autocyte depends on the feasibility of excising the *exoparasitic* twin. For **endoparasitic twins** (*fetus in fetu,* 1 in 500,000 live births) in whom one (or more) fetus exists as a benign mass in the autocyte, survival of the autocyte is unaffected.

Superfecundation, or fertilization of an ovum by an insemination that takes place after one ovum has already been fertilized, and **superfetation,** or fertilization and subsequent development of an embryo when a fetus is already present in the uterus, have been proposed as explanations for differences in size and appearance of certain twins at birth.

Complications

Problems of twin gestation include polyhydramnios, hyperemesis gravidarum, preeclampsia, premature rupture of membranes (PROM), vasa previa, velamentous insertion of the umbilical cord, abnormal presentation (breech), and premature labor. **Monoamniotic** twins have a high fatality rate because of obstruction of the circulation secondary to intertwining of the umbilical cords.

Compared with the 1st-born twin, the 2nd twin is at increased risk for respiratory distress syndrome and asphyxia. Twins are at risk for intrauterine growth restriction, twin-twin transfusion syndrome, and congenital anomalies, which occur predominantly in **monozygotic** twins. Anomalies are a result of compression *deformation* of the uterus from crowding (hip dislocation), vascular communication with embolization (ileal atresia, porencephaly, cutis aplasia) or without embolization (acardiac twin), and unknown factors (conjoined twins, anencephaly, meningomyelocele).

Twin Syndromes (TRAP, TTTS)

Placental vascular anastomoses occur with high frequency in **monochorionic** twins. In monochorionic placentas, the fetal vasculature is usually joined, sometimes in a very complex manner. They are usually balanced so that neither twin suffers. Artery-to-artery communications cross over placental veins, and when anastomoses are present, blood can readily be stroked from one fetal vascular bed to the other. Vein-to-vein communications are similarly recognized but are less common. A combination of artery-to-artery and vein-to-vein anastomoses is associated with the condition of **acardiac fetus** . This rare lethal anomaly (1 in 35,000) is secondary to the **twin reversed arterial perfusion (TRAP) syndrome** . In utero radiofrequency or laser ablation of the anastomosis or cord occlusion can be used to treat heart failure in the surviving twin. However, death of the autocyte is reported in up to 75% of cases. In rare cases, one umbilical cord may arise from the other after leaving the placenta, and the twin attached to the secondary cord usually is malformed or dies in utero.

In **twin-twin transfusion syndrome (TTTS)** , an artery from one twin acutely or chronically delivers blood that is drained into the vein of the other. The latter develops polyhydramnios, plethoric and large for dates, and the former has oligohydramnios, anemic and small (Fig. 117.4). TTTS is more common in monozygotic twins and affects up to 30% of monochorionic twins. Maternal polyhydramnios in a twin pregnancy suggests TTTS. Anticipating this possibility by preparing to transfuse the donor twin or bleed the recipient twin may be lifesaving. Death of the donor twin in utero may result in generalized fibrin thrombi in the smaller arterioles of the recipient twin, possibly as the result of transfusion of thromboplastin-rich blood from the macerating donor fetus. Disseminated intravascular coagulation (DIC) may develop in the surviving twin. Table 117.2 lists the more frequent changes associated with a large shunt. **Treatment** of this highly lethal problem includes maternal digoxin, aggressive amnioreduction for polyhydramnios, selective twin termination, and more often, laser or fetoscopic ablation of anastomosis (Fig. 117.5).

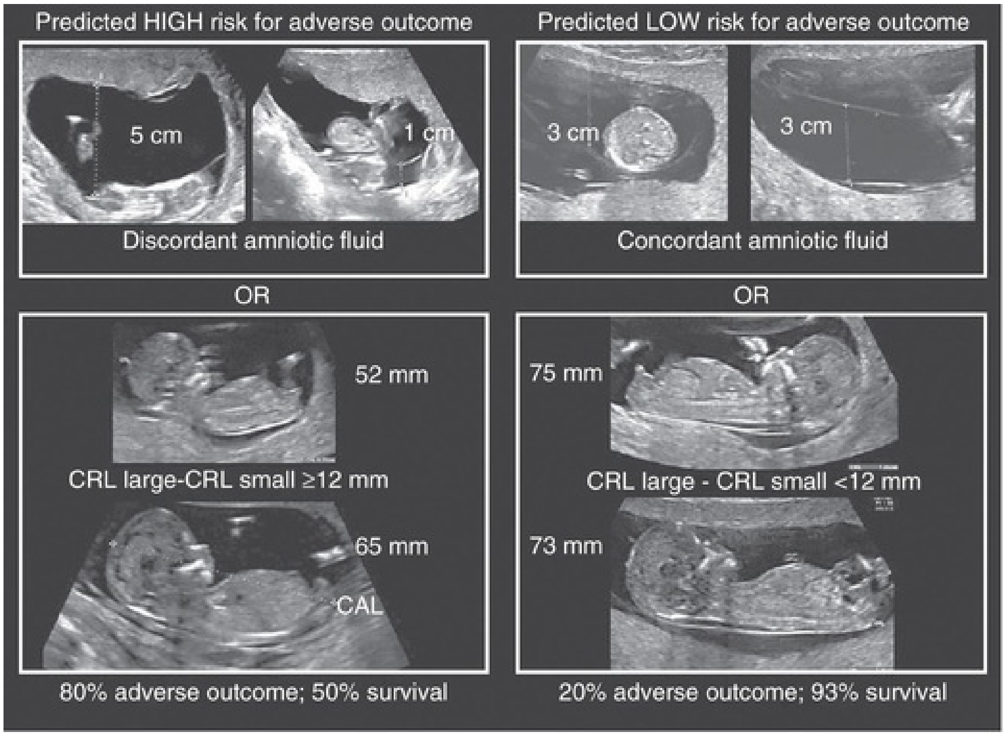
Predicted HIGH risk for adverse outcome
Predicted LOW risk for adverse outcome
5 cm
1 cm
3 cm
3 cm
Discordant amniotic fluid
Concordant amniotic fluid
OR
OR
52 mm
75 mm
CRL large-CRL small ≥12 mm
CRL large - CRL small <12 mm
65 mm
CAL
73 mm
80% adverse outcome; 50% survival
20% adverse outcome; 93% survival

FIG. 117.4 Representation of first-trimester risk assessment for the development of discordant growth, twin-twin transfusion syndrome (TTTS), or intrauterine demise. Discordant amniotic fluid in the first trimester generally corresponded with deepest vertical pockets ≤3 cm in one sac and ≥6.5 cm in the other. Discordance in crown-rump length (CRL) was present if the difference was ≥12 mm. (From Lewi L, Gucciardo L, Van Mieghem T, et al: Monochorionic diamniotic twin pregnancies: natural history and risk stratification, *Fetal Diagn Ther* 27:121–133, 2010.)

Table 117.2

Characteristic Changes in Monochorionic Twins With Uncompensated Placental Arteriovenous Shunts

TWIN ON:	
Arterial Side—Donor	**Venous Side—Recipient**
Prematurity	Prematurity
Oligohydramnios	Polyhydramnios
Small premature	Hydrops
Malnourished	Large premature
Pale	Well nourished
Anemic	Plethoric
Hypovolemic	Polycythemic
Hypoglycemic	Hypervolemic
Microcardia	Cardiac hypertrophy
Glomeruli small or normal	Myocardial dysfunction
Arterioles thin walled	Tricuspid valve regurgitation
	Right ventricular outflow obstruction
	Glomeruli large

	Arterioles thick walled

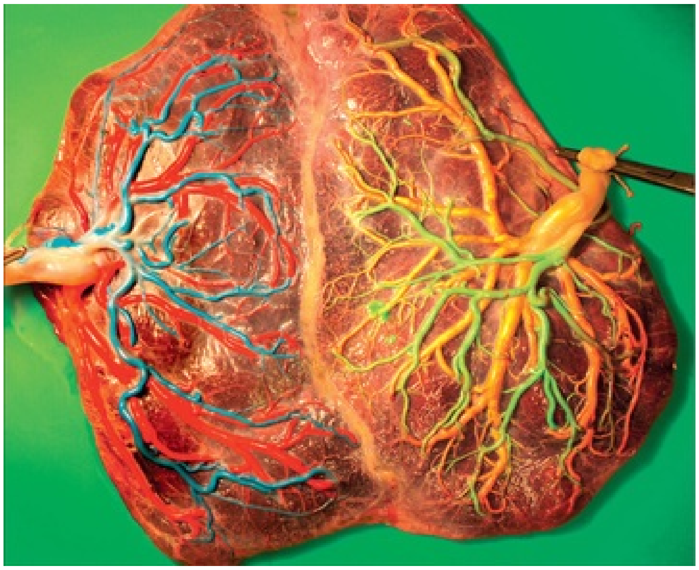

FIG. 117.5 **Color-dye-stained twin-to-twin transfusion syndrome placenta that was treated using the Solomon technique. *Blue* and *green* dye used to stain the arteries, and *pink* and *yellow* dye used to stain the veins. After identification and coagulation of each individual anastomosis, the complete vascular equator is coagulated from one placental margin to the other. (From Slaghekke F, Lopriore E, Lewi L, et al: Fetoscopic laser coagulation of the vascular equator versus selective coagulation for twin-to-twin transfusion syndrome: an open-label randomized controlled trial, *Lancet* 383:2144–2150, 2014, Fig 3.)**

Diagnosis

A prenatal diagnosis of pregnancy with twins is suggested by a uterine size that is greater than that expected for gestational age, auscultation of 2 fetal hearts, and elevated maternal serum α-fetoprotein (AFP) or human chorionic gonadotropin (hCG) levels. It is confirmed by ultrasonography. Physical examination of twins is necessary but not sufficient to determine zygosity of twins. In the event that congenital anomalies are present or there are transfusion or transplantation considerations, genetic testing of zygosity should be performed. While noninvasive prenatal testing (NIPT) is becoming more common, the results should be interpreted with caution in multiple-gestation pregnancies until more findings are better established.

Prognosis

Most twins are born prematurely, and maternal complications of pregnancy are more common than with single pregnancies. The risk for twins is most often associated with twin-twin transfusion, ART, and early-onset discordant growth. Because most twins are premature, their overall mortality is higher than that of single-birth infants. The perinatal mortality of twins is about 4 times that of singletons, with **monochorionic** twins being particularly at risk. **Monoamnionic** twins have an increased likelihood of cord entanglement, which may lead to asphyxia. Twins are at greater risk for congenital malformations, with up to 25% of monozygotic twins being affected. Theoretically, the 2nd twin is more subject to anoxia than the 1st because the placenta may separate after birth of the 1st twin and before birth of the 2nd. In addition, delivery of the 2nd twin may be difficult because it may be in an abnormal presentation (breech, entangled), uterine tone may be decreased, or the cervix may begin to close after the 1st twin's birth.

Triplet or higher-order births are associated with an increased risk of death or neurodevelopmental impairment compared with extremely-low-birthweight (ELBW) singleton and twin infants after controlling for gestational age. The mortality for multiple gestations with ≥4 fetuses is excessively high for each fetus. Because of this poor prognosis, selective fetal reduction has been offered as a treatment option. **Monozygotic** twins have an increased risk of one twin dying in utero. The surviving twin has a greater risk for cerebral palsy and other neurodevelopmental sequelae.

Treatment

Prenatal diagnosis enables the obstetrician and pediatrician to anticipate the birth of infants who are at high risk because of twinning. The risk of multiple-gestation pregnancies using ART may be reduced by elective single-embryo transfers. In addition, elective delivery of twins at 37 wk (or earlier for **monochorionic** , **monoamniotic** twins) reduces the complication rate for the fetuses and the mother. Furthermore, in twin pregnancies between 32 and 39 wk of gestation, planned vaginal delivery is preferred if the 1st twin is in the cephalic presentation. Close observation and attendance by a pediatric team are indicated in the immediate neonatal period so that prompt treatment of asphyxia or fetal transfusion syndrome can be initiated. The decision to perform an immediate blood transfusion in a severely anemic “donor twin” or a partial exchange transfusion of a “recipient twin” must be based on clinical judgment.

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117.2

Extremely and Very Preterm Infants

Jennifer M. Brady, Brenda B. Poindexter

Keywords

Ballard scoring system
extremely low birthweight

extremely low gestational age newborn
extremely preterm
kangaroo care
low birthweight
neutral thermal environment
very low birthweight

Traditionally, a delivery date is determined 280 days after the last menstrual period (LMP). However, only 4% of pregnant women actually deliver at 280 days, and only 70% deliver within 10 days of the estimated delivery date.

Infants born before 37 wk from the 1st day of the LMP are termed *premature* by WHO. Infants born before 28 wk gestation are **extremely preterm,** also referred to as **extremely low gestational age newborns (ELGANs)** ; whereas infants born between 28 and $31\frac{6}{7}$ are **very preterm** . Moderate and late preterm infants (born between 32 and $36\frac{6}{7}$ wk gestation) are discussed in Chapter 117.3 .

In addition to classification by gestational age, classification is also based on birthweight. **Extremely low birthweight (ELBW)** is used to describe infants with a birthweight <1000 g, **very low birthweight (VLBW)** describes infants <1500 g, and **low birthweight (LBW)** describes infants <2500 g at birth. Birthweight in general is a proxy for gestational age, but in the cases of intrauterine growth restriction (IUGR) and small-for-gestational-age (SGA) infants, birthweight can sometimes be misleading for true gestational age (see Chapter 117.4).

Incidence

Preterm birth , or birth before 37 wk of gestation, is fairly common. Worldwide, approximately 15 million preterm births occur annually. In the United States, approximately 10% of all births are preterm. After a prolonged period of increasing rates of preterm birth, preterm births in the United States peaked at 10.44% in 2007. From 2007 until 2014, a slow but steady decline occurred in preterm births, to 9.57% in 2014. Preliminary data show that preterm births have slightly increased since 2014, with 9.84% of all U.S. births being preterm in 2016 and a disproportionate increase in late preterm births (Fig. 117.6). Of preterm births in 2016, the majority were late preterm infants, approximately 72% of preterm births, with the remaining 28% being extremely or early preterm.

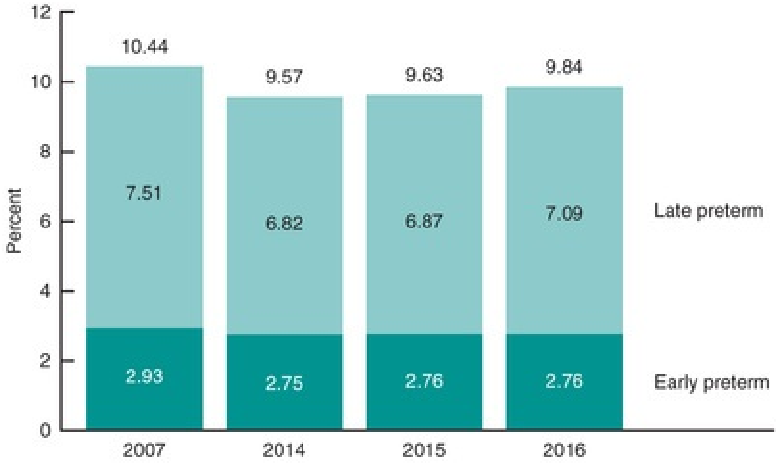

NOTES: Gestational age is measured in completed weeks based on the obstetric estimate. Early preterm is births before 32 weeks; late preterm is births at 34–36 weeks. Figures may not add to totals due to rounding.
SOURCE: NCHS, National Vital Statistics System.

FIG. 117.6 **Preterm birth rates in the United States in 2007, 2014, 2015, and 2016 (provisional). There was a recent rise in preterm birth rate from 2014 to 2016. Preterm birth rate further divided into early preterm birth (birth <32 wk) and late preterm birth (birth at $34-36\frac{6}{7}$ wk). (From Hamilton BE, Martin JA, Osterman MJK, et al: Births: provisional data for 2016, *Vital Statistics Rapid Release* 2017; 1–21, Fig 4.)**

Etiology

Despite the frequency of preterm birth, it is often difficult to determine a specific cause. The etiology of preterm birth is multifactorial and involves complex interactions between fetal, placental, uterine, and maternal factors. In the setting of maternal or fetal conditions that prompt early delivery, as well as placental and uterine pathology, causes of preterm birth can sometimes be identified (Table 117.3).

Table 117.3

Identifiable Risk Factors for Preterm Birth

FETAL
Fetal distress
Multiple gestation
Erythroblastosis

Nonimmune hydrops

PLACENTAL

Placental dysfunction
Placenta previa
Placental abruption

UTERINE

Bicornuate uterus
Incompetent cervix (premature dilation)

MATERNAL

Previous preterm birth
Preeclampsia
Black race
Chronic medical illness (cyanotic heart disease, renal disease, thyroid disease)
Short interpregnancy interval
Infection (*Listeria monocytogenes,* group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis)
Obesity
Drug abuse (cocaine)
Young or advanced maternal age

OTHER

Premature rupture of membranes
Polyhydramnios
Iatrogenic
Assisted reproductive technology
Trauma

However, most preterm births are *spontaneous* without an identifiable cause. Older maternal age, poorer maternal health, history of previous preterm delivery, short interpregnancy interval, and lower socioeconomic status (SES) have all been associated with preterm birth. Racial disparities also exist, which seem to persist when taking into account SES. Large population studies have also found associations between maternal genetics and preterm birth. Gestational duration and actual preterm birth have been noted with genetic variants in the maternal genome. Many of these genes have roles in regulation of the estrogen receptor, uterine development, maternal nutrition, or vascular reactivity. In addition, cell free RNA transcripts in maternal blood may also be of value in predicting preterm birth.

Assessment of Gestational Age

With insufficient prenatal care or discrepancies between birthweight and predicted gestational age at birth, it is often helpful to be able to assess infants at birth for an estimated gestational age. Examination and assessment is needed to distinguish SGA and IUGR infants from preterm infants. Compared with a premature infant of appropriate weight, an infant with IUGR has a reduced birthweight and may appear to have a disproportionately larger head relative to body size; infants in both groups lack subcutaneous fat. Neurologic maturity (nerve conduction velocity) in the absence of asphyxia correlates with gestational age despite reduced fetal weight. Physical signs may be useful in estimating gestational age at birth. The commonly used **Ballard scoring system** is accurate to within 2 wk of actual gestational age (Figs. 117.7 to 117.9).

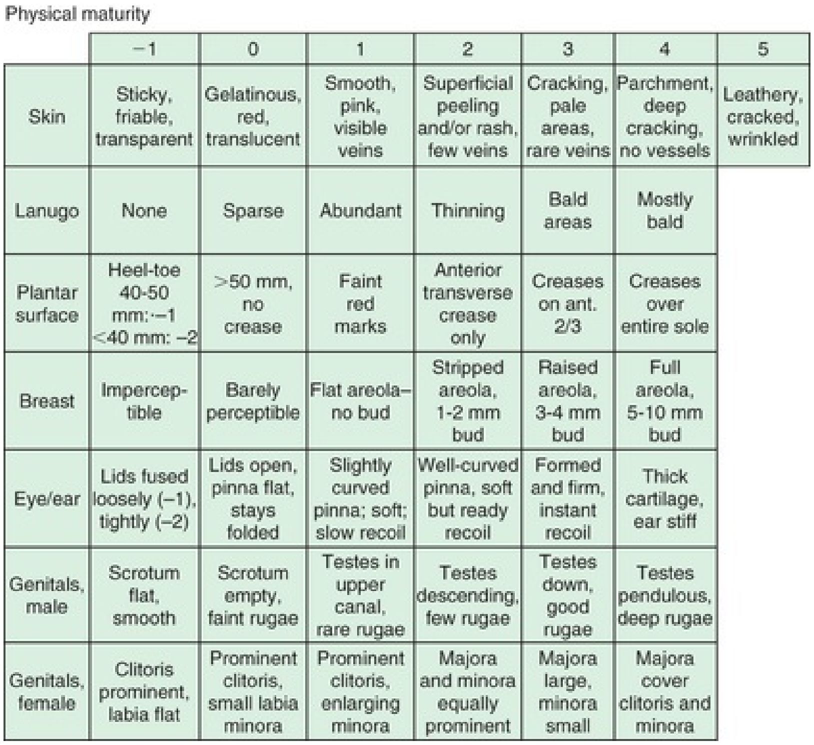

Physical maturity

	–1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm: –1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on ant. 2/3	Creases over entire sole	
Breast	Impercep-tible	Barely perceptible	Flat areola–no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely (–1), tightly (–2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

FIG. 117.7 Physical criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. (From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants, *J Pediatr* 119:417–423, 1991.)

Neuromuscular maturity

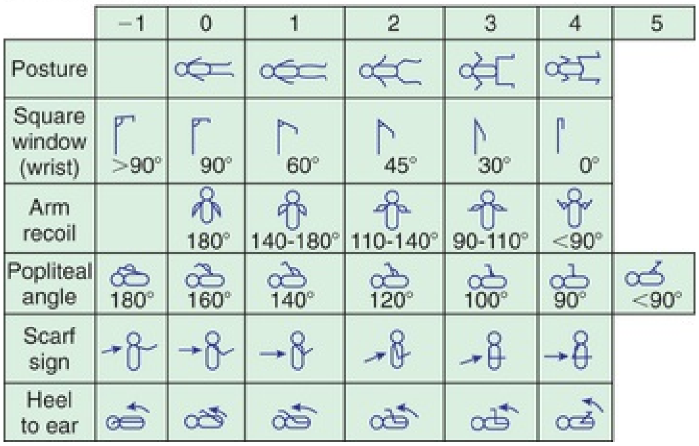

	−1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140-180°	110-140°	90-110°	<90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

FIG. 117.8 Neuromuscular criteria for maturity. The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. (From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants, *J Pediatr* 119:417–423, 1991.)

Maturity Rating

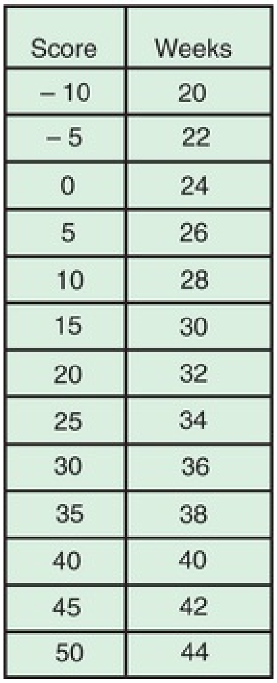

Score	Weeks
− 10	20
− 5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

FIG. 117.9 Maturity rating. The physical and neurologic scores are added to calculate gestational age. (From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants, *J Pediatr* 119:417–423, 1991.)

Nursery Care

At birth, the general measures needed to clear the airway, initiate breathing, care for the umbilical cord and eyes, and administer vitamin K are the same for premature infants as for those of normal weight and maturity (see Chapter 121). Additional considerations are the need for (1) thermal control and monitoring of the heart rate and respiration, (2) oxygen therapy, and (3) special attention to the details of fluid requirements and nutrition. Safeguards against infection can never be relaxed. Routine procedures that disturb these infants may result in hypoxia. The need for regular and active participation by the parents in the infant's care in the nursery and the question of prognosis for later growth and development require special consideration.

Thermal Control

Neonatal temperature regulation decreases the risk of morbidity and mortality in ELBW and VLBW infants. Neonates in general, and ELBW and VLBW infants to an even greater extent, are at increased risk of heat loss compared with older children due to an increased body surface/weight ratio, decreased epidermal and dermal skin thickness, minimal subcutaneous fat, and an immature nervous system.

Preterm infants should be kept in a **neutral thermal environment** . This environment is a set of thermal conditions, including air and radiating surface temperatures, relative humidity, and airflow, at which heat production (measured experimentally as oxygen consumption) is minimal and the infant's core temperature is within the normal range. The neutral thermal environment is a function of the size and postnatal age of an infant; larger, older infants require lower environmental temperatures than smaller, younger infants. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity. The optimal environmental temperature for minimal heat loss and oxygen consumption for an unclothed infant is one that maintains the infant's core temperature at 36.5-37.0°C (97.7-98.6°F). The smaller and more immature the infant, the higher is the environmental temperature required. Infant warmth can be maintained by heating the air to a desired temperature or by servo-control. Continuous monitoring of the infant's temperature is required to maintain optimal body temperature. **Kangaroo care** with direct skin-to-skin contact between infant and parent, with a hat and blanket covering the infant, is to be encouraged, without untoward effects on thermoregulation.

Maintaining a relative humidity of 40–60% aids in stabilizing body temperature by reducing heat loss at lower environmental temperatures; by preventing drying and irritation of the lining of respiratory passages, especially during the administration of oxygen and after or during endotracheal intubation; and by thinning viscid secretions and reducing insensible water loss. An infant should be weaned and then removed from the incubator or radiant warmer only when the gradual change to the atmosphere of the nursery does not result in a significant change in the infant's temperature, color, activity, or vital signs.

Oxygen Administration

Administering oxygen to reduce the risk of injury from hypoxia and circulatory insufficiency (risk of cerebral palsy, death) must be balanced against the risk of hyperoxia to the eyes (**retinopathy of prematurity, ROP**) and oxygen injury to the lungs (**bronchopulmonary dysplasia, BPD**). For ELBW infants at birth, guidelines should be followed to determine need for oxygen during resuscitation to maintain goal O_2 saturation limits (see Chapter 121).

After the initial resuscitation period, ideal target O_2 saturation limits for ELBW infants should be within the range of 90–95% for most infants.

Nutrition for the High-Risk Infant

Extreme prematurity must be considered a nutritional emergency. In the absence of early parenteral and enteral nutritional support, deficits in protein and energy will quickly accrue, placing the infant at risk for poor growth and neurodevelopmental outcomes. The goals of early nutritional support for extremely premature infants include approximating the rate and composition of growth for a normal fetus at the same postmenstrual age. Achieving this goal requires an understanding of the intrauterine growth rate to be targeted as well as the unique nutrient requirements of premature infants. Strategies to prevent growth faltering include a combined approach of early parenteral and enteral nutrition, fortification of human milk, and the use of standardized feeding guidelines. In addition, careful monitoring of not only weight gain but also length and head circumference using appropriate intrauterine growth curves, as well as consultation with an experienced neonatal dietitian, is important to achieve optimal growth outcomes.

Early Parenteral Nutrition

In the absence of intravenous amino acids, extremely premature infants lose 1-2% of body protein stores per day. IV amino acids and dextrose should be started immediately after birth. Many units use a *starter* or *stock* solution of amino acids and dextrose to accomplish this goal in infants weighing <1,500 g. A minimum of 2 g/kg of amino acids should be given in the 1st 24 hr after birth, with the goal of supplying at least 3.5 g/kg within 24-48 hr after birth. To meet total energy requirements, IV lipids will also be needed.

Benefits of Human Milk

Maternal milk is the preferred source of enteral nutrition for premature infants and is associated with decreased in-hospital morbidity, including lower rates of **necrotizing enterocolitis (NEC)** , late-onset sepsis, BPD, and severe ROP. Maternal milk feeding is also associated with superior neurodevelopmental outcomes at 18 and 30 mo corrected age compared to infants fed premature formula. Donor human milk is increasingly being used when maternal milk is not available, but is typically lower in protein and energy content than preterm maternal milk and may result in suboptimal growth unless adequately fortified. Although donor human milk has been associated with a reduction in NEC, the impact of donor human milk on neurodevelopmental outcomes remains unclear.

Enteral Nutrition

Early enteral feedings are recommended in ELBW and VLBW infants, typically beginning between 6 and 48 hr with some period of trophic/minimal enteral feeding volume. Feedings are typically advanced slowly (15-30 mL/kg/day) with a target goal of delivering approximately 110-135 kcal/kg/day and 3.5-4.5 g protein/kg/day. To accomplish these goals, human milk must be fortified, or a premature formula can be given.

Standardized Feeding Guidelines

Standardized feeding guidelines should be developed incorporating evidence-based strategies for the provision of parenteral and enteral nutrition in ELBW and VLBW infants, including a plan to manage feeding intolerance. Regardless of the specific protocol, having a feeding guideline leads to improved outcomes (e.g., time to regain birthweight, time to reach full enteral nutrition), decreased rates of late-onset sepsis and NEC, improved growth at 36 wk postmenstrual age, and reduced length of hospital stay.

Transitioning to Discharge Nutrition

The earlier an infant is born before expected, the greater the likelihood that not all nutritional deficits will be resolved before hospital discharge. Regardless of weight gain during the initial hospital stay, there is strong evidence for improved bone mineralization with the use of higher concentrations of calcium and phosphorus after discharge. Fortified human milk or preterm formula with higher protein, minerals, and trace elements is often recommended after discharge. An individualized approach to postdischarge nutrition should be developed to transition from the NICU.

Prevention of Infection

Extremely preterm infants have an increased susceptibility to infection, and thus meticulous attention to infection control is required. Prevention strategies include strict compliance with handwashing and universal precautions, minimizing the risk of catheter contamination and duration, meticulous skin care, encouraging early appropriate advancement of enteral feeding, education and feedback to staff, and surveillance of nosocomial infection rates in the nursery. Although no one with an active infection should be permitted in the nursery, the risks of infection must be balanced against the disadvantages of limiting the infant's contact with the family. Early and frequent participation by parents in the nursery care of their infant does not increase the risk of infection when preventive precautions are maintained.

Preventing transmission of infection from infant to infant is difficult because often neither term nor premature newborn infants have clear clinical evidence of an infection early in its course. When epidemics occur within a nursery, cohort nursing and isolation rooms should be used. **Hand hygiene** is of upmost importance. Because premature infants have immature immune function, some will develop nosocomial infection even when all precautions are followed.

Routine **immunizations** should be given on the regular schedule based on chronological age at standard doses.

Immaturity of Drug Metabolism

Great care must be taken when prescribing and dosing medications for premature infants (Table 117.4). Renal clearance of almost all substances excreted in the urine is diminished in newborn infants, and to even a greater extent in premature infants. The glomerular filtration rate rises with increasing gestational age; therefore, drug dosing recommendations vary with age. For drugs primarily excreted by the kidneys, longer intervals between dosages are often needed with increasing degree of prematurity. Drugs that are detoxified in the liver or require chemical conjugation before renal excretion should also be given with caution and in doses smaller than usual.

Table 117.4

Potential Adverse Reactions to Drugs Administered to Premature Infants

DRUG	REACTION(S)
Oxygen	Retinopathy of prematurity, bronchopulmonary dysplasia
Sulfisoxazole	Kernicterus
Chloramphenicol	Gray baby syndrome—shock, bone marrow suppression
Vitamin K analogs	Jaundice
Novobiocin	Jaundice
Hexachlorophene	Encephalopathy
Benzyl alcohol	Acidosis, collapse, intraventricular bleeding
Intravenous vitamin E	Ascites, shock
Phenolic detergents	Jaundice
$NaHCO_3$	Intraventricular hemorrhage
Amphotericin	Anuric renal failure, hypokalemia, hypomagnesemia
Reserpine	Nasal stuffiness
Indomethacin	Oliguria, hyponatremia, intestinal perforation
Cisapride	Prolonged QTc interval
Tetracycline	Enamel hypoplasia
Tolazoline	Hypotension, gastrointestinal bleeding
Calcium salts	Subcutaneous necrosis
Aminoglycosides	Deafness, renal toxicity
Enteric gentamicin	Resistant bacteria
Prostaglandins	Seizures, diarrhea, apnea, hyperostosis, pyloric stenosis
Phenobarbital	Altered state, drowsiness
Morphine	Hypotension, urine retention, withdrawal
Pancuronium	Edema, hypovolemia, hypotension, tachycardia, vecuronium contractions, prolonged hypotonia
Iodine antiseptics	Hypothyroidism, goiter
Fentanyl	Seizures, chest wall rigidity, withdrawal
Dexamethasone	Gastrointestinal bleeding, hypertension, infection, hyperglycemia, cardiomyopathy, reduced growth
Furosemide	Deafness, hyponatremia, hypokalemia, hypochloremia, nephrocalcinosis, biliary stones

Heparin (*not* low-dose prophylactic use)	Bleeding, intraventricular hemorrhage, thrombocytopenia
Erythromycin	Pyloric stenosis

Many drugs apparently safe for adults on the basis of toxicity studies may be harmful to newborns, especially premature infants. Oxygen and a number of drugs have proved toxic to premature infants in amounts not harmful to term infants. Thus, administering any drug, particularly in high doses, that has not undergone pharmacologic testing in premature infants should be undertaken carefully after risks have been weighed against benefits.

Morbidity and Mortality

Rates of neonatal morbidity and mortality are high in extremely preterm infants, and risks increase with decreasing gestational age and lower birthweight (Table 117.5). Data on extremely preterm infants born between 2003 and 2007 found that 42% of VLBW infants developed BPD, 12% developed ROP requiring treatment, 11% NEC, 36% late-onset sepsis, 16% grade III or IV **intraventricular hemorrhage (IVH)** , and 3% **periventricular leukomalacia (PVL)** . Morality increased with lower gestational age, with a 94% mortality in infants born at 22 wk and 8% mortality at 28 wk. As a whole, the group of extremely preterm infants had a 28% mortality rate, with 37% surviving without a significant neonatal morbidity.

Table 117.5

Neonatal Morbidities Associated With Prematurity

RESPIRATORY
Respiratory distress syndrome (hyaline membrane disease)
Bronchopulmonary dysplasia*
Pneumothorax, pneumomediastinum; interstitial emphysema
Congenital pneumonia
Apnea
CARDIOVASCULAR
Patent ductus arteriosus
Hypotension
Bradycardia (with apnea)
HEMATOLOGIC
Anemia (early or late onset)
GASTROINTESTINAL
Poor gastrointestinal function—poor motility
Necrotizing enterocolitis*

Hyperbilirubinemia—direct and indirect
Spontaneous gastrointestinal isolated perforation

METABOLIC-ENDOCRINE

Hypocalcemia
Hypoglycemia
Hyperglycemia
Metabolic acidosis
Hypothermia
Euthyroid but low thyroxine status
Osteopenia

CENTRAL NERVOUS SYSTEM

Intraventricular hemorrhage*
Periventricular leukomalacia*
Seizures
Retinopathy of prematurity*
Deafness
Hypotonia

RENAL

Hyponatremia
Hypernatremia
Hyperkalemia
Renal tubular acidosis
Renal glycosuria
Edema

OTHER

Infections* (congenital, perinatal, nosocomial: bacterial, viral, fungal, protozoal)

* Major neonatal morbidities.

Another study found that morbidity and mortality among VLBW infants decreased between 2000 and 2009. This study was limited to live-born infants with birthweight of 500-1500 g. For infants born in 2009, this study found a 12.4% mortality rate; 28% of infants developed BPD, 7% severe ROP, 5% NEC, 15% late-onset sepsis, 6% grade III or IV IVH, and 3% PVL; 51% survived without significant neonatal morbidity.

Outcomes may be slightly improving with time; survival among infants born 22-24 wk gestation increased from 30% in 2000–2003 to 36% in 2008–2011. The percentage surviving without neurodevelopmental impairment increased from 16% to 20% over this same period. However, extreme prematurity is still associated with significant risk of both mortality and major neonatal morbidities. For infants who survive to discharge, prematurity, as well as neonatal morbidities, put them at increased risk for developmental delays and impairment as they age (see Chapter 117.5).

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117.3

Moderate and Late Preterm Infants

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Keywords

late preterm
moderate preterm

WHO defines **moderate to late preterm** birth as infants born between 32 and $36\frac{6}{7}$ wk postmenstrual age (PMA). The American College of Obstetricians and Gynecologists (ACOG) further defines **late preterm** infants as those born between 34 and $36\frac{6}{7}$ wk PMA. Therefore, most define **moderate preterm** infants as those born between 32 and $33\frac{6}{7}$ wk PMA.

Moderate Preterm Infant

Moderate preterm infants are still at risk for most postnatal morbidities, although to a lesser extent than very preterm infants are at risk. These morbidities include but are not limited to poor feeding, weight loss, respiratory distress syndrome, risk of NEC, and difficulty with thermoregulation. Moderate preterm infants with birthweight >1,500 g and a fairly unremarkable NICU course are thought to be at fairly minimal risk for IVH and do not routinely need a head ultrasound. Little research has examined moderate preterm infants as an isolated group; more often these infants are grouped with very preterm infants when assessing complications and outcomes. A cohort of approximately 7,000 infants born between 29 and 33 wk gestational age were found in a recent study to have a mean hospital stay of 33.3 days. Compared with term counterparts, these infants had an increased incidence of many morbidities, including BPD, early- and late-onset sepsis, NEC, and PVL.

Late Preterm Infant

Late preterm infants account for approximately 8–9% of all births and almost three fourths of all preterm births in the United States. Historically, late preterm infants were referred to as *near-term infants*, and the approach to their care was similar to that of term infants. It has been increasingly recognized that late preterm infants have significantly increased morbidity, as well as mortality, compared with their term counterparts. There is an increased incidence of congenital anomalies in preterm infants, but even when these infants are excluded, late preterm infants continue to have significantly more morbidities. Immediately after birth, late preterm infants have an increased risk of requiring resuscitation, as well as increased incidence of hypoglycemia, respiratory distress, apnea, feeding difficulties, and jaundice. They also have a higher rehospitalization rate compared to their term peers.

Antenatal corticosteroids were traditionally only recommended for pregnant women between 24 and 34 wk gestation at risk of preterm delivery within the next 7 days, to reduce the incidence of death and respiratory distress syndrome. A randomized controlled trial of women at $34\text{–}36\frac{6}{7}$ wk gestation at risk of preterm labor found a decreased rate of respiratory complications in the newborns whose mothers received antenatal corticosteroids. An increased rate of neonatal hypoglycemia was seen in the steroid group as well, but no other significant differences were found. Based on these findings, ACOG recommends a single course of antenatal corticosteroids for pregnant women between 34 and $36\frac{6}{7}$ wk gestation at risk for preterm birth within 7 days, who have not received a previous course of antenatal corticosteroids.

Between 34 and $36\frac{6}{7}$ wk gestation is regarded as a critical period for growth and development. In the past, elective deliveries without medical indications often occurred as early as 35 wk. *ACOG recommends elective delivery without medical indications only after 39 wk gestation in well-dated pregnancies.* Some studies suggest a higher risk of lower school readiness at kindergarten and increased risk of academic difficulties in childhood when comparing late preterm infants with term peers.

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117.4

Term and Postterm Infants

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Keywords

intrauterine growth restriction
IUGR
large for gestational age
LGA
postterm infant
SGA
small for gestational age

ACOG further divides term infants into subgroups: **early term** ($37-38\frac{6}{7}$ wk), **full term** ($39-40\frac{6}{7}$ wk), and **late term** ($41-41\frac{6}{7}$ wk). Many risk factors for term infants put them at higher risk for complications, such as meconium aspiration syndrome (see Chapter 122.8), hemolytic disease of the newborn (Chapter 124.2), infant of a diabetic mother (Chapter 127.1), and neonatal abstinence syndrome (Chapter 126.1). Both small for gestational age (SGA) and large for gestational age (LGA) are associated with increased morbidities.

Small for Gestational Age and IUGR

There is an important distinction between the terms **small for gestational age (SGA)** and **intrauterine growth restriction (IUGR)** . SGA is based on physical evaluation of an infant at birth, usually by a pediatrician or neonatologist. If the infant's weight is <10th percentile, the infant is SGA. The diagnosis of SGA does not differentiate between normal biologic growth potential and a pathologic or growth-restricted state in utero. In contrast, IUGR is a prenatal diagnosis to describe a fetus who fails to reach in utero growth potential, often diagnosed by the obstetrician. Therefore, not all infants with IUGR are SGA, and similarly, not all infants who are SGA have IUGR.

Although it is important to understand the difference between SGA and IUGR, due to difficulty standardizing a classification of IUGR, many studies evaluate postnatal outcomes based on a diagnosis of either SGA or IUGR.

IUGR is associated with medical conditions that interfere with the circulation and efficiency of the placenta, with the development or growth of the fetus, or with the general health and nutrition of the mother (Table 117.6). Many factors are common to both prematurely born and LBW infants with IUGR. IUGR is associated with decreased insulin production or insulin-like growth factor (IGF) action at the receptor level. Infants with IGF-1 receptor defects, pancreatic hypoplasia, or transient neonatal diabetes have IUGR. Genetic mutations affecting the glucose-sensing mechanisms of the pancreatic islet cells result in decreased insulin release (loss of function of the glucose-sensing glucokinase gene) and give rise to IUGR.

Table 117.6

Factors Often Associated With Intrauterine Growth Restriction

FETAL
Chromosomal disorders
Chronic fetal infections (cytomegalic inclusion disease, congenital rubella, syphilis)
Congenital anomalies—syndrome complexes
Irradiation
Multiple gestation
Pancreatic hypoplasia
Insulin deficiency (production or action of insulin)
Insulin-like growth factor type I deficiency
PLACENTAL
Decreased placental weight, cellularity, or both
Decrease in surface area
Villous placentitis (bacterial, viral, parasitic)
Infarction
Tumor (chorioangioma, hydatidiform mole)
Placental separation
Twin transfusion syndrome
MATERNAL/PATERNAL
Toxemia
Hypertension or renal disease, or both
Hypoxemia (high altitude, cyanotic cardiac or pulmonary disease)
Malnutrition (micronutrient or macronutrient deficiencies)
Chronic illness
Sickle cell anemia
Drugs (narcotics, alcohol, cigarettes, cocaine, antimetabolites)

IGF2 mutation (paternal)

IUGR may be a normal fetal response to nutritional or oxygen deprivation; therefore the issue is not the IUGR but rather the ongoing risk of fetal malnutrition or hypoxia. IUGR is often classified as *reduced growth* that is *symmetric* (head circumference, length, and weight equally affected) or *asymmetric* (with relative sparing of head growth). **Symmetric IUGR** often has an earlier onset in the first trimester of pregnancy and is associated with diseases that seriously affect fetal cell number, such as conditions with chromosomal, genetic, malformation, teratogenic, infectious, or severe maternal hypertensive etiologies. It is important to assess gestational age carefully in infants suspected to have symmetric IUGR because incorrect overestimation of gestational age may lead to the diagnosis of symmetric IUGR. **Asymmetric IUGR** is often of late onset in the 2nd half of pregnancy, demonstrates preservation of Doppler waveform velocity to the carotid vessels, and is associated with poor maternal nutrition or with late onset or exacerbation of maternal vascular disease (preeclampsia, chronic hypertension).

Table 117.7 lists common problems of infants with IUGR. In addition, in both preterm and term infants, SGA has been shown to be associated with an increased risk of neurodevelopmental impairment.

Table 117.7

Problems of Infants Small for Gestational Age or With Intrauterine Growth Restriction*

PROBLEM	PATHOGENESIS
Intrauterine fetal demise	Hypoxia, acidosis, infection, lethal anomaly
Perinatal asphyxia	↓ Uteroplacental perfusion during labor ± chronic fetal hypoxia-acidosis; meconium aspiration syndrome
Hypoglycemia	↓ Tissue glycogen stores, ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, large brain
Polycythemia-hyperviscosity	Fetal hypoxia with ↑ erythropoietin production
Reduced oxygen consumption/hypothermia	Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores
Dysmorphology	Syndrome anomalads, chromosomal-genetic disorders, oligohydramnios-induced deformation, TORCH †

[*] Other problems include pulmonary hemorrhage and those common to the gestational age–related risks of prematurity if born at <37 wk.

[†] Toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex infection.

↓, Decreased; ↑, increased.

Large-for-Gestational-Age Infants

Infants with birthweight >90th percentile for gestational age are called **large for**

gestational age (LGA) . Neonatal mortality rates decrease with increasing birthweight until approximately 4,000 g, after which they increase. These oversized infants are usually born at term, but preterm infants with weights high for gestational age also have a significantly higher mortality than infants of the same size born at term; maternal diabetes and obesity are predisposing factors. Some infants are constitutionally large because of large parental size. LGA infants, regardless of their gestational age, have a higher incidence of birth injuries, such as cervical and brachial plexus injuries, phrenic nerve damage with paralysis of the diaphragm, fractured clavicles, cephalohematomas, subdural hematomas, and ecchymoses of the head and face. LGA infants are also at increased risk for hypoglycemia and polycythemia.

The incidence of congenital anomalies, particularly congenital heart disease, is also higher in LGA infants than in term infants of normal weight.

Postterm Infants

Postterm infants are those born after 42 completed wk of gestation, as calculated from the mother's LMP. Historically, approximately 12% of pregnancies resulted in delivery after 42 wk. However, with current evidence suggesting that both morbidity and mortality increase significantly after 42 wk gestation, obstetric interventions to induce labor often occur before 42 wk, resulting in a decreasing rate of postterm births. The cause of postterm birth or postmaturity is unknown. Postterm infants often have normal length and head circumference but may have decreased weight if there is placental insufficiency. Infants born postterm in association with presumed placental insufficiency may have various physical signs. Desquamation, long nails, abundant hair, pale skin, alert faces, and loose skin, especially around the thighs and buttocks, give them the appearance of having recently lost weight; meconium-stained nails, skin, vernix, umbilical cord, and placental membranes may also be noted. Common complications of postmaturity include perinatal depression, meconium aspiration syndrome, persistent pulmonary hypertension, hypoglycemia, hypocalcemia, and polycythemia.

Infants born at ≥42 wk gestational age experience approximately 3 times the mortality of infants born at term. Mortality has been greatly reduced through improved obstetric management. Data suggest that elective delivery during the 39th wk of gestation for both nulliparous and multiparous women is associated with decreased maternal and neonatal complications compared with those who were expectantly managed.

Careful obstetric monitoring, including nonstress testing (NST), biophysical profile (BPP), or Doppler velocimetry, usually provides a rational basis for choosing 1 of 3 courses: nonintervention, induction of labor, or cesarean delivery. Induction of labor or cesarean birth may be indicated in older primigravidas >2-wk beyond term, particularly if evidence of fetal distress is present. Medical problems in the newborn are treated if they arise.

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117.5

Follow-Up of High-Risk Infants After Discharge

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Keywords

corrected age
cerebral palsy
developmental delays

early intervention
Individuals with Disabilities Act
neonatal follow-up program

Discharge From the Hospital

Numerous criteria need to be met before a high-risk infant is ready for discharge from the hospital (Table 117.8). Before discharge, infants should be taking most or all nutrition by nipple, either bottle or breast. Some medically fragile infants may be discharged home while receiving gavage feedings after the parents have received appropriate training and education. Growth should be occurring at steady increments, with a goal weight gain of approximately 30 g/day. Temperature should be stable and normal in an open crib. Infants should have had no recent episodes of apnea or bradycardia requiring intervention for at least 5-7 days prior to discharge. Stable infants recovering from BPD may be discharged on a regimen of home oxygen given by nasal cannula as long as careful follow-up is arranged with home pulse oximetry monitoring and outpatient visits. All infants with birthweight <1,500 g or gestational age <30 wk at birth should undergo an eye examination to screen for ROP. If born preterm, hemoglobin or hematocrit should be determined to evaluate for possible anemia of prematurity. Every infant should have a hearing test before discharge. Routine vaccinations should be given based on chronological age before discharge. In addition, palivizumab (Synagis) should be given to eligible infants during **respiratory syncytial virus (RSV)** season immediately before discharge for prophylaxis against RSV, with continued monthly doses arranged as an outpatient as appropriate.

Table 117.8

Readiness for Discharge of High-Risk Infants Criteria

- Resolution of acute life-threatening illnesses
- Ongoing follow-up for chronic but stable problems:
    - Bronchopulmonary dysplasia
    - Intraventricular hemorrhage
    - Necrotizing enterocolitis after surgery or recovery
    - Ventricular septal defect, other cardiac lesions
    - Anemia
    - Retinopathy of prematurity
    - Hearing problems

  - Apnea
  - Cholestasis
- Stable temperature regulation
- Gain of weight with enteral feedings:
  - Breastfeeding
  - Bottle feeding
  - Gastric tube feeding
- Free of significant apnea
- Appropriate immunizations and planning for respiratory syncytial virus prophylaxis if indicated
- Hearing screenings
- Ophthalmologic examination if <30 wk of gestation or <1,500 g at birth
- Parental knowledge, skill, and confidence documented in:
  - Administration of medications (diuretics, methylxanthines, aerosols, etc.)
  - Use of oxygen, apnea monitors, oximeters
- Nutritional support:
  - Timing
  - Volume
  - Mixing concentrated formulas
- Recognition of illness and deterioration
- Basic cardiopulmonary resuscitation
- Infant safety
- Scheduling of referrals:
  - Primary care provider
  - Neonatal follow-up clinic
  - Occupational therapy/physical therapy
- Imaging (head ultrasound)
- Assessment of and solution to social risks

Data from American Academy of Pediatrics, American College of Obstetricians: *Guidelines for perinatal care,* ed 7, Elk Grove Village, IL, 2013, American Academy of Pediatrics.

If all major medical problems have resolved and the home setting is adequate, premature infants may then be discharged when their weight approaches 1,800-2,000 g, they are >34-35 wk PMA, and all the above criteria are met. Parental education, close follow-up, and healthcare provider accessibility are all essential for early discharge protocols. Ideally, the primary caregivers for the infant have a chance to provide infant care in the hospital with nursing supervision and help before discharge home. All high-risk infants should follow-up with their primary care provider within a few days of discharge.

Postdischarge Follow-Up

Medical Follow-Up

Even after discharge from the hospital, high-risk infants need very close medical follow-up. They continued to be at increased risk for poor weight gain and failure to thrive. In the setting of viral illness, premature infants are at increased risk for significant respiratory distress. Infants who are sent home on oxygen need very close medical follow-up with frequent visits and assessments, often with pulmonology. Table 117.9 lists common sequelae of prematurity.

Table 117.9

Sequelae of Prematurity

IMMEDIATE	LATE
Hypoxia, ischemia	Intellectual disability, spastic diplegia, microcephaly, seizures, poor school performance
Intraventricular hemorrhage	Intellectual disability, spasticity, seizures, post hemorrhagic hydrocephalus
Sensorineural injury	Hearing and visual impairment, retinopathy of prematurity, strabismus, myopia
Respiratory failure	Bronchopulmonary dysplasia, pulmonary hypertension, bronchospasm, malnutrition, subglottic stenosis
Necrotizing enterocolitis	Short-bowel syndrome, malabsorption, malnutrition
Cholestatic liver disease	Cirrhosis, hepatic failure, malnutrition
Nutrient deficiency	Osteopenia, fractures, anemia, growth failure
Social stress	Child abuse or neglect, failure to thrive, divorce
Other sequelae	Sudden infant death syndrome, infections, inguinal hernia, cutaneous scars (chest tube, patent ductus arteriosus ligation, intravenous infiltration), gastroesophageal reflux, hypertension, craniosynostosis, cholelithiasis, nephrocalcinosis, cutaneous hemangiomas

Medically complex infants can go home with a multitude of subspecialty appointments to help manage existing morbidities secondary to prematurity. For example, cardiology for management of a patent ductus arteriosus or pulmonary hypertension, pulmonary for BPD, nephrology for hypertension, ophthalmology for ROP, neurosurgery for hydrocephalus, and neurology for history of seizures. The extensive follow-up requirements can be overwhelming and daunting for families. It is very important that these infants have a primary care provider who serves as their “medical home” to help coordinate and assimilate the care from all these providers for families.

Developmental Follow-Up

It is well known that premature infants are at greater risk for **developmental delays** than their term counterparts; the more preterm, the greater the risk of delay. In addition, certain postnatal morbidities (severe BPD, grade III or IV intraventricular hemorrhage, severe ROP) are associated with significantly increased risk of developmental delays. It is very important that preterm infants are followed and assessed for developmental delay, so that if delays are detected, interventions can be instituted early.

It is recommended that developmental follow-up be available for infants born <32 wk PMA, or at a minimum <28 wk PMA and/or <1 kg birthweight. Developmental follow-up in the United States is most often provided in a **neonatal follow-up program** for the 1st 2-3 yr of life, and in some cases, until school age. Assessments focus on 5 main developmental domains: cognitive development, language development, fine and gross motor skills, social development, and emotional development. Although many assessments exist, the most widely used assessment in the United States is the *Bayley Scales of Infant and Toddler Development, Third Edition.*

It is important to note that for at least the 1st 2 yr of life, a child's **corrected age** should be used in determining if a delay exists. Corrected age is calculated by subtracting the weeks born premature from a child's chronological age. In doing so, a corrected age accounts for a child's prematurity. Some debate surrounds whether corrected age should continue to be used after age 2 yr.

If it is determined that a delay exists, a child should be referred for appropriate therapy to help minimize the delay as the child ages. Federal law under the Individuals with Disabilities Act requires states to provide *early intervention* services to children <3 yr old with developmental delay. States vary greatly in how delay is defined and what services are offered. Early intervention is associated with improved cognitive outcomes in infancy and preschool age, but not lasting into school age. Motor outcomes are improved in infancy for children who receive early intervention, but this has not been shown to be a lasting effect into preschool and school age.

Premature infants, especially those with a history of grade III or IV intraventricular hemorrhage or PVL seen on head imaging, are also at increased risk of motor impairments. **Cerebral palsy** is *nonprogressive* but *permanent* disorder of movement and posture caused by disturbance to the developing immature brain. Historically, cerebral palsy had not been diagnosed until 18-24 mo of age, but current tests such as the **General Movements Assessment** (GMA) and **Hammersmith Infant Neurological Examination** (HINE) are helping to identify children at high risk for cerebral palsy within the 1st few mo to yr of life. This enables these children to access early intervention services and therapy at an earlier age, as well as undergo more frequent surveillance as needed.

Children with a history of prematurity who do not show significant developmental delays in the 1st few yr of life are still at risk of later developing learning disabilities, attention problems, and decreased school achievement. Continued screening by their primary care provider may be needed as these children age.

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CHAPTER 118

Transport of the Critically Ill Newborn

Jennifer M. Brady, Brenda B. Poindexter

Regionalized Care of Newborns

The concept of **regionalized care** for neonates was first introduced in the 1976 March of Dimes Report *Toward Improving the Outcome of Pregnancy.* This report and future revisions stress the importance of providing regionalized care for infants in facilities with adequate personnel and equipment for an infant's severity of illness. Ideally, mothers deliver infants at a facility with the appropriate level of expertise and resources to care for the degree of prematurity and illness of the infant. Many studies have shown that very-low-birthweight (VLBW) infants, or infants <1,500 g at birth, have decreased morbidity and mortality when delivered at an appropriate level of care center (**Level III** hospitals). In a meta-analysis, neonatal or predischarge death occurred in 38% of VLBW infants receiving care at a non–Level III hospital and 23% of those receiving care at a Level III hospital. A main objective of *Healthy People 2020* addresses this issue, with a goal of increasing the proportion of VLBW infants born at Level III hospitals or subspecialty perinatal centers to 83.7%. Where this is not possible, the infant should be transported to an appropriate level of care hospital after birth.

Levels of Neonatal Care

Although a formal national definition of levels of neonatal care does not exist, the American Academy of Pediatrics (AAP) and March of Dimes have standardized definitions for levels I, II, III, and IV. One must understand the levels of care available before being able to arrange transport to an appropriate facility.

A **Level I** facility must be able to provide *basic neonatal care* . Appropriate equipment and staff must be available to perform neonatal resuscitation and care for healthy term and late preterm infants. In addition, Level I facilities must have the capacity to work to stabilize ill or preterm infants before transport to a higher level of care. A Level I nursery is the minimum requirement for a hospital providing inpatient maternity care. Providers at Level I facilities usually include pediatricians, family physicians, and nurse practitioners.

In addition to the care provided at a Level I facility, **Level II** nurseries must also be capable of providing care to moderately ill term infants with problems expected to resolve quickly. Level II centers also care for infants born ≥32 wk gestational age and >1,500 g at birth, and therefore must be comfortable with treating conditions common in this population, such as difficulty with oral feeds, apnea of prematurity, respiratory distress requiring continuous positive airway pressure (CPAP), and temperature regulation. These centers must also be capable of stabilizing infants born <32 wk gestation and <1,500 g until transfer to a higher-level facility is feasible, including the ability to intubate and provide mechanical ventilation for a brief duration if necessary. In addition to providers in Level I facilities, Level II facilities also typically have pediatric hospitalists, neonatologists, and neonatal nurse practitioners.

Level III neonatal intensive care units (NICUs) are equipped to care for the extremely preterm and critically ill neonates in addition to those infants cared for at Level I and II units. Level III units must have continuously available personnel and equipment to treat conditions commonly seen in this population, such as respiratory distress syndrome, pulmonary hypertension, and need for total parenteral nutrition. Resources should be available to obtain and interpret urgent imaging needed (e.g., CT, echocardiography). Pediatric subspecialists and pediatric surgeons should be available either on site or through prearranged consultative agreements.

In addition to the care available at Level III NICUs, **Level IV** NICUs are also capable of continuously available pediatric subspecialty consultation and pediatric surgical intervention. Many Level IV sites are located at regional children's hospitals and serve to provide outreach education.

Transport of the Critically Ill Neonate

In the event that a neonate requires a higher level of care after birth, transport must be arranged to a unit with the appropriate level of care available. Additional decisions that need to be made before transport include composition of the transport team, equipment required for transport, and mode of transportation.

The composition of the **transport team** varies depending on personnel available and the needs of the infant being transported. The transport team often comprises at least 2 individuals, whether 2 registered nurses (RNs), an RN and a respiratory therapist, or an RN and a paramedic. In addition, occasionally a neonatologist, neonatology fellow, or neonatal nurse practitioner will accompany the transport team for critically ill neonates. A designated **medical control physician** is available and in communication with the transport team throughout the transport as needed.

Transport staff must be competent in the treatment of common neonatal conditions and complications, as well as neonatal procedures. Many Level IV facilities have specialized teams available for neonatal transport. A Cochrane review found no evidence to support or to refute improved infant morbidity or mortality when transport occurred with a specialized team. Depending on the volume of neonatal transports and composition of the team, staff may have limited exposure to neonatal transports and procedures. **Simulation-based learning** is recommended by the AAP Section on Transport Medicine (SOTM) as a method to help achieve and retain competency in rarely experienced procedures, as well as improve team interactions for transport teams.

The **transport vehicle** should be equipped with appropriate medicines, intravenous (IV) fluids, oxygen tanks, catheters, chest tubes, endotracheal tubes (ETTs), laryngoscopes, bag-valve-mask, and infant warming device. It should be well illuminated and have ample room for emergency procedures and monitoring equipment. Additional needs for the specific transport should be anticipated (e.g., nitric oxide).

Common **modes of transport** include ground transport by ambulance and air transport by helicopter or fixed-wing aircraft. The stability of the infant, travel distance, traffic, and weather must all be taken into account when deciding the most appropriate mode of transportation.

Steps should be taken to **stabilize infants** as able in a timely fashion prior to transport. Securing an airway, providing oxygen, assisting with infant ventilation, providing antimicrobial therapy, maintaining the circulation, providing a warmed environment, checking a glucose level, and placing IV or arterial lines or chest tubes should be initiated, if indicated, before transport. Appropriate placement of lines and ETT should be evaluated before transport.

Risks of transport and transportation **consent** should be reviewed and obtained from parents before transport. Although transport teams attempt to anticipate and prepare for possible complications that could occur during transport, there is an inherent risk of complications, including death, in the event of a decompensation during transport resulting from the limited resources and personnel available. Parents should be made aware of these risks. If the infant's condition allows, efforts should be made to allow parents to see their baby briefly before transport.

Communication with the transport team as well as the receiving facility is paramount throughout the transport process. Available prenatal history, information on the infant's resuscitation and hospital course, lab data, and radiographic images should be sent with the transport team to the receiving hospital to aid in future care.

Reverse transport of an infant back to a lower level of care should be considered when infants are stabilized after transport and no longer require the higher level care available at the receiving hospital. Transport back to the birth hospital aids in appropriate utilization of resources, decreases costs of care, and may further promote parent–infant bonding because of proximity to the mother's home.

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CHAPTER 119

Clinical Manifestations of Diseases in the Newborn Period

Elizabeth Enlow, James M. Greenberg

A variety of conditions that affect the newborn originate in utero, during birth, or in the immediate postnatal period. These disorders can be caused by prematurity, congenital malformations, disruption of chromosome structure, or acquired diseases and injuries. Recognizing disease in newborn infants requires knowledge of relevant pathophysiology and evaluation of nonspecific clinical signs and symptoms.

Abnormal Movements

Neonatal seizures usually suggest a central nervous system (CNS) disorder, such as hypoxic-ischemic encephalopathy (HIE), intracranial hemorrhage, stroke, cerebral anomaly, subdural effusion, or meningitis (see Chapter 611.7). In the neonate, seizures can also be secondary to hypocalcemia, hypoglycemia, benign familial seizures, or rarely, pyridoxine dependence, hyponatremia, hypernatremia, inborn errors of metabolism, or drug withdrawal.

Seizures in premature infants are often subtle and associated with abnormal eye movement (fluttering, tonic horizontal deviation, sustained eye opening with ocular fixation) or facial movement (chewing, tongue thrusting); the motor component is often that of tonic extension of the limbs, neck, and trunk. Autonomic phenomena include hypertension and tachycardia. Term infants may have focal or multifocal, clonic or myoclonic movements, but they may also have subtler manifestations of seizure activity. **Apnea** may be the 1st manifestation of seizure activity, particularly in a premature infant. Seizures may adversely affect the subsequent neurodevelopmental outcome and may even predispose an infant to seizures outside the neonatal period. Electroencephalographic evidence of seizures can occur without clinical manifestations, particularly in preterm infants. If seizures are suspected, continuous amplitude integrated EEG (aEEG), or more accurately, long-term video EEG monitoring, will improve detection of both subtle and electrographic but clinically silent seizures. Many medications used to treat seizures have important side effects and limited efficacy, but current evidence suggests that the benefits of treating seizures outweigh the risks.

Seizures should be distinguished from the **jitteriness** , defined as *recurrent tremors,* that may be present in normal newborns, in infants of diabetic mothers, in those who experienced birth asphyxia or drug withdrawal, and in polycythemic neonates. An examiner may stop the tremors by holding the infant's extremity; jitteriness often depends on sensory stimuli and occurs when the infant is active, and it is not associated with abnormal eye movements. Tremors are often more rapid with a smaller amplitude than those of tonic-clonic seizures.

After severe birth asphyxia, infants may exhibit **motor automatisms** characterized by recurrent oral-buccal-lingual movements, rotary limb activities (rowing, pedaling, swimming), tonic posturing, or myoclonus. These motor activities are not usually accompanied by time-synchronized EEG discharges, may not signify cortical epileptic activity, respond poorly to anticonvulsant therapy, and are associated with a poor prognosis. Such automatisms may represent cortical depression that produces a brainstem release phenomenon or subcortical seizures.

Failure to move an extremity (**pseudoparalysis**) suggests fracture, dislocation, or nerve injury, often following a traumatic delivery. It is also seen in septic arthritis, osteomyelitis, and other infections that cause pain on movement of the affected part.

Altered Mental Status

Lethargy may be a manifestation of infection, asphyxia, hypoglycemia, hypercapnia, sedation from maternal analgesia or anesthesia, a cerebral defect, or, indeed, almost any severe disease, including an inborn error of metabolism. Shortly after birth, lethargy is most likely caused by maternal medications (opioids, magnesium, general anesthesia) or severe HIE. Lethargy appearing after the 2nd day should suggest infection or an inborn error of metabolism manifesting with hyperammonemia, acidosis, or hypoglycemia. Lethargy with emesis suggests increased intracranial pressure or an inborn error of metabolism.

Irritability may be a sign of discomfort accompanying intraabdominal conditions, meningeal irritation, drug withdrawal, infections, congenital glaucoma, trauma (birth, abuse), or any condition producing pain. It must be distinguished from normal crying behavior associated with hunger or benign environmental stimuli. **Hyperactivity** , especially in a premature infant, may be a sign of hypoxia, pneumothorax, emphysema, hypoglycemia, hypocalcemia, CNS damage, drug withdrawal, neonatal thyrotoxicosis, bronchospasm, esophageal reflux, or discomfort from a cold environment.

Failure to feed is an important sign of the sick newborn infants and should prompt a careful search for infection, a CNS (brain or spine) or peripheral nervous system disorder, inborn error of metabolism, intestinal obstruction, and other abnormal conditions.

Apnea

Periods of apnea, particularly in premature infants, can be attributed to many different underlying causes (see Chapter 122.2). When apnea recurs, or when the intervals are >20 sec or associated with cyanosis or bradycardia, an immediate diagnostic evaluation for the underlying cause is imperative.

Congenital Anomalies

Congenital anomalies are a major cause of stillbirths and in the United States and other developed countries are one of the main causes of neonatal mortality. In addition, congenital anomalies are a major cause of acute illness and long-term morbidity. Anomalies are discussed in general in Chapters 98 and 128 and specifically in the chapters on the various systems of the body. Early recognition of anomalies during fetal life is important to plan for delivery room management and subsequent neonatal care. Some malformations, including congenital heart disease, tracheoesophageal fistula, diaphragmatic hernia, choanal atresia, and intestinal obstruction, require immediate medical/surgical therapy for postnatal survival (Table 119.1). Parents are likely to feel anxious and guilty on learning of the existence of a congenital anomaly and require thoughtful, sensitive counseling.

Table 119.1

Common Life-Threatening Congenital Anomalies

ANOMALY	MANIFESTATIONS
Choanal atresia	Respiratory distress in delivery room; nasogastric tube cannot be passed through nares. Suspect CHARGE (coloboma of eye, heart anomaly, choanal atresia, retardation, genital and ear anomalies) syndrome.
Pierre Robin syndrome, Stickler syndrome	Micrognathia, cleft palate, airway obstruction
Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in chest, respiratory distress
Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation; nasogastric tube cannot be placed in stomach. Suspect VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia) syndrome.
Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention Suspect trisomy 21, cystic fibrosis, or cocaine use.
Gastroschisis, omphalocele	Polyhydramnios, intestinal obstruction
Renal agenesis, Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
Neural tube defects: anencephalus, meningomyelocele	Polyhydramnios, elevated α-fetoprotein, decreased fetal activity
Ductus-dependent congenital heart disease	Cyanosis, hypotension, murmur

Cyanosis

Central cyanosis generates a broad differential diagnosis encompassing respiratory, cardiac, CNS, infectious, hematologic, and metabolic etiologies (Table 119.2). Typically, 5 g/dL of deoxyhemoglobin must be present in the blood for central cyanosis to be clinically apparent. If respiratory insufficiency is caused by pulmonary conditions, respirations tend to be rapid with increased work of breathing. If caused by CNS depression, respirations tend to be irregular and weak and are often slow. Cyanosis unaccompanied by obvious signs of respiratory difficulty suggests cyanotic congenital heart disease or methemoglobinemia. Cyanosis resulting from congenital heart disease may, however, be difficult to distinguish clinically from cyanosis caused by respiratory disease. Episodes of cyanosis may also be the initial sign of hypoglycemia, bacteremia, meningitis, shock, or pulmonary hypertension. **Peripheral acrocyanosis** is common in neonates and thought to represent peripheral venous congestion associated with immature control of peripheral vascular tone. It does not usually warrant concern unless poor perfusion is suspected.

Table 119.2

Differential Diagnosis of Cyanosis in the Newborn

CENTRAL OR PERIPHERAL NERVOUS SYSTEM HYPOVENTILATION
Birth asphyxia
Intracranial hypertension, hemorrhage
Oversedation (direct or through maternal route)
Diaphragm palsy
Neuromuscular diseases
Seizures
RESPIRATORY DISEASE
Airway
Choanal atresia/stenosis
Pierre Robin syndrome
Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)
Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)
Lung
Respiratory distress syndrome
Transient tachypnea
Meconium aspiration
Pneumonia (sepsis)
Pneumothorax
Congenital diaphragmatic hernia
Pulmonary hypoplasia
CARDIAC RIGHT-TO-LEFT SHUNT
Abnormal Connections (Pulmonary Blood Flow Normal or Increased)
Transposition of great vessels
Total anomalous pulmonary venous return
Truncus arteriosus
Hypoplastic left heart syndrome
Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis
Obstructed Pulmonary Blood Flow (Pulmonary Blood Flow Decreased)
Pulmonic atresia with intact ventricular septum
Tetralogy of Fallot
Critical pulmonic stenosis with patent foramen ovale or atrial septal defect
Tricuspid atresia
Single ventricle with pulmonic stenosis
Ebstein malformation of tricuspid valve
Persistent fetal circulation (persistent pulmonary hypertension of newborn)
METHEMOGLOBINEMIA
Congenital (hemoglobin M, methemoglobin reductase deficiency)
Acquired (nitrates, nitrites)
Inadequate ambient O_2 or less O_2 delivered than expected (rare)
Disconnection of O_2 supply to nasal cannula, head hood
Connection of air, rather than O_2 , to a mechanical ventilator
SPURIOUS/ARTIFACTUAL
Oximeter artifact (poor contact between probe and skin, poor pulse searching)
Arterial blood gas artifact (contamination with venous blood)
OTHER
Hypoglycemia
Adrenogenital syndrome
Polycythemia
Blood loss

From Smith F: Cyanosis. In Kliegman RM: *Practical strategies in pediatric diagnosis and therapy,* Philadelphia, 1996, Saunders.

Gastrointestinal Disturbances

Vomiting during the 1st day of life can suggest obstruction in the upper digestive tract, metabolic disease, or increased intracranial pressure and must be distinguished from benign reflux**. Abdominal distention** with emesis**,** usually a sign of intestinal obstruction or an intraabdominal mass, may also be seen in infants with enteritis, necrotizing enterocolitis (NEC), isolated intestinal perforation, ileus accompanying sepsis, respiratory distress, ascites, or hypokalemia. Imaging studies are indicated when obstruction is suspected; proximal intestinal obstruction often occurs with a normal physical examination, whereas distal obstruction will likely be accompanied by distention. Vomiting may also be a nonspecific symptom of an illness such as septicemia with associated abdominal distention and ileus. It is a common manifestation of overfeeding, inexperienced feeding technique, or normal reflux. Rarely, vomiting is caused by pyloric stenosis, milk allergy, duodenal ulcer, stress ulcer, an inborn error of metabolism (hyperammonemia, metabolic acidosis), or adrenal insufficiency. Vomitus containing dark blood is usually a sign of a serious illness; but the benign possibility of swallowed maternal blood associated with the delivery process should also be considered. Tests for maternal vs fetal hemoglobin can help discriminate between these possibilities. Bilious emesis strongly suggests obstruction below the ampulla of Vater and warrants urgent contrast-enhanced radiography.

Diarrhea may be a symptom of overfeeding (especially high–caloric density formula), acute gastroenteritis, congenital diarrhea syndromes, or malabsorption, or it may be a nonspecific symptom of infection. Diarrhea should be differentiated from the normal loose, seedy, yellow stool seen typically in breastfed infants. Diarrhea may occur in conditions accompanied by compromised circulation of part of the intestinal or genital tract, such as mesenteric thrombosis, NEC, strangulated hernia, intussusception, and torsion of the ovary or testis.

Hypotension

Hypotension in term infants implies hypovolemic shock (hemorrhage, dehydration), a systemic inflammatory response syndrome (bacterial sepsis, intrauterine infection, NEC), cardiac dysfunction (left heart obstructive lesions: hypoplastic left heart syndrome, myocarditis, asphyxia-induced myocardial stunning, anomalous coronary artery), pneumothorax, pneumopericardium, pericardial effusion, or metabolic disorders (hypoglycemia, adrenal insufficiency).

Hypotension is a common problem in sick preterm infants and may also be caused by any of the problems noted in a term infant. Some extremely low gestational age infants do not respond to fluids or inotropic agents but may improve with administration of intravenous hydrocortisone (Fig. 119.1). Sudden onset of hypotension in a very-low-birthweight (VLBW) infant suggests pneumothorax, intraventricular hemorrhage, or subcapsular hepatic hematoma. Strategies used to support blood pressure include volume expansion (normal saline or <5% albumin), vasopressors (dopamine, dobutamine, epinephrine, norepinephrine, vasopressin), or corticosteroids (hydrocortisone) (see Chapter 121).

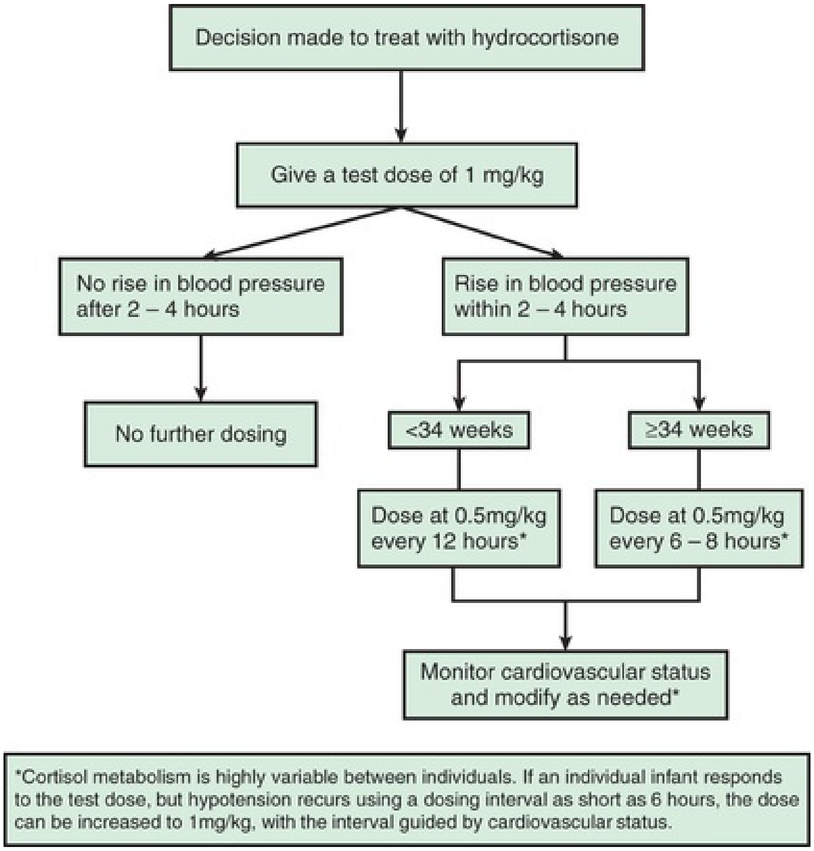
Decision made to treat with hydrocortisone
Give a test dose of 1 mg/kg
No rise in blood pressure after 2 – 4 hours
Rise in blood pressure within 2 – 4 hours
No further dosing
<34 weeks
≥34 weeks
Dose at 0.5mg/kg every 12 hours*
Dose at 0.5mg/kg every 6 – 8 hours*
Monitor cardiovascular status and modify as needed*

*Cortisol metabolism is highly variable between individuals. If an individual infant responds to the test dose, but hypotension recurs using a dosing interval as short as 6 hours, the dose can be increased to 1mg/kg, with the interval guided by cardiovascular status.

FIG. 119.1 **Suggested treatment algorithm for hydrocortisone dosing in the newborn. (From Watterberg KL: Hydrocortisone dosing for hypotension in newborn infants: less is more, *J Pediatr* 174:23–26, 2016, p 26.e1.)**

Jaundice

Jaundice during the 1st 24 hr of life warrants diagnostic evaluation and should be considered pathologic until proved otherwise. Septicemia and intrauterine or perinatal infections, such as syphilis, cytomegalovirus, and toxoplasmosis, as well as neonatal hemochromatosis, should also be considered, especially in infants with an increase in *direct* bilirubin value. Immediate evaluation includes obtaining total and direct bilirubin, and confirmation as abnormally elevated indicates albumin level, infant blood type and Coombs status, complete blood cell count (CBC), and reticulocyte count. In the case of Coombs-positive hemolysis, strong consideration should be made to giving intravenous immune globulin (IVIG) if there is no response to intensive phototherapy.

Jaundice beyond the 1st 24 hr may be *physiologic* or may be caused by a wide range of conditions, including septicemia, hemolytic anemia, galactosemia, hepatitis, congenital atresia of the bile ducts, inspissated bile syndrome after erythroblastosis fetalis, syphilis, herpes simplex other congenital infections, or other conditions (see Chapter 123.3).

Pain

Pain in neonates may be unrecognized and/or undertreated. The intensive care of neonates may involve several painful procedures, including blood sampling (heelstick, venous or arterial puncture), endotracheal intubation and suctioning, mechanical ventilation, and insertion of chest tubes and intravascular catheters. Pain in neonates results in obvious distress and acute physiologic stress responses, which may have developmental implications for pain in later life. Moreover, knowing that infants may experience pain contributes to parental stress.

Pain and discomfort are potentially avoidable problems during the treatment of sick infants. The most common causes of painful stimuli include circumcision pain and that associated with phlebotomy for metabolic screening tests. **Oral sucrose solutions** are well tolerated by most infants and have proven efficacy for procedural pain. For NICU infants, the most frequently used drugs are intermittent or continuous doses of opioids (morphine, fentanyl) and benzodiazepines (midazolam, lorazepam). Although the long-term effects of opioids and sedatives are not well established, the first concern should be the treatment and/or prevention of acute pain. Continuous opiate infusions should be used with caution. Some minor but painful procedures performed in well neonates can be managed with oral sucrose solutions (Table 119.3).

Table 119.3

Pain in the Neonate: General Considerations

- Pain in newborns is often unrecognized and/or undertreated.
- If a procedure is painful in adults, it should be considered painful in newborns.
- Healthcare institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.
- Pharmacologic agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Educational programs to increase the skills of healthcare professionals in the assessment and management of stress and pain in neonates should be provided.
- Further research is needed to develop and validate neonatal pain assessment tools that are useful in the clinical

setting; to determine optimal behavioral and pharmacologic interventions; and to study long-term effects of pain and pain management.

Data from American Academy of Pediatrics Committee on Fetus and Newborn, Committee on Drugs, Section on Anesthesiology, Section on Surgery; Canadian Paediatric Society, Fetus and Newborn Committee: Prevention and management of pain and stress in the neonate, *Pediatrics* 105:454–461, 2000; and from Anand KJS; International Evidence-Based Group for Neonatal Pain: Consensus statement for the prevention and management of pain in the newborn, *Arch Pediatr Adolesc Med* 155:173–180, 2001.

119.1

Hyperthermia

Elizabeth Enlow, James M. Greenberg

Serious infection (pneumonia, bacteremia, meningitis, and viral infections, particularly herpes simplex or enteroviruses) may cause **fever** and must be considered, although such infections often occur without provoking a febrile response in newborn infants (see Chapters 201 and 202). Providers should consider evaluation for bacterial infection in infants <28 days old with a rectal temperature ≥38°C (100.5°F), including blood culture, urine culture, and lumbar puncture (LP), although stepwise approaches to identify low-risk patients and limiting LP to a subset of higher-risk infants are gaining favor. Fever immediately after birth may be caused by radiant warmers, maternal fever, or maternal epidural analgesia. Fever may also be caused by elevated environmental temperatures because of weather, overheated nurseries, incubators, or radiant warmers, or excessive clothing. It has also been attributed to dehydration, although *dehydration fever* is a diagnosis of exclusion in newborn infants.

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119.2

Hypothermia and Cold Stress

Elizabeth Enlow, James M. Greenberg

Unexplained **hypothermia** may accompany infection or other serious disturbances of the circulation or CNS. A sudden servo-controlled increase in incubator ambient temperature to maintain body temperature is a sign of temperature instability and may be associated with sepsis or any of the conditions already mentioned.

Cold stress can lead to profound decompensation, including apnea, bradycardia, respiratory distress, hypoglycemia, and poor feeding. For this reason, it is paramount for the neonate to maintain normothermia in the delivery room and afterward, especially low-birthweight and premature infants. For VLBW infants, a combination of occlusive plastic wrap, radiant warmers, and thermal mattresses to maintain normothermia can be used to reduce cold stress.

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119.3

Edema

Elizabeth Enlow, James M. Greenberg

Generalized edema in a neonate can be caused by hydrops fetalis secondary to several underlying causes (see Chapter 124.2), excessive fluid administration, respiratory disease, sepsis, NEC, and hepatic, renal, or cardiac dysfunction. An infant with suspected hydrops in utero should be delivered at a specialty perinatal center with capacity for neonatal intubation, thoracentesis, paracentesis, and pericardiocentesis in the delivery room.

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119.4

Hypocalcemia

Elizabeth Enlow, James M. Greenberg

Hypocalcemia in a neonate can manifest as irritability, jitteriness, clonus, or seizures. Electrocardiography can show a prolonged QT interval. The cause may simply represent an exaggerated physiologic decrease in serum calcium levels within the 1st 24 hr of life or pathologic conditions such as genetic disorders (22q deletions), prematurity, growth restriction, perinatal hypoxia, hypomagnesemia, or maternal diabetes. Hypocalcemia is more common in term infants receiving formula than in those exclusively receiving breast milk. Most infants remain asymptomatic and can be managed conservatively with early nutrition and close monitoring, whereas symptomatic neonates should receive IV or oral calcium replacement.

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119.5

Hypermagnesemia

Elizabeth Enlow, James M. Greenberg

Hypermagnesemia is most often caused by maternal administration of magnesium in the perinatal period for treatment of conditions such as preeclampsia and preterm labor, and as prophylaxis to mitigate brain injury associated with preterm birth. Infants are usually present with signs at birth and improve over the next 24-48 hr. Symptoms include respiratory depression, hypotonia, lethargy, and feeding intolerance. No treatment is indicated other than supportive measures.

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CHAPTER 120

Nervous System Disorders

Stephanie L. Merhar, Cameron W. Thomas

Central nervous system (CNS) disorders are important causes of neonatal mortality and both short-term and long-term morbidity. The CNS can be injured as a result of asphyxia, hemorrhage, trauma, hypoglycemia, or direct cytotoxicity. The etiology of CNS injury is often multifactorial and includes perinatal complications, postnatal hemodynamic instability, and developmental abnormalities that may be genetic and/or environmental. Predisposing factors for brain injury include chronic and acute maternal illness resulting in uteroplacental dysfunction, intrauterine infection, macrosomia/dystocia, malpresentation, prematurity, and intrauterine growth restriction. Acute and often unavoidable emergencies during the delivery process may result in mechanical and hypoxic-ischemic brain injury.

120.1

The Cranium

Stephanie L. Merhar, Cameron W. Thomas

Erythema, abrasions, ecchymoses, and subcutaneous fat necrosis of facial or scalp soft tissues may be noted after a normal delivery or after forceps or vacuum-assisted deliveries. The location depends on the area of contact with the pelvic bones or application of the forceps. Traumatic hemorrhage may involve any layer of the scalp as well as intracranial contents (Fig. 120.1).

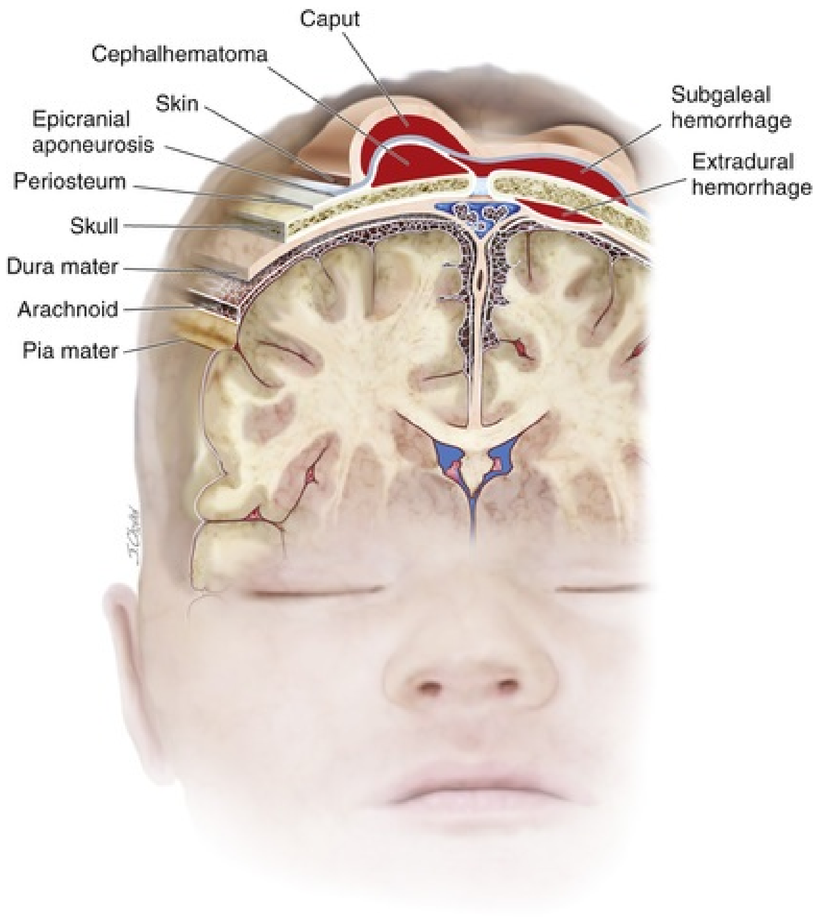
Caput
Cephalhematoma
Skin
Epicranial aponeurosis
Periosteum
Skull
Dura mater
Arachnoid
Pia mater
Subgaleal hemorrhage
Extradural hemorrhage

FIG. 120.1 **Sites of extracranial (and extradural) hemorrhages in the newborn. Schematic diagram of important tissue planes from skin to dura. (From Volpe JJ: Injuries of extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier, Fig 36-1.)**

Caput succedaneum is a diffuse, sometimes ecchymotic, edematous swelling of the soft tissues of the scalp involving the area presenting during vertex delivery. It may extend across the midline and across suture lines. The edema disappears within the 1st few days of life. Molding of the head and overriding of the parietal bones are frequently associated with caput succedaneum and become more evident after the caput has receded; they disappear during the 1st few weeks of life. Rarely, a hemorrhagic caput may result in shock and require blood transfusion. Analogous swelling, discoloration, and distortion of the face are seen in face presentations. No specific treatment is needed, but if extensive ecchymoses are present, hyperbilirubinemia may develop.

Cephalohematoma is a subperiosteal hemorrhage and thus always limited to the *surface* of one cranial bone (Fig. 120.2). Cephalohematomas occur in 1–2% of live births. No discoloration of the overlying scalp occurs, and swelling is not usually visible for several hours after birth because subperiosteal bleeding is a slow process. The lesion becomes a firm, tense mass with a palpable rim localized over one area of the skull. Most cephalohematomas are resorbed within 2 wk to 3 mo, depending on their size. They may begin to calcify by the end of the 2nd wk. A few remain for years as bony protuberances and are detectable on radiographs as widening of the diploic space; cystlike defects may persist for months or years. An underlying skull fracture, usually linear and not depressed, may be associated with 10–25% of cases. A sensation of central depression suggesting but not indicative of an underlying fracture or bony defect is usually encountered on palpation of the organized rim of a cephalohematoma. Cephalohematomas require no treatment, although phototherapy may be necessary to treat hyperbilirubinemia. Infection of the hematoma is a very rare complication.

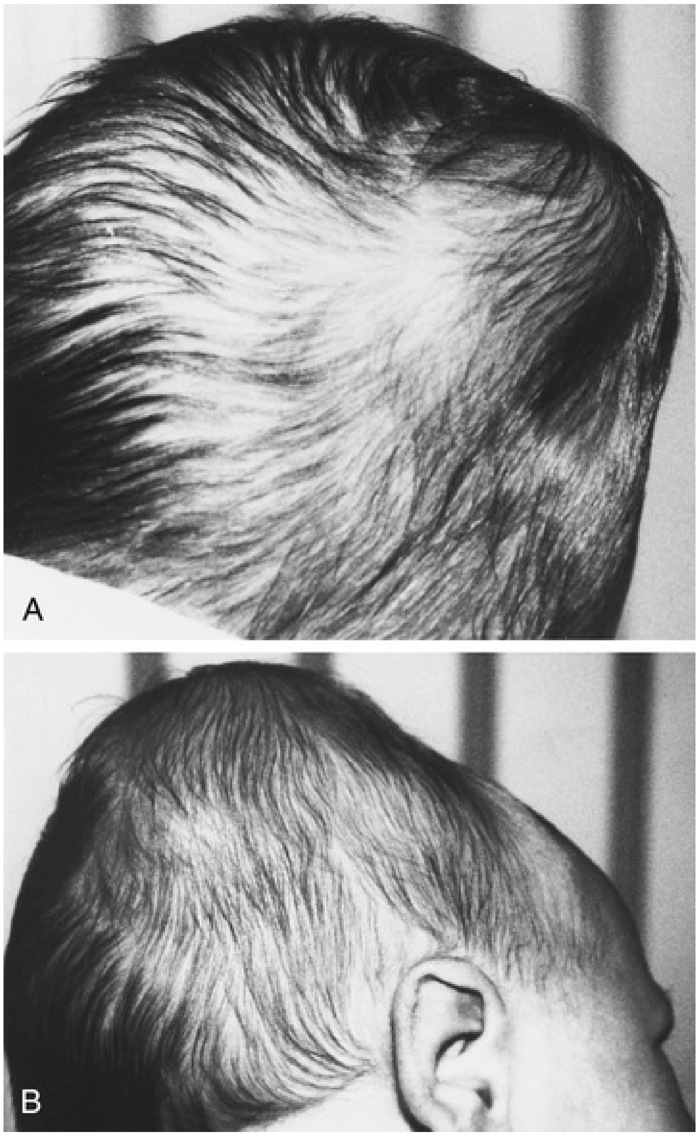

FIG. 120.2 Parietal cephalhematoma. Clinical appearance of 10 day old infant delivered with the aid of mid-forceps. A, Posterior view. B, Right lateral view. Note prominent swelling that extends medially to the sagittal suture, posteriorly to the lambdoid suture, and laterally to the squamosal suture. (From Volpe JJ: Injuries of extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier, Fig 36-3.)

A **subgaleal hemorrhage** is a collection of blood beneath the aponeurosis that covers the scalp and serves as the insertion for the occipitofrontalis muscle (see Fig. 120.1). Bleeding can be very extensive into this large potential space and may even dissect into subcutaneous tissues of the neck. There is often an association with vacuum-assisted delivery. The mechanism of injury is most likely secondary to rupture of emissary veins connecting the dural sinuses within the skull and the superficial veins of the scalp. Subgaleal hemorrhages are sometimes associated with skull fractures, suture diastasis, and fragmentation of the superior margin of the parietal bone. Extensive subgaleal bleeding is occasionally secondary to a hereditary coagulopathy (**hemophilia**). A subgaleal hemorrhage manifests as a fluctuant mass that straddles cranial sutures or fontanels that increases in size after birth. Some patients have a consumptive coagulopathy from massive blood loss. Patients should be monitored for hypotension, anemia, and hyperbilirubinemia. These lesions typically resolve over 2-3 wk.

Fractures of the skull may be caused by pressure from forceps or the maternal pelvis or by accidental falls after birth. *Linear fractures*, the most common, cause no symptoms and require no treatment. Linear fractures should be followed up to demonstrate healing and to detect the possible complication of a leptomeningeal cyst. *Depressed fractures* indent the calvaria similar to dents in a Ping-Pong ball. They are generally a complication of forceps delivery or fetal compression. Affected infants may be asymptomatic unless they have associated intracranial injury; it is advisable to elevate severe depressions to prevent cortical injury from sustained pressure. Although some may elevate spontaneously, some require treatment. Use of a breast pump or vacuum extractor may obviate the need for neurosurgical intervention. Suspected skull fractures should be evaluated with CT (3D reconstruction may be helpful) to confirm fracture and rule out associated intracranial injury.

Subconjunctival and **retinal hemorrhages** are frequent; petechiae of the skin of the head and neck are also common. All are probably secondary to a sudden increase in intrathoracic pressure during passage of the chest through the birth canal. Parents should be assured that these hemorrhages are temporary and the result of normal events of delivery. The lesions resolve rapidly within the 1st 2 wk of life.

120.2

Traumatic, Epidural, Subdural, and Subarachnoid Hemorrhage

Stephanie L. Merhar, Cameron W. Thomas

Traumatic epidural, subdural, or subarachnoid hemorrhage is especially likely when the fetal head is large in proportion to the size of the mother's pelvic outlet, with prolonged labor, in breech or precipitous deliveries, or as a result of mechanical assistance with delivery. Massive **subdural hemorrhage** , often associated with tears in the tentorium cerebelli or less frequently in the falx cerebri, is rare but is encountered more often in full-term than in premature infants. Patients with massive hemorrhage caused by tears of the tentorium or falx cerebri rapidly deteriorate and may die soon after birth. Most subdural and epidural hemorrhages resolve without intervention. Consultation with a neurosurgeon is recommended. Asymptomatic subdural hemorrhage may be noted within 48 hr of birth after vaginal or cesarean delivery. These are typically small hemorrhages, especially common in the posterior fossa, discovered incidentally in term infants imaged in the neonatal period and usually of no clinical significance. The diagnosis of large subdural hemorrhage may be delayed until the chronic subdural fluid volume expands and produces macrocephaly, frontal bossing, a bulging fontanel, anemia, and sometimes seizures. CT scan and MRI are useful imaging techniques to confirm these diagnoses. Symptomatic subdural hemorrhage in term infants can be treated by a neurosurgical evacuation of the subdural fluid collection by a needle placed through the lateral margin of the anterior fontanel. In addition to birth trauma, **child abuse** must be suspected in all infants with subdural effusion after the immediate neonatal period. Most asymptomatic subdural hemorrhages following labor should resolve by 4 wk of age.

Subarachnoid hemorrhage is often clinically silent in the neonate. Anastomoses between the penetrating leptomeningeal arteries or the bridging veins are the most likely source of the bleeding. Most affected infants have no clinical symptoms, but the subarachnoid hemorrhage may be detected because of an elevated number of red blood cells in a lumbar puncture sample. Some infants experience short, benign seizures, which tend to occur on the 2nd day of life. Rarely, an infant has a catastrophic hemorrhage and dies. There are usually no neurologic abnormalities during the acute episode or on follow-up. Significant neurologic findings should suggest an arteriovenous malformation, which can best be detected on CT or MRI.

120.3

Intracranial-Intraventricular Hemorrhage and Periventricular Leukomalacia

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Stephanie L. Merhar, Cameron W. Thomas

Etiology

Intracranial hemorrhage in preterm infants usually develops spontaneously. Less frequently, it may be caused by trauma or asphyxia, and rarely, it occurs from a primary hemorrhagic disturbance or congenital cerebrovascular anomaly. Intracranial hemorrhage often involves the ventricles (**intraventricular hemorrhage, IVH**) of premature infants delivered spontaneously without apparent trauma. The IVH in premature infants is usually not present at birth but may develop during the 1st week of life. Primary hemorrhagic disturbances and vascular malformations are rare and usually give rise to subarachnoid or intracerebral hemorrhage. In utero hemorrhage associated with maternal idiopathic or, more often, fetal alloimmune thrombocytopenia may appear as severe cerebral hemorrhage or as a porencephalic cyst after resolution of a fetal cortical hemorrhage. Intracranial bleeding may be associated with disseminated intravascular coagulation, isoimmune thrombocytopenia, and neonatal vitamin K deficiency, especially in infants born to mothers receiving phenobarbital or phenytoin.

Epidemiology

The overall incidence of IVH has decreased over the past decades as a result of improved perinatal care, increased use of antenatal corticosteroids, surfactant to treat respiratory distress syndrome (RDS), and possibly prophylactic indomethacin. It continues to be an important cause of morbidity in preterm infants, as approximately 30% of premature infants <1,500 g have IVH. The risk is inversely related to gestational age and birthweight; 7% of infants weighing 1,001-1,500 g have a severe IVH (grade III or IV), compared to 14% of infants weighing 751-1,000 g and 24% of infants ≤750 g. In 3% of infants <1,000 g, **periventricular leukomalacia (PVL)** develops.

Pathogenesis

The major neuropathologic lesions associated with very-low-birthweight (VLBW) infants are IVH and PVL. IVH in premature infants occurs in the gelatinous subependymal **germinal matrix** . This periventricular area is the site of origin for embryonal neurons and fetal glial cells, which migrate outwardly to the cortex. Immature blood vessels in this highly vascular region of the developing brain combined with poor tissue vascular support predispose premature infants to hemorrhage. The germinal matrix involutes as the infant approaches full-term gestation, and the tissue's vascular integrity improves; therefore IVH is much less common in the term infant. The cerebellum also contains a germinal matrix and is susceptible to hemorrhagic injury. **Periventricular hemorrhagic infarction** , previously known as **grade IV intraventricular hemorrhage** , often develops after a large IVH because of venous congestion. Predisposing factors for IVH include prematurity, RDS, hypoxia-ischemia, exaggerated fluctuations in cerebral blood flow (hypotensive injury, hypervolemia, hypertension), reperfusion injury of damaged vessels, reduced vascular integrity, increased venous pressure (pneumothorax, venous thrombus), or thrombocytopenia.

Understanding of the pathogenesis of PVL is evolving, and it appears to involve both intrauterine and postnatal events. A complex interaction exists between the development of the cerebral vasculature and the regulation of cerebral blood flow (both of which depend on gestational age), disturbances in the oligodendrocyte precursors required for myelination, and maternal/fetal infection and inflammation. Postnatal hypoxia or hypotension, necrotizing enterocolitis (NEC) with its resultant inflammation, and severe neonatal infection may all result in white matter injury. PVL is characterized by focal necrotic lesions in the periventricular white matter and/or more diffuse white matter damage. Destructive focal necrotic lesions resulting from massive cell death are less common in the modern era. Instead, diffuse injury leading to abnormal maturation of neurons and glia is more frequently seen. The risk for PVL increases in infants with severe IVH or ventriculomegaly. Infants with PVL are at higher risk of cerebral palsy because of injury to the corticospinal tracts that descend through the periventricular white matter.

Clinical Manifestations

Most infants with **IVH** , including some with moderate to severe hemorrhages, have no initial clinical signs (**silent** IVH). Some premature infants in whom severe IVH develops may have acute deterioration on the 2nd or 3rd day of life (**catastrophic** presentation). Hypotension, apnea, pallor, stupor or coma, seizures, decreased muscle tone, metabolic acidosis, shock, and decreased hematocrit (or failure of hematocrit to increase after transfusion) may be the first clinical indications. A saltatory progression may evolve over several hours to days and manifest as intermittent or progressive alterations of levels of consciousness, abnormalities of tone and movement, respiratory signs, and eventually other features of the acute catastrophic IVH. Rarely, IVH may manifest at birth or even prenatally; 50% of cases are diagnosed within the 1st day of life, and up to 75% within the 1st 3 days. A small percentage of infants have late hemorrhage, between days 14 and 30. IVH as a primary event is rare after the 1st mo of life.

PVL is usually clinically asymptomatic until the neurologic sequelae of white matter damage become apparent in later infancy as spasticity and/or motor deficits. PVL may be present at birth but usually occurs later, when the echodense phase is seen on ultrasound (3-10 days of life), followed by the typical echolucent/cystic phase (14-20 days).

The severity of hemorrhage is defined by the location and degree of bleeding and ventricular dilation on cranial imaging. In a **grade I** hemorrhage, bleeding is isolated to the subependymal area. In **grade II** hemorrhage, there is bleeding within the ventricle without evidence of ventricular dilation. **Grade III** hemorrhage is IVH with ventricular dilation. In **grade IV** hemorrhage, there is intraventricular and parenchymal hemorrhage (Fig. 120.3). Another grading system describes 3 levels of increasing severity of IVH detected on ultrasound: In **grade I,** bleeding is confined to the germinal matrix–subependymal region or to <10% of the ventricle (approximately 35% of IVH cases); **grade II** is defined as intraventricular bleeding with 10–50% filling of the ventricle (40% of IVH cases); and in **grade III** , >50% of the ventricle is involved, with dilated ventricles (Fig. 120.3). **Ventriculomegaly** is defined as mild (0.5-1 cm dilation), moderate (1.0-1.5 cm dilation), or severe (>1.5 cm dilation).

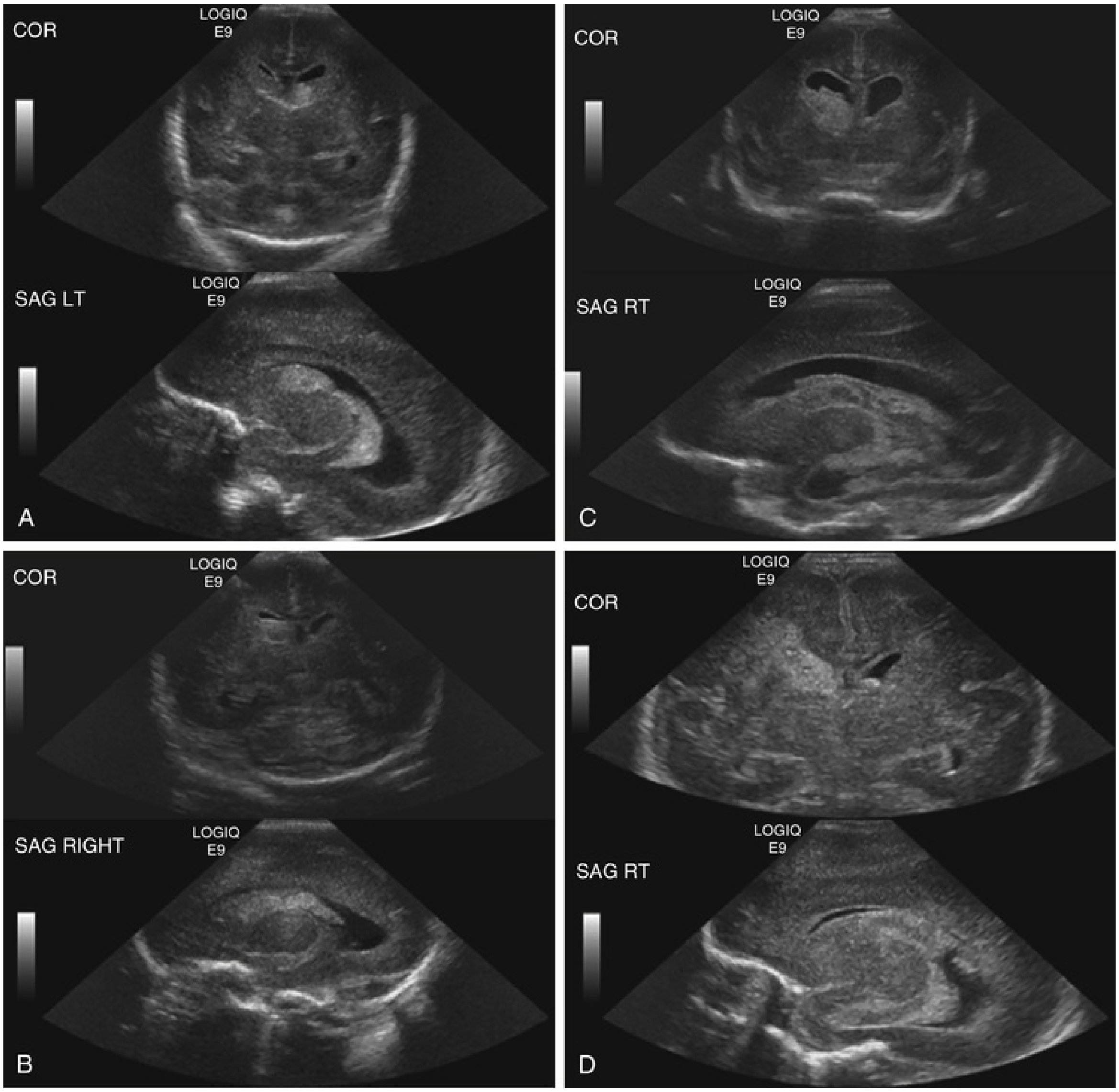
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FIG. 120.3 **Grading of the severity of germinal matrix–intraventricular hemorrhage (IVH): coronal (cor) and parasagittal (sag) ultrasound scans. A, Germinal matrix hemorrhage, grade I. B, IVH (filling <50% of ventricular area), grade II. C, IVH with ventricular dilatation, grade III. D, Large IVH with associated parenchymal echogenicity (hemorrhagic infarct), grade IV. (From Inder TE, Perlman JM, Volpe JJ: Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier, Fig 24-2.)**

Diagnosis

Intracranial hemorrhage is suspected on the basis of history, clinical manifestations, and knowledge of the birthweight-specific risks for **IVH** . Associated clinical signs of IVH are typically nonspecific or absent; therefore, it is recommended that premature infants <32 wk of gestation be evaluated with routine real-time cranial ultrasonography (US) through the anterior fontanel to screen for IVH. Infants <1,000 g are at highest risk and should undergo cranial US within the 1st 3-7 days of age, when approximately 75% of lesions will be detectable. US is the preferred imaging technique for screening because it is noninvasive, portable, reproducible, and sensitive and specific for detection of IVH. All at-risk infants should undergo follow-up US at 36-40 wk postmenstrual age to evaluate adequately for PVL, as cystic changes related to perinatal injury may not be visible for up to 1 mo. In one study, 29% of low-birthweight (LBW) infants who later experienced cerebral palsy did not have radiographic evidence of PVL until after 28 days of age. US also detects the precystic and cystic symmetric lesions of PVL and the asymmetric intraparenchymal echogenic lesions of cortical hemorrhagic infarction (Fig. 120.4). Cranial US may be useful in monitoring delayed development of cortical atrophy, porencephaly, and the severity, progression, or regression of posthemorrhagic hydrocephalus.

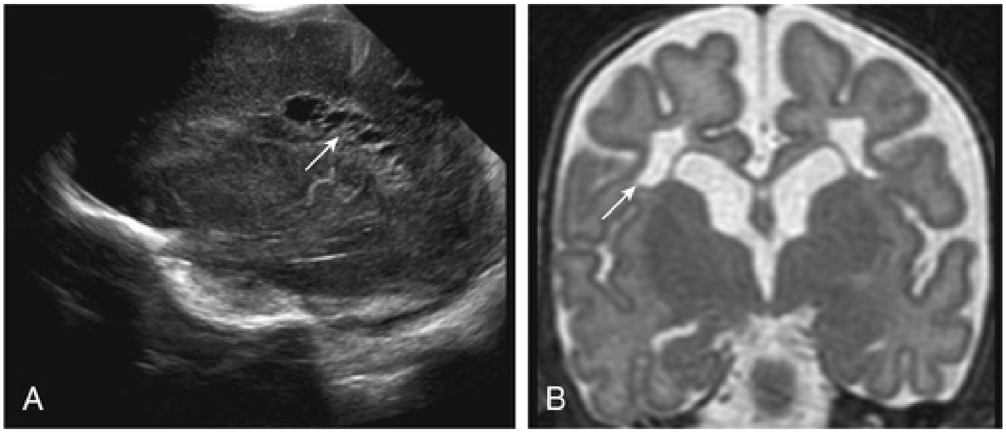

FIG. 120.4 **Severe cystic periventricular leukomalacia. A, Parasagittal ultrasound image showing numerous large cysts superolateral to the lateral ventricle *(arrow)* . B, Coronal T_2 -weighted MR image in which cysts are present superolateral to the lateral ventricles *(arrow)* . (From Neil JJ, Volpe JJ: Encephalopathy of prematurity: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier, Fig 16-1.)**

Approximately 3–5% of VLBW infants develop **posthemorrhagic hydrocephalus (PHH)** . If the initial US findings are abnormal, additional interval US studies are indicated to monitor for the development of hydrocephalus and potential need for ventriculoperitoneal shunt insertion.

IVH represents only 1 facet of brain injury in the term or preterm infant. MRI is a more sensitive tool for evaluation of white matter abnormalities and cerebellar injury and may be more predictive of adverse long-term outcome.

Prognosis

The degree of **IVH** and presence of **PVL** are strongly linked to survival and neurodevelopmental impairment (Tables 120.1 and 120.2). For infants with birthweight <1,000 g, the incidence of severe neurologic impairment (defined as Bayley Scales of Infant Development II mental developmental index <70, psychomotor development index <70, cerebral palsy, blindness, or deafness) after IVH is highest with grade IV hemorrhage and lower birthweight. PVL, cystic PVL, and progressive hydrocephalus requiring shunt insertion are each independently associated with a poorer prognosis (Table 120.3). Current data suggest that outcomes for infants with grade III/IV intraventricular hemorrhage may be improving, with rates of cerebral palsy and neurodevelopmental impairment closer to 30–40% at age 2 yr.

Table 120.1

Short-Term Outcome of Germinal Matrix–Intraventricular Hemorrhage as a Function of Severity of Hemorrhage and Birthweight[*]

SEVERITY OF HEMORRHAGE	DEATHS IN FIRST 14 DAYS[c]		PVD (SURVIVORS >14 DAYS)	
	<750 g (*n* = 75)	**751-1500 g (*n* = 173)**	**<750 g (*n* = 56)**	**751-1500 g (*n* = 165)**
Grade I	3/24 (12)	0/80 (0)	1/21 (5)	3/80 (4)
Grade II	5/21 (24)	1/44 (2)	1/16 (6)	6/43 (14)
Grade III	6/19 (32)	2/26 (8)	10/13 (77)	18/24 (75)
Grade III and apparent PHI	5/11 (45)	5/23 (22)	5/6 (83)	12/18 (66)

[*] Values are *n* (%). Deaths occurring later in the neonatal period are not shown; the total mortality rates (early and late deaths) are approximately 50–100% greater for each grade of hemorrhage and birthweight than those shown in the table for early deaths alone.

PHI, Periventricular hemorrhagic infarction; PVD, progressive ventricular dilation.

Data from Murphy BP, Inder TE, Rooks V, Taylor GA, et al. Posthemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome, *Arch Dis Child Fetal Neonatal Ed* 87:F37–F41, 2002.

Adapted from Inder TE, Perlman JM, Volpe JJ: Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier (Table 24-15).

Table 120.2

Long-Term Outcome: Neurologic Sequelae in Survivors With Germinal Matrix–Intraventricular Hemorrhage as a Function of Severity of Hemorrhage[*]

SEVERITY OF HEMORRHAGE[b]	INCIDENCE OF DEFINITE NEUROLOGIC SEQUELAE [†] (%)
Grade I	15
Grade II	25
Grade III	50
Grade III and apparent PVI	75

[*] Data are derived from reports published since 2002 and include personal published and unpublished cases. Mean values (to nearest 5%); considerable variability among studies was apparent, especially for the severe lesions.

[†] Definite neurologic sequelae included principally cerebral palsy or mental retardation, or both.

PVI, Periventricular hemorrhagic infarction.

Adapted From Inder TE, Perlman JM, Volpe JJ: Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier (Table 24-16).

Table 120.3

Ultrasonographic (US) Diagnosis of Periventricular Leukomalacia

US APPEARANCE	TEMPORAL FEATURES	NEUROPATHOLOGIC CORRELATION
Echogenic foci, bilateral, posterior > anterior	1st wk	Necrosis with congestion and/or hemorrhage (size >1 cm)
Echolucent foci (“cysts”)	1-3 wk	Cyst formation secondary to tissue dissolution (size >3 mm)
Ventricular enlargement, often with disappearance of “cysts”	≥2-3 mo	Deficient myelin formation; gliosis, often with collapse of cyst

From Neil JJ, Volpe JJ: Encephalopathy of prematurity: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier (Table 16-6).

Most infants with IVH and acute ventricular distention do not have **PHH** . Only 10–15% of LBW neonates with IVH develop PHH, which may initially present without clinical signs (enlarging head circumference, lethargy, a bulging fontanel or widely split sutures, apnea, and bradycardia). In infants in whom symptomatic hydrocephalus develops, clinical signs may be delayed 2-4 wk despite progressive ventricular distention and compression and thinning of the cerebral cortex. Many infants with PHH have spontaneous regression; only 3–5% of VLBW infants with PHH ultimately require shunt insertion. Those infants who require shunt insertion for PHH have lower cognitive and psychomotor performance at 18-22 mo.

Prevention

Improved perinatal care is imperative to minimize traumatic brain injury and decrease the risk of preterm delivery. The incidence of traumatic intracranial hemorrhage may be reduced by judicious management of cephalopelvic disproportion and operative (forceps, vacuum) delivery. Fetal or neonatal hemorrhage caused by maternal idiopathic thrombocytopenic purpura or alloimmune thrombocytopenia may be reduced by maternal treatment with corticosteroids, intravenous immune globulin (IVIG), fetal platelet transfusion, or cesarean birth. Meticulous care of the LBW infant's respiratory status and fluid-electrolyte management—avoidance of acidosis, hypocarbia, hypoxia, hypotension, wide fluctuations in neonatal blood pressure or P_{CO_2} (and secondarily fluctuation in cerebral perfusion pressure), and pneumothorax—are important factors that may affect the risk for development of IVH and PVL.

A single course of antenatal corticosteroids is recommended in pregnancies 24-37 wk of gestation that are at risk for preterm delivery. Antenatal steroids decrease the risk of death, grades III and IV intraventricular hemorrhage, and PVL in the neonate. The prophylactic administration of low-dose indomethacin (0.1 mg/kg/day for 3 days) to VLBW preterm infants reduces the incidence of severe IVH.

Treatment

Although no treatment is available for **IVH** that has occurred, it may be associated with other complications that require therapy. Seizures should be treated with anticonvulsant drugs. Anemia and coagulopathy require transfusion with packed red blood cells or fresh-frozen plasma. Shock and acidosis are treated with fluid resuscitation.

Insertion of a **ventriculoperitoneal shunt** is the preferred method to treat progressive and symptomatic **PHH** . Some infants require temporary cerebrospinal fluid diversion before a permanent shunt can be safety inserted. Diuretics and acetazolamide are not effective. Ventricular taps or reservoirs and externalized ventricular drains are potential temporizing interventions, although there is an associated risk of infection and *puncture porencephaly* from injury to the surrounding parenchyma. A **ventriculosubgaleal shunt** inserted from the ventricle into a surgically created subgaleal pocket provides a closed system for constant ventricular decompression without these additional risk factors. Decompression is regulated by the pressure gradient between the ventricle and the subgaleal pocket.

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120.4

Hypoxic-Ischemic Encephalopathy

Cameron W. Thomas, Stephanie L. Merhar

Hypoxemia , a decreased arterial concentration of oxygen, frequently results in **hypoxia** , or decreased oxygenation to cells or organs. **Ischemia** refers to blood flow to cells or organs that is inadequate to maintain physiologic function. **Hypoxic-ischemic encephalopathy (HIE)** is a leading cause of neonatal brain injury, morbidity, and mortality globally. In the developed world, incidence is estimated at 1-8 per 1,000 live births, and in the developing world, estimates are as high as 26 per 1,000.

Approximately 20–30% of infants with HIE (depending on the severity) die in the neonatal period, and 33–50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, decreased IQ, learning/cognitive impairment). The greatest risk of adverse outcome is seen in infants with severe fetal acidosis (pH <6.7) (90% death/impairment) and a base deficit >25 mmol/L (72% mortality). Multiorgan failure and insult can occur (Table 120.4).

Table 120.4

Multiorgan Systemic Effects of Asphyxia

SYSTEM	EFFECTS
Central nervous	Hypoxic-ischemic encephalopathy, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stunning, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, respiratory distress syndrome
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integumentary	Subcutaneous fat necrosis
Hematologic	Disseminated intravascular coagulation

Etiology

Most neonatal encephalopathy and seizure, in the absence of major congenital malformations or metabolic or genetic syndromes, appear to be caused by perinatal events. Brain MRI or autopsy findings in full-term neonates with encephalopathy demonstrate that 80% have acute injuries, <1% have prenatal injuries, and 3% have non–hypoxic-ischemic diagnoses. Fetal hypoxia may be caused by various disorders in the mother, including: (1) inadequate oxygenation of maternal blood from hypoventilation during anesthesia, cyanotic heart disease, respiratory failure, or carbon monoxide poisoning; (2) low maternal blood pressure from acute blood loss, spinal anesthesia, or compression of the vena cava and aorta by the gravid uterus; (3) inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by the administration of excessive oxytocin; (4) premature separation of the placenta; (5) impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord; and (6) placental insufficiency from maternal infections, exposures, diabetes, toxemia or postmaturity.

Placental insufficiency often remains undetected on clinical assessment. Intrauterine growth restriction may develop in chronically hypoxic fetuses without the traditional signs of fetal distress. Doppler umbilical waveform velocimetry (demonstrating increased fetal vascular resistance) and cordocentesis (demonstrating fetal hypoxia and lactic acidosis) identify a chronically hypoxic infant (see Chapter 115). Uterine contractions may further reduce umbilical oxygenation, depressing the fetal cardiovascular system and CNS and resulting in low Apgar scores and respiratory depression at birth.

After birth, hypoxia may be caused by (1) failure of oxygenation as a result of severe forms of cyanotic congenital heart disease or severe pulmonary disease; (2) severe anemia (severe hemorrhage, hemolytic disease); (3) shock severe enough to interfere with the transport of oxygen to vital organs from overwhelming sepsis, massive blood loss, and intracranial or adrenal hemorrhage; or (4) failure to breathe after birth because of in utero CNS injury or drug-induced suppression.

Pathophysiology and Pathology

The topography of cerebral injury typically correlates with areas of decreased cerebral blood flow and areas of relatively higher metabolic demand, although regional vulnerabilities are impacted by gestational age and severity of insult (Table 120.5). After an episode of hypoxia and ischemia, anaerobic metabolism occurs and generates increased amounts of lactate and inorganic phosphates. Excitatory and toxic amino acids, particularly glutamate, accumulate in the damaged tissue. prompting overactivation of *N* -methyl-ᴅ -aspartate (NMDA), amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and kainate receptors. This receptor overactivation increases cellular permeability to sodium and calcium ions. Because of inadequate intracellular energy, normal sodium and calcium homeostasis is lost, and intracellular accumulation of these ions results in cytotoxic edema and neuronal death. Intracellular calcium accumulation may also result in apoptotic cell death. Concurrent with the excitotoxic cascade, there is also increased production of damaging free radicals and nitric oxide in these tissues. The initial circulatory response of the fetus is increased shunting through the ductus venosus, ductus arteriosus, and foramen ovale, with transient maintenance of perfusion of the brain, heart, and adrenals in preference to the lungs, liver, kidneys, and intestine. Thus, serum laboratory evidence of injury to these organs may be present in more severe cases.

Table 120.5

Topography of Brain Injury in Term Infants With Hypoxic-Ischemic Encephalopathy and Clinical Correlates

AREA OF INJURY	LOCATION OF INJURY	CLINICAL CORRELATES	LONG-TERM SEQUELAE
Selective neuronal necrosis	Entire neuraxis, deep cortical area, brainstem and pontosubicular	Stupor or coma Seizures Hypotonia Oculomotor abnormalities Suck/swallow abnormalities	Cognitive delay Cerebral palsy Dystonia Seizure disorder Ataxia Bulbar and pseudobulbar palsy
Parasagittal injury	Cortex and subcortical white matter Parasagittal regions, especially posterior	Proximal-limb weakness Upper extremities affected > lower extremities	Spastic quadriparesis Cognitive delay Visual and auditory processing difficulty
Focal ischemic necrosis	Cortex and subcortical white matter Vascular injury (usually middle cerebral artery distribution)	Unilateral findings Seizures common and typically focal	Hemiparesis Seizures Cognitive delays
Periventricular injury	Injury to motor tracts, especially lower extremity	Bilateral and symmetric weakness in lower extremities More common in preterm infants	Spastic diplegia

Adapted from Volpe JJ, editor: *Neurology of the newborn* , ed 4, Philadelphia, 2001, Saunders.

The pathology of hypoxia-ischemia outside the CNS depends on the affected organ and the severity of the injury. Early congestion, fluid leak from increased capillary permeability, and endothelial cell swelling may lead to signs of coagulation necrosis and cell death. Congestion and petechiae are seen in the pericardium, pleura, thymus, heart, adrenals, and meninges. Prolonged intrauterine hypoxia may result in inadequate perfusion of the periventricular white matter, resulting in PVL. Pulmonary arteriole smooth muscle hyperplasia may develop, which predisposes the infant to pulmonary hypertension (see Chapter 122.9). If fetal distress produces gasping, amniotic fluid contents (meconium, squames, lanugo) may be aspirated into the trachea or lungs with subsequent complications, including pulmonary hypertension and pneumothoraces.

Clinical Manifestations

Intrauterine growth restriction with increased vascular resistance may be an indication of chronic fetal hypoxia before the peripartum period. During labor, the fetal heart rate slows and beat-to-beat variability declines. Continuous heart rate recording may reveal a variable or late deceleration pattern (see Chapter 115 , Fig. 115.4). Particularly in infants near term, these signs should lead to the administration of high concentrations of oxygen to the mother and consideration of immediate delivery to avoid fetal death and CNS damage.

At delivery, the presence of meconium-stained amniotic fluid indicates that fetal distress may have occurred. At birth, affected infants may have neurologic impairment and may fail to breathe spontaneously. Pallor, cyanosis, apnea, a slow heart rate, and unresponsiveness to stimulation are also nonspecific initial signs of potential HIE. During the ensuing hours, infants may be hypotonic, may change from a hypotonic to a hypertonic state, or their tone may appear normal (Tables 120.6 and 120.7). Cerebral edema may develop during the next 24 hr and result in profound brainstem depression. During this time, seizure activity may occur; it may be severe and refractory to typical doses of anticonvulsants. Although most often a result of the HIE, seizures in asphyxiated newborns may also be caused by vascular events (hemorrhage, arterial ischemic stroke, or sinus venous thrombosis), metabolic derangements (hypocalcemia, hypoglycemia), CNS infection, and cerebral dysgenesis or genetic disorders (nonketotic hyperglycinemia, vitamin-dependent epilepsies, channelopathies). Conditions that result in neuromuscular weakness and poor respiratory effort may also result secondarily in neonatal hypoxic brain injury and seizure. Such conditions might include congenital myopathies, congenital myotonic dystrophy, or spinal muscular atrophy.

Table 120.6

Poor Predictive Variables for Death/Disability After Hypoxic-Ischemic Encephalopathy

- Low (0–3) 10 min Apgar score
- Need for CPR in the delivery room
- Delayed onset (≥20 min) of spontaneous breathing
- Severe neurologic signs (coma, hypotonia, hypertonia)
- Seizures onset ≤12 hr or difficult to treat
- Severe, prolonged (~7 days) EEG findings including burst suppression pattern
- Prominent MRI basal ganglia/thalamic lesions
- Oliguria/anuria >24 hr
- Abnormal neurologic exam ≥14 days

Table 120.7

Hypoxic-Ischemic Encephalopathy in Term Infants

SIGNS	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalographic findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr to 14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

Adapted from Sarnat HB, Sarnat MS: Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study, *Arch Neurol* 33:696–705, 1976.Copyright 1976, American Medical Association.

In addition to CNS dysfunction, systemic organ dysfunction is noted in up to 80% of affected neonates. Myocardial dysfunction and cardiogenic shock, persistent pulmonary hypertension, RDS, gastrointestinal perforation, and acute kidney and liver injury are associated with perinatal asphyxia secondary to inadequate perfusion (see Table 120.4).

The severity of neonatal encephalopathy depends on the duration and timing of injury. A clinical grading score first proposed by Sarnat continues to be a useful tool. Symptoms develop over days, making it important to perform serial neurologic examinations (see Tables 120.6 and 120.7). During the initial hours after an insult, infants have a depressed level of consciousness. Periodic breathing with apnea or bradycardia is present, but cranial nerve functions are often spared, with intact pupillary response and spontaneous eye movement. Seizures are common with extensive injury. Hypotonia is also common as an early manifestation of HIE, but it should be distinguished from other causes by history and serial examination.

Diagnosis

MRI is the most sensitive imaging modality for detecting hypoxic brain injury in the neonate. Although such injury can be detected at various times and with varying pulse sequences, diffusion-weighted sequences obtained in the 1st 3-5 days following a presumed sentinel event are optimal for identifying acute injury. (Figs. 120.5 to 120.8 and Table 120.8). Where MRI is unavailable or prevented by clinical instability, CT scans may be helpful in ruling out focal hemorrhagic lesions or large arterial ischemic strokes. Loss of gray-white differentiation and injury to the basal ganglia in more severe HIE can be detected on CT by experienced readers, but CT often misses subtler forms of neonatal hypoxic brain injury. US has limited utility in evaluation of hypoxic injury in the term infant, but it too can be useful for excluding hemorrhagic lesions. Because of factors of size and clinical stability, US is the initial preferred (and sometimes only feasible) modality in evaluation of the preterm infant.

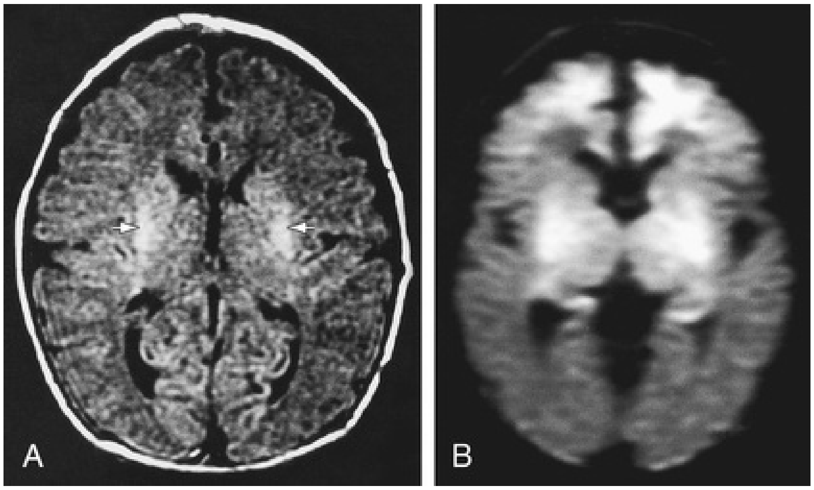

FIG. 120.5 MR images of selective neuronal injury. The infant experienced intrapartum asphyxia and had seizures on the 1st postnatal day. MRI was performed on the 5th postnatal day. A, Axial, fluid-attenuated, inversion recovery image shows increased signal in the putamen bilaterally *(arrows)* but no definite abnormality in the cerebral cortex. B, By contrast, a diffusion-weighted image shows striking increased signal intensity (i.e., decreased diffusion) in the frontal cortex (in addition to a more pronounced basal ganglia abnormality). (From Volpe JJ, editor: *Neurology of the newborn* , ed 5, Philadelphia, 2008, Saunders/Elsevier, p 420.)

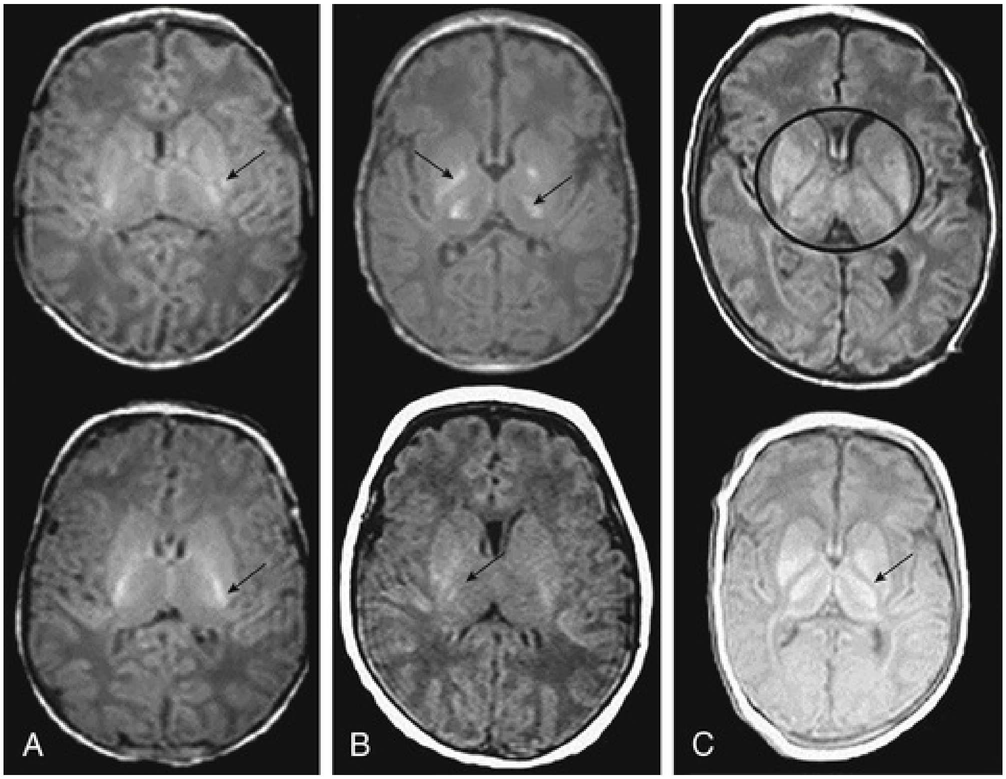

FIG. 120.6 MR images of basal ganglia/thalamic (BG/T) injury and signal intensity. *Top row,* Axial T1-weighted MR images showing A, mild BG/T lesions *(arrow)* ; B, moderate BG/T injury *(arrows)* ; and C, severe BG/T abnormalities *(circled)* . *Bottom row,* Axial T1-weighted MR images showing A, normal signal intensity (SI) in the posterior limb of the internal capsule (PLIC) *(arrow)* ; B, equivocal, asymmetric, and slightly reduced SI in the PLIC *(arrow)* ; and C, abnormal, absent SI in the PLIC *(arrow)* . (From Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM. Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy, *Early Hum Dev* 86:675–682, 2010.)

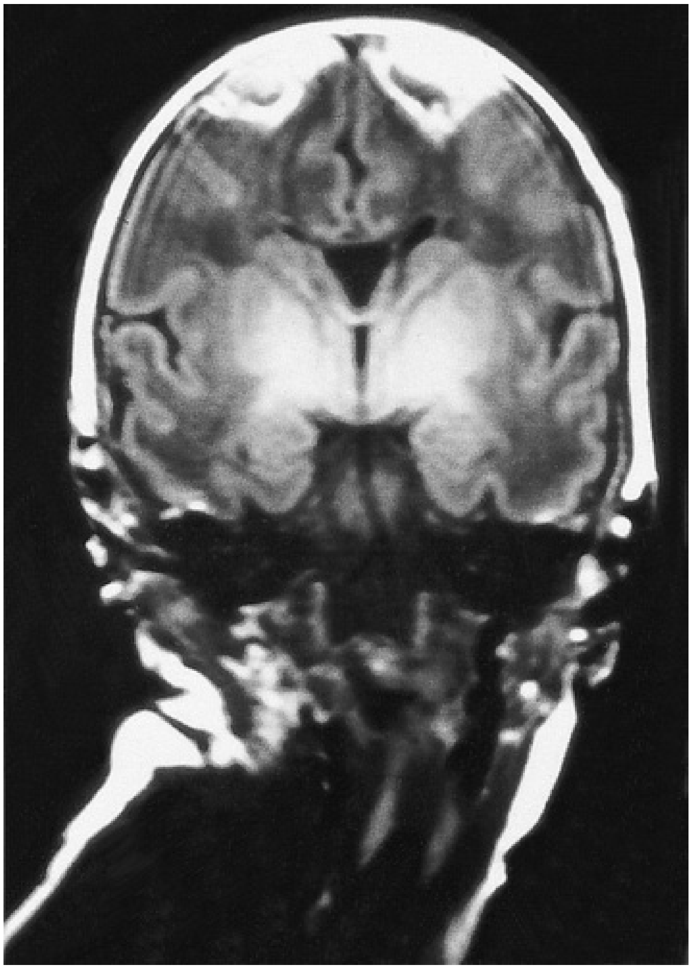

FIG. 120.7 MR image of a parasagittal cerebral injury. Coronal T1-weighted image, obtained on the 5th postnatal day in an asphyxiated term infant, shows striking triangular lesions in the parasagittal areas bilaterally; increased signal intensity is also apparent in the basal ganglia and thalamus bilaterally. (From Volpe JJ, editor: *Neurology of the newborn* , ed 5, Philadelphia, 2008, Saunders/Elsevier, p 421.)

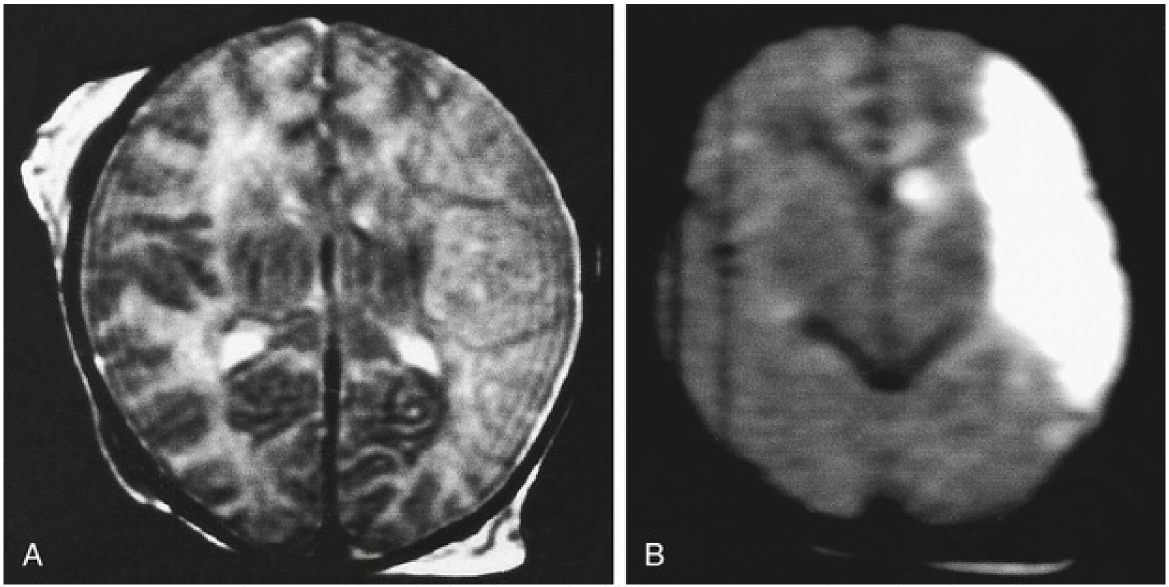

FIG. 120.8 MR images of focal ischemic cerebral injury. MRI was performed on the 3rd postnatal day. A, Axial T2-weighted mage shows a lesion in the distribution of the main branch of the left middle cerebral artery. B, Diffusion-weighted image demonstrates the lesion more strikingly. (From Volpe JJ, editor: *Neurology of the newborn* , ed 5, Philadelphia, 2008, Saunders/Elsevier, p 422.)

Table 120.8

Major Aspects of MRI in Diagnosis of Hypoxic-Ischemic Encephalopathy in the Term Infant

MAJOR CONVENTIONAL MR FINDINGS IN 1ST WEEK
Cerebral cortical gray-white differentiation lost (on T1W or T2W)
Cerebral cortical high signal (T1W and FLAIR), especially in parasagittal perirolandic cortex
Basal ganglia/thalamus, high signal (T1W and FLAIR), usually associated with the cerebral cortical changes but possibly alone with increased signal in brainstem tegmentum in cases of acute severe insult
Parasagittal cerebral cortex, subcortical white matter, high signal (T1W and FLAIR)
Periventricular white matter, decreased signal (T1W) or increased signal (T2W)
Posterior limb of internal capsule, decreased signal (T1W or FLAIR)
Cerebrum in a vascular distribution, decreased signal (T1W), but much better visualized as decreased diffusion (increased signal) on diffusion-weighted MRI
Diffusion-weighted MRI more sensitive than conventional MRI, especially in 1st days after birth, when former shows decreased diffusion (increased signal) in injured areas

FLAIR, Fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; T1W and T2W, T1- and T2-weighted images.

From Volpe JJ, editor: *Neurology of the newborn,* ed 5, Philadelphia, 2008, Elsevier (Table 9-16).

Amplitude-integrated electroencephalography (aEEG) may help to determine which infants are at highest risk for developmental sequelae of neonatal brain injury (Tables 120.9 and 120.10). The aEEG background voltage ranges, signal patterns, and rates of normalization, as assessed at various points in the 1st hours and days of life, can provide valuable prognostic information, with positive predictive value of 85% and negative predictive value of 91–96% for infants who will have adverse neurodevelopmental outcome. Unfortunately, even with recent improvements in technology, aEEG still has difficulty detecting seizures, particularly those that are brief or originate far from the electrodes. Sensitivity of aEEG for seizure detection, when used by a typical reader, is <50%. For this reason, *conventional EEG montage with concurrent video of the patient are preferred for seizure monitoring*.

Table 120.9

Value of Electroencephalography in Assessment of Asphyxiated Term Infants

Detection of severe abnormalities (i.e., CLV, FT, BSP) in 1st hours of life has a positive predictive value of an unfavorable outcome of 80–90%.
Severe abnormalities may improve within 24 hr (~50% of BSP and 10% of CLV/FT).
Rapid recovery of severe abnormalities is associated with a favorable outcome in 60% of cases.
The *combination* of early neonatal neurologic examination and early aEEG enhances the positive predictive value and specificity.

aEEG, Amplitude-integrated encephalography; BSP, burst-suppression pattern; CLV, continuous low voltage; FT, flat trace.

From Inder TE, Volpe JJ: Hypoxic-ischemic injury in the term infant: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier (Table 20-28).

Table 120.10

Electroencephalographic Patterns of Prognostic Significance in Asphyxiated Term Infants*

ASSOCIATED WITH FAVORABLE OUTCOME
Mild depression (or less) on day 1
Normal background by day 7
ASSOCIATED WITH UNFAVORABLE OUTCOME
Predominant interburst interval >20 sec on any day
Burst-suppression pattern on any day
Isoelectric tracing on any day
Mild (or greater) depression after day 12

* Associations with favorable or unfavorable outcome are generally ≥90%, but the clinical context must be considered.

From Inder TE, Volpe JJ: Hypoxic-ischemic injury in the term infant: clinical-neurological features, diagnosis, imaging, prognosis, therapy. In *Volpe's neurology of the newborn,* ed 6, Philadelphia, 2018, Elsevier (Table 20-26).

Treatment

Therapeutic hypothermia , whether head cooling or systemic cooling (by servo-control to a core rectal or esophageal temperature of 33.5°C [92.3°F] within the 1st 6 hr after birth and maintained for 72 hr), has been shown in various trials to reduce mortality and major neurodevelopmental impairment at 18 mo of age. Infants treated with systemic hypothermia have a lower incidence of cortical neuronal injury on MRI, suggesting systemic hypothermia may result in more uniform cooling of the brain and deeper CNS structures than selective head cooling. The therapeutic effect of hypothermia likely results from decreased secondary neuronal injury achieved by reducing rates of apoptosis and production of mediators known to be neurotoxic, including extracellular glutamate, free radicals, nitric oxide, and lactate. There is also benefit in seizure reduction. The therapeutic benefit of hypothermia noted at 18-22 mo of age is maintained later in childhood. Once established, hypothermia may not alter the prognostic findings on MRI.

Numerous studies seeking ways to extend the benefits of therapeutic hypothermia have been attempted. Assessment of deeper or longer cooling failed to show benefit in short-term outcomes, although longer-term developmental outcomes of that trial are not yet published. Investigations into extending the therapeutic time window of hypothermia initiation beyond 6 hr or offering hypothermia to preterm infants are ongoing.

In addition to extending the benefit of therapeutic hypothermia, there is great interest in augmenting its benefit through other means. High-dose **erythropoietin** given as an adjunct to therapeutic hypothermia shows some promise in decreasing MRI indicators of brain injury and short-term motor outcomes. Further study as well as longitudinal follow-up of the study cohort is warranted to confirm these findings.

Complications of induced hypothermia include thrombocytopenia (usually without bleeding), reduced heart rate, and subcutaneous fat necrosis (sometimes with associated hypercalcemia) as well as the potential for overcooling and the cold injury syndrome. The latter is usually avoided with a servo-controlled cooling system. Therapeutic hypothermia may theoretically alter drug metabolism, prolong the QT interval, and affect the interpretation of blood gases. In clinical practice, these concerns have not been observed.

For treating seizures associated with HIE, **phenobarbital** , the historical first-line drug for neonatal seizures, continues to be used in many instances. It is typically given by intravenous loading dose (20 mg/kg). Additional doses of 5-10 mg/kg (up to 40-50 mg/kg total) may be needed. Phenobarbital levels should be monitored 24 hr after the loading dose has been given and maintenance therapy (5 mg/kg/24 hr) begun. Therapeutic phenobarbital levels are 20-40 µg/mL. Animal models demonstrate decreased neurodevelopmental impact of hypoxic brain injury in animals that received a high-dose prophylactic injection of phenobarbital before onset of therapeutic hypothermia. Whether this benefit translates to humans is controversial.

For refractory seizures, there is a high degree of variability regarding choice of 2nd agent. Historically, phenytoin (20 mg/kg loading dose) or lorazepam (0.1 mg/kg) have been preferred, currently the use of **levetiracetam** is preferred (at times even as a first-line agent) as the most used second-line agent. Early reports of administration of levetiracetam in the neonate used low doses, but subsequent pharmacokinetic data suggest that due to the higher volume of distribution created by higher relative body water content in neonates, loading doses should be higher than in older children or adults. Suggested appropriate loading doses may be closer to 60 mg/kg. In addition to levetiracetam and phenytoin, other second- or third-line agents commonly used include midazolam, topiramate, and lidocaine. Pyridoxine should also be attempted, particularly in ongoing refractory seizures with highly abnormal EEG background.

Status epilepticus, multifocal seizures, and multiple anticonvulsant medications during therapeutic hypothermia are associated with a poor prognosis.

Additional therapy for infants with HIE includes supportive care directed at management of organ system dysfunction. Hyperthermia has been associated with impaired neurodevelopment and should be prevented, particularly in the interval between initial resuscitation and initiation of hypothermia. Careful attention to ventilatory status and adequate oxygenation, blood pressure, hemodynamic status, acid-base balance, and possible infection is important. Secondary hypoxia or hypotension from complications of HIE must be prevented. Aggressive treatment of seizures is critical and may necessitate continuous EEG monitoring. In addition, hyperoxia, hypocarbia, and hypoglycemia are associated with poor outcomes, so careful attention to resuscitation, ventilation, and blood glucose homeostasis is essential.

Prognosis

The outcome of HIE, which correlates with the timing and severity of the insult, ranges from complete recovery to death. The prognosis varies depending on the severity of the insult and the treatment. Infants with initial cord or initial blood pH <6.7 have a 90% risk for death or severe neurodevelopmental impairment at 18 mo of age. In addition, infants with Apgar scores of 0-3 at 5 min, high base deficit (>20-25 mmol/L), decerebrate posture, severe basal ganglia/thalamic (BG/T) lesions (Fig. 120.9 ; see also Fig. 120.6), persistence of severe HIE by clinical examination at 72 hr, and lack of spontaneous activity are also at increased risk for death or impairment. These predictor variables can be combined to determine a score that helps with prognosis (see Table 120.6). Infants with the highest risk are likely to die or have severe disability despite aggressive treatment, including hypothermia. Those with intermediate scores are likely to benefit from treatment. In general, severe encephalopathy, characterized by flaccid coma, apnea, absence of oculocephalic reflexes, and refractory seizures, is associated with a poor prognosis (see Table 120.7). Apgar scores alone can also be associated with subsequent risk of neurodevelopmental impairment. At 10 min, each point decrease in Apgar score increases odds of death or disability by 45%. Death or disability occurs in 76–82% of infants with Apgar scores of 0-2 at 10 min. Absence of spontaneous respirations at 20 min of age and persistence of abnormal neurologic signs at 2 wk of age also predict death or severe cognitive and motor deficits.

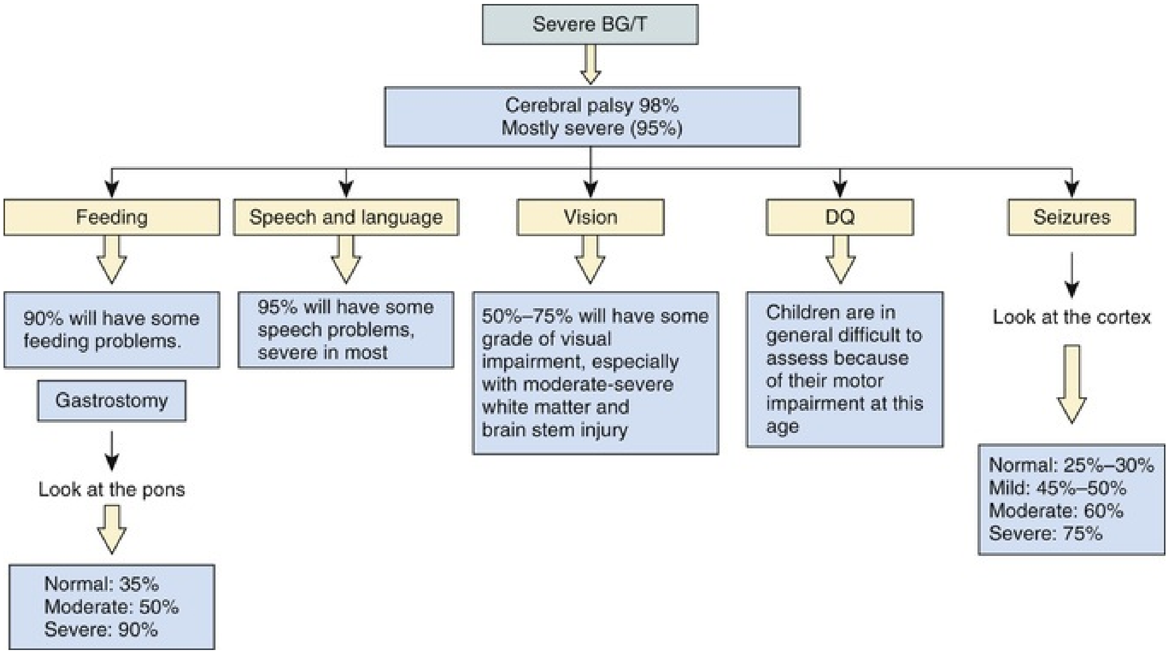
Severe BG/T
Cerebral palsy 98%
Mostly severe (95%)
Feeding
Speech and language
Vision
DQ
Seizures
90% will have some feeding problems.
Gastrostomy
Look at the pons
Normal: 35%
Moderate: 50%
Severe: 90%
95% will have some speech problems, severe in most
50%–75% will have some grade of visual impairment, especially with moderate-severe white matter and brain stem injury
Children are in general difficult to assess because of their motor impairment at this age
Look at the cortex
Normal: 25%–30%
Mild: 45%–50%
Moderate: 60%
Severe: 75%

FIG. 120.9 Flow chart showing patterns of outcome with severe basal ganglia/thalamic (BG/T) injury. *DQ* , Developmental quotient. (From Martinez-Biarge M, Diez-Sebastian J, Rutherford MA, Cowan FM: Outcomes after central grey matter injury in term perinatal hypoxic-ischaemic encephalopathy, *Early Hum Dev* 86:675–682, 2010.)

The combined use of early conventional EEG or aEEG and MRI offers additional insight in predicting outcome in term infants with HIE (see Table 120.10). EEG or aEEG background characteristics such as pattern, voltage, reactivity, state change, and evolution after acute injury are important predictors of outcome. MRI markers include location of injury, identification of injury by certain pulse sequences, measurement of diffusivity and/or fractional anisotropy, and presence of abnormal metabolite ratios on MR spectroscopy, and all have shown correlation with outcome. There is also growing interest in quantitative measures (volumetric analysis, diffusion tensor imaging) of MRI as potential predictors of outcome. Severe BG/T lesions with abnormal signal in the posterior limb of the internal capsule is highly predictive of the poorest cognitive and motor prognosis (see Fig. 120.9). Normal MRI and EEG findings are associated with a good recovery.

Microcephaly and poor head growth during the 1st year of life also correlate with injury to the basal ganglia and white matter and adverse developmental outcome at 12 mo. All survivors of moderate to severe encephalopathy require comprehensive high-risk medical and developmental follow-up. Early identification of neurodevelopmental problems allows prompt referral for developmental, rehabilitative, and neurologic early intervention services so that the best possible outcomes can be achieved.

Brain death after neonatal HIE is diagnosed from the clinical findings of coma unresponsive to pain, auditory, or visual stimulation; apnea with P_{CO_2} rising from 40 to >60 mm Hg without ventilatory support; and absence of brainstem reflexes (pupillary, oculocephalic, oculovestibular, corneal, gag, sucking) (see Chapter 86). These findings must occur in the absence of hypothermia, hypotension, and elevations of depressant drugs (phenobarbital), which may take days to weeks to be metabolized and cleared completely from the blood. An absence of cerebral blood flow on radionuclide scans and of electrical activity on EEG (electrocerebral silence) is inconsistently observed in clinically brain-dead neonatal infants. Persistence of the clinical criteria for 24 hr in term infants predicts brain death in most asphyxiated newborns. There is no agreement on brain death criteria in preterm infants. Because of inconsistencies and difficulties in applying standard criteria, *no universal agreement has been reached regarding the definition of neonatal brain death.* Consideration of withdrawal of life support should include discussions with the family, the healthcare team, and, if there is disagreement, an ethics committee. The best interest of the infant involves judgments about the benefits and harm of continuing therapy or avoiding ongoing futile therapy.

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120.5

Spine and Spinal Cord

Cameron W. Thomas, Stephanie L. Merhar

See also Chapter 729 .

Injury to the spine/spinal cord during birth is rare but can be devastating. Strong traction exerted when the spine is hyperextended or when the direction of pull is lateral, or forceful longitudinal traction on the trunk while the head is still firmly engaged in the pelvis, especially when combined with flexion and torsion of the vertical axis, may produce fracture and separation of the vertebrae. Such injuries are most likely to occur when difficulty is encountered in delivering the shoulders in cephalic presentations and the head in breech presentations. The injury occurs most often at the level of the 4th cervical vertebra with cephalic presentations and the lower cervical–upper thoracic vertebrae with breech presentations. Transection of the cord may occur *with or without* vertebral fractures; hemorrhage and edema may produce neurologic signs that are indistinguishable from those of transection, except that they may not be permanent. Areflexia, loss of sensation, and complete paralysis of voluntary motion occur below the level of injury, although the persistence of a withdrawal reflex mediated through spinal centers distal to the area of injury is frequently misinterpreted as representing voluntary motion.

If the injury is severe, the infant, who from birth may be in poor condition because of respiratory depression, shock, or hypothermia, may deteriorate rapidly to death within several hours before any neurologic signs are obvious. Alternatively, the course may be protracted, with symptoms and signs appearing at birth or later in the 1st wk; Horner syndrome, immobility, flaccidity, and associated brachial plexus injuries may not be recognized for several days. Constipation may also be present. Some infants survive for prolonged periods, their initial flaccidity, immobility, and areflexia being replaced after several weeks or months by rigid flexion of the extremities, increased muscle tone, and spasms. Apnea on day 1 and poor motor recovery by 3 mo are poor prognostic signs.

The **differential diagnosis** of neonatal spine/spinal cord injury includes amyotonia congenita and myelodysplasia associated with spina bifida occulta, spinal muscular atrophy (type 0), spinal vascular malformations (e.g., arteriovenous malformation causing hemorrhage or stroke), and congenital structural anomalies (syringomyelia, hemangioblastoma). US or MRI confirms the diagnosis. Treatment of the survivors is supportive, including home ventilation; patients often remain permanently disabled. When a fracture or dislocation is causing spinal compression, the prognosis is related to the time elapsed before the compression is relieved.

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120.6

Peripheral Nerve Injuries

Cameron W. Thomas, Stephanie L. Merhar

See also Chapter 731 .

Brachial Palsy

Brachial plexus injury is a common problem, with an incidence of 0.6-4.6 per 1,000 live births. Injury to the brachial plexus may cause paralysis of the upper part of the arm with or without paralysis of the forearm or hand or, more often, paralysis of the entire arm. These injuries occur in macrosomic infants and when lateral traction is exerted on the head and neck during delivery of the shoulder in a vertex presentation, when the arms are extended over the head in a breech presentation, or when excessive traction is placed on the shoulders. Approximately 45% of brachial plexus injuries are associated with shoulder dystocia.

In **Erb-Duchenne paralysis** the injury is limited to the 5th and 6th cervical nerves. The infant loses the power to abduct the arm from the shoulder, rotate the arm externally, and supinate the forearm. The characteristic position consists of adduction and internal rotation of the arm with pronation of the forearm. Power to extend the forearm is retained, but the biceps reflex is absent; the Moro reflex is absent on the affected side (Fig. 120.10). The outer aspect of the arm may have some sensory impairment. Power in the forearm and hand grasps is preserved unless the lower part of the plexus is also injured; the presence of hand grasp is a favorable prognostic sign. When the injury includes the phrenic nerve, alteration in diaphragmatic excursion may be observed with US, fluoroscopy, or as asymmetric elevation of the diaphragm on chest radiograph.

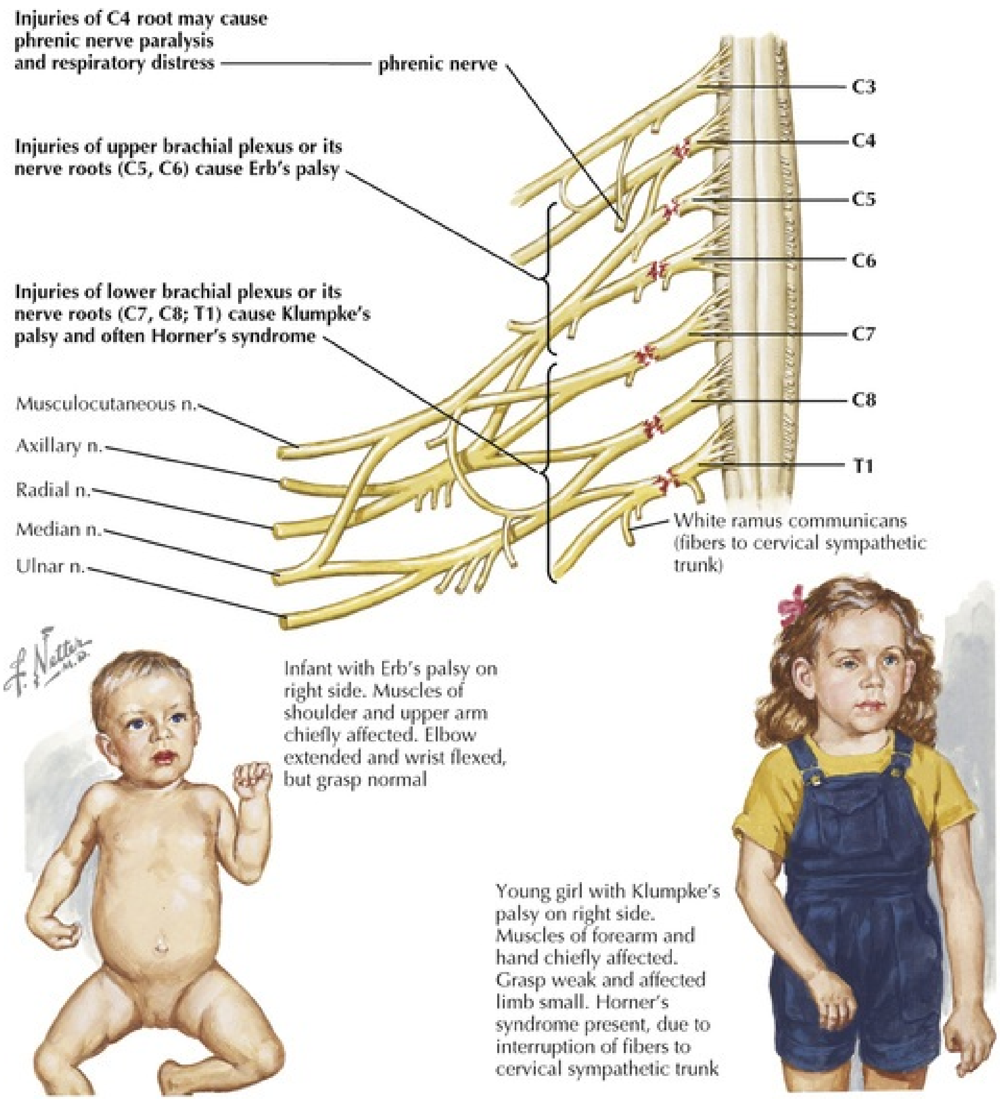
Injuries of C4 root may cause phrenic nerve paralysis and respiratory distress
phrenic nerve
Injuries of upper brachial plexus or its nerve roots (C5, C6) cause Erb's palsy
Injuries of lower brachial plexus or its nerve roots (C7, C8; T1) cause Klumpke's palsy and often Horner's syndrome
C3
C4
C5
C6
C7
C8
T1
Musculocutaneous n.
Axillary n.
Radial n.
Median n.
Ulnar n.
White ramus communicans (fibers to cervical sympathetic trunk)
Infant with Erb's palsy on right side. Muscles of shoulder and upper arm chiefly affected. Elbow extended and wrist flexed, but grasp normal
Young girl with Klumpke's palsy on right side. Muscles of forearm and hand chiefly affected. Grasp weak and affected limb small. Horner's syndrome present, due to interruption of fibers to cervical sympathetic trunk

FIG. 120.10 **Schematic representation of the brachial plexus with its terminal branches. The major sites of brachial plexus injury are shown. (Courtesy of Netter Images, Image ID 19943. www.netterimages.com .)**

Klumpke paralysis is a rare form of brachial palsy in which injury to the 7th and 8th cervical nerves and the 1st thoracic nerve produces a paralyzed hand and ipsilateral ptosis and miosis (**Horner syndrome**) if the sympathetic fibers of the 1st thoracic root are also injured. Mild cases may not be detected immediately after birth. Differentiation must be made from cerebral injury; from fracture, dislocation, or epiphyseal separation of the humerus; and from fracture of the clavicle. MRI demonstrates nerve root rupture or avulsion.

Most patients have full recovery. If the paralysis was a result of edema and hemorrhage around the nerve fibers, function should return within a few months; if it resulted from laceration, permanent damage may result. Involvement of the deltoid is usually the most serious problem and may result in **shoulder drop** secondary to muscle atrophy. In general, paralysis of the upper part of the arm has a better prognosis than paralysis of the lower part.

Treatment consists of initial conservative management with monthly follow-up and a decision for surgical intervention by 3 mo if function has not improved. Partial immobilization and appropriate positioning are used to prevent the development of contractures. In upper arm paralysis, the arm should be abducted 90 degrees with external rotation at the shoulder, full supination of the forearm, and slight extension at the wrist with the palm turned toward the face. This position may be achieved with a brace or splint during the 1st 1-2 wk. Immobilization should be intermittent throughout the day while the infant is asleep and between feedings. In lower arm or hand paralysis, the wrist should be splinted in a neutral position and padding placed in the fist. When the entire arm is paralyzed, the same treatment principles should be followed. Gentle massage and range-of-motion exercises may be started by 7-10 days of age. Infants should be closely monitored with active and passive corrective exercises. If the paralysis persists without improvement for 3 mo, neuroplasty, neurolysis, end-to-end anastomosis, and nerve grafting offer hope for partial recovery.

The type of treatment and the prognosis depend on the mechanism of injury and the number of nerve roots involved. The mildest injury to a peripheral nerve (**neurapraxia**) is caused by edema and heals spontaneously within a few weeks. **Axonotmesis** is more severe and is a consequence of nerve fiber disruption with an intact myelin sheath; function usually returns in a few months. Total disruption of nerves (**neurotmesis**) or root avulsion is the most severe, especially if it involves C5-T1; microsurgical repair may be indicated. Fortunately, most (75%) injuries are at the root level C5-C6, involve neurapraxia and axonotmesis, and should heal spontaneously. Botulism toxin may be used to treat biceps-triceps co-contractions.

Phrenic Nerve Paralysis

Phrenic nerve injury (3rd, 4th, 5th cervical nerves) with diaphragmatic paralysis must be considered when cyanosis and irregular and labored respirations develop. Such injuries, usually unilateral, are associated with ipsilateral upper brachial plexus palsies in 75% of cases. Because breathing is thoracic in type, the abdomen does not bulge with inspiration. Breath sounds are diminished on the affected side. The thrust of the diaphragm, which may often be felt just under the costal margin on the normal side, is absent on the affected side. The diagnosis is established by US or fluoroscopic examination, which reveals elevation of the diaphragm on the paralyzed side and seesaw movements of the 2 sides of the diaphragm during respiration. It may also be apparent on chest or abdominal radiograph.

Infants with phrenic nerve injury should be placed on the involved side and given oxygen if necessary. Some may benefit from pressure introduced by continuous positive airway pressure (CPAP) to expand the paralyzed hemidiaphragm. In extreme cases, mechanical ventilation cannot be avoided. Initially, intravenous feedings may be needed; later, progressive gavage or oral feeding may be started, depending on the infant's condition. Pulmonary infections are a serious complication. If the infant fails to demonstrate spontaneous recovery in 1-2 mo, surgical plication of the diaphragm may be indicated.

Facial Nerve Palsy

Facial palsy is usually a peripheral paralysis that results from pressure over the facial nerve in utero, during labor, or from forceps use during delivery. Rarely, it may result from nuclear agenesis of the facial nerve.

Peripheral facial paralysis is flaccid and, when complete, involves the entire side of the face, including the forehead. When the infant cries, movement occurs only on the nonparalyzed side of the face, and the mouth is drawn to that side. On the affected side the forehead is smooth, the eye cannot be closed, the nasolabial fold is absent, and the corner of the mouth droops. **Central facial paralysis** spares the forehead (e.g., forehead wrinkles will still be apparent on the affected side) because the nucleus that innervates the upper face has overlapping dual innervation by corticobulbar fibers originating in bilateral cerebral hemispheres. The infant with central facial paralysis usually has other manifestations of intracranial injury, most often 6th nerve palsy from the proximity of the 6th and 7th cranial nerve nuclei in the brainstem. Prognosis depends on whether the nerve was injured by pressure or the nerve fibers were torn; improvement occurs within a few weeks in the former case. Care of the exposed eye is essential. Neuroplasty may be indicated when the paralysis is persistent. Facial palsy may be confused with absence of the depressor muscles of the mouth, which is a benign problem or with variants of Möbius syndrome.

Other peripheral nerves are seldom injured in utero or at birth except when they are involved in fractures or hemorrhage.

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CHAPTER 121

Neonatal Resuscitation and Delivery Room Emergencies

Jennifer M. Brady, Beena D. Kamath-Rayne

Most infants complete the transition to extrauterine life without difficulty; however, a small proportion require resuscitation after birth (Fig. 121.1). For a newborn infant, the need for resuscitation is often caused by a problem with respiration leading to inadequate ventilation. This is in contrast to an adult cardiac arrest, which is usually caused by inadequate circulation. The goals of neonatal resuscitation are to reestablish adequate spontaneous respirations, obtain adequate cardiac output, and prevent the morbidity and mortality associated with hypoxic-ischemic tissue (brain, heart, kidney) injury. High-risk situations should be *anticipated* from pregnancy history and labor. Improved perinatal care and prenatal diagnosis of fetal anomalies allow for appropriate maternal transports for high-risk deliveries. Infants who are born limp, cyanotic, apneic, or pulseless require immediate resuscitation before assignment of the 1 min Apgar score. Rapid and appropriate resuscitative efforts improve the likelihood of preventing brain damage and achieving a successful outcome.

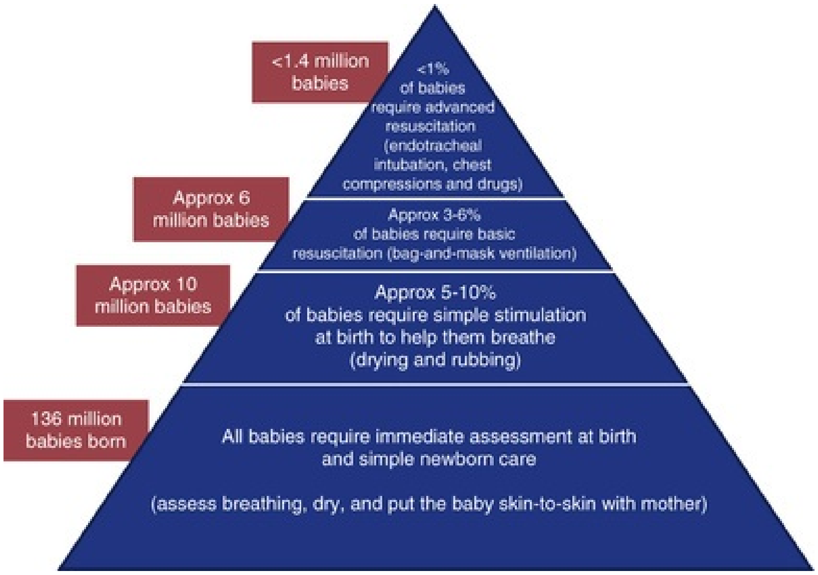
<1.4 million babies
<1% of babies require advanced resuscitation (endotracheal intubation, chest compressions and drugs)
Approx 6 million babies
Approx 3-6% of babies require basic resuscitation (bag-and-mask ventilation)
Approx 10 million babies
Approx 5-10% of babies require simple stimulation at birth to help them breathe (drying and rubbing)
136 million babies born
All babies require immediate assessment at birth and simple newborn care
(assess breathing, dry, and put the baby skin-to-skin with mother)

FIG. 121.1 **Estimates of infants requiring resuscitation at birth. (From Wall SN, Lee ACC, Niermeyer S, et al: Neonatal resuscitation in low-resource settings: what, who, and how to overcome challenges to scale up? *Int J Gynaecol Obstet* 107:S47–S64, 2009, Fig 1.)**

Neonatal Resuscitation

See also Chapter 81 .

Guidelines for the **Neonatal Resuscitation Program (NRP)** are based on recommendations from the International Liaison Committee on Resuscitation Consensus on Treatment Recommendations. These recommendations propose an *integrated* assessment/response approach for the initial evaluation of an infant, consisting of simultaneous assessment of infant general appearance and risk factors. The fundamental principles include evaluation of the airway and establishing effective respirations and adequate circulation. The guidelines also highlight the assessment and response to the neonatal heart rate.

Before the birth of a baby, sufficient preparation for the birth should occur. At least 1 individual capable of neonatal resuscitation should be present at the delivery, and if advanced resuscitation is anticipated, more individuals should be available to help. Necessary equipment should be available, which routinely includes: a warmer bed, blankets, infant hat, stethoscope, bulb suction, suction catheter with wall suction, bag-mask device, oxygen source with blender, pulse oximeter, laryngoscope with blade, and endotracheal tubes (ETTs). Based on the specific details of the pregnancy, further equipment that may be needed should be anticipated and readily available. The equipment should be checked to make sure it is functioning appropriately. Team members should introduce themselves, define a team leader, assign roles for the resuscitation, and discuss what actions they will take during the resuscitation. For complex resuscitations, there may be 1 individual whose sole job is to keep track of time and record what interventions are taken, both to ensure the correct steps are performed in a timely manner and to review during debriefing later.

Immediately after birth, all term infants should be dried, warmed, and stimulated. If the infant does not need resuscitation, these steps can occur on the mother's abdomen while delayed cord clamping is taking place. Simultaneously, the infant's tone, respiratory effort, and heart rate should be assessed (Fig. 121.2).

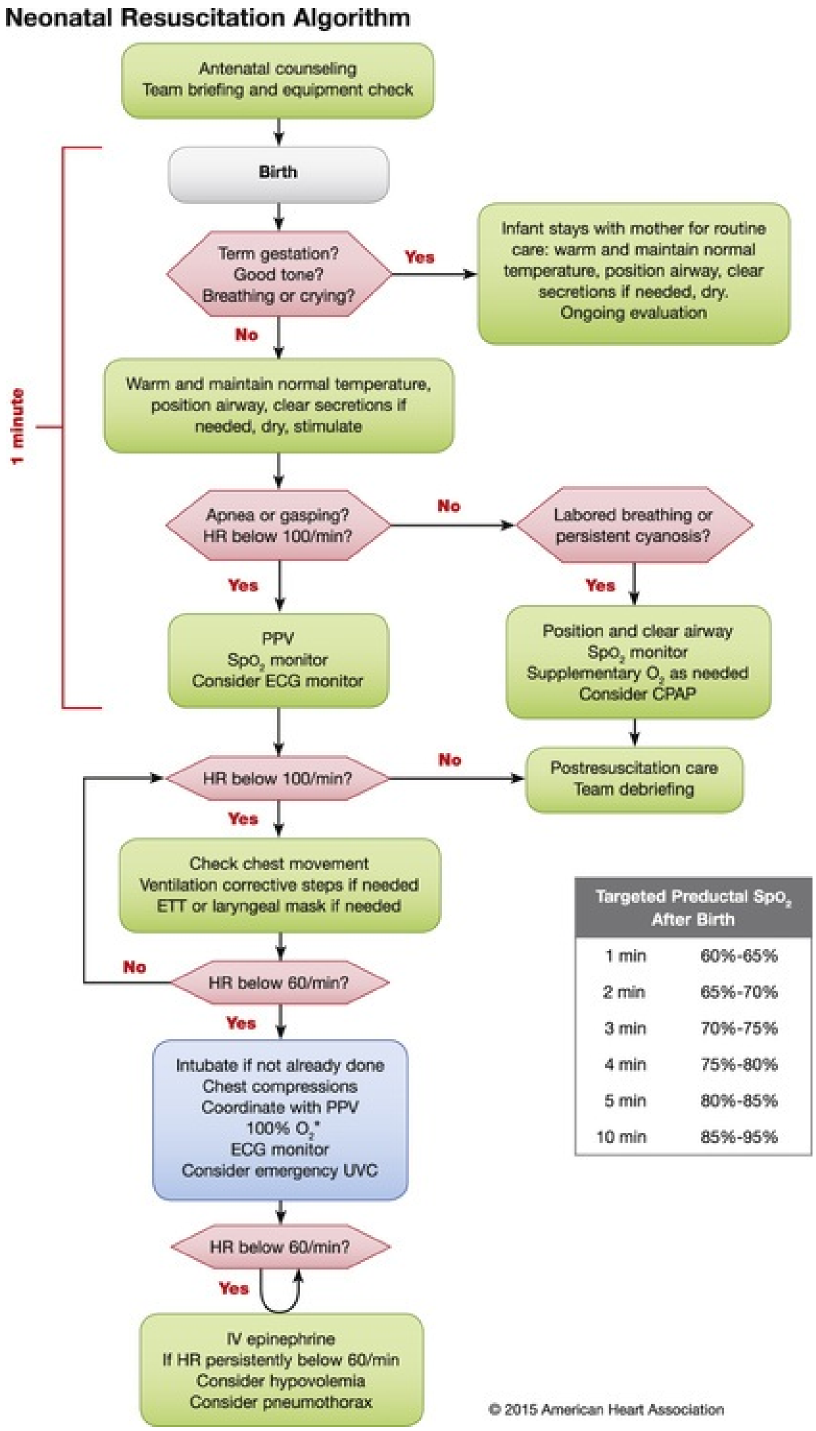
Neonatal Resuscitation Algorithm
Antenatal counseling
Team briefing and equipment check
1 minute
Birth
Term gestation?
Good tone?
Breathing or crying?
Yes
Infant stays with mother for routine care: warm and maintain normal temperature, position airway, clear secretions if needed, dry.
Ongoing evaluation
No
Warm and maintain normal temperature, position airway, clear secretions if needed, dry, stimulate
Apnea or gasping?
HR below 100/min?
No
Labored breathing or persistent cyanosis?
Yes
PPV
SpO₂ monitor
Consider ECG monitor
Yes
Position and clear airway
SpO₂ monitor
Supplementary O₂ as needed
Consider CPAP
HR below 100/min?
No
Postresuscitation care
Team debriefing
Yes
Check chest movement
Ventilation corrective steps if needed
ETT or laryngeal mask if needed
No
HR below 60/min?
Yes
Intubate if not already done
Chest compressions
Coordinate with PPV
100% O₂*
ECG monitor
Consider emergency UVC
HR below 60/min?
Yes
IV epinephrine
If HR persistently below 60/min
Consider hypovolemia
Consider pneumothorax

Targeted Preductal SpO_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%

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FIG. 121.2 **Newborn resuscitation algorithm. CPAP, Continuous positive airway pressure; ETT, endotracheal tube; HR, heart rate; IV, intravenous; PPV, positive pressure ventilation; UVC, umbilical venous catheter. *At this point in resuscitation 100% oxygen is instituted. (From Wyckoff MH, Aziz K, Escobedo MB, et al. Part 13. Neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care, *Circulation* 132(Suppl 2):S542–S560, 2015, Fig 1.)**

Failure to initiate or sustain respiratory effort is fairly common at birth, with

5–10% of births requiring some intervention. Infants with **primary apnea** respond to stimulation by establishing normal breathing. Infants with **secondary apnea** require some ventilatory assistance in order to establish spontaneous respiratory effort. Secondary apnea usually originates in the central nervous system (CNS) as a result of asphyxia or peripherally because of neuromuscular disorders. The lungs in infants affected by conditions such as pulmonary hypoplasia and prematurity may be noncompliant, and initial efforts to begin respirations may be inadequate to initiate sufficient ventilation.

The steps in neonatal resuscitation follow the ABCs: **A,** anticipate and establish a patent **airway** by positioning the baby with the head slightly extended, sniffing position, and suctioning if secretions are blocking the airway; **B,** initiate **breathing** first by using tactile stimulation, followed by positive pressure ventilation (PPV) with a bag-mask device and ETT insertion should the baby remain apneic or PPV is not achieving effective ventilation; and **C,** maintain the **circulation** with chest compressions and medications, if needed. Fig. 121.2 outlines the steps to follow for immediate neonatal evaluation and resuscitation.

In term infants after stimulation, if no respirations are noted, or if the heart rate is <100 beats/min, PPV should be given through a tightly fitted and appropriately sized bag-mask device. PPV should be initiated at pressures of approximately 20 cm H_2O at a rate of 40-60 breaths/min initially with 21% fraction of inspired oxygen (FIO_2) for full-term infants.

At the same time PPV is initiated, a pulse oximeter should be placed on the right hand (preductal) and cardiac leads placed on the chest. In the past the recommended inspired gas for neonatal resuscitation had been 100% oxygen. However, resuscitation with room air in *term infants* is equally effective and may reduce the risk of hyperoxia, which is associated with decreased cerebral blood flow and generation of oxygen free radicals. Room air is the preferred *initial gas* for neonatal resuscitation in term infants. O_2 concentration administered should then be titrated as needed to obtain expected O_2 saturations in a term infant after birth, as defined by normal reference range by minute of life (see Fig. 121.2).

Successful and effective ventilation is signified by adequate chest rise, symmetric breath sounds, improved pink color, heart rate >100 beats/min, increasing O_2 saturation, spontaneous respirations, and improved tone. *If after 30 sec of providing PPV there are no signs of effective ventilation, corrective steps should be performed to improve ventilation.* The 6 ventilation corrective steps can be remembered with the mnemonic **MRSOPA** : *m* ask readjustment, *r* eposition the head, *s* uction mouth and nose, *o* pen the mouth, *p* ressure increase, and *a* lternative airway).

In infants with severe respiratory depression who do not respond to PPV by bag-mask, after corrective steps have been taken, endotracheal intubation should be performed. For infants with an otherwise normal airway weighing <1,000 g, ETT size is usually 2.5 mm; for infants 1,000-2,000 g, 3 mm; and for infants >2,000 g, 3.5 mm. A general rule for depth of insertion from upper lip in centimeters is 6 plus infant's weight in kilograms. Poor response to ventilation may be a result of a loosely fitted mask, poor positioning of the ETT, esophageal intubation, airway obstruction, insufficient pressure, pleural effusions, pneumothorax, excessive air in the stomach leading to abdominal competition, asystole, hypovolemia, diaphragmatic hernia, or prolonged intrauterine asphyxia. Various devices to detect exhaled CO_2 and to confirm accurate ETT placement are available. A laryngeal mask airway may also be an effective tool to establish an airway, especially if PPV is ineffective and intubation attempts are unsuccessful.

The underlying cause for the vast majority of infants having a low heart rate is not a primary cardiac cause, but instead the result of **ineffective ventilation** . Therefore, if the heart rate remains <60 beats/min after 60 sec of PPV with corrective MRSOPA steps, the infant should be intubated (if not already done) to achieve effective ventilation. *Once the infant is intubated, if the heart rate remains <60 beats/min, chest compressions should be initiated with continued ventilation, and* F_{IO_2} *increased to 100%.* Chest compressions should be initiated over the lower third of the sternum at a rate of 90/min. The ratio of compressions to ventilation is 3 : 1 (90 compressions:30 breaths). A provider, separate from the person providing ventilation, is needed to administer chest compressions. Two different techniques exist for performing chest compressions: the thumb technique and the 2-finger technique. For the *thumb technique* the tips of both thumbs are used to depress the sternum, with the fingers on each side encircling the chest; this is the preferred method to administer chest compressions, because it has been shown to achieve a higher blood pressure, increase coronary perfusion, and result in less fatigue. The *2-finger technique* involves depressing the sternum with the tips of the middle finger and index finger while supporting the back with the palm of the other hand. In infants, regardless of whether an alternative airway has been secured, chest compressions are always coordinated with PPV. Chest compressions should continue uninterrupted for 45-60 sec before reassessing heart rate to determine next steps.

Medications are rarely required, but **epinephrine** should be administered when the heart rate is <60 beats/min after 60 sec of combined ventilation and chest compressions or during asystole. Persistent **bradycardia** in neonates is usually attributable to hypoxia resulting from respiratory arrest and often responds rapidly to effective ventilation alone. Persistent bradycardia despite what appears to be adequate resuscitation suggests inadequate ventilation or more severe cardiac compromise.

The umbilical vein can generally be readily cannulated and is the preferred method for administration of medications and volume expanders during neonatal resuscitation (Fig. 121.3). The ETT may be used for the administration of epinephrine if intravenous access is not yet available. Epinephrine (1 : 10,000 solution at 0.1-0.3 mL/kg *intravenously* or 0.5-1 mL/kg *intratracheally*) is given for asystole or for continued heart rate <60 beats/min after 60 sec of combined resuscitation. The dose may be repeated every 3-5 min. If adequate resuscitation continues for 10 min without a detectable heart rate, it is reasonable to stop resuscitative efforts.

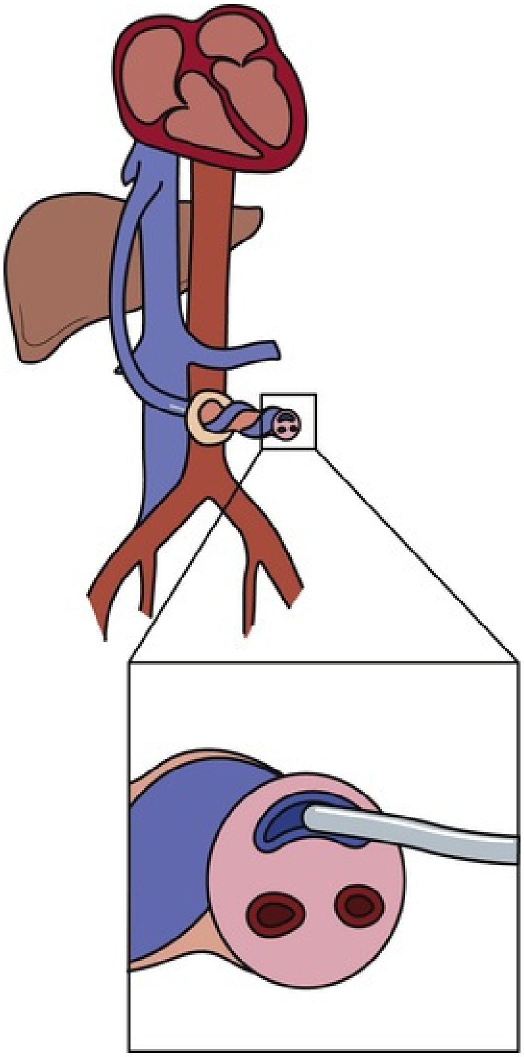

FIG. 121.3 Emergently placed umbilical venous catheter suitable for neonatal resuscitation.

Resuscitation of the Preterm Infant

Resuscitation of the preterm infant should follow the same steps as a term infant, with some special considerations. Whereas resuscitation of term infants should start with room air, resuscitation of most preterm infants can be initiated with slightly higher FIO_2, 21–30%. Pulse oximetry of the preductal (right) hand should be used to titrate O_2 concentrations for targeted saturations per the NRP algorithm (see Fig. 121.2).

Special attention should be paid to *keeping the preterm infant warm in the delivery room*. Quality improvement projects have initiated bundles to improve admission temperatures of preterm infants to the neonatal intensive care unit (NICU) and have included such interventions as higher ambient temperatures in the delivery room, immediate placement of preterm infants into a plastic bag or under plastic wrap rather than drying, and exothermic mattress for resuscitation and transport of the preterm infant.

Delayed cord clamping for 1-3 min can be performed in both preterm and term infants but is especially recommended for preterm infants. Benefits to term infants include higher hemoglobin levels at birth with improved iron stores in the 1st several mo of life. Additional benefits for preterm infants include improved hemodynamic stability, decreased need for inotropic support, decreased need for transfusions, and decreased risk of necrotizing enterocolitis and intraventricular hemorrhage. The American College of Obstetricians and Gynecologists (ACOG) recommends at least 30-60 sec of delayed cord clamping after birth for vigorous term and preterm infants. It is unclear, however, whether delayed cord clamping should be continued when an infant requires resuscitation. Studies are investigating whether the onset of respirations before delayed cord clamping is beneficial for both hemodynamic stability and decreased neonatal mortality.

Special Circumstances in the Delivery Room

Meconium

Meconium staining of the amniotic fluid may be an indication of fetal stress. Previously, the presence of meconium-stained amniotic fluid in a *nonvigorous* infant required tracheal intubation to attempt to aspirate meconium below the cords; NRP recommendations (7th edition) no longer support this practice. If an infant is born through meconium-stained amniotic fluid, it does not matter whether they are vigorous or nonvigorous; the infant should receive the same initial steps of basic resuscitation and should be assessed as any other infant. Tracheal intubation may delay the initiation of effective PPV, which will help the baby to breathe and achieve effective gas exchange.

Placental Abruption

Placental abruption (abruptio placentae) at birth can lead to massive fetal blood loss and a hypovolemic, anemic infant at delivery. Infants can present pale and apneic with poor tone, decreased perfusion, and bradycardia. In addition to performing routine neonatal resuscitation, when an infant is suspected to be symptomatic from a placental abruption, an emergency low-lying umbilical venous catheter (UVC) should be placed and emergent type O Rh-negative blood should be obtained. In acute blood loss, the blood should be administered as quickly as possible in 10 mL/kg aliquots in the delivery room**.** Adequate communication between obstetrics and pediatrics regarding suspected abruption is crucial to early recognition and treatment of the infant.

Neonatal Encephalopathy

Infants with neonatal encephalopathy are born with abnormal neurologic function, including level of consciousness, muscle tone, and reflexes. Although there are many possible etiologies, when symptoms are accompanied by a defined perinatal event such as cord prolapse or placental abruption, **hypoxic-ischemic brain injury** is the presumed cause. These infants are often born with impaired respiratory drive. In addition to routine neonatal resuscitation, term infants with concern for neonatal encephalopathy should be passively cooled in the delivery room by not turning on the warmer bed. After initial resuscitation and stabilization, a more thorough neurologic examination can be performed to assess if the infant meets formal criteria for moderate to severe encephalopathy in order to proceed with whole body cooling (see Chapter 120.4).

Airway Obstruction

Hypoplasia of the mandible with posterior displacement of the tongue may result in upper airway obstruction (Pierre Robin, Stickler, DiGeorge, and other syndromes; see Chapter 337). Symptoms may sometimes be temporarily relieved by pulling the tongue or mandible forward or placing the infant in the prone position. Other rare causes of upper airway obstruction at birth include laryngeal atresia or stenosis, teratomas, hygromas, and oral tumors. Critical fetal and then neonatal airway obstruction represents an emergency in the delivery room. High-risk perinatal care has led to the more frequent prenatal diagnosis of these disorders. When diagnosed prenatally, planning can identify the location of delivery and interventions available at delivery. The **ex utero intrapartum treatment (EXIT)** procedure allows time to secure the airway in an infant known prenatally to have critical airway obstruction, before the infant is separated from the placenta (Fig. 121.4). Uteroplacental gas exchange is maintained throughout the procedure.

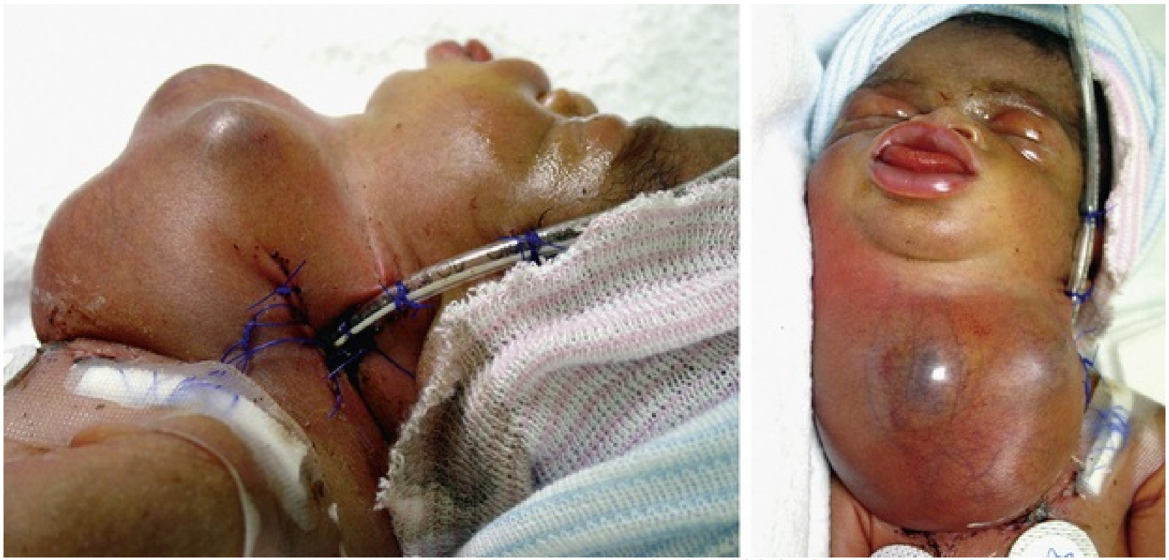

FIG. 121.4 **EXIT procedure. Baby with teratoma and critical high airway obstruction syndrome. Trachea is displaced to the lateral neck. (Courtesy of Dr. Mark Wulkan, Pediatric Surgery, Emory University.)**

Respiratory Distress

Both congenital abnormalities and iatrogenic causes secondary to required resuscitation can contribute to respiratory distress in the neonate. A **scaphoid abdomen** suggests a diaphragmatic hernia**,** as does asymmetry in contour or movement of the chest. An infant with a known diaphragmatic hernia should be immediately intubated in the delivery room and an orogastric tube placed to avoid gaseous distention of the bowel from crying or PPV. The infant should then be transferred to a tertiary referral center for surgical evaluation and treatment (see Chapter 122.1).

In infants with a prenatal diagnosis of hydrops, pleural effusions may be present at delivery, preventing adequate lung expansion and gas exchange. Similarly, infants requiring PPV in the delivery room are at risk for developing a **pneumothorax** . Infants with pulmonary hypoplasia or meconium-stained fluid are at increased risk of this complication. Clinically, infants with a pleural effusion or pneumothorax present with respiratory distress and hypoxia, with *diminished* breath sounds on the affected side. Transillumination may be helpful to confirm the diagnosis. Emergency evacuation of a pneumothorax or pleural effusion without radiographic confirmation is indicated in an infant who is unresponsive to resuscitation efforts and has asymmetric breath sounds, bradycardia, and cyanosis. An angiocatheter attached to a stopcock and syringe should be used for evacuation. For a pneumothorax, an angiocatheter should be inserted perpendicular to the chest wall above the rib in the 2nd intercostal space in the midclavicular line and air evacuated. For a pleural effusion, with the infant in the supine position, the angiocatheter should be inserted in the 4th or 5th intercostal space in the anterior axillary line and directed posteriorly to evacuate the fluid (see Chapter 122).

Abdominal Wall and Neural Tube Defects

Appropriate management of patients with abdominal wall defects (omphalocele, gastroschisis) in the delivery room prevents excessive fluid loss and minimizes the risk for injury to the exposed viscera. **Gastroschisis** is the more common defect, and typically the intestines are not covered by a membrane. The exposed intestines should be gently placed in a sterile clear plastic bag after delivery. A membrane often covers an **omphalocele** , and care should be taken to prevent its rupture. A nasogastric tube should be placed and the infant transferred to a tertiary referral center for surgical consultation and evaluation for associated anomalies (see Chapter 125).

Similarly, infants born with neural tube defects such as a **myelomeningocele** need special care at delivery to protect the exposed neural tube tissue from trauma and infection; infants should be placed on their side or abdomen for resuscitation. The site of the neural tube defect should be covered with a moist sterile dressing to prevent drying and infection. The infant should then be transferred to a tertiary referral center for surgical evaluation and treatment.

Injury During Delivery

Central Nervous System

Both extracranial and intracranial birth injuries can be seen in infants after birth. **Extracranial** lesions include cephalohematoma, caput succedaneum, and subgaleal hemorrhage. **Intracranial** birth injuries include subdural hemorrhage, subarachnoid hemorrhage, and epidural hematoma. The most common intracranial injury experienced at birth is **subdural hemorrhage** , with increasing incidence seen with instrument-assisted vaginal deliveries (see Chapters 120.1 and 120.2).

Fractures

The clavicle is the most frequently fractured bone during labor and delivery. It is particularly vulnerable to injury with difficult delivery of the shoulder in the setting of **shoulder dystocia** , as well as with extended arms in breech deliveries. In the treatment of shoulder dystocia, the obstetrician may intentionally fracture the clavicle so that delivery can proceed. Symptoms of a clavicular fracture include an infant not moving the arm freely on the affected side, palpable crepitus or bony irregularity, and asymmetric or absent Moro reflex on the affected side. The prognosis for this fracture is excellent. Often, no specific treatment is needed, although in some cases the arm and shoulder on the affected side are immobilized for comfort.

Fractures of the long bones are fairly rare. Injuries often present with absent spontaneous movement of the extremity. Associated nerve involvement may also occur. Treatment involves immobilization of the affected extremity with a splint and orthopedic follow-up.

Brachial Plexus Injuries

Brachial plexus injuries result from stretching and tearing of the brachial plexus (spinal roots C5-T1) at delivery. Although shoulder dystocia is associated with an increased risk of brachial plexus injury, it can also occur during a routine delivery (see Chapter 120.6).

Ongoing Care After Resuscitation

The “golden hour” after a baby's birth should emphasize effective neonatal resuscitation, postresuscitation care, prevention of hypothermia, immediate breastfeeding if able, prevention of hypoglycemia, and therapeutic hypothermia for cases of moderate to severe neonatal encephalopathy (birth asphyxia). After supportive measures have stabilized the infant's condition, a specific diagnosis should be established and appropriate continuing treatment instituted.

After initial resuscitation and stabilization, an infant with a significant metabolic acidosis may potentially require further treatment with sodium bicarbonate and/or 10 mL/kg of volume expander. If infection is suspected, appropriate antibiotics should be started as soon as possible. Severe neonatal encephalopathy may also depress myocardial function and cause cardiogenic shock despite the recovery of heart and respiratory rates. Fluids and dopamine or epinephrine as a continuous infusion should be started after initial resuscitation efforts, to improve cardiac output in an infant with poor peripheral perfusion, weak pulses, hypotension, tachycardia, or poor urine output. Regardless of the severity of neonatal encephalopathy or the response to resuscitation, asphyxiated infants should be monitored closely for signs of multiorgan hypoxic-ischemic tissue injury (see Chapter 120.4).

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CHAPTER 122

Respiratory Tract Disorders

Shawn K. Ahlfeld

Respiratory disorders are the most frequent cause of admission for neonatal intensive care in both term and preterm infants. Signs and symptoms of respiratory distress include cyanosis, expiratory grunting, nasal flaring, retractions, tachypnea, decreased breath sounds with or without rales and/or rhonchi, and pallor. A wide variety of pathologic lesions may be responsible for respiratory disturbances, including pulmonary, airway, cardiovascular, central nervous system, infectious, and other disorders (Fig. 122.1).

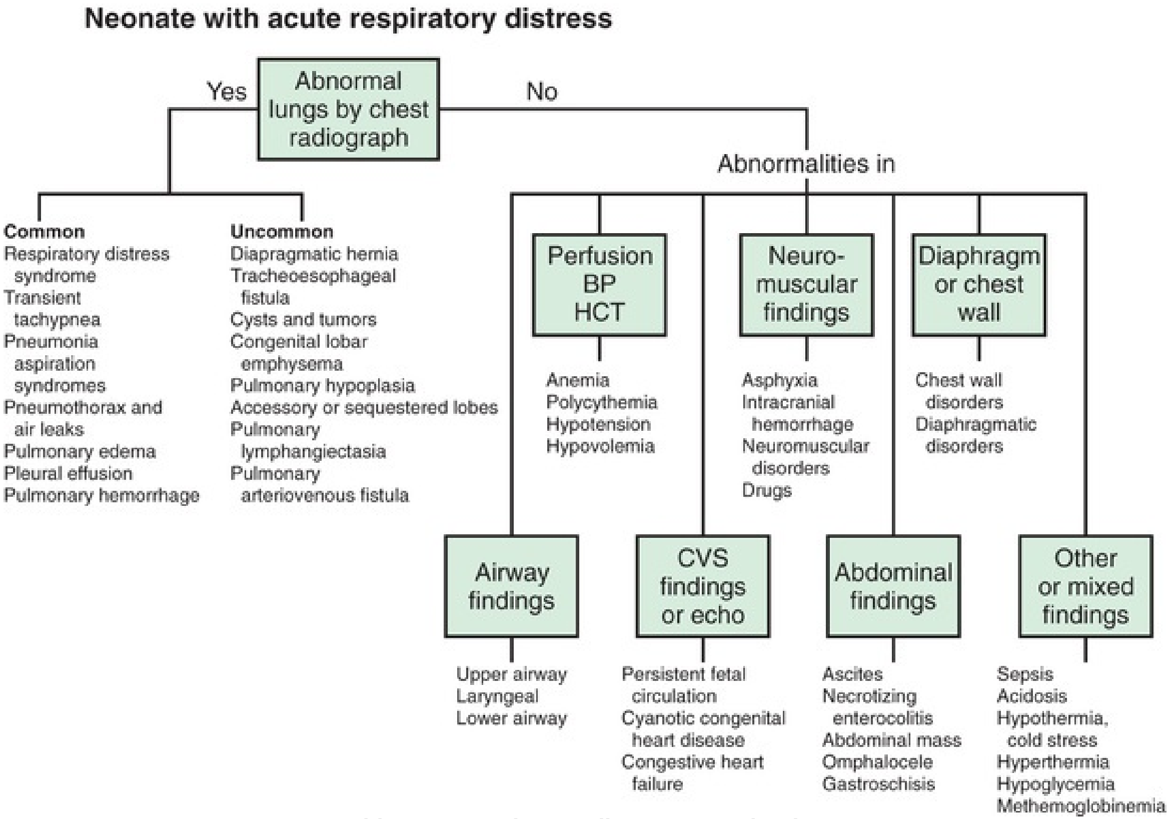
Neonate with acute respiratory distress
Abnormal lungs by chest radiograph
Yes
No
Common
Respiratory distress syndrome
Transient tachypnea
Pneumonia aspiration syndromes
Pneumothorax and air leaks
Pulmonary edema
Pleural effusion
Pulmonary hemorrhage
Uncommon
Diapragmatic hernia
Tracheoesophageal fistula
Cysts and tumors
Congenital lobar emphysema
Pulmonary hypoplasia
Accessory or sequestered lobes
Pulmonary lymphangiectasia
Pulmonary arteriovenous fistula
Abnormalities in
Perfusion BP HCT
Anemia
Polycythemia
Hypotension
Hypovolemia
Neuro-muscular findings
Asphyxia
Intracranial hemorrhage
Neuromuscular disorders
Drugs
Diaphragm or chest wall
Chest wall disorders
Diaphragmatic disorders
Airway findings
Upper airway
Laryngeal
Lower airway
CVS findings or echo
Persistent fetal circulation
Cyanotic congenital heart disease
Congestive heart failure
Abdominal findings
Ascites
Necrotizing enterocolitis
Abdominal mass
Omphalocele
Gastroschisis
Other or mixed findings
Sepsis
Acidosis
Hypothermia, cold stress
Hyperthermia
Hypoglycemia
Methemoglobinemia

FIG. 122.1 **Neonate with acute respiratory distress. BP, Blood pressure; CVS, cardiovascular system; HCT, hematocrit. (From Battista MA, Carlo WA: Differential diagnosis of acute respiratory distress in the neonate. In Frantz ID, editor: *Tufts University of School of Medicine and Floating Hospital for Children reports on neonatal respiratory diseases,* vol 2, issue 3, Newtown, PA, 1992, Associates in Medical Marketing Co.)**

It is occasionally difficult to distinguish respiratory from nonrespiratory etiologies on the basis of clinical signs alone. Signs of respiratory distress are an indication for a physical examination and diagnostic evaluation, including determination of ventilation by arterial blood gases and oxygenation by pulse oximetry, and assessment of lung fields with chest radiography. Timely and appropriate therapy is essential to improve outcome.

122.1

Transition to Pulmonary Respiration

Shawn K. Ahlfeld

Keywords

fetal lung fluid
functional residual capacity
positive pressure ventilation
surfactant
periodic breathing

Successful establishment of adequate lung function at birth depends on airway patency, functional lung development, and maturity of respiratory control. *Fetal lung fluid* must be removed and replaced with gas. This process begins before birth as active sodium transport across the pulmonary epithelium drives liquid from the lung lumen into the interstitium with subsequent absorption into the vasculature. Increased levels of circulating catecholamines, vasopressin, prolactin, and glucocorticoids enhance lung fluid adsorption and trigger the change in lung epithelia from chloride secretion to sodium reabsorption. **Functional residual capacity (FRC)** must be established and maintained to develop a ventilation-perfusion relationship that will provide optimal exchange of oxygen and carbon dioxide between alveoli and blood.

The First Breath

Initiation of the first breath is caused by a decline in arterial oxygen tension (PaO_2) and pH and a rise in arterial carbon dioxide partial tension ($PaCO_2$) as a result of interruption of the placental circulation, redistribution of cardiac output, decrease in body temperature, and various tactile and sensory inputs. The relative contributions of these stimuli to the onset of respiration are uncertain.

Although spontaneously breathing infants do not need to generate an opening pressure to create airflow, infants requiring **positive pressure ventilation (PPV)** at birth need an opening pressure of 13-32 cm H_2O and are more likely to establish FRC if they generate a spontaneous, negative pressure breath. Expiratory esophageal pressures associated with the 1st few spontaneous breaths in term newborns range from 45-90 cm H_2O. This high pressure, caused by expiration against a partially closed glottis, may aid in the establishment of FRC but would be difficult to mimic safely with artificial ventilation. The higher pressures needed to initiate respiration are required to overcome the opposing forces of surface tension (particularly in small airways) and the viscosity of liquid remaining in the airways, as well as to introduce about 50 mL/kg of air into the lungs, 20-30 mL/kg of which remains after the first breath to establish FRC. **Surfactant** lining the alveoli enhances the aeration of gas-free lungs by reducing surface tension, thereby lowering the pressure required to open alveoli. Air entry into the lungs displaces fluid, decreases hydrostatic pressure in the pulmonary vasculature, and increases pulmonary blood flow. The greater blood flow in turn increases the blood volume of the lung and the effective vascular surface area available for fluid uptake. The remaining fluid is removed by the pulmonary lymphatics, upper airway, mediastinum, and pleural space. Fluid removal may be impaired after cesarean birth or as a result of surfactant deficiency, endothelial cell damage, hypoalbuminemia, high pulmonary venous pressure, or neonatal sedation.

Compared with term infants, preterm infants have a very compliant chest wall and may be at a disadvantage in establishing FRC. Abnormalities in ventilation-perfusion ratio are greater and persist for longer periods in preterm infants and may lead to hypoxemia and hypercarbia as a result of atelectasis, intrapulmonary shunting, hypoventilation, and gas trapping. The smallest immature infants have the most profound disturbances as a consequence of **respiratory distress syndrome (RDS)** . However, even in healthy term infants, oxygenation is impaired immediately after birth, and oxygen saturation (SO_2) gradually increases and exceeds 90% only at about 5 min. In addition, because of the relatively high pulmonary arterial pressure present in the fetal lung, right-to-left shunting across the ductus arteriosus is common soon after birth. If pulse oximetry is performed soon after birth, the recommendation is to measure preductal SO_2 in the right upper extremity.

Breathing Patterns in Newborns

During sleep in the 1st few mo after birth, normal full-term infants (and more frequently preterm infants) may have episodes when regular breathing is interrupted by short pauses. This **periodic breathing** pattern is characterized by brief episodes of respiratory pauses lasting 5-10 sec, followed by a burst of rapid respirations at a rate of 50-60 breaths/min for 10-15 sec. The brief interruptions in respiration are not associated with change in color or heart rate. Periodic breathing is a normal characteristic of neonatal respiration and has no prognostic significance.

122.2

Apnea

Shawn K. Ahlfeld

Keywords

- apnea
- mixed apnea
- central apnea
- obstructive apnea
- apnea of prematurity
- nasal continuous positive airway pressure
- heated humidified high-flow nasal cannula
- methylxanthines
- caffeine
- gastroesophageal reflux
- home monitoring
- sudden infant death syndrome

Apnea is a prolonged cessation of respiration and must be distinguished from **periodic breathing** because apnea is often associated with serious illness. Although there is no universal agreement, apnea is usually defined as cessation of breathing for a period of ≥20 sec, or a period <20 sec that is associated with a change in tone, pallor, cyanosis, or bradycardia (<80-100 beats/min). Based on the absence of respiratory effort and/or airflow, apnea can be obstructive, central, or mixed. **Obstructive apnea** (pharyngeal instability, neck flexion) is characterized by absence of airflow but persistent chest wall motion. Pharyngeal collapse may follow the negative airway pressures generated during inspiration, or it may result from incoordination of the tongue and other upper airway muscles involved in maintaining airway patency. **Central apnea,** which is caused by decreased central nervous system (CNS) stimuli to respiratory muscles, results in both airflow and chest wall motion being absent. Gestational age is the most important determinant of respiratory control, with the frequency of central apnea being inversely related to gestational age. The immaturity of the brainstem respiratory centers is manifest by an attenuated response to CO_2 and a paradoxical response to hypoxia that results in central apnea rather than hyperventilation. **Mixed apnea** is most often observed in **apnea of prematurity** (50–75% of cases), with obstructive apnea preceding central apnea. Short episodes of apnea are usually central, whereas prolonged ones are often mixed. Apnea depends on the sleep state; its frequency increases during active (rapid eye movement) sleep.

Although apnea is usually observed in preterm infants as a result of immature respiratory control or an associated illness, apnea in term infants is uncommon, often associated with serious pathology, and demands prompt diagnostic evaluation. Apnea accompanies many primary diseases that affect neonates (Table 122.1). These disorders produce apnea by direct depression of CNS control of respiration (hypoglycemia, meningitis, drugs, intracranial hemorrhage, seizures), disturbances in oxygen delivery (shock, sepsis, anemia), or ventilation defects (obstruction of the airway, pneumonia, muscle weakness).*The term neonate with apnea should receive continuous cardiorespiratory monitoring while performing an assessment for bacterial or viral sepsis/meningitis, intracranial hemorrhage, seizures, and airway instability.* Supportive care and close monitoring are essential while the underlying etiology is ascertained and appropriately treated.

Table 122.1

Potential Causes of Neonatal Apnea and Bradycardia

Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), spinal cord injury after general anesthesia
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature,

	hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center, sleep state Sudden unexpected postnatal collapse

Apnea of Prematurity

Apnea of prematurity results from immature respiratory control, most frequently occurs in infants <34 wk of gestational age (GA), and occurs in the absence of identifiable predisposing diseases. The incidence of idiopathic apnea of prematurity varies inversely with GA. Apnea of prematurity is almost universal in infants born at <28 wk GA, and the incidence rapidly decreases from 85% of infants <30 wk GA to 20% of infants <34 wk GA. The onset of apnea of prematurity can be during the initial days to weeks of age but is often delayed if there is RDS or other causes of respiratory distress. In premature infants without respiratory disease, apneic episodes can occur throughout the 1st 7 postnatal days with equal frequency.

Apnea in preterm infants is defined as cessation of breathing for ≥20 sec or for any duration if accompanied by cyanosis and bradycardia (<80-100 beats/min). The incidence of associated bradycardia increases with the length of the preceding apnea and correlates with the severity of hypoxia. Short apnea episodes (10 sec) are rarely associated with bradycardia, whereas longer episodes (>20 sec) have a higher incidence of bradycardia. **Bradycardia** follows the apnea by 1-2 sec in >95% of cases and is most often sinus, but on occasion it can be nodal. Vagal responses and rarely heart block are causes of bradycardia *without* apnea. Short, self-resolving oxygen desaturation episodes noted with continuous monitoring are normal in neonates, and treatment is not necessary.

Preterm infants born at <35 wk GA are at risk for apnea of prematurity and therefore should receive cardiorespiratory monitoring. Apnea that occurs in the absence of other clinical signs of illness in the 1st 2 wk in a preterm infant is likely apnea of prematurity, and therefore additional evaluation for other etiologies is often unwarranted. However, the onset of apnea in a previously well preterm neonate after the 2nd wk of life (or, as previously, in a term infant at any time) is a critical event that may be associated with serious underlying pathology. Prompt investigation for medication side effects, metabolic derangements, structural CNS anomalies, intracranial hemorrhage, seizures, or sepsis/meningitis is warranted.

Treatment

Gentle tactile stimulation or provision of flow and/or supplemental oxygen by nasal cannula is often adequate therapy for mild and intermittent episodes. **Nasal continuous positive airway pressure** (nCPAP, 3-5 cm H_2 O) and **heated humidified high-flow nasal cannula** (HHHFNC, 1-4 L/min) are appropriate therapies for mixed or obstructive apnea. The efficacy of both nCPAP and HHHFNC is related to their ability to splint the upper airway to prevent airway obstruction. Both are used widely, but nCPAP may be preferred in extremely preterm infants because of its proven efficacy and safety.

Recurrent or persistent apnea of prematurity is effectively treated with **methylxanthines** . Methylxanthines increase central respiratory drive by lowering the threshold of response to hypercapnia as well as enhancing contractility of the diaphragm and preventing diaphragmatic fatigue. Caffeine and theophylline are similarly effective methylxanthines, but caffeine is preferred because of its longer half-life and lower potential for side effects (less tachycardia and feeding intolerance). In preterm infants, caffeine reduces the incidence and severity of apnea of prematurity, facilitates successful extubation from mechanical ventilation, reduces the rate of **bronchopulmonary dysplasia (BPD)** , and improves neurodevelopmental outcomes. Caffeine therapy can be safely administered orally (PO) or intravenously (IV) with an initial loading dose of 20 mg/kg of caffeine citrate followed 24 hr later by once-daily maintenance doses of 5 mg/kg (increased to 10 mg/kg daily as needed for persistent apnea). Because the therapeutic window is wide (therapeutic level: 8-20 µg/mL) and serious side effects associated with caffeine are rare, monitoring of serum drug concentrations are usually unnecessary. Monitoring is primarily through observation of vital signs (tachycardia) and clinical response. Higher doses of caffeine may be more effective without serious adverse events, but additional studies are needed to ensure safety. Retrospective cohort studies suggest that initiation of caffeine in the 1st 3 days of age in extremely preterm infants (<28 wk GA) may improve outcomes. However, it is reasonable to delay caffeine therapy until apnea occurs. Caffeine therapy is usually continued until an infant is free of clinically significant apnea or bradycardia for 5-7 days without positive pressure respiratory support, or at 34 wk postmenstrual age (PMA).

In an infant with significant anemia, transfusion of packed red blood cells (RBCs) increases blood O_2 -carrying capacity, improves tissue oxygenation, and is associated with a short-term reduction in apnea. However, a long-term benefit in regard to apnea appears unlikely. **Gastroesophageal reflux (GER)** is common in neonates, but despite being associated with apnea anecdotally, data *do not* support a causal relationship between GER and apneic events. In preterm infants, medications that inhibit gastric acid production have potentially harmful side effects (increased incidence of sepsis, necrotizing enterocolitis, death) and may actually increase the incidence of apnea and bradycardia. Therefore the routine use of medications that inhibit gastric acid synthesis or promote gastrointestinal motility to reduce the frequency of apnea in preterm infants should be discouraged.

Prognosis

In 92% of infants by 37 wk PMA and in 98% of infants by 40 wk PMA, apnea of prematurity resolves spontaneously. However, infants born well before 28 wk GA may experience apnea and bradycardic events until 44 wk PMA. Beyond 44 wk PMA, extreme events (apnea >30 sec and/or bradycardia <60 beats/min for >10 sec) are very rare. The period that an infant should be observed to ensure resolution of apnea and bradycardia is not defined and among institutions is highly variable. However, many experts would recommend that an infant demonstrate an event-free period of 5-7 days before discharge. Although the nature and severity of events should dictate the length of observation, sufficiently large retrospective cohort studies suggest that a 1-3 day (infants born at ≥30 wk GA), 9-10 day (27-28 wk GA), or 13-14 day (<26 wk GA) event-free period predicts resolution of apnea in up to 95% of infants successfully. Brief, isolated bradycardic episodes associated with oral feeding are common in preterm infants and are generally not considered significant during the event-free period. While not recommended routinely for preterm infants with apnea of prematurity, in *rare* cases an infant with persistent, prolonged apnea may be discharged with home cardiorespiratory monitoring. In the absence of significant events, home monitoring can be safely discontinued at 44 wk PMA. There is no evidence that home monitoring prevents death.

Despite its high frequency in preterm infants, the harm associated with apnea of prematurity is unknown. However, apnea of prematurity does not appear to alter an infant's prognosis unless it is severe, recurrent, and refractory to therapy. Prompt, effective therapy and careful monitoring are vital to avoid prolonged, severe hypoxia, which may increase the risk of death and neurodevelopmental impairment.

Apnea of Prematurity and Sudden Infant Death Syndrome

Although preterm infants are at higher risk for sudden infant death syndrome (SIDS), apnea of prematurity does not further increase that risk. The peak incidence of SIDS occurs earlier in infants born at 24-28 wk GA (47.1 wk PMA vs 53.5 wk PMA). The epidemiologic evidence that placing babies supine during sleep reduces the rate of SIDS deaths by >50% suggests that positioning, and not prematurity, primarily influences the incidence of SIDS. Supine positioning on a firm sleep surface separate from the parents' bed, promotion of breastfeeding, and pacifier use during sleep reduce the incidence of SIDS. Avoidance of cigarette smoke exposure and no parental use of alcohol or illicit drugs during pregnancy and after birth are also important in the prevention of SIDS.

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122.3

Respiratory Distress Syndrome (Hyaline Membrane Disease)

Shawn K. Ahlfeld

Keywords

respiratory distress syndrome
hyaline membrane disease

surfactant
oxygen toxicity
tachypnea
expiratory grunting
nasal flaring
retractions
antenatal corticosteroids
betamethasone
nasal continuous positive airway pressure
heated humidified high-flow nasal cannula
surfactant replacement therapy
mechanical ventilation
bronchopulmonary dysplasia
respiratory compliance
volume-targeted ventilation
pressure-limited ventilation
high-frequency ventilation
permissive hypercapnia
extrapulmonary air leak

Incidence

Respiratory distress syndrome (RDS) occurs primarily in premature infants; its incidence is inversely related to gestational age and birthweight. It occurs in 60–80% of infants <28 wk GA, in 15–30% of those between 32 and 36 wk GA, and rarely in those >37 wk GA. The risk for development of RDS increases with maternal diabetes, multiple births, cesarean delivery, precipitous delivery, asphyxia, cold stress, and a maternal history of previously affected infants. The risk of RDS is reduced in pregnancies with chronic or pregnancy-associated hypertension, maternal heroin use, prolonged rupture of membranes, and antenatal corticosteroid prophylaxis.

Etiology and Pathophysiology

Surfactant deficiency (decreased production and secretion) is the primary cause of RDS. In the absence of pulmonary surfactant, significantly increased alveolar surface tension leads to atelectasis, and the ability to attain an adequate FRC is impaired. As a consequence of progressive injury to epithelial and endothelial cells from atelectasis (atelectrauma), volutrauma, ischemic injury, and oxygen toxicity, effusion of proteinaceous material and cellular debris into the alveolar spaces (forming the classic *hyaline membranes*) further impairs oxygenation. Alveolar atelectasis, hyaline membrane formation, and interstitial edema make the lungs less compliant in RDS, so greater pressure is required to expand the alveoli and small airways. Additionally, compared with the mature infant, the highly compliant chest wall of the preterm infant offers less resistance to the natural tendency of the lungs to collapse. Thus, at end-expiration, the volume of the thorax and lungs tends to approach residual volume. Although surfactant is present in high concentrations in fetal lung homogenates by 20 wk of gestation, it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32 wk. Mature levels of pulmonary surfactant are present usually after 35 wk of gestation.

The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, SP-B, SP-C, and SP-D), and cholesterol (Fig. 122.2). With advancing GA, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells (Fig. 122.3). These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability at end-expiration. Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia, hypotension, and cold stress, may suppress surfactant synthesis. The epithelial lining of the lungs may also be injured by high O_2 concentrations and mechanical ventilation, thereby further reducing secretion of surfactant.

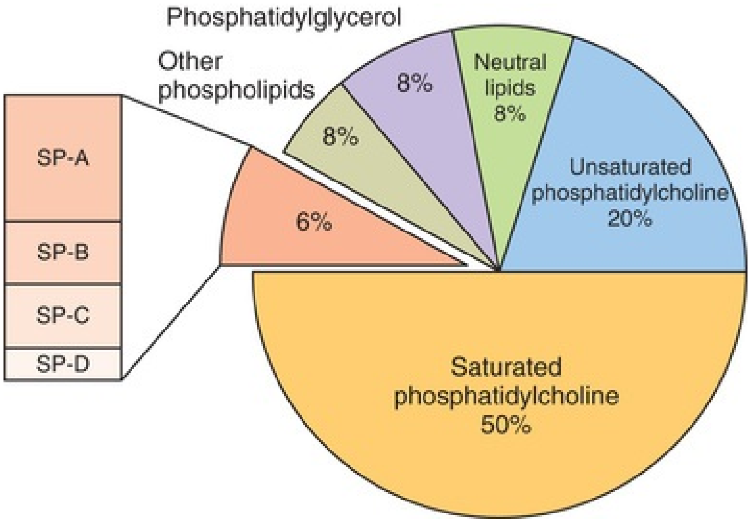

FIG. 122.2 **Composition of surfactant. SP-A, Surfactant-associated protein A; SP-B, surfactant-associated protein B; SP-C, surfactant-associated protein C; SP-D, surfactant-associated protein D. (From Jobe AH, Ikegami M: Biology of surfactant, *Clin Perinatol* 28:655–669, 2001.)**

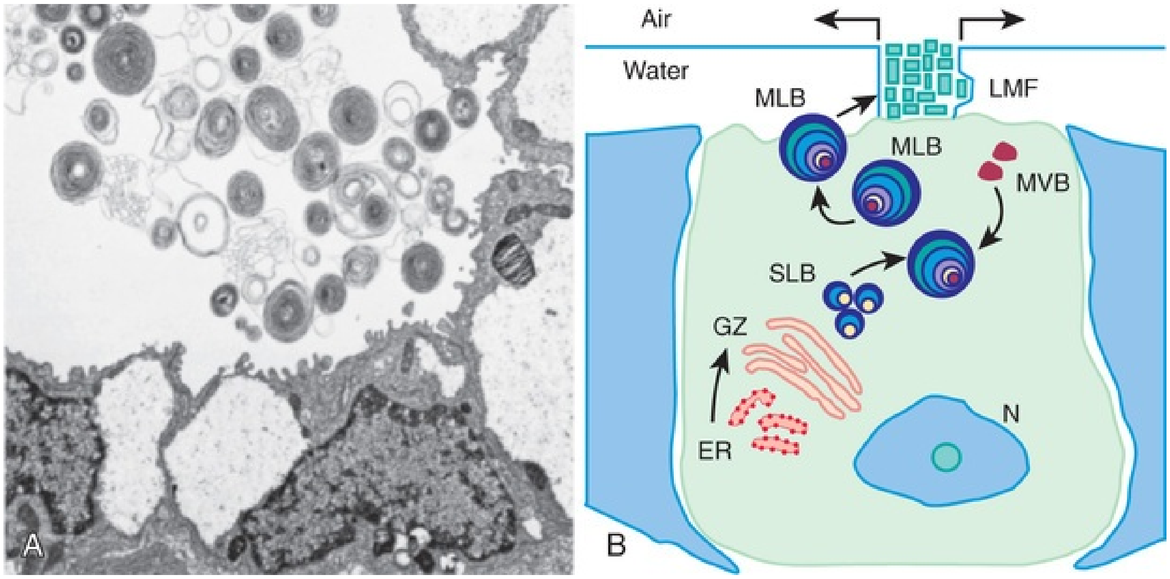

FIG. 122.3 **A,** Fetal rat lung (low magnification), day 20 (term: day 22) showing developing type II cells, stored glycogen *(pale areas),* secreted lamellar bodies, and tubular myelin. **B,** Possible pathway for transport, secretion, and reuptake of surfactant. ER, Endoplasmic reticulum; GZ, Golgi zone; LMF, lattice (tubular) myelin figure; MLB, mature lamellar body; MVB, multivesicular body; N, nucleus; SLB, small lamellar body. (**A,** Courtesy of Mary Williams, MD, University of California, San Francisco; **B,** from Hansen T, Corbet A: Lung development and function. In Taeusch HW, Ballard RA, Avery MA, editors: *Schaffer and Avery's diseases of the newborn,* ed 6, Philadelphia, 1991, Saunders.)

Atelectasis results in perfused but not ventilated alveoli, causing hypoxia. Decreased lung compliance, small tidal volumes, increased physiologic dead space, and insufficient alveolar ventilation eventually result in hypercapnia. The combination of hypercapnia, hypoxia, and acidosis produces pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus and within the lung itself. Progressive injury to epithelial and endothelial cells and formation of hyaline membranes further impairs oxygenation, leading to a vicious cycle of diminished surfactant production, worsening atelectasis, lung injury, and severe hypoxia (Fig. 122.4).

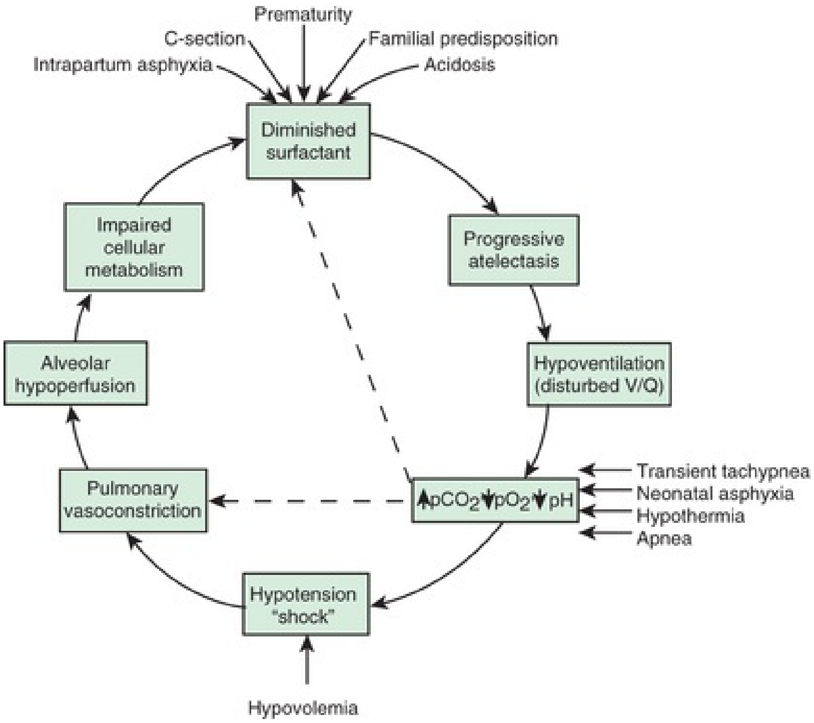
Prematurity
C-section
Familial predisposition
Intrapartum asphyxia
Acidosis
Diminished surfactant
Progressive atelectasis
Hypoventilation (disturbed V/Q)
↑pCO2 ↓pO2 ↓pH
Transient tachypnea
Neonatal asphyxia
Hypothermia
Apnea
Hypotension "shock"
Hypovolemia
Pulmonary vasoconstriction
Alveolar hypoperfusion
Impaired cellular metabolism

FIG. 122.4 **Contributing factors in the pathogenesis of hyaline membrane disease. The potential "vicious circle" perpetuates hypoxia and pulmonary insufficiency. V/Q, Ventilation-perfusion ratio. (From Farrell P, Zachman R: Pulmonary surfactant and the respiratory distress syndrome. In Quilligan EJ, Kretchmer N, editors: *Fetal and maternal medicine,* New York, 1980, Wiley. Reprinted by permission of John Wiley and Sons, Inc.)**

Clinical Manifestations

Signs of RDS usually appear within minutes of birth, although they may not be recognized for several hours in larger premature infants, until rapid, shallow respirations become more obvious. A later onset of tachypnea should suggest other conditions. Some patients require resuscitation at birth because of intrapartum asphyxia or initial severe respiratory distress (especially with birthweight <1,000 g). Characteristically, tachypnea, prominent (often audible) expiratory grunting, intercostal and subcostal retractions, nasal flaring, and cyanosis are noted. Breath sounds may be normal or diminished with a harsh tubular quality, and on deep inspiration, fine crackles may be heard. The natural course of untreated RDS is characterized by progressive worsening of cyanosis and dyspnea. If the condition is inadequately treated, blood pressure may fall; cyanosis and pallor increase, and grunting decreases or disappears, as the condition worsens. *Apnea and irregular respirations are ominous signs requiring immediate intervention.* Untreated patients may also have a mixed respiratory-metabolic acidosis, edema, ileus, and oliguria. Respiratory failure may occur in infants with rapid progression of the disease. In most cases the signs reach a peak within 3 days, after which improvement is gradual. Improvement is often heralded by spontaneous diuresis and improved blood gas values at lower inspired O_2 levels and/or lower ventilator support. Death can result from severe impairment of gas exchange, alveolar air leaks (pulmonary interstitial emphysema, pneumothorax), pulmonary hemorrhage, or intraventricular hemorrhage (IVH).

Diagnosis

The clinical course, chest x-ray findings, and blood gas values help establish the clinical diagnosis. On chest radiograph, the lungs may have a characteristic but not pathognomonic appearance that includes low lung volumes, a diffuse, fine reticular granularity of the parenchyma (ground-glass appearance), and air bronchograms (Fig. 122.5). The initial x-ray appearance is occasionally normal, with the typical pattern developing during the 1st day. Considerable variation in radiographic findings may be seen, especially in infants who have already received treatment with surfactant replacement and/or positive pressure respiratory support; this variation often results in poor correlation between radiographic findings and the clinical course. Blood gas findings are characterized initially by hypoxemia and later by progressive hypoxemia, hypercapnia, and variable metabolic acidosis.

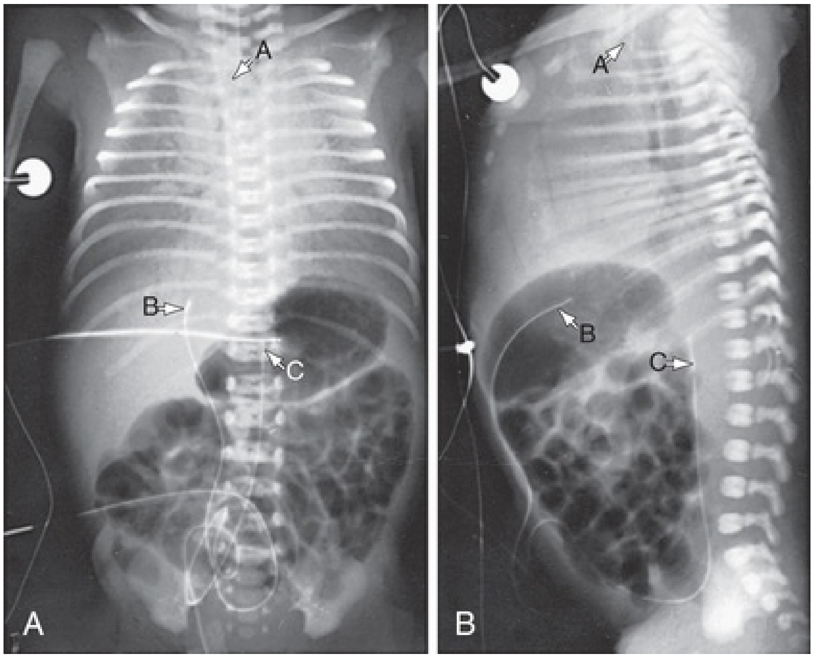

FIG. 122.5 Infant with respiratory distress syndrome. Note the granular lungs, air bronchogram, and air-filled esophagus. A, Anteroposterior, and B, lateral, radiographs are needed to distinguish the umbilical artery from the vein catheter and to determine the appropriate level of insertion. The lateral view clearly shows that the catheter has been inserted into an umbilical vein and is lying in the portal system of the liver. *A* indicates endotracheal tube; *B* indicates the umbilical venous catheter at the junction of the umbilical vein, ductus venosus, and portal vein; *C* indicates the umbilical artery catheter passed up the aorta to T12. (Courtesy of Walter E. Berdon, Babies Hospital, New York City.)

In the differential diagnosis, early-onset sepsis may be indistinguishable from RDS. In neonates with pneumonia, the chest radiograph may be identical to that for RDS. Clinical factors such as maternal group B streptococcal colonization with inadequate intrapartum antibiotic prophylaxis, maternal fever (>38.6°C) or chorioamnionitis, or prolonged rupture of membranes (>12 hr) are associated with an increased risk of early-onset sepsis. Although complete blood counts are neither sensitive nor specific in the diagnosis of early-onset sepsis, the presence of marked neutropenia has been associated with increased risk. Cyanotic congenital heart disease (in particular, total anomalous pulmonary venous return) can also mimic RDS both clinically and radiographically. Echocardiography with color-flow imaging should be performed in infants who show no response to surfactant replacement, to rule out cyanotic congenital heart disease as well as ascertain patency of the ductus arteriosus and assess pulmonary vascular resistance (PVR). Persistent pulmonary hypertension, aspiration (meconium, amniotic fluid) syndromes, spontaneous pneumothorax, pleural effusions, and congenital anomalies (pulmonary congenital airway malformations, pulmonary lymphangiectasia, diaphragmatic hernia, lobar emphysema) must be considered in patients with an atypical clinical course but can generally be differentiated from RDS through radiographic and other evaluations. Transient tachypnea may be distinguished by its shorter and milder clinical course and is characterized by low or no need for O_2 supplementation.

Although rare, genetic disorders may contribute to respiratory distress. Abnormalities in surfactant protein B and C genes as well as a gene responsible for transporting surfactant across membranes, ABC transporter 3 (*ABCA3*), are associated with severe and often lethal familial respiratory disease. **Congenital alveolar proteinosis** (congenital surfactant protein B deficiency) is a rare familial disease that manifests as severe and lethal RDS in predominantly term and near-term infants (see Chapter 434). In atypical cases of RDS, a lung profile (lecithin:sphingomyelin ratio and phosphatidylglycerol determination) performed on a tracheal aspirate can be helpful in establishing a diagnosis of surfactant deficiency. Other familial causes of neonatal respiratory distress (not RDS) include mucopolysaccharidosis, acinar dysplasia, pulmonary lymphangiectasia, and alveolocapillary dysplasia.

Prevention

Avoidance of unnecessary or poorly timed early (<39 wk GA) cesarean delivery or induction of labor, appropriate management of high-risk pregnancy and labor (including administration of antenatal corticosteroids), and prediction of pulmonary immaturity with possible in utero acceleration of maturation (see Chapter 119) are important preventive strategies. Antenatal and intrapartum fetal monitoring may decrease the risk of fetal asphyxia; asphyxia is associated with an increased incidence and severity of RDS.

Administration of antenatal corticosteroids to women before 37 wk gestation significantly reduces the incidence and mortality of RDS as well as overall neonatal mortality. Antenatal steroids also reduce (1) overall mortality, (2) admission to the neonatal intensive care unit (NICU) and need for/duration of ventilatory support, and (3) incidence of severe IVH, necrotizing enterocolitis (NEC), and neurodevelopmental impairment. Postnatal growth is not adversely affected. Antenatal corticosteroids do not increase the risk of maternal death, chorioamnionitis, or puerperal sepsis. **Betamethasone** and **dexamethasone** have both been used antenatally. Betamethasone may reduce neonatal death to a greater extent than dexamethasone.

Although classically, antenatal corticosteroids were reserved for preterm birth before 34 wk gestation, the administration of betamethasone before late preterm birth (34^{+0} to 36^{+6} wk gestation) significantly reduces the need for respiratory support and the incidence of severe respiratory complications. Therefore the American College of Obstetricians and Gynecologists (ACOG) recommends that for all women between 24 and 36 wk gestation who present in preterm labor and are likely to deliver a fetus within 1 wk, antenatal corticosteroid administration should be considered.

Treatment

The basic defect requiring treatment in RDS is inadequate pulmonary O_2 -CO_2 exchange. Basic supportive care (thermoregulatory, circulatory, fluid, electrolyte, and respiratory) is essential while FRC is established and maintained. Careful and frequent monitoring of heart and respiratory rates, SaO_2 , PaO_2 , $PaCO_2$, pH electrolytes, glucose, hematocrit, blood pressure, and temperature are essential. Arterial catheterization is frequently necessary. Because most cases of RDS are self-limited, the goal of treatment is to minimize abnormal physiologic variations and superimposed iatrogenic problems. Treatment of infants with RDS is best carried out in the NICU.

Periodic monitoring of PaO_2 , $PaCO_2$, and pH is an important part of the management and is used to provide supportive care; if assisted ventilation is being used, such monitoring is essential. Oxygenation (SO_2) should be assessed by continuous pulse oximetry. Capillary blood samples are of limited value for determining PO_2 but may be useful for PCO_2 and pH monitoring. Monitoring of blood gas parameters and mean arterial blood pressure through an umbilical or peripheral arterial catheter is useful in managing the shock-like state that may occur during the initial hours in premature infants who have been asphyxiated or have severe RDS (see Fig. 121.3). The position of a radiopaque umbilical catheter should be checked radiographically after insertion (see Fig. 122.5). The tip of an umbilical artery catheter should lie at L3-L5 just above the bifurcation of the aorta or at T6-T10. The placement and supervision should be carried out by skilled and experienced personnel. Catheters should be removed as soon as patients no longer have any indication for their continued use—usually when an infant is stable and the fraction of inspired oxygen (FIO_2) is <40%.

Nasal Continuous Positive Airway Pressure

Warm, humidified oxygen should be provided at a concentration sufficient to keep PaO_2 between 50 and 70 mm Hg (91–95% SaO_2) to maintain normal tissue oxygenation while minimizing the risk of O_2 toxicity. If there is significant respiratory distress (severe retractions and expiratory grunting) or if SaO_2 cannot be kept >90% at FIO_2 of $\geq$40–70%, applying nCPAP at 5-10 cm H_2O is indicated and usually produces a rapid improvement in oxygenation. Nasal CPAP reduces collapse of surfactant-deficient alveoli and improves both FRC and ventilation-perfusion matching. *Early use of nCPAP for stabilization of at-risk preterm infants beginning early (in the delivery room) reduces the need for mechanical ventilation.*

Recognizing the benefits of surfactant replacement therapy, in addition to the potential protective effects of prophylactic nCPAP, some experts recommend intubation for prophylactic or early rescue surfactant replacement therapy, followed by extubation back to nCPAP immediately once the infant is stable (usually within minutes to <1 hr). The aforementioned method is commonly referred to as **intubate surfactant and extubate** (INSURE). A variation of the INSURE method has evolved known as MIST (**minimally invasive surfactant therapy**) or LISA (**less invasive surfactant administration**), in which a small feeding tube, rather than an endotracheal tube (ETT), is used to deliver intratracheal surfactant to a spontaneously breathing infant on nCPAP. The combination of early rescue surfactant by the INSURE, MIST, or LISA method with nCPAP has been associated with the reduced need for mechanical ventilation, and emerging evidence suggests modest benefits in terms of preventing BPD. The amount of nCPAP required usually decreases after approximately 72 hr of age, and most infants can be weaned from nCPAP shortly thereafter. *Assisted ventilation and surfactant are indicated for infants with RDS who cannot keep oxygen saturation >90% while breathing 40–70% oxygen and receiving nCPAP.*

In an effort to minimize ventilator-associated lung injury and prevent long-term pulmonary complications, the use of nCPAP as the initial respiratory support for extremely preterm infants is preferred. The decreased need for ventilator support with the use of nCPAP may allow lung inflation to be maintained while preventing lung injury. Early nCPAP is beneficial compared to intubation and prophylactic surfactant, because avoidance of mechanical ventilation is associated with a reduction in death and/or BPD. Infants at the extremes of GA (<24 wk) and those that were not exposed to antenatal corticosteroids may still benefit from intubation and surfactant prophylaxis.

Mechanical Ventilation

Infants with respiratory failure or persistent apnea require assisted mechanical ventilation. Strict definitions for respiratory failure in extremely preterm infants with RDS are not agreed on universally, but reasonable measures of respiratory failure are (1) arterial blood pH <7.20, (2) $Pa\text{CO}_2$ ≥60 mm Hg, (3) $Sa\text{O}_2$ <90% at O_2 concentration of 40–70% and nCPAP of 5-10 cm H_2O, and (4) persistent or severe apnea. The goal of mechanical ventilation is to improve oxygenation and ventilation without causing pulmonary injury or oxygen toxicity. Acceptable ranges of ABG values vary significantly among institutions but generally range from $Pa\text{O}_2$ 50-70 mm Hg, $Pa\text{CO}_2$ 45-65 mm Hg (and higher after the 1st few day when risk of IVH is less), and pH 7.20-7.35. During mechanical ventilation, oxygenation is improved by increasing either $F\text{IO}_2$ or the mean airway pressure. The mean airway pressure can be increased by raising the peak inspiratory pressure (PIP), inspiratory time, ventilator rate, or positive end-expiratory pressure (PEEP). Adjustment in pressure is usually most effective. However, excessive PEEP may impede venous return, thereby reducing cardiac output and O_2 delivery. Assisted ventilation for infants with RDS should always include appropriate PEEP (see Chapter 89.1). PEEP levels of 4-6 cm H_2O are usually safe and effective. CO_2 elimination is determined by the minute ventilation, which is a product of the tidal volume (dependent on the inspiratory time and PIP) and ventilator rate. Because of the homogeneous nature of the lung pathology associated with RDS, a high rate (≥60/min), low tidal volume (4-6 mL/kg) strategy is generally effective. Meta-analyses comparing high (>60 breaths/min) and low (usually 30-40 breaths/min) rates (and presumed low vs high tidal volumes, respectively) revealed that the high ventilatory rate strategy led to fewer air leaks and a trend for increased survival. With use of high ventilatory rates, sufficient expiratory time should be allowed to avoid air-trapping and inadvertent PEEP.

Modes of Mechanical Ventilation

Synchronized intermittent mechanical ventilation (SIMV) delivered by time-cycled, pressure-limited, continuous flow ventilators is a common method of conventional ventilation for newborns. With pressure-limited SIMV, a set PIP is delivered in synchrony with the patient's own breaths for a specified rate per minute. For breaths above the set rate, pressure support breaths (8-10 cm H_2O above PEEP) are provided to help overcome the resistance associated with spontaneous breathing through the ETT. In *pressure-limited ventilation* the delivered tidal volume is directly proportional to the respiratory compliance. Rapid changes in compliance occur with surfactant replacement therapy, requiring careful attention to tidal volumes and appropriate adjustments in PIP. Advances in ventilator technology have allowed the delivery of very small (<10 mL) tidal volume breaths consistently. In *volume-targeted ventilation* a specific tidal volume is set, and the PIP required to deliver it varies inversely with the respiratory compliance. Other modes of volume-targeted ventilation calculate the lowest effective PIP to deliver the set tidal volume. Evidence suggests that volume-targeted ventilation results in fewer air leaks and may improve survival without BPD.

High-frequency ventilation (HFV) achieves desired alveolar ventilation by using smaller tidal volumes and higher rates (300-1,200 breaths/min or 5-20 Hz). HFV may improve elimination of CO_2 and improve oxygenation in patients who show no response to conventional ventilators, as well as those who have severe RDS, interstitial emphysema, recurrent pneumothoraces, or meconium aspiration pneumonia. **High-frequency oscillatory ventilation** (HFOV) and **high-frequency jet ventilation** (HFJV) are the most frequently used methods. HFOV may reduce BPD but the effect size is likely small. In severe respiratory failure unresponsive to conventional mechanical ventilation, HFOV strategies that promote lung recruitment, combined with surfactant therapy, may improve gas exchange. HFJV is particularly useful to facilitate resolution of air leaks. Elective use of either HFV method, in comparison with conventional ventilation, generally does not offer advantages when used as the initial ventilation strategy to treat infants with RDS.

Permissive Hypercapnia and Avoidance of Hyperoxia

Permissive hypercapnia is a strategy for management of patients receiving ventilatory support in whom priority is given to limiting ventilator-associated lung injury by tolerating relatively high levels of $Paco_2$ (>60-70 mm Hg). Permissive hypercapnia can be implemented during nCPAP and mechanical ventilation but has not been shown to significantly impact outcomes. **Hyperoxia**

may also contribute to lung injury in preterm infants. However, a lower target range of oxygenation (85–89%) compared with a higher range (91–95%) increases mortality and does not alter rates of BPD, BPD/death, blindness, or neurodevelopmental impairment. *Therefore the currently recommended range of oxygen saturation targets is 91–95%.*

Discontinuation of Mechanical Ventilation

Strategies for weaning infants from ventilators vary widely and are influenced by lung mechanics as well as the availability of ventilatory modes. Extubation to nCPAP prevents postextubation atelectasis and reduces the need for reintubation. Synchronized **nasal intermittent positive pressure ventilation** (NIPPV) also decreases the need for reintubation in premature infants, but ventilators capable of synchronization with nasal ventilation are not widely available. HHHFNC (1-8 L/min) oxygen is typically used to support term and near-term infants following extubation. It is not clear whether nCPAP, NIPPV, or HHHFNC is more efficacious for promoting normal lung development and preventing BPD, but there is more evidence associated with nCPAP in extremely preterm infants. Preloading with methylxanthines enhances the success of extubation.

Surfactant Replacement Therapy

Surfactant deficiency is the primary pathophysiology of RDS. Immediate effects of surfactant replacement therapy include improved alveolar-arterial oxygen gradients, reduced ventilatory support, increased pulmonary compliance, and improved chest radiograph appearance. In the past, intratracheal surfactant replacement for symptomatic premature infants immediately after birth (prophylactic) or during the 1st few hr of life (early rescue) showed reduced air leak and mortality from RDS. However, substantial evidence supports the feasibility and efficacy of prophylactic nCPAP as the *primary* means of respiratory support for preterm infants with RDS. CPAP started at birth is as effective as prophylactic or early surfactant and is associated with a reduction in BPD. *Prophylactic nCPAP is therefore the approach of choice for the delivery room management of a preterm neonate at risk for RDS.*

In neonates with RDS who fail nCPAP and require intubation and mechanical ventilation, treatment with endotracheal surfactant should be initiated immediately to avoid lung injury. Repeated dosing is given every 6-12 hr for a total of 2-4 doses, depending on the preparation. Exogenous surfactant should be given by a physician who is qualified in neonatal resuscitation and respiratory management. Additional required onsite staff support includes nurses and respiratory therapists experienced in the ventilatory management of preterm infants. Appropriate monitoring equipment (radiology, blood gas laboratory, pulse oximetry) must also be available. Complications of surfactant replacement therapy include transient hypoxia, hypercapnia, bradycardia and hypotension, blockage of ETT, and pulmonary hemorrhage.

A number of surfactant preparations are available, including synthetic surfactants and natural surfactants derived from animal sources. There do not appear to be significant, consistent benefits to one preparation over another. Infants requiring ventilator support after 1 wk of age may experience transient episodes of surfactant dysfunction temporally associated with episodes of infection and respiratory deterioration. Surfactant treatment may be beneficial in these infants.

Other Pharmacologic Therapies

There are no pharmacologic therapies superior or equal to the efficacy of maintaining FRC (through noninvasive respiratory support and mechanical ventilation when necessary) and providing surfactant replacement therapy in the treatment of RDS. Systemic corticosteroids (predominantly dexamethasone), although effective in improving respiratory mechanics and preventing BPD and death, are associated with increased risk of cerebral palsy and neurodevelopmental impairment when used indiscriminately. Thus, routine use of systemic corticosteroids for the prevention or treatment of BPD is not recommended by the Consensus Group of the American Academy of Pediatrics and the Canadian Pediatric Society. Early (1st 10 days of life), low-dose administration (1 mg/kg/day hydrocortisone twice daily for 7 days; 0.5 mg/kg/day for 3 days) may reduce the risk of BPD in neonates <28 wk GA. In general, administration of inhaled corticosteroids to ventilated preterm infants during the 1st 2 wk after birth has not proved to be consistently advantageous.

Inhaled nitric oxide (iNO) has been evaluated in preterm infants following the observation of its effectiveness in term and near-term infants with hypoxemic respiratory failure. Although iNO improves oxygenation in term and near-term infants with hypoxic respiratory failure or persistent pulmonary hypertension of the neonate, trials in preterm infants have not shown significant benefit. The most current data do not support the routine administration of iNO in preterm infants with hypoxemic respiratory failure.

Hypotension and low flow in the superior vena cava have been associated with higher rates of CNS morbidity and mortality and should be treated with cautious administration of crystalloid (if volume depletion due to hemorrhage or excessive insensible fluid losses is suspected) and early use of vasopressors. Dopamine is more effective in raising blood pressure than dobutamine. Hypotension that is refractory to vasopressor therapy, especially in neonates <1,000 g, may be caused by transient adrenal insufficiency. Administration of intravenous hydrocortisone at 1-2 mg/kg/dose every 6-12 hr may improve blood pressure and allow weaning of vasopressors.

Because of the difficulty in distinguishing group B streptococcal or other bacterial infections from RDS, empirical antibiotic therapy may be indicated until the results of blood cultures are available. Penicillin or ampicillin with an aminoglycoside is suggested, although the choice of antibiotics should be based on the recent pattern of bacterial sensitivity in the hospital where the infant is being treated (see Chapter 129).

Complications

Early provision of intensive observation and care of high-risk newborn infants can significantly reduce the morbidity and mortality associated with RDS and other acute neonatal illnesses. Antenatal corticosteroids, postnatal surfactant use, and improved modes of ventilation have resulted in low mortality from RDS (approximately 10%). Mortality increases with decreasing gestational age. Optimal results depend on the availability of experienced and skilled personnel, care in specially designed and organized regional hospital units, proper equipment, and lack of complications such as severe asphyxia, intracranial hemorrhage, or irremediable congenital malformation.

The most serious complications of endotracheal intubation are **pulmonary air leaks** , asphyxia from obstruction or dislodgment of the tube, bradycardia during intubation or suctioning, and the subsequent development of **subglottic stenosis** . Other complications include bleeding from trauma during intubation, posterior pharyngeal pseudodiverticula, need for tracheostomy, ulceration of the nares caused by pressure from the tube, permanent narrowing of the nostril as a result of tissue damage and scarring from irritation or infection around the tube, erosion of the palate, avulsion of a vocal cord, laryngeal ulcer, papilloma of a vocal cord, and persistent hoarseness, stridor, or edema of the larynx.

Measures to reduce the incidence of these complications include skillful intubation, adequate securing of the tube, use of polyvinyl ETTs, use of the smallest tube that will provide effective ventilation in order to reduce local pressure necrosis and ischemia, avoidance of frequent changes and motion of the tube in situ, avoidance of too frequent or too vigorous suctioning, and prevention of infection through meticulous cleanliness and frequent sterilization of all apparatus attached to or passed through the tube. The personnel inserting and caring for the ETT should be experienced and skilled in such care.

Extrapulmonary air leaks (pneumothorax, pneumomediastinum, pulmonary interstitial emphysema) are observed in 3–9% of extremely preterm infants with RDS (see Chapter 122.12). PPV with excessive inspiratory pressures (and therefore excessive tidal volumes), either during resuscitation at delivery or in the initial hours of mechanical ventilation, is a common risk factor, but air leaks can also occur in infants breathing spontaneously. Although the risk of air leak was increased in infants receiving a higher level of nCPAP (up to 8 cm H_2O) in the CPAP or Intubation at Birth (COIN) trial, subsequent trials have not demonstrated a similar effect.

Risks associated with **umbilical arterial catheterization** include vascular embolization, thrombosis, spasm, and vascular perforation; ischemic or chemical necrosis of abdominal viscera; infection; accidental hemorrhage; hypertension; and impairment of circulation to a leg with subsequent gangrene. Aortography has demonstrated that clots form in or about the tips of 95% of catheters placed in an umbilical artery. Aortic ultrasonography can also be used to investigate for the presence of thrombosis. **Renovascular hypertension** may occur days to weeks after umbilical arterial catheterization in a small proportion of neonates. Transient blanching of the leg may occur during catheterization of the umbilical artery. It is usually caused by reflex arterial spasm, the incidence of which is lessened by using the smallest available catheter, particularly in very small infants. The catheter should be removed immediately; catheterization of the other artery may then be attempted. **Umbilical vein catheterization** is associated with many of the same risks as umbilical artery catheterization. Additional risks are cardiac perforation and pericardial tamponade; improperly placed catheters in the portal vein can lead to thrombosis. The risk of a serious clinical complication resulting from umbilical catheterization is probably 2–5%.

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122.4

Bronchopulmonary Dysplasia

Shawn K. Ahlfeld

Keywords

bronchopulmonary dysplasia
BPD
chronic lung disease of prematurity
alveolar simplification
atelectrauma
volutrauma

pulmonary hypertension
inhaled nitric oxide
systemic corticosteroids
dexamethasone
hydrocortisone
inhaled corticosteroids
budesonide
beclomethasone
surfactant replacement therapy
caffeine
furosemide
chlorothiazide
sildenafil
albuterol
ipratropium
cor pulmonale

Incidence

Bronchopulmonary dysplasia (**BPD** , also known as **chronic lung disease of prematurity**) is a clinical pulmonary syndrome that develops in the majority of extremely preterm infants and is defined by a prolonged need for respiratory support and supplemental oxygen. Almost 60% of infants born at ≤28 wk gestation will develop BPD, and the incidence of BPD increases inversely with gestational age. For infants born at the extreme of viability (22-24 wk), essentially 100% will develop BPD, the majority of whom will have moderate to severe disease. As neonatal care has improved and use of antenatal corticosteroids has become the standard of care, survival of infants born at the extreme of viability has improved, and BPD is encountered with increased prevalence. In the United States, an additional 10,000-15,000 new cases occur annually. Despite decades of experience, the incidence of BPD remains largely unchanged.

Etiology and Pathophysiology

BPD develops following preterm birth and the necessary life-supporting interventions (particularly mechanical ventilation and supplemental oxygen) that cause neonatal lung injury. As the limit of viability has been lowered by advances in neonatal care, the clinical syndrome associated with BPD has evolved. The clinical, radiographic, and lung histology of classic BPD described in 1967, before widespread use of antenatal corticosteroids and postnatal surfactant, was that of a disease of preterm infants who were more mature. During that era, infants born ≤30-32 wk gestation rarely survived. Infants who developed BPD demonstrated classic RDS initially, but the injurious mechanical ventilation and excessive supplemental oxygen required to support them resulted in a progressive, severe fibroproliferative lung disease. Improvements in respiratory care, as well as the introduction of surfactant and antenatal steroids, have allowed for gentle respiratory support strategies, and the need for excessive ventilator support and high percentages of inspired supplemental oxygen has decreased.

Despite a reduction in the fibroproliferative disease described previously, infants born in the modern era of neonatal care continued to require supplemental oxygen for prolonged periods. The *new* BPD is a disease primarily of infants with birthweight <1,000 g who were born at <28 wk gestation, some of whom have little or no lung disease at birth but over the 1st weeks of age experience progressive respiratory failure. Infants with the new BPD are born at a more immature stage of distal lung development, and lung histology demonstrates variable saccular wall fibrosis, minimal airway disease, abnormal pulmonary microvasculature development, and alveolar simplification. Although the etiology remains incompletely understood, the histopathology of BPD indicates interference with normal alveolar septation and microvascular maturation.

The pathogenesis of BPD is likely multifactorial, but pulmonary inflammation and lung injury are consistently observed. Alveolar collapse (**atelectrauma**) as a consequence of surfactant deficiency, together with ventilator-induced phasic overdistention of the lung (**volutrauma**), promotes lung inflammation and injury. Supplemental oxygen produces free radicals that cannot be metabolized by the immature antioxidant systems of very-low-birthweight (VLBW) neonates and further contributes to the injury. Pulmonary inflammation evidenced by infiltration of neutrophils and macrophages in alveolar fluid, as well as a host of proinflammatory cytokines, contributes to the progression of lung injury. Pre- and postnatal infection, excessive pulmonary blood flow via the patent ductus arteriosus (PDA), excessive administration of intravenous fluid, and pre- and postnatal growth failure are also significantly associated with the development of BPD. While the mechanisms are unclear, all likely promote lung injury by necessitating increased or prolonged respiratory support or interfering with lung repair. Regardless, the result is an interference with normal development of the alveolar-capillary unit and interference with normal gas exchange.

Clinical Manifestations

Over the 1st several wk of age, infants developing BPD demonstrate persistent, often progressive respiratory distress and the need for respiratory support and supplemental oxygen. In extremely-low-birthweight (ELBW) infants at risk for BPD, the need for supplemental oxygen over the 1st 2 wk of age follows 1 of 3 distinct patterns. Infants that follow the natural course of RDS, and by the 3-4 days of age require minimal (FIO_2 <0.25) supplemental oxygen, have a low (<20%) risk of developing BPD. Infants who initially have a low O_2 requirement (FIO_2 <0.25) during the 1st wk, but then experience early pulmonary deterioration and increased O_2 requirement (FIO_2 >0.25) during the 2nd wk, have a modest risk (approximately 50%) of developing BPD. Infants that have an early, persistently high (FIO_2 >0.25) need for supplemental oxygen have a significantly high (70%) risk of developing BPD.

Respiratory distress, commonly characterized by tachypnea and retractions, persists or worsens and is associated with hypercapnia, hypoxia, and oxygen dependence. The chest radiograph evolves from that of RDS to relative hyperinflation and fine, diffuse interstitial opacities. Wandering atelectasis is common. In the most severe cases, usually associated with prolonged mechanical ventilation and chronically high supplemental oxygen needs, frank cystic changes and/or pneumatoceles are observed (Fig. 122.6). Infants with severe BPD often demonstrate airway obstruction. Excessive airway mucus and edema, airway instability caused by acquired tracheobronchomalacia, and bronchospasm are proposed etiologies. Acute airway obstruction is manifest clinically by abrupt hypoxemia and bradycardia and is often referred to as *BPD spells* . Acute, intermittent right-to-left intracardiac or intrapulmonary shunting caused by abrupt elevations in pulmonary artery pressure may also contribute. Spells are notoriously difficult to control, but occasionally will respond to bronchodilators and sedation acutely.

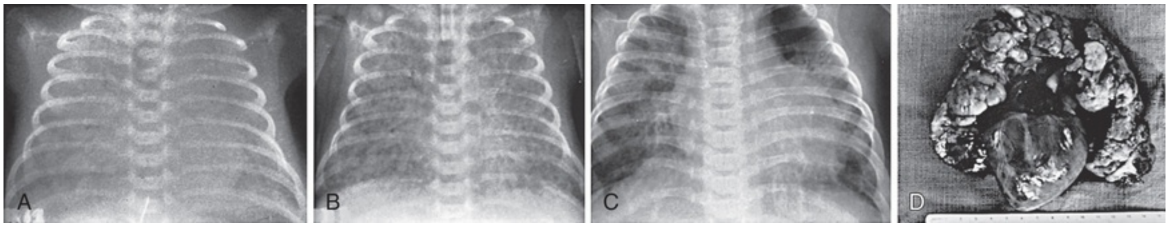

FIG. 122.6 **Pulmonary changes in infants treated with prolonged, intermittent positive pressure breathing with air containing 80–100% oxygen in the immediate postnatal period for the clinical syndrome of hyaline membrane disease. A, A 5 day old infant with nearly complete opacification of the lungs. B, A 13 day old infant with "bubbly lungs" simulating the radiographic appearance of the Wilson-Mikity syndrome. C, A 7 mo old infant with irregular, dense strands in both lungs, hyperinflation, and cardiomegaly suggestive of chronic lung disease. D, Large right ventricle and a cobbly, irregular aerated lung of an infant who died at 11 mo of age. This infant also had a patent ductus arteriosus. (From Northway WH Jr, Rosan RC, Porter DY: Pulmonary disease following respiratory therapy of hyaline-membrane disease, *N Engl J Med* 276:357–368, 1967.)**

A common, increasingly recognized complication of BPD is **pulmonary hypertension** . Prospective surveillance indicates that in approximately 15% of all infants born at <1,000 g and <28 wk GA, echocardiographic signs of pulmonary hypertension will develop. Prenatal growth restriction, prolonged duration of mechanical ventilation and supplemental oxygen, and increasing severity of BPD are all associated with an increased risk. Pulmonary hypertension has been reported in as many as 40% of infants with the most severe BPD and can progress to right-sided heart failure. Consistently, pulmonary hypertension complicating BPD has been associated with increased mortality.

Diagnosis

BPD is diagnosed when a preterm infant requires supplemental oxygen for the 1st 28 postnatal days, and it is further classified at 36 wk PMA according to the degree of O_2 supplementation (Table 122.2). Neonates receiving positive pressure support or ≥30% supplemental O_2 at 36 wk PMA or at discharge (whichever occurs first) are diagnosed as having **severe** BPD; those requiring 22–29% supplemental O_2 have **moderate** BPD; and those who previously required O_2 supplementation for at least 28 days but are currently breathing room air have **mild** BPD. Infants receiving <30% supplemental O_2 should undergo a stepwise 2% reduction in supplemental O_2 to room air while under continuous observation and with So_2 monitoring to determine whether they can be weaned off oxygen (physiologic definition of BPD). This test is highly reliable and correlated with discharge home on oxygen, length of hospital stay, and hospital readmissions in the 1st yr of life. The risk of neurodevelopmental impairment and pulmonary morbidity and the severity of BPD are directly correlated.

Table 122.2

Definition of Bronchopulmonary Dysplasia (BPD): Diagnostic Criteria[*]

	GESTATIONAL AGE	
	<32 Wk	**≥32 Wk**
Time point of assessment	36 wk PMA or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus** :	>28 days but <56 days postnatal age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus** :
Mild BPD	Breathing room air at 36 wk PMA or discharge home, whichever comes first	Breathing room air by 56 days postnatal age or discharge home, whichever comes first
Moderate BPD	Need[†] for <30% oxygen at 36 wk PMA or discharge home, whichever comes first	Need[†] for <30% oxygen at 56 days postnatal age or discharge home, whichever comes first
Severe BPD	Need[†] for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk PMA or discharge home, whichever comes first	Need[†] for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge home, whichever comes first

[*] BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most frequently respiratory distress syndrome (RDS). Persistence of the clinical features of respiratory disease (tachypnea, retractions, crackles) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with >21% oxygen and/or PPV for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless parenchymal lung disease also develops and they have clinical features of respiratory distress. A day of treatment with >21% oxygen means that the infant received >21% oxygen for >12 hr on that day. Treatment with >21% oxygen and/or PPV at 36 wk PMA or at 56 days postnatal age or discharge should not reflect an “acute” event, but should rather reflect the infant's usual daily therapy for several days preceding and after 36 wk PMA, 56 days postnatal age, or discharge.

[†] A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

NCPAP, Nasal continuous positive airway pressure; PMA, postmenstrual age; PPV, positive pressure ventilation.

From Jobe AH, Bancalari E: Bronchopulmonary dysplasia, *Am J Respir Crit Care Med* 163:1723–1729, 2001.

Despite its simplicity, the current severity-based definition of BPD has limitations. Because of incomplete or inaccurate data related to hospital transfer or early discharge, in a significant number of infants the diagnosis of BPD is either not documented or misapplied. Additionally, those infants requiring O_2 support at relatively high flow (>2 L/min) or very low (<0.25 L/min) are not well characterized. Calculation of *effective oxygen* may be helpful but is cumbersome and not well validated. Many clinical trials have simply relied on the need for supplemental O_2 at 36 wk PMA to define BPD. While this definition can diagnose BPD in the highest percentage of infants, it cannot discriminate between infants with milder BPD from those with most severe forms of BPD. In general, any definition of BPD striving to identify infants who benefit from long-term follow up and therapy has been disappointing. Therefore an improved yet feasible definition of BPD is required that accurately evaluates the utility of investigational therapies, predicts long-term outcomes, and directs clinical care.

Prevention

In general, there remains a lack of effective interventions that prevent BPD. Avoidance of mechanical ventilation with the early use of **nCPAP** and early, selective **surfactant** replacement therapy with rapid extubation decrease the incidence of BPD modestly. The avoidance of mechanical ventilation achieved by the combination of early rescue surfactant by the INSURE, MIST, or LISA method with nCPAP has been associated with a modest reduction in BPD. Gentle ventilation strategies, including volume-targeted ventilation and HFOV, have also been associated with small, inconsistent reductions in BPD. **Caffeine** therapy for apnea of prematurity has also been associated with a decreased risk of BPD. Although the mechanisms are unknown, caffeine likely supports effective spontaneous respiration and decreases the likelihood that an infant will need invasive mechanical ventilation.

Animal models of BPD have consistently demonstrated that **vitamin A** supplementation promotes distal alveolar development. Previously, provision of intramuscular (IM) vitamin A (5,000 IU 3 times/wk for 4 wk) to VLBW infants was shown to reduce the risk of BPD (1 case prevented for every 14-15 infants treated). However, with the widespread use of early nCPAP, it is unclear if a significant benefit remains, and therefore the use of vitamin A has been inconsistent. Despite promising preclinical data in animal models, the use of prophylactic iNO does not consistently prevent BPD, and its routine use is not recommended.

Systemic corticosteroids (dexamethasone) given either early (<7 days of age to ventilated infants at risk of BPD) or late (>7 days of age to infants with progressing lung disease) prevent both mortality and BPD significantly, but because of the increased risk of **cerebral palsy (CP)** and **neurodevelopmental impairment** , their routine use is not recommended. The risk of neurodevelopmental impairment related to systemic corticosteroid use may be offset by the risk associated with BPD. A systematic review suggested that systemic corticosteroid therapy, when directed to infants with a ≥65% risk of developing BPD, may actually reduce the risk of neurodevelopmental impairment and CP. Although predictive models that use clinical characteristics have been described with promising accuracy, randomized trials using them to guide corticosteroid therapy have not been performed. Systemic hydrocortisone given early to extremely preterm infants at risk for BPD, especially those exposed to chorioamnionitis, may prevent BPD without neurodevelopmental impairment. However, at this time there are insufficient data on safety to support its routine use. **Inhaled corticosteroids** administered to VLBW infants requiring mechanical ventilation at 7-14 days of age did not prevent BPD significantly. However, early, prolonged administration to mechanically ventilated extremely preterm infants until they no longer require oxygen or positive pressure support has been shown to reduce the risk of BPD, but with a concerning trend toward increased mortality. Experience with local delivery of corticosteroids by spiking surfactant with **budesonide** is emerging, and early data suggest that **endotracheal** administration of corticosteroids may reduce pulmonary inflammation and the risk of BPD and death. However, additional evidence is needed before widespread use is implemented. The routine use of antibiotics, inhaled bronchodilators, or diuretics has not been shown to prevent BPD.

Treatment

Treatment of evolving and established BPD is supportive, and evidence-based therapies are lacking. The basic tenets of therapy should include appropriate support of ventilation and aggressive nutritional support to optimize linear growth and encourage normal lung repair and development. Despite a lack of support from investigational studies in the current era of BPD, numerous medical interventions are employed. Available evidence suggests short-term benefits (improved pulmonary mechanics, modest reductions in respiratory support parameters) without an indication of impact on clinically relevant outcomes (survival, need for long-term respiratory support, recurrent hospitalization). Currently, available evidence does not support the routine use of any pharmacologic agents in infants with evolving or established BPD. Treatment decisions must weigh the perceived benefit against the potential harm, since data on not only efficacy, but more importantly safety, remain inadequate.

Diuretics and Fluid Restriction

Infants with BPD often have excessive pulmonary interstitial fluid that compromises lung function and increases work of breathing. Diuretic therapy (usually with furosemide or chlorothiazide) has been associated with short-term, temporary improvements in pulmonary compliance and the ability to wean respiratory support. **Furosemide** (1 mg/kg/dose IV or 2 mg/kg/dose PO every 12-24 hr) has been demonstrated to decrease pulmonary interstitial emphysema and PVR, improve pulmonary function, and facilitate weaning from mechanical ventilation and oxygen. Adverse effects of long-term furosemide therapy are common and include hyponatremia, hypokalemia, alkalosis, azotemia, hypocalcemia, hypercalciuria, cholelithiasis, renal stones, nephrocalcinosis, and ototoxicity. Potassium chloride supplementation is often necessary. Thiazide diuretics (e.g., chlorothiazide, 5-10 mg/kg/dose every 12 hr) have been used as an alternative to avoid hypercalciuria, limit nephrocalcinosis, and preserve bone development. Although avoidance of excessive fluid administration in the 1st few wk of age is associated with a reduced risk of BPD, there is no evidence that fluid restriction (130-140 mL/kg/day) in established BPD has any impact. Whether using diuretics or fluid restriction, careful attention to maintaining appropriate electrolyte levels as well as providing adequate caloric intake (often >120-130 kcal/kg/day) is paramount to avoid negatively impacting nutrition.

Bronchodilators

Inhaled bronchodilators improve lung mechanics by decreasing airway resistance. **Albuterol** is a specific β_2 -agonist used to treat bronchospasm in infants with BPD. Albuterol may improve lung compliance by decreasing airway resistance secondary to smooth muscle cell relaxation. Changes in pulmonary mechanics may last as long as 4-6 hr. Hypertension and tachycardia are common adverse effects. **Ipratropium bromide** is a muscarinic antagonist related to atropine, but the bronchodilator effect is more potent. Use of ipratropium bromide in BPD has been associated with improved pulmonary mechanics.

Compared to either agent used alone, combined use of albuterol and ipratropium bromide may be more effective. Few adverse effects have been noted. With current aerosol administration strategies, exactly how much medication is delivered to the airways and lungs of infants with BPD, especially if they are ventilator dependent, is unclear.

Corticosteroids

In addition to their use at an early age (<7 days) to prevent BPD, **systemic corticosteroids** have also been used to treat evolving and established BPD. In mechanically ventilated infants, systemic corticosteroids improve pulmonary mechanics, allow weaning of ventilator support and supplemental O_2 , and facilitate extubation. When given at >7 days of age, long-term benefits include a reduced need for O_2 at 36 wk PMA, improved survival, and decreased need for home O_2 . Short-term adverse effects include hyperglycemia, hypertension, and transient hypertrophic obstructive cardiomyopathy. Long-term adverse effects include osteopenia, severe retinopathy of prematurity (ROP), abnormal neurological examination, poor brain growth, neurodevelopmental impairment, and CP. Although meta-analyses suggest that the long-term detrimental effects on neurodevelopment might be mitigated by later postnatal use, open-label use of corticosteroids in control groups makes analysis of safety unreliable. A strategy that utilizes a low cumulative dose (0.89 mg/kg given over 10-day taper) in preterm infants who remain ventilator dependent after 7 days of age (and therefore have a high risk of developing BPD) facilitates weaning of ventilator and oxygen support and promotes successful extubation without an impact on long-term outcomes, including the incidence of BPD or neurodevelopmental impairment. However, randomized controlled trials (RCTs) with appropriate power to assess safety are lacking. The controversy concerning the appropriate use of systemic corticosteroids to prevent and/or treat BPD is ongoing, and until additional evidence is available, their use remains limited to infants with severe respiratory failure (ventilator dependent at >7-14 days of age with significant respiratory and oxygen support needs) at high risk for imminent death.

In an effort to avoid the detrimental effects of systemic corticosteroids, **inhaled corticosteroids** (budesonide, fluticasone, and beclomethasone) have been described as an alternative antiinflammatory therapy in evolving or established BPD. Small RCTs and case reports in infants with established moderate-severe BPD have not shown a significant benefit for pulmonary mechanics or reduction in the need for ventilator or oxygen support.

Pulmonary Vasodilators

Many infants with evolving or established moderate and severe BPD demonstrate pulmonary vascular resistance caused by pulmonary microvascular maldevelopment and abnormal vasoreactivity. In infants with BPD with pulmonary hypertension, acute exposure to even modest levels of hypoxemia can cause pulmonary artery pressure (PAP) to increase abruptly. Maintaining infants with established BPD and pulmonary hypertension at higher SO_2 targets (92–96%) can lower PAP effectively. For infants in whom appropriate O_2 supplementation and support of ventilation are ineffective, the use of low-dose **inhaled NO** may improve oxygenation anecdotally. Despite its frequent use, there is no evidence to support the use of iNO to improve lung function, cardiac function, or oxygenation in evolving BPD. Several case series have reported on the use of the phosphodiesterase-5 inhibitor **sildenafil** in treating pulmonary hypertension in established moderate to severe BPD. Despite its widespread use, no RCTs are evaluating the safety and efficacy of sildenafil in preterm infants with BPD. However, many experts would recommend a trial of low-dose sildenafil (1 mg/kg/dose every 8 hr) for infants with evidence of pulmonary hypertension and persistent respiratory instability despite appropriate oxygen and ventilator support.

Chronic Respiratory Support

Evidence is lacking to guide respiratory management in evolving and established BPD. Experience suggests that maintaining FRC with appropriate positive pressure support (with noninvasive support whenever possible) promotes optimal lung growth and development. Provision of nCPAP until respiratory status improves and oxygen dependence resolves, with subsequent transition directly to room air, may be beneficial but is not based on evidence. Continuation of caffeine therapy may facilitate spontaneous breathing and weaning from support. Established severe BPD with cystic, heterogeneous lung disease requires prolonged mechanical ventilation. A long inspiratory time is required to adequately ventilate diseased lung units, and appropriate expiratory time is required to allow exhalation. The use of a low rate (<20-30 breaths/min), long inspiratory time (≥0.6 sec) strategy is usually required. To attain appropriate minute ventilation, larger tidal volumes (10-12 mL/kg) are necessary. Higher PEEP (often >6-8 cm) may be needed to attain adequate expansion and minimize gas-trapping caused by dynamic airway collapse. Gradual weaning of ventilator settings should be attempted as the infant grows and lung disease improves, but the incidence of death or tracheostomy placement for chronic ventilation may be as high as 20%. By 2-3 yr of age, the majority of infants who undergo tracheostomy for severe BPD are successfully liberated from mechanical ventilation.

Prognosis

Compared with extremely preterm infants without BPD, infants with BPD have higher rates of neurodevelopmental impairment, lung diffusion impairment, wheezing and airflow obstruction, rehospitalization, and mortality. The risk of these complications increases with BPD severity. Prolonged mechanical ventilation, IVH, pulmonary hypertension, cor pulmonale, and oxygen dependence beyond 1 yr of life are poor prognostic signs. Mortality in infants with BPD ranges from 10–25% and is highest in infants who remain ventilator dependent for >6 mo. Cardiorespiratory failure associated with cor pulmonale and acquired infection (respiratory syncytial virus) are common causes of death. Infants are at risk for severe RSV infections and must receive prophylactic therapy (see Chapter 287).

Pulmonary function slowly improves in most survivors because of ongoing lung repair and the natural period of lung growth and alveolarization. *Rehospitalization* for impaired pulmonary function is most common during the 1st 3 yr of life and is much more common in infants requiring respiratory support at discharge. The incidence of physician-diagnosed asthma, use of bronchodilators, and wheezing is elevated. Despite a gradual decrease in symptom frequency, persistence of respiratory symptoms and abnormal pulmonary function test results are measurable in children, adolescence, and young adults. Although not always clinically apparent, pulmonary function testing consistently reveals impaired exercise capacity, reduced pulmonary diffusing capacity, and persistent expiratory flow obstruction. High-resolution chest CT scanning or MRI studies in children and adults with a history of BPD reveal lung abnormalities that correlate directly with the degree of pulmonary function abnormality. The ultimate long-term pulmonary health of survivors of

BPD is unknown. As trajectories of developing lung function remain abnormal in survivors of BPD, concerns have been raised highlighting the potential for pulmonary emphysema, chronic obstructive pulmonary disease, and pulmonary vascular disease resulting in early debilitating lung dysfunction.

Other complications of BPD include growth failure, neurodevelopmental impairment, and parental stress, as well as sequelae of therapy, such as nephrolithiasis, osteopenia, and electrolyte imbalance. Airway problems such as vocal cord paralysis, subglottic stenosis, and tracheomalacia are common and may aggravate or cause pulmonary hypertension. Subglottic stenosis may require tracheotomy or an anterior cricoid split procedure to relieve upper airway obstruction. Cardiac complications of BPD include pulmonary hypertension, cor pulmonale, systemic hypertension, left ventricular hypertrophy, and development of aortopulmonary collateral vessels, which, if large, may cause heart failure.

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122.5

Patent Ductus Arteriosus

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Keywords

patent ductus arteriosus
PDA
indomethacin
ibuprofen
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surgical ligation

Incidence and Pathophysiology

Some neonates with RDS may have clinically significant shunting through a patent ductus arteriosus (**PDA**). Although ductal closure occurs by 72 hr after birth in almost all term infants, at the same age in 65% of preterm infants born at <30 wk GA, the ductus remains patent. Risk factors for delayed closure of the PDA include hypoxia, acidosis, increased pulmonary pressure secondary to vasoconstriction, systemic hypotension, immaturity, and local release of prostaglandins (which dilate the ductus). Shunting through the PDA may initially be bidirectional or right to left. As respiratory distress syndrome (RDS) resolves, pulmonary vascular resistance (PVR) decreases, and left-to-right shunting may occur, leading to left ventricular (LV) volume overload and pulmonary edema.

Clinical Manifestations

Manifestations of PDA may include (1) a hyperdynamic precordium, bounding peripheral pulses, wide pulse pressure, and a machine-like continuous or systolic murmur; (2) radiographic evidence of cardiomegaly and increased pulmonary vascular markings; (3) hepatomegaly; (4) increasing oxygen dependence; (5) carbon dioxide retention; and (6) renal failure. Infants with a hemodynamically significant PDA often require escalation of ventilator and oxygen support. The diagnosis is confirmed by echocardiographic visualization of a PDA with Doppler flow imaging that demonstrates left-to-right or bidirectional shunting.

Treatment

Management of the PDA is controversial, and evidence to guide treatment is limited. Prophylactic closure before signs of a PDA, closure of the asymptomatic but clinically detected PDA, and closure of the symptomatic PDA are 3 management strategies. Interventions to encourage ductal closure include fluid restriction, cyclooxygenase (COX) inhibitors (indomethacin or ibuprofen), and surgical ligation. Short-term benefits of any therapy have to be balanced against adverse effects, such as transient renal dysfunction and fluid imbalances associated with indomethacin.

By the time of discharge in the majority of extremely preterm infants (>90%), the PDA will close spontaneously. Spontaneous ductal closure may be facilitated by general supportive measures, including early (<7 days of age) avoidance of excessive fluid administration and judicious use of diuretics to manage pulmonary edema. However, within the 1st week of age, in 30% of infants with birthweight <1,500 g and 70% of infants <1,000 g, the PDA persists. Although many preterm infants with persistent PDA will remain clinically stable while awaiting spontaneous closure, approximately 60% of infants <1,000 g will develop significant clinical instability (hypotension, renal failure, worsening respiratory failure secondary to pulmonary edema). Pharmacologic and surgical ductal closure may be indicated in the premature infant with a moderate to large, hemodynamically significant PDA when there is a delay in clinical improvement or deterioration.

Pharmacologic Closure

Pharmacologic closure of the PDA has been described using COX inhibitors that inhibit prostaglandin production, with equivalent efficacy and safety profiles described for ibuprofen and indomethacin. The efficacy of pharmacological therapy is inversely proportional to the gestational and postnatal age, and closure is more likely when medication is administered before 14-21 days of age. However, successful closure has been reported up to 8 wk of age. Whether indomethacin or ibuprofen is used, 20–40% of infants demonstrate treatment failure, and of those infants, 10–20% require eventual surgical ligation. Rates of recurrence following successful pharmacologic closure in general are low (<15%). Neither therapy significantly impacts the rate of NEC, BPD, or mortality. **General contraindications** to both indomethacin and ibuprofen include thrombocytopenia (<50,000 platelets/mm^3), active hemorrhage (including severe IVH), NEC or isolated intestinal perforation, elevated plasma creatinine (>1.8 mg/dL), or oliguria (urine output <1 mL/kg/hr).Importantly, the concomitant use of hydrocortisone and indomethacin in extremely preterm infants must be avoided, because the combination is associated with a dramatic increase in spontaneous intestinal perforation. Despite that indomethacin reduces mesenteric blood flow, mounting experience suggests that low-volume trophic enteral feeding during administration is safe.

Prophylactic **indomethacin** given over the 1st 72 hr of age to preterm infants with birthweight <1,000 g reduces the incidence of severe IVH (grade III/IV), pulmonary hemorrhage, symptomatic PDA, and need for surgical PDA ligation. Although often implicated in spontaneous intestinal perforation and NEC, RCTs have failed to demonstrate that indomethacin increases their risk significantly. Short-term side effects include reductions in cerebral, mesenteric, and renal blood flow. Oliguria unresponsive to diuretic therapy is observed frequently. Dosing regimens for indomethacin vary considerably, but it usually is administered as a slow IV infusion (0.1-0.2 mg/kg/dose over 30 min) every 12-24 hr for 3 doses. A repeat course can be attempted if the duct fails to close or reopens, but additional (>2) courses do not appear to be efficacious. Longer courses (5-7 days) of indomethacin are not recommended because of to an increased risk of NEC in one trial.

Ibuprofen is as effective as indomethacin in closing a PDA, but ibuprofen is associated with reduced rates of oliguria and a small but significant reduction in the length of mechanical ventilation. Although higher doses may improve closure rates in the most immature infants, the typical IV or enteral dosing regimen for ibuprofen is 10 mg/kg for 1 dose, followed by 2 doses of 5 mg/kg every 24 hr. As with indomethacin, a repeat course may be considered, but additional courses of ibuprofen are not efficacious and not recommended. Risk of NEC is not increased with indomethacin, but ibuprofen reduces the relative risk of NEC comparatively. Unlike indomethacin, ibuprofen has not been shown to reduce the risk of severe IVH. Compared to the IV route, enteral ibuprofen may be more efficacious. Whether ibuprofen used in combination with hydrocortisone results in increased risk of spontaneous intestinal perforation is unknown.

Preliminary studies suggest that **acetaminophen** may be an effective drug to close a PDA, with fewer side effects than existing agents.

Surgical Ligation

The infant whose symptomatic PDA fails to close with pharmacologic interventions or who has contraindications to COX inhibitors is a candidate for surgical closure. Although the long-term benefits are unclear, surgical ligation in infants born at <28 wk GA and <1,250 g is associated with improved survival. Surgical mortality is very low even in ELBW infants. However, **postligation cardiac syndrome** , a significant drop in blood pressure 6-12 hr after ductal ligation, is experienced by up to 50% of LBW infants. The hypotension has been attributed to increased systemic vascular resistance along with decreased pulmonary venous return, resulting in impaired preload and LV function. Fluid resuscitation, inotropic support (with dobutamine or milrinone), and hydrocortisone are usually effective. Other complications of surgery include hemorrhage, pneumothorax, chylothorax, Horner syndrome, and injury to the recurrent laryngeal nerve resulting in vocal cord dysfunction. Inadvertent ligation of the left pulmonary artery or the transverse aortic arch has rarely been reported. Increased rates of neurodevelopmental impairment have been reported following surgical ligation, although a causal relationship remains uncertain.

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122.6

Transient Tachypnea of the Newborn

Shawn K. Ahlfeld

Keywords

transient tachypnea of the newborn
TTN
fetal lung fluid
albuterol
salbutamol

Transient tachypnea of the newborn (**TTN**) is a clinical syndrome of self-limited tachypnea associated with delayed clearance of fetal lung fluid. Although the actual incidence is likely underreported, it is estimated at 3-6 per 1,000 term infant births, making TTN the most common etiology of tachypnea in the newborn. Twin gestation, maternal asthma, late prematurity, precipitous delivery, gestational diabetes, and cesarean delivery without labor are common associated risk factors. Clearance of fetal lung fluid occurs through increased expression of epithelial sodium channels (ENaC) and sodium-potassium adenosine triphosphatase (Na^+ ,K^+ -ATPase) that drive active sodium (and thereby fluid) reabsorption. TTN is believed to result from ineffective expression or activity of ENaC and Na^+ ,K^+ -ATPase, which slows absorption of fetal lung fluid and results in decreased pulmonary compliance and impeded gas exchange.

TTN is characterized by the early onset of tachypnea (>60 breaths/min), sometimes with retractions or expiratory grunting and occasionally with cyanosis that is relieved by minimal O_2 supplementation (<40%). The chest generally sounds clear without crackles or wheeze, and the chest radiograph shows prominent perihilar pulmonary vascular markings, fluid in the intralobar fissures, and rarely small pleural effusions. Hypercapnia and acidosis are uncommon. Respiratory failure requiring positive pressure support (either with nCPAP or mechanical ventilation) also is uncommon, but when it occurs usually resolves rapidly (<12-24 hr). Most infants recover with supportive care alone, and over the first 24-72 hours the tachypnea and O_2 requirements slowly resolve. Distinguishing TTN from RDS and other respiratory disorders (e.g., pneumonia) may be difficult, and transient tachypnea is frequently a diagnosis of exclusion. The distinctive features of TTN are rapid recovery of the infant and the absence of radiographic findings for RDS (low lung volumes, diffuse reticulogranular pattern, air bronchograms) and other lung disorders.

Treatment for TTN is supportive. There is no evidence supporting the use of oral furosemide or nebulized racemic epinephrine in this disorder. Inhaled β_2 -agonists such as albuterol (salbutamol) increase expression and activation of ENaC and Na^+ ,K^+ -ATPase and facilitate fluid clearance. Emerging evidence suggests that when given early in the course of TTN, albuterol may improve oxygenation, shorten the duration of supplemental O_2 therapy, and expedite recovery.

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122.7

Aspiration of Foreign Material (Fetal Aspiration Syndrome, Aspiration Pneumonia)

Shawn K. Ahlfeld

Keywords

aspiration pneumonia
tracheoesophageal fistula
gastroesophageal reflux

With fetal distress, infants often initiate vigorous respiratory movements in utero because of interference with the supply of oxygen through the placenta. Under such circumstances, the infant may aspirate amniotic fluid containing vernix caseosa, epithelial cells, meconium, blood, or material from the birth canal, which may block the smallest airways and interfere with alveolar exchange of O_2 and CO_2 . Pathogenic bacteria may accompany the aspirated material, and pneumonia may ensue, but even in noninfected cases, respiratory distress accompanied by radiographic evidence of aspiration is seen (Fig. 122.7).

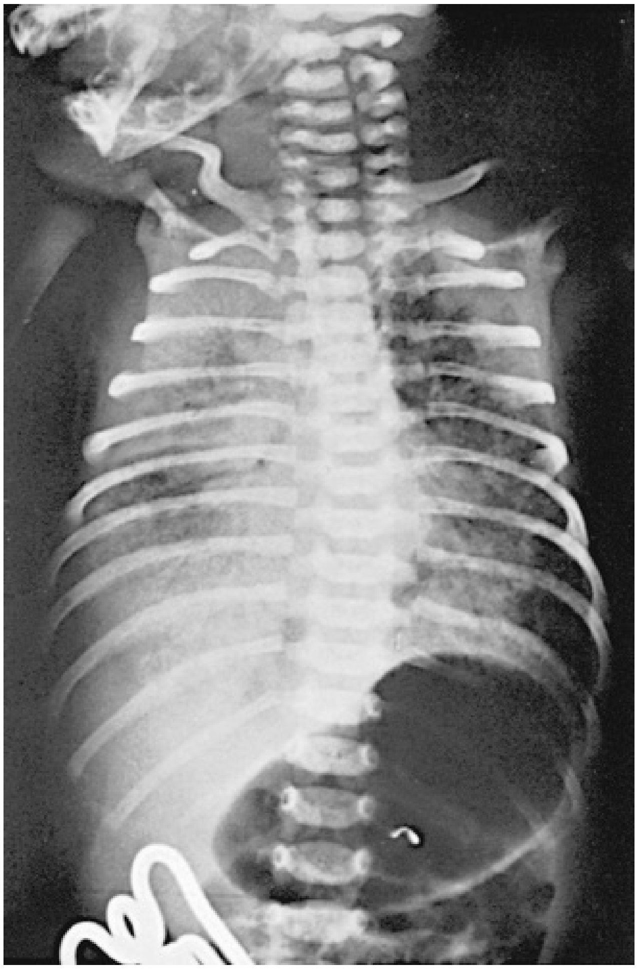

FIG. 122.7 Fetal aspiration syndrome (aspiration pneumonia). Note the coarse granular pattern with irregular aeration typical of fetal distress from the aspiration of material contained in amniotic fluid, such as vernix caseosa, epithelial cells, and meconium. (From Goodwin SR, Grave SA, Haberkern CM: Aspiration in intubated premature infants, *Pediatrics* 75:85–88, 1985.)

Postnatal pulmonary aspiration may also occur in newborn infants as a result of prematurity, tracheoesophageal fistula, esophageal and duodenal obstruction, gastroesophageal reflux, improper feeding practices, and administration of depressant medicines. To avoid aspiration of gastric contents, the stomach should be aspirated using a soft catheter just before surgery or other major procedures that require anesthesia or conscious sedation. The treatment of **aspiration pneumonia** is symptomatic and may include respiratory support and systemic antibiotics. Gradual improvement generally occurs over 3-4 days.

122.8

Meconium Aspiration

Shawn K. Ahlfeld

Keywords

meconium aspiration syndrome
MAS
persistent pulmonary hypertension
pneumothorax

Meconium-stained amniotic fluid is found in 10–15% of births and usually occurs in term or postterm infants. **Meconium aspiration syndrome (MAS)** develops in 5% of such infants; 30% require mechanical ventilation, and 3–5% die. Usually, but not invariably, fetal distress and hypoxia occur before the passage of meconium into amniotic fluid. The infants are meconium stained and may be depressed and require resuscitation at birth. Fig. 122.8 shows the pathophysiology of the MAS. Infants with MAS are at increased risk of **persistent pulmonary hypertension** (see Chapter 122.9).

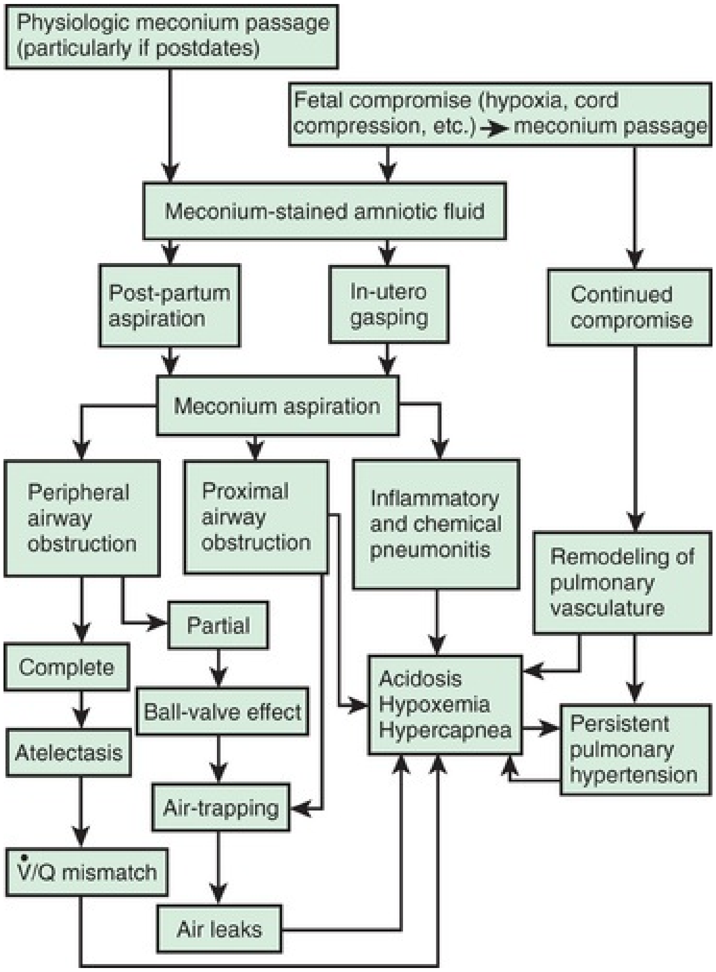
Physiologic meconium passage (particularly if postdates)
Fetal compromise (hypoxia, cord compression, etc.) → meconium passage
Meconium-stained amniotic fluid
Post-partum aspiration
In-utero gasping
Continued compromise
Meconium aspiration
Peripheral airway obstruction
Proximal airway obstruction
Inflammatory and chemical pneumonitis
Remodeling of pulmonary vasculature
Partial
Complete
Ball-valve effect
Atelectasis
Acidosis Hypoxemia Hypercapnea
Persistent pulmonary hypertension
Air-trapping
V̇/Q mismatch
Air leaks

FIG. 122.8 Pathophysiology of meconium passage and the meconium aspiration syndrome. V̇/Q̇, Ventilation-perfusion ratio. (From Wiswell TE, Bent RC: Meconium staining and the meconium aspiration syndrome: unresolved issues, *Pediatr Clin North Am* 40:955–981, 1993.)

Clinical Manifestations

Either in utero or with the first breath, thick, particulate meconium is aspirated into the lungs. The resulting small airway obstruction may produce respiratory distress within the 1st hours, with tachypnea, retractions, grunting, and cyanosis observed in severely affected infants. Partial obstruction of some airways may lead to pneumomediastinum, pneumothorax, or both. Overdistention of the chest may be prominent. The condition usually improves within 72 hr, but when its course requires assisted ventilation, it may be severe with a high risk for mortality. Tachypnea may persist for many days or even several weeks. The typical chest radiograph is characterized by patchy infiltrates, coarse streaking of both lung fields, increased anteroposterior diameter, and flattening of the diaphragm. A normal chest radiograph in an infant with severe hypoxemia and no cardiac malformation suggests the diagnosis of pulmonary hypertension.

Prevention

The risk of meconium aspiration may be decreased by rapid identification of fetal distress and initiation of prompt delivery in the presence of late fetal heart rate deceleration or poor beat-to-beat FHR variability. Despite initial enthusiasm for amnioinfusion, it does not reduce the risk of MAS, cesarean delivery, or other major indicators of maternal or neonatal morbidity. Intrapartum nasopharyngeal suctioning in infants with meconium-stained amniotic fluid does not reduce the risk for MAS. Routine intubation and aspiration of depressed infants (those with hypotonia, bradycardia, or decreased respiratory effort) born through meconium-stained fluid is not effective in reducing the MAS or other major adverse outcomes and is not recommended for neonatal resuscitation.

Treatment

Treatment of the MAS includes supportive care and standard management for respiratory distress. The beneficial effect of mean airway pressure on oxygenation must be weighed against the risk of pneumothorax. Administration of exogenous surfactant and/or iNO to infants with MAS and hypoxemic respiratory failure, or pulmonary hypertension requiring mechanical ventilation, decreases the need for extracorporeal membrane oxygenation (ECMO), which is required by the most severely affected infants who show no response to therapy. In infants with MAS who demonstrate no other signs of sepsis, there is no role for routine antibiotic therapy. Severe meconium aspiration may be complicated by persistent pulmonary hypertension. Patients with MAS refractory to conventional mechanical ventilation may benefit from HFV or ECMO (see Chapter 122.9).

Prognosis

The mortality rate of meconium-stained infants is considerably higher than that of nonstained infants. The decline in neonatal deaths caused by MAS in recent decades is related to improvements in obstetric and neonatal care. Residual lung problems are rare but include symptomatic cough, wheezing, and persistent hyperinflation for up to 5-10 yr. The ultimate prognosis depends on the extent of CNS injury from asphyxia and the presence of associated problems such as pulmonary hypertension.

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122.9

Persistent Pulmonary Hypertension

# of the Newborn (Persistent Fetal Circulation)

Shawn K. Ahlfeld

Keywords

persistent pulmonary hypertension of the newborn
PPHN
persistent fetal circulation
extracorporeal membrane oxygenation
ECMO
inhaled nitric oxide
iNO
sildenafil
high-frequency oscillatory ventilation
HFOV
alveolocapillary dysplasia
ACD

Persistent pulmonary hypertension of the newborn (**PPHN**) occurs in term and postterm infants most often. Predisposing factors include birth asphyxia, MAS, early-onset sepsis, RDS, hypoglycemia, polycythemia, maternal use of nonsteroidal antiinflammatory drugs with in utero constriction of the ductus arteriosus, maternal late trimester use of selective serotonin reuptake inhibitors, and pulmonary hypoplasia caused by diaphragmatic hernia, amniotic fluid leak, oligohydramnios, or pleural effusions. PPHN is often idiopathic. Some patients with PPHN have low plasma arginine and NO metabolite concentrations and polymorphisms of the carbamoyl phosphate synthase gene, findings suggestive of a possible subtle defect in NO production. The incidence is 1 in 500-1,500 live births, with a wide variation among clinical centers. Regardless of etiology of PPHN, profound hypoxemia from right-to-left shunting and normal or elevated $PaCO_2$ are present (Fig. 122.9).

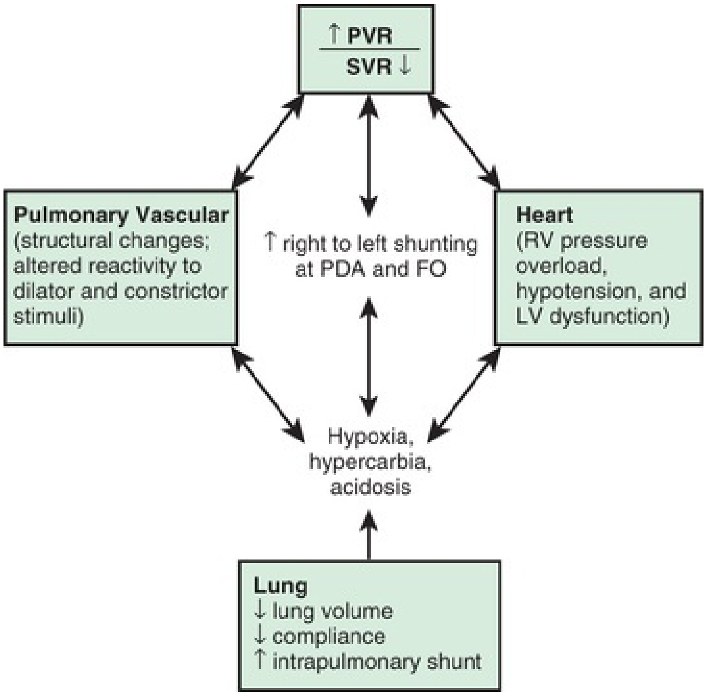
↑ PVR
SVR ↓
Pulmonary Vascular
(structural changes; altered reactivity to dilator and constrictor stimuli)
↑ right to left shunting at PDA and FO
Heart
(RV pressure overload, hypotension, and LV dysfunction)
Hypoxia, hypercarbia, acidosis
Lung
↓ lung volume
↓ compliance
↑ intrapulmonary shunt

FIG. 122.9 **Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn (PPHN). FO, Foramen ovale; LV, left ventricular; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; RV, right ventricular; SVR, systemic vascular resistance. (From Kinsella JP, Abman SH: Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn, *J Pediatr* 126:853–864, 1995.)**

Pathophysiology

Persistence of the fetal circulatory pattern of right-to-left shunting through the PDA and foramen ovale after birth is a result of excessively high pulmonary vascular resistance (PVR). Fetal PVR is usually elevated relative to fetal systemic or postnatal pulmonary pressure. This fetal state normally permits shunting of oxygenated umbilical venous blood to the left atrium (and brain) through the foramen ovale, from which it bypasses the lungs through the ductus arteriosus and passes to the descending aorta. After birth, PVR normally declines rapidly as a consequence of vasodilation secondary to lung inflation, a rise in postnatal PaO_2 , a reduction in $PaCO_2$, increased pH, and release of vasoactive substances. Increased neonatal PVR may be (1) **maladaptive** from an acute injury (not demonstrating normal vasodilation in response to increased O_2 and other changes after birth); (2) the result of increased pulmonary artery medial muscle thickness and extension of smooth muscle layers into the usually nonmuscular, more peripheral pulmonary arterioles in response to chronic fetal hypoxia; (3) a consequence of **pulmonary hypoplasia** (diaphragmatic hernia, Potter syndrome); or (4) **obstructive** as a result of polycythemia, total anomalous pulmonary venous return (TAPVR), or congenital diffuse development disorders of acinar lung development.

Clinical Manifestations

PPHN usually manifests in the delivery room or within the 1st 12 hr after birth. Idiopathic PPHN or PPHN related to polycythemia, hypoglycemia, hypothermia, or asphyxia may result in severe cyanosis and respiratory distress. In some cases, however, initial signs of respiratory distress may be minimal. Infants who have PPHN associated with meconium aspiration, group B streptococcal pneumonia, diaphragmatic hernia, or pulmonary hypoplasia usually exhibit cyanosis, grunting, flaring, retractions, tachycardia, and shock. Multiorgan involvement may be present (see Table 119.2). Myocardial ischemia, papillary muscle dysfunction with mitral and tricuspid regurgitation, and biventricular dysfunction produce cardiogenic shock with decreases in pulmonary blood flow, tissue perfusion, and O_2 delivery.

Hypoxemia is often labile and out of proportion to the findings on chest radiographs. In asphyxia-associated and idiopathic PPHN, chest x-ray findings are often normal, whereas in PPHN associated with **pneumonia** and **diaphragmatic hernia** , parenchymal opacification and bowel/liver in the chest, respectively, are seen.

Diagnosis

Independent of the prenatal history, PPHN should be suspected in all term infants who have cyanosis. Hypoxemia is universal and intermittently unresponsive to 100% O_2 given by oxygen hood. A transient improvement may occur in response to hyperoxic hyperventilation administered by positive pressure ventilation. A PaO_2 or SaO_2 gradient between a preductal (right radial artery) and a postductal (umbilical artery) site of blood sampling suggests right-to-left shunting through the ductus arteriosus. Intracardiac shunting through the patent foramen ovale does not lead to a Pa_{O_2} or Sa_{O_2} gradient.

Real-time echocardiography combined with Doppler flow imaging is very helpful in evaluating PPHN. Systolic flattening of the interventricular septum as the right ventricular systolic pressure approaches the left ventricular systolic pressure can be used to estimate the degree of pulmonary hypertension. The peak velocity of the tricuspid valve regurgitation jet, when present, yields a quantitative estimate of the right ventricular systolic pressure. Likewise, the direction and velocity of a shunt across the PDA provides a quantitative comparison between the aortic and pulmonary artery pressures. In advanced cases, right-to-left or bidirectional shunting across a PDA and a patent foramen ovale can be observed.

The differential diagnosis of PPHN includes cyanotic heart disease (especially obstructed TAPVR), idiopathic pulmonary vein stenosis, congenital surfactant deficiency syndromes, pulmonary artery thrombosis, and congenital diffuse development disorders of acinar lung development (acinar dysplasia, congenital alveolar dysplasia, and alveolar capillary dysplasia with misalignment of the pulmonary veins).

Alveolocapillary dysplasia (ACD) is a rare, highly lethal autosomal recessive disorder of distal lung development characterized by immature lobular development and reduced capillary density. Infants with ACD present with idiopathic PPHN, demonstrating little or no parenchymal lung disease and profound hypoxemia. Over 60% of infants with ACD manifest hypoxemia and respiratory failure within 48 hr of birth, while some with milder disease present beyond 6 mo of age. The diagnosis is made on autopsy in 90% of cases, and the constellation of findings include thickened alveolar septa, increased muscularization of the pulmonary arterioles, a reduced number of capillaries, with the remaining capillaries demonstrating abnormal apposition to the air interface, and misalignment of the intrapulmonary veins. In up to 80% of cases, extrapulmonary malformations of the genitourinary, gastrointestinal, or cardiovascular system are present. Mutations in the transcription factor gene *FOXFI* have been identified in up to 40% of cases, but the diagnosis continues to rest on clinical and histopathologic features. ACD is uniformly lethal and should be suspected in infants with idiopathic PPHN who fail to respond to maximal medical therapy, or when symptoms recur after successful weaning from ECMO. In a United Kingdom ECMO report, up to 14% of infants who failed ECMO ultimately were diagnosed with ACD. Regardless of the timing of presentation, ACD is uniformly fatal, and lung transplantation remains the sole, experimental therapy.

Treatment

Therapy for PPHN is directed toward correcting any predisposing condition (e.g., hypoglycemia, polycythemia) and improving poor tissue oxygenation. The response to therapy is often unpredictable, transient, and complicated by the adverse effects of drugs or mechanical ventilation. Initial management includes O_2 administration and correction of acidosis, hypotension, and hypercapnia. Persistent hypoxemia should be managed with intubation and mechanical ventilation.

Infants with PPHN are usually managed without hyperventilation or alkalization. Gentle ventilation with normocarbia or permissive hypercarbia and avoidance of hypoxemia result in excellent outcomes and a low incidence of chronic lung disease and ECMO use.

Because of their instability and ability to fight the ventilator, newborns with PPHN usually require **sedation** . The use of paralytic agents is controversial and reserved for the newborn who cannot be treated with sedatives alone. Muscle relaxants may promote atelectasis of dependent lung regions and ventilation-perfusion mismatch and may be associated with an increased risk of death.

Inotropic therapy is frequently needed to support blood pressure and perfusion. Whereas dopamine is frequently used as a first-line agent, other agents, such as dobutamine, epinephrine, and milrinone, may be helpful when myocardial contractility is poor. Some of the sickest newborns with PPHN demonstrate hypotension refractory to vasopressor administration. This results from desensitization of the cardiovascular system to catecholamines by overwhelming illness and relative adrenal insufficiency. Hydrocortisone rapidly upregulates cardiovascular adrenergic receptor expression and serves as a hormone substitute in cases of adrenal insufficiency.

Inhaled NO is an endothelium-derived signaling molecule that relaxes vascular smooth muscle and can be delivered to the lung by inhalation. *Use of iNO reduces the need for ECMO support by approximately 40%.* The optimal starting dose is 20 ppm. Higher doses have not been shown to be more effective and are associated with side effects, including methemoglobinemia and increased levels of nitrogen dioxide, a pulmonary irritant. Most newborns require iNO for <5 days. Although NO has been used as long-term therapy in children and adults with primary pulmonary hypertension, prolonged dependency is rare in neonates and suggests the presence of lung hypoplasia, congenital heart disease, or ACD. The maximal safe duration of iNO therapy is unknown. The infant can be weaned to 5 ppm after 6-24 hr of therapy. The dose can then be reduced slowly and discontinued when FIO_2 is <0.6 and the iNO dose is 1 ppm. Abrupt discontinuation should be avoided because it may cause rebound pulmonary hypertension. iNO should be used only at institutions that offer ECMO support or have the capability of transporting an infant on iNO therapy if a referral for ECMO is necessary. Some infants with PPHN do not respond adequately to iNO. Therapy with continuous inhaled or IV prostacyclin (prostaglandin I_2) has improved oxygenation and outcome in infants with PPHN. The safety and efficacy of sildenafil (type 5 phosphodiesterase inhibitor) in newborns with PPHN is under investigation; initial results are promising.

In 5–10% of patients with PPHN, the response to 100% O_2, mechanical ventilation, and drugs is poor, and many of these infants benefit from ECMO. In such patients, 2 parameters have been used to predict mortality: the alveolar-arterial oxygen gradient ($PA\text{-}aO_2$), and the oxygenation index (OI), calculated as FIO_2 (as %) × MAP/PaO_2. A $PA\text{-}aO_2$ >620 for 8-12 hr and OI >40 unresponsive to iNO predict a high mortality rate (>80%) and are indications for ECMO. In carefully selected, severely ill infants with hypoxemic respiratory failure caused by RDS, meconium aspiration pneumonia, congenital diaphragmatic hernia, PPHN, or sepsis, ECMO significantly improves survival.

ECMO is a form of cardiopulmonary bypass that augments systemic perfusion and provides gas exchange. Most experience has been with *venoarterial bypass*, which requires carotid artery ligation and the placement of large catheters in the right internal jugular vein and carotid artery. *Venovenous bypass* avoids carotid artery ligation and provides gas exchange, but it does not support cardiac output. Blood is initially pumped through the ECMO circuit at a rate that approximates 80% of the estimated cardiac output, 150-200 mL/kg/min. Venous return passes through a membrane oxygenator, is rewarmed, and returns to the aortic arch in venoarterial ECMO and to the right atrium in venovenous ECMO. Venous O_2 saturation values are used to monitor tissue O_2 delivery and subsequent extraction for infants undergoing venoarterial ECMO, whereas arterial O_2 saturation values are used to monitor oxygenation for infants receiving venovenous ECMO.

Because ECMO requires complete heparinization to prevent clotting in the circuit, its use is generally avoided in patients with existing intracranial hemorrhage or who are at high risk of developing IVH (weight <2 kg, gestational age <34 wk). In addition, infants being considered for ECMO should have reversible lung disease, no signs of systemic bleeding, and no severe asphyxia or lethal malformations, and they should have been ventilated for <10 days. Complications of ECMO include thromboembolism, air embolization, bleeding, stroke, seizures, atelectasis, cholestatic jaundice, thrombocytopenia, neutropenia, hemolysis, infectious complications of blood transfusions, edema formation, and systemic hypertension.

Prognosis

Survival in patients with PPHN varies with the underlying diagnosis. The long-term outcome for infants with PPHN is related to the associated **hypoxic-ischemic encephalopathy** and the ability to reduce PVR. The long-term prognosis for infants who have PPHN and who survive after treatment with hyperventilation is comparable to that for infants who have underlying illnesses of equivalent severity (e.g., birth asphyxia, hypoglycemia, polycythemia). The outcome for infants with PPHN who are treated with ECMO is also favorable; >80–90% survive, and 60–75% of survivors appear normal at 1-3.5 yr of age.

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122.10

Diaphragmatic Hernia

Shawn K. Ahlfeld

Keywords

congenital diaphragmatic hernia
CDH
hiatal hernia
Bochdalek hernia
Morgagni hernia
paraesophageal hernia
extracorporeal membrane oxygenation
inhaled nitric oxide
sildenafil
high-frequency oscillatory ventilation
in utero tracheal occlusion
observed-to-expected total lung volume
observed-to-expected lung-to-head ratio

A *diaphragmatic hernia* is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax (Fig. 122.10). The etiology is rarely traumatic and usually congenital. The symptoms and prognosis depend on the location of the defect and associated anomalies. The defect may be at the esophageal hiatus (**hiatal hernia**); paraesophageal, adjacent to the hiatus (**paraesophageal hernia** ; Chapter 122.12); retrosternal (**foramen of Morgagni hernia** ; Chapter 122.11); or at the posterolateral portion of the diaphragm (**Bochdalek hernia**). In **congenital diaphragmatic hernia (CDH)** the Bochdalek hernia accounts for up to 90% of the hernias seen, with 80–90% occurring on the left side. The Morgagni hernia accounts for 2–6% of CDH. The size of the defect is highly variable, ranging from a small hole to complete agenesis of this area of the diaphragm. These lesions may cause significant respiratory distress at birth, can be associated with other congenital anomalies, and have significant mortality and long-term morbidity. The overall survival from the CDH Study Group is approximately 70%, but survival is >80% at many centers.

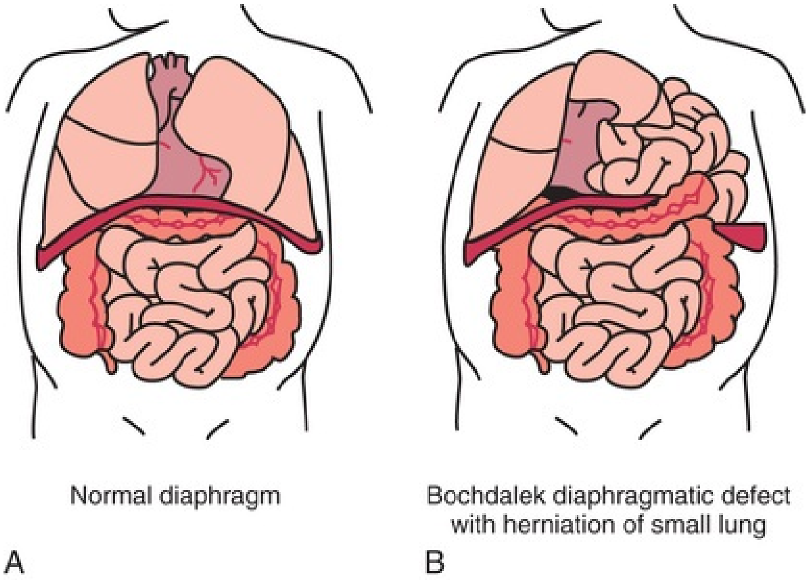

FIG. 122.10 **A,** A normal diaphragm separating the abdominal and thoracic cavity. **B,** Diaphragmatic hernia with a small lung and abdominal contents in the thoracic cavity.

Congenital Diaphragmatic Hernia (Bochdalek)

Pathology and Etiology

Although CDH is characterized by a structural diaphragmatic defect, a major limiting factor for survival is the associated **pulmonary hypoplasia** . Lung hypoplasia was initially thought to be solely caused by the compression of the lung from the herniated abdominal contents, which impaired lung growth. However, emerging evidence indicates that pulmonary hypoplasia, at least in some cases, may precede the development of the diaphragmatic defect.

Pulmonary hypoplasia is characterized by a reduction in pulmonary mass and the number of bronchial divisions, respiratory bronchioles, and alveoli. The pathology of pulmonary hypoplasia and CDH includes abnormal septa in the terminal saccules, thickened alveoli, and thickened pulmonary arterioles. Biochemical abnormalities include relative surfactant deficiencies, increased glycogen in the alveoli, and decreased levels of phosphatidylcholine, total DNA, and total lung protein, all of which contribute to limited gas exchange.

Epidemiology

The incidence of CDH is between 1 in 2,000 and 1 in 5,000 live births, with females affected twice as often as males. Defects are more common on the left (85%) and are occasionally bilateral (<5%). Pulmonary hypoplasia and malrotation of the intestine are part of the lesion, not associated anomalies. Most cases of CDH are sporadic, but familial cases have been reported. Associated anomalies have been reported in up to 30% of cases, including CNS lesions, esophageal atresia, omphalocele, and cardiovascular lesions. CDH is recognized as part of several chromosomal syndromes: trisomies 21, 13, and 18 and Fryns, Brachmann–de Lange, Pallister-Killian, and Turner syndromes.

Diagnosis and Clinical Presentation

In >50% of cases, CDH can be diagnosed on prenatal ultrasonography (US) between 16 and 24 wk of gestation. High-speed fetal MRI can further define the lesion. US findings may include polyhydramnios, chest mass, mediastinal shift, gastric bubble or a liver in the thoracic cavity, and fetal hydrops. Certain imaging features may predict outcome; these include liver position in the chest, observed-to-expected total lung volume (TLV), and observed-to-expected lung-to-head ratio (LHR). Nonetheless, no definitive characteristic reliably predicts outcome. After delivery, a chest radiograph is needed to confirm the diagnosis (Fig. 122.11). In some infants with an echogenic chest mass, further imaging is required. The differential diagnosis may include other diaphragm disorders, such as eventration or a cystic lung lesion (pulmonary sequestration, cystic adenomatoid malformation).

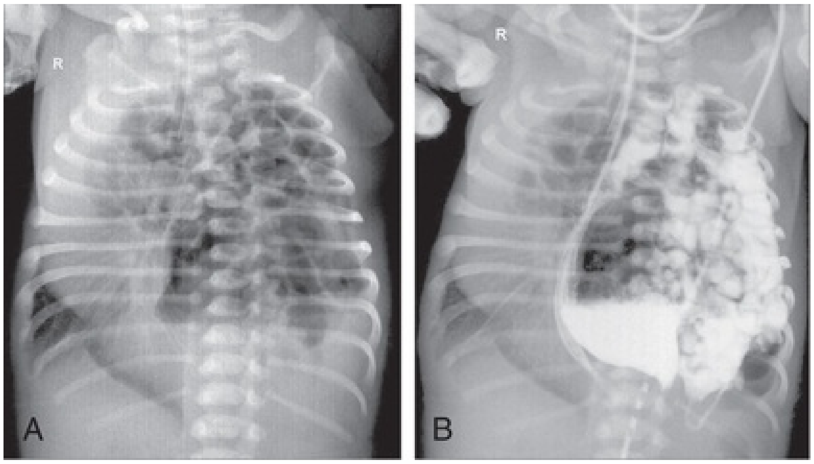

FIG. 122.11 **Bochdalek hernia. A, Chest radiograph showing herniated bowel loops in the left hemithorax, displacement of the mediastinum to the contralateral side, severely reduced lung space, and unclear lung fields bilaterally. B, Upper gastrointestinal tract radiograph showing the stomach and bowel loops stained with contrast in the left hemithorax. (From Hu X, Liu B: Bochdalek hernia, *Lancet* 392:60, 2018.)**

Arriving at the diagnosis early in pregnancy allows for prenatal counseling, possible fetal interventions, and planning for postnatal care. A referral to a center providing high-risk obstetrics, pediatric surgery, and tertiary care neonatology is advised. Careful evaluation for other anomalies should include echocardiography and amniocentesis. To avoid unnecessary pregnancy termination and unrealistic expectations, an experienced multidisciplinary group must carefully counsel the parents of a child diagnosed with a diaphragmatic hernia.

Respiratory distress is a cardinal sign in babies with CDH. It may occur immediately after birth, or there may be a “honeymoon” period of up to 48 hr during which the baby is relatively stable. Early respiratory distress, within 6 hr after birth, is thought to be a poor prognostic sign. Respiratory distress is characterized clinically by tachypnea, grunting, use of accessory muscles, and cyanosis. Children with CDH may also have a scaphoid abdomen and increased chest wall diameter. Bowel sounds may also be heard in the chest with decreased breath sounds bilaterally. The point of maximal cardiac impulse may be displaced away from the side of the hernia if mediastinal shift has occurred. A chest radiograph and passage of a nasal gastric tube are usually sufficient to confirm the diagnosis.

A small group of infants with CDH present beyond the neonatal period. Patients with a delayed presentation may experience vomiting as a result of intestinal obstruction or mild respiratory symptoms. Occasionally, incarceration of the intestine proceeds to ischemia with sepsis and shock. Unrecognized diaphragmatic hernia is a rare cause of sudden death in infants and toddlers. Group B streptococcal sepsis has been associated with delayed onset of symptoms and a CDH (often right side).

Treatment

Initial Management

Delivery at a tertiary center with experience in the management of CDH is required to provide early, appropriate respiratory support. In the delivery room, infants with respiratory distress should be rapidly stabilized with endotracheal intubation. *Prolonged mask ventilation in the delivery room, which enlarges the stomach and small bowel and thus makes oxygenation more difficult, must be avoided and a naso- or orogastric tube placed immediately for decompression.* Arterial (preductal and postductal) and central venous (umbilical) lines are mandated, as are a urinary catheter and nasogastric tube. A preductal arterial oxygen saturation (SpO_2) value ≥85% should be the minimum goal. Volutrauma is a significant problem. *Gentle ventilation with permissive hypercapnia* reduces lung injury, need for ECMO, and mortality. Factors that contribute to pulmonary hypertension (hypoxia, acidosis, hypothermia) should be avoided. Echocardiography is important to guide therapeutic decisions by measuring pulmonary and system vascular pressures and defining the presence of cardiac dysfunction. Routine use of inotropes is indicated in the presence of left ventricular dysfunction. Babies with CDH may be surfactant deficient. Although surfactant is frequently used, no study has proved that it is beneficial in treatment of CDH, and it may precipitate decompensation. In infants with severe respiratory failure and hypoxemia, sedation and paralysis may be required.

Ventilation Strategies

Conventional mechanical ventilation, high-frequency oscillatory ventilation (HFOV), and ECMO are the 3 main strategies to support respiratory failure in the newborn with CDH. The goal is to maintain oxygenation and CO_2 elimination without inducing volutrauma. Conventional ventilation using a gentle, lung protective strategy (PIP <25, PEEP 3-5 cm H_2O) that allows for permissive hypercapnia (PaCO_2 <65-70 mm Hg) is recommended. Permissive hypercapnia (as opposed to hyperventilation with high PIP) has reduced lung injury and improved survival. HFOV as a rescue therapy is indicated if a PIP

>25 is required to maintain appropriate ventilation or if hypoxemia persists.

Inhaled NO is a selective pulmonary vasodilator. Its use reduces ductal shunting and pulmonary pressures and results in improved oxygenation. Although iNO has been helpful in PPHN, randomized trials have not demonstrated improved survival or reduced need for ECMO when iNO is used in newborns with CDH. Nonetheless, iNO is used in patients with CDH as a bridge to ECMO.

Extracorporeal Membrane Oxygenation

The availability of ECMO and the utility of preoperative stabilization has improved survival of babies with CDH. ECMO is the therapeutic option for children in whom conventional ventilation or HFOV fails. ECMO is most often used before repair of the defect. Several objective criteria for ECMO have been developed. Birthweight and the 5 min Apgar score may be the best predictors of outcome in patients treated with ECMO. There is no strict lower weight limit for ECMO, but generally, vessels in infants <1,800-2,000 g are too small to cannulate.

The duration of ECMO for neonates with diaphragmatic hernia is longer (7-14 days) than for those with PPHN (persistent fetal circulation) or meconium aspiration and may last up to 2-4 wk. Timing of repair of the diaphragm while the infant receives ECMO is controversial; some experts prefer early repair to allow a greater duration of ECMO after the repair, whereas many defer repair until the infant has demonstrated the ability to tolerate weaning from ECMO. The recurrence of pulmonary hypertension is associated with high mortality and weaning from ECMO support should be cautious. If the patient cannot be weaned from ECMO after repair of CDH, options include discontinuing support and, in rare cases, lung transplantation.

Novel Strategies for Infants With Congenital Diaphragmatic Hernia

The most reliable prenatal predictors of outcome in children with CDH studied is fetal US. A prospective study of US at 24-26 wk compared fetal LHR with mortality. There were no survivors with LHR <1, but all babies with LHR >1.4 survived. A 2nd important consideration was the presence of liver in the thoracic cavity, which is a poor prognostic feature. Human studies have shown no benefit for in utero repair of CDH. In another single-center study, a late gestation (32-34 wk) fetal MRI-derived TLV >40 mL was associated with >90% survival and only 10% need for ECMO, while TLV <20 mL was associated with <35% survival and >85% need for ECMO.

Based on the observation that hydrostatic pressure exerted by fetal lung fluid plays a critical role in lung growth and maturity, a promising experimental therapy is **in utero tracheal occlusion** . Although initial studies in affected fetuses did not demonstrate success, emerging preliminary reports in those with severe CDH (LHR <1 and intrathoracic liver) suggest that fetoscopic tracheal occlusion is associated with significantly reduced mortality and need for ECMO (see Chapter 116).

Surgical Repair

The ideal time to repair the diaphragmatic defect is under debate. Most experts wait at least 48 hr after stabilization and resolution of the pulmonary hypertension. Good relative indicators of stability are the requirement for conventional ventilation only, a low peak inspiratory pressure, and FIO_2 <50. If the newborn is receiving ECMO, an ability to be weaned from this support should be a consideration before surgical repair. In some centers the repair is done with the cannulas in place; in other centers the cannulas are removed. A subcostal approach is most frequently used (Fig. 122.12). This allows for good visualization of the defect, and if the abdominal cavity cannot accommodate the herniated contents, a polymeric silicone (Silastic) patch can be placed. Both laparoscopic and thoracoscopic repairs have been reported, but these should be reserved for only the most stable infants.

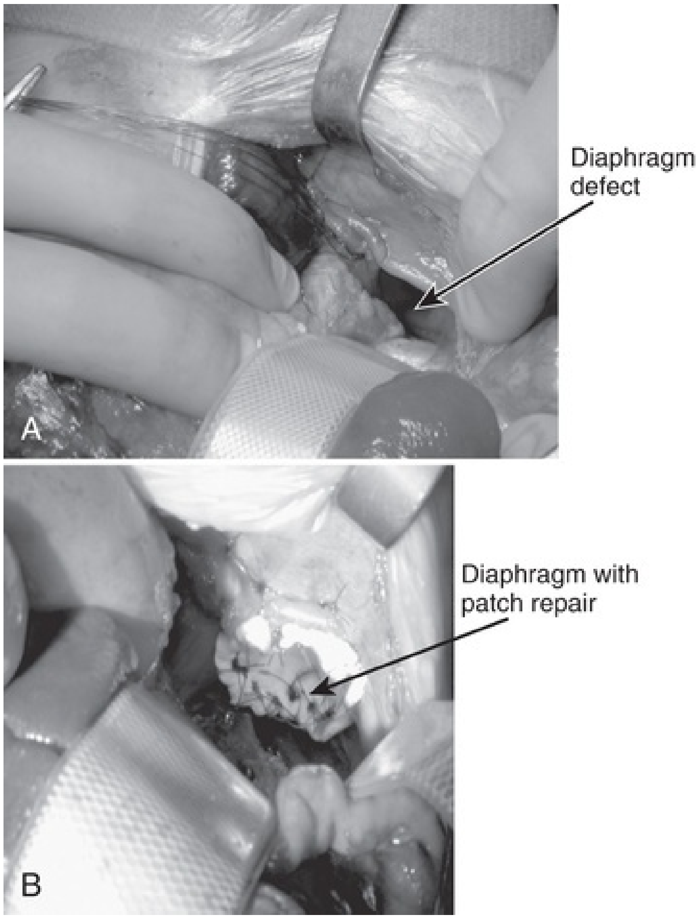

FIG. 122.12 **A,** Intraoperative photo of congenital diaphragmatic hernia (CDH) before repair. **B,** Intraoperative photo of patch repair of CDH.

The defect size and amount of native diaphragm present are variable. Whenever possible, a primary repair using native tissue is performed. If the defect is too large, a porous polytetrafluoroethylene (Gore-Tex) patch is used. There is a higher recurrence rate of CDH in children with patches (the patch does not grow as the child grows) than in those with native tissue repairs. A loosely fitted patch may reduce the recurrence rates.

Following surgical repair, the infant must be carefully monitored for worsening pulmonary hypertension. In some patients, a postoperative course of ECMO is needed. Other recognized complications include bleeding, chylothorax, and bowel obstruction.

Outcome and Long-Term Survival

Overall survival of liveborn infants with CDH is 71%. Relative predictors of a poor prognosis include an associated major anomaly, symptoms before 24 hr of age, severe pulmonary hypoplasia, herniation to the contralateral lung, and the need for ECMO. The size of the defect appears to be the strongest predictor of morbidity.

Pulmonary problems continue to be a source of morbidity for long-term survivors of CDH. Children receiving CDH repair who were studied at 6-11 yr of age demonstrated significant decreases in forced expiratory flow at 50% of vital capacity and decreased peak expiratory flow. Both obstructive and restrictive patterns can occur. Those without severe pulmonary hypertension and barotrauma do the best. Those at highest risk include children who required ECMO and patch repair, but the data clearly show that CDH survivors who did not require ECMO also need frequent attention to pulmonary issues. At discharge, up to 20% of infants require oxygen, but only 1–2% require oxygen past 1 yr old. BPD is frequently documented radiographically but will improve as more alveoli develop and the child ages.

Gastroesophageal reflux disease (GERD) is reported in >50% of children with CDH. GERD is more common in children whose diaphragmatic defect involves the esophageal hiatus. **Intestinal obstruction** is reported in up to 20% of children and may result from a midgut volvulus, adhesions, or a recurrent hernia that became incarcerated. **Recurrent diaphragmatic hernia** is reported in 5–20% in most series. Children with patch repairs are at highest risk.

Children with CDH typically have delayed growth in the 1st 2 yr of life. Contributing factors include poor intake, GERD, and a caloric requirement that may be higher because of the energy required to breathe. Many children normalize and “catch up” in growth by the time they are 2 yr old.

Neurocognitive defects are common and may result from the disease or the interventions. The incidence of neurologic abnormalities is higher in infants who require ECMO (67% vs 24% of those who do not). The abnormalities are similar to those seen in neonates treated with ECMO for other diagnoses and include transient and permanent developmental delay, abnormal hearing or vision, and seizures. Serious hearing loss may occur in up to 28% of children who underwent ECMO. The majority of neurologic abnormalities are classified as mild to moderate.

Other long-term problems include pectus excavatum and scoliosis. Survivors of CDH repair, particularly those requiring ECMO support, have a variety of long-term abnormalities that appear to improve with time but require close monitoring and multidisciplinary support.

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122.11

Foramen of Morgagni Hernia

Shawn K. Ahlfeld

Failure of the sternal and crural portions of the diaphragm to meet and fuse produces the foramen of Morgagni hernia. These defects are usually small, with a greater transverse than anteroposterior diameter, and are more often right sided (90%) but may be bilateral. The transverse colon, small intestine, or liver is usually contained in the hernial sac. Most children with these defects are asymptomatic and are diagnosed beyond the neonatal period, often by chest radiograph performed for evaluation of another condition. The anterolateral radiograph shows a structure behind the heart, and a lateral film localizes the mass to the retrosternal area. Chest CT or MRI confirms the diagnosis. When symptoms occur, they can include recurrent respiratory infections, cough, vomiting, or reflux; in rare cases, incarceration may occur. Repair is recommended for all patients, in view of the risk of bowel strangulation, and can be accomplished laparoscopically. Prosthetic material is rarely required.

122.12

Paraesophageal Hernia

Shawn K. Ahlfeld

Paraesophageal hernia is differentiated from the hiatal hernia in that the gastroesophageal junction is in the normal location. The herniation of the stomach alongside or adjacent to the gastroesophageal junction is prone to incarceration with strangulation and perforation. A previous Nissen fundoplication and other diaphragmatic procedures are risk factors. This unusual diaphragmatic hernia should be repaired promptly after identification.

122.13

Eventration

Shawn K. Ahlfeld

Eventration of the diaphragm is an abnormal elevation consisting of a thinned diaphragmatic muscle that causes elevation of the entire hemidiaphragm or more often the anterior aspect of the hemidiaphragm. This elevation produces a paradoxical motion of the affected hemidiaphragm. Most eventrations are asymptomatic and do not require repair. A congenital form is the result of either incomplete development of the muscular portion or central tendon or abnormal development of the phrenic nerves. Congenital eventration may affect lung development, but it has not been associated with pulmonary hypoplasia. The differential diagnosis includes diaphragmatic paralysis, diaphragmatic hernia, traction injury, and iatrogenic injury after heart surgery. Eventration is also associated with pulmonary sequestration, congenital heart disease, spinal muscular atrophy with respiratory distress, and chromosomal trisomies. Most eventrations are asymptomatic and do not require repair. The indications for surgery include continued need for mechanical ventilation, recurrent infections, and failure to thrive. Large or symptomatic eventrations can be repaired by plication through an abdominal or thoracic approach that is minimally invasive.

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122.14

Extrapulmonary Air Leaks: Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium

Shawn K. Ahlfeld

Keywords

pneumothorax
pneumomediastinum
pulmonary interstitial emphysema

- pneumopericardium
- pulmonary hypoplasia
- tension pneumothorax

Asymptomatic pneumothorax, usually unilateral, is estimated to occur in 1–2% of all newborn infants; symptomatic pneumothorax and pneumomediastinum are less common (see Chapter 113). The incidence of pneumothorax is increased in infants with lung diseases such as meconium aspiration and RDS; in those who receive assisted ventilation, especially if high-frequency ventilation (HFV) support is necessary; and in infants with urinary tract anomalies or oligohydramnios.

Etiology and Pathophysiology

The most common cause of pneumothorax is overdistention resulting in alveolar rupture. Alveolar overdistention can occur with positive pressure ventilation during neonatal resuscitation, or it may occur in association with the “ball-valve” phenomenon that results from aspiration (classically meconium) and bronchial/bronchiolar obstruction. Although **spontaneous rupture** of an underlying pulmonary malformation (e.g., lobar emphysema, congenital lung cyst, pneumatocele) occurs, it is usually in an otherwise normal lung, and no etiology is identified.

Pneumothorax associated with **pulmonary hypoplasia** is common, tends to occur during the 1st few hr after birth, and is caused by reduced alveolar surface area and poorly compliant lungs. It is associated with disorders of decreased amniotic fluid volume (Potter syndrome, renal agenesis, renal dysplasia, chronic amniotic fluid leak), decreased fetal breathing movement (oligohydramnios, neuromuscular disease), pulmonary space-occupying lesions (diaphragmatic hernia, pleural effusion, chylothorax), and thoracic abnormalities (thoracic dystrophies).

Gas from a ruptured alveolus escapes into the interstitial spaces of the lung, where it tracks along small conducting airways and dissects along the peribronchial and perivascular connective tissue sheaths to the hilum of the lung (pulmonary interstitial emphysema). If the volume of escaped air is great enough, it may collect in the mediastinal space (**pneumomediastinum**) or rupture into the pleural space (**pneumothorax**), subcutaneous tissue (**subcutaneous emphysema**), peritoneal cavity (**pneumoperitoneum**), and/or pericardial sac (**pneumopericardium**). Rarely, increased mediastinal pressure may compress the pulmonary veins at the hilum and thereby interfere with pulmonary venous return to the heart and cardiac output. On occasion, air may embolize into the circulation (pulmonary air embolism) and cause cutaneous blanching, air in intravascular catheters, an air-filled heart and vessels on chest radiographs, and death.

Tension pneumothorax occurs if an accumulation of air within the pleural space is sufficient to elevate intrapleural pressure above atmospheric pressure. Unilateral tension pneumothorax results in impaired ventilation not only in the ipsilateral lung but also in the contralateral lung because of a shift in the mediastinum toward the contralateral side. Compression of the vena cava and torsion of the great vessels may interfere with venous return.

Clinical Manifestations

The physical findings of a clinically asymptomatic pneumothorax are hyperresonance and diminished ipsilateral breath sounds with or without tachypnea. Symptomatic pneumothorax is characterized by respiratory distress, which varies from merely high respiratory rate to severe dyspnea, tachypnea, and cyanosis. Irritability and restlessness or apnea may be the earliest signs. The onset is usually sudden but may be gradual; an infant may rapidly become critically ill. Physical exam findings include chest asymmetry with an increased anteroposterior diameter, hyperresonance, and diminished or absent breath sounds. The heart is displaced toward the contralateral side, resulting in displacement of the cardiac apex and point of maximal impulse. The diaphragm is displaced downward, as is the liver with right-sided pneumothorax, and may result in abdominal distention. Because pneumothorax may be bilateral in approximately 10% of patients, symmetry of findings does not rule it out. In tension pneumothorax, signs of shock are typical.

Pneumomediastinum can occur in patients with pneumothorax and is usually asymptomatic. The degree of respiratory distress depends on the amount of trapped gas; if great, bulging of the midthoracic area is observed, the neck veins are distended, and blood pressure is low. The last 2 findings are a result of tamponade of the systemic and pulmonary veins. Although often asymptomatic, subcutaneous emphysema in newborn infants is almost pathognomonic of pneumomediastinum.

Pulmonary interstitial emphysema (PIE) may precede the development of a pneumothorax or may occur independently and lead to increasing respiratory distress as a result of decreased compliance, hypercapnia, and hypoxemia. Hypoxemia is caused by an increased $\mathrm{PA\text{-}aO}_2$ and intrapulmonary shunting. Progressive enlargement of blebs of gas may result in cystic dilation and respiratory deterioration resembling pneumothorax. In severe cases, pulmonary interstitial emphysema precedes the development of BPD. Avoidance of high inspiratory or mean airway pressures may prevent the development of pulmonary interstitial emphysema. Treatment may include bronchoscopy in patients with evidence of mucous plugging, selective intubation and ventilation of the uninvolved bronchus, oxygen, general respiratory care, and HFV.

Diagnosis

Pneumothorax and other air leaks should be suspected in newborn infants who show signs of respiratory distress, are restless or irritable, or have a sudden change in condition. The diagnosis of **pneumothorax** is established by chest radiography, with the edge of the collapsed lung standing out in relief against the pneumothorax (Fig. 122.13). **Pneumomediastinum** is signified by hyperlucency around the heart border and between the sternum and the heart border (Fig. 122.14). *Transillumination* of the thorax is often helpful in the emergency diagnosis of pneumothorax; the affected side transmits excessive light. Associated renal anomalies are identified by US. **Pulmonary hypoplasia** is suggested by signs of uterine compression (extremity contractures), a small thorax on chest radiographs, severe hypoxia with hypercapnia, and signs of the primary disease (hypotonia, diaphragmatic hernia, Potter syndrome).

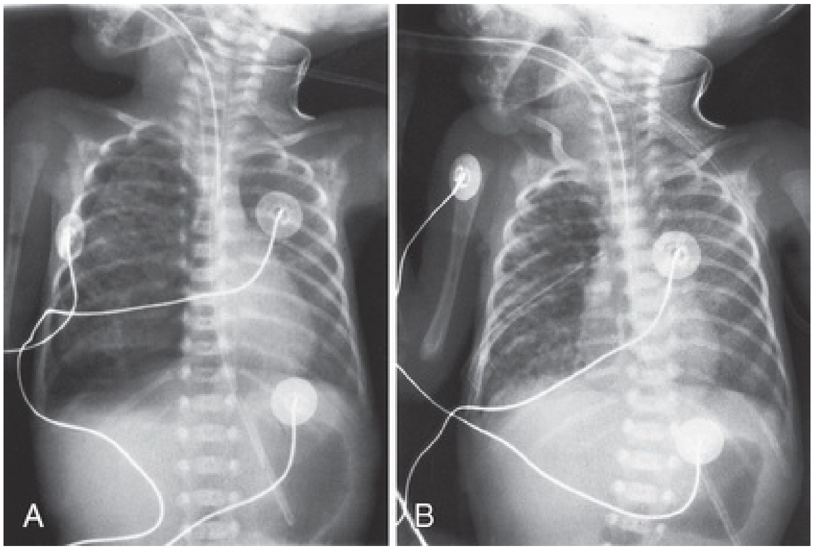

FIG. 122.13 **A,** Right-sided tension pneumothorax and widespread right lung pulmonary interstitial emphysema in a preterm infant receiving intensive care. **B,** Resolution of pneumothorax with a chest tube in place. Pulmonary interstitial emphysema (PIE) persists. (From Meerstadt PWD, Gyll C: *Manual of neonatal emergency x-ray interpretation,* Philadelphia, 1994, Saunders, p 73.)

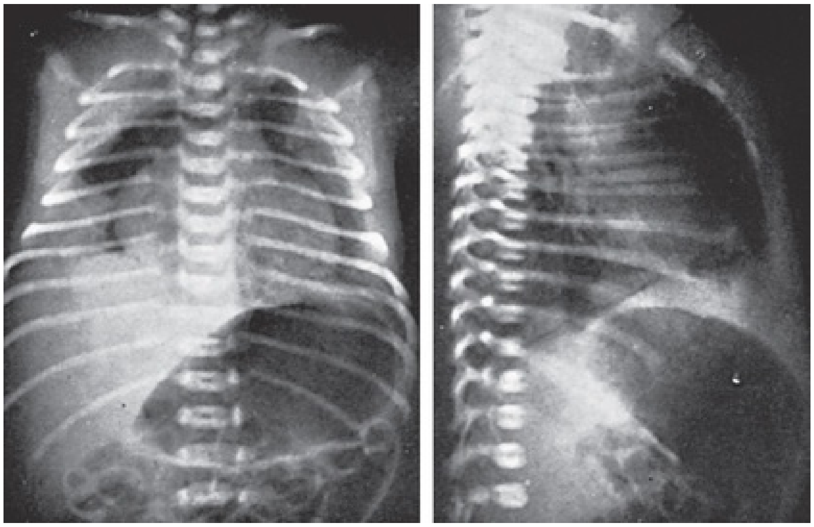

FIG. 122.14 **Pneumomediastinum in newborn infant. The anteroposterior view (*left*) demonstrates compression of the lungs, and the lateral view (*right*) shows bulging of the sternum, each resulting from distention of the mediastinum by trapped air.**

Pneumopericardium may be asymptomatic, requiring only general supportive treatment, but it usually manifests as sudden shock with tachycardia, muffled heart sounds, and poor pulses suggesting tamponade.

Pneumoperitoneum from air dissecting through the diaphragmatic apertures during mechanical ventilation may be confused with intestinal perforation. Abdominal paracentesis can be helpful in differentiating the 2 conditions. The presence of organisms on Gram stain of intestinal contents suggests the latter. Occasionally, pneumoperitoneum can result in an abdominal compartment syndrome requiring decompression.

Treatment

Without a continued air leak, asymptomatic and mildly symptomatic, small pneumothoraces require only close observation. Conservative management of a pneumothorax is effective even in selected infants requiring ventilatory support. Frequent small feedings may prevent gastric dilation and minimize crying, which can further compromise ventilation and worsen the pneumothorax. Breathing 100% oxygen in term infants may accelerate the resorption of free pleural air into blood by reducing the nitrogen tension in blood and producing a resultant nitrogen pressure gradient from the trapped gas in the blood; the clinical effectiveness is not proved, however, and the benefit must be weighed against the risks of O_2 toxicity. With severe respiratory or circulatory embarrassment, emergency decompression by *needle thoracentesis* using a soft, small catheter is indicated. Either immediately or after catheter aspiration, a **chest tube** should be inserted and attached to underwater seal drainage (see Fig. 122.13). If the air leak is ongoing, continuous suction (−5 to −20 cm H_2O) may be needed to evacuate the pneumothorax completely. A pneumopericardium requires prompt evacuation of entrapped air. Severe localized PIE may respond to selective bronchial intubation. Surfactant therapy for RDS reduces the incidence of pneumothorax.

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122.15

Pulmonary Hemorrhage

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Keywords

pulmonary hemorrhage
surfactant
excessive pulmonary blood flow
indomethacin
patent ductus arteriosus

Massive pulmonary hemorrhage is a relatively uncommon, but catastrophic complication with a high risk of morbidity and mortality. Some degree of pulmonary hemorrhage occurs in about 10% of extremely preterm infants. However, massive pulmonary hemorrhage is less common and can be fatal. Autopsy demonstrates massive pulmonary hemorrhage in 15% of neonates who die in the 1st 2 wk of life. The reported incidence at autopsy varies from 1-4 per 1,000 live births. Approximately 75% of affected patients weigh <2,500 g at birth. Prophylactic indomethacin in ELBW infants reduces the incidence of pulmonary hemorrhage.

Most infants with pulmonary hemorrhage have had symptoms of respiratory distress that are indistinguishable from those of RDS. The onset may occur at birth or may be delayed several days. **Hemorrhagic pulmonary edema** is the source of blood in many cases and is associated with significant ductal shunting and high pulmonary blood flow or severe left-sided heart failure resulting from hypoxia. In severe cases, sudden cardiovascular collapse, poor lung compliance, profound cyanosis, and hypercapnia may be present. Radiographic findings are varied and nonspecific, ranging from minor streaking or patchy infiltrates to massive consolidation.

The risk of pulmonary hemorrhage is increased in association with acute pulmonary infection, severe asphyxia, RDS, assisted ventilation, PDA, congenital heart disease, erythroblastosis fetalis, hemorrhagic disease of the newborn, thrombocytopenia, inborn errors of ammonia metabolism, and cold injury. Pulmonary hemorrhage is the only severe complication in which the rate is *increased* with surfactant treatment. Pulmonary hemorrhage is seen with all surfactants; the incidence ranges from 1–5% of treated infants and is higher with natural surfactant. Bleeding is predominantly alveolar in approximately 65% of cases and interstitial in the rest. Bleeding into other organs is observed at autopsy of severely ill neonates, suggesting an additional bleeding diathesis, such as disseminated intravascular coagulation. Acute pulmonary hemorrhage may rarely occur in previously healthy full-term infants. The cause is unknown. Pulmonary hemorrhage may manifest as hemoptysis or blood in the nasopharynx or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients present with acute, severe respiratory failure requiring mechanical ventilation. Chest radiographs usually demonstrate bilateral alveolar infiltrates. The condition usually responds to intensive supportive treatment (see Chapter 436).

Treatment of pulmonary hemorrhage includes blood replacement, suctioning to clear the airway, intratracheal administration of epinephrine, and tamponade with increased mean airway pressure (often requiring HFV). Although surfactant treatment has been associated with the development of pulmonary hemorrhage, administration of exogenous surfactant after the bleeding has occurred can improve lung compliance, because the presence of intraalveolar blood and protein can inactivate surfactant.

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CHAPTER 123

Digestive System Disorders

123.1

Meconium Ileus, Peritonitis, and Intestinal Obstruction

Juan P. Gurria, Rebeccah L. Brown

Keywords

anorectal plugs
cystic fibrosis
Gastrografin enema
meconium ileus
meconium peritonitis
meconium plugs

Meconium consists of bile salts, bile acids, and debris shed from the intestinal mucosa in the intrauterine period. More than 90% of full-term newborn infants and 80% of very-low-birthweight (VLBW) infants pass meconium within the 1st 24 hr. The possibility of intestinal obstruction should be considered in any infant who does not pass meconium by 24-36 hr.

Meconium Plugs

Meconium plugs syndrome refers to intestinal obstruction, usually in the distal colon, rectum, and anal canal, caused by meconium plugs (Fig. 123.1). Resulting from a disproportionately low amount of water in the intestinal lumen, meconium plugs are a rare cause of intrauterine intestinal obstruction and meconium peritonitis unrelated to cystic fibrosis (CF). **Anorectal plugs** may also cause mucosal ulceration from bowel wall erosion and subsequent intestinal perforation. **Meconium plugs** are associated with small left colon syndrome in infants of diabetic mothers, CF (40%), Hirschsprung disease (40%), maternal opiate use, magnesium sulfate therapy for preeclampsia, and tocolysis. Up to 30% of patients can have spontaneous resolution. Initial treatment may include administration of a glycerin suppository or rectal irrigation with isotonic saline. In up to 95% of patients, a Gastrografin enema (meglumine diatrizoate, a hyperosmolar, water-soluble, radiopaque solution containing 0.1% polysorbate 80 [Tween 80] and 37% organically bound iodine) will be both diagnostic and therapeutic, inducing passage of the plug, presumably because the high osmolarity (1,900 mOsm/L) of the solution draws fluid rapidly into the intestinal lumen and loosens the inspissated material. Such rapid loss of fluid into the bowel may result in acute fluid shifts with dehydration and shock, so it is advisable to dilute the contrast material with an equal amount of water and provide intravenous (IV) fluids, during and for several hours after the procedure, sufficient to maintain normal vital signs, urine output, and electrolytes. After removal of a meconium plug, the infant should be observed closely and consideration given to performing diagnostic testing to identify **Hirschsprung disease** (congenital aganglionic megacolon; see Chapter 358.4) and CF (see Chapter 432).

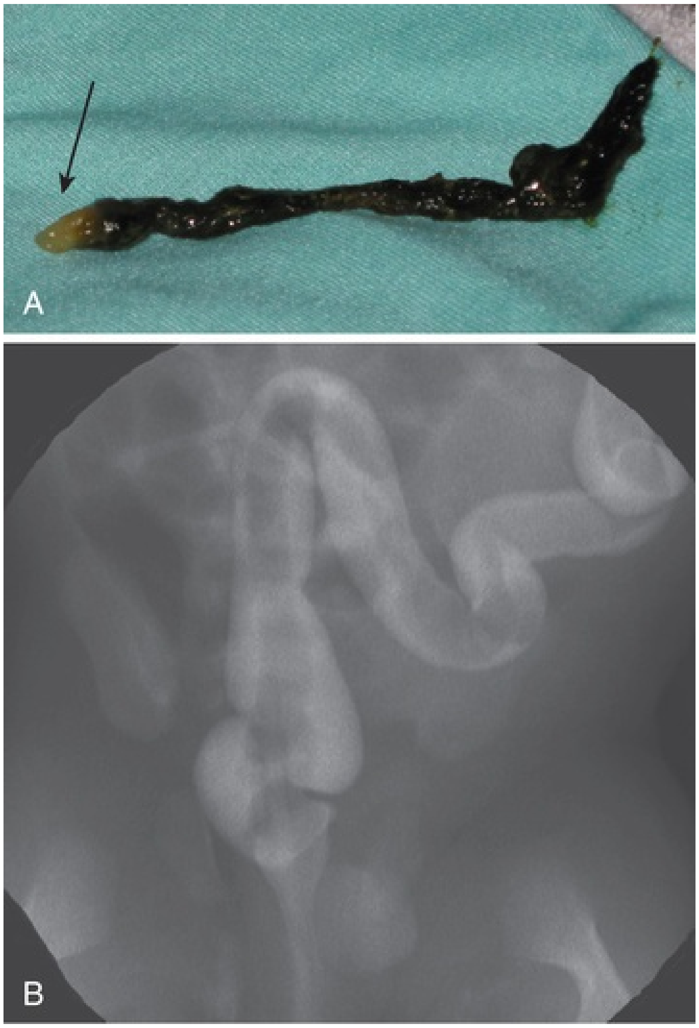

FIG. 123.1 **Meconium plug. A, Meconium plug evacuated after a diagnostic contrast enema demonstrated the distinctive white tip *(arrow)* . B, Image from a contrast enema in a term neonate with vomiting and bowel distension demonstrates the long filling defect characteristic of meconium plug syndrome. The child was relieved of the obstruction after evacuation of the plug, without recurrence of symptoms. (From Hernanz-Schulman M: Congenital and neonatal disorders. In Coley BD, editor: *Caffey's pediatric diagnostic imaging,* ed 12, Philadelphia, 2013, Elsevier, Fig 106-14.)**

Meconium Ileus

Meconium ileus, or impaction of inspissated meconium in the distal small bowel, accounts for up to 30% of cases of neonatal intestinal obstruction. It is common in patients with CF in whom the lack of fetal pancreatic enzymes inhibits digestive mechanisms, and meconium becomes viscid and mucilaginous. Clinically, neonates present with intestinal obstruction with or without perforation. Abdominal distention is prominent, and vomiting, often bilious, becomes persistent, although occasionally inspissated meconium stools may be passed shortly after birth. Meconium ileus can present as early as in utero, in which the fetus develops acute intestinal obstruction resulting in volvulus or perforation, peritoneal ascites, meconium peritonitis, and hydrops; if untreated, fetal loss may occur.

Meconium ileus is primarily associated with cystic fibrosis transmembrane regulator (CFTR) mutations F508del, G542X, W1282X, R553X, and G551D. Patients with two copies of the F508del mutation have a 25% chance of presenting with meconium ileus. F508del plus any other CF mutation confers 17% risk, and two other CF mutations confer a 12% risk of meconium ileus. In addition, non-CFTR genetic modifier genes influence meconium ileus. In families who already have at least one child with CF complicated by meconium ileus, there is a 39% risk for meconium ileus in subsequent children, which is more than the rates expected with autosomal recessive inheritance. In a twin study, 82% of monozygotic twins showed concordance for meconium ileus, whereas only 22% of dizygotic and 24% of two affected siblings showed concordance. Positive newborn screening for CF should prompt sweat testing when the infant weighs >2 kg and is at least 36 wk of corrected gestational age. Genetic testing confirms the diagnosis of CF (see Chapter 432).

The differential diagnosis involves other causes of intestinal obstruction, including intestinal pseudoobstruction, and other causes of pancreatic insufficiency (see Chapter 377). Prenatal diagnosis is readily achieved by ultrasound with identification of enlarged bowel loops or a mass with distention of the proximal small bowel. Clinically the diagnosis can be made with a history of CF in a sibling, by palpation of doughy or cordlike masses of intestines through the abdominal wall, and from the radiographic appearance. Plain radiographs reveal small bowel obstruction. Air-fluid levels may not be apparent because of the thickened meconium.

In contrast to the generally evenly distended intestinal loops above an atresia, the loops may vary in width and are not as evenly filled with gas. At points of heaviest meconium concentration, the infiltrated gas may create a bubbly, granular appearance (Figs. 123.2 and 123.3).

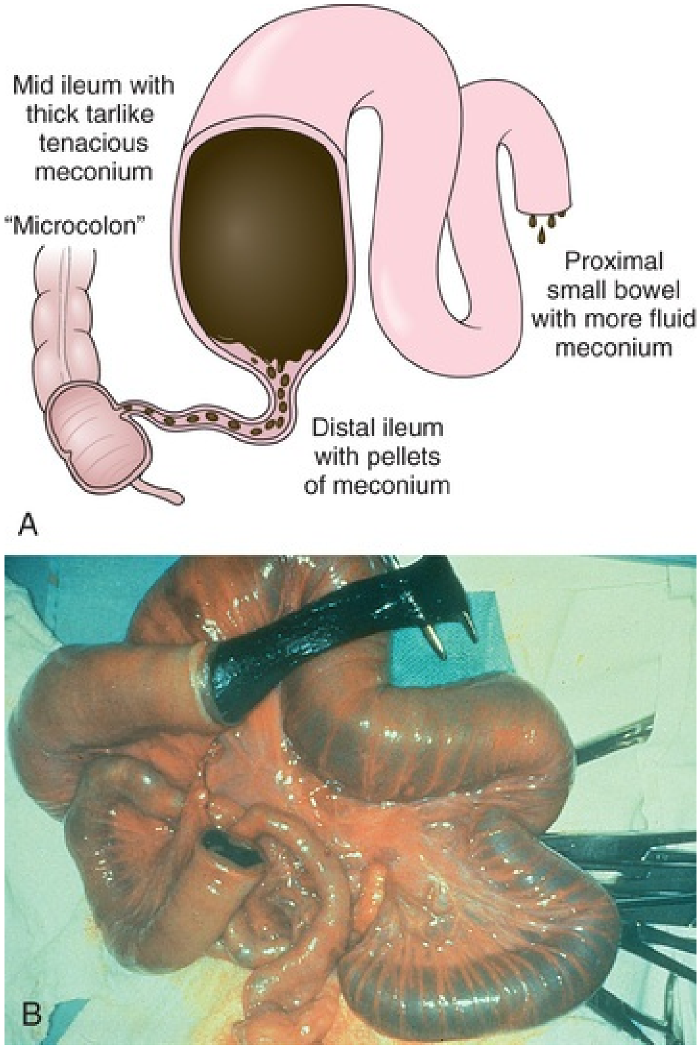
Mid ileum with thick tarlike tenacious meconium
"Microcolon"
Proximal small bowel with more fluid meconium
Distal ileum with pellets of meconium
A
B

FIG. 123.2 Meconium ileus. A, Schematic drawing of uncomplicated meconium ileus. Pellets of inspissated meconium fill the terminal ileum proximal to a microcolon. Several loops of more proximal ileum contain thick, tenacious meconium. B, Enterotomy of proximal bowel and the nature of the thick and tenacious meconium. Note the dilated proximal loops of bowel filled with meconium and the progressively small caliber of the distal bowel leading to the microcolon. (A, From Leonidas JC, Berdon WE, et al: Meconium ileus and its complications: a reappraisal of plain film roentgen diagnostic criteria, *Am J Roentgenol Radium Ther Nucl Med* 108[3]:598–609, 1970; *B,* courtesy of Dr. Wallace W. Neblett III, Nashville, Ten)

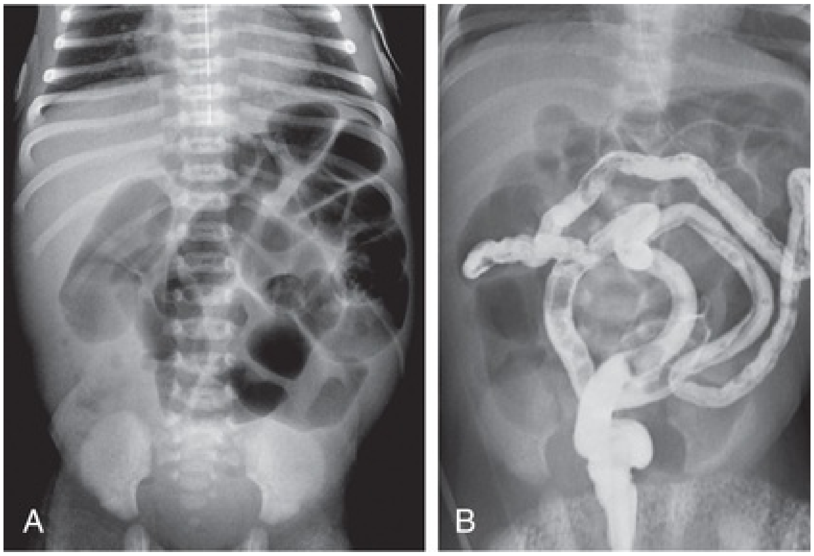

FIG. 123.3 **Uncomplicated meconium ileus. A, Abdominal radiograph in 3 day old infant with abdominal distention and bilious aspirates shows dilation of multiple loops of bowel. No calcifications are seen on the radiograph to suggest complicated meconium ileus. Orogastric tube near the gastroesophageal junction was subsequently advanced. B, Contrast enema demonstrates a microcolon, with multiple meconium plugs, consistent with the diagnosis of meconium ileus. (From Hernanz-Schulman M: Congenital and neonatal disorders. In Coley BD, editor: *Caffey's pediatric diagnostic imaging,* ed 13, Philadelphia, 2019, Elsevier, Fig 102-36).**

Treatment for simple meconium ileus is a high-osmolarity Gastrografin enema, as described for meconium plugs. If the procedure is unsuccessful or perforation of the bowel wall is suspected, a laparotomy is performed and the ileum opened at the point of largest diameter of the impaction. Approximately 50% of these infants have associated intestinal atresia, stenosis, or volvulus that requires surgery. The inspissated meconium is removed by gentle and patient irrigation with warm isotonic sodium chloride or *N* -acetylcysteine (Mucomyst) solution through a catheter passed between the impaction and the bowel wall. Some patients will require bowel resection with a temporary double-barrel enterostomy followed by serial irrigations and distal refeeding, or primary anastomosis at the initial operation. Most infants with meconium ileus survive the neonatal period. If meconium ileus is associated with CF, the long-term prognosis depends on the severity of the underlying disease (see Chapter 432).

Meconium Peritonitis

Perforation of the intestine may occur in utero or shortly after birth. Frequently, the intestinal perforation seals naturally with relatively little meconium leakage into the peritoneal cavity. Perforations occur most often as a complication of meconium ileus in infants with CF but occasionally result from a meconium plug or in utero intestinal obstruction of another cause.

Cases at the most severe end of the spectrum may be diagnosed on prenatal ultrasound with fetal ascites, polyhydramnios, bowel dilation, intraabdominal calcifications, and hydrops fetalis (Fig. 123.4). At the other end are cases in which an intestinal perforation may seal spontaneously and patients remain asymptomatic, except when meconium becomes calcified and is later discovered on radiographs. Alternatively, the clinical picture may be dominated by signs of intestinal obstruction (as in meconium ileus) with abdominal distention, vomiting, and absence of stools or chemical peritonitis presenting with sepsis. Treatment consists primarily of elimination of the intestinal obstruction and drainage of the peritoneal cavity with a timely surgical intervention proved to result in high survival rate and favorable outcome even in complicated meconium peritonitis.

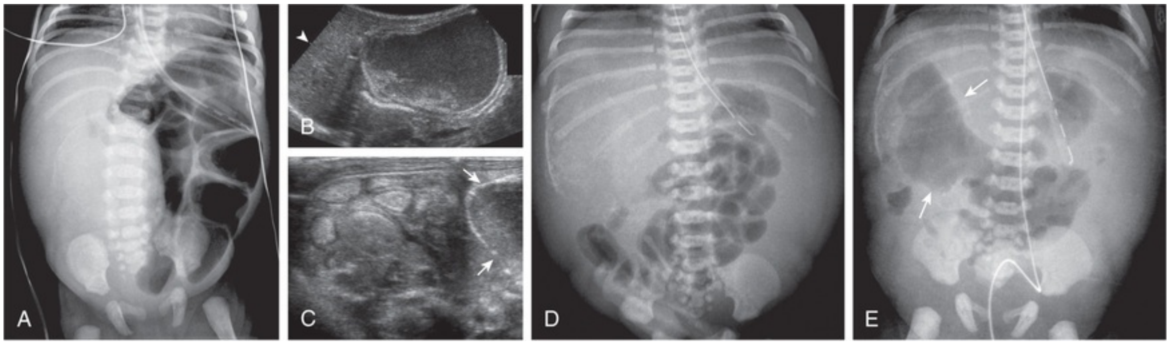

FIG. 123.4 Complicated meconium ileus. A, Abdominal radiograph in 2 day old girl with abdominal distention and bilious aspirates shows absence of bowel gas in the right abdomen with a partly calcified mass displacing gas-filled dilated loops of bowel to the left. B, Ultrasound image demonstrates the subhepatic, partly calcified mass with internal debris and fluid-fluid level. C, Additional ultrasound image shows a portion of the cyst wall *(arrows)* and multiple, abnormal, hyperechoic loops of bowel. D, Abdominal radiograph in different 1 day old infant shows a calcified mass in right upper quadrant, shown at sonography to represent a loculated complex meconium collection. E, Radiograph a few hours later of the same infant shown in D shows a persistent perforation with gas entering into the right upper quadrant collection. (From Hernanz-Schulman M: Congenital and neonatal disorders. In Coley BD, editor: *Caffey's pediatric diagnostic imaging,* ed 13, Philadelphia, 2019, Elsevier, Fig 102-37).

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123.2

Necrotizing Enterocolitis

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Keywords

biomarkers
necrotizing enterocolitis
NEC
pneumatosis intestinalis
primary peritoneal drainage
PPD
probiotics

Necrotizing enterocolitis (NEC) is the most common life-threatening emergency of the gastrointestinal (GI) tract in the newborn period. The disease is characterized by various degrees of mucosal or transmural necrosis of the intestine. The cause of NEC remains unclear but is most likely multifactorial. The incidence of NEC is 5–10% among infants with birthweight <1500 g, with mortality rates of 20–30% and approaching 50% in infants who require surgery. Both incidence and case fatality rates increase with decreasing birthweight and gestational age.

Pathology and Pathogenesis

Many factors contribute to the development of the pathologic findings of NEC, including mucosal ischemia and subsequent necrosis, gas accumulation in the submucosa of the bowel wall (pneumatosis intestinalis), and progression of the necrosis to perforation, peritonitis, sepsis, and death. The distal part of the ileum and the proximal segment of colon are involved most frequently; in fatal cases, gangrene may extend from the stomach to the rectum (NEC totalis). The pathogenesis of NEC remains to be completely elucidated, but 3 major risk factors have been implicated: prematurity, bacterial colonization of the gut, and formula feeding. NEC develops primarily in premature infants with exposure to metabolic substrate in the context of immature intestinal immunity, microbial dysbiosis, and mucosal ischemia. An underlying genetic predisposition is being recognized with variants in genes regulating immunomodulation and inflammation (e.g., Toll-like receptor-4, IL-6), apoptosis and cellular repair (e.g., platelet-activating factor), and oxidant stress (e.g., vascular endothelial growth factor, arginine, nitric oxide). *The greatest risk factor for NEC is prematurity.*

NEC rarely occurs before the initiation of enteral feeding and is much less common in infants fed human milk. Aggressive enteral feeding may predispose to the development of NEC.

Although nearly 90% of all cases of NEC occur in preterm infants, the disease can occur in full-term neonates. NEC in term infants is often a secondary disease, seen more frequently in infants with history of birth asphyxia, Down syndrome, congenital heart disease, rotavirus infections, gastroschisis, and Hirschsprung disease.

Clinical Manifestations

Infants with NEC have a variety of signs and symptoms and may have an insidious or sudden catastrophic onset (Table 123.1). The onset of NEC is usually in the 2nd or 3rd week of life but can be as late as 3 mo in VLBW infants. Age of onset is inversely related to gestational age. The first signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to GI pathology, such as abdominal distention, feeding intolerance, and bloody stools. Because of nonspecific signs, sepsis may be suspected before NEC. The spectrum of illness is broad, ranging from mild disease with only guaiac-positive stools to severe illness with bowel perforation, peritonitis, systemic inflammatory response syndrome, shock, and death. Laboratory derangements may include neutropenia, anemia, thrombocytopenia, coagulopathy, and metabolic acidosis. Hypotension and respiratory failure are common. Progression may be rapid, but it is unusual for the disease to progress from mild to severe after 72 hr.

Table 123.1

Signs and Symptoms Associated With Necrotizing Enterocolitis

GASTROINTESTINAL
Abdominal distention Abdominal tenderness Feeding intolerance Delayed gastric emptying Vomiting Occult/gross blood in stool Change in stool pattern/diarrhea Abdominal mass

Erythema of abdominal wall
SYSTEMIC
Lethargy Apnea/respiratory distress Temperature instability “Not right” Acidosis (metabolic and/or respiratory) Glucose instability Poor perfusion/shock Disseminated intravascular coagulopathy Positive results of blood cultures

From Kanto WP Jr, Hunter JE, Stoll BJ: Recognition and medical management of necrotizing enterocolitis, *Clin Perinatol* 21:335–346, 1994.

Diagnosis

A very high index of suspicion in treating preterm at-risk infants is crucial. Plain abdominal radiographs are essential to make a diagnosis of NEC. The finding of **pneumatosis intestinalis** (air in the bowel wall) confirms the clinical suspicion of NEC and is diagnostic; 50–75% of patients have pneumatosis when treatment is started (Fig. 123.5). Portal venous gas is a sign of severe disease, and **pneumoperitoneum** indicates a perforation (Figs. 123.6 and 123.7). Ultrasound with Doppler flow assessment may be useful to evaluate for free fluid, abscess, and bowel wall thickness, peristalsis, and perfusion.

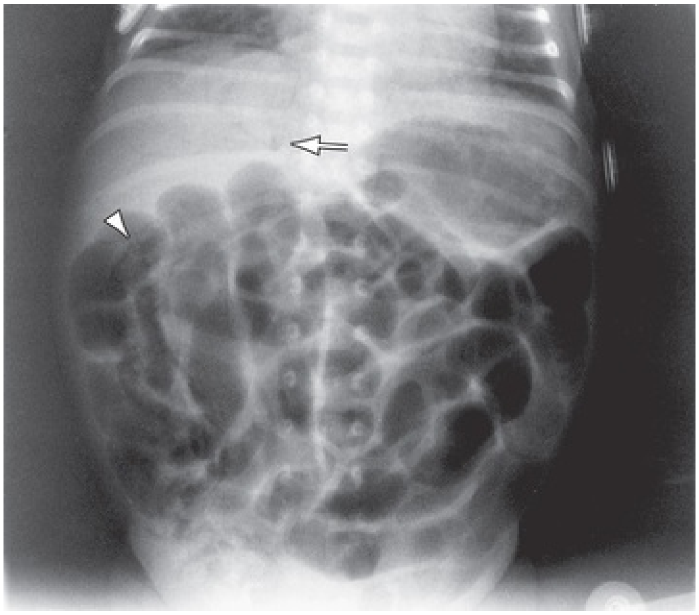

FIG. 123.5 Necrotizing enterocolitis (NEC). Kidney-ureter-bladder film demonstrates abdominal distention, hepatic portal venous gas *(arrow),* and a bubbly appearance of pneumatosis intestinalis (*arrowhead;* right lower quadrant). The latter 2 signs are thought to be pathognomonic for neonatal NEC.

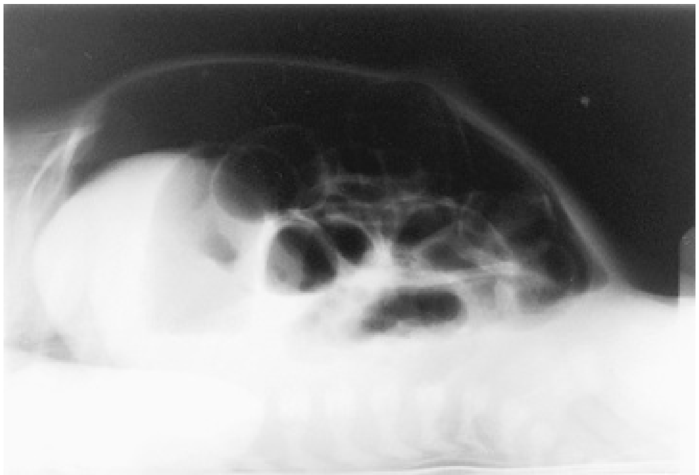

FIG. 123.6 Intestinal perforation. Cross-table abdominal radiograph in patient with neonatal NEC demonstrates marked distention and massive pneumoperitoneum, as evidenced by the free air below the anterior abdominal wall.

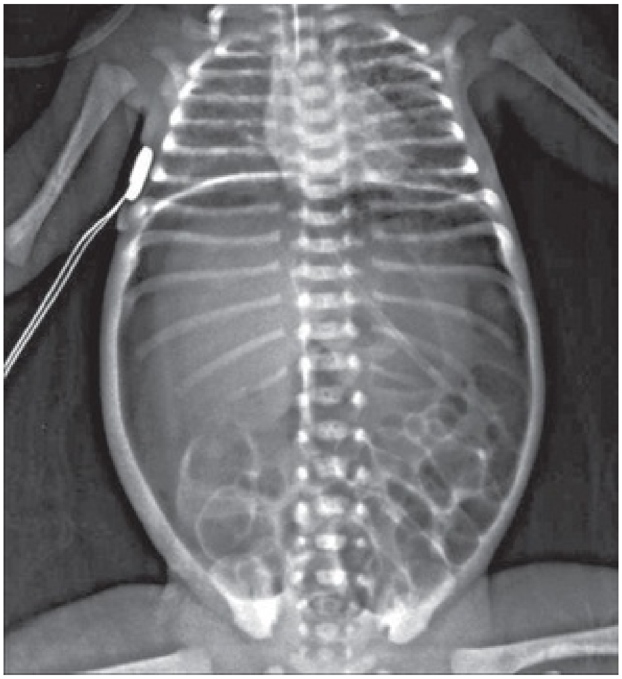

FIG. 123.7 Necrotizing enterocolitis (NEC). Plain abdominal x-ray film of an infant with

perforated NEC showing pneumoperitoneum. (From Tam PKH, Chung PHY, St Peter SD, et al: Advances in paediatric gastroenterology. *Lancet* 390:1072–1082, 2017, Fig 4).

The differential diagnosis of NEC includes specific infections (systemic or intestinal), GI obstruction, volvulus, and isolated intestinal perforation. **Idiopathic focal intestinal perforation** can occur spontaneously or after the early use of postnatal corticosteroids and indomethacin. Pneumoperitoneum develops in such patients, but they are usually less ill than those with NEC.

Treatment

Rapid initiation of therapy is required for infants with suspected as well as proven NEC. There is no definitive treatment for established NEC, so therapy is directed at providing supportive care and preventing further injury with cessation of feeding, nasogastric decompression, and administration of IV fluids. Careful attention to respiratory status, coagulation profile, and acid-base and electrolyte balances are important. Once blood has been drawn for culture, systemic antibiotics (with broad coverage based on the antibiotic sensitivity patterns of the gram-positive, gram-negative, and anaerobic organisms in the particular neonatal ICU) should be started immediately. If present, umbilical catheters should be removed, but good IV access needs to be maintained. Ventilation should be assisted in the presence of apnea or if abdominal distention is contributing to hypoxia and hypercapnia. Intravascular volume replacement with crystalloid or blood products, cardiovascular support with fluid boluses and/or inotropes, and correction of hematologic, metabolic, and electrolyte abnormalities are essential to stabilize the infant with NEC.

The patient's course should be monitored closely by means of frequent physical assessments; sequential anteroposterior and cross-table lateral or lateral decubitus abdominal radiographs to detect intestinal perforation; and serial determinations of hematologic, electrolyte, and acid-base status. Gown and glove isolation and grouping of infants at similar increased risks into cohorts separate from other infants should be instituted to contain an epidemic.

A surgeon should be consulted early in the course of treatment. The only absolute indication for surgery is evidence of perforation on abdominal radiograph (pneumoperitoneum) present in less than half of infants with perforation or necrosis at operative exploration. Progressive clinical deterioration despite maximum medical management, a single fixed bowel loop on serial radiographs, and abdominal wall erythema are relative indications for exploratory laparotomy. Ideally, surgery should be performed after intestinal necrosis develops but before perforation and peritonitis occur. The optimal surgical approach, however, remains controversial. The options for surgical treatment include **primary peritoneal drainage (PPD)** or exploratory laparotomy with resection of the necrotic intestine and usually stoma creation. Two randomized clinical trials in the mid-2000s comparing these approaches failed to demonstrate significant differences in survival, nutritional outcomes, or length of stay. A Cochrane analysis combining the results of both trials concluded that there were no significant benefits or harms of PPD over exploratory laparotomy. A 3rd randomized clinical trial (Necrotizing Enterocolitis Surgery Trial, NCT01029353) compares the 2 surgical approaches, with the primary outcome being death or neurodevelopmental outcomes at 18-22 mo adjusted age. A large, multicenter cohort study of 8,935 patients demonstrated that laparotomy was the initial therapy in two thirds of VLBW infants with surgical NEC, even in those <1,000 g. Mortality was about 30% in both the laparotomy group and the PPD-converted-to-laparotomy group (46% of PPD group eventually required laparotomy). PPD was found to be an independent risk factor for death (50% mortality), likely from its preferential use in the more seriously ill, unstable patients; however, 27% of patients undergoing PPD survived without further surgery. *The surgical approach depends on surgeon preference and physiologic status of the patient.*

Prognosis

Medical management fails in approximately 20–40% of patients with pneumatosis intestinalis at diagnosis; of these, 20–50% die. Early postoperative complications include wound infection, dehiscence, and stomal problems (prolapse, necrosis). Later complications include **intestinal strictures** , which occur in approximately 10% of surgically or medically managed patients. After massive intestinal resection, complications from postoperative NEC include **short bowel syndrome** (malabsorption, growth failure, malnutrition), complications related to central venous catheters (sepsis, thrombosis), and cholestatic jaundice. Preterm infants with NEC who require surgical intervention are at increased risk for adverse growth and neurodevelopmental outcomes.

Prevention

The most effective preventive strategy for NEC is the use of **human milk** . It is well documented that newborns exclusively breastfed have a reduced risk of NEC. However, because human milk does not provide complete nutritional support, fortification is essential for preterm infants. Some studies have suggested that an “exclusive human milk diet” using human rather than bovine fortifiers may further reduce the risk of NEC. Despite concerns about increased risk of NEC with early and aggressive feeding regimens in VLBW infants, a safe protocol remains unknown. While extensive data and meta-analyses would support the use of **probiotics** to prevent NEC, there is no clear consensus on the safest, most effective formulation, timing of administration, or length of therapy. Other preventive strategies using **prebiotics** and **synbiotics** have also been studied, with variable outcomes. Inhibitors of gastric acid secretion (H_2 -receptor blockers, proton pump inhibitors) or prolonged empirical antibiotics in the early neonatal period have been associated with increased risk of NEC and should be avoided.

Because early detection and treatment may prevent late deleterious consequences of NEC, considerable research is focused on identification of **biomarkers** for early identification of NEC, including C-reactive protein (CRP), urinary intestinal fatty acid–binding protein (I-FABP), claudin-3 (a tight junction protein), fecal calprotectin, acylcarnitine, IL-6, IL-8, and the heart rate characteristics (HRC) index. Near-infrared spectroscopy (NIRS) may be a promising predictive diagnostic modality for NEC.

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123.3

Jaundice and Hyperbilirubinemia in the Newborn

Erin E. Shaughnessy, Neera K. Goyal

Keywords

- breast milk jaundice
- breastfeeding jaundice
- Crigler-Najjar syndrome
- hyperbilirubinemia
- jaundice
- kernicterus
- physiologic jaundice
- unconjugated hyperbilirubinemia

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. **Jaundice** is observed during the 1st wk after birth in approximately 60% of term infants and 80% of preterm infants. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin. This unconjugated bilirubin (designated **indirect-acting** by nature of the van den Bergh reaction) is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase and nonenzymatic reducing agents in the reticuloendothelial cells. It may also be partly caused by deposition of pigment from conjugated bilirubin, the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid (UDP)–glucuronyl transferase to form the polar, water-soluble glucuronide of bilirubin **(direct-reacting).** Although bilirubin may have a physiologic role as an antioxidant, elevations of indirect, unconjugated bilirubin are potentially neurotoxic. Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates potentially serious hepatic disorders or a systemic illness.

Etiology

During the neonatal period, metabolism of bilirubin is in transition from the *fetal* *stage,* during which the placenta is the principal route of elimination of the lipid-soluble, unconjugated bilirubin, to the *adult stage,* during which the water-soluble conjugated form is excreted from hepatic cells into the biliary system and gastrointestinal tract. **Unconjugated hyperbilirubinemia** may be caused or increased by any factor that (a) increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, bruising or internal hemorrhage, shortened red blood cell [RBC] life as a result of immaturity or transfusion of cells, increased enterohepatic circulation, infection); (b) damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency); (c) competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation); or (d) leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, prematurity). Gene polymorphisms in the hepatic uridine diphosphate glucuronosyltransferase isoenzyme 1A1 (*UGT1A1*) and the solute carrier organic anion transporter 1B1 (*SLCO1B1*), alone or in combination, influence the incidence of neonatal hyperbilirubinemia.

The toxic effects of elevated serum concentrations of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation (hypoproteinemia, displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam, acidosis, and increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia). Neurotoxic effects are directly related not only to the permeability of the blood-brain barrier and nerve cell membranes but also to neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection. Early and frequent feeding decreases, whereas breastfeeding and dehydration increase, serum levels of bilirubin. Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic recirculation after deconjugation by intestinal glucuronidase (Fig. 123.8). Drugs such as oxytocin (in the mother) and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia.

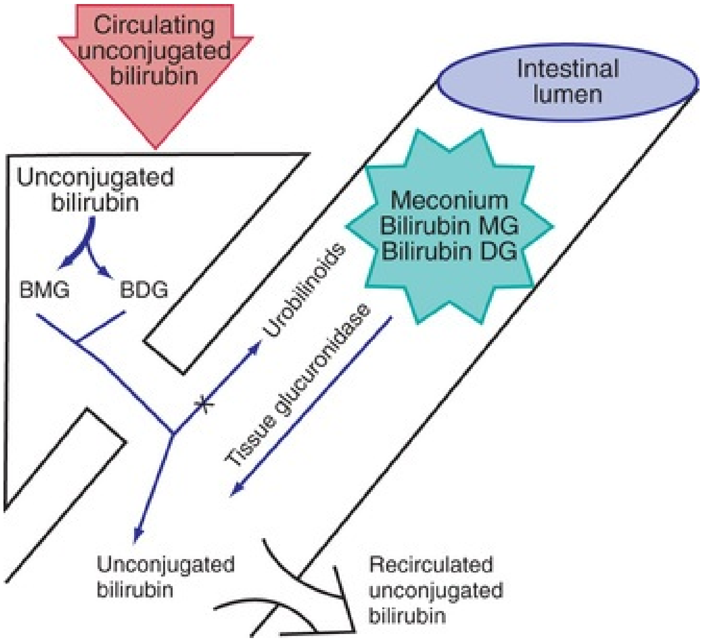
Circulating unconjugated bilirubin
Intestinal lumen
Unconjugated bilirubin
Meconium
Bilirubin MG
Bilirubin DG
BMG
BDG
Urobilinoids
Tissue glucuronidase
Unconjugated bilirubin
Recirculated unconjugated bilirubin

FIG. 123.8 Metabolism of bilirubin in the neonatal period. Neonatal production rate of bilirubin is 6-8 mg/kg/24 hr (in contrast to 3-4 mg/kg/24 hr in adults). Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (bilitranslocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione *S* -transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucuronide (BDG) must be deconjugated by tissue β-glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

Clinical Manifestations

Jaundice usually appears during the early neonatal period, depending on etiology. Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange, jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. Dermal pressure may reveal the anatomic progression of jaundice (face, approximately 5 mg/dL; mid-abdomen, 15 mg/dL; soles, 20 mg/dL), but clinical examination cannot reliably estimate serum levels. Noninvasive techniques for transcutaneous measurement of bilirubin that correlate with serum levels may be used to *screen* infants, but determination of serum bilirubin level is indicated in patients with elevated age-specific transcutaneous bilirubin measurement, progressing jaundice, or risk for hemolysis or sepsis. Infants with severe hyperbilirubinemia may present with lethargy and poor feeding and, without treatment, can progress to acute bilirubin encephalopathy (kernicterus) (see Chapter 123.4).

Differential Diagnosis

The distinction between *physiologic* and *pathologic* jaundice relates to the timing, rate of rise, and extent of hyperbilirubinemia, because some of the same causes of physiologic jaundice (e.g., large RBC mass, decreased capacity for bilirubin conjugation, increased enterohepatic circulation) can also result in pathologic jaundice. Evaluation should be determined on the basis of risk factors, clinical appearance, and severity of the hyperbilirubinemia (Tables 123.2 to 123.4). Jaundice that is present at birth or appears within the 1st 24 hr after birth should be considered **pathologic** and requires immediate attention. Potential diagnoses would include erythroblastosis fetalis, concealed hemorrhage, sepsis, or congenital infections, including syphilis, cytomegalovirus (CMV), rubella, and toxoplasmosis. Hemolysis is suggested by a rapid rise in serum bilirubin concentration (>0.5 mg/dL/hr), anemia, pallor, reticulocytosis, hepatosplenomegaly, and a positive family history. An unusually high proportion of direct-reacting bilirubin may characterize jaundice in infants who have received intrauterine transfusions for erythroblastosis fetalis. Jaundice that first appears on the 2nd or 3rd day is usually **physiologic** but may represent a more severe form. Familial nonhemolytic icterus (**Crigler-Najjar syndrome**) and early-onset breastfeeding jaundice are seen initially on the 2nd or 3rd day. Jaundice appearing after the 3rd day and within the 1st week suggests bacterial sepsis or urinary tract infection; it may also be caused by other infections, notably syphilis, toxoplasmosis, CMV, and enterovirus. Jaundice secondary to extensive ecchymosis or blood extravasation may occur during the 1st day or later, especially in premature infants. Polycythemia may also lead to early jaundice.

Table 123.2

Risk Factors for Development of Severe Hyperbilirubinemia*

MAJOR RISK FACTORS
Predischarge TSB or TcB level in the high-risk zone (see Fig. 123.10) Jaundice observed in the 1st 24 hr Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (G6PD deficiency), elevated end-tidal CO concentration Gestational age 35-36 wk Previous sibling received phototherapy Cephalohematoma or significant bruising Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive East Asian race [†]
MINOR RISK FACTORS
Predischarge TSB or TcB level in the high intermediate-risk zone Gestational age 37-38 wk Jaundice observed before discharge Previous sibling with jaundice Macrosomic infant of a diabetic mother Maternal age ≥25 yr Male gender
DECREASED RISK [‡]
TSB or TcB level in the low-risk zone (see Fig. 123.10) Gestational age ≥41 wk Exclusive bottle feeding Black race Discharge from hospital after 72 hr

[*] In infants ≥35 wk of gestation; factors in approximate order of importance.

[†] Race as defined by mother's description.

[‡] These factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance.

G6PD, Glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

Adapted from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297–316, 2004.

Table 123.3

Evaluation of the Neonate With Significant Jaundice

CONCERN	POSSIBLE DIAGNOSIS	INITIAL LABORATORY TESTS
Jaundice on day 1	Hemolysis [++] TORCH/sepsis Hepatic failure syndromes[*] Internal hemorrhage	CBC, smear Total and direct bilirubin Blood type and Coombs test
Jaundice requiring phototherapy	Hemolysis [++] TORCH/sepsis	As above

Direct/conjugated hyperbilirubinemia	TORCH/sepsis Biliary atresia Other causes of cholestasis [+] Hepatic failure syndromes*	Hepatic enzymes, INR, check newborn screen for metabolic disease, blood glucose, blood ammonia and lactate, urine and blood cultures, CMV and HSV PCR

[+] See Chapter 383 .

[++] Hemolysis may be immune or nonimmune (RBC membrane or enzyme defects).

CMV, Cytomegalovirus; CBC, complete blood count; HSV, herpes simplex virus; PCR, polymerase chain reaction; INR, international normalized ratio; TORCH, toxoplasmosis, other, rubella, CMV, herpes; * Hepatic failure syndromes: HSV, CMV, gestational alloimmune liver disease, mitochondrial liver disease, familial hemophagocytic syndrome; RBC, red blood cell.

Table 123.4

Diagnostic Features of the Various Types of Neonatal Jaundice

DIAGNOSIS	NATURE OF VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	COMM
		Appears	Disappears	mg/dL	Age in Days		
“Physiologic jaundice”:							Usually degree c
Full-term	Indirect	2-3 days	4-5 days	10-12	2-3	<5	
Premature	Indirect	3-4 days	7-9 days	15	6-8	<5	
Hyperbilirubinemia caused by metabolic factors:							Metabol hypoxia distress, carbohy
Full-term	Indirect	2-3 days	Variable	>12	1st wk	<5	Hormon influenc hormone syndrom
Premature	Indirect	3-4 days	Variable	>15	1st wk	<5	Gen Crig synd Gilb synd Drug K, n
Hemolytic states and hematoma	Indirect	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Eryt Rh, cong hem sphe nons

							Infa pyk Dru Encl hem hem
Mixed hemolytic and hepatotoxic factors	Indirect and direct	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Infe bact pyel hepa toxo cyto inclu dise syph Dru
Hepatocellular damage	Indirect and direct	Usually 2-3 days; may appear by 2nd wk	Variable	Unlimited	Variable	Variable, can be >5	Biliary paucity familial galactos hepatitis

From Brown AK: Neonatal jaundice, *Pediatr Clin North Am* 9:575–603, 1962.

There is a long differential diagnosis for jaundice first recognized *after* the 1st week of life, including breast milk jaundice, septicemia, congenital atresia or paucity of the bile ducts, hepatitis, galactosemia, hypothyroidism, CF, and congenital hemolytic anemia crises related to RBC morphology and enzyme deficiencies (Fig. 123.9). The differential diagnosis for persistent jaundice during the 1st mo of life includes hyperalimentation-associated cholestasis, hepatitis, cytomegalic inclusion disease, syphilis, toxoplasmosis, familial nonhemolytic icterus, congenital atresia of the bile ducts, galactosemia, and inspissated bile syndrome following hemolytic disease of the newborn. Rarely, physiologic jaundice may be prolonged for several weeks, as in infants with hypothyroidism or pyloric stenosis.

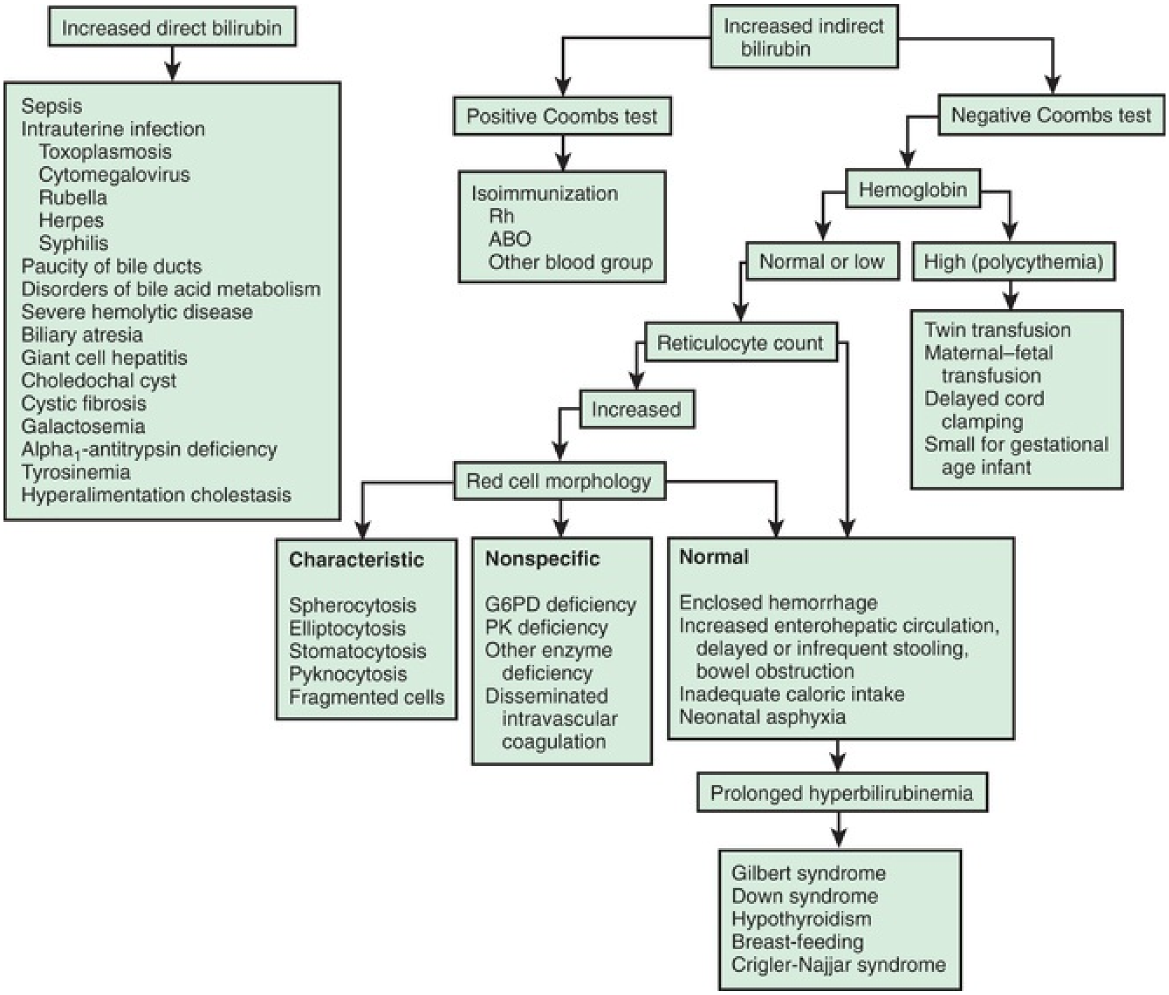
Increased direct bilirubin
Sepsis
Intrauterine infection
Toxoplasmosis
Cytomegalovirus
Rubella
Herpes
Syphilis
Paucity of bile ducts
Disorders of bile acid metabolism
Severe hemolytic disease
Biliary atresia
Giant cell hepatitis
Choledochal cyst
Cystic fibrosis
Galactosemia
Alpha$_1$-antitrypsin deficiency
Tyrosinemia
Hyperalimentation cholestasis
Increased indirect bilirubin
Positive Coombs test
Isoimmunization
Rh
ABO
Other blood group
Negative Coombs test
Hemoglobin
Normal or low
High (polycythemia)
Twin transfusion
Maternal–fetal transfusion
Delayed cord clamping
Small for gestational age infant
Reticulocyte count
Increased
Red cell morphology
Characteristic
Spherocytosis
Elliptocytosis
Stomatocytosis
Pyknocytosis
Fragmented cells
Nonspecific
G6PD deficiency
PK deficiency
Other enzyme deficiency
Disseminated intravascular coagulation
Normal
Enclosed hemorrhage
Increased enterohepatic circulation, delayed or infrequent stooling, bowel obstruction
Inadequate caloric intake
Neonatal asphyxia
Prolonged hyperbilirubinemia
Gilbert syndrome
Down syndrome
Hypothyroidism
Breast-feeding
Crigler-Najjar syndrome

FIG. 123.9 **Schematic approach to the diagnosis of neonatal jaundice. G6PD, Glucose-6-phosphate dehydrogenase; PK, pyruvate kinase. (From Oski FA: Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, editors: *Schaffer and Avery's diseases of the newborn,* ed 6, Philadelphia, 1991, Saunders.)**

Regardless of gestation or time of appearance of jaundice, patients with *significant* hyperbilirubinemia *and* those with symptoms or signs require a complete diagnostic evaluation, which includes determination of direct and indirect bilirubin fractions, hemoglobin, reticulocyte count, blood type, Coombs test, and examination of a peripheral blood smear. Indirect hyperbilirubinemia, reticulocytosis, and a smear with evidence of RBC destruction suggest hemolysis (see Table 123.3). In the absence of blood group incompatibility, non–immunologically induced hemolysis should be considered. If the reticulocyte count, Coombs test result, and direct bilirubin value are normal, physiologic or pathologic indirect hyperbilirubinemia may be present (see Fig. 123.9). If direct hyperbilirubinemia is present, diagnostic possibilities include hepatitis, congenital bile duct disorders (biliary atresia, paucity of bile ducts, Byler disease), cholestasis, inborn errors of metabolism, CF, congenital hemosiderosis, and sepsis.

Physiologic Jaundice (Icterus Neonatorum)

Under normal circumstances, the level of indirect bilirubin in umbilical cord serum is 1-3 mg/dL and rises at a rate of <5 mg/dL/24 hr; thus, jaundice becomes visible on the 2nd or 3rd day, usually peaking between the 2nd and 4th days at 5-6 mg/dL and decreasing to <2 mg/dL between the 5th and 7th days after birth. Jaundice associated with these changes is designated *physiologic* and is believed to be the result of increased bilirubin production from the breakdown of fetal RBCs combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver.

Overall, 6–7% of full-term infants have indirect bilirubin levels >13 mg/dL, and <3% have levels >15 mg/dL. Risk factors for elevated indirect bilirubin include maternal age, race (Chinese, Japanese, Korean, Native American), maternal diabetes, prematurity, drugs (vitamin K_3 , novobiocin), altitude, polycythemia, male sex, trisomy 21, cutaneous bruising, blood extravasation (cephalohematoma), oxytocin induction, breastfeeding, weight loss (dehydration or caloric deprivation), delayed bowel movement, and a family history of, or a sibling who had, physiologic jaundice (see Table 123.2). In infants without these variables, indirect bilirubin levels rarely rise >12 mg/dL, whereas infants with several risk factors are more likely to have higher bilirubin levels. A combination of breastfeeding, variant-glucuronosyltransferase activity (1A1), and alterations of the organic anion transporter-2 gene increases the risk of hyperbilirubinemia. Predicting which neonates are at risk for exaggerated physiologic jaundice can be based on *hour-specific* bilirubin levels in the 1st 24-72 hr of life (Fig. 123.10). Transcutaneous measurements of bilirubin are linearly correlated with serum levels and can be used for screening. Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10-14 days of life. Persistent indirect hyperbilirubinemia beyond 2 wk suggests hemolysis, hereditary glucuronyl transferase deficiency, breast milk jaundice, hypothyroidism, or intestinal obstruction. Jaundice associated with pyloric stenosis may be the result of caloric deprivation, relative deficiency of hepatic UDP–glucuronyltransferase, or an increase in the enterohepatic circulation of bilirubin from the ileus. In premature infants, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants. Peak levels of 8-12 mg/dL are not usually reached until the 4th-7th day, and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion.

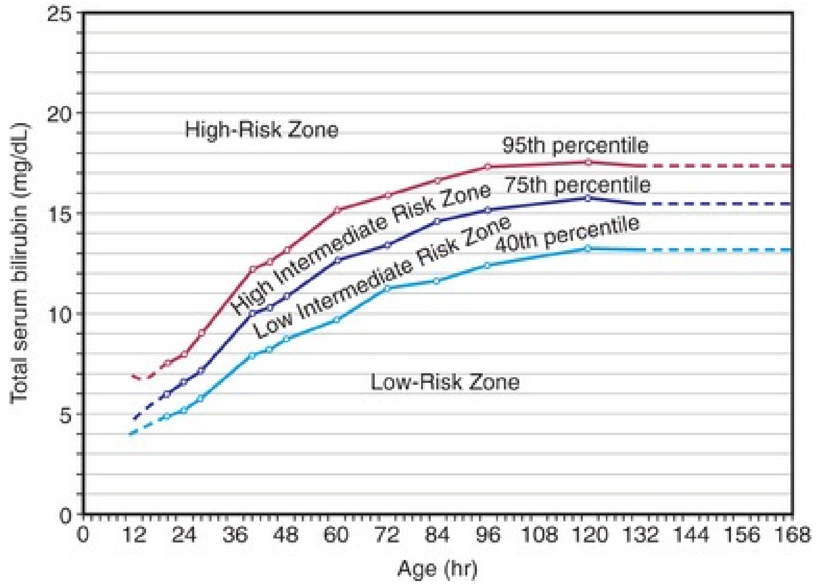

FIG. 123.10 Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values. The high-risk zone is subdivided by the 95th percentile track. The intermediate -risk zone is subdivided into upper and lower risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track. (From Bhutani VK, Johnson L, Sivieri EM: Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns, *Pediatrics* 103:6–14, 1999.)

The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice on the basis of the history, clinical findings, and laboratory data (see Table 123.4). In general, a search to determine the cause of jaundice should be made if (1) it appears in the 1st 24-36 hr after birth, (2) serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr, (3) serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant, (4) jaundice persists after 10-14 days after birth, or (5) direct bilirubin fraction is >2 mg/dL at any time. Other factors suggesting a pathologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower the bilirubin level, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, bleeding disorder, and signs of kernicterus (see Chapter 123.4).

Pathologic Hyperbilirubinemia

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice, or if the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity. It may not be possible to determine the precise cause of an abnormal elevation of unconjugated bilirubin, but many infants with this finding have associated risk factors such as Asian race, prematurity, breastfeeding, and weight loss. Frequently, the terms *exaggerated physiologic jaundice* and *hyperbilirubinemia of the newborn* are used in infants whose primary problem is probably a deficiency or inactivity of bilirubin glucuronyl transferase (**Gilbert syndrome**) rather than an excessive load of bilirubin for excretion (see Table 123.2). The combination of glucose-6-phosphate dehydrogenase (G6PD) deficiency and a mutation of the promoter region of UDP-glucuronyl transferase-1 produces indirect hyperbilirubinemia in the absence of signs of hemolysis. Nonphysiologic hyperbilirubinemia may also be caused by mutations in the gene for bilirubin UDP–glucuronyl transferase.

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction, which typically occurs with high indirect bilirubin levels (see Chapter 123.4). The development of kernicterus (bilirubin encephalopathy) depends on the level of indirect bilirubin, duration of exposure to bilirubin elevation, the cause of jaundice, and the infant's well-being. Neurologic injury including kernicterus may occur at lower bilirubin levels in preterm infants and in the presence of asphyxia, intraventricular hemorrhage, hemolysis, or drugs that displace bilirubin from albumin. The exact serum indirect bilirubin level that is harmful for VLBW infants is unclear.

Jaundice Associated With Breastfeeding

Significant elevation in unconjugated bilirubin (**breast milk jaundice**) develops in an estimated 2% of breastfed term infants after the 7th day, with maximal concentrations as high as 10-30 mg/dL reached during the 2nd-3rd wk. If breastfeeding is continued, the bilirubin gradually decreases but may persist for 3-10 wk at lower levels. If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal range within a few days. With resumption of breastfeeding, bilirubin seldom returns to previously high levels. Phototherapy may be of benefit (see Chapter 123.4). Although uncommon, kernicterus can occur in patients with breast milk jaundice. The etiology of breast milk jaundice is not entirely clear, although β-glucuronidase resulting in deconjugation of bilirubin and increased enterohepatic circulation and other factors in breast milk that might interfere with bilirubin conjugation (e.g., pregnanediol, free fatty acids) have been implicated.

The late jaundice associated with breast milk should be distinguished from an *early onset* , accentuated unconjugated hyperbilirubinemia known as **breastfeeding jaundice** , which occurs in the 1st week after birth in breastfed infants, who normally have higher bilirubin levels than formula-fed infants (Fig. 123.11). Lower milk intake before breast milk production is established can result in dehydration, which hemoconcentrates bilirubin, while also causing fewer bowel movements, which in turn increases the enterohepatic circulation of bilirubin. Prophylactic supplements of glucose water to breastfed infants are associated with higher bilirubin levels, in part because of reduced intake of the higher–caloric density breast milk, and are *not* indicated. Frequent breastfeeding (>10 in 24 hr), rooming-in with night feeding, and ongoing lactation support may reduce the incidence of early breastfeeding jaundice. In addition, supplementation with formula or expressed breast milk is appropriate if the intake seems inadequate, weight loss is excessive, or the infant appears dehydrated.

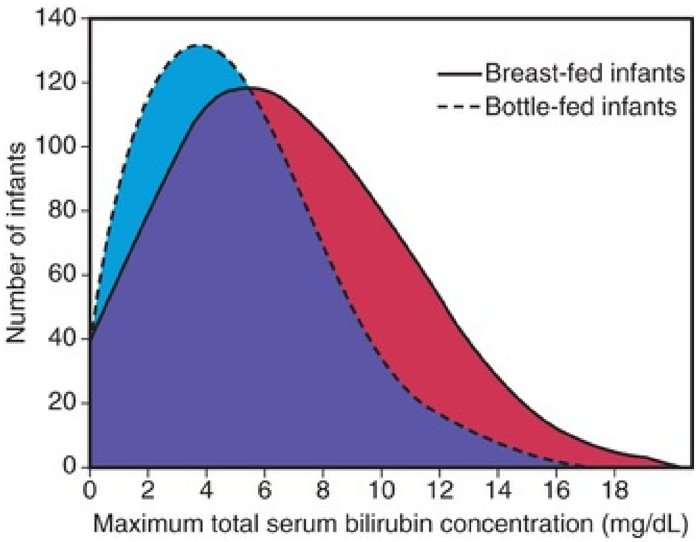

FIG. 123.11 Distribution of maximal bilirubin levels during the 1st wk of life in breastfed and formula-fed white infants weighing >2,500 g. (From Maisels MJ, Gifford K: Normal serum bilirubin levels in the newborn and the effect of breast-feeding, *Pediatrics* 78:837–843, 1986.)

Neonatal Cholestasis

See Chapter 383.1 .

Congenital Atresia of the Bile Ducts

See Chapter 383.1 .

Jaundice persisting for >2 wk or associated with acholic stools and dark urine suggests biliary atresia. All infants with such findings require immediate diagnostic evaluation, including determination of direct bilirubin.

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123.4

Kernicterus

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Keywords

bilirubin encephalopathy
bronze baby syndrome
exchange transfusion
hyperbilirubinemia
kernicterus

metalloporphyrins
opisthions
phototherapy

Kernicterus, or **bilirubin encephalopathy** , is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the blood-brain barrier (BBB), and neuronal susceptibility to injury. Disruption of the BBB by disease, asphyxia, and other factors and maturational changes in BBB permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable. In a large series, however, kernicterus occurred only in infants with a bilirubin >20 mg/dL, 90% of whom were previously healthy, predominantly breastfed, term and near-term infants. The duration of exposure to high bilirubin levels needed to produce toxic effects are unknown; the more immature the infant, the greater the susceptibility to kernicterus. Chapter 123.3 discusses the factors that potentiate the movement of bilirubin across the BBB and into brain cells.

Clinical Manifestations

Signs and symptoms of kernicterus usually appear 2-5 days after birth in term infants and as late as the 7th day in preterm infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill and prostrate, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill, high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched (Table 123.5). Rigidity is rare at this late stage.

Table 123.5

Clinical Features of Kernicterus

ACUTE FORM
Phase 1 (1st 1-2 days): poor suck, stupor, hypotonia, seizures Phase 2 (middle of 1st wk): hypertonia of extensor muscles, opisthotonos, retrocollis, fever Phase 3 (after the 1st wk): hypertonia
CHRONIC FORM
1st yr: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills After 1st yr: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

From Dennery PA, Seidman DS, Stevenson DK: Neonatal hyperbilirubinemia, *N Engl J Med* 344:581–590, 2001.

Many infants who progress to these severe neurologic signs die; the survivors are usually seriously damaged but may appear to recover and for 2-3 mo show few abnormalities. Later in the 1st yr, opisthotonos, muscle rigidity, irregular movements, and convulsions tend to recur. In the 2nd yr the opisthotonos and seizures abate, but irregular, involuntary movements, muscle rigidity, or, in some infants, hypotonia increase steadily. By 3 yr of age, the complete neurologic syndrome is often apparent: bilateral choreoathetosis with involuntary muscle spasms, extrapyramidal signs, seizures, mental deficiency, dysarthric speech, high-frequency hearing loss, squinting, and defective upward eye movements. Pyramidal signs, hypotonia, and ataxia occur in a few infants. In mildly affected infants, the syndrome may be characterized only by mild to moderate neuromuscular incoordination, partial deafness, or “minimal brain dysfunction,” occurring singly or in combination; these problems may be unapparent until the child enters school (see Table 123.5).

Incidence and Prognosis

By pathologic criteria, kernicterus develops in 30% of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25-30 mg/dL. The incidence at autopsy in hyperbilirubinemic preterm infants is 2–16% and is related to the risk factors discussed in Chapter 123.3 . Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs carry a grave prognosis; >75% of infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Developmental delay, deafness, and spastic quadriplegia are common.

Prevention

Although kernicterus has been thought to be a disease of the past, there are reports of neurotoxic effects of bilirubin in term and near-term infants who were discharged as healthy newborns. Effective prevention requires ongoing vigilance and a practical, system-based approach to distinguish infants with benign newborn jaundice from those whose course may be less predictable and potentially harmful. Experts recommend predischarge universal screening for hyperbilirubinemia and assessment of clinical risk factors for severe jaundice and bilirubin-induced neurologic dysfunction. Either total serum bilirubin or transcutaneous bilirubin measurement (interchangeably) is recommended for initial screening, although transcutaneous instruments may be less accurate at higher bilirubin levels (>15 mg/dL) or for infants with darker skin. If transcutaneous levels are documented as ≥15 mg/dL or rising rapidly, confirmation with a total serum bilirubin is recommended. Serum values should also be measured once infants begin phototherapy, because transcutaneous measurement may falsely underestimate total bilirubin in this setting.

Protocols using the hour-specific bilirubin nomogram (see Fig. 123.10), physical examination, and clinical risk factors have been successful in identifying patients at risk for hyperbilirubinemia and candidates for targeted management. Potentially preventable causes of kernicterus include (1) early discharge (<48 hr) with no early follow-up (within 48 hr of discharge); this problem is particularly important in near-term infants (35-37 wk of gestation); (2) failure to check the bilirubin level in an infant noted to be jaundiced in the 1st 24 hr; (3) failure to recognize the presence of risk factors for hyperbilirubinemia; (4) underestimation of the severity of jaundice by clinical (visual) assessment; (5) lack of concern regarding the presence of jaundice; (6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy. Fig. 123.12 provides an evidence-based management algorithm for infants. In addition, it is recommended to determine before discharge each infant's risk factors from established protocols (see Table 123.2).

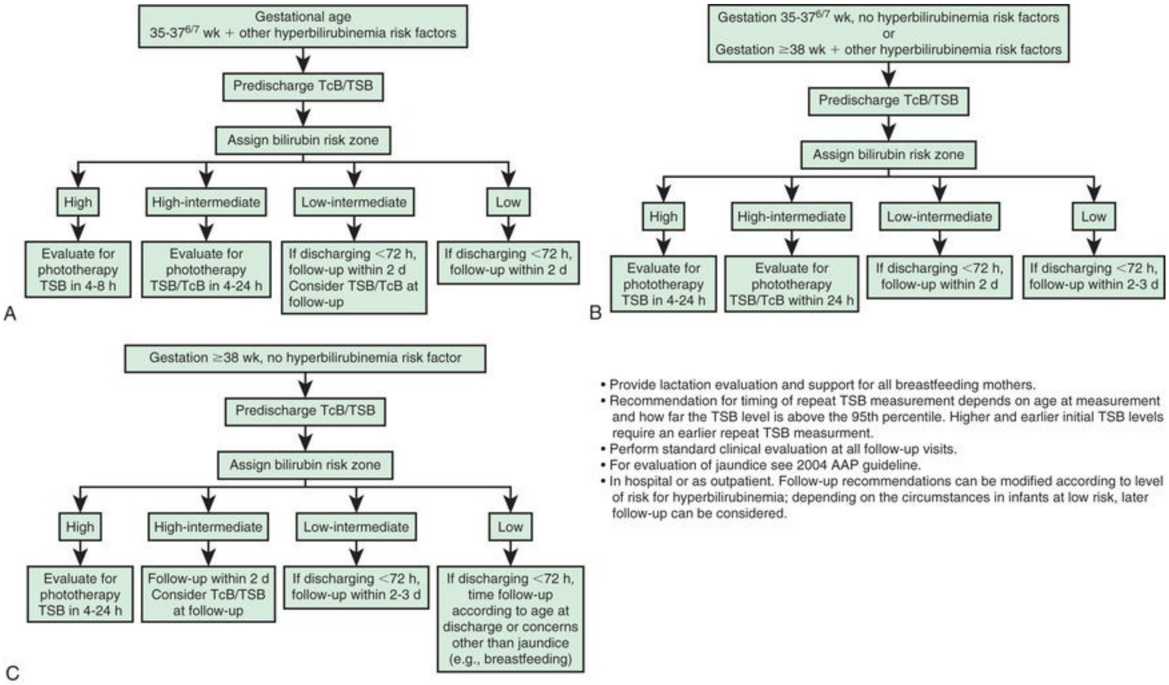
Gestational age
35-37 6/7 wk + other hyperbilirubinemia risk factors
Predischarge TcB/TSB
Assign bilirubin risk zone
High
High-intermediate
Low-intermediate
Low
Evaluate for phototherapy TSB in 4-8 h
Evaluate for phototherapy TSB/TcB in 4-24 h
If discharging <72 h, follow-up within 2 d Consider TSB/TcB at follow-up
If discharging <72 h, follow-up within 2 d
A
Gestation 35-37 6/7 wk, no hyperbilirubinemia risk factors or Gestation ≥38 wk + other hyperbilirubinemia risk factors
Predischarge TcB/TSB
Assign bilirubin risk zone
High
High-intermediate
Low-intermediate
Low
Evaluate for phototherapy TSB in 4-24 h
Evaluate for phototherapy TSB/TcB within 24 h
If discharging <72 h, follow-up within 2 d
If discharging <72 h, follow-up within 2-3 d
B
Gestation ≥38 wk, no hyperbilirubinemia risk factor
Predischarge TcB/TSB
Assign bilirubin risk zone
High
High-intermediate
Low-intermediate
Low
Evaluate for phototherapy TSB in 4-24 h
Follow-up within 2 d Consider TcB/TSB at follow-up
If discharging <72 h, follow-up within 2-3 d
If discharging <72 h, time follow-up according to age at discharge or concerns other than jaundice (e.g., breastfeeding)
C

- Provide lactation evaluation and support for all breastfeeding mothers.
- Recommendation for timing of repeat TSB measurement depends on age at measurement and how far the TSB level is above the 95th percentile. Higher and earlier initial TSB levels require an earlier repeat TSB measurment.
- Perform standard clinical evaluation at all follow-up visits.
- For evaluation of jaundice see 2004 AAP guideline.
- In hospital or as outpatient. Follow-up recommendations can be modified according to level of risk for hyperbilirubinemia; depending on the circumstances in infants at low risk, later follow-up can be considered.

FIG. 123.12 **Treatment of hyperbilirubinemia. Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia. TcB, Transcutaneous bilirubin; TSB, total serum bilirubin. (Data from Maisels MJ, Bhutani VK, Bogen D, et al: Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: an update with clarifications, *Pediatrics* 124:1193–1198, 2009.)**

The following approach is further recommended: (1) any infant who is jaundiced before 24 hr requires measurement of total *and* direct serum bilirubin levels and, if it is elevated, evaluation for possible hemolytic disease, and (2) follow-up should be provided within 2-3 days of discharge to all neonates discharged earlier than 48 hr after birth. Early follow-up is particularly important for infants <38 wk of gestation. The timing of follow-up depends on the age at discharge and the presence of risk factors. In some cases, follow-up within 24 hr is necessary. Postdischarge follow-up is essential for early recognition of problems related to hyperbilirubinemia and disease progression. Parental communication with regard to concerns about the infant's skin color and behavioral activities should be addressed early and frequently, including education about potential risks and neurotoxicity. Ongoing lactation promotion, education, support, and follow-up services are essential throughout the neonatal period. Mothers should be advised to nurse their infants every 2-3 hr and to avoid routine supplementation with water or glucose water to ensure adequate hydration and caloric intake.

Treatment of Hyperbilirubinemia

Regardless of the cause, the goal of therapy is to prevent neurotoxicity related to indirect-reacting bilirubin while not causing undue harm. Phototherapy and, if it is unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below pathologic levels (Table 123.6 and Figs. 123.13 and 123.14). The risk of injury to the central nervous system from bilirubin must be balanced against the potential risk of treatment. There is lack of consensus regarding the exact bilirubin level at which to initiate phototherapy. Because phototherapy may require 6-12 hr to have a measurable effect, it must be started at bilirubin levels below those indicated for exchange transfusion. When identified, underlying medical causes of elevated bilirubin and physiologic factors that contribute to neuronal susceptibility should be treated, with antibiotics for septicemia and correction of acidosis (Table 123.7).

Table 123.6

Suggested Maximal Indirect Serum Bilirubin Concentrations (mg/dL) in Preterm Infants

BIRTHWEIGHT (g)	UNCOMPLICATED*	COMPLICATED*
<1,000	12-13	10-12
1,000-1,250	12-14	10-12
1,251-1,499	14-16	12-14
1,500-1,999	16-20	15-17
2,000-2,500	20-22	18-20

[*] Complications include perinatal asphyxia, acidosis, hypoxia, hypothermia, hypoalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus. Phototherapy is usually started at 50–70% of the maximal indirect level. If values greatly exceed this level, if phototherapy is unsuccessful in reducing the maximal bilirubin level, or if signs of kernicterus are evident, exchange transfusion is indicated.

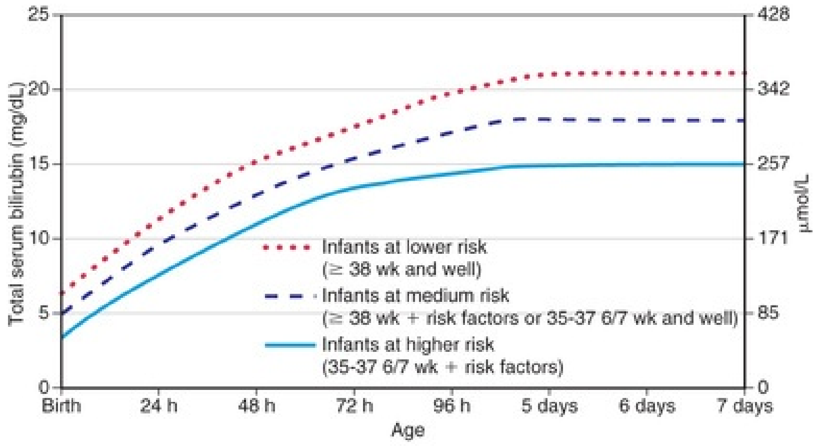

- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0 g/dL (if measured).
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

FIG. 123.13 Guidelines for phototherapy in hospitalized infants of ≥35 wk of gestation. *Note:* These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the total serum bilirubin (TSB) exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin. "Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths approximately 430-490 nm) of at least 30 μW/cm^2 /nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's skin surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system. If TSB levels approach or exceed the exchange transfusion line (see Fig. 123.14), the sides of the bassinette, incubator, or warmer should be lined with aluminum foil or white material, to increase both the surface area of the infant exposed and the efficacy of phototherapy. The presence of hemolysis is strongly suggested if the TSB does not decrease or continues to rise in an infant who is receiving intensive phototherapy. Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin value (cholestatic jaundice) may inconsistently have the bronze baby syndrome. G6PD, Glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297–316, 2004.)

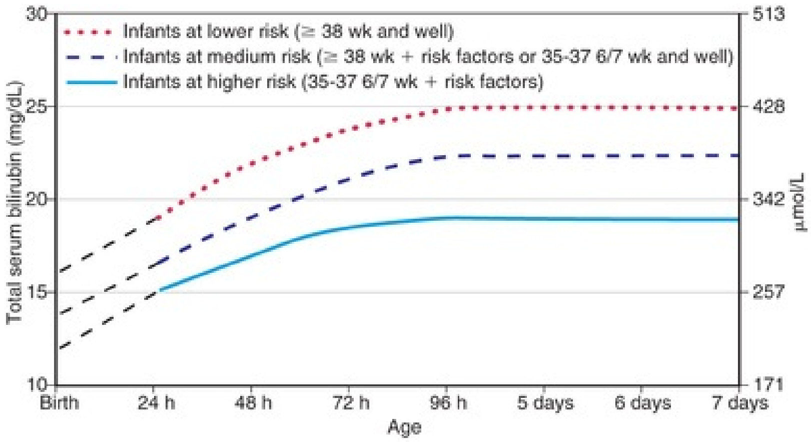

- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥ 5 mg/dL (85 μmol/L) above these lines.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (see legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

FIG. 123.14 Guidelines for exchange transfusion in hospitalized infants of ≥35 wk of gestation. *Note:* These suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin (TSB) rises to these levels despite intensive phototherapy. In a readmitted infant, if the TSB level is above the exchange level, TSB measurement should be repeated every 2-3 hr; exchange transfusion should be considered if the TSB remains above the levels indicated after intensive phototherapy for 6 hr. The following B:A (bilirubin:albumin) ratios can be used together with, but not instead of, the TSB level as an additional factor in determining the need for exchange transfusion. G6PD, Glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297–316, 2004.)

Table 123.7

Example of a Clinical Pathway for Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion

TREATMENT
Use intensive phototherapy and/or exchange transfusion as indicated in Figs. 123.13 and 123.14 .
LABORATORY TESTS
TSB and direct bilirubin levels Blood type (ABO, Rh) Direct antibody test (Coombs) Serum albumin Complete blood cell count with differential and smear for red cell morphology Reticulocyte count

End-tidal CO concentration (if available)
Glucose-6-phosphate dehydrogenase if suggested by ethnic or geographic origin or if poor response to phototherapy
Urine for reducing substances
If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture.
INTERVENTIONS
If TSB ≥25 mg/dL (428 µmol/L) or ≥20 mg/dL (342 µmol/L) in a sick infant or infant <38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary.
In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2-3 mg/dL (34-51 µmol/L) of exchange level (see Fig. 123.14), administer intravenous immune globulin 0.5-1 g/kg over 2 hr and repeat in 12 hr if necessary.
If infant's weight loss from birth is >12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids.
FOR INFANTS RECEIVING INTENSIVE PHOTOTHERAPY:
Breastfeed or bottle-feed (formula or expressed breast milk) every 2-3 hr.
If TSB ≥25 mg/dL (428 µmol/L), repeat TSB within 2-3 hr.
If TSB 20-25 mg/dL (342-428 µmol/L), repeat within 3-4 hr. If TSB <20 mg/dL (342 µmol/L), repeat in 4-6 hr. If TSB continues to fall, repeat in 8-12 hr.
If TSB is not decreasing or is moving closer to level for exchange transfusion, or if the TSB/albumin ratio exceeds levels shown in Fig. 123.14 , consider exchange transfusion (see Fig. 123.14 for exchange transfusion recommendations).
When TSB is <13-14 mg/dL (239 µmol/L), discontinue phototherapy.
Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 hr after discharge to check for rebound.

TSB, Total serum bilirubin.

From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, *Pediatrics* 114:297–316, 2004.

Phototherapy

Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to high-intensity light in the visible spectrum. Bilirubin absorbs light maximally in the blue range (420-470 nm). Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels. Bilirubin in the skin absorbs light energy, causing several photochemical reactions. One major product from phototherapy is a result of a reversible photoisomerization reaction converting the toxic native unconjugated 4Z,15Z-bilirubin into an unconjugated configurational isomer, 4Z,15E-bilirubin, which can then be excreted in bile without conjugation. The other major product from phototherapy is lumirubin, which is an irreversible structural isomer converted from native bilirubin that can be excreted by the kidneys in the unconjugated state.

The therapeutic effect of phototherapy depends on the light energy emitted in the effective range of wavelengths, the distance between the lights and the infant, and the surface area of exposed skin, as well as the rate of hemolysis and in vivo metabolism and excretion of bilirubin. Available commercial phototherapy units vary considerably in spectral output and the intensity of radiance emitted; therefore the wattage can be accurately measured only at the patient's skin surface. Dark skin does not reduce the efficacy of phototherapy. Maximal intensive phototherapy should be used when indirect bilirubin levels approach those noted in Fig. 123.13 and Table 123.7 . Such therapy includes using “special blue” fluorescent tubes, placing the lamps within 15-20 cm (6-8 inches) of the infant, and putting a fiberoptic phototherapy blanket under the infant's back to increase the exposed surface area.

The use of phototherapy has decreased the need for exchange transfusion in term and preterm infants with hemolytic and nonhemolytic jaundice. When indications for exchange transfusion are present, phototherapy should not be used as a substitute; however, phototherapy may reduce the need for repeated exchange transfusions in infants with hemolysis. Conventional phototherapy is applied continuously, and the infant is turned frequently for maximal skin surface area exposure. It should be discontinued as soon as the indirect bilirubin concentration has reduced to levels considered safe with respect to the infant's age and condition. Serum bilirubin levels and hematocrit should be monitored every 4-8 hr in infants with hemolytic disease and those with bilirubin levels near toxic range for the individual infant. Others, particularly older neonates, may be monitored less frequently. Serum bilirubin monitoring should continue for at least 24 hr after cessation of phototherapy in patients with hemolytic disease, because unexpected rises in bilirubin may occur, requiring further treatment. Skin color cannot be relied on for evaluating the effectiveness of phototherapy; the skin of babies exposed to light may appear to be almost without jaundice in the presence of marked hyperbilirubinemia. Although not necessary for all affected infants, intravenous fluid supplementation added to oral feedings may be beneficial in dehydrated patients or infants with bilirubin levels nearing those requiring exchange transfusion.

Complications associated with phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyrinemia, overheating, dehydration (increased insensible water loss, diarrhea), hypothermia from exposure, and a benign condition called “bronze baby syndrome,” which occurs in the presence of direct hyperbilirubinemia. Phototherapy is contraindicated in the presence of porphyria. Before phototherapy is initiated, the infant's eyes should be closed and adequately covered to prevent light exposure and corneal damage. Body temperature should be monitored, and the infant should be shielded from bulb breakage. Irradiance should be measured directly. In infants with hemolytic disease, care must be taken to monitor for the development of anemia, which may require transfusion. *Anemia may develop despite lowering of bilirubin levels.* Clinical experience suggests that long-term adverse biologic effects of phototherapy are absent, minimal, or unrecognized.

The term **bronze baby syndrome** refers to a dark, grayish brown skin discoloration sometimes noted in infants undergoing phototherapy. Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease. The discoloration may result from photo-induced modification of porphyrins, which are often present during cholestatic jaundice and may last for many months. Despite the bronze baby syndrome, phototherapy can continue if needed.

Intravenous Immune Globulin

The administration of intravenous immunoglobulin (IVIG) is an adjunctive treatment for hyperbilirubinemia caused by *isoimmune hemolytic disease* . Its use is recommended when serum bilirubin is approaching exchange levels despite maximal interventions, including phototherapy. IVIG (0.5-1.0 g/kg/dose; repeat in 12 hr) reduces the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis.

Metalloporphyrins

A possible adjunct therapy is the use of metalloporphyrins for hyperbilirubinemia. The metalloporphyrin Sn-mesoporphyrin (SnMP) offers promise as a drug candidate. The proposed mechanism of action is competitive enzymatic inhibition of the rate-limiting conversion of heme-protein to biliverdin (an intermediate metabolite in the production of unconjugated bilirubin) by heme-oxygenase. A single intramuscular dose on the 1st day of life may reduce the need for subsequent phototherapy. Such therapy may be beneficial when jaundice is anticipated, particularly in patients with ABO incompatibility or G6PD deficiency, or when blood products are objected to, as with Jehovah's Witness patients. Complications from metalloporphyrins include transient erythema if the infant is receiving phototherapy. Administration of SnMP may reduce bilirubin levels and decrease both the need for phototherapy and the duration of hospital stay; however, it remains unclear whether treatment with metalloporphyrins for unconjugated hyperbilirubinemia will alter the risk of kernicterus or long-term neurodevelopment impairment. Data on efficacy, toxicity, and long-term benefit are still being evaluated.

Exchange Transfusion

Double-volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels to a safe range and the risk of kernicterus exceeds the procedural risk. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, NEC, infection, graft-versus-host disease, and death. This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range (see Fig. 123.14 and Table 123.7).

Various factors may influence the decision to perform a double-volume exchange transfusion in an individual patient. The appearance of clinical signs suggesting kernicterus is an indication for exchange transfusion at any level of serum bilirubin. A healthy full-term infant with physiologic or breast milk jaundice may tolerate a concentration slightly higher than 25 mg/dL with no apparent ill effect, whereas kernicterus may develop in a sick premature infant at a significantly lower level. A level approaching that considered critical for the individual infant may be an indication for exchange transfusion during the 1st or 2nd day after birth, when a further rise is anticipated, but not typically after the 4th day in a term infant or after the 7th day in a preterm infant, because an imminent fall may be anticipated as the hepatic conjugating mechanism becomes more effective.

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CHAPTER 124

Blood Disorders

124.1

Anemia in the Newborn Infant

Patrick T. McGann, Russell E. Ware

Keywords

ABO incompatibility
anemia of prematurity
fetomaternal hemorrhage
G6PD deficiency
hereditary spherocytosis
physiologic nadir

Anemia is a common laboratory and clinical finding in the newborn period and carries a broad differential diagnosis. Anemia in the newborn may be acute or chronic, and its clinical manifestations range from an asymptomatic laboratory finding to life-threatening signs and symptoms. The diagnosis and interpretation of anemia in the newborn infant are therefore complex and require careful consideration of the gestational age and general health of the infant, details of the perinatal course and delivery, and information regarding the general health of the mother both during pregnancy and through delivery into the postpartum period.

Before interpreting hemoglobin and hematocrit values for infants, it is important to understand the pathophysiology of hemoglobin-oxygen binding and delivery, both before and after birth. Because of the hypoxic environment in utero and the lack of direct gas exchange with the ambient atmosphere, fetal hemoglobin (HbF) predominates throughout late gestation because of its increased affinity to bind and transport oxygen compared to the mother's adult hemoglobin. Despite the predominance of HbF, the in utero environment remains hypoxic, such that the normal hemoglobin concentration is relatively high at birth.

Normal Hematocrit and Hemoglobin Concentrations in Newborn Infants

The diagnostic approach to anemia in the newborn infant begins comparing laboratory results with reference ranges for both gestational age and postnatal age. Although significant variability exists in suggested reference ranges, data collected from more than 25,000 preterm and term infants through the 1st 28 days of life have provided robust data-driven reference ranges. These data, illustrated in Fig. 124.1 , demonstrate a near-linear increase in hemoglobin and hematocrit between 22 and 40 wk of gestation. Notably, the mean corpuscular volume (MCV) in neonates is strikingly higher than toddlers and older children, with normal values ranging from about 100-115 fL at birth. An MCV <100 fL at birth should prompt consideration of underlying α-thalassemia trait or maternal iron deficiency.

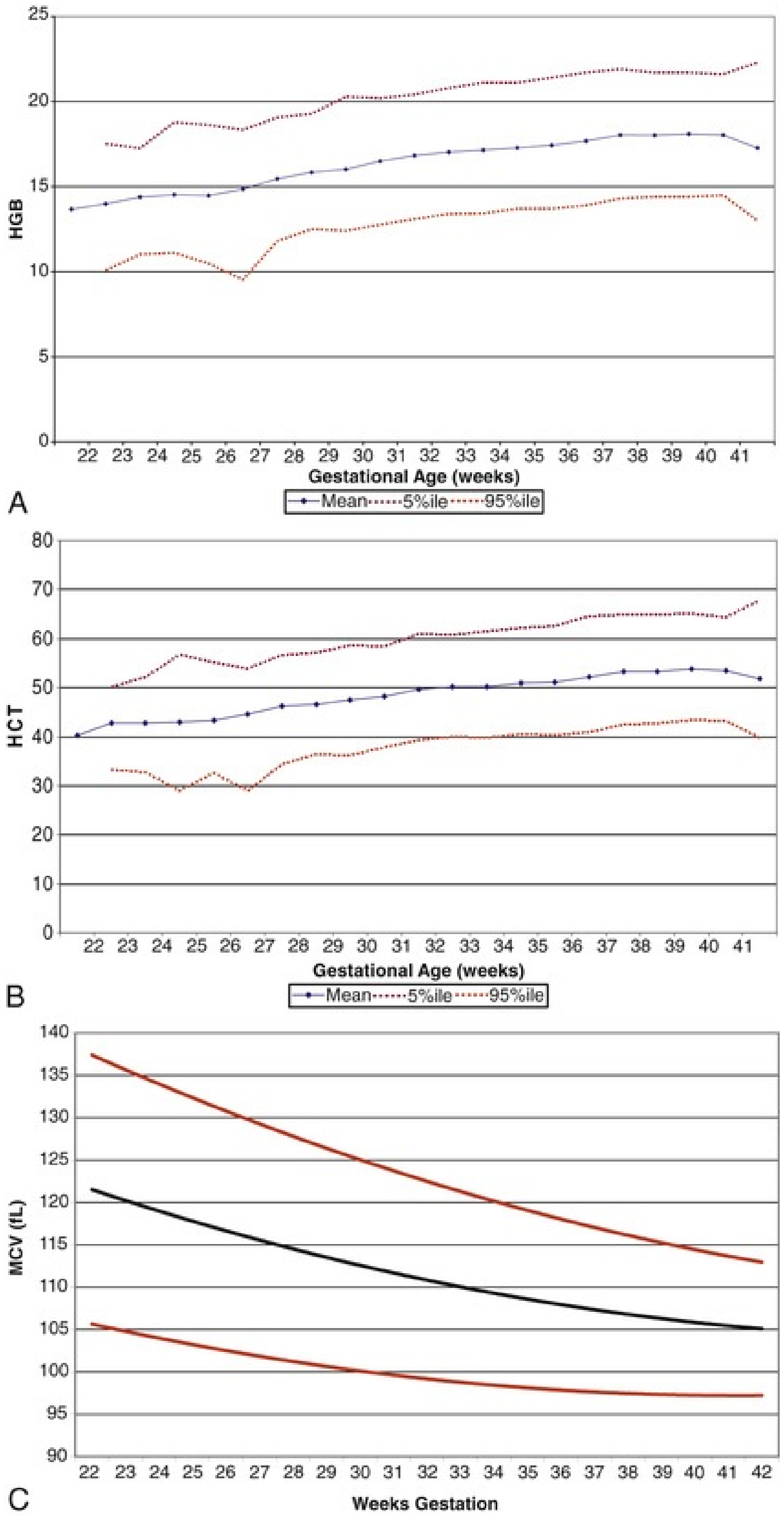

FIG. 124.1 Reference range for hematocrit and hemoglobin concentration according to gestational age. A and B, Reference ranges (5th percentile, mean, and 95th percentile) are shown for blood hemoglobin (A) and hematocrit (B). Concentrations were obtained during the 1st 6 hr after birth, among patients 22-42 wk gestation. Values were

excluded if the diagnosis included abruption, placenta previa, or known fetal anemia, or if a blood transfusion was given before the first hemoglobin was measured. C, References ranges for mean corpuscular volume (MCV) in neonates on 1st day after birth. The *lower line* shows the 5th percentile values, the *middle line* shows the mean values, and the *upper line* shows the 95th percentile values. (From Christensen RD, Jopling HE, Jopling J, Wiedemeir SE: The CBC: reference ranges for neonates, *Semin Perinatol* 33(1):3–11, 2009.)

Over the first days and weeks of postnatal life, increased oxygen in the environment reduces the erythropoietic drive, and this normal developmental and physiologic process results in a slow decrease in hematocrit and hemoglobin concentration. Fig. 124.2 demonstrates the expected decrease in hematocrit and hemoglobin concentration according to postnatal age for both term/postterm (Fig. 124.2*A* and *B*) and preterm (29-34 wk gestation) infants. The *lower dashed lines* in Fig. 124.2 represent the 5th percentile, below which a diagnosis of neonatal anemia should be defined. Eventually, oxygen delivery becomes limiting enough to stimulate new active erythropoiesis, and the hemoglobin concentration begins to rise. This **physiologic nadir** usually occurs between 6 and 10 wk of life for term infants, with a typical low hemoglobin value of 9-11 g/dL, while preterm infants reach their nadir earlier, at 4-8 wk of age with a hemoglobin concentration of 7-9 g/dL.

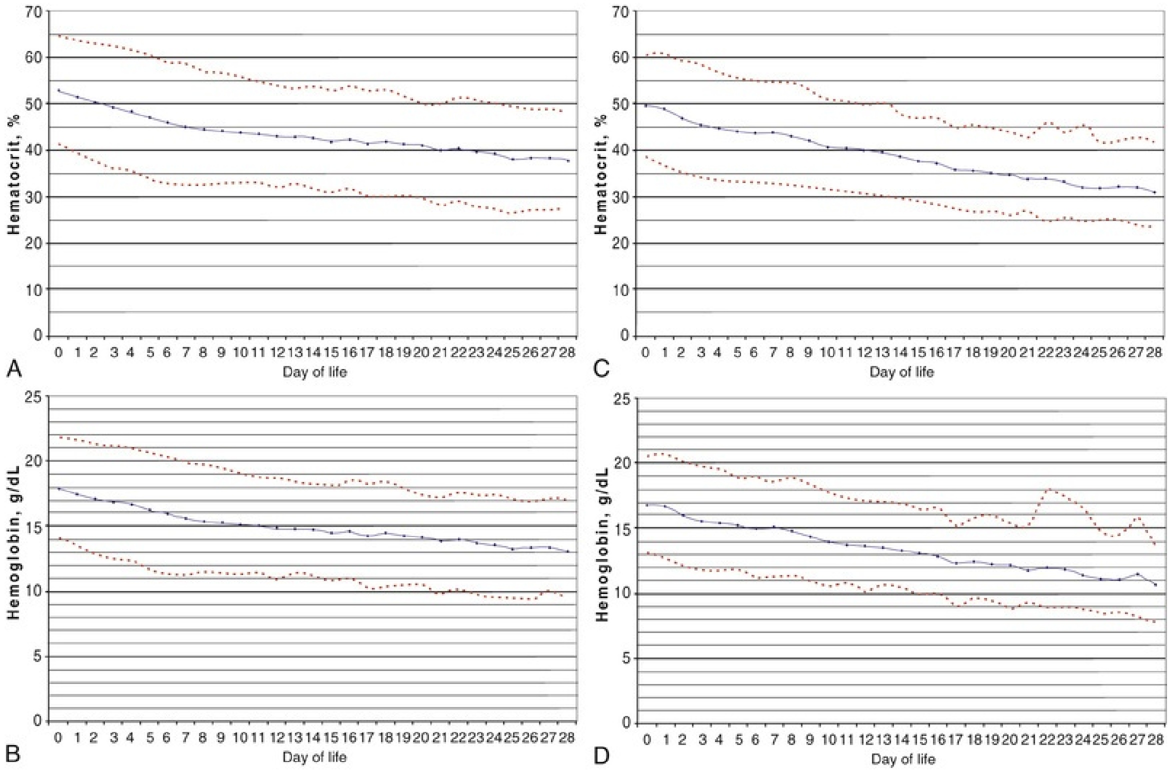

FIG. 124.2 **Reference range for hematocrit and hemoglobin concentration during 1st 28 days of life. A and B, Late preterm and term infants (35-42 wk gestation). C and D, Preterm infants (29-34 wk gestation). The reference ranges are shown for hematocrit (A and C) (41,957 patients) and blood hemoglobin (B and D) (39,559 patients) during the 28 days after birth. Values were divided into 2 groups (A/B and C/D) on the basis of gestational age at delivery. Patients were excluded when their diagnosis included abruption, placenta previa, or fetal anemia, or when a blood transfusion was given. Analysis was not possible for patients <29 wk gestation because virtually all these had repeated phlebotomy and erythrocyte transfusions. (From Jopling J, Henry E, Wiedmeier SE, Christensin RD: Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period: data from a multihospital health care system, *Pediatrics* 123(2):e333–e337, 2009.)**

Classification of Anemia and Diagnostic Evaluation

As with any diagnostic approach to anemia, low hemoglobin concentration in the newborn period can be classified into 3 broad categories: blood loss; erythrocyte destruction; or underproduction of erythrocytes. Table 124.1 summarizes the most common causes of neonatal anemia according to these categories.

Table 124.1

Differential Diagnosis of Neonatal Anemia

BLOOD LOSS	**↑ RBC DESTRUCTION**	**↓ RBC PRODUCTION**
Iatrogenic blood loss (phlebotomy)	***Immune-Mediated Hemolysis***	Physiologic anemia and anemia of prematurity
Placental hemorrhage	Rh incompatibility	Infection (rubella, CMV, parvovirus B19)
Placental previa	ABO incompatibility	Bone marrow suppression (acute stress in perinatal period)
Injury of umbilical or placental vessels	Minor antigen incompatibility	Hemoglobinopathy (γ-globin mutation, unstable β-hemoglobinopathy, α-thalassemia major)
Fetomaternal transfusion	***RBC Membrane Disorders***	Bone marrow suppression (CMV, EBV)
Fetoplacental transfusion	Hereditary spherocytosis	Diamond Blackfan anemia
Twin-twin transfusion	Hereditary elliptocytosis	Schwachman-Diamond syndrome
Acute perinatal hemorrhage (e.g., cesarean birth, other obstetric trauma)	Hereditary pyropoikilocytosis	Congenital dyserythropoietic anemia
Chronic in utero blood loss	Hereditary stomatocytosis	Fanconi anemia
	RBC Enzyme Disorders	Pearson syndrome
	G6PD deficiency	Congenital leukemia
	Pyruvate kinase	

	deficiency	

CMV, Cytomegalovirus, EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; RBC, red blood cell.

Prior to laboratory testing, a complete medical history, including careful review of the pregnancy and perinatal course, and a careful physical examination are important because they often suggest a specific diagnosis more effectively than extensive laboratory testing. A simple and efficient laboratory workup is critical to the timely diagnosis and associated treatment of neonatal anemia. In addition to a complete blood count (CBC), additional laboratory tests on the infant include the reticulocyte count, direct antiglobulin test, serum bilirubin, infant and maternal blood ABO group, and Rh type. The mother should also be screened with an indirect (serum) antiglobulin test for erythrocyte alloantibodies, and the Kleihauer-Betke test can identify fetal erythrocytes in the maternal circulation (Fig. 124.3). Fig. 124.4 shows a proposed diagnostic approach to anemia in newborn infants. Hemolytic anemia is usually associated with difficult-to-treat **hyperbilirubinemia** (Fig. 124.5), whereas **congenital aregenerative anemias** (e.g., Diamond-Blackfan anemia) usually do not manifest jaundice but have other features (Table 124.2).

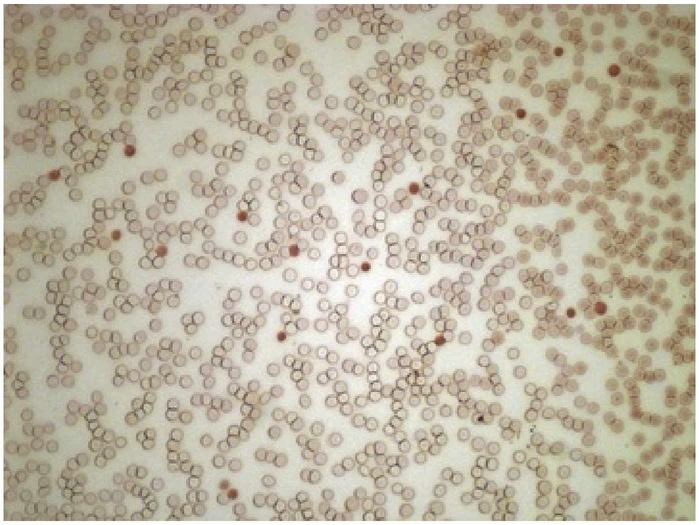

FIG. 124.3 **Acid elution technique of Kleithauer (Kleihauer-Betke test). Fetal red blood cells stain with eosin and appear *dark* . Adult RBCs do not stain and appear as “ghosts.” (From Liley HG, Gardener G, Lopriore E, Smits-Wintjens V: Immune hemolytic disease. In Orkin SH, Nathan DG, Ginsburg D, et al, editors: *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, Philadelphia, 2015, Elsevier, Fig 3-2.)**

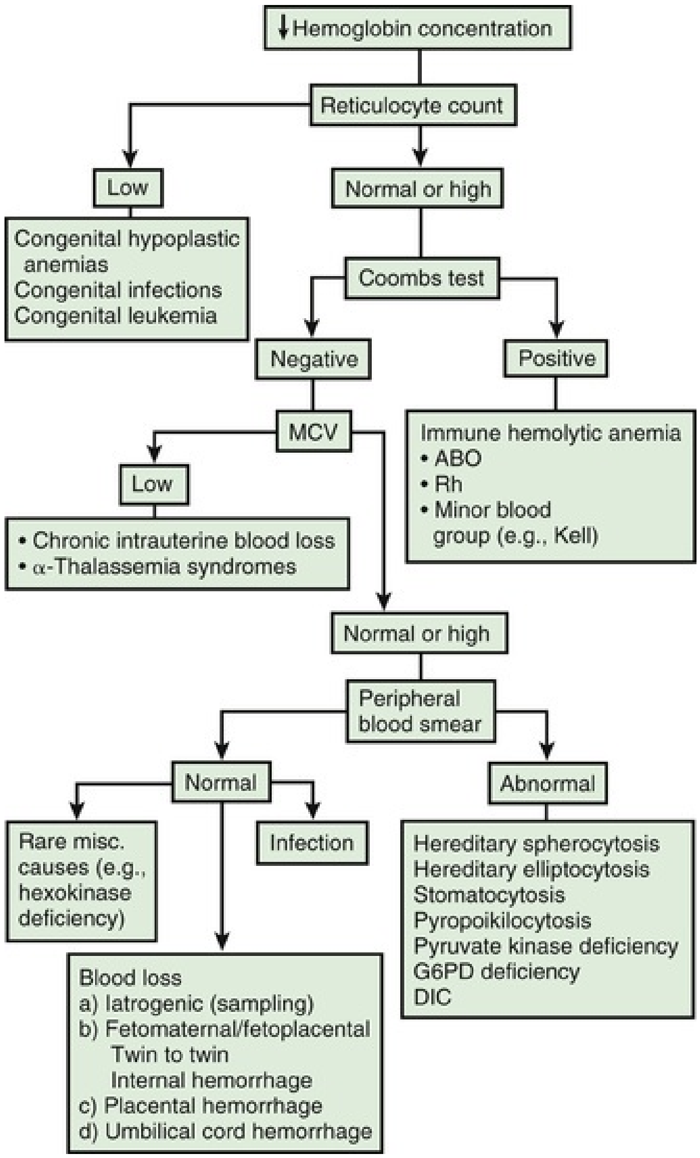
↓Hemoglobin concentration
Reticulocyte count
Low
Congenital hypoplastic anemias
Congenital infections
Congenital leukemia
Normal or high
Coombs test
Negative
Positive
Immune hemolytic anemia
• ABO
• Rh
• Minor blood group (e.g., Kell)
MCV
Low
• Chronic intrauterine blood loss
• α-Thalassemia syndromes
Normal or high
Peripheral blood smear
Normal
Abnormal
Rare misc. causes (e.g., hexokinase deficiency)
Infection
Blood loss
a) Iatrogenic (sampling)
b) Fetomaternal/fetoplacental
Twin to twin
Internal hemorrhage
c) Placental hemorrhage
d) Umbilical cord hemorrhage
Hereditary spherocytosis
Hereditary elliptocytosis
Stomatocytosis
Pyropoikilocytosis
Pyruvate kinase deficiency
G6PD deficiency
DIC

FIG. 124.4 **Diagnostic algorithm showing the approach to anemia in newborn infants. DIC, Disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; MCV, mean corpuscular volume. (Modified from Blanchette VS, Zipursky A: Assessment of anemia in newborn infants, *Clin Perinatol* 11:489–510, 1984.)**

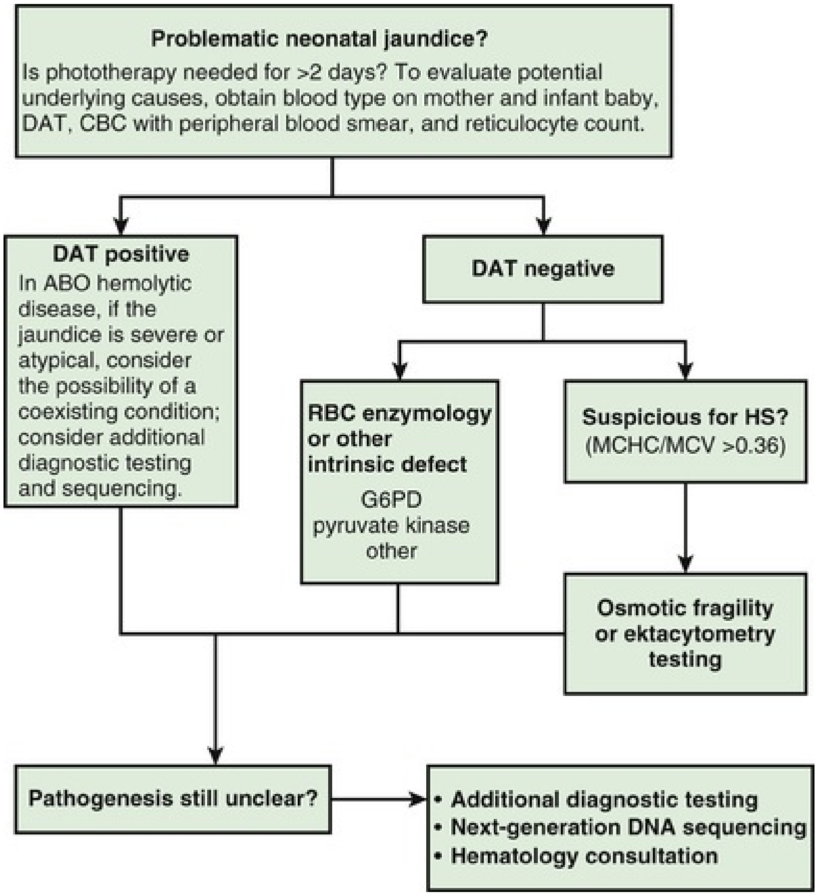
Problematic neonatal jaundice?
Is phototherapy needed for >2 days? To evaluate potential underlying causes, obtain blood type on mother and infant baby, DAT, CBC with peripheral blood smear, and reticulocyte count.
DAT positive
In ABO hemolytic disease, if the jaundice is severe or atypical, consider the possibility of a coexisting condition; consider additional diagnostic testing and sequencing.
DAT negative
RBC enzymology or other intrinsic defect
G6PD
pyruvate kinase
other
Suspicious for HS? (MCHC/MCV >0.36)
Osmotic fragility or ektacytometry testing
Pathogenesis still unclear?
• Additional diagnostic testing
• Next-generation DNA sequencing
• Hematology consultation

FIG. 124.5 Evaluation of neonate with problematic jaundice of unclear cause. Not all neonates who receive phototherapy for 2 days or more have hemolytic jaundice. However, if hemolytic jaundice is suspected, this algorithm for stepwise evaluation of the cause might be useful. CBC, Complete blood count; DAT, direct antiglobulin test; EMA, eosin 5-maleimide; G6PD, glucose 6-phosphate dehydrogenase; HS, hereditary spherocytosis; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell. (From Christensen RD: Neonatal erythrocyte disorders. In Gleason CA, Juul SE, editors: *Avery's diseases of the newborn,* ed 10, Philadelphia, 2018, Elsevier, Fig 81-15.)

Table 124.2

Syndromes Associated With Congenital Hyporegenerative Anemia

SYNDROME	PHENOTYPIC FEATURES	GENOTYPIC FEATURES
Adenosine deaminase deficiency	Autoimmune hemolytic anemia, reduced erythrocyte adenosine deaminase activity	AR, 20q13.11
Congenital dyserythropoietic anemias	Type I (rare): megaloblastoid erythroid hyperplasia and nuclear chromatin bridges between nuclei Type II (most common): hereditary erythroblastic multinuclearity with positive acidified serum test result,	Type I: 15q15.1-q15.3 Type II: 20q11.2 Type III: 15q21

	increased lysis to anti-i antibodies Type III: erythroblastic multinuclearity (“gigantoblasts”), macrocytosis	
Diamond-Blackfan syndrome	Steroid-responsive hypoplastic anemia, often macrocytic after 5 mo of age	AR; sporadic mutations and AD inheritance described; 19q13.2, 8p23.3-p22
Dyskeratosis congenita	Hypoproliferative anemia usually presenting between 5 and 15 yr of age	X-linked recessive, locus on Xq28; some cases with AD inheritance
Fanconi syndrome	Steroid-responsive hypoplastic anemia, reticulocytopenia, some macrocytic RBCs, shortened RBC life span Cells are hypersensitive to DNA cross-linking agents.	AR, multiple genes: complementation; group A 16q24.3; group B Xp22.3; group C 9q22.3; group D2 3p25.3; group E 6p22-p21; group F 11p15; group G 9p13
Osler hemorrhagic telangiectasia syndrome	Hemorrhagic anemia	AD, 9q34.1
Osteopetrosis	Hypoplastic anemia from marrow compression; extramedullary erythropoiesis	AR, 16p13, 11q13.4-q13.5; AD, 1p21; lethal, reduced levels of osteoclasts
Pearson syndrome	Hypoplastic sideroblastic anemia, marrow cell vacuolization	Pleioplasmatic rearrangement of mitochondrial DNA; X-linked or AR
Peutz-Jeghers syndrome	Iron-deficiency anemia from chronic blood loss	AD, 19p13.3
ATR-X and ATR-16 syndromes	ATR-X: hypochromic, microcytic anemia; mild form of hemoglobin H disease ATR-16: more significant hemoglobin H disease and anemia are present.	ATR-16, 16p13.3, deletions of α-globin locus

AD, Autosomal dominant; AR, autosomal recessive; ATR-16, chromosome 16–related α-thalassemia/mental retardation; ATR-X, X-linked α-thalassemia/mental retardation; RBC, red blood cell.

From Christensen RD: Neonatal erythrocyte disorders. In Gleason CA, Juul SE, editors: *Avery's diseases of the newborn,* ed 10, Philadelphia, 2018, Elsevier (Table 81-2).

Review of the peripheral blood smear is an essential component of the evaluation of neonatal anemia. The presence of reticulocytes and nucleated red blood cells (RBCs) indicate chronic anemia with compensatory active erythropoiesis, while distinct erythrocyte morphologies (e.g., elliptocytes, acanthocytes) suggest a congenital intrinsic hemolytic anemia. The presence of spherocytes (often **microspherocytes**) is consistent with immune-mediated hemolysis but can also indicate **hereditary spherocytosis** ; the direct antiglobulin test (DAT, formerly the direct Coombs test) is needed to distinguish these 2 important diagnoses (Fig. 124.6). Neonatal blood smears often include atypical erythrocyte morphology with macrocytosis, poikilocytosis, and anisocytosis that reflect normal fetal erythropoiesis, and an experienced hematologist or pathologist may be required to identify a pathologic feature (Table 124.3) (see Chapter 474).

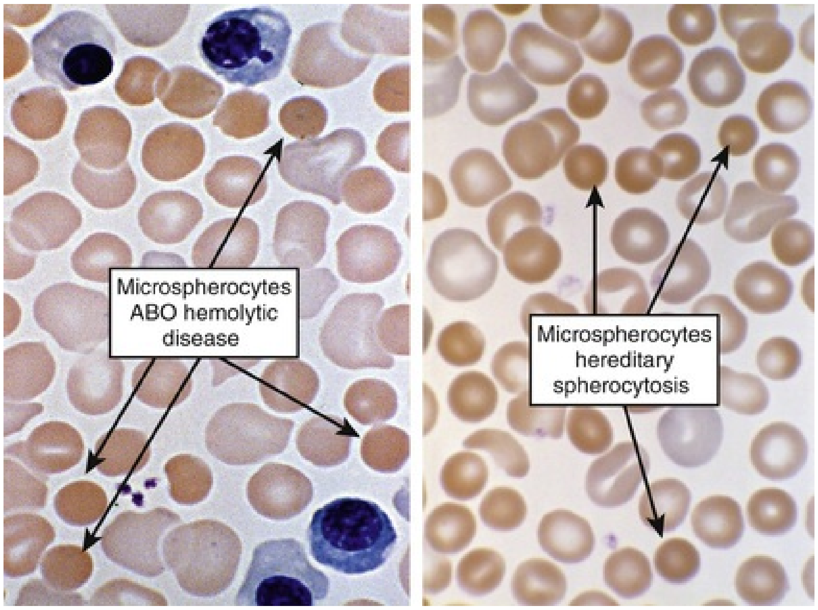

FIG. 124.6 Microspherocytes. *Left,* Neonate with ABO hemolytic disease. *Right,* Neonate with hereditary spherocytosis (*right*). (From Christensen RD: Neonatal erythrocyte disorders. In Gleason CA, Juul SE, editors: *Avery's diseases of the newborn,* ed 10, Philadelphia, 2018, Elsevier, Fig 81-8.)

Table 124.3

Morphologic Abnormalities of Erythrocytes From Neonates With Jaundice

ABNORMAL ERYTHROCYTE MORPHOLOGY	MOST LIKELY CAUSES	SUGGESTED LABORATORY TESTING/FINDINGS	OTHER FEATURES
Microspherocytes	Hereditary spherocytosis	DAT (−) EMA flow (+) Persistent spherocytosis Reticulocytosis	MCHC/MCV elevated (>36, likely >40)
	ABO hemolytic disease	DAT (+) Transient spherocytosis Reticulocytosis	MCHC/MCV normal (<36, likely <34)
Elliptocytes	Hereditary elliptocytosis	DAT (−)	MCHC normal MCV normal
Bite and blister cells	G6PD deficiency	G6PD enzyme activity	Typically affects males, but rarely females are also affected Ethnicity of equatorial origin
	Unstable hemoglobin	Heinz body preparation	
Echinocytes	PK deficiency	PK enzyme activity	Autosomal recessive, likely to have no family history
	Other	Quantify activity of	

	glycolytic enzyme deficiency	other glycolytic enzymes	
Schistocytes	DIC and/or perinatal asphyxia Heinz body HA	Low levels of FV and FVIII, elevated levels of D-dimers Positive result of Heinz body preparation	Low or falling platelet count Normal to high IPF Normal to high MPV DIC, perinatal asphyxia ADAMTS-13 deficiency, early neonatal HUS, and giant hemangiomas all involve platelet consumption from endothelial injury and all have a similar neonatal presentation
	ADAMTS-13 deficiency (TTP)	Severely decreased ADAMTS-13 activity (<0.1 U/mL) high levels of LDH	
	Neonatal hemolytic-uremic syndrome	Acute renal failure	
	Homozygous protein C deficiency	Severely decreased functional protein C activity (<1%)	
	Giant hemangioma	May be internal or external	

DAT, Direct antiglobulin test; DIC, disseminated intravascular coagulation; EMA, eosin 5-maleimide; FV, factor V; FVIII, factor VIII; G6PD, glucose-6-phosphate dehydrogenase; HA, hemolytic anemia; HUS, hemolytic uremic syndrome; IPF, immature platelet fraction; LDH, lactic dehydrogenase; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PK, pyruvate kinase; TTP, thrombotic thrombocytopenic purpura.

From Christensen RD, Yaish HM: Hemolytic disorders causing severe neonatal hyperbilirubinemia, *Clin Perinatol* 42:515–527, 2015 (Table 3).

Red Blood Cell Loss

Blood loss is the most common cause of neonatal anemia. Repeated or frequent phlebotomy for routine laboratory tests, especially from premature or acutely ill neonates, is one of the most common causes of anemia. Several reports have documented large volumes of blood removed for laboratory testing among children in neonatal intensive care units (NICUs), with weekly phlebotomy volumes ranging from 15–30% of the infant's total blood volume (11-22 mL/kg/wk). Most other causes of blood loss occur just before or during delivery, such as placental abruption, and fetal hemorrhage is more common in emergent or traumatic deliveries (see Table 124.1).

Fetomaternal hemorrhage (FMH) is caused by bleeding from the fetal into the maternal circulation, either before or during delivery. Such bleeding occurs to some extent in most pregnancies, although the volume lost is typically small.

Estimates suggest that more substantial FMH, defined as >30 mL of fetal blood, occurs in 3 per 1,000 births, with *large* (>80 mL) or *massive* (>150 mL) FMH occurring in 0.9 and 0.2 per 1,000 births, respectively. Blood loss during gestation can be slow and well compensated by the fetus in terms of both blood volume and oxygen delivery, but faster or larger bleeds will not be fully compensated. Therefore the presentation of FMH is variable, but *decreased or absent fetal movement* is the most common antenatal presentation and should be associated with a high degree of clinical suspicion. After delivery, infant pallor, hypotension, and poor perfusion will indicate severe anemia. To diagnose FMH, the classic *Kleihauer-Betke test*, which identifies fetal erythrocytes containing HbF resistant to acid elution, is technically the gold standard but is labor intensive, highly dependent on the skills of the technician, and often not available as a rapid or point-of-care test (see Fig. 124.3). Some advanced laboratories offer a more precise test using flow cytometry to quantify fetal cells in the maternal circulation.

Red Blood Cell Destruction

RBC destruction is an important cause of neonatal anemia and most frequently reflects elimination of erythrocytes by immune-mediated mechanisms, which result from RBC antigen incompatibilities between the infant and mother. **Hemolytic disease of the fetus and newborn (HDFN)** is a broad term used to describe any fetus or infant who develops alloimmune hemolysis caused by the presence of maternal antibodies against RBC antigens within the circulation of the child (see Chapter 124.2). HDFN caused by anti-RhD antibodies, occurring in RhD-positive infants born to RhD-negative mothers, is the most severe form because of the highly immunogenic nature of the RhD antigen. ABO incompatibility, most often a mismatch between group O mothers and their non–group O infants, affects approximately 15% of pregnancies but is usually less severe than Rh disease, with only 4% of incompatible pregnancies resulting in neonatal hemolytic disease. Unlike Rh disease, in which sensitization usually occurs in the first pregnancy and HDFN occurs in subsequent pregnancies, ABO incompatibility can occur during a woman's first pregnancy, since group O mothers have naturally occurring anti-A and anti-B antibodies. A positive DAT on the infant's blood and a positive indirect antiglobulin test (IAT; also known as the antibody screen) in the mother provide diagnostic evidence of HDFN.

In addition to immune-mediated mechanisms of erythrocyte destruction,

congenital RBC enzyme and membrane disorders also can result in hemolytic anemia and jaundice within the neonatal period. The erythrocyte membrane is a complex structure with numerous critical proteins and lipids that result in a durable, flexible, circulating biconcave disc shape. Genetic deficiencies or abnormalities in RBC membrane proteins (e.g., ankyrin, band 3, α-spectrin, β-spectrin, protein 4.2) result in instability of the RBC membrane, decreased cellular deformability, and shape changes; the abnormal erythrocytes undergo splenic entrapment and removal by macrophages. **Hereditary spherocytosis (HS)** , an autosomal dominant condition characterized by spherical erythrocytes, is the most common RBC membrane disorder, affecting 1 in 2,500-5,000 individuals of European descent. Nearly half of infants born with HS will develop jaundice early in the newborn period.

Hereditary elliptocytosis (HE) , another autosomal dominant inherited erythrocyte membranopathy, characterized by elliptical-shaped erythrocytes, is a less common and less severe RBC membrane disorder. In contrast, **hereditary pyropoikilocytosis (HPP)** is an autosomal recessive RBC membrane disorder resulting in striking morphologic shape changes (poikilocytosis) noted on the peripheral blood smear, some of which resemble thermally damaged erythrocytes. HPP is most common in infants of African descent and can be associated with severe anemia and hemolysis in the newborn period. There is substantial clinical and genetic overlap between HPP and HE, because infants with HPP often have a family history of HE and may develop a milder condition resembling HE later in childhood. Clinical suspicion for a RBC membranopathy begins with a positive family history of hemolytic anemia, especially in an infant who develops early jaundice in the 1st 24 hr of life. The diagnostic evaluation should include a negative DAT, indirect hyperbilirubinemia, and hallmark features noted on the peripheral blood smear. The degree of anemia is variable, and reticulocytosis may also be present.

Erythrocyte enzymopathies are another important, but less common, etiology of neonatal anemia. Circulating RBCs lack a nucleus, mitochondria, or other essential organelles and thus rely solely on critical metabolic pathways to allow for their function in the transport and delivery of oxygen. Several enzymes are especially important to RBC metabolism and may result in hemolytic anemia when deficient. **Glucose-6-phosphate dehydrogenase (G6PD) deficiency** is the most common of these RBC enzymopathies. G6PD deficiency is a common X-linked disorder affecting >400 million people worldwide. There are several classes of G6PD deficiency with varying degrees of clinical severity, but most affected persons are asymptomatic. In the setting of oxidative stress (drugs, infection, certain foods), however, some persons with G6PD deficiency may develop acute hemolytic anemia. There is a several-fold increase in the incidence of neonatal jaundice in G6PD-deficient infants, with jaundice typically occurring on day 2-3 of life. Severe anemia with reticulocytosis is not common, but hyperbilirubinemia in the setting of G6PD deficiency can be severe and prolonged. Clinical testing measuring G6PD activity can be performed (<1–2% suggests G6PD deficiency), but the testing will not be accurate in the setting of acute hemolysis or an elevated reticulocyte count, because reticulocytes have higher enzyme activity. **Pyruvate kinase (PK) deficiency** is the 2nd most common RBC enzymopathy and may also be associated with neonatal jaundice and bizarre morphology featuring acanthocytes.

Red Blood Cell Production

RBC underproduction is also common in the neonate, particularly among preterm infants. Because of relative polycythemia and the physiologic right shift in the oxyhemoglobin dissociation curve, there is typically sufficient oxygen delivery to the tissues during the 1st weeks of postuterine life. The erythropoietic drive is thus limited, and active erythropoiesis does not commence until the 2nd mo of life. This physiologic underproduction of erythrocytes appears to be prolonged in preterm infants and results in a steeper physiologic nadir referred to as **anemia of prematurity** . Anemia of prematurity is exacerbated by acute illness, frequent phlebotomy, and other comorbidities observed in premature infants.

In addition to physiologic underproduction of erythrocytes, several acquired and congenital conditions may further suppress bone marrow production (see Table 124.2). Both bacterial and viral infections may result in suppression of erythropoiesis and contribute to neonatal anemia; infectious etiologies are numerous but TORCH infections and parvovirus B19 are the most common. Tables 124.1 and 124.2 list congenital causes of neonatal anemia, including congenital leukemia, bone marrow failure syndromes (Fanconi anemia, Schwachman-Diamond syndrome), Diamond-Blackfan anemia), and variants in γ-globin, β-globin, or α-globin. Notably, common β-hemoglobinopathies such as sickle cell disease and thalassemia do not present in the neonatal period, as a result of the protective effect of high levels of HbF in the first few months of life.

Treatment Options for Neonatal Anemia

Packed Red Blood Cell Transfusions

Treatment of neonatal anemia by blood transfusion depends on the severity of symptoms, the hemoglobin concentration, and the presence of comorbidities (e.g., bronchopulmonary dysplasia, cyanotic congenital heart disease, respiratory distress syndrome) that interfere with oxygen delivery. The benefits of blood transfusion should be balanced against its risks, which include hemolytic and nonhemolytic reactions; exposure to blood product preservatives and toxins; volume overload; possible increased risk of retinopathy of prematurity and necrotizing enterocolitis; graft-versus-host reaction; and transfusion-acquired infections such as cytomegalovirus (CMV), HIV, parvovirus, and hepatitis B and C (see Chapter 501). The frequency of transfusion for neonates in the NICU is high, particularly among premature and very-low-birthweight (VLBW) infants.

Few studies have evaluated the efficacy or safety of specific hemoglobin/hematocrit thresholds, but a Cochrane review summarized the available evidence and proposed guidelines for transfusion of VLBW infants. The review identified 4 trials comparing *restrictive* (lower) to *liberal* (higher) hemoglobin thresholds. There were no statistically significant differences in death or serious morbidity, and the restrictive thresholds modestly reduced exposure to blood products. Evidence was inconclusive, however, regarding the effectiveness of either threshold in optimizing long-term neurocognitive outcomes. The proposed guideline for the transfusion of neonates was based primarily on postnatal age and the presence or absence of respiratory support (Table 124.4). In addition to these factors, transfusion should be considered for infants with acute blood loss (>20%) or significant hemolysis, as well as before surgery. With no similar evidence-based guidelines for term infants, transfusion should be based on hemodynamic stability, respiratory status, overall clinical condition, and laboratory values.

Table 124.4

Suggested Transfusion Thresholds

POSTNATAL AGE	PRESENCE OF RESPIRATORY SUPPORT	ABSENCE OF RESPIRATORY SUPPORT
	Hemoglobin Concentration, g/dL (Hematocrit %)	
Week 1	11.5 (35%)	10.0 (30%)

Week 2	10.0 (30%)	8.5 (25%)
Week 3	8.5 (25%)	7.5 (23%)

When the decision to transfuse has been made, the appropriate blood product should be selected and a safe volume of blood should be transfused at a safe rate. It is important to transfuse packed erythrocytes (PRBCs) to all neonates in the form of **leukocyte-reduced** or **CMV-seronegative** PRBCs, to reduce the risk of CMV transmission. **Irradiation** of PRBCs removes the risk of transfusion-associated graft-versus-host disease (GVHD) *but does not eliminate* the risk of CMV transmission. The volume of transfusion should achieve the intended therapeutic goal while limiting blood product exposure. Typical transfusion protocols choose a transfusion volume ranging from 10-20 mL/kg. There are no clear data to favor a specific amount, but lower volumes exposure infants to risks unnecessarily while higher volumes may cause fluid overload. One logical goal is to target a specific goal hemoglobin (Hb) concentration. The following commonly used shorthand equation can provide a good estimate of required blood volume, which usually results in a transfusion volume within the 10-20 mL/kg range:

$$\text{PRBC transfusion volume} = (\text{Desired Hb [g/dL]} - \text{Actual Hb}) \\ \times \text{Weight (kg)} \times 3$$

Transfusion of PRBCs is typically delivered at a rate of 3-5 mL/kg/hr, with a slower rate preferred for very small, acutely ill infants with a tenuous fluid status. Each transfusion should be completed within 4 hours.

Erythropoietin

Because of the low physiologic levels of erythropoietin in neonates, the role of recombinant human erythropoietin (**rhEPO**) has been investigated for the treatment of anemia in neonates, particularly VLBW infants. A Cochrane review documented that rhEPO is associated with a significant reduction in the number of blood transfusions per infant, but also a significantly increased risk of retinopathy of prematurity. There were no differences in mortality or other neonatal morbidities among infants who did or did not receive rhEPO. Because of these limited benefits and potential serious risks of early rhEPO therapy, there is currently no strong indication for the routine use of rhEPO in infants with anemia, although it should be considered in individual settings.

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124.2

Hemolytic Disease of the Fetus and Newborn

Omar Niss, Russell E. Ware

Keywords

exchange transfusion
fetal anemia
hemolytic anemia
intrauterine transfusion
Rh alloimmunization

Hemolytic disease of the fetus and newborn (**HDFN**), also known as **erythroblastosis fetalis** , is caused by the transplacental passage of maternal antibodies directed against paternally derived red blood cell (RBC) antigens, which causes increased RBC destruction (hemolysis) in the infant. HDFN is an important cause of anemia and jaundice in newborn infants, and early recognition and diagnosis are crucial for proper management. Although more than 60 different RBC antigens are capable of eliciting a maternal antibody response, clinically significant disease is associated primarily with incompatibility of **ABO blood groups** and the **RhD antigen** . Less frequently, hemolytic disease may be caused by differences in other antigens of the Rh system or by other RBC antigens such as C^W , C^X , D^U , K (**Kell**), M, Duffy, S, P, MNS, Xg, Lutheran, Diego, and Kidd. Notably, anti-Lewis maternal antibodies rarely cause HDFN.

Hemolytic Disease Caused by Rh Incompatibility

The Rh antigenic determinants are genetically transmitted from each parent and determine the Rh blood type by directing the production of Rh proteins (C, c, D, E, and e) on the RBC surface. **RhD** is responsible for 90% of HDFN cases involving the Rh antigen system, but other Rh antigens (especially E and c) also can be etiologic.

Pathogenesis

Alloimmune hemolytic disease from RhD antigen incompatibility is approximately 3 times more common among whites than among blacks, because of differences in Rh allele frequency. Approximately 85% of Caucasians express RhD antigen (**Rh-positive**), whereas 99% of persons from Africa or Asia are Rh-positive. When Rh-positive blood is infused into an unsensitized Rh-negative woman, antibody formation against the mismatched Rh antigen is induced in the recipient. This can occur through transfusion, but the typical scenario is when small quantities (usually >1 mL) of Rh-positive fetal blood, inherited from an Rh-positive father, enter the maternal circulation during pregnancy, through spontaneous or induced abortion, or at delivery. Once sensitization has occurred, considerably smaller doses of antigen can stimulate an increase in antibody titer. Initially, a rise in immunoglobulin (Ig) M antibody occurs, which is later replaced by IgG antibody. Unlike IgM antibodies, IgG readily crosses the placenta to cause hemolytic manifestations.

HDFN requires Rh-antigen mismatch between the infant and the mother, with prior maternal exposure to RBCs expressing the cognate antigen. Hemolytic disease rarely occurs during a first pregnancy because transfusion of Rh-positive fetal blood into an Rh-negative mother usually occurs near the time of delivery, which is too late for the mother to become sensitized and transmit antibody to that infant before delivery. However, fetal-to-maternal transfusion is thought to occur in only 50% of pregnancies, so Rh incompatibility does not always lead to

Rh sensitization. Another important factor is the allele frequency of the RhD antigen because homozygous Rh-positive fathers must transmit the antigen to the fetus, whereas heterozygous fathers have only a 50% chance of having Rh-positive offspring. A smaller family size also reduces the risk of sensitization.

The outcome for Rh-incompatible fetuses varies greatly, depending on the characteristics of both the RBC antigen and the maternal antibodies. Not all maternal-fetal antigen incompatibility leads to alloimmunization and hemolysis. Factors that affect the outcome of antigen-positive fetuses include differential immunogenicity of blood group antigens (RhD antigen being the most immunogenic), a threshold effect of fetomaternal transfusions (a certain amount of the immunizing blood cell antigen is required to induce the maternal immune response), the type of antibody response (IgG antibodies are more efficiently transferred across the placenta to the fetus), and differences in the maternal immune response, presumably related to differences in the efficiency of antigen presentation by various major histocompatibility complex (MHC) loci.

Notably, when the mother and fetus are also ABO incompatible, the Rh-negative mother is partially protected against sensitization due to rapid removal of the fetal Rh-positive cells by maternal isohemagglutinins (preexisting IgM anti-A or anti-B antibodies that do not cross the placenta). Once a mother has been sensitized, all subsequent infants expressing that cognate antigen on RBCs are at risk for HDFN. The severity of Rh illness typically worsens with successive pregnancies because of repeated immune stimulation. The likelihood that Rh sensitization affects a mother's childbearing potential argues urgently for the prevention of sensitization. The injection of anti-Rh immune globulin (RhoGAM) into the Rh-negative mother, both during pregnancy and immediately after the delivery of each Rh-positive infant, reduces HDFN caused by RhD alloimmunization.

Clinical Manifestations

The severity of HDFN is variable, ranging from only laboratory evidence of mild hemolysis to severe anemia with compensatory hyperplasia of erythropoietic tissues, leading to massive enlargement of the liver and spleen. When hemolysis exceeds the compensatory capacity of the hematopoietic system, profound anemia occurs and results in pallor, signs of cardiac decompensation (cardiomegaly, respiratory distress), massive anasarca, and circulatory collapse. This clinical picture of excessive abnormal fluid in 2 or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid), termed **hydrops fetalis** , frequently results in death in utero or shortly after birth.

The severity of hydrops is related to the level of anemia and the degree of edema caused by a reduction in serum albumin (oncotic pressure), which is partly a result of hepatic congestion and hepatic dysfunction. Alternatively, heart failure may increase right-sided heart pressure, with the subsequent development of edema and ascites. Failure to initiate spontaneous effective ventilation because of pulmonary edema or bilateral pleural effusions results in birth asphyxia. After successful resuscitation, severe respiratory distress may develop. Petechiae, purpura, and thrombocytopenia may also be present in severe cases, as a result of decreased platelet production or the presence of concurrent disseminated intravascular coagulation (DIC). Fortunately, with the routine use of RhoGAM to prevent Rh sensitization, *hydrops caused by HDFN has become rare and is more frequently encountered in nonhemolytic conditions.*

Jaundice may be absent at birth because of effective placental clearance of lipid-soluble unconjugated bilirubin, but in severe cases, bilirubin pigments can stain the amniotic fluid, cord, and vernix caseosa. *Jaundice is generally evident in the initial 24 hr of life, which is always pathologic,* because the infant's bilirubin-conjugating and excretory systems are unable to cope with the load resulting from massive hemolysis. Indirect-reacting bilirubin accumulates postnatally and may rapidly reach extremely high levels and present a significant risk of bilirubin encephalopathy (kernicterus). The risk of development of kernicterus from HDFN is greater than from comparable nonhemolytic hyperbilirubinemia, although the risk in an individual patient may be affected by other complications such as hypoxia or acidosis. **Hypoglycemia** also occurs in infants with severe HDFN and may be related to hyperinsulinism and hypertrophy of the pancreatic islet cells in these infants.

Infants with signs of severe disease in utero (hydrops, severe fetal anemia) may benefit from **intrauterine transfusion** , given either directly into the peritoneum or through the umbilical cord. Such infants usually have very high (but extremely variable) cord levels of bilirubin, reflecting the severity of the hemolysis and its effects on hepatic function. Infants treated with transfusions in utero may also have a benign postnatal course if the anemia and hydrops resolve before birth. Ongoing hemolysis can be masked by the previous intrauterine transfusion.

Laboratory Data

Before treatment, the direct antiglobulin test (DAT), or Coombs test, is positive, and anemia is generally present. The cord blood hemoglobin content varies and is usually proportional to the severity of the disease. In cases of hydrops fetalis, the hemoglobin concentration may be as low as 3-4 g/dL. Alternatively, despite hemolysis, hemoglobin may be within the normal range because of compensatory bone marrow and extramedullary hematopoiesis. The initial *reticulocyte count* is increased, another abnormal finding at birth, and the peripheral blood smear typically shows polychromasia with a marked increase in nucleated RBCs. The white blood cell count is usually normal but may be elevated, and thrombocytopenia develops in severe cases. Cord bilirubin levels are generally between 3 and 5 mg/dL; the *direct-reacting (conjugated) bilirubin* content may also be elevated (from cholestasis), especially if there was a previous intrauterine transfusion. Indirect-reacting bilirubin content rises rapidly to high levels in the 1st 6-12 hr of life.

After intrauterine transfusions, cord blood may show a normal hemoglobin concentration, *negative* DAT result, predominantly Rh-negative adult RBCs, low/normal reticulocyte count, and relatively normal blood smear findings.

Diagnosis

Definitive diagnosis of HDFN requires demonstration of blood group incompatibility between mother and infant and corresponding maternal antibody bound to the infant's RBCs.

Antenatal Diagnosis

Without proof of immunoglobulin prophylaxis, any Rh-negative women with previous pregnancy or abortion, prior exposure to transfused blood, or receipt of an organ transplant should be considered at risk for Rh sensitization. During pregnancy, the expectant parents should have blood tested for potential incompatibility, particularly for ABO and Rh antigens. If RhD incompatible, the maternal titer of IgG antibodies to the RhD antigen should be measured early in pregnancy. Paternal blood can be tested to determine the fetal risk of inheriting the cognate antigen, typically either 50% or 100% depending on whether the father is heterozygous or homozygous for the antigen. However, paternal serologic testing alone is not fully accurate to predict the zygosity of RhD antigen, and molecular genotyping is recommended for both parents in this setting.

Fetal RBC genotyping provides an accurate prediction for the development of HDFN in sensitized mothers. Fetal Rh status is available by isolating fetal cells or fetal DNA (plasma) from the maternal circulation, which is replacing the more invasive and risky fetal amniocyte testing by amniocentesis and chorionic villus sampling methods. The presence of elevated antibody titers or rising titers increases the risk of the baby developing severe HDFN.

Although maternal antibody titers are often used to predict the risk of HDFN, there is a poor correlation between the anti-D titer level and the severity of the disease, especially in subsequent pregnancies. If an Rh-negative mother is found to have RhD antibody titers of ≥1 : 16 (15 IU/mL in Europe) at any time during a subsequent pregnancy, the severity of fetal anemia should be monitored by Doppler ultrasonography (US) of the middle cerebral artery (MCA) and then percutaneous umbilical blood sampling (PUBS) if indicated (Fig. 124.7). If the mother has a history of a previously affected infant or a stillbirth, an Rh-positive infant is usually equally or more severely affected than the previous infant, and the severity of disease in the fetus should be monitored starting at 16-24 wk of gestation.

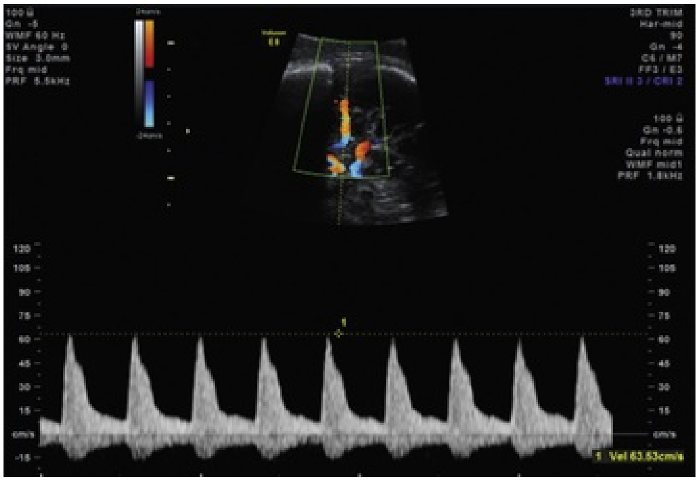

FIG. 124.7 **Middle cerebral artery (MCA) Doppler study of elevated peak systolic velocity (PSV). MCA-PSV can predict fetal anemia with sufficient accuracy to determine management, including the need for intrauterine transfusion or, in the mid- to late third trimester, early delivery. Fetal hemoglobin is typically measured at the start and end of intravascular transfusion to validate the prediction from MCA-PSV results. The reliability of MCA-PSV can decrease after intrauterine transfusion because of the altered rheostatic characteristics of transfused adult blood. This is now the method of choice for detecting fetal anemia. (From Liley HG, Gardener G, Lopriore E, Smits-Wintjens V: Immune hemolytic disease. In Orkin SH, Nathan DG, Ginsburg D, et al,**

editors: *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, Philadelphia, 2015, Elsevier, Fig 3-6.)

Pregnancies at risk for HDFN should be managed by maternal-fetal specialists. Assessment of the fetus includes US and PUBS. Real-time US is used to detect signs of hydrops (skin or scalp edema, pleural or pericardial effusions, and ascites) and fetal heart rate monitoring. Early US signs of hydrops include organomegaly (liver, spleen, heart), the double–bowel wall sign (bowel edema), and placental thickening. Progression to polyhydramnios, ascites, pleural or pericardial effusions, and skin or scalp edema may then follow. Extramedullary hematopoiesis and hepatic congestion compress the intrahepatic vessels and produce venous stasis with portal hypertension, hepatocellular dysfunction, and decreased albumin synthesis. *Hydrops is typically present when fetal hemoglobin level is <5 g/dL.* Hydrops is also frequently seen with a fetal hemoglobin level <7 g/dL, and in some cases between 7 and 9 g/dL.

Doppler US assesses fetal distress by demonstrating increased vascular resistance in fetal arteries, especially in the infant MCA (see Fig. 124.7). In fetuses without hydrops, moderate to severe anemia can be detected noninvasively by demonstration of an increase in the peak velocity of systolic blood flow in the MCA. The velocity of blood flow correlates with the severity of the anemia and therefore can be used as a noninvasive surrogate marker that can be followed. In pregnancies with moderate-severe fetal anemia (demonstrated by high cerebral velocities) or US evidence of hemolysis (hepatosplenomegaly), early or late hydrops, or fetal distress, further and more direct assessment of fetal hemolysis should be performed.

Amniocentesis was the classic method for assessing fetal hemolysis, by measuring changes in optical density of the amniotic fluid with serial determination of bilirubin levels. However, amniocentesis is an invasive procedure with risks to both the fetus and the mother, including fetal death, bleeding, bradycardia, worsening of alloimmunization, premature rupture of membranes, preterm labor, and chorioamnionitis. Doppler measurement of the peak velocity of systolic blood flow in the MCA has essentially replaced invasive testing in the management of HDFN.

PUBS is the standard approach to the assessment of the fetus if Doppler and real-time US findings suggest that the fetus has moderate to severe anemia. PUBS is performed to determine fetal hemoglobin levels and to transfuse packed RBCs into fetuses with serious fetal anemia (hematocrit <30%) who are immature and not suitable for delivery.

Postnatal Diagnosis

Immediately after the birth of an infant to an Rh-negative woman, or any infant with the appearance of hydrops, blood from the umbilical cord or the infant should be tested for ABO blood group, Rh type, hematocrit and hemoglobin, reticulocyte count, serum bilirubin, and the DAT. A positive DAT result indicates the presence of maternal antibody on the infant RBC, and the incompatible RBC antigen must be identified. The infant's cells can be investigated, but maternal serum should also be screened for RBC antibodies using commercially available panels. These tests not only help establish the diagnosis, but also enable selection of compatible blood for exchange transfusion of the infant, if necessary. The DAT is usually strongly positive in clinically affected infants and may remain so for weeks or even several months.

Treatment

The main goals of therapy for HDFN are (1) to prevent intrauterine or extrauterine death from severe anemia and hypoxia, (2) to prevent neurodevelopmental damage in affected children, and (3) to avoid neurotoxicity from hyperbilirubinemia.

Treatment of the Unborn Fetus

Survival of severely affected fetuses has improved with the advent of fetal US to assess the need for in utero transfusion. Intravascular (umbilical vein) transfusion of packed erythrocytes (PRBCs) is the preferred treatment of choice for fetal anemia, although intrauterine transfusion into the fetal peritoneal cavity is also effective. Hydrops or fetal anemia (hematocrit <30%) is an indication for umbilical vein transfusion in infants with pulmonary immaturity.

Fetal transfusion is facilitated by maternal and hence fetal sedation. PRBCs are slowly infused after being cross-matched against the mother's serum. The erythrocytes should be selected from a donor who is group O, negative for the mismatched antigen (e.g., RhD-negative), and CMV-negative. The blood should also be leukocyte-reduced to reduce the risk of allergic and nonhemolytic reactions and irradiated to avoid transfusion-associated GVHD. Some centers use extended group matching (e.g., RhCE, Kell) to decrease the risk of additional maternal antibody formation. Transfusions should achieve a posttransfusion hematocrit of 45–55% and can be repeated every 3-5 wk.

Intrauterine transfusions ameliorate neurologic complications in many fetuses; however, those with severe hydrops are at risk for cerebral palsy, developmental delay, and deafness. The overall survival rate after intrauterine transfusions is 89%, and the complication rate is 1–3%. In contrast, the outcome after cordocentesis and intrauterine transfusions performed earlier, such as the second trimester, is poor. Complications include rupture of the membranes and preterm delivery, infection, fetal distress requiring emergency cesarean delivery, and perinatal death. Maternal plasma exchange and intravenous immune globulin (IVIG) have been used as adjunctive therapies in women with prior severe HDFN, but there is limited evidence to support their routine use. Indications for early delivery include pulmonary maturity, fetal distress, complications of PUBS, and 35-37 wk of gestation. Careful antenatal care, including intrauterine transfusions, has decreased the need for postdelivery exchange transfusion.

Treatment of the Liveborn Infant

The birth should be attended by a physician skilled in neonatal resuscitation. Fresh, leukoreduced, and irradiated group O and Rh-negative blood, which has been cross-matched against maternal serum, should be immediately available. If clinical signs of **severe hemolytic anemia** (pallor, hepatosplenomegaly, edema, petechiae, ascites) are evident at birth, immediate resuscitation and supportive therapy, temperature stabilization, and monitoring before proceeding with exchange transfusion may save severely affected infants. Such therapy should include a small transfusion of compatible PRBCs to correct anemia; volume expansion for hypotension, especially in those with hydrops; correction of acidosis with 1-2 mEq/kg of sodium bicarbonate; and assisted ventilation for respiratory failure. Infants with HDFN should be closely monitored with frequent hemoglobin and bilirubin testing to determine their need for phototherapy, simple transfusion, or exchange transfusion.

Exchange Transfusion

The decision to proceed with an immediate full or partial exchange transfusion should be based on the infant's clinical condition at birth, with a judgment specifically regarding the likelihood of the infant rapidly developing a dangerous degree of anemia or hyperbilirubinemia. Cord hemoglobin value of ≤10 g/dL or bilirubin concentration ≥5 mg/dL suggest severe hemolysis, but neither consistently predicts the need for exchange transfusion. Some physicians consider previous kernicterus or severe HDFN in a sibling, reticulocyte counts >15%, and prematurity to be additional factors supporting a decision for early exchange transfusion (see Chapters 123.3 and 123.4).

The hemoglobin concentration and serum bilirubin level should be measured at 4-6 hr intervals initially, with extension to longer intervals as the rate of change diminishes. The decision to perform an exchange transfusion is often based on the likelihood that the bilirubin levels, which can be plotted against postnatal hours of life, will reach dangerous levels (see Fig. 123.14 and Table 123.7 in Chapter 123). *Term infants with bilirubin levels ≥20 mg/dL have an increased risk of kernicterus.* Simple transfusions of ABO-compatible, Rh-negative, leukoreduced, and irradiated RBCs may be necessary to correct anemia up to 6-8 wk of age, after which the infant's own erythropoiesis can be expected to overcome any lingering hemolysis. Weekly determinations of hemoglobin values should be performed until the physiologic nadir is passed and a spontaneous rise has been demonstrated.

Careful monitoring of the serum bilirubin level is essential until a decline has been documented in the absence of phototherapy (see Chapter 123.3). Even then, an occasional infant, particularly if premature, may experience a significant rebound in serum bilirubin as late as the 7th day of life. Attempts to predict dangerously high levels of bilirubin based on levels exceeding 6 mg/dL in the 1st 6 hr of life, or 10 mg/dL in the 2nd 6 hr of life, or on increasing rates exceeding 0.5-1.0 mg/dL/hr, are often quoted but not necessarily reliable.

Procedure

The actual exchange transfusion can be performed most easily through an umbilical vein catheter or through peripheral arterial (remove) and venous (return) lines. The exchange should be carried out over 45-60 min and involves serial removal of 15-20 mL aliquots of infant blood (term infant), alternating with infusion of an equivalent volume of donor blood. Smaller, 5-10 mL aliquots may be better tolerated by sick or premature infants. The goal should be an isovolemic exchange of approximately 2 blood volumes of the infant (2 × 100 mL/kg) to achieve 90% replacement of fetal RBCs and 50% removal of bilirubin.

Blood for exchange transfusion should be as fresh as possible. Standard anticoagulants and preservatives such as citrate-phosphate-dextrose-adenine solution can be used. Blood selection is similar to that of intrauterine transfusions, typically leukoreduced and irradiated erythrocytes from a group O and Rh-negative donor. Although the blood should be negative for the mismatched Rh antigen, a complete crossmatch should be performed before transfusion. Packed erythrocytes should be reconstituted with fresh-frozen plasma to a hematocrit of about 40% before the procedure. Blood should be gradually warmed and maintained at a temperature between 35°C and 37°C throughout the exchange transfusion. It should be kept well mixed by gentle squeezing or agitation of the bag to avoid sedimentation. The infant's stomach should be emptied before transfusion to prevent aspiration, and body temperature should be maintained and vital signs monitored. A competent assistant should be present to help monitor, tally the volume of blood exchanged, and perform emergency procedures.

Infants with acidosis and hypoxia from respiratory distress, sepsis, or shock may be further compromised by the significant exposure to citrate, which provides both an acute acid load (pH 7.0-7.2) and calcium binding. The subsequent metabolism of citrate may later result in metabolic alkalosis. Fresh heparinized blood avoids this problem but is not readily available in most settings. During the exchange transfusion, blood pH and PaO_2 should be serially monitored to avoid acidosis and hypoxia. Symptomatic hypoglycemia may occur before, during, or after an exchange transfusion in moderately to severely affected infants. Additional acute complications, noted in 5–10% of infants, include transient bradycardia with or without calcium infusion, cyanosis, transient vasospasm, thrombosis, thrombocytopenia, apnea with bradycardia requiring resuscitation, and death. Infectious risks include CMV, HIV, and hepatitis. Necrotizing enterocolitis is a rare complication of exchange transfusion for HDFN.

There is a risk of death from an exchange transfusion, even when performed by an experienced physician team, estimated at 3 per 1,000 procedures. With the fortunate decline of this procedure because of phototherapy and prevention of sensitization, experience with such procedures and physician competence are diminishing, and exchange should be performed only at experienced neonatal referral centers.

After exchange transfusion, the bilirubin level must be measured at frequent intervals (every 4-8 hr) because the serum value may rebound 40–50% because of reequilibration and ongoing production. Repeated exchange transfusions are occasionally necessary, with the primary aim of keeping the indirect bilirubin fraction from exceeding dangerous levels indicated in Table 123.7 (see Chapter

123) for preterm infants and 20 mg/dL for term infants. Signs and symptoms suggestive of kernicterus are mandatory indications for exchange transfusion at any time.

Intravenous Immune Globulin

Because of its ability to interfere with immune-mediated clearance of antibody-sensitized RBCs, early administration of IVIG may be an effective therapeutic intervention for HDFN. IVIG can prevent immune hemolysis, lower peak serum bilirubin levels, shorten the duration of phototherapy, and reduce both length of hospitalization and need for exchange transfusion. However, IVIG does not effectively prevent anemia, which results from both immune-mediated RBC destruction and inadequate erythropoiesis. Consequently, simple transfusions are usually needed as an adjunct to IVIG therapy. An IVIG dose of 0.5-1 g/kg is typically used, but optimal dosing has not been established. Treated infants with blood groups A or B should be monitored for worsening hemolysis caused by anti-A or anti-B antibodies present in IVIG.

Late Complications

Infants with HDFN, including those who have had an intrauterine or postnatal exchange transfusion, must be observed carefully for the development of late anemia and cholestasis.

Late anemia , operationally defined as occurring after the 1st 4-6 wk of life, can result from either persistent hemolysis caused by circulating maternal alloantibodies or from effects on the bone marrow. **Late hyporegenerative anemia** in HDFN results from suppression of erythropoiesis, in part from the higher hemoglobin concentration provided through an intrauterine or exchange transfusion. Late hyporegenerative anemia can be distinguished from hemolytic anemia by a low or absent reticulocyte count and a normal bilirubin level. Infants should be monitored for symptoms and signs of anemia, including poor feeding, sleepiness, and poor growth. Hemoglobin and reticulocyte counts should be monitored weekly to determine the need for transfusion, until the marrow spontaneously recovers after several weeks to months. Neutropenia can also be observed during recovery from HDFN or in association with the late hyporegenerative anemia. In addition to transfusion, treatment with supplemental iron or erythropoietin may be helpful to accelerate marrow recovery.

Inspissated bile syndrome refers to the rare occurrence of persistent icterus in association with significant elevations in both direct and indirect bilirubin levels in infants with hemolytic disease. The cause is unclear, but jaundice clears spontaneously within a few weeks or months with conservative management. **Portal vein thrombosis** and portal hypertension may occur in children who have been subjected to exchange transfusion as newborn infants. It is probably associated with prolonged, traumatic, or septic umbilical vein catheterization.

Prevention of Rh Sensitization

The risk of initial sensitization of Rh-negative mothers has been reduced to less than 0.1% by the routine administration of Rh-immunoglobulin (RhoGAM) to all mothers at risk for Rh alloimmunization. The Rh-immunoglobulin product is administered to Rh-negative mothers as an intramuscular injection of 300 µg (1 mL) of human anti-D globulin within 72 hr of delivery of an Rh-positive infant. Additional clinical indications for RhoGAM administration include ectopic pregnancy, abdominal trauma during pregnancy, amniocentesis, chorionic villus biopsy, or abortion. This quantity of antibody is sufficient to eliminate approximately 10 mL of potentially antigenic fetal Rh-positive cells within the maternal circulation. Larger fetal-to-maternal transfers of blood will require proportionately more human anti-D globulin. RhoGAM administration provided at 28-32 wk of gestation and again at birth is more effective than a single dose.

It is also critical to use appropriately matched blood for all transfusions to Rh-negative girls and young women of childbearing years, including the use of group O, Rh-negative blood during emergencies, as a primary measure to prevent Rh antigen exposure. This approach, coupled with the use of anti-D immunoglobulin during/after pregnancy, plus improved methods of detecting maternal sensitization and measuring the extent of fetal-to-maternal transfusion, have dramatically decreased the incidence and severity of HDFN in developed countries. In addition, the use of fewer obstetric procedures that increase the risk of fetal-to-maternal bleeding should further reduce the incidence of this disorder. However, because serologic testing does not always accurately predict RhD type, since there are now well-recognized weak and partial RhD antigens, the use of fetal RhD genotyping will better guide appropriate use of Rh-immunoglobulin therapy in Rh-negative women.

Hemolytic Disease Caused by Blood Group A and B Incompatibility

Although ABO incompatibility is the most common cause of HDFN, this form is usually much milder than Rh disease and rarely requires aggressive clinical management or therapeutic intervention. Approximately 20% of live births are at theoretical risk for immune-mediated hemolysis based on ABO mismatch, most often the mother being group O and the infant either group A or B. Less often, the mother will be group A and the infant group B, or vice versa.

However, clinical manifestations of hemolysis develop in only 1–10% of at-risk infants, primarily because naturally occurring maternal antibodies against ABO blood group antigens are almost exclusively IgM and therefore do not cross the placenta. Some group O mothers will produce IgG antibodies against blood group A or B antigens, and these can cross the placenta and cause immune-mediated hemolysis. For example, an A-O incompatibility can cause hemolysis even in a firstborn infant, if the mother (group O) produces some anti-A IgG antibodies. A 2nd factor that accounts for the lower-than-predicted incidence of severe ABO hemolytic disease is the relatively low antigen frequency and expression on the RBC of the fetus and newborn infant. With few strong binding sites available for the maternal antibodies to bind, there is less hemolysis.

Clinical Manifestations

Most cases of ABO incompatibility are mild, with jaundice the only clinical manifestation. The infant is not generally affected at birth but will develop jaundice in the 1st 24 hr, which is always abnormal. Pallor and hepatosplenomegaly are not present, and the development of hydrops fetalis or kernicterus is extremely rare.

Diagnosis

A presumptive diagnosis is based on the presence of serologic ABO incompatibility between the mother and infant, plus a weakly to moderately positive DAT result. Hyperbilirubinemia is often the main laboratory abnormality. In 10–20% of affected infants, the unconjugated serum bilirubin level may reach 20 mg/dL or more unless phototherapy is administered. Usually the infant has mild anemia and reticulocytosis; the peripheral blood smear may show polychromasia, nucleated RBCs, and spherocytes. However, the persistence of hemolytic anemia or spherocytosis beyond 2 wk should suggest an alternative diagnosis, such as hereditary (congenital) spherocytosis (see Fig. 124.6).

Treatment

Phototherapy may be effective in lowering serum bilirubin levels (see Chapter 123.4). In severe cases, IVIG administration can be helpful by reducing the rate of hemolysis and the need for exchange transfusion. Exchange transfusions with group O and Rh-compatible blood type may be needed in some cases to correct dangerous degrees of anemia or hyperbilirubinemia. Indications for this procedure are similar to those previously described for hemolytic disease caused by Rh incompatibility . Some infants with ABO hemolytic disease may require transfusion of PRBC at several weeks of age because of hyporegenerative or slowly progressive anemia. *Postdischarge monitoring of hemoglobin or hematocrit is essential in newborns with ABO hemolytic disease.*

Other Forms of Hemolytic Disease

Blood group incompatibilities other than Rh or ABO account for <5% of HDFN. The pathogenesis of hemolytic disease in this setting is similar, because of other RBC antigens that are mismatched between mother and infant. The likelihood of encountering mismatches for minor antigen mismatches relates to their frequency in the population, their density on the RBC surface, their immunogenicity in the mother, and the index of suspicion. Minor RBC antigen mismatch (especially on Kell group) is emerging as a common cause of HDFN in the developed countries where anti-D immunoglobulin is routinely used. In all cases, the maternal serum should have RBC alloantibodies identified that react against the infant (and paternal) erythrocytes. In addition, the infant's DAT result is invariably positive, and elution techniques can identify the antigen specificity.

Common RBC antigens that can lead to clinically relevant incompatibility include those in the Kell, Duffy, and MNS blood groups. Notably, maternal anti-Lewis antibodies do not lead to HDFN because they are IgM and do not cross the placenta, and Lewis antigens are poorly expressed on fetal erythrocytes. **Kell** is a particularly dangerous incompatibility because the severity of the hemolytic anemia is difficult to predict based on previous obstetric history, amniotic fluid bilirubin determinants, or maternal antibody titer. Kell-alloimmunized infants often have inappropriately low numbers of circulating reticulocytes caused by erythroid suppression, and even low maternal titers of anti-Kell antibodies may cause significant hypoproliferative anemia. Table 124.5 summarizes the clinical characteristics of hemolytic disease caused by Rh, ABO, and Kell antigen systems. There are no specific pharmacologic therapies available to prevent sensitization caused by any blood group other than RhD. As with cases of Rh and ABO incompatibility, exchange transfusion may be indicated for severe hyperbilirubinemia or severe anemia in infants with HDFN caused by minor antigen incompatibility.

Table 124.5

Hemolytic Disease of the Fetus and Newborn

	Rh	**ABO**	**KELL**
BLOOD GROUPS			
Mother	Rh-negative	O (occasionally B)	K1-negative
Infant	Rh-positive (D is most common)	A (sometimes B)	K1-positive
CLINICAL FEATURES			
Occurrence in firstborn	5%	40–50%	Rare
Severity in subsequent pregnancies:	Predictable	Difficult to predict	Somewhat predictable
Stillbirth/hydrops	Frequent (less with Rh-immunoglobulin use)	Rare	10%
Severe anemia	Frequent	Rare	Frequent
Jaundice	Prominent, severe	Mild-moderate	Mild
LABORATORY TESTS			
Direct antiglobulin test (infant)	Positive	Positive or negative	Positive or negative
Reticulocyte count	Elevated	Elevated	Variable
Red blood cell (RBC) antibodies (mother)	Usually detectable Antibody titers may help predict severity of fetal disease.	May not be detectable Antibody titers may not correlate with fetal disease.	Usually detectable Antibody titers may not correlate with fetal disease; fetus can be affected at titers lower than for Rh-mediated hemolysis.

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124.3

Neonatal Polycythemia

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hyperviscosity
polycythemia

Neonatal polycythemia is defined as a central hemoglobin or hematocrit (Hct) exceeding 2 standard deviations (SD) above the normal value for gestational and postnatal age. A full-term infant is therefore considered to have polycythemia when the hemoglobin concentration is ≥22 g/dL or Hct is ≥65%. Measuring the *central hemoglobin* using an automated blood counter is important because both peripheral (heelstick) and capillary tube microcentrifugation yield higher Hct values than central values, by up to 15%. Timing is also important; because of fluid shifts in the newborn period, Hct peaks during the 1st 2-3 hr of life. The frequency of neonatal polycythemia is also increased for births at higher altitudes (5% at high altitude vs 1–2% at sea level). Polycythemia predisposes to **hyperviscosity** (not clinically measurable), which may be the primary issue. When Hct is >65%, hyperviscosity may rapidly increase.

Etiologies of neonatal polycythemia are numerous but can be grouped into two broad categories based on passive RBC transfusion into the fetus and increased intrauterine erythropoiesis. Causes of passive fetal RBC transfusion include delayed clamping of the umbilical cord (most common cause in term infants), twin-twin transfusion for the recipient, and rarely, maternal-fetal transfusions. In contrast, neonatal polycythemia secondary to increased fetal erythropoiesis has many causes, including postmaturity (3%) vs term (1–2%) infants; small-for-gestational-age (8%) or large-for-gestational-age (3%) vs average-for-gestational-age (1–2%) infants; infants of diabetic mothers; infants with trisomy 13, 18, or 21; adrenogenital syndrome; neonatal Graves disease;

hypothyroidism; infants of hypertensive mothers or those taking propranolol; and Beckwith-Wiedemann syndrome. Although the pathogenesis of increased erythropoiesis is not always fully understood, infants of diabetic or hypertensive mothers and those with growth restriction may have been exposed to chronic fetal hypoxia, which stimulates erythropoietin production and increases RBC production.

Signs and symptoms of polycythemia can result from hyperviscosity (sluggish blood flow causing decreased tissue perfusion) or metabolic disturbances, or both. Most polycythemic infants are asymptomatic. Symptoms often appear in the 1st few hr of life but can be delayed by up to 2-3 days. Symptoms include irritability, lethargy, tachypnea, respiratory distress, cyanosis, feeding disturbances, hyperbilirubinemia, hypoglycemia, and thrombocytopenia. Severe complications include seizures, stroke, pulmonary hypertension, necrotizing enterocolitis (NEC), renal vein thrombosis, and renal failure. Because most infants are asymptomatic and these symptoms overlap with many neonatal conditions, other respiratory, cardiovascular, and neurologic diseases should be ruled out. Dehydration should also always be considered as a cause. Whether these symptoms are truly caused by, or just associated with, polycythemia is undetermined. Hyperviscosity in infancy may be accentuated because neonatal RBCs are large and have decreased deformability, which together predispose to stasis in the microcirculation.

The **treatment** of polycythemia varies among centers and is often based primarily on local expert opinion. A capillary Hct >65% should always be confirmed with a venous sample and dehydration should be treated. All polycythemic infants should be closely monitored for intake and output, and blood glucose and bilirubin levels should be closely followed. Asymptomatic infants whose central Hct is 60–70% can be monitored closely and hydrated with adequate enteral intake or administration of intravenous (IV) fluids. Treatment of symptomatic polycythemic newborns is not well defined. A partial exchange transfusion (with normal saline) can be used in infants with severe polycythemia and symptoms of hyperviscosity and should be considered if the Hct is ≥70–75% and symptoms worsen despite aggressive IV hydration. Partial exchange transfusion lowers Hct and viscosity acutely and improves acute symptoms but may not affect long-term outcome in polycythemic infants.

Polycythemic infants treated with partial exchange transfusion may be at increased risk of NEC, and their long-term prognosis is unclear. Reported adverse outcomes include speech deficits, abnormal fine motor control, reduced

IQ, school problems, and other neurologic abnormalities. The underlying etiology (**chronic intrauterine hypoxia**) is likely the determinant of these outcomes rather than polycythemia itself. Most asymptomatic infants develop normally.

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124.4

Hemorrhage in the Newborn Infant

Cristina Tarango, Russell E. Ware

Keywords

disseminated intravascular coagulation
DIC
hemorrhagic disease of the newborn
neonatal hemorrhage
phytonadione
PIVKA
vitamin K deficiency bleeding

Neonates have a unique hemostatic system that places them at high risk for hemorrhagic complications, especially in the presence of illness or other stress. Plasma levels of the vitamin K–dependent coagulation factors (II, VII, IX, X, protein C, protein S) and antithrombin are low at birth and do not reach adult ranges until approximately 6 mo of age. Thrombin generation and platelet function are also altered in normal newborns. Consequently, both congenital and acquired bleeding disorders that affect primary or secondary hemostasis can manifest in the newborn period. In general, hemorrhage in a *healthy* neonate suggests an inherited coagulation defect or immune-mediated thrombocytopenia, whereas bleeding symptoms in a *sick* neonate are more likely to reflect underproduction or consumption of coagulation factors and/or platelets. *Congenital hemorrhagic disorders such as hemophilia can present with bleeding in the newborn period.* Common acquired hemorrhagic disorders include vitamin K deficiency bleeding, disseminated intravascular coagulation (see Chapter 510), and immune-mediated thrombocytopenia (Chapter 511.9).

Vitamin K Deficiency Bleeding

Vitamin K deficiency bleeding, previously referred to as **hemorrhagic disease of the newborn** , results from transient but severe deficiencies in the vitamin K–dependent factors and is characterized by hemorrhage that is most frequently gastrointestinal, nasal, subgaleal, intracranial, or postcircumcision. Prodromal or warning signs (mild bleeding) may occur before serious intracranial hemorrhage. Laboratory testing reveals that both the prothrombin time (PT) and partial thromboplastin time are prolonged, and plasma levels of prothrombin (II) and factors VII, IX, and X are substantially decreased. The pathophysiology of this acquired hemorrhagic disorder results because vitamin K facilitates posttranscriptional carboxylation of factors II, VII, IX, and X, which is necessary for its full coagulation effects. In the absence of carboxylation, such factors form **PIVKA** (proteins induced in vitamin K absence), which have greatly reduced function; these can be measured and represent a sensitive marker for vitamin K status. In contrast, factors V and VIII, fibrinogen, bleeding time, clot retraction, and platelet count and function are normal for maturity.

Classically, *vitamin K deficiency bleeding occurs early in the newborn period,* typically between day 2 and 7 of life, and most often in exclusively breastfeeding infants who did not receive vitamin K prophylaxis at birth. Severe vitamin K deficiency is also more common in premature infants. This pathogenesis occurs from a lack of free vitamin K from the mother, coupled with absence of bacterial intestinal flora normally responsible for the synthesis of vitamin K. Breast milk is a poor source of vitamin K, which explains why hemorrhagic complications are more frequent in exclusively breastfed than in mixed-fed or formula-fed infants. This classic form of hemorrhagic disease of the newborn, which is responsive to (and entirely prevented by) exogenous vitamin K therapy, should be distinguished from rare congenital deficiencies of clotting factors that are unresponsive to vitamin K, which can occur in otherwise well-appearing infants (see Chapter 503).

Early-onset vitamin K deficiency bleeding (after birth but in 1st 24 hr) occurs if the mother has been treated chronically with certain drugs (e.g., anticoagulant warfarin, anticonvulsant phenytoin or phenobarbital, cholesterol-lowering medication) that interfere with vitamin K absorption or function. These infants can have severe bleeding, which is usually corrected promptly by vitamin K administration, although some have a poor or delayed response. If a mother is known to be receiving such drugs late in gestation, an infant PT should be measured using cord blood, and *the infant immediately given 1-2 mg of vitamin K intravenously.* If PT is greatly prolonged and fails to improve, or in the presence of significant hemorrhage, *10-15 mL/kg of fresh-frozen plasma should be administered.* In contrast, **late-onset** vitamin K deficiency bleeding (after 2 wk of life) is usually associated with conditions that feature malabsorption of the fat-soluble vitamin K, such as cystic fibrosis, neonatal hepatitis, or biliary atresia, and bleeding can be severe (Table 124.6).

Table 124.6

Vitamin K Deficiency Bleeding (Hemorrhagic Disease of the Newborn)

	EARLY-ONSET DISEASE	**CLASSIC DISEASE**	**LATE-ONSET DISEASE**
Age	0-24 hr	2-7 days	1-6 mo
Potential sites of hemorrhage	Cephalohematoma	Gastrointestinal	Intracranial
	Subgaleal	Ear-nose-throat-mucosal	Gastrointestinal
	Intracranial	Intracranial	Cutaneous
	Gastrointestinal	Post-circumcision	Ear-nose-throat-mucosal
	Umbilicus	Cutaneous	Injection sites
	Intraabdominal	Injection sites	Thoracic
Etiology/risks	Maternal drugs (phenobarbital, phenytoin, warfarin, rifampin, isoniazid) that interfere with vitamin K levels or absorption	Vitamin K deficiency Exclusive breastfeeding	Cholestasis: malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis)
	Inherited coagulopathy		Abetalipoprotein deficiency Idiopathic in Asian breastfed infants Warfarin ingestion
Prevention	Avoidance of high-risk medications Possibly antenatal vitamin K to treatment of mother (20 mg) before birth and postnatal administration to infant soon after birth	Prevented by parenteral vitamin K at birth Oral vitamin K regimens require repeated dosing.	Prevented by parenteral and high-dose oral vitamin K during periods of malabsorption or cholestasis
Incidence	Very rare	~2% if infant not given vitamin K soon after birth	Dependent on primary disease

Intramuscular (IM) administration of 1 mg of vitamin K (typically **phytonadione** , or vitamin K_1 , the only form of vitamin K available in the United States) soon after birth prevents the pathologic decrease in vitamin K–dependent factors in full-term infants. However, such vitamin K prophylaxis is not uniformly effective to prevent all hemorrhagic disease of the newborn, particularly in exclusively breastfed and premature infants. When an infant presents with hemorrhage, a slow IV infusion of 1-5 mg of vitamin K_1 is effective treatment and leads to improvement in coagulation defects and cessation of bleeding within a few hours. Serious bleeding, particularly in premature infants or those with liver disease, may require transfusion of fresh-frozen plasma or even whole blood. With prompt recognition and treatment, the mortality rate is low.

Decades of experience have demonstrated that the routine use of IM vitamin K for prophylaxis in the United States is safe, and specifically is *not* associated with an increased risk of childhood cancer or leukemia. Although multiple doses of oral vitamin K (1-2 mg at birth, again at discharge, and again at 3-4 wk of life) has been suggested as an alternative, *oral vitamin K is less effective* in preventing late-onset vitamin K deficiency bleeding and thus cannot be recommended for routine therapy. The IM route of vitamin K prophylaxis remains the method of choice.

Other forms of neonatal bleeding may be clinically indistinguishable from hemorrhagic disease of the newborn due to vitamin K deficiency, but they are neither prevented nor successfully treated with vitamin K. For example, an identical clinical presentation may also result from any congenital defect in blood coagulation factors (see Chapters 503 and 504). Hematomas, melena, and postcircumcision and umbilical cord bleeding may be present; up to 70% cases of hemophilia (factor VIII or IX deficiency) are clinically apparent in the newborn period. Treatment of these congenital deficiencies of coagulation factors requires specific factor replacement or fresh-frozen plasma if factor concentrate is not available.

Disseminated Intravascular Coagulopathy

Disseminated intravascular coagulation (**DIC**) in newborn infants results from consumption of circulating coagulation factors and platelets and therefore can present with either bleeding or thrombosis and usually with evidence of end-organ damage and increased mortality. Affected infants are often premature; their clinical course is frequently characterized by asphyxia, hypoxia, acidosis, shock, hemangiomas, or infection. Since DIC is a secondary event, the most effective treatment is directed at correcting the primary clinical problem, such as infection, to interrupt consumption of clotting factors and allow time to replace them (see Chapter 510). *Infants with DIC who have central nervous system hemorrhage, or other bleeding posing an immediate threat to life, should receive fresh-frozen plasma, vitamin K, and blood* if needed. However, treatment should always be preceded by specific testing for coagulation studies, as well as measurement of the platelet count.

Neonatal Thrombocytopenia

See Chapter 511 .

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124.5

Nonimmune Hydrops

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Keywords

hydrops fetalis
mirror syndrome
nonimmune hydrops

Because of the success in preventing Rh alloimmune fetal hemolysis, nonimmune and often nonhematologic hydrops fetalis is the most common cause of fetal hydrops. **Hydrops** is defined by ≥2 abnormal fetal fluid collections, such as ascites, pleural, pericardial, or cutaneous edema (>5 mm) (Fig. 124.8). In addition, there may be associated placental edema (>6 mm), polyhydramnios (50%), and the rare occurrence of the **mirror syndrome** , in which the mother becomes edematous.

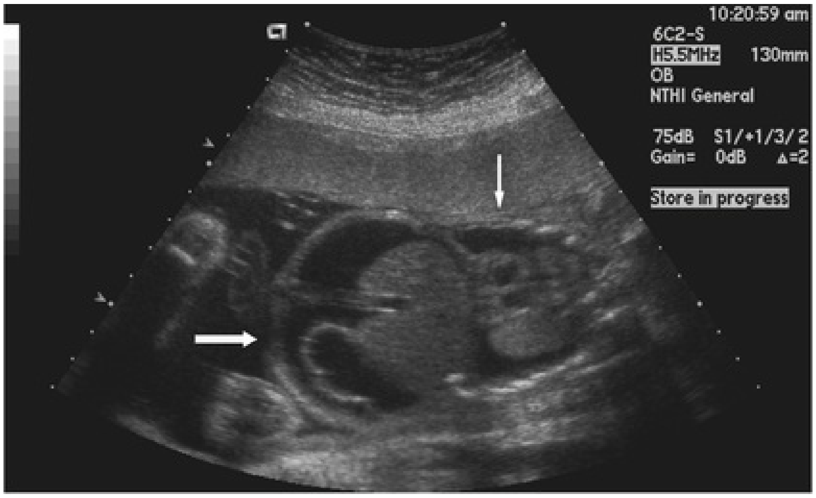

FIG. 124.8 **Hydrops fetalis. Longitudinal sonographic image of the fetus, with ascitic fluid outlining the liver *(large arrow).* The *small arrow* shows pleural effusion above the diaphragm. (From Wilkins I: Nonimmune hydrops. In Creasy RK, Resnick R, Iams JD, et al, editors: *Creasy & Resnik's maternal-fetal medicine,* ed 7, Philadelphia, 2014, Elsevier, Fig 37-2.)**

The incidence of nonimmune hydrops is approximately 1 in 3,000 births, many of whom are premature. The etiologies are broad; cardiac (structural and SVT) and chromosome disorders are the most common identifiable etiologies (Table 124.7). The etiology is unknown in 10–20%. The mechanisms for the development of nonimmune hydrops are not well established (Fig. 124.9).

Table 124.7

Conditions Associated With Nonimmune Hydrops

CARDIOVASCULAR	**HEMATOLOGIC**
Malformation	α-Thalassemia
Left heart hypoplasia	Fetomaternal transfusion
Atrioventricular canal defect	Parvovirus B19 infection
Right heart hypoplasia	In utero hemorrhage
Closure of foramen ovale	G6PD deficiency
Single ventricle	Red cell enzyme deficiencies
Transposition of the great vessels	**THORACIC**
Ventral septal defect	Congenital cystic adenomatoid malformation of lung
Atrial septal defect	Diaphragmatic hernia
Tetralogy of Fallot	Intrathoracic mass
Ebstein anomaly	Pulmonary sequestration
Premature closure of ductus	Chylothorax
Truncus arteriosus	Airway obstruction
Tachyarrhythmia	Pulmonary lymphangiectasia
Atrial flutter	Pulmonary neoplasia
Paroxysmal atrial tachycardia	Bronchogenic cyst
Wolff-Parkinson-White syndrome	**INFECTIONS**
Supraventricular tachycardia	

Bradyarrhythmia
Other arrhythmias
High-output failure
Neuroblastoma
Sacrococcygeal teratoma
Large fetal angioma
Placental chorioangioma
Umbilical cord hemangioma
Cardiac rhabdomyoma
Other cardiac neoplasia
Cardiomyopathy

CHROMOSOMAL

45,X
Trisomy 21
Trisomy 18
Trisomy 13
18q+
13q−
45,X/46,XX
Triploidy
Other

CHONDRODYSPLASIAS

Thanatophoric dwarfism
Short rib polydactyly
Hypophosphatasia
Osteogenesis imperfecta
Achondrogenesis

TWIN PREGNANCY

Twin-twin transfusion syndrome
Acardiac twin

OTHER

Familial hemophagocytic lymphohistiocytosis
Fetal akinesia syndromes
Congenital leukemia
Infantile arterial calcification syndrome
Maternal diabetes
Lymphatic disorders
IPEX
Idiopathic

Cytomegalovirus
Toxoplasmosis
Parvovirus B19 (fifth disease)
Syphilis
Herpes
Rubella

MALFORMATION SEQUENCES

Noonan syndrome
Arthrogryposis
Multiple pterygia
Neu-Laxova syndrome
Pena-Shokeir syndrome
Myotonic dystrophy
Saldino-Noonan syndrome

METABOLIC

Gaucher disease
GM_1 gangliosidosis
Sialidosis
Mucopolysaccharide disorders

URINARY

Urethral stenosis or atresia
Posterior urethral valves
Congenital nephrosis (Finnish)
Prune-belly syndrome

GASTROINTESTINAL

Midgut volvulus
Malrotation of the intestines
Duplication of the intestinal tract
Meconium peritonitis
Hepatic fibrosis
Cholestasis
Biliary atresia
Hepatic vascular malformations

IPEX, Immune dysregulation polyendocrinopathy enteropathy, X-linked.

Adapted from Wilkins I: Nonimmune hydrops. In Creasy RK, Resnick R, Iams JD, et al, editors: *Creasy & Resnik's maternal-fetal medicine,* ed 7, Philadelphia, 2014, Elsevier (Box 37-1).

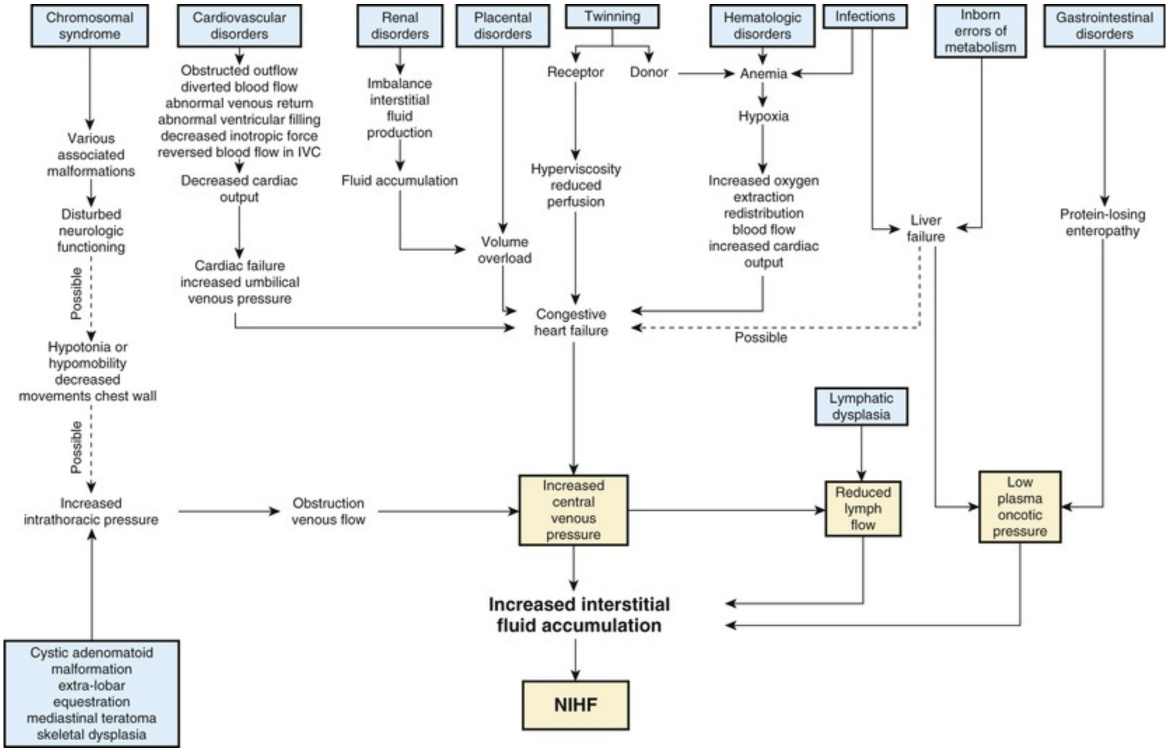
Chromosomal syndrome
Cardiovascular disorders
Renal disorders
Placental disorders
Twinning
Hematologic disorders
Infections
Inborn errors of metabolism
Gastrointestinal disorders
Obstructed outflow
diverted blood flow
abnormal venous return
abnormal ventricular filling
decreased inotropic force
reversed blood flow in IVC
Imbalance interstitial fluid production
Receptor
Donor
Anemia
Hypoxia
Various associated malformations
Decreased cardiac output
Fluid accumulation
Hyperviscosity reduced perfusion
Increased oxygen extraction redistribution blood flow increased cardiac output
Liver failure
Protein-losing enteropathy
Disturbed neurologic functioning
Possible
Volume overload
Cardiac failure increased umbilical venous pressure
Congestive heart failure
Possible
Hypotonia or hypomobility decreased movements chest wall
Lymphatic dysplasia
Possible
Increased intrathoracic pressure
Obstruction venous flow
Increased central venous pressure
Reduced lymph flow
Low plasma oncotic pressure
Increased interstitial fluid accumulation
Cystic adenomatoid malformation extra-lobar equestration mediastinal teratoma skeletal dysplasia
NIHF

FIG. 124.9 **Impact of various etiologies for nonimmune hydrops on fluid homeostasis. IVC, Inferior vena cava; NIHF, nonimmune hydrops fetalis. (Adapted from Bellini C, Hennekam RCM: Non-immune hydrops fetalis: a short review of etiology and pathophysiology, *Am J Med Genet* 158A:597–605, 2012.)**

In utero treatment has been successful for fetal supraventricular tachycardia (SVT), twin-twin transfusion syndrome, nonimmune fetal anemias, and some surgically treatable fetal conditions. Postnatal therapy includes a team approach to the delivery room management that often requires immediate endotracheal tube intubation and packed RBC transfusion in the presence of anemias. In premature infants, endotracheal surfactant is indicated; drainage of large pleural or pericardial effusions may also be needed. Once the infant is stabilized, diagnostic testing will direct further therapy based on the etiology. For patients with no obvious etiology, lymphangiography, whole exome (or genome) sequencing, and microarray duplication/deletion studies are recommended to establish a diagnosis.

Mortality is approximately 50% and is highest in the most premature infants, those with aneuploidy, and those with fetal anasarca.

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CHAPTER 125

The Umbilicus

Amy T. Nathan

Umbilical Cord

The umbilical cord typically consists of 2 umbilical arteries, the umbilical vein, and a gelatinous substance called Wharton's jelly, all contained within a sheath derived from the amnion and coiled into a helical shape. The muscular umbilical arteries carry deoxygenated blood from the fetus to the placenta and are contiguous with the fetal internal iliac arteries. The umbilical vein carries oxygenated blood from the placenta back to the fetus, where it flows into the inferior vena cava by way of the ductus venosus. The umbilical cord itself contains an estimated 20 mL/kg of blood, and current recommendations are to delay clamping of the cord at delivery for 30-60 sec, to facilitate placental transfusion. At term, a normal umbilical cord is approximately 55 cm long. Abnormally short cords are associated with conditions causing decreased fetal movement, including fetal hypotonia, oligohydramnios, and uterine constraint, and lead to increased risk for complications during labor and delivery for both mother and infant. Long cords (>70 cm) increase the risk for true knots, wrapping around the fetus, and/or prolapse. Straight uncoiled cords are associated with anomalies, fetal distress, and intrauterine fetal demise.

When the cord is cut after birth, portions of these structures remain in the base but gradually become obliterated. The blood vessels are functionally closed but anatomically patent for 10-20 days. The umbilical arteries become the lateral umbilical ligaments; the umbilical vein, the ligamentum teres; and the ductus venosus, the ligamentum venosum. The umbilical cord stump usually sloughs within 2 wk. Delayed separation of the cord, after more than 1 mo, has been associated with neutrophil chemotactic defects and overwhelming bacterial infection (see Chapter 153).

A single umbilical artery is present in approximately 5-10/1,000 births; the frequency is higher (35-70/1,000) in twin births. It is estimated that 30% of infants with a single umbilical artery have other (and often multiple) congenital structural abnormalities. The presence of multiple anomalies is suggestive of an abnormal karyotype, including trisomies. Infants with isolated single umbilical artery are not thought to be at increased risk of having a chromosomal anomaly, and no specific evaluation is indicated for these infants aside from a thorough physical examination.

The **omphalomesenteric duct (OMD)** is an embryonic connection between the developing midgut and the primitive yolk sac. It typically involutes at 8-9 wk gestation, but failure of this process can leave an abnormal connection between the umbilical cord and the gastrointestinal (GI) tract. The most common remnant of the OMD is a **Meckel diverticulum** (see Chapter 357), whereas abnormalities that would become symptomatic in the neonatal period include a **sinus** or **fistula** that would drain mucus or intestinal contents through the umbilicus. An umbilical **polyp** is one of the least common OMD remnants and represents exposed GI mucosa at the umbilical stump. The tissue of the polyp is bright red, firm, and has a mucoid secretion. Therapy for all OMD remnants is surgical excision of the anomaly.

A **persistent urachus** (urachal cyst, sinus, patent urachus, or diverticulum) is a result of failure of closure of the allantoic duct and may be associated with bladder outlet obstruction. Patency should be suspected if a clear, light-yellow, urine-like fluid is being discharged from the umbilicus. Symptoms include drainage, a mass or cyst, abdominal pain, local erythema, and infection. Urachal anomalies should be investigated by ultrasonography and a cystogram. Therapy for a persistent urachus is surgical excision of the anomaly and correction of any bladder outlet obstruction if present.

Hemorrhage

Hemorrhage from the umbilical cord may be the result of trauma, inadequate ligation of the cord, or failure of normal thrombus formation. It may also indicate hemorrhagic disease of the newborn or other coagulopathies (especially factor XIII deficiency), septicemia, or local infection. The infant should be observed frequently during the first few days of life so that if hemorrhage does occur, it will be detected promptly.

Granuloma

The umbilical cord stump usually dries and separates within 1-2 wk after birth. The raw surface becomes covered by a thin layer of skin; scar tissue forms, and the wound is usually healed within 12-15 days. The presence of saprophytic organisms delays separation of the cord and increases the possibility of invasion by pathogenic organisms. Mild infection or incomplete epithelialization may result in a moist, granulating area at the base of the cord with a slight mucoid or mucopurulent discharge. Good results are usually obtained by cleansing with alcohol several times daily.

Persistence of granulation tissue at the base of the umbilicus is common. The tissue is soft, 3-10 mm in size, vascular and granular, colored dull red or pink, and may have a seropurulent discharge. Granulation tissue is treated by cauterization with silver nitrate, repeated at intervals of several days until the base is dry.

Infections

The devitalized umbilical cord provides an ideal medium for bacterial growth and a potential portal of entry for microbes. The term **omphalitis** refers to infection of the umbilical cord stump, navel, or the surrounding abdominal wall. The presence of cellulitis is associated with a high incidence of bacteremia, and complicated omphalitis may spread to the peritoneum, the umbilical or portal vessels, or the liver. **Necrotizing fasciitis** (which is often polymicrobial) is associated with a high mortality rate. Treatment of omphalitis includes prompt antibiotic therapy with agents effective against *Staphylococcus aureus* and *Escherichia coli* , such as an antistaphylococcal penicillin or vancomycin in combination with an aminoglycoside. If abscess formation has occurred, surgical incision and drainage may be required.

In community and primary care settings in developing countries, topical application of chlorhexidine to the umbilical cord has been shown to reduce omphalitis and neonatal mortality. However, the ideal approach to postnatal cord care in hospital settings in developed countries is still debated. There is no convincing evidence that application of antiseptics (including triple dye, alcohol, or chlorhexidine) is superior to dry cord care in minimizing the risk of omphalitis for infants in these settings, although these treatments do reduce bacterial colonization. The American Academy of Pediatrics does not currently recommend any particular method of cord care as superior in the prevention of infection.

Umbilical Hernia

Often associated with **diastasis recti** , an umbilical hernia is caused by incomplete closure or weakness of the muscular umbilical ring. Predisposing factors include black race and low birthweight. The hernia appears as a soft swelling covered by skin that protrudes during crying, coughing, or straining and can be reduced easily through the fibrous ring at the umbilicus. The hernia consists of omentum or portions of the small intestine. The size of the defect varies from <1 cm in diameter to as much as 5 cm (2 inches), but large defects are rare. Most umbilical hernias that appear before age 6 mo disappear spontaneously by 1 yr. Even large hernias (5-6 cm in all dimensions) have been known to disappear spontaneously by 5-6 yr. **Strangulation** of intestinal contents is extremely rare. Surgery is not advised unless the hernia persists to age 4-5 yr, causes symptoms, becomes strangulated, or becomes progressively larger after age 1-2 yr. Defects exceeding 2 cm are less likely to close spontaneously.

Congenital Omphalocele

An **omphalocele** is a herniation or protrusion of the abdominal contents into the base of the umbilical cord (Fig. 125.1). In contrast to the more common umbilical hernia, the sac is covered with peritoneum without overlying skin, and the insertion of the distal umbilical cord into the sac itself distinguishes this condition from other abdominal wall defects such as gastroschisis. The size of the sac that lies outside the abdominal cavity depends on its contents. **Herniation** of intestines into the cord occurs in approximately 1/5,000 births, and herniation of liver and intestines in 1/10,000 births. The abdominal cavity may be proportionately small because of the lack of space-occupying viscera. Treatment for an omphalocele consists of covering the sac with moist, sterile dressings, then initiating prompt surgical repair if the abdomen is able to accommodate the eviscerated organs. If the omphalocele is too large to allow immediate repair, continued dressings may temporize and encourage epithelialization of the sac. Occasionally, mesh or similar synthetic material may be used to cover the viscera if the sac has ruptured or if excessive mobilization of the tissues would be necessary to cover the mass and its intact sac.

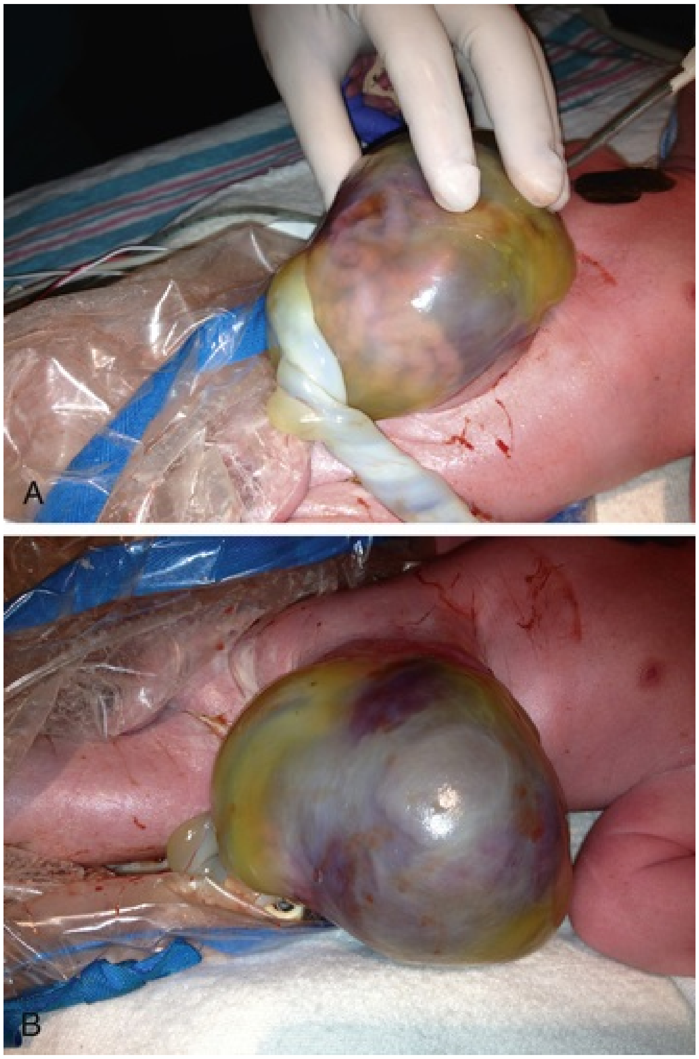

FIG. 125.1 **A,** Omphalocele with umbilical cord insertion into the sac and intestine visible. **B,** Omphalocele with sac containing liver. (Courtesy of Dr. Foong Lim, Cincinnati Fetal Center at Cincinnati Children's Hospital Medical Center.)

Many infants with omphalocele (50–70%) have associated malformations, and about 30% have chromosomal abnormalities. The likelihood of an abnormal karyotype is increased when the liver is *intracorporeal* (not within the sac). Omphalocele can be part of well-defined syndromes, including **Beckwith-Wiedemann syndrome** , characterized by omphalocele, macrosomia, and hypoglycemia. The survival rate for affected infants is largely determined by the presence of associated malformations or chromosomal abnormalities. For patients with isolated omphalocele, the survival rate is >90%.

Tumors

Tumors of the umbilicus are rare and include angioma, enteroteratoma, dermoid cyst, myxosarcoma, and cysts of urachal or OMD remnants.

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CHAPTER 126

Abstinence Syndromes

126.1

Neonatal Abstinence (Withdrawal)

Scott L. Wexelblatt

Keywords

- benzodiazepine
- buprenorphine
- cocaine
- MAT
- medication-assisted treatment
- methadone
- methamphetamine
- NAS
- neonatal abstinence syndrome
- opioid
- phenobarbital

Neonatal abstinence syndrome (NAS) is the clinical diagnosis given to infants who experience withdrawal signs after in utero exposure to opioids. Withdrawal signs develop in 55–94% of opioid-exposed infants, 30–65% of whom need pharmacologic treatment for severe withdrawal. The incidence of NAS has been increasing yearly since 2004 and was 5 times more prevalent in 2013 than 2004. This increase in NAS is caused by increased use of prescription medication by pregnant women, an increase in **medication-assisted treatment (MAT)** for opioid addiction, an increase in illicit use of prescription medications, and increased use of heroin. In 2011, 1.1% of pregnant women in the United States abused pain relievers and heroin, and up to 12.9–28% of women were prescribed an opioid at some point during their pregnancy. Many factors affect the severity and duration of withdrawal, including tobacco use during pregnancy, breastfeeding after delivery, rooming-in and parental involvement, genetic makeup, and polysubstance use.

The clinical signs of NAS result from central nervous system (CNS) hyperexcitability and autonomic instability (Fig. 126.1). NAS signs can begin within 24 hr of birth after heroin exposure, within 48 hr after short-acting opioids, and 72-96 hr after exposure to long-acting opioids such as methadone and buprenorphine. Tremors, poor feeding, excessive crying, poor sleeping, and hyperirritability are the most prominent signs of NAS. Other signs include sneezing, yawning, hiccups, myoclonic jerks, skin breakdown and abrasions, vomiting, loose stools, nasal stuffiness, and seizures in the most severe cases.

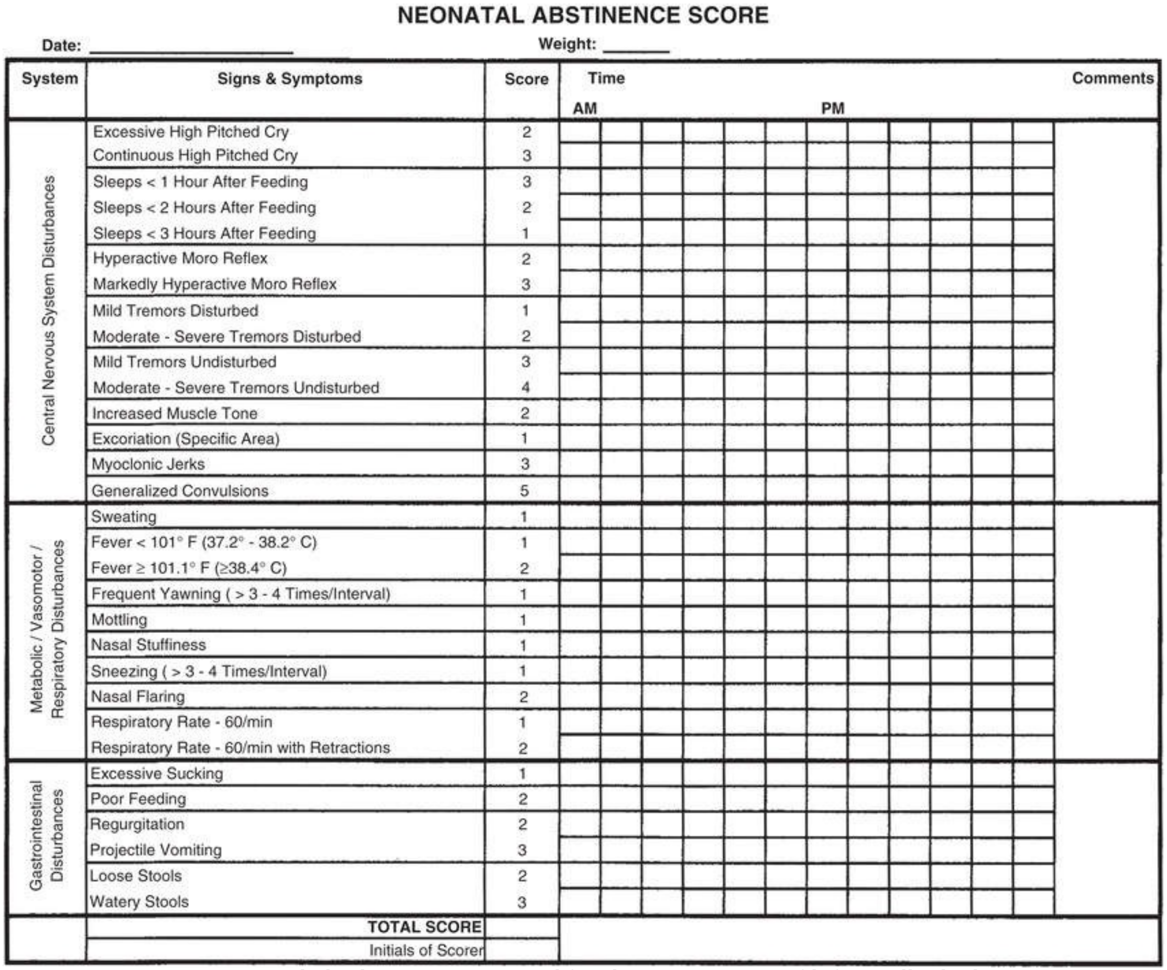

NEONATAL ABSTINENCE SCORE

Date: ____________________ Weight: _______

System	Signs & Symptoms	Score	Time												Comments
			AM						PM						
Central Nervous System Disturbances	Excessive High Pitched Cry	2													
	Continuous High Pitched Cry	3													
	Sleeps < 1 Hour After Feeding	3													
	Sleeps < 2 Hours After Feeding	2													
	Sleeps < 3 Hours After Feeding	1													
	Hyperactive Moro Reflex	2													
	Markedly Hyperactive Moro Reflex	3													
	Mild Tremors Disturbed	1													
	Moderate - Severe Tremors Disturbed	2													
	Mild Tremors Undisturbed	3													
	Moderate - Severe Tremors Undisturbed	4													
	Increased Muscle Tone	2													
	Excoriation (Specific Area)	1													
	Myoclonic Jerks	3													
	Generalized Convulsions	5													
Metabolic / Vasomotor / Respiratory Disturbances	Sweating	1													
	Fever < 101° F (37.2° - 38.2° C)	1													
	Fever ≥ 101.1° F (≥38.4° C)	2													
	Frequent Yawning (> 3 - 4 Times/Interval)	1													
	Mottling	1													
	Nasal Stuffiness	1													
	Sneezing (> 3 - 4 Times/Interval)	1													
	Nasal Flaring	2													
	Respiratory Rate - 60/min	1													
	Respiratory Rate - 60/min with Retractions	2													
Gastrointestinal Disturbances	Excessive Sucking	1													
	Poor Feeding	2													
	Regurgitation	2													
	Projectile Vomiting	3													
	Loose Stools	2													
	Watery Stools	3													
	TOTAL SCORE														
	Initials of Scorer														

FIG. 126.1 Neonatal abstinence score used for the assessment of infants displaying neonatal abstinence syndrome. Evaluator should check sign or symptom observed at various time intervals. Add scores for total at each evaluation. (Adapted from Finnegan LP, Kaltenbach K. The assessment and management of neonatal abstinence syndrome. In Hoekelman RA et al, editors: *Primary pediatric care,* ed 3, St Louis, 1992, Mosby, p 1367.)

Identifying which infants are at risk for NAS before discharge is important because of the late onset of signs. Universal maternal screening for drug use is recommended by the American College of Obstetricians and Gynecologists (ACOG), and maternal consent should be obtained if drug testing is indicated. Universal maternal drug testing has been shown to improve identification of infants at risk for NAS but is more expensive and may not be helpful in states with punitive legislation. Maternal testing is preferred over infant testing because results are available promptly, typically by the time the infant is delivered. Testing mothers on admission to the hospital can also exclude iatrogenic exposure. Infant urine, meconium and umbilical cord testing are also used to help identify infants at risk for withdrawal and identify more distant use by the mother. Timing of these results and special collection methods makes routine use of these tests more difficult. Detectability in the neonatal urine specimen is typically 2-3 days for methadone (up to 6 days for methadone metabolites) and buprenorphine and 1-2 days for heroin.

MAT has been shown to be useful for pregnant women with an opioid substance use disorder. Mothers receiving MAT have a decreased mortality, reduced illicit drug use, reduced seroconversion of HIV, and decreased criminal activity. The most common medications in MAT are methadone or buprenorphine. Methadone is a full μ-opioid agonist with a half-life of 24-36 hr, given once daily in methadone clinics because of the potential for overdose. Buprenorphine is a partial μ-opioid agonist with a half-life of 36-48 hr, prescribed monthly as home therapy because a ceiling effect protects against overdosages.

Treatment

The first line of treatment for all opioid-exposed infants is **nonpharmacologic support** , which includes swaddling, placing the infant in a dark and quiet environment (e.g., dimmed lights, muted televisions), holding and Kangaroo care, reducing stimulation, and breastfeeding. Illicit (if continued) drug use is a contraindication to breastfeeding infants with NAS. Maternal methadone or buprenorphine use and hepatitis C are not contraindications to breastfeeding. Standardization of nonpharmacologic care with increased emphasis on clinical assessment(i.e., is the infant feeding well, sleeping well, and easily consoled?) over formal scoring tools, which typically require disturbing the infant, was associated with significantly less opioid use among infants with in utero methadone exposure.

The decision for pharmacologic treatment has been traditionally based on the nursing scoring assessment tool. The most widely used tools are the Finnegan and Modified Finnegan (Fig. 126.1). Other scoring tools include the Lipsitz, Neonatal Narcotic Withdrawal Index, Neonatal Withdrawal Inventory, and MOTHER NAS Scale. The main objectives when initiating pharmacologic treatment are to improve signs and comfort of the infant and to prevent worsening withdrawal that could lead to seizures.

Pharmacologic treatment for NAS, when necessary, is typically morphine or methadone (Table 126.1). **Morphine** is a short-acting opioid given every 3-4 hr as a weight-based or symptom-based regimen. **Methadone** is long-acting opioid that can be given twice a day after loading doses, and a pharmacokinetic weight-based weaning protocol is available. Sublingual **buprenorphine** has been proposed as an alternate treatment. Buprenorphine and some methadone formulations contain high ethanol levels, which may be deleterious to the infant. Following a stringent NAS protocol with guidelines on initiation and weaning has been shown to decrease both length of stay and number of opioid treatment days and may be as important as which primary opioid is used for first-line treatment.

Table 126.1

Medications Used in Pharmacologic Treatment of Neonatal Abstinence Syndrome (NAS)

DRUG	INITIAL DOSING	DOSING INCREASES	WEANING SCHEDULE	ADD ADJUVANT THERAPY
Morphine	0.05 mg/kg/dose q3h	Increase dose 10–20%	10% of stabilizing dose q24h	>1 mg/kg/day of morphine Unable to wean for 2 days
Methadone	0.1 mg/kg/dose q6h for 4 doses	Increase to q4h if unable to capture	0.7 mg/kg/dose q12h × 2 doses, then 0.05 mg/kg/dose q12h × 2; 0.04 mg/kg/dose q12h × 2; 0.03 mg/kg/dose q12h × 2; 0.02 mg/kg/dose q12h × 2; 0.01 mg/kg/dose q12h × 2; 0.01 mg/kg/dose q24h × 1	Unable to wean for 2 days
Buprenorphine	4 µg/kg q8h	2 µg/kg until maximum of 15 µg/kg	3 µg/kg/dose q8h × 3 doses; 2 µg/kg/dose q8h × 3; 2 µg/kg/dose q8h × 2; 2 µg/kg/dose q24h × 1	Unable to wean for 2 days
Phenobarbital	20 mg/kg	—	5 mg/kg daily	N/A
Clonidine	1.5 µg/kg/dose q3h	25% dose escalation q24hr	10% every day	N/A

N/A, Not available; q24h, every 24 hours.

Adjuvant therapy is initiated when the primary opioid is not effective in controlling the signs of NAS. The 2 most common medications used as adjuvant therapy are **phenobarbital** and **clonidine** . Infants with NAS may also expend additional energy. Therefore, the infant should be weighted regularly and strategies to increase caloric intake implemented if weight loss beyond that expected in the 1st week of life occurs.

The long-term prognosis for infants with NAS is multifactorial and not fully known. Close follow-up needs to be initiated to monitor growth and development, visual disturbances, and behavioral/learning problems.

Phenobarbital and benzodiazepine withdrawal may occur in infants of mothers addicted to these drugs, but signs are self-limiting and do not require pharmacologic treatment. Signs may be late onset and begin at a median age of 7 days (range: 2-14 days). Infants may have a brief acute stage consisting of irritability, constant crying, sleeplessness, hiccups, and mouthing movements, followed by a prolonged stage consisting of increased appetite, frequent spit-ups and gagging, irritability, sweating, and a disturbed sleep pattern, all of which may last for weeks.

Cocaine and methamphetamine abuse in pregnant women is less common than opioid abuse, and acute withdrawal in these infants is unusual. However, labor complications can be severe with both drugs and may include preterm labor, placental abruption, intrauterine growth restriction, and fetal asphyxia. Detection in neonatal urine is 6-8 hr for cocaine and 1-2 days for methamphetamine. Early on, exposed infants may have abnormal sleep patterns, poor feeding, tremors, and hypertonia. Long-term outcomes include impaired auditory information processing, developmental delay, and learning disabilities. At age 4 yr, children exposed prenatally to cocaine demonstrate cognitive impairments and are less likely to have an IQ above the normative mean.

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126.2

Maternal Selective Serotonin Reuptake Inhibitors and Neonatal Behavioral Syndromes

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Jennifer McAllister

Keywords

persistent pulmonary hypertension
PPHN
poor neonatal adaptation syndrome
PNAS
selective norepinephrine reuptake inhibitor
SNRI
selective serotonin reuptake inhibitor
SSRI
TCA
tricyclic antidepressant

Approximately 18% of women have depression during pregnancy. When pharmacologic treatment is required, selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine) are most frequently prescribed. Additionally, serotonin norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine) and tricyclic antidepressants (TCAs) have been used to treat pregnant women with depression or anxiety disorders. About 3.5% of all pregnant women in the Western world use psychotropic medications during their pregnancy, and all these agents cross the placenta. Exposure to these medications in utero may lead to a higher risk of congenital malformations, **poor neonatal adaptation syndrome** (PNAS), and **persistent pulmonary**

hypertension (PPHN).

Studies are conflicted on the risk of major birth defects, specifically cardiac defects, and antidepressant use in pregnancy. Use of paroxetine and fluoxetine are thought to have the highest risk of birth defects. Some reported defects include anencephaly, atrial septal defect, right ventricular outflow tract obstruction, omphalocele, and gastroschisis. Although the relative risk may be increased, the occurrence of birth defects is low.

PNAS symptoms usually appear within the 1st 8 hr after birth and often persist for the 1st 2-6 days of life. If symptoms do not develop within 48 hr, the infant is not likely to experience PNAS. PNAS affects the neurologic, autonomic, respiratory, and gastrointestinal systems. Symptoms include a weak suck reflex, irritability, tremors, hypertonia and hypotonia, hyperthermia, weak or absent cry, sleep disturbances, hypoglycemia, respiratory problems, vomiting and diarrhea, and seizures. Most symptoms are mild, and severe symptoms are rare. No deaths have been reported. Many researchers believe that the etiology of PNAS results from both toxicity and withdrawal from the antidepressant medications, and the symptoms of both toxicity and withdrawal are similar. Symptoms related to toxicity often occur *immediately after birth* when medication levels in the infant are high, whereas symptoms related to withdrawal often occur *8-48 hr after birth* when drug concentrations in the infants are low.

Most studies have reported incidence of PNAS with SSRI exposure to be approximately 30%. Exposure to SNRIs has a similar risk as SSRIs. Infants exposed to TCAs have a 20–50% risk of PNAS.

PPHN is often observed immediately after delivery, but symptoms can be variable in intensity, from mild respiratory insufficiency to severe respiratory failure. SSRI exposure later in pregnancy has been associated with a higher risk of PPHN.

Treatment consists of supportive measures, and most cases are mild, of short duration, and self-limiting. Small, frequent, on-demand feedings; swaddling; and skin-to-skin contact are beneficial to support infants through this process. Breastfeeding is protective against developing PNAS and should be encouraged because many antidepressant medications are safe with breastfeeding. Infants can be observed on the maternity ward with their mothers unless specific symptoms warrant further evaluation and treatment. Infants should be observed for a minimum of 48 hr to ensure they do not develop significant symptoms of PNAS. There have been no reported differences in IQ or development in infants with PNAS. Further research is needed to examine long-term effects of in utero antidepressant exposure.

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126.3

Fetal Alcohol Exposure

Carol Weitzman

Keywords

fetal alcohol spectrum disorder
FASD
prenatal alcohol exposure
PAE

Epidemiology

Approximately 1 in 10 pregnant women report consuming alcohol within the past 30 days, and 1 in 33 report binge drinking. When pregnant women report binge drinking, they report an average of 4.6 binge-drinking episodes. Of nonpregnant women of childbearing age, approximately 50% report consuming alcohol within the last 30 days, with about 1 in 5 reporting binge drinking. Because almost 50% of pregnancies in the United States are unplanned, unintentional **prenatal alcohol exposure (PAE)** can occur before a woman knows she is pregnant.

Alcohol is a known teratogen that can cause irreversible CNS damage leading to CNS dysfunction that can range from relatively mild to severe. PAE affects all stages of brain development from neurogenesis to myelination, through mechanisms that include disrupted cell-cell interactions, altered gene expression, and oxidative stress leading to abnormalities such as reduced brain volume in the frontal lobe, striatum and caudate nucleus, thalamus, and cerebellum; thinning of the corpus callosum; and abnormal functioning of the amygdala.

Fetal alcohol spectrum disorders (FASDs) are the most common causes of preventable developmental delay and intellectual disability. Prevalence rates vary for several reasons. First, the method of ascertainment and the specific diagnostic definitions used can influence rates. Further, it is often difficult to obtain accurate information regarding PAE because mothers often deny the extent of alcohol use due to fear of child protective services and removal of their child from the home, shame and guilt associated with alcohol use during pregnancy, and fear of judgment. Lastly, mothers are often not asked in enough detail during or after pregnancy about alcohol consumption during pregnancy to accurately assess the extent of PAE. The U.S. Centers for Disease Control and Prevention (CDC) Fetal Alcohol Syndrome (FAS) Surveillance Network used medical records in several states and identified 0.3 children with FAS per 1,000 children age 7-9 yr. This prevalence rate is much lower than that obtained by active case ascertainment studies in the United States and Western Europe, which have estimated prevalence rates of 2–5%. Another study reported similar rates, 24-48 cases per 1,000 children (2.4–4.8%) for all FASDs, and 6-9 cases per 1,000 (0.6–0.9%) for FAS specifically. Studies that have examined PAE by anonymous meconium testing demonstrate 4.26 times greater identification of alcohol use during pregnancy compared with maternal self-report. Rates of FASDs have been reported to be higher in children living in poverty, in American Indian populations, and in children living in foster care. They often go undetected in these children, and as many as 86.5% of foster and adopted youth with FASDs go undiagnosed or are diagnosed incorrectly within the FAS spectrum.

Diagnostic Criteria

Updated clinical guidelines for diagnosing FASDs in the United States were published in 2016, as were updated Canadian guidelines, which overlap U.S. guidelines but also have important distinctions. PAE can result in a child having 1 of the FASDs, a nondiagnostic umbrella term in the United States. Diagnoses are determined based on the presence or absence of (1) the characteristic facial features; (2) prenatal/postnatal growth deficiency; (3) deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology; (4) neurobehavioral impairment; and (5) maternal alcohol consumption during pregnancy.

FASDs include **fetal alcohol syndrome** (FAS), **partial fetal alcohol syndrome** (pFAS), **alcohol-related neurodevelopmental disorder** (ARND), **alcohol-related birth defect** (ARBD), and **neurobehavioral disorder associated with prenatal alcohol exposure** (ND-PAE), a term introduced in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Table 126.2 describes specific diagnostic features of each of the FASDs. The diagnosis of **FAS** and **pFAS** are the only FASDs that can be diagnosed in the absence of a confirmed maternal history of PAE. The key facial dysmorphologic features include short palpebral fissures, a thin vermilion border of the upper lip, and a smooth philtrum (Fig. 126.2). The differential diagnosis for FAS includes Williams syndrome, Dubowitz syndrome, fetal valproate syndrome, maternal phenylketonuria (PKU) effects, and other prenatal toxin exposures, and when there is unconfirmed PAE, a genetics evaluation may be warranted. **ND-PAE** is included in the DSM-5 as a “condition for further study” and is also provided as an example under “Other Specified Neurodevelopmental Disorder.” Although the diagnosis of ND-PAE overlaps with **ARND** , ND-PAE aims to describe the behavioral and mental health effects on an individual with PAE. Unlike ARND, a diagnosis of ND-PAE can be given in addition to FAS or pFAS. ND-PAE has organized the deficits seen into 3 areas: neurocognitive impairment, impaired self-regulation, and impairment in adaptive functioning. In the updated Canadian guidelines, “fetal alcohol spectrum disorder” is considered a diagnostic term with 2 categories: FASD with sentinel facial features and FASD without sentinel facial features. These guidelines have also eliminated *growth restriction* as a diagnostic criterion and have included an at-risk category for children with confirmed PAE who were too young to meet the criteria for neurodevelopmental deficits, or in whom assessment was incomplete, and for children with cardinal facial features without documentation or evidence of severe impairment in neurodevelopmental domains.

Table 126.2

Diagnostic Features of Fetal Alcohol Spectrum Disorders (FASDs)

TYPE OF FASD	FACIAL DYSMORPHOLOGY	GROWTH		DEFICIENT BRAIN GROWTH, ABNORMAL MORPHOGENESIS, OR ABNORMAL NEUROPHYSIOLOGY	NEUROBEHAVIOR FEATURES
Fetal alcohol syndrome (FAS)	≥2 of the following: Short palpebral fissures (≤10th centile) Thin vermilion border of upper lip Smooth philtrum	Height and/or weight ≤10th centile	*OR*	Head circumference ≤10th centile Structural brain anomalies Recurrent nonfebrile seizures	*With cognitive impairment:* Evidence of globa impairment (gene conceptual ability ≥1.5 SD below th mean *or* Cognitive deficit i at least 2

					neurobehavioral domains ≥1.5 SD below the mean *With behavioral impairment witho cognitive impairment:* Evidence of behavioral deficit at least 2 domains ≥1.5 SD below th mean
Partial FAS (pFAS)	≥2 of the following: Short palpebral fissures (≤10th centile) Thin vermilion border of upper lip Smooth philtrum	Height and/or weight ≤10th centile	*OR*	Head circumference ≤10th centile Structural brain anomalies Recurrent nonfebrile seizures	*With cognitive impairment:* Evidence of globa impairment (gene conceptual ability ≥1.5 SD below th mean *or* Cognitive deficit i at least 2 neurobehavioral domains ≥1.5 SD below the mean *With behavioral impairment witho cognitive impairment:* Evidence of behavioral deficit at least 2 domains ≥1.5 SD below th mean
Alcohol-related neurodevelopmental disorder (ARND)	—	—		—	*With cognitive impairment:* Evidence of globa impairment (gene conceptual ability ≥1.5 SD below th mean *or* Cognitive deficit i at least 2 neurobehavioral domains ≥1.5 SD below the mean *With behavioral impairment witho cognitive impairment:* Evidence of behavioral deficit at least 2 domains ≥1.5 SD below th mean

Alcohol-related birth defect (ARBD)	—	—		One or more specific major malformations demonstrated in animal models and human studies to be the result of prenatal alcohol exposure	—
Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE)	—	—		—	**Neurocognitive impairment (1)** Global intellect Executive functioning Learning Memory Visual-spatial reasoning **Impaired self-regulation (1)** Mood or behavior Attention Impulse control **Impairments in adaptive functioning (2)** Language Social communication a interaction Daily living skills Motor skills

* Documented prenatal alcohol exposure:
- ≥6 drinks/wk for ≥2 wk during pregnancy.
- ≥3 drinks per occasion on ≥2 occasions during pregnancy.
- Documentation of alcohol-related social or legal problems in proximity to (before or during) the index pregnancy (e.g., driving while intoxicated or history of treatment of an alcohol-related condition).
- Documentation of intoxication during pregnancy by blood, breath, or urine alcohol content testing.
- Increased prenatal risk associated with drinking during pregnancy as assessed by a validated screening tool.

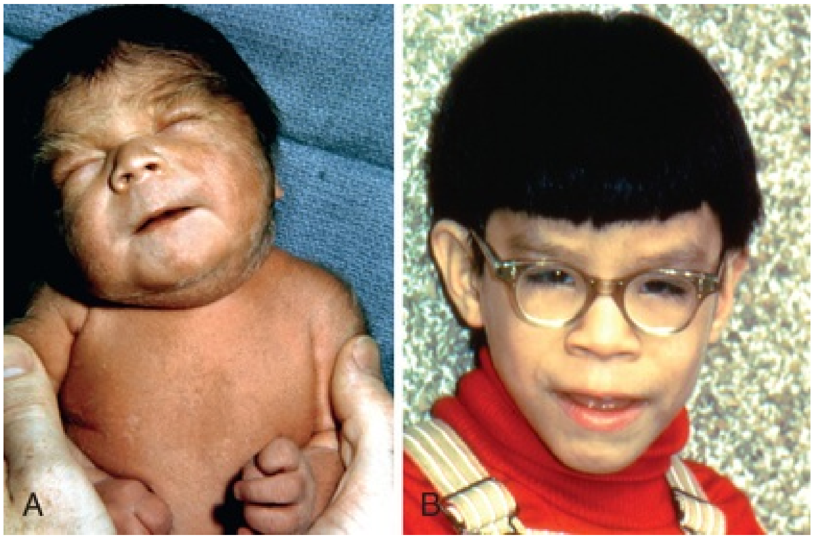

FIG. 126.2 **Characteristics of fetal alcohol syndrome. At birth (A) and at 4 yr of age (B). Note the short palpebral fissures; long, smooth philtrum with vermilion border; and hirsutism in the newborn. (From Jones KL, Smith DW: Recognition of the fetal alcohol syndrome in early infancy, *Lancet* 2:999–1001, 1973.)**

A safe threshold or pattern of alcohol consumption has not been identified, and any PAE is believed to present a risk to a developing fetus. Significant alcohol exposure has been carefully defined in the updated guidelines, and information can be obtained from a variety of sources, including, in addition to the birth mother, family members, foster or adoptive parents, social service agencies who observed maternal alcohol consumption during pregnancy, or medical records that document PAE, alcohol treatment, or social, legal, or medical problems related to drinking during pregnancy. PAE in the first trimester leads to the classic *facial dysmorphia* associated with FAS and other structural defects. PAE can have other deleterious effects (e.g., spontaneous abortion, growth defect) on the fetus throughout the pregnancy. Several well-validated screens are used to identify alcohol use in pregnant and nonpregnant women of childbearing years, including the T-ACE (Tolerance, Annoyance, Cut Down, Eye-Opener), CAGE (Cut Back, Annoyed, Guilty, Eye-Opener), CRAFFT, Audit-C (Alcohol Use Disorders Identification Test), and TWEAK (Tolerance, Worried, Eye opener, Amnesia, Kut Down). There are no well-validated screens designed to ask about past consumption of alcohol. Pediatricians can ask the following 2 questions to determine the likelihood of significant PAE: “In the 3 months before you knew you were pregnant, how many times did you have 4 or more alcohol drinks in a day?” and “During your pregnancy, how many times did you have any alcohol?” If a positive response is given to either question, the clinician can follow up to determine the level of PAE by asking, (1) “During your pregnancy, on average, how many days per week did you have any alcohol?” (2) “During your pregnancy, on a typical day when you had an alcoholic beverage, how many drinks did you have?” and (3) “During your pregnancy, what was the maximum number of drinks that you had in a day?”

Clinical Features

There is tremendous variability in the presentation of the neurobehavioral and neurocognitive features of children with FASD due to the timing and amount of PAE and unique characteristics of the birth mother and the child. Presentation can range from relatively mild developmental delays to severe intellectual disability, although approximately 75% of individuals with an FASD do not have intellectual disability. In infants, the symptoms can be nonspecific and may include irritability, poor feeding, sleep difficulties, a tendency to become easily overstimulated, or difficulty forming attachments with caregivers. Young children may demonstrate developmental delays, inattention, impulsivity, internalizing and externalizing problems, social impairments and difficulty with peers, and behavioral difficulties such as mood lability, frequent tantrums or aggression. The neurocognitive profile of children with an FASD that emerges in elementary or middle school includes challenges with processing speed, memory, visual-spatial reasoning, math, auditory comprehension, use of pragmatic language, and executive functioning skills. Learning strengths often include decoding, reading, and speech. In adolescents, difficulties with abstract reasoning, time and money management, and social and adaptive skills may become more pronounced.

The most common comorbid mental health condition seen in children with an FASD is attention-deficit/hyperactivity disorder (see Chapter 49), which occurs in >50% of children. Individuals with FASD may present with problems of self-regulation, impulse control, and adaptive functioning. Additional mental health disorders typically seen in children and adolescents with an FASD include oppositional defiant and conduct disorder, anxiety disorder, adjustment disorder, sleep disorder, mood disorders (e.g., depression, bipolar disorder), and disinhibited social engagement disorder. FASD may increase the severity or complexity of these conditions.

Interventions and Treatment

Given the heterogeneity of presenting problems associated with the FASDs, interventions need to be tailored to address each individual child or adolescent's profile of strengths and difficulties. Although the evidence base examining interventions for children and adolescents with an FASD is limited, with most studies having small sample sizes, there is emerging evidence for effective programs and treatments specifically designed for children with an FASD. Studies support that the most successful interventions begin early and continue across the life span, include a preventive focus, are intensive and individualized, address multiple domains of functioning, include parent education and training, and are coordinated across systems of care. Children with an FASD often need support and intervention in the areas of learning, executive functioning, adaptive skills, social skills and peer relations, and mental health. To enhance generalizability of skills and to ensure they are encoded into memory, children with an FASD require consistent and predictable interventions, simplified directions, repeated instructions, and reduced distractions. Many children are treated with psychotropic medications, with stimulants most frequently prescribed. Children with an FASD are often treated with a higher number of drugs and at higher doses, likely because of atypical or less favorable responses.

Outcomes

Children with an FASD are at higher risk for **victimization and bullying** , often due to poor social judgment. Children and adolescents who are not identified early and aggressively treated are significantly more likely to have secondary disabilities, including encounters with juvenile justice and incarceration, substance abuse problems, severe mental health problems, sexual promiscuity and other inappropriate sexual behaviors, high rates of school failure, dropout and under- or unemployment, and health problems. Children and adolescents with an FASD have a 95% lifetime likelihood of having a mental health diagnosis and are at higher risk for **suicide** . Although an FASD cannot be cured, the long-term negative effects of the brain damage caused by PAE can be reduced through aggressive, sustained intervention initiated early. The estimated lifetime cost of caring for a child with FAS is $1.4 million, with average medical expenditures 9 times higher than expenses for children without FAS. These numbers increase significantly when the costs of caring for all children with any FASD are included.

The Pediatrician's Role

Pediatricians play an important role in identifying children and adolescents with an FASD, by asking parents about PAE and counseling mothers to abstain from alcohol consumption if they are planning to have additional children. Pediatricians need to screen all mothers for PAE and reduce the stigma associated with asking. They need to consider an FASD in a child who presents with complex neurodevelopmental and neurobehavioral problems, structural abnormalities, growth deficits, and facial dysmorphology. It is important that pediatricians remember that despite the increased risk in certain groups, FASDs occur across all economic, racial, and ethnic groups. Pediatricians need to document findings related to PAE and establish a **medical home** for the child with an FASD that includes a network of professionals who can help and support the child and family. The American Academy of Pediatrics has developed an FASD toolkit (www.aap.org/fasd) to assist primary care providers in identifying children with an FASD and managing their challenges in an effort to reduce the lifelong adverse consequences.

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CHAPTER 127

The Endocrine System

Nicole M. Sheanon, Louis J. Muglia

Endocrine emergencies in the newborn period are uncommon, but prompt identification and proper treatment are vital to reduce morbidity and mortality.

Pituitary dwarfism (growth hormone deficiency) is not usually apparent at birth, although male infants with **panhypopituitarism** may have neonatal hypoglycemia, hyperbilirubinemia, and micropenis. Conversely, **primordial dwarfism** manifests as in utero growth failure that continues postnatally, with length and weight suggestive of prematurity when born after a normal gestational period; otherwise, physical appearance is normal.

Congenital hypothyroidism is one of the most common preventable causes of developmental disability. Congenital screening followed by thyroid hormone replacement treatment started within 30 days after birth can normalize cognitive development in children with congenital hypothyroidism. Congenital hypothyroidism occurs in approximately 1/2,000 infants worldwide (see Chapter 581). Because most infants with congenital hypothyroidism are asymptomatic at birth, all states screen for it. Even though screening is standard in many countries, millions of infants born throughout the world are not screened for congenital hypothyroidism. Thyroid deficiency may also be apparent at birth in genetically determined cretinism and infants of mothers with hyperthyroidism during pregnancy treated with antithyroid medications (PTU). Infants with trisomy 21 have a higher incidence of congenital hypothyroidism and should be screened in the newborn period. Constipation, prolonged jaundice, goiter, lethargy, umbilical hernia, macroglossia, hypotonia with delayed reflexes, mottled skin, or cold extremities should suggest severe chronic hypothyroidism. **Levothyroxine** is the treatment of choice, with the goal of rapid normalization of thyroid-stimulating hormone (TSH, thyrotropin) and free thyroxine (T_4) to achieve the best outcome. Thyroid hormone treatment is aimed to maintain total thyroxine or free thyroxine in the upper half of the normal range during the 1st 3 yr after birth. Early diagnosis and treatment of congenital thyroid hormone deficiency improve intellectual outcome and are facilitated by screening of all newborn infants for this deficiency. Newborn screening, with early referral to a pediatric endocrinologist for abnormal results, has improved early diagnosis and treatment of congenital hypothyroidism and improved intellectual outcome.

Transient hypothyroxinemia of prematurity is most common in ill and very premature infants. These infants have low thyroxine levels but normal levels of serum thyrotropin and other tests of the pituitary-hypothalamic axis indicating that they are probably chemically euthyroid. Trials of thyroid hormone replacement have reported no difference in developmental outcomes or other morbidities. Current practice is to follow thyroxine until levels normalize. **Transient hyperthyroidism** may occur at birth in infants of mothers with established or cured hyperthyroidism (e.g., Graves disease with positive TSH receptor–stimulating antibodies). See Chapter 584 for details on diagnosis and treatment.

Transient hypoparathyroidism may manifest as tetany or seizure of the newborn due to hypocalcemia and is associated with low levels of parathyroid hormone and hyperphosphatemia. Testing for DiGeorge syndrome should be considered. (see Chapter 589).

Subcutaneous fat necrosis can cause **hypercalcemia** and can occur after a traumatic birth. On examination, firm purple nodules can be appreciated on the trunk or extremities. An infant with hypercalcemia presents with irritability, vomiting, increased tone, poor weight gain, and constipation. Other causes of hypercalcemia in the newborn period are iatrogenic (excess calcium or vitamin D), maternal hypoparathyroidism, Williams syndrome, parathyroid hyperplasia, and idiopathic.

The adrenal glands are subject to numerous disturbances, which may become apparent and require lifesaving treatment during the neonatal period. Acute **adrenal hemorrhage** and adrenal failure are uncommon in the neonatal period. Risk factors include vaginal delivery, macrosomia, and fetal acidemia. The clinical presentation is often mild, with spontaneous regression. In neonates with bilateral adrenal hemorrhage, an evaluation of cortisol production is required (high-dose ACTH stimulation test), and, if insufficient, treatment with glucocorticoids and mineralocorticoids is indicated. Differentiation of unilateral adrenal hemorrhage from neuroblastoma is important. All patients should have sonographic and clinical follow-up to ensure resolution.

Congenital adrenal hyperplasia (CAH) is suggested by vomiting, diarrhea, dehydration, hyperkalemia, hyponatremia, shock, ambiguous genitalia, or clitoral enlargement. Some infants have ambiguous genitalia and hypertension. In an infant with ambiguous genitalia, both pelvic and adrenal ultrasound can be performed to aid in diagnosis. An adrenal ultrasound showing bilateral, enlarged, coiled or cerebriform pattern is specific for CAH. Diagnosis is confirmed with an elevated 17-hydroxyprogesterone level for gestational age. Because the condition is genetically determined, newborn siblings of patients with the salt-losing variety of adrenocortical hyperplasia should be closely observed for manifestations of adrenal insufficiency. Newborn screening and early diagnosis and therapy for this disorder may prevent severe salt wasting and adverse outcomes. Congenitally hypoplastic adrenal glands may also give rise to adrenal insufficiency during the 1st few wk of life (*DAX1* mutation).

Disorders of sexual development can present in the newborn period with ambiguous or atypical genitalia, including bilateral cryptorchidism, hypospadias, micropenis, hypoplastic scrotum, or clitoromegaly. More than 20 genes have been associated with disorders of sexual development. The initial management should involve a multidisciplinary team (endocrinology, urology, genetics, and neonatology) and open communication with the family. Sex assignment and naming of the infant should be delayed until appropriate testing is completed. For more about disorders of sexual development, see Chapter 606 .

Female infants with webbing of the neck, lymphedema, hypoplasia of the nipples, cutis laxa, low hairline at the nape of the neck, low-set ears, high-arched palate, deformities of the nails, cubitus valgus, and other anomalies should be suspected of having **Turner syndrome** . Lymphedema of the hands or lower extremities can sometimes be the only indication. A karyotype can confirm diagnosis (see Chapter 604.1).

Transient neonatal diabetes mellitus (TNDM) is rare and typically presents on day 1 of life (see Chapter 607). It usually manifests as polyuria, dehydration, loss of weight, or acidosis in infants who are small for gestational age. The most common cause (70%) is a disruption of the imprinted locus at chromosome 6q24. A select group of patients with TNDM are at risk for recurrence of diabetes later in life.

127.1

Infants of Diabetic Mothers

Nicole M. Sheanon, Louis J. Muglia

Keywords

diabetic embryopathy
gestational diabetes
hyperglycemia
hyperinsulinemia
hyperinsulinism
hypoglycemia
IDMs
infants of diabetic mothers
pregestational diabetes

Diabetes (type 1, type 2, or gestational) in pregnancy increases the risk of complications and adverse outcomes in the mother and the baby. Complications related to diabetes are milder in gestational vs pregestational (preexisting type 1 or type 2) diabetes. Pregnancy outcomes are correlated with onset, duration, and severity of maternal hyperglycemia. Prepregnancy planning and tight glycemic control (hemoglobin A_{1c} [HbA_{1c}] <6.5%) is crucial in **pregestational diabetes** in order to achieve the best outcomes for the mother and the baby. The risk of **diabetic embryopathy** (neural tube defects, cardiac defects, caudal regression syndrome) and spontaneous abortions is highest in those with pregestational diabetes who have poor control (HbA_{1c} >7%) in the first trimester. The risk of congenital malformations in **gestational diabetes** is only slightly increased compared to the general population, since the duration of diabetes is less and hyperglycemia occurs later in gestation (typically >25 wk).

Mothers with pregestational and gestational diabetes have a high incidence of complications during the pregnancy. Polyhydramnios, preeclampsia, preterm labor (induced and spontaneous), and chronic hypertension occur more frequently in mothers with diabetes. Accelerated fetal growth is also common, and 36–45% of **infants of diabetic mothers (IDMs)** are born large for gestational age (LGA). Restricted fetal growth is seen in mothers with pregestational diabetes and vascular disease, but it is less common. Fetal mortality rate is greater in both pregestational and gestational diabetic mothers than in nondiabetic mothers, but the rates have dropped precipitously over the years. Fetal loss throughout pregnancy is associated with poorly controlled maternal diabetes, especially **diabetic ketoacidosis** . The neonatal mortality rate of IDMs is >5 times that of infants of nondiabetic mothers and is higher at all gestational ages and in every birthweight for gestational age category. The rate is higher in women with pregestational diabetes, smoking, obesity, hypertension, and poor prenatal care.

Pathophysiology

The probable pathogenic sequence is that maternal hyperglycemia causes fetal **hyperglycemia** , and the fetal pancreatic response leads to fetal **hyperinsulinemia** , or **hyperinsulinism** . It is important to recognize that while maternal glucose crosses the placenta, maternal and exogenous insulin dose not. Fetal hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis, and augmented protein synthesis (Fig. 127.1). Related pathologic findings are hypertrophy and hyperplasia of the pancreatic β cells, increased weight of the placenta and infant organs (except the brain), myocardial hypertrophy, increased amount of cytoplasm in liver cells, and extramedullary hematopoiesis. Hyperinsulinism and hyperglycemia produce fetal acidosis, which may result in an increased rate of stillbirth. Separation of the placenta at birth suddenly interrupts glucose infusion into the neonate without a proportional effect on hyperinsulinism, leading to hypoglycemia during the 1st few hr after birth. The risk of rebound hypoglycemia can be diminished by tight blood glucose control during labor and delivery.

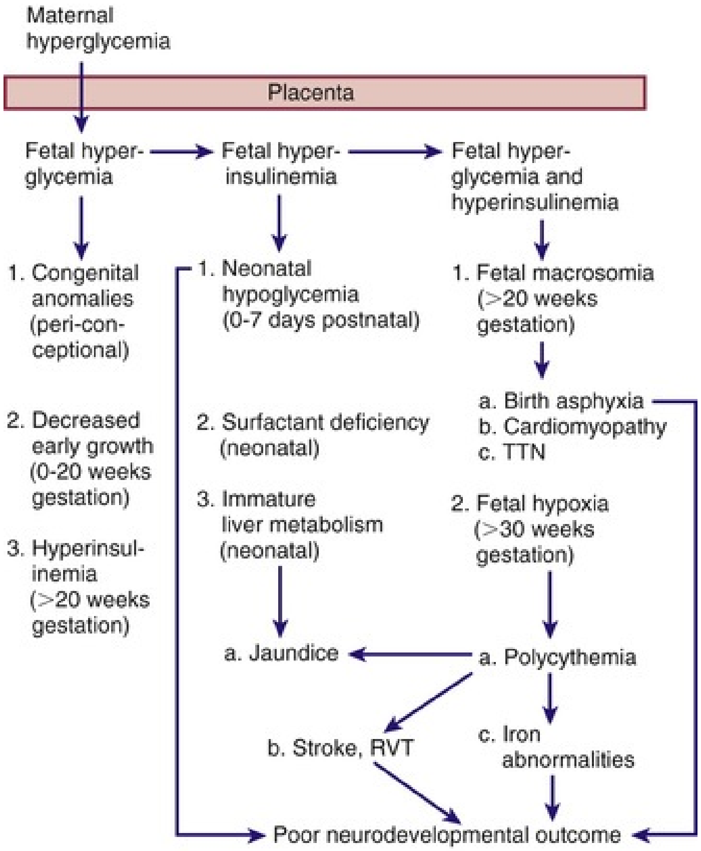
Maternal hyperglycemia
Placenta
Fetal hyper-glycemia
Fetal hyper-insulinemia
Fetal hyper-glycemia and hyperinsulinemia
1. Congenital anomalies (peri-con-ceptional)
2. Decreased early growth (0-20 weeks gestation)
3. Hyperinsul-inemia (>20 weeks gestation)
1. Neonatal hypoglycemia (0-7 days postnatal)
2. Surfactant deficiency (neonatal)
3. Immature liver metabolism (neonatal)
1. Fetal macrosomia (>20 weeks gestation)
a. Birth asphyxia
b. Cardiomyopathy
c. TTN
2. Fetal hypoxia (>30 weeks gestation)
a. Jaundice
a. Polycythemia
b. Stroke, RVT
c. Iron abnormalities
Poor neurodevelopmental outcome

FIG. 127.1 The fetal and neonatal events attributable to fetal hyperglycemia *(column 1),* fetal hyperinsulinemia *(column 2),* or both in synergy *(column 3).* Time of risk is denoted in parentheses. RVT, Renal vein thrombosis; TTN, transient tachypnea of the newborn. (From Nold JL, Georgieff MK: Infants of diabetic mothers, *Pediatr Clin North Am* 51:619–637, 2004.)

Hyperinsulinemia has been documented in infants of mothers with pregestational and gestational diabetes. The infants of mothers with *pregestational* diabetes have significantly higher fasting plasma insulin levels than normal newborns, despite similar glucose levels, and respond to glucose with an abnormally prompt elevation in plasma insulin. After arginine administration, they also have an enhanced insulin response and increased disappearance rates of glucose compared with normal infants. In contrast, fasting glucose production and utilization rates are diminished in infants of mothers with *gestational* diabetes. Although hyperinsulinism is probably the main cause of hypoglycemia, the diminished epinephrine and glucagon responses that occur may be contributing factors. Infants of mothers with pregestational and gestational diabetes are at risk for neonatal hypoglycemia in the 1st hours of life, with an increased risk in both large- and small-for-gestational-age infants. Aggressive screening and treatment is recommended as outlined later.

Clinical Manifestations

Infants of mothers with pregestational diabetes and those of mothers with gestational diabetes often bear a surprising resemblance to each other (Fig. 127.2). They tend to be large and plump as a result of increased body fat and enlarged viscera, with puffy, plethoric facies resembling that of patients who have been receiving corticosteroids. These infants may also be of normal birthweight if diabetes is well controlled; or low birthweight if they are delivered before term or if their mothers have associated diabetic vascular disease. Infants that are macrosomic or LGA are at high risk of birth trauma (brachial plexus injury) and birth asphyxia because of not only their large size but also their decreased ability to tolerate stress, especially if they have cardiomyopathy and other effects of fetal hyperinsulinemia (Table 127.1).

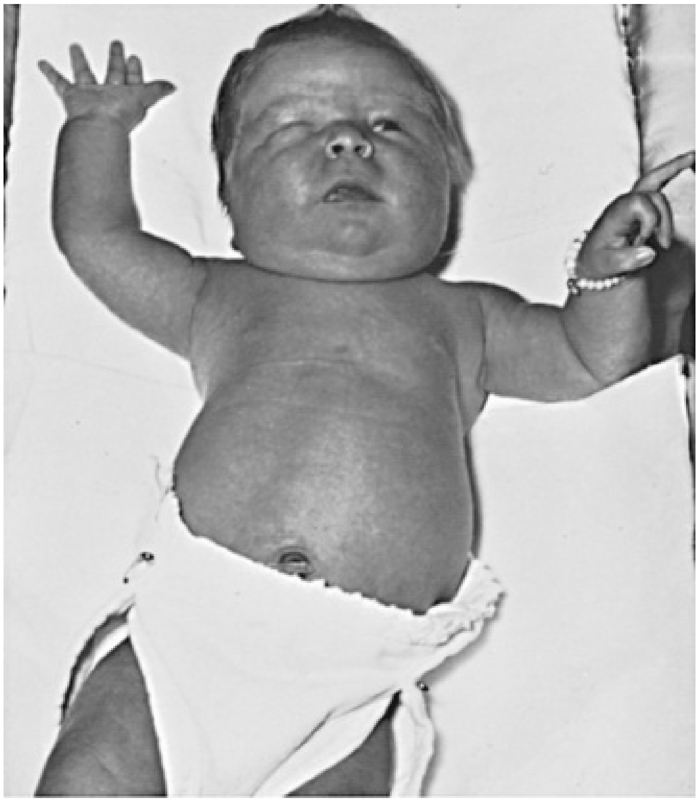

FIG. 127.2 **Large, plump, plethoric infant of a mother with gestational diabetes. The baby was born at 38 wk of gestation but weighed 9 lb, 11 oz (4,408 g). Mild respiratory distress was the only symptom other than appearance.**

Table 127.1

Morbidity in Infants of Diabetic Mothers

- Congenital anomalies
- Heart failure and septal hypertrophy of heart
- Surfactant deficiency, respiratory distress syndrome, transient tachypnea of the newborn, persistent pulmonary hypertension
- Hyperbilirubinemia
- Hypoglycemia, hypocalcemia, hypomagnesemia
- Macrosomia, nerve injury related to birth trauma
- Renal vein thrombosis
- Small left colon
- Unexplained intrauterine demise
- Polycythemia
- Visceromegaly
- Predisposition to later-life obesity, insulin resistance, and diabetes

From Devaskar SU, Garg M: Disorders of carbohydrate metabolism in the neonate. In Martin RJ, Fanaroff AA, Walsh MC, editors: *Fanaroff & Martin's neonatal-perinatal medicine,* ed 10, Philadelphia, 2015, Elsevier (Box 95-3).

Hypoglycemia develops in approximately 25–50% of infants of mothers with pregestational diabetes and 15–25% of infants of mothers with gestational diabetes, but only a small percentage of these infants become symptomatic. The probability that hypoglycemia will develop in such infants increases with higher cord or maternal fasting blood glucose levels. The nadir in an infant's blood glucose concentration is usually reached between 1 and 3 hr of age. Hypoglycemia can persist for 72 hr and in rare cases last up to 7 days. Frequent feedings can be used to treat the hypoglycemia, but some infants require intravenous (IV) dextrose.

The infants tend to be jittery, tremulous, and hyperexcitable during the 1st 3 days after birth, although hypotonia, lethargy, and poor sucking may also occur. Early appearance of these signs is more likely to be related to hypoglycemia but can also be caused by hypocalcemia and hypomagnesemia, which also occur in the 1st 24-72 hr of life due to delayed response of the parathormone system. Perinatal asphyxia is associated with increased irritability and also increases the risk of hypoglycemia, hypomagnesemia, and hypocalcemia.

Tachypnea develops in many IDMs during the 1st 2 days after birth and may be a manifestation of hypoglycemia, hypothermia, polycythemia, cardiac failure, transient tachypnea, or cerebral edema from birth trauma or asphyxia. IDMs have a higher incidence of **respiratory distress syndrome** (RDS) than do infants of nondiabetic mothers born at comparable gestational age. The greater incidence is possibly related to an antagonistic effect of insulin on stimulation of surfactant synthesis by cortisol, leading to a delay in lung maturation. Polycythemia often occurs with RDS as they are both a result of fetal hyperinsulinism.

Cardiomegaly is common (30%), and heart failure occurs in 5-10% of IDMs. Interventricular septal hypertrophy may occur and may manifest as transient idiopathic hypertrophic subaortic stenosis. This is thought to result from chronic hyperglycemia and chronic hyperinsulinism leading to glycogen loading in the heart. Inotropic agents worsen the obstruction and are contraindicated. β-Adrenergic blockers have been shown to relieve the obstruction, but ultimately the condition resolves spontaneously over time.

Acute neurologic abnormalities (lethargy, irritability, poor feeding) can be seen immediately after birth and the cause elucidated by the timing of symptoms, as previously discussed (hypoglycemia, hypocalcemia, hypomagnesemia, or birth asphyxia). The symptoms will resolve with treatment of the underlying cause but may persist for weeks if caused by birth asphyxia. Neurologic development and ossification centers tend to be immature and to correlate with brain size (which is not increased) and gestational age rather than total body weight in infants of mothers with gestational and pregestational diabetes. In addition, IDMs have an increased incidence of hyperbilirubinemia, polycythemia, iron deficiency, and renal vein thrombosis. Renal vein thrombosis should be suspected in the infant with a flank mass, hematuria, and thrombocytopenia.

There is a 4-fold increase in **congenital anomalies** in infants of mothers with pregestational diabetes, and the risk varies with HbA_{1c} during the first trimester when organogenesis occurs. The recommended goal for periconceptual HbA_{1c} is <6.5%. Although the risk of congenital malformations increases with increasing HbA_{1c} levels, there may still be an increased risk in the therapeutic goal range. Congenital anomalies of the central nervous system and cardiovascular system are most common, including failure of neural tube closure (encephalocele, meningomyelocele, and anencephaly), transposition of great vessels, ventricular septal defect (VSD), atrial septal defect (ASD), hypoplastic left heart, aortic stenosis, and coarctation of the aorta. Other, less common anomalies include caudal regression syndrome, intestinal atresia, renal agenesis, hydronephrosis, and cystic kidneys. **Small left colon syndrome** is a rare anomaly that develops in the second and third trimester because of rapid fluctuations in maternal and therefore fetal glucose, leading to impaired intestinal motility and subsequent intestinal growth. Prenatal ultrasound and a thorough newborn physical examination will identify most of these anomalies. High clinical suspicion and a good prenatal history will help identify needed screening for subtle anomalies.

Treatment

Preventive treatment of IDMs should be initiated before birth by means of preconception and frequent prenatal evaluations of all women with preexisting diabetes and pregnant women with gestational diabetes. This involves evaluation of fetal maturity, biophysical profile, Doppler velocimetry, and planning of the delivery of IDMs in hospitals where expert obstetric and pediatric care is continuously available. Preconception glucose control reduces the risk of anomalies and other adverse outcomes in women with pregestational diabetes, and glucose control during labor reduces the incidence of neonatal hypoglycemia. Women with type 1 diabetes who have tight glucose control during pregnancy (average daily glucose levels <95 mg/dL) deliver infants with birthweight and anthropomorphic features similar to those of infants of nondiabetic mothers. Treatment of gestational diabetes (diet, glucose monitoring, metformin, and insulin therapy as needed) decreases the rate of serious perinatal outcomes (death, shoulder dystocia, bone fracture, or nerve palsy). Women with gestational diabetes may also be treated successfully with **glyburide** , which may not cross the placenta. In these mothers, the incidence of macrosomia and neonatal hypoglycemia is similar to that in mothers with insulin-treated gestational diabetes. Women with diabetes can begin to express breast milk before the birth of the baby (≥36 wk gestational age); this will provide an immediate supply of milk to prevent hypoglycemia.

Regardless of size, IDMs should initially receive close observation and care (Fig. 127.3). Infants should initiate feedings within 1 hr after birth. A screening glucose test should be performed within 30 min of the first feed. Transient **hypoglycemia** is common during the 1st 1-3 hr after birth and may be part of normal adaptation to extrauterine life. The target plasma glucose concentration is ≥40 mg/dL before feeds in the 1st 48 hr of life. Clinicians need to assess the overall metabolic and physiologic status, considering these in the management of hypoglycemia. Treatment is indicated if the plasma glucose is <47 mg/dL.

Feeding is the initial treatment for *asymptomatic* hypoglycemia. Oral or gavage feeding with breast milk or formula can be given. An alternative is prophylactic use of **dextrose** gel, although early feedings may be equally effective. Recurrent hypoglycemia can be treated with repeat feedings or IV glucose as needed. Infants with *persistent* (and unresponsive to oral therapy) glucose levels <25 mg/dL during the 1st 4 hr after birth and <35 mg/dL at 4-24 hr after birth should be treated with IV glucose, especially if symptomatic. A small bolus of 200 mg/kg of dextrose (2 mL/kg of 10% dextrose) should be administered to infants with plasma glucose below these limits. The small bolus should be followed by a continuous IV glucose infusion to avoid hypoglycemia. If question arises about an infant's ability to tolerate oral feeding, a continuous peripheral IV infusion at a rate of 4-8 mg/kg/min should be given. Neurologic symptoms of hypoglycemia *must* be treated with IV glucose. Bolus injections of hypertonic (25%) glucose should be avoided because they may cause further hyperinsulinemia and potentially produce rebound hypoglycemia (see Chapter 111). For treatment of hypocalcemia and hypomagnesemia, see Chapters 119.4 and 119.5 ; for RDS treatment, see Chapter 122.3 ; and for treatment of polycythemia, see Chapter 124.3 .

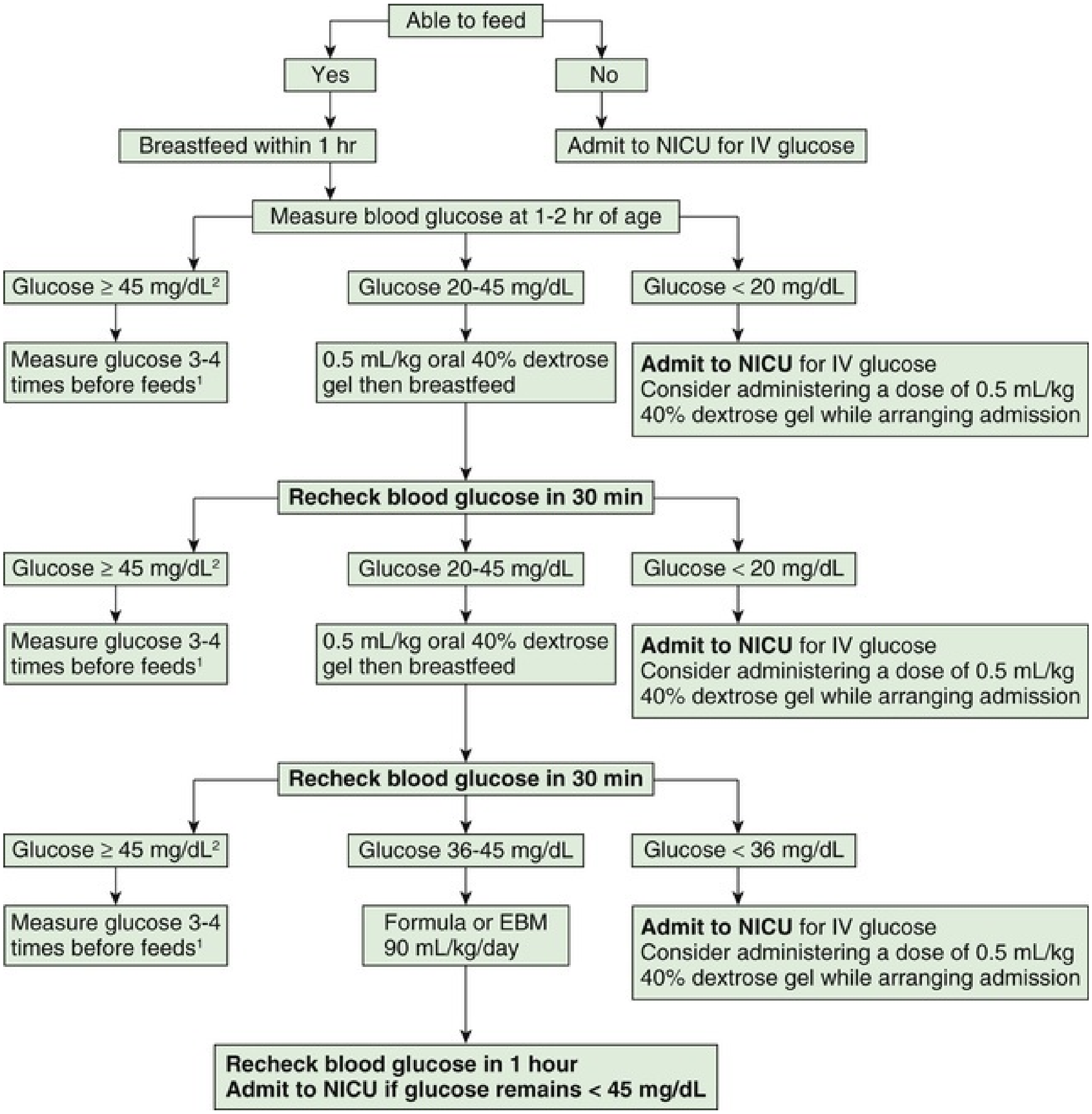
Able to feed
Yes
No
Breastfeed within 1 hr
Admit to NICU for IV glucose
Measure blood glucose at 1-2 hr of age
Glucose ≥ 45 mg/dL²
Glucose 20-45 mg/dL
Glucose < 20 mg/dL
Measure glucose 3-4 times before feeds¹
0.5 mL/kg oral 40% dextrose gel then breastfeed
Admit to NICU for IV glucose Consider administering a dose of 0.5 mL/kg 40% dextrose gel while arranging admission
Recheck blood glucose in 30 min
Glucose ≥ 45 mg/dL²
Glucose 20-45 mg/dL
Glucose < 20 mg/dL
Measure glucose 3-4 times before feeds¹
0.5 mL/kg oral 40% dextrose gel then breastfeed
Admit to NICU for IV glucose Consider administering a dose of 0.5 mL/kg 40% dextrose gel while arranging admission
Recheck blood glucose in 30 min
Glucose ≥ 45 mg/dL²
Glucose 36-45 mg/dL
Glucose < 36 mg/dL
Measure glucose 3-4 times before feeds¹
Formula or EBM 90 mL/kg/day
Admit to NICU for IV glucose Consider administering a dose of 0.5 mL/kg 40% dextrose gel while arranging admission
Recheck blood glucose in 1 hour
Admit to NICU if glucose remains < 45 mg/dL

FIG. 127.3 Screening algorithm for *asymptomatic* hypoglycemia during first day of life among at-risk infants. Screening is indicated for late preterm infants, those who are small for gestational age/intrauterine growth restriction, and infants of obese or diabetic mothers. [1] Continue monitoring blood glucose concentrations until 3 consecutive blood glucose concentrations have been ≥45-50 mg/dL. [2] There is no consensus for a threshold definition for neonatal hypoglycemia in the first day of life. Nonetheless, if the blood glucose is less than 45-50 mg/dL **AND** symptoms compatible with hypoglycemia are present (see text), treatment must be initiated with an IV minibolus of 10% glucose at 200 mg/kg **followed** by a continuous IV infusion of glucose at a starting rate of 5-8 mg/kg/min. IV, Intravenous; EBM, expressed breast milk. (Modified from Newborn Services Clinical Guidelines for the Management of Hypoglycaemia http://www.adhb.govt.nz/newborn/Guidelines/Nutrition/HypoglycaemiaManagement.htm .)

Prognosis

The subsequent incidence of diabetes mellitus in IDMs is higher than that in the general population because of genetic susceptibility in all types of diabetes. Infants of mothers with either pregestational diabetes or gestational diabetes are at risk for obesity and impaired glucose metabolism in later life as a result of intrauterine exposure to hyperglycemia. Disagreement persists about whether IDMs have a slightly increased risk of impaired intellectual development because of the many confounding factors (e.g., parental education, maternal age, neonatal complications). In general, the outcomes have improved over the last several decades due to increased awareness, screening, and improved prenatal care for pregnant women with diabetes.

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CHAPTER 128

Dysmorphology

Anne M. Slavotinek

Dysmorphology is the study of differences in human form and the mechanisms that cause them. It has been estimated that 1 in 40 newborns, or 2.5%, have a recognizable birth defect or pattern of malformations at birth; approximately half these newborns have a single, isolated malformation, whereas in the other half, multiple malformations are present. From 20–30% of infant deaths and 30–50% of deaths after the neonatal period are caused by congenital abnormalities (http://www.marchofdimes.com/peristats/). In 2001, birth defects accounted for 1 in 5 infant deaths in the United States, with a rate of 137.6 deaths per 100,000 live births, which was higher than other causes of mortality, such as preterm/low birthweight (109.5/100,000), sudden infant death syndrome (55.5/100,000), maternal complications of pregnancy (37.3/100,000), and respiratory distress syndrome (25.3/100,000).

Classification of Birth Defects

Birth defects can be subdivided into isolated (single) defects or multiple congenital anomalies (multiple defects) in one individual. An isolated primary defect can be classified, according to the nature of the presumed cause of the defect, as a malformation, dysplasia, deformation, or disruption (Table 128.1 and Fig. 128.1). Most birth defects are malformations. A **malformation** is a structural defect arising from a localized error in morphogenesis that results in the abnormal formation of a tissue or organ. **Dysplasia** refers to the abnormal organization of cells into tissues. Malformations and dysplasias can both affect intrinsic structure. In contrast, a **deformation** is an alteration in shape or structure of a structure or organ that has developed, or differentiated, normally. A **disruption** is a defect resulting from the destruction of a structure that had formed normally before the insult.

Table 128.1

Mechanisms, Terminology, and Definitions of Dysmorphology

TERMINOLOGY	DEFINITION	EXAMPLE
Sequence	Single error in morphogenesis that results in a series of subsequent defects	Pierre-Robin sequence, in which a small jaw results in glossoptosis and cleft palate DiGeorge sequence of primary 4th brachial arch and 3rd and 4th pharyngeal pouch defects, leading to aplasia or hypoplasia of the thymus and parathyroid glands, aortic arch anomalies, and micrognathia
Deformation sequence	Mechanical (uterine) force that alters structure of intrinsically normal tissue	Oligohydramnios produces deformations by in utero compression of limbs (e.g., dislocated hips, equinovarus foot deformity), crumpled ears, or small thorax
Disruption sequence	In utero tissue destruction after a period of normal morphogenesis	Amnionic membrane rupture sequence, leading to amputation of fingers/toes, tissue fibrosis, and tissue bands
Dysplasia sequence	Atypical organization of cells into tissues or organs	Neurocutaneous melanosis sequence, with atypical migration of melanocyte precursor cells from the neural crest to the periphery, manifesting as melanocytic hamartomas of skin and meninges
Malformation syndrome	Appearance of multiple malformations in unrelated tissues that have a known, unifying cause	Trisomy 21 Teratogens Numerous multiple congenital anomaly syndromes as described above

From Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, Elsevier Saunders.

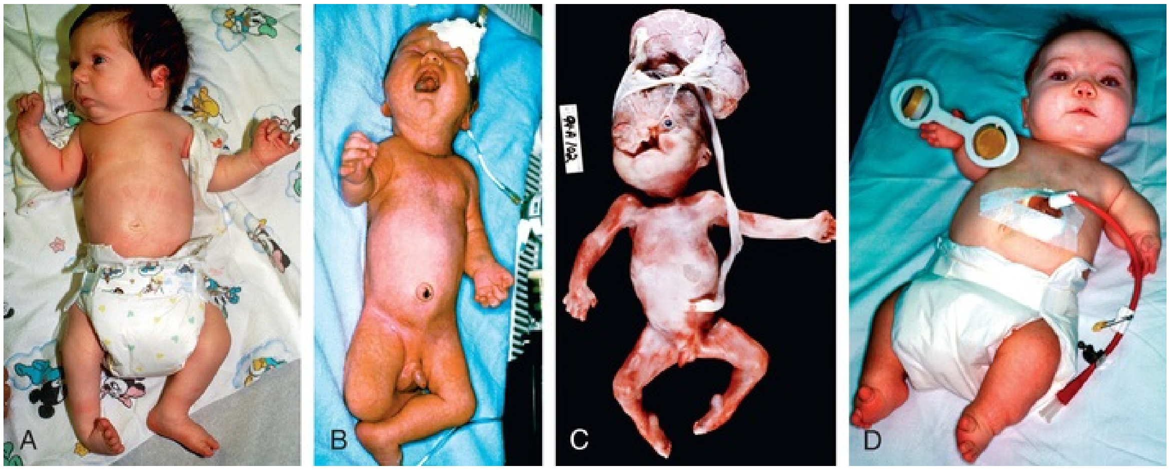

FIG. 128.1 **Four major types of problems in morphogenesis: malformation, deformation, disruption, and dysplasia. A, Infant with camptomelic dysplasia syndrome, which results in a multiple malformation syndrome caused by a mutation in *SOX9* . B, Infant with oligohydramnios deformation sequence caused by premature rupture of membranes from 17 wk gestation until birth at 36 wk; the infant was delivered from**

persistent transverse lie. C, Fetus with early amnion rupture sequence with attachment of the placenta to the head and resultant disruption of craniofacial structures with distal limb contractures. D, Infant with diastrophic dysplasia caused by inherited autosomal recessive mutations in a sulfate transporter protein. (From Graham Jr JM: *Smith's recognizable patterns of human deformation,* ed 3, Philadelphia, 2007, Saunders, Fig 1-1, p 4.)

Most inherited human disorders with altered morphogenesis display multiple malformations rather than isolated birth defects. When several malformations coexist in a single individual, they can be classified as a syndrome, sequence, or an association. A **syndrome** is defined as a pattern of multiple abnormalities that are related by pathophysiology, resulting from a single, defined etiology. **Sequences** consist of multiple malformations that are caused by a single event, although the sequence itself can have different etiologies. An **association** refers to a nonrandom grouping of malformations in which there is an unclear, or unknown, relationship among the malformations, such that they do not fit the criteria for a syndrome or sequence.

Malformations and Dysplasias

Human malformations and dysplasias can be caused by gene mutations, chromosome aberrations and copy number variants, environmental factors, or interactions between genetic and environmental factors (Table 128.2). Some malformations are caused by deleterious sequence variants in single genes, whereas other malformations arise because of deleterious sequence variants in multiple genes acting in combination (*digenic* or *oligogenic* inheritance). In 1996 it was thought that malformations were caused by monogenic defects in 7.5% of patients; chromosomal anomalies in 6%; multigenic defects in 20%; and known environmental factors, such as maternal diseases, infections, and teratogens, in 6–7% (Table 128.3). In the remaining 60–70% of patients, malformations were classified as caused by unknown etiologies. Currently, the percentages have increased for all categories of known causes of malformations, the result of improved cytogenetic and molecular genetic methods for detecting small chromosomal abnormalities and next-generation sequencing studies that can screen multiple genes simultaneously and identify novel genes and deleterious sequence variants.

Table 128.2

Examples of Malformations with Distinct Causes, Clinical

Features, and Pathogenesis

DISORDER	CAUSE/INHERITANCE	SELECTED CLINICAL FEATURES	PATHOGENESIS
Spondylocostal dysostosis syndrome	Mendelian; autosomal recessive	Abnormal vertebral and rib segmentation	Deleterious sequence variants in *DLL3* and other genes
Rubinstein-Taybi syndrome	Autosomal dominant	Intellectual disability Broad thumbs and halluces; valgus deviation of these digits Hypoplastic maxillae Prominent nose and columella Congenital heart disease	Deleterious sequence variants in *CBP* and *EP300*
X-linked lissencephaly	X-linked	Male: severe intellectual disability, seizures Female: variable	Deleterious sequence variants in *DCX*
Aniridia	Autosomal dominant	Absent iris or iris/foveal hypoplasia	Deleterious sequence variants in *PAX6*
Waardenburg syndrome, type I	Autosomal dominant	Deafness White forelock Wide-spaced eyes Iris heterochromia and/or pale skin pigmentation	Deleterious sequence variants in *PAX3*
Holoprosencephaly	Loss of function or heterozygosity for multiple genes	Microcephaly Cyclopia Single central incisor	*SHH*, multiple other genes
Velocardiofacial syndrome	Microdeletion 22q11.2	Congenital heart disease, including conotruncal defects Cleft palate T-cell defects Facial anomalies	*TBX1* haploinsufficiency/mutations; haploinsufficiency for other genes in the deleted interval also contributes to the phenotype.
Down syndrome	Additional copy of chromosome 21 (trisomy 21)	Intellectual disability Characteristic dysmorphic features Congenital heart	Increase in dosage of an estimated 250 genes on chromosome 21

		disease	
		Increased risk of leukemia	
		Alzheimer disease	
Neural tube defects	Multifactorial	Meningomyelocele	Defects in folate sensitive enzymes or folic acid uptake
Fetal alcohol syndrome	Teratogenic	Microcephaly	Ethanol toxicity to developing brain
		Developmental delay	
		Facial abnormalities	
		Behavioral abnormalities	
Retinoic acid embryopathy	Teratogenic	Microtia	Isotretinoin effects on neural crest and branchial arch development
		Congenital heart disease	

Table 128.3

Causes of Congenital Malformations

MONOGENIC
X-linked hydrocephalus Achondroplasia Ectodermal dysplasia Apert syndrome Treacher Collins syndrome
CHROMOSOMAL ABERRATIONS and COPY NUMBER VARIANTS
Trisomy 21, 18, 13 XO, XXY Deletions 4p−, 5p−, 7q−, 13q−, 18p−, 18q−, 22q− Prader-Willi syndrome (70% of affected patients have deletion of chromosome 15 q11.2-q13)
MATERNAL INFECTION
Intrauterine infections (e.g., herpes simplex virus, cytomegalovirus, varicella-zoster virus, rubella virus, Zika virus, toxoplasmosis)
MATERNAL ILLNESS
Diabetes mellitus Phenylketonuria Hyperthermia
UTERINE ENVIRONMENT
Deformation Uterine pressure, oligohydramnios: clubfoot, torticollis, congenital hip dislocation, pulmonary hypoplasia, 7th nerve palsy Disruption Amniotic bands, congenital amputations, gastroschisis, porencephaly, intestinal atresia Twinning
ENVIRONMENTAL AGENTS
Polychlorinated biphenyls Herbicides Mercury Alcohol
MEDICATIONS
Thalidomide

Diethylstilbestrol Phenytoin Warfarin Cytotoxic drugs Paroxetine Angiotensin-converting enzyme inhibitors Isotretinoin (vitamin A) D-Penicillamine Valproic acid Mycophenolate mofetil
UNKNOWN ETIOLOGIES
Neural tube defects, such as anencephaly and spina bifida Cleft lip/palate Pyloric stenosis
SPORADIC SEQUENCE COMPLEXES
VATER/VACTERL sequence (vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula with esophageal atresia, radial and renal anomalies) Pierre Robin sequence
NUTRITIONAL
Neural tube defects due to low folic acid

From Behrman RE, Kliegman RM, editors: *Nelson's essentials of pediatrics,* ed 4, Philadelphia, 2002, Saunders.

Many developmental abnormalities that are caused by deleterious sequence variants (mutations)in a single gene display characteristic, mendelian patterns of inheritance (autosomal dominant, autosomal recessive, and X-linked inheritance). Genes that cause birth defects or multiple congenital anomaly syndromes are often transcription factors, part of evolutionarily conserved signal transduction pathways, or regulatory proteins required for key developmental events (Figs. 128.2 and 128.3). Examples include spondylocostal dysostosis syndromes, Smith-Lemli-Opitz syndrome, Rubinstein-Taybi syndrome, and X-linked lissencephaly (“smooth brain”) syndrome (see Table 128.2).

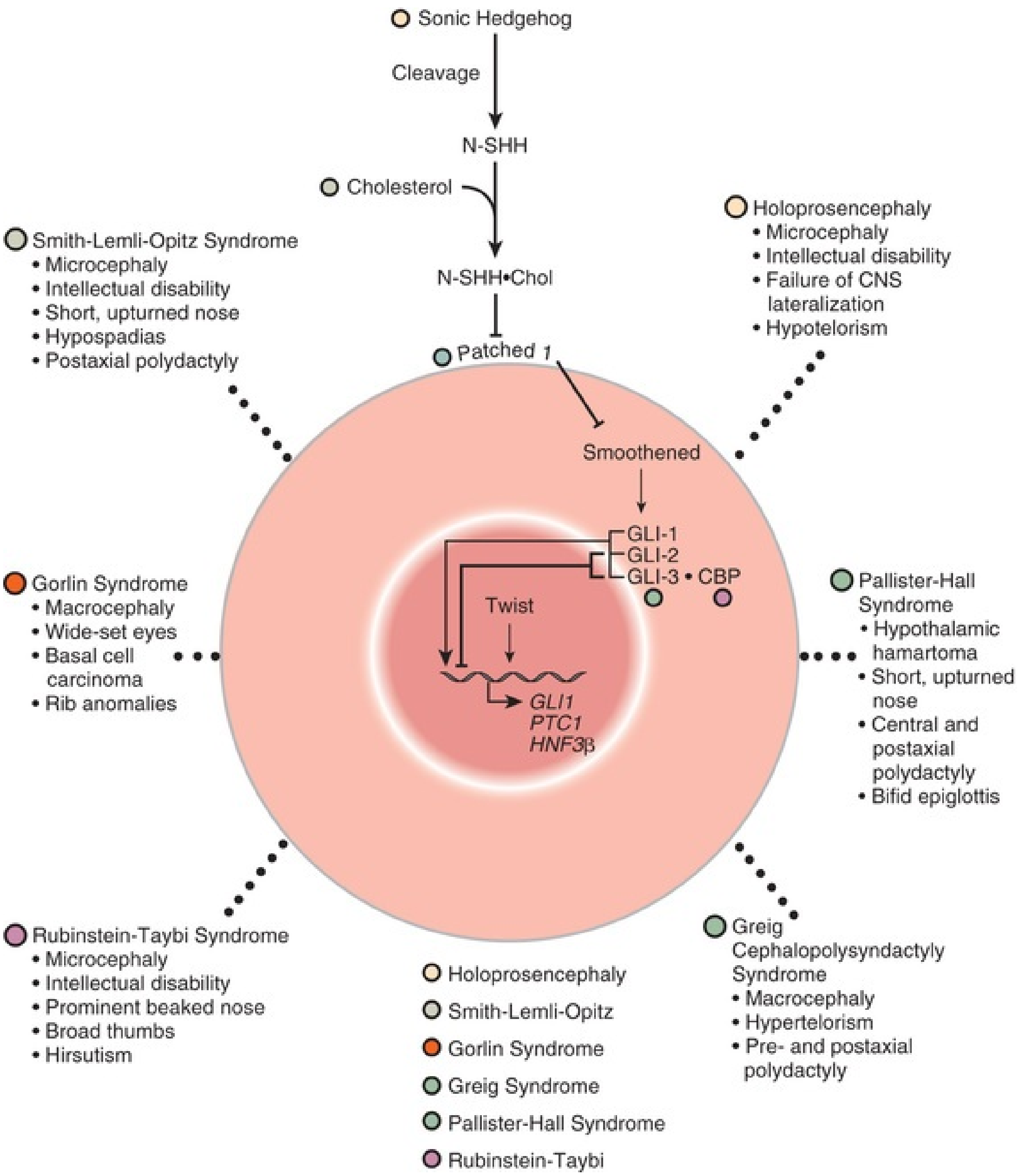
Sonic Hedgehog
Cleavage
N-SHH
Cholesterol
N-SHH•Chol
Patched 1
Smoothened
GLI-1
GLI-2
GLI-3 • CBP
Twist
GLI1
PTC1
HNF3β
Smith-Lemli-Opitz Syndrome
• Microcephaly
• Intellectual disability
• Short, upturned nose
• Hypospadias
• Postaxial polydactyly
Holoprosencephaly
• Microcephaly
• Intellectual disability
• Failure of CNS lateralization
• Hypotelorism
Gorlin Syndrome
• Macrocephaly
• Wide-set eyes
• Basal cell carcinoma
• Rib anomalies
Pallister-Hall Syndrome
• Hypothalamic hamartoma
• Short, upturned nose
• Central and postaxial polydactyly
• Bifid epiglottis
Rubinstein-Taybi Syndrome
• Microcephaly
• Intellectual disability
• Prominent beaked nose
• Broad thumbs
• Hirsutism
Greig Cephalopolysyndactyly Syndrome
• Macrocephaly
• Hypertelorism
• Pre- and postaxial polydactyly
Holoprosencephaly
Smith-Lemli-Opitz
Gorlin Syndrome
Greig Syndrome
Pallister-Hall Syndrome
Rubinstein-Taybi

FIG. 128.2 Deleterious sequence variants in genes that function together in a developmental pathway typically have overlapping clinical manifestations. Several components of the sonic hedgehog (SHH) pathway have been identified, and their relationships elucidated (see text for further details). Mutations in several members of this pathway result in phenotypes with facial dysmorphism, as seen in holoprosencephaly, Smith-Lemli-Opitz syndrome, Gorlin syndrome, Greig cephalopolysyndactyly syndrome, Pallister-Hall syndrome, and Rubinstein-Taybi syndrome. CNS, Central nervous system.

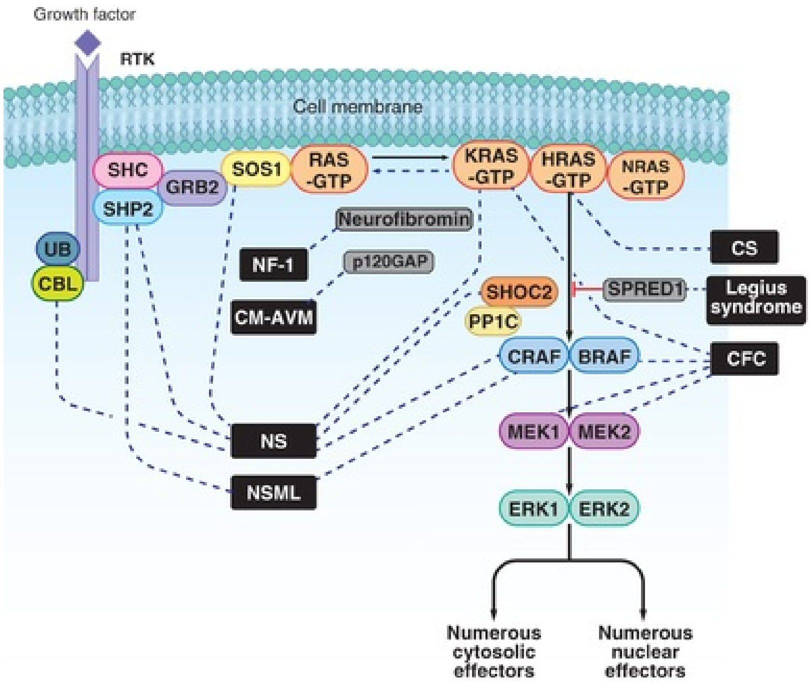
Growth factor
RTK
Cell membrane
SHC
GRB2
SOS1
RAS -GTP
KRAS -GTP
HRAS -GTP
NRAS -GTP
SHP2
UB
CBL
Neurofibromin
NF-1
p120GAP
CM-AVM
CS
SHOC2
SPRED1
Legius syndrome
PP1C
CRAF
BRAF
CFC
NS
MEK1
MEK2
NSML
ERK1
ERK2
Numerous cytosolic effectors
Numerous nuclear effectors

FIG. 128.3 **The RAS/MAPK signal transduction pathway. The MAPK signaling pathway of protein kinases is critically involved in cellular proliferation, differentiation, motility, apoptosis, and senescence. The RASopathies are medical genetic syndromes caused by mutations in genes that encode components or regulators of the Ras/MAPK pathway (indicated by *dashed lines*). These disorders include neurofibromatosis type 1 (NF1), Noonan syndrome (NS), Noonan syndrome with multiple lentigines (NSML), capillary malformation–arteriovenous malformation syndrome (CM-AVM), Costello syndrome (CS), cardiofaciocutaneous syndrome (CFC), and Legius syndrome. RAS/MAPK, RAS protein family/mitogen-activated protein kinase. (From Rauen KA: The RASopathies, *Annu Rev Genom Hum Genet* 14:355–369, 2013.)**

Patients with **spondylocostal dysostosis (SCD)** display a characteristic pattern of vertebral segmentation defects associated with a number of other malformations, such as neural tube defects. The **SCD syndromes** are etiologically heterogeneous and are often caused by mutations in the gene coding for delta-like 3 (*DLL3*), a ligand of the Notch receptors. The Notch/delta pathway is conserved throughout evolution and regulates a number of developmental events. **Smith-Lemli-Opitz syndrome (SLOS)** results from mutations in the sterol delta-7-dehydrocholesterol reductase (*DHCR7*) gene, an enzyme critical for normal cholesterol biosynthesis. Patients with SLOS (see Fig. 128.2) display syndactyly (fusion of the fingers and toes), in particular affecting the 2nd and 3rd toes; postaxial polydactyly (extra digits); anteverted (upturned) nose; ptosis; cryptorchidism; and holoprosencephaly (failure of separation of the 2 cerebral hemispheres). Many of the features in SLOS are shared with those arising from deleterious sequence variants in the *SHH* genes, and these mutations link cholesterol biosynthesis pathogenically to the sonic hedgehog (SHH) pathway, because SHH is posttranslationally modified by cholesterol (see Chapter 97). **Rubinstein-Taybi syndrome** (see Fig. 128.2) typically results from heterozygous, loss-of-function deleterious sequence variants in a gene coding for a broadly acting transcriptional coactivator called *CREB-binding protein* (CBP) and from deleterious sequence variants in the *EP300* gene. The CBP coactivator regulates the transcription of a number of genes, which is why patients with deleterious sequence variants in *CBP* have a pleiotropic phenotype that includes developmental delays and intellectual disability, broad and angulated thumbs and halluces (1st toes), and congenital heart disease. One of the transcription factors that binds to CBP is *GLI3,* a member of the SHH pathway (see Fig. 128.2). **X-linked lissencephaly** is a severe neuronal migration defect that causes a smooth brain with reduction or absence of gyri and sulci in males and that gives rise to a variable pattern of intellectual disability and seizures in females. X-linked lissencephaly is caused by deleterious sequence variants in *DCX* . The DCX protein regulates the activity of dynein motors that contribute to movement of the cell nucleus during neuronal migration.

Malformation syndromes can also be caused by chromosomal aberrations or copy number variants and teratogens (see Tables 128.2 and 128.3). **Down syndrome** typically results from an extra copy of an entire chromosome 21 or, less frequently, an extra copy of the Down syndrome critical region on chromosome 21. Chromosome 21 is a small chromosome that contains an estimated 250 genes, and thus individuals with Down syndrome typically have an increased dosage of the numerous genes encoded by this chromosome that causes their physical differences (see Chapter 98.2).

Neural tube defects (NTDs) are an example of a birth defect that displays multifactorial inheritance in most cases. NTDs and a number of other congenital malformations, such as cleft lip and palate, can recur in families, but inheritance for the majority of affected individuals does not occur in a straightforward, mendelian inheritance pattern, and in this situation, multiple genes and environmental factors together likely contribute to the pathogenesis (see Table 128.2). Many of the genes involved in NTDs are unknown, so one cannot predict with certainty the mode of inheritance or a precise recurrence risk in the individual case. Empirical recurrence risks can be provided on the basis of population studies and the presence of single or multiple family members with the same malformation. However, one important gene/environment interaction has been identified for NTDs (see Chapter 609.1). **Folic acid deficiency** is associated with NTDs and can result from a combination of dietary factors and increased utilization during pregnancy. A common variant in the gene for an enzyme in the folate recycling pathway, 5,10-methylene-tetrahydrofolate reductase (*MTHFR*), that makes this enzyme less stable, may also be important in folic acid status. Several teratogenic causes of birth defects have been described (see Tables 128.2 and 128.3). **Ethanol** causes a recognizable malformation syndrome that is variably called fetal alcohol syndrome (FAS), fetal alcohol spectrum disorder (FASD), or fetal alcohol effects (FAE) (see Chapter 126.3). Children who were exposed to ethanol during the pregnancy can display microcephaly, developmental delays, hyperactivity, and facial dysmorphic features. Ethanol, which is toxic to the developing central nervous system (CNS), causes cell death in developing neurons.

Deformations

Many deformations involve the musculoskeletal system (Fig. 128.4). Fetal movement is required for the proper development of the musculoskeletal system, and restriction of fetal movement can cause musculoskeletal deformations such as clubfoot (talipes). Two major intrinsic causes of deformations are primary neuromuscular disorders and **oligohydramnios,** or decreased amniotic fluid, which can be caused by fetal renal defects. The major extrinsic causes of deformation are those that result in fetal crowding and restriction of fetal movement. Examples of extrinsic causes include oligohydramnios resulting from chronic leakage of amniotic fluid and abnormal shape of the amniotic cavity. When a fetus is in the breech position (Fig. 128.5), the incidence of deformations is increased 10-fold. The shape of the amniotic cavity also has a profound effect on the shape of the fetus and is influenced by many factors, including uterine shape, volume of amniotic fluid, and the size and shape of the fetus (Fig. 128.6).

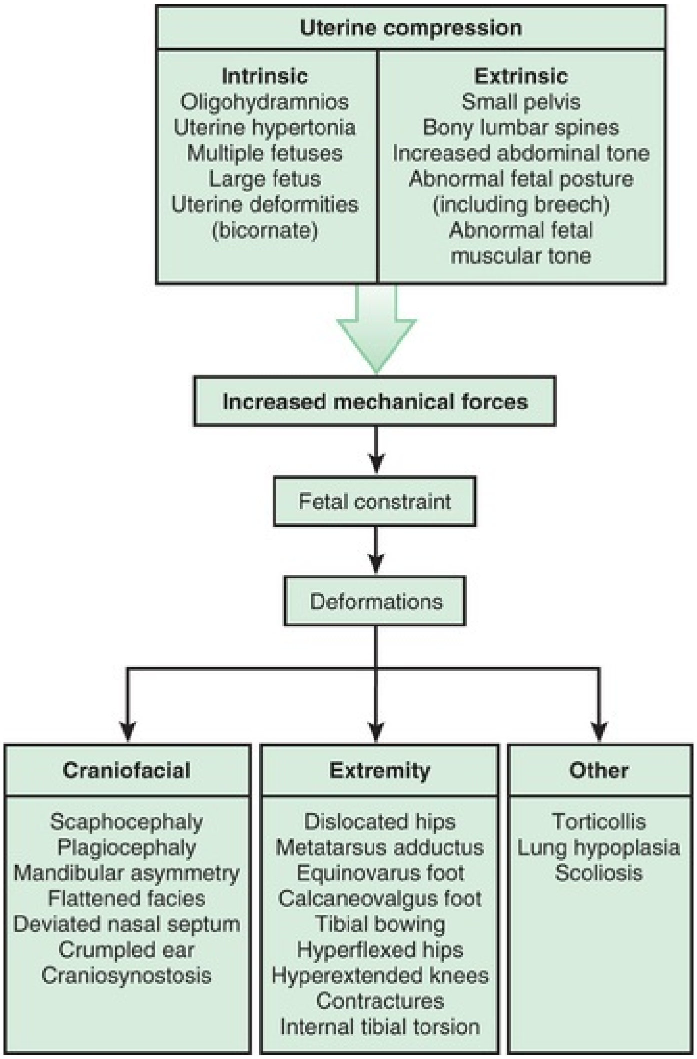
Uterine compression
Intrinsic
Oligohydramnios
Uterine hypertonia
Multiple fetuses
Large fetus
Uterine deformities (bicornate)
Extrinsic
Small pelvis
Bony lumbar spines
Increased abdominal tone
Abnormal fetal posture (including breech)
Abnormal fetal muscular tone
Increased mechanical forces
Fetal constraint
Deformations
Craniofacial
Scaphocephaly
Plagiocephaly
Mandibular asymmetry
Flattened facies
Deviated nasal septum
Crumpled ear
Craniosynostosis
Extremity
Dislocated hips
Metatarsus adductus
Equinovarus foot
Calcaneovalgus foot
Tibial bowing
Hyperflexed hips
Hyperextended knees
Contractures
Internal tibial torsion
Other
Torticollis
Lung hypoplasia
Scoliosis

FIG. 128.4 **Deformation abnormalities resulting from uterine compression. (From Kliegman RM, Jenson HB, Marcdante KJ, et al, editors: *Nelson essentials of pediatrics,* ed 5, Philadelphia, 2005, Saunders.)**

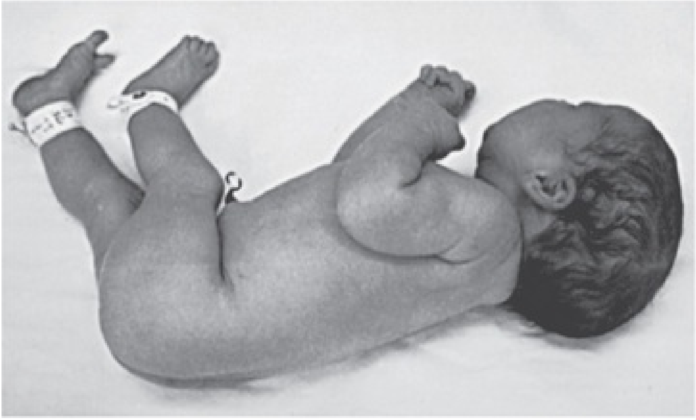

FIG. 128.5 **Breech deformation sequence.**

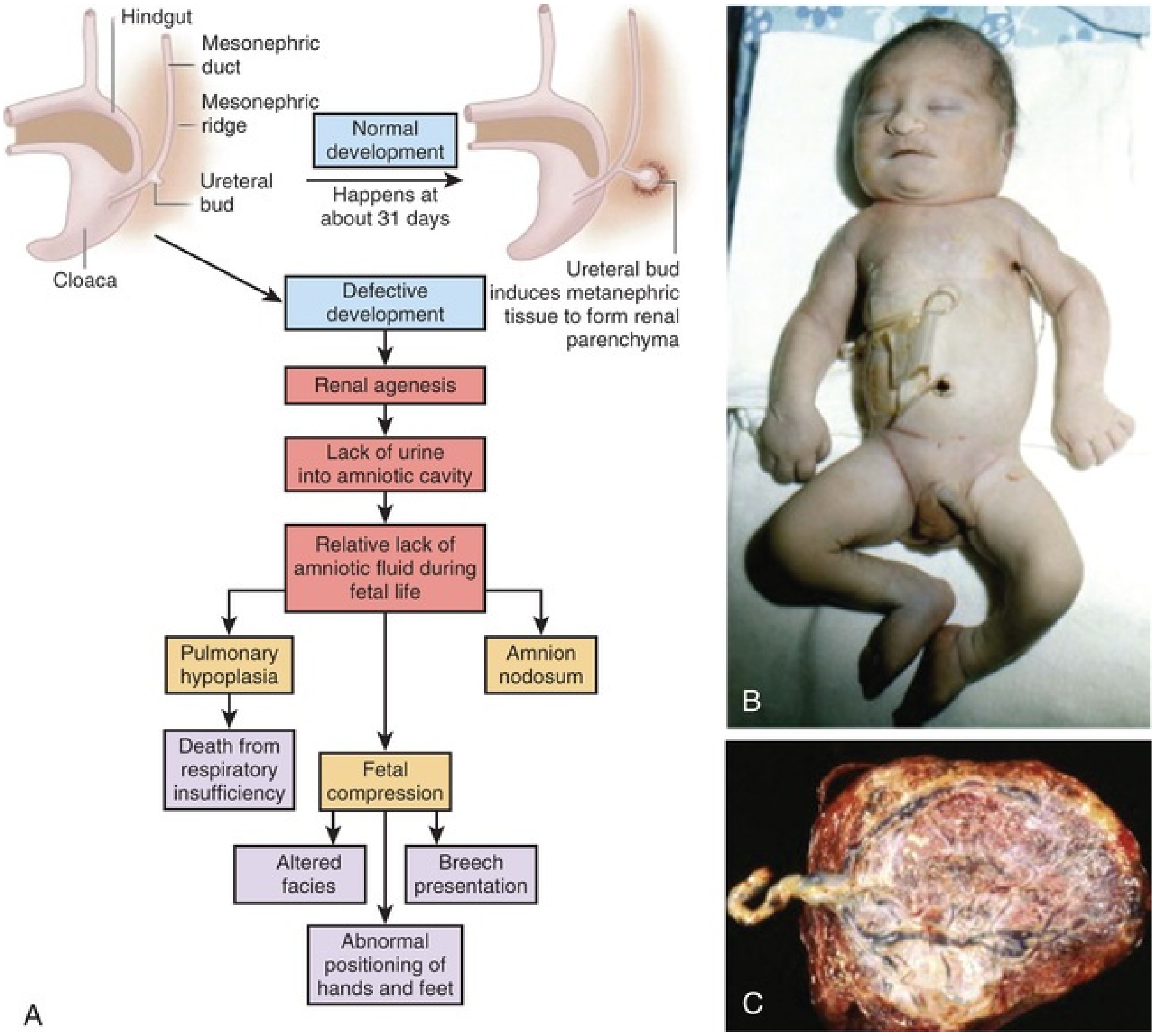
Hindgut
Mesonephric duct
Mesonephric ridge
Ureteral bud
Cloaca
Normal development
Happens at about 31 days
Ureteral bud induces metanephric tissue to form renal parenchyma
Defective development
Renal agenesis
Lack of urine into amniotic cavity
Relative lack of amniotic fluid during fetal life
Pulmonary hypoplasia
Amnion nodosum
Death from respiratory insufficiency
Fetal compression
Altered facies
Breech presentation
Abnormal positioning of hands and feet
A
B
C

FIG. 128.6 **A,** Consequences of renal agenesis. **B,** Multiple deformational

defects. **C,** Defects in amnion nodosum; brown-yellow granules from vernix have been ribbed into defects of the amniotic surface. (From Jones KL, Jones MC, Del Campo M, editors: *Smith's recognizable patterns of human malformation,* ed 7, Philadelphia, 2013, Elsevier, p 821.)

It is important to determine whether deformations result from intrinsic or extrinsic causes. Most children with deformations from *extrinsic* causes are otherwise completely normal, and their prognosis is usually excellent. Correction typically occurs spontaneously. Deformations caused by *intrinsic* factors, such as multiple joint contractures resulting from CNS or peripheral nervous system defects, have a different prognosis and may be much more significant for the child (Fig. 128.7).

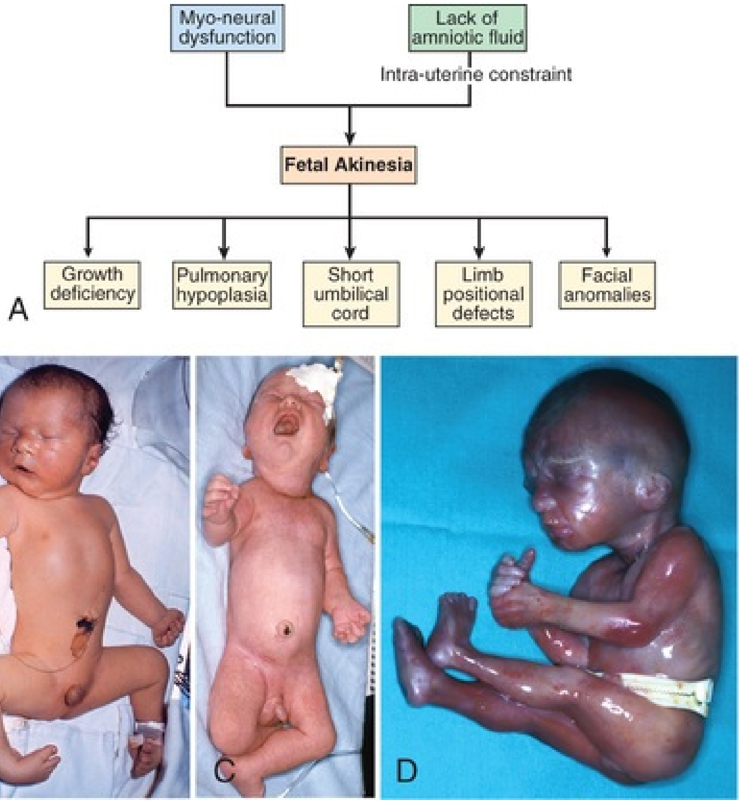
Myo-neural dysfunction
Lack of amniotic fluid
Intra-uterine constraint
Fetal Akinesia
Growth deficiency
Pulmonary hypoplasia
Short umbilical cord
Limb positional defects
Facial anomalies
A
B
C
D

FIG. 128.7 **A,** Diagram demonstrates the etiologically heterogeneous phenotype that results from fetal akinesia. **B,** Infant born with myotonic dystrophy to a mother with the same condition. He had multiple joint contractures with thin bones and respiratory insufficiency. **C,** Infant immobilized in a transverse lie after amnion rupture at 26 wk. **D,** Fetus with bilateral renal agenesis resulting in oligohydramnios. (From Graham JL. *Smith's recognizable patterns of human malformation,* ed 3, Philadelphia, 2007, Elsevier, Fig 47-2.)

Disruptions

Disruptions are caused by destruction of a previously normally formed organ or body part. At least 2 mechanisms are known to produce disruptions. One involves entanglement, followed by tearing apart or amputation, of a normally developed structure, usually a digit or limb, by strands of amnion floating within amniotic fluid (amniotic bands) (Fig. 128.8). The other mechanism involves interruption to the blood supply to a developing part, which can lead to infarction, necrosis, and resorption of structures distal to the insult. If interruption to the blood supply occurs early in gestation, the disruptive defect typically involves **atresia,** or absence of a body part. Genetic factors were previously considered to play a minor role in the pathogenesis of disruptions; most occur as sporadic events in otherwise healthy individuals. The prognosis for a disruptive defect is determined entirely by the extent and location of the tissue loss.

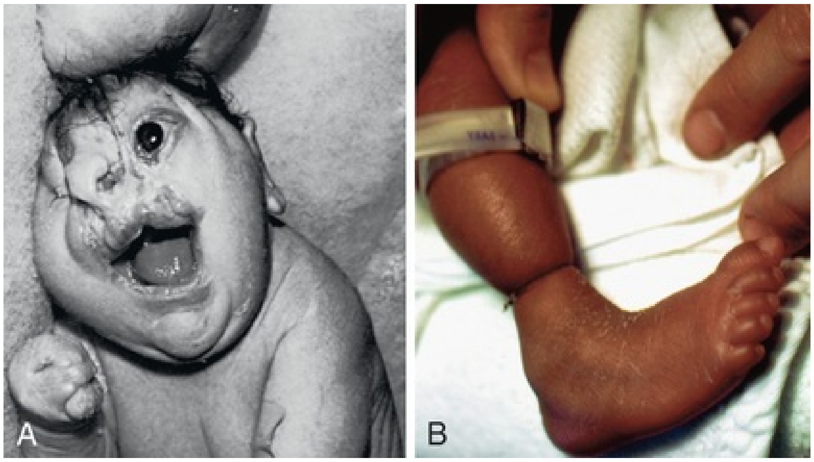

FIG. 128.8 **A,** Amniotic band disruption sequence. **B,** Bands constricting the ankle leading to deformational defects and amputations. (From Jones KJ: *Smith's recognizable patterns of human malformation,* ed 6, Philadelphia, 2006, Saunders.)

Multiple Anomalies: Syndromes and Sequences

The pattern of multiple anomalies that occurs when a single primary defect in early development produces multiple abnormalities because of a cascade of secondary and tertiary developmental anomalies is called a *sequence* (see Fig. 128.9). When evaluating a child with multiple congenital anomalies, the physician must differentiate between multiple anomalies that are caused by a single localized error in morphogenesis (a sequence) from syndromes with multiple malformations. In the former, recurrence risk counseling for the multiple anomalies depends entirely on the risk of recurrence for the single, localized malformation. **Pierre-Robin sequence** is a pattern of multiple anomalies produced by mandibular hypoplasia. Because the tongue is relatively large for the oral cavity, it drops back (glossoptosis), blocking closure of the posterior palatal shelves and causing a U -shaped cleft palate. There are numerous causes of mandibular hypoplasia, all of which can result in characteristic features of Pierre-Robin sequence.

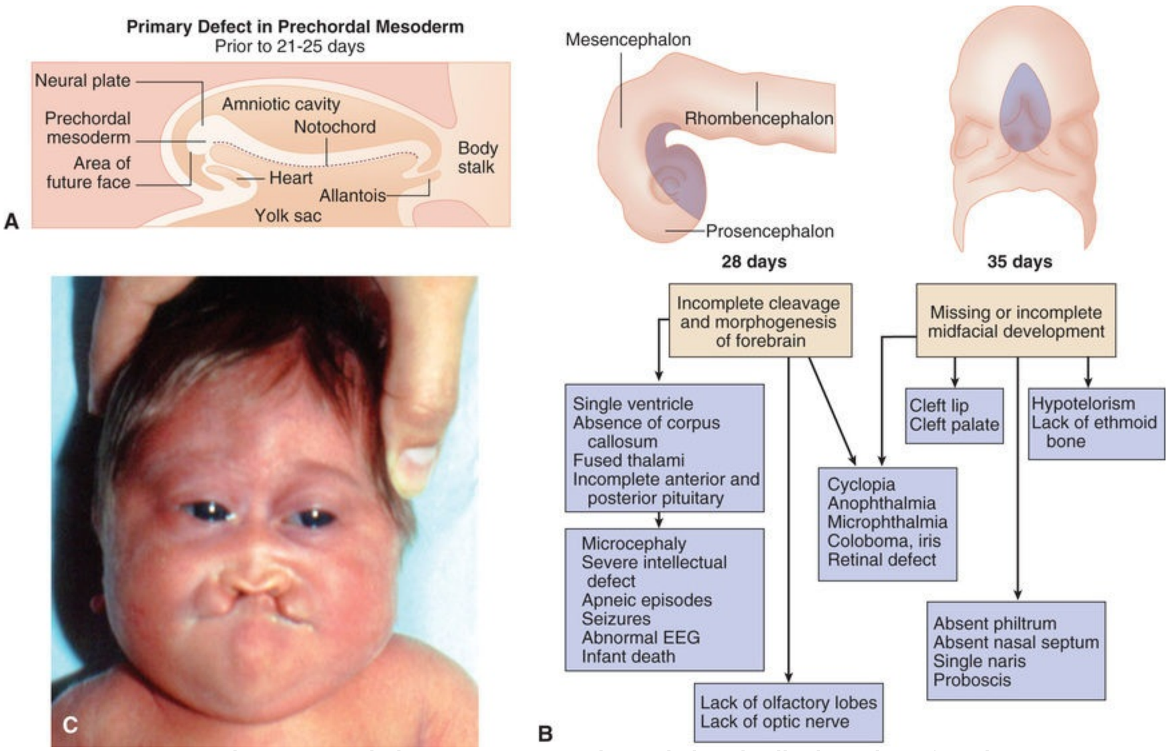
Primary Defect in Prechordal Mesoderm
Prior to 21-25 days
Neural plate
Prechordal mesoderm
Area of future face
Amniotic cavity
Notochord
Body stalk
Heart
Allantois
Yolk sac
A
Mesencephalon
Rhombencephalon
Prosencephalon
28 days
35 days
Incomplete cleavage and morphogenesis of forebrain
Missing or incomplete midfacial development
Single ventricle
Absence of corpus callosum
Fused thalami
Incomplete anterior and posterior pituitary
Microcephaly
Severe intellectual defect
Apneic episodes
Seizures
Abnormal EEG
Infant death
Cyclopia
Anophthalmia
Microphthalmia
Coloboma, iris
Retinal defect
Cleft lip
Cleft palate
Hypotelorism
Lack of ethmoid bone
Absent philtrum
Absent nasal septum
Single naris
Proboscis
Lack of olfactory lobes
Lack of optic nerve
C
B

FIG. 128.9 **Holoprosencephaly sequence. A, Schematic longitudinal section of 21-day embryo. B, Developmental pathogenesis of the sequence. C, Affected individual. (From Jones KL, Jones MC, Del Campo M, editors: *Smith's recognizable patterns of human malformation,* ed 7, Philadelphia, 2013 Elsevier, pp 802–803.)**

Molecular Mechanisms of Malformations

Inborn Errors of Development

Genes that cause malformation syndromes (as well as genes whose expression is disrupted by environmental agents or teratogens) can be part of numerous cellular processes, including evolutionarily conserved signal transduction pathways, transcription factors, or regulatory proteins required for key developmental events. When malformations are considered as alterations resulting from disturbances to important developmental pathways, this provides a molecular framework for understanding the birth defects.

Sonic Hedgehog Pathway As Model

The SHH pathway is developmentally important during embryogenesis to induce controlled proliferation in a tissue-specific manner; disruption of specific steps in this pathway results in a variety of related developmental disorders and malformations (see Fig. 128.2). Activation of this pathway in the adult leads to abnormal proliferation and cancer. The SHH pathway transduces an external signal, in the form of a *ligand,* into changes in gene transcription by binding of the ligand to specific cellular receptors. SHH is a ligand expressed in the embryo in regions important for development of the brain, face, limbs, and the gut.

Deleterious sequence variants in *SHH* can cause **holoprosencephaly** (see Fig. 128.2), a variably severe, midline defect associated with clinical effects ranging from cyclopia to a single maxillary incisor with hypotelorism or close spacing of the ocular orbits. The SHH protein is processed by proteolytic cleavage to an active N-terminal form, which is then further modified by the addition of cholesterol. Defects in cholesterol biosynthesis, in particular the sterol, delta-7-dehydrocholesterol reductase gene, result in **SLOS** , which is also associated with holoprosencephaly. The modified and active form of SHH binds to its transmembrane receptor Patched (PTCH1). SHH binding to PTCH1 inhibits the activity of the transmembrane protein Smoothened (SMO). SMO act to suppress downstream targets of the SHH pathway, the GLI family of transcription factors, so inhibition of SMO by PTCH1 results in activation of GLI1, GLI2, and GLI3, resulting in alteration of transcription of GLI targets. *PTCH1* and its orthologue, *PTCH2* , can act as tumor suppressors, and somatic, inactivating sequence variants can be associated with loss of tumor suppressor function, whereas activating mutations in *SMO* can also be oncogenic, particularly in basal cell carcinomas and medulloblastomas. Germline, inactivating mutations in *PTCH1* result in **Gorlin syndrome** (see Fig. 128.4), an autosomal dominant disorder characterized by dysmorphic features (broad face, dental anomalies, rib defects, short metacarpals), basal cell nevi that can undergo malignant transformation, and an increased risk of cancers, including medulloblastomas and rhabdomyosarcomas. *GLI1* amplification has been found in several human tumors, including glioblastoma, osteosarcoma, rhabdomyosarcoma, and B cell lymphomas; mutations or alterations in *GLI3* have been found in **Greig cephalopolysyndactyly syndrome** (GCPS), **Pallister-Hall syndrome (** PHS), postaxial polydactyly type A (and A/B), and preaxial polydactyly type IV (see Fig. 128.2). GCPS consists of hypertelorism (wide-spaced eyes), syndactyly, preaxial polydactyly, and broad thumbs and halluces. PHS is an autosomal dominant disorder characterized by postaxial polydactyly, syndactyly, hypothalamic hamartomas, imperforate anus, and occasionally holoprosencephaly. GLI3 binds to CBP, the protein that is haploinsufficient in **Rubinstein-Taybi syndrome** .

Disorders that are caused by mutations in genes that function together in a developmental pathway typically have overlapping clinical manifestations. In this case, the overlapping features result from the expression domains of SHH that are important for development of the brain, face, limbs, and gut. Brain defects are found in holoprosencephaly (Fig. 128.9), SLOS, and PHS. Facial abnormalities are found in holoprosencephaly, SLOS, Gorlin syndrome, GCPS, and PHS. Limb defects are found in SLOS, Gorlin syndrome, GCPS, PHS, and the polydactyly syndromes. Overexpression, or activating mutations, affecting the SHH pathway results in cancer, including basal cell carcinomas, medulloblastomas, glioblastomas, and rhabdomyosarcomas.

The SHH pathway interaction with the primary cilium is critical to transduce the SHH extracellular signal through to the nuclear machinery. A number of disorders, including Bardet-Biedl syndrome, oral-facial-digital (OFD) syndrome type I, and Joubert syndrome, are caused by mutations in genes that function in the primary cilium. These disorders, called **ciliopathies** , overlap clinically with some of the phenotypic features described previously, again demonstrating that perturbations of conserved developmental pathways can cause overlapping presentations (Table 128.4).

Table 128.4

Childhood Diseases and Syndromes Associated with Motile and Sensory Ciliopathies

PEDIATRIC CILIOPATHY	CLINICAL MANIFESTATIONS	SELECTED GENE(S)
MOTOR		
Primary ciliary dyskinesia	Chronic bronchitis, rhinosinusitis, otitis media, laterality defects, infertility, CHD	*DNAI1, DNAH5, DNAH11, DNAI2, KTU, TXNDC3, LRRC50, RSPH9, RSPH4A, CCDC40, CCDC39*
SENSORY		
Autosomal recessive polycystic kidney disease	RFD, CHF	*PKHD1*
Nephronophthisis	RFD, interstitial nephritis, CHF, RP	*NPHP1-8, ALMS1, CEP290*
Bardet-Biedl syndrome	Obesity, polydactyly, ID, RP, renal anomalies, anosmia, CHD	*BBS1-12, MKS1, MKS3, CEP290*
Meckel-Gruber syndrome	RFD, polydactyly, ID, CNS anomalies, CHD, cleft lip, cleft palate	*MKS1-6, CC2D2A, CEP290, TMEM216*
Joubert syndrome	CNS anomalies, ID, ataxia, RP, polydactyly, cleft lip, cleft palate	*NPHP1, JBTS1, JBTS3, JBTS4, CORS2, AHI1, CEP290, TMEM216*
Alstrom syndrome	Obesity, RP, DM, hypothyroidism, hypogonadism, skeletal dysplasia, cardiomyopathy, pulmonary fibrosis	*ALMS1*
Orofaciodigital syndrome type I	Polydactyly, syndactyly, cleft lip, cleft palate, CNS anomalies, ID, RFD	*OFD1*
Ellis van Creveld syndrome	Chondrodystrophy, polydactyly, ectodermal dysplasia, CHD	*EVC, EVC2*
Jeune asphyxiating thoracic dystrophy	Narrow thorax, RFD, RP, dwarfism, polydactyly	*IFT80*
Sensenbrenner syndrome	Dolichocephaly, ectodermal dysplasia, dental dysplasia, narrow thorax, RFD, CHD	*IFT122, IFT43, WDR35*
Short rib–polydactyly syndromes	Narrow thorax, short limb dwarfism, polydactyly, renal dysplasia	*WDR35, DYNC2H1, NEK1*

CHD, Congenital heart disease; CHF, congenital hepatic fibrosis; CNS, central nervous system; DM, diabetes mellitus; ID, intellectual disabilities; RFD, renal fibrocystic disease; RP, retinitis pigmentosa.

From Ferkol TW, Leigh MW: Ciliopathies: the central role of cilia in a spectrum of pediatric disorders, *J Pediatr* 160:366–371, 2012.

Cytogenetic Aberrations and Chromosomal Imbalance

Cytogenetic imbalances resulting from an additional copy of a whole human chromosome can result in characteristic and recognizable syndromes. An additional copy of chromosome 21 results in **Down syndrome** (see Chapter 98.2); loss of one of the X chromosomes results in **Turner syndrome** (see Chapter 98 for discussion of syndromes with whole chromosomal imbalances). With the advent of high-resolution cytogenetic techniques, such as fluorescence in situ hybridization (FISH), array comparative genomic hybridization (array CGH), and single nucleotide polymorphism (SNP) arrays, it has become possible to identify **submicroscopic chromosome deletions and duplications** . A number of recurrent deletions and duplications have been identified that cause characteristic and recognizable syndromes, including **Williams syndrome** (deletion of chromosome 7q11.23), **Miller-Dieker syndrome** (deletion of chromosome 17p13.3), **Smith-Magenis syndrome** (deletion of chromosome 17p11.2), and 22q11 deletion syndrome (deletion of chromosome 22q11.2, also known as **velocardiofacial/DiGeorge syndrome**). Array CGH and SNP arrays have also made it possible to uncover rarer microdeletions and microduplications associated with birth defects, intellectual disability, and neuropsychiatric disorders. The sensitivity and specificity chromosome microarrays have made this the technique of choice for the initial evaluation of a child with multiple congenital anomalies and/or intellectual disability, although it is important to note that all individuals may carry numerous small microdeletions and microduplications as normal or familial variation. Therefore, it is important to compare copy number variants in these children with birth defects with their parents' chromosome analyses and with databases of normal variants detected in individuals without such birth defects.

Approach to the Dysmorphic Child

One approach to the dysmorphic child is the *pattern recognition* approach, which compares the manifestations in the patient against a broad and memorized (or computerized) knowledge of human pleiotropic disorders. Although this approach can be appropriate for a small number of experienced dysmorphologists, a systematic *genetic mechanism* approach can also be effective for clinicians who are not dysmorphology experts. By gathering and analyzing the clinical data, the general pediatrician can diagnose the patient in a straightforward case or initiate a referral to an appropriate specialist.

Medical History

The history for a patient with birth defects includes a number of elements related to etiologic factors. The *pedigree* or family history is necessary to assess the inheritance pattern, or lack thereof, for the disorder. For disorders that have a simple mendelian inheritance pattern, its recognition can be critical for narrowing the differential diagnosis, then prioritizing common genes with the appropriate inheritance pattern causing the patient's clinical features. A number of common birth defects have a complex or multifactorial genetic etiology, such as isolated cleft palate and spina bifida. The recognition of a close relative affected with a birth defect that is similar to that in the proband can be useful. Typically, a 3-generation pedigree is sufficient for this purpose (see Chapter 97).

The perinatal history is also an essential component of the history. It includes the pregnancy history of the mother (useful for recognition of recurrent miscarriages that may be indicative of a chromosomal disorder), factors that may relate to deformations or disruptions (oligohydramnios), and maternal exposures to teratogenic drugs or chemicals (isotretinoin and ethanol are potential causes of microcephaly).

Another component of the history that is often useful is the natural history of the **phenotype** . Malformation syndromes caused by chromosomal aberrations and single-gene disorders are frequently *static,* meaning that, although the patients can experience new complications over time, the phenotype is typically not progressive. In contrast, disorders that cause dysmorphic features because of metabolic perturbations (e.g., Hunter or Sanfilippo syndrome) can be mild or may not be apparent at birth, but they can progress relentlessly, causing deterioration of patient status over time.

Physical Examination

The physical examination is very important for the diagnosis of a dysmorphic syndrome. The essential element of the physical evaluation is an objective assessment of the patient's clinical findings. The clinician needs to perform an organized evaluation of the size and formation of various body structures. Familiarity with the nomenclature of dysmorphic signs is helpful (Table 128.5). The size and shape of the head is relevant; for example, many children with Down syndrome have mild microcephaly and brachycephaly (shortened anteroposterior dimension of skull). Eye position and shape are useful signs for many disorders. Reference standards are available with which physical measurements (e.g., interpupillary distance) can also be compared. It is also useful to categorize abnormalities as “major” or “minor” birth defects. Major defects either cause significant dysfunction (e.g., absence of a digit) or require surgical correction (e.g., polydactyly), and minor defects neither cause significant dysfunction nor require surgical correction (e.g, mild clinodactyly)

(Table 128.6 and Fig. 128.10). By cataloging physical parameters, the clinician may be able to recognize the diagnosis.

Table 128.5

Definitions of Common Clinical Signs of Dysmorphic Syndromes

SIGN	DEFINITION
Brachycephaly	A condition in which head shape is shortened from front to back along the sagittal plane; typically the back of the skull (occiput) and face are flatter than normal.
Brachydactyly	Short digits.
Brushfield spots	Speckled white spots or rings about two thirds of the distance to the periphery of the iris of the eye.
Camptodactyly	Permanent flexion of 1 or more fingers that can be associated with missing interphalangeal crease.
Clinodactyly	A medial or lateral curving of the fingers or toes; usually refers to incurving of the 5th finger.
Hypoplastic or small nail	A small nail on a digit.
Low-set ears	This designation is made when the helix meets the cranium at a level below a horizontal plane that is an extension of a line through both inner canthi.
Melia	A suffix meaning “limb” (e.g., amelia—missing limb; brachymelia—short limb).
Ocular hypertelorism or wide-set eyes	Increased distance between the center of the pupils of the 2 eyes; also known as *increased interpupillary distance* (IPD).
Plagiocephaly	A condition in which head shape is asymmetric in the sagittal or coronal plane; can result from asymmetry in cranial suture closure, asymmetry of brain growth, or deformation of the skull.
Posterior hair whorl	A single hair whorl occurs to the right or left of midline and is within 2 cm anterior to the posterior fontanel in 95% of cases.
Postaxial polydactyly	Extra finger or toe present on the lateral side of the hand or foot.
Preaxial polydactyly	Extra finger or toe present on the medial side of the hand or foot.
Prominent lateral palatine ridges	Relative overgrowth of the lateral palatine ridges that can be caused by a deficit of tongue thrust into the hard palate.
Scaphocephaly	A condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic; also termed *dolichocephaly* .
Shawl scrotum	The scrotal skin joins around the superior aspect of the penis and represents a mild deficit in full migration of the labial-scrotal folds.
Short palpebral fissures	Decreased horizontal distance of the eyelid folds based on measurements from the inner canthus to the outer canthus,
Syndactyly	Incomplete separation of the fingers or toes. It most commonly occurs between the 3rd and 4th fingers and between the 2nd and 3rd toes.
Synophrys	Eyebrows that meet in the midline.
Telecanthus	Lateral displacement of the inner canthi. The inner canthal distance (ICD) is increased, but the interpupillary distance (IPD) is normal.
Widow's peak	V -shaped midline, downward projection of the scalp hair in the frontal region. It represents an upper forehead intersection of the bilateral fields of periocular hair growth suppression. It usually occurs because the fields are widely spaced, as in ocular hypertelorism.

Table 128.6

Minor Anomalies and Phenotype Variants*

CRANIOFACIAL
Large anterior fontanel Flat or low nasal bridge Anteverted (upturned) nose Mild micrognathia Cutis aplasia of scalp
EYE
Epicanthus Telecanthus Slanting of the palpebral fissures Hypertelorism (widely spaced eyes) Brushfield spots
EAR
Lack of helical folds Posteriorly rotated pinna Small pinnae Auricular or preauricular pit Atypical folding of helices Crushed (crumpled) ear Asymmetric ear sizes Low-set ears
SKIN
Skin dimpling over bones Capillary hemangioma (face, posterior neck) Dermal melanosis (African Americans, Asians) Sacral dimple Pigmented nevi Redundant skin Cutis marmorata
HAND
Single palmar creases Bridged palmar creases Clinodactyly of 5th digits Hyperextensibility of thumbs Mild partial cutaneous syndactyly Polydactyly Short, broad thumb Narrow, hyperconvex nails Small nails Camptodactyly Shortened 4th digit
FOOT
Partial syndactyly of 2nd and 3rd toes Asymmetric toe length Clinodactyly of 2nd toe Overlapping toes Small nails Wide gap between hallux and 2nd toe (wide sandal gap) Deep plantar crease between hallux and 2nd toe

OTHER
Hydrocele
Shawl scrotum
Hypospadias
Hypoplasia of labia majora

[*] Approximately 15% of newborns have 1 minor anomaly, 0.8% have 2 minor anomalies, and 0.5% have 3. If 2 minor anomalies are present, the probability of an underlying syndrome or a major anomaly (congenital heart disease, renal, central nervous system, limbic) is 5-fold that in the general population. If 3 minor anomalies are present, there is a 20–30% probability of a major anomaly.

From Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, Elsevier Saunders.

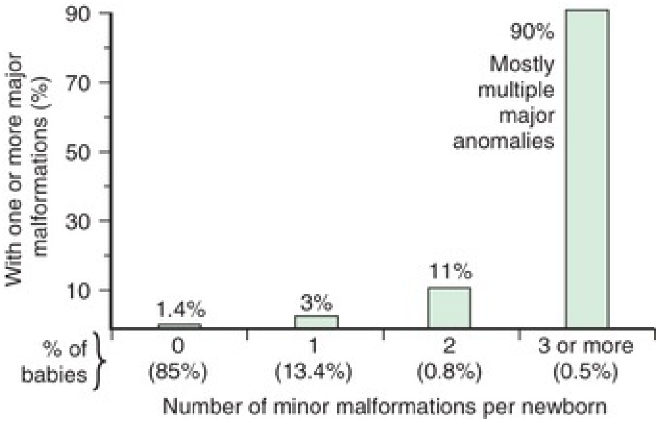

FIG. 128.10 Frequency of major malformations in relation to the number of minor anomalies detected in a given newborn baby. (From Jones KJ: *Smith's recognizable patterns of human malformation,* ed 6, Philadelphia, 2006, Saunders.)

Imaging Studies

Imaging studies can be critical in diagnosing an underlying genetic etiology. If short stature or disproportionate stature (e.g., long trunk and short limbs) is noted, a full skeletal survey with radiographs should be performed. The skeletal survey can detect anomalies in bone number or structure that can be used to narrow the differential diagnosis. When there are abnormal neurologic signs or symptoms, such as microcephaly or hypotonia, brain imaging can be indicated. Other studies, such as echocardiography and renal ultrasonography, can also be useful to identify additional major or minor malformations that may serve as diagnostic clues.

Diagnosis

The examining physician should gather data on the patient's pedigree and perinatal and pediatric (for older children) history and should have an appreciation for the natural history of the clinical findings. At this point, the physician has examined the child, identified atypical physical features, and obtained appropriate imaging studies.

The clinician should now attempt to organize the findings to elucidate potential developmental processes. An assessment based on **specificity** can be helpful for this process. If a child has multiple findings, such as a patent ductus arteriosus (PDA), mild growth restriction, mild microcephaly, and holoprosencephaly, micropenis, and ptosis, a selection of the rarer or pathognomonic findings may be prioritized. The PDA, ptosis, mild growth restriction, and mild microcephaly are considered to be largely *nonspecific findings* (present in many disorders or often present as isolated features that are not part of a syndrome), whereas holoprosencephaly and micropenis are present in fewer syndromes and are not considered part of normal variation. The clinician can therefore search for disorders that include both holoprosencephaly and micropenis. The search can be performed manually using the features index of a textbook such as *Smith's Recognizable Patterns of Human Malformation* or a computerized database such as Online Mendelian Inheritance in Man (OMIM). Searching for both holoprosencephaly and micropenis returns a list of diagnostic possibilities, and the physician can then return to the patient to examine for additional features of the leading possible candidate disorders. Appropriate genetic testing can then be undertaken to confirm the clinician's hypothesis and verify the diagnosis.

Laboratory Studies and Genetic Testing

The laboratory evaluation of the dysmorphic child can be critical to reach or confirm the correct diagnosis. Cytogenetic studies with Giemsa-banded (G-banded) chromosome analysis, or karyotyping, was the gold standard previously performed in the evaluation of a dysmorphic patient. Array CGH and SNP arrays enable copy number variant detection and, in the case of SNP arrays, evaluation of loss of heterozygosity. Chromosome deletion syndromes may also be identified with specific and sensitive FISH analysis (Table 128.7). These tests are the most sensitive methods for the detection of cytogenetic alterations associated with birth defects and multiple congenital anomalies.

Table 128.7

Chromosomal Deletion Syndromes

CONDITION	BRIEF DESCRIPTION	PROBE
Williams syndrome	Proportionate short stature, mild-moderate to severe intellectual disability, "cocktail patter" for conversation, stellate pattern of iris pigmentation, supravalvular aortic stenosis, recessed nasal bridge, and wide mouth with full lips	7q11
WAGR syndrome	Wilms tumor, aniridia, growth delay, intellectual disability, and genitourinary anomalies	11p13
Prader-Willi syndrome Angelman syndrome	Distinct syndromes with common or overlapping areas of deletion; phenotype depends on gender of the parent of origin of the deletion. Prader-Willi syndrome: hypotonia in infancy, short stature, obesity, mild-moderate and occasionally severe intellectual disability, small hands and feet (caused by paternal deletion of 15q11-13 or maternal uniparental disomy for chromosome 15) Angelman syndrome: severe intellectual disability, absence of speech, ataxia, tremulous movements, large mouth, frequent drooling (caused by maternal deletion of chromosome 15q11-13 or paternal uniparental disomy)	15q11
Smith-Magenis syndrome	Brachycephaly, prognathism, self-destructive behavior, wrist biting, pulling out nails, head banging, indifference to pain, severe intellectual disability, hyperactivity, social behavior problems	17p11.2
Miller-Dieker syndrome	Microcephaly, narrow temples, hypotonia/hypertonia, abnormal posturing, seizures, severe to profound intellectual disability, poor growth, lissencephaly and other brain abnormalities on CT or MRI	17p13
Velocardiofacial (VCF) syndrome (overlaps with DiGeorge syndrome)	VCF: cleft palate, congenital heart disease, learning/behavior problems, long face, prominent nose, limb hypotonia, slender hands with tapering fingers DiGeorge syndrome: T-cell deficiency, immunoglobulin deficiency	22q11

CT, Computed tomography; MRI, magnetic resonance imaging; WAGR, Wilms tumor, aniridia, genitourinary anomalies, and mental retardation.

From Kliegman RM, Lye PS, et al, editors: *Nelson pediatric symptom-based diagnosis,* Philadelphia, 2018, Elsevier (Table 25-10).

Molecular testing for deleterious sequence variants that cause pleiotropic malformation syndromes is also available for many disorders as clinical or research testing. In most cases, however, such testing should not be performed indiscriminately, but instead should be ordered thoughtfully after the differential diagnosis has been considered. The introduction of **next-generation sequencing** has led to the identification of innumerable novel genes and revolutionized the testing that is now available for patients and families with intellectual disability, birth defects, or other suspected genetic diseases. A strong suspicion of a genetic diagnosis warrants consideration of testing to confirm the diagnosis, facilitate patient treatment and anticipatory guidance, clarify recurrence risks, and enable carrier testing for relevant inheritance patterns. Single nucleotide variants, exons, or genes are tested by *Sanger sequencing* targeting single or multiple exons. However, for diagnoses that have substantial genetic heterogeneity (e.g., hearing loss), *panel testing,* in which multiple relevant genes can be interrogated for single nucleotide variants, gene deletions, and gene duplications, is more expeditious than Sanger sequencing. Panel tests also frequently have the advantage of providing high coverage for the genes on the panel, compared to coverage for the same genes obtained by exome sequencing. However, in situations with diagnostic uncertainty, such as the investigation of a child with intellectual disability and dysmorphic features, for which there is no clinically recognizable pattern, exome sequencing may be most useful as a broad testing approach. **Whole exome sequencing** (WES) examines approximately 200,000 exons, or the 1–2% of the DNA that comprises the coding regions of the genome. WES is typically performed with a *trio* approach, in which the patient and both biological parents are tested simultaneously, so that the inheritance pattern, or segregation, of deleterious sequence variants can be determined, thus simplifying analysis. Trio sequencing has resulted in higher diagnostic yields than proband-only sequencing and can approach 30–40% for indications such as intellectual disability. In contrast, **whole genome sequencing** (WGS) examines all the DNA content, including noncoding regions, and includes analysis for cytogenetic rearrangements in addition to copy number loss or gain. WES and WGS are applicable to a wide range of birth defects and genetic diseases and can discover causative variants in known or novel genes associated with a particular condition.

Management and Counseling

Management of the affected patient and genetic counseling are essential aspects of the approach to the dysmorphic patient. Children with Down syndrome have a high incidence of hypothyroidism, and children with achondroplasia have a high incidence of cervicomedullary junction abnormalities. One of the many benefits of an early and accurate diagnosis is that **anticipatory guidance and medical monitoring** of patients for syndrome-specific medical risks can prolong and improve their quality of life. When a diagnosis is made, the treating physicians can access published information on the natural history and management of the disorder through published papers, genetics reference texts, and databases.

The 2nd major benefit of an accurate diagnosis is that it provides data for appropriate **recurrence risk** estimates. Genetic disorders may have direct effects on only 1 member of the family, but the diagnosis of the condition can have implications for the entire family. One or both parents may be carriers; siblings may be carriers or may want to know their genetic status when they reach their reproductive years. Recurrence risk provision is an important component of genetic counseling and should be included in all evaluations for families affected with birth defects or other inherited disorders (see Chapter 94).

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CHAPTER 129

Epidemiology of Infections

David B. Haslam

Infections in the newborn are often classified by their timing relative to birth and include congenital, perinatal, early-onset, and late-onset disease. These are clinically useful designations because the mechanisms of infection, etiologies, and outcomes are distinct at each stage. **Congenital infection** denotes infection acquired in utero. Such infections are generally caused by viral or other non-bacterial organisms and are often associated with injury to developing organs (see Chapter 131). **Perinatal infection** indicates acquisition around the time of delivery. Perinatally acquired organisms include both bacteria and viruses, some of which are the same as those causing congenital infection but often manifest with different features. **Early-onset infection** occurs in the 1st wk of life and is generally the consequence of infection caused by organisms acquired during the perinatal period. **Late-onset infection** occurs between 7 and 30 days of life and may include bacteria, viruses, or other organisms that are typically acquired in the postnatal period. **Hospital-acquired infections** typically occur beyond the 1st wk of life (see Chapter 130).

Neonates are uniquely prone to invasive disease because of their lack of fully responsive innate immunity (Fig. 129.1). Attenuated immune responses often result in minimal or nonspecific clinical manifestations, and effective treatment requires attention to subtle signs of infection. Compared to older infants, newborns are often treated empirically while awaiting results of laboratory investigations. Preterm infants are particularly susceptible to infection because of their decreased innate immune and barrier defenses and their prolonged stay in hospital settings.

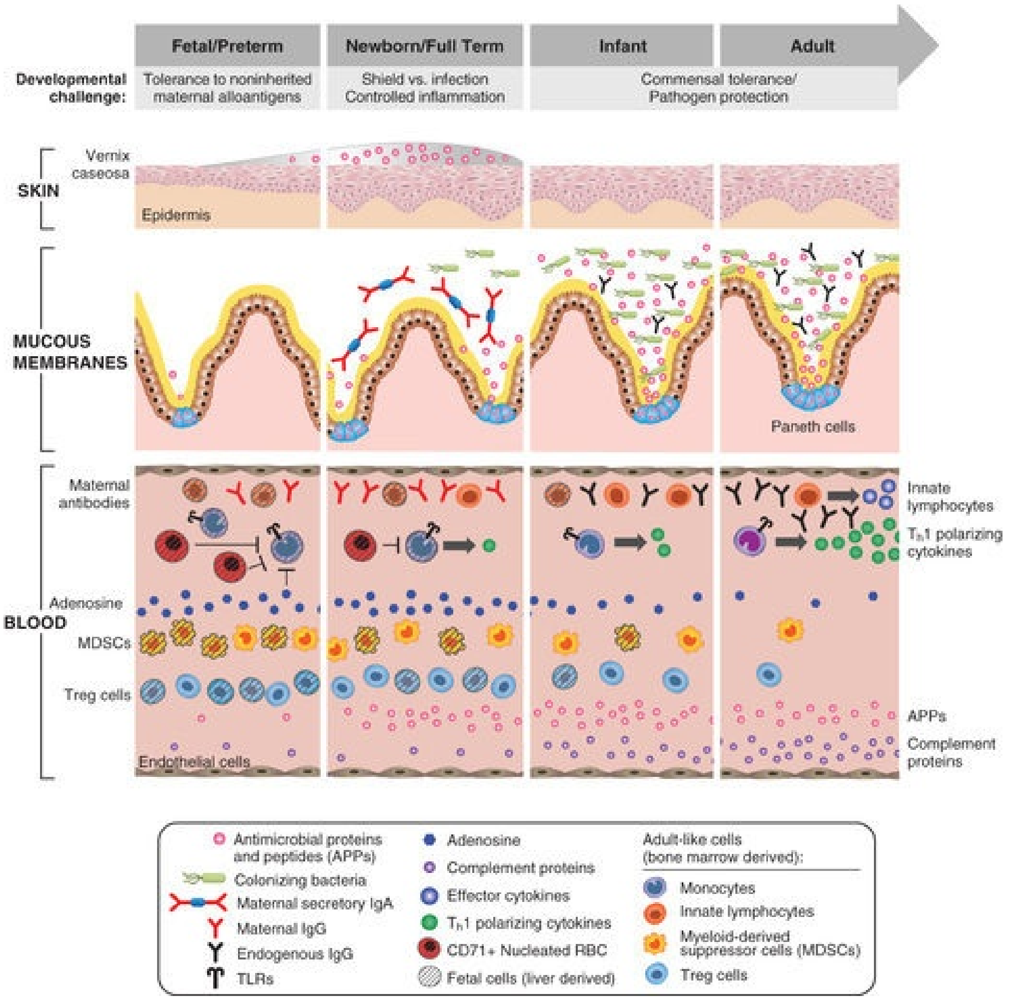
Fetal/Preterm
Newborn/Full Term
Infant
Adult
Developmental challenge:
Tolerance to noninherited maternal alloantigens
Shield vs. infection Controlled inflammation
Commensal tolerance/ Pathogen protection
SKIN
Vernix caseosa
Epidermis
MUCOUS MEMBRANES
Paneth cells
BLOOD
Maternal antibodies
Adenosine
MDSCs
Treg cells
Endothelial cells
Innate lymphocytes
Th1 polarizing cytokines
APPs
Complement proteins
Antimicrobial proteins and peptides (APPs)
Colonizing bacteria
Maternal secretory IgA
Maternal IgG
Endogenous IgG
TLRs
Adenosine
Complement proteins
Effector cytokines
Th1 polarizing cytokines
CD71+ Nucleated RBC
Fetal cells (liver derived)
Adult-like cells (bone marrow derived):
Monocytes
Innate lymphocytes
Myeloid-derived suppressor cells (MDSCs)
Treg cells

FIG. 129.1 Ontogeny of skin, soluble, and cellular innate defense systems. Host-protective barrier functions include physical, chemical, and functional components of the skin and mucous membrane epithelia of the fetus, neonate (birth to 28 days of age), and infant (1 mo to 1 yr of age). Skin: while physical and chemical barriers are impaired in early in life, especially in the preterm newborn, the vernix caseosa and skin epithelia of full-term newborns robustly express antimicrobial proteins and peptides (APPs). Mucous membranes: in parallel with and induced by an increasingly complex microbiota, the newborn intestinal mucosal epithelium rapidly changes structurally, with an increase in the population of crypts and crypt-based Paneth cells, as well as functionally with increasing APP expression. Blood: the composition of neonatal blood is distinct, with relatively low concentrations of complement components and APPs and high concentrations of the immunosuppressive purine metabolite adenosine. Plasma also contains maternal antibodies that are transferred beginning midgestation and supplemented by postnatal factors derived from breast milk. Innate immunity is detectable from the end of the 1st mo of gestation, with changes driven largely by the increasing exposure to environmental microbes. Neonatal antigen-presenting cells such as blood monocytes express pattern recognition receptors (e.g., Toll-like receptors, TLRs) with distinct functional responses, including limited Th1-polarizing cytokine production, to most stimuli. Adaptive immunity develops from 4 wk of gestation onward, with changes driven by an evolving chimerism reflecting fetal (liver-derived, *shaded cells*) regulatory T (Treg)-cell–rich lymphocytes, and more adultlike (bone marrow derived, *unshaded cells*) lymphocytes with distinct, epigenetically encoded functional programs. Ig, Immunoglobulin; RBC, red blood cell. (Modified from Kollmann TR, Kampmann B, Mazmanian SK, et al: Protecting the newborn and young infant from infectious diseases: lessons from immune ontogeny. *Immunity* 2007;46:350–363.)

Incidence and Epidemiology

Despite advances in maternal and neonatal care, infections remain a frequent and important cause of neonatal and infant morbidity and mortality. Up to 10% of infants have infections in the 1st mo of life. Newborn infection is more common in areas with limited access to healthcare than in areas with well-established healthcare infrastructure. The overall incidence of neonatal sepsis ranges from 1 to 5 cases per 1,000 live births. Estimated incidence rates vary based on the case definition and the population studied. Globally, neonatal sepsis and other severe infections were responsible for an estimated 430,000 neonatal deaths in 2013, accounting for approximately 15% of all neonatal deaths.

A number of bacterial and nonbacterial agents may infect newborns in the intrapartum or postpartum period (Table 129.1). Although herpes simplex virus (HSV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and tuberculosis (TB) can each result in transplacental infection, the most common mode of transmission for these agents is **intrapartum** , during labor and delivery with passage through an infected birth canal (HIV, HSV, HBV), or **postpartum** , from contact with an infected mother or caretaker (TB) or with infected breast milk (HIV) (Fig. 129.2 and Table 129.2). Any microorganism inhabiting the genitourinary or lower gastrointestinal tract may cause intrapartum and postpartum infection. The most common bacteria are group B streptococcus (GBS), *Escherichia coli,* and *Klebsiella* spp. *Salmonella* spp. are common causes of gram-negative sepsis in developing countries; less common causes of bacterial infection in the United States include *Citrobacter* , enterococci, gonococci, *Listeria monocytogenes* , *Streptococcus pneumoniae,* and *Haemophilus influenzae* . The more common viruses are cytomegalovirus (CMV), HSV, enteroviruses, and HIV (Table 129.2).

Table 129.1

Nonbacterial Causes of Systemic Neonatal Infections

VIRUSES
Adenovirus
Cytomegalovirus (CMV)
Enteroviruses
Parechoviruses

Hepatitis B and C viruses
Herpes simplex virus (HSV)
Human immunodeficiency virus (HIV)
Parvovirus
Rubella virus
Varicella-zoster virus (VZV)

MYCOPLASMA

Mycoplasma hominis
Ureaplasma urealyticum

FUNGI

Candida spp.
Malassezia spp.

PROTOZOA

Plasmodia
Toxoplasma gondii
Trypanosoma cruzi

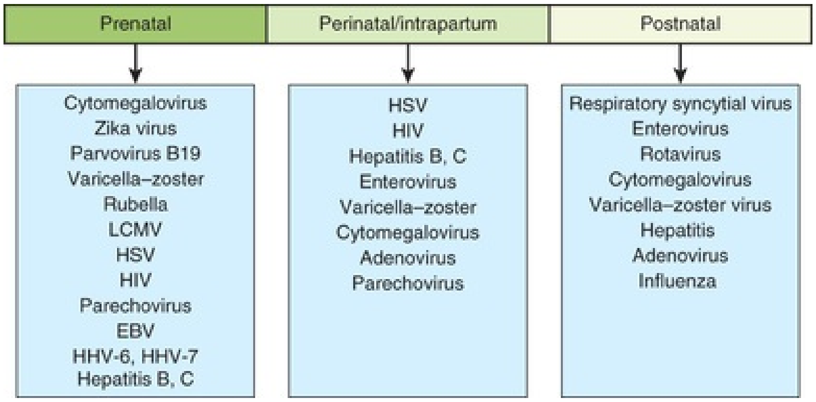
Prenatal
Perinatal/intrapartum
Postnatal
Cytomegalovirus
Zika virus
Parvovirus B19
Varicella–zoster
Rubella
LCMV
HSV
HIV
Parechovirus
EBV
HHV-6, HHV-7
Hepatitis B, C
HSV
HIV
Hepatitis B, C
Enterovirus
Varicella–zoster
Cytomegalovirus
Adenovirus
Parechovirus
Respiratory syncytial virus
Enterovirus
Rotavirus
Cytomegalovirus
Varicella–zoster virus
Hepatitis
Adenovirus
Influenza

FIG. 129.2 **Relative importance of neonatal viral infections related to the timing of acquisition of infection. Viruses are listed in declining order of importance relative to prenatal, perinatal (intrapartum), and postnatal timing of typical infection. Some neonatal virus infections (e.g., cytomegalovirus) can be substantial causes of disease whether acquired during gestation or acquired postpartum, whereas others (e.g., respiratory syncytial virus) are typically acquired in the postnatal period. EBV, Epstein-Barr virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis virus. (From Schleiss MR, Marsh KJ: Viral infections of the fetus and newborn. In Gleason CA, Juul SE, editors: *Avery's diseases of the newborn,* ed 10, Philadelphia, 2018, Elsevier, Fig 37-1.)**

Table 129.2

Period of Transmission of Selected Viruses to the Fetus or Newborn Infant

VIRUSES	CONGENITAL	NATAL	POSTNATAL
Adenovirus	+	+	+
Chikungunya	++	+	−

Cytomegalovirus	++	++	++
Dengue	++	−	−
Ebola virus	++	+	+
Echoviruses	+	+	+
Epstein-Barr	+	−	+
Hepatitis A	−	++	+
Hepatitis B	+	++	+
Hepatitis C	+	++	−
Herpes simplex	+	++	+
Herpesvirus-6	+	−	+
Human immunodeficiency virus	+	++	+
Human parvovirus B19	+	−	−
Influenza	(+)	−	+
Lymphocytic choriomeningitis virus	++	−	−
Measles	+	−	+
Mumps	+	−	−
Parechovirus	−	+	+
Polioviruses	+	+	+
Rubella	++	−	−
Smallpox	+	+	+
St. Louis encephalitis	(+)	−	(+)
Type B coxsackieviruses	+	+	+
Vaccinia	+	+	+
Varicella-zoster virus	++	+	+
West Nile virus	+	−	+
Western equine encephalitis	+	−	+
Zika virus	++	?	(+)

++ , Major demonstrated route; +, minor demonstrated route; (+), suggested route, few supporting data; −, route not demonstrated.

From Harrison GJ: Approach to infections in the fetus and newborn. In Cherry JD, Demmler-Harrison GJ, Kaplan SL, et al, editors: *Feigin and Cherry's textbook of pediatric infectious diseases,* ed 7, Philadelphia, 2014, Elsevier (Table 66.1, p 878).

Microorganisms causing pneumonia acquired during labor and delivery include GBS, gram-negative enteric aerobes, *L. monocytogenes*, genital *Mycoplasma*, *Chlamydia trachomatis*, CMV, HSV, and *Candida* spp. (Table 129.3).

Table 129.3

Etiologic Agents of Neonatal Pneumonia According to Timing of Acquisition

TRANSPLACENTAL
Cytomegalovirus (CMV)
Herpes simplex virus (HSV)
Mycobacterium tuberculosis
Rubella virus

Treponema pallidum
Varicella-zoster virus (VZV)
Listeria monocytogenes

PERINATAL

Anaerobic bacteria
Chlamydia
CMV
Enteric bacteria
Group B streptococci
Haemophilus influenzae
HSV
Listeria monocytogenes
Mycoplasma

POSTNATAL

Adenovirus
Candida spp.*
Coagulase-negative staphylococci
CMV
Enteric bacteria*
Enteroviruses
Influenza viruses A, B
Parainfluenza
Pseudomonas *
Respiratory syncytial virus (RSV)
Staphylococcus aureus
Mycobacterium tuberculosis
Legionella

* More likely with mechanical ventilation or indwelling catheters, or after abdominal surgery.

The most common bacterial causes of **neonatal meningitis** are GBS, *E. coli*, and *L. monocytogenes. S. pneumoniae*, other streptococci, nontypable *H. influenzae*, both coagulase-positive and coagulase-negative staphylococci, *Klebsiella*, *Enterobacter*, *Pseudomonas*, *Treponema pallidum*, and *Mycobacterium tuberculosis* infection involving the central nervous system (CNS) may also result in meningitis.

Early- and Late-Onset Neonatal Infections

The terms *early-onset infection* and *late-onset infection* refer to the different ages at onset of infection in the neonatal period. **Early-onset sepsis** is defined as the onset of symptoms before 7 days of age, although some experts limit the definition to infections occurring within the 1st 72 hr of life. **Late-onset sepsis** is generally defined as the onset of symptoms at ≥7 days of age. Similar to early-onset sepsis, there is variability in the definition, ranging from an onset at >72 hr of life to ≥7 days of age. Early-onset infections are acquired before or during delivery (**vertical** mother-to-child transmission). Late-onset infections develop after delivery from organisms acquired in the hospital or the community. The age at onset depends on the timing of exposure and virulence of the infecting organism. **Very-late-onset infections** (onset after age 1 mo) may also occur, particularly in very-low-birthweight (VLBW) preterm infants or term infants requiring prolonged neonatal intensive care.

The incidence of neonatal bacterial sepsis varies from 1-4 per 1,000 live births, with geographic variation and changes over time. Studies suggest that term male infants have a higher incidence of sepsis than term females. This sex difference is less clear in preterm low-birthweight (LBW) infants. Attack rates of neonatal sepsis increase significantly in LBW infants in the presence of maternal chorioamnionitis, congenital immune defects, mutations of genes involved in the innate immune system, asplenia, galactosemia *(E. coli)*, and malformations leading to high inocula of bacteria (e.g., obstructive uropathy).

Data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network documented rates of early-onset sepsis among almost 400,000 live births at Network centers. The overall rate of early-onset sepsis was 0.98 cases per 1,000 live births, with rates inversely related to birthweight: 401-1,500 g, 10.96 per 1,000 births; 1,501-2,500 g, 1.38/1,000; and >2,500 g, 0.57/1,000 (Table 129.4).

Table 129.4

Rates of Early-Onset Sepsis Per 1,000 Live Births[*]

	BIRTHWEIGHT (g)			
	401-1,500	**1,501-2,500**	**>2,500**	**All**
All	10.96	1.38	0.57	0.98
Group B streptococci	2.08	0.38	0.35	0.41
Escherichia coli	5.09	0.54	0.07	0.28

[*] NICHD Neonatal Research Network/CDC Surveillance Study of Early-Onset Sepsis.

Adapted from Stoll BJ, Hansen NI, Sanchez PJ, et al: Early onset neonatal sepsis: the burden of group B streptococcal and *E. coli* disease continues, *Pediatrics* 127(5):817–826, 2011.

The incidence of meningitis is 0.2-0.4 per 1,000 live births in newborn infants and is higher in preterm infants. Bacterial meningitis may be associated with sepsis or may occur as a local meningeal infection. *Up to one third of VLBW infants with late-onset meningitis have negative blood culture results* . The discordance between results of blood and cerebrospinal fluid (CSF) cultures suggests that meningitis may be underdiagnosed among VLBW infants and emphasizes the need for culture of CSF in VLBW infants when *late-onset sepsis* is suspected and in all infants who have positive blood culture results. Most neonates with sepsis presenting in the 1st day of life have a positive blood culture; analysis of CSF is usually deferred until the unstable cardiorespiratory status (shock, respiratory failure) has stabilized.

Pathogenesis

Early-Onset Infections

In most cases, the fetus or neonate is not exposed to potentially pathogenic bacteria until the membranes rupture and the infant passes through the birth canal and/or enters the extrauterine environment. The human birth canal is colonized with aerobic and anaerobic organisms that may result in ascending amniotic infection and/or colonization of the neonate at birth. Vertical transmission of bacterial agents that infect the amniotic fluid and vaginal canal may occur in utero or, more often, during labor and delivery (Fig. 129.3).

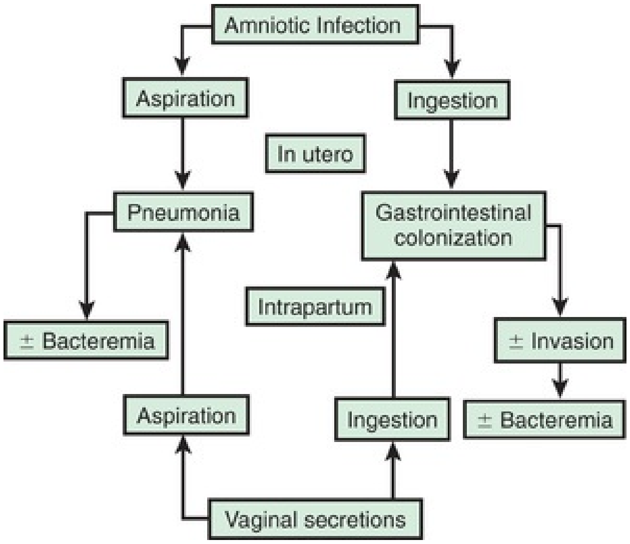
Amniotic Infection
Aspiration
Ingestion
In utero
Pneumonia
Gastrointestinal colonization
± Bacteremia
Intrapartum
± Invasion
Aspiration
Ingestion
± Bacteremia
Vaginal secretions

FIG. 129.3 **Pathways of ascending or intrapartum infection.**

Chorioamnionitis results from microbial invasion of amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane. Amniotic infection may also occur with apparently intact membranes or with a relatively brief duration of membrane rupture. The term *chorioamnionitis* refers to the clinical syndrome of intrauterine infection, which includes maternal fever, with or without local or systemic signs of chorioamnionitis (uterine tenderness, foul-smelling vaginal discharge/amniotic fluid, maternal leukocytosis, maternal and/or fetal tachycardia). Chorioamnionitis may also be asymptomatic, diagnosed only by amniotic fluid analysis or pathologic examination of the placenta. The rate of histologic chorioamnionitis is inversely related to gestational age at birth (Fig. 129.4) and directly related to duration of membrane rupture.

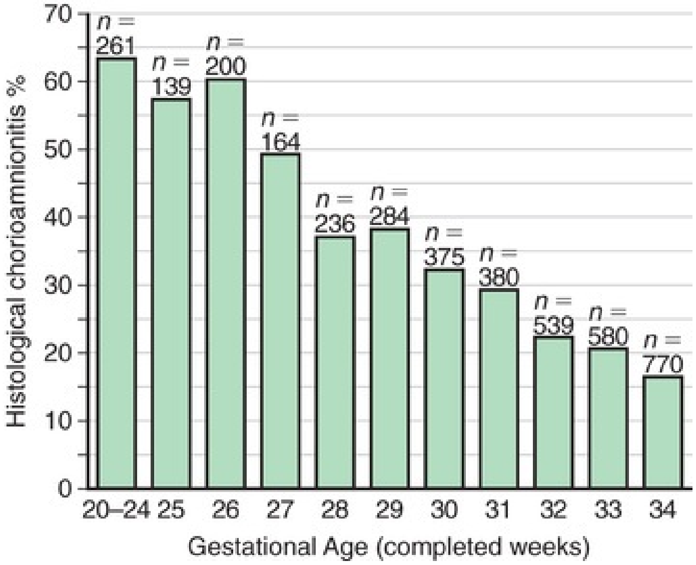

FIG. 129.4 **Histologic chorioamnionitis in liveborn preterm babies by gestational age (*n* = 3,928 babies). (From Lahra MM, Jeffery HE: A fetal response to chorioamnionitis is associated with early survival after preterm birth, *Am J Obstet Gynecol* 190:147–151, 2004.)**

Chorioamnionitis was thought to result from infection of the amniotic fluid but is now better defined by the term **intrauterine inflammation or infection at birth (Triple I)** . This is defined by fetal tachycardia, maternal leukocytosis (>15,000 cells in the absence of corticosteroids), purulent fluid from the cervical os, biochemical or microbiologic amniotic fluid changes consistent with infection, and fever (≥39.0°C/10.2°F) (see Chapter 131.2).

Rupture of membranes for >24 hr was once considered prolonged because microscopic evidence of inflammation of the membranes is uniformly present when the duration of rupture exceeds 24 hr. At 18 hr of membrane rupture, however, the incidence of early-onset disease with group B streptococcus (GBS) increases significantly; 18 hr is the appropriate cutoff for increased risk of neonatal infection (see Chapter 211).

Bacterial colonization does not always result in disease. Factors influencing which colonized infant will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies (Fig. 129.5). Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (failure to breathe, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

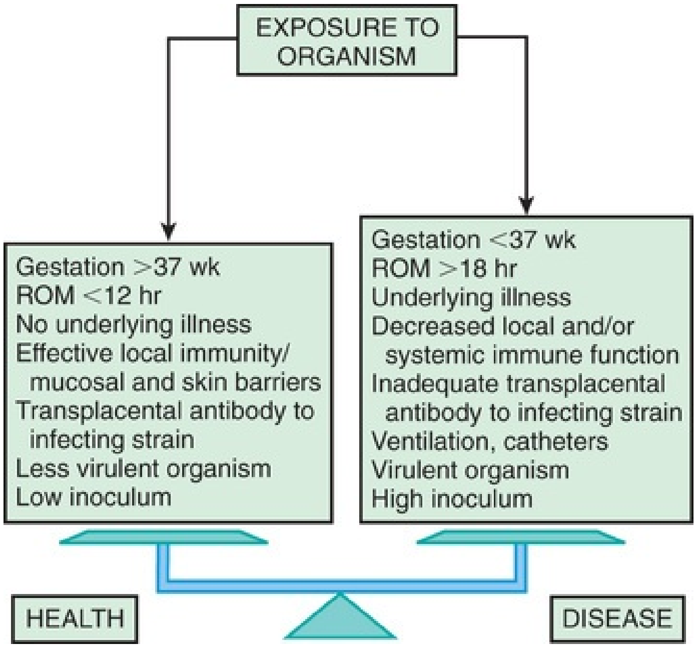
EXPOSURE TO ORGANISM
Gestation >37 wk
ROM <12 hr
No underlying illness
Effective local immunity/ mucosal and skin barriers
Transplacental antibody to infecting strain
Less virulent organism
Low inoculum
Gestation <37 wk
ROM >18 hr
Underlying illness
Decreased local and/or systemic immune function
Inadequate transplacental antibody to infecting strain
Ventilation, catheters
Virulent organism
High inoculum
HEALTH
DISEASE

FIG. 129.5 **Factors influencing the balance between health and disease in neonates exposed to a potential pathogen. ROM, Rupture of membranes. (Adapted from Baker CJ: Group B streptococcal infections, *Clin Perinatol* 24:59–70, 1997.)**

Resuscitation at birth, particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter, or both, is associated with an increased risk of bacterial infection. Explanations include the presence of infection at the time of birth or acquisition of infection during the invasive procedures associated with resuscitation.

Late-Onset Infections

After birth, neonates are exposed to infectious agents in the neonatal intensive care unit (NICU), the nursery, or in the community (including family). Postnatal infections may be transmitted by direct contact with hospital personnel, the mother, or other family members; from breast milk (HIV, CMV); or from inanimate sources such as contaminated equipment. The most common source of postnatal infections in hospitalized newborns is *hand contamination* of healthcare personnel, underscoring the importance of handwashing.

Most cases of meningitis result from hematogenous dissemination. Less often, meningitis results from contiguous spread as a result of contamination of open neural tube defects, congenital sinus tracts, or penetrating wounds from fetal scalp sampling or internal fetal electrocardiographic monitors. Cerebral abscess formation, ventriculitis, septic infarcts, hydrocephalus, and subdural effusions are complications of meningitis that occur more often in newborn infants than in older children. Metabolic factors, including hypoxia, acidosis, hypothermia, and inherited metabolic disorders (e.g., galactosemia), are likely to contribute to risk for and severity of neonatal sepsis

Infection in Premature Infants

The most important neonatal factor predisposing to infection is prematurity or LBW. Preterm LBW infants have a 3- to 10-fold higher incidence of infection than full-term normal-birthweight infants. Possible explanations include (1) maternal genital tract infection is considered to be an important cause of preterm labor, with an increased risk of vertical transmission to the newborn; (2) the frequency of intraamniotic infection is inversely related to gestational age (see Figs. 129.1 and 129.5); (3) premature infants have documented immune dysfunction; and (4) premature infants often require prolonged intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, putting them at continued risk for hospital-acquired infections.

Clinical Manifestations

The maternal history provides important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, maternal chorioamnionitis). Signs and symptoms in the neonate are often subtle and nonspecific. Temperature instability, tachypnea, lethargy, and poor feeding are common initial signs and should raise suspicion for systemic or focal infection (Table 129.5).

Table 129.5

Initial Signs and Symptoms of Infection in Newborn Infants

GENERAL
Fever, temperature instability
“Not doing well”
Poor feeding
Edema
GASTROINTESTINAL SYSTEM
Abdominal distention
Vomiting
Diarrhea
Hepatomegaly
RESPIRATORY SYSTEM
Apnea, dyspnea
Tachypnea, retractions
Flaring, grunting
Cyanosis
RENAL SYSTEM
Oliguria
CARDIOVASCULAR SYSTEM
Pallor; mottling; cold, clammy skin
Tachycardia
Hypotension
Bradycardia
CENTRAL NERVOUS SYSTEM
Irritability, lethargy
Tremors, seizures
Hyporeflexia, hypotonia
Abnormal Moro reflex
Irregular respirations
Full fontanel
High-pitched cry
HEMATOLOGIC SYSTEM
Jaundice
Splenomegaly
Pallor
Petechiae, purpura
Bleeding

Bacterial Sepsis

Neonates with bacterial sepsis may have either nonspecific manifestations or focal signs of infection (Table 129.5), including temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding. Table 129.6 lists World Health Organization *international criteria* for bacterial sepsis. The initial manifestation may involve only limited symptomatology and only one system, such as apnea alone or tachypnea with retractions, or tachycardia, or the infant may present with an acute catastrophic manifestation with multiorgan dysfunction and shock. Infants should be reevaluated over time to determine whether the symptoms have progressed from mild to severe. Later complications of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anemia), and disseminated intravascular coagulopathy (DIC).

Table 129.6

Clinical Criteria for the Diagnosis of Sepsis in the International Setting

IMCI AND WHO CRITERIA FOR SEVERE INFECTIONS IN CHILDREN

Neurologic: convulsions, drowsy or unconscious, decreased activity, bulging fontanel
Respiratory: respiratory rate >60 breaths/min, grunting, severe chest indrawing, central cyanosis
Cardiac: poor perfusion, rapid and weak pulse
Gastrointestinal: jaundice, poor feeding, abdominal distention
Dermatologic: skin pustules, periumbilical erythema or purulence
Musculoskeletal: edema or erythema overlying bones or joints
Other: temperature >37.7°C (99.9°F; or feels hot) or <35.5°C (95.9°F; or feels cold)

IMCI, Integrated Management of Childhood Illness; WHO, World Health Organization.

Adapted from WHO: *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses,* ed 2, Geneva, 2013, WHO, pp 45–69. http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/ .

A variety of noninfectious conditions can occur together with neonatal infection or can make the diagnosis of infection more difficult. Respiratory distress syndrome (RDS) secondary to surfactant deficiency can coexist with bacterial pneumonia. Because bacterial sepsis can be rapidly progressive, the physician must be alert to the signs and symptoms of possible infection and must initiate diagnostic evaluation and empirical therapy in a timely manner. The differential diagnosis of many of the signs and symptoms that suggest infection is extensive; noninfectious disorders must also be considered (Table 129.7).

Table 129.7

Serious Systemic Illness in Newborns: Differential Diagnosis of Neonatal Sepsis

CARDIAC
Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN)
Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN
GASTROINTESTINAL
Necrotizing enterocolitis
Spontaneous gastrointestinal perforation
Midgut volvulus
Hepatic failure (inborn errors of metabolism, neonatal iron storage disease)
HEMATOLOGIC
Neonatal purpura fulminans
Immune-mediated thrombocytopenia
Immune-mediated neutropenia
Severe anemia
Malignancies (congenital leukemia)
Langerhans cell histiocytosis
Hereditary clotting disorders
Familial hemophagocytosis syndrome
METABOLIC
Hypoglycemia
Adrenal disorders: adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia
Inborn errors of metabolism: organic acidurias, lactic acidoses, urea cycle disorders, galactosemia
NEUROLOGIC
Intracranial hemorrhage: spontaneous, caused by child abuse
Hypoxic-ischemic encephalopathy
Neonatal seizures
Infant botulism
RESPIRATORY
Respiratory distress syndrome
Aspiration pneumonia: amniotic fluid, meconium, or gastric contents
Lung hypoplasia
Tracheoesophageal fistula
Transient tachypnea of the newborn

Systemic Inflammatory Response Syndrome

The clinical manifestations of infection depend on the virulence of the infecting organism and the body's inflammatory response. The term *systemic inflammatory response syndrome* (SIRS) is most frequently used to describe this unique process of infection and the subsequent systemic response (see Chapters

88). In addition to infection, SIRS may result from trauma, hemorrhagic shock, other causes of ischemia, necrotizing enterocolitis, and pancreatitis.

Patients with SIRS have a spectrum of clinical symptoms that represent progressive stages of the pathologic process. In adults, SIRS is defined by the presence of 2 or more of the following: (1) fever or hypothermia, (2) tachycardia, (3) tachypnea, and (4) abnormal white blood cell (WBC) count or an increase in immature forms. In neonates and pediatric patients, SIRS manifests as temperature instability, respiratory dysfunction (altered gas exchange, hypoxemia, acute respiratory distress syndrome), cardiac dysfunction (tachycardia, delayed capillary refill, hypotension), and perfusion abnormalities (oliguria, metabolic acidosis) (Table 129.8). Increased vascular permeability results in capillary leak into peripheral tissues and the lungs, with resultant peripheral and pulmonary edema. DIC results in the more severely affected cases. The cascade of escalating tissue injury may lead to multisystem organ failure and death.

Table 129.8

Definitions of Systemic Inflammatory Respiratory Response Syndrome (SIRS) and Sepsis in Pediatric Patients

SIRS: the systemic inflammatory response to a variety of clinical insults, manifested by 2 or more of the following conditions:

- Temperature instability <35°C (95°F) or >38.5°C (101.3°F)
- Respiratory dysfunction:
  - Tachypnea >2 SD above the mean for age
  - Hypoxemia ($\mathrm{PaO_2}$ <70 mm Hg on room air)
- Cardiac dysfunction:
  - Tachycardia >2 SD above the mean for age
  - Delayed capillary refill >3 sec
  - Hypotension >2 SD below the mean for age
- Perfusion abnormalities:
  - Oliguria (urine output <0.5 mL/kg/hr)
  - Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25)
  - Altered mental status

Sepsis: the systemic inflammatory response to an infectious process

From Adams-Chapman I, Stoll BJ: Systemic inflammatory response syndrome, *Semin Pediatr Infect Dis* 12:5–16, 2001.

Temperature Instability

Fever or hypothermia may be the only initial manifestation of serious infection in newborns. However, only approximately 50% of infected newborn infants have a temperature >37.8°C (100°F) (axillary) (see Chapter 202). Fever in newborn infants does not always signify infection; it may be caused by increased ambient temperature, isolette or radiant warmer malfunction, dehydration, CNS disorders, hyperthyroidism, familial dysautonomia, or ectodermal dysplasia. A single temperature elevation is infrequently associated with infection; fever sustained over 1 hr is more likely to be caused by infection. Most febrile infected infants have additional signs compatible with infection, although a focus of infection is not always apparent. Acute febrile illnesses occurring later in the neonatal period may be caused by urinary tract infection, meningitis, pneumonia, osteomyelitis, or gastroenteritis, in addition to sepsis, thus underscoring the importance of a diagnostic evaluation that includes blood culture, urine culture, lumbar puncture (LP), and other studies as indicated. Many agents may cause these late infections, including HSV, enteroviruses, respiratory syncytial virus (RSV), and bacterial pathogens. In premature infants, hypothermia or temperature instability requiring increasing ambient (isolette, warmer) temperatures is more likely to accompany infection.

Respiratory and Cardiovascular Symptoms

Early signs and symptoms of **pneumonia** may be nonspecific, including poor feeding, lethargy, irritability, cyanosis, temperature instability, and the overall impression that the infant is not well. Respiratory symptoms of increasing severity are grunting, tachypnea, retractions, flaring of the alae nasi, cyanosis, apnea, and progressive respiratory failure. If the infant is premature, signs of progressive respiratory distress may be superimposed on RDS or bronchopulmonary dysplasia (BPD). For infants on mechanical ventilation, the need to increase ventilator support may indicate infection. Although a common finding in neonatal sepsis, tachycardia is nonspecific. Bradycardia may also occur. Poor perfusion and hypotension are more sensitive indicators of sepsis but tend to be late findings. In a prospective national surveillance study, 40% of neonates with sepsis required volume expansion, and 29% required vasopressor support.

Signs of pneumonia on physical examination, such as dullness to percussion, change in breath sounds, and the presence of rales or rhonchi, are very difficult to appreciate in a neonate. Radiographs of the chest may reveal new infiltrates or an effusion, but if the neonate has underlying RDS or BPD, it is very difficult to determine whether the radiographic changes represent a new process or worsening of the underlying disease.

The progression of neonatal pneumonia can be variable. Fulminant infection is most frequently associated with pyogenic organisms such as GBS (see Chapter 211). Onset may occur during the 1st hours or days of life, with the infant often manifesting rapidly progressive circulatory collapse and respiratory failure. With early-onset pneumonia in premature infants, the clinical course and chest radiographs may be indistinguishable from those with severe RDS.

In contrast to the rapid progression of pneumonia caused by pyogenic organisms, an indolent course may be seen in nonbacterial infection. The onset can be preceded by upper respiratory tract symptoms or conjunctivitis. The infant may demonstrate a nonproductive cough, and the degree of respiratory compromise is variable. Fever is usually absent or low grade, and radiographic examination of the chest shows focal or diffuse interstitial pneumonitis or hyperinflation. Infection is generally caused by *C. trachomatis,* CMV, *Ureaplasma urealyticum,* or one of the respiratory viruses. Rhinovirus has been reported to cause severe respiratory compromise in infants, particularly those who are preterm. Although *Pneumocystis (carinii) jiroveci* was implicated in the past, its etiologic role is now in doubt, except in newborns infected with HIV.

Conjunctivitis

Conjunctival infection is relatively common and may be caused by a variety of organisms. The presentation includes periorbital swelling, conjunctival injection, and purulent conjunctival drainage. *C. trachomatis* and *Neisseria gonorrhea* are common causes; other gram-positive and gram-negative organisms are occasionally involved. *Pseudomonas aeruginosa* is an important pathogen in hospitalized VLBW infants and may be a precursor to invasive disease. Viral infections (e.g., HSV, adenovirus) are occasionally seen. Recognition of HSV infection is important to prevent corneal injury and dissemination to systemic sites.

Skin and Soft Tissue Infection

Cutaneous manifestations of infection include omphalitis, cellulitis, mastitis, and subcutaneous abscesses. Pustules likely indicate the presence of staphylococcal infection but must be distinguished from the vesicular rash of HSV infection. Staphylococcal pustulosis results in larger, pus-filled lesions 1 mm in diameter and often scattered around the umbilicus, whereas HSV infection often appears as tiny vesicles in crops, often on the scalp. **Ecthyma gangrenosum** indicates infection with *Pseudomonas* spp. and is rare except in VLBW infants. The presence of small, salmon-pink papules suggests *L. monocytogenes* infection. Mucocutaneous lesions suggest *Candida* spp. (see Chapter 261.1). Petechiae and purpura may be the result of systemic viral or bacterial infection.

Omphalitis

Omphalitis is a neonatal infection resulting from unhygienic care of the umbilical cord, which continues to be a problem, particularly in developing countries. The umbilical stump is colonized by bacteria from the maternal genital tract and the environment (see Chapter 125). The necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. Omphalitis may remain a localized infection or may spread to the abdominal wall, the peritoneum, the umbilical or portal vessels, and the liver. Abdominal wall cellulitis or **necrotizing fasciitis** , with associated sepsis and a high mortality rate, may develop in infants with omphalitis. Prompt diagnosis and treatment are necessary to avoid serious complications. *Staphylococcus aureus* and gram-negative organisms are common pathogens involved.

Tetanus

Neonatal tetanus remains a serious infection in resource-limited countries (see Chapter 238). It results from unclean delivery and unhygienic management of the umbilical cord in an infant born to a mother who has not been immunized against tetanus. The surveillance case definition of neonatal tetanus requires the ability of a newborn to suck at birth and for the 1st few days of life, followed by an inability to suck. Neonatal tetanus typically occurs in infants 5-7 days after birth (range: 3-24 days), difficulty swallowing, spasms, stiffness, seizures, and death. **Bronchopneumonia** , presumably resulting from aspiration, is a common complication and cause of death. Neonatal tetanus can be prevented by immunizing mothers before or during pregnancy and by ensuring a clean delivery, sterile cutting of the umbilical cord and proper cord care after birth.

Laboratory Findings

Maternal history and infant signs should guide diagnostic evaluation (Table 129.9). Additionally, signs of systemic infection in newborn infants may be unrevealing, so laboratory investigation plays a particularly important role in diagnosis. Cultures and cell counts are obtained from blood and urine. CSF should be sent for Gram stain, routine culture, cell count with differential, and protein/glucose concentrations. Surface swabs, blood, and CSF are often obtained for HSV testing. Except for culture and directed pathogen testing, no single laboratory test is completely reliable for diagnosis of invasive infection in the newborn. Complete blood count may demonstrate elevated or decreased WBC count, often with a shift toward more immature forms. Thrombocytopenia can be seen in systemic bacterial or viral infection. Hyponatremia, acidosis, and other electrolyte abnormalities can be seen. Hyperbilirubinemia is nonspecific but may be an indication of systemic infection. Elevated serum transaminases may be a clue to systemic HSV or enterovirus infection.

Table 129.9

Evaluation of a Newborn for Infection or Sepsis

HISTORY (SPECIFIC RISK FACTORS)

- Maternal infection during gestation or at parturition (type and duration of antimicrobial therapy):
    - Urinary tract infection
    - Chorioamnionitis
- Maternal colonization with group B streptococci, *Neisseria gonorrhoeae* , herpes simplex
- Low gestational age/birthweight
- Multiple birth
- Duration of membrane rupture
- Complicated delivery
- Fetal tachycardia (distress)
- Age at onset (in utero, birth, early postnatal, late)
- Location at onset (hospital, community)
- Medical intervention:
    - Vascular access
    - Endotracheal intubation
    - Parenteral nutrition
    - Surgery

EVIDENCE OF OTHER DISEASES *

- Congenital malformations (heart disease, neural tube defect)
- Respiratory tract disease (respiratory distress syndrome, aspiration)
- Necrotizing enterocolitis
- Metabolic disease (e.g., galactosemia)

EVIDENCE OF FOCAL OR SYSTEMIC DISEASE

- General appearance, neurologic status
- Abnormal vital signs

Organ system disease
Feeding, stools, urine output, extremity movement
LABORATORY STUDIES
Evidence of Infection
Culture from a normally sterile site (blood, CSF, other)
Demonstration of a microorganism in tissue or fluid
Molecular detection (blood, urine, CSF) by specific PCR and/or 16S ribosomal DNA
Maternal or neonatal serology (syphilis, toxoplasmosis)
Evidence of Inflammation
Leukocytosis, increased immature/total neutrophil count ratio
Acute-phase reactants: C-reactive protein, erythrocyte sedimentation rate, procalcitonin
Cytokines: interleukin-6, interleukin-B, tumor necrosis factor
Pleocytosis in CSF or synovial or pleural fluid
Disseminated intravascular coagulation: fibrin degradation products, D-dimer
Evidence of Multiorgan System Disease
Metabolic acidosis: pH, P_{CO_2}
Pulmonary function: P_{O_2}, P_{CO_2}
Renal function: blood urea nitrogen, creatinine
Hepatic injury/function: bilirubin, alanine transaminase, aspartate transaminase, ammonia, prothrombin time, partial thromboplastin time
Bone marrow function: neutropenia, anemia, thrombocytopenia

[*] Diseases that increase the risk of infection or may overlap with signs of sepsis.

CSF, Cerebrospinal fluid; PCR, polymerase chain reaction.

Various serum biomarkers have been investigated for their ability to identify infants with **serious bacterial infection** (SBI). An immature-to-total phagocyte count (I/T ratio) (≥0.2) has the best sensitivity of the neutrophil indices for predicting neonatal sepsis. After the newborn period, serum C-reactive protein (CRP) and procalcitonin have demonstrated reasonable sensitivity and specificity for SBI. CRP may be monitored in newborn infants to assess response to therapy. Their value in the initial diagnosis of sepsis in the newborn period has yet to be clarified, as does the value of these biomarkers in determining optimal length of empirical therapy in infants with negative cultures. Cytokines (both proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-α and antiinflammatory cytokines such as IL-4 and IL-10), chemokines, and other biomarkers are increased in infected infants. Elevations of serum amyloid A and the cell surface antigen CD64 also have high sensitivity for identifying infants with sepsis. Chest radiography is generally not indicated in infants without signs of respiratory infection.

Table 129.9 and 129.10 list clinical features and laboratory parameters that are useful in the diagnosis of neonatal infection or sepsis.

Table 129.10

Culture-Based and Non–Culture-Based Diagnostics for

Neonatal Sepsis

CATEGORY	PARAMETER	OPTIMAL TIMING, VOLUME OF SPECIMEN, ROUTINE/INVESTIGATIONAL*	APPLICABILITY FOR NEONATAL SEPSIS
CULTURE BASED			
Blood	Culture	>1 mL of whole blood, from 2 sites	Gold standard for bacteremia
CSF	Culture	When clinically feasible	Optimize antimicrobial therapy
Urine	Culture	>72 hr of life	Not useful for EOS; potential benefits for LOS
Tracheal aspirate	Culture	Neonates with endotracheal tube in place and signs of progressive respiratory distress	Usually reflects colonization
NON–CULTURE BASED			
Immune function	MHC II TNF-α	Investigational Investigational	Both decreased in chorioamnionitis and sepsis
Neutrophil indices	Neutropenia Absolute neutrophil count Absolute immature neutrophil count	After 12 hr of life Consider GA, delivery mode, altitude, arterial versus venous sampling, time since birth	Neutropenia better predictor for sepsis than leukocytosis
Neutrophil markers	CD64	Elevated for 24 hr after infection Requires 50 µL blood Results within hours Investigational	Cut points between 2.38 and 3.62 optimal sensitivity, specificity, and NPV for EOS
Platelet count	Thrombocytopenia and thrombocytosis	Late findings; slow to respond	Thrombocytopenia associated with fungal infection
CSF cell count	CSF WBC	Uninfected neonates: mean 10 cells/mm^3 ; range up to 20 cells/mm^3	Does not predict culture-proven meningitis
CSF chemistries	CSF protein CSF glucose	Term <100 mg/dL Preterm higher; 70–80% of serum glucose	Elevated in fungal meningitis Low glucose specific for bacterial meningitis
Acute phase reactants	CRP Procalcitonin	8–24 hr after infection 2–12 hr after infection	Good NPV Better sensitivity but less specificity than CRP
Sepsis panels/scores		After 24 hr of life Investigational	Most useful for NPV and discontinuation of antimicrobial therapy

[*] *Investigational* refers to an assay or parameter that is undergoing evaluation for clinical use and applicability.

CRP, C-reactive protein; CSF, cerebrospinal fluid; EOS, early-onset sepsis; GA, gestational age; LOS, late-onset sepsis; MHC II, major histocompatibility complex class II; NPV, negative predictive value; TNF, tumor necrosis factor; WBC, white blood cell count.

From Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis, *Am J Perinatol* 30(2):131–141, 2013.

General Approach to Management

In the absence of specific signs of focal infection, therapy for presumed infection in the neonate is often empirical and initiated on the basis of fever or hypothermia, listlessness, irritability, or apneic episodes. Antibiotics are chosen to cover the organisms typically causing neonatal sepsis, including GBS, gram-negative organisms, *Listeria* , and *Enterococcus* . Since the latter 2 organisms are intrinsically resistant to cephalosporins, ampicillin is generally included in the empirical treatment of infants with presumed neonatal infection (Table 129.11).

Table 129.11

Management and Prevention of Neonatal Sepsis

CONDITION	**THERAPY**	**ADDITIONAL CONSIDERATIONS**
EMPIRICAL MANAGEMENT		
Early-onset sepsis	Ampicillin + aminoglycoside 10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections	Consider a third-generation cephalosporin (cefotaxime preferred) or carbapenem for meningitis. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Late-onset sepsis	Vancomycin + aminoglycoside Duration dependent on pathogen and site	Alternatives to vancomycin may be considered based on local epidemiology and clinical presentation. Aminoglycoside-based regimen preferred to cephalosporin given reduced risk of resistance. Consider cephalosporin if meningitis suspected. Consider a carbapenem if third-generation cephalosporin recently received. Consider amphotericin for fungal etiologies. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
NONANTIMICROBIAL TREATMENT STRATEGIES		
Recombinant G-CSF Recombinant GM-CSF	Enhance neutrophil number and function, but no reduction in infection when administered as prophylaxis or improvement in survival when administered as therapy.	Insufficient evidence to support the clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections.
IVIG	Augments antibody-dependent cytotoxicity and improves neutrophilic function, *but* no evidence that IVIG in suspected or proven sepsis reduces death.	Insufficient evidence from 10 RCTs or quasi-RCTs to support use in neonates with confirmed or suspected sepsis.
PREVENTION STRATEGIES		

IAP	Administration of penicillin or ampicillin 4 hr before parturition	Successfully reduces rates of EOS caused by GBS No effect on LOS GBS
Fluconazole prophylaxis	Administration of weight-based dosing to neonates <1,500 g	Most beneficial in NICUs with high baseline rates of invasive candidiasis
BLF supplementation with a probiotic, *Lactobacillus rhamnosus* (GG)	BLF is a human milk glycoprotein with a role in innate immune response. LGG enhances the activity of lactoferrin.	BLF supplementation with and without LGG reduced the incidence of 1st LOS in 472 VLBW neonates in large randomized, double-blind RCT. Additional confirmatory studies warranted.

BLF, Bovine lactoferrin supplementation; EOS, early-onset sepsis; GBS, group B streptococcus; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IAP, intrapartum antimicrobial prophylaxis; IVIG, intravenous immune globulin, LGG, *Lactobacillus rhamnosus* GG; LOS, late-onset sepsis; NICUs, neonatal intensive care units; RCTs, randomized controlled trials; VLBW, very-low-birthweight.

Created with data from Carr R, Modi N, Doré C: G-CSF and GM-CSF for treating or preventing neonatal infections, *Cochrane Database Syst Rev* (3):CD003066, 2003; Brocklehurst P, Farrell B, King A, et al; INIS Collaborative Group: Treatment of neonatal sepsis with intravenous immune globulin, *N Engl J Med* 365:1201–1211, 2011; and Manzoni P, Decembrino L, Stolfi I, et al; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology: Lactoferrin and prevention of late-onset sepsis in the pre-term neonates, *Early Hum Dev* 86(Suppl 1):59–61, 2010.

Used with permission from Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. *Am J Perinatol* 30(2):131–141, 2013.

An empirical regimen for suspected early-onset sepsis in a term or late preterm infant is **ampicillin** , 150 mg/kg/dose intravenously (IV) every 12 hr, and **gentamicin** , 4 mg/kg/dose IV every 24 hr. This has long been a standard regimen for early-onset sepsis and provides coverage for the most prevalent organisms, predominantly GBS and gram-negative ones. Ampicillin plus **cefotaxime** (if available) or **cefepime** may be substituted if the patient presents with infection after discharge from the nursery, or when infection with ampicillin-resistant *E. coli* is suspected. **Ceftriaxone** may be substituted if premature infants are ≥41 wk postconception age; it may be used in term infants if they are not receiving intravenous calcium or do not have hyperbilirubinemia. There is concern this regimen may be associated with higher rates of mortality in NICU patients compared to ampicillin and gentamicin. Alterations to the standard regimen may be appropriate in some circumstances, such as suspected infection with *S. aureus* , in which case **vancomycin** may be substituted for ampicillin, and in environments where infections from antibiotic-resistant bacteria are prevalent.

Herpes simplex virus infection may present without cutaneous signs, in the absence of maternal history of infection, and in mothers receiving suppressive antiviral therapy. Therefore, management of the ill newborn requires a high index of suspicion for HSV infection. Surface swabs, blood, and CSF are obtained for HSV culture or PCR, and empirical acyclovir is often recommended while the results of these studies are pending (see Chapters 202 and 279).

Systemic infection caused by *Candida* spp. is a concern in hospitalized infants, particularly VLBW infants with central venous access catheters and prior antibiotic use. Empirical therapy for fungal infection is generally not recommended unless the patient fails to respond to broad-spectrum antibiotic therapy.

Definitive therapy is based on identification and susceptibility of the offending organism. In almost all circumstances, the *leas* t *broad* antibiotic with activity against the organism is chosen. Duration of therapy depends on the organism and the site of infection. In neonates with culture-proven sepsis, the usual course of therapy is 10 days. Longer treatment courses may be warranted if a specific focus of infection is identified (e.g., meningitis, osteomyelitis, septic arthritis). Antimicrobial therapy should be altered based on the susceptibility profile of the pathogen isolated. In infants with a negative blood culture but a clinical status that remains concerning for a systemic infection, antibiotic therapy can be extended for as long as a total of 5 to 10 days. Sepsis is unlikely in these infants if they remain well and the blood culture is sterile at 48 hr. Empirical antibiotic therapy should be discontinued after 48 hr in these neonates.

Prevention

Intrapartum antibiotics are used to reduce vertical transmission of GBS (Table 129.12), as well as to lessen neonatal morbidity associated with preterm labor and preterm premature rupture of membranes (see Figs. 211.2 and 211.3 in Chapter 211). With introduction of selective intrapartum antibiotic prophylaxis to prevent perinatal transmission of GBS, rates of early-onset neonatal GBS infection in the United States declined from 1.7/1,000 live births to 0.25/1,000. Intrapartum chemoprophylaxis does *not* reduce the rates of late-onset GBS disease and has no effect on the rates of infection with non-GBS pathogens (see Chapter 211). Of concern is a possible increase in gram-negative infections (especially *E. coli*) in VLBW and possibly term infants despite a reduction in early GBS sepsis by intrapartum antibiotics.

Table 129.12

Indications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset GBS Disease

INTRAPARTUM GBS PROPHYLAXIS INDICATED	INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy	GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)	Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: Delivery at <37 weeks' gestation* Amniotic membrane rupture ≥18 hr Intrapartum temperature ≥38.0°C (100.4°F) † Intrapartum NAAT ‡ positive for GBS	Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

* Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Chapter 211 .

† If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

‡ If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 wk gestation, amniotic membrane rupture ≥18 hr, or temperature ≥38.0°C/100.4°F) is present, intrapartum antibiotic prophylaxis is indicated.

GBS, Group B streptococcus; NAAT, nucleic acid amplification test.

From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, *MMWR Recomm Rep* 59(RR-10):1–36, 2010.

Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy during labor, along with rapid delivery of the infant, reduces the risk of early-onset neonatal sepsis. Vertical transmission of GBS and early-onset GBS disease is significantly reduced by selective intrapartum chemoprophylaxis (see Fig. 211.4). A number of candidate GBS vaccines are currently being studied. Neonatal infection with *Chlamydia* can be prevented by identification and treatment of infected pregnant women (see Chapter 253). Mother-to-child transmission of HIV is significantly reduced by maternal antiretroviral therapy during pregnancy, labor, and delivery, by cesarean delivery before rupture of membranes, and by antiretroviral treatment of the infant after birth (see Chapter 302).

Prevention of congenital and perinatal infections predominantly focuses on maternal health. The Centers for Disease Control and Prevention (CDC) recommends the following screening tests and treatment when indicated:

1. All pregnant women should be offered voluntary and confidential HIV testing at the first prenatal visit, as early in pregnancy as possible. HIV screening should be part of routine prenatal testing, unless the mother declines testing (opt-out screening). For women at high risk of infection during pregnancy (multiple sexual partners or STIs during pregnancy, intravenous drug use, HIV-infected partners), repeat testing in the third trimester is recommended. Rapid HIV screening is indicated for any women who presents in labor with an undocumented HIV status, unless she declines testing.
2. A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit. Repeat screenings early in the third trimester and again at delivery are recommended for women in whom syphilis test results in the first trimester were positive and for those at high risk for infection during pregnancy. Infants should not be discharged from the hospital unless the syphilis status of the mother has been determined at least once during pregnancy and preferably again at delivery.
3. Serologic testing for hepatitis B surface antigen (HBsAg) should be performed at the first prenatal visit, even if the woman has been previously vaccinated or tested. Women who were not screened prenatally, those who are at high risk for infection (multiple sexual partners, intravenous drug use, HBsAg-positive sex partner) and those with clinical hepatitis should be retested at the time of delivery.
4. A maternal genital culture for *C. trachomatis* should be performed at the first prenatal visit. Young women (<25 yr) and those at increased risk for infection (new or multiple partners during pregnancy) should be retested during the third trimester.
5. A maternal culture for *Neisseria gonorrhoeae* should be performed at the first prenatal visit. Those at high risk for infection should be retested in the third trimester.
6. All pregnant women at high risk for hepatitis C infection (intravenous drug use, blood transfusion or organ transplantation before 1992) should be screened for hepatitis C antibodies at the first prenatal visit.

7. Evidence does not support routine testing for bacterial vaginosis in pregnancy. For asymptomatic women at high risk for preterm delivery, testing may be considered. Symptomatic women should be tested and treated.
8. The CDC recommends universal screening for rectovaginal GBS colonization of all pregnant women at 35-37 wk gestation, and a screening-based approach to selective intrapartum antibiotic prophylaxis against GBS (Table 129.12) (see Figs. 211.2 and 211.3). Fig. 211.4 shows the approach to the infant born after intrapartum prophylaxis (see Chapter 211).

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CHAPTER 130

Healthcare-Acquired Infections

David B. Haslam

Premature and very-low-birthweight (VLBW) infants often have prolonged hospitalizations and are particularly prone to healthcare-acquired infection (**HAI**) because of their inefficient innate immunity, deficient skin barriers, presence of indwelling catheters and other devices, and prolonged endotracheal intubation (Table 130.1). HAIs are associated with increased length of hospitalization, increased cost of care, and significant morbidity and mortality.

Table 130.1

Definitions of Healthcare-Acquired Infections for Patients <12 Mo Old*

NOSOCOMIAL BLOODSTREAM INFECTIONS
Laboratory-Confirmed Bloodstream Infection (LCBI)
Must meet 1 of the following definitions:
• Recognized pathogen in 1 or more blood specimens (culture-based or non–culture-based microbiologic methods), performed for clinical diagnostic or therapeutic purposes *and* not related to infection at another site.
• Commensal organism (e.g., coagulase-negative staphylococci, diphtheroids, bacillus, viridans streptococci, aerococcus, micrococcus, propionibacterium), identified from 2 or more blood specimens obtained on separate instances (culture- or non–culture-based microbiologic methods), performed for clinical diagnostic or therapeutic purposes *and* not related to infection at another site *and* at least 1 of the following signs: (1) fever (temperature >38.0°C), (2) hypothermia (temperature <36.0°C), or (3) apnea or bradycardia.
Central Line–Associated Bloodstream Infection (CLABSI)
• LCBI (as defined above) *and*
• Central line or umbilical catheter in place for >2 days *and*
• Central line in place on day of or day before CLABSI diagnosis.
Pneumonia
• Two or more serial chest radiographs with new/progressive and persistent infiltrate, cavitation, consolidation, or pneumatoceles for patients with underlying pulmonary or cardiac disease (respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema) *or* 1 chest radiograph with the aforementioned abnormalities for patients without underlying pulmonary or cardiac disease *and*
• Worsening gas exchange *and*
• At least 3 of the following; (1) temperature instability; (2) white blood cell count <4,000/μL or >15,000/μL with

10% or more bands, (3) new-onset purulent sputum, change in character of sputum, increased respiratory secretions, or increased suctioning requirements; (4) physical examination findings consistent with increased work of breathing or apnea, wheezing, rales, or rhonchi; (5) cough; (6) bradycardia (<100 beats/min), and (7) tachycardia (>170 beats/min).
Ventilator-Associated Pneumonia (VAP)
• Pneumonia (as defined above) *and*
• Patient on ventilator for >2 days *and*
• Ventilator in place on day of or day before VAP diagnosis
URINARY TRACT INFECTION
Symptomatic Urinary Tract Infection (SUTI)
• At least 1 of the following symptoms: (1) fever (temperature >38.0°C), (2) hypothermia (temperature <36.0°C), (3) apnea, (4) bradycardia, (5) lethargy, (6) vomiting, or (7) suprapubic tenderness *and*
• Urine culture with no more than 2 species identified, at least 1 of which is present at $>10^5$ CFU/mL.
Asymptomatic Bacteremic Urinary Tract Infection (ABUTI)
• Urine culture with no more than 2 species identified, at least 1 of which is present at $>10^5$ CFU/mL *and*
• Bacteria identified in blood (culture-based or nonculture-based microbiologic method) that matches at least one of the bacteria present at more than 10^5 CFU/mL in urine.
Catheter–Associated Urinary Tract Infection:
• Urinary tract infection (as defined above, either SUTI or ABUTI) *and*
• Indwelling urinary catheter for >2 days *and*
• Urinary catheter in place on day of or day before urinary tract infection diagnosis.

[*] Centers for Disease Control and Prevention/National Healthcare Safety Network.

CFU, Colony-forming units.

Adapted from Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting, *Am J Infect Control* 36:309–332, 2008.

Incidence

The most common HAIs in the neonatal intensive care unit (NICU) are bloodstream infections, predominantly central line–associated bloodstream infections. Ventilator-associated pneumonia (VAP) is the next most common, followed by surgical site infection and catheter-associated urinary tract infection.

Approximately 11% of NICU patients develop nosocomial infection during their hospitalization; up to 25% of VLBW infants will have blood culture–proven sepsis during their hospitalization. Infection rates are highest among the most premature infants. Ventilator-associated pneumonia accounts for approximately 25% of HAIs.

Epidemiology

HAIs in the NICU are predominantly caused by gram-positive organisms. The largest fraction of **bloodstream infections (BSIs)** in the NICU are caused by coagulase-negative staphylococci (Table 130.2). Other agents that often cause HAIs in the newborn include *Staphylococcus aureus*, enterococci, gram-negative bacilli *(Escherichia coli, Klebsiella pneumoniae, Enterobacter* spp., *Pseudomonas aeruginosa*), and *Candida.* Viruses contributing to HAIs in the neonate include rotavirus, enteroviruses, hepatitis A virus (HAV), adenoviruses, influenza, respiratory syncytial virus (RSV), rhinovirus, parainfluenza, and herpes simplex virus (HSV).

Table 130.2

Distribution of Organisms Responsible for Late-Onset Sepsis

ORGANISM	VLBW INFANTS: NICHD NRN (%)		
	1991–1993	1998–2000	2002–2008
Incidence of late-onset sepsis	25	21	25
GRAM POSITIVE			
Staphylococcus, coagulase-negative	55	48	53
Staphylococcus aureus	9	8	11
Enterococcus /group D streptococcus	5	3	4
Group B streptococcus	2	2	2
Other	2	9	7
GRAM NEGATIVE			
Enterobacter	4	3	3
Escherichia coli	4	5	5
Klebsiella	4	4	4
Pseudomonas	2	3	2
Other	4	1	2
Fungi			
Candida albicans	5	6	5
Candida parapsilosis			
Other	2	2	1

VLBW, Very-low-birthweight (≤1,500 g); NICHD NRN, National Institutes of Child Health and Human Development Neonatal Research Network.

Data from (1) 1991–1993: Stoll BJ, Gordon T, Korones SB, et al: Late-onset sepsis in very low birth weight neonates: a report from the NICHD NRN, *J Pediatr* 129:63–71, 1996; (2) 1998–2000: Stoll BJ, Hansen N, Fanaroff AA, et al: Late-onset sepsis in very low birth weight neonates: the experience of the NICHD NRN, *Pediatrics* 110:285–291, 2002; (3) 2002–2008: Boghossian NS, Page GP, Bell EF, et al: Late-onset sepsis in very low birth weight infants from singleton and multiple gestation births, J Pediatr 162:1120–1120, 2015.

Adapted from Ramasethu J. Prevention and treatment of neonatal nosocomial infections, *Matern Health Neonatol Perinatol* 3(5), 2017.

Bacteria responsible for most cases of nosocomial **pneumonia** typically include staphylococcal species, gram-negative enteric aerobes, and occasionally, *P. aeruginosa*. Fungi are responsible for an increasing number of systemic infections, usually acquired during prolonged hospitalization of preterm neonates. Respiratory viruses cause isolated cases and outbreaks of nosocomial pneumonia. These viruses, usually endemic during the winter months and acquired from infected hospital staff or visitors to the nursery, include RSV, parainfluenza virus, influenza viruses, and adenovirus.

Pathogenesis

Colonization of the skin, oropharynx, or gastrointestinal (GI) tract is an important precursor to infection in hospitalized infants. Premature infants may first be exposed to pathogenic organisms from a parent or more frequently from the hospital environment. Hospitalized infants are more likely to be colonized with *Staphylococcus aureus* , pathogenic gram-negative bacteria, and *Candida* than are infants in the community setting. Antibiotic exposure, indwelling devices, and frequent contact with contaminated medical equipment or healthcare providers all likely contribute to high rates of pathogen colonization. Following colonization, organisms may gain access to the bloodstream directly through damaged skin or central venous catheters. Recent evidence suggests the intestine is an important reservoir for invasive organisms, which may transit directly from the gut to the bloodstream. Oropharyngeal colonization with subsequent aspiration into the lower respiratory tract is thought to be the major route of infection in infants with ventilator-associated pneumonia.

Gestational age and birthweight are the most important risk factors for HAI. Prolonged use of central venous or umbilical catheters, exposure to broad-spectrum antibiotics, parenteral nutrition, and high nurse-to-patient ratios are other documented risk factors. These factors may alter the patient's endogenous microbial community, placing the infant at risk for colonization with pathogenic organisms.

Types of Infection

Central Line–Associated Bloodstream Infection

Central venous catheters have become an essential component of the care of critically ill newborns. Presence of a percutaneous or umbilical catheter introduces risk for infection and thrombosis. Central line–associated bloodstream infection (**CLABSI**) is the most common HAI in NICUs, imposing significant burden on the affected infant and on healthcare systems. Each episode has an attributable mortality of 4–20%. Infants with CLABSI subsequently have increased requirement for NICU stay, mechanical ventilation, and increased rates of bronchopulmonary dysplasia and necrotizing enterocolitis. The median estimated additional cost per CLABSI episode is $42,609, and hospitalization is prolonged for a median of 24 days.

Coagulase-negative staphylococci (CoNS) are the most common cause of CLABSI, accounting for approximately half of cases. CoNS are much more likely to cause clinically evident sepsis in VLBW infants than in term infants of comparable postnatal age, despite the organism's low pathogenic potential. Isolation of the organism from blood culture may represent contamination from the infant's or healthcare worker's skin, and blood cultures should be obtained from both peripheral and central venous sites. If both yield CoNS, the likelihood of true infection is high, whereas a single positive is considered questionable. In practice, often a single culture is obtained, and antibiotics are initiated before availability of a 2nd culture. In this circumstance, clinical judgment is often used to assess the need for targeted therapy. *S. aureus* , *Enterococcus* spp., and gram-negative rods account for most of the remaining CLABSIs during the 1st mo of hospitalization. Thereafter, *Candida* spp. become more prevalent, caused at least in part by their enrichment after broad-spectrum antibiotic exposure.

CLABSIs are generally thought to result from contamination of the central venous catheter, predominantly at the connecting hub or the skin entry site. An association has been shown between density of hub colonization and risk for CLABSI. Prevention of CLABSI is aimed at reducing contamination of these sites. BSI may also result from direct transit from the GI tract or other cutaneous or mucosal surfaces, analogous to recently defined **mucosal barrier injury–associated** BSIs. The contribution of mucosal sites to direct invasive infection remains to be clarified but has implications for infection prevention.

Healthcare-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is overall the 2nd most common HAI in neonatal units, although reported VAP rates vary widely (0.2-1.6 per 1,000 ventilator days). There is also variability in diagnosis of VAP, which consists of clinical, radiographic, and laboratory criteria, some of which are subjective or may be seen in noninfectious circumstances. The National Healthcare Safety Network and Centers for Disease Control and Prevention (CDC) definition of VAP requires at least 48 hr of mechanical ventilation accompanied by new and persistent radiographic infiltrates after the initiation of mechanical ventilation. In addition to these criteria, infants <1 yr old must exhibit worsening gas exchange and at least 3 of the following: (1) temperature instability with no other recognized cause; (2) leukopenia (white blood cell count <4,000/mm^3); (3) change in the character of sputum of increased respiratory secretions or suctioning requirements; (4) apnea, tachypnea, nasal flaring, or grunting; (5) wheezing, rales, rhonchi, or cough; or (6) bradycardia (<100 beats/min) or tachycardia (>170 beats/min). In practice, the diagnosis is often made on the basis of increased need for supplemental oxygen or new infiltrates on chest radiograph; either of which may be caused by factors other than infection. Further complicating the diagnosis of VAP, secretions aspirated from the airways of mechanically ventilated children often yield multiple organisms in culture, whether or not they have signs of infection. The most commonly reported organisms associated with VAP are gram-negative rods (including *Pseudomonas*), *S. aureus* , and *Enterococcus* . The source of infecting organisms is generally thought to be the infant's oropharynx, although contaminated respiratory equipment and tracheal suction catheters are occasionally implicated.

Skin and Soft Tissue Infection

Cutaneous infections are relatively common among hospitalized premature infants. Simple abrasions of frail skin, frequent vascular access, and surgical procedures predispose the skin to infection. *Staphylococcus aureus* is the most frequently isolated organism. **Methicillin-susceptible *S. aureus* (MSSA)** predominates despite increases in **methicillin-resistant *S. aureus* (MRSA)** infection rates during the last 2 decades. Gram-negative organisms and *Candida* spp. may occasionally be seen, particularly after intraabdominal surgery.

Invasive Fungal Infection

Up to 3% of VLBW and 20% of extremely-low-birthweight (ELBW) infants will develop invasive fungal infection, with a cumulative incidence of 1–4% of all

NICU admissions (see Chapter 261.1). Colonization, a requisite for subsequent infection is common after the 1st wk of hospitalization and is seen in >60% of infants at 1 mo in the NICU. *Candida albicans* accounts for most cases of colonization and infection, although *C. parapsilosis* and *C. glabrata* are prevalent in some NICUs. As with other BSIs, invasive candidiasis is often central venous catheter associated. In addition to gestational age and birthweight, risk factors include exposure to ≥2 antibiotics, receipt of H_2 blockers, parenteral nutrition (especially use of lipid emulsifiers), lack of enteral feeding, and GI surgery. Invasive candidiasis is associated with greater morbidity and mortality than invasive bacterial infection, with mortality rates >20% and long term developmental abnormalities seen in >50% of surviving infants.

Viral Infection

Nosocomially acquired viral infections receive less attention than invasive bacterial or fungal infections but can account for significant morbidity. Approximately 10% of reported episodes in NICUs are caused by viruses. The most common viral agent is **rotavirus** , followed by RSV, enterovirus, HAV, adenovirus, and influenza. Consistent with the viral etiology, GI illness is the most frequently reported virus-associated condition. In most cases of viral infection in the NICU, the source cannot be identified, making it difficult to focus preventive efforts. Response to viral outbreaks in the NICU can include enhanced patient surveillance, patient cohorting, and occasionally, closure of the affected patient care area.

Prevention

Hand Hygiene

Hand hygiene is the single most important intervention proven to prevent nosocomial infections, whereas *lack* of hand hygiene is one of the strongest correlates of HAI. Colonization with pathogenic organisms is known to increase with longer time spent performing patient interactions. The CDC and the World Health Organization have published guidelines on timing and choice of sanitizing agent during patient care (Table 130.3). Alcohol-based hand sanitizers are at least as effective as chlorhexidine-containing soaps in decreasing bacterial burden but have poor activity against certain important pathogens, including

Clostridium difficile , HAV, rotavirus, enterovirus, and adenovirus. Time constraints and workload are considered important barriers to adequate hand care, and recent evidence suggests that shortening the application time of alcohol-based sanitizers to 15 sec may improve frequency of use without impacting antimicrobial efficacy. Observational studies suggest that monitoring with personal or group-level feedback is among the most effective means to improve hand hygiene compliance.

Table 130.3

U.S. Centers for Disease Control and Prevention (CDC) Guidelines for Hand Hygiene

• When hands are visibly dirty or contaminated with proteinaceous material or are visibly soiled with blood or other body fluids, wash hands with either a nonantimicrobial soap and water or an antimicrobial soap and water (categorization of recommendation: IA)
• If hands are not visibly soiled, use an alcohol-based hand rub for routinely decontaminating hands in all other clinical situations described below (categorization of recommendation: IA). Alternatively, wash hands with an antimicrobial soap and water in all clinical situations described below (categorization of recommendation: IB).
• Decontaminate hands before having direct contact with patients (categorization of recommendation: IB).
• Decontaminate hands before donning sterile gloves when inserting an intravascular catheter (categorization of recommendation: IB).
• Decontaminate hands before inserting indwelling urinary catheters, peripheral vascular catheters, or other invasive devices that do not require a surgical procedure (categorization of recommendation: IB).
• Decontaminate hands after contact with a patient's intact skin (categorization of recommendation: IB).
• Decontaminate hands after contact with body fluids or excretions, mucous membranes, nonintact skin, and wound dressings if hands are not visibly soiled (categorization of recommendation: IB).
• Decontaminate hands if moving from a contaminated body site to a clean body site during patient care (categorization of recommendation: II).
• Decontaminate hands after contact with inanimate objects (including medical equipment) in the immediate vicinity of the patient (categorization of recommendation: II).
• Decontaminate hands after removing gloves (categorization of recommendation: IB).
• Before eating and after using a restroom, wash hands with a nonantimicrobial soap and water or with antimicrobial soap and water (categorization of recommendation: IB).
• Antimicrobial-impregnated wipes may be considered as an alternative to washing hands with nonantimicrobial soap and water. Because they are not as effective as alcohol-based hand rubs or washing hands with an antimicrobial soap and water for reducing bacterial counts on the hands of healthcare workers, they are not a substitute for hand antisepsis (categorization of recommendation: IB).
• Wash hands with nonantimicrobial soap and water or with antimicrobial soap and water if exposure to *Bacillus anthracis* is suspected or proven (categorization of recommendation: II).
• No recommendation can be made regarding the routine use of non–alcohol-based hand rubs for hand hygiene in healthcare settings. Unresolved issue.
CDC/Healthcare Infection Control Practices Advisory Committee System for Categorizing Recommendations
Category IA: Strongly recommended for implementation and strongly supported by well-designed experimental, clinical, or epidemiologic studies.
Category IB: Strongly recommended for implementation and supported by certain experimental, clinical, or epidemiologic studies and using theoretical rationale.
Category IC: Required for implementation, as mandated by federal or state regulation or standard.

Category II: Suggested for implementation and supported by suggestive clinical or epidemiologic studies or a theoretic rationale.
No recommendation; Unresolved issue: Practices for which insufficient evidence or no consensus regarding efficacy exists.

Adapted from Boyce JM, Pittet D; Healthcare Infection Control Practices Advisory Committee: Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HIPAC/SHEA/APIC/IDSA Hand Hygiene Task Force, *Am J Infect Control* 30(8):S1–S46, 2002.

Central Line–Associated Bloodstream Infection

Hand hygiene is the most important intervention to prevent CLABSI in the NICU. “Care bundles” have been studied in numerous neonatal populations and found to reduce catheter-related infection. **Insertion bundles** include a combination of barrier precaution, hand hygiene standards, skin disinfection, dedicated teams and equipment, catheter site evaluation, checklists, and empowerment to stop the procedure. **Maintenance bundles** include recommendations for aseptic technique when accessing the line, dressing change protocols, and prompt removal when the line is no longer required (Table 130.4).

Table 130.4

Interventions to Prevent Catheter-Related Infections

• Perform effective hand hygiene before and after any interaction with the catheter.
• Use sterile gowns, gloves, drapes, cap, and mask during catheter insertion.
• Disinfect skin with appropriate agent (chlorhexidine is most often used in United States; other disinfectants may be as effective).
• Use a transparent, semipermeable dressing to cover catheter site.
• Change the dressing when soiled or loose.
• Scrub access point with alcoholic chlorhexidine for at least 15 sec.
• Use aseptic nontouch technique to access the catheter.
• Change administration sets no more frequently than 96 hr unless required by the infused product.
• Avoid use of systemic prophylactic antibiotics for catheter insertion.
• Evaluate daily, and remove central venous catheter when no longer required.
• Ensure all healthcare professionals who interact with the patient are educated on central line management.

Adapted from Taylor JE, McDonald SJ, Tan K: Prevention of central venous catheter–related infection in the neonatal unit: a literature review, *J Matern Fetal Neonatal Med* 28(10):1224–1230, 2015.

Ventilator-Associated Pneumonia

VAP prevention bundles have been applied to adult patients but are not readily adapted to premature infants. Thus far, few studies have demonstrated efficacy of infection control measures in preventing VAP in NICUs. A number of measures are believed to be helpful, including caregiver education, hand hygiene, donning of gloves when in contact with secretions, minimizing days of ventilation to the extent possible, suctioning the oropharynx, and removing condensate from the ventilator circuit.

Early Feeding and Human Milk

Several studies have demonstrated benefit to feeding infants maternal milk. Enteral feeding of human milk within 2-3 days of life is associated with decreased rates of necrotizing enterocolitis and nosocomial infection. Human milk contains a number of factors thought to contribute to beneficial effects, including secretory antibody, lactoferrin, phagocytes, and oligosaccharides that shape the neonatal microbial community. Interestingly, the benefits of human milk are not as evident when the milk comes from a donor other than the infant's mother, suggesting important compositional differences in maternal milk.

Antifungal Prophylaxis

Prophylactic administration of **fluconazole** during the 1st 6 wk of life reduces fungal colonization and invasive fungal infection in ELBW infants (<1000 g). In addition to the individual benefit afforded by prophylaxis for VLBW neonates, fluconazole prophylaxis may have a community impact by decreasing the overall fungal burden of a NICU. Results from more than 14 trials at multiple institutions with 3,100 neonates suggests that fluconazole prophylaxis decreases colonization of the urine, GI tract, and integument, without promoting the development of resistance and without adverse effects. Based on an annual U.S. preterm birth cohort of approximately 30,000 VLBW infants, fluconazole prophylaxis could prevent an estimated 2,000-3,000 cases of invasive candidiasis, 200-300 deaths, and the adverse neurodevelopmental outcomes of invasive candidiasis in 400-500 infants per year. Differing baseline rates of fungal infections, practices related to central venous catheter removal, severity of illness, and administration practices for broad-spectra antimicrobials make universal recommendations regarding prophylaxis challenging. A meta-analysis using patient-level data found that fluconazole prophylaxis was effective at preventing colonization and invasive *Candida* infection and was not associated with adverse drug reactions or increased rates of fluconazole resistance.

Neonatal practices that may reduce the risks of invasive candidiasis include limited use of broad-spectrum antimicrobials, use of an aminoglycoside instead of a cephalosporin for empirical therapy when meningitis or antimicrobial resistance is not suspected, limitation of postnatal corticosteroid use in VLBW infants, early enteral feeding, and establishment of the neonatal gut microbiome with human milk feeding.

Nasal Decolonization

Staphylococcus aureus is the 2nd most common cause of HAI in neonatal units. MSSA generally causes more invasive infections than MRSA, but most prevention efforts have been focused on MRSA. Several studies have documented MRSA transmission within the NICU and have identified nasal colonization as an important risk factor for subsequent invasive infection. Various measures have been implemented in attempt to decrease transmission and invasive infection, including contact precautions, cohorting and isolation, and **nasal decolonization** with **mupirocin** . Contact precautions have been associated with decreased rates of MRSA infection in NICU patients. Studies in other patient populations (predominantly adults undergoing peritoneal dialysis) found increased rates of gram-negative infection in those receiving mupirocin treatment. However, a recent multicenter study of mupirocin use in the NICU found a 64% decrease in gram-positive infections, with no change in gram-negative infection rates, among 384 treated infants.

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CHAPTER 131

Congenital and Perinatal Infections

Felicia A. Scaggs Huang, Rebecca C. Brady

Infections are a frequent and important cause of neonatal morbidity and mortality. **Congenital** or **intrauterine** infections (i.e., those transmitted across the placenta) and **perinatal** infections (i.e., those transmitted from the mother to the fetus or newborn infant during the birth process) represent 2 major routes of neonatal infection.

131.1

Congenital Infections

Felicia A. Scaggs Huang, Rebecca C. Brady

As many as 2% of fetuses are infected in utero; disease can be acquired prenatally from a wide variety of etiologic agents, including bacteria, viruses, fungi, and protozoa. Clinical manifestations can range from asymptomatic or subclinical to life-threatening disease. History and physical examination findings provide insight into the best approach for this immunologically immature population. (See Fig. 129.2 and Table 129.2 in Chapter 129 .)

General Approach

Infectious as well as noninfectious processes, such as underlying congenital heart disease, genetic disorders, and inborn errors of metabolism, should be considered in the differential diagnosis of congenital and perinatal infections. Because maternal infection is a prerequisite for infection in the fetus, a thorough history is essential to assess the mother for her symptoms, travel, diet, medication use, occupational exposures, and any **sexually transmitted infections (STIs)** during pregnancy. Clinical manifestations are varied and overlap for many of the pathogens causing intrauterine infection. Laboratory testing and/or radiologic imaging is often required to confirm the diagnosis. Treatment depends on the specific pathogen and can range from symptomatic management with close follow-up for long-term sequelae to targeted antimicrobial therapy.

Pathogenesis

The route and timing of infection can provide helpful clues as to the potential infectious etiology (Fig. 131.1 and Table 131.1). First-trimester infection may alter embryogenesis and result in malformations of the heart and eyes, as seen in congenital rubella syndrome. Third-trimester infection (e.g., congenital toxoplasmosis) can result in active infection with signs of hepatomegaly, splenomegaly, and generalized lymphadenopathy at birth. Infections that occur late in gestation (e.g., congenital syphilis) may lead to a delay in clinical manifestations until weeks to years after birth.

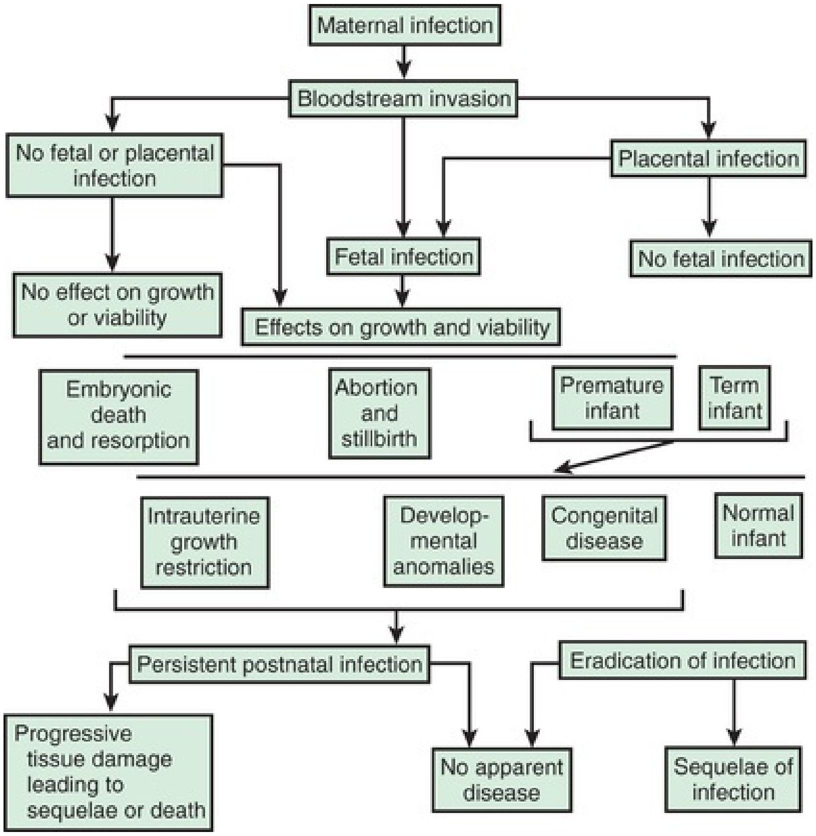
Maternal infection
Bloodstream invasion
No fetal or placental infection
Placental infection
Fetal infection
No fetal infection
No effect on growth or viability
Effects on growth and viability
Embryonic death and resorption
Abortion and stillbirth
Premature infant
Term infant
Intrauterine growth restriction
Develop-mental anomalies
Congenital disease
Normal infant
Persistent postnatal infection
Eradication of infection
Progressive tissue damage leading to sequelae or death
No apparent disease
Sequelae of infection

FIG. 131.1 Pathogenesis of hematogenous transplacental infections. (Adapted from Klein JO, Remington JS: Current concepts of infections of the fetus and newborn infant. In Remington JS, Klein JO, editors: *Infectious diseases of the fetus and newborn infant,* ed 5, Philadelphia, 2002, Saunders.)

Table 131.1

Specific Agents in Effects of Transplacental Fetal Infection on the Fetus and Newborn Infant

ORGANISM	DISEASE				
	Prematurity	**Intrauterine Growth Restriction/Low Birthweight**	**Developmental Anomalies**	**Congenital Disease**	**Persistent Postnatal Infection**
Viruses	CMV HSV Rubeola Smallpox HBV HIV*	CMV Rubella VZV* HIV*	CMV Rubella VZV Coxsackievirus B* HIV* Zika	CMV Rubella VZV HSV Mumps* Rubeola Vaccinia Smallpox Coxsackievirus	CMV Rubella VZV HSV HBV HIV Zika

				B Poliovirus HBV HIV LCV Parvovirus	
Bacteria	*Treponema pallidum* *Mycobacterium tuberculosis* *Listeria monocytogenes* *Campylobacter fetus* *Salmonella typhi*			*T. pallidum* *M. tuberculosis* *L. monocytogenes* *C. fetus* *S. typhi* *Borrelia burgdorferi*	*T. pallidum* *M. tuberculosis*
Protozoa	*Toxoplasma gondii* *Plasmodium*[*] *Trypanosoma cruzi*	*T. gondii* *Plasmodium* *T. cruzi*		*T. gondii* *Plasmodium* *T. cruzi*	*T. gondii* *Plasmodiu*

[*] Association of effect with infection has been suggested and is under consideration.

CMV , Cytomegalovirus; *HBV* , hepatitis B virus; *HIV* , human immunodeficiency virus; *HSV* , herpes simplex virus; *LCV* , lymphocytic choriomeningitis virus; *VZV* , varicella-zoster virus.

From Maldonado YA, Nizet V, Klein JO, et al: Current concepts of infections of the fetus and newborn infant. In Wilson CB, Nizet V, Maldonado Y, et al, editors: *Remington and Klein's infectious diseases of the fetus and newborn,* ed 8, Philadelphia, 2016, Elsevier (Table 1-5).

Intrauterine infection from cytomegalovirus (CMV), *Treponema pallidum* , *Toxoplasma gondii* , rubella virus, varicella-zoster virus (VZV), and human parvovirus B19 may cause minimal or no symptoms in the mother but still may be transmitted across the placenta to the fetus. The presence of maternal antibodies to rubella prevents infection, but transmission of CMV can occur despite preexisting antibodies. Regardless of the mother's immune status, the placenta may act as a barrier, and the fetus may or may not be infected. If infection occurs, signs may or may not be noted in the fetus during pregnancy. Infection can result in spontaneous abortion, congenital malformation, intrauterine growth restriction (IUGR), premature birth, stillbirth, acute or delayed disease in the neonate, or asymptomatic persistent infection with sequelae later in life.

Clinical Manifestations

The clinical manifestations of intrauterine infections can range from asymptomatic to severe multiorgan system complications. For some agents (e.g., CMV, *T. pallidum*), ongoing injury after birth leads to late sequelae. The specific clinical signs in the newborn period are usually not sufficient to make a definitive diagnosis but are useful to guide more specific laboratory testing. Symptomatic congenital infections often affect the central nervous system (CNS; brain and eyes) and the reticuloendothelial system (RES; bone marrow, liver, and spleen). Table 131.2 presents the clinical manifestations of some specific congenital infections. Congenital Zika virus infection has features that are rarely seen with other congenital infections (Table 131.3). No hematologic or hepatic laboratory abnormalities have been documented in infants with congenital Zika virus infection. Table 131.4 provides late sequelae of some congenital infections.

Table 131.2

Clinical Manifestations of Specific Neonatal Infections Acquired in Utero or at Delivery

Rubella Virus	**Cytomegalovirus**	***Toxoplasma gondii***	**Herpes Simplex Virus**	***Trepo***
Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Adenopathy Hearing deficits Myocarditis Congenital defects[*] Bone lesions[*] Glaucoma[*] Chorioretinitis *or* retinopathy[*] Cataracts[*] Microphthalmia	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Microcephaly[*] Intracranial calcifications[*] Hearing deficits Chorioretinitis *or* retinopathy Optic atrophy	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus[*] Microcephaly Maculopapular exanthems Intracranial calcifications[*] Myocarditis Bone lesions Chorioretinitis *or* retinopathy[*] Cataracts Optic atrophy Microphthalmia Uveitis	Hepatosplenomegaly Jaundice Pneumonitis Petechiae *or* purpura Meningoencephalitis Hydrocephalus Microcephaly Maculopapular exanthems Vesicles[*] Myocarditis Chorioretinitis *or* retinopathy Cataracts Conjunctivitis *or* keratoconjunctivitis[*]	He Ja Pn Pe M Ac M ex Bo Gl Ch ret Uv

[*] Has special diagnostic significance for this infection

From Maldonado YA, Nizet V, Klein JO, et al: Current concepts of infections of the fetus and newborn infant. In Wilson CB, Nizet V, Maldonado Y, et al, editors: *Remington and Klein's infectious diseases of the fetus and newborn,* ed 8, Philadelphia, 2016, Elsevier (Table 1-6).

Table 131.3

Syndromes in the Neonate Caused by Other Congenital Infections

ORGANISM	SIGNS
VZV	Limb hypoplasia, cicatricial skin lesions, ocular abnormalities, cortical atrophy
Parvovirus B19	Nonimmune hydrops fetalis
HIV	Severe thrush, failure to thrive, recurrent bacterial infections, calcification of basal ganglia
Zika virus	Microcephaly, lissencephaly, cerebellar hypoplasia, akinesia syndrome, macular scarring, retinal mottling, subcortical calcifications, hypertonia

HIV , Human immunodeficiency virus; *VZV* , varicella-zoster virus.

From Maldonado YA, Nizet V, Klein JO, et al: Current concepts of infections of the fetus and newborn infant. In Wilson CB, Nizet V, Maldonado Y, et al, editors: *Remington and Klein's infectious diseases of the fetus and newborn,* ed 8, Philadelphia, 2016, Elsevier (Table 1-7).

Table 131.4

Late Sequelae of Intrauterine Infections.

CLINICAL SIGN	INFECTION			
	Cytomegalovirus	**Rubella Virus**	***Toxoplasma gondii***	***Treponema pallidum***
Deafness	+	+	+	+
Dental/skeletal problems	+	+	(−)	+
Mental retardation	+	+	+	+
Seizures	+	+	+	+

+, Present; (−), rare or absent.

Diagnosis

During Pregnancy

The presence of IUGR or a physical abnormality on a prenatal fetal ultrasound raises concern for a congenital infection. The well-known acronym **TORCH** —***T*** *oxoplasma gondii* , **O** ther (*Treponema pallidum* , human parvovirus B19, HIV, Zika virus, others), **R** ubella, **C** ytomegalovirus, and **H** erpes simplex virus (HSV)—is a useful mnemonic. However, the routine ordering of TORCH serology panels is *not* recommended because the presence of a TORCH agent IgG antibody in the mother indicates past infection but does not establish if the infection occurred during pregnancy. Maternal IgM titers to *specific* pathogens are only moderately sensitive, and a negative result cannot be used to exclude infection.

In certain cases, a fetal blood sample with cordocentesis can be obtained and tested for total and pathogen-specific IgM assays, polymerase chain reaction assays (PCRs), or cultures. A total IgM concentration is a helpful screening test because a normal fetal IgM is <5 mg/dL, so any elevation in total IgM may indicate an underlying infection. A positive *pathogen-specific* IgM test is strongly suggestive of infection, but a negative test does not rule out the organism as the cause of the fetopathy. Amniotic fluid can also be obtained and sent for PCR or culture. The presence of CMV, *T. gondii* , or human parvovirus B19 in amniotic fluid indicates the fetus likely is infected but cannot establish the severity of disease. Although HSV is included in the TORCH acronym, it is rarely isolated from amniotic fluid and is rarely transmitted across the placenta from mother to fetus. Fetal blood can be collected to test for human parvovirus B19 IgM and PCR.

Newborn Infant

When a congenital infection is suspected because clinical signs are present, a complete blood count with differential and platelet count along with measurements of transaminases and total/direct bilirubin are routinely performed. Additional evaluations may include a dilated funduscopic examination, auditory brainstem response (ABR) for those failing the newborn hearing screen, and CNS imaging. If available, pathologic examination of the placenta may be informative. Infectious diseases consultation is valuable in guiding the evaluation.

Neonatal antibody titers for specific pathogens are often difficult to interpret because IgG is acquired from the mother by transplacental passage, and a positive result may reflect the mother's past infection and *not* infection of the newborn. Neonatal IgM antibody titers to specific pathogens have high specificity and only moderate sensitivity; a negative result cannot be used to exclude infection. Paired maternal and fetal-neonatal IgG antibody titers showing higher or rising infant IgG antibodies can diagnose some congenital infections (e.g., syphilis). Total cord blood IgM and IgA are not actively transported across the placenta to the fetus and are not specific for intrauterine infection.

Although viral culture has long been considered the standard for CMV and other viral infections, PCR is sensitive, specific, and now widely accepted. The Palo Alto Medical Foundation Toxoplasma Serology Laboratory (PAMF-TSL; Palo Alto, CA: www.pamf.org/serology/ ; telephone: (650) 853-4828; e-mail: toxolab@pamf.org) offers specialized tests and physician experts to aid in the diagnosis of congenital toxoplasmosis. If there is concern for congenital Zika virus infection, healthcare providers should refer to the Centers for Disease Control and Prevention (CDC) Guidance for US Laboratories Testing for Zika Virus Infection (www.cdc.gov/zika/laboratorie/lab-guidance.html) to assist in collecting and sending appropriate laboratory tests from the mother, newborn infant, placenta, and umbilical cord. Currently, testing for Zika virus with real-time reverse-transcription PCR (rRT-PCR) and IgM enzyme-linked immunosorbent assay (ELISA) from neonatal urine and serum specimens is recommended. However, the most reliable method of testing has not been established. In endemic areas, this workup should be done within 2 days of delivery because it is difficult to distinguish congenital from postnatal infection if testing is done later.

Specific Infectious Agents

Important congenital infections include more than the TORCH agents. The following is a list of pathogens that may be transmitted across the placenta and the respective chapters where they are discussed in more detail, including treatment.

Bacteria

- *Listeria monocytogenes* (Chapter 215)
- Syphilis (*Treponema pallidum*) (Chapter 245)

Viruses

- Cytomegalovirus (Chapter 282)
- Hepatitis B (Chapter 385)
- Hepatitis C (Chapter 385)
- Herpes simplex virus (Chapter 279)
- Human immunodeficiency virus (Chapter 302)
- Human parvovirus B19 (Chapter 278)
- Lymphocytic choriomeningitis virus (Chapter 298)
- Rubella (Chapter 274)

Varicella-zoster virus (Chapter 280)
Zika virus (Chapter 294.12)

Parasite

Toxoplasmosis (*Toxoplasma gondii*) (Chapter 316)

131.2

Perinatal Infections

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Perinatal infections are defined as those that are transmitted from the mother to the fetus or newborn infant during the birth process. Despite recommended universal screening of pregnant women for *Chlamydia trachomatis* and gonorrhea, transmission to the newborn still occurs. In addition to these STIs, other bacteria, viruses, and *Candida* spp. may cause perinatal infections. Similar to congenital infections, their presentation can range from asymptomatic to a sepsis-like syndrome.

General Approach

The general approach is similar to that for congenital infections and includes a detailed maternal history and a careful examination of the newborn **(** see Chapter 129). Many clinical syndromes overlap, and therefore laboratory testing is usually required to establish a specific microbiologic etiology and guide management decisions.

Pathogenesis

The human birth canal is colonized with aerobic and anaerobic bacteria. **Ascending amniotic infection** may occur with either apparently intact membranes or relatively brief duration of membrane rupture. Infectious agents can also be acquired as the newborn infant passes through the vaginal canal. This acquisition may result in either colonization or disease. Factors influencing which colonized infants will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies.

Chorioamnionitis has been historically used to refer to microbial invasion of the amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane for >18 hr. The term *chorioamnionitis* is confusing because it does not convey the spectrum of inflammatory or infectious diseases, it leaves out other intrauterine components that can be involved (e.g., decidua), and it results in significant variability in clinical practice, with the potential for a significant number of well newborns being exposed to antimicrobial agents. The term **intrauterine inflammation or infection at birth** , abbreviated as **Triple I** , has become more accepted because of the heterogeneous nature of conditions that can affect the mother and neonate (Table 131.5). Regardless of the definition used, prematurity (<37 wk) is associated with a greater risk of early-onset sepsis, especially with group B streptococcus.

Table 131.5

Classification of Triple I and Isolated Maternal Fever

TERMINOLOGY	FEATURES
Isolated maternal fever	Maternal oral temperature ≥39°C is considered a "documented fever." If the oral temperature is ≥38°C but ≤39°C, repeat the measurement in 30 min. If the repeat value is ≥38°C, it is considered a "documented fever."
Suspected Triple I	Fever without a clear source with *any* of the following:
	1. Baseline fetal tachycardia (>160 beats/min for 10 min) 2. Maternal WBC >15,000/mm^3 3. Purulent fluid from the cervical os
Confirmed Triple I	All the above (from suspected Triple I) with *any* of the following:
	1. Amniocentesis-proven infection through positive Gram stain 2. Low glucose of amniotic fluid or positive amniotic fluid culture 3. Placental pathology consistent with infection

Triple I, Intrauterine inflammation or infection at birth; WBC, white blood cell count.

Adapted from Higgins RD, Saade G; Chorioamnionitis Workshop participants: Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop, *Obstet Gynecol* 127(3):426–436, 2016.

Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (failure to breathe, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

Clinical Manifestations

Most perinatal infections present clinically during the 1st mo of life. Initial signs and symptoms may be either nonspecific or focal (see Chapter 129). Additional information on specific infectious agents and their management are reviewed in the chapters indicated below.

Specific Infectious Agents

Bacteria

Chlamydia trachomatis (Chapter 253)
Escherichia coli (Chapter 227)
Genital mycoplasmas (Chapter 251)
Group B streptococci (Chapter 211)
Neisseria gonorrhoeae (Chapter 219)
Syphilis (*Treponema pallidum*) (Chapter 245)

Viruses

Cytomegalovirus (Chapter 282)
Enteroviruses (Chapter 277)
Hepatitis B (Chapter 385)
Herpes simplex virus (Chapter 279)
Human immunodeficiency virus (Chapter 302)

Fungi

Candida spp. (Chapter 261)

Diagnosis

The maternal history provides important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, chorioamnionitis). STIs acquired by a pregnant woman, including syphilis, *N. gonorrhoeae* , and *C. trachomatis*, have the potential for perinatal transmission.

Neonates with perinatal infections often present with nonspecific symptoms and signs; therefore the general diagnostic evaluation for the ill neonate as discussed in Chapter 202 should be followed. Table 131.6 provides a summary of laboratory tests that are useful to diagnose specific perinatal infections.

Table 131.6

Laboratory Tests in the Diagnosis of Specific Perinatal Infections

INFECTIOUS AGENT	ACCEPTABLE SPECIMEN(S) FROM INFANT UNLESS OTHERWISE INDICATED	LABORATORY TEST
Chlamydia trachomatis	Conjunctiva, nasopharyngeal swab, tracheal aspirate	Culture using special transport media Nucleic acid amplification tests (NAATs) are not FDA-approved for specimens from neonates.*
Genital mycoplasmas (*Mycoplasma hominis* , *M. genitalium* , *Ureaplasma urealyticum*)	Tracheal aspirate, blood, or cerebrospinal fluid (CSF)	Culture using special transport media Real-time polymerase chain reactions (PCRs)
Neisseria gonorrhoeae	Conjunctiva, blood, CSF, or synovial fluid	Finding gram-negative intracellular diplococci on Gram stain is suggestive. Culture on special media establishes the diagnosis.
Syphilis (*Treponema pallidum*)	Serum (mother)	Rapid plasma reagin (RPR) and if reactive, a specific treponemal test †
	Serum	RPR
	CSF	Venereal Disease Research Laboratories (VDRL)
Cytomegalovirus	Urine, saliva, blood, or CSF	PCR for detection of CMV DNA

		Obtain within 2-4 wk of birth.
Enteroviruses	Blood, nasopharyngeal swab, throat swab, conjunctival swab, tracheal aspirate, urine, stool, rectal swab, or CSF	PCR Cell culture (sensitivity depends on serotype and cell lines used)
Hepatitis B	Serum (mother)	Hepatitis B surface antigen (HBsAg)
	Serum	If mother's HBsAg is positive, at age 9 mo, test the infant for HBsAg and hepatitis B surface antibody.
Herpes simplex viruses 1 and 2	Conjunctiva, skin vesicle scraping, whole blood, or mouth vesicles	PCR or cell culture
	CSF	PCR
	“Surface cultures” (mouth, nasopharynx, conjunctiva, and anus)	PCR or cell culture
Human immunodeficiency virus (HIV)	Serum (mother)	Fourth-generation HIV antigen/antibody test
	Whole blood	HIV DNA PCR
Candida species	Blood, skin biopsy, or CSF	Culture
Zika virus	Blood, urine, CSF	NAT and serum IgM NAT may be falsely negative IgG antibodies may reflect maternal exposure Antibodies may cross react with other flaviviruses

[*] Published evaluations of NAATs for these indications are limited, but sensitivity and specificity is expected to be at least as high as those for culture. FDA, U.S. Food and Drug Administration.

[†] Treponemal tests include the *T. pallidum* particle agglutination (TP-PA) test, *T. pallidum* enzyme immunoassay (TP-EIA), *T. pallidum* chemiluminescent assay (TP-CIA), and fluorescent treponemal antibody absorption (FTA-ABS) test.

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PART XII
Adolescent Medicine

OUTLINE

Chapter 132 Adolescent Physical and Social Development
Chapter 133 Gender and Sexual Identity
Chapter 134 Gay, Lesbian, and Bisexual Adolescents
Chapter 135 Transgender Care
Chapter 136 The Epidemiology of Adolescent Health Problems
Chapter 137 Delivery of Healthcare to Adolescents
Chapter 138 Transitioning to Adult Care
Chapter 139 Violent Behavior
Chapter 140 Substance Abuse
Chapter 141 The Breast
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Chapter 144 Adolescent Pregnancy
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CHAPTER 132

Adolescent Physical and Social Development

Cynthia M. Holland-Hall

See also Part XV and Chapters 577 and 578 .

During the preteen, teenage, and young adult years, young people undergo not only dramatic changes in physical appearance, but also rapid changes in physiologic, psychological, and social functioning. Hormonally driven physiologic changes and ongoing neurologic development occur in the setting of social structures that foster the transition from childhood to adulthood. This period of development comprises **adolescence** , which is divided into 3 phases—early, middle, and late adolescence—each marked by a characteristic set of biologic, cognitive, and psychosocial milestones (Table 132.1). Although individual variations in the timing and pace of development undoubtedly exist, these changes follow a fairly predictable pattern of occurrence. Gender and culture profoundly affect the developmental course, as do physical, social, and environmental influences. Given the interaction of these domains, a biopsychosocial perspective is best suited to approach the healthcare of the adolescent.

Table 132.1

Milestones in Early, Middle, and Late Adolescent Development

VARIABLE	EARLY ADOLESCENCE	MIDDLE ADOLESCENCE	LATE ADOLESCENCE
Approximate age range	10-13 yr	14-17 yr	18-21 yr
Sexual maturity rating*	1-2	3-5	5

Physical	Females: secondary sex characteristics (breast, pubic, axillary hair), start of growth spurt Males: testicular enlargement, start of genital growth	Females: peak growth velocity, menarche (if not already attained) Males: growth spurt, secondary sex characteristics, nocturnal emissions, facial and body hair, voice changes Change in body composition Acne	Physical maturation slows Increased lean muscle mass in males
Cognitive and moral	Concrete operations Egocentricity Unable to perceive long-term outcome of current decisions Follow rules to avoid punishment	Emergence of abstract thought (formal operations) May perceive future implications, but may not apply in decision-making Strong emotions may drive decision-making Sense of invulnerability Growing ability to see others' perspectives	Future-oriented with sense of perspective Idealism Able to think things through independently Improved impulse control Improved assessment of risk vs reward Able to distinguish law from morality
Self-concept/identity formation	Preoccupied with changing body Self-consciousness about appearance and attractiveness	Concern with attractiveness Increasing introspection	More stable body image Attractiveness may still be of concern Consolidation of identity
Family	Increased need for privacy Exploration of boundaries of dependence vs independence	Conflicts over control and independence Struggle for greater autonomy Increased separation from parents	Emotional and physical separation from family Increased autonomy Reestablishment of “adult” relationship with parents
Peers	Same-sex peer affiliations	Intense peer group involvement Preoccupation with peer culture Conformity	Peer group and values recede in importance
Sexual	Increased interest in sexual anatomy Anxieties and questions about pubertal changes Limited capacity for intimacy	Testing ability to attract partner Initiation of relationships and sexual activity Exploration of sexual identity	Consolidation of sexual identity Focus on intimacy and formation of stable relationships Planning for future and commitment

[*] See text and Figs. 132.1 and 132.2 .

Physical Development

Puberty is the biologic transition from childhood to adulthood. Pubertal changes include the appearance of the secondary sexual characteristics, increase in height, change in body composition, and development of reproductive capacity. Adrenal production of androgen, mainly dehydroepiandrosterone sulfate (DHEAS), may occur as early as 6 yr of age, with development of underarm odor and faint genital hair (**adrenarche**). Maturation of the gonadotropin-releasing hormone (GnRH) pulse generator is among the earliest neuroendocrine changes associated with the onset of puberty. Under the influence of GnRH, the pituitary gland secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH); initially this occurs in a pulsatile fashion primarily during sleep, but this diurnal variation diminishes throughout puberty. LH and FSH stimulate corresponding increases in gonadal androgens and estrogens. The triggers for these changes are incompletely understood but may be mediated in part by the hormone leptin, high concentrations of which are associated with increased body fat and earlier onset of puberty. Both genetic and environmental (epigenetic) contributions to the regulation of pubertal timing are likely.

Sexual Development

The progression of the development of the secondary sex characteristics may be described using the **sexual maturity rating (SMR)** scale (ranging from 1, preadolescence, to 5, sexual maturity), or **Tanner stages** . Figs. 132.1 and 132.2 depict the physical findings of breast and pubic hair maturation at each SMR (Tables 132.2 and 132.3). Although the ages at which individual pubertal changes occur may vary, the timing and sequence of these changes relative to one another is predictable (Figs. 132.3 and 132.4). The wide range of normal progress through sexual maturation is affected by genetics, the psychosocial environment, nutrition, and overall health status. Environmental exposures may play a role as well.

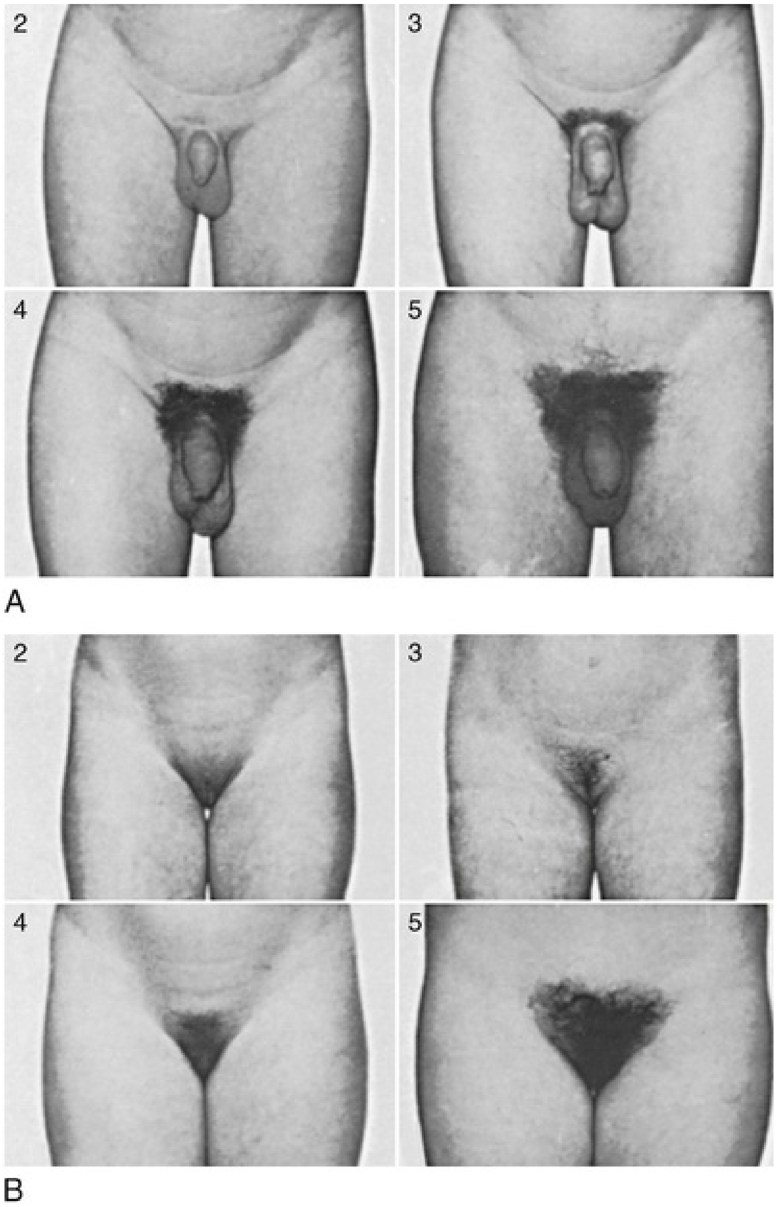

FIG. 132.1 Sexual maturity ratings (2-5) of pubic hair changes in adolescent males (**A**) and females (**B**) (see Tables 132.2 and 132.3). (Courtesy of J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London.)

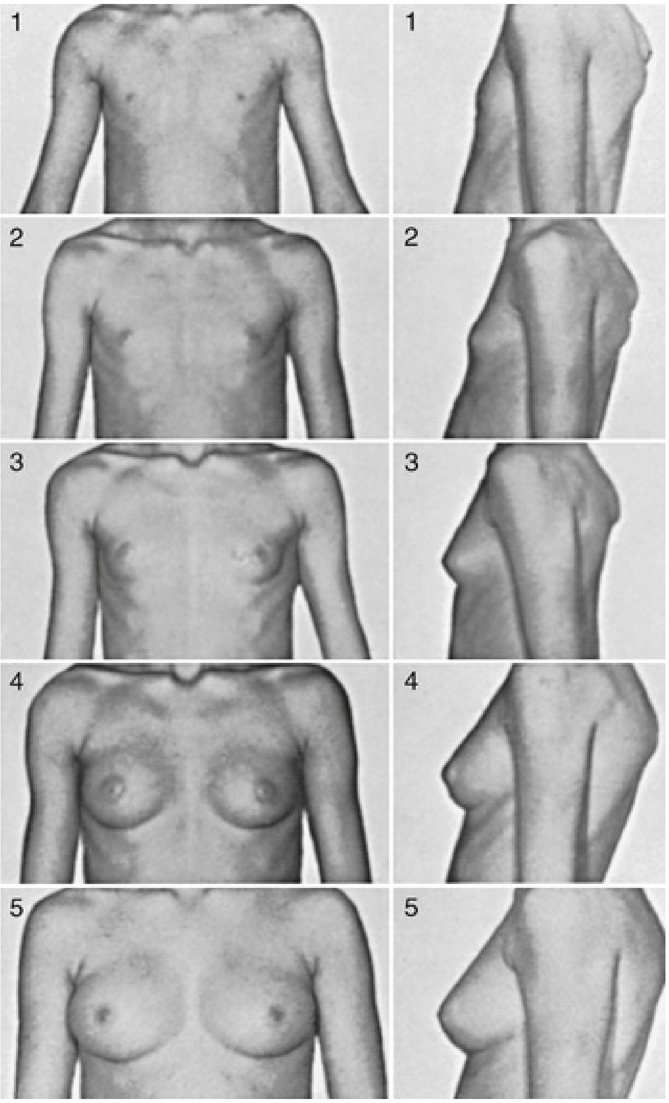

FIG. 132.2 Sexual maturity ratings (1-5) of breast changes in adolescent females. (Courtesy of J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London.)

Table 132.2

Sexual Maturity Rating (SMR) Stages in Females

SMR STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound

5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

From Tanner JM: *Growth at adolescence,* ed 2, Oxford, England, 1962, Blackwell Scientific.

Table 132.3

Sexual Maturity Rating (SMR) Stages in Males

SMR STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scant, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

From Tanner JM: *Growth at adolescence,* ed 2, Oxford, England, 1962, Blackwell Scientific.

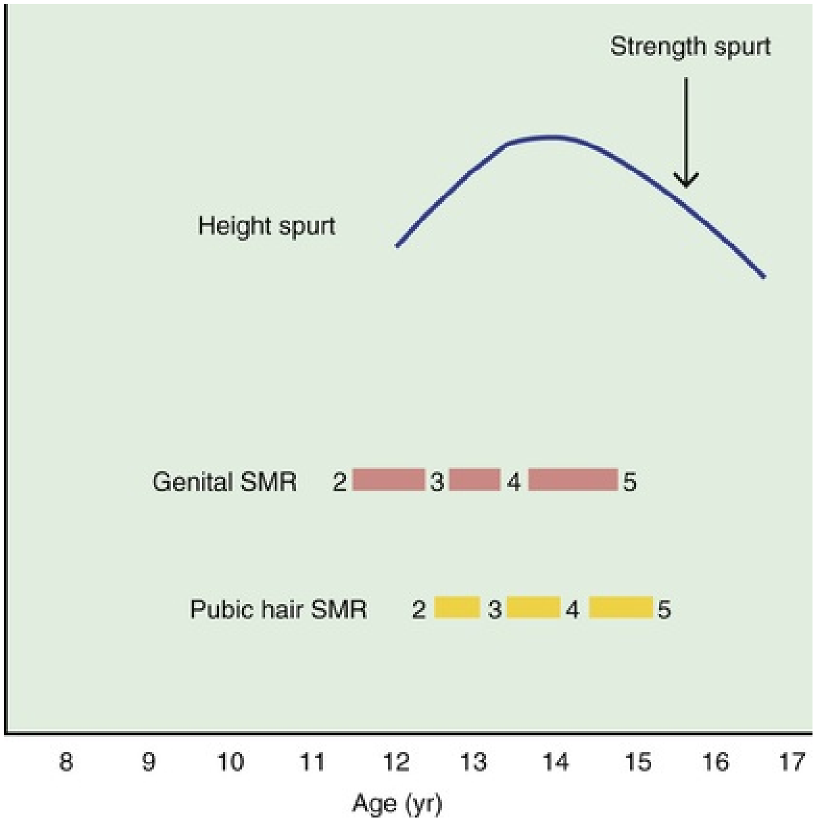

FIG. 132.3 Sequence of pubertal events in males. Although the age of

onset of puberty is variable, the sequence of events relative to one another is predictable. SMR, Sexual maturity rating.

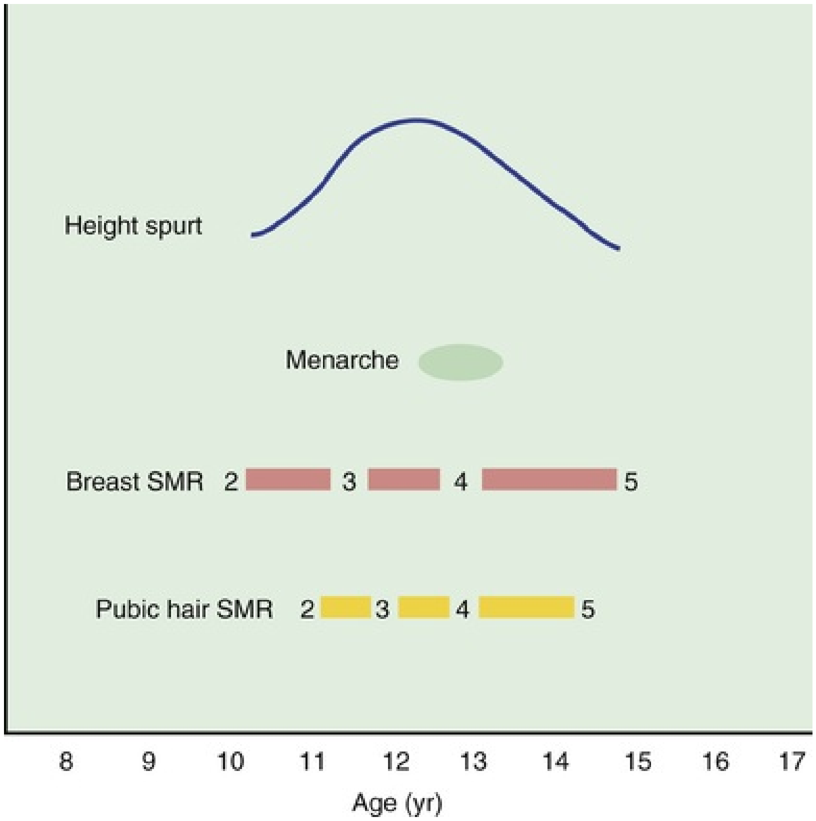

FIG. 132.4 Sequence of pubertal events in females. Although the age of onset of puberty is variable, the sequence of events relative to one another is predictable. SMR, Sexual maturity rating.

In **males** the first visible sign of puberty and the hallmark of SMR 2 is testicular enlargement, beginning as early as 9.5 yr, followed by the development of pubic hair. This is followed by penile growth during SMR 3. Peak growth occurs when testis volumes reach approximately 9-10 cm^3 during SMR 4. Under the influence of LH and testosterone, the seminiferous tubules, epididymis, seminal vesicles, and prostate enlarge. Sperm may be found in the urine by SMR 3; nocturnal emissions may be noted at this time as well. Some degree of breast tissue growth, typically bilateral, occurs in 40–65% of males during SMR 2-4 as a presumed consequence of a relative excess of estrogenic stimulation. This usually resolves with ongoing maturation.

In **females** , typically the first visible sign of puberty and the hallmark of

SMR 2 is the appearance of breast buds (**thelarche**), between 7 and 12 yr of age. A significant minority of females develops pubic hair (**pubarche**) prior to thelarche. Less visible changes include enlargement of the ovaries, uterus, labia, and clitoris and thickening of the endometrium and vaginal mucosa. A clear vaginal discharge may be present before menarche (physiologic leukorrhea). Menses typically begins within 3 yr of thelarche, during SMR 3-4 (average age 12.5 yr; normal range 9-15 yr) (see Fig. 132.4). The timing of **menarche** is determined largely by genetics; contributing factors likely include adiposity, chronic illness, nutritional status, and the physical and psychosocial environment. Early menstrual cycles often are anovulatory and thus somewhat irregular, but typically occur every 21-45 days and include 3-7 days of bleeding, even during the 1st year following menarche.

The **onset of puberty** and menarche appear to be occurring at earlier ages than previously reported in the United States. Several studies from 1948–1981 identified the average age for the onset of breast development as ranging from 10.6-11.2 yr of age. Multiple reports since 1997 suggest a significantly earlier average age of onset, ranging from 8.9-9.5 yr in black females to 10.0-10.4 yr in white females. Almost 25% of black females and 10% of white females initiate breast development by 7 yr of age. Early breast development may be associated with a slower tempo of puberty (i.e., longer time to menarche). There also appears to be a trend toward decreasing ages for the onset of pubic hair development and menarche. Data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative, longitudinal survey in the United States, show a decline in the average age of menarche of 4.9 mo between the 1960s and 2002. Changes in the timing of menarche *within* ethnic groups, however, were significantly smaller. The larger change seen in the population as a whole may be partially explained by changes in the ethnic makeup of the sample. The reasons for the larger decrease in age for breast development have been postulated to include the epidemic of childhood obesity as well as exposure to estrogen-like environmental toxins (endocrine disruptors), but further research in this area is needed.

Although fewer data are available on changes in the timing of puberty in males, they appear to be experiencing a similar trend. Although the method of assessing the onset of puberty (i.e., inspection vs. palpation of the testes) varies between studies, it appears that the average age for the onset of genital and pubic hair development may have decreased by 1-2 yr over the past several decades in many industrialized countries. Evidence for an association of obesity with the timing of puberty in males has been inconsistent.

Somatic Growth

Linear growth acceleration begins in early adolescence for both genders, with 15–20% of adult height accrued during puberty. Females attain a **peak height velocity (PHV)** of 8-9 cm/yr at SMR 2-3, approximately 6 mo before menarche. Males typically begin their growth acceleration at a later SMR stage, achieve a PHV of 9-10 cm/yr later in the course of puberty (SMR 3-4), and continue their linear growth for approximately 2-3 yr after females have stopped growing (Fig. 132.5). The growth spurt begins distally, with enlargement of the hands and feet, followed by the arms and legs, and finally the trunk and chest. This growth pattern imparts a characteristic “awkward” appearance to some early adolescents. Body composition changes as well, after attainment of PHV. Males undergo an increase in lean body mass (“strength spurt”), whereas females develop a higher proportion of body fat. Scoliosis, if present, may progress with rapid axial skeleton growth (see Chapter 699.1). From 50–65% of total body calcium is laid down during puberty. Bone growth precedes increases in bone mineralization and bone density, which may increase the adolescent's risk of fracture during times of rapid growth. Since skeletal growth precedes muscle growth, sprains and strains may be more common during this time as well.

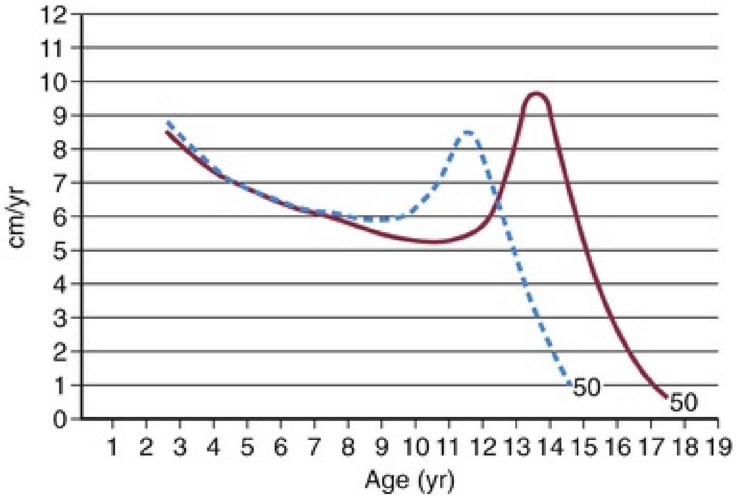

FIG. 132.5 Height velocity curves for American males *(solid line)* and females *(dashed line)* who have their peak height velocity at the average age (i.e., average growth tempo). (From Tanner JM, Davies PSW: Clinical longitudinal standards for height and height velocity for North American

children, *J Pediatr* 107:317, 1985.)

Cardiovascular changes in middle adolescence include increased heart size, higher blood pressure, and increases in blood volume and hematocrit, particularly in males. Coupled with an increase in lung vital capacity, these changes lead to greater aerobic capacity. Androgenic stimulation of sebaceous and apocrine glands may result in acne and body odor. Rapid enlargement of the larynx, pharynx, and lungs leads to changes in vocal quality in males, typically preceded by vocal instability (voice cracking). Elongation of the optic globe may result in the development of myopia (see Chapter 638). Dental changes include jaw growth, loss of the final deciduous teeth, and eruption of the permanent cuspids, premolars, and finally, molars (see Chapter 333). Orthodontic appliances may be needed, secondary to growth exacerbations of bite disturbances. Physiologic changes in sleep patterns and increased sleep requirements occur, causing many adolescents to delay sleep onset at night, with subsequent difficulty awakening for early school start times in the morning (see Chapter 31).

Neurologic, Cognitive, and Moral Development

As children progress through adolescence, they develop and refine their ability to use formal operational thought processes. Abstract, symbolic, and hypothetical thinking replaces the need to manipulate concrete objects. Middle and late adolescents develop the ability to consider multiple options and to assess the long-term consequences of their actions. The capacity for verbal expression is enhanced. Since adolescents' decision-making and subsequent behaviors are the primary determinants of their mortality and morbidity, understanding these cognitive processes is of critical importance.

Both structural and functional brain development continue throughout adolescence. Cortical gray matter volume peaks in preadolescence, then decreases because of selective “pruning” of rarely used synaptic connections. Cerebral white matter volume increases until mid-to-late adolescence, reflecting increasing myelination and subsequent facilitation of integrated brain activity and more efficient transmission of information between different regions of the brain, enhancing the “signal-to-noise” ratio. Although the frontal lobes and prefrontal cortex, regions of the brain associated with executive function, have been considered to be among the last regions to mature, other cortical regions show similarly prolonged trajectories of maturation. Without question, adolescents are capable of the complex cognitive processes attributed to frontal lobe function. *Cognitive control* , however, continues to improve into adulthood, with progressive maturation and *integration* of component processes such as working memory, inhibition and impulse control, performance monitoring, and motivational circuitry.

The behavioral correlates of adolescent neurodevelopment remain speculative but are increasingly supported by a rapidly expanding body of research. Adolescents appear to demonstrate a unique sensitivity to the effects of dopamine on reward-relevant subcortical structures such as the ventral striatum, with some studies demonstrating increased activation in this region when receiving rewards, relative to children or adults. Other studies show reduced responsiveness to aversive stimuli in adolescents. This altered responsiveness to risk vs reward may underlie the increased risk taking and novelty seeking seen in adolescents. Early maturation and distinct patterns of neural reactivity in the amygdala and other limbic structures may explain the strong role that social and emotional stimuli play in adolescents, overwhelming the frontal executive function systems that facilitate the interpretation and regulation of those social and emotional experiences. This may explain why adolescents are more likely to make poor decisions in highly emotionally charged situations, relative to mature adults. These “hot cognition” processes may result in the adolescent making a different decision in the context of a strong affective experience than he or she would in a less emotional state (“cool cognition”). These 2 types of cognitive processes may not develop at the same rate; the adolescent may be able to use higher brain structures and functions more effectively when in states of lower emotional arousal.

Early adolescents often continue to employ the concrete operational cognitive processes of childhood. Although formal operational cognition is developing, it may be applied inconsistently across different domains. A young adolescent may be able to use abstract thought when completing schoolwork, but not when working through a personal dilemma. Early adolescence also is characterized by egocentricity—the belief of some adolescents that they are the center of everyone's attention. Despite being largely imagined, this perception of always being “on stage” can be stressful for adolescents, who may feel that others are constantly judging or evaluating them. Early adolescents express a greater need for privacy than they did in childhood and begin to appreciate the privacy of their own thoughts. With ongoing cognitive development, **middle** adolescents are more able to consider the needs and feelings of other people. Their creativity and intellectual abilities are enhanced. Because of their increased capacity for abstract thought in combination with a persistent perception of uniqueness, middle adolescents may feel a sense of immortality and immunity to the consequences of risky behaviors. **Late** adolescents are more future oriented and able to delay gratification. They can think more independently, consider others' views, and compromise. They have a stronger sense of self and more stable interests. Under times of stress, adolescents may temporarily revert back to the cognitive processes and coping strategies used at younger ages.

Moral development generally accompanies cognitive development. Preadolescents, concrete and individualistic, follow rules in order to please authority figures and avoid punishment. As they move into early adolescence, they develop a stronger sense of right and wrong but are likely to perceive these as absolute and unquestionable. Middle and late adolescents may establish a sense of morality driven by their desire to be seen as a good person, to behave in a manner according to their perceived place in society, or by their sense of obligation to care for others. Moral decision-making, however, still may be highly subject to emotional context. Late adolescents may develop a rational conscience and an independent system of values, although these often are largely consistent with parental values. While going through this complex developmental process, religious or political organizations that promote simple answers to complex social or moral questions may hold great appeal to the adolescent.

Psychosocial Development

In contrast to cognitive development, psychosocial development correlates more strongly with pubertal status and physical maturation than with chronologic age. Whereas cognitive development is more biologically determined, psychosocial development is subject to greater environmental and cultural influences. Indeed, cultural variation can be dramatic. Some late adolescents move immediately from high school into marriage, childbearing, working, and financial independence; others remain dependent on the parents while pursuing their own education for several more years, in a period sometimes referred to as *emerging adulthood* . Psychosocial development also may be nonlinear, with different domains of growth progressing along different timelines. An overriding theme of psychosocial development is the concept of identity formation and consolidation as the adolescent moves away from the nurturing protection of the family, develops an increased affiliation with the peer group(s), and ultimately defines himself or herself as an individual.

Separation from the parents is a hallmark of adolescent development. Early adolescents start to seek out more privacy at home, spending less time with the parents. They begin to reject parental advice and involvement in their decision-making as they explore the boundaries of their dependence on, and independence from, their parents. With evolving cognitive skills, an adolescent can conceive of an ideal parent and contrast this ideal with his or her own parents. Adolescents may seek out alternative adult role models, such as teachers, coaches, or parents of friends. Parent–child conflict often peaks during middle adolescence, with disagreements over privileges, independence, and other limits set by the parents. Adolescents may appear intermittently to seek and reject parental acceptance. It is theorized that perhaps the adolescent *needs* to conceive of the parents as “wrong” in order to ameliorate the pain of separating from them. Throughout this time, however, the parents remain a critical source of nurturing and support for the adolescent and continue to exert significant influence over the adolescent's decision-making. Paradoxically, frequent arguments and conflict may coexist with strong emotional bonds and closeness. The late adolescent may reestablish a more “adult–adult” type of relationship with the parents, once again seeking out and considering parental advice and guidance as they enter adulthood.

Increasing importance of the **peer group** also may buffer the emotional trauma of separating from the parents. Early adolescents tend to socialize largely with same-sex peers, both in their individual friendships and larger groups. Females' peer groups tend to be more relationship oriented, whereas males' peer groups are more likely to be centered around a particular interest or activity. In both cases, group cohesion and a sense of belonging become important. Peers become increasingly important in middle adolescence, during which time the adolescent may experiment with being a part of different groups and “try on” different identities. These groups may include both sexes. Peer groups may arise from organized activities, such as sports or clubs, or may simply be friendship based. Gang membership is another form of peer acceptance. **Conformity** with the peers in manners of dress, speech, and behavior is a normal part of this process, and should not necessarily be viewed negatively. Similarly, **peer**

pressure may exist, but its influence over the adolescent's decision-making may be positive, negative, or negligible. Acceptance and successful navigation of peer groups during adolescence may give the individual more confidence to move into and out of various social, academic, and professional groups in the future. Late adolescents are less vulnerable to peer group influence, having moved closer to establishing their own stable identity. Their cognitive skills allow them to choose selectively among different peer groups, endorsing and adopting individual values and behaviors that best reflect who they are becoming.

Early adolescents have increased **sexual awareness and interest** , which may manifest as sexual talk and gossip, and often is focused on sexual anatomy. Masturbation and other sexual exploration, sometimes with same-sex peers, are common. The prevalence of other forms of sexual behavior varies by culture; in general, these behaviors are less common in early adolescents. Romantic relationships, if they exist at all, lack emotional depth. Sexual curiosity, experimentation, and activity become more common among middle adolescents. Same-sex attraction is common; sexual orientation may become clear to some adolescents, but still may be evolving in others during this time. Dating behaviors may be seen, but this is culture dependent and may not be a popular construct for all adolescents. Individual relationships often continue to emphasize sexual attraction over emotional intimacy; the latter may not be seen until late adolescence. At that time, relationships increasingly involve love and commitment and demonstrate greater stability.

Body image may affect (and be affected by) adolescents' psychosocial development as well. Early and middle adolescence are usually the ages at which poor or distorted body image and eating disorders develop. Early adolescents undergo rapid physical changes and may experience uncertainty about whether all these anatomic and physiologic changes are progressing normally. Reassurance from adults, including their healthcare providers, may be comforting. As puberty comes to an end and these changes slow, the middle adolescent's preoccupation may shift to whether the adolescent is attractive to others. A strong emphasis on physical appearance during this time is normal. Although this focus on physical appearance may continue into adulthood, late adolescence generally is characterized by a shifting balance toward introspection, with somewhat less emphasis placed on external characteristics.

The **timing of pubertal changes** also can affect psychosocial development and well-being. The progression of pubertal changes in males is generally associated with a positive self-image. Females may initially perceive these changes in their physical appearance more negatively. This appears to be especially true for early-maturing females, some of whom experience greater decreases in self-esteem, engage in more disruptive behaviors, and have more conflict with their parents than do on-time or late-maturing females. Perhaps because they are more comfortable associating with older peers, early-maturing females are vulnerable to making poor decisions when exposed to high-risk situations, still lacking the cognitive skills to effectively navigate these situations. Early-maturing males tend to have greater self-confidence, social, and academic success, while later-maturing males are at risk for more internalizing behaviors and diminished self-esteem. Many other factors influence how adolescents experience puberty, and supportive peers and adults can have a positive impact on psychosocial development. With successful navigation of these domains, emerging adults move into the world with a strong sense of personal identity and their place in society. They are able to work toward a vocation and financial independence and to manage the responsibilities of adulthood.

Implications for Providers, Parents, and Policymakers

Providers can help parents approach their child's adolescent years by reframing some of the “challenges” of adolescence as normal developmental milestones that should be anticipated and accepted. Puberty and emerging sexuality should be approached as positive and health-affirming life changes, rather than focusing discussions only on the negative reproductive risks and outcomes. Even good-natured teasing about bodily changes can be detrimental to the adolescent's self-image. Early-maturing females and late-maturing males should be supported, recognizing their potential increased risk for psychosocial challenges. Emerging positive coping strategies should be promoted in all youth, particularly those with chronic illness or other challenges. Providers need to determine the young adolescent's cognitive development and capacity for abstract thought and tailor their communication and counseling style accordingly. Physical examinations should be performed in private with the parent outside the exam room (provided the adolescent is comfortable with this), which also affords the adolescent and provider an opportunity to discuss confidential issues. Reassurance of normal development should be provided.

As adolescents develop more independence and parent–child conflict peaks, providers should remind parents that this is typical, and that arguing does not mean the adolescent does not value the parents' input and perspectives. Although some may rebel initially, most adolescents ultimately adopt a value system very similar to that of their parents. Even if discussions feel ineffective to parents, they should continue to demonstrate and model these values to their child. Similarly, rather than categorically dismissing their child's “negative” interests, such as playing a violent video game, parents should be encouraged to use these opportunities to model critical thinking about the impact of such an activity. Potentially negative peer groups may be approached the same way, while fostering the development of positive peer networks. **Authoritative parenting** , in which clear and appropriate negotiated limits are set in the context of a caring and mutually respectful parent–child relationship, is most strongly associated with positive psychosocial development. Parental connectedness and close supervision or monitoring of the youth's activities and peer group can be protective against early onset of sexual activity and involvement in other risk-taking behaviors and can foster positive youth development. Parents should also assume an active role in their adolescent's transition to adulthood to ensure that their child receives appropriate preventive health services.

Parents and providers may each work with adolescents to foster good decision-making. In addition to providing adolescents with accurate and complete health information, the adolescent's cognitive ability to use this information in various contexts must be considered. Adolescents may find themselves needing to make important decisions in highly charged situations where they may be unable to manage their emotions and use their higher cognitive functions to examine the consequences of their decision. For example, a couple in a sexual situation with high emotional arousal may make the decision to proceed with unprotected intercourse. By anticipating this situation ahead of time, under conditions of lower emotional arousal, and making a plan to deal with this, they may make a different decision (e.g., stick with their prior decision never to have sex without protection), when the time comes. Parents and healthcare providers are in a position to encourage and foster this anticipation and planning under conditions of “cool cognition.”

Providers may need to help parents distinguish normal adolescent development and risk-taking behaviors from possible signs of a more serious mental health or conduct problem. Bids for **autonomy** , such as avoiding family activities, demanding privacy, and increasing argumentativeness, are normal; extreme **withdrawal** or **antagonism** may be dysfunctional, signaling a mental health or substance use concern. Bewilderment and dysphoria at the start of middle school are normal; continued failure to adapt several months later suggests a more serious problem. Although some degree of risk taking is normal, progressive escalation of risk-taking behaviors is problematic. In general, when the adolescent's behaviors cause significant dysfunction in the domains of home life, academics, or peer relationships, they should be addressed by the parents and healthcare provider, and referral to a mental health provider may be considered. In most cases, parents can be reassured that although adolescence can pose unique challenges, their adolescent, like most adolescents, will come through it to become a successful and happy adult.

At national and international levels, adolescents are at risk for environmental, health, behavioral, and societal challenges. Table 132.4 provides suggestions to address these issues.

Table 132.4

Recommended Action Bundles* for Adolescent and Young Adult Health Problems and Risks

PROBLEM/RISK AREA	STRUCTURAL	SOCIAL MARKETING	COMMUNITY INTERVENTIONS INCLUDING FAMILY	ELECTRONIC HEALTH, MOBILE HEALTH	SCHOO
Sexual and reproductive health, including HIV	**Legislation** *18 years as the minimum age of marriage* *Allow provision of contraception to legal minors* *Legalize abortion*	*Promote community support for sexual and reproductive health, and HIV health access for adolescents*	**Cash transfer programs, with payments linked to staying in school** *Positive youth development* *Peer education*	*Target knowledge, attitudes, and risk behaviors*	**Qual** **secon** **educa** **Com** **sexua** **educa** **Safe** **with** **toilet** **facili** **mens** **Scho** **healt** **with** **and r** **contr**
Undernutrition	**Fortification of**		**Micronutrient**		**Micr**

	foods (e.g., iron, folate)		**supplements (particularly in pregnancy)** **Protein-energy supplementation** **Deworming** *Cash transfer program* *Nutrition education*		**suppl** **Healt** **meal**
Infectious diseases			*Deworming* *Bednet distribution*		**HPV vacci** *Dewo*
Violence	**Gun control** *Legalize homosexuality and protect women from violence and sexual coercion* *Youth justice reforms to promote second chances and diversion from custody* *16 years as the minimum age for criminal responsibility*	*Promote knowledge of the effects of violence and available services*	*Promote parent skills and parent–child communication* *Positive youth development* *Promote gender equality* *Economic empowerment* *Group training for awareness, knowledge, and skills*		**Multicor interven target vi behavior substanc**
Unintentional injury	**Graduated licensing** **Mandatory helmet wearing** **Multicomponent traffic injury control**	*Promote knowledge of risks*	*Police enforcement of traffic injury control*		
Alcohol and illicit drugs	**Limit alcohol sales to underage adolescents** **Taxation on alcohol** **Drink-driving legislation**	**Advertising restrictions** *Campaigns to build community awareness*	*Promote parent–child communication and parenting skills* *Needle-syringe exchange access* *Mentoring*	*Target knowledge, attitudes, and risk behaviors*	*Alcohol-*

	Restrict illicit alcohol **Interventions in licensed premises** **Diversion from youth justice and custody** *Graduated drinking*				
Tobacco	**Tobacco control including taxation, pricing, and advertising control** **Youth access restrictions** **Legislation for smoke-free air**	**Anti-tobacco campaigns**	*Interventions to promote parent skills and parent–child communication*	*Text messaging adjunct to quitting*	*Smok polic* *Multi*
Mental disorders and suicide	**Restriction of access to means**	*Promote adolescent mental health literacy*	*Gatekeeper training*	*Electronic mental health interventions*	*Educ interv* *Gatel traini* *Schoo ment servic*
Chronic physical disorders			*Peer support initiatives*		*School-b services*
Overweight and obesity	**Taxation of high-sugar, high-salt, and high-fat foods** *Front-of-pack nutrition labels* *Restriction of fast food advertising*	*Promote physical activity*	*Create opportunities for maintenance of physical activity in daily life*	*Interactive or personalized feedback interventions*	*Multicon intervent involving about hea and incre opportun physical*

[*] Actions in **bold** have an evidence base, and actions in *italics* are promising but without yet a strong evidence base, in adolescents and young adults.

HIV, Human immunodeficiency virus; HPV, human papillomavirus; STI, sexually transmitted infection.

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CHAPTER 133

Gender and Sexual Identity

Walter O. Bockting

Terms and Definitions

Sex and Sexual Identity

Sex is multifaceted, with at least 9 components: chromosomal sex, gonadal sex, fetal hormonal sex (prenatal hormones produced by the gonads), internal morphologic sex (internal genitalia), external morphologic sex (external genitalia), hypothalamic sex (sex of the brain), sex of assignment and rearing, pubertal hormonal sex, and gender identity and role. **Sexual identity** is a self-perceived identification distilled from any or all aspects of sexuality and has at least 4 components: sex assigned at birth, gender identity, gender expression, and sexual orientation.

Sex Assigned at Birth

A newborn is assigned a sex before (typically through ultrasound) or at birth based on the external genitalia (natal sex). In case of a *disorder of sex development (intersex)* , these genitalia may appear ambiguous, and additional components of sex (e.g., chromosomal, gonadal, hormonal sex) are assessed. In consultation with specialists, parents assign the child a sex that they believe is most likely to be consistent with gender identity, which cannot be assessed until later in life (see Chapter 606).

Gender Terms

Gender identity refers to a person's basic sense of being a boy/man, girl/woman, or other gender (e.g., transgender, genderqueer, nonbinary, gender fluid). **Gender role** refers to one's role in society, typically the male or female role. Gender identity needs to be distinguished from **gender expression** , which refers to characteristics in personality, appearance, and behavior that are, in a given culture and time, considered masculine or feminine. Gender role is about one's presentation as a boy/man or girl/woman, whereas gender expression is about the masculine and/or feminine characteristics one exhibits in a given gender role. Both boys/men, girls/women, and transgender, genderqueer, or nonbinary persons can be masculine and/or feminine to varying degrees; gender identity and gender expression are not necessarily congruent. A child or adolescent might be **gender nonconforming** , that is, a predominantly feminine boy or a predominantly masculine girl.

Sexual Orientation and Behavior

Sexual orientation refers to attractions, behaviors, fantasies, and emotional attachments toward men, women, or both. **Sexual behavior** refers to any sensual activity to pleasure oneself or another person sexually.

Transgender

Transgender people are a diverse group of individuals whose gender identity differs from their sex assigned at birth. They include **transsexuals** (usually referred to as transgender) (who typically live in the other gender role and seek hormonal and/or surgical interventions to modify primary or secondary sex characteristics); **cross-dressers** (who wear clothing and adopt behaviors associated with the other sex for emotional or sexual gratification and may spend part of the time in the other gender role); **drag queens** and **kings** (female and male impersonators); and individuals identifying as **genderqueer** (differently gendered), **nonbinary** (neither male nor female, both, or in-between), or **gender fluid** (not fixed but changing). Transgender individuals may be attracted to men, women, or other transgender persons.

Factors That Influence Sexual Identity Development

During prenatal sexual development, a gene located on the Y chromosome (*XRY*

) induces the development of testes. The hormones produced by the testes direct sexual differentiation in the male direction resulting in the development of male internal and external genitalia. In the absence of this gene in XX chromosomal females, ovaries develop and sexual differentiation proceeds in the female direction, resulting in female internal and external genitalia. These hormones may also play a role in sexual differentiation of the brain. In disorders of sex development, chromosomal and prenatal hormonal sex varies from this typical developmental pattern and may result in ambiguous genitalia at birth.

Gender identity develops early in life and is typically fixed by 2-3 yr of age. Children first learn to identify their own and others' sex (**gender labeling**), then learn that gender is most often stable over time (**gender constancy**), and finally learn that gender is typically permanent (**gender consistency**). What determines gender identity remains largely unknown, but it is thought to be an interaction of biologic, environmental, and sociocultural factors.

Some evidence shows the impact of biologic and environmental factors on gender expression, whereas their impact on gender identity remains less clear. Animal research shows the influence of prenatal hormones on sexual differentiation of the brain. In humans, prenatal exposure to unusually high levels of androgens in girls with **congenital adrenal hyperplasia** is associated with more masculine gender expression, transgender identity, and same-sex sexual orientation, but cannot account for all the variance found (see Chapter 594). Research on environmental factors has focused on the influence of sex-typed socialization. Gender-based stereotypes develop early in life. Until later in adolescence, boys and girls are typically socially segregated by gender, reinforcing sex-typed characteristics such as boys' focus on “rough-and-tumble play” and asserting dominance, and girls focus on verbal communication and creating relationships. Parents, other adults, teachers, peers, and the media serve as gender-socializing role models and agents by treating boys and girls differently.

For information on the development of sexual orientation, see Chapter 134 .

Nonconformity in Gender Expression Among Children and Adolescents

Prevalence

Nonconformity in gender expression needs to be distinguished from a transgender identity. The former operates on the level of personality, appearance, and behavior (masculinity, femininity), whereas the latter is about self-perceived, core gender identity. Nonconformity in gender expression is more common among girls (7%) than boys (5%), but boys are referred more often than girls for concerns regarding gender identity and expression. This is likely a result of parents, teachers, and peers being less tolerant of gender nonconformity in boys than in girls.

Nonconformity in gender expression as part of exploring one's gender identity and role is part of normal sexual development. Gender nonconformity in childhood may or may not persist into adolescence. Marked gender nonconformity in adolescence often persists into adulthood. Only a minority of gender-nonconforming children develop an adult transgender identity; most develop a gay or lesbian identity, and some, a heterosexual identity.

Etiology of Gender-Nonconforming Behavior

Prenatal hormones play a role in the development of nonconformity in gender expression, but cannot completely account for all the variance. A heritable component of gender-nonconforming behavior likely exists, but twin studies indicate that genetic factors also do not account for all of the variance. Family-of-origin factors hypothesized to play a role in the development of gender nonconformity lack empirical support. Maternal psychopathology and emotional absence of the father are the only possible factors associated with gender nonconformity, yet it is unclear whether these factors are cause or effect.

Stigma, Stigma Management, and Advocacy

Gender nonconforming children are subject to **ostracism** and **bullying** (see Chapter 14.1) from peers, which may negatively impact their psychosocial adjustment and lead to social isolation, loneliness, low self-esteem, depression, suicide, and behavioral problems. To assist children and families, individual stigma management strategies, as well as interventions to change the environment, can be offered. **Stigma management** might involve consultation with a health professional to provide support and education, normalizing gender-nonconforming behavior and encouraging the child and family to build on the child's strengths and interests to foster self-esteem. It might also involve making choices about certain preferences (e.g., a boy who likes to wear feminine attire) to limit these to times and environments that are more accepting. *Most health professionals agree that too much focus on curtailing gender-nonconforming behavior leads to increased shame and undermines the child's self-esteem.*

The health professional and family can also assist the child or adolescent to find others with similar interests (within and beyond the gender-related interests) to strengthen positive peer support. Equally important are interventions in school and society to raise awareness and promote accepting and positive attitudes, take a stand against bullying and abuse, and implement antibullying policies and initiatives. *Gay, lesbian, bisexual, transgender, and straight alliance groups are helpful in providing a haven for gender-nonconforming youth, as well as recognizing them as part of diversity to be respected and embraced within the school system.* Healthcare system level approaches are outlined in Table 133.1 .

Table 133.1

Systems-Level Principles Underlying Lesbian, Gay, Bisexual, Transgender, Questioning (LGBTQ) Youth-Friendly Services

PRINCIPLE	DEFINITION	EXAMPLES
Availability	The presence of healthcare providers with knowledge, competence, and experience working with young people and with people with current or possibly developing LGBTQ identities, feelings, and/or behavior	Providers from various disciplines (e.g., physicians, nonphysician healthcare professionals) provide care sensitive to the needs of LGBTQ youth. Quality of care is high, with LGBTQ youth (and when appropriate, their caregivers) universally receiving recommended screening and anticipatory guidance.
Accessibility	The relative ease with which LGBTQ youth can obtain care from an available provider	Clinical services are located near where LGBTQ youth live, study, work, or otherwise spend time. Clinical services are easily obtained, with expanded hours during evenings and weekends, same-day urgent bookings, drop-in visits, and allowances for late appointments. Technology (e.g., online patient portals, email, telemedicine) is increasingly used to improve access for youth.
Acceptability	The extent to which clinical services are culturally competent and developmentally appropriate for LGBTQ youth, and to which confidentiality is ensured and protected	The clinic has a policy affirming its inclusive services for LGBTQ, and the clinical environment has signs, stickers, and other statements showing it is LGBT-friendly. Health brochures and other reading materials are tailored to the needs of

		LGBTQ youth. Confidentiality is ensured and protected in every patient encounter, and healthcare providers spend time one-on-one with patients to elicit sensitive information.
Equity	The degree to which clinical care is friendly to *all* LGBTQ youth, regardless of race, ethnicity, language, ability to pay, housing status, and insurance status, among other factors	High-quality care is provided to all youth, regardless of whether they are lesbian, gay, bisexual, or transgender. Culturally competent care is provided to LGBTQ youth of color, and services are available for patients who are not native English speaking. Services are provided free-of-charge for uninsured LGBTQ youth.

Adapted from Tylee A, Haller DM, Graham T, et al. Youth-friendly primary-care services: how are we doing and what more needs to be done? *Lancet* 369(9572):1565–1573, 2007; and Department of Maternal Newborn Child and Adolescent Health. Making health services adolescent friendly—developing national quality standards for adolescent friendly health services, Geneva, 2012, World Health Organization.

Transgender and Gender-Nonconforming Identities Among Children and Adolescents

Prevalence

Approximately 1% of parents of 4-11 yr old boys report that their son wished to be of the other sex, with 3.5% for 4-11 yr old girls. Only a minority of children's gender identity concerns persist into adolescence (20% in one study of boys). Persistence of gender identity concerns from adolescence into adulthood is higher; the majority identify as transgender in adulthood and may pursue **gender-affirming medical interventions** (i.e., hormone therapy, surgery). The prevalence of transgender adults in the United States is estimated at 1 : 200.

Etiology of Transgender or Gender-Nonconforming Identities

The etiology of transgender and gender-nonconforming identities remains unknown. Environmental and biologic factors are hypothesized to play a role in the development of a transgender or gender-nonconforming identity. Gender-nonconforming children seem to have more trouble than other children with basic cognitive concepts concerning their gender. They may experience emotional distance from their father. Whether these factors are cause or effect remains unclear.

Prenatal and perinatal hormones may influence sexual differentiation of the brain. Some girls with congenital adrenal hyperplasia develop a male gender identity, but most do not. The size of the sex-dimorphic central part of the bed nucleus of the stria terminalis in the hypothalamus of transgender women is smaller than in males and within the range of nontransgender women; the opposite is true for transgender men. This structure is regulated by hormones in animals, but in humans no evidence yet exists of a direct relationship between prenatal and perinatal hormones and the sexually dimorphic nature of this nucleus. In addition, differences have been shown between transgender men and women and nontransgender controls in white matter microstructure of the brain.

Clinical Presentation

Children and adolescents with a gender-nonconforming identity may experience 2 sources of stress: internal distress inherent to the incongruence between sex assigned at birth and gender identity (gender dysphoria) or distress associated with social stigma. The 1st source of distress is reflected in discomfort with the developing primary and secondary sex characteristics and the gender role assigned at birth. The 2nd source of distress relates to feeling different, not fitting in, peer ostracism, and social isolation, and may result in shame, low self-esteem, anxiety, or depression.

Boys with a gender-nonconforming identity may at an early age identify as a girl, expect to grow up female, or express the wish to do so. They may experience distress about being a boy and/or having a male body, prefer to urinate in a sitting position, and express a specific dislike of their male genitals and even want to cut off their genitals. They may dress up in girls' clothes as part of playing dress up or in private. Girls may identify as a boy and expect or wish to grow up male. They may experience distress about being a girl and/or having a female body, pretend to have a penis, or expect to grow one. Girls may express a dislike of feminine clothing and hairstyles. In early childhood, children may spontaneously express these concerns, but depending on the response of the social environment, these feelings may go underground and may be kept more private. The distress may intensify by the onset of puberty; the physical changes of puberty are described by many transgender adolescents and adults as “traumatic.” Boys and girls may also identify outside of the gender binary (e.g., as boygirl, girlboy, genderqueer, gender fluid) and describe their identity as neither male nor female, both male and female, in-between, or some other alternative gender different from their sex assigned at birth. Adopting a **nonbinary identity** may be part of identity exploration or constitute a gender identification that persists over time.

Gender-nonconforming children and transgender adolescents may struggle with a number of general behavior problems. Both boys and girls predominantly internalize (anxious and depressed) rather than externalize behavioral difficulties. Boys are more prone to anxiety, have more negative emotions and a higher stress response, and are rated lower in self-worth, social competence, and psychological well-being. Gender-nonconforming children have more peer relationship difficulties than controls. Both femininity in boys and masculinity in girls are socially stigmatized, although the former seems to carry a higher level of stigma. Boys have been shown to be teased more than girls; teasing for boys increases with age. *Poor peer relations* is the strongest predictor of behavior problems in both boys and girls.

Transgender adolescents may struggle with a number of adjustment problems as a result of social stigma and lack of access to gender-affirming healthcare. Transgender youth, especially those of ethnic/racial minority groups, are vulnerable to verbal and physical abuse, academic difficulties, school dropout, illicit hormone and silicone use, substance use, difficulty finding employment, homelessness, sex work, forced sex, incarceration, HIV/sexually transmitted infections (STIs), and suicide. Parental support can buffer against psychological distress, but many parents react negatively to their child's gender nonconformity, although mothers tend to be more supportive than fathers.

The Diagnosis of Gender Dysphoria: Criteria and Critique

Gender dysphoria (or **gender incongruence**) is classified as a mental disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and *International Classification of Diseases* (ICD), which, particularly for children, is controversial (Table 133.2). Critics have argued that the distress children experience is mainly the result of social stigma rather than being inherent to gender nonconformity and thus should not be considered a mental disorder.

Critics have also expressed concern about children with normal variation in gender role being labeled with a mental disorder perpetuating social stigma, yet there is a tendency of clinicians to underdiagnose rather than overdiagnose children whose gender nonconformity goes beyond behavior and who report gender dysphoria. These children may benefit from the diagnosis to receive early treatment in the form of support, education, advocacy, and, in case of clinically significant distress, changes in gender role, **puberty suppression, and/or feminizing or masculinizing hormone therapy in adolescence** .

Table 133.2

Summary of DSM-5 Diagnostic Criteria for Gender Dysphoria

GENDER DYSPHORIA IN CHILDREN (302.6) (F64.2)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 6 of the following (1 of which must be criterion A1):
    1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
    2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
    3. A strong preferences for cross-gender roles in make-believe play or fantasy play.
    4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
    5. A strong preference for playmates of the other gender.
    6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
    7. A strong dislike of one's sexual anatomy.
    8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

GENDER DYSPHORIA IN ADOLESCENTS OR ADULTS

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 2 of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

SPECIFY IF POSTTRANSITION: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen, namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Adapted from the American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders* , ed 5, Washington, DC, 2013, American Psychiatric Publishing.

Transgender Identity Development

A stages model of coming out might be helpful to understand the experience and potential challenges transgender youth might face. In the **pre–coming out** stage, the child or adolescent is aware that their gender identity is different from that of most boys and girls. In addition to a gender identity that varies from sex assigned at birth, some of these children are also nonconforming in gender expression while others are not. Those who are also nonconforming in gender expression cannot hide their transgender identity, are noticed for who they are, and may face teasing, ridicule, abuse, and rejection. They must learn to cope with these challenges at an early age and usually proceed quickly to the next stage of **coming out** . Children who are not visibly nonconforming in gender expression are able to avoid stigma and rejection by hiding their transgender feelings. They often experience a split between their gender identity cherished in private and expressed in fantasy and a false self presented outwardly to fit in and meet gendered expectations. These children and adolescents often proceed to coming out later in adolescence or adulthood.

Coming out involves acknowledging one's transgender identity to self and others (parents, other caregivers, trusted health providers, peers). An open and accepting attitude is essential; rejection can perpetuate stigma and its negative emotional consequences. By accessing transgender community resources, including peer support (either online or offline), transgender youth can then proceed to the **exploration** stage. This is a time of learning as much as possible about being transgender, getting to know similar others, and experimenting with various options for gender expression. Changes in gender role are carefully considered, as are medical interventions to delay puberty and/or feminize or masculinize the body to alleviate dysphoria. Successful resolution of this stage is a sense of pride in being transgender and comfort with gender role and expression.

Once gender dysphoria has been alleviated, youth can proceed with other human development tasks, including dating and relationships in the **intimacy** stage. As a result of social stigma and rejection, transgender youth may struggle with feeling unlovable. Sexual development has often been compromised by gender and genital dysphoria. Now that greater comfort has been achieved with gender identity and gender expression, dating and sexual intimacy have a greater chance of succeeding. Finally, in the **integration** stage, transgender is no longer the most important signifier of identity, but one of several important parts of overall identity.

Interventions and Treatment

Health providers can assist gender-nonconforming children, transgender adolescents, and their families by directing them to resources and by helping them to make informed decisions about changes in gender role and the available medical interventions to reduce intense and persistent gender dysphoria. To alleviate socially induced distress, interventions focus on stigma management and stigma reduction. It might be in the child's best interest to set reasonable limits on gender expression contributing to teasing and ridicule. The main goal of these interventions is not to change the child's gender-nonconforming behavior but to assist families, schools, and the wider community to create a supportive environment where the child can thrive and safely explore his or her gender identity and expression. Decisions to change gender roles, particularly in school, are not to be taken lightly and are best carefully anticipated and planned in consultation with parents, child, teachers, school counselor, and other providers involved in the adolescent's care. Medical interventions are available as early as Tanner Stage 2. Such treatment is guided by the Standards of Care set forth by the **World Professional Association for Transgender Health** (WPATH). Although some controversy still exists about the appropriateness of early medical intervention, follow-up studies of adolescents treated in accordance with these guidelines show its effectiveness in alleviating intense and persistent gender dysphoria.

Pubertal suppression with gonadotrophin-releasing hormone analogues (usually begun in early puberty) that delay puberty are helpful before gender-affirmation hormone therapies. Certain features of puberty are difficult to reverse (e.g., male facies, Adam's apple), so pubertal suppression avoids these physical features. Pubertal suppression may also reduce gender dysphoria. Gender-affirming hormones can then be initiated; testosterone for masculinizing and estrogen plus an adrogen inhibitor for feminization. Gender-affirming surgery (most commonly "top" surgery) to create a male-typical chest is usually delayed until adulthood.

Pediatricians who encounter transgender youth in their practice should be careful not to make assumptions about gender and sexual identity, but rather ask youth how they would describe themselves. This includes asking if they like being a boy or girl, have ever questioned this, wished they were born the other sex, or define their gender identity in a nonbinary or otherwise different way; and if they have a preferred nickname or pronoun (*he/him* , *she/her,* or *they/them;* if not sure, avoid pronouns). It also includes asking how they feel about their maturing body and sex characteristics, and what they would change about that if they could. Extra caution should be exercised during physical and genital exams because transgender youth may be particularly uncomfortable with their anatomy. When considering contraceptive options for female-to-male transgender youth, alternatives to feminizing agents should be explored. *For gender-affirming medical interventions, transgender youth should be referred to specialists in the treatment of gender dysphoria* (see www.wpath.org). For other health concerns, ensure referral to transgender or lesbian, gay, bisexual, transgender (LGBT)-friendly providers, especially in the case of gender-segregated treatment facilities. **Gender Spectrum** (www.genderspectrum.org), **Advocates for Youth** (www.advocatesforyouth.org), and **Parents, Families and Friends of Lesbians and Gays** (www.pflag.org) offer excellent support resources for transgender youth and their families.

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CHAPTER 134

Gay, Lesbian, and Bisexual Adolescents

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Understanding a child's or adolescent's sexual and emotional development is an essential part of any comprehensive pediatric evaluation. For youth who are or might be gay, lesbian, or bisexual (**GLB**), such understanding is particularly important. GLB youth as a group have the same health and developmental needs as all youth, and their sexual orientation is part of the spectrum of human sexuality. However, they encounter distinct developmental challenges and can have additional physical and mental health needs related to their orientation and others' reaction to it. Their sexual orientation is often different from that expected by family, peers, and society (although expectations have been changing in many contexts), and they must cope with peer rejection, bullying, or family nonacceptance more frequently than most youth. Although the majority of GLB adolescents grow up physically and mentally healthy, they are at increased risk for certain health problems as a result of these stresses and the epidemiology of health threats such as HIV and other sexually transmitted infections (STIs). Pediatric clinicians are key in monitoring for such issues, supporting healthy development, and intervening when necessary to prevent or treat the problems for which GLB youth are at increased risk.

Sexual orientation refers to an individual's attraction to others based on sex or gender. It encompasses emotional and erotic desires, physiologic arousal, sexual behavior, sexual identity, and social role. As sexuality develops, youth can be oriented entirely toward a particular sex or gender, or more than one, to various degrees on a continuum. **Homosexuality** involves orientation toward people of one's same sex or gender, and **bisexuality** involves orientation toward males and females. **Gay** is a common term for homosexual males and females; **lesbian** refers to homosexual females. Some do not fit these categories and use other terms to describe themselves. Those unsure of their orientation are **curious** or **questioning** . The term **young men who have sex with men** (**YMSM**) is sometimes used in the research literature to denote male youth who engage in sexual activity with other males, regardless of how they identify themselves.

Prevalence of Homosexuality and Bisexuality in Youth

Some junior high and high school students self-identify as gay, lesbian, or bisexual. Some who do not identify as GLB report same-sex attraction, fantasies, or behavior. Some are unsure of their sexual orientation. Certainty about sexual orientation tends to increase through adolescence with sexual experience, although one can be aware of one's orientation without having had sexual partners. Those who fear nonacceptance may try to suppress or deny their orientation. Consequently, various aspects of orientation—attraction, behavior, and identity—may not be consistent in an individual and may change during development. Not all youth with homosexual attraction or experience identify as "gay," consistent in part with reluctance about having or revealing a gay identity and underscoring the differences among attraction, behavior, and identity. A report providing national estimates of the number of high school students with GLB identity in 2015 found that across 25 states and 19 large urban school districts, a median of 2.7% said they were gay/lesbian, 6.4% said they were bisexual, and 4.0% reported being unsure of their sexual orientation.

Development of Sexual Orientation in Childhood and Adolescence

Sexual orientation development appears to begin prenatally and continue through childhood and adolescence and into adulthood. Both gender role behavior in childhood and sexual orientation in puberty and adolescence are partly influenced by prenatal genetic and neuroendocrine factors. Sociocultural and psychological factors also influence sexual development. A gay or lesbian sexual orientation is sometimes preceded developmentally in childhood by **nonconforming gender expression** , or variation from population averages in expression of **gender-related behavior** such as activities, interests, styles, and other attributes recognized as masculine or feminine, such as toy preferences and preference for playmates of a particular gender. Although childhood gender nonconformity is not experienced by all gay or lesbian people—and not all children with nonconforming gender role behavior grow up to be gay or lesbian—nonconformity is not uncommon (particularly among males) and leads many gay or lesbian people to feel different from peers in childhood, even before sexual desire or identity emerges. Depending on the setting, gender-nonconforming children may experience ostracism, bullying, or family nonacceptance. These reactions to gender nonconformity can lead to later difficulty with gender-related self-esteem and long-term mental health problems.

Less frequently, gay or lesbian sexual orientation in adolescence is preceded by childhood **gender variant identity** , a phenomenon in which the gender identity of an individual at any age differs from phenotypic sex and assigned sex at birth (see Chapter 135).

Stigma, Risk, and Resilience

Homosexuality has been documented across cultures and historical periods. However, its meaning and acceptance vary greatly with social context. Although gay people are now generally more visible and accepted than previously, youth are often exposed to antihomosexual attitudes. For many GLB youth, revealing their sexual orientation (“coming out”) to family, peers, healthcare providers, and others is a significant step. Specific racial/ethnic, religious, and other demographic groups may experience distinct developmental stressors. For example, black youth report feeling less comfortable than white peers with a gay identity and less comfortable disclosing it.

Some GLB youth experience difficulty coping with **stigma** . A longitudinal study that investigated **bullying** and **victimization** among youth from 5th through 10th grade found that the girls and boys that identified as GLB in 10th grade were more likely than their peers to report that they had been bullied and victimized across grades. GLB youth may be perceived by others as different before they themselves have any GLB attraction or experience, or identify as GLB. Even when not overtly threatened, GLB youth frequently encounter negative attitudes that force them to hide at a time when acceptance holds great developmental significance. Family nonacceptance, feeling unsafe due to school harassment, and peer bullying related to sexual orientation elevate risk in GLB adolescents for depression, anxiety, substance abuse, suicidal thoughts and attempts, and social problems such as truancy, dropping out, running away, and homelessness. Mental health problems, sexual risk taking, or substance use may increase exposure to HIV and other STIs. Stigma may also impede access to healthcare in some communities. Thus, along with factors influencing exposure and susceptibility to health threats, stigma partly mediates elevated risk for health and mental health problems in GLB youth.

Nevertheless, most GLB youth are resilient, with good physical and mental health despite pervasive stress. Family connectedness and school support and safety are important protective factors against depression, suicidal thoughts and attempts, and substance abuse. GLB antiharassment policies and organizations such as **genders and sexualities alliances** (also sometimes called gay-straight alliances) and antibullying programs are associated with increased school safety for GLB youth. It is therefore important to reduce stigma, support acceptance, and promote resilient coping.

Health

Depression and Suicidality

Compared to their heterosexual peers, GLB youth and those who are not sure of their sexual orientation have higher prevalence of suicidality. Family rejection, bullying, and other victimization motivated by homophobia account statistically for increased depression and suicidal thoughts and attempts in GLB adolescents. Suicidal thoughts or attempts are highest during the interval following recognition of same-sex attraction or a same-sex sexual experience but prior to self-acceptance as gay.

Sexually Transmitted Infections

The epidemiology of STIs, related to specific sexual practices as well as prevalence of certain STIs in GLB communities, informs recommended counseling, screening, and treatment strategies. Anal intercourse has been shown to be the most efficient route of infection by hepatitis B (Chapter 385), cytomegalovirus (Chapter 282), and HIV (Chapter 302). Oral-anal and digital-anal contact can transmit enteric pathogens, such as hepatitis A. Unprotected oral sex also can lead to oropharyngeal disease in the receptive partner and gonococcal and nongonococcal urethritis in the insertive partner. Certain STIs, particularly ulcerative diseases, such as syphilis and herpes simplex virus infection, facilitate spread of HIV.

Among U.S. adolescents and young adults, YMSM, and especially black YMSM, continue to face the greatest prevalence of HIV/AIDS. Although possible, female-to-female sexual transmission of HIV is inefficient, and females who only engage in sex with females are less likely than other youth to acquire an STI. However, boys and girls who identify as gay or lesbian may engage in sexual activity with partners of the other sex, so counseling and screening for all types of STIs are still relevant.

Substance Abuse

Compared with their heterosexual peers, GLB youth appear to use alcohol and other substances at higher rates, including more binge drinking and earlier onset and more rapid trajectory of substance use. More substantial substance use may be greatest in youth who do not identify as GLB but have same-sex attractions or engage in same-sex sexual behavior.

Obesity and Disordered Eating

Compared with heterosexual girls, lesbian and bisexual girls are generally more likely to be obese or overweight. In contrast, young gay and bisexual males are more likely to have body image concerns and to restrict eating or engage in compensatory weight loss strategies compared to heterosexual boys. Binge eating may also be more common in GLB youth.

Psychosocial Problems

Academic underachievement, truancy, and dropping out of school are frequently associated in GLB adolescents with homophobic victimization, harassment, violence, and feeling unsafe at school. Studies suggest that youth who eventually identify as GLB have higher rates than other youth of experiencing child abuse and of running away or being kicked out of their homes. GLB young people are overrepresented among homeless and runaway populations across the United States, which can expose them to drugs, sexual abuse and other health risks.

Recommendations for Care

Evaluation

The goal of GLB pediatric care is physical health, social and emotional well-being, and healthy development. Physicians should provide nonjudgmental care to all adolescents, including those who are GLB or questioning (see Chapter 133 , Table 133.1). They should receive the age-appropriate history, examination, and anticipatory guidance recommended for adolescents in general. With some exceptions noted later, the physical examination and laboratory evaluation of GLB and questioning adolescents are the same as for any teenager. However, providers should appropriately screen for special potential medical and psychosocial threats to GLB teenagers' health.

A nonjudgmental healthcare environment is important, with open communication and a positive relationship with youth and families. In the waiting room, written material about sexual orientation, support groups, and community resources will signal openness to discussing sexuality. Registration forms recognizing the possibility of same-gender parents signal a safe setting (e.g., forms can list parent/guardian #1, parent/guardian #2). Sexual history questions should avoid heterosexual assumptions (e.g., "Are you dating someone?" vs "Do you have a boyfriend/girlfriend?"). This is important at all ages. For example, asking a 6 yr old boy if he has a girlfriend may convey an unsupportive message if he discovers later that he would like a boyfriend. Explaining confidentiality and incorporating into each adolescent visit private time with no parent in the room (see Chapter 137) may facilitate discussing sexual orientation, as may use of appropriate health history forms such as the American Medical Association's Guidelines for Adolescent Prevention Services Questionnaire.

Clinicians should remember that any youth might be GLB whether or not they are identified or perceived as such, so clinicians should not presuppose a particular orientation. Competency in conveying sensitivity, acceptance, and respectfulness; effective communication skills; and appropriate attention to privacy and confidentiality (including practices related to billing and record requests) are fundamental to providing high-quality care. While remaining attuned to youth's preferences, explicit or implied, for discussing sexual orientation, providers can tactfully take the lead, if necessary, regarding any pressing areas of clinical concern.

Medical and Sexual Health

STIs are covered in Chapter 146 , but issues specific to GLB youth are included here. Use of latex condoms for fellatio, and dental dams and cut-open latex condoms for anilingus and cunnilingus, should be discussed with adolescents. Recommendations also include use of latex condoms for sexual appliances. In addition, it is important to emphasize that people who have been using alcohol or other drugs are at increased likelihood for engaging in riskier sexual activity. It is important not to assume that a gay boy or lesbian girl who does not identify as bisexual has not had sex with someone of a different sex or gender. For example, lesbians can still have an unplanned pregnancy. Therefore, prevention counseling about unintended pregnancy is relevant to all adolescents. Similarly, youth who identify as heterosexual and whose attractions are not to those of the same sex or gender may still have sexual activity with a partner of the same sex or gender.

Although vaccination against hepatitis A and B is recommended for all children, it is particularly recommended that nonvaccinated adolescent males who are having sex or are likely to have sex with males receive catch-up vaccines. The same recommendation applies to the human papillomavirus (HPV) vaccine for males. The Centers for Disease Control and Prevention (CDC) recommends that males who are engaging in sexual activity with males have annual testing for HIV, hepatitis A, hepatitis B, syphilis, urethral gonorrhea and chlamydia (if engaging in insertive oral or anal intercourse), oral gonorrhea (if engaging in receptive oral intercourse), and rectal gonorrhea and chlamydia (if engaging in receptive anal intercourse).

Mental Health

Awareness of mental health and social problems is important when caring for GLB youth, as for all youth. Clinicians should monitor for depression, suicidality, anxiety, and substance abuse and know their community's mental health resources. Minor psychosocial problems might be handled by referral to a support group for patients (e.g., GLSEN, formerly known as the Gay, Lesbian and Straight Education Network) or for parents and others (e.g., Parents, Families and Friends of Lesbians and Gays). In some communities, agencies and organizations serving the GLB community can help with social, educational, vocational, housing, and other needs.

Individuals or families who harbor negative attitudes may inquire about mental health treatment to avert or change a homosexual or bisexual orientation. However, a GLB orientation is not an illness, and leading health organizations, including the American Academy of Pediatrics, American Academy of Family Physicians, Society for Adolescent Health and Medicine, American Academy of Child and Adolescent Psychiatry, and American Medical Association, have concluded that such change is neither possible nor warranted. It is important to distinguish between a GLB orientation, which is not a mental illness, and mental health problems (e.g., depression) for which GLB youth are at elevated risk. While understanding different families' values, clinicians must recognize the morbidity and mortality associated with stigma and attempt to foster physical and emotional health. Individual or family therapy might be indicated.

Clinicians should also monitor for specific stressors, such as bullying and other homophobic victimization, family nonacceptance, and abuse. Failure to confront harassment constitutes tacit assent.

Anticipatory guidance, referral, and substance abuse treatment should be considered for the subset of GLB youth who use alcohol, drugs, or tobacco, some of whom may be using these to manage painful feelings related to conflicts over their sexuality.

Adolescents with serious psychiatric symptoms, such as suicidality, depression, and substance abuse, should be referred to mental health specialists with competency in treating GLB adolescents. It is essential to know how to recognize and manage psychiatric emergencies such as suicidal thoughts and attempts (see Chapter 40).

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CHAPTER 135

Transgender Care

Walter O. Bockting

Transgender individuals have a gender identity that differs significantly from the sex they were assigned at birth (see Chapter 133). They may experience **gender dysphoria** , defined as clinically significant distress or impairment in social, school/occupational, or other important areas of functioning associated with incongruence between one's experienced/expressed gender and assigned gender, for at least 6 mo in duration. **Gender-affirming care** has been shown to alleviate gender dysphoria and may include psychological evaluation and supportive therapy, puberty suppression, feminizing or masculinizing hormone therapy, and surgery. Such care is guided by the Standards of Care for **transsexual** , **transgender** , and **gender-nonconforming** people set forth by the World Professional Association for Transgender Health (WPATH). In addition, the Endocrine Society has issued practice guidelines for endocrine treatment to alleviate gender dysphoria.

Transgender and gender-nonconforming children and adolescents have increased vulnerability to mental health concerns because of social stigma attached to gender nonconformity. Moreover, transgender and gender-nonconforming children and adolescents may present with general health concerns unrelated to their gender identity or gender expression, but may experience barriers to care that include a lack of cultural competence on the part of healthcare providers or the healthcare systems in which they practice. Therefore, to serve the youth and their families adequately, attention to both cultural and clinical competency is critical and should be improved. The American Psychological Association and the American Association of Child and Adolescent Psychiatrists have published practice guidelines to promote improved access to competent care.

Cultural and Clinical Competence

Cultural competence refers to the ability to communicate effectively with patients from various backgrounds. This includes appropriate assessment and clinical documentation of both gender identity (What is your current gender identity?) and sex assigned at birth (What sex were you assigned at birth [on your original birth certificate]?), use of preferred names and pronouns, and availability of all-gender bathrooms. It also includes recognition of and respect for gender diversity: children and adolescents may identify as girl, boy, boygirl, girlboy, transgender, genderqueer, nonbinary, gender fluid, gender questioning, or any other way in which they may describe their gender identity and expression (see Chapter 133). Particularly with children and adolescents, it is imperative not to label prematurely a young person's gender identity, but rather allow ample time for them to explore their gender identity and expression.

Clinical competence in transgender care refers to training and experience in providing gender-affirming care to facilitate gender identity development, alleviate any gender dysphoria, and promote resilience in the face of stigma. Care should ideally be provided by an interdisciplinary team or, alternatively, in consultation with other providers involved in the child or adolescent's care. This may include primary care providers, pediatric endocrinologists, and mental health professionals. The WPATH Standards of Care recommend that providers be competent in working with children and adolescents; be able to screen for coexisting mental health concerns; be knowledgeable about gender-nonconforming identities and expressions; and be knowledgeable and engaged in continuing education about the assessment and treatment of gender dysphoria.

Gender Literacy

For both providers and patients (child or adolescent and family), an up-to-date understanding of gender diversity is key. Much is yet to be learned about transgender identity development, but we do know that gender is not necessarily *binary,* and transgender and gender-nonconforming children and adolescents may identify and express their gender identity along a spectrum. The implication for care is that not all these children and adolescents need to change their gender role from male to female or female to male, and are in need of early medical interventions. Certainly, for some transgender and gender-nonconforming children and adolescents, these interventions are medically necessary and lifesaving, and evidence to date indicates that for those who meet criteria for a DSM-5 diagnosis of gender dysphoria, treatment appears safe and effective in reducing gender dysphoria and optimizing mental health and well-being. Others, however, do not identify with the gender binary (i.e., do not identify as male or female, but rather as an alternative gender) and need a more individualized approach that may or may not include changes in gender role and/or any of the available medical interventions. For all young people, it is imperative to support them in the process of identity exploration and tolerate any ambiguity and uncertainty, as well as evaluate and treat their concerns in light of their overall child and adolescent development.

Assessment

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) outlines criteria for a diagnosis of gender dysphoria in children as well as in adolescents and adults (see Table 133.2). For children, these criteria must include a strong desire or insistence to be of the other gender (or some alternative gender that differs from one's assigned gender). For adolescents, this may include a marked incongruence between one's experienced/expressed gender and (anticipated) primary and/or secondary sex characteristics; a strong desire for the sex characteristics of the other gender (or some alternative gender that differs from one's assigned gender), and/or a strong desire to be treated as another gender.

There is considerable variation in the clinical presentation, severity, and persistence of gender dysphoria among children and adolescents. It is therefore important to obtain a history of gender identification and expression and monitor ongoing identity exploration and development. Coexisting mental health concerns of anxiety, depression, nonsuicidal self-injury, suicidal ideation, and suicide attempts are not uncommon and should be assessed. There also is a higher prevalence of autism spectrum disorder among children and adolescents presenting with gender dysphoria.

Treatment

Transgender and gender-nonconforming children and adolescents can benefit greatly from a nonjudgmental and empathetic stance, patient education about gender diversity and the available options to alleviate gender dysphoria and affirm gender identity, access to community resources, and family support. Attention to behavioral problems and therapy for any mental health concerns caused by gender nonconformity and the attached social stigma should be incorporated into the treatment plan.

Treatment of gender dysphoria may include psychotherapy to reduce distress related to gender dysphoria or any other psychosocial difficulties. *Gender nonconformity in and of itself is not pathologic.* In addition, it is not ethical to try to change gender identity and expression to become more congruent with sex assigned at birth, because this has proved unsuccessful, particularly in the long term. Instead, psychotherapy (by a professional trained in transgender health) should support the unfolding process of identity exploration and development and assist the patient and family to manage any uncertainty and anxiety about the eventual outcome. Options to affirm gender identity include changes in gender role and expression, puberty suppression, feminizing or masculinizing hormones, and surgery. Changes in gender role may include changes in name and pronouns.

Puberty suppression with GnRH analogs, a reversible early medical intervention to reduce dysphoria by preventing the development of unwanted sex characteristics, is available as early as Tanner Stage 2. Feminizing or masculinizing **hormone therapy** , only partially reversible, is available and should be tailored to the somatic, emotional, and mental development of the adolescent. **Masculinizing chest surgery** , irreversible, is available preferably after ample experience living in a gender role congruent with the adolescent's gender identity. **Breast augmentation** is available, particularly after feminizing hormones have reached their maximum impact on breast growth. Hormone therapy or chest/breast surgery is indicated in patients with persistent, well-documented gender dysphoria who have the capacity to make a fully informed decision and to consent for treatment. **Genital surgery** (phalloplasty, metoidioplasty, vaginoplasty), irreversible, is available after living for a least 12 mo in a gender role congruent with the adolescent's gender identity, and preferably after the legal age of majority to give consent for medical procedures has been reached. For all these options, informed consent and support from family are critically important.

Early medical interventions have shown great promise in reducing gender dysphoria and optimizing psychosocial adjustment and well-being, but much remains unknown, particularly about the long-term effects of puberty suppression. Moreover, gender identity and expression should be evaluated within the larger context of identity and human development, especially during the formative years of childhood and adolescence.

Many transgender people choose hormone therapy and do not undergo surgery of breast/chest or genitals. The implications for fertility and options for fertility preservation should be discussed and considered before hormone therapy and surgery. Indeed, there are transgender individuals who elect to have children and nurse the child after birth. Rather than using the term *breastfeeding* , the term *chest feeding* may be preferred. When transgender adults seek primary healthcare, attention must be focused on gender- as well as sex organ–specific preventive screening (e.g., Pap smear, mammography, prostate exam).

Families

Family support is an important resource for transgender and gender-nonconforming youth and has been shown to buffer the negative impact of stigma on mental health. Family support also is a prerequisite for initiation of puberty suppression, feminizing or masculinizing hormone therapy, or any surgery before the age of legal majority has been reached. Providers are encouraged to include family in all aspects of treatment, while understanding that family members may be at different points in the process of coming to terms with having a transgender or gender-nonconforming loved one. Family members may benefit from online and community resources to educate themselves about gender diversity and to connect with similar others. Transgender and gender-nonconforming children and adolescents as well as their families are encouraged to learn as much as possible to be able to make fully informed decisions, in consultation with clinically competent transgender care providers, about the available behavioral and medical treatment options to affirm gender identity.

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CHAPTER 136

The Epidemiology of Adolescent Health Problems

Gale R. Burstein

Adolescence is the first period of life where the major determinants of morbidity and mortality are *behavioral* rather than congenital or infectious. As adolescents make the transition from childhood to adulthood, they establish **behaviors** that affect both their current and future health. Adolescence is a time of immense **biologic, psychological, and social change** (see Chapter 132). Many of the psychological changes have a biologic substrate in the development and eventual maturation of the central nervous system, particularly the frontal lobe areas responsible for executive functioning (Fig. 136.1). In addition to cognitive development, there are both risk and protective factors for adverse adolescent health behaviors that are dependent on the social environment as well as the mental health of an adolescent (Table 136.1).

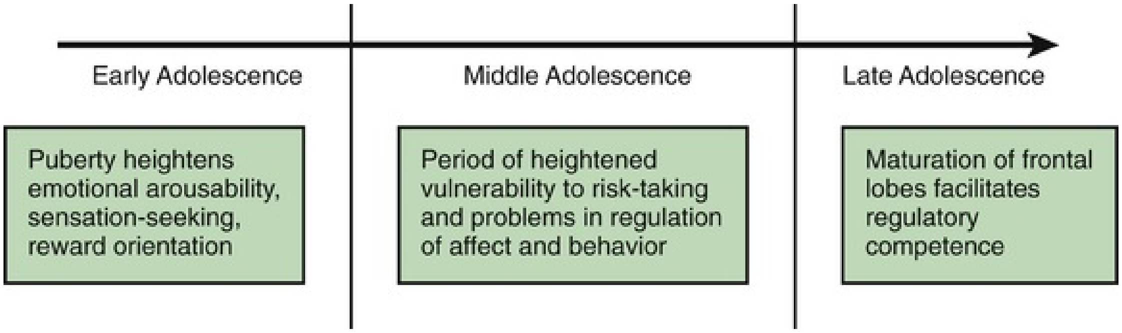
Early Adolescence
Middle Adolescence
Late Adolescence
Puberty heightens emotional arousability, sensation-seeking, reward orientation
Period of heightened vulnerability to risk-taking and problems in regulation of affect and behavior
Maturation of frontal lobes facilitates regulatory competence

FIG. 136.1 It has been speculated that the impact of puberty on arousal and motivation occurs before the maturation of the frontal lobes is complete. This gap may create a period of heightened vulnerability to problems in the regulation of affect and behavior, which might help to explain the increased potential in adolescence for risk taking, recklessness, and the onset of emotional and behavioral problems. (From Steinberg L:

Cognitive and affective development in adolescence, *Trends Cogn Sci* 9:69–74, 2005.)

Table 136.1

Identified Risk and Protective Factors for Adolescent Health Behaviors

BEHAVIOR	RISK FACTORS	PROTECTIVE FACTORS
Smoking	Depression and other mental health problems, alcohol use, disconnectedness from school or family, difficulty talking with parents, minority ethnicity, low school achievement, peer smoking	Family connectedness, perceived healthiness, higher parental expectations, low prevalence of smoking in school
Alcohol and drug misuse	Depression and other mental health problems, low self-esteem, easy family access to alcohol, working outside school, difficulty talking with parents, risk factors for transition from occasional to regular substance misuse (smoking, availability of substances, peer use, other risk behaviors)	Connectedness with school and family, religious affiliation
Teenage pregnancy	Deprivation, city residence, low educational expectations, lack of access to sexual health services, drug and alcohol use	Connectedness with school and family, religious affiliation
Sexually transmitted infections	Mental health problems, substance misuse	Connectedness with school and family, religious affiliation

Adapted from McIntiosh N, Helms P, Smyth R, editors. *Fofar and Arneil's textbook of pediatrics,* ed 6, Edinburgh, 2003, Churchill Livingstone, pp 1757–1768; and Viner R, Macfarlane A: Health promotion, *BMJ* 330:527–529, 2005.

Many adolescents continually confront the task of making healthy choices while struggling with impulsivity that can lead to unintentional consequences, such as injuries, sexually transmitted infections (STIs), or drug overdoses. Adolescents are also challenged with adopting behaviors that will affect their future adult health, such as eating nutritiously, engaging in physical activity, and choosing not to use tobacco. Environmental factors, such as family, peers, school, community, and religiosity, also contribute to adolescents' health and risk behaviors. The U.S. Centers for Disease Control and Prevention (CDC) **Youth Risk Behavior Surveillance Survey** , a school-based survey of a nationally representative sample of U.S. high school students, demonstrates that youth begin engaging in behaviors that place their health at risk during adolescence (Fig. 136.2).

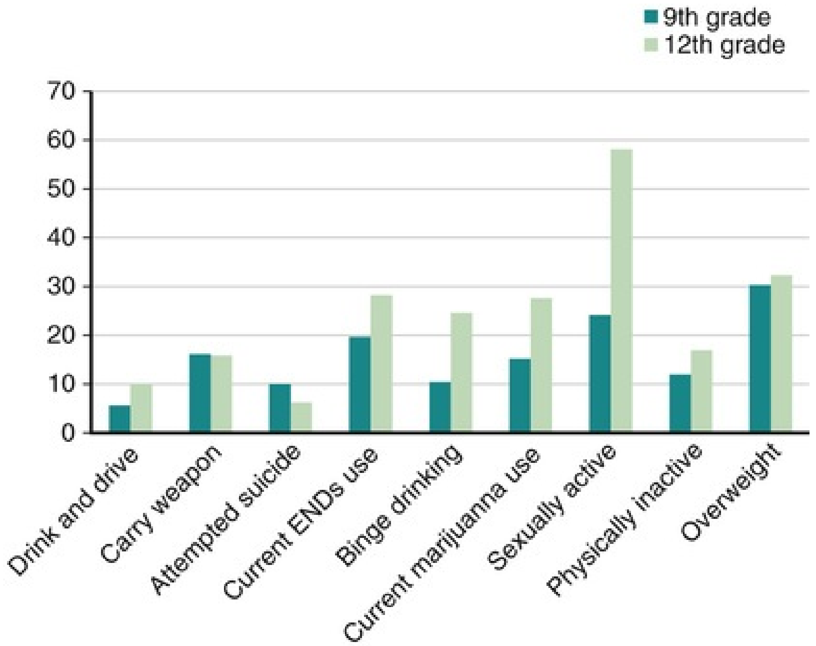

FIG. 136.2 Selected health behaviors among 9th and 12th grade high school students. ENDs, Electronic nicotine delivery system. (Data from Centers for Disease Control and Prevention: 1991–2015 High school youth risk behavior survey data. http://nccd.cdc.gov/youthonline .)

Although according to the 2015 CDC National Health Interview Survey (https://www.cdc.gov/nchs/nhis/shs/tables.htm), a probability sample survey conducted annually, an estimated 82% of 12-17 yr olds report excellent or very good health, 11% reported limitation in usual activities due to one or more chronic conditions, 10% missed 6-10 school days in the past year, 6% are uninsured, 6% have no usual place of healthcare, 10% have asthma, 12% have respiratory allergies, 10% have a learning disability, 14% have attention-deficit/hyperactivity disorder, and 18% take prescription medications routinely. In 2014 the mortality rate among adolescents 15-19 yr of age was 45 deaths per 100,000 population. While varying by gender, the leading **causes of death** overall among adolescents 15-19 yr of age are (1) unintentional injuries; (2) suicide; and (3) homicide (Table 136.2).

Table 136.2

Leading Causes of Death Among 15-19 Yr Olds by Gender, United States, 2014*

LEADING	MALE	FEMALE

CAUSES OF DEATH	Cause of Death	Mortality Rate per 100,000 Population	Cause of Death	Mortality Rate per 100,000 Population
#1	Accidents (unintentional injuries)	24.9	Accidents (unintentional injuries)	10.1
#2	Intentional self-harm (suicide)	13.0	Intentional self-harm (suicide)	4.2
#3	Assault (homicide)	11.2	Malignant neoplasms	2.5

[*] Based on data from Heron M: Deaths: leading causes for 2014, *Natl Vital Stat Rep* 65(5), 2016.

Within the adolescent population, **disparities in health** occur. Adolescent health outcomes and behaviors vary among populations that can be defined by race or ethnicity, gender, education or income, disability, geographic location (e.g., rural or urban), or sexual orientation. Health disparities result from multiple factors, including poverty, environmental threats, inadequate access to healthcare, individual and behavioral factors, and educational inequalities (Table 136.3).

Table 136.3

Adolescent Health Outcomes by Race/Ethnicity, United States, 2010–2012

OUTCOME	WHITE	BLACK	AI/AN	API	HISPANIC
Deaths[*]	43.5	62.3	49.7	23.1	38.1
Births[†]	17.3	34.9	27.3	7.7	38.0
Obese[‡]	12.4	16.8	15.9	5.5[§]	16.4
Asthma[‡]	22.1	27.8	17.7	17.7[§]	22.5
Depressed[‡]	28.6	25.2	34.9	22.9[§]	35.3
Chlamydia[*]	775.2	4,200.8	2,229.6	267.9[§]	1,067.0
Gonorrhea[*]	94.4	1,218.5	393.8	37.6[§]	150.6
HIV[*]	1.8	36.2	4.9	2.8[§]	7.0

[*] 2015 Rates per 100,000 15-19 yr old population by race/ethnicity.

[†] 2014 Rates of births in per 1,000 15-19 yr old females by race/ethnicity.

[‡] Percent high school students reporting health outcome in 2015.

[§] Rates of Asian-only race.

AI/AN, American Indian or Alaska Native; API, Asian or Pacific Islander; HIV, human immunodeficiency virus.

Access to Healthcare

Adolescents in the United States make fewer visits to physicians for ambulatory office visits than any other age group; school-age children and adolescents are more likely than younger children to have unmet health needs and delayed medical care. Adolescents who actually receive preventive care may still not have access to **time alone with their provider** to discuss confidential health issues such as STIs, HIV, or pregnancy prevention. Less than half (40%) of adolescents have time alone with their healthcare provider during a preventive healthcare visit; sexually experienced teens report sexual health discussions more often than nonsexually experienced teens, but the frequency is still low at 64% and 33.5% for sexually experienced females and males, respectively.

Young adults 18-24 yr are more likely to be insured with the 2010 Patient Protection and Affordable Care Act (**ACA**). Currently, the ACA permits children to receive benefits from their parents' health plans through age 26 yr. *Healthy People* provides science-based, 10-yr national objectives for measuring and improving the health of all Americans by establishing benchmarks and monitoring progress over time. The ***Healthy People 2020*** agenda includes 11 adolescent-specific objectives with a goal of improving the healthy development, health, safety, and well-being of adolescents and young adults over the next 10 yr (Table 136.4). This science-based initiative is centered around a framework for public health prevention priorities and actions to improve the health status of U.S. youth.

Table 136.4

Healthy People 2020 Adolescent Health (AH) Objectives

- **AH-1** : Increase the proportion of adolescents who have had a wellness checkup in the past 12 months
- **AH-2** : Increase the proportion of adolescents who participate in extracurricular and out-of-school activities
- **AH-3** : Increase the proportion of adolescents who are connected to a parent or other positive adult caregiver
    - **AH-3.1** : Increase the proportion of adolescents who have an adult in their lives with whom they can talk about serious problems

  - **AH-3.2** : Increase the proportion of parents who attend events and activities in which their adolescents participate
- **AH-4** : (Developmental) Increase the proportion of adolescents and young adults who transition to self-sufficiency from foster care
- **AH-5** : Increase educational achievement of adolescents and young adults
  - **AH-5.1** ***(Leading Health Indicator)*** : Increase the proportion of students who graduate with a regular diploma 4 years after starting 9th grade
  - **AH-5.2** : Increase the proportion of students who are served under the Individuals with Disabilities Education Act who graduate high school with a diploma
  - **AH-5.3** : Increase the proportion of students whose reading skills are at or above the proficient achievement level for their grade
  - **AH-5.4** : Increase the proportion of students whose mathematics skills are at or above the proficient achievement level for their grade
  - **AH-5.5** : Increase the proportion of adolescents who consider their school work to be meaningful and important
  - **AH-5.6** : Decrease school absenteeism among adolescents due to illness or injury
- **AH-6** : Increase the proportion of schools with a school breakfast program
- **AH-7** : Reduce the proportion of adolescents who have been offered, sold, or given an illegal drug on school property
- **AH-8** : Increase the proportion of adolescents whose parents consider them to be safe at school
- **AH-9** : (Developmental) Increase the proportion of middle and high schools that prohibit harassment based on a student's sexual orientation or gender identity
- **AH-10** : Decrease the proportion of public schools with a serious violent incident
- **AH-11** : Reduce adolescent and young adult perpetration of, as well as victimization by, crimes
  - **AH-11.1** : Decrease the rate of minor and young adult perpetration of violent crimes
  - **AH-11.2** : Decrease the rate of minor and young adult perpetration of serious property crimes

AH-11.3 : (Developmental) Decrease the percentage of counties and cities reporting youth gang activity

AH-11.4 : (Developmental) Reduce the rate of adolescent and young adult victimization from crimes of violence

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From US Department of Health and Human Services: *Healthy People 2020*, available at: https://www.healthypeople.gov/2020/topics-objectives/topic/Adolescent-Health/objectives .

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CHAPTER 137

Delivery of Healthcare to Adolescents

Gale R. Burstein

Healthcare providers play an important role in nurturing healthy behaviors among adolescents, because the leading causes of death and disability among adolescents are preventable. Adolescence provides a unique opportunity to prevent or modify health conditions arising from behaviors that develop in the 2nd decade of life and that can lead to substantial morbidity and mortality, such as trauma, cardiovascular and pulmonary disease, type 2 diabetes, reproductive health disease, and cancer (see Chapter 132 , Table 132.4).

Health systems in each community should be in place to ensure comprehensive and high-quality care to adolescents. **Health insurance coverage** that is affordable, continuous, confidential, and not subject to exclusion for preexisting conditions should be available for all adolescents and young adults. **Comprehensive, coordinated benefits** should meet the developmental needs of adolescents, particularly for reproductive, mental health, dental, and substance abuse services. **Safety net providers and programs** that provide confidential services, such as school-based health centers, federally qualified health centers, family planning services, and clinics that treat sexually transmitted infections (**STIs**) in adolescents and young adults, need to have assured funding for viability and sustainability. **Quality-of-care** data should be collected and analyzed by age so that the performance measures for age-appropriate healthcare needs of adolescents are monitored. **Affordability** is important for access to preventive services. Family involvement should be encouraged, but **confidentiality** and adolescent consent are critically important. **Healthcare providers** , trained and experienced in adolescent care, should be available in all communities. Healthcare providers should be adequately compensated to support the range and intensity of services required to address the developmental and health service needs of adolescents. The development and dissemination of provider education about **adolescent preventive health guidelines** have been demonstrated to improve the content of recommended care (Table 137.1). The ease of recognition or expectation that an adolescent's needs can be addressed in a setting relates to the **visibility and flexibility** of sites and services. Staff at sites should be approachable, linguistically capable, and culturally competent. Health services should be coordinated to respond to goals for adolescent health at the local, state, and national levels. The coordination should address service financing and delivery in a manner that reduces disparities in care.

Table 137.1

Bright Futures/American Academy of Pediatrics Recommendations for Preventive Healthcare for 11-21 Yr Olds

	PERIODICITY AND INDICATIONS
HISTORY	Annual
MEASUREMENTS	
Body mass index	Annual
Blood pressure	Annual
SENSORY SCREENING	
Vision	At 12 yr and 15 yr visits or if risk assessment positive
Hearing	Screen with audiometry, including 6,000 and 8,000 Hz high frequencies once at 11-14 yr, once at 15-17 yr, and once at 18-21 yr.
DEVELOPMENTAL/BEHAVIORAL ASSESSMENT	
Developmental surveillance	Annual
Psychosocial/behavioral assessment	Annual
Depression screening	Annual for 12 yr and older
Tobacco, alcohol, and drug use assessment	If risk assessment positive
PHYSICAL EXAMINATION	Annual
PROCEDURES	
Immunization*	Annual
Hematocrit or hemoglobin	If risk assessment positive
Tuberculin test	If risk assessment positive
Dyslipidemia screening	Once at 9-11 yr, and once at 17-21 yr
STI screening	If sexually active
HIV screening †	Once between ages 15 and 18 yr Discuss and offer at earlier age and annually if risk assessment positive.
Cervical dysplasia screening ‡	Beginning at age 21 yr
ORAL HEALTH	Annual; refer to dental home
ANTICIPATORY	Annual §

GUIDANCE	

[*] Schedules per the Advisory Committee on Immunization Practices, published annually at http://www.cdc.gov/vaccines/schedules/hcp/index.html and http://redbook.solutions.aap.org/SS/Immunization_Schedules.aspx .

[†] CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. The American Academy of Pediatrics recommends offering routine HIV screening to all adolescents at least once by 16-18 yr of age and to those younger if at risk. US Preventive Services Task Force recommends offering routine HIV screening to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

[‡] Screening for cervical cancer, April 2012, US Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm .

[§] Refer to specific guidance by age as listed in *Bright Futures* guidelines.

HIV, Human immunodeficiency virus; STI, sexually transmitted infection.

Adapted from Hagan JF, Shaw JS, Duncan PM, editors: *Bright Futures: guidelines for health supervision of infants, children, and adolescents,* ed 4, Elk Grove Village, IL, 2017, American Academy of Pediatrics.

Although most adolescents in the United States have seen a healthcare provider in the past year and report a usual source of healthcare, adolescents are less likely to receive **preventive care** services. According to the 2011 National Health Interview Survey, an estimated 90% of 12-17 yr old U.S. adolescents had 1 or more contacts with a healthcare professional in the past year, 98% identify a usual source of care at a physician's office or clinic, and 17% made at least 1 emergency department visit in the past year. Uninsured adolescents are the least likely to receive care. In 2015, 63% of people under age 19 yr were covered at some point during the year by private insurance, and 43% of children had public health insurance at some point during 2015. However, even among adolescents who are fully insured with a usual source of care, most do not receive preventive healthcare. An analysis of claims data from a large Minnesota health plan with approximately 700,000 members found that among patients age 11-18 yr who were enrolled for at least 4 yr between 1998 and 2007, few received preventive care visits. One third of adolescents had no preventive care visits from age 13 through 17 yr, and another 40% had only a single such visit. Nonpreventive care visits were more frequent in all age-groups, averaging about 1 per yr at age 11 yr, climbing to about 1.5 per yr at age 17 yr. Among older adolescents, females had both more preventive care and more nonpreventive care visits than did males.

The **Patient Protection and Affordable Care Act (ACA)** , enacted in March 2010, has expanded access to both commercial health plans and Medicaid for young adults age 19-26 yr (Fig. 137.1). From June 2010 through June 2012, the proportion of young adults with insurance increased from 65.7% to 73.8%. Currently, ACA provisions require that commercial health plans (1) continue dependent coverage to 26 yr, regardless of the young adult's financial or dependent status, marriage, or educational enrollment; (2) mandate university and college student health plans to enhance consumer protections for students; (3) provide financial assistance for young adults to enroll into health insurance exchanges with incomes ranging from 133–399% of the federal poverty level in **Medicaid expansion states** ; and (4) offer preventive healthcare services free of any cost sharing, deductibles, or copayments. In states that have expanded Medicaid coverage, all adults with incomes <133% of the federal poverty level are eligible to enroll.

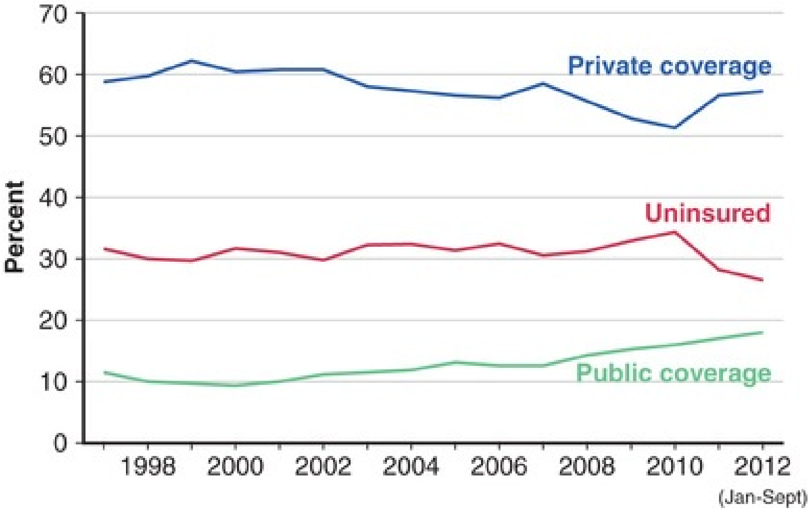

FIG. 137.1 Percentage of adults age 19-25 yr with health insurance by coverage type and percentage uninsured at the time of the interview: United States, 1997–September, 2012. *Note:* Estimates for 2012 are based on data collected in January through September. Data are based on household interviews of a sample of the civilian noninstitutionalized population. (Data from CDC/NCHS, National Health Interview Survey, 1997–2012, Family Core Component.)

The complexity and interaction of physical, cognitive, and psychosocial **developmental processes** during adolescence require sensitivity and skill on the part of the health professional (see Chapter 132). Health education and promotion, as well as disease prevention, should be the focus of every visit. In 2017 the American Academy of Pediatrics (AAP) in collaboration with the U.S.

Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, published the 4th edition of *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents* , which offers providers a strategy for delivery of adolescent preventive health services with screening and counseling recommendations for early, middle, and late adolescence (Table 137.2). *Bright Futures* is rooted in the philosophy of preventive care and reflects the concept of caring for children in a “medical home.” These guidelines emphasize effective partnerships with parents and the community to support the adolescent's health and development.

Table 137.2

Adolescent Screening Recommendations

	11-14 YR OLD VISIT	**15-17 YR OLD VISIT**	**18-21 YR OLD VISIT**
Universal Screening	**Action**	**Action**	**Action**
Cervical dysplasia*	N/A	N/A	Pap smear all young women at 21 yr visit
Depression	Adolescent depression screen beginning at 12 yr visit	Adolescent depression screen	Adolescent depression screen
Dyslipidemia	Lipid screen once at 9-11 yr	Lipid screen once at 17-21 yr	Lipid screen once at 17-21 yr
Hearing	Once at 11-14 yr Audiometry, including 6,000 and 8,000 Hz high frequencies	Once at 15-17 yr Audiometry, including 6,000 and 8,000 Hz high frequencies	Once at 18-21 yr Audiometry, including 6,000 and 8,000 Hz high frequencies
HIV †	Selective screening (see below)	HIV test once at 15-18 yr	HIV test once at 15-18 yr
Tobacco, alcohol, or drug use	Tobacco, alcohol, or drug use screen	Tobacco, alcohol, or drug use screen	Tobacco, alcohol, or drug use screen
Vision	At 12 yr visit Objective measure with age-appropriate visual-acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters	At 15 yr visit Objective measure with age-appropriate visual-acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters	N/A

		11-14 YR OLD VISIT	**15-17 YR OLD VISIT**	**18-21 YR OLD VISIT**
Selective	**Risk Assessment**	**Action If RA+**	**Action If RA+**	**Action If RA+**

Screening	**(RA)**			
Anemia	+ on risk screening questions	Hemoglobin or hematocrit	Hemoglobin or hematocrit	Hemoglobin or hematocrit
Dyslipidemia (if not universally screened at this visit	+ on risk screening questions and not previously screened with normal results	Lipid profile	Lipid profile	Lipid profile
HIV †	+ on risk screening questions	HIV test	HIV test (if not universally screened at this visit)	HIV test (if not universally screened at this visit)
Oral health (through 16 yr visit)	Primary water source fluoride deficient	Oral fluoridation supplementation	Oral fluoridation supplementation	N/A
STIs				
• Chlamydia • Gonorrhea	Sexually active females Sexually active males and + on risk screening questions	Chlamydia and gonorrhea NAAT (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea NAAT (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea NAAT (use tests appropriate for population and clinical setting)
• Syphilis	Sexually active and + on risk screening questions	Syphilis test	Syphilis test	Syphilis test
Tuberculosis	+ on risk screening questions	Tuberculin skin test	Tuberculin skin test	Tuberculin skin test
Vision at other ages	+ on risk screening questions at 11, 13, and 14 yr visits	Objective measure with age-appropriate visual-acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters	Objective measure with age-appropriate visual-acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters	Objective measure with age-appropriate visual-acuity measurement using HOTV or Lea symbols, Sloan letters, or Snellen letters

[*] Screening for Cervical Cancer. April 2012. U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm .

[†] Centers for Disease Control and Prevention recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. American Academy of Pediatrics recommends routine HIV screening offered to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends routine HIV screening offered to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

NA, Not applicable; NAAT, nucleic acid amplification test; STIs, sexually transmitted infections.

Adapted from Hagan JF, Shaw JS, Duncan PM, editors: *Bright Futures: guidelines for health supervision of infants, children, and adolescents,* ed 4, Elk Grove Village, IL, 2017, American

Academy of Pediatrics; and Bright Futures/American Academy of Pediatrics: Recommendations for Preventive Pediatric Health Care (Periodicity Schedule), 2017. https://www.aap.org/en-us/Documents/periodicity_schedule.pdf .

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) currently recommends routine **adolescent vaccines** for universal administration beginning at the 11-12 yr old visit, or as soon as possible, (a) tetanus–diphtheria–acellular pertussis vaccine (Tdap), (b) the meningococcal conjugate vaccine (MCV4) with a booster at age 16 yr, and (c) the human papillomavirus vaccine (HPV) series (see Chapter 197). ACIP recommends annual influenza vaccination and hepatitis A virus (HAV) vaccination to adolescents and young adults who have not previously received the HAV vaccine series if immunity against HAV is desired or for those at increased risk for infection, such as men who have sex with men (MSM), injection drug users (IDU), and those with chronic liver disease or clotting factor disorders, or who live in areas that target older children for HAV vaccine.

The time spent on various elements of the screening will vary with the issues that surface during the assessment. For **gay and lesbian youth** (see Chapter 134), emotional and psychological issues related to their experiences, from fear of disclosure to the trauma of homophobia, may direct the clinician to spend more time assessing emotional and psychological supports in the young person's environment. For youth with **chronic illnesses or special needs** , the assessment of at-risk behaviors should not be omitted or deemphasized by assuming they do not experience the "normal" adolescent vulnerabilities.

137.1

Legal Issues

Gale R. Burstein

The rights of an individual, including those of adolescents, vary widely between nations. In the United States, the right of a minor to consent to treatment without parental knowledge differs between states and is governed by **state-specific**

minor consent laws . Some consent laws are based on a minor's status, such as minors who are emancipated, parents, married, pregnant, in the armed services, or mature. In some states, minors can be considered *emancipated* if they are or have served in the armed services or are living apart from parents and are economically independent through gainful employment. A *mature minor* is a minor who is emotionally and intellectually mature enough to give informed consent and who lives under the supervision of a parent or guardian. Courts have held that if a minor is mature, a physician is not liable for providing beneficial treatment. There is no formal process for recognition of a mature minor. The determination is made by the healthcare provider.

Some minor consent laws are based on services a minor is seeking, such as emergency care, sexual healthcare, substance abuse, or mental healthcare (Table 137.3). All 50 states and the District of Columbia explicitly allow minors to consent for their own health services for **STIs** . Approximately 25% of states require that minors be a certain age (generally 12-14 yr) before they can consent for their own care for STIs. No state requires parental consent for STI care or requires that providers notify parents that an adolescent minor child has received STI services, except in limited or unusual circumstances.

Table 137.3

Types of Minor Consent Statutes or Rules of Common Law That Allow for Medical Treatment of a Minor Patient Without Parental Consent

LEGAL EXCEPTIONS TO INFORMED CONSENT REQUIREMENT	MEDICAL CARE SETTING
The “emergency” exception	• The child is suffering from an emergent condition that places his or her life or health in danger. • The child's legal guardian is unavailable or unable to provide consent for treatment or transport. • Treatment or transport cannot be safely delayed until consent can be obtained. • The professional administers only treatment for emergent conditions that pose an immediate threat to the child.
The “emancipated minor” exception	• Married • Economically self-supporting and not living at home • Active-duty status in the military • In some states, a minor who is a parent or pregnant • Some states might require a court to declare the emancipation of a minor.
The “mature	Most states recognize a mature minor, in which a minor, usually ≥14 yr, displays sufficient

minor" exception	maturity and intelligence to understand and appreciate the benefits, risks, and alternatives of the proposed treatment and to make a voluntary and reasonable choice on the basis of that information. States vary or whether a judicial determination is required.
Exceptions based on specific medical condition (state laws vary)	Minor seeks: • Mental health services • Pregnancy and contraceptive services • Testing or treatment for HIV infection or AIDS • Sexually transmitted infection testing and treatment • Drug and alcohol addiction treatment

Data from American Academy of Pediatrics: Consent for emergency medical services for children and adolescents, *Pediatrics* 128:427–433, 2011.

Minors' right to consent for **contraceptive services** varies from state to state. Almost 50% of states and the District of Columbia explicitly authorize all minors to consent for their own contraceptive services; and 50% of states permit minors to consent for their own contraceptive services under specific circumstances, such as being married, a parent, currently or previously pregnant, over a certain age, or a high school graduate, or per physician's discretion.

A minor's right to consent for **mental healthcare** and **substance abuse** treatment services vary by state and age of minor, whether care is medical vs nonmedical (e.g., counseling), and whether care is delivered as an inpatient vs outpatient basis. Minor consent laws often contain provisions regarding confidentiality and disclosure, even when general state consent laws do not have such provisions.

The **confidentiality** of medical information and records of a minor who has consented for his or her own *reproductive healthcare* is governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI or contraceptive services for which minors have given their own consent and do not allow disclosure of the information without the minor's consent. In other states, laws grant physicians discretion to disclose information to parents.

The confidentiality of medical information and records of a minor who has consented for his or her own healthcare is also governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI, contraceptive, or mental health services for which minors have given their own consent, and do not allow disclosure of the information without the minor's consent. In other states, laws grant physicians discretion to disclose information to parents. Title X and Medicaid both provide confidentiality protection for family planning services provided to minors with funding from these programs.

Federal regulations issued under the Federal Health Insurance Portability and Accountability Act of 1996, known as the **HIPAA Privacy Rule** , defer to state and "other applicable laws" with respect to the question of whether parents have access to information about care for which a minor has given consent. Thus, both the state laws that either prohibit or permit disclosure of confidential information and the federal Title X and Medicaid laws that protect the confidentiality of care for adolescents are important under the HIPAA Privacy Rule in determining when confidential information about health services for minors can be disclosed to parents.

Billing for confidential services is complex. Commercial health plans send home an **explanation of benefit (EOB)** to the primary insured or the primary beneficiary, listing services rendered by the provider and reimbursed by the health plan. An EOB documenting that confidential health services were rendered to their adolescent dependent that is received by a parent may disclose those services. In addition, copayments automatically generated with certain billing codes for office visits and medications can be a barrier for adolescents receiving care, including treatment.

Providers may elect to establish a policy of discussing with their adolescent patients when medical records and other information will be disclosed and developing a mechanism to alert office staff as to what information in the chart is confidential. For legal and other reasons, a chaperone should be present whenever an adolescent female patient is examined by a male physician.

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137.2

Screening Procedures

Gale R. Burstein

Interviewing the Adolescent

The preparation for a successful interview with an adolescent patient varies based on the history of the relationship with the patient. Patients (and their parents) who are going from preadolescence to adolescence while seeing the same provider should be guided through the transition. Although the rules for confidentiality are the same for new and continuing patients, the change in the **physician–patient relationship** , allowing more privacy during the visit and more autonomy in the health process, may be threatening for the parent as well as the adolescent. For new patients, the initial phases of the interview are more challenging given the need to establish rapport rapidly with the patient in order to meet the goals of the encounter. Issues of **confidentiality and privacy** should be explicitly stated along with the conditions under which that confidentiality may need to be altered, that is, in life- or safety-threatening situations. For new patients, the parents should be interviewed with the adolescent or before the adolescent to ensure that the adolescent does not perceive a breach of confidentiality. The clinician who takes time to listen, avoids judgmental statements and the use of street jargon, and shows respect for the adolescent's emerging maturity will have an easier time communicating with the adolescent. The use of open-ended questions, rather than closed-ended questions, will further facilitate history taking. (The closed-ended question, “Do you get along with your father?” leads to the answer “yes” or “no,” in contrast to the question, “What might you like to be different in your relationship with your mother?” which may lead to an answer such as, “I would like her to stop always worrying about me.”)

The **goals** of the interview or clinical encounter are to establish an information base, identify problems and issues from the patient's perspective, and identify problems and issues from the perspective of the clinician, based on knowledge of the health and other issues relevant to the adolescent age-group. The adolescent should be given an opportunity to express concerns and the reasons for seeking medical attention. The adolescent as well as the parent should be allowed to express the strengths and successes of the adolescent, in addition to communicating problems.

The effectiveness of an interview can be compromised when the interviewer is distracted by other events or individuals in the office, when extreme time limitations are obvious to either party, or when there is expressible discomfort with either the patient or the interviewer. The need for an **interpreter** when a patient is hearing impaired or if the patient and interviewer are not language compatible provides a challenge but not necessarily a barrier under most circumstances (see Chapter 11). Observations during the interview can be useful to the overall assessment of the patient's maturity, presence or absence of depression, and the parent–adolescent relationship. Given the key role of a successful interview in the screening process, adequate training and experience should be sought by clinicians providing comprehensive care to adolescent patients.

Psychosocial Assessment

A few questions should be asked to identify the adolescent who is having difficulty with **peer relationships** (Do you have a best friend with whom you can share even the most personal secret?), **self-image** (Is there anything you would like to change about yourself?), **depression** (What do you see yourself doing 5 yr from now?), **school** (How are your grades this year compared with last year?), **personal decisions** (Are you feeling pressured to engage in any behavior for which you do not feel you are ready?), and an **eating disorder** (Do you ever feel that food controls you, rather than vice versa?). *Bright Futures* materials provide questions and patient encounter forms to structure the assessments. The **HEADS/SF/FIRST** mnemonic, basic or expanded, can be useful in guiding the interview if encounter forms are not available (Table 137.4). Based on the assessments, appropriate counseling or referrals are recommended for more thorough probing or for in-depth interviewing.

Table 137.4

Adolescent Psychosocial Assessment: HEADS/SF/FIRST Mnemonic

***H* ome.** Space, privacy, frequent geographic moves, neighborhood

***E* ducation/School.** Frequent school changes, repetition of a grade/in each subject, teachers' reports, vocational goals, after-school educational clubs (e.g., language, speech, math), learning disabilities

***A* buse.** Physical, sexual, emotional, verbal abuse; parental discipline

***D* rugs.** Tobacco, electronic cigarettes or vaping devices, alcohol, marijuana, inhalants, “club drugs,” “rave” parties, others; drug of choice, age at initiation, frequency, mode of intake, rituals, alone or with peers, quit methods, number of attempts

***S* afety.** Seat belts, helmets, sports safety measures, hazardous activities, driving while intoxicated

***S* exuality/*S* exual Identity.** Reproductive health (use of contraceptives, presence of sexually transmitted infections, feelings, pregnancy)

***F* amily and *F* riends**

Family: Family constellation; genogram; single/married/separated/divorced/blended family; family occupations and shifts; history of addiction in first- and second-degree relatives; parental attitude toward alcohol and drugs; parental rules; chronically ill, physically or mentally challenged parent

Friends: Peer cliques and configuration (“preppies,” “jocks,” "nerds," "computer geeks," cheerleaders), gang or cult affiliation

***I* mage.** Height and weight perceptions, body musculature and physique, appearance (including dress, jewelry, tattoos, body piercing as fashion trends or other statement)

***R* ecreation.** Sleep, exercise, organized or unstructured sports, recreational activities (television, video games, computer games, internet and chat rooms, church or community youth group activities [e.g., Boy (BSA)/Girl Scouts; Big Brother/Sister groups, campus groups]). How many hours per day, days per week involved?

***S* pirituality and Connectedness.** Use HOPE* or FICA [†] acronym; adherence, rituals, occult practices, community service or involvement

***T* hreats and Violence.** Self-harm or harm to others, running away, cruelty to animals, guns, fights, arrests, stealing, fire setting, fights in school

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[*] HOPE, *H* ope or security for the future; *o* rganized religion; *p* ersonal spirituality and *p* ractices; *e* ffects on medical care and end-of-life issues.

[†] FICA, Faith beliefs; importance and influence of faith; community support.

From Dias PJ: Adolescent substance abuse: assessment in the office, *Pediatr Clin North Am* 49:269–300, 2002.

Physical Examination

Vision Testing

The pubertal growth spurt may involve the optic globe, resulting in its elongation and myopia in genetically predisposed individuals (see Chapter 636). Vision testing should therefore be performed to detect this problem before it affects school performance.

Audiometry

Highly amplified music of the kind enjoyed by many adolescents may result in hearing loss or tinnitus (see Chapter 654). A hearing screening is recommended by the *Bright Futures* guidelines for adolescents who are exposed to loud noises regularly, have had recurring ear infections, or report problems.

Blood Pressure Determination

Criteria for a diagnosis of hypertension are based on age-specific norms that increase with pubertal maturation (see Chapter 449). An individual whose blood pressure (BP) exceeds the 95th percentile for his or her age is suspect for having hypertension, regardless of the absolute reading. Those adolescents with BP between the 90th and 95th percentiles should receive appropriate counseling relative to weight and have a follow-up examination in 6 mo. Those with BP above the 90th percentile should have their BP measured on 3 separate occasions to determine the stability of the elevation before moving forward with an intervention strategy. The technique is important; false-positive results may be obtained if the cuff covers less than two thirds of the upper arm. The patient should be seated, and an average should be taken of the 2nd and 3rd consecutive readings, using the change rather than the disappearance as the diastolic pressure. Most adolescents with BP elevation have labile hypertension. If BP is below 2 standard deviations (SD) for age, anorexia nervosa and Addison disease should be considered.

Scoliosis

See Chapter 699 .

Approximately 5% of male and 10–14% of female adolescents have a mild curvature of the spine. This is 2-4 times the rate in younger children. Scoliosis is typically manifested during the peak of the height velocity curve, at approximately 12 yr in females and 14 yr in males. Curves measuring >10 degrees should be monitored by an orthopedist until growth is complete.

Breast Examination

See Chapters 141 and 556 .

Visual inspection of the young and middle adolescent female adolescent's breasts is performed to evaluate progression of sexual maturation and provide reassurance about development.

Scrotum Examination

Visual inspection of the young and middle adolescent male testicles is performed to evaluate progression of sexual maturation and provide reassurance about development. The peak incidence of germ cell tumors of the testes is in late adolescence and early adulthood. Palpation of the testes may have an immediate yield and should serve as a model for instruction of self-examination. Because varicoceles often appear during puberty, the examination also provides an opportunity to explain and reassure the patient about this entity (see Chapter 560).

Pelvic Examination

See Chapter 563 .

Laboratory Testing

The increased incidence of iron-deficiency **anemia** after menarche directs the performance of a hematocrit annually in females with moderate to heavy menses. The reference standard for this test changes with progression of puberty, as estrogen suppresses erythropoietin (see Chapter 474). Populations with nutritional risk should also have the hematocrit monitored. Androgens have the opposite effect, causing the hematocrit to rise during male puberty; sexual maturity rating (SMR) 1 males have an average hematocrit of 39%, whereas those who have completed puberty (SMR 5; see Chapter 132) have an average value of 43%. **Tuberculosis (TB)** testing is important in adolescents with risk factors, such as an adolescent with HIV, living in the household with someone with HIV, the incarcerated or homeless adolescent, adolescents from a country where TB is common, or those with other risk factors, because puberty has been shown to activate this disease in those not previously treated. **Hepatitis C virus (HCV)** screening should be offered to adolescents who report risk factors, such as IDU, received blood products or organ donation before 1992, or long-term hemodialysis. Almost 10% of all HCV cases reported to CDC in 2015 were among 15-24 yr olds. CDC HCV surveillance data demonstrates that from 2006 to 2014, the number of reported HCV infections among females of reproductive age (15-44 yrs) doubled. Nearly half of those cases were among females 15-30 yrs of age. Two thirds (67%) of those with a known risk factor reported intravenous drug use.

Sexually active adolescents should undergo screening for **STIs** per CDC guidelines, regardless of symptoms (see Chapter 146). There are clear indications for chlamydia and gonorrhea screening of females ≤24 yr old, but less sufficient evidence to support routine screening in young men. Based on feasibility, efficacy, and cost-effectiveness, evidence is insufficient to recommend routine chlamydia screening in all sexually active young men. However, screening of sexually active young males should be considered in clinical settings associated with high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, sexually transmitted disease clinics) and should be offered to all young MSM. **HIV** screening should be discussed and offered at least once to all adolescents aged 15-18 yr and to younger and older adolescents who are at increased risk. Routine screening of adolescents who are asymptomatic for certain STIs (e.g., syphilis, trichomoniasis, herpes simplex virus, HPV) is not recommended. However, young MSM and pregnant adolescent females might require more thorough evaluation for all sexually transmitted diseases. Because cervical cancer incidence is low and complications from procedures may outweigh benefits of screening adolescent females, cervical cancer screening should not begin until age 21 yr.

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CHAPTER 138

Transitioning to Adult Care

Cynthia M. Holland-Hall, Gale R. Burstein, Lisa K. Tuchman

The importance of successfully transitioning the care of adolescents with **special healthcare needs (SHCN)** from pediatric to adult services has been recognized for more than 2 decades. Successful transition is associated with improved health outcomes and quality of life; poorly managed transition may lead to loss of a medical home and worsening of chronic disease control and previous care.

The American Academy of Pediatrics, in conjunction with other key professional societies, published detailed, comprehensive guidelines for incorporating transition services into the **medical home** for all adolescents, regardless of the presence or absence of SHCN. These guidelines are based on expert opinion because the evidence on transition outcomes is limited. This clinical report emphasizes that **transition** encompasses much more than simply the transfer of care to another provider. The guidelines go beyond recommendations for the pediatric medical home by providing guidance and practice-based resources for implementing elements of transition support in family medicine and internal medicine practices. This includes providing assistance for the patient in adapting to an adult model of healthcare delivery. Table 138.1 represents the key elements of healthcare transition. Tools to assist providers with these steps are available online from the National Center for Health Care Transition Improvement (www.gottransition.org).

Table 138.1

Key Elements of the Transition of Healthcare Process

- **Written transition policy** to be shared with youth, families, providers, and staff, explaining the process and the responsibilities of all team members

- **Transitioning youth registry** to track the progress of each patient through the transition process
- **Longitudinal readiness checklists** assessing the youth's ability for independence, self-management, and communicating with the adult healthcare system, as well as the family's readiness to assist the patient in achieving these goals
- **Written transition plan** documenting the steps to be conducted to meet the needs identified in the readiness assessment, as well as identifying appropriate adult care resources
- For youth with SHCN, expanded transition services, including attention to insurance, entitlements, guardianship, and vocational needs, in addition to adult subspecialty care
- Appropriate communication between the pediatric and adult medical home and subspecialists, including a **portable medical summary** and care plan delivered to the patient and caregivers
- Transfer of care, within the 18-21 yr old range, to adult providers, to whom pediatric providers continue to serve as a resource until transition is complete

The process begins with the development of a transition policy and its dissemination to all families of young adolescents, ensuring that families understand that transition planning will be an element of health maintenance and chronic care management visits throughout the adolescent years. By middle adolescence, a transition plan should be developed with the youth and family caregivers and updated at subsequent visits until the patient is ready for implementation of the adult care model in early adulthood. Periodic **readiness assessments** are key to plan and anticipate challenges. Critical to the transition process is **skills training** for the adolescent in communication, self-advocacy, and self-care. Some youth with SHCN depend on caregivers for navigating the healthcare system on their behalf, and it is not realistic to expect increased independence. For these youth, addressing guardianship, long-term care planning, and advanced directives are important. **Care coordination** has been found to facilitate navigation and engagement in an adult-oriented health system, especially for adolescents with SHCN. The goal is to help all youth maximize their potential as they become young adults.

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CHAPTER 139

Violent Behavior

Michael N. Levas, Marlene D. Melzer-Lange

Violence is recognized by the World Health Organization (WHO) as a leading worldwide public health problem. WHO defines **violence** as “the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community that either results in or has a high likelihood of resulting in injury, death, psychologic harm, maldevelopment or deprivation” (see Chapter 14). Youths may be perpetrators, victims, or observers of violence (or any combination of the 3 roles), with varying severity of impact on the individual, family, and larger community. Risk factors for youth violence include poverty, relative social disadvantage, war, substance abuse, mental health disorders, and poor family functioning.

Epidemiology

In 2015, **homicide** in the United States was the 3rd leading cause of death for 10-24 yr olds, totaling 4,979 deaths, which were largely males (87%) killed by a handgun (90.1%). The 2015 homicide rate for teens ages 12-17 yr was 3.1/100,000 youth, down 65% from 8.4/100,000 youth in 1993. WHO reports that other than the United States, where the youth and young adult homicide rate was 11 per 100,000, most countries with homicide rates above 10 per 100,000 are developing nations or countries with rapid socioeconomic changes. In the United States the prevalence of behaviors that contribute to violence has not decreased since 1999; fighting, weapon carrying, and gang involvement remain prevalent among youth. Gang-related homicides among youth in 5 major U.S. cities are more likely to involve young (15-19 yr) males (80%), racial/ethnic minorities (73%), and a firearm (90%) in comparison to homicides unrelated to gang activity. In addition, gang homicides are more likely to occur in public places, in the afternoon/evening hours, and rarely are related to drug trade/use. Furthermore, the rate of homicide in youth had been declining but showed an increase in 2015 (Fig. 139.1).

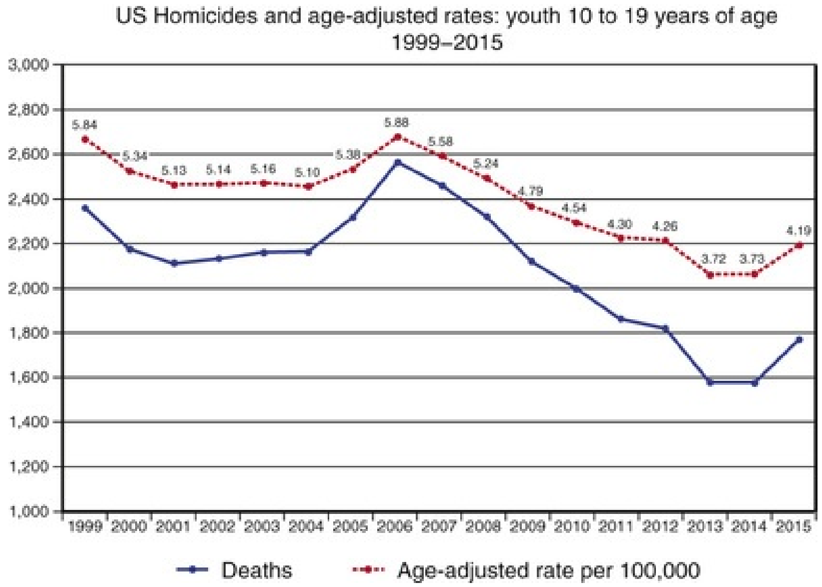

FIG. 139.1 Homicides and age-adjusted rates: youth age 10-19 yr, United States, 1999–2015. (Data from Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Web-based Injury Statistics Query and Reporting System [WISQARS], 1999–2015. http://www.cdc.gov/ncipc/wisqars .)

Adolescent reports of **physical fighting** have decreased from 42% in 1991 to 23% in 2015. Violence at U.S. schools remains a significant problem, however, with 7.8% of students reporting being in a physical fight on school property 1 or more times in the preceding 12 mo. The 2015 Youth Risk Behavior Surveillance System reported 16.2% of youths overall carried a weapon such as a gun, knife, or club in the last 30 days; 4.1% carried the weapon to school; and 6.0% reported being threatened or injured with a type of weapon on school property. Males are more likely than females to carry a gun or weapon and therefore may need more support and engagement at home and at school. **Weapon carrying** is highest among white males overall, which may begin as early as 9th grade. These violence-related behaviors at school affect the general students' perception of safety. More than 5.6% of students did not go to school on 1 or more days in the preceding 30 days because they felt it was unsafe. School-based prevention programs initiated at the elementary school level have been found to decrease violent behaviors in students. Increased surveillance of students is warranted both on and around school property to improve student safety.

Dating violence (or intimate partner violence) occurs between 2 people in a close relationship and can be physical (punching, kicking, hitting, shoving), emotional (shaming, bullying, controlling, stalking), or sexual (forcing partner to engage in a sexual act when he/she does not consent to it). Incidents of dating violence often occur during the adolescent years, with 22.4% of women and 15% of men experiencing some type of partner violence between the ages of 11 and 17 yr. The highest prevalence rates are seen in black students and older students. It may start with teasing, name calling, or shaming but often progresses electronically, as frequent calls, texting, or posting sexual pictures of a partner on social media. Risk factors for being a victim of dating violence includes those who use alcohol, believe dating violence is acceptable, have lack of parental supervision, or have a friend who is in a violent relationship. Most teens do not report the behaviors due to fear of retaliation from the partner. Teens who are victims of dating violence are more likely to experience decreased school performance, have thoughts about suicide, use drugs and alcohol, develop an eating disorder, experience depression, and are more likely to be victimized during college. School-based prevention programs that address attitudes and behaviors linked with dating violence, such as **Safe Dates** and **Dating Matters** , offer training experiences to change social norms among teens.

Etiology

WHO places youth violence in a model within the context of 3 larger types of violence: self-inflicted, interpersonal, and collective. **Interpersonal violence** is subdivided into violence largely between family members or partners and includes child abuse. **Community violence** occurs between individuals who are unrelated. **Collective violence** incorporates violence by people who are members of an identified group against another group of individuals with social, political, or economic motivation. The types of violence in this model have behavioral links, such that child abuse victims are more likely to experience violent and aggressive interpersonal behavior as adolescents and adults. Overlapping risk factors for the types of violence include firearm availability, alcohol use, and socioeconomic inequalities. The benefit to identifying common risk factors for the types of violence lies in the potential for intervening with prevention efforts and gaining positive outcomes for more than 1 type of violent behavior. The model further acknowledges 4 categories that explore the potential nature of violence as involving physical, sexual, or psychological force, and deprivation.

The social-ecologic model of public health focuses on both population-level and individual-level determinants of health and their respective interventions. On the individual level, there may be 2 types of antisocial youth: life course persistent and limited. **Life course–limited offenders** have no childhood aberrant behaviors and are more likely to commit *status* offenses such as vandalism, running away, and other behaviors symbolic of their struggle for autonomy from parents. **Life course–persistent offenders** exhibit aberrant behavior in childhood, such as problems with temperament, behavioral development, and cognition; as adolescents they participate in more *victim-oriented* crimes. The existence of **adverse childhood events** foretells future health issues and subsequent violence. This hypothesis proposes that precursors such as child abuse and neglect, a child witnessing violence, adolescent sexual and physical abuse, and adolescent exposure to violence and violent assaults predispose youths to outcomes of violent behavior, violent crime, delinquency, violent assaults, suicide, or premature death. This public health model also emphasizes the community environment and other external influences. An additional common paradigm for high-risk violence behavior poses a balance of risk and protective factors at the individual, family, and community levels.

Clinical Manifestations

The identified risk factors for youth violence include poverty, association with delinquent peers, poor school performance or low education status, disconnection from adult role models or mentors, prior history of violence or victimization, poor family functioning, childhood abuse, substance abuse, and certain mental health disorders. The most common disorders associated with **aggressive behavior** in adolescents are mental retardation, learning disabilities, moderately severe language disorders, and mental disorders such as attention-deficit/hyperactivity disorder (ADHD) and mood disturbances. The link between severe mental illness and violent behaviors is strongest for those with coexisting alcohol or substance abuse or dependence.

Inability to master prosocial skills such as the establishment and maintenance of positive family/peer relations and poor resolution of conflict may put adolescents with these disorders at higher risk of physical violence and other risky behaviors. **Conduct disorder** and **oppositional defiant disorder** are specific psychiatric diagnoses whose definitions are associated with violent behavior (Table 139.1). They occur with other disorders such as ADHD (see Chapter 49) and increase an adolescent's vulnerability for juvenile delinquency, substance use or abuse, sexual promiscuity, adult criminal behavior, incarceration, and antisocial personality disorder. Other co-occurring risk factors for youth violence include use of anabolic steroids, gang tattoos, belief in one's premature death, preteen alcohol use, and placement in a juvenile detention center.

Table 139.1

Oppositional Defiant Disorder, Conduct Disorder, and Juvenile Delinquency

PSYCHIATRIC DISORDER LABELS		**Legal Label Juvenile Delinquency**
Oppositional Defiant Disorder	**Conduct Disorder**	
Recurrent pattern of negativistic, defiant, disobedient, and hostile behavior toward authority figures that has a significant adverse effect on functioning (e.g., social, academic, occupational)	Repetitive and persistent pattern of behavior that violates the basic rights of others or major age-appropriate societal norms or rules	Offenses that are illegal because of age; illegal acts
Examples: losing temper; arguing with adults; defying or refusing to comply with request or rules of adults; annoying behavior; blaming others; being irritable, spiteful, resentful	Examples: physical fighting, deceitfulness, stealing, destruction of property, threatening or causing physical harm to people or animals, driving without a license, prostitution, rape (even if not adjudicated in the legal system)	Examples: single or multiple instances of being arrested or adjudicated for any of the following: stealing, destruction of property, threatening or causing physical harm to people or animals, driving without a license, prostitution, rape
Diagnosed by a mental health clinician	Diagnosed by a mental health practitioner	Adjudicated in the legal system

From Greydanus DE, Pratt HD, Patel DR, et al: The rebellious adolescent, *Pediatr Clin North Am* 44:1460, 1997.

Diagnosis

The assessment of an adolescent at risk or with a history of violent behavior or victimization should be a part of the health maintenance visit of all adolescents. The answers to questions about recent history of involvement in a physical fight, carrying a weapon, or firearms in the household, as well as concerns that the adolescent may have about personal safety, may suggest a problem requiring a more in-depth evaluation. The **FISTS** mnemonic provides guidance for structuring the assessment (Table 139.2). The additional factors of physical or sexual abuse, serious problems at school, poor school performance and attendance, multiple incidents of trauma, substance use, and symptoms associated with mental disorders are indications for evaluation by a mental health professional. In a situation of acute trauma, assault victims are not always forthcoming about the circumstances of their injuries for fear of retaliation or police involvement. Stabilization of the injury or the gathering of forensic evidence in sexual assault is the treatment priority; however, once this is achieved, addressing a more comprehensive set of issues surrounding the assault is appropriate.

Table 139.2

FISTS Mnemonic to Assess an Adolescent's Risk of Violence

F: Fighting (How many fights were you in last year? What was the last?)
I: Injuries (Have you ever been injured? Have you ever injured someone else?)
S: Sex (Has your partner hit you? Have you hit your partner? Have you ever been forced to have sex?)
T: Threats (Has someone with a weapon threatened you? What happened? Has anything changed to make you feel safer?)
S: Self-defense (What do you do if someone tries to pick a fight? Have you carried a weapon in self-defense?)

The FISTS mnemonic is adapted with permission from the Association of American Medical Colleges. Alpert EJ, Sege RD, Bradshaw YS: Interpersonal violence and the education of physicians, *Acad Med* 72:S41–S50, 1997.

Treatment

In the patient with acute injury secondary to violent assault, the treatment plan should follow standards established by the American Academy of Pediatrics model protocol, which includes the stabilization of the injury, evaluation and treatment of the injury, evaluation of the assault circumstance, psychological evaluation and support, social service evaluation of the circumstance surrounding the assault, and a treatment plan on discharge that is designed to protect the adolescent from subsequent injury episodes, prevent retaliation, and minimize the development of psychological disability. Victims as well as witnesses of violence are at risk for posttraumatic stress disorder and future aggressive or violent behavior. Utilizing a **trauma-informed care** approach enables providers to help these victims and witnesses so that they can develop linkages to recovery and resilience. **Hospital-based violence intervention programs** have shown success by supporting youth who have sustained a violent injury in the emergency department, hospital, or community.

Multiple treatment modalities are used simultaneously in managing adolescents with persistent violent and aggressive behavior and range from cognitive-behavioral therapy involving the individual and family to specific family interventions (parent management training, multisystemic treatment) and pharmacotherapy. Treatment of comorbid conditions, such as ADHD, depression, anxiety, and substance abuse, appears to reduce aggressive behavior.

Prevention

The WHO recognizes a multifactorial approach to prevention: parenting and early childhood development strategies; school-based academic and social skills development strategies, strategies for young people at higher risk of or already involved in violence, and community-and society-level strategies (Table 139.3). **Parenting and early childhood development approaches** concentrate on working with families to provide nonviolent parenting through home visitation and parent groups as well as teaching coping strategies and nonviolent conflict resolution for all children and families. **School-based social skills development strategies** focus on students' families and peer relationships, especially those with the potential to trigger aggressive or violent responses. Solutions include improving skills in coping or problem solving in bullying, peer mediation, dating violence prevention, and after-school programs. **Strategies for young people at higher risk of, or already involved in, violence** include therapeutic mental health approaches, crime victim services, vocational training, mentoring, and gang intervention. These youth are at highest risk for repeat injury or incarceration. **Community- and societal-level approaches** include broader advocacy and legislative actions, as well as changing the cultural norm toward violent behaviors.

Table 139.3

WHO Youth Violence Prevention Strategies: Effectiveness by Context

STRATEGIES	CONTEXT/PROGRAMS	EFFECTIVENESS
Parenting and early childhood development strategies	Home visiting programs	?
	Parenting programs	+
	Early childhood development programs	+
School-based academic and social skills development strategies	Life and social skills development	+
	Bullying prevention	+
	Academic enrichment programs	
	Dating violence prevention programs	+
	Financial incentives for adolescents to attend school	?
	Peer mediation	+/−
	After-school and other structured leisure-time activities	?
Strategies for young people at higher risk of, or already involved in, violence	Therapeutic approaches	+
	Vocational training	?
	Mentoring	?
	Gang and street violence prevention programs	?
Community- and society-level strategies	“Hot spots” policing	+
	Community- and problem-oriented policing	+
	Reducing access to and the harmful use of alcohol	+
	Drug control programs	+
	Reducing access to and misuse of firearms	+
	Spatial modification and urban upgrading	+
	Poverty deconcentration	+

+, Promising (strategies that include 1 or more programs supported by at least 1 well-designed study showing prevention of perpetration and/or experiencing of youth violence, or at least 2 studies showing positive changes in key risk or protective factors for youth violence).

?, Unclear because of insufficient evidence (strategies that include 1 or more programs of unclear effectiveness).

+/−, Unclear because of mixed results (strategies for which the evidence is mixed; some programs have a significant positive effect and others a significant negative effect on youth violence).

From World Health Organization (WHO) Library Cataloguing-in Publication Data, Preventing youth violence: an overview of the evidence, 2015.

A specific prevention strategy can incorporate several approaches, such as the handgun/firearm prevention recommendations that include gun-lock safety, public education, and legislative advocacy. Other efforts are directed toward establishing a national database to track and define the problem of youth violence. The **National Violent Death Reporting System** collects and analyzes violent death data from 40 states and aims to improve surveillance of current trends, to share information state to state, to build partnerships among state and community organizations, and to develop and implement prevention and intervention programs. The Centers for Disease Control and Prevention characterizes specific successful prevention programs and summarizes program content on its website (www.cdc.gov).

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CHAPTER 140

Substance Abuse

Cora Collette Breuner

Although varying in percentages by nation and culture, a substantial proportion of adolescents will engage in the use of a wide range of substances, including alcohol, tobacco, natural and synthetic marijuana, opiates, and stimulants. Their reactions to and the consequences of these exposures are influenced by a complex interaction among biologic and psychosocial development, environmental messages, legality, and societal attitudes. The potential for adverse outcomes even with occasional use in adolescents, such as motor vehicle crashes and other injuries, is sufficient justification to consider any drug use in adolescents a considerable risk.

Individuals who initiate drug use at an early age are at a greater risk for becoming addicted than those who try drugs in early adulthood. Drug use in younger adolescents can act as a substitute for developing age-appropriate coping strategies and enhance vulnerability to poor decision-making. First use of the most commonly used drug (alcohol) occurs before age 18 yr, with 88% of people reporting age of first alcohol use at <21 yr old, the legal drinking age in the United States. Interestingly, inhalants have been identified as a popular first drug for youth in 8th grade (age 13-14 yr).

When drug use begins to negatively alter functioning in adolescents at school and at home, and risk-taking behavior is seen, intervention is warranted. Serious drug use is a pervasive phenomenon and infiltrates every socioeconomic and cultural segment of the population. It is one of the costliest and most challenging public health problems facing all societies and cultures. The challenge to the clinician is to identify youths at risk for substance abuse and offer early intervention. The challenge to the community and society is to create norms that decrease the likelihood of adverse health outcomes for adolescents and promote and facilitate opportunities for adolescents to choose healthier and safer options.

Recognizing those drugs with the greatest *harm* , and at times focusing on *harm reduction* with or without abstinence, is an important modern approach to adolescent substance abuse (Figs. 140.1 and 140.2).

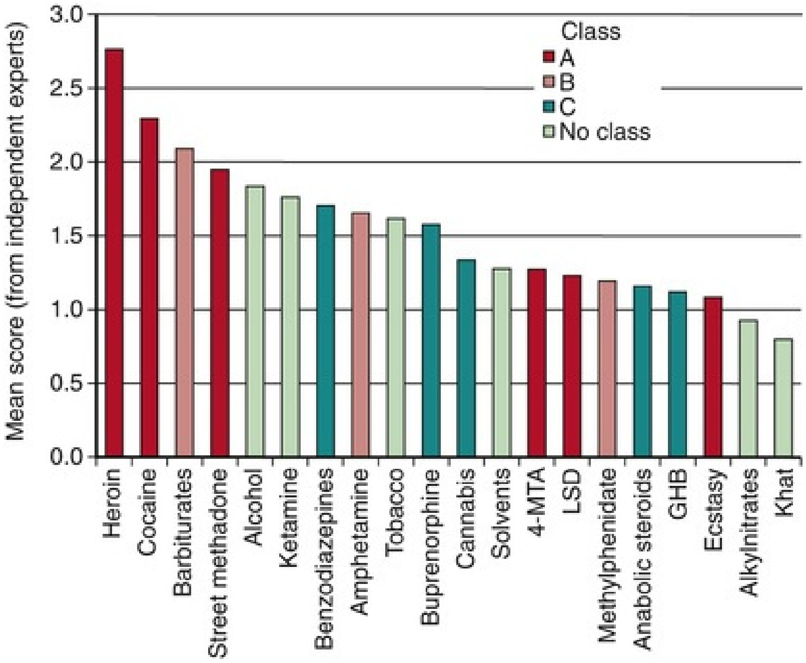

FIG. 140.1 Mean harm scores for 20 substances as determined by an expert panel based on 3 criteria: physical harm to user; potential for dependence; and effect on family, community, and society. Classification under the Misuse of Drugs Act, when appropriate, is shown by the color of each bar. Class A drugs are deemed potentially most dangerous; class C least dangerous. (From Nutt D, King LA, Saulsbury W, et al: Development of a rational scale to access the harm of drugs of potential misuse, *Lancet* 369:1047–1053, 2007.)

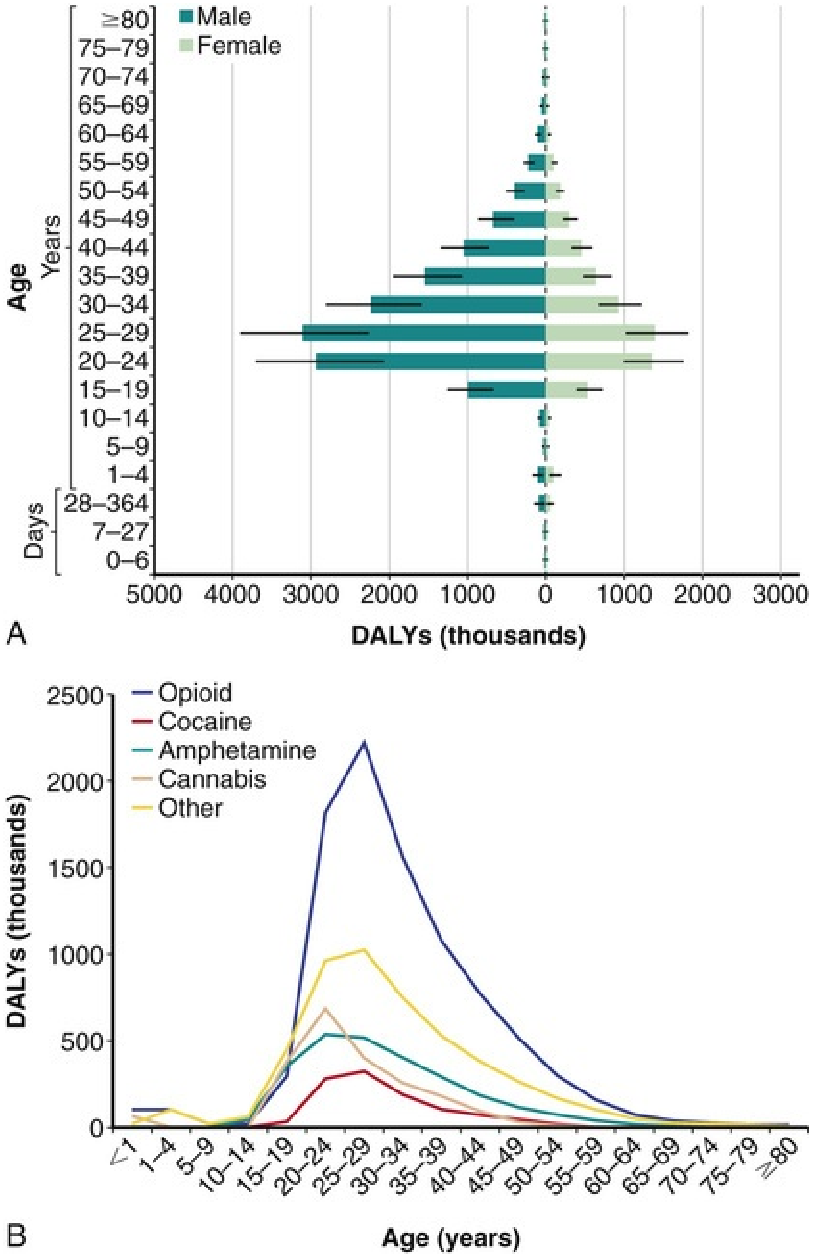

FIG. 140.2 Total burden (DALYs) of drug dependence by age and sex in 2010. A, DALYs attributable to drug dependence, by age and sex. B, DALYs attributable to each type of drug dependence by age. DALYs, Disability-adjusted life years. (From: Degenhardt L, Whitford HA, Ferrari AJ, et al: Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease study 2010, *Lancet* 382:1569, 2013.)

Etiology

Substance abuse has multifactorial origins (Fig. 140.3). Biologic factors, including genetic predisposition, are established contributors. Behaviors such as rebelliousness, poor school performance, delinquency, and criminal activity and personality traits such as low self-esteem, anxiety, and lack of self-control are frequently associated with or predate the onset of drug use. Psychiatric disorders often coexist with adolescent substance use. Conduct disorders and antisocial personality disorders are the most common diagnoses coexisting with substance abuse, particularly in males. Teens with depression (see Chapter 39.1), attention deficit disorder (Chapter 49), anxiety (Chapter 38), and eating disorders (Chapter 41) have high rates of substance use. The determinants of adolescent substance use and abuse are explained using numerous theoretical models, with factors at the individual level, the level of significant relationships with others, and the level of the setting or environment. Models include a balance of risk and protective or coping factors contributing to individual differences among adolescents with similar risk factors who escape adverse outcomes.

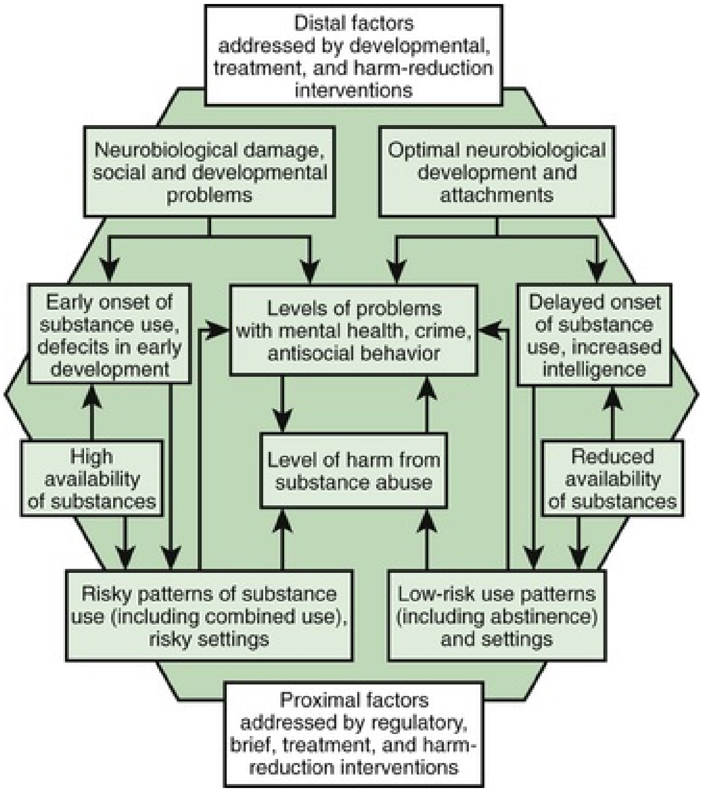
Distal factors addressed by developmental, treatment, and harm-reduction interventions
Neurobiological damage, social and developmental problems
Optimal neurobiological development and attachments
Early onset of substance use, defects in early development
Levels of problems with mental health, crime, antisocial behavior
Delayed onset of substance use, increased intelligence
High availability of substances
Level of harm from substance abuse
Reduced availability of substances
Risky patterns of substance use (including combined use), risky settings
Low-risk use patterns (including abstinence) and settings
Proximal factors addressed by regulatory, brief, treatment, and harm-reduction interventions

FIG. 140.3 Protection and risk model for distal and proximal determinants of risky substance use and related harms. (From Toumbourou JW, Stockwell T, Neighbors C, et al: Interventions to reduce harm associated with adolescent substance use, *Lancet* 369:1391–1401, 2007.)

Risk factors for adolescent *drug use* may differ from those associated with adolescent *drug abuse* . Adolescent *use* is more commonly related to social and peer factors, whereas *abuse* is more often a function of psychological and biologic factors. The likelihood that an otherwise normal adolescent would experiment with drugs may depend on the availability of the drug to the adolescent, the perceived positive or otherwise functional value to the adolescent, the perceived risk associated with use, and the presence or absence of restraints, as determined by the adolescent's cultural or other important value systems. An adolescent who abuses drugs may have genetic or biologic factors coexisting with dependence on a particular drug for coping with day-to-day activities.

Specific historical questions can assist in determining the severity of the drug problem through a rating system (Table 140.1). The type of drug used (marijuana vs heroin), the circumstances of use (alone or in a group setting), the frequency and timing of use (daily before school vs occasionally on a weekend), current mental health status, and general functional status, including sleep habits and screen use, should all be considered in evaluating any child or adolescent found to be using a drug. The stage of drug use/abuse should also be considered (Table 140.2). A teen may spend months or years in the experimentation phase trying a variety of illicit substances, including the most common drugs: cigarettes, alcohol, and marijuana. Often it is not until regular use of drugs resulting in negative consequences (problem use) that the teen is identified as having a problem, either by parents, friends, teachers, or a healthcare provider. Certain protective factors play a part in buffering the risk factors as well as assisting in anticipating the long-term outcome of experimentation. Having emotionally supportive parents with open communication styles, involvement in organized school activities, having mentors or role models outside the home, and recognition of the importance of academic achievement are examples of the important protective factors.

Table 140.1

Assessing the Seriousness of Adolescent Drug Abuse

VARIABLE	0	+1	+2
Age (yr)	>15	<15	
Sex	Male	Female	
Family history of drug abuse		Yes	

Setting of drug use	In group		Alone
Affect before drug use	Happy	Always poor	Sad
School performance	Good, improving		Recently poor
Use before driving	None		Yes
History of accidents	None		Yes
Time of week	Weekend	Weekdays	
Time of day		After school	Before or during school
Type of drug	Marijuana, beer, wine	Hallucinogens, amphetamines	Whiskey, opiates, cocaine, barbiturates

Total score: 0-3, less worrisome; 3-8, serious; 8-18, very serious.

Table 140.2

Stages of Adolescent Substance Abuse

STAGE	DESCRIPTION
1	Potential for abuse • Decreased impulse control • Need for immediate gratification • Available drugs, alcohol, inhalants • Need for peer acceptance
2	Experimentation: learning the euphoria • Use of inhalants, tobacco, marijuana, and alcohol with friends • Few, if any, consequences • Use may increase to weekends regularly • Little change in behavior
3	Regular use: seeking the euphoria • Use of other drugs, e.g., stimulants, LSD, sedatives • Behavioral changes and some consequences • Increased frequency of use; use alone • Buying or stealing drugs
4	Regular use: preoccupation with the “high” • Daily use of drugs • Loss of control • Multiple consequences and risk taking • Estrangement from family and “straight” friends
5	Burnout: use of drugs to feel normal • Polysubstance use/cross-addiction • Guilt, withdrawal, shame, remorse, depression • Physical and mental deterioration • Increased risk taking, self-destructive, suicidal

Epidemiology

Alcohol, cigarettes, and marijuana are the most commonly reported substances used among U.S. teens (Table 140.3). The prevalence of substance use and associated risky behaviors vary by age, gender, race/ethnicity, and other sociodemographic factors. Younger teenagers tend to report less use of drugs than do older teenagers, except for inhalants (in 2016, 4.4% in 8th grade, 2.8% in 10th grade, 1.0% in 12th grade). Males have higher rates of both licit and illicit drug use than females, with greatest differences seen in their higher rates of frequent use of smokeless tobacco, cigars, and anabolic steroids. For a number of years, black 12th graders have reported lifetime, annual, 30-day, and daily prevalence levels for nearly all drugs that were lower than those for white or Hispanic 12th graders. That is less true today, with levels of drug use among blacks more similar to the other groups.

Table 140.3

Trends in Annual Prevalence (%) of Use of Various Drugs for Grades 8, 10, and 12 Combined

	1991	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
Any illicit drug [c]	20.2	19.7	23.2	27.6	31.0	33.6	34.1	32.2	31.9	31.4	31.8	30.2	28.4	27.6	27.1
Any illicit drug other than marijuana [c]	12.0	12.0	13.6	14.6	16.4	*17.0*	16.8	15.8	15.6	15.3 ‡	*16.3*	14.6	13.7	13.5	13.1
Any illicit drug including inhalants [c]	23.5	23.2	26.7	31.1	34.1	36.6	*36.7*	35.0	34.6	34.1	34.3	32.3	30.8	30.1	30.1
Marijuana/hashish	15.0	14.3	17.7	22.5	26.1	29.0	**30.1**	28.2	27.9	27.2	27.5	26.1	24.6	23.8	23.4
Synthetic marijuana	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Inhalants	7.6	7.8	8.9	9.6	**10.2**	9.9	9.1	8.5	7.9	7.7	6.9	6.1	6.2	6.7	7.0
Hallucinogens	3.8	4.1	4.8	5.2	6.6	*7.2*	6.9	6.3	6.1	5.4 ‡	**6.0**	4.5	4.1	4.0	3.9
LSD	3.4	3.8	4.3	4.7	5.9	**6.3**	6.0	5.3	5.3	4.5	4.1	2.4	1.6	1.6	1.5
Hallucinogens other than LSD	1.3	1.4	1.7	2.2	2.7	*3.2*	*3.2*	3.1	2.9	2.8 ‡	**4.0**	3.7	3.6	3.6	3.4
Ecstasy (MDMA), [d] original	—	—	—	—	—	3.1	3.4	2.9	3.7	5.3	**6.0**	4.9	3.1	2.6	2.4
MDMA, revised	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Salvia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cocaine	2.2	2.1	2.3	2.8	3.3	4.0	4.3	**4.5**	**4.5**	3.9	3.5	3.7	3.3	3.5	3.5
Crack	1.0	1.1	1.2	1.5	1.8	2.0	2.1	**2.4**	2.2	2.1	1.8	2.0	1.8	1.7	1.6
Other cocaine	2.0	1.8	2.0	2.3	2.8	3.4	3.7	3.7	**4.0**	3.3	3.0	3.1	2.8	3.1	3.0
Heroin	0.5	0.6	0.6	0.9	1.2	**1.3**	**1.3**	1.2	**1.3**	**1.3**	0.9	1.0	0.8	0.9	0.8
With a needle	—	—	—	—	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	0.5	0.5	0.5	0.5	0.5	0.5
Without a needle	—	—	—	—	0.9	0.9	1.0	0.9	1.0	**1.1**	0.7	0.7	0.6	0.7	0.7
OxyContin	—	—	—	—	—	—	—	—	—	—	—	2.7	3.2	3.3	3.4
Vicodin	—	—	—	—	—	—	—	—	—	—	—	6.0	**6.6**	5.8	5.7
Amphetamines [c]	7.5	7.3	8.4	9.1	10.0	10.4	10.1	9.3	9.0	9.2	9.6	8.9	8.0	7.6	7.0
Ritalin	—	—	—	—	—	—	—	—	—	—	**4.2**	3.8	3.5	3.6	3.3
Adderall	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Methamphetamine	—	—	—	—	—	—	—	—	**4.1**	3.5	3.4	3.2	3.0	2.6	2.4
Bath salts (synthetic stimulants)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tranquilizers	2.8	2.8	2.9	3.1	3.7	4.1	4.1	4.4	4.4	**4.5** ‡	***5.5***	5.3	4.8	4.8	4.7
OTC cough/cold medicines	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rohypnol	—	—	—	—	—	*1.1*	*1.1*	*1.1*	0.8	0.7	0.9 ‡	0.8	0.8	**0.9**	0.8
GHB [b]	—	—	—	—	—	—	—	—	—	**1.4**	1.2	1.2	1.2	1.1	**0.8**
Ketamine [b]	—	—	—	—	—	—	—	—	—	**2.0**	1.9	**2.0**	1.7	1.3	1.0
Alcohol	67.4	66.3 ‡	59.7	60.5	60.4	60.9	**61.4**	59.7	59.0	59.3	58.2	55.3	54.4	54.0	51.9
Been drunk	35.8	34.3	34.3	35.0	35.9	36.7	**36.9**	35.5	36.0	35.9	35.0	32.1	31.2	32.5	30.8
Flavored alcoholic beverages	—	—	—	—	—	—	—	—	—	—	—	—	—	**44.5**	43.9
Alcoholic beverages containing caffeine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Any vaping	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Dissolvable tobacco products	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Snus	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	1.2	1.1	1.0	1.2	1.3	1.1	1.2	1.3	1.7	1.9	**2.0**	**2.0**	1.7	1.6	1.3

	2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2016–2017 CHANGE**	**PEA CHA**
														Abs Cha
Any illicit drug [c]	25.8	24.8	24.9	25.9	27.3	27.6	27.1	28.6 ‡	**27.2**	26.8	25.3	26.5	+1.2	-0.7
Any illicit drug other than marijuana [c]	12.7	12.4	11.9	11.6	11.8	11.3	10.8	11.4‡	**10.9**	10.5	9.7	9.4	-0.3	-1.5
Any illicit drug including inhalants [c]	28.7	27.6	27.6	28.5	29.7	29.8	29.0	30.5 ‡	**28.5**	28.4	26.3	28.3	+2.0 ss	-0.2
Marijuana/hashish	22.0	21.4	21.5	22.9	24.5	25.0	24.7	25.8	24.2	23.7	22.6	23.9	+1.3 s	-6.2
Synthetic marijuana	—	—	—	—	—	—	**8.0**	6.4	4.8	4.2	3.1	2.8	-0.4 s	-5.2
Inhalants	6.9	6.4	6.4	6.1	6.0	5.0	4.5	3.8	3.6	3.2	2.6	2.9	+0.2	-7.3
Hallucinogens	3.6	3.8	3.8	3.5	3.8	3.7	3.2	3.1	2.8	2.8	2.8	2.7	0.0	-3.2
LSD	1.4	1.7	1.9	1.6	1.8	1.8	1.6	1.6	1.7	1.9	2.0	2.1	+0.1	-4.3
Ecstasy (MDMA), [d] original	2.7	3.0	2.9	3.0	3.8	3.7	2.5	2.8	2.2	—	—	—	—	—
MDMA, revised	—	—	—	—	—	—	—	—	**3.4**	2.4	1.8	1.7	-0.1	-1.6
Salvia	—	—	—	—	3.5	**3.6**	2.7	2.3	1.4	1.2	1.2	0.9	-0.3 ss	-2.7
Cocaine	3.5	3.4	2.9	2.5	2.2	2.0	1.9	1.8	1.6	1.7	1.4	1.6	+0.2	-2.9

Crack	1.5	1.5	1.3	1.2	1.1	1.0	0.9	0.8	0.7	0.8	0.6	0.7	+0.1	-1.7
Other cocaine	3.1	2.9	2.6	2.1	1.9	1.7	1.7	1.5	1.5	1.5	1.2	1.3	+0.1	-2.7
Heroin	0.8	0.8	0.8	0.8	0.8	0.7	0.6	0.6	0.5	0.4	0.3	0.3	0.0	-1.0
With a needle	0.5	0.5	0.5	0.5	0.6	0.5	0.4	0.4	0.4	0.3	0.3	0.2	0.0	-0.5
Without a needle	0.6	0.7	0.6	0.5	0.6	0.5	0.4	0.4	0.3	0.3	0.2	0.2	0.0	-0.9
OxyContin	3.5	3.5	3.4	3.9	3.8	3.4	2.9	2.9	2.4	2.3	2.1	1.9	-0.2	-2.0
Vicodin	6.3	6.2	6.1	6.5	5.9	5.1	4.3	3.7	3.0	2.5	1.8	1.3	-0.5	-5.2
Amphetamines [c]	6.8	6.5	5.8	5.9	6.2	5.9	5.6	7.0 ‡	**6.6**	6.2	5.4	5.0	-0.4	-1.6
Ritalin	3.5	2.8	2.6	2.5	2.2	2.1	1.7	1.7	1.5	1.4	1.1	0.8	-0.2	-3.4
Adderall	—	—	—	4.3	**4.5**	4.1	4.4	4.4	4.1	4.5	3.9	3.5	-0.3	-0.5
Methamphetamine	2.0	1.4	1.3	1.3	1.3	1.2	1.0	1.0	0.8	0.6	0.5	0.5	0.0	-3.6
Bath salts (synthetic stimulants)	—	—	—	—	—	—	0.9	**0.9**	0.8	0.7	0.8	0.5	-0.3 s	-0.4
Tranquilizers	4.6	4.5	4.3	4.5	4.4	3.9	3.7	3.3	3.4	3.4	3.5	3.6	+0.1	-1.9
OTC cough/cold medicines	**5.4**	5.0	4.7	5.2	4.8	4.4	4.4	4.0	3.2	3.1	3.2	3.0	-0.2	-2.4
Rohypnol	0.7	0.8	0.7	0.6	0.8	0.9	0.7	0.6	0.5	0.5	0.7	0.5	-0.2 s	-0.5
GHB [b]	0.9	0.7	0.9	0.9	0.8	0.8	—	—	—	—	—	—	—	—
Ketamine [b]	1.1	1.0	1.2	1.3	1.2	1.2	—	—	—	—	—	—	—	—
Alcohol	50.7	50.2	48.7	48.4	47.4	45.3	44.3	42.8	40.7	39.9	36.7	36.7	0.0	-24.
Been drunk	30.7	29.7	28.1	28.7	27.1	25.9	26.4	25.4	23.6	22.5	20.7	20.4	-0.3	-16.
Flavored alcoholic beverages	42.4	40.8	39.0	37.8	35.9	33.7	32.5	31.3	29.4	28.8	25.3	25.9	+0.5	-18.
Alcoholic beverages containing caffeine	—	—	—	—	—	**19.7**	18.6	16.6	14.3	13.0	11.2	10.6	-0.6	-9.1
Any vaping	—	—	—	—	—	—	—	—	—	—	—	21.5	—	—
Vaping nicotine	—	—	—	—	—	—	—	—	—	—	—	13.9	—	—
Vaping marijuana	—	—	—	—	—	—	—	—	—	—	—	6.8	—	—
Vaping just flavoring	—	—	—	—	—	—	—	—	—	—	—	17.2	—	—
Dissolvable tobacco products	—	—	—	—	—	—	**1.4**	1.4	1.2	1.1	0.9	0.9	0.0	-0.5
Snus	—	—	—	—	—	—	**5.6**	4.8	4.1	3.8	3.6	2.6	-1.0 sss	-3.0
Steroids	1.3	1.1	1.1	1.0	0.9	0.9	0.9	0.9	0.9	1.0	0.8	0.8	0.0	-1.2

[a] The proportional change is the percent by which the most recent year deviates from the peak year (or the low year) for the drug in question. Thus, if a drug was at 20% prevalence in the peak year and declined to 10% prevalence in the most recent year, this would reflect a proportional decline of 50%.

[b] Question was discontinued among 8th and 10th graders in 2012.

[c] In 2013, for the questions on the use of amphetamines, the text was changed on 2 of the questionnaire forms for 8th and 10th graders and 4 of the questionnaire forms for 12th graders. This change also impacted the any illicit drug indices. Data presented here include only the changed forms beginning in 2013.

[d] In 2014, the text was changed on 1 of the questionnaire forms for 8th, 10th, and 12th graders to include “Molly” in the description. The remaining forms were changed in 2015. Data for both versions of the question are presented here.

Notes: "—" indicates data not available; "‡ " indicates a change in the question text. When a question change occurs, peak levels after that change are used to calculate the peak year to current year difference.

Values in **bold** equal peak levels since 1991. Values in *italics* equal peak level before wording change. Underlined values equal lowest level since recent peak level.

Level of significance of difference between classes: s = .05, ss = .01, sss = .001.

Any apparent inconsistency between the change estimate and the prevalence estimates for the 2 most recent years is caused by rounding.

From Johnston LD, Miech RA, O'Malley PM, et al: Monitoring the Future national survey results on drug use: 1975–2017. Overview, key findings on adolescent drug use. Ann Arbor, 2018, Institute for Social Research, University of Michigan. http://www.monitoringthefuture.org//pubs/monographs/mtf-overview2017.pdf .

The distribution of annual marijuana use by race/ethnicity varies by grade level. In all 3 grades, prevalence is highest among Hispanic students. Differences in prevalence across the groups are proportionately largest in 8th grade (13% for Hispanics, 7.8% for whites), somewhat smaller in 10th grade (27% for Hispanics, 24% for whites), and negligible in 12th grade (37% for Hispanics, 35% for whites). Blacks fall between whites and Hispanics in 8th and 10th grade but are slightly below them in 12th grade (35%).

The number of 12th graders who report using any of the prescription psychotherapeutic drugs, including amphetamines, sedatives (barbiturates), tranquilizers, and narcotics other than heroin, decreased in 2016 (Table 140.4). Prevalence was 18.0%, 12.0%, and 5.4% for lifetime, annual, and 30-day use, respectively, indicating that a substantial portion of adolescents still use prescription drugs nonmedically. Rural adolescents were 26% more likely than urban adolescents to have used prescription drugs nonmedically. Use was associated with decreased health status, major depressive episode(s), and other drug use (marijuana, cocaine, hallucinogens, inhalants) and alcohol use. In a large-scale study of 16,209 adolescent exposures to prescription drugs, 52.4% were females, and the mean age was 16.6 yr. The 5 most frequently misused or abused drugs were hydrocodone (32%), amphetamines (18%), oxycodone (15%), methylphenidate (14%), and tramadol (11%). Many of these drugs can be found in the parents' home, some are over-the-counter (OTC) drugs (dextromethorphan, pseudoephedrine), whereas others are purchased from drug dealers at schools and colleges. Teen users of nonmedical opioids use other substances concurrently. Most frequently, teens combine opioids with marijuana, alcohol, cocaine, and tranquilizers, putting them at risk for serious complications and overdose.

Table 140.4

Commonly Abused Prescription Drugs

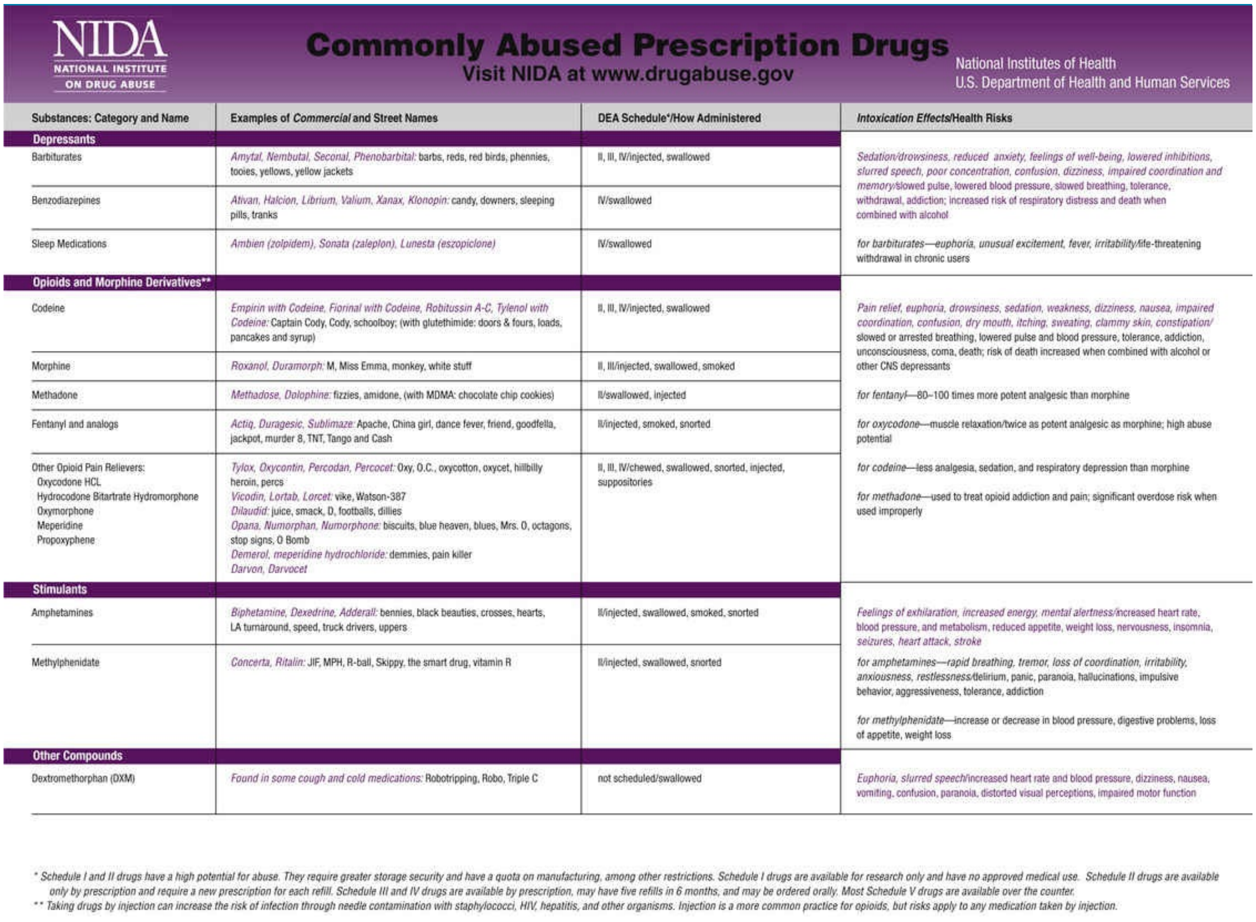

NIDA
NATIONAL INSTITUTE ON DRUG ABUSE

Commonly Abused Prescription Drugs
Visit NIDA at www.drugabuse.gov

National Institutes of Health
U.S. Department of Health and Human Services

Substances: Category and Name	Examples of *Commercial* and Street Names	DEA Schedule*/How Administered	*Intoxication Effects*/Health Risks
Depressants			
Barbiturates	*Amytal, Nembutal, Seconal, Phenobarbital:* barbs, reds, red birds, phennies, tooies, yellows, yellow jackets	II, III, IV/injected, swallowed	*Sedation/drowsiness, reduced anxiety, feelings of well-being, lowered inhibitions, slurred speech, poor concentration, confusion, dizziness, impaired coordination and memory*/slowed pulse, lowered blood pressure, slowed breathing, tolerance, withdrawal, addiction; increased risk of respiratory distress and death when combined with alcohol *for barbiturates—euphoria, unusual excitement, fever, irritability*/life-threatening withdrawal in chronic users
Benzodiazepines	*Ativan, Halcion, Librium, Valium, Xanax, Klonopin:* candy, downers, sleeping pills, tranks	IV/swallowed	
Sleep Medications	*Ambien (zolpidem), Sonata (zaleplon), Lunesta (eszopiclone)*	IV/swallowed	
Opioids and Morphine Derivatives**			
Codeine	*Empirin with Codeine, Fiorinal with Codeine, Robitussin A-C, Tylenol with Codeine:* Captain Cody, Cody, schoolboy; (with glutethimide: doors & fours, loads, pancakes and syrup)	II, III, IV/injected, swallowed	*Pain relief, euphoria, drowsiness, sedation, weakness, dizziness, nausea, impaired coordination, confusion, dry mouth, itching, sweating, clammy skin, constipation*/slowed or arrested breathing, lowered pulse and blood pressure, tolerance, addiction, unconsciousness, coma, death; risk of death increased when combined with alcohol or other CNS depressants *for fentanyl*—80–100 times more potent analgesic than morphine *for oxycodone*—muscle relaxation/twice as potent analgesic as morphine; high abuse potential *for codeine*—less analgesia, sedation, and respiratory depression than morphine *for methadone*—used to treat opioid addiction and pain; significant overdose risk when used improperly
Morphine	*Roxanol, Duramorph:* M, Miss Emma, monkey, white stuff	II, III/injected, swallowed, smoked	
Methadone	*Methadose, Dolophine:* fizzies, amidone, (with MDMA: chocolate chip cookies)	II/swallowed, injected	
Fentanyl and analogs	*Actiq, Duragesic, Sublimaze:* Apache, China girl, dance fever, friend, goodfella, jackpot, murder 8, TNT, Tango and Cash	II/injected, smoked, snorted	
Other Opioid Pain Relievers: Oxycodone HCL Hydrocodone Bitartrate Hydromorphone Oxymorphone Meperidine Propoxyphene	*Tylox, Oxycontin, Percodan, Percocet:* Oxy, O.C., oxycotton, oxycet, hillbilly heroin, percs *Vicodin, Lortab, Lorcet:* vike, Watson-387 *Dilaudid:* juice, smack, D, footballs, dillies *Opana, Numorphan, Numorphone:* biscuits, blue heaven, blues, Mrs. O, octagons, stop signs, O Bomb *Demerol, meperidine hydrochloride:* demmies, pain killer *Darvon, Darvocet*	II, III, IV/chewed, swallowed, snorted, injected, suppositories	
Stimulants			
Amphetamines	*Biphetamine, Dexedrine, Adderall:* bennies, black beauties, crosses, hearts, LA turnaround, speed, truck drivers, uppers	II/injected, swallowed, smoked, snorted	*Feelings of exhilaration, increased energy, mental alertness*/increased heart rate, blood pressure, and metabolism, reduced appetite, weight loss, nervousness, insomnia, *seizures, heart attack, stroke* *for amphetamines—rapid breathing, tremor, loss of coordination, irritability, anxiousness, restlessness*/delirium, panic, paranoia, hallucinations, impulsive behavior, aggressiveness, tolerance, addiction *for methylphenidate*—increase or decrease in blood pressure, digestive problems, loss of appetite, weight loss
Methylphenidate	*Concerta, Ritalin:* JIF, MPH, R-ball, Skippy, the smart drug, vitamin R	II/injected, swallowed, snorted	
Other Compounds			
Dextromethorphan (DXM)	*Found in some cough and cold medications:* Robotripping, Robo, Triple C	not scheduled/swallowed	*Euphoria, slurred speech*/increased heart rate and blood pressure, dizziness, nausea, vomiting, confusion, paranoia, distorted visual perceptions, impaired motor function

* *Schedule I and II drugs have a high potential for abuse. They require greater storage security and have a quota on manufacturing, among other restrictions. Schedule I drugs are available for research only and have no approved medical use. Schedule II drugs are available only by prescription and require a new prescription for each refill. Schedule III and IV drugs are available by prescription, may have five refills in 6 months, and may be ordered orally. Most Schedule V drugs are available over the counter.*

** *Taking drugs by injection can increase the risk of infection through needle contamination with staphylococci, HIV, hepatitis, and other organisms. Injection is a more common practice for opioids, but risks apply to any medication taken by injection.*

Courtesy of the National Institute on Drug Abuse, US Department of Health and Human Services, National Institutes of Health. www.drugabuse.gov .

Clinical Manifestations

Although manifestations vary by the specific substance of use, adolescents who use drugs often present in an office setting with no obvious physical findings. Drug use is more frequently detected in adolescents who experience trauma such as motor vehicle crashes, bicycle injuries, or violence. Eliciting appropriate historical information regarding substance use, followed by blood alcohol and urine drug screens, is recommended in emergency settings. Although waning in popularity, the illicit substances known as “club drugs” still need to be considered in the differential diagnosis of a teen with an altered sensorium (Table 140.5). An adolescent presenting to an emergency setting with an impaired sensorium should be evaluated for substance use as a part of the differential diagnosis (Table 140.6). Screening for substance use is recommended for patients with psychiatric and behavioral diagnoses. Other clinical manifestations of substance use are associated with the route of use; intravenous drug use is associated with venous “tracks” and needle marks, and nasal mucosal injuries are associated with nasal insufflation of drugs. Seizures can be a direct effect of drugs such as cocaine, synthetic marijuana, and amphetamines or an effect of drug withdrawal in the case of barbiturates or tranquilizers.

Table 140.5

Common Names and Salient Features of Club Drugs Used Recreationally

	MDMA	**EPHEDRINE**	**γ-HYDROXYBUTYRATE**	**γ-BUTYROLACTONE**	**1,4-BUTANEDIOL**	**KI**
Common name	Ecstasy, XTC, E, X, Adam, hug drug, Molly	Herbal Ecstasy, herbal fuel, zest	Liquid Ecstasy, goop soap, Georgia homeboy, grievous bodily harm	Blue nitro, longevity, revivarant, GH revitalizer, gamma G, nitro, insom-X, remforce, firewater, invigorate	Thunder nectar, serenity, pine needle extract, zen, enliven, revitalize plus, lemon drops	K, vit ke
Duration of action	4-6 hr	4-6 hr	1.5-3.5 hr	1.5-3.5 hr	1.5-3.5 hr	1-
Elimination half-life	8-9 hr	5-7 hr	27 min	ND	ND	2
Peak plasma concentration	1-3 hr	2-3 hr	20-60 min*	15-45 min	15-45 min	20
Physical dependence	No	No	Yes	Yes	Yes	N
Antidote	No	No	No	No	No	N
DEA schedule	I	None	III	None	None	III
Detection with routine drug screen	Yes †	Yes †	No	No	No	N
Best detection method (time frame)	GC/MS (4 hr–2 days)	GC/MS (4 hr–2 days)	GC/MS (1-12 hr)	GC/MS (1-12 hr)	GC/MS (1-12 hr)	G da

* Depends on dose.

[†] Concentrations that are sufficiently high can give positive results for amphetamine because of cross-reactions.

[‡] Flunitrazepam can give positive results for benzodiazepines; ketamine can give positive results for phencyclidine.

DEA, U.S. Drug Enforcement Agency, currently reviewing possibility of flunitrazepam being placed into schedule of the U.S. Controlled Substance Act; GC/MS, gas chromatography–mass spectroscopy. Duration, half-life, and peak plasma are probably different after high or sequential doses because of nonlinear kinetics; ND, not determined in humans.

Modified from Ricaurte GA, McCann UD: Recognition and management of complications of new recreational drug use. *Lancet* 365:2137–2145, 2005.

Table 140.6

Most Common Toxic Syndromes

ANTICHOLINERGIC SYNDROMES	
Common signs	Delirium with mumbling speech, tachycardia, dry, flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, and decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.
Common causes	Antihistamines, antiparkinsonian medication, atropine, scopolamine, amantadine, antipsychotic agents, antidepressant agents, antispasmodic agents, mydriatic agents, skeletal muscle relaxants, and many plants (notably jimsonweed and *Amanita muscaria*).
SYMPATHOMIMETIC SYNDROMES	
Common signs	Delusions, paranoia, tachycardia (or bradycardia if the drug is a pure α-adrenergic agonist), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, and hyperreflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.
Common causes	Cocaine, amphetamine, methamphetamine (and its derivatives 3,4-methylenedioxyamphetamine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxyethamphetamine, and 2,5-dimethoxy-4-bromoamphetamine), some synthetic marijuana, and OTC decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.
OPIATE, SEDATIVE, OR ETHANOL INTOXICATION	
Common signs	Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia, pulmonary edema, decreased bowel sounds, hyporeflexia, and needle marks. Seizures may occur after overdoses of some narcotics, notably propoxyphene.
Common causes	Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, and guanabenz.
CHOLINERGIC SYNDROMES	
Common signs	Confusion, central nervous system depression, weakness, salivation, lacrimation, urinary and fecal incontinence, gastrointestinal cramping, emesis, diaphoresis, muscle fasciculations, pulmonary edema, miosis, bradycardia or tachycardia, and seizures.
Common causes	Organophosphate and carbamate insecticides, physostigmine, edrophonium, and some mushrooms.

From Kulig K: Initial management of ingestions of toxic substances, *N Engl J Med* 326:1678, 1992. ©1992 Massachusetts Medical Society. All rights reserved.

Screening for Substance Abuse Disorders

In a primary care setting the annual health maintenance examination provides an opportunity for identifying adolescents with substance use or abuse issues. The direct questions as well as the assessment of school performance, family relationships, and peer activities may necessitate a more in-depth interview if there are suggestions of difficulties in those areas. Several self-report screening questionnaires also are available, with varying degrees of standardization, length, and reliability. The **CRAFFT mnemonic** is specifically designed to screen for adolescents' substance use in the primary setting (Table 140.7). Privacy and confidentiality must be established when asking the teen about specifics of their substance experimentation or use. Interviewing the parents can provide additional perspective on early warning signs that go unnoticed or disregarded by the teen. Examples of early warning signs of teen substance use are change in mood, appetite, or sleep pattern; decreased interest in school or school performance; loss of weight; secretive behavior about social plans; or valuables such as money or jewelry missing from the home. The use of urine drug screening is recommended when select circumstances are present: (1) psychiatric symptoms to rule out comorbidity or dual diagnoses, (2) significant changes in school performance or other daily behaviors, (3) frequently occurring accidents, (4) frequently occurring episodes of respiratory problems, (5) evaluation of serious motor vehicular or other injuries, and (6) as a monitoring procedure for a recovery program. Table 140.8 shows common tests used for detection by substance, along with the approximate retention time between use and identification in the urine. Most initial screening uses an immunoassay method, such as the enzyme-multiplied immunoassay technique, followed by a confirmatory test using highly sensitive, highly specific gas chromatography–mass spectrometry. The substances that can cause false-positive results should be considered, especially when there is a discrepancy between the physical findings and the urine drug screen result. In 2007 the American of Academy of Pediatrics (AAP) released guidelines that strongly discourage routine home-based or school-based testing.

Table 140.7

CRAFFT Mnemonic Tool

- Have you ever ridden in a **C** ar driven by someone (including yourself) who was high or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to **R** elax, feel better about yourself or fit in?
- Do you ever use alcohol or drugs while you are by yourself (**A** lone)?
- Do you ever **F** orget things you did while using alcohol or drugs?
- Do your Family or **F** riends ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into **T** rouble while you were using alcohol or drugs?

From the Center for Adolescent Substance Abuse Research (CeASAR): *The CRAFFT screening interview.* (Copyright John R. Knight, MD, Boston Children's Hospital, 2015.)

Table 140.8

Urine Screening for Drugs Commonly Abused by Adolescents

DRUG	MAJOR METABOLITE	INITIAL	FIRST CONFIRMATION	SECOND CONFIRMATION	APPROXIMATE RETENTION TIME
Alcohol (blood)	Acetaldehyde	GC	IA		7-10 hr
Alcohol (urine)	Acetaldehyde	GC	IA		10-13 hr
Amphetamines		TLC	IA	GC, GC/MS	48 hr
Barbiturates		IA	TLC	GC, GC/MS	Short-acting (24 hr); long-acting (2-3 wk)
Benzodiazepines		IA	TLC	GC, GC/MS	3 days
Cannabinoids	Carboxy- and hydroxymetabolites	IA	TLC	GC/MS	3-10 days (occasional user); 1-2 mo (chronic user)
Cocaine	Benzoylecgonine	IA	TLC	GC/MS	2-4 days
Methaqualone	Hydroxylated metabolites	TLC	IA	GC/MS	2 wk
Opiates					
Heroin	Morphine	IA	TLC	GC, GC/MS	2 days
	Glucuronide				
Morphine	Morphine	IA	TLC	GC, GC/MS	2 days
	Glucuronide				
Codeine	Morphine	IA	TLC	GC, GC/MS	2 days
	Glucuronide				

Phencyclidine		TLC	IA	GC, GC/MS	8 days

GC, Gas chromatography; IA, immunoassay; MS, mass spectrometry; TLC, thin-layer chromatography.

Modified from Drugs of abuse—urine screening [physician information sheet], Los Angeles, Pacific Toxicology. From MacKenzie RG, Kipke MD: Substance use and abuse. In Friedman SB, Fisher M, Schonberg SK, editors: *Comprehensive adolescent health care,* St Louis, 1998, Mosby.

Diagnosis

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) no longer identifies substance use disorders as those of *abuse* or of *dependence* . A substance use disorder is defined by a cluster of cognitive, behavioral, and physiologic symptoms that indicate that an adolescent is using a substance even though there is evidence that the substance is harming the adolescent. Even after detoxification, a substance use disorder may leave persisting changes in brain circuits with resulting behavioral changes. There are 11 criteria that describe a pathologic pattern of behaviors related to use of the substance, falling into 4 categories: impaired control, social impairment, increased risk, and pharmacologic criteria. The 1st category, **impaired control** , describes an individual taking increasing amounts of the substance who expresses a persistent desire to decrease use, with unsuccessful efforts. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects and expresses an intense desire for the drug, usually in settings where the drug had been available, such as a specific type of social situation. The 2nd cluster of criteria (5-7) reflects **social impairment,** including the inability to perform as expected in school, at home, or at a job; increasing social problems; and withdrawing from the family. The 3rd cluster of 2 criteria addresses **increased risk** associated with use of the substance, and the 4th cluster includes 2 criteria addressing **pharmacologic responses** (tolerance and/or withdrawal). The total number of criteria present is associated with a determination of a *mild, moderate,* or *severe* disorder.

These criteria may have limitations with adolescents because of differing patterns of use, developmental implications, and other age-related consequences. Adolescents who meet diagnostic criteria should be referred to a program for substance use disorder treatment unless the primary care physician has additional training in addiction medicine.

Complications

Substance use in adolescence is associated with comorbidities and acts of juvenile delinquency. Youth may engage in other high-risk behaviors such as robbery, burglary, drug dealing, or prostitution for the purpose of acquiring the money necessary to buy drugs or alcohol. Regular use of any drug eventually diminishes judgment and is associated with unprotected sexual activity with its consequences of pregnancy and sexually transmitted infections, including HIV, as well as physical violence and trauma. Drug and alcohol use is closely associated with trauma in the adolescent population. Several studies of adolescent trauma victims have identified cannabinoids and cocaine in blood and urine samples in significant proportions (40%), in addition to the more common identification of alcohol. Any use of injected substances involves the risk of hepatitis B and C viruses as well as HIV (see Chapter 302).

Treatment

Adolescent drug abuse is a complex condition requiring a multidisciplinary approach that attends to the needs of the individual, not just drug use. Fundamental principles for treatment include accessibility to treatment; utilizing a multidisciplinary approach; employing individual or group counseling; offering mental health services; monitoring of drug use while in treatment; and understanding that recovery from drug abuse/addiction may involve multiple relapses. For most patients, remaining in treatment for a minimum period of 3 mo will result in a significant improvement.

Prognosis

For adolescent substance abusers who have been referred to a drug treatment program, positive outcomes are directly related to regular attendance in posttreatment groups. For males with learning problems or conduct disorder, outcomes are poorer than for those without such disorders. Peer use patterns and parental use have a major influence on outcome for males. For females, factors such as self-esteem and anxiety are more important influences on outcomes. The chronicity of a substance use disorder makes **relapse** an issue that must always be considered when managing patients after treatment, and appropriate assistance from a health professional qualified in substance abuse management should be obtained.

Prevention

Preventing drug use among children and teens requires prevention efforts aimed at the individual, family, school, and community levels. The National Institute on Drug Abuse (NIDA) of the U.S. National Institutes of Health has identified essential principles of successful prevention programs. Programs should enhance *protective factors* (parent support) and reduce *risk factors* (poor self-control); should address all forms of drug abuse (legal and illegal); should address the specific type(s) of drug abuse within an identified community; and should be culturally competent to improve effectiveness (Table 140.9). The highest-risk periods for substance use in children and adolescents are during life transitions, such as the move from elementary school to middle school, or from middle school to high school. Prevention programs need to target these emotionally and socially intense times for teens to adequately anticipate potential substance use or abuse. Examples of effective research-based drug abuse prevention programs featuring a variety of strategies are listed on the NIDA website (www.drugabuse.gov), and on the Center for Substance Abuse Prevention website (www.prevention.samhsa.gov).

Table 140.9

Domains of Risk and Protective Factors for Substance Abuse Prevention

RISK FACTORS	DOMAIN	PROTECTIVE FACTORS
Early aggressive behavior	Individual	Self-control
Lack of parental supervision	Family	Parental monitoring
Substance abuse	Peer	Academic competence
Drug availability	School	Anti–drug use policies
Poverty	Community	Strong neighborhood attachment

From National Institute on Drug Abuse: *Preventing drug use among children and adolescents: a research-based guide for parents, educators, and community leaders,* NIH Pub No 04-4212(B), ed 2, Bethesda, MD, 2003, NIDA.

140.1

Alcohol

Cora Collette Breuner

Alcohol is the most widely used substance of abuse among America's youth, and a higher proportion use alcohol than use tobacco or other drugs, but the numbers are trending down. According to the 2016 **Monitoring the Future (MTF)** study, 19.9% (down from 27.6%) of 10th graders reported using alcohol in the past 30 days. Early initiation of alcohol use increases the risk for a variety of developmental problems during adolescence and is frequently an indicator of future substance use. Drinking by children, adolescents, and young adults has serious negative consequences for the individuals, their families, their communities, and society as a whole. Underage drinking contributes to a wide range of costly health and social problems, including motor vehicle crashes (the greatest single mortality risk for underage drinkers); suicide; interpersonal violence (e.g., homicides, assaults, rapes); unintentional injuries such as burns, falls, and drowning; brain impairment; alcohol dependence; risky sexual activity; academic problems; and alcohol and drug poisoning. On average, alcohol is a factor in the deaths of approximately 4,300 youths in the United States per year, shortening their life by an average of 60 yr.

According to the Centers for Disease Control and Prevention (CDC) 2015 Youth Risk Behavior Survey (YRBS), 63.2% of students had had at least 1 drink of alcohol on at least 1 day during their life (i.e., ever drank alcohol). The prevalence of having ever drunk alcohol was higher among female (65.3%) than male (61.4%) students; higher among black female (57.9%) and Hispanic female (68.6%) than black male (51.0%) and Hispanic male (63.4%) students, respectively; and higher among female (53.0%) than male (48.9%) 9th graders.

The prevalence of having ever drunk alcohol was higher among white (65.3%) and Hispanic (65.9%) than black (54.4%) students, higher among white female (66.7%) and Hispanic female (68.6%) than black female (57.9%) students, and higher among white male (64.0%) and Hispanic male (63.4%) than black male (51.0%) students.

The prevalence of having ever drunk alcohol was higher among 10th graders (60.8%), 11th graders (70.3%), and 12th graders (73.3%) than 9th graders

(50.8%); higher among 11th-grade female (72.1%) and 12th-grade female (75.2%) than 9th-grade female (53.0%) and higher among 10th-grade male (58.8%), 11th-grade male (68.7%), and 12th-grade male (71.5%) than 9th-grade male (48.9%) students.

Multiple factors can affect a young teen's risk of developing a drinking problem at an early age (Table 140.10). One third of high school seniors admit to combining drinking behaviors with other risky behaviors, such as driving or taking additional substances. **Binge drinking** remains especially problematic among the older teens and young adults; 31% of high school seniors report having 5 or more drinks in a row in the last 30 days. Higher use is seen in males (23.8%) than in females (19.8%), and whites (24.0%) and Hispanics (24.2%) than in blacks (12.4%). Teens with binge-drinking patterns are more likely to be assaulted, engage in high-risk sexual behaviors, have academic problems, and be injured than those teens without binge drinking patterns.

Table 140.10

Risk Factors for a Teen Developing a Drinking Problem

Family Risk Factors

- Low parental supervision
- Poor parent to teen communication
- Family conflicts
- Severe or inconsistent family discipline
- Having a parent with an alcohol or drug problem

Individual Risk Factors

- Poor impulse control
- Emotional instability
- Thrill-seeking behaviors
- Behavioral problems
- Perceived risk of drinking is low
- Begins drinking before age 14 yr

Alcohol contributes to more **deaths** in young individuals in the United States than all the illicit drugs combined. Among studies of adolescent trauma victims, alcohol is reported to be present in 32–45% of hospital admissions. Motor vehicle crashes are the most frequent type of event associated with alcohol use, but the injuries spanned several types, including self-inflicted wounds.

Alcohol is often mixed with energy drinks (caffeine, taurine, sugars), which can result in a spectrum of alcohol-related negative behaviors. **Caffeine** may counter the sedative effects of alcohol, resulting in more alcohol consumption and a perception of not being intoxicated, thus leading to risk-taking behavior such as driving while intoxicated. In addition, aggressive behavior, including sexual assaults and motor vehicle or other injuries, has been reported. Both alcohol and caffeine overdoses have also been reported.

Pharmacology and Pathophysiology

Alcohol (ethyl alcohol or ethanol) is rapidly absorbed in the stomach and is transported to the liver and metabolized by 2 pathways. The primary metabolic pathway contributes to the excess synthesis of triglycerides, a phenomenon that is responsible for producing a **fatty liver** , even in those who are well nourished. Engorgement of hepatocytes with fat causes necrosis, triggering an inflammatory process (**alcoholic hepatitis**), later followed by fibrosis, the hallmark of **cirrhosis** . Early hepatic involvement may result in elevation in γ-glutamyltransferase (GGT) and serum glutamic-pyruvic transaminase (alanine transaminase). The 2nd metabolic pathway, which is utilized at high serum alcohol levels, involves the microsomal enzyme system of the liver, in which the cofactor is reduced nicotinamide-adenine dinucleotide phosphate. The net effect of activation of this pathway is to decrease metabolism of drugs that share this system and to allow for their accumulation, enhanced effect, and possible toxicity.

Clinical Manifestations

Alcohol acts primarily as a central nervous system (CNS) depressant. It produces euphoria, grogginess, talkativeness, impaired short-term memory, and an increased pain threshold. Alcohol's ability to produce vasodilation and hypothermia is also centrally mediated. At very high serum levels, respiratory depression occurs. Its inhibitory effect on pituitary antidiuretic hormone release is responsible for its diuretic effect. The gastrointestinal (GI) complications of alcohol use can occur from a single large ingestion. The most common is acute **erosive gastritis** , manifesting as epigastric pain, anorexia, vomiting, and heme-positive stools. Less frequently, vomiting and mid-abdominal pain may be caused by acute alcoholic **pancreatitis** ; diagnosis is confirmed by the finding of elevated serum amylase and lipase levels.

Diagnosis

Primary care settings provide the opportunity to screen teens for alcohol use or problem behaviors. Brief alcohol screening instruments such as CRAFFT (see Table 140.7) or AUDIT (Alcohol Use Disorders Identification Test, Table 140.11) perform well in a clinical setting as techniques to identify alcohol use disorders. A score of ≥8 on the AUDIT questionnaire identifies people who drink excessively and who would benefit from reducing or ceasing drinking. Teenagers in the early phases of alcohol use exhibit few physical findings. Recent use of alcohol may be reflected in elevated GGT and aspartate transaminase levels.

Table 140.11

Alcohol Use Disorders Identification Test (AUDIT)

	SCORE (0-4)*
1. How often do you have a drink containing alcohol?	Never (0) to more than 4 per wk (4)
2. How many drinks containing alcohol do you have on a typical day?	One or 2 (0) to more than 10 (4)
3. How often do you have 6 or more drinks on 1 occasion?	Never (0) to daily or almost daily (4)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) to daily or almost daily (4)
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) to daily or almost daily (4)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) to daily or almost daily (4)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) to daily or almost daily (4)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) to daily or almost daily (4)
9. Have you or someone else been injured as a result of your drinking?	No (0) to yes, during the last year (4)
10. Has a relative, friend, doctor or other health worker been concerned about your drinking or suggested that you should cut down?	No (0) to yes, during the last year (4)

[*] Score ≥8 = problem drinking.

From Schuckit MA: Alcohol-use disorders, *Lancet* 373:492–500, 2009.

In acute care settings the **alcohol overdose syndrome** should be suspected in any teenager who appears disoriented, lethargic, or comatose. Although the distinctive aroma of alcohol may assist in diagnosis, confirmation by analysis of blood is recommended. At levels >200 mg/dL, the adolescent is at risk of death, and levels >500 mg/dL (median lethal dose) are usually associated with a fatal outcome. When the level of obtundation appears excessive for the reported blood alcohol level, head trauma, hypoglycemia, or ingestion of other drugs should be considered as possible confounding factors.

Treatment

The usual mechanism of death from the alcohol overdose syndrome is **respiratory depression** , and artificial ventilatory support must be provided until the liver can eliminate sufficient amounts of alcohol from the body. In a patient without alcoholism, it generally takes 20 hr to reduce the blood level of alcohol from 400 mg/dL to zero. Dialysis should be considered when the blood level is >400 mg/dL. As a follow-up to acute treatment, referral for treatment of the alcohol use disorder is indicated. Group counseling, individualized counseling, and multifamily educational intervention have proved to be effective interventions for teens.

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140.2

Tobacco and Electronic Nicotine Delivery Systems

Brian P. Jenssen

Keywords

cigarettes
e-cigarettes
electronic nicotine delivery system
ENDS
nicotine
nicotine replacement therapy
NRT
smoking cessation
tobacco
tobacco dependence treatment
vaping

Cigarettes

Tobacco use and addiction almost always start in childhood or adolescence, a period when the brain has heightened susceptibility to nicotine addiction. Nearly 90% of adult smokers began smoking before age 18. Factors associated with youth tobacco use include exposure to smokers (friends, parents), tobacco availability, low socioeconomic status, poor school performance, low self-esteem, lack of perceived risk of use, and lack of skills to resist influences to use tobacco.

From 2011–2017, among all US high school students, current use of cigarettes decreased from 15.8% to 7.6%. During the same time period, however, current use of e-cigarettes and hookah (water pipes used to smoke tobacco) increased significantly among middle and high school students. In 2017, e-cigarettes (11.7%) were the most commonly used tobacco product among high school students. Cigars (7.7%) and cigarettes (7.6%) were the second and third most commonly used tobacco products among high school students, followed by smokeless tobacco (5.5%), hookah (3.3%), and pipe tobacco (0.8%).

Tobacco use is associated with other high-risk behaviors. Teens who smoke are more likely than nonsmokers to use alcohol and engage in unprotected sex, are 8 times more likely to use marijuana, and are 22 times more likely to use cocaine.

Tobacco is used by teens in all regions of the world, although the form of tobacco used differs. In the Americas and Europe, cigarette smoking is the predominant form of tobacco use, followed by cigars and smokeless tobacco; in the Eastern Mediterranean, hookah use is prevalent; in Southeast Asia, smokeless tobacco products are used; in the Western Pacific, betel nut is chewed with tobacco; and pipe, snuff, and rolled tobacco leaves are used in Africa. Cigarette use by teens in low- and middle-income nations is increasing.

Pharmacology

Nicotine , the primary active ingredient in cigarettes, is addictive. Nicotine is absorbed by multiple sites in the body, including the lungs, skin, GI tract, and buccal and nasal mucosa. The action of nicotine is mediated through nicotinic acetylcholine receptors located on noncholinergic presynaptic and postsynaptic sites in the brain and causes increased levels of dopamine. Nicotine also stimulates the adrenal glands to release epinephrine, causing an immediate elevation in blood pressure, respiration, and heart rate. The dose of nicotine delivered to the user in a cigarette depends on a variety of factors, including puffing characteristics. A smoker typically takes 10 puffs within the span of 5 minutes and absorbs 1-2 mg of nicotine (range: 0.5–3 mg). **Cotinine,** the major metabolite of nicotine, has a biologic half-life of 19-24 hr and can be detected in urine, serum, and saliva.

Clinical Manifestations

Cigarettes are addictive by design and result in life-shortening diseases in half their long-term users. Each year, approximately 480,000 deaths are attributable to smoking, responsible for 1 of every 5 deaths and 1 of every 3 cancer deaths in the United States. Cigarette smoking has severe adverse health consequences for youth and young adults, including increased prevalence of chronic cough, sputum production, wheezing, and worsening asthma. Smoking during pregnancy increases prenatal and perinatal morbidity and mortality, either causing or exacerbating the risks of preterm birth, low birthweight, congenital malformations, stillbirth, and sudden infant death syndrome (SIDS). **Withdrawal** symptoms, including irritability, decreased concentration, increased appetite, and strong cravings for tobacco, can occur when adolescents try to quit.

Electronic Cigarettes (E-Cigarettes)

E-cigarettes, also known as **electronic nicotine delivery systems (ENDS)** , are handheld devices that produce an aerosol created from a solution of nicotine, flavoring chemicals, propylene glycol, and often other constituents unknown and unadvertised to the consumer. There is wide variability in terminology, product design, and engineering of these products, with alternative names including e-cigs, electronic cigars, electronic hookah, e-hookah, personal vaporizers, vape pens, and vaping devices. The industry continues to develop new products, such as JUUL, which contain nicotine but may not be recognized as a tobacco product by teens. The unique flavors offered in e-cigarette solution, the majority of which are confectionary in nature and appealing to children, have been shown to encourage youth experimentation, regular use, and addiction.

Adverse effects to users include dry cough, throat irritation, and lipoid pneumonia. Nonusers could be impacted by the secondhand and thirdhand aerosol (residual nicotine and other chemicals left on surfaces), which have been shown to contain known toxicants, including nicotine, carcinogens, and metal particles. Rates of acute nicotine poisoning have increased from unintentional exposure of children to the concentrated nicotine–containing e-cigarette solution. Studies of adolescents suggest a strong association between e-cigarette use at baseline and progression to traditional cigarette smoking. E-cigarettes may contribute to subsequent cigarette use through nicotine addiction and social normalization of smoking behaviors.

E-cigarettes are not U.S. Food and Drug Administration (FDA) approved and have not been shown to be safe or effective for smoking cessation treatment. Unless the quality of the evidence improves, adolescent smokers interested in quitting should seek and be referred to evidence-based treatments. In August 2016 the FDA finalized a rule that extends its regulatory authority to all tobacco products, including e-cigarettes, affecting how these products are manufactured, marketed, and sold. It requires manufacturers to report product ingredients and undergo the agency's premarket review to receive marketing authorization. In 2017, however, the FDA delayed implementation of this rule until 2022, allowing e-cigarettes (as of April 2019) to remain on the market without premarket review.

Hookah

Hookah (water pipe) smoking uses specially treated tobacco that comes in a variety of flavors. Emerging evidence indicates that hookah may involve comparable health risks to cigarettes, including nicotine dependence. Both human and machine simulation studies of hookah use consistently find that smoke content and user toxicant exposure, including carbon monoxide, tar, and nicotine, are at least comparable to that of cigarettes. Secondhand smoke from hookahs can be a health risk for nonsmokers exposed to harmful toxicants.

Treatment

Tobacco prevention interventions delivered in pediatric settings, including individual encounters or connection to educational materials, can reduce the risk for smoking initiation in school-age children and adolescents. Messages should be clear, personally relevant, and age appropriate. Adolescents may be more responsive to messages that emphasize the effects of tobacco use on appearance, breath, and sports performance; lack of benefit for weight loss; monetary cost of tobacco addiction; and deceptive marketing by the tobacco industry.

The approach to smoking cessation in adolescents includes the **5 A** s **(ask, advise, assess, assist,** and **arrange)** and use of **nicotine replacement therapy (NRT)** in addicted teens who are motivated to quit. Consensus panels recommend the 5 As, although evidence of efficacy in adolescents is limited. Studies of the NRT patch in adolescents suggest a positive effect on reducing withdrawal symptoms; pharmacotherapy should be combined with behavioral therapy to increase cessation and lower relapse rates. In a limited number of studies, cessation rates of 15% were reported at 3 and 6 mo. NRT is also available as a gum, inhaler, nasal spray, lozenge, or microtab (Table 140.12). Medications such as bupropion and varenicline improve smoking cessation rates in adults but are not FDA approved for use in adolescents <18 yr old. Preliminary studies in adolescents report cessation efficacy with 150 mg of bupropion twice daily. In postmarketing surveillance, suicidal ideation and suicide have been reported among patients taking bupropion and varenicline.

Table 140.12

Smoking Cessation Pharmacotherapy Available in the United States

THERAPY BRAND	NAME	STRENGTHS	FDA-APPROVED ADULT DOSING	AVAILABILITY*	STUDIED IN ADOLESCENTS	QUIT DATE
NICOTINE REPLACEMENT THERAPY						
Gum ‡	Nicorette	2 mg, 4 mg	The 4-mg strength should be used by patients who smoke ≥25 cigarettes a day; otherwise, 2-mg strength should be used. Wk 1-6: 1 piece every	OTC*	Yes	

			1-2 hr Wk 7-9: 1 piece every 2-4 hr Wk 10-12: 1 piece every 4-8 hr			
Inhaler	Nicotrol Inhaler	4 mg	6-16 cartridges a day for up to 12 wk	Rx	No	
Lozenge	Commit, Nicorette mini	2 mg, 4 mg	The 4-mg strength should be used by patients who smoke 1st cigarette within 30 min of waking; otherwise, 2-mg strength should be used. Wk 1-6: 1 lozenge every 1-2 hr Wk 7-9: 1 lozenge every 2-4 hr Wk 10-12: 1 lozenge every 4-8 hr	OTC	No	Prior to beginning nicotine replacement therapy
Nasal Spray	Nicotrol NS	0.5 mg/spray	1-2 sprays/hr up to a maximum of 80 sprays per day	Rx	Yes	
Transdermal Patch ‡	NicoDerm CQ	7, 14, 21 mg/24 hr	For patients who smoke >10 cigarettes daily: Step 1: one 21-mg patch daily for wk 1-6 Step 2: one 14-mg patch daily for wk 7-8 Step 3: one 7-mg patch daily for wk	OTC	Yes	

			9-10 For patients who smoke <10 cigarettes daily: Begin with 14-mg patch daily for 6 wk, followed by 7-mg patch for 2 wk.			
NONNICOTINE THERAPY						
Bupropion SR[‡]	Zyban	150-mg sustained-release tablets	150 mg PO in morning for 3 days, then increase to 150 mg PO bid	Rx	Yes	1 wk after starting therapy
Varenicline	Chantix	0.5-, 1-mg tablets	0.5 mg PO in morning for 3 days; increase to 0.5 mg PO bid for 4 days, then increase to 1 mg PO bid	Rx	No	

[*] OTC, Over the counter; Rx, prescription product; PO, by mouth (orally); bid, twice daily.

[‡] Generics available.

[†] None is FDA approved for use in patients younger than 18 yr.

From JP Karpinski et al: Smoking cessation treatment for adolescents, *J Pediatr Pharmacol Ther* 15(4):249–260, 2010.

Pediatric clinicians can connect patients to effective behavioral interventions, including telephone, text message, smartphone app, internet, and community-based resources. Free telephone-based treatment (1-800-QUIT-NOW) has been shown to improve smoking cessation rates. Smoke-free TXT, offered by the National Cancer Institute, engages teens to quit smoking using free, daily text messaging. Teens can sign up online (teen.smokefree.gov) or text QUIT to iQUIT (47848). A smartphone-based app, QuitSTART, helps teens track cravings, monitor moods, use cessation tips, and follow quitting attempts. The American Lung Association's **Not-On-Tobacco Program (NOT)** is a nationally recognized best-practice model for teen smoking cessation (see www.lung.org).

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140.3

Marijuana

Cora Collette Breuner

Keywords

THC
synthetic marijuana

Marijuana (cannabis, pot, weed, hash, grass), derived from the *Cannabis sativa* hemp plant, is the most commonly abused illicit drug. The main active chemical, tetrahydrocannabinol (**THC**), is responsible for its hallucinogenic properties. THC is absorbed rapidly by the nasal or oral routes, producing a peak of subjective effect at 10 min and 1 hr, respectively. Marijuana is generally smoked as a cigarette (reefer, joint) or in a pipe. Although there is much variation in content, each cigarette contains 8–10% THC. Another popular form that is smoked, a “blunt,” is a hollowed-out small cigar refilled with marijuana. Marijuana products (hash oil or leaf) can also be used in some vaping devices or hookah pens. **Hashish** is the concentrated THC resin in a sticky black liquid or oil. Although marijuana use by U.S. teens has declined in the last decade, 23.1% of high school students have used marijuana at least once during the previous 30 days, and current marijuana use is highest in black males and high school seniors. About 8% of students report having tried marijuana before age 13, with a range of 4.3–18.5% across various states, indicating the need for early prevention efforts. Adolescents living in states where medical marijuana is legal report a higher use of cannabis “edibles.” It is important to recognize that as perceived harm drops, marijuana use increases (Fig. 140.4).

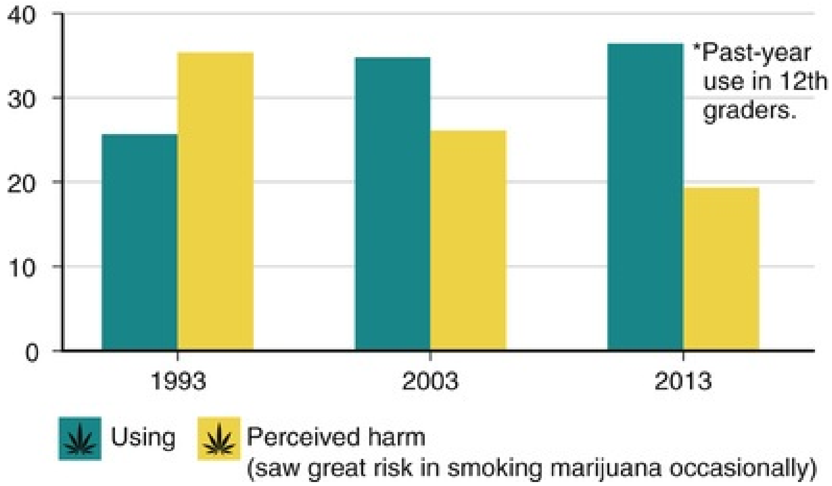

FIG. 140.4 As the perceived harm of marijuana drops, use goes up. The 36.4% using in 2013 equates to about 11 students in the average class. (From NIH National Institute on Drug Abuse.)

Clinical Manifestations

In addition to the “desired” effects of elation and euphoria, marijuana may cause impairment of short-term memory, poor performance of tasks requiring divided attention (e.g., those involved in driving), loss of critical judgment, decreased coordination, and distortion of time perception (Table 140.13). Visual hallucinations and perceived body distortions occur rarely, but “flashbacks” or recall of frightening hallucinations experienced under marijuana's influence may occur, usually during stress or with fever.

Table 140.13

Acute and Chronic Adverse Effects of Cannabis Use

Acute Adverse Effects

- Anxiety and panic, especially in naïve users

- Psychotic symptoms (at high doses)
- Road crashes if a person drives while intoxicated

Chronic Adverse Effects

- Cannabis dependence syndrome (in about 1 in 10 users)
- Chronic bronchitis and impaired respiratory function in regular smokers
- Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders
- Impaired educational attainment in adolescents who are regular users
- Subtle cognitive impairment in those who are daily users for 10 yr or more

From Hall W, Degenhardt L: Adverse health effects of non-medical cannabis use, *Lancet* 374:1383–1390, 2009.

Smoking marijuana for a minimum of 4 days/wk for 6 mo appears to result in dose-related suppression of plasma testosterone levels and spermatogenesis, prompting concern about the potential deleterious effect of smoking marijuana before completion of pubertal growth and development. There is an antiemetic effect of oral THC or smoked marijuana, often followed by appetite stimulation, which is the basis of the drug's use in patients receiving cancer chemotherapy. Although the possibility of teratogenicity has been raised because of findings in animals, there is no evidence of such effects in humans.

An **amotivational syndrome** has been described in long-term marijuana users who lose interest in age-appropriate behavior; proof of the causative relationship remains equivocal. Chronic use is associated with increased anxiety and depression, learning problems, poor job performance, hyperemesis, and respiratory problems such as pharyngitis, sinusitis, bronchitis, and asthma (see Table 140.13).

The **cannabinoid hyperemesis syndrome** is characterized by recurrent episodes of vomiting associated with abdominal pain and nausea; patients often find relief by taking a hot shower or bath. Cannabis use has been chronic (>1-2 yr) and frequent (multiple times per week). Treatment includes stopping marijuana use, antiemetics, and topical capsaicin.

The increased THC content of marijuana of 5-15–fold compared to that of the

1970s is related to the observation of a **withdrawal syndrome** , occurring 24-48 hr after discontinuing the drug. Heavy users experience malaise, irritability, agitation, insomnia, drug craving, shakiness, diaphoresis, night sweats, and GI disturbance. The symptoms peak by the 4th day and resolve in 10-14 days. Certain drugs may interact with marijuana to potentiate sedation (alcohol, diazepam) and stimulation (cocaine, amphetamines) or may be antagonistic (propranolol, phenytoin).

Behavioral interventions, including **cognitive-behavioral therapy (CBT)** and motivational incentives, have shown to be effective in treating marijuana dependency.

Synthetic Marijuana

Spice, K2, crazy clown, aroma, black mamba, blaze, dream, and funky monkey are some of the common street names for synthetic marijuana, which is a mixture of herbs or plant materials that have been sprayed with artificial chemicals similar to THC, the psychoactive ingredient in marijuana. One active group of chemicals is the **carboxamides,** which are not detected by standard assays to detect THC. In the United States the chemicals in “Spice” are designated a Schedule I controlled substance (as is marijuana) by the Drug Enforcement Administration (DEA), thereby making it illegal to sell, buy, or possess them. Nonetheless, synthetic marijuana is the 2nd most common illicit drug used by high school seniors. More than 10% of high school seniors used synthetic marijuana in the last year.

Synthetic marijuana is mainly used by smoking, or mixed with marijuana, or brewed as a tea for drinking. The chemicals in synthetic marijuana affect the same receptors as THC and produce similar effects as seen in cannabis use, such as relaxation, elevated mood, and altered perception. In addition, sympathomimetic symptoms are quite common and are the cause of significant toxicity. Symptoms of **intoxication** include vomiting, tachycardia, hypertension, hyperthermia, confusion, extreme anxiety, profuse sweating, agitation, aggression, dysphoria, hallucinations, seizures, rhabdomyolysis, dystonia, unresponsiveness, confusion, catatonia, “zombie-like” behaviors, and myocardial ischemia. In response to legislation to ban the chemicals in OTC synthetic marijuana products, manufacturers alter and substitute the chemicals in the product, keeping it on the legal market and leaving teens particularly vulnerable to potential health effects.

Synthetic marijuana are not detected by standard toxicology screening but can be identified in specialized laboratories.

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140.4

Inhalants

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Keywords

huffing

Inhalants, found in many common household products, comprise a diverse group of volatile substances whose vapors can be inhaled to produce psychoactive effects. The practice of inhalation is popular among younger adolescents and decreases with age. Young adolescents are attracted to these substances because of their rapid action, easy availability, and low cost. Products that are abused as inhalants include *volatile solvents* (paint thinners, glue, e-cigarette solvents known as "dripping," toluene, acetone, refrigerants, gasoline, cleaning fluids, correction fluids), *aerosols* (spray paint, nitrous oxide, hair spray), *gases* (propane tanks, lighter fluid), *nitrites* ("poppers" or "video head cleaner"), and *propellants* used in whipped cream dispensers. The most popular inhalants among young adolescents are glue, shoe polish, and spray paint. The various products contain a wide range of chemicals with serious adverse health effects (Table 140.14). **Huffing** , the practice of inhaling fumes, can be accomplished using a paper bag containing a chemical-soaked cloth, spraying aerosols directly into the nose/mouth, or using a balloon, plastic bag, or soda can filled with fumes. The percentage of adolescents using inhalants has remained stable, with 5.8% of high school students reporting having ever used inhalants. Eighth and 9th graders report highest use, suggesting targeted prevention strategies for this age-group.

Table 140.14

Hazards of Chemicals Found in Commonly Abused Inhalants

Amyl nitrite, butyl nitrite (“poppers,” “video head cleaner”): sudden sniffing death syndrome, suppressed immunologic function, injury to red blood cells (interfering with oxygen supply to vital tissues)
Benzene (found in gasoline): bone marrow injury, impaired immunologic function, increased risk of leukemia, reproductive system toxicity
Butane, propane (found in lighter fluid, hair and paint sprays): sudden sniffing death syndrome via cardiac effects, serious burn injuries (because of flammability)
Freon (used as a refrigerant and aerosol propellant): sudden sniffing death syndrome, respiratory obstruction and death (from sudden cooling/cold injury to airways), liver damage
Methylene chloride (found in paint thinners and removers, degreasers): reduction of oxygen-carrying of blood, changes to the heart muscle and heartbeat
Nitrous oxide (“laughing gas”), **hexane** : death from lack of oxygen to the brain, altered perception and motor coordination, loss of sensation, limb spasms, blackouts caused by blood pressure changes, depression of heart muscle functioning
Toluene (found in gasoline, paint thinners and removers, correction fluid): brain damage (loss of brain tissue mass, impaired cognition, gait disturbance, loss of coordination, loss of equilibrium, limb spasms, hearing and vision loss), liver and kidney damage
Trichloroethylene (found in spot removers, degreasers): sudden sniffing death syndrome, cirrhosis of the liver, reproductive complications, hearing and vision damage

Clinical Manifestations

The major effects of inhalants are psychoactive (Table 140.15). The intoxication lasts only a few minutes, so a typical user will huff repeatedly over an extended period (hours) to maintain the high. The immediate effects of inhalants are similar to alcohol: euphoria, slurred speech, decreased coordination, and dizziness. **Toluene** , the main ingredient in model airplane glue and some rubber cements, causes relaxation and pleasant hallucinations for up to 2 hr. Euphoria is followed by violent excitement; coma may result from prolonged or rapid inhalation. **Volatile nitrites** , such as amyl nitrite, butyl nitrite, and related compounds marketed as room deodorizers, are used as euphoriants, enhancers of musical appreciation, and sexual enhancements among older adolescents and young adults. They may result in headaches, syncope, and lightheadedness; profound hypotension and cutaneous flushing followed by vasoconstriction and tachycardia; transiently inverted T waves and depressed ST segments on electrocardiography; methemoglobinemia; increased bronchial irritation; and increased intraocular pressure. There may be dermatologic findings, including perianal/perioral dermatitis (“huffer rash”), frostbite, and contact dermatitis, as well as epistaxis, nasal ulcers, and conjunctivitis.

Table 140.15

Stages in Symptom Development After Use of Inhalants

STAGE	SYMPTOMS
1: Excitatory	Euphoria, excitation, exhilaration, dizziness, hallucinations, sneezing, coughing, excess salivation, intolerance to light, nausea and vomiting, flushed skin and bizarre behavior
2: Early CNS depression	Confusion, disorientation, dullness, loss of self-control, ringing or buzzing in the head, blurred or double vision, cramps, headache, insensitivity to pain, and pallor or paleness
3: Medium CNS depression	Drowsiness, muscular uncoordination, slurred speech, depressed reflexes, and nystagmus or rapid involuntary oscillation of the eyeballs
4: Late CNS depression	Unconsciousness that may be accompanied by bizarre dreams, epileptiform seizures, and EEG changes

CNS, Central nervous system; EEG, electroencephalogram.

From Harris D: Volatile substance abuse, *Arch Dis Child Educ Pract Ed* 91:ep93-ep100, 2006.

Complications

Model airplane glue is responsible for a wide range of complications, related to chemical toxicity, to the method of administration (in plastic bags, with resultant suffocation), and to the dangerous setting in which the inhalation occurs (inner-city roof tops). Common neuromuscular changes reported in chronic inhalant abusers include difficulty coordinating movement, gait disorders, muscle tremors, and spasticity, particularly in the legs (Table 140.16). Chronic use may cause pulmonary hypertension, restrictive lung defects or reduced diffusion capacity, peripheral neuropathy, hematuria, tubular acidosis, and possibly cerebral and cerebellar atrophy. Chronic inhalant abuse has long been linked to widespread brain damage and cognitive abnormalities that can range from mild impairment (poor memory, decreased learning ability) to severe dementia. High-frequency inhalant users were significantly more likely than moderate- and low-frequency users to experience adverse consequences of inhalant intoxication, such as behavioral, language, and memory problems. Certain risky behaviors and consequences, such as engaging in unprotected sex or fighting while high on inhalants, were dramatically more common among high-frequency than low-frequency inhalant users. Death in the acute phase may result from cerebral or pulmonary edema or myocardial involvement (Table 140.16).

Table 140.16

Documented Clinical Presentations of Acute and Chronic Volatile Substance Abuse

Ventricular fibrillation	Muscle weakness
Asystolic cardiac arrest	Abdominal pain
Myocardial infarction	Cough
Ataxia	Aspiration pneumonia
Agitation	Chemical pneumonitis
Limb and trunk uncoordination	Coma
Tremor	Visual and auditory hallucinations
Visual loss	Acute delusions
Tinnitus	Nausea and vomiting
Dysarthria	Pulmonary edema
Vertigo	Photophobia
Hyperreflexia	Rash
Acute confusional state	Jaundice
Conjunctivitis	Anorexia
Acute paranoia	Slurred speech
Depression	Diarrhea
Oral and nasal mucosal ulceration	Weight loss
Halitosis	Epistaxis
Convulsions/fits	Rhinitis
Headache	Cerebral edema
Peripheral neuropathy	Visual loss
Methemoglobinemia	Burns
Acute trauma	Renal tubular acidosis

Diagnosis

Diagnosis of inhalant abuse is difficult because of the ubiquitous nature of the products and decreased parental awareness of the dangers. In the primary care setting, providers need to ask parents if they have witnessed any unusual behaviors in their teen; noticed high-risk products in the teen's bedroom; seen paint on the teen's hands, nose, or mouth; or found paint- or chemical-coated rags. Complete blood count, coagulation studies, and hepatic and renal function studies may identify the complications. In extreme intoxication, a user may manifest symptoms of restlessness, general muscle weakness, dysarthria, nystagmus, disruptive behavior, and occasionally hallucinations. Toluene is excreted rapidly in the urine as hippuric acid, with the residual detectable in the serum by gas chromatography.

Treatment

Treatment is generally supportive and directed toward control of arrhythmia and stabilization of respirations and circulation. Withdrawal symptoms do not usually occur.

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140.5

Hallucinogens

Cora Collette Breuner

Keywords

LSD
MDMA
PCP

Several naturally occurring and synthetic substances are used by adolescents for their hallucinogenic properties. They have chemical structures similar to neurotransmitters such as serotonin, but their exact mechanism of action remains unclear. Lysergic acid diethylamide (**LSD**) and methylenedioxymethamphetamine (**MDMA**) are the most commonly reported hallucinogens used. 251-NBOMe (“N-Bomb”) is a new designer drug that interacts with the 5HT-2a receptor and has sympathomimetic and hallucinogenic properties.

Lysergic Acid Diethylamide

LSD (acid, big “d,” blotters) is a very potent hallucinogen that is made from lysergic acid found in ergot, a fungus that grows on rye and other grains. Its high potency allows effective doses to be applied to absorbent paper, or it can be taken as a liquid or a tablet. The onset of action can be 30-60 min, and it peaks at 2-4 hr. By 10-12 hr, individuals return to the predrug state. Among U.S. 12th graders, 4% report trying LSD at least once.

Clinical Manifestations

The effects of LSD can be divided into 3 categories: somatic (physical effects), perceptual (altered changes in vision and hearing), and psychic (changes in sensorium). The common somatic symptoms are dizziness, dilated pupils, nausea, flushing, elevated temperature, and tachycardia. The sensation of *synesthesia,* or "seeing" smells and "hearing" colors, as well as major distortions of time and self, have been reported with high doses of LSD. Delusional ideation, body distortion, and suspiciousness to the point of toxic psychosis are the more serious of the psychic symptoms. LSD is not considered to be an addictive drug because it does not typically produce drug-seeking behavior.

Treatment

An individual is considered to have a "bad trip" when the sensory experiences causes the user to become terrified or panicked. These episodes should be treated by removing the individual from the aggravating situation and placing him in a quiet room with a calming friend. In situations of extreme agitation or seizures, use of benzodiazepines may be warranted. "Flashbacks" or LSD-induced states after the drug has worn off and tolerance to the effects of the drug are additional complications of its use.

Methylenedioxymethamphetamine

MDMA ("X," Ecstasy, Molly), a phenylisopropylamine hallucinogen, is a synthetic compound similar to hallucinogenic mescaline and the stimulant methamphetamine. Like other hallucinogens, this drug is proposed to interact with serotoninergic neurons in the central nervous system (CNS). It is the preferred drug at "raves," all-night dance parties, and is also known as one of the "club drugs" along with γ-hydroxybutyrate (GHB) and ketamine (see Table 140.5). Between 2009 and 2010, past-year use of MDMA increased among U.S. 8th and 10th graders but then declined in both grades. Nationwide, the prevalence of having ever used MDMA was 8.4% of college students. In 2016, MDMA use by blacks (2.2%) in 12th grade was lower than for Hispanics (2.8%) or whites (3.3%).

Clinical Manifestations

Euphoria, a heightened sensual awareness, and increased psychic and emotional energy are acute effects. Compared to other hallucinogens, MDMA is less likely to produce emotional lability, depersonalization, and disturbances of thought. Nausea, jaw clenching, teeth grinding, and blurred vision are somatic symptoms, whereas anxiety, panic attacks, and psychosis are the adverse psychiatric outcomes. A few deaths have been reported after ingestion of the drug. In high doses, MDMA can interfere with the body's ability to regulate temperature. The resultant hyperthermia in association with vigorous dancing at a “rave” has resulted in severe liver, kidney, and cardiovascular system failure and death. There are no specific treatment regimens recommended for acute toxicity.

Chronic MDMA use can lead to changes in brain function, affecting cognitive tasks and memory. These symptoms may occur because of MDMA's effects on neurons that use serotonin as a neurotransmitter. The serotonin system plays an important role in regulating mood, aggression, sexual activity, sleep, and sensitivity to pain. A high rate of dependence has been found among MDMA users. MDMA exposure may be associated with long-term neurotoxicity and damage to serotonin-containing neurons. In nonhuman primates, exposure to MDMA for only 4 days caused damage to serotonin nerve terminals that was evident 6-7 yr later. There are no specific pharmacologic treatments for MDMA addiction. Drug abuse recovery groups are recommended.

Phencyclidine

Phencyclidine (**PCP**) (sternyl, angel dust, hog, peace pill, sheets) is an arylcyclohexalamine whose popularity is related in part to its ease of synthesis in home laboratories. One of the by-products of home synthesis causes cramps, diarrhea, and hematemesis. It is a “dissociative drug” that produces feelings of detachment from the surrounding environment and self. The drug is thought to potentiate adrenergic effects by inhibiting neuronal reuptake of catecholamines. PCP is available as a tablet, liquid, or powder, which may be used alone or sprinkled on cigarettes (joints). The powders and tablets generally contain 2-6 mg of PCP, whereas joints average 1 mg for every 150 mg of tobacco leaves, or approximately 30-50 mg per joint. The prevalence of PCP use (hallucinogenic drug) among U.S. 12th graders was 1.3%.

Clinical Manifestations

The clinical manifestations are dose related and produce alterations of perception, behavior, and autonomic functions. Euphoria, nystagmus, ataxia, and emotional lability occur within 2-3 min after smoking 1-5 mg and last for 4-6 hr. At these low doses the user is likely to experience shallow breathing, flushing, generalized numbness of extremities, and loss of motor coordination. Hallucinations may involve bizarre distortions of body image that often precipitate panic reactions. With doses of 5-15 mg, a toxic psychosis may occur, with disorientation, hypersalivation, and abusive language lasting for >1 hr. Hypotension, generalized seizures, and cardiac arrhythmias typically occur with plasma concentrations of 40-200 mg/dL. Death has been reported during psychotic delirium, from hypertension, hypotension, hypothermia, seizures, and trauma. The **coma** of PCP may be distinguished from that of the opiates by the absence of respiratory depression; the presence of muscle rigidity, hyperreflexia, and nystagmus; and lack of response to naloxone. PCP psychosis may be difficult to distinguish from schizophrenia. In the absence of a history of use, the diagnosis depends on urinalysis.

Treatment

Management of the PCP-intoxicated patient includes placement in a darkened, quiet room on a floor pad, safe from injury. Acute alcohol intoxication may also be present. For recent oral ingestion, gastric absorption is poor, and induction of emesis or gastric lavage is useful. Diazepam, in a dose of 5-10 mg orally or 2-5 mg intravenously, may be helpful if the patient is agitated and not comatose. Rapid excretion of the drug is promoted by acidification of the urine. Supportive therapy of the comatose patient is indicated with particular attention to hydration, which may be compromised by PCP-induced diuresis. Inpatient and/or behavioral treatments can be helpful for chronic PCP users.

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140.6

Cocaine

Cora Collette Breuner

Cocaine, an alkaloid extracted from the leaves of the South American *Erythroxylum coca*, is supplied as the hydrochloride salt in crystalline form. With **snorting** , it is rapidly absorbed into the bloodstream from the nasal mucosa, detoxified by the liver, and excreted in the urine as benzoylecgonine. Smoking the cocaine alkaloid (**freebasing**) involves inhaling the cocaine vapors in pipes, or cigarettes mixed with tobacco or marijuana. Accidental burns are potential complications of this practice. With **crack** cocaine, the crystallized rock form, the smoker feels “high” in <10 sec. The risk of addiction with this method is higher and more rapidly progressive than from snorting cocaine. Tolerance develops, and the user must increase the dose or change the route of administration, or both, to achieve the same effect. To sustain the high, cocaine users repeatedly use cocaine in short periods of time known as “binges.” Drug dealers often place cocaine in plastic bags or condoms and swallow these containers during transport. Rupture of a container produces a sympathomimetic crisis (see Table 140.6). Cocaine use among U.S. high school students has decreased in the last decade, as noted in the MTF 2016 data, with 3.7% of 12th graders having tried the drug (any route) at least once.

Clinical Manifestations

Cocaine is a strong CNS stimulant that increases dopamine levels by preventing reuptake. Cocaine produces euphoria, increased motor activity, decreased fatigability, and mental alertness. Its sympathomimetic properties are responsible for pupillary dilation, tachycardia, hypertension, and hyperthermia. Snorting cocaine chronically results in loss of sense of smell, nosebleeds, and chronic rhinorrhea. Injecting cocaine increases risk for HIV infection. Chronic abusers experience anxiety, irritability, and sometimes paranoid psychosis. Lethal effects are possible, especially when cocaine is used in combination with other drugs, such as heroin, in an injectable form known as a “speedball.” Cocaine, when taken with alcohol, is metabolized by the liver to produce cocaethylene, a substance that enhances the euphoria and is associated with a greater risk of sudden death than cocaine alone. Pregnant adolescents who use cocaine place their fetus at risk of premature delivery, complications of low birthweight, and possibly developmental disorders.

Treatment

There are no FDA-approved medications for treatment of cocaine addiction. CBT has been shown to be effective when provided in combination with additional services and social support. Oral sustained-release dexamfetamine has been shown to be partially effective in adults with cocaine dependence.

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140.7

Amphetamines

Cora Collette Breuner

Methamphetamine, commonly known as “ice,” is a nervous system stimulant and schedule II drug with a high potential for abuse. Most of the methamphetamine currently abused is produced in illegal laboratories. It is a white, odorless, bitter-tasting powder that is particularly popular among adolescents and young adults because of its potency and ease of absorption. It can be ingested orally, smoked, needle-injected, or absorbed across mucous membranes. Amphetamines have multiple CNS effects, including release of neurotransmitters and an indirect catecholamine agonist effect. In recent years, there has been a general decline of methamphetamine use among high school students. In the 2012 MTF Study, 1.1% of 12th graders reported using methamphetamine at least once, reflecting a steady decline in use.

Clinical Manifestations

Methamphetamine rapidly increases the release and blocks the reuptake of dopamine, a powerful “feel good” neurotransmitter (Table 140.17). The effects of amphetamines can be dose related. In small amounts, amphetamine effects resemble other stimulants: increased physical activity, rapid and/or irregular heart rate, increased blood pressure, and decreased appetite. High doses produce slowing of cardiac conduction in the face of ventricular irritability. Hypertensive and hyperpyrexic episodes can occur as seizures (see Table 140.6). Binge effects result in the development of psychotic ideation with the potential for sudden violence. Cerebrovascular damage, psychosis, severe receding of the gums with tooth decay, and infection with HIV and hepatitides B and C can result from long-term use. A withdrawal syndrome is associated with amphetamine use, with early, intermediate, and late phases (Table 140.17). The early phase is characterized as a “crash” phase with depression, agitation, fatigue, and desire for more of the drug. Loss of physical and mental energy, limited interest in the environment, and anhedonia mark the intermediate phase. In the final phase, drug craving returns, often triggered by particular situations or objects.

Table 140.17

Signs and Symptoms of Intoxication and Withdrawal

	OPIATES	AMPHETAMINES/COCAINE	BENZODIAZEPINES
INTOXICATION			
Behavior	Apathy and sedation; disinhibition; psychomotor retardation; impaired attention and judgment	Euphoria and sensation of increased energy; hypervigilance; grandiosity, aggression, argumentative; labile mood; repetitive stereotyped behaviors; hallucinations, usually with intact orientation; paranoid ideation; interference with personal functioning	Euphoria; apathy and sedation; abusiveness or aggression; labile mood; impaired attention; anterograde amnesia; impaired psychomotor performance; interference with personal functioning
Signs	Drowsiness; slurred speech; pupillary constriction (except anoxia from severe overdose—dilation); decreased level of consciousness	Dilated pupils; tachycardia (occasionally bradycardia, cardiac arrhythmias); hypertension; nausea/vomiting; sweating and chills; evidence of	Unsteady gait; difficulty in standing; slurred speech; nystagmus; decreased level consciousness; erythematous skin lesions or blisters

		weight loss; dilated pupils; chest pain; convulsions	
Overdose	Respiratory depression; hypothermia	Sympathomimetic symptoms	Hypotension; hyperthermia; depression of gag reflex; coma
Withdrawal	Craving to use; lacrimation; yawning; rhinorrhea/sneezing; muscle aches or cramps; abdominal cramps; nausea/vomiting/diarrhea; sweating; dilated pupils; anorexia; irritability; tremor; piloerection/chills; restlessness; disturbed sleep	Dysphoric mood (sadness/anhedonia); lethargy and fatigue; psychomotor retardation or agitation; craving; increased appetite; insomnia or hypersomnia; bizarre or unpleasant dreams	Tremor of tongue, eyelids, or outstretched hands; nausea or vomiting; tachycardia; postural hypotension; psychomotor agitation; headache; insomnia; malaise or weakness; transient visual, tactile, or auditory hallucinations or illusions; paranoid ideation; grand mal convulsions

From Haber PS, Demirkol A, Lange K, et al: Management of injecting drug users admitted to hospital, *Lancet* 374:1284–1292, 2009.

Treatment

Acute agitation and delusional behaviors can be treated with haloperidol or droperidol. Phenothiazines are contraindicated and may cause a rapid drop in blood pressure or seizure activity. Other supportive treatment consists of a cooling blanket for hyperthermia and treatment of the hypertension and arrhythmias, which may respond to sedation with lorazepam or diazepam. For the chronic user, comprehensive CBT interventions have been demonstrated as effective treatment options.

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Stimulant Abuse and Diversion

Cora Collette Breuner

In MTF 2016, 6.4% of 12th graders reported using OTC diet pills in their lifetime, and 2.1% in the past 30 days. These include nonprescription stimulants of 2 general types: pseudoamphetamines, usually sold by internet/mail order, and OTC stimulants, primarily diet and “stay-awake” pills. These drugs usually contain caffeine, ephedrine, and/or phenylpropanolamine. Stay-awake pills were used less often in 2016, with 3.6% of 12th graders reporting lifetime use and a 30-day prevalence of 1.7%. Even fewer students indicated use of look-alike products (2.3% lifetime and 0.9% monthly prevalence).

The *misuse* of a stimulant medication, defined as taking a stimulant not prescribed by a health care provider and not in accordance with health care provider guidance, has been growing over the past 2 decades, with a surge in prevalence rates of nonprescription stimulant use among both adolescents and young adults in the past 10 years. Nonprescription use of methylphenidate (**MPH**) in 2000 was 1.2%, increasing to 2% for MPH and 7.5% for nonprescription mixed amphetamine salts (**AMPs**) in 2015.

The majority of nonprescription stimulant users reported obtaining the drugs by **diversion** , a process for obtaining the drug from peers. Diversion occurs quite often and can begin in childhood, adolescence, or young adulthood. Lifetime rates of diversion ranged from 16–29% of students with stimulant prescriptions. One survey reported that 23.3% of middle and high school students taking prescribed stimulants had been solicited to divert their medication to others at a rate that increased from middle to high school. It has been shown that 54% of college students prescribed stimulants for attention-deficit/hyperactivity disorder (ADHD) had been approached to divert their medication.

In U.S. college students, nonprescription use of stimulants (Ritalin, Adderall, Dexedrine) is more prevalent among particular subgroups (male, white, members of fraternities/sororities, with lower grade point averages, more likely to use alcohol, cigarettes, marijuana, MDMA, or cocaine) and types of colleges (northeastern region, with more competitive admission standards). Lifetime prevalence of nonprescription stimulant use was 6.9% and past-month prevalence 2.1%. According to a survey of 334 ADHD-diagnosed college students taking prescription stimulants, 25% misused their own prescription medications. Scholastic pressures, including the need to succeed academically, and persistent social and financial demands place many students at an increased risk for misuse of various drugs, especially at the end of school terms. A web-based survey of medical and health profession students found that the most common reason for nonprescription stimulant use was to focus and concentrate during studying.

Clinical Manifestations

Misuse of stimulants is associated with psychosis, seizures, myocardial infarction, cardiomyopathy, and even sudden death. Intentional misuse of MPH or AMPs in combination with other substances leads to adverse medical consequences. One study revealed an increase in emergency department (ED) visits involving AMP misuse from 862 in 2006 to 1,489 in 2011. Importantly, 14% of the ED visits for stimulant use were associated with cardiovascular (CV) events. Psychosis includes visual hallucinations, delusions, anorexia, flattening of affect, and insomnia mediated by dopaminergic excess. The CV effects include hypertension, arrhythmias, tachycardia, cardiomyopathy, cardiac dysrhythmias, necrotizing vasculitis, and CV accidents. Case reports include serious CV adverse drug reactions (ADRs), sudden death, and psychiatric disorders. Many patients report sleep difficulties (72%), irritability (62%), dizziness and lightheadedness (35%), headaches (33%), stomach aches (33%), and sadness (25%). Other health risks include loss of appetite, weight loss, and nervousness. Many users are involved in heavy episodic alcohol use while using MPH or AMPs. Most users of MPH or AMPs are unaware of these adverse effects and predominantly “feel good” about taking these medications.

Despite reports that MPH misuse is a healthcare issue, >82% of primary care physicians did not suspect misuse of prescribed ADHD medication in one report, and <1% thought that their patients were diverting prescribed ADHD medication. Improved monitoring for malingering and patient misuse may assist stopping diversion of these medications. ADHD diagnosis should be confirmed in those requesting ADHD medication, and they should be screened for use of other drugs.

Treatment

Treatment for nonprescription stimulant overdose is similar as that for amphetamine overdose. Haloperidol or droperidol is recommended for acute agitation and delusional behaviors. Phenothiazines are contraindicated and may cause a rapid drop in blood pressure or seizure activity. Hyperthermia may require use of a cooling blanket, and sedation with a benzodiazepine is recommended for treatment of the hypertension and arrhythmias. In those with chronic use, inpatient or outpatient substance abuse interventions utilizing CBT has been shown to be the most effective treatment option.

Monitoring of the diversion and misuse of pharmaceutical stimulants must be a priority. More data need to be obtained on the prevalence, patterns, and harmful effects in adolescents and young adults.

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140.9

Opiates

Cora Collette Breuner

Heroin is a highly addictive synthetic opiate drug made from a naturally occurring substance (**morphine**) in the opium poppy plant. It is a white or brown powder that can be injected (intravenously or subcutaneously), snorted/sniffed, or smoked. Intravenous (IV) injection produces an immediate effect, whereas effects from the subcutaneous route occur in minutes, and from snorting, in 30 minutes. After injection, heroin crosses the blood-brain barrier, is converted to morphine, and binds to opiate receptors. Tolerance develops to the euphoric effect, and the chronic user must take more heroin to achieve the same intense effect. Heroin use among U.S. teens peaked in the mid-1990s but is resurgent in some suburban communities, as is the use of **prescription opioids** found in the home. Nationwide, 2.9% of high school students report having tried heroin at least once. Highest use is seen in black males, with a growing prevalence in suburban high school students; ranges vary from 0.8% to 5.3% across large urban, suburban, and rural school districts. **Fentanyl** is a more potent opiate and is responsible for many opiate overdoses. *Recreational (illegal) use of prescription opiate medications by oral or injection (dissolving the pill) is a major source of opiate addiction and opiate overdoses.*

Clinical Manifestations

The clinical manifestations are determined by the purity of the heroin or its adulterants, combined with the route of administration. The immediate effects include euphoria, diminution in pain, flushing of the skin, and pinpoint pupils (see Table 140.17). An effect on the hypothalamus is suggested by the lowering of body temperature. The most common dermatologic lesions are the “tracks,” the hypertrophic linear scars that follow the course of large veins. Smaller, discrete peripheral scars, resembling healed insect bites, may be easily overlooked. The adolescent who injects heroin subcutaneously may have fat necrosis, lipodystrophy, and atrophy over portions of the extremities. Attempts to conceal these stigmata may include amateur tattoos in unusual sites. Skin abscesses secondary to unsterile techniques of drug administration are usually found. There is a loss of libido; the mechanism is unknown. The chronic heroin user may resort to prostitution to support the habit, thus increasing the risk of sexually transmitted diseases (including HIV), pregnancy, and other infectious diseases. Constipation results from decreased smooth muscle propulsive contractions and increased anal sphincter tone. The absence of sterile technique in injection may lead to cerebral microabscesses or endocarditis, usually caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa.* Abnormal serologic reactions are also common, including false-positive Venereal Disease Research Laboratories and latex fixation tests. Infectious complications are usually not seen with oral prescription opioid use unless the pills are dissolved and injected.

Withdrawal

After ≥8 hr without heroin, the addicted individual undergoes a series of physiologic disturbances over 24-36 hr, referred to collectively as “withdrawal” or the **abstinence syndrome** (see Table 140.17). The earliest sign is yawning, followed by lacrimation, mydriasis, restlessness, insomnia, “goose flesh,” cramping of the voluntary musculature, bone pain, hyperactive bowel sounds and diarrhea, tachycardia, and systolic hypertension. Although the administration of methadone is the most common method of detoxification, the addition of **buprenorphine** , an opiate agonist-antagonist, is available for detoxification and maintenance treatment of heroin and other opiates. Buprenorphine has the advantage of offering less risk of addiction, overdose, and withdrawal effects, and can be dispensed in the privacy of a physician's office.

Combined with behavioral interventions, it has a greater success rate of detoxification. A combination drug, buprenorphine plus naloxone, has been formulated to minimize abuse during detoxification. Clonidine and tramadol have also been used to manage opioid withdrawal.

Drugs used to treat **opioid use disorder** , a chronic relapsing problem, traditionally include methadone maintenance and buprenorphine. Abuse-deterrent opioid pill formulations (when pain control requires an opioid) include pills resistant to crushing that form a viscous gel when dissolved or pills with a sequestered opioid antagonist (naltrexone).

Overdose Syndrome

The overdose syndrome is an acute reaction after administration of an opiate. It is the leading cause of death among drug users. The clinical signs include stupor or coma, seizures, miotic pupils (unless severe anoxia has occurred), respiratory depression, cyanosis, and pulmonary edema. The differential diagnosis includes CNS trauma, diabetic coma, hepatic (and other) encephalopathy, Reye syndrome, and overdose of alcohol, barbiturates, PCP, or methadone. Diagnosis of opiate toxicity is facilitated by IV administration of naloxone, 0.01 mg/kg (2 mg is a common initial dose for an adolescent), which causes dilation of pupils constricted by the opiate. Diagnosis is confirmed by the finding of morphine in the serum.

Treatment

Treatment of acute heroin overdose consists of maintaining adequate oxygenation and continued administration of **naloxone** , a pure opioid antagonist. It may be given intravenously, intramuscularly, subcutaneously, as a nasal spray, or by endotracheal tube. Naloxone has an ultrarapid onset of action (1 min) and duration of action of 20-60 min. Naloxone is often available in the field, carried by first responders. Take-home naloxone may also be given to drug users, their family, or friends; such programs have been effective in treating overdoses. If there is no response, other etiologies for the respiratory depression must be explored. Naloxone may have to be continued for 24 hr if methadone, rather than shorter-acting heroin, has been taken. Admission to the intensive care unit is indicated for patients who require continuous naloxone infusions (rebound coma, respiratory depression) and for those with life-threatening arrhythmias, shock, and seizures.

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140.10

Bath Salts

Cora Collette Breuner

Bath salts refers to a group of previously OTC, but now illicit, substances containing 1 or more synthetic chemicals similar to **cathinone** , an amphetamine-like stimulant found in the khat plant. The bath salts, marketed under brand names (e.g., Lunar Wave, Cloud Nine, Vanilla Sky), are sold online or in drug paraphernalia stores as a white or brown crystalline powder and can be ingested, inhaled, or injected. The most current information about teen use of bath salts is from the 2016 MTF survey of 8th, 10th, and 12th graders, who report use of 0.9%, 0.8%, and 0.8%, respectively. The synthetic cathinones found in bath salts include methylone, mephedrone, and 3,4-methylenedioxypyrovalerone (MDPV), all of which are chemically similar to amphetamines and MDMA (Ecstasy).

Clinical Manifestations

The chemicals in bath salts raise brain dopamine levels, causing the user to feel a surge of euphoria, with increased sociability and sex drive. In addition, the user may experience a surge in norepinephrine, causing reactions such as an elevated heart rate, chest pain, vasoconstriction, diaphoresis, hyperthermia, dilated pupils, seizures, arrhythmias, and high blood pressure. Users also experience psychiatric symptoms such as aggressive behavior, panic attacks, paranoia, psychosis, delirium, self-mutilation, and hallucinations caused by elevated serotonin levels. Intoxication from bath salts may cause **excited delirium syndrome** , which includes dehydration, rhabdomyolysis, and kidney failure.

Treatment

Treatment of overdose should be directed at specific complications but often includes benzodiazepines or propofol for agitation and other neuropsychiatric manifestations. The synthetic cathinones in bath salts are highly addictive, triggering intense cravings in those who consume them frequently. This may result in dependence, tolerance, and strong withdrawal symptoms, as seen in other highly addictive substances. The sale of 2 of the synthetic cathinones, mephedrone and MDPV, is illegal in the United States.

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CHAPTER 141

The Breast

Cynthia M. Holland-Hall

Breast development is often the first visible sign of puberty in the adolescent female. Pediatric practitioners must be able to distinguish normal breast development, including normal variants, from pathologic breast disorders. Visual inspection of the breast tissue should routinely be a component of the young adolescent's general physical examination. Breast development during puberty is described using the **Sexual Maturity Rating (SMR)** scale, progressing from SMR 1 to SMR 5 as the breast becomes more mature (see Chapter 132 , Fig. 132.2).

Female Disorders

See Chapter 566 .

Male Disorders

Pubertal gynecomastia occurs in up to 65% of healthy adolescent males (see Chapter 603). Although this finding has long been attributed to a transient imbalance of estrogen and androgen concentrations, this biochemical imbalance has not been clearly demonstrated. Recent studies suggest that elevations of insulin-like growth factor (IGF)-I may have a stronger association. Onset typically is between 10 and 13 yr, peaking at SMR 3-4. Careful physical examination is essential to distinguish between **true gynecomastia** , characterized by a discrete disk of palpable glandular tissue under the nipple-areolar complex, and **pseudogynecomastia** , characterized by more diffuse, bilateral adiposity of the anterior chest wall. Physiologic gynecomastia regresses spontaneously in up to 90% of adolescents within 18-24 mo. Reassurance and continued observation are recommended in most patients; surgery may be indicated in severe or persistent cases. No medical therapies for gynecomastia have been approved for use in adolescents by the U.S. Food and Drug Administration. Small, noncontrolled trials of antiestrogens, such as tamoxifen, appear promising, but more evidence is needed. Conditions associated with nonphysiologic gynecomastia include endocrine disorders, liver disease, neoplasms, chronic disease, and trauma. Although dozens of medications are implicated as possible causes of gynecomastia, convincing evidence exists only for a few, including several antiandrogens and other exogenous hormones, antiretrovirals, and histamine$_2$ receptor blockers. Calcium channel blockers, certain antipsychotics, proton pump inhibitors, lavender, and tea tree oil may be causative. Among drugs of abuse, alcohol, opioids, and anabolic steroids may be associated with gynecomastia, but minimal evidence supports an association with marijuana or amphetamines.

Other breast pathology in males is uncommon. Benign masses such as neurofibromas, lipomas, and dermoid cysts have been reported in the male breast. Males with Klinefelter syndrome have an elevated risk of breast cancer (see Chapter 601), but this malignancy is otherwise exceedingly rare in adolescents.

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CHAPTER 142

Menstrual Problems

Krishna K. Upadhya, Gina S. Sucato

See also Chapter 565 .

Menstrual disturbances, including delayed onset, irregularity, heavy flow, and pain, occur in 75% of females during adolescence. Menstrual problems vary in presentation. For adolescents with minor variations from normal (Table 142.1), an explanation of symptoms and reassurance may be all that is needed. Severe dysmenorrhea or prolonged menstrual bleeding can be not only frightening, but a cause of persistent morbidity requiring more aggressive management, potentially including referral to a specialist in adolescent gynecology.

Table 142.1

Characteristics of Normal Menses[*]

Cycle length	21-35 days from the 1st day of one period to the 1st day of the next (during 1st 3 yr after menarche can be 21-45 days)
Duration of menses	7 or fewer days
Blood flow	6 or fewer (soaked) pads or tampons per day

[*] Adolescents with 2 or more cycles outside this range or who skip their period for 3 consecutive mo warrant evaluation.

Normal Menstruation

Data from many countries, including the United States, suggest that the average age of menarche, or first menses, varies according to ethnic origin and socioeconomic status. There is often a close concordance of the age at menarche between mother and daughter, suggesting that genetic factors are determinants in addition to individual factors such as weight, exercise level, and chronic medical conditions. The age of menarche has declined in countries and populations experiencing improved nutritional standards and other living conditions. In U.S. females, the average age of menarche, 12.5 years, has been relatively stable over the last few decades; it is slightly older for non-Hispanic whites, and slightly younger for non-Hispanic blacks and Hispanic Americans.

Menarche typically occurs within 2-3 yr of the onset of breast budding (**thelarche**), which is the 1st sign of puberty in most females. Menarche usually occurs during breast **sexual maturity rating** (**SMR** ; i.e., Tanner stage) 4. Periods gradually become more regular, initially with longer cycle lengths ranging between 21 and 45 days. The older the age at which menarche occurs, the longer it takes for consistently ovulatory cycles to be established. However, for most adolescents, by 3 yr after menarche, menstrual cycles are similar to that of adults: between 21 and 35 days long.

Menstrual Irregularities

In young adolescents, many variations in menstruation are explained by **anovulation** that results from immaturity of the hypothalamic-pituitary-ovarian axis governing menstrual cyclicity. Significant deviations from normal should prompt a search for organic pathology in a logical and cost-effective manner. An accurate menstrual history is an important, but often lacking, 1st step toward a diagnosis. At menarche, all patients should be encouraged to track their periods, which several free smartphone and tablet applications can facilitate.

Previously, a range of terms has been used to describe abnormal menstrual bleeding. These include “menorrhagia” to indicate regularly occurring bleeding that was excessive in amount or duration, and “metrorrhagia” to indicate irregular bleeding between periods. Such terms are imprecise, confusing, and not linked to any specific underlying pathology. **Abnormal uterine bleeding (AUB)** is the preferred term for uterine bleeding that is abnormal in regularity, volume, frequency, or duration. AUB is further specified by adding terms that describe the bleeding as heavy *menstrual* bleeding, or *intermenstrual* bleeding. A qualifying letter is added to indicate the etiology of the abnormal bleeding. Of the 9 categories of etiologies, the 3 most relevant to adolescents are **ovulatory dysfunction** (AUB-**O**), previously referred to as “dysfunctional uterine bleeding” and discussed in Chapter 142.2 ; **coagulopathy** (AUB-**C**); and **not yet classified** (AUB-**N**).

In addition to a standard medical history noting hospitalizations, chronic illness, and medication use, a complete history for evaluating a patient with menstrual irregularity should include the timing of pubertal milestones, such as onset of pubic and axillary hair and breast development; a detailed patient menstrual history; age of menarche and overall menstrual pattern of mother and sisters; and a family history of gynecologic problems. The complete review of systems should elicit any changes in headache pattern or vision; the presence of galactorrhea; and any changes in skin, hair, or bowel patterns. Changes in diet, level of exercise, and sports participation are also important factors when generating a differential diagnosis. As with all adolescent visits, the patient should be interviewed alone, and the confidential history should assess substance use, consensual sexual activity, forced sexual behavior, abuse, and other psychosocial stressors.

In addition to the basic growth parameters of weight, height, blood pressure, heart rate, and body mass index, a careful review of the patient's growth chart is indicated. Physical examination should document SMR; signs of androgen excess, such as hirsutism or severe acne; and signs suggestive of an eating disorder (see Chapter 41), such as lanugo or knuckle calluses. A careful external genital examination should be performed, but in the absence of sexual activity, an internal pelvic examination is rarely necessary. If being considered for the young adolescent, an internal exam should be performed by a physician with expertise in this age-group using proper equipment and technique. Transabdominal pelvic ultrasound can be a useful adjunct for evaluating anatomic abnormalities in the adolescent; when indicated, MRI can provide greater detail of pelvic anatomy.

142.1

Amenorrhea

Krishna K. Upadhya, Gina S. Sucato

Keywords

amenorrhea
polycystic ovary syndrome
PCOS
female athlete triad

Amenorrhea, the absence of menstruation, generally requires evaluation at age 15 yr, or if there has been no menstruation within 3 yr of the onset of puberty (**primary amenorrhea**), or if there has been no menstruation for the length of 3 previous cycles in a postmenarchal patient (**secondary amenorrhea**). However, the following caveats exist: lack of any pubertal signs by age 13 yr in a girl should prompt evaluation for pubertal delay; in sexually active patients, or those with other symptoms suggesting pathology, evaluation should be initiated without waiting for 3 missed cycles; in patients whose breast development started between age 8 and 9 yr, observation for >3 yr may be warranted in some cases, given data suggesting that the age of thelarche has decreased but the age of menarche has not. Conversely, expectant management with close follow-up can be considered in a patient whose history, physical examination (showing some signs of pubertal development), and family history suggest constitutional delay of puberty.

The differential diagnosis of amenorrhea is broad (Table 142.2) and requires a careful history and physical exam to guide any necessary diagnostic studies. Key to the evaluation is understanding the timing and tempo of the patient's pubertal milestones. The evaluation of a patient presenting with amenorrhea should begin by ascertaining whether she has ever had any prior menstrual bleeding. Some aspects of the evaluation of both primary and secondary amenorrhea are identical; conditions that can interrupt the menstrual cycle can also prevent menarche. In females with primary amenorrhea, however, genetic and anatomic conditions must also be considered (Table 142.3).

Table 142.2

Causes of Amenorrhea (Primary or Secondary)

- Pregnancy (regardless of history can cause primary or secondary amenorrhea)
- Functional hypothalamic causes (stress, weight loss, undernutrition, high

- levels of exercise, energy deficit even at normal weight)
- Female athlete triad (inadequate energy intake, amenorrhea, and low bone density)
- Eating disorders
- Premature ovarian insufficiency (autoimmune, idiopathic, galactosemia, or secondary to radiation or chemotherapy)
- Hypothalamic and/or pituitary damage (e.g., irradiation, tumor, traumatic brain injury, surgery, hemochromatosis, midline central nervous system defects such as septooptic dysplasia, autoimmune pituitary hypophysitis)
- Thyroid disease (hyper- or hypo-; hypothyroidism more likely to be associated with increased bleeding)
- Prolactinoma
- Systemic disease (e.g., inflammatory bowel disease, cyanotic congenital heart disease, sickle cell disease, cystic fibrosis, celiac disease)
- Hyperandrogenism (polycystic ovary syndrome, nonclassic congenital adrenal hyperplasia, adrenal tumor or dysfunction)
- Drugs and medications (e.g., illicit drugs, atypical antipsychotics, hormones)
- Turner syndrome (including mosaicism)

Table 142.3

Additional Causes of Primary Amenorrhea

- Physiologic/constitutional delay
- Anatomic abnormalities
    - Müllerian agenesis
    - Imperforate hymen
    - Transverse vaginal septum
- Genetic disorders
    - 46,XY disorders of sexual development (e.g., androgen insensitivity syndrome, 5α-reductase deficiency, 17α-hydroxylase deficiency)
    - Mixed gonadal dysgenesis (associated with a number of different chromosome patterns)
    - Turner syndrome (resulting from 45,X or a variety of mosaic or other abnormal karyotypes)
    - Genetic hypogonadotropic hypogonadism (e.g., X-linked

Kallmann syndrome)

History and Physical Examination

Important elements of the history include dietary intake, exercise level, and a thorough review of any ongoing symptoms, including fever, headache, vision changes, chronic respiratory or gastrointestinal (GI) complaints, changes in bowel history, galactorrhea, changes in hair or nails, excessive body hair, severe acne, unexplained musculoskeletal complaints, and changes in vaginal discharge (which can disappear in females who are hypoestrogenic for reasons such as poor caloric intake). Any underlying medical conditions and the adequacy of their control should be noted, as well as the presence of any renal or skeletal anomalies, some of which may be associated with reproductive system anomalies. Medications, particularly those for psychiatric conditions, should be documented. Family history of menarcheal age, eating disorders (see Chapter 41), and **polycystic ovary syndrome (PCOS** ; see Chapter 567) should be elicited. A thorough social history is necessary, especially concerning the presence or absence of sexual activity or abuse (see Chapter 16.1).

Physical examination should begin with careful attention to growth chart trajectories. In addition to a search for undiagnosed systemic disease, clues to an eating disorder, thyroid disease, or hyperandrogenism should be sought. The exam should assess for body mass index, orthostatic pulses, blood pressure, abnormal dentition, anosmia or hyposmia (suggestive of Kallmann syndrome; see Chapter 601.2), parotid enlargement, thyroid gland palpation, hepatosplenomegaly or other abdominal mass, lymphadenopathy, presence or absence of breast tissue (by palpation, not inspection), and SMR (see Chapter 132). Skin examination should note any lanugo, dry or doughy skin, loss of hair from scalp or eyebrows, striae, acanthosis nigricans, or acne. The genital exam should note SMR and appearance of the vagina, which should be pink and moist; thin, dry, reddened mucosa suggests estrogen deficiency. The clitoral width should be <1 cm. In the patient with primary amenorrhea, vaginal patency can be assessed painlessly using a slender saline-moistened swab and careful avoidance of the hymen. If physical assessment of the cervix and uterus is not tolerated, a pelvic ultrasound is advisable in patients with primary amenorrhea, followed by MRI if more detail is needed.

Laboratory Studies

A urine pregnancy test, serum levels of prolactin, thyroid-stimulating hormone, and follicle-stimulating hormone (FSH) are reasonable to measure in all patients presenting with amenorrhea (Fig. 142.1). Elevation of FSH (>30 mIU/mL) in an amenorrheic female suggests ovarian insufficiency, and if confirmed with repeat testing, should be followed with a pelvic ultrasound, karyotype, and specialist referral. Diagnostic tests in the patient presenting with amenorrhea should be tailored to her history and physical exam (Table 142.4).

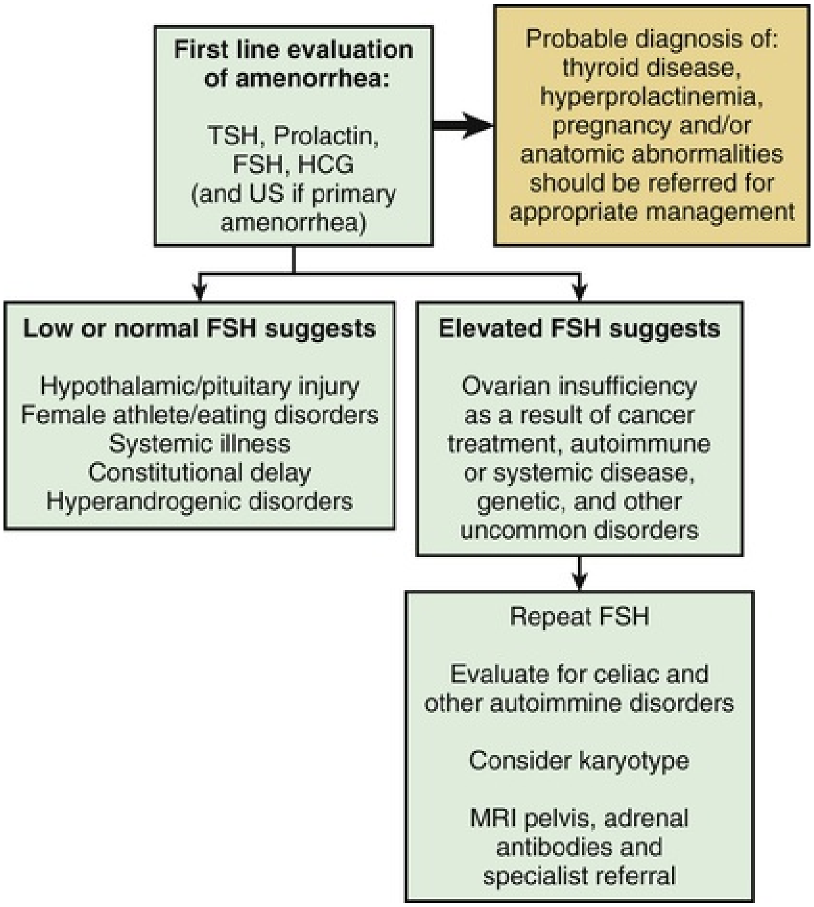
First line evaluation of amenorrhea:
TSH, Prolactin, FSH, HCG (and US if primary amenorrhea)
Probable diagnosis of: thyroid disease, hyperprolactinemia, pregnancy and/or anatomic abnormalities should be referred for appropriate management
Low or normal FSH suggests
Hypothalamic/pituitary injury
Female athlete/eating disorders
Systemic illness
Constitutional delay
Hyperandrogenic disorders
Elevated FSH suggests
Ovarian insufficiency as a result of cancer treatment, autoimmune or systemic disease, genetic, and other uncommon disorders
Repeat FSH
Evaluate for celiac and other autoimmine disorders
Consider karyotype
MRI pelvis, adrenal antibodies and specialist referral

FIG. 142.1 Initial diagnostic testing to evaluate amenorrhea. FSH, Follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; US, ultrasound.

Table 142.4

Laboratory Tests to Evaluate Patients With

Total and free testosterone[*]
Liver, kidney, and thyroid function studies
Complete blood count with platelets
Urine pregnancy test (regardless of history)
Nucleic acid amplification test (NAAT) or other equivalent testing for *Chlamydia*, gonorrhea, and *Trichomonas*
Prothrombin time and partial thromboplastin time
Ferritin level
Von Willebrand factor antigen, ristocetin cofactor, and factor VIII[†] activities
Pelvic ultrasound (if bleeding persists despite treatment)

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[*] In patients with signs or symptoms suggestive of polycystic ovary syndrome, such as acne, hirsutism, obesity, acanthosis nigricans, and a history of infrequent menses.

[†] Any abnormalities should be followed with a ristocetin-induced platelet aggregation and von Willebrand factor multimers. Testing in the 1st 3 days of menses and before any estrogen treatment is started minimizes the chances of false-negative tests. Repeat testing can be warranted in patients for whom there is a high pretest suspicion.

In patients with signs of androgen excess (e.g., severe acne or hirsutism) or other physical stigmata associated with PCOS (rapid pubertal weight gain, acanthosis nigricans) consider measuring levels of 17-hydroxyprogesterone (17-OHP) (collected in the morning, approximately 8 AM), free and total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione. PCOS affects up to 15% of females; diagnostic criteria for adolescents are controversial but include variations of menstrual irregularity (ranging from amenorrhea to AUB) and physical or biochemical evidence of androgen excess. The interpretation of polycystic ovarian morphology identified on ultrasound in adolescents can be challenging, and an ultrasound is not necessary for diagnosis in adolescents.

With the exceptions of pregnancy, constitutional delay, and imperforate hymen, conditions causing primary amenorrhea are associated with reduced fertility; thus their diagnosis may cause profound emotional responses in patients and families. Therefore, before ordering studies to confirm these diagnoses (e.g., karyotype, MRI of reproductive anatomy), the clinician should carefully consider the implications and be prepared to refer to specialists with experience managing the long-term treatment of such diagnoses.

In patients presumed to have hypothalamic amenorrhea, based on prepubertal luteinizing hormone (LH) and low FSH levels using an ultrasensitive assay and consistent history and physical exam, MRI of the brain is not necessary in all patients. However, MRI should be considered for patients presenting with a headache history that is a change from baseline, persistent emesis, change in thirst, urination, or vision, elevated prolactin or galactorrhea, or other neurologic symptoms.

Treatment

Treatment for amenorrhea varies widely depending on the underlying cause. Many diagnoses require referral to clinicians in specialties such as endocrinology, adolescent medicine, gynecology, and other surgical subspecialists; often, collaboration with other disciplines such as psychology or nutrition is also indicated. For patients with **PCOS** , the mainstay of treatment is suppression of ovarian androgens (typically with combined hormonal contraception, i.e., estrogen and progestin) and lifestyle modifications to decrease obesity and insulin resistance. Patients with abnormal glucose tolerance may benefit from the addition of metformin. Spironolactone, an androgen receptor blocker, can also be used to reduce androgen effects, including hirsutism. Because of the high prevalence of **metabolic syndrome** in PCOS, evaluation of comorbid diabetes and hyperlipidemia with periodic lipid screening and oral glucose tolerance testing should be considered, particularly for obese patients, those with familial risk factors, and those with other signs such as acanthosis nigricans and hypertension. For patients with eating disorders or other conditions of energy imbalance that render them hypoestrogenic, normalizing weight and improving nutritional status are the keys to treatment. Initiation of hormonal therapy is not recommended routinely in these patients. However, for those who remain amenorrheic after a trial of nutritional and activity modification, short-term use of **transdermal estrogen therapy** (E2) may be considered to protect bone health. For females with amenorrhea based on ovarian insufficiency (or absence), exogenous hormones are required for all pubertal development. Experts recommend starting at age 10-12 yr with low-dose transdermal estrogen, progressing to increased doses of estrogen and cyclic progestin. Continued maintenance therapy can be accomplished with higher-dose combination products, as found in typical combined hormonal contraceptive pills, patches, and rings.

For patients with **secondary amenorrhea** , use of hormones to bring on monthly bleeding (e.g., with combined hormonal contraception) in the absence of a clear indication (e.g., PCOS, contraception) is not recommended, because this will mask the patient's subsequent menstrual pattern. However, in patients with normal postpubertal estrogen levels, progesterone can be useful to periodically (every 4-12 wk) induce shedding of the endometrial lining to avoid buildup and subsequent heavy menses. One commonly used regimen is medroxyprogesterone, 10 mg daily for the 1st 12 days of the month.

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142.2

Abnormal Uterine Bleeding

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Keywords

abnormal uterine bleeding
AUB
von Willebrand disease

Abnormal uterine bleeding (AUB) is a broad term used to describe any menstrual bleeding pattern that is outside what is considered physiologic. Clinicians are encouraged to categorize the abnormal pattern based on the patient's complaint, which will usually be menses that are irregular (AUB/**IMB: intermenstrual bleeding**) or heavy (AUB/**HMB: heavy menstrual bleeding**).

Irregular Menstrual Bleeding

The American Academy of Pediatrics (AAP) advocates treating menstrual status as a *vital sign* at routine visits. Although menses are frequently irregular in the early postmenarcheal years, further evaluation is necessary when menstrual patterns vary too widely from what is normal for age. Even in the 1st postmenarcheal year, menses should not be less frequent than every 45 days. Menses become increasingly regular with age, and by 3 years after menarche typically occur every 21-35 days, lasting 3-7 days. An adolescent's personal cycle duration is usually established by age 19 or 20 yr.

Adolescents rarely present with complaints of unusually short or light menses. However, short, light, or infrequent menses should be evaluated similarly to secondary amenorrhea. Females whose menses are excessive are much more likely to come to attention for AUB.

In the early postmenarcheal years, the most common cause of AUB in adolescents is anovulation caused by immaturity of the hypothalamic-pituitary-ovarian axis. In the absence of a mid-cycle surge of LH to stimulate ovulation, there is no corpus luteum production of progesterone. Without the stabilizing effects of progesterone on the endometrial lining, there is increased risk of irregular bleeding. Irregular bleeding because of anovulation, in the absence of anatomic, systemic, or endocrinologic disease, is categorized as **AUB caused by ovulatory dysfunction** (**AUB-O** ; previously referred to as dysfunctional uterine bleeding). Although it is the most common cause of abnormal menstrual bleeding in adolescents, AUB-O is a diagnosis of exclusion. In generating a differential diagnosis, it is important to remember that most conditions that lead to amenorrhea can cause anovulation first, and anovulation is a key risk for heavy irregular bleeding. Table 142.5 lists the causes of AUB.

Table 142.5

Causes of Irregular Menstrual Bleeding/Abnormal Uterine Bleeding (AUB)

CAUSES OF AUB	EXAMPLES	FEATURES
Immature hypothalamic-pituitary-ovarian axis (AUB-O)	Patient within 2 yr of menarche	Painless; patient responds to hormonal treatment.
Weight changes, disordered eating, or excessive exercise	Anorexia nervosa, bulimia, weight gain or loss of more than 10 pounds from any etiology	Weight loss more frequently results in lighter, less frequent menses.
Endocrinologic causes	Thyroid disease, polycystic ovary syndrome (PCOS)	Bleeding typically increases with hypothyroidism and decreases with PCOS and hyperthyroidism.
Complication of pregnancy	Threatened abortion, postpartum or postabortal endometritis	History of sexual activity and/or pregnancy
Infection	Cervicitis, condyloma, pelvic inflammatory disease	Bleeding is usually not heavy and may occur with sexual intercourse.

Trauma	Sexual assault, straddle injuries	History will be evident in patients of menstruating age unless there is cognitive disability.
Vaginal foreign body	Toilet paper, broken condoms, tampons	Associated with odor and vaginal discharge, but usually not heavy bleeding.
Hematologic causes	Von Willebrand disease, platelet function disorder, thrombocytopenia (idiopathic thrombocytopenic purpura, drug induced), hemophilia carriage, clotting factor deficiency, leukemia	Bleeding is heavy and/or long and frequently regular, may present at menarche, and may be accompanied by a suggestive family history (hysterectomy, uterine ablation, cautery for epistaxis) or physical exam (ecchymoses, petechiae).
Medications	Estrogens, progestins, (in pills, patches, rings, injections, implants, and intrauterine devices), androgens, drugs that cause prolactin release (estrogens, phenothiazines, tricyclic antidepressants, metoclopramide), anticoagulants (heparin, warfarin, aspirin, NSAIDs), SSRIs	Affect the hypothalamic-pituitary-ovarian axis, endometrial lining, platelets, or coagulation pathway.
Anatomic	Partial obstruction of vagina or uterus causing asynchronous bleeding; cervical or endometrial polyps or myomas; hemangioma; uterine vascular malformation; genital/reproductive tract cancer	Most of these entities are extremely rare, especially reproductive tract cancers.
Systemic disease	Celiac disease, rheumatoid arthritis, Ehlers-Danlos syndrome	Accompanied by other signs of the condition.

Unscheduled bleeding during the use of hormonal contraception frequently occurs, particularly with progestin-only methods. Common causes include medication nonadherence, interacting medications (prescribed or over-the-counter), and smoking. Patients should be reassured such bleeding is benign and not an indication to stop an otherwise satisfactory contraceptive method.

Heavy and Prolonged Menstrual Bleeding

Irregular bleeding, particularly that resulting from anovulation, can be long and heavy (Table 142.5). However, in patients who have regular, cyclic menses that are long and/or heavy, particularly if menses are heavy from the onset of menarche, a hematologic cause should be strongly considered. **Von Willebrand disease** and coagulation disorders are found in up to 13% and 20%, respectively, of women with heavy menstrual bleeding; prevalence goes up significantly among women with bleeding severe enough to warrant hospitalization. Other symptoms suggestive of bleeding disorders include *flooding* (changing a pad or tampon more than hourly), passing clots larger than 1 inch in diameter, menses longer than 7 days, a history of hemorrhagic ovarian cysts, excessive bleeding from wounds or postoperatively, and first-degree relatives with heavy menses or epistaxis requiring medical treatment.

Laboratory Findings

Table 142.4 lists laboratory tests to be considered in patients with long, heavy bleeding. Females with persistent heavy bleeding despite negative testing should be referred to a hematologist for testing for platelet function disorders, factor deficiencies, and other less common disorders. In the initial evaluation, rapidity of blood loss in conjunction with the hemoglobin establishes the **severity of the bleeding: mild (** hemoglobin > 10 g/dL), **moderate** (hemoglobin 8-10 g/dL), or **severe** (hemoglobin < 8 g/dL).

Treatment

In **mild** bleeding, iron supplementation is recommended, and the patient should keep a menstrual calendar to follow the subsequent flow patterns. Nonsteroidal antiinflammatory drugs (NSAIDs; e.g., naproxen) are more effective than placebo in treating heavy bleeding and also would help treat any concurrent dysmenorrhea. Active bleeding typically responds well to cycling with any combined hormonal contraceptive (containing estrogen and progestin) method starting with twice-daily dosing if needed until bleeding stops. Patients with estrogen contraindications can be treated with progestins alone, such as medroxyprogesterone or norethindrone acetate, 10 mg orally (PO) per day, either continuously or for 12 days per month. The latter regimen will be followed by monthly bleeding.

With **moderate** anemia, any of the hormonal regimens above can be used. However, it may be necessary to start with 3-4 combined oral contraceptive (COC) pills (or 3-4 doses of medroxyprogesterone 10 mg) per day, with additional medication to control nausea. The dose can usually be tapered to daily dosing over the next 2 wk. Patients with ongoing rapid bleeding, syncope or lightheadedness, or hemodynamic instability should be treated in the hospital, as should most patients with a hemoglobin of <8 g/dL.

Patients with **severe** anemia should be treated with 1 of the hormone tapers described above, in addition to fluid or blood products as indicated; it is advisable to draw necessary laboratory studies before transfusion. Patients with emesis or other significant symptoms may be treated initially with conjugated estrogens, 25 mg intravenously (IV) every 4-6 hr for 1-2 days. A COC or progestin regimen should be added within the 1st day because progestin is needed to stabilize the endometrial lining and can be used as maintenance therapy after hospital discharge. In the exceptionally rare case of a patient whose bleeding cannot be controlled hormonally, options for gynecologic interventions include intrauterine Foley balloon placement or uterine packing to tamponade the uterus mechanically. Dilation and curettage, performed frequently in adult women, is almost never indicated in adolescents and can increase blood loss in women with bleeding disorders.

Hormonal treatment for AUB should continue for at least 3-6 mo, depending on the patient's age, prior menstrual history, and severity of presentation, before reassessing the need for ongoing therapy. Additional options for maintenance therapy include combined hormonal transdermal patches and vaginal rings; depot medroxyprogesterone acetate, 150 mg intramuscularly (IM) or 104 mg subcutaneously (SC) every 3 mo; and placement of a levonorgestrel intrauterine device (IUD), depending on the patient's concurrent need for long-term contraception. For patients who choose to avoid hormonal therapy, tranexamic acid, 1,300 mg PO 3 times daily, can be used for up to the 1st 5 days of menses in patients who do not have an increased risk of thrombosis.

For young women with bleeding disorders, formulation of a long-term treatment plan is best done in collaboration with the patient's hematologist. Females with a known bleeding disorder may be up to 5 times more likely to develop heavy menstrual bleeding. Therefore, it can be helpful while the patient is still premenarcheal to put a proactive plan in place in the event of acute heavy menstrual bleeding, which can occur with a patient's first menstrual period.

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142.3

Dysmenorrhea

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Keywords

dysmenorrhea
endometriosis

Dysmenorrhea, painful uterine cramps that precede and accompany menses, occur in up to 90% of women age 17-24. Although dysmenorrhea is frequently severe enough to interfere with school and other activities, many adolescents undertreat their symptoms, and fewer still seek medical care for relief.

Dysmenorrhea may be primary or secondary. **Primary dysmenorrhea** , characterized by the absence of any specific pelvic pathologic condition, is by far the more commonly occurring form, accounting for approximately 90% of cases. After ovulation, withdrawal of progesterone results in synthesis of prostaglandins by the endometrium, which stimulates local vasoconstriction, uterine ischemia and pain, and smooth muscle contraction, explaining both uterine and GI symptoms. Because of the association with ovulation, primary dysmenorrhea typically presents at least 12 mo after menarche.

Secondary dysmenorrhea results from underlying pathology, such as anatomic abnormality, or infection, such as pelvic inflammatory disease. However, the most common cause of secondary dysmenorrhea in adolescents is **endometriosis** , a condition in which implants of endometrial tissue are found outside the uterus, usually near the fallopian tubes and ovaries. Often, other family members have endometriosis. Although characteristically there is severe pain at menses, adolescents can present with noncyclic pain as well.

Although primary dysmenorrhea is almost always the cause, a careful history and physical examination are required for adolescents who present with pelvic pain. An internal pelvic exam is not required in females who are not sexually experienced and whose presentation is consistent with primary dysmenorrhea. Constipation can vary cyclically in many females, especially those with irritable bowel syndrome, and often significantly contributes to the pain. **Mittelschmerz** , brief severe pain with ovulation, occurs at mid-cycle and can explain what initially appeared to be noncyclic pelvic pain. Table 142.6 lists the differential diagnosis and "red flags" for secondary dysmenorrhea. Ovarian cysts, a frequent concern of families, are usually transient and painless.

Table 142.6

Differential Diagnosis of Dysmenorrhea in Adolescents*

	PRESENTATION	DIAGNOSIS
Primary	Crampy pelvic pain may be accompanied by aching/heaviness in lower back and upper thighs, nausea, emesis, diarrhea, headache, mastalgia, fatigue, and dizziness; symptoms begin at or shortly before onset of menstrual flow and last 1-3 days.	Normal physical exam; internal exam only for sexually active adolescents. Ultrasound can be reserved for those patients with atypical presentations (e.g., onset at menarche) or those whose pain does not respond to NSAIDs and hormonal therapy.
Endometriosis and adenomyosis †	**Increasingly severe dysmenorrhea despite adequate therapy;** pain exacerbated during menses can occur acyclically as well.	Increased risk in patients with obstructive anomalies and possibly bleeding disorders; however, most teenagers with endometriosis have normal anatomy and bleeding indices; diagnosis is made visually during surgery. *Found in up to 69% of adolescents who underwent laparoscopy for persistent pelvic pain.*
Müllerian anomalies	**Pain begins at or shortly after menarche** and occurs with bleeding;	Pelvic ultrasound will demonstrate uterine anomalies (e.g., rudimentary uterine horn); MRI may be required

with partial outflow obstruction	presence of **known renal tract anomaly** (often coexists with müllerian anomaly).	to identify some lesions (e.g., obstructed hemivagina). *Found in 8% of adolescents who underwent laparoscopy for persistent pelvic pain.*
Pelvic inflammatory disease	Abrupt onset of dysmenorrhea more severe than baseline in a sexually active adolescent; presentation can range from mild discomfort to acute abdomen.	Clinical diagnosis made by findings of uterine or adnexal tenderness on bimanual pelvic examination (see Chapter 146); supporting features include dysuria, dyspareunia, **vaginal discharge,** fever, and increased white blood cell count.
Pregnancy complication	Coincident pain and bleeding may be misdiagnosed as dysmenorrhea.	Urine test positive for human chorionic gonadotropin.

[*] **Bold** entries indicate ”red flags” for diagnosis.

[†] Adenomyosis is the presence of endometrial tissue within the uterine myometrium.

Treatment for primary dysmenorrhea is aimed at preventing or decreasing prostaglandin production. The mainstay of treatment is prostaglandin synthetase inhibition with NSAIDs (Table 142.7) beginning at, or preferably the day before, menstruation. High doses of around-the-clock treatment are rarely needed for more than the 1st 2 days. More data are needed to make specific treatment recommendations regarding exercise, but females should be reassured that participation in usual sports and extracurricular activities is not only permissible but a benchmark of adequate treatment.

Table 142.7

Treatment for Dysmenorrhea

	MEDICATION	REGIMEN	COMMENTS
NSAIDs for up to 5 days)	Ibuprofen, 200 mg	2 tablets PO q 4-6 hr	Over-the-counter
	Naproxen sodium, 275 mg	550 mg loading dose, then 275 mg PO q 6 hr	Patients may prefer the equivalent 550 mg PO q 12 hr dosing regimen.
	Celecoxib (cyclooxygenase [COX]-2 inhibitor)[*]	400 mg, then 200 mg PO q 12 hr prn pain	Can be used for patients with von Willebrand disease.
Hormonal contraception	Combined oral contraceptive pills or vaginal ring	Continuous hormone regimens (vs standard 21 hormone days followed by 7 placebo days) may offer better relief but may increase the risk of unscheduled intermenstrual bleeding.	The data favoring rings and pills over the combined hormone patch for this indication are sparse; treatment can be based on patient preference.
	Progestin-only methods	DMPA 150 mg IM or 104 mg SC q 3 mo; levonorgestrel intrauterine device for up to 5 yr; etonogestrel implant for up to 3 yr	DMPA has potential side effects of weight gain and interference with expected bone density increase during adolescence, as well as a higher discontinuation rate than LARC methods.
Gonadotropin-releasing	Depot leuprolide	11.25 mg IM q 3 mo	Consider for patients with presumed endometriosis not responsive to

hormone agonist			hormonal methods; add-back hormones are recommended to prevent bone loss.

[*] This medication may cause serious cardiovascular and gastrointestinal events. Use with caution in patients with impaired renal or liver dysfunction, heart failure, or a history of GI bleeding or ulcer. Full prescribing information can be found at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020998s033 ,021156s003lbl.pdf.

DMPA, Depot medroxyprogesterone acetate; LARC, long-acting reversible contraceptive; NSAIDs, nonsteroidal antiinflammatory drugs.

For those adolescents whose pain does not respond to optimally dosed NSAIDs, or who also require contraception, the currently available forms of hormonal contraception will improve dysmenorrhea. A number of trials have investigated adjuvant treatments including heat, aromatherapy, acupressure, acupuncture, transcutaneous nerve stimulation, herbal remedies, yoga, and dietary supplements; however, the mainstay second-line treatment is hormones. The mechanisms are not fully delineated but are presumed to include elimination of progesterone production from the corpus luteum for those methods that prevent ovulation, and decreased prostaglandin production from the diminished endometrial lining. Up to 3 cycles may be required to appreciate the full benefit. Methods and regimens that eliminate a placebo interval may provide better relief. Females whose pain persists despite more than 3 mo of adequate hormonal therapy require further evaluation and treatment.

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142.4

Premenstrual Syndrome and Premenstrual Dysphoric Disorder

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Keywords

premenstrual syndrome
PMS
premenstrual dysphoric disorder
PMDD

Premenstrual dysphoric disorder (PMDD) is a depressive disorder that is distinguished from other depressive disorders by its timing. Symptoms of anxiety and depressed mood begin in the luteal phase of the menstrual cycle (i.e., in the 2nd half, after ovulation) and improve within a few days after the onset of menses. PMDD causes significant distress and functional impairment and may be accompanied by physical and behavioral symptoms. PMDD occurs in 2–6% of menstruating females worldwide. Based on a large body of scientific evidence, it has been included in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) as a distinct, treatment-responsive, depressive disorder (Table 142.8). PMDD is distinguished from **premenstrual syndrome (PMS)** , which has similar timing and occurs in up to 30% of adolescents, by the severity and consequences of the affective symptoms. Premenstrual symptoms are precipitated by ovulation; symptoms recur in the luteal phase and should disappear at the end of menstruation. Up to half of women who report PMS do not meet diagnostic criteria for PMDD when symptoms are rated prospectively. Consequently, use of a menstrual calendar to document symptoms prospectively is necessary, because it is important to distinguish PMDD from anxiety, depression, or another mental health disorder, the symptoms of which are exacerbated cyclically but occur throughout the cycle.

Table 142.8

Criteria for Premenstrual Dysphoric Disorder

A. In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to *improve* with a few days after the onset of menses, and become *minimal* or absent in the week post menses.

B. One (or more) of the following symptoms must be present:

1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).
2. Marked irritability or anger or increased interpersonal conflicts.
3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.
4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.

C. One (or more) of the following symptoms must additionally be present, to reach a total of 5 symptoms when combined with symptoms from criterion B above.

1. Decreased interest in usual activities (e.g., work, school, friends, and hobbies).
2. Subjective difficulty in concentration.
3. Lethargy, easy fatigability, or marked lack of energy.
4. Marked change in appetite; overeating; or specific food cravings.
5. Hypersomnia or insomnia.
6. A sense of being overwhelmed or out of control.
7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of “bloating,” or weight gain.

Note: The symptoms in criteria A-C must have been met for most menstrual cycles that occurred in the preceding year.

D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).

E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).

F. Criterion A should be confirmed by prospective daily ratings during at least

2 symptomatic cycles. (*Note:* The diagnosis may be made provisionally prior to this confirmation).

G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

From *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (Copyright 2013), American Psychiatric Association, pp 171–172.

Treatment success is gauged by improvement in patient symptoms. In mild cases of PMS, adolescents may have adequate relief following education about the relationship of symptoms to the menstrual cycle and instruction on stress management techniques, including exercise. There is not strong evidence supporting the effectiveness of most combined hormonal contraceptive methods for PMS, particularly in adolescents. However, some experts suggest this treatment option for those patients who also have dysmenorrhea or contraceptive needs.

The treatment option for severe PMS and PMDD with the most supportive evidence is use of selective serotonin reuptake inhibitors (SSRIs), which are first-line therapy for adult women. In contrast to the treatment of depression, SSRIs can be rapidly effective for PMDD and thus can be prescribed either continuously or intermittently, beginning at ovulation (or whenever in the luteal phase symptoms begin) and ending when symptoms resolve. Adolescents can be prescribed the standard doses used for adults, such as fluoxetine, 20 mg PO daily.

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CHAPTER 143

Contraception

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The untoward consequences of sexual activity, including unintended pregnancy (see Chapter 144) and sexually transmitted infections (STIs; Chapter 146), are experienced by adolescents at unacceptably high rates. Adolescents often do not seek reproductive healthcare until 6-12 mo after initiating sex; many will become pregnant and/or acquire an STI during this interval. Early and appropriate counseling and educational interventions with adolescents, including direct discussion of unwanted pregnancy and STI prevention, can decrease risky sexual behavior; adolescents who plan sexual initiation are 75% more likely to use contraception at sexual debut. Therefore, appropriate counseling and provision of contraception as warranted are a critical component in comprehensive healthcare for adolescents.

Contraceptive Effectiveness

To decrease rates of unintended pregnancy, the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG) recommend adolescents use the most effective forms of reversible contraception. Comparing typical effectiveness of contraceptive methods the chart illustrates a tiered system of contraceptive methods ranging from more effective to less effective methods (Fig. 143.1). These tiers are categorized by **typical-use failure rates** , which reflect the effectiveness of a method for the average person who may not consistently use the method or may not always use the method correctly (Table 143.1). For example, for oral contraceptive pills, the typical-use failure rate is 7%, whereas the *perfect-use* failure rate is <1%. **Tier 1** methods, the most effective, include those with failure rates of <1 pregnancy per 100 women in a year of typical use, and reversible Tier 1 methods include intrauterine devices (IUDs) and implants. **Tier 2** methods have failure rates of 4-7 pregnancies per 100 women in a year of typical use and include injectable contraception, oral contraceptive pills, contraceptive patch, and vaginal ring. **Tier 3** methods have failure rates of >13 pregnancies per 100 women per year of typical use and include the male and female condom, the diaphragm, withdrawal, the sponge, fertility awareness–based methods, and spermicides.

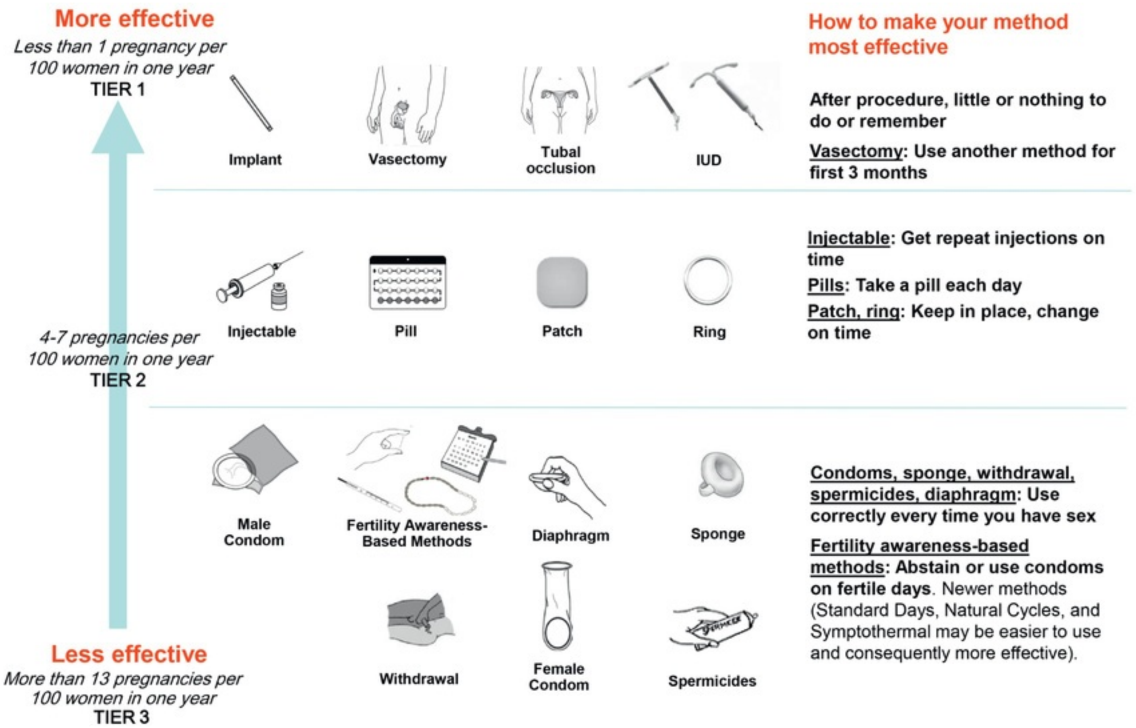
More effective
Less than 1 pregnancy per 100 women in one year
TIER 1
Implant
Vasectomy
Tubal occlusion
IUD
How to make your method most effective
After procedure, little or nothing to do or remember
Vasectomy: Use another method for first 3 months
Injectable
Pill
Patch
Ring
4-7 pregnancies per 100 women in one year
TIER 2
Injectable: Get repeat injections on time
Pills: Take a pill each day
Patch, ring: Keep in place, change on time
Male Condom
Fertility Awareness-Based Methods
Diaphragm
Sponge
Withdrawal
Female Condom
Spermicides
Less effective
More than 13 pregnancies per 100 women in one year
TIER 3
Condoms, sponge, withdrawal, spermicides, diaphragm: Use correctly every time you have sex
Fertility awareness-based methods: Abstain or use condoms on fertile days. Newer methods (Standard Days, Natural Cycles, and Symptothermal may be easier to use and consequently more effective).

FIG. 143.1 Effectiveness of contraceptive methods. (From Trussell J, Aiken ARA, Micks E, Guthrie K. Contraceptive efficacy, safety, and personal considerations. In Hatcher RA, Nelson AL, Trussell J, et al, eds. *Contraceptive technology,* ed 21, New York, 2018, Ayer Company Publishers p. 102.)

Table 143.1

Efficacy of Contraceptives

METHOD	FAILURE RATE*		SOME ADVANTAGES	SOME ADVERSE EFFECTS AND DISADVANTAGES
	Typical Use	Perfect Use		
Implant			Convenience; long-term contraception; no patient compliance required; rapid	Irregular bleeding; removal complications
Nexplanon	0.1%	0.1%		

			return of fertility after removal	
Intrauterine devices (lUDs)			Convenience; long-term contraception; no patient compliance required; rapid return of fertility after removal	Rare uterine perforation; risk of infection with insertion; anemia
ParaGard T380A	0.8%	0.6%	Effective for 10 yr; nonhormonal	Irregular/heavy bleeding and dysmenorrhea
Mirena	0.1%	0.1%	Decreased menstrual bleeding and dysmenorrheal	Irregular bleeding in 1st 3-6 mo, followed by amenorrhea; ovarian cysts
Liletta	0.1%	0.1%	Decreased menstrual bleeding and dysmenorrheal	Irregular bleeding in 1st 3-6 mo; ovarian cysts
Kyleena	0.2%	0.2%	Smaller T-frame and narrower insertion tube	Irregular bleeding in 1st 3-6 mo; ovarian cysts; amenorrhea in 13% of users after 1 yr
Skyla	0.4%	0.3%	Smaller T -frame and narrower insertion tube	Irregular bleeding in 1st 3-6 mo; ovarian cysts; amenorrhea in only 6% of users after 1 yr
Sterilization				
Female	0.5%	0.5%	Long-term contraception; no patient compliance required	Potential for surgical complications; regret among young women; reversal often not possible and expensive
Male	0.15%	0.1%	Long-term contraception; no patient compliance required	Pain at surgical site, regret among young men; reversal often not possible and expensive
Injectable			Convenience; same as progestin-only oral contraceptives	Delayed return to fertility, irregular bleeding and amenorrhea; weight gain; may decrease bone mineral density
Depo-Provera	4%	0.2%		
Combination oral contraceptives	7%	0.3%	Protection against ovarian and endometrial cancer, PID, and dysmenorrhea	Increased rate of thromboembolism, stroke, and myocardial infarction in older smokers; nausea; headache; contraindicated with breastfeeding
Progestin-only oral contraceptives	7%	0.3%	Protection against PID. iron-deficiency anemia, and dysmenorrhea; safe in breastfeeding women and those with cardiovascular risk	Irregular, unpredictable bleeding; must take at same time every day
Transdermal			Convenience of once-weekly application; same benefits as combination oral contraceptives	Dysmenorrhea and breast discomfort may be more frequent than with oral contraceptives; application site reactions; detachment; increased estrogen exposure compared to oral contraceptives
Evra	7%	0.3%		
Vaginal			Excellent cycle control; rapid return to fertility after removal; convenience of once-monthly insertion	Discomfort; vaginal discharge
NuvaRing	7%	0.3%		
Diaphragm with spermicide	17%	16%	Low cost; may reduce risk of cervical cancer	High failure rate; cervical irritation; increased risk of urinary tract infection and toxic shock syndrome; some require fitting by healthcare professional; may be difficult to obtain; available only by prescription
Condom without spermicide				
Female	21%	5%	Protection against STIs; covers external genitalia;	High failure rate; difficult to insert; poor acceptability

			OTC	
Male	13%	2%	Protection against STIs, OTC	High failure rate; allergic reactions; poor acceptability; breakage possible
Withdrawal	20%	4%	No drugs or devices	High failure rate
Sponge	14-27%	9-20%	OTC; low cost; no fitting required; provides 24 hr of protection	High failure rate; contraindicated during menses; increased risk of toxic shock syndrome
Fertility awareness–based methods	15%	-	Low cost; no drugs or devices	High failure rate; may be difficult to learn; requires relatively long periods of abstinence
Standard Days method	12%	5%		
TwoDay method	14%	4%		
Ovulation method	23%	3%		
Symptothermal method	2%	0.4%		
Spermicide alone	21%	16%	OTC	High failure rate; local irritation; must be reapplied with repeat intercourse; increased risk of HIV transmission
No method	85%	85%	-	–

[*] Risk of unintended pregnancy during first year of use; data from Trussel J, et al: In Hatcher RA et al: *Contraceptive technology.* ed 21, New York, 2018, Ayer Company Publishers.

STIs, Sexually transmitted infections; PID, pelvic inflammatory disease; OTC, over the counter.

Adapted from *The Medical Letter* : Choice of contraceptives. *Med Lett* 57(1477):128, 2015.

143.1

Contraceptive Use

Tara C. Jatlaoui, Yokabed Ermias, Lauren B. Zapata

Keywords

sexual activity
sexual debut

Sexual Activity

According to the Youth Risk Behavior Surveillance System 2015, 41.2% of U.S. high school students had ever had sexual intercourse and approximately one-third reported being currently sexually active.

Although U.S. teens and European teens have similar levels of **sexual activity** and ages of **sexual debut** , U.S. teens are less likely to use contraception and less likely to use the most effective methods. Teen pregnancy rates have been declining worldwide as a result of delayed initiation of sexual activity and increased contraceptive use. Despite declines, the United States still had the highest 2013 teen birthrate in the Western industrialized world, with 26.5 live births per 1,000 females aged 15-19 yr (Fig. 143.2). This is almost 1.5 times higher than the 2013 teen birthrate in the United Kingdom, which has the highest rate in Western Europe, and almost 8 times higher than the teen birthrate in Switzerland, which has the lowest rate in Western Europe. In 2011, of the 574,000 teen pregnancies in the United States, 75% were unintended, indicating an unmet need for reliable, effective contraception that teens will correctly and consistently use.

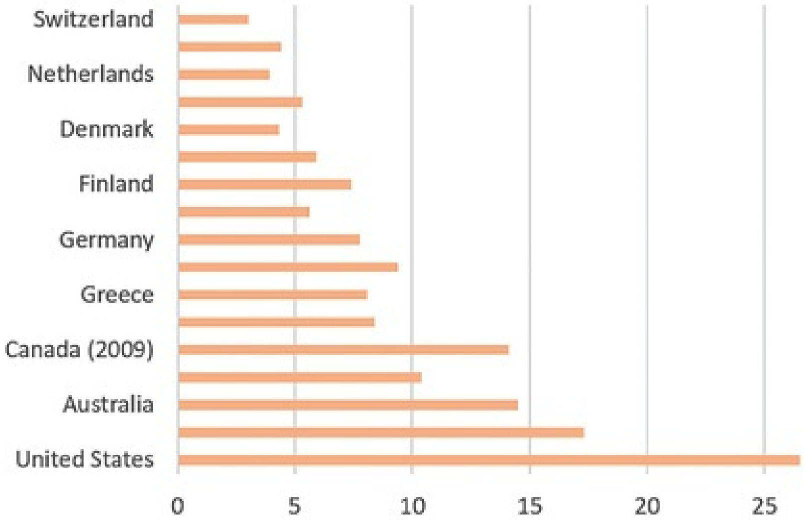

FIG. 143.2 **Teen birthrates in high-income countries, 2013. Live births per 1,000 females age 15-19 yr. (Data from United Nations Statistical Division. Demographic Yearbook 2014, New York, http://unstats.un.org/unsd/demographic/products/dyb/dyb2014.htm , and Martin JA, Hamilton BE, Osterman MJK, et al: Births: final data for 2013, *Natl Vital Stat Rep* 64(1):1–68, 2015.)**

Use of Contraception Among Teens

According to the National Survey of Family Growth, 2011–2013, virtually all sexually experienced teens have used some method of contraception in the past. The most commonly used method by teenage females is the *condom* , followed by withdrawal (both least effective methods) and then the pill (a moderately effective method). IUDs and implants, the most effective reversible methods, are only used by 4.3% of female contraceptive users age 15-19 yr. Use of contraception at **first sex** has greatly increased over the last 50 yr. As of 2010, the condom is the most common method used at first sex, reported by >75% of males and females. Factors associated with contraception use at first sex include increasing age among teens up to age 17 yr; time spent in college; and planning their sexual debut.

More than half of sexually experienced female teens are currently using the most effective reversible contraceptives or moderately effective contraceptive methods. U.S. teens' use of hormonal methods at last intercourse is less frequent compared to teens in other developed countries: 52% of U.S. teens, 56% of Swedish 18-19 yr olds, 67% of French 15-19 yr olds, 72% of British 16-19 yr olds, and 73% of Canadian 15-19 yr olds use hormonal methods. A higher likelihood of female current contraceptive use is associated with older age at sexual initiation, aspirations for higher academic achievement, acceptance of one's own sexual activity, and a positive attitude toward contraception. Despite the importance of dual protection to protect against both unwanted pregnancy and STIs, only 21.3% of sexually active female U.S. teens are using condoms in addition to another, more effective contraceptive method.

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143.2

Contraceptive Counseling

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Keywords

counseling
effectiveness
typical-use failure rates
confidentiality
teen-friendly

The health screening interview during the adolescent preventive visit offers opportunities to identify and discuss unsafe sexual practices among all adolescents and to identify and reinforce safe sexual behaviors, including abstinence (see Chapter 137). Adolescents with medical conditions, either chronic or acute, are particularly vulnerable to having sexual and reproductive health omitted from their visits, although they have similar sexual health and contraceptive needs as healthy adolescents (see Chapter 734). Their comorbidities or concurrent medication use may make unintended pregnancy an increased health risk and may also reduce contraceptive options. The **U.S. Medical Eligibility Criteria for Contraceptive Use** outlines medical conditions associated with increased risk for adverse health events as a result of pregnancy and also provides recommendations for who can safely use specific contraceptive methods.

The goals of counseling with adolescents are to (1) understand adolescent experiences, preferences, perceptions, and misperceptions about pregnancy and use of contraceptives; (2) help adolescents put unprotected intercourse risk in a personal perspective; (3) educate adolescents about the various methods available using information that is medically accurate, balanced, and provided in a nonjudgmental manner; and (4) help adolescents choose a safe and effective method that can either be provided on site or be easily obtained through prescription or by referral. Counseling should include a review of all contraceptive methods available that the adolescent can use safely (see U.S. Medical Eligibility Criteria), starting with the most effective methods. **Long-acting reversible contraception** (IUDs and implants) is a safe and effective option for many adolescents, including those who have not been pregnant or given birth. The adolescent should be counseled about method effectiveness using typical-use failure rates. It is important to ask about use of **withdrawal** because 60% of female teens have used it for contraception and it has a typical-use failure rate of 20%. **Abstinence** should also be discussed as an option even if teens have engaged in sexual intercourse in the past. Situational abstinence may be the best option if they do not have another method available at a particular time.

Necessary concepts to address while discussing individual methods include how effective the method is, how long the method works, what behaviors are required for correct and consistent use, what side effects may be seen, any noncontraceptive benefits of the method (e.g., reduced menstrual bleeding, protection from STIs), and what signs or symptoms of complications should prompt a return visit. Reviewing common side effects allows teens to anticipate and cope with any changes with reassurance and may avoid method discontinuation. Weighing the possibility of certain side effects with the possibility of an unintended pregnancy may also help with the conversation. It is also important to address any specific misperceptions teens may have for certain contraceptives regarding side effects, effectiveness, or any other concept discussed.

Once an adolescent chooses a method, the provider and adolescent should discuss clear plans on correct and consistent use of the chosen method and strategies for appropriate follow-up (Table 143.1). Providers should help the adolescent consider potential barriers to correct and consistent use (e.g., forgetting to take a pill daily) and develop strategies to deal with each barrier (e.g., use of reminder systems such as daily text messages or phone alarms). The provider should assess whether the teen understood the information discussed and may confirm by asking the teen to repeat back key concepts.

The U.S. Selected Practice Recommendations for Contraceptive Use provides guidance for providers regarding when to start contraception, how to be certain the woman is not pregnant at contraception initiation, and what examinations and tests are recommended before initiating contraception. Generally, women may start a contraceptive method other than an IUD at any time, and an IUD may be placed when a provider is reasonably certain that a woman is not pregnant. Most women do not require any exams or tests before initiating contraception. A pelvic examination is only required for placement of an IUD, unless otherwise indicated. STI screening is appropriate at IUD placement once sexual activity has begun, but most women do not require additional screening if they have been recently screened according to CDC sexually transmitted disease (STD) treatment guidelines. Gonorrhea and chlamydia screening using a self- or provider-collected vaginal swab or urine sample is recommended unless symptoms require a pelvic exam. IUD placement should not be delayed to receive screening results. ACOG guidelines recommend that the female teen should first visit a gynecologist between age 13 and 15 yr, unless necessary at an earlier age. This visit aims to establish rapport, educate the patient and parents or guardian on healthy sexual development, and provide routine preventive services. Cervical cancer screening is not recommended until age 21.

Providers should offer confidential services to adolescents and observe all relevant state laws and legal obligations (e.g., notification or reporting of sexual abuse). Chapter 137 discusses confidentiality and consent issues related to contraceptive management. Providers should also encourage adolescents to involve parents or guardians in their healthcare decisions, while giving parents clear information on their teen's right to confidentiality, privacy, and informed consent. All services should be provided in a youth-friendly manner, meaning that they are accessible, equitable, acceptable, appropriate, comprehensive, effective, and efficient. Resources are available that describe ways to ensure a **teen-friendly** reproductive health visit.

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143.3

Long-Acting Reversible Contraception

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Keywords

LARC
intrauterine devices
implants

Long-acting reversible contraception (**LARC**) includes 4 **levonorgestrel (LNG)** IUDs, the **copper (Cu)** IUD, and the etonogestrel subdermal implant. LARC methods are the only Tier 1 methods that are reversible (see Fig. 143.1). Considered "forgettable" contraception, LARC does not require frequent office or pharmacy visits and does not depend on user compliance for effectiveness. In the Contraceptive CHOICE Project in St. Louis, MO, >9,000 women were given the contraceptive method of their choice at no cost and were followed for 2-3 yr. The failure rates among women who used oral contraceptive pills, transdermal patch, or vaginal ring were >20 times higher than the failure rates for women using a LARC method. Acceptance, continuation, and satisfaction in this project were also higher among adolescents using LARC compared with adolescents using non-LARC methods. *ACOG and AAP support the use of LARC methods for adolescents.* The U.S. Medical Eligibility Criteria supports safe use of both IUDs and implants for adolescents and nulliparous women. Implants are considered category 1 for all ages, and IUDs are considered category 2 for women <20 yr old and for nulliparous women (Table 143.2).

Table 143.2

Categories of Medical Eligibility Criteria for Contraceptive Use

Category 1 : A condition for which there is no restriction for the use of the contraceptive method.

Category 2 : A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.

Category 3 : A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.

Category 4 : A condition that represents an unacceptable health risk if the contraceptive method is used.

Intrauterine Devices

IUDs are small, flexible, plastic objects introduced into the uterine cavity through the cervix. They differ in size, shape, and the presence or absence of pharmacologically active substances. In the United States, 5 IUDs are currently approved by the Food and Drug Administration (FDA): the CuT380A (Paragard) and 4 LNG IUDs (Liletta, Kyleena, Mirena, and Skyla). The effectiveness of the Cu IUD is enhanced by the copper ions released into the uterine cavity, with possible mechanisms including inhibition of sperm transport and prevention of implantation; this IUD is effective for at least 10 yr.

The LNG IUDs also have various actions, from thickening of cervical mucus and inhibiting sperm survival to suppressing the endometrium. LNG IUDs are effective for at least 3 and 5 years. All IUDs have typical-use failure rates of <1% (see Fig. 143.1).

Common misconceptions of IUDs among healthcare providers are that IUDs cause infections, infertility, and generally are not safe for teens or nulliparous women to use; these misconceptions are a barrier to teens accessing these highly effective and acceptable methods. IUDs do not increase risk of infertility and may be inserted safely in teens as well as nulliparous women (category 2; see Table 143.2).

Although early studies suggested an increased risk for upper genital tract infection, theoretically as a result of passing a foreign body through the cervix, newer work has refuted these earlier concerns. Therefore, clinicians are encouraged to consider use of IUDs in adolescents despite relatively high prevalence rates of STIs in this population. Teens should be screened for gonorrhea and chlamydia at or before IUD placement, although placement should not be delayed if results have not returned and there are no signs of current infection (e.g., purulent discharge, erythematous cervix). If STI testing is positive with an IUD in place, the patient may be treated without removing the IUD if she wants to continue the method. Evidence from 2 systematic reviews did not find benefit in routinely administering misoprostol to women undergoing routine IUD placement to decrease pain or improve provider ease of insertion. A paracervical block with lidocaine may reduce patient discomfort during placement and, along with other medications (e.g., NSAIDs, anxiolytics), may be considered on an individual patient basis, but these are not routinely recommended.

Implants

Currently, one contraceptive implant is available in the United States. Originally FDA approved in 2006, the single rod that releases 60 µg/day of **etonogestrel** has been updated to a radiopaque rod with a new inserter. This **progestin-only method** keeps etonogestrel at steady serum levels for at least 3 yr and primarily works to inhibit ovulation. Similar to the levonorgestrel IUD, the progestin acts on the uterus to cause an atrophic endometrium and thicken cervical mucus to block sperm penetration; its typical-use failure rate is also <1% (see Fig. 143.1). Unlike the IUD, no pelvic exam is required for insertion. A trained provider can quickly place or remove the implant in the upper arm under local anesthesia. Common side effects include amenorrhea, irregular bleeding, or infrequent bleeding, and less often, prolonged or frequent bleeding. One potential unique complication of this method relates to localized infection and other side effects after implantation, such as bleeding, hematoma, or scarring, and if inserted too deeply into the muscle, neural damage or migration; however, these events are rare, occurring in <1% of patients. Minor side effects, such as bruising or skin irritation, are more common but most often resolve without treatment.

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143.4

Other Progestin-Only Methods

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Keywords

Depo-Provera
depot medroxyprogesterone acetate
DMPA
progestin-only pills
mini pills

Several progestin-only contraceptive methods are available and include the LNG IUDs and implant (see Chapter 143.3), as well as an injectable and progestin-only pills. These methods do not contain estrogen and may be useful for teens with contraindications to estrogen (Table 143.3) and are considered generally safe for use in teens (category 1 or 2; see Table 143.2). Progestins thicken cervical mucus to block sperm entry into the uterine cavity as well as induce an atrophic endometrium leading to either amenorrhea or less menstrual blood loss; the implant and injectable additionally suppress ovulation. Teens should be provided anticipatory counseling regarding bleeding irregularities that may normally occur in the 1st 3-6 mo of hormonal contraception use.

Table 143.3

Conditions Classified as Category 3 and 4 for Combined Hormonal Contraceptive Use

Category 4

Complicated valvular heart disease
Current breast cancer
Severe decompensated cirrhosis
Deep venous thrombosis/pulmonary embolism (acute; history, not on anticoagulation or on established therapy for at least 3 mo with higher risk recurrence; major surgery with prolonged immobilization)
Complicated diabetes with nephropathy, retinopathy, neuropathy, or other vascular disease or duration of diabetes >20 yr
Migraine with aura
Hypertension (blood pressure >160/100 mm Hg) or hypertension with vascular disease
Ischemic heart disease (history of or current)
Hepatocellular adenoma
Malignant liver tumor
Peripartum cardiomyopathy (diagnosed <6 mo prior or with moderately or severely impaired cardiac function)
Postpartum <21 days
History of cerebrovascular accident
Systemic lupus erythematosus with positive antiphospholipid antibodies
Thrombogenic mutations
Viral hepatitis (acute or flare)

Category 3

Past breast cancer with no evidence of disease for 5 yr
Breastfeeding and <1 mo postpartum
Deep venous thrombosis/pulmonary embolism (history of DVT/PE with lower risk recurrence)
Gallbladder disease (current, medically treated)
History of malabsorptive bariatric surgery
History of cholestasis and past combined oral contraceptive–related
Hypertension (adequately controlled or blood pressure <160/100 mm Hg)
Peripartum cardiomyopathy with mild impairment or >6 mo
Postpartum 21-42 days with other risk factors for venous thromboembolism
Drug interactions (Ritonavir-boosted protease inhibitors; certain anticonvulsants; rifampin or rifabutin)

From Curtis KM, Tepper NK, Jatlaoui TC, et al: U.S. medical eligibility criteria for contraceptive use, 2016, *MMWR Recomm Rep* 65(RR-3):1–104, 2016.

Depo-Provera

An *injectable progestin,* depot **medroxyprogesterone acetate** (**DMPA** , Depo-Provera) is a Tier 2 contraceptive method available as a deep intramuscular (IM) injection (150 mg), or as a subcutaneous (SC) injection (104 mg) with typical-use failure rates of 4% (see Table 143.1). Both preparations must be readministered every 3 mo (13 wk) and act to inhibit ovulation. DMPA is particularly attractive for adolescents who have difficulty with compliance, are intellectually or physically impaired, and are chronically ill or have a condition for which estrogen use is not recommended. Common concerns with DMPA include bleeding changes, bone effects, and weight gain. After 1 yr of use, 50% of DMPA users develop amenorrhea, which may be an added advantage for teens with heavy menstrual bleeding, dysmenorrhea, anemias, or blood dyscrasias, or for those with impairments that make hygiene difficult. Although studies have demonstrated bone mineral density (BMD) loss in adolescents, potentially increasing their risk for osteoporosis later in life, other studies have found that BMD is recovered after discontinuation of this method, and it is thus considered safe for use in this population. Healthcare providers may want to consider a contraceptive containing estrogen in teens who are already at high risk for low BMD, such as those receiving chronic corticosteroid therapy or those with eating disorders (see Chapter 726). Although the FDA issued a black box warning in 2004, AAP and ACOG do not recommend limiting DMPA use to 2 yr for all women and do not recommend routine BMD screening for females using DMPA. Early weight gain may be predictive of progressive gain over time; thus those teens gaining weight in the 1st 3-6 mo should consider another method.

Progestin-Only Pills

Progestin-only oral contraceptive pills (**POPs**) are available for the adolescent in whom the use of estrogen is potentially harmful, such those with active liver disease, replaced cardiac valves, or hypercoagulable states (see Table 143.3). POPs (**mini pills**) are quickly effective after 2 days of initiation in thickening cervical mucus, but are less reliable in inhibiting ovulation. Effects are short-lived, and pill-taking must be punctual, which may be difficult for teens. If a pill is >3 hr late from normal time, an unintended pregnancy may occur. POPs have a typical-use failure rate of 7% (see Table 143.1). Acceptance by adolescents is limited by the necessity of taking the pill at the same time daily and bleeding irregularities, including amenorrhea and breakthrough bleeding.

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143.5

Combined Hormonal Contraceptives

Tara C. Jatlaoui, Yokabed Ermias, Lauren B. Zapata

Keywords

combined hormonal contraceptives
oral contraceptive pills
combined pills
patch
ring

Combined hormonal contraceptives (**CHCs**) are methods that include an estrogenic substance in combination with a progestin; methods available in the United States include several formulations of combined oral contraceptives (**COCs**), a transdermal patch, and a vaginal ring. The major mechanism of action of the **estrogen-progestin** combination is to prevent the surge of luteinizing hormone and thereby inhibit ovulation. Additional effects to the reproductive tract include thickening of the cervical mucus, which prevents sperm penetration, and thinning of the endometrial lining, which may decrease menstrual blood loss. Typical-use failure rates for all CHCs are the same at 7%.

The COCs, patch, and vaginal ring are classified together as CHCs in the U.S. Medical Eligibility Criteria for Contraceptive Use, and recommendations mostly consider estrogen exposure for a given condition or characteristic (see Table 143.3). Venous thromboembolism, hepatic adenomas, myocardial infarction, and stroke are some of the more serious potential complications of exogenous estrogen use. These serious adverse events are exceedingly rare in adolescents. Even though teenage smokers who use oral contraceptives have more than twice the risk of myocardial infarction, the likelihood of its occurrence is very small, and thus clinically insignificant, compared to the risk of dying from other pregnancy-related complications.

Combined Oral Contraceptives

Oral contraceptive pills (OCs) can be either COCs or progestin-only pills and are commonly referred to as “the pill.” The pill is one of the most common contraceptive methods used among women of all ages. To decrease risk of pregnancy and increase continuation, providers are encouraged to provide OCs at the time of patient presentation to start immediately rather than waiting for next menses, as long as the provider is reasonably sure that the patient is not pregnant. Providers are also encouraged to provide up to 13 pill packs at a time, based on evidence that more pill packs given is associated with higher continuation rates. Advanced provision of emergency contraceptive pills is also recommended should patients miss pills and have unprotected sex. The effectiveness of COCs depends on compliance, and unfortunately, adolescents may forget to take a pill each day. Figs. 143.3 and 143.4 list the rules for missed pills or following vomiting or diarrhea.

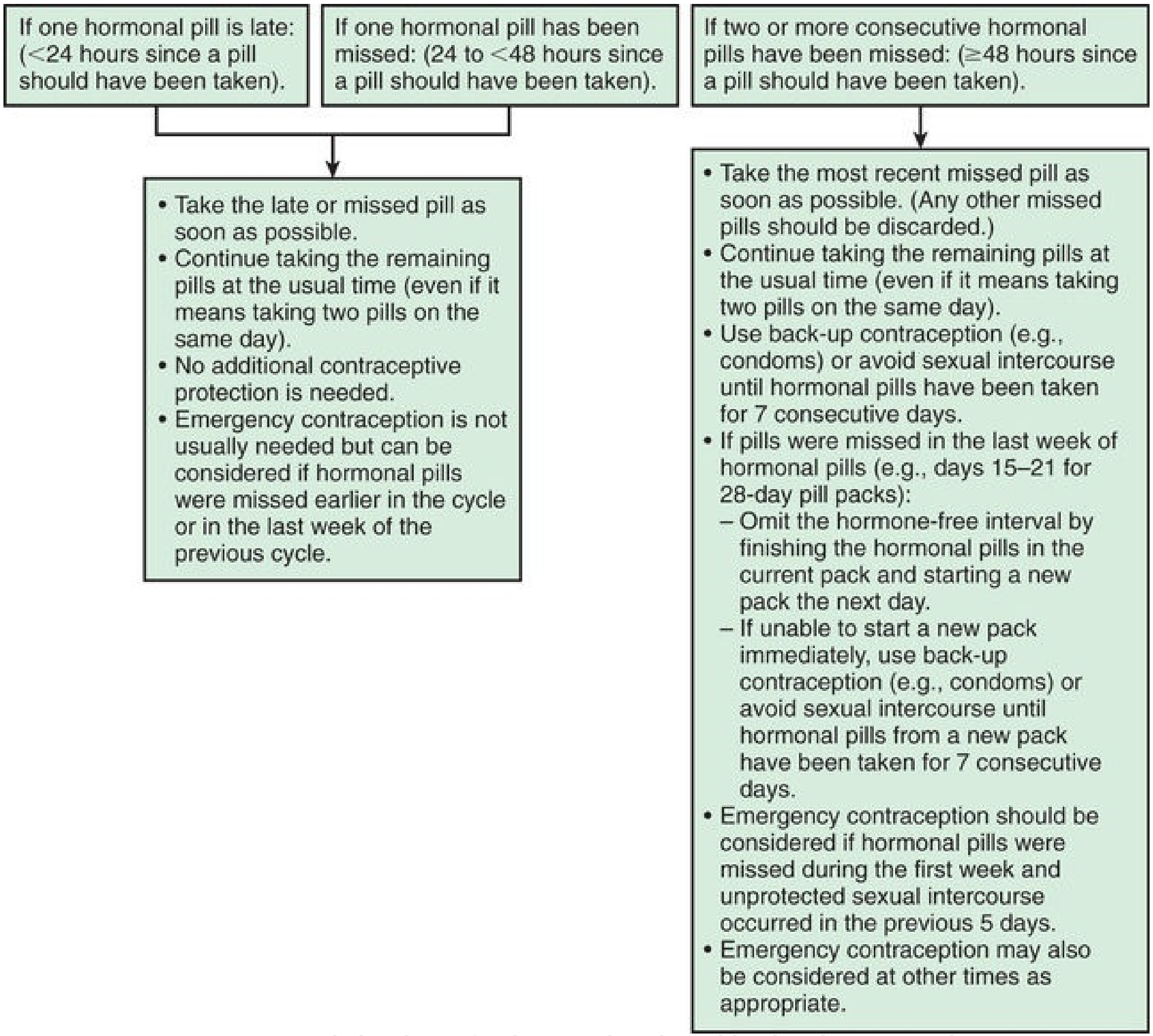

If one hormonal pill is late: (<24 hours since a pill should have been taken).

If one hormonal pill has been missed: (24 to <48 hours since a pill should have been taken).

- Take the late or missed pill as soon as possible.
- Continue taking the remaining pills at the usual time (even if it means taking two pills on the same day).
- No additional contraceptive protection is needed.
- Emergency contraception is not usually needed but can be considered if hormonal pills were missed earlier in the cycle or in the last week of the previous cycle.

If two or more consecutive hormonal pills have been missed: (≥48 hours since a pill should have been taken).

- Take the most recent missed pill as soon as possible. (Any other missed pills should be discarded.)
- Continue taking the remaining pills at the usual time (even if it means taking two pills on the same day).
- Use back-up contraception (e.g., condoms) or avoid sexual intercourse until hormonal pills have been taken for 7 consecutive days.
- If pills were missed in the last week of hormonal pills (e.g., days 15–21 for 28-day pill packs):
  - Omit the hormone-free interval by finishing the hormonal pills in the current pack and starting a new pack the next day.
  - If unable to start a new pack immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until hormonal pills from a new pack have been taken for 7 consecutive days.
- Emergency contraception should be considered if hormonal pills were missed during the first week and unprotected sexual intercourse occurred in the previous 5 days.
- Emergency contraception may also be considered at other times as appropriate.

FIG. 143.3 **Recommended actions after late or missed combined oral contraceptives. (From Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(RR-4):1–66, 2016, Fig 2, p 28.)**

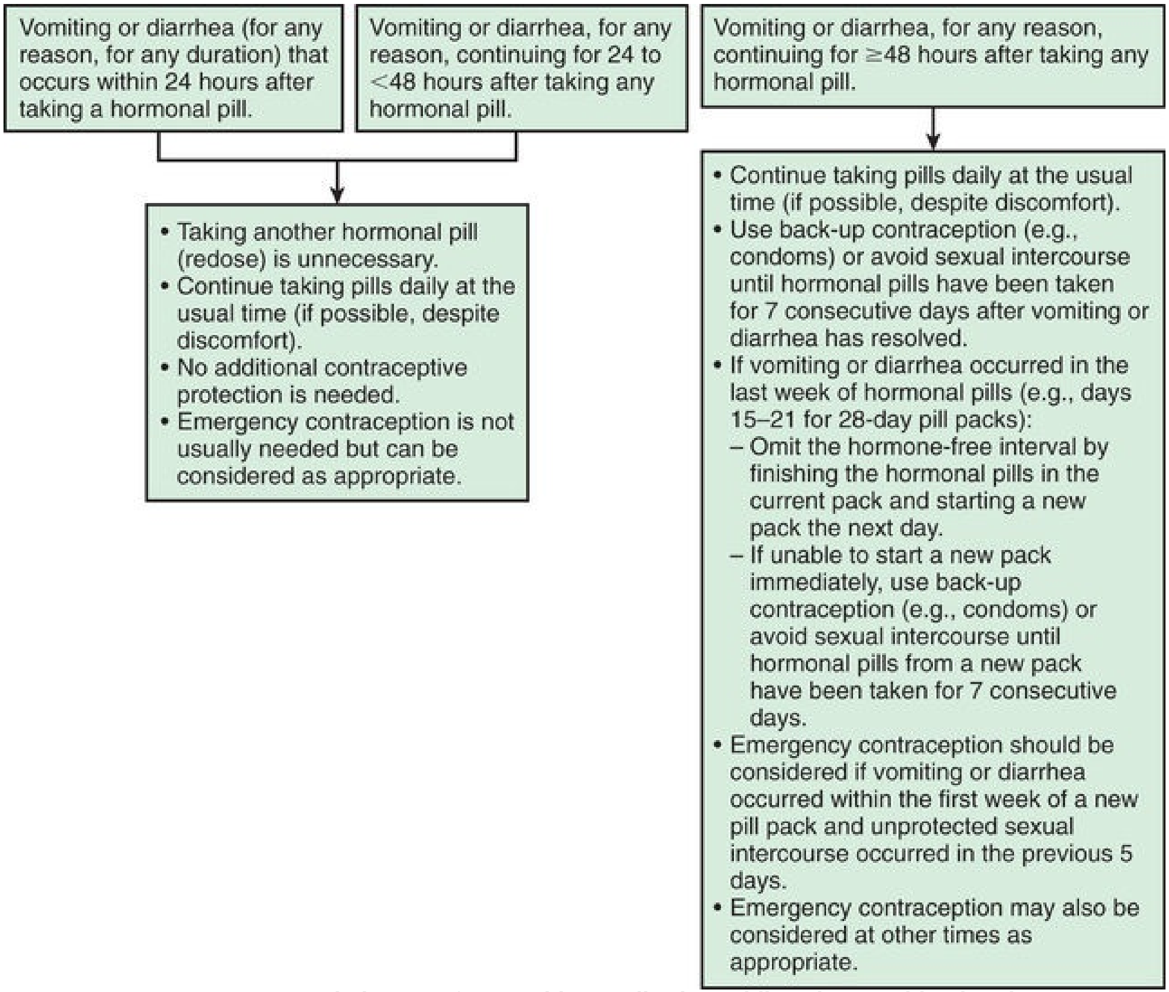

Vomiting or diarrhea (for any reason, for any duration) that occurs within 24 hours after taking a hormonal pill.

Vomiting or diarrhea, for any reason, continuing for 24 to <48 hours after taking any hormonal pill.

- Taking another hormonal pill (redose) is unnecessary.
- Continue taking pills daily at the usual time (if possible, despite discomfort).
- No additional contraceptive protection is needed.
- Emergency contraception is not usually needed but can be considered as appropriate.

Vomiting or diarrhea, for any reason, continuing for ≥48 hours after taking any hormonal pill.

- Continue taking pills daily at the usual time (if possible, despite discomfort).
- Use back-up contraception (e.g., condoms) or avoid sexual intercourse until hormonal pills have been taken for 7 consecutive days after vomiting or diarrhea has resolved.
- If vomiting or diarrhea occurred in the last week of hormonal pills (e.g., days 15–21 for 28-day pill packs):
  - Omit the hormone-free interval by finishing the hormonal pills in the current pack and starting a new pack the next day.
  - If unable to start a new pack immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until hormonal pills from a new pack have been taken for 7 consecutive days.
- Emergency contraception should be considered if vomiting or diarrhea occurred within the first week of a new pill pack and unprotected sexual intercourse occurred in the previous 5 days.
- Emergency contraception may also be considered at other times as appropriate.

FIG. 143.4 Recommended steps after vomiting or diarrhea while using combined oral contraceptives. (From Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(RR-4):1–66, 2016, Fig 5, p 30.)

COCs contain 50, 35, 30, 25, or 20 µg of estrogenic substance, typically **ethinyl estradiol** , and as many as 10 progestins have been available in the United States for combined pills. Multiple preparations are available to help select the formulation that satisfies an individual patient, with minimal side effects.

COCs can be packaged as 28-day *monophasic* pills, which contain the same dose of active pills for 21 or 24 days, followed by 7 or 4 days of placebo pills, respectively. Monophasic formulations are also available for extended cycles of 91 days or 1 yr so that withdrawal bleeding does not occur each month, but at the end of each extended cycle. **Extended cycling** of monophasic COCs for adolescents has some anticipated benefits associated with increased ovarian activity suppression and may decrease failure rates. Other advantages include diminished frequency of hormonal withdrawal (premenstrual) effects, including headaches and migraines, mood changes, and heavy monthly bleeding. The most common side effect of extended-cycle OCs is intermenstrual bleeding and/or spotting, with the total days of bleeding over the 1st yr of treatment being similar for extended-cycle users and users following a 28-day cycle regimen. The unscheduled bleeding pattern diminishes over time. *Multiphasic* pill packs contain various levels of estrogen and progestin for 21 active pills and contains 7 placebo pills. Multiphasic formulations are not available for extended-cycle use. Providers can refer to the U.S. Selected Practice Recommendations for Contraceptive Use to counsel patients on how to manage late or missed COCs.

The short-term adverse effects of COCs, such as nausea and weight gain, often interfere with compliance in adolescent patients. These effects are usually transient and may be overshadowed by the beneficial effects of a shortened menses and the relief of dysmenorrhea. The inhibition of ovulation or the suppressant effect of estrogens on prostaglandin production by the endometrium makes COCs effective in preventing dysmenorrhea (see Chapter 142). Acne may be worsened by some and improved by other oral contraceptive preparations (see Chapter 689). The pills with nonandrogenic progestins are particularly effective in reducing acne and hirsutism. **Drospirenone** , a progestin with antimineralocorticoid activity, has been shown to reduce premenstrual symptomatology, but the potential for hyperkalemia as a side effect eliminates patients with renal, liver, or adrenal diseases and patients taking certain medications.

As of 2011, the FDA has concluded that drospirenone-containing OCs may be associated with a higher risk of venous thromboembolism (VTE) than other progestin-containing pills. Although no studies have provided consistent estimates of the comparative risk of VTE between OCs that contain drospirenone and those that do not, or accounted for patient characteristics that may affect VTE risk, there has been a 3-fold increased risk of VTE reported for drospirenone compared with products containing levonorgestrel or other progestins. As a result, the FDA is requiring that labeling be revised for the OCs marketed under the Beyaz, Safyral, Yasmin, and Yaz brands. Despite the risk of VTE with all OCs, the absolute risk remains lower than the risk of developing VTE during pregnancy or the postpartum period.

Transdermal Patch

The transdermal patch (Ortho Evra or Xulane) releases 20 µg ethinyl estradiol and 150 µg norelgestromin daily and is applied to the lower abdomen, buttocks, or upper body, excluding the breasts. It is worn continuously for 1 wk and changed weekly for a total of 3 wk, then no patch is worn for the 4th week, at which time bleeding occurs (see Table 143.1). Limited studies in adolescents suggest higher rates of partial or full detachment compared to adults, with high patient satisfaction and 50–83% continuation rates from 3-18 mo of use (Fig. 143.5). As with other combined hormonal methods, the patch is a Tier 2 contraceptive. Providers can refer to the U.S. Selected Practice Recommendations to counsel patients on how to manage delayed application or detachment of the patch.

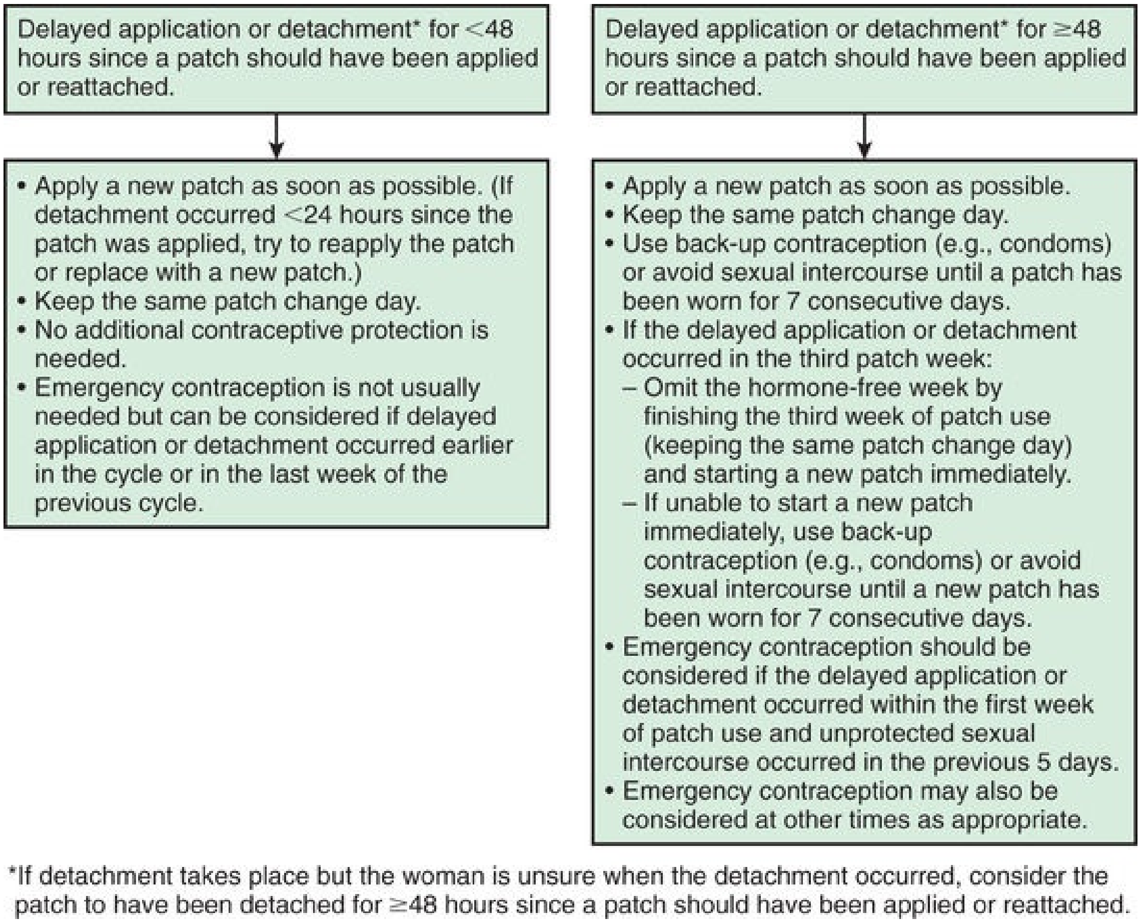

Delayed application or detachment* for <48 hours since a patch should have been applied or reattached.

- Apply a new patch as soon as possible. (If detachment occurred <24 hours since the patch was applied, try to reapply the patch or replace with a new patch.)
- Keep the same patch change day.
- No additional contraceptive protection is needed.
- Emergency contraception is not usually needed but can be considered if delayed application or detachment occurred earlier in the cycle or in the last week of the previous cycle.

Delayed application or detachment* for ≥48 hours since a patch should have been applied or reattached.

- Apply a new patch as soon as possible.
- Keep the same patch change day.
- Use back-up contraception (e.g., condoms) or avoid sexual intercourse until a patch has been worn for 7 consecutive days.
- If the delayed application or detachment occurred in the third patch week:
  - – Omit the hormone-free week by finishing the third week of patch use (keeping the same patch change day) and starting a new patch immediately.
  - – If unable to start a new patch immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until a new patch has been worn for 7 consecutive days.
- Emergency contraception should be considered if the delayed application or detachment occurred within the first week of patch use and unprotected sexual intercourse occurred in the previous 5 days.
- Emergency contraception may also be considered at other times as appropriate.

*If detachment takes place but the woman is unsure when the detachment occurred, consider the patch to have been detached for ≥48 hours since a patch should have been applied or reattached.

FIG. 143.5 Recommended actions after delayed application or detachment with combined hormonal patch. (From Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(RR-4):1–66, 2016, Fig 3, p 28.)

Vaginal Ring

The vaginal contraceptive ring (NuvaRing) is a flexible, transparent, colorless vaginal ring that measures about 2.1 inches in diameter and is inserted into the vagina by the patient. It releases 15 µg ethinyl estradiol and 120 µg etonogestrel per day and remains in place for 3 weeks, during which time these hormones are absorbed. If the ring is accidentally expelled or removed for intercourse, it should be reinserted; however, if it is out of place ≥48 hr, a backup method of contraception should be used (Fig. 143.6). As with other combined hormonal methods, the vaginal ring is a Tier 2 contraceptive. Providers can refer to the U.S. Selected Practice Recommendations to counsel patients on how to manage delayed insertion or reinsertion with the vaginal ring.

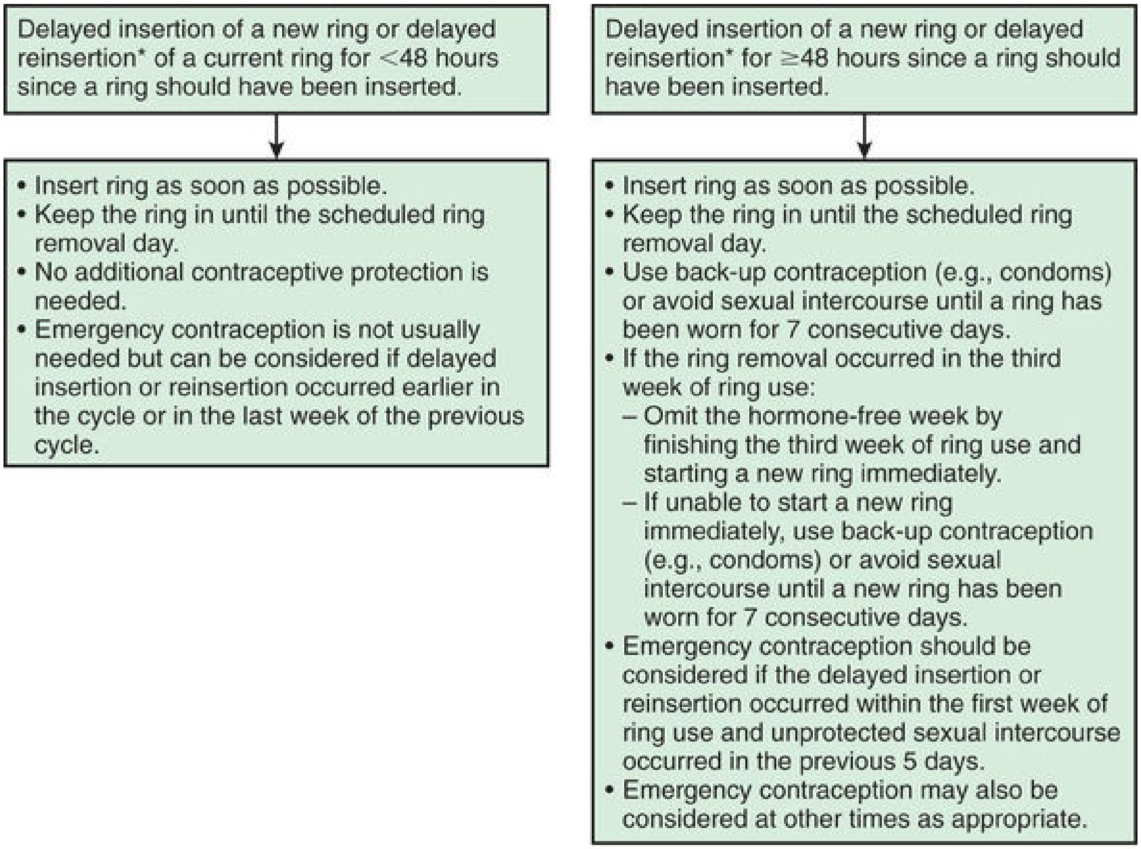

Delayed insertion of a new ring or delayed reinsertion* of a current ring for <48 hours since a ring should have been inserted.

- Insert ring as soon as possible.
- Keep the ring in until the scheduled ring removal day.
- No additional contraceptive protection is needed.
- Emergency contraception is not usually needed but can be considered if delayed insertion or reinsertion occurred earlier in the cycle or in the last week of the previous cycle.

Delayed insertion of a new ring or delayed reinsertion* for ≥48 hours since a ring should have been inserted.

- Insert ring as soon as possible.
- Keep the ring in until the scheduled ring removal day.
- Use back-up contraception (e.g., condoms) or avoid sexual intercourse until a ring has been worn for 7 consecutive days.
- If the ring removal occurred in the third week of ring use:
  - Omit the hormone-free week by finishing the third week of ring use and starting a new ring immediately.
  - If unable to start a new ring immediately, use back-up contraception (e.g., condoms) or avoid sexual intercourse until a new ring has been worn for 7 consecutive days.
- Emergency contraception should be considered if the delayed insertion or reinsertion occurred within the first week of ring use and unprotected sexual intercourse occurred in the previous 5 days.
- Emergency contraception may also be considered at other times as appropriate.

*If removal takes place but the woman is unsure of how long the ring has been removed, consider the ring to have been removed for ≥48 hours since a ring should have been inserted or reinserted.

FIG. 143.6 **Recommended actions after delayed insertion or reinsertion with combined vaginal ring. (From Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016, *MMWR Recomm Rep* 65(RR-4):1–66, 2016, Fig 4, p 29.)**

Contraindications

Contraindications to the use of estrogen-containing methods include those conditions for which CHCs pose an unacceptable health risk (category 4) in the U.S. Medical Eligibility Criteria for Contraceptive Use (see Table 143.3): current breast cancer, severe cirrhosis, acute deep venous thrombosis/pulmonary embolism or history of DVT/PE with higher risk for recurrence, major surgery with prolonged immobilization, diabetes with nephropathy, retinopathy or neuropathy, migraines with aura, stage II hypertension, vascular disease, ischemic heart disease, hepatocellular adenoma or malignant liver tumors, multiple risk factors for cardiovascular disease, peripartum cardiomyopathy, postpartum <21 days, complicated solid-organ transplantation, history of cerebrovascular accident, systemic lupus erythematosus with positive antiphospholipid antibodies, thrombogenic mutations, and complicated valvular heart disease. The initial history taken before prescribing CHCs should specifically address these risks. The U.S. Medical Eligibility Criteria provides contraceptive safety guidance with >1,800 recommendations for >120 medical conditions or characteristics.

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143.6

Emergency Contraception

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Keywords

ulipristal
Plan B
levonorgestrel
LNG
EC
Yuzpe

Unprotected intercourse at mid-cycle carries a pregnancy risk of 20–30%. At other times during the cycle, the risk is 2–4%. The risk may be reduced or eliminated by interventions known collectively as emergency contraception (**EC**) up to 120 hr after unprotected intercourse or contraceptive failure. Table 143.4 lists the indications for use of EC. EC methods include the Cu IUD and emergency contraceptive pills, which include ulipristal acetate, levonorgestrel (LNG), and COCs following the Yuzpe method. Although the mechanism of action of the Cu IUD as EC is unclear, all emergency contraceptive pills work to delay ovulation and are effective only for intercourse that occurs before administration. Initiation of a regular contraceptive method is necessary to prevent pregnancy for any intercourse that occurs for the remainder of the cycle and for future cycles. If pregnancy has already occurred, emergency contraceptive pills will not cause an abortion or have teratogenic effects on the fetus.

Table 143.4

Possible Indications for Emergency Contraception

HIGH RISK SEXUAL ACTIVITY
No contraception during intercourse
Rape
Coitus interruptus
Intoxication (alcohol, drugs)
CONTRACEPTION FAILURES
Condom breaking, spillage, leaks, removal by male (purposeful)
Dislodgement, breaking of diaphragm, female condom, cervical cap
Expulsion of IUD
Spermicide failure to melt before coitus
DELAYED OR MISSED CONTRACEPTION
2 consecutive missed days of combined oral contraceptive
1 missed day of progestin only oral contraceptives
> 2-week late injection of depot medroxyprogesterone
≥ 2 day late start of vaginal ring or patch cycle
OTHER
Exposure to teratogens in absence of contraception

Teens can access EC information through a hotline at 1-888-NOT-2-LATE to obtain EC pills over the counter (OTC). AAP recommends advance provision of EC pills for teens who are or may become sexually active. A follow-up appointment is also recommended to determine the effectiveness of treatment and to diagnose a possible early pregnancy. The visit also provides an opportunity to counsel the adolescent, explore the situation leading up to the unprotected intercourse or contraceptive failure, test for STIs, offer HIV testing, and initiate continuing contraception when appropriate. Pap smear screening is not initiated until age 21.

Copper IUD

The CuT380A (Paragard) is FDA approved for EC and has been shown to be >99% effective if used within 5 days (120 hr) after unprotected sex. The additional benefit of using the Cu IUD for EC is it also provides long-term reversible contraception.

Ulipristal Acetate

This formulation is available for EC and was FDA approved in 2010 for use up to 120 hr after unprotected sex. Ulipristal acetate is available only by prescription regardless of age. A few studies have shown it to be more effective than LNG at and beyond 72 hr. If starting regular contraception after taking ulipristal acetate, it is recommended to start or resume hormonal contraception no sooner than 5 days after taking ulipristal, to avoid a potential interaction and its decreased effectiveness. If starting a method requires an extra visit (e.g., IUDs, implant, Depo-Provera), starting the method at the time of ulipristal may be considered, weighing the risk of decreasing the effectiveness of ulipristal with the risk of not starting a contraceptive method.

Levonorgestrel

In 2013 the FDA approved the emergency contraceptive drug **Plan B** One-Step as an OTC option for all women of childbearing potential. Experience in adolescent women demonstrates more effective use of EC with advance provision, and it is not associated with more frequent unprotected intercourse or less condom or pill use. Nausea and vomiting are uncommon side effects, and in a recent comparison, LNG proved more effective at preventing pregnancy than the Yuzpe method.

The **Yuzpe method** has been replaced by the more effective LNG pills but may be useful for women who already have COCs at home and are in need of EC. For EC, pills consist of COCs totaling 200 µg ethinyl estradiol and 2.0 mg norgestrel or 1.0 mg levonorgestrel. This method is effective in reducing the risk of pregnancy by 75%. The most common side effects are nausea (50%) and vomiting (20%), prompting some clinicians to prescribe or recommend antiemetics along with the COCs.

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143.7

Dual Protection

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Keywords

condoms
dual protection
female condom

Dual protection refers to contraceptive use that protects against STIs/HIV as well as pregnancy. Although correct and consistent condom use with every act of sexual intercourse provides dual protection, providers should encourage adolescents to use condoms for STI/HIV protection along with a more effective method for pregnancy protection.

Condoms

This method prevents sperm from being deposited in the vagina. No major side effects are associated with the use of a condom. The risk of HIV may have increased the use of condoms among adolescents, with 46.2% of high school students in 1991 reporting using a condom at last sexual intercourse increasing to 56.9% in 2015. The main advantages of condoms are their low price, availability without prescription, little need for advance planning, and, most important for this age-group, their effectiveness in preventing transmission of STIs, including HIV and human papillomavirus (HPV). The typical-use failure rate for male condoms is 13%. For the most effective dual protection, **male latex condoms** are recommended as protection against STIs, and should be used with an effective contraceptive method for adolescents, such as a LARC. According to the National Survey of Family Growth, only 21.3% of females used another contraceptive method along with a condom at last sex during the past 12 mo.

A **female condom** is available OTC in single-size disposable units. It is a 2nd choice over the male latex condom because of the complexity of properly using the device, its high typical-use failure rate of 21%, and the lack of human studies demonstrating its effectiveness against STIs. Most adolescents would require intensive education and hands-on practice to use it effectively.

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143.8

Other Barrier Methods

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Keywords

cervical cap
sponge
diaphragm

Diaphragm, Cervical Cap, and Sponge

These methods have few side effects but are much less likely to be used by teenagers. Typical use failure rates exceed 14%. The **cervical cap** and **sponge** have lower failure rates in nulliparous women, while the **diaphragm** has similar rates among nulliparous and parous women. Adolescents tend to object to the messiness of the jelly or the insertion of a diaphragm interrupting the spontaneity of sex (to be inserted before sex and left in for several hours afterward), or they may express discomfort about touching their genitals.

143.9

Other Contraceptive Methods

Tara C. Jatlaoui, Yokabed Ermias, Lauren B. Zapata

Keywords

spermicide
withdrawal
fertility awareness–based methods
lactational amenorrhea method

Spermicides

A variety of agents containing the spermicide **nonoxynol-9** are available as foams, jellies, creams, films, or effervescent vaginal suppositories. They must be placed in the vaginal cavity shortly before intercourse and reinserted before each subsequent ejaculation to be effective. Rare side effects include contact vaginitis. Some concern surrounds the vaginal and cervical mucosal damage observed with nonoxynol-9, and the overall impact on HIV transmission is unknown. The finding that nonoxynol-9 is gonococcicidal and spirocheticidal has not been substantiated in randomized clinical trials. Spermicides should be used in combination with other barrier methods because their typical-use failure rate alone is 21%.

Withdrawal

The pregnancy risk for use of withdrawal as a contraceptive method is probably underestimated in adolescents, and high typical-use failure rate of 20% should be specifically addressed with young adolescents; especially since 60% of teens have used withdrawal for contraception.

Fertility Awareness–Based Methods

These include the Standard Days method, basal body temperature method, and Billings method and may also include combinations as well. Since fertility awareness methods are based on regular ovulatory cycles, which are less common in teens, these should be used with caution.

Lactational Amenorrhea Method

The lactational amenorrhea method may be a highly effective, temporary contraceptive method if the following criteria are met: (1) no return of menses,

(2) the infant is <6 mo old, and (3) exclusively breastfeeding.

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CHAPTER 144

Adolescent Pregnancy

Cora Collette Breuner

Epidemiology

There has been a trend of decreasing teen births and pregnancies since 1991 (Figs. 144.1 and 144.2). Teen birthrates in the United States are at a historic low secondary to increased use of contraception at first intercourse and use of dual methods of condoms and hormonal contraception among sexually active teenagers. Despite these data, the United States continues to lead other industrialized countries in having high rates of adolescent pregnancy, with >700,000 pregnancies per year. Nonetheless, the National Survey of Family Growth (NSFG) 2006–2010 revealed that less than one third of 15-19 yr old females consistently used contraceptive methods at last intercourse.

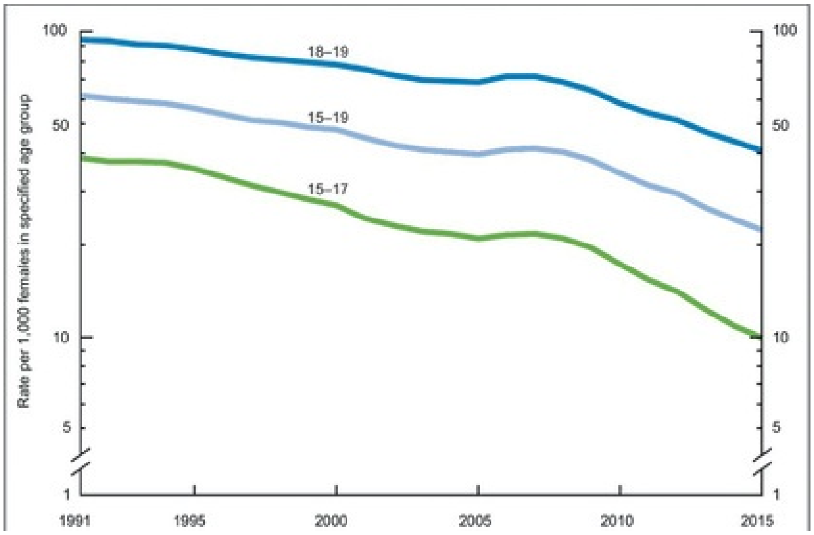

FIG. 144.1 Birthrates for females age 15-19, by age group: United States, 1991–2015. Rates are plotted on a logarithmic scale. For each age group, differences are significant

($p < 0.05$) from 1991–2015, 2007–2015, and 2014–2015. (From Martin JA, Hamilton BE, Osterman MJK, et al: Births: final data for 2015, *Natl Vital Stat Rep* 66(1), 2017, Division of Vital Statistics, National Center for Health Statistics, National Vital Statistics System, Natality. Access data table at http://www.cdc.gov/nchs/data/databriefs/db259_table.pdf#1 .)

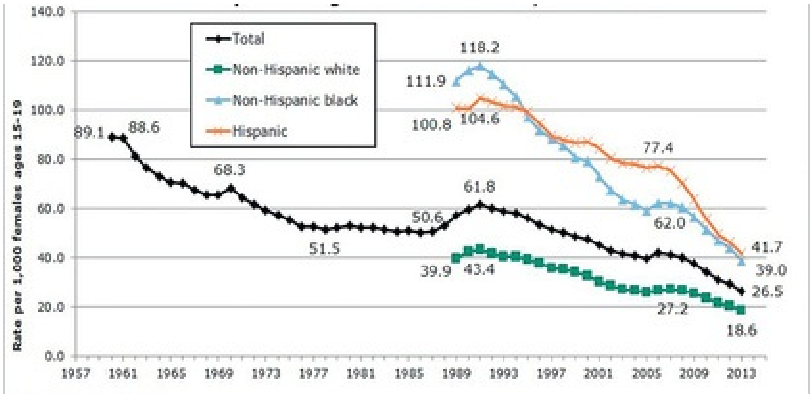

FIG. 144.2 Birthrates (per 1,000) for femals ages 15-19, by race and Hispanic origin: Selected years, 1960–2014. Differences in teen childbearing across the race and Hispanic-origin groups have narrowed from 1991 to 2015. In 1991, there was a difference of 77 births per 1,000 teenagers age 15-19 between the lowest rate (27.3 for Asian Pacific Islander [API] females) and the highest rate (104.6 for Hispanic females), compared with a difference of 28 births between the lowest rate (6.9 for API females) and the highest rate (34.9 for Hispanic females) in 2015. From 2014 to 2015, the birthrate for females age 15-19 declined 10% for API (to 6.9), 9% for non-Hispanic black (31.8), 8% for both non-Hispanic white (16.0) and Hispanic (34.9), and 6% for American Indian or Alaska Native (AIAN) (25.7) females. Since 2007, declines in teen birthrates have ranged from 41% for non-Hispanic white females to 54% for Hispanic females. Since 1991, declines have ranged from 63% for non-Hispanic white females to 75% for API females. Data for 2014 are preliminary. (Data for 1960 from National Center for Health Statistics: Health, United States, 2001 with urban and rural health chartbook, Hyattsville, MD, 2001, Table 3; data for 1970–2011 from Martin JA et al: Births: final data for 2011, *Natl Vital Stat Rep* 62(1), 2013, http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_01.pdf ; data for 2012 from Martin JA et al: Births: final data for 2012, *Natl Vital Stat Rep* 62(9), 2013, http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_09.pdf ; data for 2013 from Martin JA et al: Births: preliminary data for 2013, *Natl Vital Stat Rep* 63(2), 2014, http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_02.pdf .)

The improvement in U.S. female teen birthrates is attributed to 3 factors: more teens are delaying the onset of sexual intercourse, are using some form of contraception when they begin to have sexual intercourse, and are using long-lasting contraceptive agents such as injections, implants, and intrauterine devices (IUDs).

Most pregnancies among U.S. adolescents are **unintended** (unwanted or mistimed); 88% of births to teenagers 15-17 yr old were the result of unintended pregnancies. Birthrate statistics underestimate actual adolescent pregnancy rates because the birthrate numerator includes the number of actual births per 1000 individuals in that age-group, but the pregnancy rate includes actual births, abortions, and best estimates of fetal loss per 1,000 adolescents in that age-group.

The abortion rate among adolescents 15-19 yr old was 14.3 per 1,000 females and accounted for 16.2% of all abortions in 2008. During the decade 1999–2008, the abortion rate decreased by 20.7% among adolescents 15-19 yr old, with a 5.8% decrease noted from 2004–2008.

Etiology

In industrialized countries with policies supporting access to protection against pregnancy and sexually transmitted infections (**STIs**), older adolescents are more likely to use hormonal contraceptives and condoms, resulting in a lowered risk of unplanned pregnancy. Younger teenagers are likely to be less deliberate and logical about their sexual decisions, and their sexual activity is likely to be sporadic or even coercive, contributing to inconsistent contraceptive use and a greater risk of unplanned pregnancy. Better personal hopes for employment and higher educational goals are associated with lowered probability of childbearing in most groups. In nonindustrialized countries, laws permitting marriage of young and mid-teens, poverty, and limited female education are associated with increased adolescent pregnancy rates.

Clinical Manifestations

Adolescents may experience the traditional symptoms of pregnancy: morning sickness (vomiting, nausea that may also occur *any* time of the day), swollen tender breasts, weight gain, and amenorrhea. Often the presentation is less classic; headache, fatigue, abdominal pain, dizziness, and scanty or irregular menses are common presenting complaints.

In the pediatric office, some teens are reluctant to divulge concerns of pregnancy. Denial of sexual activity and menstrual irregularity should not preclude the diagnosis in face of other clinical or historical information. An unanticipated request for a complete checkup or a visit for contraception may uncover a suspected pregnancy. Pregnancy is still the most common diagnosis when adolescents present with secondary amenorrhea.

Diagnosis

Table 144.1 provides classic symptoms, laboratory tests, and physical changes in the diagnosis of pregnancy.

Table 144.1

Diagnosis of Pregnancy Dated from First Day of Last Menstrual Cycle

Classic Symptoms

Missed menses, breast tenderness, nipple sensitivity, nausea, vomiting, fatigue, abdominal and back pain, weight gain, urinary frequency.

Teens may present with unrelated symptoms that enable them to visit the doctor and maintain confidentiality.

Laboratory Diagnosis

Tests for human chorionic gonadotropin in urine or blood may be positive 7-10 days after fertilization, depending on sensitivity.

Irregular menses make ovulation/fertilization difficult to predict.

Home pregnancy tests have a high error rate.

Physical Changes

2-3 wk after implantation: cervical softening and cyanosis.
8 wk: uterus size of orange.
12 wk: uterus size of grapefruit and palpable suprapubically.
20 wk: uterus at umbilicus.
If physical findings are not consistent with dates, ultrasound will confirm.

On physical examination, the findings of an enlarged uterus, cervical cyanosis (**Chadwick sign**), a soft uterus (**Hegar sign**), or a soft cervix (**Goodell sign**) are highly suggestive of an intrauterine pregnancy. A confirmatory pregnancy test is always recommended, either *qualitative* or *quantitative* . Modern **qualitative** urinary detection methods are efficient at detecting pregnancy, whether performed at home or in the office. These tests are based on detection of the beta subunit of human chorionic gonadotropin (**hCG**). Although claims for nonprescription home pregnancy tests may indicate 98% detection on the day of the 1st missed menstrual period, sensitivity and accuracy vary considerably. Office or point-of-care tests have increased standardization and generally have increased sensitivity, with the possibility of detecting a pregnancy within 3-4 days after implantation. However, in any menstrual cycle, ovulation may be delayed, and in any pregnancy, the day of implantation may vary considerably, as may rate of production of hCG. This variability, along with variation of urinary concentration, may affect test sensitivity. *Consequently, each negative test should be repeated in 1-4 wk if there is a heightened suspicion of pregnancy.* The most sensitive pregnancy detection test is a serum **quantitative** βhCG radioimmunoassay, with reliable results within 7 days after fertilization. This more expensive test is used primarily during evaluations for ectopic pregnancy, to detect retained placenta after pregnancy termination, or in the management of a molar pregnancy. It is used when serial measurements are necessary in clinical management.

Although not used for primary diagnosis of pregnancy, pelvic or vaginal **ultrasound** can be helpful in detecting and dating a pregnancy. Pelvic ultrasound will detect a gestational sac at about 5-6 wk (dated from last menstrual period) and vaginal ultrasound at 4.5-5 wk. This tool may also be used to distinguish diagnostically between intrauterine and ectopic pregnancies.

Pregnancy Counseling and Initial Management

Once the diagnosis of pregnancy is made, it is important to begin addressing the psychosocial, as well as the medical, aspects of the pregnancy. The patient's response to the pregnancy should be assessed and her emotional issues addressed. It should not be assumed that the pregnancy was unintended. Discussion of the patient's options should be initiated. These options include (a) releasing the child to an adoptive family, (b) electively terminating the pregnancy, and (c) raising the child herself with the help of family, father of the baby, friends, and/or other social resources. Options should be presented in a supportive, informative, nonjudgmental fashion; for some young women, they may need to be discussed over several visits. Physicians who are uncomfortable in presenting options to their young patients should refer their patients to a provider who can provide this service expeditiously. Pregnancy terminations implemented early in the pregnancy are generally less risky and less expensive than those initiated later.

Other issues that may need discussion are how to inform and involve the patient's parents and the father of the infant; implementing strategies for insuring continuation of the young mother's education; discontinuation of tobacco, alcohol, and illicit drug use; discontinuance and avoidance of any medications that may be considered teratogenic; starting folic acid, calcium, and iron supplements; proper nutrition; and testing for STIs. Especially in younger adolescents, the possibility of **coercive sex** (see Chapter 145) must be considered and appropriate social work/legal referrals made if abuse has occurred, although most pregnancies are not a result of coercive sex. Patients who elect to continue their pregnancy should be referred as soon as possible to an adolescent-friendly obstetric provider.

Risk factors for teen pregnancy include growing up in poverty, having parents with low levels of education, growing up in a single-parent family, fewer opportunities in their community for positive youth involvement, neighborhood physical disorder, foster care (are more than twice as likely to become pregnant than those not in foster care), and having poor performance in school (see later, Psychosocial Outcomes/Risks for Mother and Child).

The Importance of Prevention

Teen pregnancy and childbearing bring substantial social and economic costs through immediate and long-term impacts on teen parents and their children. In 2010, teen pregnancy and childbirth accounted for at least $9.4 billion in costs to U.S. taxpayers for increased healthcare and foster care, increased incarceration rates among children of teen parents, and lost tax revenue because of lower educational attainment and income among teen mothers.

Adolescent Fathers

Those who become fathers as adolescents also have poorer educational achievement than their age-matched peers. They are more likely than other peers to have been involved with illegal activities and with the use of illegal substances. Adult men who father the children of teen mothers are poorer and educationally less advanced than their age-matched peers and tend to be 2-3 yr older than the mother; any combination of age differences may exist. Younger teen mothers are more likely to have a greater age difference between themselves and the father of their child, raising the issue of coercive sex or statutory rape (see Chapter 145).

Male partners have a significant influence on the young woman's decision/desire to become pregnant and to parent her child. Sensitively and appropriately including the male partner in discussions of family planning, contraception, and pregnancy options may be a useful strategy in improving outcomes for all. This can only be successful if the young female patient is willing to have her partner involved in such discussions.

Medical Complications of Mothers and Babies

Although pregnant teens are at higher-than-average risk for some complications of pregnancy, most teenagers have pregnancies that are without major medical complications, delivering healthy infants. The miscarriage/stillbirth risk for adolescents is estimated at 15–20%. In the United States, elective pregnancy termination rates peaked from 1985–1988 at 41–46%, decreasing since then to approximately 30% in 2008. Teen mothers have low rates of age-related chronic disease (diabetes or hypertension) that might affect the outcomes of a pregnancy. They also have lower rates of twin pregnancies than older women. They tolerate childbirth well with few operative interventions. However, compared with 20-39 yr old mothers, teens have higher incidences of low birthweight infants, preterm infants, neonatal deaths, passage of moderate to heavy fetal meconium during parturition, and infant deaths within 1 yr after birth. The highest rates of poor outcomes occur in the youngest and most economically disadvantaged mothers. *Gastroschisis,* although rare, has a much higher incidence in infants of teen mothers, for reasons that are unclear. Teen mothers also have higher rates of anemia, pregnancy-associated hypertension, and eclampsia, with the youngest teens having rates of pregnancy-associated hypertension higher than the rates of women in their 20s and 30s. The youngest teens also have a higher incidence of poor weight gain (<16 lb) during their pregnancy. This correlates with a decrease in the birthweights of their infants. Poor maternal weight gain also has correlated strongly with teens’ late entrance into prenatal care and with inadequate utilization of prenatal care. Sexually active teens have higher rates of STIs than older sexually active women.

Globally, many young women who become pregnant have been exposed to violence or abuse in some form during their lives. There is some evidence that teenage women have the highest rates of **violence** during pregnancy of any group. Violence has been associated with injuries and death as well as preterm births, low birthweight, bleeding, substance abuse, and late entrance into prenatal care. An analysis of the Pregnancy Mortality Surveillance System indicates that in the United States 1991–1999, homicide was the 2nd leading cause of injury-related deaths in pregnant and postpartum women. Women age 19 yr and younger had the highest pregnancy-related homicide rate (see Chapter 139).

Ectopic pregnancy occurs in 1–2% of conceptions and is more common in women with a previous history of an ectopic pregnancy, pelvic inflammatory disease, prior appendicitis, infertility, in utero exposure to diethylstilbestrol, and possibly an IUD. Most ectopic pregnancies are in the fallopian tube (tubal pregnancy). Manifestations include vaginal spotting after a missed menstrual period that may progress to more intense vaginal bleeding (suggestive of spontaneous abortion); vaginal bleeding is absent in 10–20%. Abdominal pain is associated with distention of the fallopian tube; tubal rupture results in more intense pain, hemorrhagic shock, and peritonitis. Some women have nonspecific abdominal complaints and are misdiagnosed with gastroenteritis. Cervical motion and adnexal tenderness (and adnexal mass) may be present. **Transvaginal sonography** (not transabdominal) is the diagnostic test of choice to detect an ectopic pregnancy and reveals an adnexal mass and no uterine pregnancy. Nonetheless, some women will have pregnancy of unknown location by transvaginal sonography; approximately 20% of these will have an ectopic pregnancy. Measurement of sensitive quantitative serum βhCG levels together with transvaginal sonography has value in diagnosing an ectopic pregnancy. If the initial βhCG is above the *discriminatory zone* (level at which one expects an intrauterine pregnancy) but on transvaginal sonography there is no intrauterine pregnancy, there may be an ectopic pregnancy or an abnormal uterine pregnancy. In addition, if the βhCG is below the discriminatory level (usually <3000 mIU/mL) with no definitive diagnosis by sonography, serial βhCG testing should be performed every 48 hr. In a normal uterine pregnancy, βhCG levels should increase approximately 50% every 48 hr; declining levels may suggest a miscarriage or an ectopic pregnancy. Some would perform a dilation and curettage and check for products of conception or follow serial βhCG levels. If there are no products of conception or if βhCG levels plateau or increase, an ectopic pregnancy is present. Treatment of unstable or advanced patients is usually by laparoscopic surgery or by laparotomy. Because of early detection, many patients remain stable *(unruptured)*. Stable patients with an unruptured ectopic pregnancy may be treated with single-dose, or more often multidose, methotrexate to induce abortion. Contraindications to methotrexate in a stable patient include size of the ectopic mass (>3.5 cm) and embryonic cardiac motion.

Prematurity and low birthweight increase the perinatal morbidity and mortality for infants of teen mothers. These infants also have higher-than-average rates of sudden infant death syndrome (see Chapter 402), possibly because of less use of the supine sleep position or cosleeping, and are at higher risk of both intentional and unintentional injury (see Chapter 16). One study showed that risk of homicide is 9-10 times higher if a child born to a teen mother is not the mother's firstborn compared with the risk to a firstborn of a woman age 25 yr or older. The perpetrator is often the father, stepfather, or boyfriend of the mother.

After childbirth, **depressive symptoms** may occur in as many as 50% of teen mothers. Depression seems to be greater with additional social stressors and with decreased social supports. Support from the infant's father and the teen's mother seems to be especially important in preventing depression. Pediatricians who care for parenting teens should be sensitive to the possibility of depression, as well as to inflicted injury to mother or child; appropriate diagnosis, treatment, and referral to mental health or social agencies should be offered and facilitated.

Psychosocial Outcomes/Risks for Mother and Child

Educational Issues

Pregnancy and birth are significant contributors to high school dropout rates among girls. Only about 50% of teen mothers receive a high school diploma by age 22, whereas approximately 90% of women who do not give birth during adolescence graduate from high school. Mothers who have given birth as teens generally remain 2 yr behind their age-matched peers in formal educational attainment at least through their 3rd decade. Maternal lack of education limits the income of many of these young families (see Chapter 1).

The children of teenage mothers are more likely to have lower school achievement and to drop out of high school, have more health problems, and face unemployment as a young adult.

Substance Use

See also Chapter 140 .

Teenagers who abuse drugs, alcohol, and tobacco have higher pregnancy rates than their peers. Most substance-abusing mothers appear to decrease or stop their substance use while pregnant. Use begins to increase again about 6 mo postpartum, complicating the parenting process and the mother's return to school.

Repeat Pregnancy

In the United States, approximately 20% of all births to adolescent mothers (age 15-19) are second order or higher. Prenatal care is begun even later with a 2nd pregnancy, and the 2nd infant is at higher risk of poor outcome than the 1st birth. Mothers at risk of early repeat pregnancy (<2 yr) include those who do not initiate long-acting contraceptives after the index birth, those who do not return to school within 6 mo of the index birth, those with mood disorders, those receiving major childcare assistance from the adolescent's mother, those who are married or living with the infant's father, those having peers who were adolescent parents, and those who are no longer involved with the baby's father and who meet a new boyfriend who wants to have a child. To reduce repeat pregnancy rates in these teens, programs must be tailored for this population, preferably offering comprehensive healthcare for both the young mother and her child (Table 144.2). Healthcare providers should remember to provide positive reinforcement for teen parenting successes (i.e., compliment teen parents when they are doing a good job).

Table 144.2

2012 American Academy of Pediatrics Clinical Guidelines: Care of Adolescent Parents and Their Children

GUIDELINE	**INTERVENTIONS**
Create a medical home for adolescent parents and their children.	Involve both adolescent mothers and coparenting father. Emphasize anticipatory guidance, parenting, and basic childcare skills, especially for teen dads.
Provide comprehensive, multidisciplinary care.	Access community resources such as special Supplemental Nutrition Program for Women, Infants, and Children. Provide medical and developmental services to low-income parents and children. Facilitate coordination of services.
Contraceptive counseling.	Emphasize condom use. Encourage long-acting contraceptive methods.
Encourage breastfeeding.	Support breastfeeding in home, work, and school settings.
Encourage high school completion.	
Assess risk of domestic violence.	
Encourage adolescent parenting.	Work with other involved adults such as grandparents to encourage developmental growth of adolescent as parent as well as optimize infant developmental outcomes.
Adapt counseling to developmental level of adolescent.	Utilize school-, home-, and office-based interventions. Consider use of support groups.
Awareness and monitoring of developmental progression of infant and adolescent parent.	Advocate for high-quality community resources for adolescents, including developmental resources, childcare, and parenting classes. Facilitate access to Head Start and education resources for individuals with disability.

Data from Pinzon JL, Jones VF; Committee on Adolescence and Committee on Early Childhood: Care of adolescent parents and their children, *Pediatrics* 130(6):e1743–e1755, 2012.

Children Born to Teen Mothers

Many children born to teen mothers have behavioral problems that may be seen as early as the preschool period. Many drop out of school early (33%), become adolescent parents (25%), or, if male, are incarcerated (16%). Explanations for these poor outcomes include poverty, parental learning difficulties, negative parenting styles of teen parents, maternal depression, parental immaturity, poor parental modeling, social stress, exposure to surrounding violence, and conflicts with grandparents, especially grandmothers. Continued positive paternal involvement throughout the child's life may be somewhat protective against negative outcomes. Many of these poor outcomes appear to be attributable to the socioeconomic/demographic situation in which the teen pregnancy has occurred, not solely to maternal age. Even when socioeconomic status and demographics are controlled, infants of teen mothers have lower achievement scores, lower high school graduation rates, increased risk of teen births themselves, and, at least in Illinois (where records include age of birth mother), a higher probability of abuse and neglect.

Comprehensive programs focused on supporting adolescent mothers and infants utilizing life skills training, medical care, and psychosocial support demonstrate higher employment rates, higher income, and less welfare dependency in participating adolescents.

Prevention of Teen Pregnancies

Adolescent pregnancy is a multifaceted problem that requires multifactorial solutions. The provision of contraception and education about fertility risk from the primary care physician is important, but insufficient to address the problem fully. Family and community involvement are essential elements for teen pregnancy prevention. Strategies for primary prevention (preventing 1st birth) are different from the strategies needed for secondary prevention (preventing 2nd or more births). Over the last 30 yr, many models of teen pregnancy prevention programs have been implemented and evaluated. Table 144.3 lists the common components of many successful evidence-based programs.

Table 144.3

Common Components of Most Successful Evidence-Based Programs to Prevent Teen Pregnancy

- Information is provided about the benefits of abstinence.
- Information is provided about contraception for those who are already sexually active.
- Information is provided about the signs and symptoms of STIs and how to prevent STIs.
- Interactive sessions on peer pressure are presented.
- Teenagers are taught communication skills.
- Programs are tailored to meet the needs of specific groups of young people (e.g., young men or young women, cultural groups, younger or older teens).

Adapted from Suellentrop K: *What works 2011–2012: curriculum-based programs that help prevent teen pregnancy*, Washington, DC, National Campaign to Prevent Teen and Unplanned Pregnancy. http://www.c-hubonline.org/sites/default/files/resources/main/What_Works_0.pdf .

Abstinence-only sexual education aims to teach adolescents to wait until marriage to initiate sexual activity but, unfortunately, does not mention contraception. Abstinence education is sometimes coupled with “virginity pledges” in which teenagers pledge to remain abstinent until they marry. Other educational programs emphasize HIV and STI prevention and in the process prevent pregnancy, whereas others include both abstinence and contraception in their curricula. Sex education and teaching about contraception do not lead to an increase in sexual activity. Teenagers who participate in programs with **comprehensive** sex education components generally have lower rates of pregnancy than those exposed solely to abstinence-only programs or no sex education at all.

In many U.S. communities, programs that engage youth in community service and that combine sex education and youth development are also successful in deterring pregnancy. Programs vary in their sites of service from schools to social agencies, health clinics, youth organizations, and churches. Programs must be tailored to the cultural background, ethnicity, age-group, and gender of the group being targeted for the prevention services.

Secondary prevention programs are fewer in number. In the United States, some communities have tried to “pay” young mothers not to become pregnant again, but these efforts have not always been fruitful. **Home visiting** by nurses has been successful in some areas, and many communities have developed “Teen Tot” Clinics that provide a “one-stop shopping model” for healthcare for both the teen mother and the baby in the same site at the same time. Both programs have reported some successes.

In the practice setting, the identification of the sexually active adolescent through a confidential clinical interview is a first step in pregnancy prevention. The primary care physician should provide the teenager with factual information in a nonjudgmental manner and then guide the teenager in the decision-making process of choosing a contraceptive (see Chapter 143). The practice setting is an ideal setting to support the teenager who chooses to remain abstinent. When a teenager does become pregnant and requires prenatal care services, healthcare providers should remember that the pregnant teenager is an adolescent who has become pregnant, not a pregnant woman who happens to be an adolescent.

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CHAPTER 145

Adolescent Sexual Assault

Allison M. Jackson, Norrell Atkinson

Sexual assault is an act of violence that may or may not involve rape. Rape, also an act of violence, is not an act of sex. Rape is historically defined as coercive sexual intercourse involving physical force or psychological manipulation of a female or a male. Recognizing that sexual intercourse is not a requirement for the definition, the U.S. Department of Justice (DOJ) defines rape as “the penetration, no matter how slight, of the vagina or anus with any body part or object, or oral penetration by a sex organ of another person, without the consent of the victim.”

Epidemiology

Exact figures on the incidence of rape are unavailable because many rapes are not reported. It is estimated that 1 in 5 women and 1 in 71 men will be raped in their lifetime. Females exceed males as reported rape victims, but male rape may be more underreported than female rape. In 2010 the DOJ National Crime Victimization Survey reported that the annual rates of **sexual victimization** per 1,000 persons were 4.1 for ages 12-17 yr and 3.7 for 18-34 yr. Between 1995 and 2013 the rate of rape and sexual assault was highest for adolescent females between ages 18 and 24 yr. The National Survey of Children's Exposure to Violence (NatSCEV 2014), revealed that 12.9% of 14-17 yr olds experienced any sexual victimization in the past year, 21.7% had experienced any sexual victimization in their lifetime; and 4.2% experienced **sexual assault** in the past year and 10.2% in their lifetime. This survey also demonstrated how other experiences with violence compound the risk for sexual victimization. Youth with a history of maltreatment by a caregiver were 4 times more likely to experience sexual victimization and >4 times more likely to experience sexual victimization if they had any witness to violence. Among older adolescents age 18-24 yr, the rate of rape and sexual assault was 1.2 times higher for those not enrolled in college than those in college. Further, several studies of youth in the juvenile justice system demonstrate a particularly high prevalence of prior sexual victimization of girls in the juvenile justice system.

Rape occurs worldwide and is especially prevalent in war and armed conflicts. The World Health Organization estimates that rape and domestic violence are responsible for 5–16% of healthy years of life lost by females of reproductive age.

Female adolescents and young adults have the highest rates of rape compared to any other age-group. The normal developmental growth tasks of adolescence may contribute to this vulnerability in the following ways: (1) the emergence of independence from parents and the establishment of relationships outside the family may expose adolescents to environments with which they are unfamiliar and situations that they are unprepared to handle; (2) dating and becoming comfortable with one's sexuality may result in activities that are unwanted, but the adolescent is too inexperienced to avoid the unwanted actions; and (3) young adolescents may be naïve and more trusting than they should be (see Chapter 132). Many teens are technologically competent, which gives sexual perpetrators access to unsuspecting vulnerable populations who were previously beyond their reach. Social media, chat rooms, and online dating sites represent a major risk for adolescents, resulting in correspondence with individuals unknown to them or protective family members, while simultaneously providing a false sense of security because of remote electronic communications. A determined perpetrator can obtain specific information to identify the adolescent and arrange for a meeting that is primed for sexual victimization.

Some adolescents are at higher risk of being victims of rape than others (Table 145.1).

Table 145.1

Adolescents at High Risk of Rape Victimization

Male and Female Adolescents

Drug and alcohol users
Runaways

- Those with intellectual disability or developmental delay
- Street youths
- Transgender youth
- Youths with a parental history of sexual abuse
- Sex trafficking

Primarily Females

- Survivors of prior sexual assault
- Newcomers to a town or college

Primarily Males

- Those in institutionalized settings (detention centers, prison)
- Young male homosexuals

Types of Rape

Rape and sexual assault can occur in a variety of circumstances (Tables 145.2 and 145.3). A victim can be sexually assaulted or raped by someone they know or a by stranger, though more often the assailant is someone known to the victim. Understanding those circumstances allows for a more trauma-sensitive approach and may impact the medical management and response to the patient. The circumstances and relationship of the assailant to the victim may impact if, when, and how a patient discloses. The gender of the victim may also affect disclosure; transgendered people and males are uniformly less likely to disclose rape/sexual assault than females. The gender of the assailant may be the same or different than the victim's, and there may be one or more than one perpetrator. In any scenario the sexual assault/rape can be facilitated by threats or coercion, physical force, or drugs.

Table 145.2

Types of Nonstranger Rape

Acquaintance Rape

Most common form of rape for adolescents age 16-24 yr.
Assailant may be a neighbor, classmate, or friend of the family.
Victims are more likely to delay seeking medical care, may never report the crime (males > females), and are less likely to proceed with criminal prosecution even after reporting the incident(s).

Date Rape

Assailant is in an intimate relationship with the victim.
May be associated with intimate partner violence.
Assailant may engage in more sexual activities than other men his age and often has a history of aggressive behavior toward women.

Sexual Abuse

All sexual contact or exposure between an adult and a minor, or when there is a significant age or developmental difference between the youth.
The assailant may be a relative, close family friend, or someone of authority.

Statutory Rape

Sexual activity between an adult and an adolescent under the age of legal consent, as defined by individual state law.
Based on the premise that below a certain age or beyond a specific age difference with the assailant, an individual is not legally capable of giving consent to engage in sexual intercourse.
The intent of such laws is to protect youth from being victimized, but they may inadvertently lead a teenager to withhold pertinent sexual information from a clinician for fear that her sexual partner will be reported to the law.

Male Rape

Same-sex rape of males.

More prevalent in institutional settings.

Males are less likely than females to report rape and less likely to seek professional help.

Gang Rape

See Table 145.3 .

Table 145.3

Types of Stranger Rape

Sex Trafficking and Commercial Sexual Exploitation of Children (CSEC)

The average age of recruitment into CSEC is between 12 and 13 yr.

The assailant(s) can be the pimp (acquaintance) or the john/“date” (stranger).

Victims often have a history of child maltreatment.

Fear of the pimp results in reluctance to disclose.

Drug-Facilitated Rape

Alcohol is the most common drug associated with sexual victimization.

Gang Rape

When a group of males rapes a solitary female victim.

May be part of a ritualistic activity or rite of passage for some male groups (e.g., gang, college fraternity), or may be displaced rage on the part of the assailants.

Victims may fear retaliation or confrontation with assailants.

Victims may desire or require relocation.

Acquaintance rape , the most common form of rape, is committed by a person known to the victim outside of the family. If the known assailant is a family member, caregiver, or someone in a position of authority, it would be considered **sexual abuse** . The victim–assailant relationship may cause conflicting loyalties in families, and the teen's report may be received with disbelief and/or skepticism by the family. Adolescent acquaintance rape differs from adult acquaintance rape because weapons are less often used, and victims are less likely to sustain physical injuries.

Date rape is sexual violence perpetrated by a person in an intimate relationship with the victim. These victims may be new to a specific environment (college freshman, newcomer to a town or high school) and lack strong social support. Victims may have difficulty establishing boundaries or limits with their partner and in some cases may be intoxicated when the incident takes place. The assailant may interpret passivity as assent and deny the charge of coercion or force, and he may also be intoxicated at the time of the assault.

Drug-facilitated rape may involve illicit and/or legal substances. The opportunity for acquaintance and date rape may be greater with individuals under the influence of alcohol. Even more predatory is the furtive administration of pharmaceuticals to potential victims. In these scenarios, date rape drugs such as γ-hydroxybutyric acid (GHB), flunitrazepam (Rohypnol), and ketamine hydrochloride are the leading agents used for these illegal purposes, but may also include alcohol, benzodiazepines, stimulants, barbiturates, opiates, and other drugs (see Chapter 140). Their pharmacologic properties make these drugs effective for this use because they have simple modes of administration, are easily concealed (colorless, odorless, tasteless), have rapid onset of action with resulting induction of anterograde amnesia, and have rapid elimination because of a short half-life. Detection of these drugs requires a high index of suspicion and medical evaluation within 8-12 hr, prompting specific testing because routine toxicology screening is insufficient.

Acquaintance and date rape victims often experience long-term issues of trust, self-blame, and guilt, resulting in lost confidence in judgment concerning future relationships. Survivors are nearly always ashamed of the incident and are less likely to report the rape. They are also typically reluctant to talk about the rape to family, friends, or a counselor and may never heal from the psychological scars that ensue. For those adolescents who are LGBTQ, the shame and reluctance to disclose the rape may be even greater.

The **commercial sexual exploitation of children (CSEC)** , also known as **sex trafficking** , is a more complex form of sexual victimization and is considered a form of child abuse (see Chapter 15). Sex trafficking is federally defined as the recruiting, harboring, transporting, providing, obtaining, patronizing, or soliciting of an individual through the means of force, fraud, or coercion for commercial sex. While a pimp often personally recruits victims, he may use others to recruit. These youth may experience physical and sexual assault by the pimp as well as the "johns." Many of these youth have a history of child maltreatment, increasing their vulnerability to this form of abuse. Fear of the consequences of disclosure and the survival skills acquired often yield a very guarded presentation in the healthcare setting.

Male rape generally refers to same-sex rape of males. Specific subgroups of young men are at high risk of being victims of rape (see Table 145.1). Male rape that occurs outside of institutional settings typically involves coercion of the male teen by someone considered an authority figure, either male or female. Male rape victims often experience conflicted sexual identity about whether they are homosexual. Issues of loss of control and powerlessness are particularly bothersome for male rape victims, and these young men usually have symptoms of anxiety, depression, sleep disturbance, and suicidal ideation.

Stranger rape occurs less frequently within the adolescent population and is similar to adult rape. There can be a variety of scenarios for stranger rape (see Table 145.3). Nevertheless, such rapes frequently occur with abduction, use of weapons, and increased risk of physical injuries. These rapes are more likely to be reported and prosecuted.

Clinical Manifestations

The adolescent's acute presentation following a rape may vary considerably, from histrionics to near-mute withdrawal. Even if they do not appear afraid, most victims are extremely fearful and very anxious about the incident, the rape report, examination, and the entire process, including potential repercussions. Because adolescents are between the developmental lines of childhood and adulthood, their responses to rape may have elements of both child and adult behaviors. Many teens, particularly young adolescents, may experience some level of cognitive disorganization.

Adolescents may be reluctant to report rape for a variety of reasons, including self-blame, fear, embarrassment, or in the circumstances of drug-facilitated rape, uncertainty of event details. Adolescent victims, unlike child victims who elicit sympathy and support, often face intense scrutiny regarding their credibility and inappropriately misplaced societal blame for the assault. This view is baseless and should not be used during an evaluation of any teenage victim, including acquaintance rape.

When adolescents do not report a rape, they may present at a future date with concerns for pregnancy, symptoms of or concerns for a sexually transmitted infection (STI), and symptoms of posttraumatic stress disorder (see Chapter 38), such as sleep disturbances, nightmares, mood swings, and flashbacks. Other teens may present with psychosomatic complaints or difficulties with schoolwork; all adolescents should be screened for possible sexual victimization at most health examination visits.

Interview and Physical Examination

The purpose of the adolescent medical evaluation following a sexual assault is to provide medical care for the teen and to collect and document evidence of the assault when applicable. Although many teens delay seeking medical care, others present to a medical facility within 72 hr (or up to 96 hr depending on the protocol used) of the rape, at which time forensic evidence collection should be offered to the patient. Experienced clinicians with training and knowledge of forensic evidence collection and medical-legal procedures should complete the rape evaluation or supervise the evaluation when possible.

The clinician's responsibilities are to provide support, obtain the history in a nonjudgmental manner, conduct a complete examination without retraumatizing the victim, and collect forensic evidence. The clinician must complete laboratory testing, administer prophylaxis treatment for STIs and emergency contraception, arrange for counseling services, and file a report to appropriate authorities in accordance with the law. It is not the clinician's responsibility to decide whether a rape has occurred; the legal system will make that determination.

Ideally, a clinician trained in forensic interviewing should obtain the history. In all cases, the history should be obtained by asking *only* open-ended questions to obtain information about (1) what happened; (2) where it happened; (3) when it happened; and (4) who did it. After obtaining a concise history, including details of the type of physical contact that occurred between the victim and the assailant, the clinician should conduct a thorough and complete physical examination and document all injuries. Clinicians should provide sensitive, nonjudgmental support during the entire evaluation, as the adolescent victim has experienced a major trauma and is susceptible to retraumatization during this process. Each component of the evaluation should be explained in detail to the victim, allowing the adolescent as much control as possible, including refusal to complete any part or all of the forensic evidence collection process. It is often useful to permit a trusted supportive person, such as a family member, friend or rape crisis advocate, to be present during the evaluation if that is the adolescent's wish.

The examining clinician should be familiar with the **forensic evidence collection** kit prior to initiating the examination. In the United States, each state's forensic evidence kit is different, but most include some or all of the following components: forensic evidence of semen deposits detected by a fluorescent lamp with a wavelength near 490 nm (many Woods lamps are inadequate); swabs of bite mark impressions to collect genetic markers (DNA, ABO group); swabs of any penetrated orifice or body surface where saliva may be present; and documentation of acute cutaneous injuries using body diagram charts and photographs with visible standard measurements. Areas of restraint should be carefully inspected for injuries; these areas include extremities, neck, and the inner aspect of the oral mucosa, where a dentition impression may be seen.

The genital examination of a female rape victim should be undertaken with the patient in the lithotomy position. The prone knee-chest position may be used as an exam-clarifying technique, specifically to evaluate the posterior rim of the hymen. The genital exam of a male rape victim should be undertaken with the patient in supine position. The clinician's exam should include careful inspection of the entire pelvic, genital, and perianal areas. The clinician should document any acute injuries such as edema, erythema, petechiae, bruising, hemorrhage, or tearing. Aqueous solution of toluidine blue (1%), which adheres to nucleated cells, may be used during the acute examination to improve visualization of microtrauma in the perianal area. Any disruption to the superficial epidermis will allow for dye uptake and thus cannot differentiate between disruption of the skin from trauma, irritation, or infection. Additionally, a colposcope may be used to provide magnification and photo documentation of injuries.

Laboratory Data

When adolescents present for medical care within 72-96 hr of a sexual assault, a forensic evidence collection kit should be offered to the patient. Regardless of an adolescent's decision to have evidence collection completed, medical care, including physical examination, laboratory testing (Table 145.4), and prophylactic therapies, should be offered to the patient. Follow-up evaluations should be scheduled to repeat these laboratory studies.

Table 145.4

Laboratory Evaluation of Sexual Assault

Within 8-12 hr (if Indicated by History)

Urine and blood for date rape drugs (GHB, Rohypnol, ketamine)

Within 24 hr (if Indicated by History)

Blood for comprehensive toxicology screen (for other classes of drugs)

Within 72 hr (or Up to 96 hr Depending on the Protocol Used)

Forensic evidence kit
Pregnancy test
Hepatitis B screen (hepatitis B surface antigen, surface antibody, and core antibody)
Syphilis (rapid plasma reagin [RPR], Venereal Disease Research Laboratories [VDRL])
HIV infection
Bacterial vaginosis (BV) and candidiasis: point-of-care testing and/or wet mouth with measurement of vaginal pH and KOH application for whiff test
Trichomonas vaginalis : nucleic acid amplification tests (NAATs) by urine or vaginal specimen or point-of-care testing (DNA probes) from vaginal specimen
Chlamydia and *Neisseria gonorrhoeae* : nucleic acid amplification testing (NAATs) at sites of penetration or possible penetration:

1. *N. gonorrhoeae:* oropharynx, rectum, urine*
2. *Chlamydia* : urine,* rectum

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* Dirty urine sample may be used as alternate for genital swab.

From Centers for Disease Control and Prevention: Sexually transmitted diseases:

treatment guidelines 2015, *MMWR Recomm Rep* 64(RR-3):1–140, 2015, and Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016.

Treatment

Treatment includes **prophylactic antimicrobials** for STIs (see Chapter 146) and emergency contraception (see Chapter 143). The Centers for Disease Control and Prevention (CDC) reports that trichomoniasis, bacterial vaginosis, gonorrhea, and chlamydial infection are the most frequently diagnosed infections among women who have been sexually assaulted. Antimicrobial prophylaxis is recommended for adolescent rape victims because of the risk of acquiring an STI and the risk of pelvic inflammatory disease (Table 145.5). A two- or three-drug antiretroviral regimen for HIV **postexposure prophylaxis (PEP)** must be considered and an infectious disease specialist consulted if higher transmission risk factors are identified (e.g., knowing that the perpetrator is HIV-positive, significant mucosal injury of the victim) to prescribe a triple-antiretroviral regimen (Fig. 145.1). Similar considerations should be made for possible exposure to the hepatitis B virus in vaccinated/unvaccinated individuals. Clinicians should review the importance for patient's compliance with medical and psychological treatment and follow-up care.

Table 145.5

Postexposure Prophylaxis (PEP) for Acute Sexual Assault Victims

Routine

Recommended Regimen for STI Prophylaxis

> Ceftriaxone 250 mg intramuscularly
> *plus*
> Azithromycin 1g orally in a single dose
> *plus*
> Metronidazole 2 g orally in a single dose *or*
> Tinidazole 2 g orally in a single dose

Pregnancy Prophylaxis*

Levonorgestrel (Plan B) 1.5 mg orally in a single dose
OR
Ulipristal acetate (Ella) 30 mg is effective for up to 120 hr.

Human Papillomavirus (HPV)

Assess HPV vaccine history; to unimmunized, administer initial vaccine at initial exam, with 2 follow-up doses at 1-2 mo and at 6 mo if >15 yr old *or* a single follow-up dose at 6-12 mo if ≤15 yr old

As Indicated

All persons offered PEP should be prescribed a 28-day course of a two- or three-drug antiretroviral regimen.

Human Immunodeficiency Virus (HIV) †

Preferred regimen:

Tenofovir 300 mg and fixed-dose combination emtricitabine, 200 mg (Truvada) once daily
plus
Raltegravir 400 mg twice daily *or*
Dolutegravir 50 mg daily ‡

Alternative regimens available (The National Clinicians Consultation Center is a resource for providers prescribing PEP, reachable at 1-888-448-4911.)

Hepatitis B virus (HBV)

Specific indications for vaccine, immunoglobulin and/or booster dependent upon assailant's status

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[*] Provided for patients with negative urine pregnancy screen. In addition, antiemetic (Compazine, Zofran) can be prescribed for patients receiving emergency contraception.

[†] HIV PEP is provided for patients with penetration and when the assailant is known to be HIV-positive or at high risk because of a history of incarceration, intravenous drug use, or multiple sexual partners. If provided, laboratory studies must be drawn before administration of medication (HIV, CBC, LFTs, BUN/Cr, amylase, lipase), and follow-up must be arranged.

[‡] Dolutegravir has been associated with neural tube defects if the exposure occurs within the first trimester of pregnancy. Therefore it should be avoided in pregnant patients or those at risk for becoming pregnant. U.S. Department of Health and Human Services, U.S. Food & Drug Administration. Julica, Tivicay, Triumeq (dolutegravir): FDA to evaluate potential risk of neural tube birth defects. May 18, 2018. https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanme
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Data from Centers for Disease Control and Prevention: Sexually transmitted diseases: treatment guidelines 2015, *MMWR Recomm Rep* 64(RR-3):1–140, 2015, and Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016.

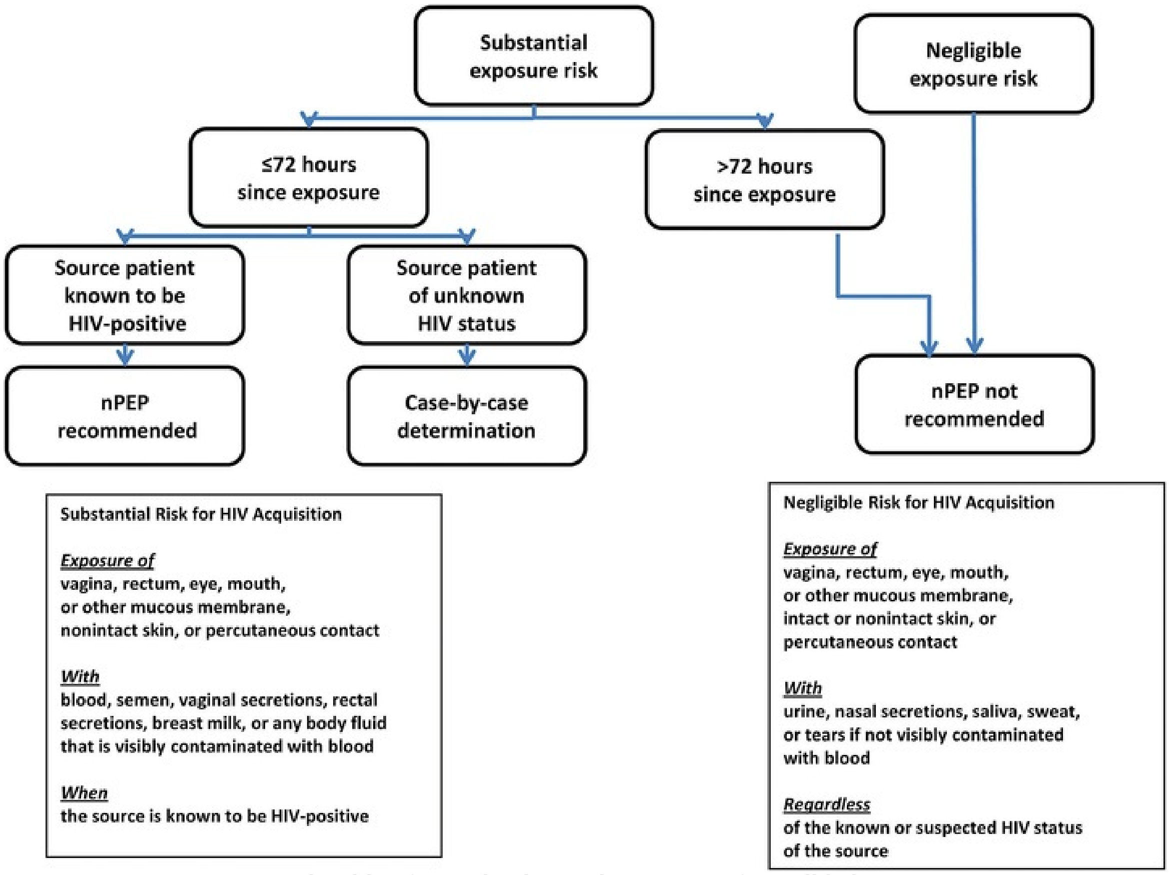
Substantial exposure risk
Negligible exposure risk
≤72 hours since exposure
>72 hours since exposure
Source patient known to be HIV-positive
Source patient of unknown HIV status
nPEP recommended
Case-by-case determination
nPEP not recommended

Substantial Risk for HIV Acquisition

Exposure of
vagina, rectum, eye, mouth,
or other mucous membrane,
nonintact skin, or percutaneous contact

With
blood, semen, vaginal secretions, rectal
secretions, breast milk, or any body fluid
that is visibly contaminated with blood

When
the source is known to be HIV-positive

Negligible Risk for HIV Acquisition

Exposure of
vagina, rectum, eye, mouth,
or other mucous membrane,
intact or nonintact skin, or
percutaneous contact

With
urine, nasal secretions, saliva, sweat,
or tears if not visibly contaminated
with blood

Regardless
of the known or suspected HIV status
of the source

FIG. 145.1 Algorithm for evaluation and treatment of possible human immunodeficiency virus (HIV) infection. nPEP, Nonoccupational postexposure prophylaxis. (From Seńa AC, Hsu KK, Kellogg N, et al: Sexual assault and sexually transmitted infections in adults, adolescents, and children, *Clin Infect Dis* 61(Suppl 8):S859, 2015.)

At the time of presentation, the clinician should address the need for follow-up care, including psychological counseling. Adolescent victims are at increased risk of posttraumatic stress disorder, depression, self-abusive behaviors, suicidal ideation, delinquency, substance abuse, eating disorders, and sexual revictimization. It is important for the adolescent victim and parents to understand the value of timely counseling services to decrease these potential long-term sequelae. Counseling services should be arranged during the initial evaluation, with follow-up arranged with the primary care physician to improve compliance. Counseling services for family members of the victim may improve their ability to provide appropriate support to the adolescent victim. Caution parents not to use the assault as a validation of their parental guidance, as it will only serve to place blame inappropriately on the adolescent victim.

Prevention

Primary prevention may be accomplished through education of preadolescents and adolescents on the issues of rape, healthy relationships, internet dangers, and drug- and alcohol-facilitated rape. Prevention messages should be targeted to both males and females at high schools and colleges. Particular emphasis on prevention efforts during college orientation is highly recommended. High-risk situations that may increase the likelihood of a sexual assault (use of drugs or alcohol) should be discouraged. **Secondary prevention** includes informing adolescents of the benefits of timely medical evaluations when rape has occurred. Individual clinicians should ask adolescents about past experiences of forced and unwanted sexual behaviors and offer help in dealing with those experiences. The importance of prevention cannot be overstated because adolescents are disproportionately affected by rape, and they are particularly vulnerable to long-term consequences.

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CHAPTER 146

Sexually Transmitted Infections

Gale R. Burstein

Age-specific rates of many sexually transmitted infections (**STIs**) are highest among sexually experienced adolescents and young adults, after controlling for sexual activity. Although some STI pathogens present as STI syndromes with a specific constellation of symptoms, most are asymptomatic and only detected by a laboratory test. The approach to prevention and control of these infections lies in education, screening, and early diagnosis and treatment.

Etiology

Any adolescent who has had oral, vaginal, or anal sexual intercourse is at risk for acquiring an STI. Not all adolescents are at equal risk; physical, behavioral, and social factors contribute to the adolescent's higher risk (Table 146.1). Adolescents who initiate sex at a younger age, youth residing in detention facilities, youth attending sexually transmitted disease (STD) clinics, young men having sex with men, and youth who are injection drug users are at higher risk for STIs. Risky behaviors, such as sex with multiple concurrent partners or multiple sequential partners of limited duration, failure to use barrier protection consistently and correctly, and increased biologic susceptibility to infection, also contribute to risk. Although all 50 states and the District of Columbia explicitly allow minors to consent for their own sexual health services, many adolescents encounter multiple obstacles to accessing this care. Adolescents who are victims of sexual assault may not consider themselves “sexually active,” given the context of the encounter, and need reassurance, protection, and appropriate intervention when these circumstances are uncovered (see Chapter 145).

Table 146.1

Circumstances Contributing to Adolescents' Susceptibility to Sexually Transmitted Infections

Physical

Younger age at puberty
Cervical ectopy
Smaller introitus leading to traumatic sex
Asymptomatic nature of sexually transmitted infection
Uncircumcised penis

Behavior Limited by Cognitive Stage of Development

Early adolescence: have not developed ability to think abstractly
Middle adolescence: develop belief of uniqueness and invulnerability

Social Factors

Poverty
Limited access to “adolescent-friendly” healthcare services
Adolescent health-seeking behaviors (forgoing care because of confidentiality concerns or denial of health problem)
Sexual abuse, trafficking, and violence
Homelessness
Drug use
Young adolescent females with older male partners
Young men having sex with men

From Shafii T, Burstein G: An overview of sexually transmitted infections among adolescents, *Adolesc Med Clin* 15:207, 2004.

Epidemiology

STI prevalence varies by age, gender, and race/ethnicity. In the United States, although adolescents and young adults ages 15-24 yr represent 25% of the sexually experienced population, this age-group accounts for almost 50% of all incident STIs each year. Adolescents and young adults <25 yr of age have the highest reported prevalence of **gonorrhea** (see Chapter 219) and **chlamydia** (see Chapter 253); among females and males, rates are highest in the 15-24 yr old age-groups (Fig. 146.1). In 2015, females age 20-24 yr had the highest reported chlamydia rate (3,730 per 100,000 population), followed by females 15-19 yr of age (2,994/100,000). The reported 2015 chlamydia rate for 15-19 yr old females was almost 4 times higher than for 15-19 yr old males. Chlamydia is common among all races and ethnic groups; Blacks, Native American/Alaska Native, and Hispanic females are disproportionately affected. In 2015, non-Hispanic black females 20-24 yr of age had the highest chlamydia rate of any group (6,783), followed by black females 15-19 yr of age (6,340). Data from the 2007–2012 National Health and Nutrition Examination Survey (NHANES) estimated the prevalence of chlamydia among the U.S. population was highest among African Americans (Fig. 146.2).

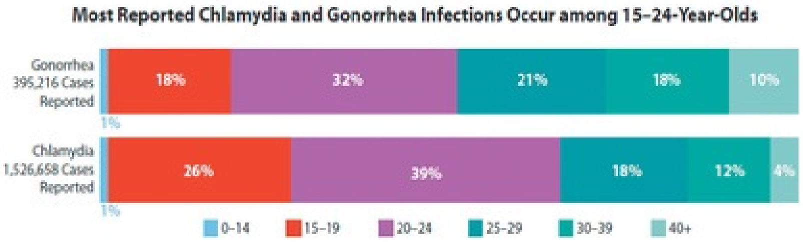

FIG. 146.1 Proportion of reported gonorrhea and chlamydia cases by age, United States, 2015. (Adapted from Centers for Disease Control and Prevention: Reported STDs in the United States. https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/STD-Trends-508.pdf .)

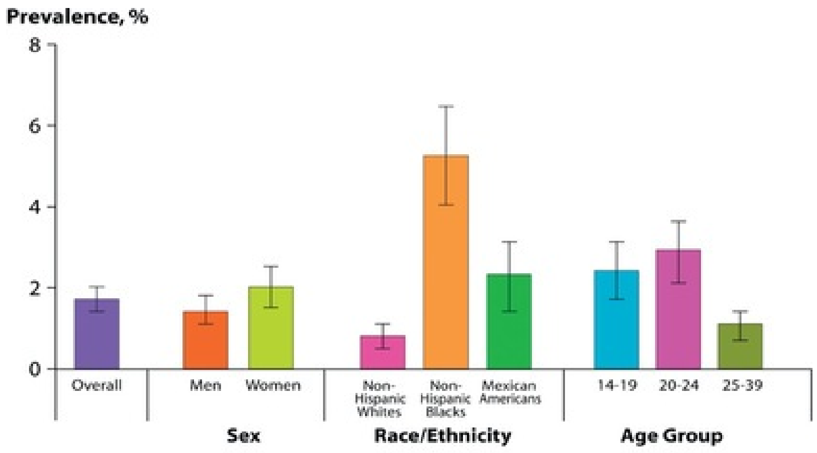

NOTE: Error bars indicate 95% confidence intervals.

FIG. 146.2 Chlamydia prevalence among persons age 14-39 yr by sex, race/ethnicity, and age-group, National Health and Nutrition Examination Survey, 2007–2012. (From Centers for Disease Control and Prevention: Sexually transmitted disease surveillance, 2015. https://www.cdc.gov/std/stats15/slides/chlamydia.pptx .)

Reported rates of other bacterial STIs are also high among adolescents and young adults. In 2015, 20-24 yr old females had the highest (547/100,000) and 20-24 yr old males had the second highest **gonorrhea rates** (539/100,000) compared to any other age/sex group (see Chapter 219). Gonorrhea rates among 15-24 yr old males and females increased between 2014 and 2015. **Syphilis rates** are increasing at an alarming rate, especially among males, accounting for >90% of all primary and secondary syphilis cases. Of those male cases, **men who have sex with men (MSM)** account for 82% of male cases when the gender of the sex partner is known. Males age 20-24 yr have the 2nd highest rate of primary and secondary syphilis among males of any age-group (36/100,000); whereas rates among males 15-19 yr old (8/100,000) are much lower. Female primary and secondary syphilis rates are much lower than male rates (5/100,000 among 20-24 yr olds; 3/100,000 among 15-19 yr olds) (see Chapter 245). **Pelvic inflammatory disease (PID)** rates are highest among females age 15-24 compared with older women.

Adolescents also carry a large burden of viral STIs. U.S. youth are at persistent risk for **HIV infection** (see Chapter 302). In 2015, youth age 13-24 yr accounted for 22% (8,807) of all new HIV diagnoses in the United States, with most (81%) occurring among gay and bisexual males. Of those new infections, 55% (4,881) were among blacks, 22% (1,957) among Hispanic/Latinos, and 17% (1,506) among whites. Only 10% of high school students have been tested for HIV. Among male students who had sexual contact with other males, only 21% have ever been tested for HIV.

Human papillomavirus (HPV) is the most frequently acquired STI in the United States. According to NHANES, prevalence of HPV vaccine types 6, 11, 16, and 18 (**4vHPV**) declined between the prevacccine (2003–2006) and vaccine (2009–2012) eras: from 11.5% to 4.3% among females age 14-19 yr and from 18.5% to 12.1% among females age 20-24 (see Chapter 293).

Herpes simplex virus type 2 **(HSV-2)** is the most prevalent viral STI (see Chapter 279). NHANES data show that among 14-19 yr olds, HSV-2 seroprevalence has remained low (<2%, in 1999–2010 surveys). In addition, according to NHANES, HSV-1 seroprevalence among 14-19 yr olds has significantly decreased, from 39% in 1999–2004 to 30% in 2005–2010, indicating less orolabial infection in this age-group. Studies have also found that genital HSV-1 infections are increasing among young adults. Youth who lack HSV-1 antibodies at sexual debut are more susceptible to acquiring a genital HSV-1 infection and developing symptomatic disease from primary genital HSV-2 infection. Increasing oral sex among adolescents and young adults also has been suggested as a contributing factor in the rise in genital HSV-1 infections.

Pathogenesis

During puberty, increasing levels of estrogen cause the vaginal epithelium to thicken and cornify and the cellular glycogen content to rise, the latter causing the vaginal pH to fall. These changes increase the resistance of the vaginal epithelium to penetration by certain organisms (including *Neisseria gonorrhoeae*) and increase the susceptibility to others (*Candida albicans* and *Trichomonas* ; see Chapter 310). The transformation of the vaginal cells leaves columnar cells on the ectocervix, forming a border of the 2 cell types on the ectocervix, known as the squamocolumnar junction. The appearance is referred to as **ectopy** (Fig. 146.3). With maturation, this tissue involutes. Prior to involution, it represents a unique vulnerability to infection for adolescent females. The association of early sexual debut and younger gynecologic age with increased risk of STIs supports this explanation of the pathogenesis of infection in young adolescents.

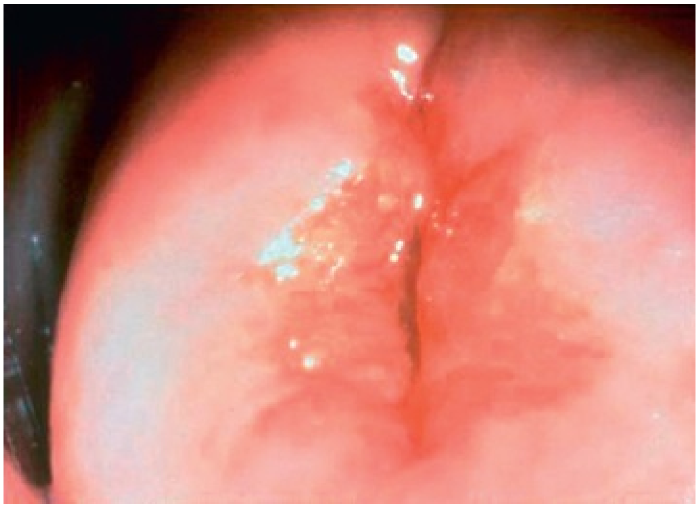

FIG. 146.3 Cervical ectopy. (From Seattle STD/HIV Prevention Training Center, University of Washington, Claire E. Stevens.)

Screening

Early detection and treatment are primary **STI control** strategies. Some of the most common STIs in adolescents, including HPV, HSV, chlamydia, and gonorrhea, are usually asymptomatic and if undetected can be spread inadvertently by the infected host. **Screening** initiatives for chlamydial infections have demonstrated reductions in PID cases by up to 40%. Although federal and professional medical organizations recommend annual chlamydia screening for sexually active females <25 yr old, according to the National Center for Quality Assurance, in 2015 among sexually active 16-20 yr old females, approximately 42% of commercial health maintenance organization (HMO) members and 52% Medicaid HMO members were tested for chlamydia during the previous year. The lack of a dialog about STIs or the provision of STI services at annual preventive service visits to sexually experienced adolescents are missed opportunities for screening and education. Comprehensive, confidential, reproductive health services, including STI screening, should be offered to all sexually experienced adolescents (Table 146.2).

Table 146.2

Routine Laboratory Screening Recommendations for Sexually Transmitted Infections in Sexually Active Adolescents and

Young Adults

Chlamydia Trachomatis and *Neisseria Gonorrhoeae*

- Routine screening for *C. trachomatis* and *N. gonorrhoeae* of all sexually active females aged <25 yr is recommended annually.
- Routinely screen sexually active adolescent and young adult MSM at sites of contact for chlamydia (urethra, rectum) and gonorrhea (urethra, rectum, pharynx) at least annually regardless of condom use. More frequent screening (i.e., at 3-6 mo intervals) is indicated for MSM who have multiple or anonymous partners or who have sex with illicit drug use.
- Consider screening for *C. trachomatis* of sexually active adolescent and young adult males annually who have a history of multiple partners in clinical settings with high prevalence rates, such as jails or juvenile corrections facilities, national job training programs, STD clinics, high school clinics, or adolescent clinics.

Human Immunodeficiency Virus (HIV)

- HIV screening should be discussed and offered to all adolescents at least once by age 16-18 yr and throughout young adulthood in healthcare settings. HIV risk should be assessed annually for >13 yr and offered if HIV risk factors identified.
- Routinely screen sexually active adolescent and young adult MSM at least annually regardless of condom use. More frequent screening (i.e., at 3-6 mo intervals) is indicated for MSM who have multiple or anonymous partners or who have sex with illicit drug use.

Syphilis

- Syphilis screening should be offered to sexually active adolescents reporting risk factors, including MSM.
- Routinely screen sexually active adolescent and young adult MSM at least annually regardless of condom use. More frequent screening (i.e., at 3-6 mo intervals) is indicated for MSM who have multiple or anonymous partners

or who have sex with illicit drug use.

- Providers should consult with their local health department regarding local syphilis prevalence and associated risk factors that are associated with syphilis acquisition.

Hepatitis C Virus (HCV)

- Screening adolescents for HCV who report risk factors, i.e., injection drug use, receipt of an unregulated tattoo, received blood products or organ donation before 1992, received clotting factor concentrates before 1987, long-term hemodialysis.
- Given the high HCV prevalence among young injection drug users, screening should be strongly considered.

MSM, Men who have sex with men; STD, sexually transmitted disease.

From Centers for Disease Control and Prevention. https://www.cdc.gov/std/tg2015/screening-recommendations.htm .

Common Infections and Clinical Manifestations

STI syndromes are generally characterized by the location of the manifestation (vaginitis) or the type of lesion (genital ulcer). Certain constellations of presenting symptoms suggest the inclusion of a possible STI in the differential diagnosis.

Urethritis

Urethritis is an STI syndrome characterized by inflammation of the urethra, usually caused by an infectious etiology. Urethritis may present with urethral discharge, dysuria, urethral irritation, or meatal pruritus. Urgency, frequency of urination, erythema of the urethral meatus, and urethral pain or burning are less common clinical presentations. Approximately 30–50% of males are asymptomatic but may have signs of discharge on diagnosis. On examination, the classic finding is mucoid or purulent discharge from the urethral meatus (Fig. 146.4). If no discharge is evident on exam, providers may attempt to express discharge by applying gentle pressure to the urethra from the base distally to the meatus 3-4 times. *Chlamydia trachomatis* and *N. gonorrhoeae* are the most commonly identified pathogens. *Mycoplasma genitalium* has been associated with urethritis, but data supporting *Ureaplasma urealyticum* have been inconsistent. *Trichomonas vaginalis* can cause nongonococcal urethritis (NGU), but the prevalence varies. HSV-1, HSV-2, and Epstein-Barr virus (EBV) are also potential urethritis pathogens in some cases. Sensitive diagnostic *C. trachomatis* and *N. gonorrhoeae* tests are available for the evaluation of urethritis. However, other pathogens can be considered when NGU is not responsive to treatment, although commercial diagnostic tests are not available for males. Noninfectious causes of urethritis include urethral trauma or foreign body. Unlike in females, urinary tract infections (UTIs) are rare in males who have no genitourinary medical history. In the typical sexually active adolescent male, dysuria and urethral discharge suggest the presence of an STI unless proven otherwise.

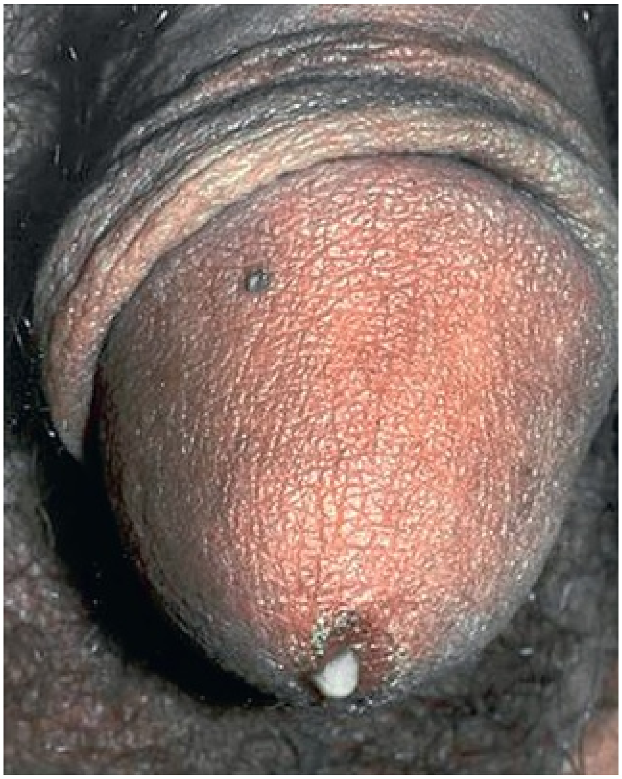

FIG. 146.4 **Gonococcal urethral discharge. (From Seattle STD/HIV Prevention Training Center, University of Washington, Connie Celum and Walter Stamm.)**

Epididymitis

The inflammation of the epididymis in adolescent males is most often associated with an STI, most frequently *C. trachomatis* or *N. gonorrhoeae* . The presentation of unilateral scrotal swelling and tenderness, often accompanied by a hydrocele and palpable swelling of the epididymis, associated with the history of urethral discharge, constitute the presumptive diagnosis of epididymitis. Males who practice insertive anal intercourse are also vulnerable to *Escherichia coli* infection. **Testicular torsion** , a surgical emergency usually presenting with sudden onset of severe testicular pain, should be considered in the differential diagnosis (see Chapter 560). The evaluation for epididymitis should include obtaining evidence of urethral inflammation by physical exam, Gram stain of urethral secretions, urine leukocyte esterase test, or urine microscopy. A *C. trachomatis* and *N. gonorrhoeae* **nucleic acid amplification test (NAAT)** should be performed.

Vaginitis

Vaginitis is a superficial infection of the vaginal mucosa frequently presenting as a vaginal discharge, with or without vulvar involvement (see Chapter 564). **Bacterial vaginosis** , **vulvovaginal candidiasis** , and **trichomoniasis** are the predominant infections associated with vaginal discharge. Bacterial vaginosis is replacement of the normal hydrogen peroxide (H_2O_2)–producing *Lactobacillus* species vaginal flora by an overgrowth of anaerobic microorganisms, as well as *Gardnerella vaginalis, Ureaplasma* , and *Mycoplasma* . Although bacterial vaginosis is not categorized as an STI, sexual activity is associated with increased frequency of vaginosis. Vulvovaginal candidiasis, usually caused by *C. albicans* , can trigger vulvar pruritus, pain, swelling, and redness and dysuria. Findings on vaginal examination include vulvar edema, fissures, excoriations, or thick curdy vaginal discharge. Trichomoniasis is caused by the protozoan *T. vaginalis* . Infected females may present with symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation or may be diagnosed by screening an asymptomatic patient. Cervicitis can sometimes cause a vaginal discharge. Laboratory confirmation is recommended because clinical presentations may vary and patients may be infected with >1 pathogen.

Cervicitis

The inflammatory process in cervicitis involves the deeper structures in the mucous membrane of the cervix uteri. Vaginal discharge can be a manifestation, but cervicitis frequently is asymptomatic, Patients also present with complaints of irregular or postcoital bleeding. Two major diagnostic signs characterize cervicitis: (1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (e.g., swab sign; Fig. 146.5), called **mucopurulent cervicitis** or cervicitis, and (2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os, signifying friability. Cervical changes associated with cervicitis must be distinguished from cervical ectopy in the younger adolescent to avoid the overdiagnosis of inflammation (Fig. 146.6 ; see Fig. 146.3). The pathogens identified most frequently with cervicitis are *C. trachomatis* and *N. gonorrhoeae*, although no pathogen is identified in most cases. HSV is a less common pathogen associated with ulcerative and necrotic lesions on the cervix.

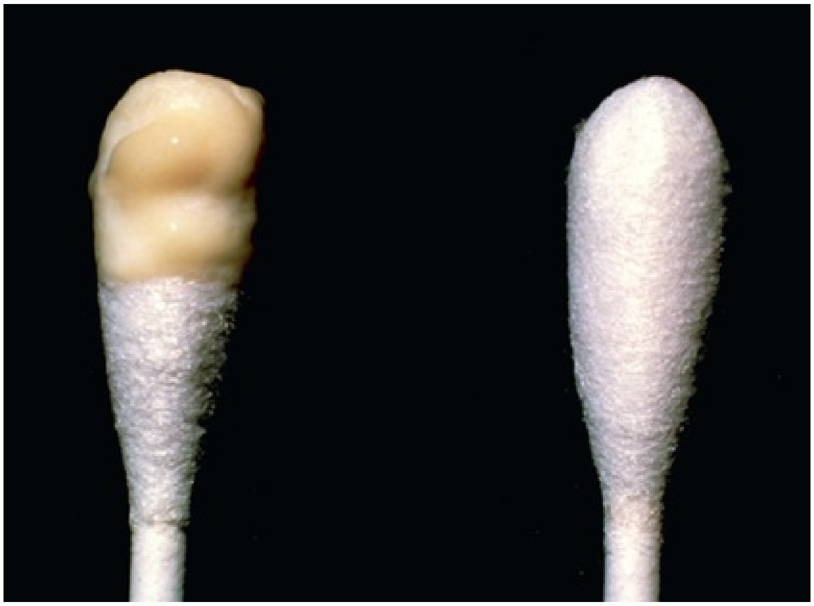

FIG. 146.5 **Mucopurulent cervical discharge positive swab test. (From Seattle STD/HIV Prevention Training Center, University of Washington, Claire E. Stevens and Ronald E. Roddy. http://www2a.cdc.gov/stdtraining/ready-to-use/pid.htm .)**

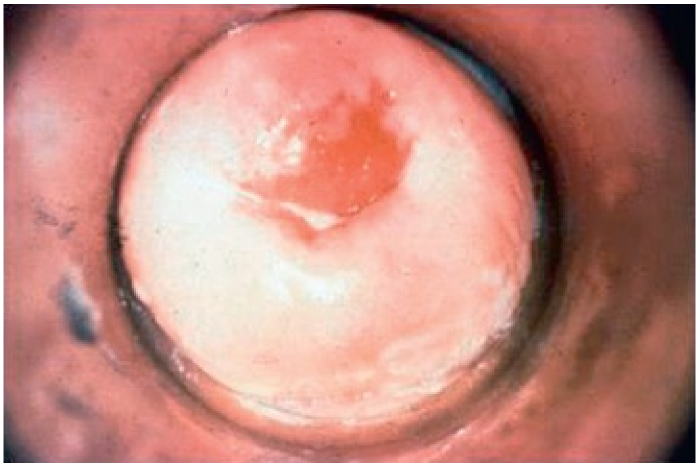

FIG. 146.6 Inflamed cervix caused by gonococcal cervicitis. (From Centers for Disease Control and Prevention: STD clinical slides. http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm .)

Pelvic Inflammatory Disease

PID encompasses a spectrum of inflammatory disorders of the female upper genital tract, including **endometritis** , **salpingitis** , **tuboovarian abscess** , and **pelvic peritonitis** , usually in combination rather than as separate entities. *N. gonorrhoeae* and *C. trachomatis* predominate as the involved pathogenic organisms in younger adolescents (see Chapters 219 and 253), although PID should be approached as multiorganism etiology, including pathogens such as anaerobes, *G. vaginalis* , *Haemophilus influenzae* , enteric gram-negative rods, and *Streptococcus agalactiae.* In addition, cytomegalovirus, *Mycoplasma hominis* , *Ureaplasma urealyticum* , and *M. genitalium* may be associated with PID. PID (tuboovarian abscess) has rarely been reported in virgins and is usually caused by *E. coli* and associated in some patients with obesity and possible pooling of urine in the vagina.

PID is difficult to diagnose because of the wide variation in the symptoms and signs. Many females with PID have subtle or mild symptoms, resulting in many unrecognized cases. Healthcare providers should consider the possibility of PID in young, sexually active females presenting with vaginal discharge or abdominal pain.

The clinical diagnosis of PID is based on the presence of at least 1 of the minimal criteria, either cervical motion tenderness, uterine tenderness, or adnexal tenderness, to increase the diagnostic sensitivity and reduce the likelihood of missed or delayed diagnosis. Providers should also consider that adolescents are the population in whom PID is typically diagnosed and thus should have a low threshold for initiating empirical treatment. In addition, the majority of females with PID have either mucopurulent cervical discharge or evidence of white blood cells (WBCs) on a microscopic evaluation of a vaginal fluid–saline preparation. If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be investigated. Specific, but not always practical, criteria for PID include evidence of endometritis on biopsy, transvaginal sonography or MRI evidence of thickened, fluid-filled tubes, or Doppler evidence of tubal hyperemia or laparoscopic evidence of PID.

Genital Ulcer Syndromes

An **ulcerative lesion** in a mucosal area exposed to sexual contact is the unifying characteristic of infections associated with these syndromes. These lesions are most frequently seen on the penis and vulva but also occur on oral and rectal mucosa, depending on the adolescent's sexual practices. HSV and *Treponema pallidum* (syphilis) are the most common organisms associated with genital ulcer syndromes.

Genital herpes , the most common ulcerative STI among adolescents, is a chronic, lifelong viral infection. Two sexually transmitted HSV types have been identified, HSV-1 and HSV-2. The majority of cases of recurrent genital herpes are caused by HSV-2. However, among young women and MSM, an increasing proportion of anogenital herpes has been HSV-1. Most HSV-2–infected persons are unaware of their diagnosis because they experience mild or unrecognized infections but continue to shed virus intermittently in the genital tract. Therefore, most genital herpes infections are transmitted by asymptomatic persons who are unaware of their infection.

Although the initial herpetic lesion is a vesicle, by the time the patient presents clinically, the vesicle most often has ruptured spontaneously, leaving a shallow, painful ulcer (Fig. 146.7*A*), although recurrences are generally less intense and painful (Fig. 146.7*B*). Up to 50% of first genital herpes episodes are caused by HSV-1, but recurrences and subclinical shedding are much more frequent for genital HSV-2 infection.

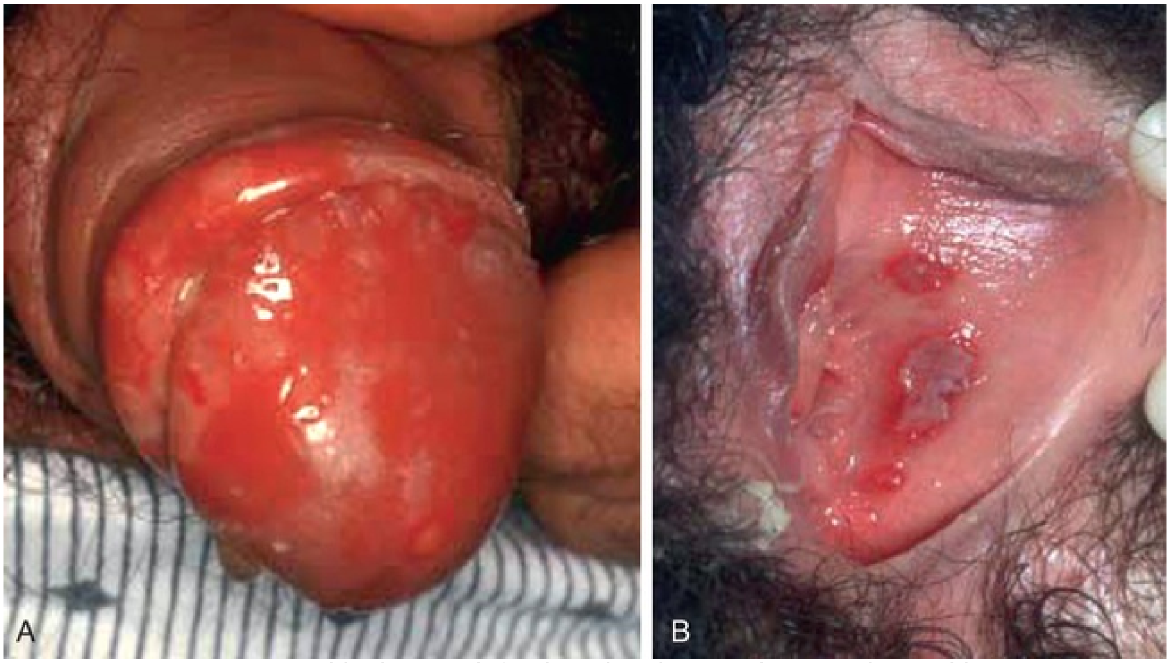

FIG. 146.7 **A,** Initial herpes infection showing multiple erosions with polycyclic outlines surrounded by an erythematous halo and associated with intense pain. **B,** Erosions surrounded by an erythematous halo. Clinical signs and symptoms of recurrences are usually less intense than those of initial infection. (From Martín JM, Villalón G, Jordá E: Update on treatment of genital herpes, *Actas Dermosifiliogr* 100:22–32, 2009, Figs 1 and 2.)

Syphilis is a less common cause of genital ulcers in adolescents than in adults. **Lymphogranuloma venereum** caused by *C. trachomatis* serovars L1-L3 is uncommon, although outbreaks do occur in MSM. In these circumstances, proctitis or proctocolitis is the usual manifestation. HIV is often present in affected men. Unusual infectious causes of genital, anal, or perianal ulcers in the United States and other industrialized countries include chancroid and donovanosis.

Table 146.3 presents the clinical characteristics differentiating the lesions of the most common infections associated with genital ulcers, along with the required laboratory diagnosis to identify the causative agent accurately. The differential diagnosis includes Behçet disease (see Chapter 186), Crohn disease (Chapter 362), aphthous ulceration, and **acute genital ulcers** caused by cytomegalovirus (Chapter 282) or Epstein-Barr virus (Chapter 281). Acute genital ulcers often follow a flu or mononucleosis-like illness in an immunocompetent female and is unrelated to sexual activity. The lesions are 0.5-2.5 cm in size, bilateral, symmetric, multiple, painful, and necrotic, and are associated with inguinal lymphadenopathy. This primary infection is also associated with fever and malaise. The diagnosis may require Epstein-Barr virus titers, or polymerase chain reaction (PCR) testing. Treatment is supportive care including pain management.

Table 146.3

Signs, Symptoms, and Presumptive and Definitive Diagnoses of Genital Ulcers

SIGNS/SYMPTOMS	HERPES SIMPLEX VIRUS	SYPHILIS (PRIMARY)	CHANCROID
Ulcers	Vesicles rupture to form shallow ulcers	Ulcer with well-demarcated indurated borders and a clean base (chancre)	Unindurated and undermined borders and a purulent base
Painful	Painful	Painless*	Painful
Number of lesions	Usually multiple	Usually single	Multiple
Inguinal lymphadenopathy	First-time infections may cause constitutional symptoms and lymphadenopathy.	Usually mild and minimally tender	Unilateral or bilateral painful adenopathy in >50% Inguinal bubo formation and rupture may occur.
Clinical suspicion	Typical lesions; positive HSV-2 type-specific serology test	Early syphilis: typical chancre plus reactive nontreponemal test (RPR, VDRL) and no history of syphilis, or 4-fold increase in quantitative nontreponemal test in person with history of syphilis; positive treponemal EIA with reactive nontreponemal test (RPR, VDRL) and no prior history of syphilis treatment	Exclusion of other causes of ulcers in the presence of (a) typical ulcers and lymphadenopathy, (b) typical Gram stain, and (c) history of contact with high-risk individual (prostitute) or living in an endemic area
Definitive diagnosis	Detection of HSV by culture or PCR from ulcer scraping or aspiration of vesicle fluid	Identification of *Treponema pallidum* from a chancre or lymph node aspirate on dark-field microscopy	Detection of *Haemophilus ducreyi* by culture

* Primary syphilitic ulcers may be painful if they become co-infected with bacteria or 1 of the other organisms responsible for genital ulcers.

DFA, Direct fluorescent antibody; EIA, enzyme immunoassay; HSV, herpes simplex virus; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories.

Data from Centers for Disease Control and Prevention: Sexually transmitted diseases: treatment guidelines, *MMWR* 64(RR-3), 2015. https://www.cdc.gov/std/tg2015/default.htm .

Genital Lesions and Ectoparasites

Lesions that present as outgrowths on the surface of the epithelium and other limited epidermal lesions are included under this categorization of syndromes. HPV can cause genital warts and genital-cervical abnormalities that can lead to cancer (see Chapter 293). **Genital HPV** types are classified according to their association with cervical cancer. Infections with low-risk types, such as **HPV types 6 and 11** , can cause benign or low-grade changes in cells of the cervix, genital warts, and recurrent respiratory papillomatosis. High-risk HPV types can cause cervical, anal, vulvar, vaginal, and head and neck cancers. **High-risk HPV types 16 and 18** are detected in approximately 70% of **cervical cancers** . Persistent infection increases the risk of cervical cancer. **Molluscum contagiosum** and **condyloma latum** associated with secondary syphilis complete the classification of genital lesion syndromes.

As a result of the close physical contact during sexual contact, common ectoparasitic infestations of the pubic area occur as **pediculosis pubis** or the papular lesions of **scabies** (see Chapter 688).

HIV Disease and Hepatitis B

HIV and hepatitis B virus (HBV) present as asymptomatic, unexpected occurrences in most infected adolescents. High vaccination coverage rates among infants and adolescents have resulted in substantial declines in acute HBV incidence among U.S.-born adolescents. Risk factors identified in the history or routine screening during prenatal care are much more likely to result in suspicion of infection, leading to the appropriate laboratory screening, than are clinical manifestations in this age-group (see Chapters 302 and 385).

Diagnosis

Most often, adolescents infected with viral and bacterial STI pathogens do not report symptoms suggestive of infection. With the use of very sensitive, noninvasive chlamydia and gonorrhea NAAT, providers are finding that most genital infections in females as well as many males are asymptomatic. A thorough sexual history is key to identifying adolescents who should be screened for STIs and for identifying those who require a laboratory diagnostic evaluation for an STI syndrome.

When eliciting a sexual health history, discussions should be appropriate for the patient's developmental level. In addition to questions regarding vaginal or urethral discharge, genital lesions, and lower abdominal pain among females, one should ask about prior treatment of any STI symptoms, including self-treatment using nonprescription medications. **Dyspareunia** is a consistent symptom in adolescents with **PID** . Providers must ask about oral or anal sexual activity to determine sites for specimen collection.

Urethritis should be objectively documented by evidence of inflammation or infectious etiology. Patient complaint without objective clinical or laboratory evidence does not fulfill diagnostic criteria. Inflammation can be documented by (a) observing urethral mucopurulent discharge, (b) ≥2 WBCs per high-power field on microscopic examination of Gram stain urethral secretions, (c) urine microscopic findings of ≥10 WBCs per high-power field of first-void urine specimen, or (d) a positive urine leukocyte esterase test of a first-void specimen. Laboratory evaluation is essential to identify the involved pathogens to determine treatment, partner notification, and disease control. *C. trachomatis* and *N. gonorrhoeae* NAATs of a urine specimen are recommended. The presence of gram-negative intracellular diplococci on microscopy obtained from a male urethral specimen confirms the diagnosis of gonococcal urethritis.

An essential component of the diagnostic evaluation of vaginal, cervical, or urethral discharge is a chlamydia and gonorrhea NAAT. NAATs are the most sensitive chlamydia and gonorrhea tests available and are licensed for use with urine, urethral, vaginal, and cervical specimens. Many of the chlamydia NAATs are approved by the U.S. Food and Drug Administration (FDA) to test patient-collected vaginal swabs in the clinical setting and liquid cytology specimens. Female vaginal swab specimens and male first-void urine are considered the optimal specimen types. Female urine remains an acceptable chlamydia and gonorrhea NAAT specimen, but may have slightly reduced performance when compared with cervical or vaginal swab specimens. Urine is the recommended specimen for male urethral infection. Gonorrhea and chlamydia NAATs perform well on rectal and oropharyngeal specimens and can be performed by clinical laboratories that have completed the appropriate verification studies to obtain Clinical Laboratory Improvement Amendments (CLIA) approval, which includes most clinical laboratories.

Evaluation of adolescent females with **vaginitis** includes laboratory data. Traditionally, the cause of vaginal symptoms was determined by pH and microscopic examination of the discharge. However, CLIA-waived point-of-care vaginitis tests are available. Using pH paper, an elevated pH (i.e., >4.5) is common with bacterial vaginosis or trichomoniasis. Because pH testing is not highly specific, discharge should be further examined. For microscopic exam, a slide can be made with the discharge diluted in 1-2 drops of 0.9% normal saline solution and another slide with discharge diluted in 10% potassium hydroxide (KOH) solution. Examining the saline specimen slide under a microscope may reveal motile or dead *T. vaginalis* or clue cells (epithelial cells with borders obscured by small bacteria), which are characteristic of **bacterial vaginosis** . WBCs without evidence of trichomonads or yeast are usually suggestive of cervicitis. The yeast or pseudohyphae of ***Candida*** species are more easily identified in the KOH specimen (Fig. 146.8). The sensitivity of microscopy is approximately 50% and requires immediate evaluation of the slide for optimal results. Therefore, lack of findings does not eliminate the possibility of infection. More sensitive point-of-care vaginitis tests include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), an immunochromatographic capillary flow dipstick technology with reported 83% sensitivity. The OSOM BVBLUE Test (Sekisui) detects elevated vaginal fluid sialidase activity, an enzyme produced by bacterial pathogens associated with bacterial vaginosis, including *Gardnerella* , *Bacteroides* , *Prevotella*, and *Mobiluncus* , and has a reported 90% sensitivity. Both tests are CLIA waived, with results available in 10 min.

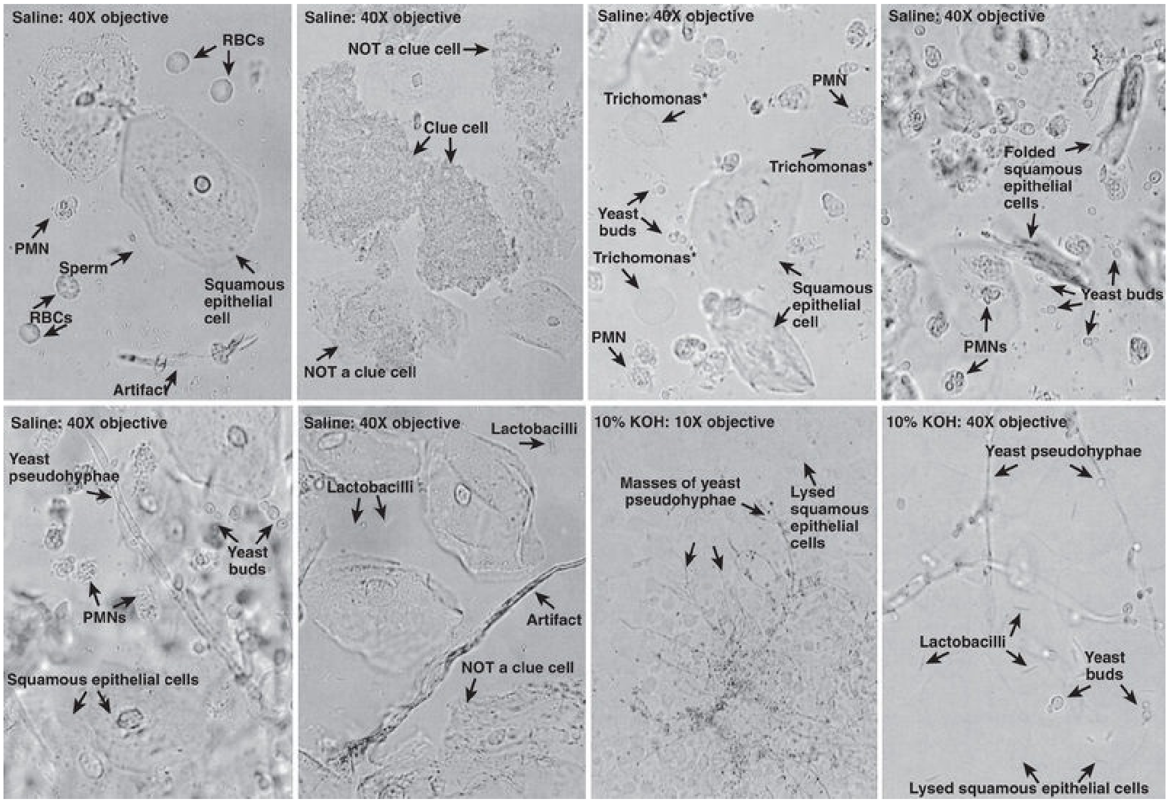
Saline: 40X objective
RBCs
PMN
Sperm
Squamous epithelial cell
RBCs
Artifact
Saline: 40X objective
NOT a clue cell
Clue cell
NOT a clue cell
Saline: 40X objective
Trichomonas*
PMN
Trichomonas*
Yeast buds
Trichomonas*
Squamous epithelial cell
PMN
Saline: 40X objective
Folded squamous epithelial cells
Yeast buds
PMNs
Saline: 40X objective
Yeast pseudohyphae
Yeast buds
PMNs
Squamous epithelial cells
Saline: 40X objective
Lactobacilli
Lactobacilli
Artifact
NOT a clue cell
10% KOH: 10X objective
Masses of yeast pseudohyphae
Lysed squamous epithelial cells
10% KOH: 40X objective
Yeast pseudohyphae
Lactobacilli
Yeast buds
Lysed squamous epithelial cells

FIG. 146.8 Common normal and abnormal microscopic findings during examination of vaginal fluid. KOH, Potassium hydroxide solution; PMN, polymorphonuclear leukocyte; RBCs, red blood cells. (From *Adolescent medicine: state of the art reviews,* vol 14, no 2, Philadelphia, 2003, Hanley & Belfus, pp 350–351.)

Clinical laboratory–based vaginitis tests are also available. The Affirm VPIII (Becton Dickenson, San Jose, CA) is a moderate-complexity nucleic acid probe test that evaluates for *T. vaginalis* , *G. vaginalis* , and *C. albicans* and has a sensitivity of 63% and specificity >99.9%, with results available in 45 min. Some gonorrhea and chlamydia NAATs also offer an assay for *T. vaginalis* testing of female specimens tested for *N. gonorrhoeae* and *C. trachomatis* , considered the gold standard for *Trichomonas* testing.

Objective signs of vulvar inflammation in the absence of vaginal pathogens, along with a minimal amount of discharge, suggest the possibility of mechanical, chemical, allergic, or other noninfectious irritation of the vulva (Table 146.4).

Table 146.4

Pathologic Vaginal Discharge

INFECTIVE DISCHARGE	OTHER REASONS FOR DISCHARGE

COMMON CAUSES	**COMMON CAUSES**
Organisms	Retained tampon or condom
Candida albicans	Chemical irritation
Trichomonas vaginalis	Allergic responses
Chlamydia trachomatis	Ectropion
Neisseria gonorrhoeae	Endocervical polyp
Mycoplasma genitalium	Intrauterine device
Conditions	Atrophic changes
Bacterial vaginosis	**LESS COMMON CAUSES**
Acute pelvic inflammatory disease	Physical trauma
Postoperative pelvic infection	Vault granulation tissue
Postabortal sepsis	Vesicovaginal fistula
Puerperal sepsis	Rectovaginal fistula
LESS COMMON CAUSES	Neoplasia
Ureaplasma urealyticum	Cervicitis
Syphilis	
Escherichia coli	

From Mitchell H: Vaginal discharge—causes, diagnosis, and treatment, *BMJ* 328:1306–1308, 2004.

The **definitive diagnosis of PID** is difficult based on clinical findings alone. Clinical diagnosis is imprecise, and no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Clinical criteria have a positive predictive value of only 65–90% compared with laparoscopy. Although healthcare providers should maintain a low threshold for the diagnosis of PID, additional criteria to enhance specificity of diagnosis, such as transvaginal ultrasonography, can be considered (Table 146.5).

Table 146.5

Evaluation for Pelvic Inflammatory Disease (PID)

2015 CDC Diagnostic Criteria

Minimal Criteria

- Cervical motion tenderness

or

- Uterine tenderness

or

- Adnexal tenderness

Additional Criteria to Enhance Specificity of the Minimal Criteria

- Oral temperature >38.3°C (101°F)
- Abnormal cervical or vaginal mucopurulent discharge*
- Presence of abundant numbers of WBCs on saline microscopy of vaginal secretions*
- Elevated ESR or C-reactive protein
- Laboratory documentation of cervical *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection

Most Specific Criteria to Enhance the Specificity of the Minimal Criteria

- Transvaginal sonography or MRI techniques showing thickened, fluid-filled tubes, with or without free pelvic fluid or tuboovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)
- Endometrial biopsy with histopathologic evidence of endometritis
- Laparoscopic abnormalities consistent with PID

Differential Diagnosis (Partial List)

- Gastrointestinal: appendicitis, constipation, diverticulitis, gastroenteritis, inflammatory bowel disease, irritable bowel syndrome
- Gynecologic: ovarian cyst (intact, ruptured, or torsed), endometriosis, dysmenorrhea, ectopic pregnancy, mittelschmerz, ruptured follicle, septic or threatened abortion, tuboovarian abscess
- Urinary tract: cystitis, pyelonephritis, urethritis, nephrolithiasis

ESR, Erythrocyte sedimentation rate; WBCs, white blood cells.

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* If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be investigated.

Adapted from Centers for Disease Control and Prevention (CDC). https://www.cdc.gov/std/tg2015/screening-recommendations.htm .

Cell culture and polymerase chain reaction (PCR) are the preferred **HSV tests** . Viral culture sensitivity is low, and intermittent viral shedding causes false-negative results. NAATs, including PCR assays for HSV DNA, are more sensitive and increasingly available for diagnosing genital HSV. The Tzanck test is insensitive and nonspecific and should not be considered reliable.

Accurate type-specific **HSV serologic assays** are based on the HSV-specific glycoproteins G2 (HSV-2) and G1 (HSV-1). Both laboratory-based point-of-care tests are available. Because almost all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibody implies anogenital infection. The presence of HSV-1 antibody alone is more difficult to interpret because of the frequency of oral HSV infection acquired during childhood. Type-specific HSV serologic assays might be useful in the following scenarios: (1) recurrent genital symptoms or atypical symptoms with negative HSV cultures; (2) a clinical diagnosis of genital herpes without laboratory confirmation; and (3) a patient with a partner with genital herpes, especially if considering suppressive antiviral therapy to prevent transmission.

For **syphilis testing** , nontreponemal tests, such as the rapid plasma reagin (RPR) or Venereal Disease Research Laboratories (VDRL), and treponemal testing, such as fluorescent treponemal antibody absorbed tests, the *T. pallidum* passive particle agglutination (TP-PA) assay, and various enzyme and chemiluminescence immunoassays (EIA/CIA), are recommended. However, many clinical laboratories have adopted a *reverse sequence* of screening in which a treponemal EIA/CIA is performed first, followed by testing of reactive sera with a nontreponemal test (e.g., RPR). A positive treponemal EIA or CIA test can identify both *previously treated and untreated or incompletely treated syphilis* . False-positive results can occur, particularly among populations with low syphilis prevalence. Persons with a positive treponemal screening test should have a standard nontreponemal test with titer (RPR or VDRL) to guide patient management decisions. If EIA/CIA and RPR/VDRL results are discordant, the laboratory should perform a different treponemal test to confirm the results of the initial test. Patients with discordant serologic results by EIA/CIA and RPR/VDRL testing whose sera are reactive by TP-PA testing are considered to have past or present syphilis; if sera is TP-PA nonreactive, syphilis is unlikely (Fig. 146.9).

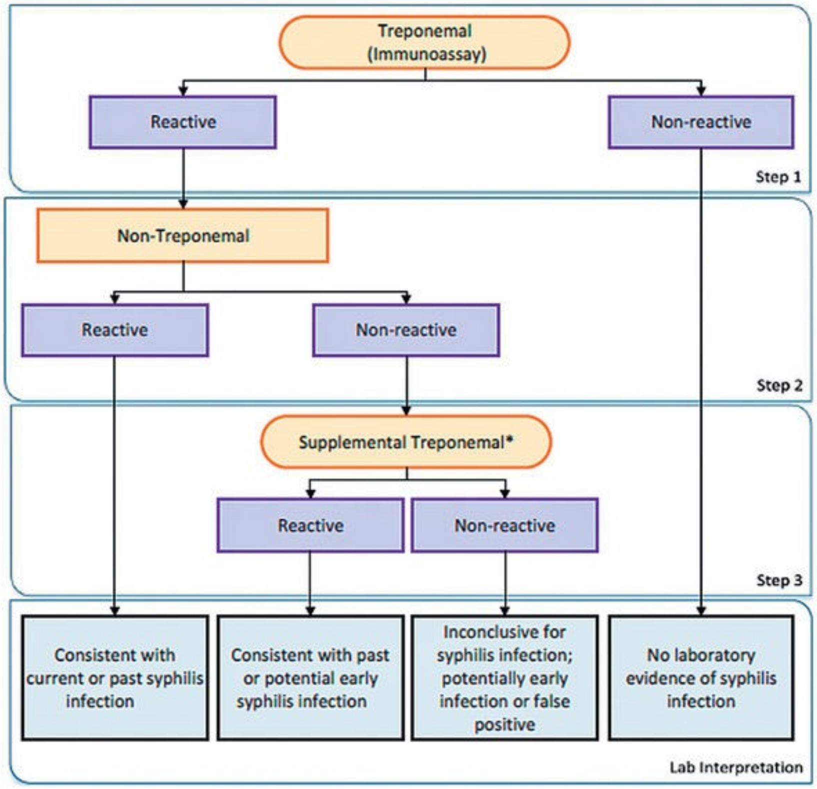
Treponemal (Immunoassay)
Reactive
Non-reactive
Step 1
Non-Treponemal
Reactive
Non-reactive
Step 2
Supplemental Treponemal*
Reactive
Non-reactive
Step 3
Consistent with current or past syphilis infection
Consistent with past or potential early syphilis infection
Inconclusive for syphilis infection; potentially early infection or false positive
No laboratory evidence of syphilis infection
Lab Interpretation

**The supplemental treponemal test should utilize a unique platform and or antigen, different than the first treponemal test.*

FIG. 146.9 Centers for Disease Control and Prevention (CDC) recommended algorithm for reverse-sequence syphilis screening: treponemal test screening followed by nontreponemal test confirmation. (From Association of Public Health Laboratories: Suggested reporting language for syphilis serology testing, 2015.)

Rapid HIV testing with results available in 10-20 min can be useful when the likelihood of adolescents returning for their results is low. Point-of-care CLIA-waived tests for whole blood fingerstick and oral fluid specimen testing are available. Clinical studies have demonstrated that the rapid HIV test performance is comparable to those of EIAs. Because some reactive test results may be false positive, every reactive rapid test must be confirmed.

Treatment

See Part XVI for chapters on the treatment of specific microorganisms and Tables 146.6 to 146.8 . Treatment regimens using nonprescription products for candidal vaginitis and pediculosis reduce financial and access barriers to rapid treatment for adolescents, but potential risks for inappropriate self-treatment and complications from untreated more serious infections must be considered before using this approach. Minimizing noncompliance with treatment, notifying and treating the sexual partners, addressing prevention and contraceptive issues, offering available vaccines to prevent STIs, and making every effort to preserve fertility are additional physician responsibilities.

Table 146.6

Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Chlamydia trachomatis	Azithromycin 1 g orally once *or* Doxycycline 100 mg orally twice daily for 7 days	**For pregnancy:** Azithromycin 1 g orally once **Alternative regimens:** Erythromycin base 500 mg orally 4 times daily for 7 days *or* Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days *or* Levofloxacin 500 mg orally once daily for 7 days *or* Ofloxacin 300 mg orally twice daily for 7 days
Neisseria gonorrhoeae (cervix, urethra, and rectum)	Ceftriaxone 250 mg IM in a single dose *plus* Azithromycin 1 g orally once	Single-dose injectable cephalosporin regimens (other than ceftriaxone 250 mg IM) that are safe and effective against uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime 500 mg IM, cefoxitin 2 g IM with probenecid 1 g orally, and cefotaxime 500 mg IM *plus* Azithromycin 1 g orally once *Alternative if unable to offer IM:* Cefixime 400 mg orally in a single dose *plus* Azithromycin 1 g orally in a single dose **If patient is allergic to azithromycin:** Doxycycline 100 mg orally twice daily for 7 days may be substituted for azithromycin as the 2nd antimicrobial. **Severe cephalosporin allergy:** Gemifloxacin 320 mg orally *plus* azithromycin 2 g orally in a single dose *or* Gentamicin 240 mg IM *plus* oral azithromycin 2 g orally in a single dose
N. gonorrhoeae (pharynx)	Ceftriaxone 250 mg IM in a single dose *plus* Azithromycin 1 g orally once	**No recommended alternative therapy** Possibly gemifloxacin *plus* azithromycin as above for cervix, urethra, rectum Patients treated with an alternative regimen should return 14 days after treatment for a test of cure using either culture or NAAT.
Treponema pallidum (primary and	Benzathine penicillin G 2.4 million units IM in a	**Penicillin allergy:** Doxycycline 100 mg orally twice daily for 14 days, *or* tetracycline 500 mg orally 4 times daily for

secondary syphilis or early latent syphilis, i.e., infection <12 mo)	single dose	14 days. Limited data suggest ceftriaxone 1-2 g daily either IM or IV for 10-14 days. *or* Azithromycin 2 g orally in a single dose has been effective. but treatment failures have been documented.
T. pallidum (late latent syphilis or syphilis of unknown duration)	Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1 wk intervals	**Penicillin allergy:** Doxycycline 100 mg orally twice daily for 28 days, *or* tetracycline 500 mg orally 4 times daily for 28 days, with close serologic and clinical follow-up
Haemophilus ducreyi (chancroid: genital ulcers, lymphadenopathy)	Azithromycin 1 g orally in a single dose *or* Ceftriaxone 250 mg IM in a single dose *or* Ciprofloxacin 500 mg orally twice daily for 3 days *or* Erythromycin base 500 mg orally 3 times daily for 7 days	
C. trachomatis serovars L1, L2, or L3 (lymphogranuloma venereum)	Doxycycline 100 mg orally twice daily for 21 days	**Alternative:** Erythromycin base 500 mg orally 4 times daily for 21 days *or* Azithromycin 1 g orally once weekly for 3 wk

IM, Intramuscularly; IV, intravenously; NAAT, nucleic acid amplification test.

Adapted for Centers for Disease Control and Prevention: Sexually transmitted diseases: treatment guidelines, *MMWR* 64(RR-3), 2015. https://www.cdc.gov/std/tg2015/default.htm .

Table 146.7

Management Guidelines for Uncomplicated Miscellaneous Sexually Transmitted Infections in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Trichomonas vaginalis	Metronidazole 2 g orally in a single dose *or* Tinidazole 2 g orally in a single dose	Metronidazole 500 mg orally twice daily for 7 days
Phthirus pubis (pubic lice)	Permethrin 1% cream rinse applied to affected areas and washed off after 10 min *or* Pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 min	Malathion 0.5% lotion applied for 8-12 hr and washed off *or* Ivermectin 250 µg/kg orally, repeat in 2 wk

	Launder clothing and bedding	
Sarcoptes scabiei (scabies)	Permethrin 5% cream applied to all areas from the neck down, washed off after 8-14 hr or Ivermectin 200 µg/kg orally, repeated in 2 wk Launder clothing and bedding	Lindane (1%) 1 oz of lotion or 30 g of cream in thin layer to all areas of body from neck down; wash off in 8 hr

Adapted from Centers for Disease Control and Prevention: Sexually transmitted diseases: treatment guidelines, *MMWR* 64(RR-3), 2015. https://www.cdc.gov/std/tg2015/default.htm .

Table 146.8

Management Guidelines for Uncomplicated Genital Warts and Genital Herpes in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
HUMAN PAPILLOMAVIRUS (HPV)		
External anogenital warts (penis, groin, scrotum, vulva, perineum, external anus, and perianus)	**Patient applied:** Imiquimod 3.75% cream self-applied to warts at bedtime nightly for up to 16 wk; wash off after 6-10 hr *or* Imiquimod 3 5% cream self-applied to warts at bedtime 3 times weekly for up to 16 wk; wash off after 6-10 hr *or* Podofilox 0.5% solution or gel self-applied to warts twice daily for 3 consecutive days each wk followed by 4 days of no therapy. May be repeated for up to 4 cycles. *or* Sinecatechins 15% ointment self-applied 3 times daily for up to 16 wk. Do not wash off after use, and avoid genital, anal, and oral sexual contact while ointment is on skin. **Provider-administered:** Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1-2 wk. *or* Surgical removal either by electrocautery, tangential	**Provider administered:** Podophyllin resin 10–25% in a compound tincture of benzoin applied to each wart and then allowed to air-dry; thoroughly wash after off 1-4 hr; can be repeated weekly. Systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hr. Many persons with external anal warts also have intraanal warts and might benefit from inspection of anal canal by digital examination, standard anoscopy, or high-resolution anoscopy.

	excision with scissors or scalpel, or by carbon dioxide (CO_2) laser *or* Trichloroacetic acid (TCA) or bichloracetic acid (BCA) 80–90%; small amount applied only to warts and allowed to dry, when white “frosting” develops; can be repeated weekly.	
Cervical warts	Cryotherapy with liquid nitrogen *or* Surgical removal *or* TCA or BCA 80–90% solution Management should include consultation with a specialist.	
Vaginal warts	Cryotherapy with liquid nitrogen; avoid cryoprobe use. *or* Surgical removal *or* TCA or BCA 80–90%; small amount applied only to warts and allowed to dry, when white “frosting” develops; can be repeated weekly.	
Urethral meatal warts	Cryotherapy with liquid nitrogen *or* Surgical removal	
Intraanal Warts	Cryotherapy with liquid nitrogen *or* Surgical removal *or* TCA or BCA 80-90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white “frosting” develops. Can be repeated weekly	Management of intraanal warts should include consultation with a specialist.
HERPES SIMPLEX VIRUS (HSV; GENITAL HERPES)		
First clinical episode	**Treat for 7-10 days with 1 of the following:** Acyclovir 400 mg orally 3 times daily Acyclovir 200 mg orally 5 times daily	Consider extending treatment if healing is incomplete after 10 days of therapy

	Valacyclovir 1 g orally twice daily Famciclovir 250 mg orally 3 times daily	
Episodic therapy for recurrences	**Treat with 1 of the following:** Acyclovir 400 mg orally 3 times daily for 5 days Acyclovir 800 mg orally twice daily for 5 days Acyclovir 800 mg orally 3 times daily for 2 days Valacyclovir 500 mg orally twice daily for 3 days Valacyclovir 1,000 mg orally once daily for 5 days Famciclovir 125 mg orally twice daily for 5 days Famciclovir 1,000 mg orally twice daily for 1 day Famciclovir 500 mg orally once, then 250 mg twice daily for 2 days	Effective episodic treatment of recurrences requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.
Suppressive therapy to reduce frequency of recurrences	**Treat with 1 of the following:** Acyclovir 400 mg orally twice daily Valacyclovir 500 mg orally once daily[*] or 1 g orally once daily Famciclovir 250 mg orally twice daily	All patients should be counseled regarding suppressive therapy availability, regardless of number of outbreaks per year. Since the frequency of recurrent outbreaks diminishes over time in many patients, providers should periodically discuss the need to continue therapy.

[*] Valacyclovir 500 mg once daily might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per year).

Adapted from Centers for Disease Control and Prevention: Sexually transmitted diseases: treatment guidelines, *MMWR* 64(RR-3), 2015. https://www.cdc.gov/std/tg2015/default.htm .

Chlamydia- and gonorrhea-infected males and females should be retested approximately 3 mo after treatment, regardless of whether they believe that their sex partners were treated, or whenever persons next present for medical care in the 12 mo following initial treatment. Once an infection is diagnosed, partner evaluation, testing, and treatment are recommended for sexual contacts within 60 days of symptoms or diagnosis, or the most recent partner if sexual contact was >60 days, even if the partner is asymptomatic. Abstinence is recommended for at least 7 days after both patient and partner are treated. A test for pregnancy should be performed for all females with suspected PID because the test outcome will affect management. Repeat testing 3 mo after treatment is also recommended for *Trichomonas* infection.

Diagnosis and therapy are often carried out within the context of a **confidential** relationship between the physician and the patient. Therefore, the need to report certain STIs to health department authorities should be clarified at the outset. Health departments are Health Insurance Portability and Affordability Act (HIPAA) exempt and will not violate confidentiality. The health department's role is to ensure that treatment and case finding have been accomplished and that sexual partners have been notified of their STI exposure. **Expedited partner therapy (EPT)** , the clinical practice of treating sex partners of patients diagnosed with chlamydia or gonorrhea, by providing prescriptions or medications to the patient to take to the partner without the healthcare provider first examining the partner, is a strategy to reduce further transmission of infection. In randomized trials, EPT has reduced the rates of persistent or recurrent gonorrhea and chlamydia infection. Serious adverse reactions are rare with recommended chlamydia and gonorrhea treatment regimens, such as doxycycline, azithromycin, and cefixime. Transient gastrointestinal side effects are more common but rarely result in severe morbidity. Most states expressly permit EPT or may allow its practice. Resources for information regarding EPT and state laws are available at the Centers for Disease Control and Prevention website (http://www.cdc.gov/std/ept/).

Prevention

Healthcare providers should integrate **sexuality education** into clinical practice with children from early childhood through adolescence. Providers should counsel adolescents regarding sexual behaviors associated with risk of STI acquisition and should educate using evidence-based prevention strategies, which include a discussion of abstinence and other risk reduction strategies, such as consistent and correct condom use. The U.S. Preventive Services Task Force recommends **high-intensity behavioral counseling** to prevent STIs for all sexually active adolescents. The HPV vaccine (Gardasil 9) is recommended for 11 and 12 yr old males and females as routine immunization. Catch-up vaccination is recommended for females age 13-26 and for males age 13-21 who have not yet received or completed the vaccine series; males age 22 through 26 may be vaccinated.

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CHAPTER 147

Chronic Overlapping Pain Conditions

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In chronic overlapping pain conditions (**COPCs**), several painful symptoms affecting different body systems coexist without clear underlying pathophysiology. Other terms for COPCs include **medically unexplained symptoms** , **functional somatic syndromes** (FSS), and **central sensitivity syndromes** . These disorders are probably highly prevalent; for example, 2 COPCs, irritable bowel syndrome (IBS) and migraine, *each* affect 10–20% of the population. Pediatric COPC studies usually focus on populations with 1 painful condition (headaches) and their psychiatric comorbidities, rather than somatic comorbidities. The overlap of these disorders with psychiatric conditions has led both the public and the medical specialists to dichotomize these disorders artificially into “physical,” by implication, “real” disorders; and “psychological,” by implication, “not real” disorders. This classification ignores the unity of brain and body and hinders progress in understanding these disorders. COPC connotes a nonassumptive neutral position, appropriately attributing no assumed pathophysiology to the disorder, in contrast to other terms, such as “medically unexplained syndrome,” subtly suggesting a psychological process, more strongly implied in the term “functional.”

Prevalence

The prevalence of COPCs is unknown, ranging from 20% to >50% depending on which symptom is being assessed and how much overlap exists across disorders. A large study from 28 countries (about 400,000 participants) found a prevalence of headache of 54%, stomachache 50%, and backache 37%, occurring at least once a month for at least 6 mo. Females had a higher prevalence of having all 3 complaints when compared to males; the prevalence increased with age. These three pain syndromes, headache, stomach-ache and backache, frequently coexist.

IBS and chronic abdominal pain affect 6–20% of children and adolescents. Idiopathic musculoskeletal pain affects about 16% of schoolchildren age 5-16 yr and is often associated with sleep disturbances, headache, abdominal pain, daytime tiredness, and feeling sad (see Chapter 193). Migraines present >6 mo occur in about 8% of the population (children and adolescents <20 yr) (see Chapter 613.1). **Fibromyalgia** is present in 1.2–6% (see Chapter 193.3). The prevalence of chronic disabling fatigue increases during adolescence from about 1.9% at age 13 to 3% at 18 yr (see Chapter 147.1). As with most COPCs, fibromyalgia has many comorbid disorders, such as sleep disturbance, fatigue, headache, sore throat, joint pain, and abdominal pain. The American College of Rheumatology definition of fibromyalgia incorporates some of these comorbid conditions.

Symptom/Disorder Overlap

Diagnostic criteria of many of these disorders overlap with one another, making differentiation between two disorders more of a semantic issue rather than a clinical differentiation. **Chronic fatigue syndrome (CFS)** , clinically the most concerning symptom, shares many of the diagnostic criteria with fibromyalgia. Patients with a single pain condition, such as fibromyalgia, CFS, IBS, multiple chemical sensitivity (MCS), headaches, or temporomandibular joint disorder (TMJD), will typically have another disorder. This overlap of symptoms may reflect a shared pathophysiology, possibly a central nervous system (CNS) dysfunction, as was implied in the prior term “central sensitization syndrome”. A CNS pathophysiology would also explain the “invisibility” of these disorders to usual screening tools that most often target an end organ.

COPCs also harbor many symptoms that are not strictly “pain,” although they may be equally or more disabling. Adolescents seen in a tertiary referral center with a **functional gastrointestinal disorder (FGID)** also manifest dizziness, chronic nausea, chronic fatigue and sleep disturbance, as well as migraines. Up to 50% of adolescents complain of weekly fatigue, and 15%, daily fatigue.

Migraine headaches are frequently associated with anxiety and depression. **Anxiety** also predicts the persistence of migraine headaches. Sleep disturbance and migraine also interact closely. Poor sleep can trigger a migraine or a migraine cluster; migraine headache itself disturbs sleep. Juvenile fibromyalgia is associated with sleep disturbances such as prolonged sleep latency, frequent awakening, less total sleep time, and periodic limb movements. Adult patients with IBS also have sleep disturbances, correlating with anxiety, depression, and stress.

The comorbidities of **hypermobility Ehlers-Danlos** (**hEDS**) and **postural orthostatic tachycardia syndrome (POTS)** have been significant. Patients with hEDS may complain of widespread and sometimes debilitating pain with or after activity, severe fatigue, handwriting difficulties, "cracking" of joints, joint swelling, joint dislocation, subluxation, or back pain. The chronic pain reduces exercise tolerance, with poorer quality of life and an ever-worsening cycle because exercise is a key piece of management. Patients with FGID may also have hEDS, fibromyalgia, chronic pains, and higher somatizations scores than those with organic gastrointestinal (GI) disorders.

Diagnosis of **pediatric POTS** requires an increase in heart rate >40 beats/min in the 1st 10 min of upright tilt test associated with orthostatic symptoms. POTS is also associated with multiple comorbidities, including sleep disruption, chronic pain, Raynaud-like symptoms, GI abnormalities, and less frequently headaches, syncope, and urinary complaints. Patients with both POTS and hEDS usually have more migraines and syncope than those with POTS alone. The prevalence of comorbid disorders in children with COPC is identical whether they have POTS or hEDS.

Psychiatric Comorbidities

Many of these disorders have significant psychiatric comorbidities. Juvenile fibromyalgia is associated with anxiety disorders and major mood disorders. Children with medically unexplained symptoms generally have more anxiety and depression than children with other chronic disorders. Other associations include disruptive behaviors, symptom internalization, fearfulness, greater dependency, hyperactivity, and concern about sickness.

Predisposing Factors

Female gender and older age (adolescence) increase the risk of COPCs. Certain conditions (e.g., headache) are more common in males or have similar prevalence across genders during childhood, but the prevalence in females increases after puberty. Trauma or posttraumatic stress disorder increases psychological comorbidities in juvenile fibromyalgia. Some studies suggest that anxiety predisposes to chronic pain. A population-based study following children from 18 mo to 14 yr of age suggested that maternal psychological distress in early childhood and depressive and pain complaints in preadolescence increase the risk of recurrent abdominal pain at age 14. Postinfectious IBS is an identifiable risk factor for new-onset anxiety, depression, and sleep disruption in adults. Children with recurrent abdominal pain often have parents with abdominal pain. It is unclear if this association is caused by a common environmental/genetic factor or a learned behavior of the child imitating the parent.

Natural History

The natural history of COPC is not well known. Chronic disabling fatigue in the general adolescent population persists 2-3 yr in about 25% of patients, but only 8% of youth affected at age 13 still had the complaints at ages 16 and 18. A meta-analysis suggests that the prognosis of CFS in children is usually good, with a small minority having persistent disabling symptoms. The patient's belief in an underlying physical disorder and the presence of psychiatric comorbidities predicts a poorer outcome.

In a study of children with FGID, the outcome depended on specific variables. Those who perceived their abdominal pain as more threatening, with high levels of pain catastrophization and little capacity to cope with pain because of reduced activity levels, had a poorer outcome. This “high pain dysfunctional profile” subgroup was predominantly female (70%) with a mean age of 12.2 yr. Two thirds of this subgroup still complained of FGID at follow-up, vs about one third of those in the other groups. These groups included a “high pain adaptive profile” group with similar pain levels but better adaptive skills and less catastrophization, predominantly slightly younger (11.8 yr) females, and a “low pain adaptive profile” group, slightly younger (11.1 yr), with equal males and females but less abdominal pain, better coping mechanisms, and less impairment of daily activities. In the high pain dysfunctional profile group, 41% had both FGID and nonabdominal chronic pain at follow-up, vs 11% in the high pain adaptive and 17% in the low pain adaptive group. Another study following children age 4-16.6 yr with IBS demonstrated resolution of symptoms in 58%, usually without medication. The differences between these studies may result from the age of the groups, with better outcome in the younger patients, as well as the number of comorbidities and psychological profile.

Proposed Pathophysiology

There may be dysfunction in the hypothalamic-hypophyseal-adrenal axis, circadian patterns, autonomic responses, some aspects of CNS processing, the inflammatory immune response, and the musculoskeletal system. Vagal tone measured by heart rate variability is decreased in some children with FGID symptoms and in children with COPCs. Alterations in the autonomic nervous system may affect the immune system, as well as circadian patterns. The stress response may increase muscle tone, which in turn leads to body aches and tension headaches. In fibromyalgia the cortisol response is altered, with lower cortisol levels on awakening and throughout the day. **Orthostatic intolerance** from autonomic abnormalities may also contribute to poor concentration from brain hypoperfusion and blood pooling in the lower extremities.

The pathophysiology has been better studied in myalgic encephalomyelitis (ME)/CFS (Chapter 147.1). ME/CFS has been associated with joint hypermobility, orthostatic intolerance, decreased range of motion, and reduced activity. These patients demonstrate excessive glial activation resulting in neuroexcitation, neuroinflammation, and possibly neurodegeneration. These features may contribute to the cognitive issues and fatigue present in this disorder.

Neuroinflammation and other changes in processing may lead to abnormal descending inhibitory pain pathways, resulting in distal pain and “central sensitization.” The malfunction of descending antinociceptive pathways allows pain to spread in the body, associated with increased activity of the nociceptive facilitator pathways. These facilitator pathways are further activated by psychological factors, such as catastrophization, depression, lack of acceptance, and hypervigilance. Other signals such as pressure, sound, heat, and cold are also aberrantly processed, with activation of areas of the brain that are typically activated only by acute pain stimuli, such as the insula, prefrontal cortex, and anterior cingulate cortex, as well as some regions usually not involved in pain processing.

Treatment

As general rules, *chronic pain should never be treated with opioids* , and *cognitive-behavioral therapy (CBT) and a gradually progressive exercise program constitute the cornerstones of treatment*. The complex comorbid nature of COPCs typically requires a multidisciplinary approach. Since neither CBT nor exercise will have any effect in the absence of full patient engagement and understanding, the team must include the family and the patient, a pain psychologist with experience in CBT, a physical therapist, and the primary care physician. Depending on comorbid conditions, rheumatology, neurology, or gastroenterology may have important roles for symptom management and possible alternative diagnosis. Depending on the initial symptomatology, the differential diagnosis should include inflammatory bowel disease, celiac disease, juvenile idiopathic arthritis, systemic lupus erythematosus, dermatomyositis, autoinflammatory disorders, Fabry disease, porphyrias, hereditary sensory-autonomic neuropathies, and Ehlers-Danlos syndrome.

When a thorough evaluation for a structural cause of symptoms is unrevealing, an important next step is patient and family **education** . This should include the common presentation, the expectation that “markers” for these types of disorders would typically be absent, and the presence of solid management tools with high probability of improvement. Families and patients need to receive encouragement to stop seeking a “magic diagnosis and cure” and to begin the path to full recovery. Without this step, critical patient engagement in the treatment will not occur. In our practice, we sometimes call *functional* disorders a problem of “software,” in contrast to *structural* issues that would involve “hardware.” We explain that successful management must change the software, not just mask symptoms. Approaches that accomplish such a goal include CBT, and a rehabilitative program that may require physical therapy, vigorous exercise program with interval training, meditation, and/or yoga. Patients are often deconditioned and may need to start with a very low level of physical activity. In addition, their exercise tolerance may be significantly hampered by an orthostatic intolerance syndrome (e.g., POTS). For these reasons, we frequently recommend starting with a *water aerobics* program, which provides several benefits: (1) very low gravitational force, so the patient can be set up for success, working only on conditioning and not simultaneously fighting an orthostatic challenge; (2) builds both limb and core strength; and (3) gentle on joints for those with arthralgias or a hypermobility syndrome. When water is unavailable, we recommend starting with a recumbent exercise program such as a recumbent stationary bike. In both circumstances, we then slowly introduce upright aerobic activities on land over 2-3 mo. Strength exercises are also useful. A Cochrane Review in adults with painful disorders showed exercise to have minimal side effects, to improve functionality, reduce pain, and improve quality of life. Patients with fibromyalgia who undergo a 3 mo multidisciplinary program with twice-weekly physical therapy and CBT benefited in function and physical activity level, and most importantly continued to exercise regularly at 1 yr follow-up. Pharmacologic interventions have less impact than nonmedical treatments.

When children are missing school or are homebound, it is important to work closely with the school to encourage reentry to school. This may require modifying the school schedule initially, starting with fewer hours at school, and providing extra time for homework on days that the children are not feeling well.

Although medications such as tricyclic antidepressants are often added to the treatment, the improvement with these medications for chronic pain is minimal, and the side effects need to be considered. Nonetheless, **amitriptyline** is often used because it helps in treating headaches and abdominal pain and improves sleep quality, a critical element to manage any chronic pain condition.

147.1

Chronic Fatigue Syndrome

Mark R. Magnusson

Keywords

myalgic encephalomyelitis
ME/CFS
systemic exertion intolerance disease
SEID

postexertion malaise
infectious mononucleosis
neutrally mediated hypotension
postural orthostatic tachycardia syndrome
fibromyalgia
cognitive impairment
cognitive-behavioral therapy
orthostatic intolerance

Chronic fatigue syndrome (**CFS**), also known as **myalgic encephalomyelitis (ME)** , is a complex, diverse, and debilitating illness characterized by chronic or intermittent fatigue accompanied by select symptoms and occurring in children, adolescents, and adults. The combination of fatigue and other symptoms interferes significantly with daily activities and has no identified medical explanation (Fig. 147.1). The fatigue does not require exertion by the patient, nor does rest relieve it. Some consider **postexertion malaise,** or worsening of the fatigue with additional symptoms after mental or physical exertion and lasting >24 hr, to be characteristic of CFS. A definitive causal agent or process has not been identified, although the differential diagnosis includes infectious, inflammatory, metabolic, genetic, and autoimmune diseases. Our understanding of this condition is largely from studies of adults and adolescents, with limited descriptions of chronic fatiguing illnesses in younger children.

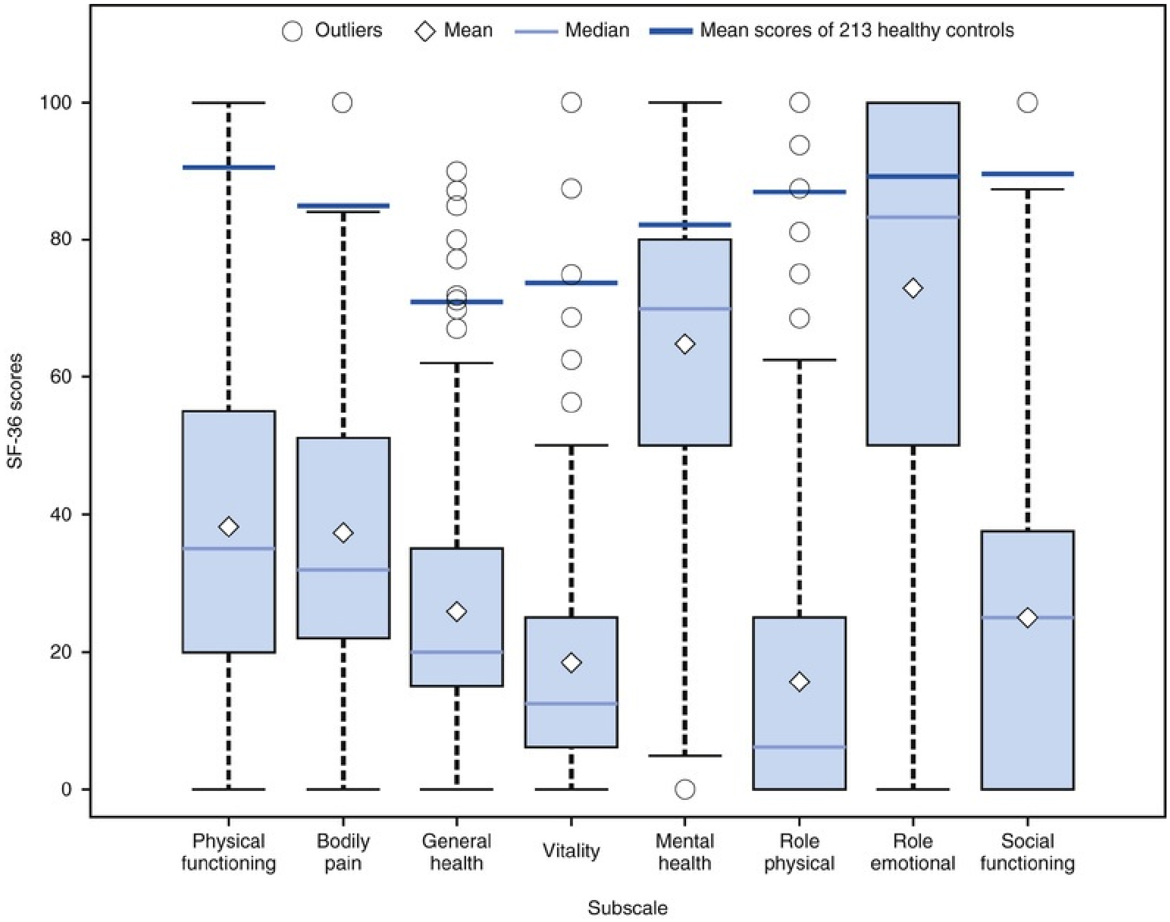

FIG. 147.1 Functional status* of 471 patients enrolled in CDC Multisite Clinical Assessment[†] of ME/CFS[§] —United States, September 2015. *Measured by box plots of scores in the 8 subscales of Short-Form Health Survey (SF-36) scores (25th and 75th percentile at *bottom* and *top* of box). SF-36 scores range from 0-100, with higher scores indicating better functioning. [†] https://www.cdc.gov/cfs/programs/clinical-assessment/index.html . [§] ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) patients show significant impairment, particularly in vitality and physical functioning subscale scores, but with preservation of mental health and emotional role functioning. (From Unger ER, Lin JMS, Brimmer DJ, et al: CDC Grand Rounds: Chronic fatigue syndrome—advancing research and clinical education, *MMWR* 65(50-51):1434–1438, 2016.)

The illness was formally defined in 1988 as *chronic fatigue syndrome* because persistent unexplained fatigue was considered the principal and invariable physical symptom. A variety of other names have been used to describe the illness, including chronic mononucleosis, chronic Epstein-Barr virus (EBV) infection, postinfection syndrome, and immune dysfunction syndrome. Several case definitions have been developed and are in use in both clinical care and research (Table 147.1).

Table 147.1

Overview of Current Case Definitions for Systemic Exertion Intolerance Disease (SEID) and Past Definitions of Chronic Fatigue Syndrome or Myalgic Encephalomyelitis

SYMPTOM	SEID	CFS	ME
Fatigue and impairment of daily function	≥ 6 mo	≥ 6 mo	≥ 6 mo
Sudden onset	Yes	Yes	
Muscle weakness			Yes
Muscle pain		Yes	
Postexertional symptoms	Yes	Yes	Yes
Sleep disturbance	Yes		Yes
Memory or cognitive disturbances	Yes		Yes
Autonomic symptoms			Yes
Sore throat		Yes	
Lymph node involvement		Yes	
Cardiovascular symptoms	Yes		
Headaches		Yes	
Arthralgias		Yes	Yes

CFS, Chronic fatigue syndrome; ME, myalgic encephalomyelitis.

Data from Institute of Medicine: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Redefining an Illness. Washington, DC, National Academies Press 2015; Jason L, Evans M, Porter N, et al: The development of a revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition. Am J Biochem Biotechnol 6:120 135, 2010; Reeves WC, Wagner D, Nisenbaum R, et al: Chronic fatigue syndrome—a clinically empirical approach to its definition and study. BMC Med 3:19, 2005.

The Institute of Medicine (IOM) 2015 recommendations apply to all ages and include a special focus on pediatrics. The IOM suggested new diagnostic criteria and a new name, **systemic exertion intolerance disease (SEID)** , to emphasize the postexertion malaise criterion and better understand the illness (Table 147.2). The most recent expert consensus report (June 2017) from the International Writing Group for Pediatric ME/CFS provides a primer for diagnosis and management.

Table 147.2

Criteria for Diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Patient has each of the following 3 symptoms at least half the time, to at least a moderately severe degree:

- A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for >6 mo and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.
- Postexertional malaise*
- Unrefreshing sleep*

Plus at least 1 of the 2 following manifestations (chronic, severe):

- Cognitive impairment*
- Orthostatic intolerance

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[*] Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

From Institute of Medicine: *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness*, Washington, DC, 2015, National Academies Press.

Epidemiology

Based on worldwide studies, 0.2–2.3% of adolescents or children have CFS. Most epidemiology studies use the 1994 definition. CFS is more prevalent in adolescents than in younger children. The variation in CFS prevalence estimates may result from variations in case definition, study methodology and application, study population composition (specialty vs general practice or general population), and data collection (parent, self-reporting vs clinician evaluation). Gender distribution in children differs from that in adults, with a more equal distribution in children <15 yr old, while remaining 2-3–fold higher in females 15-18 yr old. Few studies have reported the incidence of CFS among children <10 yr old, leading to uncertainty in this group. In adolescents in The Netherlands, the pediatrician-diagnosed incidence of CFS/ME was 0.01%, and in the United Kingdom, 0.5%.

Pathogenesis

Although etiology and pathophysiology of CFS are unknown, some patients and clinicians correlate the onset with a recent episode of a viral illness such as infectious mononucleosis (10–12%) (EBV; see Chapter 281). A pathophysiologic relationship of CFS to infection is suggested because the symptoms and biologic markers elicited by the nonspecific innate host responses to infections in general are present in CFS. CFS-like illness after infectious mononucleosis is not predicted by viremia or altered host response to EBV infection but is associated with the severity of the primary infection. A wide variety of other candidate viral infections have been associated with postinfectious fatigue syndromes, particularly in adolescents and adults. There are ongoing efforts to determine if infections with these or other agents may produce the illness.

Similarities between CFS symptoms and those experienced by patients with autoimmune and other inflammatory disorders suggests primary perturbation of immune function in the pathogenesis of CFS. Hypo- and hypergammaglobulinemia, immunoglobulin subclass deficiencies, elevated levels of circulating immune complexes, altered helper/suppressor lymphocyte ratios, natural killer cell dysfunction, elevated cytokines, and monocyte dysfunction have been reported in adult patients with CFS. These findings have not been consistent among studies. CFS patients as a group differ from healthy controls, but most laboratory values of the immune parameters are not outside the normal range.

Autonomic nervous system (ANS) changes are suggested by the **orthostatic intolerance** (OI) experienced by some patients with CFS. OI syndromes with circulatory dysfunction include **neutrally mediated hypotension** and **postural orthostatic tachycardia syndrome** (POTS) (see Chapter 147) have been observed in some patients with CFS and could contribute to the syndrome. The pathophysiology of these manifestations among adolescents with CFS is unclear, but in postinfectious states could be associated with unreplenished fluid and electrolyte losses associated with acute infection or immune-mediated injury (autoantibodies directed against ANS).

Because the widespread musculoskeletal pain in CFS is similar to **fibromyalgia** (see Chapter 193.3), and because some consider these to be overlapping syndromes, fibromyalgia and CFS may share similarities in pathogenesis. Other hypotheses under investigation for the biologic basis of CFS involve alterations in energy metabolism (e.g., mitochondrion, particularly as related to exercise intolerance and postexertion malaise), alterations in sleep, the stress response, hypothalamic-pituitary axis. Understanding CFS has proved so challenging because it likely represents more than 1 underlying pathophysiology. Current studies and guidelines are attempting to stratify or subgroup patients to address this possibility.

Clinical Manifestations

The dominant symptom expressed by adolescents and adults is a substantial reduction or impairment in the ability to engage in preillness levels of activity, accompanied by fatigue (see Fig. 147.1). In younger children, who often do not spontaneously report symptoms, exertion induces behavioral changes, manifested by a lack of their usual energy and reduced participation in activities. In adolescents, fatigue and postexertion malaise may lead to decreased participation in school, family activities, and social exchange.

Cognitive impairment includes reported difficulties in concentrating, which are common and indicated by reduced participation in school, difficulty keeping up with homework, and drop in grades. Sleep may be impaired, and nonrestorative sleep is common. Other sleep complaints include difficulty falling asleep and staying asleep, whereas diagnosed sleep disorders, including restless legs syndrome, parasomnias, and sleep apnea, are less common. Myalgia and arthralgia may accompany fatigue and altered sleep. Sore throat and cervical lymph node tenderness can occur but may be part of an inciting illness. Adolescents also have increased reports of headache, abdominal pain, nausea, and sensitivity to light and sound with amplified pain.

Patients diagnosed with CFS in primary care practices are more likely to report abrupt onset of their symptoms, often as part of an initial virus-like illness, whereas gradual onset is more common in those identified in population-based studies. School absenteeism is a major social issue. In one study, two thirds of adolescents missed >2 wk over a 6 wk observation period, and one third required home tutoring. Unlike school phobia, inactivity due to CFS persists on the weekends and during holidays the same as it does during the school week.

Although fatigue and accompanying symptoms are subjective, the magnitude of impairment of each component can be measured by questionnaires addressing pain and function or, in the case of suspected orthostatic instability, by recording routine supine and standing heart rate and blood pressure measurement's. Fatigue cannot be dismissed as a minor ailment. It generally manifests as lassitude, profound tiredness, intolerance of exertion with easy fatigability, and general malaise.

Abnormal physical examination findings are conspicuously absent, providing both reassurance and consternation for the patient, family, and physician. The presence of “alarm symptoms” such as weight loss, chest pain with exertion, paresthesia, dry mouth and eyes, fevers, diarrhea, cough, night sweats, and rash is uncommon and warrants consideration of a diagnosis other than CFS.

Diagnosis

There are no pathognomonic signs or diagnostic tests for CFS. The diagnosis is clinically defined based on inclusion and exclusion criteria (Fig. 147.2). The diagnostic criteria are applicable to adults and adolescents >11 yr old because of the current requirement for a self-generated history. Whereas duration of symptoms is 3- 6 mo, depending on age, symptom management should not wait until this criterion is met.

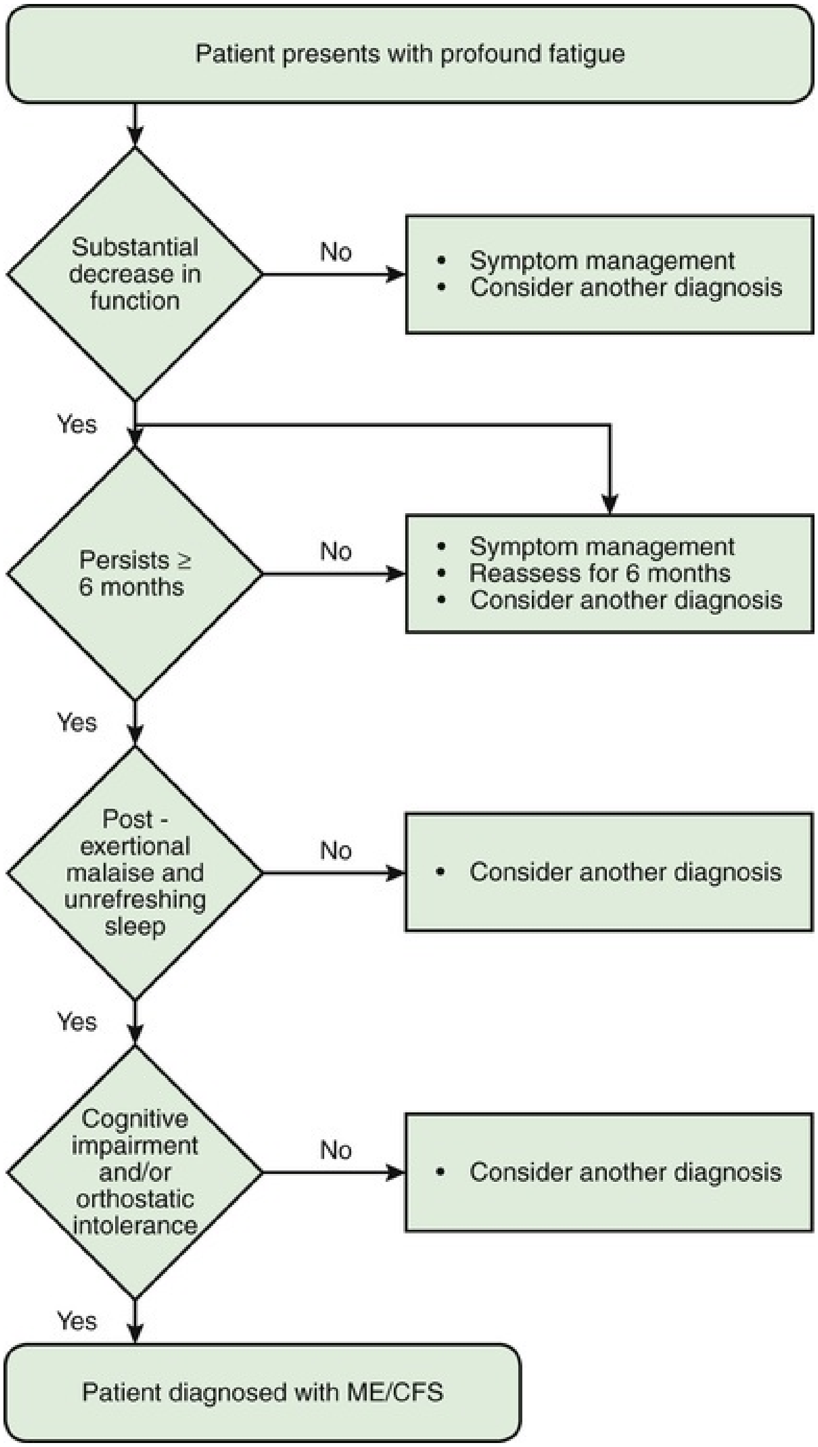
Patient presents with profound fatigue
Substantial decrease in function
No
Symptom management
Consider another diagnosis
Yes
Persists ≥ 6 months
No
Symptom management
Reassess for 6 months
Consider another diagnosis
Yes
Post - exertional malaise and unrefreshing sleep
No
Consider another diagnosis
Yes
Cognitive impairment and/or orthostatic intolerance
No
Consider another diagnosis
Yes
Patient diagnosed with ME/CFS

FIG. 147.2 **Diagnostic algorithm for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). (From Institute of Medicine: *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness,* Washington, DC, 2015, National Academies Press.)**

CFS is difficult to diagnose in children, who may have difficulty describing their symptoms and articulating their concerns. Sole reliance on parental history can be fraught with confusion because parents may also struggle to interpret their children's symptoms and feelings in providing accurate historical information. A combination of child and parent reporting is most effective. It is important to document the child's activity levels and worsening of symptoms after physical or mental endeavors. Changes in participation in hobbies and family or other social activities can help identify the impact of CFS on function.

The diagnosis of CFS can be established only after other medical and psychiatric causes of fatigue and other symptoms, many of which are treatable, have been excluded. These include medical conditions presenting with chronic symptoms, such as hypothyroidism, adrenal insufficiency, respiratory and food allergies, sleep apnea, narcolepsy, substance abuse, posttraumatic stress disorder, adverse drug reactions, and obesity. A previously diagnosed medical condition with incomplete or uncertain resolution that may explain fatigue needs be considered.

Certain illnesses (e.g., fibromyalgia), amplified pain, and depression share similar symptoms with CFS but are not exclusionary diagnoses. These should be considered in the differential diagnosis in select cases. There is concern that CFS might be mistaken for readily identifiable psychiatric disorders such as anxiety and mood disorders, but evidence supports differences in their clinical presentation from CFS. CFS should not be diagnosed in persons with prior diagnosis of major depressive disorder with psychotic or melancholic features, bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementia of any subtype, eating disorder of any type, or alcohol or other substance abuse within 2 yr before the onset of the chronic fatigue or any time thereafter.

Although evaluation of each patient should be individualized, initial laboratory evaluation should be limited to screening laboratory testing sufficient to provide reassurance of the lack of significant medical illness. Further evaluation should be directed primarily toward excluding treatable illnesses that may be suggested by the history, symptoms, signs, or physical exam findings present in specific patients.

Management

Management of CFS is based on relief of the core and most disruptive symptoms in the individual patient. The diagnostic criterion of 6 mo duration of illness should not delay evaluation and symptom management, since these may be initiated as soon as the child or adolescent presents with a CFS-like picture. Problems with sleep can be addressed by encouraging patients to adopt good sleep habits using standard sleep hygiene techniques. It may be beneficial to refer the patient to a sleep medicine specialist for the identification and treatment of sleep disorders and disturbances. Once pain is found not to be related to other specific disease of illness, nonpharmacologic treatment is indicated.

One of the nonpharmacologic approaches to pain management, **cognitive-behavioral therapy** (CBT), may also assist patient in managing and coping with CFS. Through explanation and changes in perception of the illness, CBT may help patients and their families develop coping skills and provide emotional support. Improved methods of coping may allow some improved function while living with the illness. Comorbid psychiatric conditions such as anxiety require appropriate evaluation and intervention. Guided graded-exercise therapy may be beneficial and added to CBT.

While the overall goal is to help patients with CFS tolerate activity, children and adolescents with CFS should limit physical or mental efforts that result in aggravated symptoms. Return to school should be initiated gradually and systematically with the goal return to full-time attendance. Home tutoring, cyberschool, and partial attendance can be interim steps. Parents and clinicians can work with teachers and school administrators to define appropriate expectations for attendance and performance for children with CFS. Because of the crucial importance of learning socialization skills, even brief attendance in school or participation in school activities should be encouraged, remembering that too rapid remobilization usually exacerbates symptoms and should be avoided.

Continued **empathy and support** by the treating physician are crucial in maintaining a physician–parent–patient relationship that is conducive to managing this illness. Careful attention must be directed to family dynamics to identify and resolve family problems or psychopathology that may be contributing to children's perception of their symptoms.

Prognosis

The natural history of CFS is highly variable, and patients and families understand that the symptoms will wax and wane. Children and adolescents with CFS appear to have a more optimistic outcome than adults, typically with an undulating course of gradual improvement over several years. Overall, a good functional outcome has been reported in up to 80% of patients. Poor prognostic factors include gradual onset, increased school absenteeism, lower socioeconomic status, chronic maternal health problems, and untreated comorbid individual and family psychiatric disorders. Favorable prognostic factors include patient control of the rehabilitation program, with continuing support from health professionals and family members, and improvement in orthostatic intolerance.

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PART XIII

Immunology

OUTLINE

Section 1 Evaluation of the Immune System

Section 2 The T-, B-, and NK-Cell Systems

Section 3 The Phagocytic System

Section 4 The Complement System

Section 5 Hematopoietic Stem Cell Transplantation

SECTION 1

Evaluation of the Immune System

OUTLINE

Chapter 148 Evaluation of Suspected Immunodeficiency

CHAPTER 148

Evaluation of Suspected Immunodeficiency

Kathleen E. Sullivan, Rebecca H. Buckley

Primary care physicians must have a high index of suspicion to diagnose immune system defects early enough to institute appropriate treatment before irreversible damage develops. Diagnosis can be difficult because most affected patients do not have abnormal physical features. The most typical manifestation of immunodeficiency in children is *recurrent sinopulmonary infections.* Although infections are common in children in general, an infection exceeding the expected frequency and usually involving multiple sites can suggest immunodeficiency. A single, severe, opportunistic, or unusual infection can also be the presentation of an immunodeficiency (Table 148.1). Increasingly recognized is the co-occurrence of autoimmune disease or inflammatory conditions and recurrent infections. Newborn screening for T-cell lymphopenia has been instituted in most states; this has led to the identification of some infants with immunodeficiency before any clear manifestations but is limited to T-cell deficiencies. Additional clues to immunodeficiency include failure to thrive with or without chronic diarrhea, persistent infections after receiving live vaccines, and chronic oral or cutaneous candidiasis (Tables 148.2 and 148.3).

Table 148.1

Predisposition to Specific Infections in Humans

PATHOGEN	PRESENTATION	AFFECTED GENE/CHROMOSOMAL REGION	COMMENTS
BACTERIA			
Streptococcus pneumoniae	Invasive disease	*IRAK4*, MyD88, *C1QA*, *C1QB*, *C1QC*, C4A^{+} C4B,	Also susceptible to other encapsulated bacteria

		C2, C3	
Neisseria	Invasive disease	C5, C6, C7, C8A, C8B, C8G, C9, properdin	Recurrent disease common
Burkholderia cepacia	Invasive disease not pulmonary colonization	*CYBB, CYBA, NCF1, NCF2*	Also susceptible to staphylococcal and fungal infections
Nocardia	Invasive disease	*CYBB, CYBA, NCF1, NCF2*	Also susceptible to staphylococcal and fungal infections
Mycobacteria	Usually nontuberculous mycobacteria	IL12B, IL12RB1, IKBKG, IFNGR1, IFNGR2, STAT1 (loss of function)	Also susceptible to *Salmonella typhi* infections
VIRUSES			
Herpes simplex virus	Herpes simplex encephalitis	*TRAF3, TRIF, TBK, UNC93B1, TLR3,* STAT1	Age of onset is typically outside the neonatal period.
Epstein-Barr virus	Severe infectious mononucleosis, hemophagocytic syndrome	*SH2DIA, XIAP, ITK, CD27, PRF1, STXBP2, UNC13D, LYST, RAB27A, STX11, AP3B1*	Fulminant infectious mononucleosis, malignant and nonmalignant lymphoproliferative disorders, dysgammaglobulinemia, autoimmunity
Papillomavirus	Warts	*RHOH, EVER1, EVER2, CXCR4, DOCK8, GATA2, STK4, SPINK5*	Warts are often progressive despite therapy.
Global susceptibility to viral infection	Severe, progressive viral infections	All types of severe combined immune deficiency, *IFNAR2*	Presentation depends on virus and infected organ
FUNGI			
Candida	Mucocutaneous candida	*AIRE*, STAT1 (gain of function), *CARD9*, STAT3, IL17F, IL17RC, IL17RA, *ACT1*	*AIRE* deficiency is associated with endocrinopathies, STAT1 (GOF) is associated with autoimmunity
Dermatophytes	Tissue invasion	*CARD9*	Autosomal recessive
Aspergillus	Deep infections	*CYBB, CYBA, NCF1, NCF2*	
Environmental fungi	Deep infections	*CYBB, CYBA, NCF1, NCF2, GATA2,* STAT1 (gain of function), *CD40L*	

Table 148.2

Characteristic Clinical Patterns in Some Primary Immunodeficiencies

FEATURES	DIAGNOSIS
IN NEWBORNS AND YOUNG INFANTS (0-6 mo)	
Hypocalcemia, unusual facies and ears, heart disease	22q11.2 deletion syndrome, DiGeorge anomaly
Delayed umbilical cord detachment, leukocytosis, recurrent infections	Leukocyte adhesion defect
Persistent thrush, failure to thrive, pneumonia, diarrhea	Severe combined immunodeficiency
Bloody stools, draining ears, atopic eczema	Wiskott-Aldrich syndrome
IN INFANTS AND YOUNG CHILDREN (6 mo to 5 yr)	
Recurrent staphylococcal abscesses, staphylococcal pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis	Hyper-IgE syndrome, PGM3 deficiency

Persistent thrush, nail dystrophy, endocrinopathies	Autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasia
Short stature, fine hair, severe varicella	Cartilage hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infection, hemophagocytic syndrome	Chédiak-Higashi syndrome, Griscelli syndrome, Hermansky-Pudlak syndrome

Table 148.3

Clinical Aids to the Diagnosis of Immunodeficiency

Suggestive of B-Cell Defect (Humoral Immunodeficiency)

- Recurrent bacterial infections of the upper and lower respiratory tracts
- Recurrent skin infections, meningitis, osteomyelitis secondary to encapsulated bacteria *(Streptococcus pneumoniae. Haemophilus influenzae. Staphylococcus aureus. Neisseria meningitidis)*
- Paralysis after vaccination with live-attenuated poliovirus
- Reduced levels of immunoglobulins

Suggestive of T-Cell Defect (Combined Immunodeficiency)

- Systemic illness after vaccination with any live virus or bacille Calmette-Guérin (BCG)
- Unusual life-threatening complication after infection with benign viruses (giant cell pneumonia with measles; varicella pneumonia)
- Chronic oral candidiasis after age 6 mo
- Chronic mucocutaneous candidiasis
- Graft-versus-host disease after blood transfusion
- Reduced lymphocyte counts for age
- Low levels of immunoglobulins
- Absence of lymph nodes and tonsils
- Small thymus
- Chronic diarrhea
- Failure to thrive
- Recurrent infections with opportunistic organisms

Suggestive of Macrophage Dysfunction

Disseminated atypical mycobacterial infection, recurrent Salmonella infection
Fatal infection after BCG vaccination

Congenital Syndromes With Immunodeficiency

Ataxia-telangiectasia: ataxia, telangiectasia
Autoimmune polyglandular syndrome: hypofunction of 1 or more endocrine organs, chronic mucocutaneous candidiasis
Cartilage-hair hypoplasia: short-limbed dwarfism, sparse hair, neutropenia
Wiskott-Aldrich syndrome: thrombocytopenia, male gender, eczema
Chédiak–Higashi syndrome: oculocutaneous albinism, nystagmus, recurrent bacterial infections, peripheral neuropathies
DiGeorge syndrome (22q deletion syndrome): unusual facies, heart defect, hypocalcemia

Suggestive of Asplenia

Heterotaxia. complex congenital heart disease, Howell-Jolly bodies on blood smear, sickle cell anemia

From Kliegman RM, Lye PS, Bordini BJ, ET AL, editors: *Nelson pediatric symptom-based diagnosis*, Philadelphia, 2018, Elsevier, p 750.

With >300 distinct primary immunodeficiencies, in order to focus the diagnostic approach and appropriate testing. it is often useful to consider 5 categories: T-cell disorders, B-cell and antibody disorders, complement disorders, phagocytic disorders, and natural killer cell disorders (Table 148.4 and Fig. 148.1).

Table 148.4

Characteristic Features of Primary Immunodeficiency

CHARACTERISTIC	PREDOMINANT T-CELL DEFECT	PREDOMINANT B-CELL DEFECT	GRANULOCYTE DEFECT	CYTOLYTIC DEFECT	COM DEF
Age at onset of	Early onset, usually	Onset after maternal	Early onset most	Childhood onset	Onse

infection	2-6 mo	antibodies diminish, usually after 5-7 mo, later childhood to adulthood	frequently	generally	
Specific pathogens involved	Bacteria: common gram-positive and gram-negative bacteria and mycobacteria	Bacteria: pneumococci, streptococci, staphylococci, *Haemophilus*, *Campylobacter*, *Mycoplasma*	Bacteria: staphylococci, *Serratia*, *Salmonella*, mycobacteria	None usually	Bact enca orga C2, (FP, C3, C8,
	Viruses: CMV, EBV, adenovirus, parainfluenza 3, varicella, enterovirus	Viruses: enterovirus*	None generally	CMV, EBV	None
	Fungi: *Candida* and *Pneumocystis jiroveci*	Fungi and parasites: *Giardia*, Cryptosporidia	Fungi and parasites: *Candida*, *Nocardia*, *Aspergillus*	None generally	None
Affected organs	Extensive mucocutaneous candidiasis, lungs, failure to thrive, protracted diarrhea	Recurrent sinopulmonary infections, chronic gastrointestinal symptoms, malabsorption, arthritis, enteroviral meningoencephalitis*	Skin: abscesses, impetigo, cellulitis Lymph nodes: suppurative adenitis Oral cavity: gingivitis, mouth ulcers Internal organs: abscesses, osteomyelitis	Hemophagocytic syndrome can affect any organ.	Deep infec
Special features	Graft-vs-host disease caused by maternal engraftment or nonirradiated blood transfusion Postvaccination disseminated BCG or varicella Autoimmunity common in mild-moderate T-cell defects	Autoimmunity Lymphoreticular malignancy: lymphoma, thymoma	Prolonged attachment of umbilical cord, poor wound healing		SLE Glo (C3), hem synd MC

[*] X-linked (Bruton) agammaglobulinemia.

BCG, Bacille Calmette-Guérin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus.

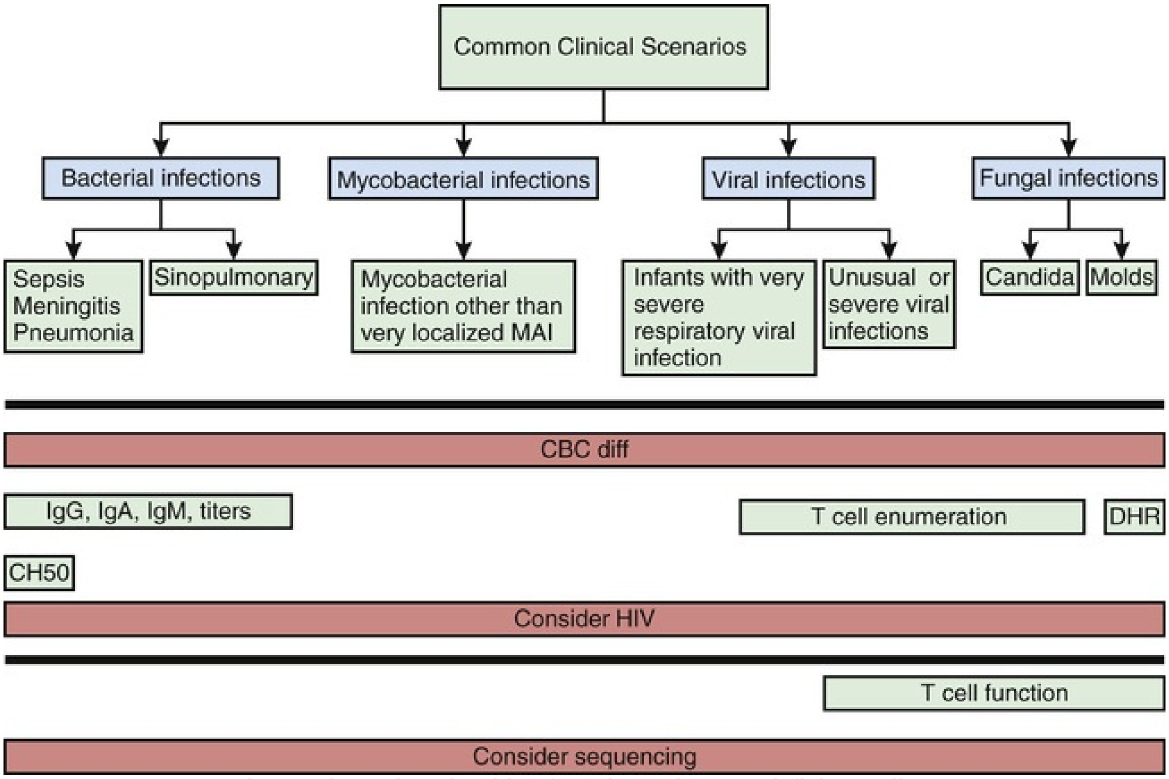
Common Clinical Scenarios
Bacterial infections
Mycobacterial infections
Viral infections
Fungal infections
Sepsis Meningitis Pneumonia
Sinopulmonary
Mycobacterial infection other than very localized MAI
Infants with very severe respiratory viral infection
Unusual or severe viral infections
Candida
Molds
CBC diff
IgG, IgA, IgM, titers
T cell enumeration
DHR
CH50
Consider HIV
T cell function
Consider sequencing

FIG. 148.1 **Diagnostic testing algorithm for primary immunodeficiency diseases. Common clinical scenarios are listed at the *top.* The 1st tier of testing is listed below each category between the *dark lines.* The 2nd tier of testing is located below the 2nd *dark line.* CBC, Complete blood count; DHR, dihydrorhodamine; MAI, *Mycobacterium avium-intracellulare* infection.**

The initial evaluation of immunologic function includes a thorough history, physical examination, and family history (Table 148.5). Over 10 immunodeficiencies are X-linked, and a growing number are autosomal dominant with variable expressivity and/or incomplete penetrance. Close attention to physical signs of autoimmune disease or end-organ effects from recurrent infections should be noted. The history of infections should include the age of onset, severity, involved locations, and assessment of the underlying microbial cause. Viral, bacterial, fungal, and mycobacterial infections all require distinct arms of the immune system for eradication; therefore identification of microbiologic causes of infection can be extremely helpful in defining the deficiency states in people with primary immunodeficiencies.

Table 148.5

Special Physical Features Associated With Immunodeficiency Disorders

CLINICAL FEATURES	**DISORDERS**
DERMATOLOGIC	
Eczema	Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency
Sparse and/or hypopigmented hair	Cartilage-hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome
Ocular telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Severe dermatitis	Omenn syndrome
Erythroderma	Omenn syndrome, SCID, graft-vs-host disease, Comel-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver, and rectum especially	CGD
Recurrent abscesses or cellulitis	CGD, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	CGD, SCID, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, -17, -23 deficiencies; *CARD9* deficiency; STAT1 deficiency
Vitiligo	B-cell defects, mucocutaneous candidiasis
Alopecia	B-cell defects, mucocutaneous candidiasis
Chronic conjunctivitis	B-cell defects
EXTREMITIES	
Clubbing of nails	Chronic lung disease caused by antibody defects
Arthritis	Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome
ENDOCRINOLOGIC	
Hypoparathyroidism	DiGeorge syndrome, mucocutaneous candidiasis
Endocrinopathies (autoimmune)	Mucocutaneous candidiasis
Diabetes, hypothyroid	IPEX and IPEX-like syndromes
Growth hormone deficiency	X-linked agammaglobulinemia
Gonadal dysgenesis	Mucocutaneous candidiasis
HEMATOLOGIC	
Hemolytic anemia	B- and T-cell immune defects, ALPS
Thrombocytopenia, small platelets	Wiskott-Aldrich syndrome
Neutropenia	Hyper-IgM syndrome, Wiskott-Aldrich variant, CGD
Immune thrombocytopenia	B-cell immune defects, ALPS
SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T- and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage-hair hypoplasia

ADA, Adenosine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.

From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders, p 1599.

Most immunologic defects can be excluded at minimal cost with the proper choice of screening tests, which should be broadly informative, reliable, and cost-effective (Table 148.6 and Figs. 148.2 and 148.3). A complete blood count

(CBC) with differential is the initial study if neutropenia is a consideration but is less recognized as a screening test for T-cell defects. Lymphopenia is seen the majority of T-cell defects. If an infant's neutrophil count is persistently elevated in the absence of any signs of infection, a leukocyte adhesion deficiency should be suspected. Normal lymphocyte counts are higher in infancy and early childhood than later in life (Fig. 148.4). Knowledge of normal values for absolute lymphocyte counts at various ages in infancy and childhood is crucial in the detection of T-cell defects. Additional clues from the CBC include absence of Howell-Jolly bodies, which argues against congenital asplenia. Normal platelet size or count excludes Wiskott-Aldrich syndrome. When immunodeficiency is suspected, obtaining IgG, IgA, IgM, and IgE levels can be a useful strategy, since antibody defects are the most common type of immunodeficiency. Immunoglobulin levels must be interpreted within the context of age-specific normative data.

Table 148.6

Initial Screening Immunologic Testing of the Child With Recurrent Infections

Complete Blood Count, Differential, and Erythrocyte Sedimentation Rate

Absolute lymphocyte count (normal result rules against T-cell defect)
Absolute neutrophil count (normal result rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections)
Platelet count (normal result excludes Wiskott-Aldrich syndrome)
Howell-Jolly bodies (absence rules against asplenia)
Erythrocyte sedimentation rate (normal result indicates chronic bacterial or fungal infection unlikely)

Screening Tests for B-Cell Defects

IgG, IgA, IgM (low in most antibody defects)
Isohemagglutinins (low in agammaglobulinemia)
Antibody titers tetanus, diphtheria, *Haemophilus influenzae* , and

pneumococcus (low in most antibody defects)

Screening Tests for T-Cell Defects

Absolute lymphocyte count (normal result indicates T-cell defect unlikely)

Flow cytometry to examine for the presence of naïve T cells ($CD3^+$ $CD45RA^+$ cells)

Screening Tests for Phagocytic Cell Defects

Microscopy (abnormal in some neutropenias)

Respiratory burst assay (abnormal in chronic granulomatous disease)

Screening Test for Complement Deficiency

CH_{50} (nearly absent in classical pathway and terminal component deficiencies)

AH_{50} (nearly absent in alternative pathway and terminal component deficiencies)

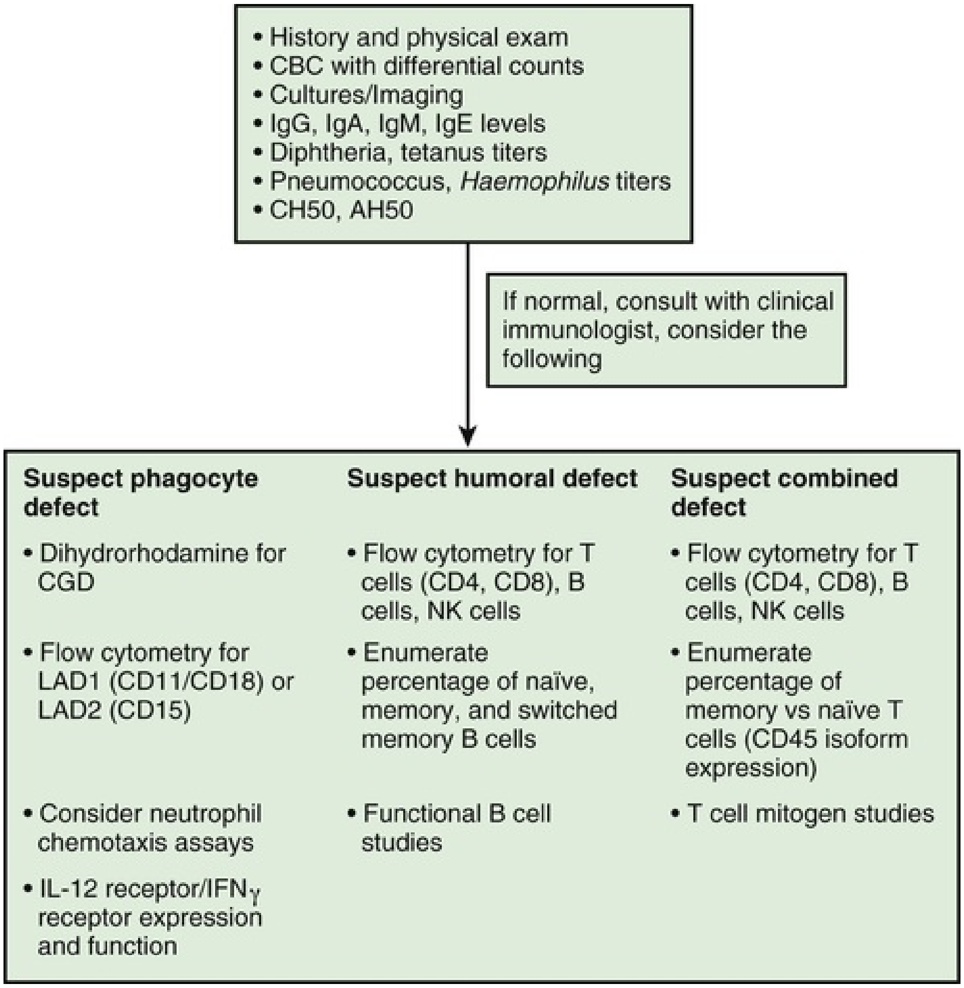
• History and physical exam
• CBC with differential counts
• Cultures/Imaging
• IgG, IgA, IgM, IgE levels
• Diphtheria, tetanus titers
• Pneumococcus, *Haemophilus* titers
• CH50, AH50
If normal, consult with clinical immunologist, consider the following
Suspect phagocyte defect
• Dihydrorhodamine for CGD
• Flow cytometry for LAD1 (CD11/CD18) or LAD2 (CD15)
• Consider neutrophil chemotaxis assays
• IL-12 receptor/IFN$_\gamma$ receptor expression and function
Suspect humoral defect
• Flow cytometry for T cells (CD4, CD8), B cells, NK cells
• Enumerate percentage of naïve, memory, and switched memory B cells
• Functional B cell studies
Suspect combined defect
• Flow cytometry for T cells (CD4, CD8), B cells, NK cells
• Enumerate percentage of memory vs naïve T cells (CD45 isoform expression)
• T cell mitogen studies

FIG. 148.2 Initial workup and follow-up studies of patients with suspected immunodeficiency. Consultation with a clinical immunologist is recommended to guide advanced testing and interpret results. CBC, Complete blood count; CGD, chronic granulomatous disease; LAD, leukocyte adhesion defect; NK, natural killer cell; IL, interleukin; IFN, interferon. (From Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis,* Philadelphia, 2018, Elsevier, p 753.)

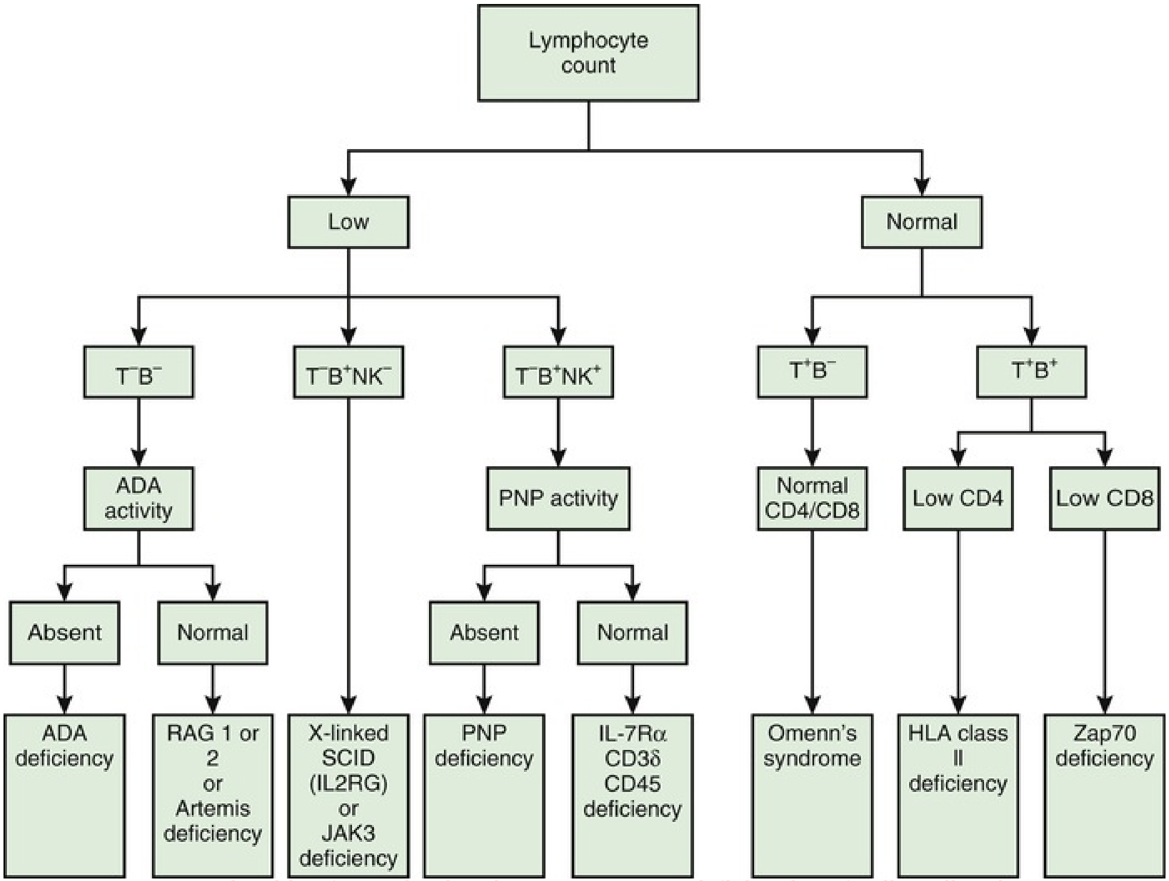
Lymphocyte count
Low
Normal
T⁻B⁻
T⁻B⁺NK⁻
T⁻B⁺NK⁺
T⁺B⁻
T⁺B⁺
ADA activity
PNP activity
Normal CD4/CD8
Low CD4
Low CD8
Absent
Normal
Absent
Normal
ADA deficiency
RAG 1 or 2 or Artemis deficiency
X-linked SCID (IL2RG) or JAK3 deficiency
PNP deficiency
IL-7Rα CD3δ CD45 deficiency
Omenn's syndrome
HLA class II deficiency
Zap70 deficiency

FIG. 148.3 Algorithm for evaluating the most common deficiencies of cell-mediated immunity. ADA, Adenosine deaminase; PNP, purine nucleoside phosphorylase. (From Leung DYM, Szefler SJ, Bonilla FA, et al, editors: *Pediatric allergy: principles and practice,* ed 3, St Louis, 2016, Elsevier, p 68.)

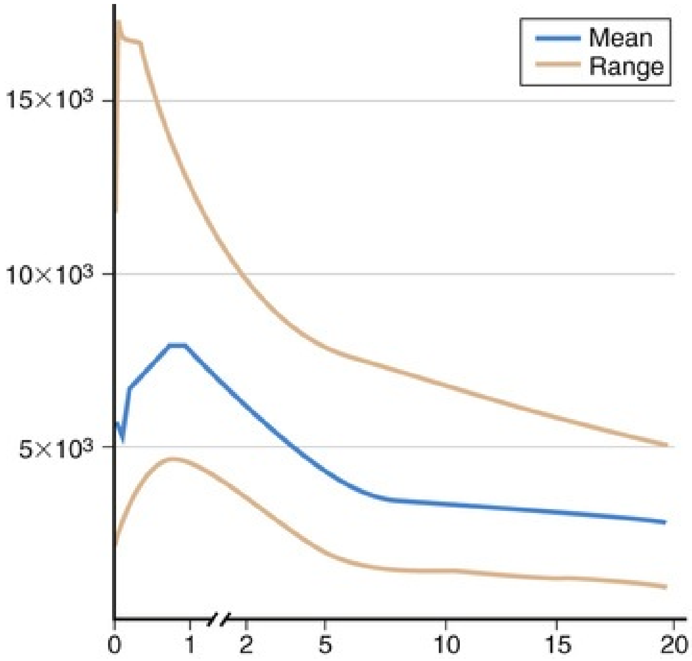

FIG. 148.4 Absolute lymphocyte counts in a normal individual during maturation. (Data graphed from Altman PL: *Blood and other body fluids.* Prepared under the auspices of the Committee on Biological Handbooks, Washington, DC, 1961, Federation of American Societies for Experimental Biology.)

Advanced Testing

Additional testing should be focused based on the phenotype and suspected category of immune deficiency (Table 148.7 ; see Figs. 148.2 and 148.3). For patients with recurrent sinopulmonary infections in whom an antibody defect is suspected, further attention to antibody testing may be revealing. In addition to Ig levels, responses to vaccines should also be pursued in this setting. A small but significant subset of patients with antibody deficiencies will have normal Ig levels but abnormal function, as detected by poor responses to vaccines. When hypogammaglobulinemia is identified, it is important to determine whether it is primary or secondary. Patients receiving corticosteroids or who have protein-losing states (nephrosis, protein-losing enteropathy) often have low serum IgG concentrations but produce normal responses to vaccines. Thus, if Ig levels are low, it is crucial before starting immune globulin replacement therapy that antibody titers to vaccines are measured. Antibody titers are not interpretable after the patient has received a blood transfusion, fresh-frozen plasma, or immune globulin therapy.

Table 148.7

Laboratory Tests in Immunodeficiency

SCREENING TESTS	ADVANCED TESTS	RESEARCH/SPECIAL TESTS
B-CELL DEFICIENCY		
IgG, IgM, IgA, and IgE levels	B-cell enumeration (CD19 or CD20)	Advanced B-cell phenotyping
Isohemagglutinin titers		Biopsies (e.g., lymph nodes)
Ab response to vaccine antigens (e.g., tetanus, diphtheria, pneumococci, *Haemophilus influenzae*)	Ab responses to boosters or to new vaccines	Ab responses to special antigens (e.g., bacteriophage φX174), mutation analysis
T-CELL DEFICIENCY		
Lymphocyte count	T-cell subset enumeration (CD3, CD4, CD8)	Advanced flow cytometry
Chest x-ray examination for thymic size*	Proliferative responses to mitogens, antigens, allogeneic cells	Enzyme assays (e.g., ADA, PNP)
TRECs	22q11.2 deletion analysis	Mutation analysis T-cell activation studies
PHAGOCYTIC DEFICIENCY		
WBC count, morphology	Adhesion molecule assays (e.g., CD11b/CD18, selectin ligand)	Mutation analysis Macrophage functional testing
Respiratory burst assay	Mutation analysis	
COMPLEMENT DEFICIENCY		
CH_{50} activity	AH_{50} , activity	Specific component assays

* In infants only.

Ab, Antibody; ADA, adenosine deaminase; C, complement; CH, hemolytic complement; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leukocyte antigen; Ig, immunoglobulin; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; PNP, purine nucleoside phosphorylase; TRECs, T-cell receptor rearrangement excision circle; WBC, white blood cell; φX, phage antigen.

One useful test for B-cell function is to determine the presence and titer of **isohemagglutinins** , or natural antibodies to type A and B red blood cell polysaccharide antigens. This test measures predominantly IgM antibodies. Isohemagglutinins may be absent normally in the first 2 yr of life and are always absent if the patient is blood type AB.

Because most infants and children are immunized with diphtheria-tetanus-pertussis (dTP), conjugated *Haemophilus influenzae* type b, and pneumococcal conjugate vaccine, it is often informative to test for specific antibodies to diphtheria, tetanus, *H. influenzae* polyribose phosphate, and pneumococcal antigens. If the titers are low, measurement of antibodies to diphtheria or tetanus toxoids before and 2-8 wk after a pediatric dTP or dT booster is helpful in assessing the capacity to form IgG antibodies to protein antigens. To evaluate a patient's ability to respond to polysaccharide antigens, antipneumococcal antibodies can be measured before and 4-8 wk after immunization with 23-valent unconjugated pneumococcal polysaccharide vaccine in patients ≥2 yr old. Antibodies detected in these tests are of the IgG isotype. These antibody studies can be performed in several different laboratories, but it is important to choose a reliable laboratory and to use the same laboratory for pre- and postimmunization titers.

Patients with defective B-cell maturation due to a class-switching defects produce neither IgA nor IgG antibodies normally. IgM is normal or elevated. Vaccine responses are uniformly low. If antibody responses to vaccines are normal and the IgG level is low, studies should be performed to evaluate the possible loss of immunoglobulins through the urinary or gastrointestinal tract (nephrotic syndrome, protein-losing enteropathies, intestinal lymphangiectasia). Another common confounder is the use of rituximab or corticosteroids, leading to hypogammaglobulinemia. Very high serum concentrations of 1 or more Ig classes suggest HIV infection, chronic granulomatous disease, chronic inflammation, or autoimmune lymphoproliferative syndrome.

IgG subclass measurements are seldom helpful in assessing immune function in young children with recurrent infections. They are strongly developmentally regulated with highly variable production in early childhood. It is difficult to know the biologic significance of the various mild to moderate deficiencies of IgG subclasses, particularly when completely asymptomatic individuals have been described as totally lacking IgG1, IgG2, IgG4, and/or IgA1 because of Ign heavy-chain gene deletions. Many healthy children have been described as having low levels of IgG2 but normal responses to polysaccharide antigens when immunized. In older children and adults, a low IgG2 maybe an antecedent finding before evolving into **common variable immunodeficiency (CVID).** Specific vaccine responses are usually much more useful than IgG subclass determinations.

Patients found to be **agammaglobulinemic** should have their blood B cells enumerated by flow cytometry using dye-conjugated monoclonal antibodies to B-cell–specific CD antigens (usually CD19 or CD20). Normally, approximately 5–10% of circulating lymphocytes are B cells. B cells are absent in X-linked agammaglobulinemia (XLA) and in several very rare autosomal recessive conditions, but they are usually present in CVID, IgA deficiency, and hyper-IgM syndromes. This distinction is important, because children with hypogammaglobulinemia from XLA and CVID can have different clinical problems, and the 2 conditions clearly have different inheritance patterns. Patients with CVID have more problems with autoimmune diseases and lymphoid hyperplasia. Molecular testing for XLA and other B-cell defects (see Chapter 150.1) is indicated in cases without a family history to aid genetic counseling.

T cells and T cell subpopulations can be enumerated by flow cytometry using dye-conjugated monoclonal antibodies recognizing CD antigens present on T cells (i.e., CD2, CD3, CD4, and CD8). This is a particularly important test to perform on any infant who is lymphopenic, because $CD3^+$ T cells usually constitute 70% of peripheral lymphocytes. Regardless of molecular type, infants with SCID are unable to produce T cells, so are lymphopenic at birth. The flow cytometry for infants suspected of having SCID should also include monoclonal antibodies to naïve (CD45RA) and memory (CD45RO) T cells. In normal infants, >95% of the T cells are $CD45RA^+$ (naïve) T cells. If the infant has SCID, there could be transplacentally transferred maternal T cells detected by flow cytometry, but they would be predominantly $CD45RO^+$ T cells. SCID is a pediatric emergency that can be successfully treated by hematopoietic stem cell transplantation in more than 90% of cases if diagnosed before serious, untreatable infections develop. Normally, there are about twice as many $CD4^+$ (helper) T cells as there are $CD8^+$ (cytotoxic) T cells. Because some severe immunodeficiencies have phenotypically normal T cells, tests of T-cell function can be helpful. T cells can be stimulated directly with **mitogens** such as phytohemagglutinin, concanavalin A, or pokeweed mitogen. After 3-5 days of incubation with the mitogen, the proliferation of T cells is measured. Other stimulants that can be used to assess T-cell function in the same type of assay include antigens (*Candida,* tetanus toxoid) and allogeneic cells.

Natural killer (NK) cells can be enumerated by flow cytometry using monoclonal antibodies to NK-specific CD antigens, CD16 and CD56. NK function is assessed by killing of target cells and flow cytometry for CD107a, a marker of degranulation.

Chronic granulomatous disease should be suspected if a patient has recurrent staphylococcal abscesses or fungal infections. It can be evaluated by screening tests measuring the neutrophil respiratory burst after phorbol ester stimulation. **Leukocyte adhesion defects** (LAD) can be easily diagnosed by flow cytometric assays of blood lymphocytes or neutrophils, using monoclonal antibodies to CD18 or CD11 (LAD1) or to CD15 (LAD2). **Neutrophil defects** are most often associated with neutropenia or morphologic abnormalities visible by microscopy. Therefore, a combination of a CBC with differential, microscopic evaluation, and the flow cytometric approaches previously described often yields a diagnosis. The same is not true for **macrophage defects** , which are usually associated with susceptibility to mycobacteria, and testing requires advanced functional analyses or sequencing.

When invasive infection with encapsulated organisms or *Neisseria* leads to a suspicion of a complement defect, a **CH_{50} test** should be obtained. This bioassay measures the intactness of the entire complement pathway and yields abnormal results if classical pathway or terminal components are missing. Genetic deficiencies in the complement system often have a CH_{50} that is almost absent, although the most frequent cause of a slightly low CH50 is improper transport of the specimen. Complement proteins are highly labile and must be transported on ice. Specific factor assays are available at reference laboratories. Rare causes of neisserial susceptibility include alternative pathway defects, and the test for these deficiencies is the **AH_{50} test.** Identifying the specific component deficiency in the mode of inheritance is important for genetic counseling. Properdin deficiency is X-linked, and other deficiencies are autosomal recessive or autosomal dominant.

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SECTION 2

The T-, B-, and NK-Cell Systems

OUTLINE

Chapter 149 Lymphocyte Development and Function
Chapter 150 Primary Defects of Antibody Production
Chapter 151 Primary Defects of Cellular Immunity
Chapter 152 Immunodeficiencies Affecting Multiple Cell Types

CHAPTER 149

Lymphocyte Development and Function

Kathleen E. Sullivan, Rebecca H. Buckley

Defense against infectious agents is secured through a combination of anatomic physical barriers, including the skin, mucous membranes, mucous blanket, and ciliated epithelial cells, and the components of the immune system. The **immune system** of vertebrates integrates 2 fundamental response mechanisms. **Innate (natural) immunity** is rapid and utilizes receptors encoded in the germline. The innate defenses comprise cell-intrinsic responses to viral infections, leukocyte responses to pathogens, and soluble mediators such as complement proteins. **Acquired (adaptive) immunity** is specific to T and B cells. These cells undergo DNA recombination to generate receptors and require an education process to minimize autoreactive cells. In addition, there are lymphocyte subsets that are innate in nature and either do not require DNA recombination or utilize a single recombination event to generate a monospecific receptor.

Lymphopoiesis in the Fetus

Pluripotential hematopoietic stem cells first appear in the yolk sac at 2.5-3 wk of gestational age, migrate to the fetal liver at 5 wk gestation, and later reside in the bone marrow, where they remain throughout life (Fig. 149.1). Lymphoid stem cells develop and differentiate into T, B, or natural killer (NK) cells, depending on the organs or tissues to which the stem cells traffic. Development of the **primary lymphoid organs** —thymus and bone marrow—begins during the middle of the 1st trimester of gestation and proceeds rapidly. Development of the **secondary lymphoid organs** —spleen, lymph nodes, tonsils, Peyer patches, and lamina propria—soon follows. These organs serve as sites of differentiation of T, B, and NK lymphocytes from stem cells throughout life. Both the initial organogenesis and the continued cell differentiation result from the interaction of a vast array of lymphocytic and microenvironmental cell surface molecules and proteins secreted by the involved cells. **Clusters of differentiation (CD)** refer to cellular protein (Table 149.1), whereas **cytokines** and **chemokines** refer to soluble mediators of immune function (Table 149.2).

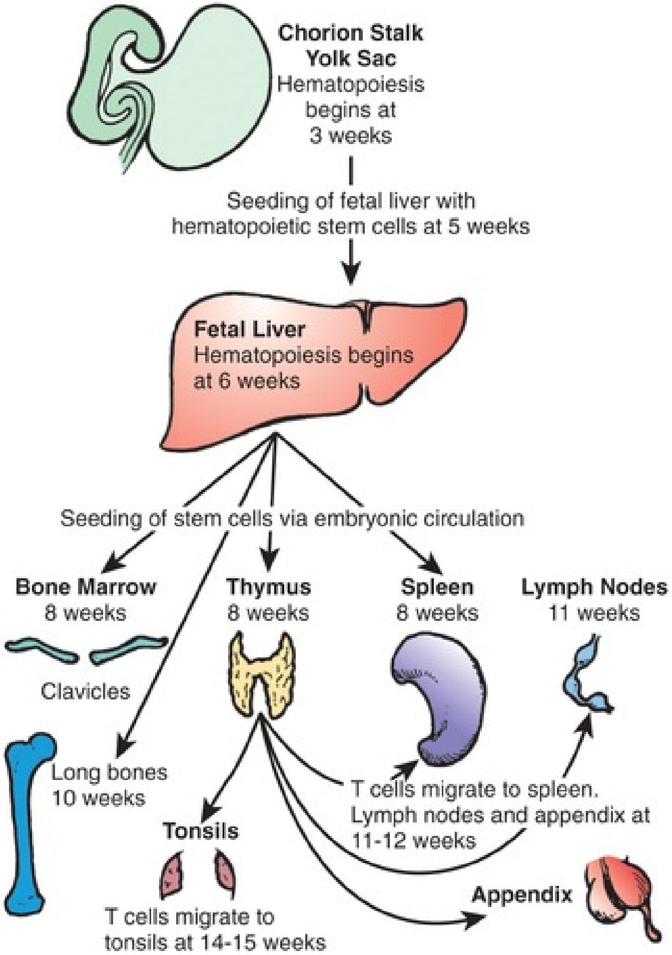
Chorion Stalk
Yolk Sac
Hematopoiesis
begins at
3 weeks
Seeding of fetal liver with
hematopoietic stem cells at 5 weeks
Fetal Liver
Hematopoiesis begins
at 6 weeks
Seeding of stem cells via embryonic circulation
Bone Marrow
8 weeks
Thymus
8 weeks
Spleen
8 weeks
Lymph Nodes
11 weeks
Clavicles
Long bones
10 weeks
Tonsils
T cells migrate to spleen.
Lymph nodes and appendix at
11-12 weeks
Appendix
T cells migrate to
tonsils at 14-15 weeks

FIG. 149.1 Migration patterns of hematopoietic stem cells and mature lymphocytes during human fetal development. (From Haynes BF, Denning SM: Lymphopoiesis. In Stamatoyannopoulis G, Nienhuis A, Majerus P, editors: *Molecular basis of blood diseases,* ed 2, Philadelphia, 1994, Saunders.)

Table 149.1

CD Classification of Some Lymphocyte Surface Molecules

CD Classification of Some Lymphocyte Surface Molecules

CD NUMBER	TISSUE/LINEAGE	FUNCTION
CD1	Cortical thymocytes; Langerhans cells	Lipid antigen presentation to TCRγδ cells
CD2	T and NK cells	Binds LFA-3 (CD58); alternative pathway of T-cell activation
CD3	T cells	TCR associated; transduces signals from TCR
CD4	T-helper cell subset	Receptor for HLA class II antigens; associated with p56 *Ick* tyrosine kinase
CD7	T and NK cells and their precursors	Mitogenic for T lymphocytes
CD8	Cytotoxic T-cell subset; also on 30% of NK cells	Receptor for HLA class I antigens; associated with p56 *Ick* tyrosine kinase
CD10	B-cell progenitors	Peptide cleavage
CD11a	T, B, and NK cells	With CD18, ligand for ICAMs 1, 2, and 3
CD11b, c	NK cells	With CD18, receptors for C3bi
CD16	NK cells	FcR for IgG
CD19	B cells	Regulates B-cell activation
CD20	B cells	Mediates B-cell activation
CD21	B cells	C3d, also the receptor for EBV; CR2
CD25	T, B, and NK cells	Mediates signaling by IL-2
CD34	Stem cells	Binds to L -selectin
CD38	T, B, and NK cells and monocytes	Associates with hyaluronic acid
CD40	B cells and monocytes	Initiates isotype switching in B cells when ligated
CD44	Bone marrow stromal and many other cells	Matrix adhesion molecule
CD45	All leukocytes	Tyrosine phosphatase that regulates lymphocyte activation; CD45R0 isoform on memory T cells, CD45RA isoform on naïve T cells
CD56	NK cells	Mediates NK homotypic adhesion
CD62L	Marker for recent thymic emigrants Also found on other leukocytes	Cell adhesion molecule
CD69	T cells and NK cells	Early activation marker
CD73	T and B cells	Associates with AMP
CD80	B cells	Co-stimulatory with CD28 on T cells to upregulate high-affinity IL-2 receptor
CD86	B cells	Co-stimulatory with CD28 on T cells to upregulate high-affinity IL-2 receptor
CD117	Pro-B cells, double-negative thymocytes	Receptor for stem cell factor
CD127	T cells	Mediates IL-7 signaling
CD132	T, B, and NK cells	Mediates signaling by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
CD154	Activated CD4$^+$ T cells	Ligates CD40 on B cells and initiates isotype switching
CD278	T cells	Interacts with B7-H2

AMP, Adenosine monophosphate; EBV, Epstein-Barr virus; ICAMs, intracellular adhesion molecules; IL, interleukin; LFA, leukocyte function–activating antigen; NK, natural killer; TCR, T-cell receptor.

Table 149.2

Common Cytokines

CATEGORY	CYTOKINE	FUNCTION
Interferons	IFN-α	Antiviral defense
	IFN-β	Antiviral defense
	IFN-γ	Antiviral defense
Innate responses	TNF	Regulates endothelial adhesion molecules for recruitment of neutrophils; activates macrophages for killing
	IL-1β	Drives the inflammatory response, fever
	IL-12	Polarizes T cells toward Th1; activates NK cells
Lymphocyte regulation	IL-2	Key growth factor for T cells
	IL-4	Polarizes T cells toward Th2
	IL-6	Growth factor for B cells
	IL-7	T-cell homeostatic factor
	IL-10	Growth factor for B cells, immunosuppressive
	IL-12	Polarizes T cells toward Th1, activates NK cells
	IL-17	Polarizes T cells toward Th17, stimulates antimicrobial peptide expression
	IL-21	Supports B-cell class switching

IL, Interleukin; NK, natural killer; Th, T-helper cell; TNF, tumor necrosis factor.

T-Cell Development and Differentiation

The primitive thymic rudiment is formed from the ectoderm of the 3rd branchial cleft and endoderm of the 3rd branchial pouch at 4 wk gestation. Beginning at 7-8 wk, the right and left rudiments fuse in the midline. Bloodborne T-cell precursors from the fetal liver then begin to colonize the perithymic mesenchyme at 8 wk gestation and move into the thymus at 8.0-8.5 wk. The earliest cells to enter the thymus are found in the subcapsular region and do not express CD3, CD4, CD8, or either type of T-cell receptor (TCR). These lymphoid cell precursors are triggered to proliferate and become thymocytes through interactions with the thymic stroma. The cells are arrested at this stage until they productively rearrange the β-chain locus of the TCR. The β chain then pairs with the surrogate pre-T α chain. This tests the function of the β chain, and if signaling occurs, β-chain rearrangement ceases. CD4 and CD8 are then expressed simultaneously (i.e., they are double-positive thymocytes). Fetal cortical thymocytes are among the most rapidly dividing cells in the body and increase in number by 100,000-fold within 2 wk after stem cells enter the thymus. As these cells proliferate and mature, they migrate deeper into the thymic cortex. The double-positive thymocytes begin efficient rearrangement of the α-chain locus. TCR gene rearrangement occurs by a process in which large, noncontiguous blocks of DNA are spliced together. **V (variable)** , **D (diversity)** , and **J (joining)** blocks exist in families of minimally different segments. Random combinations of the segments account for much of the enormous diversity of TCRs that enables humans to recognize millions of different antigens. TCR gene rearrangement requires the presence of **recombinase-activating genes** , *RAG1* and *RAG2,* as well as other recombinase components.

As immature cortical thymocytes begin to express TCRs, the processes of positive and negative selection take place. **Positive selection** occurs in immature thymocytes, recognizing major histocompatibility complex (MHC) antigens present on cortical thymic epithelial cells. Some cells are selected to mature into CD4 or CD8 single-positive cells. **Negative selection** occurs next in the thymic medulla on medullary thymic epithelial cells. Autoreactive T cells undergo apoptosis and die. T cells begin to emigrate from the thymus to the spleen, lymph nodes, and appendix at 11-12 wk of embryonic life and to the tonsils by 14-15 wk. They leave the thymus via the bloodstream and are distributed throughout the body, with the heaviest concentrations in the paracortical areas of lymph nodes, the periarteriolar areas of the spleen, and the thoracic lymph duct. Recent thymic emigrants co-express the CD45RA isoforms and CD62L (L -selectin).

Rearrangement of the TCR locus during intrathymic T-cell development results in the excision of DNA and the excised elements form circular episomes as a by-product. These **TCR recombination excision circles** can be detected in T cells that are recent thymic emigrants. TCR recombination excision circles detected in dried-blood spots collected from infants shortly after birth is the test used for newborn screening for severe combined immunodeficiency (SCID). By 12 wk gestation, T cells can proliferate in response to plant lectins, such as phytohemagglutinin and concanavalin A. Antigen-specific T cells have been found by 20 wk gestation. **Hassall corpuscles (bodies),** which are swirls of terminally differentiated medullary epithelial cells, are first seen in the thymic medulla at 16-18 wk of embryonic life.

B-Cell Development and Differentiation

B-cell development begins in the fetal liver by 7 wk gestation. Fetal liver CD34 stem cells are seeded to the bone marrow of the clavicles by 8 wk of embryonic life and to that of the long bones by 10 wk (see Fig. 149.1). As B cells differentiate from primitive stem cells, they proceed through stages that are marked by the sequential rearrangement of immunoglobulin gene segments to generate a diverse repertoire of antigen receptors. The early **pro-B cell** is the first descendent of the pluripotential stem cell committed to B-lineage development, and in this stage the heavy chain locus rearranges first. In the early pro-B cell, D-J rearrangements are made on both chromosomes. In the late pro-B cell, the V segment rearranges to a D-J gene segment. The next stage is the **pre-B cell** , during which immunoglobulin (Ig) light-chain genes are rearranged. The **pre-B cell** is distinguished by the expression of cytoplasmic μ heavy chains but no **surface** IgM (sIgM), because Ig light chains are not yet produced. Next is the **immature B-cell** stage, during which the light-chain genes have already been rearranged, and sIgM but not sIgD is expressed. Immature B cells leave the bone marrow for secondary lymphoid organs. The last stage of antigen-independent B-cell development is the **mature naïve B cell,** which co-expresses both sIgM and sIgD. Pre-B cells can be found in fetal liver at 7 wk gestation, sIgM+ and sIgG+ B cells at 7-11 wk, and sIgD+ and sIgA+ B cells by 12-13 wk. By 14 wk of embryonic life, the percentage of circulating lymphocytes bearing sIgM and sIgD is the same as in cord blood and slightly higher than in the blood of adults.

Antigen-dependent stages of B-cell development are those that develop after the mature B cell is stimulated by antigen in secondary lymphoid organs**.** Once antigen stimulation has occurred, the mature B cells can become memory B cells or plasmablasts. Both outcomes require the presence of T-cell help.

There are 5 **immunoglobulin isotypes** , which are defined by unique heavy chains: IgM, IgG, IgA, IgD, and IgE. IgG and IgM, the only complement-fixing isotypes, are the most important immunoglobulins in the blood and other internal body fluids for protection against infectious agents. IgM is confined primarily to the intravascular compartment because of its large size, whereas IgG is present in all internal body fluids. IgA is the major protective immunoglobulin of external secretions—in the gastrointestinal, respiratory, and urogenital tracts—but it is also present in the circulation. IgE, present in both internal and external body fluids, has a major role in host defense against parasites. Because of high-affinity IgE receptors on basophils and mast cells, however, IgE is the principal mediator of allergic reactions of the immediate type. The significance of IgD is still not clear. There are also **immunoglobulin subclasses** , including 4 subclasses of IgG (IgG1, IgG2, IgG3, and IgG4) and 2 subclasses of IgA (IgA1 and IgA2). These subclasses each have different biologic roles. Secreted IgM and IgE have been found in as young as 10 wk gestation, and IgG as early as 11-12 wk.

Even though these B-cell developmental stages have been described in the context of B-cell ontogeny in utero, it is important to recognize that the process of B-cell development from pluripotential stem cells goes on throughout postnatal life. Plasma cells are not usually found in lymphoid tissues of a fetus until about 20 wk gestation, and then only rarely, because of the sterile environment of the uterus. Intestinal lymphoid development occurs relatively late. Peyer patches have been found in significant numbers by the 5th intrauterine mo, and plasma cells have been seen in the lamina propria by 25 wk gestation. Before birth there may be primary follicles in lymph nodes, but secondary follicles are usually not present.

A human fetus begins to receive significant quantities of maternal IgG transplacentally at around 12 wk gestation, and the quantity steadily increases until, at birth, cord-blood serum contains a concentration of IgG comparable to or greater than that of maternal serum. IgG is the only class to cross the placenta to any significant degree. All 4 IgG subclasses cross the placenta, but IgG2 does so least well. A small amount of IgM (10% of adult levels) and a few nanograms of IgA, IgD, and IgE are normally found in cord blood serum. Because none of these proteins crosses the placenta, they are presumed to be of fetal origin. These observations suggest that certain antigenic stimuli normally cross the placenta to provoke responses, even in uninfected fetuses. Some atopic infants occasionally have IgE antibodies to antigens, such as egg white, to which they have had no known exposure during postnatal life, suggesting that synthesis of these antibodies could have been induced in the fetus by antigens ingested by the mother.

Natural Killer–Cell Development

NK cell activity is found in human fetal liver cells at 8-11 wk of gestation. NK lymphocytes are also derived from bone marrow precursors. Thymic processing is not necessary for NK-cell development, although NK cells have been found in the thymus. After release from bone marrow, NK cells enter the circulation or migrate to the spleen, with very few NK cells in lymph nodes. In normal individuals, NK cells represent 8–10% of lymphocytes. Certain tissues harbor large numbers of NK cells.

Unlike T and B cells, NK cells do not rearrange antigen receptor genes during their development but are defined by their functional capacity to mediate non–antigen-specific cytotoxicity. NK cells have killer inhibitory receptors that recognize certain MHC antigens and inhibit the killing of self tissues. NK-activating receptors recognize stress protein, and the balance of activating and inhibitory receptor engagement determines the action of the NK cells. If a viral infection drives down MHC class I expression, the loss of inhibitory function drives cytotoxicity. High levels of stress proteins, typically seen in viral infections, can also activate cytotoxicity.

Lymphocyte Choreography

The main functions of T cells are to signal B cells to make antibody, to kill virally infected cells or tumor cells, and to activate macrophages for intracellular killing. The subset of **regulatory T cells** (Tregs), is critical in the prevention of autoimmune responses. T cells are activated by antigen presented by **antigen-presenting cells (APCs)** . These are usually dendritic cells, macrophages, or B cells. For high-affinity binding of T cells to APCs, several molecules on T cells, in addition to TCRs, bind to molecules on APCs or target cells. The CD4 molecule binds directly to MHC class II molecules on APCs. CD8 on cytotoxic T cells binds the MHC class I molecule on the target cell. Lymphocyte function–associated antigen 1 (**LFA-1**) on the T cell binds a protein called **ICAM-1** (intracellular adhesion molecule 1), designated **CD54** , on APCs. CD2 on T cells binds LFA-3 (CD58) on the APCs. With the adhesion of T cells to APCs (the immunologic synapse), **T-helper (Th)** cells are stimulated to make interleukins and upregulate cell surface molecules, such as the CD40 ligand (CD154), that provide help for B cells, and cytotoxic T cells are stimulated to kill their targets. A key safety net to ensure appropriate activation of T cells in the setting of a true threat is the requirement for co-stimulation of the T cells. APCs that have encountered a pathogen express CD80 and CD86. Engagement of these molecules provides the 2nd, co-stimulatory, signal. Without co-stimulation, the T cell will be rendered *anergic*, or nonfunctional.

In the **primary antibody response** , native antigen is carried to a lymph node draining the site, captured by complement, taken up by specialized cells called **follicular dendritic cells (FDCs)** , and expressed on their surfaces. Mature B cells bearing sIgM specific for that antigen then bind to the antigen on the surfaces of the FDCs. If the affinity of the B-cell sIgM antibody for the antigen present on the FDCs is sufficient, and if other signals are provided by activated T cells, the B cell develops into a memory B cells or antibody-producing plasma cell. The signals from activated T cells include several cytokines (IL-4, IL-5, IL-

6, IL-10, IL-13, and IL-21) that they secrete (see Table 149.2) and a surface T-cell molecule, the CD40 ligand or CD154, which, on contact of the activated $CD4^+$ T cell with the B cell, binds to CD40 on the B-cell surface. Binding of CD40 on B cells by CD154 on T cells in the presence of certain cytokines causes the B cells to undergo proliferation and to initiate immunoglobulin synthesis. In the primary immune response, only IgM antibody is usually made, and most of it is of relatively low affinity. Some B cells become memory B cells during the primary immune response. The **secondary antibody response** occurs when these memory B cells again encounter that antigen. Developing memory B cells switch their Ig genes so that IgG, IgA, and/or IgE antibodies of higher affinity are formed on a secondary exposure to the same antigen. Plasma cells form, just as in the primary response; however, many more cells are rapidly generated, and IgG, IgA, and IgE antibodies are made. In addition, genetic changes in Ig genes (somatic hypermutation) lead to increased affinity of those antibodies.

The exact pattern of isotype response to antigen in normal individuals varies, depending on the type of antigen and the cytokines present in the microenvironment. Both class switching and somatic hypermutation are completely dependent on T-cell help. Thus, T cells represent a kind of gatekeeper for specific antibody production.

Postnatal Lymphocyte Behavior

Virtually all T cells in cord blood bear the CD45RA (naïve) isoform, and a dominance of CD45RA over CD45RO T cells persists during childhood. After mid-adulthood, the CD45RO (memory) T cells predominate. CD4 T cells can be further subdivided according to the cytokines they produce when activated. **Th1 cells** produce interleukin (IL)-2 and interferon (IFN)-γ, which promote cytotoxic T-cell or delayed hypersensitivity types of responses, whereas **Th2 cells** produce IL-4, IL-5, IL-6, IL-13, and IL-21 (see Table 149.2), which promote B-cell responses and allergic sensitization, **Th17** cells produce IL-17, and **Tregs** produce IL-10 (Fig. 149.2). Differentiation into these memory subsets is dictated by the cytokine milieu regulating specific transcription factors and epigenetic changes. In vivo, these subsets are largely stable but in some circumstances can change to a different subset. The importance of these subsets is that memory cells respond to antigen more quickly and are primed to produce the cytokines most likely to drive pathogen clearance.

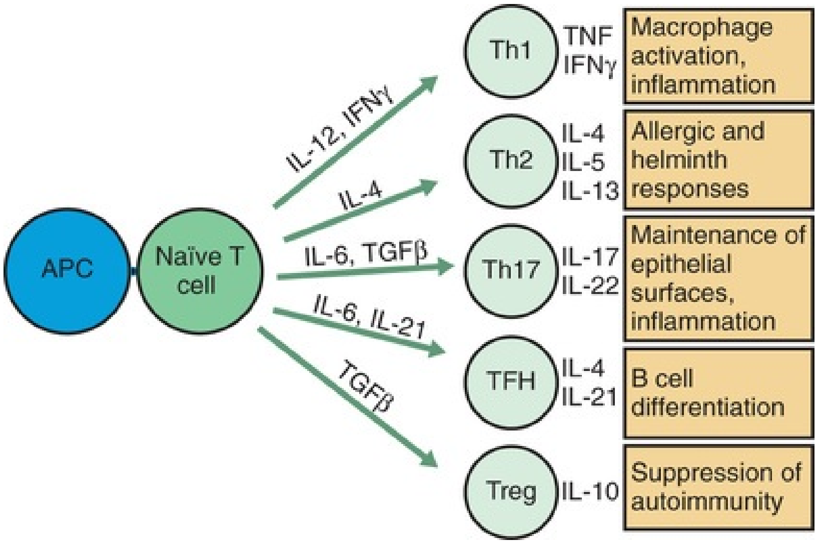
APC
Naïve T cell
IL-12, IFNγ
IL-4
IL-6, TGFβ
IL-6, IL-21
TGFβ
Th1
TNF
IFNγ
Macrophage activation, inflammation
Th2
IL-4
IL-5
IL-13
Allergic and helminth responses
Th17
IL-17
IL-22
Maintenance of epithelial surfaces, inflammation
TFH
IL-4
IL-21
B cell differentiation
Treg
IL-10
Suppression of autoimmunity

FIG. 149.2 T-cell differentiation into memory subsets is tightly regulated by cytokines. Specific subsets have distinct roles in host defense. APC, Antigen-presenting cell; IFN, interferon; IL, interleukin; Th, T-helper cell; TFH, follicular helper T cell; TGF, transforming growth factor; TNF, tumor necrosis factor.

Newborn infants have increased susceptibility to infections with gram-negative organisms because IgM antibodies, powerful **opsonins** that enhance phagocytosis, do not cross the placenta. The other major opsonin, C3b, is also lower in newborn serum than in adults. These factors probably account for impaired phagocytosis of some organisms by newborn polymorphonuclear cells. Maternally transmitted IgG antibodies serve quite adequately for most gram-positive bacteria, and IgG antibodies to viruses offer protection against those agents. Because there is a relative deficiency of the IgG2 subclass in infancy, antibodies to capsular polysaccharide antigens may be deficient. Because premature infants have received less maternal IgG by the time of birth than full-term infants, their serum opsonic activity is low for all types of organisms.

Neonates begin to synthesize antibodies of the IgM class at an increased rate very soon after birth in response to the immense antigenic stimulation of their new environment. Premature infants appear to be as capable of doing this as are full-term infants. At about 6 days after birth, the serum concentration of IgM rises sharply. This rise continues until adult levels are achieved by approximately 1 yr of age. Cord serum from noninfected normal newborns does not contain detectable IgA. Serum IgA is normally first detected at around the 13th day of postnatal life but remains low throughout infancy. Cord serum contains an IgG concentration comparable to or greater than that of maternal serum. Maternal

IgG gradually disappears during the 1st 6-8 mo of life, while the rate of infant IgG synthesis increases (IgG1 and IgG3 faster than IgG2 and IgG4 during the 1st yr) until adult concentrations of total IgG are reached and maintained by 7-8 yr. IgG1 and IgG4 reach adult levels first, followed by IgG3 at 10 yr and IgG2 at 12 yr. The serum IgG level in infants usually reaches a low point at about 3-4 mo of postnatal life. The rate of development of IgE generally follows that of IgA.

After adult concentrations of each of the 3 major immunoglobulins are reached, these levels remain remarkably constant for a normal individual. The capacity to produce specific antibodies to protein antigens is intact at birth, but infants cannot usually produce antibodies to polysaccharide antigens until after 2 yr of age unless the polysaccharide is conjugated to a protein carrier, as is the case for the conjugate *Haemophilus influenzae* type b and *Streptococcus pneumoniae* vaccines.

The percentage of NK cells in cord blood is usually lower than in the blood of children and adults, but the absolute number of NK cells is approximately the same because of the higher lymphocyte count. The capacity of cord blood NK cells to mediate target lysis in either NK-cell assays or antibody-dependent cellular cytotoxicity assays is about two-thirds that of adults.

Lymphoid Organ Development

Lymphoid tissue is proportionally small but rather well developed at birth and matures rapidly in the postnatal period. The thymus is largest relative to body size during fetal life and at birth is ordinarily two-thirds its mature weight, which it attains during the 1st yr of life. It reaches its peak mass, however, just before puberty, then gradually involutes thereafter. By 1 yr of age, all lymphoid structures are mature histologically. Absolute lymphocyte counts in the peripheral blood also reach a peak during the 1st yr of life (see Fig. 149.2). The spleen, however, gradually accrues its mass during maturation and does not reach full weight until adulthood. The mean number of Peyer patches at birth is one-half the adult number, and gradually increases until the adult mean number is exceeded during adolescent years.

Inheritance of Abnormalities in T-, B-, and NK-Cell Development

More than 300 immunodeficiency syndromes have been described. Specific molecular defects have been identified for most diseases. Most are recessive traits with X-linked, autosomal dominant loss of function, and autosomal dominant gain of function also is seen. Defects include those associated with absence of a cell type, either a lineage (e.g., absence of T cells in SCID), absence of a subset of cells (e.g., absence of Tregs in immune dysregulation, polyendocrinopathy, X-linked syndrome), or dysfunction of a cell (e.g., the hemophagocytic lymphohistiocytosis disorders). In some cases, multiple cell types are affected, and in some syndromes, excess of a certain cell type or function disrupts the critical balance needed for immune homeostasis.

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CHAPTER 150

Primary Defects of Antibody Production

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Of the primary immunodeficiency diseases, those affecting antibody production are the most prevalent. Selective absence of IgA is the most common defect, with rates ranging from 1 in 333 to 1 in 18,000 persons among different races and ethnicities. Patients with antibody deficiency are usually recognized because they have recurrent infections with encapsulated bacteria, predominantly in the upper and lower respiratory tracts. Some individuals with selective IgA deficiency or infants with transient hypogammaglobulinemia may have few or no infections. These conditions have a complex and likely polygenic inheritance, as do the common variable immunodeficiency (CVID) syndromes. The gene defects for many primary antibody deficiency disorders have been identified (Table 150.1) and localized (Fig. 150.1). Sometimes the defect is not in the B cell itself but in T cells, which are required for complete B-cell function. Some disorders are caused by unknown factors or are secondary to an underlying disease or its treatment (Table 150.2).

Table 150.1

Genetic Basis of the Most Common Primary Antibody Deficiency Disorders

GENE	PHENOTYPE	DISORDER
BAFFR	CVID	Hypogammaglobulinemia
CD19	CVID	Hypogammaglobulinemia
CD20	CVID	Hypogammaglobulinemia
CD21	CVID	Hypogammaglobulinemia
CD81	CVID	Hypogammaglobulinemia
CTLA4	CVID	Hypogammaglobulinemia, pronounced lymphoproliferation and autoimmunity
ICOS	CVID	Hypogammaglobulinemia, autoimmunity, neoplasia

LRBA	CVID	Hypogammaglobulinemia, pronounced lymphoproliferation and autoimmunity
NFKB2	CVID	Hypogammaglobulinemia, autoimmunity
NFKB1	CVID	Hypogammaglobulinemia, autoimmunity
PIK3CD	CVID	Hypogammaglobulinemia, adenopathy
PI3KR1 (AD)	CVID	Hypogammaglobulinemia
TNFRSF13B	CVID	Hypogammaglobulinemia, low penetrance of disease
Unknown	CVID	Hypogammaglobulinemia, autoimmunity Majority of patients with CVID have no known gene defect.
Unknown	IgG subclass deficiency	Variable association with infection
Unknown	Specific antibody deficiency	Normal immunoglobulin levels with poor vaccine responses
Unknown	Transient hypogammaglobulinemia of infancy	Vaccine responses are usually preserved, and most children outgrow this by age 3 yr.
Unknown	Selective IgA deficiency	Low or absent IgA; low concentrations of all immunoglobulins and of switched memory B cells in CVID
BLNK	Agammaglobulinemia	Absence of antibody production, lack of B cells
BTK	Agammaglobulinemia	Absence of antibody production, lack of B cells, X-linked agammaglobulinemia
CD79A	Agammaglobulinemia	Loss of the Igα required for signal transduction, absence of antibody production, lack of B cells
CD79B	Agammaglobulinemia	Loss of the Igβ required for signal transduction, absence of antibody production, lack of B cells
IGHM	Agammaglobulinemia	Loss of the Ig heavy chain, absence of antibody production, lack of B cells
IGLL1	Agammaglobulinemia	Loss of the surrogate light chain, absence of antibody production, lack of B cells
PI3KR1 (AR)	Agammaglobulinemia	Loss of signal transduction through the B-cell receptor, absence of antibody production, lack of B cells
TCF3	Agammaglobulinemia	Loss of a key transcription factor for B-cell development, absence of antibody production, lack of B cells
AID	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
CD40	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, *Pneumocystis* and *Cryptosporidium* susceptibility
CD154	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, *Pneumocystis* and *Cryptosporidium* susceptibility
INO80	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
MSH6	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies, malignancy
UNG	Class switch defect	Failure to produce IgG, IgA, and IgE antibodies
SH2D1A	X-linked lymphoproliferative disease	Various phenotypes including hypogammaglobulinemia
XIAP	X-linked lymphoproliferative disease	Various phenotypes including hypogammaglobulinemia
CD27	EBV lymphoproliferation	Memory B-cell deficiency Hypogammaglobulinemia
NEMO	Anhidrotic ectodermal dysplasia with immunodeficiency	Phenotype highly variable but includes specific antibody deficiency and CVID

CVID, Common variable immunodeficiency; EBV, Epstein-Barr virus.

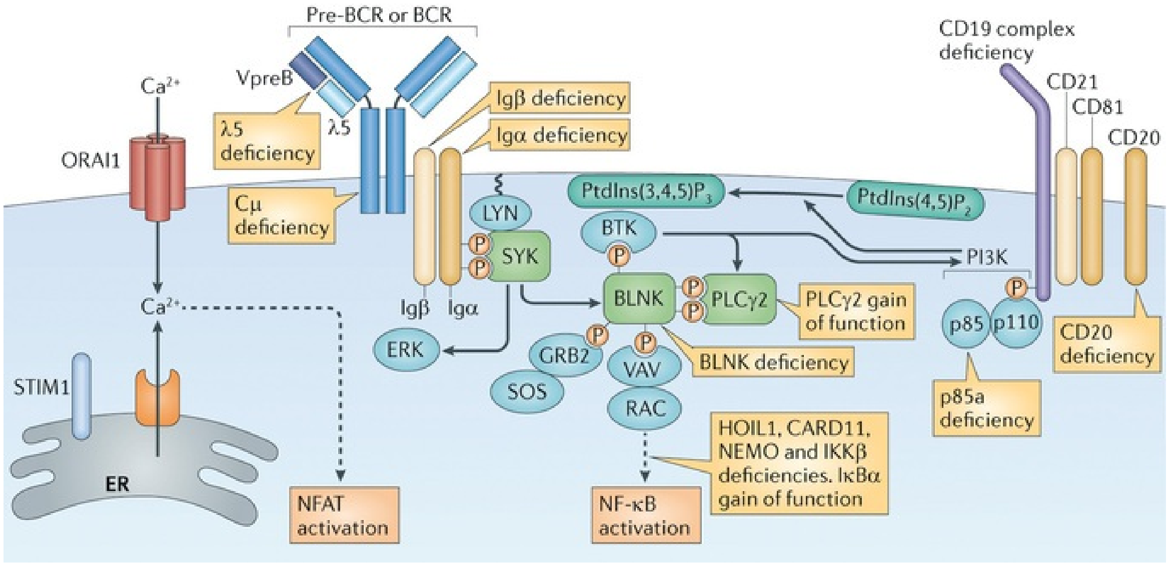
Pre-BCR or BCR
CD19 complex deficiency
Ca2+
VpreB
λ5
λ5 deficiency
Igβ deficiency
Igα deficiency
CD21
CD81
CD20
ORAI1
Cμ deficiency
LYN
PtdIns(3,4,5)P3
PtdIns(4,5)P2
BTK
P
SYK
PI3K
Ca2+
Igβ
Igα
BLNK
PLCγ2
PLCγ2 gain of function
p85
p110
CD20 deficiency
ERK
GRB2
VAV
BLNK deficiency
STIM1
SOS
RAC
p85a deficiency
HOIL1, CARD11, NEMO and IKKβ deficiencies. IκBα gain of function
ER
NFAT activation
NF-κB activation

FIG. 150.1 The pre-B cell receives proliferation and differentiation signals through the pre–B-cell receptor (BCR) and the co-receptors Igα and Igβ. Signaling from the pre-BCR involves the immunoreceptor tyrosine-based activation motifs (ITAMs) of the co-receptors Igα and Igβ, which scaffold and activate the tyrosine kinase SYK. SYK either activates the extracellular signal–regulated kinase (ERK) pathway or phosphorylates (P) (together with LYN) the adaptor protein B-cell linker (BLNK) and Bruton tyrosine kinase (BTK), leading to the activation of phospholipase Cγ2 (PLCγ2) and the phosphoinositide-3 kinase (PI3K) pathway. Defects in this pathway affect the pre-BCR (in Cμ or pseudo light-chain λ5), the pre-BCR signal transduction molecules Igα and Igβ, the downstream molecules BTK, BLNK, and PI3K, components of the co-stimulatory CD19 complex (CD19, CD21, and CD81), and the B-cell marker CD20. The BCR triggers the canonical nuclear factor-κB (NF-κB) pathway through the scaffolding protein CARD11 and activation of the IκB kinase (IKK) complex (comprising IKKα, IKKβ, and NEMO [NF-κB essential modulator]). IKK activation leads to the phosphorylation and degradation of NF-κB inhibitor-α (IκBα) and the subsequent release of the p50-p65 NF-κB heterodimer, which then translocates to the nucleus to regulate gene transcription (*not shown*). Following antigen binding to antigen receptors (e.g., BCR), endoplasmic reticulum Ca^{2+} stores are depleted, STIM1 is activated, and ORAI1 Ca^{2+} release-activated Ca^{2+} channels open, resulting in store-operated Ca^{2+} entry. This influx results in activation of the transcription factor NFAT (nuclear factor of activated T cell). The *dashed arrows* indicate downstream signaling events. ER, Endoplasmic reticulum; PAD, primary antibody deficiency; PtdIns(4,5)P_2 , phosphatidylinositol-4,5-bisphosphate; PtdIns(3,4,5)P_3 , phosphatidylinositol-3,4,5-trisphosphate. (From Durandy A, Kracker S, Fischer A. Primary antibody deficiencies. *Nat Rev Immunol* 13:521, 2013).

Table 150.2

Other Conditions Associated With Humoral Immunodeficiency

GENETIC DISORDERS	
T-cell defects	Most T-cell defects can have a secondary deficit in immunoglobulin.
Complex syndromes	Transcobalamin II deficiency and hypogammaglobulinemia, Wiskott-Aldrich syndrome, ataxia telangiectasia, etc.
Chromosomal anomalies	Chromosome 18q− syndrome 22q11.2 deletion Trisomy 8, trisomy 21
SYSTEMIC DISORDERS	
Malignancy	Chronic lymphocytic leukemia Immunodeficiency with thymoma T-cell lymphoma
Metabolic or physical loss	Immunodeficiency caused by hypercatabolism of immunoglobulin
	Immunodeficiency caused by excessive loss of immunoglobulins and lymphocytes
ENVIRONMENTAL EXPOSURES	
Drug induced	Antimalarial agents Captopril Carbamazepine Glucocorticoids Fenclofenac Gold salts Imatinib Penicillamine Phenytoin Sulfasalazine
Infectious diseases	Congenital rubella Congenital infection with cytomegalovirus Congenital infection with *Toxoplasma gondii* Epstein-Barr virus Human immunodeficiency virus

X-Linked Agammaglobulinemia

Patients with X-linked agammaglobulinemia (**XLA**), or **Bruton agammaglobulinemia** , have a profound defect in B-lymphocyte development resulting in severe hypogammaglobulinemia, an absence of circulating B cells, small to absent tonsils, and no palpable lymph nodes.

Genetics and Pathogenesis

The abnormal gene in XLA maps to q22 on the long arm of the X chromosome and encodes the B-cell protein tyrosine kinase **Btk** (Bruton tyrosine kinase). Btk is a member of the Tec family of cytoplasmic protein tyrosine kinases and is expressed at high levels in all B-lineage cells, including pre-B cells. Some pre-B cells are found in the bone marrow, but the percentage of peripheral blood B lymphocytes is <1%. The percentage of T cells is increased, ratios of T-cell subsets are normal, and T-cell function is intact. The thymus is normal.

Seven **autosomal recessive defects** have also been shown to result in **agammaglobulinemia with an absence of circulating B cell** s (see Table 150.1), including mutations in the genes encoding (1) the μ heavy chain gene; (2) the Igα and (3) Igβ signaling molecules; (4) B-cell linker adaptor protein (BLNK); (5) the surrogate light chain, λ5/14.1; (6) leucine-rich repeat-containing 8 (LRRC8); and (7) the p85α subunit of phosphatidylinositol-3 kinase. These are rare but are clinically indistinguishable from the X-linked form.

Clinical Manifestations

Most boys afflicted with XLA remain well during the first 6-9 mo of life by virtue of maternally transmitted IgG antibodies. Thereafter, they acquire infections with extracellular pyogenic organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae,* unless they are given prophylactic antibiotics or immunoglobulin therapy. Infections include sinusitis, otitis media, pneumonia, or, less often, sepsis or meningitis. Infections with *Mycoplasma* are also particularly problematic. Chronic fungal infections are seen; *Pneumocystis jiroveci* pneumonia rarely occurs. Viral infections are usually handled normally, with the exceptions of hepatitis viruses and enteroviruses. There were several examples of **paralysis** when live polio vaccine was administered to these patients, and chronic, eventually fatal, central nervous system (CNS) infections with various echoviruses and coxsackieviruses have occurred in a significant number of patients. An enterovirus-associated **myositis** resembling dermatomyositis has also been observed. **Neutropenia** , typically seen at diagnosis when infected, can be associated with *Pseudomonas* or staphylococcal infections.

Diagnosis

The diagnosis of XLA should be suspected if **lymphoid hypoplasia** is found on physical examination (minimal or no tonsillar tissue and no palpable lymph nodes), and serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits for appropriate age- and race-matched controls; total immunoglobulins are usually <100 mg/dL. Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low in XLA, whereas they are typically normal in transient hypogammaglobulinemia of infancy. Flow cytometry is an important test to demonstrate the **absence of circulating B cells** , which will distinguish XLA from most types of CVID, the hyper-IgM syndrome, and transient hypogammaglobulinemia of infancy.

Common Variable Immunodeficiency

CVID is a syndrome characterized by hypogammaglobulinemia. Serum IgG must be <2 standard deviations below the age-adjusted norms, with low IgA and or IgM levels. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that enterovirus meningoencephalitis is rare in patients with CVID (Table 150.3). In contrast to XLA, the sex distribution in CVID is almost equal, the age at onset is later, and infections may be less severe. CVID is the most common of the antibody defects.

Table 150.3

Main Phenotypes of Primary Antibody Deficiencies

PHENOTYPE	MAIN CLINICAL FEATURES	MAIN B-CELL FEATURES
Agammaglobulinemia	Bacterial infections (in respiratory tract) and enterovirus infections	Absence of CD19 B cells
Combined variable immunodeficiency (CVID)	Bacterial infections (in respiratory tract and gut), autoimmunity, cancer, and increased risk of granuloma	Highly variable; may see decreased memory B cells
Class switch defects	Bacterial and opportunistic infections	Decreased frequency of memory B cells
Selective IgA deficiency	Most often asymptomatic	Normal
IgG subclass deficiency	Frequent bacterial infections; diagnosis after age 2 yr	B-cell subsets normal
Selective polysaccharide antibody deficiency	Bacterial infections (after age 2 yr)	Normal IgG (including IgG2 and IgG4) levels, normal B-cell subsets

Genetics and Pathogenesis

CVID is a phenotypic diagnosis with a polygenic inheritance in most cases.

Genes known to produce the CVID phenotype when mutated include *ICOS* (inducible co-stimulator) deficiency, *SH2DIA* (responsible for X-linked lymphoproliferative disease [XLP]), *CD19*, *CD20*, *CD21*, *CD81*, *BAFF-R* (B-cell–activating factor of the tumor necrosis factor family of receptors), *TACI* (transmembrane activator, calcium modulator, and cyclophilin ligand interactor). These mutations in aggregate account for <10% of all cases of CVID. With rare exceptions, management of CVID does not depend on a genetic diagnosis. In the setting of atypical infections or autoimmunity, pursuing a genetic diagnosis can be useful because some genetic etiologies can have a poor prognosis and transplantation should be considered.

Despite normal numbers of circulating B cells in many patients and the presence of lymphoid cortical follicles, blood B cells from CVID patients do not differentiate normally into immunoglobulin-producing cells. They may have a deficiency of switched memory B cells.

Clinical Manifestations

The serum immunoglobulin and antibody deficiencies in CVID are associated with recurrent sinopulmonary infections. Repeated pulmonary infections may produce bronchiectasis. Sepsis and meningitis with encapsulated bacteria occur more frequently than in the general population. Patients with recurrent infections as their only manifestation typically have a normal life expectancy and do well with immunoglobulin replacement. The presence of autoimmune disease or lymphoproliferation confers a poor prognosis. Patients with CVID often have autoantibody formation and normal-sized or enlarged tonsils and lymph nodes; about 25% of patients have splenomegaly. CVID has also been associated with a spruelike enteropathy with or without nodular lymphoid hyperplasia of the intestine. Other autoimmune diseases include alopecia areata, hemolytic anemia, thrombocytopenia, gastric atrophy, achlorhydria, and pernicious anemia. Lymphoid interstitial pneumonia, intestinal lung disease, pseudolymphoma, B-cell lymphomas, amyloidosis, and noncaseating sarcoid-like granulomas of the lungs, spleen, skin, and liver also occur. There is an increased risk of lymphomas.

Selective IgA Deficiency

An isolated absence or near absence (<5 mg/dL) of serum and secretory IgA is the most common well-defined immunodeficiency disorder, with a disease frequency as high as 0.33% in some populations. Patients may be asymptomatic or may develop sinopulmonary or gastrointestinal (GI) infections (especially *Giardia*). IgA deficiency is also associated with celiac disease and autoimmune disorders. The diagnosis cannot be made until about 4 yr of age, when IgA levels should be matured to adult levels.

The basic defect resulting in IgA deficiency is unknown. Phenotypically normal blood B cells are present. This defect also often occurs in pedigrees containing individuals with CVID. Indeed, IgA deficiency may evolve into CVID. IgA deficiency is noted in patients treated with the same drugs associated with producing CVID (phenytoin, D -penicillamine, gold, and sulfasalazine), suggesting that environmental factors may trigger this disease in a genetically susceptible person.

Clinical Manifestations

Infections occur predominantly in the respiratory, GI, and urogenital tracts. Bacterial agents responsible are the same as in other antibody deficiency syndromes. Intestinal giardiasis is common. Serum concentrations of other immunoglobulins are usually normal in patients with selective IgA deficiency, although IgG2 (and other) subclass deficiency has been reported.

Serum antibodies to IgA are reported in as many as 44% of patients with selective IgA deficiency. These antibodies can cause nonhemolytic transfusion reactions. Washed erythrocytes (frozen blood would have this done routinely) or blood products from other IgA-deficient individuals should be administered to patients with IgA deficiency. Many intravenous immune globulin (IVIG) preparations contain sufficient IgA to cause reactions. However, administration of IVIG, which is >99% IgG, is not indicated because most IgA-deficient patients make IgG antibodies normally.

IgG Subclass Deficiencies

Some patients have deficiencies of 1 or more of the 4 subclasses of IgG despite normal or elevated total IgG serum concentration. Some patients with absent or very low concentrations of IgG2 also have IgA deficiency. Other patients with IgG subclass deficiency have gone on to develop CVID, suggesting that the presence of IgG subclass deficiency may be a marker for more generalized immune dysfunction. The biologic significance of the numerous moderate deficiencies of IgG subclasses that have been reported is difficult to assess. IgG subclass measurement is not cost-effective in evaluating immune function in the child with recurrent infection. The more relevant issue is a patient's capacity to make specific antibodies to protein and polysaccharide antigens, because profound deficiencies of antipolysaccharide antibodies have been noted even in the presence of normal concentrations of IgG2. IVIG should not be administered to patients with IgG subclass deficiency unless they are shown to have a deficiency of antibodies to a broad array of antigens.

Immunoglobulin Heavy- and Light-Chain Deletions

Some completely asymptomatic individuals have been documented to have a total absence of IgG1, IgG2, IgG4, and/or IgA1 as a result of gene deletions. These patients illustrate the importance of assessing specific antibody formation before deciding to initiate IVIG therapy in IgG subclass–deficient patients.

Transient Hypogammaglobulinemia of Infancy

A common laboratory finding in infants, transient hypogammaglobulinemia represents developmental delay in the production of immunoglobulin. It is thought to occur in as many as 1 : 1000 children. Most infants begin to produce IgG in the 1st 3 mo of life, and the quantity produced increases throughout infancy. For reasons incompletely understood, a small number of infants either begin late or do not increases their production as expected. This condition will resolve with no intervention but represents a source of diagnostic confusion. A key distinction is that responses to vaccines are usually preserved in this condition, whereas in the others, responses will be low to absent.

Class Switch Defects

The **hyper-IgM syndrome** is genetically heterogeneous and characterized by normal or elevated serum IgM levels associated with low or absent IgG, IgA, and IgE serum levels, indicating a defect in the class switch recombination (CSR) process. Causative mutations have been identified in the CD40 ligand gene on the X chromosome and 3 genes on autosomal chromosomes: the activation-induced cytidine deaminase (**AID**) gene, the uracil DNA glycosylase gene (**UNG**), and the **CD40** gene on chromosome 20. Distinctive clinical features permit presumptive recognition of the type of mutation in these patients, thereby aiding proper choice of therapy. All such patients should undergo molecular analysis to ascertain the affected gene for purposes of genetic counseling, carrier detection, and decisions regarding definitive therapy.

X-Linked Hyper-IgM Caused by Mutations in CD40 Ligand Gene

X-linked hyper IgM is caused by mutations in the gene that encodes the CD40 ligand (CD154, CD40L), which is expressed on activated T-helper (Th) cells. Boys with this syndrome have very low serum concentrations of IgG and IgA, with a usually normal or sometimes elevated concentration of polyclonal IgM; may or may not have small tonsils; usually have no palpable lymph nodes; and often have profound neutropenia.

Genetics and Pathogenesis

The B cells are actually normal in this condition; the defect is in the T cells. CD40L is the ligand for CD40, which is present on B cells and monocytes. CD40L is upregulated on activated T cells. Mutations result in an inability to signal B cells to undergo isotype switching, and thus the B cells produce only IgM. The failure of T cells to interact with B cells through this receptor-ligand pair also causes a failure of upregulation of the B-cell and monocyte surface molecules CD80 and CD86 that interact with CD28/CTLA4 on T cells, resulting in failure of “crosstalk” between immune system cells.

Clinical Manifestations

Similar to patients with XLA, boys with the CD40 ligand defect become symptomatic during the 1st or 2nd yr of life with recurrent pyogenic infections, including otitis media, sinusitis, pneumonia, and tonsillitis. They have marked susceptibility to *P. jiroveci* pneumonia and can be neutropenic. Lymph node histology shows only abortive germinal center formation with severe depletion and phenotypic abnormalities of follicular dendritic cells. These patients have normal numbers of circulating B lymphocytes, but a decreased frequency of CD27+ memory B cells. Circulating T cells are also present in normal number and in vitro responses to mitogens are normal, but there is decreased antigen-specific T-cell function. In addition to opportunistic infections such as *P. jiroveci* pneumonia, there is an increased incidence of extensive verruca vulgaris lesions, *Cryptosporidium* enteritis, subsequent liver disease, and an increased risk of malignancy.

Treatment

Because of the poor prognosis, the treatment of choice is an HLA-identical hematopoietic stem cell transplant at an early age. Alternative treatment for this condition is monthly infusion of IVIG. In patients with severe neutropenia, the use of granulocyte colony-stimulating factor has been beneficial.

Autosomal Recessive Hyper-IgM

Genetics and Pathogenesis

In contrast to patients with the CD40L defect, B cells from these patients are not able to switch from IgM-secreting to IgG-, IgA-, or IgE-secreting cells, even when co-cultured with normal T cells. The defects are all B cell intrinsic. The most common autosomal recessive defect in a gene that encodes AID. AID deaminates cytosine into uracil in targeted DNA, which is followed by uracil removal by UNG. Severely impaired CSR was found in 3 hyper-IgM patients reported to have UNG deficiency. Their clinical characteristics were similar to those with AID deficiency, with increased susceptibility to bacterial infections and lymphoid hyperplasia. Histologic examination of the enlarged lymph nodes reveals the presence of giant germinal centers (5-10 times > normal) filled with highly proliferating B cells. Autosomal recessive hyper-IgM can be caused by defects in CD40. Clinical manifestations included recurrent sinopulmonary infections, *P. jiroveci* pneumonia, and *Cryptosporidium parvum* infections, very similar to the manifestations seen in X-linked hyper IgM syndrome.

Clinical Manifestations

Concentrations of serum IgG, IgA, and IgE are very low in AID, UNG, and CD40 deficiencies. In contrast to the CD40 ligand defect, however, the serum

IgM concentration in patients with AID deficiency is usually markedly elevated and polyclonal. Patients with AID and UNG mutations have lymphoid hyperplasia, are generally older at age at onset, do not have susceptibility to *P. jiroveci* pneumonia, often do have isohemagglutinins, and are much less likely to have neutropenia unless it occurs on an autoimmune basis. They have a tendency, however, to develop autoimmune and inflammatory disorders, including diabetes mellitus, polyarthritis, autoimmune hepatitis, hemolytic anemia, immune thrombocytopenia, Crohn disease, and chronic uveitis.

Treatment and Prognosis

With early diagnosis and monthly infusions of IVIG, as well as good management of infections with antibiotics, patients with AID and UNG mutations generally have a more benign course than do boys with the CD40L or CD40 defects. CD40 deficiency is rare but appears to mimic the manifestations of CD40L quite closely.

X-Linked Lymphoproliferative Disease

There are two types of X-linked lymphoproliferative disease (Table 150.4). They have distinct clinical features but share a susceptibility to **Epstein-Barr virus (EBV)** and the development of **hemophagocytic lymphohistiocytosis (HLH)** .

Table 150.4

Features of SAP (SH2D1A) and XIAP Deficiency

FEATURE	SAP DEFICIENCY (XLP)	XIAP DEFICIENCY
CLINICAL MANIFESTATIONS		
HLH	Yes	Yes
Hypogammaglobulinemia	Yes	Yes
Lymphoma	Yes	No
Aplastic anemia	Yes	No
Vasculitis	Yes	No
GENETICS		
Causative gene	*SH2D1A*	*XIAP*
Genetic locus	Xq25	Xq25
Encoded protein	SAP	XIAP
Effect of mutation	Reduced, absent protein expression	Reduced, absent or truncated protein
IMMUNE CELL FUNCTIONS		

Natural killer T (NKT) cell cytotoxicity/degranulation	Reduced	Normal
NKT cell number (blood)	Absent	Variable
Restimulation-induced death	Reduced	Increased
Memory B-cell numbers	Reduced	Not reported
TREATMENT OPTIONS		
HLH	Immunosuppression and/or chemotherapy (etoposide) Consideration of rituximab	Immunosuppression and/or chemotherapy (etoposide)
Humoral deficiency	Intravenous IgG infusions	Consider rituximab for EBV-positive cases Intravenous IgG infusions
Lymphoma	Standard chemotherapy	
Curative therapy	Stem cell transplantation	Stem cell transplantation

EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; SAP, SLAM-associated protein; XIAP, X-linked inhibitor of apoptosis protein.

From Rezaei N, Mahmoudi E, Aghamohamadi A, et al: X-linked lymphoproliferative syndrome: a genetic condition typified by the triad of infection, immunodeficiency and lymphoma, *Br J Haematol* 152:14, 2010.

Genetics and Pathogenesis

The defective gene in **XLP type I** was localized to Xq25, cloned, and the gene product was initially named SAP (SLAM-associated protein), but is now known officially as SH2D1A. SLAM (signaling lymphocyte activation molecule) is an adhesion molecule that is upregulated on both T and B cells with infection and other stimulation. The absence of SH2D1A can lead to an uncontrolled cytotoxic T-cell immune response to EBV. The SH2D1A protein associates permissively with 2B4 on natural killer (NK) cells; thus selective impairment of 2B4-mediated NK-cell activation also contributes to the immunopathology of XLP.

XLP type 2 is caused by a mutation in *XIAP* (X-linked inhibitor of apoptosis protein). Disease manifestations are similar to XLP. The precise role of this protein in the susceptibility to EBV has not been elucidated.

Clinical Manifestations

Affected males are usually healthy until they acquire EBV infection. The mean age of presentation is <5 yr. There are 3 major clinical phenotypes: (1) fulminant, often fatal, infectious mononucleosis (50% of cases); (2) lymphomas, predominantly involving B-lineage cells (25%); and (3) acquired hypogammaglobulinemia (25%). A less common manifestation is CNS vasculitis. There is a marked impairment in production of antibodies to the EBV nuclear antigen, whereas titers of antibodies to the viral capsid antigen have ranged from absent to greatly elevated. XLP has an unfavorable prognosis. Unless there is a family history of XLP, diagnosis before the onset of complications is difficult because affected individuals are asymptomatic initially.

In 2 pedigrees reported, boys in one arm of each pedigree were diagnosed with CVID, whereas those in the other arms had fulminant infectious mononucleosis. The family members with CVID never gave a history of infectious mononucleosis. All affected members of each pedigree had the same distinct *SH2D1A* mutation, however, despite the different clinical phenotypes. Because the *SH2D1A* mutation was the same but the phenotype varied in these families, XLP should be considered in all males with a diagnosis of CVID, particularly if there is more than 1 male family member with this phenotype.

150.1

Treatment of B-Cell Defects

Kathleen E. Sullivan, Rebecca H. Buckley

Except for the CD40 ligand defect and XLP, for which stem cell transplantation is recommended, judicious use of antibiotics to treat documented infections and regular administration of immunoglobulin are the only effective treatments for primary B-cell disorders. The most common forms of replacement therapy are either intravenous or subcutaneous immune globulin (IVIG or SCIG). Broad antibody deficiency should be carefully documented before such therapy is initiated. The rationale for the use of IVIG or SCIG is to provide missing antibodies, not to raise the serum IgG or IgG subclass level. The development of safe and effective immunoglobulin preparations is a major advance in the treatment of patients with severe antibody deficiencies, although it is expensive and there have been national shortages. Almost all commercial preparations are isolated from normal plasma by the Cohn alcohol fractionation method or a modification of it. Cohn fraction II is then further treated to remove aggregated IgG. Additional stabilizing agents such as sugars, glycine, and albumin are added to prevent reaggregation and protect the IgG molecule during lyophilization. The ethanol used in preparation of immunoglobulin inactivates HIV, and an organic solvent/detergent step inactivates hepatitis B and C viruses. Some preparations are also nanofiltered to remove infectious agents. Most commercial lots are produced from plasma pooled from 10,000 to 60,000 donors and therefore contain a broad spectrum of antibodies. Each pool must contain adequate levels of antibody to antigens in various vaccines, such as tetanus and measles. However, there is no standardization based on titers of antibodies to more clinically relevant organisms, such as *S. pneumoniae* and *H. influenzae* type b.

The IVIG and SCIG preparations available in the United States have similar efficacy and safety. Rare transmission of hepatitis C virus has occurred in the past, but this has been resolved by the additional treatment step. There has been no documented transmission of HIV by any of these preparations. *IVIG or SCIG at a dose of 400 mg/kg per month* achieves trough IgG levels close to the normal range. Higher doses are indicated in patients with chronic or severe respiratory infections. Systemic reactions may occur, but rarely are these true anaphylactic reactions. Neutropenia associated with B-cell defects has responded to granulocyte colony-stimulating factor.

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CHAPTER 151

Primary Defects of Cellular Immunity

Kathleen E. Sullivan, Rebecca H. Buckley

Defects in cellular immunity, historically referred to *T-cell defects,* comprise a large number of distinct immune deficiencies. The manifestations usually include prolonged viral infections, opportunistic fungal or mycobacterial infections, and a predisposition to autoimmunity. To facilitate conceptualization of this large and complex category, this chapter describes immunodeficiencies where the defect primarily affects T cells and those where the defect alters function of many cell types. Chapter 152.1 describes severe combined immunodeficiency (SCID). These disorders are further approached clinically by considering whether or not nonhematologic features are present.

Chromosome 22Q11.2 Deletion Syndrome

Chromosome 22q11.2 deletion syndrome is the most common of the T-cell disorders, occurring in about 1 in 3,000 births in the United States. Chromosome 22q11.2 deletion disrupts development of the 3rd and 4th pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands. Other structures forming at the same age are also frequently affected, resulting in anomalies of the great vessels (right-sided aortic arch), esophageal atresia, bifid uvula, congenital heart disease (conotruncal, atrial, and ventricular septal defects), a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and posteriorly rotated ears (see Chapters 98 and 128). The diagnosis is often first suggested by hypocalcemic seizures during the neonatal period.

Genetics and Pathogenesis

Chromosome 22q11.2 deletions occur with high frequency because complex repeat sequences that flank the region represent a challenge for DNA polymerase. This condition is inherited in an autosomal dominant fashion and occurs with comparable frequency in all populations. Within the deleted region, haplosufficiency for the TBX1 transcription factor appears to underlie the majority of the phenotype. The phenotype is highly variable; a subset of patients has a phenotype that has also been called **DiGeorge syndrome** , **velocardiofacial syndrome** , or **conotruncal anomaly face syndrome** .

Variable hypoplasia of the thymus occurs in 75% of the patients with the deletion, which is more frequent than total aplasia; aplasia is present in <1% of patients with 22q11.2 deletion syndrome. Slightly less than half of patients with complete thymic aplasia are hemizygous at chromosome 22q11.2. Approximately 15% are born to diabetic mothers. Another 15% of infants have no identified risk factors. Approximately one third of infants with complete DiGeorge syndrome have **CHARGE association** (*c* oloboma, *h* eart defect, choanal *a* tresia, growth or developmental *r* etardation, *g* enital hypoplasia, and *e* ar anomalies including deafness). Mutations in the chromodomain helicase DNA-binding protein 7 (CHD7) gene on chromosome 8q12.2 are found in approximately 60–65% of individuals with CHARGE syndrome; a minority have mutations in *SEMA3E* .

Absolute lymphocyte counts are usually only moderately low for age. The CD3 T-cell counts are variably decreased in number, corresponding to the degree of thymic hypoplasia. Lymphocyte responses to mitogen stimulation are absent, reduced, or normal, depending on the degree of thymic deficiency. Immunoglobulin levels are often normal, but there is an increased frequency of IgA deficiency, low IgM levels, and some patients develop progressive hypogammaglobulinemia.

Clinical Manifestations

Children with partial thymic *hypoplasia* may have little trouble with infections and grow normally. Patients with thymic *aplasia* resemble patients with SCID in their susceptibility to infections with low-grade or opportunistic pathogens, including fungi, viruses, and *Pneumocystis jiroveci* , and to graft-versus-host disease from nonirradiated blood transfusions. Patients with complete DiGeorge syndrome can develop an atypical phenotype in which oligoclonal T-cell populations appear in the blood associated with rash and lymphadenopathy. These atypical patients appear phenotypically similar to patients with **Omenn syndrome** or maternal T-lymphocyte engraftment.

It is critical to ascertain in a timely manner whether an infant has thymic aplasia, because this disease is fatal without treatment. A T-cell count should be obtained on all infants born with primary hypoparathyroidism, CHARGE syndrome, and conotruncal cardiac anomalies with syndromic features. Some infants are being identified by newborn screening for SCID and when 22q11.2 deletion is suspected, a calcium level should be obtained at the time of T-cell evaluation. The 3 manifestations with the highest morbidity in early infancy are profound immunodeficiency, severe cardiac anomaly, and seizures from hypocalcemia. Thus an early focus on these concerns is warranted even before the diagnosis is confirmed. Affected patients may develop autoimmune cytopenias, juvenile idiopathic arthritis, atopy, and malignancies (lymphomas).

Treatment

The immunodeficiency in thymic aplasia is correctable by cultured unrelated **thymic tissue transplants** . Some infants with thymic aplasia have been given nonirradiated unfractionated bone marrow or peripheral blood transplants from a human leukocyte antigen–identical sibling, with subsequent improved immune function because of adoptively transferred T cells. Infants and children with low T-cell counts but not low enough to consider transplantation should be monitored for evolution of immunoglobulin defects. Infections in these patients are multifactorial. Their anatomy may not favor drainage of secretions; they have a higher rate of atopy, which may complicate infections; and their host defense may allow persistence of infections. Interventions range from hand hygiene, probiotics, prophylactic antibiotics, and risk management to immunoglobulin replacement for those who have demonstrated defective humoral immunity.

T-Cell Activation Defects

T-cell activation defects are characterized by the presence of normal or elevated numbers of blood T cells that appear phenotypically normal but fail to proliferate or produce cytokines normally in response to stimulation with mitogens, antigens, or other signals delivered to the TCR, owing to defective signal transduction from the TCR to intracellular metabolic pathways (Fig. 151.1). These patients have problems similar to those of other T-cell–deficient individuals, and some with severe T-cell activation defects may clinically resemble SCID patients (Table 151.1). In some cases, susceptibility to a single pathogen or a limited number of pathogens dominates the clinical phenotype. Susceptibility to Epstein-Barr virus, cytomegalovirus, and papillomavirus is common in this set of T-cell defects. Most individuals with significant T-cell activation defects will require a hematopoietic stem cell transplant. Although each infection may be manageable early in life, the long-term prognosis is not favorable in many of these conditions.

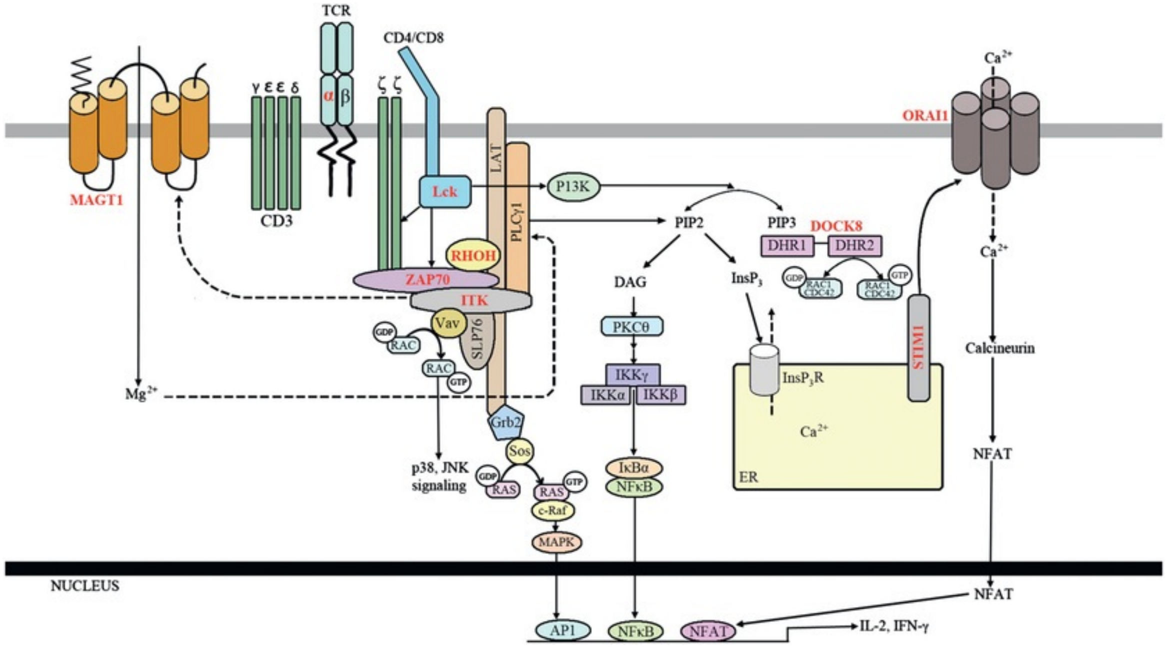
TCR
CD4/CD8
γ ε ε δ
α β
ζ ζ
MAGT1
CD3
Lck
LAT
PI3K
PLCγ1
PIP2
PIP3
DOCK8
DHR1
DHR2
RHOH
ZAP70
ITK
DAG
InsP$_3$
GDP
RAC1 CDC42
GTP
Vav
GDP
RAC
SLP76
PKCθ
RAC
GTP
IKKγ
IKKα
IKKβ
InsP$_3$R
STIM1
ORAI1
Ca^{2+}
Calcineurin
Mg^{2+}
Grb2
Sos
Ca^{2+}
p38, JNK signaling
GDP
RAS
RAS
GTP
IκBα
NFκB
ER
NFAT
c-Raf
MAPK
NUCLEUS
NFAT
AP1
NFκB
NFAT
IL-2, IFN-γ

FIG. 151.1 Schematic representation of signaling through the T-cell receptor–CD3 complex. Molecules for which mutations have been associated with partial defect of T-cell development and impaired T-cell function are indicated in *red* and highlighted in boldface . AP1, Activator protein 1; DHR, DOCK-homology region; Grb2, growth factor receptor-bound protein 2; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NFAT, nuclear factor of activated T cells; NFκB, nuclear factor κB; PI3K, phosphoinositide-3 kinase; PIP3, phosphatidylinositol (3,4,5)-triphosphate. (From Notarangelo L: Partial defects of T-cell development associated with poor T-cell function, *J Allergy Clin Immunol* 131:1299, 2013.)

Table 151.1

Genetic Basis of Primary Cellular Immunodeficiency Diseases

GENE PRODUCT	**EFFECT ON T CELLS**	**INFECTION SUSCEPTIBILITY**
Lck	↓↓ CD4 CD8	Viral infections predominantly
CD8α	↓↓ CD8 deficiency	Viral infections predominantly
ZAP-70	CD8 deficiency	Viral infections predominantly
RhoH	↓ Naïve $CD4^{+}$ cells	Warts
ITK	↓ Naïve $CD4^{+}$ cells Absence of NKT cells	Epstein-Barr virus
22q11.2 deletion	Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)	Highly variable
CD3γ and ε	CD3 deficiency	Viral infections predominantly
TRAC	TCR-αβ T-cell deficiency	Similar to SCID
Coronin-1A	↓↓ CD4 ↓↓ CD8	Similar to SCID
MST1/STK4	↓ Naïve T cells Low number of recent thymic emigrants, restricted T-cell repertoire	Warts
AIRE	APECED, chronic mucocutaneous candidiasis, parathyroid and adrenal autoimmunity	Candida
TBX1	Thymic hypoplasia	Similar phenotype with 22q11.2 deletion

AIRE, Autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis–ectodermal dysplasia; Ig, immunoglobulin; ITK, IL-2–inducible tyrosine kinase deficiency; MST1, macrophage-stimulating factor 1; NKT, natural killer T; RhoH, Ras homology family member H; SCID, severe combined immunodeficiency; STK4, serine threonine kinase 4; TCR, T-cell receptor; TRAC, T-cell receptor α chain constant region; ZAP-70, zeta-associated protein 70.

Chronic Mucocutaneous Candidiasis

Chronic mucocutaneous candidiasis (**CMC**) is a syndrome characterized by impaired immune responsiveness to *Candida.* Some of the known gene defects with CMC have **autoimmune polyendocrinopathy syndrome type 1** (**APS1** , or autoimmune polyendocrinopathy-candidiasis–ectodermal dystrophy [**APECED**]). One of the other genetic types of CMC is associated with autoimmunity and predisposition to other infections (*STAT1* gain-of-function mutations). However, most of the specific genetic types of CMC have isolated susceptibility to *Candida* . These types of CMC relate to defects in the Th17 cell pathway. Autosomal recessive deficiency in the interleukin-17 receptor A (IL-17RA) chain, and an autosomal dominant deficiency of the cytokine IL-17F are both associated with predisposition to *Candida* . Other immunodeficiencies in which *Candida* occurs in the context of other infections also affect the Th17 cells. Another CMC genetic type, caused by mutations in *CARD9* , has a strong predisposition to *Candida* but also to other fungi.

Although the underlying gene defects are varied, the clinical presentation of CMC is usually similar. Symptoms can begin in the 1st mo of life or as late as the 2nd decade. The disorder is characterized by chronic and severe *Candida* skin and mucous membrane infections. Patients rarely develop systemic *Candida* disease, except as noted below. Topical antifungal therapy can provide limited improvement early in the course of the disease, but systemic courses of azoles are usually necessary; antifungal resistance often develops later in life. The infection usually responds temporarily to treatment, but it is not eradicated and recurs. Patients with *CARD9* gene mutations have a more severe fungal susceptibility than typical CMC patients. Two described patients with *CARD9* mutations had fungal sepsis in addition to CMC; deep tissue dermatophyte infections were also present.

Autoimmune Polyendocrinopathy-Candidiasis–Ectodermal Dysplasia

Patients with this syndrome present with CMC and autoimmune polyendocrinopathy, usually developing hypoparathyroidism and Addison disease before adulthood. Additional features include male and female hypogonadism, chronic active hepatitis, alopecia, vitiligo, pernicious anemia, enamel hypoplasia, type 1 diabetes, asplenia, malabsorption, interstitial nephritis, hypothyroidism, hypopituitarism, and Sjögren syndrome. APECED, or APS1, is caused by a mutation in the autoimmune regulator *(AIRE)* gene (see Table 151.1). The gene product, AIRE, is expressed at high levels in purified human thymic medullary stromal cells and is thought to regulate the cell surface expression of tissue-specific proteins such as insulin and thyroglobulin. Expression of these self proteins allows for the negative selection of autoreactive T cells during their development. Failure of negative selection results in organ-specific autoimmune destruction.

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CHAPTER 152

Immunodeficiencies Affecting Multiple Cell Types

Jennifer R. Heimall, Jennifer W. Leiding, Kathleen E. Sullivan, Rebecca H. Buckley

The manifestations of immune deficiencies that affect multiple cell types range from profound to mild; these conditions can present with severe infection, recurrent infections, unusual infections, or autoimmunity. The most profound disorder is severe combined immunodeficiency. Other combined immunodeficiencies include defects of innate immunity and defects leading to immune dysregulation; the latter category is typically associated with profound autoimmunity. Combined immunodeficiencies are characterized by a predisposition to viral infections, and the innate immunodeficiencies are susceptible to a range of bacteria.

152.1

Severe Combined Immunodeficiency

Kathleen E. Sullivan, Rebecca H. Buckley

Keywords

SCID

newborn screening
lymphoid development

Severe combined immunodeficiency (**SCID**) is caused by diverse genetic mutations that lead to absence of T- and B-cell function. Patients with this group of disorders have the most severe immunodeficiency.

Pathogenesis

SCID is caused by mutations in genes crucial for lymphoid cell development (Table 152.1 and Fig. 152.1). All patients with SCID have very small thymuses that contain no thymocytes and lack corticomedullary distinction or Hassall corpuscles. The thymic epithelium appears histologically normal. Both the follicular and the paracortical areas of the spleen are depleted of lymphocytes. Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped.

Table 152.1

Genetic Basis of SCID and SCID Variants

DISEASE	INHERITANCE	PRESUMED PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Reticular dysgenesis	AR	Impaired mitochondrial energy metabolism and leukocyte differentiation	Severe neutropenia, deafness. Mutations in adenylate kinase 2	GCSF, HSCT
Adenosine deaminase deficiency	AR	Accumulation of toxic purine nucleosides	Neurologic, hepatic, renal, lung, and skeletal and bone marrow abnormalities	HSCT, PEG-ADA, gene therapy
IL-2Rγ deficiency	X-linked	Abnormal signaling through by IL-2 receptor and other receptors containing γc (IL-4, -7, -9, -15, -21)	None	HSCT
Jak3 deficiency	AR	Abnormal signaling downstream of γc	None	HSCT
RAG1 and RAG2 deficiency	AR	Defective V(D)J recombination	None	HSCT
Artemis deficiency	AR	Defective V(D)J recombination, radiation sensitivity	*DCLERE1C* gene defects	HSCT
DNA-PK deficiency	AR	Defective V(D)J recombination	None	HSCT
DNA ligase IV	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bone	HSCT

deficiency			marrow abnormalities, lymphoid malignancies	
Cernunnos-XLF	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, birdlike facies, bone defects	HSCT
CD3δ deficiency	AR	Arrest of thymocytes differentiation at $CD4^-$ $CD8^-$ stage	Thymus size may be normal	HSCT
CD3ε deficiency	AR	Arrest of thymocytes differentiation at $CD4^-$ $CD8^-$ stage	γ/δ T cells absent	HSCT
CD3ζ deficiency	AR	Abnormal signaling	None	HSCT
IL-7Rα deficiency	AR	Abnormal IL-7R signaling	Thymus absent	HSCT
CD45 deficiency	AR		None	HSCT
Coronin-1A deficiency	AR	Abnormal T-cell egress from thymus and lymph nodes	Normal thymus size. Attention deficit disorder.	HSCT

AR, Autosomal recessive; GCSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; IL, interleukin; Jak3, Janus kinase 3; PEG-ADA, polyethylene glycol-modified adenosine deaminase; RAG1, RAG2, recombinase-activating genes 1 and 2; V(D)J, variable, diversity, joining domains.

(Adapted from Roifman, CM. Grunebaum E: Primary T-cell immunodeficiencies. In Rich RR, Fleisher TA, Shearer WT, et al, editors: *Clinical immunology,* ed 4. Philadelphia, 2013, Saunders, pp 440–441).

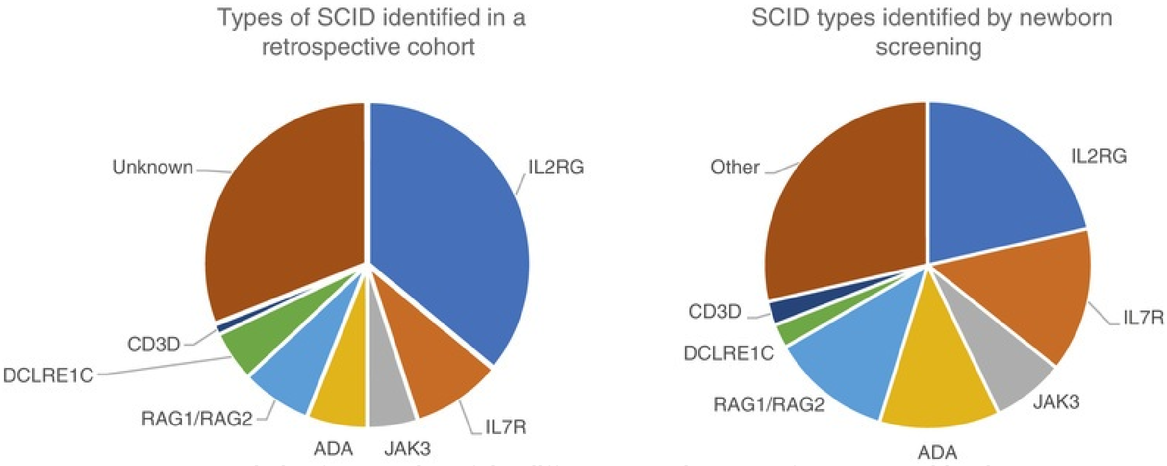

FIG. 152.1 **Relative frequencies of the different genetic types of severe combined immunodeficiency (SCID). ADA, Adenosine deaminase; IL-7R, interleukin 7 receptor; JAK, Janus kinase; RAG, recombinase-activating gene.**

Clinical Manifestations

SCID is included in the newborn screening program in many states. Thus, infants are identified prior to symptoms, which has dramatically improved the survival of infants with SCID. A few genetic types of SCID are not detected by newborn screening, and there are a few states where newborn screening for SCID is not yet performed.

When infants with SCID are not detected through newborn screening, they most often present with **infection** . Diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections are common presentations. Infections with a variety of opportunistic organisms, either through direct exposure or immunization, can lead to death. Potential threats include *Candida albicans, Pneumocystis jiroveci* , parainfluenza 3 virus, adenovirus, respiratory syncytial virus (RSV), rotavirus vaccine, cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus, measles virus, MMRV (measles, mumps, rubella, varicella) vaccine, or bacille Calmette-Guérin (BCG) vaccine. Affected infants also lack the ability to reject foreign tissue and are therefore at risk for severe or fatal **graft-versus-host disease (GVHD)** from T lymphocytes in nonirradiated blood products or maternal immunocompetent T cells that crossed the placenta while the infant was in utero. This devastating presentation is characterized by expansion of the allogeneic cells, rash, hepatosplenomegaly and diarrhea. A 3rd presentation is often called **Omenn syndrome** , in which a few cells generated in the infant expand and cause a clinical picture similar to GVHD (Fig. 152.2). The difference in this case is that the cells are the infant's own cells.

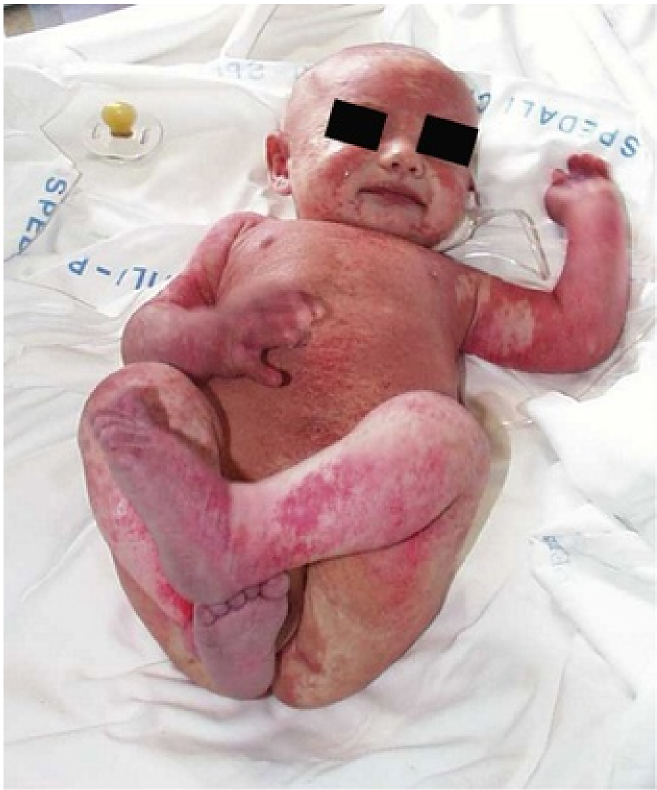

FIG. 152.2 **Typical clinical features in an infant with Omenn syndrome. Note generalized erythroderma with scaly skin, alopecia, and edema. (From Leung DYM, Szefler SJ, Bonilla FA, et al, editors: *Pediatric allergy: principles and practice,* ed 3, Philadelphia, 2016, Saunders, p 82).**

A key feature of SCID is that almost all patients will have a low lymphocyte count. A combination of opportunistic infections and a persistently low lymphocyte count is an indication to test for SCID. The diagnostic strategy both for symptomatic infants and those detected by newborn screening is to perform flow cytometry to quantitate the T, B, and natural killer (NK) cells in the infant. The CD45RA and CD45RO markers can be helpful to distinguish maternal engraftment and Omenn syndrome. T-cell function is also often assessed by measuring proliferative responses to stimulation.

All genetic types of SCID are associated with profound immunodeficiency. A small number have other associated features or atypical features that are important to recognize. Adenosine deaminase (ADA) deficiency can be associated with pulmonary alveolar proteinosis and chondroosseous dysplasia. Adenylate kinase 2 (AK2) deficiency causes a picture referred to as **reticular dysgenesis** where neutrophils, myeloid cells, and lymphocytes are all low. This condition is also often associated with deafness.

Treatment

SCID is a true pediatric immunologic emergency. Unless immunologic reconstitution is achieved through hematopoietic stem cell transplantation (**HSCT**) or gene therapy, death usually occurs during the 1st yr of life and almost invariably before 2 yr of age. *HSCT in an infant prior to infection is associated with a 95% survival rate.* ADA-deficient SCID and X-linked SCID have been treated successfully with gene therapy. Early trials of gene therapy were associated with a risk of malignancy, but this has not been seen in trials with new vectors. ADA-deficient SCID can also be treated with repeated injections of polyethylene glycol–modified bovine ADA (**PEG-ADA**), although the immune reconstitution achieved is not as effective as with stem cell or gene therapy.

Genetics

The 4 most common types of SCID are the X-linked form, caused by mutations in *CD132* ; autosomal recessive *RAG1* and *RAG2* deficiencies; and *ADA* deficiency. Additional forms are listed in Table 152.1 . For X-linked SCID and ADA deficiency, gene therapy exists, but genetic counseling is the most compelling reason for genetic sequencing to identify the gene defect. Several specific gene defects are associated with increased sensitivity to radiation and chemotherapy, and their early identification can lead to a better transplant experience.

Sequencing is often done by requesting a SCID gene panel. There are certain laboratory features that predict specific gene defects. When both T cells and B cells are low, often a gene encoding a protein involved in V(D)J recombination is the cause. Similarly, certain cytokine receptor defects are associated with specific lymphocyte phenotypes.

Hypomorphic mutations in genes most often associated with SCID can lead to varied phenotypes. This condition is often referred to as *leaky SCID,* referring to the mutation being "leaky" for some lymphocyte development. Leaky phenotypes range from the dramatic Omenn syndrome phenotype to later-onset immunodeficiency, granulomas, and autoimmunity.

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152.2

Combined Immunodeficiency

Kathleen E. Sullivan, Rebecca H. Buckley

Keywords

cartilage-hair hypoplasia
Wiskott-Aldrich syndrome
lymphopenia

Combined immunodeficiency (**CID**) is distinguished from SCID by the presence of low but not absent T-cell function. CID is a syndrome of diverse genetic causes. Patients with CID have recurrent or chronic pulmonary infections, failure to thrive, oral or cutaneous candidiasis, chronic diarrhea, recurrent skin infections, gram-negative bacterial sepsis, urinary tract infections, and severe varicella in infancy. Although they usually survive longer than infants with SCID, they fail to thrive and often die before adulthood. Neutropenia and eosinophilia are common. Serum immunoglobulins may be normal or elevated for all classes, but selective IgA deficiency, marked elevation of IgE, and elevated IgD levels occur in some cases. Although antibody-forming capacity is impaired in most patients, it is not absent.

Studies of cellular immune function show lymphopenia, deficiencies of T cells, and extremely low but not absent lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Peripheral lymphoid tissues demonstrate paracortical lymphocyte depletion. The thymus is usually small, with a paucity of thymocytes and usually no Hassall corpuscles.

Cartilage-Hair Hypoplasia

Cartilage-hair hypoplasia (CHH) is an unusual form of **short-limbed dwarfism** with frequent and severe infections. It occurs with a high frequency among the Amish and Finnish people.

Genetics and Pathogenesis

CHH is an autosomal recessive condition. Numerous mutations that cosegregate with the CHH phenotype have been identified in the untranslated RNase MRP (*RMRP*) gene. The RMRP endoribonuclease consists of an RNA molecule bound to several proteins and has at least 2 functions: cleavage of RNA in mitochondrial DNA synthesis and nucleolar cleaving of pre-RNA. Mutations in *RMRP* cause CHH by disrupting a function of *RMRP* RNA that affects multiple organ systems. In vitro studies show decreased numbers of T cells and defective T-cell proliferation because of an intrinsic defect related to the G1 phase, resulting in a longer cell cycle for individual cells. NK cells are increased in number and function.

Clinical Manifestations

Clinical features include short, pudgy hands; redundant skin; hyperextensible joints of hands and feet but an inability to extend the elbows completely; and fine, sparse, light hair and eyebrows. Infections range from mild to severe. Associated conditions include deficient erythrogenesis, Hirschsprung disease, and an increased risk of malignancies. The bones radiographically show scalloping and sclerotic or cystic changes in the metaphyses and flaring of the costochondral junctions of the ribs. Some patients have been treated with HSCT.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome is an X-linked recessive disorder characterized by atopic dermatitis, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and susceptibility to infection.

Genetics and Pathogenesis

The Wiskott-Aldrich syndrome protein (WASP) binds CDC42H2 and Rac, members of the Rho family of guanosine triphosphatases. WASP controls the assembly of actin filaments required for cell migration and cell-cell interactions.

Clinical Manifestations

Patients often have prolonged bleeding from the circumcision site or bloody diarrhea during infancy. The thrombocytopenia is not initially caused by antiplatelet antibodies. **Atopic dermatitis** and **recurrent infections** usually develop during the 1st yr of life. *Streptococcus pneumoniae* and other bacteria having polysaccharide capsules cause otitis media, pneumonia, meningitis, and sepsis. Later, infections with agents such as *P. jiroveci* and the herpesviruses become more frequent. Infections, bleeding, and EBV-associated malignancies are major causes of death.

Patients with this defect uniformly have an impaired humoral immune response to polysaccharide antigens, as evidenced by absent or greatly diminished isohemagglutinins, and poor or absent antibody responses after immunization with polysaccharide vaccines. The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal or slightly low IgG concentration. Because of their profound antibody deficiencies, these patients should be given immunoglobulin replacement regardless of their serum levels of the different immunoglobulin isotypes. Percentages of T cells are moderately reduced, and lymphocyte responses to mitogens are variably depressed.

Treatment

Good supportive care includes appropriate nutrition, immunoglobulin replacement, use of killed vaccines, and aggressive management of eczema and associated cutaneous infections. HSCT is the treatment of choice when a high-quality matched donor is available and is usually curative. Gene-corrected autologous HSCT has resulted in sustained benefits in 6 patients.

Ataxia-Telangiectasia

Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities.

Genetics and Pathogenesis

The ataxia-telangiectasia mutation (*ATM*) gene encodes a protein critical for responses to DNA damage. Cells from patients, as well as from heterozygous carriers, have increased sensitivity to ionizing radiation, defective DNA repair, and frequent chromosomal abnormalities.

In vitro tests of lymphocyte function have generally shown moderately depressed proliferative responses to T- and B-cell mitogens. Percentages of CD3 and CD4 T cells are moderately reduced, with normal or increased percentages of CD8 and elevated numbers of γ/δ T cells. The thymus is very hypoplastic, exhibits poor organization, and lacks Hassall corpuscles.

Clinical Manifestations

The most prominent clinical features are progressive **cerebellar ataxia, oculocutaneous telangiectasias, chronic sinopulmonary disease** , a high incidence of malignancy, and variable humoral and cellular immunodeficiency. Ataxia typically becomes evident soon after these children begin to walk and progresses until they are confined to a wheelchair, usually by age 10-12 yr. The telangiectasias begin to develop at 3-6 yr. The most frequent humoral immunologic abnormality is the selective absence of IgA, which occurs in 50–80% of these patients. IgG2 or total IgG levels may be decreased, and specific antibody titers may be decreased or normal. Recurrent sinopulmonary infections occur in approximately 80% of these patients. Although common viral infections have not usually resulted in untoward sequelae, fatal varicella has occurred. The malignancies associated with ataxia-telangiectasia are usually of the lymphoreticular type, but adenocarcinomas also occur. Unaffected carriers of mutations have an increased incidence of malignancy.

Therapy in ataxia-telangiectasia is supportive.

Autosomal Dominant Hyper-IgE

Syndrome

This syndrome is associated with early-onset atopy and recurrent skin and lung infections.

Genetics and Pathogenesis

The autosomal dominant hyper-IgE syndrome is caused by heterozygous mutations in the gene encoding signal transducer and activator of transcription 3 (STAT-3). These mutations result in a dominant negative effect. The many clinical features are caused by compromised signaling downstream of the interleukin (IL)-6, type I interferon, IL-22, IL-10 and epidermal growth factor (EGF) receptors.

Clinical Manifestations

The characteristic clinical features are staphylococcal abscesses, pneumatoceles, osteopenia, and unusual facial features. There is a history from infancy of recurrent staphylococcal abscesses involving the skin, lungs, joints, viscera, and other sites. Persistent pneumatoceles develop as a result of recurrent pneumonia. Patients often have a history of sinusitis and mastoiditis. *Candida albicans* is the 2nd most common pathogen. Allergic respiratory symptoms are usually absent. The pruritic dermatitis that occurs is not typical atopic eczema and does not always persist. There can be a prominent forehead, deep-set wide-spaced eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy, although these are most evident in adulthood. In older children, delay in shedding primary teeth, recurrent fractures, and scoliosis occur.

These patients demonstrate an **exceptionally high serum IgE concentration** ; an elevated serum IgD concentration; usually normal concentrations of IgG, IgA, and IgM; pronounced blood and sputum eosinophilia; and poor antibody and cell-mediated responses to neoantigens. Traditionally, IgE levels >2000 IU/mL confirm the diagnosis. However, IgE levels may fluctuate and even decrease in adults. In neonates and infants with the pruritic pustular dermatosis, IgE levels will be elevated for age and are usually in the 100s. In vitro studies show normal percentages of blood T, B, and NK lymphocytes, except for a decreased percentage of T cells with the memory (CD45RO) phenotype and an absence or deficiency of T-helper type 17 (Th17) cells. Most patients have normal T-lymphocyte proliferative responses to mitogens but very low or absent responses to antigens or allogeneic cells from family members. Blood, sputum, and histologic sections of lymph nodes, spleen, and lung cysts show striking eosinophilia. Hassall corpuscles and thymic architecture are normal. Therapy is generally directed at prevention of infection using antimicrobials and immunoglobulin replacement.

DOCK8 Deficiency

Deficiency of DOCK8 (dedicator of cytokinesis 8) is an autosomal recessive condition that most often presents with impressively severe eczema in infancy and toddlerhood. **Cutaneous viral infections** and **susceptibility to CMV, EBV, and cryptosporidia** are common (Fig. 152.3). The infectious susceptibility tends to worsen over time, as do the laboratory features of immune dysfunction, most often low T-cell counts and poor proliferative function. Although these patients can survive to adulthood without transplantation, they suffer many complications and their quality of life is often poor. For this reason, most patients are now transplanted early in life to avoid the later complications.

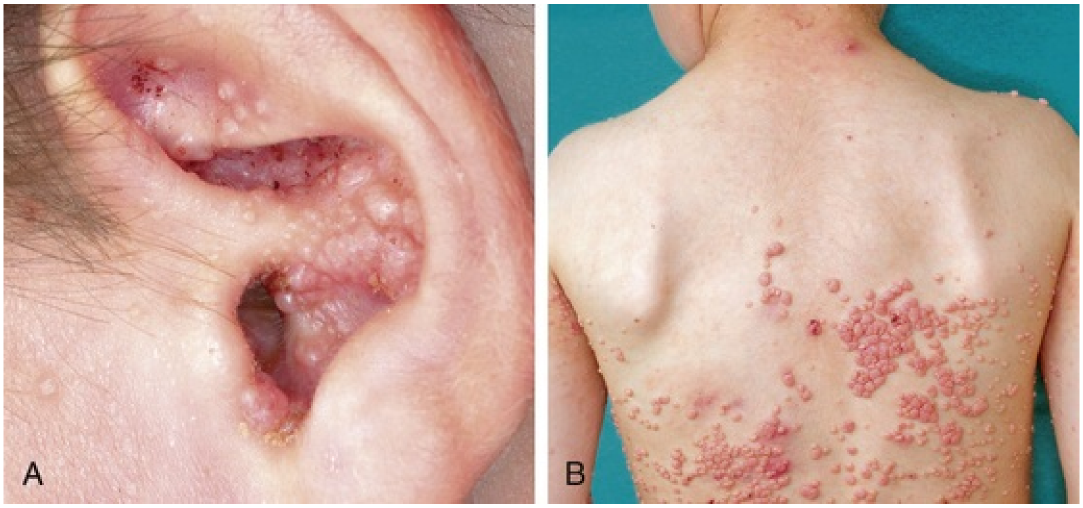

FIG. 152.3 Extensive sheets of molluscum on the ear (**A**) and trunk (**B**). (From Purcell C, Cant A, Irvine AD: DOCK8 primary immunodeficiency syndrome, Lancet 386:982, 2015.)

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152.3

Defects of Innate Immunity

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Keywords

TLR
NK cells
mycobacteria

The innate immune system is the earliest responding feature of host defense in vertebrates. Components include the physical barrier function of the skin and mucosal surfaces, complement, neutrophils, macrophages, dendritic cells (DCs), NK cells, and their associated cytokines. The activation of innate immunity is critically reliant on a group of **pattern recognition receptors (PRRs)** that respond to host infections or tissue damage within minutes. These receptors are all germline encoded and are therefore able to be expressed in all cells, where they serve as critical monitors for the presence of **pathogen-associated molecular patterns (PAMPs)** .

Interferon-γ Receptors 1 and 2, IL-12 Receptor β_1 , and IL-12P40 Defects

Among the best-described defects of innate immunity are those associated with susceptibility to nontuberculous mycobacteria. These defects are associated with abnormalities in the interferon-gamma (IFN-γ)–IL-12 signaling axis.

Pathogenesis

Interleukin-12 is a cytokine secreted by macrophages, neutrophils, and DCs in response to infection with mycobacterial and other microbes. IL-12 then binds to receptors on NK cells and T cells to stimulate secretion of IFN-γ. IFN-γ is critical in the activation of phagocyte secretion of tumor necrosis factor alpha (TNF-α) and destruction of the phagocytosed microbe. IFN-γ activates phagocytes via binding of IFN-γ receptor 1 (IFN-γR1) which is found in a homodimerized form associated with Janus-associated kinase-1 (Jak1) that recruits and binds IFN-γ receptor 2 (IFN-γR2) which is associated with Janus-associated kinase-2 (Jak2). Jak1 and Jak2 are then transphosphorylated, which leads to phosphorylation of IFN-γR1 and subsequent docking of signal transducer and activator of transcription 1 (STAT1). Phosphorylated STAT1 then homodimerizes and translocates to the cell nucleus to induce gene transcription. Deficiency of any of these components has a significant impact on phagocyte activation.

Clinical Manifestations

IFN-γR1 deficiency leads to impaired IFN-γ binding and signaling and inability to form mature granulomas and indicates a risk of **susceptibility to *Mycobacteria*** species and *Salmonella* . There are both autosomal recessive (AR) and autosomal dominant (AD) forms of this defect. In the AR form are both partial and complete defects. In the complete AR form, patients present with early onset of disseminated *Mycobacteria*, and some have been reported to present with nontyphoid *Salmonella* or *Listeria monocytogenes* . Treatment should be directed at the presenting infection, with multiple antimicrobial agents used without interruption. HSCT has been used once mycobacterial disease is controlled but requires conditioning to permit the myeloid engraftment necessary to correct the underlying disease. In the partial AR form, IFN-γR1 deficiency remains associated with disseminated *Mycobacteria* and S*almonella* infections but is managed with symptomatic treatment of infections and consideration of IFN-γ therapy to induce higher serum IFN-γ levels. The AD form is also a partial defect in IFN-γ signaling and most often presents with *Mycobacteria* osteomyelitis, although *Salmonella* and *Histoplasma* infections have also been described. Similar to the partial AR defect, these patients are able to be managed with antimicrobial therapy of infections and supplemental IFN-γ injections. Deficiency of IFN-γR2 is an AR defect that also has partial and complete forms. The complete form is a phenocopy to complete IFN-γR1, presenting with early-onset, severe, and disseminated mycobacterial infections. Treatment involves uninterrupted multidrug therapy for the infections and consideration for HSCT. A partial form of IFN-γR2 also presents with mild but potentially disseminated *Mycobacteria* or *Salmonella* infections, which can be controlled with antibiotic therapy that can be stopped once the infection is resolved.

Deficiencies of the IL-12 receptor (IL-12R) components have also been described as inherited in an AR fashion, with defects in both the IL-12p40 chain as well as the shared IL-12/IL-23Rβ_1 , causing impaired IFN-γ secretion and resultant susceptibility to *Mycobacteria* and *Salmonella.* Both forms of IL-12R defects are characterized by relatively mild disease, with some ability to form granulomatous lesions in response to *Mycobacteria* infections. These defects can usually be managed with antimicrobials and supplemental IFN-γ. Partial defects in STAT1, inherited in an AD fashion, are associated with *Mycobacteria* susceptibility, whereas complete AR defects in STAT1 are associated with mycobacterial susceptibility as well as defects in responses to IFN-α and IFN-β, leading to fulminant herpesvirus infections. Other defects associated with poor production of IFN-γ leading to increased *Mycobacteria* susceptibility include AR inherited defects in **ISG-15** , which is associated with *Mycobacteria*-induced brain calcifications, and **RORγC** deficiency, which leads to a lack of IL-17–producing T cells, in addition to lack of IFN-γ production. RORγC defects are associated with an increased risk of candidiasis in addition to *Mycobacteria* infections. Defects in **Tyk2** , inherited in an AR fashion, generally present with susceptibility to intracellular bacteria, fungi and viruses. AD mutations in interferon regulatory factor 8 (*IRF8*) are also associated with impaired IL-12 production by the CD1-DCs, leading to increased risk of recurrent mycobacterial infection, which can be treated with antimicrobial therapy.

IL-1R–Associated Kinase 4 Deficiency and Myeloid Differentiation Factor 88

Toll-like receptors (**TLRs**) are the best described of the PRRs in humans, and deficiencies almost uniformly cause infection susceptibility.

Pathogenesis

Among those expressed on the cell surface, TLRs 1, 2, and 6 bind lipoproteins and are important in defense to bacteria and fungi, TLR4 binds lipopolysaccharides and has an important role in defense from gram-negative bacteria as well as the fusion protein of RSV. TLR5 binds flagellin, found in many bacterial organisms. The remaining TLRs (3, 7, 8, and 9) are expressed intracellularly, respond to nucleic acids and are initiators for the host response for viral defense. When bound to their PAMP, TLRs activate an intracellular signaling cascade that in most cases utilizes myeloid differentiation primary response gene 88 (MyD88) and IL-1R–associated kinase 4 (IRAK4). TLR4 also signals using the Toll/IL-1R domain-containing adaptor-inducing interferon-B (TRIF). Both MyD88 and TRIF can lead to activation of the nuclear factor (NF)-κB pathway via the IKK complex to induce proinflammatory cytokine production. The IKK complex is composed of IKKα and IKKβ, and IKKγ (NF-κB essential modulator, or NEMO).

Clinical Manifestations

IRAK4 and *MYD88* deficiencies have identical features and are associated with deep infections such as pneumonia, meningitis, or sepsis with encapsulated organisms early in life. The main organisms recovered from patients are *Staphylococcus aureus* , *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa.* This is one of the few types of immunodeficiency where clostridial infections are also seen with increased frequency. Most patients have an improved infection risk after adolescence. Therapy has generally focused on education of parents and clinicians to the life-threatening nature of the infections with encouragement of timely cultures and empirical antibiotic use. These patients may have a **blunted febrile response** , and clinical features of infection may be subtle.

Among the first-described defects of TLR signaling were X-linked mutations in *NEMO* , which causes a broad range of clinical manifestations, with most demonstrating a poor inflammatory response. NEMO is typically considered in the category of combined immunodeficiency because of its impact on both innate and adaptive immune responses. Severely affected patients may present with disseminated *Mycobacteria* infections, severe infections from encapsulated organisms such as *S. pneumoniae* or other opportunistic infections. In addition to the infectious phenotype, these patients characteristically have conical or peg-shaped teeth, hypohydrosis, and hypotrichosis from anhidrotic ectodermal dysplasia (EDA). Patients should be treated with immunoglobulin replacement, antibiotic prophylaxis with trimethoprim/sulfamethoxazole, azithromycin, and/or penicillin VK. HSCT is a treatment consideration, but myeloid lineage engraftment is needed to fully correct the underlying immunodeficiency.

Natural Killer Cell Deficiency

NK cells are the major lymphocytes of the innate immune system. NK cells recognize virally infected and malignant cells and mediate their elimination. Individuals with absence or functional deficiencies of NK cells are rare, and they typically have susceptibility to the herpesviruses (including varicella-zoster virus, herpes simplex virus (HSV), CMV, and EBV) as well as papillomaviruses. A number of gene defects are associated with these isolated abnormalities in NK cells. Autosomal recessive CD16 gene mutations were described in 3 separate families and altered the first immunoglobulin-like domain of this important NK cell activation receptor. Patients with these mutations have NK cells that are functionally impaired and have clinical susceptibility to **herpesviruses** . AD deficiency of NK cells occurs in individuals with mutations in the **GATA2 transcription factor** . These patients also have cytopenias and very low numbers of monocytes. They have extreme susceptibility to **human papillomavirus** (HPV) as well as mycobacteria, the latter presumably from the monocytic defect. They are at risk for alveolar proteinosis, myelodysplasia, and leukemia. AR mutations in the *MCM4* gene have been identified in a cohort of patients who had growth failure and susceptibility to herpesviruses. Therapeutically, patients should be maintained on antiviral prophylaxis, and HSCT has been successful in certain cases.

Defects in Innate Responses to Viral

Infection

Defects in both the JAK-STAT signaling pathways and the TLR signaling pathways have been implicated in patients with increased susceptibility to severe viral infections. AR defects in STAT1 cause a complete lack of response to INF-γ and IFN-α/β, affecting the function of T and NK cells as well as monocytes, leading to disseminated mycobacterial infections as well as severe herpesvirus infections, including recurrent **HSV encephalitis** and EBV-driven lymphoproliferative disease. In these patients, lifelong antibiotic therapy to protect from *Mycobacteria* and antiviral therapy for herpesviruses is recommended, and HSCT should be considered. Defects in STAT2, inherited in an AR fashion, lead to poor T- and NK-cell responses to IFN-α and IFN-β, leading to increased viral susceptibility, in particular development of **disseminated vaccine strain measles** with central nervous system (CNS) involvement despite development of normal vaccine titers. The interferon response factor 7 (IRF7) is important in induction of IFN-α/β via the both the MyD88-dependent and independent pathways of TLR signaling. AR defects in IRF7 have been associated with severe respiratory distress with influenza A infection in a patient with otherwise normal vaccine responses and T- and B-cell populations.

HSV-1 encephalitis has been associated with a group of defects in TLR signaling that lead to decreased production of IFN-α/β/λ causing impaired immunity to HSV-1 but not other viral infections. The first described was deficiency of UNC93B1, a protein involved in trafficking of the TLRs 7 and 9 and inherited in an AR fashion. Subsequently, defects in TLR3 and TRIF as well as the other TLR pathway signaling molecules tumor necrosis factor (TNF), receptor–associated factor 3 (TRAF3), and tank-binding kinase 1 (TBK1) were described to lead to decreased production of IFN-α/β/λ and an associated risk of sporadic HSV-1 encephalitis that can be recurrent. The symptoms were controlled with acyclovir prophylaxis.

Defects in Innate Responses to Fungi

Although **chronic mucocutaneous candidiasis (CMC)** can be seen in association with CID, T-cell disorders, and hyper-IgE syndromes, there are also innate defects known to cause CMC (see Chapter 151). The most common include AD gain-of-function mutations in *STAT1* , where an increased response to IFN-α/β/γ leads to decreased Th17 differentiation. In addition to CMC, these patients also have increased susceptibility to bacterial, fungal, and HSV viral infections; autoimmunity; and enteropathy. Patients with CMC are managed with antifungal, antibacterial, and acyclovir prophylaxis, and HSCT should be considered as a treatment option. Mutations in the IL-17RA and IL-17F have also been described to increase risk of CMC; IL-17RA and IL-17F deficiencies are also associated with *S. aureus* folliculitis, likely from impaired skin β-defensin production. Treatment includes **fluconazole** and sulfamethoxazole/trimethoprim prophylaxis. TRAF3-interacting protein 2 (TRAF3IP2) interacts with IL-17RA on binding of IL-17; AR mutations in TRAF3IP2 have been described in patients with CMC, blepharitis, folliculitis, and macroglossia. CMC is also seen in 25% of patients with IL-12RB1 and IL12p40 defects. Invasive fungal infections, including invasive **dermatophyte infections** and *Candida* brain abscesses, have been seen in addition to CMC in patients with AR inherited defects in CARD9. CARD9 leads to NF-κB–induced cytokine production in response to fungal PAMPS that bind to C-type lectin receptors, including Dectin 1, Dectin 2, and MINCLE. Both granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF have been successfully used to control refractory brain lesions, and once identified, these patients should be maintained on fluconazole prophylaxis.

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152.4

Treatment of Cellular or Combined Immunodeficiency

Kathleen E. Sullivan, Rebecca H. Buckley

Good supportive care, including prevention and treatment of infections, is critical while patients await more definitive therapy (Table 152.2). Having knowledge of the pathogens causing disease with specific immune defects is also useful.

Table 152.2

Infection in the Host Compromised by B- and T-Cell Immunodeficiency Syndromes

IMMUNODEFICIENCY SYNDROME	OPPORTUNISTIC ORGANISMS ISOLATED MOST FREQUENTLY	APPROACH TO TREATMENT OF INFECTIONS	PREVENTION OF INFECTIONS
B-cell immunodeficiencies	Encapsulated bacteria (*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae* , and *Neisseria meningitidis*), *Pseudomonas aeruginosa, Campylobacter* spp., enteroviruses, rotaviruses, *Giardia lamblia, Cryptosporidium* spp., *Pneumocystis jiroveci, Ureaplasma urealyticum* , and *Mycoplasma pneumoniae*	IVIG, 200-800 mg/kg Vigorous attempt to obtain specimens for culture before antimicrobial therapy Incision and drainage if abscess present Antibiotic selection on the	Maintenance IVIG for patients with quantitative and qualitative defects in IgG metabolism (400-800 mg/kg every 3-5 wk) In chronic recurrent respiratory disease, vigorous attention to

		basis of sensitivity data	postural drainage In selected cases (recurrent or chronic pulmonary or middle ear), prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole
T-cell immunodeficiencies	Encapsulated bacteria (*S. pneumoniae, H. influenzae, S. aureus*), facultative intracellular bacteria (*Mycobacterium tuberculosis* , other *Mycobacterium* spp., and *Listeria monocytogenes*); *Escherichia coli; P. aeruginosa; Enterobacter* spp.; *Klebsiella* spp.; *Serratia marcescens; Salmonella* spp.; *Nocardia* spp.; viruses (cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, rotaviruses, adenoviruses, enteroviruses, respiratory syncytial virus, measles virus, vaccinia virus, and parainfluenza viruses); protozoa (*Toxoplasma gondii* and *Cryptosporidium* spp.); and fungi (*Candida* spp., *Cryptococcus neoformans, Histoplasma capsulatum* , and *P. jiroveci*)	Vigorous attempt to obtain specimens for culture before antimicrobial therapy Incision and drainage if abscess present Antibiotic selection on the basis of sensitivity data Early antiviral treatment for herpes simplex, cytomegalovirus, and varicella-zoster viral infections Topical and nonadsorbable antimicrobial agents frequently are useful	Prophylactic administration of trimethoprim-sulfamethoxazole for prevention of *P. jiroveci* pneumonia Oral nonadsorbable antimicrobial agents to lower concentration of gut flora No live virus vaccines or bacille Calmette-Guérin vaccine Careful tuberculosis screening

IVIG, Intravenous immune globulin.

From Stiehm ER, Ochs HD, Winkelstein JA: *Immunologic disorders in infants and children* , ed 5, Philadelphia, 2004, Saunders.

Transplantation of major histocompatibility complex (MHC)–compatible sibling or rigorously T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cells is the treatment of choice for patients with fatal T-cell or combined T- and B-cell defects. The major risk to the recipient from transplants of bone marrow or peripheral blood stem cells is GVHD from donor T cells. Patients with less severe forms of cellular immunodeficiency, including some forms of CID, Wiskott-Aldrich syndrome, cytokine deficiency, and MHC antigen deficiency, reject even HLA-identical marrow grafts unless chemoablative treatment is given before transplantation. Several patients with these conditions have been treated successfully with hematopoietic stem cell transplantation after conditioning.

More than 90% of patients with primary immunodeficiency transplanted with HLA-identical related marrow will survive with immune reconstitution. T-cell–depleted haploidentical-related marrow transplants in patients with primary immunodeficiency have had their greatest success in patients with SCID, who do not require pretransplant conditioning or GVHD prophylaxis. Of patients with SCID, 92% have survived after T-cell–depleted parental marrow is given soon after birth when the infant is healthy, without pretransplant chemotherapy or posttransplant GVHD prophylaxis. Bone marrow transplantation remains the most important and effective therapy for SCID. In ADA-deficient and X-linked SCID, there has been success in correcting the immune defects with ex vivo gene transfer to autologous hematopoietic stem cells. Gene therapy has also been successful in the Wiskott-Aldrich syndrome. Initial protocols of gene therapy for X-linked SCID resulted in **insertional mutagenesis** with the development of leukemic-like clonal T cells or lymphoma in some patients. Modification of the gene therapy protocol has greatly reduced the risk of insertional mutagenesis.

152.5

Immune Dysregulation With Autoimmunity or Lymphoproliferation

Jennifer W. Leiding, Kathleen E. Sullivan, Rebecca H. Buckley

Keywords

ALPS
cytopenias

IPEX

Primary immunodeficiency diseases characterized by immune dysregulation, autoimmunity, and autoinflammation are monogenic defects of the immune system. These complex multisystem diseases often have a progressive phenotype with organ-specific autoimmunity, specific infectious susceptibility, and lymphoproliferation.

Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome (**ALPS**), also known as Canale-Smith syndrome, is a disorder of abnormal lymphocyte apoptosis leading to polyclonal populations of T cells (double-negative T cells), which express CD3 and α/β antigen receptors but do not have CD4 or CD8 co-receptors (CD3^{+} T-cell receptor α/β^{+} , CD4^{-} CD8^{-}). These T cells respond poorly to antigens or mitogens and do not produce growth or survival factors (IL-2). The genetic deficit in most patients is a germline or somatic mutation in the *FAS* gene, which produces a cell surface receptor of the TNF receptor superfamily (TNFRSF6), which, when stimulated by its ligand, will produce programmed cell death (Table 152.3). Persistent survival of these lymphocytes leads to immune dysregulation and autoimmunity. ALPS is also caused by other genes in the Fas pathway (*FASLG* and *CASP10*). In addition, ALPS-like disorders are associated with other mutations: RAS-associated autoimmune lymphoproliferative disorder (RALD), caspase-8 deficiency, Fas-associated protein with death domain deficiency (FADD), and protein kinase C delta deficiency (PRKCD). These disorders have varying degrees of immunodeficiency, autoimmunity, and lymphoproliferation.

Table 152-3

Revised Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome*

REQUIRED
1. Chronic (>6 months), nonmalignant, noninfectious lymphadenopathy, splenomegaly or both
2. Elevated CD3+TCRαβ+CD4-CD8- DNT cells (≥1.5% of total lymphocytes or 2.5% of CD3+ lymphocytes) in

the setting of normal or elevated lymphocyte counts
ACCESSORY
Primary
1. Defective lymphocyte apoptosis (in 2 separate assays) 2. Somatic or Germline pathogenic mutation in *FAS* , *FASLG* , or *CASP10*
Secondary
1. Elevated plasma sFasL levels (>200 pg/mL) OR elevated plasma interleukin-10 levels (>20 pg/mL) OR elevated serum or plasma vitamin B 12 levels (>1500 ng/L) OR elevated plasma interleukin-18 levels >500 pg/mL 2. Typical immunohistological findings as reviewed by an experienced hematopathologist 3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated immunoglobulin G levels (polyclonal hypergammaglobulinemia) 4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

[*] A *definitive* diagnosis is based on the presence of both required criteria plus one primary accessory criterion. A *probable* diagnosis is based on the presence of both required criteria plus one secondary accessory criterion.

From Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors: Textbook of pediatric rheumatology, ed 7, Philadelphia, 2016, Elsevier, Box 46-2.

Clinical Manifestations

ALPS is characterized by **autoimmunity, chronic persistent or recurrent lymphadenopathy** , splenomegaly, hepatomegaly (in 50%), and hypergammaglobulinemia (IgG, IgA). Many patients present in the 1st yr of life, and most are symptomatic by age 5 yr. Lymphadenopathy can be striking (Fig. 152.4). Splenomegaly may produce hypersplenism. Autoimmunity also produces anemia (Coombs-positive hemolytic anemia) or thrombocytopenia or a mild neutropenia. The lymphoproliferative process (lymphadenopathy, splenomegaly) may regress over time, but autoimmunity does not regress and is characterized by frequent exacerbations and recurrences. Other autoimmune features include urticaria, uveitis, glomerulonephritis, hepatitis, vasculitis, panniculitis, arthritis, and CNS involvement (seizures, headaches, encephalopathy).

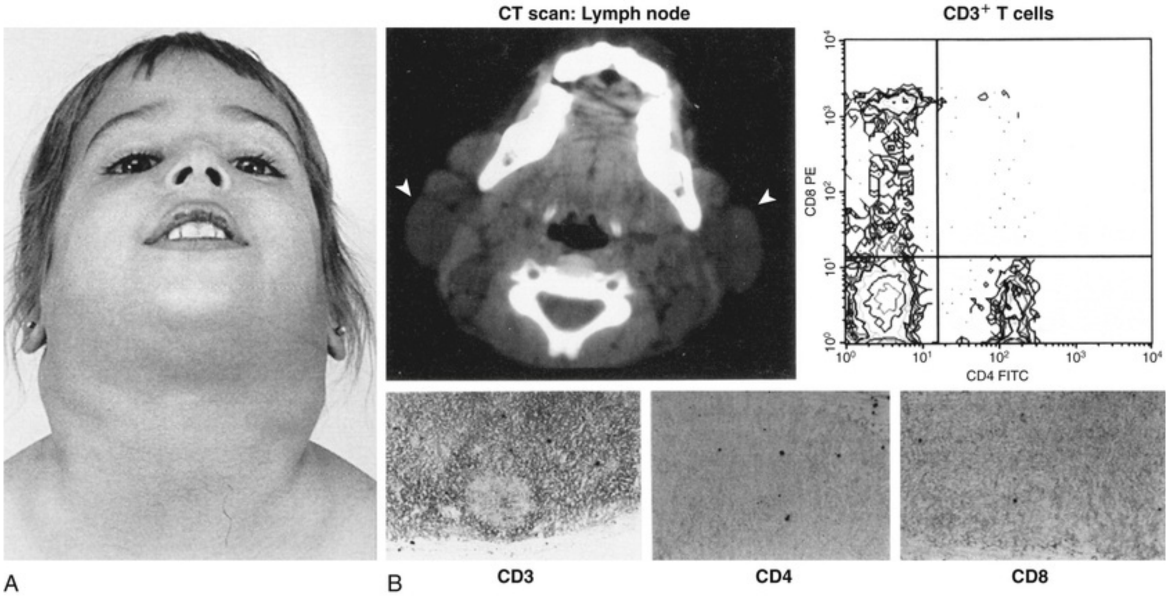

FIG. 152.4 Clinical, radiographic, immunologic, and histologic characteristics of the autoimmune lymphoproliferative syndrome. A, Front view of the National Institutes of Health patient. B, *Top middle,* a CT scan of the neck is shown demonstrating enlarged preauricular, cervical, and occipital lymph nodes. *Arrowheads* denote the most prominent lymph nodes. The *top right* panels show the flow-cytometric analysis of peripheral blood T cells from a patient with autoimmune lymphoproliferative syndrome (ALPS), with CD8 expression on the vertical axis and CD4 on the horizontal axis. The *lower left quadrant* contains CD4$^-$ CD8$^-$ (double-negative) T cells, which are usually present at <1% of T cells expressing the αβ T-cell receptor. The *bottom panels* show CD3, CD4, and CD8 staining on serial sections of a lymph node biopsy specimen from a patient with ALPS, and also show that large numbers of DNCD3$^+$ CD4$^-$ CD8$^-$ (double-negative) T cells are present in the interfollicular areas of the lymph node. (Adapted from Siegel RM, Fleisher TA: The role of Fas and related death receptors in autoimmune and other disease states, *J Allergy Clin Immunol* 103:729–738, 1999.)

Malignancies are also more common in patients with ALPS and include Hodgkin and non-Hodgkin lymphomas and solid-tissue tumors of thyroid, skin, heart, or lung. ALPS is one cause of Evan syndrome (immune thrombocytopenia and immune hemolytic anemia).

Diagnosis

Laboratory abnormalities depend on the lymphoproliferative organ response (hypersplenism) or the degree of autoimmunity (anemia, thrombocytopenia). There may be lymphocytosis or lymphopenia. Table 152.3 lists the criteria for the diagnosis. Flow cytometry helps identify the lymphocyte type (see Fig. 152.4). Functional genetic analysis for the *TNFRSF6* gene often reveals a heterozygous mutation.

Treatment

Rapamycin (sirolimus) will often control the adenopathy and autoimmune cytopenias. Malignancies can be treated with the usual protocols used in patients unaffected by ALPS. Stem cell transplantation is another possible option in treating the autoimmune manifestations of ALPS.

Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked Syndrome

This immune dysregulation syndrome is characterized by onset within the 1st few wk or mo of life with watery diarrhea (autoimmune enteropathy), an eczematous rash (erythroderma in neonates), insulin-dependent diabetes mellitus, hyperthyroidism or more often hypothyroidism, severe allergies, and other autoimmune disorders (Coombs-positive hemolytic anemia, thrombocytopenia, neutropenia). Psoriasiform or ichthyosiform rashes and alopecia have also been reported.

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (**IPEX**) syndrome is caused by a mutation in the *FOXP3* gene, which encodes a forkhead-winged helix transcription factor *(scurfin)* involved in the function and development of CD4$^+$ CD25$^+$ regulatory T cells (Tregs). The absence of Tregs may predispose to abnormal activation of effector T cells. Dominant gain-of-function mutations in *STAT1* and other gene mutations (Table 152.4) produce an IPEX-like syndrome, also associated with compromised Tregs.

Table 152.4

Clinical and Laboratory Features of IPEX and IPEX-Like Disorders

	IPEX	**CD25**	**STAT5B**	**STAT1**	**ITCH**
AUTOIMMUNITY					
Eczema	+++	+++	++	++	++
Enteropathy	+++	+++	++	++	++
Endocrinopathy	+++	++	+	++	++
Allergic disease	+++	+	+	++	++

Cytopenias	++	++	++	–	
Lung disease	+	++	+++	+	+++
INFECTIONS					
Yeast	–	++	–	+++	–
Herpes virus	–	+++ (EBV/CMV)	++ (VZV)	++	–
Bacterial	+/–	++	++	++	+
Associated features	None	None	Growth failure	Vascular anomalies	Dysmorphic growth failure
Serum immunoglobulins	Elevated	Elevated or normal	Elevated or normal	Low, normal, or high	Elevated
Serum IgE	Elevated	Normal or elevated	Normal or elevated	Normal or mildly elevated	Elevated
CD25 expression	Normal	Absent	Normal or low	Normal	Not tested
$CD4^+$ CD45RO	Elevated	Elevated	Elevated	Normal or high	Not tested
FOXP3 expression	Absent or normal	Normal or low	Normal or low	Normal	Not tested
IGF-1, IGFBP-3	Normal	Normal	Low	Normal	Not tested
Prolactin	Normal	Normal	Elevated	Normal	Not tested

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor–binding protein 3; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; VZV, varicella-zoster virus; ITCH, ubiquitin ligase deficiency.

From Verbsky JW, Chatila TA: Immune dysregulation, polyendocrinopathy, enteropathy, X–linked (IPEX) and IPEX–related disorders: an evolving web of heritable autoimmune diseases, *Curr Opin Pediatr* 25:709, 2013.

Clinical Manifestations

Watery diarrhea with intestinal **villous atrophy** leads to failure to thrive in most patients. Cutaneous lesions (usually eczema) and insulin-dependent diabetes begin in infancy. Lymphadenopathy and splenomegaly are also present. Serious bacterial infections (meningitis, sepsis, pneumonia, osteomyelitis) may be related to neutropenia, malnutrition, or immune dysregulation. Laboratory features reflect the associated autoimmune diseases, dehydration, and malnutrition. In addition, serum IgE levels are elevated, with normal levels of IgM, IgG, and IgA. The diagnosis is made clinically and by mutational analysis of the *FOXP3* gene.

Treatment

Inhibition of T-cell activation by cyclosporine, tacrolimus, or sirolimus with corticosteroids is the treatment of choice, along with the specific care of the endocrinopathy and other manifestations of autoimmunity. These agents are typically used as a bridge to transplant. HSCT is the only possibility for curing IPEX.

Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) Deficiency

Patients with CTLA4 deficiency have lost the ability to maintain immune tolerance, leading to a disease characterized by autoimmunity and multiorgan lymphocytic infiltration of lymphoid and nonlymphoid organs. CTLA4, also known as CD152, is a protein receptor that is expressed on activated T cells. It acts as an immune checkpoint, downregulating immune responses, on T-cell activation. CTLA4 deficiency is inherited in a haploinsufficient manner.

Autoimmune cytopenias, **lymphoid infiltration of lymphoid and nonlymphoid organs** , granulomatous disease, hypogammaglobulinemia, and recurrent respiratory infections are key features. Nonlymphoid organs most often affected with lymphoid infiltration are the brain and gastrointestinal (GI) tract. The immune phenotype of CTLA4-deficient patients includes reduced naïve T cells ($CD4^+$ $CD45RA^+$ $CD62L^+$), loss of circulating B cells, and reduced Treg expression. Treatment is symptom specific, although use of abatacept, a CTLA4-Ig fusion protein, has alleviated disease-specific symptoms in several patients. When refractory to therapy, *HSCT has led to remission of symptoms and cure of disease.*

Lipopolysaccharide (Lps)-Responsive Beige-Like Anchor Protein (LRBA) Deficiency

Homozygous mutations in *LRBA* cause a syndrome of early-onset hypogammaglobulinemia, autoimmunity, lymphoproliferation, and inflammatory bowel disease.

LRBA is a member of the pleckstrin homology-beige and Chédiak-Higashi–tryptophan–aspartic acid dipeptide (PH-BEACH-WD40) protein family. Much is unknown about the function of LRBA. However, in normal T cells, LRBA co-localizes with CTLA4 within recycling endosomes, suggesting that LRBA may play a specific role in the regulation of recycling endosomes. Homozygous mutations in *LRBA* abrogate LRBA protein expression.

Immune dysregulation consisting of enteropathy, autoimmune cytopenias, granulomatous-lymphocytic **interstitial lung disease** , **lymphadenopathy** , and hepatomegaly or splenomegaly are the most common manifestations. Other, less common symptoms of immune dysregulation include cerebral granulomas, type 1 diabetes mellitus, alopecia, uveitis, myasthenia gravis, and eczema. Growth failure occurs in many patients, complicated especially by enteropathy. Bacterial, fungal, and viral infections have been reported in about 50% of patients. The immune phenotype is variable but can consist of reduced T-cell quantities ($CD3^+$), elevated double-negative T cells ($CD3^+$ $CD4^-$ $CD8^-$), normal T-cell proliferation to mitogens and antigens, reduced Treg numbers ($CD4^+$ $CD25^+$ $FoxP3^+$), reduced NK cells ($CD56^+$), and reduced B cells ($CD19^+$). Immunoglobulin quantities are also variable, with hypogammaglobulinemia occurring most frequently.

The focus of therapy is treatment of the immunodysregulatory features with immunosuppression. Corticosteroids, immunoglobulin replacement, mycophenolate mofetil, tacrolimus, rapamycin, budesonide, cyclosporine, azathioprine, rituximab, infliximab, and hydroxychloroquine have all been used with mixed success. Abatacept has been successful in treating the immunodysregulatory features. HSCT has been successfully performed in LRBA-deficient patients as well.

Activated Phosphoinositide 3-Kinase (PI3K) δ Syndromes

These syndromes are primary immunodeficiencies that cause a spectrum of immunodeficiency, lymphadenopathy, and senescent T cells. PI3K molecules are composed of a p110 catalytic subunit (p110α, p110β, or p110δ) and a regulatory subunit (p85α, p55α, p50α, p85β, or p55γ). PI3Ks convert phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-triphosphate (PIP_3), an important second messenger.

Autosomal dominant gain-of-function mutations in *PIK3CD* , the gene that encodes for the catalytic unit, p110δ, leads to hyperactivated PI3Kδ signaling. AD mutations in *PI3KR*, the gene that encodes the regulatory subunit (p85α, p55α, and p50α) of PI3Ks are associated with the same phenotype. Defects in this pathway lead to a syndrome of chronic lymphoproliferation and T-cell senescence.

Early-onset respiratory tract infections, noninfectious lymphadenopathy, and hepatosplenomegaly are the most common features. A large proportion of patients develop early-onset **bronchiectasis** as a result of recurrent pneumonia. Persistent, severe, or recurrent herpesvirus infections are also common. **Lymphadenopathy** often starts in childhood and localizes to sites of infection. However, lymphadenopathy may be diffuse and is usually associated with chronic CMV or EBV viremia. **Mucosal lymphoid hyperplasia** of the respiratory and GI tracts is also frequent. Histologically, lymph nodes show atypical follicular hyperplasia. **Autoimmune cytopenias** are the most frequent autoimmune manifestation, but others include glomerulopathies, autoantibody-mediated thyroid disease, and sclerosing cholangitis. Early-onset lymphoma, as early as the 2nd yr of life, have been reported as well and are a major cause of mortality. Growth impairment affecting weight and height and developmental delay with mild cognitive impairment also may occur.

The immunophenotype consists of reduced naïve T cell (CD3$^+$ CD4$^+$) and B-cell counts (CD19$^+$) and normal NK cell counts (CD56$^+$). More specifically, reduced numbers of recent thymic emigrants (CD3$^+$ CD4$^+$ CD45RA$^+$ CD31$^+$) with increased effector memory cytotoxic T-cell counts (CD3$^+$ CD8$^+$ CCR7$^-$ CD45RA$^{+/-}$), increased transitional B cells (CD19$^+$ IgM$^+$ CD38$^+$), and reduced nonswitched memory B cells (CD19$^+$ IgD$^+$ CD27$^+$) and class-switched memory B cells (CD19$^+$ IgD$^+$ CD27$^+$) are hallmark. Immunoglobulin levels are variable, but typically there are increased serum quantities of IgM, reduced or normal IgG, and reduced or normal IgA.

Treatment is symptom specific but can include antimicrobial prophylaxis and immunoglobulin replacement. Various immunosuppressive agents (e.g., rituximab, rapamycin) have been used to treat the lymphoproliferative disease and autoimmune cytopenias that are often present. HSCT has also been successfully performed in those refractory to medical therapy.

Signal Transducer and Activator of Transcription (STAT) Pathway Defects

The Janus kinase (JAK)-STAT signal transduction pathway is used for signal transduction by type 1 and type 2 cytokine receptors within most hematopoietic cells. Cytokines bind to their cognate receptor, triggering JAK-STAT pathways, ultimately leading to the upregulation of genes involved in the immune response against many pathogens. There are 4 JAK proteins (Jak1, Jak2, Jak3, Tyk2) and 6 STATs (1-6). Mutations in several JAKs and STATs cause immunodeficiency. Table 152.5 includes diseases affecting STAT proteins characterized by immune dysregulation. Chronic immunosuppression is necessary for control of STAT defects. Ruxolitinib, a JAK-STAT inhibitor, has been used with some success. With the advent of JAK-STAT immunomodulating therapies, more treatment options will be available to patients.

Table 152.5

Defects of STAT Proteins Associated With Immunodysregulation

PROTEIN	LOF/GOF	AUTOIMMUNE OR INFLAMMATORY COMPLICATIONS	OTHER CHARACTERISTICS	IMMUNOPHENOTYPE
STAT1	GOF	IPEX-like enteropathy, enteropathy, endocrinopathy, dermatitis, cytopenias	Infections CMC Viral infections NTM Dimorphic mold Respiratory bacterial	Variable lymphopenia, hypogammaglobulinemia, abnormal T-cell function, reduced Th17 expression
STAT3	GOF	Early onset enteropathy, severe growth failure, lymphoproliferation, autoimmune cytopenias, inflammatory lung disease, type 1 diabetes, dermatitis, arthritis	Respiratory tract infections Herpes viral infections T-cell LGL leukemia NTM	Increased DNT ($CD3^+$ $CD4^-$ $CD8^-$) Hypogammaglobulinemia T-cell lymphopenia B-cell lymphopenia
STAT5B	LOF	Severe growth hormone resistant growth failure, lymphocytic interstitial pneumonitis, atopic dermatitis	Respiratory tract infections Viral infections	Lymphopenia Reduced Treg cells Reduced γδ T cells Reduced NK cells

STAT, Signal transducer and activator of transcription; GOF, gain of function; LOF, loss of function; IPEX, immunodysregulation, polyendocrinopathy, enteropathy, X-linked; CMC, chronic mucocutaneous candidiasis; NTM, nontuberculous mycobacteria; DNT, double-negative T cell.

Nuclear Factor-κB Pathway Defects

The NF-κB pathways consists of canonical (NF-κB1) and noncanonical (NF-κB2) pathways. On cellular activation, both pathways lead to activation and translocation of NF-κB proteins into the nucleus, where they initiate downstream inflammatory responses. Defects in many proteins in both pathways have been described. Table 152.6 describes immune defects of the NF-κB pathways that cause symptoms of immune dysregulation or autoimmunity. Treatment of NF-κB defects includes prevention of infections and replacement of immunoglobulin and has included HSCT.

Table 152.6

Defects of Nuclear Factor-κB Pathways Associated With Immune Dysregulation

PROTEIN	INHERITANCE	AUTOIMMUNE OR INFLAMMATORY COMPLICATIONS	OTHER MANIFESTATIONS	IMMUNOLOGIC PHENOTYPE
IKBKG (NEMO)	XL	Colitis	Ectodermal dysplasia Osteopetrosis Lymphedema Bacterial infections Opportunistic infections DNA viral infections	Hypogammaglobulinemia Hyper IgM Hyper IgA Hyper IgD Poor antibody responses Decreased NK cell function Decreased TLR responses
NF-κB1	AD	Pyoderma gangrenosum Lymphoproliferation Cytopenia Hypothyroidism Alopecia areata Enteritis LIP NRH	Atrophic gastritis Squamous cell carcinoma Respiratory tract infections Superficial skin infections Lung adenocarcinoma Respiratory insufficiency Aortic stenosis Non-Hodgkin lymphoma	Hypogammaglobulinemia IgA deficiency
NF-κB2	AD	Alopecia totalis Trachyonychia Vitiligo Autoantibodies: thyroid peroxidase, glutamate decarboxylase, thyroglobulin Central adrenal	Viral respiratory infections Pneumonias Sinusitis Otitis media Recurrent herpes Asthma Type 1 Chiari malformation	Early-onset hypogammaglobulinemia Low vaccine responses Variable B-cell counts Low switched memory B cells (CD19^{+} CD27^{+} IgD $^{-}$) Low marginal zone B cells (CD19^{+} CD27^{+}

		insufficiency	Interstitial lung disease	IgD$^+$)

XL, X-linked; AD, autosomal dominant; LIP, lymphocytic interstitial pneumonitis; NRH, nonregenerative hyperplasia.

Tetratricopeptide Repeat Domain 7A (TTC7A) Deficiency

Combined immunodeficiency with T-cell and B-cell defects had long accompanied hereditary **multiple intestinal atresia** . Mutations in *TTC7A* are causative of the combined intestinal and immunologic defects. TTC7A is involved in cell cycle control, cytoskeletal organization, cell shape and polarity, and cell adhesion. Deficiency of TTC7A is inherited in an autosomal recessive manner. Multiple intestinal atresia with disruption of intestinal architecture is a universal feature. Often, early-onset severe enterocolitis occurs concurrently. Immunodeficiency with severe T-cell lymphopenia has been described; B- and NK-cell defects are variable. T-cell proliferative responses are also abnormal. Severe hypogammaglobulinemia is common. Treatment includes removal of atretic areas of the intestine and antimicrobial prophylaxis in immunodeficient patients. Bowel transplant has also been performed with some success.

Deficiency of Adenosine Deaminase 2 (DADA2)

Deficiency in ADA2 is a cause of early **vasculopathy, stroke** , and immunodeficiency. DADA2 is secondary to autosomal recessive mutations in cat-eye syndrome chromosome region 1 (*CECR1*), mapped to chromosome 22q11.1. ADA2 is important in purine metabolism converting adenosine to inosine and 2′-deoxyadenosine to 2′-deoxyinosine. The pathogenesis is not exactly known, but ADA2 is mostly secreted by myeloid cells, and deficiency leads to upregulation of proinflammatory genes and increased secretion of proinflammatory cytokines. DADA2 is characterized by chronic or recurrent inflammation with elevated acute-phase reactants and fever. Skin manifestations include livedo reticularis, maculopapular rash, nodules, purpura, erythema nodosum, Raynaud phenomenon, ulcerative lesions, and digital necrosis. CNS involvement is variable but can include transient ischemic attacks and ischemic or hemorrhagic stroke. Peripheral neuropathy is also common. GI manifestations include hepatosplenomegaly, gastritis, bowel perforation, and portal hypertension. Nephrogenic hypertension is common and can be associated with glomerulosclerosis or amyloidosis. Immunodeficiency consists of hypogammaglobulinemia and variable decreases in IgM.

Treatment with chronic long-term corticosteroids and anti-TNF-α agents have shown modest control of disease manifestations. HSCT has been successful in 2 patients as well.

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SECTION 3

The Phagocytic System

OUTLINE

Chapter 153 Neutrophils
Chapter 154 Monocytes, Macrophages, and Dendritic Cells
Chapter 155 Eosinophils
Chapter 156 Disorders of Phagocyte Function
Chapter 157 Leukopenia
Chapter 158 Leukocytosis

CHAPTER 153

Neutrophils

Thomas D. Coates

The Phagocytic Inflammatory Response

The phagocyte system includes both granulocytes (neutrophils, eosinophils, and basophils) and mononuclear phagocytes (monocytes and tissue macrophages). Neutrophils and mononuclear phagocytes share primary functions, including the defining properties of large-particle ingestion and microbial killing. Phagocytes participate primarily in the innate immune response but also help initiate acquired immunity. Mononuclear phagocytes, including tissue macrophages and circulating monocytes, are discussed in Chapter 154 .

Neutrophils provide the rapid effector arm of the innate immune system. They circulate in the bloodstream for only about 6 hr (Table 153.1), but on encountering specific chemotactic signals, they adhere to the vascular endothelium and transmigrate into tissues. There they ingest and kill microbes and release chemotactic signals to recruit more neutrophils and to attract dendritic cells and other initiators of the acquired immune response.

Table 153.1

Neutrophil and Monocyte Kinetics

NEUTROPHILS	
Average time in mitosis (myeloblast to myelocyte)	7-9 days
Average time in postmitosis and storage (metamyelocyte to neutrophil)	3-7 days
Average half-life in the circulation	6 hr
Average total body pool	6.5 × 10^8 cells/kg
Average circulating pool	3.2 × 10^8 cells/kg
Average marginating pool	3.3 × 10^8 cells/kg
Average daily turnover rate	1.8 × 10^8 cells/kg
MONONUCLEAR PHAGOCYTES	

Average time in mitosis	30-48 hr
Average half-life in the circulation	36-104 hr
Average circulating pool (monocytes)	1.8 × 10^7 cells/kg
Average daily turnover rate	1.8 × 10^9 cells/kg
Average survival in tissues (macrophages)	Months

From Boxer LA: Function of neutrophils and mononuclear phagocytes. In Bennett JC, Plum F, editors: *Cecil textbook of internal medicine,* ed 20, Philadelphia, 1996, Saunders.

Hematopoiesis

The hematopoietic progenitor system can be viewed as a continuum of functional compartments, with the most primitive compartment composed of very rare **pluripotential stem cells** , which have high self-renewal capacity and give rise to more mature stem cells, including cells that are committed to either lymphoid or myeloid development (Fig. 153.1). Common lymphoid progenitor cells give rise to T- and B-cell precursors and their mature progeny (see Chapter 149). Common myeloid progenitor cells eventually give rise to committed single-lineage progenitors of the recognizable precursors through a random process of lineage restriction in a stepwise process (see Chapter 473). The capacity of lineage-specific committed progenitors to proliferate and differentiate in response to demand provides the hematopoietic system with a remarkable range of response to changing requirements for mature blood cell production.

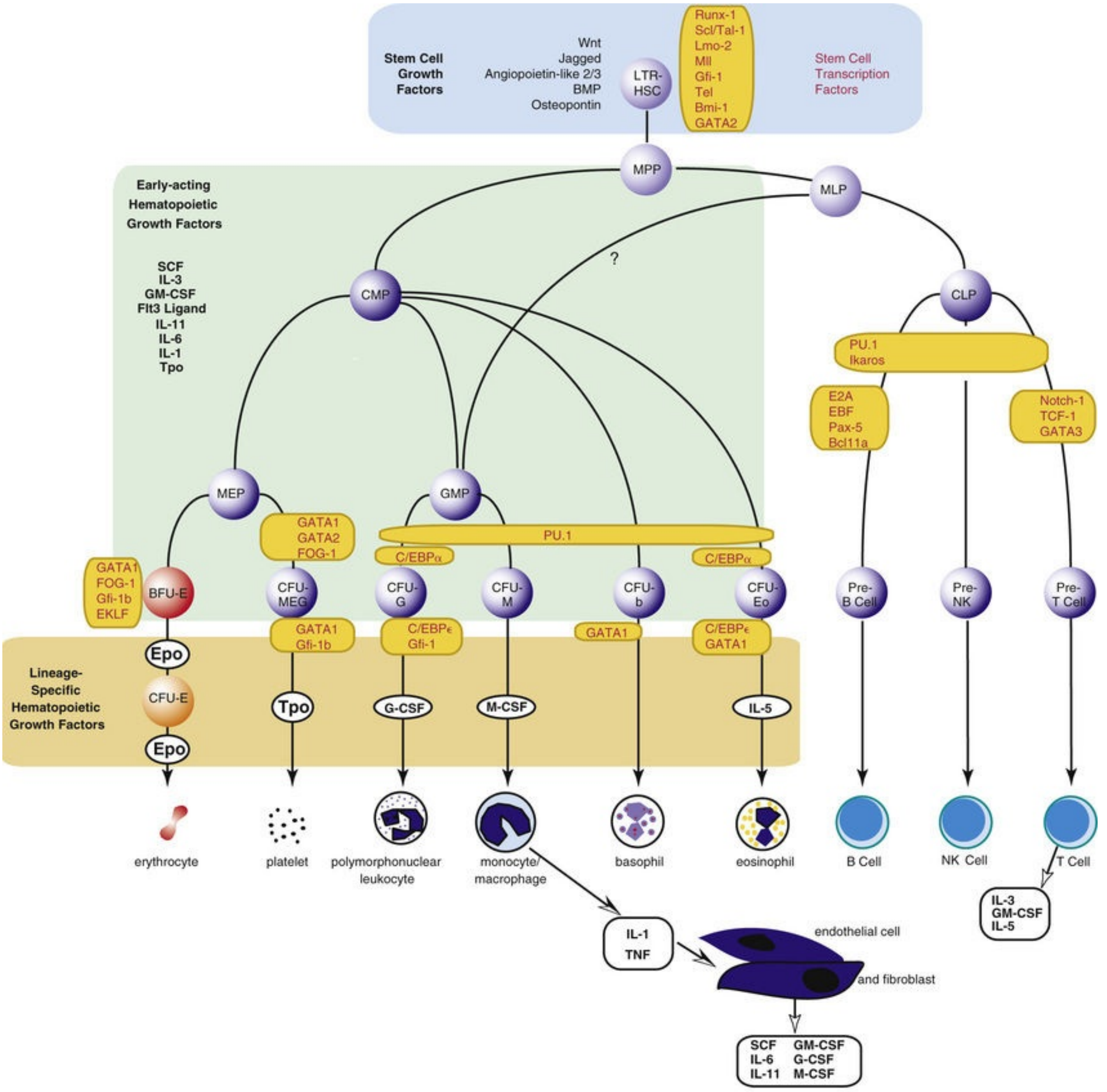
Stem Cell Growth Factors
Wnt
Jagged
Angiopoietin-like 2/3
BMP
Osteopontin
LTR-HSC
Runx-1
Scl/Tal-1
Lmo-2
Mll
Gfi-1
Tel
Bmi-1
GATA2
Stem Cell Transcription Factors
MPP
MLP
Early-acting Hematopoietic Growth Factors
SCF
IL-3
GM-CSF
Flt3 Ligand
IL-11
IL-6
IL-1
Tpo
CMP
?
CLP
PU.1
Ikaros
E2A
EBF
Pax-5
Bcl11a
Notch-1
TCF-1
GATA3
MEP
GMP
GATA1
GATA2
FOG-1
PU.1
C/EBPα
C/EBPα
GATA1
FOG-1
Gfi-1b
EKLF
BFU-E
CFU-MEG
CFU-G
CFU-M
CFU-b
CFU-Eo
Pre-B Cell
Pre-NK
Pre-T Cell
GATA1
Gfi-1b
C/EBPε
Gfi-1
GATA1
C/EBPε
GATA1
Epo
Lineage-Specific Hematopoietic Growth Factors
CFU-E
Epo
Tpo
G-CSF
M-CSF
IL-5
erythrocyte
platelet
polymorphonuclear leukocyte
monocyte/macrophage
basophil
eosinophil
B Cell
NK Cell
T Cell
IL-3
GM-CSF
IL-5
IL-1
TNF
endothelial cell
and fibroblast
SCF
IL-6
IL-11
GM-CSF
G-CSF
M-CSF

FIG. 153.1 Major cytokine sources and actions and transcription factor requirements for hematopoietic cells. Cells of the bone marrow microenvironment, such as macrophages, endothelial cells, and reticular fibroblastoid cells, produce macrophage, granulocyte-macrophage, and granulocyte colony-stimulating factors (M-CSF, GM-CSF, G-CSF), interleukin-6 (IL-6), and probably stem cell factor (SCF) (cellular sources not precisely determined) after induction with endotoxin (macrophage) or IL-1/tumor necrosis factor (TNF) (endothelial cells and fibroblasts). T cells produce IL-3, GM-CSF, and IL-5 in response to antigenic and IL-1 stimulation. These cytokines have overlapping actions during hematopoietic differentiation, as indicated, and for all lineages, optimal development requires a combination of early-acting and late-acting factors. Transcription factors important for survival or self-renewal of stem cells are shown in *red* at the *top,* whereas stages of hematopoiesis blocked after the depletion of indicated transcription factors are shown in *red* for multipotent and committed progenitors. (From *Nathan & Oski's hematology and oncology of infancy and childhood,* ed 8, vol 2, Philadelphia, 2015, Elsevier, p 10.)

The proliferation, differentiation, and survival of immature hematopoietic progenitor cells are governed by hematopoietic growth factors, a family of glycoproteins (see Chapter 473). Besides regulating proliferation and differentiation of progenitors, these factors influence the survival and function of mature blood cells. During granulopoiesis and monopoiesis, multiple cytokines regulate the cells at each stage of differentiation from pluripotent stem cells to nondividing, terminally differentiated cells (monocytes, neutrophils, eosinophils, and basophils). As cells mature, they lose receptors for most cytokines, especially those that influence early cell development; however, they retain receptors for cytokines that affect their mobilization and function, such as granulocyte and macrophage colony-stimulating factors. Mature phagocytes also express receptors for chemokines, which help direct the cells to sites of inflammation. Chemokine receptors such as CXCR4 and its ligand SDF-1 play a key role in retention of developing myeloid cells within bone marrow.

Neutrophil Maturation and Kinetics

The process of intramedullary granulocyte maturation involves changes in nuclear configuration and accumulation of specific intracytoplasmic granules. The bone marrow microenvironment supports the normal steady-state renewal of peripheral blood neutrophils through the generation of growth and differentiation factors by stromal cells. Growth factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) not only stimulate cell division, but also induce the expression of transcription factors that regulate the biosynthesis of functional components of the neutrophil, such as granule proteins. The transcription factor PU.1 is essential for myelopoiesis, both as a positive regulatory element and as a suppressor of GATA1, a transcription factor that directs nonmyeloid differentiation. Other transcription factors, such as Runx1 (AML1), c-myb, CDP, C/EBPα, C/EBPγ, and MEF, are expressed in the myeloblast and promyelocyte, and some of these are required for azurophil granule protein expression. As cells enter the myelocyte stage, Runx1 and myb are downregulated, whereas PU.1 and C/EBPε expression rises to initiate terminal differentiation.

Granulocytes survive for only 6-12 hr in the circulation, and therefore daily production of 2×10^4 granulocytes/μL of blood is required to maintain a level of circulating granulocytes of 5×10^3 /μL (see Table 153.1). The relatively small peripheral blood pool includes the rapidly interchanging circulating and marginating pools; the latter provides entrance into the tissue phase, where neutrophils may survive for hours or days. The circulating pool is fed and buffered by a much larger marrow population of mature neutrophils and myeloid precursors, representing the marrow reserve and proliferating pools, respectively. Proliferation of myeloid cells, encompassing approximately 5 mitotic divisions, takes place only during the first 3 stages of neutrophil development, in myeloblasts, promyelocytes, and myelocytes. After the myelocyte stage, the cells terminally differentiate into nondividing, maturing metamyelocytes, bands, and neutrophils.

Neutrophil maturation is associated with nuclear condensation and lobulation and the sequential production of characteristic granule populations. A **myeloblast** is a relatively undifferentiated cell with a large oval nucleus, a sizable nucleolus, and a deficiency of granules. **Promyelocytes** acquire peroxidase-positive azurophilic (primary) granules, and then **myelocytes** and **metamyelocytes** acquire specific (secondary) granules; tertiary granules and secretory vesicles develop in the final stage of neutrophil maturation.

Neutrophil Function

Neutrophil responses are initiated as circulating neutrophils flowing through the postcapillary venules detect low levels of chemokines and other chemotactic substances released from a site of infection. The sequence of events as the neutrophil moves from circulating in the blood to the encounter and destruction of bacteria is carefully orchestrated by a series of biochemical events, defects of which are associated with genetic disorders of neutrophil function (Fig. 153.2). In fact, these disorders of neutrophil function lead to our understanding of the cell biology of phagocyte function. A subset of circulating neutrophils loosely adheres to the endothelium through low-affinity receptors called **selectins** and rolls along the endothelium, forming the marginated pool. Soluble effectors of inflammation trigger subtle changes in surface adhesion molecules on endothelial cells at the site of infection. The rolling of neutrophils allows more intense exposure of neutrophils to activating factors such as tumor necrosis factor or interleukin-1 (Fig. 153.2). Exposure of neutrophils to these same activating factors induces qualitative and quantitative changes in the family of β_2 -integrin adhesion receptors (the CD11/CD18 group of surface molecules), leading to tight adhesion between neutrophils and endothelial cells at the site of inflammation and ultimately to transmigration of the neutrophil into the tissue.

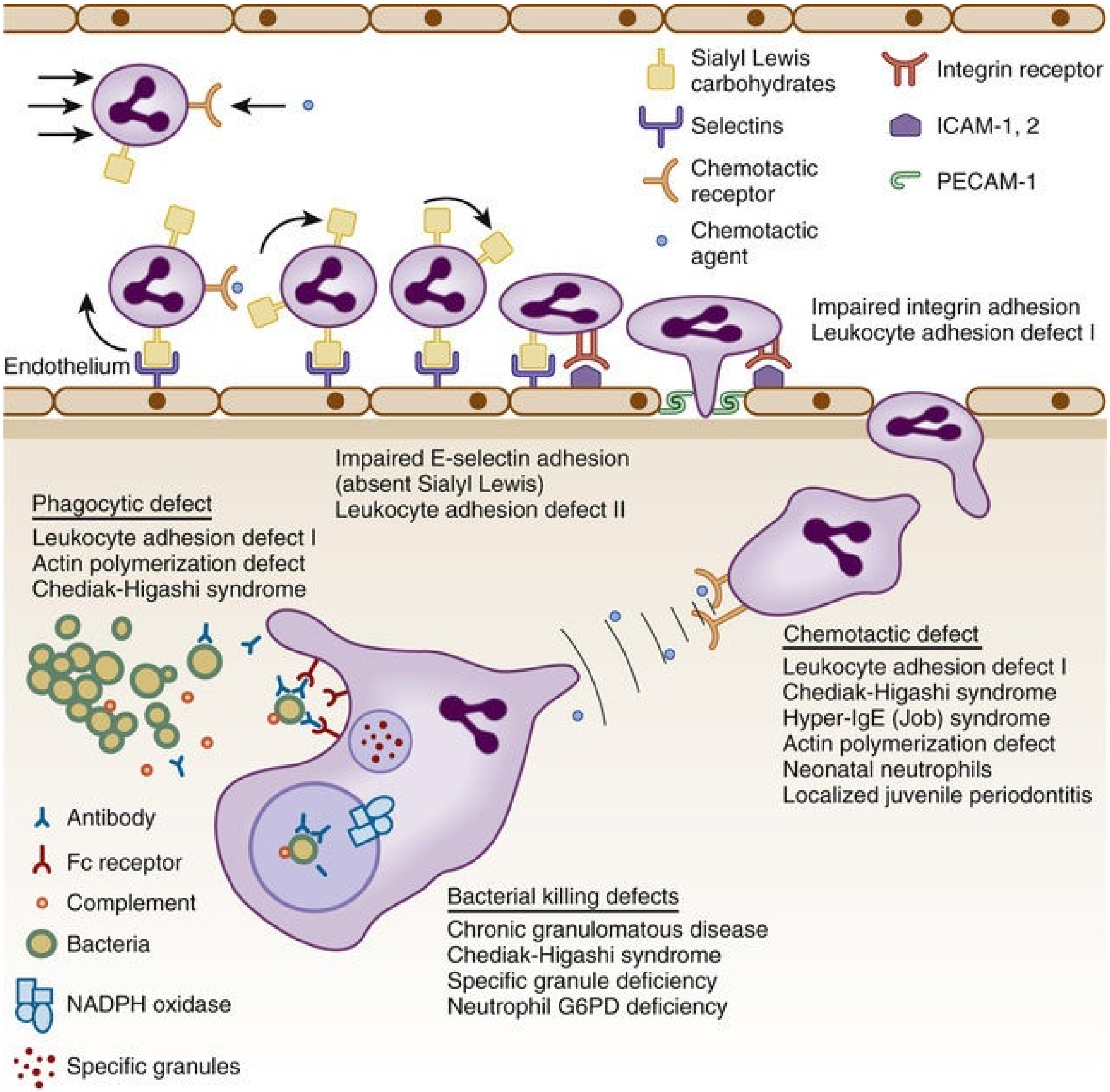
Sialyl Lewis carbohydrates
Integrin receptor
Selectins
ICAM-1, 2
Chemotactic receptor
PECAM-1
Chemotactic agent
Impaired integrin adhesion
Leukocyte adhesion defect I
Endothelium
Impaired E-selectin adhesion
(absent Sialyl Lewis)
Leukocyte adhesion defect II
Phagocytic defect
Leukocyte adhesion defect I
Actin polymerization defect
Chediak-Higashi syndrome
Chemotactic defect
Leukocyte adhesion defect I
Chediak-Higashi syndrome
Hyper-IgE (Job) syndrome
Actin polymerization defect
Neonatal neutrophils
Localized juvenile periodontitis
Antibody
Fc receptor
Complement
Bacteria
NADPH oxidase
Specific granules
Bacterial killing defects
Chronic granulomatous disease
Chediak-Higashi syndrome
Specific granule deficiency
Neutrophil G6PD deficiency

FIG. 153.2 **The neutrophil-mediated inflammatory response and associated neutrophil dysfunction syndromes. Circulating neutrophils loosely attach to endothelium via selectins and roll along the vessel wall until they arrive at the site of infection. Inflammatory monokines, interleukin-1 (IL-1), and tumor necrosis factor (TNF) activate endothelial cells to express E- and P-selectins. E- and P-selectins serve as counter-receptors for neutrophils sialyl Lewis X and Lewis X to cause low-avidity neutrophil rolling. Activated endothelial cells express ICAM-1, which serves as a counter-receptor for neutrophil β_2 -integrin molecules, leading to high-avidity leukocyte spreading and the start of transendothelial migration at the infection site. Neutrophils invade through the vascular basement membrane with the release of proteases and reactive oxidative intermediates, causing local destruction of surrounding tissue at sites of high concentrations of chemotactic factors, and migrate to the site of infection, where they ingest and kill the bacteria. (Modified from Kyono W, Coates TD: A practical approach to neutrophil disorders, *Pediatr Clin North Am* 49:929, 2002.)**

Once through the endothelium, the neutrophil senses the gradient of chemokines or other chemoattractants and migrates to sites of infection. **Neutrophil migration** is a complex process involving rounds of receptor engagement, signal transduction, and remodeling of the actin microfilaments composing in part the cytoskeleton. Actin polymerization-depolymerization occurs in approximately 8 sec cycles and drives cyclic extension and retraction of the actin-rich lamella at the front of the neutrophil. Receptors at the leading edge of the lamella detect the gradient of attractant and follow microorganisms, then ingest and destroy them. When the neutrophil reaches the site of infection, it recognizes pathogens by means of Fc immunoglobulin and complement receptors, Toll-like receptors, fibronectin receptors, and other adhesion molecules.

The neutrophil ingests microbes that are coated by **opsonins** , serum proteins such as immunoglobulin and complement component **C3** . The pathogens are engulfed into a closed vacuole, the **phagosome** (Fig. 153.3), where 2 cellular responses essential for optimal microbicidal activity occur concomitantly: degranulation and activation of nicotinamide-adenine dinucleotide phosphate (NADPH)–dependent oxidase. Fusion of neutrophil granule membranes with the phagosome membrane delivers potent antimicrobial proteins and small peptides into the phagosome.

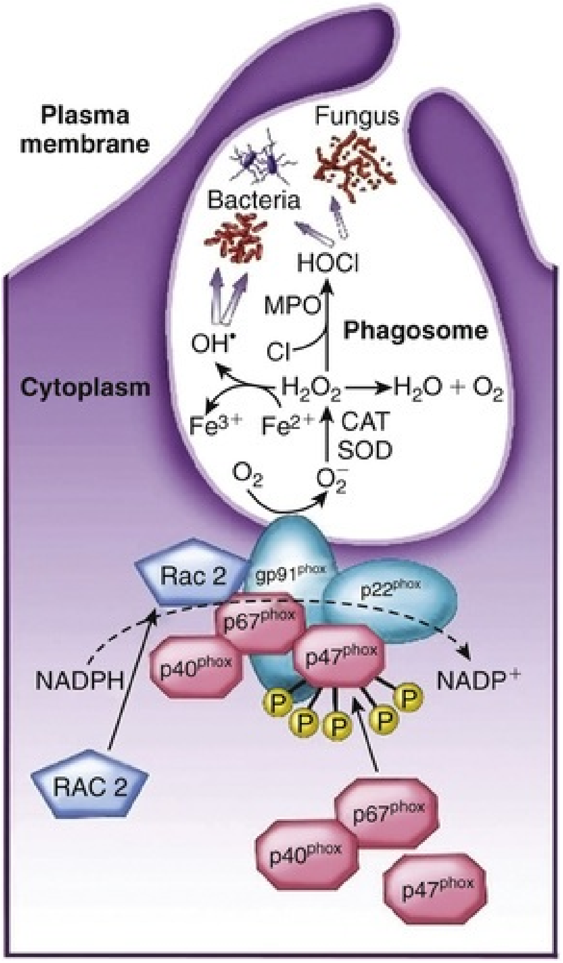
Plasma membrane
Fungus
Bacteria
HOCl
MPO
Cl⁻
Phagosome
OH•
Cytoplasm
Fe3+
Fe2+
H2O2
H2O + O2
CAT
SOD
O2
O2⁻
Rac 2
gp91phox
p22phox
p67phox
p40phox
p47phox
NADPH
NADP+
P
RAC 2
p67phox
p40phox
p47phox

FIG. 153.3 Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase components and activation. On activation of phagocytic cells, the 3 cytosolic components *(red)* of the NADPH oxidase (p67 ^{phox} , p47 ^{phox} , and p40 ^{phox}), plus the small guanosine triphosphatase (GTPase) protein Rac2, are translocated to the membrane of the phagocytic vacuole. The p47 ^{phox} subunit binds to the flavocytochrome $_{b558}$ membrane component *(blue-green)* of the NADPH oxidase (gp91 ^{phox} plus p22 ^{phox}). The NADPH oxidase catalyzes the formation of superoxide by transferring an electron from NADPH to molecular oxygen (O_2), thereby forming the superoxide free radical. The unstable superoxide anion is converted to hydrogen peroxide, either spontaneously or by superoxide dismutase (SOD). H_2O_2 can follow different metabolic pathways into more potent reactive oxidants, such as OH* or HOCl) or degradation to $H_2O + O_2$. (Adapted from Stiehm ER, Ochs HD, Winkelstein JA: *Immunologic disorders in infants and children,* ed 5, Philadelphia, 2004, Saunders, p 622.)

Assembly and activation of NADPH oxidase occur at the phagosome membrane as well (see Fig. 153.3), generating large amounts of superoxide (O_2^-) from molecular oxygen, which in turn decomposes to produce hydrogen peroxide (H_2O_2) and singlet oxygen. **Myeloperoxidase,** a major azurophil granule component, catalyzes the reaction of H_2O_2 with ubiquitously present chloride ions to create hypochlorous acid (HOCl) in the phagosome. H_2O_2 and HOCl are potent microbicidal agents that break down and clear pathogens from sites of infection.

In addition, neutrophils secrete a wide variety of cytokines and chemokines that recruit more neutrophils to fight the infection, attract monocytes and macrophages that possess both microbicidal and scavenger functions, and promote antigen presentation to help initiate the adaptive immune response. Also, the reactive oxidants can inactivate chemotactic factors and may serve to terminate the process of neutrophil influx, thereby attenuating the inflammatory process. Finally, the release of reactive oxygen species, granule proteins, and cytokines can also damage local tissues, leading to the classic signs of inflammation or to more permanent impairment of tissue integrity and function.

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CHAPTER 154

Monocytes, Macrophages, and Dendritic Cells

Richard B. Johnston Jr.

Mononuclear phagocytes (monocytes, macrophages) are distributed across all body tissues and play a central role in maintaining immunologic and metabolic homeostasis. They are essential for innate host defense against infection, tissue repair and remodeling, and the antigen-specific adaptive immune response. No human has been identified as having congenital absence of this cell line, probably because macrophages are required to remove primitive tissues during fetal development as new tissues develop to replace them. Monocytes and tissue macrophages in their several forms have variable morphology, surface markers, and transcriptional profiles but common functions, particularly phagocytosis (Table 154.1). Dendritic cells (DCs) are specialized derivatives of this mononuclear phagocyte system that develop from myeloid cell precursors or monocytes themselves.

Table 154.1

Principal Sites of Macrophages in Tissues

Liver (Kupffer cells)
Lung (interstitial and alveolar macrophages)
Connective tissue, adipose tissue, and interstitium of major organs and skin
Serosal cavities (pleural and peritoneal macrophages)
Synovial membrane (type A synoviocytes)
Bone (osteoclasts)
Brain and retina (microglial cells)
Spleen, lymph nodes, bone marrow

Intestinal wall
Breast milk
Placenta
Granulomas (multinucleated giant cells)

Development

Monocytes develop more rapidly during bone marrow hematopoiesis and remain longer in the circulation than do neutrophils (see Table 153.1). The **monoblast** is the first recognizable monocyte precursor, followed by the **promonocyte** , with cytoplasmic granules and an indented nucleus, and finally the fully developed monocyte with cytoplasmic granules filled with hydrolytic enzymes. The transition from monoblast to mature circulating monocyte requires about 6 days.

Three major subsets of human monocytes can be identified on the basis of surface antigens: CD14^{++} CD16^{-} *classical* monocytes that constitute the majority of total monocytes in the resting state; the more mature CD14^{++} CD16^{+} *proinflammatory* (*intermediate*) monocytes, which produce proinflammatory hormone-like factors termed **cytokines** , such as tumor necrosis factor-α (TNF-α), in response to microbial stimuli; and *nonclassical* (*regulatory)* monocytes (CD14^{+} CD16^{++}) that promote wound healing. Monocytes from these subsets migrate into tissues in response to localized inflammation or injury and provide proinflammatory host defense or antiinflammatory responses and wound healing.

Tissue (organ)-specific macrophages arise from macrophage progenitors that develop in the yolk sac and fetal liver before hematopoiesis occurs in the bone marrow. These cells maintain their population through self-renewal. Tissue macrophages can also be populated to some extent by circulating monocytes. Monocytes or macrophages at sites of active inflammation mature into proinflammatory (M1) macrophages or proresolving (M2) macrophages. In ongoing tissue injury or inflammation, many (perhaps most) of the macrophages will express a mix of the properties of the classic types.

Whether embryonic or blood derived, tissue macrophages are directed by organ-specific factors to differentiate into macrophages characteristic of that organ. Embryonic progenitors or monocytes in the liver become **Kupffer cells** that bridge the sinusoids separating adjacent plates of hepatocytes. Those at the lung airway surface become large ellipsoid **alveolar macrophages** , those in the bone become **osteoclasts** , and those in brain or retina become **microglia** . All macrophages, however, have at least 3 major functions in common: phagocytosis, presentation of antigens to lymphocytes, and enhancement or suppression of the immune response through release of a variety of potent cytokines. At sites of inflammation, monocytes and macrophages can fuse to form **multinucleated giant cells** ; these cells maintain the antimicrobial functions of macrophages.

Activation

The most important step in the maturation of tissue macrophages is the conversion from a resting to a more functionally active cell, a process driven primarily by certain cytokines and microbial products. *Macrophage activation* is a generic term, with the functional characteristics of an activated macrophage population varying with the cytokine or other stimulus (microbial, chemical) to which the population has been exposed.

Classical activation refers to a response to infection that is driven by specifically activated T-helper (Th) type 1 (Th1-type) lymphocytes and natural killer (NK) cells through their release of interferon-γ (IFN-γ). TNF-α secreted by activated macrophages amplifies their activation, as does bacterial cell wall protein or endotoxin through Toll-like receptors (TLRs). **Alternative activation** is driven by Th2-type lymphocytes through release of interleukin-4 (IL-4) and IL-13, cytokines that regulate antibody responses, allergy, and resistance to parasites. Alternatively activated macrophages may have particular functional advantages, such as in wound healing and immunoregulation. In the traditional context of host defense, the term *activated macrophage* indicates that the “classically activated” cell has an enhanced capacity to kill microorganisms or tumor cells. These macrophages are larger, with more pseudopods and pronounced ruffling of the plasma membrane, and they exhibit accelerated activity of many functions (Table 154.2). Considering the variety of macrophage activities essential to the maintenance of homeostasis, it seems likely that so-called classically activated, M1-type, and alternatively activated, M2-type, macrophages are extremes of a continuum of physiologic functions expressed by these long-lived cells in response to the specific task at hand.

Table 154.2

Upregulated Functions in Macrophages Activated in Response to Infection

Microbicidal and tumoricidal activity
Phagocytosis (of most particles) and pinocytosis
Phagocytosis-associated respiratory burst (O_2^-, H_2O_2)
Generation of nitric oxide
Chemotaxis
Glucose transport and metabolism
Membrane expression of MHC, CD40, TNF receptor
Antigen presentation
Secretion:
    Complement components
    Lysozyme, acid hydrolases, and cytolytic proteinases
    Collagenase
    Plasminogen activator
    Interleukins, including IL-1, IL-12, and IL-15
    TNF-α
    Interferons, including IFN-α and IFN-β
    Antimicrobial peptides (cathelicidin, defensins)
    Angiogenic factors

H_2O_2, Hydrogen peroxide; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; O_2^-, superoxide anion; TNF, tumor necrosis factor.

Classical macrophage activation is accomplished during infection with intracellular pathogens (e.g., mycobacteria, *Listeria*) through crosstalk between Th1 lymphocytes and antigen-presenting macrophages mediated by the engagement of a series of ligands and receptors on the 2 cell types, including class II major histocompatibility complex (MHC) molecules and CD40 on macrophages and CD40 ligand on Th1 cells, and through secretion of cytokines. Macrophages encountering microorganisms release IL-12, which stimulates T cells to release IFN-γ. These interactions constitute the basis of cell-mediated immunity. IFN-γ is an especially important macrophage-activating cytokine; it is currently used as a therapeutic agent.

Functional Activities

Numerous functions are upregulated when the macrophage is activated in response to infection (see Table 154.2). Of importance are the ingestion and killing of *intracellular* pathogens such as mycobacteria, *Listeria, Leishmania, Toxoplasma*, and some fungi. Killing of the ingested organisms of any kind depends heavily on products of the *respiratory burst* (e.g., hydrogen peroxide) and on nitric oxide, and release of these metabolites is enhanced in activated macrophages. Whether activated or not, splenic and hepatic macrophages are essential for clearing the bloodstream of *extracellular* pathogens such as pneumococci.

The capacity to undergo diapedesis across the endothelial wall of blood vessels and to migrate to sites of microbial invasion is essential to monocyte function. Chemotactic factors for monocytes include complement products and chemotactic peptides (**chemokines**) derived from neutrophils, lymphocytes, and other cell types. Phagocytosis of the invading organisms can then occur, influenced by the presence of opsonins for the invader (antibody, complement, mannose-binding and surfactant proteins), the inherent surface properties of the microorganism, and the state of activation of the macrophage.

Monocytes migrating to intestinal mucosa are modified by stromal factors so that they lose innate receptors for microbial products such as endotoxin, and they do not effectively produce proinflammatory cytokines. They retain, however, the capacity to ingest and kill microbes. They have been modified during evolution to allow the absence of inflammation typical of normal intestinal mucosa despite its constant exposure to huge numbers of microbes and their inflammatory by-products.

Macrophages play an essential role in the disposal of damaged and dying cells, helping resolve the inflammatory response and heal wounds. Brain microglia demonstrate these functions particularly well. In conditions such as stroke, neurodegenerative disease, and tumor invasion, these cells can become activated, surround damaged and dead cells, and clear cellular debris. Macrophages lining the sinusoids of the spleen are especially important in ingesting aged or autoantibody-coated erythrocytes or platelets; splenectomy is used to manage autoimmune cytopenias. In the process of **efferocytosis** , macrophages in inflammatory sites can recognize changes in phosphatidylserine on the membrane of neutrophils undergoing apoptosis, and these can be removed before they spill their toxic contents into the tissue. Macrophages also remove the extracellular traps exuded by inflammatory neutrophils, thus reducing the risk of autoimmunity. Macrophages can be identified early in fetal development, where they function to remove debris as one maturing embryonic tissue replaces another; in the brain, microglia prune synapses opsonized with C1q. Macrophages are also important in removing inorganic particles, such as elements of cigarette smoke, that enter the alveoli.

Macrophages are involved in the induction and expression of adaptive immune responses, including antibody formation and cell-mediated immunity. This depends on their capacity to break down foreign material, then present individual antigens on their surface as peptides or polysaccharides bound to MHC class II molecules. Monocytes, B lymphocytes, and most effectively, DCs, also present antigens to T cells for the specific immune response. Activated macrophages express increased MHC class II molecules, and antigen presentation is more effective.

The heightened capacity of activated macrophages to synthesize and release various hydrolytic enzymes and microbicidal materials contributes to their increased killing capacity (see Table 154.2). The macrophage is an extraordinarily active secretory cell shown to secrete >100 distinct substances, including cytokines, growth factors, and sterol hormones, placing it in a class with the hepatocyte. Because of the profound effect of some of these secretory products on other cells and the large number and widespread distribution of macrophages, this network of cells can be viewed as an important endocrine organ. IL-1 illustrates this point. Microbes and microbial products, burns, ischemia–reperfusion, and other causes of inflammation or tissue damage stimulate the release of IL-1, mainly by monocytes, macrophages, and epithelial cells. In turn, IL-1 elicits fever, sleep, and release of IL-6, which induces production of acute-phase proteins.

The complex relationship between mononuclear phagocytes and cancer is becoming more clear. Macrophages have been demonstrated to kill tumor cells by ingestion and by means of secreted products, including lysosomal enzymes, nitric oxide, oxygen metabolites, and TNF-α. In contrast, M2-type **tumor-associated macrophages (TAMs)** can stimulate growth of tumors through secretion of growth and angiogenic factors such as vascular endothelial growth factor (VEGF), promote metastasis, and inhibit T-cell antitumor immune responses. TAMs are currently targets of clinical trials studying attempts to reprogram them to antitumor macrophages or otherwise blunt their tumor-supportive capacity.

As traumatic damage and infection subside, the macrophage population shifts toward playing an essential role in tissue repair and healing through removal of apoptotic cells and secretion of IL-10, transforming growth factor-β, lipoxins, and the “specialized proresolving mediators,” omega-3 fatty acid–derived resolvins, protectins, and maresins.

Dendritic Cells

Dendritic cells are a type of mononuclear phagocyte found in blood, lymphoid organs, and all tissues. DCs are specialized to capture, process, and present antigens to T cells to generate adaptive immunity or tolerance to self-antigens. Human monocytes can be induced to differentiate into DCs in some circumstances, particularly inflammation. DCs express retractable dendritic (branched) extensions and potent endocytic capacity but are a heterogeneous population from the standpoint of location, surface markers, level of antigen-presenting activity, and function. Single-cell RNA sequencing has defined 6 human DC subtypes; but 2 major functional types of DCs can be identified: *conventional* DCs, which include Langerhans cells in the epithelial surfaces of skin and mucosa, dermal or interstitial DCs in subepithelial skin, and interstitial DCs in solid organs; and *plasmacytoid* DCs, sentinels for viral infection and principal source of antiviral IFN-α and IFN-β.

DCs migrating from the bloodstream enter skin, epithelial surfaces, and lymphoid organs where, as immature cells, they internalize self and foreign antigens. Microbial products, cytokines, or molecules exposed in damaged tissue (“danger signals” or “alarmins”) induce DC maturation, with upregulation of cytokine receptors and MHC class II and co-stimulatory molecules that expedite cell-cell binding. Stimulated DCs in the periphery migrate to lymphoid organs, where they continue to mature. They function there as the most potent cells that present antigens to T lymphocytes and induce their proliferation, activities that are central to the antigen-specific adaptive immune response. Macrophage IL-10 acts to suppress DC maturation during resolution of inflammation.

DCs from cancer patients have been used in an attempt to control their cancer. The patient's DCs are amplified and matured from blood monocytes or marrow progenitor cells by cytokines, exposed to antigens from the patient's tumor, then injected into the patient as a “vaccine” against the cancer.

Abnormalities of Monocyte-Macrophage or Dendritic Cell Function

Mononuclear phagocytes and neutrophils from patients with **chronic granulomatous disease (CGD)** exhibit a profound defect of phagocytic killing (see Chapter 156). The inability of affected macrophages to kill ingested organisms leads to abscess formation and characteristic granulomas at sites of macrophage accumulation beneath the skin and in the liver, lungs, spleen, and lymph nodes. IFN-γ is used to prevent infection in CGD patients and to treat the decreased bone resorption of **congenital osteopetrosis** , which is caused by decreased function of osteoclasts. Genetic deficiency of the CD11/CD18 complex of membrane adherence glycoproteins **(leukocyte adhesion defect 1),** which includes a receptor for opsonic complement component 3, results in impaired phagocytosis by monocytes (see Chapter 156).

The monocyte-macrophage system is prominently involved in **lipid storage diseases** called sphingolipidoses (see Chapter 104). In these conditions, macrophages express a systemic enzymatic defect that permits accumulation of cell debris that they normally clear. Resistance to infection can be impaired, at least partly because of impairment in macrophage function. In **Gaucher disease** , the prototype for these disorders, the enzyme glucocerebrosidase functions abnormally, allowing accumulation of glucocerebroside from cell membranes in Gaucher cells throughout the body. In all locations the Gaucher cell is an altered macrophage. These patients can be treated with infusions of the normal enzyme modified to expose mannose residues, which bind to mannose receptors on macrophages.

The cytokine IL-12 is a powerful inducer of IFN-γ production by T cells and NK cells. Individuals with inherited deficiency in macrophage receptors for IFN-γ or lymphocyte receptors for IL-12, or in IL-12 itself, undergo a severe, selective susceptibility to infection by nontuberculous mycobacteria such as *Mycobacterium avium* complex or bacille Calmette-Guérin (see Chapter 152). About half these patients have had disseminated *Salmonella* infection. These abnormalities are grouped as **defects in the IFN- γ–IL-12 axis** .

Monocyte-macrophage function has been shown to be partially abnormal in various clinical conditions. Cultured mononuclear phagocytes of newborns are more readily infected than adult cells by HIV-1 and measles virus. Macrophages from newborns release less granulocyte colony-stimulating factor (G-CSF) and

IL-6 in culture, and this deficiency is accentuated in cells from preterm infants. This finding supports the observations that G-CSF levels are significantly decreased in blood from newborns, and that the marrow granulocyte storage pool is diminished in infants, particularly preterm infants. Mononuclear cells from newborns produce less IFN-γ and IL-12 than do adult cells, and macrophages cultured from cord blood are not activated normally by IFN-γ. This combination of deficiencies would be expected to blunt the newborn's response to infection by viruses, fungi, and intracellular bacteria.

More than 100 different subtypes of the **histiocytoses** have been organized into 5 major groups based on clinical, pathologic, genetic, and other features. These rare disorders are characterized by accumulation of macrophages or DCs in tissues or organs. “Histiocyte” is a histologic term and not cell specific, but it has been retained because of its long usage to identify the classic members of this family. Familial and secondary **hemophagocytic lymphohistiocytosis** is characterized by uncontrolled activation of T cells and macrophages, with resultant fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, marked elevation of serum proinflammatory cytokines, and macrophage hemophagocytosis (see Chapter 534). The familial form usually presents in the 1st yr of life. Up to 5% of children with systemic-onset juvenile rheumatoid arthritis develop an acute severe complication termed **macrophage activation syndrome** , with persistent fever (rather than typical febrile spikes), hepatosplenomegaly, pancytopenia, macrophage hemophagocytosis, and coagulopathy, which can progress to disseminated intravascular coagulation and death if not recognized (see Chapter 180).

Two genetic autoinflammatory diseases result from dysregulation of the mononuclear phagocyte–produced proinflammatory cytokine IL-1. In **neonatal-onset multisystem inflammatory disorder** , monocytes overproduce IL-1. In **deficiency of the IL-1 receptor antagonist** , normal activity levels of IL-1 go unopposed. In both conditions, patients present in the 1st few days or weeks of life with pustular or urticarial rash, bony overgrowth, sterile osteomyelitis, elevated erythrocyte sedimentation rate, and other evidence of systemic inflammation. The recombinant IL-1 receptor antagonist anakinra is effective treatment for both these disorders (Chapter 188).

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CHAPTER 155

Eosinophils

Benjamin L. Wright, Brian P. Vickery

Eosinophils are distinguished from other leukocytes by their morphology, constituent products, and association with specific diseases. Eosinophils are nondividing, fully differentiated cells with a diameter of approximately 8 μm and a bilobed nucleus. They differentiate from stem cell precursors in the bone marrow under the control of T-cell–derived interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and especially IL-5. Their characteristic membrane-bound specific granules stain bright pink with eosin and consist of a crystalline core made up of major basic protein (MBP) surrounded by a matrix containing the eosinophil cationic protein (ECP), eosinophil peroxidase (EPX), and eosinophil-derived neurotoxin (EDN). These basic proteins are cytotoxic for the larval stages of helminthic parasites and are also thought to contribute to much of the inflammation associated with chronic allergic diseases such as asthma (see Chapter 169).

Eosinophil MBP, ECP, and EPX are also present in large quantities in the airways of patients who have died of asthma and are thought to inflict epithelial cell damage leading to airway hyperresponsiveness, although recent studies indicate the role of these granule proteins may be more nuanced and not purely destructive. Eosinophil granule contents also contribute to eosinophilic endomyocardial disease associated with the hypereosinophilic syndrome. MBP has the potential to activate other proinflammatory cells, including mast cells, basophils, neutrophils, and platelets. Eosinophils have the capacity to generate large amounts of the lipid mediators platelet-activating factor and leukotriene C_4, both of which can cause vasoconstriction, smooth muscle contraction, and mucus hypersecretion (Fig. 155.1). Eosinophils are a source of a number of proinflammatory cytokines, including IL-1, IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF. They have also been shown to influence T-cell recruitment and immune polarization in inflammatory settings. Thus, eosinophils have considerable potential to initiate and sustain the inflammatory response of the innate and acquired immune systems.

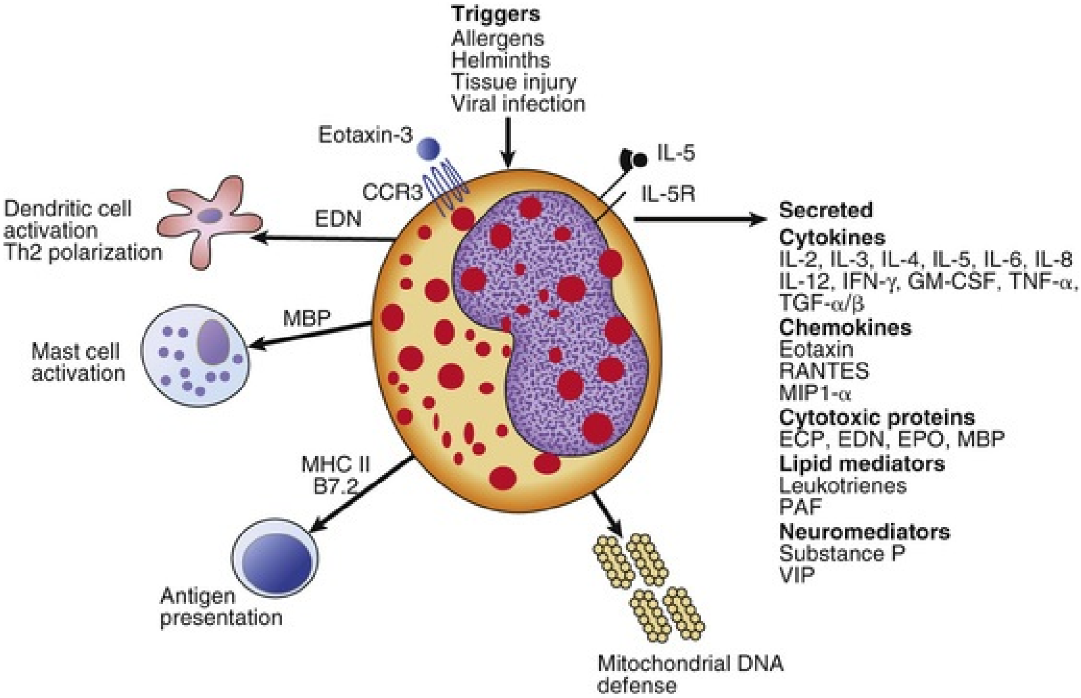
Triggers
Allergens
Helminths
Tissue injury
Viral infection
Eotaxin-3
CCR3
IL-5
IL-5R
EDN
Dendritic cell activation
Th2 polarization
MBP
Mast cell activation
MHC II
B7.2
Antigen presentation
Mitochondrial DNA defense
Secreted
Cytokines
IL-2, IL-3, IL-4, IL-5, IL-6, IL-8
IL-12, IFN-γ, GM-CSF, TNF-α,
TGF-α/β
Chemokines
Eotaxin
RANTES
MIP1-α
Cytotoxic proteins
ECP, EDN, EPO, MBP
Lipid mediators
Leukotrienes
PAF
Neuromediators
Substance P
VIP

FIG. 155.1 **Schematic diagram of an eosinophil and its diverse properties. Eosinophils are bilobed granulocytes that respond to diverse stimuli, including allergens, helminths, viral infections, allografts, and nonspecific tissue injury. Eosinophils express the receptor for IL-5, a critical eosinophil growth and differentiation factor, as well as the receptor for eotaxin and related chemokines (CCR3). The secondary granules contain four primary cationic proteins designated eosinophil peroxidase (EPO), major basic protein (MBP), eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN). All 4 proteins are cytotoxic molecules; also, ECP and EDN are ribonucleases. In addition to releasing their preformed cationic proteins, eosinophils can release a variety of cytokines, chemokines and neuromediators and generate large amounts of LTC4. Lastly, eosinophils can be induced to express MHC class II and co-stimulatory molecules and may be involved in propagating immune responses by presenting antigen to T cells. (From Leung YM, Szefler SJ, Bomilla FA, Akdis CA, Sampson HA: *Pediatric allergy principles and practice,* ed 3, Philadelphia, 2016, Elsevier, p 42.)**

Eosinophil migration from the vasculature into the extracellular tissue is mediated by the binding of leukocyte adhesion receptors to their ligands or counterstructures on the postcapillary endothelium. Similar to neutrophils (see Fig. 153.2), transmigration begins as the eosinophil selectin receptor binds to the endothelial carbohydrate ligand in loose association, which promotes eosinophils rolling along the endothelial surface until they encounter a priming stimulus such as a chemotactic mediator. Eosinophils then establish a high-affinity bond between integrin receptors and their corresponding immunoglobulin-like ligand. Unlike neutrophils, which become flattened before transmigrating between the tight junctions of the endothelial cells, eosinophils can use unique integrins, known as very late antigens (VLA-4), to bind to vascular cell adhesion molecule (VCAM)-1, which enhances eosinophil adhesion and transmigration through endothelium. Eosinophils are recruited to tissues in inflammatory states by a group of chemokines known as **eotaxins** (eotaxin 1, 2, and 3). These unique pathways account for selective accumulation of eosinophils in allergic and inflammatory disorders. Eosinophils normally dwell primarily in tissues, especially tissues with an epithelial interface with the environment, including the respiratory, gastrointestinal (GI), and lower genitourinary tracts. The life span of eosinophils may extend for weeks within tissues.

IL-5 selectively enhances eosinophil production, adhesion to endothelial cells, and function. Considerable evidence shows that IL-5 has a pivotal role in promoting eosinophilpoeisis. It is the predominant cytokine in allergen-induced pulmonary late-phase reaction, and antibodies against IL-5 (mepolizumab, reslizumab, benralizumab), decrease sputum eosinophils and reduce exacerbations in a subset of patients with asthma. Eosinophils also bear unique receptors for several chemokines, including RANTES (regulated on activation, normal T-cell expressed and secreted), eotaxin, and monocyte chemotactic proteins 3 and 4. These chemokines appear to be key mediators in the induction of tissue eosinophilia.

Diseases Associated With Eosinophilia

The **absolute eosinophil count** (**AEC**) is used to quantify peripheral blood eosinophilia. Calculated as the white blood cell (WBC) count/µL × percent of eosinophils, it is usually <450 cells/µL and varies diurnally, with eosinophil numbers higher in the early morning and diminishing as endogenous glucocorticoid levels rise.

Many diseases with allergic, infectious, hematologic, autoimmune, or idiopathic origins are associated with moderate (AEC 1,500-5,000 cells/µL) or severe (AEC >5,000 cells/µL) eosinophilia in peripheral blood (Table 155.1). These disorders may range from mild and transient to chronic and life threatening. Importantly, blood eosinophil numbers do not always reflect the extent of eosinophil involvement in tissues and degranulation products may more accurately reflect disease activity. Because prolonged eosinophilia is associated with end-organ damage, especially involving the heart, patients with persistently elevated AECs should undergo a thorough evaluation to search for an underlying cause.

Table 155.1

Causes of Eosinophilia

Allergic Disorders

- Allergic rhinitis
- Asthma
- Acute and chronic urticaria
- Eczema
- Angioedema
- Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
- Eosinophilic gastrointestinal disorders
- Interstitial nephritis

Infectious Diseases

Tissue-Invasive Helminth Infections

- Trichinosis
- Toxocariasis
- Strongyloidosis
- Ascariasis
- Filariasis
- Schistosomiasis
- Echinococcosis
- Amebiasis
- Malaria
- Scabies
- Toxoplasmosis

Other Infections

Pneumocystis jirovecii
Scarlet fever
Allergic bronchopulmonary aspergillosis (ABPA)
Coccidioidomycosis
Human immunodeficiency virus (HIV)

Malignant Disorders

Hodgkin disease and T-cell lymphoma
Acute myelogenous leukemia
Myeloproliferative disorders
Eosinophilic leukemia
Brain tumors

Gastrointestinal Disorders

Inflammatory bowel disease
Peritoneal dialysis
Chronic active hepatitis
Eosinophilic gastrointestinal disorders:
  Eosinophilic esophagitis
  Eosinophilic gastroenteritis
  Eosinophilic colitis

Rheumatologic Disease

Rheumatoid arthritis
Eosinophilic fasciitis
Scleroderma
Dermatomyositis
Systemic lupus erythematosus
IgG4-related disease
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis)

Immunodeficiency/Immune Dysregulation Disease

Hyperimmunoglobulin E syndromes
Wiskott-Aldrich syndrome
Graft-versus-host disease
Omenn syndrome
Severe congenital neutropenia
Autoimmune lymphoproliferative syndromes (ALPS)
Immune dysregulation, polyendocrinopathy, X-linked (IPEX)
Transplant rejection (solid organ)

Miscellaneous

Thrombocytopenia with absent radii
Hypersensitivity pneumonitis
Adrenal insufficiency
Postirradiation of abdomen
Histiocytosis with cutaneous involvement
Hypereosinophilic syndromes
Cytokine infusion
Pemphigoid

Allergic Diseases

Allergy is the most common cause of eosinophilia in children in the United States. Patients with allergic asthma typically have eosinophils in the blood, sputum, and/or lung tissue. **Hypersensitivity drug reactions** can elicit eosinophilia, and when associated with organ dysfunction (e.g., DRESS [drug rash with eosinophilia and systemic symptoms]), these reactions can be serious (see Chapter 177). If a drug is suspected of triggering eosinophilia, biochemical evidence of organ dysfunction should be sought, and if found, the drug should be discontinued. Various skin diseases have also been associated with eosinophilia, including atopic dermatitis/eczema, pemphigus, urticaria, and toxic epidermal necrolysis.

Eosinophilic gastrointestinal diseases are important emerging allergic causes of eosinophilia in tissue and, in some cases, peripheral blood (see Chapter 363). In these conditions, eosinophils are recruited to esophagus, stomach, and/or intestine, where they cause tissue inflammation and clinical symptoms such as dysphagia, food aversion, abdominal pain, vomiting, and diarrhea. Treatment options include allergen elimination diets and swallowed or inhaled corticosteroids.

Infectious Diseases

Eosinophilia is often associated with invasive infection with multicellular helminthic parasites, which are the most common cause in developing countries. Table 155.1 includes examples of specific organisms. The level of eosinophilia tends to parallel the magnitude and extent of tissue invasion, especially by larvae such as **visceral larva migrans** (see Chapter 324). Eosinophilia often *does not* occur in established parasitic infections that are well contained within tissues or are solely intraluminal in the gastrointestinal tract, such as *Giardia lamblia* and *Enterobius vermicularis* infection.

In evaluating patients with unexplained eosinophilia, the dietary history and geographic or travel history may indicate potential exposures to helminthic parasites. It is frequently necessary to examine the stool for ova and larvae at least 3 times. Additionally, the diagnostic parasite stages of many of the helminthic parasites that cause eosinophilia never appear in feces. Thus, normal results of stool examinations do not absolutely preclude a helminthic cause of eosinophilia; diagnostic blood tests or tissue biopsy may be needed. *Toxocara* causes visceral larva migrans usually in toddlers with pica (see Chapter 324). Most young children are asymptomatic, but some develop fever, pneumonitis, hepatomegaly, and hypergammaglobulinemia accompanied by severe eosinophilia. Isohemagglutinins are frequently elevated, and serology can establish the diagnosis.

Two fungal diseases may be associated with eosinophilia: aspergillosis in the form of **allergic bronchopulmonary aspergillosis** (see Chapter 264.1) and **coccidioidomycosis** (see Chapter 267) following primary infection, especially in conjunction with erythema nodosum. HIV infection can also be associated with peripheral eosinophilia.

Hypereosinophilic Syndrome

The idiopathic hypereosinophilic syndrome is a heterogeneous group of disorders characterized by sustained overproduction of eosinophils. The 3 diagnostic criteria for this disorder are (1) AEC >1,500 cells/μL persisting for 6 mo or longer or at least on 2 occasions or with evidence of tissue eosinophilia;

(2) absence of another diagnosis to explain the eosinophilia; and (3) signs and symptoms of organ involvement. The clinical signs and symptoms of hypereosinophilic syndrome can be heterogeneous because of the diversity of potential organ (pulmonary, cutaneous, neurologic, serosal, GI) involvement. Eosinophilic endomyocardial disease, one of the most serious and life-threatening complications, can cause heart failure from endomyocardial thrombosis and fibrosis. Eosinophilic leukemia, a clonal myeloproliferative variant, may be distinguished from idiopathic hypereosinophilic syndrome by demonstrating a clonal interstitial deletion on chromosome 4q12 that fuses the platelet-derived growth factor receptor-α (*PDGFRA*) and FIP1-like-1 (*FIP1L1*) genes; this disorder is treated with imatinib mesylate, a tyrosine kinase inhibitor, which helps target the fusion oncoprotein (Fig. 155.2).

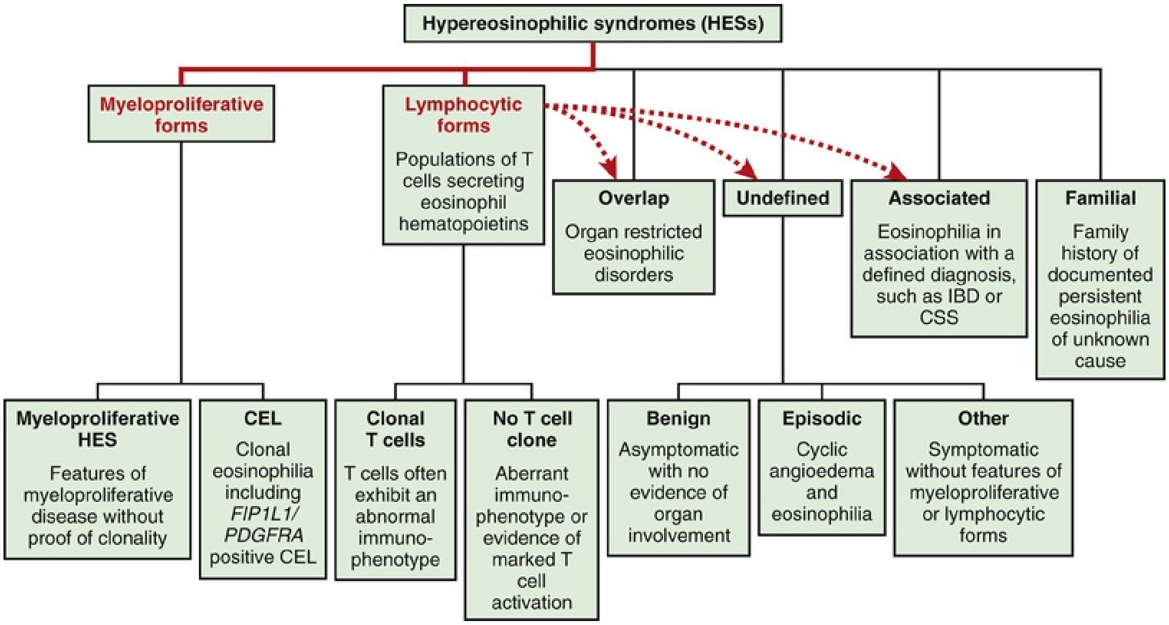
Hypereosinophilic syndromes (HESs)
Myeloproliferative forms
Lymphocytic forms
Populations of T cells secreting eosinophil hematopoietins
Overlap
Organ restricted eosinophilic disorders
Undefined
Associated
Eosinophilia in association with a defined diagnosis, such as IBD or CSS
Familial
Family history of documented persistent eosinophilia of unknown cause
Myeloproliferative HES
Features of myeloproliferative disease without proof of clonality
CEL
Clonal eosinophilia including FIP1L1/PDGFRA positive CEL
Clonal T cells
T cells often exhibit an abnormal immuno-phenotype
No T cell clone
Aberrant immuno-phenotype or evidence of marked T cell activation
Benign
Asymptomatic with no evidence of organ involvement
Episodic
Cyclic angioedema and eosinophilia
Other
Symptomatic without features of myeloproliferative or lymphocytic forms

FIG. 155.2 **Revised classification of hypereosinophilic syndromes. Changes from the previous classification are indicated in *red. Dashed arrows* identify hypereosinophilic syndrome (HES) forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin–producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. CEL, Chronic eosinophilic leukemia; CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. (From Simon HU, Rothenberg ME, Bocher BS, et al: Refining the definition of hypereosinophilic syndrome, *J Allergy Clin Immunol* 126:47, 2010.)**

Therapy is aimed at suppressing eosinophilia and is initiated with corticosteroids. Imatinib mesylate may be effective in FIP1L1-PDGFRA–negative patients. Hydroxyurea or interferon-alfa may be beneficial in patients unresponsive to corticosteroids. Specific anti–IL-5 monoclonal antibodies (mepolizumab) target this cytokine, which has a central role in eosinophil differentiation, mobilization, and activity. With therapy, the eosinophil count declines and corticosteroid doses may be reduced. For patients with prominent organ involvement who fail to respond to therapy, the mortality is about 75% after 3 yr.

Miscellaneous Diseases

Eosinophilia is observed in many patients with primary immunodeficiency syndromes, especially hyper-IgE syndrome, Wiskott-Aldrich syndrome, and Omenn syndrome (see Chapters 148 and 152). Eosinophilia is also frequently present in the syndrome of thrombocytopenia with absent radii and in familial reticuloendotheliosis with eosinophilia. Eosinophilia can be found in patients with Hodgkin disease, as well as in acute lymphoid and myeloid leukemia. Other considerations include GI disorders such as ulcerative colitis, Crohn disease during symptomatic phases, chronic hepatitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis), and adrenal insufficiency.

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CHAPTER 156

Disorders of Phagocyte Function

Thomas D. Coates

Neutrophils are the first line of defense against microbial invasion. They arrive at the site of inflammation during the critical 2-4 hr after microbial invasion to contain the infection and prevent hematogenous dissemination. This well-orchestrated process is one of the most interesting stories in modern cell biology. In fact, much of our knowledge about neutrophil function derives from studies done in patients with genetic errors in neutrophil function. These critical functions and their associated disorders are depicted in Fig. 153.2 . Children with phagocytic dysfunction present at a young age with recurrent infections that often involve unusual organisms and are poorly responsive to treatment.

Primary defects of phagocytic function comprise <20% of immunodeficiencies, and there is significant overlap in the presenting signs and symptoms between phagocytic disorders and lymphocyte and humeral disorders. Children with phagocytic defects present with deep tissue infection, pneumonia, adenitis, or osteomyelitis rather than bloodstream infections (Tables 156.1 and 156.2 and Fig. 156.1). A few clinical features point to phagocyte defects rather than other immunodeficiencies, but correct diagnosis relies on highly specialized laboratory tests.

Table 156.1

Infections and White Blood Cell Defects: Features That Can Be Seen in Phagocyte Disorders

SEVERE INFECTIONS		RECURRENT INFECTIONS		SPECIFIC INFECTIONS		UNUSUALLY LOCATED INFECTIONS	
Type of Infection	**Diagnosis to Consider**	**Site of Infection**	**Diagnosis to Consider**	**Microorganism**	**Diagnosis to Consider**	**Site of Infection**	**Diagno to**

							Consid
Cellulitis	Neutropenia, LAD, CGD, HIES	Cutaneous	Neutropenia, CGD, LAD, HIES	*Staphylococcus epidermidis*	Neutropenia, LAD	Umbilical cord	LAD
Colitis	Neutropenia, CGD	Gums	LAD, neutrophil motility disorders	*Serratia marcescens, Nocardia, Burkholderia cepacia*	CGD	Liver abscess	CGD
Osteomyelitis	CGD, MSMD pathway defects	Upper and lower respiratory tract	Neutropenia, HIES, functional neutrophil disorders	*Aspergillus*	Neutropenia, CGD, HIES	Gums	LAD, neutrop motilit disorde
		Gastrointestinal tract	CGD, MSMD pathway defects (salmonella)	Nontuberculous mycobacteria, BCG	MSMD pathway defects, SCID, CGD		
		Lymph nodes	CGD, MSMD pathway defects (mycobacteria)	*Candida*	Neutropenia, CGD, MPO		
		Osteomyelitis	CGD, MSMD				

BCG, Bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyper-IgE syndrome; LAD, leukocyte adhesion deficiency; MSMD, mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.

From Leung DYM: *Pediatric allergy principles and practice* , ed 2, Philadelphia, 2010, Saunders, p 134.

Table 156.2

Clinical Disorders of Neutrophil Function

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DEGRANULATION ABNORMALITIES			
Chédiak-Higashi syndrome (CHS)	Autosomal recessive; disordered coalescence of lysosomal granules; responsible gene is *CHSI/LYST* , which encodes a protein hypothesized to regulate granule fusion	Decreased neutrophil chemotaxis, degranulation, and bactericidal activity; platelet storage pool defect; impaired NK function, failure to disperse melanosomes	Neutropenia; recurrent pyogenic infections; propensity to develop marked hepatosplenomegaly as a manifestation of hemophagocytic syndrome
Specific granule deficiency	Autosomal recessive; functional loss of myeloid transcription factor arising from a mutation or arising from reduced expression of *Gfi-1* or *C/EBPε* , which regulates specific granule formation	Impaired chemotaxis and bactericidal activity; bilobed nuclei in neutrophils; defensins, gelatinase, collagenase, vitamin B_{12} –binding protein,	Recurrent deep-seated abscesses

		and lactoferrin	
ADHESION ABNORMALITIES			
Leukocyte adhesion deficiency 1 (LAD-1)	Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins (β_2 -integrins) on leukocyte membranes most commonly arising from failure to express CD18 messenger RNA	Decreased binding of iC3b to neutrophils and impaired adhesion to ICAM-1 and ICAM-2	Neutrophilia; recurrent bacterial infection associated with a lack of pus formation
Leukocyte adhesion deficiency 2 (LAD-2)	Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol conjugates arising from mutations of GDP-fucose transporter	Decreased adhesion to activated endothelium expressing ELAM	Neutrophilia; recurrent bacterial infection without pus
Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome)	Autosomal recessive; impaired integrin function arising from mutations of *FERMT3* , which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to β-integrin and thereby transmits integrin activation	Impaired neutrophil adhesion and platelet activation	Neutrophilia, recurrent infections, bleeding tendency
DISORDERS OF CELL MOTILITY			
Enhanced motile responses; FMF	Autosomal recessive gene responsible for FMF on chromosome 16, which encodes for a protein called pyrin; pyrin regulates caspase-1 and thereby IL-1β secretion; mutated pyrin may lead to heightened sensitivity to endotoxin, excessive IL-1β production, and impaired monocyte apoptosis	Excessive accumulation of neutrophils at inflamed sites, possibly the result of excessive IL-1β production	Recurrent fever, peritonitis, pleuritis, arthritis, amyloidosis
DEPRESSED MOTILE RESPONSES			
Defects in the generation of chemotactic signals	IgG deficiencies; C3 and properdin deficiency can arise from genetic or acquired abnormalities; mannose-binding protein deficiency predominantly in neonates	Deficiency of serum chemotaxis and opsonic activities	Recurrent pyogenic infections
Intrinsic defects of the neutrophil, e.g., LAD, CHS, specific granule deficiency, neutrophil actin dysfunction, neonatal neutrophils	In the neonatal neutrophil there is diminished ability to express β_2 -integrins, and there is a qualitative impairment in β_2 -integrin function	Diminished chemotaxis	Propensity to develop pyogenic infections
Direct inhibition of neutrophil mobility, e.g., drugs	Ethanol, glucocorticoids, cyclic AMP	Impaired locomotion and ingestion; impaired adherence	Possible cause for frequent infections; neutrophilia seen with epinephrine arises from cyclic AMP release from endothelium
Immune complexes	Bind to Fc receptors on neutrophils in patients with rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory states	Impaired chemotaxis	Recurrent pyogenic infections
Hyper-IgE syndrome	Autosomal dominant; responsible gene is *STAT3*	Impaired chemotaxis at times; impaired regulation of cytokine production	Recurrent skin and sinopulmonary infections, eczema, mucocutaneous candidiasis, eosinophilia,

			retained primary teeth, minimal trauma fractures, scoliosis, and characteristic facies
Hyper-IgE syndrome–AR	Autosomal recessive; more than 1 gene likely contributes to its etiology	High IgE levels, impaired lymphocyte activation to staphylococcal antigens	Recurrent pneumonia without pneumatoceles sepsis, enzyme, boils, mucocutaneous candidiasis, neurologic symptoms, eosinophilia
MICROBICIDAL ACTIVITY			
Chronic granulomatous disease (CGD)	X-linked and autosomal recessive; failure to express functional gp91 ^{phox} in the phagocyte membrane in p22 ^{phox} (AR) Other AR forms of CGD arise from failure to express protein p47 ^{phox} or p67 ^{phox}	Failure to activate neutrophil respiratory burst, leading to failure to kill catalase-positive microbes	Recurrent pyogenic infections with catalase-positive microorganisms
G6PD deficiency	<5% of normal activity of G6PD	Failure to activate NADPH-dependent oxidase; hemolytic anemia	Infections with catalase-positive microorganisms
Myeloperoxidase deficiency	Autosomal recessive; failure to process modified precursor protein arising from missense mutation	H_2O_2 -dependent antimicrobial activity not potentiated by myeloperoxidase	None
Rac2 deficiency	Autosomal dominant; dominant negative inhibition by mutant protein of Rac2-mediated functions	Failure of membrane receptor–mediated O_2^- generation and chemotaxis	Neutrophilia, recurrent bacterial infections
Deficiencies of glutathione reductase and glutathione synthetase	AR; failure to detoxify H_2O_2	Excessive formation of H_2O_2	Minimal problems with recurrent pyogenic infections

AMP, Adenosine monophosphate; AR, autosomal recessive; C, complement; CD, cluster of differentiation; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; IL-1, interleukin-1; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

Adapted from Curnutte JT, Boxer LA: Clinically significant phagocytic cell defects. In Remington JS, Swartz MN, editors: *Current clinical topics in infectious disease* , ed 6, New York, 1985, McGraw-Hill, p 144.

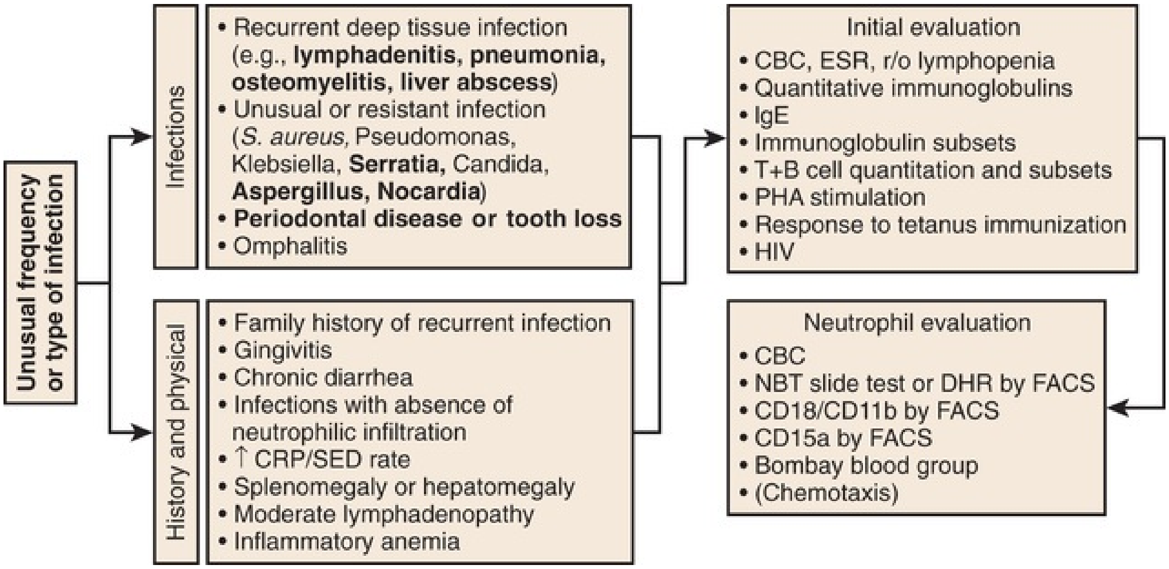
Unusual frequency or type of infection
Infections
• Recurrent deep tissue infection (e.g., lymphadenitis, pneumonia, osteomyelitis, liver abscess)
• Unusual or resistant infection (S. aureus, Pseudomonas, Klebsiella, Serratia, Candida, Aspergillus, Nocardia)
• Periodontal disease or tooth loss
• Omphalitis
History and physical
• Family history of recurrent infection
• Gingivitis
• Chronic diarrhea
• Infections with absence of neutrophilic infiltration
• ↑ CRP/SED rate
• Splenomegaly or hepatomegaly
• Moderate lymphadenopathy
• Inflammatory anemia
Initial evaluation
• CBC, ESR, r/o lymphopenia
• Quantitative immunoglobulins
• IgE
• Immunoglobulin subsets
• T+B cell quantitation and subsets
• PHA stimulation
• Response to tetanus immunization
• HIV
Neutrophil evaluation
• CBC
• NBT slide test or DHR by FACS
• CD18/CD11b by FACS
• CD15a by FACS
• Bombay blood group
• (Chemotaxis)

FIG. 156.1 **Algorithm for clinical evaluation of patients with recurrent infections. Shown are the evaluations that can be done in a routine clinical laboratory. The complete blood count (CBC) can detect marked leukocytosis in leukocyte adhesion deficiency (LAD) and giant granules of Chédiak-Higashi syndrome may be seen on the smear. Chemotaxis and all other neutrophil functions assays require highly specialized research laboratories. CD, Cluster of differentiation; CRP, C-reactive protein; DHR, dihydrorhodamine; ESR, erythrocyte sedimentation rate; FACS, fluorescence-activated cell sorter; HIV, human immunodeficiency virus; IgE, immunoglobulin E; NBT, nitroblue tetrazolium; PHA, phytohemagglutinin. (Adapted from Dinauer, MC, Coates TD, Disorders of neutrophil function. In Hoffman R, Benz EJ, Silberstein LE, Helsop H, Weitz J, Anastasi J, editors: *Hematology: basic principles and practice,* ed 6, Philadelphia, 2012, Saunders.)**

Chemotaxis , the direct migration of cells into sites of infection, involves a complex series of events (see Chapter 153). Disorders of adhesion or granule abnormalities can have intermediate or profound motility defects, and the propensity to infections is related to a combination of these functional deficits. One family with recessively inherited neutrophil actin dysfunction demonstrated that a pure severe chemotactic defect can result in fatal recurrent infection. Defective in vitro chemotaxis of neutrophils can be detected in children with various clinical conditions. However, unless chemotaxis is essentially absent, it is difficult to establish whether frequent infections arise from a primary chemotactic abnormality or occur as secondary medical complications of the underlying disorder. Dental infection with *Capnocytophaga* is associated with a clear neutrophil motility defect that resolves when the infection is eliminated.

Motility defects present with significant skin and mucosal infections. Tender cutaneous nodular lesions may also be present and characteristically do not contain neutrophils. In fact, presence of a true abscess makes the diagnosis of a significant chemotactic defect less likely.

Laboratory tests of chemotaxis are biologic assays and have high variability except in the most experienced hands. The assays must be done on freshly obtained blood and are affected by many factors related to blood sampling itself. It is best to assay other features of the suspected disorder, such as surface marker expression, to establish a specific diagnosis.

Leukocyte Adhesion Deficiency

Leukocyte adhesion deficiency types 1 (LAD-1), 2 (LAD-2), and 3 (LAD-3) are rare autosomal recessive disorders of leukocyte function. LAD-1 affects about 1 per 10 million individuals and is characterized by recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia (Table 156.3). The neutrophils have significant defects in adhesion, motility, and ability to phagocytose bacteria.

Table 156.3

Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	**TYPE 1 (LAD-1)**	**TYPE 2 (LAD-2 or CDG-IIc)**	**TYPE 3 (LAD-3)**	**E-SELECTIN DEFICIENCY**	**Rac2 DEFICIENCY**
OMIM	116920	266265	612840	131210	602049
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive	Unknown	Autosomal dominant
Affected protein(s)	β_2 -Integrin common chain (CD18)	Fucosylated proteins (e.g., sialyl-Lewis^x , CD15s)	Kindlin 3	Endothelial E-selectin expression	Rac2
Neutrophil function affected	Chemotaxis, tight adherence	Rolling, tethering	Chemotaxis, adhesion, superoxide production	Rolling, tethering	Chemotaxis, superoxide production
Delayed umbilical cord separation	Yes (severe phenotype only)	Yes	Yes	Yes	Yes
Leukocytosis/neutrophilia	Yes	Yes	Yes	No (mild neutropenia)	Yes

CDG-IIc, Congenital disorder of glycosylation IIc, OMIM, Online Mendelian Inheritance in Man.

From Leung DYM: *Pediatric allergy principles and practice* , ed 2, Philadelphia, 2010, Saunders, p 139.

Genetics and Pathogenesis

LAD-1 results from mutations of the gene on chromosome 21q22.3 encoding CD18, the 95-kDa β_2 -leukocyte transmembrane integrin subunit. Normal neutrophils express 4 heterodimeric adhesion molecules: LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, also known as CR3 or iC3b receptor), p150,95 (CD11c/CD18), and α_1 β_2 (CD11d/CD18). These 4 transmembrane adhesion molecules are composed of unique extracellular α_1 encoded on chromosome 16, and they share a common β_2 subunit (CD18) that links them to the membrane and connects them to intracellular signal transduction machinery. This group of leukocyte integrins is responsible for the tight adhesion of neutrophils to the endothelial cell surface, egress from the circulation, and adhesion to iC3b-coated microorganisms, which promotes phagocytosis and particulate activation of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Some mutations of CD11/CD18 allow a low level of assembly and activity of integrin molecules, resulting in retention of some neutrophil integrin adhesion function and a moderate phenotype.

Because of their inability to adhere firmly to intercellular adhesion molecules 1 (ICAM-1) and 2 (ICAM-2) expressed on inflamed endothelial cells (see Chapter 153), neutrophils cannot transmigrate through the vessel wall and move to the site infection. Furthermore, neutrophils that do arrive at inflammatory sites fail to recognize microorganisms opsonized with complement fragment **iC3b** , an important stable opsonin formed by the cleavage of C3b. Therefore, other neutrophil functions such as degranulation and oxidative metabolism normally triggered by iC3b binding are also greatly compromised in LAD-1 neutrophils, resulting in impaired phagocytic function and high risk for serious and recurrent bacterial infections.

Monocyte function is also impaired, with poor fibrinogen-binding function, an activity that is promoted by the CD11/CD18 complex. Consequently, such cells are unable to participate effectively in wound healing.

Children with **LAD-2** share the clinical features of LAD-1 but have normal CD11/CD18 integrins. Features unique to LAD-2 include neurologic defects, cranial facial dysmorphism, and absence of the erythrocyte ABO blood group antigen (**Bombay** phenotype). LAD-2 (also known as **congenital disorder of glycosylation IIc (CDG-IIc)** derives from mutations in the gene encoding a specific guanosine diphosphate (GDP)-L -fucose transporter of the Golgi apparatus. This abnormality prevents the incorporation of fucose into various cell surface glycoproteins, including the carbohydrate structure sialyl Lewis X that is critical for low-affinity rolling adhesion of neutrophils to vascular endothelium. This is an important initial step necessary for subsequent integrin-mediated activation, spreading, and transendothelial migration. Infections in LAD-2 are milder than that in LAD-1.

LAD-3 is characterized by a **Glanzmann thrombasthenia** –like bleeding disorder, delayed separation of the umbilical cord, and serious skin and soft tissue infections similar to those seen in LAD-1, and failure of leukocytes to undergo β_2 - and β_1 -integrin–mediated adhesion and migration. Mutations in *KINDLIN3* affect integrin activation.

Clinical Manifestations

Patients with the severe clinical form of LAD-1 express <0.3% of the normal amount of the β_2 -integrin molecules, whereas patients with the moderate phenotype may express 2–7% of the normal amount. Children with severe forms of LAD present in infancy with recurrent, indolent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa. Significant neutrophilic leukocytosis, often >25,0000/mm^3 , is a prominent feature. They may have a history of delayed separation of the umbilical cord, usually with associated infection of the cord stump. The presence of significant omphalitis is an important feature that distinguishes these rare patients from the 10% of healthy infants who can have cord separation at age 3 wk or later. Skin infection may progress to large chronic ulcers with polymicrobial infection, including anaerobic organisms (Fig. 156.2). The ulcers heal slowly, need months of antibiotic treatment, and often require plastic surgery grafting. Severe gingivitis can lead to early loss of primary and secondary teeth (Fig. 156.3). Infected areas characteristically have very little neutrophilic infiltration.

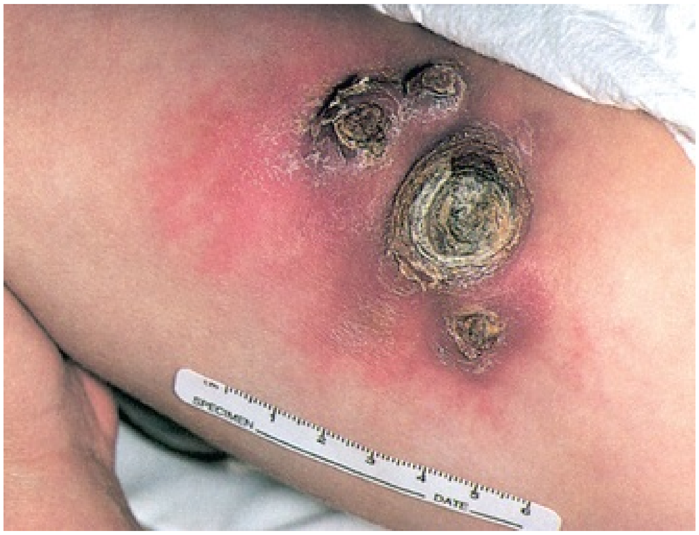

FIG. 156.2 Skin infection of a patient with leukocyte adhesion deficiency type 1. Failure to form pus, inability to demarcate the fibrotic skin debris, and limited inflammation. *Enterococcus gallinarium* was cultured from the wound. (From Rich RR: *Clinical immunology principles and practices* , ed 4, Philadelphia, 2013, Saunders, p 273).

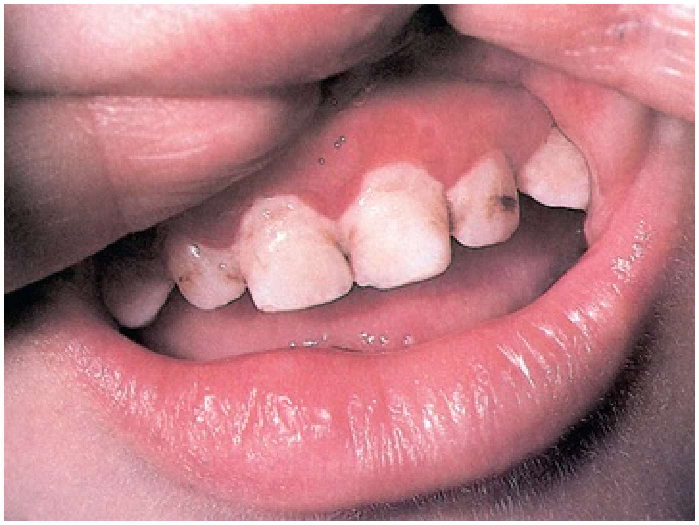

FIG. 156.3 Oral pathology in a patient with leukocyte adhesion deficiency type 1. Gingivitis and severe periodontitis are hallmarks of LAD-1. (From Rich RR: *Clinical immunology principles and practices* , ed 4, Philadelphia, 2013, Saunders, p 273.)

The pathogens infecting patients with LAD-1 are similar to those affecting patients with severe neutropenia (see Chapter 157) and include *Staphylococcus aureus* and enteric gram-negative organisms such as *Escherichia coli*. These patients are also susceptible to opportunistic infection by fungi such as *Candida* and *Aspergillus*. Typical signs of inflammation, such as swelling, erythema, and warmth, may be absent. Pus does not form, and few neutrophils are identified microscopically in biopsy specimens of infected tissues. Despite the paucity of neutrophils within the affected tissue, the circulating neutrophil count during infection typically exceeds 30,000/µL and can surpass 100,000/µL. During intervals between infections, the peripheral blood neutrophil count may chronically exceed 12,000/µL. LAD-1 genotypes with only moderate, rather than absent, amounts of functional integrins at the surface of the neutrophil have significantly reduced severity and frequency of infections compared to children with the severe form, although gingival disease is still a prominent feature.

Laboratory Findings

The diagnosis of LAD-1 is established most readily by flow cytometric measurements of surface CD11b/CD18 in stimulated and unstimulated neutrophils. Neutrophil and monocyte adherence, aggregation, chemotaxis, and iC3b-mediated phagocytosis demonstrate striking abnormalities. However, these assays are not clinically available. Delayed-type hypersensitivity reactions are normal, and most individuals have normal specific antibody synthesis, although some patients have impaired T-lymphocyte–dependent antibody responses. The diagnosis of LAD-2 is established by flow cytometric measurement of sialyl Lewis X (CD15) on neutrophils. It is important to note that the flow cytometric assays are not done the same as the more common lymphocyte subset analysis and require specialized approaches to detect levels of surface expression, especially to detect milder phenotypes.

Treatment

Treatment of LAD-1 depends on the phenotype, as determined by the level of expression of functional CD11/CD18 integrins. Early allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice for severe LAD-1 (and LAD-3). One patient was successfully treated with ustekinumab, an inhibitor of interleukins 12 and 23. Other treatment is largely supportive. Patients can be maintained on prophylactic trimethoprim/sulfamethoxazole (TMP/SMX) and should have close surveillance for early identification of infections and initiation of empirical treatment with broad-spectrum antibiotics. Specific determination of the etiologic agent by culture or biopsy is important because of the prolonged antibiotic treatment required in the absence of neutrophil function.

Some LAD-2 patients have responded to fucose supplementation, which induced a rapid reduction in the circulating leukocyte count and appearance of the sialyl Lewis X molecules, accompanied by marked improvement in leukocyte adhesion.

Prognosis

The severity of infectious complications correlates with the degree of β_2 -integrin deficiency. Patients with severe deficiency may die in infancy, and those surviving infancy have a susceptibility to severe life-threatening systemic infections. Patients with moderate deficiency have infrequent life-threatening infections and relatively long survival.

Chédiak-Higashi Syndrome

Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by increased susceptibility to infection caused by defective degranulation of neutrophils, a mild bleeding diathesis, partial oculocutaneous albinism, progressive peripheral neuropathy, and a tendency to develop a life-threatening form of **hemophagocytic lymphohistiocytosis** (see Chapter 534.2). CHS is caused by a fundamental defect in granule morphogenesis that results in abnormally large granules in multiple tissues. Pigmentary dilution involving the hair, skin, and ocular fundi results from pathologic aggregation of melanosomes. Neurologic deficits are associated with a failure of decussation of the optic and auditory nerves. Patients exhibit an increased susceptibility to infection that can be explained only in part by defects in neutrophil function. The patients have progressive neutropenia as well as abnormalities in natural killer (NK) function, again related to granule dysfunction.

Genetics and Pathogenesis

LYST (for lysosomal traffic regulator), the gene mutated in CHS, is located at chromosome 1q2-q44. The LYST/CHS protein is thought to regulate vesicle transport by mediating protein-protein interaction and protein-membrane associations. Loss of function may lead to indiscriminate interactions with lysosomal surface proteins, yielding giant granules through uncontrolled fusion of lysosomes with each other.

Almost all cells of patients with CHS show some oversized and dysmorphic lysosomes, storage granules, or related vesicular structures. Melanosomes are oversized, and delivery to the keratinocytes and hair follicles is compromised, resulting in hair shafts devoid of pigment granules. This abnormality in melanosomes leads to the macroscopic impression of hair and skin that is lighter than expected from parental coloration. The same abnormality in melanocytes leads to the partial ocular albinism associated with light sensitivity.

Beginning early in neutrophil development, spontaneous fusion of giant primary granules with each other or with cytoplasmic membrane components results in huge secondary lysosomes with reduced contents of hydrolytic enzymes, including proteinases, elastase, and cathepsin G. This deficiency of proteolytic enzymes may be responsible for the impaired killing of microorganisms by CHS neutrophils.

Clinical Manifestations

Patients with CHS have light skin and silvery hair and frequently complain of solar sensitivity and photophobia that is associated with rotary nystagmus. Other signs and symptoms vary considerably, but frequent infections and neuropathy are common. The infections involve mucous membranes, skin, and respiratory tract. Affected children are susceptible to gram-positive bacteria, gram-negative bacteria, and fungi, with *Staphylococcus aureus* being the most common offending organism. The **neuropathy** may be sensory or motor in type, and ataxia may be a prominent feature. Neuropathy often begins in the teenage years and becomes the most prominent problem.

Patients with CHS have prolonged bleeding times with normal platelet counts, resulting from impaired platelet aggregation associated with a deficiency of the dense granules containing adenosine diphosphate and serotonin.

The most life-threatening complication of CHS is the development of an accelerated phase characterized by pancytopenia, high fever, and lymphohistiocytic infiltration of liver, spleen, and lymph nodes. The onset of the accelerated phase, which can occur at any age, is now recognized to be a genetic form of hemophagocytic lymphohistiocytosis. This occurs in 85% of patients and usually results in death.

Laboratory Findings

The diagnosis of CHS is established by finding large inclusions in all nucleated blood cells. These can be seen on Wright-stained blood films and are accentuated by a peroxidase stain. Because of impaired egress from the bone marrow, cells containing the large inclusions may be missed on peripheral blood smear but readily identified on bone marrow examination. The patients have progressive neutropenia and abnormal platelet, neutrophil, and NK function.

Treatment

High-dose ascorbic acid (200 mg/day for infants; 2,000 mg/day for adults) may improve the clinical status of some children in the stable phase. Although controversy surrounds the efficacy of ascorbic acid, given the safety of the vitamin, it is reasonable to administer ascorbic acid to all patients.

The only curative therapy to prevent the accelerated phase is HSCT. Normal stem cells reconstitute hematopoietic and immunologic function, correct the NK cell deficiency, and prevent conversion to the accelerated phase, but cannot correct or prevent the neuropathy. If the patient is in the accelerated phase with active hemophagocytic lymphohistiocytosis, HSCT often fails to prevent death.

Myeloperoxidase Deficiency

Myeloperoxidase (MPO) deficiency is an autosomal recessive disorder of oxidative metabolism and is one of the most common inherited disorders of phagocytes, occurring at a frequency approaching 1 per 2,000 individuals. MPO is a green heme protein located in the azurophilic lysosomes of neutrophils and monocytes and is the basis for the greenish tinge to pus accumulated at a site of infection.

Clinical Manifestations

MPO deficiency is usually clinically silent. Rarely, patients may have disseminated candidiasis, usually in conjunction with diabetes mellitus. Acquired partial MPO deficiency can develop in acute myelogenous leukemia and in myelodysplastic syndromes.

Laboratory Findings

Deficiency of neutrophil and monocyte MPO can be identified by histochemical analysis. Severe MPO deficiency can cause the dihydrorhodamine (DHR) flow cytometric assay for chronic granulomatous disease (CGD) to be falsely positive. Unlike CGD, eosinophils in severe MPO deficiency will still reduce DHR and yield a normal reaction.

Treatment

There is no specific therapy for MPO deficiency. Aggressive treatment with antifungal agents should be provided for candidal infections. The prognosis is usually excellent.

Chronic Granulomatous Disease

Chronic granulomatous disease is characterized by neutrophils and monocytes capable of normal chemotaxis, ingestion, and degranulation, but unable to kill **catalase-positive microorganisms** because of a defect in the generation of microbicidal oxygen metabolites. CGD is a rare disease, affecting 4-5 per 1 million individuals; it is caused by 4 genes: 1 X-linked and 3 autosomal recessive in inheritance (Table 156.4).

Table 156.4

Classification of Chronic Granulomatous Disease

COMPONENT AFFECTED	INHERITANCE	SUBTYPE[*]	FLAVOCYTOCHROME b SPECTRUM	NBT SCORE (% Positive)	INCIDENCE (% of Cases)
gp91 *phox*	X	$X91^0$	0	0	60
		$X91^-$	Low	80-100 (weak)	5
		$X91^-$	Low	5-10	<1
		$X91^+$	0	0	1
p22 *phox*	A	$A22^0$	0	0	4
		$A22^+$	N	0	<1
p47 *phox*	A	$A47^0$	N	0[†]	25
p67 *phox*	A	$A67^0$	N	0	5
		$A67^+$	N	0	<1
p40 *phox*	A	$A40^-$	N	100	<1

[*] In this nomenclature, the first letter represents the mode of inheritance (X-linked [X] or autosomal recessive [A]), whereas the number indicates the *phox* component that is genetically affected. The superscript symbols indicate whether the level of protein of the affected component is undetectable (^{0}), diminished ($^-$), or normal ($^+$), as measured by immunoblot analysis.

[†] Can be weakly positive.

NBT, Nitroblue tetrazolium.

From *Nathan & Oski's hematology and oncology of infancy and childhood,* ed 8, Philadelphia, 2015, Elsevier, p 833.

Genetics and Pathogenesis

Activation of the phagocyte NADPH oxidase requires stimulation of the neutrophils and involves assembly from cytoplasmic and integral membrane subunits (see Fig. 153.3). Oxidase activation initiates with phosphorylation of a cationic cytoplasmic protein, p47 ^{phox} (47-kDa phagocyte oxidase protein). Phosphorylated p47 ^{phox} , together with 2 other cytoplasmic components of the oxidase, p67 ^{phox} and the low-molecular-weight guanosine triphosphatase Rac2, translocates to the membrane, where they combine with the cytoplasmic domains of the transmembrane flavocytochrome b_{558} to form the active oxidase complex. The flavocytochrome is a heterodimer composed of p22 ^{phox} and highly glycosylated gp91 ^{phox} . The gp91 ^{phox} glycoprotein catalyzes electron transport through its NADPH-binding, flavin-binding, and heme-binding domains. Defects in any of these NADPH oxidase components can lead to CGD.

Approximately 65% of patients with CGD are males who inherit their disorder as a result of mutations in *CYBB* , an X-chromosome gene encoding gp91 ^{phox} . Approximately 35% of patients inherit CGD in an autosomal recessive fashion resulting from mutations in the *NCF1* gene on chromosome 7, encoding p47 ^{phox} . Defects in the genes encoding p67 ^{phox} (*NCF2* on chromosome 1) and p22 ^{phox} (*CYBA* on chromosome 16) are inherited in an autosomal recessive manner and account for approximately 5% of cases of CGD.

The CGD phagocytic vacuoles lack microbicidal reactive oxygen species and remain acidic, so bacteria are not killed or digested properly (Fig. 156.4). Hematoxylin-eosin–stained sections from patients’ tissues show multiple granulomas that give CGD its descriptive name.

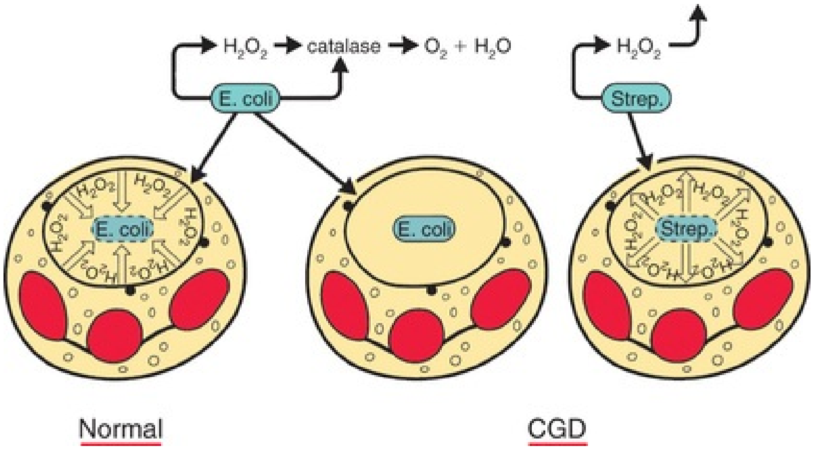

FIG. 156.4 Pathogenesis of chronic granulomatous disease (CGD). The manner in which the metabolic deficiency of the CGD neutrophil predisposes the host to infection is shown schematically. Normal neutrophils stimulate hydrogen peroxide (H_2O_2) in the phagosome containing ingested *Escherichia coli.* Myeloperoxidase is delivered to the phagosome by degranulation, as indicated by the *closed circles.* In this setting, H_2O_2 acts as a substrate for myeloperoxidase to oxidize halide to hypochlorous acid and chloramines that kill the microbes. The quantity of H_2O_2 produced by the normal neutrophil is sufficient to exceed the capacity of catalase, an H_2O_2-catabolizing enzyme of many aerobic microorganisms, including *Staphylococcus aureus,* most gram-negative enteric bacteria, *Candida albicans,* and *Aspergillus.* When organisms such as *E. coli* gain entry into CGD neutrophils, they are not exposed to H_2O_2 because the neutrophils do not produce it, and the H_2O_2 generated by microorganisms themselves is destroyed by their own catalase. When CGD neutrophils ingest streptococci, which lack catalase, the organisms generate enough H_2O_2 to result in a microbicidal effect. As indicated *(middle),* catalase-positive microbes such as *E. coli* can survive within the phagosome of the CGD neutrophil. (Adapted from Boxer LA: Quantitative abnormalities of granulocytes. In Beutler E, Lichtman MA, Coller BS, et al, editors: *Williams hematology,* ed 6, New York, 2001, McGraw-Hill, p 845.)

Clinical Manifestations

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. Any patient with recurrent pneumonia, lymphadenitis, hepatic, subcutaneous, or other abscesses, osteomyelitis at multiple sites, a family history of recurrent infections, or any infection with an unusual catalase-positive organism requires evaluation. Other clinical features include chronic colitis or enteritis, gastric outlet or ureteral obstruction from granulomas, or bloodstream infection caused by *Salmonella* , *Burkholderia cepacia*, or *Candida* .

The onset of clinical signs and symptoms usually occurs in early infancy, although a few patients with very rare CGD subtypes have presented later in life. The attack rate and severity of infections are exceedingly variable; however, the infection incidence decreases in the 2nd decade, coincident with maturation of the lymphocyte and humoral immunity. The most common pathogen is *S. aureus*, but any catalase-positive microorganism may be involved. Other organisms frequently causing infections include *Serratia marcescens, B. cepacia, Aspergillus, Candida albicans, Nocardia,* and *Salmonella.* There may also be increased susceptibility to mycobacteria, including the bacille Calmette-Guérin vaccine. Pneumonia, lymphadenitis, osteomyelitis, and skin infections are the most common illnesses encountered. Bacteremia or fungemia occurs but is much less common than focal infections and usually only occurs when local infections have been inappropriately treated for long periods. Patients may have sequelae of chronic infection, including anemia of chronic disease, poor growth, lymphadenopathy, hepatosplenomegaly, chronic purulent dermatitis, restrictive lung disease, gingivitis, hydronephrosis, esophageal dysmotility, and pyloric outlet narrowing. Perirectal abscesses and recurrent skin infections, including folliculitis, cutaneous granulomas, and discoid lupus erythematosus, also suggest CGD.

Granuloma formation and inflammatory processes are a hallmark of CGD and may be the presenting symptoms that prompt testing for CGD if they cause pyloric outlet obstruction, bladder outlet or ureter obstruction, or rectal fistulas and granulomatous colitis simulating Crohn disease. More than 80% of CGD patients have positive serology for Crohn disease. Persistent fever, especially with splenomegaly and cytopenia warrants an evaluation for secondary macrophage activation syndrome. This has been seen in CGD and may require treatment with corticosteroids and discontinuation of interferon-γ treatment.

Laboratory Findings

The diagnosis is most often made by performing flow cytometry using DHR to measure oxidant production through its increased fluorescence when oxidized by hydrogen peroxide (H_2O_2). The nitroblue tetrazolium dye test is frequently cited in the literature but is now only rarely used clinically. The X-linked carrier state is usually easily diagnosed in the mother by DHR fluorescence through a bimodal response to stimulation. It is important to test the mother as some extremely lyonized carriers with <5% positive cells may have chronic clinical problems as well. Ideally, at least the first patient in a kindred should have DNA analysis to facilitate prenatal diagnosis and for genetic counseling purposes.

A few individuals have been described with apparent CGD caused by severe glucose-6-phosphate dehydrogenase deficiency, leading to insufficient NADPH substrate for the phagocyte oxidase. The erythrocytes of these patients also lack the enzyme, leading to chronic hemolysis.

Treatment

HSCT is the only known cure for CGD, although gene therapy has been transiently successful in a few patients and is the topic of active research. HSCT transplant for all patients with CGD is strongly recommended if a suitable sibling or unrelated donor can be identified. The long-term outcome for survival late into adulthood is not good, even in the hands of experienced CGD physicians.

Patients with CGD should be given daily oral TMP/SMX because it reduces the number of bacterial infections. A placebo-controlled study found that interferon-γ 50 μg/m^2 3 times/wk significantly reduces the number of hospitalizations and serious infections, although the mechanism of action is unclear. Itraconazole (200 mg/day for patients weighing >50 kg and 100 mg/day for patients <50 kg and ≤5 yr old) administered prophylactically reduces the frequency of fungal infections.

Management of infection is dramatically different than in normal children. CGD patients are always at risk for deep-seated, indolent bacterial infections that can become widespread if not treated properly. They also develop the same kinds of infections that occur in normal children, so determination of the appropriate treatment can be difficult. The erythrocyte sedimentation rate (ESR) can be quite helpful. If the child does not have a deep-seated infection, the ESR will be normal or will normalize within several days with standard management. If it does not, however, a search for deep tissues is warranted, as is consideration of empirical antibiotics. Cultures should be obtained, but are usually negative. Because all neutrophil functions in CGD except killing are normal, there is often an exuberant inflammatory reaction to a very small number of organisms. Thus, blood cultures and direct cultures of biopsy samples are usually negative unless there are many organisms. Most abscesses require surgical drainage for therapeutic and diagnostic purposes. Prolonged use of antibiotics is required even for common bacterial infections. A simple pneumonia may require 6-8 wk or more of parenteral antibiotics. Infections should be treated for at least 1 wk past normalization of ESR to prevent recurrence. Severe pneumonias can be cleared completely but may require many months of parenteral antibiotics. Especially because cultures are often not helpful, many support an “antibiotic sensitivity by sedimentation rate response” approach to treatment. The ESRs are often 40-80 mm/hr or more with severe infection and will drop monotonically over a week or so after starting antibacterial drugs. It is important to check the ESR daily or every other day because of moderate variability in this test, and changes in treatment need to be based on trends rather than individual values. If there is a clear downward trend over 3-10 days, continue with antibacterials alone. If this is not the case, parenteral voriconazole should be added to cover *Aspergillus* . Failure of the ESR to drop suggests another antimicrobial approach needs to be tried. This sequential addition of antimicrobials offers some insight into the nature of the infection. If both antibacterials and antifungal are started at the same time, one cannot know what caused a response.

Because of the rarity of this disorder, it is critical to seek counsel from someone with significant direct experience with management of several CGD patients. Granulocyte transfusions have been used, but their benefit is unclear. The ESR should be regularly monitored in well patients and whenever they appear ill. A high ESR itself is usually not enough to trigger treatment. However, in the presence of symptoms, one should search for sources at least by contrast CT of the sinus, chest, and abdomen. If the patient is unstable or has very high fevers, *B. cepacia* should be considered and empirically covered. This organism can cause septic shock quickly, unlike the usual smoldering infections seen in CGD. The patient can be treated with antibiotics until the ESR is normal and radiographic evidence of infection has been cleared, if possible. The overall incidence of infection decreases in the 2nd decade of life as nonneutrophil immunity matures, but increased risk of infection is lifelong.

Corticosteroids may be useful for the treatment of children with antral and urethral obstruction or severe granulomatous colitis. Corticosteroids can also be helpful in pneumonia to shrink granulomas in the lung and promote drainage. Short (4-6 days) pulses of 1-2 mg/kg of prednisone are recommended, with rapid taper to avoid long-term side effects and risk of fungus. Pulses can be repeated if clinical effect has not been achieved.

Genetic Counseling

Identifying a patient's specific genetic subgroup by DNA analysis is useful primarily for genetic counseling and prenatal diagnosis. In X-linked CGD, all possibly affected females should be tested by DHR to exclude carrier state. Diagnosis by DNA is strongly recommended in suspected carriers with normal

DHR who are related to a known proband, because rarely DHR testing is normal in obligate carriers. Counseling is best done by a physician who has direct knowledge of the clinical manifestations of CGD.

Prognosis

The overall mortality rate for CGD is about 2 patient deaths per year per 100 cases, with the highest mortality among young children. The development of effective infection prophylaxis regimens, close surveillance for signs of infections, and aggressive surgical and medical interventions have improved the prognosis.

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CHAPTER 157

Leukopenia

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Leukopenia refers to an abnormally low number of white blood cells (WBCs) in the circulating blood secondary to a paucity of lymphocytes, granulocytes, or both. Because there are marked developmental changes in normal values for WBC counts during childhood (see Chapter 748), normal ranges must be considered in the context of age. For newborns, the mean WBC count at birth is high, followed by a rapid fall beginning at 12 hr through the 1st wk of life. Thereafter, values are stable until 1 yr of age, after which a slow, steady decline in the WBC count continues throughout childhood until adult values are reached during adolescence. Evaluation of patients with leukopenia begins with a thorough history, physical examination, and at least 1 confirmatory complete blood count with differential. Further evaluation then depends on whether the leukopenia represents a decreased number of neutrophils, lymphocytes, or both cell populations (Table 157.1). Treatment depends on the etiology and clinical manifestations of the leukopenia.

Table 157.1

Diagnostic Approach for Patients With Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION	
• History of acute or chronic leukopenia	
• General medical history including prior serious, recurrent or unusual infections and malignancy	Congenital syndromes (severe congenital neutropenia, cyclic neutropenia, Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport, GATA2 haploinsufficiency, and primary immunodeficiencies)
• Physical examination: stomatitis, gingivitis, dental defects, warts,	

lymphedema, congenital anomalies	
• Spleen size	Hypersplenism
• History of drug exposure	Drug-associated neutropenia
• Complete blood count with differential and reticulocyte counts	Neutropenia, aplastic anemia, autoimmune cytopenias
IF ANC <1,000/µL	
Evaluation of Acute-Onset Neutropenia	
• Repeat blood counts in 3-4 wk	Transient myelosuppression (e.g., viral)
• Serology and cultures for infectious agents	Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia
• Discontinue drug(s) associated with neutropenia	Drug-associated neutropenia
• Test for antineutrophil antibodies	Autoimmune neutropenia
• Measure quantitative immunoglobulins (IgG, IgA, IgM, IgE), lymphocyte subsets	Neutropenia associated with disorders of immune function
IF ANC <500/µL ON 3 SEPARATE TESTS	
• Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, cyclic neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia; reticular dysgenesis
• Glucocorticoid stimulation test	Chronic benign or idiopathic neutropenia, some autoimmune neutropenias
• Serial CBCs (3/wk for 6 wk)	Cyclic neutropenia
• Exocrine pancreatic function	Shwachman-Diamond syndrome
• Skeletal radiographs	Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
IF ALC <1000/µL	
• Repeat blood counts in 3-4 weeks	Transient leukopenia (e.g., viral)
IF ALC <1000/µL ON 3 SEPARATE TESTS	
• HIV-1 antibody or RNA test	HIV-1 infection, AIDS
• Quantitative immunoglobulins (IgG, IgA, IgM, IgE), vaccine titers, lymphocyte subsets	Congenital or acquired disorders of immune function
IF THERE IS PANCYTOPENIA	
• Bone marrow aspiration and biopsy	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia
• Bone marrow cytogenetics and flow cytometry	Myelodysplasia, leukemia
• Vitamin B_{12} and folate levels	Vitamin deficiencies

ALC, Absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

Neutropenia

Neutropenia is defined as a decrease in the absolute number of circulating segmented neutrophils and bands in the peripheral blood. The **absolute neutrophil count (ANC)** is determined by multiplying the total WBC count by the percentage of segmented neutrophils plus bands. Normal neutrophil counts must be stratified for age and race. Neutrophils predominate at birth but rapidly decrease in the 1st few days of life. During infancy, neutrophils constitute 20–30% of circulating leukocyte populations. Near-equal numbers of neutrophils and lymphocytes are found in the peripheral circulation at 5 yr of age, and the characteristic 70% predominance of neutrophils that occurs in adulthood is usually attained during puberty. For white children >12 mo old, the lower limit of normal for the ANC is 1,500/µL; for black children >12 mo old, the lower limit of normal is 1,200/µL. The relatively lower limit of normal in blacks likely reflects the prevalence of the Duffy negative (Fy−/−) blood group, which is enriched in populations in the malarial belt of Africa and is associated with ANCs 200-600/µL less than those who are Duffy positive.

Neutropenia may be characterized as **mild** (ANC 1,000-1,500/µL), **moderate** (ANC 500-1,000/µL), or **severe** (ANC <500/µL). ANC <200 is also termed **agranulocytosis** . This stratification aids in predicting the risk of pyogenic infection in patients who have neutropenia resulting from disorders of bone marrow production, because only patients with severe neutropenia have a significantly increased susceptibility to life-threatening infections. Neutropenia associated with monocytopenia, lymphocytopenia, or hypogammaglobulinemia increases the risk for infection compared to isolated neutropenia. *Patients with neutropenia caused by increased destruction (e.g., autoimmune) may tolerate very low ANCs without increased frequency of infection,* because of their often robust ability to generate additional neutrophils from their functioning marrow when needed.

Acute neutropenia evolves over a few days and is often a result of rapid neutrophil use and compromised neutrophil production. **Chronic neutropenia** by definition lasts longer than 3 mo and arises from reduced production, increased destruction, or excessive splenic sequestration of neutrophils. The etiology of neutropenia can be classified as either an acquired disorder or extrinsic insult (Table 157.2) or more rarely an inherited, intrinsic defect (Table 157.3).

Table 157.2

Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Clinical features and laboratory findings of the infectious agent
Drug induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody
Immune neutropenia	Alloimmune, autoimmune	Myeloid hyperplasia with left shift in bone marrow (may appear to be "arrest" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Myelofibrosis, malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, marrow fibrosis, malignant cells in bone marrow sites of extramedullary hematopoesis
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

Table 157.3

Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12} , copper, or folate deficiency	Malnutrition; congenital deficiency of B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hypersegmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birthweight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect secondary to mutation of *PIGA* gene	Pancytopenia, thrombosis (hepatic vein thrombosis)

Clinical Manifestations of Neutropenia

Individuals with neutrophil counts <500/µL are at substantial risk for developing infections, primarily from their endogenous flora as well as from nosocomial organisms. However, some patients with isolated chronic neutropenia may not experience many serious infections, probably because the remainder of the immune system remains intact or because neutrophil delivery to tissues is preserved, as in autoimmune neutropenias. In contrast, children whose neutropenia is secondary to acquired disorders of production, as occurs with cytotoxic therapy, immunosuppressive drugs, or radiation therapy, are likely to develop serious bacterial infections because many arms of the immune system are markedly compromised and the ability of the marrow to robustly generate new phagocytes is impaired. Neutropenia associated with additional monocytopenia or lymphocytopenia is more highly associated with serious infection than neutropenia alone. The integrity of skin and mucous membranes, the vascular supply to tissues, and nutritional status also influence the risk of infection.

The most common clinical presentation of profound neutropenia includes fever, aphthous stomatitis, and gingivitis. Infections frequently associated with neutropenia include cellulitis, furunculosis, perirectal inflammation, colitis, sinusitis, warts, and otitis media, as well as more serious infections such as pneumonia, deep tissue abscess, and sepsis. The most common pathogens causing infections in neutropenic patients are *Staphylococcus aureus* and gram-negative bacteria. Isolated neutropenia does not heighten a patient's susceptibility to parasitic or viral infections or to bacterial meningitis but does increase the risk of fungal pathogens causing disease. The usual signs and symptoms of local infection and inflammation (e.g., exudate, fluctuance, regional lymphadenopathy) may be diminished in the absence of neutrophils because of the inability to form pus, but patients with agranulocytosis still experience fever and feel pain at sites of inflammation.

Laboratory Findings

Isolated absolute neutropenia has a limited number of causes (see Tables 157.2 to 157.5). The duration and severity of the neutropenia greatly influence the extent of laboratory evaluation. Patients with chronic neutropenia since infancy and a history of recurrent fevers and chronic gingivitis should have WBC counts and differential counts determined 3 times/wk for 6-8 wk to evaluate for periodicity suggestive of **cyclic neutropenia** . Bone marrow aspiration and biopsy should be performed on select patients to assess cellularity and myeloid maturation. Additional marrow studies, such as cytogenetic analysis and special stains for detecting leukemia and other malignant disorders, should be obtained for patients with suspected intrinsic defects in the myeloid progenitors and for patients with suspected malignancy. Selection of further laboratory tests is determined by the duration and severity of the neutropenia and the associated findings on physical examination (see Table 157.1).

Table 157.4

Infections Associated With Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella, HHV-6
Bacterial	*Brucella*, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, Shigella, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	*Anaplasma* (formerly *Ehrlichia*) *phagocytophilum*, psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

Table 157.5

Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses required
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasia

Acquired Neutropenia

Infection-Related Neutropenia

Transient neutropenia often accompanies or follows **viral infections** and is the most frequent cause of neutropenia in childhood (Table 157.4). Viruses causing acute neutropenia include influenzas A and B, adenovirus, respiratory syncytial virus, enteroviruses, human herpesvirus 6, measles, rubella, and varicella. Parvovirus B19 and hepatitis A or B may also cause neutropenia, but are more often associated with pure red cell aplasia or multiple cytopenias, respectively. Viral-associated acute neutropenia often occurs during the 1st 24-48 hr of illness and usually persists for 3-8 days, which generally corresponds to the period of viremia. The neutropenia is related to virus-induced redistribution of neutrophils from the circulating to the marginating pool. In addition, neutrophil sequestration may occur after virus-induced tissue damage or splenomegaly.

Significant neutropenia also may be associated with severe bacterial, protozoal, rickettsial, or fungal infections (see Table 157.4). **Bacterial sepsis** is a particularly serious cause of neutropenia, especially among younger infants and children. Premature neonates are especially prone to exhausting their marrow reserve and rapidly succumbing to bacterial sepsis.

Chronic neutropenia often accompanies infection with Epstein-Barr virus, cytomegalovirus, or HIV and certain immunodeficiencies such as X-linked agammaglobulinemia, hyper IgM syndrome and HIV. The neutropenia associated with AIDS probably arises from a combination of viral bone marrow suppression, antibody-mediated destruction of neutrophils, and effects of antiretroviral or other drugs.

Drug-Induced Neutropenia

Drugs constitute a common cause of neutropenia (Table 157.5). The incidence of drug-induced neutropenia increases dramatically with age; only 10% of cases occur among children and young adults. The majority of cases occur among adults >65 yr, likely reflecting the more frequent use of multiple medications in that age-group. Almost any drug can cause neutropenia. The most common offending drug classes are antimicrobial agents, antithyroid drugs, antipsychotics, antipyretics, and antirheumatics. Drug-induced neutropenia has several underlying mechanisms—immune-mediated, toxic, idiosyncratic, hypersensitivity, idiopathic—that are distinct from the severe neutropenia that predictably occurs after administration of antineoplastic drugs or radiotherapy.

Drug-induced neutropenia from immune mechanisms usually develops abruptly, is accompanied by fever, and lasts for about 1 wk after the discontinuation of the drug. The process likely arises from effects of drugs such as propylthiouracil or penicillin that act as haptens to stimulate antibody formation, or drugs such as quinine that induce immune complex formation.

Other drugs, including the antipsychotic drugs such as the phenothiazines, can cause neutropenia when given in toxic amounts, but some individuals, such as those with preexisting neutropenia, may be susceptible to levels at the high end of the usual therapeutic range. Late-onset neutropenia can occur after rituximab therapy. Idiosyncratic reactions, for example to chloramphenicol, are unpredictable with regard to dose or duration of use. Hypersensitivity reactions are rare and may involve arene oxide metabolites of aromatic anticonvulsants. Fever, rash, lymphadenopathy, hepatitis, nephritis, pneumonitis, and aplastic anemia are often associated with hypersensitivity-induced neutropenia. Acute hypersensitivity reactions such as those caused by phenytoin or phenobarbital may last for only a few days if the offending drug is discontinued. Chronic hypersensitivity may last for months to years.

Once neutropenia occurs, the most effective therapeutic measure is withdrawal of nonessential drugs, particularly drugs most commonly associated with neutropenia. Usually the neutropenia will resolve soon after withdrawal of the offending drug. If the neutropenia fails to improve with drug withdrawal and the patient is symptomatic with infection or stomatitis, subcutaneous administration of recombinant human granulocyte colony-stimulating factor (filgrastim, 5 µg/kg/day) should be considered. Drug-induced neutropenia may be asymptomatic and noted only as an incidental finding or because of regular monitoring of WBC counts during drug therapy. For patients who are asymptomatic, continuation of the suspected offending drug depends on the relative risks of neutropenia vs discontinuation of a possibly essential drug. If the drug is continued, blood counts should be monitored for possible progression to agranulocytosis.

Neutropenia usually and predictably follows the use of anticancer drugs or radiation therapy, especially radiation directed at the pelvis or vertebrae, secondary to cytotoxic effects on rapidly replicating myeloid precursors. A decline in the WBC count typically occurs 7-10 days after administration of the anticancer drug and may persist for 1-2 wk. The neutropenia accompanying malignancy or following cancer chemotherapy is frequently associated with compromised cellular immunity and barrier compromise secondary to central venous lines and mucositis, thereby predisposing patients to a much greater risk of infection (see Chapter 205) than found in disorders associated with isolated neutropenia. Patients with chemotherapy/radiation-related neutropenia and fever must be treated aggressively with broad-spectrum antibiotics.

Nutrition-Related Neutropenia

Poor nutrition can contribute to neutropenia. Ineffective myelopoiesis may result in neutropenia caused by acquired dietary copper, vitamin B_{12} , or folic acid deficiency. In addition, megaloblastic pancytopenia also can result from extended use of antibiotics such as trimethoprim/sulfamethoxazole that inhibit folic acid metabolism and from the use of phenytoin, which may impair folate absorption in the small intestine, or from surgical resection of the small intestine. Neutropenia also occurs with starvation and marasmus in infants, with anorexia nervosa, and occasionally among patients receiving prolonged parenteral nutrition without vitamin supplementation.

Immune-Mediated Neutropenia

Immune-mediated neutropenia is usually associated with the presence of circulating antineutrophil antibodies, which may mediate neutrophil destruction by complement-mediated lysis or splenic phagocytosis of opsonized neutrophils, or by accelerated apoptosis of mature neutrophils or myeloid precursors.

Alloimmune neonatal neutropenia occurs after transplacental transfer of maternal alloantibodies directed against antigens on the infant's neutrophils, analogous to Rh-hemolytic disease. Prenatal sensitization induces maternal IgG antibodies to neutrophil antigens on fetal cells. The neutropenia is often severe and infants may present within the 1st 2 wk of life with skin or umbilical infections, fever, and pneumonia caused by the usual microbes that cause neonatal disease. By 7 wk of age, the neutrophil count usually returns to normal, reflecting the decay of maternal antibodies in the infant's circulation. Treatment consists of supportive care and appropriate antibiotics for clinical infections, plus granulocyte colony-stimulating factor (G-CSF) for severe infections without neutrophil recovery.

Mothers with autoimmune disease may give birth to infants who develop transient neutropenia, known as **neonatal passive autoimmune neutropenia** . The duration of the neutropenia depends on the time required for the infant to clear the maternally transferred circulating IgG antibody. It persists in most cases for a few weeks to a few months. Neonates almost always remain asymptomatic.

Autoimmune neutropenia (AIN) of infancy is a benign condition with an annual incidence of approximately 1 per 100,000 among children between infancy and 10 yr of age. Patients usually have severe neutropenia on presentation, with ANC <500/µL, but the total WBC count is generally within normal limits. Monocytosis or eosinophilia may occur but does not impact the low rate of infection. The median age of presentation is 8-11 mo, with a range of 2-54 mo. The diagnosis is often evident when a blood count incidentally reveals neutropenia in a child with a minor infection or when a routine complete blood count is obtained at the 12 mo well-child visit. Occasionally, children may present with more severe infections, including abscesses, pneumonia, or sepsis. The diagnosis may be supported by the presence of antineutrophil antibodies in serum; however, the test has frequent false-negative and false-positive results, so the absence of detectable antineutrophil antibodies does not exclude the diagnosis, and a positive result does not exclude other conditions. Therefore the diagnosis is best made clinically based on a benign course and, if obtained, a normal or hyperplastic myeloid maturation in the bone marrow. There is considerable overlap between AIN of infancy and “chronic benign neutropenia.”

Treatment is not generally necessary because the disease is only rarely associated with severe infection and usually remits spontaneously. Low-dose G-CSF may be useful for severe infections, to promote wound healing following surgery, or to avert emergency room visits or hospitalizations for febrile illnesses. Longitudinal studies of infants with AIN demonstrate median duration of disease ranging from 7-30 mo. Affected children generally have no evidence or risk of other autoimmune diseases.

AIN in older children can occur as an isolated process, as a manifestation of other autoimmune diseases, or as a secondary complication of infection, drugs, or malignancy. In primary AIN, low circulating neutrophil counts are the only hematologic finding, and associated diseases or other factors that cause neutropenia are absent. Secondary AIN associated with immune dysregulation or other factors is more often identified in older children and is less likely to remit spontaneously. AIN is distinguished from other forms of neutropenia by the demonstration of antineutrophil antibodies (with caveats previously discussed) and myeloid hyperplasia on bone marrow examination. The most common antineutrophil antibody targets are human neutrophil antigens 1a, 1b, and 2.

Treatment of AIN relies on management of any underlying disorders. In addition, judicious use of appropriate antibiotics for bacterial infections and regular dental hygiene are generally beneficial, as is family and primary care provider education. Infections tend to be less frequent in AIN than with the corresponding degree of neutropenia from other causes, probably because tissue delivery of neutrophils is greater than that in conditions resulting from impaired production. Prophylactic antibiotics may be helpful for the management of recurrent minor infections. For patients with serious or recurrent infections, G-CSF is generally effective at raising the ANC and preventing infection. Very low doses (<1-2 μg/kg/day) are usually effective, and administration of standard doses can lead to severe bone pain from marrow expansion.

Neutropenia Secondary to Bone Marrow Replacement

Various acquired bone marrow disorders lead to neutropenia, usually accompanied by anemia and thrombocytopenia. Hematologic malignancies, including leukemia, lymphoma, and metastatic solid tumors, suppress myelopoiesis by infiltrating the bone marrow with tumor cells. Neutropenia may also accompany aplastic anemia, myelodysplastic disorders, or preleukemic syndromes, which are characterized by multiple cytopenias and often macrocytosis. Treatment requires management of the underlying disease.

Neutropenia Secondary to Reticuloendothelial Sequestration

Splenic enlargement resulting from intrinsic splenic disease (storage disease), portal hypertension, or systemic causes of splenic hyperplasia (inflammation or neoplasia) can lead to neutropenia. Most often the neutropenia is mild to moderate and is accompanied by corresponding degrees of thrombocytopenia and anemia. The reduced neutrophil survival corresponds to the size of the spleen, and the extent of the neutropenia is inversely proportional to bone marrow compensatory mechanisms. Usually the neutropenia can be corrected by successfully treating the underlying disease. In select cases, splenectomy may be necessary to restore the neutrophil count to normal, but results in increased risk of infections by encapsulated bacterial organisms. Patients undergoing splenectomy should receive appropriate preoperative immunizations and may benefit from antibiotic prophylaxis after splenectomy to help mitigate the risk of sepsis. Splenectomy should be avoided in patients with common variable immunodeficiency (CVID), autoimmune lymphoproliferative disease, and other immunodeficiency syndromes because of the higher risk of sepsis.

Inherited Neutropenia

Intrinsic disorders of proliferation or maturation of myeloid precursor cells are rare. Table 157.6 presents a classification based on genetics and molecular mechanisms; select disorders are discussed next.

Table 157.6

Intrinsic Disorders of Myeloid Precursor Cells

SYNDROME	INHERITANCE *(GENE)*	CLINICAL FEATURES (INCLUDING STATIC NEUTROPENIA UNLESS OTHERWISE NOTED)
PRIMARY DISORDERS OF MYELOPOIESIS		
Cyclic neutropenia	AD *(ELANE)*	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD (primarily *ELANE*, also *GFI* and others)	Risk of MDS/AML
	AR *(G6PC3, HAX1)* (*HAX1* = Kostmann syndrome)	*G6PC3:* cardiac and urogenital anomalies, venous angioectasias; *HAX1:* neurologic abnormalities, risk of MDS/AML
	XL *(WAS)*	Neutropenic variant of Wiskott-Aldrich syndrome
DISORDERS OF MOLECULAR PROCESSING		
Shwachman-Diamond syndrome	Ribosomal defect: AR *(SBDS, DNAJC21, EFL1, SRP54)*	Pancreatic insufficiency, metaphyseal dysostosis, bone marrow failure, MDS/AML
Dyskeratosis congenita	Telomerase defects: XL *(DKC1)*, AD *(TERC)*, AR *(TERT)*	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure
DISORDERS OF VESICULAR TRAFFICKING		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired NK cell function, HLH
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired NK cell function, neurologic impairment, HLH
Cohen syndrome	AR *(COH1)*	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism
Hermansky-Pudlak syndrome, type II	AR *(AP3B1)*	Cyclic neutropenia, partial albinism, HLH
p14 deficiency	Probable AR *(MAPBPIP)*	Partial albinism, decreased B and T cells
VPS45 defects	AR *(VPS45)*	Neutrophil dysfunction, bone marrow fibrosis, nephromegaly
DISORDERS OF METABOLISM		
Glycogen storage disease, type 1b	AR *(G6PT1)*	Hepatic enlargement, growth retardation, impaired neutrophil motility
Methylmalonic/propionic acidemias	AR Mutase or cobalamin transporters/propionyl coenzyme A carboxylase	Ketoacidosis, metabolic stroke, depressed consciousness
Barth syndrome	XL *(TAZ1)*	Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria
Pearson syndrome	Mitochondrial (DNA deletions)	Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys
NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION		
Common variable immunodeficiency	Familial, sporadic *(TNFRSF13B)*	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or *TNFRSF13B*)	Decreased IgA

Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL *(HIGM1)*	Absent IgG, elevated IgM, autoimmune cytopenias
WHIM syndrome	AD *(CXCR4)*	Warts, hypogammaglobulinemia, infections, myelokathexis
Cartilage-hair hypoplasia	AR *(RMRP)*	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	Probable AR *(SMARCAL1)*	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure
X-linked agammaglobulinemia	Bruton tyrosine kinase (Btk)	Agammaglobulinemia, neutropenia in ~25%

AD, Autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplastic syndrome; XL, X-linked.

Primary Disorders of Granulocytopoiesis

Cyclic neutropenia is an autosomal dominant congenital granulopoietic disorder occurring with an estimated incidence of 0.5-1 cases per 1 million population. The disorder is characterized by regular, periodic oscillations, with the ANC ranging from normal to <200/µL, mirrored by reciprocal cycling of monocytes. Cyclic neutropenia is sometimes termed *cyclic hematopoiesis* because of the secondary cycling of other blood cells, such as platelets and reticulocytes. The mean oscillatory period of the cycle is 21 days (±4 days). During the neutropenic nadir, many patients develop malaise, fever, oral and genital ulcers, gingivitis, periodontitis, or pharyngitis, and occasionally lymph node enlargement. More serious infections occasionally occur, including pneumonia, mastoiditis, and intestinal perforation with peritonitis leading to life-threatening clostridial sepsis. Before the availability of G-CSF, approximately 10% of patients developed fatal clostridial or gram-negative infections. Cyclic neutropenia arises from a regulatory abnormality involving early hematopoietic precursor cells and is almost invariably associated with mutations in the neutrophil elastase gene, *ELANE* , that lead to accelerated apoptosis as a result of abnormal protein folding. Many patients experience abatement of symptoms with age. The cycles tend to become less noticeable in older patients, and the hematologic picture often begins to resemble that of chronic idiopathic neutropenia.

Cyclic neutropenia is diagnosed by obtaining blood counts 3 times/wk for 6-8 wk. The requirement for repeated blood counts is necessary because some of the elastase mutations overlap with those in patients who have **severe congenital neutropenia** . Demonstrating oscillation or a lack thereof in the blood counts helps to identify the patients' risk for progression to **myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML)** , a risk that is only associated with severe congenital neutropenia. The diagnosis can be confirmed with genetic studies demonstrating a mutation in *ELANE* . Affected patients with neutrophil nadirs <200/µL are treated with G-CSF, and their cycle of profound neutropenia changes from a 21-day period with at least 3-5 days of profound neutropenia to 9-11 days with 1 day of less profound neutropenia. The dose needed to maintain nadirs >500/µL is usually 2-4 µg/kg/day administered daily or every other day.

Severe congenital neutropenia (SCN) is a rare, genetically heterogeneous, congenital granulopoietic disorder with an estimated incidence of 1-2 cases per 1 million population. The disorder is characterized by an arrest in myeloid maturation at the promyelocyte stage in the bone marrow, resulting in ANCs consistently <200/µL and may occur sporadically, with autosomal dominant or recessive inheritance. The **dominant** form is caused most often by mutations in *ELANE* , which accounts for 60–80% of SCN cases, whereas **recessive** forms arise from mutations in *HAX1* (the form also known as **Kostmann disease**) or *G6PC3* (encoding a myeloid-specific isoform of glucose-6-phosphatase). *HAX1* mutations may be associated with neurologic deficits, and *G6PC3* with heart defects, urogenital abnormalities, and venous angiectasia. In addition to severe neutropenia, peripheral blood counts generally show monocytosis and many also exhibit eosinophilia; chronic inflammation may lead to secondary anemia and thrombocytosis. Patients who have SCN experience frequent episodes of fever, skin infections (including omphalitis), oral ulcers, gingivitis, pneumonia, and perirectal abscesses, typically appearing in the 1st few mo of life. Infections often disseminate to the blood, meninges, and peritoneum and are usually caused by *S. aureus* , *Escherichia coli,* and *Pseudomonas* species. Without filgrastim therapy, most patients die of infectious complications within the first 1-2 yr of life despite prophylactic antibiotics.

More than 95% of SCN patients respond to filgrastim treatment with an increase in the ANC and a decrease in infections. Doses required to achieve an ANC >1000/uL vary greatly. A starting dose of filgrastim at 5 µg/kg/day is recommended; the dose should be gradually increased, if necessary, as high as 100 µg/kg/day to attain an ANC of 1,000-2,000/µL. The 5% of patients who do not respond to filgrastim or who require high doses (>8 µg/kg/day) should be considered for hematopoietic stem cell transplantation (HSCT). Besides infections, patients with SCN are at risk for developing MDS associated with monosomy 7 and AML. For this reason, regular monitoring with blood counts and yearly bone marrow surveillance, including karyotyping and fluorescence in situ hybridization, should be performed on all SCN patients. Although clonal cytogenetic abnormalities may spontaneously remit, their appearance should be considered a strong indication for HSCT, which is much more likely to be successful before progression to MDS/AML.

Disorders of Molecular Processing

Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder classically characterized by neutropenia, pancreatic insufficiency, and short stature with skeletal abnormalities. SDS is most commonly caused by proapoptotic mutations of the *SBDS* gene, which encodes a protein that plays a role in ribosome biogenesis and RNA processing. The initial symptoms are usually steatorrhea and failure to thrive because of malabsorption, which usually develops by 4 mo of age, although the gastrointestinal symptoms may be subtle in some patients and go unrecognized. Patients have also been reported to have respiratory problems with frequent otitis media, pneumonia, and eczema. Virtually all patients with SDS have neutropenia, with the ANC periodically <1000/µL. Some children have defects in chemotaxis or in the number or function of B, T, and natural killer (NK) cells that may contribute to the increased susceptibility to pyogenic infection. The diagnosis of SDS is based on clinical phenotype; approximately 90% of patients have mutations identified in *SBDS* with additional mutations now recently discovered in *DNAJC21*, *EFL1*, and *SRP54* . SDS may progress to bone marrow hypoplasia or MDS/AML; cytogenetic abnormalities, particularly isochromosome i(7q) and del(20q), often precede conversion to MDS, so bone marrow monitoring is warranted. Treatment includes pancreatic enzyme replacement, plus G-CSF in patients with severe neutropenia.

Dyskeratosis congenita , a disorder of telomerase activity, most often presents as bone marrow failure rather than isolated neutropenia. The classic phenotype also includes nail dystrophy, leukoplakia, malformed teeth, and reticulated hyperpigmentation of the skin, although many patients, particularly young ones, do not exhibit these clinical features.

Vesicular Trafficking Disorders

This group of rare **primary immunodeficiency syndromes** (see Table 157.6) derives from autosomal recessive defects in the biogenesis or trafficking of lysosomes and related endosomal organelles. As a result, the syndromes share phenotypic characteristics, including defects in melanosomes contributing to partial albinism, abnormal platelet function, and immunologic defects involving not only neutrophil number, but also the function of neutrophils, B lymphocytes, NK cells, and cytotoxic T lymphocytes. The syndromes share a high risk of hemophagocytic lymphohistiocytosis (HLH) as a result of defects in T and NK cells.

Chédiak-Higashi syndrome , best known for the characteristic giant cytoplasmic granules in neutrophils, monocytes, and lymphocytes, is a disorder of subcellular vesicular dysfunction caused by mutations in the *LYST* gene, with resultant giant granules in all granule-bearing cells. Patients have increased susceptibility to infections, mild bleeding diathesis, progressive peripheral neuropathy, and predisposition to life-threatening HLH. The only curative treatment is HSCT, but transplant does not treat all aspects of the disorder.

Griscelli syndrome type II also features neutropenia, partial albinism, and a high risk of HLH, but peripheral blood granulocytes do not show giant granules. Patients often have hypogammaglobulinemia. The disorder is caused by mutations in *RAB27a* , which encodes a small guanosine triphosphatase that regulates granule secretory pathways. The only curative treatment is HSCT.

Disorders of Metabolism

Recurrent infections with neutropenia are a distinctive feature of **glycogen storage disease (GSD) type Ib** . As in classic **von Gierke disease** (GSDIa), glycogen storage in GSDIb causes massive hepatomegaly and severe growth retardation. Mutations in glucose-6-phosphate transporter 1, *G6PT1* , inhibit glucose transport in GSDIb, resulting in both defective neutrophil motility and increased apoptosis associated with neutropenia and recurrent bacterial infections. Treatment with G-CSF can correct the neutropenia but does not correct the underlying functional neutrophil defects.

Neutropenia in Disorders of Immune Dysfunction

Congenital immunologic disorders that have severe neutropenia as a clinical feature include X-linked agammaglobulinemia (XLA), CVID, the severe combined immunodeficiencies, autoimmune lymphoproliferative syndrome, hyperimmunoglobulin M syndrome, WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, GATA2 haploinsufficiency, and a number of even rarer immunodeficiency disorders (see Table 157.6).

Unclassified Neutropenic Disorders

Chronic benign neutropenia of childhood represents a common group of disorders characterized by mild to moderate neutropenia that does not lead to an increased risk of pyogenic infections. Spontaneous remissions are often reported, although these may represent misdiagnosis of AIN of infancy, in which remissions often occur during childhood. Chronic benign neutropenia may be sporadic or inherited in either dominant or recessive form. Because of the relatively low risk of serious infection, patients usually do not require any therapy.

Idiopathic chronic neutropenia is characterized by the onset of neutropenia after 2 yr of age, with no identifiable etiology. Patients with an ANC persistently <500/µL may have recurrent pyogenic infections involving the skin, mucous membranes, lungs, and lymph nodes. Bone marrow examination reveals variable patterns of myeloid formation with arrest generally occurring between the myelocyte and band forms. The diagnosis overlaps with chronic benign and AINs.

Treatment

The management of acquired transient neutropenia associated with malignancies, myelosuppressive chemotherapy, or immunosuppressive chemotherapy differs from that of congenital or chronic forms of neutropenia. In the former situation, infections sometimes are heralded only by fever, and sepsis is a major cause of death. Early recognition and treatment of infections may be lifesaving (see Chapter 205). Therapy of severe chronic neutropenia is dictated by the clinical manifestations. Patients with benign neutropenia and no evidence of repeated bacterial infections or chronic gingivitis require no specific therapy. Superficial infections in children with mild to moderate neutropenia may be treated with appropriate oral antibiotics. In patients who have invasive or life-threatening infections, broad-spectrum intravenous antibiotics should be started promptly.

Subcutaneously administered G-CSF can provide effective treatment of severe chronic neutropenia, including SCN, cyclic neutropenia, and chronic symptomatic idiopathic neutropenias. Treatment leads to dramatic increases in neutrophil counts, resulting in marked attenuation of infection and inflammation. Doses range from 2-5 µg/kg/day for cyclic, idiopathic, and autoimmune neutropenias, to 5-100 µg/kg/day for SCN. The long-term effects of G-CSF therapy include a propensity for the development of moderate splenomegaly, thrombocytopenia, and rarely vasculitis; only patients with SCN are at risk for MDS/AML.

Patients with SCN or SDS who develop MDS or AML respond only to HSCT; chemotherapy is ineffective. HSCT is also the treatment of choice for aplastic anemia or familial HLH.

Lymphopenia

The definition of **lymphopenia** , as with neutropenia, is age dependent and can have acquired or inherited causes. **The absolute lymphocyte count (ALC)** is determined by multiplying the total WBC count by the percentage of total lymphocytes. For children <12 mo old, lymphopenia is defined as an ALC <3,000 cells/µL. For older children and adults, an ALC <1,000 cells/µL is considered lymphopenia. In isolation, mild to moderate lymphopenia is generally a benign condition often detected only in the evaluation of other illnesses. However, severe lymphopenia can result in serious, life-threatening illness. Lymphocyte subpopulations can be measured by flow cytometry, which uses the pattern of lymphocyte antigen expression to quantitate and classify T, B, and NK cells.

Acquired Lymphopenia

Acute lymphopenia is most often a result of infection and/or is iatrogenic from lymphocyte-toxic medications and treatments (Table 157.7). Microbial causes include viruses (e.g., respiratory syncytial virus, cytomegalovirus, influenza, measles, hepatitis), bacterial infections (e.g., tuberculosis, typhoid fever, histoplasmosis, brucellosis), and malaria. The mechanisms behind infection-associated lymphopenia are not fully elucidated but probably include lymphocyte redistribution and accelerated apoptosis. Corticosteroids are a common cause of medication-induced lymphopenia, as are lymphocyte-specific immunosuppressive agents (e.g., antilymphocyte globulin, alemtuzumab, rituximab), chemotherapy drugs, and radiation. In most cases, infectious and iatrogenic causes of acute lymphopenia are reversible, although full lymphocyte recovery from chemotherapy and lymphocyte-specific immunosuppressive agents may take several months to years. Prolonged lymphopenia (Table 157.7) may be caused by recurrent infection; persistent infections, mostly notably HIV; malnutrition; mechanical loss of lymphocytes through protein-losing enteropathy or thoracic duct leaks; or systemic diseases such as lupus erythematosus, rheumatoid arthritis, sarcoidosis, renal failure, lymphoma, and aplastic anemia.

Table 157.7

Causes of Lymphocytopenia

ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure, sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury
INHERITED	
Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxia-telangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome

PUVA, Psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

Inherited Lymphopenia

Primary immunodeficiencies and bone marrow failure syndromes are the main cause of inherited lymphopenia in children (see Table 157.7). Primary immunodeficiency may result in a severe quantitative defect, as in XLA and severe combined immunodeficiency (SCID), or a qualitative or progressive defect, as in Wiskott-Aldrich syndrome and CVID. XLA is characterized by a near-absence of mature B cells because of a mutation in *BTK* that results in a dysfunctional tyrosine kinase. SCIDs are a genetically heterogeneous group of disorders characterized by abnormalities of thymopoiesis and T-cell maturation. Newborn screening for severe T-cell deficiency, by analysis of T-cell receptor excision circles from dried blood spot Guthrie cards, aids in the rapid identification and treatment of infants with SCID and other T-cell disorders. Quantitative defects in lymphocytes can also be appreciated in select forms of inherited bone marrow failure such as reticular dysgenesis, SCN secondary to *GFI1* mutation, and dyskeratosis congenita.

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CHAPTER 158

Leukocytosis

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Leukocytosis is an elevation in the total leukocyte or white blood cell (WBC) count that is 2 SD above the mean for age (see Chapter 748). It is most often caused by elevated numbers of neutrophils (i.e., neutrophilia), although marked increases in monocytes, eosinophils, basophils, and lymphocytes can be seen. Before extensive evaluation, it is important to assess for spurious elevations in the WBC count caused by platelet clumping (secondary to insufficient sample anticoagulation or the presence of EDTA-dependent agglutinins), high numbers of circulating nucleated red blood cells (RBCs), and the presence of cryoglobulins by review of the peripheral smear.

Malignancy, namely leukemia and lymphoma, is a primary concern for patients with leukocytosis. For discussion of WBC elevation caused by immature leukocytes in acute and chronic leukemias, see Chapter 522 . Nonmalignant WBC counts exceeding 50,000/µL have historically been termed a **leukemoid reaction.** Unlike leukemia, leukemoid reactions show relatively small proportions of immature myeloid cells, consisting largely of band forms, occasional metamyelocytes, and progressively rarer myelocytes, promyelocytes, and blasts. Leukemoid reactions are most often neutrophilic and are frequently associated with severe bacterial infections, including shigellosis, salmonellosis, and meningococcemia; physiologic stressors; and certain medications.

The presence of a **left shift** , defined as having >5% immature neutrophils in the peripheral blood, is consistent with marrow stress. Higher degrees of left shift with more immature neutrophil precursors are indicative of serious bacterial infections and may be a dire sign of depletion of the bone marrow reserve pool of neutrophils. Marked left shift may occasionally be encountered with trauma, burns, surgery, acute hemolysis, or hemorrhage.

Neutrophilia

Neutrophilia is an increase in the total number of blood neutrophils that is 2 SD above the mean count for age (see Chapter 748). Elevated absolute neutrophil counts represent disturbances of the normal equilibrium involving bone marrow neutrophil production, migration out of the marrow compartments into the circulation, and neutrophil destruction. Neutrophilia may arise either alone or in combination with enhanced mobilization into the **circulating pool** from either the bone marrow storage compartment or the peripheral blood **marginating pool** , by impaired neutrophil egress into tissues, or by expansion of the circulating neutrophil pool secondary to increased granulocytopoiesis. Myelocytes are not released to the blood except under extreme circumstances.

Acute Acquired Neutrophilia

Neutrophilia is usually an acquired, secondary finding associated with inflammation, infection, injury, or an acute physical or emotional stressor (Table 158.1). Bacterial infections, trauma (especially with hemorrhage), and surgery are among the most common causes encountered in clinical practice. Neutrophilia may also be associated with heat stroke, burns, diabetic ketoacidosis, pregnancy, or cigarette use.

Table 158.1

Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis, cigarette exposure
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease, pregnancy, Sweet syndrome
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

Drugs commonly associated with neutrophilia include epinephrine, corticosteroids, and recombinant growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF) and recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF). Epinephrine causes release into the circulation of a sequestered pool of neutrophils that normally marginate along the vascular endothelium. Corticosteroids accelerate the release of neutrophils and bands from a large storage pool within the bone marrow and impair the migration of neutrophils from the circulation into tissues. G-CSF and GM-CSF cause acute and chronic neutrophilia by mobilizing cells from the marrow reserves and stimulating neutrophil production.

Acute neutrophilia in response to inflammation and infections occurs because of release of neutrophils from the marrow storage pool. The postmitotic marrow neutrophil pools are approximately 10 times the size of the blood neutrophil pool, and about half of these cells are bands and segmented neutrophils. Exposure of blood to foreign substances such as hemodialysis membrane activates the complement system and causes transient neutropenia, followed by neutrophilia secondary to release of bone marrow neutrophils. Reactive neutrophils often have toxic granulation and Döhle bodies present.

Chronic Acquired Neutrophilia

Chronic acquired neutrophilia is usually associated with continued stimulation of neutrophil production resulting from persistent inflammatory reactions or chronic infections (e.g., tuberculosis), vasculitis, postsplenectomy states, Hodgkin disease, chronic myelogenous leukemia, chronic blood loss, sickle cell disease, some chronic hemolytic anemias, and prolonged administration of corticosteroids (see Table 158.1). Chronic neutrophilia can arise after expansion of cell production secondary to stimulation of cell divisions within the mitotic precursor pool, which consists of promyelocytes and myelocytes. Subsequently, the size of the postmitotic pool increases. These changes lead to an increase in the marrow reserve pool, which can be readily mobilized for release of neutrophils into the circulation. The neutrophil production rate can increase greatly in response to exogenously administered hematopoietic growth factors, such as G-CSF, with a maximum response taking at least 1 wk to develop.

Lifelong Neutrophilia

Congenital or acquired asplenia is associated with lifelong neutrophilia. Some patients with trisomy-21 also have neutrophilia. Uncommon genetic disorders that present with neutrophilia include leukocyte function disorders such as leukocyte adhesion deficiency and Rac2 deficiency (see Chapter 156) and systemic disorders such as familial cold urticaria, periodic fever syndromes, and familial myeloproliferative disease (see Table 158.1). Rare patients with an autosomal dominant hereditary neutrophilia have been reported.

Evaluation of persistent neutrophilia requires a careful history, physical examination, and laboratory studies to search for infectious, inflammatory, and neoplastic conditions. The leukocyte alkaline phosphatase score of circulating neutrophils can differentiate chronic myelogenous leukemia, in which the level is uniformly almost zero, from reactive or secondary neutrophilia, which features normal to elevated levels.

Additional Forms of Leukocytosis

Monocytosis

The average absolute blood monocyte count varies with age, which must be considered in the assessment of monocytosis. Given the role of monocytes in antigen presentation and cytokine secretion and as effectors of ingestion of invading organisms, it is not surprising that many clinical disorders give rise to monocytosis (Table 158.2). Typically, monocytosis occurs in patients recovering from myelosuppressive chemotherapy and is a harbinger of the return of the neutrophil count to normal. Monocytosis is occasionally a sign of an acute bacterial, viral, protozoal, or rickettsial infection and may also occur in some forms of chronic neutropenia and postsplenectomy states. Chronic inflammatory conditions can stimulate sustained monocytosis, as can preleukemia, chronic myelogenous leukemia, and lymphomas.

Table 158.2

Causes of Monocytosis

CAUSE	EXAMPLE
Infections	
Bacterial infections	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis, typhoid
Nonbacterial	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus

infections	
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

Eosinophilia

Eosinophilia is defined as an absolute eosinophil count >1500 cells/μL. The majority of eosinophilic conditions are reactive, including infections (especially parasitic diseases), connective tissue disorders, allergic and hyperinflammatory diseases, pulmonary disorders, and dermatologic conditions. Hypereosinophilic syndrome and systemic mastocytosis are additional important causes of an elevated eosinophil count. However, persistent eosinophilia can also herald a malignancy such as leukemia, lymphoma, or carcinoma.

Basophilia

Basophilia is defined as an absolute basophil count >120 cells/μL. Basophilia is a nonspecific sign of a wide variety of disorders and is usually of limited diagnostic importance. Basophilia is most often present in hypersensitivity reactions and frequently accompanies the leukocytosis of chronic myeloid leukemia.

Lymphocytosis

The most common cause of lymphocytosis is an acute viral illness, as part of the normal T-cell response to the infection. In infectious mononucleosis, the B cells are infected with the Epstein-Barr virus, and the T cells react to the viral antigens present in the B cells, resulting in **atypical lymphocytes** with characteristic large, vacuolated morphology. Other viral infections classically associated with lymphocytosis are cytomegalovirus and viral hepatitis. Chronic bacterial infections such as tuberculosis and brucellosis may lead to a sustained lymphocytosis. Pertussis is accompanied by marked lymphocytosis in approximately 25% of infants infected before 6 mo of age. Thyrotoxicosis and Addison disease are endocrine disorders associated with lymphocytosis.

Persistent or pronounced lymphocytosis suggests acute lymphocytic leukemia.

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SECTION 4

The Complement System

OUTLINE

Chapter 159 Complement Components and Pathways
Chapter 160 Disorders of the Complement System

CHAPTER 159

Complement Components and Pathways

Richard B. Johnston Jr.

Complement is an exquisitely balanced, highly influential system that is fundamental to the clinical expression of host defense and inflammation. The complement system also has the capacity to perform functions beyond host defense, such as promoting phagocytic removal of dying cells, molecular debris, and weak or superfluous synapses during brain formation. Complement components and receptors function within individual cells and can stabilize intracellular homeostasis. However, complement activation can also cause harm and has been implicated in many illnesses.

The complement system, an essential component of innate and adaptive immunity, is broadly conceptualized as (1) the classical, lectin, and alternative **pathways** , which interact and depend on each other for their full activity; (2) the **membrane attack complex** (C5b6789), formed from activity of any pathway; (3) cell membrane **receptors** that bind complement components or fragments to mediate complement activity; and (4) a large array of serum and membrane **regulatory proteins** (Table 159.1 and Fig. 159.1). The circulating components and regulators together comprise approximately 15% of the globulin fraction and 4% of the total proteins in serum. The normal concentrations of serum complement components vary by age (see Chapter 748); newborn infants have mild to moderate deficiencies of all components.

Table 159.1

Constituents of the Complement System

Serum Components That Are the Core of the Complement System

Classical pathway: C1q, C1r, C1s, C4, C2, C3
Alternative pathway: factor B, factor D
Lectin pathway: Mannose-binding lectin (MBL), ficolins 1/2/3, MBL-associated serine proteases (MASPs) 1/2/3
Membrane attack complex: C5, C6, C7, C8, C9
Regulatory protein, enhancing: properdin
Regulatory proteins, downregulating: C1 inhibitor (C1 INH), C4-binding protein (C4-bp), factor H, factor I, vitronectin, clusterin, carboxypeptidase N (anaphylatoxin inactivator)

Membrane Regulatory Proteins

CR1 (CD35), membrane cofactor protein (MCP; CD46), decay-accelerating factor (DAF, CD55), CD59 (membrane inhibitor of reactive lysis)

Membrane Receptors

CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18), CR4 (CD11c/CD18), C3a receptor, C5a receptor, C1q receptors, complement receptor of the immunoglobulin superfamily (CRIg)

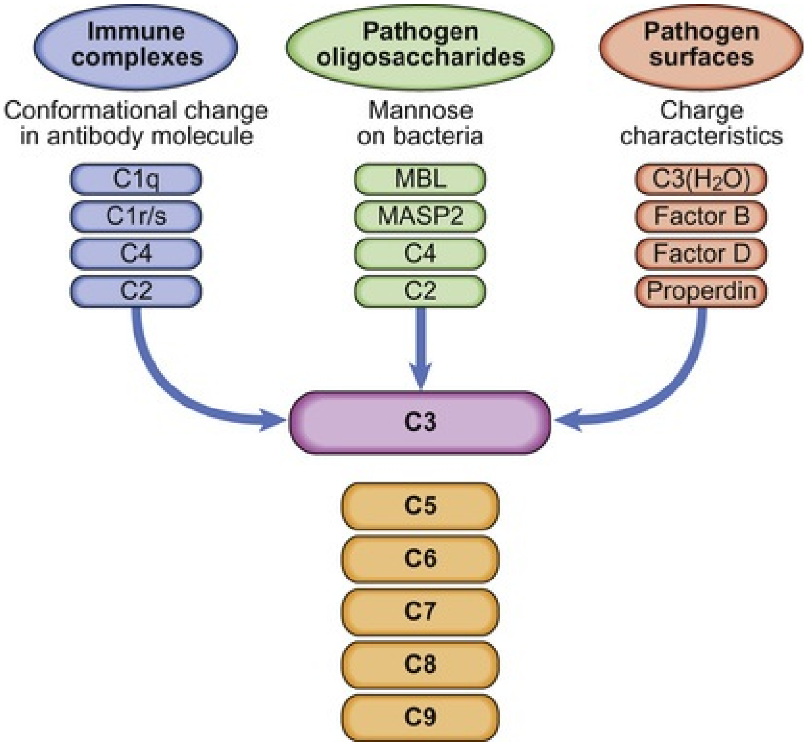
Immune complexes
Conformational change in antibody molecule
C1q
C1r/s
C4
C2
Pathogen oligosaccharides
Mannose on bacteria
MBL
MASP2
C4
C2
Pathogen surfaces
Charge characteristics
C3(H2O)
Factor B
Factor D
Properdin
C3
C5
C6
C7
C8
C9

FIG. 159.1 Activation of the complement cascade. The classical pathway is activated primarily by antibody, whereas the mannose-binding lectin and alternative pathways are activated directly by pathogens. In each case, the activation arm leads to cleavage of C3. (From Leung DYM, editor: *Pediatric allergy principles and practice* , ed 2, Philadelphia, 2010, Saunders, p 121.)

After C1423, complement nomenclature is logical and consists of only a few rules. Fragments of components resulting from cleavage by other components acting as enzymes are assigned lowercase letters (a, b, c, d, e); with the exception of C2 fragments, the smaller piece that is released into surrounding fluids is assigned the lowercase letter a, and the major part of the molecule, bound to other components or to some part of the immune complex, is assigned letter b, such as C3a and C3b. Components of the alternative pathway, B and D, have been assigned uppercase letters, as have the control proteins I and H, which downregulate both pathways. **C3** , and especially its major fragment **C3b** , is a component of both classical and alternative pathways.

Complement is a system of interacting proteins. The biologic functions of the system depend on the interactions of individual components, which occur in sequential, cascade fashion. Activation of each component, except the 1st, depends on activation of the prior component or components in the sequence. Interaction occurs along the 3 pathways (Fig. 159.2): the **classical pathway** , in the order antigen–antibody–C142356789; the **lectin** (carbohydrate-binding) **pathway** , in the order microbial carbohydrate–lectin (mannose-binding lectin

[MBL] or ficolin)–MBL-associated serine protease–C42356789; and the **alternative pathway,** in the order activator–C3bBD–C356789. Antibody accelerates the rate of activation of the alternative pathway, but activation can occur on appropriate surfaces in the absence of antibody. The classical and the alternative pathways interact with each other through the ability of both to activate C3.

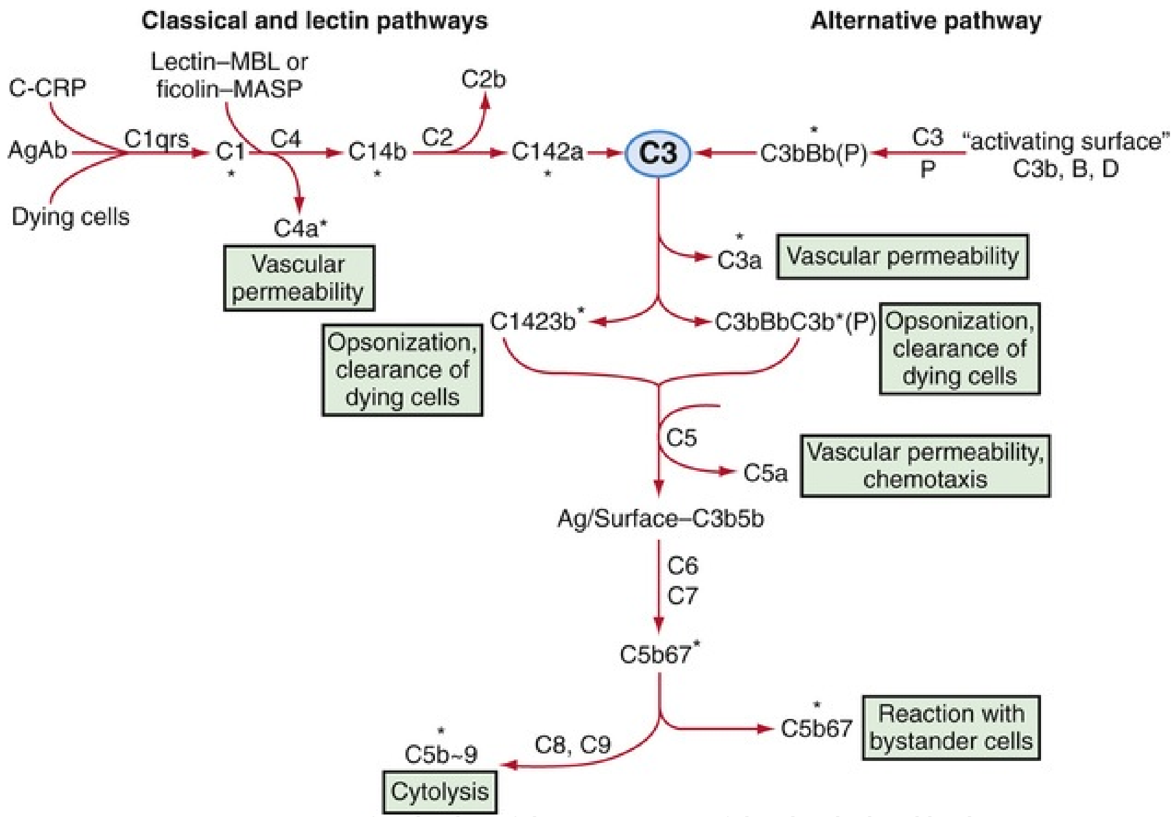
Classical and lectin pathways
Alternative pathway
C-CRP
Lectin–MBL or ficolin–MASP
AgAb
Dying cells
C1qrs
C1*
C4
C14b*
C2
C2b
C142a*
C4a*
Vascular permeability
C3
C3bBb(P)*
C3
P
"activating surface"
C3b, B, D
C3a*
Vascular permeability
C1423b*
C3bBbC3b*(P)
Opsonization, clearance of dying cells
Opsonization, clearance of dying cells
C5
C5a
Vascular permeability, chemotaxis
Ag/Surface–C3b5b
C6
C7
C5b67*
C8, C9
C5b~9*
Cytolysis
C5b67*
Reaction with bystander cells

FIG. 159.2 Sequence of activation of the components of the classical and lectin pathways of complement and interaction with the alternative pathway. MBL, Mannose-binding lectin; MASP, MBL-associated serine protease. Activation of C3 is the essential target. Functional activities generated during activation are enclosed in *boxes.* The multiple sites at which inhibitory regulator proteins *(not shown)* act are indicated by *asterisks,* emphasizing the delicate balance between action and control in this system that is essential for host defense yet capable of profound damage to host tissues. Ab, Antibody (immunoglobulin G or M class); Ag, antigen (bacterium, virus, tumor or tissue cell); B, D, I, P, factors B, D, I, and properdin; C-CRP, carbohydrate–carbohydrate-reactive protein; C4-bp, C4-binding protein; MBL, mannose-binding lectin; MASP, MBL-associated serine protease.

Activation of the early-acting components of complement (C1423) results in the generation of a series of active enzymes, C1, C42, and C423, on the surface of the immune complex or underlying cell. These enzymes cleave and activate the next component in the sequence. In contrast, the interaction among C5b, C6, C7, C8, and C9 is nonenzymatic and depends on changes in molecular configuration.

Classical and Lectin Pathways

The classical pathway sequence begins with fixation of C1, by way of C1q, to the Fc, non–antigen-binding part of the antibody molecule after antigen-antibody interaction. The C1 tricomplex changes configuration, and the C1s subcomponent becomes an active enzyme, “C1 esterase.” Certain bacteria, RNA viruses, and the lipid A component of bacterial endotoxin can activate C1q directly and trigger the full complement cascade.

As part of the **innate immune response** , broadly reactive “natural” antibodies and C-reactive protein, which reacts with carbohydrate from microorganisms and with dying cells, can substitute for specific antibody in the fixation of C1q and initiate reaction of the entire sequence. Endogenous agents, including uric acid crystals, amyloid deposits, DNA, and components of damaged cells such as apoptotic blebs and mitochondrial membranes, can activate C1q directly. In this case, however, the ligand-C1q complex interacts strongly with the inhibitors C4-binding protein and factor H, allowing some C3-mediated opsonization and phagocytosis but limiting the full inflammatory response typically triggered by microbes. C1q synthesized in the brain and retina fixes to superfluous synapses, which then can be cleared through C1q receptors on microglia, clearing the way for fresh synapses to populate the developing nervous system.

There are 4 recognition molecules in the lectin pathway: **mannose-binding lectin (MBL)** and **ficolins** 1, 2, and 3. MBL is the prototype of the collectin family of carbohydrate-binding proteins (**lectins**) that are believed to play an important part in innate, nonspecific immunity; its structure is homologous to that of C1q. These lectins, in association with **MBL-associated serine proteases** 1, 2, and 3 (**MASPs** 1, 2, 3), can bind to mannose, lipoteichoic acid, and other carbohydrates on the surface of bacteria, fungi, parasites, and viruses. There, MASPs then function like C1s to cleave C4 and C2 and activate the complement cascade. The peptide C4a has weak “anaphylatoxin” activity and reacts with mast cells to release the chemical mediators of immediate hypersensitivity, including histamine. C3a and C5a, released later in the sequence, are potent anaphylatoxins, and C5a is also an important chemotactic factor. Fixation of C4b to the complex permits it to adhere to neutrophils, macrophages, B cells, dendritic cells, and erythrocytes. MASP-2 can activate clotting by generating thrombin from prothrombin, which could prevent microbial spread.

Cleavage of C3 and generation of C3b is the next step in the sequence. The serum concentration of C3 is the highest of any component, and its activation is the most crucial step in terms of biologic activity. Cleavage of C3 can be achieved through the **C3 convertase** of the classical pathway, C142, or of the alternative pathway, C3bBb. Once C3b is fixed to a complex or dead or dying host cell, it can bind to cells with receptors for C3b (complement receptor 1 [**CR1**]), including B lymphocytes, erythrocytes, and phagocytic cells (neutrophils, monocytes, and macrophages). Efficient **phagocytosis** of most microorganisms, especially by neutrophils, requires binding of C3 to the microbe. The severe pyogenic infections that frequently occur in C3-deficient patients illustrate this point. The biologic activity of C3b is controlled by cleavage by **factor I** to iC3b, which promotes phagocytosis on binding to the **iC3b receptor (CR3)** on phagocytes. Further degradation of iC3b by factor I and proteases yields C3dg, then C3d; C3d binds to CR2 on B lymphocytes and thereby serves as a co-stimulator of antigen-induced B-cell activation.

Alternative Pathway

The alternative pathway can be activated by C3b generated through classical pathway activity or proteases from neutrophils or the clotting system. It can also be activated by a form of C3 created by low-grade, spontaneous reaction of native C3 with a molecule of water, a “tickover” that occurs constantly in plasma. Once formed, C3b or the hydrolyzed C3 can bind to any nearby cell or to factor B. **Factor B** attached to C3b in the plasma or on a surface can be cleaved to Bb by the circulating protease **factor D** . The complex C3bBb becomes an efficient C3 convertase, which generates more C3b through an amplification loop. **Properdin** can bind to C3bBb, increasing stability of the enzyme and protecting it from inactivation by **factors I and H** , which modulate the loop and the pathway.

Certain “activating surfaces” promote alternative pathway activation if C3b is fixed to them, including bacterial teichoic acid and endotoxin, virally infected cells, antigen–immunoglobulin A complexes, and cardiopulmonary bypass and renal dialysis membranes. These surfaces act by protecting the C3bBb enzyme from the control otherwise exercised by factors I and H. Rabbit red blood cell membrane is such a surface, which serves as the basis for an assay of serum alternative pathway activity. Conversely, sialic acid on the surface of microorganisms or cells prevents formation of an effective alternative pathway C3 convertase by promoting activity of factors I and H. In any event, significant activation of C3 can occur through the alternative pathway, and the resultant biologic activities are qualitatively the same as those achieved through activation by C142 (see Fig. 159.2).

Membrane Attack Complex

The sequence leading to cytolysis begins with the attachment of C5b to the C5-activating enzyme from the classical pathway, C4b2a3b, or from the alternative pathway, C3bBb3b. C6 is bound to C5b without being cleaved, stabilizing the activated C5b fragment. The C5b6 complex then dissociates from C423 and reacts with C7. C5b67 complexes must attach promptly to the membrane of the parent or a bystander cell, or they lose their activity. Next, C8 binds, and the C5b678 complex then promotes the addition of multiple C9 molecules. The C9 polymer of at least 3-6 molecules forms a transmembrane channel, and lysis ensues.

Control Mechanisms

Without control mechanisms acting at multiple points, there would be no effective complement system, and unbridled consumption of components would generate severe, potentially lethal damage to the host. At the 1st step, **C1 inhibitor (C1 INH)** inhibits C1r and C1s enzymatic activity, and thus the cleavage of C4 and C2. C1 INH also inhibits MASP-2, factors XIa and XIIa of the clotting system, and kallikrein of the contact system. Activated C2 has a short half-life, and this relative instability limits the effective life of C42 and C423. The alternative pathway enzyme that activates C3, C3bBb, also has a short half-life, although it can be prolonged by the binding of properdin (P) to the enzyme complex. P can also bind directly to microbes and promote assembly of the alternative pathway C3 convertase.

Serum contains the enzyme carboxypeptidase N, which cleaves the N-terminus arginine from C4a, C3a, and C5a, thereby limiting their biologic activity. Factor I inactivates C4b and C3b; factor H accelerates inactivation of C3b by factor I; and an analogous factor, C4-binding protein (**C4-bp**), accelerates C4b cleavage by factor I, thus limiting assembly of the C3 convertase. Three protein constituents of cell membranes—**CR1** , membrane cofactor protein (**MCP**), and decay-accelerating factor (**DAF**)—promote the disruption of C3 and C5 convertases assembled on those membranes. Another cell membrane–associated protein, **CD59** , can bind C8 or both C8 and C9 and thereby interfere with insertion of the membrane attack complex (C5b6789). The serum proteins **vitronectin** and **clusterin** can inhibit attachment of the C5b67 complex to cell membranes, bind C8 or C9 in a full membrane attack complex, or otherwise interfere with the formation or insertion of this complex. Vitronectin also promotes macrophage uptake of dying neutrophils. The genes for the regulatory proteins factor H, C4-bp, MCP, DAF, CR1, and CR2 are clustered on chromosome 1.

Participation in Host Defense

Neutralization of virus by antibody can be enhanced with C1 and C4 and further enhanced by the additional fixation of C3b through the classical or alternative pathway. Complement may therefore be particularly important in the early phases of a viral infection when antibody is limited. Antibody and the full complement sequence can also eliminate infectivity of at least some viruses by the production of typical complement “holes,” as seen by electron microscopy. Fixation of C1q can opsonize (promote phagocytosis) through binding to the phagocyte C1q receptor.

C4a, C3a, and C5a can bind to mast cells and thereby trigger release of histamine and other mediators, leading to vasodilation and the swelling and redness of inflammation. C5a can enhance macrophage phagocytosis of C3b-opsonized particles and induce macrophages to release the cytokines tumor necrosis factor and interleukin-1. C5a is a major chemotactic factor for neutrophils, monocytes, and eosinophils, which can efficiently phagocytize microorganisms opsonized with C3b or cleaved C3b (iC3b). Further inactivation of cell-bound C3b by cleavage to C3d and C3dg removes its opsonizing activity, but it can still bind to B cells. Fixation of C3b to a target cell can enhance its lysis by natural killer cells or macrophages.

Insoluble immune complexes can be solubilized if they bind C3b, apparently because C3b disrupts the orderly antigen-antibody lattice. Binding C3b to a complex also allows it to adhere to C3 receptors (CR1) on red blood cells, which then transport the complexes to hepatic and splenic macrophages for removal.

This phenomenon may at least partially explain the immune complex disease found in patients who lack C1, C4, C2, or C3.

The complement system serves to link the innate and adaptive immune systems. C4b or C3b coupled to immune complexes promotes their binding to antigen-presenting macrophages, dendritic cells, and B cells. Coupling of antigen to C3d allows binding to CR2 on B cells, which greatly reduces the amount of antigen needed to trigger an antibody response.

Neutralization of endotoxin in vitro and protection from its lethal effects in experimental animals require C1 INH and later-acting components of complement, at least through C6. Finally, activation of the entire complement sequence can result in lysis of virus-infected cells, tumor cells, and most types of microorganisms. Bactericidal activity of complement has not appeared to be important to host defense, except for the occurrence of *Neisseria* infections in patients lacking later-acting components of complement (see Chapter 160).

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CHAPTER 160

Disorders of the Complement System

160.1

Evaluation of the Complement System

Richard B. Johnston Jr.

Keywords

hereditary angioedema
total hemolytic complement activity
CH_{50}
alternative pathway activity
AP_{50}

Testing for **total hemolytic complement activity (CH_{50})** effectively screens for most of the common diseases of the complement system. A normal result in this assay depends on the ability of all 11 components of the classical pathway and membrane attack complex to interact and lyse antibody-coated sheep erythrocytes. The dilution of serum that lyses 50% of the cells determines the end-point. In **congenital deficiencies** of C1 through C8, the CH_{50} value is 0 or close to 0; in C9 deficiency the value is approximately half-normal. Values in the acquired deficiencies vary with the type and severity of the underlying disorder.

This assay does not detect deficiency of mannose-binding lectin (MBL), factor D or B of the alternative pathway, or properdin (Fig. 160.1). Deficiency of factor I or H permits persistence of the classical and alternative pathway convertase and thus consumption of C3, with reduction in the CH_{50} value. When clotted blood or serum sits at room temperature or warms, CH_{50} activity begins to decline, leading to values that are falsely low but not zero. It is important to separate the serum and freeze it at −70°C (−94°F) by no more than 1 hr after blood draw.

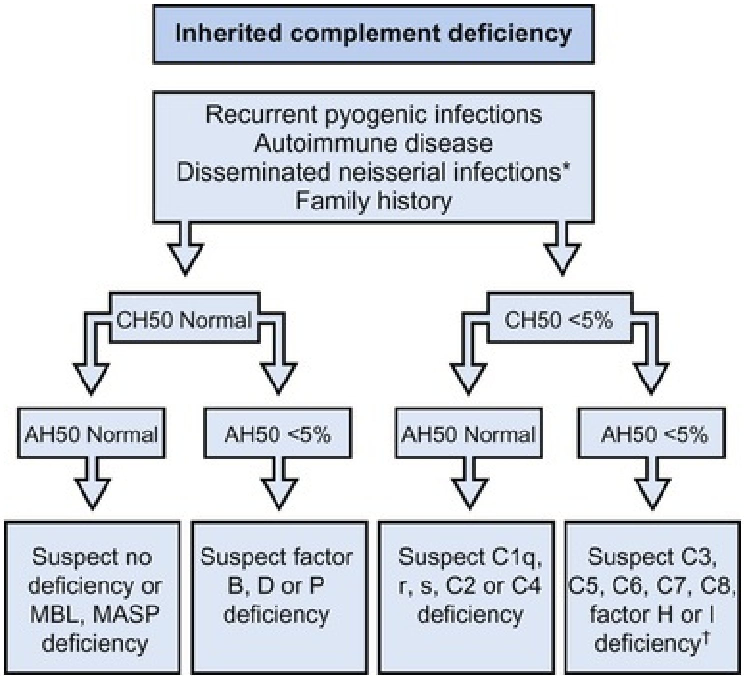
Inherited complement deficiency
Recurrent pyogenic infections
Autoimmune disease
Disseminated neisserial infections*
Family history
CH50 Normal
CH50 <5%
AH50 Normal
AH50 <5%
AH50 Normal
AH50 <5%
Suspect no deficiency or MBL, MASP deficiency
Suspect factor B, D or P deficiency
Suspect C1q, r, s, C2 or C4 deficiency
Suspect C3, C5, C6, C7, C8, factor H or I deficiency†

FIG. 160.1 **Flow chart for the evaluation of inherited complement deficiencies using hemolytic screening assays for the classical (CH50) and alternative pathways (AH50). For each assay, the entire activation pathway, including the membrane attack complex, is required for lysis. MASP, MBL-associated serine protease; MBL, mannose-binding lectin. *Gonococcal and meningococcal. † C9 deficiency may have up to 30% normal CH50 with low AH50. (Adapted from Rich RR, Fleisher TA, Shearer WT, et al, editors: *Clinical immunology: principles and practice* , ed 4, Philadelphia, 2012, Saunders, p 262.)**

In **hereditary angioedema** , depression of C4 and C2 during an attack significantly reduces the CH_{50} . Typically, C4 is low and C3 normal or slightly decreased. Concentrations of C1 inhibitor protein will be normal in 15% of cases; but C1 acts as an esterase, and the diagnosis can be established by showing increased capacity of the patient's sera to hydrolyze synthetic esters.

A decrease in serum concentration of both C4 and C3 suggests activation of the *classical pathway* by immune complexes. Decreased C3 and normal C4 levels suggest activation of the *alternative pathway.* This difference is particularly useful in distinguishing nephritis secondary to immune complex deposition from that caused by **NeF** (nephritic factor). In the latter condition and in deficiency of factor I or H, factor B is consumed and C3 serum concentration is low. Alternative pathway activity can be measured with a relatively simple and reproducible hemolytic assay that depends on the capacity of rabbit erythrocytes to serve as both an activating (permissive) surface and a target of alternative pathway activity. This assay, **AP_{50}** , detects deficiency of properdin, factor D, and factor B. Immunochemical methods can be used to quantify individual components and split products of all 3 pathways, guided by results of the screening hemolytic assays.

A defect of complement function should be considered in any patient with recurrent angioedema, autoimmune disease (especially SLE), chronic nephritis, hemolytic-uremic syndrome, or partial lipodystrophy, or with recurrent pyogenic infections, disseminated meningococcal or gonococcal infection, or a 2nd episode of bacteremia at any age. A previously well adolescent or young adult with meningococcal meningitis caused by an uncommon serotype (not A, B, or C) should undergo screening for a late-component or alternative pathway deficiency with CH_{50} and AP_{50} assays.

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160.2

Genetic Deficiencies of Complement Components

Richard B. Johnston Jr.

Keywords

complement component deficiencies
C1q deficiency
C3 deficiency
MBL deficiency
complement deficiency and meningitis

Congenital deficiencies of all 11 components of the classical–membrane attack pathway and of factors D and B and properdin of the alternative pathway are described in Table 160.1 . All components of the classical and alternative pathways except properdin and factor B are inherited as autosomal recessive co-dominant traits. Each parent transmits a gene that codes for synthesis of half the serum level of the component. Deficiency results from inheritance of 1 null gene from each parent; the hemizygous parents typically have low normal CH_{50} levels and no consequences of the partial deficiency. Properdin deficiency is transmitted as an X-linked trait. Factor B is an autosomal recessive non–co-dominant trait.

Table 160.1

Complement Defects

DISEASE	GENETIC DEFECT/PRESUMED PATHOGENESIS	INHERITANCE	FUNCTIONAL DEFECT	ASSOCIATED FEATURES
C1q deficiency	Mutation in *C1QA* , *C1QB* , *C1QC:* classical complement pathway	AR	Absent CH_{50} hemolytic activity; defective activation of the classical pathway,	SLE, infections with encapsulated organisms

	components		diminished clearance of apoptotic cells	
C1r deficiency	Mutation in *C1R:* classical complement pathway component	AR	Absent CH$_{50}$ hemolytic activity; defective activation of the classical pathway	SLE, infections with encapsulated organisms
C1s deficiency	Mutation in *C1S:* classical complement pathway component	AR	Absent CH$_{50}$ hemolytic activity; defective activation of the classical pathway	SLE, infections with encapsulated organisms
C4 deficiency	Mutation in *C4A* , *C4B:* classical complement pathway components	AR	Absent CH$_{50}$ hemolytic activity; defective activation of the classical pathway, defective humoral immune response to carbohydrate antigens in some patients	SLE, infections with encapsulated organisms
C2 deficiency	Mutation in *C2:* classical complement partway component	AR	Absent CH$_{50}$ hemolytic activity; defective activation of the classical pathway	SLE, infections with encapsulated organisms, atherosclerosis
C3 deficiency	Mutation in *C3:* central complement component	AR, gain-of-function AD	Absent CH$_{50}$ and AH$_{50}$ hemolytic activity; defective opsonization, defective humoral immune response	Infections; glomerulonephritis, aHUS with gain-of-function mutations
C5 deficiency	Mutation in *C5:* terminal complement component	AR	Absent CH$_{50}$ and AH$_{50}$ hemolytic activity; defective bactericidal activity	Neisserial infections
C6 deficiency	Mutation in *C6:* terminal complement component	AR	Absent CH$_{50}$ and AH$_{50}$ hemolytic activity; defective bactericidal activity	Neisserial infections
C7 deficiency	Mutation in *C7:* terminal complement component	AR	Absent CH$_{50}$ and AH$_{50}$ hemolytic activity; defective bactericidal activity	Neisserial infections
C8 α-γ deficiency	Mutation in *C8A, C8G:* terminal complement components	AR	Absent CH$_{50}$ and AH$_{50}$ hemolytic activity; defective bactericidal activity	Neisserial infections
C8b deficiency	Mutation in *C8B:* terminal complement component	AR	Absent CH$_{50}$ and AH$_{50}$ hemolytic activity. defective bactericidal activity	Neisserial infections
C9 deficiency	Mutation in *C9:* terminal complement component	AR	Reduced CH$_{50}$ and AH$_{50}$ hemolytic activity; deficient bactericidal activity	Mild susceptibility to neisserial infections
C1 inhibitor deficiency	Mutation in *C1NH:* regulation of kinins and complement activation	AD	Spontaneous activation of the complement pathway with consumption of C4/C2; spontaneous activation of the contact system with generation of bradykinin from high-molecular-weight kininogen	Hereditary angioedema
Factor B	Mutation in *CFB:* activation of the alternative pathway	AD	Gain-of-function mutation with increased spontaneous AH$_{50}$	aHUS
Factor D deficiency	Mutation in *CFD:* regulation of the alternative complement pathway	AR	Absent AH$_{50}$ hemolytic activity	Neisserial infections

Properdin deficiency	Mutation in *CFP:* regulation of the alternative complement pathway	XL	Absent AH_{50} hemolytic activity	Neisserial infections
Factor I deficiency	Mutation in *CFI:* regulation of the alternative complement pathway	AR	Spontaneous activation of the alternative complement pathway with consumption of C3	Infections, neisserial infections, aHUS, preeclampsia, membranoproliferative glomerulonephritis
Factor H deficiency	Mutation in *CFH:* regulation of the alternative complement pathway	AR	Spontaneous activation of the alternative complement pathway with consumption of C3	Infections, neisserial infections, aHUS, preeclampsia, membranoproliferative glomerulonephritis
MASP-1 deficiency	Mutation in *MASP1:* cleaves C2 and activates MASP-2	AR	Deficient activation of the lectin activation pathway, cell migration	Infections, 3MC syndrome

AD, Autosomal dominant; aHUS, atypical hemolytic-uremic syndrome; AR, autosomal recessive; SLE, systemic lupus erythematosus; XL, X-linked; 3MC, previously Carnevale, Mingarelli, Malpuech, and Michels syndromes.

From Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis,* Philadelphia, 2018, Elsevier, Table 41.11, p 765.

Most patients with primary **C1q deficiency** have systemic lupus erythematosus (SLE); some have an SLE-like syndrome without typical SLE serology, a chronic rash with underlying vasculitis, or membranoproliferative glomerulonephritis (MPGN). Some C1q-deficient children have serious infections, including septicemia and meningitis. Individuals with **C1r, C1s, combined C1r/C1s, C4, C2,** or **C3 deficiency** also have a high incidence of autoimmune syndromes (see Table 160.1), especially SLE or an SLE-like syndrome, without an elevated antinuclear antibody level.

C4 is encoded by 2 genes, *C4A* and *C4B* . **C4 deficiency** represents absence of both gene products. Complete deficiency of only C4A, present in approximately 1% of the population, also predisposes to SLE, although C4 levels are only partially reduced. Patients with only C4B deficiency may be predisposed to infection. A few patients with **C5, C6, C7,** or **C8 deficiency** have SLE, but recurrent meningococcal infections are much more likely to be the major problem.

There are at least 2 possible reasons for the concurrence of complement component deficiencies, especially C1, C4, C2, or C3 deficiency, and autoimmune–immune complex diseases. First, deposition of C3 on autoimmune complexes facilitates their removal from the circulation through binding to complement receptor 1 (CR1) on erythrocytes and transport to the spleen and liver. Second, the early components, particularly C1q and C3, expedite the clearance of necrotic and apoptotic cells, which are sources of autoantigens.

Individuals with **C2 deficiency** carry the risk of life-threatening septicemic illnesses, usually caused by pneumococci. However, most have not had problems with other increased susceptibility to infection, presumably because of the protective function of the alternative pathway, particularly if enhanced by pneumococcal and *Haemophilus influenzae* immunization. The genes for C2, factor B, and C4 are situated close to each other on chromosome 6, and a partial depression of factor B levels can occur in conjunction with C2 deficiency. Persons with a deficiency of both proteins may be at particular risk. One percent of European Caucasians carry 1 null gene for C2.

Because C3 can be activated by C142 or by the alternative pathway, a defect in the function of either pathway can be compensated for, at least to some extent. Without C3, however, opsonization of bacteria is inefficient, and the chemotactic fragment from C5 (C5a) is not generated. Some organisms must be well opsonized in order to be cleared, and genetic **C3 deficiency** has been associated with recurrent, severe pyogenic infections caused by pneumococci, *H. influenzae* , and meningococci.

More than half the individuals reported to have congenital **C5, C6, C7,** or **C8 deficiency** have had meningococcal meningitis or extragenital gonococcal infection. **C9 deficiency** is most often reported in individuals of Japanese or Korean descent. C9-deficient individuals retain about one-third normal CH_{50} titers; some have had *Neisseria* disease. In studies of patients ≥10 yr old with systemic meningococcal disease, 3–15% have had a genetic deficiency of C5, C6, C7, C8, C9, or properdin. Among patients with infections caused by the uncommon *Neisseria meningitidis* serogroups (X, Y, Z, W135, 29E, or nongroupable; but not A, B, or C), 33–45% have an underlying complement deficiency. It is not clear why patients with a deficiency of one of the late-acting components have a particular predisposition to *Neisseria* infections. It may be that serum bacteriolysis is uniquely important in defense against this organism. Many persons with such a deficiency have no significant illness.

A few individuals have been identified with **deficiency of factor D or Factor B** of the alternative pathway, all with recurrent infections, most often neisserial or pneumococcal. Hemolytic complement activity and C3 levels in their serum were normal, but alternative pathway activity was markedly deficient or absent.

Mutations in the structural gene encoding MBL or polymorphisms in the promoter region of the gene result in pronounced interindividual variation in the level of circulating MBL. More than 90% of individuals with **MBL deficiency** do not express a predisposition to infection. Those with a very low level of MBL have a predisposition to recurrent respiratory infections in infancy and to serious pyogenic and fungal infections if there is another underlying defect of host defense. MBL-associated serine protease (**MASP)-2 deficiency** has been reported with SLE-like symptoms and recurrent pneumococcal pneumonia. Homozygous **ficolin-3 deficiency** has been associated with repeated pneumonia since early childhood, cerebral abscesses, and bronchiectasis.

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160.3

Deficiencies of Plasma, Membrane, or Serosal Complement Control Proteins

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Richard B. Johnston Jr.

Keywords

atypical hemolytic-uremic syndrome
properdin deficiency
hereditary angioedema
paroxysmal nocturnal hemoglobinuria
factor I deficiency

Congenital deficiencies of 5 plasma complement control proteins have been described (see Table 160.1). **Factor I deficiency** was reported originally as a deficiency of C3 resulting from hypercatabolism. The 1st patient described had suffered a series of severe pyogenic infections similar to those associated with agammaglobulinemia or congenital deficiency of C3. Factor I is an essential regulator of both pathways. Its deficiency permits prolonged existence of C3b as a part of the C3 convertase of the alternative pathway, C3bBb. This results in constant activation of the alternative pathway and cleavage of more C3 to C3b, in circular fashion. Intravenous infusion of plasma or purified factor I induced a prompt rise in serum C3 concentration in the patient and a return to normal of C3-dependent functions in vitro, such as opsonization.

The effects of **factor H deficiency** are similar to those of factor I deficiency because factor H also assists in dismantling the alternative pathway C3 convertase. A trigger event such as infection initiates uninhibited continuous activation of the alternative pathway, which consumes C3, factor B, total hemolytic activity, and alternative pathway activity. Patients have sustained systemic infections due to pyogenic bacteria, particularly *Neisseria meningitidis*. Many have had glomerulonephritis or **atypical hemolytic-uremic syndrome** (aHUS) (see Chapter 538.5). Mutations in genes encoding membrane cofactor protein (MCP, CD46), factors I or B, C3, or the endothelial antiinflammatory protein thrombomodulin, or autoantibodies to factors H or B, are also associated with aHUS. The majority of patients with factor H deficiency and aHUS, typically <2 yr old, develop end-stage renal disease, and many die.

The few patients thus far reported as having **C4-binding protein deficiency** have approximately 25% of the normal levels of the protein and no typical disease presentation, although one patient had angioedema and Behçet disease.

Persons with **properdin deficiency** have a striking predisposition to *N. meningitidis* meningitis. All reported patients have been male. The predisposition to infection in these patients demonstrates clearly the need for the alternative pathway in defense against bacterial infection. Serum hemolytic complement activity is normal in these patients, and if the patient has specific antibacterial antibody from immunization or prior exposure, the need for the alternative pathway and properdin is greatly reduced. Several patients have had dermal vasculitis or discoid lupus.

Hereditary angioedema occurs in persons unable to synthesize normal levels of functional C1 inhibitor (C1 INH). In 85% of affected families, the patient has markedly reduced concentrations of inhibitor, averaging 30% of normal; the other 15% have normal or elevated concentrations of an immunologically cross-reacting but nonfunctional protein. Both forms of the disease are transmitted as autosomal dominant traits. C1 INH suppresses the complement proteases C1rs and MASP-2 and the activated proteases of the contact and fibrinolysis systems. In the absence of full C1 INH function, activation of any of these proteases tips the balance toward the protease. This activation leads to uncontrolled C1 and kallikrein activity with breakdown of C4 and C2 and release of bradykinin, which interacts with vascular endothelial cells to cause vasodilation, producing localized, nonpitting edema. The biochemical triggers that induce attacks of angioedema in these patients are not well understood.

Swelling of the affected part progresses rapidly, without urticaria, itching, discoloration, or redness and often without severe pain. Swelling of the intestinal wall, however, can lead to intense abdominal cramping, sometimes with vomiting or diarrhea. Concomitant subcutaneous edema is often absent, and patients have undergone abdominal surgery or psychiatric examination before the true diagnosis was established. Laryngeal edema can be fatal. Attacks last 2-3 days and then gradually abate. They may occur at sites of trauma, especially dental, after vigorous exercise, or with menses, fever, or emotional stress. Attacks begin in the 1st 5 yr of life in almost half of patients, but are usually not severe until late childhood or adolescence. **Acquired C1 INH deficiency** can occur in association with B-cell cancer or autoantibody to C1 INH. SLE and glomerulonephritis have been reported in patients with the congenital disease (for treatment see Chapter 160.5).

Three of the membrane complement control proteins—CR1, MCP (CD46), and decay-accelerating factor (DAF)—prevent the formation of the full C3-cleaving enzyme, C3bBb, which is triggered by C3b deposition. CD59 (membrane inhibitor of reactive lysis) prevents the full development of the membrane attack complex that creates the "hole." **Paroxysmal nocturnal hemoglobinuria** (PNH) is a hemolytic anemia that occurs when DAF and CD59 are not expressed on the erythrocyte surface. The condition is acquired as a somatic mutation in a hematopoietic stem cell of the *PIGA* gene on the X chromosome. The product of this gene is required for normal synthesis of a glycosyl-phosphatidylinositol molecule that anchors about 20 proteins to cell membranes, including DAF and CD59. One patient with **genetic isolated CD59 deficiency** had a mild PNH-like disease despite normal expression of membrane DAF. In contrast, **genetic isolated DAF deficiency** has not resulted in hemolytic anemia (for treatment see Chapter 160.5).

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160.4

Secondary Disorders of Complement

Richard B. Johnston Jr.

Keywords

immune complex disease
systemic lupus erythematosus
SLE
nephritic factor

Partial deficiency of C1q has occurred in patients with severe combined immunodeficiency disease or hypogammaglobulinemia, apparently secondary to the deficiency of IgG, which normally binds reversibly to C1q and prevents its rapid catabolism.

Chronic membranoproliferative glomerulonephritis can be caused by nephritic factor (NeF), an IgG autoantibody to the C3-cleaving enzyme of the classical pathway (C4b2a) or alternative pathway (C3bBb). NeF protects the enzyme from inactivation and promotes consumption of C3 and decreased concentration of serum C3. Pyogenic infections, including meningitis, may occur if the serum C3 level drops to <10% of normal. This disorder has been found in children and adults with dense-deposit disease or partial lipodystrophy. Adipocytes are the main source of factor D and synthesize C3 and factor B; exposure to NeF induces their lysis. The IgG NeF that inhibits the classical pathway C3 convertase has been described in acute postinfectious nephritis and in SLE. The consumption of C3 that characterizes poststreptococcal nephritis and SLE could be caused by this factor, by immune complex activation, or by both.

Newborn infants have mild to moderate reductions in all plasma components of the complement system. Opsonization and generation of chemotactic activity in serum from full-term newborns can be markedly deficient through either the classical or the alternative pathway. Complement activity is even lower in preterm infants. Patients with severe chronic cirrhosis of the liver, hepatic failure, malnutrition, or anorexia nervosa can have significant deficiency of complement components and functional activity. Synthesis of components is depressed in these conditions, and serum from some patients with malnutrition also contains immune complexes that could accelerate depletion.

Patients with **sickle cell disease** have normal activity of the classical pathway, but some have defective function of the alternative pathway in opsonization of pneumococci, in bacteriolysis and opsonization of *Salmonella,* and in lysis of rabbit erythrocytes. Deoxygenation of erythrocytes from patients with sickle cell disease alters their membranes to increase exposure of phospholipids that can activate the alternative pathway and consume its components. This activation is accentuated during painful crisis. Children with **nephrotic syndrome** may have decreased serum levels of factors B and D and subnormal serum opsonizing activity.

Immune complexes initiated by microorganisms or their by-products can induce complement consumption. Activation occurs primarily through fixation of C1 and initiation of the classical pathway. Formation of immune complexes and consumption of complement have been demonstrated in lepromatous leprosy, bacterial endocarditis, infected ventriculojugular shunts, malaria, infectious mononucleosis, dengue hemorrhagic fever, and acute hepatitis B. Nephritis or arthritis can develop as a result of deposition of immune complexes and activation of complement in these infections. In SLE, immune complexes activate C142, and C3 is deposited at sites of tissue damage, including kidneys and skin; depressed synthesis of C3 is also noted. The syndrome of recurrent urticaria, angioedema, eosinophilia, and hypocomplementemia secondary to activation of the classical pathway may be caused by autoantibody to C1q and circulating immune complexes. Circulating immune complexes and decreased C3 have been reported in some patients with dermatitis herpetiformis, celiac disease, primary biliary cirrhosis, and Reye syndrome.

Circulating bacterial products in **sepsis** or tissue factors released after severe **trauma** can initiate activation of the classical and alternative pathways, leading to increased serum levels of C3a, C5a, and C5b-9 and systemic inflammatory response syndrome (SIRS) and multi-organ failure. C5a and its receptors, particularly on neutrophils, appear to be central to the pathogenesis of SIRS. Intravenous injection of iodinated roentgenographic contrast medium can trigger a rapid and significant activation of the alternative pathway, which may explain the occasional reactions that occur in patients undergoing this procedure.

Burns can induce massive activation of the complement system, especially the alternative pathway, within a few hours after injury. Resulting generation of C3a and C5a stimulates neutrophils and induces their sequestration in the lungs, leading to shock lung. Cardiopulmonary bypass, extracorporeal membrane oxygenation, plasma exchange, or hemodialysis using **cellophane membranes** may be associated with a similar syndrome as a result of activation of plasma complement, with release of C3a and C5a. In patients with **erythropoietic protoporphyria** or **porphyria cutanea tarda** , exposure of the skin to light of certain wavelengths activates complement, generating chemotactic activity. This chemotactic activity leads to lysis of capillary endothelial cells, mast cell degranulation, and the appearance of neutrophils in the dermis.

Some tumor cells can avoid complement-mediated lysis by overexpressing DAF, MCP, CD59, CR1, or factor H, or by secreting proteases that cleave tumor-bound C3b. Microorganisms have evolved similar evasive mechanisms; for example, HIV-1 particles budding from infected cells acquire the membrane proteins DAF and CD59, and staphylococci can produce multiple complement inhibitors.

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160.5

Treatment of Complement Disorders

Richard B. Johnston Jr.

Keywords

C1-esterase inhibitor
immunization
complement deficiency

No specific therapy is available at present for genetic deficiencies of the components of the classical, alternative, and lectin complement pathways. Much can be done, however, to protect patients with any of these disorders from serious complications; and specific treatment is available for 3 disorders caused by control-protein deficiencies: hereditary angioedema, aHUS, and PNH.

Management of **hereditary angioedema** starts with avoidance of precipitating factors, usually trauma. Infusion of C1 INH concentrate (nanofiltered **C1-esterase inhibitor**) was approved by the U.S. Food and Drug Administration (FDA) for use in children in 2016. An inhibitor of kallikrein (**ecallantide**) that blocks bradykinin production and an antagonist of the bradykinin receptor (**icatibant**) are approved in the United States for use in adolescents and adults for long-term prophylaxis, preparation for surgery or dental procedures, or treatment of acute attacks. The synthetic androgen **oxandrolone** increases the level of functional C1 INH several-fold and is approved for cautious use in children. Antihistamines, epinephrine, and corticosteroids have no effect.

Lanadelumab, a selective inhibitor of kallikein, has potential as a prophylactic agent. **Eculizumab** , a humanized monoclonal antibody to C5, prevents generation of the membrane-attack complex C5b9 and is an effective treatment for **PNH** and **aHUS** .

Effective supportive management is available for other primary diseases of the complement system, and identification of a specific defect in the complement system can have an important impact on management. Concern for the associated complications, such as autoimmune disease and infection, should encourage vigorous diagnostic efforts and earlier institution of therapy. Individuals with SLE and a complement defect generally respond as well to therapy as do those without complement deficiency. With the onset of unexplained fever, cultures should be obtained and antibiotic therapy instituted more quickly and with less stringent indications than in a normal child.

The parent or patient should be given letters describing any predisposition to systemic bacterial infection or autoimmune disease associated with the patient's deficiency, along with the recommended initial approach to management, for possible use by school, camp, or emergency department physicians. The patient and close household contacts should be immunized against *H. influenzae, Streptococcus pneumoniae,* and *N. meningitidis.* High titers of specific antibody might opsonize effectively without the full complement system, and immunization of household members could reduce the risk of exposing patients to these particularly threatening pathogens. *Repeat immunization of patients is advisable since complement deficiency can be associated with a blunted or shorter-lived antibody response than normal.*

Heparin , which inhibits both classical and alternative pathways, has been used to prevent “postpump syndrome.”

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SECTION 5

Hematopoietic Stem Cell Transplantation

OUTLINE

Chapter 161 Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation

Chapter 162 Hematopoietic Stem Cell Transplantation From Alternative Sources and Donors

Chapter 163 Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease

Chapter 164 Infectious Complications of Hematopoietic Stem Cell Transplantation

Chapter 165 Late Effects of Hematopoietic Stem Cell Transplantation

CHAPTER 161

Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation

Rachel A. Phelan, David Margolis

Allogeneic (from a donor) or **autologous** (from the same individual) hematopoietic stem cells have been used to cure both malignant and nonmalignant disorders. **Autologous** transplantation is employed as a rescue strategy after delivering otherwise lethal doses of chemotherapy with or without radiotherapy in children with hematologic malignancies such as relapsed lymphoma or selected solid tumors (e.g., neuroblastoma, brain tumors). **Allogeneic** transplantation is used to treat children with genetic diseases of blood cells, such as hemoglobinopathies, primary immunodeficiency diseases, various inherited metabolic diseases, and bone marrow failure. Allogeneic transplant is also used as treatment for hematologic malignancies, such as leukemia and myelodysplastic syndromes. Bone marrow had represented the only source of hematopoietic progenitors employed. Growth factor (granulocyte colony-stimulating factor)–mobilized peripheral blood hematopoietic stem cells and umbilical cord blood hematopoietic progenitors have now also been regularly used in clinical practice to perform hematopoietic stem cell transplantation (**HSCT**).

An HLA-matched sibling was once the only type of donor employed. Currently, matched unrelated volunteers, full-haplotype mismatched family members, and unrelated cord blood donors have been largely employed to transplant patients lacking an HLA-identical relative.

Protocols for allogeneic HSCT consist of 2 parts: the preparative regimen and transplantation itself. During the **preparative conditioning regimen** , chemotherapy, at times associated with irradiation, is administered to destroy the patient's hematopoietic system and to suppress the immune system, especially T cells, so that graft rejection is prevented. In patients with malignancies, the preparative regimen also serves to significantly reduce the tumor burden. The patient then receives an intravenous infusion of hematopoietic cells from the donor. Less aggressive conditioning regimens, known as **reduced-intensity conditioning regimens** , are also used in pediatric patients. These regimens are mainly immunosuppressive and aim at inducing a state of reduced immune competence of the recipient to avoid the rejection of donor cells.

The immunology of HSCT is distinct from that of other types of transplant because, in addition to stem cells, the graft contains mature blood cells of donor origin, including T cells, B cells, natural killer cells, and dendritic cells. These cells repopulate the recipient's lymphohematopoietic system and give rise to a new immune system, which helps eliminate residual leukemia cells that survive the conditioning regimen. This effect is known as the **graft-versus-leukemia (GVL) effect.**

The donor immune system exerts its T-cell–mediated GVL effect through alloreactions directed against histocompatibility antigens displayed on recipient leukemia cells. Because some of these histocompatibility antigens are also displayed on tissues, however, unwanted T-cell–mediated alloreactions may ensue. Specifically, donor alloreactive cytotoxic $CD8^+$ effector T cells may attack recipient tissues, particularly the skin, gastrointestinal (GI) tract, and liver, causing acute **graft-versus-host disease (GVHD)** , a condition of varying severity that in some cases can be life threatening or even fatal (see Chapter 163).

The success of allogeneic HSCT is undermined by diversity between donors and recipients in major and minor histocompatibility antigens. The **human leukocyte antigens (HLA)** , including HLA-A, HLA-B, and HLA-C major histocompatibility complex (MHC) class I molecules, present peptides to $CD8^+$ T cells, whereas the HLA-DR, HLA-DQ, and HLA-DP MHC class II molecules present peptides to $CD4^+$ T cells. There are 100s of variant forms of each class I and class II molecule, and even small differences can elicit alloreactive T-cell responses that mediate graft rejection and/or GVHD. Disparities for HLA-A, -B, -C, or -DRB1 alleles in the donor-recipient pair are independent risk factors for both acute and chronic GVHD. There is also increasing evidence that HLA-DQ and HLA-DP may play a role, prompting some transplant centers to also explore matching at these alleles.

Minor histocompatibility antigens derive from differences between the HLA-matched recipient and donor in peptides that are presented by the same HLA allotype. These antigens result from polymorphisms of non-HLA proteins, differences in the level of expression of proteins, or genetic differences between males and females. An example of the latter is represented by the H-Y antigens encoded by the Y chromosome, which can stimulate GVHD when a female donor is employed to transplant an HLA-identical male recipient. Thus, from this evidence, it is clear that GVHD may occur even when the donor and recipient are HLA identical.

The preferred donor for any patient undergoing HSCT is an HLA-identical sibling. Because polymorphic HLA genes are closely linked and usually constitute a single genetic locus**, any pair of siblings has a 25% chance of being HLA identical** . Thus, also in view of the limited family size in the developed countries, <25–30% of patients in need of an allograft can receive their transplant from an HLA-identical sibling. This percentage is even lower in patients with inherited disorders since affected siblings will not be considered donor candidates.

HSCT From an HLA-Identical Sibling Donor

Allogeneic HSCT from an HLA-compatible sibling is the treatment of choice for children with hematologic malignancies and various congenital or acquired diseases (Table 161.1). Best results are achieved in patients with congenital or acquired nonmalignant disorders because the risk of disease recurrence is low and the cumulative transplantation-related mortality is lower than in children receiving transplants for hematologic malignancies.

Table 161.1

Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

Malignancy

- Acute lymphoblastic leukemia (ALL)
    - First complete remission for patients at very high risk of relapse
    - T-cell immunophenotype and poor response to corticosteroid

    - therapy
    - Not in remission at the end of the induction phase
    - Marked hypodiploidy (<43 chromosomes)
    - Minimal residual disease at the end of consolidation therapy
- High-risk infant ALL
    - Second complete remission
    - Third or later complete remission
- Acute myeloid leukemia in 1st complete remission or in advanced-disease phase
- Philadelphia chromosome–positive chronic myeloid leukemia
- Myelodysplastic syndromes
- Hodgkin and non-Hodgkin lymphomas
- Selected solid tumors
    - Metastatic neuroblastoma
    - Rhabdomyosarcoma refractory to conventional treatment
    - Very-high-risk Ewing sarcoma

Anemias

- Severe acquired aplastic anemia
- Fanconi anemia
- Paroxysmal nocturnal hemoglobinemia
- Congenital dyskeratosis
- Diamond-Blackfan anemia
- Thalassemia major
- Sickle cell disease
- Shwachman-Diamond syndrome

Immunologic Disorders

- Variants of severe combined immunodeficiency
- Hyper-IgM syndrome
- Leukocyte adhesion deficiency
- Omenn syndrome
- Zap-70 kinase deficiency
- Cartilage-hair hypoplasia

PNP deficiency
CD40 ligand deficiency
MHC class II deficiency
Wiskott-Aldrich syndrome
Chédiak-Higashi syndrome
Kostmann syndrome (infantile malignant agranulocytosis)
Chronic granulomatous disease
Autoimmune lymphoproliferative syndrome
X-linked lymphoproliferative disease (Duncan syndrome)
IPEX syndrome
Interleukin-10 receptor deficiency
Hemophagocytic lymphohistiocytosis
Interferon-γ receptor deficiency
Griscelli disease
Granule deficiency

Other Disorders

- Selected severe variants of platelet function disorders (e.g., Glanzmann thromboasthenia, congenital amegakaryocytic thrombocytopenia)
- Selected types of mucopolysaccharidosis (e.g., Hurler disease) or other liposomal/peroxisomal disorders (e.g., Krabbe disease, adrenoleukodystrophy)
- Infantile malignant osteopetrosis
- Life-threatening cytopenia unresponsive to conventional treatments

IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase.

Acute Lymphoblastic Leukemia

Allogeneic HSCT is used for pediatric patients with acute lymphoblastic leukemia (**ALL**), either in the 1st complete remission when a child is considered to be at high risk of leukemia recurrence (e.g., those carrying poor-risk cytogenetic characteristics or with high levels of minimal residual disease), or in

2nd or further complete remission after previous marrow relapse. ALL is the most common indication for HSCT in childhood. Several patient-, donor-, disease-, and transplant-related variables may influence the outcome of patients with ALL given an allogeneic HSCT. The long-term probabilities of **event-free survival (EFS)** for patients with ALL transplanted in the 1st or 2nd complete remission is 60–70% and 40–60%, respectively. Inferior results are obtained in patients receiving transplants in more advanced disease phases. The use of **total body irradiation (TBI)** during the preparative regimen offers an advantage in terms of better EFS compared to a regimen consisting of cytotoxic drugs alone (Fig. 161.1), but it can induce more long-term side effects. This has prompted more investigation into TBI-sparing alternatives. Less intensive GVHD prophylaxis is also associated with a better outcome. Bone marrow is generally still the preferred source of stem cells to be employed for transplantation, although this differs among transplant centers.

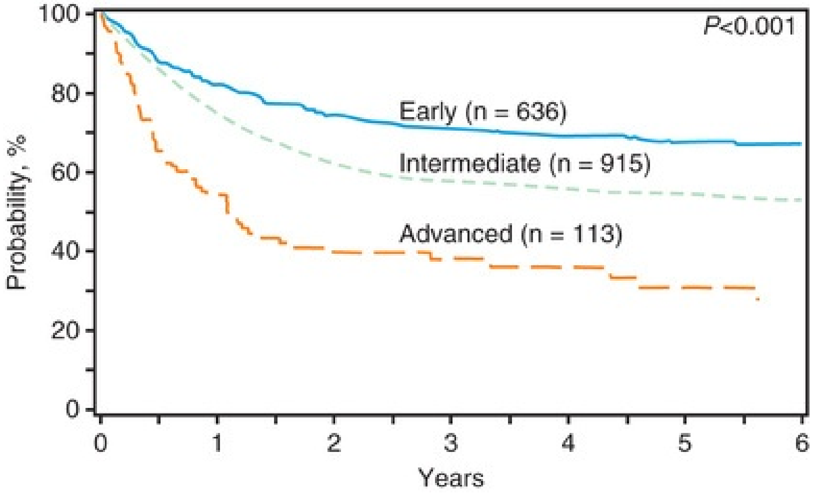

FIG. 161.1 Survival after HLA-matched sibling donor hematopoietic stem cell transplantation for acute lymphoblastic leukemia (ALL), age <18 yr, 2004–2014. *Early,* first complete remission (CR1); *Intermediate,* second or greater complete remission (CR2+); *Advanced,* active disease. (From D'Souza A, Zhu X: Current uses and outcomes of hematopoietic cell transplantation (HCT), CIBMTR Summary Slides, 2016. http://www.cibmtr.org .)

Although the main benefit for allogeneic HSCT recipients with leukemia derives from the GVL effect displayed by immunocompetent cells, disease recurrence remains the main cause of treatment failure. The risk of failing to eradicate leukemia is influenced by many variables, including disease phase, molecular lesions of tumor cells, and disparity for major or minor histocompatibility antigens in the donor/recipient pairs. To overcome the hurdle of tumor elusion caused by HLA loss on malignant cells, the use of non-HLA–restricted **chimeric antigen receptors (CARs)** has been proposed. This therapeutic strategy is based on genetic reprogramming of T cells through artificial immune receptors that reproducibly and efficiently redirect the antigen specificity of polyclonal T lymphocytes toward target antigens expressed by leukemic cells. When expressed by T cells, CARs mediate antigen recognition and tumor cytolysis in an MHC-unrestricted fashion and can target any molecule (protein, carbohydrate, or glycolipid) expressed on the surface of tumor cells, thus bypassing one of the major tumor escape mechanisms based on the downregulation of MHC molecules. CARs are composed of an extracellular specific antigen-binding moiety, obtained from the variable regions of a monoclonal antibody, linked together to form a single-chain antibody (scFv), and of an intracellular signaling component derived from the ζ chain of the T-cell–receptor (TCR)–CD3 complex. The addition to the *CAR* gene construct of co-stimulation signals and cytokines promoting T-cell expansion and survival improves the antitumor efficiency of the engineered T cells and their survival in the tumor milieu. Gamma retrovirus and lentiviruses are usually used to transduce CARs into T lymphocytes to be employed in the clinical setting. These vectors have been shown to efficiently infect T lymphocytes, integrate into the host genome, and produce robust expression of the gene in human T cells and their progeny.

Acute Myeloid Leukemia

Allogeneic HSCT from an HLA-identical sibling is largely employed as postremission treatment of pediatric patients with acute myeloid leukemia (**AML**). Children with AML in 1st complete remission who are given allogeneic HSCT as consolidation therapy have a better probability of EFS than those treated with either chemotherapy alone or autologous transplantation. Results obtained in patients given HSCT from an HLA-identical sibling after either a TBI-containing or a chemotherapy-based preparative regimen are similar, the probability of EFS being in the order of 70%. Therefore, for AML, conditioning regiments generally omit the use of TBI because of associated long-term side effects. Children with acute promyelocytic leukemia in molecular remission at the end of treatment with chemotherapy and all-*trans* -retinoic acid, or with

AML and translocation t(8;21); inversion of chromosome 16 (inv16), translocation t(16;16), or normal cytogenetics and presence of *NPM1* or *CEPB* α mutation are no longer considered eligible for allogeneic HSCT in 1st complete remission in view of their improved prognosis with alternative treatments. Studies suggest restricting the use of HSCT to those patients with poor molecular lesions, such as FLT3-internal tandem duplication or mixed-lineage leukemia abnormalities, or with high levels of minimal residual disease at the end of induction therapy. Approximately 40–60% of pediatric patients with AML in the 2nd complete remission can be rescued by HSCT.

Chronic Myelogenous Leukemia

For many years, allogeneic HSCT has been considered the only proven curative treatment for children with Philadelphia-positive (Ph+) chronic myelogenous leukemia. Leukemia-free survival of chronic myelogenous leukemia patients after an allograft is 45–80%. The phase of disease (chronic phase, accelerated phase, blast crisis), recipient age, type of donor employed (related or unrelated), and time between diagnosis and HSCT are the main factors influencing the outcome. The best results are obtained in children transplanted during the chronic phase from an HLA-identical sibling within 1 yr from diagnosis. Unlike other forms of pediatric leukemia, infusion of donor leukocytes can reinduce a state of complete remission in a large proportion of patients experiencing leukemia relapse.

Treatment with the specific BCR-ABL tyrosine protein kinase inhibitors (imatinib mesylate, dasatinib, nilotinib), targeting the enzymatic activity of the BCR-ABL fusion protein, has modified the natural history of the disease and thus the indications for transplantation. The indication for HSCT in this population is thus evolving and is generally reserved for patients with a poor response to tyrosine kinase inhibitors or those who do not tolerate their side effects.

Juvenile Myelomonocytic Leukemia

Juvenile myelomonocytic leukemia (**JMML**) is a rare hematopoietic malignancy of early childhood, representing 2–3% of all pediatric leukemias. JMML is characterized by hepatosplenomegaly and organ infiltration, with excessive proliferation of cells of monocytic and granulocytic lineages. Hypersensitivity to granulocyte-macrophage colony-stimulating factor (GM-CSF) and pathologic activation of the RAS-RAF-MAP (mitogen-activated protein) kinase signaling pathway play an important role in the pathophysiology. JMML usually runs an aggressive clinical course, with a median duration of survival for untreated children of <12 mo from diagnosis. Rare patients with *CBL1* or *N-RAS* mutations can survive for years without an allograft.

HSCT is able to cure approximately 50–60% of patients with JMML. Patients who receive a transplant from an unrelated donor have comparable outcome to those given HSCT from an HLA-compatible related donor. Cord blood transplantation represents a suitable alternative option. Leukemia recurrence is the main cause of treatment failure in children with JMML after HSCT, with the relapse rate as high as 40–50%. Because children with JMML frequently have massive spleen enlargement, splenectomy has been performed before transplantation. However, spleen size at the time of HSCT and splenectomy before HSCT do not appear to affect the posttransplantation outcome. Unlike in CML, donor leukocyte infusion is not useful to rescue patients experiencing disease recurrence; a 2nd allograft can induce sustained remission in approximately one third of children with JMML relapsing after a 1st HSCT.

Myelodysplastic Syndromes Other Than Juvenile Myelomonocytic Leukemia

Myelodysplastic syndromes are a heterogeneous group of clonal disorders characterized by ineffective hematopoiesis leading to peripheral blood cytopenia and a propensity to evolve toward AML. HSCT is the treatment of choice for children with **refractory anemia with excess of blasts (RAEB)** and for those with RAEB in transformation (RAEB-t). The probability of survival without evidence of disease for these children is 65–70%. It is still unclear whether patients with myelodysplastic syndromes and a blast percentage >20% benefit from pretransplantation chemotherapy. HSCT from an HLA-identical sibling is also the preferred treatment for all children with refractory cytopenia. Transplantation from an alternative donor is also employed in children with refractory cytopenia associated with monosomy 7, complex karyotype, life-threatening infections, profound neutropenia, or transfusion dependency. For children with refractory cytopenia, the probability of EFS after HSCT may be as high as 80%, disease recurrence being rarely observed. This observation has provided the rationale for testing reduced-intensity regimens in these patients.

Non-Hodgkin Lymphoma and Hodgkin Disease

Childhood non-Hodgkin lymphoma (NHL) and Hodgkin disease (HD) are very responsive to conventional chemoradiotherapy, but some patients have refractory disease or are at high risk for relapse. HSCT can cure a proportion of patients with relapsed NHL and HD and should be offered early after relapse, while the disease is still sensitive to therapy. If an HLA-matched donor is available, allogeneic transplantation can be offered to patients with NHL to take advantage of the GVL effect. Patients with sensitive disease and limited tumor burden have favorable outcomes, with EFS rates of 50–60%. Studies also suggest that patients with relapsed or refractory HD do well after autologous HSCT, with EFS of 50–60%. HD patients may also benefit from a GVL effect when given an allograft.

Acquired Aplastic Anemia

Because the probability of long-term survival for a matched-*sibling* bone marrow transplant (BMT) is reproducibly >80% for children and young adults, BMT is the treatment of choice for children and young adults with acquired severe aplastic anemia. Historically, the treatment of choice for children and young adults without an HLA-matched sibling has been intensive immunosuppression. Because the outcomes of matched *unrelated donor* transplant for children with acquired aplastic anemia have improved to probability of survival rates >75%, the use of unrelated donor HSCT upfront *without* prior immunosuppressive therapy is being considered more frequently; 2-year overall survival can be as high as 96% in upfront, matched unrelated donor recipients.

For patients who do not have a matched-sibling donor or well-matched unrelated donor, historically the transplant options were very disappointing. Fortunately, there is hope in current studies looking at haploidentical transplant for this disease. Although numbers are small, the use of posttransplant cyclophosphamide has shown significant improvement over prior experiences.

There is hope that all children and young adults who need a transplant for severe aplastic anemia will have the opportunity to do well with a BMT.

Inherited Bone Marrow Failure Syndromes

Fanconi anemia and dyskeratosis congenita are genetic disorders associated with a high risk of developing pancytopenia. **Fanconi anemia** (FA) is an autosomal recessive disease characterized by spontaneous chromosomal fragility, which is increased after exposure of peripheral blood lymphocytes to DNA cross-linking agents, including clastogenic compounds such as diepoxybutane, mitomycin C, and melphalan. Patients with FA, besides being at risk for pancytopenia, show a high propensity to develop clonal disorders of hematopoiesis, such as myelodysplastic syndromes and AML. HSCT can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders. In view of their defects in DNA repair mechanisms, which are responsible for the chromosomal fragility, FA patients have an exquisite sensitivity to alkylating agents and radiation therapy. Thus, they must be prepared for the allograft with reduced doses of cyclophosphamide and only judicious use of radiation. Many FA patients were once successfully transplanted after receiving low-dose cyclophosphamide and thoracoabdominal irradiation. However, the use of this regimen is associated with an increased incidence of posttransplantation head and neck cancers. Low-dose cyclophosphamide combined with fludarabine has been very well tolerated in patients with FA who have a matched-related donor. The addition of low-dose TBI and antithymocyte globulin (ATG) for those with an unrelated donor has shown similar success. Currently, the 5-yr overall survival is >90% in patients with FA who receive HSCT before the transformation to hematologic malignancy. Because of their underlying disorder, however, patients with FA must be monitored closely in the years after transplant to assess for late effects, including secondary malignancies and endocrinopathies.

Allogeneic HSCT remains the only potentially curative approach for severe bone marrow failure associated with **dyskeratosis congenita** , a rare congenital syndrome characterized also by atrophy and reticular pigmentation of the skin, nail dystrophy, and leukoplakia of mucous membranes. Results of allograft in these patients have been relatively poor, with 10-yr survival of 20–30%, because of both early and late complications, reflecting increased sensitivity of endothelial cells to radiotherapy and alkylating agents.

Thalassemia

Conventional treatment (i.e., regular blood transfusion and iron-chelation therapy) has dramatically improved both the survival and the quality of life of patients with thalassemia, changing a previously fatal disease with early death to a chronic, slowly progressive disease compatible with prolonged survival. However, HSCT remains the only curative treatment for patients with thalassemia. In these patients the risk of dying from transplant-related complications depends primarily on patient age, iron overload, and concomitant hepatic viral infections. Adults, especially when affected by chronic active hepatitis, have a poorer outcome than children. Among children, 3 classes of risk have been identified on the basis of 3 parameters: regularity of previous iron chelation, liver enlargement, and presence of portal fibrosis. In pediatric patients without liver disease who have received regular iron chelation (class 1 patients), the probability of survival with transfusion independence is >90%, whereas for patients with low compliance with iron chelation and signs of severe liver damage (class 3 patients), the probability of survival has been 60%.

With improvements in supportive care and conditioning regimens, even patients with more advanced liver disease have had excellent outcomes (Fig. 161.2). The most effective pharmacologic combinations (e.g., including cyclosporine and methotrexate) should be employed to prevent GVHD. The outcome of patients transplanted from an unrelated donor has been reported similar to that of HLA-identical sibling recipients. The increased use of umbilical cord blood and haploidentical donors in this population is being explored to expand the number of patients eligible for HSCT. Also, advancements in gene therapy are being made in thalassemia in early trials, which may eventually change the approach to this disease.

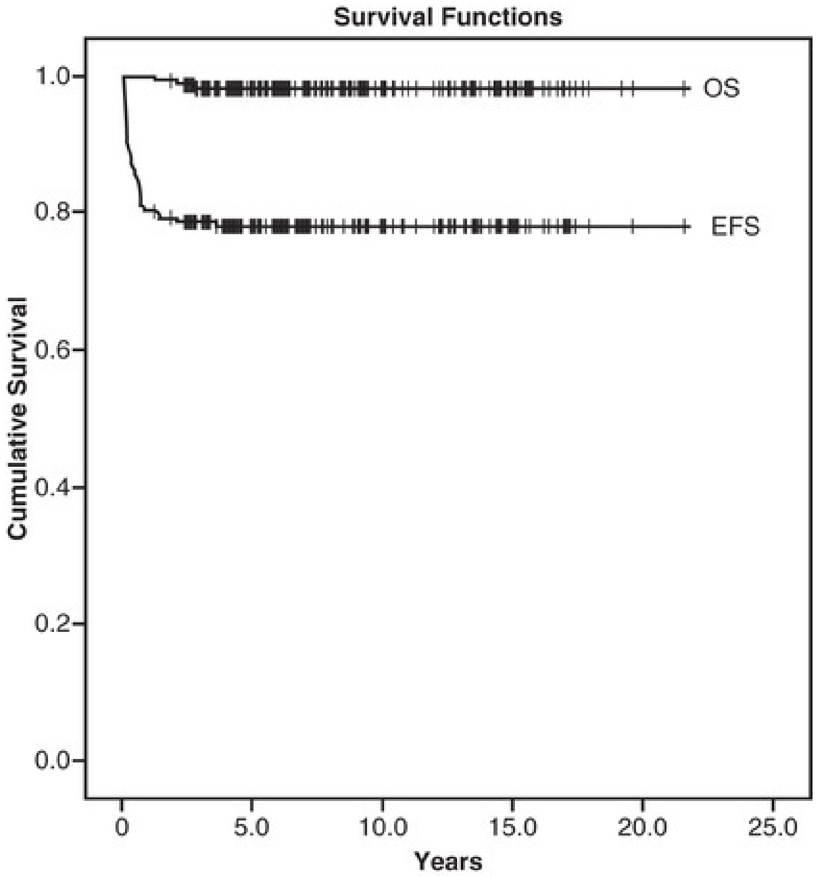

FIG. 161.2 Overall survival (OS) and event-free (graft failure) survival (EFS) after hematopoietic stem cell transplantation in children ≥1 yr from transplant for β-thalassemia major. (From Chaudhury S, Ayas M, Rosen C, et al: A multicenter retrospective analysis stressing the importance of long-term follow-up after hematopoietic cell transplantation for β-thalassemia, *Biol Blood Marrow Transplant* 23(10):1695–1700, 2017.)

Sickle Cell Disease

Disease severity varies greatly among patients with sickle cell disease, with 5–20% of the overall population suffering significant morbidity from vasoocclusive crises and pulmonary, renal, or neurologic damage. Hydroxyurea, an agent favoring the synthesis of fetal hemoglobin, reduces the frequency and severity of vasoocclusive crises and improves the quality of life for patients with sickle cell disease; however allogeneic HSCT is the only curative treatment for this disease at this time. Although HSCT can cure homozygous hemoglobin S, hemoglobin Sβ0, or hemoglobin SC disease, selecting appropriate candidates for transplantation is difficult. Patients with sickle cell disease may survive for decades, but some patients have a poor quality of life, with repeated hospitalizations for painful vasoocclusive crises and central nervous system (CNS) infarcts. The main indications for performing HSCT in patients with sickle cell disease are history of strokes, MRI of CNS lesions associated with impaired neuropsychologic function, failure to respond to hydroxyurea as shown by recurrent acute chest syndrome, and/or recurrent vasoocclusive crises, severe anemia, or osteonecrosis. The results of HSCT are best when performed in children with an HLA-identical sibling, with a probability of cure of 80–90%. However, the use of alternative donor transplants in this population, including matched unrelated donors and haploidentical donors, is being investigated through a number of clinical trials and may increase the number of patients eligible to undergo potentially curative HSCT. Reduced-intensity and reduced-toxicity regimens are also being explored to further decrease transplant-related morbidity and mortality, although graft failure remains an important issue in this patient population.

Immunodeficiency Disorders

HSCT is the treatment of choice for children affected by severe combined immunodeficiency (SCID), as well as for other inherited immunodeficiencies, including Wiskott-Aldrich syndrome, leukocyte adhesion deficiency (LAD), and chronic granulomatous disease (see Table 161.1). With an HLA-identical sibling, the probability of survival approaches 100%, with less favorable results for patients transplanted from an HLA–partially matched relative. Some children with SCID, mainly those without residual natural killer activity or maternal T-cell engraftment, may be transplanted without receiving any preparative regimen, the donor lymphoid cells usually being the only elements that engraft. Sustained donor engraftment is more difficult to achieve in children with Omenn syndrome, **hemophagocytic lymphohistiocytosis** , or LAD. Life-threatening opportunistic fungal and viral infections occurring before the allograft adversely affect the patient's outcome after HSCT. Because of this, patients with the most severe immunodeficiencies must be transplanted as early as possible to prevent infectious complications.

Inherited Metabolic Diseases

Inherited metabolic diseases are a broad group of diseases that result from the accumulation of substrate within tissues caused by dysfunction of the lysosome or peroxisome. The use of HSCT has been established for a variety of inherited metabolic diseases, including mucopolysaccharidosis type 1 (Hurler syndrome) and adrenoleukodystrophy (ALD). Although some of these diseases are treatable with exogenous enzyme replacement therapy, the clinical manifestations of disease tend to progress over time, especially disease in the CNS, where enzyme is unable to be reliably delivered. It is thought that undergoing HSCT results in the engraftment of microglial cells that are able to provide new enzyme to the areas where enzyme replacement therapy, if available, cannot have a substantial impact. Multiple studies have shown significantly improved outcomes for patients who are diagnosed with their underlying conditions relatively early and are able to undergo HSCT expeditiously, before significant damage from accumulated substrate that may be irreversible.

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CHAPTER 162

Hematopoietic Stem Cell Transplantation From Alternative Sources and Donors

Rachel A. Phelan, David Margolis

Two thirds of patients who need allogeneic hematopoietic stem cell transplantation (HSCT) do not have an available HLA-identical sibling. Alternative sources of hematopoietic stem cells (HSCs) are being increasingly used and include **matched unrelated donors, unrelated umbilical cord blood** , and **HLA-haploidentical relatives** . Each of these 3 options has advantages and limitations, but rather than being considered competing alternatives, they should be regarded as complementary strategies to be chosen after a careful evaluation of the relative risks and benefits in the patient's best interest. The choice of the donor will depend on various factors related to urgency of transplantation, patient-, disease-, transplant-related factors, center experience, and physician preference.

Unrelated Donor Transplants

One of the most widely used strategies for children who need an allograft and do not have an available HLA-identical sibling is to identify an unrelated HLA-matched donor in a registry (Fig. 162.1). Worldwide international registries include almost 27 million HLA-typed volunteer donors. HLA-A, -B, -C class I loci, and the DRB1 class II locus are the HLA loci most influencing outcome after HSCT from an unrelated volunteer. Other class II loci (namely, DQB1 and DP1 loci), as well as KIR haplotypes, are also being increasingly considered when choosing a donor, although their impact on outcome is less well studied.

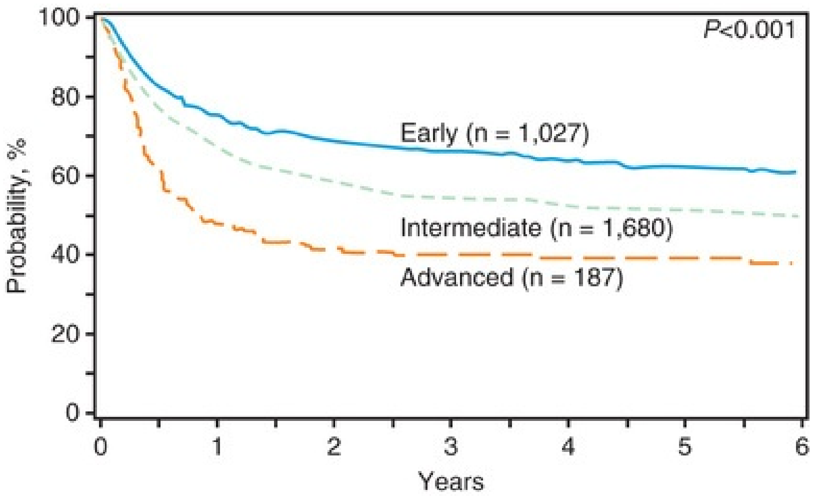

FIG. 162.1 Survival after unrelated donor HCT for acute lymphoblastic leukemia (ALL), age <18 yr, 2004–2014. *Early,* first complete remission (CR1); *Intermediate,* second or greater complete remission (CR2+); *Advanced,* active disease. (From D'Souza A, Zhu X: Current uses and outcomes of hematopoietic cell transplantation (HCT), CIBMTR Summary Slides, 2016. http://www.cibmtr.org .)

Although in the past serologic (low-resolution) typing was used for HLA-A and HLA-B loci, currently the unrelated donors are selected using high-resolution (allelic) molecular typing of loci HLA-A, -B, -C, and -DRB1. Less stringent HLA typing is required for cord blood units, where only HLA-A, -B, and -DRB1 are used. The chance of finding an HLA-matched unrelated donor depends on the frequency of the HLA phenotype, which is closely linked to the ethnic origin of the registry donors. Data from the National Marrow Donor Program (NMDP) donor registry and banked cord blood units estimated that essentially every patient in need of a transplant would be able to find a donor in a timely fashion, despite the recipient's race/ethnic group, donor availability, and cell dose. However, many of those patients may not have access to an “ideal” graft, defined as HLA matching of 8/8 for bone marrow and 6/6 for cord blood. It is also estimated that an additional 5.5 million donors will be added to the registry by 2017, making it even more likely for a potential, and more ideal, donor to be identified.

Initially, HLA polymorphism and the intrinsic limitations of conventional (i.e., serologic) HLA-typing techniques unfavorably affected the accuracy of matching, thus increasing rejection rates and the incidence of acute and chronic graft-versus-host disease (GVHD). The advent of both high-resolution molecular HLA classes I and II loci typing coupled with progress in the prophylaxis and treatment of GVHD has resulted in a reduction of transplantation-related mortality and improvement in outcome. Indeed, outcomes from a fully matched unrelated volunteer donor are now similar to those of HSCT from an HLA-identical sibling. The outcomes of haploidentical transplantation are similarly reaching that of matched unrelated donors as well as matched sibling donors.

Although a single locus disparity in patients with leukemia may be seen as beneficial by a reduction in the relapse rate caused by the graft-versus-leukemia (GVL) effect, in patients with nonmalignant disorders in whom GVL is not beneficial, optimal results are obtained only when a donor matched at the allelic level with the recipient is selected. In general, a single HLA disparity in the donor-recipient pair, irrespective of whether antigenic or allelic in nature, predicts a greater risk of nonleukemia mortality; multiple allelic disparities at different HLA loci have an additive detrimental effect and are associated with an even worse outcome. To reduce the risk of acute GVHD, **ex vivo T-cell depletion of the graft** has been employed, with variable efficacy. Studies are looking at selectively depleting donor α/β T cells, which are the T cells that drive GVHD, while preserving the T cells and natural killer (NK) cells, which may be responsible for GVL and protection from infection.

Although the majority of patients who have required a matched unrelated donor transplant have received a bone marrow or peripheral stem cell graft, for patients who urgently need a transplant, the time required to identify a suitable donor from a potential panel, establish eligibility, and harvest the cells may lead to relapse and failure to transplant. For this subset of patients who urgently need a transplant, attention has focused on unrelated cord blood and HLA-haploidentical, mismatched family donors.

Umbilical Cord Blood Transplants

Umbilical cord blood transplantation (UCBT) is a viable option for children who need allogeneic HSCT. UCBT offers the advantages of absence of risks to donors, reduced risk of transmitting infections, and for transplants from unrelated donors, immediate availability of cryopreserved cells, with the median time from start of search to transplantation only 3-4 wk. Compared with bone marrow transplantation (BMT), the advantages of UCBT are also represented by lower incidence of chronic GVHD and the possibility of using donors showing HLA disparities with the recipient. Despite these advantages, the large experience gained over the last 2 decades has demonstrated that UCBT patients may be exposed to an increased risk of early fatal complications, mainly because of a lower engraftment rate of donor hematopoiesis, delayed kinetics of neutrophil recovery, and lack of adoptive transfer of pathogen-specific memory T cells. Transfer of donor-derived, memory T cells significantly contributes to early immunologic reconstitution of children after unmanipulated allogeneic bone marrow or peripheral blood stem cell transplantation.

Concerning the issues of engraftment and hematopoietic recovery, it has been demonstrated that an inverse correlation exists between the number of nucleated cord blood cells infused per kilogram recipient body weight and the risk of dying for transplantation-related causes. In particular, engraftment is a major concern when the nucleated cells are $<2.5 \times 10^7$ /kg of recipient body weight. Since a cord blood unit usually contains between 1×10^9 and 1.8×10^9 cells, it is not surprising that UCBT has been less frequently employed for adolescents or adults with body weight >40 kg. Indeed, it can be estimated that only 30% of the UCB units available in the bank inventory could suffice for a 75 kg patient, according to the recommended threshold cell dose. Efforts have focused on approaches capable of increasing the number of UCB cells to be transplanted. Selection of the richest cord blood units, infusion of 2 units in the same recipient (i.e., double UCBT), and transplantation of ex vivo expanded progenitors have been explored to improve the results of UCBT, opening new scenarios for a wider application of the procedure. The results of these studies have been mixed, with one large study demonstrating no survival advantage for children and adolescents that receive double UCBT.

The long-term results of UCB transplants are similar to those after transplantation from other sources of HSCs for pediatric hematologic malignancies. In patients with hematologic malignancies, recipients of UCBT may be transplanted from donors with greater HLA disparities, receive 1-log fewer nucleated cells, have delayed neutrophil and platelet recovery, and show reduced incidence of GVHD compared with children given BMT from unrelated donors. In one study, there were similar rates of acute GVHD, but significantly less chronic GVHD in patients who received UCBT. Nevertheless, both the relapse rate and the overall survival probability did not differ in unrelated UCBT or BMT pediatric recipients. Thus, in the absence of an HLA-identical family donor, unrelated UCBT can be considered a suitable option for children with malignant and nonmalignant disorders. Results of UCBT have been of particular interest in children with certain nonmalignant disorders to proceed to transplant quickly and prevent further progression of disease. An additional benefit is the potential for lower rates of GVHD, which serves no benefit in a patient receiving a transplant for a nonmalignant disorder.

Haploidentical Transplants

HSCT from an HLA-haploidentical (**haplo-HSCT**) donor offers an immediate source of HSCs to almost all patients who fail to find a matched donor, whether related or unrelated, or a suitable cord blood unit. Indeed, almost all children have at least 1 haploidentical–3 loci mismatched family member who is promptly available as donor. The few patients who reject the haploidentical transplant also have the advantage of another immediately available donor within the family. Moreover, this may represent an approach that would be attractive in the global health setting, where more sophisticated donor registries and cell-processing techniques are unavailable.

Efficient T-cell depletion of the graft has been demonstrated to prevent acute and chronic GVHD even when using haploidentical parental bone marrow differing at the 3 major HLA loci. This can be done ex vivo or in vivo with the use of chemotherapeutic agents before and after cell infusion. The use of **posttransplant cyclophosphamide** is one such in vivo technique now being widely incorporated into haploidentical transplant regimens. The benefits of T-cell depletion were first demonstrated in transplantation of children with severe combined immunodeficiency (SCID). More than 300 transplants in SCID patients using haploidentical donors have been performed worldwide, with a high rate of long-term partial or complete immune reconstitution.

The elimination of mature T cells from the graft, necessary for preventing GVHD in a context of great immune genetic disparity, results in recipients being unable to benefit from the adoptive transfer of donor memory T lymphocytes that, through their peripheral expansion, are the main factor responsible for protection from infections in the 1st few mo after transplantation. A state of profound immunodeficiency lasts for at least 4-6 mo after transplantation in haplo-HSCT recipients. Sophisticated strategies of adoptive infusions of T-cell lines or clones specific for the most common and life-threatening pathogens (Epstein-Barr virus [EBV], human cytomegalovirus, *Aspergillus* , adenovirus) have been successfully tested in a few pilot trials, to protect the recipients in the early posttransplant period.

Selective approaches of graft manipulation in haploidentical and unrelated donor transplant have also been developed. In particular, promising results have been obtained through a negative depletion of T lymphocytes carrying the α/β chains of the T-cell receptor, which are believed to be the mediators of GVHD. B lymphocytes are also depleted to prevent EBV-related lymphoproliferative disease. Through this approach the patient can benefit from the adoptive transfer of committed hematopoietic progenitors, mature NK cells and γ/δ+ T cells, which can confer a protection against life-threatening infections as well as provide a GVL effect.

The outcomes of haplo-HSCT have been more extensively reported in adults than in children. The reported probability of survival at 3-4 yr after a haplo-HSCT in children with acute leukemia ranged from 18–48%. Survival was influenced by many factors, most importantly the state of remission at transplantation, with poorer outcomes in children with myeloid leukemias than in those with lymphoid leukemia. In haplotype-mismatched parent-to-child HSCT, patients with acute leukemia grafted from the mother had reduced relapse rates compared with recipients of paternal grafts, translating into better event-free survival.

For many years the absence of the T-cell–mediated GVL effect has been considered as rendering the recipients of a T-cell–depleted allograft more susceptible to leukemia relapse. However, it has been demonstrated that a GVL effect displayed by donor NK cells can compensate for this lack of T-specific alloreactivity when an HLA-disparate NK-alloreactive relative is employed as a donor.

Donor Versus Recipient NK-Cell Alloreactivity

Natural killer cells are the first lymphocytes derived from the donor to recover after allogeneic HCT. Donor vs recipient NK-cell alloreactivity derives from a mismatch between donor NK clones, carrying specific inhibitory receptors for self–major histocompatibility complex (MHC) class I molecules, and MHC class I ligands on recipient cells. NK cells are primed to kill by several activating receptors, which play an important role in the NK cell–mediated GVL effect. Human NK cells discriminate allelic forms of MHC molecules via **killer cell immunoglobulin-like receptors (KIRs),** which are clonally distributed with each cell in the repertoire bearing at least 1 receptor that is specific for self-MHC class I molecules. Because NK cells co-express inhibitory receptors for self-MHC class I molecules, autologous cells are not killed. When faced with mismatched allogeneic targets, NK cells sense the missing expression of self–class I alleles and mediate alloreactions. In mismatched transplants, there are many donor recipient pairs in which the donor NK inhibitory cells do not recognize the recipient's class I alleles as self. Consequently, the donor NK cells are not blocked and are activated to lyse the recipient's lymphohematopoietic cells.

Haplo-HSCT trials demonstrate that MHC class I mismatches, which generate an alloreactive NK-cell response in the graft-vs-host direction, eradicate leukemia cells, improve engraftment, and protect from T-cell–mediated GVHD. The potential for donor vs recipient NK-cell alloreactivity, which can be predicted by standard HLA typing, is increasingly being examined when selecting the donor of choice. Although the importance of KIR haplotype in transplants other than haploidentical transplantation has still not been fully elucidated in the pediatric population, its role in preventing GVHD as well as relapse has been shown to be increasingly beneficial in the adult population.

Autologous Hematopoietic Stem Cell Transplantation

Autologous transplantation , using the patient's own stored marrow, is associated with a low risk of life-threatening transplant-related complications, although the main cause of failure is disease recurrence. Bone marrow was once the only source of stem cells employed in patients given an autograft. In the past few years, the vast majority of patients treated with autologous HSCT receive hematopoietic progenitors mobilized in peripheral blood by either cytokines alone (mainly granulocyte colony-stimulating factor) or by cytokines plus cytotoxic agents. A CXCR4 antagonist (plerixafor) can be extremely effective in mobilizing hematopoietic progenitors in the periphery. Compared with bone marrow, the use of peripheral blood progenitors is associated with a faster hematopoietic recovery and a comparable outcome. A major concern in patients with malignancies given autologous HSCT is represented by the risk of reinfusing malignant cells with the graft; tumor progenitors contained in the graft can contribute to recurrence of the original malignant disease. This observation has provided the rationale for **tumor purging** using elaborate strategies aimed at reducing or eliminating tumor contamination of the graft.

Autologous HSCT is employed primarily for selected children with relapsed lymphomas and select solid tumors (Table 162.1).

Table 162.1

Indications for Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Relapsed Hodgkin or non-Hodgkin lymphoma
- Stage IV or relapsed neuroblastoma
- High-risk, relapsed, or resistant brain tumors
- Stage IV Ewing sarcoma
- Life-threatening autoimmune diseases resistant to conventional treatments

Patients with sensitive lymphomas and minimal tumor burden have favorable outcomes after autologous HSCT, with disease-free survival rates of 50–60%, whereas high-risk patients with bulky tumor or poorly responsive disease have a poor outcome, with survival rates of 10–20%.

Autologous HSCT in patients with high-risk neuroblastoma is associated with a better outcome than conventional chemotherapy. A Children's Oncology Group (COG) study demonstrated further survival advantage by performing 2 sequential, or **tandem** , transplants that use different chemotherapeutic agents. Because of these improved outcomes, tandem autologous transplants are now considered the standard recommended treatment. In these patients, posttransplantation infusion of a monoclonal antibody directed against a molecule (GD2) expressed on the surface of neuroblastoma cells confers a protection against the risk of tumor recurrence.

For children with brain tumors at high risk of relapse, or resistant to conventional chemotherapy and irradiation, the dose-limiting toxicity for intensifying therapy is myelosuppression, thus providing a role for stem cell rescue. Several studies provide encouraging results for patients with different histologic types of brain tumors treated with autologous HSCT.

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CHAPTER 163

Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease

Rachel A. Phelan, David Margolis

A major cause of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (HSCT) is **graft-versus-host disease (GVHD)** , which is caused by engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host who shows histocompatibility differences with the donor. These differences between the donor and the host may result in donor T-cell activation against either recipient major histocompatibility complex (MHC) antigens or minor histocompatibility antigens. GVHD is usually subdivided in 2 forms: **acute GVHD** , which occurs within 3 mo after transplantation, and **chronic GVHD** , which, although related, is a different disease, occurring later and displaying some clinical and pathologic features that resemble those observed in selected autoimmune disorders (e.g., systemic sclerosis, Sjögren syndrome).

Acute Graft-Versus-Host Disease

Acute GVHD is caused by the alloreactive, donor-derived T cells contained in the graft, which attack nonshared recipient's antigens on target tissues. A 3-step process generates the clinical syndrome. First, conditioning-induced tissue damage activates recipient antigen-presenting cells, which present recipient alloantigens to the donor T cells transferred with the graft and secrete **cytokines** , such as interleukin (IL)-12, favoring the polarization of T-cell response in the type 1 direction. Second, in response to recipient antigens, donor T cells become activated, proliferate, expand, and generate cytokines such as tumor necrosis factor (TNF)-α, IL-2, and interferon (IFN)-γ. In the 3rd step of the process, these cytokines cause tissue damage and promote differentiation of cytotoxic CD8$^+$ T cells, which, together with macrophages, kill recipient cells and further disrupt tissues.

Acute GVHD usually develops 2-8 wk after transplantation. The primary manifestations depend on the sites of involvement and may include an erythematous maculopapular rash (Figs. 163.1 and 163.2), persistent anorexia, vomiting and/or diarrhea, and liver disease with increased serum levels of bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP). Diagnosis may benefit from skin, liver, or gastrointestinal (GI) biopsy for confirmation. Endothelial damage and lymphocytic infiltrates are seen in all affected organs. The epidermis and hair follicles of the skin are damaged, the hepatic small bile ducts show segmental disruption, and there is destruction of the crypts and mucosal ulceration of the GI tract. Grade I acute GVHD (skin rash alone) has a favorable prognosis and often requires no treatment, or topical treatment alone. Grade II GVHD is a moderately severe multiorgan disease requiring immunosuppressive therapy. Grade III GVHD is a severe multiorgan disease, and grade IV GVHD is a life-threatening, often fatal condition (Table 163.1).

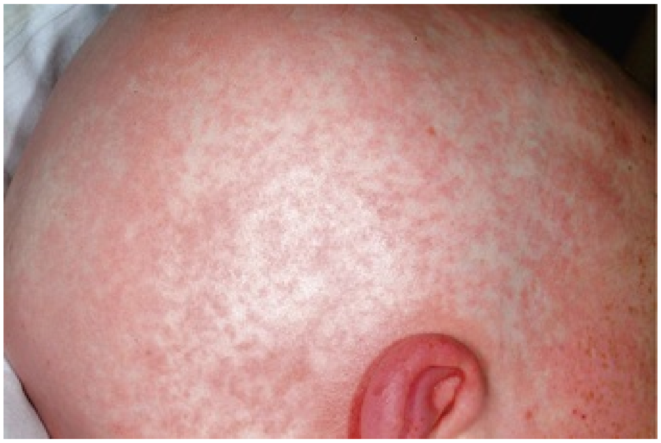

FIG. 163.1 **Acute graft-versus-host disease. Involvement of the scalp, ears, palms, and soles is common. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology,* ed 5, Philadelphia, 2016, Elsevier, p 577.)**

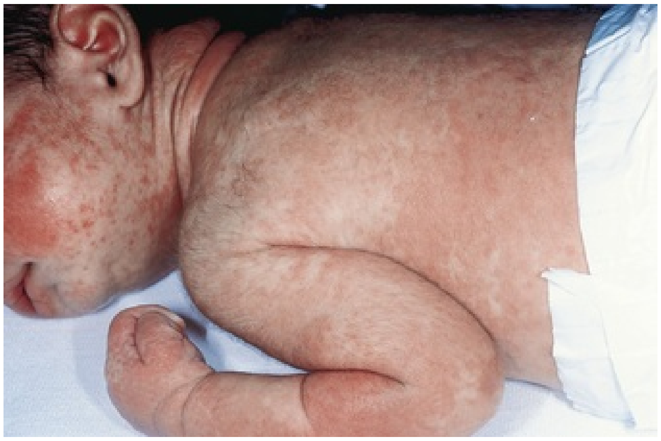

FIG. 163.2 Acute graft-versus-host disease. Almost confluent eruption of erythematous macules and papules in an immunodeficient neonate treated with extracorporeal membrane oxygenation (ECMO) and transfusion of nonirradiated blood. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology,* ed 5, Philadelphia, 2016, Elsevier, p 577.)

Table 163.1

Clinical Staging and Grading* of Graft-Versus-Host Disease (GVHD)

STAGE	SKIN (ACTIVE ERYTHEMA ONLY)	LIVER (BILIRUBIN)	UPPER GI	LOWER GI (STOOL OUTPUT/DAY)
0	No active (erythematous) GVHD rash	<2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500 mL/day or <3 episodes/day Child: <10 mL/kg/day or <4 episodes/day
1	Maculopapular rash <25% BSA	2-3 mg/dL	Persistent nausea, vomiting or anorexia	Adult: 500-999 mL/day or 3-4 episodes/day Child: 10-19.9 mL/kg/day or 4-6 episodes/day
2	Maculopapular rash 25-50% BSA	3.1-6 mg/dL		Adult: 1000-1500 mL/day or 5-7 episodes/day Child: 20-30 mL/kg/day or 7-10 episodes/day
3	Maculopapular rash >50% BSA	6.1-15 mg/dL		Adult: >1500 mL/day or >7 episodes/day Child: >30 mL/kg/day or >10 episodes/day
4	Generalized erythroderma (>50% BSA) plus bullous formation and desquamation >5% BSA	>15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)

* Overall clinical grade (based on most severe target organ involvement):

Grade 0: no stage 1-4 of any organ.

Grade I: stage 1-2 skin without liver, upper GI, or lower GI involvement.

Grade II: stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.

Grade III: stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.

Grade IV: stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

GI, Gastrointestinal; BSA, body surface area.

From Harris AC, Young R, Devine S, et al: International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai Acute GVHD International Consortium, Biol Blood Marrow Transplant 22:4–10, 2016.

The standard **pharmacologic prophylaxis** of GVHD after an unmanipulated allograft relies mainly on posttransplant administration of immunosuppressive drugs, such as cyclosporine or tacrolimus or combinations of either with methotrexate or prednisone, anti–T-cell antibodies, mycophenolate mofetil (MMF), and other immunosuppressive agents. Infusion of cyclophosphamide on days +3 and +5 after transplantation has been proposed as a strategy to deplete alloreactive donor T lymphocytes that become activated after exposure to recipient antigens. This approach has been successful in patients undergoing haploidentical transplantation. Pretransplantation infusion of either antithymocyte globulin (ATG) or monoclonal antibodies (mAbs) such as alemtuzumab is largely used to modulate alloreactivity of donor T cells, in particular in patients given the allograft from either an unrelated donor or a partially matched relative. An alternative approach, which has been widely used in clinical practice, is the removal of T lymphocytes from the graft (**T-cell depletion**). Other approaches, through clinical trials, are being used to selectively remove the α/β T cells, which are thought to be responsible for the development of GVHD, while preserving the γ/δ T cells in order to sustain GVL and the ability to fight infection. Any form of GVHD prophylaxis in itself may impair posttransplantation immunologic reconstitution, increasing the risk of infection-related deaths. Traditional T-cell depletion of the graft is also associated with an increased risk of leukemia recurrence in patients transplanted from an HLA-identical sibling or an unrelated volunteer.

Despite prophylaxis, significant acute GVHD develops in approximately 30% of recipients of HSCT from matched siblings and in as many as 60% of HSCT recipients from unrelated donors. These numbers are estimates, and the actual risk of acute GVHD is highly variable depending on several factors. Risk for development of GVHD is increased by diagnosis of malignant disease, older donor and recipient age, and in patients given an unmanipulated allograft, GVHD prophylaxis including only 1 drug. The most important risk factor for acute GVHD is the presence of disparities for HLA molecules in the donor-recipient pair.

Acute GVHD is usually initially treated with glucocorticoids; approximately 40–50% of patients show a complete response to corticosteroids. The risk of transplantation-related mortality is much higher in patients who do not respond to corticosteroids than in those showing a complete response. Promising results in children with steroid-resistant acute GVHD have been obtained using **mesenchymal stromal cells** , which are able to blunt the inflammatory response associated with acute GVHD. MMF, pentostatin, or mAbs targeting molecules expressed on T cells or cytokines released during the inflammatory cascade (including infliximab and etanercept targeting TNF, and tocilizumab targeting IL-6), which underlies the pathophysiology of GVHD, have been used in patients with steroid-resistant acute GVHD. There are no clear data showing the superiority of one of these approaches over the others. **Extracorporeal photopheresis** is another second-line treatment for GVHD and is most efficacious for skin GVHD. A patient's peripheral blood is exposed to a photosensitive compound and then exposed to ultraviolet light. The cells are then reinfused into the patient. It is thought that this process results in an increase in apoptosis of lymphocytes responsible for GVHD as well as the upregulation of antiinflammatory cytokines and regulatory T cells.

Chronic Graft-Versus-Host Disease

Chronic GVHD develops or persists >3 mo after transplantation and is the most frequent late complication of allogeneic HSCT with an incidence of approximately 25% in pediatric patients. Chronic GVHD is the major cause of nonrelapse mortality and morbidity in long-term HSCT survivors. Acute GVHD is recognized as the most important factor predicting the development of the chronic form of the disease. The use of matched unrelated volunteers as donors and use of peripheral blood as the stem cell source have increased the incidence and severity of chronic GVHD. Other factors that predict occurrence of chronic GVHD include older donor and recipient ages, female donor for male recipient, diagnosis of malignancy, and use of total body irradiation (TBI) as part of the preparative regimen.

Chronic GVHD is a disorder of immune regulation characterized by autoantibody production, increased collagen deposition and fibrosis, and clinical symptoms similar to those seen in patients with autoimmune diseases (Table 163.2). The predominant cytokines involved in the pathophysiology of chronic GVHD are usually type II cytokines such as IL-4, IL-5, and IL-13. IL-4 and IL-5 contribute to eosinophilia, B-cell hyperactivity with elevated IgM, IgG, and IgE titers. Associated monoclonal gammopathies indicate clonal dysregulation. Chronic GVHD is dependent on the development and persistence of donor T cells that are not tolerant to the recipient. Maturation of transplanted stem cells within a damaged thymus could lead to errors in negative selection and production of cells that have not been tolerized to recipient antigens and are therefore autoreactive or, more accurately, **recipient reactive** . This ongoing immune reactivity results in clinical features resembling a systemic autoimmune disease with lichenoid and sclerodermatous skin lesions, malar rash, sicca syndrome, arthritis, joint contractures, bronchiolitis obliterans, and bile duct degeneration with cholestasis.

Table 163.2

Clinical Findings in Chronic Graft-Versus-Host Disease

ORGAN SYSTEM	SYMPTOMS AND SIGNS
Systemic	Immunodeficiency and recurrent infections
Skin	Lichen planus, scleroderma, hyperpigmentation or hypopigmentation, erythema, freckling, ichthyosis, ulcerations Flexion contractures Vaginal scars Onycholysis Nail loss
Hair	Alopecia; scarring or nonscarring
Mouth	Sicca syndrome, lichen planus, depapillation of tongue with variegations, scalloping of lateral margins, xerostomia, mucocele
Joints	Diffuse myositis/tendonitis, arthritis, contractures
Eyes	Decreased tearing, injected sclerae, scarring conjunctivitis, keratopathy
Liver	Increased enzymes, cholestasis, hepatomegaly, cirrhosis
Gastrointestinal	Failure to thrive, malabsorption, chronic diarrhea Esophageal strictures

Lung	Cough, dyspnea, wheezing Bronchiolitis obliterans, chronic rales, pneumothorax, fibrosis
Hematology	Thrombocytopenia, eosinophilia, Howell-Jolly bodies (splenic dysfunction)

Patients with chronic GVHD involving only the skin and liver have a favorable course (Figs. 163.3 and 163.4). Extensive multiorgan disease may be associated with a very poor quality of life, recurrent infections associated with prolonged immunosuppressive regimens to control GVHD, and a high mortality rate. Morbidity and mortality are highest in patients with a **progressive onset** of chronic GVHD that directly follows acute GVHD, intermediate in those with a **quiescent onset** after resolution of acute GVHD, and lowest in patients with **de novo onset** in the absence of acute GVHD. Chronic GVHD can be classified as mild, moderate, or severe depending on extent of involvement. Single-agent prednisone is standard treatment at present, although other agents, including extracorporeal photopheresis, MMF, anti-CD20 mAb, and pentostatin, have been employed with variable success. Treatment with imatinib mesylate, which inhibits the synthesis of collagen, has been effective in some patients with chronic GVHD and sclerotic features. As a consequence of prolonged immunosuppression, patients with chronic GVHD are particularly susceptible to infections and should receive appropriate antibiotic prophylaxis, including trimethoprim/sulfamethoxazole (TMP/SMX). Chronic GVHD resolves in most pediatric patients but may require 1-3 yr of immunosuppressive therapy before the drugs can be withdrawn without the disease recurring. Chronic GVHD promotes the development of secondary neoplasms, in particular in patients with Fanconi anemia, and has a significant impact on quality of life.

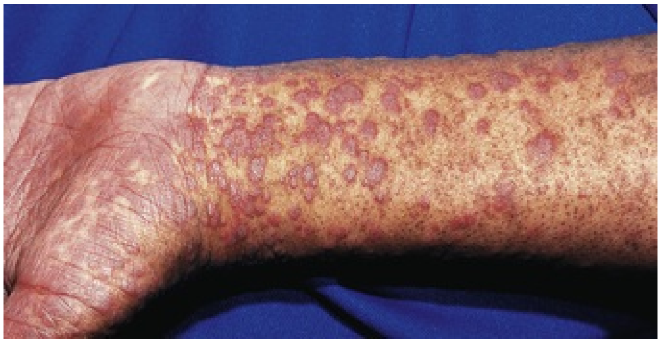

FIG. 163.3 **Chronic graft-versus-host disease (GVHD), lichenoid. After bone marrow transplantation, this boy had acute GVHD and subsequently developed cutaneous scaling papules and plaques typical of lichen planus. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology,* ed 5, Philadelphia, 2016, Elsevier, p 577.)**

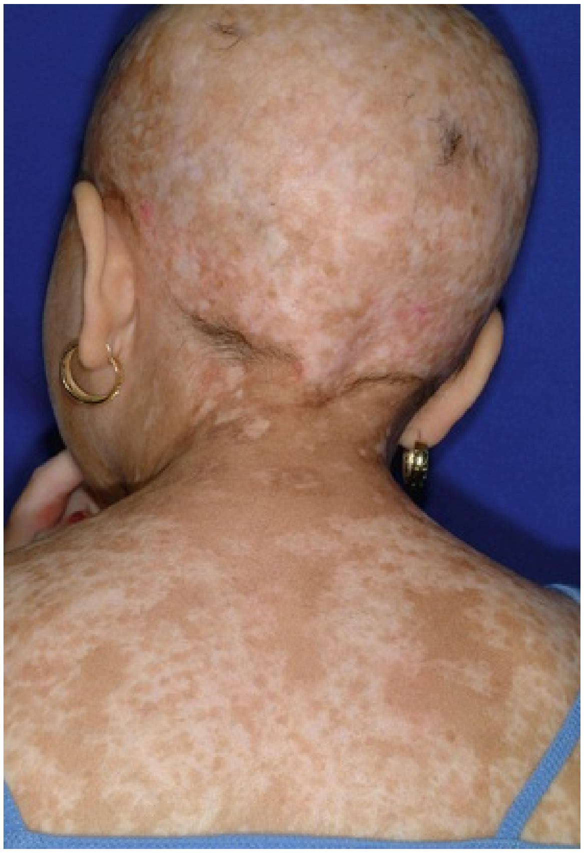

FIG. 163.4 Chronic graft-versus-host disease. Note the extensive alopecia of the scalp with dyschromia and numerous sclerodermatous plaques of the scalp and back. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology,* ed 5, Philadelphia, 2016, Elsevier, p 579.)

Graft Failure

Graft failure is a serious complication exposing patients to a high risk of fatal infection. **Primary graft failure** is defined as failure to achieve a neutrophil count of 0.5×10^9 /L after transplantation. **Secondary graft failure** is loss of peripheral blood counts following initial transient engraftment of donor cells. Causes of graft failure after autologous and allogeneic transplantation include transplantation of an inadequate stem cell dose (more frequently observed in children given cord blood transplantation) and viral infections such as with cytomegalovirus or human herpesvirus type 6, which are often associated with activation of recipient macrophages. Graft failure after allogeneic transplantation, however, is mainly caused by immunologically mediated rejection of the graft by residual recipient-type T cells that survive the conditioning regimen.

Diagnosis of graft failure resulting from immunologic mechanisms is based on examination of peripheral blood and marrow aspirate and biopsy, along with molecular analysis of chimerism status. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immunologic rejection. The risk of immune-mediated graft rejection is higher in patients given HLA-disparate, T-cell–depleted grafts, reduced-intensity conditioning regimens, and transplantation of low numbers of stem cells, and in recipients who are sensitized toward HLA antigens or, less frequently, minor histocompatibility antigens. Allosensitization develops as a consequence of preceding blood product transfusions and is observed particularly in recipients with aplastic anemia, sickle cell disease, and thalassemia. In HSCT for nonmalignant diseases, such as mucopolysaccharidoses, graft failure is also facilitated by the absence of previous treatment with cytotoxic and immunosuppressive drugs. In thalassemia, graft failure is promoted by expansion of recipient hematopoietic cells. GVHD prophylaxis with methotrexate, an antimetabolite, and antiinfective prophylaxis with TMP/SMX or ganciclovir may also delay engraftment.

Treatment of graft failure usually requires removing all potentially myelotoxic agents from the treatment regimen and attempting a short trial of hematopoietic growth factors, such as granulocyte colony-stimulating factor. A 2nd transplant, usually preceded by a highly immunosuppressive regimen, is frequently employed to rescue patients experiencing graft failure. High-intensity regimens are generally tolerated poorly if administered within 100 days from a 1st transplant because of cumulative toxicities, but this risk must be balanced with the risk of infection from prolonged neutropenia and lymphocytopenia.

Venoocclusive Disease

Hepatic venoocclusive disease (**VOD**), also known as **sinusoidal obstruction syndrome** , presents with hepatomegaly, right upper quadrant tenderness, jaundice, and weight gain from fluid retention and ascites. It results from endothelial damage within the liver, which can then progress to multiorgan dysfunction. Onset is usually within 30 days of transplantation, with an incidence of approximately 15%, depending on the intensity of the conditioning protocol. Risk factors include young age, prior hepatic disease (fibrosis, cirrhosis), abdominal radiation, repeated transplantations, neuroblastoma, osteopetrosis, and familial hemophagocytic lymphohistiocytosis. The severe form of VOD has a high mortality rate (>80%) without treatment.

Prophylaxis has traditionally used ursodeoxycholic acid and occasionally heparin; only **defibrotide** has demonstrated some efficacy in preventing and treating VOD. A phase 3 study demonstrated improvement in survival and response rate to VOD in patients treated with defibrotide. Defibrotide is a combination of porcine oligodeoxyribonucleotides that reduces procoagulant activity and enhances fibrinolytic properties of endothelial cells. Defibrotide is U.S. Food and Drug Administration (FDA) approved for the treatment of VOD in adult and pediatric patients with renal or pulmonary dysfunction after HSCT. Defibrotide is often used as prophylaxis in Europe, with data showing efficacy, but this use is not yet approved in the United States.

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CHAPTER 164

Infectious Complications of Hematopoietic Stem Cell Transplantation

Anna R. Huppler

Hematopoietic stem cell transplantation (HSCT) recipients experience a transient but profound state of immune deficiency. The risk of infection depends on the stage after transplantation (pre- vs postengraftment), ongoing immunosuppression, disruption in barrier functions (indwelling catheters, graft-versus-host disease [GVHD], mucositis) and preexisting infections (Fig. 164.1). Management approaches may include the use of prophylactic antimicrobials, preemptive antimicrobials for infection prior to symptomatic disease, or antimicrobial treatment of documented or suspected infection.

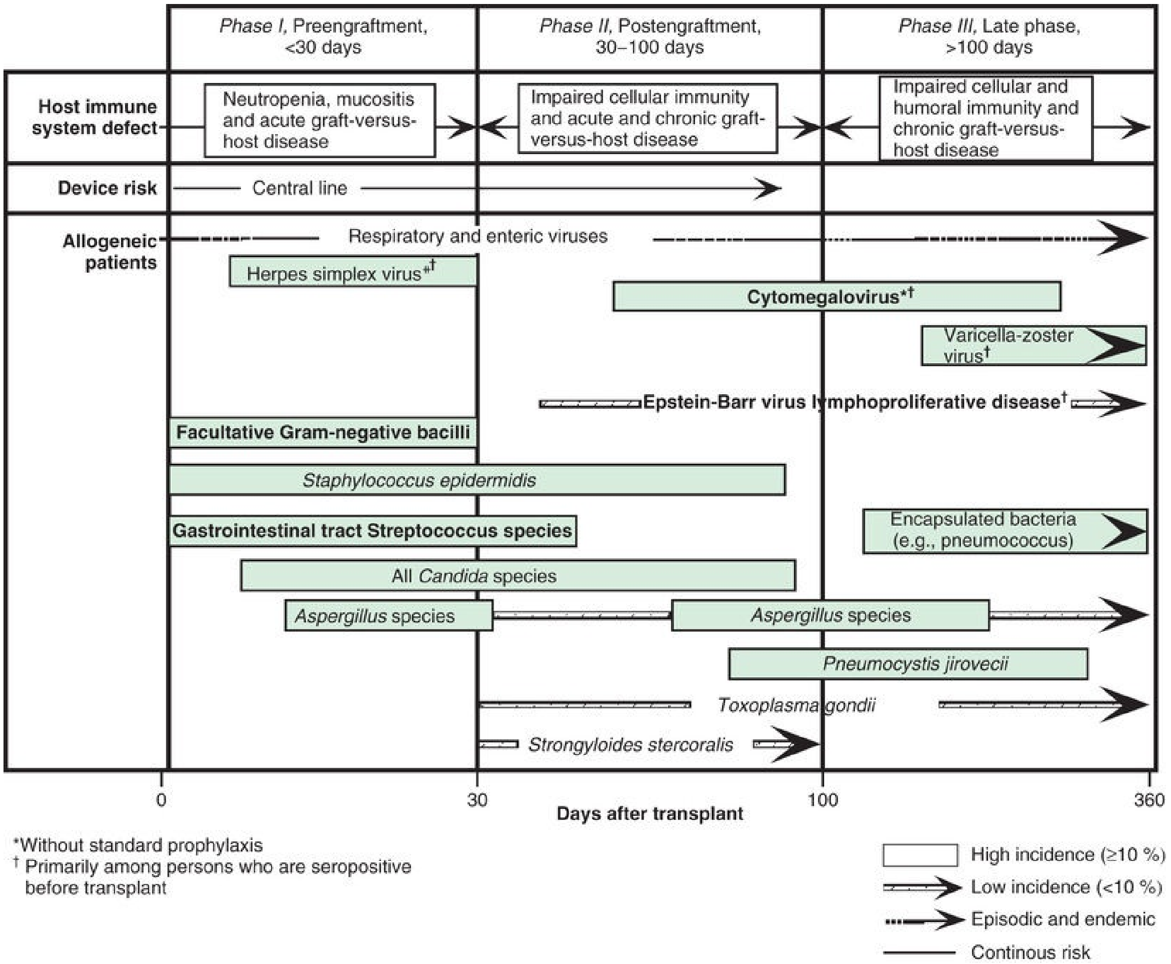
Phase I, Preengraftment, <30 days
Phase II, Postengraftment, 30–100 days
Phase III, Late phase, >100 days
Host immune system defect
Neutropenia, mucositis and acute graft-versus-host disease
Impaired cellular immunity and acute and chronic graft-versus-host disease
Impaired cellular and humoral immunity and chronic graft-versus-host disease
Device risk
Central line
Allogeneic patients
Respiratory and enteric viruses
Herpes simplex virus*†
Cytomegalovirus*†
Varicella-zoster virus†
Epstein-Barr virus lymphoproliferative disease†
Facultative Gram-negative bacilli
Staphylococcus epidermidis
Gastrointestinal tract Streptococcus species
Encapsulated bacteria (e.g., pneumococcus)
All Candida species
Aspergillus species
Aspergillus species
Pneumocystis jirovecii
Toxoplasma gondii
Strongyloides stercoralis
0
30
100
360
Days after transplant
*Without standard prophylaxis
† Primarily among persons who are seropositive before transplant
High incidence (≥10 %)
Low incidence (<10 %)
Episodic and endemic
Continous risk

FIG. 164.1 **Phases of opportunistic infections among allogenic HSCT recipients. (From Centers for Disease Control and Prevention: Guidelines for preventing opportunistic infections among hematopoietic sickle cell transplant recipients, *MMWR* 49(RR-10):1–128, 2000.)**

Immediately after transplantation, the absence or paucity of neutrophils (**neutropenia**) renders patients susceptible to bacterial and fungal infections. Consequently, most centers start antipseudomonal and antifungal prophylaxis during the conditioning regimen. Despite these prophylactic measures, the majority of patients will develop fever and signs of infection in the early posttransplantation period. The common pathogens include enteric gram-negative bacteria and fungi. An indwelling central venous line, routinely employed in all children given HSCT, is a significant risk factor for infection. Staphylococcal species and *Candida* are the most frequent pathogens in catheter-related infections (see Chapter 206). Multidrug-resistant strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* are an emerging problem, with prevalence highly variable among centers. Severe lower respiratory tract disease caused by seasonal respiratory viruses, such as influenza, respiratory syncytial virus (RSV), parainfluenza virus, and human metapneumovirus, can occur during the pre- or postengraftment phase. Published guidelines from the Infectious Disease Society of America and the U.S. Centers for Disease Control and Prevention (CDC) address the management of fever and neutropenia after HSCT.

HSCT recipients remain at increased risk of developing severe infections even after the neutrophil count has normalized because of prolonged depression in T-cell number and function. The manifestations of GVHD, as well as the associated immunosuppressive therapy, are additional risk factors for fungal and viral opportunistic infections. After umbilical cord blood transplant (UCBT), infections are the consequence of both slow neutrophil engraftment and donor T-cell naïveté. In haploidentical transplantation, T-cell depletion results in an increased risk of infection in the first 4-6 mo. Recipients of this type of transplantation, as well as those receiving UBCT, do not have the benefit of adoptive transfer of donor-derived, antigen-experienced T cells. For HSCT recipients after engraftment, invasive fungal disease, herpesviruses, and adenovirus infections represent life-threatening complications that significantly affect outcomes. Additional pathogens to consider include nontuberculous mycobacteria, BK virus, *Clostridium difficile*, and norovirus.

Invasive fungal disease (IFD) remains a significant cause of infectious morbidity and mortality in allogeneic HSCT recipients. Empirical treatment for IFD is considered for HSCT patients with persistent fever despite 96 hr of broad-spectrum antibiotic treatment. The most common organisms are *Aspergillus* and *Candida* species. Infections also occur with non-*Aspergillus* molds, including *Mucor* and *Rhizopus* species (among other agents of mucormycosis), *Fusarium,* and *Scedosporium* species. *Pneumocystis jiroveci* is a unique, noncultivatable cause of fungal pneumonia in immunocompromised patients. Despite prompt and aggressive administration of potent antifungal agents, proven cases of IFD carry case fatality rates of 20–70%. IFD can present early after transplant, although there is a shift toward presentation of infection in the postengraftment period in the presence of GVHD. The risk of developing IFD is mainly influenced by history of previous fungal infection, duration of neutropenia, use of corticosteroid therapy, mucosal tissue damage (GVHD, posttransplant CMV infection, viral respiratory tract infections), and for candidiasis, presence of central venous catheters.

Disseminated candidiasis presents frequently as a central venous catheter–associated infection. However, up to 50% of patients with disseminated candidiasis do not present with positive blood cultures. Patients with and without candidemia can have infection of normally sterile organs, including liver, spleen, kidney, brain, heart, and eye. Mortality rates in pediatric series range from 10–25%. **Echinocandins** (micafungin, caspofungin) are the initial drugs of choice for candidiasis in immunocompromised patients.

The most common presentation of invasive **aspergillosis** is pulmonary aspergillosis. The upper airway mucosa (nose and sinuses) can also be a site of initial infection. Infection progresses from lung or sinus sites by direct extension across tissue or angioinvasion resulting in hematogenous dissemination to brain and other organs. The earliest imaging finding is classically 1 or more small pulmonary nodules (Figs. 164.2 and 164.3). As a nodule enlarges, the dense central core of infarcted tissue may become surrounded by edema or hemorrhage, forming a hazy rim known as the *halo sign.* When bone marrow function recovers, the infarcted central core may cavitate, creating the *crescent sign.* Unfortunately, radiographic signs, including the halo sign, crescent sign, and cavitation, have low sensitivity in pediatric patients. Clinical criteria are used to diagnose proven or probable IFD, requiring direct or indirect microbiologic data. Direct, culture-based diagnosis requires invasive procedures, such as sinus endoscopy or lung biopsy. Indirect measures, known as *fungal biomarkers,* are used in adult HSCT patients to screen or diagnose for aspergillosis. Fewer data are available for pediatric patients, and currently no major guidelines support routine use of fungal biomarkers to diagnose IFD in immunocompromised children. **Galactomannan** from serum or bronchoalveolar lavage fluid is a promising adjunct to current diagnostic strategies because of a high negative predictive value for aspergillosis; however, lack of detection of mucormycosis limits its utility as a single diagnostic test. Other tests used in adult patients, such as (1→3)-β-D -glucan, are insufficiently studied for routine use in pediatric patients.

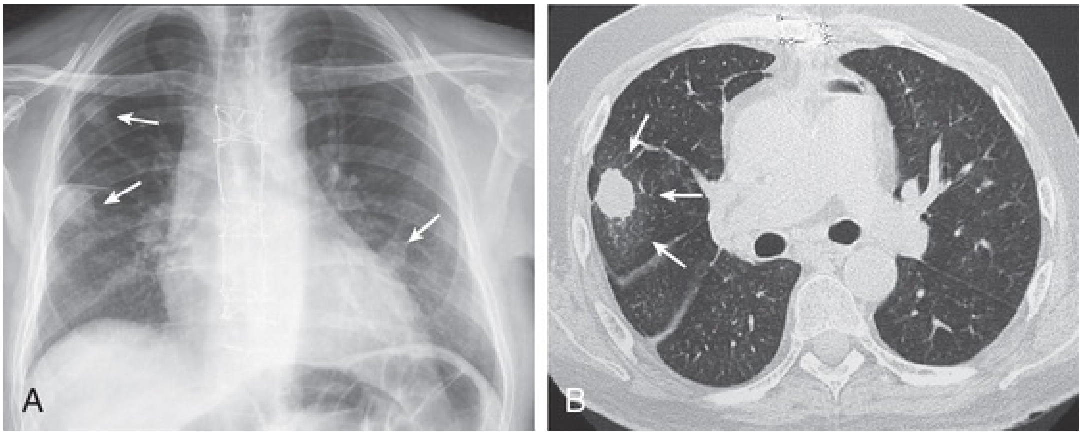

FIG. 164.2 Angioinvasive aspergillosis. A, Posteroanterior radiograph shows multiple nodules in the lungs *(arrows).* B, CT section at the level of the intermediary bronchus shows a nodule surrounded by a halo of ground-glass attenuation *(arrows).* (From Haaga JR, Boll DT, editors: *CT and MRI of the whole body,* ed 6, vol 1, Philadelphia, 2017, Elsevier, p 933.)

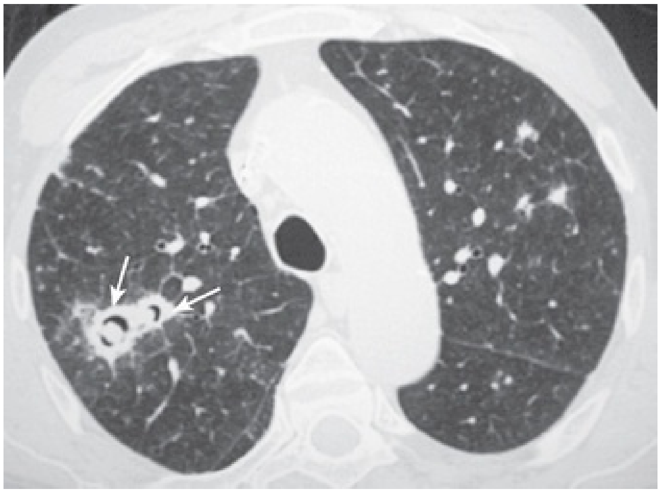

FIG. 164.3 Angioinvasive aspergillosis. CT section at the level of the lower trachea shows a consolidation with an eccentric cavitation and air crescent sign *(arrows).* This finding in this neutropenic patient is highly diagnostic of angioinvasive aspergillosis. (From Haaga JR, Boll DT, editors: *CT and MRI of the whole body,* ed 6, vol 1, Philadelphia, 2017, Elsevier, p 933.)

Fungal infection prevention includes isolation of the patient in a laminar airflow or positive pressure room. Universal prophylaxis to prevent *Pneumocystis* pneumonia is advocated until the return of T-cell function in HSCT patients; the primary agent for prophylaxis is trimethoprim/sulfamethoxazole. Alternative agents are pentamidine, dapsone, and atovaquone. For prevention and treatment of other IFD, liposomal amphotericin B, azole compounds (itraconazole, voriconazole, posaconazole) and echinocandins (caspofungin, micafungin) are used. **Voriconazole** represents the treatment of choice for adult patients with invasive aspergillosis, but achieving adequate trough levels can be challenging in young children. The agents of mucormycosis are resistant to most azole and echinocandin medications, which makes liposomal **amphotericin B** the initial drug of choice. IFD often does not respond satisfactorily to antifungal agents alone, and infection may persist until immune function recovers.

Herpesviruses , including cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus (HSV1 and HSV2), and varicella-zoster virus (VZV) are pathogens that can cause significant disease after HSCT. Because herpesviruses can establish latency in the human host, symptomatic infection can occur from viral reactivation as well as acquisition from the donor or de novo infection. Baseline susceptibility to disease and viremia before symptom development can be established with laboratory monitoring (pretransplant donor-recipient serology, posttransplant viral load monitoring) and can inform decisions on prophylactic and preemptive antiviral treatment.

CMV infection remains the most common and potentially severe viral complication in patients receiving allogeneic HSCT. Risk factors for CMV viremia include recipient seropositivity, UCBT, and acute GVHD. The period of maximal risk for CMV disease is 1-4 mo after transplantation. Late presentation of CMV disease is associated with GVHD. Until CMV-specific T-cell responses develop months after transplant, CMV infection may result in a variety of syndromes, including fever, leukopenia, thrombocytopenia, hepatitis, pneumonitis, retinitis, esophagitis, gastritis, and colitis. CMV pneumonia has been reported to occur in up to 15–20% of bone marrow transplant recipients, with a case fatality rate of 85% in the absence of early treatment. Tachypnea, hypoxia, and nonproductive cough signal respiratory involvement. Chest radiography often reveals bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly. Gastrointestinal CMV involvement may lead to ulcers of the esophagus, stomach, small intestine, and colon with complications of bleeding or perforation. Fatal CMV infections are often associated with persistent viremia and multiorgan involvement.

CMV disease has largely been prevented through prophylaxis or preemptive approaches. Prophylaxis is based on administration of antiviral drugs to at-risk transplanted patients for a median duration of 3 mo after transplantation. The major drawbacks of this approach are drug toxicity, late CMV disease after withdrawal of prophylaxis, potential unnecessary treatment of patients who would not have reactivated CMV infection, and low cost-effectiveness. Preemptive therapy aims at treating only patients who experience CMV reactivation and thus are at risk of developing overt disease; it starts on detection of CMV in blood but before symptom development. The major drawback of this strategy is the need of serial monitoring of CMV by polymerase chain reaction (PCR) in blood. First-line therapy is usually ganciclovir, with foscarnet as an alternative for resistant strains or ganciclovir intolerance.

EBV-related posttransplant lymphoproliferative disease (PTLD) is a major complication in HSCT and solid-organ transplantation. In patients receiving HSCT, selective procedures of T-cell depletion–sparing B lymphocytes and use of HLA–partially matched family and unrelated donors are risk factors for the development of PTLD. PTLD usually presents in the first 4-6 mo after transplantation as high-grade, diffuse, large-cell B-cell lymphomas that are oligoclonal or monoclonal. High EBV viral loads in blood by PCR predict development of PTLD. Standard treatment of PTLD includes the reduction of immunosuppression, monoclonal antibodies directed against CD20 on B cells (rituximab), or cytotoxic chemotherapy. Prophylactic strategies with rituximab for EBV-positive recipients during conditioning for HSCT have also been employed. Histologic diagnosis of PTLD is required to assess for the emergence of neoplasms in which cells are $CD19^+$ but $CD20^-$, thus eliminating susceptibility to rituximab.

Disseminated adenovirus infection is a life-threatening complication of HSCT recipients. Clinical manifestations include fever, hepatitis, enteritis, meningoencephalitis, and pneumonia. Young children or recipients of donor cells naïve to adenovirus (T-cell–depleted grafts or UCBT) are at particular risk of developing this complication. Diagnosis is based on the demonstration of high viral loads by PCR in blood or recovery of virus in tissue biopsies. Pharmacologic treatment of adenovirus infections is with the antiviral cidofovir, which has significant renal toxicity and limited potency at controlling viral replication. Alternative delivery systems for this drug, such as enterally available prodrugs, are currently being investigated in research settings. Recovery of immune system function is associated with improved survival with disseminated adenovirus infection.

In immunocompromised hosts, severe viral infections, including PTLD and adenovirus infection, originate from a deficiency of virus-specific **cytotoxic T**

lymphocytes (CTLs). This finding provides the rationale for developing strategies of adoptive cell therapy to restore virus-specific immune competence. Multiple protocols are under development and available at some centers for the rapid generation of specific CTL lines of donor or third-party origin.

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CHAPTER 165

Late Effects of Hematopoietic Stem Cell Transplantation

Rachel A. Phelan, David Margolis

Pediatric hematopoietic stem cell transplantation (HSCT) is considered standard-of-care treatment for a number of malignant and nonmalignant conditions. Treatment generally involves exposure to chemotherapy and occasionally radiation to encourage engraftment of donor stem cells and prevent donor and recipient rejection. The period of time immediately after transplant is associated with the risk for a number of serious acute complications, including profound immunosuppression and subsequent risk for infection, graft-versus-host disease (GVHD), and organ toxicities. Fortunately, significant progress has been made in supportive care strategies to reduce the risk of acute complications and treat them more effectively if they do arise. This has resulted in a growing number of pediatric patients who are now long-term survivors following HSCT. The estimated total number of HSCT survivors in 2009 was 108,900, and this is expected to increase 5 times by 2030 to 502,000. Of these survivors, approximately 14% (64,000) in 2030 will have received a transplant in childhood (<18 yr of age).

Exposure to chemotherapy, radiation, or both places patients at similar long-term risks as the pediatric cancer population; the high doses and types of chemotherapy and radiation often amplify the risk for issues such as ovarian failure/infertility and neurocognitive difficulties. Total body irradiation (TBI) has been shown to increase dramatically the risk for late complications after transplant. In addition, late effects may be additive if the patient received therapy before HSCT for their underlying malignancy. Moreover, the indication for transplant in pediatric patients is not always related to malignancy, but rather an underlying immunodeficiency, bone marrow failure syndrome, or metabolic disorder. These patients are potentially at risk for late effects related to this underlying disease alone and require different types of monitoring.

Essentially, every organ system can be impacted by the long-term effects of therapy, and each must be considered when undergoing late effects surveillance (Table 165.1). As a result of growing evidence of the importance of lifelong care for HSCT survivors, multiple groups have published recent consensus guidelines to help in caring for this patient population. As the field of survivorship continues to expand, *we recommend the following reference for real-time evidence-based recommendations from the* ***Children's Oncology Group*** : http://survivorshipguidelines.org .

Table 165.1

Summary of Late Effects After Hematopoietic Stem Cell Transplantation (HSCT) in Childhood

EXPOSURE	LATE EFFECT*
HSCT experience in general	Dental abnormalities Renal toxicity Hepatic toxicity Low BMD Avascular necrosis Increased risk of second cancers Adverse psychosocial/quality-of-life effects Mental health disorders, risk behaviors Psychosocial disability caused by pain or fatigue
TRANSPLANTATION CONDITIONING	
Alkylating agent	Cataract (busulfan) Pulmonary fibrosis (busulfan) Renal toxicity Urinary tract toxicity Gonadal dysfunction Therapy-related AML/MDS Bladder cancer
Epipodophyllotoxin** DNA intersecting and cross-linking agents (i.e., platinum, heavy metal)	Therapy-related AML/MDS Ototoxicity Renal toxicity Gonadal toxicity
TBI †	Neurocognitive deficits Leukoencephalopathy Cataract Dental abnormalities GH deficiency Hypothyroidism, thyroid nodule Pulmonary toxicity Breast tissue hypoplasia Cardiac toxicity Renal toxicity Gonadal dysfunction

	Uterine vascular insufficiency Diabetes Dyslipidemia Musculoskeletal growth problems Second cancers
PRETRANSPLANTATION EXPOSURES (Not Listed Above)	
Anthracycline/anthraquinone	Cardiac toxicity Therapy-related AML/MDS
Bleomycin	Pulmonary toxicity
Cytarabine	Neurocognitive deficits Leukoencephalopathy
Methotrexate	Neurocognitive deficits Leukoencephalopathy Renal toxicity Low BMD
Corticosteroid	Cataract Low BMD Avascular necrosis
Cranial radiation [‡]	Neurocognitive deficits Leukoencephalopathy Cerebrovascular disease Cataract Craniofacial abnormalities Dental abnormalities, xerostomia GH deficiency Hypothyroidism thyroid nodule Increased obesity Precocious puberty Brain tumor
Spinal radiation (in addition to cranial dose)	Cardiac toxicity Scoliosis/kyphosis, musculoskeletal problems
AFTER TRANSPLANTATION (Not Listed Above)	
Chronic GVHD	Xerophthalmia Xerostomia, dental abnormalities Pulmonary toxicity Gastrointestinal strictures Genitourinary strictures Skin and joint changes Immunodeficiency Second cancers, especially skin, oral, cervical, lymphoma
Tyrosine kinase inhibitor	Acute cardiac toxicity reported, but not known to cause late cardiotoxicity
OTHER EXPOSURES	
Blood transfusions	Hepatitis C, HIV

[*] Focused on those late effects that can develop or persist even after cessation of therapy.

[†] At given total dose, risks greater for single-fraction vs fractionated total body irradiation (TBI); single-fraction myeloablative TBI (>500 cGy) now rarely used.

[‡] Effects listed are those more likely to be associated with doses used in HSCT survivors (e.g., those given for leukemia treatment, <25 Gy); late effects are more likely if TBI also given.

[**] Include etoposide, teniposide.

AML/MDS, Acute myeloid leukemia/myelodysplastic syndrome; BMD, bone mineral density; GH, growth hormone; GVHD, graft-vs-host disease; HIV, human immunodeficiency virus.

From Chow EJ, Anderson L, Baker KS, et al: Late effects surveillance recommendations among survivors of childhood hematopoietic cell transplantation: a Children's Oncology Group report, *Biol Blood Marrow Transplant* 22:783–784, 2016.

Endocrine Effects

Children given HSCT before puberty may develop **growth impairment** , precluding achievement of the genetic target for adult height. The decrease in growth velocity is similar for boys and girls and is more frequently observed in patients given TBI as part of the preparative regimen. Chronic GVHD and its treatment with corticosteroids may also contribute to growth impairment.

Growth impairment of patients given TBI is mainly a result of direct damage of cartilage plates and to the effect of TBI on the hypothalamic-pituitary axis, which leads to an inappropriately low production of **growth hormone** (GH). GH deficiency is susceptible to at least partial correction through administration of hormonal replacement therapy. Annual growth evaluation should be performed in all children after HSCT. Children showing a decreased growth velocity should be further investigated through evaluation of bone age and secretion of GH in response to pharmacologic stimulus.

The use of TBI during the preparative regimen involves the thyroid gland in the irradiation field and may result in **hypothyroidism** . Younger children are at greater risk of developing hypothyroidism. Chemotherapy-only preparative regimens have far fewer adverse effects on normal thyroid function. The site of injury by irradiation is at the level of the thyroid gland rather than at the pituitary or hypothalamus. Therapy with thyroxine is very effective for overt hypothyroidism. The cumulative incidence of hypothyroidism increases over time, underscoring the importance of annual thyroid function studies.

Gonadal hormones are essential for normal pubertal growth, as well as for development of secondary sexual characteristics. A significant proportion of patients receiving TBI-containing preparative regimens as well as high doses of alkylating agents show delayed development of secondary sexual characteristics, resulting from primary ovarian or testicular failure. Laboratory evaluation of these patients reveals elevated follicle-stimulating hormone and luteinizing hormone levels with depressed estradiol and testosterone serum levels. These patients benefit from careful follow-up with evaluation of annual sexual maturity rating (Tanner) scores and endocrine function. Supplementation of gonadal hormones is useful for primary gonadal failure and is administered with GH to promote pubertal growth. **Infertility** during adulthood remains a common problem of these children, especially those undergoing traditional myeloablative conditioning for HSCT. The use of reduced-intensity regimens may result in sparing fertility in a large proportion of patients, although conditioning regimens vary and studies are limited.

Bone health of HSCT survivors can also be impacted by hormonal changes as well as lifestyle practices, such as inadequate exercise and/or dietary intake of vitamin D. Prior exposures, including corticosteroid use, can result in changes to bone density as well as predispose to the development of avascular necrosis. Dual-energy x-ray absorptiometry (DXA) scans are routinely incorporated into the care of those patients at risk for low bone mineral density.

Cardiovascular Effects

Survivors of childhood HSCT are at risk for the future development of cardiovascular complications. This population can be prone to developing **metabolic syndrome** (dyslipidemia, hypertension, diabetes mellitus, obesity), especially those with a history of TBI exposure and subsequent hormonal derangements. Prior exposures such as anthracycline chemotherapy and chest radiation further increase the risk for **cardiomyopathy** as well as **atherosclerosis** . As a result, routine anthropometric, imaging, and laboratory screening should be performed in survivors of childhood HSCT to assess and monitor their cardiovascular health.

Secondary Malignancy

The overall risk of developing a secondary form of cancer is significantly higher after HSCT than in the general population. Although few studies have specifically analyzed pediatric patients, available evidence indicates that the cumulative incidence of 2nd malignancies shows a slight, but continuous, tendency to increase over time. The development of myelodysplastic syndrome as well as secondary leukemias must be considered in survivors of HSCT. Several other types of secondary tumors have been identified in patients given HSCT. The most frequently diagnosed neoplasms are thyroid carcinoma, brain tumors, and epithelial cancers. Young age, male gender, use of TBI during the preparative regimen, chronic GVHD, and an intrinsic genetic predisposition to develop cancer (Fanconi anemia) have been reported to be risk factors for development of secondary malignancies after HSCT. Routine physical exams, including yearly skin in exams in those that received TBI are important in the care of these patients.

Graft-Versus-Host Disease

In the posttransplant period, multiple studies have shown that quality of life is severely impacted by the presence of GVHD**,** which is an issue that is also unique to HSCT (see Chapter 163).

Other Effects

HSCT patients can also experience complications related to their pulmonary function, renal function, dental health, and gastrointestinal system, often related to prior exposures as well as their conditioning regimen. It is also important to note that long-term survivors must be monitored for psychological issues because of their prior and current underlying health conditions. They may need extra assistance with school and vocational attainment. These patients are also often at higher risk for depression and anxiety; yearly psychosocial assessments can identify survivors who need additional therapy or psychotropic medication. Parents may also have posttraumatic stress from the experience.

Special Considerations

Certain patient populations who undergo HSCT are at increased risk for late effects. Young children appear to be at a heightened risk for late complications related to TBI, especially those related to growth, thyroid function, and neurocognition. Patients with an **underlying genetic condition** must also be monitored more closely for specific consequences of therapy, such as specific secondary malignancies in the Fanconi anemia population caused by an underlying DNA repair defect and patients with sickle cell anemia and thalassemia who are predisposed to iron overload.

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PART XIV

Allergic Disorders

OUTLINE

Chapter 166 Allergy and the Immunologic Basis of Atopic Disease
Chapter 167 Diagnosis of Allergic Disease
Chapter 168 Allergic Rhinitis
Chapter 169 Childhood Asthma
Chapter 170 Atopic Dermatitis (Atopic Eczema)
Chapter 171 Insect Allergy
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CHAPTER 166

Allergy and the Immunologic Basis of Atopic Disease

Cezmi A. Akdis, Scott H. Sicherer

Allergic or atopic patients have an altered state of reactivity to common environmental and food antigens that do not cause clinical reactions in unaffected people. Patients with clinical allergy usually produce immunoglobulin E (IgE) antibodies to the antigens that trigger their illness. The term *allergy* represents the clinical expression of IgE-mediated allergic diseases that have a familial predisposition and that manifest as hyperresponsiveness in target organs such as the lung, skin, gastrointestinal (GI) tract, and nose. The significant increase in the prevalence of allergic diseases in the last few decades is attributed to changes in environmental factors such as exposure to tobacco smoke, air pollution, indoor and outdoor allergens, respiratory viruses, obesity, and perhaps a decline in certain infectious diseases (hygiene hypothesis).

Key Elements of Allergic Diseases

Allergens

Allergens are almost always *proteins*, but not all proteins are allergens. For a protein antigen to display allergenic activity, it must induce IgE production, which must lead to a type 1 hypersensitivity response on subsequent exposure to the same protein. Biochemical properties of the allergen; stimulating factors of the innate immune response around the allergen substances at the time of exposure; stability of the allergen in the tissues, digestive system, skin, or mucosa; and the dose and time of stay in lymphatic organs during the interaction with the immune system are factors that may cause an antigen to become an allergen. This is distinguished from general antigen responses, which induce a state of immune responsiveness without associated IgE production.

Most allergens are proteins with molecular weight of 10-70 kDa. Molecules <10 kDa do not bridge adjacent IgE antibody molecules on the surfaces of mast cells or basophils. Most molecules >70 kDa do not pass through mucosal surfaces, a feature needed to reach **antigen-presenting cells (APCs)** for stimulation of the immune system. Allergens frequently contain **proteases** , which promote skin and mucosal epithelial barrier dysfunction and increase allergen penetration into host tissues. Low-molecular-weight moieties, such as drugs, can become allergens by reacting with serum proteins or cell membrane proteins to be recognized by the immune system. Carbohydrate structures can also be allergens and are most relevant with the increasing use of *biologics* in clinical practice; patients with cetuximab-induced anaphylaxis have IgE antibodies specific for galactose-α-1,3-galactose.

T Cells

Everyone is exposed to potential allergens. Atopic individuals respond to allergen exposure with rapid expansion of **T-helper type 2 (Th2)** cells that secrete cytokines, such as interleukin (IL)-4, IL-5, and IL-13, favoring IgE synthesis and eosinophilia. Allergen-specific IgE antibodies associated with atopic response are detectable by serum testing or positive immediate reactions to allergen extracts on skin-prick testing. The Th2 cytokines IL-4 and IL-13 play a key role in immunoglobulin isotype switching to IgE (Fig. 166.1). IL-5 and IL-9 are important in differentiation and development of eosinophils. The combination of IL-3, IL-4, and IL-9 contributes to mast cell activation. IL-9 is responsible for mucus production. Th2 cytokines are important effector molecules in the pathogenesis of asthma and allergic diseases; acute allergic reactions are characterized by infiltration of Th2 cells into affected tissues. In addition, IL-25, IL-33, and **thymic stromal lymphopoietin (TSLP)** secreted from epithelial cells on exposure to allergens and respiratory viruses contribute to Th2 response and eosinophilia.

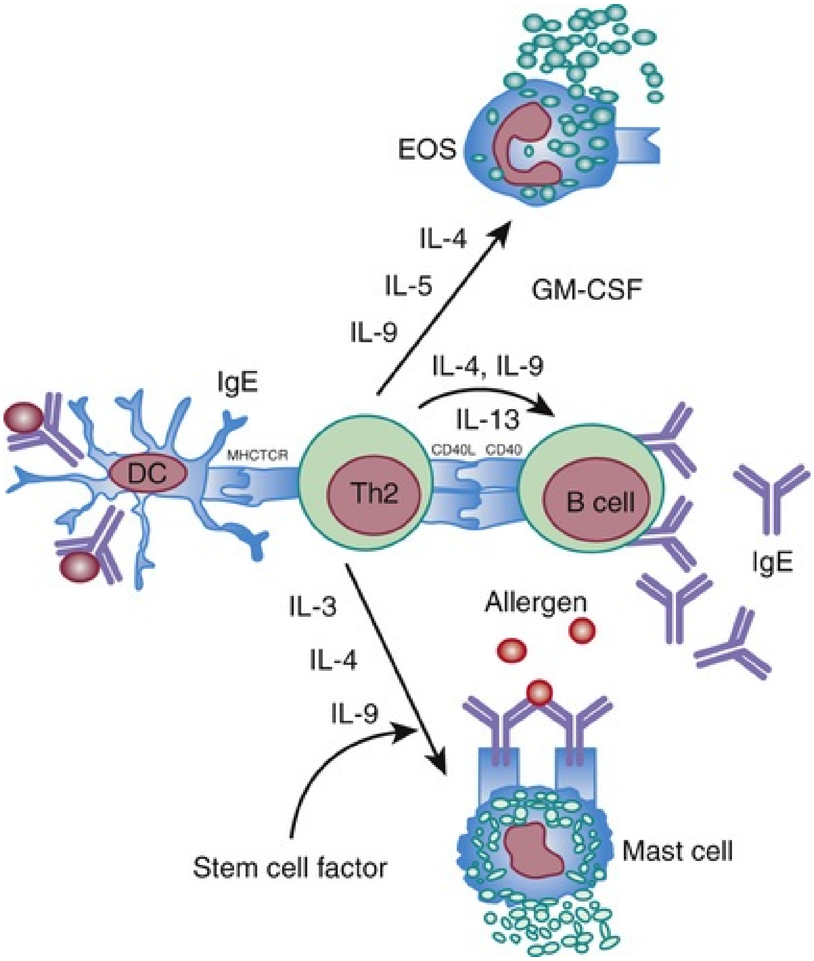

FIG. 166.1 **Role of Th2 cytokines in allergic cascade. DC, Dendritic cell; EOS, eosinophil; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; Th2, T-helper type 2 cell.**

A fraction of the immune response to allergen results in proliferation of **T-helper type 1 (Th1)** cells. Th1 cells are typically involved in the eradication of intracellular organisms, such as mycobacteria, because of the ability of Th1 cytokines to activate phagocytes and promote the production of opsonizing and complement-fixing antibodies. The Th1 component of allergen-specific immune response contributes to chronicity and the effector phase in allergic disease. Activation and apoptosis of epithelial cells induced by Th1 cell–secreted interferon-γ (IFN-γ), tumor necrosis factor (TNF)-α, and Fas ligand constitute an essential pathogenetic event for the formation of eczematous lesions in atopic dermatitis and bronchial epithelial cell shedding in asthma.

Chronic lesions of allergic reactions are characterized by infiltration of Th1 and **Th17 cells** . This is important because Th1 cytokines such as IFN-γ can potentiate the function of allergic inflammatory effector cells such as eosinophils and thereby contribute to disease severity. Th17 and Th22 cells link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both T-helper cell subsets play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. Cytokines in the IL-17 family act on multiple cell types, including epithelial cells and APCs, to cause the release of chemokines, antimicrobial peptides, and proinflammatory cytokines to enhance inflammation and antimicrobial responses. In addition, Th9 cells produce IL-9, but not other typical Th1, Th2, and Th17 cytokines, and constitute a distinct population of effector T cells that promotes tissue inflammation. Fig. 166.2 depicts the complex cytokine cascades involving Th1, Th2, Th9, Th17, and Th22 cells.

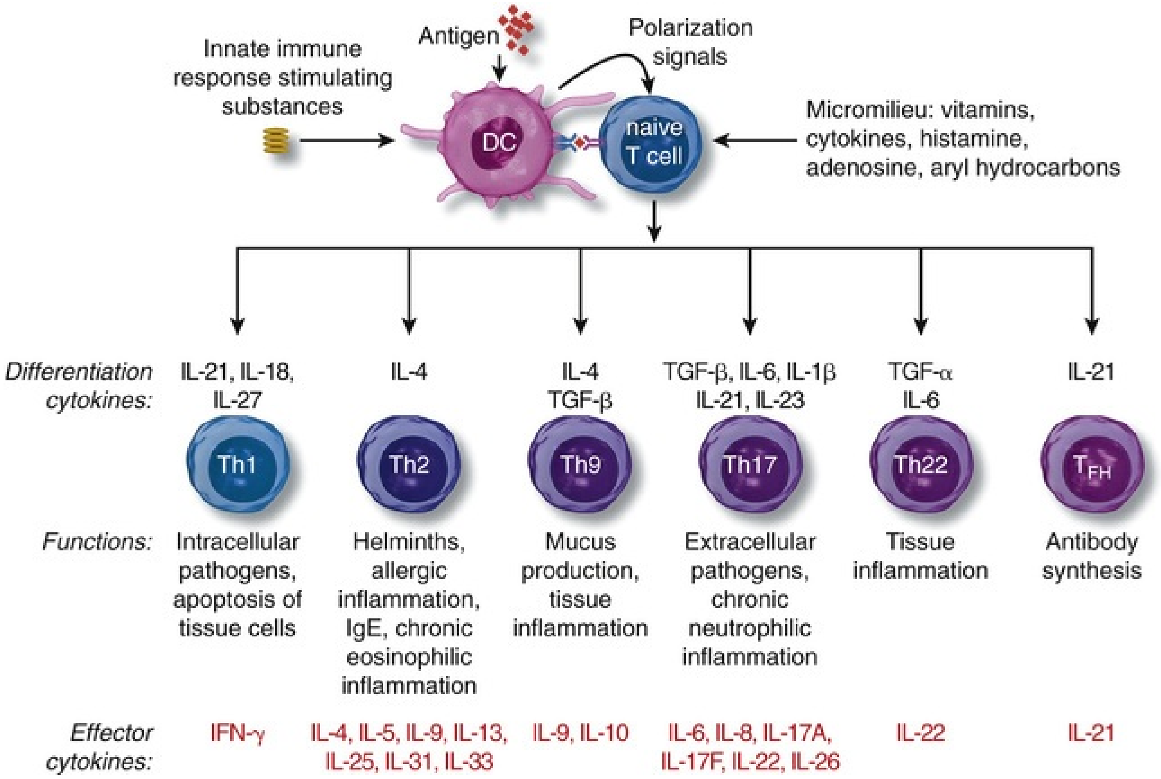
Antigen
Polarization signals
Innate immune response stimulating substances
DC
naive T cell
Micromilieu: vitamins, cytokines, histamine, adenosine, aryl hydrocarbons
Differentiation cytokines:
IL-21, IL-18, IL-27
IL-4
IL-4 TGF-β
TGF-β, IL-6, IL-1β IL-21, IL-23
TGF-α IL-6
IL-21
Th1
Th2
Th9
Th17
Th22
T$_{FH}$
Functions:
Intracellular pathogens, apoptosis of tissue cells
Helminths, allergic inflammation, IgE, chronic eosinophilic inflammation
Mucus production, tissue inflammation
Extracellular pathogens, chronic neutrophilic inflammation
Tissue inflammation
Antibody synthesis
Effector cytokines:
IFN-γ
IL-4, IL-5, IL-9, IL-13, IL-25, IL-31, IL-33
IL-9, IL-10
IL-6, IL-8, IL-17A, IL-17F, IL-22, IL-26
IL-22
IL-21

FIG. 166.2 Effector T-cell subsets. Following antigen presentation by dendritic cells (DCs), naïve T cells differentiate into Th1, Th2, Th9, Th17, Th22, and follicular helper (TFH) effector subsets. Their differentiation requires cytokines and other cofactors that are released from DCs and also expressed in the micromilieu. T-cell activation in the presence of interleukin-4 (IL-4) enhances differentiation and clonal expansion of Th2 cells, perpetuating the allergic response. IFN-γ, Interferon-γ; TGF-β, transforming growth factor-β. (From Akdis M, Palomares O, van de Veen W, et al: TH17 and TH22 cells: a confusion of antimicrobial response with tissue inflammation versus protection, *J Allergy Clin Immunol* 129:1438–1449, 2012.)

T-regulatory (or regulatory T) **cells (Tregs)** are a subset of T cells thought to play a critical role in expression of allergic and autoimmune diseases. These cells have the ability to suppress effector T cells of Th1, Th2, Th9, Th17, and Th22 phenotypes (Fig. 166.3). Tregs express $CD4^+$ $CD25^+$ surface molecules and immunosuppressive cytokines such as IL-10 and transforming growth factor-β (TGF-β_1). The forkhead box/winged-helix transcription factor gene *FOXP3* is expressed specifically by $CD4^+$ $CD25^+$ Tregs and programs their development and function. Adoptive transfer of Tregs inhibits the development of airway eosinophilia and protects against airway hyperreactivity in animal models of asthma. T-cell response to allergens in healthy individuals shows a wide range, from no detectable response to involvement of active peripheral tolerance mechanisms mediated by different subsets of Tregs. Individuals who are not allergic even though they are exposed to high doses of allergens, such as beekeepers and cat owners, show a detectable allergen-specific IgG4 response accompanied by IL-10–producing Tregs. It is thought that $CD4^+$ $CD25^+$ Tregs play an important role in mitigating the allergic immune response, and that the lack of such cells may predispose to the development of allergic diseases. Patients with mutations in the human *FOXP3* gene lack $CD4^+$ $CD25^+$ Tregs and develop severe immune dysregulation, with polyendocrinopathy, food allergy, and high serum IgE levels (XLAAD/IPEX disease) (see Chapter 152). In addition to Treg cells, IL-10–secreting and allergen-specific Breg cells increase during allergen-specific immunotherapy and may play a role in allergen tolerance.

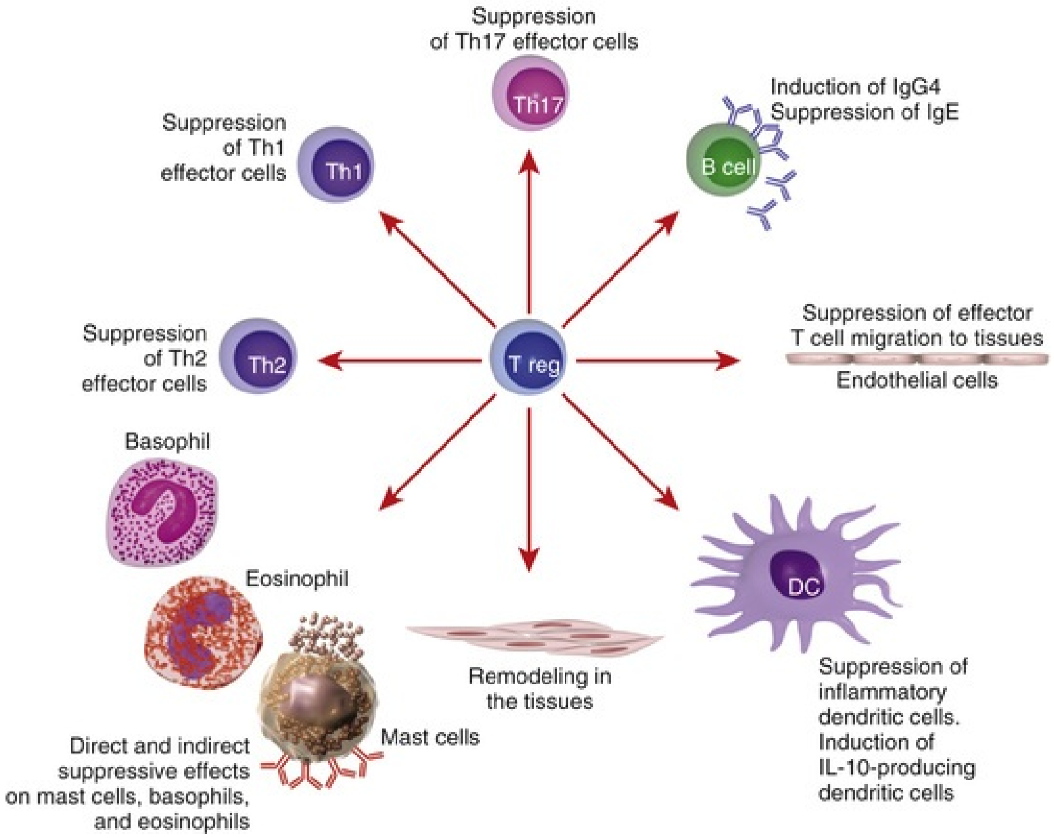
Suppression
of Th17 effector cells
Th17
Induction of IgG4
Suppression of IgE
B cell
Suppression
of Th1
effector cells
Th1
Suppression of effector
T cell migration to tissues
Endothelial cells
Suppression
of Th2
effector cells
Th2
T reg
Basophil
Eosinophil
DC
Remodeling in
the tissues
Mast cells
Suppression of
inflammatory
dendritic cells.
Induction of
IL-10-producing
dendritic cells
Direct and indirect
suppressive effects
on mast cells, basophils,
and eosinophils

FIG. 166.3 Control of allergen-specific immune responses. FoxP3$^+$, CD4$^+$, CD25$^+$, and Tr1 cells contribute to the control of allergen-specific immune responses in several major ways: Suppression of dendritic cells (DCs) that support the generation of effector T cells; suppression of Th1, Th2, and Th17 cells; suppression of allergen-specific IgE, and induction of IgG$_4$ and/or IgA; suppression of mast cells, basophils, and eosinophils; interaction with resident tissue cells and remodeling, and suppression of effector T-cell migration to tissues. IL-10, Interleukin-10. (From Akdis CA, Akdis M: Mechanisms and treatment of allergic disease in the big picture of regulatory T cells, *J Allergy Clin Immunol* 123:735–746, 2009.)

Innate Lymphoid Cells

Immune responses in populations of lymphoid cells that lack rearranged T- and B-cell antigen receptors and surface markers for myeloid and lymphoid lineages, such as T, B, and natural killer (NK) cells, show similarities to Th1, Th2, and Th17/Th22 types of immune responses. These latter cells are defined as the innate lymphoid cells **ILC1s, ILC2s,** and **ILC3s,** respectively, based on their transcription factors and cytokine production patterns. ILC1s mainly produce IFN-γ; ILC2s produce IL-5, IL-9, and IL-13; and ILC3s produce IL-17 and IL-22 without any need of antigen/allergen exposure. Strong evidence indicates that ILCs play substantial roles in protection against infection and the pathogenesis of inflammatory diseases, such as asthma, allergic diseases, and autoimmune diseases. ILCs control the mucosal environment through close interaction with epithelial cells and other tissue cells, cytokine production, and induction of chemokines that recruit suitable cell populations to initiate and promote distinct types of immune response development and tissue inflammation. ILC2s are likely involved in the induction of asthma, allergic rhinitis, eosinophilic esophagitis, and atopic dermatitis through activation by epithelium-derived cytokines (e.g., IL-33, IL-25, TSLP) and interaction with other immune cells.

Antigen-Presenting Cells

Dendritic cells (DCs), Langerhans cells, monocytes, and macrophages have the ability to present allergens to T cells and thereby modulate allergic inflammation by controlling the type of T-cell development. APCs are a heterogeneous group of cells that share the property of antigen presentation in the context of the major histocompatibility complex (MHC) and are found primarily in lymphoid organs and the skin. DCs and Langerhans cells are unique in their ability to prime naïve T cells and are responsible for the primary immune response, or the **sensitization phase** of allergy. Monocytes and macrophages are thought to contribute to activating memory T-cell responses on reexposure to allergen, which characterizes the **elicitation phase** of allergy.

Peripheral DCs residing in sites such as the skin, intestinal lamina propria, and lung are relatively immature. These immature DCs take up antigens in tissues and then migrate to the T-cell areas in locally draining lymph nodes. The DCs undergo phenotypic and functional changes during migration, characterized by increased expression of MHC class I, MHC class II, and co-stimulatory molecules that react with CD28 expressed on T cells. In the lymph nodes, they directly present processed antigens to resting T cells to induce their proliferation and differentiation.

Mature DCs have been designated as **myeloid** or **plasmacytoid** on the basis of their ability to favor Th1 or Th2 differentiation, respectively. The critical factor for polarization to Th1 cells is the level of IL-12 produced by myeloid DC. By contrast, plasmacytoid DCs have low levels of IL-12. Plasmacytoid DC particularly play a role in antiviral immunity by rapid production of high amounts of IFN-α and also help B cells for antibody production. There is considerable interest in the role of TSLP, which is overexpressed in the mucosal surfaces and skin of atopic individuals. TSLP enhances Th2 differentiation by inducing expression of OX40L on immature myeloid DCs in the absence of IL-12 production.

Presence of allergen-specific IgE on the cell surfaces of APCs is a unique feature of atopy. Importantly, the formation of high-affinity IgE receptor I (**FcεRI**)/IgE/allergen complexes on APC surfaces greatly facilitates allergen uptake and presentation. The clinical importance of this phenomenon is supported by the observation that FcεRI-positive Langerhans cells bearing IgE molecules are a prerequisite for skin-applied, aeroallergen provocation of eczematous lesions in patients with atopic dermatitis. The role of the low-affinity IgE receptor II (**FcεRII, CD23**) on monocytes/macrophages is less clear, although under certain conditions it apparently can also facilitate antigen capture. Cross-linking of FcεRII, as well as FcεRI, on monocytes/macrophages leads to the release of inflammatory mediators. There is a critical role for DCs in induction of oral tolerance; tolerogenic DCs are compartmentalized within the mucosa and present antigen through a mechanism designed to produce a Th1/Treg-suppressive response that ablates allergen-specific T cells.

Immunoglobulin E and Its Receptors

The acute allergic response depends on IgE and its ability to bind selectively to the α chain of the high-affinity FcεRI or the low-affinity FcεRII (CD23). Cross-linking of receptor-bound IgE molecules by allergen initiates a complex intracellular signaling cascade, followed by the release of various mediators of allergic inflammation from mast cells and basophils. The FcεRI molecule is also found on the surface of antigen-presenting DCs (e.g., Langerhans cells), but differs from the structure found on mast cells/basophils in that the FcεRI molecule found on DCs lacks the β chain. CD23 is found on B cells, eosinophils, platelets, and DCs. Cross-linking and FcεRI aggregation on mast cells and basophils can also lead to anaphylaxis (see Chapter 174). Differential expression of tyrosine kinases responsible for positive and negative regulation of mast cell/basophil degranulation are thought to be responsible for this aberrant allergic response.

The induction of IgE synthesis requires 2 major signals. The 1st signal (signal 1) initiates IL-4 or IL-13 activation of germline transcription at the ε Ig locus, which dictates isotype specificity. The 2nd signal (signal 2) involves the engagement of CD40 on B cells by CD40 ligand expressed on T cells. This engagement results in activation of the recombination machinery, resulting in

DNA switch recombination. Interactions between several co-stimulatory molecule pairs (CD28 and B7; lymphocyte function–associated antigen-1 and intercellular adhesion molecule-1; CD2 and CD58) can further amplify signal 1 and signal 2 to enhance IgE synthesis. Factors that inhibit IgE synthesis include Th1-type cytokines (IL-12, IFN-α, IFN-γ), IL-10 from Tregs, Breg cells, as well as regulatory DCs and microbial DNA containing CpG (cytosine-phosphate-guanine) repeats.

Eosinophils

Allergic diseases are characterized by peripheral blood and tissue eosinophilia. Eosinophils participate in both innate and adaptive immune responses and, like mast cells, contain dense intracellular granules that are sources of inflammatory proteins (see Fig. 155.1). These granule proteins include major basic protein, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Eosinophil granule proteins damage epithelial cells, induce airway hyperresponsiveness, and cause degranulation of basophils and mast cells. Major basic protein released from eosinophils can bind to an acidic moiety on the M2 muscarinic receptor and block its function, thereby leading to increased acetylcholine levels and the development of increased airway hyperreactivity. Eosinophils are also a rich source of prostaglandins and leukotrienes; in particular, cysteinyl leukotriene C4 contracts airway smooth muscle and increases vascular permeability. Other secretory products of eosinophils include cytokines (IL-4, IL-5, TNF-α), proteolytic enzymes, and reactive oxygen intermediates, all of which significantly enhance allergic tissue inflammation.

Several cytokines regulate the function of eosinophils in allergic disease. Eosinophils develop and mature in the bone marrow from myeloid precursor cells activated by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Allergen exposure of allergic patients causes resident hematopoietic CD34 cells to express the IL-5 receptor. The IL-5 receptor activation induces eosinophil maturation, causing eosinophils to synthesize granule proteins, prolonging their survival, potentiating degranulation of eosinophils, and stimulating release of eosinophils from the bone marrow. GM-CSF also enhances proliferation, cell survival, cytokine production, and degranulation of eosinophils. Certain chemokines, such as RANTES (regulated on activation, normal T-cell expressed and secreted), macrophage inflammatory protein-1α (MIP-1α), and eotaxins, are important for recruiting eosinophils into local allergic tissue inflammatory reactions. Eotaxins mobilize IL-5–dependent eosinophil colony–forming progenitor cells from the bone marrow. These progenitors are rapidly cleared from the blood and either return to the bone marrow or are recruited to inflamed tissue sites.

Mast Cells

Mast cells are derived from CD34 hematopoietic progenitor cells that arise in bone marrow. On entering the circulation, they travel to peripheral tissue, where they undergo tissue-specific maturation. Mast cell development and survival relies on interactions between the tyrosine kinase receptor c-kit expressed on the surface of mast cells and the fibroblast-derived c-kit ligand, the stem cell factor. Unlike mature basophils, mature mast cells do not typically circulate in the blood. They are instead widely distributed throughout connective tissues, where they often lie adjacent to blood vessels and beneath epithelial surfaces that are exposed to the external environment, such as the respiratory tract, gastrointestinal (GI) tract, and skin. So placed, mast cells are positioned anatomically to participate in allergic reactions. At least 2 subpopulations of human mast cells are recognized: mast cells with tryptase and mast cells with both tryptase and chymase. Mast cells with tryptase are the predominant type found in the lung and small intestinal mucosa, whereas mast cells with both tryptase and chymase are the predominant type found in skin, the GI submucosa, and blood vessels.

Mast cells contain, or produce on appropriate stimulation, a diverse array of mediators that have different effects on allergic inflammation and organ function. They include preformed granule-associated mediators (histamine, serine proteases, proteoglycans) and membrane-derived lipid, cytokine, and chemokine mediators arising from de novo synthesis and release. The most important mast cell–derived lipid mediators are the **cyclooxygenase** and **lipoxygenase** metabolites of arachidonic acid, which have potent inflammatory activities. The major cyclooxygenase product of mast cells is **prostaglandin D_2** , and the major lipoxygenase products are the sulfidopeptide **leukotrienes** (LTs): LTC_4 and its peptidolytic derivatives LTD_4 and LTE_4 . Mast cells also can produce cytokines that promote Th2-type responses (IL-4, IL-13, GM-CSF) and inflammation (TNF-α, IL-6) and regulate tissue remodeling (TGF, vascular endothelial cell growth factor). Immunologic activation of mast cells and basophils typically begins with cross-linkage of IgE bound to the FcεRI with multivalent allergen. Mast cell surface FcεRI is increased by IL-4 and IgE. Surface levels of FcεRI decrease in patients receiving treatment with anti-IgE antibody that lowers serum IgE, which is of potential therapeutic interest.

Mechanisms of Allergic Tissue Inflammation

IgE-mediated immune responses can be classified chronologically according to 3 reaction patterns. The **early-phase response** is the immediate response after allergen is introduced into target organs. This response is characterized by mast cell degranulation and release of preformed mediators, occurring within an immediate time frame of 1-30 min after allergen exposure and resolving within 1-3 hr. Acute reactions are associated with increased local vascular permeability, which leads to leakage of plasma proteins, tissue swelling, and increased blood flow, as well as itching, sneezing, wheezing, and acute abdominal cramps in the skin, nose, lung, and GI tract, respectively, depending on the targeted organ.

A 2nd, **late-phase response** can occur within hours of allergen exposure, reaching a maximum at 6-12 hr and resolving by 24 hr. Late-phase responses are characterized in the skin by edema, redness, and induration; in the nose by sustained nasal blockage; and in the lung by airway obstruction and persistent wheezing. In general, late-phase responses are associated with early infiltration of neutrophils and eosinophils, followed by basophils, monocytes, macrophages, and Th2-type cells. Recruitment of inflammatory cells from the circulation requires increased expression of adhesion molecules on their cell surfaces and expression of their ligand on endothelial cells, which are under the control of cytokines. Several hours after allergen exposure, TNF-α released by activated mast cells induces the vascular endothelial expression of cell adhesion molecules, and this change leads to transendothelial migration of various inflammatory cells. Preferential accumulation of eosinophils occurs through interactions between selective adhesion molecules on the eosinophil cell surface (e.g., α_4 β_1 integrin or very late antigen-4); vascular cell adhesion molecule-1 surface expression can be enhanced by IL-4 and IL-13 on endothelial cells. ILC2s receive signals from the epithelial cells, such as IL-33, TSLP, and IL-25, and are activated and start to release their cytokines IL-5 and IL-13 to initiate a type 2 immune response.

Chemokines are chemotactic cytokines that play a central role in tissue-directed migration of inflammatory cells. RANTES, MIP-1α, monocyte chemotactic protein (MCP)-3, and MCP-4 are chemoattractants for eosinophils and mononuclear cells, whereas eotaxins are relatively selective for eosinophils. These chemoattractants have been detected in epithelium, macrophages, lymphocytes, and eosinophils at sites of late-phase responses and allergic tissue inflammation. Blockade of these chemokines leads to significant reduction in tissue-directed migration of allergic effector cells.

In the 3rd reaction pattern, **chronic allergic disease** , tissue inflammation can persist for days to years. Several factors contribute to persistent tissue inflammation, including recurrent exposure to allergens and microbial agents. The repeated stimulation of allergic effector cells such as mast cells, basophils, eosinophils, and Th2 cells contributes to unresolved inflammatory conditions. Additionally, Th2-type cytokines (IL-3, IL-5, GM-CSF) secreted during allergic reactions can prolong survival of allergic effector cells by delaying apoptosis. Local differentiation of tissue-infiltrating eosinophil precursors induced by IL-5 results in self-generation of eosinophils, further sustaining damage of local tissue. Tissue remodeling leading to irreversible changes in target organs is also a feature of chronic allergic disease. In asthma, **remodeling** involves thickening of the airway walls and submucosal tissue, as well as smooth muscle hypertrophy and hyperplasia, which are associated with a decline in lung function. This is an unexpected role for eosinophils in airway remodeling as well as chronic inflammation. In atopic dermatitis, lichenification is an obvious manifestation of skin remodeling.

Generally, it is considered that a type 2 immune response underlines a majority of asthma cases, atopic dermatitis, chronic rhinosinusitis, and allergic rhinitis as a general characteristic of an immune/inflammatory response. Type 2 immune response involves Th2 cells, type 2 B cells, ILC2, IL-4 secreting NK T cells, basophils, eosinophils and mast cells and their major cytokines. From a complex network of cytokines, IL-4, IL-5, IL-9, and IL-13 are mainly secreted from the immune system cells, and IL-25, IL-31, IL-33, and TSLP from tissue cells, particularly epithelial cells. Many asthma-related antigens, such as protease allergens, fungal extracts, and viral infection, trigger IL-33, TSLP, and IL-25 production from epithelial cells and various immune cells and induce eosinophilic asthma–like airway inflammation through activation of lung ILC2s.

IL-31, on the other hand, plays a role in pruritus in atopic dermatitis. Th2 cytokines do not only maintain allergic inflammation but also influence tissue remodeling by activating resident cells in target organs; IL-4, IL-9, and IL-13 induce mucus hypersecretion and metaplasia of mucus cells; IL-4 and IL-13 stimulate fibroblast growth and synthesis of extracellular matrix proteins; and IL-5 and IL-9 increase subepithelial fibrosis. TGF-β produced by eosinophils and fibroblasts can also enhance subepithelial fibrosis. IL-11 expressed by eosinophils and epithelial cells contributes to subepithelial fibrosis, in addition to enhancing deposition of collagen and the accumulation of fibroblasts. The resulting tissue injury amplifies further epithelial injury through proinflammatory cytokine release, extracellular matrix deposition in target organs, and angiogenesis. Genetic predisposition to aberrant injury-repair responses may contribute to chronicity of illness. Once the allergic immune response is established, it can be self-perpetuating due to a general type 2 immune response and can lead to chronic disease in genetically predisposed individuals. The subsequent infiltration of Th1 cells and Th17 cells enhances the inflammatory potential of allergic effector cells and contributes to chronic tissue inflammatory responses through the release of proinflammatory cytokines and chemokines. In addition, an autoimmune response might be playing a causative role in allergic inflammation resulting from possible mechanisms through IgE autoantibodies, IgG autoantibodies, and Th1-cell and Th17-cell autoreactivity.

Genetic Basis of Atopy

Allergic diseases are complex genetic conditions susceptible to environmental triggers. Several major groups of genes are associated with allergic diseases: genes that regulate systemic expression of atopy (increased IgE synthesis, eosinophilia, mast cell responses) and that are usually expressed among various allergic diseases, genes that control barrier function in specific target organs (e.g., skin in atopic dermatitis, lung in asthma, GI tract in food allergy), and genes encoding pattern-recognition receptors of the innate immune system that engage microbial pathogens and influence adaptive immune responses. Once allergic responses have been initiated, a genetic predisposition to chronic allergic inflammation and aberrant injury-repair responses contribute to tissue remodeling and persistent disease.

Atopic diseases have a strong familial predisposition, with approximately 60% heritability found in twin studies of asthma and atopic dermatitis. The 5q23-35 region comprises several genes implicated in allergic disease pathogenesis, including genes coding for Th2 cytokines (IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF). Among these, *IL4* is a well-studied potential candidate gene. A nucleotide change at position 589 of the *IL4* promoter region is associated with the formation of a unique binding site for NF-AT (**n** uclear **f** actor for **a** ctivated **T** cells) transcription factor, increased IL-4 gene transcription, higher NF-AT binding affinity, and increased IgE production. Similarly, *IL13* coding region variants have been associated with asthma and atopic dermatitis. An association has been found between atopy and a gain-of-function polymorphism on chromosome 16, which codes for the α subunit of the IL-4R. This finding is consistent with the important role of IL-4, IL-13, and their receptors in the immunopathogenesis of allergic diseases.

Genome-wide searches have also linked atopy to chromosome region 11q13. The gene encoding the β subunit of FcεRI-β has been proposed to be the candidate gene in this region. The β subunit gene modifies the FcεRI activity on mast cells, and several genetic variants of FcεRI-β are associated with asthma and atopic dermatitis. Chromosome 6 contains genes coding for human leukocyte antigen class I and class II molecules, which regulate the specificity and intensity of the immune responses to specific allergens. IgE responses to specific allergens, such as ragweed antigen Amb a V and mite allergen *Der p* I, have been linked to specific MHC class II loci. TNF-α, a key cytokine that contributes to the influx of inflammatory cells, is also located on chromosome 6. TNF-α polymorphisms are associated with asthma. A recent genome-wide association study showed that genetic polymorphisms in the gene encoding IL-33, which is a major activator of ILC2s, and its receptor IL-1RL1 (ST2) are strongly linked to asthma development.

Barrier dysfunction has a key role in the pathogenesis of allergic diseases. Genetic linkage studies of atopic dermatitis have demonstrated the importance of chromosome 1q21, which contains a cluster of genes involved in epidermal differentiation. **Filaggrin** is a protein that is essential in the formation of the stratum corneum. Null mutations of the filaggrin gene are strongly associated with early onset and severe atopic dermatitis. Mutations in the gene encoding the serine protease inhibitor SPINK5 has been shown to cause **Netherton disease** , a single-gene disorder associated with erythroderma, food allergy, and high serum IgE levels. A common polymorphism in SPINK5 (in particular, Glu420Lys) increases the risk of developing atopic dermatitis and asthma. SPINK5 is expressed in the outer epidermis and is thought to be critical to neutralizing the proteolytic activity of *Staphylococcus aureus* and common allergens such as *Der p* I, which use these proteases to penetrate the skin to induce allergic responses. Barrier dysfunction is involved in other allergic diseases, such as asthma and rhinosinusitis, but likely involves other barrier genes, such as those encoding gap junctions.

Candidate genes associated with asthma susceptibility have been identified by positional cloning: *GPRA* (G-protein coupled receptor for asthma susceptibility on chromosome 7p14), *ADAM-33* (a disintegrin and metalloproteinase 33 on chromosome 20p), and *DPP10* (dipeptidyl peptidase 10 on chromosome 2q14). The functions of these genes do not fit into classical pathways of atopy and therefore provide new insights into asthma pathogenesis. *GPRA* encodes a G-protein coupled receptor, with isoforms expressed in bronchial epithelial cells and smooth muscle in asthmatic persons, suggesting an important role for these tissues in asthma. *ADAM-33* is expressed in bronchial smooth muscle and has been linked to bronchial hyperresponsiveness. *DPP10* encodes a dipeptidyl dipeptidase that can remove the terminal 2 peptides from certain proinflammatory chemokines, a change that may modulate allergic inflammation.

Pattern-recognition receptors of the innate immune system, which are expressed by epithelial cells and DCs, are associated with disease susceptibility. These receptors recognize specific microbial components. Polymorphisms in CD14 (engages endotoxin), Toll-like receptor 2 (which engages *S. aureus*), and T-cell immunoglobulin domain and mucin domain (which engage hepatitis A virus) correlate with asthma and/or atopic dermatitis susceptibility. Dysregulation of these frontline immune defense systems would permit abnormal response to common environmental allergens.

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CHAPTER 167

Diagnosis of Allergic Disease

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Allergy History

Obtaining a complete history from the allergic patient involves eliciting a description of all symptoms along with their timing and duration, exposure to common allergens, and responses to previous therapies. Because patients often suffer from more than one allergic disease, the presence or absence of other allergic diseases, including allergic rhinoconjunctivitis, asthma, food allergy, eosinophilic esophagitis, atopic dermatitis, and drug allergy, should be determined. A family history of allergic disease is common and is one of the most important factors predisposing a child to the development of allergies. The risk of allergic disease in a child approaches 50% when 1 parent is allergic and 66% when both parents are allergic, with maternal history of atopy having a greater effect than paternal history.

Several characteristic behaviors are often seen in allergic children. Because of nasal pruritus and rhinorrhea, children with allergic rhinitis often perform the **allergic salute** by rubbing their nose upward with the palm of their hand. This repeated maneuver may give rise to the **nasal crease** , a horizontal wrinkle over the bridge of the nose. Characteristic vigorous **grinding** of the eyes with the thumb and side of the fist is frequently observed in children with allergic conjunctivitis. The **allergic cluck** is produced when the tongue is placed against the roof of the mouth to form a seal and withdrawn rapidly in an effort to scratch the palate. The presence of other symptoms, such as fever, unilateral nasal obstruction, and purulent nasal discharge, suggests other diagnoses.

The timing of onset and the progression of symptoms are relevant. The onset of recurrent or persistent nasal symptoms coinciding with placement in a daycare center might suggest recurrent infection rather than allergy. When patients present with a history of episodic acute symptoms, it is important to review the setting in which symptoms occur as well as the activities and exposures that immediately precede their onset. Symptoms associated with lawn mowing suggest allergy to grass pollen or fungi, whereas if symptoms occur in homes with pets, animal dander sensitivity is an obvious consideration. Reproducible reactions after ingestion of a specific food raise the possibility of food allergy. When symptoms wax and wane but evolve gradually and are more chronic in duration, a closer look at whether the timing and progression of symptoms correlate with exposure to a seasonal aeroallergen is warranted.

Aeroallergens , such as pollens and fungal spores, are prominent causes of allergic disease. The concentrations of these allergens in outdoor air fluctuate seasonally. Correlating symptoms with seasonal pollination patterns of geographically relevant plants and trees along with information provided by local pollen counts can aid in identifying the allergen. Throughout most of the United States, trees pollinate in the early spring, grasses pollinate in the late spring and early summer, and weeds pollinate in late summer through the fall. The presence of fungal spores in the atmosphere follows a seasonal pattern in the northern United States, with spore counts rising with the onset of warmer weather and peaking in late summer months, only to recede again with the first frost through the winter. In warmer regions of the southern United States, fungal spores and grass pollens may cause symptoms on a perennial basis.

Rather than experiencing seasonal symptoms, some patients suffer allergic symptoms year-round. In these patients, sensitization to perennial allergens usually found indoors, such as dust mites, animal dander, cockroaches, and fungi, warrants consideration. Species of certain fungi, such as *Aspergillus* and *Penicillium,* are found indoors, whereas *Alternaria* is found in both indoor and outdoor environments. Cockroach and rodent allergens are often problematic in inner-city environments. Patients sensitive to perennial allergens often also become sensitized to seasonal allergens and experience baseline symptoms year-round with worsening during the pollen seasons.

The age of the patient is an important consideration in identifying potential allergens. Infants and young children are first sensitized to allergens that are in their environment on a continuous basis, such as dust mites, animal dander, and fungi. Sensitization to seasonal allergens usually takes several seasons of exposure to develop and is thus unlikely to be a significant trigger of symptoms in infants and toddlers.

Food allergies are more common in infants and young children, resulting primarily in cutaneous, gastrointestinal, and, less frequently, respiratory and cardiovascular symptoms. Symptoms of immediate or IgE-mediated hypersensitivity food reactions develop within minutes to 2 hr after ingestion of the offending food. Symptoms of non–IgE-mediated food allergies are often delayed or chronic (see Chapter 176).

Complete information from previous evaluations and prior treatments for allergic disease should be reviewed, including impact of changes in local environment (e.g., home vs school), response to medications, elimination diets, and duration and impact of allergen immunotherapy (if applicable). Improvement in symptoms with medications or avoidance strategies used to treat allergic disease provides additional evidence for an allergic process.

A thorough environmental survey should be performed, focusing on potential sources of allergen and/or irritant exposure, particularly when respiratory symptoms (upper/lower) are reported. The age and type of the dwelling, how it is heated and cooled, the use of humidifiers or air filtration units, and any history of water damage should be noted. Forced air heating may stir up dust mite, fungi, and animal allergens. The irritant effects of wood-burning stoves, fireplaces, and kerosene heaters may provoke respiratory symptoms. Increased humidity or water damage in the home is often associated with greater exposure to dust mites and fungi. Carpeting serves as a reservoir for dust mites, fungi, and animal dander. The number of domestic pets and their movements about the house should be ascertained. Special attention should be focused on the bedroom, where a child spends a significant proportion of time. The age and type of bedding, the use of dust mite covers on pillows and mattresses, the number of stuffed animals, type of window treatments, and the accessibility of pets to the room should be reviewed. The number of smokers in the home, and what and where they smoke is useful information. Activities that might result in exposure to allergens or respiratory irritants such as paint fumes, cleansers, sawdust, or glues should be identified. Similar information should be obtained in other environments where the child spends long periods, such as a relative's home or school setting.

Physical Examination

In patients with **asthma** , *spirometry* should be performed. If **respiratory distress** is observed, *pulse oximetry* should be performed.

The child presenting with a chief complaint of rhinitis or rhinoconjunctivitis should be observed for mouth breathing, paroxysms of sneezing, sniffing/snorting, throat clearing, and rubbing of the nose and eyes (representing pruritus). Infants should be observed during feeding for nasal obstruction severe enough to interfere with feeding or for more obvious signs of aspiration or gastroesophageal reflux. The frequency and nature of coughing that occurs during the interview and any positional change in coughing or wheezing should be noted. Children with asthma should be observed for congested or wet cough, tachypnea at rest, retractions, and audible wheezes, which may worsen with crying. Patients with atopic dermatitis should be monitored for repetitive scratching and the extent of skin involvement.

Because children with severe asthma as well as those receiving chronic or frequent oral corticosteroids may experience growth suppression, an accurate height should be plotted at regular intervals. Long-term follow-up studies suggest that use of inhaled glucocorticoids in prepubertal children is associated with a small initial decrease in attained height (1 cm) that may persist as a reduction in adult height. Poor weight gain in a child with chronic chest symptoms should prompt consideration of cystic fibrosis. Anthropometric measures are also important to monitor in those on restricted diets because of multiple food allergies or eosinophilic esophagitis. Blood pressure should be measured to evaluate for steroid-induced hypertension. The patient with acute asthma may present with **pulsus paradoxus** , defined as a drop in systolic blood pressure during inspiration >10 mm Hg. Moderate to severe airway obstruction is indicated by a decrease of >20 mm Hg. An increased heart rate may be the result of an asthma flare or the use of a β-agonist or decongestant. Fever is not caused by allergy alone and should prompt consideration of an infectious process, which may exacerbate asthma.

Parents are often concerned about blue-gray to purple discolorations beneath their child's lower eyelids, which can be attributed to venous stasis and are referred to as **allergic shiners** (Fig. 167.1). They are found in up to 60% of allergic patients and almost 40% of patients *without* allergic disease. Thus, “shiners” may suggest, but are not diagnostic of, allergic disease. In contrast, the **Dennie-Morgan folds** (Dennie lines) are a feature of atopic dermatitis (Fig. 167.1). These are prominent infraorbital skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin.

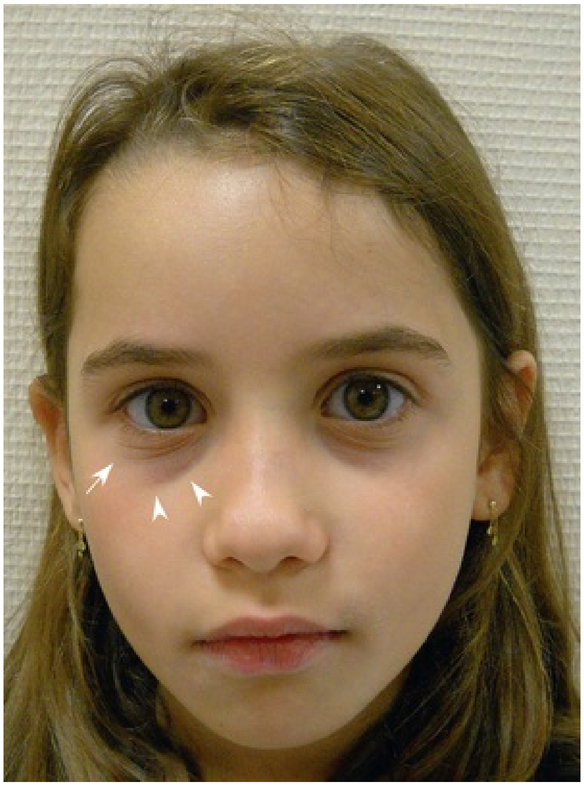

FIG. 167.1 Bilateral Dennie-Morgan folds. Several linear wrinkles beneath the lower eyelashes *(white arrow)* associated with bilateral allergic shiners: dark circles beneath the lower eyelid *(arrowheads).* (From Blanc S, Bourrier T, Albertini M, et al: Dennie-Morgan fold plus dark circles: suspect atopy at first sight, *J Pediatr* 166:1541, 2015.)

In patients with **allergic conjunctivitis** , involvement of the eyes is typically bilateral. Examination of the conjunctiva reveals varying degrees of lacrimation, conjunctival injection, and edema. In severe cases, periorbital edema involving primarily the lower eyelids or **chemosis** (conjunctival edema that is gelatinous in appearance) may be observed. The classic discharge associated with allergic conjunctivitis is usually described as “stringy” or “ropy.” In children with vernal conjunctivitis, a more severe, chronic phenotype, examination of the tarsal conjunctiva may reveal cobblestoning. **Keratoconus** , or protrusion of the cornea, may occur in patients with vernal conjunctivitis or periorbital atopic dermatitis as a result of repeated trauma produced by persistent rubbing of the eyes. Children treated with high-dose or chronic corticosteroids are at risk for development of posterior subcapsular cataracts.

The external ear should be examined for eczematous changes in patients with atopic dermatitis, including the postauricular area and base of the earlobe. Because otitis media with effusion is common in children with allergic rhinitis, pneumatic otoscopy should be performed to evaluate for the presence of fluid in the middle ear and to exclude infection.

Examination of the nose in allergic patients may reveal the presence of a nasal crease. Nasal patency should be assessed, and the nose examined for structural abnormalities affecting nasal airflow, such as septal deviation, turbinate hypertrophy, and nasal polyps. Decrease or absence of the sense of smell should raise concern about chronic sinusitis or nasal polyps. Nasal polyps in children should raise concerns of cystic fibrosis. The nasal mucosa in allergic rhinitis is classically described as pale to purple compared with the beefy-red mucosa of patients with nonallergic rhinitis. Allergic nasal secretions are typically thin and clear. Purulent secretions suggest another cause of rhinitis. The frontal and maxillary sinuses should be palpated to identify tenderness to pressure that might be associated with acute sinusitis.

Examination of the lips may reveal cheilitis caused by drying of the lips from continuous mouth breathing or repeated licking of the lips in an attempt to replenish moisture and relieve discomfort (**lip licker's dermatitis**). Tonsillar and adenoidal hypertrophy along with a history of impressive snoring raises the possibility of obstructive sleep apnea. The posterior pharynx should be examined for the presence of postnasal drip and posterior pharyngeal lymphoid hyperplasia (“cobblestoning”).

Chest findings in asthmatic children vary significantly and may depend on disease duration, severity, and activity. In a child with well-controlled asthma, the chest should appear entirely normal on examination between asthma exacerbations. Examination of the same child during an acute episode of asthma may reveal hyperinflation, tachypnea, use of accessory muscles (retractions), wheezing, and decreased air exchange with a prolonged expiratory time. Tachycardia may be caused by the asthma exacerbation or accompanied by jitteriness after treatment with β-agonists. Decreased airflow or rhonchi and wheezes over the right chest may be noted in children with mucus plugging and right middle lobe atelectasis. The presence of cyanosis indicates severe respiratory compromise. Unilateral wheezing after an episode of coughing and choking in a small child without a history of previous respiratory illness suggests **foreign body aspiration** . Wheezing limited to the larynx in association with inspiratory stridor may be seen in older children and adolescents with **vocal cord dysfunction.** Digital clubbing is rarely seen in patients with uncomplicated asthma and should prompt further evaluation to rule out other potential chronic diagnoses, such as cystic fibrosis.

The skin of the allergic patient should be examined for evidence of urticaria/angioedema or atopic dermatitis. **Xerosis** , or dry skin, is the most common skin abnormality of allergic children. **Keratosis pilaris** , often found on facial cheeks and extensor surfaces of the upper arms and thighs, is a benign condition characterized by skin-colored or slightly pink papules caused by keratin plugs lodged in the openings of hair follicles. Examination of the skin of the palms and soles may reveal thickened skin and exaggerated palmar and plantar creases (**hyperlinearity**) in children with moderate to severe atopic dermatitis.

Diagnostic Testing

In Vitro Tests

Allergic diseases are often associated with increased numbers of eosinophils circulating in the peripheral blood and invading the tissues and secretions of target organs. **Eosinophilia** , defined as the presence of >500 eosinophils/µL in peripheral blood, is the most common hematologic abnormality of allergic patients. Seasonal increases in the number of circulating eosinophils may be observed in sensitized patients after exposure to allergens such as tree, grass, and weed pollens. The number of circulating eosinophils can be suppressed by certain infections and systemic corticosteroids. In certain pathologic conditions, such as drug reactions, eosinophilic pneumonias, and eosinophilic esophagitis, significantly increased numbers of eosinophils may be present in the target organ in the absence of peripheral blood eosinophilia. Increased numbers of eosinophils are observed in a wide variety of disorders in addition to allergy; eosinophil counts >1500 without an identifiable etiology should suggest 1 of the 2 hypereosinophilic syndromes (Table 167.1 ; see Chapter 155).

Table 167.1

Differential Diagnosis of Childhood Eosinophilia

Physiologic

Prematurity
Infants receiving hyperalimentation
Hereditary

Infectious

Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)
Mycobacterial (tuberculosis, leprosy)
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)

Pulmonary

Allergic (rhinitis, asthma)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Loeffler syndrome
Hypersensitivity pneumonitis
Eosinophilic pneumonia (chronic, acute)
Pulmonary interstitial eosinophilia

Dermatologic

Atopic dermatitis
Pemphigus
Dermatitis herpetiformis
Infantile eosinophilic pustular folliculitis
Eosinophilic fasciitis (Schulman syndrome)
Eosinophilic cellulitis (Wells syndrome)
Kimura disease (angiolymphoid hyperplasia with eosinophilia)

Hematologic/Oncologic

Neoplasm (lung, gastrointestinal, uterine)
Leukemia/lymphoma

Myelofibrosis
Myeloproliferative (FIP1L1-PDGFRA–positive) hypereosinophilic syndrome
Lymphatic hypereosinophilic syndrome
Systemic mastocytosis

Immunologic

T-cell immunodeficiencies
Hyper-IgE (Job) syndrome
Wiskott-Aldrich syndrome
Graft-versus-host disease
Drug hypersensitivity
Postirradiation
Postsplenectomy

Endocrine

Addison disease
Hypopituitarism

Cardiovascular

Loeffler disease (fibroplastic endocarditis)
Congenital heart disease
Hypersensitivity vasculitis
Eosinophilic myocarditis

Gastrointestinal

Benign proctocolitis
Inflammatory bowel disease
Eosinophilic gastrointestinal diseases (EGID)

FIP1L1-PDGFRA, FIP1-like 1–platelet-derived growth factor receptor α.

Nasal and bronchial secretions may be examined for the presence of eosinophils. The presence of eosinophils in the sputum of asthmatic patients is classic. An increased number of eosinophils in a smear of nasal mucus with Hansel stain is a more sensitive indicator of nasal allergies than peripheral blood eosinophilia and can aid in distinguishing allergic rhinitis from other causes of rhinitis. An elevated IgE value is often found in the serum of allergic patients, because IgE is the primary antibody associated with immediate hypersensitivity reactions. IgE values are measured in international units (IU), with 1 IU equal to 2.4 ng of IgE. Maternal IgE (unlike IgG) does not cross the placenta. Serum IgE levels gradually rise over the first years of life to peak in the teen years and decrease steadily thereafter. Additional factors, such as genetic influences, race, gender, certain diseases, and exposure to cigarette smoke and allergens, also affect serum IgE levels. Total serum IgE levels may increase 2- to 4-fold during and immediately after the pollen season and then gradually decline until the next pollen season. Comparison of total IgE levels among patients with allergic diseases reveals that those with atopic dermatitis tend to have the highest levels, whereas patients with allergic asthma generally have higher levels than those with allergic rhinitis. Although average total IgE levels are higher in populations of allergic patients than in comparable populations without allergic disease, the overlap in levels is such that the diagnostic value of a total IgE level is poor. Approximately half of patients with allergic disease have total IgE levels in the normal range. However, measurement of total IgE is indicated when the diagnosis of **allergic bronchopulmonary aspergillosis** is suspected because total serum IgE concentration >1,000 ng/mL is a criterion for diagnosis of this disorder (see Chapter 264.1). Total serum IgE may also be elevated in several nonallergic diseases (Table 167.2 ; see Chapter 152).

Table 167.2

Nonallergic Diseases Associated With Increased Serum IgE Concentrations

Parasitic Infestations

Ascariasis
Capillariasis
Echinococcosis
Fascioliasis

Filariasis
Hookworm
Onchocerciasis
Malaria
Paragonimiasis
Schistosomiasis
Strongyloidiasis
Trichinosis
Visceral larva migrans

Infections

Allergic bronchopulmonary aspergillosis
Candidiasis, systemic
Coccidioidomycosis
Cytomegalovirus mononucleosis
HIV type 1 infections
Infectious mononucleosis (Epstein-Barr virus)
Leprosy
Pertussis
Viral respiratory infections

Immunodeficiency

Autosomal dominant hyper-IgE syndrome (*STAT3* mutations)
Autosomal recessive hyper-IgE syndrome (*DOCK8, TYK2* mutations)
IgA deficiency, selective
Nezelof syndrome (cellular immunodeficiency with immunoglobulins)
Thymic hypoplasia (DiGeorge anomaly)
Wiskott-Aldrich syndrome

Neoplastic Diseases

Hodgkin disease
IgE myeloma
Bronchial carcinoma

Other Diseases and Disorders

Alopecia areata
Bone marrow transplantation
Burns
Cystic fibrosis
Dermatitis, chronic acral
Erythema nodosum, streptococcal infection
Guillain-Barré syndrome
Kawasaki disease
Liver disease
Medication related
Nephritis, drug-induced interstitial
Nephrotic syndrome
Pemphigus, bullous
Polyarteritis nodosa, infantile
Primary pulmonary hemosiderosis
Juvenile idiopathic arthritis

The presence of IgE specific for a particular allergen can be documented in vivo by skin testing or in vitro by the measurement of **allergen-specific IgE (sIgE)** levels in the serum (Table 167.3). The first test for documenting the presence of sIgE was called the radioallergosorbent test (RAST) because it used a radiolabeled anti-IgE antibody. The RAST has been replaced by an improved generation of automated enzymatic sIgE immunoassays. These assays use solid-phase supports to which allergens of an individual allergen extract are bound. A small amount of the patient's serum is incubated with the allergen-coated support. The allergen-coated support bound to the patient's sIgE is then incubated with enzyme-conjugated antihuman IgE. Incubation of this sIgE–antihuman IgE complex with a fluorescent substrate of the conjugated enzyme results in the generation of fluorescence that is proportional to the amount of sIgE in the serum sample. The amount of sIgE is calculated by interpolation from a standard calibration curve and reported in arbitrary mass units (kilo-IU of allergen-specific antibody per unit volume of sample, kU_A /L). Laboratory reports may specify classes, counts, or units, but quantification of results in kU_A /L is most useful. The 3 commercial detection systems approved by the U.S.

Food and Drug Administration have excellent performance characteristics, but the individual systems do not measure sIgE antibodies with comparable efficiencies and thus are not interchangeable. **Component testing** refers to diagnostic tests where sIgE is measured to specific proteins that comprise allergens (e.g., Ara h 2 from peanut, Bet v 1 from birch pollen), rather than to a mixture of the allergens extracted from the source. Testing sIgE to component allergens may add additional diagnostic value by differentiating immune responses that are directed toward clinically relevant allergenic proteins.

Table 167.3

Determination of Allergen-Specific IgE by Skin Testing vs In Vitro Testing

VARIABLE	SKIN TEST*	sIgE ASSAY
Risk of allergic reaction	Yes (especially ID)	No
Relative sensitivity	High	High
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermographism	Yes	No
Broad selection of antigens	Fewer	Yes
Immediate results	Yes	No
Expensive	No	Yes
Lability of allergens	Yes	No
Results evident to patient	Yes	No

* Skin testing may be the prick test or intradermal (ID) injection.

In Vivo Tests

Allergen skin testing is the primary in vivo procedure for the diagnosis of allergic disease. Mast cells with sIgE antibodies attached to high-affinity receptors on their surface reside in the skin of allergic patients. The introduction of minute amounts of an allergen into the skin of the sensitized patient results in cross-linking of IgE antibodies on the mast cell surface, thereby triggering local mast cell activation. Once activated, these mast cells release a variety of preformed and newly generated mediators that act on surrounding tissues. **Histamine** is the mediator most responsible for the immediate **wheal and flare reactions** observed in skin testing. Examination of the site of a positive skin test result reveals a pruritic wheal surrounded by erythema. The time course of these reactions is rapid in onset, reaching a peak within 10-20 min and usually resolving over the next 30 min.

Skin testing is performed using the **prick/puncture technique.** With this technique, a small drop of allergen is applied to the skin surface, and a tiny amount is introduced into the epidermis by lightly pricking or puncturing the outer layer of skin through the drop of extract with a small needle or other device. When the **skin-prick test (SPT)** result is negative but the history suggestive, selective skin testing (for vaccines, venom, drugs, and aeroallergens) using the **intradermal technique** may be performed. This technique involves using a 26-gauge needle to inject 0.01-0.02 mL of an allergen extract diluted 1,000- to 10-fold into the dermis of the arm. Intradermal skin tests are *not recommended for use with food allergens* because of the risk of triggering anaphylaxis. Irritant rather than allergic reactions can occur with intradermal skin testing if higher concentrations of extracts are used. Although skin-prick testing is less sensitive than intradermal skin testing, positive SPT results tend to correlate better with clinical symptoms.

The number of skin tests performed should be individualized, with the allergens suggested by the history. A positive and negative control SPT, using histamine and saline, respectively, is performed with each set of skin tests. A negative control is necessary to assess for **dermatographism** , in which reactions are caused merely by applying pressure to overly sensitive skin. A positive control is necessary to establish the presence of a cutaneous response to histamine. Medications with antihistaminic properties, in addition to adrenergic agents such as ephedrine and epinephrine, suppress skin test responses and should be avoided for appropriate intervals (approximately 5 half-lives) before skin testing. Prolonged courses of systemic corticosteroids may suppress cutaneous reactivity by decreasing the number of tissue mast cells as well as their ability to release mediators.

Whether identified via serologic or skin testing, detection of sIgE denotes a sensitized state (i.e., atopy or a tendency toward development of allergic disease) but is not equivalent to a clinically relevant allergic diagnosis. *Many children with positive tests have no clinical symptoms on exposure to the allergen* . Increasingly strong test results (higher serum sIgE results or larger SPT wheal sizes) generally correlate with increasing likelihood of clinical reactivity (but not severity). Neither serologic testing nor skin testing for allergy is predictive of reaction severity or threshold of reactivity, and these tests will be negative when the allergy is not IgE mediated, such as in food protein–induced enterocolitis syndrome. The limitations of these test modalities underscore the need for a detailed medical history that can guide the selection and interpretation of test results. Large panels of indiscriminately performed screening tests may provide misleading information and are not recommended.

Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties. The benefits of the serologic immunoassays are that performance is not limited by presence of skin disease (i.e., active atopic dermatitis) or medication use (i.e., antihistamines). Advantages of skin testing are that they provide rapid results to the patient/family during the clinic visit, do not require venipuncture, and are less costly.

Under certain circumstances, **provocation testing** is performed to examine the association between allergen exposure and the development of symptoms. The bronchial provocation test most frequently performed clinically is the **methacholine challenge,** which causes potent bronchoconstriction of asthmatic but not of normal airways; it is performed to document the presence and degree of bronchial hyperreactivity in a patient with suspected asthma. After baseline spirometry values are obtained, increasing concentrations of nebulized methacholine are inhaled until a drop occurs in lung function, specifically a 20% decrease in FEV_1 (forced expiratory volume in 1st second of expiration), or the patient is able to tolerate the inhalation of a set concentration of methacholine, typically 25 mg/mL.

Oral **food challenges** are performed to determine whether a specific food causes symptoms or whether a suspected food can be added to the diet. Food challenges are performed when the history and results of skin tests and immunoassays for sIgE fail to clarify the diagnosis of an allergy. These challenges may be performed in an open single-blind, double-blind, or double-blind placebo-controlled manner and involve the ingestion of gradually increasing amounts of the suspected food at set intervals until the patient either experiences a reaction or tolerates a normal portion (i.e., 1 serving size) of the food openly. Although the double-blind placebo-controlled food challenge is currently the gold standard test for diagnosing food allergy, it is typically only performed in research studies due to the time and labor-intensive nature of this method. Because of the potential for significant allergic reactions, oral food challenges should be performed only in an appropriately equipped facility with personnel experienced in the performance of food challenges and the treatment of anaphylaxis, including cardiopulmonary resuscitation.

Upper gastrointestinal **endoscopy** is required to confirm the diagnosis of eosinophilic esophagitis. One or more biopsy specimens from the proximal and distal esophagus must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils/hpf (high-power field) (peak value) is considered a minimum threshold for the diagnosis.

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CHAPTER 168

Allergic Rhinitis

Henry Milgrom, Scott H. Sicherer

Allergic rhinitis (AR) is a common chronic disease affecting 20–30% of children. AR is an inflammatory disorder of the nasal mucosa marked by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival inflammation. Its recognition as a major chronic respiratory disease of children derives from its high prevalence, detrimental effects on quality of life and school performance, and comorbidities. Children with AR often have related conjunctivitis, sinusitis, otitis media, serous otitis, hypertrophic tonsils and adenoids, and eczema. Childhood AR is associated with a 3-fold increase in risk for asthma at an older age. Over the past 50 yr an upsurge in AR has been observed throughout the world, with some symptom surveys reporting incidence rates approaching 40%. Heritability of allergic conditions attests to genetic factors, but the increase stems from changes in the environment, diet, and the microbiome. The symptoms may appear in infancy; with the diagnosis generally established by the time the child reaches age 6 yr. The prevalence peaks late in childhood.

Risk factors include family history of atopy and serum IgE higher than 100 IU/mL before age 6 yr. Early life exposures and/or their absence have a profound influence on the development of the allergic phenotype. The risk increases in children whose mothers smoke heavily, even before delivery and above all before the infants reach 1 yr, and those with heavy exposure to indoor allergens. A critical period exists early in infancy when the genetically susceptible child is at greatest risk of sensitization. Delivery by cesarean section is associated with AR and atopy in children with a parental history of asthma or allergies. This association may be explained by the lack of exposure to the maternal microbiota through fecal/vaginal flora during delivery.

Children between 2 and 3 yr old who have elevated anticockroach and antimouse IgE are at increased risk of wheezing, AR, and atopic dermatitis. The occurrence of 3 or more episodes of rhinorrhea in the 1st yr of life is associated with AR at age 7 yr. Favorably, the exposure to dogs, cats, and endotoxin early in childhood protects against the development of atopy. Prolonged breastfeeding, not necessarily exclusive, is beneficial. There is also a decreased risk of asthma, AR, and atopic sensitization with early introduction to wheat, rye, oats, barley, fish, and eggs. However, reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age.

Etiology and Classification

Two factors necessary for expression of AR are sensitivity to an allergen and the presence of the allergen in the environment. AR classification as **seasonal** or **perennial** is giving way to the designations **intermittent** and **persistent.** The 2 sets of terms are based on different suppositions, but inhalant allergens are the main cause of all forms of AR irrespective of terminology. AR may also be categorized as **mild-intermittent, moderate-severe intermittent, mild-persistent,** and **moderate-severe persistent** (Fig. 168.1). The symptoms of intermittent AR occur on <4 days per week or for <4 consecutive weeks. In persistent AR, symptoms occur on >4 days per week and/or for >4 consecutive weeks. The symptoms are considered mild when they are not troublesome, the sleep is normal, there is no impairment in daily activities, and there is no incapacity at work or school. Severe symptoms result in sleep disturbance and impairment in daily activities and school performance.

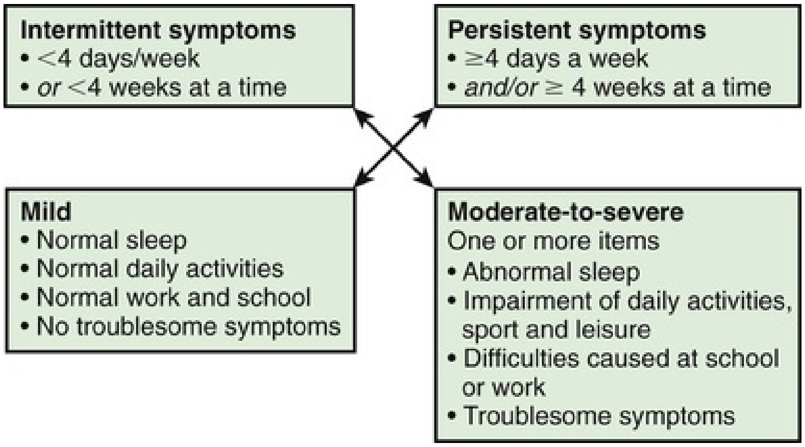
Intermittent symptoms
• <4 days/week
• or <4 weeks at a time
Persistent symptoms
• ≥4 days a week
• and/or ≥ 4 weeks at a time
Mild
• Normal sleep
• Normal daily activities
• Normal work and school
• No troublesome symptoms
Moderate-to-severe
One or more items
• Abnormal sleep
• Impairment of daily activities, sport and leisure
• Difficulties caused at school or work
• Troublesome symptoms

FIG. 168.1 ARIA classification of allergic rhinitis. Every box can be subclassified

further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-severe persistent seasonal rhinitis in June and July and may be suitable for specific allergen immunotherapy. ARIA, Global Allergic Rhinitis and its Impact on Asthma. (From Scadding GK, Durham SR, Mirakian R, et al: BASCI guidelines for the management of allergic and non-allergic rhinitis, *Clin Exp Allergy* 38:19–42, 2008.)

In temperate climates, airborne pollen responsible for exacerbation of intermittent AR appear in distinct phases: trees pollinate in the spring, grasses in the early summer, and weeds in the late summer. In temperate climates, mold spores persist outdoors only in the summer, but in warm climates they persist throughout the year. Symptoms of intermittent AR typically cease with the appearance of frost. Knowledge of the time of symptom occurrence, the regional patterns of pollination and mold sporulation, and the patient's allergen-specific IgE (**sIgE**) is necessary to recognize the cause of intermittent AR. Persistent AR is most often associated with the indoor allergens: house dust mites, animal danders, mice, and cockroaches. Cat and dog allergies are of major importance in the United States. The allergens from saliva and sebaceous secretions may remain airborne for a prolonged time. The ubiquitous major cat allergen, Fel d 1, may be carried on cat owners’ clothing into such “cat-free” settings as schools and hospitals.

Pathogenesis

The exposure of an atopic host to an allergen leads to the production of sIgE, which is strongly associated with eczema throughout childhood and with asthma and rhinitis after age 4 yr. The clinical reactions on reexposure to the allergen have been designated as *early-phase* and *late-phase* allergic responses. Bridging of the IgE molecules on the surface of mast cells by allergen initiates the early-phase allergic response, characterized by degranulation of mast cells and release of preformed and newly generated inflammatory mediators, including histamine, prostaglandin 2, and the cysteinyl leukotrienes. The late-phase allergic response appears 4-8 hr following allergen exposure. Inflammatory cells, including basophils, eosinophils, neutrophils, mast cells, and mononuclear cells, infiltrate the nasal mucosa. Eosinophils release proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and serve as a source of interleukin-3 (IL-3), IL-5, granulocyte-macrophage colony-stimulating factor, and IL-13. Repeated intranasal introduction of allergens causes “priming”—a more brisk response even with a lesser provocation. Over the course of an allergy season, a multifold increase in submucosal mast cells takes place. These cells, once thought to have a role exclusively in the early-phase allergic response, have an important function in sustaining chronic allergic disease.

Clinical Manifestations

Symptoms of AR may be ignored or mistakenly attributed to a respiratory infection. Older children blow their noses, but younger children tend to sniff and snort. Nasal itching brings on grimacing, twitching, and picking of the nose that may result in epistaxis. Children with AR often perform the **allergic salute** , an upward rubbing of the nose with an open palm or extended index finger. This maneuver relieves itching and briefly unblocks the nasal airway. It also gives rise to the **nasal crease** , a horizontal skin fold over the bridge of the nose. The diagnosis of AR is based on symptoms in the absence of an upper respiratory tract infection and structural abnormalities. Typical complaints include intermittent nasal congestion, itching, sneezing, clear rhinorrhea, and conjunctival irritation. Symptoms increase with greater exposure to the responsible allergen. The patients may lose their sense of smell and taste. Some experience headaches, wheezing, and coughing. Preschoolers with chronic wheezing and rhinitis experience more severe wheezing than children without rhinitis. Nasal congestion is often more severe at night, inducing mouth breathing and snoring, interfering with sleep, and rousing irritability.

Signs on physical examination include abnormalities of facial development, dental malocclusion, the **allergic gape** (continuous open-mouth breathing), chapped lips, **allergic shiners** (dark circles under the eyes; see Fig. 167.1), and the transverse nasal crease. Conjunctival edema, itching, tearing, and hyperemia are frequent findings. A nasal exam performed with a source of light and a speculum may reveal clear nasal secretions; edematous, boggy, and bluish mucus membranes with little or no erythema; and swollen turbinates that may block the nasal airway. It may be necessary to use a topical decongestant to perform an adequate examination. Thick, purulent nasal secretions indicate the presence of infection.

Differential Diagnosis

Evaluation of AR entails a thorough history, including details of the patient's environment and diet and a family history of allergic conditions (e.g., eczema, asthma, AR), physical examination, and laboratory evaluation. The history and laboratory findings provide clues to the provoking factors. Symptoms such as sneezing, rhinorrhea, nasal itching, and congestion and lab findings of elevated IgE, sIgE antibodies, and positive allergy skin test results typify AR. Intermittent AR differs from persistent AR by history and skin test results. **Nonallergic rhinitides** give rise to sporadic symptoms; their causes are often unknown. Nonallergic inflammatory rhinitis with eosinophils imitates AR in presentation and response to treatment, but without elevated IgE antibodies. **Vasomotor rhinitis** is characterized by excessive responsiveness of the nasal mucosa to physical stimuli. Other nonallergic conditions, such as infectious rhinitis, structural problems (e.g., nasal polyps, septal deviation), **rhinitis medicamentosa** (caused by overuse of topical vasoconstrictors), hormonal rhinitis associated with pregnancy or hypothyroidism, neoplasms, vasculitides, and granulomatous disorders may mimic AR (Table 168.1 and Fig. 168.2). Occupational risks for rhinitis include exposure to allergens (grain dust, insects, latex, enzymes) and irritants (wood dust, paint, solvents, smoke, cold air).

Table 168.1

Causes of Rhinitis

ALLERGIC RHINITIS

- Seasonal
- Perennial
- Perennial with seasonal exacerbations

NONALLERGIC RHINITIS

Structural/Mechanical Factors

- Deviated septum/septal wall anomalies
- Hypertrophic turbinates
- Adenoidal hypertrophy
- Foreign bodies
- Nasal tumors
    - Benign

    - Malignant
- Choanal atresia

Infectious

- Acute infections
- Chronic infections

Inflammatory/Immunologic

- Granulomatosis with polyangiitis
- Sarcoidosis
- Midline granuloma
- Systemic lupus erythematosus
- Sjögren syndrome
- Nasal polyposis

Physiologic

- Ciliary dyskinesia syndrome
- Atrophic rhinitis
- Hormonally induced
    - Hypothyroidism
    - Pregnancy
    - Oral contraceptives
    - Menstrual cycle
    - Exercise
    - Atrophic
- Drug induced
    - Rhinitis medicamentosa
    - Oral contraceptives
    - Antihypertensive therapy
    - Aspirin
    - Nonsteroidal antiinflammatory drugs
- Reflex induced
    - Gustatory rhinitis

    - Chemical or irritant induced
    - Posture reflexes
    - Nasal cycle
- Environmental factors
    - Odors
    - Temperature
    - Weather/barometric pressure
    - Occupational

NONALLERGIC RHINITIS WITH EOSINOPHILIA SYNDROME
PERENNIAL NONALLERGIC RHINITIS (VASOMOTOR RHINITIS)
EMOTIONAL FACTORS

From Skoner DP: Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis, *J Allergy Clin Immunol* 108(1 Suppl);108:S2–S8, 2001 (original source).

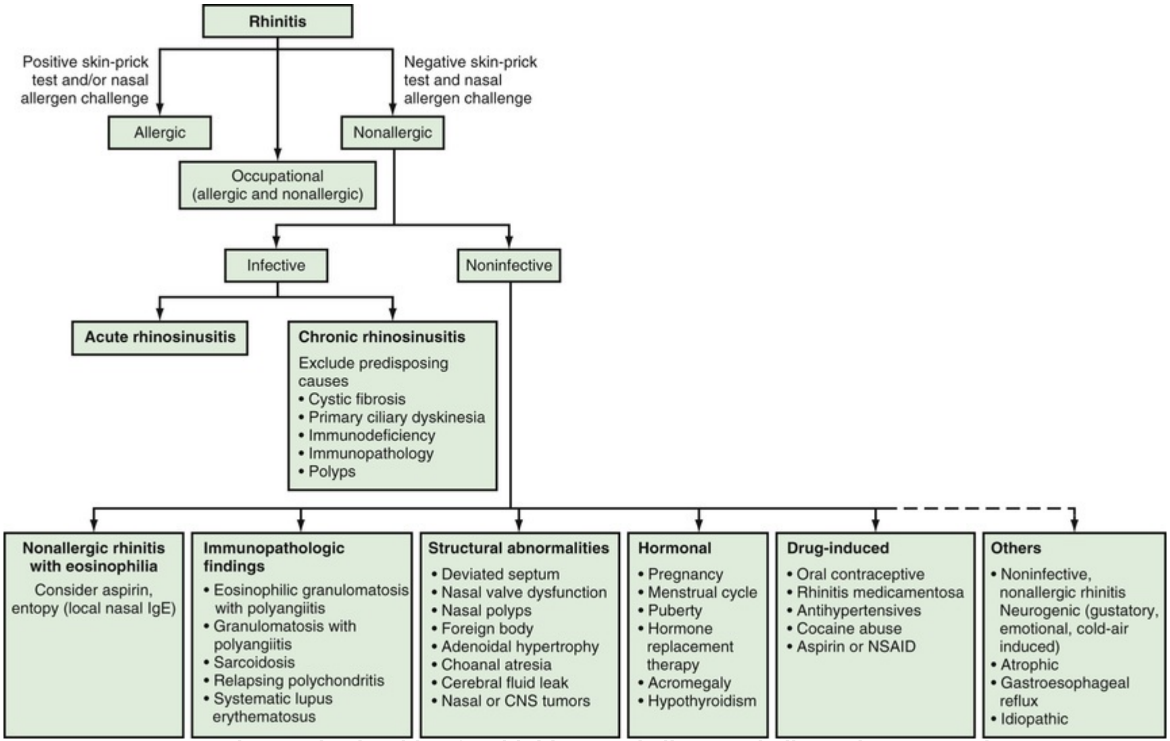
Rhinitis
Positive skin-prick test and/or nasal allergen challenge
Negative skin-prick test and nasal allergen challenge
Allergic
Nonallergic
Occupational (allergic and nonallergic)
Infective
Noninfective
Acute rhinosinusitis
Chronic rhinosinusitis
Exclude predisposing causes
• Cystic fibrosis
• Primary ciliary dyskinesia
• Immunodeficiency
• Immunopathology
• Polyps
Nonallergic rhinitis with eosinophilia
Consider aspirin, entopy (local nasal IgE)
Immunopathologic findings
• Eosinophilic granulomatosis with polyangiitis
• Granulomatosis with polyangiitis
• Sarcoidosis
• Relapsing polychondritis
• Systematic lupus erythematosus
Structural abnormalities
• Deviated septum
• Nasal valve dysfunction
• Nasal polyps
• Foreign body
• Adenoidal hypertrophy
• Choanal atresia
• Cerebral fluid leak
• Nasal or CNS tumors
Hormonal
• Pregnancy
• Menstrual cycle
• Puberty
• Hormone replacement therapy
• Acromegaly
• Hypothyroidism
Drug-induced
• Oral contraceptive
• Rhinitis medicamentosa
• Antihypertensives
• Cocaine abuse
• Aspirin or NSAID
Others
• Noninfective, nonallergic rhinitis Neurogenic (gustatory, emotional, cold-air induced)
• Atrophic
• Gastroesophageal reflux
• Idiopathic

FIG. 168.2 **Diagnostic algorithm for rhinitis. Nasal allergen challenge is a research procedure and is not undertaken routinely. CNS, Central nervous system; NSAID, nonsteroidal antiinflammatory drug. (From Greiner AN, Hellings PW, Rotiroti G, Scadding GK: Allergic rhinitis, *Lancet* 378:2112–2120, 2011.)**

Complications

AR is associated with complications and comorbid conditions. Undertreated AR detracts from the quality of life, aggravates asthma, and enhances its progression. Children with AR experience frustration over their appearance. Allergic conjunctivitis, characterized by itching, redness, and swelling of the conjunctivae, has been reported in at least 20% of the population and >70% of patients with AR, most frequently in older children and young adults. The 2 conditions share pathophysiologic mechanisms and epidemiologic characteristics (see Chapter 172). Chronic sinusitis is a common complication of AR, sometimes associated with purulent infection, but most patients have negative bacterial cultures despite marked mucosal thickening, and sinus opacification. The inflammatory process is characterized by marked eosinophilia.

Allergens, possibly fungal, are the inciting agents. The sinusitis of **triad asthma** (asthma, sinusitis with nasal polyposis, and aspirin sensitivity) often responds poorly to therapy. Patients who undergo repeated endoscopic surgery derive diminishing benefit with each successive procedure.

Rhinitis that coexists with asthma may be taken too lightly or completely overlooked. Up to 78% of patients with asthma have AR, and 38% of patients with AR have asthma. Aggravation of AR coincides with exacerbation of asthma, and treatment of nasal inflammation reduces bronchospasm, asthma-related emergency department visits, and hospitalizations. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Eustachian tube obstruction and middle ear effusion are frequent complications. Chronic allergic inflammation causes hypertrophy of adenoids and tonsils that may be associated with eustachian tube obstruction, serous effusion, otitis media, and obstructive sleep apnea. AR is linked to snoring in children. The association between rhinitis and sleep abnormalities and subsequent daytime fatigue is well documented and may require multidisciplinary intervention.

The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is suitable for children 6-12 yr old, and the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ) is appropriate for patients 12-17 yr. Children with rhinitis have anxiety and physical, social, and emotional issues that affect learning and the ability to integrate with peers. The disorder contributes to headaches and fatigue, limits daily activities, and interferes with sleep. There is evidence of impaired cognitive functioning and learning that may be exacerbated by the adverse effects of sedating medications. AR causes an estimated 824,000 missed school days and 4,230,000 days of decline in quality-of-life activities. Patients with AR report an impairment in the activities of daily living similar to patients with moderate to severe asthma. Some (but not many) patients improve during their teenage years, only to develop symptoms again as young adults. Symptoms often abate in the 5th decade of life.

Laboratory Findings

Epicutaneous skin tests provide the best method for detection of sIgE, with a positive predictive value (PPV) of 48.7% for epidemiologic diagnosis of AR. Skin tests are inexpensive and sensitive, and the risks and discomfort are minimal. Responses to seasonal respiratory allergens are rare before 2 seasons of exposure, and children <1 yr old seldom display positive skin test responses to these allergens. To avoid false-negative results, montelukast should be withheld for 1 day, most sedating antihistamine preparations for 3-4 days, and nonsedating antihistamines for 5-7 days. Serum immunoassays for sIgE provide a suitable alternative (PPV of 43.5%) for patients with dermatographism or extensive dermatitis, those taking medications that interfere with mast cell degranulation, others at high risk for anaphylaxis, and some who cannot cooperate with the procedure. Presence of eosinophils in the nasal smear supports the diagnosis of AR, and neutrophils suggest infectious rhinitis. Eosinophilia and measurements of total serum IgE concentrations have relatively low sensitivity.

Treatment

Guideline-directed management has been shown to improve disease control. **Global Allergic Rhinitis and its Impact on Asthma (ARIA)** provides an evidence-based approach to treatment and includes quality-of-life measures useful for the evaluation of symptoms and the assessment of the response to therapy. Safe effective prevention and relief of symptoms are the current goals of treatment. *Specific measures to limit indoor allergen exposure may reduce the risk of sensitization and symptoms of allergic respiratory disease.* Sealing the patient's mattress, pillow, and covers in allergen-proof encasings reduces the exposure to mite allergen. Bed linen and blankets should be washed every week in hot water (>54.4°C [130°F]). The only effective measure for avoiding animal allergens in the home is the removal of the pet. Avoidance of pollen and outdoor molds can be accomplished by staying in a controlled environment. Air conditioning allows for keeping windows and doors closed, reducing the pollen exposure. High-efficiency particulate air (HEPA) filters lower the counts of airborne mold spores.

Oral antihistamines help reduce sneezing, rhinorrhea, and ocular symptoms. Administered as needed, antihistamines provide acceptable treatment for mild-intermittent disease. Antihistamines have been classified as **first generation** (relatively sedating) or **second generation** (relatively nonsedating). Antihistamines usually are administered by mouth but are also available for topical ophthalmic and intranasal use. Both first- and second-generation antihistamines are available as nonprescription drugs. *Second-generation antihistamines are preferred because they cause less sedation* . Preparations containing **pseudoephedrine** , typically in combination with other agents, are used for relief of nasal and sinus congestion and pressure and other symptoms such as rhinorrhea, sneezing, lacrimation, itching eyes, oronasopharyngeal itching, and cough. Pseudoephedrine is available without prescription (generally in fixed combination with other agents such as first-generation antihistamines: brompheniramine, chlorpheniramine, triprolidine; second-generation antihistamines: desloratadine, fexofenadine, loratadine; antipyretics: acetaminophen, ibuprofen; antitussives: guaifenesin, dextromethorphan; anticholinergic: methscopolamine). Pseudoephedrine is an oral vasoconstrictor distrusted for causing irritability and insomnia and for its association with infant mortality. Because younger children (2-3 yr) are at increased risk of overdosage and toxicity, some manufacturers of oral nonprescription cough and cold preparations have voluntarily revised their product labeling to warn against the use of preparations containing pseudoephedrine for children <4 yr old. Pseudoephedrine is misused as a starting material for the synthesis of methamphetamine and methcathinone. Tables 168.2 , 168.3 , and 168.4 provide examples of prescription, nonprescription, and combined oral agents, respectively, for treatment of AR.

Table 168.2

Oral Allergic Rhinitis Treatments (Prescription, Examples)

GENERIC/BRAND	**STRENGTH**	**FORMULATIONS**	**DOSING**
SECOND-GENERATION ANTIHISTAMINES			
Desloratadine			
Clarinex Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Clarinex Tablets	5 mg	Tabs	Children 12 mo-5 yr: 1.25 mg once daily
Clarinex Syrup	0.5 mg/mL	Syrup	Children 6-11 yr: 2.5 mg once daily
			Adults and adolescents ≥12 yr: 5 mg once daily
Levocetirizine dihydrochloride			
Xyzal Oral Solution	0.5 mg/mL	Solution	6 mo-5 yr: max 1.25 mg once daily in the PM
			6-11 yr: max 2.5 mg once daily in the PM
LEUKOTRIENE ANTAGONIST			
Montelukast			
Singulair	10 mg	Tablets	6 mo-5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

* Contains phenylalanine.

Dosing recommendations taken in part from Engorn B, Flerlage J, for the Johns Hopkins Hospital: *The Harriet Lane Handbook* , ed 20, Philadelphia, 2015, Elsevier/Saunders.

Table 168.3

Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

GENERIC/BRAND	**STRENGTH**	**FORMULATIONS**	**DOSING**
FIRST-GENERATION H_1 ANTAGONISTS			
Chlorpheniramine maleate			
Chlor-Trimeton OTC (over the counter)	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (max 6 mg/day) 6-11 yr: 2 mg every 4-6 hr (max 12 mg/day)
Chlor-Trimeton Syrup OTC	2 mg/5 mL	Syrup	>12 yr: 4 mg every 4-6 hr (max 24 mg/day)
SECOND-GENERATION H_1 ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup OTC	1 mg/mL	Syrup	6-12 mo: 2.5 mg once daily
Children's Zyrtec Chewable OTC	5 mg, 10 mg	Chewable tablets	12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Zyrtec tablets	5 mg, 10 mg	Tablets	2-5 yr: 2.5 mg/day; may be increased to max of 5

OTC			mg/day given either as a single dose or divided into 2 doses
Zyrtec Liquid Gels OTC	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into 2 doses
Levocetirizine Xyzal	5 mg 0.5 mg/mL	Tablet Oral solution	2-5 yr: 1.25 mg once daily in the evening 6-11 yr: 2.5 mg orally once daily in the evening ≥12 yr: 5 mg orally once daily in the evening
Desloratadine Clarinex	0.5 mg/mL	Oral solution	6-11 mo: 2 mL once daily 12 mo-5 yr: 2.5 mL once daily 6-11 yr: 5 mL once daily
Desloratadine Clarinex	5 mg	Tablet	12-adult: 5 mg once daily
Fexofenadine HCl OTC	30 mg, 60 mg, 180 mg	Tablet	6-11 yr: 30 mg twice daily 12-adult: 60 mg twice daily; 180 mg once daily
Children's Claritin OTC	5 mg/5 mL	Syrup	2-5 yr: 5 mg once daily 6-adult: 10 mg once daily
Children's Allegra OTC ODT*	30 mg	Orally disintegrating tablets	6-11 yr: 30 mg twice daily
Children's Allegra Oral Suspension OTC	30 mg/5 mL	Suspension	>2-11 yr: 30 mg every 12 hr
Allegra OTC	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg once daily
Loratadine			
Alavert OTC ODT*	10 mg 10 mg 10 mg 5 mg 1 mg/mL	Orally disintegrating tablets Tablets Liquid-filled caps Chewable tablets Syrup	2-5 yr: 5 mg once daily >6 yr: 10 mg once daily or 5 mg twice daily

* Contains phenylalanine.

Dosing recommendations taken in part from Engorn B, Flerlage J, for the Johns Hopkins Hospital: *The Harriet Lane Handbook* , ed 20. Philadelphia, 2015 Elsevier/Saunders.

Table 168.4

Combined Antihistamine + Sympathomimetic (Examples)

GENERIC	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate Phenylephrine	4 mg 10 mg	Tablets	>12 yr: 1 tablet every 4 hr, not to exceed 6 tablets per day

HCl Sudafed Sinus & Allergy			
Cetirizine + pseudoephedrine Zyrtec-D 12 hour	5 mg cetirizine + 120 mg pseudoephedrine	Extended-release tablet	>12 yr: 1 tablet every 12 hr

Dosing recommendations taken in part from Engorn B, MD, Flerlage J for the Johns Hopkins Hospital: *The Harriet Lane Handbook* , ed 20. Philadelphia, 2015 Elsevier/Saunders.

The anticholinergic **nasal spray** ipratropium bromide is effective for the treatment of *serous* rhinorrhea (Table 168.5). **Intranasal decongestants** (oxymetazoline and phenylephrine) should be used for <5 days and should not to be repeated more than once a month to avoid rebound nasal congestion. Sodium cromoglycate (available as nonprescription drug) is effective but requires frequent administration, every 4 hr. Leukotriene-modifying agents have a modest effect on rhinorrhea and nasal blockage (see Chapter 169 for additional indications and side effects). Nasal saline irrigation is a good adjunctive option with all other treatments of AR. Patients with more persistent, severe symptoms require **intranasal corticosteroids** , the most effective therapy for AR, which may also be beneficial for concomitant allergic conjunctivitis (Table 168.6). These agents reduce the symptoms of AR with eosinophilic inflammation, but not those of rhinitis associated with neutrophils or free of inflammation. Beclomethasone, triamcinolone, and flunisolide are absorbed from the gastrointestinal tract, as well as from the respiratory tract; budesonide, fluticasone, mometasone, and ciclesonide offer greater topical activity with lower systemic exposure. More severely affected patients may benefit from simultaneous treatment with oral antihistamines and intranasal corticosteroids.

Table 168.5

Miscellaneous Intranasal Sprays

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Ipratropium bromide:	*I:* Symptomatic relief of rhinorrhea *M:* Anticholinergic	Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin. Safety and efficacy of use beyond 4 days in patients with the common cold have not been established. *Adverse effects:* Epistaxis, nasal dryness, nausea
Atrovent nasal spray (0.06%)	Colds (symptomatic relief of rhinorrhea): 5-12 yr: 2 sprays in each nostril tid ≥12 yr and adults: 2 sprays in each nostril tid-qid	
Azelastine:	*I:* Treatment of rhinorrhea, sneezing, and nasal pruritus	May cause drowsiness *Adverse effects:* Headache, somnolence,

	M: Antagonism of histamine H_1 receptor	bitter taste
Astelin	6-12 yr: 1 spray bid >12 yr: 1-2 sprays bid	
Cromolyn sodium:	*I:* AR. *M:* Inhibition of mast cell degranulation	Not effective immediately; requires frequent administration
NasalCrom	>2 yr: 1 spray tid-qid; max 6 times daily	
Oxymetazoline: Afrin Nostrilla	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic agonist, vasoconstricting agent 0.05% solution: instill 2-3 sprays into each nostril bid; therapy should not exceed 3 days.	Excessive dosage may cause profound central nervous system (CNS) depression. Use in excess of 3 days may result in severe rebound nasal congestion. Do not repeat more than once a month. Use with caution in patients with hyperthyroidism, heart disease, hypertension, or diabetes. *Adverse effects:* Hypertension, palpitations, reflex bradycardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision
Phenylephrine:	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic, vasoconstricting agent	Use in excess of 3 days may result in severe rebound nasal congestion. Do not repeat more than once a month. 0.16% and 0.125% solutions are not commercially available. *Adverse effects:* Reflex bradycardia, excitability, headache, anxiety, dizziness
Neo-Synephrine	2-6 yr: 1 drop every 2-4 hr of 0.125% solution as needed. *Note:* Therapy should not exceed 3 continuous days. 6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed. *Note:* Therapy should not exceed 3 continuous days. >12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion. *Note:* Therapy should not exceed 3 continuous days.	

bid, 2 times daily; tid, 3 times daily; qid, 4 times daily.

Table 168.6

Intranasal Inhaled Corticosteroids

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Beclomethasone: OTC (over the	*I:* AR *M:* Antiinflammatory,	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril.

counter)	immune modulator	*Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth.
Beconase AQ (42 µg/spray) Qnasl (80 µg/spray) OTC	6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid >12 yr: 1 or 2 sprays in each nostril bid	
Flunisolide OTC	6-14 yr: 1 spray each nostril tid *or* 2 sprays in each nostril bid; not to exceed 4 sprays/day in each nostril ≥15 yr: 2 sprays each nostril bid (morning and evening); may increase to 2 sprays tid; maximum dose: 8 sprays/day in each nostril (400 µg/day)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril. *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth.
Triamcinolone Nasacort AQ (55 µg/spray) OTC Fluticasone propionate (available as generic preparation): OTC	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril. *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth.
	2-6 yr: 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	
	I: AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril. Ritonavir significantly increases fluticasone serum concentrations and may result in systemic corticosteroid effects. Use fluticasone with caution in patients receiving ketoconazole or other potent cytochrome P450 3A4 isoenzyme inhibitor. *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth.
Flonase (50 µg/spray) OTC	≥4 yr: 1-2 sprays in each nostril qd	
Fluticasone furoate: Veramyst (27.5 µg/spray)	2-12 yr: Initial dose: 1 spray (27.5 µg/spray) per nostril qd (55 µg/day) Patients who do not show adequate response may use 2 sprays per nostril qd (110 µg/day) Once symptoms are controlled, dosage may be reduced to 55 µg qd Total daily dosage should not exceed 2 sprays in each nostril	

	(110 μg)/day ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 μg/spray) per nostril qd (110 μg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril qd (55 μg/day). Total daily dosage should not exceed 2 sprays in each nostril (110 μg)/day.	
Mometasone:	*I:* AR *M:* Antiinflammatory, immune modulator	Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses. Preventive treatment of seasonal AR should begin 2-4 wk prior to pollen season. Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril. *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth.
Nasonex (50 μg/spray)	2-12 yr: 1 spray in each nostril qd >12 yr: 2 sprays in each nostril qd	
Budesonide: OTC	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril. *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth.
Rhinocort Aqua (32 μg/spray) OTC	6-12 yr: 2 sprays in each nostril qd >12 yr: up to 4 sprays in each nostril qd (max dose)	
Ciclesonide:	*I:* AR *M:* Antiinflammatory, immune modulator	Prior to initial use, gently shake, then prime the pump by actuating 8 times. If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears.
Omnaris Zetonna (50 μg/spray)	2-12 yr: 1-2 sprays in each nostril qd >12 yr: 2 sprays in each nostril qd	
Azelastine/fluticasone (137 μg azelastine/50 μg fluticasone) Dymista	>12 yr: 1 spray in each nostril bid	Shake bottle gently before using. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator tip ¼ to ½ inch into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray.

qd, Once daily; bid, 2 times daily; tid, 3 times daily.

Allergen-specific immunotherapy is a well-defined treatment for IgE-mediated allergic disease. It may be administered by subcutaneous or sublingual routes. **Sublingual immunotherapy** (SLIT) has been used successfully in Europe and South America and is now approved by the U.S. Food and Drug Administration.

Allergy immunotherapy (AIT) is an effective treatment for AR and allergic conjunctivitis. In addition to reducing symptoms, it may change the course of allergic disease and induce allergen-specific immune tolerance. Immunotherapy should be considered for children in whom IgE-mediated allergic symptoms cannot be adequately controlled by avoidance and medication, especially in the presence of comorbid conditions. Immunotherapy for AR prevents the onset of asthma. Moreover, progress in molecular characterization of allergens raises the possibility of defined vaccines for allergen immunotherapy. Omalizumab (anti-IgE antibody) is effective for difficult-to-control asthma and is likely to have a beneficial effect on coexisting AR.

Typically, treatment of AR with oral antihistamines and nasal corticosteroids provides sufficient relief for most patients with coexisting **allergic conjunctivitis** . If it fails, additional therapies directed primarily at allergic conjunctivitis may be added (see Chapter 172). Intranasal corticosteroids are of some value for the treatment of ocular symptoms, but ophthalmic corticosteroids remain the most potent pharmacologic agents for ocular allergy, although they carry the risk of adverse effects such as delayed wound healing, secondary infection, elevated intraocular pressure, and formation of cataracts. Ophthalmic corticosteroids are only suited for the treatment of allergic conjunctivitis that does not respond to the medications previously discussed. Sound practice calls for the assistance of an ophthalmologist.

Prognosis

Therapy with nonsedating antihistamines and topical corticosteroids, when taken appropriately, improves health-related quality-of-life measures in patients with allergic rhinitis. The reported rates of remission among children are 10–23%. Pharmacotherapy that will target cells and cytokines involved in inflammation and treat allergy as a systemic process is on the horizon, and more selective targeting of drugs based on the development of specific biomarkers and genetic profiling may soon be realized.

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CHAPTER 169

Childhood Asthma

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Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. This chronic inflammation heightens the twitchiness of the airways—**airways hyperresponsiveness (AHR)—** to common provocative exposures. Asthma management is aimed at reducing airways inflammation by minimizing proinflammatory environmental exposures, using daily controller antiinflammatory medications, and controlling comorbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, with fewer exacerbations and decreased need for quick-reliever asthma medications. Nevertheless, exacerbations can still occur. Early intervention with systemic corticosteroids greatly reduces the severity of such episodes. Advances in asthma management and especially pharmacotherapy enable all but the uncommon child with difficult asthma to live normally.

Etiology

Although the cause of childhood asthma has not been determined, a combination of environmental exposures and inherent biologic and genetic susceptibilities has been implicated (Fig. 169.1). In the susceptible host, immune responses to common airways exposures (e.g., respiratory viruses, allergens, tobacco smoke, air pollutants) can stimulate prolonged, pathogenic inflammation and aberrant repair of injured airways tissues (Fig. 169.2). Lung dysfunction (AHR, reduced airflow) and airway remodeling develop. These pathogenic processes in the growing lung during early life adversely affect airways growth and differentiation, leading to altered airways at mature ages. Once asthma has developed, ongoing inflammatory exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.

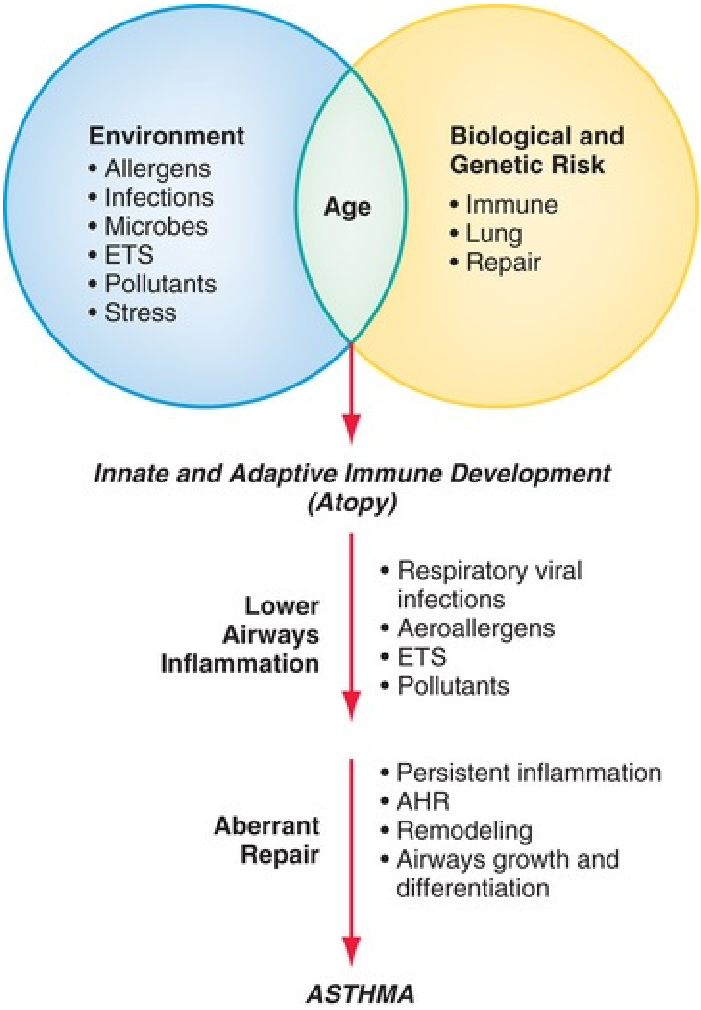
Environment
• Allergens
• Infections
• Microbes
• ETS
• Pollutants
• Stress
Age
Biological and Genetic Risk
• Immune
• Lung
• Repair
Innate and Adaptive Immune Development (Atopy)
Lower Airways Inflammation
• Respiratory viral infections
• Aeroallergens
• ETS
• Pollutants
Aberrant Repair
• Persistent inflammation
• AHR
• Remodeling
• Airways growth and differentiation
ASTHMA

FIG. 169.1 Etiology and pathogenesis of asthma. A combination of environmental and genetic factors in early life shape how the immune system develops and responds to ubiquitous environmental exposures. Respiratory microbes, inhaled allergens, and pollutants that can inflame the lower airways target the disease process to the lungs. Aberrant immune and repair responses to airways injury underlie persistent disease. AHR, Airways hyperresponsiveness; ETS, environmental tobacco smoke.

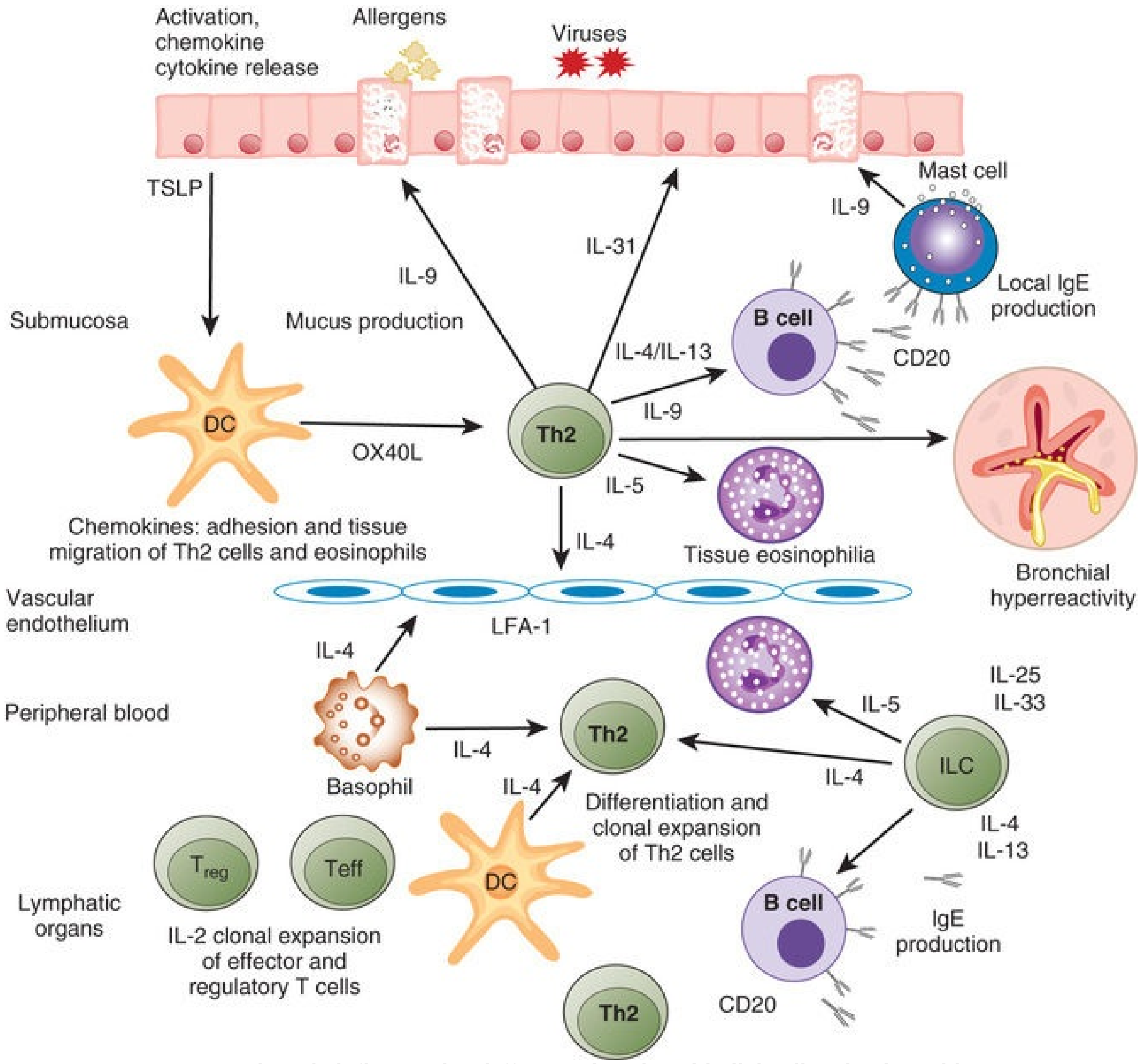
Activation, chemokine cytokine release
Allergens
Viruses
TSLP
Mast cell
IL-9
IL-31
IL-9
Local IgE production
Submucosa
Mucus production
B cell
IL-4/IL-13
CD20
DC
OX40L
Th2
IL-9
IL-5
IL-4
Chemokines: adhesion and tissue migration of Th2 cells and eosinophils
Tissue eosinophilia
Bronchial hyperreactivity
Vascular endothelium
LFA-1
IL-4
IL-25
IL-33
Peripheral blood
IL-5
Th2
IL-4
ILC
IL-4
Basophil
IL-4
Differentiation and clonal expansion of Th2 cells
IL-4
IL-13
Treg
Teff
DC
B cell
Lymphatic organs
IL-2 clonal expansion of effector and regulatory T cells
IgE production
CD20
Th2

FIG. 169.2 Asthmatic inflammation (effector phase). Epithelial cell activation with production of proinflammatory cytokines and chemokines induces inflammation and contributes to a T-helper cell type 2 (Th2) response with tumor necrosis factor (TNF)-α, interleukin (IL)-13, thymic stromal lymphopoietin (TSLP), IL-25, IL-31, and IL-33. Migration of inflammatory cells to asthmatic tissues is regulated by chemokines. Th2 and eosinophil migration are induced by eotaxin, monocyte-derived chemokine (MDC), and activation-regulated chemokine (TARC). Epithelial apoptosis and shedding is observed, mainly mediated by interferon (IFN)-γ and TNF-α. The adaptive Th2 response includes the production of IL-4, IL-5, IL-9, and IL-13. Innate lymphoid cells, particularly ILC2, also secrete IL-5 and IL-13. Tissue eosinophilia is regulated by IL-5, IL-25, and IL-33. Local and systemic IgE production is observed in bronchial mucosa. Cross-linking of IgE receptor FcεRI on the surface of mast cells and basophils and their degranulation take place on allergen challenge. (From Leung DYM, Szefler SJ, Bonilla FA, et al, editors: *Pediatric allergy principles and practice,* ed 3, Philadelphia, 2016, Elsevier, p 260).

Genetics

To date, more than 100 genetic loci have been linked to asthma, although relatively few have consistently been linked to asthma in different study cohorts. Consistent loci include genetic variants that underlie susceptibility to common exposures such as respiratory viruses and air pollutants.

Environment

Recurrent wheezing episodes in early childhood are associated with common respiratory viruses, especially rhinoviruses, respiratory syncytial virus (RSV), influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus. This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in early childhood. Other airways exposures can also exacerbate ongoing airways inflammation, increase disease severity, and drive asthma persistence. Home allergen exposures in sensitized individuals can initiate airways inflammation and hypersensitivity to other irritant exposures and are causally linked to disease severity, exacerbations, and persistence. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms and can sometimes cure asthma. Environmental tobacco smoke and common air pollutants can aggravate airways inflammation and increase asthma severity. Cold, dry air, hyperventilation from physical play or exercise, and strong odors can trigger bronchoconstriction. Although many exposures that trigger and aggravate asthma are well recognized, the causal environmental features underlying the development of host susceptibilities to the various common airway exposures are not as well defined. Living in rural or farming communities may be a protective environmental factor.

Epidemiology

Asthma is a common chronic disease, causing considerable morbidity. In 2011, >10 million children (14% of U.S. children) had ever been diagnosed with asthma, with 70% of this group reporting current asthma. Male gender and living in poverty are demographic risk factors for having childhood asthma in the United States. About 15% of boys vs 13% of girls have had asthma; and 18% of all children living in poor families (income <$25,000/yr), vs 12% of children in families not classified as poor, have had asthma.

Childhood asthma is among the most common causes of childhood emergency department visits, hospitalizations, and missed school days. In the United States in 2006, childhood asthma accounted for 593,000 emergency department (ED) visits, 155,000 hospitalizations, and 167 deaths. A disparity in asthma outcomes links high rates of asthma hospitalization and death with poverty, ethnic minorities, and urban living. In the past 2 decades, black children have had 2-7 times more ED visits, hospitalizations, and deaths as a result of asthma than nonblack children. Although current asthma prevalence is higher in black than in nonblack U.S. children (in 2011, 16.5% vs 8.1% for white and 9.8% for Latino children), prevalence differences cannot fully account for this disparity in asthma outcomes.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. Although childhood asthma may have plateaued in the United States after 2008, numerous studies conducted in other countries have reported an increase in asthma prevalence of approximately 50% per decade. Globally, childhood asthma prevalence varies widely in different locales. A study of childhood asthma prevalence in 233 centers in 97 countries (International Study of Asthma and Allergies in Childhood, Phase 3) found a wide range in the prevalence of current wheeze in 6-7 yr (2.4–37.6%) and 13-14 yr old children (0.8–32.6%). Asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence. Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries and farming communities with domestic animals are less likely to experience asthma and allergy.

Approximately 80% of all asthmatic patients report disease onset prior to 6 yr of age. However, of all young children who experience recurrent wheezing, only a minority go on to have persistent asthma in later childhood. Early childhood risk factors for persistent asthma have been identified (Table 169.1) and have been described as major (parent asthma, eczema, inhalant allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, ≥4% peripheral blood eosinophils, food allergen sensitization) risk factors. *Allergy in young children with recurrent cough and/or wheeze* is the strongest identifiable factor for the persistence of childhood asthma.

Table 169.1

Early Childhood Risk Factors for Persistent Asthma

Parental asthma*
Allergy:
  - Atopic dermatitis (eczema)*
  - Allergic rhinitis
  - Food allergy
  - Inhalant allergen sensitization*
  - Food allergen sensitization

Severe lower respiratory tract infection:
  - Pneumonia
  - Bronchiolitis requiring hospitalization

Wheezing apart from colds
Male gender
Low birthweight
Environmental tobacco smoke exposure
Reduced lung function at birth
Formula feeding rather than breastfeeding

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[*] Major risk factors.

Types of Childhood Asthma

There are 2 common types of childhood asthma based on different natural courses: (1) **recurrent wheezing** in *early* childhood, primarily triggered by common respiratory viral infections, usually resolves during the preschool/lower school years; and (2) **chronic asthma** associated with *allergy* that persists into later childhood and often adulthood (Table 169.2). School-age children with mild-moderate persistent asthma generally improve as teenagers, with some (about 40%) developing intermittent disease. Milder disease is more likely to remit. Inhaled corticosteroid controller therapy for children with persistent asthma does not alter the likelihood of outgrowing asthma in later childhood; however, because children with asthma generally improve with age, their need for controller therapy subsequently lessens and often resolves. Reduced growth and progressive decline in lung function can be features of persistent, problematic disease.

Table 169.2

Asthma Patterns in Childhood, Based on Natural History and Asthma Management

Transient Nonatopic Wheezing

Common in early preschool years

Recurrent cough/wheeze, primarily triggered by common respiratory viral infections

Usually resolves during the preschool and lower school years, without increased risk for asthma in later life

Reduced airflow at birth, suggestive of relatively narrow airways; AHR near birth; improves by school age

Persistent Atopy-Associated Asthma

Begins in early preschool years

Associated with atopy in early preschool years:

- Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
- Biologic (e.g., early inhalant allergen sensitization, increased serum IgE, increased blood eosinophils)
- Highest risk for persistence into later childhood and adulthood

Lung function abnormalities:

- Those with onset before 3 yr of age acquire reduced airflow by school age.
- Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood.

Asthma With Declining Lung Function

Children with asthma with progressive increase in airflow limitation

Associated with hyperinflation in childhood, male gender

Asthma Management Types

(From national and international asthma management guidelines)

Severity Classification*

- Intrinsic disease severity while not taking asthma medications

Intermittent

Persistent:

- Mild
- Moderate
- Severe

Control Classification*

- Clinical assessment while asthma being managed and treated

Well controlled

Not well controlled

Very poorly controlled

Management Patterns

- **Easy-to-control:** well controlled with low levels of daily controller therapy
- **Difficult-to-control:** well controlled with multiple and/or high levels of controller therapies
- **Exacerbators:** despite being well controlled, continue to have severe exacerbations
- **Refractory:** continue to have poorly controlled asthma despite multiple and high levels of controller therapies

AHR, Airways hyperresponsiveness.

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* From National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): *Guideline for the diagnosis and management of asthma*, NIH Pub No 07-4051, Bethesda, MD, 2007, US Department of Health and Human Services;

National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report .

Asthma is also classified by **disease severity** (e.g., intermittent or persistent [mild, moderate, or severe]) or **control** (e.g., well, not well, or very poorly controlled), especially for asthma management purposes. Because most children with asthma can be well controlled with conventional management guidelines, children with asthma can also be characterized according to treatment response and medication requirements as being (1) **easy to control** : well controlled with low levels of controller therapy; (2) **difficult to control** : not as well controlled with multiple and/or high levels of controller therapies; (3) **exacerbators** : despite being controlled, continue to have severe exacerbations; and (4) **refractory asthma** : continue to have poorly controlled asthma despite multiple and high levels of controller therapies (Table 169.2). Different airways pathologic processes, causing airways inflammation, AHR, and airways congestion and blockage, are believed to underlie these different types of asthma.

Pathogenesis

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airway lumen; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airways lumen. Helper T lymphocytes and other immune cells that produce proallergic, proinflammatory cytokines (interleukin [IL]-4, IL-5, IL-13), and chemokines (eotaxins) mediate this inflammatory process (see Fig. 169.2). Pathogenic immune responses and inflammation may also result from a breach in normal immune regulatory processes (e.g., regulatory T lymphocytes that produce IL-10 and transforming growth factor-β) that dampen effector immunity and inflammation when they are no longer needed. Hypersensitivity or susceptibility to a variety of provocative exposures or triggers (Table 169.3) can lead to airways inflammation, AHR, edema, basement membrane thickening, subepithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucus hypersecretion—all processes that contribute to airflow obstruction.

Table 169.3

Asthma Triggers

COMMON VIRAL INFECTIONS OF RESPIRATORY TRACT

AEROALLERGENS IN SENSITIZED ASTHMATIC PATIENTS

Indoor Allergens

- Animal dander
- Dust mites
- Cockroaches
- Molds

Seasonal Aeroallergens

- Pollens (trees, grasses, weeds)
- Seasonal molds

AIR POLLUTANTS

- Environmental tobacco smoke
- Ozone
- Nitrogen dioxide
- Sulfur dioxide
- Particulate matter
- Wood- or coal-burning smoke
- Mycotoxins
- Endotoxin
- Dust

STRONG OR NOXIOUS ODORS OR FUMES

- Perfumes, hairsprays
- Cleaning agents

OCCUPATIONAL EXPOSURES

- Farm and barn exposures
- Formaldehydes, cedar, paint fumes

COLD DRY AIR
EXERCISE
CRYING, LAUGHTER, HYPERVENTILATION
COMORBID CONDITIONS

- Rhinitis
- Sinusitis
- Gastroesophageal reflux

DRUGS

- Aspirin and other nonsteroidal antiinflammatory drugs
- β-Blocking agents

Clinical Manifestations and Diagnosis

Intermittent dry coughing and expiratory wheezing are the most common chronic symptoms of asthma. Older children and adults report associated shortness of breath and chest congestion and tightness; younger children are more likely to report intermittent, nonfocal chest pain. Respiratory symptoms can be worse at night, associated with sleep, especially during prolonged exacerbations triggered by respiratory infections or inhalant allergens. Daytime symptoms, often linked with physical activities (exercise-induced) or play, are reported with greatest frequency in children. Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue (possibly resulting from sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (bronchodilators) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms can be triggered by numerous common events or exposures: physical exertion and hyperventilation (laughing), cold or dry air, and airways irritants (see Table 169.3). Exposures that induce airways inflammation, such as infections with common respiratory pathogens (rhinovirus, RSV, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*), and inhaled allergens in sensitized children, also increase AHR to dry, cold air and irritant exposures. An environmental history is essential for optimal asthma management.

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergies), parental asthma, and/or symptoms apart from colds, supports the diagnosis of asthma. During routine clinic visits, children with asthma typically present without abnormal signs, emphasizing the importance of the medical history in diagnosing asthma. Some may exhibit a dry, persistent cough. The chest findings are often normal. Deeper breaths can sometimes elicit otherwise undetectable wheezing. In clinic, quick resolution (within 10 min) or convincing improvement in symptoms and signs of asthma with administration of an **inhaled short-acting β-agonist** (**SABA** ; e.g., albuterol) is supportive of the diagnosis of asthma.

Asthma exacerbations can be classified by their severity based on symptoms, signs, and functional impairment (Table 169.4). Expiratory wheezing and a prolonged exhalation phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior lung field, are consistent with regional hypoventilation caused by airways obstruction. **Rhonchi** and **crackles** (or **rales**) can sometimes be heard, resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate acute asthma management. In severe exacerbations the greater extent of airways obstruction causes labored breathing and respiratory distress, which manifests as inspiratory and expiratory wheezing, increased prolongation of exhalation, poor air entry, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In extremis, airflow may be so limited that wheezing cannot be heard (**silent chest**).

Table 169.4

Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting[*]

	MILD	**MODERATE**	**SEVERE**	**SUBSET: RESPIRATORY ARREST IMMINENT**
SYMPTOMS				
Breathlessness	While walking	While at rest (infant—softer, shorter cry, difficulty feeding)	While at rest (infant—stops feeding)	Extreme dyspnea Anxiety
	Can lie down	Prefers sitting	Sits upright	Upright, leaning forward
Talks in…	Sentences	Phrases	Words	Unable to talk
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
SIGNS				
Respiratory rate[†]	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min)[‡]	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
FUNCTIONAL ASSESSMENT				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40–69% or response lasts <2 hr	<40%	<25%[§]
PaO$_2$ (breathing air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or				
PCO$_2$	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
SaO$_2$ (breathing air) at	>95% (test not	90–95% (test not usually	<90%	Hypoxia despite

sea level	usually necessary)	necessary)		oxygen therapy
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

[*] Notes:

[†] Normal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.

[‡] Normal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.

[§] Peak expiratory flow testing may not be needed in very severe attacks.

- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other; thus they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

Adapted from National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): *Guideline for the diagnosis and management of asthma,* NIH Pub No 07-4051, Bethesda, MD, 2007, US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report .

Differential Diagnosis

Many childhood respiratory conditions can present with symptoms and signs similar to those of asthma (Table 169.5). Besides asthma, other common causes of chronic, intermittent coughing include gastroesophageal reflux (GER) and rhinosinusitis. Both GER and chronic sinusitis can be challeng spirometric lung function testing ing to diagnose in children. Often, GER is clinically silent in children, and children with chronic sinusitis do not report sinusitis-specific symptoms, such as localized sinus pressure and tenderness. In addition, both GER and rhinosinusitis are often comorbid with childhood asthma and, if not specifically treated, may make asthma difficult to manage.

Table 169.5

Differential Diagnosis of Childhood Asthma

Upper Respiratory Tract Conditions

Allergic rhinitis*
Chronic rhinitis*
Sinusitis*
Adenoidal or tonsillar hypertrophy
Nasal foreign body

Middle Respiratory Tract Conditions

Laryngotracheobronchomalacia*
Laryngotracheobronchitis (e.g., pertussis)*
Laryngeal web, cyst, or stenosis
Exercise-induced laryngeal obstruction
Vocal cord dysfunction*
Vocal cord paralysis
Tracheoesophageal fistula
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
Endobronchial tumor
Foreign body aspiration*
Chronic bronchitis from environmental tobacco smoke exposure*
Repaired tracheoesophageal fistula
Toxic inhalations

Lower Respiratory Tract Conditions

Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
Viral bronchiolitis*
Gastroesophageal reflux*
Causes of bronchiectasis:
  - Cystic fibrosis
  - Immunodeficiency
  - Allergic bronchopulmonary mycoses (e.g., aspergillosis)
  - Chronic aspiration

Primary ciliary dyskinesia, immotile cilia syndrome
Bronchiolitis obliterans
Interstitial lung diseases

Hypersensitivity pneumonitis
Eosinophilic granulomatosis with angiitis
Eosinophilic pneumonia
Pulmonary hemosiderosis
Tuberculosis
Pneumonia
Pulmonary edema (e.g., congestive heart failure)
Vasculitis
Sarcoidosis
Medications associated with chronic cough:

- Acetylcholinesterase inhibitors
- β-Adrenergic antagonists
- Angiotensin-converting enzyme inhibitors

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* More common asthma masqueraders.

In early life, chronic coughing and wheezing can indicate recurrent aspiration, **tracheobronchomalacia** (congenital anatomic abnormality of airways), foreign body aspiration, cystic fibrosis, or bronchopulmonary dysplasia.

In older children and adolescents, **vocal cord dysfunction (VCD)** can manifest as intermittent daytime wheezing. The vocal cords involuntarily close inappropriately during inspiration and sometimes exhalation, producing shortness of breath, coughing, throat tightness, and often audible laryngeal wheezing and/or stridor. In most cases of VCD, spirometric lung function testing reveals truncated and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. VCD can coexist with asthma. Hypercarbia and severe hypoxia are uncommon in VCD. Flexible rhinolaryngoscopy in the patient with symptomatic VCD can reveal paradoxical vocal cord movements with anatomically normal vocal cords. Prior to the diagnosis, patients with VCD are often treated unsuccessfully with multiple different classes of asthma medications. This condition can be well managed with specialized speech therapy training in the relaxation and control of vocal cord movement. Furthermore, treatment of underlying causes of vocal cord irritability (e.g., high GER/aspiration, allergic rhinitis, rhinosinusitis, asthma) can improve VCD. During acute VCD exacerbations, relaxation breathing techniques in conjunction with inhalation of heliox (a mixture of 70% helium and 30% oxygen) can relieve vocal cord spasm and VCD symptoms.

In some locales, hypersensitivity pneumonitis (farming communities, homes of bird owners), pulmonary parasitic infestations (rural areas of developing countries), or tuberculosis may be common causes of chronic coughing and/or wheezing. Rare mimics of asthma in childhood are noted in Table 169.5 . Chronic pulmonary diseases often produce clubbing, but clubbing is a very unusual finding in childhood asthma.

Laboratory Findings

Lung function tests can help to confirm the diagnosis of asthma and to determine disease severity.

Pulmonary Function Testing

Forced expiratory airflow measures are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in children with asthma who are poor perceivers of airflow obstruction, or when physical signs of asthma do not occur until airflow obstruction is severe.

Many asthma guidelines promote spirometric measures of airflow and lung volumes during forced expiratory maneuvers as standard for asthma assessment. **Spirometry** is a helpful objective measure of airflow limitation (Fig. 169.3). Spirometry is an essential assessment tool in children who are at risk for severe asthma exacerbations and those who have poor perception of asthma symptoms. Valid spirometric measures depend on a patient's ability to properly perform a full, forceful, and prolonged expiratory maneuver, usually feasible in children >6 yr old (with some younger exceptions).

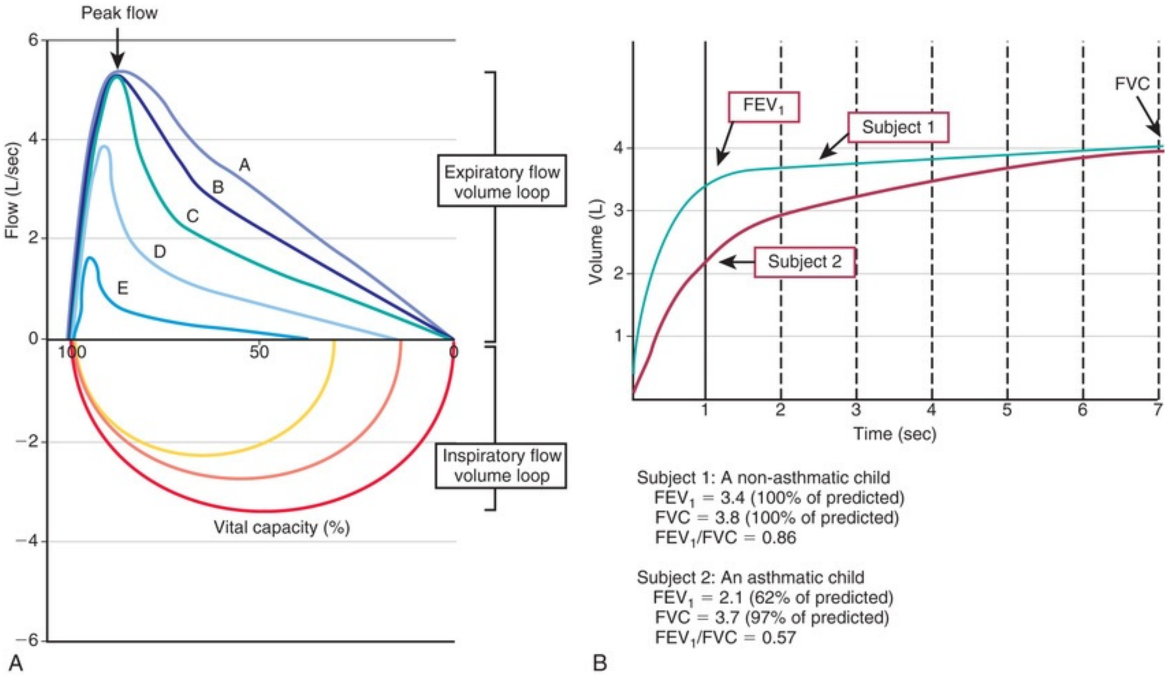

Subject 1: A non-asthmatic child
FEV$_1$ = 3.4 (100% of predicted)
FVC = 3.8 (100% of predicted)
FEV$_1$/FVC = 0.86

Subject 2: An asthmatic child
FEV$_1$ = 2.1 (62% of predicted)
FVC = 3.7 (97% of predicted)
FEV$_1$/FVC = 0.57

FIG. 169.3 **Spirometry. A, Spirometric flow-volume loops. Loop A is an expiratory flow-volume loop of a nonasthmatic person without airflow limitation. B through E are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping." B, Spirometric volume-time curves. Subject 1 is a nonasthmatic person; subject 2 is an asthmatic patient. Note how the FEV$_1$ and FVC lung volumes are obtained. The FEV$_1$ is the volume of air exhaled in the 1st sec of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort, or forced vital capacity. Note that subject 2's FEV$_1$ and FEV$_1$:FVC ratio are smaller than subject 1's, demonstrating airflow limitation. Also, subject 2's FVC is very close to what is expected.**

In asthma, airways blockage results in reduced airflow with forced exhalation (see Fig. 169.3). Because asthmatic patients typically have hyperinflated lungs, forced expiratory volume in 1 sec (FEV$_1$) can be simply adjusted for full expiratory lung volume—the forced vital capacity (FVC)—with an FEV$_1$ /FVC ratio. Generally, an FEV$_1$ /FVC ratio <0.80 indicates airflow obstruction (Table 169.6). Normative values for FEV$_1$ have been determined for children by height, gender, and ethnicity. Abnormally low FEV$_1$ as a percentage of predicted norms is 1 of 6 criteria used to determine asthma severity and control in asthma management guidelines sponsored by the U.S. National Institutes of Health (NIH) and the **Global Initiative for Asthma (GINA)** .

Table 169.6

Lung Function Abnormalities in Asthma and

Assessment of Airway Inflammation

Spirometry (in clinic) [‡] [†] :

Airflow limitation:

- Low FEV_1 (relative to percentage of predicted norms)
- FEV_1 /FVC ratio <0.80

Bronchodilator response (to inhaled β-agonist) assesses *reversibility* of airflow limitation.

Reversibility is determined by an increase in either FEV_1 >12% or predicted FEV_1 >10% after inhalation of a short-acting β-agonist (SABA)*

Exercise challenge:

- Worsening in FEV_1 ≥15%*

Daily peak expiratory flow (PEF) [‡] **or FEV_1 monitoring:** day-to-day and/or AM -to-PM variation ≥20%*

Exhaled nitric oxide (FeNO)

- A value of >20 ppb supports the clinical diagnosis of asthma in children
- FeNO can be used to predict response to ICS therapy:
  - <20 ppb: Unlikely to respond to ICS because eosinophilic inflammation unlikely
  - 20-35 ppb: Intermediate, may respond to ICS
  - >35 ppb: Likely to respond to ICS because eosinophilic inflammation is likely

FEV_1 , forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroid; ppb, parts per billion.

[‡] PEF variability is insensitive, while being highly specific for asthma.

[†] Of note, >50%of children with mild to moderate asthma will have a normal FEV_1 and will not have a significant bronchodilator response.

[*] Main criteria consistent with asthma.

Such measures of airflow alone are not diagnostic of asthma, because numerous other conditions can cause airflow limitation. In addition, approximately 50% of children with mild-moderate persistent asthma will have normal spirometric values when well. **Bronchodilator response** to an inhaled β-agonist (e.g., albuterol) is greater in asthmatic patients than nonasthmatic persons; an improvement in FEV_1 ≥12% is consistent with asthma. **Bronchoprovocation challenges** can be helpful in diagnosing asthma and optimizing asthma management. Asthmatic airways are hyperresponsive and therefore more sensitive to inhaled methacholine, mannitol, and cold or dry air. The degree of AHR to these exposures correlates to some extent with asthma severity and airways inflammation. Although bronchoprovocation challenges are carefully dosed and monitored in an investigational setting, their use is rarely practical in general practice. **Exercise challenges** (aerobic exertion or "running" for 6-8 min) can help to identify children with exercise-induced bronchospasm. Although the airflow response of nonasthmatic persons to exercise is to increase functional lung volumes and improve FEV_1 slightly (5–10%), exercise often provokes airflow obstruction in persons with inadequately treated asthma. Accordingly, in asthmatic patients, FEV_1 typically decreases during or after exercise by >15% (see Table 169.6). The onset of exercise-induced bronchospasm usually begins within 5 min, reaching a peak at 15 min following vigorous exercise, and often spontaneously resolves within 30-60 min. Studies of exercise challenges in school-age children typically identify an additional 5–10% with exercise-induced bronchospasm and previously unrecognized asthma. There are 2 caveats regarding exercise challenges: (1) treadmill challenges in the clinic are not completely reliable and can miss exertional asthma that can be demonstrated on the playing field; and (2) exercise challenges can induce severe exacerbations in at-risk patients. Careful patient selection for exercise challenges and preparedness for severe asthma exacerbations are required.

Peak expiratory flow (PEF) monitoring devices provide simple and inexpensive home-use tools to measure airflow and can be helpful in a number of circumstances (Fig. 169.4). Similar to spirometry in clinics, poor perceivers of asthma may benefit by monitoring PEFs at home to assess their airflow as an indicator of asthma control or problems. PEF devices vary in the ability to detect airflow obstruction; they are less sensitive and reliable than spirometry to detect airflow obstruction, such that, in some patients, PEF values decline only when airflow obstruction is severe. Therefore, PEF monitoring should be started by measuring morning and evening PEFs (best of 3 attempts) for several weeks for patients to practice the technique, to determine diurnal variation and a “personal best,” and to correlate PEF values with symptoms (and ideally spirometry). Diurnal variation in PEF >20% is consistent with asthma (see Fig. 169.4 and Table 169.6).

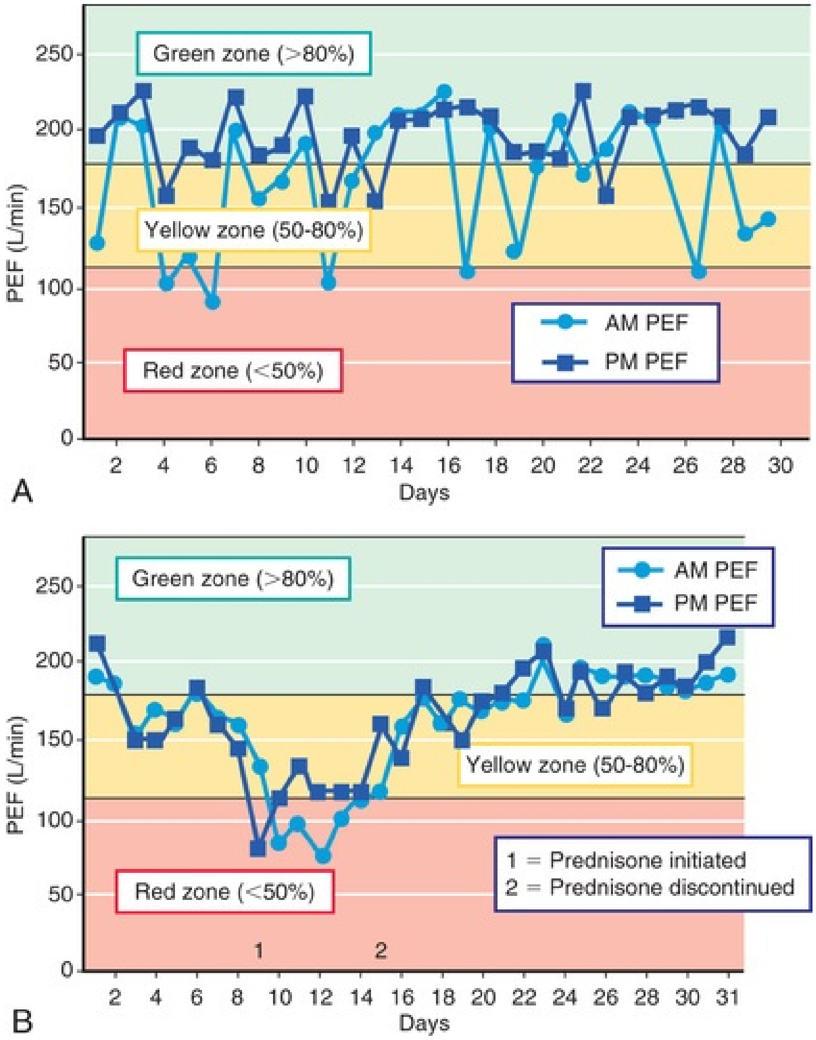

FIG. 169.4 **Example of the role of peak expiratory flow (PEF) monitoring in childhood asthma. A, PEFs performed and recorded twice daily, in the morning (AM) and evening (PM), over 1 mo in an asthmatic child. This child's “personal best” PEF value is 220 L/min; therefore the *green* zone (>80–100% of best) is 175-220 L/min; the *yellow* zone (50–80%) is 110-175 L/min; and the *red* zone (<50%) is <110 L/min. Note that this child's PM PEF values are almost always in the *green* zone, whereas his AM PEFs are often in the *yellow* or *red* zone. This pattern illustrates the typical diurnal AM -to-PM variation of inadequately controlled asthma. B, PEFs performed twice daily, in the morning (AM) and evening (PM), over 1 mo in an asthmatic child in whom an asthma exacerbation developed from a viral respiratory tract infection. Note that the child's PEF values were initially in the *green* zone. A viral respiratory tract infection led to asthma worsening, with a decline in PEF to the *yellow* zone that continued to worsen until PEF values were in the *red* zone. At that point, a 4-day prednisone course was administered, followed by improvement in PEF back to the *green* zone.**

Exhaled Nitric Oxide (FeNO)

Exhaled nitric oxide is a noninvasive measure of allergic airways inflammation used in clinical settings. Nitric oxide (NO) is a marker of allergic/eosinophilic inflammation that is easily and quickly measured in exhaled breath. Children as young as 5 yr can perform this test. FeNO can be used to distinguish asthma from other airways diseases that are mediated by nonallergic/noneosinophilic inflammation, such as GER, VCD, and cystic fibrosis. FeNO can substantiate the diagnosis of asthma, complement the assessment of asthma control, predict response to inhaled corticosteroid (ICS) therapy, assess adherence with ICS therapy, predict loss of control with ICS tapering, and predict future asthma exacerbations.

Radiology

The findings of chest radiographs (posteroanterior and lateral views) in children with asthma often appear to be normal, aside from subtle and nonspecific findings of hyperinflation (e.g., flattening of the diaphragms) and peribronchial thickening (Fig. 169.5). Chest radiographs can help identify abnormalities that are hallmarks of asthma mimics (aspiration pneumonitis, hyperlucent lung fields in bronchiolitis obliterans) and complications during asthma exacerbations (atelectasis, pneumomediastinum, pneumothorax). Some lung abnormalities can be better appreciated with high-resolution, thin-section chest CT scans. **Bronchiectasis** , which is sometimes difficult to appreciate on chest radiograph but is clearly seen on CT scan, implicates an asthma mimic such as cystic fibrosis, allergic bronchopulmonary mycoses (aspergillosis), ciliary dyskinesias, or immune deficiencies.

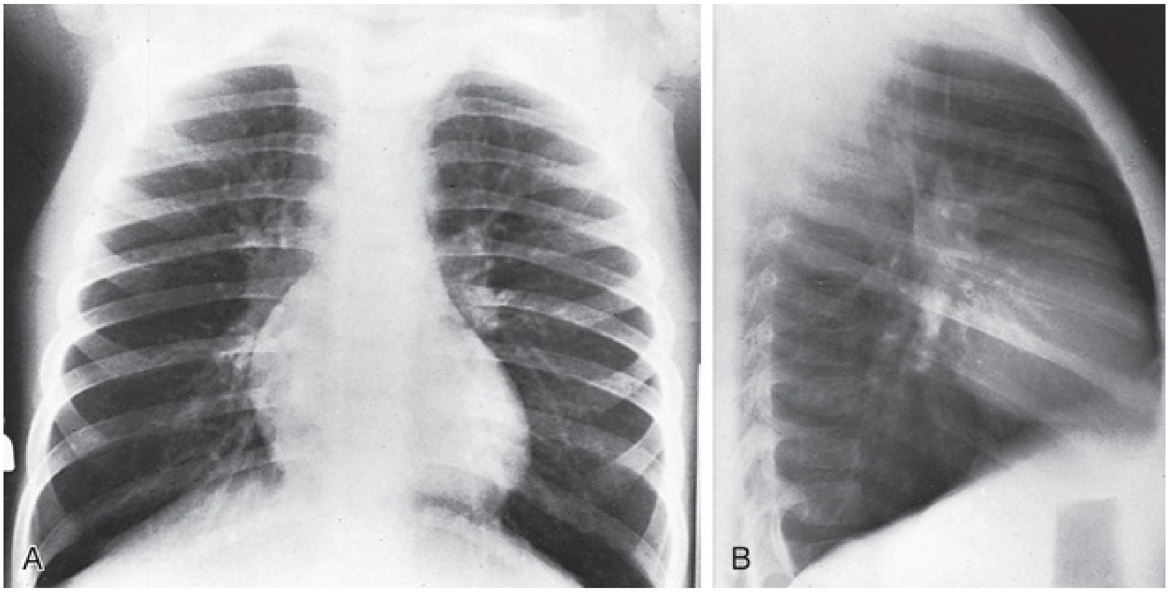

FIG. 169.5 A 4-year-old boy with asthma. Frontal (A) and lateral (B) radiographs show pulmonary hyperinflation, flattening of the diaphragms, and minimal peribronchial thickening. No asthmatic complication is apparent.

Other tests, such as allergy testing to assess sensitization to inhalant allergens, help with the management and prognosis of asthma. In a comprehensive U.S. study of 5-12 yr old asthmatic children, the **Childhood Asthma Management Program (CAMP)** , 88% of patients had inhalant allergen sensitization according to results of allergy skin-prick testing.

Treatment

The NIH-sponsored **National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3)** , *Guidelines for the Diagnosis and Management of Asthma 2007,* is available online.* Similar guidelines from GINA, *Global Strategy for Asthma Management and Prevention, 2016* , are also available (www.ginasthma.org). The key components to optimal asthma management are specified (Fig. 169.6). Management of asthma should have the following components: (1) assessment and monitoring of disease activity; (2) education to enhance patient and family knowledge and skills for self-management; (3) identification and management of precipitating factors and comorbid conditions that worsen asthma; and (4) appropriate selection of medications to address the patient's needs. The long-term goal of asthma management is attainment of optimal asthma control.

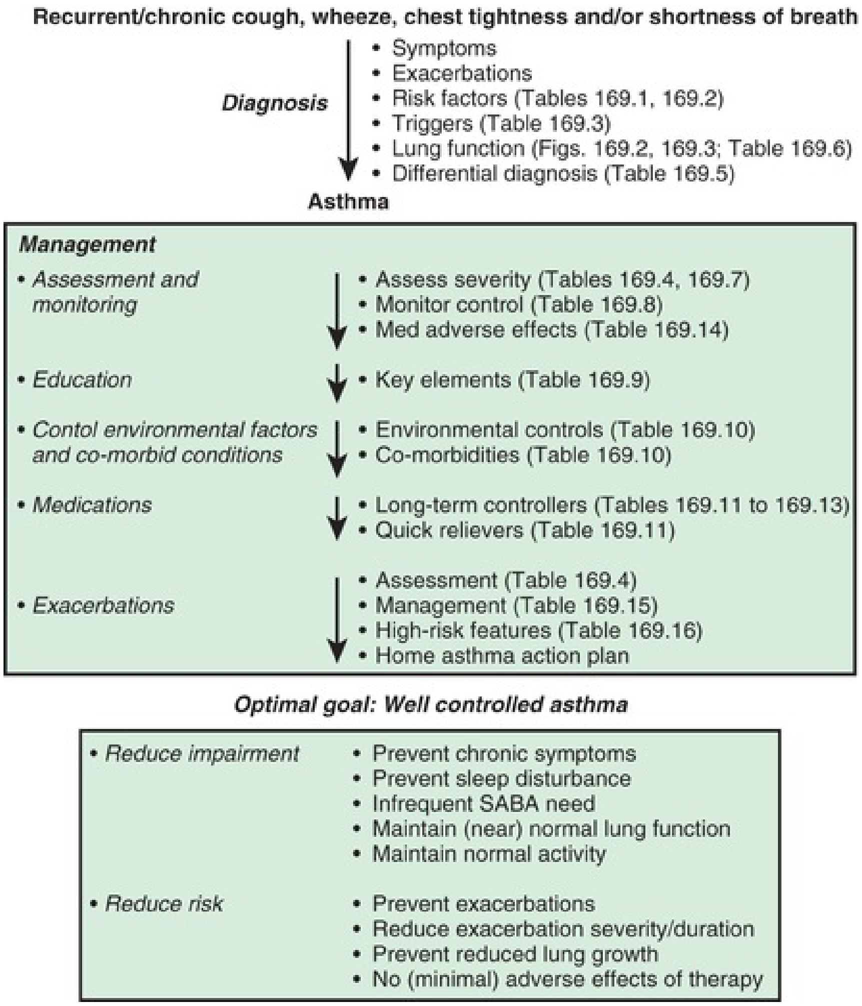
Recurrent/chronic cough, wheeze, chest tightness and/or shortness of breath
Diagnosis
• Symptoms
• Exacerbations
• Risk factors (Tables 169.1, 169.2)
• Triggers (Table 169.3)
• Lung function (Figs. 169.2, 169.3; Table 169.6)
• Differential diagnosis (Table 169.5)
Asthma
Management
• Assessment and monitoring
• Assess severity (Tables 169.4, 169.7)
• Monitor control (Table 169.8)
• Med adverse effects (Table 169.14)
• Education
• Key elements (Table 169.9)
• Contol environmental factors and co-morbid conditions
• Environmental controls (Table 169.10)
• Co-morbidities (Table 169.10)
• Medications
• Long-term controllers (Tables 169.11 to 169.13)
• Quick relievers (Table 169.11)
• Exacerbations
• Assessment (Table 169.4)
• Management (Table 169.15)
• High-risk features (Table 169.16)
• Home asthma action plan
Optimal goal: Well controlled asthma
• Reduce impairment
• Prevent chronic symptoms
• Prevent sleep disturbance
• Infrequent SABA need
• Maintain (near) normal lung function
• Maintain normal activity
• Reduce risk
• Prevent exacerbations
• Reduce exacerbation severity/duration
• Prevent reduced lung growth
• No (minimal) adverse effects of therapy

FIG. 169.6 **The key elements to optimal asthma management. SABA, Short-acting β-agonist.**

Component 1: Regular Assessment and Monitoring

Regular assessment and monitoring are based on the concepts of asthma severity, asthma control, and responsiveness to therapy. **Asthma severity** is the intrinsic intensity of disease, and assessment is generally most accurate in patients not receiving controller therapy. Therefore, assessing asthma severity directs the initial level of therapy. The 2 general categories are **intermittent** asthma and **persistent** asthma, the latter being further subdivided into **mild, moderate,** and **severe.** In contrast, **asthma control** is dynamic and refers to the day-to-day variability of an asthmatic patient. In children receiving controller therapy, assessment of asthma control is important in adjusting therapy and is categorized in 3 levels: well controlled, not well controlled, and very poorly controlled. **Responsiveness to therapy** is the ease or difficulty with which asthma control is attained by treatment.

Classification of asthma severity and control is based on the domains of **impairment** and **risk** . These domains do not necessarily correlate with each other and may respond differently to treatment. Childhood asthma is characterized by minimal day-to-day impairment, with the potential for frequent, severe exacerbations most often triggered by viral infections, whereas adults with asthma have greater impairment with less potential for risk. The NIH guidelines have distinct criteria for 3 childhood age groups—0-4 yr, 5-11 yr, and ≥12 yr—for the evaluation of both severity (Table 169.7) and control (Table 169.8). The level of asthma severity or control is based on the most severe impairment or risk category. In assessing asthma severity, **impairment** consists of an assessment of the patient's recent symptom frequency (daytime and nighttime, with subtle differences in numeric cutoffs between the 3 age-groups), SABA use for quick relief, ability to engage in normal or desired activities, and airflow compromise evaluated by spirometry in children ≥5 yr. **Risk** refers to the likelihood of developing severe asthma exacerbations. Of note, even in the absence of frequent symptoms, persistent asthma can be diagnosed and long-term controller therapy initiated. For children ≥5 yr, 2 exacerbations requiring oral corticosteroids in 1 yr, and for infants and preschool-aged children who have risk factors for asthma (see earlier) and 4 or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep, or 2 or more exacerbations in 6 mo requiring systemic corticosteroids, qualifies them as having persistent asthma.

Table 169.7

Assessing Asthma Severity and Initiating Treatment for Patients Who Are Not Currently Taking Long-Term Control Medications*

	CLASSIFICATION OF ASTHMA SEVERITY			
	INTERMITTENT	**PERSISTENT**		
		Mild	**Moderate**	**Severe**
COMPONENTS OF SEVERITY				
Impairment				
Daytime symptoms	≤2 days/wk	>2 days/wk but	Daily	Throughout the day

		not daily		
Nighttime awakenings:				
Age 0-4 yr	0	1-2×/mo	3-4×/mo	>1×/wk
Age ≥5 yr	≤2×/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
Short-acting β_2 -agonist use for symptoms (not for EIB prevention)	≤2 days/wk	>2 days/wk but not daily, and not more than 1× on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function:				
FEV_1 % predicted, age ≥5 yr	Normal FEV_1 between exacerbations >80% predicted	≥80% predicted	60–80% predicted	<60% predicted
FEV_1 /FVC ratio [†] :				
Age 5-11 yr	>85%	>80%	75-80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
Risk				
Exacerbations requiring systemic corticosteroids:				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic CS *or* ≥4 wheezing episodes/yr lasting >1 day *and* risk factors for persistent asthma		
Age ≥ 5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
Consider severity and interval since last exacerbation. *Frequency and severity may fluctuate over time for patients in any severity category.* *Relative annual risk of exacerbations may be related to FEV_1 .*				
RECOMMENDED STEP FOR INITIATING THERAPY				
(See Table 169.11 for treatment steps.) The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.				
All ages	Step 1	Step 2		
Age 0-4 yr			Step 3 and consider a short course of systemic CS	Step 3 and consider a short course of systemic CS
Age 5-11 yr			Step 3: medium-dose ICS option and consider a short course of systemic CS	Step 3: medium-dose ICS option *or* Step 4 and consider a short course of CS
	In 2-6 wk, depending on severity, evaluate level of asthma control that is achieved. • Children 0-4 yr old: If no clear benefit is observed in 4-6 wk, stop treatment and consider alternative diagnoses or adjusting therapy accordingly. • Children 5-11 yr old: Adjust therapy accordingly.			

[*] Notes:

[†] Normal FEV_1 /FVC: 8-19 yr, 85%; 20-39 yr, 80%.

- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.

- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 mo, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma, may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

FEV_1 , Forced expiratory volume in 1 sec; FVC, forced vital capacity; CS corticosteroid; ICS, inhaled corticosteroid: EIB, exercise-induced bronchospasm.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma—summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94–S138, 2007.

Table 169.8

Assessing Asthma Control and Adjusting Therapy in Children*

	CLASSIFICATION OF ASTHMA CONTROL		
	Well-Controlled	**Not Well-Controlled**	**Very Poorly Controlled**
COMPONENTS OF CONTROL			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1×/mo	>1×/mo	>1×/wk
Age 5-11 yr	≤1×/mo	≥2×/mo	≥2×/wk
Age ≥12 yr	≤2×/mo	1-3×/wk	≥4×/wk
Short-acting β_2 -agonist use for symptoms (not for EIB pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
FEV_1 /FVC:	>80%	75-80%	<75%
Age ≥12 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
Validated questionnaires † :			
Age ≥12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15

Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Reduction in lung growth *or* progressive loss of lung function	Evaluation requires long-term follow-up care.		
RECOMMENDED ACTION FOR TREATMENT			
	Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well controlled for at least 3 mo.	Step up [‡] (1 step) and reevaluate in 2-6 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.	Consider short course of oral corticosteroids. Step up [§] (1-2 steps) and reevaluate in 2 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.

[*] Notes:

[†] Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:

[‡] ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

[§] Before step-up therapy: (a) review adherence to medications, inhaler technique, and environmental control; (b) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0.
- ACQ, Asthma Control Questionnaire; MID = 0.5.
- ACT, Asthma Control Test; MID not determined.

FEV$_1$, Forced expiratory volume in 1 sec; FVC, forced vital capacity; EIB, exercise-induced bronchospasm; N/A, not available.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94–S138, 2007.

Asthma management can be optimized through regular clinic visits every 2-6 wk until good asthma control is achieved. For children on controller medication therapy, management is tailored to the child's level of control. The NIH guidelines provide tables for evaluating asthma control for the 3 age-groups (see Table 169.8). In evaluation of asthma control, as in severity assessment, impairment includes an assessment of the patient's symptom frequency (daytime and nighttime), SABA use for quick relief, ability to engage in normal or desired activities, and for older children, airflow measurements. Validated asthma control questionnaires such as the **Asthma Control Test** (ACT, for adults and children ≥12 yr) and the Childhood ACT (C-ACT, for children 4-11 yr) can also be used to assess level of control. An ACT score of ≥20 indicates a child with **well-controlled** asthma, a value of 16-19 indicates **not well-controlled** asthma, and ≤15 indicates **very poorly controlled** asthma. For the C-ACT, a score ≥20 indicates *well controlled* , 13-19 indicates *not well controlled* ; and ≤12 indicates *very poorly controlled* .

Assessment of risk, in addition to considering severity and frequency of exacerbations requiring systemic corticosteroids, includes tracking the lung growth of older children, in an attempt to identify those with reduced and/or progressive loss of lung function, and monitoring adverse effects of medications. The degree of impairment and presence of risk are used to determine the patient's level of asthma control as well controlled, not well controlled, or very poorly controlled. Children with *well-controlled asthma* have daytime symptoms ≤2 days/wk and need a rescue bronchodilator ≤2 days/wk; an FEV_1 of >80% of predicted (and FEV_1 /FVC ratio >80% for children 5-11 yr); no interference with normal activity; and <2 exacerbations in the past year and an ACT score of ≥20. The impairment criteria vary slightly depending on age-group. Children whose status does not meet all the criteria of well-controlled asthma are determined to have either *not well-controlled* or *very poorly controlled* asthma, which is determined by the single criterion with the poorest rating.

Two to four asthma checkups per year are recommended for reassessing and maintaining good asthma control. Lung function testing (spirometry) is recommended at least annually and more often if asthma is poorly perceived, is inadequately controlled, and/or lung function is abnormally low. PEF monitoring at home can be helpful in the assessment of asthmatic children with poor symptom perception, moderate to severe asthma, or a history of severe asthma exacerbations. PEF monitoring is feasible in children as young as 4 yr who are able to master this skill. Use of a **stoplight zone system** tailored to each child's “personal best” PEF values can optimize effectiveness and interest (see Fig. 169.4): The green zone (80–100% of personal best) indicates good control; the yellow zone (50–80%) indicates less-than-optimal control and necessitates increased awareness and treatment; and the red zone (<50%) indicates poor control and greater likelihood of an exacerbation, requiring immediate intervention. In actuality, these ranges are approximate and may need to be adjusted for many asthmatic children by raising the ranges that indicate inadequate control (e.g., yellow zone, 70–90% in children with poor perception and those with lung hyperinflation). Once-daily PEF monitoring is preferable in the morning when peak flows are typically lower. Adherence to PEF monitoring is difficult, results may be variable and PEF monitoring alone is not more effective than symptoms monitoring on influencing asthma outcomes. Therefore, although PEF may be helpful in some circumstances to monitor those who are poor perceivers of airway obstruction, PEF monitoring is no longer generally recommended.

Component 2: Patient Education

Specific educational elements in the clinical care of children with asthma are believed to make an important difference in home management and in adherence of families to an optimal plan of care, eventually impacting patient outcomes (Table 169.9). Every visit presents an important opportunity to educate the child and family, allowing them to become knowledgeable partners in asthma management, because optimal management depends on their daily assessments and implementation of any management plan. Effective communications take into account sociocultural and ethnic factors of children and their families, provide an open forum for concerns about asthma and its treatment to be raised and addressed, and include patients and families as active participants in the development of treatment goals and selection of medications. Self-management skills should be reevaluated regularly (e.g., inhaler medication technique).

Table 169.9

Key Elements of Productive Clinic Visits for

Asthma

Standardize assessment of asthma control (e.g., Asthma Control Test, exacerbations in past 12 mo)

Specify goals of asthma management

Explain basic facts about asthma:

- Contrast normal vs asthmatic airways.
- Link airways inflammation, “twitchiness,” and bronchoconstriction.
- Long-term-control and quick-relief medications
- Address concerns about potential adverse effects of asthma pharmacotherapy.

Teach, demonstrate, and have patient show proper technique for:

- Inhaled medication use (spacer use with metered-dose inhaler)

Investigate and manage factors that contribute to asthma severity:

- Environmental exposures
- Comorbid conditions

Create written 2-part Asthma Action Plan (see Fig. 169.7):

- Daily management
- Action plan for asthma exacerbations

Regular follow-up visits:

- Twice yearly (more often if asthma not well controlled)
- Monitor lung function at least annually

During initial patient visits, a basic understanding of the pathogenesis of asthma (chronic inflammation and AHR underlying a clinically intermittent presentation) can help children with asthma and their parents understand the importance of recommendations aimed at reducing airways inflammation to achieve and maintain good asthma control. It is helpful to specify the expectations of good asthma control resulting from optimal asthma management (see Fig. 169.6). Addressing concerns about potential adverse effects of asthma pharmacotherapeutic agents, especially their risks relative to their benefits, is essential in achieving long-term adherence with asthma pharmacotherapy and environmental control measures.

All children with asthma should benefit from a written Asthma Action Plan (Fig. 169.7). This plan has two main components: (1) a daily “routine” management plan describing regular asthma medication use and other measures to keep asthma under good control; and (2) an action plan to manage worsening asthma, describing indicators of impending exacerbations, identifying what medications to take, and specifying when and how to contact the regular physician and/or obtain urgent/emergency medical care.

Asthma Action Plan

For: ______________________________ Doctor: ______________________________ Date: ______________

Doctor's Phone Number ______________________________ Hospital/Emergency Department Phone Number ______________________________

GREEN ZONE

Doing Well

- No cough, wheeze, chest tightness, or shortness of breath during the day or night
- Can do usual activities

And, if a peak flow meter is used,

Peak flow: more than ______________
(80 percent or more of my best peak flow)

My best peak flow is: ______________

Take these long-term control medicines each day (include an anti-inflammatory).

Medicine	How much to take	When to take it

Before exercise ☐ ______________ ☐ 2 or ☐ 4 puffs ______________ 5 minutes before exercise

YELLOW ZONE

Asthma Is Getting Worse

- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

-Or-

Peak flow: ________ to ________
(50 to 79 percent of my best peak flow)

First

Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.

______________________________ ☐ 2 or ☐ 4 puffs, every 20 minutes for up to 1 hour
(short-acting beta$_2$-agonist) ☐ Nebulizer, once

Second

If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:
☐ Continue monitoring to be sure you stay in the green zone.

-Or-

If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:
☐ Take: ______________________________ ☐ 2 or ☐ 4 puffs or ☐ Nebulizer
(short-acting beta$_2$-agonist)
☐ Add: ______________________________ mg per day For ________ (3–10) days
(oral steroid)
☐ Call the doctor ☐ before/ ☐ within ________ hours after taking the oral steroid.

RED ZONE

Medical Alert!

- Very short of breath, or
- Quick-relief medicines have not helped, or
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone

-Or-

Peak flow: less than ______________
(50 percent of my best peak flow)

Take this medicine:

☐ ______________________________ ☐ 4 or ☐ 6 puffs or ☐ Nebulizer
(short-acting beta$_2$-agonist)
☐ ______________________________ mg
(oral steroid)

Then call your doctor NOW. Go to the hospital or call an ambulance if:
- You are still in the red zone after 15 minutes AND
- You have not reached your doctor.

DANGER SIGNS
- **Trouble walking and talking due to shortness of breath**
- **Lips or fingernails are blue**

- **Take ☐ 4 or ☐ 6 puffs of your quick-relief medicine AND**
- **Go to the hospital or call for an ambulance ______________ NOW!**
(phone)

See the reverse side for things you can do to avoid your asthma triggers.

How To Control Things That Make Your Asthma Worse

This guide suggests things you can do to avoid your asthma triggers. Put a check next to the triggers that you know make your asthma worse and ask your doctor to help you find out if you have other triggers as well. Then decide with your doctor what steps you will take.

Allergens

☐ Animal Dander

Some people are allergic to the flakes of skin or dried saliva from animals with fur or feathers.

The best thing to do:
- Keep furred or feathered pets out of your home.

If you can't keep the pet outdoors, then:
- Keep the pet out of your bedroom and other sleeping areas at all times, and keep the door closed.
- Remove carpets and furniture covered with cloth from your home. If that is not possible, keep the pet away from fabric-covered furniture and carpets.

☐ Dust Mites

Many people with asthma are allergic to dust mites. Dust mites are tiny bugs that are found in every home—in mattresses, pillows, carpets, upholstered furniture, bedcovers, clothes, stuffed toys, and fabric or other fabric-covered items.

Things that can help:
- Encase your mattress in a special dust-proof cover.
- Encase your pillow in a special dust-proof cover or wash the pillow each week in hot water. Water must be hotter than 130° F to kill the mites. Cold or warm water used with detergent and bleach can also be effective.
- Wash the sheets and blankets on your bed each week in hot water.
- Reduce indoor humidity to below 60 percent (ideally between 30—50 percent). Dehumidifiers or central air conditioners can do this.
- Try not to sleep or lie on cloth-covered cushions.
- Remove carpets from your bedroom and those laid on concrete, if you can.
- Keep stuffed toys out of the bed or wash the toys weekly in hot water or cooler water with detergent and bleach.

☐ Cockroaches

Many people with asthma are allergic to the dried droppings and remains of cockroaches.

The best thing to do:
- Keep food and garbage in closed containers. Never leave food out.
- Use poison baits, powders, gels, or paste (for example, boric acid). You can also use traps.
- If a spray is used to kill roaches, stay out of the room until the odor goes away.

☐ Indoor Mold
- Fix leaky faucets, pipes, or other sources of water that have mold around them.
- Clean moldy surfaces with a cleaner that has bleach in it.

☐ Pollen and Outdoor Mold

What to do during your allergy season (when pollen or mold spore counts are high):
- Try to keep your windows closed.
- Stay indoors with windows closed from late morning to afternoon, if you can. Pollen and some mold spore counts are highest at that time.
- Ask your doctor whether you need to take or increase anti-inflammatory medicine before your allergy season starts.

Irritants

☐ Tobacco Smoke
- If you smoke, ask your doctor for ways to help you quit. Ask family members to quit smoking, too.
- Do not allow smoking in your home or car.

☐ Smoke, Strong Odors, and Sprays
- If possible, do not use a wood-burning stove, kerosene heater, or fireplace.
- Try to stay away from strong odors and sprays, such as perfume, talcum powder, hair spray, and paints.

Other things that bring on asthma symptoms in some people include:

☐ Vacuum Cleaning
- Try to get someone else to vacuum for you once or twice a week, if you can. Stay out of rooms while they are being vacuumed and for a short while afterward.
- If you vacuum, use a dust mask (from a hardware store), a double-layered or microfilter vacuum cleaner bag, or a vacuum cleaner with a HEPA filter.

☐ Other Things That Can Make Asthma Worse
- Sulfites in foods and beverages: Do not drink beer or wine or eat dried fruit, processed potatoes, or shrimp if they cause asthma symptoms.
- Cold air: Cover your nose and mouth with a scarf on cold or windy days.
- Other medicines: Tell your doctor about all the medicines you take. Include cold medicines, aspirin, vitamins and other supplements, and nonselective beta-blockers (including those in eye drops).

U.S. Department of Health and Human Services
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National **Heart**
Lung and Blood Institute

For More Information, go to: www.nhlbi.nih.gov

NIH Publication No. 07-5251
April 2007

FIG. 169.7 Asthma action plan for home use. This plan has two main components: (1) a daily management plan to keep asthma in good control; and (2) an action plan to recognize and manage worsening asthma. (From US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, NIH Pub No 07-5251, April 2007. https://www.nhlbi.nih.gov/health/resources/lung/asthma-action-plan).

Regular follow-up visits are recommended to help to maintain optimal asthma control. In addition to determining disease control level, revising PEF values daily and exacerbation management plans accordingly, follow-up visits are important teaching opportunities to encourage open communication of concerns with asthma management recommendations (e.g., daily administration of controller medications). Reassessing patients' and parents' understanding of the role of different medications in asthma management and control, and their technique in using inhaled medications, can be insightful and can help guide teaching to improve adherence to a management plan that might not have been adequately or properly implemented.

Adherence

Asthma is a chronic condition that is usually best managed with daily controller medication. However, symptoms wax and wane, severe exacerbations are infrequent, and when asthma is asymptomatic, a natural tendency is to reduce or discontinue daily controller therapies. As such, adherence to a daily controller regimen is frequently suboptimal; ICSs are underused 60% of the time. In one study, children with asthma who required an oral corticosteroid course for an asthma exacerbation had used their daily controller ICS 15% of the time. Misconceptions about controller medication time to onset, efficacy, and safety often underlie poor adherence and can be addressed by asking about such concerns at each visit.

Component 3: Control of Factors Contributing to Asthma Severity

Controllable factors that can worsen asthma can be generally grouped as (1) environmental exposures and (2) comorbid conditions (Table 169.10).

Table 169.10

Control of Factors Contributing to Asthma

Severity

Eliminate or Reduce Problematic Environmental Exposures

Environmental tobacco smoke elimination or reduction in home and automobiles

Allergen exposure elimination or reduction in sensitized asthmatic patients:

- Animal danders: pets (cats, dogs, rodents, birds)
- Pests (mice, rats)
- Dust mites
- Cockroaches
- Molds

Other airway irritants:

- Wood- or coal-burning smoke
- Strong chemical odors and perfumes (e.g., household cleaners)
- Dusts

Treat Comorbid Conditions

- Rhinitis
- Sinusitis
- Gastroesophageal reflux

Eliminating and Reducing Problematic Environmental Exposures

Most children with asthma have an **allergic component** to their disease; steps should be taken to investigate and minimize allergen exposures in sensitized asthmatic patients. The medical history should identify exposure to smoke, pollutant, and potential allergen triggers (see later), especially in the patient's home. Since often patients have chronic symptoms and cannot identify potential triggers, **allergy testing** should be considered for at least those with persistent asthma. For asthmatic patients who are allergic to allergens in their homes and/or schools or daycare centers, reducing or eliminating these indoor allergen exposures can reduce asthma symptoms, medication requirements, AHR, severe exacerbations, and disease persistence. Common home, school, and daycare allergen exposures include furred or feathered animals as pets (cats, dogs, rodents, birds) or as pests (mice, rats, cockroaches), and occult indoor allergens such as dust mites and molds. Although removing or eradicating these exposures from the home, school, and daycare setting of sensitized asthmatic patients is the most effective means of greatly reducing problematic allergen exposures, it can take ≥6 mo for the levels of these indoor allergens to drop significantly. Dust mite allergen exposure can be reduced by (1) encasing bedding and pillows in allergen-impermeable covers; (2) washing bedding weekly in hot water (> 130°F); (3) removing wall-to-wall carpeting and upholstered furniture; and (4) reducing and maintaining indoor humidity <50%.

Tobacco, wood and coal smoke, dusts, strong odors, and noxious air pollutants (e.g., nitrogen dioxide from inadequately vented gas stoves and furnaces) can aggravate asthma. These airway irritants should be eliminated from or reduced in the homes, schools/daycare centers, and automobiles/school transportation used by children with asthma. Annual influenza vaccination continues to be recommended for all children with asthma to reduce the risk of severe complications, although influenza is not responsible for the large majority of virus-induced asthma exacerbations experienced by children.

Treating Comorbid Conditions

Rhinitis, sinusitis, and GER often accompany asthma and worsen disease severity. They can also mimic asthma symptoms and lead to misclassification of asthma severity and control. Indeed, these conditions, along with asthma are the most common causes of chronic cough. Effective management of these comorbid conditions may improve asthma symptoms and disease severity, such that less asthma medication is needed to achieve good asthma control.

Gastroesophageal reflux is common in children with persistent asthma (see Chapter 349). GER may worsen asthma through 2 postulated mechanisms: (1) aspiration of refluxed gastric contents (micro- or macro-aspiration); and (2) vagally mediated reflex bronchospasm. Occult GER should be suspected in individuals with difficult-to-control asthma, especially patients who have prominent nocturnal asthma symptoms or who prop themselves up in bed to reduce nocturnal symptoms. GER can be demonstrated by reflux of barium into the esophagus during a barium swallow procedure or by esophageal probe monitoring. Because radiographic studies lack sufficient sensitivity and specificity, extended esophageal monitoring is the method of choice for diagnosing GER. If significant GER is noted, reflux precautions should be instituted (no food 2 hr before bedtime, head of bed elevated 6 inches, avoidance of caffeinated beverages), and medications such as proton pump inhibitors (omeprazole, lansoprazole) or H_2 -receptor antagonists (cimetidine, ranitidine) administered for 8-12 wk. Of note, proton pump inhibition did not improve asthma control in a study of children with persistent, poorly controlled asthma and GER.

Rhinitis is usually comorbid with asthma, detected in about 90% of children with asthma. Rhinitis can be seasonal and/or perennial, with allergic and nonallergic components. Rhinitis complicates and worsens asthma via numerous direct and indirect mechanisms. Nasal breathing may improve asthma and reduce exercise-induced bronchospasm by humidifying and warming inspired air and filtering out allergens and irritants that can trigger asthma and worsen airway inflammation. Reduction of nasal congestion and obstruction can help the nose to perform these humidifying, warming, and filtering functions. In asthmatic patients, improvement in rhinitis is also associated with modest reductions in AHR, airways inflammation, asthma symptoms, and asthma medication use. Optimal rhinitis management in children is similar to asthma management in regard to the importance of interventions to reduce nasal inflammation (see Chapter 168).

Radiographic evidence for **sinus disease** is common in patients with asthma. There is usually significant improvement in asthma control in patients diagnosed and treated for sinus disease. A coronal, “screening” or “limited” CT scan of the sinuses is the gold standard test for sinus disease and can be helpful if recurrent sinusitis has been suspected and repeatedly treated without such evidence. In comparison, sinus radiographs are inaccurate and should be avoided. If the patient with asthma has clinical and radiographic evidence for sinusitis, topical therapy to include nasal saline irrigations, intranasal corticosteroids, and a 2-3 wk course of antibiotics should be considered.

Component 4: Principles of Asthma Pharmacotherapy

The current version of NIH asthma guidelines (2007) provides treatment recommendations that vary by level of asthma severity and age-groups (Table 169.11). There are 6 treatment steps. Patients at **Treatment Step 1** have intermittent asthma. Children with mild persistent asthma are at **Treatment Step 2** . Children with moderate persistent asthma can be at **Treatment Step 3 or 4** .

Children with severe persistent asthma are at **Treatment Steps 5 and 6** . The goals of therapy are to achieve a well-controlled state by reducing the components of both impairment (e.g., preventing or minimizing symptoms, infrequently needing quick-reliever medications, maintaining “normal” lung function and normal activity levels) and risk (e.g., preventing recurrent exacerbations, reduced lung growth, and medication adverse effects). The recommendations for initial therapy are based on assessment of asthma severity, while level of control determines any modifications of treatment in children who are already using controller therapy. A major objective of this approach is to identify and treat all “persistent” and inadequately controlled asthma with antiinflammatory controller medication. Management of Treatment Step 1 (intermittent asthma) is simply the use of a SABA as needed for symptoms and for pretreatment in those with exercise-induced bronchospasm (see Table 169.11).

Table 169.11

Stepwise Approach for Managing Asthma in Children*

AGE	THERAPY †	INTERMITTENT ASTHMA	PERSISTENT ASTHMA: DAILY MEDICATION				
		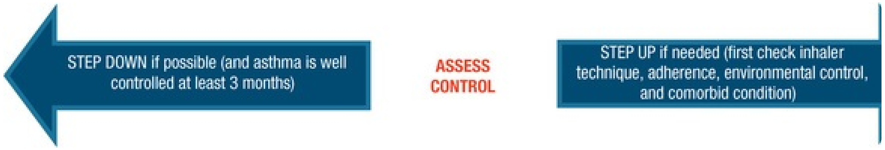 STEP DOWN if possible (and asthma is well controlled at least 3 months) ASSESS CONTROL STEP UP if needed (first check inhaler technique, adherence, environmental control, and comorbid condition)					
		Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**S**
0-4 yr	Preferred	SABA prn	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + *either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA	
	Alternative		Cromolyn or montelukast				
5-11 yr	Preferred	SABA prn	Low-dose ICS	*Either* low-dose ICS ± LABA, LTRA, or theophylline *or*	Medium-dose ICS + LABA	High-dose ICS + LABA	

				Medium-dose ICS			
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline		Medium-dose ICS + *either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline	
≥12 yr	Preferred	SABA prn	Low-dose ICS	Low-dose ICS + LABA *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA *and* Consider omalizumab for patients with allergies	
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS + LTRA, theophylline, or zileuton	Medium-dose ICS + LTRA, theophylline, or zileuton		
	Each step: Patient education, environmental control, and management of comorbidities. Age ≥5 yr: Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic ast						
	QUICK-RELIEF MEDICATION FOR ALL PATIENTS						
	SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatm intervals as needed. Short course of oral systemic corticosteroids may be needed. *Caution:* Use of SABA >2 days/wk for symptom relief (not prevention of exercise-induced bronchospas indicates inadequate control and the need to step up treatment. For ages 0-4 yr: With viral respiratory infection: SABA q4-6h up to 24 hr (longer with physician consul short course of systemic corticosteroids if exacerbation is severe or patient has history of previous sever exacerbations.						

[*] Notes:

[†] Alphabetical order is used when more than 1 treatment option is listed within *either* preferred or alternative therapy.

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels. The 2016 GINA guidelines do not recommend the use of theophylline as a controller medication and in IV forms to treat status asthmaticus due to its severe adverse effects profile.
- Zileuton is less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function.

ICS, Inhaled corticosteroid; LABA, inhaled long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; prn, as needed; SABA, inhaled short-acting β_2 -agonist.

Adapted from the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma—summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94–S138, 2007.

The preferred treatment for all patients with persistent asthma is ICS therapy, as monotherapy or in combination with adjunctive therapy. The type(s) and amount(s) of daily controller medications to be used are determined by the asthma severity and control rating.

Low-dose ICS therapy is the treatment of choice for all children at Treatment Step 2 (mild persistent asthma). Alternative medications include a leukotriene-modifying agent (montelukast), nonsteroidal antiinflammatory drugs (cromolyn, nedocromil), and theophylline. There are 4 co-equal choices for the treatment of school-aged children at Treatment Step 3 (moderate persistent asthma): medium-dose ICS, combination low-dose ICS and **inhaled long-acting β_2 -agonist (LABA)** , a **leukotriene receptor antagonist (LTRA)** , or theophylline. In a study of children with uncontrolled asthma receiving low-dose ICS, the addition of LABA provided greater improvement than either adding an **LTRA** or increasing ICS dosage. However, some children had a good response to medium-dose ICS or the addition of an LTRA, justifying them as step-up controller therapy options. The preferred therapy for children at Treatment Step 4 (also moderate persistent asthma) is medium-dose ICS/LABA combination. Alternatives include medium-dose ICS with either theophylline or an LTRA. For young children (≤4 yr) at Treatment Step 3, medium-dose ICS is recommended, while medium-dose ICS plus either an LABA or an LTRA are recommended for preschool-age children at Treatment Step 4.

Children with severe persistent asthma (Treatment Steps 5 and 6) should receive combination high-dose ICS plus LABA. Long-term administration of oral corticosteroids as controller therapy is effective but is rarely required. In addition, omalizumab can be used in children ≥6 yr old with severe allergic asthma, while mepolizumab is approved for children ≥12 yr with severe asthma eosinophilic asthma. A rescue course of systemic corticosteroids may be necessary at any step for very poorly controlled asthma. For children age ≥5 yr with allergic asthma requiring Treatment Steps 2-4 care, allergen immunotherapy can also be considered.

“Step-Up, Step-Down” Approach

The NIH guidelines emphasize initiating higher-level controller therapy at the outset to establish prompt control, with measures to “step-down” therapy once good asthma control is achieved. Initially, airflow limitation and the pathology of asthma may limit the delivery and efficacy of ICS such that stepping up to higher doses and/or combination therapy may be needed to gain asthma control. Furthermore, ICS requires weeks to months of daily administration for optimal efficacy to occur. Combination pharmacotherapy can achieve relatively immediate improvement while also providing daily ICS to improve long-term control and reduce exacerbation risk.

Asthma therapy can be stepped down after good asthma control has been achieved and maintained for at least 3 mo. By determining the lowest number or dose of daily controller medications that can maintain good control, the potential for medication adverse effects is reduced. Regular follow-up is still emphasized because the variability of asthma's course is well recognized. When asthma is not well controlled, therapy should be escalated by increasing controller treatment step by 1 level and closely monitoring for clinical improvement. For a child with very poorly controlled asthma, the recommendations are to consider a short course of prednisone, or to increase therapy by 2 steps, with reevaluation in 2 wk. If step-up therapy is being considered, it is important to check inhaler technique and adherence, implement environmental control measures, and identify and treat comorbid conditions.

Referral to Asthma Specialist

Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties in achieving or maintaining good asthma control. For children <4 yr, referral is recommended if the patient requires at least Treatment Step 3 care, and should be considered if the patient requires Treatment Step 2 care. For children ≥5 yr, consultation with a specialist is recommended if the patient requires Treatment Step 4 care or higher, and should be considered if Treatment Step 3 is required. Referral is also recommended if allergen immunotherapy or biologic therapy is being considered.

Long-Term Controller Medications

All levels of persistent asthma should be treated with ICS therapy to reduce airway inflammation and improve long-term control (see Table 169.11). Other long-term controller medications include LABAs, leukotriene modifiers, cromolyn, sustained-release theophylline, and tiotropium in adolescents. Omalizumab (Xolair) and mepolizumab (Nucala) are approved by the U.S. Food and Drug Administration (FDA) for use as an add-on therapy in children ≥6 yr and ≥12 yr who have severe allergic asthma or eosinophilic asthma, respectively, that remains difficult to control. Corticosteroids are the most potent and most effective medications used to treat both the acute (administered systemically) and the chronic (administered by inhalation) manifestations of asthma. They are available in inhaled, oral, and parenteral forms (Tables 169.12 and 169.13).

Table 169.12

Usual Dosages for Long-Term Control Medications

MEDICATION	**AGE**		
	0-4 yr	**5-11 yr**	**≥12 yr**
INHALED CORTICOSTEROIDS (see Table 169.13)			
Methylprednisolone: 2, 4, 8, 16, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL, 15 mg/5 mL Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/mL, 5 mg/5 mL	0.25-2 mg/kg daily in single dose in AM or qod as needed for control Short-course “burst”: 1-2 mg/kg/day; maximum 30 mg/day for 3-10 days	0.25-2 mg/kg daily in single dose in AM or qod as needed for control Short-course “burst”: 1-2 mg/kg/day; maximum 60 mg/day for 3-10 days	7.5-60 mg daily in a single dose in AM or qod as needed for control Short-course “burst” to achieve control: 40-60 mg/day as single or 2 divided doses for 3-10 days
Fluticasone/salmeterol (Advair):	N/A		
DPI: 100, 250, or 500 µg/50 µg		1 inhalation bid; dose depends on level of severity or control (the 100/50 dosage is indicated in children ≥4 yr)	1 inhalation bid; dose depends on level of severity or control
HFA: 45 µg/21 µg, 115 µg/21 µg, 230 µg/21 µg			2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol (Symbicort): HFA: 80 µg/4.5 µg, 160 µg/4.5 µg	N/A		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol (Dulera):			2 inhalations bid; dose depends on level of severity

HFA: 100 µg/5 µg, 200 µg/5 µg			or control
Leukotriene receptor antagonists:			
Montelukast (Singulair): 4 or 5 mg chewable tablet 4 mg granule packets 10 mg tablet	4 mg qhs (1-5 yr of age)	5 mg qhs (6-14 yr)	10 mg qhs (indicated in children ≥15 yr)
Zafirlukast (Accolate): 10 or 20 mg tablet	N/A	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)
5-Lipoxygenase inhibitor: (Zileuton CR): 600 mg tablet	N/A	N/A	1,200 mg bid (give 2 tablets bid)
Immunomodulators:			
Omalizumab (anti-IgE; Xolair): SC injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection	N/A	N/A	150-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level
Mepolizumab (anti–IL-5; Nucala): SC injection, 100 mg after reconstitution with 1.2 mL sterile water for injection	N/A	N/A	100 mg SC q 4 wk

bid, 2 times daily; DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; q, every; qhs, every night; qid, 4 times daily; qod, every other day; SC, subcutaneous(ly).

Table 169.13

Estimated Comparative Inhaled Corticosteroid Doses

GLUCOCORTICOID	**LOW DAILY DOSE**	**MEDIUM DAILY DOSE**	**HIGH DAILY DOSE**
Beclomethasone (Qvar) MDI: 40 or 80 µg (Approved for children ≥5 yr)	80-160 µg	160-320 µg	>320 µg
Budesonide (Pulmicort Flexhaler) DPI: 90, 180 µg (Approved for children ≥6 yr)	200 µg	200-400 µg	>400 µg
Budesonide suspension for nebulization (Generic and Pulmicort Respules) 0.25 mg, 0.5 mg, 1 mg (Approved for children 1-8 yr)	0.5 mg	1.0 mg	2.0 mg
Ciclesonide (Alvesco) MDI: 80, 160 µg	80 µg	80-160 µg	160 µg

(Approved for children ≥12 yr)			
Flunisolide (Aerospan) MDI: 80 µg/puff (Approved for children ≥6 yr)	80 µg	80-160 µg	160 µg
Fluticasone propionate (Flovent, Flovent Diskus) MDI: 44, 110, 220 µg DPI: 50, 100, 250 µg (44 and 50 µg approved for children ≥4 yr)	88-176 µg 100-200 µg	176-440 µg 200-500 µg	>440 µg >500 µg
Fluticasone furoate (Arnuity Ellipta) DPI: 100, 200 µg (Approved for children ≥12 yr)	100 µg	100-200 µg	200 µg
Mometasone Furoate (Asmanex, Asmanex Twisthaler) MDI: 100, 200 µg DPI: 110, 220 µg (Approved for children ≥4 yr)	110 µg 100 µg	110 µg 100 µg	110 µg 100 µg

DPI, Dry powder inhaler; MDI, metered-dose inhaler.

Adapted from National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3): Guidelines for the diagnosis and management of asthma—summary report 2007, *J Allergy Clin Immunol* 120(Suppl):S94–S138, 2007.

Inhaled Corticosteroids

ICS therapy improves lung function; reduces asthma symptoms, AHR, and use of "rescue" medications; improves quality of life; and most importantly reduces the need for prednisone, urgent care visits, and hospitalizations by approximately 50%. Epidemiologic studies have also shown that ICS therapy substantially lowers the risk of death attributable to asthma if used regularly. Because ICS therapy can achieve all the goals of asthma management, it is viewed as first-line treatment for persistent asthma.

Seven ICSs are FDA approved for use in children. The NIH and GINA guidelines provide equivalence classifications (see Table 169.13), although direct comparisons of efficacy and safety outcomes are lacking. ICSs are available in metered-dose inhalers (MDIs) using hydrofluoroalkane (HFA) as their propellant, in dry powder inhalers (DPIs), or in suspension for nebulization. Fluticasone propionate, fluticasone furoate, mometasone furoate, ciclesonide, and to a lesser extent budesonide are considered "second-generation" ICSs, in that they have greater antiinflammatory potency and less *systemic* bioavailability (and thus potential for systemic adverse effects) because of their extensive first-pass hepatic metabolism. The selection of the initial ICS dose is based on the determination of disease severity.

Even though ICSs can be very effective, there has been some reluctance to treat children with ICSs due to parental and occasionally physician concerns regarding their potential for adverse effects with chronic use. The adverse effects that occur with long-term systemic corticosteroid therapy have not been seen or have only rarely been reported in children receiving ICSs in recommended doses. The risk of adverse effects from ICS therapy is related to the dose and frequency of administration (Table 169.14). High doses (≥1,000 µg/day in children) and frequent administration (4 times/day) are more likely to have both local and systemic adverse effects. Children who receive maintenance therapy with higher ICS doses are also likely to require frequent systemic corticosteroid courses for asthma exacerbations, further increasing their risk of corticosteroid adverse effects.

Table 169.14

Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 169.13)	Monitor blood pressure and weight with each physician visit. Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay. Encourage regular physical exercise. Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed. Avoid smoking and alcohol. Ensure TSH status if patient has history of thyroid abnormality.
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 169.13) At least 4 courses of OCS/yr	As above, *plus* : Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma Baseline bone densitometry (DEXA scan) Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness).
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥7 OCS burst treatments/year Very-high-dose ICS (e.g., fluticasone propionate ≥800 µg/day)	As above, *plus* : DEXA scan: if DEXA z score ≤1.0, recommend close monitoring (every 12 mo) Consider referral to a bone or endocrine specialist. Bone age assessment Complete blood count Serum calcium, phosphorus, and alkaline phosphatase determinations Urine calcium and creatinine measurements Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin Urine telopeptides for those receiving long-term systemic or frequent OCS treatment Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness).

[*] Risk factors for osteoporosis: presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, alcohol intake).

DEXA, Dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; OCS, oral corticosteroid; TSH, thyroid-stimulating hormone.

The most commonly encountered ICS adverse effects are local: oral **candidiasis** (thrush) and **dysphonia** (hoarse voice). Thrush results from propellant-induced mucosal irritation and local immunosuppression, and dysphonia is the result of vocal cord myopathy. These effects are dose dependent and are most common in individuals receiving high-dose ICS or oral corticosteroid therapy. The incidence of these local effects can be greatly minimized by using a spacer with an MDI with the ICS, because spacers reduce oropharyngeal deposition of the drug and propellant. Mouth rinsing using a "swish and spit" technique after ICS use is also recommended.

The potential for growth suppression and osteoporosis with long-term ICS use had been an unanswered concern. However, a long-term, prospective NIH-sponsored study (CAMP) followed the growth and bone mineral density (BMD) of >1,000 children (age 6-12 yr at entry) with mild to moderate asthma until they reached adulthood and found slight growth suppression and osteopenia in some children who received long-term ICS therapy. A small (1.1 cm), limited (1 year) growth suppressive effect was noted in children receiving budesonide, 200 µg twice daily, after 5 yr of therapy. Height was then followed until all children had reached adulthood (mean age 25 yr). Those who received ICS therapy remained approximately 1 cm shorter than those who received placebo. Thus, children treated with long-term ICS therapy are likely to be about 1 cm shorter than expected as an adult, which is of little clinical significance. BMD was no different in those receiving budesonide vs placebo during the duration of the study, while a follow-up study after a mean of 7 years found a slight dose-dependent effect of ICS therapy on bone mineral accretion only among males. A much greater effect on BMD was observed with increasing numbers of oral corticosteroid bursts for acute asthma, as well as an increase in risk for osteopenia, which was again limited to males. These findings were with use of low-dose budesonide; higher ICS doses, especially of agents with increased potency, have a greater potential for adverse effects. Thus, corticosteroid adverse effects screening and osteoporosis prevention measures are recommended for patients receiving higher ICS doses, since these patients are also likely to require systemic courses for exacerbations (see Table 169.14).

Systemic Corticosteroids

The development of second-generation ICSs, especially when used in combination with a LABA in a single device, have allowed the vast majority of children with asthma to achieve and maintain good control without need for maintenance oral corticosteroid (OCS) therapy. Thus, OCSs are used primarily to treat asthma exacerbations and, rarely, in children with very severe disease. In these patients, every attempt should be made to exclude comorbid conditions and to keep the OCS dose at ≤20 mg every other day. Doses exceeding this amount are associated with numerous adverse effects (see Chapter 593). To determine the need for continued OCS therapy, tapering of the OCS dose over several weeks should be attempted, with close monitoring of the patient's symptoms and lung function.

Prednisone, prednisolone, and methylprednisolone are rapidly and completely absorbed, with peak plasma concentrations occurring within 1-2 hr. Prednisone is an inactive prodrug that requires biotransformation via first-pass hepatic metabolism to prednisolone, its active form. Corticosteroids are metabolized in the liver into inactive compounds, with the rate of metabolism influenced by drug interactions and disease states. Anticonvulsants (phenytoin, phenobarbital, carbamazepine) increase the metabolism of prednisolone, methylprednisolone, and dexamethasone, with methylprednisolone most significantly affected. Rifampin also enhances the clearance of corticosteroids and can result in diminished therapeutic effect. Other medications (ketoconazole, oral contraceptives) can significantly delay corticosteroid metabolism. Some macrolide antibiotics, such as erythromycin and clarithromycin, delay the clearance of only methylprednisolone.

Long-term OCS therapy can result in a number of adverse effects over time (see Chapter 595). Some occur immediately (metabolic effects), whereas others can develop insidiously over several months to years (growth suppression, osteoporosis, cataracts). Most adverse effects occur in a cumulative dose- and duration-dependent manner. Children who require routine or frequent short courses of OCSs, especially with concurrent high-dose ICSs, should receive corticosteroid adverse effects screening (see Table 169.14) and osteoporosis preventive measures (see Chapter 726).

Long-Acting Inhaled β-Agonists

Although considered daily controller medications, *LABAs (salmeterol,* *formoterol) are not intended for use as monotherapy for persistent asthma because they can increase the risk for serious asthma exacerbations (ICU admission, endotracheal intubation) and asthma-related deaths when used without an ICS.* The likely mechanism involves the ability of LABAs to “mask” worsening asthma inflammation and asthma severity, leading to a delay in seeking urgent care and increased risk of a life-threatening exacerbation. Although both salmeterol and formoterol have a prolonged duration of effect (≥12 hr), salmeterol has a prolonged onset of effect (60 min), while formoterol's onset of effect is rapid (5-10 min) after administration. Given their long duration of action, LABAs are well suited for patients with nocturnal asthma and for individuals who require frequent use of SABA inhalations during the day to prevent exercise-induced bronchospasm (EIB), but only in combination with ICSs. Of note, the FDA requires all LABA-containing medications to be labeled with a warning of an increase in severe asthma episodes associated with these agents. In addition, the FDA recommends that once a patient is well controlled on combination ICS/LABA therapy, the LABA component should be discontinued while continuing treatment with the ICS.

Combination ICS/LABA Therapy

Combination ICS/LABA therapy is recommended for patients who are suboptimally controlled with ICS therapy alone and those with moderate or severe persistent asthma. In those inadequately controlled with ICS alone, combination ICS/LABA therapy is superior to add-on therapy with either an LTRA or theophylline or doubling the ICS dose. Benefits include improvement in baseline lung function, less need for rescue SABA therapy, improved quality of life, and fewer asthma exacerbations. A large study by the NIH-sponsored CARE Network found that in children inadequately controlled with low-dose ICS therapy, combination low-dose fluticasone/salmeterol (100 µg/21 µg) twice daily was almost twice as effective as other step-up regimens, including fluticasone (250 µg) twice daily or low-dose fluticasone (100 µg twice daily) plus montelukast once daily, with the greatest improvement in reducing exacerbations requiring prednisone and study withdrawals due to poorly controlled asthma. In addition, combination fluticasone/salmeterol was as effective as medium-dose fluticasone and was superior to combination fluticasone/montelukast therapy in black children, arguing against the notion that black children are more prone to serious asthma exacerbations than white children when treated with combination ICS/LABA therapy.

Despite their efficacy and widespread use, the long-term safety of LABAs, even when used in combination with ICS in a single inhaler, has been questioned. To address this concern of rare, severe asthma-related events with LABA/ICS use, large randomized controlled trials (RCTs) compared the safety of combination ICS/LABA vs ICS monotherapy. Two studies of >23,000 adults and adolescents ≥12 yr old with various levels of asthma severity were randomized to receive ICS (low or medium dose) monotherapy vs equivalent ICS/LABA (fluticasone vs fluticasone/salmeterol; budesonide vs budesonide/formoterol) over 26 weeks to determine if small but significant differences might occur in asthma hospitalization, intubation, or death attributable to ICS/LABA. No intubations or asthma deaths occurred during the study, and no differences in asthma hospitalizations between treatment groups were observed. The similar pediatric study enrolled >6,000 children age 4-11 yr with various levels of asthma severity to receive either fluticasone (low or medium dose) or equivalent fluticasone/salmeterol dose over 26 weeks, with similar findings of no significant differences in severe asthma-related events between treatment groups. *These results strongly suggest that the use of combination ICS/LABA products in children and adults with moderate to severe persistent asthma is both effective and safe.*

Leukotriene-Modifying Agents

Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, and airways edema. Two classes of leukotriene modifiers have been developed: inhibitors of leukotriene synthesis and leukotriene receptor antagonists (LTRAs). Zileuton, the only synthesis inhibitor, is not approved for use in children <12 yr. Because zileuton can result in elevated liver function enzyme values in 2–4% of patients, and interacts with medications metabolized via the cytochrome P450 system, it is rarely prescribed for children with asthma.

LTRAs have bronchodilator and targeted antiinflammatory properties and reduce exercise-, aspirin-, and allergen-induced bronchoconstriction. LTRAs are recommended as an alternative treatment for mild persistent asthma and as an add-on medication with ICS for moderate persistent asthma. Two LTRAs with FDA-approved use in children are montelukast and zafirlukast. Both medications improve asthma symptoms, decrease the need for rescue β-agonist use, and modestly improve lung function. **Montelukast** is approved for use in children ≥1 yr of age and is administered once daily, whereas **zafirlukast** is approved in children ≥5 yr and is given twice daily. LTRAs are less effective than ICSs in patients with mild persistent asthma (e.g., ICSs improve baseline lung function 5–15%, whereas LTRAs improve lung function 2.5–7.5%). LTRAs have few, if any, significant adverse effects, although case reports have described mood changes and suicidality in adolescents soon after instituting montelukast. When initially prescribing montelukast, a precaution is to inform the child and family that, if mood changes are noted after starting montelukast, they should discontinue its use and contact their physician.

Nonsteroidal Antiinflammatory Agents

Cromolyn and **nedocromil** are considered nonsteroidal antiinflammatory drugs (NSAIDs), although they have little efficacy as a long-term controller for asthma. They can block EIB and bronchospasm caused by allergen challenge. Although both drugs are considered alternative controller agents for children with mild persistent asthma, *the 2016 GINA guidelines no longer recommend cromolyn or nedocromil*. Because they inhibit EIB and allergen-triggered responses, cromolyn (nedocromil is no longer available in the United States) can be used as an alternative or add-on to SABAs for these specific circumstances.

Theophylline is a phosphodiesterase inhibitor with bronchodilator and antiinflammatory effects that can reduce asthma symptoms and rescue SABA use. Although the National Heart, Lung, and Blood Institute (NHLBI) guidelines continue to include theophylline as an add-on agent to ICS in school-age children at Treatment Step 3 and beyond, it is rarely used in children today because of its potential toxicity. Theophylline has a narrow therapeutic window, with overdosage associated with headaches, vomiting, cardiac arrhythmias, seizures, and death. Therefore, when used, serum theophylline levels need to be carefully and routinely monitored, especially if the patient has a viral illness associated with a fever or is concomitantly taking a medication known to delay theophylline clearance. As a result, *the 2016 GINA guidelines no longer recommend theophylline* at any level of asthma severity or control.

Long-Acting Inhaled Anticholinergics

Tiotropium is a long-acting anticholinergic agent (24-hr duration of action) that is FDA approved for use in children with asthma ≥12 yr old. Studies in adults and adolescents have found tiotropium to be equivalent to a LABA when used in combination with an ICS. It has also been found to reduce exacerbations and improve lung function in patients with inadequately controlled asthma despite treatment with combination ICS/LABA products.

Allergen Immunotherapy

Allergen immunotherapy (**AIT**) involves administering gradually increasing doses of allergens to a person with allergic disease to reduce or eliminate the patient's allergic response to those allergens, including allergic rhinoconjunctivitis and asthma. When properly administered to an appropriate candidate, AIT is a safe, effective therapy capable not only of reducing or preventing symptoms, but also of potentially altering the natural history of the disease by minimizing disease duration and preventing disease progression. Conventional AIT is given subcutaneously (subcutaneous immunotherapy, **SCIT**) under the direction of an experienced allergist. Sublingual immunotherapy (**SLIT**) is less potent but can still be effective, and has less potential for severe allergic adverse reactions.

The goal of SCIT or SLIT is to increase the dose of allergen extract administered in order to reach a therapeutic maintenance dose of each major allergen, in a manner that minimizes the likelihood of systemic allergic reactions. For SCIT, allergen extracts are formulated for each patient based on documented allergen sensitizations and problematic exposures. Maintenance doses are generally given monthly for SCIT or daily for SLIT, to complete a 3-5 yr course. Most of the controlled trials examining AIT efficacy on seasonal or perennial allergic asthma are favorable. A meta-analysis of 20 trials examining the effects of SCIT on allergic asthma revealed significant improvement with fewer symptoms, improved lung function, less need for medication, and AHR reduction.

Although AIT is regarded as safe, the potential for **anaphylaxis** always exists when patients receive extracts containing allergens to which they are sensitized. Local transient allergic reactions are common (SCIT: injection site allergic reaction; SLIT: mild oral itching). Systemic allergic reactions have been very rarely reported with SLIT, such that it is typically administered at home. In comparison, systemic allergic reactions occur more often with SCIT, with fatal anaphylaxis occurring in approximately 1 per 2 million injections. Because of the risks of systemic allergic reactions to SCIT, standard precautions include administering SCIT in medical settings where a physician with access to emergency equipment and medications required for the treatment of anaphylaxis is available (see Chapter 174). Patients should be observed in the office for 30 min after each injection because most systemic reactions to SCIT begin within this time frame. *SCIT should never be given at home or by untrained personnel.* Because of the complexities and risks of administration, SCIT should only be administered by an experienced allergist.

AIT should be discontinued in patients who have not shown improvement after 1 yr of receiving maintenance doses of an appropriate allergen extract(s), or who have a serious systemic allergic or adverse reaction.

Biologic Therapies

Biologic therapies are genetically engineered proteins derived from human genes and designed to inhibit specific immune mediators of disease. Several are FDA approved as add-on controller therapies (i.e., in addition to conventional controller therapies) for severe asthma in adults and children.

Omalizumab (Anti-IgE Antibody).

Omalizumab is a humanized monoclonal antibody (mAb) that binds IgE and prevents its binding to the high-affinity IgE receptor, thereby blocking IgE-mediated allergic responses and inflammation. It is FDA approved for patients >6 yr old with severe allergic asthma who continue to have inadequate disease control despite treatment with high-dose ICS and/or OCS. Omalizumab is given every 2-4 wk subcutaneously, with the dosage based on body weight and serum IgE levels. Omalizumab can improve asthma control while allowing ICS and/or OCS dose reduction. Omalizumab has been studied in inner-city children with exacerbation-prone asthma. When added to guideline-based controller management, omalizumab reduced exacerbations (50%) that peak in the spring and fall seasons. A follow-up prospective preseasonal treatment study confirmed the effect on fall seasonal exacerbations and demonstrated how omalizumab restores antiviral (IFN-α) immune responses to rhinovirus (the most common infectious trigger of exacerbations) that are impaired by IgE-mediated mechanisms. Omalizumab is well tolerated, although local injection site reactions can occur. Hypersensitivity reactions (including anaphylaxis) have been reported following approximately 0.1% of injections. As a result, omalizumab has an FDA black box warning of potentially serious and life-threatening anaphylactic adverse reactions.

Mepolizumab (Anti–IL-5 Antibody).

Mepolizumab, an anti–IL-5 antibody that blocks IL-5-mediated eosinophilopoiesis, reduces severe asthma exacerbations and lowers sputum and blood eosinophils while allowing for a significant reduction in OCS dose in adults with severe exacerbation-prone eosinophilic asthma. It is administered subcutaneously every 4 wk and is FDA approved for severe eosinophilic asthmatic children ≥12 yr old. **Reslizumab** , another anti–IL-5 antibody therapeutic, is administered intravenously and is FDA approved for severe asthmatics ≥18 yr old (i.e., not currently approved for use in children).

Dupilumab (Anti–IL-4 Receptor α Antibody).

Dupilumab, an anti–IL-4 receptor antibody that inhibits both IL-4 and IL-13 production (both cytokines share the same IL-4 receptor) and atopic immune responses, reduces exacerbations and symptoms and improves lung function in moderate to severe asthmatic patients with persistent eosinophilia. Although not yet FDA approved, studies are ongoing in both children and adults.

Quick-Reliever Medications

Quick-reliever or “rescue” medications (SABAs, inhaled anticholinergics, and short-course systemic corticosteroids) are used in the management of acute asthma symptoms (Table 169.15).

Table 169.15

Management of Asthma Exacerbation (Status Asthmaticus)

RISK ASSESSMENT ON ADMISSION		
Focused history	Onset of current exacerbation Frequency and severity of daytime and nighttime symptoms and activity limitation Frequency of rescue bronchodilator use Current medications and allergies Potential triggers History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes	
Clinical assessment	Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status Pulse oximetry Lung function (defer in patients with moderate to severe distress or history of labile disease)	
Risk factors for asthma morbidity and death	See Table 169.16 .	
TREATMENT		
Drug and Trade Name	**Mechanisms of Action and Dosing**	**Cautions and Adverse Effects**

Oxygen (mask or nasal cannula)	Treats hypoxia	Monitor pulse oximetry to maintain O_2 saturation >92% Cardiorespiratory monitoring
Inhaled short-acting β-agonists:	Bronchodilator	During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, V̇/Q̇ mismatch, and hypoxemia. Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume.
Albuterol MDI (90 µg/puff)	2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed	For MDI: use spacer/holding chamber
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects.
Systemic corticosteroids:	Antiinflammatory	If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis. For daily dosing, 8 AM administration minimizes adrenal suppression. Children may benefit from dosage tapering if course exceeds 7 days. Adverse effects monitoring: frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 595); see Table 169.14 for adverse effects screening recommendations.
Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution	0.5-1 mg/kg every 6-12 hr for 48 hr, then 1-2 mg/kg/day bid (maximum 60 mg/day)	
Depo-Medrol (IM);	Short-course “burst” for exacerbation: 1-2	

Solu-Medrol (IV)	mg/kg/day qd or bid for 3-7 days	
Dexamethasone	See text	See text
Anticholinergics:	Mucolytic/bronchodilator	Should not be used as first-line therapy; added to β_2 -agonist therapy
Ipratropium:		
Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 µg/inhalation)	Nebulizer: 0.5 mg q6-8h (tid-qid) as needed MDI: 2 puffs qid	
Ipratropium with albuterol:		
DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	1 vial by nebulizer qid	Nebulizer: may mix ipratropium with albuterol
Injectable sympathomimetic epinephrine:	Bronchodilator	For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)
Adrenalin 1 mg/mL (1 : 1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	SC or IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min	
Terbutaline:		Terbutaline is β-agonist–selective relative to epinephrine. Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia
Brethine 1 mg/mL	Continuous IV infusion (terbutaline only): 2-10 µg/kg loading dose, followed by 0.1-0.4 µg/kg/min Titrate in 0.1-0.2 µg/kg/min increments every 30 min, depending on clinical response.	
RISK ASSESSMENT FOR DISCHARGE		
Medical stability	Discharge home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air.	
Home supervision	Capability to administer intervention and to observe and respond appropriately to clinical deterioration	
Asthma education	See Table 169.8 .	

IM, Intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist; SC, subcutaneous; V/Q̇, ventilation/perfusion; bid, 2 times daily; tid, 3 times daily; qid; 4 times daily; qd, every day.

Short-Acting Inhaled β-Agonists

Given their rapid onset of action, effectiveness, and 4-6 hr duration of action, SABAs (albuterol, levalbuterol, terbutaline, pirbuterol) are the drugs of choice for acute asthma symptoms (“rescue” medication) and for preventing EIB. β-Adrenergic agonists cause bronchodilation by inducing airway smooth muscle relaxation, reducing vascular permeability and airways edema, and improving mucociliary clearance. Levalbuterol, the R-isomer of albuterol, is associated with less tachycardia and tremor, which can be bothersome to some asthmatic patients. Overuse of β-agonists is associated with an increased risk of death or near-death episodes from asthma. This is a major concern for some patients with asthma who rely on the frequent use of SABAs as a “quick fix” for their asthma, rather than using controller medications in a preventive manner. It is helpful to monitor the frequency of SABA use, in that use of at least 1 MDI/mo or at least 3 MDIs/year (200 inhalations/MDI) indicates inadequate asthma control and necessitates improving other aspects of asthma therapy and management.

Anticholinergic Agents

As bronchodilators, the anticholinergic agents (e.g., ipratropium bromide) are less potent than the β-agonists. Inhaled ipratropium is used primarily in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium can improve lung function and reduce the rate of hospitalization in children who present to the ED with acute asthma. Ipratropium has few central nervous system adverse effects and is available in both MDI and nebulizer formulations. Although widely used in all children with asthma exacerbations, it is FDA approved for use in children >12 yr old. A combination ipratropium/albuterol product is also available in both nebulized (generic and Duoneb) and mist formulations (Combivent Respimat).

Delivery Devices and Inhalation Technique

Inhaled medications are delivered in aerosolized form in a MDI, as a DPI formulation, or in a suspension form delivered via a nebulizer. **Spacer devices** , recommended for the administration of all MDI medications, are simple and inexpensive tools that (1) decrease the coordination required to use MDIs, especially in young children; (2) improve the delivery of inhaled drug to the lower airways; and (3) minimize the risk of drug and propellant-mediated oropharyngeal adverse effects (dysphonia and thrush). Optimal inhalation technique for each puff of MDI-delivered medication is a slow (5 sec) inhalation, then a 5-10 sec breathhold. No waiting time is required between puffs of medication. Preschool-age children cannot perform this inhalation technique. As a result, MDI medications in this age-group are delivered with a spacer and mask, using a different technique: Each puff is administered with regular breathing for about 30 sec or 5-10 breaths; a tight seal must be maintained; and talking, coughing, or crying will blow the medication out of the spacer. This technique will not deliver as much medication per puff as the optimal MDI technique used by older children and adults.

Dry powder inhaler devices (e.g., Diskus, Flexhaler, Autohaler, Twisthaler, Aerolizer, Ellipta) are popular because of their simplicity of use, although adequate inspiratory flow is needed. DPIs are breath-actuated devices (the drug comes out only as it is breathed in), and spacers are not needed. Mouth rinsing is recommended after ICS use to remove ICS deposited on the oral mucosa and reduce the swallowed ICS and the risk of thrush.

Nebulizers are the mainstay of aerosol treatment for infants and young children. An advantage of using nebulizers is the simple technique required of relaxed breathing. The preferential nasal breathing, small airways, low tidal volume, and high respiratory rate of infants greatly increase the difficulty of inhaled drug therapy targeting the lung airways. Disadvantages of nebulizers include need for a power source, inconvenience in that treatments take about 5 min, expense, and potential for bacterial contamination.

Asthma Exacerbations and Their Management

Asthma exacerbations are acute or subacute episodes of progressively worsening symptoms and airflow obstruction. Airflow obstruction during exacerbations can become extensive, resulting in life-threatening respiratory insufficiency. Often, asthma exacerbations worsen during sleep (between midnight and 8 AM), when airways inflammation and hyperresponsiveness are at their peak. Importantly, SABAs, which are first-line therapy for asthma symptoms and exacerbations, increase pulmonary blood flow through obstructed, unoxygenated areas of the lungs with increasing dosage and frequency. When airways obstruction is not resolved with SABA use, ventilation/perfusion mismatching can cause hypoxemia, which can perpetuate bronchoconstriction and further worsen the condition. Severe, progressive asthma exacerbations need to be managed in a medical setting, with administration of supplemental oxygen as first-line therapy and close monitoring for potential worsening. Complications that can occur during severe exacerbations include atelectasis (common) and air leaks in the chest (pneumomediastinum, pneumothorax; rare).

A severe exacerbation of asthma that does not improve with standard therapy is termed **status asthmaticus** . Immediate management of an asthma exacerbation involves a rapid evaluation of the severity of obstruction and assessment of risk for further clinical deterioration (Fig. 169.8 ; see Tables 169.14 and 169.15). For most patients, exacerbations improve with frequent bronchodilator treatments and a course of systemic (oral or intravenous) corticosteroid. However, the optimal management of a child with an asthma exacerbation should include a more comprehensive assessment of the events leading up to the exacerbation and the underlying disease severity. Indeed, the frequency and severity of asthma exacerbations help define the severity of a patient's asthma. Whereas most children who experience life-threatening asthma episodes have moderate to severe asthma by other criteria, some children with asthma appear to have mild disease except when they have severe, even near-fatal exacerbations. The biologic, environmental, economic, and psychosocial risk factors associated with asthma morbidity and death can further guide this assessment (Table 169.16).

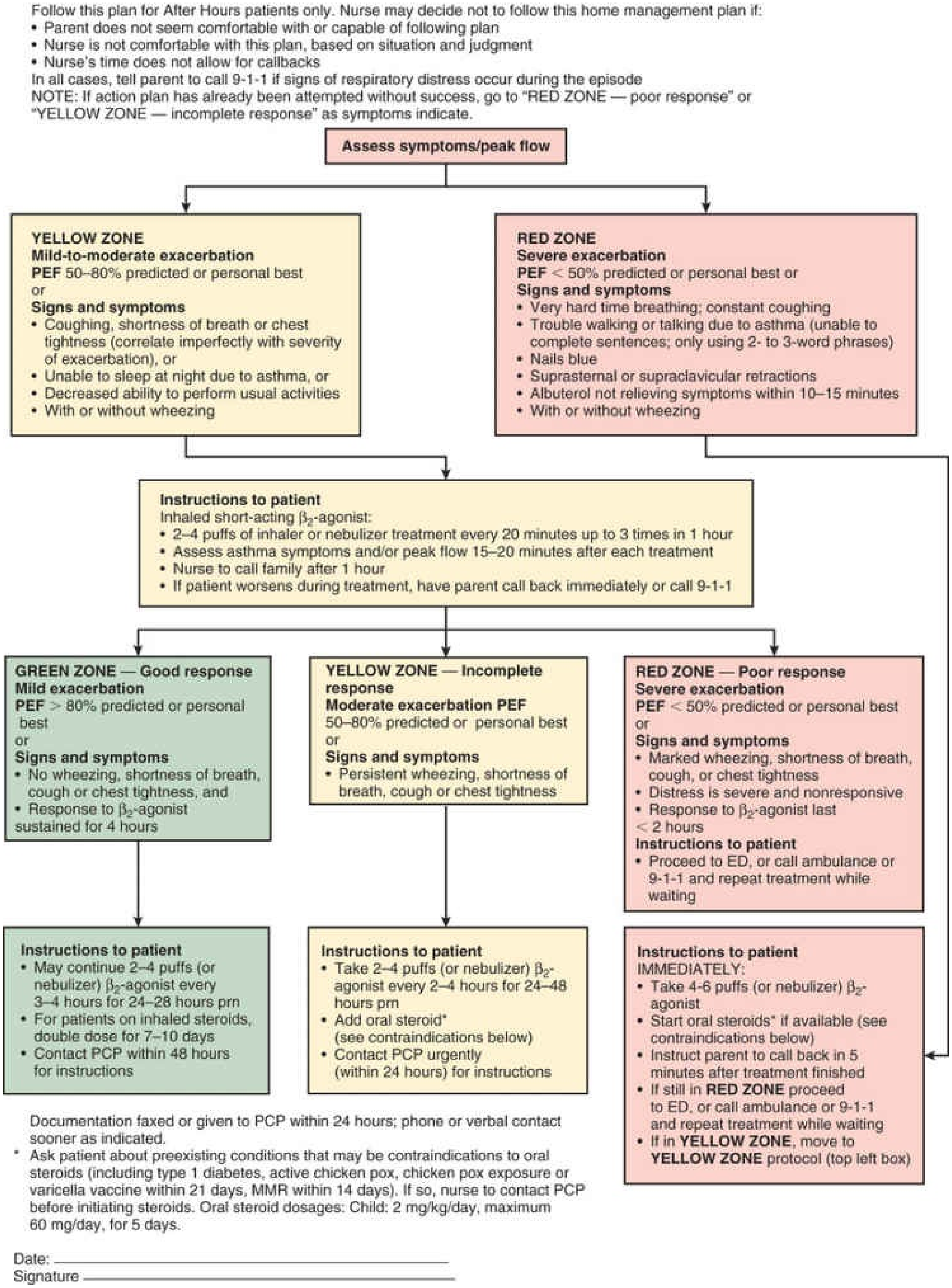

Follow this plan for After Hours patients only. Nurse may decide not to follow this home management plan if:
- Parent does not seem comfortable with or capable of following plan
- Nurse is not comfortable with this plan, based on situation and judgment
- Nurse's time does not allow for callbacks

In all cases, tell parent to call 9-1-1 if signs of respiratory distress occur during the episode
NOTE: If action plan has already been attempted without success, go to "RED ZONE — poor response" or "YELLOW ZONE — incomplete response" as symptoms indicate.

Assess symptoms/peak flow

YELLOW ZONE
Mild-to-moderate exacerbation
PEF 50–80% predicted or personal best
or
Signs and symptoms
- Coughing, shortness of breath or chest tightness (correlate imperfectly with severity of exacerbation), or
- Unable to sleep at night due to asthma, or
- Decreased ability to perform usual activities
- With or without wheezing

RED ZONE
Severe exacerbation
PEF < 50% predicted or personal best or
Signs and symptoms
- Very hard time breathing; constant coughing
- Trouble walking or talking due to asthma (unable to complete sentences; only using 2- to 3-word phrases)
- Nails blue
- Suprasternal or supraclavicular retractions
- Albuterol not relieving symptoms within 10–15 minutes
- With or without wheezing

Instructions to patient
Inhaled short-acting β_2-agonist:
- 2–4 puffs of inhaler or nebulizer treatment every 20 minutes up to 3 times in 1 hour
- Assess asthma symptoms and/or peak flow 15–20 minutes after each treatment
- Nurse to call family after 1 hour
- If patient worsens during treatment, have parent call back immediately or call 9-1-1

GREEN ZONE — Good response
Mild exacerbation
PEF > 80% predicted or personal best
or
Signs and symptoms
- No wheezing, shortness of breath, cough or chest tightness, and
- Response to β_2-agonist sustained for 4 hours

YELLOW ZONE — Incomplete response
Moderate exacerbation PEF
50–80% predicted or personal best
or
Signs and symptoms
- Persistent wheezing, shortness of breath, cough or chest tightness

RED ZONE — Poor response
Severe exacerbation
PEF < 50% predicted or personal best
or
Signs and symptoms
- Marked wheezing, shortness of breath, cough, or chest tightness
- Distress is severe and nonresponsive
- Response to β_2-agonist last < 2 hours

Instructions to patient
- Proceed to ED, or call ambulance or 9-1-1 and repeat treatment while waiting

Instructions to patient
- May continue 2–4 puffs (or nebulizer) β_2-agonist every 3–4 hours for 24–28 hours prn
- For patients on inhaled steroids, double dose for 7–10 days
- Contact PCP within 48 hours for instructions

Instructions to patient
- Take 2–4 puffs (or nebulizer) β_2-agonist every 2–4 hours for 24–48 hours prn
- Add oral steroid*
(see contraindications below)
- Contact PCP urgently
(within 24 hours) for instructions

Instructions to patient
IMMEDIATELY:
- Take 4-6 puffs (or nebulizer) β_2-agonist
- Start oral steroids* if available (see contraindications below)
- Instruct parent to call back in 5 minutes after treatment finished
- If still in **RED ZONE** proceed to ED, or call ambulance or 9-1-1 and repeat treatment while waiting
- If in **YELLOW ZONE**, move to **YELLOW ZONE** protocol (top left box)

Documentation faxed or given to PCP within 24 hours; phone or verbal contact sooner as indicated.

* Ask patient about preexisting conditions that may be contraindications to oral steroids (including type 1 diabetes, active chicken pox, chicken pox exposure or varicella vaccine within 21 days, MMR within 14 days). If so, nurse to contact PCP before initiating steroids. Oral steroid dosages: Child: 2 mg/kg/day, maximum 60 mg/day, for 5 days.

Date: ____________________
Signature ____________________

FIG. 169.8 Algorithm for treatment of acute asthma symptoms. PEF, Peak expiratory flow; ED, emergency department; PCP, primary care physician.

(Courtesy of BJC Healthcare/Washington University School of Medicine, Community Asthma Program, January 2000.)

Table 169.16

Risk Factors for Asthma Morbidity and Mortality

Biologic

Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)
Sudden asphyxia episodes (respiratory failure, arrest)
Two or more hospitalizations for asthma in past year
Three or more emergency department visits for asthma in past year
Increasing and large diurnal variation in peak flows
Use of >2 canisters of short-acting β-agonists per month
Poor response to systemic corticosteroid therapy
Male gender
Low birthweight
Nonwhite (especially black) ethnicity
Sensitivity to *Alternaria*

Environmental

Allergen exposure
Environmental tobacco smoke exposure
Air pollution exposure
Urban environment

Economic and Psychosocial

Poverty
Crowding
Mother <20 yr old
Mother with less than high school education
Inadequate medical care:

    - Inaccessible
    - Unaffordable
    - No regular medical care (only emergency)
    - Lack of written Asthma Action Plan
    - No care sought for chronic asthma symptoms
    - Delay in care of asthma exacerbations
    - Inadequate hospital care for asthma exacerbation
- Psychopathology in the parent or child
- Poor perception of asthma symptoms or severity
- Alcohol or substance abuse

Asthma exacerbations characteristically vary among individuals but tend to be similar in the same patient. Severe asthma exacerbations, resulting in respiratory distress, hypoxia, hospitalization, and respiratory failure, are the best predictors of future life-threatening exacerbations or a fatal asthma episode. In addition to distinguishing such high-risk children, some experience exacerbations that develop over days, with airflow obstruction resulting from progressive inflammation, epithelial sloughing, and cast impaction of small airways. When such a process is extreme, respiratory failure as a result of fatigue can ensue, necessitating mechanical ventilation for numerous days. In contrast, some children experience abrupt-onset exacerbations that may result from extreme AHR and physiologic susceptibility to airways closure. Such exacerbations, when extreme, are asphyxial in nature, often occur outside medical settings, are initially associated with very high arterial partial pressure of carbon dioxide (P_{CO_2}) levels, and tend to require only brief periods of supportive ventilation. Recognizing the characteristic differences in asthma exacerbations is important for optimizing their early management.

Home Management of Asthma Exacerbations

Families of all children with asthma should have a **written Asthma Action Plan** (see Fig. 169.7) to guide their recognition and management of exacerbations, along with the necessary medications and tools to manage them. Early recognition of asthma exacerbations in order to intensify treatment early can often prevent further worsening and keep exacerbations from becoming severe. A written home action plan can reduce the risk of asthma death by 70%. The NIH guidelines recommend immediate treatment with “rescue” medication (inhaled SABA, up to 3 treatments in 1 hr). A good response is characterized by resolution of symptoms within 1 hr, no further symptoms over the next 4 hr, and improvement in PEF value to at least 80% of personal best. The child's physician should be contacted for follow-up, especially if bronchodilators are required repeatedly over the next 24-48 hr. If the child has an incomplete response to initial treatment with rescue medication (persistent symptoms and/or PEF <80% of personal best), a short course of OCS therapy (prednisone, 1-2 mg/kg/day [not to exceed 60 mg/day] for 4 days) should be instituted, in addition to inhaled β-agonist therapy. The physician should also be contacted for further instructions. Immediate medical attention should be sought for severe exacerbations, persistent signs of respiratory distress, lack of expected response or sustained improvement after initial treatment, further deterioration, or high-risk factors for asthma morbidity or mortality (e.g., previous history of severe exacerbations). For patients with severe asthma and/or a history of life-threatening episodes, especially if abrupt in onset, an epinephrine autoinjector and perhaps portable oxygen at home can be considered. Use of either of these extreme measures for home management of asthma exacerbations would be an indication to call 911 for emergency support services.

Emergency Department Management of Asthma Exacerbations

In the ED, the primary goals of asthma management include correction of hypoxemia, rapid improvement of airflow obstruction, and prevention of progression or recurrence of symptoms. Interventions are based on clinical severity on arrival, response to initial therapy, and presence of risk factors associated with asthma morbidity and mortality (see Table 169.16). Indications of a severe exacerbation include breathlessness, dyspnea, retractions, accessory muscle use, tachypnea or labored breathing, cyanosis, mental status changes, a silent chest with poor air exchange, and severe airflow limitation (PEF or FEV_1 value <50% of personal best or predicted values). Initial treatment includes supplemental oxygen, inhaled β-agonist therapy every 20 min for 1 hr, and, if necessary, oral or intravenous (IV) systemic corticosteroids (see Table 169.15 and Fig. 169.8). In the ED, single oral, intravenous, or intramuscular (IM) dose dexamethasone (0.6 mg/kg, maximum 16 mg) has been found to be an effective alternative to prednisone and with a lower incidence of emesis. In addition, a second dose of dexamethasone should be given the next day whether discharged or admitted to the hospital. Inhaled ipratropium may be added to the β-agonist treatment if no significant response is seen with the 1st inhaled β-agonist treatment. An IM injection of epinephrine or other β-agonist may be administered in severe cases. Oxygen should be administered and continued for at least 20 min after SABA administration to compensate for possible ventilation/perfusion abnormalities caused by SABAs.

Close monitoring of clinical status, hydration, and oxygenation are essential elements of immediate management. A poor response to intensified treatment in the 1st hr suggests that the exacerbation will not remit quickly. The patient may be discharged home if there is sustained improvement in symptoms, normal physical findings, PEF >70% of predicted or personal best, and oxygen saturation >92% while the patient is breathing room air for 4 hr. Discharge medications include administration of an inhaled β-agonist up to every 3-4 hr plus a 3-7 day course of an OCS. Optimizing controller therapy before discharge is also recommended. The addition of ICS to a course of OCS in the ED setting reduces the risk of exacerbation recurrence over the subsequent month.

Hospital Management of Asthma Exacerbations

For patients with severe exacerbations that do not adequately improve within 1-2 hr of intensive treatment, observation and/or admission to the hospital, at least overnight, is likely to be needed. Other indications for hospital admission include high-risk features for asthma morbidity or death (see Table 169.16). Admission to an intensive care unit (ICU) is indicated for patients with severe respiratory distress, poor response to therapy, and concern for potential respiratory failure and arrest.

Supplemental oxygen, frequent or continuous administration of an inhaled bronchodilator, and systemic corticosteroid therapy are the conventional interventions for children admitted to the hospital for status asthmaticus (see Table 169.15). Supplemental oxygen is administered because many children hospitalized with acute asthma have or eventually have hypoxemia, especially at night and with increasing SABA administration. SABAs can be delivered frequently (every 20 min to 1 hr) or continuously (at 5-15 mg/hr). When administered continuously, significant systemic absorption of β-agonist occurs, and thus continuous nebulization can obviate the need for IV β-agonist therapy. Adverse effects of frequently administered β-agonist therapy include tremor, irritability, tachycardia, and hypokalemia; lactic acidosis is an uncommon complication. Patients requiring frequent or continuous nebulized β-agonist therapy should have ongoing cardiac monitoring. Because frequent β-agonist therapy can cause ventilation/perfusion mismatch and hypoxemia, oximetry is also indicated. Inhaled ipratropium is often added to albuterol every 6 hr if patients do not show a remarkable improvement, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled β-agonist therapy and systemic corticosteroids. In addition to its potential to provide a synergistic effect with a β-agonist agent in relieving severe bronchospasm, ipratropium may be beneficial in patients who have mucus hypersecretion or who are receiving β-blockers.

Short-course systemic corticosteroid therapy is recommended for use in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms. Corticosteroids are effective as single doses administered in the ED, short courses in the clinic setting, and both oral and IV formulations in hospitalized children. Studies in children hospitalized with acute asthma have found corticosteroids administered orally to be as effective as IV corticosteroids. Accordingly, OCS therapy can often be used, although children with sustained respiratory distress and those unable to tolerate oral preparations or liquids are obvious candidates for IV corticosteroid therapy.

Patients with persistent severe dyspnea and high-flow oxygen requirements require additional evaluation, such as complete blood count, arterial blood gases, serum electrolytes, and chest radiograph, to monitor for respiratory insufficiency, comorbidities, infection, and dehydration. Hydration status monitoring is especially important in infants and young children, whose increased respiratory rate (insensible losses) and decreased oral intake put them at higher risk for dehydration. Further complicating this situation is the association of increased antidiuretic hormone secretion with status asthmaticus. Administration of fluids at or slightly below maintenance fluid requirements is recommended. Chest physical therapy, incentive spirometry, and mucolytics are not recommended during the early acute period of asthma exacerbations because they can trigger severe bronchoconstriction.

Despite intensive therapy, some asthmatic children remain critically ill and at risk for respiratory failure, intubation, and mechanical ventilation. Complications (e.g., air leaks) related to asthma exacerbations increase with intubation and assisted ventilation, so every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including parenteral β-agonists, magnesium sulfate (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 min), and inhaled heliox (helium and oxygen mixture) have demonstrated some benefit as adjunctive therapies in patients with severe status asthmaticus. Administration of magnesium sulfate requires monitoring of serum levels and cardiovascular status. Parenteral (SC, IM, or IV) epinephrine or terbutaline sulfate may be effective in patients with life-threatening obstruction that is not responding to high doses of inhaled β-agonists, because inhaled medication may not reach the lower airway in such patients.

Rarely, a severe asthma exacerbation in a child results in respiratory failure, and intubation and mechanical ventilation become necessary. **Mechanical ventilation** in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction while reducing hyperinflation, air trapping, and the likelihood of barotrauma (pneumothorax, pneumomediastinum) (see Chapter 439). To minimize the likelihood of such complications, mechanical ventilation should be anticipated, and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric ICU. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to moderate hypercapnia (P_{CO_2} 50-70 mm Hg) to minimize barotrauma. Volume-cycled ventilators, using short inspiratory and long expiratory times, 10-15 mL/kg tidal volume, 8-15 breaths/min, peak pressures <60 cm H_2O, and without positive end-expiratory pressure are starting mechanical ventilation parameters that can achieve these goals. As measures to relieve mucus plugs, chest percussion and airways lavage are not recommended because they can induce further bronchospasm. One must consider the nature of asthma exacerbations leading to respiratory failure; those of rapid or abrupt onset tend to resolve quickly (hours to 2 days), whereas those that progress gradually to respiratory failure can require days to weeks of mechanical ventilation. Such prolonged cases are further complicated by corticosteroid-induced myopathy, which can lead to severe muscle weakness requiring prolonged rehabilitation.

In children, management of severe exacerbations in medical centers is usually successful, even when extreme measures are required. Consequently, asthma deaths in children rarely occur in medical centers; most occur at home or in community settings before lifesaving medical care can be administered. This point highlights the importance of home and community management of asthma exacerbations, early intervention measures to keep exacerbations from becoming severe, and steps to reduce asthma severity. A follow-up appointment within 1-2 wk of a child's discharge from the hospital after resolution of an asthma exacerbation should be used to monitor clinical improvement and to reinforce key educational elements, including action plans and controller medications.

Special Management Circumstances

Management of Infants and Young Children

Recurrent wheezing episodes in preschool-age children are common, occurring in as much as one third of this population. Of these, most improve and even become asymptomatic during the prepubescent school-age years, whereas others have lifelong persistent asthma. All require management of their recurrent wheezing problems (see Tables 169.5 , 169.6 , and 169.11). The NIH guidelines recommend risk assessment to identify preschool-age children who are likely to have persistent asthma. One implication of this recommendation is that these at-risk children may be candidates for conventional asthma management, including daily controller therapy and early intervention with exacerbations (see Tables 169.7 , 169.8 , and 169.11). For young children with a history of moderate to severe exacerbations, nebulized budesonide is FDA approved, and its use as a controller medication could prevent subsequent exacerbations.

Using aerosol therapy in infants and young children with asthma presents unique challenges. There are 2 delivery systems for inhaled medications for this age-group: the nebulizer and the MDI with spacer/holding chamber and face mask. Multiple studies demonstrate the effectiveness of both nebulized albuterol in acute episodes and nebulized budesonide in the treatment of recurrent wheezing in infants and young children. In such young children, inhaled medications administered via MDI with spacer and face mask may be acceptable, although perhaps not preferred because of limited published information and lack of FDA approval for children <4 yr of age.

Asthma Management During Surgery

Patients with asthma are at risk from disease-related complications from surgery, such as bronchoconstriction and asthma exacerbation, atelectasis, impaired coughing, respiratory infection, and latex exposure, which may induce asthma complications in patients with latex allergy. All patients with asthma should be evaluated before surgery, and those who are inadequately controlled should allow time for intensified treatment to improve asthma stability before surgery, if possible. A systemic corticosteroid course may be indicated for the patient who is having symptoms and/or FEV_1 or PEF values <80% of the patient's personal best. In addition, patients who have received >2 wk of systemic corticosteroid and/or moderate- to high-dose ICS therapy may be at risk for intraoperative adrenal insufficiency. For these patients, anesthesia services should be alerted to provide “stress” replacement doses of systemic corticosteroid for the surgical procedure and possibly the postoperative period.

Prognosis

Recurrent coughing and wheezing occurs in 35% of preschool-age children. Of these, approximately one third continue to have persistent asthma into later childhood, and approximately two thirds improve on their own through their teen years. Asthma severity by ages 7-10 yr is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years); however, complete remission for 5 yr in childhood is uncommon.

Prevention

Although chronic airways inflammation may result in pathologic remodeling of lung airways, conventional antiinflammatory interventions—the cornerstone of asthma control—do not help children outgrow their asthma. Although controller medications reduce asthma morbidities, most children with moderate to severe asthma continue to have symptoms into young adulthood. Investigations into the environmental and lifestyle factors responsible for the lower prevalence of childhood asthma in rural areas and farming communities suggest that early immunomodulatory intervention might prevent asthma development. A *hygiene hypothesis* purports that naturally occurring microbial exposures in early life might drive early immune development away from allergic sensitization, persistent airways inflammation, and remodeling through early microbiome and innate immune development. If these natural microbial exposures truly have an asthma-protective effect, without significant adverse health consequences, these findings may foster new strategies for asthma prevention.

Several nonpharmacotherapeutic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 mo), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Immunizations are currently not considered to increase the likelihood of development of asthma; therefore all standard childhood immunizations are recommended for children with asthma, including varicella and annual influenza vaccines.

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CHAPTER 170

Atopic Dermatitis (Atopic Eczema)

Donald Y.M. Leung, Scott H. Sicherer

Atopic dermatitis (AD) , or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10–30% of children worldwide and frequently occurs in families with other atopic diseases. Infants with AD are predisposed to development of food allergy, allergic rhinitis, and asthma later in childhood, a process called *the atopic march* .

Etiology

AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and polarized adaptive immune responses to environmental allergens and microbes that lead to chronic skin inflammation.

Pathology

Acute AD skin lesions are characterized by **spongiosis** , or marked intercellular edema, of the epidermis. In AD, dendritic antigen-presenting cells (APCs) in the epidermis, such as Langerhans cells, exhibit surface-bound IgE molecules with cell processes that reach into upper epidermis to sense allergens and pathogens. These APCs play an important role in cutaneous responses to type 2 immune responses (see Chapter 166). There is marked perivenular T-cell and inflammatory monocyte-macrophage infiltration in acute AD lesions. Chronic, lichenified AD is characterized by a hyperplastic epidermis with hyperkeratosis and minimal spongiosis. There are predominantly IgE-bearing Langerhans cells in the epidermis, and macrophages in the dermal mononuclear cell infiltrate. Mast cell and eosinophil numbers are increased, contributing to skin inflammation.

Pathogenesis

AD is associated with multiple phenotypes and endotypes that have overlapping clinical presentations. **Atopic eczema** is associated with IgE-mediated sensitization (at onset or during the course of eczema) and occurs in 70–80% of patients with AD. **Nonatopic eczema** is not associated with IgE-mediated sensitization and is seen in 20–30% of patients with AD. Both forms of AD are associated with eosinophilia. In atopic eczema, circulating T cells expressing the skin homing receptor **cutaneous lymphocyte-associated antigen** produce increased levels of T-helper type 2 (Th2) cytokines, including interleukin (IL)-4 and IL-13, which induce isotype switching to IgE synthesis. Another cytokine, IL-5, plays an important role in eosinophil development and survival. Nonatopic eczema is associated with lower IL-4 and IL-13 but increased IL-17 and IL-23 production than in atopic eczema. Age and race have also been found to affect the immune profile in AD.

Compared with the skin of healthy individuals, both unaffected skin and acute skin lesions of patients with AD have an increased number of cells expressing IL-4 and IL-13. Chronic AD skin lesions, by contrast, have fewer cells that express IL-4 and IL-13, but increased numbers of cells that express IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and interferon (IFN)-γ than acute AD lesions. Despite increased type 1 and type 17 immune responses in chronic AD, IL-4 and IL-13 as well as other type 2 cytokines (e.g. TSLP, IL-31, IL-33) predominate and reflect increased numbers of Type 2 innate lymphoid cells and Th2 cells. The infiltration of IL-22–expressing T cells correlates with severity of AD, blocks keratinocyte differentiation, and induces epidermal hyperplasia. The importance of IL-4 and IL-13 in driving severe persistent AD has been validated by multiple clinical trials now demonstrating that biologics blocking IL-4 and IL-13 action lead to clinical improvement in moderate to severe AD.

In healthy people the skin acts as a protective barrier against external irritants, moisture loss, and infection. Proper function of the skin depends on adequate moisture and lipid content, functional immune responses, and structural integrity. *Severely dry skin is a hallmark of AD.* This results from compromise of the epidermal barrier, which leads to excess transepidermal water loss, allergen penetration, and microbial colonization. **Filaggrin** , a structural protein in the epidermis, and its breakdown products are critical to skin barrier function, including moisturization of the skin. Genetic mutations in the filaggrin gene *(FLG)* family have been identified in patients with ichthyosis vulgaris (dry skin, palmar hyperlinearity) and in up to 50% of patients with severe AD. *FLG* mutation is strongly associated with development of food allergy and eczema herpeticum. Nonetheless, up to 60% of carriers of a *FLG* mutation do not develop atopic diseases. Cytokines found in allergic inflammation, such as IL-4, IL-13, IL-22, IL-25, and tumor necrosis factor, can also reduce filaggrin and other epidermal proteins and lipids. AD patients are at increased risk of bacterial, viral, and fungal infection related to impairment of innate immunity, disturbances in the microbiome, skin epithelial dysfunction, and overexpression of polarized immune pathways, which dampen host antimicrobial responses.

Clinical Manifestations

AD typically begins in infancy. Approximately 50% of patients experience symptoms in the 1st yr of life, and an additional 30% are diagnosed between 1 and 5 yr of age. Intense **pruritus** , especially at night, and **cutaneous reactivity** are the cardinal features of AD. Scratching and excoriation cause increased skin inflammation that contributes to the development of more pronounced eczematous skin lesions. Foods (cow's milk, egg, peanut, tree nuts, soy, wheat, fish, shellfish), aeroallergens (pollen, grass, animal dander, dust mites), infection (*Staphylococcus aureus* , herpes simplex, coxsackievirus, molluscum), reduced humidity, excessive sweating, and irritants (wool, acrylic, soaps, toiletries, fragrances, detergents) can trigger pruritus and scratching.

Acute AD skin lesions are intensely pruritic with erythematous papules (Figs. 170.1 and 170.2). Subacute dermatitis manifests as erythematous, excoriated, scaling papules. In contrast, chronic AD is characterized by **lichenification** (Fig. 170.3), or thickening of the skin with accentuated surface markings, and **fibrotic papules** . In chronic AD, all 3 types of skin reactions may coexist in the same individual. Most patients with AD have dry, lackluster skin regardless of their stage of illness. Skin reaction pattern and distribution vary with the patient's age and disease activity. AD is generally more acute in infancy and involves the face, scalp, and extensor surfaces of the extremities. The diaper area is usually spared. Older children and children with chronic AD have lichenification and localization of the rash to the flexural folds of the extremities. AD can go into remission as the patient grows older, however, many children with AD have persistent eczema as an adult (Fig. 170.1*C*).

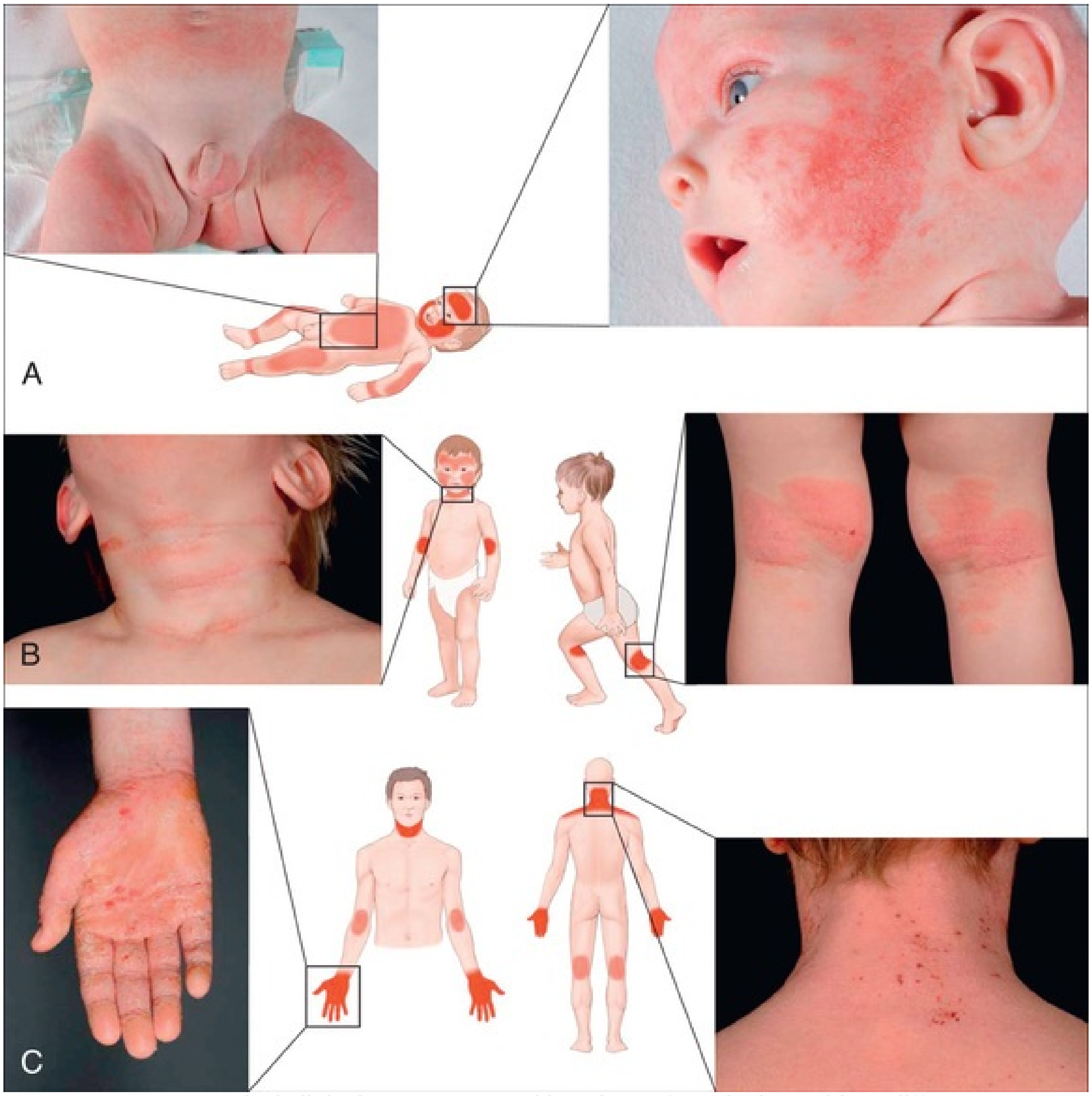

FIG. 170.1 Typical clinical appearance and locations of atopic dermatitis at different ages. Top row, In infants, atopic dermatitis is generally acute, with lesions mainly on the face and the extensor surfaces of the limbs. The trunk might be affected, but the napkin area is typically spared. Middle row, From age 1-2 yr onward, polymorphous manifestations with different types of skin lesions are seen, particularly in flexural folds. Bottom row, Adolescents and adults often present lichenified and excoriated plaques at flexures, wrists, ankles, and eyelids; in the head and neck type, the upper trunk, shoulders, and scalp are involved. Adults might have only chronic hand eczema or present with prurigo-like lesions. (From Weidinger S, Novak N: Atopic dermatitis, *Lancet* 387:1111, 2016.)

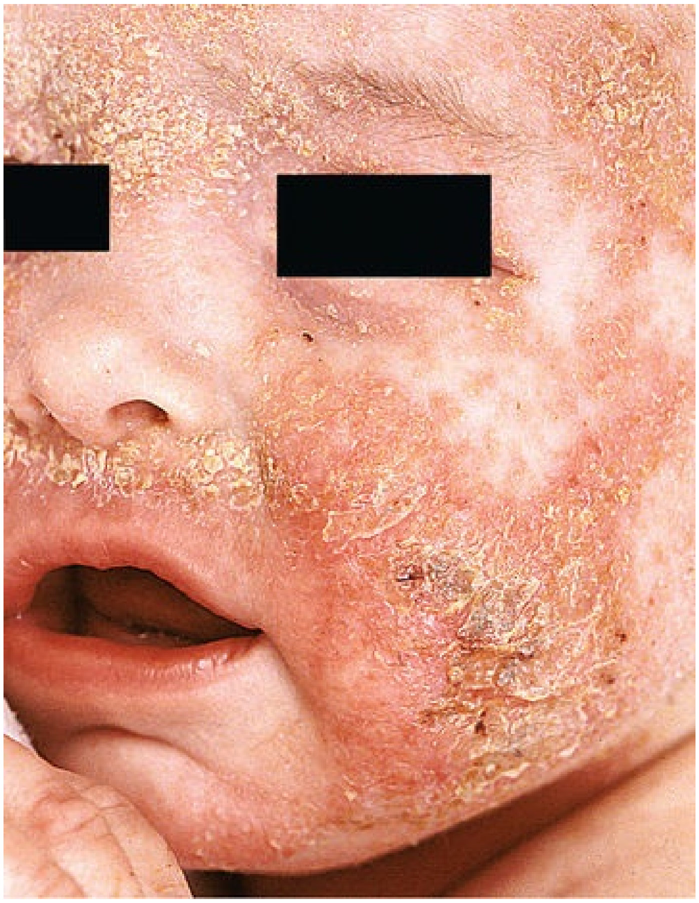

FIG. 170.2 Crusted lesions of atopic dermatitis on the face. (From Eichenfield LF, Friedan IJ, Esterly NB: *Textbook of neonatal dermatology,* Philadelphia, 2001, Saunders, p 242.)

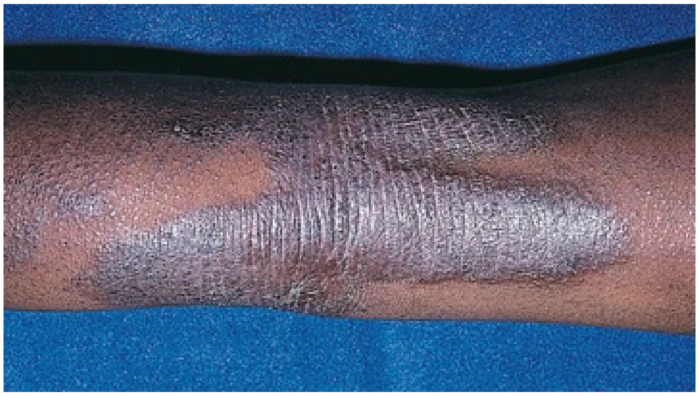

FIG. 170.3 Lichenification of the popliteal fossa from chronic rubbing of the skin in atopic dermatitis. (From Weston WL, Lane AT, Morelli JG: *Color textbook of pediatric dermatology,* ed 2, St Louis, 1996, Mosby, p 33.)

Laboratory Findings

There are no specific laboratory tests to diagnose AD. Many patients have peripheral blood eosinophilia and increased serum IgE levels. Serum IgE measurement or skin-prick testing can identify the allergens (foods, inhalant/microbial allergens) to which patients are sensitized. The diagnosis of clinical allergy to these allergens requires confirmation by history and environmental challenges.

Diagnosis and Differential Diagnosis

AD is diagnosed on the basis of 3 major features: pruritus, an eczematous dermatitis that fits into a typical pattern of skin inflammation, and a chronic or chronically relapsing course (Table 170.1). Associated features, such as a family history of asthma, hay fever, elevated IgE, and immediate skin test reactivity, reinforce the diagnosis of AD.

Table 170.1

Clinical Features of Atopic Dermatitis

Major Features

- Pruritus
- Facial and extensor eczema in infants and children
- Flexural eczema in adolescents
- Chronic or relapsing dermatitis
- Personal or family history of atopic disease

Associated Features

- Xerosis
- Cutaneous infections (*Staphylococcus aureus*, group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)
- Nonspecific dermatitis of the hands or feet
- Ichthyosis, palmar hyperlinearity, keratosis pilaris
- Nipple eczema

White dermatographism and delayed blanch response
Anterior subcapsular cataracts, keratoconus
Elevated serum IgE levels
Positive results of immediate-type allergy skin tests
Early age at onset
Dennie lines (Dennie-Morgan infraorbital folds)
Facial erythema or pallor
Course influenced by environmental and/or emotional factors

Many inflammatory skin diseases, immunodeficiencies, skin malignancies, genetic disorders, infectious diseases, and infestations share symptoms with AD and should be considered and excluded before a diagnosis of AD is established (Tables 170.2 and 170.3). Severe combined immunodeficiency (see Chapter 152.1) should be considered for infants presenting in the first yr of life with diarrhea, failure to thrive, generalized scaling rash, and recurrent cutaneous and/or systemic infection. Histiocytosis should be excluded in any infant with AD and failure to thrive (see Chapter 534). Wiskott-Aldrich syndrome, an X-linked recessive disorder associated with thrombocytopenia, immune defects, and recurrent severe bacterial infections, is characterized by a rash almost indistinguishable from that in AD (see Chapter 152.2). One of the hyper-IgE syndromes is characterized by markedly elevated serum IgE values, recurrent deep-seated bacterial infections, chronic dermatitis, and refractory dermatophytosis. Many of these patients have disease as a result of autosomal dominant *STAT3* mutations. In contrast, some patients with hyper-IgE syndrome present with increased susceptibility to viral infections and an autosomal recessive pattern of disease inheritance. These patients may have a *DOCK8* (dedicator of cytokinesis 8 gene) mutation. This diagnosis should be considered in young children with severe eczema, food allergy, and disseminated skin viral infections.

Table 170.2

Differential Diagnosis of Atopic Dermatitis (AD)

	MAIN AGE GROUP AFFECTED	FREQUENCY*	CHARACTERISTICS AND CLINICAL FEATURES
OTHER TYPES OF DERMATITIS			
Seborrheic	Infants	Common	Salmon-red greasy scaly lesions, often on the scalp (cradle

dermatitis			cap) and napkin area; generally presents in the 1st 6 wk of life; typically clears within weeks
Seborrheic dermatitis	Adults	Common	Erythematous patches with yellow, white, or grayish scales in seborrheic areas, particularly the scalp, central face, and anterior chest
Nummular dermatitis	Children and adults	Common	Coin-shaped scaly patches, mostly on legs and buttocks; usually no itch
Irritant contact dermatitis	Children and adults	Common	Acute to chronic eczematous lesions, mostly confined to the site of exposure; history of locally applied irritants is a risk factor; might coexist with AD
Allergic contact dermatitis	Children and adults	Common	Eczematous rash with maximum expression at sites of direct exposure but might spread; history of locally applied irritants is a risk factor; might coexist with AD
Lichen simplex chronicus	Adults	Uncommon	One or more localized, circumscribed, lichenified plaques that result from repetitive scratching or rubbing because of intense itch
Asteatotic eczema	Adults	Common	Scaly, fissured patches of dermatitis overlying dry skin, most often on lower legs
INFECTIOUS SKIN DISEASES			
Dermatophyte infection	Children and adults	Common	One or more demarcated scaly plaques with central clearing and slightly raised reddened edge; variable itch
Impetigo	Children	Common	Demarcated erythematous patches with blisters or honey-yellow crusting
Scabies	Children	Common †	Itchy superficial burrows and pustules on palms and soles, between fingers, and on genitalia; might produce secondary eczematous changes
HIV	Children and adults	Uncommon	Seborrhea-like rash
CONGENITAL IMMUNODEFICIENCIES (see Table 170.3)			
Keratinization Disorders			
Ichthyosis vulgaris	Infants and adults	Uncommon	Dry skin with fine scaling, particularly on the lower abdomen and extensor areas; perifollicular skin roughening; palmar hyperlinearity; full form (i.e., 2 *FLG* mutations) is uncommon; often coexists with AD
NUTRITIONAL DEFICIENCY–METABOLIC DISORDERS			
Zinc deficiency (acrodermatitis enteropathica)	Children	Uncommon	Erythematous scaly patches and plaques, most often around the mouth and anus; rare congenital form accompanied by diarrhea and alopecia
Biotin deficiency (nutritional or biotinidase deficiency)	Infants	Uncommon	Scaly periorofacial dermatitis, alopecia, conjunctivitis, lethargy, hypotonia
Pellagra (niacin deficiency)	All ages	Uncommon	Scaly crusted epidermis, desquamation, sun-exposed areas, diarrhea
Kwashiorkor	Infants and children	Geographic dependent	Flaky scaly dermatitis, swollen limbs with cracked peeling patches
Phenylketonuria	Infants	Uncommon	Eczematous rash, hypopigmentation, blonde hair, developmental delay
NEOPLASTIC DISEASE			
Cutaneous T-cell lymphoma	Adults	Uncommon	Erythematous pink-brown macules and plaques with a fine scale; poorly responsive to topical corticosteroids; variable itch (in early stages)
Langerhans cell histiocytosis	Infants	Uncommon	Scaly and purpuric dermatosis, hepatosplenomegaly, cytopenias

[*] Common = approximately 1 in 10 to 1 in 100; uncommon = 1 in 100 to 1 in 1000; rare = 1 in 1000 to 1 in 10,000; very rare = <1 in 10,000.

[†] Especially in developing countries.

FLG, filaggrin gene.

Table 170.3

Features of Primary Immunodeficiencies Associated With Eczematous Dermatitis

DISEASE	GENE	INHERITANCE	CLINICAL FEATURES	LAB ABNORMALITIES
AD-HIES	*STAT3*	AD, less commonly sporadic	Cold abscesses Recurrent sinopulmonary infections Mucocutaneous candidiasis Coarse facies Minimal trauma fractures Scoliosis Joint hyperextensibility Retained primary teeth Coronary artery tortuosity or dilation Lymphoma	High IgE (>2000 IU/µL) Eosinophilia
DOCK8 deficiency	*DOCK8*	AR	Severe mucocutaneous viral infections Mucocutaneous candidiasis Atopic features (asthma, allergies) Squamous cell carcinoma Lymphoma	High IgE Eosinophilia With or without decreased IgM
PGM3 deficiency	*PGM3*	AR	Neurologic abnormalities Leukocytoclastic vasculitis Atopic features (asthma, allergies) Sinopulmonary infections Mucocutaneous viral infections	High IgE Eosinophilia
WAS	*WASP*	XLR	Hepatosplenomegaly Lymphadenopathy Atopic diathesis Autoimmune conditions (especially hemolytic anemia) Lymphoreticular malignancies	Thrombocytopenia (<80,000/µL) Low mean platelet volume Eosinophilia is common Lymphopenia Low IgM, variable IgG
SCID	Variable, depends on type	XLR and AR most common	Recurrent, severe infections Failure to thrive Persistent diarrhea Recalcitrant oral candidiasis Omenn syndrome: lymphadenopathy, hepatosplenomegaly,	Lymphopenia common Variable patterns of reduced lymphocyte subsets (T, B, natural killer cells) Omenn syndrome: high lymphocytes, eosinophilia, high IgE

			erythroderma	
IPEX	*FOXP3*	XLR	Severe diarrhea (autoimmune enteropathy) Various autoimmune endocrinopathies (especially diabetes mellitus, thyroiditis) Food allergies	High IgE Eosinophilia Various autoantibodies
Netherton syndrome	*SPINK5*	AR	Hair shaft abnormalities Erythroderma Ichthyosis linearis circumflexa Food allergies Recurrent gastroenteritis Neonatal hypernatremic dehydration Upper and lower respiratory infections	High IgE Eosinophilia

AD, Autosomal dominant; AD-HIES, autosomal-dominant hyper-IgE syndrome; AR, autosomal recessive; *DOCK8* , dedicator of cytokinesis 8 gene; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PGM3, phosphoglucomutase 3; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome.

From Kliegman RM, Bordini BJ, editors: *Undiagnosed and Rare Diseases in Children* 64(1):41–42, 2017.

Adolescents who present with an eczematous dermatitis but no history of childhood eczema, respiratory allergy, or atopic family history may have allergic **contact dermatitis** (see Chapter 674.1). A contact allergen may be the problem in any patient whose AD does not respond to appropriate therapy. Sensitizing chemicals, such as parabens and lanolin, can be irritants for patients with AD and are commonly found as vehicles in therapeutic topical agents. Topical glucocorticoid contact allergy has been reported in patients with chronic dermatitis receiving topical corticosteroid therapy. Eczematous dermatitis has also been reported with HIV infection as well as with a variety of infestations such as scabies. Other conditions that can be confused with AD include psoriasis, ichthyosis, and seborrheic dermatitis.

Treatment

The treatment of AD requires a systematic, multifaceted approach that incorporates skin moisturization, topical antiinflammatory therapy, identification and elimination of flare factors (Table 170.4), and, if necessary, systemic therapy. Assessment of the severity also helps direct therapy (Table 170.5).

Table 170.4

Counseling and Aggravating Factors for Patients With Atopic Dermatitis (AD)

Maintain cool temperature in bedroom, and avoid too many bed covers.
Increase emollient use with cold weather.
Avoid exposure to herpes sores; urgent visit if flare of unusual aspect.
Clothing: Avoid skin contact with irritating fibers (wool, large-fiber textiles).
- Do not use tight and too-warm clothing, to avoid excessive sweating.
- New, nonirritating clothing designed for AD children is being evaluated.

Tobacco: Avoid exposure.
Vaccines: Normal schedule in noninvolved skin, including egg-allergic patients (see text).
Sun exposure: No specific restriction.
- Usually helpful because of improvement of epidermal barrier.
- Encourage summer holidays in altitude or at beach resorts.

Physical exercise, sports: no restriction.
- If sweating induces flares of AD, progressive adaptation to exercise.
- Shower and emollients after swimming pool.

Food allergens:
- Maintain breastfeeding exclusively to 4-6 mo if possible.
- Consider evaluation for early introduction of allergens (see Chapter 176).
- Otherwise normal diet, unless an allergy workup has proved the need to exclude a specific food.

Indoor aeroallergens: House dust mites
- Use adequate ventilation of housing; keep the rooms well aerated even in winter.
- Avoid wall-to-wall carpeting.
- Remove dust with a wet sponge.
- Vacuum floors and upholstery with an adequately filtered cleaner once a week.
- Avoid soft toys in bed (cradle), except washable ones.

  - Wash bedsheets at a temperature higher than 55°C (131°F) every 10 days.
  - Use bed and pillow encasings made of Gore-Tex or similar material.

Furred pets: Advise to avoid. If allergy is demonstrated, be firm on avoidance measures, such as pet removal.

Pollen: Close windows during peak pollen season on warm and dry weather days, and restrict, if possible, time outdoors.

  - Windows may be open at night and early in the morning or during rainy weather.
  - Avoid exposure to risk situations (lawn mowing).
  - Use pollen filters in motor vehicles.
  - Clothes and pets can vectorize aeroallergens, including pollen.

Adapted from Darsow U, Wollenberg A, Simon D, et al: ETFAD/EADV Eczema Task Force 2009 position paper on diagnosis and treatment of atopic dermatitis, *J Eur Acad Dermatol Venereol* 24:321, 2010.

Table 170.5

Categorization of Physical Severity of Atopic Eczema

Clear —Normal skin, with no evidence of atopic eczema

Mild —Areas of dry skin, infrequent itching (with or without small areas of redness)

Moderate —Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)

Severe —Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

From Lewis-Jones S, Mugglestone MA; Guideline Development Group: Management of atopic eczema in children aged up to 12 years: summary of NICE guidance, *BMJ* 335:1263–1264, 2007.

Cutaneous Hydration

Because patients with AD have impaired skin barrier function from reduced filaggrin and skin lipid levels, they present with diffuse, abnormally dry skin, or **xerosis** . *Moisturizers are first-line therapy.* Lukewarm soaking baths or showers for 15-20 min followed by the application of an occlusive emollient to retain moisture provide symptomatic relief. Hydrophilic ointments of varying degrees of viscosity can be used according to the patient's preference. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and may induce the development of folliculitis. In these patients, less occlusive agents should be used. Several prescription (classified as a medical device) “therapeutic moisturizers” or “barrier creams” are available, containing components such as ceramides and filaggrin acid metabolites intended to improve skin barrier function. There are minimal data demonstrating their efficacy over standard emollients.

Hydration by baths or wet dressings promotes transepidermal penetration of topical glucocorticoids. Dressings may also serve as effective barriers against persistent scratching, in turn promoting healing of excoriated lesions. Wet dressings are recommended for use on severely affected or chronically involved areas of dermatitis refractory to skin care. It is critical that wet dressing therapy be followed by topical emollient application to avoid potential drying and fissuring from the therapy. Wet dressing therapy can be complicated by maceration and secondary infection and should be closely monitored by a physician.

Topical Corticosteroids

Topical corticosteroids are the cornerstone of antiinflammatory treatment for acute exacerbations of AD. Patients should be carefully instructed on their use of topical glucocorticoids to avoid potential adverse effects. There are 7 classes of topical glucocorticoids, ranked according to their potency, as determined by vasoconstrictor assays (Table 170.6). Because of their potential adverse effects, the ultrahigh-potency glucocorticoids should not be used on the face or intertriginous areas and should be used only for very short periods on the trunk and extremities. Mid-potency glucocorticoids can be used for longer periods to treat chronic AD involving the trunk and extremities. Long-term control can be maintained with twice-weekly applications of topical fluticasone or mometasone to areas that have healed but are prone to relapse, once control of AD is achieved after a daily regimen of topical corticosteroids. Compared with creams, ointments have a greater potential to occlude the epidermis, resulting in enhanced systemic absorption.

Table 170.6

Selected Topical Corticosteroid Preparations*

Group 1

Clobetasol propionate (Temovate) 0.05% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel
Fluocinonide (Vanos) 0.1% cream

Group 2

Mometasone furoate (Elocon) 0.1% ointment
Halcinonide (Halog) 0.1% cream
Fluocinonide (Lidex) 0.05% ointment/cream
Desoximetasone (Topicort) 0.25% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% cream

Group 3

Fluticasone propionate (Cutivate) 0.005% ointment
Halcinonide (Halog) 0.1% ointment
Betamethasone valerate (Valisone) 0.1% ointment

Group 4

Mometasone furoate (Elocon) 0.1% cream
Triamcinolone acetonide (Kenalog) 0.1% ointment/cream
Fluocinolone acetonide (Synalar) 0.025% ointment

Group 5

Fluocinolone acetonide (Synalar) 0.025% cream

Hydrocortisone valerate (Westcort) 0.2% ointment

Group 6

Desonide (DesOwen) 05% ointment/cream/lotion
Alclometasone dipropionate (Aclovate) 0.05% ointment/cream

Group 7

Hydrocortisone (Hytone) 2.5%, 1%, 0.5% ointment/cream/lotion

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[*] Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).

Adapted from Stoughton RB: Vasoconstrictor assay-specific applications. In Malbach HI, Surber C, editors: *Topical corticosteroids,* Basel, Switzerland, 1992, Karger, pp 42–53.

Adverse effects of topical glucocorticoids can be divided into local adverse effects and systemic adverse effects, the latter resulting from suppression of the hypothalamic-pituitary-adrenal axis. *Local* adverse effects include the development of striae and skin atrophy. *Systemic* adverse effects are related to the potency of the topical corticosteroid, site of application, occlusiveness of the preparation, percentage of the body surface area covered, and length of use. The potential for adrenal suppression from potent topical corticosteroids is greatest in infants and young children with severe AD requiring intensive therapy.

Topical Calcineurin Inhibitors

The nonsteroidal topical calcineurin inhibitors are effective in reducing AD skin inflammation. Pimecrolimus cream 1% (Elidel) is indicated for mild to moderate AD. Tacrolimus ointment 0.1% and 0.03% (Protopic) is indicated for moderate to severe AD. Both are approved for short-term or intermittent long-term treatment of AD in patients ≥2 yr whose disease is unresponsive to or who are intolerant of other conventional therapies or for whom these therapies are inadvisable because of potential risks. Topical calcineurin inhibitors may be better than topical corticosteroids in the treatment of patients whose AD is poorly responsive to topical steroids, patients with steroid phobia, and those with face and neck dermatitis, in whom ineffective, low-potency topical corticosteroids are typically used because of fears of steroid-induced skin atrophy.

Phosphodiesterase Inhibitor

Crisaborole (Eucrisa) is an approved nonsteroidal topical antiinflammatory phosphodiesterase-4 (PDE-4) inhibitor indicated for the treatment of mild to moderate AD down to age 2 yr. It may be used as an alternative to topical corticosteroids or calcineurin inhibitors.

Tar Preparations

Coal tar preparations have antipruritic and antiinflammatory effects on the skin; however, their antiinflammatory effects are usually not as pronounced as those of topical glucocorticoids or calcineurin inhibitors. Therefore, topical tar preparations are not a preferred approach for management of AD. Tar shampoos can be particularly beneficial for scalp dermatitis. Adverse effects associated with tar preparations include skin irritation, folliculitis, and photosensitivity.

Antihistamines

Systemic antihistamines act primarily by blocking the histamine H_1 receptors in the dermis, thereby reducing histamine-induced pruritus. Histamine is only one of many mediators that induce pruritus of the skin, so patients may derive minimal benefit from antihistaminic therapy. Because pruritus is usually worse at night, sedating antihistamines (hydroxyzine, diphenhydramine) may offer an advantage with their soporific side effects when used at bedtime. Doxepin hydrochloride has both tricyclic antidepressant and H_1 - and H_2 -receptor blocking effects. Short-term use of a sedative to allow adequate rest may be appropriate in cases of severe nocturnal pruritus. Studies of newer, nonsedating antihistamines have shown variable effectiveness in controlling pruritus in AD, although they may be useful in the small subset of patients with AD and concomitant urticaria. For children, melatonin may be effective in promoting sleep because production is deficient in AD.

Systemic Corticosteroids

Systemic corticosteroids are rarely indicated in the treatment of chronic AD. The dramatic clinical improvement that may occur with systemic corticosteroids is frequently associated with a severe rebound flare of AD after therapy discontinuation. Short courses of oral corticosteroids may be appropriate for an acute exacerbation of AD while other treatment measures are being instituted in parallel. If a short course of oral corticosteroids is given, as during an asthma exacerbation, it is important to taper the dosage and begin intensified skin care, particularly with topical corticosteroids, and frequent bathing, followed by application of emollients or proactive topical corticosteroids, to prevent rebound flaring of AD.

Cyclosporine

Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription and has been shown to be effective in the control of severe AD. Cyclosporin forms a complex with an intracellular protein, cyclophilin, and this complex in turn inhibits calcineurin, a phosphatase required for activation of NFAT (nuclear factor of activated T cells), a transcription factor necessary for cytokine gene transcription. Cyclosporine (5 mg/kg/day) for short-term and long-term (1 yr) use has been beneficial for children with severe, refractory AD. Possible adverse effects include renal impairment and hypertension.

Dupilumab

A monoclonal antibody that binds to the IL-4 receptor α subunit, dupilumab (Dupixent) inhibits the signaling of IL-4 and IL-13, cytokines associated with AD. In adults with moderate to severe AD not controlled by standard topical therapy, dupilumab reduces pruritus and improves skin clearing.

Antimetabolites

Mycophenolate mofetil is a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation that has been used for treatment of refractory AD. Aside from immunosuppression, herpes simplex retinitis and dose-related bone marrow suppression have been reported with its use. Of note, not all patients benefit from treatment. Therefore, mycophenolate mofetil should be discontinued if the disease does not respond within 4-8 wk.

Methotrexate is an antimetabolite with potent inhibitory effects on inflammatory cytokine synthesis and cell chemotaxis. Methotrexate has been used for patients with recalcitrant AD. In AD, dosing is more frequent than the weekly dosing used for psoriasis.

Azathioprine is a purine analog with antiinflammatory and antiproliferative effects that has been used for severe AD. Myelosuppression is a significant adverse effect, and thiopurine methyltransferase levels may identify individuals at risk.

Before any of these drugs is used, patients should be referred to an AD specialist who is familiar with treatment of severe AD to weigh relative benefits of alternative therapies.

Phototherapy

Natural sunlight is often beneficial to patients with AD as long as sunburn and excessive sweating are avoided. Many phototherapy modalities are effective for AD, including ultraviolet A-1, ultraviolet B, narrow-band ultraviolet B, and psoralen plus ultraviolet A. Phototherapy is generally reserved for patients in whom standard treatments fail. Maintenance treatments are usually required for phototherapy to be effective. Short-term adverse effects with phototherapy include erythema, skin pain, pruritus, and pigmentation. Long-term adverse effects include predisposition to cutaneous malignancies.

Unproven Therapies

Other therapies may be considered in patients with refractory AD.

Interferon-γ

IFN-γ is known to suppress Th2-cell function. Several studies, including a multicenter, double-blind, placebo-controlled trial and several open trials, have demonstrated that treatment with recombinant human IFN-γ results in clinical improvement of AD. Reduction in clinical severity of AD correlated with the ability of IFN-γ to decrease total circulating eosinophil counts. Influenza-like symptoms are common side effects during the treatment course.

Omalizumab

Treatment of patients who have severe AD and elevated serum IgE values with monoclonal anti-IgE may be considered in those with allergen-induced flares of AD. However, there have been no published double-blind, placebo-controlled trials of omalizumab's use. Most reports have been case studies and show inconsistent responses to anti-IgE.

Allergen Immunotherapy

In contrast to its acceptance for treatment of allergic rhinitis and extrinsic asthma, immunotherapy with aeroallergens in the treatment of AD is controversial. There are reports of both disease exacerbation and improvement. Studies suggest that specific immunotherapy in patients with AD sensitized to dust mite allergen showed improvement in severity of skin disease, as well as reduction in topical corticosteroid use.

Probiotics

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG has been shown to reduce the incidence of AD in at-risk children during the 1st 2 yr of life. The treatment response has been found to be more pronounced in patients with positive skin-prick test results and elevated IgE values. Other studies have not demonstrated a benefit.

Chinese Herbal Medications

Several placebo-controlled clinical trials have suggested that patients with severe AD may benefit from treatment with traditional Chinese herbal therapy. The patients had significantly reduced skin disease and decreased pruritus. The beneficial response of Chinese herbal therapy is often temporary, and effectiveness may wear off despite continued treatment. The possibility of hepatic toxicity, cardiac side effects, or idiosyncratic reactions remains a concern. The specific ingredients of the herbs also remain to be elucidated, and some preparations have been found to be contaminated with corticosteroids. At present, Chinese herbal therapy for AD is considered investigational.

Vitamin D

Vitamin D deficiency often accompanies severe AD. Vitamin D enhances skin barrier function, reduces corticosteroid requirements to control inflammation, and augments skin antimicrobial function. Several small clinical studies suggest vitamin D can enhance antimicrobial peptide expression in the skin and reduce severity of skin disease, especially in patients with low baseline vitamin D, as during winter, when exacerbation of AD often occurs. Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.

Avoiding Triggers

It is essential to identify and eliminate triggering factors for AD, both during the period of acute symptoms and on a long-term basis to prevent recurrences (see Table 170.4).

Irritants

Patients with AD have a low threshold response to irritants that trigger their itch-scratch cycle. Soaps or detergents, chemicals, smoke, abrasive clothing, and exposure to extremes of temperature and humidity are common triggers. *Patients with AD should use soaps with minimal defatting properties and a neutral pH.* New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals. Residual laundry detergent in clothing may trigger the itch-scratch cycle; using a liquid rather than powder detergent and adding a 2nd rinse cycle facilitates removal of the detergent.

Every attempt should be made to allow children with AD to be as normally active as possible. A sport such as swimming may be better tolerated than others that involve intense perspiration, physical contact, or heavy clothing and equipment. Rinsing off chlorine immediately and lubricating the skin after swimming are important. Although ultraviolet light may be beneficial to some patients with AD, high–sun protection factor (SPF) sunscreens should be used to avoid sunburn.

Foods

Food allergy is comorbid in approximately 40% of infants and young children with moderate to severe AD (see Chapter 176). Undiagnosed food allergies in patients with AD may induce eczematous dermatitis in some patients and urticarial reactions, wheezing, or nasal congestion in others. Increased severity of AD symptoms and younger age correlate directly with the presence of food allergy. Removal of food allergens from the diet leads to significant clinical improvement but requires much education, because most common allergens (egg, milk, peanut, wheat, soy) contaminate many foods and are difficult to avoid.

Potential allergens can be identified by a careful history and performing selective skin-prick tests or in vitro blood testing for allergen-specific IgE. Negative skin and blood test results for allergen-specific IgE have a high predictive value for excluding suspected allergens. Positive results of skin or blood tests using foods often do not correlate with clinical symptoms and should be confirmed with controlled food challenges and elimination diets. Extensive elimination diets, which can be nutritionally deficient, are rarely required. Even with multiple positive skin test results, the majority of patients react to fewer than 3 foods under controlled challenge conditions.

Aeroallergens

In older children, AD flares can occur after intranasal or epicutaneous exposure to aeroallergens such as fungi, animal dander, grass, and ragweed pollen. Avoiding aeroallergens, particularly dust mites, can result in clinical improvement of AD. Avoidance measures for dust mite–allergic patients include using dust mite–proof encasings on pillows, mattresses, and box springs; washing bedding in hot water weekly; removing bedroom carpeting; and decreasing indoor humidity levels with air conditioning.

Infections

Patients with AD have increased susceptibility to bacterial, viral, and fungal skin infections. Antistaphylococcal antibiotics are very helpful for treating patients who are heavily colonized or infected with *Staphylococcus aureus.* Erythromycin and azithromycin are usually beneficial for patients who are not colonized with a resistant *S. aureus* strain; a first-generation cephalosporin (cephalexin) is recommended for macrolide-resistant *S. aureus* . Topical mupirocin is useful in the treatment of localized impetiginous lesions, with systemic clindamycin or trimethoprim/sulfamethoxazole needed for methicillin-resistant *S. aureus* (MRSA). Cytokine-mediated skin inflammation contributes to skin colonization with *S. aureus* . This finding supports the importance of combining effective antiinflammatory therapy with antibiotics for treating moderate to severe AD to avoid the need for repeated courses of antibiotics, which can lead to the emergence of antibiotic-resistant strains of *S. aureus*. Dilute bleach baths (½ cup of bleach in 40 gallons of water) twice weekly may be also considered to reduce *S. aureus* colonization. In one randomized trial, the group who received the bleach baths plus intranasal mupirocin (5 days/mo) had significantly decreased severity of AD at 1 and 3 mo compared with placebo. Patients rinse off after the soaking. Bleach baths may not only reduce *S. aureus* abundance on the skin but also have antiinflammatory effects.

Herpes simplex virus (HSV) can provoke recurrent dermatitis and may be misdiagnosed as *S. aureus* infection (Fig. 170.4). The presence of punched-out erosions, vesicles, and infected skin lesions that fail to respond to oral antibiotics suggests HSV infection, which can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base or by viral polymerase chain reaction or culture. Topical corticosteroids should be temporarily discontinued if HSV infection is suspected. Reports of life-threatening dissemination of HSV infections in patients with AD who have widespread disease mandate antiviral treatment. Persons with AD are also susceptible to **eczema vaccinatum** , which is similar in appearance to eczema herpeticum and historically follows smallpox (vaccinia virus) vaccination.

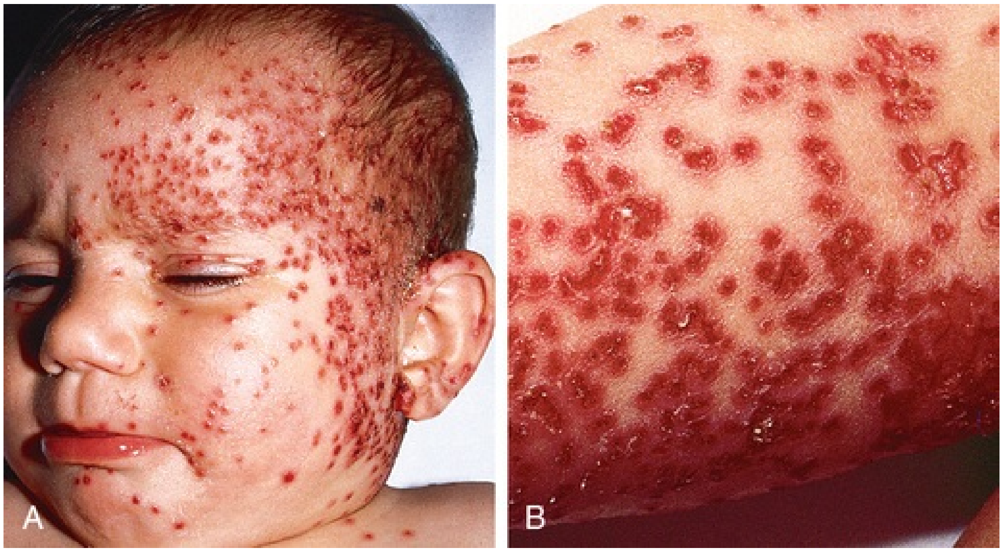

FIG. 170.4 Eczema herpeticum infection in a patient with atopic dermatitis. Numerous

punched-out vesicles and erosions involving the face (A) and extremities (B). (From Papulosquamous eruptions. In Cohen BA, editor: *Pediatric dermatology,* Philadelphia,2013, Saunders, pp 68–103.)

Cutaneous warts, coxsackievirus, and molluscum contagiosum are additional viral infections affecting children with AD.

Dermatophyte infections can also contribute to exacerbation of AD. Patients with AD have been found to have a greater susceptibility to *Trichophyton rubrum* fungal infections than nonatopic controls. There has been particular interest in the role of *Malassezia furfur* (formerly known as *Pityrosporum ovale*) in AD because it is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* have been found in patients with head and neck dermatitis. A reduction of AD severity has been observed in these patients after treatment with antifungal agents.

Complications

Exfoliative dermatitis may develop in patients with extensive skin involvement. It is associated with generalized redness, scaling, weeping, crusting, systemic toxicity, lymphadenopathy, and fever and is usually caused by superinfection (e.g., with toxin-producing *S. aureus* or HSV infection) or inappropriate therapy. In some cases the withdrawal of systemic glucocorticoids used to control severe AD precipitates exfoliative erythroderma.

Eyelid dermatitis and chronic blepharitis may result in visual impairment from corneal scarring. **Atopic keratoconjunctivitis** is usually bilateral and can have disabling symptoms that include itching, burning, tearing, and copious mucoid discharge. Vernal conjunctivitis is associated with papillary hypertrophy or cobblestoning of the upper eyelid conjunctiva. It typically occurs in younger patients and has a marked seasonal incidence with spring exacerbations. **Keratoconus** is a conical deformity of the cornea believed to result from chronic rubbing of the eyes in patients with AD. Cataracts may be a primary manifestation of AD or from extensive use of systemic and topical glucocorticoids, particularly around the eyes.

Prognosis

AD generally tends to be more severe and persistent in young children, particularly if they have null mutations in their filaggrin genes. Periods of remission occur more frequently as patients grow older. Spontaneous resolution of AD has been reported to occur after age 5 yr in 40–60% of patients affected during infancy, particularly for mild disease. Earlier studies suggested that approximately 84% of children outgrow their AD by adolescence; however, later studies reported that AD resolves in approximately 20% of children monitored from infancy until adolescence and becomes less severe in 65%. Of those adolescents treated for mild dermatitis, >50% may experience a relapse of disease as adults, which frequently manifests as *hand dermatitis*, especially if daily activities require repeated hand wetting. Predictive factors of a poor prognosis for AD include widespread AD in childhood, *FLG* null mutations, concomitant allergic rhinitis and asthma, family history of AD in parents or siblings, early age at onset of AD, being an only child, and very high serum IgE levels.

Prevention

Breastfeeding may be beneficial. Probiotics and prebiotics may also reduce the incidence or severity of AD, but this approach is unproven. If an infant with AD is diagnosed with food allergy, the breastfeeding mother may need to eliminate the implicated food allergen from her diet. For infants with severe eczema, introduction of infant-safe forms of peanut as early as 4-6 mo, after other solids are tolerated, is recommended after consultation with the child's pediatrician and/or allergist for allergy testing. This approach may prevent peanut allergy (see Chapter 176). Identification and elimination of triggering factors are the mainstay for prevention of flares as well as for the long-term treatment of AD.

Emollient therapy applied to the whole body for the 1st few mo of life may enhance the cutaneous barrier and reduce the risk of eczema.

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CHAPTER 171

Insect Allergy

Julie Wang, Scott H. Sicherer

Allergic responses to stinging or, more rarely, biting insects vary from localized cutaneous reactions to systemic anaphylaxis. **Allergic reactions** caused by inhalation of airborne particles of insect origin result in acute and chronic respiratory symptoms of seasonal or perennial rhinitis, conjunctivitis, and asthma.

Etiology

Most reactions to stinging and biting insects, such as those induced by wasps, mosquitoes, flies, and fleas, are limited to a primary lesion isolated to the area of the sting or bite and do not represent an allergic response. Occasionally, insect stings or bites induce pronounced localized reactions or systemic reactions that may be based on immediate or delayed hypersensitivity reactions. Systemic allergic responses to insects are usually attributed to IgE antibody–mediated responses, which are caused primarily by stings from venomous insects of the order **Hymenoptera** and more rarely from ticks, spiders, scorpions, and *Triatoma* (kissing bug). Members of the order Hymenoptera include *apids* (honeybee, bumblebee), *vespids* (yellow jacket, wasp, hornet), and *formicids* (fire and harvester ants) (Fig. 171.1). Among winged stinging insects, yellow jackets are the most notorious for stinging because they are aggressive and ground dwelling, and they linger near activities involving food. Hornets nest in trees, whereas wasps build honeycomb nests in dark areas such as under porches; both are aggressive if disturbed. Honeybees are less aggressive and nest in tree hollows; unlike the stings of other flying Hymenoptera, honeybee stings almost always leave a barbed stinger with venom sac.

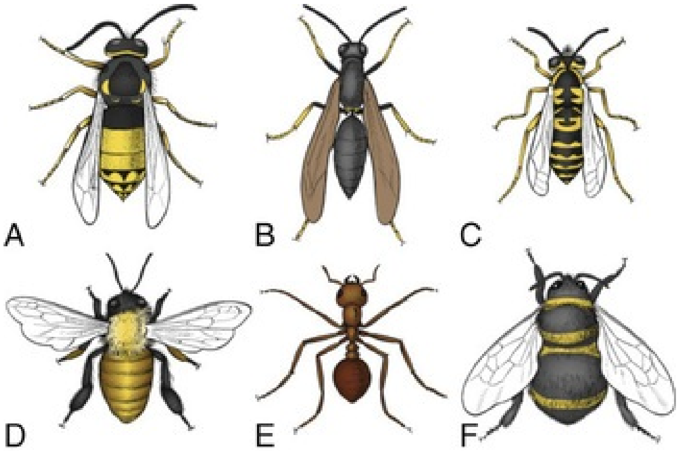

FIG. 171.1 Representative venomous Hymenoptera. A, Hornet *(Vespula maculata)* . B, Wasp *(Chlorion ichneumerea)* . C, Yellowjacket *(Vespula maculiforma)* . D, Honeybee *(Apis mellifera)* . E, Fire ant *(Solenopsis invicta)* . F, Bumblebee *(Bombus species)* . (From Erickson TB, Marquez A: Arthropod envenomation and parasitism. In Auerbach PS, Cushing TA, Harris NS (eds): Auerbach's wilderness medicine, ed 7, Philadelphia, 2017, Elsevier, Fig 41-1, p 937.)

In the United States, fire ants are found increasingly in the Southeast, living in large mounds of soil. When disturbed, the ants attack in large numbers, anchor themselves to the skin by their mandibles, and sting multiple times in a circular pattern. Sterile pseudopustules form at the sting sites. Systemic reactions to stinging insects occur in 0.4–0.8% of children and 3% of adults and account for approximately 40 deaths each year in the United States.

Although reactions to insect bites are common, IgE-mediated reactions are infrequently reported and anaphylaxis is rare. The *Triatoma* (kissing bug) bite causes an erythematous plaque that is painless. Mosquito bites generally result in local reactions that are pruritic. Large, local reactions to mosquito bites can occur in some young children; this is known as **skeeter syndrome** and is often misdiagnosed as cellulitis. The *tabanid* species (horsefly, deerfly), typically found in rural and suburban areas, are large flies that induce painful bites.

IgE antibody–mediated allergic responses to airborne particulate matter carrying insect emanations contribute to seasonal and perennial symptoms affecting the upper and lower airways. Seasonal allergy is attributed to exposures to a variety of insects, particularly aquatic insects such as the caddis fly and midge, or lake fly, at a time when larvae pupate and adult flies are airborne. **Perennial allergy** is attributed to sensitization to insects such as cockroaches and ladybugs, as well as house dust mite, which is phylogenetically related to spiders rather than insects and has 8 rather than 6 legs.

Pathogenesis

Hymenoptera venoms contain numerous components with toxic and pharmacologic activity and with allergenic potential. These constituents include vasoactive substances such as histamine, acetylcholine, and kinins; enzymes such as phospholipase and hyaluronidase; apamin; melittin; and formic acid. The majority of patients who experience systemic reactions after Hymenoptera stings have IgE-mediated sensitivity to antigenic substances in the venom. Some venom allergens are homologous among members of the Hymenoptera order; others are family specific. There is substantial cross-reactivity among vespid venoms, but these venom allergies are distinct from honeybee venom allergies.

Localized skin responses to biting insects are caused primarily by vasoactive or irritant materials derived from insect saliva; they rarely occur from IgE-associated responses. Systemic IgE-mediated allergic reactions to salivary proteins of biting insects such as mosquitoes are reported but uncommon.

A variety of proteins derived from insects can become airborne and induce IgE-mediated respiratory responses, causing inhalant allergies. The primary allergen from the caddis fly is a hemocyanin-like protein, and that from the midge fly is derived from hemoglobin. Allergens from the cockroach are the best studied and are derived from cockroach saliva, secretions, fecal material, and debris from skin casts.

Clinical Manifestations

Clinical reactions to stinging venomous insects are categorized as local, large local, generalized cutaneous, systemic, toxic, and delayed/late. Simple **local reactions** involve limited swelling and pain and generally last <24 hr. **Large local reactions** develop over hours and days, involve swelling of extensive areas (>10 cm) that are contiguous with the sting site, and may last for days. **Generalized cutaneous reactions** typically progress within minutes and include cutaneous symptoms of urticaria, angioedema, and pruritus beyond the site of the sting. **Systemic reactions** are identical to anaphylaxis from other triggers and may include symptoms of generalized urticaria, laryngeal edema, bronchospasm, and hypotension. Stings from a large number of insects at once may result in **toxic reactions** of fever, malaise, emesis, and nausea because of the chemical properties of the venom in large doses. Serum sickness, nephrotic syndrome, vasculitis, neuritis, or encephalopathy may occur as **delayed/late**

reactions to stinging insects.

Insect bites are usually urticarial but may be papular or vesicular. **Papular urticaria** affecting the lower extremities in children is usually caused by multiple bites. Occasionally, individuals have large, local reactions. IgE antibody–associated immediate- and late-phase allergic responses to mosquito bites sometimes mimic cellulitis.

Inhalant allergy caused by insects results in clinical disease similar to that induced by other inhalant allergens such as pollens. Depending on individual sensitivity and exposure, reactions may result in seasonal or perennial rhinitis, conjunctivitis, or asthma.

Diagnosis

The diagnosis of allergy from stinging and biting insects is generally evident from the history of exposure, typical symptoms, and physical findings. The diagnosis of Hymenoptera allergy rests in part on the identification of venom-specific IgE by skin-prick testing or in vitro testing. The primary reasons to pursue testing are to confirm reactivity when venom immunotherapy (**VIT**) is being considered or when it is clinically necessary to confirm venom hypersensitivity as a cause of a reaction. Venoms of 5 Hymenoptera (honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp), as well as the jack jumper ant in Australia and whole body extract of fire ant, are available for skin testing. Although skin tests are considered to be the most sensitive modality for detection of venom-specific IgE, additional evaluation with an in vitro serum assay for venom-specific IgE is recommended if skin test results are negative in the presence of a convincing history of a severe systemic reaction. In vitro tests have a 20% incidence of both false-positive and false-negative results, so it is not appropriate to exclude venom hypersensitivity based on this test alone. If initial skin-prick and in vitro test results are negative in the context of a convincing history of a severe reaction, repeat testing is recommended before concluding that allergy is unlikely. Skin tests are usually accurate within 1 wk of a sting reaction, but occasionally a refractory period is observed that warrants retesting after 4-6 wk if the initial results are negative.

An elevated **basal tryptase** level is associated with more severe reactions to venom stings. Therefore, basal tryptase should be measured if there is a history of severe reaction to a sting, hypotensive reaction, lack of urticaria in a systemic sting reaction, or negative venom IgE in a patient who has a history of systemic reaction to a sting. As many as 40% of skin test–positive patients may not experience anaphylaxis on sting challenge, so testing without an appropriate clinical history is potentially misleading.

The diagnosis of inhalant insect allergy may be evident from a history of typical symptoms. A chronic respiratory symptom during long-term exposure, as may occur with cockroach allergy, is less amenable to identification by history alone. Skin-prick or in vitro immunoassay tests for specific IgE to the insect are used to confirm inhalant insect allergy. Allergy tests may be particularly warranted for potential cockroach allergy in patients with persistent asthma and known cockroach exposure.

Treatment

For local cutaneous reactions caused by insect stings and bites, treatment with cold compresses, topical medications to relieve itching, and occasionally a systemic antihistamine and oral analgesic are appropriate. Stingers should be removed promptly by scraping, with caution not to squeeze the venom sac because doing so could inject more venom. Sting sites rarely become infected, possibly because of the antibacterial actions of venom constituents. Vesicles left by fire ant stings that are scratched open should be cleansed to prevent secondary infection.

Anaphylactic reactions after a Hymenoptera sting are treated the same as anaphylaxis from any cause; *epinephrine is the drug of choice.* Adjunctive treatment includes antihistamines, corticosteroids, intravenous fluids, oxygen, and transport to the emergency department (see Chapter 174). Referral to an allergist-immunologist should be considered for patients who have experienced a generalized cutaneous or systemic reaction to an insect sting, who need education about avoidance and emergency treatment, who may be candidates for VIT, or who have a condition that may complicate management of anaphylaxis (e.g., use of β-blockers).

Venom Immunotherapy

Hymenoptera VIT is highly effective (95–97%) in decreasing the risk for **severe anaphylaxis** . The selection of patients for VIT depends on several factors (Table 171.1). Individuals with local reactions, regardless of age, are not at increased risk for severe systemic reactions on a subsequent sting and are not candidates for VIT. The risk of a systemic reaction for those who experienced a large, local reaction is approximately 7%; testing or VIT is usually not recommended, and prescription of self-injectable epinephrine is considered optional but usually not necessary. There is growing evidence that VIT can reduce the size and duration of large, local reactions, and therefore VIT may be considered for those with frequent or unavoidable large, local reactions. *Those who experience severe systemic reactions, such as airway involvement or hypotension, and who have specific IgE to venom allergens should receive immunotherapy.* Immunotherapy against winged Hymenoptera is generally not required when stings have caused only generalized urticaria or angioedema, because the risk for a systemic reaction after a subsequent sting is approximately 10% and the chance of a more severe reaction is <3%. VIT may be considered if there are potential high-risk cofactors such as comorbid cardiovascular disease or use of specific cardiovascular medications (e.g., ACE inhibitors, β-blockers), elevated basal tryptase level, or high likelihood of future stings. VIT is usually not indicated if there is no evidence of IgE to venom.

Table 171.1

Indications for Venom Immunotherapy (VIT) Against Winged Hymenoptera

SYMPTOMS	SKIN TEST/IN VITRO TEST	RISK OF SYSTEMIC REACTION IF UNTREATED*	VIT RECOMMENDED
Large local reaction	Usually not indicated	~7%	Usually not indicated
Generalized cutaneous reaction	Usually not indicated	10%	Usually not indicated
Systemic reaction	Positive result	Child: 40% Adult: 30–60%	Yes
	Negative result	—	Usually not indicated

[*] Risks generally decrease after 10 yr.

The incidence of adverse effects in the course of treatment is not trivial in adults; 50% experience large, local reactions, and about 10% experience systemic reactions. The incidence of both local and systemic reactions is much lower in children. Patients treated with honeybee venom are at higher risk for systemic reactions to VIT than those receiving treatment with vespid venom. Individuals with mast cell disorders are at increased risk for severe anaphylaxis and more frequent systemic reactions with VIT; thus some experts recommend basal tryptase level for risk assessment purposes.

It is uncertain how long immunotherapy with Hymenoptera venom should continue. In general, treatment duration of 3-5 yr is recommended because >80% of adults who have received 5 yr of therapy tolerate challenge stings without systemic reactions for 5-10 yr after completion of treatment. Long-term responses to treatment are even better for children. Follow-up over a mean of 18 yr of children with moderate to severe insect sting reactions who received VIT for a mean of 3-5 yr and were stung again showed a reaction rate of only 5%; untreated children experienced a reaction rate of 32%. Whereas duration of therapy with VIT may be individualized, it is clear that a significant number of untreated children retain their allergy. Extended or lifelong treatment may be considered for those who have had life-threatening anaphylaxis with insect stings, those with honeybee allergy, and those with occupational exposures to Hymenoptera. Lifelong VIT should also be considered for patients with mast cell disorders because they have a higher rate of failure of VIT and relapse when VIT is discontinued.

Less is known about the natural history of fire ant hypersensitivity and efficacy of immunotherapy for this allergy. The criteria for starting immunotherapy are similar to those for hypersensitivities to other Hymenoptera, but there is stronger consideration to treat patients who have only cutaneous systemic reactions with VIT. Only whole body fire ant extract is commercially available for diagnostic skin testing and immunotherapy.

Inhalant Allergy

The symptoms of inhalant allergy caused by insects are managed as for other causes of seasonal or perennial rhinitis (see Chapter 168), conjunctivitis (Chapter 172), and asthma (Chapter 169).

Prevention

Avoidance of stings and bites is essential. To reduce the risk of stings, sensitized individuals should have known or suspected nests near the home removed by trained professionals, should wear gloves when gardening, should wear long pants and shoes with socks when walking in the grass or through fields, and should avoid or be cautious about eating or drinking outdoors. Typical insect repellents do not guard against Hymenoptera.

Individuals who are at high risk for future severe reactions to Hymenoptera stings should have immediate access to self-injectable epinephrine. High-risk individuals include those who have a history of severe reactions, are prescribed angiotensin-converting enzyme (ACE) inhibitors or β-adrenergic blockers, or have elevated basal tryptase level. Adults responsible for allergic children and older patients who can self-treat must be carefully taught the indications and technique of administration for this medication. Particular attention is necessary for children in out-of-home daycare centers, at school, or attending camps, to ensure that an emergency action plan is in place. The individual at risk for anaphylaxis from an insect sting should also wear an identification bracelet indicating the allergy.

Avoidance of the insect is the preferred management of inhalant allergy. This can prove difficult, particularly for those living in apartments, where eradication of cockroaches may be problematic. Immunotherapy for dust mites is effective and should be considered in conjunction with avoidance measures. In contrast, there is limited data regarding the efficacy of cockroach immunotherapy.

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CHAPTER 172

Ocular Allergies

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The **eye** is a common target of allergic disorders because of its marked vascularity and direct contact with allergens in the environment. The **conjunctiva** is the most immunologically active tissue of the external eye. Ocular allergies can occur as isolated target organ disease or more often in conjunction with nasal allergies. Ocular symptoms can significantly affect quality of life.

Clinical Manifestations

There are a few distinct entities that constitute allergic eye disease, all of which have bilateral involvement. Sensitization is necessary for all these except giant papillary conjunctivitis. Vernal and atopic keratoconjunctivitis are potentially sight threatening (see Chapter 652).

Allergic Conjunctivitis

Allergic conjunctivitis is the most common hypersensitivity response of the eye, affecting approximately 25% of the general population and 30% of children with atopy. It is caused by direct exposure of the mucosal surfaces of the eye to environmental allergens. Patients complain of variable ocular itching, rather than pain, with increased tearing. Clinical signs include bilateral injected conjunctivae with vascular congestion that may progress to *chemosis*, or conjunctival swelling, and a watery discharge (Fig. 172.1).

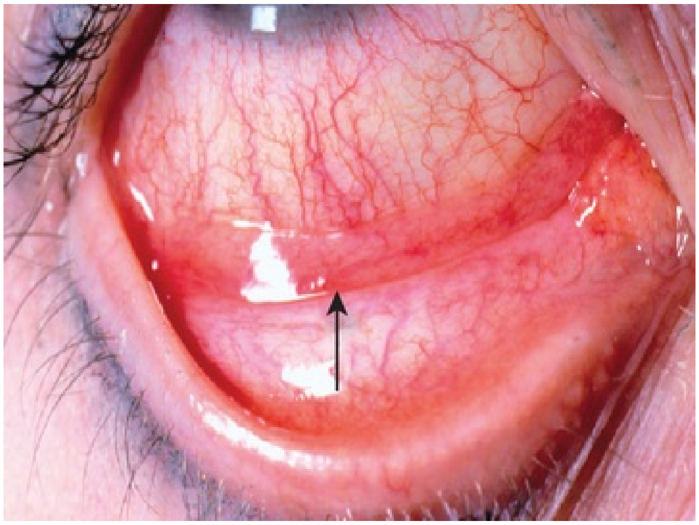

FIG. 172.1 Allergic conjunctivitis. *Arrow* indicates area of chemosis in the conjunctivitis. (From Adkinson NF Jr, Bochner BS, Burks AW, et al, editors: *Middleton's allergy: principles & practice,* ed 8, vol 1, St Louis, Mosby/Elsevier, 2014, p 619.)

Allergic conjunctivitis occurs in a seasonal or, less frequently, perennial form. **Seasonal allergic conjunctivitis** is typically associated with allergic rhinitis (see Chapter 168) and is most commonly triggered by pollens. Major pollen groups in the temperate zones include trees (late winter to early spring), grasses (late spring to early summer), and weeds (late summer to early fall), but seasons can vary significantly in different parts of the United States. Mold spores can also cause seasonal allergy symptoms, principally in the summer and fall. Seasonal allergy symptoms may be aggravated by coincident exposure to perennial allergens. **Perennial allergic conjunctivitis** is triggered by allergens such as animal danders or dust mites that are present throughout the year. Symptoms are usually less severe than with seasonal allergic conjunctivitis. Because pollens and soil molds may be present intermittently by season, and exposure to allergens such as furred animals may be perennial, classification as intermittent (symptoms present <4 days/wk or for <4 wk) and persistent (symptoms present >4 days/wk and for >4 wk) has been proposed.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a severe bilateral chronic inflammatory process of the upper tarsal conjunctival surface that occurs in a limbal or palpebral form. It may threaten eyesight if there is corneal involvement. Although vernal keratoconjunctivitis is not IgE mediated, it occurs most frequently in children with seasonal allergies, asthma, or atopic dermatitis. Vernal keratoconjunctivitis affects boys twice as often as girls and is more common in persons of Asian and African descent. It affects primarily children in temperate areas, with exacerbations in the spring and summer, but can occur throughout the year. Symptoms include severe ocular itching exacerbated by exposure to irritants, light, or perspiration. In addition, patients may complain of severe photophobia, foreign body sensation, and lacrimation. Giant papillae occur predominantly on the upper tarsal plate and are typically described as *cobblestoning* (Fig. 172.2). Other signs include a stringy or thick, ropey discharge, cobblestone papillae, transient yellow-white points in the limbus *(Trantas dots)* and conjunctiva *(Horner points)* , corneal “shield” ulcers, and Dennie lines (Dennie-Morgan folds), which are prominent symmetric skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin. Children with vernal keratoconjunctivitis have measurably longer eyelashes, which may represent a reaction to ocular inflammation.

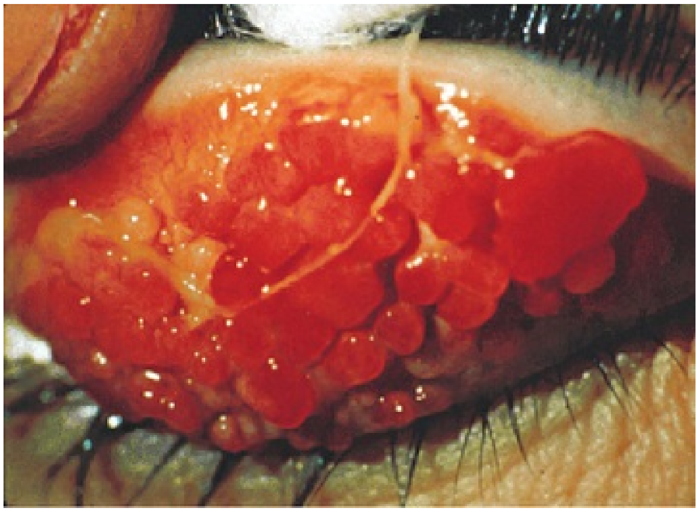

FIG. 172.2 **Vernal keratoconjunctivitis. Cobblestone papillae and ropey discharge are seen on the underside (tarsal conjunctiva) of the upper eyelid. (From Adkinson NF Jr, Bochner BS, Burks AW, et al, editors: *Middleton's allergy: principles & practice,* ed 8, vol 1, St Louis, Mosby/Elsevier, 2014, p 627.)**

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is a chronic inflammatory ocular disorder most often involving the lower tarsal conjunctiva. It may threaten eyesight if there is corneal involvement. Almost all patients have atopic dermatitis, and a significant number have asthma. Atopic keratoconjunctivitis rarely presents before late adolescence. Symptoms include severe bilateral ocular itching, burning, photophobia, and tearing with a mucoid discharge that are much more severe than in allergic conjunctivitis and persist throughout the year. The bulbar conjunctiva is injected and chemotic; cataracts may occur. Trantas dots or giant papillae may also be present. Eyelid eczema can extend to the periorbital skin and cheeks with erythema and thick, dry scaling. Secondary staphylococcal blepharitis is common because of eyelid induration and maceration. Chronic eye rubbing associated with vernal and atopic keratoconjunctivitis can lead to **keratoconus** , a noninflammatory cone-shaped corneal ectasia. This may lead to corneal thinning and perforation.

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis has been linked to chronic exposure to foreign bodies, such as contact lenses, both hard and soft, ocular prostheses, and sutures. Symptoms and signs include mild bilateral ocular itching, tearing, a foreign body sensation, and excessive ocular discomfort with mild mucoid discharge with white or clear exudate on awakening, which may become thick and stringy. Trantas dots, limbal infiltration, bulbar conjunctival hyperemia, and edema may develop.

Contact Allergy

Contact allergy typically involves the eyelids but can also involve the conjunctivae. It is being recognized more frequently in association with increased exposure to topical medications, contact lens solutions, and preservatives.

Diagnosis

Nonallergic conjunctivitis can be viral, bacterial, or chlamydial in origin. It is typically unilateral but can be bilateral with symptoms initially developing in 1 eye (see Chapter 644). Symptoms include stinging or burning rather than itching and often a foreign body sensation. Ocular discharge can be watery, mucoid, or purulent. Masqueraders of ocular allergy also include nasolacrimal duct obstruction, foreign body, blepharoconjunctivitis, dry eye, uveitis, and trauma.

Treatment

Primary treatment of ocular allergies includes avoidance of allergens, cold compresses, and lubrication. **Secondary treatment** regimens include the use of oral or topical antihistamines and, if necessary, topical decongestants, mast cell stabilizers, and antiinflammatory agents (Table 172.1). Drugs with dual antihistamine and mast cell–blocking activities provide the most advantageous approach in treating allergic conjunctivitis, with both fast-acting symptomatic relief and disease-modifying action. Children often complain of stinging or burning with use of topical ophthalmic preparations and usually prefer oral antihistamines for allergic conjunctivitis. It is important not to contaminate topical ocular medications by allowing the applicator tip to contact the eye or eyelid. Using refrigerated medications may decrease some of the discomfort associated with their use. Topical decongestants act as vasoconstrictors, reducing erythema, vascular congestion, and eyelid edema, but do not diminish the allergic response. Adverse effects of topical vasoconstrictors include burning or stinging and rebound hyperemia or conjunctivitis medicamentosa with chronic use. Combined use of an antihistamine and a vasoconstrictor is more effective than use of either agent alone. Use of topical nasal corticosteroids for allergic rhinoconjunctivitis decreases ocular symptoms, presumably through a nasoocular reflex.

Table 172.1

Topical Ophthalmic Medications for Allergic Conjunctivitis

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Azelastine hydrochloride 0.05% Optivar	Antihistamine Children ≥3 yr: 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Emedastine difumarate 0.05% Emadine	Antihistamine Children ≥3 yr: 1 gtt qid	Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.
Levocabastine hydrochloride 0.05% Livostin	Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment.
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms. Not for use with contact lenses.
0.3% Naphazoline	Children >6 yr: 1-2 gtt qid	

hydrochloride		
0.025%		
Naphcon-A, Opcon-A		
Cromolyn sodium 4% Crolom, Opticrom	Mast cell stabilizer Children >4 yr: 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.
Lodoxamide tromethamine 0.1% Alomide	Mast cell stabilizer Children ≥2 yr: 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.
Nedocromil sodium 2% Alocril	Mast cell stabilizer Children ≥3 yr: 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.
Pemirolast potassium 0.1% Alamast	Mast cell stabilizer Children >3 yr: 1-2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Epinastine hydrochloride 0.05% Elestat	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid	Contact lenses should be removed before use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.
Ketotifen fumarate 0.025% Zaditor	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Olopatadine hydrochloride 0.1%, 0.2%, 0.7% Patanol Pataday Pazeo	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart) Children≥2 yr: 1 gtt qd	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer Children > 2 yr: 1 gtt bid q8-12h	Contact lenses should be removed before application; may be inserted after 10 min. Not for the treatment of contact lens irritation.
Bepotastine besilate 1.5% Bepreve	Antihistamine/mast cell stabilizer Children >2 yr: 1 gtt bid q8-12h	Contact lenses should be removed before application, may be inserted after 10 min. Not for the treatment of contact lens irritation.
Ketorolac tromethamine 0.5% Acular	NSAID Children ≥3 yr: 1 gtt qid	Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight threatening. *Do not use while wearing contact lenses.*
Fluorometholone 0.1%, 0.25% suspension (0.1%, 0.25%) and ointment	Fluorinated corticosteroid Children ≥2 yr, 1 gtt into conjunctival sac of affected eye(s) bid-qid. During initial 24-48 hr, dosage may be	If improvement does not occur after 2 days, patient should be reevaluated. Patient should remove soft contact lenses before administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 min after administration. Close monitoring for

(0.1%) FML, FML Forte, Flarex	increased to 1 gtt q4h. Ointment (~1.3 cm in length) into conjunctival sac of affected eye(s) 1-3 times daily. May be applied q4h during initial 24-48 hr of therapy.	development of glaucoma and cataracts.

NSAID, Nonsteroidal antiinflammatory drug; bid, 2 times daily; gtt, drops; qid, 4 times daily; q4-6h; every 4-6 hr; qd, every day.

Tertiary treatment of ocular allergy includes topical (or rarely oral) corticosteroids and should be conducted in conjunction with an ophthalmologist. Local administration of topical corticosteroids may be associated with increased intraocular pressure, viral infections, and cataract formation. Other immunomodulatory medications, such as topical tacrolimus or topical cyclosporine, are used as steroid-sparing agents by ophthalmologists. Allergen immunotherapy can be very effective in seasonal and perennial allergic conjunctivitis, especially when associated with rhinitis, and can decrease the need for oral or topical medications to control allergy symptoms.

Because vernal and atopic keratoconjunctivitis can be associated with visual morbidity, if these diagnoses are suspected, the patient should be referred to an ophthalmologist. *Symptoms that should prompt referral to an ophthalmologist include unilateral red eye with pain, photophobia, change in vision, refractory dry eyes, or corneal abnormality.*

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CHAPTER 173

Urticaria (Hives) and Angioedema

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Urticaria and angioedema affect 20% of individuals at some point in their life. Episodes of hives that last for <6 wk are considered *acute*, whereas those that occur on most days of the week for >6 wk are designated *chronic*. The distinction is important, because the causes and mechanisms of urticaria formation and the therapeutic approaches are different in each instance.

Etiology and Pathogenesis

Acute urticaria and angioedema are often caused by an allergic IgE–mediated reaction (Table 173.1). This form of urticaria is a self-limited process that occurs when an allergen activates mast cells in the skin. Common causes of acute generalized urticaria include foods, drugs (particularly antibiotics), and stinging-insect venoms. If an allergen (latex, animal dander) penetrates the skin locally, hives often can develop at the site of exposure. Acute urticaria can also result from non–IgE-mediated stimulation of mast cells, caused by radiocontrast agents, viral agents (including hepatitis B and Epstein-Barr virus), opiates, and nonsteroidal antiinflammatory drugs (NSAIDs). The diagnosis of **chronic urticaria** is established when lesions occur on most days of the week for >6 wk and are not physical urticaria or recurrent acute urticaria with repeated exposures to a specific agent (Tables 173.2 and 173.3). In about half the cases, chronic urticaria is accompanied by angioedema. Rarely, angioedema occurs without urticaria. Angioedema without urticaria is often a result of allergy, but recurrent angioedema suggests other diagnoses.

Table 173.1

Etiology of Acute Urticaria

Etiology of Acute Urticaria

Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, (direct mast cell degranulation)
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	**Bacterial** (streptococcal pharyngitis, *Mycoplasma* , sinusitis); viral (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); **Parasitic** *(Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella);* **Fungal** (dermatophytes, *Candida*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or IV immune globulin administration

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: *Allergy in primary care* , Philadelphia, 2000, Saunders, p 232.

Table 173.2

Etiology of Chronic Urticaria

Idiopathic/autoimmune	Approximately 30% of chronic urticaria cases are physical urticaria, and 60–70% are idiopathic. Of the idiopathic cases approximately 35–40% have anti-IgE or anti-FcεRI (high-affinity IgE receptor α chain) autoantibodies (autoimmune chronic urticaria)
Physical	Dermatographism
	Cholinergic urticaria
	Cold urticaria (see Table 173.5)
	Delayed pressure urticaria
	Solar urticaria
	Vibratory urticaria
	Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus
	Juvenile idiopathic arthritis
	Thyroid disease (Graves, Hashimoto)
	Celiac disease
	Inflammatory bowel disease
	Leukocytoclastic vasculitis
Autoinflammatory/periodic fever syndromes	See Tables 173.3 and 173.5 .
Neoplastic	Lymphoma
	Mastocytosis
	Leukemia
Angioedema	Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor)
	Acquired angioedema
	Angiotensin-converting enzyme inhibitors

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: *Allergy in primary care* , Philadelphia, 2000, Saunders, p 234.

Table 173.3

Febrile Autoinflammatory Diseases Causing Urticaria in Children

DISEASE	GENE (PROTEIN)	INHERITANCE	ATTACK LENGTH	TIMING OF ONSET	CUTANEOUS FEATURES	EXTRACUTAN CLINICAL FE
FCAS	*NLRP3* (cryopyrin)	AD	Brief; minutes to 3 days	Neonatal or infantile	Cold-induced urticaria	Arthralgia Conjunctiviti Headache
Muckle-Wells syndrome	*NLRP3* (cryopyrin)	AD	1-3 days	Neonatal, infantile, childhood (can be later)	Widespread urticaria	Arthralgia/ar Sensorineura loss Conjunctiviti Headache Amyloidosis
Chronic infantile neurologic cutaneous articular syndrome; neonatal-onset multisystem inflammatory disease	*NLRP3* (cryopyrin)	AD	Continuous flares	Neonatal or infantile	Widespread urticaria	Deforming osteoarthropa epiphyseal o Sensorineura loss Dysmorphic Chronic asep meningitis, h papilledema, Conjunctiviti optic atrophy Growth retar Developmen Amyloidosis
HIDS	*MVK* (mevalonate kinase)	AR	3-7 days	Infancy (<2 yr)	Intermittent morbilliform or urticarial rash Aphthous mucosal ulcers Erythema nodosum	Arthralgia/ar Cervical lymphadenop Severe abdo Diarrhea/von Headache Elevated IgD antibody leve Elevated urin acid during a
Tumor necrosis factor receptor–associated periodic syndrome	*TNFRSF1A* (TNFR1)	AD	>7 days	Childhood	Intermittent migratory erythematous macules and edematous plaques overlying areas of myalgia, often on limbs Periorbital edema	Migratory m Conjunctiviti Serositis Amyloidosis
Systemic-	Polygenic	Varies	Daily	Peak	Nonfixed	Polyarthritis

onset juvenile idiopathic arthritis (SoJIA)			(quotidian)	onset at 1-6 yr	erythematous rash; may be urticarial With or without dermatographism With or without periorbital edema	Myalgia Hepatosplen Lymphadeno Serositis
PLAID	*PLCG2*	AD	N/A	Infancy	Urticaria induced by evaporative cooling Ulcers in cold-exposed areas	Allergies Autoimmune Recurrent sin infections Elevated IgE levels Decreased Ig antibody leve Often elevate antinuclear a titers

AD, Autosomal dominant; AR, autosomal recessive; HIDS, hyperimmunoglobulinemia D syndrome; FCAS, familial cold-induced autoinflammatory syndrome; N/A, not available; PLAID, PLCγ2-associated antibody deficiency and immune dysregulation.

From Youseff MJ, Chiu YE: Eczema and urticaria as manifestations of undiagnosed and rare diseases, *Pediatr Clin North Am* 64:39–56, 2017 (Table 2, pp 49–50).

A typical **hive** is an erythematous, pruritic, raised wheal that blanches with pressure, is transient, and resolves without residual lesions, unless the area was intensely scratched. In contrast, urticaria associated with serum sickness reactions, systemic lupus erythematosus (SLE), or other vasculitides in which a skin biopsy reveals a small-vessel vasculitis, often have distinguishing clinical features. Lesions that burn more than itch, last >24 hr, do not blanch, blister, heal with scarring, or that are associated with bleeding into the skin (purpura) suggest urticarial vasculitis. Atypical aspects of the gross appearance of the hives or associated symptoms should heighten concern that the urticaria or angioedema may be the manifestation of a systemic disease process (Table 173.4).

Table 173.4

Distinguishing Features Between Urticaria and Systemic Urticarial Syndromes

COMMON URTICARIA	URTICARIAL SYNDROMES (≥1 of following)
Only typical wheals: Erythematous edematous lesions Transient (<24-36 hr) Asymmetric distribution Resolution without signs No associated different elementary lesions (papules, vesicles, purpura, crustae)	Atypical “wheals”: Infiltrated plaques Persistent (>24-36 hr) Symmetric distribution Resolution with signs (hypo/hyperpigmentation, bruising, or scarring) Associated different elementary lesions (papules, vesicles, purpura, scaling, crustae)

Pruritic (rarely stinging/burning) Possibly associated with angioedema No associated systemic symptoms	Not pruritic; rather painful or burning Usually no associated angioedema Often associated with systemic symptoms (fever, malaise, arthralgia, abdominal pain, weight loss, acral circulatory abnormalities, neurologic signs

From Peroni A, Colato C, Zanoni G, Girolomoni G: Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria, *J Am Acad Dermatol* 62(4):559, 2009.

Physical Urticaria

Physically induced urticaria and angioedema share the common property of being induced by an environmental stimulus, such as a change in temperature or direct stimulation of the skin with pressure, stroking, vibration, or light (see Table 173.2).

Cold-Dependent Disorders

Cold urticaria is characterized by the development of localized pruritus, erythema, and urticaria/angioedema after exposure to a cold stimulus. Total body exposure, as seen with swimming in cold water, can cause massive release of vasoactive mediators, resulting in hypotension, loss of consciousness, and even death if not promptly treated. The diagnosis is confirmed by challenge testing for an *isomorphic cold reaction* by holding an ice cube in place on the patient's skin for 5 min. In patients with cold urticaria, an urticarial lesion develops about 10 min after removal of the ice cube and on rewarming of the chilled skin. Cold urticaria can be associated with the presence of **cryoproteins** such as cold agglutinins, cryoglobulins, cryofibrinogen, and the Donath-Landsteiner antibody seen in secondary syphilis (paroxysmal cold hemoglobinuria). In patients with cryoglobulins the isolated proteins appear to transfer cold sensitivity and activate the complement cascade on in vitro incubation with normal plasma. The term **idiopathic cold urticaria** generally applies to patients without abnormal circulating plasma proteins such as cryoglobulins. Cold urticaria has also been reported after viral infections. Cold urticaria must be distinguished from the **familial cold autoinflammatory syndrome** (see later, Diagnosis) (Table 173.5 ; see also Table 173.3 and Chapter 188).

Table 173.5

Hereditary Diseases With Cold-Induced Urticaria

		EPISODIC SYMPTOMS	SUSTAINED/PROGRESSIVE SYMPTOMS
CAPS	FCAS	Urticarial rash, arthralgia, myalgia, chills, fever, swelling of extremities	Renal amyloidosis
	MWS	Urticarial rash, arthralgia, chills, fever	Sensorineural deafness, renal amyloidosis
	CINCA	Fever	Rash, arthritis, chronic meningitis, visual defect, deafness, growth retardation, renal amyloidosis
NAPS12 (FCAS2)		Fever, arthralgia, myalgia, urticaria, abdominal pain, aphthous ulcers, lymphadenopathy	Sensorineural deafness
PLAID (FCAS3)		Urticaria induced by evaporative cooling, sinopulmonary infections	Serum low IgM and IgA levels; high IgE levels; decreased B and NK cells; granulomata; antinuclear antibodies

CAPS, Cryopyrin-associated periodic syndromes; FCAS, familial cold-induced autoinflammatory syndrome; MWS, Muckle-Wells syndrome; CINCA, chronic infantile neurologic cutaneous articular syndrome; NAPS, NLRP-12–associated periodic syndrome; PLAID, PLCG2-associated antibody deficiency and immune dysregulation.

From Kanazawa N: Hereditary disorders presenting with urticaria, *Immunol Allergy Clin NORTH Am* 34:169–179, 2014 (Table 4, p 176).

Cholinergic Urticaria

Cholinergic urticaria is characterized by the onset of small, punctate pruritic wheals surrounded by a prominent erythematous flare and associated with exercise, hot showers, and sweating. Once the patient cools down, the rash usually subsides in 30-60 min. Occasionally, symptoms of more generalized cholinergic stimulation, such as lacrimation, wheezing, salivation, and syncope, are observed. These symptoms are mediated by cholinergic nerve fibers that innervate the musculature via parasympathetic neurons and innervate the sweat glands by cholinergic fibers that travel with the sympathetic nerves. Elevated plasma histamine values parallel the onset of urticaria triggered by changes in body temperature.

Dermatographism

The ability to write on skin, dermatographism (also called *dermographism* or *urticaria factitia*) may occur as an isolated disorder or may accompany chronic urticaria or other physical urticaria. It can be diagnosed by observing the skin after stroking it with a tongue depressor. In patients with dermatographism, a linear response occurs secondary to reflex vasoconstriction, followed by pruritus, erythema, and a linear flare caused by secondary dilation of the vessel and extravasation of plasma.

Pressure-Induced Urticaria and Angioedema

Pressure-induced urticaria differs from most types of urticaria or angioedema in that symptoms typically occur 4-6 hr after pressure has been applied. The disorder is clinically heterogeneous. Some patients may complain of swelling, with or without pruritus, secondary to pressure, with normal-appearing skin (no urticaria), so the term *angioedema* is more appropriate. Other lesions are predominantly urticarial and may or may not be associated with significant swelling. When urticaria is present, an infiltrative skin lesion is seen, characterized by a perivascular mononuclear cell infiltrate and dermal edema similar to that seen in chronic idiopathic urticaria. Symptoms occur at sites of tight clothing; foot swelling is common after walking; and buttock swelling may be prominent after sitting for a few hours. This condition can coexist with chronic idiopathic urticaria or can occur separately. The diagnosis is confirmed by challenge testing in which pressure is applied perpendicular to the skin. This is often done with a sling attached to a 10 lb weight that is placed over the patient's arm for 20 min.

Solar Urticaria

Solar urticaria is a rare disorder in which urticaria develops within minutes of direct sun exposure. Typically, pruritus occurs first, in approximately 30 sec, followed by edema confined to the light-exposed area and surrounded by a prominent erythematous zone. The lesions usually disappear within 1-3 hr after cessation of sun exposure. When large areas of the body are exposed, systemic symptoms may occur, including hypotension and wheezing. Solar urticaria has been classified into 6 types, depending on the wavelength of light that induces skin lesions and the ability or inability to transfer the disorder passively with serum IgE. The rare inborn error of metabolism **erythropoietic protoporphyria** can be confused with solar urticaria because of the development of itching and burning of exposed skin immediately after sun exposure. In erythropoietic protoporphyria, fluorescence of ultraviolet-irradiated red blood cells can be demonstrated, and protoporphyrins are found in the urine.

Aquagenic Urticaria

Patients with aquagenic urticaria demonstrate small wheals after contact with water, regardless of its temperature, and are thereby distinguishable from patients with cold urticaria or cholinergic urticaria. Direct application of a compress of water to the skin is used to test for the presence of aquagenic urticaria. Rarely, chlorine or other trace contaminants may be responsible for the reaction.

Chronic Idiopathic Urticaria and Angioedema

A common disorder of unknown origin, chronic idiopathic urticaria and angioedema is often associated with normal routine laboratory values and no evidence of systemic disease. Chronic urticaria does not appear to result from an allergic reaction. It differs from allergen-induced skin reactions and from physically induced urticaria in that histologic studies reveal cellular infiltrate predominantly around small venules. Skin examination reveals infiltrative hives with palpably elevated borders, sometimes varying greatly in size and shape but generally being rounded.

Biopsy of a typical lesion reveals nonnecrotizing, perivascular, mononuclear cellular infiltration. Varying histopathologic processes can occur in the skin and manifest as urticaria. Patients with **hypocomplementemia** and **cutaneous vasculitis** can have urticaria and/or angioedema. Biopsy of these lesions in patients with urticaria, arthralgias, myalgias, and an elevated erythrocyte sedimentation rate (ESR) as manifestations of necrotizing venulitis can reveal fibrinoid necrosis with a predominantly neutrophilic infiltrate. However, the urticarial lesions may be clinically indistinguishable from those seen in the more typical, nonvasculitic cases.

Chronic urticaria is increasingly associated with the presence of antithyroid antibodies. Affected patients generally have antibodies to thyroglobulin or a microsomally derived antigen (peroxidase), even if they are euthyroid. The incidence of elevated thyroid antibodies in patients with chronic urticaria is approximately 12%, compared with 3–6% in the general population. Although some patients show clinical reduction of the urticaria with thyroid replacement therapy, others do not. The role of thyroid autoantibodies in chronic urticaria is uncertain; their presence may reflect a tendency of the patient to develop autoantibodies, but they may not play a direct role in chronic urticaria. Of patients with chronic urticaria, 35–40% have a positive **autologous serum skin test** result: If serum from these patients is intradermally injected into their skin, a significant wheal and flare reaction develops. Such patients frequently have a complement-activating IgG antibody directed against the α subunit of the IgE receptor that can cross-link the IgE receptor (α subunit) and degranulate mast cells and basophils. An additional 5–10% of patients with chronic urticaria have anti-IgE antibodies rather than an anti–IgE receptor antibody.

Diagnosis

The diagnosis of both acute and chronic urticaria is primarily clinical and requires that the physician be aware of the various forms of urticaria.

Urticaria is transient, pruritic, erythematous, raised wheals that may become tense and painful. The lesions may coalesce and form polymorphous, serpiginous, or annular lesions (Figs. 173.1 and 173.2). Individual lesions usually last 20 min to 3 hr and rarely more than 24 hr. The lesions often disappear, only to reappear at another site. **Angioedema** involves the deeper subcutaneous tissues in locations such as the eyelids, lips, tongue, genitals, dorsum of the hands or feet, or wall of the gastrointestinal (GI) tract.

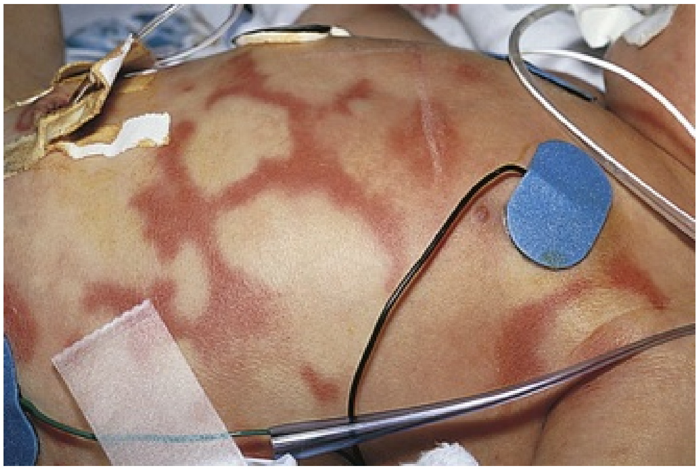

FIG. 173.1 Polycyclic lesions of urticaria associated with prostaglandin E_2 infusion. (From Eichenfield LF, Friedan IJ, Esterly NB: *Textbook of neonatal dermatology* , Philadelphia, 2001, WB Saunders, p. 300.)

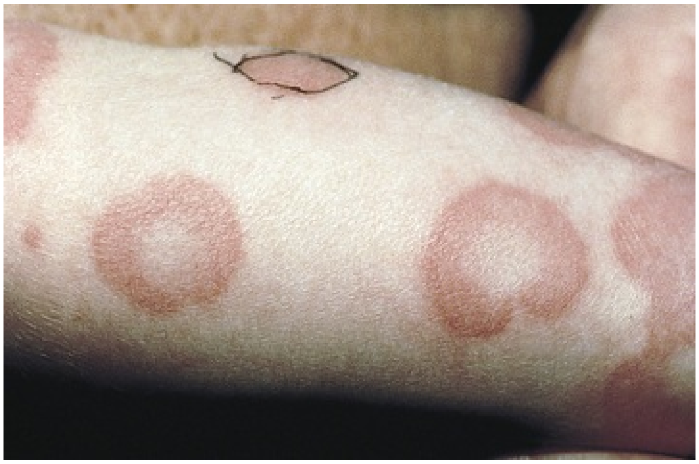

FIG. 173.2 Annular urticaria of unknown etiology. (From Eichenfield LF, Friedan IJ, Esterly NB: *Textbook of neonatal dermatology* , Philadelphia, 2001, WB Saunders, p. 301.)

Drugs and foods are the most common causes of acute urticaria. In children, viral infections also frequently trigger hives. Allergy skin testing for foods can be helpful in sorting out causes of acute urticaria, especially when supported by historical evidence. The role of an offending food can then be proved by elimination and careful challenge in a controlled setting, when needed. In the absence of information implicating an ingestant cause, skin testing for foods and implementation of elimination diets are generally not useful for either acute or chronic urticaria. Patients with delayed urticaria 3-6 hr after a meal consisting of mammalian meat should be evaluated for IgE to galactose-α-1,3-galactose (“alpha-gal”), a carbohydrate allergen. Alpha-gal has been identified as a trigger in this circumstance, with sensitization apparently linked to tick bites in specific geographic regions, such as the mid-Atlantic area of the United States. Skin testing for aeroallergens is not indicated unless there is a concern about contact urticaria (animal dander or grass pollen). Dermatographism is common in patients with urticaria and can complicate allergy skin testing by causing false-positive reactions, but this distinction is usually discernible.

Autoimmune diseases are rare causes of chronic urticarial or angioedema. In vitro testing for serum-derived activity that activates basophils involves detection of the expression of the surface marker CD63 or CD203c by donor basophils after incubation with patient serum. The clinical applicability and significance of these tests remains debated. The **differential diagnosis** of chronic urticaria includes cutaneous or systemic mastocytosis, complement-mediated mast cell degranulation as may occur with circulating immune complexes, malignancies, mixed connective tissue diseases, and cutaneous blistering disorders (e.g., bullous pemphigoid; see Table 173.2). In general, laboratory testing should be limited to a complete blood cell count with differential, ESR determination, urinalysis, thyroid autoantibody testing, and liver function tests. Further studies are warranted if the patient has fever, arthralgias, or elevated ESR (Table 173.6 ; see also Table 173.4). Testing for antibodies directed at the high-affinity IgE receptor may be warranted in patients with intractable urticaria. **Hereditary angioedema** is potentially life threatening, usually associated with deficient C1 inhibitor activity, and the most important familial form of angioedema (see Chapter 160.3), but it is not associated with typical urticaria. In patients with eosinophilia, stools should be obtained for ova and parasite testing, because infection with helminthic parasites has been associated with urticaria. A syndrome of episodic angioedema/urticaria and fever with associated **eosinophilia** has been described in both adults and children. In contrast to other hypereosinophilic syndromes, this entity has a benign course.

Table 173.6

Diagnostic Testing for Urticaria and Angioedema

DIAGNOSIS	DIAGNOSTIC TESTING
Food and drug reactions	Elimination of offending agent, skin testing, and challenge with suspected foods
Autoimmune urticaria	Autologous serum skin test; antithyroid antibodies; antibodies against the high-affinity IgE receptor
Thyroiditis	Thyroid-stimulating hormone; antithyroid antibodies
Infections	Appropriate cultures or serology
Collagen vascular diseases and cutaneous vasculitis	Skin biopsy, CH_{50} , C1q, C4, C3, factor B, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins
Malignancy with angioedema	CH_{50} , C1q, C4, C1-INH determinations
Cold urticaria	Ice cube test usually positive but may be negative in some familial autoinflammatory disorders
Solar urticaria	Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin
Dermatographism	Stroking with narrow object (e.g., tongue blade, fingernail)
Pressure urticaria	Application of pressure for defined time and intensity
Vibratory urticaria	Vibration for 4 min
Aquagenic urticaria	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermatographism
Hereditary angioedema	C4, C2, CH_{50} , C1-INH testing by protein and function
Familial cold urticaria	Challenge by cold exposure, measurement of temperature, white blood cell count, erythrocyte sedimentation rate, skin biopsy
C3b inactivator deficiency	C3, factor B, C3b inactivator determinations
Chronic idiopathic urticaria	Skin biopsy, immunofluorescence (negative result), autologous skin test

Skin biopsy for diagnosis of possible **urticarial vasculitis** is recommended for urticarial lesions that persist at the same location for >24 hr, those with pigmented or purpuric components, and those that burn more than itch. Collagen vascular diseases such as SLE may manifest urticarial vasculitis as a presenting feature. The skin biopsy in urticarial vasculitis typically shows endothelial cell swelling of postcapillary venules with necrosis of the vessel wall, perivenular neutrophil infiltrate, diapedesis of red blood cells, and fibrin deposition associated with deposition of immune complexes.

Mastocytosis is characterized by mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, and skin. Clinical effects of mast cell activation are common, including pruritus, flushing, urtication, abdominal pain, nausea, and vomiting. The diagnosis is confirmed by a bone marrow biopsy showing increased numbers of spindle-shaped mast cells that express CD2 and CD25. **Urticaria pigmentosa** is the most common skin manifestation of mastocytosis and may occur as an isolated skin finding. It appears as small, yellow-tan to reddish brown macules or raised papules that urticate on scratching (**Darier sign**). This sign can be masked by antihistamines. The diagnosis is confirmed by a skin biopsy that shows increased numbers of dermal mast cells.

Physical urticaria should be considered in any patient with chronic urticaria and a suggestive history (see Table 173.2). Papular urticaria often occurs in small children, generally on the extremities. It manifests as grouped or linear, highly pruritic wheals or papules mainly on exposed skin at the sites of insect bites.

Exercise-induced anaphylaxis manifests as varying combinations of pruritus, urticaria, angioedema, wheezing, laryngeal obstruction, or hypotension after exercise (see Chapter 174). Cholinergic urticaria is differentiated by positive results of heat challenge tests and the rare occurrence of anaphylactic shock. The combination of ingestion of various food allergens and postprandial exercise has been associated with urticaria/angioedema and anaphylaxis. In patients with this combination disorder, food or exercise alone does not produce the reaction.

Muckle-Wells syndrome and familial cold autoinflammatory syndrome are rare, dominantly inherited conditions associated with recurrent urticaria-like lesions. **Muckle-Wells syndrome** is characterized by arthritis and joint pain that usually appears in adolescence. It is associated with progressive nerve deafness, recurrent fever, elevated ESR (see Tables 173.3 and 173.5), hypergammaglobulinemia, renal amyloidosis, and a poor prognosis. **Familial cold autoinflammatory syndrome** is characterized by a cold-induced rash that has urticarial features but is rarely pruritic. Cold exposure leads to additional symptoms such as conjunctivitis, sweating, headache, and nausea. Patient longevity is usually normal.

Treatment

Acute urticaria is a self-limited illness requiring little treatment other than antihistamines and avoidance of any identified trigger. Hydroxyzine and diphenhydramine are sedating but are effective and frequently used for treatment of urticaria. Loratadine, fexofenadine, and cetirizine are also effective and are preferable because of reduced frequency of drowsiness and longer duration of action (Table 173.7). Epinephrine 1 : 1,000, 0.01 mL/kg (maximum 0.3 mL) intramuscularly, usually provides rapid relief of acute, severe urticaria/angioedema but is seldom required. A short course of oral corticosteroids should be given only for severe episodes of urticaria and angioedema that are unresponsive to antihistamines.

Table 173.7

Treatment of Urticaria and Angioedema

CLASS/DRUG	DOSE	FREQUENCY
ANTIHISTAMINES, TYPE H_1 (SECOND GENERATION)		
Fexofenadine	6-11 yr: 30 mg	Twice daily
	>12 yr: 60 mg	
	Adult: 180 mg	Once daily
Loratadine	2-5 yr: 5 mg	Once daily
	>6 yr: 10 mg	
Desloratadine	6-11 mo: 1 mg 12 mo-5 yr: 1.25 mg	Once daily
	6-11 yr: 2.5 mg >12 yr: 5 mg	
Cetirizine	6-23 mo: 2.5 mg	Once daily
	2-6 yr: 2.5-5 mg	
	>6 yr: 5-10 mg	
Levocetirizine	6 mo-5 yr: 1.25 mg	Once daily
	6-11 yr: 2.5 mg	Once daily
	>12 yr: 5 mg	Once daily
ANTIHISTAMINES, TYPE H_2		
Cimetidine	Infants: 10-20 mg/kg/day	Divided q6-12h
	Children: 20-40 mg/kg/day	
Ranitidine	1 mo-16 yr: 5-10 mg/kg/day	Divided q12h
Famotidine	3-12 mo: 1 mg/kg/day	Divided q12h
	1-16 yr: 1-2 mg/kg/day	
LEUKOTRIENE PATHWAY MODIFIERS		

Montelukast	12 mo-5 yr: 4 mg	Once daily
	6-14 yr: 5 mg	
	>14 yr: 10 mg	
Zafirlukast	5-11 yr: 10 mg	Twice daily
IMMUNOMODULATORY DRUGS		
Omalizumab (anti IgE)	>11 yr: 150 mg or 300 mg	Every 28 days
Cyclosporine	3-4 mg/kg/day	Divided q12h[*]
Sulfasalazine	>6 yr: 30 mg/kg/day	Divided q6h [†]
Intravenous immune globulin (IVIG)	400 mg/kg/day	5 consecutive days

[*] Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

[†] Monitor complete blood count and liver function tests at baseline, every 2 wk for 3 mo, and then every 1-3 mo.

The best treatment of physical urticaria is avoidance of the stimulus. Antihistamines are also helpful. Cyproheptadine in divided doses is the drug of choice for cold-induced urticaria. Treatment of dermatographism consists of local skin care and antihistamines; for severe symptoms, high doses may be needed. The initial objective of therapy is to decrease pruritus so that the stimulation for scratching is diminished. A combination of antihistamines, sunscreens, and avoidance of sunlight is helpful for most patients.

Chronic urticaria only rarely responds favorably to dietary manipulation. The mainstay of therapy is the use of nonsedating or low-sedating H_1 antihistamines. In those patients not showing response to standard doses, pushing the H_1 blockade with higher than the usual recommended doses of these agents is a common next approach. The 3-drug combination of H_1 and H_2 antihistamine with a leukotriene receptor antagonist (montelukast) is helpful for many patients. If hives persist after maximal H_1 - and/or H_2 -receptor blockade has been achieved, a brief course of oral corticosteroids may be considered, but long-term steroid use is best avoided. The monoclonal antibody omalizumab (anti-IgE) is FDA approved for the treatment of chronic urticaria in children 12 years and older. Other agents that have been used for chronic urticaria but are not approved by the U.S. Food and Drug Administration (FDA) for this condition include cyclosporine, hydroxychloroquine, sulfasalazine, colchicine, dapsone, mycophenolate, intravenous immune globulin (IVIG), and plasmapheresis.

Hereditary Angioedema

Hereditary angioedema (**HAE** , types 1 and 2) is an inherited autosomal dominant disease caused by low functional levels of the plasma protein **C1**

inhibitor (C1-INH) (see Chapter 160.3). Patients typically report episodic attacks of angioedema or deep localized swelling, most often on a hand or foot, that begin during childhood and become much more severe during adolescence. Cutaneous nonpitting and nonpruritic edema not associated with urticaria is the most common symptom. The swelling usually becomes more severe over about 1.5 days and then resolves over about the same period. However, the duration of attacks can be quite variable. In some patients, attacks are preceded by the development of a rash, **erythema marginatum** , that is erythematous, not raised, and not pruritic. A 2nd major symptom complex noted by patients is attacks of severe abdominal pain caused by edema of the mucosa of any portion of the GI tract. The intensity of the pain can approximate that of an acute abdomen, often resulting in unnecessary surgery. Either constipation or diarrhea during these attacks can be noted. The GI edema generally follows the same time course to resolution as the cutaneous attacks and often does not occur at the same time as the peripheral edema. Patients usually have a *prodrome*, a tightness or tingling in the area that will swell, usually lasting several hours, followed by the development of angioedema.

Laryngeal edema , the most feared complication of HAE, can cause complete respiratory obstruction. Although life-threatening attacks are infrequent, more than half of patients with HAE experience laryngeal involvement at some time during their lives. Dental work with the injection of procaine hydrochloride (Novocain) into the gums is a common precipitant, but laryngeal edema can be spontaneous. The clinical condition may deteriorate rapidly, progressing through mild discomfort to complete airway obstruction over hours. Soft tissue edema can be readily seen when the disease involves the throat and uvula. If this edema progresses to difficulty swallowing secretions or a change in the tone of the voice, the patient may require emergency intubation or even tracheostomy to ensure an adequate airway. Other presentations are less common. These patients typically do not respond well to treatment with epinephrine, antihistamines, or glucocorticoids.

In most cases the cause of the attack is unknown, but in some patients, trauma or emotional stress clearly precipitates attacks. Drugs such as angiotensin-converting enzyme (ACE) inhibitors that inhibit the degradation of bradykinin make the disease strikingly worse, and estrogens also make attacks more severe. In some females, menstruation also regularly induces attacks. The frequency of attacks varies greatly among affected individuals and at different times in the same individual. Some individuals experience weekly episodes, whereas others may go years between attacks. Episodes can start at any age.

C1-INH is a member of the serpin family of proteases, similar to α-antitrypsin, antithrombin III, and angiotensinogen. These proteins stoichiometrically inactivate their target proteases by forming stable, 1 : 1 complexes with the protein to be inhibited. Synthesized primarily by hepatocytes, C1-INH is also synthesized by monocytes. The regulation of the protein production is not completely understood, but it is believed that androgens may stimulate C1-INH synthesis, because patients with the disorder respond clinically to androgen therapy with elevated serum C1-INH levels. C1-INH deficiency is an autosomal dominant disease, with as many as 25% of patients giving no family history. Because all C1-INH–deficient patients are heterozygous for this gene defect, it is believed that half the normal level of C1-INH is not sufficient to prevent attacks. Fig. 173.3 shows the diagnostic approach.

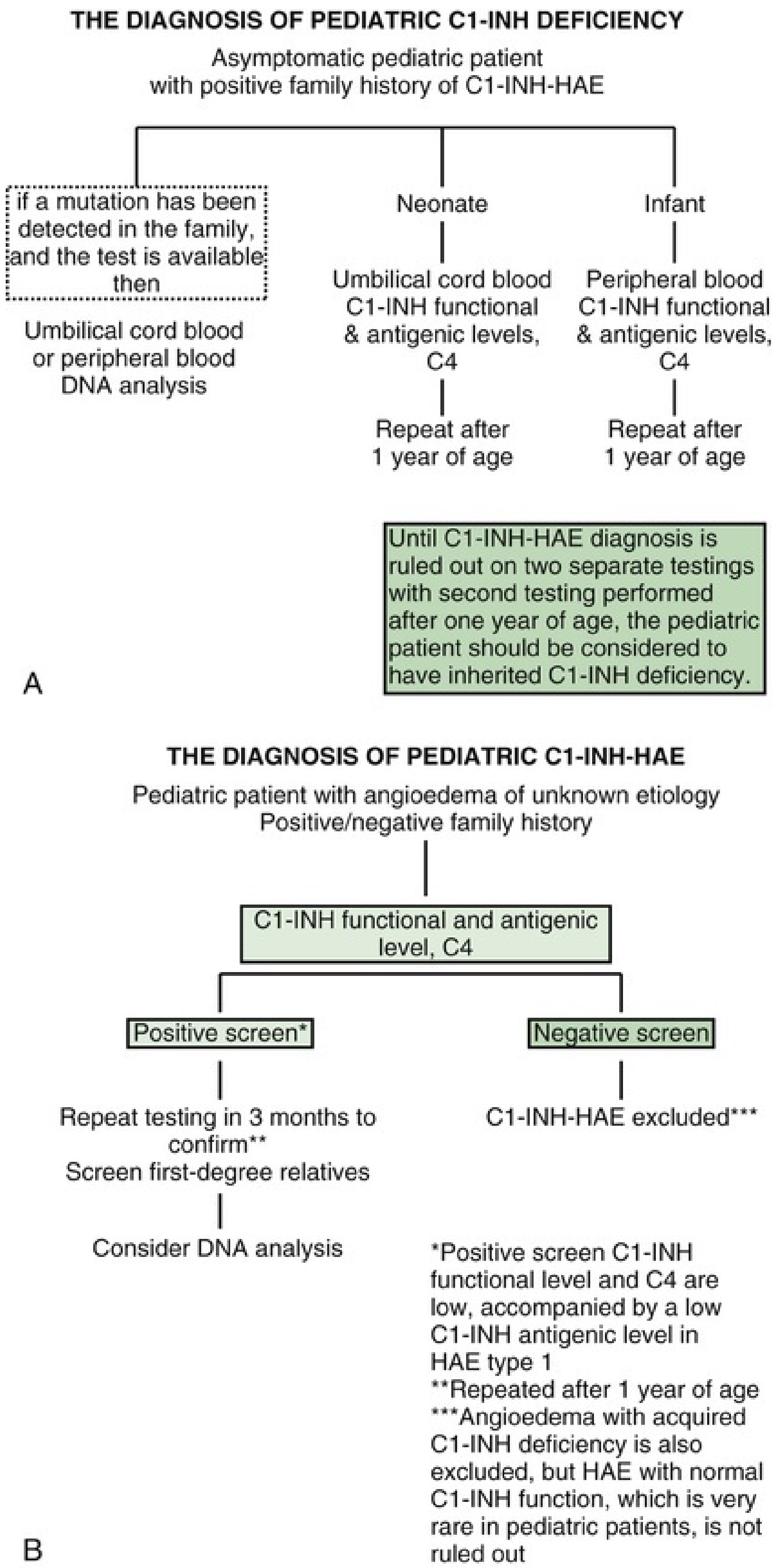
THE DIAGNOSIS OF PEDIATRIC C1-INH DEFICIENCY
Asymptomatic pediatric patient with positive family history of C1-INH-HAE
if a mutation has been detected in the family, and the test is available then
Umbilical cord blood or peripheral blood DNA analysis
Neonate
Umbilical cord blood C1-INH functional & antigenic levels, C4
Repeat after 1 year of age
Infant
Peripheral blood C1-INH functional & antigenic levels, C4
Repeat after 1 year of age
Until C1-INH-HAE diagnosis is ruled out on two separate testings with second testing performed after one year of age, the pediatric patient should be considered to have inherited C1-INH deficiency.
A
THE DIAGNOSIS OF PEDIATRIC C1-INH-HAE
Pediatric patient with angioedema of unknown etiology Positive/negative family history
C1-INH functional and antigenic level, C4
Positive screen*
Repeat testing in 3 months to confirm**
Screen first-degree relatives
Consider DNA analysis
Negative screen
C1-INH-HAE excluded***
*Positive screen C1-INH functional level and C4 are low, accompanied by a low C1-INH antigenic level in HAE type 1
**Repeated after 1 year of age
***Angioedema with acquired C1-INH deficiency is also excluded, but HAE with normal C1-INH function, which is very rare in pediatric patients, is not ruled out
B

FIG. 173.3 **A,** Diagnosis of C1-INH deficiency in families with known C1-INH-HAE. **B,** Diagnosis of C1-INH-HAE in pediatric patients with

angioedema of unknown etiology. (From Farkas H, Martinez-Saguer I, Bork K, et al: International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. Eur J Allergy Clin Immunol 72:300-313, 2017, Fig.1, p. 304.)

Although named for its action on the 1st component of complement (C1 esterase), C1-INH also inhibits components of the fibrinolytic, clotting, and kinin pathways. Specifically, C1-INH inactivates plasmin-activated Hageman factor (factor XII), activated factor XI, plasma thromboplastin antecedent, and kallikrein. Within the complement system, C1-INH blocks the activation of C1 and the rest of the classical complement pathway by binding to C1r and C1s. Without adequate C1-INH, unchecked activation of C1 causes cleavage of C4 and C2, the proteins following in the complement cascade. Levels of C3 are normal. C1-INH also inhibits serine proteases associated with activation of the lectin activation pathway. The major factor responsible for the edema formation is bradykinin, an important nonapeptide mediator that can induce leakage of postcapillary venules. Bradykinin is derived from cleavage of the circulating protein high-molecular-weight kininogen by the plasma enzyme kallikrein.

Two major genetic types of C1-INH deficiency are described that result in essentially the same phenotypic expression. The C1-INH gene is located on chromosome 11 in the p11-q13 region. The inheritance is autosomal dominant with incomplete penetrance. Persons inheriting the abnormal gene can have a clinical spectrum ranging from asymptomatic to severely affected. **Type 1** HAE is the most common form, accounting for approximately 85% of cases. Synthesis of C1-INH is blocked at the site of the faulty allele, or the protein is not secreted normally because of faulty protein processing, but secretion occurs at the normal allele. The result is secretion of the normal protein, yielding quantitative serum concentrations of C1-INH approximately 20–40% of normal. **Type 2** HAE accounts for approximately 15% of cases. Mutations of 1 of the amino acids near the active site of the inhibitor lead to synthesis of nonfunctional C1-INH protein and again less than half of the normal functioning protein. Patients with type 2 HAE have either normal or increased concentrations of the protein but low values in assays of C1-INH function.

A clinical syndrome resembling HAE termed **HAE with normal C1-INH** has been described that affects mostly women, with a tendency to cause fewer abdominal attacks and more upper airway attacks. In this condition, no abnormalities of complement or of C1-INH have been described. Approximately 20% of affected patients have been found to have a gain-of-function abnormality of clotting factor XII, but the fundamental cause is of this syndrome still unknown.

The FDA has approved purified C1-INH for prophylaxis to prevent attacks. **Androgens** like the gonadotropin inhibitor danazol were previously used to prevent attacks. Weak androgens have many side effects that preclude their use in some patients. Their use in children is problematic because of the possibility of premature closure of the epiphyses, and these agents are not used in pregnant women. The fibrinolysis inhibitor ε-aminocaproic acid (**EACA**) is also effective in preventing attacks and has been used in children, but its use is attended by the development of severe fatigue and muscle weakness over time. A cyclized analog of EACA, **tranexamic acid** , has been used extensively in Europe; because of limited availability, it has been used less extensively in the United States. Tranexamic acid is believed to be more effective than EACA and has lower toxicity, but there have been few direct studies. Its mechanism of action is not clearly defined, and not all patients respond to this agent.

In 2008 the FDA approved, for adolescents and older patients, the use of purified C1-INH (Cinryze), prepared from human plasma and given intravenously, for *prophylaxis* of this disease. The half-life of this plasma protein is relatively short, about 40 hr, and the approved regimen is 1,000 units twice a week. In 2009 a similar purified C1-inhibitor product, Berinert, administered as 20 U/kg intravenously, was approved for the *treatment* of acute attacks. A recombinant C1-INH product has been FDA approved for *treatment* of acute attacks (and in Europe). In 2009 the FDA approved a kallikrein inhibitor, **ecallantide** , given subcutaneously, for *acute treatment* in patients age 16 yr and older. This 60–amino acid peptide causes anaphylaxis rarely and is approved only for administration by medical personnel. In 2010 a bradykinin type 2 receptor antagonist, **icatibant** , was approved for *acute treatment* in patients age 18 yr and older and in summer 2016 was approved for the treatment of all children. All treatments are most effective when given early in an attack and begin to have noticeable effect about 1-4 hr after treatment.

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CHAPTER 174

Anaphylaxis

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Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. Anaphylaxis in children, particularly infants, is underdiagnosed. Anaphylaxis occurs when there is a sudden release of potent, biologically active mediators from mast cells and basophils, leading to cutaneous (urticaria, angioedema, flushing), respiratory (bronchospasm, laryngeal edema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (nausea, colicky abdominal pain, vomiting, diarrhea) symptoms (Table 174.1 and Fig. 174.1).

Table 174.1

Symptoms and Signs of Anaphylaxis in Infants

ANAPHYLAXIS SYMPTOMS THAT INFANTS CANNOT DESCRIBE	ANAPHYLAXIS SIGNS THAT MAY BE DIFFICULT TO INTERPRET/UNHELPFUL IN INFANTS, AND WHY	ANAPHYLAXIS SIGNS IN INFANTS
GENERAL		
Feeling of warmth, weakness, anxiety, apprehension, impending doom	Nonspecific behavioral changes such as persistent crying, fussing, irritability, fright, suddenly becoming quiet	
SKIN/MUCOUS MEMBRANES		
Itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, etc.; mouth-tingling or metallic taste	Flushing (may also occur with fever, hyperthermia, or crying spells)	Rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations will be absent in young infants); angioedema (face, tongue, oropharynx)
RESPIRATORY SYSTEM		

Nasal congestion, throat tightness; chest tightness; shortness of breath	Hoarseness, dysphonia (common after a crying spell); drooling or increased secretions (common in infants)	Rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis
GASTROINTESTINAL SYSTEM		
Dysphagia, nausea, abdominal pain/cramping	Spitting up/regurgitation (common after feeds), loose stools (normal in infants, especially if breastfed); colicky abdominal pain	Sudden, profuse vomiting
CARDIOVASCULAR SYSTEM		
Feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing	Hypotension (need appropriate-size blood pressure cuff; low systolic blood pressure for children is defined as <70 mm Hg from 1 mo to 1 yr, and less than (70 mm Hg + [2 × age in yr]) from 1-10 yr; tachycardia, defined as >140 beats/min from 3 mo to 2 yr, inclusive; loss of bowel and bladder control (ubiquitous in infants)	Weak pulse, arrhythmia, diaphoresis/sweating, collapse/unconsciousness
CENTRAL NERVOUS SYSTEM		
Headache	Drowsiness, somnolence (common in infants after feeds)	Rapid onset of unresponsiveness, lethargy, or hypotonia; seizures

Adapted from Simons FER: Anaphylaxis in infants: can recognition and management be improved? *J Allergy Clin Immunol* 120:537–540, 2007.

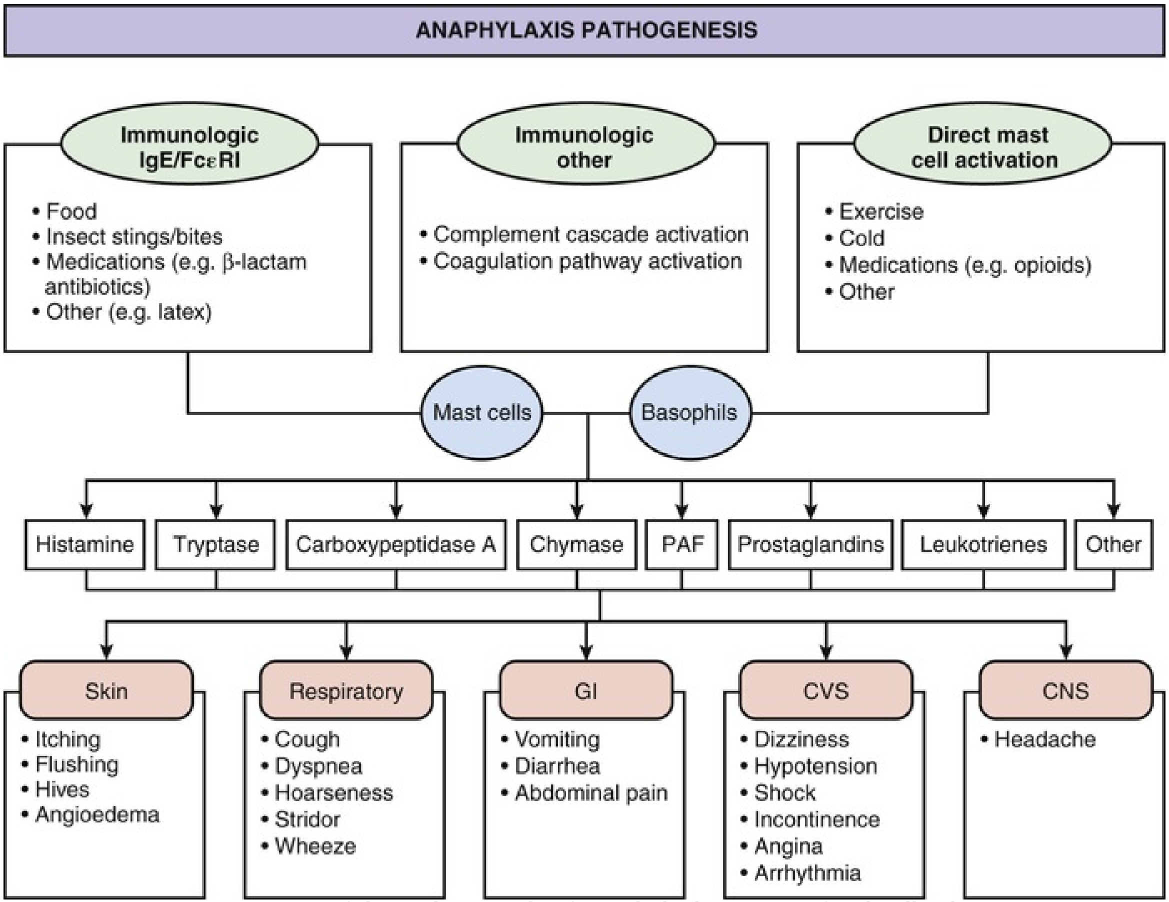
ANAPHYLAXIS PATHOGENESIS
Immunologic IgE/FcεRI
• Food
• Insect stings/bites
• Medications (e.g. β-lactam antibiotics)
• Other (e.g. latex)
Immunologic other
• Complement cascade activation
• Coagulation pathway activation
Direct mast cell activation
• Exercise
• Cold
• Medications (e.g. opioids)
• Other
Mast cells
Basophils
Histamine
Tryptase
Carboxypeptidase A
Chymase
PAF
Prostaglandins
Leukotrienes
Other
Skin
• Itching
• Flushing
• Hives
• Angioedema
Respiratory
• Cough
• Dyspnea
• Hoarseness
• Stridor
• Wheeze
GI
• Vomiting
• Diarrhea
• Abdominal pain
CVS
• Dizziness
• Hypotension
• Shock
• Incontinence
• Angina
• Arrhythmia
CNS
• Headache

FIG. 174.1 **Summary of the pathogenesis of anaphylaxis. See text for details about mechanisms, triggers, key cells, and mediators. Two or more target organ systems are typically involved in anaphylaxis. CNS, Central nervous system; CVS, cardiovascular system; GI, gastrointestinal; PAF, platelet-activating factor. (From Leung DYM, Szefler SJ, Bonilla FA Akdis CA, Sampson HA, editors: *Pediatric allergy principles and practice,* ed 3, Philadelphia, 2016, Elsevier, p 525.)**

Etiology

The most common causes of anaphylaxis in children are different for hospital and community settings. Anaphylaxis occurring in the hospital results primarily from allergic reactions to medications and latex. **Food allergy** is the most common cause of anaphylaxis occurring outside the hospital, accounting for about half the anaphylactic reactions reported in pediatric surveys from the United States, Italy, and South Australia (Table 174.2). **Peanut allergy** is an important cause of food-induced anaphylaxis, accounting for the majority of fatal and near-fatal reactions. In the hospital, latex is a particular problem for children undergoing multiple operations, such as patients with spina bifida and urologic disorders, and has prompted many hospitals to switch to latex-free products. Patients with **latex allergy** may also experience food-allergic reactions from homologous proteins in foods such as bananas, kiwi, avocado, chestnut, and passion fruit. Anaphylaxis to galactose-α-1,3-galactose has been reported 3-6 hr after eating red meat.

Table 174.2

Anaphylaxis Triggers in the Community*

Allergen Triggers (IgE-Dependent Immunologic Mechanism)*

Foods (e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose])
Food additives (e.g., spices, colorants, vegetable gums, contaminants)
Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, fire ants)
Medications (e.g., β-lactam antibiotics, ibuprofen)
Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy])
Natural rubber latex
Vaccines
Inhalants (rare) (e.g., horse or hamster dander, grass pollen)
Previously unrecognized allergens (foods, venoms, biting insect saliva, medications, biologic agents)

Other Immune Mechanisms (IgE Independent)

IgG mediated (infliximab, high-molecular-weight dextrans)
Immune aggregates (IVIG)
Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing)
Complement activation
Physical factors (e.g., exercise, [†] cold, heat, sunlight/ultraviolet radiation)
Ethanol
Idiopathic*

IVIG, Intravenous immune globulin; NSAID, nonsteroidal antiinflammatory drug.

[*] In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.

[†] Exercise with or without a co-trigger, such as a food or medication, cold air, or cold water.

Adapted from Leung DYM, Sampson HA, Geha RS, et al: *Pediatric allergy principles and practice* , Philadelphia, 2010, Elsevier, p 652.

Epidemiology

The overall annual incidence of anaphylaxis in the United States is estimated at 42 cases per 100,000 person-years, totaling >150,000 cases/yr. Food allergens are the most common trigger in children, with an incidence rate of approximately 20 per 100,000 person-years. An Australian parental survey found that 0.59% of children 3-17 yr of age had experienced at least 1 anaphylactic event. Having asthma and the severity of asthma are important anaphylaxis risk factors (Table 174.3). In addition, patients with systemic mastocytosis or monoclonal mast cell–activating syndrome are at increased risk for anaphylaxis, as are patients with an elevated baseline serum tryptase level.

Table 174.3

Patient Risk Factors for Anaphylaxis

Age-Related Factors

- Infants: anaphylaxis can be difficult to recognize, especially if the first episode; patients cannot describe symptoms.
- Adolescents and young adults: increased risk-taking behaviors, such as failure to avoid known triggers and to carry an epinephrine autoinjector consistently
- Pregnancy: risk of iatrogenic anaphylaxis, as from β lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex
- Older people: increased risk of death because of concomitant disease and drugs

Concomitant Diseases

Asthma and other chronic respiratory diseases
Cardiovascular diseases
Systemic mastocytosis or monoclonal mast cell–activating syndrome
Allergic rhinitis and eczema*
Depression, cognitive dysfunction, substance misuse

Drugs

β-Adrenergic blockers †
Angiotensin-converting enzyme (ACE) inhibitors †
Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient's ability to recognize triggers and symptoms.

Factors That May Increase Risk for Anaphylaxis or Make It More Difficult to Treat

Age
Asthma
Atopy
Drugs
Alcohol
Other cofactors such as exercise, infection, menses

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* Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings.

† Patients taking β-blockers or ACE inhibitors seem to be at increased risk for severe anaphylaxis. In addition, those taking β-blockers may not respond optimally to epinephrine treatment and may need glucagon, a polypeptide with non–catecholamine-dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.

Adapted from Lieberman P, Nicklas RA, Randolph C, et al: Anaphylaxis—a practice parameter update 2015, *Ann Allergy Asthma Immunol* 115(5):341–384, 2015, Table I-9.

Pathogenesis

Principal pathologic features in fatal anaphylaxis include acute bronchial obstruction with pulmonary hyperinflation, pulmonary edema, intraalveolar hemorrhaging, visceral congestion, laryngeal edema, and urticaria and angioedema. Acute hypotension is attributed to vasomotor dilation and cardiac dysrhythmias.

Most cases of anaphylaxis are believed to be the result of activation of mast cells and basophils via cell-bound allergen-specific IgE molecules (see Fig. 174.1). Patients initially must be exposed to the responsible allergen to generate allergen-specific antibodies. In many cases the child and the parent are unaware of the initial exposure, which may be from passage of food proteins in maternal breast milk or exposure to inflamed skin (e.g., eczematous lesions). When the child is reexposed to the sensitizing allergen, mast cells and basophils, and possibly other cells such as macrophages, release a variety of mediators (histamine, tryptase) and cytokines that can produce allergic symptoms in any or all target organs. Clinical anaphylaxis may also be caused by mechanisms other than IgE-mediated reactions, including direct release of mediators from mast cells by medications and physical factors (morphine, exercise, cold), disturbances of leukotriene metabolism (aspirin and nonsteroidal antiinflammatory drugs), immune aggregates and complement activation (blood products), probable complement activation (radiocontrast dyes, dialysis membranes), and IgG-mediated reactions (high-molecular-weight dextran, chimeric or humanized monoclonal antibodies) (see Table 174.2).

Idiopathic anaphylaxis is a diagnosis of exclusion when no inciting agent is identified and other disorders have been excluded (see Chapter 678.1). Symptoms are similar to IgE mediated causes of anaphylaxis; episodes often recur.

Clinical Manifestations

The onset of symptoms may vary depending on the cause of the reaction.

Reactions from ingested allergens (foods, medications) are delayed in onset (minutes to 2 hr) compared with those from injected allergens (insect sting, medications) and tend to have more gastrointestinal (GI) symptoms. Initial symptoms may include any of the following constellation of symptoms: pruritus about the mouth and face; flushing, urticaria and angioedema, oral or cutaneous pruritus; a sensation of warmth, weakness, and apprehension (sense of doom); tightness in the throat, dry staccato cough and hoarseness, periocular pruritus, nasal congestion, sneezing, dyspnea, deep cough and wheezing; nausea, abdominal cramping, and vomiting, especially with ingested allergens; uterine contractions (manifesting as lower back pain); and faintness and loss of consciousness in severe cases. Some degree of obstructive laryngeal edema is typically encountered with severe reactions. Cutaneous symptoms may be absent in up to 10% of cases, and the *acute* onset of severe bronchospasm in a previously well person with asthma should suggest the diagnosis of anaphylaxis. Sudden collapse in the absence of cutaneous symptoms should also raise suspicion of vasovagal collapse, myocardial infarction, aspiration, pulmonary embolism, or seizure disorder. Laryngeal edema, especially with abdominal pain, may also be a result of hereditary angioedema (see Chapter 173). Symptoms in infants may not be easy to identify (see Table 174.1).

Laboratory Findings

Laboratory studies may indicate the presence of IgE antibodies to a suspected causative agent, but this result is not definitive. Plasma histamine is elevated for a brief period but is unstable and difficult to measure in a clinical setting. **Plasma tryptase** is more stable and remains elevated for several hours but often is not elevated, especially in food-induced anaphylactic reactions.

Diagnosis

A National Institutes of Health (NIH)–sponsored expert panel has recommended an approach to the diagnosis of anaphylaxis (Table 174.4). The differential diagnosis includes other forms of shock (hemorrhagic, cardiogenic, septic); vasopressor reactions, including flushing syndromes (e.g., carcinoid syndrome); ingestion of monosodium glutamate; scombroidosis; and hereditary angioedema. In addition, panic attack, vocal cord dysfunction, pheochromocytoma, and red man syndrome (caused by vancomycin) should be considered.

Table 174.4

Diagnosis of Anaphylaxis

Anaphylaxis is **highly likely** when *any 1 of the following 3 criteria* is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (e.g., *generalized* hives, pruritus or flushing, swollen lips/tongue/uvula)
   AND *at least 1 of the following* :
    a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. *Two or more of the following* that occur rapidly after exposure **to a likely allergen for that patient** (minutes to several hours):
    a. Involvement of the skin/mucosal tissue (e.g., *generalized* hives, itch/flush, swollen lips/tongue/uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. **Persistent** gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP following exposure to **known allergen for that patient** (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or >30% drop in systolic BP
    b. Adults: systolic BP <90 mm Hg or >30% drop from patient's baseline

BP, Blood pressure; PEF, peak expiratory flow.

Adapted from Sampson HA, Muñoz-Furlong A, Campbell RL, et al: Second Symposium on the Definition and Management of Anaphylaxis: summary report, Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium, *J Allergy Clin Immunol* 117:391–397, 2006.

Treatment

Anaphylaxis is a medical emergency requiring aggressive management with intramuscular (IM, first line) or intravenous (IV) epinephrine, IM or IV H_1 and H_2 antihistamine antagonists, oxygen, IV fluids, inhaled β-agonists, and corticosteroids (Table 174.5 and Fig. 174.2). The initial assessment should ensure an adequate airway with effective respiration, circulation, and perfusion. **Epinephrine** is the most important medication, and there should be no delay in its administration. Epinephrine should be given by the IM route to the lateral thigh (1 : 1000 dilution, 0.01 mg/kg; maximum 0.5 mg). For children ≥12 yr, many recommend the 0.5 mg IM dose. The IM dose can be repeated at intervals of 5-15 min if symptoms persist or worsen. If there is no response to multiple doses of epinephrine, IV epinephrine using the 1 : 10,000 dilution may be needed. If IV access is not readily available, epinephrine can be administered via the endotracheal or intraosseous routes.

Table 174.5

Management of a Patient With Anaphylaxis

TREATMENT	MECHANISM(S) OF EFFECT	DOSAGE(S)	COMMENTS; ADVERSE REACTIONS
PATIENT EMERGENCY MANAGEMENT (dependent on severity of symptoms)			
Epinephrine (adrenaline)	α_1-, β_1-, β_2-Adrenergic effects	0.01 mg/kg, up to 0.5 mg IM in lateral thigh Adrenaclick, Auvi-Q, EpiPen Jr/EpiPen: 0.15 mg IM for 8-25 kg 0.3 mg IM for 25 kg or more Epinephrine autoinjector: 0.1 mg for 7.5-15	Tachycardia, hypertension, nervousness, headache, nausea, irritability, tremor

		kg 0.15 mg for 15 to 25 kg 0.3 mg for 25 kg or more	
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid: 5 mg/5 mL 0.25 mg/kg, up to 10 mg PO	Hypotension, tachycardia, somnolence
Alternative: Diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO or IM	Hypotension, tachycardia, somnolence, paradoxical excitement
Transport to an emergency facility			
EMERGENCY PERSONNEL MANAGEMENT (dependent on severity of symptoms)			
Epinephrine (adrenaline)	α_1 -, β_1 -, β_2 - Adrenergic effects	0.01 mg/kg, up to 0.5 mg IM in lateral thigh Epinephrine autoinjector: 0.1 mg for 7.5-15 kg 0.15 mg for 15 to 25 kg 0.3 mg for 25 kg or more 0.01 mL/kg/dose of 1 : 1,000 (vial) solution, up to 0.5 mL IM May repeat every 10-15 min For severe hypotension: 0.01 mL/kg/dose of 1 : 10,000 slow IV push	Tachycardia, hypertension, nervousness, headache, nausea, irritability, tremor
Supplemental oxygen and airway management			
Volume Expanders			
Crystalloids (normal saline or Ringer lactate)		30 mL/kg in 1st hr	Rate titrated against BP response If tolerated, place patient supine with legs raised.
Colloids (hydroxyethyl starch)		10 mL/kg rapidly followed by slow infusion	Rate titrated against BP response If tolerated, place patient supine with legs raised.
Antihistamines			
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid: 5 mg/5 mL 0.25 mg/kg, up to 10 mg PO	Hypotension, tachycardia, somnolence
Alternative: Diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg, up to 50 mg PO, IM, or IV	Hypotension, tachycardia, somnolence, paradoxical excitement
Ranitidine	Antihistamine (competitive of H_2	1 mg/kg, up to 50 mg IV	Headache, mental confusion

	receptor)	Should be administered slowly	
Alternative: Cimetidine	Antihistamine (competitive of H_2 receptor)	4 mg/kg, up to 200 mg IV Should be administered slowly	Headache, mental confusion
Corticosteroids			
Methylprednisolone	Antiinflammatory	Solu-Medrol (IV): 1-2 mg/kg, up to 125 mg IV Depo-Medrol (IM): 1 mg/kg, up to 80 mg IM	Hypertension, edema, nervousness, agitation
Prednisone	Antiinflammatory	1 mg/kg up, to 75 mg PO	Hypertension, edema, nervousness, agitation
Nebulized albuterol	β-Agonist	0.83 mg/mL (3 mL) via mask with O_2	Palpitations, nervousness, CNS stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat
POSTEMERGENCY MANAGEMENT			
Antihistamine		Cetirizine (5-10 mg qd) or loratadine (5-10 mg qd) for 3 days	
Corticosteroids		*Optional:* Oral prednisone (1 mg/kg up to 75 mg) daily for 3 days	
Preventive Treatment Prescription for epinephrine autoinjector and antihistamine Provide written plan outlining patient emergency management (may download form from http://www.aap.org or http://www.foodallergy.org) Follow-up evaluation to determine/confirm etiology Immunotherapy for insect sting allergy			
Patient Education Instruction on avoidance of causative agent Information on recognizing early signs of anaphylaxis Stress early treatment of allergic symptoms to avoid systemic anaphylaxis Encourage wearing medical identification jewelry			

BP, Blood pressure; CNS, central nervous system; IM, Intramuscularly; IV, intravenously; PO, orally; qd, every day.

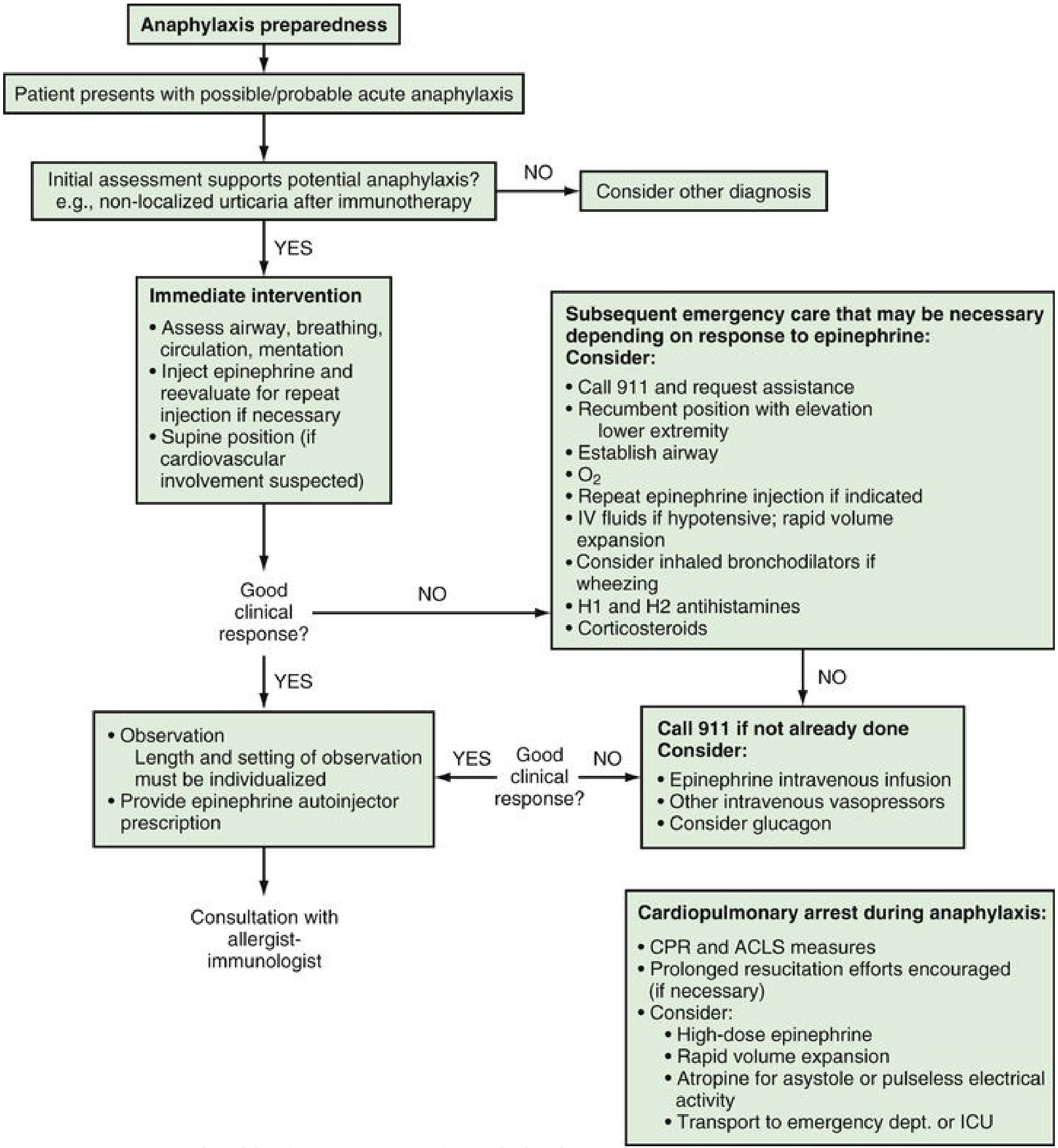
Anaphylaxis preparedness
Patient presents with possible/probable acute anaphylaxis
Initial assessment supports potential anaphylaxis? e.g., non-localized urticaria after immunotherapy
NO
Consider other diagnosis
YES
Immediate intervention
• Assess airway, breathing, circulation, mentation
• Inject epinephrine and reevaluate for repeat injection if necessary
• Supine position (if cardiovascular involvement suspected)
Good clinical response?
NO
Subsequent emergency care that may be necessary depending on response to epinephrine: Consider:
• Call 911 and request assistance
• Recumbent position with elevation lower extremity
• Establish airway
• O2
• Repeat epinephrine injection if indicated
• IV fluids if hypotensive; rapid volume expansion
• Consider inhaled bronchodilators if wheezing
• H1 and H2 antihistamines
• Corticosteroids
YES
NO
• Observation Length and setting of observation must be individualized
• Provide epinephrine autoinjector prescription
YES
Good clinical response?
NO
Call 911 if not already done Consider:
• Epinephrine intravenous infusion
• Other intravenous vasopressors
• Consider glucagon
Consultation with allergist-immunologist
Cardiopulmonary arrest during anaphylaxis:
• CPR and ACLS measures
• Prolonged resuscitation efforts encouraged (if necessary)
• Consider:
• High-dose epinephrine
• Rapid volume expansion
• Atropine for asystole or pulseless electrical activity
• Transport to emergency dept. or ICU

FIG. 174.2 **Algorithm for treatment of anaphylactic event in outpatient setting. ACLS, Advance cardiac life support; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IV, intravenous. (From Lieberman P, Nicklas RA, Oppenheimer J, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update, *J Allergy Clin Immunol* 126:477–480 e471–442, 2010.)**

For refractory hypotension, other vasopressors may be used as alternative agents to epinephrine. Anaphylaxis refractory to repeated doses of epinephrine in a patient receiving β-adrenergic blockers has anecdotally been treated with glucagon. The patient should be placed in a supine position when there is concern for hemodynamic compromise. Fluids are also important in patients with shock. Other drugs (antihistamines, glucocorticosteroids) have a secondary role in the management of anaphylaxis.

Patients may experience **biphasic anaphylaxis** , which occurs when anaphylactic symptoms recur after apparent resolution. The mechanism of this phenomenon is unknown, but it appears to be more common when therapy is initiated late and symptoms at presentation are more severe. It does not appear to be affected by the administration of corticosteroids during the initial therapy. More than 90% of biphasic responses occur within 4 hr, so patients should be observed for at least 4 hr before being discharged from the emergency department. Referrals should be made to appropriate specialists for further evaluation and follow-up.

Prevention

For patients experiencing anaphylactic reactions, the triggering agent should be avoided, and education regarding early recognition of anaphylactic symptoms and administration of emergency medications should be provided. Patients with food allergies must be educated in allergen avoidance, including active reading of food ingredient labels and knowledge of potential contamination and high-risk situations. Any child with food allergy and a history of asthma, peanut, tree nut, fish, or shellfish allergy or a previous systemic reaction should be given an epinephrine autoinjector. The expert panel also indicates that epinephrine autoinjectors should be considered for any patient with IgE-mediated food allergy. In addition, liquid cetirizine (or alternatively, diphenhydramine) and a written emergency plan should also be provided in case of accidental ingestion or allergic reaction. A form can be downloaded from the American Academy of Pediatrics (www.aap.org) or Food Allergy Research & Education (www.foodallergy.org).

In cases of food-associated exercise-induced anaphylaxis, children must not exercise within 2-3 hr of ingesting the triggering food and, as in children with exercise-induced anaphylaxis, should exercise with a friend, learn to recognize the early signs of anaphylaxis (sensation of warmth, facial pruritus), stop exercising, and seek help immediately if symptoms develop. Children experiencing a systemic anaphylactic reaction, including respiratory symptoms, to an insect sting should be evaluated and treated with immunotherapy, which is >90% protective. Reactions to medications can be reduced and minimized by using oral medications instead of injected forms and avoiding cross-reacting medications. Low-osmolarity radiocontrast dyes and pretreatment can be used in patients with suspected reactions to previous radiocontrast dye. Nonlatex gloves and materials should be used in children undergoing multiple operations.

Any child at risk for anaphylaxis should receive emergency medications (including epinephrine autoinjector), education on identification of signs and symptoms of anaphylaxis and proper administration of medications (Table 174.6), and a written emergency plan in case of accidental exposure. They should be encouraged to wear medical identification jewelry.

Table 174.6

Considerations With Epinephrine Injection for Anaphylaxis

Why Healthcare Professionals Fail to Inject Epinephrine Promptly

- Lack of recognition of anaphylaxis symptoms; failure to diagnose anaphylaxis
- Episode appears mild, or there is a history of previous mild episode(s)*
- Inappropriate concern about transient mild pharmacologic effects of epinephrine (e.g., tremor)
- Lack of awareness that serious adverse effects are almost always attributable to epinephrine overdose or IV administration, especially IV bolus, rapid IV infusion, or IV infusion of a 1 : 1,000 epinephrine solution instead of an appropriately diluted solution (1 : 10,000 or 1 : 100,000 concentration)

Why Patients and Caregivers Fail to Inject Epinephrine Promptly

- Lack of recognition of anaphylaxis symptoms; failure to diagnose anaphylaxis
- Episode appears mild, or there is a history of previous mild episode(s)*
- H_1 antihistamine or asthma puffer is used initially instead, relieving early warning signs such as itch or cough, respectively.
- Prescription for epinephrine autoinjectors (EAIs) is not provided by physician.
- Prescription for EAIs is provided but not filled at pharmacy (e.g., not affordable).

- Patients do not carry EAIs consistently (due to size and bulk, or “don't think they’ll need it”).
- Patients and caregivers are afraid to use EAIs (concern about making an error when giving the injection or about a bad outcome).
- Patients and caregivers are concerned about injury from EAIs.
- Competence in using EAIs is associated with regular allergy clinic visits; it decreases as time elapses from first EAI instruction; regular retraining is needed.
- Difficulty in understanding how to use EAIs (15% of mothers with no EAI experience could not fire an EAI immediately after a one-on-one demonstration)
- Errors in EAI use can occur despite education, possibly related to the design of some EAIs.

Why Patients Occasionally Fail to Respond to Epinephrine Injection

- Delayed recognition of anaphylaxis symptoms; delayed diagnosis
- Error in diagnosis: problem being treated (e.g., foreign body inhalation) is not anaphylaxis.
- Rapid progression of anaphylaxis [†]

    Epinephrine [†] :

    - Injected too late; dose too low on mg/kg basis; dose too low because epinephrine solution has degraded (e.g., past the expiration date, stored in a hot place)
    - Injection route or site not optimal; dose took too long to be absorbed.
    - Patient suddenly sits up or walks or runs, leading to the empty ventricle syndrome.
    - Concurrent use of certain medications (e.g., β-adrenergic blockers)

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[*] Subsequent anaphylaxis episodes can be more severe, less severe, or similar in severity.

[†] Median times to respiratory or cardiac arrest are 5 min in iatrogenic anaphylaxis, 15 min in stinging-insect venom anaphylaxis, and 30 min in food anaphylaxis; however, regardless of the trigger, respiratory or cardiac arrest can occur within 1 min in anaphylaxis.

Adapted from Leung DYM, Szefler SJ, Bonilla FA Akdis CA, Sampson HA, editors: *Pediatric allergy principles and practice*, Philadelphia, 2016, Elsevier, p 531.

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CHAPTER 175

Serum Sickness

Anna Nowak-Węgrzyn, Scott H. Sicherer

Serum sickness is a systemic, immune complex–mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins or other medications (Table 175.1).

Table 175.1

Proteins and Medications That Cause Serum Sickness*

Proteins From Other Species

- Antibotulinum globulin
- Antithymocyte globulin
- Antitetanus toxoid
- Antivenin (Crotalidae) polyvalent (horse serum based)
- Crotalidae polyvalent immune Fab (ovine serum based)
- Antirabies globulin
- Infliximab
- Rituximab
- Etanercept
- Anti-HIV antibodies ([PE]HRG214)
- Hymenoptera stings
- Streptokinase
- H1N1 influenza vaccine

Drugs

Antibiotics

- Cefaclor
- Penicillins
- Trimethoprim sulfate
- Minocycline
- Meropenem

Neurologic

- Bupropion
- Carbamazepine
- Phenytoin
- Sulfonamides
- Barbiturates

HIV, Human immunodeficiency virus.

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[*] Based on review of most current literature. Other medications that are not listed might also cause serum sickness.

From Aceves SS: Serum sickness. In Burg FD, Ingelfinger JR, Polin RA, Gershon AA, editors: *Current pediatric therapy* , ed 18, Philadelphia, 2006, Elsevier, p 1138.

Etiology

Immune complexes involving heterologous (animal) serum proteins and complement activation are important pathogenic mechanisms in serum sickness. Antibody therapies derived from the horse, sheep, or rabbit are available for treatment of envenomation by the black widow spider and a variety of snakes, for treatment of botulism, and for immunosuppression (**antithymocyte globulin** , ATG). The availability of alternative medical therapies, modified or bioengineered antibodies, and biologics of human origin have supplanted the use of nonhuman antisera, reducing the risk of serum sickness. However, rabbit-generated ATGs, which target human T cells, continue to be widely used as immunosuppressive agents during treatment of kidney allograft recipients; serum sickness is associated with a late graft loss in kidney transplant recipients. A **serum sickness–like reaction** may be attributed to drug allergy, triggered by antibiotics (particularly cefaclor). In contrast to a true serum sickness, serum sickness–like reactions do not exhibit the immune complexes, hypocomplementemia, vasculitis, and renal lesions that are seen in serum sickness reactions.

Pathogenesis

Serum sickness is a classic example of a type III hypersensitivity reaction caused by antigen-antibody complexes. In the rabbit model using bovine serum albumin as the antigen, symptoms develop with the appearance of antibody against the injected antigen. As free antigen concentration falls and antibody production increases over days, antigen-antibody complexes of various sizes develop in a manner analogous to a precipitin curve. Whereas small complexes usually circulate harmlessly and large complexes are cleared by the reticuloendothelial system, intermediate-sized complexes that develop at the point of slight antigen excess may deposit in blood vessel walls and tissues. There the immune microprecipitates induce vascular (leukocytoclastic vasculitis with immune complex deposition) and tissue damage through activation of complement and granulocytes.

Complement activation (C3a, C5a) promotes chemotaxis and adherence of neutrophils to the site of immune complex deposition. The processes of immune complex deposition and of neutrophil accumulation may be facilitated by increased vascular permeability, because of the release of vasoactive amines from tissue mast cells. Mast cells may be activated by binding of antigen to IgE or through contact with anaphylatoxins (C3a). Tissue injury results from the liberation of proteolytic enzymes and oxygen radicals from the neutrophils.

Clinical Manifestations

The symptoms of serum sickness generally begin 7-12 days after injection of the foreign material, but may appear as late as 3 wk afterward. The onset of symptoms may be accelerated if there has been earlier exposure or previous allergic reaction to the same antigen. A few days before the onset of generalized symptoms, the site of injection may become edematous and erythematous.

Symptoms usually include fever, malaise, and rashes. Urticaria and morbilliform rashes are the predominant types of skin eruptions (Fig. 175.1). In a prospective study of serum sickness induced by administration of equine ATG, an initial rash was noted in most patients. It began as a thin, serpiginous band of erythema along the sides of the hands, fingers, feet, and toes at the junction of the palmar or plantar skin with the skin of the dorsolateral surface. In most patients the band of erythema was replaced by petechiae or purpura, presumably because of low platelet counts or local damage to small blood vessels. Additional symptoms include edema, myalgia, lymphadenopathy, symmetric arthralgia or arthritis involving multiple joints, and gastrointestinal complaints, including pain, nausea, diarrhea, and melena. Symptoms typically resolve within 2 wk of removal of the offending agent, although in unusual cases, symptoms can persist for as long as 2-3 mo.

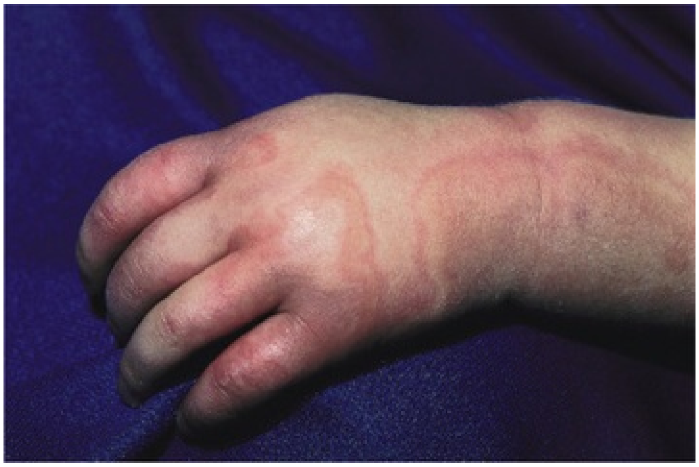

FIG. 175.1 **Serum sickness–like reaction (SSLR). Note the swollen hand and large urticarial wheals in this girl with SSLR and arthralgias. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology* , ed 5, Philadelphia, 2016, Elsevier, p 476.)**

Carditis, glomerulonephritis, Guillain-Barré syndrome, and peripheral neuritis are rare complications. Serum sickness–like reactions from drugs are characterized by fever, pruritus, urticaria, and arthralgias that usually begin 1-3 wk after drug exposure. The urticarial skin eruption becomes increasingly erythematous as the reaction progresses and can evolve into dusky centers with round plaques.

Differential Diagnosis

The differential diagnosis of serum sickness and serum sickness–like reactions includes viral illnesses with exanthems, hypersensitivity vasculitis, Kawasaki disease, acute rheumatic fever, acute meningococcal or gonococcal infection, endocarditis, systemic-onset juvenile idiopathic arthritis (Still disease), Lyme disease, hepatitis, and other types of drug reactions (see Chapter 177).

Diagnosis

In most patients the diagnosis of serum sickness is made clinically based on the characteristic pattern of acute or subacute onset of a rash, fever, and severe arthralgia and myalgia disproportionate to the degree of swelling, occurring after exposure to a potential culprit. Patients who appear moderately or severely ill, or who are not taking a medication that can be readily identified as the culprit, should be evaluated with the following laboratory tests:

◆ Complete blood count and differential; thrombocytopenia is often present.
◆ Erythrocyte sedimentation rate (ESR) and C-reactive protein; ESR is usually elevated.
◆ Urinalysis; mild proteinuria, hemoglobinuria, and microscopic hematuria may be seen.
◆ Serum chemistries, including blood urea nitrogen, creatinine, and liver function tests.
◆ Complement studies, including CH_{50} , C3, and C4; serum complement levels (C3 and C4) are generally decreased and reach a nadir at about day 10. C3a anaphylatoxin may be increased.
◆ Testing for specific infectious diseases, if indicated by the history or physical examination.

◆ Appropriate viral or bacterial cultures if an infection is suspected.

Skin biopsies are not usually necessary for confirming the diagnosis, because the findings are variable and not specific for serum sickness. Direct immunofluorescence studies of skin lesions often reveal immune deposits of IgM, IgA, IgE, or C3.

Treatment

There are no evidence-based guidelines or controlled trials on which to base therapy recommendations. Treatment is primarily supportive, consisting of discontinuation of the offending agent, antihistamines for pruritus, and nonsteroidal antiinflammatory drugs and analgesics for low-grade fever and mild arthralgia. When the symptoms are especially severe, for example, fever >38.5°C (101.3°F), severe arthralgia or myalgia, or renal dysfunction, systemic corticosteroids can be used. Prednisone (1-2 mg/kg/day; maximum 60 mg/day) for 1-2 wk is usually sufficient. Once the offending agent is discontinued and depending on its half-life, symptoms resolve spontaneously in 1-4 wk. Symptoms lasting longer suggest another diagnosis.

Prevention

The primary mode of prevention of serum sickness is to seek alternative therapies. In some cases, non–animal-derived formulations may be available (human-derived botulinum immune globulin). Other alternatives are partially digested antibodies of animal origin and engineered (humanized) antibodies. The potential of these therapies to elicit serum sickness–like disease appears low. When only animal-derived antitoxin/antivenom is available, skin tests should be performed before administration of serum, but this procedure indicates the risk only of anaphylaxis, not of serum sickness. For patients who have evidence of anaphylactic sensitivity to horse serum, a risk/benefit assessment must be made to determine the need to proceed with treatment. If needed, the serum can usually be successfully administered by a process of rapid desensitization using protocols of gradual administration outlined by the manufacturers. Serum sickness is not prevented by desensitization or by pretreatment with corticosteroids.

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CHAPTER 176

Food Allergy and Adverse Reactions to Foods

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Adverse reactions to foods consist of any untoward reaction following the ingestion of a food or food additive and are classically divided into **food intolerances** (e.g., **lactose intolerance**), which are adverse *physiologic* responses, and **food allergies,** which are adverse *immunologic* responses and can be IgE mediated or non–IgE mediated (Tables 176.1 and 176.2). As with other atopic disorders, food allergies appear to have increased over the past 3 decades, primarily in countries with a Western lifestyle. Worldwide, estimates of food allergy prevalence range from 1–10%; food allergies affect an estimated 3.5% of the U.S. population. Up to 6% of children experience food allergic reactions in the 1st 3 yr of life, including approximately 2.5% with cow's milk allergy, 2% with egg allergy, and 2–3% with peanut allergy. **Peanut allergy** prevalence tripled over the past decade. Most children “outgrow” milk and egg allergies, with approximately 50% doing so by school-age. In contrast, 80–90% of children with peanut, tree nut, or seafood allergy retain their allergy for life.

Table 176.1

Adverse Food Reactions

Food Intolerance (non–immune system mediated, nontoxic, noninfectious)

Host Factors

Enzyme deficiencies—lactase (primary or secondary), sucrase/isomaltase, hereditary fructose intolerance, galactosemia
Gastrointestinal disorders—inflammatory bowel disease, irritable bowel

syndrome, pseudoobstruction, colic
Idiosyncratic reactions—caffeine in soft drinks (“hyperactivity”)
Psychologic—food phobias, obsessive/compulsive disorder
Migraines (rare)

Food Factors (Toxic or Infectious or Pharmacologic)

Infectious organisms—*Escherichia coli*, *Staphylococcus aureus*, *Clostridium perfringens*, *Shigella*, botulism, *Salmonella*, *Yersinia*, *Campylobacter*
Toxins—histamine (scombroid poisoning), saxitoxin (shellfish)
Pharmacologic agents—caffeine, theobromine (chocolate, tea), tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)
Contaminants—heavy metals, pesticides, antibiotics

Food Allergy

IgE Mediated

Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial
Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis
Respiratory—acute rhinoconjunctivitis, bronchospasm
Generalized—anaphylactic shock, exercise-induced anaphylaxis

Mixed IgE Mediated and Non–IgE Mediated

Cutaneous—atopic dermatitis, contact dermatitis
Gastrointestinal—allergic eosinophilic esophagitis and gastroenteritis
Respiratory—asthma

Non–IgE Mediated

Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)
Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease

Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)
Unclassified

IgE, Immunoglobulin E.

Table 176.2

Differential Diagnosis of Adverse Food Reactions

Gastrointestinal Disorders (with vomiting and/or diarrhea)

- Structural abnormalities (pyloric stenosis, Hirschsprung disease, reflux)
- **Enzyme deficiencies (primary or secondary)** :
  - Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase
  - Galactosemia
- Malignancy with obstruction
- Other: pancreatic insufficiency (cystic fibrosis), peptic disease

Contaminants and Additives

- Flavorings and preservatives—rarely cause symptoms:
  - Sodium metabisulfite, monosodium glutamate, nitrites
- Dyes and colorings—very rarely cause symptoms (urticaria, eczema):
  - Tartrazine
- Toxins:
  - Bacterial, fungal (aflatoxin), fish related (scombroid, ciguatera)
- Infectious organisms:
  - Bacteria *(Salmonella, Escherichia coli, Shigella)*
  - Virus (rotavirus, enterovirus)
  - Parasites (*Giardia, Akis simplex* [in fish])
- Accidental contaminants:
  - Heavy metals, pesticides
- Pharmacologic agents:
  - Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese)

Psychologic Reactions

Food phobias

Genetics

Genetic factors play an important role in the development of food allergy. Family and twin studies show that family history confers a 2-10–fold increased risk, depending on the study setting, population, specific food, and diagnostic test. Candidate gene studies suggest that genetic variants in the HLA-DQ locus (HLA-DQB1*02 and DQB1*06:03P), filaggrin, interleukin-10, *STAT6*, and *FOXP3* genes are associated with food allergy, although the results are inconsistent across different populations. In a genome-wide association study, differential methylation at the HLA-DR and -DQ regions was associated with food allergy. Epigenetic studies implicate DNA methylation effects on interleukins 4, 5, and 10 and interferon (IFN)-γ genes and in the mitogen-activated protein kinase (MAPK) pathway.

Pathogenesis

Food intolerances are the result of a variety of mechanisms, whereas food allergy is predominantly caused by IgE-mediated and cell-mediated immune mechanisms. In susceptible individuals exposed to certain allergens, food-specific IgE antibodies are formed that bind to Fcε receptors on mast cells, basophils, macrophages, and dendritic cells. When food allergens penetrate mucosal barriers and reach cell-bound IgE antibodies, mediators are released that induce vasodilation, smooth muscle contraction, and mucus secretion, which result in symptoms of immediate hypersensitivity (allergy). Activated mast cells and macrophages may release several cytokines that attract and activate other cells, such as eosinophils and lymphocytes, leading to prolonged inflammation. Symptoms elicited during acute IgE-mediated reactions can affect the skin (urticaria, angioedema, flushing), gastrointestinal (GI) tract (oral pruritus, angioedema, nausea, abdominal pain, vomiting, diarrhea), respiratory tract (nasal congestion, rhinorrhea, nasal pruritus, sneezing, laryngeal edema, dyspnea, wheezing), and cardiovascular system (dysrhythmias, hypotension, loss of consciousness). In non-IgE food allergies, lymphocytes, primarily food allergen–

specific T cells, secrete excessive amounts of various cytokines that lead to a “delayed,” more chronic inflammatory process affecting the skin (pruritus, erythematous rash), GI tract (failure to thrive, early satiety, abdominal pain, vomiting, diarrhea), and respiratory tract (food-induced pulmonary hemosiderosis). Mixed IgE and cellular responses to food allergens can also lead to chronic disorders, such as atopic dermatitis, asthma, eosinophilic esophagitis, and gastroenteritis.

Children who develop IgE-mediated food allergies may be sensitized by food allergens penetrating the GI barrier, referred to as **class 1 food allergens** , or by food allergens that are partially homologous to plant pollens penetrating the respiratory tract, referred to as **class 2 food allergens** . Any food may serve as a class 1 food allergen, but *egg, milk, peanuts, tree nuts, fish, soy,* and *wheat* account for 90% of food allergies during childhood. Many of the major allergenic proteins of these foods have been characterized. There is variable but significant cross-reactivity with other proteins within an individual food group. Exposure and sensitization to these proteins often occur very early in life. Virtually all milk allergies develop by 12 mo of age and all egg allergies by 18 mo, and the median age of 1st peanut allergic reactions is 14 mo. Class 2 food allergens are typically vegetable, fruit, or nut proteins that are partially homologous with pollen proteins (Table 176.3). With the development of seasonal allergic rhinitis from birch, grass, or ragweed pollens, subsequent ingestion of certain uncooked fruits or vegetables provokes the **oral allergy syndrome** . *Intermittent ingestion* of allergenic foods may lead to acute symptoms such as urticaria or anaphylaxis, whereas *prolonged exposure* may lead to chronic disorders such as atopic dermatitis and asthma. Cell-mediated sensitivity typically develops to class 1 allergens.

Table 176.3

Natural History of Food Allergy and Cross-Reactivity Between Common Food Allergies

FOOD	USUAL AGE AT ONSET OF ALLERGY	CROSS REACTIVITY	USUAL AGE AT RESOLUTION
Hen's egg white	0-1 yr	Other avian eggs	7 yr (75% of cases resolve)*
Cow's milk	0-1 yr	Goat's milk, sheep's milk, buffalo milk	5 yr (76% of cases resolve)*
Peanuts	1-2 yr	Other legumes, peas, lentils; coreactivity with tree nuts	Persistent (20% of cases resolve)

Tree nuts	1-2 yr; in adults, onset occurs after cross reactivity to birch pollen	Other tree nuts; co-reactivity with peanuts	Persistent (9% of cases resolve)
Fish	Late childhood and adulthood	Other fish (low cross-reactivity with tuna and swordfish)	Persistent [†]
Shellfish	Adulthood (in 60% of patients with this allergy)	Other shellfish	Persistent
Wheat[*]	6-24 mo	Other grains containing gluten (rye, barley)	5 yr (80% of cases resolve)
Soybeans[*]	6-24 mo	Other legumes	2 yr (67% of cases resolve)
Kiwi	Any age	Banana, avocado, latex	Unknown
Apples, carrots, and peaches [§]	Late childhood and adulthood	Birch pollen, other fruits, nuts	Unknown

[*] Recent studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kU_A /L.

[†] Fish allergy that is acquired in childhood can resolve.

[§] Allergy to fresh apples, carrots, and peaches (**oral allergy syndrome**) is typically caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.

Adapted from Lack G: Food allergy, *N Engl J Med* 359:1252–1260, 2008.

Clinical Manifestations

From a clinical and diagnostic standpoint, it is most useful to subdivide food hypersensitivity disorders according to the predominant target organ (Table 176.4) and immune mechanism (see Table 176.1).

Table 176.4

Symptoms of Food-Induced Allergic Reactions

TARGET ORGAN	IMMEDIATE SYMPTOMS	DELAYED SYMPTOMS
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper	Nasal congestion	

respiratory	Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough, dyspnea, wheezing
Gastrointestinal (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	
Gastrointestinal (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	
Miscellaneous	Uterine contractions Sense of “impending doom”	

From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, *J Allergy Clin Immunol* 126(6):S1–S58, 2010 (Table IV, p S19).

Gastrointestinal Manifestations

GI food allergies are often the 1st form of allergy to affect infants and young children and typically manifest as irritability, vomiting or “spitting-up,” diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement predominate, making standard allergy tests such as skin-prick tests and in vitro tests for food-specific IgE antibodies of little diagnostic value.

Food protein–induced enterocolitis syndrome (FPIES) typically manifests in the 1st several mo of life as irritability, intermittent vomiting, and protracted diarrhea and may result in dehydration (Table 176.5). Vomiting generally occurs 1-4 hr after feeding, and continued exposure may result in abdominal distention, bloody diarrhea, anemia, and failure to thrive. Symptoms are most often provoked by cow's milk or soy protein–based formulas. A similar enterocolitis syndrome occurs in older infants and children from rice, oat, wheat, egg, peanut, nut, chicken, turkey, or fish. Hypotension occurs in approximately 15% of patients after allergen ingestion and may initially be thought to be caused by sepsis. FPIES usually resolves by age 3-5 yr.

Table 176.5

Food Protein–Induced Gastrointestinal Syndromes

	FPIES	PROCTOCOLITIS	ENTEROPATHY	EOSINOPHILIC GASTROENTEROPATHIES*
Age at onset	1 day–1 year	1 day–6 months	Dependent of age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
Food proteins implicated				
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy, egg white, wheat, peanut
Less common	Rice, chicken, turkey, fish, pea	Egg, corn, chocolate	Wheat, egg	Meats, corn, rice, fruits, vegetables, fish
Multiple food hypersensitivities	>50% both cow's milk and soy	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breastfeeding	Formula	Formula
Atopic background				
Family history of atopy	40–70%	25%	Unknown	~50% (often history of eosinophilic esophagitis)
Personal history of atopy	30%	22%	22%	~50%
Symptoms				
Emesis	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Laboratory findings				
Anemia	Moderate	Mild	Moderate	Mild-moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild-severe
Methemoglobinemia	May be present	No	No	No
Allergy evaluation				
Food skin-prick test	Negative †	Negative	Negative	Positive in ~50%

Serum food allergen IgE	Negative[†]	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
Biopsy findings				
Colitis	Prominent	Focal	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation, and basal zone hyperplasia
Food challenge	Vomiting in 1-4 hr; diarrhea in 5-8 hr	Rectal bleeding in 6-72 hr	Vomiting, diarrhea, or both in 40-72 hr	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge under supervision in 1.5-2 yr	Protein elimination, symptoms clear in 3 days with casein hydrolysate; resume/continue breastfeeding on maternal antigen-restricted diet; reintroduce at home after 9-12 mo of age	Protein elimination, symptoms clear in 1-3 wk; rechallenge and biopsy in 1-2 yr	Protein elimination, good response to casein hydrolysate, excellent response to elemental diet; symptoms clear in 2-3 wk, excellent acute response to steroids; rechallenge by introducing food at home and biopsy in 1-2 yr
Natural history	Cow's milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr	Resolved by 9-12 mo	Most cases resolve in 2-3 yr	Typically a prolonged, relapsing course
Reintroduction of the food	Supervised food challenge	At home, gradually advancing from 1 oz to full feedings over 2 wk	Home, gradually advancing	Home, gradually advancing

[*] Eosinophilic gastroenteropathies encompass esophagitis, gastritis, and gastroenterocolitis.

[†] If positive, may be a risk factor for persistent disease.

FPIES, Food protein–induced enterocolitis syndrome.

From Nowak-Węgrzyn A, Muraro A: Food protein-induced enterocolitis syndrome, *Curr Opin Allergy Immunol* 9:371–377, 2009 (Table 1, p 372).

Food protein–induced allergic proctocolitis (FPIAP) presents in the 1st few mo of life as blood-streaked stools in otherwise healthy infants (Table 176.5). Approximately 60% of cases occur among breastfed infants, with the remainder largely among infants fed cow's milk or soy protein–based formula. Blood loss is typically modest but can occasionally produce anemia.

Food protein–induced enteropathy (FPE) often manifests in the 1st several mo of life as diarrhea, often with steatorrhea and poor weight gain (Table 176.5). Symptoms include protracted diarrhea, vomiting in up to 65% of cases, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemia occur occasionally. **Cow's milk sensitivity** is the most common cause of FPE in young infants, but it has also been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. **Celiac disease** , the most severe form of FPE, occurs in about 1 per 100 U.S. population, although it may be “silent” in many patients (see Chapter 364.2). The full-blown form is characterized by extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption may occur. Genetically susceptible individuals (HLA-DQ2 or HLA-DQ8) demonstrate a cell-mediated response to tissue transglutaminase deamidated gliadin (a fraction of gluten), which is found in wheat, rye, and barley.

Eosinophilic esophagitis (EoE) may appear from infancy through adolescence, more frequently in boys (see Chapter 350). In young children, EoE is primarily cell mediated and manifests as chronic gastroesophageal reflux (GER), intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional GER medications. EoE is a clinicopathologic diagnosis. The diagnosis is confirmed when 15 eosinophils per high-power field are seen on esophageal biopsy following treatment with proton pump inhibitors. **Eosinophilic gastroenteritis** occurs at any age and causes symptoms similar to those of EoE, as well as prominent weight loss or failure to thrive, both of which are the hallmarks of this disorder. More than 50% of patients with this disorder are atopic; however, food-induced IgE-mediated reactions have been implicated only in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked protein-losing enteropathy.

Oral allergy syndrome (pollen-associated food allergy syndrome) is an IgE-mediated hypersensitivity that occurs in many older children with birch and ragweed pollen–induced allergic rhinitis. Symptoms are usually confined to the oropharynx and consist of the rapid onset of oral pruritus; tingling and angioedema of the lips, tongue, palate, and throat; and occasionally a sensation of pruritus in the ears and tightness in the throat. Symptoms are generally short lived and are caused by local mast cell activation following contact with fresh raw fruit and vegetable proteins that cross-react with birch pollen (apple, carrot, potato, celery, hazel nuts, peanuts, kiwi, cherry, pear), grass pollen (potato, tomato, watermelon, kiwi), and ragweed pollen (banana, melons such as watermelon and cantaloupe).

Acute gastrointestinal allergy generally manifests as acute abdominal pain, vomiting, or diarrhea that accompanies IgE-mediated allergic symptoms in other target organs.

Skin Manifestations

Cutaneous food allergies are also common in infants and young children.

Atopic dermatitis is a form of eczema that generally begins in early infancy and is characterized by pruritus, a chronically relapsing course, and association with asthma and allergic rhinitis (see Chapter 170). Although not often apparent from history, at least 30% of children with moderate to severe atopic dermatitis have food allergies. The younger the child and the more severe the eczema, the more likely food allergy is playing a pathogenic role in the disorder.

Acute urticaria and angioedema are among the most common symptoms of food allergic reactions (see Chapter 173). The onset of symptoms may be very rapid, within minutes after ingestion of the responsible allergen. Symptoms result from activation of IgE-bearing mast cells by food allergens that are absorbed and circulated rapidly throughout the body. Foods most commonly incriminated in children include egg, milk, peanuts, and nuts, although reactions to various seeds (sesame, poppy) and fruits (kiwi) are becoming more common. Chronic urticaria and angioedema are rarely caused by food allergies.

Perioral dermatitis is often a contact dermatitis caused by substances in toothpaste, gums, lipstick, or medications. **Perioral flushing** is often noted in infants fed citrus fruits and may be caused by benzoic acid in the food. It may also occur during nursing. In both situations the effect is benign. Flushing may also be caused by auriculotemporal nerve (Frey) syndrome (familial, forceps delivery), which resolves spontaneously.

Respiratory Manifestations

Respiratory food allergies are uncommon as isolated symptoms. Although many parents believe that nasal congestion in infants is often caused by milk allergy, studies show this not to be the case. **Food-induced rhinoconjunctivitis** symptoms typically accompany allergic symptoms in other target organs, such as skin, and consist of typical allergic rhinitis symptoms (periocular pruritus and tearing, nasal congestion and pruritus, sneezing, rhinorrhea). Wheezing occurs in approximately 25% of IgE-mediated food allergic reactions, but only 10% of asthmatic patients have food-induced respiratory symptoms.

Anaphylaxis

Anaphylaxis is defined as a serious, multisystem allergic reaction that is rapid in onset and potentially fatal. Food allergic reactions are the most common cause of anaphylaxis seen in U.S. hospital emergency departments. In addition to the rapid onset of cutaneous, respiratory, and GI symptoms, patients may demonstrate cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias, which are presumably caused by massive mast cell–mediator release. **Food-dependent exercise-induced anaphylaxis** occurs more frequently among teenage athletes, especially females (see Chapter 174).

Diagnosis

A thorough medical history is necessary to determine whether a patient's symptomatology represents an adverse food reaction (see Table 176.2), whether it is an intolerance or food allergic reaction, and if the latter, whether it is likely to be an IgE-mediated or a cell-mediated response (Fig. 176.1). The following facts should be established: (1) the food suspected of provoking the reaction and the quantity ingested, (2) the interval between ingestion and the development of symptoms, (3) the types of symptoms elicited by the ingestion, (4) whether ingesting the suspected food produced similar symptoms on other occasions, (5) whether other inciting factors, such as exercise, are necessary, and (6) the interval from the last reaction to the food.

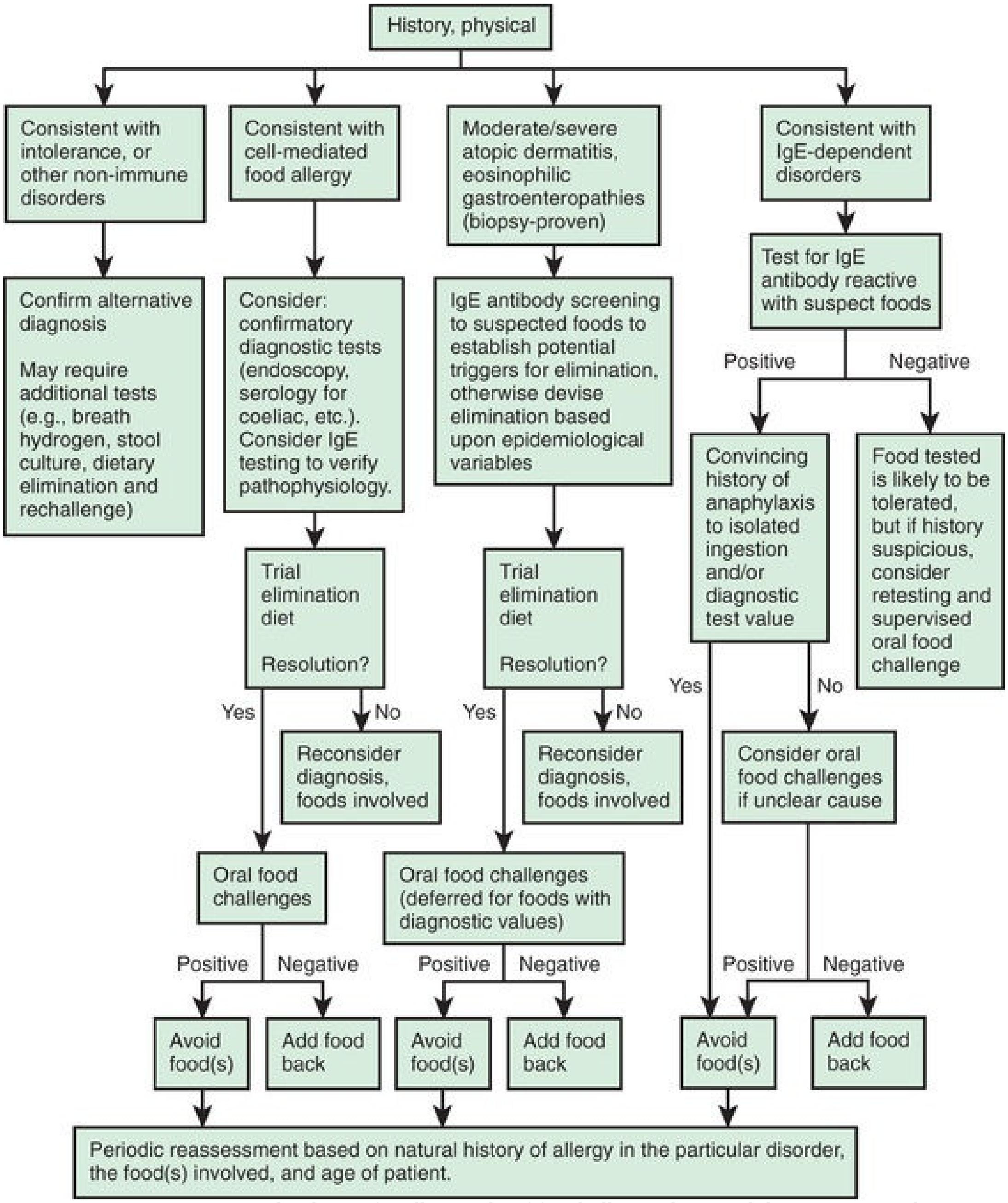
History, physical
Consistent with intolerance, or other non-immune disorders
Consistent with cell-mediated food allergy
Moderate/severe atopic dermatitis, eosinophilic gastroenteropathies (biopsy-proven)
Consistent with IgE-dependent disorders
Confirm alternative diagnosis
May require additional tests (e.g., breath hydrogen, stool culture, dietary elimination and rechallenge)
Consider: confirmatory diagnostic tests (endoscopy, serology for coeliac, etc.). Consider IgE testing to verify pathophysiology.
IgE antibody screening to suspected foods to establish potential triggers for elimination, otherwise devise elimination based upon epidemiological variables
Test for IgE antibody reactive with suspect foods
Positive
Negative
Convincing history of anaphylaxis to isolated ingestion and/or diagnostic test value
Food tested is likely to be tolerated, but if history suspicious, consider retesting and supervised oral food challenge
Trial elimination diet
Resolution?
Trial elimination diet
Resolution?
Yes
No
Yes
No
Yes
No
Reconsider diagnosis, foods involved
Reconsider diagnosis, foods involved
Consider oral food challenges if unclear cause
Oral food challenges
Oral food challenges (deferred for foods with diagnostic values)
Positive
Negative
Positive
Negative
Positive
Negative
Avoid food(s)
Add food back
Avoid food(s)
Add food back
Avoid food(s)
Add food back
Periodic reassessment based on natural history of allergy in the particular disorder, the food(s) involved, and age of patient.

FIG. 176.1 **General scheme for diagnosis of food allergy. (From Sicherer SH: Food allergy, *Lancet* 360:701–710, 2002.)**

Skin-prick tests and in vitro laboratory tests are useful for demonstrating *IgE sensitization*, defined as presence of food-specific IgE antibodies. Many fruits and vegetables require skin-prick testing with fresh produce because labile proteins are destroyed during commercial preparation. A negative skin test result virtually excludes an IgE-mediated form of food allergy. Conversely, most children with positive skin test responses to a food do not react when the food is ingested, so more definitive tests, such as quantitative IgE tests or food elimination and challenge, are often necessary to establish a diagnosis of food allergy. Serum food-specific IgE levels ≥15 kU_A /L for milk (≥5 kU_A /L for children ≤1 yr), ≥7 kU_A /L for egg (≥2 kU_A /L for children <2 yr), and ≥14 kU_A /L for peanut are associated with a >95% likelihood of clinical reactivity to these foods in children with suspected reactivity. In the absence of a clear history of reactivity to a food and evidence of food-specific IgE antibodies, definitive studies must be performed before recommendations are made for avoidance or the use of highly restrictive diets that may be nutritionally deficient, logistically impractical, disruptive to the family, expensive, or a potential source of future feeding disorders. IgE-mediated food allergic reactions are generally very food specific, so the use of broad exclusionary diets, such as avoidance of all legumes, cereal grains, or animal products, is not warranted (Table 176.6 ; see also Table 176.3).

Table 176.6

Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy

FOOD FAMILY	RISK OF ALLERGY TO ≥1 MEMBER (%; approximate)	FEATURE(S)
Legumes	5	Main causes of reactions are peanut, soybean, lentil, lupine, and garbanzo (chickpea).
Tree nuts (e.g., almond, cashew, hazelnut, walnut, brazil)	35	Reactions are often severe.
Fish	50	Reactions can be severe.
Shellfish	75	Reactions can be severe.
Grains	20	
Mammalian milks	90	Cow's milk is highly cross-reactive with goat's or sheep's milk (92%) but not with mare's milk (4%).
Rosaceae (pitted fruits)	55	Risk of reactions to >3 related foods is very low (<10%); symptoms are usually mild (oral allergy syndrome).
Latex-food	35	For individuals allergic to latex, banana, kiwi, fig, chestnut, and avocado are the main causes of reactions.
Food-latex	11	Individuals allergic to banana, kiwi, fig, chestnut, and avocado may be at an increased risk of reactions to latex.

Modified from Sicherer SH: Food allergy, *Lancet* 360:701–710, 2002.

There are no laboratory studies to help identify foods responsible for cell-mediated reactions. Consequently, *elimination diets followed by oral food* *challenges* are the only way to establish the diagnosis. Allergists experienced in dealing with food allergic reactions and able to treat anaphylaxis should perform food challenges. Before a food challenge is initiated, the suspected food should be eliminated from the diet for 10-14 days for IgE-mediated food allergy and up to 8 wk for some cell-mediated disorders, such as EoE. Some children with cell-mediated reactions to cow's milk do not tolerate hydrolysate formulas and must receive amino acid–derived formulas. If symptoms remain unchanged despite appropriate elimination diets, it is unlikely that food allergy is responsible for the child's disorder.

Treatment

Appropriate identification and elimination of foods responsible for food hypersensitivity reactions are the only validated treatments for food allergies. Complete elimination of common foods (milk, egg, soy, wheat, rice, chicken, fish, peanut, nuts) is very difficult because of their widespread use in a variety of processed foods. The lay organization **Food Allergy Research and Education** (**FARE** , www.foodallergy.org) provides excellent information to help parents deal with both the practical and emotional issues surrounding these diets. Validated educational materials are also available through the **Consortium of Food Allergy Research** (www.cofargroup.org).

Children with asthma and IgE-mediated food allergy, peanut or nut allergy, or a history of a previous severe reaction should be given self-injectable epinephrine and a written emergency plan in case of accidental ingestion (see Chapter 174). Because many food allergies are outgrown, children should be reevaluated periodically by an allergist to determine whether they have lost their clinical reactivity. A number of clinical trials are evaluating the efficacy of oral, sublingual, and epicutaneous (patch) immunotherapy for the treatment of IgE-mediated food allergies (milk, egg, peanut). Combining oral immunotherapy with anti-IgE treatment (omalizumab) may improve safety compared to oral immunotherapy alone. Furthermore, extensively heated milk or egg in baked products are tolerated by the majority of milk and egg–allergic children. Regular ingestion of baked products with milk and egg appears to accelerate resolution of milk and egg allergy. Table 176.7 provides vaccination recommendations for egg-allergic children who require immunization.

Table 176.7

ACIP and AAP Recommendations for Administering Vaccines to Patients With Egg Allergy

VACCINE	ACIP, CDC, 2016	AAP, 2016
MMR/MMRV	May be used	May be used
Influenza	Receive with no special precautions*	Receive with no special precautions*
Rabies	Use caution	No specific recommendation
Yellow fever	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)

* In 2016, recommendations changed to suggest all children with any severity of egg allergy receive the injectable influenza vaccine as appropriate for age in a medical setting without any special testing and with the same precautions as those suggested for other vaccinations, including a 15 minute observation period and being in a setting where personnel and equipment are available to recognize and treat allergic reactions and anaphylaxis.

ACIP, Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention; AAP, American Academy of Pediatrics; PI, product insert.

From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, *J Allergy Clin Immunol* 126(6):S1–S58, 2010 (Table V, p S31).

Prevention

It was once thought that avoidance of allergenic foods and delayed introduction to the diet would prevent allergy, but the opposite is probably true; *delayed introduction of these foods may increase the risk of allergy,* especially in children with atopic dermatitis. A trial of early introduction of dietary peanut randomized 640 infants age 4-11 mo with severe eczema, egg allergy, or both to consume or avoid peanut until age 60 mo. The early introduction of peanut dramatically decreased the development of peanut allergy among children at high risk for this allergy. A theory behind this approach is that early oral introduction of peanut induces oral tolerance that precedes the potential sensitization to peanut via the disrupted skin barrier. Infants with early-onset atopic disease (e.g., severe eczema) or egg allergy in the 1st 4 to 6 mo of life might benefit from evaluation by an allergist or physician trained in management of allergic diseases to diagnose any food allergy and assist in implementing appropriate early peanut introduction. The clinician can perform an observed peanut challenge for those with evidence of a positive peanut skin test response or serum peanut-specific IgE >0.35 kU_A /L to determine whether they are clinically reactive before initiating at-home introduction of infant-safe forms of peanut. Additional details for the early introduction of peanut are available from the National Institute of Allergy and Infectious Diseases (NIAID).*

There is no compelling evidence to support the practice of restricting the maternal diet during pregnancy or while breastfeeding, or of delaying introduction of various allergenic foods to infants from atopic families (Table 176.8). Exclusive breastfeeding for the 1st 4-6 mo of life may reduce allergic disorders in the 1st few yr of life in infants at high risk for development of allergic disease. Potentially allergenic foods (eggs, milk, wheat, soy, peanut/tree nut products, fish) should be introduced after this period of exclusive breastfeeding and may prevent the development of allergies later in life. Use of hydrolyzed formulas may be beneficial if breastfeeding cannot be continued for 4-6 mo or after weaning, especially to prevent eczema in high-risk families, but this approach remains controversial. **Probiotic supplements** may also reduce the incidence and severity of eczema. Because some **skin preparations** contain peanut oil, which may sensitize young infants, especially those with cutaneous inflammation, such preparations should be avoided. Since inflamed/disrupted skin barrier is a risk factor for food allergy, trials are underway to enhance the skin barrier from birth, using emollients and decreasing bathing frequency, to reduce the incidence of atopic dermatitis in high-risk neonates.

Table 176.8

Prevention of Food Allergy

Breastfeed exclusively for 4-6 mo.
Introduce solid (complementary) foods after 4-6 mo of exclusive breastfeeding.
Introduce low-risk complementary foods 1 at a time.
Introduce potentially highly allergenic foods (fish, eggs, peanut, milk, wheat) soon after the lower-risk foods (no need to avoid or delay).
    Infants with early-onset atopic disease (e.g., severe eczema) or egg allergy in the 1st 4-6 mo of life.
Do not avoid allergenic foods during pregnancy or nursing.
Soy-based formulas do not prevent allergic disease.

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[*] https://www.niaid.nih.gov/diseases-conditions/guidelines-clinicians-and-patients-food-allergy .

CHAPTER 177

Adverse Reactions to Drugs

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Adverse drug reactions can be divided into predictable (type A) and unpredictable (type B) reactions. **Predictable drug reactions** , including drug toxicity, drug interactions, and adverse effects, are dose dependent, can be related to known pharmacologic actions of the drug, and occur in patients without any unique susceptibility. **Unpredictable drug reactions** are dose independent, often are not related to the pharmacologic actions of the drug, and occur in patients who are genetically predisposed. These include idiosyncratic reactions, allergic (hypersensitivity) reactions, and pseudoallergic reactions. **Allergic reactions** require prior sensitization, manifest as signs or symptoms characteristic of an underlying allergic mechanism, such as anaphylaxis or urticaria, and occur in genetically susceptible individuals. They can occur at doses significantly below the therapeutic range. **Pseudoallergic reactions** resemble allergic reactions but are caused by non–IgE-mediated release of mediators from mast cells and basophils. Drug-independent cross-reactive antigens can induce sensitization manifesting as drug allergy. Patients with cetuximab-induced anaphylaxis have IgE antibodies in pretreatment samples specific for galactose-α-1,3-galactose. This antigen is present on the antigen-binding portion of the cetuximab heavy chain and is similar to structures in the ABO blood group. Sensitization to galactose-α-1,3-galactose may occur from tick bites caused by cross-reactive tick salivary antigens.

Epidemiology

The incidence of adverse drug reactions (ADRs) in the general as well as pediatric populations remains unknown, although data from hospitalized patients show it to be 6.7%, with a 0.32% incidence of fatal ADRs. Databases such as the

U.S. Food and Drug Administration (FDA) MedWatch program (http://www.fda.gov/medwatch/index.html) likely suffer from underreporting. Cutaneous reactions are the most common form of ADRs, with ampicillin, amoxicillin, penicillin, and trimethoprim/sulfamethoxazole (TMP/SMX) being the most frequently implicated drugs (Tables 177.1 and 177.2). Although the majority of ADRs do not appear to be allergic in nature, 6–10% can be attributed to an allergic or immunologic mechanism. Importantly, given the high probability of recurrence of allergic reactions, these reactions should be preventable, and information technology–based interventions may be especially useful to reduce risk of reexposure.

Table 177.1

Heterogeneity of Drug-Induced Allergic Reactions

ORGAN-SPECIFIC REACTIONS	CLINICAL FEATURES	EXAMPLES OF CAUSATIVE AGENTS
CUTANEOUS		
Exanthems	Diffuse fine macules and papules evolve over days after drug initiation Delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides
Urticaria, angioedema	Onset within minutes of drug initiation Potential for anaphylaxis Often IgE mediated	IgE mediated: β-lactam antibiotics Bradykinin mediated: ACEI
Fixed drug eruption	Hyperpigmented plaques Recur at same skin or mucosal site	Tetracycline, sulfonamides, NSAIDs, and carbamazepine
Pustules	Acneiform Acute generalized exanthematous pustulosis (AGEP)	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium-channel blockers
Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
SJS	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, and allopurinol
TEN	Similar features as SJS but >30% epidermal detachment Mortality as high as 50%	Same as SJS
Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium channel blockers, ACEIs
Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Paraaminosalicylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol
MULTIORGAN REACTIONS		

Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions	β-Lactam antibiotics, monoclonal antibodies
DRESS	Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

ACEI, Angiotensin-converting enzyme inhibitor; DRESS, drug rash with eosinophilia and systemic symptoms; NSAID, nonsteroidal antiinflammatory drug; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

From Khan DA, Solensky R: Drug allergy, *J Allergy Clin Immunol* 125:S126–S137, 2010 (Table 1, p S127).

Table 177.2

Delayed Hypersensitivity Drug Rashes by Category

MACULOPAPULAR EXANTHEMS—ANY DRUG CAN PRODUCE A RASH 7-10 DAYS AFTER THE FIRST DOSE

Allopurinol

Antibiotics: penicillin, sulfonamides

Antiepileptics: phenytoin, phenobarbital

Antihypertensives: captopril, thiazide diuretics

Contrast dye: iodine

Gold salts

Hypoglycemic drugs

Meprobamate

Phenothiazines

Quinine

DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

Anticonvulsants: phenytoin, phenobarbital, valproate, lamotrigine

Antibiotics: sulfonamides, minocycline, dapsone, ampicillin, ethambutol, isoniazid, linezolid, metronidazole, rifampin, streptomycin, vancomycin

Antihypertensives: amlodipine, captopril

Antidepressants: bupropion, fluoxetine

Allopurinol

Celecoxib

Ibuprofen

Phenothiazines

ERYTHEMA MULTIFORME/STEVENS-JOHNSON SYNDROME

Sulfonamides, phenytoin, barbiturates, carbamazepine, allopurinol, amikacin, phenothiazines

Toxic epidermal necrolysis: same as for erythema multiforme but also acetazolamide, gold, nitrofurantoin, pentazocine, tetracycline, quinidine

ACUTE GENERALIZED EXANTHEMIC PUSTULOSIS

Antibiotics: penicillins, macrolides, cephalosporins, clindamycin, imipenem, fluoroquinolones, isoniazid, vancomycin, minocycline, doxycycline, linezolid

Antimalarials: chloroquine, hydroxychloroquine

Antifungals: terbinafine, nystatin

Anticonvulsants: carbamazepine

Calcium-channel blockers

Furosemide

Systemic corticosteroids

Protease inhibitors

COLLAGEN VASCULAR OR LUPUS-LIKE REACTIONS

Procainamide, hydralazine, phenytoin, penicillamine, trimethadione, methyldopa, carbamazepine, griseofulvin, nalidixic acid, oral contraceptives, propranolol

ERYTHEMA NODOSUM

Oral contraceptives, penicillin, sulfonamides, diuretics, gold, clonidine, propranolol, opiates

FIXED DRUG REACTIONS

Phenolphthalein, barbiturates, gold, sulfonamides, meprobamate, penicillin, tetracycline, analgesics

See Chapter 664 and Table 664.3 .

From Duvic M: Urticaria, drug hypersensitivity rashes, nodules and tumors, and atrophic diseases. In Goldman L, Schafer AI, editors: Goldman-Cecil medicine, ed 25, Philadelphia, 2016, Elsevier, Table 440.3.

Pathogenesis and Clinical Manifestations

Immunologically mediated ADRs have been classified according to the Gell and Coombs classification: immediate hypersensitivity reactions (**type I**), cytotoxic antibody reactions (**type II**), immune complex reactions (**type III**), and delayed-type hypersensitivity reactions (**type IV**). **Immediate hypersensitivity reactions** occur when a drug or drug metabolite interacts with preformed drug-specific IgE antibodies that are bound to the surfaces of tissue mast cells and/or circulating basophils. The cross-linking of adjacent receptor-bound IgE by antigen causes the release of preformed and newly synthesized mediators, such as histamine and leukotrienes, that contribute to the clinical development of urticaria, bronchospasm, or anaphylaxis. **Cytotoxic antibody reactions** involve IgG or IgM antibodies that recognize drug antigen on the cell membrane. In the presence of serum complement, the antibody-coated cell is either cleared by the monocyte-macrophage system or is destroyed. Examples are drug-induced hemolytic anemia and thrombocytopenia. **Immune complex reactions** are caused by soluble complexes of drug or metabolite in slight antigen excess with IgG or IgM antibodies. The immune complex is deposited in blood vessel walls and causes injury by activating the complement cascade, as seen in serum sickness. Clinical manifestations include fever, urticaria, rash, lymphadenopathy, and arthralgias. Symptoms typically appear 1-3 wk after the last dose of an offending drug and subside when the drug and/or its metabolite is cleared from the body. **Delayed-type hypersensitivity reactions** are mediated by drug-specific T lymphocytes. Sensitization usually occurs by the topical route of administration, resulting in allergic contact dermatitis. Commonly implicated drugs include neomycin and local anesthetics in topical formulations.

Certain ADRs, including drug fever and the morbilliform rash seen with use of ampicillin or amoxicillin in the setting of Epstein-Barr virus (EBV) infection, are not easily classified. Studies point to the role of T cells and eosinophils in delayed maculopapular reactions to a number of antibiotics. The mechanisms of T-cell–mediated drug hypersensitivity are not well understood. A novel hypothesis, the **p-i concept** , suggests pharmacologic interactions of drugs with immune receptors as another class of drug hypersensitivity. In T-cell–mediated allergic drug reactions, the specificity of the T-cell receptor (TCR) that is stimulated by the drug may be directed to a cross-reactive major histocompatibility complex (MHC)–peptide compound. This information suggests that even poorly reactive native drugs are capable of transmitting a stimulatory signal through the TCR, which activates T cells and results in proliferation, cytokine production, and cytotoxicity. Previous contact with the causative drug is not obligatory, and an immune mechanism should be considered as the cause of hypersensitivity, even in reactions that occur with first exposure. Such reactions have been described for radiocontrast media and neuromuscular blocking agents.

Drug Metabolism and Adverse Reactions

Most drugs and their metabolites are not immunologically detectable until they have become covalently attached to a macromolecule. This multivalent hapten-protein complex forms a new immunogenic epitope that can elicit T- and B-lymphocyte responses. The penicillins and related β-lactam antibiotics are highly reactive with proteins and can directly haptenate protein carriers, possibly accounting for the frequency of immune-mediated hypersensitivity reactions with this class of antibiotics.

Incomplete or delayed metabolism of some drugs can give rise to toxic metabolites. Hydroxylamine, a reactive metabolite produced by cytochrome P450 oxidative metabolism, may mediate adverse reactions to sulfonamides. Patients who are *slow acetylators* appear to be at increased risk (see Chapter 72). In addition, cutaneous reactions in patients with AIDS treated with TMP/SMX, rifampin, or other drugs may be caused by glutathione deficiency resulting in toxic metabolites. Serum sickness–like reactions in which immune complexes have not been documented, which occur most often with cefaclor, may result from an inherited propensity for hepatic biotransformation of drugs into toxic or immunogenic metabolites.

Risk Factors for Hypersensitivity Reactions

Risk factors for ADRs include prior exposure, previous reactions, age (20-49 yr), route of administration (parenteral or topical), dose (high), and dosing schedule (intermittent), as well as genetic predisposition (slow acetylators). Atopy does not appear to predispose patients to allergic reactions to low-molecular-weight compounds, but atopic patients in whom an allergic reaction develops have a significantly increased risk of serious reaction. Atopic patients also appear to be at greater risk for pseudoallergic reactions induced by radiocontrast media. Pharmacogenomics has an important role in identifying individuals at risk for certain drug reactions (see Chapter 72).

Diagnosis

An accurate medical history is an important first step in evaluating a patient with a possible ADR. Suspected drugs need to be identified, along with dosages, route of administration, previous exposures, and dates of administration. In addition, underlying hepatic or renal disease may influence drug metabolism. A detailed description of past reactions may yield clues to the nature of the ADR. The propensity for a particular drug to cause the suspected reaction can be checked with information in *Physicians' Desk Reference, Drug Eruption Reference Manual,* or directly from the drug manufacturer. It is important to remember, however, that the history may be unreliable, and many patients are inappropriately labeled as being “drug allergic.” This label can result in inappropriate withholding of a needed drug or class of drugs. In addition, relying solely on the history can lead to overuse of drugs reserved for special indications, such as vancomycin in patients in whom penicillin allergy is suspected. *Approximately 90% of patients with a clinical history of penicillin allergy do not have evidence of penicillin-specific IgE antibodies on testing.*

Skin testing is the most rapid and sensitive method of demonstrating the presence of *IgE antibodies* to a specific allergen. It can be performed with high-molecular-weight compounds, such as foreign antisera, hormones, enzymes, and toxoids. Reliable skin testing can also be performed with penicillin, but not with most other antibiotics. Most immunologically mediated ADRs are caused by metabolites rather than by parent compounds, and the metabolites for most drugs other than penicillin have not been defined. In addition, many metabolites are unstable or must combine with larger proteins to be useful for diagnosis. Testing with nonstandardized reagents requires caution in interpretation of both positive and negative results, because some drugs can induce nonspecific irritant reactions. Whereas a wheal and flare reaction is suggestive of drug-specific IgE antibodies, a negative skin test result does not exclude the presence of such antibodies because the relevant immunogen may not have been used as the testing reagent.

A positive skin test response to the major or minor determinants of penicillin has a 60% positive predictive value (PPV) for an immediate hypersensitivity reaction to penicillin. In patients in whom skin test responses to the major and minor determinants of penicillin are negative, 97–99% (depending on the reagents used) tolerate the drug without an immediate reaction. At present, the major determinant of penicillin testing reagent benzylpenicilloyl polylysine (Pre-Pen) in the United States is available, but the minor determinant mixture has not been FDA approved as a testing reagent. Limited studies utilizing serum tests for IgE to β-lactams suggest high specificity (97–100%) but low sensitivity (29–68%). The PPV and negative predictive value (NPV) of skin testing for antibiotics other than penicillin are not well established. Nevertheless, positive immediate hypersensitivity skin test responses to nonirritant concentrations of nonpenicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents.

Results of direct and indirect Coombs tests are often positive in drug-induced hemolytic anemia. Assays for specific IgG and IgM have been shown to correlate with a drug reaction in immune cytopenia, but in most other reactions, such assays are not diagnostic. In general, many more patients express humoral or T-cell immune responses to drug determinants than express clinical disease. Serum **tryptase** is elevated with systemic mast cell degranulation and can be seen with drug-associated mast cell activation, although it is not pathognomonic for drug hypersensitivity, and nonelevated tryptase values can be seen in well-defined anaphylaxis. **Patch testing** is the most reliable technique for diagnosis of contact dermatitis caused by topically applied drugs. **Graded challenge** is the administration of a drug under medical supervision in an incremental fashion dosed faster than used for desensitization (see later) until a therapeutic dose is achieved. This can be attempted when the risk of reactions are judged to be low, and is a means to prove that the drug is tolerated or to identify an adverse or allergic reaction.

Treatment

Specific **desensitization** , which involves the progressive administration of an allergen to render effector cells less reactive, is reserved for patients with IgE antibodies to a particular drug for whom an alternative drug is not available or appropriate. Specific protocols for many different drugs have been developed. Desensitization should be performed in a hospital setting, usually in consultation with an allergist and with resuscitation equipment available at all times. Although mild complications, such as pruritus and rash, are fairly common and often respond to adjustments in the drug dose or dosing intervals and medications to relieve symptoms, more severe systemic reactions can occur. Oral desensitization may be less likely to induce anaphylaxis than parenteral administration. Protocols for gradual exposure are also used for adverse reaction to drugs that are not IgE mediated, for example for aspirin- or nonsteroidal antiinflammatory drug (NSAID)–intolerant patients, particularly those with respiratory reactions and those with mild rashes from TMP/SMX. Pretreatment with antihistamines or corticosteroids is not usually recommended. It is important to recognize that desensitization to a drug is effective only while the drug continues to be administered, and that after a period of interruption or discontinuation, hypersensitivity can recur. Patients with severe non–IgE-mediated hypersensitivity reactions should not receive the predisposing agents even in the small amounts used for skin testing (see Table 177.2).

β-Lactam Hypersensitivity

Penicillin is a frequent cause of anaphylaxis and is responsible for the majority of all drug-mediated anaphylactic deaths in the United States. If a patient requires penicillin and has a previous history suggestive of penicillin allergy, it is necessary to perform skin tests on the patient for the presence of penicillin-specific IgE, ideally with both the major and minor determinants of penicillin. Skin tests for minor determinants of penicillin are important because approximately 20% of patients with documented anaphylaxis do not demonstrate skin reactivity to the major determinant. The major determinant is commercially available (Pre-Pen). The minor determinant mixture is currently not licensed and is synthesized as a nonstandardized testing reagent at select academic centers. Penicillin G is often used as a substitute for the minor determinant mixture and may have NPV similar to testing with major and minor determinants. Patients should be referred to an allergist capable of performing appropriate testing. If the skin test response is positive to either major or minor determinants of penicillin, the patient should receive an alternative non–cross-reacting antibiotic. If administration of penicillin is deemed necessary, desensitization can be performed by an allergist in an appropriate medical setting. Skin testing for penicillin-specific IgE is not predictive for delayed-onset cutaneous, bullous, or immune complex reactions. In addition, penicillin skin testing does not appear to resensitize the patient.

Other β-lactam antibiotics, including semisynthetic penicillins, cephalosporins, carbacephems, and carbapenems, share the β-lactam ring structure. Patients with late-onset morbilliform rashes with amoxicillin are not considered to be at risk for IgE-mediated reactions to penicillin and do not require skin testing before penicillin administration. Many patients with EBV infections treated with ampicillin or amoxicillin can experience a nonpruritic rash. Similar reactions occur in patients who receive allopurinol as treatment for elevated uric acid or have chronic lymphocytic leukemia. If the rash to ampicillin or amoxicillin is urticarial or systemic or the history is unclear, the patient should undergo penicillin skin testing if a penicillin is needed. There have been reports of antibodies specific for semisynthetic penicillin side chains in the absence of β-lactam ring–specific antibodies, although the clinical significance of such side chain–specific antibodies is unclear.

Varying degrees of in vitro cross-reactivity have been documented between *cephalosporins* and penicillins. Although the risk of allergic reactions to cephalosporins in patients with positive skin test responses to penicillin appears to be low (<2%), anaphylactic reactions have occurred after administration of cephalosporins in patients with a history of penicillin anaphylaxis. If a patient has a history of penicillin allergy and requires a cephalosporin, skin testing for major and minor determinants of penicillin should preferably be performed to determine whether the patient has penicillin-specific IgE antibodies. If skin test results are negative, the patient can receive a cephalosporin with no greater risk than found in the general population. If skin test results are positive for penicillin, recommendations may include administration of an alternative antibiotic; cautious graded challenge with appropriate monitoring, with the recognition that there is a 2% chance of inducing an anaphylactic reaction; and desensitization to the required cephalosporin. Cross-reactivity is most likely when the cephalosporin shares the same side chain as the penicillin (Table 177.3).

Table 177.3

Groups of β-Lactam Antibiotics That Share Identical R1-Group Side Chains*

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

* Each column represents a group with identical R1 side chains.

From Solensky R, Khan DA: Drug allergy: an updated practice parameter, *Ann Allergy Asthma Immunol* 105:273e1–273e78, 2010 (Table 16, p 273e49).

Conversely, patients who require penicillin and have a history of an IgE-mediated reaction to a cephalosporin should also undergo penicillin skin testing. Patients with a negative result can receive penicillin. Patients with a positive result should either receive an alternative medication or undergo desensitization to penicillin. In patients with a history of allergic reaction to one cephalosporin who require another cephalosporin, skin testing with the required cephalosporin can be performed, with the recognition that the NPV of such testing is unknown. If the skin test response to the cephalosporin is positive, the significance of the test should be checked further in controls to determine whether the positive response is IgE mediated or an irritant response. The drug can then be administered by graded challenge or desensitization.

Carbapenems (imipenem, meropenem) represent another class of β-lactam antibiotics with a bicyclic nucleus that demonstrate a high degree of cross-reactivity with penicillins, although prospective studies suggest incidence of cross-reactivity on skin testing of approximately 1%. In contrast to β-lactam antibiotics, *monobactams* (aztreonam) have a monocyclic ring structure. Aztreonam-specific antibodies have been shown to be predominantly side chain-specific; data suggest that aztreonam can be safely administered to most penicillin-allergic patients. On the other hand, administration of aztreonam to a patient with ceftazidime allergy may be associated with increased risk of allergic reaction because of the similarity of side chains.

Sulfonamides

The most common type of reaction to sulfonamides is a maculopapular eruption often associated with fever that occurs after 7-12 days of therapy. Immediate reactions, including anaphylaxis, as well as other immunologic reactions, have also been suggested. Hypersensitivity reactions to sulfonamides occur with much greater frequency in HIV-infected individuals. For patients in whom maculopapular rashes develop after sulfonamide administration, both graded challenge and desensitization protocols have been shown to be effective. These regimens should not be used in individuals with a history of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Hypersensitivity reactions to *sulfasalazine* used for treatment of inflammatory bowel disease appear to result from the sulfapyridine moiety. Slow desensitization over about 1 mo permits tolerance of the drug in many patients. In addition, oral and enema forms of 5-aminosalicylic acid, thought to be the pharmacologically active agent in sulfasalazine, are effective alternative therapies.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Blistering mucocutaneous disorders induced by drugs encompass a spectrum of reactions, including SJS and TEN (see Chapters 673.2 and 673.3). While their pathophysiology remains incompletely understood, HLA associations including

HLA-B*1502 with carbamazepine-induced TEN have been recognized, and the pathogenic roles of drug-specific cytotoxic T cells and granulysin have been reported. Epidermal detachment of <10% is suggestive of SJS, 30% detachment suggests TEN, and 10–30% detachment suggests overlap of the 2 syndromes. The features of SJS include confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than 1 mucosal surface, accompanied by fever and constitutional symptoms. Ocular involvement may be particularly severe, and the liver, kidneys, and lungs may also be involved. TEN, which appears to be related to keratinocyte apoptosis, manifests as widespread areas of confluent erythema followed by epidermal necrosis and detachment with severe mucosal involvement. Skin biopsy differentiates subepidermal cleavage characteristic of TEN from intraepidermal cleavage characteristic of the scalded-skin syndrome induced by staphylococcal toxins. The risks of infection and mortality remain high, but improved outcomes have been demonstrated by immediate withdrawal of the implicated drug, early transfer to an intensive care or burn unit, and aggressive supportive care. Additional management is reviewed in Chapter 673.3 .

Hypersensitivity to Antiretroviral Agents

A growing number of ADRs have been observed with antiretroviral agents, including reverse-transcriptase inhibitors, protease inhibitors, and fusion inhibitors. Hypersensitivity to abacavir is a well-recognized, multiorgan, potentially life-threatening reaction that occurs in HIV-infected children. The reaction is independent of dose, with onset generally within 9-11 days of initiation of drug therapy. Rechallenge can be accompanied by significant hypotension and potential mortality (rate of 0.03%), and thus hypersensitivity to abacavir is an absolute contraindication for any subsequent use. Prophylaxis with prednisolone does not appear to prevent hypersensitivity reactions to abacavir. Importantly, genetic susceptibility appears to be conferred by the HLA-B*5701 allele, with a PPV >70% and NPV of 95–98%. Genetic screening would be cost-effective in white populations but not in populations of African or Asian descent, in which HLA-B*5701 allele frequency is <1%.

Chemotherapeutic Agents

Hypersensitivity reactions to chemotherapeutic drugs have been described, including to monoclonal antibodies. Rapid desensitization to a variety of unrelated agents, including carboplatin, paclitaxel, and rituximab, can be safely achieved in a 12-step protocol. Of note, this approach appears to be successful in both IgE-mediated and non–IgE-mediated reactions.

Biologics

An increasing number of biologic agents have become available for the treatment of autoimmune, allergic, cardiovascular, infectious, and neoplastic diseases. Their use may be associated with a variety of ADRs, including hypersensitivity reactions. Given the occurrence of anaphylaxis, including cases with delayed onset and protracted progression in spontaneous postmarketing adverse event reports, the FDA issued a black box warning regarding risk of anaphylaxis and need for patient monitoring with use of omalizumab (see Chapter 169).

Vaccines

Allergy to vaccines may occur from reactivity to various vaccine components. Measles-mumps-rubella (MMR) vaccine has been shown to be safe in egg-allergic patients (although rare reactions to gelatin or neomycin can occur). The ovalbumin content in influenza vaccine is extremely low. Skin testing with the influenza vaccine is not recommended for egg-allergic patients but may be helpful if allergy to the vaccine itself is suspected. Egg-allergic patients do not appear to be at higher risk of reacting to the influenza vaccine than those without egg allergy, and they may receive it in the usual manner with the same 15-min waiting period suggested for other vaccinations and in a medical setting prepared to treat anaphylaxis.

Perioperative Agents

Anaphylactoid (non–IgE-mediated anaphylaxis) reactions occurring during general anesthesia may be caused by induction agents (thiopental) or muscle-relaxing agents (succinylcholine, pancuronium). Quaternary ammonium muscle relaxants (succinylcholine) can act as bivalent antigens in IgE-mediated reactions. Negative skin test results do not necessarily predict that a drug will be tolerated. Latex allergy should always be considered in the differential diagnosis of a perioperative reaction.

Local Anesthetics

ADRs associated with local anesthetic agents are primarily toxic reactions resulting from rapid drug absorption, inadvertent intravenous (IV) injection, or overdose. Local anesthetics are classified as esters of benzoic acid (group I) or amides (group II). Group I includes benzocaine and procaine; group II includes lidocaine, bupivacaine, and mepivacaine. In suspected local anesthetic allergy, skin testing followed by a graded challenge can be performed or an anesthetic agent from a different group can be used.

Insulin

Insulin use has been associated with a spectrum of ADRs, including local and systemic IgE-mediated reactions, hemolytic anemia, serum sickness reactions, and delayed-type hypersensitivity. In general, human insulin is less allergenic than porcine insulin, which is less allergenic than bovine insulin, but for individual patients, porcine or bovine insulin may be the least allergenic. Patients treated with nonhuman insulin have had systemic reactions to recombinant human insulin even on the first exposure. More than 50% of patients who receive insulin develop antibodies against the insulin preparation, although there may not be any clinical manifestations. Local cutaneous reactions usually do not require treatment and resolve with continued insulin administration, possibly because of IgG-blocking antibodies. More severe local reactions can be treated with antihistamines or by splitting the insulin dose between separate administration sites. Local reactions to the protamine component of neutral protamine Hagedorn insulin may be avoided by switching to Lente insulin. Immediate-type reactions to insulin, including urticaria and anaphylactic shock, are unusual and almost always occur after reinstitution of insulin therapy in sensitized patients.

Insulin therapy should not be interrupted if a systemic reaction to insulin occurs, and continued insulin therapy is essential. Skin testing may identify a less antigenic insulin preparation. The dose following a systemic reaction is usually reduced to one-third, and successive doses are increased in 2-5 unit increments until the dose resulting in glucose control is attained. Insulin skin testing and desensitization are required if insulin treatment is subsequently interrupted for >24-48 hr.

Immunologic resistance usually occurs when high titers of predominantly IgG antibodies to insulin develop. A rare form of insulin resistance caused by circulating antibodies to tissue insulin receptors is associated with acanthosis nigricans and lipodystrophy. Coexisting insulin allergy may be present in up to one third of patients with insulin resistance. Approximately half of affected patients benefit from substitution with a less reactive insulin preparation, based on skin testing.

Drug-Induced Hypersensitivity Syndrome

Drug-induced hypersensitivity syndrome, or **DRESS** (drug rash with eosinophilia and systemic symptoms) syndrome, is a potentially life-threatening syndrome that has been described primarily with anticonvulsants, although many other medications have been implicated (see Tables 177.1 and 177.2). It is characterized by fever, maculopapular rash, facial edema, eosinophilia, generalized lymphadenopathy, and potentially life-threatening damage of one or more organs, usually renal or hepatic. Onset is delayed, usually weeks after initiation of the medication. It has been associated with reactivation of human herpesvirus 6. Treatment is withdrawal of the medication, systemic steroids, and supportive care, but symptoms can worsen or persist for weeks to months after the drug has been discontinued.

Red Man Syndrome

Red man syndrome is caused by nonspecific histamine release and is most often described with administration of IV vancomycin. It can be prevented by slowing the vancomycin infusion rate or by preadministration of H_1 -receptor blockers.

Radiocontrast Media

Anaphylactoid reactions to radiocontrast media or dye can occur after intravascular administration and during myelograms or retrograde pyelograms. No single pathogenic mechanism has been defined, but it is likely that mast cell activation accounts for the majority of these reactions. Complement activation has also been described. There is no evidence that sensitivity to seafood or iodine predisposes to radiocontrast media reactions. Predictive tests are not available. Patients who have atopic profiles, who are taking β-blockers, and who have had prior anaphylactoid reactions are at increased risk. Other diagnostic alternatives should be considered, or patients can be given low-osmolality radiocontrast media with a pretreatment regimen including oral prednisone, diphenhydramine, and albuterol, with or without cimetidine or ranitidine.

Narcotic Analgesics

Opiates such as morphine and related narcotics can induce direct mast cell degranulation. Patients may experience generalized pruritus, urticaria, and occasionally, wheezing. If there is a suggestive history and analgesia is required, a nonnarcotic medication should be considered. If this intervention does not control pain, graded challenge with an alternative opiate is an option.

Aspirin and Nonsteroidal Antiinflammatory Drugs

Aspirin and NSAIDs can cause anaphylactoid reactions or urticaria and angioedema in children and, rarely, asthma with or without rhinoconjunctivitis in adolescents. There is no skin or in vitro test to identify patients who may react to aspirin or other NSAIDs. Once aspirin or NSAID intolerance has been established, options include avoidance and pharmacologic desensitization and subsequent continued treatment with aspirin or NSAIDs, if indicated. A number of studies suggest that cyclooxygenase-2 inhibitors are tolerated by the majority of patients with NSAID-induced adverse reactions.

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PART XV

Rheumatic Diseases of Childhood (Connective Tissue Disease, Collagen Vascular Diseases)

OUTLINE

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CHAPTER 178

Evaluation of Suspected Rheumatic Disease

C. Egla Rabinovich

Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune marker and other serologic tests, tissue pathology, and imaging. Defined diagnostic criteria exist for most rheumatic diseases. Recognition of clinical patterns remains essential for diagnosis because there is no single diagnostic test, and results may be positive in the absence of disease. Further complicating the diagnosis, children sometimes present with partial criteria that evolve over time or with features of more than one rheumatic disease (**overlap syndromes**). The primary mimics of rheumatic diseases are **infection** and **malignancy** but also include metabolic, orthopedic, immune deficiencies, autoinflammatory diseases, and chronic pain conditions. Exclusion of possible mimicking disorders is essential before initiation of treatment for a presumptive diagnosis, especially corticosteroids. After careful evaluation has excluded nonrheumatic causes, referral to a pediatric rheumatologist for confirmation of the diagnosis and treatment should be considered.

Symptoms Suggestive of Rheumatic Disease

There are no classic symptoms of a rheumatic disease, but common symptoms include joint pain, fever, fatigue, and rash. Presenting signs and symptoms help direct the evaluation and limit unnecessary testing. Once a differential diagnosis is developed on the basis of history and physical findings, a directed assessment assists in determining the diagnosis.

Arthralgias are common in childhood and are a frequent reason for referral to pediatric rheumatologists. Arthralgias without physical findings for arthritis suggest infection, malignancy, orthopedic conditions, benign syndromes, or pain syndromes such as fibromyalgia (Table 178.1). Although rheumatic diseases may manifest as arthralgias, **arthritis** is a stronger predictor of the presence of rheumatic disease and a reason for referral to a pediatric rheumatologist. The timing of joint pain along with associated symptoms, including poor sleep and interference with normal activities, provides important clues. Poor sleep, debilitating generalized joint pain that worsens with activity, school absences, and normal physical and laboratory findings in an adolescent suggest a **pain syndrome** (e.g., fibromyalgia). If arthralgia is accompanied by a history of dry skin, hair loss, fatigue, growth disturbance, or cold intolerance, testing for **thyroid disease** is merited. Nighttime awakenings because of severe pain along with decreased platelet or white blood cell count or, alternatively, a very high WBC count, may lead to the diagnosis of malignancy, especially marrow-occupying lesions such as **acute lymphocytic leukemia** and **neuroblastoma** . Pain with physical activity suggests a mechanical problem such as an overuse syndrome or orthopedic condition. An adolescent girl presenting with knee pain aggravated by walking up stairs and on patellar distraction likely has **patellofemoral syndrome** . Children age 3-10 yr who have a history of episodic pain that occurs at night after increased daytime physical activity that is relieved by rubbing, but who have no limp or complaints in the morning, likely have **growing pains** . There is often a positive family history for growing pains, which may aid in this diagnosis. Intermittent pain in a child, especially a girl 3-10 yr old, that is increased with activity and is associated with hyperextensible joints on examination, is likely **benign hypermobility syndrome** . Many febrile illnesses cause arthralgias that improve when the temperature normalizes, and arthralgias are part of the diagnostic criteria for **acute rheumatic fever** (**ARF** ; see Chapter 210.1).

Table 178.1

Symptoms Suggestive of Rheumatic Disease

SYMPTOM	RHEUMATIC DISEASE(S)	POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS
Fevers	Systemic JIA, SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD	Malignancies, infections and postinfectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP
Arthralgias	JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma,	Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overuse syndromes

	sarcoidosis	
Weakness	JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma	Muscular dystrophies, metabolic and other myopathies, hypothyroidism
Chest pain	Juvenile idiopathic arthritis, SLE (with associated pericarditis or costochondritis)	Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation
Back pain	Enthesitis-related arthritis, juvenile ankylosing spondylitis	Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury
Fatigue	SLE, JDM, MCTD, vasculitis, JIA	Pain syndromes, chronic infections, chronic fatigue syndrome, depression

HSP, Henoch-Schönlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus.

Arthralgia may also be a presenting symptom of pediatric **systemic lupus erythematosus** (**SLE**) and chronic childhood arthritis such as **juvenile idiopathic arthritis (JIA).** Interestingly, many children with JIA do not complain of joint symptoms at presentation. Other symptoms more suggestive of arthritis include morning stiffness, joint swelling, limited range of motion, pain with joint motion, gait disturbance, fever, and fatigue or stiffness after physical inactivity *(gelling phenomenon)* . A diagnosis of JIA cannot be made without the finding of arthritis on physical examination (see Chapters 180 and 181). No laboratory test is diagnostic of JIA or any other chronic inflammatory arthritis in childhood.

Fatigue is a nonspecific symptom that may point to the presence of a rheumatic disease but is also common in nonrheumatic causes, such as viral infections, pain syndromes, depression, and malignancy. Fatigue, rather than the specific complaints of muscle weakness, is a common presenting complaint in **juvenile dermatomyositis (JDM)** . It is also frequently present in SLE, vasculitis, and the chronic childhood arthritides. Overwhelming fatigue with inability to attend school is more suggestive of chronic fatigue syndrome, pediatric fibromyalgia, or other amplified pain syndrome.

Signs Suggestive of Rheumatic Disease

A complete physical examination is mandated in any child with suspected rheumatic disease, because many diseases have associated subtle physical findings that will further refine the differential diagnosis. In addition, many rheumatic diseases have multisystem effects, and a stepped assessment should focus on delineating the extent of organ system involvement (e.g., skin, joints, muscle, hepatic, renal, cardiopulmonary).

Presence of a **photosensitive malar rash** that spares the nasolabial folds is suggestive of SLE (Table 178.2 ; see Fig. 183.1*A*), especially in an adolescent girl. Diffuse facial rash is more indicative of JDM. A hyperkeratotic rash on the face or around the ears of an adolescent black girl may represent discoid lupus (see Fig. 183.1*D*). A palpable purpuric rash on the extensor surfaces of the lower extremities points to **Henoch-Schönlein purpura** (see Fig. 192.2*A*). Less localized purpuric rashes and petechiae are present in systemic vasculitis or blood dyscrasias, including coagulopathies. Nonblanching erythematous papules on the palms are seen in vasculitis and SLE as well as endocarditis. Gottron papules (see Fig. 184.2) and heliotrope rashes (see Fig. 184.1) along with erythematous rashes on the elbows and knees are pathognomonic of JDM. Dilated capillary loops in the nail beds (periungual telangiectasias; see Fig. 184.3) are common in JDM, scleroderma, and secondary Raynaud phenomenon. An evanescent macular rash associated with fever is part of the diagnostic criteria for systemic-onset arthritis (see Fig. 180.12). Sun sensitivity or photosensitive rashes are indicative of SLE or JDM but can also be caused by antibiotics.

Table 178.2

Signs Suggestive of Rheumatic Disease

SIGN	RHEUMATIC DISEASES	COMMENTS	NONRHEUMATIC CAUSES
Malar rash	SLE, JDM	SLE classically spares nasolabial folds	Sunburn, parvovirus B19 (fifth disease), Kawasaki disease
Oral ulcers	SLE, Behçet disease	Behçet disease also associated with genital ulcers	HSV infection, PFAPA syndrome
Purpuric rash	Vasculitis, e.g., ANCA-associated vasculitis, HSP	HSP typically starts as small lesions on lower extremities and buttocks that coalesce	Meningococcemia, thrombocytopenia, clotting disorders
Gottron papules	JDM	Look for associated heliotrope rash, periungual telangiectasias	Psoriasis, eczema
Arthritis	Juvenile idiopathic arthritis, SLE, vasculitis, HSP, MCTD, scleroderma, acute rheumatic fever, reactive arthritis	Chronic joint swelling (>6 wk) required for diagnosis of chronic arthritis of childhood; MCTD associated with diffuse puffiness of hands	Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes

ANCA, Antineutrophil cytoplasmic antibody; HSP, Henoch-Schönlein purpura; HSV, herpes simplex virus; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis; SLE, systemic lupus erythematosus.

Mouth ulcers are part of the diagnostic criteria for SLE and Behçet disease (see Fig. 183.1*C*); painless nasal ulcers and erythematous macules on the hard palate are also common in SLE. Cartilage loss in the nose, causing a saddle nose deformity, is classically present in granulomatosis with polyangiitis (formally Wegener granulomatosis; see Fig. 192.8) but is also seen in relapsing polychondritis and syphilis. Alopecia can be associated with SLE but is also found in localized scleroderma (see Fig. 185.4) and JDM. **Raynaud phenomenon** may be a primary benign idiopathic disorder or can be a presenting complaint in the child with scleroderma, lupus, mixed connective tissue disease (MCTD), or an overlap syndrome. Diffuse lymphadenopathy is present in many rheumatic diseases, including SLE, polyarticular JIA, and systemic JIA. Irregular pupils may represent the insidious and unrecognized onset of **uveitis** associated with JIA. Erythematous conjunctivae may be a result of uveitis or episcleritis associated with JIA, SLE, sarcoidosis, spondyloarthropathies, or vasculitis.

A pericardial rub and orthopnea are suggestive of **pericarditis** , often seen in systemic JIA, SLE, and sarcoid. Coronary artery dilation is strongly suggestive of Kawasaki disease but may also be a finding in systemic arthritis and other forms of systemic vasculitis. Interstitial lung disease, suggested by dyspnea on exertion or the finding of basilar rales with decreased carbon monoxide diffusion capacity, occurs in SLE, MCTD, and systemic sclerosis. Signs consistent with pulmonary hemorrhage points to granulomatosis with polyangiitis, microscopic angiitis, or SLE. Pulmonary vascular aneurysms are indicative of Behçet disease.

Arthritis is defined by the presence of intraarticular swelling or 2 or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Arthritis is present in all the chronic childhood arthritis syndromes, along with SLE, JDM, vasculitis, Behçet disease, sarcoidosis, Kawasaki disease, and Henoch-Schönlein purpura. Nonrheumatic causes of arthritis include malignancy, septic arthritis, Lyme disease, osteomyelitis, viral infections (e.g., rubella, hepatitis B, parvovirus B19, chikungunya), and postinfectious etiologies such as Epstein-Barr virus (EBV), ARF, and reactive arthritis. ARF typically involves a migratory (lasting hours to days), painful arthritis. Pain on palpation of long bones is suggestive of malignancy. Specific muscle testing for weakness should be performed in a child presenting with fatigue or difficulty with daily tasks, because both these symptoms may be manifestations of muscle inflammation.

Laboratory Testing

There are no specific screening tests for rheumatologic disease. Once a differential diagnosis is determined, appropriate testing can be performed (Tables 178.3 and 178.4). Initial studies are generally performed in standard local laboratories. Screening for specific autoantibodies can be performed in commercial laboratories, but confirmation of results in a tertiary care center immunology laboratory is often necessary.

Table 178.3

Autoantibody Specificity and Disease Associations

ANTIBODY	DISEASE	PREVALENCE (%)	SPECIFICITY
Antinuclear antibody (ANA)	SLE, juvenile rheumatoid arthritis, dermatomyositis, scleroderma, psoriatic arthritis, MCTD	—	Associated with increased risk of uveitis in JIA and psoriatic arthritis Up to 30% of children testing positive for ANAs have no underlying rheumatic disease
Double-stranded DNA (dsDNA)	SLE	60-70	High specificity for SLE; associated with lupus nephritis
Smith (Sm)	SLE	20-30	Highly specific for SLE; associated with lupus nephritis
Smooth muscle (Sm)	Autoimmune hepatitis	—	—
Pm-Scl (polymyositis-scleroderma)	Sclerodermatomyositis	—	—
SSA (Ro)	SLE, Sjögren syndrome	25-30	Associated with neonatal lupus syndrome, subacute cutaneous lupus, thrombocytopenia
SSB (La)	SLE, Sjögren syndrome	25-30	Usually coexists with anti-SSA antibody
Ribonuclease protein (RNP)	MCTD, SLE	30-40	Suggestive of MCTD unless meets criteria for SLE
Histone	Drug-induced lupus, SLE	—	—
Centromere	Limited cutaneous systemic sclerosis	70	Nonspecific for systemic sclerosis
Topoisomerase I (Scl-70)	Systemic sclerosis	—	Rare in childhood
Antineutrophil cytoplasmic antibodies (ANCAs)	Vasculitis	—	—
Cytoplasmic (cANCAs)/PR3-ANCA		—	cANCAs associated with granulomatosis with polyangiitis (Wegener), cystic fibrosis
Perinuclear (pANCAs)/MPO-ANCA		—	pANCAs associated with microscopic polyangiitis, polyarteritis nodosa, SLE, inflammatory bowel disease, cystic fibrosis,

			primary sclerosing cholangitis, Henoch-Schönlein purpura, Kawasaki disease, Churg-Strauss syndrome
Anticitrullinated protein (ACPA); also called anti–cyclic citrullinated protein (anti-CCP)	RF-positive JIA	50-90	Specific for JIA (RF+), may be positive before RF

MCTD, Mixed connective tissue disease; MPO-ANCA, antimyeloperoxidase; PR3-ANCA, antiproteinase 3; RF, rheumatoid factor; SLE, systemic lupus erythematosus.

Adapted from Aggerwal A: Clinical application of tests used in rheumatology, *Indian J Pediatr* 69:889–892, 2002.

Table 178.4

Evaluation Based on Suspected Diagnosis of Rheumatic Disease

SUSPECTED RHEUMATIC DISEASE(S)	INITIAL EVALUATION	FURTHER EVALUATION	SUBSPECIALTY EVALUATION
Systemic lupus erythematosus (SLE) Mixed connective tissue disease (MCTD)	CBC, ESR, ANA, ALT, AST, CPK, creatinine, albumin, total protein, urinalysis, BP, thyroid profile	If ANA test result is positive: anti-SSA (Ro), anti-SSB (La), anti-Smith, and anti-RNP Abs; anti-dsDNA Ab, C3, C4, Coombs, spot urine protein/creatinine ratio, CXR	Antiphospholipid Abs, lupus anticoagulant, anti–β_2 -glycoprotein, echocardiogram; consider renal biopsy, PFTs, bronchoscopy with lavage, HRCT of chest; consider lung biopsy
Juvenile dermatomyositis (JDM)	CBC, CPK, ALT, AST, LDH, aldolase, ANA; check gag reflex	Consider MRI of muscle	Consider electromyography and possible muscle biopsy, PFTs, swallowing study, serum neopterin
Juvenile idiopathic arthritis (JIA)	CBC, ESR, creatinine, ALT, AST, consider anti–streptolysin O/anti–DNAase B for streptococcus-induced arthritis, Epstein-Barr virus titers, Lyme titer, parvovirus B19 titer, plain radiograph of joints	Consider Ab titers to unusual infectious agents, purified protein derivative, RF, ANA, HLA-B27, anti-CCP	MRI
Granulomatosis with polyangiitis (Wegener granulomatosis)	CBC, ANCA, AST, ALT, albumin, creatinine, ESR, urinalysis, CXR, BP	Spot urine protein/creatinine ratio, anti–myeloperoxidase and anti–proteinase-3 Abs, PFTs	Bronchoscopy with lavage, HRCT chest; consider lung and kidney biopsies
Sarcoidosis	CBC, electrolytes, AST, ALT, albumin, creatinine, calcium, phosphorous, ACE, BP	CXR, PFTs	Consider testing for Blau syndrome in infants (see Chapter 184); HRCT of chest; consider renal and lung biopsy

Localized scleroderma	Skin biopsy, CBC, ESR		Serum IgG, ANA, RF, single-stranded DNA Ab, antihistone Ab, CPK
Systemic scleroderma	ANA, CBC, ESR, BP, AST, ALT, CPK, creatinine, CXR	Anti-Scl70, PFTs	HRCT of chest, echocardiogram, upper GI radiography series

Ab, Antibody; ACE, angiotensin-converting enzyme (normally elevated in childhood; interpret with caution); ALT, alanine transaminase; ANA, antinuclear antibody; anti-dsDNA Ab, anti–double-stranded DNA antibody; AST, aspartate transaminase; BP, blood pressure; CBCD, complete blood count with differential; CCP, cyclic citrullinated protein; CPK, creatine phosphokinase; CXR, chest radiograph; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HRCT, high-resolution CT; LDH, lactate dehydrogenase; PFTs, pulmonary function tests; RF, rheumatoid factor; RNP, ribonucleoprotein.

One essential laboratory test for rheumatic disease assessment is the *complete blood count* (CBC), since it yields many diagnostic clues. Elevated WBC count is compatible with malignancy, infection, systemic JIA, and vasculitis. Leukopenia can be postinfectious, especially viral, or caused by SLE or malignancy. Lymphopenia is more specific for SLE than is leukopenia. Platelets are acute-phase reactants and are therefore elevated with inflammatory markers. Exceptions are a bone marrow–occupying malignancy, such as leukemia or neuroblastoma, SLE, and early Kawasaki disease. **Anemia** is nonspecific and may be caused by any chronic illness, but hemolytic anemia (positive Coombs test result) may point to SLE or MCTD. Rheumatoid factor (RF) is present in <10% of children with JIA and thus has poor sensitivity as a diagnostic tool; RF may be elevated by infections such as endocarditis, tuberculosis, syphilis, and viruses (parvovirus B19, hepatitides B and C, mycoplasma), as well as primary biliary cirrhosis and malignancies. In a child with chronic arthritis, RF serves as a prognostic indicator.

Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein) are nonspecific and are elevated in infections and malignancies as well as rheumatic diseases (Tables 178.5 and 178.6). Their levels may also be normal in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis. Inflammatory marker measurements are more useful in rheumatic diseases for following response to treatment than as diagnostic tests. Muscle enzymes include aspartate transaminase (AST), alanine transaminase (ALT), creatinine phosphokinase (CPK), aldolase, and lactate dehydrogenase (LDH), any of which may be elevated in JDM as well as in other diseases causing muscle breakdown. Muscle-building supplements, medications, and extreme physical activity may also cause muscle breakdown and enzyme elevations. AST, ALT, and aldolase are also elevated secondary to liver disease, and a γ-glutamyltransferase (GGT) measurement may help differentiate whether the source is muscle or liver.

Table 178.5

Comparison of Erythrocyte Sedimentation Rate and C-Reactive Protein

	ERYTHROCYTE SEDIMENTATION RATE	C-REACTIVE PROTEIN
Advantages	Much clinical information in the literature May reflect overall health status	Rapid response to inflammatory stimuli Wide range of clinically relevant values are detectable Unaffected by age and gender Reflects value of a single acute-phase protein Can be measured on stored sera Quantitation is precise and reproducible
Disadvantages	Affected by red blood cell morphology Affected by anemia and polycythemia Reflects levels of many plasma proteins, not all of which are acute-phase proteins Responds slowly to inflammatory stimuli Requires fresh sample May be affected by drugs (IVIG)	Not sensitive to changes in SLE disease activity

IVIG, Intravenous immune globulin; SLE, systemic lupus erythematosus.

From Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley & Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2017, Elsevier (Table 57.3 , p 849).

Table 178.6

Conditions Associated With Elevated C-Reactive Protein Levels

Normal Or Minor Elevation (<1 mg/dL)

1. Vigorous exercise
2. Common cold
3. Pregnancy
4. Gingivitis
5. Seizures
6. Depression
7. Insulin resistance and diabetes
8. Several genetic polymorphisms

9. Obesity

Moderate Elevation (1-10 mg/dL)

1. Myocardial infarction
2. Malignancies
3. Pancreatitis
4. Mucosal infection (bronchitis, cystitis)
5. Most systemic autoimmune diseases
6. Rheumatoid arthritis

Marked Elevation (>10 mg/dL)

1. Acute bacterial infection (80–85%)
2. Major trauma, surgery
3. Systemic vasculitis

From Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley & Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2017, Elsevier (Table 57-4, p 849).

The use of an antinuclear antibody (ANA) measurement as a screening test is *not* recommended because it has low specificity. A positive ANA test result may be induced by infection, especially EBV infection, endocarditis, and parvovirus B19 infection. The ANA test result is also positive in up to 30% of normal children, and ANA level is increased in those with a first-degree relative with a known rheumatic disease. In the majority of children with a positive ANA test result without signs of a rheumatic disease on initial evaluation, autoimmune disease does not develop over time, so this finding does not necessitate referral to a pediatric rheumatologist. A positive ANA test result is found in many rheumatic diseases, including JIA, in which it serves as a predictor of the risk for inflammatory eye disease (Table 178.7). Once a positive ANA test result is discovered in a child, the need for specific autoantibody testing is directed by the presence of clinical signs and symptoms (see Table 178.3).

Table 178.7

Other Nonrheumatic Conditions With Elevated Acute Phase Responses

Neuroendocrine Changes

Fever, somnolence, and anorexia
Increased secretion of corticotropin-releasing hormone, corticotropin, and cortisol
Increased secretion of arginine vasopressin
Decreased production of insulin-like growth factor I
Increased adrenal secretion of catecholamines

Hematopoietic Changes

Anemia of chronic disease
Leukocytosis
Thrombocytosis

Metabolic Changes

Loss of muscle and negative nitrogen balance
Decreased gluconeogenesis
Osteoporosis
Increased hepatic lipogenesis
Increased lipolysis in adipose tissue
Decreased lipoprotein lipase activity in muscle and adipose tissue
Cachexia

Hepatic Changes

Increased metallothionein, inducible nitric oxide synthase, heme oxygenase, manganese superoxide dismutase, and tissue inhibitor of metalloproteinase 1
Decreased phosphoenolpyruvate carboxykinase activity

Changes in Nonprotein Plasma Constituents

Hypozincemia, hypoferremia, and hypercupremia
Increased plasma retinol and glutathione concentrations

From Gabay C, Kushner I: Acute-phase proteins and other systemic responses to inflammation, *N Engl J Med* 340:448–454, 1999.

Imaging Studies

Plain radiographs are useful in evaluation of arthralgias and arthritis, as they offer reassurance in benign pain syndromes and their findings may be abnormal in malignancies, osteomyelitis, and long-standing chronic juvenile arthritis. Radionucleotide bone scans help localize areas of abnormality in the patient with diffuse pains caused by osteomyelitis, neuroblastoma, chronic multifocal osteomyelitis, and systemic arthritis. MRI findings are abnormal in inflammatory myositis and suggest the optimal site for biopsy. *MRI is more sensitive than plain radiographs in detecting the presence of early erosive arthritis and demonstrates increased joint fluid, synovial enhancement, and sequela of trauma with internal joint derangement.* MRI is also helpful in ruling out infection or malignancy. Cardiopulmonary evaluation is suggested for diseases commonly affecting the heart and lung, including SLE, systemic scleroderma, MCTD, JDM, and sarcoid, as clinical manifestations may be subtle. This evaluation, which may include echocardiogram, pulmonary function tests, and high-resolution CT of the lungs along with consideration of bronchoalveolar lavage, is generally performed by a pediatric rheumatologist to whom the patient is referred (see Table 178.4).

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CHAPTER 179

Treatment of Rheumatic Diseases

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Nonpharmacologic as well as pharmacologic interventions are often necessary to meet the desired goals of disease management. Optimal disease management requires family-centered care delivered by a multidisciplinary team of healthcare professionals providing medical, psychological, social, and school support. Rheumatologic conditions most often follow a course marked by flares and periods of remission, although some children have unremitting disease. The goals of treatment are to control disease, relieve discomfort, avoid or limit drug toxicity, prevent or reduce organ damage, and maximize the physical function and quality of life of affected children. Nonpharmacologic therapy is an important adjunct to medical management of rheumatic diseases (see Chapter 76). A key predictor of long-term outcome is early recognition and referral to a rheumatology team experienced in the specialized care of children with rheumatic diseases. Significant differences in outcome are seen 10 yr after disease onset in patients with **juvenile idiopathic arthritis (JIA)** depending on whether referral to a pediatric rheumatology center was accomplished within 6 mo of onset.

Pediatric Rheumatology Teams and Primary Care Physicians

The **multidisciplinary pediatric rheumatology team** offers coordinated services for children and their families (Table 179.1). General principles of treatment include: early recognition of signs and symptoms of rheumatic disease with timely referral to rheumatology for prompt initiation of treatment; monitoring for disease complications and adverse effects of treatment;

coordination of subspecialty care and rehabilitation services with communication of clinical information; and child- and family-centered chronic illness care, including self-management support, alliance with community resources, partnership with schools, resources for dealing with the financial burdens of disease, and connection with advocacy groups. Planning for transition to adult care providers needs to start in adolescence. Central to effective care is partnership with the primary care provider, who helps coordinate care, monitor compliance with treatment plans, ensure appropriate immunization, monitor for medication toxicities, and identify disease exacerbations and concomitant infections. Communication between the primary care provider and subspecialty team permits timely intervention when needed.

Table 179.1

Multidisciplinary Treatment of Rheumatic Diseases in Childhood

Accurate diagnosis and education of family	Pediatric rheumatologist Pediatrician
	Nurse: • Disease-related education • Medication administration (injection teaching) • Safety monitoring
	Social worker: • Facilitation of school services • Resource identification (community, government, financial, advocacy groups, vocational rehabilitation)
Physical medicine and rehabilitation	Physical therapy: • Addressing deficits in joint or muscle mobility, limb length discrepancies, gait abnormalities, and weakness
	Occupational therapy: • Splinting to reduce joint contractures/deformities and lessen stress on joints; adaptive devices for activities of daily living
Consultant team	Ophthalmology: • Eye screening for uveitis (see Table 180.4) • Screening for medication-related ocular toxicity (hydroxychloroquine, glucocorticoids)
	Nephrology
	Orthopedics
	Dermatology
	Gastroenterology
Physical and psychosocial growth and development	Nutrition: • Addressing undernourishment from systemic illness and obesity/overnourishment from glucocorticoids
	School integration: • Individualized educational plan (IEP) or 504 plan
	Peer-group relationships

	Individual and family counseling
Coordination of care	Involvement of patient and family as active team members
	Communication among healthcare providers
	Involvement of school (school nurse) and community (social worker) resources

Therapeutics

A key principle of pharmacologic management of rheumatic diseases is that early disease control, striving for induction of remission, leads to less tissue and organ damage with improved short- and long-term outcomes. Medications are chosen from broad therapeutic classes on the basis of diagnosis, disease severity, anthropometrics, and adverse effect profile. Many drug therapies used do not have U.S. Food and Drug Administration (FDA) indications for pediatric rheumatic diseases given the relative rarity of these conditions. The evidence base may be limited to case series, uncontrolled studies, or extrapolation from use in adults. The exception is JIA, for which there is a growing body of randomized controlled trial (RCT) evidence, particularly for newer therapeutics. Therapeutic agents used for treatment of childhood rheumatic diseases have various mechanisms of action, but all suppress inflammation (Table 179.2). *Both biologic and nonbiologic* **disease-modifying antirheumatic drugs (DMARDs** *) directly affect the immune system.* DMARDs should be prescribed by specialists. Live vaccines are contraindicated in patients taking immunosuppressive glucocorticoids or DMARDs. A negative test result for tuberculosis (purified protein derivative and/or QuantiFERON-TB Gold) should be verified and the patient's immunization status updated, if possible, before such treatment is initiated. Killed vaccines are not contraindicated, and annual injectable influenza vaccine is recommended.

Table 179.2

Therapeutics for Childhood Rheumatic Diseases[*]

CLASSIFICATION	THERAPEUTIC [†]	DOSE	INDICATION [†]	ADVERSE REACTIONS
Nonsteroidal antiinflammatory drugs (NSAIDs) [‡]	Etodolac [a]	PO once-daily dose: 20-30 kg: 400 mg 31-45 kg: 600 mg 46-60 kg: 800	JIA Spondyloarthropathy Pain Serositis Cutaneous vasculitis Uveitis	GI intolerance (abdominal pain, nausea), gastritis, hepatitis, tinnitus, anemia, pseudoporphyria, aseptic meningitis,

		mg >60 kg: 1,000 mg		headache, renal disease
	Ibuprofen [a]	40 mg/kg/day PO in 3 divided doses Max: 2400 mg/day		
	Naproxen [a]	15 mg/kg/day PO in 2 divided doses Max 1,000 mg/day		
	Celecoxib [a]	10-25 kg: 50 mg PO bid >25 kg: 100 mg PO bid		
	Meloxicam [a]	0.125 mg/kg PO qd Max 7.5 mg		
Disease-modifying antirheumatic drugs (DMARDs)	Methotrexate [a]	10-20 mg/m^2 /wk (0.35-0.65 mg/kg/wk) PO 20-30 mg/m^2 /wk (0.65-1 mg/kg/wk) SC; higher doses better absorbed by SC injection	JIA Uveitis	GI intolerance (nausea, vomiting), hepatitis, myelosuppression, mucositis, teratogenesis, lymphoma, interstitial pneumonitis
	Leflunomide	PO once daily: 10 to <20 kg: 10 mg 20-40 kg: 15 mg >40 kg: 20 mg	JIA	Hepatitis, hepatic necrosis, cytopenias, mucositis, teratogenesis, peripheral neuropathy
	Hydroxychloroquine	5 mg/kg PO qd; do not exceed 5 mg/kg/daily Max 400 mg daily	SLE JDMS Antiphospholipid antibody syndrome	Retinal toxicity, GI intolerance, rash, skin discoloration, anemia, cytopenias, myopathy, CNS stimulation, death (overdose)
	Sulfasalazine [a]	30-50 mg/kg/day in 2 divided doses Adult max 3 g/day	Spondyloarthropathy, JIA	GI intolerance, rash, hypersensitivity reactions, Stevens-Johnson syndrome, cytopenias, hepatitis, headache

Tumor necrosis factor (TNF)-α antagonists	Adalimumab [a]	SC once every other wk: 10 to <15 kg: 10 mg 15 to <30 kg: 20 mg ≥30 kg: 40 mg	JIA Spondyloarthropathy Psoriatic arthritis Uveitis	Injection site reaction, infection, rash, cytopenias, lupus-like syndrome, potential increased malignancy risk
	Etanercept [a]	0.8 mg/kg SC once weekly (max 50 mg/dose) or 0.4 mg/kg SC twice weekly (max 25 mg/dose)	JIA	Injection site reactions, infections, rash, demyelinating disorders, cytopenias, potential increased malignancy risk
	Infliximab	5-10 mg/kg IV every 4-8 wk	JIA Spondyloarthropathy Uveitis Sarcoidosis	Infusion reactions, hepatitis, potential increased malignancy risk
Modulate T-cell activation	Abatacept [a]	IV every 2 wk ×3 doses, then monthly for ≥6 yr of age: <75 kg: 10 mg/kg 75-100 kg: 750 mg >100 kg: 1,000 mg	JIA	Infection, headache, potential increased malignancy risk
		SC once weekly: 10 to <25 kg: 50 mg ≥25 to <50 kg: 87.5 mg ≥50 kg: 125 mg		
Anti-CD20 (B-cell) antibody	Rituximab	575 mg/m^2 , max 1,000 mg, IV on days 1 and 15	SLE	Infusion reactions, lymphopenia, reactivation hepatitis B, rash, serum sickness, arthritis, PML
Anti-BLyS antibody	Belimumab [e]	10 mg/kg IV every 2 wk ×3 doses, then every 4 wk	SLE	Infusion reactions, infection, depression
Interleukin (IL)-1 antagonist	Anakinra	1-2 mg/kg/daily Adult max 100 mg	Systemic JIA CAPS	Injection site reactions, infection
	Canakinumab [b]	Given SC every 8 wk (CAPS) every 4 wk (systemic JIA): 15-40 kg: 2 mg/kg (up to 3 mg/kg if	CAPS Systemic JIA	Injection site reaction, infection, diarrhea, nausea, vertigo, headache

		needed) >40 kg: 150 mg		
		IV: <30 kg: 10 mg/kg/dose every 4 wk ≥30 kg: 8 mg/kg/dose every 4 wk; maximum dose: 800 mg/dose SC: <30 kg: 162 mg/dose once every 3 wk ≥30 kg: 162 mg/dose once every 2 wk	Polyarticular JIA	
IL-6 antagonist	Tocilizumab [a]	≥2 yr and ≥30 kg: 8 mg/kg/dose every 2 wk ≥2 yr and ≤30 kg: 12 mg/kg/dose every 2 wk	Systemic JIA	Infusion reactions, elevated LFTs, elevated lipids, thrombocytopenia, infections
Intravenous immune globulin	IVIG [c]	1,000-2,000 mg/kg IV infusion For JDMS, give monthly	Kawasaki disease JDMS SLE	Infusion reaction, aseptic meningitis, renal failure
Cytotoxic	Cyclophosphamide	0.5-1 g/m^2 IV (max 1.5 g) monthly for 6 mo induction, then every 2-3 mo Oral regimen: 1-2 mg/kg/daily; max 150 mg/daily	SLE Vasculitis JDMS Pulmonary hemorrhage	Nausea, vomiting, myelosuppression, mucositis, hyponatremia, alopecia, hemorrhagic cystitis, gonadal failure, teratogenesis, secondary malignancy
Immunosuppressive	Mycophenolate mofetil	Oral suspension: max 1,200 mg/m^2 /day PO (up to 2 g/day) divided bid Capsules: max 1,500 mg/day PO for BSA 1.25-1.5 m^2 , 2 g/day PO for BSA >1.5 m^2 divided bid	SLE Uveitis	GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML

Glucocorticoids	Prednisone[a, d-f]	0.05-2 mg/kg/day PO given in 1-4 divided doses; max varies by individual (80 mg/daily) Adverse effects are dose dependent; lowest effective dose should be used	SLE JDMS Vasculitis JIA Uveitis Sarcoidosis	Cushing syndrome, osteoporosis, increased appetite, weight gain, striae, hypertension, adrenal suppression, hyperglycemia, infection, avascular necrosis
	Methylprednisolone[a, d-g]	0.5-1.7 mg/kg/day or 5-25 mg/m^2 /day IM/IV in divided doses every 6-12 hr For severe manifestations: 30 mg/kg/dose (max 1 g) daily for 1-5 days	SLE JDMS Vasculitis Sarcoidosis Localized scleroderma	
	Intraarticular	Dose varies by joint and formulation	JIA	Subcutaneous atrophy, skin hypopigmentation, calcification, infection
	Prednisolone ophthalmic suspension	1-2 drops into eye up to every hr while awake Needs monitoring by ophthalmologist	Uveitis	Ocular hypertension, glaucoma, nerve damage, cataract, infection

[*] Consult a clinical pharmacology reference for current dosing and monitoring guidelines, and complete list of known adverse effects.

[†] Therapeutics used in practice may not have a FDA-approved indication. Individual therapeutics annotated with FDA-approved indication as follows: a , JIA; b , CAPS; c , Kawasaki disease; d , sarcoidosis; e , SLE; f , uveitis; g , dermatomyositis.

[‡] Many more products available in this class.

qd, Once daily; bid, twice daily; Blys, B-lymphocyte stimulator; BMP, basic metabolic panel; BSA, body surface area; BUN, blood urea nitrogen; CAPS, cryopyrin-associated periodic syndrome; CBC, complete blood count; CNS, central nervous system; dsDNA, double-stranded DNA; GI, gastrointestinal; IM, intramuscular(ly); IV, intravenous(ly); IVIG, intravenous immune globulin; JDMS, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LFTs, liver function tests; PML, progressive multifocal leukoencephalopathy; PO, by mouth; SC, subcutaneous(ly); SLE, systemic lupus erythematosus; TB, tuberculosis.

Nonsteroidal Antiinflammatory Drugs

NSAIDs are prescribed to decrease both the pain and the acute and chronic inflammation associated with arthritis, pleuritis, pericarditis, uveitis, and cutaneous vasculitis, but they are not disease modifying. NSAID antiinflammatory effects require regular administration at adequate doses based on weight (mg/kg) or body surface area (mg/m^2), for longer periods than needed for analgesia alone. The mean time to achieve antiinflammatory effect in JIA is 4-6 wk of consistent administration. NSAIDs work primarily by inhibiting the enzyme cyclooxygenase (COX), which is critical in the production of **prostaglandins** , a family of substances that promote inflammation. Two types of COX receptors have been demonstrated; **selective** COX-2 inhibitors such as *celecoxib* and *meloxicam* inhibit receptors responsible for promoting inflammation, with potential for fewer gastrointestinal (GI) adverse effects. Clinical trials in children with JIA found that celecoxib and meloxicam were similar in effectiveness and tolerability to the **nonselective** NSAID *naproxen* .

The most frequent adverse effects of NSAIDs in children are nausea, decreased appetite, and abdominal pain. Gastritis or ulceration occurs less frequently in children. Less common adverse effects(≤5% of children undergoing long-term NSAID therapy), include mood change, concentration difficulty that can simulate attention deficit disorder, sleepiness, irritability, headache, tinnitus, alopecia, anemia, elevated liver enzyme values, proteinuria, and hematuria. Certain agents (indomethacin) have a higher risk of toxicity than others (ibuprofen); naproxen has an intermediate risk. These NSAID-associated adverse effects reverse quickly once the medication is stopped. Additional rare NSAID-specific adverse reactions may also occur. Aseptic meningitis has been associated with ibuprofen, primarily in patients with lupus. Naproxen is more likely than other NSAIDs to cause a unique skin reaction called **pseudoporphyria** , which is characterized by small, hypopigmented depressed scars occurring in areas of minor skin trauma, such as fingernail scratches. Pseudoporphyria is more likely to occur in fair-skinned individuals and on sun-exposed areas. If pseudoporphyria develops, the inciting NSAID should be discontinued because scars can persist for years or may be permanent. NSAIDs should be used cautiously in patients with dermatomyositis or systemic vasculitis because of an increased frequency of GI ulceration with these disorders. *Salicylates have been supplanted by other NSAIDs because of the relative frequency of salicylate hepatotoxicity and the association with Reye syndrome.*

The response to NSAIDs varies greatly among individual patients, but overall, 40–60% of children with JIA experience improvement in their arthritis with NSAID therapy. Patients may try several different NSAIDs for 6 wk trials before finding one that demonstrates clinical benefit. NSAIDs with longer half-lives or sustained-release formulations allow for once- or twice-daily dosing and improve compliance. Laboratory monitoring for toxicity includes a complete blood count (CBC), serum creatinine, liver function tests (LFTs), and urinalysis every 6-12 mo, although guidelines for frequency of testing are not established.

Nonbiologic Disease-Modifying Antirheumatic Drugs

Methotrexate

Methotrexate (MTX), an antimetabolite, is a cornerstone of therapy in pediatric rheumatology because of its sustained effectiveness and relative low toxicity over prolonged periods of treatment. The mechanism of action low-dose MTX in arthritis is complex but is believed to result from the inhibition of folate-dependent processes by MTX polyglutamates, primarily their effect on the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, leading to an increase of extracellular adenosine and consequently, cyclic adenosine monophosphate (cAMP), which inhibits the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β and their downstream effects on lymphocyte activation and proliferation.

MTX has a central role in the treatment of arthritis, especially in children with polyarticular JIA. The response to oral MTX (10 mg/m^2 once a week) is better than the response to placebo (63% vs 36%). Children who show no response to standard doses of MTX often do show response to higher doses (15 or 30 mg/m^2 /wk). Subcutaneous (SC) administration of MTX is similar in absorption and pharmacokinetic properties to intramuscular (IM) injection, with less pain. MTX is typically used in treatment of juvenile dermatomyositis as a steroid-sparing agent, with efficacy in 70% of patients. It has also been used successfully at a dosage of 10-20 mg/m^2 /wk in patients with systemic lupus erythematosus (SLE) to treat arthritis, serositis, and rash.

Because of the lower dose used in treating rheumatic diseases, MTX is well tolerated by children, with toxicity being milder and qualitatively different from that observed with treatment of neoplasms. Adverse effects include elevated liver enzyme values (15%), GI toxicity (13%), stomatitis (3%), headache (1–2%), and leukopenia, interstitial pneumonitis, rash, and alopecia (<1%). Hepatotoxicity observed among adults with rheumatoid arthritis (RA) treated with MTX has raised concern about similar problems in children. Analysis of liver biopsy specimens in children with JIA undergoing long-term MTX treatment has revealed occasional mild fibrosis but no evidence of even moderate liver damage. Children receiving MTX should be counseled to avoid alcohol, smoking, and pregnancy. *Folic acid* (1 mg daily) is given as an adjunct to minimize adverse effects. Lymphoproliferative disorders have been reported in adults treated with MTX, primarily in association with Epstein-Barr virus (EBV) infection. Regression of lymphoma may follow withdrawal of MTX.

Monitoring laboratory tests for MTX toxicity include CBC and LFTs at regular intervals, initially every 4 wk for the 1st 3 mo of treatment, then every 8-12 wk, with more frequent intervals after dosing adjustments or in response to abnormal values.

Hydroxychloroquine

Hydroxychloroquine sulfate is an antimalarial drug important in the treatment of SLE and dermatomyositis, particularly cutaneous manifestations of disease and to reduce lupus flares. It is not indicated to treat JIA because of lack of efficacy. The most significant potential adverse effect is retinal toxicity, which occurs rarely but results in irreversible color blindness or loss of central vision. Complete ophthalmologic examinations, including assessment of peripheral vision and color fields, are conducted at baseline and every 6-12 mo to screen for retinal toxicity. Retinal toxicity is rare (1/5,000 patients) and is associated with weight-based dosing exceeding 6.5 mg/kg/day; therefore recommended dosing is <6.5 mg/kg/day, not to exceed 400 mg/day. Other potential adverse effects include rash, skin discoloration, gastric irritation, bone marrow suppression, central nervous system (CNS) stimulation, and myositis.

Leflunomide

Leflunomide is a DMARD approved for treatment of RA that offers an alternative to MTX for treatment of JIA. MTX outperformed leflunomide for treatment of JIA in a randomized trial (at 16 wk, 89% of patients receiving MTX achieved a 30% response rate vs 68% of those receiving leflunomide), although both drugs were effective. Dosing is oral, once daily, and weight based: 10 mg for children 10 to <20 kg, 15 mg for children 20-40 kg, and 20 mg for children >40 kg. Adverse reactions include paresthesias and peripheral neuropathy, GI intolerance, elevated liver transaminases and hepatic failure, cytopenias, alopecia, and teratogenesis. Leflunomide has a long half-life, and in cases in which discontinuation of the agent is required, a drug elimination protocol with cholestyramine may be indicated. Avoidance of pregnancy is essential. Laboratory tests (e.g., CBC, LFTs) are monitored every 4 wk for the 1st 6 mo of treatment, then every 8-12 wk.

Sulfasalazine

Sulfasalazine is used to treat children with polyarticular JIA, oligoarticular JIA, and the peripheral arthritis and enthesitis associated with **juvenile ankylosing spondylitis** . In JIA, sulfasalazine, 50 mg/kg/day (adult maximum: 3,000 mg/day), achieves greater improvement in joint inflammation, global assessment parameters, and laboratory parameters than placebo. More than 30% of sulfasalazine-treated patients withdraw from the treatment because of adverse effects, primarily GI irritation and skin rashes. Sulfasalazine is associated with severe systemic hypersensitivity reactions, including Stevens-Johnson syndrome. Sulfasalazine is generally considered contraindicated in children with active systemic JIA because of increased hypersensitivity reactions. Sulfasalazine should not be used in patients with sulfa or salicylate hypersensitivity or porphyria.

Monitoring laboratory tests for sulfasalazine toxicity include CBC, LFTs, serum creatinine/blood urea nitrogen (BUN), and urinalysis, every other week for the 1st 3 mo of treatment, monthly for 3 mo, every 3 mo for 1 yr, then every 6 mo.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug approved by the FDA for organ transplant rejection. In rheumatology, MMF is used primarily for treatment of lupus, uveitis, and autoimmune skin manifestations. In adult clinical trials, MMF was noninferior to cyclophosphamide for induction therapy of lupus nephritis, with a potential for less adverse effects (infection, gonadal toxicity). Dosing is based on body surface area (BSA): 600 mg/m^2 orally twice daily, with maximum dosage limits varying by formulation and BSA. The most common adverse reaction is GI intolerance; infections, cytopenias, and secondary malignancies are also reported.

Glucocorticoids

Glucocorticoids are given through oral, intravenous (IV), ocular, topical, and intraarticular administration as part of treatment of rheumatic disease. **Oral** corticosteroids are foundational treatment for moderate to severe lupus, dermatomyositis, and most forms of vasculitis; their long-term use is associated with many well-described, dose-dependent complications, including linear growth suppression, Cushingoid features, osteoporosis, avascular necrosis, hypertension, impaired glucose tolerance, mood disturbance, and increased infection risk. Glucocorticoids should be tapered to the lowest effective dose over time and DMARDs introduced as steroid-sparing agents.

Intravenous corticosteroids have been used to treat severe, acute manifestations of systemic rheumatic diseases such as SLE, dermatomyositis, and vasculitis. The IV route allows for higher doses to obtain an immediate, profound antiinflammatory effect. *Methylprednisolone,* 10-30 mg/kg/dose up to a maximum of 1 g, given over 1 hr daily for 1-5 days, is the IV preparation of choice. Although generally associated with fewer adverse effects than oral corticosteroids, IV steroids are associated with significant and occasionally life-threatening toxicities, such as cardiac arrhythmia, acute hypertension, hypotension, hyperglycemia, shock, pancreatitis, and avascular necrosis.

Ocular corticosteroids are prescribed by ophthalmologists as ophthalmologic drops or injections into the soft tissue surrounding the globe (sub–Tenon capsule injection) for active **uveitis** . Long-term ocular corticosteroid use leads to cataract formation and glaucoma. Current ophthalmologic management has significantly decreased the frequency of blindness as a complication of JIA-associated uveitis.

Intraarticular corticosteroids are being used with increasing frequency as initial therapy for children with oligoarticular JIA or as bridge therapy while awaiting efficacy of a DMARD in polyarticular disease. Most patients have significant clinical improvement within 3 days. Duration of response depends on steroid preparation used, joint affected, and arthritis subtype; the anticipated response rate to knee injection is 60–80% at 6 mo. Intraarticular administration may result in subcutaneous atrophy and hypopigmentation of the skin at the injection site, as well as subcutaneous calcifications along the needle track.

Biologic Agents

Biologic agents are proteins that have been engineered to target and modulate specific components of the immune system, with the goal of decreasing the inflammatory response. Antibodies have been developed to target specific cytokines such as IL-1 and IL-6 or to interfere with specific immune cell function through depletion of B cells or suppression of T-cell activation (Table 179.3). The availability of biologic agents has dramatically increased the therapeutic options for treating rheumatic disease recalcitrant to nonbiologic therapies, and in some cases biologics are becoming first-line interventions. A primary concern is the increased risk of malignancy when biologics are combined with other immunosuppressants.

Table 179.3

Method of Action of Biologic Therapies Studied in Juvenile Idiopathic Arthritis

DRUG	METHOD OF ACTION
Etanercept	Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α
Infliximab	Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action
Adalimumab	A humanized IgG_1 monoclonal antibody that binds to TNF-α
Abatacept	Soluble, fully human fusion protein of the extracellular domain of (CTLA-4, linked to a modified Fc portion of the human IgG_1 . It acts as a co-stimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation
Tocilizumab	A humanized anti–human IL-6 receptor monoclonal antibody
Anakinra	An IL-1 receptor antagonist (IL-1RA)

CTLA, Cytotoxic T lymphocyte–associated antigen; IL, interleukin; TNF, tumor necrosis factor.

From Beresford MW, Baildam EM: New advances in the management of juvenile idiopathic arthritis. Part 2. The era of biologicals, *Arch Dis Child Educ Pract Ed* 94:151–156, 2009.

Tumor Necrosis Factor-α Antagonists

Two TNF antagonists have an FDA indication for treatment of children with moderate to severe polyarticular JIA (etanercept and adalimumab). *Etanercept* is a genetically engineered fusion protein consisting of 2 identical chains of the recombinant extracellular TNF receptor monomer fused with the Fc domain of human immunoglobulin G_1 . Etanercept binds both TNF-α and lymphotoxin-α (formerly called TNF-β) and inhibits their activity. Three fourths of children with active polyarticular JIA that fails to respond to MTX demonstrate response to etanercept after 3 mo of therapy. Dosing is 0.8 mg/kg subcutaneously weekly (max 50 mg/dose) or 0.4 mg/kg SC twice weekly (max 25 mg/dose). *Adalimumab* is a fully human anti-TNF monoclonal antibody (mAb) used alone or in combination with MTX. In a placebo-controlled withdrawal-design study, children continuing to receive adalimumab were less likely to experience disease flares (43% vs. 71%) even if they were also taking MTX (37% vs 65%). Adalimumab is administered subcutaneously every other week at a dose of 10 mg for children weighing 10 to <15 kg, 20 mg for children weighing 15 to <30 kg and 40 mg for those weighing ≥30 kg.

Infliximab, a chimeric mouse-human mAb, was tested in an RCT for use in JIA but did not achieve study end-points. However, it is FDA approved for pediatric inflammatory bowel disease and has been used “off label” for treatment of polyarticular JIA, uveitis, Behçet syndrome, and sarcoidosis. Two additional anti-TNF agents—*golimumab* , a human mAb against TNF, and *certolizumab pegol* , a pegylated humanized antibody against TNF—have been approved by the FDA for RA in adults and are currently in pediatric trials.

The most common adverse effects are injection site reactions that diminish over time. TNF blockade is associated with an increased frequency of serious systemic infections, including sepsis, dissemination of latent tuberculosis (TB), and invasive fungal infections in endemic areas. TNF blockade should not be initiated in patients with a history of chronic or frequent recurrent infections. TB testing should be done before initiation of therapy with TNF antagonists. If test results are positive, antitubercular treatment must be administered before anti-TNF treatment can be started. Theoretically, risk of malignancy increases with TNF-α antagonists. Case reports describe the development of lupus-like syndromes, leukocytoclastic vasculitis, interstitial lung disease, demyelinating syndromes, antibody formation to the drug, rashes, cytopenias, anaphylaxis, serum sickness, and other reactions. The benefit/risk profile appears favorable after a decade of experience with this therapeutic class; the safety of longer-term suppression of TNF function is unknown.

Modulator of T-Cell Activation

Abatacept is a selective inhibitor of T-cell co-stimulation resulting in T-cell anergy. It is FDA approved for treatment of moderate to severe polyarticular JIA. In a double-blind withdrawal RCT in children whose disease had not responded to DMARDs, 53% of placebo-treated patients vs 20% of abatacept-treated patients experienced disease flares during the withdrawal period. The frequency of adverse events did not differ between the groups. Abatacept is administered

IV every other week for 3 doses (<75 kg: 10 mg/kg/dose; 75-100 kg: 750 mg/dose; >100 kg: 1,000 mg/dose; maximum 1,000 mg/dose at 0, 2, and 4 wk) and then monthly thereafter. Abatacept administered by SC injection was given FDA approval in March 2017 for children ≥4 yr old for treatment of polyarticular JIA, at doses given weekly: 50 mg for 10-25 kg, 87.5 mg for ≥25 to <50 kg, and 125 mg for ≥50 kg.

B-Cell Depletion

Rituximab is a chimeric mAb to the antigen CD20, a transmembrane protein on the surface of B-cell precursors and mature B lymphocytes. This antibody induces B-cell apoptosis and causes depletion of circulating and tissue-based B cells. Antibody production is not completely abrogated because plasma cells are not removed. Rituximab is licensed for treatment of B-cell non-Hodgkin lymphoma and is FDA approved for use in adult RA and idiopathic thrombocytopenic purpura but does not have a pediatric indication. Rituximab may also have a role in treatment of SLE, particularly its hematologic manifestations. Adverse events include serious infusion reactions, cytopenias, hepatitis B virus reactivation, hypogammaglobulinemia, infections, serum sickness, vasculitis, and a rare but fatal side effect, **progressive multifocal leukoencephalopathy** . Resistance to rituximab may develop over time in patients being treated for lymphoma.

Belimumab is a human mAb to B-lymphocyte stimulator that negatively affects B-cell proliferation, differentiation, and long-term survival. It is approved for treatment of SLE in adults, and studies of long-term safety and efficacy are ongoing. Belimumab is *not* FDA approved for use in pediatric SLE.

Interleukin-1 Antagonists

Anakinra, a recombinant form of the human IL-1 receptor antagonist, competitively inhibits binding of IL-1α and IL-1β to the natural receptor, interrupting the cytokine proinflammatory cascade. Anakinra has been approved for RA in adults. In meta-analyses of treatments for RA, anakinra was outperformed by TNF-α antagonists but has a special niche in pediatric rheumatology for treatment of **systemic JIA (sJIA)** and other autoinflammatory syndromes, such as **cryopyrin-associated periodic syndrome (CAPS)** . The medication is dosed SC, 1-2 mg/kg, once daily. An IL-1β mAb, *canakinumab,* is FDA approved for use in CAPS, dosed SC every 8 wk, and sJIA, dosed SC every

4 wk. Adverse reactions include significant injection site reactions and increased bacterial infections.

Interleukin-6 Receptor Antagonist

Tocilizumab is an anti–IL-6 receptor antibody binding to both soluble as well as membrane-associated receptors. Tocilizumab has FDA approval for treatment of sJIA and polyarticular JIA. Adverse reactions include transaminase and lipid elevations. Tocilizumab is given as an IV infusion every 2 wk (sJIA) to 4 wk (polyarticular JIA), and SC for polyarticular JIA 162 mg every 3 wk for those <30 kg and every 2 wk for ≥30 kg.

Intravenous Immune Globulin

IVIG is thought to be beneficial in various clinical conditions. IVIG significantly improves the short- and long-term natural history of **Kawasaki disease** . Open studies have supported benefit for juvenile dermatomyositis, lupus-associated thrombocytopenia, and polyarticular JIA. IVIG is given as 1-2 g/kg/dose, administered once monthly. It has been occasionally associated with severe, systemic allergy–like reactions and postinfusion aseptic meningitis (headache, stiff neck).

Cytotoxics

Cyclophosphamide

Cyclophosphamide requires metabolic conversion in the liver to its active metabolites, which alkylate the guanine in DNA, leading to immunosuppression by inhibition of the S2 phase of mitosis. The subsequent decrease in numbers of T and B lymphocytes results in diminished humoral and cellular immune responses. Cyclophosphamide infusions (500-1,000 mg/m^2) given monthly for 6 mo, then every 3 mo for 12-18 mo, have been shown to reduce the frequency of renal failure in patients with lupus and diffuse proliferative glomerulonephritis. Open trials suggest efficacy in severe CNS lupus. Oral cyclophosphamide (1-2 mg/kg/day) is effective as induction treatment of severe antineutrophilic cytoplasmic antibody (ANCA)–associated vasculitis and other forms of systemic vasculitis, as well as interstitial lung disease or pulmonary hemorrhage associated with rheumatic disease.

Cyclophosphamide is a potent cytotoxic drug associated with significant toxicities. Potential short-term adverse effects include nausea, vomiting, anorexia, alopecia, mucositis, hemorrhagic cystitis, and bone marrow suppression. Long-term complications include an increased risk for sterility and cancer, especially leukemia, lymphoma, and bladder cancer. In adult women with lupus treated with IV cyclophosphamide, 30–40% become infertile; the risk of ovarian failure appears to be significantly lower in adolescent and premenarchal girls. Ovarian suppression with an inhibitor of gonadotropin-releasing hormone to preserve fertility is currently being studied.

Other Drugs

Azathioprine is sometimes used to treat ANCA-associated vasculitis following induction therapy or to treat SLE. *Cyclosporine* has been used occasionally in the treatment of dermatomyositis on the basis of uncontrolled studies and is helpful in the treatment of macrophage activation syndrome complicating sJIA (see Chapter 155). Case reports describe the successful use of *thalidomide* , or its analog *lenalidomide*, as treatment for sJIA, inflammatory skin disorders, and Behçet disease.

Several drugs commonly used in the past to treat arthritis are no longer part of standard treatment, including salicylates, gold compounds, and D -penicillamine.

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CHAPTER 180

Juvenile Idiopathic Arthritis

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and one of the more common chronic illnesses of childhood. JIA represents a heterogeneous group of disorders sharing the clinical manifestation of arthritis. The etiology and pathogenesis of JIA are largely unknown, and the genetic component is complex, making clear distinction among various subtypes difficult. As a result, several classification schemes exist, each with its own limitations. The former classification of the **American College of Rheumatology (ACR)** uses the term *juvenile rheumatoid arthritis* and categorizes the disease into 3 onset types (Table 180.1). Attempting to standardize nomenclature, the **International League of Associations for Rheumatology (ILAR)** proposed a different classification using the term *juvenile idiopathic arthritis* (Table 180.2), inclusive of all subtypes of chronic juvenile arthritis. We refer to the ILAR classification criteria; see Chapter 181 for enthesitis-related arthritis (ERA) and psoriatic JIA (Tables 180.3 and 180.4).

Table 180.1

Criteria for the Classification of Juvenile Rheumatoid Arthritis

Age at onset: <16 yr
Arthritis (swelling or effusion, or the presence of ≥2 of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joint
Duration of disease: ≥6 wk
Onset type defined by type of articular involvement in the 1st 6 mo after onset:

Polyarthritis: ≥5 inflamed joints
Oligoarthritis: ≤4 inflamed joints
Systemic-onset disease: arthritis with rash and a characteristic quotidian fever
Exclusion of other forms of juvenile arthritis

Adapted from Cassidy JT, Levison JE, Bass JC, et al: A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis, *Arthritis Rheum* 29:174–181, 1986.

Table 180.2

International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA)

CATEGORY	DEFINITION	EXCLUSIONS
Systemic JIA	Arthritis in ≥1 joint with, or preceded by, fever of at least 2 wk in duration that is documented to be daily (quotidian[*]) for at least 3 days and accompanied by ≥1 of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly or splenomegaly or both 4. Serositis [†]	a. Psoriasis or a history of psoriasis in patient or first-degree relative b. Arthritis in an HLA-B27–positive boy beginning after 6th birthday c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis, or history of 1 of these disorders in first-degree relative d. Presence of IgM RF on at least 2 occasions at least 3 mo apart
Oligoarthritis	Arthritis affecting 1-4 joints during 1st 6 mo of disease; 2 subcategories are recognized: 1. Persistent oligoarthritis—affecting ≤4 joints throughout the disease course 2. Extended oligoarthritis—affecting >4 joints after 1st 6 mo of disease	a, b, c, d (above) *plus* e. Presence of systemic JIA in the patient
Polyarthritis (RF negative)	Arthritis affecting ≥5 joints during 1st 6 mo of disease; a test for RF is negative	a, b, c, d, e
Polyarthritis (RF positive)	Arthritis affecting ≥5 joints during 1st 6 mo of disease; ≥2 tests for RF at least 3 mo apart during 1st 6 mo of disease are positive	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following:	b, c, d, e
	1. Dactylitis [‡] 2. Nail pitting [§] and onycholysis 3. Psoriasis in first-degree relative	
Enthesitis-related arthritis	Arthritis and enthesitis, [‖] or arthritis or enthesitis with at least 2 of the following:	a, d, e
	1. Presence of or history of sacroiliac joint	

	tenderness or inflammatory lumbosacral pain, or both[¶] 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male >6 yr old 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, or acute anterior uveitis in first-degree relative	
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in ≥2 of the above categories.	

[*] *Quotidian fever* is defined as a fever that rises to 39°C (102.2°F) once daily and returns to 37°C (98.6°F) between fever peaks.

[†] *Serositis* refers to pericarditis, pleuritis, or peritonitis, or some combination of the 3.

[‡] *Dactylitis* is swelling of ≥1 digit(s), usually in an asymmetric distribution, that extends beyond the joint margin.

[§] A minimum of 2 pits on any 1 or more nails at any time.

[‖] *Enthesitis* is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.

[¶] *Inflammatory lumbosacral pain* refers to lumbosacral pain at rest with morning stiffness that improves on movement.

IBD, Inflammatory bowel disease; RF, rheumatoid factor.

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: *Kelley's textbook of rheumatology,* ed 8, Philadelphia, 2009, Saunders.

Table 180.3

Characteristics of ACR and ILAR Classifications of Childhood Chronic Arthritis

PARAMETER	**ACR (1977)**	**ILAR (1997)**
Term	Juvenile rheumatoid arthritis (JRA)	Juvenile idiopathic arthritis (JIA)
Minimum duration	≥6 wk	≥6 wk
Age at onset	<16 yr	<16 yr
≤4 joints in 1st 6 mo after presentation	Pauciarticular	Oligoarthritis: Persistent: <4 joints for course of disease Extended: >4 joints after 6 mo
>4 joints in 1st 6 mo after presentation	Polyarticular	Polyarthritis, RF negative Polyarthritis, RF positive
Fever, rash, arthritis	Systemic onset	Systemic

Other categories included	Exclusion of other forms	Psoriatic arthritis Enthesitis-related arthritis Undifferentiated: Fits no other category Fits >1 category
Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis	No (see Chapter 181)	Yes

ACR, American College of Rheumatology; ILAR, International League of Associations for Rheumatology; RF, rheumatoid factor.

Table 180.4

Overview of Main Features of Subtypes of Juvenile Idiopathic Arthritis (JIA)

ILAR SUBTYPE	PEAK AGE at ONSET (yr)	FEMALE:MALE RATIO	% of ALL JIA CASES	ARTHRITIS PATTERN	EXTRAARTICULAR FEATURES	LABORA INVESTI
Systemic arthritis	1-5	1 : 1	5-15	Polyarticular, often affecting knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis; pleuritis	Anemia; W ESR ↑↑; C ferritin ↑; p (normal or MAS)
Oligoarthritis	2-4	3 : 1	40-50 (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in 30% of cases	ANA positi 60%; other results usu normal; ma mildly ↑ E
Polyarthritis:						
RF negative	2-4 and 10-14	3 : 1 and 10 : 1	20-35	Symmetric or asymmetric; small and large joints; cervical spine; temporomandibular joint	Uveitis in 10%	ANA positi 40%; RF n ESR ↑ or ↑ or normal; anemia

RF positive	9-12	9 : 1	<10	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive CRP ↑/norr anemia
Psoriatic arthritis	2-4 and 9-11	2 : 1	5-10	Asymmetric arthritis of small or medium-sized joints	Uveitis in 10%; psoriasis in 50%	ANA positi 50%; ESR or normal; anemia
Enthesitis-related arthritis	9-12	1 : 7	5-10	Predominantly lower limb joints affected; sometimes axial skeleton (but less than in adult, ankylosing spondylitis)	Acute anterior uveitis; association with reactive arthritis and inflammatory bowel disease	80% of pati positive for B27

ILAR, International League of Associations for Rheumatology; ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MAS, macrophage activation syndrome; MTX, methotrexate; NSAIDs, nonsteroidal antiinflammatory drugs; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: *Kelley's textbook of rheumatology,* ed 8, Philadelphia, 2009, Saunders.

Epidemiology

The worldwide incidence of JIA ranges from 0.8-22.6 per 100,000 children per year, with prevalence ranges from 7-401 per 100,000. These wide-ranging numbers reflect population differences, particularly environmental exposure and immunogenetic susceptibility, along with variations in diagnostic criteria, difficulty in case ascertainment, and lack of population-based data. An estimated 300,000 U.S. children have arthritis, including 100,000 with a form of JIA. **Oligoarthritis** is the most common subtype (40–50%), followed by **polyarthritis** (25–30%) and **systemic JIA** (5–15%) (see Table 180.4). There is no sex predominance in systemic JIA (**sJIA**), but more girls than boys are affected in both oligoarticular (3 : 1) and polyarticular (5 : 1) JIA. The peak age at onset is 2-4 yr for oligoarticular disease. Age of onset has a bimodal distribution in polyarthritis, with peaks at 2-4 yr and 10-14 yr. sJIA occurs throughout childhood, with a peak at 1-5 yr.

Etiology

The etiology and pathogenesis of JIA are not completely understood, although both immunogenetic susceptibility and an external trigger are considered necessary. Twin and family studies suggest a substantial role for **genetic** factors. JIA is a complex genetic trait in which multiple genes may affect disease susceptibility. Variants in major histocompatibility complex (MHC) class I and class II regions have indisputably been associated with different JIA subtypes. Non-HLA candidate loci are also associated with JIA, including polymorphisms in the genes encoding protein tyrosine phosphatase nonreceptor 22 (PTPN22), tumor necrosis factor (TNF)-α, macrophage inhibitory factor, interleukin (IL)-6 and its receptor, and IL-1α. Possible **nongenetic** triggers include bacterial and viral infections, enhanced immune responses to bacterial or mycobacterial heat shock proteins, abnormal reproductive hormone levels, and joint trauma.

Pathogenesis

JIA is an autoimmune disease associated with alterations in both humoral and cell-mediated immunity. T lymphocytes have a central role, releasing proinflammatory cytokines favoring a type 1 helper T lymphocyte response. Studies of T-cell receptor expression confirm recruitment of T lymphocytes specific for synovial non–self-antigens. B-cell activation, immune complex formation, and complement activation also promote inflammation. Inheritance of specific cytokine alleles may predispose to upregulation of inflammatory networks, resulting in systemic disease or more severe articular disease.

Systemic JIA is characterized by dysregulation of the innate immune system with a lack of autoreactive T cells and autoantibodies. It therefore may be more accurately classified as an **autoinflammatory disorder** , more like familial Mediterranean fever, than the other subtypes of JIA. This theory is also supported by work demonstrating similar expression patterns of a phagocytic protein (S100A12) in sJIA and familial Mediterranean fever, as well as the same marked responsiveness to IL-1 inhibitors.

All these immunologic abnormalities cause inflammatory synovitis, characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the synovial tissue. Vascular endothelial hyperplasia is prominent and is characterized by infiltration of mononuclear and plasma cells with a predominance of T lymphocytes (Fig. 180.1). Advanced and uncontrolled disease leads to pannus formation and progressive erosion of articular cartilage and contiguous bone (Figs. 180.2 and 180.3).

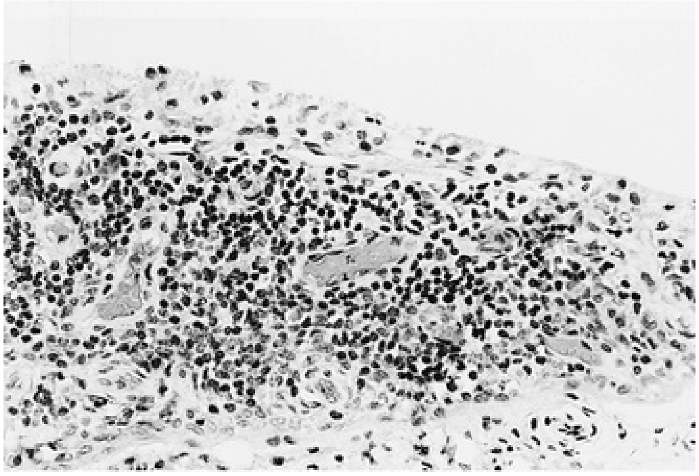

FIG. 180.1 Synovial biopsy specimen from a 10 yr old child with oligoarticular juvenile idiopathic arthritis. There is a dense infiltration of lymphocytes and plasma cells in the synovium.

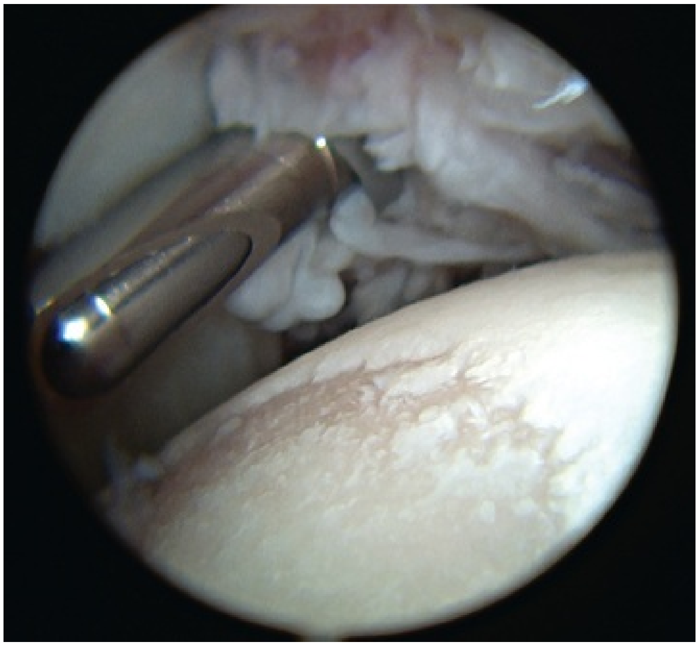

FIG. 180.2 Arthroscopy in the shoulder of a child with juvenile idiopathic arthritis showing pannus formation and cartilage erosions. (Courtesy of Dr. Alison Toth.)

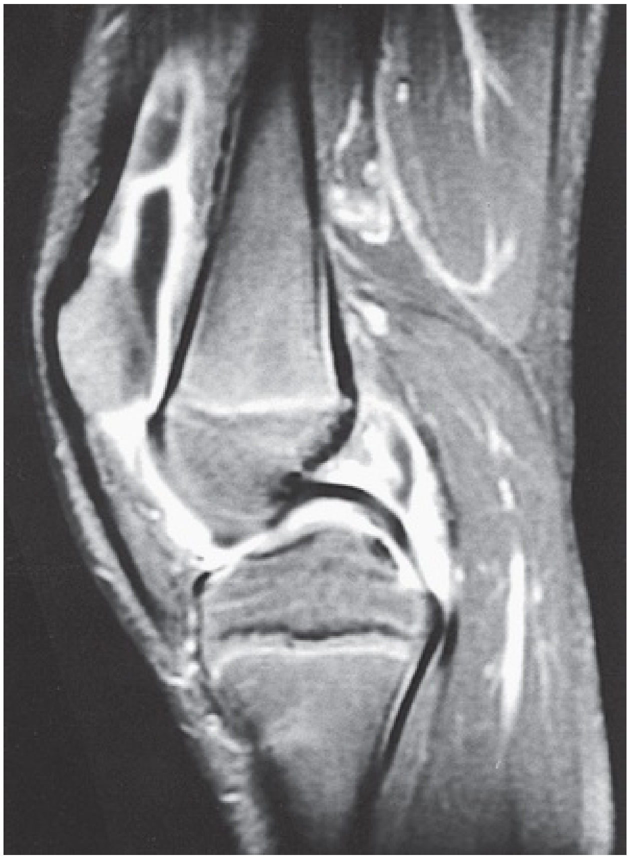

FIG. 180.3 MRI with gadolinium of a 10 yr old child with juvenile idiopathic arthritis (same patient as in Fig. 180.1). The dense white signal in the synovium near the distal femur, proximal tibia, and patella reflects inflammation. MRI of the knee is useful to exclude ligamentous injury, chondromalacia of the patella, and tumor.

Clinical Manifestations

Arthritis must be present ≥6 wk to make a diagnosis of any JIA subtype. Arthritis is defined by intraarticular swelling or the presence of ≥2 of the following signs: limitation in range of motion (ROM), tenderness or pain on motion, and warmth. Initial symptoms may be subtle or acute and often include morning stiffness with a limp or gelling after inactivity. Easy fatigability and poor sleep quality may be present. Involved joints are often swollen, warm to touch, and uncomfortable on movement or palpation with reduced ROM, but usually are not erythematous. Arthritis in large joints, especially knees, initially accelerates linear growth and causes the affected limb to be longer, resulting in a discrepancy in limb lengths. Continued inflammation stimulates rapid and premature closure of the growth plate, resulting in shortened bones.

Oligoarthritis is defined as involving ≤4 joints within the 1st 6 mo of disease onset, and often only a single joint is involved (see Table 180.4). It predominantly affects the large joints of the lower extremities, such as the knees and ankles (Fig. 180.4). Isolated involvement of upper-extremity large joints is less common. Those in whom disease never develops in >4 joints are regarded as having **persistent oligoarticular JIA** , whereas evolution of disease in >4 joints after 6 mo changes the classification to **extended oligoarticular JIA** and is associated with a worse prognosis. Isolated involvement of the hip is *almost never* a presenting sign and suggests ERA (see Chapter 181) or a nonrheumatic cause. The presence of a positive antinuclear antibody (ANA) test confers increased risk for asymptomatic anterior uveitis, requiring periodic slit-lamp examination (Table 180.5). ANA positivity may also be correlated with younger age at disease onset, female sex, asymmetric arthritis, and fewer involved joints over time.

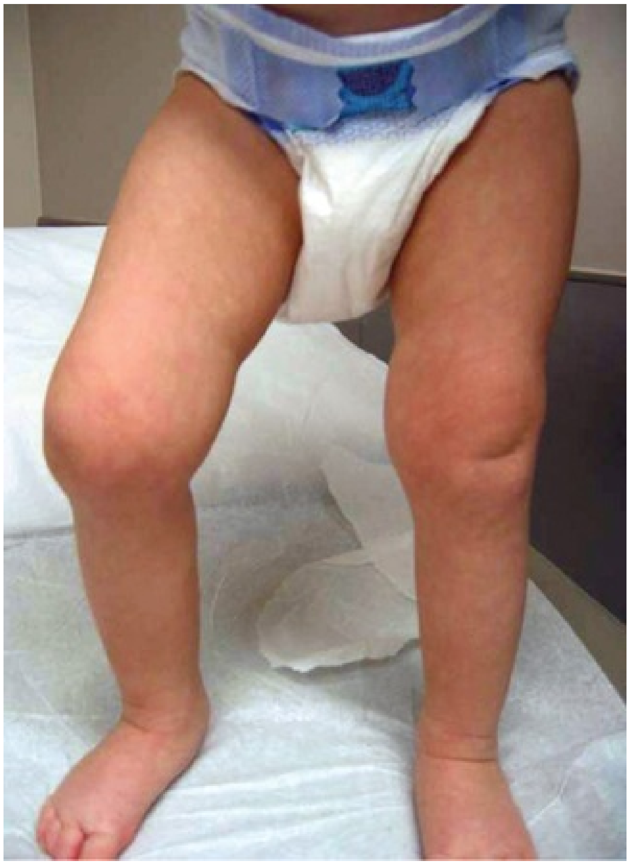

FIG. 180.4 Oligoarticular juvenile idiopathic arthritis with swelling and flexion contracture of the right knee.

Table 180.5

Frequency of Ophthalmologic Examination in Patients With Juvenile Idiopathic Arthritis

Referral	
• Patients should be referred at time of diagnosis, or suspicion, of JIA	
Initial screening examination	
• Should occur as soon as possible and no later than 6 wk from referral	
• Symptomatic ocular patients should be seen within a week of referral	
Ongoing screening	
• Screening at two monthly intervals from onset of arthritis for 6 mo	
• Followed by 3-4 monthly screening for time outlined below	
Oligoarticular JIA, psoriatic arthritis, and enthesitis-related arthritis irrespective of ANA status, onset under 11 yr	
AGE AT ONSET (YR)	**LENGTH OF SCREENING (YR)**
<3	8
3-4	6
5-8	3
9-10	1

Polyarticular, ANA-positive JIA, onset <10 yr	
AGE AT ONSET (YR)	**LENGTH OF SCREENING (YR)**
<6	5
6-9	2
• Polyarticular, ANA-negative JIA, onset <7 yr	
• 5-yr screening for all children	
• Systemic JIA and rheumatoid factor–positive polyarticular JIA	
Uveitis risk very low; however, diagnostic uncertainty in the early stages and overlap of symptoms may mean initial screening is indicated	
• All categories, onset >11 yr	
1-yr screening for all children	
• After stopping immunosuppression (eg, methotrexate)	
Two monthly screening for 6 mo, then revert to previous screening frequency as above	
• After discharge from screening	
Patients should receive advice about regular self-monitoring by checking vision uniocularly once weekly and when to seek medical advice	
Screening may need to continue indefinitely in situations where a young person may be unable to detect a change in vision or be unwilling to seek re-referral	
Annual check by optometrist as a useful adjunct	

From Clarke SLN, Sen ES, Ramanan AV: Juvenile idiopathic arthritis-associated uveitis. *Pediatr Rheumatol* 14:27, 2016. p. 3.

Polyarthritis is characterized by inflammation of ≥5 joints in both upper and lower extremities (Figs. 180.5 and 180.6). Rheumatoid factor (RF)–positive polyarthritis resembles the characteristic symmetric presentation of adult rheumatoid arthritis. **Rheumatoid nodules** on the extensor surfaces of the elbows, spine, and over the Achilles tendons, although unusual, are associated with a more severe course and almost exclusively occur in RF-positive individuals (Fig. 180.7). **Micrognathia** reflects chronic temporomandibular joint disease (Fig. 180.8). Cervical spine involvement (Fig. 180.9), manifesting as decreased neck extension, occurs with a risk of atlantoaxial subluxation and neurologic sequelae. Hip disease may be subtle, with findings of decreased or painful ROM on examination (Fig. 180.10).

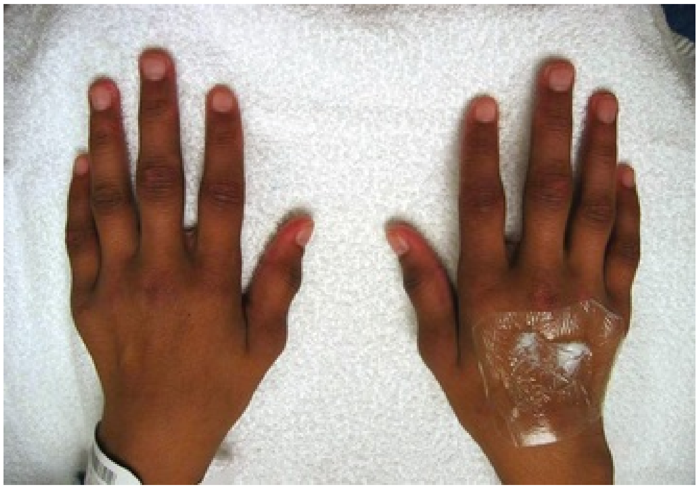

FIG. 180.5 Hands and wrists of a girl with polyarticular juvenile idiopathic arthritis, rheumatoid factor negative. Notice the symmetric involvement of the wrists, metacarpophalangeal joints, and proximal and distal interphalangeal joints. In this photograph, there is cream with occlusive dressing on the patient's right hand in preparation for placement of an intravenous line for administration of a biologic agent.

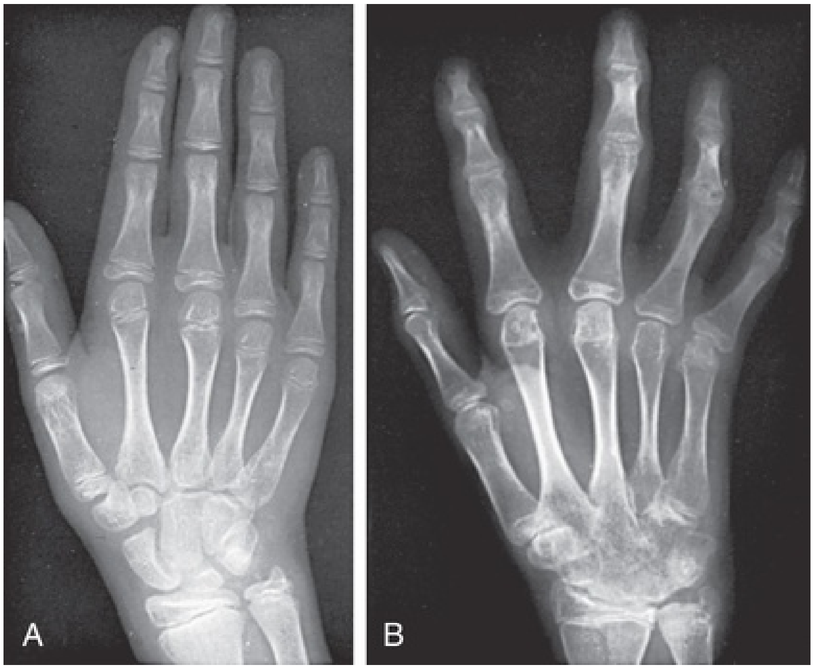

FIG. 180.6 Progression of joint destruction in a girl with polyarticular juvenile idiopathic arthritis, rheumatoid factor positive, despite doses of corticosteroids sufficient to suppress symptoms in the interval between the radiographs shown in **A** and **B. A,** Radiograph of the hand at onset. **B,** Radiograph taken 4 yr later, showing a loss of articular cartilage and

destructive changes in the distal and proximal interphalangeal and metacarpophalangeal joints as well as destruction and fusion of wrist bones.

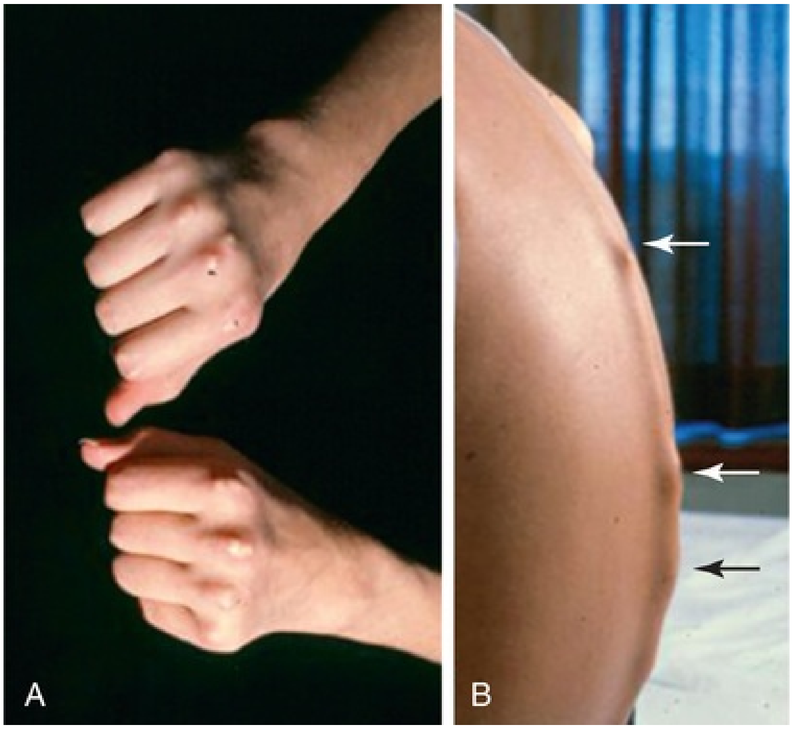

FIG. 180.7 Rheumatoid nodules overlying bony prominences in an adolescent with rheumatoid factor–positive polyarthritis. (From Rosenberg AM, Oen KG: Polyarthritis. In Cassiday JT, Petty RE, Laxer RM, et al, editors: *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2011, Saunders Elsevier, Fig 15-5, p 257.)

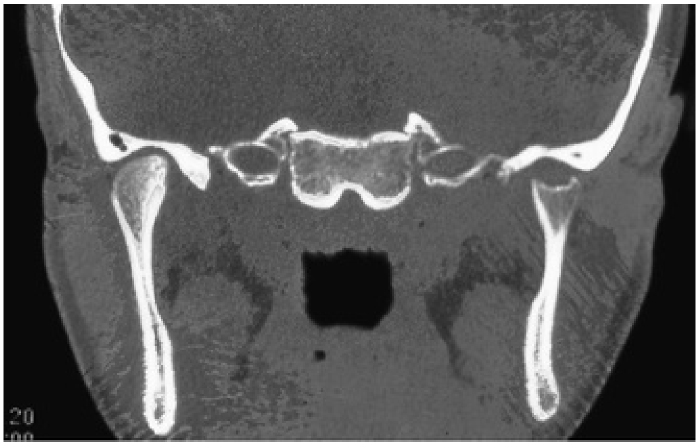

FIG. 180.8 CT scan of the temporomandibular joint of a patient with juvenile idiopathic arthritis exhibiting destruction on the right.

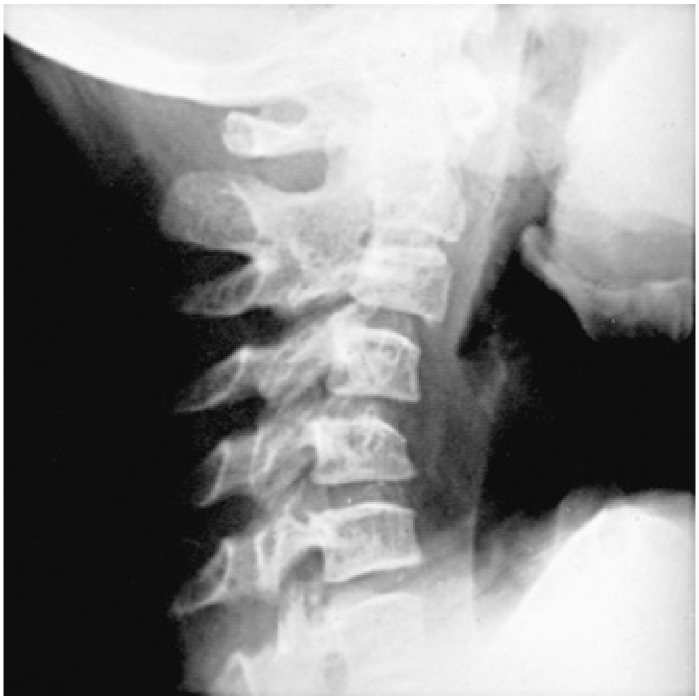

FIG. 180.9 Radiograph of the cervical spine of a patient with active juvenile idiopathic arthritis, showing fusion of the neural arch between joints C2 and C3, narrowing and erosion of the remaining neural arch joints, obliteration of the apophyseal space, and loss of the normal lordosis.

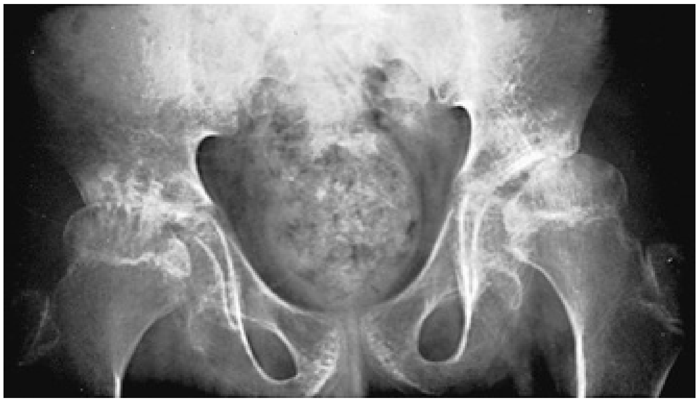

FIG. 180.10 Severe hip disease in 13 yr old boy with active systemic juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The patient had received corticosteroids systemically for 9 yr.

Systemic JIA is characterized by arthritis, fever, rash, and prominent visceral involvement, including hepatosplenomegaly, lymphadenopathy, and serositis (pericarditis). The characteristic fever, defined as spiking temperatures to ≥39°C (102.2°F), occurs on a daily or twice-daily basis for at least 2 wk, with a rapid return to normal or subnormal temperatures (Fig. 180.11). The fever is often present in the evening and is frequently accompanied by a characteristic faint, erythematous, macular rash. The evanescent **salmon-colored lesions,** classic for sJIA, are linear or circular and are usually distributed over the trunk and proximal extremities (Fig. 180.12). The classic rash is nonpruritic and migratory with lesions lasting <1 hr. **Koebner phenomenon** , a cutaneous hypersensitivity in which classic lesions are brought on by superficial trauma, is often present. Heat can also evoke rash. Fever, rash, hepatosplenomegaly, and lymphadenopathy are present in >70% of affected children. Without arthritis, the **differential diagnosis** includes the episodic fever (autoinflammatory) syndromes (see Chapter 188), infection (endocarditis, rheumatic fever, brucellosis), other rheumatic disorders (SLE, vasculitis syndromes, serum sickness, Kawasaki disease, sarcoidosis, Castleman disease), inflammatory bowel disease, hemophagocytic syndromes, and malignancy. Some children initially present with only systemic features and evolve over time, but definitive diagnosis requires presence of arthritis. Arthritis may affect any number of joints, but the course is classically polyarticular, may be very destructive, and can include hip, cervical spine, and temporomandibular joint involvement.

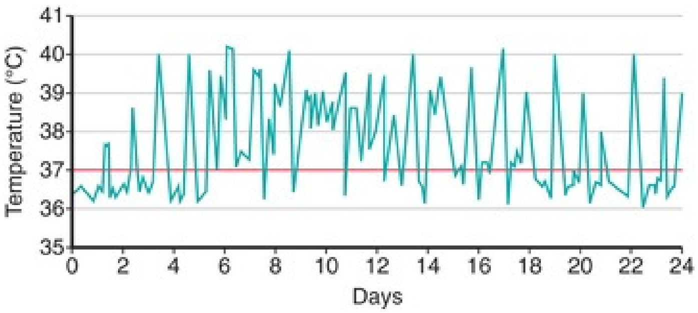

FIG. 180.11 High-spiking intermittent fever in 3 yr old patient with systemic juvenile idiopathic arthritis. (From Ravelli A, Martini A: Juvenile idiopathic arthritis, *Lancet* 369:767–778, 2007.)

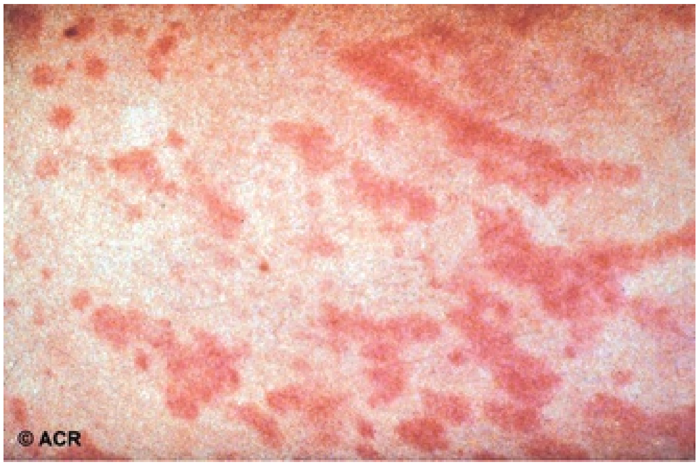

FIG. 180.12 The rash of systemic juvenile idiopathic arthritis is salmon-colored, macular, and nonpruritic. Individual lesions are transient and occur in crops over the trunk and extremities. (Reprinted from the American College of Rheumatology: *Clinical slide collection on the rheumatic diseases,* Atlanta, copyright 1991, 1995, 1997, ACR. Used with permission of the American College of Rheumatology.)

Macrophage activation syndrome (MAS) is a rare but potentially fatal complication of sJIA that can occur at any time (onset, medication change, active or remission) during the disease course. It is also referred to as *secondary hemophagocytic syndrome* or *hemophagocytic lymphohistiocytosis* (HLH) (see Chapter 534.2). There is increasing evidence that sJIA/MAS and HLH share similar functional defects in granule-dependent cytotoxic lymphocyte activity. In addition, sJIA-associated MAS and HLH share genetic variants in approximately 35% of patients with sJIA/MAS. MAS classically manifests as acute onset of high-spiking fevers, lymphadenopathy, hepatosplenomegaly, and encephalopathy. Laboratory evaluation shows thrombocytopenia and leukopenia with elevated liver enzymes, lactate dehydrogenase, ferritin, and triglycerides. Patients may have purpura and mucosal bleeding, as well as elevated fibrin split product values and prolonged prothrombin and partial prothromboplastin times. The erythrocyte sedimentation rate (ESR) falls because of hypofibrinogenemia and hepatic dysfunction, a feature useful in distinguishing MAS from a flare of systemic disease (Table 180.6). An international consensus panel developed a set of classification criteria for sJIA-associated MAS, including hyperferritinemia (>684 ng/mL) and any 2 of the following: thrombocytopenia (≤181 × 10^9 /L), elevated liver enzymes (aspartate transaminase >48 U/L), hypertriglyceridemia (>156 mg/dL), and hypofibrinogenemia (≤360 mg/dL) (Table 180.6). These criteria apply to a febrile patient suspected of sJIA *and* in the absence of disorders such as immune-mediated thrombocytopenia, infectious hepatitis, familial hypertriglyceridemia or visceral leishmaniasis. *A relative change in laboratory values is likely more relevant in making an early diagnosis than are absolute normal values* . A bone marrow aspiration and biopsy may be helpful in diagnosis, but evidence of hemophagocytosis is not always evident. Emergency treatment with high-dose intravenous methylprednisolone, cyclosporine, or anakinra may be effective. Severe cases may require therapy similar to that for primary HLH (see Chapter 534.2).

Table 180.6

Macrophage Activation Syndrome (MAS)

Laboratory Features*

1. Cytopenias
2. Abnormal liver function tests
3. Coagulopathy (hypofibrinogenemia)
4. Decreased erythrocyte sedimentation rate
5. Hypertriglyceridemia
6. Hyponatremia
7. Hypoalbuminemia
8. Hyperferritinemia
9. Elevated sCD25 and sCD163

Clinical Features*

1. Nonremitting fever
2. Hepatomegaly
3. Splenomegaly
4. Lymphadenopathy
5. Hemorrhages
6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)

Histopathologic Features*

1. Macrophage hemophagocytosis in the bone marrow aspirate
2. Increased CD163 staining of the bone marrow

Proposed Criteria for MAS in sJIA †

- Serum ferritin >684 ng/mL *and*
- Any 2 of the following:
    - Thrombocytopenia (≤181 × 10^9 /L)
    - Elevated liver enzymes (aspartate transaminase >48 U/L)
    - Hypertriglyceridemia (>156 mg/dL)
    - Hypofibrinogenemia (≤360 mg/dL)

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* From Ravelli A, Grom A, Behrens E, Cron R: Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment, *Genes Immun* 13:289–298, 2012.

† From Ravelli A, Minoia F, Davì S, et al: 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation collaborative initiative, *Arthritis Rheumatol* 68:566-576, 2016.

Bone mineral metabolism and skeletal maturation are adversely affected in children with JIA, regardless of subtype. Children with JIA have decreased bone mass (osteopenia), which appears to be associated with increased disease activity. Increased levels of cytokines such as TNF-α and IL-6, both key regulators in bone metabolism, have deleterious effects on bone within the joint as well as systemically in the axial and appendicular bones. Abnormalities of skeletal maturation become most prominent during the pubertal growth spurt.

Diagnosis

JIA is a clinical diagnosis without any diagnostic laboratory tests. The meticulous clinical exclusion of other diseases and many mimics is therefore essential. Laboratory studies, including tests for ANA and RF, are only supportive or prognostic, and their results may be normal in patients with JIA (see Tables 180.1 , 180.3 , and 180.4).

Differential Diagnosis

The differential diagnosis for arthritis is broad and a careful, thorough investigation for other underlying etiology is imperative (Table 180.7). History, physical examination, laboratory tests, and radiography may help exclude other possible causes. Arthritis can be a presenting manifestation for any of the multisystem rheumatic diseases of childhood, including systemic lupus erythematosus (see Chapter 183), juvenile dermatomyositis (see Chapter 184), sarcoidosis (see Chapter 190), and the vasculitic syndromes (see Chapter 192). In scleroderma (see Chapter 185), limited ROM caused by sclerotic skin overlying a joint may be confused with sequelae from chronic inflammatory arthritis. **Acute rheumatic fever** is characterized by exquisite joint pain and tenderness, remittent fever, and migratory polyarthritis. **Autoimmune hepatitis** can also be associated with an acute arthritis.

Table 180.7

Conditions Causing Arthritis or Extremity Pain

Rheumatic and Inflammatory Diseases

Juvenile idiopathic arthritis

Systemic lupus erythematosus
Juvenile dermatomyositis
Polyarteritis nodosa
Scleroderma
Sjögren syndrome
Behçet disease
Overlap syndromes
Antineutrophilic cytoplasmic antibody (ANCA)–associated vasculitis
Sarcoidosis
Kawasaki syndrome
Henoch-Schönlein purpura
Chronic recurrent multifocal osteomyelitis

Seronegative Spondyloarthropathies

Juvenile ankylosing spondylitis
Inflammatory bowel disease
Psoriatic arthritis
Reactive arthritis associated with urethritis, iridocyclitis, and mucocutaneous lesions

Infectious Illnesses

Bacterial arthritis (septic arthritis, *Staphylococcus aureus, Kingella kingae*, pneumococcal, gonococcal, *Haemophilus influenzae*)
Lyme disease
Viral illness (parvovirus, rubella, mumps, Epstein-Barr, hepatitis B, chikungunya)
Fungal arthritis
Mycobacterial infection
Spirochetal infection
Endocarditis

Reactive Arthritis

Acute rheumatic fever

Reactive arthritis (postinfectious caused by *Shigella*, *Salmonella*, *Yersinia*, *Chlamydia*, or meningococcus)
Serum sickness
Toxic synovitis of the hip
Postimmunization

Immunodeficiencies

Hypogammaglobulinemia
Immunoglobulin A deficiency
Common variable immunodeficiency disease (CVID)
Human immunodeficiency virus (HIV)

Congenital and Metabolic Disorders

Gout
Pseudogout
Mucopolysaccharidoses
Thyroid disease (hypothyroidism, hyperthyroidism)
Hyperparathyroidism
Vitamin C deficiency (scurvy)
Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome)
Fabry disease
Farber disease
Amyloidosis (familial Mediterranean fever)

Bone and Cartilage Disorders

Trauma
Patellofemoral syndrome
Hypermobility syndromes
Osteochondritis dissecans
Avascular necrosis (including Legg-Calvé-Perthes disease)
Hypertrophic osteoarthropathy
Slipped capital femoral epiphysis

- Osteolysis
- Benign bone tumors (including osteoid osteoma)
- Langerhans cell histiocytosis
- Rickets

Neuropathic Disorders

- Peripheral neuropathies
- Carpal tunnel syndrome
- Charcot joints

Neoplastic Disorders

- Leukemia
- Neuroblastoma
- Lymphoma
- Bone tumors (osteosarcoma, Ewing sarcoma)
- Histiocytic syndromes
- Synovial tumors

Hematologic Disorders

- Hemophilia
- Hemoglobinopathies (including sickle cell disease)

Miscellaneous Disorders

- Autoinflammatory diseases
- Recurrent multifocal osteomyelitis
- Pigmented villonodular synovitis
- Plant-thorn synovitis (foreign body arthritis)
- Myositis ossificans
- Eosinophilic fasciitis
- Tendinitis (overuse injury)
- Raynaud phenomenon

Hemophagocytic syndromes

Pain Syndromes

Fibromyalgia
Growing pains
Depression (with somatization)
Complex regional pain syndrome

Many infections are associated with arthritis, and a recent history of infectious symptoms may help make a distinction. Viruses, including parvovirus B19, rubella, Epstein-Barr virus, hepatitis B virus, and HIV, can induce a transient arthritis. Arthritis may follow enteric infections (see Chapter 182). **Lyme disease** should be considered in children with oligoarthritis living in or visiting endemic areas (see Chapter 249). Although a history of tick exposure, preceding flulike illness, and subsequent rash should be sought, these are not always present. Monoarticular arthritis unresponsive to antiinflammatory treatment may be the result of chronic mycobacterial or other infection, such as *Kingella kingae* , and the diagnosis is established by synovial fluid analysis (PCR) or biopsy. Acute onset of fever and a painful, erythematous, hot joint suggests septic arthritis (see Chapter 705). Isolated hip pain with limited ROM suggests suppurative arthritis, osteomyelitis (see Chapter 704), toxic synovitis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and chondrolysis of the hip (see Chapter 698).

Lower-extremity arthritis and tenderness over insertion of ligaments and tendons, especially in a boy, suggests ERA (see Chapter 181). **Psoriatic arthritis** can manifest as limited joint involvement in an unusual distribution (e.g., small joints of hand and ankle) years before onset of cutaneous disease. **Inflammatory bowel disease** may manifest as oligoarthritis, usually affecting joints in the lower extremities, as well as gastrointestinal symptoms, elevations in ESR, and microcytic anemia.

Many conditions present solely with arthralgia (i.e., joint pain). Hypermobility may cause joint pain, especially in the lower extremities. Growing pains should be suspected in a child age 4-12 yr complaining of leg pain in the evening with normal investigative studies and no morning symptoms. Nocturnal pain that awakens the child also alerts to the possibility of a malignancy. An adolescent with missed school days may suggest a diagnosis of fibromyalgia (see Chapter 193).

Children with **leukemia** or **neuroblastoma** may have joint or bone pain resulting from malignant infiltration of the bone, synovium, or more often the bone marrow, sometimes months before demonstrating lymphoblasts on peripheral blood smear. Physical examination may reveal no tenderness, a deeper pain with palpation of the bone, or pain out of proportion to exam findings. Malignant pain often awakens the child from sleep and may cause cytopenias. Because platelets are an acute-phase reactant, a high ESR with leukopenia and a low normal platelet count may also be a clue to underlying leukemia. In addition, the characteristic quotidian fever of sJIA is absent in malignancy. Bone marrow examination is necessary for diagnosis. Some diseases, such as cystic fibrosis, diabetes mellitus, and the glycogen storage diseases, have associated arthropathies (see Chapter 194). Swelling that extends beyond the joint can be a sign of lymphedema or Henoch-Schönlein purpura (see Chapter 192.1). A peripheral arthritis indistinguishable from JIA occurs in the humoral immunodeficiencies (see Chapter 150), such as common variable immunodeficiency and X-linked agammaglobulinemia. Skeletal dysplasias associated with a degenerative arthropathy are diagnosed from their characteristic radiologic abnormalities.

Systemic onset of JIA often presents as a fever of unknown origin (see Chapter 204). Important considerations in the differential diagnosis include infections (endocarditis, brucellosis, cat scratch disease, Q fever, mononucleosis), autoinflammatory disease (see Chapter 188) malignancy (leukemia, lymphoma, neuroblastoma) and HLH (see Chapter 534.2).

Laboratory Findings

Hematologic abnormalities often reflect the degree of systemic or articular inflammation, with elevated white blood cell (WBC) and platelet counts and a microcytic anemia. Inflammation may also cause elevations in ESR and C-reactive protein, although it is not unusual for both to be normal in children with JIA.

Elevated ANA titers are present in 40–85% of children with oligoarticular or polyarticular JIA, but are rare with sJIA. ANA seropositivity is associated with increased risk of **chronic uveitis** in JIA. Approximately 5–15% of patients with polyarticular JIA are seropositive for RF. Anti–cyclic citrullinated peptide antibody, as with RF, is a marker of more aggressive disease. Both ANA and RF seropositivity can occur in association with transient events, such as viral infection.

Children with sJIA usually have striking elevations in inflammatory markers and WBC and platelet counts. Hemoglobin levels are low, typically 7-10 g/dL, with indices consistent with anemia of chronic disease. The ESR is usually high, except in MAS. Although immunoglobulin levels tend to be high, ANA and RF are uncommon. Ferritin values are typically elevated and can be markedly increased in MAS (>10,000 ng/mL). In the setting of MAS, all cell lines have the potential to decline precipitously because of the consumptive process. A low or normal WBC count and/or platelet count in a child with active sJIA should raise concerns for MAS.

Early radiographic changes of arthritis include soft tissue swelling, periarticular osteopenia, and periosteal new-bone apposition around affected joints (Fig. 180.13). Continued active disease may lead to subchondral erosions, loss of cartilage, with varying degrees of bony destruction, and fusion. Characteristic radiographic changes in cervical spine, most frequently in the neural arch joints at C2-C3 (see Fig. 180.9), may progress to atlantoaxial subluxation. MRI is more sensitive than radiography to detect early changes (Fig. 180.14).

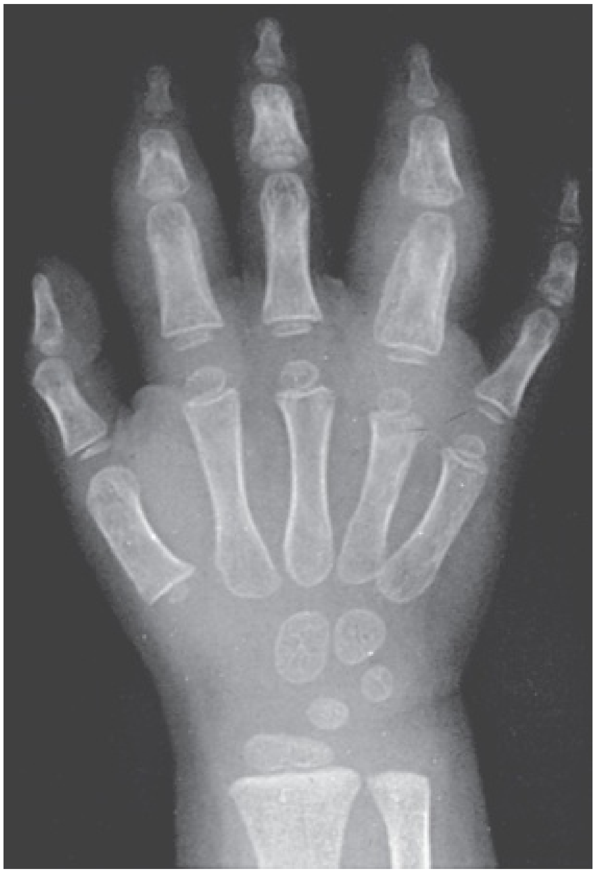

FIG. 180.13 Early (6 mo duration) radiographic changes of juvenile idiopathic arthritis. Soft-tissue swelling and periosteal new bone formation appear adjacent to the 2nd and 4th proximal interphalangeal joints.

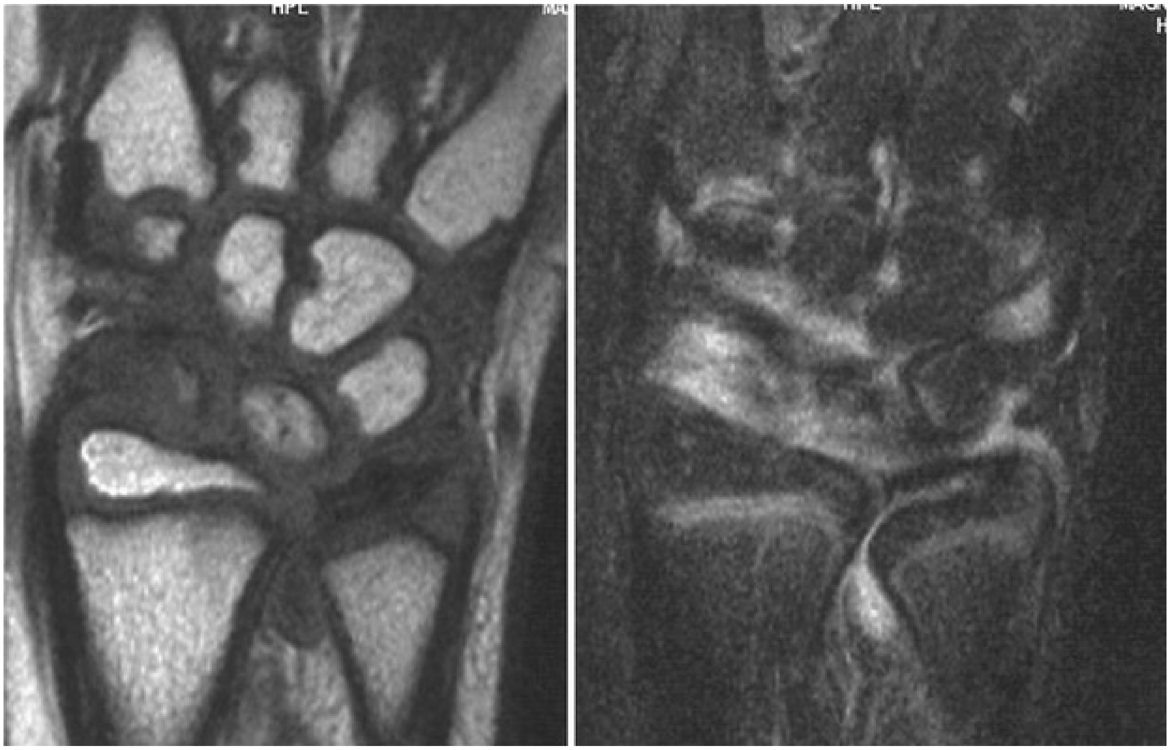

FIG. 180.14 MRI of the wrist in a child with wrist arthritis. *Left,* Image shows multiple erosions of carpal bones. *Right,* Image obtained after administration of gadolinium contrast agent reveals uptake consistent with active synovitis.

Treatment

The goals of treatment are to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. All children with JIA need individualized treatment plans, and management is tailored according to disease subtype and severity, presence of poor prognostic indicators, and response to medications. Disease management also requires monitoring for potential medication toxicities (see Chapter 179).

Children with oligoarthritis often show partial response to nonsteroidal antiinflammatory drugs (NSAIDs), with improvement in inflammation and pain (Table 180.8). Those who have no or partial response after 4-6 wk of treatment with NSAIDs, or who have functional limitations such as joint contracture or leg-length discrepancy, benefit from injection of intraarticular corticosteroids. *Triamcinolone hexacetonide* is a long-lasting preparation that provides a prolonged response. A substantial fraction of patients with oligoarthritis show no response to NSAIDs and injections, and therefore require treatment with disease-modifying antirheumatic drugs (DMARDs), including methotrexate, and, if no response, TNF inhibitors.

Table 180.8

Pharmacologic Treatment of Juvenile Idiopathic Arthritis (JIA)

TYPICAL MEDICATIONS	TYPICAL DOSES	JIA SUBTYPE	SIDE EFFECT(S)
NONSTEROIDAL ANTIINFLAMMATORY DRUGS			
Naproxen	15 mg/kg/day PO divided bid (maximum dose 500 mg bid)	Polyarthritis Systemic Oligoarthritis	Gastritis, renal and hepatic toxicity, pseudoporphyria
Ibuprofen	40 mg/kg/day PO divided tid (maximum dose 800 mg tid)	Same as above	Same as above
Meloxicam	0.125 mg/kg PO once daily (maximum dose 15 mg daily)	Same as above	Same as above
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS			
Methotrexate	0.5-1 mg/kg PO or SC weekly (maximum dose 25 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Nausea, vomiting, oral ulcerations, hepatic toxicity, blood count dyscrasias, immunosuppression, teratogenicity
Sulfasalazine	Initial 12.5 mg/kg PO daily; increase by 10 mg/kg/day Maintenance: 40-50 mg/kg divided bid (maximum dose 2 g/day)	Polyarthritis	GI upset, allergic reaction, pancytopenia, renal and hepatic toxicity, Stevens-Johnson syndrome
Leflunomide*	10-20 mg PO daily	Polyarthritis	GI upset, hepatic toxicity, allergic rash, alopecia (reversible), teratogenicity (needs washout with cholestyramine)
BIOLOGIC AGENTS			
Anti–Tumor Necrosis Factor-α			
Etanercept	0.8 mg/kg SC weekly or 0.4 mg/kg SC twice weekly (maximum dose 50 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Immunosuppressant, concern for malignancy, demyelinating disease, lupus-like reaction, injection site reaction
Infliximab*	3-10 mg/kg IV q4-8 wk	Same as above	Same as above, infusion reaction
Adalimumab	10 to <15 kg: 10 mg SC every other week 15 to <30 kg: 20 mg SC every other week >30 kg: 40 mg SC every other week	Same as above	Same as above
Anticytotoxic T-Lymphocyte–Associated Antigen-4 Immunoglobulin			
Abatacept	<75 kg: 10 mg/kg/dose IV q4wk 75-100 kg: 750 mg/dose	Polyarthritis	Immunosuppressant, concern for malignancy, infusion reaction

	IV q4wk >100 kg: 1,000 mg/dose IV q4wk SC once weekly: 10 to <25 kg: 50 mg ≥25 to <50 kg: 87.5 mg ≥50 kg: 125 mg		
Anti-CD20			
Rituximab*	750 mg/m^2 IV 2 wk × 2 (maximum dose 1,000 mg)	Polyarthritis	Immunosuppressant, infusion reaction, progressive multifocal encephalopathy
Interleukin-1 Inhibitors			
Anakinra*	1-2 mg/kg SC daily (maximum dose 100 mg/day)	Systemic	Immunosuppressant, GI upset, injection site reaction
Canakinumab	15-40 kg: 2 mg/kg/dose SC q8wk >40 kg: 150 mg SC q8wk	Systemic	Immunosuppressant, headache, GI upset, injection site reaction
Rilonacept*	2.2 mg/kg/dose SC weekly (maximum dose 160 mg)	Systemic	Immunosuppressant, allergic reaction, dyslipidemia, injection site reaction
Interleukin-6 Receptor Antagonist			
Tocilizumab	IV q2 wk: <30 kg: 12 mg/kg/dose q2wk >30 kg: 8 mg/kg/dose q2wk (maximum dose 800 mg)	Systemic Polyarthritis	Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction
	SC: <30 kg: 162 mg/dose q3wk ≥30 kg: 162 mg/dose q2wk	Polyarthritis	

* Not indicated by the U.S. Food and Drug Administration for use in JIA as of 2018.

bid, Twice daily; GI, gastrointestinal; IV, intravenous; PO, oral; q, every; SC, subcutaneous; tid, 3 times daily.

NSAIDs alone rarely induce remission in children with polyarthritis or sJIA. *Methotrexate* is the oldest and least toxic of the DMARDs available for adjunctive therapy. It may take 6-12 wk to see the effects of methotrexate. Failure of methotrexate monotherapy warrants the addition of a biologic DMARD. Biologic medications that inhibit proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, demonstrated excellent disease control. TNF-α antagonists (e.g., *etanercept, adalimumab*) are used to treat children with an inadequate response to methotrexate, with poor prognostic factors, or with severe disease onset. Early aggressive therapy with a combination of methotrexate and a TNF-α antagonist may result in earlier achievement of clinically inactive disease. *Abatacept*, a selective inhibitor of T-cell activation, and *tocilizumab*, an IL-6 receptor antagonist, have demonstrated efficacy in and are approved for treatment of polyarticular JIA (Table 180.8).

TNF inhibition is not as effective for the systemic symptoms found in sJIA. When systemic symptoms dominate, systemic corticosteroids are started followed by the initiation of IL-1 or IL-6 antagonist therapy, which often induces a dramatic and rapid response. Patients with severe disease activity may go directly to anakinra. *Canakinumab,* an IL-1β inhibitor, and tocilizumab are FDA-approved treatments for sJIA in children older than 2 yr (Table 180.8). Standardized consensus treatment plans to guide therapy for sJIA outline 4 treatment plans based on glucocorticoids, methotrexate, anakinra, or tocilizumab, with optional glucocorticoid use in the latter 3 plans as clinically indicated.

With the advent of newer DMARDs, the use of systemic corticosteroids can often be avoided or minimized. Systemic corticosteroids are recommended only for management of severe systemic illness, for *bridge therapy* during the wait for therapeutic response to a DMARD, and for control of uveitis. Steroids impose risks of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia, and they do not prevent joint destruction.

Oral Janus kinase (JAK) inhibitors (tofacitinib, ruxolitinib) inhibit JAK signaling pathways involved in immune activation and inflammation. *Tofacitinib* is FDA approved for adults with rheumatoid arthritis.

Management of JIA must include periodic slit-lamp ophthalmologic examinations to monitor for asymptomatic uveitis (Figs. 180.15 and 180.16 ; see Table 180.4). Optimal treatment of uveitis requires collaboration between the ophthalmologist and rheumatologist; initial management may include mydriatics and corticosteroids used topically, systemically, or through periocular injection. DMARDs allow for a decrease in exposure to steroids, and methotrexate and TNF-α inhibitors (adalimumab and infliximab) are effective in treating severe uveitis.

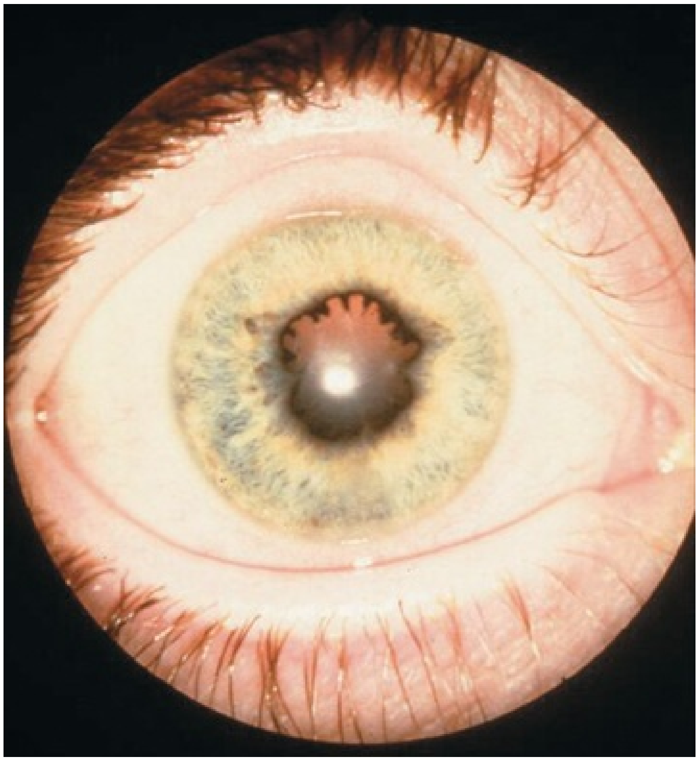

FIG. 180.15 Chronic anterior uveitis demonstrating posterior synechiae and absence of significant scleral inflammation. (From Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley & Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2017, Elsevier, Fig 107-5, p 1838.)

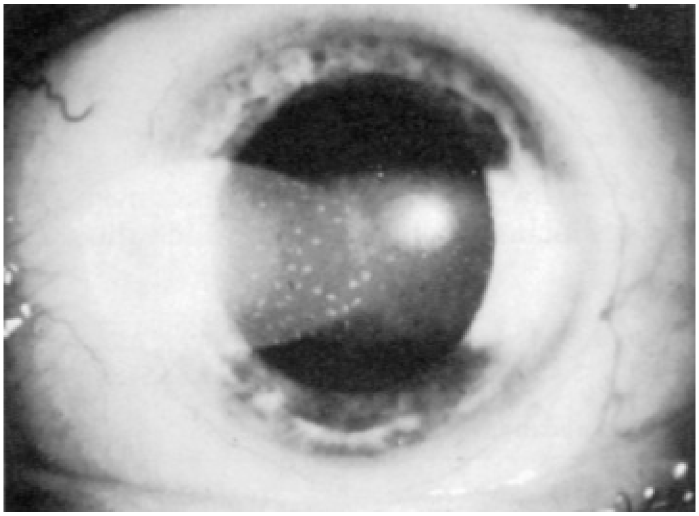

FIG. 180.16 Slit-lamp examination shows “flare” in the fluid of the anterior chamber (caused by increased protein content) and keratic precipitates on the posterior surface of the cornea, representing small collections of inflammatory cells. (Courtesy of Dr. H.J. Kaplan. From Petty RE,

Rosenbaum JT: Uveitis in juvenile idiopathic arthritis. In Cassidy JT, Petty RE, Laxer RM, et al, editors, *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2011, Saunders, Fig 20-3, p 309.)

Dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, and caloric intake are important for children with JIA. Physical therapy and occupational therapy are invaluable adjuncts to any treatment program. A social worker and nurse clinician can be important resources for families, to recognize stresses imposed by a chronic illness, to identify appropriate community resources, and to aid compliance with the treatment protocol.

Prognosis

Although the course of JIA in an individual child is unpredictable, some prognostic generalizations can be made on the basis of disease type and course. Studies analyzing management of JIA in the pre–TNF-α era indicate that up to 50% of patients with JIA have active disease persisting into early adulthood, often with severe limitations of physical function.

Children with persistent oligoarticular disease fare well, with a majority achieving disease remission. Those with extended oligoarticular disease have a poorer prognosis. Children with oligoarthritis, particularly girls who are ANA positive and with onset of arthritis before 6 yr of age, are at greatest risk for development of chronic uveitis. There is no association between the activity or severity of arthritis and uveitis. Persistent, uncontrolled anterior uveitis (see Fig. 180.15) can cause posterior synechiae, cataracts, glaucoma, and band keratopathy, with resultant blindness. Morbidity can be averted with early diagnosis and implementation of systemic therapy.

The child with polyarticular JIA often has a more prolonged course of active joint inflammation and requires early and aggressive therapy. Predictors of severe and persistent disease include young age at onset, RF seropositivity or rheumatoid nodules, presence of anti–cyclic citrullinated peptide antibodies, and many affected joints. Disease involving the hip and hand/wrist is also associated with a poorer prognosis and may lead to significant functional impairment.

Systemic JIA is often the most difficult to control in terms of both articular inflammation and systemic manifestations. Poorer prognosis is related to polyarticular distribution of arthritis, fever lasting >3 mo, and increased inflammatory markers, such as platelet count and ESR, for >6 mo. IL-1 and IL-6 inhibitors have changed the management and improved the outcomes for children with severe and prolonged systemic disease.

Orthopedic complications include leg length discrepancy and flexion contractures, particularly of the knees, hips, and wrists. Discrepancies in leg length can be managed with a shoe lift on the shorter side to prevent secondary scoliosis. Joint contractures require aggressive medical control of arthritis, often in conjunction with intraarticular corticosteroid injections, appropriate splinting, and stretching of the affected tendons. Popliteal cysts may require no treatment if they are small or respond to intraarticular corticosteroids in the anterior knee.

Psychosocial adaptation may be affected by JIA. Studies indicate that, compared with controls, a significant number of children with JIA have problems with lifetime adjustment and employment. Disability not directly associated with arthritis may continue into young adulthood in as many as 20% of patients, together with continuing chronic pain syndromes at a similar frequency. Psychological complications, including problems with school attendance and socialization, may respond to counseling by mental health professionals.

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CHAPTER 181

Ankylosing Spondylitis and Other Spondyloarthritides

Pamela F. Weiss, Robert A. Colbert

The diseases collectively referred to as *spondyloarthritides* include **ankylosing spondylitis (AS)** , arthritis associated with inflammatory bowel disease (IBD) or psoriasis, and reactive arthritis following gastrointestinal (GI) or genitourinary (GU) infections (Table 181.1 and Table 181.2). **Spondyloarthritis** is more common in adults, but all forms can present during childhood with varying symptoms and signs. Many children with spondyloarthritis are classified in the **juvenile idiopathic arthritis (JIA)** categories of **enthesitis-related arthritis (ERA)** or psoriatic arthritis. Children and adolescents with spondyloarthritis who may not meet JIA criteria include arthritis associated with IBD, juvenile ankylosing spondylitis (JAS), and reactive arthritis.

Table 181.1

Overlapping Characteristics of the Spondyloarthritides*

CHARACTERISTIC	JUVENILE ANKYLOSING SPONDYLITIS	JUVENILE PSORIATIC ARTHRITIS	INFLAMMATORY BOWEL DISEASE	REACTIVE ARTHRITIS
Enthesitis	+++	+	+	++
Axial arthritis	+++	++	++	+
Peripheral arthritis	+++	+++	+++	+++
HLA-B27 positive	+++	+	++	+++
Antinuclear antibody positive	−	++	−	−
Rheumatoid factor positive	−	−	−	−
SYSTEMIC DISEASE:				
Eyes	+	+	+	+
Skin	−	+++	+	+
Mucous membranes	−	−	+	+

Gastrointestinal tract	−	−	++++	+++

[*] Frequency of characteristics: −, absent; +, <25%; ++, 25–50%; +++, 50–75%; ++++, ≥75%.

From Cassidy JT, Petty RE: *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2011, Elsevier/Saunders.

Table 181.2

Etiologic Microorganisms of Reactive Arthritis

Probable

Chlamydia trachomatis
Shigella species
Salmonella enteritidis
Salmonella typhimurium
Yersinia enterocolitica
Yersinia pseudotuberculosis
Campylobacter jejuni and *coli*

Possible

Neisseria gonorrhoeae
Mycoplasma fermentans
Mycoplasma genitalium
Ureaplasma urealyticum
Escherichia coli
Cryptosporidium
Entamoeba histolytica
Giardia lamblia
Brucella abortus
Clostridium difficile
Streptococcus pyogenes
Chlamydia pneumoniae
Chlamydia psittaci

From Kim PS, Klausmeier TL, Orr DP: Reactive arthritis: a review, *J Adolesc*

Health 44:309–315, 2009 (Table 2, p 311).

Epidemiology

JIA is diagnosed in 90 per 100,000 U.S. children every year (see Chapter 180). ERA accounts for 10–20% of JIA, and has a mean age at onset of 12 yr. In India, ERA is the most common category of JIA, accounting for 35% of cases. Unlike other JIA categories, males are affected more often than females, accounting for 60% of ERA cases. AS occurs in 0.2–0.5% of adults, with approximately 15% of cases beginning in childhood. These disorders can be familial, largely as a result of the influence of human leukocyte antigen (**HLA**)-**B27** , which is found in 90% of JAS and 50% of ERA patients compared to 7% of healthy individuals. Approximately 20% of children with ERA have a family history of HLA-B27–associated disease, such as reactive arthritis, AS, or IBD with sacroiliitis.

Etiology and Pathogenesis

Spondyloarthritides are complex diseases in which susceptibility is largely genetically determined. Only 30% of heritability has been defined, with HLA-B27 responsible for two thirds of the total, and >100 additional genetic loci accounting for only one third. Genes that influence interleukin (IL)-23 responses (e.g., *CARD9* , *IL23R, JAK2, TYK2* , *STAT3*) and the function of HLA-B27 *(ERAP1)* are particularly important. Unusual properties of HLA-B27, such as its tendency to misfold and form abnormal cell surface structures, may have a role. Infection with certain GI or GU pathogens can trigger reactive arthritis (see Table 181.2 and Chapter 182). Altered gut microbiota and an abnormal immune response to normal microbiota may also play a role in pathogenesis. Inflamed joints and entheses in spondyloarthritis contain T and B cells, macrophages, osteoclasts, proliferating fibroblasts, and osteoblasts, with activation of the IL-23/IL-17 pathway. Bone loss and osteoproliferation in and around vertebral bodies and facet joints in long-standing AS contribute to significant morbidity.

Clinical Manifestations and Diagnosis

Clinical manifestations that help distinguish spondyloarthritis from other forms of juvenile arthritis include arthritis of the axial skeleton (sacroiliac joints) and hips, enthesitis (inflammation at the site of tendon, ligament, or joint capsule attachment to bone), symptomatic eye inflammation (acute anterior uveitis), and GI inflammation (even in the absence of IBD) (Tables 181.1 and 181.3).

Table 181.3

Assessment in Spondyloarthritis International Society (ASAS) Classification Criteria for Spondyloarthritis (SpA)

AXIAL SpA			**PERIPHERAL SpA**
In patients with ≥3 mo back pain and age at onset <45 yr			In patients with peripheral symptoms ONLY
Sacroiliitis on imaging * *plus* ≥1 SpA feature(s)	*or*	**HLA-B27** *plus* ≥2 other SpA features	**Arthritis** *or* **enthesitis** *or* **dactylitis** *plus*
SpA features • Inflammatory back pain (IBP) • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn disease/ulcerative colitis • Good response to NSAIDs • Family history for SpA • HLA-B27 • Elevated CRP			≥1 SpA feature(s) • Uveitis • Psoriasis • Crohn disease/ulcerative colitis • Preceding infection • HLA-B27 • Sacroiliitis on imaging* *or* ≥2 other SpA features • Arthritis • Enthesitis • Dactylitis • IBP ever • Family history for SpA

* Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA. Definite radiographic sacroiliitis according to modified NY criteria.

CRP, C-reactive protein; NSAIDs, nonsteroidal antiinflammatory drugs.

Adapted from Rudwaleit M, van der Heijde D, Landewé R, et al: The development of Assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis. Part II. Validation and final selection, Ann Rheum Dis 68(6):777–783, 2009; and The Assessment of Spondyloarthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general, Ann Rheum Dis 70(1):25–31, 2011.

Enthesitis-Related Arthritis

Children have ERA if they have *either* arthritis and enthesitis *or* arthritis or enthesitis, with at least 2 of the following characteristics: (1) sacroiliac joint tenderness or inflammatory lumbosacral pain, (2) presence of HLA-B27, (3) onset of arthritis in a male older than 6 yr, (4) acute anterior uveitis, and (5) a family history of an HLA-B27–associated disease (ERA, sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis) in a first-degree relative. Patients with psoriasis (or a family history of psoriasis in a first-degree relative), a positive–rheumatoid factor (RF) test result, or systemic arthritis are excluded from this group. During the 1st 6 mo of disease the arthritis is typically asymmetric and involves ≤4 joints. most frequently the knees, ankles, and hips. Inflammation of the small joints of the foot, or *tarsitis,* is highly suggestive of ERA. Enthesitis is typically symmetric and typically affects the lower limbs. Up to 40% of children develop clinical or radiographic evidence of sacroiliac joint arthritis as part of their disease; approximately 20% have evidence of sacroiliac joint arthritis at diagnosis. When the sacroiliac or other axial joints are involved, children may experience **inflammatory back pain** (Table 181.4), hip pain, and alternating buttock pain. Patients may also experience pain with palpation of the lower back or with pelvic compression. The risk of sacroiliac joint arthritis is highest in children who are HLA-B27 positive and have an elevated C-reactive protein (CRP). Untreated sacroiliitis may, but does not always, evolve into AS; additional risk factors for progression are unclear.

Table 181.4

Symptoms Characteristic of Inflammatory Back Pain

Pain at night with morning stiffness (and improvement on arising)
No improvement with rest
Improvement with exercise
Insidious onset
Good response to nonsteroidal antiinflammatory drugs

Psoriatic Arthritis

Psoriatic arthritis accounts for approximately 5% of JIA. Common clinical features of psoriatic arthritis are nail pitting (Fig. 181.1), onycholysis, and dactylitis (sausage-like swelling of fingers or toes).

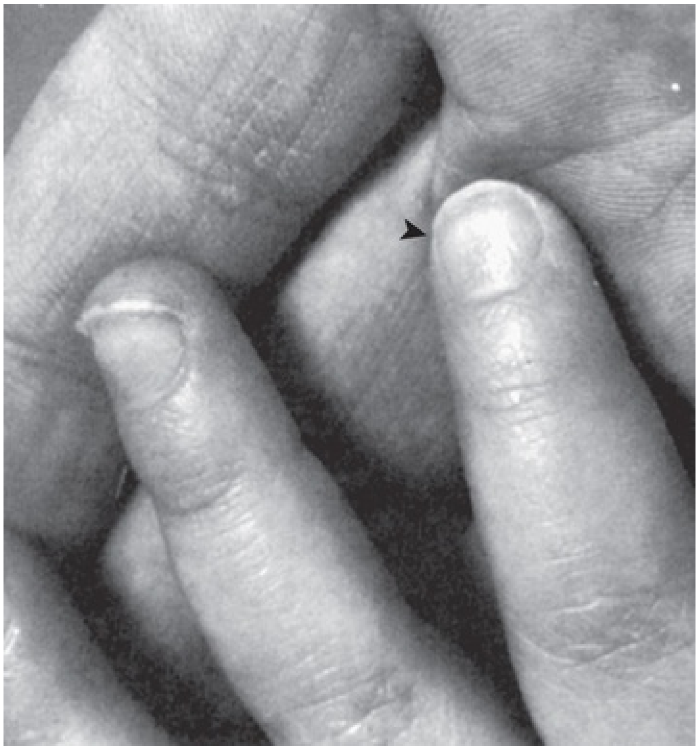

FIG. 181.1 Nail pitting *(arrowhead)* and "sausage digit" (dactylitis) of the left index finger of a girl with juvenile psoriatic arthritis. (From Petty RE, Malleson P: Spondyloarthropathies of childhood, *Pediatr Clin North Am* 33:1079–1096, 1986.)

Children have psoriatic arthritis if they have arthritis and psoriasis *or* arthritis and at least 2 of the following: (1) dactylitis, (2) nail pitting or onycholysis, and (3) psoriasis in a first-degree relative. The presence of psoriasis aids in diagnosis but is not required. Disease onset peaks during the preschool and early adolescent years. Children with onset during the preschool years are more often female, antinuclear antibody (ANA) positive, and at risk for asymptomatic ocular inflammation. Disease onset during adolescence is equally common among males and females. In the majority of children the arthritis is asymmetric and affects ≤4 joints at presentation. Large (knees and ankles) and small (fingers and toes) joints may be involved. Although distal interphalangeal joint involvement is uncommon, it is highly suggestive of the diagnosis. Enthesitis is detectable in 20–60% of patients and seems to be more frequent in those who present at an older age. Axial (sacroiliac) and root (hip) joints may be affected in up to 30% of children; the risk of axial arthritis is highest in those who are HLA-B27 positive.

Juvenile Ankylosing Spondylitis

JAS frequently begins with oligoarthritis and enthesitis. The arthritis occurs predominantly in the lower extremities and often involves the hips. In comparison to adult-onset AS, axial disease and inflammatory back pain are less frequent at disease onset, whereas enthesitis and peripheral arthritis are more common. AS is diagnosed according to the modified New York (NY) criteria if there is sufficient radiographic evidence of sacroiliitis (sacroiliitis of grade 2 or greater bilaterally or at least grade 3 unilaterally) and if the patient meets at least 1 clinical criterion involving inflammatory back pain, limitation of motion in the lumbar spine (Fig. 181.2), or limitation of chest expansion. JAS is present if the patient is <16 yr old. Juvenile-*onset* AS is frequently used to describe adult AS when the symptoms began before 16 yr of age, but full criteria were not met until later.

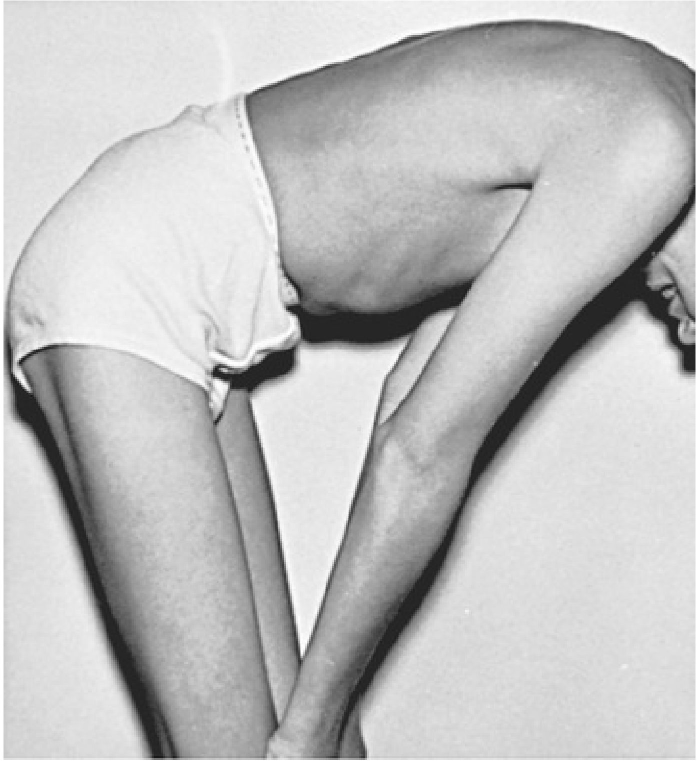

FIG. 181.2 Loss of lumbodorsal spine mobility in a boy with ankylosing spondylitis. The lower spine remains straight when the patient bends forward.

To fulfill the modified NY criteria for AS, patients must have radiographic changes in the sacroiliac joints as well as clinical sequelae of axial disease. Because radiographic sacroiliitis can take many years to develop in adults and even longer in children, and clinical sequelae may lag further behind, criteria to identify preradiographic axial spondyloarthritis were developed by the **Assessment of SpondyloArthritis International Society** . To meet criteria for axial spondyloarthritis (SpA), patients must have at least 3 mo of back pain and sacroiliitis on imaging (acute inflammation on MRI or definite radiographic sacroiliitis by NY criteria) plus 1 feature of SpA (inflammatory back pain, arthritis, enthesitis [heel], uveitis, dactylitis, psoriasis, Crohn disease/ulcerative colitis, good response to nonsteroidal antiinflammatory drugs [NSAIDs], family history for SpA, HLA-B27, or elevated C-reactive protein). Alternatively, patients can fulfill axial SpA criteria if they are HLA-B27 positive and have at least 2 SpA features. These criteria have low sensitivity and specificity in the pediatric population but, in the absence of alternate pediatric criteria, may be useful as a guide to evaluating preradiographic axial SpA.

Arthritis With Inflammatory Bowel Disease

The presence of erythema nodosum, pyoderma gangrenosum, oral ulcers, abdominal pain, diarrhea, fever, weight loss, or anorexia in a child with chronic arthritis should raise suspicion of IBD. Two patterns of arthritis complicate IBD. **Polyarthritis** affecting large and small joints is most common and often reflects the activity of the intestinal inflammation. Less frequently, **arthritis of the axial skeleton** , including the sacroiliac joints, occurs. As with psoriatic arthritis, the presence of HLA-B27 is a risk factor for the development of axial disease. The severity of axial involvement is independent of the activity of the GI inflammation.

Laboratory Findings

Laboratory evidence of systemic inflammation with elevation of the erythrocyte sedimentation rate (ESR) and/or CRP value is variable in most spondyloarthritides and may or may not be present at the onset of disease. RF and ANAs are absent, except in children with psoriatic arthritis, as many as 50% of whom are ANA positive. HLA-B27 is present in approximately 90% of children with JAS, compared with 7% of healthy individuals, but is less frequent in ERA and other SpA types.

Imaging

Conventional radiographs detect chronic bony changes and damage but not active inflammation. Early radiographic changes in the sacroiliac joints include indistinct margins and erosions that can result in joint space widening. **Sclerosis** typically starts on the iliac side of the joint (Fig. 181.3). Peripheral joints may exhibit periarticular **osteoporosis** , with loss of sharp cortical margins in areas of enthesitis, which may eventually show erosions or bony spurs (enthesophytes). Squaring of the corners of the vertebral bodies and syndesmophyte formation resulting in the classic "bamboo spine" characteristic of advanced AS is rare in early disease, particularly in childhood. CT, like radiographs, can detect chronic bony changes but not active inflammation and has the disadvantage of more radiation exposure. The gold standard for early visualization of sacroiliitis is evidence of bone marrow edema adjacent to the joint on MRI with fluid-sensitive sequences such as short-T1 inversion recovery (STIR). Gadolinium does not add value to the study of the sacroiliac joints if STIR is used. MRI will reveal abnormalities before the plain radiograph. Whole body MRI is also used to evaluate the axial skeleton in adults with early disease because it can detect vertebral lesions in addition to sacroiliac changes.

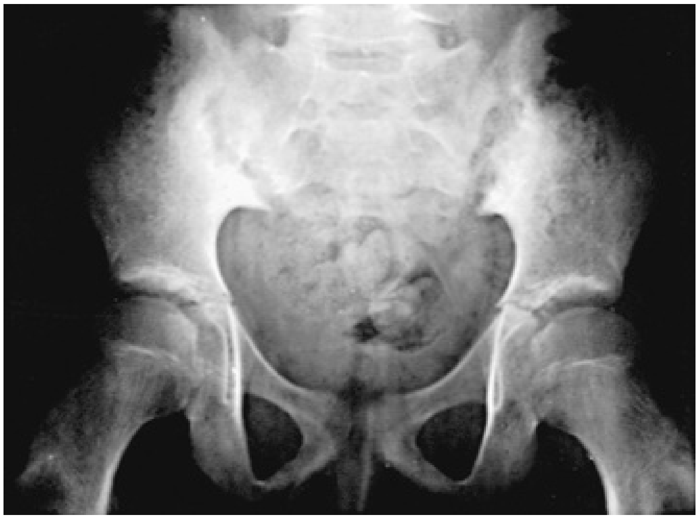

FIG. 181.3 Well-developed sacroiliitis in a boy with ankylosing spondylitis. Both sacroiliac joints show extensive sclerosis, erosion of joint margins, and apparent widening of the joint space.

Differential Diagnosis

The onset of arthritis following a recent history of diarrhea or symptoms of urethritis or conjunctivitis may suggest **reactive arthritis** (see Chapter 182). Lower back pain can be caused by suppurative arthritis of the sacroiliac joint, osteomyelitis of the pelvis or spine, osteoid osteoma of the posterior elements of the spine, pelvic muscle pyomyositis, or malignancies. In addition, mechanical conditions such as spondylolysis, spondylolisthesis, and Scheuermann disease should be considered. Back pain secondary to **fibromyalgia** usually affects the soft tissues of the upper back in a symmetric pattern and is associated with well-localized tender points and sleep disturbance (see Chapter 193.3). Legg-Calvé-Perthes disease (avascular necrosis of the femoral head), slipped capital femoral epiphysis, and chondrolysis may also manifest as pain over the inguinal ligament and loss of internal rotation of the hip joint, but without other SpA features, such as involvement of other entheses and/or joints. Radiography or MRI is critical for distinguishing these conditions.

Treatment

The goals of therapy are to control inflammation, minimize pain, preserve function, and prevent ankylosis (fusion of adjacent bones) using a combination of antiinflammatory medications, physical therapy, and education. Treatment regimens for SpA include monotherapy or combination therapy with NSAIDs, disease-modifying antirheumatic drugs (DMARDs), or biologic agents. NSAIDs, such as naproxen (15-20 mg/kg/day), are frequently used initially and may slow the progression of structural damage (syndesmophyte formation and growth) if used continually. With relatively mild disease, intraarticular corticosteroids (e.g., triamcinolone acetonide/hexacetonide) may also help to control peripheral joint inflammation. However, for moderate disease and JAS, it is typically necessary to add a second-line agent. DMARDs such as sulfasalazine (up to 50 mg/kg/day; maximum 3 g/day) or methotrexate (10 mg/m^2) may be beneficial for peripheral arthritis, but these medications have not been shown to improve axial disease in adults. Tumor necrosis factor (TNF) inhibitors (e.g., etanercept, infliximab, adalimumab) have been efficacious in reducing symptoms and improving function in adults with AS, and there is evidence that similar responses are seen in children. It remains unclear whether TNF inhibitors have an impact on structural damage in established AS, underscoring the need for earlier recognition and better therapies. Drugs that target IL-17 and IL-23/IL-12 (secukinumab and ustekinumab, respectively) also reduce clinical disease activity in adults with AS, but have not been studied in children.

Physical therapy and low-impact exercise should be included in the treatment program for all children with spondyloarthritis. Exercise to maintain range of motion in the back, thorax, and affected joints should be instituted early in the disease course. Custom-fitted insoles and heel cups are particularly useful in management of painful entheses around the feet, and the use of pillows to position the lower extremities while the child is in bed can be helpful.

Prognosis

Observational studies suggest that ongoing disease activity for >5 yr in juvenile spondyloarthritis predicts disability. Disease remission occurs in <20% of children with spondyloarthritis 5 yr after diagnosis. Factors associated with disease progression include tarsitis, HLA-B27 positivity, hip arthritis within the 1st 6 mo, and disease onset after age 8. Important questions, such as which patients with ERA will go on to have JAS/AS, have yet to be addressed. Outcomes for JAS compared with adult-onset AS suggest that hip disease requiring replacement is more common in children but axial disease is more severe in adults.

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CHAPTER 182

Reactive and Postinfectious Arthritis

Pamela F. Weiss, Robert A. Colbert

In addition to causing arthritis by means of direct microbial infection (i.e., septic arthritis; see Chapter 705), microbes activate innate and adaptive immune responses, which can lead to the generation and deposition of immune complexes as well as antibody or T cell–mediated cross-reactivity with self. In addition, microbes may influence the immune system in ways that promote immune-mediated inflammatory diseases such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), and spondyloarthritis. **Reactive arthritis** and **postinfectious arthritis** are defined as joint inflammation caused by a sterile inflammatory reaction following a recent infection. We use *reactive arthritis* to refer to arthritis that occurs following enteropathic or urogenital infections and *postinfectious arthritis* to describe arthritis that occurs after infectious illnesses not classically considered in the reactive arthritis group, such as infection with group A streptococcus or viruses. In some patients, nonviable components of the initiating organism have been demonstrated in affected joints, and the presence of viable, yet nonculturable, bacteria within the joint remains an area of investigation.

The course of reactive arthritis is variable and may remit or progress to a chronic spondyloarthritis, including ankylosing spondylitis (see Chapter 181). In postinfectious arthritis the pain or joint swelling is usually transient, lasting <6 wk, and does not necessarily share the typical spondyloarthritis pattern of joint involvement. The distinction between postinfectious arthritis and reactive arthritis is not always clear, either clinically or pathophysiologically.

Pathogenesis

Reactive arthritis typically follows enteric infection with *Salmonella* species, *Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni* , or genitourinary (GU) tract infection with *Chlamydia trachomatis* . *Escherichia coli* and *Clostridium difficile* are also causative enteric agents, although less common (see Table 181.2). Acute **rheumatic fever** caused by group A streptococcus (see Chapters 182 and 210.1), arthritis associated with infective endocarditis (see Chapter 464), and the tenosynovitis associated with *Neisseria gonorrhoeae* are similar in some respects to reactive arthritis.

Approximately 75% of patients with reactive arthritis are HLA-B27 positive. Incomplete elimination of bacteria and bacterial products, such as DNA, has been proposed as a factor in reactive arthritis. A relationship with clinical characteristics of specific infectious disorders is not present. In postinfectious arthritis, several viruses (rubella, varicella-zoster, herpes simplex, cytomegalovirus) have been isolated from the joints of patients. Antigens from other viruses (e.g., hepatitis B, adenovirus) have been identified in immune complexes from joint tissue.

Patients with reactive arthritis who are HLA-B27 positive have an increased frequency of acute and symptomatic uveitis and other extraarticular features. In addition, HLA-B27 is a risk factor for persistent gastrointestinal (GI) inflammation following enteric infections, even after resolution of the initial infection, and significantly increases the risk that the individual will develop chronic spondyloarthritis. Nevertheless, reactive arthritis also occurs in HLA-B27–negative patients, emphasizing the importance of other genes in disease susceptibility.

Clinical Manifestations and Differential Diagnosis

Symptoms of reactive arthritis begin approximately 3 days to 6 wk following infection. The classic triad of arthritis, urethritis, and conjunctivitis is relatively uncommon in children. The arthritis is typically asymmetric, oligoarticular, with a predilection for lower extremities. Dactylitis may occur, and enthesitis is common, affecting as many as 90% of patients (Fig. 182.1). Cutaneous manifestations can occur and may include circinate balanitis, ulcerative vulvitis, erythematous oral macules or plaques or erosions, erythema nodosum, paronychia, painful erosions or pustules on fingertips, and keratoderma blennorrhagica, which is similar in appearance to pustular psoriasis (Fig. 182.2).

Systemic symptoms may include fever, malaise, and fatigue. Less common features may include conjunctivitis, optic neuritis, aortic valve involvement, sterile pyuria, and polyneuropathy. Early in the disease course, markers of inflammation—erythrocyte sedimentation rate (ESR), C-reactive protein, and platelets—may be greatly elevated. The clinical manifestations may last for weeks to months.

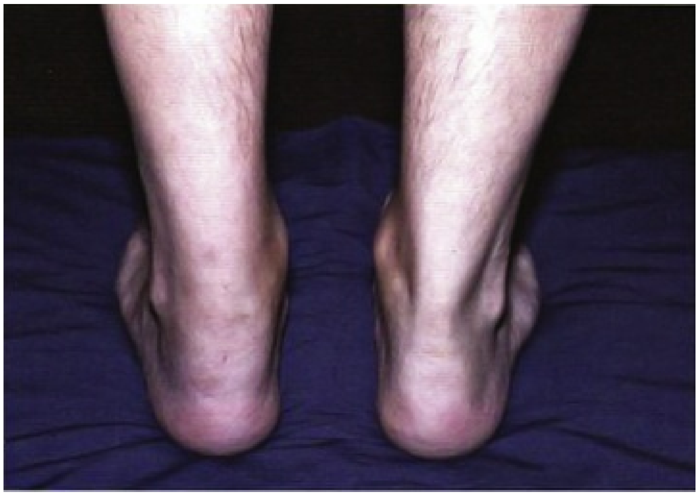

FIG. 182.1 Enthesitis—swelling of the posterior aspect of the left heel and lateral aspect of the ankle. (Courtesy of Nora Singer, Case Western Reserve University and Rainbow Babies' Hospital.)

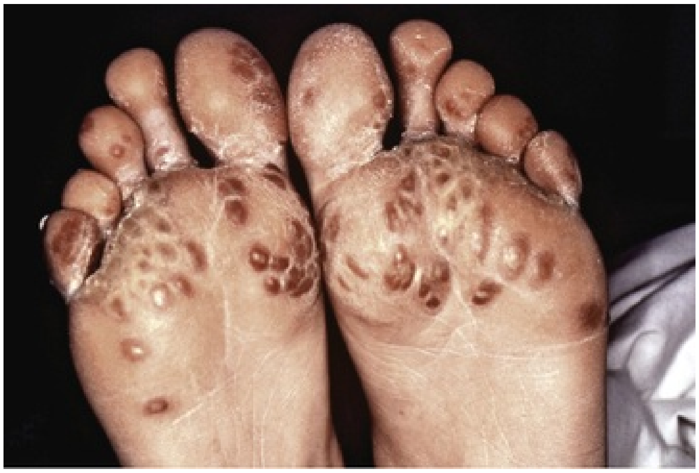

FIG. 182.2 Keratoderma blennorrhagica. (Courtesy of Dr. M.F. Rein and Centers for Disease Control and Prevention Public Health Image Library,

1976. Image #6950.)

Familiarity with other causes of postinfectious arthritis is vital when a diagnosis of reactive arthritis is being considered. Numerous viruses are associated with postinfectious arthritis and may result in particular patterns of joint involvement (Table 182.1). Rubella and hepatitis B virus typically affect the small joints, whereas mumps and varicella often involve large joints, especially the knees. The **hepatitis B arthritis–dermatitis syndrome** is characterized by urticarial rash and a symmetric migratory polyarthritis resembling that of serum sickness. Rubella-associated arthropathy may follow natural rubella infection and, infrequently, rubella immunization. It typically occurs in young women, with an increased frequency with advancing age, and is uncommon in preadolescent children and in males. Arthralgia of the knees and hands usually begins within 7 days of onset of the rash or 10-28 days after immunization. Parvovirus B19, which is responsible for erythema infectiosum (fifth disease), can cause arthralgia, symmetric joint swelling, and morning stiffness, particularly in adult women and less frequently in children. Arthritis occurs occasionally during cytomegalovirus infection and may occur during varicella infections but is rare after Epstein-Barr virus infection. Varicella may also be complicated by suppurative arthritis, usually secondary to group A streptococcus infection. HIV is associated with an arthritis that resembles psoriatic arthritis more than JIA (see Chapter 180).

Table 182.1

Viruses Associated With Arthritis

TOGAVIRUSES

Rubivirus

Rubella

Alphaviruses

Ross River
Chikungunya
O'nyong-nyong
Mayaro

Sindbis
Ockelbo
Pogosta

Orthopoxviruses

Variola virus (smallpox)
Vaccinia virus
Parvoviruses

Adenoviruses

Adenovirus 7

Herpesviruses

Epstein-Barr
Cytomegalovirus
Varicella-zoster
Herpes simplex

Paramyxoviruses

Mumps

Flavivirus

Zika virus

Hepadnavirus

Hepatitis B

Enteroviruses

Echovirus
Coxsackievirus B

Adapted from Infectious arthritis and osteomyelitis. In Petty RE, Laxer R, Lindsley CB, et al: *Textbook of pediatric rheumatology*, ed 7, Philadelphia, 2015, Saunders Elsevier.

Poststreptococcal arthritis may follow infection with either group A or group G streptococcus. It is typically oligoarticular, affecting lower-extremity joints, and mild symptoms can persist for months. Poststreptococcal arthritis differs from rheumatic fever, which typically manifests with painful migratory polyarthritis of brief duration. Because valvular lesions have occasionally been documented by echocardiography after the acute illness, some clinicians consider poststreptococcal arthritis to be an incomplete form of acute rheumatic fever (see Chapter 210.1). Certain HLA-DRB1 types may predispose children to development of either poststreptococcal arthritis (HLA-DRB1*01) or acute rheumatic fever (HLA-DRB1*16).

Transient synovitis (toxic synovitis) , another form of postinfectious arthritis, typically affects the hip, often after an upper respiratory tract infection (see Chapter 698.2). Boys 3-10 yr of age are most often affected and have acute onset of severe pain in the hip (groin), with referred pain to the thigh or knee, lasting approximately 1 wk. ESR and white blood cell count are usually normal. Radiologic or ultrasound examination may confirm widening of the joint space secondary to an effusion. Aspiration of joint fluid is often necessary to exclude septic arthritis and typically results in dramatic clinical improvement. The trigger is presumed to be viral, although responsible microbes have not been identified.

Nonsuppurative arthritis has been reported in children, usually adolescent boys, in association with **s** evere truncal acne. Patients often have fever and persistent infection of the pustular lesions. **Pyogenic (sterile) arthritis, pyoderma gangrenosum, and acne (cystic) syndrome** , an autosomal dominant disorder caused by a mutation in the *PSTPIP1* gene, is a difficult-to-treat but rare autoinflammatory disorder that has responded to anakinra or anti–tumor necrosis factor antibody therapy in a few patients. Recurrent episodes of erosive arthritis begin in childhood; cystic acne and the painful ulcerating lesions of pyoderma gangrenosum begin during adolescence. Recurrent episodes may also be associated with a sterile myopathy and may last for several months.

Infective endocarditis can be associated with arthralgia, arthritis, or signs suggestive of vasculitis, such as Osler nodes, Janeway lesions, and Roth spots. Postinfectious arthritis, perhaps because of immune complexes, also occurs in children with *N. gonorrhoeae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b, and *Mycoplasma pneumoniae* infections.

Diagnosis

A recent GU or GI infection may suggest the diagnosis of reactive arthritis, but there is no diagnostic test. A complete blood count, acute-phase reactants, complete metabolic panel, and urinalysis may be helpful to exclude other etiologies. Although stool or urogenital tract cultures can be performed in an attempt to isolate it, the triggering organism is not typically found at the time arthritis presents. Imaging findings are nonspecific or normal. Documenting previous streptococcal infection with antibody testing (anti-streptolysin O and anti-DNAse B) may help to diagnose postinfectious arthritis. Serum sickness associated with the antibiotic treatment of preceding infection must be excluded.

Because the preceding infection can be remote or mild and often not recalled by the patient, it is also important to rule out other causes of arthritis. Acute and painful arthritis affecting a single joint suggests septic arthritis, mandating joint aspiration. Osteomyelitis may cause pain and an effusion in an adjacent joint but is more often associated with focal bone pain and tenderness at the site of infection. Arthritis affecting a single joint, particularly the knee, may also be secondary to Lyme disease in endemic areas. The diagnosis of postinfectious arthritis is often established by exclusion and after the arthritis has resolved. Arthritis associated with GI symptoms or abnormal liver function test results may be triggered by infectious or autoimmune hepatitis. Arthritis or spondyloarthritis may occur in children with IBD, such as Crohn disease or ulcerative colitis (see Chapter 362.1). Parvovirus infection, macrophage activation (hemophagocytic) syndrome, and leukemia should be strongly considered when 2 or more blood cell lines are low or progressively decrease in a child with arthritis. Persistent arthritis (>6 wk) suggests the possibility of a chronic rheumatic disease, including JIA (see Chapters 180) and systemic lupus erythematosus (see Chapter 183).

Treatment

Specific treatment is unnecessary for most cases of reactive or postinfectious arthritis. Nonsteroidal antiinflammatory drugs (NSAIDs) are often needed for management of pain and functional limitation. Unless ongoing *Chlamydia* infection is suspected, attempts to treat the offending organism are not warranted. If swelling or arthralgia recurs, further evaluation may be necessary to exclude active infection or evolving rheumatic disease. Intraarticular corticosteroid injections may be given for refractory or severely involved joints once acute infection has been ruled out. Systemic corticosteroids or disease-modifying antirheumatic drugs (DMARDs) are rarely indicated but may be considered for chronic disease. Participation in physical activity should be encouraged, and physical therapy may be needed to maintain normal function and prevent muscle atrophy. For postinfectious arthritis caused by streptococcal disease, current recommendations include penicillin prophylaxis for at least 1 yr. Long-term prophylaxis is often recommended, but the duration is controversial and may need to be individualized.

Complications and Prognosis

Postinfectious arthritis following viral infections usually resolves without complications unless it is associated with involvement of other organs, such as **encephalomyelitis** . Children with reactive arthritis after enteric infections occasionally experience IBD months to years after onset. Both **uveitis** and **carditis** have been reported in children diagnosed with reactive arthritis. Reactive arthritis, especially after bacterial enteric infection or GU tract infection with *C. trachomatis*, has the potential for evolving to chronic arthritis, particularly spondyloarthritis (see Chapter 181). The presence of HLA-B27 or significant systemic features increases the risk of chronic disease.

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CHAPTER 183

Systemic Lupus Erythematosus

Rebecca E. Sadun, Stacy P. Ardoin, Laura E. Schanberg

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens. SLE occurs in both children and adults, disproportionately affecting females of reproductive age. Although nearly every organ may be affected, most frequently involved are the skin, joints, kidneys, blood-forming cells, blood vessels, and central nervous system. Systemic signs of inflammation such as fever and lymphadenopathy can also be seen. Compared with adults, children and adolescents with SLE have more severe disease and more widespread organ involvement.

Etiology

The pathogenesis of SLE remains largely unknown, but several factors likely influence risk and severity of disease, including genetics, hormonal milieu, and environmental exposures. A genetic predisposition to SLE is suggested by the association with specific genetic abnormalities, including congenital deficiencies of C1q, C2, and C4, as well as several polymorphisms (e.g., interferon regulatory factor 5, protein tyrosine phosphatase N22), and familial clustering of SLE or other autoimmune disease. In addition, certain human leukocyte antigen (HLA) types (including HLA-B8, HLA-DR2, and HLA-DR3) occur with increased frequency in patients with SLE. Although SLE clearly has a genetic component, its occurrence is sporadic in families and its concordance incomplete (estimated at 2–5% among dizygotic twins and 25–60% among monozygotic twins), suggesting **nonmendelian genetics** as well as involvement of epigenetic and environmental factors. Patients with SLE often have family members, especially mothers and sisters, with SLE or other autoimmune diseases.

Because SLE preferentially affects females, especially during their reproductive years, it is suspected that hormonal factors are important in pathogenesis. Of individuals with SLE, 90% are female, making **female sex** the strongest risk factor for SLE. Estrogens are likely to play a role in SLE, and both in vitro and animal model studies suggest that estrogen exposure promotes B-cell autoreactivity. Estrogen-containing oral contraceptives do not appear to induce flares in quiescent SLE, although the risk of flares may be increased in postmenopausal women receiving hormone replacement therapy.

Environmental exposures that may trigger the development of SLE remain largely unknown; certain viral infections, including Epstein-Barr virus (EBV), may play a role in susceptible individuals, and ultraviolet light exposure is known to trigger SLE disease activity. Environmental influences also may induce epigenetic modifications to DNA, increasing the risk of SLE and drug-induced lupus. In mouse models, drugs such as procainamide and hydralazine can promote lymphocyte hypomethylation, causing a lupus-like syndrome.

Epidemiology

The reported prevalence of SLE in children and adolescents (1-6/100,000) is lower than that in adults (20-70/100,000). Prevalence of SLE is highest among blacks, Asians, Hispanics, Native Americans, and Pacific Islanders for both adult and pediatric populations. SLE predominantly affects females, with reported 2-5:1 ratio before puberty, 9:1 ratio during reproductive years, and return to near-prepubertal ratios in the postmenopausal period. Childhood SLE is rare before 5 yr of age and is usually diagnosed in adolescence, with a median age at diagnosis of 11-12 yr. Up to 20% of all individuals with SLE are diagnosed before age 16 yr. Some define pediatric-onset lupus as onset of symptoms before age 16, and others as onset before age 18.

Pathology

Histologic features most suggestive of SLE include findings in the kidney and skin. Renal manifestations of SLE are classified histologically according to the criteria of the International Society of Nephrology (see Chapter 538.2). The finding of diffuse proliferative glomerulonephritis (class IV) significantly increases risk for renal morbidity. Renal biopsies are helpful to establish the diagnosis of SLE and to stage disease. Immune complexes are typically found with “full house” deposition of immunoglobulin and complement.

The characteristic **discoid rash** depicted in Figure 183.1*D* is characterized on biopsy by hyperkeratosis, follicular plugging, and infiltration of mononuclear cells into the dermal-epidermal junction (DEJ). The histopathology of photosensitive rashes can be nonspecific, but immunofluorescence examination of both affected and nonaffected skin may reveal deposition of immune complexes within the DEJ. This finding is called the **lupus band test** , which is specific for SLE.

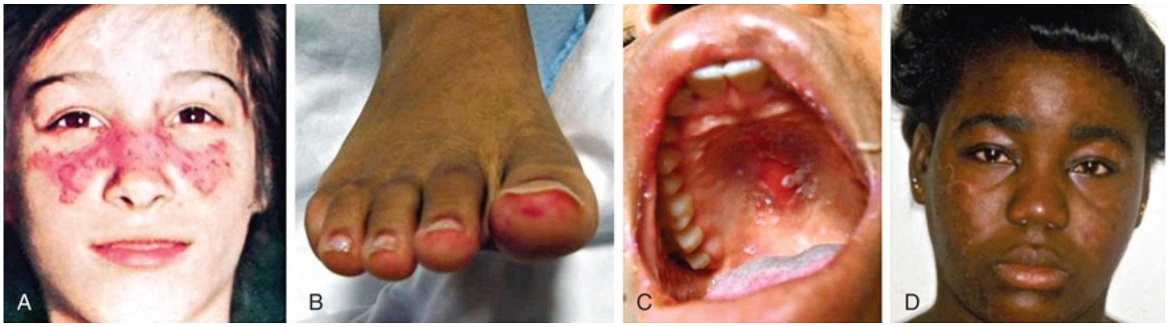

FIG. 183.1 Mucocutaneous manifestations of SLE. A, Malar rash; B, vasculitic rash on toes; C, oral mucosal ulcers; D, discoid rash in malar distribution.

Pathogenesis

A hallmark of SLE is the generation of **autoantibodies** directed against self-antigens, particularly nucleic acids. These intracellular antigens are ubiquitously expressed but are usually inaccessible and cloistered within the cell. During cell necrosis or apoptosis, the antigens are released. SLE skin cells are highly susceptible to damage from ultraviolet (UV) light, and the resulting cell death leads to release of cell contents, including nucleic antigens. Individuals with SLE may have greatly increased levels of apoptosis or significantly impaired ability to clear cell debris, causing prolonged exposure to nucleic antigens in the bloodstream and increased opportunity for recognition by immune cells, leading to B-cell stimulation and autoantibody production. Circulating autoantibodies form immune complexes and deposit in tissues, leading to local complement activation, initiation of a proinflammatory cascade, and, ultimately, tissue damage. Antibodies to **double-stranded (ds) DNA** can form immune complexes, deposit in glomeruli, and initiate inflammation leading to glomerulonephritis. However, many individuals with SLE have circulating antibodies to dsDNA but do not have nephritis, suggesting that autoantibodies are not the only pathway leading to end-organ damage in SLE.

Both the innate and the adaptive arms of the immune system have been implicated in the dysregulation of the immune system seen in SLE. High levels of interferon (IFN)-α production by plasmacytoid dendritic cells (DCs) promote expression of other proinflammatory cytokines and chemokines, maturation of monocytes into myeloid DCs, promotion of autoreactive B and T cells, and loss of self-tolerance. Almost 85% of patients with SLE exhibit this cytokine profile, known as the **type I interferon signature** . Other cytokines with increased expression in SLE include interleukin (IL)-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-21, anti–tumor necrosis factor-α, and IFN-γ, and B-lymphocyte stimulator (**BLyS**), also known as B-cell activating factor (**BAFF**). Both B and T cells demonstrate functional impairments in SLE. In active SLE, B-cell populations have impaired tolerance and increased autoreactivity, enhancing their ability to produce autoantibodies after exposure to self-antigen. In addition, cytokines such as BLyS/BAFF may promote abnormal B-cell number and function. T-cell abnormalities in SLE include increased numbers of memory T cells and decreased number and function of T-regulatory cells. SLE T cells display aberrant signaling and increased autoreactivity. As a result, they are resistant to attrition by normal apoptosis pathways. In addition, a neutrophil signature can be identified in 65% of adult SLE patients and has recently been recognized as a potential biomarker for active lupus nephritis.

Clinical Manifestations

Any organ system can be involved in SLE, so the potential clinical manifestations are myriad (Tables 183.1 and 183.2). The presentation of SLE in childhood or adolescence differs somewhat from that seen in adults. The most common presenting complaints of children with SLE include fever, fatigue, hematologic abnormalities, arthralgia, and arthritis. Arthritis is usually present in the 1st yr of diagnosis; arthritis may be painful or painless swelling, often with stiffness in the morning, and is usually a **symmetric polyarthritis** affecting large and small joints. Tenosynovitis is often present, but joint erosions or other radiographic changes are rare.

Table 183.1

Potential Clinical Manifestations of Systemic Lupus Erythematosus

TARGET ORGAN	POTENTIAL CLINICAL MANIFESTATIONS
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, tendonitis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neuropsychiatric	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex), polyneuropathy, myasthenia gravis, chorea, optic neuritis, cranial nerve palsies, plexopathy, acute confusional states, dural sinus thrombosis, aseptic meningitis, depression, psychosis, anxiety disorder
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis
Other	Macrophage activation syndrome

Table 183.2

Frequency of Clinical Features of Children and Adolescents With Systemic Lupus Erythematosus

CLINICAL FEATURE*	WITHIN 1 YR OF DIAGNOSIS (%)	ANY TIME (%)
Fever	35-90	37-100
Lymphadenopathy	11-45	13-45
Hepatosplenomegaly	16-42	19-43
Weight loss	20-30	21-32
Arthritis	60-88	60-90
Myositis	<5	<5
Any skin involvement	60-80	60-90
Malar rash	22-68	30-80
Discoid rash	<5	<5
Photosensitivity	12-45	17-58
Mucosal ulceration	25-32	30-40
Alopecia	10-30	15-35
Other rashes	40-52	42-55
Nephritis	20-80	48-100
Neuropsychiatric disease	5-30 †	15-95 ‡

Psychosis	5-12	8-18
Seizures	5-15	5-47
Headache	5-22	10-95
Cognitive dysfunction	6-15	12-55
Acute confusional state	5-15	8-35
Peripheral nerve involvement	<5	<5
Cardiovascular disease	5-30	25-60
Pericarditis	12-20	20-30

[*] Not all reports commented on all features or incidence in 1st yr.

[†] Had highest prevalence of central nervous system disease but did not describe incidence in 1st yr.

[‡] Headache reported in 95% of patients.

From Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors: *Textbook of pediatric rheumatology,* ed 7, Philadelphia, 2016, Elsevier (Table 23.5, p 291).

Renal disease in SLE is often asymptomatic, underscoring the need for careful monitoring of blood pressure and urinalyses; in adolescents, SLE can present with **nephrotic syndrome** and/or **renal failure** with the predominant symptoms being edema, fatigue, changes in urine color, and nausea/vomiting. Because SLE symptoms and findings may develop serially over several years, and not all may be present simultaneously, the diagnosis may require longitudinal follow up. SLE is often characterized by periods of flare and disease quiescence but may follow a more smoldering disease course. The **neuropsychiatric complications** of SLE may occur with or without apparently active SLE, posing a particularly difficult diagnostic challenge in adolescents, who are already at high risk for mood disorders (Fig. 183.2). Long-term complications of SLE and its therapy, including accelerated atherosclerosis and osteoporosis, become clinically evident in young to middle adulthood. SLE is a disease that evolves over time in each affected individual, and new manifestations arise even many years after diagnosis.

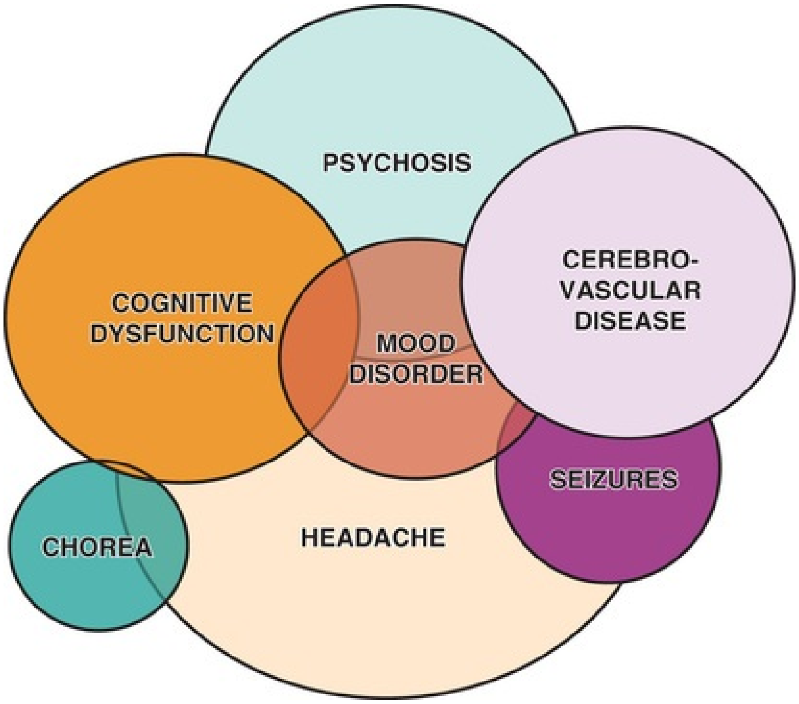

FIG. 183.2 **Overlapping neuropsychiatric symptoms in pediatric SLE. Patients with pediatric SLE typically have >1 neuropsychiatric symptom—in particular for seizures. (From Silverman E, Eddy A: Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al, editors, *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2011, Saunders Elsevier, Fig 21-17, p 329.)**

Diagnosis

The diagnosis of SLE requires a comprehensive clinical and laboratory assessment revealing characteristic multisystem disease and excluding other etiologies, including infection and malignancy. Presence of 4 of the 11 **American College of Rheumatology (ACR)** 1997 revised classification criteria for SLE simultaneously or cumulatively over time establishes the diagnosis (Table 183.3). Of note, although a positive antinuclear antibody (ANA) test result is not required for the diagnosis of SLE, ANA-negative lupus is extremely rare. ANA is very sensitive for SLE (95–99%), but it is not very specific (50%). The ANA may be positive many years before a diagnosis of SLE is established. However, most asymptomatic, ANA-positive patients do not have SLE or other autoimmune disease.

Table 183.3

American College of Rheumatology (ACR)

1997 Revised Classification Criteria for Systemic Lupus Erythematosus*

- Malar rash
- Discoid rash
- Photosensitivity
- Oral or nasal ulcers
- **Arthritis**
  - Nonerosive, ≥2 joints
- **Serositis**
  - Pleuritis, pericarditis, or peritonitis
- **Renal manifestations** †
  - Consistent renal biopsy
  - Persistent proteinuria or renal casts
- Seizure or psychosis
- **Hematologic manifestations** †
  - Hemolytic anemia
  - Leukopenia (<4,000 leukocytes/mm^3)
  - Lymphopenia (<1,500 leukocytes/mm^3)
  - Thrombocytopenia (<100,000 thrombocytes/mm^3)
- **Immunologic abnormalities** †
  - Positive anti–double-stranded DNA or anti-Smith antibody
  - False-positive rapid plasma reagin test result, positive lupus anticoagulant test result, or elevated anticardiolipin IgG or IgM antibody
- Positive antinuclear antibody test result

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* The presence of 4 of 11 criteria establishes the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

† Each of these criteria counts as a single criterion whether 1 or more definitions are satisfied.

Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, *Arthritis*

Rheum 40:1725, 1997.

Antibodies against dsDNA and **anti-Smith** are specific for SLE (98%) but not as sensitive (40–65%). **Hypocomplementemia** , although common in SLE, is not one of the ACR classification criteria; however, hypocomplementemia has been added to updated criteria validated by the **Systemic Lupus International Collaborating Clinics (SLICC)** in 2012 (Table 183.4). Other differences in the SLICC criteria include the addition of nonscarring alopecia, additional cutaneous and neurologic manifestations of lupus, and a positive direct Coombs test in the absence of hemolytic anemia. The SLICC criteria have been validated in pediatric SLE and have been shown to have higher sensitivity (93% vs 77%) but lower specificity (85% vs 99%) than the ACR criteria.

Table 183.4

Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus*

Clinical Criteria

Acute cutaneous lupus

Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus

Chronic cutaneous lupus

Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematous tumidus, chilblains lupus, discoid lupus/lichen planus overlap

Oral or nasal ulcers

Nonscarring alopecia

Synovitis (≥2 joints)

Serositis

Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis

Renal

Presence of red blood cell casts or urine protein/creatinine ratio representing >500 mg protein/24 hr

Neurologic

Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state

Hemolytic anemia

Leukopenia (<4,000/mm^3) or lymphopenia (<1,000/mm^3)

Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

Positive antinuclear antibody

Positive double-stranded DNA antibody

Positive anti-Smith antibody

Antiphospholipid antibody positivity

Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium- to high-titer anticardiolipin antibody level (IgA, IgG, IgM), or positive anti–β_2 -glycoprotein-1 antibody (IgA, IgG, IgM)

Low complement

Low C3, C4, or CH_{50} level

Positive direct Coombs test

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[*] The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE. Biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA also satisfies the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

Adapted from Petri M: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, *Arthritis Rheum* 64(8):2677–2686, 2012.

Differential Diagnosis

Multiorgan disease is the hallmark of SLE. Given its wide array of potential clinical manifestations, SLE is in the differential diagnosis of many clinical scenarios, including unexplained fevers, joint pain or arthritis, rash, cytopenias, nephritis, nephrotic syndrome, pleural or pericardial effusions or other cardiopulmonary abnormalities, and new-onset psychosis, movement disorders, or seizures. For patients ultimately diagnosed with pediatric SLE, the initial differential diagnosis often includes infections (sepsis, EBV, parvovirus B19, endocarditis), malignancies (leukemia, lymphoma), poststreptococcal glomerulonephritis, other rheumatologic conditions (juvenile idiopathic arthritis, vasculitides), and drug-induced lupus.

Drug-induced lupus refers to the presence of SLE manifestations triggered by exposure to specific medications, including hydralazine, minocycline, many anticonvulsants, sulfonamides, and antiarrhythmic agents (Table 183.5). In individuals prone to SLE, these agents may act as a trigger for true SLE, but more often these agents provoke a reversible lupus-like syndrome. Unlike SLE, drug-induced lupus affects males and females equally. A genetic predisposition toward slow drug acetylation may increase the risk of drug-induced lupus. Circulating **antihistone antibodies** are often present in drug-induced SLE; these antibodies are only detected in up to 20% of individuals with SLE. Hepatitis, which is rare in SLE, is more common in drug-induced lupus. Individuals with drug-induced lupus are less likely to demonstrate antibodies to dsDNA, hypocomplementemia, and significant renal or neurologic disease. In contrast to SLE, manifestations of drug-induced lupus typically resolve after withdrawal of the offending medication; however, complete recovery may take several months to years, requiring treatment with hydroxychloroquine, NSAIDs, and/or corticosteroids.

Table 183.5

Medications Associated With Drug-Induced Lupus

Definite Association

Minocycline, procainamide, hydralazine, isoniazid, penicillamine, diltiazem, interferon-α, methyldopa, chlorpromazine, etanercept, infliximab, adalimumab

Probable Association

Phenytoin, ethosuximide, carbamazepine, sulfasalazine, amiodarone, quinidine, rifampin, nitrofurantoin, β-blockers, lithium, captopril, interferon-γ, hydrochlorothiazide, glyburide, docetaxel, penicillin, tetracycline, statins, gold, valproate, griseofulvin, gemfibrozil, propylthiouracil

Laboratory Findings

A positive ANA test is present in 95–99% of SLE patients. ANA has poor specificity for SLE, however, because up to 20% of healthy individuals also have a positive ANA test result, making the ANA a poor screen for SLE when used in isolation. High titers are more suggestive of underlying autoimmune disease, but ANA titers do not correlate with disease activity, so repeating ANA titers after diagnosis is not helpful. Antibodies to dsDNA are specific for SLE, and in many individuals, anti-dsDNA levels correlate with disease activity, particularly in those with significant nephritis. Anti-Smith antibody, although found specifically in patients with SLE, does not correlate with disease activity. Serum levels of total hemolytic complement (CH_{50}), C3, and C4 are typically decreased in active disease and often improve with treatment. Table 183.6 lists autoantibodies found in SLE along with their clinical associations. Hypergammaglobulinemia is a common but nonspecific finding. Inflammatory markers, particularly erythrocyte sedimentation rate, are often elevated in active disease. C-reactive protein (CRP) correlates less well with disease activity; significantly elevated CRP values often reflect infection, whereas chronic mild elevation may indicate increased cardiovascular risk.

Table 183.6

Autoantibodies Typically Associated With Systemic Lupus Erythematosus

ANTIBODY	CLINICAL ASSOCIATION
Anti–double-stranded DNA	Specific for the diagnosis of SLE Correlates with disease activity, especially nephritis, in some with SLE
Anti-Smith antibody	Specific for the diagnosis of SLE
Antiribonucleoprotein (anti-RNP) antibody	Increased risk for Raynaud phenomenon, insterstitial lung disease, and pulmonary hypertension

Anti-Ro antibody (anti-SSA antibody) Anti-La antibody (anti-SSB antibody)	Associated with sicca syndrome May suggest diagnosis of Sjögren syndrome Increased risk of neonatal lupus in offspring (congenital heart block) May be associated with cutaneous and pulmonary manifestations of SLE May be associated with isolated discoid lupus
Antiphospholipid antibodies (including anticardiolipin antibodies)	Increased risk for venous and arterial thrombotic events
Antihistone antibodies	Present in a majority of patients with drug-induced lupus May be present in SLE

Antiphospholipid antibodies , which increase clotting risk, can be found in up to 66% of children and adolescents with SLE. Antiphospholipid laboratory findings include the presence of anticardiolipin or anti–β_2 -glycoprotein antibodies, prolonged phospholipid-dependent coagulation test results (partial thromboplastin time, dilute Russell viper-venom time), and circulating **lupus anticoagulant** (which confirms that a prolonged PPT is not corrected with mixing studies). When an arterial or venous clotting event occurs in the presence of an antiphospholipid antibody, **antiphospholipid antibody syndrome** is diagnosed, which can occur in the context of SLE (secondary) or independent of SLE (primary) (see Chapter 479).

Treatment

Treatment of SLE is tailored to the individual and is based on specific disease manifestations and medication tolerability. For all patients, sunscreen and avoidance of prolonged direct sun exposure and other UV light may help control disease and should be reinforced at every visit with the patient. *Hydroxychloroquine* is recommended for all individuals with SLE when tolerated. In addition to treating mild SLE manifestations such as rash and mild arthritis, hydroxychloroquine prevents SLE flares, improves lipid profiles, and may improve mortality and renal outcomes. Potential toxicities include retinal deposition and subsequent vision impairment; therefore, annual ophthalmology exams are recommended for patients taking hydroxychloroquine, including automated visual field testing as well as spectral-domain optical coherence tomography (SD-OCT). Given that risk factors for ocular toxicity include duration of use and dose, hydroxychloroquine in SLE should never be prescribed at doses >6.5 mg/kg (maximum 400 mg daily), and newer ophthalmology guidelines recommend limiting maintenance dosing to 4-5 mg/kg.

Corticosteroids are a treatment mainstay for significant manifestations of

SLE and work quickly to improve acute deterioration; side effects often limit patient adherence, especially in adolescence, and potential toxicities are worrisome. It is important to limit dose and length of exposure to corticosteroids whenever possible. Potential consequences of corticosteroid therapy include growth disturbance, weight gain, striae, acne, hyperglycemia, hypertension, cataracts, avascular necrosis, and osteoporosis. The optimal dosing of corticosteroids in children and adolescents with SLE remains unknown; severe disease is often treated with high doses of intravenous (IV) methylprednisolone (e.g., 30 mg/kg/day to a maximum of 1,000 mg/day for 3 days, sometimes followed by a period of weekly pulses) and/or high doses of oral prednisone (1-2 mg/kg/day). As disease manifestations improve, corticosteroid dosages are gradually tapered over months. For most patients it is necessary to introduce a steroid-sparing immunosuppressive medication to limit cumulative steroid exposure.

Steroid-sparing immunosuppressive agents for the treatment of pediatric SLE include methotrexate, leflunomide, azathioprine, mycophenolate mofetil (MMF), tacrolimus, cyclophosphamide, rituximab, and belimumab. Methotrexate, leflunomide, and azathioprine are often used to treat persistent moderate disease, including arthritis, significant cutaneous or hematologic involvement, and pleural disease. Cyclophosphamide, MMF, and azathioprine are appropriate for the treatment of lupus nephritis, whereas MMF and rituximab are often used for significant hematologic manifestations, including severe leukopenia, hemolytic anemia, or thrombocytopenia.

Cyclophosphamide , usually administered intravenously, is reserved for the most severe, potentially life-threatening SLE manifestations, such as renal, neurologic, and cardiopulmonary disease. Although cyclophosphamide is highly effective in controlling disease, the potential toxicities are significant, including cytopenias, infection, hemorrhagic cystitis, premature gonadal failure, and increased risk of future malignancy. Attention to adequate hydration can attenuate the risk of hemorrhagic cystitis. Fortunately, young girls are at much lower risk of gonadal failure than older women, and the use of gonadotropin-releasing hormone agonists, such as leuprolide acetate, may help prevent gonadal failure.

The **Childhood Arthritis Rheumatology Research Alliance (CARRA)** consensus treatment plan for induction therapy of newly diagnosed **proliferative lupus nephritis** (class IV) is specific to the pediatric SLE population. The treatment is considered necessary for class IV lupus nephritis but also appropriate for certain patients with class III, V, or VI lupus nephritis. The CARRA treatment plans advise 6 mo of induction therapy with either cyclophosphamide (given per NIH Protocol as 500-1000 mg/m^2 IV monthly) or MMF (600 mg/m^2 , up to 1500 mg, twice daily), used in combination with 1 of 3 standardized glucocorticoid regimens. For patients who fail to achieve a partial response in 6 mo, it is appropriate to switch agents. For adult-weight adolescents, the cyclophosphamide dosing regimen used in the **Euro-Lupus Nephritis Trial** can be considered instead of the above 6 mo therapy to reduce toxicity from cyclophosphamide exposure. Per this protocol, a fixed dose of 500 mg is given every 2 wk for 3 mo; this regimen is thought to reduce adverse effects while maintaining comparable efficacy for lupus nephritis in adults, but has not been studied specifically in pediatric lupus. Oral medication adherence is very poor in pediatric SLE, which must be considered when weighing the benefits of an IV infusion vs a twice-daily oral medication such as MMF. Maintenance therapy of lupus nephritis consists of cyclophosphamide every 3 mo, or MMF, or azathioprine, typically for 36 mo after completion of induction therapy.

Clinical trial data on the use of *rituximab* in SLE with treatment-resistant glomerulonephritis has been largely disappointing, but results from the LUNAR study suggest a possible benefit for subpopulations of SLE patients. The U.S. Food and Drug Administration (FDA) has approved the use of *belimumab* , a monoclonal antibody against BLyS/BAFF, for the treatment of lupus in adults; when added to standard SLE therapy, belimumab improves multiple markers of disease severity. Other therapies being studied for treatment of lupus include rigerimod (a polypeptide corresponding to a sequence of the snRNP protein) and anifrolumab (monoclonal antibody to IFN-α receptor), all with encouraging phase II results.

Given the lifelong nature of SLE, optimal care of children and adolescents with this disease also involves preventive practices. Because of the enhanced risk of atherosclerosis in SLE, attention to cholesterol levels, smoking status, body mass index, blood pressure, and other traditional cardiovascular risk factors is warranted. Even though the **Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE)** study failed to support placing all children with SLE on a statin, post hoc analyses suggest that statins should be considered for primary prevention of atherosclerotic disease in certain clinical circumstances, particularly pubertal patients with an elevated CRP.

SLE patients with antiphospholipid antibody syndrome (antiphospholipid antibodies *and* a history of clot) are treated with long-term anticoagulation to prevent thrombotic events. For SLE patients who are antiphospholipid antibody positive without a history of clot, many pediatric rheumatologists prescribe aspirin (81 mg daily).

For all SLE patients, adequate intake of calcium and vitamin D is necessary to prevent future osteoporosis, particularly as vitamin D levels are lower in pediatric SLE patients compared to age-matched healthy controls. Studies suggest a link between hypovitaminosis D and SLE susceptibility, with a possible emerging role for vitamin D in immunomodulation.

Infections, particularly pneumococcal disease, frequently complicate SLE, so routine immunization is recommended, including the annual influenza vaccination. In addition, pediatric SLE patients age 6 or older should receive an additional pneumococcal 13 vaccination, followed by the pneumococcal 23 vaccination at least 2 mo later. It is important to note that many of the immunosuppressants used in SLE contraindicate live vaccines. Prompt attention to febrile episodes should include an evaluation for serious infections. Because pediatric SLE patients are at high risk for developing anxiety and depression, screening for depression is also essential. Peer support and cognitive-behavioral therapy interventions reduce pain and enhance resilience in pediatric SLE.

It should be remembered that pregnancy can worsen SLE, and obstetric complications are common. In addition, many medications used to treat SLE are teratogenic, so it is important to counsel adolescent girls about these risks and facilitate access to appropriate contraceptive options. Hydroxychloroquine is recommended throughout the pregnancy of all SLE patients, and other medications may need to be adjusted.

Complications

Within the first several years of diagnosis, the most common causes of death in SLE patients are infection and complications of glomerulonephritis and neuropsychiatric disease (Table 183.7). Over the long-term, the most common causes of mortality are complications of atherosclerosis and malignancy. The increased risk of premature atherosclerosis in SLE is not explained by traditional risk factors and is partly a result of the chronic immune dysregulation and inflammation associated with SLE. Increased malignancy rates may be caused by immune dysregulation as well as exposure to medications with carcinogenic potential.

Table 183.7

Morbidity in Childhood Lupus

SYSTEM	MORBIDITY
Renal	Hypertension, dialysis, transplantation
Central nervous	Organic brain syndrome, seizures, psychosis, neurocognitive dysfunction
Cardiovascular	Atherosclerosis, myocardial infarction, cardiomyopathy, valvular disease
Immune	Recurrent infection, functional asplenia, malignancy
Musculoskeletal	Osteopenia, compression fractures, avascular necrosis
Ocular	Cataracts, glaucoma, retinal detachment, blindness
Endocrine	Diabetes, obesity, growth failure, infertility, fetal wastage

From Cassidy JT, Petty RE: *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2011, Elsevier Saunders.

Prognosis

The severity of pediatric SLE is notably worse than the typical course for adult-onset SLE. However, because of advances in the diagnosis and treatment of SLE, survival has improved dramatically over the past 50 yr. Currently, the 5 yr survival rate for pediatric SLE is approximately 95%, although the 10 yr survival rate remains 80–90%. Given their long burden of disease, children and adolescents with SLE face high risks of future morbidity and mortality from the disease and its complications, as well as medication side effects (see Table 183.7). Given the complex and chronic nature of SLE, it is optimal for children and adolescents with SLE to be treated by pediatric rheumatologists in a multidisciplinary clinic with access to a full complement of pediatric subspecialists.

183.1

Neonatal Lupus

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Keywords

NLE
congenital heart block
hydrops fetalis
IVIG

Neonatal lupus erythematosus (NLE), an entity distinct from SLE, is one of the few rheumatic disorders manifesting in the neonate. NLE is not an autoimmune disease of the fetus but instead results from passively acquired autoimmunity, when maternal immunoglobulin G autoantibodies cross the placenta and enter the fetal circulation. In contrast to SLE, neonatal lupus is not characterized by ongoing immune dysregulation, although infants with neonatal lupus may be at some increased risk for development of future autoimmune disease. The vast majority of NLE cases are associated with maternal **anti-Ro** (also known as anti-SSA), **anti-La** antibodies (also known as anti-SSB), or **anti-RNP** (antiribonucleoprotein) autoantibodies. Despite the clear association with maternal autoantibodies, their presence alone is not sufficient to cause disease, because only 2% of offspring born to mothers with anti-Ro and anti-La antibodies develop neonatal lupus. Siblings of infants with NLE have a 15–20% chance of developing NLE. Neonatal lupus seems to be independent of maternal health since many mothers are asymptomatic and only identified to have anti-Ro/anti-La antibodies subsequent to the diagnosis of NLE. Half the infants with NLE are born to the mothers with a defined rheumatic disease, such as Sjögren syndrome or SLE.

Clinical manifestations of neonatal lupus include a characteristic annular or macular rash typically affecting the face (especially the periorbital area), trunk, and scalp (Fig. 183.3). The rash can be present at birth but more often appears within the first 6-8 wk of life, after exposure to UV light, and typically lasts 3-4 mo. Infants may also have cytopenias and hepatitis, each occurring in approximately 25% of cases, but the most feared complication is **congenital heart block** .

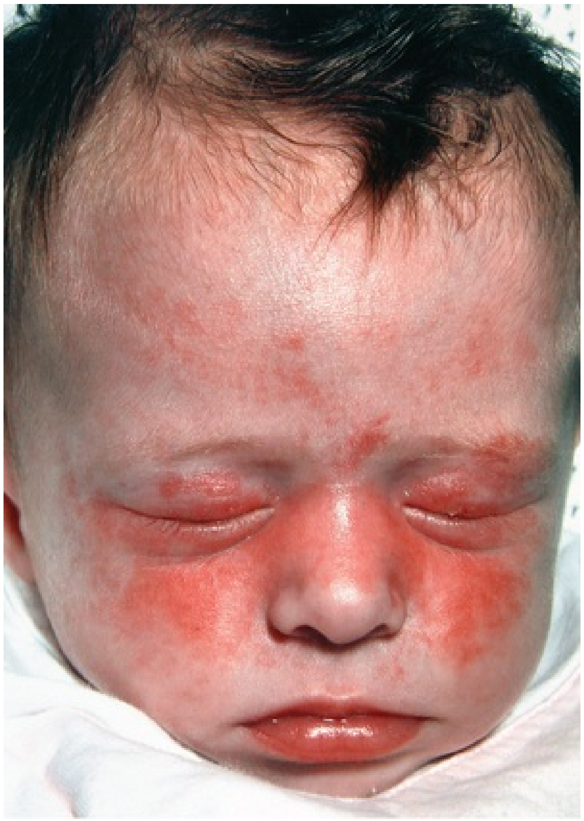

FIG. 183.3 Neonatal lupus syndrome. Typical rash, often photosensitive with a malar distribution, appearing as plaques with erythema and scaling. (Reproduced, with written parental permission, from Pain C, Beresford MW: Neonatal lupus syndrome, *Paediatr Child Health* 17:223–227, 2007.)

Conduction system abnormalities range from prolongation of the PR interval to complete heart block, with development of progressive cardiomyopathy in the most severe cases. The noncardiac manifestations of NLE are usually reversible, whereas third-degree congenital heart block is permanent. Conduction system abnormalities can be detected in utero by fetal echocardiogram beginning at 16 wk gestational age. Neonatal lupus cardiac disease has a mortality rate of approximately 20%. Cardiac NLE can manifest as heart block, cardiomyopathy, valvular dysfunction, and endocardial fibroelastosis. Fetal bradycardia from heart block can lead to **hydrops fetalis** .

In vitro studies suggest that during cardiac development via apoptosis, Ro and La antigens may be exposed on the surface of cardiac cells in the proximity of the atrioventricular node, making the antigens accessible to maternal autoantibodies. Binding incites a local immune response, resulting in fibrosis within the conduction system as well as more extensive disease in fatal cases. In the skin, exposure to ultraviolet light results in cell damage and the subsequent exposure of Ro and La antigens, inducing a similar local inflammatory response that produces the characteristic rash.

Although the scant clinical trial data have been mixed, fluorinated corticosteroids (dexamethasone or betamethasone), intravenous immune globulin (IVIG) at 1–2 g/kg maternal weight, plasmapheresis, hydroxychloroquine, and terbutaline (combined with steroids) have been used in pregnant women with anti-Ro or anti-La antibodies to prevent occurrence or progression of fetal cardiac abnormalities.

Most encouraging are retrospective cohort studies suggesting maternal treatment with *hydroxychloroquine* may reduce the frequency and recurrence of congenital heart block. In a case control study of women with lupus and known anti-Ro autoantibodies, maternal use of hydroxychloroquine decreased the rate of cardiac disease (odds ratio 0.28). This was confirmed in an expanded international study in which the recurrence rate of cardiac disease was 64% lower in pregnant women given hydroxychloroquine than controls (7.5% vs 21.2%). All clinical data on the use of hydroxychloroquine in pregnancy point to safety; prospective clinical studies are examining efficacy in the prevention of recurrent congenital heart block in pregnant women known to be anti-Ro and/or anti-La positive.

In utero, fluorinated corticosteroids seem to improve cases of hydrops fetalis. Furthermore, the addition of β-agonist therapy to increase fetal heart rate, used in combination with corticosteroids or IVIG, may help prevent hydrops in cases of severe fetal heart block. However, recent data from the **Research Registry for Neonatal Lupus** suggest that dexamethasone is not efficacious in preventing progression of isolated third-degree block, influencing the need for pacing after birth, or overall survival.

Significant conduction system abnormalities after birth are treated with cardiac pacing and occasionally IVIG and corticosteroids, whereas severe cardiomyopathy may require cardiac transplantation. If the conduction defect is not addressed, affected children are at risk for exercise intolerance, arrhythmias, and death. With cardiac pacing, children with conduction system disease in the absence of cardiomyopathy have an excellent prognosis.

Noncardiac manifestations are typically transient and are conservatively managed, often with supportive care alone. Topical corticosteroids can be used to treat moderate to severe NLE rash. Cytopenias may improve over time, but severe cases occasionally require IVIG. Supportive care is usually appropriate for hepatic and neurologic manifestation. As the neonate clears maternal autoantibodies over the 1st 6 mo of life, these inflammatory manifestations gradually resolve.

Because maternal autoantibodies gain access to the fetus through the placenta via FcRn at about 12 wk of gestation, all pregnant women with circulating anti-Ro and/or anti-La antibodies, or those with a history of offspring with NLE or congenital heart block, are monitored by a pediatric cardiologist, with screening fetal echocardiography performed weekly from 16-26 wk of gestation and then biweekly through 34 wk. The period of greatest vulnerability is usually 18-24 wk. If fetal bradycardia is found during in utero monitoring, and if fetal echocardiography confirms a conduction defect, screening for maternal anti-Ro and anti-La antibodies is warranted. Figure 183.4 presents a proposed management algorithm.

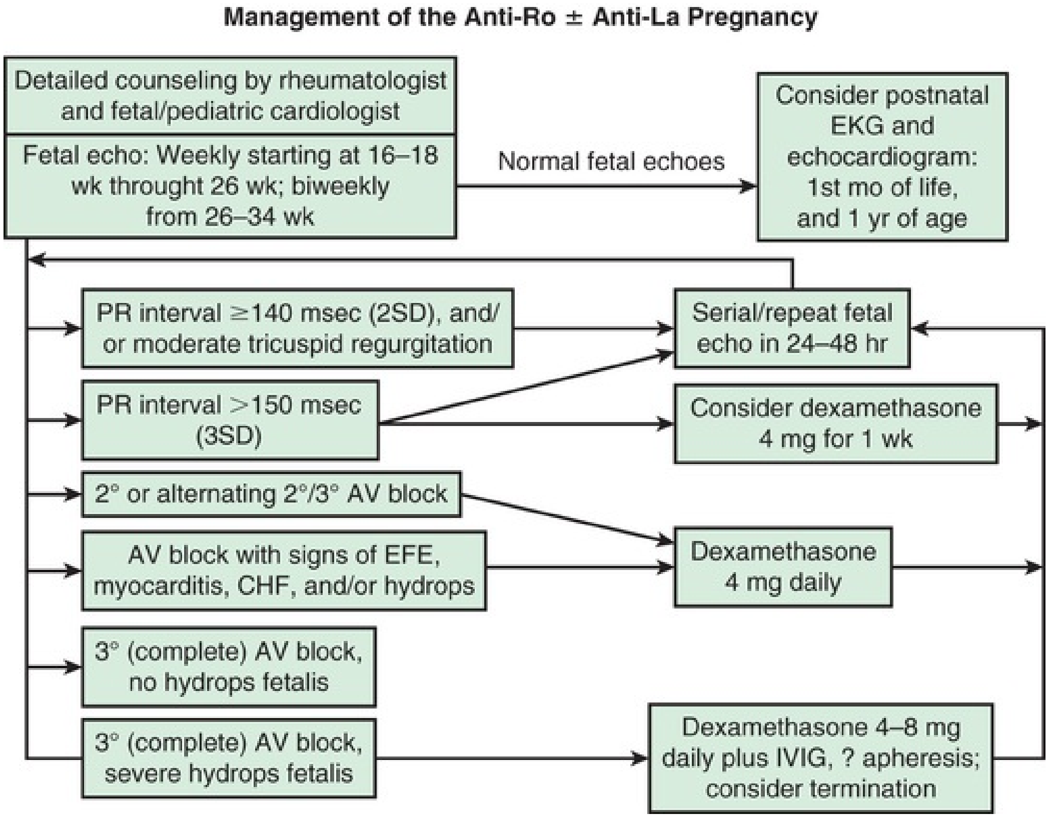
Management of the Anti-Ro ± Anti-La Pregnancy
Detailed counseling by rheumatologist and fetal/pediatric cardiologist
Fetal echo: Weekly starting at 16–18 wk throught 26 wk; biweekly from 26–34 wk
Normal fetal echoes
Consider postnatal EKG and echocardiogram: 1st mo of life, and 1 yr of age
PR interval ≥140 msec (2SD), and/or moderate tricuspid regurgitation
Serial/repeat fetal echo in 24–48 hr
PR interval >150 msec (3SD)
Consider dexamethasone 4 mg for 1 wk
2° or alternating 2°/3° AV block
AV block with signs of EFE, myocarditis, CHF, and/or hydrops
Dexamethasone 4 mg daily
3° (complete) AV block, no hydrops fetalis
3° (complete) AV block, severe hydrops fetalis
Dexamethasone 4–8 mg daily plus IVIG, ? apheresis; consider termination

FIG. 183.4 Algorithm for the management of the anti-Ro ± anti-La pregnancy. All such pregnancies should include counseling and serial fetal echocardiograms. AV, Atrioventricular; CHF, congestive heart failure; EFE, endocardial fibroelastosis; SD, standard deviations.

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CHAPTER 184

Juvenile Dermatomyositis

Angela Byun Robinson, Ann M. Reed

Juvenile dermatomyositis (JDM) is the most common inflammatory myositis in children, distinguished by proximal muscle weakness and a characteristic rash. Inflammatory cell infiltrates result in *vascular inflammation,* the underlying pathology in this disorder.

Etiology

Evidence suggests that the etiology of JDM is multifactorial, based on genetic predisposition and an unknown environmental trigger. Human leukocyte antigen (HLA) alleles such as B8, DRB1*0301, DQA1*0501, and DQA1*0301 are associated with increased susceptibility to JDM in selected populations. Maternal microchimerism may play a part in the etiology of JDM by causing graft-versus-host disease (GVHD) or autoimmune phenomena. Persistent maternal cells have been found in blood and tissue samples of children with JDM. An increased number of these maternal cells are positive for HLA-DQA1*0501, which may assist with transfer or persistence of chimeric cells. Specific cytokine polymorphisms in tumor necrosis factor (TNF)-α promoter and variable-number tandem repeats of the interleukin (IL)-1 receptor antagonist may increase genetic susceptibility. These polymorphisms are common in the general population. A history of infection in the 3 mo before disease onset is usually reported; multiple studies have failed to produce a causative organism. Constitutional signs and upper respiratory symptoms predominate, but one third of patients report preceding gastrointestinal (GI) symptoms. Group A streptococcus, upper respiratory infections, GI infections, coxsackievirus B, toxoplasma, enteroviruses, parvovirus B19, and multiple other organisms have been postulated as possible pathogens in the etiology of JDM. Despite these concerns, results of serum antibody testing and polymerase chain reaction amplification of the blood and muscle tissue for multiple infectious diseases have not been revealing. Environmental factors may also play a contributing role, with geographic and seasonal clustering reported. Short-term increases in UV index prior to onset of disease have been reported; however, no clear theory of etiology has emerged.

Epidemiology

The incidence of JDM is approximately 3 cases/1 million children/yr, without racial predilection. Peak age of onset is 4-10 yr. A 2nd peak of dermatomyositis onset occurs in late adulthood (45-64 yr), but adult-onset dermatomyositis appears to be a distinctly separate entity in prognosis and etiology. In the United States the ratio of girls to boys with JDM is 2 : 1. Multiple cases of myositis in a single family are rare, but familial autoimmune disease may be increased in families with children who have JDM than in families of healthy children. Reports of seasonal association have not been confirmed, although clusters of cases may occur.

Pathogenesis

Interferon (IFN) upregulates genes critical in immunoregulation and major histocompatibility complex (MHC) class I expression, activates natural killer (NK) cells, and supports dendritic cell (DC) maturation. Upregulation of gene products controlled by type I IFNs occurs in patients with dermatomyositis, potentially correlating with disease activity and holding promise as clinical biomarkers.

It appears that children with genetic susceptibility to JDM (HLA-DQA1*0501, HLA-DRB*0301) may have prolonged exposure to maternal chimeric cells and/or an unknown environmental trigger. Once triggered, an inflammatory cascade with type I IFN response leads to upregulation of MHC class I expression and maturation of DCs. Overexpression of MHC class I upregulates adhesion molecules, which influence migration of lymphocytes, leading to inflammatory infiltration of muscle. In an autoregulatory feedback loop, muscle inflammation increases the type I IFN response, regenerating the cycle of inflammation. Cells involved in the inflammatory cascade include NK cells (CD56), T-cell subsets (CD4, CD8, Th17), monocytes/macrophages (CD14), and plasmacytoid DCs. Neopterin, IFN-inducible protein 10, monocyte chemoattractant protein, myxovirus resistance protein, and von Willebrand factor products, as well as other markers of vascular inflammation, may be elevated in patients with JDM who have active inflammation.

Clinical Manifestations

Children with JDM present with either rash, insidious onset of weakness, or both. Fevers, dysphagia or dysphonia, arthritis, muscle tenderness, and fatigue are also commonly reported at diagnosis (Tables 184.1 and 184.2).

Table 184.1

Diagnostic Criteria for Juvenile Dermatomyositis

Classic rash	Heliotrope rash of the eyelids Gottron papules
Plus 3 of the following:	
Weakness	Symmetric Proximal
Muscle enzyme elevation (≥1)	Creatine kinase Aspartate transaminase Lactate dehydrogenase Aldolase
Electromyographic changes	Short, small polyphasic motor unit potentials Fibrillations Positive sharp waves Insertional irritability Bizarre, high-frequency repetitive discharges
Muscle biopsy	Necrosis Inflammation

Data from Bohan A, Peter JB: Polymyositis and dermatomyositis (2nd of 2 parts), *N Engl J Med* 292:403–407, 1975.

Table 184.2

Clinical Features of Juvenile Dermatomyositis During Disease Course

FEATURE	%
Muscle weakness	90-100
Dysphagia or dysphonia	13-40
Muscle atrophy	10
Muscle pain and tenderness	30-75

Skin lesions	85-100
Heliotrope rash of eyelids	66-95
Gottron papules	57-95
Erythematous rash of malar/facial area	42-100
Periungual (nail fold) capillary changes	80-90
Photosensitive rash	5-42
Ulcerations	22-30
Calcinosis	12-30
Lipodystrophy	11-14
Raynaud phenomenon	2-15
Arthritis and arthralgia	22-58
Joint contractures	26-27
Fever	16-65
Gastrointestinal signs and symptoms	8-37
Restrictive pulmonary disease	4-32
Interstitial lung disease	1-7
Cardiac involvement	0-3

From Rider LG, Lindsley CB, Cassidy JT: Juvenile dermatomyositis. In Cassidy JT, Petty RE, Laxer RM, et al, editors: *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2011, Saunders (Table 24.20, p 410).

Rash develops as the first symptom in 50% of patients and appears concomitant with weakness only 25% of the time. Children often exhibit extreme photosensitivity to ultraviolet (UV) light exposure with generalized erythema in sun-exposed areas. If seen over the chest and neck, this erythema is known as the **shawl sign** . Erythema is also commonly seen over the knees and elbows. The characteristic **heliotrope rash** is a blue-violet discoloration of the eyelids that may be associated with periorbital edema (Fig. 184.1). Facial erythema crossing the nasolabial folds is also common, in contrast to the malar rash without nasolabial involvement typical of systemic lupus erythematosus (SLE). Classic **Gottron papules** are bright-pink or pale, shiny, thickened or atrophic plaques over the proximal interphalangeal joints and distal interphalangeal joints and occasionally on the knees, elbows, small joints of the toes, and ankle malleoli (Fig. 184.2). The rash of JDM is sometimes mistaken for eczema or psoriasis. Rarely, a thickened erythematous and scaly rash develops in children over the palms (known as **mechanic's hands**) and soles along the flexor tendons, which is associated with anti–Jo-1 antibodies.

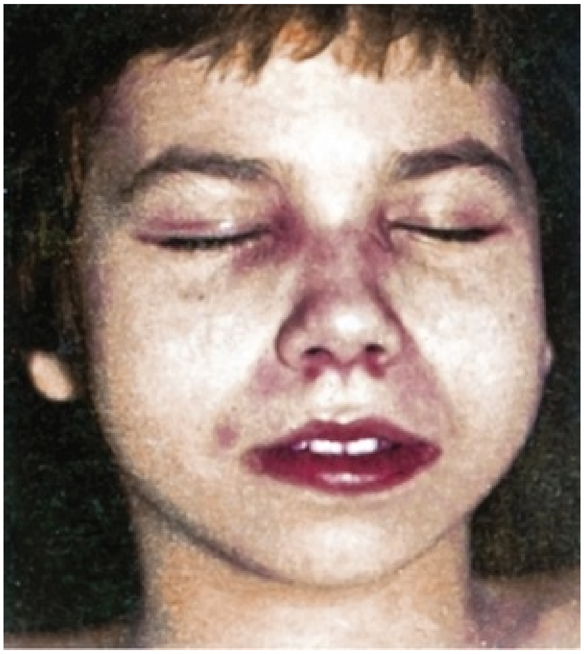

FIG. 184.1 The facial rash of juvenile dermatomyositis. There is erythema over the bridge of the nose and malar areas with violaceous (heliotropic) discolorations of the upper eyelids.

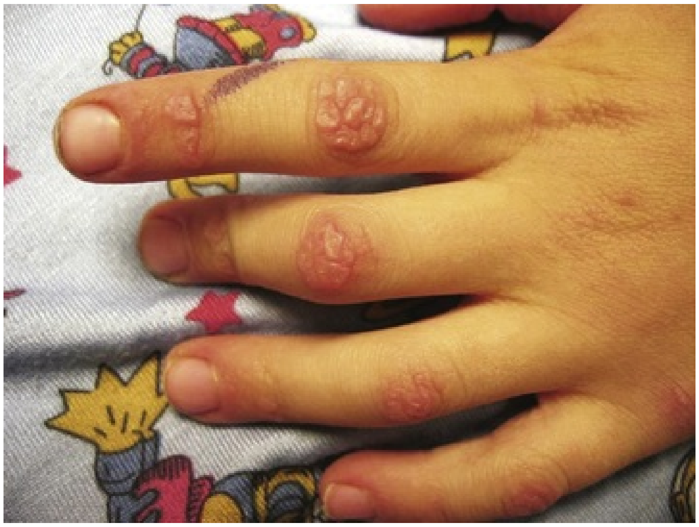

FIG. 184.2 The rash of juvenile dermatomyositis. The skin over the metacarpal and proximal interphalangeal joints may be hypertrophic and pale red (Gottron papules).

Evidence of small-vessel inflammation is often visible in the nail folds and gums as individual capillary loops that are thickened, tortuous, or absent (Fig. 184.3*C*). Telangiectasias may be visible to the naked eye but are more easily visualized under capillaroscopy or with a magnifier (e.g., ophthalmoscope). Severe vascular inflammation causes cutaneous ulcers on toes, fingers, axillae, or epicanthal folds.

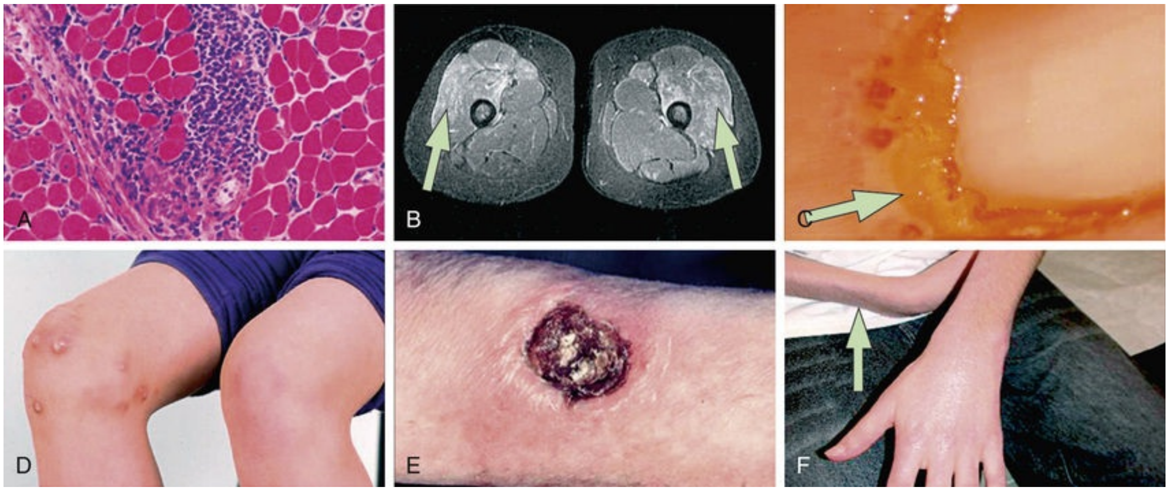

FIG. 184.3 Features of juvenile dermatomyositis. A, Perivascular and perifascicular inflammatory infiltrates with necrotic fibers, perifascicular atrophy, and regeneration in a muscle biopsy. B, MRI is a sensitive indicator of myositis. Inflamed areas appear bright on short-tau inversion recovery–weighted images *(arrows).* C, Capillaries are most often abnormal when viewed at the nail fold. Typical changes of dilation with adjacent dropout *(arrow)* is seen. D, About 30% of juvenile dermatomyositis (JDM) patients have dystrophic calcinosis. E, Cutaneous ulceration with central necrosis, crust, and surrounding erythema at the elbow of 10-year-old boy with severe JDM. F, Lipoatrophy of the forearm *(arrow)* in a boy with JDM. (From Feldman BM, Rider LG, Reed AM, Pachman LM: Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood, *Lancet* 371:2201–2212, 2008, Fig 3, p 2205.)

Weakness associated with JDM is often insidious and difficult to differentiate from fatigue at onset. It is typically symmetric, affecting proximal muscles such as the neck flexors, shoulder girdle, and hip flexors. Parents may report difficulty climbing stairs, combing hair, and getting out of bed. Examination reveals inability to perform a sit-up, head lag in a child after infancy, and **Gower sign** (use of hands on thighs to stand from a sitting position). Patients with JDM may roll to the side rather than sit straight up from lying to compensate for truncal weakness. Approximately half of children exhibit muscle tenderness as a result of muscle inflammation.

Esophageal and respiratory muscles are also affected, resulting in aspiration or respiratory failure. It is essential to assess for dysphonia or nasal speech, palatal elevation with gag, dysphagia, and gastroesophageal reflux by means of history, physical examination, and swallow study, if symptoms are present. Respiratory muscle weakness can be a medical emergency and lead to respiratory failure.

Children with respiratory muscle weakness do *not* manifest typical symptoms of impending respiratory failure with increased work of breathing, instead demonstrating **hypercarbia** rather than hypoxemia.

Diagnosis

Diagnosis of dermatomyositis requires the presence of characteristic rash as well as at least 3 signs of muscle inflammation and weakness (see Table 184.1). Diagnostic criteria developed in 1975 predate the use of MRI and have not been validated in children. Diagnosis is often delayed because of the insidious nature of disease onset.

Electromyography (EMG) shows signs of myopathy (increased insertional activity, fibrillations, sharp waves) as well as muscle fiber necrosis (decreased action potential amplitude and duration). Nerve conduction studies are typically normal unless severe muscle necrosis and atrophy are present. It is important that EMG be performed in a center with experience in pediatric EMG and its interpretation. Muscle biopsy is typically indicated when diagnosis is in doubt or for grading disease severity (Fig. 184.3*A*). Biopsy of involved muscle reveals focal necrosis and phagocytosis of muscle fibers, fiber regeneration, endomysial proliferation, inflammatory cell infiltrates and vasculitis, and tubuloreticular inclusion bodies within endothelial cells. Findings of lymphoid structures and vasculopathy may portend more severe disease.

Some children present with classic rash but no apparent muscle weakness or inflammation; this variation is called **amyopathic JDM** or **dermatomyositis sine myositis** . It is unclear whether these children have isolated skin disease or mild undetected muscle inflammation, risking progression to more severe muscle involvement with long-term sequelae such as calcinosis and lipodystrophy if untreated.

Differential Diagnosis

Differential diagnosis depends on the presenting symptoms. If the presenting complaint is solely weakness without rash or atypical disease, other causes of myopathy should be considered, including polymyositis, infection-related myositis (influenza A and B, coxsackievirus B, and other viral illnesses), muscular dystrophies (e.g., Duchenne, Becker), myasthenia gravis, Guillain-

Barré syndrome, endocrinopathies (hyperthyroidism, hypothyroidism, Cushing syndrome, Addison disease, parathyroid disorders), mitochondrial myopathies, TNF receptor–associated periodic syndrome (TRAPS), and metabolic disorders (glycogen and lipid storage diseases). Infections associated with prominent muscular symptoms include trichinosis, *Bartonella* infection, toxoplasmosis, and staphylococcal pyomyositis. Blunt trauma and crush injuries may lead to transient rhabdomyolysis with myoglobinuria. Myositis in children may also be associated with vaccinations, drugs, growth hormone, and GVHD. The rash of JDM may be confused with eczema, dyshidrosis, psoriasis, erythema nodosa, malar rash from SLE, capillary telangiectasias from Raynaud phenomenon, and other rheumatic diseases. Muscle inflammation is also seen in children with SLE, juvenile idiopathic arthritis, mixed connective tissue disease, inflammatory bowel disease, and antineutrophil cytoplasmic antibody–positive vasculitides. Necrotizing immune-mediated myopathies are characterized by muscle necrosis without lymphocytic infiltration. Antibodies to signal recognition particle (SRP) or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) distinguish two types from each other and from JDM. Table 184.3 compares other juvenile idiopathic inflammatory myositis disorders: JDM, juvenile polymyositis, and juvenile connective tissue myositis.

Table 184.3

Frequency of Manifestations of Juvenile Dermatomyositis, Juvenile Polymyositis, and Overlap Myositis

Manifestation	**FREQUENCY AT ONSET (%)**		
	JDM	**JPM**	**Overlap Myositis**
Progressive proximal muscle weakness	82-100	100	100
Easy fatigue	80-100	85	84
Gottron papules	57-91	0	74-80
Heliotrope rash	66-87	0	40-59
Erythematous rash of malar/facial area	42-100	0-6	20-51
Periungual nailfold capillary changes	35-91	33	67-80
Muscle pain or tenderness	25-83	61-66	55
Weight loss	33-36	52	53
Falling episodes	40	59	29
Arthritis	10-65	0-45	69-80
Fever	16-65	0-41	0-49
Lymphadenopathy	8-75	0-12	20-22
Dysphagia or dysphonia	15-44	39	40
Joint contractures	9-55	17-42	57-60
V- or shawl-sign rashes	19-29	3-6	8-14

Dyspnea on exertion	5-43	17-42	40
Gastrointestinal symptoms	5-37	9-33	6-53
Photosensitive rashes	5-51	0-6	22-40
Raynaud phenomenon	9-28	0-24	41-60
Edema	11-34	15	20
Gingivitis	6-30	9	0-37
Cutaneous ulceration	5-30	3	20-22
Calcinosis	3-34	6	24
Cardiac involvement	2-13	36	19
Interstitial lung disease	5	15	26
Lipodystrophy	4-14	3	0-6
Gastrointestinal bleeding or ulceration	3-4	3	4-10

JDM, Juvenile dermatomyositis; JPM, juvenile polymyositis.

From Rider LG, Lindsley CB, Miller FW: Juvenile Dermatomyositis. IN Petty RE, Laxer RM, Lindsley CB, Wedderburn L, editors: *Textbook of pediatric rheumatology,* ed 7, Philadelphia, 2016, Elsevier, Table 26.4.

Laboratory Findings

Elevated serum levels of muscle-derived enzymes (creatine kinase [CK], aldolase, aspartate transaminase, alanine transaminase [ALT], lactate dehydrogenase) reflect muscle inflammation. Not all enzyme levels rise with inflammation in a specific individual; ALT is usually elevated on initial presentation, whereas CK level may be normal. The erythrocyte sedimentation rate (ESR) is often normal, and the rheumatoid factor (RF) test result is typically negative. There may be anemia consistent with chronic disease. Antinuclear antibody (ANA) is present in >80% of children with JDM. Serologic testing results are divided into 2 groups: **myositis-associated antibodies (MAAs)** and **myositis-specific antibodies (MSAs)** . MAAs are associated with JDM, but are not specific and can be seen in both overlap conditions and other rheumatic diseases. MSAs are specific for myositis. Presence of MAAs such as SSA, SSB, Sm, ribonucleoprotein (RNP), and double-stranded (ds) DNA may increase the likelihood of overlap disease or connective tissue myositis. Antibodies to Pm/Scl identify a small, distinct subgroup of myopathies with a protracted disease course, often complicated by pulmonary interstitial fibrosis and cardiac involvement. Similar to what is seen in adults, the presence of MSAs in JDM such as anti–Jo-1, anti–Mi-2, anti-p155/140, anti-NXP2, and other myositis-specific autoantibodies help define distinct clinical subsets and may predict the development of complications, although differences remain in certain aspects such as malignancy between adults and children. Anti-p155/140 antibodies also known as TIF-1-γ are reported in 23–30% of children with JDM and are associated with photosensitive rashes, ulceration, and lipodystrophy. Unlike in adults, this antibody is not associated with malignancy in children with JDM. Anti-MJ antibodies, also known as NXP2, are reported in 12–23% of children with JDM and are associated with cramps, muscle atrophy, contractures, and dysphonia. Anti-MDA5 antibodies have been recently reported in 7–33% of children with JDM, and are concerning for development of interstitial lung disease.

Radiographic studies aid both diagnosis and medical management. MRI using T2-weighted images and fat suppression (Fig. 184.3*B*) identifies active sites of disease, reducing sampling error and increasing the sensitivity of muscle biopsy and EMG, results of which are nondiagnostic in 20% of cases if the procedures are not directed by MRI. Extensive rash and abnormal MRI findings may be found despite normal serum levels of muscle-derived enzymes. Muscle biopsy often demonstrates evidence of disease activity and chronicity that is not suspected from the levels of the serum enzymes alone.

A contrast swallow study may document palatal dysfunction and risk of aspiration. Pulmonary function testing detects a restrictive defect consistent with respiratory weakness and reduced diffusion capacity of carbon monoxide from alveolar fibrosis associated with other connective tissue diseases. Serial measurement of vital capacity or negative inspiratory force can document changes in respiratory weakness, especially in an inpatient setting. **Calcinosis** is seen easily on radiographs, along the fascial planes and within muscles (Figs. 184.3*D, E* and 184.4).

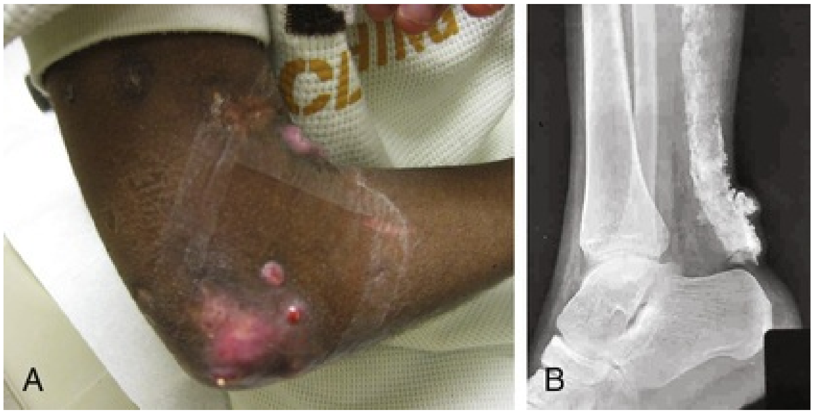

FIG. 184.4 Calcifications in dermatomyositis. A, Skin effects of calcification. B, Radiographic evidence of calcification.

Treatment

The aid of an experienced pediatric rheumatologist is invaluable in outlining an appropriate course of treatment for a child with JDM. Before the advent of corticosteroids, one third of patients spontaneously improved, a third had a chronic, lingering course, and a third died from the disease. Corticosteroids have altered the course of disease, lowering morbidity and mortality. *Methotrexate* decreases the length of treatment with corticosteroids, thereby reducing morbidity from steroid toxicity. Intravenous (IV) gamma globulin is frequently used as an adjunct for treatment of severe disease and can be given at 2 g/kg (maximum 70 g) every 2 wk for 3 doses, then every 4 wk as needed. Consensus treatment plans for guiding treatment of North American children with JDM are available from the **Childhood Arthritis and Rheumatology Research Alliance** online through PubMed.

Corticosteroids are still the mainstay of treatment. In a clinically stable child without debilitating weakness, oral prednisone at 2 mg/kg/day (maximum 60 mg daily) is usually started. Children with GI involvement have decreased absorption of oral corticosteroids and require IV administration. In more severe cases with respiratory or oropharyngeal weakness, high-dose pulse methylprednisolone is used (30 mg/kg/day for 3 days, maximum dose 1 g/day) with ongoing weekly or monthly IV dosing along with daily oral corticosteroids as needed. Corticosteroid dosage is slowly tapered over 12 mo, after indicators of inflammation (muscle enzymes) normalize and strength improves.

Weekly oral, IV, or subcutaneous methotrexate (the lesser of 1 mg/kg or 15 mg/m^2 , maximum 40 mg) is often used as a steroid-sparing agent in JDM. The concomitant use of methotrexate halves the cumulative dosage of steroids needed for disease control. Risks of methotrexate include immunosuppression, blood count dyscrasias, chemical hepatitis, pulmonary toxicity, nausea/vomiting, and teratogenicity. Folic acid is typically given with methotrexate starting at a dose of 1 mg daily to reduce toxicity and side effects of folate inhibition (oral ulcers, nausea, anemia). Children who are taking immunosuppressive medications such as methotrexate should avoid live-virus vaccination, although inactivated influenza vaccination is recommended yearly. An international trial found the combination of methotrexate plus corticosteroids to perform better than corticosteroids alone and with fewer side effects than corticosteroids plus cyclosporine A.

Hydroxychloroquine has little toxicity risk and is used as a secondary disease-modifying agent to reduce rash and maintain remission. Typically, it is administered at doses of 4-6 mg/kg/day orally in either tablet or liquid form. Ophthalmologic follow-up 1-2 times per year to monitor for rare retinal toxicity is recommended. Other side effects include hemolysis in patients with glucose-6-phosphate deficiency, GI intolerance, and skin/hair discoloration.

The use of *rituximab* in a trial of steroid-dependent patients with resistant inflammatory myopathies, including JDM, did not meet the primary study end-point showing a difference in time to improvement between individuals given rituximab at baseline or at 8 wk, but overall, 83% of all patients met the definition of improvement in the trial. Reports of the use of other biologic agents are based on case reports with mixed results.

Other medications for severe unresponsive disease include intravenous immune globulin, mycophenolate mofetil, cyclosporine, and cyclophosphamide. Children with pharyngeal weakness may need nasogastric or gastrostomy feedings to avoid aspiration, whereas those with GI vasculitis require full bowel rest. Rarely, children with severe respiratory weakness require ventilator therapy and even tracheostomy until the respiratory weakness improves.

Physical therapy and **occupational therapy** are integral parts of the treatment program, initially for passive stretching early in the disease course and then for direct reconditioning of muscles to regain strength and range of motion. Therapy may improve strength muscle measures and cardiovascular fitness. Bed rest is not indicated, because weight bearing improves bone density and prevents contractures. Social work and psychology services may facilitate adjustment to the frustration of physical impairment in a previously active child and aid with sleep disturbances associated with rheumatic disease.

All children with JDM should avoid sun exposure and apply high-SPF (sun protection factor) sunscreen daily, even in winter and on cloudy days. Vitamin D and calcium supplements are indicated for all children undergoing long-term corticosteroid therapy to reduce drug-induced osteopenia and osteoporosis.

Complications

Most complications from JDM are related to prolonged and severe weakness from muscle atrophy to cutaneous calcifications and scarring or atrophy to lipodystrophy. Secondary complications from medical treatments are also common. Children with acute and severe weakness are at risk for aspiration pneumonia and respiratory failure and occasionally require nasogastric feeding and mechanical ventilation until weakness improves. Rarely, **vasculitis** of the GI tract develops in children with severe JDM. Crampy abdominal pain and occult GI bleeding may indicate bowel wall vasculitis and lead to ischemia, GI bleeding, and perforation if not treated with complete bowel rest and aggressive treatment for the underlying inflammation. Surgery should be avoided if possible, because the GI vasculitis is diffuse and not easily amenable to surgical intervention. Contrast-enhanced CT may show dilation or thickening of the bowel wall, intraluminal air, or evidence of bowel necrosis.

Involvement of the cardiac muscle with pericarditis, myocarditis, and conduction defects with arrhythmias has been reported, as well as reduced diastolic and systolic function related to ongoing disease activity.

Lipodystrophy and **calcinosis** are thought to be associated with long-standing or undertreated disease (Fig. 184.3, *D-F*). Dystrophic deposition of calcium phosphate, hydroxyapatite, or fluoroapatite crystals occurs in subcutaneous plaques or nodules, resulting in painful ulceration of the skin with extrusion of crystals or calcific liquid. Calcification is found in up to 40% of large cohorts of children with JDM. Pathologic calcifications may be related to severity of disease and prolonged delay to treatment and potentially to genetic polymorphisms of TNF-α-308. Calcium deposits tend to form in subcutaneous tissue and along muscle. Some ulcerate through the skin and drain a soft calcific liquid, and others manifest as hard nodules along extensor surfaces or embedded along muscle. Draining lesions serve as a nidus for cellulitis or osteomyelitis. Nodules cause skin inflammation that may mimic cellulitis. Spontaneous regression of calcium deposits may occur, but there is no evidence-based recommendation for treatment of calcinosis. Some experts recommend aggressive treatment of underlying myositis. Others have recommended bisphosphonates, TNF inhibitors, and sodium thiosulfate, but no evidence-based trials have been conducted for this condition.

Lipodystrophy manifests in 10–40% of patients with JDM and can be difficult to recognize. Lipodystrophy results in progressive loss of subcutaneous and visceral fat, typically over the face and upper body, and may be associated with a metabolic syndrome similar to polycystic ovarian syndrome with insulin resistance, hirsutism, acanthosis, hypertriglyceridemia, and abnormal glucose tolerance. Lipodystrophy may be generalized or localized.

Children receiving prolonged corticosteroid therapy are prone to complications such as cessation of linear growth, weight gain, hirsutism, adrenal suppression, immunosuppression, striae, cushingoid fat deposition, mood changes, osteoporosis, cataracts, avascular necrosis, and steroid myopathy. Families should be counseled on the effects of corticosteroids and advised to use medical alert identification and to consult a nutritionist regarding a low-salt, low-fat diet with adequate vitamin D and calcium supplementation.

An association with malignancy at disease onset is observed in adults with dermatomyositis but very rarely in children.

Prognosis

The mortality rate in JDM has decreased since the advent of corticosteroids, from 33% to currently approximately 1%; little is known about the long-term consequences of persistent vascular inflammation. The period of active symptoms has decreased from about 3.5 yr to <1.5 yr with more aggressive immunosuppressive therapy; the vascular, skin, and muscle symptoms of children with JDM generally respond well to therapy. At 7 yr of follow-up, 75% of patients have little to no residual disability, but 25% continue to have chronic weakness and 40% have chronic rash. Up to one-third may need long-term medications to control their disease. Children with JDM appear able to repair inflammatory damage to vasculature and muscle, but there is some emerging concern about long-term effects on cardiovascular risk.

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CHAPTER 185

Scleroderma and Raynaud Phenomenon

Heather A. Van Mater, C. Egla Rabinovich

Juvenile scleroderma encompasses a range of conditions unified by the presence of fibrosis of the skin. Juvenile scleroderma is divided into 2 major categories, **juvenile localized scleroderma** (**JLS** , also known as **morphea**), which is largely limited to the skin, and **juvenile systemic sclerosis** (**JSSc**), with multisystem organ involvement. Localized disease is the predominant type seen in pediatric populations (>95%), but systemic sclerosis is associated with mortality and severe multiorgan morbidity.

Etiology and Pathogenesis

The etiology of scleroderma is unknown, but the mechanism of disease appears to be a combination of a vasculopathy, autoimmunity, immune activation, and fibrosis. Triggers, including trauma, infection, and, possibly, subclinical graft-versus-host reaction from persistent maternal cells (*microchimerism*), injure vascular endothelial cells, resulting in increased expression of adhesion molecules. These molecules entrap platelets and inflammatory cells, resulting in vascular changes with manifestations such as Raynaud phenomenon and pulmonary hypertension. Inflammatory cells infiltrate the area of initial vascular damage, causing further vascular damage and resulting in thickened artery walls and reduction in capillary numbers. Macrophages and other inflammatory cells then migrate into affected tissues and secrete cytokines that induce fibroblasts to reproduce and synthesize excessive amounts of collagen, resulting in fibrosis and subsequent lipoatrophy, dermal fibrosis, with loss of sweat glands and hair follicles. In late stages the entire dermis may be replaced by compact collagen fibers.

Autoimmunity is believed to be a key process in the pathogenesis of both localized and systemic scleroderma, given the high percentage of affected children with autoantibodies. Children with localized disease often have a positive antinuclear antibody (ANA) test result (42%), and 47% of this subgroup have antihistone antibodies. Children with JSSc have higher rates of ANA positivity (80.7%) and may have anti–Scl-70 antibody (34%, antitopoisomerase I). The relationship between specific autoantibodies and the various forms of scleroderma is not well understood, and all antibody test results may be negative, especially in JLS.

Classification

Localized scleroderma is distinct from systemic scleroderma and rarely progresses to systemic disease. The category of JLS includes several subtypes differentiated by both the distribution of the lesions and the depth of involvement (Tables 185.1 and 185.2). Up to 15% of children have a combination of 2 or more subtypes.

Table 185.1

Classification of Pediatric Scleroderma (Morphea)

Localized Scleroderma

Plaque Morphea

- Confined to dermis, occasionally superficial panniculus
- Well-circumscribed circular area of induration, often a central waxy, ivory-colored area surrounded by a violaceous halo; unilateral

Generalized Morphea

- Involves dermis primarily, occasionally panniculus
- Defined as confluence of individual morphea plaques or lesions in ≥3 anatomic sites; more likely to be bilateral

Bullous Morphea

Bullous lesions that can occur with any of the subtypes of morphea

Linear Scleroderma

Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral

Limbs/trunk:

- One or more linear streaks of the extremities or trunk
- Flexion contracture occurs when lesion extends over a joint; limb length discrepancies

En coup de sabre:

- Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches

Parry-Romberg syndrome:

- Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement

Deep Morphea

Involves deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral

Subcutaneous morphea:

- Primarily involves the panniculus or subcutaneous tissue
- Plaques are hyperpigmented and symmetric

Eosinophilic fasciitis:

- Fasciitis with marked blood eosinophilia
- Fascia is the primary site of involvement; typically involves extremities
- Classic description is “peau d'orange” or orange peel texture, but early disease manifests as edema (see Fig. 185.2)

Morphea profunda:

- Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk

Disabling pansclerotic morphea of childhood:

Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing fingertips and toes

Systemic Sclerosis

Diffuse

Most common type in childhood

Symmetric thickening and hardening of the skin (sclerosis) with fibrous and degenerative changes of viscera

Limited

Rare in childhood

Previously known as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome

Table 185.2

Provisional Criteria for Classification of Juvenile Systemic Sclerosis (JSSc)

Major Criterion (Required)*

Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints

Minor Criteria (at Least 2 Required)

Cutaneous: Sclerodactyly

Peripheral vascular: Raynaud phenomenon, nail fold capillary abnormalities (telangiectasias), digital tip ulcers

Gastrointestinal: Dysphagia, gastroesophageal reflux

Cardiac: Arrhythmias, heart failure

Renal: Renal crisis, new-onset arterial hypertension

Respiratory: Pulmonary fibrosis (high-resolution CT/radiography), decreased diffusing capacity for carbon monoxide, pulmonary arterial hypertension

Neurologic: Neuropathy, carpal tunnel syndrome

Musculoskeletal: Tendon friction rubs, arthritis, myositis

Serologic: Antinuclear antibodies—SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin, or anti-RNA polymerase I or III

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[*] Diagnosis requires at least 1 major and at least 2 minor criteria.

From Zulian F, Woo P, Athreya BH, et al: The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis, *Arthritis Rheum* 57:203–212, 2007.

Epidemiology

Juvenile scleroderma is rare, with an estimated prevalence of 1 in 100,000 children. LS is much more common than SSc in children, by a 10 : 1 ratio, with **linear scleroderma** being the most common subtype. LS is predominantly a pediatric condition, with 65% of patients diagnosed before age 18 yr. After age 8 yr the female/male ratio for both LS and SSc is approximately 3 : 1, whereas in patients younger than 8 yr, there is no sex predilection.

Clinical Manifestations

Localized Scleroderma

The onset of scleroderma is generally insidious, and manifestations vary according to disease subtype. The initial skin manifestations of localized disease usually include erythema or a bluish hue seen around an area of waxy induration; subtle erythema may be the only presenting sign (Fig. 185.1). Edema and erythema are followed by indurated, hypopigmented or hyperpigmented atrophic lesions (Fig. 185.2). LS varies in size from a few centimeters to the entire length of the extremity, with varying depth. Patients may present with arthralgias, synovitis, or flexion contractures (Fig. 185.3). Children also experience limb length discrepancies as a result of growth impairment caused by involvement of muscle and bone. Children with **en coup de sabre** may have symptoms unique to central nervous system (CNS) involvement, such as seizures, hemifacial atrophy, ipsilateral uveitis, and learning/behavioral changes (Fig. 185.4). Up to 25% of children with LS have extracutaneous manifestations, most frequently arthritis (47%) and neurologic symptoms (17%) associated with en coup de sabre.

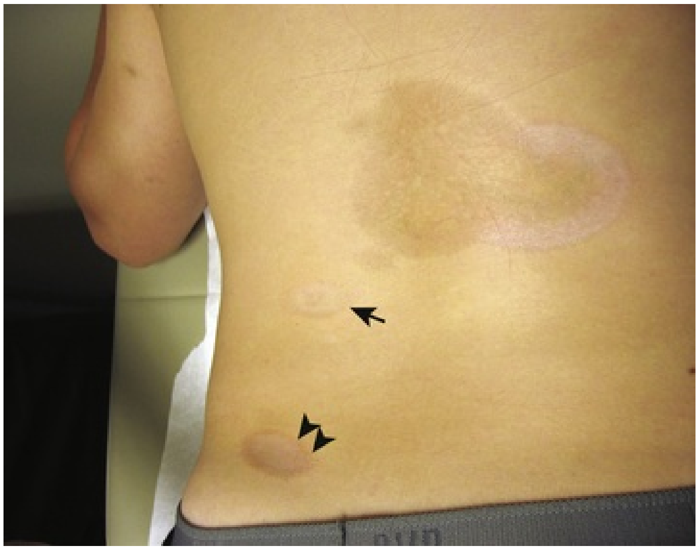

FIG. 185.1 **Boy with generalized morphea. Note the active circular lesion *(arrowheads)* with a surrounding rim of erythema. The largest lesion has areas of postinflammatory hyperpigmentation and depression with an area of erythema on the right. The small lesion *(arrow)* demonstrates depression caused by lipoatrophy.**

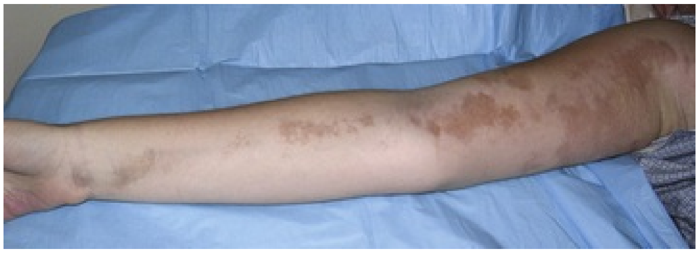

FIG. 185.2 Inactive linear scleroderma demonstrating hyperpigmented lesion with areas of normal skin (skip lesions).

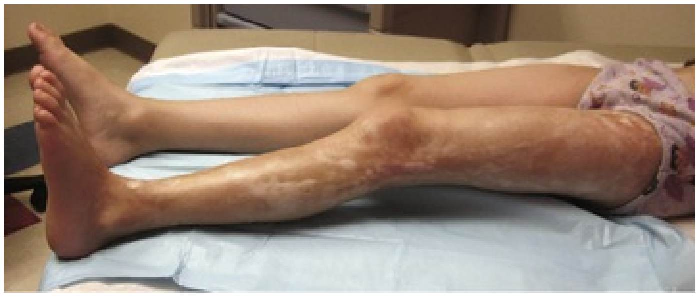

FIG. 185.3 Child with untreated linear scleroderma resulting in knee contracture, immobility of ankle, chronic skin breakdown of scar on the lateral knee, and areas of hypopigmentation and hyperpigmentation. The affected leg is 1 cm shorter.

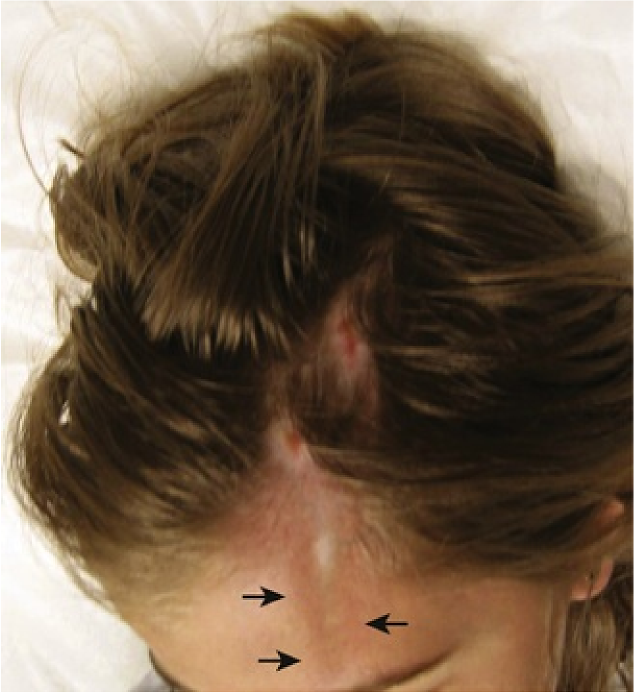

FIG. 185.4 **Child with en coup de sabre lesion on scalp extending down to forehead. Before treatment, the skin on the scalp was bound down with chronic skin breakdown. Note the area of hypopigmentation extending down the forehead *(arrows).***

Systemic Scleroderma

SSc also has an insidious onset with a prolonged course characterized by periods of remission and exacerbation, ending in either remission or, more often, chronic disability and death.

The **skin manifestations** of SSc include an early phase of edema that spreads proximally from the dorsum of the hands and fingers and includes the face. An eventual decrease in edema is followed by induration and fibrosis of skin, ultimately resulting in loss of subcutaneous fat, sweat glands, and hair follicles. Later, atrophic skin becomes shiny and waxy in appearance. As lesions spread proximally, flexion contractures develop at the elbows, hips, and knees associated with secondary muscle weakness and atrophy. In the face, this process results in a small oral stoma with decreased mouth aperture. Skin ulceration over pressure points, such as the elbows, may be associated with subcutaneous calcifications. Severe **Raynaud phenomenon** causes ulceration of the fingertips with subsequent loss of tissue pulp and tapered fingers (**sclerodactyly**) (Fig. 185.5). Resorption of the distal tufts of the distal phalanges may occur (**acroosteolysis**). Hyperpigmented postinflammatory changes surrounded by atrophic depigmentation gives a salt-and-pepper appearance to skin. Over years, remodeling of lesions sometimes results in focal improvement in skin thickening.

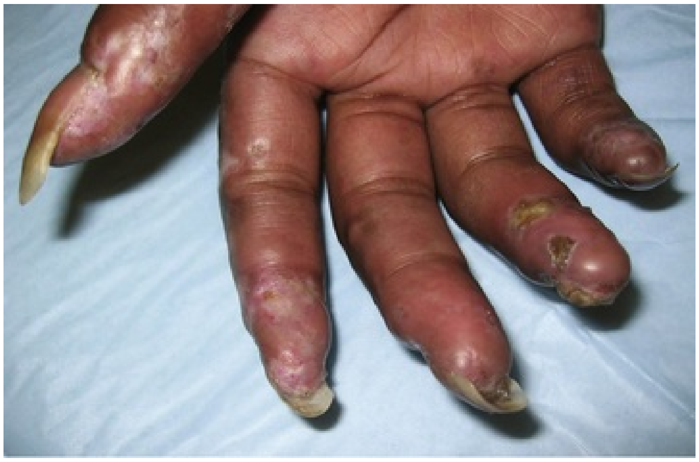

FIG. 185.5 Sclerodactyly and finger ulcerations in a patient with systemic sclerosis who is poorly compliant with treatment.

Pulmonary disease is the most common visceral manifestation of SSc and includes both arterial and interstitial involvement (alveolitis). Symptoms range from asymptomatic disease to exercise intolerance, dyspnea at rest, and right-sided heart failure. **Pulmonary arterial hypertension** is a poor prognostic sign, developing because of lung disease or independently as part of the vasculopathy. Clinical manifestations of pulmonary arterial hypertension in children appear late in the course, are subtle, and include cough and dyspnea on exertion. Pulmonary evaluation should include pulmonary function tests (PFTs) such as diffusion capacity of carbon monoxide (DLCO), bronchoalveolar lavage (BAL), and high-resolution chest computed tomography (HRCT). PFTs reveal decreased vital capacity and decreased DLCO , whereas neutrophilia or eosinophilia on BAL suggest active alveolitis. Chest CT is much more sensitive than chest radiographs, which are often normal, showing typical basilar ground-glass abnormalities, reticular linear opacities, nodules, honeycombing, and mediastinal adenopathy.

Gastrointestinal tract disease is seen in 25% of children with SSc. Common manifestations include esophageal and intestinal dysmotility resulting in dysphagia, reflux, dyspepsia, gastroparesis, bacterial overgrowth, dilated bowel loops and pseudoobstruction, and dental caries, as well as malabsorption and failure to thrive. **Renal** arterial disease can cause chronic or severe episodic hypertension; unlike adult disease, renal crisis is rare. **Cardiac** fibrosis is associated with arrhythmias, ventricular hypertrophy, and decreased cardiac function. Mortality from JSSc is usually a result of cardiopulmonary disease. A scoring system helps identify the severity of the multiorgan involvement (Table 185.3).

Table 185.3

Medsger Systemic Sclerosis Severity Scale*

ORGAN SYSTEM	0 (NORMAL)	1 (MILD)	2 (MODERATE)	3 (SEVERE)	4 (END STAGE)
General	Wt loss <5%	Wt loss 5–10%	Wt loss 10–15%	Wt loss 15–20%	Wt loss 20%+
	Hct 37%+	Hct 33–37%	Hct 29–33%	Hct 25–29%	Hct 25%
	Hb 12.3+ g/dL	Hb 11.0-12.2 g/dL	Hb 9.7-10.9 g/dL	Hb 8.3-9.6 g/dL	Hb <8.3 g/dL
Peripheral vascular	No RP; RP not requiring vasodilators	RP requiring vasodilators	Digital pitting scars	Digital tip ulcerations	Digital gangrene
Skin	TSS 0	TSS 1-14	TSS 15-29	TSS 30-39	TSS 40+
Joint/tendon	FTP 0-0.9 cm	FTP 1.0-1.9 cm	FTP 2.0-3.9 cm	FTP 4.0-4.9 cm	FTP 5.0+ cm
Muscle	Normal proximal muscle strength	Proximal weakness, mild	Proximal weakness, moderate	Proximal weakness, severe	Ambulation aids required
Gastrointestinal tract	Normal esophagogram; normal small bowel series	Distal esophageal hypoperistalsis; small bowel series abnormal	Antibiotics required for bacterial overgrowth	Malabsorption syndrome; episodes of pseudoobstruction	Hyperalimentation required
Lung	DLCO	DLCO 70–	DLCO 50–	DLCO <50%	Oxygen required

	80%+ FVC 80%+ No fibrosis on radiograph sPAP <35 mm Hg	79% FVC 70–79% Basilar rales; fibrosis on radiograph sPAP 35-49 mm Hg	69% FVC 50–69% sPAP 50-64 mm Hg	FVC <50% sPAP 65+ mm Hg	
Heart	ECG normal	ECG conduction defect	ECG arrhythmia	ECG arrhythmia requiring therapy	CHF
	LVEF 50%+	LVEF 45–49%	LVEF 40–44%	LVEF 30–40%	LVEF <30%
Kidney	No history of SRC with serum creatinine <1.3 mg/dL	History of SRC with serum creatinine <1.5 mg/dL	History of SRC with serum creatinine 1.5-2.4 mg/dL	History of SRC with serum creatinine 2.5-5.0 mg/dL	History of SRC with serum creatinine >5.0 mg/dL or dialysis required

[*] If 2 items are included for a severity grade, only 1 is required for the patient to be scored as having disease of that severity level.

CHF, Congestive heart failure; DLCO , diffusing capacity for carbon monoxide, % predicted; ECG, electrocardiogram; FTP, fingertip-to-palm distance in flexion; FVC, forced vital capacity, % predicted; Hb, hemoglobin; Hct, hematocrit; LVEF, left ventricular ejection fraction; RP, Raynaud phenomenon; sPAP, estimated pulmonary artery pressure by Doppler echo; SRC, scleroderma renal crisis; TSS, total skin score; Wt, weight.

Modified from Medsger TA Jr, Bombardieri S, Czirjak L, et al: Assessment of disease severity and prognosis, *Clin Exp Rheumatol* 21(3 Suppl 29):S51, 2003 (Table 1, p S-43).

Raynaud Phenomenon

Raynaud phenomenon (RP) is the most frequent initial symptom in pediatric systemic sclerosis, present in 70% of affected children months to years before other manifestations. RP refers to the classic triphasic sequence of blanching, cyanosis, and erythema of the digits induced by cold exposure and/or emotional stress. RP is typically independent of an underlying rheumatic disease (Raynaud disease) but can result from rheumatic diseases such as scleroderma, systemic lupus erythematosus (SLE), and mixed connective tissue disease (Fig. 185.6). The color changes are brought about by (1) initial arterial vasoconstriction, resulting in hypoperfusion and pallor (blanching), (2) venous stasis (cyanosis), and (3) reflex vasodilation caused by the factors released from the ischemic phase (erythema). The color change is classically reproduced by immersing the hands in iced water and reversed by warming. During the blanching phase, there is inadequate tissue perfusion in the affected area, associated with pain and paresthesias and resulting in ischemic damage only when associated with a rheumatic disease. The blanching usually affects the distal fingers but may also involve thumbs, toes, ears, and tip of the nose. The affected area is usually well demarcated and uniformly white. *Digital ulcers* associated with RP are indicative of underlying rheumatic disease.

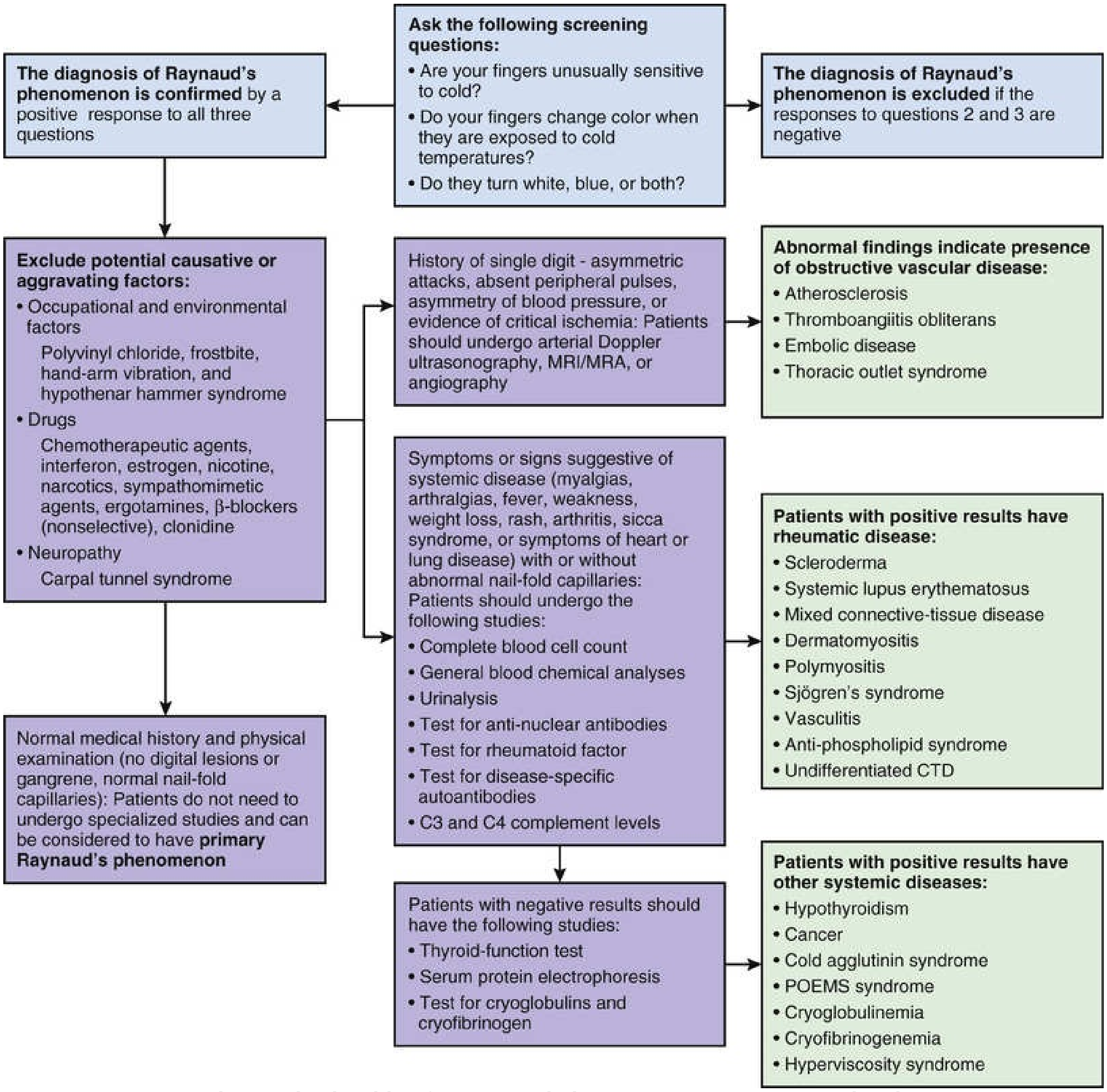

Ask the following screening questions:
- Are your fingers unusually sensitive to cold?
- Do your fingers change color when they are exposed to cold temperatures?
- Do they turn white, blue, or both?

The diagnosis of Raynaud's phenomenon is confirmed by a positive response to all three questions

The diagnosis of Raynaud's phenomenon is excluded if the responses to questions 2 and 3 are negative

Exclude potential causative or aggravating factors:
- Occupational and environmental factors
  Polyvinyl chloride, frostbite, hand-arm vibration, and hypothenar hammer syndrome
- Drugs
  Chemotherapeutic agents, interferon, estrogen, nicotine, narcotics, sympathomimetic agents, ergotamines, β-blockers (nonselective), clonidine
- Neuropathy
  Carpal tunnel syndrome

History of single digit - asymmetric attacks, absent peripheral pulses, asymmetry of blood pressure, or evidence of critical ischemia: Patients should undergo arterial Doppler ultrasonography, MRI/MRA, or angiography

Abnormal findings indicate presence of obstructive vascular disease:
- Atherosclerosis
- Thromboangiitis obliterans
- Embolic disease
- Thoracic outlet syndrome

Symptoms or signs suggestive of systemic disease (myalgias, arthralgias, fever, weakness, weight loss, rash, arthritis, sicca syndrome, or symptoms of heart or lung disease) with or without abnormal nail-fold capillaries: Patients should undergo the following studies:
- Complete blood cell count
- General blood chemical analyses
- Urinalysis
- Test for anti-nuclear antibodies
- Test for rheumatoid factor
- Test for disease-specific autoantibodies
- C3 and C4 complement levels

Patients with positive results have rheumatic disease:
- Scleroderma
- Systemic lupus erythematosus
- Mixed connective-tissue disease
- Dermatomyositis
- Polymyositis
- Sjögren's syndrome
- Vasculitis
- Anti-phospholipid syndrome
- Undifferentiated CTD

Normal medical history and physical examination (no digital lesions or gangrene, normal nail-fold capillaries): Patients do not need to undergo specialized studies and can be considered to have **primary Raynaud's phenomenon**

Patients with negative results should have the following studies:
- Thyroid-function test
- Serum protein electrophoresis
- Test for cryoglobulins and cryofibrinogen

Patients with positive results have other systemic diseases:
- Hypothyroidism
- Cancer
- Cold agglutinin syndrome
- POEMS syndrome
- Cryoglobulinemia
- Cryofibrinogenemia
- Hyperviscosity syndrome

FIG. 185.6 Diagnostic algorithm for Raynaud phenomenon. CTD, Connective tissue disease; MRA, magnetic resonance angiography; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. (From Firestein GS, Budd, RC, Gabriel SE, et al, editors: *Kelley & Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2016, Elsevier, Fig 84-3.)

Raynaud disease often begins in adolescence and is characterized by symmetric occurrence, the absence of tissue necrosis and gangrene, and the lack of manifestations of an underlying rheumatic disease. Children have normal nail fold capillaries (absence of periungual telangiectasias). RP should be distinguished from acrocyanosis and chilblains. **Acrocyanosis** is a vasospastic disorder resulting in cool, painless, bluish discoloration in the hands and sometimes feet despite normal tissue perfusion. It may be exacerbated by stimulant medications used to treat attention-deficit disorder. **Chilblains** is a condition with episodic color changes and the development of nodules related to severe cold exposure and spasm-induced vessel and tissue damage; it has been associated with SLE.

Diagnosis

The diagnosis of JLS is based on the distribution and depth of characteristic lesions. Biopsy is helpful to confirm the diagnosis. The diagnosis of JSSc requires proximal sclerosis/induration of the skin as well as the presence of 2 of 20 minor criteria (see Table 185.2).

Differential Diagnosis

The most important condition to differentiate from JLS is JSSc. Contractures and synovitis from juvenile arthritis can be differentiated from those caused by linear scleroderma by the absence of skin changes. Other conditions to consider include chemically induced scleroderma-like disease, diabetic cheiroarthropathy, pseudoscleroderma, and scleredema. **Pseudoscleroderma** comprises a group of unrelated diseases characterized by patchy or diffuse cutaneous fibrosis without the other manifestations of scleroderma. These include phenylketonuria, syndromes of premature aging, and localized idiopathic fibrosis. **Scleredema** is a transient, self-limited disease of both children and adults that has sudden onset after a febrile illness (especially streptococcal infections) and is characterized by patchy sclerodermatous lesions on the neck and shoulders and extending to the face, trunk, and arms.

Laboratory Findings

No laboratory studies are diagnostic of either localized or systemic scleroderma. Although the results of complete blood counts, serum chemistry analyses, and urinalysis are normal, children may have elevated erythrocyte sedimentation rate, eosinophilia, or hypergammaglobulinemia, all of which normalize with treatment. Elevations of muscle enzymes, particularly aldolase, can be seen with muscle involvement. Patients with JSSc may have anemia, leukocytosis, and eosinophilia and autoantibodies (ANA, anti–Scl-70). Imaging studies delineate the affected area and can be used to follow disease progression. MRI is useful in en coup de sabre and Parry-Romberg syndrome (facial hemiatrophy) for determination of CNS or orbital involvement. Infrared thermography uses the temperature variation between areas of active and inactive cutaneous disease to help differentiate active disease from damage. The role of ultrasound to examine lesion activity is evolving. HRCT, PFTs, echocardiography, and manometry are useful tools for diagnosing and monitoring visceral involvement in JSSc.

Treatment

Treatment for scleroderma varies according to the subtype and severity. Superficial morphea may benefit from topical corticosteroids or ultraviolet therapy. For lesions involving deeper structures, systemic therapy is recommended. A combination of *methotrexate* and *corticosteroids* is effective in treating **JLS** by preventing lesion extension and resulting in significant skin softening and improved range of motion of affected joints. The treatment plan for JLS includes (1) weekly subcutaneous (SC) methotrexate at 1 mg/kg (maximum dose 25 mg); (2) weekly SC methotrexate (1 mg/kg; max 25 mg) *plus* either 3 mo of high-dose intravenous (IV) corticosteroids (30 mg/kg; max 1,000 mg) for 3 consecutive days a month *or* weekly corticosteroids at the same dose for 3 mo; or (3) high-dose daily oral corticosteroids (2 mg/kg/day, max 60 mg) with a slow taper over 48 wk. *Mycophenolate mofetil* (MMF) is a second-line agent for recalcitrant disease. Physical and occupational therapy are important adjuncts to pharmacologic treatment. Eosinophilic fasciitis often responds well to corticosteroids and methotrexate.

Treatments for **JSSc** target specific disease manifestations. **RP** is treated with cold avoidance, and pharmacologic interventions are reserved for severe disease. Calcium channel blockers (nifedipine, 30-60 mg sustained-release form daily; amlodipine, 2.5-10 mg daily) are the most common pharmacologic interventions. Additional potential therapies for RP include losartan, prazosin, bosentan, and sildenafil. Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril) are recommended for hypertension associated with renal disease. Methotrexate or MMF may be beneficial for skin manifestations. Cyclophosphamide and MMF are used to treat pulmonary alveolitis and prevent fibrosis. Corticosteroids should be used cautiously in SSc because of an association with renal crisis. Adults with SSc have been successfully treated with high-dose cyclophosphamide, antithymocyte globulin, and autologous stem cell transplantation.

The treatment of **RP** begins with avoiding cold stimuli, using hand and foot warmers, and avoiding carrying bags by their handles (impairs circulation). Nifedipine (10-20 mg 3 times daily adult dose) reduces but does not eliminate the number and severity of episodes. Side effects include headache, flushing, and hypotension. Topical nitrates may result in digital vasodilation and may reduce the severity of an episode.

Prognosis

JLS is generally self-limited, with initial inflammatory stage followed by a period of stabilization and then softening, for an average disease duration of 3-5 yr, although there are reports of active disease lasting up to 20 yr. Prolonged disease activity is associated primarily with linear and deep disease subtypes. JLS, especially linear and deep subtypes, can result in significant morbidity, disfigurement, and disability as a result of joint contractures, muscle atrophy, limb shortening, facial asymmetry, and hyper- and hypopigmentation. Death from a en coup de sabre lesion with progressive neurologic decline has been reported.

JSSc has a more variable prognosis. Although many children have a slow, insidious course, others demonstrate a rapidly progressive form with early organ failure and death. Skin manifestations reportedly soften years after disease onset. Overall, the prognosis of JSSc is better than that of the adult form, with 5-, 10-, and 15-year survival rates, respectively, in children of 89%, 80–87%, and 74–87%. The most common cause of death is heart failure caused by myocardial and pulmonary fibrosis.

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CHAPTER 186

Behçet Disease

Seza Özen

Behçet disease (BD) is classified as a primary *variable vessel vasculitis* , emphasizing the involvement of any size and type (arterial, venous) of blood vessel. BD is also recognized as an autoinflammatory disease. Originally described with recurrent oral ulcerations, uveitis, and skin abnormalities, the BD spectrum is much broader.

Epidemiology

Behçet disease has a high prevalence in countries along the *Silk Road*, extending from Japan to the eastern Mediterranean. It is increasingly recognized among people of European ancestry. BD has a prevalence of 5-7 per 100,000 adults, which makes it more frequent than the other vasculitides such as granulomatosis polyangiitis (Wegener disease). The increased disease recognition might have had a role in the rising prevalence of BD as well as the immigrations of the 20th century. Prevalence in children is probably not more than 10% of the adult counterparts in eastern Mediterranean countries; boys and girls are equally affected. Family history of BD is present in approximately 20% of the cases. Onset in children is 8-12 yr of age. Newborns of affected mothers have demonstrated symptoms of BD.

Etiology and Pathogenesis

Behçet disease is a polygenic autoinflammatory disorder. Genetic contribution to BD is evident through the well-known association with HLA-B5101, the familial cases, the sibling and twin recurrence rate, the specific frequency of the disease among people along the Silk Road, evidence for genetic anticipation, and genome-wide analysis. Genome wide analysis studies among Turkish and Japanese BD patients confirm the marked association with HLA-B5101. Other significant associations include interleukin (IL)-10 and IL-23R/IL-12Rβ_2 genes. Other possible susceptibility loci in a Turkish cohort demonstrate associations with *STAT4* (a transcription factor in a signaling pathway related to cytokines such as IL-12, type I interferons, and IL-23) and *ERAP1* (an endoplasmic reticulum–expressed aminopeptidase that functions in processing of peptides onto major histocompatibility complex class I).

The autoinflammatory nature of BD is suggested by its episodic nature, the prominent innate immune system activation, the absence of identifiable autoantibodies, and the co-association with the *MEFV* (Mediterranean fever) gene. An infectious agent may be responsible for inducing the aberrant innate immune system attacks in the genetically predisposed host. A number of infectious agents have been implicated and include streptococci, herpes simplex virus type 1, and parvovirus B19.

Clinical Manifestations and Diagnosis

The course of BD is characterized by exacerbations and remissions. There is also marked heterogeneity in disease manifestation (Table 186.1).

Table 186.1

Consensus Classification of Pediatric Behçet Disease

ITEM	DESCRIPTION
Recurrent oral aphthosis	At least three attacks/year
Genital ulceration or aphthosis	Typically with scar
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum
Ocular involvement	Anterior uveitis, posterior uveitis, retinal vasculitis
Neurologic signs	With the exception of isolated headaches
Vascular signs	Venous thrombosis, arterial thrombosis, arterial aneurysm

From Koné-Paut I, Shahram F, Darce-Bello M, et al, for PEDBD group: Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD, *Ann Rheum Dis* 75:958–964, 2016.

The mean age of the first symptom is between 8 and 12 yr. The most frequent initial symptom is a painful **oral ulcer** (Fig. 186.1). The oral ulcers are often recurrent, may be single or multiple, range from 2-10 mm, and may be in any location in the oral cavity. They are often very painful. The oral ulcers last 3-10 days and heal without scarring. In contrast, the genital ulcers heal with scars. Genital scars are noted in 60–85% of the patients, usually occur after puberty, and are seen on the labia, scrotum, penis, or the anal area.

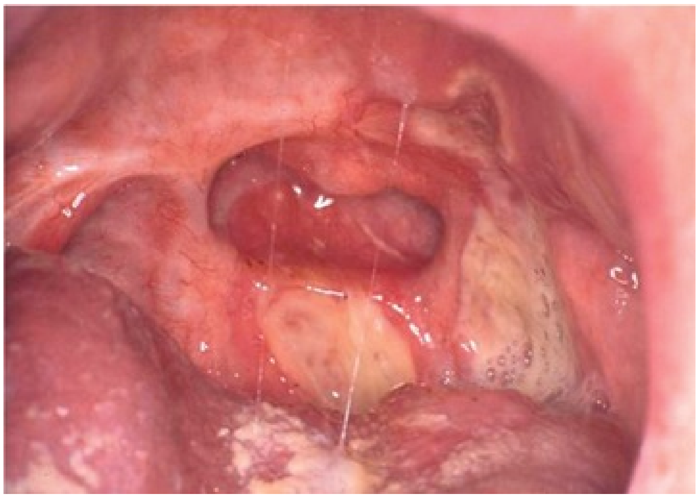

FIG. 186.1 A major aphthous ulcer in a patient with Behçet disease. (From Summers SA, Tilakaratne WM, Fortune F, Ashman N: Renal disease and the mouth. *Am J Med* 120:568-573, 2007.)

Another key feature of BD that has significant morbidity is bilateral eye involvement seen in 30–60% of pediatric patients. The main symptoms of **anterior uveitis** are blurred vision, redness, periorbital or global pain, and photophobia. Although it is often in the form of panuveitis, anterior uveitis may be seen in females. Uveitis in general is more common in males. Vitreitis and retinal vasculitis are the most prominent features of posterior involvement. Complications of uveitis include blindness (unusual with treatment), glaucoma, and cataracts. Retinal vasculitis, retinal detachment, and retrobulbar neuritis (optic neuritis) are less common eye manifestations of BD.

The **skin lesions** of BD range from erythema nodosum (seen in approximately 50% of patients) to papulopustular acneiform lesions (85%), folliculitis, purpura, and ulcers. **Pathergy** (seen in 50%) is another skin feature associated with BD and is a pustular reaction occurring 24-48 hr after a sterile needle puncture or saline injection; it is not pathognomonic of BD.

The **vasculitis** of BD involves both arteries and veins, thrombosis and aneurysm formation, occlusions, or stenosis in arteries of any size. In children, deep venous thrombosis of the lower limbs is the most frequent vasculitic feature. If the hepatic vein is thrombosed, Budd-Chiari syndrome may occur. Pulmonary aneurysms are the most severe feature of pediatric BD, associated with the highest mortality. Coronary artery aneurysms may confuse BD with Kawasaki disease. Microvascular involvement may be noted in the nail bed capillaries.

Central nervous system (CNS) manifestations (approximately 10%) in children include meningoencephalitis (headache, meningismus, cerebrospinal fluid pleocytosis), encephalomyelitis, pseudotumor cerebri, dural sinus thrombosis, and organic psychiatric disorders (psychosis, depression, dementia). **Dural sinus thrombosis** is the most common CNS manifestation in children.

Gastrointestinal (GI) involvement (seen in 10–30%) manifests with abdominal pain, diarrhea, and intestinal ulcerations, most often in the ileocecal region. Gastrointestinal BD may be difficult to distinguish from inflammatory bowel disease. Oligoarticular **arthritis/arthralgia** is present in >50% of patients and can be recurrent, but is nondeforming. Other rare manifestations include orchitis, renal vasculitis, glomerulonephritis, or amyloidosis and cardiac involvement.

The **International Study Group for Behçet Disease** (ISG) criteria are most widely used and require the presence of oral ulcers (at least 3 times per year) along with 2 other major features, including genital ulcers, a positive pathergy test, uveitis, and the characteristic skin lesions (see Table 186.1). If only 1 of the criteria is present along with oral ulcerations, the term *incomplete* or *partial Behçet disease* is applied.

Classification criteria for children have been suggested by the use of an international prospective observational cohort. According to these criteria, BD is diagnosed when 3 of the following criteria are present: recurrent oral aphthosis, genital ulcers, skin involvement (necrotic folliculitis, acneiform lesions, erythema nodosum), ocular involvement, neurologic involvement, and vascular involvement (venous thrombosis, arterial thrombosis, arterial aneurysm). These criteria performed better than the ISG criteria in the pediatric cohort.

There are no specific laboratory tests. Acute-phase reactants are often mildly elevated. The diagnosis relies on the constellation of symptoms and excluding other causes.

Treatment and Prognosis

Azathioprine is highly recommended to treat inflammatory eye disease. Anti–tumor necrosis factor (TNF) treatment and interferon (IFN)-α should be considered for refractory eye disease. For oral and genital ulcers, topical treatment is recommended (sucralfate, corticosteroids). A placebo-controlled study has shown that *apremilast*, an oral phosphodiesterase-4 inhibitor, is effective in treating the oral ulcers of Behçet disease. *Colchicine* is recommended for erythema nodosum or arthritis in males and females and for genital ulcers in females. There is no evidence-based treatment for GI disease, but thalidomide, sulfasalazine, corticosteroids, azathioprine, and anti-TNF agents have been recommended. For CNS disease and vasculitis, corticosteroids, azathioprine, cyclophosphamide, and IFN-α are recommended, and in unresponsive CNS disease, anti-TNF agents. There is no consensus about the benefit of anticoagulation in the management of vein thrombosis in BD.

In patients without major organ involvement, colchicine significantly improves oral and genital ulcers, skin features, and disease activity. In pediatric patients with vascular involvement with venous thrombosis, corticosteroids and azathioprine have been used. In patients with pulmonary arterial or cardiac involvement, cyclophosphamide is typically used initially. Patients treated with anti-TNF drugs have had persistent responses in 90%, 89%, 100%, and 91% of patients with resistant mucocutaneous, ocular, GI, and CNS involvement, respectively.

Mortality in children with BD is low except for the pulmonary aneurysms. However, BD is a chronic disease associated with significant morbidity. Early diagnosis and effective treatment improve the outcome of BD.

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CHAPTER 187

Sjögren Syndrome

C. Egla Rabinovich

Sjögren syndrome is a chronic, inflammatory, autoimmune disease characterized by progressive lymphocytic and plasma cell infiltration of the exocrine glands, especially salivary and lacrimal, with potential for systemic manifestations. It is rare in children and predominantly affects middle-age women with classic symptoms of dry eyes (**keratoconjunctivitis sicca**) and dry mouth (**xerostomia**).

Epidemiology

Sjögren syndrome typically manifests at 35-45 yr of age, with 90% of cases among women, but it is underrecognized in children because symptoms often start in childhood. The mean age at diagnosis in children is 9-10 yr; 75% are girls. The disease can occur as an isolated disorder, referred to as **primary** Sjögren syndrome (**sicca complex**), or as a **secondary** Sjögren syndrome in association with other rheumatic disorders, such as systemic lupus erythematosus (SLE), scleroderma, or mixed connective tissue disease, which usually precedes the associated autoimmune disease by years.

Etiology and Pathogenesis

The etiology of Sjögren syndrome is complex and includes genetic predisposition and possibly an infectious trigger. Lymphocytes and plasma cells infiltrate salivary glands, forming distinct periductal and periacinar foci that become confluent and may replace epithelial structure. Several genes regulating apoptosis influence the chronicity of lymphocytic infiltration.

Clinical Manifestations

International classification criteria have been developed for the diagnosis of Sjögren syndrome in adult patients, but these criteria apply poorly to children. Although diagnostic criteria in children have been proposed, they have not been validated (Table 187.1). Recurrent parotid gland enlargement and parotitis are the most common manifestations in children (>70%), whereas **sicca syndrome** (dry mouth, painful mucosa, sensitivity to spicy foods, halitosis, widespread dental caries) predominates in adults. In a cross-sectional study of children with Sjögren syndrome, manifestations included recurrent parotitis (72%), sicca symptoms (38%), polyarthritis (18%), vulvovaginitis (12%), hepatitis (10%), Raynaud phenomenon (10%), fever (8%), renal tubular acidosis (9%), lymphadenopathy (8%), and central nervous system (CNS) involvement (5%).

Table 187.1

Proposed Criteria for Pediatric Sjögren Syndrome*

I. CLINICAL SYMPTOMS

1. Oral: recurrent parotitis or enlargement of parotid gland, dry mouth (xerostomia)
2. Ocular: dry eyes (xerophthalmia) recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca
3. Other mucosal: recurrent vaginitis
4. Systemic: fever, noninflammatory arthralgias, hypokalemic paralysis, abdominal pain

II. IMMUNOLOGIC ABNORMALITIES

Presence of at least 1 of the following antibodies: anti-SSA, anti-SSB, high-titer antinuclear antibody, rheumatoid factor

III. OTHER ABNORMALITIES OR INVESTIGATIONS

1. Biochemical: elevated serum amylase
2. Hematologic: leukopenia, high erythrocyte sedimentation rate
3. Immunologic: polyclonal hyperimmunoglobulinemia
4. Renal: renal tubular acidosis
5. Histologic proof of lymphocytic infiltration of salivary glands or other organs (i.e., liver)

    6. Objective documentation of ocular dryness (rose bengal staining or Schirmer test)
    7. Positive findings of parotid gland scintigraphy

IV. Exclusion of all other autoimmune diseases

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[*] Diagnosis requires ≥4 criteria.

From Bartunkova J. Primary Sjögren syndrome in children and adolescents: proposal for diagnostic criteria, *Clin Exp Rheumatol* 17:381–386, 1999.

Subjective symptoms of xerostomia complaints are relatively rare in juvenile cases, perhaps indicating that Sjögren syndrome is a slowly progressive disease; however, increased dental caries is seen clinically in children. Serologic markers (antinuclear antibodies [ANAs], antibodies to Ro [SSA] and La [SSB]) and articular manifestations are significantly more common in adults. Reported frequencies of ANAs and SSA and SSB antibodies in children are 78%, 75%, and 65%, respectively, with rheumatoid factor present in 67%. Additional clinical manifestations from a variety of organ involvement patterns include a decreased sense of smell, hoarseness, chronic otitis media, leukocytoclastic vasculitis (purpura), and internal organ exocrine disease involving the lungs (diffuse interstitial lymphocytosis), pancreas, hepatobiliary system, gastrointestinal tract, kidneys (renal tubular acidosis), musculoskeletal (arthritis and arthralgia), hematologic (cytopenias), peripheral nervous system (sensory and autonomic neuropathy), and CNS (optic neuritis, transverse myelitis, meningoencephalitis).

Nonexocrine disease manifestations of Sjögren syndrome may be related to inflammatory vascular disease (skin, muscle and joints, serosal surfaces, CNS, peripheral nervous system), noninflammatory vascular disease (Raynaud phenomenon), mediator-induced disease (hematologic cytopenias, fatigue, fever), and autoimmune endocrinopathy (thyroiditis).

Diagnosis

Clinical presentation of recurrent **parotitis** and or recurrent parotid gland swelling in a child or adolescent is characteristic and should raise the suspicion for Sjögren syndrome. The diagnosis is based on clinical features supported by biopsy of salivary or parotid glands demonstrating foci of lymphocytic infiltration, the current gold standard for diagnosis. Children are more likely to have normal minor salivary gland but abnormal parotid gland biopsies. Supporting laboratory abnormalities include cryoglobulinemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, positive rheumatoid factor, and detection of SSA and SSB antibodies. Anti–β-fodrin autoantibodies, directed against an apoptotic cleavage product of α-fodrin, are a useful diagnostic marker for juvenile Sjögren syndrome. The **Schirmer test** detects abnormal tear production (≤5 mm of wetting of filter paper strip in 5 min). **Rose bengal staining** detects damaged ocular epithelial conjunctival and corneal cells. Imaging studies, including MRI, technetium (^{99m} Tc) scintigraphy, and sialography, are useful in the diagnostic evaluation for Sjögren syndrome (Fig. 187.1).

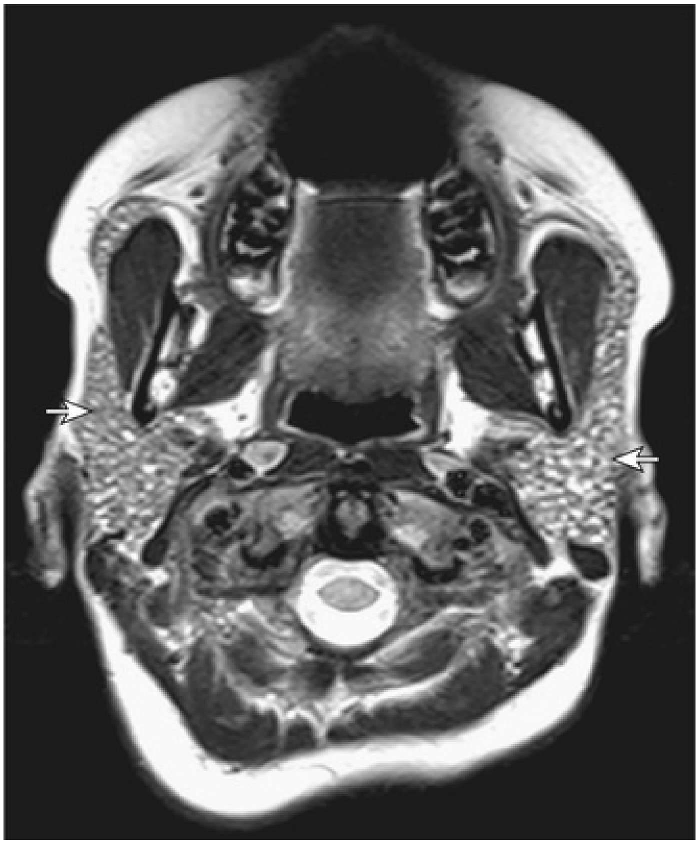

FIG. 187.1 T2-weighted MRI of child with Sjögren syndrome showing parotitis *(arrows).*

Differential Diagnosis

The differential diagnosis of Sjögren syndrome in children includes **juvenile recurrent parotitis** , characterized by intermittent unilateral parotid swelling typically lasting only a few days. It is frequently associated with fever and may undergo remission with puberty. Unlike in Sjögren syndrome, there is a male predominance, juvenile recurrent parotitis is seen in the younger children (3-6 yr), and there is a lack of focal lymphocytic infiltrates on biopsy. Other conditions in the differential diagnosis include eating disorders, infectious parotitis (mumps, streptococcal and staphylococcal infections, Epstein-Barr virus, cytomegalovirus, HIV, parainfluenza, influenza enterovirus), and local trauma to the buccal mucosa. Rarely, polycystic parotid disease, tumors, and sarcoidosis may present with recurrent parotid swelling. In these conditions, sicca complex, rash, arthralgia, and ANAs are usually absent.

Treatment

Symptomatic treatment of Sjögren syndrome includes the use of artificial tears, massage of the parotids, oral lozenges, and fluids to limit the damaging effects of decreased secretions. Corticosteroids, nonsteroidal antiinflammatory drugs, and hydroxychloroquine are among the more commonly used agents for treatment, with reports of methotrexate and etanercept used for treatment of arthritis. Stronger immunosuppressive agents, such as cyclosporine and cyclophosphamide, are reserved for severe functional disorders and life-threatening complications.

Complications and Prognosis

The symptoms of Sjögren syndrome develop and progress slowly. Diminished salivary flow typically remains constant for years. Because monoclonal B-lymphocyte disease originates chiefly from lymphocytic foci within salivary glands or from parenchymal internal organs, there is increased risk for mucosa-associated lymphoid tissue lymphoma. Maternal Sjögren syndrome can be an antecedent to the **neonatal lupus** syndrome (see Chapter 183.1).

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CHAPTER 188

Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases

James W. Verbsky

The hereditary periodic fever syndromes are a group of monogenic diseases that present with recurrent bouts of fever and associated pleural and/or peritoneal inflammation, arthritis, and various types of skin rash. A number of identifiable disorders present with recurrent episodes of inflammation, although fevers may not be common feature. Therefore the term **systemic autoinflammatory diseases** is used to include all diseases that present with seemingly unprovoked episodes of inflammation, without the high-titer autoantibodies or antigen-specific T cells typically seen in autoimmune diseases. Whereas the autoimmune diseases are disorders of the *adaptive* immune system, driven by B and T lymphocyte effector cells, autoinflammatory diseases largely represent disorders of the phylogenetically more primitive *innate* immune system, mediated by myeloid effector cells and germline-encoded receptors. Autoinflammatory diseases exhibit episodic or persistent inflammation characterized by an acute-phase response with elevation of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum amyloid A (AA). In some patients, untreated autoinflammatory disorders over time will lead to AA amyloidosis (see Chapter 189).

It is important to note that autoinflammatory disorders are rare, whereas fever in childhood caused by innocuous illness is very common. The approach to a child with fevers should include a detailed history, physical examination, and limited laboratory investigations to rule out other conditions that lead to fevers, including autoimmune disorders and malignancies (Table 188.1). If there is evidence of recurrent infections with fevers, an immune deficiency could be considered and evaluated. If the workup is reassuring, the inflammatory episodes resolve, and the child is otherwise well without unusual physical findings, observance is often warranted because these episodes are likely to resolve as the child's immune system matures.

Table 188.1

Differential Diagnosis of Periodic Fever

Hereditary

See Table 188.2 .

Nonhereditary

A. Infectious
    1. Hidden infectious focus (e.g., aortoenteric fistula, lung sequestration)
    2. Recurrent infection/reinfection (e.g., chronic meningococcemia, immune deficiency)
    3. Specific infection (e.g., Whipple disease, malaria)

B. Noninfectious inflammatory disorder:
    1. Adult-onset Still disease
    2. Systemic-onset juvenile idiopathic arthritis
    3. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
    4. Schnitzler syndrome
    5. Behçet syndrome
    6. Crohn disease
    7. Sarcoidosis

C. Neoplastic
    1. Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)
    2. Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma)
    3. Histiocytic disorders

D. Vascular (e.g., recurrent pulmonary embolism)

E. Hypothalamic

F. Psychogenic periodic fever

G. Factitious or fraudulent

Adapted from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2012, Saunders (Table 97-2).

Classification of Autoinflammatory Disorders

Because of the rapidly expanding number of autoinflammatory disorders and their varied clinical presentation, it can be difficult to group these disorders in a meaningful manner. Some autoinflammatory disorders present with prominent fevers and are known as **hereditary periodic fever syndromes** . These include 2 disorders with an *autosomal recessive* mode of inheritance, familial Mediterranean fever (**FMF** ; MIM249100) and the hyperimmunoglobulinemia D (hyper-IgD) with periodic fever syndrome (**HIDS** ; MIM260920). Hereditary periodic fever syndromes with an *autosomal dominant* mode of inheritance include the tumor necrosis factor (TNF) receptor–associated periodic syndrome (**TRAPS** ; MIM191190) and a spectrum of disorders known as the cryopyrin-associated periodic syndromes (**CAPS**), or cryopyrinopathies. From mildest to most severe, CAPS include the familial cold autoinflammatory syndrome (**FCAS1** ; MIM120100), Muckle-Wells syndrome (**MWS** ; MIM191100), and neonatal-onset multisystem inflammatory disease (**NOMID** ; MIM607115) (also known as chronic infantile neurologic cutaneous and articular syndrome, **CINCA**) (Table 188.2).

Table 188.2

Autoinflammatory Disorders

DISEASE	GENETIC DEFECT/PRESUMED PATHOGENESIS	INHERITANCE	AFFECTED CELLS	FUNCTIONAL DEFECTS	AS FE
Familial Mediterranean fever	Mutations of *MEFV* (lead to gain of pyrin function, resulting in inappropriate IL-1β release)	AR	Mature granulocytes, cytokine-activated monocytes	Decreased production of pyrin permits ASC-induced IL-1 processing and	Re fev anc inf res

				inflammation following subclinical serosal injury; macrophage apoptosis decreased	col Pre vas inf bo
Mevalonate kinase deficiency (hyper IgD syndrome)	Mutations of *MVK* (lead to a block in the mevalonate pathway). Interleukin-1β mediates the inflammatory phenotype	AR		Affecting cholesterol synthesis; pathogenesis of disease is unclear	Pe an leu wi lev
Muckle–Wells syndrome	Mutations of *NLRP3* (also called *PYPAF1* or *NALP3*) lead to constitutive activation of the NLRP3 inflammasome	AD	PMNs, monocytes	Defect in cryopyrin, involved in leukocyte apoptosis and NF-κB signaling and IL-1 processing	Ur SN am
Familial cold autoinflammatory syndrome	Mutations of *NLRP3* (see above) Mutations of *NLRP12*	AD	PMNs, monocytes	Same as above	No ur art fev leu aft ex
Neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA)	Mutations of *NLRP3* (see above)		PMNs, chondrocytes	Same as above	Ne ras me art wi inf
TNF receptor–associated periodic syndrome (TRAPS)	Mutations of *TNFRSF1A* (resulting in increased TNF inflammatory signaling)	AD	PMNs, monocytes	Mutations of 55-kDa TNF receptor leading to intracellular receptor retention or diminished soluble cytokine receptor available to bind TNF	Re fev ras or inf
Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome	Mutations of *PSTPIP1* (also called *C2BP1*) (affects both pyrin and protein tyrosine phosphatase to regulate innate and adaptive immune responses)	AD	Hematopoietic tissues, upregulated in activated T cells	Disordered actin reorganization leading to compromised physiologic signaling during inflammatory response	De art inf ski my
Blau syndrome	Mutations of *NOD2* (also called *CARD15*) (involved in various	AD	Monocytes	Mutations in nucleotide binding site of CARD15,	Uv gra sy

	inflammatory processes)			possibly disrupting interactions with lipopolysaccharides and NF-κB signaling	car ras cra neu 30 Cro
Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	Mutations of *LPIN2* (increased expression of the proinflammatory genes)	AR	Neutrophils, bone marrow cells	Undefined	Ch rec mu ost tra dep ane cut inf dis
Early-onset inflammatory bowel disease	Mutations in *IL-10* (results in increase of many proinflammatory cytokines)	AR	Monocyte/macrophage, activated T cells	IL-10 deficiency leads to increase of TNFγ and other proinflammatory cytokines	En ent per abs chr fol
Early-onset inflammatory bowel disease	Mutations in *IL-10RA* (see above)	AR	Monocyte/macrophage, activated T cells	Mutation in IL-10 receptor alpha leads to increase of TNFγ and other proinflammatory cytokines	En ent per abs chr fol
Early-onset inflammatory bowel disease	Mutations in *IL-10RB* (see above)	AR	Monocyte/macrophage, activated T cells	Mutation in IL-10 receptor beta leads to increase of TNFγ and other proinflammatory cytokines	En ent per abs chr fol

AD, autosomal dominant; AR, autosomal recessive; Ig, immunoglobulin; IL, interleukin; NF-κB, nuclear factor-κB; PMN, polymorphonuclear neutrophil; SNHL, sensorineural hearing loss; TNF, tumor necrosis factor.

From Verbsky JW, Routes JR: Recurrent fever, infections, immune disorders, and autoinflammatory diseases. In Kliegman RM, Lyse PS, Bordini BJ, et al, editors: Nelson pediatric symptom-based diagnosis. Philadelphia, 2018, Elsevier, Table 41-5.

A variety of mendelian *autoinflammatory disorders* may or may not exhibit prominent fevers and are not considered periodic fever syndromes, but do have continuous or repeated episodes of spontaneous inflammation with unique clinical characteristics. These include the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (**PAPA** ; MIM604416), deficiency of the interleukin-1 (IL-1) receptor antagonist (**DIRA** ; MIM612852), **Blau syndrome** caused by mutations in *NOD2* (also known as *early-onset sarcoidosis* ; MIM186580), autoinflammation with phospholipase Cγ_2 -associated antibody deficiency and immune dysregulation (**APLAID** ; MIM614878), and deficiency of adenosine deaminase-2 (**DADA2**). Other disorders include congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (**SIFD**) caused by biallelic mutations of the *TRNT1* gene (MIM616084), autoinflammation with infantile enterocolitis caused by mutations in *NLRC4* (**AIFEC** ; MIM616060), familial cold autoinflammatory syndrome type 2 caused by mutations in *NLRP12* (**FCAS2** ; MIM611762), **CARD14** (MIM607211), and deficiency in IL-36 receptor antagonist (**DITRA** ; 614204).

In addition to the previous autoinflammatory disorders, a variety of disorders are characterized by inappropriate *interferon expression* , the **interferonopathies** . Type 1 interferons (e.g., IFN-α, IFN-β) are cytokines expressed by many cells in response to viral infections. Disorders that result in spontaneous interferon production and inflammatory manifestations include STING-associated vasculopathy of infancy (**SAVI** ; MIM615934) and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (**CANDLE** ; MIM256040).

There are also a number of autoinflammatory disorders with a complex mode of inheritance. These include the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and adenitis (**PFAPA**) and chronic recurrent multifocal osteomyelitis (**CRMO** ; MIM259680). Other genetically complex disorders that are sometimes considered autoinflammatory include **systemic-onset juvenile idiopathic arthritis** (see Chapter 180), **Behçet disease** (see Chapter 186), and **Crohn disease** (see Chapter 362.2).

Distinguishing autoinflammatory disorders from one another can be difficult because their presentations can vary, and many display similarities. Some disorders have characteristic fever patterns (Fig. 188.1), whereas others have characteristic skin findings that can aid in a diagnosis (Table 188.3). Others can have characteristic physical features or organ involvement. Some of these disorders have bone involvement (Table 188.4). Other clinical features can also be helpful, such as ethnicity, age of onset, triggers, laboratory testing, and response to therapies (Table 188.5). Genetic panels are increasingly being used to screen for most if not all of these defects in a single test, rather than individual genetic assessment based on clinical findings.

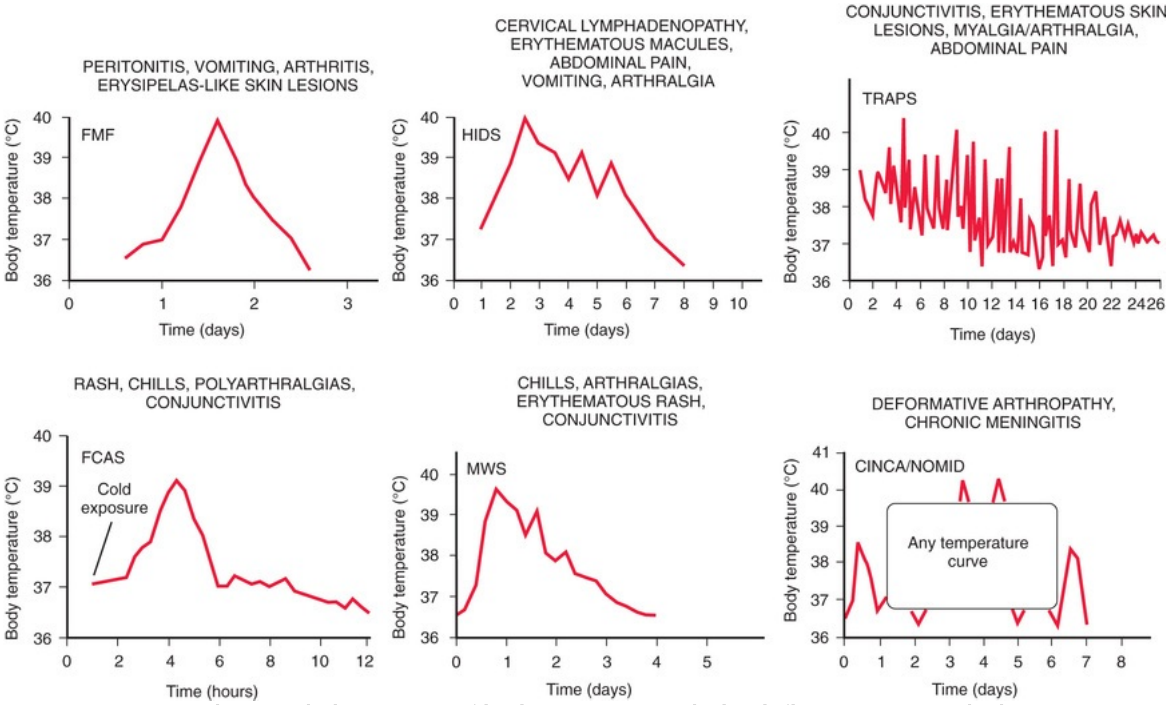

FIG. 188.1 Characteristic patterns of body temperature during inflammatory attacks in the familial autoinflammatory syndromes. Interindividual variability for each syndrome is considerable, and even for the individual patient, the fever pattern may vary greatly from episode to episode. Note the different time scales on the *x* axes. CINCA/NOMID, Chronic infantile neurologic cutaneous and articular syndrome/neonatal-onset multisystemic inflammatory disease; FCAS, familial cold autoinflammatory syndrome; HIDS, hyper-IgD syndrome; MWS, Muckle-Wells syndrome; TRAPS, tumor necrosis factor receptor–associated periodic syndrome. (From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2012, Saunders, Fig 97-1.)

Table 188.3

Clinical Grouping of Autoinflammatory Diseases by Skin Manifestations

1. Neutrophilic urticaria (the cryopyrinopathies)

    Recurrent fever attacks of short duration (typically <24 hr)
    - CAPS/FCAS: familial cold autoinflammatory syndrome
    - CAPS/MWS: Muckle-Wells syndrome
    - FCAS2/NLRP12

    Continuous low-grade fever
    - CAPS/NOMID: neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA)

2. Granulomatous skin lesions and minimal or low-grade fever attacks
    - Blau syndrome/early-onset sarcoidosis (pediatric granulomatous arthritis)
3. Pustular skin rashes and fever

    With inflammatory bone disease
    - DIRA: deficiency of interleukin-1 receptor agonist
    - Majeed syndrome

    With pyogenic arthritis
    - PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

    Without other organ involvement
    - DITRA: deficiency of interleukin-36 receptor antagonist
    - CAMPS: CARD14-mediated psoriasis
4. Atypical neutrophilic dermatosis with histiocytic-like infiltrate
    - CANDLE: proteasome associated autoinflammatory syndromes
5. Livedo reticularis, vasculopathy with ulcerations
    - SAVI; STING associated vasculopathy, infantile onset
6. Livedo racemosa, vasculitis with ulcerations
    - ADA2; adenosine deaminase-2 deficiency

CAPS, Cryopyrin-associated periodic syndromes.

Modified from Almeida de Jesus A, Goldbach-Mansky R: Monogenic autoinflammatory diseases: concept and clinical manifestations, *Clin Immunol* 147:155–174, 2013 (Table 1).

Table 188.4

Autoinflammatory Bone Disorders

	CRMO	MAJEED SYNDROME	DIRA	CHERUBISM	CMO AND LUPO MICE
Ethnicity	Worldwide, but mostly European	Arabic	European, Puerto Rican, Arabic	Worldwide	Occurs in various backgrounds
Fever	Uncommon	Common	Uncommon	No	Not assessed
Sites of osseous involvement	Metaphyses of long bones > vertebrae, clavicle,	Similar to CRMO	Anterior rib ends, metaphyses of long bones, vertebrae, others	Mandible > maxilla Rarely ribs	Vertebrae hind > forefeet

	sternum, pelvis, others				
Extraosseous manifestations	PPP, psoriasis, IBD, others	Dyserythropoietic anemia, Sweet syndrome, HSM, growth failure	Generalized pustulosis, nail changes, lung disease, vasculitis	Cervical lymphadenopathy	Dermatitis, extramedullary hematopoiesis, splenomegaly
Family history of inflammatory disorders	Psoriasis, PPP, arthritis, IBD, others	Psoriasis in some obligate carriers	No known associations	No known associations	Heterozygotes normal
Inheritance	Not clear	Autosomal recessive	Autosomal recessive	Autosomal dominant; incomplete penetrance	Autosomal recessive
Gene defect	Unknown	*LPIN2*	*IL1RN*	*SH3BP2 >> PTPN11*	*Pstpip2*
Protein name	?	Lipin2	IL-1Ra	SH3BP2	PSTPIP2 (MAYP)
Protein function	?	Fat metabolism: (PAP enzyme activity), ↑ message to oxidative stress, ? role in mitosis	Antagonist of IL-1 receptor	↑ Myeloid cell response to M-CSF and RANKL, ↑ TNF-α expression in macrophages	Macrophage proliferation, macrophage recruitment to sites of inflammation, cytoskeletal function
Cytokine abnormalities	↑ serum TNF-α	Not tested	↑ IL-1α, IL-1β, MIP-1α, TNF-α, IL-8, IL-6 ex vivo monocyte assay; skin reveals ↑ IL-17 staining	↑ serum TNF-α in mouse model	cmo: ↑ serum IL-6, MIP-1α, TNF-α, CSF-1, IP-10 Lupo: ↑ serum MIP-1α, IL-4, RANTES, TGF-β

CRMO, Chronic recurrent multifocal osteomyelitis; CSF, colony-stimulating factor; DIRA, deficiency of interleukin-1 receptor antagonist; HSM, hepatosplenomegaly; IBD, inflammatory bowel disease; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IP-10, interferon-inducible protein-10; M-CSF, macrophage colony-stimulating factor; MIP-1α, macrophage inflammatory protein-1α; PAP, phosphatidate phosphatase; PPP, palmar-plantar pustulosis; PSTPIP2, proline-serine-threonine phosphatase interacting protein; RANKL, receptor activator of nuclear factor-κB ligand; RANTES, regulated on activation, normal T cell expressed and secreted; SH3BP2, SH3 binding protein 2; TGF, transforming growth factor; TNF-α, tumor necrosis factor alpha.

From Ferguson PJ, Laxer RM: Autoinflammatory bone disorders. In Cassidy JT, Petty RE, Laxer RM, et al, editors: *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2010, Saunders (Table 44-2).

Table 188.5

Clues That May Assist in Diagnosis of Autoinflammatory Syndromes

AGE OF ONSET	
At birth	NOMID, DIRA, MWS

Infancy and 1st yr of life	HIDS, FCAS, NLRP12
Toddler	PFAPA
Late childhood	PAPA
Most common of autoinflammatory syndromes to have onset in adulthood	TRAPS, DITRA
Variable (mostly in childhood)	All others
ETHNICITY AND GEOGRAPHY	
Armenians, Turks, Italian, Sephardic Jews	FMF
Arabs	FMF, DITRA (Arab Tunisian)
Dutch, French, German, Western Europe	HIDS, MWS, NLRP12
United States	FCAS
Can occur in blacks (West Africa origin)	TRAPS
Eastern Canada, Puerto Rico	DIRA
Worldwide	All others
TRIGGERS	
Vaccines	HIDS
Cold exposure	FCAS, NLRP12
Stress, menses	FMF, TRAPS, MWS, PAPA, DITRA
Minor trauma	PAPA, MWS, TRAPS, HIDS
Exercise	FMF, TRAPS
Pregnancy	DITRA
Infections	All, especially DITRA
ATTACK DURATION	
<24 hr	FCAS, FMF
1-3 days	FMF, MWS, DITRA (fever)
3-7 days	HIDS, PFAPA
>7 days	TRAPS, PAPA
Almost always “in attack”	NOMID, DIRA
INTERVAL BETWEEN ATTACKS	
3-6 wk	PFAPA, HIDS
>6 wk	TRAPS
Mostly unpredictable	All others
Truly periodic	PFAPA, cyclic neutropenia
USEFUL LABORATORY TESTS	
Acute-phase reactants must be normal between attacks	PFAPA
Urine mevalonic acid in attack	HIDS
IgD > 100 mg/dL	HIDS
Proteinuria (amyloidosis)	FMF, TRAPS, MWS, NOMID
RESPONSE TO THERAPY	
Corticosteroid dramatic	PFAPA
Corticosteroid partial	TRAPS, FCAS, MWS, NOMID, PAPA*
Colchicine	FMF, PFAPA (30% effective)
Cimetidine	PFAPA (30% effective)
Etanercept	TRAPS, FMF arthritis
Anti–IL-1 dramatic	DIRA (anakinra), FCAS, MWS, NOMID, PFAPA
Anti–IL-1 mostly	TRAPS, FMF
Anti–IL-1 partial	HIDS, PAPA

* For intraarticular corticosteroids.

DIRA, Deficiency of IL-1 receptor antagonist; DITRA, deficiency of IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial

Mediterranean fever; HIDS, hyper-IgD syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

From Hashkes PJ, Toker O: Autoinflammatory syndromes, *Pediatr Clin North Am* 59:447–470, 2012 (Table 2).

Autoinflammatory Diseases With Periodic or Prominent Fevers

The first descriptions of autoinflammatory disorders focused on genetic diseases that presented with prominent fevers, the periodic fever syndromes. As new autoinflammatory diseases were discovered, it was clear that a variety of inflammatory disorders can occur in the absence of fever.

Familial Mediterranean Fever

FMF is a recessively inherited autoinflammatory disease usually characterized by recurrent, short-lived (1-3 days), self-limited episodes of fever, serositis, mono- or pauciarticular arthritis, or an erysipeloid rash, sometimes complicated by AA amyloidosis. Most patients with FMF present with symptoms in childhood, with 90% presenting before age 20. Clinical features of FMF may include fever, serositis presenting as pleuritic chest pain or severe abdominal pain, arthritis, and rash. The pleural pain is typically unilateral, whereas the abdominal pain (sterile peritonitis) can be generalized or localized to 1 quadrant, similar to other forms of peritonitis. FMF-associated arthritis occurs primarily in the large joints, may be accompanied by large, neutrophil-rich effusions, and is usually nonerosive and nondestructive. The hallmark cutaneous finding is an erysipeloid erythematous rash that overlies the ankle or dorsum of the foot (Fig. 188.2). Other clinical findings include scrotal pain caused by inflammation of the tunica vaginalis testis, febrile myalgia, exercise-induced myalgia (particularly common in children), and an association with various forms of vasculitis, including Henoch-Schönlein purpura, in as many as 5% of pediatric patients. FMF episodes may be triggered by stress, menses, or infections. Between flares, patients are generally symptom free but may have persistent elevation of their inflammatory markers. The attack frequency can vary from weekly to 1-2 flares per year. Table 188.6 lists diagnostic criteria for FMF.

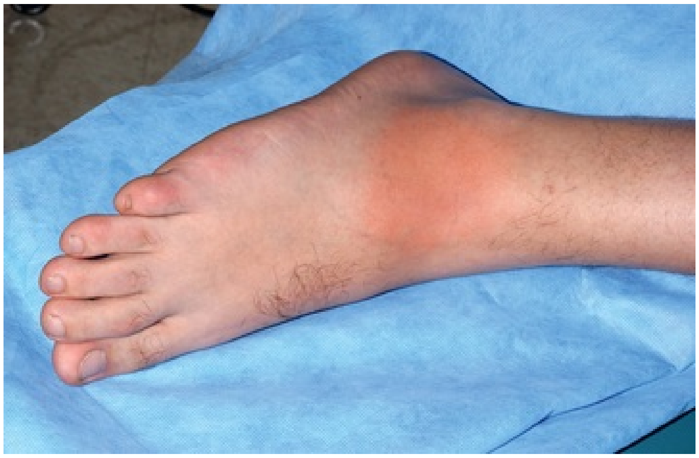

FIG. 188.2 **Characteristic erysipeloid erythema associated with familial Mediterranean fever. This rash appears during a flare and overlies the ankle or dorsum of the foot.**

Table 188.6

Diagnostic Criteria for Familial Mediterranean Fever (FMF)*

Major Criteria

1. Typical attacks [†] with peritonitis (generalized)
2. Typical attacks with pleuritis (unilateral) or pericarditis
3. Typical attacks with monoarthritis (hip, knee, ankle)
4. Typical attacks with fever alone
5. Incomplete abdominal attack

Minor Criteria

1. Incomplete attacks [‡] involving chest pain
2. Incomplete attacks involving monoarthritis
3. Exertional leg pain
4. Favorable response to colchicine

[*] Requirements for diagnosis of FMF are ≥1 major criteria or ≥2 minor criteria.

[†] Typical attacks are defined as recurrent (≥3 of the same type), febrile (≥38°C), and short (lasting between 12 hr and 3 days).

[‡] Incomplete attacks are defined as painful and recurrent attacks not fulfilling the criteria for a typical attack.

From Livneh A, Langevitz P, Zemer D, et al: Criteria for the diagnosis of familial Mediterranean fever, *Arthritis Rheum* 40:1879–1885, 1997.

FMF is caused by autosomal recessive mutations in *MEFV* , a gene encoding a 781 amino acid protein denoted *pyrin* (Greek for “fever”). Pyrin is expressed in granulocytes, monocytes, and dendritic cells (DCs) and in peritoneal, synovial, and dermal fibroblasts. The N-terminal approximately 90 amino acids of pyrin are the prototype for a motif (the PYRIN domain) that mediates protein-protein interactions and is found in >20 different human proteins that regulate inflammation and apoptosis. Many of the FMF-associated mutations in pyrin are found at the C-terminal B30.2 domain of pyrin, encoded by exon 10 of *MEFV.* More than 50 such FMF mutations are listed in an online database (http://fmf.igh.cnrs.fr/ISSAID/infevers/), almost all of which are missense substitutions. Homozygosity for the M694V mutation may be associated with an earlier age of onset, arthritis, and an increased risk of amyloidosis. The substitution of glutamine for glutamic acid at residue 148 (E148Q) is considered either a mild mutation or a functional polymorphism in the pyrin protein. The carrier frequency of FMF mutations among several Mediterranean populations is very high, suggesting the possibility of a heterozygote advantage.

FMF occurs primarily among ethnic groups of Mediterranean ancestry, most frequently Jews, Turks, Armenians, Arabs, and Italians. Because of a higher frequency of the M694V mutation, FMF is more severe and more readily recognized in the Sephardic (North African) than the Ashkenazi (East European) Jewish population. With the advent of genetic testing, mutation-positive FMF has been documented worldwide, although at lower frequency than in the Mediterranean basin and Middle East.

Through PYRIN-domain interactions, pyrin can activate **caspase-1** , the enzyme that converts the 31 kDa pro–IL-1β molecule into the biologically active 17 kDa IL-1β, which is a major mediator of fever and inflammation. FMF mutations lead to a gain-of-function activation of caspase-1 and IL-1β–

dependent inflammation, with a gene-dosage effect. These results may explain why as many as 30% of heterozygous carriers of FMF mutations have biochemical evidence of inflammation.

Prophylactic daily oral colchicine decreases the frequency, duration, and intensity of FMF flares. This regimen also prevents the development of systemic AA amyloidosis. Colchicine is generally well tolerated and safe in children, with the most common side effects being diarrhea and other gastrointestinal (GI) complaints. Some patients develop lactose intolerance while taking colchicine. GI side effects can be minimized by initiating therapy at a low dose (for young children, 0.3 mg/day) and slowly titrating upward. A dose-related transaminitis may also be observed; bone marrow suppression is rarely seen at the dosages prescribed for FMF. Pediatric patients may require doses of colchicine similar to those needed in adults (1-2 mg/day), reflecting that children metabolize the drug more rapidly than adults. It is not always possible to find a tolerated dose of colchicine at which all symptoms are suppressed, but approximately 90% of patients have a marked improvement in disease-related symptoms. A small percentage of FMF patients are either unresponsive to or intolerant of therapeutic doses of colchicine. Based on the role of pyrin in IL-1β activation, a trial demonstrated the safety and effectiveness of *rilonacept,* an IL-1 inhibitor, in FMF; there are case reports of the effectiveness of *anakinra,* a recombinant interleukin-1 receptor (IL-1R) antagonist.

Amyloidosis is the most serious complication of FMF, and in its absence FMF patients may live a normal life span. Amyloidosis may develop when serum AA, an acute-phase reactant found at extremely high levels in the blood during FMF attacks, is cleaved to produce a 76–amino acid fragment that misfolds and deposits ectopically, usually in the kidneys, GI tract, spleen, lungs, testes, thyroid, and adrenals. Rarely, cardiac amyloidosis may develop; macroglossia and amyloid neuropathy are generally not seen with the amyloidosis of FMF. The most common presenting sign of AA amyloidosis is proteinuria. The diagnosis is then usually confirmed by rectal or renal biopsy. In a small number of case reports, mostly from the Middle East, amyloidosis may actually precede overt FMF attacks, presumably because of subclinical inflammation. Risk factors for the development of amyloidosis in FMF include homozygosity for the M694V *MEFV* mutation, polymorphisms of the serum AA gene (encoding AA), noncompliance with colchicine treatment, male gender, and a positive family history of AA amyloid. For unclear reasons, country of origin is also a major risk factor for amyloidosis in FMF, with patients raised in the Middle East having a much higher risk than genotypically identical patients raised in the West. Aggressive lifelong suppression of the acute-phase reactants should be the goal in patients with FMF amyloidosis, and documented cases show this may result in resorption of amyloid deposits. The natural history of untreated amyloidosis in FMF is the inexorable progression to renal failure, often within 3-5 yr.

Hyperimmunoglobulinemia D With Periodic Fever Syndrome

HIDS, also known as **mevalonate kinase deficiency** , was initially described in a cohort of Dutch patients and occurs primarily in patients of Northern European descent. HIDS is recessively inherited and caused by mutations of *MVK* , a gene that encodes mevalonate kinase (MK). The clinical features of HIDS generally appear within the 1st 6 mo of life. Febrile attacks last 3-7 days, with abdominal pain often accompanied by diarrhea, nausea, and vomiting. Other clinical manifestations include cervical lymphadenopathy, diffuse macular rash, aphthous ulcers, headaches, and occasional splenomegaly (Figs. 188.3 to 188.5). Arthritis or arthralgia can be present in an oligoarticular or polyarticular pattern. Inflammatory disease–like illness and Kawasaki disease–like presentation have also been reported. Attacks are often precipitated by intercurrent illness, immunizations, and surgery. Families frequently recount flares around the time of birthdays, holidays, and family vacations. The symptoms of HIDS may persist for years but tend to become less prominent in adulthood. Patients with HIDS usually have a normal life span. Unlike FMF and TRAPS, the incidence of AA amyloidosis is quite low. Complete MK deficiency results in mevalonic aciduria that presents with severe mental retardation, ataxia, myopathy, cataracts, and failure to thrive (see Chapter 103).

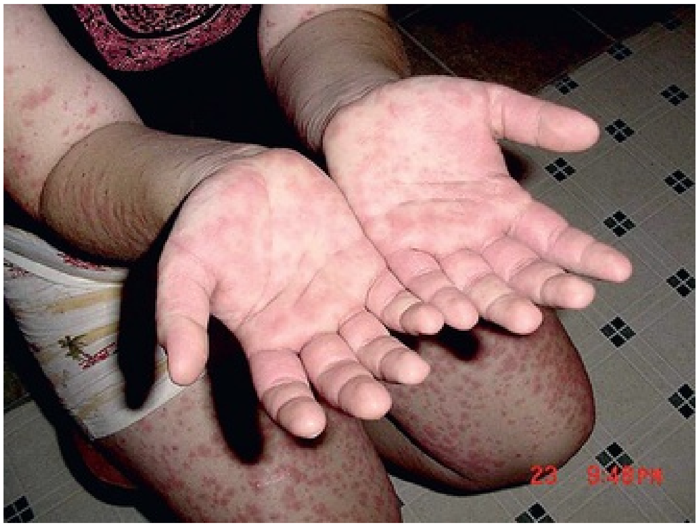

FIG. 188.3 Polymorphic rash on the hands, arms, and legs of a patient with hyper-IgD syndrome (HIDS). (From Takada K, Aksentijevich I, Mahadevan V, et al. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome, *Arthritis Rheum* 48:2646, 2003.)

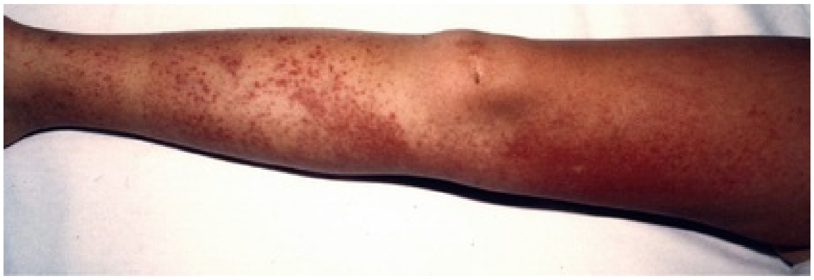

FIG. 188.4 Petechiae on the leg of a hyper-IgD syndrome patient during a febrile attack. (From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2012, Saunders, Fig 97-7.)

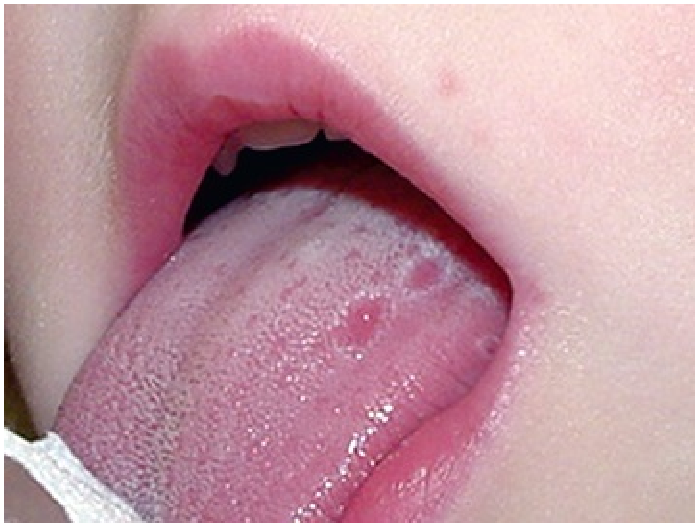

FIG. 188.5 **Aphthous ulceration detected on the tongue of a patient with hyper-IgD syndrome. (Courtesy Dr. K. Antila, North Carelian Central Hospital, Joensuu, Finland; from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2012, Saunders, Fig 97-8.)**

MK is expressed in multiple tissues and catalyzes the conversion of mevalonic acid to 5-phosphomevalonic acid in the biosynthesis of cholesterol and nonsterol isoprenoids. Patients with HIDS-associated mutations have greatly reduced, but not absent, MK enzymatic activity. HIDS patients usually have low-normal serum cholesterol levels, but the deficiency of isoprenoids may cause increased IL-1β production by aberrant activation of the small guanosine triphosphatase Rac1. Temperature elevation may further exacerbate this process by more complete inhibition of MK activity, leading to a possible positive feedback loop.

The diagnosis of HIDS may be confirmed either by 2 mutations in *MVK* (approximately 10% of patients with seemingly typical disease have only a single identifiable mutation) or by elevated levels of mevalonate in the urine during acute attacks. HIDS-associated mutations are distributed throughout the MK protein, but the 2 most common mutations are the substitution of isoleucine for valine at residue 377 (V377I), a variant that is quite common in the Dutch population, and the substitution of threonine for isoleucine at residue 268 (I268T). The eponymous elevation in serum IgD levels is not universally present, especially in young children; IgA levels can also be elevated. Conversely, serum IgD levels may be increased in other autoinflammatory disorders as well as in some chronic infections. During attacks, leukocytosis and increased serum levels of acute-phase reactants and proinflammatory cytokines are frequently present. Table 188.7 lists diagnostic criteria for HIDS.

Table 188.7

Diagnostic Indicators of Hyper-IgD Syndrome

At Time of Attacks

1. Elevated erythrocyte sedimentation rate and leukocytosis
2. Abrupt onset of fever (≥38.5°C)
3. Recurrent attacks
4. Lymphadenopathy (especially cervical)
5. Abdominal distress (e.g., vomiting, diarrhea, pain)
6. Skin manifestations (e.g., erythematous macules and papules)
7. Arthralgias and arthritis
8. Splenomegaly

Constantly Present

1. Elevated IgD (above upper limit of normal) measured on 2 occasions at least 1 mo apart*
2. Elevated IgA (≥2.6 g/L)

Specific Features

1. Mutations in mevalonate kinase gene
2. Decreased mevalonate kinase enzyme activity

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* Extremely high serum concentrations of IgD are characteristic but not obligatory.

From Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelly & Firestein's textbook of rheumatology,* ed 10, Philadelphia, 2016, Elsevier (Table 97-4, p 1674).

Standards for the **treatment** of HIDS are evolving. Very few patients respond to colchicine, and milder disease courses may respond to nonsteroidal antiinflammatory drugs (NSAIDs). Corticosteroids are of limited utility. Small trials of both etanercept and either intermittent or daily anakinra in HIDS are promising.

Tumor Necrosis Factor Receptor–Associated Periodic Syndrome

TRAPS is characterized by recurrent fevers and localized inflammation and is inherited in an autosomal dominant manner. TRAPS has a number of distinguishing clinical and immunologic features. TRAPS was first recognized in patients of Irish descent and denoted *familial Hibernian fever* to draw a contrast with FMF, but the current nomenclature was proposed when mutations in *TNFRSF1A* were discovered not only in the original Irish family, but in families from a number of other ethnic backgrounds. *TNFRSF1A* encodes the 55 kDa receptor (denoted p55, TNFR1, or CD120a) for TNF-α that is widely expressed on a number of cell types. A 2nd 75 kDa receptor is largely restricted to leukocytes.

Patients with TRAPS typically present within the 1st decade of life with flares that occur with variable frequency but of often substantially longer duration than FMF or HIDS flares. The febrile episodes of TRAPS last at least 3 days and can persist for weeks. There may be pleural and peritoneal involvement. At times, patients present with signs of an acute abdomen; on exploration such patients have *sterile peritonitis* , sometimes with adhesions from previous episodes. Patients may also have nausea and frequently report constipation at the onset of flares that progresses to diarrhea by the conclusion. Ocular signs include periorbital edema and conjunctivitis. TRAPS patients may also experience severe myalgia and on imaging, the muscle groups may have focal areas of edema. Many rashes can be seen in TRAPS patients, but the most common is an erythematous macular rash that on biopsy contains superficial and deep perivascular infiltrates of mononuclear cells. Patients often report that the rash migrates distally on a limb during its course with an underlying myalgia and can resemble cellulitis. Other rashes include erythematous annular patches as well as a serpiginous rash (Fig. 188.6). Approximately 10–15% of patients with TRAPS may develop AA amyloidosis; the presence of cysteine mutations and a positive family history are risk factors for this complication. If amyloidosis does not develop, TRAPS patients have a normal life expectancy. Table 188.8 lists diagnostic criteria.

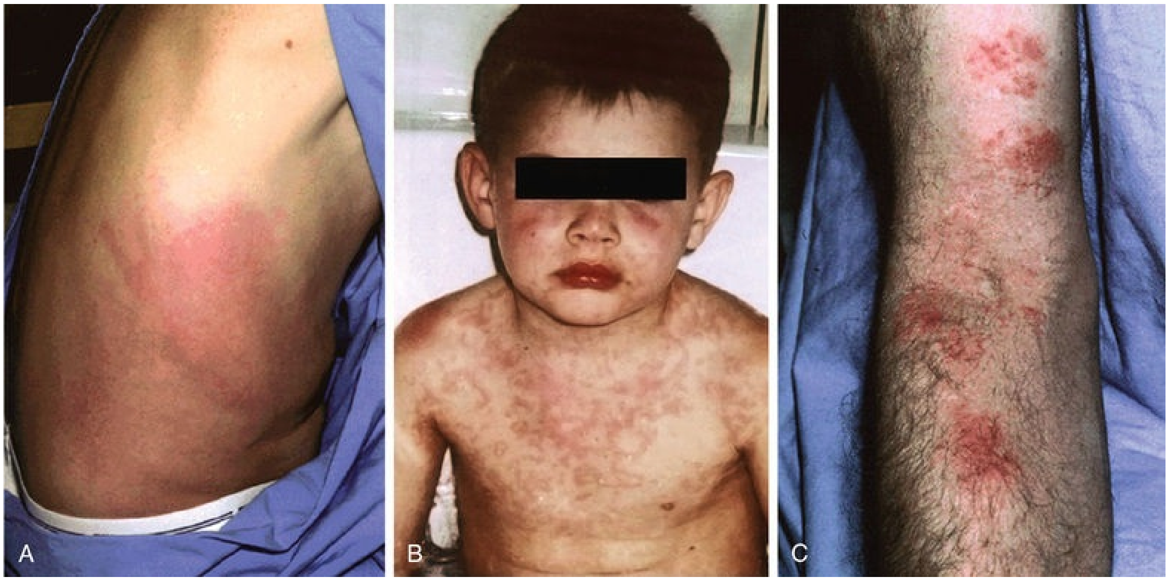

FIG. 188.6 Cutaneous manifestations of tumor necrosis factor receptor–associated periodic syndrome. A, Right flank of a patient with the T50M mutation. B, Serpiginous rash involving the face, neck, torso, and upper extremities of a child with the C30S mutation. C, Erythematous, macular patches with crusting on the flexor surface of the right arm of a patient with the T50M mutation. (From Hull KM, Drewe, Aksentijevich I, et al: The TNF receptor-associated periodic syndrome [TRAPS]: emerging concepts of an autoinflammatory syndrome, *Medicine (Baltimore)* 81:349–368, 2002.)

Table 188.8

Diagnostic Indicators of Tumor Necrosis Factor Receptor–Associated Periodic Syndrome (TRAPS)

1. Recurrent episodes of inflammatory symptoms spanning >6 mo duration (several symptoms generally occur simultaneously)
    a. Fever
    b. Abdominal pain
    c. Myalgia (migratory)
    d. Rash (erythematous macular rash occurs with myalgia)
    e. Conjunctivitis or periorbital edema
    f. Chest pain
    g. Arthralgia or monoarticular synovitis
2. Episodes last >5 days on average (although variable)
3. Responsive to glucocorticosteroids but not colchicine
4. Affects family members in autosomal dominant pattern (although may not

always be present)
5. Any ethnicity may be affected

From Hull KM, Drewe E, Aksentijevich I, et al: The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder, *Medicine (Baltimore)* 81:349–368, 2002.

Almost all the TRAPS-associated mutations are in the extracellular domain of the TNFR1 protein, with about one-third involving the substitution of another amino acid for a highly conserved cysteine residue, thus disrupting disulfide bonds and leading to protein misfolding. A number of other missense mutations not involving cysteine residues have been shown to have a similar effect on TNFR1 protein folding. Misfolded TNFR1 aggregates intracellularly and leads to constitutive signaling through mitogen-activated protein kinases or nuclear factor (NF)-κB, resulting in the release of proinflammatory cytokines such as IL-6, IL-1β and TNF-α. The substitution of glutamine for arginine at residue 92 (R92Q) and the substitution of leucine for proline at residue 46 (P46L) are seen in >1% of the white and black population, respectively. These variants do not lead to the same biochemical or signaling abnormalities seen with more-severe TRAPS mutations, and as with E148Q in FMF, debate surrounds whether they are mild mutations or functional polymorphisms.

Colchicine is generally not effective in TRAPS. For relatively mild disease, NSAIDs may suffice. For more severe disease with infrequent attacks, corticosteroids at the time of an attack may be effective, but it is not unusual for steroid requirements to increase over time. Etanercept is often effective in reducing the severity and frequency of flares, but longitudinal follow-up of TRAPS patients treated with etanercept indicates waning efficacy with time. Of note, treatment of TRAPS with anti-TNF-α monoclonal antibodies has sometimes led to a paradoxical worsening of disease. Clinical responses to anakinra, *canakinumab,* a monoclonal anti–IL-1β antibody, and *tocilizumab,* a monoclonal anti-IL6 antibody, has been favorable in TRAPS patients.

Cryopyrin-Associated Periodic Fever Syndromes

CAPS represent a spectrum of clinical disorders, including **familial cold**

autoinflammatory syndrome (FCAS), **Muckle-Wells syndrome** (MWS), and **neonatal-onset multisystem inflammatory disorder** (NOMID). Although 3 separate clinical diagnoses have been defined, it should be emphasized that the **cryopyrinopathies** are really a continuum of disease severity. This spectrum of illness is caused by mutations in *NLRP3* (formerly known as *CIAS1*), which encodes a protein called **cryopyrin** ; >100 disease-associated *NLRP3* mutations have been enumerated on the *Infevers* online database. Advances in next-generation sequencing have also permitted the identification of symptomatic individuals with somatic *NLRP3* mosaicism.

NLRP3 is a PYRIN domain-containing protein that is strongly expressed in myeloid cells and to a lesser degree in other tissues. It is a part of a macromolecular complex termed the *NLRP3 inflammasome* that activates pro–IL-1β to its mature form in response to a variety of endogenous danger-associated molecular patterns and pathogen-associated molecular patterns. Patients with cryopyrinopathies have *gain-of-function mutations* in *NLRP3* that result in constitutive or easily-triggered activation of the NLRP3 inflammasome.

The cryopyrinopathies are characterized by recurrent fevers and an urticaria-like rash that develops early in infancy (Fig. 188.7). Histopathologic examination reveals a perivascular neutrophilic infiltrate without the mast cells or mast cell degranulation seen with true urticaria. In patients with FCAS, febrile attacks generally begin 1-3 hr after generalized cold exposure. FCAS patients also experience polyarthralgia of the hands, knees, and ankles, and conjunctivitis may also develop during attacks. FCAS episodes are self-limited and generally resolve within 24 hr. AA amyloidosis rarely occurs in FCAS. Table 188.9 lists diagnostic criteria for FCAS.

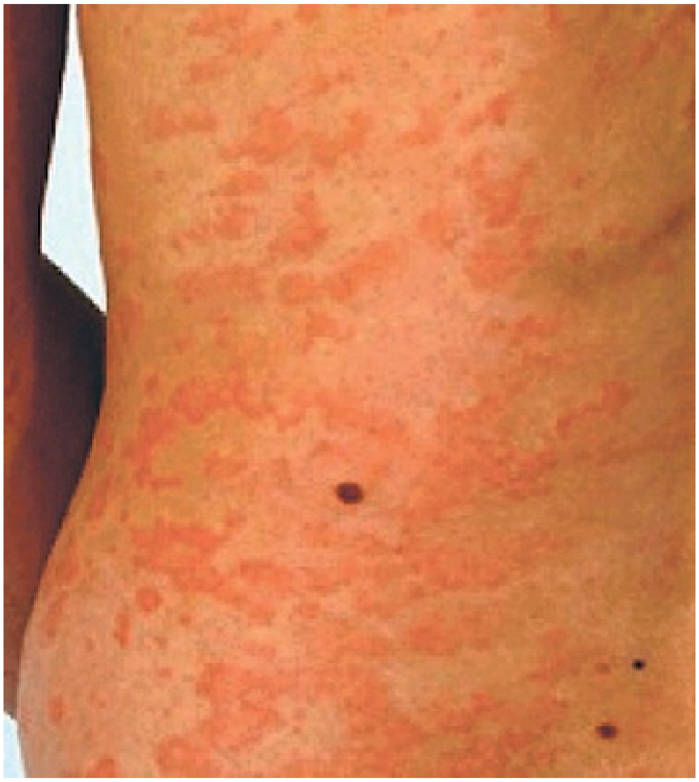

FIG. 188.7 Urticarial-like rash. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of IL-1 receptor antagonist (DIRA). This rash is not truly urticarial and occurs due to neutrophil infiltrates into the skin. (From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes. *Annu Rev Med* 65:223–244, 2014, Fig. 2.)

Table 188.9

Diagnostic Criteria for Familial Cold Autoinflammatory Syndrome (FCAS)

1. Recurrent intermittent episodes of fever and rash that primarily follow generalized cold exposures
2. Autosomal dominant pattern of disease inheritance
3. Age of onset <6 mo
4. Duration of most attacks <24 hr
5. Presence of conjunctivitis associated with attacks
6. Absence of deafness, periorbital edema, lymphadenopathy, and serositis

From Hoffman HM, Wanderer AA, Broide DH: Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever, *J Allergy Clin Immunol* 108:615–620, 2001.

In contrast to FCAS, the febrile episodes of **MWS** are not cold induced but are characterized by the same urticarial-like rash seen in FCAS (Fig. 188.8). Many MWS patients also develop progressive sensorineural hearing loss, and untreated, approximately 30% of MWS patients develop AA amyloidosis. **NOMID** patients present in the neonatal period with a diffuse, urticarial rash, daily fevers, and dysmorphic features (Fig. 188.9). Significant joint deformities, particularly of the knees, may develop because of bony overgrowth of the epiphyses of the long bones (Fig. 188.10). NOMID patients also develop chronic aseptic meningitis, leading to increased intracranial pressure, optic disc edema, visual impairment, progressive sensorineural hearing loss, and intellectual disability (Fig. 188.11).

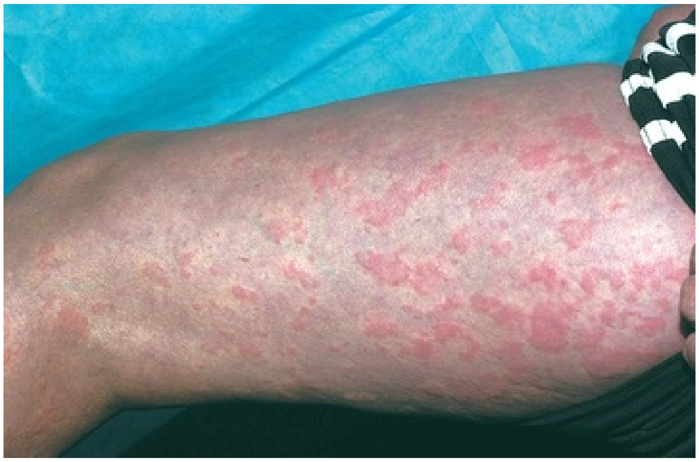

FIG. 188.8 **Urticarial-like skin rash in a patient with Muckle-Wells syndrome. (Courtesy Dr. D. L. Kastner, National Institutes of Health, Bethesda, Maryland; from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2012, Saunders, Fig 97-14.)**

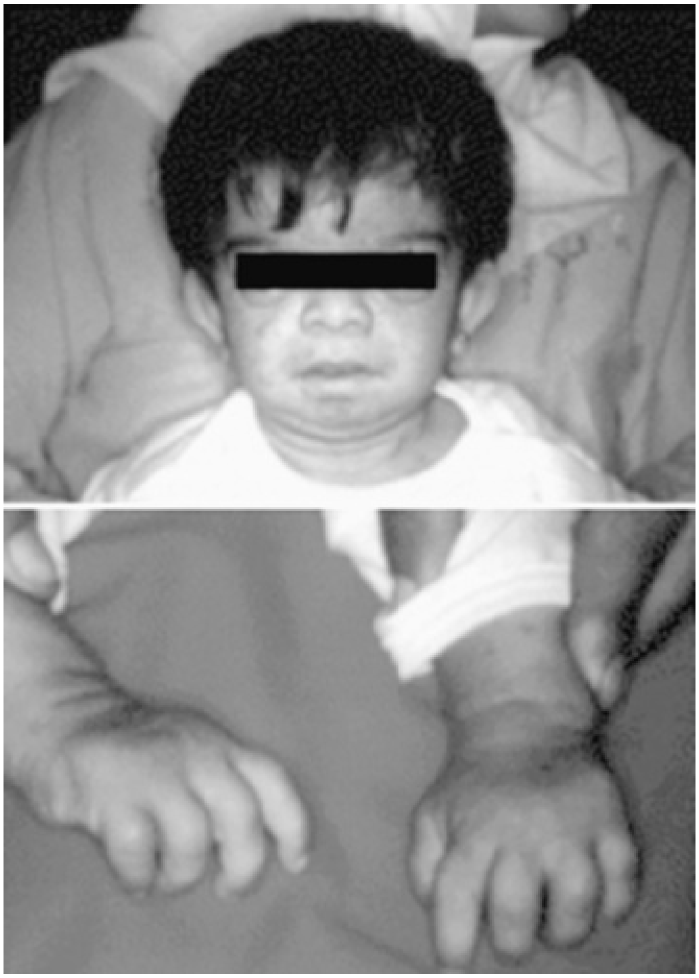

FIG. 188.9 A 3 yr old girl with NOMID/CINCA disease. Note the markedly deformed hands, rash, frontal bossing, and large head. (From Padeh S: Periodic fever syndromes, *Pediatr Clin North Am* 52:577–560, 2005.)

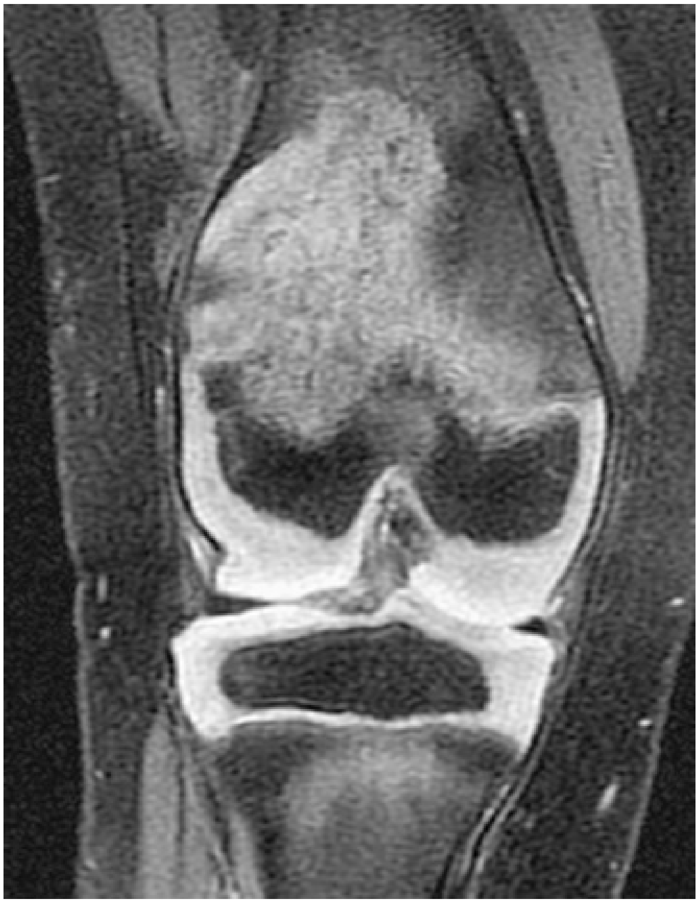

FIG. 188.10 **Metaphyseal bone overgrowth. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in NOMID, the severe form of CAPS; and DIRA. (From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes. *Annu Rev Med* 65:223–244, 2014, Fig 2.)**

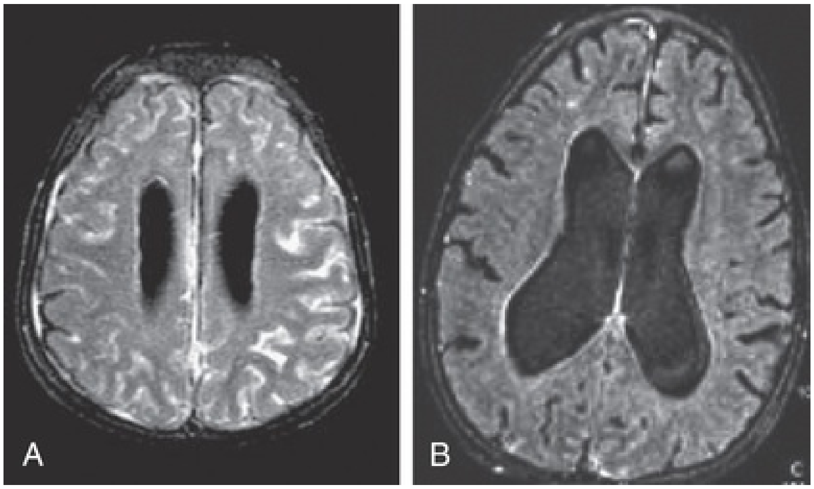

FIG. 188.11 **A,** Leptomeningeal enhancement; **B,** hydrocephalus and

cerebral atrophy. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases, NOMID (severe form of CAPS), and DIRA. (From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes, *Annu Rev Med* 65:223–244, 2014, Fig 2.)

Targeted therapy with anakinra (recombinant IL-1R antagonist) *has been life changing for NOMID patients* , not only controlling fever and rash, but also preventing end-organ damage. Anakinra, rilonocept, and canakinumab are all effective in both FCAS and MWS; they are approved by the U.S. Food and Drug Administration (FDA) for both conditions. Aggressive IL-1 blockade has resulted in attenuation of amyloidosis in the cryopyrinopathies.

Other Mendelian Autoinflammatory Diseases

Syndrome of Pyogenic Arthritis With Pyoderma Gangrenosum and Acne

PAPA syndrome is a rare autosomal dominant disorder caused by mutations in *PSTPIP1*, a gene that encodes the cytoskeletal proline serine threonine phosphatase–interacting protein-1 (PSTPIP). The PSTPIP1 protein interacts with a number of immunologically important molecules, including CD2, the Wiskott-Aldrich syndrome protein (WASP), and pyrin. PAPA-associated *PSTPIP1* mutations greatly increase its affinity to pyrin and cause increased IL-1β production.

Clinical manifestations of PAPA syndrome begin in early childhood with recurrent episodes of sterile, pyogenic arthritis that leads to erosions and joint destruction, and appears to develop spontaneously or after minor trauma. Fever is not a dominant feature. Cutaneous manifestations tend to develop in adolescence, at which time patients are prone to developing severe cystic acne. Additionally, PAPA patients commonly develop ulcerating pyoderma gangrenosum lesions (Fig. 188.12), and some develop pathergy reactions.

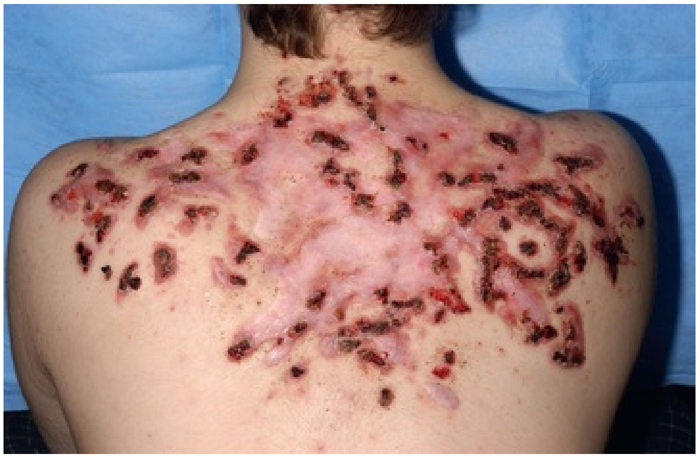

FIG. 188.12 **Pyoderma gangrenosum lesions in a patient with PAPA syndrome and the A230T mutation in *PSTPIP1.* Note the diffuse scarring indicative of prior lesions on his upper back.**

The treatment of PAPA syndrome may involve the use of corticosteroids, IL-1 antagonists, and TNF-α inhibitors, sometimes in combination. The joint manifestations of PAPA appear to respond to IL-1 blockade, whereas the cutaneous manifestations seem to respond more favorably to TNF-α blockade. Local measures, such as joint aspiration and drainage and intensive wound care, are also important in the care of PAPA patients, as is pain management for cutaneous disease. Caution should be taken when prescribing sulfonamides because some PAPA patients develop pancytopenia.

Deficiency of Interleukin-1 Receptor Antagonist

DIRA is an autosomal recessive autoinflammatory disease that is distinct from the cryopyrinopathies. DIRA typically presents in the neonatal period with systemic inflammation and a neutrophilic pustulosis, sterile multifocal osteomyelitis, widening of the anterior ends of the ribs, periostitis, and osteopenia (Figs. 188.13 and 188.14). Although fever is not a prominent clinical feature, patients do have greatly elevated acute-phase reactants. Multiorgan failure and pulmonary interstitial fibrosis can occur and can be fatal.

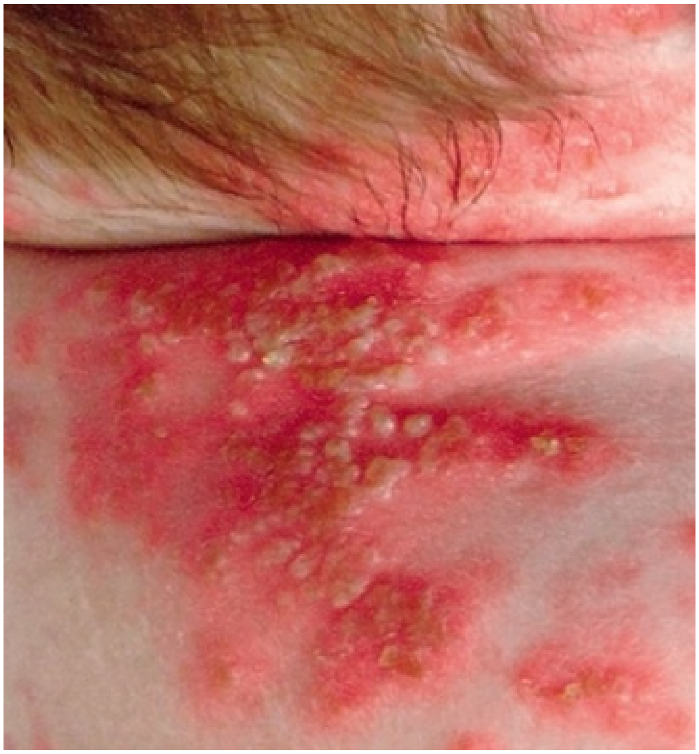

FIG. 188.13 **Pustular rash. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases, NOMID (severe form of CAPS), and DIRA. This can also be seen in deficiency of IL-36 receptor antagonist (DITRA). (From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes, *Annu Rev Med* 65:223–244, 2014, Fig 2.)**

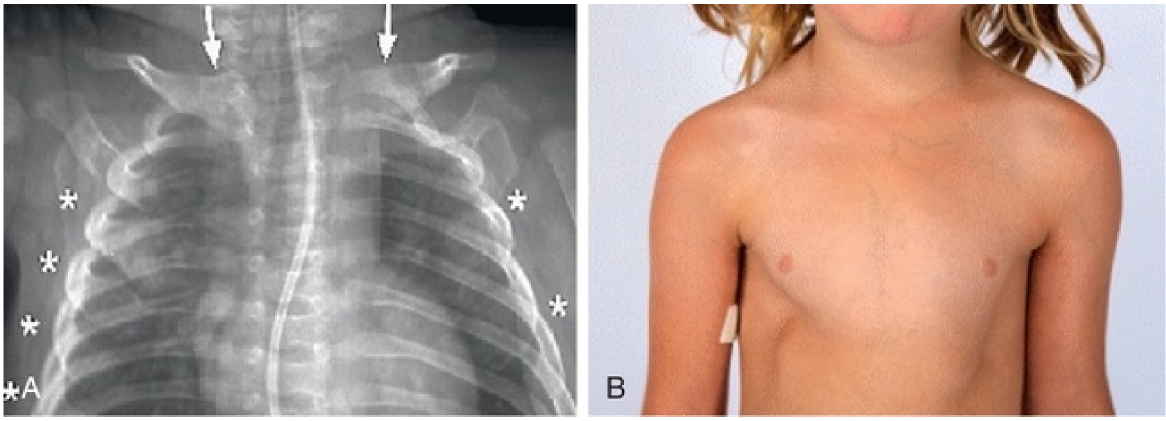

FIG. 188.14 **A,** Widening of multiple ribs (*) and clavicles *(arrows)* in DIRA osteomyelitis; **B,** chest deformity. Inflammatory clinical manifestations and organ damage in the IL-1-mediated diseases, NOMID, and DIRA. (From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes, *Annu Rev Med* 65:223–244, 2014, Fig 2.)

DIRA is caused by loss-of-function mutations in *IL1RN* , encoding the IL-1R antagonist. Because of the lack of antagonistic activity, the cells are hyperresponsive to IL-1β stimulation. Numerous treatments for DIRA have been tried, including NSAIDs, glucocorticoids, intravenous immune globulin (IVIG), methotrexate, cyclosporine, and etanercept. However, *anakinra is the treatment of choice,* essentially replacing the lost protein and resulting in a rapid clinical response. Anakinra is dosed daily, with the dose titrated to achieve a normal CRP. There are now longer-acting anti-IL-1 agents, canakinumab and rilonacept, which are effective and require less frequent dosing than anakinra.

Blau Syndrome

Blau syndrome is a rare autosomal dominant disorder that manifests as early-onset (<5 yr of age) granulomatous arthritis, uveitis, and rash. The arthritis may affect the ankles and wrists and may lead to flexion contractures of the fingers and toes (camptodactyly). **Early-onset sarcoidosis** presents with a similar clinical picture, sometimes with visceral involvement, and both conditions are caused by mutations in the caspase recruitment domain protein 15 (CARD15), also known as nucleotide-binding oligomerization domain-2 protein (NOD2). NOD2 is an intracellular sensor of bacterial products in DCs, myelomonocytic cells, and Paneth cells. Mutations in the NACHT oligomerization domain of this protein cause Blau syndrome/early-onset sarcoidosis, whereas variants primarily in the leucine-rich repeat domain are associated with susceptibility to **Crohn disease** . Corticosteroids have been the mainstay of therapy for Blau syndrome. There are a number of case reports of the beneficial effects of TNF-α inhibitors in Blau syndrome.

Autoinflammation With Phospholipase Cγ$_2$ –Associated Antibody Deficiency and Immune Dysregulation

APLAID is a dominantly inherited disorder characterized by recurrent blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, absence of autoantibodies, and mild immunodeficiency. Rash is the first manifestation of APLAID, which is described as a full-body epidermolysis bullosa–like eruption. Over time, this rash changes to recurrent plaques and vesiculopustular lesions that are triggered by heat and sunlight. Colitis also presents in childhood before age 5 yr. Ocular manifestations begin before age 1 yr and include corneal ulcerations and erosions as well as cataracts. Immune manifestations include markedly decreased class-switched memory B cells, resulting in low IgM and IgA.

Patients with APLAID show a gain-of-function missense mutation in the autoinhibitory region of phospholipase Cγ_2 (PLCγ_2), leading to increased activity of downstream mediators and stimulation of lymphocytes. Despite the enhanced signaling, the resulting populations of immune cells have poor function. Interestingly, a different mutation in the PLCγ_2 complex leads to a syndrome known as **PLCγ_2 -associated antibody deficiency and immune dysregulation (PLAID)** , characterized by cold-induced urticaria, hypogammaglobulinemia with resulting susceptibility to infection, and autoimmunity.

Because of the low number of affected patients described, there are no agreed treatment regimens for APLAID. Patients have been treated with NSAIDs, and corticosteroids can be effective, but side effects limit their long term use. TNF-α inhibitors and IL-1 inhibitors have been used with some success.

Deficiency of Adenosine Deaminase 2

DADA2 is an autoinflammatory disorder caused by loss-of-function mutations in *CECR1* , encoding adenosine deaminase 2. DADA2 presents with recurrent fevers and a spectrum of vascular manifestations that includes livedo racemosa, early-onset ischemic lacunar strokes, and systemic vasculitis of medium side vessels similar to **polyarteritis nodosa** . The lacunar strokes, typically affecting the deep brain nuclei and the brainstem, transpire before age 5 yr and typically occur during inflammatory episodes. The livedoid rash is also a prominent feature during inflammatory episodes, and biopsies demonstrate a predominance of neutrophils and macrophages as well as vasculitis in medium-sized vessels. Acute-phase reactants are typically elevated. Other features include ophthalmologic involvement, various degrees of lymphopenia, hypogammaglobulinemia (usually IgM), hepatosplenomegaly, portal hypertension, and neutropenia. Patients may meet criteria for polyarteritis nodosa and can exhibit digit necrosis and Raynaud phenomenon.

ADA2 is produced primarily by monocytes and macrophages, is found in plasma, and appears to act as a growth and differentiation factor for a subset of inflammatory macrophages. Numerous antiinflammatories have been tried in patients with DAD2, including glucocorticoids and cyclophosphamide. TNF-α inhibitors (etanercept or adalimumab) are the mainstay of treatment, and anecdotal reports have shown a benefit of anakinra. Macrophages and monocytes are the main sources of ADA2, raising the possibility of bone marrow transplant to achieve a permanent cure.

Sideroblastic Anemia With Immunodeficiency, Fevers, and Development Delay

SIFD is a syndrome characterized by systemic inflammation, fevers, enteritis, and sideroblastic anemia and caused by biallelic mutations in *TRNT1* . SIFD presents in infancy with fever, elevated inflammatory markers, gastroenteritis, and anemia. Bone marrow biopsies demonstrate ringed sideroblasts. Other features include hypogammaglobulinemia, B-cell lymphopenia, developmental delay, and variable neurodevelopmental degeneration, seizures, and sensorineural hearing loss. Brain imaging was notable for cerebellar atrophy, delayed white matter myelination, and decreased perfusion. Other, isolated clinical features include nephrocalcinosis, aminoaciduria, ichthyotic skin, cardiomyopathy, and retinitis pigmentosa. TRNT1 is an RNA polymerase that is necessary for maturation of cytosolic and mitochondrial transfer RNAs, by the addition of 2 cytosines and 1 adenosine to the tRNA ends.

Symptomatic treatment with regular blood transfusions and immunoglobulin replacement therapy is the mainstay of SIFD therapy. Iron overload from the transfusion often requires chelation therapy. Anakinra relieved the febrile episodes in one patient but did not alter the other clinical manifestations. Patients with SIFD have a high mortality rate. One patient underwent hematopoietic bone marrow transplantation at 9 mo of age that resulted in correction of the hematologic and immunologic abnormalities.

Deficiency of Interleukin-36 Receptor Antagonist (DITRA)

DITRA is characterized by episodes of diffuse erythematous pustular rash (generalized pustular psoriasis), fevers, general malaise, and systemic inflammation. Attacks can be triggered by events such as infections, pregnancy, or menstruation or can occur randomly. The underlying genetic etiology has been determined to be autosomal recessive mutations in the *IL36RN* gene, which encodes an IL-36R antagonist. IL-36 is related to and acts similarly to IL1R antagonist, preventing production of inflammatory cytokines such as IL-8. Interestingly, the rash of DITRA is similar to the rash of DIRA (IL-1R deficiency; see earlier), but DITRA is largely skin limited. DITRA has been treated with various modalities, including vitamin A analogs, cyclosporine, methotrexate, and TNF-α inhibitors. The use of anakinra has been described in case reports and results in alleviation of the symptoms.

Familial Cold Autoinflammatory Syndrome Type 2

Mutations in *NLRP12* lead to a periodic fever syndrome characterized by fevers >40°C, arthralgias, and myalgias lasting from 2-10 days. This disorder is named FCAS2 because these episodes can be precipitated by cold. Clinical findings may include an urticarial-like rash, abdominal pain and vomiting, aphthous ulcers, and lymphadenopathy. As with Muckle-Wells syndrome, sensorineural hearing loss and optic neuritis have been described. NALP12 is a member of the CATERPILLAR family of proteins, which are important in innate immunity. Similar to Toll-like receptors (TLRs) that act to recognize pathogen-associated molecular patterns (PAMPs), NLRP12 also senses PAMPs and can lead to the activation of the inflammasome and generation of IL-1β. Treatment of *NALP12* mutations was difficult until the advent of anti–IL-1 agents (e.g., anakinra), which are the preferred treatment for FCAS2 and result in remarkable resolution of symptoms. Colchicine can be partially effective, and systemic glucocorticoids can reduce the duration of the attacks.

Autoinflammation With Enterocolitis

A disorder caused by mutations in *NLRC4* was described with neonatal-onset enterocolitis, fever, and autoinflammatory episodes. Inflammatory markers are typically elevated, including CRP and ferritin. **Macrophage activation syndrome** , characterized by pancytopenia, hypertriglyceridemia, and coagulopathies, is common during acute flares, which can be precipitated by emotional and physical stress. Recurrent myalgias with febrile episodes often occur as well. This disorder is caused by gain-of-function missense mutations in NOD-like receptor C4 (NLRC4), which normally aids in the activation of the inflammasome. The resulting protein leads to constitutive production of IL-1. The mainstay of treatment is anti-IL-1 agents such as anakinra, canakinumab, and rilonacept. Before their diagnosis, patients with *NLRC4* mutations had been treated with colchicine and oral glucocorticoids, with varying success.

Majeed Syndrome

Majeed syndrome is an autosomal recessive disorder caused by mutations in the *LPIN2* gene (see Table 188.4). The clinical manifestation of Majeed syndrome begin in childhood with recurrent fevers, sterile osteomyelitis, congenital dyserythropoietic anemia (CDA), neutrophilic dermatosis, failure to thrive, and hepatomegaly. Treatment of Majeed syndrome has included NSAIDs, corticosteroids, and IL-1R antagonist. How mutations in *LPIN2* lead to an autoinflammatory disorder is not known.

Interferonopathies

Type 1 interferons (IFN-α and IFN-β) are the first line of defense against viral infections and are produced by a variety of cell types. During viral infections, a variety of products are made by the virus, including ssRNA, dsRNA, and CpG-containing DNA, and are recognized by intracellular sensors. These sensors then induce type 1 IFN production that activates IFN receptors and activates IFN-responsive genes to help control the spread of the virus until the adaptive immune system can be activated to clear the virus. Inappropriate activation of these pathways leads to IFN production and interferonopathies.

Chronic Atypical Neutrophilic Dermatosis With Lipodystrophy and Elevated Temperature

CANDLE syndrome, also known as **proteasome-associated autoinflammatory syndrome (PRAAS)** or **joint contractures, muscular atrophy, panniculitis-induced lipodystrophy (JMP) syndrome** , is an autosomal recessive disease. Patients present early in life with recurrent fevers and systemic inflammation; skin involvement, including annular erythema, erythema nodosum–like panniculitis, or neutrophilic dermatosis; small joint contractures; lipodystrophy; muscle atrophy or myositis; violaceous eyelid swelling; and anemia. Conjunctivitis, aseptic meningitis, and organomegaly are common. Acute-phase reactants and platelet counts are elevated. Autoimmunity can occur, including Coombs-positive hemolytic anemia and hypothyroidism. Intelligence and development are typically spared, although mild developmental delays have been reported. CANDLE is caused by loss-of-function mutations in *PSMB8*, the gene that encodes the β5i subunit of the proteasome. Proteosomes are important in the degradation of ubiquinated proteins to ensure proper protein homeostasis, and defects in proteasomes result in cellular stress and inflammatory cytokine release, including type 1 interferons.

There is no established treatment for CANDLE, although multiple treatment modalities have been attempted, including colchicine, dapsone, cyclosporine, infliximab, and etanercept, all with minimal success. Glucocorticoids and methotrexate have provided slight improvement in symptoms. Anakinra has not proved successful, whereas IL-6–blocking agents have shown some benefit. Since interferon receptors use the JAK/STAT pathway to signal, JAK inhibitors (tofacitinib, ruxolitinib, and baricitinib) show promise.

STING-Associated Vasculopathy With Onset in Infancy

SAVI is a rare disorder that presents in infancy. It is caused by mutations in the *TMEM173* gene, which encodes for the stimulator of interferon genes (STING). Systemic inflammation is an early manifestation, with fever and elevated inflammatory markers. Skin involvement includes a neutrophilic rash as well as violaceous lesions of fingers, toes, nose, cheeks, and ears. These lesions worsen over time and can become necrotic with vascular occlusion. Histology of the lesions reveals dermal inflammation with leukocytoclastic vasculitis and microthrombotic angiopathy. Since STING is also expressed in pulmonary epithelium, SAVI patients also developed pulmonary complications, including paratracheal adenopathy, interstitial lung disease, and fibrosis.

STING is an adapter protein of the intracellular DNA sensing machinery and mediates the production of interferon-β (IFN-β). The IFN-β then signals through the IFN receptor by activating the JAK/STAT signaling pathway and downstream IFN-responsive genes, including IL-6 and TNF-α. Mutations in STING that cause SAVI are de novo gain-of-function mutations that activate spontaneous IFN-β production.

Treatment options for patients with SAVI are limited at this time, although recent data with JAK inhibitors (tofacitinib, ruxolitinib, and baricitinib) have shown promise in blocking IFN-β receptor signaling and the activation of IFN-response genes.

Genetically Complex Autoinflammatory Diseases

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis

PFAPA is the most common recurrent fever syndrome in children. It usually presents between ages 2 and 5 yr with recurring episodes of fever, malaise, exudative-appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, oral aphthae, and less often headache, abdominal pain, and arthralgia. The episodes last 4-6 days, regardless of antipyretic or antibiotic treatment, and often occur with clock-like regularity on 3-6 wk cycles. Findings during the episodes may include mild hepatosplenomegaly, mild leukocytosis, and elevated acute-phase reactants. Both the frequency and the intensity of the episodes diminish with increasing age. The etiology and pathogenesis of PFAPA remain unknown.

Most patients show dramatic response to a single oral dose of prednisone (0.6-2.0 mg/kg), although this approach does not prevent recurrence and may actually shorten the interval between flares. Cimetidine at 20-40 mg/kg/day is effective at preventing recurrences in approximately one third of cases. Small series have shown that anakinra may be effective during a flare, but because corticosteroids are effective, this may not be a cost-effective approach. Colchicine may extend the time between flares. Complete resolution has been reported after tonsillectomy, although medical management should be the first approach.

Chronic Recurrent Multifocal Osteomyelitis

CRMO is a form of inflammatory bone disease most frequently seen in children (see Table 188.4). Histologically and radiologically, CRMO is virtually indistinguishable from infectious osteomyelitis (Fig. 188.15). Patients typically present with bone pain and may also have fever, soft tissue swelling, and elevated acute-phase reactants. Cultures are sterile. Typically involved bones include the distal femur, proximal tibia or fibula, spine, and pelvis. Both metaphyseal and epiphyseal lesions may occur; premature physeal closure may develop. Less frequently involved bones include the clavicle and mandible. The differential diagnosis includes infectious osteomyelitis, histiocytosis, and malignancy (neuroblastoma, lymphoma, leukemia, Ewing sarcoma). **SAPHO** (synovitis, acne, pustulosis, hyperostosis, and osteitis) may be an adult equivalent to CRMO. The etiology of sporadic CRMO is unknown. CRMO is seen in Majeed syndrome (see earlier), in association with inflammatory bowel disease, and inflammatory skin disease such as palmoplantar pustulosis. Initial therapy includes NSAIDs. Second-line treatments include corticosteroids, TNF inhibitors, and bisphosphonates.

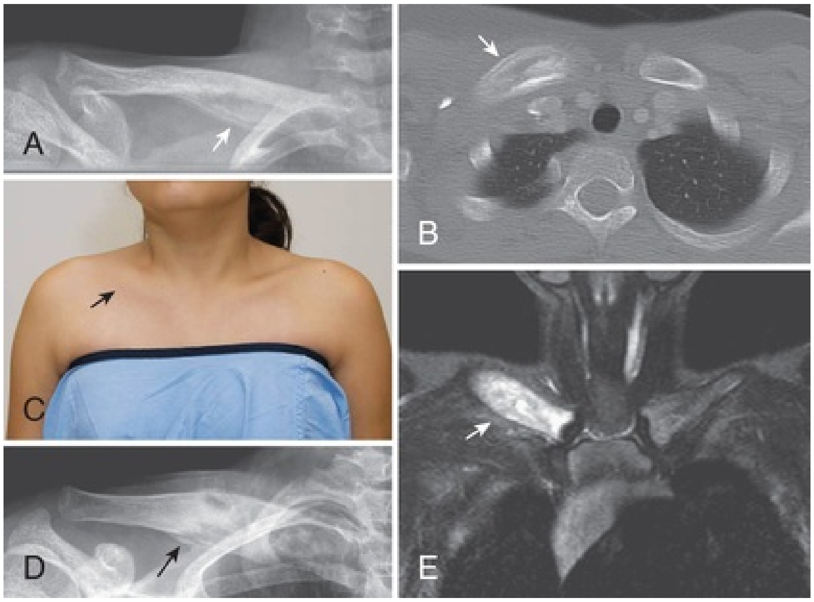

FIG. 188.15 Clavicular involvement in chronic recurrent multifocal osteomyelitis. Adolescent female with unilateral clavicular involvement. A, Plain radiograph of the right clavicle at presentation reveals widening of the medial two thirds, with associated periosteal reaction. B, Corresponding CT scan of the right clavicle demonstrates expansion of the medial right clavicle with areas of increased sclerosis accompanied by a surrounding periosteal reaction *(arrow)* . C, Flare of disease 18 months later showing further clavicular enlargement (clinical photo). D, Plain radiograph of the right clavicle at that time demonstrates marked interval sclerosis and thickening. E, MRI at the same time shows increased signal intensity on fat-suppressed contrast-enhanced T1-weighted images of the right medial clavicle consistent with continued inflammation. (Images courtesy Dr. Paul Babyn, University of Saskatchewan and Saskatchewan Health Authority, Saskatchewan, Canada.)

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CHAPTER 189

Amyloidosis

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Amyloidosis comprises a group of diseases characterized by extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues.

Etiology

Amyloidosis is a disease caused by protein misfolding. These misfolded proteins infiltrate, aggregate, and form insoluble fibrils that can affect the normal function of a number of vital organs.

In the amyloidosis nomenclature, a distinction is made between amyloidosis that develops from mutations in the *amyloid fibril protein itself* and amyloidosis associated with genetic mutation in nonamyloid proteins. The former are referred to as **hereditary amyloidoses** ; examples include mutations in the genes for transthyretin and apolipoprotein A, both of which are uncommon in young children. This is in contrast to **amyloid A (AA) amyloidosis** , which develops in patients with chronic inflammatory states. It is estimated that, worldwide, approximately 45% of all amyloid cases are AA amyloidosis. In the past, chronic infectious diseases such as tuberculosis, malaria, leprosy, and chronic osteomyelitis accounted for most cases of AA amyloidosis. With effective treatment for these infections, other causes of AA have become more common. A number of chronic inflammatory rheumatic diseases, such as **rheumatoid arthritis (RA)** , **juvenile idiopathic arthritis (JIA)** , and **ankylosing spondylitis** , as well as hereditary autoinflammatory diseases, have an increased risk for the development of AA amyloidosis. AA amyloidosis has also been associated with granulomatous diseases such as sarcoidosis, cystic fibrosis, Crohn disease, malignancies such as mesothelioma and Hodgkin diseases, intravenous drug abuse, and other infections, such as bronchiectasis and HIV.

Approximately 6% of AA amyloidosis cases have no identified disease association. **AL amyloidosis** (formerly known as *idiopathic amyloidosis* or *myeloma-associated amyloidosis*) is extremely rare in children, occurring in middle-aged or older individuals.

Epidemiology

Only AA amyloidosis affects children in appreciable numbers. The factors that determine the risk for amyloidosis as a complication of inflammation are not clear, because many individuals with long-standing inflammatory disease do not demonstrate tissue amyloid deposition, whereas some children with relatively recent onset of disease may develop amyloid. In developed countries, before the initiation of therapy with disease-modifying antirheumatic drugs (DMARDs) and biologic agents, RA was the most common inflammatory disease associated with AA amyloidosis. Patients who had a long history of poorly controlled severe disease with extraarticular manifestations were the most at risk for developing amyloidosis, and the median time from first symptoms of their rheumatic condition to the diagnosis of amyloidosis was 212 mo. The full effect of DMARD and biologic therapy in RA-associated amyloidosis has yet to be fully appreciated, but studies are showing a sustained decline in the number of new cases.

JIA is another rheumatic disease associated with development of AA amyloidosis, with the highest prevalence in patients with systemic JIA, followed by those with polyarticular disease (see Chapter 180). In the pre-DMARDs and prebiologics era, the prevalence of AA amyloidosis in JIA patients ranged from 1–10%. Higher prevalence was seen in Northern European patients, especially Polish patients, who had a prevalence of 10.6%; lower prevalence was observed in North America. The reasons for this discrepancy are not completely understood, although it is speculated that selection bias, genetic background, and tendency toward earlier, more aggressive therapy in North Americans may have played a role. AA amyloidosis has been observed in JIA patients as early as 1 yr after diagnosis. Similar to RA, the occurrence of new amyloid cases has significantly decreased in the past 20 yr because of the increased efficacy of treatment with DMARDs and biologics.

The **hereditary autoinflammatory diseases** define a group of illnesses characterized by attacks of seemingly unprovoked recurrent inflammation without significant levels of either autoantibodies or antigen-specific T cells, which are typically found in patients with autoimmune diseases (see Chapter 188). Although seemingly unprovoked, these attacks are often initiated by stress, immunization, or trauma, suggesting that gene-environment interactions play an important role in pathogenesis. Although there is some variability among the autoinflammatory diseases, common findings include fevers, cutaneous rashes, arthritis, serositis, and ocular involvement. The inflammatory attacks are accompanied by intense acute-phase responses (erythrocyte sedimentation rate and C-reactive protein) and high levels of serum amyloid A (SAA). Amyloidosis AA is associated with some but not all the hereditary autoinflammatory diseases.

Familial Mediterranean fever (FMF) is the most common of the mendelian autoinflammatory diseases and is seen most frequently in the Armenian, Arab, Turkish, and Sephardi Jewish populations. FMF is an autosomal recessive disease that results from mutations in the *MEFV* gene, which encodes the pyrin/marenostrin protein. *MEFV* mutations affecting the M680 and M694 amino acid residues are associated with early onset of FMF, severe disease, and an increased risk of AA amyloidosis. Patients residing in Armenia, Turkey, and Arabian countries have an increased risk of developing AA amyloidosis compared to patients with the same mutations of *MEFV* living in North America. While one may assume that FMF patients who have frequent, severe attacks would be at the most risk for the development of AA amyloidosis, this is not always the case. Some patients have had a history of frequent attacks and never develop amyloidosis, and others develop amyloidosis at an early age. There is also a subset of FMF patients referred to as **phenotype II** . These patients present with AA amyloidosis before their first FMF attack. In this group the distribution of the common *MEFV* mutation is similar to that found in FMF patients with typical symptoms.

Tumor necrosis factor receptor–associated periodic syndrome (TRAPS) is associated with mutations in the *TNFRSF1A* gene, which encodes the 55 kDa tumor necrosis factor (TNF) receptor protein (TNFR1). It is estimated that 14-25% of patients with TRAPS develop AA amyloidosis. Patients with mutations in *TNFRSF1A* that affect cysteine residues have the highest risk of developing AA amyloidosis. It is thought that these cysteine residues participate in assembly of disulfide bonds important for TNFR1 folding, and that disruption of these bonds affects protein folding.

Mutations in the *NLRP3* gene (also known as *CIAS1* , cold-induced autoinflammatory syndrome 1) cause 3 clinically distinct diseases: **familial cold autoinflammatory syndrome (FCAS)** , **Muckle-Wells syndrome (MWS)** , and

neonatal-onset multisystem inflammatory disease (NOMID) , also known as **chronic infantile neurologic cutaneous and articular (CINCA) syndrome** . Mutations in *NLRP3* are inherited in an autosomal dominant fashion or as de novo mutations in patients with the most severe disease. A smaller portion of patients have been found to carry somatic mutations in *NLRP3.*

FCAS is generally the least severe of the cryopyrinopathies and is rarely associated with AA amyloidosis. MWS presents with fevers, myalgias, arthralgias, urticarial-like rash, and progressive sensorineural hearing loss. AA amyloidosis is quite common in MWS, affecting up to one third of the patients. NOMID/CINCA is the most severe cryopyrinopathy. Historically, 20% of patients died before reaching adulthood, but with current therapies, many are living longer lives. Some NOMID patients develop AA amyloidosis as they get older, although not as often as MWS patients, possibly because of a shortened life span in these patients.

Hyper-IgD syndrome (HIDS) is another autoinflammatory disease that presents in early childhood with chills, high fevers, abdominal pain, lymphadenopathy, and occasional rash. HIDS is an autosomal recessive disease that involves loss-of-function mutations in the *MVK* gene that encodes the mevalonate kinase enzyme. Severe *MVK* mutations that completely abolish enzyme activity are identified in patients with **mevalonic aciduria** , who present with recurrent fevers, dysmorphic features, and developmental delays. HIDS-associated mutations are milder loss-of-function mutations. Inflammatory markers, including SAA, are high during attacks and may remain elevated in the intercurrent period. AA amyloidosis is rare in HIDS but has been reported.

Although seen less frequently than in the hereditary periodic fever syndromes, the risk of AA amyloidosis has been well established in patients with Crohn disease. AA amyloidosis occurs in an estimated 1% of U.S. patients and up to 3% in Northern European patients. Conversely, AA amyloidosis presenting in patients with ulcerative colitis is extremely rare, with estimated prevalence of 0.07%. The patients have a long-standing history of aggressive, poorly controlled disease, although there are reports of amyloidosis in patients with well-controlled inflammatory markers.

Transthyretin-related hereditary amyloidosis is an autosomal dominant disorder with variable penetrance and onset in the 2nd to 3rd decade of life. More than 120 single or double mutations in the *TTR* gene are responsible for disease. Manifestations include neuropathy (familial amyloidotic polyneuropathy: motor, sensory, autonomic), familial amyloid cardiomyopathy, nephropathy, and ocular disease.

Pathogenesis

The deposition of AA amyloid fibrils is a result of a prolonged inflammatory state that leads to misfolding of the AA amyloid protein and deposition into tissues. The precursor protein of the fibrils in AA amyloidosis is an apolipoprotein called *serum amyloid A* (SAA). SAA is expressed by 3 different genes that are localized on chromosome p15.1. SAA1 and SAA2 are 2 isoforms that are acute-phase reactants synthesized by the liver that can form amyloid. SAA is produced in response to proinflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-α and can increase >1,000-fold during inflammation. It has been speculated that SAA has a role as a chemoattractant and in lipid metabolism. Supporting this theory is the finding that amyloid deposition occurs initially in organs that are major sites of lipid and cholesterol metabolism, such as the kidney, liver, and spleen. Approximately 80% of secreted SAA1 and SAA2 are bound to lipoprotein.

Under normal circumstances, SAA secreted by the liver is completely degraded by macrophages. The secreted SAA protein is 104 amino acids in length and is primarily secreted in an α-helix structure. For reasons not completely understood, patients with AA amyloidosis have a flaw resulting in incomplete degradation and accumulation of intermediate SAA products. In these patients, SAA is transferred to the lysosome, where the c-terminal portion of the SAA protein is cleaved, allowing the remaining protein to fold into a β-pleated sheet configuration. Deposited amyloid contains only 66-76 amino acids, compared to the 104 in secreted SAA. These cleaved fragments polymerize and form fibrils that are deposited in the extracellular space and bind proteoglycans and other proteins such as serum amyloid P. These fibrils then become resistant to proteolysis and deposit in organ tissues.

Development of AA amyloid may be associated with a number of risk factors. The gene encoding SAA1 has polymorphisms that, when present, carry a 3-7–fold increased risk for the development of AA amyloidosis. Caucasian patients with RA, JIA, or autoinflammatory diseases who have the SAAα/α (alpha/alpha) genotype have an increased risk of amyloidosis. In that group of patients, the SSA1γ (gamma) allele is associated with a decreased risk of amyloidosis. Interestingly, the risk in Japanese patients is reversed, with SAAα/α genotype is associated with a decreased susceptibility to amyloidosis development but the

SAA1γ genotype carries an increased risk.

Clinical Manifestations

Although organ involvement may vary, AA amyloidosis most frequently affects the kidneys; 90% of patients have some degree of renal involvement. Unexplained proteinuria may be the presenting feature in some patients. Nephrotic syndrome and renal failure may develop if the underlying inflammatory condition is not controlled or if diagnosis is delayed. Median survival after diagnosis has been reported to be 133 mo; patients with higher SAA levels had significantly higher risk of death than those with lower SAA levels. Gastrointestinal involvement is seen in approximately 20% of patients and usually manifests as chronic diarrhea, GI bleeding, abdominal pain, and malabsorption. When biopsied, the testes are frequently involved (87%). Relatively uncommon findings associated with AA amyloidosis include anemia, amyloid goiter, hepatomegaly, splenomegaly, adrenal involvement, and pulmonary involvement. Tissues, such as the heart, tongue, and skin, are rarely involved.

Diagnosis

The diagnosis of amyloidosis is established by biopsy demonstrating amyloid fibril proteins in affected tissues. The tissues tested include kidney, rectum, abdominal fat pad, and gingiva. Amyloid deposits are composed of seemingly homogeneous eosinophilic material that stains with Congo red dye and demonstrates the pathognomonic “apple-green birefringence” in polarized light. Tissue and genetic testing is useful for transthyretin amyloidosis.

Laboratory Findings

Patients with AA amyloidosis usually show elevated acute-phase reactants and high levels of immunoglobulins. In the United States, specific laboratory testing is not commercially available for AA amyloid, but in other countries, SAA levels can be monitored and used to guide response to treatment.

Treatment

There is no established therapy for AA amyloidosis, and thus the primary approach is aggressive management of the underlying inflammatory or infectious disease, which decreases levels of SAA protein. As newer therapies are developed to treat the underlying condition, emerging evidence shows that the incidence of AA amyloidosis is decreasing. *Colchicine* is effective not only in controlling the attacks of FMF but also in preventing the development of amyloidosis associated with FMF. Children with FMF who are homozygous for the M694V mutation in *MEFV* are at greater risk for development of amyloidosis and should be monitored closely.

Unlike AA amyloidosis associated with FMF, AA amyloidosis associated with other autoinflammatory diseases (including TRAPS, cryopyrin-associated periodic syndrome, and rarely HIDS) and chronic rheumatic diseases (JIA, RA, and ankylosing spondylitis) does not respond to colchicine. Although AA amyloidosis associated with JIA may respond to *chlorambucil* , this drug is associated with chromosome breakage and a risk of subsequent malignancy.

Increasing use of biologic medicines (**biologics**) against proinflammatory cytokines to treat RA, JIA, spondyloarthropathies, and the hereditary autoinflammatory diseases seems to impact risk factors for the development of AA amyloidosis. The class of medications referred to as the *anti–TNF-α drugs* have been paramount in the management of RA and other autoimmune disease. In both autoimmune and autoinflammatory conditions with accompanying AA amyloidosis, there are reports documenting the effectiveness of anti-TNF agents in blunting the progression of amyloidosis. Adverse effects of anti-TNF medications include reactivation of tuberculosis and hepatitis B, and thus careful screening should be performed before instituting therapy. Additionally, the development of various antibodies, autoantibodies, and autoimmune disease has been noted in patients taking anti-TNF agents. Extreme caution should be used in prescribing anti-TNF agents to patients with a history of heart failure or demyelinating disease, because use can cause exacerbations in their underlying cardiac and neurologic diseases.

The IL-1 pathway is the target of multiple biologic medications used in autoimmune and autoinflammatory diseases. The 3 available IL-1 antagonists are *anakinra* (IL-1 receptor antagonist), *rilonacept* (soluble IL-1 receptor decoy), and *canakinumab* (long-acting fully humanized IgG_1 anti–IL-1β monoclonal antibody). The various IL-1 inhibitors have been successful at slowing the progression of AA amyloidosis, and in some cases treatment results in regression of amyloid-associated proteinuria.

Tocilizumab , an anti–IL-6 receptor antibody, has been shown to attenuate experimental AA amyloid and to reverse AA amyloidosis complicating FMF, JIA, and RA. A recent trial using *eprodisate disodium* in AA amyloid patients failed to meet its primary end-point of reducing progression to end-stage renal disease.

Transthyretin amyloidosis has been treated with liver transplantation and transthyretin-stabilizing agents.

Prognosis

End-stage renal failure is the underlying cause of death in 40–60% of patients with amyloidosis, with a median survival time from diagnosis of 2-10 yr. According to a large-scale study of 374 patients with AA amyloidosis, the factors associated with a poor prognosis include older age, a lower albumin serum level, end-stage renal disease at baseline, and prolonged serum elevation of SAA. An elevated SAA value was the most powerful risk factor for end-stage renal disease and death from AA amyloidosis.

Prevention

The primary means of preventing AA amyloidosis is treatment of the underlying inflammatory or infectious disease, resulting in decreases in the level of SAA protein and the risk of amyloid deposition. Although the period of latency between the onset of inflammation (of the underlying disease) and the initial clinical signs of AA amyloidosis may vary and is often prolonged, progression of the amyloid depositions can be rapid.

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CHAPTER 190

Sarcoidosis

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Sarcoidosis is a rare multisystem granulomatous disease of unknown etiology. The name is derived from a Greek word meaning "flesh-like condition," in reference to the characteristic skin lesions. There appear to be 2 distinct, age-dependent patterns of disease among children with sarcoidosis. The clinical features in older children are similar to those in adults (pediatric-onset adult sarcoidosis), with frequent systemic features (fever, weight loss, malaise), pulmonary involvement, and lymphadenopathy. In contrast, early-onset sarcoidosis manifesting in children <4 yr of age is characterized by the triad of rash, uveitis, and polyarthritis.

Etiology

The etiology of sarcoidosis remains obscure but likely results from exposure of a genetically susceptible individual to 1 or more unidentified antigens. This exposure initiates an exaggerated immunologic response that ultimately leads to the formation of granulomas. The human major histocompatibility complex is located on chromosome 6, and specific human leukocyte antigen (HLA) class I and class II alleles are associated with disease phenotype. Genetic polymorphisms involving various cytokines and chemokines may also have a role in development of sarcoidosis. Familial clustering supports the contribution of genetic factors to sarcoidosis susceptibility. Environmental and occupational exposures are also associated with disease risk. There are positive associations between sarcoidosis and agricultural employment, occupational exposure to insecticides, and moldy environments typically associated with microbial bioaerosols.

Blau syndrome is an autosomal dominant, familial form of sarcoidosis and is typified by the early onset of granulomatous inflammation involving the skin, eyes, and joints. Missense mutations in the *CARD15/NOD2* gene on chromosome 16 have been found in affected family members and appear to be associated with development of sarcoidosis. The 2 most common amino acid substitutions are R334W (arginine to glutamine) and R334Q (arginine to tryptophan). Similar genetic mutations also have been found in individuals with a sporadic **early-onset sarcoidosis (EOS)** (rash, uveitis, arthritis), suggesting that this nonfamilial form and Blau syndrome are genetically and phenotypically identical (see Chapter 188).

Epidemiology

A nationwide patient registry of childhood sarcoidosis in Denmark estimated the annual incidence to be 0.22-0.27 per 100,000 children. The incidence increases with age, and peak onset occurs at 20-39 yr. The most common age of reported childhood cases is 13-15 yr. Annual incidence is about 11 per 100,000 in adult white Americans and is 3 times higher in blacks. There is no clear sex predominance in childhood sarcoidosis. The majority of U.S. childhood sarcoidosis cases are reported in the southeastern and south-central states.

An international registry and Spanish cohort of Blau syndrome and EOS reported the mean age of disease onset as 30 mo and 36 mo, respectively. All but 3 of these young patients presented before 5 yr of age. There does not appear to be a sex predilection in either condition.

Pathology and Pathogenesis

Noncaseating, epithelioid granulomatous lesions are a cardinal feature of sarcoidosis. Activated macrophages, epithelioid cells, and multinucleated giant cells as well as $CD4^+$ T lymphocytes accumulate and become tightly packed in the center of the granuloma. The causative agent that initiates this inflammatory process is not known. The periphery of the granuloma contains a loose collection of monocytes, $CD4^+$ and $CD8^+$ T lymphocytes, and fibroblasts. The interaction between the macrophages and $CD4^+$ T lymphocytes is important in the formation and maintenance of the granuloma. The activated macrophages secrete high levels of tumor necrosis factor (TNF)-α and other proinflammatory mediators. The $CD4^+$ T lymphocytes differentiate into type 1 helper T cells and release interleukin (IL)-2 and interferon (IFN)-γ, promoting proliferation of lymphocytes. Granulomas may heal or resolve with complete preservation of the parenchyma. In approximately 20% of the lesions, the fibroblasts in the periphery proliferate and produce fibrotic scar tissue, leading to significant and irreversible organ dysfunction.

The sarcoid macrophage is able to produce and secrete 1,25-$(OH)_2$ -vitamin D or *calcitriol*, an active form of vitamin D typically produced in the kidneys. The hormone's natural functions are to increase intestinal absorption of calcium and bone resorption and decrease renal excretion of calcium and phosphate. An excess of calcitriol may result in hypercalcemia and hypercalciuria in patients with sarcoidosis.

Clinical Manifestations

Sarcoidosis is a multisystem disease, and granulomatous lesions may occur in any organ of the body. The clinical manifestations depend on the extent and degree of granulomatous inflammation and are extremely variable. Children may present with nonspecific symptoms, such as fever, weight loss, and general malaise. In adults and older children, pulmonary involvement is most frequent, with infiltration of the thoracic lymph nodes and lung parenchyma. Isolated bilateral hilar adenopathy on chest radiograph is the most common finding (Fig. 190.1), but parenchymal infiltrates and miliary nodules may also be seen (Figs. 190.2 and 190.3). Patients with lung involvement are usually found to have restrictive changes on pulmonary function testing. Symptoms of pulmonary disease are seldom severe and generally consist of a dry, persistent cough.

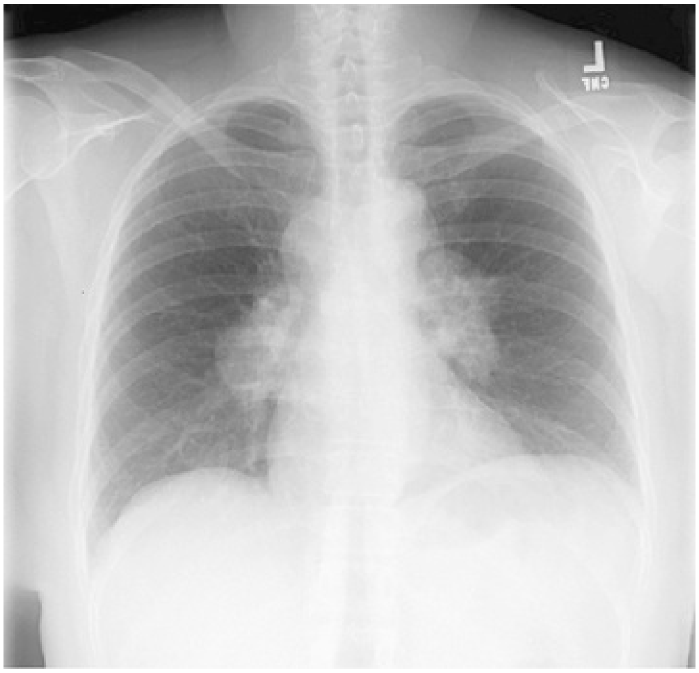

FIG. 190.1 Sarcoidosis. Chest radiograph demonstrating a stage I disease with enlarged mediastinal and hilar lymph nodes. (From Iannuzzi M: Sarcoidosis. In Goldman L, Schafer AI, editors, *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders, Fig 95-1, p 582.)

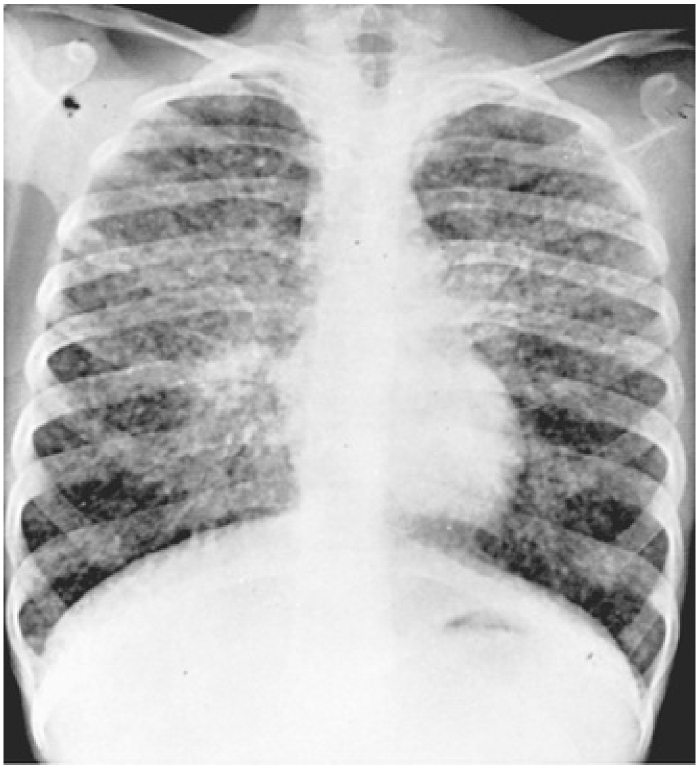

FIG. 190.2 Sarcoidosis. Chest radiograph of 10 yr old girl showing widely disseminated peribronchial infiltrates, multiple small nodular densities, hyperaeration of the lungs, and hilar lymphadenopathy.

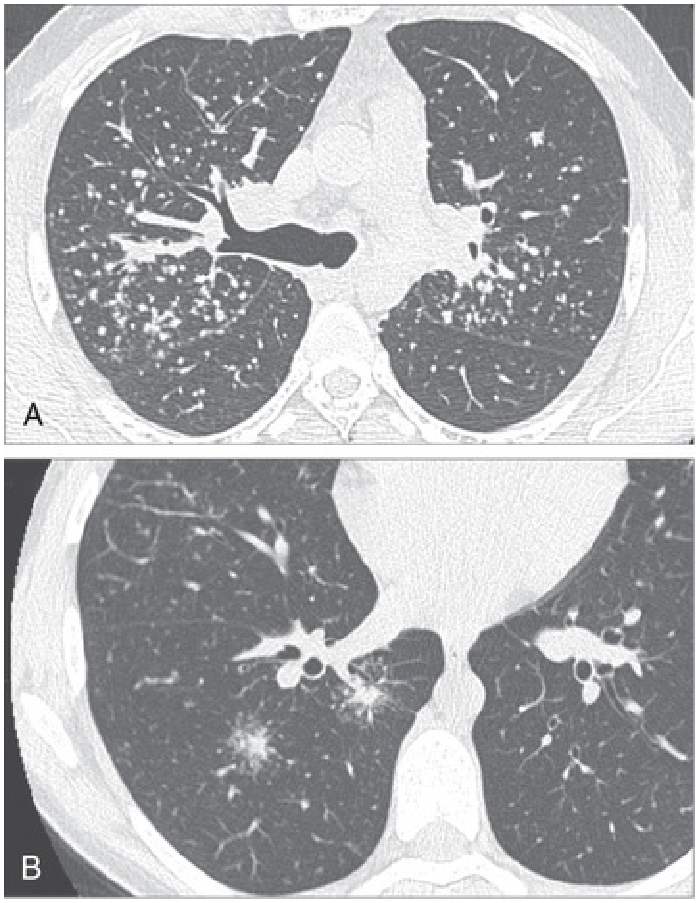

FIG. 190.3 Typical features of lung sarcoidosis on CT. A, Usual perilymphatic distribution of micronodules with fissural spreading. B, Typical nodules with irregular margins and satellite micronodules known as the *galaxy sign* . (From Valerye D, Prasse A, Nunes H, et al: Sarcoidosis, *Lancet* 383:1155–1167, 2014, Fig 2, p 1158).

Extrathoracic lymphadenopathy and infiltration of the liver, spleen, and bone marrow also occur often (Table 190.1). Infiltration of the liver and spleen typically leads to isolated hepatomegaly and splenomegaly, respectively, but actual organ dysfunction is rare. Cutaneous disease, such as plaques, nodules, erythema nodosum in acute disease, or lupus pernio in chronic sarcoidosis, appears in one quarter of cases and is usually present at onset. Red-brown to purple maculopapular lesions <1 cm on the face, neck, upper back, and extremities are the most common skin finding (Fig. 190.4). Ocular involvement is frequent and has variable manifestations, including anterior or posterior uveitis, conjunctival granulomas, eyelid inflammation, and orbital or lacrimal gland infiltration. The arthritis in sarcoidosis can be confused with **juvenile idiopathic arthritis** (JIA). Central nervous system (CNS) involvement is rare in early childhood but may manifest as seizures, cranial nerve involvement, intracranial mass lesions, and hypothalamic dysfunction (Fig. 190.5). Kidney disease occurs infrequently in children but typically manifests as renal insufficiency, proteinuria, transient pyuria, or microscopic hematuria caused by early monocellular infiltration or granuloma formation in kidney tissue. Only a small fraction of children have hypercalcemia or hypercalciuria, which is therefore an infrequent cause of kidney disease. Sarcoid granulomas can also infiltrate the heart and lead to cardiac arrhythmias and, rarely, sudden death. Other rare sites of disease involvement include blood vessels of any size, the gastrointestinal tract, parotid gland, muscles, bones, and testes.

Table 190.1

Sarcoidosis: Extrapulmonary Localizations

	SYMPTOMS
Skin	Papules, nodules, plaques, scar sarcoidosis, lupus pernio, subcutaneous sarcoidosis
Peripheral lymphadenopathy	Mostly cervical or supraclavicular; inguinal, axillary, epitrochlear, or submandibular lymph node sites also possible; painless and mobile
Eye	Anterior, intermediate, or posterior uveitis; retinal vascular change; conjunctival nodules; lacrimal gland enlargement
Liver	Often symptom free; abnormal liver function tests in 20–30% of patients; hepatomegaly; rarely hepatic insufficiency, chronic intrahepatic cholestasis, or portal hypertension
Spleen	Splenomegaly; rarely, pain or pancytopenia; very rarely, splenic rupture
Heart	Atrioventricular or bundle branch block; ventricular tachycardia or fibrillation; congestive heart failure; pericarditis; impairment of sympathetic nerve activity; sudden death
Nervous system	Facial nerve palsy, optic neuritis, leptomeningitis, diabetes insipidus, hypopituitarism, seizures, cognitive dysfunction, deficits, hydrocephalus, psychiatric manifestations, spinal cord disease, polyneuropathy, small-fiber neuropathy
Kidney	Rare symptoms; increased creatininemia sometimes associated with hypercalcemia; nephrocalcinosis; kidney stones
Parotitis	Symmetric parotid swelling; Heerfordt syndrome when associated with uveitis, fever, and facial palsy
Nose	Nasal stuffiness, nasal bleeding, crusting, anosmia
Larynx	Hoarseness, breathlessness, stridor, dysphagia
Bones	Often asymptomatic; hands and feet classically most involved, also large bones and axial skeleton
Skeletal muscles	Proximal muscle weakness, amyotrophy, myalgia, intramuscular nodules
Genitourinary tract	All organs can be involved, including breast, uterus, epididymis, and testicle
Gastrointestinal tract	Most often symptom free, but the esophagus, stomach, small intestine, and colon can be involved

Adapted from Valerye D, Prasse A, Nunes H, et al: Sarcoidosis, *Lancet* 383:1155–1167, 2014 (Table 1, p 1159).

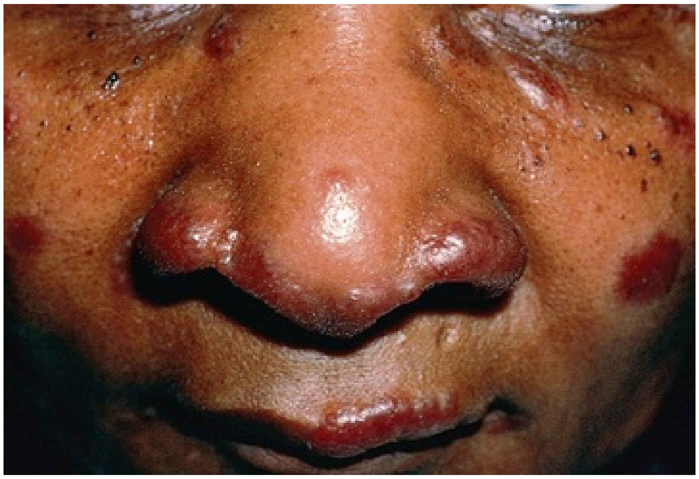

FIG. 190.4 Sarcoidosis nodules on the face. (From Shah BR, Laude TA: *Atlas of pediatric clinical diagnosis,* Philadelphia, 2000, Saunders.)

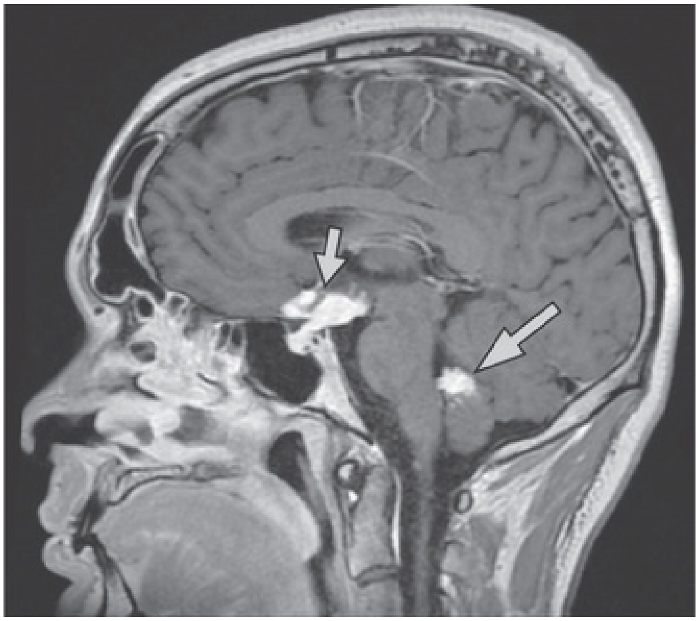

FIG. 190.5 Neurologic involvement in sarcoidosis. Typical involvement of hypothalamus, pituitary gland, and optic chiasm seen on a sagittal gadolinium-enhanced T1-weighted sequence MRI *(small arrow).* Abnormal nodular enhancement of the 4th ventricle is seen *(large arrow).* (Modified from Valerye D, Prasse A, Nunes H, et al: Sarcoidosis, *Lancet* 383:1155–1167, 2014, Fig 3d, p 1160.)

In contrast to the variable clinical presentation of sarcoidosis in older children, **Blau syndrome and EOS** (NOD2-associated sarcoidosis) classically manifests as the triad of uveitis, arthritis, and rash. These classic manifestations do not always occur simultaneously. Skin disease usually develops before 1 yr, arthritis at 2-4 yr, and uveitis before 4 yr. Pulmonary disease and lymphadenopathy are less common. The arthritis is polyarticular and symmetric, with large, boggy effusions. Large and small joints are involved. Tenosynovitis is an associated finding. Joints are stiff and moderately tender. The rash may wax and wane and is diffuse (mostly truncal), erythematous or tan, macular-papular, and often desquamates, at times being confused with eczema or ichthyosis vulgaris. Tender subcutaneous nodules resembling erythema nodosum may be seen on the legs. Noncaseating granulomas are demonstrated on biopsy of the skin or joint synovium. Insidious granulomatous iridocyclitis and posterior uveitis are often bilateral and may progress to **panuveitis** , which has a high risk for vision loss. Iris nodules, photophobia, erythema, cataracts, or glaucoma may be present or develop over time.

Most patients with Blau syndrome and EOS display this more restricted phenotype and develop all or some combination of the rash, arthritis, and uveitis. Many, however, also have an extended phenotype. Additional disease manifestations include fever, hepatosplenomegaly, lymphadenopathy, and lung, kidney, and CNS involvement.

Infantile-onset panniculitis with uveitis and systemic granulomatosis is an uncommon manifestation of sarcoidosis. Sarcoidosis has also been reported in adults treated with type 1 interferons for hepatitis or multiple sclerosis.

Laboratory Findings

There is no single standard laboratory test diagnostic of sarcoidosis. Anemia, leukopenia, and eosinophilia may be seen. Other nonspecific findings include hypergammaglobulinemia and elevations in acute-phase reactants, including erythrocyte sedimentation rate and C-reactive protein value. Hypercalcemia and/or hypercalciuria occur in only a small proportion of children with sarcoidosis. Angiotensin-converting enzyme (ACE) is produced by the epithelioid cells of the granuloma, and its serum value may be elevated, but this finding lacks diagnostic sensitivity and specificity. ACE levels are estimated to be elevated in >50% of children with sarcoidosis. In addition, ACE values may be difficult to interpret because reference values for serum ACE are age dependent. Fluorodeoxyglucose F 18 positron emission tomography can help identify nonpulmonary sites for a diagnostic biopsy.

Diagnosis

Definitive diagnosis ultimately requires demonstration of the characteristic noncaseating granulomatous lesions in a biopsy specimen (usually taken from the most readily available affected organ) and exclusion of other known causes of granulomatous inflammation. Skin and transbronchial lung biopsies have higher yield, greater specificity, and fewer associated adverse events than biopsy of mediastinal lymph nodes or liver. Additional diagnostic testing should include chest radiography, pulmonary function testing with measurement of diffusion capacity, hepatic enzyme measurements, and renal function assessment. Ophthalmologic slit-lamp examination is essential because ocular inflammation is frequently present and may be asymptomatic in sarcoidosis, and vision loss is a sequela of untreated disease.

Bronchoalveolar lavage may be used to assess for disease activity, and the fluid typically reveals an excess of lymphocytes with an increased $CD4^+$ /$CD8^+$ ratio of 2-13 : 1. In addition to flexible bronchoscopy with transbronchial biopsy, endosonographic-guided intrathoracic node aspiration has been valuable in obtaining tissue to assess for noncaseating granulomas.

Differential Diagnosis

Because of its protean manifestations, the differential diagnosis of sarcoidosis is extremely broad and depends largely on the initial clinical manifestations. **Granulomatous infections** , including tuberculosis, cryptococcosis, pulmonary mycoses (histoplasmosis, blastomycosis, coccidioidomycosis), brucellosis, tularemia, and toxoplasmosis, must be excluded. Other causes of granulomatous inflammation are granulomatosis with polyangiitis (formerly Wegener granulomatosis), hypersensitivity pneumonia, chronic berylliosis, and other occupational exposures to metals. Localized granulomatous lesions of the head and neck may be due to **orofacial granulomatosis.** Immunodeficiencies that may manifest with granulomatous lesions include common variable immunodeficiency, selective IgA deficiency, chronic granulomatous disease, ataxia telangiectasia, and severe combined immunodeficiency. Granulomas of the lung, skin, or lymph nodes have been reported in patients treated with anti-TNF agents. Lymphoma should be ruled out in cases of hilar or other lymphadenopathy. Sarcoid arthritis may mimic JIA. Evaluation for endocrine disorders is needed in the setting of hypercalcemia or hypercalciuria.

Treatment

Treatment should be based on disease severity as well as the number and type of organs involved. *Corticosteroids are the mainstay of treatment for most acute and chronic disease manifestations.* The optimal dose and duration of corticosteroid therapy in children have not been established. Induction treatment typically begins with oral prednisone or prednisolone (1-2 mg/kg/day up to 40 mg daily) for 8-12 wk until manifestations improve. Corticosteroid dosage is then gradually decreased over 6-12 mo to the minimal effective maintenance dose (e.g., 5-10 mg/day) that controls symptoms, or discontinued if symptoms resolve. *Methotrexate* or *leflunomide* may be effective as a corticosteroid-sparing agent. On the basis of the role of TNF-α in the formation of granulomas, there is rationale for use of TNF-α antagonists. Results of small clinical trials showed modest effects with *infliximab* and *adalimumab* treatment of selected disease manifestations (CNS, lupus pernio, pulmonary, ocular), whereas etanercept does not appear to be particularly effective. Other therapeutics used for sarcoidosis manifestations include topical corticosteroids (eye), inhaled corticosteroids (lung), azathioprine (CNS), cyclophosphamide (cardiac, CNS), hydroxychloroquine (skin), mycophenolate mofetil (CNS, skin), thalidomide or its analogs (skin), and nonsteroidal antiinflammatory drugs (joints).

With regard to treatment of Blau syndrome and EOS, there are few case reports and series on the successful use of corticosteroids, methotrexate, thalidomide, and TNF-α antagonists adalimumab and infliximab. Findings of elevated IL-1 levels and response to human IL-1 receptor antagonist (anakinra) have been inconsistent.

Prognosis

The prognosis of childhood sarcoidosis is not well defined. The disease may be self-limited with complete recovery or may persist with a progressive or relapsing course. Outcome is worse in the setting of multiorgan or CNS involvement. Most children requiring treatment experience considerable improvement with corticosteroids, although a significant number have morbid sequelae, mainly involving the lungs and eyes. Children with EOS have a poorer prognosis and generally experience a more chronic, progressive disease course. The greatest morbidity is associated with ocular involvement, including cataract formation, development of synechiae, and loss of visual acuity or blindness.

Long-term systemic treatment may be required for the eye disease. Progressive polyarthritis may result in joint destruction. The overall mortality rate in childhood sarcoidosis is low.

Serial pulmonary function tests and chest radiographs are useful in following the course of lung involvement. Monitoring for other organ involvement should also include electrocardiogram with consideration of an echocardiogram, urinalysis, renal function tests, and measurements of hepatic enzymes and serum calcium. Other potential indicators of disease activity include inflammatory markers and serum ACE, although changes in ACE level do not always correlate with other indicators of disease status. Given the frequency of asymptomatic eye disease and the ocular morbidity associated with pediatric sarcoidosis, all patients should have an ophthalmologic examination at presentation with monitoring at regular intervals, perhaps every 3-6 mo, as recommended in children with JIA.

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CHAPTER 191

Kawasaki Disease

Mary Beth F. Son, Jane W. Newburger

Kawasaki disease (KD), formerly known as *mucocutaneous lymph node syndrome* and *infantile polyarteritis nodosa* , is an acute febrile illness of childhood seen worldwide, with the highest incidence occurring in Asian children. KD is a systemic inflammatory disorder manifesting as a vasculitis with a predilection for the coronary arteries. Approximately 20–25% of untreated children develop **coronary artery abnormalities (CAA)** including aneurysms, whereas <5% of children treated with intravenous immune globulin (IVIG) develop CAA. Nonetheless, KD is the leading cause of acquired heart disease in children in most developed countries, including the United States and Japan.

Etiology

The cause of KD remains unknown. Certain epidemiologic and clinical features support an infectious origin, including the young age-group affected, epidemics with wavelike geographic spread of illness, the self-limited nature of the acute febrile illness, and the clinical features of fever, rash, enanthem, conjunctival injection, and cervical lymphadenopathy. Further evidence of an infectious trigger includes the infrequent occurrence of the illness in infants <3 mo old, possibly the result of maternal antibodies, and the rarity of cases in adults, possibly the result of prior exposures with subsequent immunity. However, there are features that are not consistent with an infectious origin. For example, it is unusual to have multiple cases present at the same time within a family or daycare center. Furthermore, no single infectious etiologic agent has been successfully identified, despite a comprehensive search.

A genetic role in the pathogenesis of KD seems likely, as evidenced by the higher risk of KD in Asian children regardless of country of residence and in siblings and children of individuals with a history of KD. Furthermore, linkage studies and genome-wide association studies (GWAS) have identified significant potential associations between polymorphisms in the *ITPKC* gene, a T-cell regulator, with increased susceptibility to KD and more severe disease. Other candidate genes for KD identified by GWAS include *CASP3, BLK,* and *FCGR2A.* Lastly, associations of single nucleotide polymorphisms (SNPs) in the human leukocyte antigen class II region (HLA-DQB2 and HLA-DOB) with KD have been reported. The concordance rate among identical twins, however, is approximately 13%.

Epidemiology

For the majority of patients, KD is a disease of early childhood, and nearly all epidemiologic studies show a higher susceptibility to KD in boys. Data from the Kids Inpatient Database to study trends in KD hospitalizations in 2003, 2006, 2009, and 2012 reported that U.S. hospitalizations for KD seemed to decline significantly over the study period, with 6.68 per 100,000 children hospitalized for KD in 2006 vs 6.11 per 100,000 in 2012. Children age <5 yr had the highest annual hospitalization rates, and children of Asian and Pacific Islander ancestry had the highest rates among all racial groups. In other countries, such as the United Kingdom, South Korea, and Japan, the rate of KD seems to be increasing.

In Japan, nationwide surveys have been administered every 2 yr to monitor trends in KD incidence. In 2012 the highest recorded rate thus far of 264.8 per 100,000 children ages 0-4 yr was described, with the highest rate in young children ages 9-11 mo. Fortunately, the proportion of Japanese patients with coronary aneurysm and myocardial infarction has decreased over time, at 2.8% in the most recent survey.

Several risk stratification models have been constructed to determine which patients with KD are at highest risk for CAA. Predictors of poor outcome across several studies include young age, male gender, persistent fever, poor response to IVIG, and laboratory abnormalities, including neutrophilia, thrombocytopenia, transaminitis, hyponatremia, hypoalbuminemia, elevated levels of N-terminal–brain natriuretic protein and elevated C-reactive protein (CRP) levels. Asian and Pacific Islander race and Hispanic ethnicity are also risk factors for CAA. Three specific risk scores have been constructed by Japanese researchers; of these, the **Kobayashi score** is the most widely used and has high sensitivity and specificity. Unfortunately, application of these risk scores in non-Japanese populations does not appear to accurately identify all children at risk for IVIG resistance and CAA. Body surface area (BSA)–adjusted coronary artery dimensions on baseline echocardiography in the 1st 10 days of illness appear to be good predictors of involvement during follow-up. Accordingly, baseline *z* scores may provide a useful imaging biomarker.

Pathology

KD is a vasculitis that predominantly affects the medium-size arteries. The coronary arteries are most often involved, although other arteries (e.g., axillary, subclavian, femoral, popliteal, brachial) can also develop dilation. A 3-phase process to the arteriopathy of KD has been described. The 1st phase is a neutrophilic necrotizing arteritis occurring in the 1st 2 wk of illness that begins in the endothelium and moves through the coronary wall. Saccular aneurysms may form from this arteritis. The 2nd phase is a subacute/chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils, which may last weeks to years and results in fusiform aneurysms. The vessels affected by the subacute/chronic vasculitis then develop smooth muscle cell myofibroblasts, which cause progressive stenosis in the 3rd phase. Thrombi may form in the lumen and obstruct blood flow (Fig. 191.1).

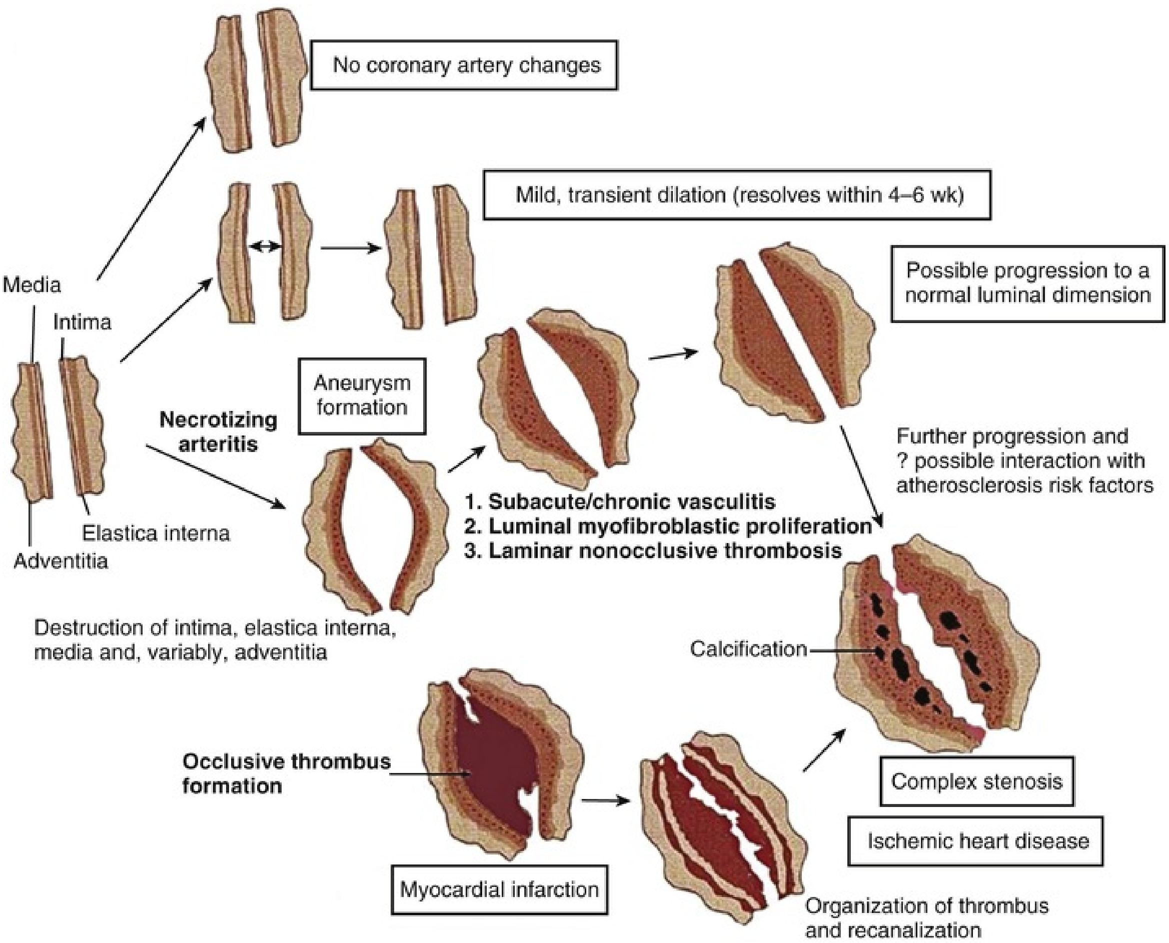
No coronary artery changes
Mild, transient dilation (resolves within 4–6 wk)
Media
Intima
Possible progression to a normal luminal dimension
Aneurysm formation
Necrotizing arteritis
Further progression and ? possible interaction with atherosclerosis risk factors
1. Subacute/chronic vasculitis
2. Luminal myofibroblastic proliferation
3. Laminar nonocclusive thrombosis
Elastica interna
Adventitia
Destruction of intima, elastica interna, media and, variably, adventitia
Calcification
Occlusive thrombus formation
Complex stenosis
Ischemic heart disease
Myocardial infarction
Organization of thrombus and recanalization

FIG. 191.1 Natural history of coronary artery abnormalities. (Modified from Kato H: Cardiovascular complications in Kawasaki disease: coronary artery lumen and long-term consequences, *Prog Pediatr Cardiol* 19:137–145, 2004.)

Clinical Manifestations

Fever is characteristically high spiking (≥38.3°C [101°F]), remitting, and unresponsive to antipyretics. The duration of fever without treatment is generally 1-2 wk but may be as short as 5 days or may persist for 3-4 wk. In addition to fever, the **5 principal clinical criteria** of KD are (1) bilateral *nonexudative* conjunctival injection with limbal sparing; (2) erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; (3) edema (induration) and erythema of the hands and feet; (4) rash of various forms (maculopapular, erythema multiforme, scarlatiniform or less often psoriatic-like, urticarial or micropustular); and (5) nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm (Table 191.1 and Figs. 191.2 to 191.5

). Perineal desquamation is common in the acute phase. Periungual desquamation of the fingers and toes begins 2-3 wk after the onset of illness and may progress to involve the entire hand and foot (Fig. 191.6).

Table 191.1

Clinical and Laboratory Features of Kawasaki Disease

Epidemiologic Case Definition (Classic Clinical Criteria)*

Fever persisting at least 5 days †
Presence of at least 4 principal features:
  Changes in extremities
    - Acute: erythema of palms, soles; edema of hands, feet
    - Subacute: periungual peeling of fingers, toes in wk 2 and 3
  Polymorphous exanthem
  Bilateral bulbar conjunctival injection without exudate
  Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
  Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Exclusion of other diseases with similar findings ‡

These features do not have to occur concurrently.

Other Clinical and Laboratory Findings

Cardiovascular System

Myocarditis, pericarditis, valvular regurgitation, shock
Coronary artery abnormalities
Aneurysms of medium-sized noncoronary arteries
Peripheral gangrene
Aortic root enlargement

Respiratory System

Peribronchial and interstitial infiltrates on chest radiograph
Pulmonary nodules

Musculoskeletal System

Arthritis, arthralgias (pleocytosis of synovial fluid)

Gastrointestinal Tract

Diarrhea, vomiting, abdominal pain
Hepatitis, jaundice
Hydrops of gallbladder
Pancreatitis

Central Nervous System

Extreme irritability
Aseptic meningitis (pleocytosis of cerebrospinal fluid)
Facial nerve palsy
Sensorineural hearing loss

Genitourinary System

Urethritis/meatitis, hydrocele

Other Findings

Desquamating rash in groin
Retropharyngeal phlegmon
Anterior uveitis by slit-lamp examination
Erythema, induration at bacille Calmette-Guérin inoculation site

Laboratory Findings in Acute Kawasaki Disease

Leukocytosis with neutrophilia and immature forms

- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Anemia
- Abnormal plasma lipids
- Hypoalbuminemia
- Hyponatremia
- Thrombocytosis after wk 1 [§]
- Sterile pyuria
- Elevated serum transaminases
- Elevated serum γ-glutamyl transpeptidase
- Pleocytosis of cerebrospinal fluid
- Leukocytosis in synovial fluid

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[*] Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.

[†] In the presence of ≥4 principal criteria, particularly when redness and swelling of the hands and feet are present, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4 in rare cases.

[‡] See differential diagnosis (Table 191.2).

[§] Some infants present with thrombocytopenia and disseminated intravascular coagulation.

From McCrindle BW, Rowley A, Newburger JW et al: Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association, Circulation 135(17):e927–e999, 2017.)

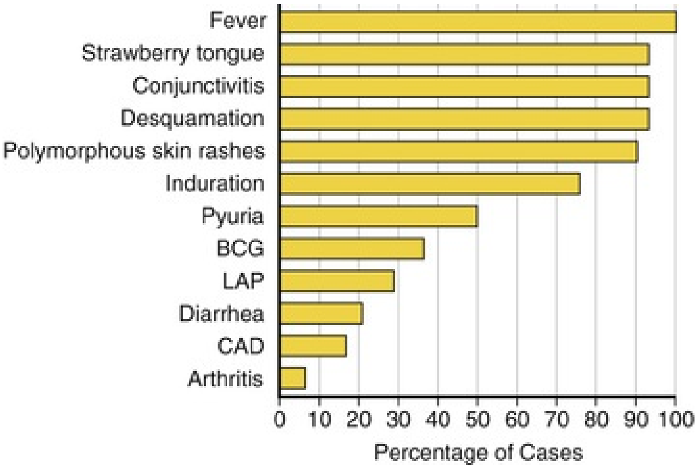

FIG. 191.2 Clinical symptoms and signs of Kawasaki disease. Summary of clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, Lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery *dilation,* defined by an internal diameter >3 mm. (From Wang CL, Wu YT, Liu CA, et al: Kawasaki disease: infection, immunity and genetics, *Pediatr Infect Dis J* 24:998–1004, 2005.)

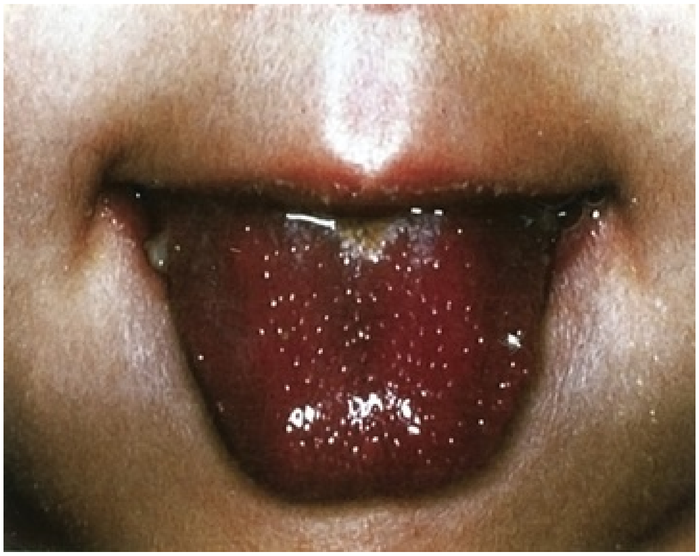

FIG. 191.3 Kawasaki disease. Strawberry tongue in patient with mucocutaneous lymph node syndrome. (Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S: *Clinical pediatric dermatology,* ed 2, Philadelphia, 1993, Saunders.)

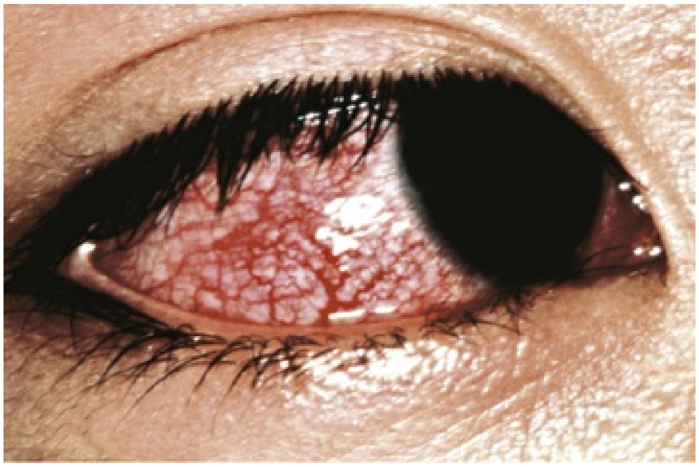

FIG. 191.4 Kawasaki disease. Congestion of bulbar conjunctiva in a patient with mucocutaneous lymph node syndrome. (Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S: *Clinical pediatric dermatology,* ed 2, Philadelphia, 1993, Saunders.)

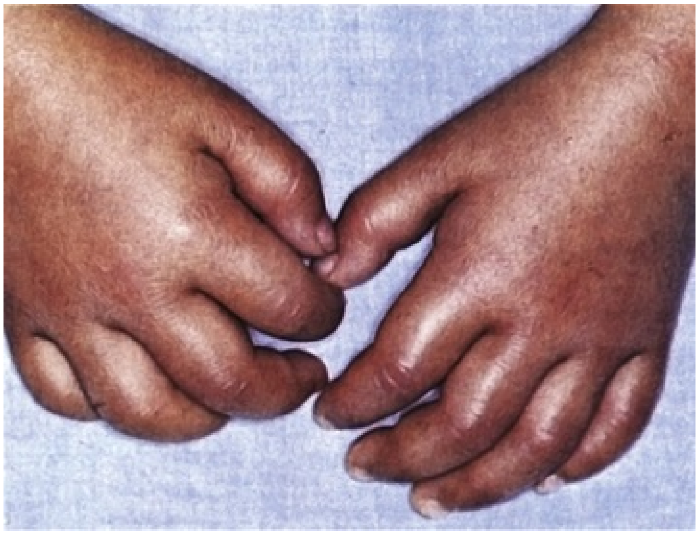

FIG. 191.5 Kawasaki disease. Indurative edema of the hands in a patient with mucocutaneous lymph node syndrome. (Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S: *Clinical pediatric dermatology,* ed 2, Philadelphia, 1993, Saunders.)

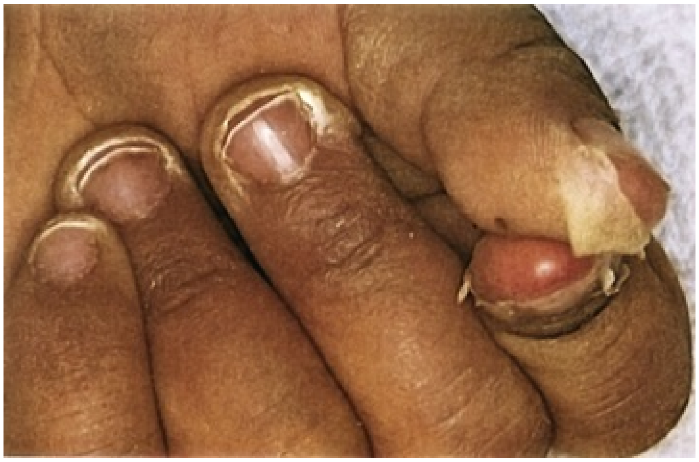

FIG. 191.6 Kawasaki disease. Desquamation of the fingers in a patient with mucocutaneous lymph node syndrome. (Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S: *Clinical pediatric dermatology,* ed 2, Philadelphia, 1993, Saunders.)

Symptoms other than the principal clinical criteria are common in the 10 days before diagnosis of KD, which may be explained in part by the finding that up to a third of patients with KD have confirmed, concurrent infections. Gastrointestinal (GI) symptoms (vomiting, diarrhea, or abdominal pain) occur in >60% of patients, and at least 1 respiratory symptom (rhinorrhea or cough) occurs in 35%. Other clinical findings include significant irritability that is especially prominent in infants and likely caused by aseptic meningitis, mild hepatitis, hydrops of the gallbladder, urethritis and meatitis with sterile pyuria, and arthritis. Arthritis may occur early in the illness or may develop in the 2nd or 3rd wk. Small or large joints may be affected, and the arthralgias may persist for several weeks. Clinical features that are *not consistent* with KD include exudative conjunctivitis, exudative pharyngitis, generalized lymphadenopathy, discrete oral lesions (ulceration or exudative pharyngitis), splenomegaly, and bullous, petechial, or vesicular rashes.

Cardiac involvement is the most important manifestation of KD. Myocarditis occurs in most patients with acute KD and manifests as tachycardia disproportionate to fever, along with diminished left ventricular systolic function. Occasionally, patients with KD present in cardiogenic shock (**KD shock syndrome**), with greatly diminished left ventricular function. Case series of KD shock syndrome indicate that these patients may be at higher risk for coronary artery dilation. Pericarditis with a small pericardial effusion can also occur during the acute illness. Mitral regurgitation of at least mild severity is evident on echocardiography in 10–25% of patients at presentation but diminishes over time, except among rare patients with coronary aneurysms and ischemic heart disease. Up to 25% of untreated patients develop CAA in the 2nd to 3rd week of illness; initially these are usually asymptomatic and detected by echocardiography. Almost all the morbidity and mortality in KD occur in patients with **large or giant coronary artery aneurysms** , defined by the 2017 American Heart Association (AHA) scientific statement on the diagnosis and treatment of KD as having a *z* score ≥10 or an absolute dimension of ≥8 mm. Specifically, large or giant aneurysms are associated with the greatest risk of thrombosis or stenosis, angina, and myocardial infarction (Figs. 191.7 and 191.8*A*). Rupture of a giant aneurysm is a rare complication that generally occurs in the 1st months after illness onset and may present as hemopericardium with tamponade. Axillary, popliteal, iliac, or other arteries may also become aneurysmal, but always in the setting of giant coronary aneurysms (Fig. 191.8*B*).

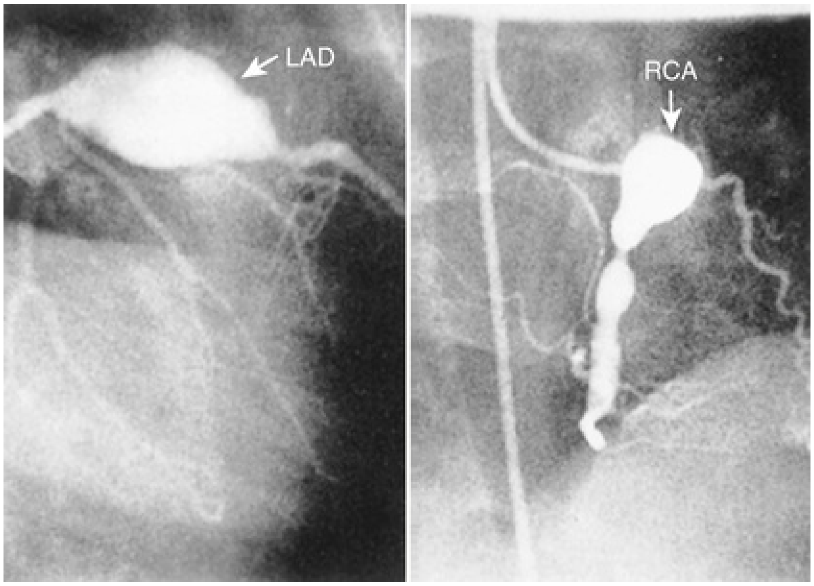

FIG. 191.7 **Coronary angiograms in 6 yr old boy with Kawasaki disease. *Left,* Giant aneurysm of the left anterior descending coronary artery (LAD) with obstruction. *Right,* Giant aneurysm of the right coronary artery (RCA) with an area of severe narrowing. (From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease, *Pediatrics* 114:1708–1733, 2004.)**

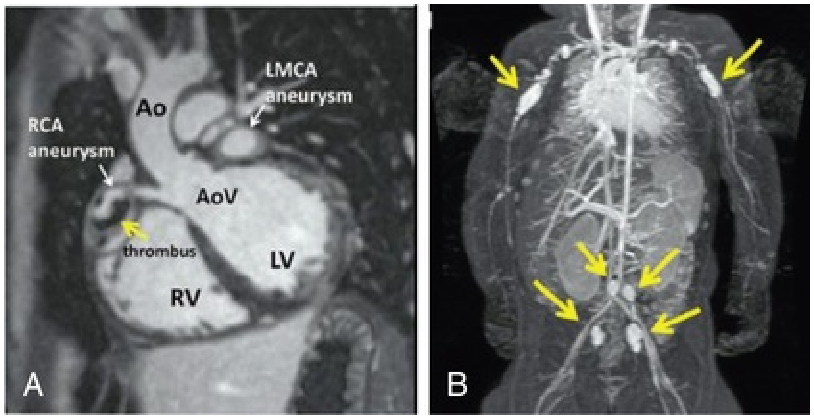

FIG. 191.8 MRI of coronary and peripheral artery aneurysms in Kawasaki disease. A, Image of left ventricular outflow tract showing a giant right coronary artery (RCA) aneurysm with nonocclusive thrombus *(yellow arrow)* and a giant left main coronary artery (LMCA) aneurysm. Ao, Aorta; AoV, aortic valve; LV, left ventricle; RV, right ventricle. B, Aneurysms in the axillary and subclavian arteries and the iliac and femoral arteries *(yellow arrows)* . (From McCrindle BW, Rowley A, Newburger JW et al: Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association, *Circulation* 135(17):e927-e999, 2017, Fig 2GH, p e935.)

Occasionally KD initially presents with only fever and lymphadenopathy (**node-first KD**). This presentation may be confused with bacterial or viral cervical lymphadenopathy or lymphadenitis and may delay the diagnosis of KD. Persistence of high fever, lack of response to antibiotics, and subsequent development of other signs of KD suggest the diagnosis. Children with node-first KD tend to be older (4 vs 2 yr) and have more days of fever and higher CRP levels. In addition to cervical adenopathy, many had retropharyngeal and peritonsillar inflammation on CT scans (Fig. 191.9).

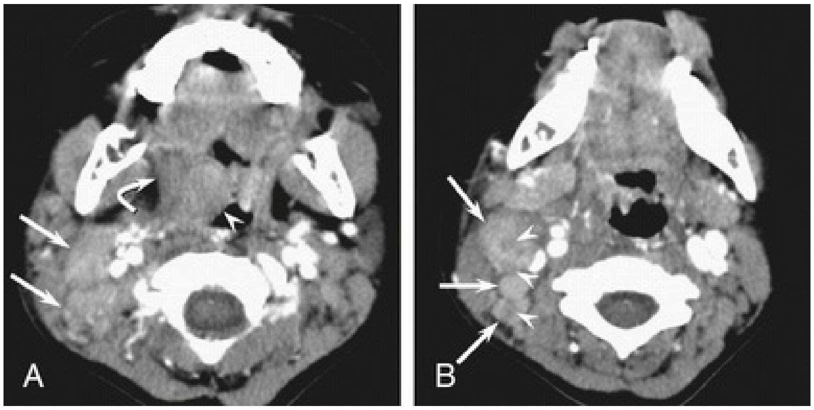

FIG. 191.9 Contrast-enhanced CT in 3 yr old boy with Kawasaki disease. A, Right-sided cervical lymphadenopathy *(arrows),* peritonsillar hypodense area *(curved arrow),* and swelling of right palatine tonsil *(arrowhead).* B, Right-sided cervical lymphadenopathy

with perinodal infiltration *(arrows)* and intranodal focal low attenuation *(arrowheads).* (From Kato H, Kanematsu M, Kato Z, et al: Computed tomographic findings of Kawasaki disease with cervical lymphadenopathy, *J Comput Assist Tomogr* 36(1):138–142, 2012, Fig 1, p 139.)

KD can be divided into 3 clinical phases. The **acute febrile phase** is characterized by fever and the other acute signs of illness and usually lasts 1-2 wk. The **subacute phase** is associated with desquamation, thrombocytosis, development of CAA, and the highest risk of sudden death in patients who develop aneurysms; it generally lasts 3 wk. The **convalescent phase** begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically 6-8 wk after the onset of illness.

Laboratory and Radiology Findings

There is no diagnostic test for KD, but patients usually have characteristic laboratory findings. The leukocyte count is often elevated, with a predominance of neutrophils and immature forms. Normocytic, normochromic anemia is common. The platelet count is generally normal in the 1st wk of illness and rapidly increases by the 2nd to 3rd wk of illness, sometimes exceeding 1 million/mm^3 . An elevated ESR or CRP value is universally present in the acute phase of illness. The ESR may remain elevated for weeks, in part from the effect of IVIG. Sterile pyuria, mild elevations of the hepatic transaminases, hyperbilirubinemia, and cerebrospinal fluid pleocytosis may also be present. KD is unlikely if the ESR, CRP, and platelet counts are normal after 7 days of fever.

Two-dimensional echocardiography is the most useful test to monitor for development of CAA. Although frank aneurysms are rarely detected in the 1st week of illness, coronary arteries are commonly ectatic. Moreover, coronary artery dimensions, adjusted for BSA (*z* scores), may be increased in the 1st 5 wk after presentation, and as previously noted, baseline *z* scores may offer prognostic information regarding ultimate coronary artery dimensions. Children with non-KD febrile illnesses also have mildly increased *z* scores compared with nonfebrile controls, but not to the same degree as patients with KD. Aneurysms have been defined with use of absolute dimensions by the Japanese Ministry of Health and are classified as small (≤4 mm internal diameter [ID]), medium (>4 to ≤8 mm ID), or giant (>8 mm ID). Some experts believe that a *z* -score–based system for classification of aneurysm size may be more discriminating, because it adjusts the coronary dimension for BSA. The AHA *z* -score classification system is as follows:

1. No involvement: always <2
2. Dilation only: 2 to <2.5; or if initially <2, a decrease in *z* score during follow-up ≥1
3. Small aneurysm: ≥2.5 to <5
4. Medium aneurysm: ≥5 to <10, and absolute dimension <8 mm
5. Large or giant aneurysm: ≥10, or absolute dimension ≥8 mm

Echocardiography should be performed at diagnosis and again after 1-2 wk of illness. If the results are normal, a repeat study should be performed 6-8 wk after onset of illness. If results of either of the initial studies are abnormal or the patient has recurrent fever or symptoms, more frequent echocardiography or other studies may be necessary. In patients without CCA at any time during the illness, echocardiography and a lipid profile are recommended 1 yr later. After this time, periodic evaluation for preventive cardiology counseling is warranted, and some experts recommend cardiologic follow-up every 5 yr. For patients with CAA, the type of testing and the frequency of cardiology follow-up visits are tailored to the patient's coronary status.

Diagnosis

The diagnosis of KD is based on the presence of characteristic clinical signs. For **classic KD** the diagnostic criteria require the presence of fever for at least 4 days and at least 4 of 5 of the other principal characteristics of the illness (see Table 191.1). The diagnosis of KD should be made within 10 days, and ideally within 7 days, of fever onset to improve coronary artery outcomes. In **atypical or incomplete KD** , patients have persistent fever but <4 of the 5 characteristic clinical signs. In these patients, laboratory and echocardiographic data can assist in the diagnosis (Fig. 191.10). Incomplete cases occur most frequently in infants, who also have the highest likelihood of development of CAA. Ambiguous cases should be referred to a center with experience in the diagnosis of KD. Establishing the diagnosis with prompt institution of treatment is essential to prevent potentially devastating coronary artery disease. For this reason, *it is recommended that any infant age ≤6 mo with fever for ≥7 days* *without explanation undergo echocardiography to assess the coronary arteries.*

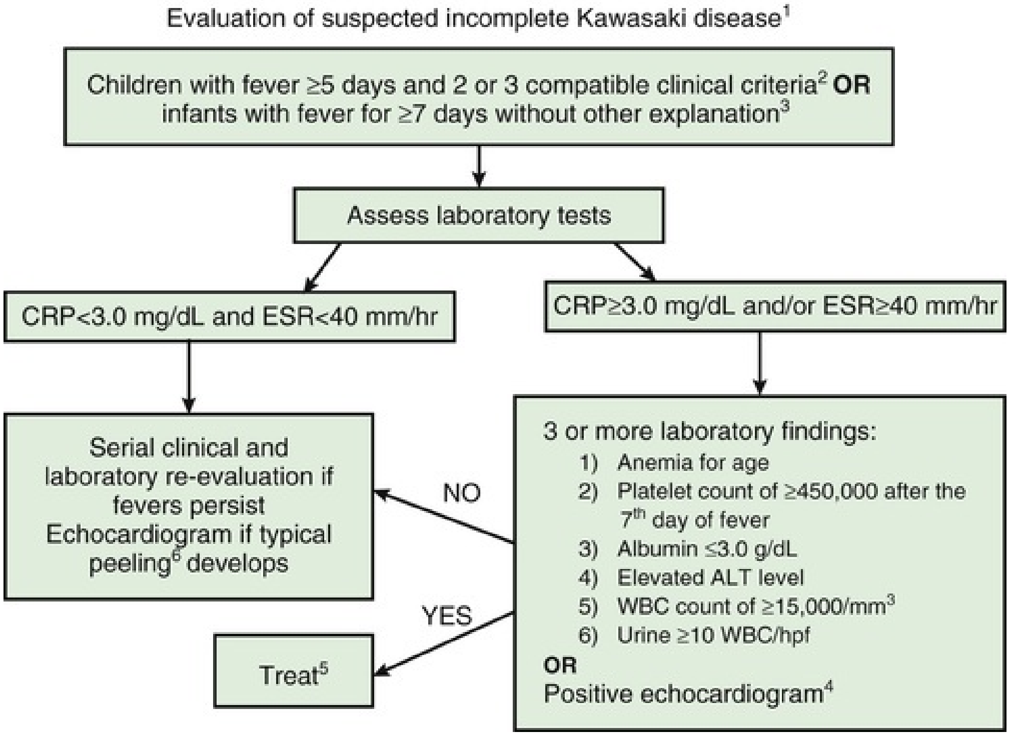
Evaluation of suspected incomplete Kawasaki disease[1]
Children with fever ≥5 days and 2 or 3 compatible clinical criteria[2] OR infants with fever for ≥7 days without other explanation[3]
Assess laboratory tests
CRP<3.0 mg/dL and ESR<40 mm/hr
CRP≥3.0 mg/dL and/or ESR≥40 mm/hr
Serial clinical and laboratory re-evaluation if fevers persist
Echocardiogram if typical peeling[6] develops
NO
YES
Treat[5]
3 or more laboratory findings:
1) Anemia for age
2) Platelet count of ≥450,000 after the 7th day of fever
3) Albumin ≤3.0 g/dL
4) Elevated ALT level
5) WBC count of ≥15,000/mm3
6) Urine ≥10 WBC/hpf
OR
Positive echocardiogram[4]

FIG. 191.10 Evaluation of suspected incomplete Kawasaki disease (KD). [1] In the absence of a gold standard for diagnosis of KD, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. [2] Clinical findings of KD are listed in Table 191.1 . Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy, and splenomegaly. [3] Infants ≤6 mo of age are most likely to develop prolonged fever without other clinical criteria for KD; these infants are at particularly high risk of developing coronary artery abnormalities. [4] Echocardiography is considered positive for purposes of this algorithm if any of 3 conditions are met: z score of left anterior descending coronary artery or right coronary artery ≥2.5; coronary artery aneurysm is observed; or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or z scores in left anterior descending coronary artery or right coronary artery of 2-2.5. [5] If the echocardiogram is positive, treatment should be given within 10 days of fever onset or after the 10th day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. [6] Typical peeling begins under the nail beds of fingers and toes. ALT, Alanine transaminase; WBC, white blood cell. (From McCrindle BW, Rowley A, Newburger JW et al: Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association, *Circulation* 135(17):e927–e999, 2017, Fig 2, p e937.)

Differential Diagnosis

Adenovirus, measles, and scarlet fever lead the list of common childhood infections that mimic KD (Table 191.2). Children with **adenovirus** typically have exudative pharyngitis and exudative conjunctivitis, allowing differentiation from KD. A common clinical problem is the differentiation of **scarlet fever** from KD in a child who is a group A streptococcal carrier. Patients with scarlet fever typically have a rapid clinical response to appropriate antibiotic therapy. Such treatment for 24-48 hr with clinical reassessment generally clarifies the diagnosis. Furthermore, ocular findings are quite rare in group A streptococcal pharyngitis and may assist in the diagnosis of KD.

Table 191.2

Differential Diagnosis of Kawasaki Disease

Viral Infections*

- Adenovirus
- Enterovirus
- Measles
- Epstein-Barr virus
- Cytomegalovirus

Bacterial Infections

- Scarlet fever
- Rocky Mountain spotted fever
- Leptospirosis
- Bacterial cervical lymphadenitis ± retropharyngeal phlegmon
- Meningococcemia
- Urinary tract infection

Rheumatologic Disease

- Systemic-onset juvenile idiopathic arthritis
- Behçet disease
- Rheumatic fever

Other

- Toxic shock syndromes
- Serum sickness
- Staphylococcal scalded skin syndrome
- Macrophage activation syndrome
- Drug hypersensitivity reactions
- Stevens-Johnson syndrome
- Aseptic meningitis

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[*] Detection of a virus does not exclude Kawasaki disease in the presence of the principal clinical features (see Table 191.1).

Features of **measles** that distinguish it from KD include exudative conjunctivitis, Koplik spots, rash that begins on the face and hairline and behind the ears, and leukopenia. **Cervical lymphadenitis** can be the initial diagnosis in children who are ultimately recognized to have KD. Less common infections such as Rocky Mountain spotted fever and leptospirosis are occasionally confused with KD. **Rocky Mountain spotted fever** is a potentially lethal bacterial infection, and appropriate antibiotics should not be withheld if the diagnosis is under consideration. Its distinguishing features include pronounced myalgias and headache at onset, centripedal rash, and petechiae on the palms and soles. **Leptospirosis** can also be an illness of considerable severity. Risk factors include exposure to water contaminated with urine from infected animals. The classic description of leptospirosis is of a biphasic illness with a few asymptomatic days between an initial period of fever and headache and a late phase with renal and hepatic failure. In contrast, patients with KD have consecutive days of fever at diagnosis and rarely have renal or hepatic failure.

Children with KD and pronounced myocarditis may demonstrate hypotension with a clinical picture similar to that of toxic shock syndrome. Features of **toxic shock syndrome** that are not usually seen in KD include renal insufficiency, coagulopathy, pancytopenia, and myositis. Drug hypersensitivity reactions, including Stevens-Johnson syndrome, share some characteristics with KD. Drug reaction features such as the presence of periorbital edema, oral ulcerations, and a normal or minimally elevated ESR are not seen in KD. Systemic-onset

juvenile idiopathic arthritis (sJIA) is also characterized by fever and rash, but physical findings include diffuse lymphadenopathy and hepatosplenomegaly. Arthritis is required to develop at some point in the disease course to make the diagnosis, but may not be present in the 1st few wk of illness. Laboratory findings may include coagulopathy, elevated fibrin degradation product values, and hyperferritinemia. Interestingly, there are reports of children with sJIA who have echocardiographic evidence of CAA. Coronary aneurysms have also been reported in Behçet disease, primary cytomegalovirus infection, and meningococcemia.

Treatment

Patients with acute KD should be treated with 2 g/kg of IVIG as a single infusion, usually administered over 10-12 hr within 10 days of disease onset, and ideally as soon as possible after diagnosis (Table 191.3). In addition, moderate (30-50 mg/kg/day divided every 6 hr) to high-dose aspirin (80-100 mg/kg/day divided every 6 hr) should be administered until the patient is afebrile, then lowered to antiplatelet doses. Other NSAIDs should not be given during therapy with aspirin because they may block the action of aspirin. The mechanism of action of IVIG in KD is unknown, but treatment results in defervescence and resolution of clinical signs of illness in approximately 85% of patients. The prevalence of coronary disease, in 20–25% in children treated with aspirin alone, is <5% in those treated with IVIG and aspirin within the 1st 10 days of illness. Strong consideration should be given to treating patients with persistent fever, abnormal dimensions of the coronary arteries, or signs of systemic inflammation who are diagnosed after the 10th day of fever. The dose of aspirin is usually decreased from antiinflammatory to antithrombotic doses (3-5 mg/kg/day as a single dose) after the patient has been afebrile for 48 hr. Aspirin is continued for its antithrombotic effect until 6-8 wk after illness onset and is then discontinued in patients who have had normal echocardiography findings throughout the course of their illness. Patients with CAA continue with aspirin therapy and may require anticoagulation, depending on the degree of coronary dilation (see later).

Table 191.3

Treatment of Kawasaki Disease

Acute Stage

Intravenous immune globulin 2 g/kg over 10-12 hr
and
Aspirin 30-50 mg/kg/day or 80-100 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr

Convalescent Stage

Aspirin 3-5 mg/kg once daily orally until 6-8 wk after illness onset if normal coronary findings throughout course

Long-Term Therapy for Patients With Coronary Abnormalities

Aspirin 3-5 mg/kg once daily orally
Clopidogrel 1 mg/kg/day (maximum 75 mg/day)
Most experts add warfarin or low-molecular-weight heparin for those patients at particularly high risk of thrombosis

Acute Coronary Thrombosis

Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under supervision of a pediatric cardiologist

Corticosteroids have been used as primary therapy with the 1st dose of IVIG in hopes of improving coronary outcomes. A North American trial using a single pulse dose of intravenous methylprednisolone (30 mg/kg) with IVIG as primary therapy did not improve coronary outcomes. However, a trial in Japan utilizing the Kobayashi score to identify high-risk children demonstrated improved coronary outcomes with a regimen of prednisolone (2 mg/kg) plus IVIG as primary therapy. Furthermore, a systematic review and meta-analysis of 16 comparative studies demonstrated that early treatment with corticosteroids improved coronary artery outcomes in children with KD. Despite these promising results, administration of corticosteroids as primary therapy to all children with KD awaits the development of a risk score that identifies high-risk children in a multiracial population.

IVIG-resistant KD occurs in approximately 15% of patients and is defined by persistent or recrudescent fever 36 hr after completion of the initial IVIG infusion. Patients with IVIG resistance are at increased risk for CAA. Therapeutic options for the child with IVIG resistance include a 2nd dose of IVIG (2 g/kg), a tapering course of corticosteroids, and/or infliximab (Table 191.4). For the most severely affected patients with enlarging coronary aneurysms, additional therapies such as cyclosporine or cyclophosphamide may be administered, with consultation from specialists in pediatric rheumatology and cardiology.

Table 191.4

Treatment Options for IVIG-Resistant Patients With Kawasaki Disease[*]

AGENT	DESCRIPTION	DOSE
MOST FREQUENTLY ADMINISTERED		
IVIG: 2nd infusion	Pooled polyclonal IG	2 g/kg IV
IVIG + prednisolone	IVIG + corticosteroid	IVIG: 2 g/kg IV + prednisolone 2 $mg \cdot kg^{-1} \cdot d^{-1}$ IV divided every 8 hr until afebrile, then prednisone orally until CRP normalized, then taper over 2-3 wk
Infliximab	Monoclonal antibody against TNF-α	Single infusion: 5 mg/kg IV given over 2 hr
ALTERNATIVE TREATMENTS		
Cyclosporine	Inhibitor of calcineurin-NFAT pathway	IV: 3 $mg \cdot kg^{-1} \cdot d^{-1}$ divided every 12 hr PO: 4-8 $mg \cdot kg^{-1} \cdot d^{-1}$ divided every 12 hr Adjust dose to achieve trough 50-150 ng/mL; 2 hr peak level 300-600 ng/mL
Anakinra	Recombinant IL-1β receptor antagonist	2-6 $mg \cdot kg^{-1} \cdot d^{-1}$ given by subcutaneous injection
Cyclophosphamide	Alkylating agent blocks DNA replication	2 $mg \cdot kg^{-1} \cdot d^{-1}$ IV
Plasma exchange	Replaces plasma with albumin	Not applicable

[*] IVIG resistance is defined as persistent or recrudescent fever at least 36 hours and <7 days after completion of 1st IVIG infusion. The top 3 treatments have been most frequently used, although no comparative effectiveness trial has been performed. Pulsed high-dose corticosteroid treatment is not recommended. The alternative treatments have been used in a limited number of patients with KD.

CRP, C-reactive protein; IG, immunoglobulin; IL, interleukin; IV, intravenous(ly); IVIG, intravenous immune globulin; NFAT, nuclear factor of activated T cells; PO, oral; TNF, tumor necrosis factor.

Complications

Patients with KD and aneurysms may experience myocardial infarction, angina, and sudden death. For this reason, antithrombotic medications are the cornerstone of therapy for the child with coronary disease. Aspirin is continued indefinitely in children with coronary aneurysms. When aneurysms are moderate sized, dual-antiplatelet therapy is sometimes administered. For those with large or giant aneurysms, anticoagulation with warfarin or low-molecular-weight heparin is added to aspirin. For acute thrombosis that occasionally occurs in an aneurysmal or stenotic coronary artery, thrombolytic therapy may be lifesaving.

Long-term follow-up of patients with coronary artery aneurysms is tailored to the past (i.e., worst-ever) and current coronary status, with a schedule of testing recommended in the 2017 AHA scientific statement on KD. Testing may include echocardiography, assessment for inducible ischemia, advanced imaging (CT, MRI, or invasive angiography), physical activity counseling, and cardiovascular risk factor assessment and management. Patients with coronary artery stenosis and inducible ischemia may be managed with coronary artery bypass grafting (CABG) or catheter interventions, including percutaneous transluminal coronary rotational ablation, directional coronary atherectomy, and stent implantation.

Patients undergoing long-term aspirin therapy should receive annual influenza vaccination to reduce the risk of Reye syndrome. A different antiplatelet agent can be substituted for aspirin during the 6 wk after varicella vaccination. IVIG may interfere with the immune response to live-virus vaccines as a result of specific antiviral antibody, so the measles-mumps-rubella and varicella vaccinations should generally be deferred until 11 mo after IVIG administration. Nonlive vaccinations do not need to be delayed.

Prognosis

The vast majority of patients with KD return to normal health; timely treatment reduces the risk of coronary aneurysms to <5%. Acute KD recurs in 1–3% of cases. The prognosis for patients with CCA depends on the severity of coronary disease; therefore, recommendations for follow-up and management are stratified according to coronary artery status. Published fatality rates are very low, generally <1.0%. Overall, 50% of coronary artery aneurysms regress to normal lumen diameter by 1-2 yr after the illness, with smaller aneurysms being more likely to regress. Intravascular ultrasonography has demonstrated that regressed aneurysms are associated with marked myointimal thickening and abnormal functional behavior of the vessel wall. Giant aneurysms are less likely to regress to normal lumen diameter and are most likely to lead to thrombosis or stenosis. CABG may be required if there is inducible ischemia; it is best accomplished with the use of arterial grafts, which grow with the child and are more likely than venous grafts to remain patent over the long-term. Heart transplantation has been required in rare cases where revascularization is not feasible because of distal coronary stenoses, distal aneurysms, or severe ischemic cardiomyopathy. A study from Japan reported outcomes in adult patients with a history of KD and giant aneurysms. These patients required multiple cardiac and surgical procedures, but the 30-yr survival rate approached 90%.

Whether children who have had KD and normal echocardiography findings throughout their course are at higher risk for the development of atherosclerotic heart disease in adulthood remains unclear. Studies of endothelial dysfunction in children with a history of KD and normal coronary dimensions have produced conflicting results. However, reassuring data suggest that the standardized mortality ratio among adults in Japan who had KD in childhood without aneurysms is indistinguishable from that of the general population. All children with a history of KD should be counseled regarding a heart-healthy diet, adequate amounts of exercise, tobacco avoidance, and intermittent lipid monitoring. Among children with coronary aneurysms, the AHA recommends treatment thresholds for risk factors for atherosclerotic heart disease that are lower than those for the normal population.

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CHAPTER 192

Vasculitis Syndromes

Vidya Sivaraman, Edward C. Fels, Stacy P. Ardoin

Childhood vasculitis encompasses a broad spectrum of diseases that share inflammation of the blood vessels as the central pathophysiology. The pathogenesis of the vasculitides is generally idiopathic. Some forms of vasculitis are associated with infectious agents and medications, whereas others may occur in the setting of preexisting autoimmune disease. The pattern of vessel injury provides insight into the form of vasculitis and serves as a framework to delineate the different vasculitic syndromes. The distribution of vascular injury includes *small vessels* (capillaries, arterioles, and postcapillary venules), *medium vessels* (renal arteries, mesenteric vasculature, and coronary arteries), and *large vessels* (the aorta and its proximal branches) (Fig. 192.1). Additionally, some forms of small vessel vasculitis are characterized by the presence of **antineutrophil cytoplasmic antibodies (ANCAs)** , whereas others are associated with **immune complex** deposition in affected tissues. A combination of clinical features, histologic appearance of involved vessels, and laboratory data is used to classify vasculitis (Tables 192.1 to 192.3). A nomenclature system from the 2012 International Chapel Hill Consensus Conference has proposed using the pathologic diagnosis rather than eponyms for vasculitis nomenclature. For example, Henoch-Schönlein purpura would be referred to as IgA vasculitis. Additionally, the classification criteria endorsed by the European League Against Rheumatism, Pediatric Rheumatology International Trial Organization, and Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) have been validated in childhood vasculitis. (Table 192.1).

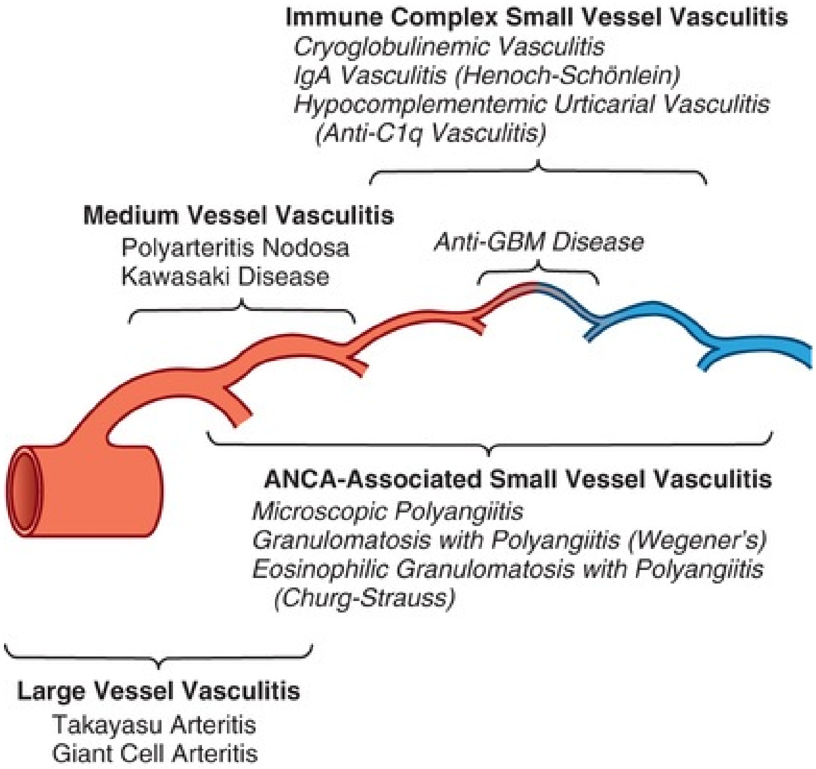
Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis
(Anti-C1q Vasculitis)
Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease
Anti-GBM Disease
ANCA-Associated Small Vessel Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis (Wegener's)
Eosinophilic Granulomatosis with Polyangiitis
(Churg-Strauss)
Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

FIG. 192.1 **Distribution of vessel involvement in large, medium, and small vessel vasculitis. There is substantial overlap with respect to arterial involvement, and all 3 major categories of vasculitis can affect any-size artery. Large vessel vasculitis affects large arteries more often than other vasculitides. Medium vessel vasculitis predominantly affects medium arteries. Small vessel vasculitis predominantly affects small vessels, but medium arteries and veins may be affected, although immune complex small vessel vasculitis rarely affects arteries. Not shown is *variable vessel vasculitis* , which can affect any type of vessel, from aorta to veins. The diagram depicts (from *left* to *right*) aorta, large artery, medium artery, small artery/arteriole, capillary, venule, and vein. ANCA, Antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane. (From Jennette JC, Falk RJ, Bacon PA, et al: 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, *Arthritis Rheum* 65(1):1–11, 2013, Fig 2, p 4.)**

Table 192.1

Classification of Childhood Vasculitis

2012 Chapel Hill Consensus Conference Nomenclature of Vasculitides	EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY Classification of Childhood Vasculitis
I. Large vessel vasculitis	Predominantly large vessel vasculitis
Takayasu arteritis	Takayasu arteritis
Giant cell arteritis	Predominantly medium vessel vasculitis
II. Medium vessel vasculitis	Childhood polyarteritis nodosa
Polyarteritis nodosa	Cutaneous polyarteritis nodosa
Kawasaki disease	Kawasaki disease
III. Small vessel vasculitis	Predominantly small vessel vasculitis
Antineutrophil cytoplasmic antibody (ANCA)–associated	Granulomatous: • Granulomatosis with polyangiitis (Wegener granulomatosis)*

vasculitis • Microscopic polyangiitis • Granulomatosis with polyangiitis • Eosinophilic granulomatosis with polyangiitis Immune complex small vessel vasculitis • Anti–glomerular basement membrane (anti-GBM) disease • IgA vasculitis (Henoch-Schönlein purpura) • Hypocomplementemic urticarial vasculitis IV. Variable vessel vasculitis Behçet disease Cogan syndrome V. Single-organ vasculitis Cutaneous leukocytoclastic vasculitis Cutaneous arteritis Primary central nervous system vasculitis Isolated aortitis Others VI. Vasculitis associated with systemic disease Lupus vasculitis Rheumatoid vasculitis Sarcoid vasculitis Others VII. Vasculitis associated with probable etiology Hepatitis C virus–associated cryoglobulinemic vasculitis Hepatitis B virus–associated vasculitis Syphilis-associated aortitis Drug-associated immune complex vasculitis Drug-associated ANCA-associated vasculitis Cancer-associated vasculitis Others	• Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)* Nongranulomatous: • Microscopic polyangiitis* • Henoch-Schönlein purpura (IgA vasculitis) • Isolated cutaneous leukocytoclastic vasculitis • Hypocomplementemic urticarial vasculitis Other vasculitides Behçet disease Vasculitis secondary to infection (including hepatitis B–associated polyarteritis nodosa), malignancies, and drugs (including hypersensitivity vasculitis) Vasculitis associated with connective tissue disease Isolated vasculitis of central nervous system Cogan syndrome Unclassified

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* Associated with antineutrophil cytoplasmic antibody.

Adapted from Jennette JC, Falk RJ, Bacon PA, et al: 2012 Revised International

Chapel Hill Consensus Conference nomenclature of vasculitides, *Arthritis Rheum* 65:1–11; 2013; and Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria, *Ann Rheum Dis* 69:798–806; 2010.

Table 192.2

Features That Suggest a Vasculitic Syndrome

Clinical Features

Fever, weight loss, fatigue of unknown origin
Skin lesions (palpable purpura, fixed urticaria, livedo reticularis, nodules, ulcers)
Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)
Arthralgia or arthritis, myalgia, or myositis, serositis
Hypertension, hematuria, renal failure
Pulmonary infiltrates or hemorrhage
Myocardial ischemia, arrhythmias

Laboratory Features

Increased erythrocytes sedimentation rate or C-reactive protein level
Leukocytosis, anemia, thrombocytosis
Eosinophilia
Antineutrophil cytoplasmic antibodies
Elevated factor VIII–related antigen (von Willebrand factor)
Cryoglobulinemia
Circulating immune complexes
Hematuria

From Petty RE, Laxer RM, Lindsley CB, Wedderburn LR: *Textbook of pediatric rheumatology,* ed 7, Philadelphia, 2016, Elsevier Saunders.

Table 192.3

Clinicopathologic Characteristics of Vasculitides in Childhood

SYNDROME	FREQUENCY	VESSELS AFFECTED	CHARACTERISTIC PATHOLOGY
Polyarteritis			
Polyarteritis nodosa	Rare	Medium-size and small muscular arteries and sometimes arterioles	Focal segmental (often near bifurcations); fibrinoid necrosis; gastrointestinal, renal microaneurysms; lesions at various stages of evolution
Kawasaki disease	Common	Coronary and other muscular arteries	Thrombosis, fibrosis, aneurysms, especially of coronary vessels
Leukocytoclastic Vasculitis			
Henoch-Schönlein purpura (IgA vasculitis)	Common	Arterioles and venules, often small arteries and veins	Leukocytoclasis; mixed cells, eosinophils, IgA deposits in affected vessels
Hypersensitivity angitis	Rare	Arterioles and venules	Leukocytoclastic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution
Granulomatous Vasculitis			
Granulomatosis with polyangiitis (Wegener granulomatosis)	Rare	Small arteries and veins, occasionally larger vessels	Upper and lower respiratory tract, necrotizing granulomata glomerulonephritis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Rare	Small arteries and veins, often arterioles and venules	Necrotizing extravascular granulomata; lung involvement; eosinophilia
Giant Cell Arteritis			
Takayasu arteries	Uncommon	Large arteries	Granulomatous inflammation, giant cells; aneurysms, dissection
Temporal arteritis	Rare	Medium-size and large arteries	Granulomatous inflammation, giant cell arteries

Adapted from Cassidy JT, Petty RE: *Textbook of pediatric rheumatology,* ed 6, Philadelphia, 2011, Elsevier Saunders.

Childhood vasculitis varies from a relatively benign and self-limited disease such as Henoch-Schönlein purpura to catastrophic disease with end-organ damage, as seen in granulomatosis with polyangiitis (formerly Wegener granulomatosis). Vasculitis generally manifests as a heterogeneous multisystem disease. Although some features, such as purpura, are easily identifiable, others, such as hypertension secondary to renal artery occlusion or glomerulonephritis, can be subtler. Ultimately, the key to recognizing vasculitis relies heavily on *pattern recognition.* Demonstration of vessel injury and inflammation on biopsy or vascular imaging is required to confirm a diagnosis of vasculitis.

192.1

Henoch-Schönlein Purpura

Vidya Sivaraman, Edward C. Fels, Stacy P. Ardoin

Henoch-Schönlein purpura (**HSP**) is the most common vasculitis of childhood and is characterized by leukocytoclastic vasculitis and immunoglobulin A deposition in the small vessels in the skin, joints, gastrointestinal tract, and kidney. According to the 2012 International Chapel Hill Consensus Conference nomenclature, HSP is also referred to as **IgA vasculitis** , based on the presence of vasculitis with predominance of IgA deposits affecting small vessels.

Epidemiology

HSP occurs worldwide and affects all ethnic groups but is more common in white and Asian populations. The incidence of HSP is estimated at 14-20 per 100,000 children per year and affects males more than females, with a 1.2-1.8 : 1 male/female ratio. Approximately 90% of HSP cases occur in children, usually between ages 3 and 10 yr. HSP is distinctly less common in adults, who often have severe and chronic complications. HSP is more common in the winter and spring and is unusual in summer months. Many cases of HSP follow a documented upper respiratory infection.

Pathology

Skin biopsies demonstrate **leukocytoclastic vasculitis** of the dermal capillaries and postcapillary venules. The inflammatory infiltrate includes neutrophils and monocytes. Renal histopathology typically shows endocapillary proliferative glomerulonephritis, ranging from a focal segmental process to extensive crescentic involvement. In all tissues, immunofluorescence identifies IgA deposition in walls of small vessels (Fig. 192.2), accompanied to a lesser extent by deposition of C3, fibrin, and IgM.

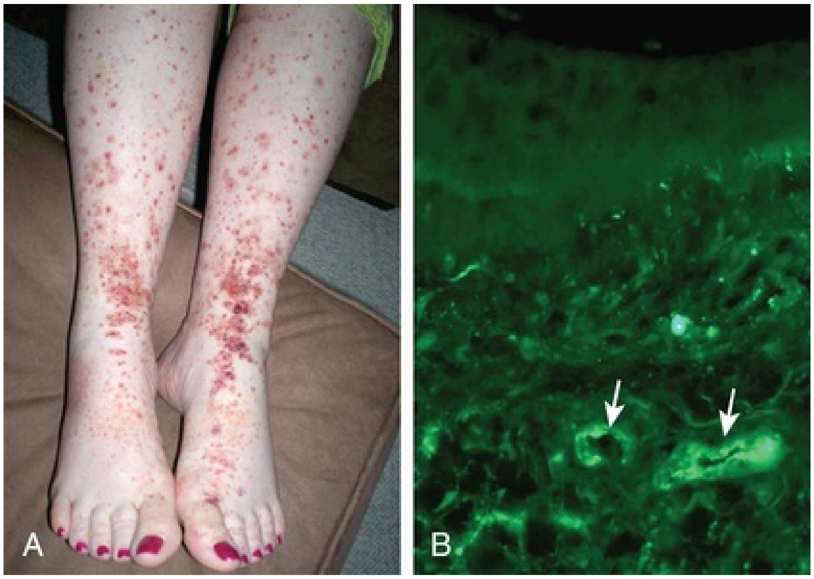

FIG. 192.2 **Girl with Henoch-Schönlein purpura. A, Typical palpable purpura in lower extremities. B, Skin biopsy of lesion shows direct immunofluorescence of IgA *(arrows)* within the walls of dermal capillaries.**

Pathogenesis

The exact pathogenesis of HSP remains unknown. Given the seasonality of HSP and the frequency of preceding upper respiratory infections, infectious triggers such as group A β-hemolytic streptococcus, *Staphylococcus aureus,* mycoplasma, and adenovirus have been suspected. The common finding of deposition of IgA, specifically IgA_1 , suggests that HSP is a disease mediated by IgA and IgA immune complexes. HSP occasionally clusters in families, suggesting a genetic component. HLA-B34 and HLA-DRB1*01 alleles have been linked to HSP nephritis. Patients with familial Mediterranean fever, hereditary periodic fever syndromes, and complement deficiencies are at increased risk for developing HSP, suggesting that genetically determined immune dysregulation may contribute.

Clinical Manifestations

The hallmark of HSP is its **rash** : palpable purpura starting as pink macules or wheals and developing into petechiae, raised purpura, or larger ecchymoses. Occasionally, bullae and ulcerations develop. The skin lesions are usually symmetric and occur in gravity-dependent areas (lower extremities), extensor aspect of the upper extremities or on pressure points (buttocks) (Figs. 192.2 and 192.3). The skin lesions often evolve in groups, typically lasting 3-10 days, and may recur up to 4 mo after initial presentation. Subcutaneous edema localized to the dorsa of hands and feet, periorbital area, lips, scrotum, or scalp is also common.

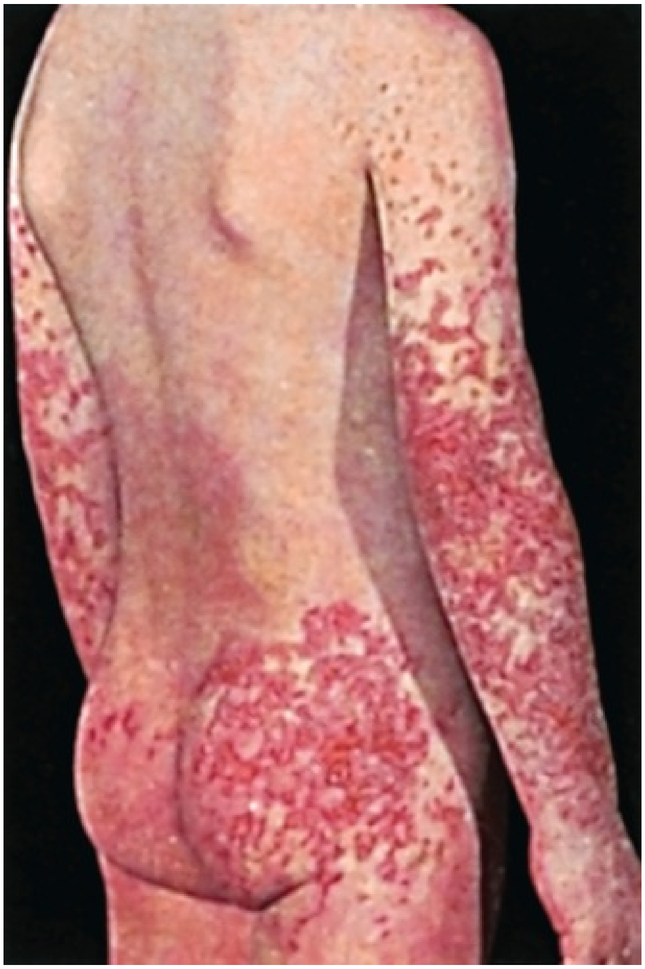

FIG. 192.3 **Henoch-Schönlein purpura. (From Korting GW: *Hautkrankheiten bei Kindern und Jungendlichen,* ed 3, Stuttgart, 1982, FK Schattaur Verlag.)**

Musculoskeletal involvement, including arthritis and arthralgias, is common, occurring in up to 75% of children with HSP. The arthritis tends to be self-limited and oligoarticular, with a predilection for large joints such as the knees and ankles, and does not lead to deformities. Periarticular swelling and tenderness without erythema or effusions are common. The arthritis usually resolves within 2 wk but can recur.

Gastrointestinal (GI) manifestations occur in up to 80% of children with HSP and include abdominal pain, vomiting, diarrhea, paralytic ileus, and melena. Intussusception, mesenteric ischemia, and intestinal perforation are rare but serious complications. Endoscopic evaluation is usually not needed but may identify vasculitis of the intestinal tract.

Renal involvement occurs in up to 30% of children with HSP, manifesting as microscopic hematuria, proteinuria, hypertension, frank nephritis, nephrotic syndrome, and acute or chronic renal failure. However, progression to end-stage renal disease (ESRD) is uncommon in children (1–2%) (see Chapter 538.3). Renal manifestations can be delayed for several months after the initial illness, so close follow-up with serial urinalyses and blood pressure monitoring is necessary.

Neurologic manifestations of HSP, caused by hypertension (posterior reversible encephalopathy syndrome) or central nervous system (CNS) vasculitis, may also occur, including intracerebral hemorrhage, seizures, headaches, depressed level of consciousness, cranial or peripheral neuropathies, and behavior changes. Other, less common potential manifestations of HSP are inflammatory eye disease, carditis, pulmonary hemorrhage, orchitis, and testicular torsion.

Diagnosis

The diagnosis of HSP is clinical and often straightforward when the typical rash is present. However, in at least 25% of cases, the rash appears after other manifestations, making early diagnosis challenging. Table 192.4 summarizes the EULAR/PRES classification criteria for HSP. Most patients are afebrile.

Table 192.4

Classification Criteria for Henoch-Schönlein Purpura*

European League Against Rheumatism/Pediatric Rheumatology European Society Criteria [†]

Palpable purpura (in absence of coagulopathy or thrombocytopenia) and 1 or more of the following criteria must be present:

- Abdominal pain (acute, diffuse, colicky pain)
- Arthritis or arthralgia
- Biopsy of affected tissue demonstrating predominant IgA deposition
- Renal involvement (proteinuria >3 g/24 hr), hematuria or red cell casts

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[*] Classification criteria are developed for use in research and not validated for clinical diagnosis.

[†] Developed for use in pediatric populations only.

Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria, *Ann Rheum Dis* 69:798–806; 2010.

The **differential diagnosis** for HSP depends on specific organ involvement but usually includes other small vessel vasculitides, infections, acute poststreptococcal glomerulonephritis, hemolytic-uremic syndrome, coagulopathies, and other acute intraabdominal processes. Additional disorders in the differential include papular-purpuric glove and sock syndrome, systemic lupus erythematosus (SLE), other vasculitides (urticarial, hypersensitivity), and thrombocytopenia.

Infantile acute hemorrhagic edema (AHE) , an isolated cutaneous leukocytoclastic vasculitis that affects infants <2 yr of age, resembles HSP clinically. AHE manifests as fever; tender edema of the face, scrotum, hands, and feet; and ecchymosis (usually larger than the purpura of HSP) on the face and extremities (Fig. 192.4). The trunk is spared, but petechiae may be seen in mucous membranes. The patient usually appears well except for the rash. The platelet count is normal or elevated, and the urinalysis results are normal. The younger age, the nature of the lesions, absence of other organ involvement, and a biopsy may help distinguish infantile AHE from HSP.

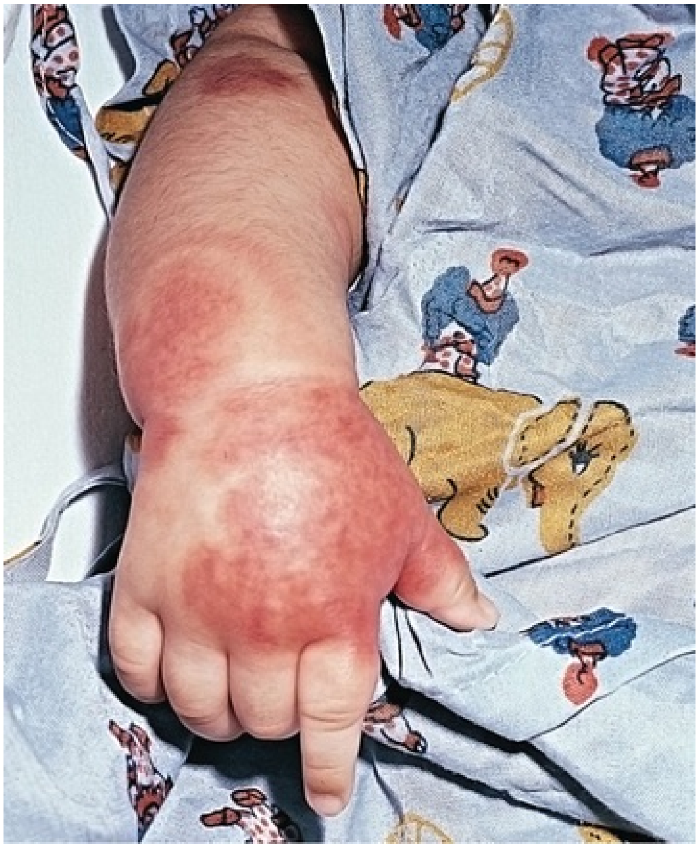

FIG. 192.4 **Infantile acute hemorrhagic edema. Typical lesions on the arm of an infant. (From Eichenfield LF, Frieden IJ, Esterly NB: *Textbook of neonatal dermatology,* Philadelphia, 2001, WB Saunders.)**

Laboratory Findings

No laboratory finding is diagnostic of HSP. Common but nonspecific findings include leukocytosis, thrombocytosis, mild anemia, and elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). *The platelet count is normal in HSP* . Occult blood is frequently found in stool specimens. Serum albumin levels may be low because of renal or intestinal protein loss. Autoantibody testing such as antinuclear antibody (ANA) is not useful diagnostically except to exclude other diseases. Serum IgA values are often elevated but are not routinely measured. Assessment of renal involvement with blood pressure, urinalysis, and serum creatinine is necessary.

Ultrasound is often used in the setting of GI complaints to look for bowel wall edema or the rare occurrence of an associated intussusception. Barium enema can also be used to both diagnose and treat intussusception. Although often unnecessary in typical HSP, biopsies of skin and kidney can provide important diagnostic information, particularly in atypical or severe cases, and characteristically show leukocytoclastic vasculitis with IgA deposition in affected tissues.

Treatment

Treatment for mild and self-limited HSP is *supportive,* with an emphasis on ensuring adequate hydration, nutrition, and analgesia. Corticosteroids are most often used to treat significant GI involvement or other life-threatening manifestations. Glucocorticoids such as oral prednisone (1-2 mg/kg/day), or in severe cases, intravenous (IV) methylprednisolone for 1-2 wk, followed by taper, reduce abdominal and joint pain but do not alter overall prognosis. Corticosteroids are not routinely recommended for prevention of complications such as nephritis. Rapid tapering of corticosteroids may lead to a flare of HSP symptoms. Although few data are available to demonstrate efficacy, intravenous immune globulin (IVIG) and plasma exchange are sometimes used for severe disease. In some patients, chronic HSP renal disease is managed with a variety of immunosuppressants, including azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. ESRD develops in <5% of children with HSP nephritis.

Complications

Acutely, serious GI involvement, including intussusception and intestinal perforation, imparts significant morbidity and mortality. Renal disease is the major long-term complication, occurring in 1–2% of children with HSP. Renal disease can develop up to 6 mo after diagnosis but rarely does so if the initial urinalysis findings are normal. Therefore, it is recommended that children with HSP undergo serial monitoring of blood pressure and urinalysis for at least 6 mo after diagnosis to monitor for development of nephritis.

Prognosis

Overall, the prognosis for childhood HSP is excellent, and most children experience an acute, self-limited course lasting on average 4 wk. However, 15–

60% of children with HSP experience 1 or more recurrences, typically within 4-6 mo of diagnosis. With each relapse, symptoms are usually milder than at presentation. Children with a more severe initial course are at higher risk for relapse. The long-term prognosis usually depends on the severity and duration of GI or renal involvement. Chronic renal disease develops in 1–2% of children with HSP, and <5% of those with HSP nephritis go on to have ESRD. The risk of HSP recurrence and graft loss following renal transplantation is estimated at 7.5% after 10 yr.

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Rev . 2014;13:355–358.

192.2

Takayasu Arteritis

Vidya Sivaraman, Edward C. Fels, Stacy P. Ardoin

Takayasu arteritis (**TA**), also known as **pulseless disease** , is a chronic large vessel vasculitis of unknown etiology that predominantly involves the aorta and its major branches.

Epidemiology

Although TA occurs worldwide and can affect all ethnic groups, the disease is most common in Asians. Age of onset is typically between 10 and 40 yr. Most children are diagnosed as adolescents, on average at age 13 yr. Up to 20% of individuals with TA are diagnosed before 19 yr. Younger children may be affected, but diagnosis in infancy is rare. TA preferentially affects females, with a reported 2-4 : 1 female/male ratio in children and adolescents and a 9 : 1 ratio among adults. Occlusive complications are more common in the United States, Western Europe, and Japan, whereas aneurysms predominate in Southeast Asia and Africa.

Pathology

TA is characterized by inflammation of the vessel wall, starting in the vasa vasorum. Involved vessels are infiltrated by T cells, natural killer cells, plasma cells, and macrophages. Giant cells and granulomatous inflammation develop in the media. Persistent inflammation damages the elastic lamina and muscular media, leading to blood vessel dilation and the formation of aneurysms. Progressive scarring and intimal proliferation can result in stenotic or occluded vessels. The subclavian, renal, and carotid arteries are the most commonly involved aortic branches; pulmonary, coronary, and vertebral arteries may also be affected.

Pathogenesis

The etiology of TA remains unknown. The presence of abundant T cells with a restricted repertoire of T-cell receptors in TA vascular lesions points to the importance of cellular immunity and suggests the existence of a specific but unknown aortic tissue antigen. Expression of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α is reported to be higher in patients with active TA than in patients with inactive TA and in healthy controls. In some patient populations, IL-1 genetic polymorphisms are linked to TA. Some individuals with TA have elevated serum values of antiendothelial antibodies. The increased prevalence of TA in certain ethnic populations and its occasional occurrence in monozygotic twins and families suggest a genetic predisposition to the disease.

Clinical Manifestations

The diagnosis of TA is challenging, because early disease manifestations are often nonspecific. As a result, diagnosis can be delayed for several months, and the time to diagnosis is usually longer in children than in adults. Fever, malaise, weight loss, headache, hypertension, myalgias, arthralgias, dizziness, and abdominal pain are common early complaints in the *pre-pulseless* phase of the disease. Among children, hypertension and headache are particularly common presenting manifestations and should prompt consideration of TA when present without alternative explanation. Some individuals with TA report no systemic symptoms and instead present with vascular complications. It is only after substantial vascular injury that evidence of hypoperfusion becomes clinically evident. Later manifestations of disease include diminished pulse, asymmetric blood pressure, claudication, Raynaud phenomenon, renal failure, and symptoms of pulmonary or cardiac ischemia. Inflammation can extend to the aortic valve, resulting in valvular insufficiency. Other findings may include pericardial effusion, pericarditis, pleuritis, splenomegaly, and arthritis.

Supradiaphragmatic (aortic arch) disease often manifests with CNS (stroke, transient ischemic attack) and cardiac (heart failure, palpitations) symptoms.

Infradiaphragmatic (mid-aortic syndrome) disease may produce hypertension, abdominal bruits, and pain. Most patients have involvement in both areas.

Diagnosis

Specific pediatric criteria for TA have been proposed (Table 192.5). *Radiographic demonstration of large vessel vasculitis is necessary* . A thorough physical examination is required to detect an aortic murmur, diminished or asymmetric pulses, and vascular bruits. Four extremity blood pressures should be measured; >10 mm Hg asymmetry in systolic pressure is indicative of disease.

Table 192.5

Proposed Classification Criteria for Pediatric-Onset Takayasu Arteritis

Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least 1 of the following criteria:

- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference between arms or legs of >10 mm Hg
- Bruits over the aorta and/or its major branches
- Hypertension (defined by childhood normative data)
- Elevated acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein)

Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria, *Ann Rheum Dis* 69:798–806; 2010.

Differential Diagnosis

In the early phase of TA, when nonspecific symptoms predominate, the differential diagnosis includes a wide array of systemic infections, autoimmune conditions, and malignancies. Although **giant cell arteritis** , also known as *temporal arteritis,* is a common large vessel vasculitis in older adults, this entity is rare in childhood. Noninflammatory conditions that can cause large vessel compromise include fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome.

Laboratory Findings

The laboratory findings in TA are nonspecific, and there is no specific diagnostic laboratory test. ESR and CRP value are typically elevated, and other nonspecific markers of chronic inflammation may include leukocytosis, thrombocytosis, anemia of chronic inflammation, and hypergammaglobulinemia. Autoantibodies, including ANA and ANCA, are not useful in diagnosing TA except to help exclude other autoimmune diseases.

Radiographic assessment is essential to establish large vessel arterial involvement. Conventional arteriography of the aorta and major branches, including carotid, subclavian, pulmonary, renal, and mesenteric branches, can identify luminal defects, including dilation, aneurysms, and stenoses, even in smaller vessels such as the mesenteric arteries. Fig. 192.5 shows a conventional arteriogram in a child with TA. Although not yet thoroughly validated in TA, magnetic resonance angiography (MRA) and computed tomography angiography (CTA) also provide important information about vessel wall thickness and enhancement, although they may not image smaller vessels as well as conventional angiography. Positron emission tomography (PET) may detect vessel wall inflammation but has not been studied extensively. Ultrasound with duplex color flow Doppler imaging may identify vessel wall thickening and assesses arterial flow. Echocardiography is recommended to assess for aortic valvular involvement. Serial vascular imaging is usually necessary to assess response to treatment and to detect progressive vascular damage.

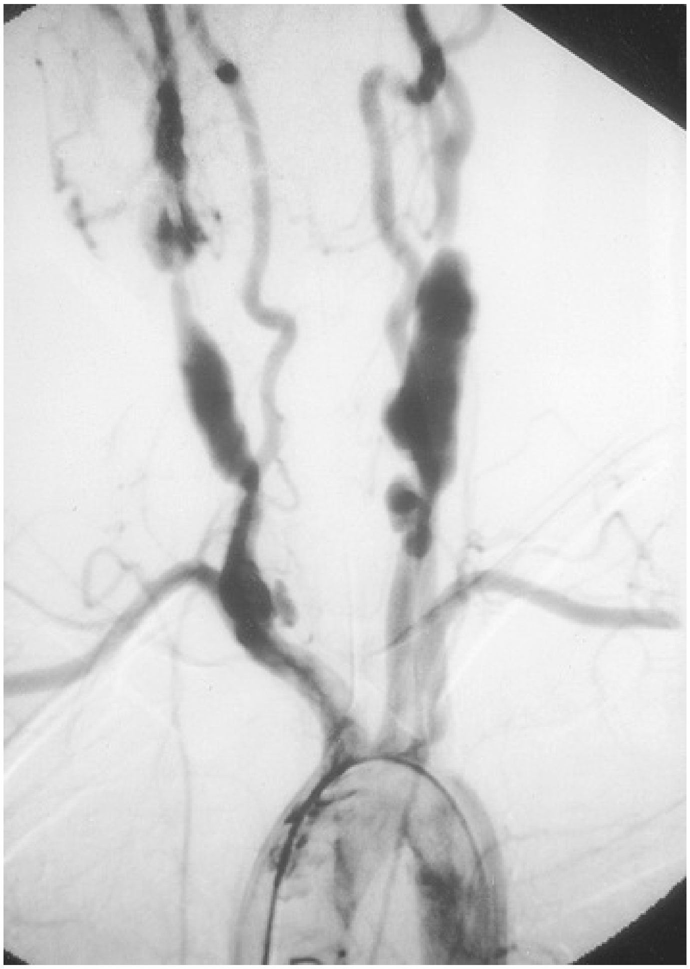

FIG. 192.5 Child with Takayasu arteritis. Conventional angiogram shows massive bilateral carotid dilation, stenosis, and poststenotic dilation.

Treatment

Glucocorticoids are the mainstay of therapy, typically starting with high doses (1-2 mg/kg/day of prednisone or methylprednisolone IV) followed by gradual dosage tapering. When TA progresses or recurs, steroid-sparing therapy is often required, usually involving methotrexate or azathioprine. *Cyclophosphamide* is reserved for severe or refractory disease. Results of small case series also suggest that *mycophenolate mofetil* or anti–TNF-α therapy may be beneficial in select patients. Anti–IL-6 therapy with tocilizumab has shown promising results in a small case series of children with TA. Antihypertensive medications are often necessary to control blood pressure caused by renovascular disease.

Complications

Progressive vascular damage can result in arterial stenoses, aneurysms, and occlusions, which produce ischemic symptoms and can be organ or life threatening. Potential ischemic complications include stroke, renal impairment or failure, myocardial infarction, mesenteric ischemia, and limb-threatening arterial disease. When these complications occur or are imminent, intervention with surgical vascular grafting or catheter-based angioplasty and stent placement may be necessary to restore adequate blood flow. A high rate of recurrent stenosis has been reported after angioplasty and stent placement. Aortic valve replacement may be required if significant aortic insufficiency develops.

Prognosis

Although up to 20% of individuals with TA have a monophasic course and achieve sustained remission, most suffer relapses. Survival for individuals with TA has improved considerably over the decades, although higher mortality rates are reported in children and adolescents. The overall estimated survival for individuals with TA is 93% at 5 yr and 87% at 10 yr. However, morbidity from vascular complications remains high, particularly when there is evidence of ongoing active inflammation as detected by elevated CRP or ESR. Given the chronic endothelial insult and inflammation, children and adolescents with TA are probably at high risk for accelerated atherosclerosis. Early detection and treatment are critical to optimizing outcome in TA.

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192.3

Polyarteritis Nodosa and Cutaneous Polyarteritis Nodosa

Vidya Sivaraman, Edward C. Fels, Stacy P. Ardoin

Polyarteritis nodosa (**PAN**) is a systemic necrotizing vasculitis affecting small and medium-size arteries. Aneurysms and stenoses form at irregular intervals throughout affected arteries. Cutaneous PAN is limited to the skin.

Epidemiology

PAN is rare in childhood. Boys and girls are equally affected, and the mean age at presentation is 9 yr. The cause is unknown, but the development of PAN following infections, including group A streptococcus and chronic hepatitis B, suggests that PAN may represent a postinfectious autoimmune response. Infections with other organisms, including Epstein-Barr virus, *Mycobacterium tuberculosis* , cytomegalovirus, parvovirus B19, and hepatitis C virus, have also been associated with PAN. There is a possible association between PAN and familial Mediterranean fever.

Pathology

Biopsies show **necrotizing vasculitis** with granulocytes and monocytes infiltrating the walls of small and medium-size arteries (Fig. 192.6). Involvement is usually segmental and tends to occur at vessel bifurcations. Granulomatous inflammation is not present, and deposition of complement and immune complexes is rarely observed. Different stages of inflammation are found, ranging from mild inflammatory changes to panmural fibrinoid necrosis associated with aneurysm formation, thrombosis, and vascular occlusion.

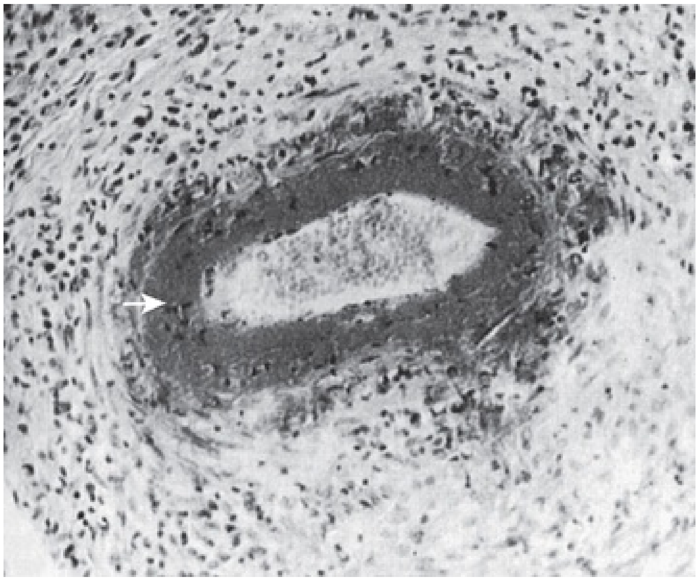

FIG. 192.6 **Polyarteritis nodosa. Biopsy specimen from a medium-size muscular artery that exhibits marked fibrinoid necrosis of the vessel wall *(arrow)* . (From Cassidy JT, Petty RE: Polyarteritis and related vasculitides. In *Textbook of pediatric rheumatology,* ed 5, Philadelphia, 2005, Elsevier/Saunders.)**

Pathogenesis

Immune complexes are believed to be pathogenic, but the mechanism is poorly understood. It is not known why PAN has a predilection for small and medium-size blood vessels. The inflamed vessel wall becomes thickened and narrowed, impeding blood flow and contributing to end-organ damage characteristic of this disease. Although there is no clear genetic association with PAN, PAN-like vasculitis is a component of 3 recently described monogenic autoinflammatory conditions.

Deficiency in **adenosine deaminase 2 (DADA2)** , caused by mutations in the *CECR1* gene, causes a familial form of vasculitis in Georgian Jewish patients with an autosomal recessive inheritance (see Chapter 188).

Clinical Manifestations

The clinical presentation of PAN is variable but generally reflects the distribution of inflamed vessels. Constitutional symptoms are present in most children at disease onset. Weight loss and severe abdominal pain suggest mesenteric arterial inflammation and ischemia. Renovascular arteritis can cause hypertension, hematuria, or proteinuria, although glomerulonephritis is not typical. Cutaneous manifestations include purpura, livedo reticularis, ulcerations, digital ischemia, and painful nodules. Arteritis affecting the nervous system can result in cerebrovascular accidents, transient ischemic attacks, psychosis, and ischemic motor or sensory peripheral neuropathy (**mononeuritis multiplex**). Myocarditis or coronary arteritis can lead to heart failure and myocardial ischemia; pericarditis and arrhythmias have also been reported. Arthralgias, arthritis, or myalgias are frequently present. Less common symptoms include testicular pain that mimics testicular torsion, bone pain, and vision loss as a result of retinal arteritis. The pulmonary vasculature is usually spared in PAN.

Diagnosis

The diagnosis of PAN requires demonstration of vessel involvement on biopsy or angiography (Table 192.6). Biopsy of cutaneous lesions shows small or medium vessel vasculitis (see Fig. 192.6). Kidney biopsy in patients with renal manifestations may show necrotizing arteritis. Electromyography in children with peripheral neuropathy identifies affected nerves, and sural nerve biopsy may reveal vasculitis. Conventional arteriography is the gold standard diagnostic imaging study for PAN and reveals areas of aneurysmal dilation and segmental stenosis, the classic “beads on a string” appearance (Fig. 192.7). MRA and CTA, less invasive imaging alternatives, are gaining acceptance, but may not be as effective in identifying small vessel disease or in younger children.

Table 192.6

Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa*

CRITERION	FINDINGS
Histopathology	Necrotizing vasculitis in medium or small arteries
Angiographic abnormalities	Angiography showing aneurysm, stenosis, or occlusion of medium or small artery not from noninflammatory cause
Cutaneous	Livedo reticularis, tender subcutaneous nodules, superficial skin ulcers, deep skin ulcers,

findings	digital necrosis, nail bed infarctions, or splinter hemorrhages
Muscle involvement	Myalgia or muscle tenderness
Hypertension	Systolic or diastolic blood pressure >95th percentile for height
Peripheral neuropathy	Sensory peripheral neuropathy, motor mononeuritis multiplex
Renal involvement	Proteinuria (>300 mg/24 hr equivalent), hematuria or red blood cell casts, impaired renal function (glomerular filtration rate <50% normal)

[*] The presence of 5 criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood-onset polyarteritis nodosa.

Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria, *Ann Rheum Dis* 69:798–806; 2010.

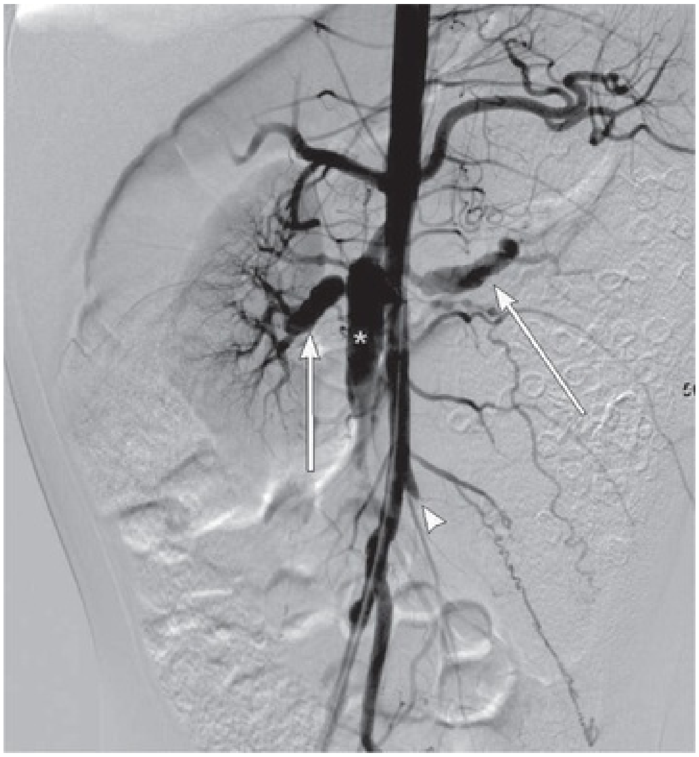

FIG. 192.7 **Child with polyarteritis nodosa. Abdominal aortogram shows bilateral renal artery aneurysms *(arrows)* , superior mesenteric artery aneurysm *(asterisk)* , and left common iliac artery occlusion *(arrowhead)* . (Courtesy of Dr. M. Hogan.)**

Differential Diagnosis

Early skin lesions may resemble those of HSP, although the finding of nodular lesions and presence of systemic features help distinguish PAN. Because pulmonary vascular involvement is very rare in PAN, pulmonary lesions suggest ANCA-associated vasculitis or Goodpasture disease. Other rheumatic diseases, including SLE, have characteristic target-organ involvement and associated autoantibodies distinguishing them from PAN. Prolonged fever and weight loss should also prompt consideration of inflammatory bowel disease or malignancy.

Laboratory Findings

Nonspecific laboratory findings include elevations of ESR and CRP, anemia, leukocytosis, and hypergammaglobulinemia. Abnormal urine sediment, proteinuria, and hematuria indicate renal disease. Laboratory findings may be normal in cutaneous PAN or similar to those of systemic PAN. Elevated hepatic enzyme values may suggest hepatitis B or C infection. Serologic tests for hepatitis (hepatitis B surface antigen and hepatitis C antibody) should be performed in all patients.

Treatment

Oral *prednisone* (1-2 mg/kg/day) or IV pulse *methylprednisolone* (30 mg/kg/day) are the mainstay of therapy. Oral or IV cyclophosphamide are often used as adjunctive therapy, and plasma exchange may be warranted for life-threatening disease. If hepatitis B is identified, appropriate antiviral therapy should be initiated (see Chapter 385). Most cases of cutaneous PAN can be treated with less intense therapy such as corticosteroids alone, nonsteroidal antiinflammatory drugs (NSAIDs), and methotrexate. Azathioprine, mycophenolate mofetil, IVIG, thalidomide, cyclosporine, and anti-TNF agents such as infliximab have all been reported as successful in treatment of refractory cutaneous or systemic PAN, although clinical trials are lacking. If an infectious trigger for PAN is identified, antibiotic prophylaxis can be considered.

Complications

Cutaneous nodules may ulcerate and become infected. Hypertension and chronic renal disease may develop from renovascular involvement in PAN. Cardiac involvement may lead to decreased cardiac function or coronary artery disease.

Mesenteric vasculitis can predispose to bowel infarction, rupture, and malabsorption. Stroke and rupture of hepatic arterial aneurysm are uncommon complications of this disorder.

Prognosis

The course of PAN varies from mild disease with few complications to a severe, multiorgan disease with high morbidity and mortality. Poor prognostic factors in PAN include elevated serum creatinine, proteinuria, severe GI involvement, cardiomyopathy, and CNS involvement. Early and aggressive immunosuppressive therapy increases the likelihood of clinical remission. Compared with disease in adults, childhood PAN is associated with less mortality. Cutaneous PAN is unlikely to transition to systemic disease. Early recognition and treatment of the disease are important to minimizing potential long-term vascular complications.

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192.4

Antineutrophilic Cytoplasmic Antibody–Associated Vasculitis

Vidya Sivaraman, Edward C. Fels, Stacy P. Ardoin

The ANCA-associated vasculitides are characterized by small vessel involvement, circulating ANCAs, and paucity of immune complex deposition in affected tissues, thus the term **pauci-immune vasculitis** . ANCA-associated vasculitis is categorized into 3 distinct forms: **granulomatosis with polyangiitis (GPA)** , formerly Wegener granulomatosis; **microscopic polyangiitis (MPA)** ; and **eosinophilic granulomatosis with polyangiitis** , formerly Churg-Strauss syndrome (**CSS**) (see Table 192.1).

Epidemiology

GPA is a necrotizing granulomatous small and medium vessel vasculitis that occurs at all ages and targets the upper and lower respiratory tracts and the kidneys. Although most cases of GPA occur in adults, the disease also occurs in children with a mean age at diagnosis of 14 yr. There is a female predominance of 3-4 : 1, and pediatric GPA is most prevalent in Caucasians.

MPA is a small vessel necrotizing vasculitis with clinical features similar to those of GPA, but without granulomas and upper airway involvement. CSS is a small vessel necrotizing granulomatous (allergic granulomatosis) vasculitis associated with a history of refractory asthma and peripheral eosinophilia. MPA and CSS are rare in children, and there does not appear to be a gender predilection in either disease.

Pathology

Necrotizing vasculitis is the cardinal histologic feature in both GPA and MPA. Kidney biopsies typically demonstrate crescentic glomerulonephritis with little or no immune complex deposition (“pauci-immune”), in contrast to biopsies from patients with SLE. Although granulomatous inflammation is common in GPA and CSS, it is typically not present in MPA. Biopsies showing perivascular eosinophilic infiltrates distinguish CSS syndrome from both MPA and GPA (Table 192.7).

Table 192.7

Differential Diagnostic Features of Small Vessel Vasculitis

FEATURE	HENOCH-SCHÖNLEIN PURPURA	GRANULOMATOSIS WITH POLYANGIITIS	CHURG-STRAUSS SYNDROME*	MICROSCOPIC POLYANGIITIS
Signs and symptoms of	+	+	+	+

small vessel vasculitis [†]				
IgA-dominant immune deposits	+	−	−	−
Circulating antineutrophil cytoplasmic antibodies	−	+ (PR3)	+ (MPO > PR3)	+ (MPO)
Necrotizing vasculitis	−	+	+	+
Granulomatous inflammation	−	+	+	−
Asthma and eosinophilia	−	−	+	−

[*] Eosinophilic granulomatosis with polyangiitis.

[†] Signs and symptoms of small vessel vasculitis include purpura, other rash, arthralgias, arthritis, and constitutional symptoms.

MPO, Myeloperoxidase-reactive antibodies; PR3, proteinase-3–reactive antibodies; +, present; −, absent.

Adapted from Jeannett JC, Falk RJ: Small-vessel vasculitis, *N Engl J Med* 337:1512–1523, 1997.

Pathogenesis

The etiology of ANCA-associated vasculitis remains unknown, although neutrophils, monocytes, and endothelial cells are involved in disease pathogenesis. Neutrophils and monocytes are activated by ANCAs, specifically by the ANCA-associated antigens proteinase-3 (PR3) and myeloperoxidase (MPO), and release proinflammatory cytokines such as TNF-α and IL-8. Localization of these inflammatory cells to the endothelium results in vascular damage characteristic of the ANCA vasculitides. Why the respiratory tract and kidneys are preferential targets in GPA and MPA is unknown.

Clinical Manifestations

Early disease course is characterized by nonspecific constitutional symptoms, including fever, malaise, weight loss, myalgias, and arthralgias. In GPA, upper airway involvement can manifest as sinusitis, nasal ulceration, epistaxis, otitis media, and hearing loss. Lower respiratory tract symptoms in GPA include cough, wheezing, dyspnea, and hemoptysis. Pulmonary hemorrhage can cause rapid respiratory failure. Compared with adults, childhood GPA is more frequently complicated by subglottic stenosis (Fig. 192.8). Inflammation-induced damage to the nasal cartilage can produce a saddle nose deformity (Fig. 192.8). Ophthalmic involvement includes conjunctivitis, scleritis, uveitis, optic neuritis, and invasive orbital pseudotumor (causing proptosis). Perineural vasculitis or direct compression on nerves by granulomatous lesions can cause cranial and peripheral neuropathies. Hematuria, proteinuria, and hypertension in GPA signal renal disease. Cutaneous lesions include palpable purpura and ulcers. Venous thromboembolism is a rare but potentially fatal complication of GPA. The frequencies of organ system involvement throughout the disease course in GPA follow: respiratory tract, 74%; kidneys, 83%; joints, 65%; eyes, 43%; skin, 47%; sinuses, 70%; and nervous system, 20%. Table 192.8 lists the classification criteria for pediatric-onset GPA.

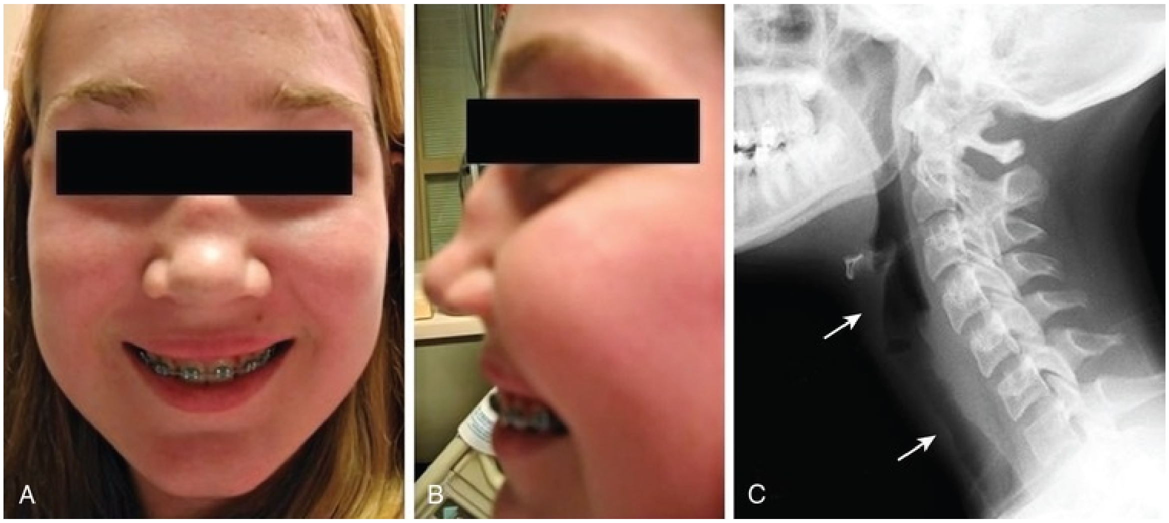

FIG. 192.8 Adolescent girl with granulomatosis with polyangiitis. A and B, Anterior and lateral views of saddle nose deformity. C, Segment of subglottic posterior tracheal irregularity (between *arrows*) on lateral neck radiograph.

Table 192.8

EULAR/PReS Classification Criteria for Pediatric-Onset Granulomatosis with Polyangiitis*

Histopathology showing granulomatous inflammation
Upper airway involvement
Laryngeal, tracheal or bronchial involvement
Antineutrophil cytoplasmic antibody (ANCA) positivity
Renal involvement

Proteinuria, hematuria, red blood cell casts, necrotizing pauci-immune glomerulonephritis

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[*] Diagnosis requires 3 of 6 criteria.

Adapted from: Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II. Final classification criteria, *Ann Rheum Dis* 69:798–806; 2010.

The clinical presentation of MPA closely resembles that of GPA, although sinus disease is less common; systemic features of fever, malaise, weight loss, myalgias, and arthralgias may be dominant. MPA predominantly affects the kidney and lungs; other organ systems include skin, CNS, muscle, heart, and eyes.

CSS frequently causes inflammation of the upper and lower respiratory tracts, but cartilage destruction is rare. CSS may initially demonstrate chronic or recurrent rhinitis/sinusitis, nasal polyposis, nonfixed pulmonary lesions, and difficult-to-treat asthma. Eosinophilia (>10% of leukocytes) with pulmonary infiltrates may precede a vasculitic phase. Other organ involvement includes skin, cardiac, peripheral neuropathy, GI tract, and muscle. Renal involvement in CSS is uncommon.

Diagnosis

GPA should be considered in children who have recalcitrant sinusitis, pulmonary infiltrates, and evidence of nephritis. Chest radiography often fails to detect pulmonary lesions, and chest CT may show nodules, ground-glass opacities, mediastinal lymphadenopathy, and cavitary lesions (Fig. 192.9). The diagnosis is confirmed by the presence of c-ANCA with anti-PR3 specificity (PR3-ANCAs) and the finding of necrotizing granulomatous vasculitis on pulmonary, sinus, or renal biopsy. The ANCA test result is positive in approximately 90% of children with GPA, and the presence of anti-PR3 increases the specificity of the test.

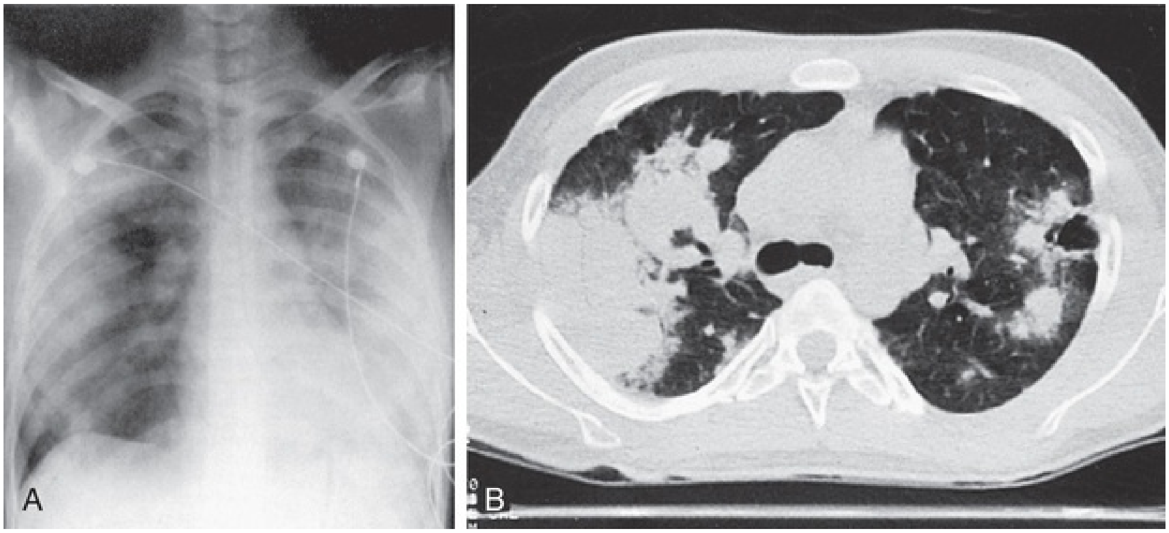

FIG. 192.9 Radiographs of lower respiratory tract disease in granulomatosis with polyangiitis (GPA). A, Chest radiograph of 14 yr old girl with GPA and pulmonary hemorrhage. Extensive bilateral, fluffy infiltrates are visualized. B, Chest CT scan in 17 yr old boy with GPA. Air space consolidation, septal thickening, and a single cavitary lesion are present. (A from Cassidy JT, Petty RE: Granulomatous vasculitis, giant cell arteritis and sarcoidosis. In *Textbook of pediatric rheumatology,* ed 3, Philadelphia, 1995, Saunders; B from Kuhn JP, Slovis TL, Haller JO: *Caffey's pediatric diagnostic imaging,* ed 10, vol 1, Philadelphia, 2004, Mosby.)

In MPA, ANCAs are also frequently present (70% of patients) but are usually p-ANCA with reactivity to MPO (MPO-ANCAs). MPA can be distinguished from PAN by the presence of ANCAs and the tendency for small vessel involvement. The ANCA test result is positive in 50–70% of cases of CSS, and MPO-ANCAs are more common than PR3-ANCAs. In addition, the presence of chronic asthma and peripheral eosinophilia suggests the diagnosis of CSS.

Differential Diagnosis

ANCAs are absent in other granulomatous diseases, such as sarcoidosis and tuberculosis. **Goodpasture syndrome** is characterized by antibodies to glomerular basement membrane. Medications such as propylthiouracil, hydralazine, and minocycline are associated with drug-induced ANCA (usually perinuclear ANCA) vasculitis. SLE and HSP can manifest as pulmonary hemorrhage and nephritis.

Laboratory Findings

Nonspecific laboratory abnormalities include elevated ESR and CRP values, leukocytosis, and thrombocytosis, which are present in most patients with an ANCA-associated vasculitis but are nonspecific. Anemia may be caused by chronic inflammation or pulmonary hemorrhage. ANCA antibodies show 2 distinct immunofluorescence patterns: *perinuclear* (p-ANCA) and *cytoplasmic* (c-ANCA). In addition, ANCAs can also be defined by their specificity for PR3 or MPO antigen. GPA is strongly associated with c-ANCAs/anti-PR3 antibodies, whereas 75% of patients with MPA have a positive p-ANCA (see Table 192.7). There is no clear correlation between ANCA titers and disease activity or relapse.

Treatment

When the lower respiratory tract or kidneys are significantly involved, initial induction therapy usually consists of prednisone (oral 2 mg/kg/day oral or IV methylprednisolone 30 mg/kg/day × 3 days) in conjunction with daily oral or monthly IV cyclophosphamide. *Rituximab* , a monoclonal antibody to CD20 on activated B cells, is an option for induction therapy in ANCA-positive vasculitides, although it has been studied primarily in adults. *Plasmapheresis* in conjunction with methylprednisolone has a role in the therapy of patients with severe disease manifestations such as pulmonary hemorrhage or ESRD, with the potential for reducing dialysis dependency. Patients are transitioned to a less toxic maintenance medication (usually methotrexate, azathioprine, or mycophenolate mofetil) within 3-6 mo once remission is achieved. Trimethoprim-sulfamethoxazole (one 180 mg/800 mg tablet 3 days/wk) is often prescribed both for prophylaxis against *Pneumocystis jiroveci* infection and to reduce upper respiratory bacterial colonization with *S. aureus,* which may trigger disease activity. If disease is limited to the upper respiratory tract, corticosteroids (1-2 mg/kg/day) and methotrexate (0.5-1.0 mg/kg/wk) may be first-line treatment.

Mepolizumab , an anti–IL-5 monoclonal antibody, may have a role in the treatment of eosinophilic granulomatosis with polyangiitis (CSS).

Complications

Upper respiratory tract lesions can invade the orbit and threaten the optic nerve, and lesions in the ear can cause permanent hearing loss. Respiratory complications include potentially life-threatening pulmonary hemorrhage and upper airway obstruction caused by subglottic stenosis. Chronic lung disease secondary to granulomatous inflammation, cavitary lesions, and scarring can predispose to infectious complications. Chronic glomerulonephritis may progress to ESRD in a subset of patients with advanced or undertreated disease.

Prognosis

The course is variable, but disease relapse occurs in up to 60% of patients. Mortality has been reduced with the introduction of cyclophosphamide and other immunosuppressive agents. Compared with adults, children are more likely to develop multiorgan involvement, renal involvement, and subglottic stenosis.

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192.5

Other Vasculitis Syndromes

Vidya Sivaraman, Edward C. Fels, Stacy P. Ardoin

Other vasculitic conditions can occur in childhood; the most common is **Kawasaki disease** (see Chapter 191). **Behçet disease** is a rare form of vasculitis seen in children of Turkish and Mediterranean descent, characterized by the triad of recurrent aphthous stomatitis, genital ulcers, and uveitis (see Chapter 186).

Hypersensitivity vasculitis is a cutaneous vasculitis triggered by medication or toxin exposure. The rash consists of palpable purpura or other, nonspecific rash. Skin biopsies reveal characteristic changes of **leukocytoclastic vasculitis**

(small vessels with neutrophilic perivascular or extravascular neutrophilic infiltration) (Table 192.9). **Hypocomplementemic urticarial vasculitis** involves small vessels and manifests as recurrent urticaria that resolves over several days but leaves residual hyperpigmentation. This condition is associated with low levels of complement component C1q and systemic findings that include fever, GI symptoms, arthritis, and glomerulonephritis. Some patients with urticarial vasculitis have normal complement levels. **Cryoglobulinemic vasculitis** can complicate mixed essential cryoglobulinemia and is a small vessel vasculitis affecting skin, joints, kidneys, and lungs.

Table 192.9

Criteria for Diagnosis of Hypersensitivity Vasculitis*

CRITERION	DEFINITION
Age at onset >16 yr	Development of symptoms after 16 yr of age
Medication at disease onset	Medication that may have been a precipitating factor was taken at the onset of symptoms
Palpable purpura	Slightly elevated purpuric rash over 1 or more areas; does not blanch with pressure and is not related to thrombocytopenia
Maculopapular rash	Flat and raised lesions of various sizes over 1 or more areas of the skin
Biopsy, including arteriole and venule	Histologic changes showing granulocytes in a perivascular or extravascular location

* For purposes of classification, a patient is said to have hypersensitivity vasculitis if at least 3 of these criteria are present. The presence of ≥3 criteria has a diagnostic sensitivity of 71.0% and specificity of 83.9%. The age criterion is not applicable for children.

Adapted from Calabrese LH, Michel BA, Bloch DA, et al: The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis, *Arthritis Rheum* 33:1108–1113, 1990 (Table 2, p 1110); and *Textbook of pediatric rheumatology,* ed 7, Philadelphia, 2016, Elsevier (Table 38.2, p 511).

Primary angiitis of the central nervous system represents vasculitis confined to the CNS and requires exclusion of other systemic vasculitides. **Large vessel disease** (angiography positive) may be progressive or nonprogressive and may manifest with focal deficits similar to an occlusive stroke, with hemiparesis, focal gross or fine motor deficits, language disorders, or cranial nerve deficits. Diffuse cognitive, memory, and concentration deficits as well as behavioral disorders are seen in 30–40% of patients. **Small vessel disease** (angiography negative, biopsy positive) more often results in language problems and diffuse deficits, such as cognitive, memory, behavior, and concentration problems, as well as focal seizures. In both types of cerebral angiitis, patients may have an elevated ESR or CRP and abnormal CSF findings (increased protein, pleocytosis), although these are not consistent findings in all patients. Diagnosis remains a challenge, and brain biopsy is often indicated to confirm the diagnosis and exclude vasculitis mimics such as infections that could worsen with immunosuppressive therapy (Table 192.10).

Table 192.10

Differential Diagnosis of Small Vessel Primary Central Nervous System (CNS) Vasculitis in Children

CNS Vasculitis Complicating Other Diseases

Infections

- Bacterial: *Mycobacterium tuberculosis, Mycoplasma pneumoniae, Streptococcus pneumoniae*
- Viral: Epstein-Barr virus, cytomegalovirus, enterovirus, varicella-zoster virus, hepatitis C virus, parvovirus B19, West Nile virus
- Fungal: *Candida albicans, Actinomyces, Aspergillus*
- Spirochetal: *Borrelia burgdorferi, Treponema pallidum*

Rheumatic and Inflammatory Diseases

- Systemic vasculitis such as granulomatosis with polyangiitis, microscopic polyangiitis, Henoch-Schönlein purpura, Kawasaki disease, polyarteritis nodosa, Behçet disease
- Systemic lupus erythematosus, juvenile dermatomyositis, morphea
- Inflammatory bowel disease
- Autoinflammatory syndromes
- Hemophagocytic lymphohistiocytosis
- Neurosarcoidosis
- Adenosine deaminase-2 deficiency

Other

- Drug-induced vasculitis
- Malignancy-associated vasculitis

Nonvasculitis Inflammatory Brain Diseases

Demyelinating Diseases

- Multiple sclerosis, acute demyelinating encephalomyelitis (ADEM), optic neuritis, transverse myelitis

Antibody-Mediated Inflammatory Brain Disease

- Anti–NMDA receptor encephalitis, neuromyelitis optica (NMO), antibody-associated limbic encephalitis (antibodies against LGI, AMP, AMP-binding protein), Hashimoto encephalopathy, celiac disease, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

T-Cell–Associated Inflammatory Brain Disease

- Rasmussen encephalitis

Other

- Febrile infection-related epilepsy syndrome (FIRES)

Noninflammatory Vasculopathies

- Hemoglobinopathies (sickle cell disease), thromboembolic disease
- Radiation vasculopathy, graft-versus-host disease
- Metabolic and genetic diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS), CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy), moyamoya disease,

Fabray disease

- Malignancy (lymphoma)

Modified from Gowdie P, Twilt M, Benseler SM: Primary and secondary central nervous system vasculitis. *J Child Neurol* 27:1448–1459, 2012.

Nonprogressive angiography-positive CNS vasculitis, also known as *transient CNS angiopathy,* represents a more benign variant and can be seen after varicella infection. **Cogan syndrome** is rare in children; its potential clinical manifestations include constitutional symptoms; inflammatory eye disease such as uveitis, episcleritis, or interstitial keratitis; vestibuloauditory dysfunction (vertigo, hearing loss, tinnitus); arthritis; and large vessel vasculitis or aortitis. Cerebral autosomal **dominant** arteriopathy with subcortical infarcts and leukoencephalopathy (**CADASIL**) is caused by mutations in the *NOTCH3* gene and manifests with stroke, mood changes, cognitive decline, and migraines; it is a vasculitis mimic and demonstrates osmophilic granules in cerebral arteries. **CARASIL** (cerebral autosomal **recessive** arteriopathy with subcortical infarcts and leukoencephalopathy) is another mimic of angiitis caused by mutations in the *HTRA1* gene. It manifests with early-onset hair loss, spasticity, stroke, memory loss, and personality changes.

Identification of these vasculitis syndromes requires a comprehensive history and physical examination. Table 192.11 outlines other diagnostic considerations. Although tailored to disease severity, treatment generally includes prednisone (up to 2 mg/kg/day). Potent immunosuppressive medications, such as cyclophosphamide, are often indicated, particularly in primary angiitis of the CNS to prevent rapid neurologic decline. For hypersensitivity vasculitis, withdrawal of the triggering medication or toxin is indicated if possible.

Table 192.11

Diagnostic Considerations for Other Vasculitis Syndromes

VASCULITIS SYNDROME	APPROACH TO DIAGNOSIS
Hypersensitivity vasculitis	Skin biopsy demonstrating leukocytoclastic vasculitis
Hypocomplementemic urticarial vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Low levels of circulating C1q
Cryoglobulinemic vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Measurement of serum cryoglobulins

	Exclusion of hepatitides B and C infections
Primary angiitis of CNS	Conventional, CT, or MRA evidence of CNS vasculitis Consideration of dura or brain biopsy
Nonprogressive angiography-positive CNS vasculitis	Conventional, CT, or MRA evidence of CNS vasculitis
Cogan syndrome	Ophthalmology and audiology evaluations Conventional, CT, or MRA evidence of CNS or aortic vasculitis

CNS, Central nervous system; CT, computed tomography; MRA, magnetic resonance angiography.

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CHAPTER 193

Musculoskeletal Pain Syndromes

Kelly K. Anthony, Laura E. Schanberg

Musculoskeletal pain is a frequent complaint of children presenting to general pediatricians and is the most common presenting problem of children referred to pediatric rheumatology clinics. Prevalence estimates of persistent musculoskeletal pain in community samples range from 10–30%. Although diseases such as juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) may manifest as persistent musculoskeletal pain, the majority of musculoskeletal pain complaints in children are benign in nature and attributable to trauma, overuse, and normal skeletal growth variations. In a subset of children, chronic pain complaints develop in the absence of physical or laboratory abnormalities. Children with idiopathic musculoskeletal pain syndromes also typically develop marked subjective distress and functional impairment. Therefore the treatment of children with musculoskeletal pain syndromes optimally includes both pharmacologic and nonpharmacologic interventions.

Clinical Manifestations

Chronic musculoskeletal pain syndromes involve pain complaints at least 3 mo in duration in the absence of objective abnormalities on physical examination or laboratory screening. Additionally, children and adolescents with musculoskeletal pain syndromes often complain of persistent pain despite previous treatment with nonsteroidal antiinflammatory drugs (NSAIDs) and analgesic agents. The location varies, with pain complaints either localized to a single extremity or more diffuse and involving multiple extremities. The pain may start in a single area of the body before intensifying and radiating to other areas over time. The prevalence of musculoskeletal pain syndromes increases with age and is higher in females, thus rendering adolescent girls at highest risk.

The somatic complaints of children and adolescents with musculoskeletal pain syndromes are typically accompanied by psychological distress, sleep difficulties, and functional impairment across home, school, and peer domains. **Psychological distress** may include symptoms of anxiety and depression, such as frequent crying spells, fatigue, sleep disturbance, feelings of worthlessness, poor concentration, and frequent worry. Indeed, a substantial number of children with musculoskeletal pain syndromes display the full range of psychological symptoms, warranting an additional diagnosis of a comorbid mood or anxiety disorder (e.g., major depressive episode, generalized anxiety disorder). **Sleep disturbance** in children with musculoskeletal pain syndromes may include difficulty falling asleep, multiple night awakenings, disrupted sleep–wake cycles with increased daytime sleeping, nonrestorative sleep, and fatigue.

For children and adolescents with musculoskeletal pain syndromes, the constellation of pain, psychological distress, and sleep disturbance often leads to a high degree of functional impairment. Poor school attendance is common, and children may struggle to complete other daily activities relating to self-care and participation in household chores. Decreased physical fitness can also occur, as well as changes in gait and posture, as children avoid contact with or use of the body area affected by pain. Peer relationships may also be disrupted by decreased opportunities for social interaction because of pain. As such, children and adolescents with musculoskeletal pain syndromes often report loneliness and social isolation characterized by few friends and lack of participation in extracurricular activities.

Diagnosis and Differential Diagnosis

The diagnosis of a musculoskeletal pain syndrome is typically one of exclusion when careful, repeated physical examinations and laboratory testing do not reveal an etiology. At initial presentation, children with pain complaints require a thorough clinical history and a complete physical examination to look for an obvious etiology (sprains, strains, or fractures), characteristics of the pain (localized or diffuse), and evidence of systemic involvement. A comprehensive history can be particularly useful in providing clues to the possibility of underlying illness or systemic disease. The presence of current or recent fever can be indicative of an inflammatory or neoplastic process if the pain is also accompanied by worsening symptoms over time or weight loss.

Subsequent, *repeated* physical examinations of children with musculoskeletal pain complaints may reveal eventual development and manifestations of rheumatic or other diseases. The need for additional testing should be individualized, depending on the specific symptoms and physical findings. Laboratory screening and radiography should be pursued if there is suspicion of certain underlying disease processes. Possible indicators of a serious, vs a benign, cause of musculoskeletal pain include pain present at rest, pain that may be relieved by activity, objective joint swelling on physical examination, stiffness or limited range of motion in joints, bony tenderness, muscle weakness, poor growth and/or weight loss, and constitutional symptoms (e.g., fever, malaise) (Table 193.1). In the case of laboratory screenings, a complete blood count (CBC) and erythrocyte sedimentation rate (ESR) are likely to be abnormal in children whose pain is secondary to a bone or joint infection, SLE, or a malignancy. Bone tumors, fractures, and other focal pathology resulting from infection, malignancy, or trauma can often be identified through imaging studies, including plain radiographs, MRI, and less often technetium-99m bone scans.

Table 193.1

Potential Indicators of Benign vs Serious Causes of Musculoskeletal Pain

CLINICAL FINDING	BENIGN CAUSE	SERIOUS CAUSE
Effects of rest vs activity on pain	Relieved by rest and worsened by activity	Present at rest and may be relieved by activity
Time of day pain occurs	End of the day and nights	Morning*
Objective joint swelling	No	Yes
Joint characteristics	Hypermobile/normal	Stiffness, limited range of motion
Bony tenderness	No	Yes
Muscle strength	Normal	Muscle weakness
Gait	Normal	Limp or refusal to walk
Growth	Normal growth pattern or weight gain	Poor growth and/or weight loss
Constitutional symptoms (e.g., fever, malaise)	Fatigue without other constitutional symptoms	Yes
Lab findings	Normal CBC, ESR, CRP	Abnormal CBC, raised ESR and CRP
Imaging findings	Normal	Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bony destruction

* Cancer pain is often severe and worst at night.

CBC, Complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.

Adapted from Malleson PN, Beauchamp RD: Diagnosing musculoskeletal pain in children, *CMAJ* 165:183–188, 2001.

The presence of persistent pain, accompanied by psychological distress, sleep disturbance, and/or functional impairment, in the absence of objective laboratory or physical examination abnormalities, suggests the diagnosis of an **idiopathic** musculoskeletal pain syndrome. All pediatric musculoskeletal pain syndromes share this general constellation of symptoms at presentation. Several more specific pain syndromes routinely seen by pediatric practitioners can be differentiated by anatomic region and associated symptoms. Table 193.2 outlines pediatric musculoskeletal pain syndromes, including growing pains (see Chapter 193.1), fibromyalgia (Chapter 193.3), complex regional pain syndrome (Chapter 193.4), localized pain syndromes, low back pain, and chronic sports-related pain syndromes (e.g., Osgood-Schlatter disease).

Table 193.2

Common Musculoskeletal Pain Syndromes in Children by Anatomic Region

ANATOMIC REGION	**PAIN SYNDROMES**	
Shoulder	Impingement syndrome	
Elbow	"Little League elbow" Avulsion fractures Osteochondritis dissecans	Tennis elbow Panner disease
Arm	Localized hypermobility syndrome Complex regional pain syndrome	
Pelvis and hip	Avulsion injuries Legg-Calvé-Perthes syndrome	Slipped capital femoral epiphysis Congenital hip dysplasia
Knee	Osteochondritis dissecans Osgood-Schlatter disease Sinding-Larsen syndrome	Patellofemoral syndrome Malalignment syndromes
Leg	Growing pains Complex regional pain syndrome Localized hypermobility syndrome	Shin splints Stress fractures Compartment syndromes
Foot	Plantar fasciitis Tarsal coalition Stress fractures	Achilles tendonitis Juvenile bunion
Spine	Musculoskeletal strain Spondylolisthesis Spondylolysis	Scoliosis Scheuermann disease (kyphosis) Low back pain
Generalized	Hypermobility syndrome Juvenile fibromyalgia Generalized pain syndrome	

Adapted from Anthony KK, Schanberg LE: Assessment and management of pain syndromes and arthritis pain in children and adolescents, *Rheum Dis Clin North Am* 33:625–660, 2007 (Box 1).

Treatment

The primary goal of treatment for pediatric musculoskeletal pain syndromes is to improve function rather than relieve pain, and these 2 desirable outcomes may not occur simultaneously. Indeed, it is common for children with musculoskeletal pain syndromes to continue complaining of pain even as they resume normal function (e.g., increased school attendance and participation in extracurricular activities). For all children and adolescents with pediatric musculoskeletal pain syndromes, regular school attendance is crucial, because this is a hallmark of normal functioning in this age-group. The dual nature of treatment, targeting both *function* and *pain*, needs to be clearly explained to children and their families to outline better the goals by which treatment success will be measured. Indeed, children and families need to be supported in disengaging from the sole pursuit of pain relief and embracing broader treatment goals of improved functioning.

Recommended treatment modalities typically include physical and/or occupational therapy, pharmacologic interventions, and cognitive-behavioral and/or other psychotherapeutic interventions. The overarching goal of **physical therapy** is to improve children's physical function and should emphasize participation in aggressive but graduated aerobic exercise. **Pharmacologic** interventions should be used judiciously. Low-dose tricyclic antidepressants (amitriptyline, 10-50 mg orally 30 min before bedtime) are indicated for treatment of sleep disturbance; selective serotonin reuptake inhibitors (sertraline, 10-20 mg daily) may prove useful in treating symptoms of depression and anxiety if present. Referral for psychological evaluation is warranted if these symptoms do not resolve with initial treatment efforts or if suicidal ideation is present. **Cognitive-behavioral therapy (CBT)** and/or other **psychotherapeutic** interventions are typically designed to teach children and adolescents coping skills for controlling the behavioral, cognitive, and physiologic responses to pain. Specific components often include cognitive restructuring, relaxation, distraction, and problem-solving skills; additional targets of therapy include sleep hygiene and activity scheduling, all with the goal of restoring normal sleep patterns and activities of daily living. Parent education and involvement in the psychological intervention is important to ensure maintenance of progress. More intensive family-based approaches are warranted if barriers to treatment success are identified at the family level. These could include parenting strategies or family dynamics that serve to maintain children's pain complaints, such as overly solicitous responses to the child's pain and maladaptive models for pain coping.

Complications and Prognosis

Musculoskeletal pain syndromes can negatively affect the child's development and future role functioning. Worsening pain and the associated symptoms of depression and anxiety can lead to substantial school absences, peer isolation, and developmental delays later in adolescence and early adulthood. Specifically, adolescents with musculoskeletal pain syndromes may fail to achieve the level of autonomy and independence necessary for age-appropriate activities, such as attending college, living away from home, and maintaining a job. Fortunately, not all children and adolescents with musculoskeletal pain syndromes experience this degree of impairment, but many children experience pain that persists for 1 yr or more. Factors that contribute to the persistence of pain are increasingly understood and include female gender, pubertal stage at pain onset, older age of pain onset, increased psychological distress associated with the pain, joint hypermobility, and greater functional impairment. The likelihood of positive health outcomes is increased with multidisciplinary treatment.

193.1

Growing Pains

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More appropriately termed **benign nocturnal pains of childhood** , growing pains affect 10–20% of children, with peak incidence between age 4 and 12 yr. Pain does not occur during periods of rapid growth or at growth sites. The most common cause of recurrent musculoskeletal pain in children, growing pains are intermittent and bilateral, predominantly affecting the anterior thigh, shin, and calf, but not joints. Occasionally, bilateral upper extremity pain may be associated with leg pain; isolated upper extremity pain does not occur. Children typically describe cramping or aching that occurs in the late afternoon or evening. Pain may wake the child from sleep and may last a few minutes to hours, but resolves quickly with massage or analgesics; pain is never present the following morning (Table 193.3). Pain often follows a day with exercise or other physical activities. Physical findings are normal, and gait is not impaired.

Table 193.3

Inclusion and Exclusion Criteria for Growing Pains Including Features of Restless Leg Syndromes (RLS)

	INCLUSIONS	EXCLUSIONS	RLS FEATURES
Nature of pain	Intermittent; some pain-free days and nights, deep aching, cramping	Persistent; increasing intensity, pain during the day	Urge to move legs often accompanied by unpleasant sensations in legs, but may not be painful
Unilateral or bilateral	Bilateral	Unilateral	
Location of pain	Anterior thigh, calf, posterior knee—in muscles not the joints	Articular, back, or groin pain	Urge to move and discomfort throughout leg
Onset of pain	Late afternoon or evening	Pain still present next morning	Worse later in day or night but also present at periods of rest or inactivity throughout the day
Physical findings	Normal	Swelling, erythema, tenderness; local trauma or infection; reduced joint range of motion; limping, fever, weight loss, mass	
Laboratory findings	Normal	Objective evidence of abnormalities; increased erythrocyte sedimentation rate or C-reactive protein; abnormal complete blood count, radiography, bone scan, or MRI	

Adapted from Evans AM, Scutter SD: Prevalence of “growing pains” in young children, *J Pediatr* 145:255–258, 2004; and Walters AS, Gabelia D, Frauscher B: Restless legs syndrome (Willis-Ekbom disease) and growing pains: are they the same thing? A side-by-side comparison of the diagnostic criteria for both and recommendations for future research, *Sleep Med* 14:1247–1252, 2013.

Although growing pains are generally considered a benign, time-limited condition, evidence suggests they represent a **pain amplification syndrome** . Indeed, growing pains persist in a significant percentage of children, with some children developing other pain syndromes such as abdominal pain and headaches. Growing pains are more likely to persist in children with a parent who has a history of a pain syndrome and in children who have lower pain thresholds not just at the site of pain, but throughout their body. Disordered somatosensory testing, lower bone strength, and lower calcium intake have also been shown to be present in children with growing pains.

Treatment should also focus on reassurance, education, and healthy sleep hygiene. Massage during the episode is very effective, and physical therapy and muscle stretching may also be important parts of treatment. NSAIDs agents may be useful for frequent episodes. CBT may be indicated if the pain persists.

Restless legs syndrome (**RLS** , Willis-Ekbom disease), seen more frequently among adolescents and adults, is a sensorimotor disturbance that may be confused with growing pains (see Chapter 31). Often familial, RLS is a difficult-to-control *urge* to move the leg that is exacerbated during rest and at night and is relieved by movement (Table 193.3). There is significant overlap in the diagnostic features of growing pains and RLS, leading to diagnostic confusion. Moreover, these conditions can be comorbid, and there is a high incidence of RLS in the parents of children with growing pains. RLS appears to be best distinguished from growing pains by the *urge* to move the legs, associated uncomfortable leg sensations that may not be described as painful; the worsening with periods of rest; and relief through movement. Iron supplementation may benefit pediatric patients with RLS.

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193.2

Small Fiber Polyneuropathy

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Many patients with juvenile-onset widespread pain syndromes, as well as patients with pediatric fibromyalgia (Chapter 193.3), complex regional pain syndrome type I (Chapter 193.4), and erythromelalgia (Chapter 193.5), have evidence of a small fiber polyneuropathy causing dysfunctional or degeneration of small-diameter unmyelinated C fibers and thinly myelinated A delta fibers that mediate nociception and the autonomic nervous system. Fibromyalgia includes **chronic widespread pain** , defined as ≥3 mo duration of axial pain that is often bilateral and that also affects the upper and lower extremities. In addition, many patients have associated chronic cardiovascular (dizziness, postural orthostasis syndrome) symptoms, as well as chronic abdominal pain and ileus, headaches, fatigue, and erythromelalgia, suggestive of **dysautonomia** .

There are no typical findings on physical examination or standard laboratory tests. The diagnosis of small fiber polyneuropathy requires distal leg immunolabeled skin biopsy to identify epidermal nociceptive fibers and autonomic function testing to examine cardiovagal, adrenergic, and sudomotor small fiber function.

Treatment of patients with small fiber polyneuropathy and isolated juvenile-onset widespread pain syndrome, or those subsets of patients with small fiber polyneuropathy and fibromyalgia, complex regional pain syndrome, or erythromelalgia, is evolving and has included prednisone or intravenous immune globulin.

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193.3

Fibromyalgia

Kelly K. Anthony, Laura E. Schanberg

Juvenile primary fibromyalgia syndrome (JPFS) is a common pediatric musculoskeletal pain syndrome. Approximately 25–40% of children with chronic pain syndromes can be diagnosed with JPFS. Although specific diagnostic criteria for JPFS have not been determined, the adult criteria set forth by the American College of Rheumatology (ACR) in 2010 have been shown to have a high degree of sensitivity and specificity in the diagnosis of JPFS (Fig. 193.1 and Table 193.4). Previous studies describing children and adolescents with JPFS noted diffuse, multifocal, waxing and waning, and at times migratory musculoskeletal pain in at least 3 areas of the body persisting for at least 3 mo in the absence of an underlying condition. Results of laboratory tests were normal, and physical examination revealed at least 5 well-defined tender points (Fig. 193.2). There is considerable overlap among symptoms associated with JPFS and complaints associated with other **functional disorders** (e.g., irritable bowel disease, migraines, temporomandibular joint disorder, premenstrual syndrome, mood and anxiety disorders, chronic fatigue syndrome), suggesting that these disorders may be part of a larger spectrum of related syndromes.

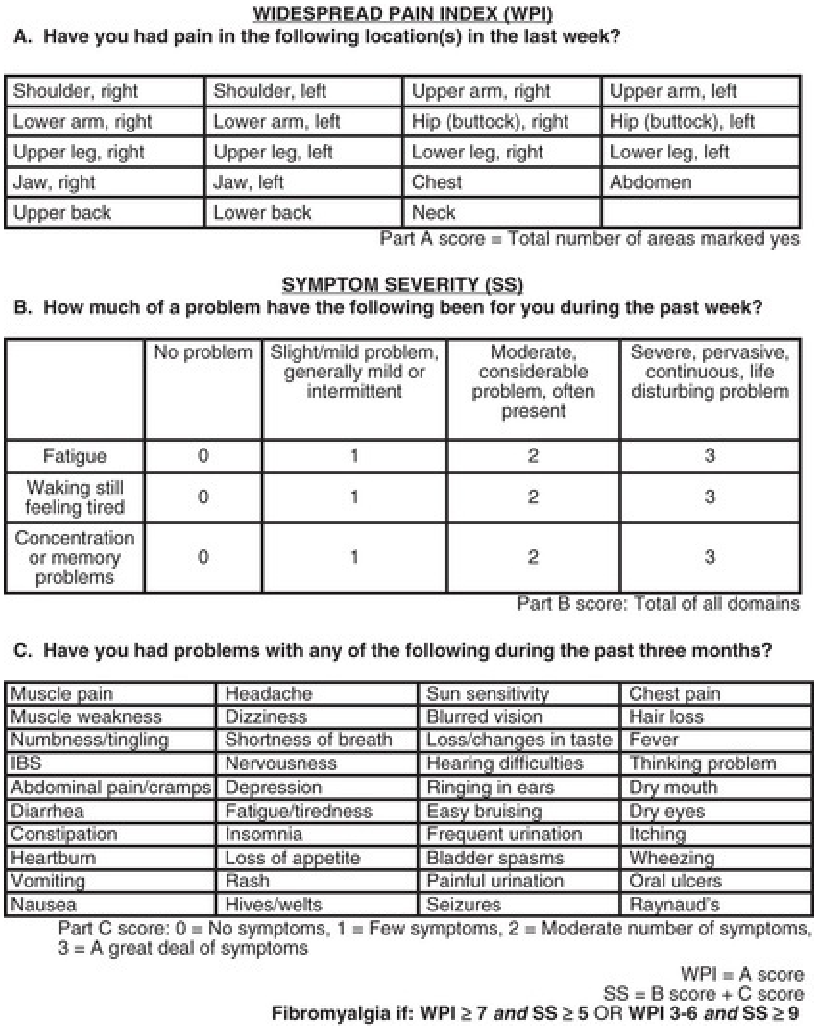

WIDESPREAD PAIN INDEX (WPI)

A. Have you had pain in the following location(s) in the last week?

Shoulder, right	Shoulder, left	Upper arm, right	Upper arm, left
Lower arm, right	Lower arm, left	Hip (buttock), right	Hip (buttock), left
Upper leg, right	Upper leg, left	Lower leg, right	Lower leg, left
Jaw, right	Jaw, left	Chest	Abdomen
Upper back	Lower back	Neck	

Part A score = Total number of areas marked yes

SYMPTOM SEVERITY (SS)

B. How much of a problem have the following been for you during the past week?

	No problem	Slight/mild problem, generally mild or intermittent	Moderate, considerable problem, often present	Severe, pervasive, continuous, life disturbing problem
Fatigue	0	1	2	3
Waking still feeling tired	0	1	2	3
Concentration or memory problems	0	1	2	3

Part B score: Total of all domains

C. Have you had problems with any of the following during the past three months?

Muscle pain	Headache	Sun sensitivity	Chest pain
Muscle weakness	Dizziness	Blurred vision	Hair loss
Numbness/tingling	Shortness of breath	Loss/changes in taste	Fever
IBS	Nervousness	Hearing difficulties	Thinking problem
Abdominal pain/cramps	Depression	Ringing in ears	Dry mouth
Diarrhea	Fatigue/tiredness	Easy bruising	Dry eyes
Constipation	Insomnia	Frequent urination	Itching
Heartburn	Loss of appetite	Bladder spasms	Wheezing
Vomiting	Rash	Painful urination	Oral ulcers
Nausea	Hives/welts	Seizures	Raynaud's

Part C score: 0 = No symptoms, 1 = Few symptoms, 2 = Moderate number of symptoms, 3 = A great deal of symptoms

WPI = A score
SS = B score + C score
Fibromyalgia if: WPI ≥ 7 *and* SS ≥ 5 OR WPI 3-6 *and* SS ≥ 9

FIG. 193.1 **Fibromyalgia questionnaire. American College of Rheumatology criteria. IBS, Irritable bowel syndrome. (Adapted from Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* 62:600–610, 2010.)**

Table 193.4

American College of Rheumatology Fibromyalgia Diagnostic Criteria

The following 3 conditions must be met:

1. Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 *or* WPI 3-6 and SS scale score ≥9.
2. Symptoms have been present at a similar level for at least 3 mo.
3. The patient does not have a disorder that would otherwise explain the pain.

Ascertainment of WPI

The WPI is the number of areas in which a patient has had pain over the last week. The score will be between 0 and 19: left shoulder girdle left, right shoulder girdle, left upper arm, right upper arm, left lower arm, right lower arm, left hip (buttock, trochanter), right hip (buttock, trochanter), left upper leg, right upper leg, left lower leg, right lower leg, left jaw, right jaw, chest, abdomen, upper back, lower back, and neck.

Ascertainment of Ss Scale Score

The SS scale score is the sum of the severity of 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) *plus* the severity of somatic symptoms in general. The final score is between 0 and 12.

- For each of the 3 symptoms, the level of severity over the past week is rated using the following scale:
  0 = No problem
  1 = Slight or mild problems, generally mild or intermittent
  2 = Moderate, considerable problems, often present and/or at a moderate level
  3 = Severe: pervasive, continuous, life-disturbing problems
- Considering somatic symptoms in general, the following scale is used to indicated the number of symptoms:
  0 = No symptoms
  1 = Few symptoms
  2 = Moderate number of symptoms
  3 = Great deal of symptoms
- Somatic symptoms that can be considered include muscle pain, irritable bowel syndrome, fatigue, thinking problems, muscle weakness, headache, abdominal pain, numbness/tingling, dizziness, insomnia, depression,

constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Adapted from Wolfe F, Clauw DJ, Fitzcharles MA, et al: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity, *Arthritis Care Res* 62: 600–610, 2010.

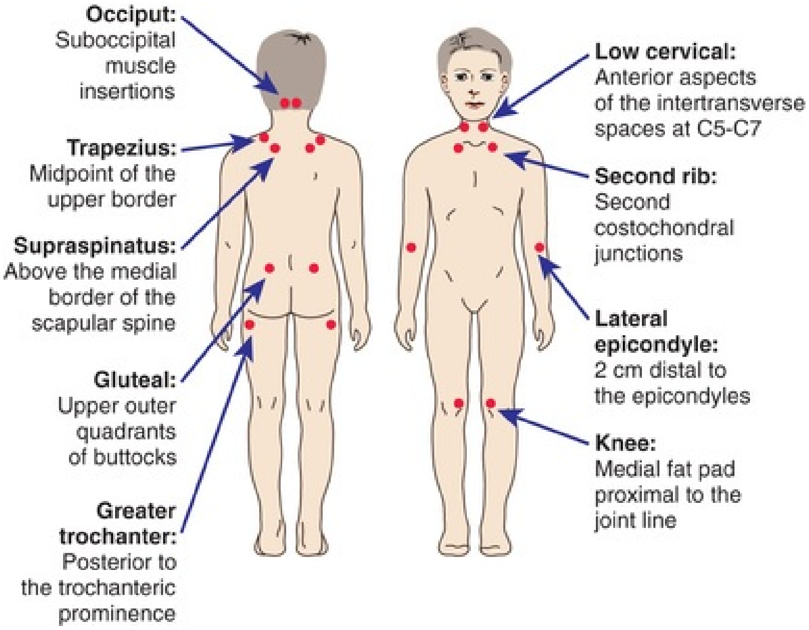
Occiput:
Suboccipital muscle insertions
Trapezius:
Midpoint of the upper border
Supraspinatus:
Above the medial border of the scapular spine
Gluteal:
Upper outer quadrants of buttocks
Greater trochanter:
Posterior to the trochanteric prominence
Low cervical:
Anterior aspects of the intertransverse spaces at C5-C7
Second rib:
Second costochondral junctions
Lateral epicondyle:
2 cm distal to the epicondyles
Knee:
Medial fat pad proximal to the joint line

FIG. 193.2 **Fibromyalgia tender points.**

Although the precise cause of JPFS is unknown, there is an emerging understanding that the development and maintenance of JPFS are related both to biologic and psychological factors. JPFS is an abnormality of central pain processing characterized by disordered sleep physiology, enhanced pain perception with abnormal levels of substance P in cerebrospinal fluid, disordered mood, and dysregulation of hypothalamic-pituitary-adrenal and other neuroendocrine axes, resulting in lower tender-point pain thresholds and increased pain sensitivity. Evolving evidence also suggests that up to 50% of patients with fibromyalgia may have a small fiber polyneuropathy (see Chapter

193.2), and that patients with JPFS may also have chronotropic incompetence (inability to increase heart rate commensurate with activity) and autonomic dysfunction at diagnosis. Children and adolescents with fibromyalgia often find themselves in a vicious cycle of pain, where symptoms build on one another and contribute to the onset and maintenance of new symptoms (Fig. 193.3).

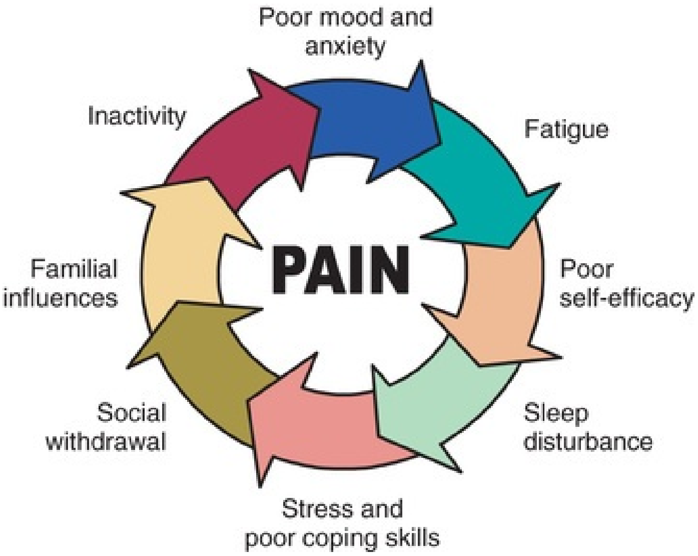

FIG. 193.3 **Juvenile primary fibromyalgia syndrome. Vicious cycle promoting symptom maintenance. (Adapted from Anthony KK, Schanberg LE: Juvenile primary fibromyalgia syndrome, *Curr Rheumatol Rep* 3:167–171, 2001, Fig. 1.)**

JPFS has a chronic course that can detrimentally affect child health and development. Adolescents with JPFS who do not receive treatment or who are inadequately treated may withdraw from school and the social milieu, complicating their transition to adulthood. **Treatment** of JPFS generally follows consensus statements of the American Pain Society. The major goals are to restore function and alleviate pain, as well as improve comorbid mood and sleep disorders. Treatment strategies include parent/child education, pharmacologic interventions, exercise-based interventions, and psychological interventions. Graduated aerobic exercise is the recommended exercise-based intervention, whereas psychological interventions should include training in pain coping skills, stress management skills, emotional support, and sleep hygiene. CBT is particularly effective in reducing symptoms of depression in children and adolescents with JPFS and also helps to reduce functional disability.

Drug therapies , although largely unsuccessful in isolation, may include tricyclic antidepressants (amitriptyline, 10-50 mg orally 30 min before bedtime), selective serotonin reuptake inhibitors (sertraline, 10-20 mg daily), and anticonvulsants. Pregabalin and duloxetine hydrochloride are approved by the U.S. Food and Drug Administration (FDA) for treatment of fibromyalgia in adults (≥18 yr of age). The safety and efficacy of *pregabalin* in adolescents age 12-17 yr was recently demonstrated in a 15 wk randomized controlled trial and 6 mo open-label study. Safety was consistent with that shown in adults, with preliminary evidence for improvement in secondary pain outcomes, impressions of change, and better sleep. *Duloxetine* has not been studied in children with JPFS. Muscle relaxants are generally not used in children because they affect school performance.

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193.4

Complex Regional Pain Syndrome

Kelly K. Anthony, Laura E. Schanberg

Complex regional pain syndrome (CRPS) is characterized by ongoing burning limb pain subsequent to an injury, immobilization, or another noxious event affecting the extremity. **CRPS1** , formerly called *reflex sympathetic dystrophy* , has no evidence of nerve injury, whereas **CRPS2** , formerly called *causalgia* , follows a prior nerve injury. Key associated features are pain disproportionate to the inciting event, persisting **allodynia** (a heightened pain response to normally nonnoxious stimuli), **hyperalgesia** (exaggerated pain reactivity to noxious stimuli), swelling of distal extremities, and indicators of **autonomic dysfunction** (cyanosis, mottling, hyperhidrosis).

There are currently no gold standard diagnostic criteria for pediatric CPRS;

although in adults, the **Budapest criteria** have been shown to be more sensitive and specific than previous diagnostic guidelines (Table 193.5). The diagnosis requires an initiating noxious event or immobilization; continued pain, allodynia, and hyperalgesia out of proportion to the inciting event; evidence of edema, skin blood flow abnormalities, or sudomotor activity; and exclusion of other disorders. Associated features include atrophy of hair or nails; altered hair growth; loss of joint mobility; weakness, tremor, dystonia; and sympathetically maintained pain.

Table 193.5

Budapest Clinical Diagnostic Criteria for Complex Regional Pain Syndrome

All the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least 1 symptom in each of the following 4 categories:
    - *Sensory* : Hyperesthesia and/or allodynia
    - *Vasomotor* : Temperature asymmetry, skin color changes, and/or skin color asymmetry
    - *Sudomotor/edema* : Edema, sweating changes, and/or sweating asymmetry
    - *Motor/trophic* : Decreased range of motion, motor dysfunction (tremor, weakness, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least 1 sign at time of evaluation in ≥2 of the following 4 categories:
    - *Sensory* : Evidence of hyperesthesia (to pin prick) and/or allodynia (to light touch, temperature sensation, deep somatic pressure, and/or joint movement)
    - *Vasomotor* : Evidence of temperature asymmetry (>1°C), skin color changes, and/or skin color asymmetry
    - *Sudomotor/edema* : Edema, sweating changes, and/or sweating asymmetry
    - *Motor/trophic* : Decreased range of motion, motor dysfunction (tremor, weakness, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms.

Adapted from Harden RN, Bruel S, Stanton-Hicks, et al: Proposed new diagnostic criteria for complex regional pain syndrome, Pain Med 8:326–331, 2007.

Although the majority of pediatric patients with CRPS present with a history of minor trauma or repeated stress injury (e.g., caused by competitive sports), a sizable proportion are unable to identify a precipitating event. Usual age of onset is between 8 and 16 yr, and girls outnumber boys with the disease by as much as 6 : 1. Childhood CRPS differs from the adult form in that lower extremities, rather than upper extremities, are most often affected. The incidence of CRPS in children is unknown, largely because it is often undiagnosed or diagnosed late, with the diagnosis frequently delayed by almost 1 yr. Left untreated, CRPS can have severe consequences for children, including bone demineralization, muscle wasting, and joint contractures.

An evidence-based approach to the **treatment** of CRPS continues to suggest a multistage approach. Aggressive *physical therapy* (PT) should be initiated as soon as the diagnosis is made and CBT added as needed. PT is recommended 3-4 times/wk, and children may need analgesic premedication at the onset, particularly before PT sessions. PT is initially limited to desensitization and then moves to weight-bearing, range-of-motion, and other functional activities. CBT used as an adjunctive therapy targets psychosocial obstacles to fully participating in PT and provides pain-coping skills training. Sympathetic and epidural *nerve blocks* should be attempted only under the auspices of a pediatric pain specialist. The goal of both pharmacologic and adjunctive treatments for CRPS is to provide sufficient pain relief to allow the child to participate in aggressive physical rehabilitation. If CRPS is identified and treated early, the majority of children and adolescents can be treated successfully with low-dose *amitriptyline* (10-50 mg orally 30 min before bedtime), aggressive PT, and CBT interventions. Opioids and anticonvulsants such as gabapentin can also be helpful. Notably, multiple studies have shown that noninvasive treatments, particularly PT and CBT, are at least as efficacious as nerve blocks in helping children with CRPS achieve resolution of their symptoms.

There is growing evidence that some patients with CRPS I have a small fiber polyneuropathy (see Chapter 193.2).

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193.5

Erythromelalgia

Laura E. Schanberg

Children with **erythromelalgia** experience episodes of intense pain, erythema, and heat in their hands and feet (Fig. 193.4). Less frequently involved are the face, ears, or knees. Symptoms may be triggered by exercise and exposure to heat, lasting for hours and occasionally for days. It is more common in girls and in the teenage years, and diagnosis is often delayed for years. Although most cases are sporadic, an autosomal dominant hereditary form results from mutations of the *SCN9A* gene on chromosome 2q31-32, causing a painful channelopathy. **Secondary** erythromelalgia is associated with an array of disorders, including myeloproliferative diseases, peripheral neuropathy, frostbite, hypertension, and rheumatic disease. Treatment includes avoidance of heat exposure and other precipitating situations and utilization of cooling techniques that do not cause tissue damage during attacks. NSAIDs, narcotics, anesthetic agents (lidocaine patch), anticonvulsants (oxcarbazepine, carbamazepine, gabapentin), and antidepressants, as well as biofeedback and hypnosis, may help manage pain. Drugs acting on the vascular system (aspirin, sodium nitroprusside, magnesium, misoprostol) may also be somewhat effective. However, a reliably efficacious treatment is not available, resulting in substantial negative impact on physical and mental health.

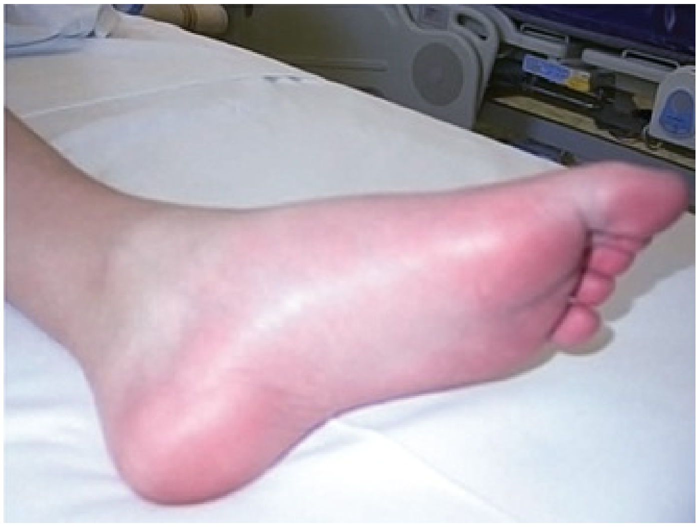

FIG. 193.4 **Erythromelalgia. Typical redness and edema of the foot. (From Pfund Z, Stankovics J, Decsi T, Illes Z: Childhood steroid-responsive acute erythromelalgia with axonal neuropathy of large myelinated fibers: a dysimmune neuropathy? *Neuromuscul Disord* 19:49–52, 2009, Fig 1A, p 50.)**

There is growing evidence that some patients with erythromelalgia have a small fiber polyneuropathy (see Chapter 193.2).

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CHAPTER 194

Miscellaneous Conditions Associated With Arthritis

Angela Byun Robinson, C. Egla Rabinovich

Relapsing Polychondritis

Relapsing polychondritis (RP) is a rare condition characterized by episodic chondritis causing cartilage destruction and deformation of the ears (sparing the earlobes), nose, larynx, and tracheobronchial tree. Antibodies to matrillin-1 and collagen (type II, IX and XI) are present in approximately 60% of patients with RP, suggesting an autoimmune pathogenesis. Patients may experience arthritis, uveitis, and hearing loss resulting from inflammation near the auditory and vestibular nerves. Children may initially relate episodes of intense erythema over the outer ears. Other dermatologic manifestations may include erythema nodosum, maculopapular rash, and purpura. Cardiac involvement, including conduction defects and coronary vasculitis, has been reported. Severe, progressive, and potentially fatal disease resulting from destruction of the tracheobronchial tree and airway obstruction is unusual in childhood. **Diagnostic criteria** established for adults are useful guidelines for evaluating children with suggestive symptoms (Table 194.1). The clinical course of RP is variable; flares of disease are often associated with elevations of acute-phase reactants and may remit spontaneously. Although seen more often in the adult population, RP may coexist with other rheumatic disease (e.g., systemic lupus erythematosus, Sjögren syndrome, Henoch-Schönlein purpura) in up to 30% of patients. The differential diagnosis includes **ANCA-associated vasculitis** (granulomatosis with polyangiitis) (see Chapter 192.4) and **Cogan syndrome** , which is characterized by auditory nerve inflammation and keratitis but not chondritis. Many children respond to nonsteroidal antiinflammatory drugs, but some require corticosteroids or other immunosuppressive agents (azathioprine, methotrexate, hydroxychloroquine, colchicine, cyclophosphamide, cyclosporine, and anti–tumor necrosis factor [TNF] agents), as reported in small series and case reports.

Table 194.1

Suggested Criteria for Relapsing Polychondritis*

MAJOR

- Typical inflammatory episodes of ear cartilage
- Typical inflammatory episodes of nose cartilage
- Typical inflammatory episodes of laryngotracheal cartilage

MINOR

- Eye inflammation (conjunctivitis, keratitis, episcleritis, uveitis)
- Hearing loss
- Vestibular dysfunction
- Seronegative inflammatory arthritis

[*] The diagnosis is established by the presence of 2 major or 1 major and 2 minor criteria. Histologic examination of affected cartilage is required when the presentation is atypical.

Data from Michet CJ Jr, McKenna CH, Luthra HS, et al: Relapsing polychondritis: survival and predictive role of early disease manifestations, *Ann Intern Med* 104:74-78, 1986.

Mucha-Habermann Disease/Pityriasis Lichenoides Et Varioliformis Acuta

Pityriasis lichenoides et varioliformis acuta (**PLEVA**) is a benign, self-limited cutaneous vasculitis characterized by episodes of macules, papules, and papulovesicular lesions that can develop central ulceration, necrosis, and crusting (Fig. 194.1). Different stages of development are usually seen at once. **PLEVA fulminans** or febrile ulceronecrotic Mucha-Habermann disease (**FUMHD**) is the severe, life threatening form of PLEVA. Large, coalescing, ulceronecrotic lesions are seen, accompanied by high fever and elevated erythrocyte sedimentation rate (ESR). Systemic manifestations can include interstitial pneumonitis, abdominal pain, malabsorption, arthritis, and neurologic manifestations. PLEVA has a male predominance and occurs more frequently in childhood. The diagnosis is confirmed by biopsy of skin lesions, which reveals perivascular and intramural lymphocytic inflammation affecting capillaries and venules in the upper dermis that may lead to keratinocyte necrosis. When disease is severe, corticosteroids have been used with questionable effect, and methotrexate has been reported to induce rapid remission in resistant cases. Cyclosporine and anti-TNF agents have also been efficacious in case reports.

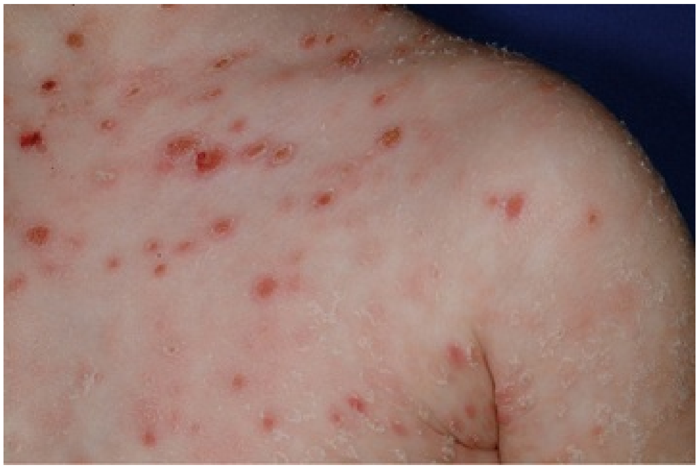

FIG. 194.1 **Pityriasis lichenoides et varioliformis acuta (PLEVA). Symmetric, oval and round, reddish brown macular, popular, necrotic, and crusted lesions on chest of 9 yr old boy. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology,* ed 5, Philadelphia, 2016, Elsevier, Fig 4-33, p 87.)**

Sweet Syndrome

Sweet syndrome, or **acute febrile neutrophilic dermatosis** , is a rare entity in children. It is characterized by fever, elevated neutrophil count, and raised, tender erythematous plaques and nodules over the face, extremities, and trunk. Skin biopsy reveals neutrophilic perivascular infiltration in the upper dermis. Female predominance is seen in the adult population, whereas gender distribution is equal in children. Established criteria are useful for diagnosis (Table 194.2). Children can also have arthritis, sterile osteomyelitis, myositis, and other extracutaneous manifestations. Sweet syndrome may be idiopathic or secondary to malignancy (particularly acute myelogenous leukemia), drugs (granulocyte colony-stimulating factor, tretinoin or trimethoprim-sulfamethoxazole), or rheumatic diseases (Behçet disease, antiphospholipid antibody syndrome, systemic lupus erythematosus). The condition usually responds to treatment with corticosteroids, treatment of underlying disease, or removal of associated medication.

Table 194.2

Diagnostic Criteria for Classic Sweet Syndrome*

Major Criteria

- Abrupt onset of painful erythematous plaques or nodules
- Histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis

Minor Criteria

- Pyrexia >38°C
- Association with underlying hematologic or visceral malignancy, inflammatory disease or pregnancy, *or* preceded by an upper respiratory or gastrointestinal infection or vaccination
- Excellent response to systemic corticosteroids or potassium iodide
- Abnormal laboratory values at presentation (3 of 4):
    - Erythrocyte sedimentation rate >20 mm/hr
    - Positive C-reactive protein test result
    - >8,000 leukocytes/mm^3
    - >70% neutrophils/mm^3

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* The diagnosis is established by the presence of 2 major criteria *plus* 2 of the 4 minor criteria.

Adapted from Walker DC, Cohen PR: Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug induced Sweet's syndrome. *J Am Acad Dermatol* 34:918–923, 1996.

Hypertrophic Osteoarthropathy

Children with chronic disease, especially pulmonary or cardiac disease, can demonstrate clubbing of the terminal phalanges and have associated periosteal reaction and arthritis. These findings characterize the classic presentation of hypertrophic osteoarthropathy. HOA can be **primary** (idiopathic) or secondary. Although rare, **secondary** HOA is more common in children and is seen in those with chronic pulmonary disease (cystic fibrosis), congenital heart disease, gastrointestinal disease (malabsorption syndromes, biliary atresia, inflammatory bowel disease), and malignancy (nasopharyngeal sarcoma, osteosarcoma, Hodgkin disease). It may precede diagnosis of cardiopulmonary disease or malignancy. The pathogenesis of secondary HOA is unknown; symptoms often improve if the underlying condition is treated successfully. HOA-related pain can be disabling; in adults, management with bisphosphonates has been reported. Evaluation of children presenting with HOA should include a chest radiograph to evaluate for pulmonary disease or intrathoracic mass. Autosomal recessive mutations in prostaglandin pathway genes have recently been described in primary HOA, also described as **pachydermoperiostosis** .

Plant Thorn Synovitis

A diagnosis of plant thorn synovitis should be considered in children with monoarticular arthritis nonresponsive to antiinflammatory therapy. Acute or chronic arthritis can occur after a plant thorn or other foreign object penetrates a joint. Unlike septic arthritis, children with plant thorn synovitis are usually afebrile. The most common organism seen with plant thorn synovitis is *Pantoea agglomerans* , although cultures are often negative. The initial injury may be unknown or forgotten, making diagnosis difficult. Ultrasound or MRI can be useful in identifying the foreign body. Removal of the foreign body using arthroscopy, followed by an antibiotic course, is the accepted therapy.

Pigmented Villonodular Synovitis

Proliferation of synovial tissue is seen in pigmented villonodular synovitis (PVNS). This proliferation is localized or diffuse and can affect the joint, tendon sheath, or bursa. Macrophages and multinucleated giant cells with brownish hemosiderin are present histologically. It is unclear if the etiology of PVNS is inflammatory or neoplastic in nature. Although findings are not pathognomonic, MRI with contrast is a useful diagnostic tool by which PVNS can be seen as a mass or bone erosion. Brown or bloody synovial fluid is seen with arthrocentesis, but the diagnosis is made by tissue biopsy. Surgical removal of the affected tissue is the therapeutic modality, and with diffuse disease, a total synovectomy is recommended.

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PART XVI

Infectious Diseases

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Section 1 General Considerations
Section 2 Preventive Measures
Section 3 Antibiotic Therapy
Section 4 Gram-Positive Bacterial Infections
Section 5 Gram-Negative Bacterial Infections
Section 6 Anaerobic Bacterial Infections
Section 7 Mycobacterial Infections
Section 8 Spirochetal Infections
Section 9 Mycoplasmal Infections
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SECTION 1

General Considerations

OUTLINE

Chapter 195 Diagnostic Microbiology
Chapter 196 The Microbiome and Pediatric Health

CHAPTER 195

Diagnostic Microbiology

Carey-Ann D. Burnham, Gregory A. Storch

Laboratory evidence to support the diagnosis of an infectious disease may be based on one or more of the following: direct examination of specimens using microscopic or antigen detection techniques, isolation of microorganisms in culture, serologic testing, host gene expression patterns, or molecular detection of an organism, resistance determinant, or virulence factor. Some additional roles of the clinical microbiology laboratory include performing antimicrobial susceptibility testing and supporting hospital infection prevention in the detection and characterization of pathogens associated with nosocomial infections.

Specimen Collection

The success of a diagnostic microbiology assay, that is, detection of a pathogen if present, is directly linked to specimen collection techniques. In general, this means collecting the correct specimen type for the disease or condition in question and promptly transporting the specimen to the laboratory for analysis. Although **swab specimens** may be necessary for some conditions, in general a swab is a suboptimal specimen. A swab is only able to hold a very small amount of specimen (approximately 100 µL), and, using a traditional swab, only a small fraction of organisms that are absorbed onto a swab will be released back into the culture. **Flocked swabs** coupled with transport medium improve organism recovery. However, when possible, fluid or tissue should be submitted to the laboratory for analysis. If anaerobic infection is suspected, the sample should be transported in appropriate medium to preserve viability of anaerobic bacteria. For the recovery of some organism types, such as viruses and *Neisseria gonorrhoeae* , specific transport media may be required. Considerations specific to the collection of blood cultures are addressed in the blood culture section.

Laboratory Diagnosis of Bacterial and Fungal Infections

Although the scope and availability of molecular methods for detection of bacterial and fungal pathogens have increased rapidly, the diagnosis of many of these infections depends on microscopic detection of organisms or cultivation of organisms on **culture media** .

Microscopy

The **Gram stain** is an extremely valuable diagnostic technique to provide rapid and inexpensive information regarding the absence or presence of inflammatory cells and organisms in clinical specimens. For some specimen types, the presence of inflammatory and epithelial cells is used to judge the suitability of a specimen for culture. For example, the presence of >10 epithelial cells per low-power field in a sputum specimen is highly suggestive of a specimen contaminated with oral secretions. In addition, a preliminary assessment of the etiologic agent can be made based on the morphology (e.g., cocci vs rods) and stain reaction (e.g., gram-positive isolates are purple; gram-negative isolates are red) of the microorganisms. However, a negative Gram stain does not rule out infection, since 10^4 to 10^5 microorganisms per milliliter (mL) in the specimen are required for detection by this method.

In addition to the Gram stain, many other stains are used in microbiology, both to detect organisms and to help infer their identity (Table 195.1).

Table 195.1

Stains Used for Microscopic Examination

TYPE OF STAIN	CLINICAL USE
Gram stain	Stains bacteria (with differentiation of gram-positive and gram-negative organisms), fungi, leukocytes, and epithelial cells.
Potassium hydroxide (KOH)	A 10% solution dissolves cellular and organic debris and facilitates detection of fungal elements in clinical specimens.
Calcofluor	Nonspecific fluorochrome that binds to cellulose and chitin in fungal cell walls, can be combined

white stain	with 10% KOH to dissolve cellular material.
Ziehl-Neelsen and Kinyoun stains	Acid-fast stains, using basic carbolfuchsin, followed by acid-alcohol decolorization and methylene blue counterstaining.
	Acid-fast organisms (e.g., *Mycobacterium*) resist decolorization and stain pink.
	A weaker decolorizing agent is used for partially acid-fast organisms (e.g., *Nocardia, Cryptosporidium, Cyclospora, Isospora*).
Auramine-rhodamine stain	Acid-fast stain using fluorochromes that bind to mycolic acid in mycobacterial cell walls and resist acid-alcohol decolorization; usually performed directly on clinical specimens.
	Acid-fast organisms stain orange-yellow against a black background.
Acridine orange stain	Fluorescent dye that intercalates into DNA, used to aid in differentiation of organisms from debris during direct specimen examination, and also for detection of organisms that are not visible with Gram stain.
	Bacteria and fungi stain orange, and background cellular material stains green.
Lugol iodine stain	Added to wet preparations of fecal specimens for ova and parasites to enhance contrast of the internal structures (nuclei, glycogen vacuoles).
Wright and Giemsa stains	Primarily for detecting blood parasites (*Plasmodium, Babesia,* and *Leishmania*), detection of amoeba in preparations of cerebrospinal fluid, and fungi in tissues (yeasts, *Histoplasma*)
Trichrome stain	Stains stool specimens for identification of protozoa.
Direct fluorescent-antibody stain	Used for direct detection of a variety of organisms in clinical specimens by using specific fluorescein-labeled antibodies (e.g., *Pneumocystis jiroveci,* many viruses).

Isolation and Identification

The approach to isolation of microorganisms in a clinical specimen will vary depending on the body site and pathogen suspected. For body sites that are usually sterile, such as cerebrospinal fluid, **nutrient-rich media** such as sheep blood agar and chocolate agar are used to aid in the recovery of fastidious pathogens. In contrast, stool specimens contain abundant amounts of commensal bacteria, and thus to isolate pathogens, selective and differential media must be used. **Selective media** will inhibit the growth of some organisms to aid in isolation of suspect pathogens; **differential media** rely on growth characteristics or carbohydrate assimilation characteristics to impart a growth pattern that differentiates organisms. MacConkey agar supports growth of gram-negative rods while suppressing gram-positive organisms, and a color change in the media from clear to pink distinguishes lactose-fermenting organisms from other gram-negative rods. Special media, such as Sabouraud dextrose agar and inhibitory mold agar, are used to recover fungi in clinical specimens. Many pathogens, including *Bartonella* , *Bordetella pertussis* , *Legionella* , *Mycoplasma* , some *Vibrio* spp., and certain fungal pathogens such as *Malassezia furfur* , require specialized growth media or incubation conditions. Consultation with the laboratory is advised when these pathogens are suspected.

Once an organism is recovered in culture, additional testing is performed to identify the isolate. Confirmation of microbial identity has classically been performed using tests that rely on the phenotypic properties of an isolate; examples include coagulase activity, carbohydrate assimilation patterns, indole production, and motility. However, phenotypic methods are not able to resolve all organisms to species level, and they require incubation time. In some instances, sequence-based identification may be necessary. For bacteria, this is usually based on sequence analysis of the bacterial 16S rRNA gene. This gene is a molecular chronometer that is highly conserved within a species but variable between species; as such, it is an excellent resource for organism identification.

Matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (**MALDI-TOF MS**) is a rapid and accurate technique that is based on generating a protein fingerprint of an organism and comparing that fingerprint to a library of known organisms to produce an identification. This method can identify bacteria or yeast that have been recovered in culture within minutes, and the consumable costs for these analyses are minimal. However, this methodology currently lacks the ability to resolve polymicrobial samples, and the biomass required for successful MALDI-TOF MS analysis generally precludes analysis directly from clinical specimens.

Blood Culture

The detection of microbes in blood culture specimens of patients with bloodstream infection is one of the most important functions of the clinical microbiology laboratory. Most blood cultures are performed by collecting blood into bottles of nutrient-rich broth to facilitate the growth of bacteria or yeast. Blood cultures are frequently submitted as a set that includes an aerobic and an anaerobic bottle, although in children, especially neonates, typically only an aerobic bottle is used. Some blood culture media contain resins or other agents to help neutralize antibiotics that may be present in the patients’ blood. Blood culture bottles are then placed into an automated blood culture incubator that will monitor the blood culture bottle at regular intervals for evidence of growth. Once the instrument detects evidence of microbial growth, an alarm alerts the laboratory. Approximately 80% of blood cultures that will ultimately be positive are identified within the 1st 24 hr of incubation. A portion of broth from a blood culture bottle that has signaled positive is then gram-stained and subsequently inoculated onto appropriate growth media so that the organism can be isolated and identified. Numerous preanalytical variables can influence the accuracy of blood culture results. To facilitate accurate interpretation of a positive blood culture, a minimum of 2 blood cultures drawn from different sites should be collected whenever possible. Growth of an organism that is part of the normal skin flora from a single blood culture raises concern that the isolate resulted from contamination of the culture.

To maximize detection of bloodstream infection, up to 4 blood cultures should be collected over 24 -hr. Proper skin antisepsis is essential before blood collection. Chlorhexidine is frequently used for this purpose, but alcohol is also used. If blood is collected through an indwelling line, proper antisepsis before collection is also important. The practice of obtaining blood for culture from intravascular catheters without accompanying peripheral venous blood cultures should be discouraged, because it is difficult to determine the significance of coagulase-negative staphylococci and other skin flora or environmental organisms isolated from blood obtained from line cultures. Differential time to positivity of 2 hr or more between paired blood cultures drawn simultaneously from a catheter and peripheral vein has been cited as an indicator of catheter-related bloodstream infection.

The volume of blood collected is also an important factor in the recovery of bloodstream pathogens, especially as the number of organisms per milliliter of blood in sepsis may be low (<10 colony-forming units/mL). The optimal amount of blood to collect from a pediatric patient varies depending on the weight of the child. The **Clinical and Laboratory Standards Institute** (CLSI) and Cumitech provide guidance on the amount of blood that is safe to collect from children of different sizes. For children from 3 to <12 kg, 3-5 mL is suggested; from 12 to <36 kg, 5-10 mL; from 36-50 kg, 10-15 mL, and >50 kg, 20 mL.

A number of **rapid diagnostic assays** can be performed directly on positive blood culture broth to identify pathogens frequently associated with bacteremia and some antimicrobial resistance determinants. Most of these rapid diagnostic assays are based on nucleic acid detection techniques. For example, the Verigene system can identify staphylococcal, streptococcal, and enterococcal species, as well as *mecA* and *vanA* genes, in positive blood culture broth in approximately 2 hr using the gram-positive blood culture panel. After specimen preparation to concentrate microorganisms and remove residual broth and blood from the blood culture specimen, MALDI-TOF MS can also be performed on blood culture broth that is positive for growth of microorganisms. These assays can help shorten the interval between a positive blood culture and definitive organism identification, with the goal of early optimization of antimicrobial therapy.

Detection of mycobacteria and some filamentous fungi (e.g., *Histoplasma* *capsulatum*) from the bloodstream is maximized using lysis-centrifugation techniques, such as the Isolator system (Wampole, Cranbury, NJ).

Cerebrospinal Fluid Culture

Cerebrospinal fluid (CSF) should be transported quickly to the laboratory and then cytocentrifuged to concentrate organisms for microscopic examination. CSF is routinely cultured on blood agar and chocolate agar, which support the growth of common pathogens causing meningitis. If tuberculosis is suspected, cultures for mycobacteria should be specifically requested. Culture of larger volumes of CSF (>10 mL) significantly improves yield of mycobacteria.

Historically, rapid antigen detection tests for bacterial pathogens such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae* were used to attempt to detect organisms in CSF without the need for culture. These techniques lack sensitivity and in some cases specificity. A cytospin Gram stain is as sensitive as bacterial antigen tests for detection of microorganisms in CSF. In contrast, the cryptococcal antigen test can be useful when cryptococcal meningitis is suspected. Historically, India ink preparations were used to detect *Cryptococcus* in CSF, but this method is insensitive compared with the antigen detection assay.

In the postvaccine era, the epidemiology of infectious meningitis is rapidly changing, and acute bacterial meningitis is now a relatively infrequent event in North America. Many CSF infections are associated with shunts or other hardware, and *Propionibacterium* and coagulase-negative staphylococci are the organisms most frequently isolated from shunt infections. The laboratory should include media to facilitate the growth of *Propionibacterium* in CSF specimens received from neurosurgery patients.

Urine Culture

Urine for culture (including colony count) can be obtained by collecting clean-voided midstream specimens, by catheterization, or by suprapubic aspiration. Urine samples collected by placing bags on the perineum are unacceptable for culture because samples are often contaminated. Rapid transport of unpreserved urine to the laboratory (<2 hr) is imperative, and delay in transport or plating of specimens renders colony counts unreliable. Refrigeration or urine transport devices with boric acid preservative may be used when delay is unavoidable.

The specific colony counts used to define growth in a urine culture as *significant* are somewhat controversial and vary by laboratory. Urine obtained by suprapubic aspirate is normally sterile, and thus any organism growth is typically considered significant. Urine collected by catheterization is likely to reflect infection if there are $\geq 10^3$ to 10^4 organisms/mL. In general, clean-voided urine is considered abnormal if $\geq 10^4$ to 10^5 organisms/mL are present, although culture interpretation can be variable depending on the patient's age and the clinical setting.

Genital Culture

Neisseria gonorrhoeae is a fragile organism, and collection and transport in special medium are essential for efficient recovery. Selective agar, such as modified Thayer-Martin medium, should be used to enhance recovery of *N. gonorrhoeae* in clinical specimens, such as genital, anorectal, and pharyngeal swabs. Antimicrobial resistance is increasing in *N. gonorrhoeae* and is cited as an Urgent Threat by the U.S. Centers for Disease Control and Prevention (CDC), although few clinical laboratories have the ability to perform antimicrobial susceptibility testing for this organism. In pediatric patients, the identification of an organism as *N. gonorrhoeae* should be confirmed using 2 independent methods.

Specimens for ***Chlamydia trachomatis*** culture are obtained by cotton-tipped, aluminum-shafted urethral swabs. Endocervical specimens, using swabs with aluminum or plastic shafts, should be collected by rubbing the swab vigorously against the endocervical wall to obtain as much cellular material as possible. *C. trachomatis* is an obligate intracellular organism and is cultured by inoculation into cell culture systems, followed by immunofluorescent staining with monoclonal antibody against the organism. Nonculture methods such as DNA amplification methods are widely used and are more cost-effective than culture.

Although **nucleic acid amplification test (NAAT) assays** for *N. gonorrhoeae* and *C. trachomatis* are not approved by the U.S. Food and Drug Administration (FDA) for use in children, these assays are frequently used in this population to detect these organisms in urine specimens, endocervical and vaginal swabs, and penile swabs. The NAAT assays exhibit superior sensitivity compared to culture-based techniques. Some laboratories take the approach of confirming all NAAT-positive specimens with an alternative NAAT test that detects an alternative genetic target.

Throat and Respiratory Culture

Streptococcal pharyngitis and tonsillitis is a common diagnosis in pediatric patients; vigorous swabbing of the tonsillar area and posterior pharynx can be done to obtain a specimen for detection of group A streptococcus *(Streptococcus pyogenes).* Rapid antigen detection assays or rapid nucleic acid detection assays are frequently used when group A streptococcus pharyngitis is suspected. Negative rapid antigen assays should be confirmed using culture-based techniques. Rapid NAAT assays for detection of group A streptococcus are also being used with increasing frequency. These assays have increased sensitivity, but clinical experience with them is still limited and there are not yet recommendations regarding whether backup culture is required. Most laboratories screen throat cultures exclusively for the presence of group A streptococci. However, large colony variants of group C and group G streptococci (*Streptococcus dysgalactiae*) have also been associated with pharyngitis but are not associated with the same postinfectious sequelae attributed to group A streptococcus; laboratory practices for detecting and reporting group C and group G streptococci are variable and an area of controversy.

In addition to the detection of pathogenic streptococci, the clinical laboratory may query for diphtheria, gonococcal pharyngitis, or infection with *Arcanobacterium haemolyticum* in pharyngeal specimens. The laboratory should be notified if any of these pathogens is suspected, to ensure that appropriate methods are used to recover these organisms if present.

Cultures for *Bordetella pertussis* can be obtained by aspiration or swabbing of the nasopharynx using a Dacron or calcium alginate swab. The aspirate or swab is inoculated onto special charcoal-blood (Regan-Lowe) or Bordet-Gengou media, although molecular assays are now frequently used for detection of *B. pertussis* in these specimens.

The cause of lower respiratory tract disease in children is frequently difficult to confirm microbiologically because of the challenge of obtaining adequate sputum specimens. Gram-stained smears of specimens should be performed to assess the adequacy of sputum samples; specimens with large numbers of epithelial cells (>10 per high-power field) or with few neutrophils are unsuitable for culture, because correlation is lacking between upper respiratory tract flora and organisms causing lower respiratory tract disease. For patients with **cystic fibrosis** , special media should be used to detect pathogens important in cystic fibrosis, such as *Burkholderia cepacia* complex.

Endotracheal aspirates from intubated patients may be useful if the Gram stain shows abundant neutrophils and bacteria, although pathogens recovered from such specimens might still reflect only contamination from the endotracheal tube or upper airway. Quantitative cultures of bronchoalveolar lavage fluid may be valuable for distinguishing upper respiratory tract contamination from lower respiratory disease.

If infection with *Legionella* is suspected, the laboratory should be alerted so that the specimen can be inoculated to special media (e.g., buffered charcoal–yeast extract agar) to facilitate the recovery of this pathogen. The *Legionella* urinary antigen test is a noninvasive, sensitive and specific method for rapid detection of *L. pneumophila* serogroup 1.

The diagnosis of pulmonary **tuberculosis** in young children is best made by culture of early-morning gastric aspirates, obtained on 3 consecutive days. Sputum induction for obtaining specimens for mycobacterial culture has also proved useful in young children but requires skilled personnel and containment facilities to prevent exposure of healthcare workers. Cultures for *Mycobacterium tuberculosis* should be processed only in laboratories equipped with appropriate biologic safety cabinets and containment facilities. NAATs for detection of *M. tuberculosis* in respiratory specimens (e.g., Cepheid Xpert MTB assay) are becoming widely available and have very high sensitivity when performed on smear-positive sputum specimens.

Detection of Enteric Pathogens

In pediatric patients with diarrheal illnesses, culture of stool for enteric pathogens may be requested. A fresh stool specimen is preferred but is not always possible to obtain. If there is an unavoidable delay in specimen transport, the specimens should be placed in an appropriate transport medium, such as Cary-Blair. Rectal swabs for enteric culture are also acceptable specimens if the swab is visibly soiled. In general, enteric cultures should be performed on specimens from outpatients or patients who have been hospitalized for <3 days, since nosocomial acquisition of an enteric pathogen is extremely uncommon.

Stool specimens are typically plated on a series of selective and differential media to decrease the overgrowth of normal flora and recover pathogenic organisms if present. The specific pathogens queried vary by laboratory. Most laboratories in North America will routinely culture for *Salmonella* , *Shigella* , *Campylobacter,* and Shiga toxin–producing strains of *Escherichia coli* . The CDC recommends that all laboratories use an agar-based medium for recovery of

E. coli O157 in addition to an assay for detection of Shiga toxin production (e.g., immunoassay to detect Shiga toxin(s), nucleic acid detection assay for stx1/stx2). Practices surrounding the routine culture for *Yersinia enterocolitica* , *Vibrio cholerae* , *Edwardsiella* , *Aeromonas,* and *Plesiomonas* will vary with local epidemiology, and the laboratory should always be notified if one of these pathogens is specifically suspected.

Clostridium difficile is an important cause of antibiotic-associated diarrhea. *C. difficile* was long characterized as a nosocomial pathogen of older adults, but community-associated disease is emerging, and the incidence and severity of *C. difficile* infection in children are increasing. The optimal method for detection of *C. difficile* in fecal specimens is highly controversial; in general, however, detection of *C. difficile* toxin in fecal specimens has higher clinical specificity than toxigenic culture or nucleic acid detection methods. Testing for *C. difficile* in children <1 yr old should be discouraged because of the high incidence of colonization in this patient population.

Viruses are an important cause of **gastroenteritis** in pediatric patients. Methods for viral detection will vary but may include antigen detection (e.g., for rotavirus or adenovirus 40/41) or nucleic acid detection methods (e.g., for norovirus). In North America the burden of *parasitic* gastroenteritis is low. Complete microscopic exams for ova and parasite detection in stool samples is usually of low yield, and antigen detection assays for *Cryptosporidium* and *Giardia* , the most commonly encountered agents, are a sensitive and cost-effective method for detection of these pathogens.

Multiplex nucleic acid detection tests for simultaneous detection of a dozen or more enteric pathogens, including bacteria, viruses, and parasites, have been FDA-cleared and are available for clinical use. The deployment of these assays in clinical laboratories is variable, and the results of this testing can be difficult to interpret, especially when multiple targets are detected in a specimen (e.g., co-detection of *C. difficile* and an enteric bacterial pathogen in a young child).Culture-independent diagnostics may also challenge the public health response if bacterial isolates are not available for epidemiologic analysis. Although these assays have great promise to expedite the detection of the causative agent of diarrhea in children, laboratories and clinicians are still in the learning phase of how best to deploy this testing.

Culture of Other Fluids and Tissues

Abscesses, wounds, pleural fluid, peritoneal fluid, joint fluid, and other purulent fluids are cultured onto solid agar and, in some cases, broth media. Whenever possible, fluid and/or tissue rather than swabs from infected sites should be sent to the laboratory, because culture of a larger volume of fluid can detect organisms present in low concentration. **Anaerobic** organisms are involved in many abdominal and wound abscesses. These specimens should be collected and transported to the laboratory rapidly in anaerobic transport medium.

Although *Staphylococcus aureus* is the most common cause of bone and joint infections, *Kingella kingae* is an important cause of **septic arthritis** in children, especially in children <4 yr old. The detection of *K. kingae* is maximized by inoculation of synovial fluid into blood culture broth in addition to plating on solid medium. A number of studies suggest that molecular detection of *K. kingae* in specimens from young patients with suspected septic arthritis may be the most sensitive way to make this diagnosis.

Screening/Surveillance Cultures

Clinical laboratories may perform surveillance cultures for specific pathogens either to assist infection control in identifying patients requiring contact isolation or for outbreak investigation. Screening cultures for detection of methicillin-resistant *S. aureus* in the anterior nares or vancomycin-resistant enterococci in fecal specimens or rectal swabs may be routinely performed in certain patient populations. In addition, hospitals with carbapenem-resistant *Enterobacteriaceae* or a high prevalence of extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBLs) may screen patients for fecal carriage of these organisms. Chromogenic media are frequently used for this purpose. These media contain proprietary compounds to select for the resistant organisms and result in growth of colored colonies to assist in the identification of the microbe of interest.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility tests are generally performed on organisms of clinical significance for which standards and interpretive criteria for susceptibility testing exist. In North America, most laboratories use commercial, automated systems for susceptibility testing. The output from these systems is a *minimum inhibitory concentration* (MIC) value and interpretation of that value as susceptible, intermediate, or resistant. The next most common technique is

Kirby-Bauer **disk diffusion** , in which a standardized inoculum of the organism is seeded onto an agar plate. Antibiotic-impregnated filter paper disks are then placed on the agar surface. After overnight incubation, the zone of inhibition of bacterial growth around each disk is measured and compared with nationally determined standards for susceptibility or resistance.

A less common technique is **broth or microbroth dilution** testing. A standard concentration of a microorganism is inoculated into serially diluted concentrations of antibiotic, and the MIC in µg/mL, the lowest concentration of antibiotic required to inhibit growth of the microorganism, is determined. The **gradient diffusion** method such as E-test is a hybrid of disk diffusion and broth dilution and can be used to determine the MIC of individual antibiotics on an agar plate. It uses a paper strip impregnated with a known continuous concentration gradient of antibiotic that diffuses across the agar surface, inhibiting microbial growth in an elliptical zone. The MIC is read off the printed strip at the point at which the zone intersects the strip. Major advantages of the gradient diffusion method are reliable interpretation, reproducibility, and applicability to organisms that require special media or growth conditions.

In addition to providing data to guide the treatment of individual patients, laboratories use aggregate susceptibility testing data to generate institution-specific **antibiogram** reports. These reports summarize susceptibility trends for common organisms and can be used to guide empirical therapy before the availability of specific susceptibility testing results.

Antimicrobial susceptibility patterns are rapidly changing as microbes evolve new resistance mechanisms. Recommendations for performance standards for antimicrobial susceptibility tests and their interpretation are regularly updated by groups such as the CLSI and **European Committee on Antimicrobial Susceptibility Testing** (EUCAST).

Fungal Cultures

Special growth media is used to recover fungi, both yeasts and molds, in clinical specimens. Since most fungi prefer reduced growth temperatures and some species grow slowly, fungal cultures are incubated at 30°C (86°F) for 4 wk. All manipulations of filamentous fungi should take place in the biologic safety cabinet to avoid infecting laboratory personnel and prevent laboratory contamination.

Most yeasts are identified using methods similar to those used for bacteria. In contrast, the standard of care for identification of filamentous fungi has not changed in nearly a century. The laboratory takes into consideration the growth rate, color, and colony characteristics of an isolate and then prepares the specimen in lactophenol alanine blue for microscopic evaluation. These features in aggregate are used to identify the isolate. In some cases, DNA sequencing is used for fungal identification, and MALDI-TOF MS is also emerging for identification of filamentous fungi. Antigen detection assays are also available for some fungal pathogens such as *Cryptococcus neoformans* and *Histoplasma capsulatum* . Assays to detect galactomannan, a molecule found in the cell wall of *Aspergillus* (in addition to some other filamentous fungi), are commercially available and increasingly used to assist in making the diagnosis of invasive aspergillosis in immunocompromised populations.

Point-of-Care Diagnostics

Some assays to detect infections may be performed in the office setting, provided the site is certified as meeting appropriate quality assurance standards specified by the **Clinical Laboratory Improvement Amendments** (CLIA) of 1988. These include procedures listed under the category of *provider-performed microscopy* such as wet mounts, potassium hydroxide preparations, pinworm examinations, and urinalysis.

Many pediatric offices perform rapid antigen and CLIA-waived nucleic acid detection assays for detection of group A streptococcal pharyngitis and common respiratory viruses such as influenza. The sensitivity of point-of-care testing depends on specimen collection technique, the type of kit used, and the concentration of target analyte present in the sample. In addition, some antigen detection assays for influenza lack sensitivity. Providers using point-of-care diagnostics should familiarize themselves with the analytical performance characteristics of these tests and seek alternative testing methods when clinically indicated.

Office laboratories licensed to perform waived tests are limited to performing these tests and avoid having to undergo inspections and proficiency testing, although they are still subject to CLIA certification requirements specific to these tests. Gram staining, culture inoculation, and isolation of bacteria are considered moderately to highly complex tests under CLIA specifications. Any office laboratory performing Gram stains or cultures must comply with the same requirements and inspections for quality assurance, proficiency testing, and personnel requirements as fully licensed microbiology laboratories.

Laboratory Detection of Parasitic Infections

Most parasites are detected by microscopic examination of clinical specimens. *Plasmodium* and *Babesia* can be detected in stained blood smears, *Leishmania* can be detected in stained bone marrow smears, and helminth eggs, *Entamoeba histolytica*, and *Giardia lamblia* can be detected in stained fecal smears (see Table 195.1). Serologic tests are important in documenting exposure to certain parasites that are not typically found in stool or blood, and thus are difficult to demonstrate in clinical specimens, such as *Trichinella* .

Pinworm is a relatively common parasitic infection in pediatric patients. A diagnosis of pinworm can be made by evaluating a pinworm prep. The best time to obtain this specimen is first thing in the morning, before the patient has bathed or had a bowel movement. A piece of clear tape is pressed onto the perianal region of the patient and then applied to a clear microscope slide. The slide is examined for recovery of pinworm eggs or worms.

Fecal specimens should not be contaminated with water or urine, because water can contain free-living organisms that can be confused with human parasites, and urine can destroy motile organisms. Mineral oil, barium, and bismuth interfere with the detection of parasites, and specimen collection should be delayed for 7-10 days after ingestion of these substances. Because *Giardia* and many worm eggs are shed intermittently into feces, a minimum of 3 specimens on nonconsecutive days are recommended to exclude the diagnosis of an enteric parasite. Because many protozoan parasites are easily destroyed, collection kits with appropriate stool preservatives should be used if a delay is anticipated between time of specimen collection and transport to the laboratory.

Ova and parasite examination of fecal specimens includes a wet mount (to detect motile organisms if fresh stool is received), concentration (to improve yield), and permanent staining (e.g., trichrome) for microscopic examination. *Cryptosporidium* , *Cyclospora*, and *Isospora* are detected by modified acid-fast stain, and microsporidia are detected by a modification of the trichrome stain. In addition, *Cyclospora* and *Isospora* autofluoresce under ultraviolet (UV) microscopy. The laboratory should be alerted if these parasites are suspected. Detection of certain intestinal parasites, especially *Giardia* and *Cryptosporidium*

, can be simplified by using antigen detection tests (immunoassays or direct fluorescent-antibody assays). In addition, *Giardia* and/or *Cryptosporidium* spp. may be targets included on multiplex molecular panels for detection of pathogens causing diarrhea.

Amebic encephalitis , caused by *Acanthamoeba* , *Balamuthia* , or *Naegleria* , is a rare but devastating and rapidly progressive disease. Special laboratory stains and procedures are required to detect these organisms. The laboratory should be notified if this infection is suspected.

Rapid antigen detection tests for *Plasmodium* spp. are available. The sensitivity and specificity of these tests vary depending on the burden of parasite in the sample and the specific *Plasmodium* species. In general, these tests are most sensitive for detecting *P. falciparum* and least sensitive for detecting *P. malariae* . These tests are particularly useful for laboratories lacking personnel trained in evaluation of thick and thin smears for malaria, or to provide a rapid preliminary result while awaiting microscopy. All positive and negative rapid malaria assays should be confirmed with blood smear analysis.

Trichomonas vaginalis is a sexually transmitted protozoan parasite that can also be transmitted on household fomites. Infected individuals may be asymptomatic or may have mild inflammation or severe inflammation and discomfort. *Trichomonas* may be detected using a wet mount, but this method is insensitive. Rapid antigen assays and culture-based methods are available. NAATs are a rapid and sensitive way to detect *Trichomonas* .

Serologic Diagnosis

Serologic tests are primarily used in the diagnosis of infectious agents that are difficult to culture in vitro or detect by direct examination, such as *Bartonella, Francisella, Legionella, Borrelia* (Lyme disease), *Treponema pallidum, Mycoplasma, Rickettsia,* some viruses (HIV, Epstein-Barr, hepatitis A), and some parasites *(Toxoplasma, Trichinella).*

Antibody tests may be specific for immunoglobulin (Ig) G or IgM or can measure antibody response regardless of immunoglobulin class. In very general terms, the IgM response occurs earlier in the illness, generally peaking at 7-10 days after infection, and usually disappears within a few weeks, but for some infections (e.g., hepatitis A, West Nile) it can persist for months. The IgG response peaks at 4-6 wk and often persists for life. Because the IgM response is transient, the presence of IgM antibody in most cases correlates with recent infection. Methods for IgM antibody detection are difficult to standardize, however, and false-positive results typically occur with some IgM assays. The presence of IgG antibody can indicate new seroconversion or past exposure to the pathogen. To confirm a new infection using IgG testing, it is essential to demonstrate either seroconversion or a rising IgG titer. A 4-fold increase in a convalescent titer obtained 3-4 wk after the acute titer is considered diagnostic in most situations. In neonates, interpretation of serologic tests is difficult because of passive transfer of maternal IgG that can persist for 6-18 mo after birth.

Context is extremely important in the interpretation of serologic findings. Important considerations are the ability of the host to mount an immune response, the background rate of seropositivity (especially for IgG detection assays), and for some diseases the antibody titer. In addition, interpretation of some serologic assays, such as those used to diagnose **Lyme disease** , are problematic because of lack of specificity of the immunoassays. A confirmatory immunoblot (Western blot) is required for all positive and equivocal enzyme immunoassay (EIA) results for Lyme disease.

Laboratory Diagnosis of Viral Infections

Viral diseases are extremely important in pediatrics, and **diagnostic virology** has long been important to pediatric practice, especially in the inpatient setting.

Specimens

Specimens for viral diagnosis are selected on the basis of knowledge of the site that is most likely to yield the suspected pathogen. When evaluating patients with acute viral infections, specimens should be collected early in the course of infection, when viral shedding tends to be maximal. Swabs should be rubbed vigorously against mucosal or skin surfaces to obtain as much cellular material as possible and sent in viral transport media that contain antibiotics to inhibit bacterial growth. Rectal swabs should contain visible fecal material. Flocked swabs have been shown to provide more material for the laboratory with consequent improvement in the performance of diagnostic tests. Fluids and respiratory secretions should be collected in sterile containers and promptly delivered to the laboratory. All specimens should be transported on ice if delay is anticipated. Freezing specimens, especially at −20°C (−4°F), can result in a significant decrease in culture sensitivity. Consultation with the laboratory is recommended, because some commercial diagnostic test kits used by laboratories may require specific collection devices.

Laboratory diagnosis of viral infections may be by electron microscopy, antigen detection, virus isolation in culture, serologic testing, or molecular techniques to detect viral nucleic acids. In the past few years, **molecular tests** have emerged as the primary means for detecting viral infections, with some virology laboratories abandoning the use of viral culture altogether. An exciting development is the availability of FDA-cleared multiplex assays that simultaneously detect multiple viruses as well as nonviral agents. Serologic testing still has an important role, especially for arboviral infections such as West Nile, Zika, chikungunya, and dengue; acute Epstein-Barr virus (EBV) infections; HIV; hepatitis A to E, and diseases of childhood such as measles, rubella, and mumps. Serology is also uniquely useful for defining immunity to specific viral infections.

Antigen Detection Tests

Immunofluorescent antibody (IFA) techniques or other methods, such as EIA, were the mainstay of the diagnosis of respiratory viral infections but are now being replaced by molecular tests. IFA assays of cellular material from respiratory secretions can identify the antigens of respiratory syncytial virus (RSV), adenovirus, influenza A and B viruses, parainfluenza virus types 1-3, and human metapneumovirus within 2-3 hr after the specimen is received. The sensitivity of IFA staining for RSV exceeds that of culture in many laboratories but is less than that of molecular tests. Sensitive IFA staining techniques are also commercially available for identifying varicella-zoster virus and herpes simplex virus. A method for detecting cytomegalovirus (CMV) pp65 antigen in blood of immunocompromised patients is also available but has been largely replaced by molecular testing. IFA is not useful for detecting viruses in specimens that do not contain an adequate number of infected cells.

Rapid antigen tests are usually based on lateral flow immunochromatography (similar to rapid tests for group A streptococcus) and have been approved by the FDA for detection of influenza A and B and RSV. Recent modifications that increase sensitivity include fluorescent labels and instrumented readers. Some rapid antigen tests have waived status under CLIA, meaning that they can be performed by personnel who are not trained laboratory technologists, with relatively little formal quality control other than controls that are incorporated into the test devices. Some require only 10 min to perform. Consequently, these tests can be performed in a physician's office or an emergency department. Sensitivity in children is 50–80%, generally higher for children than for adults. Rapid antigen tests can be useful in managing patients with acute respiratory infections, provided the caregiver keeps in mind that a negative test does not rule out the diagnosis of influenza or RSV. Positive tests that are properly read tend to be reliable, but the presence of a virus such as influenza or RSV does not rule out the presence of concomitant bacterial infection.

In addition to their role in respiratory virus infections, antigen detection EIA tests are often used for the diagnosis of viruses that are difficult to culture, such as rotavirus, enteric adenovirus, and hepatitis B virus. The detection of the p24 antigen of HIV along with HIV antibodies is included in fourth-generation EIA tests used in the diagnostic algorithm for HIV.

Viral Culture

Viruses require living cells for propagation; the cells used most often are human- or animal-derived tissue culture monolayers, such as human embryonic lung fibroblasts or monkey kidney cells. Historically, in vivo methods such as inoculation of suckling mice were also used but are rarely used today. Viral growth in susceptible cell culture is usually accomplished by detecting characteristic cytopathic effect that is visible by light microscopy under low magnification in the cultured cells. The most reliable confirmatory method for viral detection in cell culture involves fluorescein- or enzyme-labeled monoclonal antibody staining of infected cell monolayers. An important technical improvement in respiratory viral cultures is the development of cell culture systems that include more than 1 type of cell (R-Mix, Diagnostic Hybrids/Quidel, San Diego, CA) and employ IFA staining for virus detection. This system provides results in 16-40 hr from the time the specimen is received in the laboratory, compared to 2-10 days for conventional cultures. Cell culture methods are now being steadily replaced by molecular tests, which are faster, may be more sensitive, and have the potential to detect viruses that do not grow readily in cell cultures.

Molecular Diagnostics

Molecular tests to detect viruses use the polymerase chain reaction (PCR) and other comparable nucleic acid amplification methods. FDA-cleared multiplex tests have become available for the diagnosis of respiratory, gastrointestinal, and central nervous system (CNS) infections. Some of these tests detect 20 or more different agents at the same time and may require only about 65 min to perform. The infectious agents detected by multiplex panels may include bacteria, fungi, and parasites as well as viruses (Table 195.2).

Table 195.2

Multiplex Molecular Assays for Viral Diagnosis

TEST	MANUFACTURER	PATHOGENS DETECTED[*]
RESPIRATORY		
NxTag	Luminex, Austin, TX	Flu A, AH1, AH3, Flu B, RSV A/B, PIV 1-4, HMPV, RV/EV,[†] HCoV OC43/229E/NL63/HKU1, AdV, human bocavirus, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*
Verigene	Luminex, Austin, TX	Flu A, AH1, AH3, Flu B, RSV A/B, PIV 1-4, HMPV, RV, AdV, *Bordetella pertussis* , *B. parapertussis/bronchiseptica* , *B. holmesii*
FilmArray	BioFire, Salt Lake City, UT	Flu A, AH1, AH1(2009), AH3, Flu B, RSV, PIV 1-4, HMPV, RV/EV,[†] CoV OC43/229E/ NL63/HKU1, AdV, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Bordetella pertussis*
ePlex	GenMark	Flu A, AH1, AH1(2009), AH3, Flu B, RSV, PIV 1-4, HMPV, RV, AdV B/C/E
GASTROINTESTINAL		
NxTag	Luminex, Austin, TX	Rotavirus A, norovirus GI/GII, AdV 40/41, *Campylobacter* , *Clostridium difficile* toxin A/B, *Escherichia coli* O157, enterotoxigenic *E. coli* , LT/ST, Shiga-like toxin–producing *E. coli* (stx1/2), *Salmonella* , *Shigella* , *Vibrio cholerae* , *Yersinia enterocolitica*, *Cryptosporidium*, *Entamoeba histolytica*, *Giardia*
Verigene	Luminex, Austin, TX	Rotavirus, norovirus, *Campylobacter* , *Salmonella* , *Shigella*, *Vibrio* , *Yersinia* , *stx1/2*
FilmArray	BioFire, Salt Lake City, UT	Rotavirus A, norovirus GI/GII, AdV 40/41, astrovirus, sapovirus I, II, IV, V, *Campylobacter* , *C. difficile* toxin A/B, *Plesiomonas shigelloides* , *Salmonella* , *Y. enterocolitica* , *Vibrio* , enteroaggregative *E. coli* , enteropathogenic *E. coli* , enterotoxigenic *E. coli* , Shiga-like toxin–producing *E. coli* (stx1/2)/*E. coli* O157, *Shigella* /enteroinvasive *E. coli* , *Cryptosporidium* , *Cyclospora cayetanensis* , *E. histolytica* , *Giardia lamblia*
CENTRAL NERVOUS SYSTEM		
FilmArray	BioFire, Salt Lake City, UT	HSV-1, HSV-2, VZV, CMV, HHV-6, enterovirus, parechovirus, *E. coli* K1, *Haemophilus influenzae* , *Listeria monocytogenes* , *Neisseria meningitidis* , *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Cryptococcus neoformans/gattii*

[*] Cleared by the U.S. Food and Drug Administration (FDA) as of March 2017. Other versions that detect additional viruses are available outside the United States.

[†] Detects rhinoviruses and enteroviruses but does not distinguish between them.

AdV, Adenovirus; AH1, influenza A, hemagglutinin type 1; AH3, influenza A, hemagglutinin type 3; CMV, cytomegalovirus; CoV, coronavirus; EV, enterovirus; flu A, influenza A; flu B, influenza B;

HHV, human herpesvirus; HMPV, human metapneumovirus; HSV, herpes simplex virus; LT/ST, heat-labile; heat-stable toxins; PIV, parainfluenza virus; RSV, respiratory syncytial virus; RV, rhinovirus; VZV, varicella-zoster virus.

Herpes simplex virus (HSV) PCR of CSF was the first PCR-based test to become widely accepted dating to the mid-1990s. The first FDA-cleared test for this purpose was approved in 2014. Some laboratories still use laboratory-developed tests for which performance characteristics must be validated as specified by CLIA, resulting in testing that is not standardized and performance characteristics (sensitivity, specificity) that may vary from laboratory to laboratory. Well-performing CSF PCR assays for HSV have sensitivity and specificity exceeding 95% for the diagnosis of HSV encephalitis. PCR is also increasingly used to diagnose mucocutaneous HSV and varicella-zoster virus infections. Molecular testing is more sensitive than virus culture and provides a more rapid turnaround time. Because molecular tests detect nonviable as well as viable virus, they may detect virus from the healing phase of the illness, when cultures would be negative.

An FDA-cleared test for enterovirus in CSF (GeneXpert, Cepheid, Sunnyvale, CA) provides sensitive detection of enteroviruses in approximately 3 hr. Because this testing is simple, some hospital laboratories are able to perform testing around the clock, thus maximizing the clinical utility of the test. The **parechoviruses** , which may cause illnesses similar to those caused by enteroviruses, especially in infants <6 mo of age, must be detected by separate molecular assays.

Respiratory viruses detected by multiplex panels include influenza A and B, RSV, parainfluenza 1-4, human metapneumovirus, rhinovirus/enterovirus, coronaviruses OC43, 229E, NL63, and HKU1, and adenoviruses (Table 195.2). The specific viruses (and nonviral agents) included differ among tests produced by different manufacturers. In addition, rapid CLIA-waived molecular tests are available for the simultaneous detection of influenza A and B and the trio of influenza A/B and RSV. These tests are similar to cleared CLIA-waived molecular tests for group A streptococcus and have the potential to make sensitive molecular diagnosis available in emergency departments, urgent care centers, and physician offices. Molecular tests are more expensive than antigen-based tests, and studies of clinical utility and cost-effectiveness are not yet available.

Gastrointestinal multiplex panels recently FDA-approved may include tests for group A rotaviruses, noroviruses GI and GII, enteric adenoviruses (group F, serotypes 40 and 41), astrovirus, and sapovirus, but not all are included in each manufacturer's test. Tests for bacterial and parasitic causes are also included. For clinicians, these tests provide information about the presence of potential etiologic agents not previously available. Numerous questions arise about whether detected pathogens are actually clinically significant and how to sort out the detection of >1 pathogen in the same sample. For laboratories, these tests raise questions about whether they can replace previously used techniques such as bacterial culture. The clinical utility and cost-effectiveness of using these tests have not been determined.

A multiplex panel for viral and bacterial and 1 fungal agent of CNS infection was cleared by the FDA. This test provides information about the presence of diverse etiologic agents that challenged many laboratories in the past. As for the other multiplex molecular panels, clinical utility and cost-effectiveness remain to be determined. Susceptibility to contamination during performance of the assay has been a concern not yet fully resolved.

Another important area of application of molecular testing is the detection of viruses in the blood. FDA-approved assays to detect HIV RNA and hepatitis C RNA are essential for the management of these infections, including the prevention of transmission from mother to infant. Hepatitis B molecular testing is also increasingly used. In addition, molecular testing is now widely used for viruses that cause systemic disease in immunocompromised patients, especially CMV, EBV, HSV, the BK polyomavirus, and adenovirus. BK virus is often tested for in urine samples as well as in blood. For these viruses, as well as for HIV and the hepatitis viruses, quantitative testing is required. An FDA-approved PCR assay for the quantitative measurement of CMV DNA in plasma is now available. In addition, international standards for CMV, EBV, and BK virus have been developed. This is important because their utilization improves the comparability of viral levels measured in different laboratories.

Laboratory-developed PCR and other molecular assays are used by some laboratories for numerous other viruses, including parvovirus B19, human herpesvirus 6, human papillomavirus, mumps, measles, rubella, and the JC polyomavirus.

Host gene expression patterns in whole blood have been used to attempt to differentiate viral from bacterial infections. This approach may rapidly identify a viral or bacterial profile of host gene expression reprise, thus greatly shortening the time to diagnosis and potentially avoiding inappropriate treatment while suggesting indicated therapies. Implementation in the clinic awaits development of rapid tests that incorporate this information.

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CHAPTER 196

The Microbiome and Pediatric Health

Patrick C. Seed

From the time of birth, the human infant is exposed to a myriad of microbes found on the mother and in the surrounding environment. Microbes rapidly form assemblages across exposed areas of the body, including the skin and enteral tract. The microbial communities are called the **microbiota** and make a substantial impact on short- and long-term physiology, including immunologic and metabolic development and function. Together the number of body-associated bacterial cells is estimated to be 10 times greater than the number of human cells in the body. In aggregate, the totality of the microbes, including their microbial genes and environmental interactions, constitute the **microbiome** , and the microbial genes in the human microbiome are estimated to exceed the number of human genes by at least 100-fold, together making a macroorganism with an inseparable collective physiology. Current evidence indicates that the microbiome evolves over the life span to influence health and disease.

Measuring the Microbiome

Prior knowledge of microbes on and around the human body was based on specific methods to cultivate organisms. Molecular technologies have revolutionized the identification of poorly cultivatable microbes, rare microbes, and microbes in complex communities such as those associated with the human body (Fig. 196.1). The development of the polymerase chain reaction (PCR) and the availability of modern nucleic acid sequencing have improved the sensitivity of detection of many organisms and resulted in the discovery of new organisms. Modern sequencing technologies, called **next-generation**

sequencing platforms, allow sequencing in high volume and depth, with millions of sequences obtained from a single biologic sample. Three major approaches utilize next-generation sequencing to understand the composition, diversity, and activity of the microbiome: (1) sequencing species-specific regions of genomes such as ribosomal RNA–encoding tracks and intergenic regions termed **metagenomics** , (2) total DNA sequencing from a sample (e.g., feces, saliva) and assembly of the sequence fragments into large genome pieces termed **shotgun metagenomics** , and (3) RNA transcript sequencing to decipher the composition and, as a surrogate for functional activity, the transcriptional activity of a microbiome termed **metatranscriptomics** . Massive computational power and new bioinformatics tools have allowed the analysis and comparison of the large datasets arising from these methods.

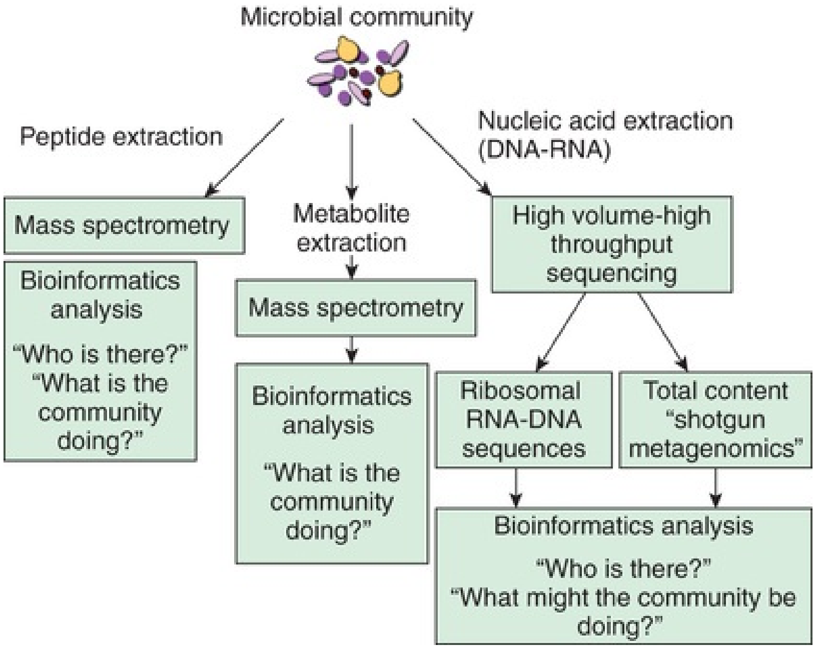
Microbial community
Peptide extraction
Nucleic acid extraction (DNA-RNA)
Mass spectrometry
Metabolite extraction
High volume-high throughput sequencing
Bioinformatics analysis
"Who is there?" "What is the community doing?"
Mass spectrometry
Bioinformatics analysis
"What is the community doing?"
Ribosomal RNA-DNA sequences
Total content "shotgun metagenomics"
Bioinformatics analysis
"Who is there?"
"What might the community be doing?"

FIG. 196.1 Common molecular methodologies for identifying the components and the functions of complex microbial communities.

Two additional approaches to measure the microbiome phenotype have rapidly developed as well. First, large-scale measurements of the peptide composition of the microbiota, called **proteomics** , have been increasingly used to describe the activity of a microbiome sample, as peptides provide information about the composition and function of a microbiome. Second, in a complementary approach called **metabolomics** , microbiome-derived metabolites are measured using advanced gas chromatography and mass spectrometry techniques. Together, proteomics and metabolomics better describe the activity of a microbiome than the nucleotide-sequencing approaches; however, at this point, they provide less depth of resolution and specificity relative to the composition and phenotype of a microbiome.

Despite the power of these methodologies to interrogate the microbiome, they do not yet replace cultivation of microbes in many clinical circumstances. *Cultivation of organisms still represents the most practical means to differentiate potential pathogenic species from more benign species* and to provide clinically actionable information such as susceptibility to a range of antimicrobials.

Early Childhood Development of the Microbiome

Emerging studies suggest that the placenta and fetus are exposed to microbes in utero, but the effect of such an exposure remains to be fully appreciated. **Prematurity** as a complication of an infection of the fetal membranes and either subclinical or clinical **chorioamnionitis** may alter the in utero exposure to microbes. The rupture of the fetal membranes and subsequent delivery provide substantial exposure to new maternal and environmental microbes that will assume common places in the developing microbiota. Mode of delivery has a major influence on the early life microbiome, with vaginally delivered infants becoming acutely colonized with intestinal organisms that reflect the mother's vaginal tract and infants delivered by cesarean section becoming colonized with organisms reflective of maternal skin and oral cavity, including staphylococci and streptococci, as well as the surrounding environment.

In the term infant delivered vaginally, the first intestinal microbes, so-called pioneering organisms, include *Escherichia* and other Enterobacteriaceae, *Bacteroides*, and *Parabacteroides* . Exclusive breastfeeding has been reported to result in high levels of bifidobacteria and *Lactobacillus* in the week following the start of feeding. These probiotic organisms have unique capacities to exclude would-be pathogens from colonization by sequestering nutrients and producing antimicrobial factors while stimulating the intestinal epithelium to tighten cellular junctions and express antimicrobial peptides. However, these genera have been notably deficient from some breastfed infant cohorts, particularly in the United States.

The premature infant is more likely to be delivered by cesarean section and thus is more abundantly colonized with skin-related organisms such as coagulase-negative staphylococci, similar to the term infant delivered by cesarean section. However, the premature infant may fail to progress through the same stages of expansion and diversification of the microbiome over the 1st week to month of life as the term infant. The factors related to the delayed maturation are not fully clear but are predictably related to delayed or limited enteral feeding, normal environmental exposure to the household environment, and exposure to medical interventions such as antimicrobial therapy.

The most significant shift in the intestinal microbiota appears to occur after weaning and the introduction of solid foods. As the infant transitions from breast milk to a solid-food diet containing complex plant-derived polysaccharides, the microbiota begins to reshape progressively into a more mature composition beginning to resemble the adult microbiota. At the same time, the metabolic potential of the microbiome shifts to accommodate the changing diet, with the newborn microbiome enriched with phosphotransferase system (PTS) genes and then shifting to increasing abundance of lactose transporter genes by 4 mo of age, reflecting milk intake, and further shifting to a high abundance of genes such as β-glucoside transporters and enzymes necessary to break down complex carbohydrates by age 12 mo. The maturation of the childhood microbiome after the early years to adulthood is less well understood, and more studies are required in large numbers of children to understand fully the developmental stages of maturation and similarity to the mature, healthy adult state.

The oral microbiota of the newborn is of maternal origin, with vaginally born infants having predominantly *Lactobacillus, Prevotella,* and *Sneathia,* whereas cesarean-born infants have more maternal skin organisms, including *Staphylococcus, Corynebacterium,* and *Propionobacterium* .Within the 1st day of life, Firmucutes dominate the oral cavity, including *Streptococcus* and *Staphylococcus.* Formula-fed babies acquire more Bacteroidetes, whereas breast-fed babies have more bacteria of the phyla Proteobacteria and Actinobacteria. With the eruption of first teeth, new environmental niches are formed to foster microbial communities. Although cariogenic bacteria such as *Streptococcus mutans* were thought to be acquired after dentition, recent data demonstrate the presence of these organisms prior to tooth eruption in a soft tissue reservoir, highlighting the importance of good infant oral care even before primary dentition.

By age 3 yr, the childhood oral and salivary microbiome is complex but less diverse than the adult microbiome. The composition of the microbiota within the oral cavity in the presence of full adult dentition has an estimated 1,000 bacterial species. Even with oral health, the diversity in the gingiva of different types of teeth (**geodiversity**) is substantial, and the diversity changes dramatically with the development of oral disease such as periodontitis. How the microbiota evolves between preschool and adulthood remains a topic for future study. Furthermore, the placement and removal of oral hardware for orthodontics is common in childhood and may produce significant alterations in the microbiome of the oral cavity.

During the 1st yr of life, the infant skin microbiome increases in diversity, including species richness and evenness. The skin of the younger infant is relatively undifferentiated between body sites, with more shared species among different body sites such as arms, forehead, and buttocks than the older infant when the microbial communities at each site undergo differentiation. As with the early infancy oral microbiota, skin of the young infant skin is predominantly colonized by Firmicutes, including Streptococcaceae and Staphylococcaceae, with the inclusion of bacteria from other phyla such as Actinobacteria, Proteobacteria, and Bacteroidetes as the skin matures. The adult skin microbiome displays a high degree of geodiversity—differences in composition depending on site and local physiology, with major differences in dry and wet skin sites. However, the linkage between skin development in childhood and maturation of the skin microbiome remains a subject of ongoing studies.

Social structure and family interactions likely play a significant role in the development of the early life microbiome. Breast milk feeding provides a microbiologic link between mothers and infants, including transmission of probiotic-like organisms such as lactobacilli and bifidobacteria, each of which may have some protective effects, including protection against diarrheal diseases and atopy. Pediatricians have long been aware of the infectious disease risks and benefits of daycare attendance, with examples of shared pneumococcal strains producing otitis media and outbreaks of respiratory syncytial virus infection and associations with reduced atopy, allergy, and possibly asthma. Family contacts are risks for acquisition of methicillin-resistant *Staphylococcus aureus* and subsequent disease. Studies also demonstrate transmission of parts of the human microbiome between household individuals and domesticated pets such as dogs and cats. For example, family members share the same strains of *Escherichia coli* known to produce urinary tract infections in one of the household members. There may be differences in the oral microbiota among infants for whom the parents did and did not use the practice of pacifier sucking for cleaning. In rural settings, microbiome sharing extends to livestock, household surfaces, and household members. Thus, development of the microbiome during childhood with environmental interactions is a complicated process that continues to be explored.

The Microbiome and Physiologic Development

Increasingly complex roles are being identified for the microbiome in the development of mammalian physiology (Fig. 196.2). These roles include the development of the enteral tract, respiratory tract, immune system, hematologic system, metabolic-endocrine system, and neurologic system. The details of how the microbiome contributes to these developmental processes in humans are still under intense investigation; however, modeling in other mammalian systems predicts that the microbiome will have a critical role across species.

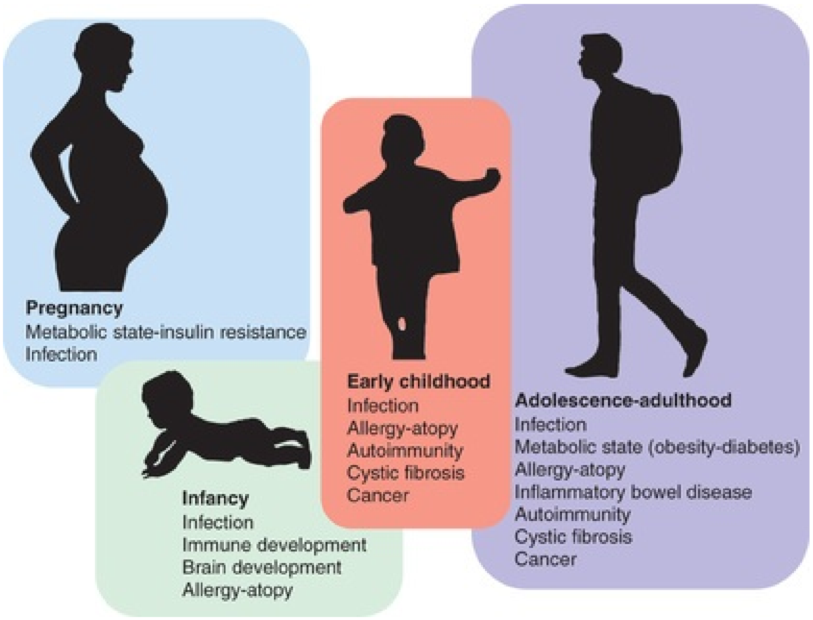
Pregnancy
Metabolic state-insulin resistance
Infection
Infancy
Infection
Immune development
Brain development
Allergy-atopy
Early childhood
Infection
Allergy-atopy
Autoimmunity
Cystic fibrosis
Cancer
Adolescence-adulthood
Infection
Metabolic state (obesity-diabetes)
Allergy-atopy
Inflammatory bowel disease
Autoimmunity
Cystic fibrosis
Cancer

FIG. 196.2 **Physiologic and pathologic roles of the microbiome relevant to pediatrics. The human microbiome has an impact on health and development from pregnancy through adulthood, including infection and non–infection-related processes.**

Microbiome and Metabolism

Soon after entry into the physical world, the mammalian *enteral tract* is colonized, and the interaction of early pioneering microbes in the enteral tract stimulates the development of the intestinal mucosa. In neonatal and juvenile animal models, delayed or absent intestinal colonization results in incomplete development of the epithelium, flattening of the intestinal crypts, loss of vasculature, and severely reduced enzymatic function, including alkaline phosphatase and glucosidases.

The enteric microbiota has a large number of roles in the physiology of the *intestinal tract* . It stimulates mucosal and systemic immune development, development and regeneration of the epithelium and endothelium, and the maturation and maintenance of metabolism. The latter includes the digestion of otherwise indigestible plant polysaccharides; (2) production of vitamins and cofactors; (3) metabolism of xenobiotics, including clinically relevant drugs; and (4) stimulation of local and systemic metabolism, including lipid storage. Germ-free animals lacking the enteric microbiota have limited nutrient extraction and have a failure-to-thrive phenotype.

Germ-free mice born into a sterile environment serve as a model to understand the role of the microbiome in health. Germ-free mice are humanized through selective colonization with human fecal microbial communities. Similar to weaning to solid-food transition, feeding the humanized mice diets with and without polysaccharides results in dramatic alterations in central metabolites. Humanized mice transitioned from a polysaccharide-rich, low-fat diet to a more Westernized diet high in fat and monosaccharides undergo a blossoming of the phyla Actinobacteria and Firmicutes in the enteric microbiota, with a commensurate reduction in Bacteroidetes, similar to observations of increased Firmicutes and reduced Bacteroidetes in human obesity.

Common patterns of mature enteric microbiota community composition and its predicted function may exist among humans. Sequencing of the fecal microbes from adults across multiple nations revealed 3 common patterns of microbial community compositions, called **biotypes** . High proportions of *Bacteroides, Prevotella*, and *Ruminococcus* in unique biotypes serve as sentinels for each different biotype, and biotypes vary in individuals from different continents, including North America, Europe, and Asia, largely reflecting cultural and dietary variances. The infant microbiome varies considerably; mature, stable biotypes form in the early postweaning period and after infancy.

Breast milk and formula feeding biotypes have been described, with notable enrichment of enteric gram-negative bacteria such as *E. coli* and anaerobic *Clostridia* spp. among the formula-fed infants. The vaginal biotypes of young and aging women are well described and vary by age, race, and ethnicity.

Microbiome, Inflammation, and Immunity

The organisms that compose the microbiome are critical for early immune programming, the development of immune tolerance, and overall maintenance of immune set points. Cells produce a variety of receptors to recognize microbial ligands in a process called **pattern recognition** . In turn, microbes produce intentional and unintentional stimulation of those cellular receptors to activate and repress inflammatory pathways. Classic examples of such regulatory interactions include peptidoglycan on bacteria binding to Toll-like receptor 2 (TLR-2, in complex with TLR-3 and TLR-6), lipopolysaccharide of gram-negative bacteria binding to TLR-4, and glucans of fungi binding to the dectin receptor. The results of these receptor interactions include the production of chemokines and cytokines, cell differentiation and development, alteration in metabolism, and stimulation of cell death and survival programs, all contingent on the type of cell, state of the cell, and magnitude of stimulation.

Microbial stimulation of these microbial recognition systems is so critical in development that animals raised in the absence of microbes have diminished innate immune responses such as antimicrobial peptides at mucosal surfaces, dysregulated proinflammatory and immunologic tolerance responses, and reduced T- and B-cell populations. Following the restoration of normal enteric tract colonization weeks after being sterile, animals retain long-term aberrant cytokine responses with hyperactive proinflammatory responses to stimuli, demonstrating the persistent consequences of altering early microbial acquisition. Different early life colonization patterns also correlate with long-term immune development. In a Scandinavian study, children with persistent early life *E. coli* colonization had higher sustained memory B-cell ($CD3^+$ $CD20^+$ $CD27^+$) levels by 1.5 yr old than children with lower levels of *E. coli* colonization, even despite abundant colonization with the prototypical probiotic bacteria *Lactobacillus* .

Microbiome-Neurobiologic Connections

Emerging studies are demonstrating a gut-brain axis that may be altered by the composition and activity of the enteric microbiome. Investigations in animal models have shown that the microbiome alters the hypothalamic-pituitary-adrenal system. Germ-free mice have exaggerated stress-anxiety behavior accompanied by elevated corticosterone and adrenocorticotropin levels compared with conventionally colonized, pathogen-free mice. *Neuroplasticity* including neurogenesis and microglia activation are regulated by the microbiota. Functional MRI has shown that the ingestion of 5 strains of probiotic-like bacteria alters brain activity in humans, resulting in decreased brain responses to emotional attention tasks in sensory and emotional input regions of the brain. Although the mechanism underlying these changes can only be inferred, the tractus solitarius and thus the vagus nerve appear to mediate the enteral tract–brain connection.

Another mechanism through which the enteric microbiome may alter brain activity is by the metabolites it produces. Administration of fermented milk with probiotic-like organisms, most notably *Bifidobacterium animalis* subsp. *lactis* , to monozygotic human twins and mice did not dramatically change the intestinal microbiome composition but did alter its transcriptional profiles, with a shift to increased carbohydrate fermentation to fatty acids, thought to attenuate sad emotional behavior in humans.

Contributions of Microbiome to Disease

Studies demonstrate that some microbial communities may act in concert to exert negative health effects, whereas other communities may be restorative or resistant to disease. Some examples of this concept of altered microbial communities, also termed **dysbiosis** , are provided in the following sections.

Microbiome of Premature Birth

Although the etiology of premature birth is multifactorial, inflammatory conditions such as subclinical and clinically overt infections of the mother and fetus instigate premature birth. Inflammatory biomarker profiling highlights this point, because women who proceed to preterm birth have increased angiotensin, interleukin-8, and tumor necrosis factor receptor 1, along with race-specific alterations in additional cytokines and chemokines. Prior work reported that women experiencing preterm birth have increased vaginal colonization with

Gardnerella spp. and *Lactobacillus crispatus.* Diversity of the microbiota of the posterior vaginal fornix of women experiencing preterm birth is lower compared to women delivering at term. A meta-analysis of early treatment of vaginosis with clindamycin before 22 wk of pregnancy demonstrated a reduction in spontaneous preterm birth at <37 wk, consistent with an association between dysbiosis of the pregnancy-associated microbiota and preterm birth.

Traditionally, the amniotic cavity and the fetus have been presumed to be sterile before the rupture of the fetal membranes and birth. However, several reports identify evidence for bacterial DNA in meconium with 2 predominant meconium types regardless of the mode of delivery: (1) dominated by Enterobacteriaceae and (2) dominated by Leuconostocaceae, Enterococcaceae, and Streptococcaceae. Furthermore, data indicate that the amniotic fluid in subclinical and clinically apparent chorioamnionitis has evidence of vaginal-derived microbes present, including poorly or noncultivatable organisms such as *Mycoplasma* spp., *Ureaplasma* spp., *Bacteroides* spp., *Fusobacterium, Sneathia sanguinegens,* and *Leptotrichia amnionii* . A correlation exists between the burden of intraamniotic organisms and the degree of prematurity. Microbial invasion of the amniotic space may lead to induction of inflammatory pathways through innate immune microbial pattern recognition receptors such as the TLRs. The result may be the induction of labor and physiologic stress on the fetus and mother. Exposure to microbial factors may have consequences on lung and intestinal development, setting the stage for postnatal pathology, including necrotizing enterocolitis. Beyond the acute threat to the maternal-fetal dyad, chorioamnionitis may not produce the long-term neurodevelopmental consequences it once was thought to cause, with formerly premature infants born to women with chorioamnionitis having similar cognitive and neuropsychiatric outcomes, even to age 18 yr, as infants not exposed to chorioamnionitis.

Changes in the Microbiome With Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a devastating disease of the neonatal intestine that disproportionately affects severely premature infants who weigh <1,500 g at birth. The pathologic steps in NEC include intestinal inflammation with loss of barrier function, microbial invasion of the bowel, and eventual death of the affected bowel. Years of research implicated specific organisms as the cause of NEC in case series; however, none of the proposed specific etiologies proved to be common to all cases of NEC and, instead, appeared to be the emergent organisms after serious intestinal pathology had ensued.

Currently, a model of dysbiosis of the early life intestinal microbiome has been favored in the pathogenesis of NEC. Epidemiologic studies in very-low-birthweight infants have demonstrated an association of cephalosporins and duration of antibiotic exposure with the development of NEC, consistent with the idea that shifts in the microbiota predispose to or incite NEC. Studies demonstrate decreased diversity of the microbiota preceding and during NEC. The NEC microbiota at the time of clinical symptoms resembles the microbiota 72 hr before onset, but not the microbiota 1 wk before onset of symptoms, suggesting that a shift in the intestinal microbiota begins well in advance of the appearance of NEC. Some differences in early colonization after birth may portend an increased risk for NEC.

Microbiome and Allergic Disorders

Given the role of the microbiome in the development and modulation of innate and adaptive immune responses, considerable interest surrounds its role in the development and exacerbation of allergic conditions such as **atopic dermatitis** . The microbiome of the skin has been studied before, during, and after treatment of flares of atopic dermatitis. Flares result in the loss of diversity of bacteria on the affected area, and treatment introduces new diversity. *Staphylococus aureus* and *S. epidermidis* increase before and during atopic flares, whereas *Streptococcus* and *Corynebacterium* spp. increase immediately preceding and during clinical improvement. In mice, oral treatment of infant animals with nonabsorbable antibiotics increases serum immunoglobulin (Ig) E, increases clinical symptoms such as itching, and produces atopic-like features. These data suggest that atopic dermatitis is influenced by the local skin microbiome and more distant microbiomes such as in the intestinal tract, also suggesting why the administration of oral probiotics such as *Lactobacillus* spp. may decrease atopic dermatitis with an accompanying shift in the T-helper cell (Th1/Th2) balance and increased interferon-γ, which are part of immune tolerance.

The respiratory tract is a common site of allergic disease, and infections have long been associated with allergic exacerbations of the respiratory tract. Traditional teaching is that the lower respiratory tree is sterile; however, studies of the airway microbiome in healthy and asthmatic children and adults indicate that this teaching is incorrect. Measured through careful bronchoscopic sampling and cytology brushings, the airways have a diverse microbiota during good health.

Measurement of the microbiota in the lower respiratory tract of healthy and asthmatic children indicates significant differences. Past culture-based studies indicate that early life colonization of the neonatal respiratory tree by *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* is associated with an increased risk for childhood asthma. These same organisms also are closely associated with exacerbations of asthma. In a mouse model, early life colonization of the neonatal nasopharynx with *H. influenzae* results in reduced airway-associated regulatory T cells, and colonized animals have enhanced airway hyperresponsiveness following allergen sensitization and inhalation challenge. *Mycoplasma pneumoniae* has been proposed as a major bacterial inducer of childhood asthma exacerbations when infection is identified. The employment of culture-independent measurements of lower airway microbiota composition (see Fig. 196.1) indicates that children with asthma are more likely to have higher levels of Proteobacteria, including *H. influenzae*, as well as Firmicutes such as *Staphylococcus* and *Streptococcus* spp. Remarkably, healthy children are more likely than age-matched asthmatic children to have lower airway Bacteroidetes, particularly *Prevotella* spp., a group of anaerobic bacteria. The association of healthy airways with an anaerobic lower respiratory tree bacterial population is unexpected because the high–oxygen tension environment was previously assumed to be toxic to anaerobes. This study indicates that the airway environment is significantly different than previously understood, and the potentially protective attributes of a native health-associated microbiota need to be studied to determine if these associations are also causal.

Airway Microbiome of Cystic Fibrosis

Cystic fibrosis (CF) is characterized by progressive airway disease and inflammation with acute exacerbations accompanied by loss of pulmonary function. An age-dependent change in lower airway colonization occurs among CF patients, which starts in early childhood with *S. aureus* and *H. influenzae* and progressively shifts toward more intrinsically multidrug-resistant organisms, including the notoriously persistent and treatment-refractory bacteria *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex. Culture-independent molecular analysis of the lung-associated microbiota in CF has revealed much more complex microbial communities than previously expected and has demonstrated an association between patient age and disease severity. In addition to the presence of a variety of previously unexpected airway organisms such as anaerobes and mycobacteria, disease severity is inversely related to the lower airway microbial community diversity, with less advanced disease associated with greater species richness and evenness. In contrast, the loss of diversity, including the shift from less complex microbial communities to those dominated by *P. aeruginosa,* is strongly correlated with disease severity, and levels of *H. influenzae*, the early childhood colonizer, have a negative correlation with disease severity. Although antibiotics decrease the rate of progressive lung function deterioration, they also decrease the community diversity, thus suggesting a balance between a diverse microbiota and reducing the dominance of certain organisms such as *P. aeruginosa* .

Microbiome During Antibiotic-Associated Diarrhea and *Clostridium difficile* Colitis

Treatment with oral and parenteral antibiotics results in a rapid and significant alteration of the intestinal microbiota. Healthy study participants taking **ciprofloxacin** experience dramatic but individualized microbiome changes in response to the antibiotic, with significant reductions in bacteria outside its expected spectrum, emphasizing the interdependence of microbial community members on one another for their stability in the community as a whole. Furthermore, the response to ciprofloxacin among participants varied by individual, suggesting different degrees of stability of the microbiota and resilience under stress such as antibiotics. In general, except for some rare members, the community was largely restored within 4 wk after completion of the antibiotic course.

Some antibiotics, such as amoxicillin-clavulanate, for which antibiotic-associated diarrhea is a well-known adverse event, produce a loss of *Clostridium* and *Bacteroides* , known to be important in the production of short-chain fatty acids (SCFAs) and the metabolism of otherwise undigestible carbohydrates. Together, their loss may decrease the metabolic integrity of the intestinal epithelium that uses SCFAs for energy, while resulting in a high-osmotic environment in which fluid is drawn into the intestinal lumen. Antibiotic-associated diarrhea may result from these combined effects.

One of the most severe complications from antibiotic exposure is the development of ***Clostridium difficile*– associated diarrhea (CDAD)** , which has high associated morbidity and even mortality. Microbiologic surveys suggest that *C. difficile* is a common constituent of the developing microbiota early in life, with less prevalence over the life span. More than 30% of infants are colonized with *C. difficile* in the 1st month of life, continuing until approximately 6 mo. By 1 yr of age, colonization ranges between approximately 15% and 70% and then declines through to adulthood, when carriage is estimated to be <3%. Although *C. difficile* has been found within the vaginal microbiota of pregnant women, vaginal delivery has not been associated with increased rates of neonatal *C. difficile* colonization, with vaginal and cesarean delivery having rates of colonization at 30% and 37%, respectively. CDAD has been reported to result in 35-45 hospitalizations per 10,000 pediatric admissions among children 1-9 yr old.

Although the studies have not yet determined the natural history of the intestinal microbiome preceding, during, and with the resolution of CDAD in children, molecular studies of the intestinal microbiota in adults provide some details of the consequences of CDAD on the intestinal microbiota. Studies employing deep sequencing of stool from individuals with CDAD and *C. difficile* colonization without disease have revealed depletion of certain bacterial genera accompanying the presence of *C. difficile* colonization. These genera include *Blautia, Pseudobutyrivibrio, Roseburia, Faecalibacterium, Anaerostipes, Subdoligranulum, Ruminococcus, Streptococcus, Dorea* , and *Coprococcus* . The causal relationship of microbiome changes and the events triggering the transition from colonization to symptomatic disease remain unknown, but presumably relate to depletion of competitive species to *C. difficile* . Similar to the studies of antibiotic-associated diarrhea, these studies also demonstrate a reduction in butyrate-producing *Clostridium* spp., which are proposed to be important for producing butyrate as an energy sources for the intestinal epithelium and its robust integrity.

Although antibiotics such as metronidazole and vancomycin have been employed to treat CDAD, traditional treatment does not eliminate recurrent CDAD to the extent that might be expected. To address this problem, **fecal transplantation** , or administration of feces from healthy donors to CDAD recipients, is cost-effective treatment and superior to antibiotics in reducing the likelihood of recurrent disease. Accompanying clinical resolution is repletion of Bacteroidetes and *Clostridium* clusters IV and XIVa with a matched decrease in Proteobacteria. A recent study of children with CDAD demonstrated 94%, 75%, and 54% successful resolution following intragastric-administered fecal transplant from a donor stool bank in previously healthy children, medically complex children, and children with IBD, respectively.

Microbiome and Association With Inflammatory Bowel Disease

Crohn disease and **ulcerative colitis** are chronic inflammatory diseases of the enteric tract and are believed to be the result of the intersection of host susceptibility and a dysbiosis, an alteration in the intestinal microbiota. Twin-twin studies indicate concordance rates in monozygotic twins of 10–15% in ulcerative colitis and 30–35% in Crohn disease, thus demonstrating a genetic component for each disease while highlighting environmental factors that likely induce and drive disease progression. More than 150 single nucleotide polymorphisms (SNPs) are associated with the diseases, revealing potential defects in handling microbes, including those involved in barrier function, innate immunity, autophagy, adaptive immunity, and metabolism and cellular homeostasis.

In inflammatory bowel disease (IBD), the microbiota undergoes a shift in association with the disease throughout the intestinal tract. Although considerable heterogeneity has been described, IBD is often demonstrated to be accompanied by a decrease in bacteroides, clostridia, bifidobacteria, and Firmicutes. Reciprocally, outgrowths of *E. coli* and other Enterobacteriaceae are described. Increased sulfur-metabolizers have been described with IBD as well. Antibiotics along with biologic therapies such as antibodies directed at neutralizing tumor necrosis factor have been employed to manage the IBD dysbiosis and inflammatory reaction. Trials of fecal transplantation are underway to determine if a noninflammatory microbiota from a healthy donor may mitigate IBD symptoms and progression.

Microbiome of Obesity

Obesity and the metabolic syndrome are associated with notable changes in the intestinal microbiome regarding composition and metabolic function, ultimately resulting in greater energy extraction from the diet. Although a highly cited early study on the microbiome in obesity observed an increase in the ratio of the phyla Firmicutes:Bacteroidetes, debate continues about obesity-specific changes in the microbiome. Multiple studies have demonstrated decreased

Firmicutes:Bacteroidetes ratios in the fecal microbiota from obese individuals compared to lean controls. Further studies show that proportions of phyla-level groups may be less important than changes in Firmicutes subgroups that produce **butyrate** , a known fatty acid substrate easily acquired and utilized by the intestinal epithelium, and thus ready calories for the host.

The intestinal microbiome benefits the host in meaningful ways, including enhancing caloric extraction from indigestible substrates such as polysaccharides in the diet. The microbiome produces degradative enzymes to break down these substrates where enzymes with comparable functions, such as some glycosyl hydrolases, are not encoded in the human genome. Molecular studies indicate that the intestinal microbiome may also interact with the intestinal epithelium in such a way as to alter general energy homeostasis and fat storage. For instance, the intestinal microbiome may produce SCFAs, which in turn alter endocrine peptide expression such as glucagon-like peptide 1 and peptide YY, which alter glucose homeostasis and satiety, respectively. Furthermore, through the production of SCFAs and ketones, the microbiota may alter sympathetic tone. Specific microbiomes are known to suppress others to induce fastening-induced **adipose factor** (also called angiopoietin-like protein 4), a lipoprotein lipase inhibitor of intestinal, hepatic, and adipose origins. Colonization with a diverse microbiota suppresses fastening-induced adipose factor expression, and dietary supplementation of a Western diet with *Lactobacillus paracasei* further suppressed otherwise high fastening-induced adipose factor expression. Mice fed a Western diet developed adiposity, which was transferrable to recipient lean mice following transplantation with the obese mice microbiota. Reciprocally, obese mice treated with antibiotics experienced less insulin resistance, lower fasting glycemic indices, and improved glucose tolerance compared to untreated counterparts, further implicating the microbiome in these physiologic changes.

Microbiome During Malnutrition

Malnutrition is a leading cause of morbidity and mortality across the world. In its most severe form, malnutrition may result in **kwashiorkor** , which is characterized by generalized edema, anorexia, enlarged fatty liver, skin ulcerations, and irritability. Ready-to-use foods are distributed to restore nutrition in areas with severe food restrictions. Monozygotic and dizygotic twins in Malawi were studied for the alterations in the microbiome in association with moderate to severe malnutrition, including kwashiorkor. Among the twins with discordant degrees of malnutrition on food supplements, the twins with mild preexisting malnutrition had intestinal microbiota that changed significantly over the course of supplementation. In contrast, the twins with preexisting kwashiorkor had microbiota with poor to no change in response to nutritional supplementation. These findings were recapitulated to some extent following transplantation of the twins’ microbiota into previous sterile mice. Those mice receiving the microbiota of Malawian twins with kwashiorkor experienced more dramatic weight loss on a Malawian-type diet and more rapid loss of their weight gain once off ready-to-use food supplements than did mice transplanted with the feces of more healthy twins. The mice with the transplanted kwashiorkor microbiota had sustained problems with carbohydrate, lipid, and amino acid metabolism despite nutritional supplementation of the Malawian diet. Together these data indicate that severe malnutrition results from the combination of nutritional deficits and a microbiome with altered metabolic capabilities that are not readily restored with contemporary nutritional supplementation treatments.

Therapeutic Manipulation of the Microbiome

Therapeutic manipulation of the microbiome falls into 6 general categories: antimicrobials, prebiotics, probiotics, synbiotics, postbiotics, and fecal transplantation (see CDAD and IBD earlier). **Postbiotics** are nonviable microbial components or metabolites that may alter the microbiota or produce physiologic changes in the host. Insufficient data exist to warrant a discussion of postbiotic therapeutics here.

Prebiotics

Prebiotic is defined as “nondigestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thereby improving host health.” Whereas antimicrobials deplete portions of the microbiota, prebiotics aim to promote the growth of beneficial organisms such as bifidobacteria and lactobacteria. Typically, prebiotics are carbohydrates such as oligosaccharides that may be selectively metabolized by constituents of the microbiota. They may not only stimulate outgrowth of desirable organisms but also may be catabolized to beneficial end products such as SCFAs, which in turn may be utilized as energy substrates by the intestinal epithelium. Prebiotic oligosaccharides are naturally found in breast milk and have been used as supplements to human breast milk and formula.

Administration of prebiotics to term infants has demonstrated the expected outgrowth of bacteria; however, clinically significant benefits from prebiotic supplementation have not been clearly established. Treatment of term infants with fructooligosaccharides increases fecal bifidobacteria but without a change in infant growth, despite some infants having increased SCFAs in the fecal mass. A systematic review of the topic provided a similar conclusion.

Preterm infants have low to absent levels of bifidobacteria and lactobacilli in their intestinal tracts, despite full breast milk nutrition. Prebiotic supplementation has been proposed to increase these bacterial populations in the preterm infant intestinal tract. Among the proposed benefits may be a decrease in NEC. However, appropriately powered, randomized trials have not been performed to demonstrate the validity of this hypothesis.

Probiotics

Probiotics are viable organisms that have health benefits after administration. Almost all probiotics are isolates from the human microbiota, although they may not necessarily reside in the individual taking them for therapeutic purposes. Alternatively, probiotics may be administrated to increase the levels of an organism already present within the microbiota. Generally, probiotics have been administered orally or as vaginal suppositories.

Multiple bacterial and fungal genera and species have been studied for probiotic effects. Common bacterial genera include bifidobacteria, lactobacilli, streptococci, enterococci, and *E. coli* . Fewer nonbacterial organisms have been studied for probiotic effects. *Saccharomyces boulardii* is related to baker's yeast (*Saccharomyces cerevisiae*) but was isolated for specific beneficial effects.

These probiotic organisms should not be confused with more pathogenic strains within their genera and species. Most probiotics have been isolated on the basis of being associated with healthy states. Bifidobacteria and lactobacilli are common to breast milk and stool among infants with low rates of diarrheal diseases and allergy. With the exception of individuals with significant immunodeficiency, severely compromised mucosal barriers, or central line catheters, where many of these organisms may adhere to the plastic with otherwise benign, transient translocation from the intestinal tract, these bacterial probiotics have proved to be relatively safe even with the administration of billions of colony-forming units. The most common adverse events associated with probiotics include abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance.

Although bacterial probiotics have been administered widely to humans, evidence for their efficacy is limited to a small number of conditions. Probiotics have consistently shown efficacy for specific conditions, including antibiotic-associated diarrhea, prevention and reduction of atopy in high-risk children, and reductions in duration and recurrence of *C. difficile* infection. Trials indicate a reduction in NEC among preterm infants. Probiotics may reduce the risk for respiratory infections and recurrent urinary tract infection while reducing the symptoms and frequency of flares in IBD.

Antibiotic-associated diarrhea is reduced in frequency and duration. Meta-analysis indicated a relative risk (RR) of antibiotic-associated diarrhea with probiotic administration of 0.58 (95% confidence interval [CI], 0.05-0.68) among combined studies using *Lactobacillus* , *Bifidobacterium* , *Saccharomyces* , *Streptococcus* , *Enterococcus* , and/or *Bacillus* . Administration of combinations of organisms has not generally resulted in greater efficacy.

Meta-analysis specifically for the efficacy of probiotics in decreasing the incidence of CDAD demonstrated moderate evidence for the practice. In an analysis of >1,800 trials, including many in the pediatric population, probiotics reduced CDAD by 64% with RR of 0.36 (95% CI, 0.26-0.51). A pediatric subgroup was analyzed across relevant studies, revealing benefit in pediatric patients and a well-child subgroup (RR, 0.37; 95% CI, 0.23-0.60). A number of probiotics were used, including different *Lactobacillus* strains and *S. boulardii* .

More than 15 trials have been performed to study the effect of probiotic administration during pregnancy and to infants to prevent atopic dermatitis. Meta-analysis suggests a modest benefit from probiotic administration to prevent the development of atopic dermatitis. Trials have primarily involved the administration of *Lactobacillus rhamnosus*. Studies included administration to the pregnant mother, or the infant, or both. The overall RR of 0.79 (95% CI, 0.71-0.88) was generally consistent regardless of the treatment of the mother, child, or both. The duration was generally >6 mo; apparently, however, duration did not significantly alter the effect. The RR was similar for the prevention of IgE- and non–IgE-associated atopic dermatitis.

Synbiotics are combinations of a probiotic and a prebiotic that is specifically used by the probiotic. A large, double-blind placebo-controlled trial of >4,500 infants in India demonstrated that a daily oral symbiotic preparation of *Lactobacillus plantarum* and fructooligosaccharide given through the neonatal period produced significant reductions in sepsis, pneumonia, skin infections, and all-cause mortality.

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SECTION 2

Preventive Measures

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CHAPTER 197

Immunization Practices

Henry H. Bernstein, Alexandra Kilinsky, Walter A. Orenstein

Immunization is one of the most beneficial and cost-effective disease-prevention measures available. As a result of effective and safe vaccines, smallpox has been eradicated, polio is close to worldwide eradication, and measles and rubella are no longer endemic in the United States. However, cases of vaccine-preventable diseases, including measles, mumps, and pertussis, continue to occur in the United States. Incidence of most vaccine-preventable diseases of childhood has been reduced by ≥99% from representative 20th century annual morbidity, usually before development of the corresponding vaccines (Table 197.1a), with most of the newer vaccines not achieving quite the same percentage decrease (Table 197.1b). An analysis of effective prevention measures recommended for widespread use by the U.S. Preventive Services Task Force (USPSTF) reported that childhood immunization received a perfect score based on clinically preventable disease burden and cost-effectiveness.

Table 197.1a

Comparison of 20th Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

DISEASE	20TH CENTURY ANNUAL MORBIDITY*	2016 REPORTED CASES †	PERCENT DECREASE
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	122	>99%
Mumps	162,344	5,629	96%
Pertussis	200,752	15,808	92%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	9	>99%
Congenital rubella syndrome	152	2	99%
Tetanus	580	31	95%

Haemophilus influenzae type b (Hib)	20,000	22 [‡]	>99%

[*] Data from Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working Group: Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States, *JAMA* 298(18):2155–2163, 2007.

[†] Data from Centers for Disease Control and Prevention: Notifiable diseases and mortality tables, *MMWR* 66(52):ND-924–ND-941, 2018.

[‡] Hib <5 yr of age. An additional 237 cases of *Haemophilus influenzae* (<5 yr of age) have been reported with unknown serotype.

Table 197.1b

Comparison of Pre–Vaccine Era Estimated Annual Morbidity With Current Estimate: Vaccine-Preventable Diseases

DISEASE	PRE–VACCINE ERA ANNUAL ESTIMATE[*]	2016 ESTIMATE (UNLESS OTHERWISE SPECIFIED)	PERCENT DECREASE
Hepatitis A	117,333[*]	4,000 [†]	97%
Hepatitis B (acute)	66,232[*]	20,900 [†]	68%
Pneumococcus (invasive)			
All ages	63,067[*]	30,400 [§]	52%
<5 yr of age	16,069[*]	1,700 [§]	89%
Rotavirus (hospitalizations, <3 yr of age)	62,500 [‡]	30,625 [‖]	51%
Varicella	4,085,120[*]	102,128 [¶]	98%

[*] Data from Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group: Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States, *JAMA* 298(18):2155–2163, 2007.

[†] Data from Centers for Disease Control and Prevention: Viral hepatitis surveillance—United States, 2016.

[‡] Data from Centers for Disease Control and Prevention: Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 58(RR-2):1–25, 2009.

[§] Data from Centers for Disease Controls and Prevention: Active bacterial core surveillance, 2016 (unpublished).

[‖] Data from New Vaccine Surveillance Network 2017 data: U.S. rotavirus disease now has biennial pattern (unpublished).

[¶] Data from Centers for Disease Control and Prevention: Varicella Program, 2017 (unpublished).

Immunization is the process of inducing immunity against a specific disease. Immunity can be induced either passively or actively**. Passive immunity** is generated through administration of an antibody-containing preparation. **Active immunity** is achieved by administering a vaccine or toxoid to stimulate the immune system to produce a prolonged humoral and/or cellular immune response. As of 2019, infants, children, and adolescents in the United States are recommended to be routinely immunized against **16 pathogens** : *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertusis*, polio virus, *Haemophilus influenzae* type b (**Hib**), hepatitis A, hepatitis B, measles virus, mumps virus, rubella virus, rotavirus, varicella zoster virus, pneumococcus, meningococcus, influenza virus, and human papillomavirus (**HPV**).

Passive Immunity

Rather than producing antibodies through the body's own immune system, passive immunity is achieved by administration of preformed antibodies. Protection is immediate, yet transient, lasting weeks to months. Products used include:

- Immunoglobulin administered intramuscularly (**IGIM**), intravenously (**IGIV**), or subcutaneously (**IGSC**)
- Specific or hyperimmune immunoglobulin preparations administered IM or IV
- Antibodies of animal origin
- Monoclonal antibodies

Passive immunity also can be induced naturally through transplacental transfer of maternal antibodies (IgG) during gestation. This transfer can provide protection during an infant's 1st few mo of life; other antibodies (IgA) are transferred to the infant during breastfeeding. Protection for some diseases can persist for as long as 1 yr after birth, depending on the quantity of antibody transferred and the time until levels fall below those considered protective.

The major indications for inducing passive immunity are immunodeficiencies in children with B-lymphocyte defects who have difficulty making antibodies (e.g., hypogammaglobulinemia, secondary immunodeficiencies), who have exposure to infectious diseases or to imminent risk of exposure when there is inadequate time for them to develop an active immune response to a vaccine (e.g., newborn exposed to maternal hepatitis B), and who have infectious diseases that require antibody administration as part of the specific therapy (Table 197.2).

Table 197.2

Immunoglobulin and Animal Antisera Preparations

PRODUCT	MAJOR INDICATIONS
Immune globulin intramuscular (IGIM)	Replacement therapy in antibody-deficiency disorders Hepatitis A prophylaxis Measles prophylaxis Rubella prophylaxis (pregnant women)
Immune globulin intravenous (IGIV)	Replacement therapy in antibody-deficiency disorders Kawasaki disease Pediatric HIV infection Hypogammaglobulinemia in chronic B-lymphocyte lymphocytic leukemia Varicella postexposure prophylaxis Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy Toxic shock syndrome May be useful in a variety of other conditions
Immune globulin subcutaneous (IGSC)	Treatment of patients with primary immunodeficiencies
Hepatitis B immunoglobulin (IM)	Postexposure prophylaxis
	Prevention of perinatal infection in infants born to hepatitis B surface antigen–positive mothers
Rabies immunoglobulin (IM)	Postexposure prophylaxis
Tetanus immunoglobulin (IM)	Wound prophylaxis
	Treatment of tetanus
Varicella-zoster immunoglobulin (VariZIG, IM)	Postexposure prophylaxis of susceptible people at high risk for complications from varicella
Cytomegalovirus (IV)	Prophylaxis of disease in seronegative transplant recipients
Vaccinia immunoglobulin (IV)	Reserved for certain complications of smallpox immunization and has no role in treatment of smallpox
Human botulism (IV), BabyBIG	Treatment of infant botulism
Diphtheria antitoxin, equine	Treatment of diphtheria
Heptavalent botulinum antitoxin against all 7 (A-G) botulinum toxin types (BAT)	Treatment of noninfant food and wound botulism
Palivizumab (monoclonal antibody), humanized mouse (IM)	Prophylaxis for infants against respiratory syncytial virus (see Chapter 287)

Data from American Academy of Pediatrics: Passive immunization. In Kimberlin DW, Brady MT, Jackson MA, Long SS, editors: *Red Book 2018: Report of the Committee on Infectious Diseases,* ed 31, Elk Grove Village, IL, 2018, American Academy of Pediatrics. (Recommendations for use of specific immune globulins are located in the sections for specific diseases in Section 3 of *Red Book* .)

Intramuscular Immunoglobulin

Immunoglobulin is a sterile antibody-containing solution, usually derived through cold ethanol fractionation of large pools of human plasma from adults. Antibody concentrations reflect the infectious disease exposure and immunization experience of plasma donors. Intramuscular immunoglobulin (IGIM) contains 15–18% protein and is predominantly IgG. Intravenous use of human IGIM is contraindicated. Immunoglobulin is not known to transmit infectious agents, including viral hepatitis and HIV. The major indications for immunoglobulin are:

- Replacement therapy for children with antibody deficiency disorders
- Measles prophylaxis
- Hepatitis A prophylaxis

For **replacement therapy** , the usual dose of IGIM is 100 mg/kg (equivalent to 0.66 mL/kg) monthly. The usual interval between doses is 2-4 wk depending on trough IgG serum concentrations and clinical response. In practice, IGIV has replaced IGIM for replacement therapy.

IGIM can be used to prevent or modify **measles** if administered to susceptible children within 6 days of exposure (usual dose: 0.5 mL/kg body weight; maximum dose: 15 mL). The recommended dose of IGIV is 400 mL/kg. Data suggest that measles vaccine, if given within 72 hr of measles exposure, will provide protection in some cases. Measles vaccine and immunoglobulin should not be administered at the same time.

Two methods are available for **postexposure prophylaxis** against **hepatitis A** depending on the patient's age: hepatitis A immunization or immunoglobulin. In those 12 mo-40 yr of age, hepatitis A immunization is preferred over immunoglobulin for postexposure prophylaxis and for protection of people traveling to areas where hepatitis A is endemic. Children 6-11 mo old should receive a dose of hepatitis A vaccine before international travel. However, the dose of hepatitis A vaccine received before 12 mo should not be counted in determining compliance with the recommended 2-dose schedule. In adults >40 yr, immunoglobulin may be administered for prophylaxis and for postexposure prophylaxis to people traveling internationally to hepatitis A–endemic areas (0.06 mL/kg). Immunoglobulin is preferred over hepatitis A immunization if there is an underlying immunodeficiency or chronic liver disease.

The most common adverse reactions to immunoglobulin are pain and discomfort at the injection site and, less commonly, flushing, headache, chills, and nausea. Serious adverse events are rare and include chest pain, dyspnea, anaphylaxis, and systemic collapse. Immunoglobulin should *not* be administered to people with selective IgA deficiency, who can produce antibodies against the trace amounts of IgA in immunoglobulin preparations and can develop reactions after repeat doses. These reactions can include fever, chills, and a shock-like syndrome. Because these reactions are rare, testing for selective IgA deficiencies is not recommended.

Intravenous Immunoglobulin

IGIV is a highly purified preparation of immunoglobulin antibodies prepared from adult plasma donors using alcohol fractionation and is modified to allow intravenous (IV) use. IGIV is more than 95% IgG and is tested to ensure minimum antibody titers to *Corynebacterium diphtheriae* , hepatitis B virus, measles virus, and poliovirus. Antibody concentrations against other pathogens vary widely among products and even among lots from the same manufacturer. Liquid and lyophilized powder preparations are available. IGIV does not contain thimerosal.

Not all IGIV products are approved by the U.S. Food and Drug Administration (FDA) for all indications. The major recommended FDA-approved indications for IGIV are:

- Replacement therapy for primary immunodeficiency disorders
- Kawasaki disease to prevent coronary artery abnormalities and shorten the clinical course

- Replacement therapy for prevention of serious bacterial infections in children infected with HIV
- Prevention of serious bacterial infections in people with hypogammaglobulinemia in chronic B-lymphocyte leukemia
- Immune-mediated thrombocytopenia to increase platelet count

IGIV may be helpful for patients with severe toxic shock syndrome, Guillain-Barré syndrome, and anemia caused by parvovirus B19. IGIV is also used for many other conditions based on clinical experience. IGIV may be used for varicella after exposure when varicella-zoster immune globulin is not available.

Reactions to IGIV may occur in up to 25% of patients. Some of these reactions appear to be related to the rate of infusion and can be mitigated by decreasing the rate. Such reactions include fever, headache, myalgia, chills, nausea, and vomiting. More serious reactions, including anaphylactoid events, thromboembolic disorders, aseptic meningitis, and renal insufficiency, have rarely been reported. Renal failure occurs mainly in patients with preexisting renal dysfunction.

Specific or hyperimmune immunoglobulin preparations are derived from donors with high titers of antibodies to specific agents and are designed to provide protection against those agents (see Table 197.2).

Subcutaneous Immunoglobulin

Subcutaneous administration of immunoglobulin (IGSC) is safe and effective in children and adults with primary immune deficiency disorders. Smaller doses administered weekly result in less fluctuation of serum IgG concentrations over time. Systemic reactions are less frequent than with IGIV, and the most common adverse effects of IGSC are injection-site reactions. There are no data on administration of IGIM by the subcutaneous route.

Hyperimmune Animal Antisera Preparations

Animal antisera preparations are derived from horses. The immunoglobulin fraction is concentrated using ammonium sulfate, and some products are further treated with enzymes to decrease reactions to foreign proteins. The following 2 equine antisera preparations are available for humans (as of 2018):

- **Diphtheria antitoxin** , which can be obtained from the U.S. Centers for Disease Control and Prevention (http://www.cdc.gov/diphtheria/dat.html) and is used to treat diphtheria.
- **Heptavalent botulinum antitoxin** , available from the CDC for use in adults with botulism. To request it, one can call the CDC's 24 hr line at 770-488-7100. This product contains antitoxin against all 7 (A-G) botulinum toxin types.

Great care must be exercised before administering animal-derived antisera because of the potential for severe allergic reactions. Due caution includes testing for sensitivity before administration, desensitization if necessary, and treating potential reactions, including febrile events, serum sickness, and anaphylaxis. *For infant botulism, IVIG (BabyBIG), a human-derived antitoxin, is licensed and should be used.*

Monoclonal Antibodies

Monoclonal antibodies (mAbs) are antibody preparations produced against a single antigen. They are mass-produced from a hybridoma, a hybrid cell used as the basis for production of large amounts of antibodies. A hybridoma is created by fusing an antibody-producing B lymphocyte with a fast-growing immortal cell such as a cancer cell. **Palivizumab** is used for prevention of severe disease from respiratory syncytial virus (RSV) among children ≤24 mo old with bronchopulmonary dysplasia (BPD, a form of chronic lung disease), a history of premature birth, or congenital heart lesions or neuromuscular diseases. The American Academy of Pediatrics (AAP) has developed specific recommendations for use of palivizumab (see Chapter 287). Monoclonal antibodies also are used to prevent transplant rejection and to treat some types of cancer, autoimmune diseases, and asthma. Use of mAbs against interleukin (IL)-2 and tumor necrosis factor (TNF)-α are being used as part of the therapeutic approach to patients with a variety of malignant and autoimmune diseases.

Serious adverse events associated with palivizumab are rare, primarily including cases of anaphylaxis and hypersensitivity reactions. Adverse reactions to mAbs directed at modifying the immune response, such as antibodies against IL-2 or TNF-α, can be more serious and include cytokine release syndrome, fever, chills, tremors, chest pain, immunosuppression, and infection with various organisms, including mycobacteria.

Active Immunization

Vaccines are defined as whole or parts of microorganisms administered to prevent an infectious disease. Vaccines can consist of whole inactivated microorganisms (e.g., polio, hepatitis A), parts of the organism (e.g., acellular pertussis, HPV, hepatitis B), polysaccharide capsules (e.g., pneumococcal and meningococcal polysaccharide vaccines), polysaccharide capsules conjugated to protein carriers (e.g., Hib, pneumococcal, and meningococcal conjugate vaccines), live-attenuated microorganisms (e.g., measles, mumps, rubella, varicella, rotavirus, and live-attenuated influenza vaccines), and toxoids (e.g., tetanus, diphtheria) (Table 197.3). A **toxoid** is a bacterial toxin modified to be nontoxic but still capable of inducing an active immune response against the toxin.

Table 197.3

Currently Available* Vaccines in the United States by Type

PRODUCT	TYPE
Adenovirus	Live, oral vaccine indicated for active immunization for the prevention of febrile acute respiratory disease caused by adenovirus types 4 and 7, for use in military populations 17-50 yr of age
Anthrax vaccine adsorbed	Cell-free filtrate of components including protective antigen
Bacille Calmette-Guérin (BCG) vaccine	Live-attenuated mycobacterial strain used to prevent tuberculosis in very limited circumstances
Cholera vaccine	Oral vaccine containing live-attenuated *Vibrio cholerae* CVD 103-HgR strain for

	protection against serogroup O1 in adults age 18-64 traveling to cholera-affected areas
Diphtheria and tetanus toxoids adsorbed	Toxoids of diphtheria and tetanus
Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine	Toxoids of diphtheria and tetanus and purified and detoxified components from *Bordetella pertussis*
DTaP–hepatitis B–inactivated polio vaccine (DTaP-HepB-IPV)	DTaP with hepatitis B surface antigen (HBsAg) produced through recombinant techniques in yeast with inactivated whole polioviruses
DTaP with IPV and *Haemophilus influenzae* type b (Hib) (DTaP-IPV/Hib)	DTaP with inactivated whole polioviruses and Hib polysaccharide conjugated to tetanus toxoid
DTaP and inactivated polio vaccine (DTaP-IPV)	DTaP with inactivated whole polioviruses
Hib conjugate vaccine (Hib)	Polysaccharide conjugated to either tetanus toxoid or meningococcal group B outer membrane protein
Hepatitis A vaccine (HepA)	Inactivated whole virus
Hepatitis A–hepatitis B vaccine (HepA-HepB)	Combined hepatitis A and B vaccine
Hepatitis B vaccine (HepB)	HBsAg produced through recombinant techniques in yeast
Human papillomavirus vaccine 9-valent (9vHPV)	The L1 capsid proteins of HPV types 6 and 11 to prevent genital warts and types 16 18, 31, 33, 45, 52, and 58 to prevent cervical cancer (9vHPV).
Influenza virus vaccine inactivated (IIV [†])	Available either as trivalent (A/H_3 N_2 , A/H_1 N_1 , and B) split and purified inactivated vaccines containing the hemagglutinin (H) and neuraminidase (N) of each type or as quadrivalent preparations (which include representative strains from 2 B strains in addition to the 2 influenza A strains in trivalent inactivated influenza vaccine)
Influenza virus vaccine live-attenuated, intranasal (LAIV)	Live-attenuated, temperature-sensitive, cold-adapted quadrivalent vaccine containing the H and N genes from the wild strains reassorted to have the 6 other genes from the cold-adapted parent
Japanese encephalitis vaccine	Purified, inactivated whole virus
Measles, mumps, rubella (MMR) vaccine	Live-attenuated viruses
Measles, mumps, rubella, varicella (MMRV) vaccine	Live-attenuated viruses
Meningococcal conjugate vaccine against serogroups A, C, W135, and Y (MCV4)	Polysaccharide from each serogroup conjugated to diphtheria toxoid CRM_{197} protein
Meningococcal polysaccharide vaccine against serogroups A, C,	Polysaccharides from each of the serogroups conjugated to diphtheria toxoid protein

W135, and Y (MPSV4)	
Meningococcal B (MenB)	Recombinant proteins from serogroup B developed in *Escherichia coli*
Pneumococcal conjugate vaccine (13 valent) (PCV13)	Pneumococcal polysaccharides conjugated to diphtheria toxin CRM$_{197}$, contains 13 serotypes that accounted for >80% of invasive disease in young children prior to vaccine licensure
Pneumococcal polysaccharide vaccine (23 valent) (PPSV23)	Pneumococcal polysaccharides of 23 serotypes responsible for 85–90% of bacteremic disease in the United States
Poliomyelitis (inactivated, enhanced potency) (IPV)	Inactivated whole virus highly purified from monkey kidney cells, trivalent types 1, 2, and 3
Rabies vaccines (human diploid and purified chicken fibroblasts)	Inactivated whole virus
Rotavirus vaccines (RV5 and RV1)	Bovine rotavirus pentavalent vaccine (RV5) live reassortment attenuated virus, and human live-attenuated virus (RV1)
Smallpox vaccine	Vaccinia virus, an attenuated poxvirus that provides cross-protection against smallpox (variola)
Tetanus and diphtheria toxoids, adsorbed (Td, adult use)	Tetanus toxoid plus a reduced quantity of diphtheria toxoid compared to diphtheria toxoid used for children <7 yr of age
Tetanus and diphtheria toxoids adsorbed plus acellular pertussis (Tdap) vaccine	Tetanus toxoid plus a reduced quantity of diphtheria toxoid plus acellular pertussis vaccine to be used in adolescents and adults and in children 7 through 10 yr of age who have not been appropriately immunized with DTaP
Typhoid vaccine (polysaccharide)	Vi capsular polysaccharide of *Salmonella typhi* Ty2 strain
Typhoid vaccine (oral)	Live-attenuated Ty21a strain of *S. typhi*
Varicella vaccine	Live-attenuated Oka/Merck strain
Yellow fever vaccine	Live-attenuated 17D-204 strain
Herpes zoster (shingles) vaccine	Live-attenuated Oka/Merck strain for use in adults ≥60 yr old (Zostavax) Recombinant zoster vaccine, adjuvanted (Shingrix) for use in adults ≥50 years

[*] As of November 2018.

[†] There are various types of inactivated flu vaccines—IIV3, IIV4, RIV4, ccIIV4, aIIV3.

Data from US Food and Drug Administration: Vaccines licensed for use in the United States. http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm .

Vaccines can contain a variety of other constituents besides the immunizing antigen. *Suspending fluids* may be sterile water or saline but can be a complex fluid containing small amounts of proteins or other constituents used to grow the immunobiologic culture. *Preservatives, stabilizers,* and *antimicrobial agents* are used to inhibit bacterial growth and prevent degradation of the antigen. Such components can include gelatin, 2-phenoxyethanol, and specific antimicrobial agents. Preservatives are added to multidose vials of vaccines, primarily to prevent bacterial contamination on repeated entry of the vial. In the past, many vaccines for children contained **thimerosal** , a preservative containing ethyl mercury. Removal of thimerosal as a preservative from vaccines for children began as a precautionary measure in 1999 in the absence of any data on harm from the preservative. This objective was accomplished by switching to single-dose packaging. Of the vaccines recommended for young children, only some preparations of influenza vaccine contain thimerosal as a preservative.*

Adjuvants are used in some vaccines to enhance the immune response. In the United States, the only adjuvants currently licensed by the FDA to be part of vaccines are **aluminum salts** ; AsO_4 , composed of 3-O-desacyl-4′-monophosphoryl 301 lipid A (MPL) adsorbed on to aluminum (as hydroxide salt); and MF59 and 1018 adjuvant. **AsO_4** is found in 1 type of HPV vaccine, no longer available in the United States, but used in Europe. **MF59** is an oil-in-water emulsion found in 1 type of influenza vaccine approved for people ≥65 yr old. 1018 is an immunostimulatory sequence adjuvant used in HepB-CpG, a hepatitis B vaccine approved for persons > 18 yr. HepB-CpG contains yeast-derived recombinant HBsAg and is prepared by combining purified HBsAg with small synthetic immunostimulatory cytidine-phosphate-guanosine oligodeoxynucleotide motifs. The 1018 adjuvant binds to Toll-like receptor 9 to simulate a directed immune response to HBsAg. Vaccines with adjuvants should be injected deeply into muscle masses to avoid local irritation, granuloma formation, and necrosis associated with SC or intracutaneous administration.

Vaccines can induce immunity by stimulating antibody formation, cellular immunity, or both. Protection induced by most vaccines is thought to be mediated primarily by B lymphocytes, which produce antibodies. Such antibodies can inactivate toxins, neutralize viruses, and prevent their attachment to cellular receptors, facilitate phagocytosis and killing of bacteria, interact with complement to lyse bacteria, and prevent adhesion to mucosal surfaces by interacting with the bacterial cell surface.

Most B-lymphocyte responses require the assistance of CD4 helper T lymphocytes. These T-lymphocyte–dependent responses tend to induce high levels of functional antibody with high avidity. The T-dependent responses mature over time from primarily an IgM response to a persistent, long-term IgG response and induce immunologic memory that leads to enhanced responses on boosting. **T-lymphocyte–dependent vaccines** , which include protein moieties, induce good immune responses even in young infants. In contrast, polysaccharide antigens induce B-lymphocyte responses in the absence of T-lymphocyte help. These **T-lymphocyte–independent vaccines** are associated with poor immune responses in children <2 yr old and with short-term immunity and absence of an enhanced or booster response on repeat exposure to the antigen. With some polysaccharide vaccines, repeat doses actually are associated with reduced responses, as measured by antibody concentrations, compared to 1st doses (i.e., *hyporesponsive*). To overcome problems with plain polysaccharide vaccines, polysaccharides have been **conjugated** , or covalently linked, to protein carriers, converting the vaccine to a T-lymphocyte–dependent vaccine. In contrast to plain polysaccharide vaccines, conjugate vaccines induce higher-avidity antibody, immunologic memory leading to booster responses on repeat exposure to the antigen, long-term immunity, and community protection by decreasing carriage of the organism (Table 197.4). As of 2018 in the United States, licensed conjugate vaccines are available to prevent Hib, pneumococcal, and meningococcal diseases.

Table 197.4

Characteristics of Polysaccharide and Conjugate Vaccines

CHARACTERISTIC	CONJUGATE	POLYSACCHARIDE
T-lymphocyte–dependent immune response	Yes	No
Immune memory	Yes	No
Persistence of protection	Yes	No
Booster effect	Yes	No
Reduction of carriage	Yes	No
Community protection	Yes	No
Lack of hyporesponsiveness	Yes	No

Serum antibodies may be detected as soon as 7-10 days after initial injection of antigen. Early antibodies are usually of the IgM class that can fix complement. IgM antibodies tend to decline as IgG antibodies increase. The IgG antibodies tend to peak approximately 1 mo after vaccination and with most vaccines persist for some time after a primary vaccine course. Secondary or booster responses occur more rapidly and result from rapid proliferation of memory B and T lymphocytes.

Assessment of the immune response to most vaccines is performed by measuring serum antibodies. Although detection of serum antibody at levels considered protective after vaccination can indicate immunity, loss of detectable antibody over time does not necessarily mean susceptibility to disease. Some vaccines induce immunologic memory, leading to a booster or anamnestic response on exposure to the microorganism, with resultant protection from disease. In some cases, cellular immune response is used to evaluate the status of the immune system. Certain vaccines (e.g., acellular pertussis) do not have an accepted serologic correlate of protection.

Live-attenuated vaccines routinely recommended for children and adolescents include measles, mumps, and rubella (**MMR**); MMR and varicella (**MMRV**); rotavirus; and varicella. In addition, a cold-adapted, live-attenuated quadrivalent influenza vaccine (**LAIV**) is available in the past for persons 2-49 yr old who do not have conditions that place them at high risk for complications from influenza. Notably lower vaccine effectiveness during the 2013–2016 influenza seasons has resulted in LAIV not being recommended in the United States for the 2016–2017 and 2017–2018 seasons; LAIV is recommended for the 2018–1019 season. **Live-attenuated vaccines** tend to induce long-term immune responses. They replicate, often similarly to natural infections, until an immune response inhibits reproduction. Most live vaccines are administered in 1-dose or 2-dose schedules. The purpose of repeat doses, such as a 2nd dose of the MMR or MMRV vaccine, is to induce an initial immune response in those who failed to respond to the 1st dose. Because influenza viruses tend to mutate to evade preexisting immunity to prior strains, at least 1 of the strains in influenza vaccines each year is often different than in the previous year. Thus, influenza vaccines are recommended to be administered yearly.

The remaining vaccines in the recommended schedule for children and adolescents are inactivated vaccines. **Inactivated vaccines** tend to require multiple doses to induce an adequate immune response and are more likely than live-attenuated vaccines to need booster doses to maintain that immunity. However, some inactivated vaccines appear to induce long-term or perhaps lifelong immunity, after a primary series, including hepatitis B vaccine and inactivated polio vaccine.

Vaccination System in the United States

Vaccine Production

Vaccine production is primarily a responsibility of private industry. Many of the vaccines recommended routinely for children are produced by only one vaccine manufacturer. Vaccines with multiple manufacturers include Hib, hepatitis B, rotavirus, **MCV4** (meningococcal conjugate vaccine against serogroups A, C, W135, and Y), diphtheria and tetanus toxoids and acellular pertussis (**DTaP**), and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines for adolescents and adults. Inactivated polio vaccine (**IPV**) as an IPV-only vaccine has only one manufacturer, but IPV is also available in combination products (DTaP–hepatitis B–IPV, DTaP-IPV/Hib, and DTaP-IPV) from different manufacturers. Influenza vaccine for children 6-35 mo of age is produced by fewer manufacturers (see http://www.cdc.gov/flu/protect/vaccine/vaccines.htm for available influenza vaccines). MMR, MMRV, varicella, pneumococcal conjugate vaccine (13 valent, **PCV13**), and tetanus and diphtheria (**Td**) vaccines also are produced by single manufacturers.

Vaccine Policy

Two major committees make vaccine policy recommendations for children: the Committee on Infectious Diseases (COID) of the AAP (the *Red Book* Committee) and the Advisory Committee on Immunization Practices (ACIP) of the CDC. Annually, the AAP, ACIP, American Academy of Family Physicians (AAFP), and American College of Obstetricians and Gynecologists (ACOG) issue a harmonized childhood and adolescent immunization schedule (http://www.cdc.gov/vaccines/schedules/index.html). The ACIP recommendations (http://www.cdc.gov/vaccines/acip/recs/index.html) are official only after adoption by the CDC director, which leads to publication in the *Morbidity and Mortality Weekly Report (MMWR Morb Mortal Wkly Rep).* The AAP recommendations are published in *Pediatrics* and the *Red Book* , which includes its continuously updated online version (aapredbook.org).

Vaccine Financing

Approximately 50% of vaccines routinely administered to children and adolescents <19 yr of age are purchased through a contract negotiated by the federal government with licensed vaccine manufacturers. Three major sources of funds are available to purchase vaccines through this contract. The greatest portion comes from the **Vaccines for Children (VFC)** program (http://www.cdc.gov/vaccines/programs/vfc/index.html), a federal entitlement program established in 1993. The VFC program covers children receiving Medicaid, children without insurance (uninsured), and Native Americans and Alaska Natives. In addition, underinsured children whose insurance does not cover immunization can be covered through VFC, but only if they go to a federally qualified health center (http://www.cms.gov/center/fqhc.asp). In contrast to other public funding sources that require approval of discretionary funding by legislative bodies, VFC funds are immediately available for new recommendations. These funds are only available if the ACIP votes the vaccine and the recommendation for its use into the VFC program, the federal government negotiates a contract, and the Office of Management and Budget (OMB) apportions funds. The VFC program can provide free vaccines to participating private providers for administration to children eligible for coverage under the program. The 2nd major federal funding source is the Section 317 **Discretionary Federal Grant Program** to states and selected localities. These funds must be appropriated annually by Congress, and in contrast to VFC, they do not have eligibility requirements for use. The 3rd major public source of funds is **state appropriations** .

The VFC program itself does not cover vaccine administration costs. Medicaid covers the administration fees for children enrolled in the program. Parents of other children eligible for VFC must pay administration fees out of pocket, although the law stipulates that no one eligible for the program can be denied vaccines because of inability to pay the administration fee. The Affordable Care Act (ACA) states that all vaccines recommended by ACIP and those included in the harmonized annual immunization schedules must be provided by qualified insurance programs with no copay and no deductible.

Vaccine Safety Monitoring

Monitoring vaccine safety is the responsibility of the FDA, CDC, and vaccine manufacturers. A critical part of that monitoring depends on reports provided to the **Vaccine Adverse Event Reporting System (VAERS)** . Adverse events following immunization can be reported by completing a VAERS form, which can be obtained from http://www.vaers.hhs.gov or by calling 1-800-822-7967. Individual VAERS case reports may be helpful in generating hypotheses about whether vaccines are causing certain clinical syndromes. In general, however, the reports are not helpful in evaluating the causal role of vaccines in the adverse event, because most clinical syndromes that follow vaccination are similar to syndromes that occur in the absence of vaccination, which constitute background rates. For causality assessment, epidemiologic studies are often necessary, comparing the incidence rate of the adverse event after vaccination with the rate in unvaccinated individuals. A statistically significant higher rate in vaccinated individuals would be consistent with causation.

The **Vaccine Safety Datalink** consists of inpatient and outpatient records of some of the largest managed-care organizations in the United States and facilitates causality evaluation. In addition, the **Clinical Immunization Safety Assessment (CISA)** network has been established to advise primary care physicians on evaluation and management of adverse events (http://www.cdc.gov/vaccinesafety/Activities/CISA.html). CISA facilitates CDC's collaboration with vaccine safety experts at leading academic medical centers and strengthens national capacity for vaccine safety monitoring. (For more information, refer to: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html .)

The Health and Medicine Division (HMD) of the National Academies of Sciences, Engineering and Medicine, previously the Institute of Medicine (IOM), has independently reviewed a variety of vaccine safety concerns and published reports summarizing its findings.* From 2001 through 2004, the IOM released 8 reports, concluding that the body of epidemiologic evidence did not show an association between vaccines and **autism** . In 2012 the IOM (HMD) report *Adverse Effects of Vaccines: Evidence and Causality* ** reviewed a list of reported adverse effects associated with 8 vaccines to evaluate the scientific evidence, if any, of an event-vaccine relationship. The IOM committee had developed 158 causality conclusions and assigned each relationship between a vaccine and an adverse health problem to 1 of 4 causation categories. The committee concluded that available evidence convincingly supported a causal relationship between **anaphylaxis** and MMR, varicella-zoster, influenza, hepatitis B, meningococcal, and tetanus-containing vaccines. Additionally, the evidence favored rejection of 5 vaccine–adverse event relationships, including MMR vaccine and autism, inactivated influenza vaccines and asthma episodes and Bell palsy, and MMR and DTaP and type 1 diabetes mellitus. For the majority of cases (135 vaccine–adverse event pairs), the evidence was inadequate to accept or reject a causal relationship because of the rarity of the events. Overall, the committee concluded that few health problems are caused by or clearly associated with vaccines.

In 2013, the HMD released the report *Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies* . [†] The HMD uncovered no evidence of major safety concerns associated with adherence to the recommended childhood immunization schedule. The HMD specifically found no links between the immunization schedule and autoimmune diseases, asthma, hypersensitivity, seizures, child developmental disorders, learning or developmental disorders, or attention-deficit or disruptive disorders. Additionally, use of nonstandard schedules is harmful, because it increases the period of risk of acquiring vaccine-preventable diseases and increases the risk of incomplete immunization. [‡] In addition, the Agency for Healthcare Research and Quality (AHRQ) contracted with the Rand Corporation for an independent systematic review of the immunization schedule. That review concluded that while some vaccines are associated with serious adverse events, these events are extremely rare and must be weighed against the protective benefits that vaccines provide. AAP has summarized the information on a variety of safety issues and different vaccines. [§]

The National Vaccine Injury Compensation Program (VICP) , established in 1988, is designed to compensate people injured by vaccines in the childhood and adolescent immunization schedule. The program is funded through an excise tax of $0.75 on vaccines recommended by the CDC per disease prevented per dose (e.g., the trivalent influenza vaccine is taxed $0.75 because it prevents one disease; the measles-mumps-rubella vaccine is taxed $2.25 because it prevents three diseases). As of 2018, this program covers all the routinely recommended vaccines that protect children against 16 diseases. The VICP was established to provide a no-fault system, with a table of related injuries and timeframes. In April 2018 the table was modified to reflect changes in the 21st Century Cures Act, requiring that the VICP cover vaccines recommended for routine administration in pregnant women. All people alleging injury from covered vaccines must first file with the program. If the injury meets the requirements of the table, compensation is automatic. If not, the claimant has the responsibility to prove causality. If compensation is accepted, the claimant cannot sue the manufacturer or physician administering the vaccine. If the claimant rejects the judgment of the compensation system, the claimant can enter the tort system, which is uncommon. Information on the VICP is available at http://www.hrsa.gov/vaccinecompensation , or by calling 1-800-338-2382. All physicians administering a vaccine covered by the program are required by law to give the approved **Vaccine Information Statement (VIS)** to the child's parent or guardian at each visit before administering vaccines. Information on the VIS can be obtained from http://www.cdc.gov/vaccines/hcp/vis/index.html .

Vaccine Delivery

To ensure potency, vaccines should be stored at recommended temperatures before and after reconstitution. A comprehensive resource for providers on vaccine storage and handling recommendations and best practice strategies is available (https://www.cdc.gov/vaccines/hcp/admin/storage/index.html). Expiration dates should be noted and expired vaccines discarded. Lyophilized vaccines often have long shelf lives. However, the shelf life of reconstituted vaccines generally is short, ranging from 30 min for varicella vaccine to 8 hr for MMR vaccine.

All vaccines have a preferred route of administration, which is specified in package inserts and in AAP and ACIP recommendations. Most inactivated vaccines, including DTaP, hepatitis A, hepatitis B, Hib, inactivated influenza vaccine (**IIV**), HPV, PCV13, MCV4, and Tdap, are administered IM. In contrast, MPSV4 and the more commonly used live-attenuated vaccines (MMR, MMRV, and varicella) should be dispensed by the SC route. Rotavirus vaccine is administered orally. IPV and **PPS23** (pneumococcal polysaccharide vaccine) can be given IM or SC. One influenza vaccine, LAIV, when recommended, is administered intranasally, and another influenza vaccine is administered by the intradermal route. For IM injections, the anterolateral thigh muscle is the preferred site for infants and young children. The recommended needle length varies depending on age and size: ⅝ inch for newborn infants, 1 inch for infants 2-12 mo old, and 1-1¼ inches for older children. For adolescents and adults, the deltoid muscle of the arm is the preferred site for IM administration with needle lengths of 1-1¼ inches depending on patient size. Most IM injections can be made with 23-25 gauge needles. For SC injections, needle lengths generally range from ⅝-¾ inch with 23-25 gauge needles.

Additional aspects of immunization important for pediatricians and other healthcare providers are detailed on the websites listed in Table 197.5 .

Table 197.5

Vaccine Websites and Resources

ORGANIZATION	WEBSITE
HEALTH PROFESSIONAL ASSOCIATIONS	
American Academy of Family Physicians (AAFP)	http://www.familydoctor.org/online/famdocen/home.html
American Academy of Pediatrics (AAP)	http://www.aap.org/

AAP Childhood Immunization Support Program	http://www.aap.org/immunization/
American Association of Occupational Health Nurses (AAOHN)	http://www.aaohn.org/
American College Health Association (ACHA)	http://www.acha.org/
American College of Obstetricians and Gynecologists (ACOG)–Immunization for Women	http://www.immunizationforwomen.org/
American Medical Association (AMA)	http://www.ama-assn.org/
American Nurses Association (ANA)	http://www.nursingworld.org/
American Pharmacists Association (APhA)	http://www.pharmacist.com/
American School Health Association (ASHA)	http://www.ashaweb.org/
American Travel Health Nurses Association (ATHNA)	http://www.athna.org/
Association for Professionals in Infection Control and Epidemiology (APIC)	http://www.apic.org/
Association of State and Territorial Health Officials (ASTHO)	http://www.astho.org/
Association of Teachers of Preventive Medicine (ATPM)	http://www.atpm.org/
National Medical Association (NMA)	http://www.nmanet.org/
Society of Teachers of Family Medicine—Group on Immunization Education	http://www.immunizationed.org/
NONPROFIT GROUPS AND UNIVERSITIES	
Albert B. Sabin Vaccine Institute	http://www.sabin.org/
Brighton Collaboration	https://brightoncollaboration.org/public
Center for Vaccine Awareness and Research—Texas Children's Center	http://www.texaschildrens.org/departments/immunization-project
Children's Vaccine Program	http://www.path.org/vaccineresources/
Every Child by Two (ECBT)	http://www.ecbt.org/
Families Fighting Flu	http://www.familiesfightingflu.org/
GAVI, the Vaccine Alliance	http://www.gavialliance.org/
Health on the Net Foundation (HON)	http://www.hon.ch/
Immunization Action Coalition (IAC)	http://www.immunize.org/
Infectious Diseases Society of America (IDSA)	http://www.idsociety.org/Index.aspx
Institute for Vaccine Safety (IVS), Johns Hopkins Bloomberg School of Public Health	http://www.vaccinesafety.edu/
National Academies: Health and Medicine Division	http://www.nationalacademies.org/hmd/
National Alliance for Hispanic Health	http://www.hispanichealth.org/
National Foundation for Infectious Diseases (NFID)	http://www.nfid.org
National Foundation for Infectious Diseases (NFID)—Childhood Influenza Immunization Coalition (CIIC)	http://www.preventchildhoodinfluenza.com/
National Network for Immunization Information (NNii)	http://www.immunizationinfo.net/
Parents of Kids with Infectious Diseases (PKIDS)	http://www.pkids.org/
PATH Vaccine Resource Library	http://www.path.org/vaccineresources/
Vaccine Education Center at the Children's Hospital of Philadelphia	http://www.chop.edu/service/vaccine-education-center/home.html
Vaccinate Your Baby	http://www.vaccinateyourbaby.org/
GOVERNMENT ORGANIZATIONS	
Centers for Disease Control and Prevention (CDC)	
Advisory Committee on Immunization Practices	http://www.cdc.gov/vaccines/acip/index.html

(ACIP)	
ACIP Vaccine Recommendations	http://www.cdc.gov/vaccines/hcp/acip-recs/index.html
Current Vaccine Delays and Shortages	http://www.cdc.gov/vaccines/vac-gen/shortages/
Epidemiology and Prevention of Vaccine-Preventable Diseases (also known as the *Pink Book*)	https://www.cdc.gov/vaccines/pubs/pinkbook/index.html
Manual for the Surveillance of Vaccine-Preventable Diseases	www.cdc.gov/vaccines/pubs/surv-manual/index.html
Public Health Image Library	https://phil.cdc.gov/phil/home.asp
Travelers' Health	http://www.cdc.gov/travel/
CDC Health Information for International Travel (also known as the *Yellow Book*)	https://wwwnc.cdc.gov/travel/yellowbook/2016/table-of-contents
Vaccine Adverse Events Reporting System (VAERS)	http://www.cdc.gov/vaccinesafety/Activities/vaers.html
Vaccine Administration: Recommendations and Guidelines	http://www.cdc.gov/vaccines/recs/vac-admin/default.htm
Vaccines and Immunizations	http://www.cdc.gov/vaccines/
Vaccines for Children Program	http://www.cdc.gov/vaccines/programs/vfc/index.html
Vaccines for Children—Vaccine Price List	http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
Vaccine Information Statements	www.cdc.gov/vaccines/hcp/vis/index.html
Vaccine Safety	http://www.cdc.gov/vaccinesafety/index.html
Vaccine Storage and Handling	http://www.cdc.gov/vaccines/recs/storage/default.htm
Department of Health and Human Services (HHS)	
National Vaccine Program Office (NVPO)	http://www.hhs.gov/nvpo/
Health Resources and Services Administration	
National Vaccine Injury Compensation Program	http://www.hrsa.gov/vaccinecompensation/
National Institute of Allergy and Infectious Diseases (NIAID)	
Vaccines	https://www.niaid.nih.gov/about/vrc
World Health Organization (WHO)	
Immunization, Vaccines, and Biologicals	http://www.who.int/immunization/en/

Recommended Immunization Schedule

All children in the United States should be vaccinated against 16 diseases (Figs. 197.1 and 197.2) (annually updated schedule available at http://www.cdc.gov/vaccines/schedules/index.html).

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger United States, 2019

These recommendations must be read with the Notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Fig.197.2). School entry and adolescent vaccine age groups are shaded in gray.

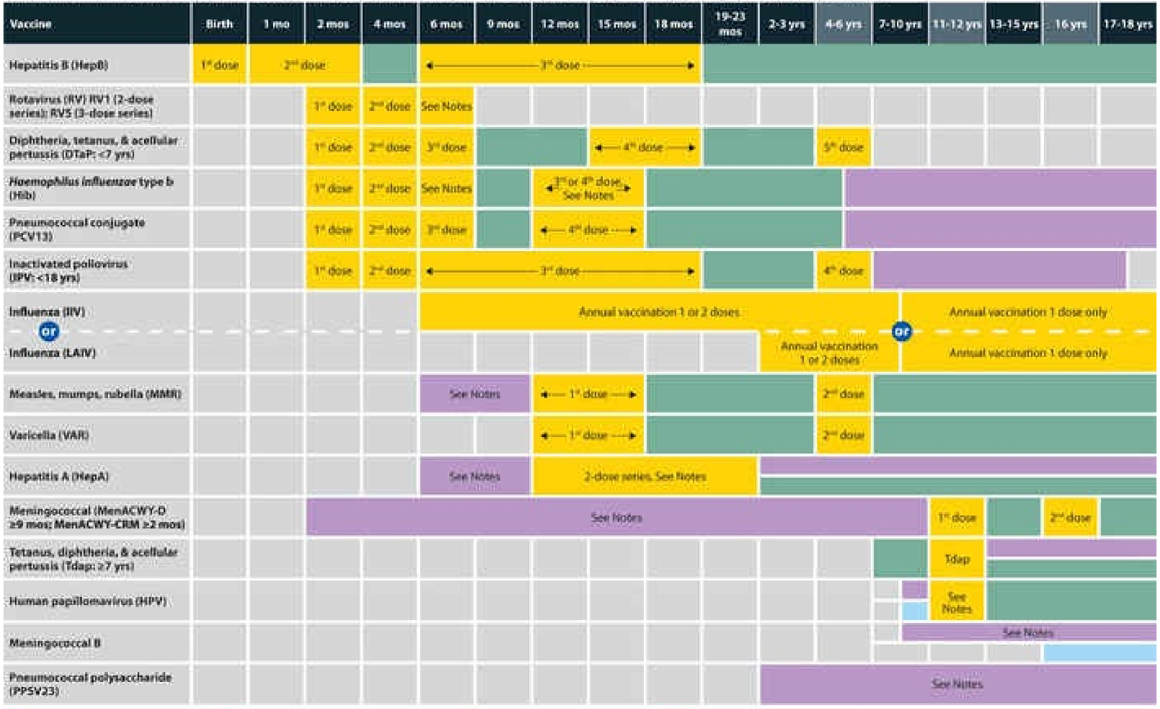

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
Hepatitis B (HepB)	1st dose	2nd dose	🟨	🟩	← 3rd dose →	🟨	🟨	🟨	🟨	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose	🟩	🟩	← 4th dose →	🟨	🟩	🟩	5th dose					
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes	🟩	← 3rd or 4th dose, See Notes →	🟨	🟩	🟩	🟩	🟩🟪	🟪	🟪	🟪	🟪	🟪
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose	🟩	← 4th dose →	🟨	🟩	🟩	🟩	🟩🟪	🟪	🟪	🟪	🟪	🟪
Inactivated poliovirus (IPV: <18 yrs)			1st dose	2nd dose	← 3rd dose →	🟨	🟨	🟨	🟨	🟩	🟩	4th dose	🟪	🟪	🟪	🟪	🟪
Influenza (IIV)					Annual vaccination 1 or 2 doses	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	Annual vaccination 1 dose only	🟨	🟨	🟨
or													or				
Influenza (LAIV)											Annual vaccination 1 or 2 doses	🟨	🟨	Annual vaccination 1 dose only	🟨	🟨	🟨
Measles, mumps, rubella (MMR)					See Notes	🟪	← 1st dose →	🟨	🟩	🟩	🟩	2nd dose	🟩	🟩	🟩	🟩	🟩
Varicella (VAR)							← 1st dose →	🟨	🟩	🟩	🟩	2nd dose	🟩	🟩	🟩	🟩	🟩
Hepatitis A (HepA)					See Notes	🟪	2-dose series, See Notes	🟨	🟨	🟨	🟪🟩	🟪🟩	🟪🟩	🟪🟩	🟪🟩	🟪🟩	🟪🟩
Meningococcal (MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)			See Notes	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	🟪	1st dose	🟩	2nd dose	🟩
Tetanus, diphtheria, & acellular pertussis (Tdap: ≥7 yrs)													🟩	Tdap	🟪🟩	🟪🟩	🟪🟩
Human papillomavirus (HPV)													🟪🟦	See Notes	🟩	🟩	🟩
Meningococcal B													🟪	See Notes	🟪	🟪🟦	🟪🟦
Pneumococcal polysaccharide (PPSV23)											See Notes	🟪	🟪	🟪	🟪	🟪	🟪

🟨 Range of recommended ages for all children

🟩 Range of recommended ages for catch-up immunization

🟪 Range of recommended ages for certain high-risk groups

🟦 Range of recommended ages for non-high-risk groups that may receive vaccine, subject to individual clinical decision-making

⬜ No recommendation

Notes Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2019

For vaccine recommendations for persons 19 years of age and older, see the Recommended Adult Immunization Schedule.

Additional information

- Consult relevant ACIP statements for detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For information on contraindications and precautions for the use of a vaccine, consult the General Best Practice Guidelines for Immunization and relevant ACIP statements at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see Table 3-1, Recommended and minimum ages and intervals between vaccine doses, in General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccine requirements and recommendations is available at wwwnc.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1, Vaccination of persons with primary and secondary immunodeficiencies, in General Best Practice Guidelines for Immunization at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Immunization in Special Clinical Circumstances (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases.* 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–111).
- For information regarding vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html.

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix or Quadracel])

Routine vaccination

- 5-dose series at 2, 4, 6, 15–18 months, 4–6 years
  - **Prospectively:** Dose 4 may be given as early as age 12 months if at least 6 months have elapsed since dose 3.
  - **Retrospectively:** A 4th dose that was inadvertently given as early as 12 months may be counted if at least 4 months have elapsed since dose 3.

Catch-up vaccination

- Dose 5 is not necessary if dose 4 was administered at age 4 years or older.
- For other catch-up guidance, see Fig. 197. 2.

Haemophilus influenzae type b vaccination (minimum age: 6 weeks)

Routine vaccination

- **ActHIB, Hiberix, or Pentacel:** 4-dose series at 2, 4, 6, 12–15 months
- **PedvaxHIB:** 3-dose series at 2, 4, 12–15 months

Catch-up vaccination

- **Dose 1 at 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at 12–15 months or 8 weeks after dose 2 (whichever is later).
- **Dose 1 at 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.
- **Dose 1 before 12 months and dose 2 before 15 months:** Administer dose 3 (final dose) 8 weeks after dose 2.
- **2 doses of PedvaxHIB before 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- **Unvaccinated at 15–59 months:** 1 dose
- For other catch-up guidance, see Fig. 197. 2.

Special situations

- **Chemotherapy or radiation treatment:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.
- **Hematopoietic stem cell transplant (HSCT):**
  - 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant regardless of Hib vaccination history
- **Anatomic or functional asplenia (including sickle cell disease):**
  12–59 months
  - Unvaccinated or only 1 dose before 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before 12 months:1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5 years or older*
  - 1 dose
- **Elective splenectomy:**
  Unvaccinated persons age 15 months or older*
  - 1 dose (preferably at least 14 days before procedure)
- **HIV infection:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

  Unvaccinated persons age 5–18 years*
  - 1 dose
- **Immunoglobulin deficiency, early component complement deficiency:**
  12–59 months
  - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
  - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose

**Unvaccinated* = Less than routine series (through 14 months) OR no doses (14 months or older)

Hepatitis A vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series (**Havrix** 6–12 months apart or **Vaqta** 6–18 months apart, minimum interval 6 months); a series begun before the 2nd birthday should be completed even if the child turns 2 before the second dose is administered.

Catch-up vaccination

- Anyone 2 years of age or older may receive HepA vaccine if desired. Minimum interval between doses: 6 months
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).

International travel

- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (wwwnc.cdc.gov/travel/):
  - **Infants age 6–11 months**: 1 dose before departure; revaccinate with 2 doses, separated by 6–18 months, between 12 to 23 months of age.
  - **Unvaccinated age 12 months and older**: 1st dose as soon as travel considered

Special situations

At risk for hepatitis A infection: 2-dose series as above

- **Chronic liver disease**
- **Clotting factor disorders**
- **Men who have sex with men**
- **Injection or non-injection drug use**
- **Homelessness**
- **Work with hepatitis A virus** in research laboratory or nonhuman primates with hepatitis A infection
- **Travel** in countries with high or intermediate endemic hepatitis A
- **Close, personal contact with international adoptee** (e.g., household or regular babysitting) in first 60 days after arrival from country with high or intermediate endemic hepatitis A (administer dose 1 as soon as adoption is planned, at least 2 weeks before adoptee's arrival)

Hepatitis B vaccination
(minimum age: birth)

Birth dose (monovalent HepB vaccine only)

- **Mother is HBsAg-negative:** 1 dose within 24 hours of birth for **all** medically stable infants ≥2,000 grams. Infants <2,000 grams: administer 1 dose at chronological age 1 month or hospital discharge.
- **Mother is HBsAg-positive:**
  - Administer **HepB vaccine** and **0.5 mL of hepatitis B immune globulin (HBIG)** (at separate anatomic sites) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.
- **Mother's HBsAg status is unknown:**
  - Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
  - For infants <2,000 grams, administer **0.5 mL of HBIG** in addition to HepB vaccine within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
  - Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **0.5 mL of HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series

- 3-dose series at 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Fig. 197. 2).
- Administration of **4 doses** is permitted when a combination vaccine containing HepB is used after the birth dose.
- **Minimum age** for the final (3rd or 4th) dose: 24 weeks
- **Minimum intervals:** dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 8 weeks / dose 1 to dose 3: 16 weeks (when 4 doses are administered, substitute "dose 4" for "dose 3" in these calculations)

Catch-up vaccination

- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB** only).
- Adolescents 18 years and older may receive a 2-dose series of HepB (**Heplisav-B**) at least 4 weeks apart.
- Adolescents 18 years and older may receive the combined HepA and HepB vaccine, **Twinrix**, as a 3-dose series (0, 1, and 6 months) or 4-dose series (0, 7, and 21–30 days, followed by a dose at 12 months).
- For other catch-up guidance, see Fig. 197. 2.

Human papillomavirus vaccination
(minimum age: 9 years)

Routine and catch-up vaccination

- HPV vaccination routinely recommended for all adolescents **age 11–12 years (can start at age 9 years)** and through age 18 years if not previously adequately vaccinated
- 2- or 3-dose series depending on age at initial vaccination:
  - **Age 9 through 14 years at initial vaccination**: 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
  - **Age 15 years or older at initial vaccination**: 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- If completed valid vaccination series with any HPV vaccine, no additional doses needed

Special situations

- **Immunocompromising conditions, including HIV infection:** 3-dose series as above
- **History of sexual abuse or assault:** Start at age 9 years
- **Pregnancy:** HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant; pregnancy testing not needed before vaccination

Inactivated poliovirus vaccination
(minimum age: 6 weeks)

Routine vaccination

- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer **the final dose on or after the 4th** birthday and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before the 4th **birthday when a combination vaccine containing IPV** is used. However, a dose is still recommended after the 4th birthday and at least 6 months after the previous dose.

Catch-up vaccination

- **In the first 6 months of life, use minimum ages and intervals** only for travel to a polio-endemic region or during an outbreak.
- **IPV is not routinely recommended for U.S. residents 18 years** and older.

Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV-only series:

- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?s_cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements. For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?s_cid=mm6606a7_w.
- For other catch-up guidance, see Fig. 197. 2.

Influenza vaccination
(minimum age: 6 months [IIV], 2 years [LAIV], 18 years [RIV])

Routine vaccination

- **1 dose any influenza vaccine appropriate for age and health** status annually (2 doses separated by at least 4 weeks for **children 6 months–8 years** who did not receive at least **2 doses of influenza vaccine before July 1, 2018)**

Special situations

- **Egg allergy, hives only: Any influenza vaccine appropriate for** age and health status annually
- **Egg allergy more severe than hives** (e.g., angioedema, **respiratory distress): Any influenza vaccine appropriate for** age and health status annually in medical setting under supervision of health care provider who can recognize and manage severe allergic conditions
- **LAIV should not be used for** those with a history of severe allergic reaction to any component of the vaccine **(excluding egg) or to a previous dose of any influenza** vaccine, children and adolescents receiving concomitant **aspirin or salicylate-containing medications, children age** 2 through 4 years with a history of asthma or wheezing, those who are immunocompromised due to any cause (including immunosuppression caused by medications and HIV infection), anatomic and functional asplenia, cochlear **implants, cerebrospinal fluid-oropharyngeal communication,** close contacts and caregivers of severely immunosuppressed persons who require a protected environment, pregnancy, **and persons who have received influenza antiviral** medications within the previous 48 hours

Measles, mumps, and rubella vaccination
(minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series at 12–15 months, 4–6 years
- **Dose 2 may be administered as early as 4 weeks after dose 1.**

Catch-up vaccination

- Unvaccinated children and adolescents: 2 doses at least **4 weeks apart**
- The maximum age for use of *MMRV* is 12 years.

Special situations

International travel

- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2 doses at 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months and older:** 2-dose series at least 4 weeks apart before departure

Meningococcal serogroup A,C,W,Y vaccination
(minimum age: 2 months [MenACWY-CRM, Menveo], 9 months [MenACWY-D, Menactra])

Routine vaccination

- 2-dose series: 11–12 years, 16 years

Catch-up vaccination

- Age 13–15 years: 1 dose now and booster at age 16–18 years (minimum interval: 8 weeks)
- Age 16–18 years: 1 dose

Special situations

Anatomic or functional asplenia (including sickle cell disease), HIV infection, persistent complement component deficiency, eculizumab use:

- **Menveo**
  - Dose 1 at age 8 weeks: 4-dose series at 2, 4, 6, 12 months
  - Dose 1 at age 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after the 1st birthday)
  - Dose 1 at age 24 months or older: 2-dose series at least 8 weeks apart
- **Menactra**
  - **Persistent complement component deficiency:**
    - Age 9–23 months: 2 doses at least 12 weeks apart
    - Age 24 months or older: 2 doses at least 8 weeks apart
  - **Anatomic or functional asplenia, sickle cell disease, or HIV infection:**
    - **Age 9–23 months**: Not recommended
    - **24 months or older**: 2 doses at least 8 weeks apart
    - **Menactra** must be administered at least 4 weeks after completion of PCV13 series.

Travel in countries with hyperendemic or epidemic meningococcal disease, including countries in the African meningitis belt or during the Hajj (wwwnc.cdc.gov/travel/):

- Children age less than 24 months:
  - **Menveo (age 2–23 months):**
    - Dose 1 at 8 weeks: 4-dose series at 2, 4, 6, 12 months
    - Dose 1 at 7–23 months: 2-dose series (dose 2 at least 12 weeks after dose 1 and after the 1st birthday)
  - **Menactra (age 9–23 months):**
    - 2-dose series (dose 2 at least 12 weeks after dose 1; dose 2 may be administered as early as 8 weeks after dose 1 in travelers)
- Children age 2 years or older: 1 dose **Menveo** or **Menactra**

First-year college students who live in residential housing (if not previously vaccinated at age 16 years or older) or military recruits:

- 1 dose **Menveo** or **Menactra**

Note: Menactra should be administered either before or at the same time as DTaP. For MenACWY booster dose recommendations for groups listed under "Special situations" above and additional meningococcal vaccination information, see meningococcal *MMWR* publications at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

Meningococcal serogroup B vaccination
(minimum age: 10 years [MenB-4C, Bexsero; MenB-FHbp, Trumenba])

Clinical discretion

- MenB vaccine may be administered based on individual clinical decision to **adolescents not at increased risk** age 16–23 years (preferred age 16–18 years):
- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 2-dose series at least 6 months apart; if dose 2 is administered earlier than 6 months, administer a 3rd dose at least 4 months after dose 2.

Special situations

Anatomic or functional asplenia (including sickle cell disease), persistent complement component deficiency, eculizumab use:

- **Bexsero:** 2-dose series at least 1 month apart
- **Trumenba:** 3-dose series at 0, 1–2, 6 months

Bexsero and **Trumenba** are not interchangeable; the same product should be used for all doses in a series.

For additional meningococcal vaccination information, see meningococcal MMWR publications at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

Pneumococcal vaccination
(minimum age: 6 weeks [PCV13], 2 years [PPSV23])

Routine vaccination with PCV13

- 4-dose series at 2, 4, 6, 12–15 months

Catch-up vaccination with PCV13

- 1 dose for healthy children age 24–59 months with any incomplete* PCV13 series
- For other catch-up guidance, see Fig. 197. 2.

Special situations

High-risk conditions below: When both PCV13 and PPSV23 are indicated, administer PCV13 first. PCV13 and PPSV23 should not be administered during same visit.

Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma treated with high-dose, oral corticosteroids); diabetes mellitus:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Cerebrospinal fluid leak, cochlear implant:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13, 8 weeks after the most recent dose and administered 8 weeks apart
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 1 dose PPSV23 at least 8 weeks later
- Any PCV13 but no PPSV23: 1 dose PPSV23 at least 8 weeks after the most recent dose of PCV13
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent dose of PPSV23

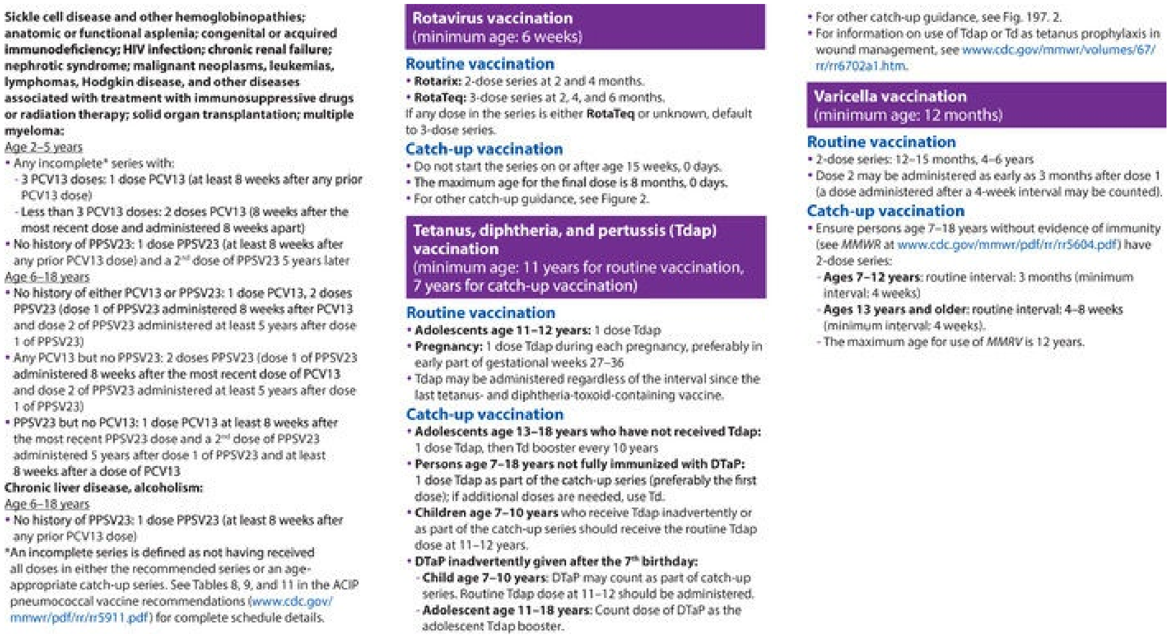

Sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiency; HIV infection; chronic renal failure; nephrotic syndrome; malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and other diseases associated with treatment with immunosuppressive drugs or radiation therapy; solid organ transplantation; multiple myeloma:

Age 2–5 years

- Any incomplete* series with:
  - 3 PCV13 doses: 1 dose PCV13 (at least 8 weeks after any prior PCV13 dose)
  - Less than 3 PCV13 doses: 2 doses PCV13 (8 weeks after the most recent dose and administered 8 weeks apart)
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose) and a 2nd dose of PPSV23 5 years later

Age 6–18 years

- No history of either PCV13 or PPSV23: 1 dose PCV13, 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- Any PCV13 but no PPSV23: 2 doses PPSV23 (dose 1 of PPSV23 administered 8 weeks after the most recent dose of PCV13 and dose 2 of PPSV23 administered at least 5 years after dose 1 of PPSV23)
- PPSV23 but no PCV13: 1 dose PCV13 at least 8 weeks after the most recent PPSV23 dose and a 2nd dose of PPSV23 administered 5 years after dose 1 of PPSV23 and at least 8 weeks after a dose of PCV13

Chronic liver disease, alcoholism:

Age 6–18 years

- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

*An incomplete series is defined as not having received all doses in either the recommended series or an age-appropriate catch-up series. See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations (www.cdc.gov/mmwr/pdf/rr/rr5911.pdf) for complete schedule details.

Rotavirus vaccination
(minimum age: 6 weeks)

Routine vaccination

- **Rotarix:** 2-dose series at 2 and 4 months.
- **RotaTeq:** 3-dose series at 2, 4, and 6 months.

If any dose in the series is either **RotaTeq** or unknown, default to 3-dose series.

Catch-up vaccination

- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Figure 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination
(minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination

- **Adolescents age 11–12 years:** 1 dose Tdap
- **Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination

- **Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td booster every 10 years
- **Persons age 7–18 years not fully immunized with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td.
- **Children age 7–10 years** who receive Tdap inadvertently or as part of the catch-up series should receive the routine Tdap dose at 11–12 years.
- **DTaP inadvertently given after the 7th birthday:**
  - **Child age 7–10 years:** DTaP may count as part of catch-up series. Routine Tdap dose at 11–12 should be administered.
  - **Adolescent age 11–18 years:** Count dose of DTaP as the adolescent Tdap booster.
- For other catch-up guidance, see Fig. 197. 2.
- For information on use of Tdap or Td as tetanus prophylaxis in wound management, see www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm.

Varicella vaccination
(minimum age: 12 months)

Routine vaccination

- 2-dose series: 12–15 months, 4–6 years
- Dose 2 may be administered as early as 3 months after dose 1 (a dose administered after a 4-week interval may be counted).

Catch-up vaccination

- Ensure persons age 7–18 years without evidence of immunity (see *MMWR* at www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2-dose series:
  - **Ages 7–12 years:** routine interval: 3 months (minimum interval: 4 weeks)
  - **Ages 13 years and older:** routine interval: 4–8 weeks (minimum interval: 4 weeks).
  - The maximum age for use of *MMRV* is 12 years.

FIG. 197.1 Recommended immunization schedule for children and adolescents age 18 yr or younger—United States, 2019. (Courtesy of US Centers for Disease Control and Prevention, Atlanta, 2019. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html .)

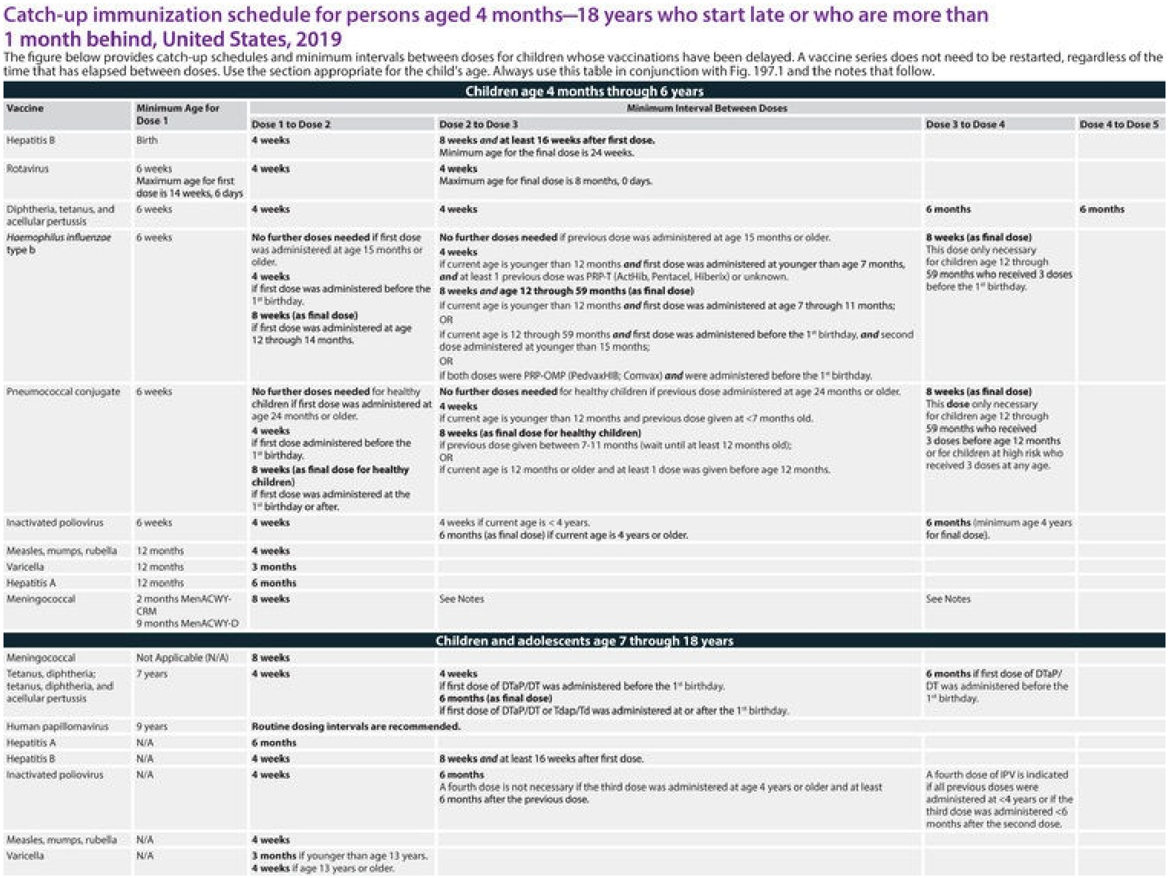

Catch-up immunization schedule for persons aged 4 months—18 years who start late or who are more than 1 month behind, United States, 2019

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Fig. 197.1 and the notes that follow.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Children age 4 months through 6 years					
Hepatitis B	Birth	**4 weeks**	**8 weeks *and* at least 16 weeks after first dose.** Minimum age for the final dose is 24 weeks.		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days	**4 weeks**	**4 weeks** Maximum age for final dose is 8 months, 0 days.		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months**
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older. **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months, ***and*** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. **8 weeks *and* age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday, ***and*** second dose administered at younger than 15 months; OR if both doses were PRP-OMP (PedvaxHIB; Comvax) ***and*** were administered before the 1st birthday.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older. **4 weeks** if first dose administered before the 1st birthday. **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after.	**No further doses needed** for healthy children if previous dose administered at age 24 months or older. **4 weeks** if current age is younger than 12 months and previous dose given at <7 months old. **8 weeks (as final dose for healthy children)** if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months.	**8 weeks (as final dose)** This **dose** only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	**4 weeks**	4 weeks if current age is < 4 years. 6 months (as final dose) if current age is 4 years or older.	**6 months** (minimum age 4 years for final dose).	
Measles, mumps, rubella	12 months	**4 weeks**			
Varicella	12 months	**3 months**			
Hepatitis A	12 months	**6 months**			
Meningococcal	2 months MenACWY-CRM 9 months MenACWY-D	**8 weeks**	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal	Not Applicable (N/A)	**8 weeks**			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	7 years	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday. **6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	**6 months** if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**			
Hepatitis A	N/A	**6 months**			
Hepatitis B	N/A	**4 weeks**	**8 weeks *and*** at least 16 weeks after first dose.		
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	**4 weeks**			
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years or older.			

FIG. 197.2 Catch-up immunization schedule for persons age 4 mo-18 yr who start late or who are more than 1 mo behind—United States, 2019. (Courtesy of US Centers for Disease Control and Prevention, Atlanta, 2019. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html .)

Hepatitis B vaccine (**HepB**) is recommended in a 3-dose schedule starting at birth. The birth dose, as well as hepatitis B immunoglobulin, is critical for infants born to mothers who are hepatitis B surface antigen (HBsAg)–positive or whose hepatitis B immune status is unknown. The recommendation is to administer the 1st hepatitis B vaccine to all newborns within 24 hr of birth, the 2nd dose at 1-2 mo, with a minimal interval between the 1st and 2nd dose of 4 wk, and the 3rd dose from 6-18 mo of age ensuring that 8 wk has passed between the 2nd and 3rd dose. If the DTaP-HepB-IPV combination vaccine is used, a 4-dose schedule is permissible, which includes the stand-alone hepatitis B vaccine at birth and the combination vaccine for the next 3 doses.

The **DTaP** series consists of 5 doses administered at 2, 4, 6, and 15 through 18 mo of age, and 4 through 6 yr of age. The 4th dose of DTaP may be administered as early as 12 mo of age, provided at least 6 mo has elapsed since the 3rd dose.

The 5th (booster) dose of DTaP vaccine is not necessary if the 4th dose was administered at 4 yr or older. One dose of an adult preparation of Tdap is recommended for all adolescents 11 through 12 yr of age, even if a dose of Tdap or DTaP was administered inadvertently or as part of the catch-up series at 7-10 yr of age. Adolescents 13 through 18 yr who missed the 11 through 12 yr Tdap booster dose should receive a single dose of Tdap if they have completed the diphtheria, tetanus, and pertussis (DTP)/DTaP series. Tdap may be given at any interval following the last Td. Table 197.6 lists preparations in which DTaP is combined with other vaccines. One dose of Tdap vaccine is recommended for pregnant adolescents with each pregnancy, preferably between 27 and 36 wk gestation, regardless of time since last Tdap or Td. Currently available data suggest that vaccinating earlier in the 27 through 36 wk period will maximize passive antibody transfer to the infant. This recommendation was made in response to data predicting lack of infant protection when maternal Tdap had been received before pregnancy.

Table 197.6

Combination Vaccines Licensed and Available in the United States

VACCINE PRODUCT (MANUFACTURER)[*]	TRADE NAME (YEAR LICENSED)	COMPONENTS	RECOMMENDED AGES	
			Primary Series	Booster Dose
DTaP-IPV/Hib (Sanofi Pasteur)	Pentacel (2008)	DTaP-IPV + PRP-T	2, 4, and 6 mo	15 through 18 mo
DTaP-HepB-IPV (GlaxoSmithKline)	Pediarix (2002)	DTaP + HepB + IPV	2, 4, and 6 mo	
DTaP-IPV (GlaxoSmithKline)	Kinrix (2008), Quadracel (2015)	DTaP + IPV		4 through 6 yr Booster for 5th dose of DTaP Booster for 4th dose of IPV
HepA-HepB (GlaxoSmithKline)	Twinrix (2001)	HepA + HepB	>18 yr of age; 0, 1, and 6 mo schedule	
MMRV (Merck & Co)	ProQuad (2005)	MMR + varicella	[†]	4 through 6 yr

[*] Dash (-) indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products are mixed or reconstituted by user.

[†] Although ProQuad is available for the 1st dose (at 12 through 15 mo of age), the CDC recommends that MMR vaccine and varicella vaccine should be administered for the 1st dose in

this age-group, unless the parent or caregiver expresses a preference for MMRV vaccine.

DTaP, Diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; IPV/Hib, trivalent inactivated polio vaccine and *Haemophilus influenzae* type b vaccine; MMRV, measles-mumps-rubella and varicella vaccine, PRP-T, H. influenzae type b capsular polysaccharide (polyribosyl-ribitol279 phosphate [PRP]) covalently bound to tetanus toxoid (PRP-T).

Adapted from Cohn AC, MacNeil JR, Clark TA, et al: Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, *MMWR* 62(2):1–28, 2013.

There are 3 licensed preparations of single-antigen **Hib** vaccines. The vaccine conjugated to tetanus toxoid (PRP-T) is given in a 4-dose series at 2, 4, 6, and 12 through 15 mo of age, and the Hib vaccine conjugated to meningococcal outer membrane protein (PRP-OMP) is recommended in a 3-dose series at 2, 4, and 12 through 15 mo of age. The 3rd Hib vaccine is licensed as a booster for children 15 mo through 4 yr of age. There are several vaccines in which Hib is a component, in addition to single-antigen Hib conjugate vaccines (see Tables 197.6 and 197.7).

Table 197.7

Vaccines Recommended for Children and Adolescents With Underlying Conditions or at High Risk

VACCINES	SPECIAL SITUATIONS
PCV13 (and PPSV23 in certain conditions)	Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), chronic liver disease, chronic renal failure Diabetes mellitus Cerebrospinal fluid leak Cochlear implant Sickle cell disease and other hemoglobinopathies Anatomic or functional asplenia HIV infection Nephrotic syndrome Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease Generalized malignancy Solid organ transplantation Congenital or acquired immunodeficiencies Multiple myeloma
Hep A	Chronic liver disease Clotting factor disorders Men who have sex with men Injection or non-injection drug use Homelessness Work with hepatitis A virus Travel in countries with high or intermediate endemic hepatitis A

	Close, personal contact with international adoptee (e.g.,household or regular babysitting)
Flu	Egg allergy more severe than hives
MCV4	Anatomic or functional asplenia (including sickle cell disease) Persistent complement component deficiency Residents of or travelers to countries in African meningitis belt or pilgrims on the Hajj During outbreaks caused by a vaccine serogroup HIV infection
MenB	Anatomic or functional asplenia (including sickle cell disease) Children with persistent complement component deficiency During serogroup B outbreaks
Hib	Persons at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency Recipients of hematopoietic stem cell transplant (HSCT) Elective splenectomy
Hep B	Infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown (administer vaccine within 12 hr of birth)
HPV	Immunocompromising conditions, including HIV infection History of sexual abuse or assault

From Centers for Disease Control and Prevention: Child and adolescent schedule. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

Influenza vaccine is recommended for all children beginning at 6 mo old, with a minimum age of 6 mo for IIVs and 24 mo for LAIV. Various influenza vaccine preparations are FDA-licensed for different age-groups.* Children 6 mo through 8 yr of age being vaccinated for the first time should receive 2 doses at least 4 wk apart. If such children only received a single dose of IIV the prior season, they need 2 doses the following season. For additional guidelines, follow dosing instructions in the influenza statement, which is updated annually by both the CDC (https://www.cdc.gov/flu/professionals/acip/index.htm) and AAP (aapredbook.org). Influenza vaccine usually is given in October or November, although there are benefits even when administered as late as February or March because influenza seasons most frequently peak in February. People ≥9 yr old should receive 1 dose of influenza vaccine annually. For the 2016–2017 flu season, the ACIP voted that LAIV should not be used at all because of low vaccine effectiveness during the previous 3 influenza seasons.

IPV should be administered at 2, 4, and 6 through 18 mo of age with a booster dose at 4 through 6 yr. The final dose in the series should be administered on or after 4 yr of age and at least 6 mo after the previous dose. The final dose in the IPV series should be administered at 4 yr or older regardless of the number of previous doses, and the minimal interval from dose 3 to dose 4 is 6 mo. For series that contain oral polio vaccine (OPV), the total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule.

Only documentation specifying receipt of trivalent OPV constitutes proof of vaccination according to the U.S. polio vaccination recommendations. This is important because since April 2016, trivalent OPV (tOPV) is no longer available with the type 2 serotype removed. Thus, children vaccinated since that time only received the type 1 and 3 components and are not immune to type 2. In contrast, IPV contains all 3 polio serotypes. For catch-up vaccine recommendations, see the recommended childhood immunization schedule at http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html .

MMR should be administered at 12 through 15 mo of age followed by a 2nd dose at 4 through 6 yr. Before all international travel, infants 6 through 11 mo of age should receive 1 dose of MMR vaccine. These children should be revaccinated with the routinely recommended 2 doses of MMR vaccine beginning at 12 mo of age. For children 12 mo or older, administer 2 doses before international travel; the 2nd dose should be administered at least 4 wk after the 1st dose.

Two doses of **varicella** vaccine should be given, the 1st at 12 through 15 mo of age and the 2nd at 4 through 6 yr. The 2nd dose may be administered before 4 yr of age provided at least 3 mo have elapsed since the 1st dose. MMR and MMRV preparations are available. The **quadrivalent MMRV** vaccine is preferred in place of separate MMR and varicella vaccines at the 4-6 yr old visit. Because of the slight increase in febrile seizures associated with combined MMRV vaccine compared to simultaneous administration of the separate products, use of MMRV is not preferred over use of separate MMR and varicella vaccines for the initial dose at 12-15 mo of age.

Protection against pneumococcal and meningococcal disease can be provided by either conjugated or polysaccharide vaccines. Conjugated vaccines offer several benefits over polysaccharide vaccines (see Table 197.4). **PCV13** is recommended as a 4-dose series at 2, 4, 6, and 12 through 15 mo of age. In the latest immunization schedule, PCV13 is the only pneumococcal vaccine that appears; references to the previously available 7-valent pneumococcal conjugate vaccine (PCV7) have been removed. All healthy children who may have received PCV7 as part of a primary series have now aged out of the recommendation for pneumococcal vaccine. PPSV23 is recommended for select children with conditions that place them at risk for pneumococcal disease.

A 2-dose series of MCV4 includes a recommended dose for all adolescents at 11 through 12 yr of age and a booster dose at 16 yr. If the 1st dose is administered at 13 through 15 yr of age, a booster dose should be administered at 16 through 18 yr. No booster dose is needed if the 1st dose is administered at 16 yr. In addition, MCV4 should be administered to people 2 mo through 55 yr of age with underlying conditions that place them at high risk of meningococcal disease. In addition, 2-3 doses of the **meningococcal B (MenB)** vaccine are recommended for persons ≥10 yr old at increased risk of meningococcal disease.

Hepatitis A vaccine, licensed for administration to children ≥12 mo old, is recommended for universal administration to all children at 12 through 23 mo of age and for certain high-risk groups. The 2 doses in the series should be separated by at least 6 mo. Children who have received 1 dose of hepatitis A vaccine before 24 mo of age should receive a 2nd dose 6-18 mo after the 1st dose. For anyone 2 yr or older who has not yet received the 2-dose hepatitis A vaccine series, 2 doses of vaccine separated by 6-18 mo may be administered if immunity against hepatitis A infection is desired. This is particularly important in people with chronic liver disease, clotting factor disorders, men who have sex with men, injection or non-injection drug use, homelessness, people exposed to hepatitis A virus at work, travel, and people in close contact with international adoptees. Before all international travel, infants 6 through 11 mo of age should receive 1 dose of hepatitis A vaccine. These children should be revaccinated with the routinely recommended 2 doses of hepatitis A vaccine beginning at 12 mo of age. For unvaccinated children 12 mo or older, 2 doses should be administered before international travel to countries with high or intermediate endemic hepatitis A; the 2nd dose should be administered at least 6 mo after the 1st dose.

The **9vHPV** vaccine is recommended at age 11 or 12 yr but can be started as early as 9 yr for males and females. For those who initiate the series before their 15th birthday, the recommended schedule is 2 doses of 9vHPV vaccine. The minimum interval is 5 mo between the 1st and 2nd dose. If the 2nd dose is given at a shorter interval, a 3rd dose should be administered a minimum of 12 wk after the 2nd dose and a minimum of 5 mo after the 1st dose. For those initiating the series on or after their 15th birthday, the recommended schedule is 3 doses of 9vHPV vaccine. The minimum intervals are 4 wk between the 1st and 2nd dose, 12 wk between the 2nd and 3rd dose, and 5 mo between the 1st and 3rd dose. For children with a history of sexual abuse or assault, ACIP recommends routine HPV vaccination beginning at age 9 yr. In males and females with primary or secondary immunocompromising conditions such as B-lymphocyte deficiencies, T-lymphocyte complete or partial defects, HIV, malignancy, transplantation, autoimmune disease, or immunosuppressive therapy, ACIP recommends vaccination with 3 doses of 9vHPV (0, 1-2, and 6 mo) because immune response to vaccination might be attenuated. 9vHPV may be used to continue or complete a vaccination series in patients who started with 4vHPV or 2vHPV.

Two **rotavirus** vaccines are available, RotaTeq (RV5) and Rotarix (RV1). With both vaccines, the 1st dose can be administered as early as 6 wk of age and must be administered by 14 wk 6 days. The final dose in the series must be administered no later than 8 mo of age. The RV5 vaccine is administered in 3 doses at least 4 wk apart. The RV1 vaccine is administered in 2 doses at least 4 wk apart. Immunization should not be initiated for infants ≥15 wk old, as stated in the immunization schedule.

The present schedule, excluding influenza vaccine, can require as many as 34 doses, including 31 that must be administered by injection. Of the doses, 25 are recommended before 2 yr of age, including 22 injections. Influenza vaccination, starting at age 6 mo, can add an additional 20 injections through 18 yr. To reduce the injection burdens, several combination vaccines are available (see Table 197.6).

The recommended childhood and adolescent immunization schedule establishes a routine adolescent visit at 11 through 12 yr of age. MCV4, a Tdap booster, and 9vHPV vaccine should be administered during this visit. Influenza vaccine should be administered annually. In addition, the 11-12 yr old visit is an opportune time to review all the immunizations the adolescent has received previously, to provide any doses that were missed, and to review other age-appropriate preventive services. The 11-12 yr visit establishes an important platform for incorporating other vaccines. Information on the current status of new vaccine licensure and recommendations for use is available.*

For children who are at least 1 mo behind in their immunizations, catch-up immunization schedules are available for children 4 mo through 18 yr of age (http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html). Also, interactive immunization schedules are available for children <6 yr of age at https://www.vacscheduler.org . Only written/electronic, dated, authentic records should be accepted as evidence of immunization. In general, when in doubt, a person with unknown or uncertain immunization status should be considered “disease susceptible,” and recommended immunizations should be initiated without delay on a schedule commensurate with the person's current age. No evidence suggests that administration of vaccines to already-immune recipients is harmful.

Vaccines Recommended in Special Situations

There are 8 vaccines—PCV13, PPSV23, MCV4, MenB, Flu, Hib, HepA, and HepB—recommended for children and adolescents at increased risk for complications from vaccine-preventable diseases or children who have an increased risk for exposure to these diseases, who are outside the age-groups for which these vaccines are normally recommended (PPSV23 and MenB are not routinely recommended for any age-group of children and are only used for children with high-risk conditions; see Table 197.7). Specific recommendations for use of these vaccines in children with underlying conditions can be found in the recommended immunization schedule.

PCV13 is recommended for children 24 mo through 5 yr of age with certain medical conditions that place them at high risk for pneumococcal disease. This recommendation includes children with sickle cell disease and other hemoglobinopathies, including hemoglobin SS, hemoglobin S-C, or hemoglobin S–β-thalassemia, or children who are functionally or anatomically asplenic; children with HIV infection; and children who have chronic disease (Table 197.7). (For further recommendations on pneumococcal vaccine recommendations, see https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html .)

Children at high risk for pneumococcal disease also should receive **PPSV23** to provide immunity to serotypes not contained in the 13-valent conjugate vaccine. PPSV23 should be administered on or after the 2nd birthday and should follow completion of the PCV13 series by at least 6-8 wk. Two doses of PPSV23 are recommended, with an interval of 5 yr between doses. Immunization of children >5 yr old with high-risk conditions can be performed with PCV13 and/or PPSV23, depending on the condition and vaccination history. When both PCV13 and PPSV23 are indicated, PCV13 should be administered first. The 2 vaccines should not be administered during the same visit.

MCV4 is recommended for HIV-infected persons ≥2 mo old, children with anatomic or functional asplenia (including sickle cell disease), and children with persistent complement component deficiency (includes persons with inherited or chronic deficiencies in C3, C5–9, properdin, factor D or factor H or taking eculizumab).

Meningococcal B (**MenB**) vaccine is recommended for persons ≥10 yr old at increased risk of meningococcal disease. This includes people with complement deficiencies or anatomic or functional asplenia, people at increased risk due to serogroup B meningococcal disease outbreaks, and microbiologists who routinely are exposed to isolates of *Neisseria meningitidis* . Young adults age 16-23 (preferred range: 16-18 yr) who are not at increased risk for meningococcal disease may be vaccinated with either of the 2 MenB vaccines, which are not interchangeable, to provide short-term protection against most strains of serogroup B meningococcal disease.

Hib vaccine and HepA vaccine are recommended for children with certain high-risk conditions. **HepB** is recommended for infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown (administer vaccine within 12 hr of birth) (see Table 197.7).

In addition to vaccines in the recommended childhood and adolescent schedule, a variety of vaccines are available for children who will be **traveling** to areas of the world where certain infectious diseases are common (Table 197.8). Vaccines for travelers include typhoid fever, hepatitis A, hepatitis B, Japanese encephalitis, MCV4 or MPS4, cholera, rabies, and yellow fever, depending on the location and circumstances of travel. **Measles** is endemic in many parts of the world. Children 6-11 mo old should receive a dose of MMR and hepatitis A vaccines before international travel. However, doses of MMR and hepatitis A vaccines received before 12 mo should not be counted in determining compliance with the recommended 2-dose MMR schedule. For unvaccinated children ≥12 mo old, administer 2 doses before international travel following the recommended schedule. (Additional information on vaccines for international travel can be found at http://wwwnc.cdc.gov/travel/ .)

Table 197.8

Recommended Immunizations for International Travel*

IMMUNIZATIONS	LENGTH OF STAY	
	Brief, <1 mo	**Long-Term/Residential, >1 mo**
Review and complete age-appropriate childhood and adolescent schedule (see text for details) • DTaP, poliovirus, pneumococcal, and *Haemophilus influenzae* type b (Hib) vaccines may be given at 4 wk intervals if necessary to complete recommended schedule before departure. • Influenza • MMR: 2 additional doses given if <12 mo old at 1st dose	+	+

• Meningococcal disease (MenACWY) [†] • Rotavirus • Varicella • Human papillomavirus (HPV) • Hepatitis A: 2 additional doses given if <12 mo old at 1st dose [‡] [§] • Hepatitis B [§] • Tdap		
Yellow fever [‖]	+	+
Typhoid fever [¶]	±	+
Rabies[**]	±	±
Japanese encephalitis [††]	±	+
Cholera [‡‡]	±	±

[*] See disease-specific chapters in the Centers for Disease Control and Prevention's *Yellow Book* for details. For further sources of information, see text.

[†] Recommended for regions of Africa with endemic infection and during local epidemics, and required for travel to Saudi Arabia for the Hajj.

[‡] For infants age 6-11 mo, 1st dose is recommended before departure for all international travel. For unvaccinated children 12 mo and older, this vaccine is indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection.

[§] If there is insufficient time to complete 6 mo primary series, accelerated series can be given.

[‖] For regions with endemic infection, see Health Information for International Travel (http://www.cdc.gov/travel). Because of the risk of serious adverse events after yellow fever vaccination, clinicians should only vaccinate people who (1) are at risk of exposure to yellow fever virus (YFV) or (2) require proof of vaccination to enter a country.

[¶] Indicated for travelers who will consume food and liquids in areas of poor sanitation.

[**] Indicated for people with high risk for animal exposure (especially to dogs) and for travelers to countries with endemic infection.

[††] For regions with endemic infection (see Health Information for International Travel). For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.

[‡‡] Cholera vaccine (CVD 103-HgR, Vaxchora) is recommended for adult (18-64 yr old) travelers to an area of active toxigenic *V. cholerae* O1 transmission.

+, Recommended; ±, consider; DTaP, diphtheria and tetanus toxoids and acellular pertussis.

Data from Centers for Disease Control and Prevention: Travelers' health. https://wwwnc.cdc.gov/travel .

Vaccine recommendations for children with **immunocompromising conditions** , either primary (inherited) or secondary (acquired), vary according to the underlying condition, the degree of immune deficit, the risk for exposure to disease, and the vaccine (Table 197.9 and Fig. 197.3). Immunization of children who are immunocompromised poses the following potential concerns: the incidence or severity of some vaccine-preventable diseases is higher, and therefore certain vaccines are recommended specifically for certain conditions; vaccines may be less effective during the period of altered immunocompetence and may need to be repeated when immune competence is restored; and because of altered immunocompetence, some children and adolescents may be at increased risk for an adverse event following receipt of a live-virus vaccine. Live-attenuated vaccines generally are contraindicated in immunocompromised persons. The exceptions include **MMR** , which may be given to a child with HIV infection provided the child is asymptomatic or symptomatic without evidence of severe immunosuppression, and **varicella** vaccine, which may be given to HIV-infected children if the $CD4^+$ lymphocyte count is at least 15%. MMRV is not recommended in these situations.

Table 197.9

Vaccination of Persons With Primary and Secondary Immune Deficiencies

PRIMARY				
CATEGORY	**SPECIFIC IMMUNODEFICIENCY**	**CONTRAINDICATED VACCINES** *	**RISK-SPECIFIC RECOMMENDED VACCINES** *	**EFFE COM**
B lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV [a] Smallpox [b] LAIV BCG Yellow fever virus (YFV) and live-bacteria vaccines [e] No data for rotavirus vaccines	Annual IIV is the only vaccine given to patients receiving IG therapy; routine inactivated vaccines can be given if not receiving IGIV.	Th an un on res PP IG wi res va VA
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV [a] BCG YFV vaccine Other live vaccines [d] appear to be safe.	Vaccines should be given as on the annual immunization schedule for immunocompetent people. [e] PPSV23 should be given beginning at 2 yr of age. [f]	Al pro Im ma
T lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines [c] , [d] , [g]	The only vaccine that should be given if the patient is receiving IG is annual IIV if there is	All ina are pro

			some residual antibody protection.	
	Partial defects (e.g., most patients with DiGeorge syndrome, hyper-IgM syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines [c], [d], [g]	Routine inactivated vaccines should be given. [e] PPSV23 should be given beginning at 2 yr of age. [f]	Effect vaccin of im
	Interferon (IFN)-γ–interleukin (IL)-12 axis deficiencies	All live vaccines for IL-12/IL-12R deficiencies, IFN-γ, IFN-α, or STAT1 deficiencies	None	None
Complement	Persistent complement, properdin, MBL, or factor B deficiency; secondary deficiency because taking eculizumab (Solaris)	None	PPSV23 should be given beginning at 2 yr of age. [f] MCV series beginning in infancy. [h] MenB series beginning at 10 yr of age	All rou probab
Phagocytic function	Chronic granulomatous disease	Live-bacteria vaccines [c]	None	Al va pr Li are eff
	Phagocytic deficiencies that are undefined or accompanied by defect in T-cell and NK-cell dysfunction (e.g., Chédiak-Higashi syndrome, leukocyte adhesion defects, myeloperoxidase deficiency)	MMR, MMRV, OPV, [a] smallpox, LAIV, YF, all bacteria vaccines	PPSV23 should be given beginning at 2 yr of age. [f] MCV series beginning in infancy. [h]	All ina are saf effecti

SECONDARY

SPECIFIC IMMUNODEFICIENCY	**CONTRAINDICATED VACCINES** *	**RISK-SPECIFIC RECOMMENDED VACCINES** *	**EFFECTIVENES COMMENTS**
HIV/AIDS	OPV [a] Smallpox BCG Combined MMRV LAIV Withhold MMR, varicella, and zoster in severely immunocompromised persons. YF vaccine may have a contraindication or	PPSV23 should be given beginning at 2 yr of age. [f] MCV series beginning in infancy. [h] Consider Hib (if not administered in infancy). [l]	Rotavirus vacc recommended schedule. MMR and VA for HIV-infecte asymptomatic immunocompr All inactivated effective.

	precaution depending on the indicators of immune function. [j]		
Generalized malignant neoplasm, transplantation, autoimmune disease, immunosuppressive or radiation therapy	Live-virus and live-bacteria vaccines, depending on immune status. [c], [d], [m]	PPSV23 should be given beginning at 2 yr of age. [f] Annual IIV (unless receiving intensive chemotherapy or anti-B cell antibodies). Hib vaccine may be indicated. [n]	Effectiveness of an on degree of immu inactivated standar indicated if not hig immunosuppresse be repeated after c
Asplenia (functional, congenital anatomic, surgical)	LAIV	PPSV23 should be given beginning at 2 yr of age. [f] MCV series beginning in infancy. [h] MenB series beginning at 10 yr of age. Hib (if not administered in infancy) [o]	All routine vaccine effective.
Chronic renal disease	LAIV	PPSV23 should given beginning at 2 yr of age. [f] HepB is indicated if not previously immunized.	All routine vaccine effective.
CNS anatomic barrier defect (cochlear implant, congenital dysplasia of the inner ear, persistent CSF communication with naso-/oropharynx)	None	PPSV23 should be given beginning at 2 yr of age. [f]	All standard vacci

[*] Other vaccines that are universally or routinely recommended should be given if not contraindicated.

[a] OPV is no longer available in the United States.

[b] This table refers to contraindications for nonemergency vaccination (i.e., ACIP recommendations)

[c] Live-bacteria vaccines: BCG and oral Ty21a *Salmonella typhi* vaccine.

[d] Live-virus vaccines: MMR, MMRV, VAR, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

[e] Children who are delayed or underimmunized should be immunized with routinely recommended vaccines, according to age and catch-up schedule.

[f] PPSV23 is begun at 2 yr or older. If PCV13 is required, PCV13 doses should be administered first, followed by PPSV23 at least 8 wk later; a 2nd dose of PPSV23 is given 5 yr after the 1st.

[g] Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

[h] Age and schedule of doses depend on the product; repeated doses are required.

[j] YF vaccine is contraindicated in HIV-infected children <6 yr old who are highly immunosuppressed. There is precaution for use of YF vaccine in asymptomatic HIV-infected children <6 yr with total lymphocyte percentage of 15–24%, and >6 yr old with $CD4^+$ T-lymphocyte

counts of 200-499 cells/mm^3 .

[k] HIV-infected children should receive immune globulin after exposure to measles and may receive varicella vaccine if CD4$^+$ T-lymphocyte percentage is ≥15% for those <6 yr old, or CD4$^+$ T-lymphocyte count ≥200 cells/mm^3 for those ≥6 yr old. People with perinatal HIV infection who were vaccinated with measles, rubella, or mumps–containing vaccine before the establishment of combination antiretroviral therapy (cART) should be considered unvaccinated and should receive 2 appropriately spaced doses of MMR vaccine once effective cART has been established (at least 6 mo with CD4$^+$ T-lymphocytes ≥15% for children <6 yr old, or CD4$^+$ T-lymphocyte count ≥200 cells/mm^3 for children ≥6 yr old).

[l] For patients 5-18 yr old who have not received a Hib primary series and a booster dose or at least 1 Hib dose after age 14 mo.

[m] Witholding inactivated vaccines also is recommended with some forms of immunosuppressive therapy, such as anti-CD20 antibodies, induction or consolidation chemotherapy, or patients with major antibody deficiencies receiving immune globulins. Inactivated influenza vaccine is an exception, but consideration should be given to repeating doses of any inactivated vaccine administered during these therapies.

[n] For persons <60 mo old undergoing chemotherapy or radiation therapy who have not received a Hib primary series plus a booster dose or at least 1 Hib dose after age 14 mo.

[o] For persons >59 mo old who are asplenic and persons ≥15 mo who are undergoing elective splenectomy and who have not received a Hib primary series and a booster dose or at least 1 Hib dose after age 14 mo.

[i] Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV13. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.

(Data from Centers for Disease Control and Prevention: Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 59[RR-07]; 1–27, 2010.)

BCG, Bacille Calmette-Guérin vaccine; CNS, central nervous system; Hib, *Haemophilus influenzae* type b vaccine; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IG, immune globulin; IIV, inactivated influenza vaccine; LAIV, live-attenuated influenza vaccine; MMR, measles, mumps, rubella vaccine; MMRV, measles-mumps-rubella-varicella; MCV, quadrivalent meningococcal polysaccharide vaccine; MenB, serogroup B meningococcal vaccine; OPV, oral poliovirus vaccine (live); PPSV23, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency disease; VAR, varicella; YF, yellow fever.

Adapted from Immunization in special circumstances. In Kimberlin DW, Brady MT, Jackson MA, Long SS, editors: *Red Book 2018: Report of the Committee on Infectious Diseases,* ed 31, Elk Grove Village, IL, 2018, American Academy of Pediatrics.

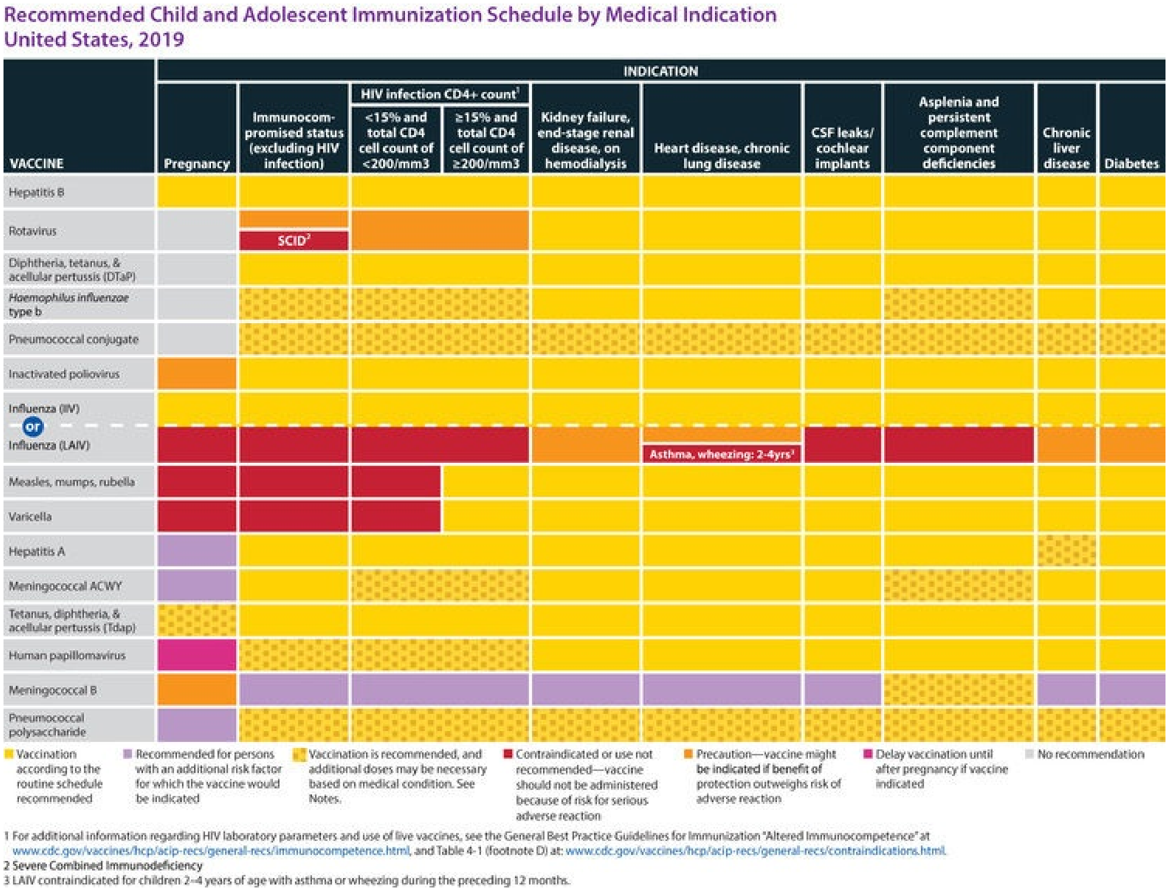

Recommended Child and Adolescent Immunization Schedule by Medical Indication
United States, 2019

VACCINE	INDICATION									
	Pregnancy	Immunocompromised status (excluding HIV infection)	HIV infection CD4+ count[1] <15% and total CD4 cell count of <200/mm3	HIV infection CD4+ count[1] ≥15% and total CD4 cell count of ≥200/mm3	Kidney failure, end-stage renal disease, on hemodialysis	Heart disease, chronic lung disease	CSF leaks/ cochlear implants	Asplenia and persistent complement component deficiencies	Chronic liver disease	Diabetes
Hepatitis B	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Rotavirus	⬜	🟧 🟥 SCID[2]	🟧	🟧	🟨	🟨	🟨	🟨	🟨	🟨
Diphtheria, tetanus, & acellular pertussis (DTaP)	⬜	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Haemophilus influenzae type b	⬜	▨	▨	▨	🟨	🟨	🟨	▨	🟨	🟨
Pneumococcal conjugate	⬜	▨	▨	▨	▨	▨	▨	▨	▨	▨
Inactivated poliovirus	🟧	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Influenza (IIV)	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
or										
Influenza (LAIV)	🟥	🟥	🟥	🟥	🟧	🟧 🟥 Asthma, wheezing: 2-4yrs[3]	🟥	🟥	🟧	🟧
Measles, mumps, rubella	🟥	🟥	🟥	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Varicella	🟥	🟥	🟥	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Hepatitis A	🟪	🟨	🟨	🟨	🟨	🟨	🟨	🟨	▨	🟨
Meningococcal ACWY	🟪	🟨	▨	▨	🟨	🟨	🟨	▨	🟨	🟨
Tetanus, diphtheria, & acellular pertussis (Tdap)	▨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨	🟨
Human papillomavirus	■	▨	▨	▨	🟨	🟨	🟨	🟨	🟨	🟨
Meningococcal B	🟧	🟪	🟪	🟪	🟪	🟪	🟪	▨	🟪	🟪
Pneumococcal polysaccharide	🟪	▨	▨	▨	▨	▨	▨	▨	▨	▨

🟨 Vaccination according to the routine schedule recommended
🟪 Recommended for persons with an additional risk factor for which the vaccine would be indicated
▨ Vaccination is recommended, and additional doses may be necessary based on medical condition. See Notes.
🟥 Contraindicated or use not recommended—vaccine should not be administered because of risk for serious adverse reaction
🟧 Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction
■ Delay vaccination until after pregnancy if vaccine indicated
⬜ No recommendation

1 For additional information regarding HIV laboratory parameters and use of live vaccines, see the General Best Practice Guidelines for Immunization "Altered Immunocompetence" at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and Table 4-1 (footnote D) at: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.
2 Severe Combined Immunodeficiency
3 LAIV contraindicated for children 2–4 years of age with asthma or wheezing during the preceding 12 months.

FIG. 197.3 Recommended child and adolescent immunization schedule by medical indication—United States, 2019. (Courtesy of US Centers for Disease Control and Prevention, Atlanta, Georgia. 2019. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-indications.html .)

Altered immunocompetence is considered a precaution for rotavirus; however, the vaccine is contraindicated in children with severe combined immunodeficiency disease. Inactivated vaccines may be administered to immunocompromised children, although their effectiveness might not be optimal depending on the immune deficit. Children with complement deficiency disorders may receive all vaccines, including live-attenuated vaccines. In contrast, children with phagocytic disorders may receive both inactivated and live-attenuated viral vaccines but not live-attenuated bacterial vaccines.*

Corticosteroids can suppress the immune system. Children receiving corticosteroids (≥2 mg/kg/day or ≥20 mg/day of prednisone or equivalent) for ≥14 days should not receive live vaccines until therapy has been discontinued for at least 1 mo. Children on the same dose levels but for <2 wk may receive live-virus vaccines as soon as therapy is discontinued, although some experts recommend waiting 2 wk after therapy has been discontinued. Children receiving lower doses of corticosteroids may be vaccinated while receiving therapy.

Children and adolescents with malignancy, and those who have undergone solid organ or hematopoietic stem cell transplantation and immunosuppressive or radiation therapy, should not receive live-virus and live-bacteria vaccines depending on their immune status. Children who have undergone chemotherapy for leukemia may need to be reimmunized with age-appropriate single doses of previously administered vaccines. Preterm infants generally can be vaccinated at the same chronological age as full-term infants according to the recommended childhood immunization schedule. An exception is the birth dose of HepB. Infants weighing ≥2 kg and who are stable should receive a birth dose within the 1st 24 hr of life. However, HepB should be deferred in infants weighing <2 kg at birth until chronological age 1 mo or hospital discharge, if born to an HBsAg-negative mother. All preterm, low-birthweight infants born to HBsAg-positive mothers should receive hepatitis B immunoglobulin (HBIG) and HepB vaccine (at separate anatomic sites) within 12 hr of birth. However, such infants should receive an additional 3 doses of vaccine starting at 30 days of age (see Fig. 197.2). Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody at 9-12 mo, or 1-2 mo after completion of the HepB series if the series was delayed. If the test is negative for antibody against the surface antigen (anti-HBs), an additional dose of HepB is recommended with testing 1-2 mo after the dose. If the child is still antibody negative, an additional 2 doses of vaccine should be administered.

If the mother's HBsAg status is unknown within 12 hr of birth, administer HepB vaccine regardless of birthweight. For infants weighing <2,000 g, administer HBIG in addition to HepB within 12 hr of birth. Determine the mother's HBsAg status as soon as possible and, if the mother is HBsAg-positive, also administer HBIG to infants weighing ≥2,000 g as soon as possible, but no later than 7 days of age.

Varicella-zoster immunoglobulin (**VariZIG**) is recommended for patients without evidence of immunity to varicella who are at high risk for severe varicella and complications, who have been exposed to varicella or herpes zoster, and for whom varicella vaccine is contraindicated. This includes immunocompromised patients without evidence of immunity, newborn infants whose mothers have signs and symptoms of varicella around the time of delivery (i.e., 5 days before to 2 days after), hospitalized premature infants born at ≥28 wk gestation whose mothers do not have evidence of immunity to varicella, hospitalized premature infants born at <28 wk gestation or who weigh ≤1,000 g at birth, regardless of their mother's evidence of immunity to varicella, and pregnant women without evidence of immunity.

Some children have situations that are not addressed directly in current immunization schedules. Physicians can use general rules to guide immunization decisions in some of these instances. In general, vaccines may be given simultaneously on the same day, whether inactivated or live. Different inactivated vaccines can be administered at any interval between doses. However, because of theoretical concerns about viral interference, different live-attenuated vaccines (MMR, varicella), if not administered on the same day, should be given at least 1 mo apart. An inactivated and a live vaccine may be spaced at any interval from each other.

Immunoglobulin does not interfere with inactivated vaccines. However, immunoglobulin can interfere with the immune response to measles vaccine and by inference to varicella vaccine. In general, immunoglobulin, if needed, should be administered at least 2 wk after the measles vaccine. Depending on the dose of immunoglobulin received, MMR should be deferred for as long as 3-11 mo. Immunoglobulin is not expected to interfere with the immune response to LAIV or rotavirus vaccines.

Certain adult (including pregnancy) immunizations are recommended to decrease the risk of infection in their children; these include influenza virus and pertussis (Tdap).

Precautions and Contraindications

Observation of valid precautions and contraindications is critical to ensure that vaccines are used in the safest manner possible and to obtain optimal immunogenicity. When a child presents for immunization with a clinical condition considered a **precaution** , the physician must weigh benefits and risks to that individual child. If benefits are judged to outweigh risks, the vaccine or vaccines in question may be administered. A **contraindication** means the vaccine should not be administered under any circumstances.

A general contraindication for all vaccines is **anaphylactic reaction** to a prior dose. Anaphylactic hypersensitivity to vaccine constituents is also a contraindication. However, if a vaccine is essential, there are desensitizing protocols for some vaccines. The major constituents of concern are *egg proteins* for vaccines grown in eggs; *gelatin*, a stabilizer in many vaccines; and antimicrobial agents. The recommendations for persons with egg allergy were modified as follows: Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive a flu vaccine. Persons who had reactions such as angioedema or respiratory distress or who required epinephrine also may receive any recommended flu vaccine. The vaccine should be administered in an inpatient or outpatient medical setting in the presence of a healthcare provider who is able to recognize and manage severe allergic conditions. LAIV should not be used for persons with a history of severe allergic reaction to any component of the vaccine (excluding egg) or to a previous dose of any influenza vaccine. The measles and mumps components of MMR are grown in chick embryo fibroblast tissue culture. However, the amount of egg protein in MMR is so small that there are no special procedures for administering the vaccine to someone with a history of anaphylaxis following egg ingestion.

Vaccines should usually be deferred in children with moderate to severe acute illnesses, regardless of the presence of fever, until the child recovers. *However, children with mild illnesses may be vaccinated.* Studies of undervaccinated children have documented opportunities that were missed because mild illness was used as an invalid contraindication. Complete tables of contraindications and contraindication misperceptions can be found at http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.html .

Medical Exemptions

All 50 states, the District of Columbia, and Puerto Rico have regulations requiring verification of immunization for child care and school attendance. This provides direct protection to the immunized population and indirect protection to those unable to be immunized. It also functions to improve timely immunization of children. Regulations also allow for medical exemption from immunization requirements in all 50 states, and the majority of states also have varied regulations that allow for nonmedical exemptions. Rare, medically recognized contraindications are important to observe. Nonmedical exemptions to immunization requirements include exemptions because of religious or philosophical beliefs. Persons with exemptions are at greater risk of vaccine-preventable diseases than the general population. When children with exemptions cluster, as can happen with nonmedical exemptions, the community may be at risk for outbreaks, leading to exposure of children who cannot be protected by vaccination to vaccine-preventable diseases, such as children too young for vaccination and those with medical contraindications. (For more information, see: http://pediatrics.aappublications.org/content/early/2016/08/25/peds.2016-2145 .)

Improving Immunization Coverage

Standards for child and adolescent immunization practices have been developed to support achievement of high levels of immunization coverage while providing vaccines in a safe and effective manner and educating parents about risks and benefits of vaccines (Table 197.10).

Table 197.10

Standards for Child and Adolescent Immunization Practices

AVAILABILITY OF VACCINES
Vaccination services are readily available. Vaccinations are coordinated with other healthcare services and provided in a medical home when possible. Barriers to vaccination are identified and minimized. Patient costs are minimized.
ASSESSMENT OF VACCINATION STATUS
Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated. Healthcare professionals assess for and follow only medically accepted contraindications.
EFFECTIVE COMMUNICATION ABOUT VACCINE BENEFITS AND RISKS
Parents or guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.* Healthcare professionals offer strong and consistent recommendations for all universally recommended vaccines according to the current immunization schedule. They use presumptive language (e.g., these vaccines are routine) and deliver this recommendation in the same manner for all vaccines. Healthcare professionals answer parents' or guardians' and patients' questions thoroughly and emphasize an unwavering commitment to the recommendation. If parents or guardians and patients are hesitant or refuse, healthcare professionals persevere and offer the vaccine again at the next most appropriate time.
PROPER STORAGE AND ADMINISTRATION OF VACCINES AND DOCUMENTATION OF VACCINATIONS
Healthcare professionals follow appropriate procedures for vaccine storage and handling. Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered. Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education. Healthcare professionals simultaneously administer as many indicated vaccine doses as possible. Vaccination records for patients are accurate, complete, and easily accessible. Healthcare professionals report adverse events following vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP). Healthcare professionals and personnel review the immunization timeline with parents or guardians and patients

and schedule follow-up immunization visits before the family leaves the care setting.

All personnel who have contact with patients are appropriately vaccinated and communicate consistent messages about vaccines.

IMPLEMENTATION OF STRATEGIES TO IMPROVE VACCINATION COVERAGE

Systems are used to remind parents or guardians, patients, and healthcare professionals when vaccinations are due and to recall those who are overdue.

Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.

Healthcare professionals practice community-based approaches.

Healthcare professionals understand cultural needs and disparities of different populations and use the most effective strategies for these populations.

Most healthcare visits (including acute care or sick visits) are viewed as opportunities to review immunization records, provide vaccines that are due, and catch up on missed vaccinations.

[*] Additional resources to help improve immunization rates include the following:

- Provider Resources for Vaccine Conversations with Parents from CDC, AAP, and American Academy of Family Physicians (www.cdc.gov/vaccines/hcp/conversations/index.html)
- American Academy of Pediatrics (AAP) Training Guide (https://shar.es/1JRNmJ)
- Centers for Disease Control and Prevention (CDC): *Pink Book*, Chapter 6 : Vaccine administration (https://www.cdc.gov/vaccines/pubs/pinkbook/vac-admin.html); and quality improvement projects and educational materials (https://www.cdc.gov/vaccines/ed/index.html)
- Immunization Action Coalition: *Suggestions to improve your immunization services* (http://www.immunize.org/catg.d/p2045.pdf)

Adapted from National Vaccine Advisory Committee: Standards for child and adolescent immunization practices, *Pediatrics* 112:958–963, 2003; and Bernstein HH, Bocchini JA; AAP Committee on Infectious Diseases: The need to optimize adolescent immunization, *Pediatrics* 139(3):e20164186, 2017, and Practical approaches to optimize adolescent immunization, *Pediatrics* 139(3):e20164187, 2017.

Despite benefits that vaccines have to offer, many children are underimmunized as a result of not receiving recommended vaccines or not receiving them at the recommended ages. Much of the underimmunization problem can be solved through physician actions. Most children have a regular source of healthcare. However, missed opportunities to provide immunizations at healthcare visits include but are not limited to failure to provide all recommended vaccines that could be administered at a single visit during that visit, failure to provide immunizations to children outside of well-child care encounters when contraindications are not present, and referral of children to public health clinics because of inability to pay for vaccines. Simultaneous administration of multiple vaccines is generally safe and effective. When the benefits of simultaneous vaccination are explained, many parents prefer such immunization to making an extra visit. Providing all needed vaccines simultaneously should be the standard of practice.

Only valid contraindications and precautions to vaccine administration should be observed. Ideally, immunizations should be provided during well-child visits; however, if no contraindications exist, it is important to administer vaccines at other visits, particularly if the child is behind in the schedule. There is no good evidence that providing immunizations outside of well-child care ultimately decreases the number of well-child visits.

Financial barriers to immunization should be minimized. Participation in the **Vaccines for Children (VFC)** program allows physicians to receive vaccines at no cost for their eligible patients, which helps such patients get immunized in their medical home.

Several interventions have been shown to help physicians increase immunization coverage in their practices. Reminder systems for children before an appointment or recall systems for children who fail to keep appointments have repeatedly been demonstrated to improve coverage. Assessment and feedback is also an important intervention. Many physicians overestimate the immunization coverage among patients they serve and thus are not motivated to make any changes in their practices to improve performance. Assessing the immunization coverage of patients served by an individual physician with feedback of results can be a major motivator for improvement. Often, public health departments can be contacted to provide the assessments and feedback. Alternatively, physicians can perform self-assessment. Review of approximately 60 consecutive charts of 2 yr old children may provide a reasonable estimate of practice coverage. Another approach is to have a staff member review the chart of every patient coming in for a visit and placing immunization needs reminders on the chart for the physician. Electronic medical records can be designed to accomplish this goal.

Vaccine Hesitancy

The WHO characterized *vaccine hesitancy* as a delay in acceptance or refusal of vaccines despite availability of vaccination services. Factors implicated in vaccine hesitancy include complacency, convenience, and confidence. In a national telephone survey of parents of 6-23 mo olds, approximately 3% of parents refused all vaccines, and 20% refused or delayed at least 1 vaccine in the recommended schedule. Concerns about vaccine safety and questions about the necessity of vaccines are often cited as reasons for refusal. Vaccine-hesitant individuals are a heterogeneous group, and their individual concerns should be respected and addressed. Multiple studies have shown that the most important factor in persuading parents to accept vaccines remains the *one-on-one contact* with an informed, caring, and concerned pediatrician. Parents should be reassured that vaccines are tested thoroughly before licensure, that ongoing mechanisms of monitoring safety exist after licensure, and that the current vaccine schedule is the only recommended schedule. It is important to stress that serious disease can occur if a child and family are not immunized, because unvaccinated children put medically exempt children who live in that same area at risk, as well as some children who have been vaccinated (while most vaccines are highly effective, no vaccine is 100% effective). Parental education can be provided through reputable sources for vaccine information (see Table 197.6). (For more information, see http://pediatrics.aappublications.org/content/early/2016/08/25/peds.2016-2146 .) Provider resources for vaccine conversations with parents are available at http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/index.html .

Physician concerns about liability should be addressed by appropriate documentation of discussions in the chart. The Committee on Bioethics of the AAP has published guidelines for dealing with parents' refusal of immunization. Physicians also might want to consider having parents sign a **refusal waiver** . A sample refusal-to-vaccinate waiver can be found at http://www2.aap.org/immunization/pediatricians/pdf/refusaltovaccinate.pdf .

197.1

International Immunization Practices

Jean-Marie Okwo-Bele, Tracey S. Goodman, John David Clemens

Vaccines are used to prevent infectious diseases around the world. However, the types of vaccines in use, the indications and contraindications, and the immunization schedules vary substantially. Most developing countries follow the immunization schedules promulgated by the World Health Organization's Immunization Programme; the latest update is available at http://www.who.int/immunization/policy/Immunization_routine_table2.pdf .

According to this schedule, all children should be vaccinated at birth against tuberculosis with bacille Calmette-Guérin (BCG) vaccine. Many children also receive a dose of the live-attenuated oral polio vaccine (OPV) at this time. Immunization visits are scheduled for 6, 10, and 14 wk of age when DTP-containing vaccine and OPV are administered. At least 1 dose of injectable inactivated polio vaccine (IPV) is recommended at 14 wk of age or later for all countries using OPV. Two doses of measles vaccines are recommended, with the 1st dose given at 9-12 mo of age and the 2nd dose at 15-18 mo. Almost all developing countries have implemented hepatitis B vaccination. Two schedule options may be used, depending on epidemiologic and programmatic considerations. Hepatitis B vaccine can be given at the same time as DTP-containing vaccine doses at 6, 10, and 14 wk of age, often in combination vaccines. To prevent perinatal transmission, a birth dose of HepB should be administered as soon as possible after birth (<24 hr) and followed by 2 or 3 subsequent doses. Yellow fever and Japanese encephalitis vaccines are recommended for infants 9 mo of age living in endemic areas. Substantial efforts have been made to incorporate *Haemophilus influenzae* type b (Hib) vaccines into all but one country worldwide, in general within a DTP-containing combination vaccine.

In the past few years, the support from GAVI, the **Vaccine Alliance** , has facilitated the introduction of rotavirus and pneumococcal conjugate vaccines into developing-country immunization programs. The increased coverage with these additional vaccines will considerably reduce the global childhood morbidity and mortality caused by pneumonia, meningitis, and diarrheal diseases.

In 1988 the World Health Assembly endorsed the goal of eradicating polio from the world by the end of 2000. Although that goal has not yet been reached, endemic polio transmission was contained to 3 countries worldwide (Afghanistan, Nigeria, and Pakistan) by the end of 2016. The principal strategy is use of OPV both for routine immunization and mass campaigns in low-coverage areas, targeting all children <5 yr old for immunization, regardless of prior immunization status. Once interruption of wild poliovirus transmission is achieved, the goal is to stop the use of OPV, which in rare cases can cause vaccine-associated polio and can mutate and take on the phenotypic characteristics of the wild viruses.

Latin American countries have maintained the elimination of indigenous circulation of measles since 2002. The strategy called for attainment of high routine immunization coverage of infants with a dose at age 9 mo, a one-time mass campaign targeting all persons age 9 mo-15 yr regardless of prior immunization status, and follow-up campaigns of children born since the prior campaign, generally every 3-5 yr. Although global measles mortality has decreased by 79% worldwide in recent years, from 651,600 deaths in 2000 to 134,200 in 2015—measles is still common in many developing countries, particularly in parts of Africa and Asia. Latin American countries achieved the elimination of indigenous rubella and congenital rubella syndrome with strategies consisting of both routine immunization and mass campaigns.

Immunization schedules in the industrialized world are substantially more variable than in the developing world. Immunization recommendations for **Canada** are developed by the Canadian National Advisory Committee on Immunization but are implemented somewhat differently by each province. The Canadian schedule is similar to the U.S. immunization schedule, with a few exceptions.* A birth dose of hepatitis B vaccine is not specifically recommended as it is in the United States, although some northern Canadian provinces do provide a birth dose. Conjugate meningococcal C vaccine is recommended in a 1- or 2-dose series, depending on the age at the time of administration (1 dose if ≥12 mo). In contrast to the U.S. situation, hepatitis A vaccine is not recommended in Canada as a routine pediatric immunization.

There is tremendous variation in vaccines used and the immunization schedules recommended in Europe. † As an example, the **United Kingdom** developed an immunization schedule during the late 1980s that includes visits at 2, 3, and 4 mo of age, when a combination DTaP-Hib-IPV vaccine is administered. Following evidence that a 3-dose series of Hib vaccine at these ages was insufficient to ensure long-term, high-grade protection, a booster dose was added at 12 mo of age. MMR is recommended in a 2-dose schedule at 12 mo and 40 mo of age. During the 2nd MMR visit, a booster of DTaP and IPV is provided. A Td/IPV booster is recommended at age 14 yr. PCV13 is recommended at 2, 4, and 12 mon of age. The UK was the first country to use conjugate meningococcal C vaccine (**MCV-C**) during a massive catch-up campaign for children, adolescents, and young adults. The effectiveness of the vaccine in the 1st year was ≥88%, and herd immunity was induced with an approximate two-thirds reduction in the incidence among unvaccinated children. Given the success of this strategy, MenC vaccination at age 3 wk was discontinued as of July 2016. Now MenC is given in combination with the 4th dose of Hib at 12 mo. MenB is given at 2, 4, and 12 mo of age. In September 2008, HPV vaccine was recommended for girls 12-13 yr old. As of April 2013, the UK schedule did not include hepatitis B vaccine, varicella vaccine, or influenza vaccine for universal childhood immunization, although annual influenza vaccination is recommended for persons ≥65 yr old (see http://www.nhs.uk/conditions/vaccinations/pages/vaccination-schedule-age-checklist.aspx).

The **Japanese** immunization schedule in 2016 is substantially different from the Y.S. schedule. [‡] The Japanese do not use MMR, instead offering the choice of MR (preferred in principle) or single-antigen measles and rubella vaccination. Mumps vaccine is available on a voluntary basis. Japanese children are vaccinated routinely; against diphtheria, tetanus, pertussis, and polio with DTaP in combination with IPV; against Japanese encephalitis; and against tuberculosis with BCG. Hib, PCV, HepB, varicella, and HPV vaccines are also included in the routine vaccination schedule and made available free of charge under the **Preventive Vaccinations Act** . Adults ≥65 yr old receive annual influenza vaccinations. Rotavirus, HepA (from age 1 yr and above), meningococcus (ACWY) (from age 2 yr and above), and yellow fever vaccines are available on a voluntary basis.

Some children come to the United States having started or completed international immunization schedules with vaccines produced outside the United States. In general, doses administered in other countries should be considered valid if administered at the same ages as recommended in the United States. For missing doses, age-inappropriate doses, lost immunization records, or other concerns, pediatricians have 2 options: administer or repeat missing or inappropriate doses, or perform serologic tests, and if they are negative, administer vaccines.

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[*] http://nationalacademies.org/hmd/Reports.aspx?filters=inmeta:activity=Immunization+Safety+Review .

[**] https://www.nap.edu/catalog/13164/adverse-effects-of-vaccines-evidence-and-causality .

[†] https://www.nap.edu/catalog/13563/the-childhood-immunization-schedule-and-safety-stakeholder-concerns-scientific-evidence .

[‡] For more information on the reports, see http://nationalacademies.org/hmd/Reports.aspx .

[§] https://www.healthychildren.org/English/safety-prevention/immunizations/Pages/Vaccine-Studies-Examine-the-Evidence.aspx .

[*] See http://www.cdc.gov/flu/protect/vaccine/vaccines.htm and http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml#flu .

[*] http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml and http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM0

[*] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/a/immuno-table.pdf

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CHAPTER 198

Infection Prevention and Control

Michael J. Chusid, Joan P. Moran

Infection prevention and control (**IPC**) programs have an important role in pediatric medicine. To be fully effective, IPC programs require a functional infrastructure that addresses collaboration with the public health system, widespread immunizations, and use of appropriate techniques to prevent transmission of infection within the general population and within healthcare institutions. The national focus on preventing **healthcare-associated infection (HAI)** is exemplified by The Joint Commission's 2017 National Patient Safety Goals, with 5 of the 16 elements related to reduction and prevention of HAI. Governmental agencies and insurance providers have reduced or eliminated payment to institutions for expenses associated with certain HAIs, and a host of national organizations have been established to monitor and report rates of HAI at healthcare facilities.

HAIs or **nosocomial infections** refer to infections acquired during hospitalization or acquired in other healthcare settings, such as nursing homes or ambulatory surgical care centers. An estimated 3–5% of children admitted to hospitals acquire an HAI. Rates are highest in patients undergoing invasive procedures. Infections can also be acquired in emergency departments, physicians' offices, daycare, and long-term care settings. **Medical device–associated infections** occur in both the home and the hospital. Adequate education of home health providers as well as of families is essential to prevent or minimize device-associated infections, since increasing numbers of children are sent home from the hospital with intravenous (IV) catheters and other medical devices in place.

Susceptibility to HAI includes host factors, recent invasive procedures, presence of catheters or other devices, prolonged use of antibiotics, contaminated physical environment, and exposure to other patients, visitors, or healthcare providers with active contagious infections or colonized with invasive microorganisms. Host factors increasing the risk for HAI include anatomic abnormalities (dermal sinuses, cleft palate, obstructive uropathy), abnormal skin, organ dysfunction, malnutrition, and underlying diseases or comorbidities. Invasive procedures can introduce potential pathogens by breaching normal anatomic host barriers. IV and other catheters provide direct access to sterile anatomic sites for usually minimally pathogenic organisms, as well as adherent surfaces for microbial binding, and can disrupt patterns of normally protective flow of mucus (e.g., nasotracheal tubes and sinus ostia). Antibiotic use can alter the composition of bowel flora and encourage the multiplication and emergence of toxigenic or invasive organisms already present in small numbers in the gut, such as *Clostridium difficile* and *Salmonella* spp.

Transmission of infectious agents occurs by various routes, but by far the most common and important route is the **hands** . Medical equipment, toys, and hospital and office furnishings can become microbially contaminated and thus have a role in transmission of potential pathogens. Pagers, phones, computer keyboards, and even neckties become easily contaminated. These inanimate objects serve as **fomites** for bacteria. There is increasing recognition of the importance of the healthcare environment in the acquisition of organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multidrug-resistant gram-negative bacilli (MDR-GNB), *C. difficile,* and respiratory syncytial virus (RSV). Thermometers and other equipment that come in contact with mucous membranes pose special risks. Some agents are easily disseminated by airborne transmission, such as varicella virus, measles virus, and *Mycobacterium tuberculosis.* Food can be contaminated and has been involved in hospital outbreaks of nosocomial infection. The hospital physical environment can also serve as a risk factor for infection, particularly for immunocompromised patients. Rainwater or plumbing leaks have been associated with bacterial and fungal infections, new construction or renovation with airborne fungal infection, and contamination of an institution's potable water supply with bacterial, fungal, and atypical mycobacterial nosocomial infections. Widespread outbreaks of infection have been associated with mycobacterial contamination of equipment during the manufacturing process.

Common causes of HAI in children are seasonal viruses such as rotavirus and respiratory viral agents, staphylococci, and gram-negative bacilli. Fungi and multidrug-resistant organisms are common causes of infection in immunocompromised children as well as those requiring intensive care and prolonged hospitalization. Common sites of infection are the respiratory tract, gastrointestinal (GI) tract, bloodstream, skin, and urinary tract.

Liberalization of visitation policies and in-hospital animal visitation has increased the likelihood of HAI acquisition. The use of contaminated pharmaceutical products such as injectable depot corticosteroids has led to outbreaks of fatal fungal HAIs.

HAIs cause considerable morbidity and occasional mortality of hospitalized children. Infections prolong hospital stays and increase healthcare costs. **Surveillance** , the initial step in identifying such infections and suggesting methods for prevention, is the responsibility of **infection preventionists** . Within hospitals, oversight of such surveillance is usually the responsibility of the **infection prevention and control committee** , a multidisciplinary group that collects and reviews surveillance data, establishes institutional policies, and investigates intrainstitutional infection outbreaks. The chair of the committee is often an infectious disease specialist. Surveillance in outpatient settings and during home care is often less well defined. Local, state, and federal health departments play important roles in identifying and controlling outbreaks and in establishing public health policy.

Hand Hygiene

The most important tool in any IPC program is good hand hygiene. Although much attention is directed at the type of cleansing agent employed, the most important aspect of handwashing is *placing the hands under water and using friction with or without soap.* Studies show that a 15-second scrub removes the majority of transient, surface flora but does not alter deeper resident flora. A variety of hand gels and rubs can be used in place of handwashing. **Waterless hand hygiene** products increase hand hygiene compliance and save time; these agents are the preferred agents for routine hand hygiene when hands are not visibly soiled. These products are effective in killing most microbes but do not remove dirt or debris. However, they are ineffective against nonenveloped agents such as norovirus and *C. difficile* spores, requiring the use of other cleansing products during hospital *C. difficile* outbreaks. Hands should be cleaned before and after every patient encounter. In hospital handwashing compliance studies, physicians are usually the least compliant group studied, and compliance programs must pay special attention to this group of caregivers.

Standard Precautions

Standard precautions, formerly known as u*niversal precautions* , are intended to protect healthcare workers from pathogens and should be used whenever there is direct contact with patients. Infected patients are often contagious before symptoms of disease develop. Asymptomatic infected patients are quite capable of transmitting infectious agents. Standard precautions involve the use of barriers—gloves, gowns, masks, goggles, and face shields—as needed, to prevent transmission of microbes associated with contact with blood and body fluids (Table 198.1).

Table 198.1

Recommendations for Application of Standard Precautions for Care of All Patients in All Healthcare Settings

COMPONENT	RECOMMENDATIONS
Hand hygiene	Before and after each patient contact, regardless of whether gloves are used. After contact with blood, body fluids, secretions, excretions, or contaminated items; immediately after removing gloves; before and after entering patient rooms. Alcohol-containing antiseptic hand rubs preferred except when hands are visibly soiled with blood or other proteinaceous material or if exposure to spores (e.g., *Clostridium difficile* , *Bacillus anthracis*) or nonenveloped viruses (norovirus) is likely to have occurred; in these cases, soap and water is required.
PERSONAL PROTECTIVE EQUIPMENT (PPE)	
Gloves	For touching blood, body fluids, secretions, excretions, or contaminated items; for touching mucous membranes and nonintact skin. Employ hand hygiene before and after glove use.
Gown	During procedures and patient-care activities when contact of clothing or exposed skin with blood, body fluids, secretions, or excretions is anticipated.
Mask, eye protection (goggles), face shield	During procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, or secretions, such as suctioning and endotracheal intubation, to protect healthcare personnel. For patient protection, use of a mask by the person inserting an epidural anesthesia needle or performing myelograms when prolonged exposure of the puncture site is likely to occur.
Soiled patient-care equipment	Handle in a manner that prevents transfer of microorganisms to others and to the environment. Wear gloves if equipment is visibly contaminated. Perform hand hygiene.

ENVIRONMENT	
Environmental control	Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient-care areas.
Textiles (linens) and laundry	Handle in a manner that prevents transfer of microorganisms to others and the environment.
PATIENT CARE	
Injection practices (use of needles and other sharps)	Do not recap, bend, break, or manipulate used needles; if recapping is required, use a one-handed scoop technique only. Use needle-free safety devices when available, placing used sharps in puncture-resistant container. Use a sterile, single-use, disposable needle and syringe for each injection. Single-dose medication vials preferred when medications may be administered to more than one patient.
Patient resuscitation	Use mouthpiece, resuscitation bag, or other ventilation devices to prevent contact with mouth and oral secretions.
Patient placement	Prioritize for single-patient room if patient is at increased risk for transmission, is likely to contaminate the environment, is unable to maintain appropriate hygiene, or is at increased risk for acquiring infection or developing adverse outcome following infection.
Respiratory hygiene/cough etiquette (source containment of infectious respiratory secretions in symptomatic patients) beginning at initial point of encounter, such as triage or reception areas in emergency department or physician office	Instruct symptomatic persons to cover nose/mouth when sneezing or coughing; use tissues with disposal in no-touch receptacles. Employ hand hygiene after soiling of hands with respiratory secretions. Wear surgical mask if tolerated or maintain spatial separation (>3 ft if possible).

Adapted from Kimberlin DW, Brady MT, Jackson MA, et al, editors: *Red Book 2018–2021: Report of the Committee on Infectious Diseases,* ed 31, Elk Grove Village, IL, 2018, American Academy of Pediatrics, pp 148–150.

Isolation

Isolation of patients infected with transmissible pathogens decreases the risk of nosocomial transmission of organisms to staff and other patients. The specific type of isolation depends on the infecting agent and potential route of transmission. **Transmission by contact** is the most common mode of pathogen transmission and involves direct contact with the patient or contact with a contaminated intermediate object. **Contact isolation** requires the use of gown and gloves when in contact with the patient or immediate surroundings. **Transmission by droplets** involves the propulsion of infectious large particles over a short distance (<3 ft), with deposition on another's mucous membranes or skin. **Droplet isolation** requires the use of gloves and gowns, as well as masks and eye guards when closer than 3 ft to the patient. **Airborne transmission** occurs by dissemination of evaporated droplet nuclei (≤5 μm) or dust particles carrying an infectious agent. **Airborne infection isolation** (**AII**) requires the use of masks and negative pressure air-handling systems to prevent spread of the infectious agent. In the case of active pulmonary tuberculosis in older children and adults, severe acute respiratory syndrome (SARS), or avian influenza, the use of special high-density masks (N-95) or self-contained breathing systems such as powered air-purifying respirators (**PAPRs**) or controlled air-purifying respirators (**CAPRs**) are recommended. Positive pressure HEPA-filtered air-handling systems are used in some institutions for housing seriously immunocompromised patients and negative pressure systems for the care of patients with highly contagious respiratory infections such as Ebola virus.

Standard precautions are indicated for all patients and are appropriate for use in the clinic as well as the hospital. Additionally, for hospitalized patients, further **transmission-based precautions** are indicated for certain infections (Table 198.2). For contact and droplet isolation, single rooms are preferred but not required. Cohorting children infected with the same pathogen is acceptable, but the etiologic diagnosis should be confirmed by laboratory methods before exposing infected children to one another. Transmission-based isolation precautions should be continued for as long as a patient is considered contagious.

Table 198.2

Clinical Syndromes and Conditions Warranting Empirical Transmission-Based Precautions in Addition to Standard Precautions Pending Confirmation of Diagnosis[*]

CLINICAL SYNDROME OR CONDITION [†]	POTENTIAL PATHOGENS [‡]	EMPIRICAL PRECAUTIONS (ALWAYS INCLUDES STANDARD PRECAUTIONS)
DIARRHEA		
Acute diarrhea with a likely infectious cause in an incontinent or diapered patient	Enteric pathogens [§]	Contact precautions (pediatrics and adult)
Meningitis	*Neisseria meningitidis*	Droplet precautions for 1st 24 hr of antimicrobial therapy; mask and face protection for intubation
	Enteroviruses	Contact precautions for infants and children
	Mycobacterium tuberculosis	Airborne precautions if pulmonary infiltrate Airborne precautions plus contact

		precautions if potentially infectious draining body fluid present
RASH OR EXANTHEMS, GENERALIZED, ETIOLOGY UNKNOWN		
Petechial/ecchymotic with fever (general)	*N. meningitidis*	Droplet precautions for 1st 24 hr of antimicrobial therapy
If positive history of travel to an area with an ongoing outbreak of VHF in the 10 days before onset of fever	Ebola, Lassa, and Marburg viruses	Droplet precautions plus contact precautions, with face/eye protection, emphasizing safety sharps and barrier precautions when blood exposure likely Use N95 or higher respiratory protection when aerosol-generating procedure performed.
Vesicular	Varicella-zoster, herpes simplex, variola (smallpox), and vaccinia viruses	Airborne precautions plus contact precautions
	Vaccinia virus	Contact precautions only if herpes simplex, localized zoster in an immunocompetent host, or vaccinia viruses likely
Maculopapular with cough, coryza, and fever	Rubeola (measles) virus	Airborne precautions
RESPIRATORY INFECTIONS		
Cough/fever/upper lobe pulmonary infiltrate in HIV-negative patient or patient at low risk for HIV infection	*M. tuberculosis* , respiratory viruses, *Streptococcus pneumoniae, Staphylococcus aureus* (MSSA or MRSA)	Airborne precautions plus contact precautions
Cough/fever/pulmonary infiltrate in any lung location in HIV-infected patient or patient at high risk for HIV infection	*M. tuberculosis* , respiratory viruses, *S. pneumoniae, S. aureus* (MSSA or MRSA)	Airborne precautions plus contact precautions Use eye/face protection if aerosol-generating procedure performed or contact with respiratory secretions anticipated. If tuberculosis is unlikely and there are no AIIRs or respirators available, use droplet precautions instead of airborne precautions. Tuberculosis is more likely in HIV-infected than in HIV-negative patients.
Cough/fever/pulmonary infiltrate in any lung location in patient with history of recent travel (10-21 days) to countries with active outbreaks of SARS, avian influenza	*M. tuberculosis* , severe acute respiratory syndrome virus (SARS-CoV), avian influenza	Airborne precautions plus contact precautions plus eye protection If SARS and tuberculosis unlikely, use droplet precautions instead of airborne precautions.
Respiratory infections, particularly bronchiolitis and pneumonia, in infants and young children	Respiratory syncytial virus, parainfluenza virus, adenovirus, influenza virus, human metapneumovirus	Contact plus droplet precautions Droplet precautions may be discontinued when adenovirus and influenza have been ruled out.
SKIN OR WOUND INFECTION		
Abscess or draining wound that cannot be covered	*S. aureus* (MSSA or MRSA), group A	Contact precautions Add droplet precautions for 1st 24

	streptococcus	hr of appropriate antimicrobial therapy if invasive group A streptococcal disease is suspected.

[*] Infection control professionals should modify or adapt this table according to local conditions. To ensure that appropriate empirical precautions are always implemented, hospitals must have systems in place to evaluate patients routinely according to these criteria as part of their preadmission and admission care.

[†] Patients with the syndromes or conditions listed may present with atypical signs or symptoms (e.g., neonates and adults with pertussis may not have paroxysmal or severe cough). The clinician's index of suspicion should be guided by the prevalence of specific conditions in the community as well as clinical judgment.

[‡] The organisms listed are not intended to represent the complete, or even most likely, diagnoses, but rather possible etiologic agents that require additional precautions beyond standard precautions, until they can be ruled out.

[§] These pathogens include enterohemorrhagic *Escherichia coli* O157:H7, *Shigella* spp., hepatitis A virus, norovirus, rotavirus, *Clostridium difficile* .

AIIRs, Airborne infection isolation rooms; HIV, human immunodeficiency virus; MRSA, methicillin-resistant *S. aureus* ; MSSA, methicillin-susceptible *S. aureus* ; VHF, viral hemorrhagic fever.

Adapted from Centers for Disease Control and Preventionwebsite,http://www.cdc.gov/hicpac/2007ip/2007ip_table2.html .

The use of isolation techniques in outpatient settings has not been well studied. Professional offices should establish procedures to ensure that proper cleaning, disinfection, and sterilization methods are employed. Many practices and clinics provide separate waiting areas for sick and well children. **Triage** of patients is essential to ensure that contagious children or adults are not present in waiting areas. Outbreaks of measles and varicella in patients within the waiting area have been reported where the air exhaust from examination rooms enters the waiting area. Cleaning the clinic environment is important, especially in high-touch areas. Toys and items that are shared among patients should be cleaned between uses; if feasible, disposable toys should be used. Toys contaminated with blood or body fluids should be autoclaved or discarded.

Additional Measures

Other preventive measures include aseptic technique, catheter care, prudent use of antibiotics through use of an effective **antibiotic stewardship program** , isolation of contagious patients, periodic cleansing of the environment, disinfection and sterilization of medical equipment, reporting of infections, safe handling of needles and other sharp instruments, and establishment of employee health services. Sterile technique must be used for all invasive procedures, including catheter placement and manipulation. The use of barrier techniques at the time of IV catheter placement has reduced the rate of catheter-related bloodstream infections by half. Appropriate catheter use also includes limiting the duration and number of catheters employed, scrubbing catheter hubs with every access, and removing catheters as soon as they become unnecessary.

Surgical Prophylaxis

Surgical antibiotic prophylaxis should be employed when there is a high risk of postoperative infection or when the consequences of such infection would be catastrophic. The choice of prophylactic antibiotic depends on the surgical site and type of surgery. A useful classification of surgical procedures based on infectious risk recognizes 4 preoperative wound categories: clean wounds, clean-contaminated wounds, contaminated wounds, and dirty and infected wounds (Table 198.3). The American College of Surgeons, Surgical Infection Society, and American Academy of Pediatrics have made clinical recommendations regarding antibiotic prophylaxis.

Table 198.3

Common Surgical Procedures for Which Perioperative Prophylactic Antibiotics Are Recommended

SURGICAL PROCEDURE	LIKELY PATHOGENS	RECOMMENDED DRUGS	NON β-LACTAM ALTERNATIVE
CLEAN WOUNDS			
Cardiac surgery (e.g., open heart surgery) Vascular surgery Neurosurgery Orthopedic surgery (e.g., joint replacement)	Skin flora, enteric gram-negative bacilli	Cefazolin or cefuroxime	Clindamycin or vancomycin
CLEAN-CONTAMINATED WOUNDS			
Head and neck surgery involving oral cavity or pharynx	Skin flora, oral anaerobes, oral streptococci	Cefazolin + metronidazole, ampicillin-sulbactam	Clindamycin
Gastrointestinal and genitourinary surgery	Enteric gram-negative bacilli, anaerobes, gram-positive cocci	Cefazolin + metronidazole, cefotetan or piperacillin-sulbactam If colon is involved, consider	Clindamycin

		bacterial reduction with oral neomycin and erythromycin.	
CONTAMINATED WOUNDS			
Traumatic wounds (e.g., compound fracture)	Skin flora	Cefazolin	Clindamycin or vancomycin
DIRTY WOUNDS			
Appendectomy, penetrating abdominal wounds, colorectal surgery	Enteric gram-negative bacilli, anaerobes, gram-positive cocci	Cefazolin + metronidazole, cefoxitin, cefotetan or ampicillin-sulbactam	Clindamycin + aminoglycoside

Adapted from Bratzler DW, Dellinger PD, Olsen KM, et al: Clinical practice guidelines from antimicrobial prophylaxis in surgery, *Am J Health Syst Pharm* 70:195–283, 2013.

Clean wounds are uninfected operative wounds where no inflammation is noted at the operative site and respiratory, alimentary, and genitourinary tracts and the oropharynx are not entered. Such wounds are often the result of nonemergent procedures with primary closure or drained by a closed system. Operative incisional wounds after nonpenetrating trauma are included in this category. For clean wounds, prophylactic antimicrobial therapy is *not* recommended except in patients at high risk for infection and in circumstances where the consequences of infection would be potentially life threatening, as with implantation of a foreign body such as a prosthetic heart valve or cerebrospinal fluid shunt, open heart surgery for repair of structural defects, and surgery in immunocompromised patients or small infants.

Clean-contaminated wounds are operative wounds in which the respiratory, alimentary, or genitourinary tract is entered under controlled conditions and that do not have unusual bacterial contamination preoperatively. These wounds occur in operations that involve the biliary tract, appendix, vagina, and oropharynx where no evidence of infection or major break in technique is encountered, as well as in urgent or emergency surgery in an otherwise clean procedure. In procedures involving clean-contaminated wounds, the risk for bacterial contamination and infection is variable. Recommendations for pediatric patients derived from adult data suggest that antibiotic prophylaxis be provided for procedures in children with obstructive jaundice, certain alimentary tract procedures, and urinary tract surgery or instrumentation in the presence of bacteriuria or obstructive uropathy.

Contaminated wounds include open, fresh, and accidental wounds; major breaks in otherwise sterile operative technique; gross spillage from the GI tract; penetrating trauma occurring <4 hr earlier; and incisions where acute nonpurulent inflammation is encountered.

Dirty and infected wounds include penetrating traumatic wounds >4 hr before surgery, wounds with retained devitalized tissue, and those in which clinical infection is apparent or the viscera have been perforated. In contaminated and dirty or infected wound procedures, antimicrobial therapy is indicated and may need to be continued for several days. In these patients, antibiotic therapy is considered therapeutic rather than truly prophylactic.

Prophylactic antibiotics should be administered, preferably intravenously, within 1 hr before skin incision, with the intent of having peak serum concentrations of the drug present in blood and tissues at the time of incision. Adequate plasma and tissue concentration of the antibiotic should be maintained until the incision is closed. Intraoperative antibiotic dosing may be necessary if surgery is prolonged or the antibiotic being employed has a short intravascular half-life. Continuation of prophylactic therapy after the procedure is not recommended. In cases of contaminated surgical sites, antibiotics are continued as therapy for infection at the site. For patients undergoing colonic procedures, additional oral antibiotics may be employed and should also be given the day before surgery.

The selection of antibiotic regimen for prophylaxis is based on the procedure, the likely contaminating organisms, and antibiotic. Because of the variety of antibiotics available, many regimens are acceptable (see Table 198.3).

Employee Health

Employee health is important in hospital-based infection control because employees are at risk for acquiring infection from patients, and infected employees pose a potential risk to patients. This risk is minimized by use of standard precautions and hand hygiene before and after all patient contacts. Within hospitals, employee health services or departments of occupational safety and health manage employee health issues. New employees should be screened for the presence of infectious diseases. Their immunization history should be noted and necessary immunizations offered.

All healthcare workers (medical and nonmedical, paid or volunteer, full-time or part-time, student or nonstudent, with or without patient care responsibilities) who work within facilities providing healthcare, inpatient or outpatient, should be immune to **measles, rubella, and varicella** . All workers who are at risk of exposure to blood or body fluids should be immunized against **hepatitis B** . In pediatric institutions, employees with patient contact should be urged to receive the **pertussis booster** vaccine. Annual **influenza** immunization is strongly recommended for all healthcare workers, and institutions are being ranked publically regarding employee immunization rates as a measure of quality of care. Many healthcare facilities have now made annual influenza vaccination mandatory for employees unless there are legitimate medical reasons for nonimmunization. Such a program reduces staff illness and absenteeism and decreases HAI. Immunizations should be encouraged and provided free of charge whenever possible to enhance compliance. All healthcare workers with duties involving face-to-face contact with patients with suspected or confirmed **tuberculosis** (including transport staff) should be included in a tuberculosis screening program at the time of hiring and may require periodic retesting if the workplace is determined to be a high-prevalence environment for tuberculosis.

Each medical office and hospital must comply with the rules developed by the U.S. Occupational Safety and Health Administration (OSHA). Each office and hospital should have written policies about exclusion of infected and ill staff from direct patient care. Staff should be encouraged not to report for work if they are ill. Regular educational sessions should be performed to ensure that staff are aware of IPC methods and that they adhere to such policies.

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CHAPTER 199

Childcare and Communicable Diseases

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More than 20 million children <5 yr old attend a childcare facility. These facilities can include part-day or full-day programs at nursery schools or preschools and full-day programs based in either a licensed childcare center or another person's home. Regardless of the age at entry, children entering daycare are more prone to infections, largely from the exposure to greater numbers of children.

Childcare facilities can be classified on the basis of number of children enrolled, ages of attendees, health status of the children enrolled, and type of setting. As defined in the United States, **childcare facilities** consist of childcare centers, small and large family childcare homes, and facilities for ill children or for children with special needs. Centers are licensed and regulated by state governments and care for a larger number of children than are typically cared for in family homes. In contrast, **family childcare homes** are designated as small (1-6 children) or large (7-12 children), may be full-day or part-day and may be designed for either daily or sporadic attendance. Family childcare homes generally are not licensed or registered, depending on state requirements.

Although the majority of children who attend childcare facilities are cared for in family childcare homes, most studies of infectious diseases in infants and toddlers have been conducted in childcare centers. Almost any organism has the potential to be spread and to cause disease in a childcare setting. Epidemiologic studies have established that children in childcare facilities are 2-18 times more likely to acquire a variety of infectious diseases than children not enrolled in childcare (Table 199.1). Children who attend childcare facilities are more likely to receive more courses of antimicrobial agents for longer periods and to acquire antibiotic-resistant organisms. Transmission of infectious agents in group care depends on the age and immune status of the children, season, hygiene practices, crowding, and environmental characteristics of the facilities. The pathogen characteristics, including infectivity, survivability in the environment, and virulence, also influence transmission in childcare settings. Rates of infection, duration of illness, and risk for hospitalization tend to decrease among children in childcare facilities after the 1st 6 mo of attendance and decline to levels observed among homebound children after 3 yr of age. Adult caregivers are also at increased risk for acquiring and transmitting infectious diseases, particularly in the 1st yr of working in these settings.

Table 199.1

Infectious Diseases in the Childcare Setting

DISEASE	**INCREASED INCIDENCE WITH CHILDCARE**
Respiratory Tract Infections	
Otitis media	Yes
Sinusitis	Probably
Pharyngitis	Probably
Pneumonia	Yes
Gastrointestinal Tract Infections	
Diarrhea (rotavirus, calicivirus, astrovirus, enteric adenovirus, *Giardia lamblia, Cryptosporidium, Shigella, Escherichia coli* O157:H7, and *Clostridium difficile*)	Yes
Hepatitis A	Yes
Skin Diseases	
Impetigo	Probably
Scabies	Probably
Pediculosis	Probably
Tinea (ringworm)	Probably
Invasive Bacteria Infections	
Haemophilus influenzae type b	No*
Neisseria meningitidis	Probably
Streptococcus pneumoniae	Yes
Aseptic Meningitis	
Enteroviruses	Probably
Herpesvirus Infections	
Cytomegalovirus	Yes
Varicella-zoster virus	Yes
Herpes simplex virus	Probably
Bloodborne Infections	
Hepatitis B	Few case reports
HIV	No cases reported
Hepatitis C	No cases reported
Vaccine-Preventable Diseases	
Measles, mumps, rubella, diphtheria, pertussis, tetanus	Not established

Polio	No
H. influenzae type b	No*
Varicella	Yes
Rotavirus	Yes

* Not in the post–vaccine era; *yes* in the pre–vaccine era.

Epidemiology

Respiratory tract infections and **gastroenteritis** are the most common diseases associated with childcare. These infections occur in children and their household contacts, as well as childcare workers, and can spread into the community. The severity of illness caused by a given respiratory and enteric pathogen depends on the person's underlying health status, the inoculum, and prior exposures to the pathogen, either by infection or immunization. Hepatitis B virus (HBV) transmission has been reported rarely in a childcare setting. Transmission of hepatitis C virus (HCV), hepatitis D virus (HDV), and HIV has not been reported in a childcare setting. Some organisms, such as hepatitis A virus (HAV), can cause subclinical disease in young children and produce overt and sometimes serious disease in older children and adults. Other diseases, such as otitis media and varicella, usually affect children rather than adults. Several agents, such as cytomegalovirus and parvovirus B19, can have serious consequences for the fetuses of pregnant women or for immunocompromised persons. Because many childcare workers are women of childbearing age, they should be encouraged to discuss possible risks with their physician if they become pregnant. Both infections and infestations of the skin and hair may be acquired through contact with contaminated linens or through close personal contact, which is inevitable in childcare settings.

Respiratory Tract Infections

Respiratory tract infections account for the majority of childcare-related illnesses. Children <2 yr old who attend childcare centers have more upper and lower respiratory tract infections than do age-matched children not in childcare. The organisms responsible for these illnesses are similar to those that circulate in the community and include respiratory syncytial virus (RSV), parainfluenza viruses, influenza viruses, human metapneumoviruses, adenoviruses, rhinoviruses, coronaviruses, parvovirus B19, and *Streptococcus pneumoniae.*

Upper respiratory tract infections, including **otitis media** , are among the most common manifestation of these infections. The risk for developing otitis media is 2-3 times greater among children who attend childcare centers than among children cared for at home. Most prescriptions for antibiotics for children <3 yr old in childcare are to treat otitis media. These children also are at increased risk for recurrent otitis media, further increasing use of antimicrobial agents in this population. Studies have demonstrated reductions in both otitis media and antibiotic use subsequent to pneumococcal vaccination implementation. Pharyngeal carriage of group A streptococcus occurs earlier among children in childcare, although outbreaks of clinical infections with this organism are uncommon. **Influenza** vaccination of younger infants reduces influenza infection and secondary sequelae in both the children and the adults who care for them, in their home and in childcare settings. Following adoption of the acellular pertussis vaccine, increases in clusters and outbreaks of infection caused by *Bordetella pertussis* have led to the recognition of less durable immunity, with older children and adults serving as reservoirs of infection.

Transmission of these organisms typically occurs through either direct or indirect contact with the respiratory droplets of an infected child. In childcare settings, contamination of surfaces occurs frequently as children mouth toys, drool, and cough or sneeze. Additionally, some respiratory pathogens are spread through large droplets that typically can travel 3-6 ft. However, intimate contact between children is a routine part of the play and care of young children, thus facilitating transmission. The most common surfaces from which airborne droplets can be spread are the hands, so the most efficient form of infection control in the childcare setting is good handwashing.

Gastrointestinal Tract Infections

Acute infectious **diarrhea** is 2-3 times more common among children in childcare than among children cared for in their homes. Outbreaks of diarrhea, which occur frequently in childcare centers, are usually caused by enteric viruses such as caliciviruses, enteric adenoviruses, and astroviruses, or by enteric parasites such as *Giardia lamblia* or *Cryptosporidium* . A dramatic and sustained decline in the burden of rotavirus infection has been demonstrated since introduction of the rotavirus vaccination program in 2006, and this trend is likely reflected in the daycare population as well. Bacterial **enteropathogens** such as *Shigella* and *Escherichia coli* O157:H7, and less often *Campylobacter,* *Clostridium difficile,* and *Bacillus cereus,* also have caused outbreaks of diarrhea in childcare settings. *Salmonella* rarely is associated with outbreaks of diarrhea in childcare settings, because person-to-person spread of this organism is uncommon.

Outbreaks of **hepatitis A** in children enrolled in childcare facilities have resulted in community-wide outbreaks. Hepatitis A is typically mild or asymptomatic in young children and often is identified only after symptomatic illness becomes apparent among either older children or adult contacts of children in childcare. Enteropathogens and HAV are transmitted in childcare facilities by the fecal-oral route and can also be transmitted through contaminated food or water. Children in diapers constitute a high risk for the spread of gastrointestinal infections through the fecal-oral route. As such, enteric illness and HAV infection are more common in centers that care for children who are not toilet-trained and where proper hygienic practices are not followed. The most common enteropathogens, such as norovirus and *G. lamblia,* are characterized by low infective doses and high rates of asymptomatic excretion among children in childcare, characteristics that facilitate transmission and outbreaks.

Skin Diseases

The most commonly recognized skin infections or infestations in children in childcare are impetigo caused by *S. aureus* or group A streptococcus, pediculosis, scabies, tinea capitis and tinea corporis, and molluscum. Many of these diseases are spread by contact with infected linens, clothing, hairbrushes, and hats and through direct personal contact; they more often affect children >2 yr old. The magnitude of these infections and infestations in children in childcare is not known.

Parvovirus B19 , which causes fifth disease (erythema infectiosum), is spread through the respiratory route and has been associated with outbreaks in childcare centers. The rash of fifth disease is a systemic manifestation of parvovirus B19 infection; the child is no longer contagious once the rash is present (see Chapter 278). The greatest health hazard is for pregnant women and immunocompromised hosts, because of their respective risks for fetal loss and aplastic crisis.

Invasive Organisms

Prior to universal immunization, *Haemophilus influenzae* type b invasive disease was more common among children in childcare than children in homecare. Although the largest burden of invasive *H. influenza* infection in the pediatric population still occurs in children <5 yr old, infection is now caused primarily by nontypeable *H. influenzae* ; there have been no reported outbreaks of nontypeable or type b *H. influenzae* in >5 yr in the United States.

Data suggest that the risk for primary disease caused by *Neisseria meningitidis* is higher among children in childcare than among children in homecare. Childcare attendance is also associated with nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* and invasive pneumococcal disease, especially among children with a history of recurrent otitis media and use of antibiotics. Secondary spread of *S. pneumoniae* and *N. meningitidis* has been reported, indicating the potential for outbreaks to occur in this setting. Routine use of pneumococcal conjugate vaccine has decreased the incidence of invasive disease and reduced carriage of serotypes of *S. pneumoniae* contained in the vaccine both in the vaccinated child and in younger siblings. The universal use of conjugate meningococcal vaccine in children <2 yr old is anticipated in the near future and will alter the epidemiology of meningococcal disease in this age-group. Outbreaks of aseptic meningitis have been reported among children in childcare centers, as well as among their parents and their teachers.

Herpesviruses

As many as 70% of diapered children who become infected with **cytomegalovirus** (CMV) shed virus in urine and saliva for prolonged periods. CMV-infected children often transmit the virus to other children with whom they have contact, as well as to their care providers and their mothers, at a rate of 8–20%/yr. Transmission occurs as a result of contact with either saliva or urine. The overwhelming majority of primary infections with and reactivation of CMV in otherwise healthy children result in asymptomatic shedding of CMV; nonetheless, this shedding can pose a health risk for previously uninfected pregnant childcare providers or immunocompromised persons. A licensed CMV vaccine is not yet available, but research is ongoing, with recent trials demonstrating tolerability and immunogenicity of candidate CMV vaccines (see Chapter 282).

Varicella often is transmitted in childcare centers, but routine use of varicella vaccine has reduced this risk. Vaccinated children who become infected with varicella often have mild, atypical symptoms and signs of disease that can result in delayed recognition and spread of infection to susceptible contacts. The role of childcare facilities in the spread of **herpes simplex virus** , especially during episodes of gingivostomatitis, requires further clarification.

Bloodborne Pathogens

Because it is impossible to identify every child who might have a bloodborne infection such as hepatitis B, C, or D or HIV, it is critical that standard precautions be observed routinely to reduce the risk for transmitting these viruses and other pathogens. Transmission of hepatitis B among children in childcare has been documented in a few instances but is rare, influenced in part by implementation of universal immunization of infants with hepatitis B vaccine. Transmission of hepatitis C or D in childcare settings has not been reported.

In the past, concerns have been raised about the risk of HIV transmission in childcare settings and the acquisition of opportunistic infections by HIV-infected children who attend childcare. It is important to note that no cases of HIV transmission in out-of-home childcare have been reported. Children with HIV infection enrolled in childcare facilities should be kept up-to-date on their vaccines and monitored for exposure to infectious diseases.

Transmission of bloodborne pathogens can theoretically occur when there is contact between blood or body fluids and a mucous membrane or an open wound. Although a common concern, bloodborne pathogens are unlikely to spread by toddler **biting** in a group setting. Most bites do not break the skin, and if a bite does break the skin, the mouth of the biter does not stay on the victim long enough for blood to transfer from the victim to the biter. If there are concerns about transmission of HBV, HCV, or HIV infection, it is recommended to check the status of the biter rather than the bite victim as part of the initial evaluation process.

Antibiotic Use and Bacterial Resistance

Antibiotic resistance has become a major global problem and threatens the health of children who attend childcare facilities, because the incidence of infection by organisms resistant to frequently used antimicrobial agents has increased dramatically. It is estimated that children in childcare are 2-4 times more likely to receive an antibiotic, and that they receive longer courses of antibiotics, compared to age-matched children in homecare. This frequency of antibiotic use combined with the propensity for person-to-person transmission of pathogens in a crowded environment has resulted in an increased prevalence of antibiotic-resistant bacteria in the respiratory and intestinal tracts, including *S. pneumoniae, H. influenzae, Moraxella catarrhalis, E. coli* O157:H7, and *Shigella* spp.

Historically found primarily in the healthcare setting, methicillin-resistant *Staphylococcus aureus* (**MRSA**) is now prevalent in the community setting. Daycare attendance is cited as a risk factor for colonization with MRSA, and carriage is associated with increased risk of infection and transmission. Population-based surveillance has demonstrated a rise in both invasive and noninvasive MRSA infections in community settings over the past 2 decades. Currently, large-scale studies investigating the epidemiology of *S. aureus* in the childcare setting are limited.

Prevention

Written policies designed to prevent or to control the spread of infectious agents in a childcare center should be available and should be reviewed regularly. All programs should use a health consultant to help with development and implementation of infection prevention and control (IPC) policies (see Chapter 198). Standards for environmental and personal hygiene should include maintenance of current immunization records for both children and staff; appropriate policies for exclusion of ill children and caretakers; targeting of potentially contaminated areas for frequent cleaning; adherence to appropriate procedures for changing diapers; appropriate handling of food; management of pets; and surveillance for and reporting of communicable diseases. Staff whose primary function is preparing food should not change diapers. Appropriate and thorough **hand hygiene** is the most important factor for reducing infectious diseases in the childcare setting. Strategies for improving adherence to these standards should be implemented. Children at risk for introducing an infectious disease should not attend childcare until they are no longer contagious (Tables 199.2 and 199.3).

Table 199.2

Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
Clostridium difficile	Exclusion until stools are contained in the diaper or child is continent and stool frequency is no more than 2 stools above that child's normal frequency for the time the child is in the program. Stool consistency does not need to return to normal to be able to return to childcare. Neither test of cure nor repeat testing should be performed for asymptomatic children in whom *C. difficile* was diagnosed previously.	Symptomatic contacts should be excluded until stools are contained in the diaper or child is continent and stool frequency is no more than 2 stools above that child's normal frequency for the time the child is in the program. Testing is not required for asymptomatic contacts.
Hepatitis A virus (HAV) infection	Serologic testing to confirm HAV infection in suspected cases. Exclusion until 1 wk after onset of illness.	In facilities with diapered children, if 1 or more cases confirmed in child or staff attendees or 2 or more cases in households of staff or attendees, hepatitis A vaccine (HepA) or immune globulin intramuscular (IGIM) should be administered within 14 days of exposure to all unimmunized staff and attendees. In centers without diapered children, HepA or IGIM should be administered to unimmunized classroom contacts of index case. Asymptomatic IGIM recipients may return after receipt of IGIM.
Impetigo	No exclusion if treatment has been initiated and as long as lesions on exposed skin are covered.	No intervention unless additional lesions develop.
Measles	Exclusion until 4 days after beginning of rash and when the child is able to participate.	Immunize exposed children without evidence of immunity within 72 hr of exposure. Children who do not receive vaccine within 72 hr or who remain unimmunized after exposure should be excluded until at least 2 wk after onset of rash in the last case of measles.
Mumps	Exclusion until 5 days after onset of parotid gland swelling.	In outbreak setting, people without documentation of immunity should be immunized or excluded. Immediate readmission may occur following immunization. Unimmunized people should be excluded for 26 or more days following onset of parotitis in last case. A 2nd dose of MMR vaccine (or MMRV, if age appropriate) should be offered to all students (including those in postsecondary school) and to all healthcare personnel born in or after 1957 who have only received 1 dose of MMR vaccine. A 2nd dose of MMR also may be considered during outbreaks for preschool-age children who have received 1 MMR dose. People previously vaccinated with 2 doses of a mumps-containing vaccine who are identified by public health as at increased risk for mumps because of an outbreak should receive a 3rd dose of a mumps-containing vaccine to improve protection against mumps disease and related complications.

Pediculosis capitis (head lice) infestation	Treatment at end of program day and readmission on completion of 1st treatment. Children should not be excluded or sent home early from school because of head lice, because this infestation has low contagion within classrooms.	Household and close contacts should be examined and treated if infested. No exclusion necessary.
Pertussis	Exclusion until completion of 5 days of the recommended course of antimicrobial therapy if pertussis is suspected. Children and providers who refuse treatment should be excluded until 21 days have elapsed from cough onset.	Immunization and chemoprophylaxis should be administered as recommended for household contacts. Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy. Untreated adults should be excluded until 21 days after onset of cough.
Rubella	Exclusion for 7 days after onset of rash for postnatal infection.	During an outbreak, children without evidence of immunity should be immunized or excluded for 21 days after onset of rash of the last case in the outbreak. Pregnant contacts should be evaluated.
Infection with *Salmonella* serotypes Typhi or Paratyphi	Exclusion until 3 consecutive stool cultures obtained at least 48 hr after cessation of antimicrobial therapy are negative, stools are contained in the diaper or child is continent, and stool frequency is no more than 2 stools above that child's normal frequency for the time the child is in the program.	When *Salmonella* serotype Typhi infection is identified in a child care staff member, local or state health departments may be consulted regarding regulations for length of exclusion and testing, which may vary by jurisdiction.
Infection with nontyphoidal *Salmonella* spp., *Salmonella* of unknown serotype	Exclusion until stools are contained in the diaper or child is continent and stool frequency is no more than 2 stools above that child's normal frequency for the time the child is in the program. Stool consistency does not need to return to normal to be able to return to childcare. Negative stool culture results *not* required for nonserotype Typhi or Paratyphi *Salmonella* spp.	Symptomatic contacts should be excluded until stools are contained in the diaper or child is continent and stool frequency is no more than 2 stools above that child's normal frequency for the time the child is in the program. Stool cultures are not required for asymptomatic contacts.
Scabies	Exclusion until after treatment given.	Close contacts with prolonged skin-to-skin contact should receive prophylactic therapy. Bedding and clothing in contact with skin of infected people should be laundered.
Infection with Shiga toxin–producing *Escherichia*	Exclusion until 2 stool cultures (obtained at least 48 hr after any antimicrobial therapy, if administered, has	Meticulous hand hygiene; stool cultures should be performed for any symptomatic contacts. In outbreak situations involving virulent STEC strains, stool cultures of asymptomatic contacts may aid controlling spread. Center(s) with cases should be closed

coli (STEC), including *E. coli* O157:H7	been discontinued) are negative, and stools are contained in the diaper or child is continent, and stool frequency is no more than 2 stools above that child's normal frequency. Some state health departments have less stringent exclusion policies for children who have recovered from less virulent STEC infection.	to new admissions during STEC outbreak.
Shigellosis	Exclusion until treatment complete and one or more posttreatment stool cultures are negative for *Shigella* spp., and stools are contained in the diaper or child is continent, and stool frequency is no more than 2 stools above that child's normal frequency for the time the child is in the program. Some states may require more than 1 negative stool culture.	Meticulous hand hygiene; stool cultures should be performed for any symptomatic contacts.
Staphylococcus aureus skin infections	Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing.	Meticulous hand hygiene; cultures of contacts are not recommended.
Streptococcal pharyngitis	Exclusion until at least 12 hr after treatment has been initiated.	Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive.
Tuberculosis	Most children younger than 10 yr are not considered contagious. For those with active disease, exclusion until determined to be noninfectious by physician or health department authority. No exclusion for latent tuberculosis infection (LTBI).	Local health department personnel should be informed for contact investigation.
Varicella	Exclusion until all lesions have crusted or, in immunized people without crusts, until no new lesions appear within 24 hr period.	For people without evidence of immunity, varicella vaccine should be administered, ideally within 3 days, but up to 5 days after exposure, or when indicated, varicella-zoster immune globulin (VariZIG) should be administered up to 10 days after exposure; if VariZIG is not available, immune globulin intravenous (IGIV) should be considered as an alternative. If vaccine cannot be administered and VariZIG/IGIV is not indicated, preemptive oral acyclovir or valacyclovir can be considered.

From Kimberlin DW, Brady MT, Jackson MA, Long SS, editors: *Red Book 2018–2021: Report of the Committee on Infectious Diseases,* ed 31, Elk Grove Village, IL, 2018, American Academy of Pediatrics (Table 2.3 , pp 130–135).

Table 199.3

General Recommendations for Exclusion of Children in Out-of-Home Childcare

SYMPTOM(S)	MANAGEMENT
Illness preventing participation in activities, as determined by childcare staff.	Exclusion until illness resolves and able to participate in activities.
Illness that requires more care than staff can provide without compromising health and safety of others.	Exclusion or placement in care environment where appropriate care can be provided without compromising care of others.
Severe illness suggested by fever with behavior changes, lethargy, irritability, persistent crying, difficulty breathing, or progressive rash.	Medical evaluation and exclusion until symptoms have resolved.
Persistent abdominal pain (≥2 hr) or intermittent abdominal pain associated with fever, dehydration, or other systemic signs and symptoms.	Medical evaluation and exclusion until symptoms have resolved.
Vomiting ≥2 times in preceding 24 hr.	Exclusion until symptoms have resolved, unless vomiting is determined to be caused by a noncommunicable condition and child is able to remain hydrated and participate in activities.
Diarrhea if stool not contained in diaper or if fecal accidents occur in a child who is normally continent; if stool frequency ≥2 above normal for child or stools contain blood or mucus.	Medical evaluation for stools with blood or mucus; exclusion until stools are contained in the diaper or when toilet-trained children no longer have accidents using the toilet and when stool frequency becomes <2 stools above child's normal frequency/24 hr.
Oral lesions	Exclusion if unable to contain drool, or if unable to participate because of other symptoms, or until child or staff member is considered to be noninfectious (lesions smaller or resolved).
Skin lesions	Exclusion if lesions are weeping and cannot be covered with a waterproof dressing.

From Kimberlin DW, Brady MT, Jackson MA, Long SS, editors: *Red Book 2018–2021: Report of the Committee on Infectious Diseases* , ed 31, Elk Grove Village, IL, 2018, American Academy of Pediatrics (Table 2.2, p 129).

Routine vaccination has had a proven significant beneficial effect on the health of children in childcare settings. In the United States, there are 16 diseases and organisms for which all children should be immunized unless there are contraindications: diphtheria, pertussis, tetanus, measles, mumps, rubella, polio, hepatitides A and B, varicella, *H. influenzae* type b, *S. pneumoniae*, rotavirus, *N. meningitidis*, influenza, and human papillomavirus (see Chapter 197). Rates of immunization among children in licensed childcare facilities are high, in part because of laws in almost all states that require age-appropriate immunizations of children who attend licensed childcare programs. Vaccines against influenza, *H. influenzae* type b, hepatitis B, rotavirus, varicella, *S. pneumoniae*, and hepatitis A are of particular benefit to children in childcare centers.

Childcare providers should receive all immunizations that are recommended routinely for adults, including Tdap (tetanus and diphtheria toxoids and acellular pertussis) booster, and have a preemployment health evaluation, with a tuberculin skin test or interferon-γ release blood assay. Local public health authorities should be notified of cases of reportable communicable disease that occur in children or providers in childcare settings.

Standards

Every state has specific standards for licensing and reviewing childcare centers and family childcare homes. The American Academy of Pediatrics, American Public Health Association, and National Resource Center jointly publish comprehensive health and safety performance standards that can be used by pediatricians and other healthcare professionals to guide decisions about management of infectious diseases in childcare facilities (available at http://nrckids.org/CFOC). Additionally, the **National Association for the Education of Young Children (NAEYC)** , a professional organization supporting early childhood education efforts and volunteer accreditation, is gaining recognition as a resource for health and safety standards for childcare facilities (http://www.naeyc.org/). Specific standards set by all states can be reviewed at the U.S. Department of Health and Human Services' **National Center on Early Childhood Quality Assurance** website (https://childcareta.acf.hhs.gov/licensing).

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CHAPTER 200

Health Advice for Children Traveling Internationally

John C. Christenson, Chandy C. John

Children are traveling internationally with increasing frequency and to more exotic destinations that pose unique injury and disease risks. Compared to adults, children are *less* likely to receive pretravel advice and *more* likely to be seen by a medical provider or be hospitalized on return for a travel-related illness. Primary care providers are confronted with the challenge of trying to ensure safe, healthy travel for their patient, whether travel is occurring for purposes of tourism, study abroad, visiting friends and relatives, or volunteerism. Whenever possible, health professionals are encouraged to consult with **travel medicine specialists** , especially when uncertain about pretravel advice, unique travel medicine vaccines (e.g., yellow fever, Japanese encephalitis, typhoid, rabies), and recommendations for malaria medications.

Travel medicine is a unique specialty, and experienced travel medicine practitioners provide specialized guidance on the infectious and noninfectious risks based on age, itinerary, duration, season, purpose of travel, and underlying traveler characteristics (health and vaccination status). A **pretravel consultation** includes the essential elements of (1) safety and preventive counseling against injuries and diseases; (2) routine, recommended, and required vaccinations, based on individual risk assessment; (3) counseling and medications for self-treatment of traveler's diarrhea; and (4) when indicated by itinerary, malaria chemoprophylaxis.

In the United States, recommendations and vaccine requirements for travel to different countries are provided by the Centers for Disease Control and Prevention (CDC) and are available online at https://wwwnc.cdc.gov/travel/page/yellowbook-home . Some travel vaccines and medications may not be recommended based on specifics of travel itinerary, trip duration, or patient characteristics. Alternatively, some vaccinations are not approved for younger children because of lack of data or limited immunologic response but may still confer potential benefit to the young traveler with off-label vaccine administration. In both scenarios, consultation or referral to a knowledgeable travel medicine practitioner is encouraged, especially if uncertainty exists regarding pretravel recommendations.

The Pediatric Travel Medicine Consultation

Parents of traveling children should seek medical consultation at least one month before departure to review the travel itinerary, obtain safety and preventive counseling, ensure adequate vaccinations (routine, recommended, and required), receive necessary medications for chronic health conditions, and obtain important medications for self-treatment of traveler's diarrhea and, when indicated, malaria chemoprophylaxis with counseling. Preparing a child to travel internationally should begin with an emphasis on the positive aspects of the upcoming trip rather than solely focusing on travel risks and diseases. Subsequent advice, vaccinations, and medications should be emphasized as important measures, with the provider goal of keeping the child healthy during travel rather than to discourage traveling.

Pediatric Travelers Visiting Friends and Relatives

Compared to most children traveling internationally, the **pediatric visiting-friends-and-relatives (VFR) traveler** is the most vulnerable population uniquely at risk for travel-related illnesses. VFR travelers may include immigrants, refugees, migrants, students, or displaced persons who are traveling back to their country of origin for purposes of visiting friends and relatives. Pediatric VFR travelers are typically children accompanying their parents or family members back to their ancestral country, where relational, social, and cultural connections remain. Compared to tourist travelers, VFR travelers are more likely to travel for longer durations, visit more remote destinations, travel by higher-risk local transportation modes, experience closer contact with the local population, and utilize fewer insect, food, and water precautions. Adult and pediatric VFR travelers are also less likely to perceive a risk of travel-related illnesses, seek pretravel advice, receive travel immunizations, or use effective malaria prophylaxis on arrival in the destination country. VFR travel comprises 50–84% of imported malaria in U.S. children (i.e., malaria acquired outside the United States), and pediatric VFR travelers are reported to be 4 times more likely than tourist travelers to acquire malaria. Among all travelers, unvaccinated pediatric VFR travelers remain at higher risk for contracting hepatitis A and having symptomatic illness. Several studies suggest that VFR travelers are at disproportionate risk of acquiring typhoid fever and possibly tuberculosis. Providers should inquire if their foreign-born patients will be traveling internationally and seek opportunities to encourage pretravel consultation for VFR travelers.

Safety and Preventive Counseling Topics

Health and Evacuation Insurance, Underlying Health Conditions, and Medications

Parents should be made aware that their medical insurance policy might not provide coverage for hospitalizations or medical emergencies in foreign countries and is unlikely to cover the high cost of an emergency medical evacuation. Supplemental **travel medical insurance** and **evacuation insurance** may be purchased and are especially recommended for prolonged travel itineraries, for remote destinations, and for children with higher-risk preexistent health conditions going to countries where inpatient care at a level comparable to the traveler's home country may not be available. A list of medical and evacuation insurance providers can be found at the U.S. Department of State International Travel advisory website (https://travel.state.gov/content/travel/en/international-travel/emergencies.html).

Parents of children with medical conditions should take with them a brief medical summary and a sufficient supply of prescription medications for their children, with bottles that are clearly identified by prescription labels. For children requiring care by specialists, an international directory for that specialty can be consulted. A directory of physicians worldwide who speak English and who have met certain qualifications is available from the **International Association for Medical Assistance to Travelers** (https://www.iamat.org/). If medical care is needed urgently when abroad, sources of information include the

U.S. embassy or consulate, hotel managers, travel agents catering to foreign tourists, and missionary hospitals.

A travel health kit consisting of prescription medications and nonprescription items, such as acetaminophen, an antihistamine, oral rehydration solution packets, antibiotic ointment, bandages, insect repellent (DEET or picaridin), and sunscreen, is highly recommended for all children. Children with persistent asthma should have bronchodilators and oral corticosteroids prescribed for treatment of any acute asthma exacerbations encountered during overseas travel. Children with a history of angioedema, anaphylaxis, or severe allergies to food or insects should have an epinephrine autoinjector (EpiPen) and antihistamines available for use during travel.

Parents and family members should be aware of the prevalence of counterfeit medication and lack of quality control of medications in many areas of the world, particularly in low- and middle-income countries. Critical medications, including insulin and newly prescribed antimalarials, should be purchased prior to international travel and packed in original prescription containers.

Safety and Injury Prevention

Motor vehicle accidents are a leading cause of traumatic injuries to, hospitalizations of, and deaths of pediatric and adult travelers. Differences in traffic patterns should be emphasized to children, and the use of safety belts should be reinforced. When possible, child safety seats should be taken on the trip. Parents should also be aware of additional risks for small children that may exist overseas, such as open balconies, windows without screens or bars, exposed wires and electrical outlets, paint chips, pest and rodent poison, and stray animals. **Water-related activities** also are associated with significant injuries in pediatric travelers, and pools and oceanfronts are often unsupervised and without lifeguards at overseas destinations.

Animal Contact

Among travelers, attacks from domestic or stray animals are much more likely to occur than attacks from wild animals. Wounds from animal bites present a risk for bacterial infections, tetanus, and rabies. **Dogs** are responsible for >95% of all **rabies** transmission in Asia, Africa, and Latin America. Globally, the World Health Organization (WHO) estimates that approximately 55,000 human deaths result from rabies each year, with the vast majority of cases occurring in South Asia, Southeast Asia, and Africa. Rabies transmission is reported less frequently after bites from cats and other carnivores, monkeys, and bats. Macaque monkeys native to Asia and North Africa can be found in urban centers and tourist sites and pose a risk for rabies and herpes B virus infections following bites and scratches.

Young children are more likely to be bitten and experience more severe facial wounds because of their short stature. As such, they are at higher risk for rabies exposure from dogs and other animals during travel and require greater supervision. Parents should always encourage their children to report bite injuries and to avoid petting, feeding, or handling dogs, monkeys, and stray animals. Before travel, **tetanus** vaccinations need to be current for all travelers. Children, long-term travelers, expatriates, and all individuals likely to come into contact with animals in a rabies-endemic region (primarily Africa and South and Southeast Asia) should consider **preexposure vaccination** for rabies before international travel (see Rabies later). Bite or scratch wounds should be washed thoroughly and for a prolonged time (15 min) with copious water and soap. Local wound care will substantially reduce the risk of canine and other mammalian rabies transmission. Rabies **postexposure vaccination** and rabies immunoglobulin should be considered. Antibiotics (amoxicillin-clavulanate) may need to be administered to a child to prevent secondary infections, especially for animal bites involving the hands and head/neck areas.

Routine Childhood Vaccinations Required for Pediatric Travel

Parents should allow at least 4 wk before departure for optimal administration of vaccines to their children. All children who travel should be immunized according to the routine childhood immunization schedule with all vaccines appropriate for their age. The immunization schedule can be accelerated to maximize protection for traveling children, especially for unvaccinated or incompletely vaccinated children (see Fig. 197.2 in Chapter 197). Routine and catch-up childhood vaccine schedules for healthcare professionals can be found at the CDC website (https://www.cdc.gov/vaccines/schedules/).

Live-attenuated viral vaccines should be administered concurrently or ≥4 wk apart to minimize immunologic interference. Intramuscular immunoglobulin interferes with the immune response to measles immunization and possibly to varicella immunization. If a child requires measles or varicella immunization, the vaccines should be given either 2 wk before or 3 mo after immunoglobulin administration (longer with higher doses of intravenous immunoglobulin). Immunoglobulin does not interfere with the immune response to oral typhoid, poliovirus, or yellow fever vaccines.

Vaccine products produced in eggs (yellow fever, influenza) may be associated with hypersensitivity responses, including anaphylaxis in persons with known severe **egg sensitivity** . Screening by inquiring about adverse effects when eating eggs is a reasonable way to identify those at risk for anaphylaxis from receiving influenza or yellow fever vaccines. Although measles and mumps vaccines are produced in chick embryo cell cultures, children with egg allergy are at very low risk for anaphylaxis with these vaccines.

Diphtheria-Tetanus-Pertussis

Children traveling internationally should be fully vaccinated with diphtheria and tetanus toxoids and acellular pertussis (DTaP), having completed the 4th or 5th booster dose by 4-6 yr of age. A single dose of an adolescent/adult preparation of tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine is recommended at 11-12 yr of age for those who have completed the recommended primary DTaP (or DTP) series.

Adolescents and adults should receive a single Tdap booster if >5 yr have elapsed since the last dose, since a tetanus-containing booster (Td or Tdap) may not be readily available for tetanus-prone wounds during international travel or in remote settings (adventure travel, wilderness).

Haemophilus influenzae Type b

Haemophilus influenzae type b (Hib) remains a leading cause of meningitis in children 6 mo to 3 yr of age in many low- and middle-income countries. Before they travel, all unimmunized children <5 yr old should be vaccinated (see Chapter 197). A single dose of Hib vaccine should also be administered to unvaccinated or partially vaccinated children ≥5 yr old if they have anatomic or functional asplenia, sickle cell disease, HIV infection, leukemia, malignancy, or other immunocompromising condition. Unvaccinated children >5 yr old do not need vaccination unless they have a high-risk condition.

Hepatitis A

Hepatitis A is a routine childhood vaccine in the United States but requires special considerations in the traveling pediatric patient, and protection from hepatitis A in specific children may also involve the provision of immunoglobulin. For this reason, hepatitis A vaccination is covered later in Specialized Pediatric Travel Vaccinations.

Hepatitis B

Hepatitis B is a travel-associated infection. Hepatitis B is highly prevalent throughout much of the world, including areas of South America, sub-Saharan Africa, eastern and southeastern Asia, and most of the Pacific basin. In certain parts of the world, 8–15% of the population may be chronically infected. Disease can be transmitted by blood transfusions not screened for hepatitis B surface antigen, exposure to unsterilized needles, close contact with local children who have open skin lesions, and sexual exposure. Exposure to hepatitis B is more likely for travelers residing for prolonged periods in endemic areas. Partial protection may be provided by 1 or 2 doses, but ideally 3 doses should be given before travel. For unvaccinated adolescents, the 1st 2 doses are 4 wk apart and are followed by a 3rd dose 8 wk later (at least 16 wk after 1st dose).

All unvaccinated children and adolescents should receive the accelerated hepatitis B vaccine series prior to travel. Because 1 or 2 doses provide some protection, hepatitis B vaccination should be initiated even if the full series cannot be completed before travel.

Influenza and Avian Influenza

Influenza remains the most common vaccine-preventable disease occurring among pediatric and adult travelers. The risk for exposure to influenza during international travel varies depending on the time of year, destination, and intermingling of persons from different parts of the world where influenza may be circulating. In tropical areas, influenza can occur throughout the year, whereas in the temperate regions of the Southern hemisphere, most activity occurs from April through September. In the Northern hemisphere, influenza generally occurs from November through March. Seasonal influenza vaccination is strongly recommended for all pediatric and adolescent travelers who do not have a contraindication or severe egg allergy.

Currently, there are no available vaccines effective against avian influenza strains such as influenza A H5N1 and H7N9, which have become a great concern worldwide. Because these strains of influenza virus are spread through contact with infected birds, these precautions include avoiding direct contact with birds or surfaces with bird droppings, avoiding poultry farms or bird markets, eating only well-cooked bird meat or products, and washing hands frequently. **Oseltamivir** is the antiviral of choice to treat infections caused by these viruses.

Measles-Mumps-Rubella

Measles is still endemic in many low- and middle-income countries and in some industrialized nations. It remains a leading cause of vaccine-preventable death in much of the world. Vaccine status for measles is important for all traveling children, particularly if they are traveling to low- and middle-income countries or areas with measles outbreaks. Measles vaccine, preferably in combination with mumps and rubella vaccines (MMR), should be given to all children at 12-15 mo and at 4-6 yr of age, unless there is a contraindication (see Chapter 197.2). In children traveling internationally, the 2nd vaccination can be given as soon as 4 wk after the 1st, to induce immunity among those children who did not respond to the 1st MMR vaccine.

Children 6-12 mo old traveling to low- and middle-income countries should be vaccinated. The monovalent measles vaccine is not available in the United States. Early vaccination (i.e., 6-12 mo of age) will provide some immunity to measles, but antibody response may not be durable or lasting. Any MMR vaccine before 12 mo of age does not count toward the routine vaccination schedule; children vaccinated early for purposes of international travel must be revaccinated on or after their 1st birthday with 2 doses, separated by at least 4 wk. Infants <6 mo old are generally protected by maternal antibodies and would not need early MMR vaccination before travel.

Pneumococcal Vaccines

Streptococcus pneumoniae is the leading cause of childhood **bacterial pneumonia** and is among the leading causes of bacteremia and bacterial meningitis in children in low- and middle-income and industrialized nations. Preparing a child to travel internationally includes routine or catch-up vaccination with 13-valent pneumococcal conjugate vaccine (PCV13) and, for children with certain high-risk conditions, use of 23-valent pneumococcal polysaccharide vaccine (PPSV23). A single dose of PCV13 should be administered to previously unvaccinated children 6-18 yr old with underlying high-risk medical conditions: anatomic or functional asplenia (including sickle cell disease), HIV infection, a congenital immunodeficiency or immunocompromising condition, chronic heart or lung disease, chronic renal failure or nephrotic syndrome, diabetes mellitus, cerebrospinal fluid leak, or cochlear implant. The Advisory Committee on Immunization Practices (ACIP) also recommends that high-risk children ≥2 yr old receive the PPSV23 vaccine ≥8 wk after their last PCV13 dose. ACIP recommendations on prevention of pneumococcal disease among infants and children using PCV13 and PPSV23 can be found at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html .

Polio Vaccine

Poliomyelitis was eradicated from the Western hemisphere in 1991. Polio remains endemic in 3 countries—Afghanistan, Nigeria, and Pakistan—with additional surrounding countries at risk for importation of polio. The poliovirus vaccination schedule in the United States is now a 4-dose, all-inactivated poliovirus (IPV) regimen (see Chapter 197). Traveling infants should begin IPV series as early as 6 wk of age (for an accelerated dosing schedule for children, see Fig. 197.2). Length of immunity conferred by IPV immunization is not known; a single booster dose of IPV is therefore recommended for previously vaccinated adolescents and adults traveling to polio-endemic areas if approximately 10 yr has elapsed since they completed their primary series. Oral poliovirus vaccine is no longer available in the United States.

Varicella

All children ≥12 mo old who have no history of varicella vaccination or chickenpox should be vaccinated unless there is a contraindication to vaccination (see Chapter 197). Infants <6 mo old are generally protected by maternal antibodies. All children now require 2 doses, the 1st at 12 mo of age and the 2nd at 4-6 yr. The 2nd dose can be given as soon as 3 mo after the 1st dose. For unvaccinated children ≥13 yr old, the 1st and 2nd doses can be separated by 4 wk.

Specialized Pediatric Travel Vaccinations

Table 200.1 summarizes the dosages and age restrictions of vaccines specifically given to children traveling internationally.

Table 200.1

Travel Vaccinations for Children

VACCINE	FORMULATION	ROUTE AND DOSE	SCHEDULE	INDICATIONS	COMMENT
Hepatitis A	Pediatric: Havrix (GlaxoSmithKline); 720 EU VAQTA (Merck); 25 U	IM; 0.5 mL	Primary series: 2 doses, 6-18 mo apart Booster: currently not recommended	Children >6 months of age	Inactivat Lifelong likely.
	Adult: Havrix (GlaxoSmithKline); 1440 EU VAQTA (Merck); 50 U	IM; 1.0 mL	Primary series: 2 doses, 6-18 mo apart Booster: currently not recommended	Adults ≥19 yr old	Inactivat Lifelong likely.
Hepatitis A and B	Twinrix (GlaxoSmithKline)	IM; 1.0 mL	Primary series: 3 doses at 0, 1, and 6 mo Accelerated schedule: 0, 7, and 21 days; 4th dose 12 mo later Boosters: not needed	Adults ≥18 yr old	Inactivat Lifelong likely. Accelera is as effe
Immunoglobulin, human	Injectable	IM	Travel up to 1 mo duration: 0.1 mL/kg Travel up to 2 mo duration: 0.2 mL/kg Travel 2 mo or more: 0.2 mL/kg (repeat every 2 mo)	Infants <1 yr old	Passive immuniz against h Its use w delay of varicella (at least
Japanese encephalitis virus (JEV)	Inactivated: Ixiaro (Intercell USA)	IM 2 mo to <3 yr old: 0.25 mL ≥3 yr old:	Primary series: 2 doses at days 0 and 28 Booster: 1 dose 1 yr later if exposure to JEV expected	Travel to high-risk areas; prolonged stays	Booster reco is extrapolat recommenda individuals ≥

		0.5 mL			
Meningococcal, polysaccharide	Quadrivalent: A, C, Y, W135	SC; 0.5 mL	Primary series: single dose Booster: 5 yr in persons ≥4 yr old; 2–3 yr in children 2–4 yr old	≥2 yr old	Requirec Saudi Ar the Hajj. Recomm travelers “meningi sub-Saha during dı This vacc used in U conjugat are more immunog
Meningococcal, conjugate	Quadrivalent: ACWY-D: Menactra (Sanofi Pasteur)	IM: 0.5 mL	Children 9-23 mo old: 2 doses, 3 mo apart 2-55 yr old: 1 dose	Routine vaccination in U.S. at ≥11-12 yr old with recommended booster 5 yr later	Requirec Saudi Ar the Hajj. Recomm travelers “meningi sub-Saha during dı This vacc not be us <9 mo ol may inte antibody by pneur conjugat
	Quadrivalent: ACWY-CRM: Menveo (Novartis)	IM; 0.5 mL	Children initiating vaccination at 2 mo: doses at 2, 4, 6, and 12 mo old Children starting vaccination at 7-23 mo old: 2 doses, with 2nd dose after 2 yr old and at least 3 mo after 1st dose	Routine vaccination in U.S. at ≥11-12 yr old with recommended booster 5 yr later	Requirec Saudi Ar the Hajj. Recomm travelers “meningi sub-Saha during dı
Rabies	Inactivated	IM; 1.0 mL	Preexposure series: 3 doses at days 0, 7, and 21 or 28 Booster: depends on risk category and serologic testing. Postexposure: rabies immune globulin; day 0; vaccines at days 0, 3, 7, and 14; 5th dose at day 28 is recommended if host is immunocompromised.		Consider for travelers plar prolonged st especially av large urban c adequate me systems and
Typhoid fever	Live-attenuated Ty21a1	Oral	1 capsule every other	Persons ≥6 yr	If series s

			day for 4 doses Boosters: every 5 yr	old	complete doses ne repeated. Contrain immunoc hosts. Ca taken wi beverage must not antibioti
	Injectable Polysaccharide Vi antigen	IM; 0.5 mL	Primary series: 1 dose Booster: every 2 yr	Persons ≥2 yr old	
Yellow fever	Live injectable	SC; 0.5 mL	Primary series: 1 dose Dose must be given at least 10 days before arrival to risk area. Booster: no longer required by WHO. U.S. travelers: recommended every 10 yr for high-risk travelers.	≥9 mo old	Contrain immunoc hosts. Av pregnanc breastfee mothers, risk trave avoided. Contrain infants < Avoid in thymus c Infants 6 consider with cau travel ca avoided; travel me specialis Caution ≥60 yr ol for vacci infection Requires certificat vaccinati

IM, Intramuscular; SC, subcutaneous; WHO, World Health Organization.

Cholera

Cholera is present in many low- and middle-income countries, but the risk for infection among travelers to these countries is extremely low. At present, no cholera vaccine is available for travelers in the United States, although an effective vaccine is available in other countries. Travelers entering countries reporting cholera outbreaks are at minimal risk of acquiring cholera if they take adequate safe food and water precautions and practice frequent handwashing. No country or territory currently requires cholera vaccination as a condition for entry.

Hepatitis A Vaccination and Preexposure Immunoglobulin

Hepatitis A virus (HAV) is endemic in most of the world, and travelers are at risk, even if their travel is restricted to the usual tourist routes. HAV infection can result from eating shellfish harvested from sewage-contaminated waters, eating unwashed vegetables or fruits, or eating food prepared by an asymptomatic HAV carrier. Young children infected with hepatitis A are often asymptomatic but can transmit infection to unvaccinated older children and adults, who are more likely to develop clinical hepatitis. Few areas carry no risk of HAV infection, and therefore immunization is recommended for all travelers. Hepatitis A vaccine (HepA) is recommended in the United States for universal immunization of all children ≥12 mo old, administered as 2 doses 6 mo apart. A single dose of HepA given to travelers will provide adequate protection. Protective immunity develops within 2 wk after the initial vaccine dose. A combined 3-dose HepA and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is available in the United States but is licensed for use only in individuals >18 yr old. Pediatric combination hepatitis A–hepatitis B vaccine (HepA-HepB) (Twinrix-Junior, GlaxoSmithKline) is licensed for use in children 1-18 yr old in Canada and Europe.

Children <1 yr old are at lower risk of clinical HAV infection, especially if they are breastfed or residing in areas with safe water for formula reconstitution. Some experts recommend use of preexposure intramuscular immunoglobulin for children <6 mo who are traveling internationally to higher-risk destinations, particularly low-income destinations or regions where hygienic or sanitary conditions are limited. However, administration of immunoglobulin diminishes the immunogenicity of live-virus vaccines, in particular measles vaccine, that may be needed for infant travelers. Vaccination against measles should occur ≥2 wk before any immunoglobulin administration, and a 3 mo interval is suggested between immunoglobulin administration and subsequent measles immunization.

Because measles-endemic countries frequently overlap with higher-risk travel destinations for HAV infection hepatitis A vaccine is recommended for infant travelers 6-11 mo of age. Several studies demonstrate that infants as young as 6 mo will develop antibodies following HepA, especially if there are no interfering maternal antibodies from prior maternal vaccination or disease. There is potential for a more durable immune response to the hepatitis A vaccination especially in later infancy, when potential interfering maternal antibody concentrations are lower. If early hepatitis A vaccination is given rather than immunoglobulin to infant travelers (age 6-11 mo), it should not count toward the routine 2-dose vaccine series. Similar to MMR vaccination, an informed decision should be made, with the parents balancing the risk of travel-associated disease and vaccine adverse events with the potential protective benefit to the traveling infant.

Japanese Encephalitis

Japanese encephalitis is a disease transmitted by mosquitoes in many areas of Asia, especially in rural farming areas. Although it is a leading cause of vaccine-preventable encephalitis in children in many Asian countries and parts of western Pacific countries, the risk of disease to nonimmune travelers is low. A map showing where Japanese encephalitis transmission occurs can be found at https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/japanese-encephalitis .

Most human infections with **Japanese encephalitis virus (JEV)** are asymptomatic, and <1% of individuals develop clinical disease. With symptomatic disease, the fatality rate is 20–30% and the incidence of neurologic or psychiatric sequelae in survivors is 30–50%. The risk of JEV disease for pediatric travelers is unknown, but among all travelers, it is estimated to be less than 1 case per 1 million travelers to Asia. However, if residing in a rural area with active JEV transmission in the raining season, the risk may increase to 5-50 cases per 100,000 population per year. Risk of Japanese encephalitis neurologic disease following mosquito-bite transmission is thought to be higher in children than adults. The disease occurs primarily from June to September in temperate zones and throughout the entire year in tropical zones. Vaccination is recommended for travelers planning visits >1 mo to rural areas of Asia, where the disease is endemic, especially areas of rice or pig farming. Vaccination is recommended for shorter visits to such areas if the traveler will often be outdoors (e.g., camping or hiking). Risk for infection can be greatly reduced by following the standard precautions to avoid mosquito bites.

The inactivated Vero cell culture–derived Japanese encephalitis vaccine (Ixiaro) has replaced the older inactivated mouse brain–derived vaccine (JE-VAX), which is no longer manufactured. Japanese encephalitis vaccine efficacy is >95% in adults who receive 2 doses administered 28 days apart. The licensed range for Japanese encephalitis vaccine has been extended to include children as young as 2 mo, with a dose administered on days 0 and 28.

Meningococcal Vaccines

Currently, 3 forms of meningococcal vaccine are available in the United States: a quadrivalent polysaccharide A/C/Y/W-135 vaccine (Menomune); 2 quadrivalent conjugate A/C/Y/W-135 vaccines, MenACWY-CRM (Menveo) and MenACWY-D (Menactra); and 2 meningococcal B vaccines (Bexcero, Trumenba).

Children traveling to those equatorial countries in sub-Saharan Africa where the incidence of meningococcal disease (especially group A) is highest should receive a *Neisseria meningitidis* quadrivalent vaccine, especially if travel is prolonged or occurs during the dry season of December to June. Risk is greatest in the meningitis belt of sub-Saharan Africa,* with rates of meningococcal disease in endemic regions reaching up to 1,000 cases per 100,000 population per year. Ongoing vaccination programs for resident populations with a monovalent group A vaccine in highly endemic areas has resulted in a decrease in cases of invasive disease. Children 9-23 mo old traveling to these equatorial African countries where meningococcal disease is hyperendemic or epidemic should receive a 2-dose series of MenACWY-D, 8-12 wk apart. Infants as young as 2 mo can receive the MenACWY-CRM vaccine, with doses administered at 2, 4, 6, and 12 mo of age. If the child is between 7 and 23 mo old, 2 doses of the vaccine are administered 8 wk apart. Conjugate vaccines are preferred in children over the less effective polysaccharide vaccine. Booster doses of conjugate A/C/Y/W-135 should occur every 3-5 yr for travelers returning to endemic areas, depending on the age of the pediatric traveler. Providers may also want to consider meningococcal vaccination for other pediatric travelers, especially if there is remote or rural travel to low-income countries with limited healthcare access, since meningococcal outbreaks can occur anywhere in the world. Proof of receipt of quadrivalent meningococcal vaccination is also necessary for individuals traveling to Saudi Arabia for the annual Hajj or Umrah pilgrimage.

Serogroups A and C are most often associated with epidemics of meningitis in sub-Saharan Africa, especially in the meningitis belt of equatorial Africa during the dry season months (December to June). Serogroups Y and W-135 have also been found in meningococcal outbreaks. Serogroup B is associated with more sporadic cases of invasive meningococcal disease in industrialized countries, including the United States. Routine vaccination of travelers with meningococcal B vaccine is currently not recommended. Additional vaccine information on meningococcal vaccination regimens and booster intervals can be found at the CDC website (https://www.cdc.gov/vaccines/vpd-vac/mening/default.html).

Rabies

Rabies is endemic in many countries in Africa, Asia, and Central and South America. Children are at particular risk because they are less likely to report bites and because facial bites are more common in children. Rabies has the potential for an extended latency period (months) and is uniformly fatal once the clinical symptoms emerge. **Preexposure prophylaxis** is recommended for ambulatory children with extended travel to high-risk regions, especially expatriate children and younger children traveling to or living in rural areas where enzootic dog rabies is endemic. Rabies preexposure vaccination should also be considered for adventure travelers (hikers, bikers), individuals likely to come into contact with rabies vectors (e.g., students working with animal or bat conservation), or travelers with itineraries to rabies-endemic regions where timely, effective **postexposure prophylaxis** might not be available following an animal bite. Most animal bites in a rabies-endemic area should be considered a medical emergency, especially bites from stray dogs, other carnivores, and bats. Immediate wound care washing should be followed by prompt administration of appropriate postexposure rabies prophylaxis at a medical facility. Postexposure prophylaxis is required even for persons who received preexposure vaccination. Algorithms for pre- and postexposure vaccination are the same regardless of patient age.

Numerous rabies vaccine formulations exist around the world. In the United States, 2 rabies vaccines are available: human diploid cell vaccine (HDCV; Imovax, Sanofi Pasteur, SA) and purified chick embryo cell (PCEC; RabAvert, Novartis) vaccine. Preexposure prophylaxis is given intramuscularly (HDCV or PCEC) as 3 doses (1 mL) on days 0, 7, and 21 or 28.

Postexposure prophylaxis is given as 4 doses (1 mL) of HDCV or PCEC vaccine intramuscularly on days 0, 3, 7, and 14. A 5th dose is recommended at day 28 for immunocompromised individuals. Two doses (1 mL) intramuscularly on days 0 and 3 are recommended for previously vaccinated individuals.

Previously unvaccinated persons should also receive **rabies immunoglobulin** (**RIG** , 20 IU/kg), with as much of the dose as possible infiltrated around the wound site at the time of initial postexposure prophylaxis. Previously vaccinated persons do not require RIG. Unpurified or purified equine RIG preparations are still used in some low- and middle-income countries and are associated with a higher risk for severe reactions, including serum sickness and anaphylaxis. Purified cell culture–derived vaccines also are not always available abroad; travelers should be aware that any rabies vaccines derived from neural tissue carry an increased risk for adverse reactions, often with neurologic sequelae. If rabies prophylaxis is initiated abroad, neutralizing titers should be checked on return and immunization completed with a cell culture–derived vaccine. If rabies prophylaxis cannot be provided abroad, children with high-risk bites (e.g., stray dog) should be emergently transported to a site where they can receive prophylaxis, because the vaccinations should be started as soon as possible after the bite and ideally within 24 hr. Infants and young children respond well to rabies vaccine, and both pre- and postexposure vaccinations can be given at any age, using the same dose and schedule as adults. Individual travelers simultaneously receiving **mefloquine** or **chloroquine** may have limited immune reactions to intradermal (ID) rabies vaccine and should be vaccinated intramuscularly. The ID administration route is not currently recommended in the United States.

Tuberculosis

The risk for tuberculosis in the typical traveler is low. Pre- and posttravel testing for tuberculosis is controversial and should be done on an individualized basis depending on the itinerary, duration, and activities (e.g., working in a hospital setting). Immunization with bacille Calmette-Guérin (BCG) is even more controversial. BCG vaccine has variable efficacy in reducing severe tuberculosis disease in infants and young children, is not available in the United States, and is generally not recommended for pediatric travelers. Infection with *Mycobacterium bovis* can be prevented through avoiding consumption of unpasteurized dairy products.

Typhoid

Salmonella typhi infection, or **typhoid fever** , is common in many low- and middle-income countries in Asia, Africa, and Latin America (see Chapter 225). Typhoid vaccination is recommended for most children ≥2 yr old who are traveling to the Indian subcontinent, because the incidence of typhoid is 10-100 times higher for travelers to the Indian subcontinent than all other travel destinations. Vaccination should be strongly considered for other travelers to low- and middle-income countries, particularly if they are VFR travelers, lack access to reliable clean water and food, are traveling for a prolonged duration, or are adventurous eaters.

Two typhoid vaccines, the intramuscular (IM) Vi-polysaccharide vaccine and the oral Ty21a strain live-attenuated vaccine, are recommended for use in children in the United States. Both produce a protective response in 50–80% of recipients. The Ty21a vaccine may offer partial protection against *Salmonella paratyphi* , another cause of enteric fever. Travelers who have had prior diagnoses of typhoid fever should still receive vaccination, because past infection does not confer long-term immunity.

The IM Vi-polysaccharide vaccine is licensed for use in children ≥2 yr old. It can be given any time before departure, but it should ideally be administered 2 wk before travel, with a booster needed 2-3 yr later. The oral Ty21a vaccine can only be used in children ≥6 yr old and is given in 4 doses over 1 wk. Enteric-coated capsules are to be swallowed with a cool or room-temperature drink, at least 1 hr before a meal, every other day until the 4 doses are completed. Oral typhoid capsules must remain refrigerated (not frozen). Capsules should never be broken open, because vaccine efficacy depends on capsules being swallowed whole in order to pass through the acidic stomach contents. The oral vaccine is associated with an immune response lasting 5-7 yr (depending on national labeling). Antibiotics inhibit the immune response to the oral Ty21a vaccine; the vaccine should not be given within 72 hr of antibiotic treatment, and antibiotics should be avoided until 7 days after completing the vaccine series. Studies demonstrate that mefloquine, chloroquine, and atovaquone-proguanil can be given concurrently with the oral Ty21a vaccine without affecting the immunogenicity of the vaccine. Oral Ty21a vaccine should not be given to immunocompromised children; these children should receive the IM Vi-polysaccharide vaccine.

Yellow Fever

Yellow fever (see Chapter 296) is a mosquito-borne viral illness resembling other viral hemorrhagic fevers (Chapter 297) but with more prominent hepatic involvement. Yellow fever is present in tropical areas of South America and Africa.

Yellow fever vaccination is indicated in children >9 mo old traveling to an endemic area. Many countries require yellow fever vaccination by law for travelers arriving from endemic areas, and some African countries require evidence of vaccination from all entering travelers. Current recommendations can be obtained by contacting state or local health departments or the Division of Vector-Borne Infectious Diseases of the CDC (800-232-4636; http://wwwnc.cdc.gov/travel/yellowbook/2016/chapter-3-infectious-diseases-related-to-travel/yellow-fever). Most countries accept a medical waiver for children who are too young to be vaccinated (<6 mo) and for persons with a contraindication to vaccination. Children with asymptomatic HIV infection may be vaccinated if exposure to yellow fever virus (YFV) cannot be avoided.

Yellow fever vaccine (0.5 mL subcutaneously), a live-attenuated vaccine (17D strain) developed in chick embryos, is safe and highly effective in children >9 mo old, but in young infants is associated with a greatly increased risk for vaccine-associated encephalitis (0.5-4/1,000) and other severe reactions. Yellow fever vaccine should *never* be given to infants <6 mo old; infants 6-8 mo old should be vaccinated only in consultation with the CDC or a travel medicine expert to assess the current epidemiology, travel itinerary and duration, and whether the YFV exposure is greater than vaccine risks. In children >9 mo old, adverse effects are rare, although vaccine-associated neurotropic and viscerotropic disease associated with the vaccine have been reported. The risk of these reactions is higher in those with thymus disease, altered immune status, age >60 yr, or multiple sclerosis and in infants <9 mo old (neurotropic disease). Yellow fever vaccination is generally contraindicated in pregnancy and for nursing mothers, unless extended travel to a yellow fever–endemic area is unavoidable.

Children with immunodeficiency or an immunosuppressed state, a thymic disorder or dysfunction (e.g., DiGeorge syndrome), or a history of anaphylactic reactions to eggs should not receive yellow fever vaccine. Long-lived immunity develops with this vaccine, perhaps even lasting for a lifetime. Effective July 2016, WHO and countries following international health regulations no longer require revaccination every 10 yr. However, individuals traveling to high-risk areas with active yellow fever transmission and who anticipate frequent or prolonged stays should be reimmunized every 10 yr.

Traveler's Diarrhea

Ingestion of contaminated food or water makes travel-associated diarrhea the most common health complaint among international travelers. Traveler's diarrhea, characterized by a 2-fold or greater increase in the frequency of unformed bowel movements, occurs in as many as 40% of all travelers overseas (see Chapter 366.1). Children, especially those <3 yr old, have a higher incidence of diarrhea, more severe symptoms, and more prolonged symptoms than adults, with a reported attack rate of 60% for those <3 yr old in one study.

An important risk factor for traveler's diarrhea is the country of destination. High-risk areas (attack rates of 25–50%) include low- and middle-income countries of Latin America, Africa, the Middle East, and Asia. Intermediate risk occurs in Mediterranean countries, China, and Israel. Low-risk areas include North America, Northern Europe, Australia, and New Zealand. Fecal-oral diarrheal pathogens that children acquire during travel are similar to those acquired by adults and include enterotoxigenic and enteroaggregative *Escherichia coli* , *Campylobacter, Salmonella* (nontyphoidal serotypes predominate), and *Shigella* spp. Enteric protozoa are a much less common cause of traveler's diarrhea than bacterial pathogens; *Giardia lamblia* is the most likely protozoal cause of persistent diarrhea. Less common travel-associated protozoa include *Cryptosporidium* spp., *Entamoeba histolytica*, and *Cyclospora* . Viral infections, particularly rotavirus and norovirus infections, may also cause travel-associated diarrhea in children. Clinicians should be aware that not all diarrheal illness in children is food-borne or water-borne; febrile children with malaria may also present with vomiting and/or nonbloody diarrhea and may be misdiagnosed as having traveler's diarrhea.

Guidance on Prevention of Traveler's Diarrhea

Food and water hygiene remain important measures to reduce the incidence of traveler's diarrhea in children. However, creating long lists of foods to avoid or offering the popular, simple advice of “Boil it, peel it, cook it, or forget it!” is generally an ineffective method of reducing traveler's diarrhea. Most studies show that these types of dietary directives are difficult to keep and may have little impact on the incidence of traveler's diarrhea. In adult studies, the risk of developing traveler's diarrhea appears to be more associated with *where you eat rather than what you eat* . Eating in a relative's or friend's home is generally safer than eating in a restaurant, where restaurant kitchen hygiene and proper refrigeration may be lacking and employee handwashing may be sporadic.

In general, travel medicine providers can give some commonsense food and water advice to family travelers. Boiled or bottled water, hot beverages, and canned or bottled beverages are generally safe to consume. Ice should be avoided. In low- and middle-income countries, tap water is generally unsafe for drinking or brushing teeth. Boiling water for ≥1 min (or 3 min at altitudes >2,000 meters) remains a reliable method of disinfecting water. Food that is thoroughly cooked and served hot is almost always safe to eat. Dry foods, such as pastry items, breads, and cookies, are generally safe to eat. Unpasteurized milk or other dairy products (cheese) should always be avoided. Breastfeeding should be encouraged for young children, especially infants <6 mo old, to reduce exposure to contaminated water or formula. All children should be reminded to wash their hands before eating and after playing around soil or animals. Chemoprophylactic agents for traveler's diarrhea are not recommended for children.

Management of Traveler's Diarrhea

Dehydration is the greatest threat presented by a diarrheal illness in a small child. Parents should be made aware of the symptoms and signs of dehydration and given instructions on how to administer rehydration solutions. Prepackaged WHO **oral rehydration solution** packets, which are available at stores or pharmacies in almost all low- and middle-income countries, should be part of a child's travel kit. Oral rehydration solution should be mixed as directed with bottled or boiled water and given slowly, as tolerated, to the child while symptoms persist.

Antimotility agents such as diphenoxylate (Lomotil) and loperamide (Imodium) should be avoided in infants and young children. The American Academy of Pediatrics (AAP) does not recommend their routine use in acute gastroenteritis. Use of antimotility agents may be beneficial in older children and adolescents with afebrile, nonbloody traveler's diarrhea. In general, antimotility agents should not distract parents from giving frequent oral rehydration solution, because ongoing intestinal fluid losses likely continue despite a decrease in stooling. Bismuth subsalicylate for acute gastroenteritis should be avoided because of concern for toxicity and Reye syndrome.

Presumptive Antibiotic Treatment

Oral rehydration is the mainstay of treatment for pediatric traveler's diarrhea. However, antibiotics should be prescribed for the pediatric traveler, with parental instructions to start presumptive treatment early in the diarrheal illness. Systemic antibiotics can shorten the duration and severity of diarrheal illness, especially if presumptive antibiotics are initiated immediately after onset of traveler's diarrhea. For children, the drug of choice is **azithromycin** (10 mg/kg once daily for up to 3 days, with maximum daily dose of 500 mg). **Ciprofloxacin** (10 mg/kg per dose twice daily for up to 3 days, maximum dose of 500 mg twice daily) is an alternative for children >1 yr old but should not be prescribed for travelers to the Indian subcontinent or Southeast Asia, where fluoroquinolone resistance is common. Shiga-toxin–producing *E. coli* such as *E. coli* O157:H7 is an extremely uncommon cause of pediatric traveler's diarrhea in nonindustrialized countries, and the benefit of presumptive antibiotic therapy in traveling children, even with bloody diarrhea, typically outweighs the low risk of developing hemolytic-uremic syndrome. Parents need to be aware that the use of antibiotics for the treatment of traveler's diarrhea has been associated with colonization with highly resistant organisms such as extended-spectrum β-lactamase–producing Enterobacteriaceae. These organisms could later cause infections once back home.

Azithromycin is highly effective against most bacterial pathogens that cause traveler's diarrhea and is the preferred antibiotic among many travel experts. Azithromycin can be prescribed in powder form that can be reconstituted with safe water into a liquid suspension when needed. Amoxicillin, trimethoprim-sulfamethoxazole (cotrimoxazole), and erythromycin should *not* be prescribed for self-treatment of traveler's diarrhea, because of widespread resistance among diarrheal pathogens. Traveler's diarrhea that results in bloody stools, persistently high fevers, systemic chills and rigors, severe or localizing abdominal pain, or continued fluid losses should prompt additional medical evaluation.

Insect-Borne Infections

Insect-borne infections for which traveling children are most at risk include malaria, dengue, chikungunya, yellow fever, Zika, and Japanese encephalitis, depending on the area of travel. **Malaria** is transmitted by nighttime biting *Anopheles* mosquitoes, whereas **dengue** occurs from mosquito species *(Culex* , *Aedes)* that are predominantly active during the day. Families should be encouraged to protect children against daytime and nighttime biting mosquitoes, since many regions of the world where malaria is found also have diseases transmitted by daytime biting mosquitoes (dengue, Zika, chikungunya). Sexually active adolescents and young adults need to be advised on the risks of traveling to Zika-endemic regions in peak season. In addition to insect bite prevention using insect repellents, methods of contraception should be discussed with the traveler.

Exposure to insect bites can be reduced by wearing appropriate attire and using insect repellents containing *N,N* -diethyl-*m* -toluamide (**DEET**) or picaridin. The AAP recommends avoiding DEET-containing repellents in children <2 mo old. Rare cases of neurologic events have been reported in very young children with exposure to inappropriate, frequent applications of DEET-containing repellents (>10 times/day) or who licked off DEET. Concentrations of 25–30% DEET need be applied every 4-6 hr as needed, whereas 5–7% DEET provides only 1-2 hr of protection time. DEET concentrations >40–50% do not confer a substantially longer protection time for children and are not recommended.

Picaridin is fragrance-free, effective, and generally well tolerated on exposed skin and faces. It has similar efficacy to DEET but with less inhalational or dermal irritation. Picaridin at concentrations of 20% or higher provides adequate protection against *Anopheles* mosquitoes that have potential to transmit malaria. When applying sunscreen and insect repellent, sunscreen should be applied first, followed by DEET or picaridin.

Spraying or treating clothing with **permethrin** , a synthetic pyrethroid, is a safe and effective method of further reducing insect bites in children. Permethrin can be applied directly to clothing, bed nets, shoes, and hats and should be allowed to dry fully before use. As an insecticide, permethrin should never be applied to skin. Permethrin-treated garments retain both repellency and insecticidal activity, even with repeated laundering. Clothing will eventually need to be re-treated to maintain repellency, according to the product label. Bed nets, particularly permethrin-impregnated bed nets, also decrease the risk of insect bites, and their use is highly recommended in malarial areas.

Malaria Chemoprophylaxis

Malaria, a mosquito-borne infection, is the leading parasitic cause of death in children worldwide (see Chapter 314). Of the 5 *Plasmodium* species that infect humans, *Plasmodium falciparum* causes the greatest morbidity and mortality. Each year, >8 million U.S. citizens visit parts of the world where malaria is endemic (sub-Saharan Africa, Central and South America, India, Southeast Asia, Oceania). Children accounted for 15–20% of imported malaria cases in a WHO study in Europe. Given the major resurgence of malaria and increased travel among families with young children, physicians in industrialized countries are increasingly required to give advice on prevention, diagnosis, and treatment of malaria. **Risk factors** for severe malaria and death include inadequate adherence to chemoprophylaxis, delay in seeking medical care, delay in diagnosis, and nonimmune status, but the case fatality rate of imported malaria remains <1% in children from nonendemic countries. The CDC maintains updated information at http://www.cdc.gov/malaria/travelers/index.html , as well as a malaria hotline for physicians (770-488-7788). It is important to check this updated information, because recommendations for prophylaxis and treatment are often modified as a result of changes in the risk for developing malaria in different areas of the world, changing *Plasmodium* resistance patterns, and the availability of new antimalarial medications.

Avoidance of mosquitoes and **barrier protection** from mosquitoes are an important part of malaria prevention for travelers to endemic areas. The *Anopheles* mosquito feeds from dusk to dawn. Travelers should remain in well-screened areas, wear clothing that covers most of the body, sleep under a bed net (ideally impregnated with permethrin), and use insect repellents with DEET during these hours. Parents should be discouraged from taking a young child on a trip that will entail evening or nighttime exposure in areas endemic for *P. falciparum.*

Chemoprophylaxis is the cornerstone of malaria prevention for nonimmune children and adults who travel to malaria-endemic areas, *but is not a replacement for other protective measures* . Travelers often do not take malaria prophylaxis as prescribed or at all. They are more likely to use prophylactic antimalarial drugs if their physicians provide appropriate recommendations and education before departure. However, in one survey, only 14% of persons who sought medical advice obtained correct information about malaria prevention and prophylaxis. Families with children visiting friends and relatives are particularly less likely to take malaria prophylaxis or seek pretravel medical advice.

Resistance of *P. falciparum* to the traditional chemoprophylactic agent,

chloroquine , is widespread, and in most areas of the world other agents must be used (Table 200.2). Factors that must be considered in choosing appropriate chemoprophylaxis medications and dosing schedules include age of the child, travel itinerary (including whether the child will be traveling to areas of risk within a particular country and whether chloroquine-resistant *P. falciparum* is present in the country), vaccinations being given, allergies or other known adverse reactions to antimalarial agents, and the availability of medical care during travel.

Table 200.2

Antimalarial Chemoprophylaxis for Children

AREA	DRUG	ADULT DOSE	PEDIATRIC DOSE	ADVANTAGES	DISADVANTAGES	COMMENT
Chloroquine-resistant area	Mefloquine*†	250 mg salt (228 mg base) tablets One tablet weekly	Weight <10 kg: 5 mg salt (4.6 mg base)/kg/wk	Once-weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria-endemic area for ≥ wk Children unlikely t take daily medicatio
			Weight 10-19 kg: ¼ tablet/wk			
			Weight 20-30 kg: ½ tablet/wk Weight 31-45 kg: ¾ tablet/wk			
			Weight >45 kg: 1 tablet/wk			
	Doxycycline‡	100 mg tablet One tablet daily	2 mg/kg daily (max: 100 mg)	Known safety profile Readily available in most pharmacies	Cannot give to children <8 yr old Daily dosing Must take with food or causes stomach upset Photosensitivity Yeast superinfections	Children ≥8 y old going to area for <4 w who cannot take or canno obtain atovaquone-proguanil

	Atovaquone-proguanil [§] (Malarone)	250/100 adult tablet One tablet daily	Pediatric tablet: 62.5 mg atovaquone/25 mg proguanil	Pediatric tablet formulation available Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children goi to malaria-endemic area for <4 wk
			Weight 5-8 kg: ½ pediatric tablet once daily			
			Weight >8-10 kg: ¾ pediatric tablet once daily			
			Weight >10-20 kg: 1 pediatric tablet once daily			
			Weight >20-30 kg: 2 pediatric tablets once daily			
			Weight >30-40 kg: 3 pediatric tablets once daily			
			Weight >40 kg: 1 adult tablet once daily			
Chloroquine-susceptible area	Chloroquine phosphate	500 mg salt (300 mg base) One tablet weekly	8.3 mg/kg salt (5 mg/kg base) weekly	Once-weekly dosing Generally well tolerated Safe in pregnancy	Bitter taste No pediatric formulation	Best medication f children traveling to areas with *Plasmodium falciparum* o *P. vivax* that i chloroquine susceptible

[*] Chloroquine and mefloquine should be started 1-2 wk before departure and continued for 4 wk after last exposure.

[†] Mefloquine resistance exists in western Cambodia and along the Thailand–Cambodia and Thailand–Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.

[‡] Doxycycline should be started 1-2 days before departure and continued for 4 wk after last

exposure. Do not use in children <8 yr old or in pregnant women.

§ Atovaquone-proguanil (Malarone) should be started 1-2 days before departure and continued for 7 days after last exposure; should be taken with food or a milky drink. Not recommended in pregnant women, children who weigh <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas.

Children traveling to areas with chloroquine-resistant *P. falciparum* can be given mefloquine, atovaquone-proguanil, or doxycycline (if >8 yr old) as malaria prophylaxis. For trips shorter than 4 wk, atovaquone-proguanil is the preferred medication, because it is given for only a short period before and after travel. Atovaquone-proguanil or doxycycline is also indicated for travel of any duration to western Cambodia and the Thailand-Cambodia and Thailand-Myanmar borders because of mefloquine resistance in these areas. For periods of travel >4 wk to all other areas with chloroquine-resistant *P. falciparum,* mefloquine is the preferred medication because it can be taken weekly.

Mefloquine is FDA-approved only for children weighing >15 kg, but the CDC recommends mefloquine prophylaxis for all children regardless of weight because the risk for acquiring severe malaria outweighs the risk for potential mefloquine toxicity. Adults taking mefloquine prophylaxis have a 10–25% incidence of sleep disturbance and dysphoria and, less frequently, more serious neuropsychiatric symptoms. These side effects appear to be less common in children. Other potential side effects of mefloquine therapy include nausea and vomiting.

The lack of a liquid or suspension formulations for all antimalarial agents can make administration difficult. For children who cannot take tablets, parents should take a chloroquine or mefloquine prescription to a compounding pharmacy, which can pulverize the tablets and place exact dosages into gel capsules. Parents can then open the gel capsules and sprinkle the powder into food. Disguising these medications, which have a bitter taste, is important; chocolate syrup has been used successfully as a vehicle for the medication. Persons with depression, neuropsychiatric disorders, seizure disorders, or cardiac conduction defects should not take mefloquine.

Atovaquone-proguanil fixed combination (Malarone) is an effective and safe chemoprophylaxis for travelers to chloroquine-resistant malaria-endemic areas. Adverse effects are infrequent and mild (abdominal pain, vomiting, and headache) and infrequently result in discontinuation of the medication. Atovaquone-proguanil prophylaxis must be taken every day with food, so it is better suited for prophylaxis during short periods of exposure. Recent data allow dosing down to 5 kg body weight, although the use of atovaquone-proguanil in children weighing 5-10 kg is considered off-label.

Daily **doxycycline** is an alternative chemoprophylaxis regimen for chloroquine-resistant *P. falciparum* malaria. Doxycycline has been used extensively and is highly effective, but it cannot be used in children <8 yr old because of the risk of permanent tooth staining. Adverse effects (nausea, vomiting, photosensitivity, vaginal candidiasis) are relatively uncommon. Persons given doxycycline prophylaxis should be warned to decrease exposure to direct sunlight to minimize the possibility of photosensitivity.

Primaquine has also been used successfully as chemoprophylaxis, especially in areas of high prevalence of *Plasmodium vivax* and *Plasmodium ovale,* but there are limited data about its use in nonimmune children. Primaquine prophylaxis for children should only be given in consultation with the CDC or a travel medicine specialist.

Chloroquine, chloroquine-proguanil, and azithromycin do not provide adequate protection for children traveling to a chloroquine-resistant malaria-endemic area.

In areas of the world where *P. falciparum* remains fully chloroquine-sensitive (Haiti, the Dominican Republic, Central America west of the Panama Canal, and some countries in the Middle East), weekly chloroquine is the drug of choice for malaria chemoprophylaxis. Updated information on chloroquine susceptibility and recommended malaria prophylaxis is available at http://wwwnc.cdc.gov/travel/yellowbook/2016/chapter-3-infectious-diseases-related-to-travel/malaria .

On leaving an area endemic for *P. vivax* or *P. ovale* after a prolonged visit (usually >3 mo), travelers should consider terminal prophylaxis with primaquine (0.5 mg/kg base) daily, up to a maximum dose of 30 mg base or 52.6 mg salt, for 14 days, to eliminate extraerythrocytic forms of *P. vivax* and *P. ovale* and prevent relapses. Screening for glucose-6-phosphate dehydrogenase deficiency is mandatory before primaquine treatment, since primaquine is contraindicated in G6PD-deficient persons because it can cause severe hemolysis.

Small amounts of antimalarial drugs are secreted into breast milk. The amounts of transferred drug are not considered to be either harmful or sufficient to provide adequate prophylaxis against malaria. Prolonged infant exposure to doxycycline through breast milk is not advisable.

Self-treatment of presumptive malaria during travel remains controversial. It should never be substituted for seeking appropriate medical care, but it can be considered in special circumstances such as travel to remote areas, intolerance of prophylaxis, or refusal of chemoprophylaxis by the traveler. Self-treatment medication should be different than the prescribed chemoprophylaxis. The CDC or a travel medicine specialist should be consulted if self-treatment medication is being considered for a traveler.

The Returning Traveler

Posttravel evaluations are part of travel medicine and continuing care. Physicians unfamiliar with diseases that occur in low- and middle-income countries often misdiagnose the cause of illness in a child returning from travel abroad. Among returning patients identified from the GeoSentinel Surveillance Network sites who were ill, the common disorders included, in descending order of frequency, malaria, giardiasis, dengue fever, campylobacteriosis, cutaneous larva migrans, enteric fever, spotted fever (rickettsiosis), chikungunya fever, hepatitis A, and influenza. Returning pediatric travelers who are severely ill or with continued fevers should be seen in consultation with a pediatric travel medicine or infectious diseases specialist. The cause of fever may be suggested by the geographic area (Table 200.3) and incubation period (Table 200.4).

Table 200.3

Common Causes of Fever by Geographic Area

GEOGRAPHIC AREA	COMMON TROPICAL DISEASE-CAUSING FEVER	OTHER INFECTIONS CAUSING OUTBREAKS OR CLUSTERS IN TRAVELERS
Caribbean	Chikungunya, dengue, malaria (Haiti), Zika	Acute histoplasmosis, leptospirosis
Central America	Chikungunya, dengue, malaria (primarily *Plasmodium vivax*), Zika	Leptospirosis, histoplasmosis, coccidioidomycosis
South America	Chikungunya, dengue, malaria (primarily *P. vivax*), Zika	Bartonellosis, leptospirosis, enteric fever, histoplasmosis
South-Central Asia	Dengue, enteric fever, malaria (primarily non-falciparum)	Chikungunya
Southeast Asia	Dengue, malaria (primarily non-falciparum)	Chikungunya, leptospirosis
Sub-Saharan Africa	Malaria (primarily *P. falciparum*), tick-borne rickettsiae (main cause of fever in southern Africa), acute schistosomiasis, dengue	

From Wilson ME: Post-travel evaluation. In CDC *Yellow Book* , Chapter 5 (Table 5.2). https://wwwnc.cdc.gov/travel/yellowbook/2018/post-travel-evaluation/fever-in-returned-travelers .

Table 200.4

Common Infections by Incubation Period

DISEASE	USUAL INCUBATION PERIOD (RANGE)	DISTRIBUTION
INCUBATION <14 DAYS		
Chikungunya	2-4 days (1-14 days)	Tropics, subtropics
Dengue	4-8 days (3-14 days)	Topics, subtropics
Encephalitis, arboviral (Japanese encephalitis, tick-borne encephalitis, West Nile virus, other)	3-14 days (1-20 days)	Specific agents vary by region
Enteric fever	7-18 days (3-60 days)	Especially in Indian subcontinent
Acute HIV	10-28 days (10 days to 6 wk)	Worldwide
Influenza	1-3 days	Worldwide, can also be acquired while traveling
Legionellosis	5-6 days (2-10 days)	Widespread
Leptospirosis	7-12 days (2-26 days)	Widespread, most common in tropical areas
Malaria, *Plasmodium falciparum*	6-30 days (98% onset within 3 mo of travel)	Tropics, subtropics
Malaria, *Plasmodium vivax*	8 days to 12 mo (almost half have onset >30 days after completion of travel)	Widespread in tropics and subtropics
Spotted-fever rickettsiae	Few days to 2-3 wk	Causative species vary by region
Zika virus infection	3-14 days	Widespread in Latin America, endemic through much of Africa, Southeast Asia, and Pacific Islands
INCUBATION 14 DAYS TO 6 WK		
Encephalitis, arboviral; enteric fever; acute HIV; leptospirosis; malaria	See above incubation periods for relevant diseases.	See above distribution for relevant diseases.
Amebic liver abscess	Weeks to months	Most common in resource-poor countries
Hepatitis A	28-30 days (15-50 days)	Most common in resource-poor countries
Hepatitis E	26-42 days (2-9 wk)	Widespread
Acute schistosomiasis (Katayama syndrome)	4-8 wk	Most common in sub-Saharan Africa
INCUBATION >6 WK		
Amebic liver abscess, hepatitis E, malaria, acute schistosomiasis	See above incubation periods for relevant diseases.	See above distribution for relevant diseases.
Hepatitis B	90 days (60-150 days)	Widespread
Leishmaniasis, visceral	2-10 mo (10 days to years)	Asia, Africa, Latin America, southern Europe, and the Middle East
Tuberculosis	Primary, weeks; reactivation, years	Global distribution, rates, and levels of resistance vary widely.

From Wilson ME: Post-travel evaluation. In CDC *Yellow Book* , Chapter 5 (Table 5.3). https://wwwnc.cdc.gov/travel/yellowbook/2018/post-travel-evaluation/fever-in-returned-travelers .

Among all persons returning from travel (children and adults), 3 major patterns of illness have been noted (Table 200.5). The etiology of each of these disease presentations in part depends on the country or geographic region visited (see Table 200.3). Table 200.6 provides suggestive clues to a diagnosis.

Table 200.5

Patterns of Illness in Returning International Travelers

SYSTEMIC FEBRILE ILLNESS
Malaria
Dengue
Zika
Enteric fever (typhoid/paratyphoid)
Chikungunya virus
Spotted-fever rickettsiae
Hepatitis A
Acute HIV
Leptospirosis
Measles
Infectious mononucleosis
Respiratory causes (pneumonia, influenza)
Undetermined fever source
ACUTE DIARRHEA
Campylobacter
Shigella spp.
Salmonella spp.
Diarrheagenic *Escherichia coli* (enterotoxigenic *E. coli* , enteroadherent *E. coli* —not tested for by routine stool culture methods)
Giardiasis (acute, persistent, or recurrent)
Entamoeba histolytica
Cryptosporidium spp.
Cyclospora cayetanensis
Presumed viral enteritis
DERMATOLOGIC MANIFESTATIONS
Rash with fever (dengue)
Arthropod-related dermatitis (insect bites)
Cutaneous larva migrans (*Ancylostoma braziliense*)
Bacterial skin infections—pyoderma, impetigo, ecthyma, erysipelas
Myiasis (tumbu and botfly)
Scabies
Tungiasis
Superficial mycosis
Animal bites
Leishmaniasis
Rickettsial diseases
Marine envenomation/dermatitis
Photoallergic dermatitis and phytophotodermatitis

Table 200.6

Common Clinical Findings and Associated Infections

COMMON CLINICAL	INFECTIONS TO CONSIDER AFTER TROPICAL TRAVEL

FINDINGS	
Fever and rash	Dengue, chikungunya, Zika, rickettsial infections, enteric fever (skin lesions may be sparse or absent), acute HIV infection, measles
Fever and abdominal pain	Enteric fever, amebic liver abscess
Undifferentiated fever and normal or low white blood cell count	Dengue, malaria, rickettsial infection, enteric fever, chikungunya, Zika
Fever and hemorrhage	Viral hemorrhagic fevers (dengue and others), meningococcemia, leptospirosis, rickettsial infections
Fever and arthralgia or myalgia, sometimes persistent	Chikungunya, dengue, Zika
Fever and eosinophilia	Acute schistosomiasis, drug hypersensitivity reaction, fascioliasis and other parasitic infections (rare)
Fever and pulmonary infiltrates	Common bacterial and viral pathogens, legionellosis, acute schistosomiasis, Q fever, leptospirosis
Fever and altered mental status	Cerebral malaria, viral or bacterial meningoencephalitis, African trypanosomiasis, scrub typhus
Mononucleosis syndrome	Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, toxoplasmosis, acute HIV infection
Fever persisting >2 wk	Malaria, enteric fever, EBV infection, CMV infection, toxoplasmosis, acute HIV infection, acute schistosomiasis, brucellosis, tuberculosis, Q fever, visceral leishmaniasis (rare)
Fever with onset >6 wk after travel	*Plasmodium vivax* or *P. ovale* malaria, acute hepatitis (B, C, or E), tuberculosis, amebic liver abscess

From Wilson ME: Post-travel evaluation. In CDC *Yellow Book,* Chapter 5 (Table 5.6). https://wwwnc.cdc.gov/travel/yellowbook/2018/post-travel-evaluation/fever-in-returned-travelers .

Fever is a particularly worrisome symptom. Children with a febrile/systemic illness following recent travel to a malarial destination should be promptly evaluated for malaria, especially if having traveled to sub-Saharan Africa and Papua New Guinea. *P. falciparum* malaria will generally present within 1-2 mo after return from travel to a malaria-endemic area, but can occur within the 1st yr after return. In contrast, symptoms of *P. vivax* or *P. ovale* malaria are typically later in onset following travel (i.e., several months), are milder in disease severity, and may occur in a relapsing pattern if undiagnosed or improperly untreated. Other symptoms of malaria can be nonspecific and include chills, malaise, headache, myalgias, vomiting, diarrhea, cough, and possible seizures. Children are more likely than adults to have higher fevers and also gastrointestinal symptoms, hepatomegaly, splenomegaly, and severe anemia. Thrombocytopenia (without increased bleeding) and fever in a child returning from an endemic area are highly suggestive of malaria.

Thick and thin blood smears need to be performed for diagnosis *if* malaria is clinically suspected. If results are negative initially, 2 or more additional smears should be done 12-24 hr after the initial smears. Rapid malaria antigen tests (BinaxNOW Malaria) are FDA-approved and sensitive for diagnosing falciparum malaria. Treatment should be initiated immediately once the diagnosis is confirmed or empirically if presentation is severe with suspected malaria. Treatment should be determined in consultation with a pediatric infectious disease specialist and/or the CDC for updated information on the drugs of choice, which are similar to those for adults (see Chapter 314). Great caution should be used with young children, nonimmune patients, and pregnant patients with falciparum malaria, and hospitalization of these patients should be strongly considered until reliable improvement is observed.

Enteric (typhoid) fever should be considered in children with persistent or recurrent fevers following return from the Indian subcontinent. Multiple blood cultures and a stool culture may both be necessary to diagnosis enteric fever. **Dengue** is another cause of fever and systemic illness in ill travelers, particularly when returning from Southeast Asia, the Caribbean, Central and South America, or the Indian subcontinent. Many bacterial and protozoal causes of acute traveler's diarrhea may also result in fever and systemic symptoms in children. Additional travel-associated febrile, diarrheal, and dermatologic illnesses exist, of which the most common etiologies can be found in Tables 200.5 and 200.6 .

The Adolescent Traveler

The preparation of an adolescent interested in traveling abroad can pose a challenge for most clinicians. Study abroad, gap year, humanitarian volunteer work, adventure, and tourism are among many reasons for travel to countries with limited resources. While many travel-related problems discussed in this chapter are relevant to this group, other high-risk activities such as sexual intercourse, alcohol consumption, driving, use of illicit drugs, and adventure travel (mountain climbing, white water rafting, kayaking, biking) require special attention and discussion with the traveler and parents/guardians. Topics such as HIV exposure, sexually transmitted infections, sexual assault, and unplanned pregnancy may require specific preventive strategies such as condom use, contraception, and postexposure HIV prophylaxis.

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[*] See the map at http://wwwnc.cdc.gov/travel/yellowbook/2016/chapter-3-infectious-diseases-related-to-travel/meningococcal-disease .

CHAPTER 201

Fever

Linda S. Nield, Deepak Kamat

Fever is defined as a rectal temperature ≥38°C (100.4°F), and a value >40°C (104°F) is called **hyperpyrexia** . Traditionally, body temperature fluctuates in a defined normal range (36.6-37.9°C [97.9-100.2°F] rectally), so that the highest point is reached in early evening and the lowest point is reached in the morning. Any abnormal rise in body temperature should be considered a symptom of an underlying condition. The range of normal temperature is broad, 35.5-37.7°C (96-100°F); if 37°C (98.6°F) is considered normal, many cluster around this temperature (36.1-37.5°C [97-99.5°F]).

Pathogenesis

Body temperature is regulated by thermosensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature, as well as by cold and warm receptors located in skin and muscles. Thermoregulatory responses include redirecting blood to or from cutaneous vascular beds, increased or decreased sweating, regulation of extracellular fluid (ECF) volume by arginine vasopressin, and behavioral responses, such as seeking a warmer or cooler environmental temperature.

Three different mechanisms can produce fever: pyrogens, heat production exceeding heat loss, and defective heat loss. The 1st mechanism involves endogenous and exogenous pyrogens that raise the hypothalamic temperature set point. **Endogenous pyrogens** include the cytokines interleukin (IL)-1 and IL-6, tumor necrosis factor (TNF)-α, and interferon (IFN)-β and IFN-γ. Stimulated leukocytes and other cells produce lipids that also serve as endogenous pyrogens. The best-studied lipid mediator is prostaglandin E_2, which attaches to the prostaglandin receptors in the hypothalamus to produce the new temperature set point. Along with infectious diseases and drugs, malignancy and inflammatory diseases can cause fever through the production of endogenous pyrogens. Some substances produced within the body are not pyrogens but are capable of stimulating endogenous pyrogens. Such substances include antigen-antibody complexes in the presence of complement, complement components, lymphocyte products, bile acids, and androgenic steroid metabolites. **Exogenous pyrogens** come from outside the body and consist of mainly infectious pathogens and drugs. Microbes, microbial toxins, or other products of microbes are the most common exogenous pyrogens, which stimulate macrophages and other cells to produce endogenous pyrogens. **Endotoxin** is one of the few substances that can directly affect thermoregulation in the hypothalamus as well as stimulate endogenous pyrogen release. Many drugs cause fever, and the mechanism for increasing body temperature varies with the class of drug. Drugs that are known to cause fever include vancomycin, amphotericin B, and allopurinol.

Heat production exceeding heat loss is the 2nd mechanism that leads to fever; examples include salicylate poisoning and malignant hyperthermia. **Defective heat loss** , the 3rd mechanism, may occur in children with ectodermal dysplasia or victims of severe heat exposure.

Etiology

The causes of fever can be organized into 4 main categories: *infectious, inflammatory, neoplastic,* and *miscellaneous.* Self-limited viral infections (common cold, influenza, gastroenteritis) and uncomplicated bacterial infections (otitis media, pharyngitis, sinusitis) are the most common causes of acute fever. The body temperature rarely rises above potentially lethal levels (42°C [107.6°F]) in the neurologically intact child unless extreme hyperthermic environmental conditions are present or other extenuating circumstances exist, such as underlying malignant hyperthermia or thyrotoxicosis.

The pattern of the fever can provide clues to the underlying etiology. Viral infections typically are associated with a slow decline of fever over 1 wk, whereas bacterial infections are often associated with a prompt resolution of fever after effective antimicrobial treatment. Although antimicrobials can result in rapid elimination of bacteria, if tissue injury has been extensive, the inflammatory response and fever can continue for days after all microbes have been eradicated.

Intermittent fever is an exaggerated circadian rhythm that includes a period of normal temperatures on most days; extremely wide fluctuations may be termed **septic** or **hectic fever** . **Sustained fever** is persistent and does not vary by >0.5°C (0.9°F)/day. **Remittent fever** is persistent and varies by >0.5°C/day. **Relapsing fever** is characterized by febrile periods separated by intervals of normal temperature; **tertian fever** occurs on the 1st and 3rd days (malaria caused by *Plasmodium vivax*), and **quartan fever** occurs on the 1st and 4th days (malaria caused by *Plasmodium malariae*). Diseases characterized by relapsing fevers should be distinguished from infectious diseases that have a tendency to relapse (Table 201.1). **Biphasic fever** indicates a single illness with 2 distinct periods (**camelback fever** pattern); poliomyelitis is the classic example. A biphasic course is also characteristic of other enteroviral infections, leptospirosis, dengue fever, yellow fever, Colorado tick fever, spirillary rat-bite fever *(Spirillum minus)*, and the African hemorrhagic fevers (Marburg, Ebola, and Lassa fevers). The term **periodic fever** is used narrowly to describe fever syndromes with a regular periodicity (cyclic neutropenia and periodic fever, aphthous stomatitis, pharyngitis, adenopathy) or more broadly to include disorders characterized by recurrent episodes of fever that do not follow a strictly periodic pattern (familial Mediterranean fever, TNF receptor–associated periodic syndrome [Hibernian fever], hyper-IgD syndrome, Muckle-Wells syndrome) (see Chapter 188). **Factitious fever** , or self-induced fever, may be caused by intentional manipulation of the thermometer or injection of pyrogenic material.

Table 201.1

Fevers Prone to Relapse

INFECTIOUS CAUSES
Relapsing fever (*Borrelia recurrentis*)
Q fever (*Coxiella burnetii*)
Typhoid fever (*Salmonella typhi*)
Syphilis (*Treponema pallidum*)
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Blastomycosis
Melioidosis (*Pseudomonas pseudomallei*)
Lymphocytic choriomeningitis (LCM) infection
Dengue fever
Yellow fever
Chronic meningococcemia

Colorado tick fever Leptospirosis Brucellosis Oroya fever (*Bartonella bacilliformis*) Acute rheumatic fever Rat-bite fever (*Spirillum minus*) Visceral leishmaniasis Lyme disease (*Borrelia burgdorferi*) Malaria Babesiosis Noninfluenza respiratory viral infection Epstein-Barr virus infection
NONINFECTIOUS CAUSES
Behçet disease Crohn disease Weber-Christian disease (panniculitis) Leukoclastic angiitis syndromes Sweet syndrome Systemic lupus erythematosus and other autoimmune disorders
PERIODIC FEVER SYNDROMES (see Chapter 188)
Familial Mediterranean fever Cyclic neutropenia Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) Hyper–immunoglobulin D syndrome Hibernian fever (tumor necrosis factor superfamily immunoglobulin A–associated syndrome [TRAPS]) Muckle-Wells syndrome Others

The **double quotidian fever** (or fever that peaks twice in 24 hr) is classically associated with inflammatory arthritis. In general, a single isolated fever spike is not associated with an infectious disease. Such a spike can be attributed to the infusion of blood products and some drugs, as well as some procedures, or to manipulation of a catheter on a colonized or infected body surface. Similarly, temperatures in excess of 41°C (105.8°F) are most often associated with a noninfectious cause. Causes for very high temperatures (>41°C [105.8°F]) include central fever (resulting from central nervous system dysfunction involving the hypothalamus or spinal cord injury), malignant hyperthermia, malignant neuroleptic syndrome, drug fever, or heat stroke. Temperatures that are lower than normal (<36°C [96.8°F]) can be associated with overwhelming sepsis but are more often related to cold exposure, hypothyroidism, or overuse of antipyretics.

Clinical Features

The clinical features of fever can range from no symptoms to extreme malaise. Children might complain of feeling hot or cold, display facial flushing, and experience shivering. Fatigue and irritability may be evident. Parents often report that the child looks ill or pale and has a decreased appetite. The underlying etiology also produces accompanying symptoms. Although the underlying etiologies can manifest in varied ways clinically, there are some predictable features. For example, **fever with petechiae** in an ill-appearing patient indicates the high possibility of life-threatening conditions such as meningococcemia, Rocky Mountain spotted fever, or acute bacterial endocarditis.

Changes in heart rate, most frequently tachycardia, accompany fever. Normally heart rate rises by 10 beats/min per 1°C (1.8°F) rise in temperature for children >2 mo old. Relative tachycardia, when the pulse rate is elevated disproportionately to the temperature, is usually caused by noninfectious diseases or infectious diseases in which a toxin is responsible for the clinical manifestations. **Relative bradycardia** (temperature-pulse dissociation), when the pulse rate remains low in the presence of fever, can accompany typhoid fever, brucellosis, leptospirosis, or drug fever. Bradycardia in the presence of fever also may be a result of a conduction defect resulting from cardiac involvement with acute rheumatic fever, Lyme disease, viral myocarditis, or infective endocarditis.

Evaluation

Most acute febrile episodes in a normal host can be diagnosed by a careful history and physical examination and require few, if any, laboratory tests. Because infection is the most likely etiology of the acute fever, the evaluation should initially be geared to discovering an underlying infectious cause (Table 201.2). The details of the history should include the onset and pattern of fever and any accompanying signs and symptoms. The patient often displays signs or symptoms that provide clues to the cause of the fever. Exposures to other ill persons at home, daycare, and school should be noted, along with any recent travel or medications. The past medical history should include information about underlying immune deficiencies or other major illnesses and receipt of childhood vaccines.

Table 201.2

Evaluation of Acute Fever

Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates), travel, medications, other underlying disorders, immunizations
Physical examination: complete, with focus on localizing symptoms
Laboratory studies on a case-by-case basis:
- Rapid antigen testing
- Nasopharyngeal: respiratory viruses by polymerase chain reaction
- Throat: group A streptococcus
- Stool: NAAT for enteric pathogens, calprotectin
- Blood: complete blood count, blood culture, C-reactive protein, sedimentation rate, procalcitonin
- Urine: urinalysis, culture
- Cerebrospinal fluid: cell count, glucose, protein, Gram stain, culture
- Chest radiograph or other imaging studies on a case-by-case basis

NAAT, Nucleic acid amplification test.

Physical examination should begin with a complete evaluation of vital signs, which should include pulse oximetry because hypoxia may indicate lower respiratory infection. In the acutely febrile child, the physical examination should focus on any localized complaints, but a complete head-to-toe screen is recommended, because clues to the underlying diagnosis may be found. For example, palm and sole lesions may be discovered during a thorough skin examination and provide a clue for infection with **coxsackievirus** .

If a fever has an obvious cause, then laboratory evaluation may not be required, and management is tailored to the underlying cause with as-needed reevaluation. If the cause of the fever is not apparent, further diagnostic evaluation should be considered on a case-by-case basis. The history of presentation and abnormal physical examination findings guide the evaluation. The child with respiratory symptoms and hypoxia may require a chest radiograph or rapid antigen testing for **respiratory syncytial virus** or **influenza** . The child with pharyngitis can benefit from rapid antigen detection testing for **group A streptococcus** and a throat culture. Dysuria, back pain, or a history of vesicoureteral reflux should prompt a urinalysis and urine culture, and bloody diarrhea should prompt a stool culture. A complete blood count and blood culture should be considered in the ill-appearing child, along with cerebrospinal fluid studies if the child has neck stiffness or if the possibility of meningitis is considered. Well-defined high-risk groups require a more extensive evaluation on the basis of age, associated disease, or immunodeficiency status and might warrant prompt antimicrobial therapy before a pathogen is identified. Fever in neonates and young infants (0-3 mo old), fever in older children, and fever of unknown origin are discussed in Chapters 202 , 203 , and 204 , respectively.

Management

Although fever is a common parental worry, no evidence supports the belief that high fever can result in brain damage or other bodily harm, except in rare instances of febrile status epilepticus and heat stroke. *Treating fever in self-limiting illnesses for the sole reason of bringing the body temperature back to normal is not necessary in the otherwise healthy child* **.** Most evidence suggests that fever is an adaptive response and should be treated only in select circumstances. In humans, increased temperatures are associated with decreased microbial replication and an increased inflammatory response. Although fever can have beneficial effects, it also increases oxygen consumption, carbon dioxide production, and cardiac output and can exacerbate cardiac insufficiency in patients with heart disease or chronic anemia (e.g., sickle cell disease), pulmonary insufficiency in patients with chronic lung disease, and metabolic instability in patients with diabetes mellitus or inborn errors of metabolism. Children between 6 mo and 5 yr of age are at increased risk for simple febrile seizures. *The focus of the evaluation and treatment of febrile seizures is aimed at determining the underlying cause of the fever.* Children with idiopathic epilepsy also often have an increased frequency of seizures associated with a fever. High fever during pregnancy may be teratogenic.

Fever with temperatures <39°C (102.2°F) in healthy children generally does not require treatment. However, as temperatures become higher, patients tend to become more uncomfortable, and treatment of fever is then reasonable. If a child is included in one of the high-risk groups previously discussed or if the child's caregiver is concerned that the fever is adversely affecting the child's behavior and causing discomfort, treatment may be given to hasten the resolution of the fever. Other than providing symptomatic relief, antipyretic therapy does not change the course of infectious diseases. Encouraging good hydration is the 1st step to replace fluids that are lost related to the increased metabolic demands and insensible losses of fever. Antipyretic therapy is beneficial in high-risk patients and patients with discomfort. **Hyperpyrexia** (>41°C [105.8°F]) indicates high probability of hypothalamic disorders or central nervous system hemorrhage and should be treated with antipyretics. Some studies show that hyperpyrexia may be associated with a significantly increased risk of serious bacterial infection, but other studies have not substantiated this relationship. The most common antipyretics are acetaminophen, 10-15 mg/kg/dose every 4 hr, and ibuprofen in children >6 mo old at 5-10 mg/kg/dose every 8 hr. Antipyretics reduce fever by reducing production of prostaglandins. If used appropriately, antipyretics are safe; potential adverse effects include liver damage (acetaminophen) and gastrointestinal or kidney disturbances (ibuprofen). To reduce fever most safely, the caregiver should choose 1 type of medication and clearly record the dose and time of administration so that overdosage does not occur, especially if multiple caregivers are involved in the management. Physical measures such as tepid baths and cooling blankets are not considered effective to reduce fever. Evidence is also scarce for the use of complementary and alternative medicine interventions.

Fever caused by specific underlying etiologies resolves when the condition is properly treated. Examples include administration of intravenous immunoglobulin to treat Kawasaki disease or the administration of antibiotics to treat bacterial infections.

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CHAPTER 202

Fever Without a Focus in the Neonate and Young Infant

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Fever is a common reason for neonates and young infants to undergo medical evaluation in the hospital or ambulatory setting. For this age-group (0-3 mo), **fever without a focus** refers to a rectal temperature of 38°C (100.4°F) or greater, without other presenting signs or symptoms. The evaluation of these patients can be challenging because of the difficulty distinguishing between a serious infection (bacterial or viral) and a self-limited viral illness. The etiology and evaluation of fever without a focus depend on the age of the child. Three age-groups are typically considered: neonates 0-28 days, young infants 29-90 days, and children 3-36 mo. This chapter focuses on neonates and young infants.

Etiology and Epidemiology

Serious bacterial infection (SBI) occurs in 7% to 13% of neonates and young infants with fever. In this group, the most common SBIs are urinary tract infection (UTI; 5–13%), bacteremia (1–2%) and meningitis (0.2–0.5%). *Escherichia coli* is the most common organism causing SBI, followed by group B streptococcus (GBS). The decrease in GBS infections is related to increased screening of pregnant women and use of intrapartum antibiotic prophylaxis. Other, less common organisms include *Klebsiella* spp., *Enterococcus* spp., *Streptococcus pneumoniae* , *Neisseria meningitidis* , and *Staphylococcus aureus* (Table 202.1). *Listeria monocytogenes* is a rare cause of neonatal infections, potentially related to changes in public health education and improvements in food safety. Additional details about specific bacteria are available in the following chapters: *Escherichia coli* (Chapter 227), GBS (Chapter 211), *Streptococcus pneumoniae* (Chapter 209), *Neisseria meningitidis* (Chapter 218), *Staphylococcus aureus* (Chapter 208.1), and *Listeria monocytogenes* (Chapter 215). Specific bacterial infections that can present with fever in this age-group, although often with symptoms other than isolated fever, include pneumonia (Chapter 428), gastroenteritis (Chapter 366), osteomyelitis (Chapter 704), septic arthritis (Chapter 705), omphalitis (Chapter 125), cellulitis, and other skin and soft tissue infections (Chapter 685).

Table 202.1

Bacterial Pathogens in Neonates and Young Infants With Urinary Tract Infection, Bacteremia, or Meningitis

FREQUENCY	URINARY TRACT INFECTION	BACTEREMIA AND MENINGITIS
Common	*Escherichia coli*	*Escherichia coli* Group B streptococcus
Less common	*Klebsiella* spp. *Enterococcus* spp.	*Streptococcus pneumoniae* *Staphylococcus aureus* *Klebsiella* spp.
Rare	Group B streptococcus	
	Staphylococcus aureus *Pseudomonas aeruginosa* *Enterobacter* spp. *Citrobacter* spp. *Proteus mirabilis*	*Listeria monocytogenes* *Neisseria meningitidis* *Salmonella* spp. *Enterobacter* spp. *Enterococcus* spp. *Cronobacter sakazakii*

Herpes simplex virus (**HSV**) infections (Chapter 279) should also be considered in febrile neonates <28 days old, particularly given the high rate of mortality and significant morbidity among survivors. Neonatal HSV is rare, with a prevalence of 0.2–0.3% among febrile neonates. Most of these infections are caused by HSV type 2, though HSV type 1 can also cause neonatal infection. Neonates with disseminated disease and skin, eye, and mouth (SEM) disease typically present at 5-12 days of life. Neonates with central nervous system (CNS) disease generally present at 16-19 days. Perinatally acquired HSV may occasionally manifests beyond 28 days of age, although some of these later-onset cases may represent postnatal acquisition.

In febrile infants who appear well, viral illnesses are much more common than bacterial or serious viral infections. The most common viruses include respiratory syncytial virus (**RSV** ; Chapter 287), enteroviruses (Chapter 277), influenza viruses (Chapter 285), parainfluenza viruses (Chapter 286), human metapneumovirus (Chapter 288), adenovirus (Chapter 289), parechoviruses

(Chapter 277), and rhinovirus (Chapter 290).

Clinical Manifestations

In neonates and young infants, bacterial and viral infections can present with isolated fever or nonspecific symptoms, making diagnosis of serious illnesses challenging. Some neonates and young infants will have signs of systemic illness at presentation, including abnormal temperature (hypothermia <36°C [96.8°F], fever ≥38°C [100.4°F), abnormal respiratory examination (tachypnea >60 breaths/min, respiratory distress, apnea), abnormal circulatory examination (tachycardia >180 beats/min, delayed capillary refill >3 sec, weak or bounding pulses), abnormal abdominal examination, abnormal neurologic examination (lethargy, irritability, alterations in tone), or abnormal skin examination (rash, petechiae, cyanosis). Infants with **septic arthritis** or **osteomyelitis** may appear well except for signs around the involved joint or bone or may only manifest with pseudoparalysis (disuse) and paradoxical irritability (pain when attempting to comfort the child).

Diagnosis

No consensus exists on the diagnosis and empirical treatment of febrile neonates and young infants. Traditionally, all neonates <60 or <90 days of age were hospitalized; underwent laboratory evaluation of the blood, urine, and cerebrospinal fluid (CSF); and received empirical antibiotics. Additionally, some patients had stool cultures, chest radiographs, HSV evaluation, and/or received empirical antiviral agents. Under this approach, many infants without SBI or serious viral infection received evaluation, treatment, and hospitalization. Protocols were subsequently developed to identify infants at lower risk of SBI, who may be managed outside the hospital setting. The 3 most widely used are the Rochester, Philadelphia, and Boston criteria (Table 202.2). Clinical prediction rules are further discussed later in the Other Diagnostic Studies section. Despite these protocols, substantial variation continues to exist in the approach to and management of the febrile infant. *It must be emphasized that these criteria apply to the well-appearing child; those who appear critically ill (septic) require prompt evaluation, resuscitation, and empirical antibiotic therapy (within 1 hr).*

Table 202.2

Protocols to Identify Febrile Infants at Low Risk of Serious Bacterial Infection (SBI)

BOSTON CRITERIA

Febrile infants 0-27 days
  1. Empirical antimicrobials
  2. Admit to hospital

Febrile infants 28-89 days: Non–low risk
  1. Empirical antimicrobials
  2. Admit to hospital

Febrile infants 28-89 days: Low risk
  1. One dose of IV Ceftriaxone
  2. Discharge to home with follow-up in 24 hr
  3. Risk of SBI 5.4%

Low Risk Criteria

1. Normal examination and well-appearing
2. Caregiver available by telephone
3. No antimicrobials, no DTaP vaccine in previous 48 hours
4. Meets all laboratory/radiographic criteria
    a. Peripheral blood: WBC count <20,000 per mm^3
    b. Urine
     i. Urinalysis with <10 WBCs per hpf
     ii. Dipstick negative for leukocyte esterase
    c. CSF: WBC count <10 per mm^3
    d. Chest radiograph: No infiltrate on chest radiograph (only obtained if signs of respiratory illness)

PHILADELPHIA CRITERIA

Febrile infants 0-28 days
  1. Empirical antimicrobials
  2. Admit to hospital

Febrile infants 29-56 days: Non–low risk
  1. Empirical antimicrobials
  2. Admit to hospital

Febrile infants 29-56 days: Low risk
  1. No antibiotics
  2. Discharge to home with follow-up in 24 hr
  3. Risk of SBI <1%

Low Risk Criteria

1. Normal examination and well-appearing
2. Caregiver available to be contacted
3. Meets all laboratory/ radiographic criteria
    a. Peripheral blood
     i. WBC count <15,000 per mm^3
     ii. Band-neutrophil ratio <0.2
    b. Urine
     i. <10 WBCs per hpf
     ii. No bacteria on Gram stain
    c. CSF
     i. WBC count <8 per mm^3
     ii. Negative Gram stain
     iii. Non-bloody specimen

        - d. Chest radiograph: No infiltrate
        - e. Stool: (only obtained if loose, watery stool)
            - i. No blood
            - ii. Few or no WBC on smear

ROCHESTER CRITERIA

Febrile infants 0-60 days: Non–low risk
1. Empirical antimicrobials
2. Admit to hospital

Febrile infants 0-60 days: Low risk
1. No antimicrobials
2. Discharge to home with follow-up in 24 hr
3. Risk of SBI 1%

Low Risk Criteria

1. Normal examination and well-appearing
2. Previously healthy, term gestation, no perinatal/recent antimicrobial therapy, no unexplained hyperbilirubinemia
3. Meets all laboratory/ radiographic criteria
    - a. Peripheral blood
        - i. WBC count 5-15,000 per mm^3
        - ii. Absolute band count ≤1500 per mm^3
    - b. Urine
        - i. ≤10 WBCs per hpf
        - ii. No bacteria on Gram stain
    - c. CSF: Not included
    - d. Chest radiograph: No infiltrate (only obtained if signs of respiratory illness)
    - e. Stool (only obtained if loose, watery stool)
        - i. ≤5 WBC per hpf

DTaP, Diphtheria-tetanus-pertussis; WBC, white blood cell; CSF, cerebrospinal fluid; IV, intravenous; SBI, serious bacterial infection; hpf, high-power field

Many experts advocate that all neonates ≤28 days old undergo a complete evaluation for serious infection, receive empirical antimicrobials, and be hospitalized. Of the 3 widely used criteria, only the Rochester criteria allow neonates ≤28 days to be designated as "low risk" and managed outside the hospital without antimicrobials. In one study, <1% of low-risk infants ≤28 days old had SBI; however, in another study applying the Boston and Philadelphia criteria to neonates, 3–4% of those classified as low risk had SBI.

Young febrile infants ≥29 days old who appear ill (with signs of systemic illness) require complete evaluation for SBI, including antimicrobials and hospitalization; however, well-appearing infants can be managed safely as outpatients using low-risk criteria as indicated in Table 202.2 . In each of these approaches, infants must have a normal physical examination, must be able to reliably obtain close follow-up, and must meet certain laboratory and/or radiographic criteria. Based on these protocols, all infants following the Boston or Philadelphia criteria would undergo lumbar puncture (LP), whereas low-risk infants following the Rochester criteria would not. There is substantial variation in clinical practice in the performance of LPs in well-appearing infants >28 days. Clinicians should consider multiple factors, including the home situation and ability to contact the family, when deciding about LP in this age-group.

In addition, approximately 35% of infants with **bacterial meningitis** do not have a positive blood culture.

The protocols discussed in Table 202.2 were initially developed for use in the emergency department (ED). Infants evaluated in the office setting may warrant a different approach when a relationship between the physician and family already exists to facilitate clear communication and timely follow-up. In one large study of febrile infants <3 mo old who were initially evaluated for fever in the office setting, clinicians hospitalized only 36% of infants but initiated antibiotics in 61 of the 63 infants with bacteremia or bacterial meningitis. These findings suggest that, with very close follow-up (including multiple in person visits or frequent contacts by telephone), some febrile infants perceived to be at low risk for **invasive bacterial infection** (**IBI** ; bacteremia and meningitis), on the basis of history, physical examination, and normal but limited laboratory testing, can be managed in an office-based setting. It is important to note that 3% of infants with SBI did not initially receive empirical antibiotics, necessitating careful consideration of risks and benefits of selective rather than universal testing and empirical antibiotic treatment of febrile infants evaluated in the office setting.

Viral Respiratory Illness

Several studies have demonstrated a decreased risk of SBI in infants with positive testing for influenza or RSV, although the risk of UTI remains significant. In one prospective study, the risk of SBI in neonates <28 days old was not altered by RSV status. Given these data, young febrile infants with bronchiolitis may not require LP, particularly if they can be closely observed or have close follow-up.

Urinary Tract Infection and Bacterial Meningitis

Traditionally, infants with abnormal findings on urinalysis (UA) would undergo complete evaluation for infection, including LP. In well-appearing infants >28 days old with an abnormal UA, some evidence suggests that the risk of bacterial meningitis is extremely low, <0.5%. For neonates 0-28 days, the risk of concomitant bacterial meningitis with UTI is 1–2%.

CSF pleocytosis in the absence of bacterial meningitis (i.e., **sterile pleocytosis**) has been reported in infants with UTI. The cause is uncertain, with some studies attributing this phenomenon to traumatic LPs or undetected viral infection rather than inflammation in the context of systemic illness.

Laboratory Diagnosis

Complete Blood Count

The peripheral complete blood cell count (CBC) and differential are frequently obtained by providers when evaluating febrile neonates and infants. The white blood cell (WBC) count alone cannot accurately predict SBI risk. In one series, isolated use of the WBC cutoffs in the Rochester criteria, outside 5-15,000 WBCs/mm^3 , would miss at least 33% of infants with bacteremia and 40% of those with meningitis. A prospective study found no increased risk of SBI in febrile, well-appearing infants with leukopenia (WBC count <5,000/mm^3). The WBC count combined with other factors may help determine an infant's risk of SBI, but it should not be used in isolation to predict infection risk.

Blood Culture

The ability to identify pathogens in the blood depends on the volume of blood, the timing of the blood culture in relation to antimicrobial administration, and to a lesser degree, on the number of blood cultures obtained. A negative blood culture does not eliminate the risk of bacterial meningitis; in one study, 38% of infants with culture-proven bacterial meningitis had negative blood cultures. For additional information on the time to positivity of blood cultures in neonates and young infants, see “Discharge from the Hospital,” later.

Urinalysis

Different methods can assist in making a presumptive diagnosis of UTI while awaiting results of a urine culture. *Traditional* UA consists of dipstick biochemical analysis of urine for nitrites or leukocyte esterase (LE) and microscopic examination of the urine for WBCs and bacteria. One study found that the traditional UA had a higher negative predictive value (NPV) than dipstick alone (99.2% vs 98.7%), but that dipstick alone had a higher positive predictive value (PPV, 66.8% for dipstick alone vs 51.2% for traditional UA). *Enhanced* UA includes hemocytometer cell count (to decrease variability of urine cell counts) and Gram stain on uncentrifuged urine. The enhanced UA has a higher sensitivity but comparable specificity to traditional UA. However, the enhanced UA has not been studied in the most common protocols for evaluation of the febrile infant, and many institutions/office practices do not perform this test.

Cerebrospinal Fluid

CSF evaluation consists of culture and Gram stain, cell count, glucose and protein. Polymerase chain reaction (PCR) testing may also be sent based on the clinical scenario, usually for enterovirus or HSV. Normal CSF parameters vary by age of the infant and should be interpreted in combination with other clinical and historical risk factors, given that some infants with normal CSF parameters may have CNS infections (Table 202.3). The CSF Gram stain can be a useful adjunct to other CSF parameters given the high specificity of the test (99.3–99.9%; i.e., relatively few false-positive results), although the range of reported sensitivity is much broader (67–94.1%).

Table 202.3

Values of Cerebrospinal Fluid (CSF) Studies in Neonates and Infants by Age

CSF WHITE BLOOD CELL COUNTS	**CELLS/mm^3**
Upper limit of normal by age*	
1-28 days	18
29-60 days	8.5
61-90 days	8.5
90th percentile by age †	
0-7 days	26
8-28 days	8–9
29-56 days	6–8
95th percentile by age ‡	
0-28 days	19
29-56 days	9
CSF Protein	**mg/dL**
Upper limit of normal by age*	
1-28 days	131
29-60 days	105.5
61-90 days	71

90th percentile by age †	
0-7 days	153
8-28 days	84–106
29-56 days	84–105
95th percentile by age §	
0-14 days	132
15-28 days	100
29-42 days	89
43-56 days	83
CSF Glucose	**mg/dL**
Lower limit of normal by age*	
1-28 days	30
29-60 days	30.5
61-90 days	33.5
10th percentile for infants 0-56 days †	38–43

[*] Data from Byington CL, Kendrick J, Sheng X: Normative cerebrospinal fluid profiles in febrile infants, *J Pediatr* 158(1):130–134, 2011. All infants had nontraumatic lumbar puncture (LP) and no evidence of bacterial or viral infection.

[†] Data from Chadwick SL, Wilson JW, Levin JE, Martin JM: Cerebrospinal fluid characteristics of infants who present to the emergency department with fever: establishing normal values by week of age, *Pediatr Infect Dis J* 30(4):e63–e67, 2011. All infants were excluded if they had identified viral or bacterial meningitis, positive blood or urine cultures, a ventriculoperitoneal shunt, recent neurosurgery/antibiotics/seizure, or a traumatic LP.

[‡] Data from Kestenbaum LA, Ebberson J, Zorc JJ, et al: Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants, *Pediatrics* 125(2):257–264, 2010. Infants were excluded for traumatic LP, serious bacterial infection, congenital infection, seizure, presence of ventricular shunt, or positive CSF testing for enterovirus.

[§] Data from Shah SS, Ebberson J, Kestenbaum LA, et al: Age-specific reference values for cerebrospinal fluid protein concentration in neonates and young infants, *J Hosp Med* 6(1):22–27, 2011. Infants were excluded for traumatic LP, serious bacterial infection, congenital infection, seizure, presence of a ventricular shunt, positive CSF testing for enterovirus, or elevated serum bilirubin.

The interpretation of CSF can be challenging in the setting of a traumatic LP, where the CSF is contaminated with peripheral blood. Some clinicians assume a ratio of WBCs to red blood cells (RBCs) of 1 : 500 in the CSF. Others advocate calculating the expected CSF WBCs based on the peripheral blood WBCs and RBCs and then using the observed-to-predicted ratio of CSF WBCs to aid in the identification of bacterial meningitis. This calculation assumes that the ratio of WBCs to RBCs in the peripheral blood remains constant after introduction into the CSF. The formula is:

$$\text{Predicted CSF WBCs} = \text{CSF RBCs} \times (\text{Peripheral blood WBCs}/\text{Peripheral blood RBCs})$$

One retrospective cohort study concluded that an observed/predicted CSF WBC ratio of ≤0.01 was helpful in predicting the absence of bacterial meningitis; however, another retrospective cohort study and one case series of traumatic LPs concluded that adjustment of CSF WBC count does not improve the accuracy of diagnosis of meningitis in patients with traumatic LPs. Clinicians may consider hospitalization and empirical antimicrobials in patients with traumatic LPs (per the Philadelphia criteria) given the challenge of interpreting the CSF WBC count when there is blood contamination of the specimen.

Treatment with antibiotics prior to LP can complicate the interpretation of CSF parameters. CSF cultures are negative relatively rapidly after antibiotic administration, within 2 hr for *N. meningitidis* and 4-24 hr for *S. pneumoniae* . In patients with bacterial meningitis, CSF glucose increases to normal range, usually within 4-24 hr of antibiotic administration, while CSF protein concentrations, despite decreasing, remain abnormal for >24 hr after antibiotic administration. Changes in CSF WBC count and absolute neutrophil count (ANC) are minimal in the 1st 24 hr of antibiotic therapy. Therefore, CSF findings can provide relevant management information even in the setting of antibiotic administration before LP. Multiplex PCR testing for common bacterial pathogens should not be affected by prior antibiotic therapy.

Herpes Simplex Virus Testing

No consensus exists on which neonates should be tested and empirically treated for HSV infection. Historical and clinical features that should raise concern for HSV include exposure to individuals infected with HSV, particularly mothers with primary HSV infections or first-time genital infections, seizure or abnormal neurologic examination, vesicular rash, ill appearance, apnea, hypothermia, petechial rash/excessive bleeding, or a history of a scalp electrode. However, neonates with HSV can present without any high-risk clinical or historical features, particularly with early isolated CNS disease. Published approaches to neonatal HSV include (1) testing and empirical treatment of all neonates <21 days old who are evaluated for infection; (2) testing and empirical treatment of neonates with the presence of high-risk clinical features for HSV; and (3) testing and empirical treatment for all neonates with high-risk features plus testing the

CSF of all neonates <21 days old while deferring empirical acyclovir in those without high-risk features, unless the CSF HSV PCR test is positive.

The American Academy of Pediatrics (AAP) Committee on Infectious Diseases recommends that neonates undergoing evaluation for HSV have the following laboratory studies performed: surface cultures of the mouth, conjunctiva, nasopharynx, rectum, and any vesicles; CSF PCR (sensitivity: 75–100%); whole blood PCR; and serum levels of alanine transaminase (ALT). HSV PCR testing of the mouth, conjunctiva, nasopharynx, rectum, and vesicles has been shown to be more sensitive than culture, with comparable specificity, although no direct comparisons have been performed in neonates.

Enterovirus Testing

Enterovirus is a common and typically benign cause of fever in febrile infants, although it can be difficult to distinguish from SBI on initial presentation. Enterovirus PCR testing of the CSF is a sensitive and rapid means to diagnose infection. One retrospective study of patients with CSF enterovirus testing found no cases of bacterial meningitis in patients with positive enterovirus PCR; this study did not include neonates ≤28 days old. Several studies have demonstrated shorter length of stay, fewer antibiotics, and lower cost among infants with positive CSF enterovirus test results. These results suggest that during local enterovirus seasons, and if PCR testing is available, testing for enterovirus may be of benefit in the evaluation of febrile infants and neonates. Some centers have implemented multiplex PCR panels, which permit testing for multiple viruses, including enterovirus and HSV (and bacteria), simultaneously.

Other Diagnostic Studies

Investigations have examined the utility of inflammatory markers such as C-reactive protein (CRP) and serum procalcitonin (PCT) in the diagnosis of SBI and, more specifically, IBI (bacteremia and meningitis). One meta-analysis reported that PCT is superior to WBC count and CRP for the detection of IBI in children <3 yr old, whereas another found that PCT was inferior to prediction rules in identifying SBI in young infants. A prospective multicenter cohort study of febrile infants 7-91 days old determined that the PCT was better at identifying patients with IBI than CRP, WBC count, or ANC. Building on these results, clinical prediction rules for febrile infants, such as the **Step-by-Step** approach, incorporate PCT (≥0.5 ng/mL) and CRP (>20 mg/L), along with age ≤21 days, ill appearance, ANC >10,000/mm^3 , and pyuria in a stepwise approach to determine which patients are high risk for IBI; only 0.7% of infants who met none of those criteria had IBI.

As previously described, older infants with positive RSV and influenza testing have a very low risk of SBI beyond UTI. One large case-based survey demonstrated decreased admission rates and antibiotic use for infants with positive respiratory viral tests, and another study demonstrated that implementation of a care algorithm incorporating viral testing led to shorter length of stay and antibiotic course.

Chest radiographs are unlikely to be clinically useful in the evaluation of the febrile infant without respiratory symptoms. Studies that have examined routine use of radiographs have found limited utility because in infants without respiratory symptoms, most results will be normal, and abnormal results can be difficult to interpret.

Treatment

Antimicrobials

Neonates and infants hospitalized for evaluation for SBI should receive antimicrobial therapy. Commonly used regimens include (1) a third-generation cephalosporin (typically cefepime), (2) a third-generation cephalosporin and ampicillin, or (3) an aminoglycoside and ampicillin.

Ampicillin is the preferred treatment of GBS and covers *L. monocytogenes* and many *Enterococcus* spp. For neonates 0-28 days, options 2 or 3 have been recommended, given the risk of *L. monocytogenes* . For young infants >28 days, option 1 (third-generation cephalosporin: ceftriaxone) can be a reasonable choice. For ill-appearing infants or those with positive CSF Gram stains, additional antibiotics may include **vancomycin** or broad-spectrum antibiotics such as carbapenems. Local epidemiology and resistance patterns may assist in these choices. Neonates with concern for HSV should be empirically treated with high-dose acyclovir (60 mg/kg/day).

Treatment duration and route of antimicrobial administration depend on the infection. Additional details based on specific infections and organisms are available in the following chapters: meningitis (Chapter 129), urinary tract infection (Chapter 553), *Escherichia coli* (Chapter 227), GBS (Chapter 211), and HSV (Chapter 279).

Discharge From the Hospital

Traditionally, infants remained in the hospital receiving antimicrobial therapy until bacterial cultures were negative for 48 hr or even longer. Multiple studies have suggested that shorter culture observation periods (i.e., 24 or 36 hr) may be reasonable since most pathogens in the blood grow within this time frame when automated blood culture monitoring systems are used. In one multicenter retrospective cross-sectional study, 91% of blood cultures were positive by 24 hr and 96% by 36 hr. Fewer studies have evaluated the **time to positivity** of CSF and urine cultures, but in one large study of febrile infants 28-90 days old, all positive CSF cultures grew within 24 hr (median time to positivity, 18 hr). For blood cultures, 1.3% grew after 24 hr (median time to positivity, 16 hr), and for urine cultures, 0.9% grew after 24 hr (median time to positivity, 16 hr). For neonates undergoing evaluation for HSV, it is reasonable to await results of HSV testing before discharge to home. For patients with identified bacterial infections or HSV infections, the duration of the hospital stay will be determined by the specific pathogen and site of infection.

Prognosis

Most well-appearing neonates and young infants with fever recover completely and relatively quickly, depending on the etiology of the fever. Most infection-related mortality and long-term morbidity results from HSV infection and bacterial meningitis. For HSV, reported mortality rates for range from 27–31% for disseminated disease and 4–6% for CNS disease. Of those who survive, 83% of patients with disseminated disease and 31% of those with CNS disease will have normal development at 12 mo old. The mortality of bacterial meningitis varies by pathogen, but ranges from 4–15%. In one study of children who had meningitis as infants, 84% had normal development at age 5 yr.

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CHAPTER 203

Fever in the Older Child

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Fever is the most common reason for a child to seek medical care. While most infants and children have benign viral causes of fever, a small percentage will have more serious infections. Unlike the situation in infants <2 mo of age, in older children with fever, pediatricians can rely more readily on symptoms and physical examination findings to establish a diagnosis. Diagnostic testing, including laboratory testing and radiographic studies, is not routinely indicated unless diagnostic uncertainty exists after examination or the patient appears critically ill. Occult infections, such as urinary tract infection, may be present, and screening for such infections should be guided by patient age, patient gender, and degree of fever.

Diagnosis

The many potential causes of fever in older infants and children can be broadly categorized into viral and bacterial infections, further organized by body region, as well as the less common inflammatory, oncologic, endocrine, and medication-induced causes (Table 203.1).

Table 203.1

Etiologies of Fever in Children >2 Mo of Age

INFECTIOUS
Central Nervous System
Bacterial meningitis Viral meningitis Viral encephalitis Epidural abscess Brain abscess

Ear, Nose, and Throat
Acute otitis media Mastoiditis Viral upper respiratory infection (i.e., common cold) Acute bacterial sinusitis Acute streptococcal pharyngitis Acute viral pharyngitis Retropharyngeal abscess Ludwig angina Peritonsillar abscess Herpangina Herpes simplex virus gingivostomatitis Acute bacterial lymphadenitis Viral laryngotracheobronchitis (i.e., croup) Bacterial tracheitis Epiglottitis Lemierre syndrome
Face and Ocular
Parotitis (viral and bacterial) Erysipelas Preseptal cellulitis Orbital cellulitis
Lower Respiratory Tract
Acute viral bronchiolitis Pneumonia (viral and bacterial) Complicated pneumonia (e.g., empyema, pleural effusion) Tuberculosis
Cardiac
Pericarditis Myocarditis Endocarditis
Gastrointestinal
Gastroenteritis (viral and bacterial) Mesenteric adenitis Acute appendicitis Hepatitis Pancreatitis Gallbladder disease (e.g., cholecystitis, cholangitis) Intraabdominal abscess
Genitourinary
Urinary tract infection/pyelonephritis Renal abscess Epididymitis Pelvic inflammatory disease Tuboovarian abscess
Skin, Soft Tissue, and Muscle
Viral exanthemas (e.g., varicella, coxsackievirus, roseola, measles) Scarlet fever Syphilis Cellulitis Abscess Necrotizing fasciitis Myositis (viral and bacterial)
Bone and Joint
Osteomyelitis

Septic arthritis Transient synovitis Discitis
Toxin Mediated
Toxic shock syndrome Staphylococcal scalded skin syndrome
Invasive Bacterial Infections
Occult bacteremia Bacterial sepsis Bacterial meningitis Disseminated gonococcal infection
Vector-Borne (Tick, Mosquito)
Lyme disease Rickettsiae (e.g., Rocky Mountain spotted fever, ehrlichiosis) Arboviruses (e.g., West Nile virus) Dengue fever
Inflammatory
Kawasaki disease Acute rheumatic fever Systemic lupus erythematosus Inflammatory bowel disease Juvenile idiopathic arthritis Henoch-Schönlein purpura Other rheumatologic diseases (e.g., dermatomyositis) Periodic fever syndromes Serum-like sickness syndrome
Oncologic
Leukemia Lymphoma Solid tumors (e.g., neuroblastoma)
Endocrine
Thyrotoxicosis/thyroid storm
Medication Induced
Serotonin syndrome Anticholinergic toxidrome (e.g., antihistamines) Sympathomimetic toxidrome (e.g., cocaine) Salicylate toxicity
Other
Hemophagocytic lymphohistiocytosis Macrophage activation syndrome Ectodermal dysplasia Dysautonomia

Viral Infections

Viral infections are the most common cause of fever, and the prevalence of specific viral infections varies by season. In the summer and early fall, enteroviruses (e.g., coxsackieviruses) predominate, usually presenting as hand-foot-and-mouth disease, herpangina, aseptic meningitis, or a variety of other manifestations. In the late fall and winter, viral upper and lower respiratory tract infections such as respiratory syncytial virus (RSV) and influenza and gastrointestinal (GI) viruses such as norovirus and rotavirus are common. Parainfluenza virus is a common cause of **laryngotracheobronchitis (croup)** and occurs primarily in the fall and spring, affecting mostly infants and toddlers. Varicella is a less common cause of fever than in the past because of childhood vaccination but still occurs, with the highest incidence in winter and early spring.

Bacterial Infections

Although viral infections are the most common cause of fever in older infants and children and are often diagnosed based on symptoms and physical examination findings, bacterial infections also occur. Common bacterial infections include acute **otitis media** and **streptococcal pharyngitis (strep throat)** . Acute otitis media is diagnosed by the presence of a bulging, erythematous, and nonmobile tympanic membrane upon insufflation. Strep throat occurs most frequently in the late fall and winter and is uncommon before age 3 yr. The presence of focal auscultatory findings, including crackles, is suggestive of a lower respiratory tract infection, such as bacterial pneumonia, but may also be present among children with **bronchiolitis** . Atypical **pneumonia** caused by mycoplasma typically occurs in school-age children and is often associated with headache, malaise, and low-grade fever. The presence of neck pain or drooling may indicate a deep neck infection such as a **retropharyngeal abscess** , which occurs in infants and young children, or a **peritonsillar abscess** , which typically affects older children. Skin and soft tissue infections such as cellulitis and abscess may also present with fever, with the buttock a common area for abscesses in young children. Bone and joint infections such as **osteomyelitis** and **septic arthritis** may present with fever and refusal to bear weight or limp in the young child. Invasive bacterial infections, including **sepsis** and **bacterial meningitis** , must be considered in young children presenting with fever. While uncommon, these infections are potentially life-threatening and require prompt recognition and treatment. Ill appearance, lethargy, and tachycardia are typically present among children with severe sepsis, and petechiae may be an early finding among children with meningococcemia or other invasive bacterial diseases. Figs. 203.1 and 203.2 show age-related diagnoses and organisms producing bacterial sepsis in infants and children. Children with fever who are immunosuppressed, such as children receiving chemotherapy or those with sickle cell disease, are at higher risk for invasive bacterial infection.

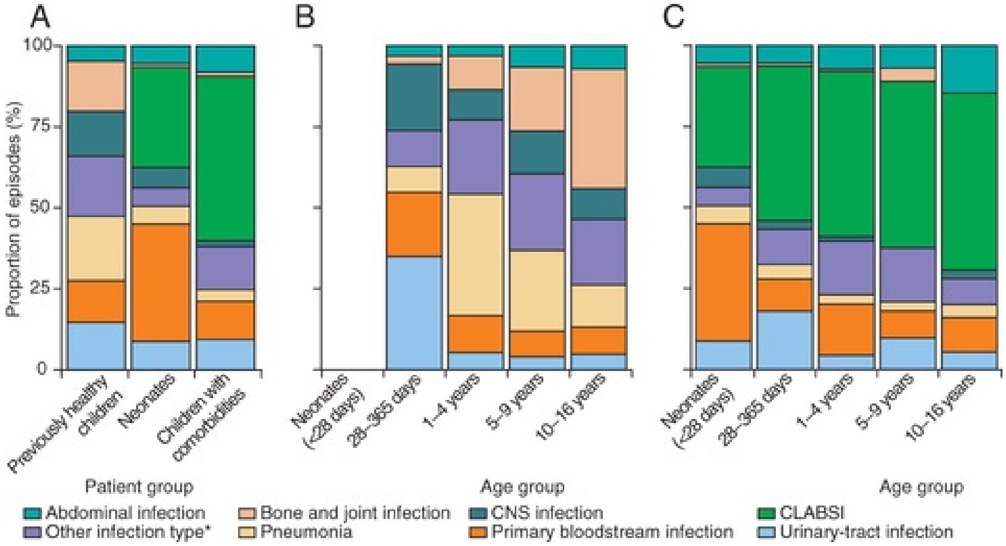

FIG. 203.1 Age distribution of sites of infection causing blood culture–proven bacterial sepsis in children. Sites of infection are shown for A, the 3 patient groups together, as well as separately for B, previously healthy children ≥28 days old, and C, neonates and children with comorbidities ≥28 days old. CLABSI, Central line–associated bloodstream infection; CNS, central nervous system. *Skin infection, wound infection, endocarditis, toxic shock syndrome; ear, nose, and throat infection; other, nonspecified focal infection. (From Agyeman PKA, Schlapbach LJ, Giannoni E, et al: Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study, *Lancet Child Adolesc* 1:124–133, 2017, Fig 3.)

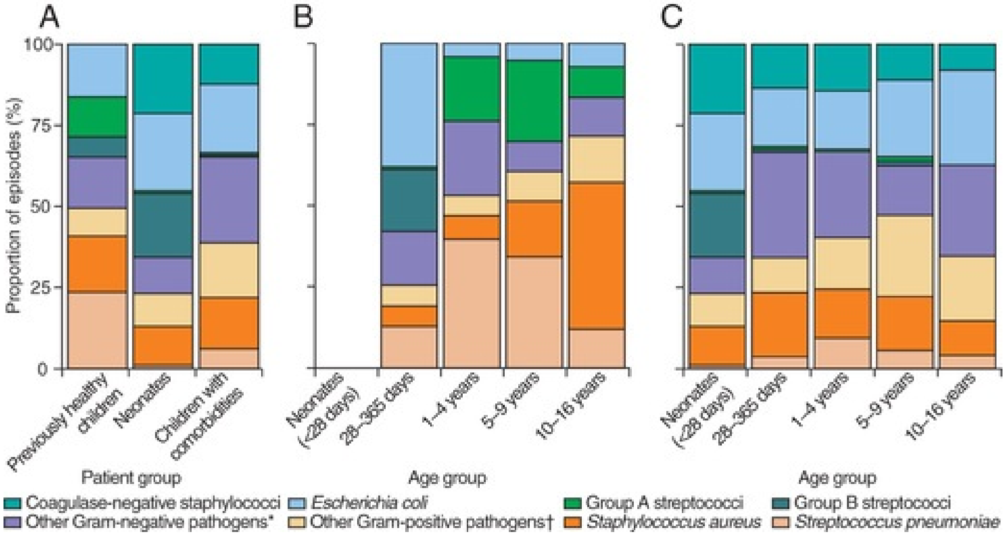

FIG. 203.2 Age distribution of pathogens causing blood culture–proven bacterial sepsis in children. Pathogens isolated in blood culture are shown for A, the 3 patient

groups together, as well as separately for B, previously healthy children ≥28 days old, and C, neonates and children with comorbidities ≥28 days old. ****Pseudomonas aeruginosa, Klebsiella* **spp.,** ***Neisseria meningitidis, Haemophilus influenzae,*** **other gram-negative pathogens. † *Enterococcus* spp., viridans group streptococci, other gram-positive pathogens. (From Agyeman PKA, Schlapbach LJ, Giannoni E, et al: Epidemiology of blood culture-proven bacterial sepsis in children in Switzerland: a population-based cohort study, *Lancet Child Adolesc* 1:124–133, 2017, Fig 4.)**

Infants and children age 2-24 mo merit special consideration because they have limited verbal skills, are at risk for occult bacterial infections, and may be otherwise asymptomatic except for fever (see Chapter 202).

Occult Urinary Tract Infection

Among children 2-24 mo old without symptoms or physical examination findings that identify another focal source of infection, the prevalence of urinary tract infection (UTI) may be as high as 5–10%. The highest risk of UTI occurs in females and uncircumcised males, with a very low rate of infection (<0.5%) in circumcised males. Table 203.2 lists risk factors for UTI.

Table 203.2

Risk Factors for Urinary Tract Infection in Children 2-24 Mo of Age

FEMALE
White race Age <1 yr Temperature ≥39°C (102.2°F) Fever duration ≥2 days No obvious source of infection
MALE
Uncircumcised boys at higher risk Nonblack race Temperature ≥39°C (102.2°F) Fever duration >1 day No obvious source of infection

Adapted from Subcommittee on Urinary Tract Infection et al. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months, *Pediatrics* 128(3):595–610, 2011.

Occult Bacteremia

Occult bacteremia is defined as a positive blood culture for a pathogen in a well-appearing child without an obvious source of infection. In the 1990s, before vaccination programs against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* , up to 5% of young children age 2 mo to 24 (up to 36) mo with fever ≥39°C (102.2°F) had occult bacteremia, most often caused by *S. pneumoniae* . Currently, the prevalence of occult bacteremia is <1% in febrile, well-appearing young children. The vast majority of pneumococcal occult bacteremia is transient, with a minority of these children developing new focal infections, sepsis, or other sequelae. Unimmunized and incompletely immunized young children remain at higher risk for occult bacteremia because of pneumococcus (see Chapter 209). Bacteremia caused by Hib or meningococcus should not be considered benign because subsequent serious invasive infection may rapidly follow the bacteremia.

General Approach

The general approach to fever in the older child begins with an assessment of the child's overall appearance and vital signs. A detailed history of the present illness and a thorough physical examination should be performed to identify the cause of the fever.

Overall Appearance and Vital Signs

Children who are ill or appear toxic or who have abnormal vital signs (e.g., tachycardia, tachypnea, hypotension) require rapid assessment, including a focused physical examination to evaluate for the presence of an invasive bacterial infection. A more detailed history and physical exam can be performed in the well-appearing child.

Symptoms

A thorough history should be obtained from the caregiver (and patient, when appropriate), including a characterization of the fever and any other associated symptoms. The degree and duration of the fever should be assessed, and the method of taking the temperature should be ascertained (e.g., rectal, oral, axillary). For children with prolonged fever, it is important to determine whether the fever has been episodic or persistent. Patients with prolonged fever may harbor occult infections, UTI, bone or soft tissue infections, or have an inflammatory or oncologic condition. Additionally, **Kawasaki disease** should be considered among children with prolonged fever, and a careful evaluation for other stigmata associated with this condition is warranted (see Chapter 191).

Following characterization of the fever, it is important to ask systematically about the presence of symptoms that may indicate an etiology for the fever, including symptoms of common viral infections such as rhinorrhea, cough, vomiting, and diarrhea. Additionally, symptoms should be elicited for each body system: headache, ear pain, sore throat, neck pain or swelling, difficulty breathing, chest pain, abdominal pain, rash or changes in skin color, extremity pain or difficulty with ambulation (including refusal to bear weight in a young child), and overall activity level. In older children, the presence of dysuria, urinary frequency, or back pain may be indicative of UTI. Assessment of oral intake and urine output is also critical, because dehydration may accompany common childhood infections and is associated with higher rates of morbidity. Presence of weight loss or night sweats may indicate leukemia, lymphoma, or tuberculosis. Additionally, a thorough social history should be performed, inquiring about attendance at daycare, any travel, and any sick contacts at daycare, school, or in the household.

Physical Examination

Following an assessment of overall appearance, vital signs should be obtained, a thorough history of present illness should be elicited, and a complete physical examination should be performed, with particular attention given to body systems with associated symptoms (e.g., thorough exam of oropharynx for child with sore throat). A complete physical examination is particularly important in young children <24 mo old who have limited verbal skills to communicate localized pain. In older children the physical exam may proceed systematically from head to toe, but in younger children, who may be fearful of the exam, it is important to auscultate the heart and lungs first before proceeding to potentially painful aspects of the examination (e.g., inspection of ears or oropharynx). In addition to a careful evaluation of each body system, a complete examination should include an assessment of neck pain and mobility, which may be limited in children with **meningitis** . Additionally, the examiner should palpate carefully for the presence of **lymphadenopathy** , which may be present with infectious as well as oncologic causes of fever. Erythema and exudate of the tonsils with palatal petechiae suggest streptococcal pharyngitis. Erythema, bulging, and decreased mobility of the tympanic membrane are the cardinal signs of acute otitis media. Diffuse crackles and wheezes on auscultation of the lungs occur with acute viral bronchiolitis, while focal crackles or decreased breath sounds are more consistent with pneumonia. Focal tenderness in the right lower quadrant of the abdomen is suggestive of **appendicitis** , and suprapubic tenderness may indicate UTI (**cystitis**). Any focal bony tenderness may reflect a diagnosis of osteomyelitis, while erythema, swelling, and limitation of range of motion suggest a diagnosis of septic arthritis. Abnormal gait or pain with ambulation without focal findings may also reflect a bone or joint infection. A careful skin examination should also be performed. The presence of petechiae may suggest meningococcal or other invasive bacterial infection, whereas viral exanthems are typically associated with a blanching macular or maculopapular rash.

Evaluation

Laboratory Testing

Laboratory testing is not routinely indicated in the well-appearing child without a focus of infection on examination. Urine testing should be considered based on the child's age and duration of fever. In general, the decision to perform laboratory testing should be guided by the overall appearance and vital signs of the child, the presence of specific symptoms or physical examination findings, and the child's age.

For children who are ill or appear toxic or who have vital sign abnormalities indicative of an invasive bacterial infection (tachycardia, hypotension), rapid laboratory evaluation should be performed. Testing should include a complete blood count (CBC) and blood culture and possibly urine and cerebrospinal fluid (CSF) cultures, depending on the age of the child and the presence or absence of physical exam findings indicative of UTI or bacterial meningitis. Children who are immunosuppressed or who have a central venous catheter should also undergo diagnostic testing and receive prompt antimicrobial therapy, given their higher risk of invasive bacterial infection.

For well-appearing children with symptoms or signs indicative of a viral upper respiratory or GI infection, routine viral testing is not generally indicated. **Influenza** testing may be indicated within 48 hr of symptom onset in certain higher-risk populations, with immunosuppression, chronic respiratory or cardiac disease, sickle cell disease, hospitalization, and age <2 yr influencing the decision to treat with an antiviral agent. Viral testing may also be useful with prolonged fever to identify a source of the fever and avoid extensive evaluation for inflammatory conditions such as Kawasaki disease.

Rapid strep testing of the oropharynx is indicated for children ≥3 yr old with signs of streptococcal pharyngitis on examination. Although strep throat is uncommon in children <3 yr old, this group should undergo rapid strep testing if they have signs of strep throat on exam and a household contact with streptococcal pharyngitis (see Chapter 210).

Febrile children 2-24 mo old with 2 or 3 of the risk factors for UTI listed in Table 203.2 , particularly females and uncircumcised males, should undergo evaluation with urine dipstick, urine microscopy, and urine culture. Females and uncircumcised males 2-6 mo old with high fever or fever that lasts ≥2 days, may undergo urine testing even in the presence of respiratory tract infection, given the higher risk of UTI in this younger group (see Chapter 553).

Given the very low risk of occult bacteremia, routine performance of blood testing (e.g., CBC, blood culture) is not indicated in the vast majority of immunized children with fever. Unimmunized and underimmunized children <2 yr old remain at higher risk of occult pneumococcal bacteremia, and CBC and blood culture may be considered in this population in the absence of another source of infection.

Imaging

The presence of focal crackles or decreased breath sounds on auscultation in the febrile child is suggestive of **pneumonia** . Current guidelines recommend presumptive antibiotic treatment for pneumonia based on clinical grounds and reserve the use of chest radiography for children with hypoxemia or significant respiratory distress and for those who fail outpatient therapy. Chest radiography is indicated for hospitalized children to assess for complicated pneumonia, including **empyema** . The performance of other imaging should be dictated by physical exam findings. The presence of drooling and neck or throat pain in an infant or toddler may be suggestive of a retropharyngeal abscess, which is usually confirmed by imaging that may include a lateral radiograph of the soft tissue of the neck or computed tomography (CT) if clinical suspicion is high. Ultrasonography (US) may be performed to assess for **appendicitis** in children with fever and focal right lower quadrant pain or abdominal pain that is severe.

However, definitive imaging, including CT or MRI, may be required if US is nondiagnostic or if clinical suspicion is high.

Management

General Management Principles

Management should be guided by the presence of specific symptoms by history or signs on physical examination. Based on the child's age and duration of fever, management may also be guided by focused diagnostic testing, such a urinalysis and selective urine culture testing among young febrile children (see Table 203.2 and Fig. 203.3). Supportive care, including the use of antipyretics and adequate hydration, should be reviewed with the patient and caregiver for all children with fever. Children with viral infections generally require supportive care only, except for children at higher risk of severe or complicated disease with **influenza virus** (see Chapter 285). Antibiotics should be reserved for children with evidence of bacterial infection on physical examination. A wait-and-see approach can be considered for children with acute **otitis media** , in whom a prescription for antibiotics can be provided to the family but instructions given to not fill the prescription unless severe or worsening symptoms develop (see Chapter 658). Oral antibiotics can be prescribed to young children >2 mo old with UTI, although children who cannot tolerate oral intake, are vomiting or dehydrated, or appear toxic require parenteral antibiotics and hospitalization.

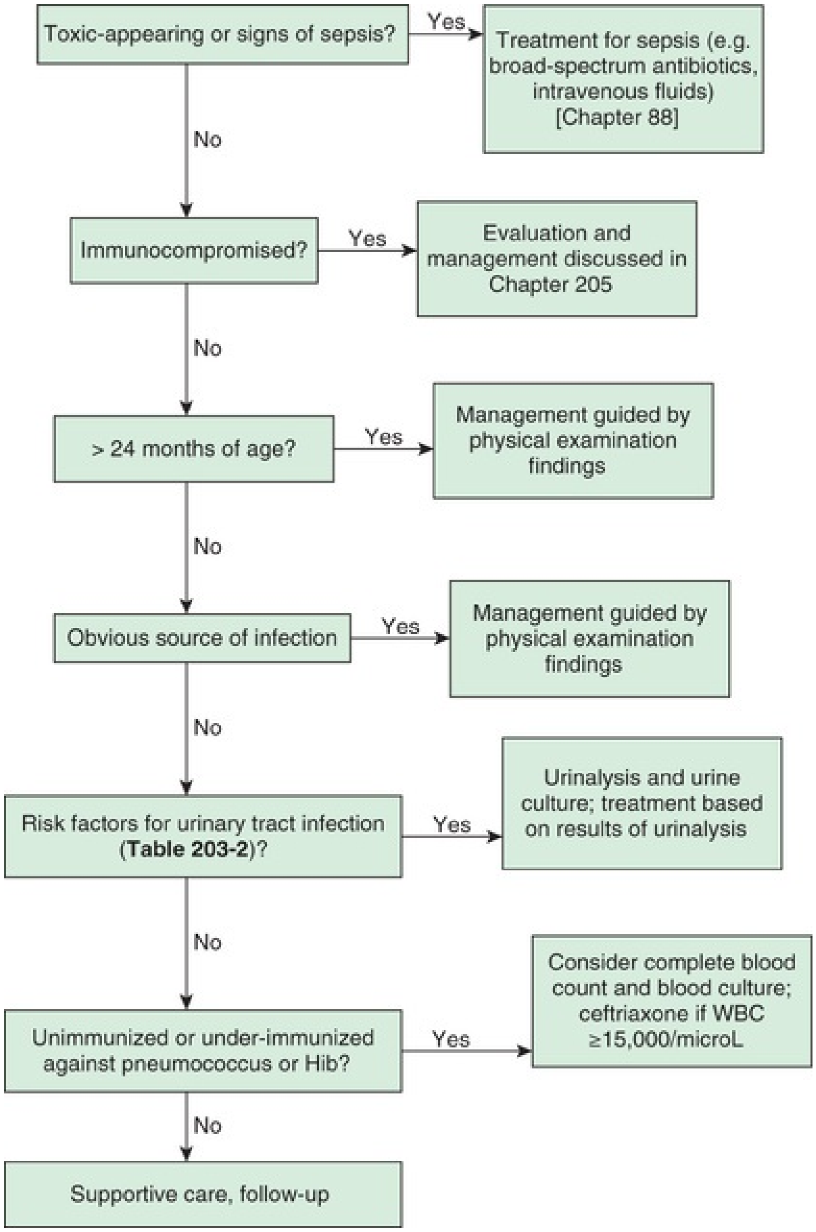
Toxic-appearing or signs of sepsis?
Yes
Treatment for sepsis (e.g. broad-spectrum antibiotics, intravenous fluids) [Chapter 88]
No
Immunocompromised?
Yes
Evaluation and management discussed in Chapter 205
No
> 24 months of age?
Yes
Management guided by physical examination findings
No
Obvious source of infection
Yes
Management guided by physical examination findings
No
Risk factors for urinary tract infection (Table 203-2)?
Yes
Urinalysis and urine culture; treatment based on results of urinalysis
No
Unimmunized or under-immunized against pneumococcus or Hib?
Yes
Consider complete blood count and blood culture; ceftriaxone if WBC ≥15,000/microL
No
Supportive care, follow-up

FIG. 203.3 **Algorithm for evaluation and management of fever in infants and children >2 mo of age. Hib, *Haemophilus influenzae* type b; WBC, white blood cell count.**

Blood tests, including CBC and blood culture, should be considered to evaluate for occult **bacteremia** in the unimmunized or ill-appearing child. One management strategy for these children is to administer a parenteral antibiotic (e.g., ceftriaxone) if leukocytosis is present (white blood cell count ≥15,000/µL) while awaiting results of blood culture. Children who appear toxic or who have signs of either sepsis or bacterial meningitis require emergent treatment with parenteral antibiotics as well as adjunct therapies to support the child's hemodynamics (see Chapter 88).

Importantly, anticipatory guidance should be provided to all families of children with fever, including the criteria to return to care and the importance of fever control and adequate hydration.

Other Considerations

Children who are unimmunized or underimmunized are at higher risk of invasive bacterial infection, as are children who are immunocompromised. Management of fever in these children is described further in Chapter 205 . Additionally, the approach to fever in the returning traveler should be focused on identifying commonly encountered infections based on the region of travel (see Chapter 200).

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CHAPTER 204

Fever of Unknown Origin

Andrew P. Steenhoff

Fever of unknown origin (**FUO**) is a diagnostic dilemma for pediatricians because it is often difficult to distinguish clinically between benign and potentially life-threatening causes. Pediatricians face the important challenge of not missing the diagnosis of a serious illness or an easily treatable condition that can result in increased morbidity. Fortunately, FUO is usually an uncommon presentation of a common disease, with most of these common diseases being easily treatable.

The classification of FUO is best reserved for children with a temperature >38°C (100.4°F) documented by a healthcare provider and for which the cause could not be identified after at least 8 days of evaluation (Table 204.1). It is important to differentiate FUO from **fever without a source** ; **FWS** is fever where the source has not yet been identified and is differentiated from FUO by the duration of the fever. FWS can progress to FUO if no cause is elicited after 7 days of evaluation.

Table 204.1

Summary of Definitions and Major Features of 4 Subtypes of Fever of Unknown Origin (FUO)

FEATURE	CLASSIC FUO	HEALTHCARE-ASSOCIATED FUO	IMMUNE-DEFICIENT FUO	HIV-RELATED FUO
Definition	>38°C (100.4°F), >3 wk, >2 visits or 1 wk in hospital	≥38°C (100.4°F), >1 wk, not present or incubating on admission	≥38°C (100.4°F), >1 wk, negative cultures after 48 hr	≥38°C (100.4°F), >3 wk for outpatients, >1 wk for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital

Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Healthcare-associated infections, postoperative complications, drug fever	Majority caused by infections, but cause documented in only 40–60%	HIV itself, typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower-limb deep veins	Wounds, drains, devices, sinuses, urine	Skin folds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

CMV, Cytomegalovirus; CXR, chest radiograph; HIV, human immunodeficiency virus; IV, intravenous line.

Adapted from Mackowak PA, Durack DT: Fever of unknown origin. In Mandell GL, Bennett, JE, Dolin R, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* , ed 7, Philadelphia, 2010, Elsevier (Table 51-1).

Etiology

The many causes of FUO in children are infectious, rheumatologic (connective tissue or autoimmune), autoinflammatory, oncologic, neurologic, genetic, factitious, and iatrogenic processes (Table 204.2). Although oncologic disorders should be seriously considered, most children with malignancies do not have fever alone. The possibility of **drug fever** should be considered if the patient is receiving any drug. Drug fever is usually sustained and not associated with other symptoms. Discontinuation of the drug is associated with resolution of the fever, generally within 72 hr, although certain drugs, such as iodides, are excreted for a prolonged period, with fever that can persist for as long as 1 mo after drug withdrawal.

Table 204.2

Diagnostic Considerations for Fever of Unknown Origin in Children

ABSCESSES
Abdominal Brain Dental Hepatic Paraspinal Pelvic Perinephric Rectal Subphrenic Psoas
BACTERIAL DISEASES
Actinomycosis *Bartonella henselae* (cat-scratch disease) Brucellosis *Campylobacter* *Chlamydia* *Francisella tularensis* (tularemia) *Listeria monocytogenes* (listeriosis) Meningococcemia (chronic) *Mycoplasma pneumoniae* Rat-bite fever (*Streptobacillus moniliformis* ; streptobacillary form of rat-bite fever) *Salmonella* Tuberculosis Whipple disease Yersiniosis
LOCALIZED INFECTIONS
Cholangitis Infective endocarditis Lymphogranuloma venereum Mastoiditis Osteomyelitis Pneumonia Pyelonephritis Psittacosis Sinusitis
SPIROCHETES
Borrelia burgdorferi (Lyme disease) Relapsing fever *(Borrelia recurrentis)* Leptospirosis Rat-bite fever (*Spirillum minus* ; spirillary form of rat-bite fever)

Syphilis
FUNGAL DISEASES
Blastomycosis (extrapulmonary) Coccidioidomycosis (disseminated) Histoplasmosis (disseminated)
RICKETTSIAE
African tick-bite fever *Ehrlichia canis* Q fever Rocky Mountain spotted fever Tick-borne typhus
VIRUSES
Cytomegalovirus Hepatitis viruses HIV Epstein-Barr virus
PARASITIC DISEASES
Amebiasis Babesiosis Giardiasis Malaria Toxoplasmosis Trichinosis Trypanosomiasis Visceral larva migrans (*Toxocara*)
RHEUMATOLOGIC DISEASES
Behçet disease Juvenile dermatomyositis Juvenile idiopathic arthritis Rheumatic fever Systemic lupus erythematosus
HYPERSENSITIVITY DISEASES
Drug fever Hypersensitivity pneumonitis Serum sickness Weber-Christian disease
NEOPLASMS
Atrial myxoma Cholesterol granuloma Hodgkin disease Inflammatory pseudotumor Leukemia Lymphoma Pheochromocytoma Neuroblastoma Wilms tumor
GRANULOMATOUS DISEASES
Granulomatosis with polyangiitis Crohn disease Granulomatous hepatitis Sarcoidosis
FAMILIAL AND HEREDITARY DISEASES
Anhidrotic ectodermal dysplasia Autonomic neuropathies Fabry disease

Familial dysautonomia
Familial Hibernian fever
Familial Mediterranean fever, many other autoinflammatory diseases (Chapter 188)
Hypertriglyceridemia
Ichthyosis
Sickle cell crisis
Spinal cord/brain injury
MISCELLANEOUS
Addison disease
Castleman disease
Chronic active hepatitis
Cyclic neutropenia
Diabetes insipidus (central and nephrogenic)
Drug fever
Factitious fever
Hemophagocytic syndromes
Hypothalamic-central fever
Infantile cortical hyperostosis
Inflammatory bowel disease
Kawasaki disease
Kikuchi-Fujimoto disease
Metal fume fever
Pancreatitis
Periodic fever syndromes
Poisoning
Pulmonary embolism
Thrombophlebitis
Thyrotoxicosis, thyroiditis

Most fevers of unknown origin result from atypical presentations of common diseases. In some cases, the presentation as an FUO is characteristic of the disease (e.g., JIA), but the definitive diagnosis can be established only after prolonged observation, because initially there are no associated or specific findings on physical examination, and all laboratory results are negative or normal.

In the United States the systemic infectious diseases most commonly implicated in children with FUO are salmonellosis, tuberculosis, rickettsial diseases, syphilis, Lyme disease, cat-scratch disease, atypical prolonged presentations of common viral diseases, Epstein-Barr virus (EBV) infection, cytomegalovirus (CMV) infection, viral hepatitis, coccidioidomycosis, histoplasmosis, malaria, and toxoplasmosis. Less common infectious causes of FUO include tularemia, brucellosis, leptospirosis, and rat-bite fever. Acquired immunodeficiency syndrome alone is not usually responsible for FUO, although febrile illnesses often occur in patients with AIDS as a result of opportunistic infections (see Table 204.1).

Juvenile idiopathic arthritis (JIA) and **systemic lupus erythematosus** (SLE) are the connective tissue diseases most often associated with FUO.

Inflammatory bowel disease (IBD) and **Kawasaki disease** are also frequently reported as causes of FUO. If **factitious fever** (inoculation of pyogenic material or manipulation of the thermometer by the patient or parent) is suspected, the presence and pattern of fever should be documented in the hospital. Prolonged and continuous observation of the patient, which can include electronic or video surveillance, is imperative. FUO lasting >6 mo is uncommon in children and suggests granulomatous, autoinflammatory, or autoimmune disease. Repeat interval evaluation is required, including history, physical examination, laboratory evaluation, and imaging studies.

Historically, 90% of pediatric FUO cases in the United States had an identifiable cause: approximately 50% infectious, 10–20% collagen vascular, and 10% oncologic. Later studies from the 1990s had variable results: 20–44% infectious, 0–7% collagen vascular, 2–3% oncologic, and up to 67% undiagnosed. The reason for the paradoxical increase in undiagnosed cases of FUO ironically is likely caused by improved infectious and autoimmune diagnostic techniques. The advent of polymerase chain reaction (PCR), improved culture techniques, and better understanding of atypical viral and bacterial pathogenesis and autoimmune processes likely contribute to earlier diagnosis of these conditions and fewer children with these conditions advancing to the category of FUO. By contrast, causes of FUO remain primarily infectious in developing settings where there is a higher infectious disease burden, and advanced diagnostics techniques are more limited.

Diagnosis

The evaluation of FUO requires a thorough history and physical examination supplemented by a few screening laboratory tests and additional laboratory and imaging evaluation informed by the history or abnormalities on examination or initial screening tests (see Table 204.2). Occasionally the **fever pattern** helps make a diagnosis (Fig. 204.1). Nonetheless, most diseases causing an FUO do not have a typical fever pattern.

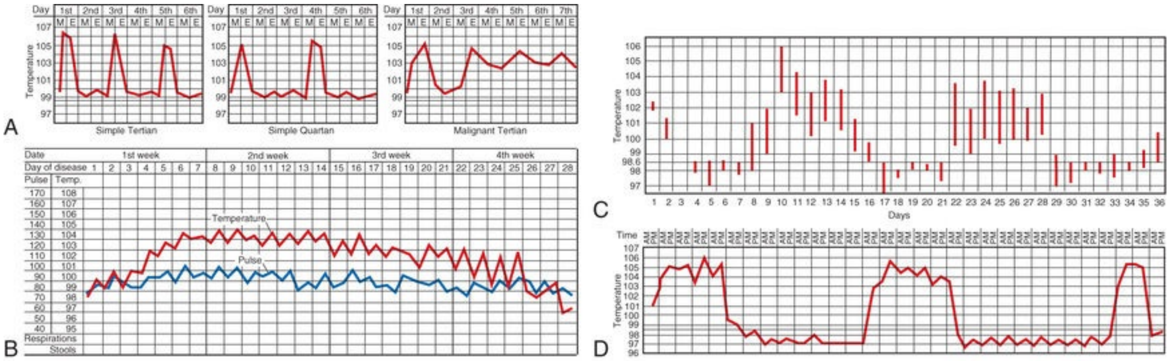

FIG. 204.1 Distinctive fever patterns. A, Malaria. B, Typhoid fever (demonstrating relative bradycardia). C, Hodgkin disease (Pel-Ebstein fever pattern). D, Borreliosis (relapsing fever pattern). (From Woodward TE: The fever pattern as a clinical diagnostic aid. In Mackowiak PA, editor: *Fever: basic mechanisms and management* , ed 2, Philadelphia, 1997, Lippincott-Raven, pp 215–236.)

History

A detailed fever history should be obtained, including onset, frequency, duration, response or nonresponse to therapy, recurrence, and associated symptoms. Repetitive chills and temperature spikes are common in children with **septicemia** (regardless of cause), particularly when associated with kidney disease, liver or biliary disease, infective endocarditis, malaria, brucellosis, rat-bite fever, or a loculated collection of pus.

The age of the patient is helpful in evaluating FUO. Children >6 yr old often have a respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JIA, or rarely, leukemia. Adolescent patients are more likely to have IBD, autoimmune processes, lymphoma, or tuberculosis, in addition to the causes of FUO found in younger children.

A history of exposure to wild or domestic **animals** should be solicited. The incidence of **zoonotic infections** in the United States is increasing, and these infections are often acquired from pets that are not overtly ill. Immunization of dogs against specific disorders such as **leptospirosis** can prevent canine disease but does not always prevent the animal from carrying and shedding leptospires, which may be transmitted to household contacts. A history of ingestion of rabbit or squirrel meat might provide a clue to the diagnosis of oropharyngeal, glandular, or typhoidal **tularemia** . A history of tick bite or travel to tick- or parasite-infested areas should be obtained.

Any history of **pica** should be elicited. Ingestion of dirt is a particularly important clue to infection with *Toxocara canis* (visceral larva migrans) or

Toxoplasma gondii (toxoplasmosis).

A history of unusual dietary habits or travel as early as the birth of the child should be sought. Tuberculosis, malaria, histoplasmosis, and coccidioidomycosis can reemerge years after visiting or living in an endemic area. It is important to identify prophylactic immunizations and precautions taken by the patient against ingestion of contaminated water or food during foreign travel. Rocks, dirt, and artifacts from geographically distant regions that have been collected and brought into the home as souvenirs can serve as vectors of disease.

A **medication** history should be pursued rigorously. This history should elicit information about nonprescription preparations and topical agents, including eyedrops, that may be associated with atropine-induced fever.

The genetic background of a patient also is important. Descendants of the Ulster Scots may have FUO because they are afflicted with nephrogenic diabetes insipidus. **Familial dysautonomia** (Riley-Day syndrome), a disorder in which hyperthermia is recurrent, is more common among Jews than among other population groups. Ancestry from the Mediterranean region should suggest **familial Mediterranean fever** . Both familial Mediterranean fever and hyper-IgD syndrome are inherited as autosomal recessive disorders. Tumor necrosis factor receptor–associated periodic syndrome and Muckle-Wells syndrome are inherited as autosomal dominant traits.

Pseudo-FUO is defined as successive episodes of benign, self-limited infections with fever that the parents perceive as 1 prolonged fever episode. This needs to be carefully ruled out before undertaking an unnecessary evaluation. Usually, pseudo-FUO starts with a well-defined infection (frequently viral) that resolves but is followed by other febrile viral illnesses that may be less well defined. Diagnosis of pseudo-FUO usually requires a careful history, focusing on identifying afebrile periods between febrile episodes. If pseudo-FUO is suspected and the patient does not appear ill, keeping a *fever diary* can be helpful.

Physical Examination

A complete physical examination is essential to search for any clues to the underlying diagnosis, and often it is worthwhile to repeat a detailed examination on different days to detect signs that may have changed or been missed (Tables 204.3 and 204.4). The child's general appearance, including **sweating** during fever, should be noted. The continuing absence of sweat in the presence of an elevated or changing body temperature suggests dehydration caused by vomiting, diarrhea, or central or nephrogenic diabetes insipidus. It also should suggest anhidrotic ectodermal dysplasia, familial dysautonomia, or exposure to atropine. The general activity of the patient and the presence or absence of rashes should also be noted.

Table 204.3

Subtle Physical Findings with Special Significance in Patients with Fever of Unknown Origin

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration	Disseminated histoplasmosis, SLE, IBD, Behçet syndrome, periodic fever syndromes
	Tender tooth	Periapical abscess, sinus referred pain
Fundi or conjunctivae	Choroid tubercle	Disseminated granulomatosis*
	Petechiae, Roth spots	Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
	Relative bradycardia	Typhoid fever, malaria, leptospirosis, psittacosis, central fever, drug fever
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
	Audible abdominal aortic or renal artery bruit	Large vessel vasculitis such as Takayasu arteritis
	Costovertebral tenderness	Chronic pyelonephritis, perinephric abscess
Rectum	Perirectal fluctuance, tenderness	Abscess
	Prostatic tenderness, fluctuance	Abscess
Genitalia	Testicular nodule	Periarteritis nodosa, cancer
	Epididymal nodule	Disseminated granulomatosis
Spine	Spinal tenderness	Vertebral osteomyelitis
	Paraspinal tenderness	Paraspinal collection
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Upper or lower extremities	Pseudoparesis	Syphilitic bone disease
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

* Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, granulomatosis with polyangiitis, and syphilis.

Adapted from Mackowak PA, Durack DT: Fever of unknown origin. In Mandell GL, Bennett, JE, Dolin R, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Elsevier (Table 51-8).

Table 204.4

Examples of Potential Diagnostic Clues to Infections Presenting as Fever of Unknown Origin

ETIOLOGY	HISTORICAL CLUES	PHYSICAL CLUES
Anaplasmosis	Transmitted by bite of *Ixodes* tick in association with outdoor activity in northern-central and eastern United States	Fever, headache, arthralgia, myalgia, pneumonitis, thrombocytopenia, lymphopenia, elevated liver enzymes
Babesiosis	Transmitted by bite of *Ixodes* tick in association with outdoor activity in northeastern United States	Arthralgias, myalgias, relative bradycardia, hepatosplenomegaly, anemia, thrombocytopenia, elevated liver enzymes
Bartonellosis	Recent travel to Andes Mountains (Oroya fever; *Bartonella bacilliformis*), association with homelessness in urban settings (*Bartonella quintana*) or scratch of infected kitten or feral cat (*Bartonella henselae*)	Conjunctivitis, retroorbital pain, anterior tibial bone pain, macular rash, nodular plaque lesions, regional lymphadenopathy
Blastomycosis	Contact with soil adjacent to Mississippi and Ohio River valleys, Saint Lawrence River in New York and Canada, and North American Great Lakes or exposure to infected dogs	Arthritis, atypical pneumonia, pulmonary nodules, and/or fulminant adult respiratory distress syndrome; verrucous, nodular, or ulcerative skin lesions; prostatitis
Brucellosis	Associated with contact or consumption of products from infected goats, pigs, camels, yaks, buffalo, or cows and with abattoir work	Arthralgias, hepatosplenomegaly, suppurative musculoskeletal lesions, sacroiliitis, spondylitis, uveitis, hepatitis, pancytopenia
Coccidioidomycosis	Exposure to soil or dust in southwestern United States	Arthralgias, pneumonia, pulmonary cavities, pulmonary nodules, erythema multiforme, erythema nodosum
Ehrlichiosis	Transmitted by bite of *Amblyomma, Dermacentor,* or *Ixodes* tick in association with outdoor activity in midwestern and southeastern United States	Pneumonitis, hepatitis, thrombocytopenia, lymphopenia
Enteric fever (*Salmonella enterica* serovar *typhi*)	Recent travel to a low- or middle-income country (LMIC) with consumption of potentially contaminated food or water	Headache, arthritis, abdominal pain, relative bradycardia, hepatosplenomegaly, leukopenia
Histoplasmosis	Exposure to bat or blackbird excreta in roosts, chicken houses, or caves in region surrounding Ohio and Mississippi River valleys	Headache, pneumonia, pulmonary cavities, mucosal ulcers, adenopathy, erythema nodosum, erythema multiforme, hepatitis, anemia, leukopenia, thrombocytopenia
Leptospirosis	Occupational exposure among workers in sewers, rice and sugarcane fields, and abattoirs; recreational water sports and exposure to contaminated waters or infected dogs	Bitemporal and frontal headache, calf and lumbar muscle tenderness, conjunctival suffusion, hepatic and renal failure, hemorrhagic pneumonitis
Leishmaniasis (visceral disease)	Associated with recent travel to areas endemic for sand flies	Hepatosplenomegaly, lymphadenopathy, and hyperpigmentation of face, hand, foot, and abdominal skin (kala-azar)
Malaria	Recent travel to endemic areas in Asia, Africa, and Central/South America	Fever, headaches, nausea, emesis, diarrhea, hepatomegaly, splenomegaly, anemia

Psittacosis (*Chlamydia psittaci*)	Associated with contact with birds, especially psittacine birds	Fever, pharyngitis, hepatosplenomegaly, pneumonia, blanching maculopapular eruptions; erythema multiforme, marginatum, and nodosum
Q fever (*Coxiella burnetii*)	Associated with farm, veterinary, or abattoir work; consumption of unpasteurized milk; contact with infected sheep, goats, or cattle	Atypical pneumonia, hepatitis, hepatomegaly, relative bradycardia, splenomegaly
Rat-bite fever (*Streptobacillus moniliformis*)	Recent bite or scratch by rat, mouse, or squirrel; ingestion of food or water contaminated by rat excrement	Headaches, myalgias, polyarthritis, and maculopapular, morbilliform, petechial, vesicular, or pustular rash over the palms, soles, and extremities
Relapsing fever (*Borrelia recurrentis*)	Associated with poverty, crowding, and poor sanitation (louse-borne), or with camping (tick-borne), particularly in the Grand Canyon	High fever with rigors, headache, delirium, arthralgias, myalgias, and hepatosplenomegaly
Rocky Mountain spotted fever	Associated with outdoor activity in the South Atlantic or southeastern United States and exposure to *Dermacentor* tick bites	Headache, petechial rash involving the extremities, palms, and soles
Tuberculosis	Recent contact with tuberculosis; recent immigration from endemic country; work or residence in homeless shelters, correctional facilities, or healthcare facilities	Night sweats, weight loss, atypical pneumonia, cavitary pulmonary lesions
Tularemia	Associated with bites by *Amblyomma* or *Dermacentor* ticks, deer flies, and mosquitoes or direct contact with tissues of infected animals such as rabbits, squirrels, deer, raccoons, cattle, sheep, and swine	Ulcerated skin lesions at a bite site, pneumonia, relative bradycardia, lymphadenopathy, conjunctivitis
Whipple disease (*Tropheryma whipplei*)	Potential association with exposure to sewage	Chronic diarrhea, arthralgia, weight loss, malabsorption, malnutrition

Adapted from Wright WF, Mackowiak PA: Fever of unknown origin. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 56-9).

A careful ophthalmic examination is important. Red, weeping eyes may be a sign of connective tissue disease, particularly polyarteritis nodosa. Palpebral **conjunctivitis** in a febrile patient may be a clue to measles, coxsackievirus infection, tuberculosis, infectious mononucleosis, lymphogranuloma venereum, or cat-scratch disease. In contrast, bulbar conjunctivitis in a child with FUO suggests Kawasaki disease or leptospirosis. Petechial conjunctival **hemorrhages** suggest infective endocarditis. Uveitis suggests sarcoidosis, JIA, SLE, Kawasaki disease, Behçet disease, and vasculitis. **Chorioretinitis** suggests CMV, toxoplasmosis, and syphilis. **Proptosis** suggests an orbital tumor, thyrotoxicosis, metastasis (neuroblastoma), orbital infection, Wegener granulomatosis (granulomatosis with polyangiitis), or pseudotumor.

The ophthalmoscope should also be used to examine nail-fold capillary abnormalities that are associated with connective tissue diseases such as juvenile dermatomyositis and systemic scleroderma. Immersion oil or lubricating jelly is placed on the skin adjacent to the nail bed, and the capillary pattern is observed with the ophthalmoscope set on +40.

FUO is sometimes caused by **hypothalamic dysfunction** . A clue to this disorder is failure of pupillary constriction because of absence of the sphincter constrictor muscle of the eye. This muscle develops embryologically when hypothalamic structure and function also are undergoing differentiation.

Fever resulting from familial dysautonomia may be suggested by lack of tears, an absent corneal reflex, or a smooth tongue with absence of fungiform papillae. Tenderness to tapping over the sinuses or the upper teeth suggests sinusitis. Recurrent oral candidiasis may be a clue to various disorders of the immune system, especially involving the T lymphocytes. Hyperactive deep tendon reflexes can suggest thyrotoxicosis as the cause of FUO.

Hyperemia of the pharynx, with or without exudate, suggests streptococcal infection, Epstein-Barr virus infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, Kawasaki disease, gonococcal infection, or leptospirosis.

The muscles and bones should be palpated carefully. Point tenderness over a bone can suggest occult osteomyelitis or bone marrow invasion from neoplastic disease. Tenderness over the trapezius muscle may be a clue to subdiaphragmatic abscess. Generalized muscle tenderness suggests dermatomyositis, trichinosis, polyarteritis, Kawasaki disease, or mycoplasma or arboviral infection.

Rectal examination can reveal perirectal lymphadenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis, or pelvic osteomyelitis. A guaiac test should be obtained; occult blood loss can suggest granulomatous colitis or ulcerative colitis as the cause of FUO.

Laboratory Evaluation

The laboratory evaluation of the child with FUO and whether inpatient or outpatient are determined on a case-by-case basis. Hospitalization may be required for laboratory or imaging studies that are unavailable or impractical in an ambulatory setting, for more-careful observation, or for temporary relief of parental anxiety. The **tempo** of diagnostic evaluation should be adjusted to the tempo of the illness; haste may be imperative in a critically ill patient, but if the illness is more chronic, the evaluation can proceed in a systematic manner and can be carried out in an outpatient setting. If there are no clues in the patient's history or on physical examination that suggest a specific infection or area of suspicion, it is unlikely that diagnostic studies will be helpful. In this common scenario, continued surveillance and repeated reevaluations of the child should be employed to detect any new clinical findings.

Although ordering a large number of diagnostic tests in every child with FUO according to a predetermined list is discouraged, certain studies should be considered in the evaluation. A complete blood cell count (CBC) with a white blood cell (WBC) differential and a urinalysis should be part of the initial laboratory evaluation. An absolute neutrophil count (ANC) of <5,000/µL is evidence against indolent bacterial infection other than typhoid fever. Conversely, in patients with a polymorphonuclear leukocyte (PMN) count of >10,000/µL or a nonsegmented PMN count of >500/µL, a severe bacterial infection is highly likely. Direct examination of the blood smear with Giemsa or Wright stain can reveal organisms of malaria, trypanosomiasis, babesiosis, or relapsing fever.

An erythrocyte sedimentation rate (ESR) >30 mm/hr indicates inflammation and the need for further evaluation for infectious, autoimmune, autoinflammatory, or malignant diseases, tuberculosis, Kawasaki disease, or autoimmune disease. A low ESR does not eliminate the possibility of infection or JIA. C-reactive protein (CRP) is another acute-phase reactant that becomes elevated and returns to normal more rapidly than the ESR. Experts recommend checking either ESR or CRP, because there is no evidence that measuring both in the same patient with FUO is clinically useful.

Blood cultures should be obtained aerobically. Anaerobic blood cultures have an extremely low yield and should be obtained only if there are specific reasons to suspect anaerobic infection. Multiple or repeated blood cultures may be required to detect bacteremia associated with infective endocarditis, osteomyelitis, or deep-seated abscesses. Polymicrobial bacteremia suggests factitious or self-induced infection or GI pathology. The isolation of leptospires, *Francisella,* or *Yersinia* requires selective media or specific conditions not routinely used. Therefore, it is important to inform the laboratory what organisms are suspected in a particular case. Urine culture should be obtained in all cases.

Tuberculin skin testing (TST) should be performed with intradermal placement of 5 units of purified protein derivative that has been kept appropriately refrigerated. In children >2 yr old, it is reasonable to test for tuberculosis using an interferon-γ release assay (IGRA).

Imaging studies of the chest, sinuses, mastoids, or GI tract may be indicated by specific historical or physical findings. Radiographic evaluation of the GI tract for IBD may be helpful in evaluating selected children with FUO and no other localizing signs or symptoms.

Examination of the bone marrow can reveal leukemia; metastatic neoplasm; mycobacterial, fungal, or parasitic infections; histiocytosis; hemophagocytosis; or storage diseases. If a bone marrow aspirate is performed, cultures for bacteria, mycobacteria, and fungi should be obtained.

Serologic tests can aid in the diagnosis of EBV infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, brucellosis, leptospirosis, cat-scratch disease, Lyme disease, rickettsial disease, and on some occasions JIA. The clinician should be aware that the reliability and the sensitivity and specificity of these tests vary; for example, serologic tests for Lyme disease outside of reference laboratories have been generally unreliable.

Radionuclide scans may be helpful in detecting abdominal abscesses as well as osteomyelitis, especially if the focus cannot be localized to a specific limb or multifocal disease is suspected. Gallium citrate localizes inflammatory tissues (leukocytes) associated with tumors or abscesses. Technetium-99m phosphate is useful for detecting osteomyelitis before plain radiographs demonstrate bone lesions. Granulocytes tagged with indium or iodinated IgG may be useful in detecting localized pyogenic processes. ^{18}F-fluorodeoxyglucose positron emission tomography (PET) is a helpful imaging modality in adults with an FUO and can contribute to an ultimate diagnosis in 30–60% of patients. Echocardiograms can demonstrate vegetation on the leaflets of heart valves, suggesting infective endocarditis. Ultrasonography (US) can identify intraabdominal abscesses of the liver, subphrenic space, pelvis, or spleen.

Total body CT or MRI (both with contrast) is usually the first imaging study of choice; both permit detection of neoplasms and collections of purulent material without the use of surgical exploration or radioisotopes. CT and MRI are helpful in identifying lesions of the head, neck, chest, retroperitoneal spaces, liver, spleen, intraabdominal and intrathoracic lymph nodes, kidneys, pelvis, and mediastinum. CT or US-guided aspiration or biopsy of suspicious lesions has reduced the need for exploratory laparotomy or thoracotomy. MRI is particularly useful for detecting osteomyelitis or myositis if there is concern about a specific limb. Diagnostic imaging can be very helpful in confirming or evaluating a suspected diagnosis. With CT scans, however, the child is exposed to large amounts of radiation. PET-CT or MRI may help localize an occult tumor.

Biopsy is occasionally helpful in establishing a diagnosis of FUO.

Bronchoscopy, laparoscopy, mediastinoscopy, and GI endoscopy can provide direct visualization and biopsy material when organ-specific manifestations are present. When employing any of the more invasive testing procedures, the risk/benefit ratio for the patient must always be considered before proceeding further.

Management

The ultimate treatment of FUO is tailored to the underlying diagnosis. Fever and infection in children are not synonymous, and **antimicrobial agents** should only be used when there is evidence of infection, with avoidance of empirical trials of medication. An exception may be the use of antituberculous treatment in critically ill children with suspected disseminated tuberculosis. Empirical trials of other antimicrobial agents may be dangerous and can obscure the diagnosis of infective endocarditis, meningitis, parameningeal infection, or osteomyelitis. After a complete evaluation, **antipyretics** may be indicated to control fever associated with adverse symptoms.

Prognosis

Children with FUO have a better prognosis than adults. The outcome in a child depends on the primary disease process. In many cases, no diagnosis can be established, and fever abates spontaneously. In as many as 25% of children in whom fever persists, the cause of the fever remains unclear, even after thorough evaluation.

In a series of 69 patients referred for “prolonged” unexplained fever, 10 were not actually having fever, and 11 had diagnoses that were readily apparent at the initial visit. The remaining 48 were classified as having FUO. The median duration of reported fever for these patients was 30 days. Fifteen received a diagnosis, and 10 (67%) had confirmed infections: acute EBV or CMV infection (n = 5; with 1 patient developing hemophagocytic lymphohistiocytosis); cat-scratch disease (3); and histoplasmosis (2). The other 5 patients had inflammatory conditions (systemic JIA, 2; IBD, 1), central fever (1), or malignancy (acute lymphoblastic leukemia, 1).

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CHAPTER 205

Infections in Immunocompromised Persons

Marian G. Michaels, Hey Jin Chong, Michael Green

Infection and disease develop when the host immune system fails to protect adequately against potential pathogens. In individuals with an intact immune system, infection occurs in the setting of naïveté to the microbe and absence of or inadequate preexisting microbe-specific immunity, or when protective barriers of the body such as the skin have been breached. Healthy children are able to meet the challenge of most infectious agents with an immunologic armamentarium capable of preventing significant disease. Once an infection begins to develop, an array of immune responses is set into action to control the disease and prevent it from reappearing. In contrast, immunocompromised children might not have this same capability. Depending on the level and type of immune defect, the affected child might not be able to contain the pathogen or develop an appropriate immune response to prevent recurrence.

General practitioners are likely to see children with an abnormal immune system in their practice because increasing numbers of children survive with primary immunodeficiencies or receive immunosuppressive therapy for treatment of malignancy, autoimmune disorders, or transplantation.

Primary immunodeficiencies are compromised states that result from genetic defects affecting one or more arms of the immune system. **Acquired,** or **secondary, immunodeficiencies** may result from infection (e.g., infection with HIV), from malignancy, or as an adverse effect of immunomodulating or immunosuppressing medications. The latter include medications that affect T cells (corticosteroids, calcineurin inhibitors, tumor necrosis factor [TNF] inhibitors, chemotherapy), neutrophils (myelosuppressive agents, idiosyncratic or immune-mediated neutropenia), specific immunoregulatory cells (TNF blockers, interleukin-2 inhibitors), or all immune cells (chemotherapy).

Perturbations of the mucosal and skin barriers or the normal microbial flora can also be characterized as secondary immunodeficiencies, predisposing the host to infections, if only temporarily.

The major pathogens causing infections among immunocompetent hosts are also the main pathogens responsible for infections among children with immunodeficiencies. In addition, less virulent organisms, including normal skin flora, commensal bacteria of the oropharynx or gastrointestinal (GI) tract, environmental fungi, and common community viruses of low-level pathogenicity, can cause severe, life-threatening illnesses in immunocompromised patients (Table 205.1). For this reason, close communication with the diagnostic laboratory is critical to ensure that the laboratory does not disregard normal flora and organisms normally considered contaminants as being unimportant.

Table 205.1

Most Common Causes of Infections in Immunocompromised Children

BACTERIA, AEROBIC
Acinetobacter
Bacillus
Burkholderia cepacia
Citrobacter
Corynebacterium
Enterobacter spp.
Enterococcus faecalis
Enterococcus faecium
Escherichia coli
Klebsiella spp.
Listeria monocytogenes
Mycobacterium spp.
Neisseria meningitidis
Nocardia spp.
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus, coagulase-negative
Streptococcus pneumoniae
Streptococcus, viridans group
BACTERIA, ANAEROBIC
Bacillus
Clostridium
Fusobacterium
Peptococcus
Peptostreptococcus
Propionibacterium
Veillonella

FUNGI
Aspergillus
Candida albicans
Other *Candida* spp.
Cryptococcus neoformans
Fusarium spp.
Pneumocystis jiroveci
Zygomycoses *(Mucor, Rhizopus, Rhizomucor)*
VIRUSES
Adenoviruses
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Human herpesvirus 6
Polyomavirus (BK)
Respiratory and enteric community-acquired viruses
Varicella-zoster virus
PROTOZOA
Cryptosporidium parvum
Giardia lamblia
Toxoplasma gondii

205.1

Infections Occurring With Primary Immunodeficiencies

Marian G. Michaels, Hey Jin Chong, Michael Green

Currently, more than 300 genes involving inborn errors of immunity have been identified, accounting for a wide array of diseases presenting with susceptibility to infection, allergy, autoimmunity, and autoinflammation, as well as malignancy.

Abnormalities of the Phagocytic System

Children with abnormalities of the phagocytic and neutrophil system have problems with bacteria as well as environmental fungi. Disease manifests as recurrent infections of the skin, mucous membranes, lungs, liver, and bones. Dysfunction of this arm of the immune system can be a result of inadequate numbers, abnormal movement properties, or aberrant function of neutrophils (see Chapter 153).

Neutropenia is defined as an absolute neutrophil count (ANC) of <1,000 cells/mm^3 and can be associated with significant risk for developing severe bacterial and fungal disease, particularly when the ANC is <500 cells/mm^3 . Although acquired neutropenia secondary to bone marrow suppression from a virus or medication is common, genetic causes of neutropenia also exist. Primary congenital neutropenia most often manifests during the 1st yr of life with cellulitis, perirectal abscesses, or stomatitis from *Staphylococcus aureus* or *Pseudomonas aeruginosa.* Episodes of severe disease, including bacteremia or meningitis, are also possible. Bone marrow evaluation shows a failure of maturation of myeloid precursors. Most forms of congenital neutropenia are autosomal dominant, but some, such as Kostmann syndrome (see Chapter 153) and Shwachman-Diamond syndrome, are caused by autosomal recessive mutations. Cyclic neutropenia can be associated with autosomal dominant inheritance or de novo sporadic mutations and manifests as fixed cycles of severe neutropenia between periods of normal granulocyte numbers. Often the ANC has normalized by the time the patient presents with symptoms, thus hampering the diagnosis. The cycles classically occur every 21 days (range: 14-36 days), with neutropenia lasting 3-6 days. Most often the disease is characterized by recurrent aphthous ulcers and stomatitis during the periods of neutropenia. However, life-threatening necrotizing myositis or cellulitis and systemic disease can occur, especially with *Clostridium septicum* or *Clostridium perfringens.* Many of the neutropenic syndromes respond to colony-stimulating factor.

Leukocyte adhesion defects are caused by defects in the β chain of integrin (CD18), which is required for the normal process of neutrophil aggregation and attachment to endothelial surfaces (see Chapter 153). In the most severe form there is a total absence of CD18. Children with this defect can have a history of delayed cord separation and recurrent infections of the skin, oral mucosa, and genital tract beginning early in life. Ecthyma gangrenosum also occurs. Because the defect involves leukocyte migration and adherence, the ANC in the peripheral blood is usually extremely elevated, but pus is not found at the site of infection. Survival is usually <10 yr in the absence of **hematopoietic stem cell transplantation (HSCT)** .

Chronic granulomatous disease (CGD) is an inherited neutrophil dysfunction syndrome, which can be either X-linked or autosomal recessive (see Chapter 156). In addition, CGD can develop in response to spontaneous mutations in the genes associated with heritable chronic granulomatous disease. Neutrophils and other myeloid cells have defects in their nicotinamide-adenine dinucleotide phosphate oxidase function, rendering them incapable of generating superoxide and thereby impairing intracellular killing. Accordingly, microbes that destroy their own hydrogen peroxide (*S. aureus*, *Serratia marcescens*, *Burkholderia cepacia*, *Nocardia* spp., *Aspergillus*) cause recurrent infections in these children. Less common but considered pathognomonic are *Granulibacter bethesdensis* , *Francisella philomiragia* , *Chromobacterium violaceum*, and *Paecilomyces* infections. Infections have a predilection to involve the lungs, liver, and bone. **Mulch pneumonitis** can be seen in patients with known CGD but also can be a unique presenting feature in adults with autosomal recessive CGD. Mulch pneumonitis can resemble hypersensitivity pneumonitis, and bronchoscopy may yield aspergillus but often may not identify a clear organism. Treatment with antifungals and corticosteroids for the inflammation is recommended. *S. aureus* abscesses can occur in the liver despite prophylaxis. In addition, these children can present with recurrent abscesses affecting the skin or perirectal region or lymph nodes. Sepsis can occur but is more common with certain gram-negative organisms such as *C. violaceum* and *F. philomiragia* .

Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX), recombinant human interferon-γ, and oral antifungal agents with activity against *Aspergillus* spp., such as itraconazole or newer azoles, substantially reduces the incidence of severe infections. Patients with life-threatening infections are also reported to benefit from aggressive treatment with white blood cell transfusions in addition to antimicrobial agents directed against the specific pathogen. It is important to remember that patients with CGD do not make pus, and thus drain placement for liver abscesses may not be effective. In addition, HSCT can be curative, and gene therapy trials are also a consideration.

Defective Splenic Function, Opsonization, or Complement Activity

Children who have congenital asplenia or splenic dysfunction associated with polysplenia or hemoglobinopathies, such as sickle cell disease, as well as those who have undergone splenectomy, are at risk for serious infections from encapsulated bacteria and bloodborne protozoa such as *Plasmodium* and *Babesia.* Prophylaxis against bacterial infection with penicillin should be considered for these patients, particularly children <5 yr of age. The most common causative organisms include *S. pneumoniae, Haemophilus influenzae* type b (Hib), and *Salmonella* , which can cause sepsis, pneumonia, meningitis, and osteomyelitis. Defects in the early complement components, particularly C2 and C3, may also be associated with severe infection from these bacteria. **Terminal complement defects** (C5, C6, C7, C8, and C9) are associated with recurrent infections with *Neisseria.* Patients with complement deficiency also have an increased incidence of autoimmune disorders. Vaccines for *S. pneumoniae,* Hib, and *N. meningitidis* should be administered to all children with abnormalities in opsonization or complement pathways (see Chapters 159 and 160).

B Cell Defects (Humoral Immunodeficiencies)

Antibody deficiencies account for the majority of primary immunodeficiencies among humans (see Chapters 149 and 150). Patients with defects in the B cell arm of the immune system fail to develop appropriate antibody responses, with abnormalities that range from complete agammaglobulinemia to isolated failure to produce antibody against a specific antigen or organism. Antibody deficiencies found in children with diseases such as **X-linked agammaglobulinemia (XLA)** or common variable immunodeficiency predispose to infections with encapsulated organisms such as *S. pneumoniae* and *H. influenzae* type b. Other bacteria can also be problematic in these children (see Table 205.1). Patients with XLA can also have neutropenia, with one case series showing 12 of 13 patients with XLA having neutropenia as part of the initial presentation. Because of the neutropenia, patients with XLA can present with *Pseudomonas* septicemia. Viral infections can also occur, with rotavirus leading to chronic diarrhea. Enteroviruses can disseminate and cause a chronic meningoencephalitis syndrome in these patients. Paralytic polio has developed after immunization with live polio vaccine. Protozoan infections such as giardiasis can be severe and persistent. Children with B cell defects can develop bronchiectasis over time following chronic or recurrent pulmonary infections.

Children with antibody deficiencies are usually asymptomatic until 5-6 mo of age, when maternally derived antibody levels begin to wane. These children begin to develop recurrent episodes of otitis media, bronchitis, pneumonia, bacteremia, and meningitis. Many of these infections respond quickly to antibiotics, delaying the recognition of antibody deficiency.

Selective IgA deficiency leads to a lack of production of secretory antibody at the mucosal membranes (see Chapter 150). Even though most patients have no increased risk for infections, some have mild to moderate disease at sites of mucosal barriers. Accordingly, recurrent sinopulmonary infection and GI disease are the major clinical manifestations. These patients also have an increased incidence of allergies and autoimmune disorders compared with the normal population.

Hyper-IgM syndrome encompasses a group of genetic defects in immunoglobulin class switch recombination. The most common type is caused by a defect in the CD40 ligand on the T cell, leading to the inability of the B cell to class switch (see Chapter 150). Similar to other patients with humoral defects, these patients are at risk for bacterial sinopulmonary infections. However, unlike a true pure antibody defect, besides being important in T cell–B cell interactions, CD40 ligand is also important in the interaction between T cells and macrophages/monocytes, influencing opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PCP) and *Cryptosporidium* intestinal infection.

T Cell Defects (Cell-Mediated Immunodeficiencies)

Children with primary cell-mediated immunodeficiencies, either isolated or more often in combination with B cell defects, present early in life and are susceptible to viral, fungal, and protozoan infections. Clinical manifestations include chronic diarrhea, mucocutaneous candidiasis, and recurrent pneumonia, rhinitis, and otitis media. In thymic hypoplasia (**DiGeorge syndrome**), hypoplasia or aplasia of the thymus and parathyroid glands occurs during fetal development in association with the presence of other congenital abnormalities. Hypocalcemia and cardiac anomalies are usually the presenting features of DiGeorge syndrome, which should prompt evaluation of the T cell system.

Chronic mucocutaneous candidiasis (CMC) is a group of immunodeficiencies leading to susceptibility to fungal infections of the skin, nails, oral cavity, and genitals. Most frequently caused by *Candida* spp., dermatophyte infections with *Microsporum* , *Epidermophyton* , and *Trichophyton* have also been described. Interestingly, patients with CMC do not have an increased risk for histoplasmosis, blastomycosis, or coccidioidomycosis. Despite chronic cutaneous and mucosal infection with *Candida* spp., these patients often lack a delayed hypersensitivity to skin tests for *Candida* antigen. Several gene defects make up this group of disorders, including *STAT1* gain-of-function mutations, *IL17R* defects, *CARD9* deficiency, and *ACT1* deficiency. Although patients with CMC generally do not develop invasive candidiasis, this differs depending on the gene defect. Endocrinopathies and autoimmunity can also be seen in affected people, especially in individuals with *STAT1* gain-of-function mutations.

Combined B Cell and T Cell Defects

Patients with defects in both the T cell and B cell components of the immune system have variable manifestations depending on the extent of the defect (see Chapters 149-152). Complete or almost complete immunodeficiency is found with **severe combined immunodeficiency disorder (SCID)** , whereas partial defects can be present in such states as ataxia-telangiectasia, Wiskott-Aldrich syndrome, hyper-IgE syndrome, and X-linked lymphoproliferative disorder. Rather than one disorder, it is now recognized that SCID represents a heterogeneous group of genetic defects that leave the infant globally immune deficient and present in the 1st 6 mo of life with recurrent and typically severe infections caused by a variety of bacteria, fungi, and viruses. Failure to thrive, chronic diarrhea, mucocutaneous or systemic candidiasis, PCP, or cytomegalovirus (CMV) infections are common early in life. Passive maternal antibody is relatively protective against the bacterial pathogens during the 1st few mo of life, but thereafter patients are susceptible to both gram-positive and gram-negative organisms. Exposure to live-virus vaccines can also lead to disseminated disease; accordingly, the use of live vaccines (including rotavirus vaccine) is contraindicated in patients with suspected or proven SCID. Without stem cell transplantation or gene therapy, most affected children succumb to opportunistic infections within the 1st yr of life.

Children with **ataxia-telangiectasia** develop late-onset recurrent sinopulmonary infections from both bacteria and respiratory viruses. In addition, these children experience an increased incidence of malignancies. **Wiskott-Aldrich syndrome** is an X-linked recessive disease associated with eczema, thrombocytopenia, reduced number of CD3 lymphocytes, moderately suppressed mitogen responses, and impaired antibody response to polysaccharide antigens. Accordingly, infections with *S. pneumoniae* or *H. influenzae* type b and PCP are common. Children with hyper-IgE syndrome have greatly elevated levels of IgE and present with recurrent episodes of *S. aureus* abscesses of the skin, lungs, and musculoskeletal system. Although the antibody abnormality is notable, these patients also have marked eosinophilia and poor cell-mediated responses to neoantigens and are at increased risk for fungal infections.

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205.2

Infections Occurring With Acquired Immunodeficiencies

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Immunodeficiencies can be secondarily acquired as a result of infections or other underlying disorders, such as malignancy, cystic fibrosis, diabetes mellitus, sickle cell disease, or malnutrition. Immunosuppressive medications used to prevent rejection after organ transplantation, to prevent **graft-versus-host disease (GVHD)** after stem cell transplantation, or to treat malignancies may also leave the host vulnerable to infections. Similarly, medications used to control rheumatologic or other autoimmune diseases may be associated with an increased risk for developing infection. Surgical removal of the spleen likewise puts a person at increased risk for infections. Further, any process that disrupts the normal mucosal and skin barriers (e.g., burns, surgery, indwelling catheters) may lead to an increased risk for infection.

Acquired Immunodeficiency From Infectious Agents

Infection with HIV, the causative agent of AIDS, remains globally an important infectious cause of acquired immunodeficiency (see Chapter 302). Left untreated, HIV infection has profound effects on many parts of the immune system but in particular T cell–mediated immunity that leads to susceptibility to the same types of infections as with primary T cell immunodeficiencies.

Other organisms can also lead to temporary alterations of the immune system. Very rarely, transient neutropenia associated with community-acquired viruses can lead to significant disease with bacterial infections. Secondary infections can occur because of impaired immunity or disruption of normal mucosal immunity, as exemplified by the increased risk for pneumonia from *S. pneumoniae* or *S. aureus* following influenza infection and group A streptococcal cellulitis and fasciitis following varicella.

Malignancies

The immune systems of children with malignancies are compromised by the therapies used to treat the cancer and, at times, by direct effects of the cancer itself. The type, duration, and intensity of anticancer therapy remain the major risk factors for infections in these children and often affect multiple arms of the immune system. The presence of mucous membrane abnormalities, indwelling catheters, malnutrition, prolonged exposure to antibiotics, and frequent hospitalizations adds to the risk for infection in these children.

Even though several arms of the immune system can be affected, the major abnormality predisposing to infection in children with cancer is **neutropenia** . The depth and duration of neutropenia are the primary predictors of the risk of infection in children being treated for cancer. Patients are at particular risk for bacterial and fungal infections if the ANC decreases to <500 cells/mm^3 , and the risk is highest in those with counts <100 cells/mm^3 . Counts of >500 cells/mm^3 but <1,000 cells/mm^3 incur some increased risk for infection, but not nearly as great. The lack of neutrophils can lead to a diminution of inflammatory response, limiting the ability to localize sites of infection and potentially leaving fever as the only manifestation of infection. Accordingly, the absence of physical signs and symptoms does not reliably exclude the presence of infection, resulting in the need for empirical antibiotics (Fig. 205.1). Because patients with **fever and neutropenia** might only have subtle signs and symptoms of infection, the presence of fever warrants an intensive investigation, including a thorough physical examination with careful attention to the oropharynx, lungs, perineum and anus, skin, nail beds, and intravascular catheter insertion sites (Table 205.2).

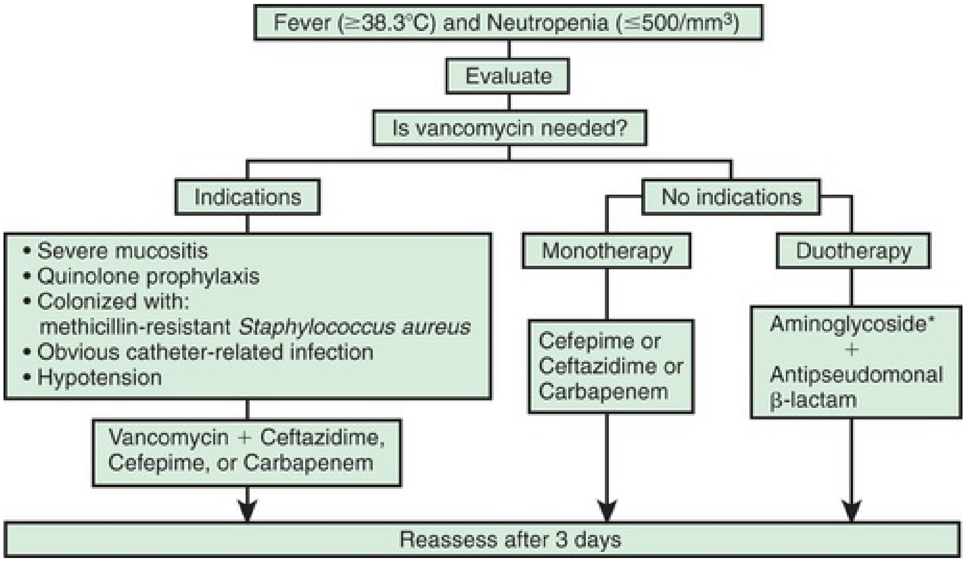
Fever (≥38.3°C) and Neutropenia (≤500/mm³)
Evaluate
Is vancomycin needed?
Indications
No indications
• Severe mucositis
• Quinolone prophylaxis
• Colonized with: methicillin-resistant *Staphylococcus aureus*
• Obvious catheter-related infection
• Hypotension
Monotherapy
Duotherapy
Cefepime or Ceftazidime or Carbapenem
Aminoglycoside* + Antipseudomonal β-lactam
Vancomycin + Ceftazidime, Cefepime, or Carbapenem
Reassess after 3 days

FIG. 205.1 **Algorithm for the initial management of the febrile neutropenic patient. Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem,piperacillin-tazobactam, or ticarcillin–clavulanic acid. *Aminoglycoside antibiotics should be avoided if the patient is also receiving nephrotoxic, ototoxic, or neuromuscular blocking agents; has renal or severe electrolyte dysfunction; or is suspected of having meningitis (because of poor blood-brain perfusion). (Adapted from Freifeld AG, Bow EJ, Sepkowitz KA, et al: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America, Clin Infect Dis 52:e56–e93, 2011.)**

Table 205.2

Host Defense Defects and Common Pathogens by Time After Bone Marrow or Hematopoietic Stem Cell Transplantation

TIME PERIOD	HOST DEFENSE DEFECTS	CAUSES	COMMON PATHOGENS
Pretransplant	Neutropenia Abnormal anatomic barriers	Underlying disease Prior chemotherapy	Aerobic gram-negative bacilli
Preengraftment	Neutropenia Abnormal anatomic barriers	Chemotherapy Radiation Indwelling catheters	Aerobic gram-positive cocci Aerobic gram-negative bacilli *Candida* *Aspergillus* Herpes simplex virus (in previously infected patients) Community-acquired viral pathogens
Postengraftment	Abnormal cell-mediated immunity	Chemotherapy	Gram-positive cocci

	Abnormal anatomic barriers	Immunosuppressive medications Radiation Indwelling catheters Unrelated cord blood donor	Aerobic gram-negative bacilli Cytomegalovirus Adenoviruses Community-acquired viral pathogens *Pneumocystis jiroveci*
Late posttransplant	Delayed recovery of immune function (cell-mediated, humoral, and abnormal anatomic barriers)	Time required to develop donor-related immune function Graft-versus-host disease	Varicella-zoster virus *Streptococcus pneumoniae*

A comprehensive laboratory evaluation, including a complete blood cell count, serum creatinine, blood urea nitrogen, and serum transaminases, should be obtained. Blood cultures should be taken from each port of any **central venous catheter** (CVC) and from a peripheral vein. Although the latter sampling is often omitted with continued fevers and neutropenia, it should be obtained before the initial antibiotic administration and reconsidered in children with 1 or more positive cultures from a CVC, facilitating localization of the source of the infection. Other microbiologic studies should be done if there are associated clinical symptoms, including a nasal aspirate for viruses in patients with upper respiratory findings; stool for viruses such as rotavirus or norovirus and for *Clostridium difficile* toxin in patients with diarrhea; urinalysis and culture in young children or in older patients with symptoms of urgency, frequency, dysuria, or hematuria; and biopsy and culture of cutaneous lesions. Chest radiographs should be obtained in any patient with lower respiratory tract symptoms, although pulmonary infiltrates may be absent in children with severe neutropenia. Sinus films should be obtained for children >2 yr of age if rhinorrhea is prolonged. Abdominal CT scans should also be considered in children with profound neutropenia and abdominal pain to evaluate for the presence of typhlitis. Chest CT scan and fungal biomarkers (e.g., galactomannan, β-D-glucan) testing should be considered for children not responding to broad-spectrum antibiotics who have continued fever and neutropenia for >96 hr. Biopsies for cytology, Gram stain, and culture should be considered if abnormalities are found during endoscopic procedures or if lung nodules are identified radiographically.

Classic studies by Pizzo and colleagues demonstrated that before the routine institution of empirical antimicrobial therapy for fever and neutropenia, 75% of children with fever and neutropenia were ultimately found to have a documented site of infection, suggesting that most children with fever and neutropenia will have an underlying infection (see Table 205.2). Currently, **gram-positive cocci** are the most common pathogens identified in these patients; however, gram-negative organisms such as *Pseudomonas aeruginosa, Escherichia coli* , and *Klebsiella* can cause life-threatening infection and must be considered in the empirical treatment regimen. Other multidrug-resistant Enterobacteriaceae are increasingly recovered in these children. Although coagulase-negative staphylococci often cause infections in these children in association with CVCs, these infections are typically indolent, and a short delay in treatment usually does not lead to a detrimental outcome. Other gram-positive bacteria, such as *S. aureus* and *S. pneumoniae* , can cause more fulminant disease and require prompt institution of therapy. Viridans streptococci are particularly important potential pathogens in patients with the oral mucositis that is often associated with use of cytarabine and in patients who experience selective pressure from treatment with certain antibiotics such as quinolones. Infection caused by this group of organisms can present as acute septic shock syndrome. Also, patients with prolonged neutropenia are at increased risk for opportunistic fungal infections, with *Candida* and *Aspergillus* spp. being the most commonly identified fungi. Other fungi that can cause serious disease in these children include *Mucor* and *Fusarium* spp. and dematiaceous molds.

Fever and Neutropenia

The use of empirical antimicrobial treatment as part of the management of fever and neutropenia decreases the risk of progression to sepsis, septic shock, acute respiratory distress syndrome, organ dysfunction, and death. In 2010 the Infectious Diseases Society of America (IDSA) updated a comprehensive guideline for the use of antimicrobial agents in neutropenic children and adults with cancer (see Fig. 205.1).

First-line antimicrobial therapy should take into consideration the types of microbes anticipated and the local resistance patterns encountered at each institution as well as the level of risk for severe infection associated with a given patient. In addition, antibiotic choices may be limited by specific circumstances, such as the presence of drug allergy and renal or hepatic dysfunction. The empirical use of oral antibiotics has been shown to be safe in some low-risk adults who have no evidence of bacterial focus or signs of significant illness (rigors, hypotension, mental status changes) and for whom a quick recovery of the bone marrow is anticipated. Guidelines for the management of fever and neutropenia in children with cancer and/or undergoing HSCT (2012) conclude that the use of oral antimicrobial therapy as either initial or stepdown therapy can be considered in low-risk children who can tolerate oral antibiotics and in whom careful monitoring can be ensured. However, the guideline emphasizes that oral medication use may present major challenges in children, including availability of liquid formulations of appropriate antibiotics, cooperation of young children, and presence of mucositis potentially interfering with absorption. Accordingly, decisions to implement this approach should be reserved for a select subset of these children presenting with fever and neutropenia.

The decision to initially use intravenous (IV) monotherapy vs an expanded regimen of antibiotics depends on the severity of illness of the patient, history of previous colonization with resistant organisms, and obvious presence of catheter-related infection. **Vancomycin** should be added to the initial empirical regimen if the patient has hypotension or other evidence of septic shock, an obvious catheter-related infection, or a history of colonization with methicillin-resistant *S. aureus* , or if the patient is at high risk for viridans streptococci (severe mucositis, acute myelogenous leukemia, or prior use of quinolone prophylaxis). Otherwise, use of monotherapy with an antibiotic such as cefepime or piperacillin-tazobactam can be considered. Ceftazidime should not be used as monotherapy if concern exists for gram-positive organisms or resistant gram-negative bacteria. Carbapenems such as imipenem/cilastin and meropenem should not be first line, aiming to prevent pressure on carbapenem-resistant Enterobacteriaceae. The addition of a 2nd anti–gram-negative bacterial agent (e.g., aminoglycoside) for empirical therapy can be considered in patients who are clinically unstable when multidrug-resistant organisms are suspected.

Regardless of the regimen chosen initially, it is critical to evaluate the patient carefully and continually for response to therapy, development of secondary infections, and adverse effects. Management recommendations for these children are evolving. Based on the 2012 guidelines, patients who have negative blood cultures at 48 hr, who have been afebrile for at least 24 hr, and who have evidence of bone marrow recovery (ANC >100 cells/mm^3) can have antibiotics discontinued. However, if symptoms persist or evolve, IV antibiotics should be continued. Continuation of antibiotics in children whose fever has abated and who are clinically well but continue to have depression of neutrophils is more controversial. The 2012 pediatric guidelines advocate for discontinuing antibiotics in low-risk patients at 72 hr for children who have negative blood cultures and who have been afebrile for at least 24 hr regardless of bone marrow recovery, as long as careful follow-up is ensured. In contrast, others continue to advocate for continuing antibiotics in this circumstance to prevent recurrence of fever.

Patients without an identified etiology but with **persistent fever** should be reassessed daily. At day 3-5 of persistent fever and neutropenia, those remaining clinically well may continue on the same regimen, although consideration should be given to discontinuing vancomycin or double gram-negative bacterial coverage if they were included initially. Patients who remain febrile with clinical progression warrant the addition of vancomycin if it was not included initially and risk factors exist; clinicians should also consider changing the empirical antibacterial regimen to cover for potential antimicrobial resistance in these children. If fever persists for >96 hr, the addition of an **antifungal agent** with antimold activity should be considered, particularly for those at high risk for invasive fungal infection (those with acute myelogenous leukemia or relapsed acute lymphocytic leukemia or who are receiving highly myelosuppressive chemotherapies for other cancers or with allogeneic HSCT). Medications, including **liposomal amphotericin** products and **echinocandins** , have been studied in children; voriconazole itraconazole, and posaconazole have been successfully used in adults, with increasing experience in children. Studies comparing caspofungin to liposomal amphotericin for children with malignancies and fever and neutropenia showed caspofungin to be noninferior.

The use of **antiviral agents** in children with fever and neutropenia is not warranted without specific evidence of viral disease. Active herpes simplex or varicella-zoster lesions merit treatment to decrease the time of healing; even if these lesions are not the source of fever, they are potential portals of entry for bacteria and fungi. CMV is a rare cause of fever in children with cancer and neutropenia. If CMV infection is suspected, assays to evaluate viral load in the blood and organ-specific infection should be obtained. Ganciclovir, foscarnet, or cidofovir may be considered while evaluation is pending, although ganciclovir can cause bone marrow suppression and foscarnet and cidofovir can be nephrotoxic. If influenza is identified, specific treatment with an antiviral agent should be administered. Choice of treatment (oseltamivir, zanamivir) should be based on the anticipated susceptibility of the circulating influenza strains.

The use of **hematopoietic growth factors** shortens the duration of neutropenia but has not been proved to reduce morbidity or mortality.

Accordingly, the 2010 IDSA recommendations do not endorse the routine use of hematopoietic growth factors in patients with established fever and neutropenia, although the recommendations do note that hematopoietic growth factors can be considered as prophylaxis in those with neutropenia at high risk for fever.

Fever Without Neutropenia

Infections occur in children with cancer in the absence of neutropenia. Most often these infections are viral in etiology. However, *Pneumocystis jiroveci* can cause pneumonia regardless of the neutrophil count. Administration of prophylaxis against *Pneumocystis* is an effective preventive strategy and should be provided to all children undergoing active treatment for malignancy. First-line therapy remains TMP-SMX, with second-line alternatives including pentamidine, atovaquone, dapsone, or dapsone-pyrimethamine. Environmental fungi such as *Cryptococcus, Histoplasma* , and C*occidioides* can also cause disease. *Toxoplasma gondii* is an uncommon but occasional pathogen in children with cancer. Infections caused by pathogens encountered in healthy children (*S. pneumoniae,* group A streptococcus) can occur in children with cancer regardless of the granulocyte count.

Transplantation

Transplantation of hematopoietic stem cells and solid organs (including heart, liver, kidney, lungs, pancreas, and intestines) is increasingly used as therapy for a variety of disorders. Children undergoing transplantation are at risk for infections caused by many of the same microbial agents that cause disease in children with primary immunodeficiencies. Although the types of infections after transplantation generally are similar among all recipients of these procedures, some differences exist between patients depending on the type of transplantation performed, the type and amount of immunosuppression given, and the child's preexisting immunity to specific pathogens.

Stem Cell Transplantation

Infections following HSCT can be classified as occurring during the **pretransplantation period, preengraftment period** (0-30 days after transplantation), **postengraftment period** (30-100 days), or **late posttransplantation period** (>100 days). Specific defects in host defenses predisposing to infection vary within each of these periods (Table 205.2). Neutropenia and abnormalities in cell-mediated and humoral immune function occur predictably during specific periods after transplantation. In contrast, breaches of anatomic barriers caused by indwelling catheters and mucositis secondary to radiation or chemotherapy create defects in host defenses that may be present any time after transplantation.

Pretransplantation Period

Children come to HSCT with a heterogeneous history of underlying diseases, chemotherapy exposure, degree of immunosuppression, and previous infections. Approximately 12% of all infections among adult HSCT recipients occur during the pretransplantation period. These infections are often caused by aerobic gram-negative bacilli and manifest as localized infections of the skin, soft tissue, and urinary tract. Importantly, the development of infection during this period does not delay or adversely affect the success of engraftment.

Preengraftment Period

Bacterial infections predominate in the preengraftment period (0-30 days). **Bacteremia** is the most common documented infection and occurs in as many as 50% of all HSCT recipients during the 1st 30 days after transplantation. Bacteremia is typically associated with the presence of either mucositis or an indwelling catheter but may also be seen with pneumonia. Similarly, >40% of children undergoing HSCT experienced 1 or more infections in the preengraftment period. Gram-positive cocci, gram-negative bacilli, yeast, and, less frequently, other fungi cause infection during this period. *Aspergillus* has been identified in 4–20% of HSCT recipients, most often after 3 wk of neutropenia. Infections caused by the emerging fungal pathogens *Fusarium* and *Pseudallescheria boydii* are associated with the prolonged neutropenia during the preengraftment period.

Viral infections also occur during the preengraftment period. Among adults, reactivation of herpes simplex virus (HSV) is the most common viral disease observed, but this is less common among children. A history of HSV infection or seropositivity indicates the need for prophylaxis. Nosocomial exposure to community-acquired viral pathogens, including respiratory syncytial virus

(RSV), influenza virus, adenovirus, rotavirus, and norovirus, represents another important source of infection during this period. There is growing evidence that community-acquired viruses cause increased morbidity and mortality for HSCT recipients during this period. Adenovirus is a particularly important viral pathogen that can occur early, although it typically presents after engraftment.

Postengraftment Period

The predominant defect in host defenses in the postengraftment period is altered cell-mediated immunity. Accordingly, organisms historically categorized as “opportunistic pathogens” predominate during this period. The risk is especially accentuated 50-100 days after transplantation, when host immunity is lost and donor immunity is not yet established. *P. jiroveci* presents during this period if patients are not maintained on appropriate prophylaxis. Reactivation of *T. gondii*, a rare cause of disease among HSCT recipients, can also occur after engraftment. Hepatosplenic candidiasis often presents during the postengraftment period, although seeding likely occurs during the neutropenic phase.

Cytomegalovirus is an important cause of morbidity and mortality among HSCT recipients. Unlike patients undergoing solid-organ transplantation, where primary infection from the donor causes the greatest harm, CMV reactivation in an HSCT recipient whose donor is naïve to the virus can cause severe disease. Disease risk from CMV after HSCT is also increased in recipients of cord blood transplants or matched unrelated T cell–depleted transplants and those with GVHD. **Adenovirus** , another important viral pathogen, has been recovered from up to 5% of adult and pediatric HSCT recipients and causes invasive disease in approximately 20% of cases. Children receiving matched unrelated donor organs or unrelated cord blood cell transplants have an incidence of adenovirus infection as high as 14% during this early postengraftment period. **Polyomaviruses** such as BK virus have been increasingly recognized as a cause of renal dysfunction and hemorrhagic cystitis after bone marrow transplantation. Infections with other herpesviruses (Epstein-Barr virus [EBV] and human herpesvirus 6) as well as community-acquired pathogens are associated with excess morbidity and mortality during this period, similar to the preengraftment period.

Late Posttransplantation Period

Infection is unusual after 100 days in the absence of chronic GVHD. However, the presence of chronic GVHD significantly affects anatomic barriers and is associated with defects in humoral, splenic, and cell-mediated immune function. Viral infections, including primary infection with or reactivation of varicella-zoster virus (VZV), are responsible for >40% of infections during this period. This may decrease over time as the Oka varicella vaccine strain has a lower rate of reactivation than wild-type varicella. Bacterial infections, particularly of the upper and lower respiratory tract, account for approximately 30% of infections. These may be associated with deficiencies in immunoglobulin production, especially IgG2. Fungal infections account for <20% of confirmed infections during the late posttransplantation period.

Solid-Organ Transplantation

Factors predisposing to infection after organ transplantation include those that either existed before transplantation or are secondary to intraoperative events or posttransplantation therapies (Table 205.3). Some of these additional risks cannot be prevented, and some risks acquired during or after the operation depend on decisions or actions of members of the transplant team. Organ recipients are at risk for infection from potential exposure to pathogens in the donor organ. Although some donor-derived infections can be anticipated through donor screening, many pathogens are not routinely screened for, and strategies defining when and how to screen for all but a small subset of potential pathogens have not been identified or implemented. Similar to other children who have undergone surgical procedures; surgical site infections are a frequent cause of infection early after transplantation. Beyond this, the need for immunosuppressive agents to prevent rejection is the major factor predisposing to infection following transplantation. Despite efforts to optimize immunosuppressive regimens to prevent or treat rejection with minimal impairment of immunity, all current regimens interfere with the ability of the immune system to prevent infection. The primary target of the majority of these immunosuppressive agents in organ recipients is the cell-mediated immune system, but regimens can and do impair many other aspects of the transplant recipient's immune system as well.

Table 205.3

Risk Factors for Infections After Solid-Organ Transplantation in Children

PRETRANSPLANTATION FACTORS
Age of patient
Underlying disease, malnutrition
Specific organ transplanted
Previous exposures to infectious agents
Previous immunizations
Presence of infection in the donor
INTRAOPERATIVE FACTORS
Duration of transplant surgery
Exposure to blood products
Technical problems
Organisms transmitted with donor organ
POSTTRANSPLANTATION FACTORS
Immunosuppression
Induction immunosuppression type
Maintenance immunosuppression
Augmented treatment for rejection
Indwelling catheters
Nosocomial exposures
Community exposures

Timing

The timing of specific types of infections is generally predictable, regardless of which organ is transplanted. Infectious complications typically develop in 1 of 3 intervals: early (0-30 days after transplantation), intermediate (30-180 days), or late (>180 days); most infections present in the 1st 180 days after transplantation. Table 205.4 should be used as a general guideline to the types of infections encountered but may be modified with the introduction of newer immunosuppressive therapies and by the use of prophylaxis.

Table 205.4

Timing of Infectious Complications After Solid-Organ Transplantation

EARLY PERIOD (0-30 DAYS)
Bacterial Infections
Gram-negative enteric bacilli
• Small bowel, liver, neonatal heart
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-positive organisms
• All transplant types
Fungal Infections
• All transplant types
Viral Infections

Herpes simplex virus
- All transplant types

Nosocomial respiratory viruses
- All transplant types

MIDDLE PERIOD (1-6 MO)

Viral Infections

Cytomegalovirus
- All transplant types
- Seronegative recipient of seropositive donor

Epstein-Barr virus
- All transplant types (small bowel the highest-risk group)
- Seronegative recipient

Varicella-zoster virus
- All transplant types
- Opportunistic infections

Pneumocystis jiroveci
- All transplant types

Toxoplasma gondii
- Seronegative recipient of cardiac transplant from a seropositive donor

Bacterial Infections

Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
- Cystic fibrosis lung

Gram-negative enteric bacilli
- Small bowel

LATE PERIOD (>6 MO)

Viral Infections

Epstein-Barr virus
- All transplant types, but less risk than middle period

Varicella-zoster virus
- All transplant types

Community-acquired viral infections
- All transplant types

Bacterial Infections

Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
- Cystic fibrosis lung
- Lung transplants with chronic rejection

Gram-negative bacillary bacteremia
- Small bowel

Fungal Infections

Aspergillus
- Lung transplants with chronic rejection

Adapted from Green M, Michaels MG: Infections in solid organ transplant recipients. In Long SS, Prober C, Fisher M, editors: *Principles and practice of pediatric infectious disease* , ed 5, Philadelphia, 2018, Elsevier (Table 95-1).

Early infections are usually the result of a complication of the transplant surgery itself, the unexpected acquisition of a bacterial or fungal pathogen from the donor, or the presence of an indwelling catheter. In contrast, infections during the intermediate period typically result from a complication of the immunosuppression, which tends to be at its greatest intensity during the 1st 6 mo after transplantation. This is the period of greatest risk for infections caused by opportunistic pathogens such as CMV, EBV, and *P. jiroveci.* Anatomic abnormalities, such as bronchial stenosis and biliary stenosis, that develop as a result of the transplant surgery can also predispose to recurrent infection in this period.

Infections developing late after transplantation typically result from uncorrected anatomic abnormalities, chronic rejection, or exposure to community-acquired pathogens. Augmented immunosuppression as treatment for late, acute cellular rejection or chronic rejection can increase the risk for late presentations with CMV, EBV, and other potential opportunistic infections. Acquisition of infection from community-acquired pathogens such as RSV can result in severe infection secondary to the immunocompromised state of the transplant recipient during the early and intermediate periods. Compared with the earlier periods, community-acquired infections in the late period are usually benign, because immunosuppression is typically maintained at significantly lower levels. However, certain pathogens such as VZV and EBV may be associated with severe disease even at this late period.

Bacterial and Fungal Infections

Although there are important graft-specific considerations for bacterial and fungal infections following transplantation, some principles are generally applicable to all transplant recipients. Bacterial and fungal infections after organ transplantation are usually a direct consequence of the surgery, a breach in an anatomic barrier, a foreign body, or an abnormal anatomic narrowing or obstruction. With the exception of infections related to the use of indwelling catheters, sites of bacterial infection tend to occur at or near the transplanted organ. Infections following abdominal transplantation (liver, intestine, or renal) usually occur in the abdomen or at the surgical wound. The pathogens are typically enteric gram-negative bacteria, *Enterococcus*, and occasionally *Candida*. Infections after thoracic transplantation (heart, lung) usually occur in the lower respiratory tract or at the surgical wound. Pathogens associated with these infections include *S. aureus* and gram-negative bacteria. Patients undergoing lung transplantation for cystic fibrosis experience a particularly high rate of infectious complications, because they are often colonized with *P. aeruginosa* or *Aspergillus* before transplantation. Even though the infected lungs are removed, the sinuses and upper airways remain colonized with these pathogens, and subsequent reinfection of the transplanted lungs can occur. Children receiving organ transplants are often hospitalized for long periods and receive many antibiotics; thus recovery of bacteria with multiple antibiotic resistance patterns is common after all types of organ transplantation. Infections caused by *Aspergillus* are less common but occur after all types of organ transplantation and are associated with high rates of morbidity and mortality.

Viral Infections

Viral pathogens, especially herpesviruses, are a major source of morbidity and mortality following solid-organ transplantation. In addition, BK virus is a major cause of renal disease after kidney transplantation. The patterns of disease associated with individual viral pathogens are generally similar among all organ transplant recipients. However, the incidence, mode of presentation, and severity differ according to type of organ transplanted and, for many viral pathogens, pretransplant serologic status of the recipient.

Viral pathogens can be generally categorized as latent pathogens, which cause infection through reactivation in the host or acquisition from the donor (e.g., CMV, EBV) or as community-acquired viruses (e.g., RSV). For CMV and EBV, primary infection occurring after transplantation is associated with the greatest degree of morbidity and mortality. The highest risk is seen in a naïve host who receives an organ from a donor who previously was infected with one of these viruses. This mismatched state is frequently associated with severe disease. However, even if the donor is negative for CMV and EBV, primary infection can be acquired from a close contact or through blood products. Secondary infections (reactivation of a latent strain within the host or superinfection with a new strain) tend to result in milder illness unless the patient is highly immunosuppressed, which can occur in the setting of treatment of significant rejection.

CMV is one of the most commonly recognized transplant viral pathogens. Disease from CMV has decreased significantly with the use of preventive strategies, including antiviral prophylaxis as well as viral load monitoring to inform preemptive antiviral therapy. Some centers have implemented a hybrid approach where surveillance viral load monitoring follows a relatively short period (2-4 wk) of chemoprophylaxis. Clinical manifestations of CMV disease can range from a syndrome of fatigue and fever to tissue invasive disease that most often affects the liver, lungs, and GI tract.

Infection caused by EBV is another important complication of solid-organ transplantation. Clinical symptoms range from a mild mononucleosis syndrome to disseminated **posttransplant lymphoproliferative disorder** . Posttransplant lymphoproliferative disorder is more common among children than adults, because primary EBV infection in the immunosuppressed host is more likely to lead to uncontrolled proliferative disorders, including posttransplant lymphoma.

Other viruses, such as adenovirus, also have the capacity to be donor associated, but appear to be less common. The unexpected development of donor-associated viral pathogens, including hepatitis B virus, hepatitis C virus, and HIV, is rare today because of intensive donor screening. However, the changing epidemiology of some viruses (e.g., dengue, chikungunya, Zika) raises concerns for the donor-derived transmission of these emerging viral pathogens.

Community-acquired viruses, including those associated with respiratory tract infection (RSV, influenza virus, adenovirus, parainfluenza virus) and GI infection (enteroviruses, norovirus, and rotavirus), can cause important disease in children after organ transplantation. In general, risk factors for more severe infection include young age, acquisition of infection early after transplantation, and augmented immune suppression. Infection in the absence of these risk factors frequently results in a clinical illness that is comparable to that seen in immunocompetent children. However, some community-acquired viruses, such as adenovirus, can be associated with graft dysfunction even when acquired late after transplantation.

Opportunistic Pathogens

Children undergoing solid-organ transplantation are also at risk for symptomatic infections from pathogens that do not usually cause clinical disease in immunocompetent hosts. Although these typically present in the intermediate period, these infections can also occur late in patients, requiring prolonged and high levels of immunosuppression. *P. jiroveci* is a well-recognized cause of pneumonia after solid-organ transplantation, although routine prophylaxis has essentially eliminated this problem. *T. gondii* can complicate cardiac transplantations because of tropism of the organism for cardiac muscle and risk for donor transmission; less often it complicates other types of organ transplantation.

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205.3

Prevention of Infection in Immunocompromised Persons

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Although infections cannot be completely prevented in children who have defects in one or more arms of their immune system, measures can be taken to decrease the risks for infection. Replacement immunoglobulin is a benefit to children with primary B cell deficiencies. Interferon (IFN)-γ, TMP-SMX, and oral antifungal agents have long been used to reduce the number of infections occurring in children with CGD, although the relative benefit of INF-γ has been questioned. Children who have depressed cellular immunity resulting from primary diseases, advanced HIV infection, or immunosuppressive medications benefit from prophylaxis against *P. jiroveci.* Immunizations prevent many infections and are particularly important for children with compromised immune systems who do not have a contraindication or inability to respond. For children rendered immunocompromised because of medication or splenectomy, immunizations should be administered before treatment. This timing allows for superior response to vaccine antigens, avoids the risk of live vaccines, which may be contraindicated depending on the immunosuppression, and importantly provides protection before the immune system is compromised.

Although immunodeficient children are a heterogeneous group, some principles of prevention are generally applicable. The use of inactivated vaccines does not lead to an increased risk for adverse effects, although their efficacy may be reduced because of an impaired immune response. In most cases, children with immunodeficiencies should receive all the recommended inactivated vaccines. Live-attenuated vaccinations can cause disease in some children with immunologic defects, and therefore alternative immunizations should be used whenever possible, such as inactivated influenza vaccine rather than live-attenuated influenza vaccine or inactivated typhoid vaccine rather than the oral live typhoid vaccine for travelers. In general, live-virus vaccines should not be used in children with primary T cell abnormalities; efforts should be made to ensure that close contacts are all immunized to decrease the risk of exposure. In some patients in whom wild-type viral infection can be severe, immunizations, even with live-virus vaccine, are warranted in the immunosuppressed child. For example, children with HIV infection and a CD4 level of >15% should receive vaccinations against measles and varicella. Some vaccines should be given to children with immunodeficiencies in addition to routine vaccinations. As an example, children with asplenia or splenic dysfunction should receive meningococcal vaccine and both the conjugate and the polysaccharide pneumococcal vaccines. Influenza vaccination is recommended for all individuals >6 mo old and should be emphasized for immunocompromised children as well as all household contacts, to minimize risk for transmission to the immunocompromised child.

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CHAPTER 206

Infection Associated With Medical Devices

Joshua Wolf, Patricia M. Flynn

Use of implanted synthetic and prosthetic devices has revolutionized pediatric practice by providing long-term venous access, limb-salvage surgery, and successful treatment of hydrocephalus, urinary retention, and renal failure. However, infectious complications of these devices remain a major concern. These infections are related to the development of **biofilms** , organized communities of microorganisms on the device surface protected from the immune system and from antimicrobial therapy. A number of factors are important to the development of infection, including host susceptibility, device composition, duration of implantation, and exposure to colonizing organisms.

Intravascular Access Devices

Intravascular access devices range from short, stainless steel needles or plastic cannulae inserted for brief periods to multilumen implantable synthetic plastic catheters that are expected to remain in use for years. Infectious complications include local skin and soft tissue infections such as exit-site, tunnel-tract, and device-pocket infections, and **catheter-related bloodstream infections (CRBSIs)** . The use of central venous devices has improved the quality of life of high-risk patients but has also increased the risk of infection.

Catheter Types

Short-term peripheral cannulae are most often used in pediatric patients, and infectious complications occur infrequently. The rate of peripheral CRBSIs in children is <0.15%. Patient age <1 yr, duration of use >144 hr, and some infusates are associated with increased risk for catheter-related infection. Catheter-associated phlebitis is more common (1–6%) but is rarely infective and can be treated conservatively by cannula removal.

Central venous catheters (CVCs), which terminate in a central vein such as the superior or inferior vena cava, are widely used in both adult and pediatric patients and are responsible for the majority of catheter-related infections. These catheters are frequently used in critically ill patients, including neonates, who have many other risk factors for nosocomial infection. Patients in an intensive care unit (ICU) with a CVC in place have a 5-fold greater risk for developing a nosocomial bloodstream infection than those without.

The use of peripherally inserted central catheters, which are inserted into a peripheral vein and terminate in a central vein, has increased in pediatric patients. Infection rates seem to be similar to long-term tunneled CVCs (approximately 2 per 1,000 catheter-days), but other complications such as fracture, dislodgment, and occlusion are more common.

When prolonged intravenous (IV) access is required, a cuffed silicone rubber (Silastic) or polyurethane catheter may be inserted into the superior vena cava through the subclavian, cephalic, or jugular vein. The extravascular segment of the catheter passes through a subcutaneous (SC) tunnel before exiting the skin, usually on the superior aspect of the chest (e.g., Broviac or Hickman catheter). A cuff around the catheter near the exit site induces a fibrotic reaction to seal the tunnel. Totally implanted devices comprise a tunneled central catheter attached to an SC reservoir or port with a self-sealing silicone septum immediately under the skin that permits repeated percutaneous needle access.

The incidence of local (exit site, tunnel, and pocket) infection with long-term catheters is 0.2-2.8/1,000 catheter-days. The incidence of Broviac or Hickman CRBSI is 0.5-11.0/1,000 catheter-days. The incidence of CRBSI in implantable devices is much lower at 0.3-1.8/1,000 catheter-days; however, treatment with total parenteral nutrition (TPN) eliminates this risk reduction because of a much greater relative increase in infection rate in ports. The risk for CRBSI is increased among premature infants, young children, and TPN patients.

Catheter-Associated Skin and Soft Tissue Infection

A number of local infections can occur in the presence of a CVC. The clinical manifestations of local infection include erythema, tenderness, and purulent discharge at the exit site or along the SC tunnel tract of the catheter. **Exit -site infection** denotes infection localized to the exit site, without significant tracking along the tunnel, often with purulent discharge. **Tunnel-tract infection** indicates infection in the SC tissues tracking along a tunneled catheter, which may also include serous or serosanguineous discharge from a draining sinus along the path. **Pocket infection** indicates suppurative infection of an SC pocket containing a totally implanted device. Bloodstream infection may coexist with local infection.

The diagnosis of local infection is established clinically, but a gram-stained smear and culture of any exit-site drainage should be performed to identify the microbiologic cause. The source is usually contamination by skin or gastrointestinal flora, and the most common organisms are *Staphylococcus aureus* , coagulase-negative staphylococci, *Pseudomonas aeruginosa, Candida* spp., and mycobacteria. Green discharge is strongly suggestive of mycobacterial infection, and appropriate stains and culture should be performed.

Treatment of local infection related to a short-term CVC should include device removal. Exit-site infection may resolve with device removal alone, but systemic symptoms should be managed with antimicrobial therapy as recommended next for treatment of CRBSI. In the case of long-term CVCs, exit-site infections usually respond to local care with topical or systemic antibiotics alone. However, tunnel or pocket infections require removal of the catheter and systemic antibiotic therapy in almost all cases. When a CVC is removed as a result of tunnel infection, the cuff should also be removed and sent for culture if possible. In cases of mycobacterial infection, wide surgical debridement of the tissues is usually required for cure.

Catheter-Related Bloodstream Infection

CRBSI occurs when microorganisms attached to the CVC are shed into the bloodstream, leading to bacteremia. The term **catheter-related bloodstream infection** is reserved for a bloodstream infection that is demonstrated by CVC tip culture or other techniques to have been caused by colonization of the device. In contrast, the more general term **central line –associated bloodstream infection (CLABSI)** is typically used for surveillance and can refer to any bloodstream infection that occurs in a patient with a CVC, unless there is an identified alternative source. On the device, the organisms are embedded in biofilms as organized communities. Colonization may be present even in the absence of symptoms or positive cultures.

Organisms may contaminate the external surface of the CVC during insertion or the intraluminal surface through handling of the catheter hub or contaminated infusate. Most cases of CRBSI appear to be caused by intraluminal colonization, but external colonization may play a greater role in infections related to recently inserted (<30 days) catheters. Gram-positive cocci predominate, with about half of infections caused by coagulase-negative staphylococci. Gram-negative enteric bacteria are isolated in approximately 20–30% of episodes, and fungi account for 5–10% of episodes.

Fever without an identifiable focus is the most common clinical presentation of CRBSI; local soft tissue symptoms and signs are usually absent. Onset of fever or rigors during or soon after flushing of a catheter is highly suggestive of CRBSI. Symptoms and signs of complicated infection, such as septic thrombophlebitis, endocarditis, or ecthyma gangrenosum, may also be present.

Blood cultures collected before beginning antibiotic therapy are generally positive from both the CVC and the peripheral blood. It is important not to collect cultures unless infection is suspected, as blood culture contamination may occur and can lead to inappropriate therapy. To help interpret positive cultures with common skin contaminants, blood cultures should be collected from at least 2 sites, preferably including all lumens of a CVC *and* the peripheral blood, before initiation of antibiotic therapy.

Tests to differentiate CRBSI from other sources of bacteremia in the presence of a CVC include culture of the catheter tip, quantitative blood cultures, or **differential time to positivity** of blood cultures drawn from different sites. Definitive diagnosis of CRBSI can be important to identify those patients who might benefit from catheter removal or adjunctive therapy. Although CVC tip culture can identify CRBSI, it precludes salvage of the catheter. The most readily available technique to confirm CRBSI without catheter removal is calculation of differential time to positivity between blood cultures drawn through a catheter and from a peripheral vein or separate lumen. During CRBSI, blood obtained through the responsible lumen will usually indicate growth at least 2-3 hr before peripheral blood or uncolonized lumens because of a higher intraluminal microorganism burden. Identical volumes of blood must be collected simultaneously from each site, and a continuously monitored blood culture system is required. Specificity of this test is good (94–100%), and sensitivity is good when a peripheral blood culture is available (approximately 90%) but poorer when comparing 2 lumens of a CVC (64%). Where available, quantitative blood culture showing at least a 3-fold higher number of organisms from central compared with peripheral blood is similarly diagnostic.

Treatment of CRBSI related to **long-term vascular access devices** (Hickman, Broviac, totally implantable devices) with systemic antibiotics is successful for many bacterial infections without removal of the device. Antibiotic therapy should be directed to the isolated pathogen and given for a total of 10-14 days from the date of blood culture clearance. Until identification and susceptibility testing are available, empirical therapy, based on local antimicrobial susceptibility data and usually including **vancomycin** plus an antipseudomonal aminoglycoside (e.g., gentamicin), penicillin (e.g., piperacillin-tazobactam), or cephalosporin (e.g., ceftazidime or cefepime) is generally indicated. An echinocandin or azole antifungal should be initiated if fungemia is suspected. Patients who have a past history of CRBSI with a resistant organism treated without CVC removal should generally receive initial empirical therapy directed against that organism, since relapse is common.

Antibiotic lock or dwell therapy , with administration of solutions of high concentrations of antibiotics or ethanol that remain in the catheter for up to 24 hr, have been proposed to improve outcomes when used as an adjuvant to systemic therapy. Antibiotic locks are recommended in patients receiving dialysis who may not have antibiotics frequently delivered through the CVC, but evidence does not suggest that routine use of lock therapy is beneficial in other patient populations, and it may cause harm. Ethanol lock therapy increases the risk of CVC occlusion, and both can result in delays to necessary CVC removal.

If blood cultures remain positive after 72 hr of appropriate therapy, or if a patient deteriorates clinically, the device should be removed. Failure of CRBSI salvage therapy is common and can be serious in infections caused by *S. aureus* (approximately 50%), *Candida* spp. (>70%), and *Mycobacterium* spp. (>70%), although some case reports of cure with antimicrobial lock therapy are promising. Other indications for removing a long-term catheter include severe sepsis, suppurative thrombophlebitis, and endocarditis. Prolonged therapy (4-6 wk) is indicated for persistent bacteremia or fungemia despite catheter removal, since this may represent unrecognized infective endocarditis or thrombophlebitis. The decision to attempt catheter salvage should weigh the risk and clinical impact of persistent or relapsed infection against the risk of surgical intervention.

CRBSI may be complicated by other intravascular infections such as septic thrombophlebitis or endocarditis. Presence of these conditions may be suggested by preexisting risk factors (e.g., congenital heart disease), signs and symptoms, or persistent bacteremia or fungemia 72 hr after device removal and appropriate therapy. Screening for these complications in otherwise low-risk children, even those with *S. aureus* infection, is not recommended, because the overall frequency is low and the tests can be difficult to interpret and may lead to inappropriate therapy.

Prevention of Infection

Catheters should routinely be removed as soon as they are no longer needed. Although prevalence of infection increases with prolonged duration of catheter use, routine replacement of a required CVC, either at a new site or over a guidewire, results in significant morbidity and is not recommended. Optimal prevention of infections related to long-term vascular access devices includes "bundles" of interventions, including meticulous aseptic surgical insertion technique in an operating room–like environment, avoidance of bathing or swimming (except with totally implantable devices), and careful catheter care. Use of antibiotic, taurolidine, or ethanol lock solutions; heparin with preservatives; and alcohol-impregnated caps, as well as antimicrobial-impregnated/coated catheters, all reduce the risk of CRBSIs and may be appropriate in high-risk populations. There is no evidence that routine replacement of short-term peripheral catheters prevents phlebitis or other complications in children, so they should only be replaced when clinically indicated (e.g., phlebitis, dysfunction, dislodgment).

Cerebrospinal Fluid Shunts

Cerebrospinal fluid (CSF) shunting is required for the treatment of many children with **hydrocephalus** . The usual procedure uses a silicone rubber device with a proximal portion inserted into the ventricle, a unidirectional valve, and a distal segment that diverts the CSF from the ventricles to either the peritoneal cavity (**ventriculoperitoneal** [VP] shunt) or right atrium (**ventriculoatrial** [VA] shunt). The incidence of shunt infection ranges from 1–20% (average, 10%). The highest rates are reported in young infants, patients with prior shunt infections, and certain etiologies of hydrocephalus. Most infections result from intraoperative contamination of the surgical wound by skin flora. Accordingly, coagulase-negative staphylococci are isolated in more than half the cases. *S. aureus* is isolated in approximately 20% and gram-negative bacilli in 15% of cases.

Four distinct clinical syndromes have been described: colonization of the shunt, infection associated with wound infection, distal infection with peritonitis, and infection associated with meningitis. The most common type of infection is **colonization of the shunt** , with nonspecific symptoms that reflect shunt malfunction as opposed to frank infection. Symptoms associated with colonized VP shunts include lethargy, headache, vomiting, a full fontanel, and abdominal pain. Fever is common but may be <39°C (102.2°F). Symptoms usually occur within months of the surgical procedure. Colonization of a VA shunt results in more severe systemic symptoms, and specific symptoms of shunt malfunction are often absent. Septic pulmonary emboli, pulmonary hypertension, and infective endocarditis are frequently reported complications of VA shunt colonization. Chronic VA shunt colonization may cause hypocomplementemic glomerulonephritis from antigen-antibody complex deposition in the glomeruli, commonly called “shunt nephritis”; clinical findings include hypertension, microscopic hematuria, elevated blood urea nitrogen and serum creatinine levels, and anemia.

Diagnosis is by Gram stain, microscopy, biochemistry, and culture of CSF. CSF should be obtained by direct aspiration of the shunt before administration of antibiotics, because CSF obtained from either lumbar or ventricular puncture is often sterile. It is unusual to observe signs of ventriculitis, and CSF findings can be only minimally abnormal. Blood culture results are usually positive in VA shunt colonization but negative in cases of VP colonization.

Wound infection presents with obvious erythema, swelling, discharge, or dehiscence along the shunt tract and most often occurs within days to weeks of the surgical procedure. *S. aureus* is the most common isolate. In addition to the physical findings, fever is common, and signs of shunt malfunction eventually ensue in most cases.

Distal infection of VP shunts with **peritonitis** presents with abdominal symptoms, usually without evidence of shunt malfunction. The pathogenesis is likely related to perforation of bowel at VP shunt placement or translocation of bacteria across the bowel wall. Thus, gram-negative isolates predominate, and mixed infection is common. The infecting organisms are often isolated from only the distal portion of the shunt.

Common pathogens responsible for community-acquired **meningitis** , including *Streptococcus pneumoniae, Neisseria meningitidis* , and *Haemophilus influenzae* type b, can also rarely cause bacterial meningitis in patients with shunts. The clinical presentation is similar to that for acute bacterial meningitis in other children (see Chapter 621.1).

Treatment of shunt colonization includes removal of the shunt and systemic antibiotic therapy directed against the isolated organisms. Treatment without removal of the shunt is rarely successful and should not be routinely attempted. After collection of appropriate samples for culture, empirical therapy is usually with vancomycin plus an antipseudomonal agent with relatively good CSF penetration, such as ceftazidime or meropenem. Definitive therapy should be directed toward the isolate and should account for poor penetration of most antibiotics into the CSF across noninflamed meninges. Accordingly, intraventricular antibiotics may be indicated but are usually reserved unless there is evidence of treatment failure. If the isolate is susceptible, a parenteral antistaphylococcal penicillin with or without intraventricular vancomycin is the treatment of choice. If the organism is resistant to penicillins, systemic vancomycin and possibly intraventricular vancomycin are recommended. In gram-negative infections, a third-generation cephalosporin with or without and intraventricular aminoglycoside is optimal. When using intraventricular antibiotics, monitoring CSF levels is necessary to avoid toxicity.

Removal of the colonized device is required for cure, and final replacement should be delayed until clearance of CSF cultures is documented. Many neurosurgeons immediately remove the shunt and place an external ventricular drain to relieve intracranial pressure (ICP), with a second-stage shunt replacement once CSF sterilization has been confirmed. Others opt initially to exteriorize the distal end of the shunt and replace the shunt in a single-stage procedure once CSF cultures remain sterile for 48-72 hr. Daily CSF cultures should be collected until clearance has been documented on 2-3 consecutive specimens, and antibiotics should be continued for at least 10 days after documented sterilization of the CSF. Gram-negative organisms may require a longer duration of therapy (up to 21 days). The CSF white cell count generally increases for the 1st 3-5 days of appropriate therapy and alone should not prompt concern for treatment failure. Distal shunt infection with peritonitis and wound infection are managed in a similar fashion.

Treatment of **bacterial meningitis** with typical community-acquired pathogens such as meningococcus or pneumococcus usually requires only systemic antibiotic therapy. Shunt replacement is not required in the absence of device malfunction, poor clinical response, persistent CSF culture positivity, or relapse of infection after antibiotic therapy.

Prevention of Infection

Prevention of shunt infection includes meticulous cutaneous preparation and surgical technique. Systemic and intraventricular antibiotics, antibiotic-impregnated shunts, and soaking the shunt tubing in antibiotics are used to reduce the incidence of infection, with varying success. Systemic prophylactic antibiotics given before and during shunt insertion can reduce the risk for infection and should be used routinely but should not be continued for more than 24 hr postoperatively. Antibiotic-impregnated catheters also appear to reduce the risk of infection and may be used in high-risk patients where the devices are available.

Urinary Catheters

Urinary catheters are a frequent cause of nosocomial infection, with about 14 infections per 1,000 admissions. As with other devices, microorganisms adhere to the catheter surface and establish a biofilm that allows proliferation. The physical presence of the catheter reduces the normal host defenses by preventing complete emptying of the bladder, thus providing a medium for growth, distending the urethra, and blocking periurethral glands. Almost all patients catheterized >30 days develop bacteriuria. The organism burden in catheter-associated urinary tract infection (UTI) is typically ≥10,000 colony-forming units/mL. Lower thresholds may be used where there is a high index of suspicion, but these episodes may represent colonization rather than infection. Urine culture should only be performed in catheterized patients when infection is suspected, because asymptomatic colonization is ubiquitous and may lead to overtreatment and subsequent development of bacterial resistance. Gram-negative bacilli and *Enterococcus* spp. are the predominant organisms isolated in catheter-related UTI; coagulase-negative staphylococci are implicated in approximately 15% of cases. Symptomatic UTIs should be treated with antibiotics and catheter removal. Catheter colonization with *Candida* spp. is common but rarely leads to invasive infection, and treatment does not have a long-term impact on colonization. Treatment for asymptomatic candiduria or bacteriuria is not recommended, except in neonates, immunocompromised patients, and those with urinary tract obstruction.

Prevention of Infection

All urinary catheters introduce a risk for infection, and their casual use should be avoided. When in place, their duration of use should be minimized. Technologic advances have led to development of silver- or antibiotic-impregnated urinary catheters that are associated with lower rates of infection. Prophylactic antibiotics do not significantly reduce the infection rates for long-term catheters but clearly increase the risk for infection with antibiotic-resistant organisms.

Peritoneal Dialysis Catheters

During the 1st yr of peritoneal dialysis for end-stage renal disease, 65% of children will have 1 or more episodes of peritonitis. Bacterial entry comes from luminal or periluminal contamination of the catheter or by translocation across the intestinal wall. Hematogenous infection is rare. Infections can be localized at the exit site or associated with peritonitis, or both. Organisms responsible for peritonitis include coagulase-negative staphylococci (30–40%), *Staphylococcus aureus* (10–20%), streptococci (10–15%), *Escherichia coli* (5-10%), *Pseudomonas* spp. (5–10%), other gram-negative bacteria (5–15%), *Enterococcus* spp. (3–6%), and fungi (2–10%). *S. aureus* is more common in localized exit-site or tunnel-tract infections (42%). Most infectious episodes are caused by a patient's own flora, and carriers of *S. aureus* have increased rates of infection compared with noncarriers.

The clinical manifestations of peritonitis may be subtle and include low-grade fever with mild abdominal pain or tenderness. Cloudy peritoneal dialysis fluid may be the first and predominant sign. With peritonitis, the peritoneal fluid cell count is usually >100 white blood cells/µL. When peritonitis is suspected, the effluent dialysate should be submitted for a cell count, Gram stain, and culture. The Gram stain is positive in up to 40% of cases of peritonitis.

Patients with cloudy fluid and clinical symptoms should receive empirical therapy, preferably guided by results of a Gram stain. If no organisms are visualized, vancomycin and either an aminoglycoside or a third- or fourth-generation cephalosporin with antipseudomonal activity should be given by the intraperitoneal route. Blood levels should be measured for glycopeptides and aminoglycosides. Patients without cloudy fluid and with minimal symptoms may have therapy withheld pending culture results. Once the cause is identified by culture, changes in the therapeutic regimen may be needed. Oral **rifampin** may be added as adjunctive therapy for *S. aureus* infections, but drug interactions must be considered. Candidal peritonitis should be treated with catheter removal and intraperitoneal or oral **fluconazole** or an intravenous **echinocandin** such as caspofungin or micafungin, depending on the *Candida* spp. Catheter retention has been associated with almost inevitable relapse and higher risk of mortality in adult studies. The duration of therapy is a minimum of 14 days, with longer treatment of 21-28 days for episodes of *S. aureus* , *Pseudomonas* spp., and resistant gram-negative bacteria and 28-42 days for fungi. Repeat episodes of peritonitis with the same organism within 4 wk of previous therapy should lead to consideration of catheter removal or attempt at salvage with administration of a fibrinolytic agent and a longer a course of up to 6 wk of antibiotic therapy.

In all cases, if the infection fails to clear following appropriate therapy, or if a patient's condition is deteriorating, the catheter should be removed. Exit-site and tunnel-tract infections may occur independently of peritonitis or may precede it. Appropriate antibiotics should be administered on the basis of Gram stain and culture findings and are typically given systemically only, unless peritonitis is also present. Some experts recommend that the peritoneal catheter be removed if *Pseudomonas* spp. or fungal organisms are isolated.

Prevention of Infection

In addition to usual hygienic practices, regular application of **mupirocin** or **gentamicin** cream to the catheter exit site reduces exit-site infections and peritonitis. Some practitioners recommend against the use of gentamicin cream because of the risk of infection with gentamicin-resistant bacteria. Systemic antibiotic prophylaxis should be considered at catheter insertion, if there is accidental contamination, and at dental procedures. Antifungal prophylaxis with oral nystatin or fluconazole should be considered during antibiotic therapy to prevent fungal infection.

Orthopedic Prostheses

Orthopedic prostheses are used infrequently in children. Infection most often follows introduction of microorganisms at surgery through airborne contamination or direct inoculation, hematogenous spread, or contiguous spread from an adjacent infection. Early postoperative infection occurs within 2-4 wk of surgery, with manifestations typically including fever, pain, and local symptoms of wound infection. Rapid assessment, including isolation of the infecting organism by joint aspiration or intraoperative culture, operative debridement, and antimicrobial treatment, may allow salvage of the implant if the duration of symptoms is <1 mo, the prosthesis is stable, and the pathogen is susceptible to antibiotics. Chronic infection presents >1 mo after surgery and is often caused by organisms of low virulence that contaminated the implant at surgery or by failure of wound healing. Typical manifestations include pain and deterioration in function. Local symptoms such as erythema, swelling, or drainage may also occur. These infections respond poorly to antibiotic treatment and usually require removal of the implant using a 1- or 2-stage procedure. Surgical irrigation and debridement of the site with retention of the prosthesis and long-term suppressive antibiotic therapy may be considered, but eradication of infection appears uncommon. Acute hematogenous infections are most often observed ≥2 yr after surgery. Retention of the prosthesis is sometimes attempted, but inadequate long-term data exist to determine the success rate. If salvage therapy is attempted, prompt debridement and appropriate antibiotic therapy are recommended. As with other long-term implanted devices, the most common organisms are coagulase-negative staphylococci and *S. aureus* . With prior antibiotic therapy, the prosthesis culture may be negative; in these situations, molecular techniques to identify the organism are available, but sensitivity and specificity are poorly understood.

Systemic antibiotic prophylaxis, antibiotic-containing bone cement, and operating rooms fitted with laminar airflow have been proposed to reduce infection. To date, results from clinical studies are conflicting.

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SECTION 3

Antibiotic Therapy

OUTLINE

Chapter 207 Principles of Antibacterial Therapy

CHAPTER 207

Principles of Antibacterial Therapy

Mark R. Schleiss

Antibacterial therapy in infants and children presents many challenges. A daunting problem is the paucity of pediatric data regarding pharmacokinetics and optimal dosages; as a consequence, pediatric recommendations are frequently extrapolated from adult studies. A 2nd challenge is the need for the clinician to consider important differences among pediatric age-groups with respect to the pathogenic species most often responsible for bacterial infections. Age-appropriate antibiotic dosing and toxicities must be considered, taking into account the developmental status and physiology of infants and children. Finally, the style of how a pediatrician uses antibiotics in children, particularly young infants, has some important differences compared with how antibiotics are used adult patients.

Specific antibiotic therapy is optimally driven by a **microbiologic diagnosis** , predicated on isolation of the pathogenic organism from a sterile body site, and supported by antimicrobial susceptibility testing. However, given the inherent difficulties that can arise in collecting specimens from pediatric patients, and given the high risk of mortality and disability associated with serious bacterial infections in very young infants, much of pediatric infectious diseases practice is based on a clinical diagnosis with **empirical** use of antibacterial agents, administered before or even without eventual identification of the specific pathogen. Although there is increasing emphasis on the importance of using empirical therapy sparingly (so as to not select for resistant organisms), there are some settings in which antimicrobials must be administered before the presence of a specific bacterial pathogen is proven. This is particularly relevant to the care of the febrile or ill-appearing neonate or young infant under 30 days of age.

Several key considerations influence decision-making regarding appropriate empirical use of antibacterial agents in infants and children. It is important to know the age-appropriate differential diagnosis with respect to likely pathogens. This information affects the choice of antimicrobial agent and also the dose, dosing interval, and route of administration (oral vs parenteral). A complete history and physical examination, combined with appropriate laboratory and radiographic studies, are necessary to identify specific diagnoses, information that in turn affects the choice, dosing, and degree of urgency of administration of antimicrobial agents. The vaccination history may confer reduced risk for some invasive infections (i.e., *Haemophilus influenzae* type b, *Streptococcus pneumoniae* , *Neisseria meningitidis*), but not necessarily elimination of risk. The risk of serious bacterial infection in pediatric practice is also affected by the child's immunologic status, which may be compromised by immaturity (neonates), underlying disease, and associated treatments (see Chapter 205). Infections in immunocompromised children may result from bacteria that are not considered pathogenic in immunocompetent children. The presence of foreign bodies (medical devices) also increases the risk of bacterial infections (see Chapter 206). The likelihood of central nervous system (CNS) involvement must be considered in all pediatric patients with serious bacterial infections, because many cases of bacteremia in childhood carry a significant risk for hematogenous spread to the CNS.

The patterns of **antimicrobial resistance** in the community and for the potential causative pathogen being empirically covered must also be considered. Resistance to penicillin and cephalosporins is commonplace among strains of *S. pneumoniae*, often necessitating the use of other classes of antibiotics. Similarly, the striking emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (**MRSA**) infections has complicated antibiotic choices for this pathogen. Extended-spectrum β-lactamase (**ESBL**)–producing gram-negative bacteria (Enterobacteriaceae) have reduced the effectiveness of penicillins and cephalosporins. Furthermore, carbapenem-resistant Enterobacteriaceae are an increasing problem among hospitalized patients, particularly in children with an epidemiologic connection to regions of the world, such as India, where such strains are frequently encountered.

Antimicrobial resistance occurs through many modifications of the bacterial genome (Tables 207.1 and 207.2). Mechanisms include enzyme inactivation of the antibiotic, decreased cell membrane permeability to intracellularly active antibiotics, efflux of antibiotics out of the bacteria, protection or alteration of the antibiotic target site, excessive production of the target site, and bypassing the antimicrobial site of action.

Table 207.1

Mechanisms of Resistance to β-Lactam Antibiotics

- I. Alter target site (PBP)
  - A. Decrease affinity of PBP for β-lactam antibiotic
    - 1. Modify existing PBP
      - a. Create mosaic PBP
        - (1) Insert nucleotides obtained from neighboring bacteria (e.g., penicillin-resistant *Streptococcus pneumoniae*)
        - (2) Mutate structural gene of PBP(s) (e.g., ampicillin-resistant β-lactamase–negative *Haemophilus influenzae*)
    - 2. Import new PBP (e.g., mecA in methicillin-resistant *Staphylococcus aureus*)
- II. Destroy β-lactam antibiotic
  - A. Increase production of β-lactamases, carbapenemases
    - 1. Acquire more efficient promoter
      - a. Mutate existing promoter
      - b. Import new promoter
    - 2. Deregulate control of β-lactamase production
      - a. Mutate regulator genes (e.g., ampD in “stably derepressed” *Enterobacter cloacae*)
  - B. Modify structure of resident β-lactamase
    - 1. Mutate structural gene (e.g., ESBLs in *Klebsiella pneumoniae*)
  - C. Import new β-lactamase(s) with different spectrum of activity
- III. Decrease concentration of β-lactam antibiotic inside cell
  - A. Restrict its entry (loss of porins)
  - B. Pump it out (efflux mechanisms)

ESBLs, Extended-spectrum β-lactamases; PBP, Penicillin-binding protein.

Adapted from Opal SM, Pop-Vicas A: Molecular mechanisms of antibiotic resistance in bacteria. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 18-4).

Table 207.2

Aminoglycoside-Modifying Enzymes*

ENZYMES	USUAL ANTIBIOTICS MODIFIED	COMMON GENERA
PHOSPHORYLATION		
APH(2″)	K, T, G	SA, SR
APH(3′)-I	K	E, PS, SA, SR
APH(3′)-III	K ± A	E, PS, SA, SR
ACETYLATION		
AAC(2′)	G	PR
AAC(3)-I	±T, G	E, PS
AAC(3)-III, -IV, or -V	K, T, G	E, PS
AAC(6′)	K, T, A	E, PS, SA
ADENYLATION		
ANT(2″)	K, T, G	E, PS
ANT(4′)	K, T, A	SA
BIFUNCTIONAL ENZYMES		

AAC(6′)-APH(2″)	G, Ar	SA, Ent
AAC(6′)-lbcr	G, K, T, FQ[*]	E

[*] Aminoglycoside-modifying enzymes confer antibiotic resistance through 3 general reactions: N-acetylation, O-nucleotidylation, and O-phosphorylation. For each of these general reactions, there are several different enzymes that attack a specific amino or hydroxyl group.

A, Amikacin; AAC, aminoglycoside acetyltransferase; ANT, aminoglycoside nucleotidyltransferase; APH, aminoglycoside phosphotransferase; cr, ciprofloxacin resistance; Ar, arbekacin, E, Enterobacteriaceae; Ent, enterococci, FQ, fluoroquinolone (acetylates the piperazine ring in some fluoroquinolones), G, gentamicin; K, kanamycin; PR, *Providencia-Proteus* ; PS, pseudomonads; SA, staphylococci; SR, streptococci; T, tobramycin.

Adapted from Opal SM, Pop-Vicas A: Molecular mechanisms of antibiotic resistance in bacteria. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 18-5).

Antimicrobial resistance has reached *crisis proportions* , driven by the emergence of new resistance mechanisms (e.g., carbapenemases, including *Klebsiella pneumoniae* –associated carbapenemases, or **KPCs**) and by overuse of antibiotics, both in healthcare and in other venues, such as agribusiness and animal husbandry. This increase in antibiotic resistance has rendered some bacterial infections encountered in clinical practice virtually untreatable. Accordingly, there is an urgent need to develop new antimicrobials, as well as rediscover some older antibiotics that have been out of use in recent decades but still retain activity against resistant organisms. It is vital that practitioners use antibiotics only as necessary, with the narrowest feasible antimicrobial spectrum, to help thwart emergence of resistance. In addition, advocacy for **vaccines** , particularly conjugate pneumococcal vaccine, can also decrease the selective pressure that excessive antimicrobial use exerts on resistance.

Effective antibiotic action requires achieving therapeutic levels of the drug at the site of infection. Although measuring the level of antibiotic at the site of infection is not always possible, one may measure the serum level and use this level as a surrogate marker for achievement of the desired effect at the tissue level. Various target serum levels are appropriate for different antibiotic agents and are assessed by the peak and trough serum levels and the area under the therapeutic drug level curve (Fig. 207.1). These levels in turn are a reflection of the route of administration, drug absorption (IM, PO), volume of distribution, and drug elimination half-life, as well as of drug-drug interactions that might enhance or impede enzymatic inactivation of an antibiotic or result in antimicrobial synergism or antagonism (Fig. 207.2).

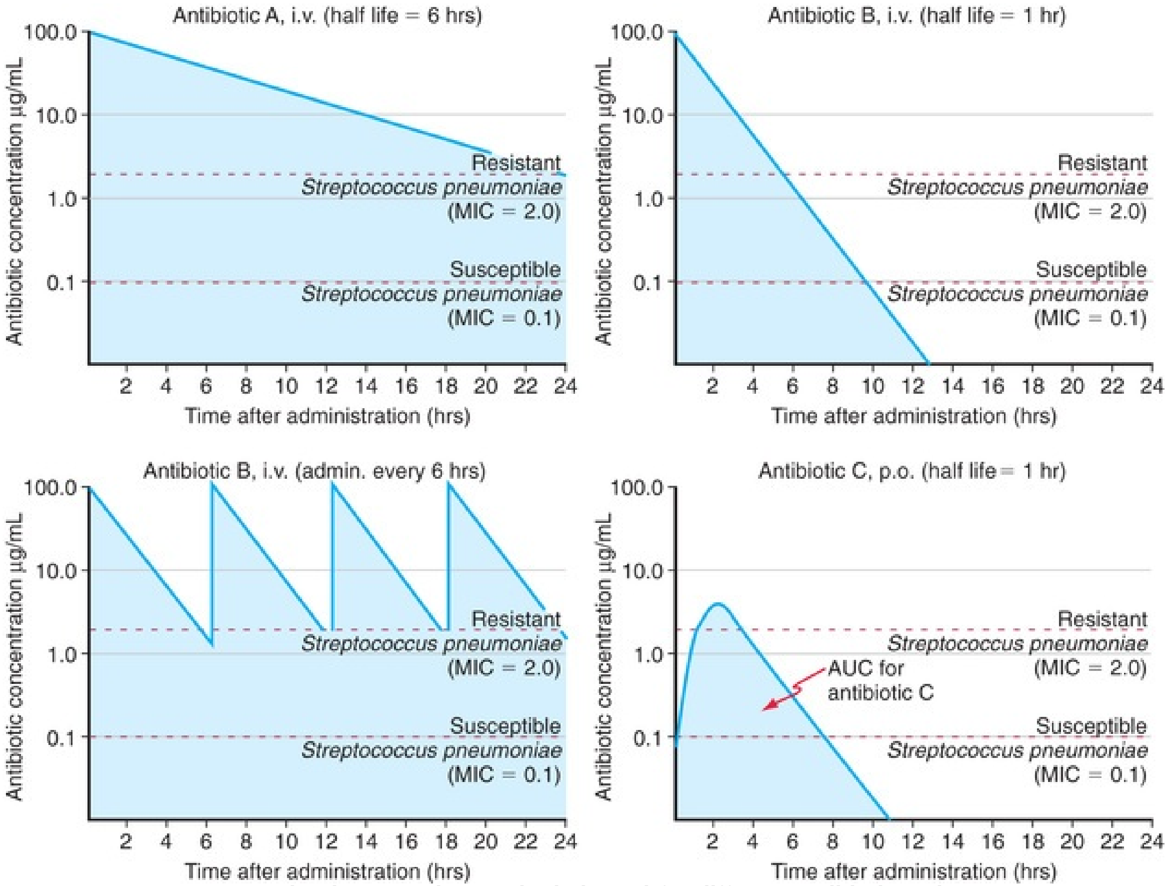

FIG. 207.1 Area under the curve (AUC; *shaded area*) for different antibiotics. The AUC provides a measure of antibiotic exposure to bacterial pathogens. The greatest exposure comes with antibiotics that have a long serum half-life and are administered parenterally (*upper left panel,* antibiotic A). The lowest exposure occurs with oral administration (*lower right panel,* antibiotic C). Dosing of antibiotic B once a day *(upper right panel)* provides far less exposure than dosing the same antibiotic every 6 hr *(lower left panel).* MIC, Minimal inhibitory concentration. (From Pong AL, Bradley JS: Guidelines for the selection of antibacterial therapy in children, *Pediatr Clin North Am* 52:869–894, 2005.)

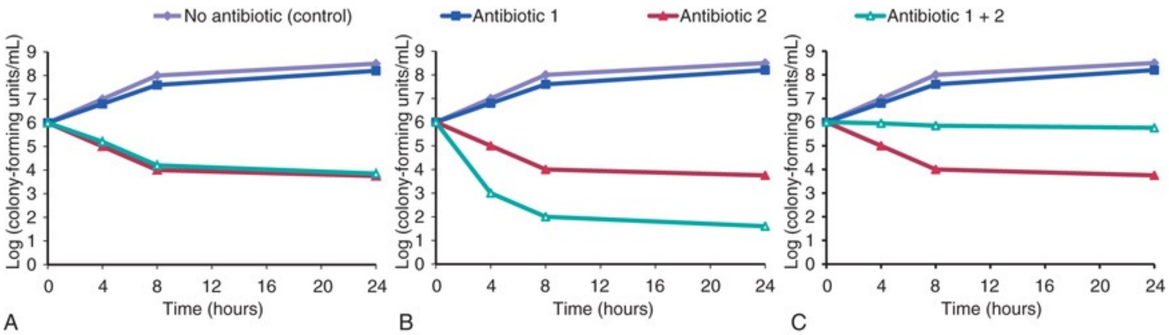

FIG. 207.2 Antibacterial effects of antibiotic combinations. A, Combination of antibiotics 1 and 2 is *indifferent* ; killing by antibiotic 2 is unchanged when antibiotic 1 is added. B, Combination of antibiotics 1 and 2 results in *synergy* ; killing by antibiotic

2 is significantly enhanced when antibiotic 1 is added at a subinhibitory concentration. C, Combination of antibiotics 1 and 2 is *antagonistic* ; killing by antibiotic 2 is diminished in the presence of antibiotic 1. (From Eliopoulos GM, Moellering RC Jr: Principles of anti-infective therapy. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier, Fig 17-1.)

Age- and Risk-Specific Use of Antibiotics in Children

Neonates

The causative pathogens associated with neonatal infections are typically acquired around the time of delivery. Thus, empirical antibiotic selection must take into account the importance of these organisms (see Chapter 129). Among the causes of neonatal sepsis in infants, **group B streptococcus** (GBS) is the most common. Although intrapartum antibiotic prophylaxis administered to women at increased risk for transmission of GBS to the infant has greatly decreased the incidence of this infection in neonates, particularly with respect to early-onset disease, GBS infections are still frequently encountered in clinical practice (see Chapter 211). Gram-negative enteric organisms acquired from the maternal birth canal, in particular *Escherichia coli*, are also common causes of neonatal sepsis. Although less common, *Listeria monocytogenes* is an important pathogen to consider, insofar as the organism is intrinsically resistant to cephalosporin antibiotics, which are often used as empirical therapy for serious bacterial infections in young children. *Salmonella* bacteremia and **meningitis** on a global basis is a well-recognized infection in infants. All these organisms can be associated with meningitis in the neonate; therefore lumbar puncture should always be considered with bacteremic infections in this age-group, and if meningitis cannot be excluded, antibiotic management should include agents capable of crossing the blood-brain barrier.

Older Children

Antibiotic choices in toddlers and young children were once driven by the high risk of this age-group to invasive disease caused by *H. influenzae* type b (**Hib** ; see Chapter 221). With the advent of conjugate vaccines against Hib, invasive disease has declined dramatically. However, outbreaks still occur, and have been observed in the context of parental refusal of vaccines. Therefore, it is still important to use antimicrobials that are active against Hib in many clinical settings, particularly if meningitis is a consideration. Other important pathogens to consider in this age-group include *E. coli* , *S. pneumoniae, N. meningitidis,* and *S. aureus* . Strains of *S. pneumoniae* that are resistant to penicillin and cephalosporin antibiotics are frequently encountered in clinical practice. Similarly, MRSA is highly prevalent in children in the outpatient setting. Resistance of *S. pneumoniae* as well as MRSA is a result of mutations that confer alterations in penicillin-binding proteins, the molecular targets of penicillin and cephalosporin activity (see Table 207.1).

Depending on the specific clinical diagnosis, other pathogens encountered among older children include *Moraxella catarrhalis,* nontypeable (nonencapsulated) strains of *H. influenzae,* and *Mycoplasma pneumoniae,* which cause upper respiratory tract infections and pneumonia; group A streptococcus, which causes pharyngitis, skin and soft tissue infections, osteomyelitis, septic arthritis, and rarely, bacteremia with toxic shock syndrome; *Kingella kingae,* which causes bone and joint infections; viridians group streptococci and *Enterococcus,* which cause endocarditis; and *Salmonella* spp., which cause enteritis, bacteremia, osteomyelitis, and septic arthritis. Vector-borne bacterial infections, including *Borrelia burgdorferi* , *Rickettsia rickettsii* , and *Anaplasma phagocytophilum* , are increasingly recognized in certain regions, with an evolving epidemiology triggered by climate change. These complexities underscore the importance of formulation of a complete differential diagnosis in children with suspected severe bacterial infections, including an assessment of the severity of the infection undertaken in parallel with consideration of local epidemiological disease trends, including knowledge of the antimicrobial susceptibility patterns in the community.

Immunocompromised and Hospitalized Patients

It is important to consider the risks associated with immunocompromising conditions (malignancy, solid-organ or hematopoietic stem cell transplantation) and the risks conferred by conditions leading to prolonged hospitalization (intensive care, trauma, burns). Serious viral infections, particularly influenza, can also predispose to invasive bacterial infections, especially those caused by *S. aureus* . Immunocompromised children are predisposed to develop a wide range of bacterial, viral, fungal, or parasitic infections. Prolonged hospitalization can lead to nosocomial infections, often associated with indwelling lines and catheters and caused by highly antibiotic-resistant gram-negative enteric organisms. In addition to bacterial pathogens already discussed, *Pseudomonas aeruginosa* and enteric organisms, including *E. coli, K. pneumoniae, Enterobacter,* and *Serratia* , are important opportunistic pathogens in these settings. Selection of appropriate antimicrobials is challenging because of the diverse causes and scope of antimicrobial resistance exhibited by these organisms. Many strains of enteric organisms have resistance because of ESBLs (see Table 207.1). Class B metallo-β-lactamases (also known as New Delhi metallo-β-lactamases) that hydrolyze all β-lactam antibiotics except aztreonam are increasingly being described, as well as KPCs that confer resistance to carbapenems. Reports of **carbapenemases** are increasingly being described for Enterobacteriaceae. Carbapenemase-producing Enterobacteriaceae are different from other multidrug-resistant microorganisms in that they are susceptible to few (if any) antibacterial agents.

Other modes of antimicrobial resistance are being increasingly recognized. *P. aeruginosa* encodes proteins that function as efflux pumps to eliminate multiple classes of antimicrobials from the cytoplasm or periplasmic space. In addition to these gram-negative pathogens, infections caused by *Enterococcus faecalis* and *E. faecium* are inherently difficult to treat. These organisms may cause urinary tract infection (UTI) or infective endocarditis in immunocompetent children and may be responsible for a variety of syndromes in immunocompromised patients, especially in the setting of prolonged intensive care. The emergence of infections caused by **vancomycin-resistant enterococcus (VRE)** has further complicated antimicrobial selection in high-risk patients and has necessitated the development of newer antimicrobials that target these highly resistant gram-positive bacteria.

Infections Associated With Medical Devices

A special situation affecting antibiotic use is the presence of an indwelling medical device, such as venous catheter, ventriculoperitoneal shunts, stents, or other catheters (see Chapter 206). In addition to *S. aureus,* coagulase-negative staphylococci are also a major consideration. Coagulase-negative staphylococci seldom cause serious disease in the absence of risk factors such as indwelling catheters. Empirical antibiotic regimens must take this risk into consideration. In addition to appropriate antibiotic therapy, removal or replacement of the colonized prosthetic material is usually required for cure.

Antibiotics Commonly Used in Pediatric Practice

Table 207.3 lists antibiotic medications and pediatric indications.

Table 207.3

Selected Antibacterial Medications (Antibiotics)*

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Amikacin sulfate Amikin Injection: 50 mg/mL, 250 mg/mL	**Aminoglycoside antibiotic active against gram-negative bacilli, especially** ***Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia,*** **and** ***Pseudomonas*** Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 7.5 mg/kg q12-18h IV or IM; weight >2,000 g: 10 mg/kg q12h IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 7.5 mg/kg q8-12h IV or IM; weight >2,000 g: 10 mg/kg q8h IV or IM Children: 15-25 mg/kg/24 hr divided q8-12h IV or IM Adults: 15 mg/kg/24 hr divided q8-12h IV or IM	*Cautions:* Anaerobes, *Streptococcus* (including *S. pneumoniae*) are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 25-40 mg/L; trough <10 mg/L
Amoxicillin Amoxil, Polymox Capsule: 250, 500 mg Tablet: chewable: 125, 250 mg Suspension: 125 mg/5 mL, 250 mg/5 mL Drops: 50 mg/mL	**Penicillinase-susceptible β-lactam: gram-positive pathogens except** ***Staphylococcus; Salmonella, Shigella, Neisseria, E. coli*** **, and** ***Proteus mirabilis*** Children: 20-50 mg/kg/24 hr divided q8-12h PO. Higher dose of 80-90 mg/kg 24 hr PO for otitis media Adults: 250-500 mg q8-12h PO Uncomplicated gonorrhea: 3 g with 1 g probenecid PO	*Cautions:* Rash, diarrhea, abdominal cramping. Drug eliminated renally *Drug interaction:* Probenecid
Amoxicillin-clavulanate Augmentin Tablet: 250, 500, 875 mg Tablet, chewable: 125, 200, 250, 400 mg Suspension: 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL, 400 mg/5 mL	**β-Lactam (amoxicillin) combined with β-lactamase inhibitor (clavulanate) enhances amoxicillin activity against penicillinase-producing bacteria.** ***S. aureus*** **(not methicillin-resistant organism),** ***Streptococcus, Haemophilus influenzae, Moraxella catarrhalis, E. coli, Klebsiella, Bacteroides fragilis*** Neonates: 30 mg/kg/24 hr divided q12h PO	*Cautions:* Drug dosed on amoxicillin component. May cause diarrhea, rash. Drug eliminated renally *Drug interaction:* Probenecid *Comment:* Higher dose may be active against

	Children: 20-45 mg/kg 24 hr divided q8-12h PO. Higher dose 80-90 mg/kg/24 hr PO for otitis media	penicillin-tolerant/resistant *S. pneumoniae*
Ampicillin Polycillin, Omnipen Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL Injection	**β-Lactam with same spectrum of antibacterial activity as amoxicillin** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 50 mg/kg/24 hr IV or IM q12h (meningitis: 100 mg/kg/24 hr divided q12h IV or IM); weight >2,000 g: 75 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr divided q8h IV or IM). Postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV or IM q12h (meningitis: 100 mg/kg/24 hr divided q12h IV or IM); weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr divided q8hr IV or IM); weight >2,000 g: 100 mg/kg/24 hr divided q6h IV or IM (meningitis: 200 mg/kg/24 hr divided q6h IV or IM) Children: 100-200 mg/kg/24 hr divided q6h IV or IM (meningitis: 200-400 mg/kg/24 hr divided q4-6h IV or IM) Adults: 250-500 mg q4-8h IV or IM	*Cautions:* Less bioavailable than amoxicillin, causing greater diarrhea *Drug interaction:* Probenecid
Ampicillin-sulbactam Unasyn Injection	**β-Lactam (ampicillin) and β-lactamase inhibitor (sulbactam) enhances ampicillin activity against penicillinase-producing bacteria: *S. aureus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis*** Children: 100-200 mg/kg/24 hr divided q4-8h IV or IM Adults: 1-2 g q6-8h IV or IM (max daily dose: 8 g)	*Cautions:* Drug dosed on ampicillin component. May cause diarrhea, rash. Drug eliminated renally *Note:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae* *Drug interaction:* Probenecid
Azithromycin Zithromax Tablet: 250 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Azalide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Mycoplasma, Legionella, Chlamydia trachomatis, Babesia microti*** Children: 10 mg/kg PO on day 1 (max dose: 500 mg) followed by 5 mg/kg PO q24h for 4 days Group A streptococcus pharyngitis: 12 mg/kg/24 hr PO (max dose: 500 mg) for 5 days Adults: 500 mg PO day 1 followed by 250 mg for 4 days Uncomplicated *C. trachomatis* infection: single 1 g dose PO	*Note:* Very long half-life permitting once-daily dosing. No metabolic-based drug interactions (unlike erythromycin and clarithromycin), limited GI distress. Shorter-course regimens (e.g., 1-3 days) under investigation. 3 day, therapy (10 mg/kg/24 hr × 3 days) and single-dose therapy (30 mg/kg): use with increasing frequency (not for streptococcus pharyngitis)
Aztreonam Azactam Injection	**β-Lactam (monobactam) antibiotic with activity against gram-negative aerobic bacteria, Enterobacteriaceae, and *Pseudomonas aeruginosa*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 60 mg/kg/24 hr divided q12h IV or	*Cautions:* Rash, thrombophlebitis, eosinophilia. Renally eliminated *Drug interaction:* Probenecid

	IM; weight >2,000 g: 90 mg/kg/24 hr divided q8h IV or IM; postnatal age >7 days weight <1,200 g: 60 mg/kg/24 hr divided q12h IV or IM; weight 1,200-2,000 g: 90 mg/kg/24 hr divided q8h IV or IM; weight >2,000 g: 120 mg/kg/24 hr divided q6-8h IV or IM Children: 90-120 mg/kg/24 hr divided q6-8h IV or IM. For cystic fibrosis, up to 200 mg/kg/24 hr IV Adults: 1-2 g IV or IM q8-12h (max dose: 8 g/24 hr)	
Cefadroxil Generic Capsule: 500 mg Tablet: 1,000 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella* , and *Proteus*** Children: 30 mg/kg/24 hr divided q12h PO (max dose: 2 g) Adults: 250-500 mg q8-12h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Long half-life permits q12-24h dosing *Drug interaction:* Probenecid
Cefazolin Ancef, Kefzol Injection	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella* , and *Proteus*** Neonates: Postnatal age ≤7 days 40 mg/kg/24 hr divided q12h IV or IM; >7 days 40-60 mg/kg/24 hr divided q8h IV or IM Children: 50-100 mg/kg/24 hr divided q8h IV or IM Adults: 0.5-2g q8h IV or IM (max dose: 12 g/24 hr)	*Caution:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS *Drug interaction:* Probenecid
Cefdinir Omnicef Capsule: 300 mg Oral suspension: 125 mg/5 mL	**Extended-spectrum, semisynthetic cephalosporin** Children 6 mo-12 yr: 14 mg/kg/24 hr in 1 or 2 doses PO (max dose: 600 mg/24 hr) Adults: 600 mg q24h PO	*Cautions:* Reduce dosage in renal insufficiency (creatinine clearance <60 mL/min). Avoid taking concurrently with iron-containing products and antacids because absorption is markedly decreased; take at least 2 hr apart *Drug interaction:* Probenecid
Cefepime Maxipime Injection	**Expanded-spectrum, fourth-generation cephalosporin active against many gram-positive and gram-negative pathogens, including *P. aeruginosa* and many multidrug-resistant pathogens** Children: 100-150 mg/kg/24 hr q8-12h IV or IM Adults: 2-4 g/24 hr q12h IV or IM	*Adverse events:* Diarrhea, nausea, vaginal candidiasis Cautions: β-lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Cefixime Suprax Tablet: 200, 400 mg Suspension: 100 mg/5 mL	**Third-generation cephalosporin active against streptococci, *H. influenzae, M. catarrhalis, Neisseria gonorrhoeae, Serratia marcescens* , and *Proteus vulgaris* . No**	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not

	antistaphylococcal or antipseudomonal activity Children: 8 mg/kg/24 hr divided q12-24h PO Adults: 400 mg/24 hr divided q12-24h PO	adequately penetrate CNS *Drug interaction:* Probenecid
Cefoperazone sodium Cefobid Injection	**Third-generation cephalosporin active against many gram-positive and gram-negative pathogens** Neonates: 100 mg/kg/24 hr divided q12h IV or IM Children: 100-150 mg/kg/24 hr divided q8-12h IV or IM Adults: 2-4 g/24 hr divided q8-12h IV or IM (max dose: 12 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin with limited potency reflected by weak antipseudomonal activity. Variable Gram-positive activity. Primarily hepatically eliminated in bile *Drug interaction:* Disulfiram-like reaction with alcohol
Cefotaxime sodium Claforan Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Neonates: ≤7 days: 100 mg/kg/24 hr divided q12h IV or IM; >7 days: weight <1,200 g 100 mg/kg/24 hr divided q12h IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q8h IV or IM Children: 150 mg/kg/24 hr divided q6-8h IV or IM (meningitis: 200 mg/kg/24 hr divided q6-8h IV) Adults: 1-2 g q8-12h IV or IM (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Each gram of drug contains 2.2 mEq sodium. Active metabolite *Drug interaction:* Probenecid
Cefotetan disodium Cefotan Injection	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus* , and *Bacteroides* . Inactive against *Enterobacter*** Children: 40-80 mg/kg/24 hr divided q12h IV or IM Adults: 2-4 g/24 hr divided q12h IV or IM (max dose: 6 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin, poor CNS penetration; β-lactam safety profile (rash, eosinophilia), disulfiram-like reaction with alcohol. Renally eliminated (~20% in bile)
Cefoxitin sodium Mefoxin Injection	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, Klebsiella, Proteus* , and *Bacteroides* . Inactive against *Enterobacter*** Neonates: 70-100 mg/kg/24 hr divided q8-12h IV or IM Children: 80-160 mg/kg/24 hr divided q6-8h IV or IM Adults: 1-2 g q6-8h IV or IM (max dose: 12 g/24 hr)	*Cautions:* Poor CNS penetration; β-lactam safety profile (rash, eosinophilia). Renally eliminated. Painful given intramuscularly *Drug interaction:* Probenecid
Cefpodoxime proxetil Vantin Tablet: 100 mg, 200 mg Suspension: 50 mg/5 mL, 100 mg/5 mL	**Third-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, N. gonorrhoeae, E. coli, Klebsiella* , and *Proteus* . No antipseudomonal activity** Children: 10 mg/kg/24 hr divided q12h PO Adults: 200-800 mg/24 hr divided q12h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability when

	(max dose: 800 mg/24 hr) Uncomplicated gonorrhea: 200 mg PO as single-dose therapy	taken with food *Drug interaction:* Probenecid; antacids and H_2 receptor antagonists may decrease absorption
Ceftaroline fosamil Teflaro Injection	**Fifth-generation cephalosporin active against *S. aureus* (including MRSA when used for skin and soft tissue infection), *Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae, H. influenzae,* and *Klebsiella oxytoca*** Children: skin/skin structure infections *or* community-acquired pneumonia, 24 mg/kg/24 hr divided q8h IV (2-23 mo old) ×5-14 days; 36 mg/kg/24 hr divided q8h IV (weight ≤33 kg) ×5-14 days; 400 mg q8h IV (weight >33 kg) Adults: 600 mg q12h IV	*Caution:* β-Lactam safety profile (rash, eosinophilia) *Drug interaction:* Probenecid
Cefprozil Cefzil Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella* , and *Proteus* spp.** Children: 30 mg/kg/24 hr divided q8-12h PO Adults: 500-1,000 mg/24 hr divided q12h PO (max dose: 1.5 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Good bioavailability; food does not affect bioavailability *Drug interaction:* Probenecid
Ceftazidime Fortaz, Ceptaz, Tazicef, Tazidime Injection	**Third-generation cephalosporin active against gram-positive and gram-negative pathogens, including *P. aeruginosa*** Neonates: Postnatal age ≤7 days: 100 mg/kg/24 hr divided q12h IV or IM; >7 days weight ≤1,200 g: 100 mg/kg/24 hr divided q12h IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q8h IV or IM Children: 150 mg/kg/24 hr divided q8h IV or IM (meningitis: 150 mg/kg/24 hr IV divided q8h) Adults: 1-2 g q8-12h IV or IM (max dose: 8-12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use *Drug interaction:* Probenecid
Ceftizoxime Cefizox Injection	**Third-generation cephalosporin active against gram-positive and gram-negative pathogens. No antipseudomonal activity** Children: 150 mg/kg/24 hr divided q6-8h IV or IM Adults: 1-2 g q6-8h IV or IM (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Ceftriaxone sodium Rocephin Injection	**Third-generation cephalosporin widely active against gram-positive and gram-negative pathogens. No antipseudomonal activity** Neonates: 50-75 mg/kg q24h IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Eliminated via kidney (33–65%) and bile; can

	Children: 50-75 mg/kg q24h IV or IM (meningitis: 75 mg/kg dose once then 80-100 mg/kg/24 hr divided q12-24h IV or IM) Adults: 1-2 g q24h IV or IM (max dose: 4 g/24 hr)	cause sludging. Long half-life and dose-dependent protein binding favors q24h rather than q12h dosing. Can add 1% lidocaine for IM injection *Drug interaction:* Probenecid. In neonates, co-administration with calcium-containing products can result in severe precipitation and attendant embolic complications
Cefuroxime (cefuroxime axetil for oral administration) Ceftin, Kefurox, Zinacef Injection Suspension: 125 mg/5 mL Tablet: 125, 250, 500 mg	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella* , and *Proteus*** Neonates: 40-100 mg/kg/24 hr divided q12h IV or IM Children: 200-240 mg/kg/24 hr divided q8h IV or IM; PO administration: 20-30 mg/kg/24 hr divided q8-12h PO Adults: 750-1,500 mg q8h IV or IM (max dose: 6 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Food increases PO bioavailability *Drug interaction:* Probenecid
Cephalexin Keflex, Keftab Capsule: 250, 500 mg Tablet: 500 mg, 1 g Suspension: 125 mg/5 mL, 250 mg/5 mL, 100 mg/mL drops	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella* , and *Proteus*** Children: 25-100 mg/kg/24 hr divided q6-8h PO Adults: 250-500 mg q6h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Cephradine Velosef Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella* , and *Proteus*** Children: 50-100 mg/kg/24 hr divided q6-12h PO Adults: 250-500 mg q6-12h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Ciprofloxacin Cipro Tablet: 100, 250, 500, 750 mg Injection Ophthalmic solution and ointment Otic suspension Oral suspension: 250 and 500 mg/5 mL	**Quinolone antibiotic active against *P. aeruginosa, Serratia, Enterobacter, Shigella, Salmonella, Campylobacter, N. gonorrhoeae, H. influenzae, M. catarrhalis,* some *S. aureus* , and some *Streptococcus*** Neonates: 10 mg/kg q 12 hr PO or IV Children: 15-30 mg/kg/24 hr divided q12h PO or IV; cystic fibrosis: 20-40 mg/kg/24 hr divided q8-12h PO or IV Adults: 250-750 mg q12h; 200-400 mg IV q12h PO (max dose: 1.5 g/24 hr)	*Cautions:* Concerns of joint destruction in juvenile animals not seen in humans; tendonitis, superinfection, dizziness, confusion, crystalluria, some photosensitivity *Drug interactions:* Theophylline; magnesium-, aluminum-, or calcium-containing antacids; sucralfate;

		probenecid; warfarin; cyclosporine
Clarithromycin Biaxin Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Macrolide antibiotic with activity against *S. aureus, Streptococcus, H. influenzae, Legionella, Mycoplasma,* and *C. trachomatis*** Children: 15 mg/kg/24 hr divided q12h PO Adults: 250-500 mg q12h PO (max dose: 1 g/24 hr)	*Cautions:* Adverse events less than erythromycin; GI upset, dyspepsia, nausea, cramping *Drug interactions:* Same as erythromycin: astemizole carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus
Clindamycin Cleocin Capsule: 75, 150, 300 mg Suspension: 75 mg/5 mL Injection Topical solution, lotion, and gel Vaginal cream	**Protein synthesis inhibitor active against most gram-positive aerobic and anaerobic cocci except *Enterococcus*** Neonates: Postnatal age ≤7 days weight <2,000 g; 10 mg/kg/24 hr divided q12h IV or IM; weight >2,000 g: 15 mg/kg/24 hr divided q8h IV or IM; >7 days weight <1,200 g: 10 mg/kg/24 hr IV or IM divided q12h; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q8h IV or IM; weight >2,000 g: 20 mg/kg/24 hr divided q8h IV or IM Children: 10-40 mg/kg/24 hr divided q6-8h IV, IM, or PO Adults: 150-600 mg q6-8h IV, IM, or PO (max dose: 5 g/24 hr IV or IM or 2 g/24 hr PO)	*Cautions:* Diarrhea, nausea, *Clostridium difficile* –associated colitis, rash. Administer slow IV over 30-60 min. Topically active as an acne treatment
Cloxacillin sodium Tegopen Capsule: 250, 500 mg Suspension: 125 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 50-100 mg/kg/24 hr divided q6h PO Adults: 250-500 mg q6h PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily hepatically eliminated; requires dose reduction in renal disease. Food decreases bioavailability *Drug interaction:* Probenecid
Colistin (Colistimethate sodium; polymyxin E) Injection Inhalation	**Treatment of multidrug resistant gram-negative organisms (*Enterobacteriaceae* including extended-spectrum beta lactamase and carbapenemase-producing strains)** Children: 2.5-5 mg/kg/day divided in 2-4 divided doses IV Adults: 300 mg/day in 2-4 divided doses IV	*Cautions:* Nephrotoxicity (~3% in young children; higher rates in adolescents and adults); adjust dose for renal insufficiency; neurotoxicity (headaches, paresthesia, ataxia) *Drug interactions:* Should not be administered concomitantly with polymyxins or aminoglycosides

Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMX) Bactrim, Cotrim, Septra, Sulfatrim Tablet: SMX 400 mg and TMP 80 mg Tablet DS: SMX 800 mg and TMP 160 mg Suspension: SMX 200 mg and TMP 40 mg/5 mL Injection	**Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: *Shigella, Legionella, Nocardia, Chlamydia, Pneumocystis jiroveci.* Dosage based on TMP component** Children: 6-20 mg TMP/kg/24 hr or IV divided q12h PO *Pneumocystis carinii* pneumonia: 15-20 mg TMP/kg/24 hr divided q12h PO or IV *P. carinii* prophylaxis: 5 mg TMP/kg/24 hr or 3 times/wk PO Adults: 160 mg TMP q12h PO	*Cautions:* Drug dosed on TMP (trimethoprim) component. Sulfonamide skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure *Drug interactions:* Protein displacement with warfarin, possibly phenytoin, cyclosporine
Daptomycin Cubicin	**Disrupts bacterial cell membrane function, causing depolarization leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. Active against enterococci (including glycopeptide-resistant strains), staphylococci (including MRSA), streptococci, and corynebacteria. Approved for skin and soft tissue infections. Acceptable for bacteremia and right-sided endocarditis with susceptible strains** Adults: In skin and soft tissue infections, 4 mg/kg daptomycin IV once daily. For *S. aureus* bacteremia or right-sided endocarditis, 6 mg/kg IV once daily Children: For skin/skin structure infections, 12-23 mo, 10 mg/kg IV q24h; 2-6 yr, 9 mg/kg IV q24h; 7-11 yr, 7 mg/kg q24h; 12-17 yr, 5 mg/kg q24h, all for up to 14 days. For staphylococcal bacteremia, 1-6 yr, 12 mg/kg q24h; 7-11 yr, 9 mg/kg q24h; 12-17 yr, 7 mg/kg q24h; all for up to 42 days. For staphylococcal endocarditis, 1-5 yr, 10 mg/kg IV q24h for at least 6 wk; ≥6 yr, 6 mg/kg IV q24h for at least 6 wk	*Cautions:* Should not be used for pneumonia because drug inactivated by surfactants. Associated with rash, renal failure, anemia, and headache. Is reported to cause myopathy, rhabdomyolysis, and eosinophilic pneumonia *Drug interactions:* Should not be administered with statins
Demeclocycline Declomycin Tablet: 150, 300 mg Capsule: 150 mg	**Tetracycline active against most gram-positive cocci except *Enterococcus* , many gram-negative bacilli, anaerobes, *Borrelia burgdorferi* (Lyme disease), *Mycoplasma,* and *Chlamydia*** Children: 8-12 mg/kg/24 hr divided q6-12h PO Adults: 150 mg PO q6-8h Syndrome of inappropriate antidiuretic hormone secretion: 900-1,200 mg/24 hr or 13-15 mg/kg/24 hr divided q6-8h PO with dose reduction based on response to 600-900 mg/24 hr	*Cautions:* Teeth staining, possibly permanent (if administered <8 yr old) with prolonged use; photosensitivity, diabetes insipidus, nausea, vomiting, diarrhea, superinfections *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc- and iron-containing food,

		milk, dairy products may decrease absorption
Dicloxacillin Dynapen, Pathocil Capsule: 125, 250, 500 mg Suspension: 62.5 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 12.5-100 mg/kg/24 hr divided q6h PO Adults: 125-500 mg q6h PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily renally (65%) and bile (30%) elimination. Food may decrease bioavailability *Drug interaction:* Probenecid
Doripenem Doribax Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes** Children: dose unknown. Adults: 500 mg q8h IV	*Cautions:* β-Lactam safety profile; does not undergo hepatic metabolism. Renal elimination (70–75%); dose adjustment for renal failure *Drug interactions:* Valproic acid, probenecid
Doxycycline Vibramycin, Doxy Injection Capsule: 50, 100 mg Tablet: 50, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL	**Tetracycline antibiotic active against most gram-positive cocci except *Enterococcus* , many gram-negative bacilli, anaerobes, *B. burgdorferi* (Lyme disease), *Mycoplasma* , and *Chlamydia*** Children: 2-5 mg/kg/24 hr divided q12-24h PO or IV (max dose: 200 mg/24 hr) Adults: 100-200 mg/24 hr divided q12-24h PO or IV	*Cautions:* Teeth staining, possibly permanent (<8 yr old) with prolonged use; photosensitivity, nausea, vomiting, diarrhea, superinfections *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc-, iron-, kaolin-, and pectin-containing products, food, milk, dairy products may decrease absorption. Carbamazepine, rifampin, and barbiturates may decrease half-life
Erythromycin E-Mycin, Ery-Tab, Eryc, Ilosone Estolate 125, 500 mg Tablet EES: 200 mg Tablet base: 250, 333, 500 mg Suspension: estolate 125 mg/5 mL, 250 mg/5 mL, EES 200 mg/5 mL, 400 mg/5 mL Estolate drops: 100 mg/mL. EES drops: 100 mg/2.5 mL. Available in combination with	**Bacteriostatic macrolide antibiotic most active against gram-positive organisms, *Corynebacterium diphtheriae* , and *Mycoplasma pneumoniae*** Neonates: Postnatal age ≤7 days: 20 mg/kg/24 hr divided q12h PO; >7 days weight <1,200 g: 20 mg/kg/24 hr divided q12h PO; weight >1,200 g: 30 mg/kg/24 hr divided q8h PO (give as 5 mg/kg/dose q6h to improve feeding intolerance) Children: Usual max dose: 2 g/24 hr Base: 30-50 mg/kg/24 hr divided q6-8h PO Estolate: 30-50 mg/kg/24 hr divided q8-12h PO Stearate: 20-40 mg/kg/24 hr divided q6h PO	*Cautions:* Motilin agonist leading to marked abdominal cramping, nausea, vomiting, and diarrhea. Associated with hypertrophic pyloric stenosis in young infants. Many different salts with questionable tempering of GI adverse events. Rare cardiac toxicity with IV use. Dose of salts differ. Topical formulation for

sulfisoxazole (Pediazole), dosed on erythromycin content	Lactobionate: 20-40 mg/kg/24 hr divided q6-8h IV Gluceptate: 20-50 mg/kg/24 hr divided q6h IV; usual max dose: 4 g/24 hr IV Adults: Base: 333 mg PO q8h; estolate/stearate/base: 250-500 mg q6h PO	treatment of acne *Drug interactions:* Antagonizes hepatic CYP 3A4 activity: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus, carbamazepine
Gentamicin Garamycin Injection Ophthalmic solution, ointment, topical cream	**Aminoglycoside antibiotic active against gram-negative bacilli, especially *E. coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 2.5 mg/kg q12-18h IV or IM; weight <2,000 g: 2.5 mg/kg q12h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 2.5 mg/kg q8-12h IV or IM; weight >2,000 g: 2.5 mg/kg q8h IV or IM Children: 2.5 mg/kg/24 hr divided q8-12h IV or IM. Alternatively, may administer 5-7.5 mg/kg/24 hr IV once daily Intrathecal: Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr intrathecal; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q8h IV or IM	*Cautions:* Anaerobes, *S. pneumoniae,* and other *Streptococcus* are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 6-12 mg/L; trough >2 mg/L with intermittent daily dose regimens only
Imipenem-cilastatin Primaxin Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *Stenotrophomonas maltophilia*** Neonates: Postnatal age ≤7 days weight <1,200 g: 20 mg/kg q18-24h IV or IM; weight >1,200 g: 40 mg/kg divided q12h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 40 mg/kg q12h IV or IM; weight >2,000 g: 60 mg/kg q8h IV or IM Children: 60-100 mg/kg/24 hr divided q6-8h IV or IM Adults: 2-4 g/24 hr divided q6-8h IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated *Drug interaction:* Possibly ganciclovir
Linezolid Zyvox Tablet: 400, 600 mg Oral suspension: 100 mg/5 mL Injection: 100 mg/5 mL	**Oxazolidinone antibiotic active against gram-positive cocci (especially drug-resistant organisms), including *Staphylococcus, Streptococcus, E. faecium,* and *Enterococcus faecalis* . Interferes with protein synthesis by binding to 50S ribosome subunit** Children: 10 mg/kg q12h IV or PO Adults: Pneumonia: 600 mg q12h IV or PO;	*Adverse events:* Myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache *Drug interaction:* Probenecid

	skin infections: 400 mg q12h IV or PO	
Loracarbef Generic Capsule: 200 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Carbacephem very closely related to cefaclor (second-generation cephalosporin) active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, E. coli, Klebsiella* , and *Proteus*** Children: 30 mg/kg/24 hr divided q12h PO (max dose: 2 g) Adults: 200-400 mg q12h PO (max dose: 800 mg/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Meropenem Merrem Injection	**Carbapenem antibiotic with broad-spectrum activity against gram-positive cocci and gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *S. maltophilia*** Children: 60 mg/kg/24 hr divided q8h IV meningitis: 120 mg/kg/24 hr (max dose: 6 g/24 hr) q8h IV Adults: 1.5-3 g q8h IV	*Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem. 80% renal elimination *Drug interaction:* Probenecid
Metronidazole Flagyl, Metro I.V., Topical gel, vaginal gel Injection Tablet: 250, 500 mg	**Highly effective in the treatment of infections caused by anaerobes. Oral therapy of *C. difficile* colitis** Neonates: weight <1,200 g: 7.5 mg/kg/48 hr PO or IV; postnatal age ≤7 days weight 1,200-2,000 g: 7.5 mg/kg/24 hr q24h PO or IV; weight 2,000 g: 15 mg/kg/24 hr divided q12h PO or IV; postnatal age <7 days weight 1,200-2,000 g: 15 mg/kg/24 hr divided q12h PO or IV; weight >2,000 g: 30 mg/kg/24 hr divided q12 h PO or IV Children: 30 mg/kg/24 hr divided q6-8h PO or IV Adults: 30 mg/kg/24 hr divided q6h PO or IV (max dose: 4 g/24 hr)	*Cautions:* Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. Administer IV slow over 30-60 min. Adjust dose with hepatic impairment *Drug interactions:* Carbamazepine, rifampin, phenobarbital may enhance metabolism; may increase levels of warfarin, phenytoin, lithium
Mezlocillin sodium Mezlin Infection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia* , and *Bacteroides;* limited antipseudomonal activity** Neonates: Postnatal age ≤7 days: 150 mg/kg/24 hr divided q12h IV; >7 days: 225 mg/kg divided q8h IV Children: 200-300 mg/kg/24 hr divided q4-6h IV; cystic fibrosis 300-450 mg/kg/24 hr IV Adults: 2-4 g/dose q4-6h IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.8 mEq sodium. Interferes with platelet aggregation with high doses; increases noted in liver function test results. Renally eliminated. Inactivated by β-lactamase enzyme *Drug interaction:* Probenecid
Mupirocin Bactroban Ointment	**Topical antibiotic active against *Staphylococcus* and *Streptococcus*** Topical application: Nasal (eliminate nasal carriage) and to the skin 2-4 times daily	*Caution:* Minimal systemic absorption because drug metabolized within the skin
Nafcillin sodium	**Penicillinase-resistant penicillin active**	*Cautions:* β-Lactam

Nafcil, Unipen Injection Capsule: 250 mg Tablet: 500 mg	**against *S. aureus* and other gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q12h IV or IM; weight >2,000 g: 75 mg/kg/24 hr divided q8h IV or IM; postnatal age >7 days weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h; weight >2,000 g: 100 mg/kg/24 hr divided q6-8h IV (meningitis: 200 mg/kg/24 hr divided q6h IV) Children: 100-200 mg/kg/24 hr divided q4-6h IV Adults: 4-12 g/24 hr divided q4-6h IV (max dose: 12 g/24 hr)	safety profile (rash, eosinophilia), phlebitis; painful given intramuscularly; oral absorption highly variable and erratic (not recommended) *Adverse effect:* Neutropenia
Nalidixic acid NegGram Tablet: 250, 500, 1,000 mg Suspension: 250 mg/5 mL	**First-generation quinolone effective for short-term treatment of lower UTIs caused by *E. coli, Enterobacter, Klebsiella* , and *Proteus*** Children: 50-55 mg/kg/24 hr divided q6h PO; suppressive therapy: 25-33 mg/kg/24 hr divided q6-8h PO Adults: 1 g q6h PO; suppressive therapy: 500 mg q6h PO	*Cautions:* Vertigo, dizziness, rash. Not for use in systemic infections *Drug interactions:* Liquid antacids
Neomycin sulfate Mycifradin Tablet: 500 mg Topical cream, ointment Solution: 125 mg/5 mL	**Aminoglycoside antibiotic used for topical application or orally before surgery to decrease GI flora (nonabsorbable) and hyperammonemia** Infants: 50 mg/kg/24 hr divided q6h PO Children: 50-100 mg/kg/24 hr divided q6-8h PO Adults: 500-2,000 mg/dose q6-8h PO	*Cautions:* In patients with renal dysfunction because small amount absorbed may accumulate *Adverse events:* Primarily related to topical application, abdominal cramps, diarrhea, rash Aminoglycoside ototoxicity and nephrotoxicity if absorbed
Nitrofurantoin Furadantin, Furan, Macrodantin Capsule: 50, 100 mg Extended-release capsule: 100 mg Macrocrystal: 50, 100 mg Suspension: 25 mg/5 mL	**Effective in treatment of lower UTIs caused by gram-positive and gram-negative pathogens** Children: 5-7 mg/kg/24 hr divided q6h PO (max dose: 400 mg/24 hr); suppressive therapy 1-2.5 mg/kg/24 hr divided q12-24h PO (max dose: 100 mg/24 hr) Adults: 50-100 mg/24 hr divided q6h PO	*Cautions:* Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use with moderate to severe renal dysfunction *Drug interactions:* Liquid antacids
Ofloxacin Ocuflox 0.3% ophthalmic solution: 1, 5, 10 mL Floxin 0.3% otic solution: 5, 10 mL	**Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution) and otitis externa or chronic suppurative otitis media (otic solution) caused by susceptible gram-positive, gram-negative, anaerobic bacteria, or *C. trachomatis*** *Child >1-12 yr:* Conjunctivitis: 1-2 drops in affected eye(s)	*Adverse events:* Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed

	q2-4h for 2 days, then 1-2 drops qid for 5 days Corneal ulcers: 1-2 drops q 30 min while awake and at 4 hr intervals at night for 2 days, then 1-2 drops hourly for 5 days while awake, then 1-2 drops q6h for 2 days Otitis externa (otic solution): 5 drops into affected ear bid for 10 days Chronic suppurative otitis media: treat for 14 days *Child >12 yr and adults:* Ophthalmic solution doses same as for younger children. Otitis externa (otic solution): Use 10 drops bid for 10 or 14 days as for younger children	
Oxacillin sodium Prostaphlin Injection Capsule: 250, 500 mg Suspension: 250 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q12h IV; weight >2,000 g: 75 mg/kg/24 hr IV divided q8h IV; postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV divided q12h IV; weight 1,200-2,000 g: 75 mg/kg/24 hr divided q8h IV; weight >2,000 g: 100 mg/kg/24 hr IV divided q6h IV Infants: 100-200 mg/kg/24 hr divided q4-6h IV Children: PO 50-100 mg/kg/24 hr divided q4-6h IV Adults: 2-12 g/24 hr divided q4-6h IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia) Moderate oral bioavailability (35–65%) Primarily renally eliminated *Drug interaction:* Probenecid *Adverse effect:* Neutropenia
Penicillin G Injection Tablets	**Penicillin active against most gram-positive cocci; *S. pneumoniae* (resistance is increasing), group A streptococcus, and some gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50,000 units/kg/24 hr divided q12h IV or IM (meningitis: 100,000 U/kg/24 hr divided q12h IV or IM); weight >2,000 g: 75,000 U/kg/24 hr divided q8h IV or IM (meningitis: 150,000 U/kg/24 hr divided q8h IV or IM); postnatal age >7 days weight ≤1,200 g: 50,000 U/kg/24 hr divided q12h IV (meningitis: 100,000 U/kg/24 hr divided q12h IV); weight 1,200-2,000 g: 75,000 U/kg/24 hr q8h IV (meningitis: 225,000 U/kg/24 hr divided q8h IV); weight >2,000 g: 100,000 U/kg/24 hr divided q6h IV (meningitis: 200,000 U/kg/24 hr divided q6h IV) Children: 100,000-250,000 units/kg/24 hr divided q4-6h IV or IM (max dose: 400,000 U/kg/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid

	Adults: 2-24 million units/24 hr divided q4-6h IV or IM	
Penicillin G, benzathine Bicillin Injection	**Long-acting repository form of penicillin effective in treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk), e.g., group A streptococcus pharyngitis, rheumatic fever prophylaxis** Neonates weight >1,200 g: 50,000 units/kg IM once Children: 300,000-1.2 million units/kg q 3-4 wk IM (max dose: 1.2-2.4 million units/dose) Adults: 1.2 million units IM q 3-4 wk	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, procaine Crysticillin Injection	**Repository form of penicillin providing low penicillin concentrations for 12 hr** Neonates weight >1,200 g: 50,000 units/kg/24 hr IM Children: 25,000-50,000 units/kg/24 hr IM for 10 days (max dose: 4.8 million units/dose) Gonorrhea: 100,000 units/kg (max dose: 4.8 million units/24 hr) IM once with probenecid 25 mg/kg (max dose: 1 g) Adults: 0.6-4.8 million units q12-24h IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia) allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin V Pen VK, V-Cillin K Tablet: 125, 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Preferred oral dosing form of penicillin, active against most gram-positive cocci; *S. pneumoniae* (resistance is increasing), other streptococci, and some gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Children: 25-50 mg/kg/24 hr divided q4-8h PO Adults: 125-500 mg q6-8h PO (max dose: 3 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with renal disease. Substantial pathogen resistance. Primarily renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid
Piperacillin Pipracil Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*** Neonates: Postnatal age ≤7 days 150 mg/kg/24 hr divided q8-12h IV; >7 days; 200 mg/kg divided q6-8h IV Children: 200-300 mg/kg/24 hr divided q4-6h IV; cystic fibrosis: 350-500 mg/kg/24 hr IV Adults: 2-4 g/dose q4-6h (max dose: 24 g/24 hr) IV	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation/serum sickness–like reaction with high doses; increases in liver function test results. Renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid

Piperacillin-tazobactam Zosyn Injection	**Extended-spectrum penicillin (piperacillin) combined with a β-lactamase inhibitor (tazobactam) active against *S. aureus, H. influenzae, E. coli, Enterobacter, Serratia, Acinetobacter, P. aeruginosa,* and *Bacteroides*** Children: 300-400 mg/kg/24 hr divided q6-8h IV or IM Adults: 3.375 g q6-8h IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium Interferes with platelet aggregation, serum sickness–like reaction with high doses, increases in liver function test results. Renally eliminated *Drug interaction:* Probenecid
Quinupristin/dalfopristin Synercid IV injection: powder for reconstitution, 10 mL contains 150 mg quinupristin, 350 mg dalfopristin	**Streptogramin antibiotic (quinupristin) active against vancomycin-resistant *E. faecium* (VRE) and methicillin-resistant *S. aureus* (MRSA). Not active against *E. faecalis*** Children and adults: VRE: 7.5 mg/kg q8h IV for VRE; skin infections: 7.5 mg/kg q12h IV	*Adverse events:* Pain, edema, or phlebitis at injection site, nausea, diarrhea *Drug interactions* : Synercid is a potent inhibitor of CYP 3A4
Sulfadiazine Tablet: 500 mg	**Sulfonamide antibiotic primarily indicated for treatment of lower UTIs caused by *E. coli, P. mirabilis,* and *Klebsiella*** Toxoplasmosis: Neonates: 100 mg/kg/24 hr divided q12h PO with pyrimethamine 1 mg/kg/24 hr PO (with folinic acid) Children: 120-200 mg/kg/24 hr divided q6h PO with pyrimethamine 2 mg/kg/24 hr divided q12h PO ≥3 days, then 1 mg/kg/24 hr (max dose: 25 mg/24 hr) with folinic acid Rheumatic fever prophylaxis: weight ≤30 kg: 500 mg/24 hr q24h PO; weight >30 kg: 1 g/24 hr q24h PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life: ~10 hr *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Sulfamethoxazole Gantanol Tablet: 500 mg Suspension: 500 mg/5 mL	**Sulfonamide antibiotic used for treatment of otitis media, chronic bronchitis, and lower UTIs caused by susceptible bacteria** Children: 50-60 mg/kg/24 hr divided q12h PO Adults: 1 g/dose q12h PO (max dose: 3 g/24 hr)	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life: ~12 hr. Initial dose often a loading dose (doubled) *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Sulfisoxazole Gantrisin Tablet: 500 mg Suspension: 500 mg/5 mL Ophthalmic solution,	**Sulfonamide antibiotic used for treatment of otitis media, chronic bronchitis, and lower UTIs caused by susceptible bacteria** Children: 120-150 mg/kg/24 hr divided q4-6h PO (max dose: 6 g/24 hr)	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic

ointment	Adults: 4-8 g/24 hr divided q4-6h PO	elimination; avoid use with renal disease. Half-life: ~7-12 hr. Initial dose often a loading dose (doubled) *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Tigecycline Tygacil Injection	**Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and anaerobes** Children: unknown Adults: 100 mg loading dose followed by 50 mg q12h IV	*Cautions:* Pregnancy; children <8 yr old; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance) *Drug interaction:* Warfarin; mycophenolate mofetil
Tobramycin Nebcin, Tobrex Injection Ophthalmic solution, ointment	**Aminoglycoside antibiotic active against gram-negative bacilli, especially *E. coli, Klebsiella, Enterobacter, Serratia, Proteus,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 2.5 mg/kg q12-18h IV or IM; weight >2,000 g: 2.5 mg/kg q12h IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 2.5 mg/kg q8-12h IV or IM; weight >2,000 g: 2.5 mg/kg q8h IV or IM Children: 2.5 mg/kg/24 hr divided q8-12h IV or IM. Alternatively, may administer 5-7.5 mg/kg/24 hr IV. Preservative-free preparation for intraventricular or intrathecal use: neonate, 1 mg/24 hr; children, 1-2 mg/24 hr; adults, 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q8h IV or IM	*Cautions: S. pneumoniae* , other *Streptococcus,* and anaerobes are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 6-12 mg/L; trough <2 mg/L
Trimethoprim Proloprim, Trimpex Tablet: 100, 200 mg	**Folic acid antagonist effective in prophylaxis and treatment of *E. coli, Klebsiella, P. mirabilis,* and *Enterobacter* UTIs; *P. carinii* pneumonia** Children: For UTI: 4-6 mg/kg/24 hr divided q12h PO Children >12 yr and adults: 100-200 mg q12h PO. *P. carinii* pneumonia (with dapsone): 15-20 mg/kg/24 hr divided q6h for 21 days PO	*Cautions:* Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash *Drug interactions:* Possible interactions with phenytoin, cyclosporine, rifampin, warfarin
Vancomycin Vancocin, Lyphocin Injection Capsule: 125 mg, 250 mg Suspension	**Glycopeptide antibiotic active against most gram-positive pathogens including staphylococci (including MRSA and coagulase-negative staphylococci), *S. pneumoniae* including penicillin-resistant strains, *Enterococcus* (resistance is increasing), and *C. difficile* –associated colitis** Neonates: Postnatal age ≤7 days, weight	*Cautions:* Ototoxicity and nephrotoxicity particularly when co-administered with other ototoxic and nephrotoxic drugs Infuse IV over 45-60 min. Flushing (red man syndrome) associated

	<1,200 g: 15 mg/kg/24 hr divided q24h IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q12-18h IV; weight >2,000 g: 30 mg/kg/24 hr divided q12h IV; postnatal age >7 days, weight <1,200 g: 15 mg/kg/24 hr divided q24h IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q8-12h IV; weight >2,000 g: 45 mg/kg/24 hr divided q8h IV Children: 45-60 mg/kg/24 hr divided q8-12h IV; *C. difficile* –associated colitis; 40-50 mg/kg/24 hr divided q6-8h PO	with rapid IV infusions, fever, chills, phlebitis (central line is preferred). Renally eliminated. *Target serum concentrations:* Peak (1 hr after 1 hr infusion) 30-40 mg/L; trough 5-10 mg/L

[*] In the Drug column, the generic drug name is in **bold** . In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

CNS, Central nervous system; GI, gastrointestinal; IM, intramuscular/ly; IV, intravenous/ly; PO, oral/ly; q12-24h, every 12 to 24 hours; bid, twice daily; qid, 4 times daily; UTIs, urinary tract infections.

Penicillins

Although there has been ever-increasing emergence of resistance to penicillins, these agents remain valuable and are commonly used for management of many pediatric infectious diseases.

Penicillins remain the drugs of choice for pediatric infections caused by group A and group B streptococcus, *Treponema pallidum* (syphilis), *L. monocytogenes,* and *N. meningitidis.* The **semisynthetic penicillins** (nafcillin, cloxacillin, dicloxacillin) are useful for management of susceptible (non-MRSA) staphylococcal infections. The **aminopenicillins** (ampicillin, amoxicillin) were developed to provide broad-spectrum activity against gram-negative organisms, including *E. coli* and *H. influenzae*, but the emergence of resistance (typically mediated by a β-lactamase) has limited their utility in many clinical settings. The **carboxypenicillins** (ticarcillin) and **ureidopenicillins** (piperacillin, mezlocillin, azlocillin) also have bactericidal activity against most strains of *P. aeruginosa.*

Resistance to penicillin is mediated by a variety of mechanisms (see Table 207.1). The production of β-lactamase is a common mechanism exhibited by many organisms that may be overcome, with variable success, by including a β-lactamase inhibitor in the therapeutic formulation with the penicillin. Such combination products (ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin–clavulanic acid [no longer available in the U.S.], piperacillin-tazobactam) are potentially very useful for management of resistant isolates, but only if the resistance is β-lactamase mediated. Notably, MRSA and *S. pneumoniae* mediate resistance to penicillins through mechanisms other than β-lactamase production, rendering these combination agents of little value for the management of these infections.

Table 207.4 lists adverse reactions to penicillins.

Table 207.4

Adverse Reactions to Penicillins

TYPE OF REACTION	FREQUENCY (%)	OCCURS MOST FREQUENTLY WITH
ALLERGIC		
Immunoglobulin E antibody	0.04-0.015	Penicillin G
Anaphylaxis*		
Early urticaria* (<72 hr)		
Cytotoxic antibody	Rare	Penicillin G
Hemolytic anemia*		
Antigen-antibody complex disease	Rare	Penicillin G
Serum sickness*		
Delayed hypersensitivity	2-5	Ampicillin, amoxicillin
Contact dermatitis*		
IDIOPATHIC	2-5	Ampicillin
Skin rash		
Fever		
Late-onset urticaria		
GASTROINTESTINAL		
Diarrhea	3-11	Ampicillin
C. difficile –associated colitis	Rare	Ampicillin
HEMATOLOGIC		
Hemolytic anemia	Rare	Penicillin G
Neutropenia	10-17	Penicillin G, nafcillin, oxacillin †
Platelet dysfunction	43-73	Piperacillin
HEPATIC		
Elevated serum aspartate transaminase	0.01-22	Flucloxacillin, oxacillin
ELECTROLYTE DISTURBANCE		
Hypokalemia	Rare	Nafcillin, oxacillin
Hyperkalemia, acute	Rare	Penicillin G
NEUROLOGIC		
Seizures	Rare	Penicillin G
Bizarre sensations	Rare	Procaine penicillin
RENAL		
Interstitial nephritis*	Variable	Any penicillin

* Reaction can occur with any of the penicillins.

† With prolonged therapy.

Adapted from Doi Y, Chambers HF: Penicillins and β-lactamase inhibitors. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 20-7).

Cephalosporins

Cephalosporins differ structurally from penicillins insofar as the β-lactam ring exists as a 6-member ring, compared to the 5-member ring structure of the penicillins. These agents are widely used in pediatric practice, both in oral and parenteral formulations (Table 207.5). The **first-generation cephalosporins** (e.g., cefazolin, a parenteral formulation, and cephalexin, an oral equivalent) are commonly used for management of skin and soft tissue infections caused by susceptible strains of *S. aureus* and group A streptococcus. The **second-generation cephalosporins** (e.g., cefuroxime, cefoxitin) have better activity against gram-negative bacterial infections than first-generation cephalosporins and are used to treat respiratory tract infections, UTIs, and skin and soft tissue infections. A variety of orally administered second-generation agents (cefaclor, cefprozil, loracarbef, cefpodoxime) are commonly used in the outpatient management of sinopulmonary infections and otitis media. The **third-generation cephalosporins** (cefotaxime [no longer available], ceftriaxone, and ceftazidime) are typically used for serious pediatric infections, including meningitis and sepsis. Ceftazidime is highly active against most strains of *P. aeruginosa,* making this a useful agent for febrile, neutropenic oncology patients. The U.S. Food and Drug Administration (FDA) approved the combination of ceftazidime and the novel β-lactamase inhibitor *avibactam* in 2015. Current indications include complicated intraabdominal infections and UTIs. The combination may also be useful for the treatment of infection caused by KPCs. Pediatric experience is limited. Ceftriaxone should not be mixed or reconstituted with a calcium-containing product, such as Ringer or Hartmann solution or parenteral nutrition containing calcium, because particulate formation can result. Cases of fatal reactions with ceftriaxone–calcium precipitates in lungs and kidneys in neonates have been reported. A **fourth-generation cephalosporin** called *cefepime* has activity against *P. aeruginosa* and retains good activity against methicillin-susceptible staphylococcal infections. A **fifth -generation cephalosporin** called *ceftaroline* has been licensed. Ceftaroline is the active metabolite of the prodrug ceftaroline fosamil (which is the agent administered to the patient). Ceftaroline is a broad-spectrum cephalosporin with bactericidal activity against resistant gram-positive organisms, including MRSA, and common gram-negative pathogens. It has FDA approval and is licensed for use in children. Ceftaroline is indicated for MRSA in the treatment of skin and soft tissue infections. It is also licensed for treatment of community-acquired pneumonia but is not indicated for MRSA pneumonia. Ceftaroline's activity is attributed to its ability to bind to penicillin-binding protein 2a with higher affinity than other β-lactams. Another fifth-generation cephalosporin with a similar spectrum of activity, *ceftobiprole* , has been approved for use in Canada and the European Union.

Table 207.5

Classification of Parenteral and Oral Cephalosporins

CEPHALOSPORINS	FIRST GENERATION	SECOND GENERATION	CEPHAMYCINS	THIRD GENERATION	FOURTH GENERATI
Parenteral	Cefazolin (Ancef, Kefzol)	Cefamandole (Mandol)*	Cefmetazole (Zefazone)*	Cefoperazone (Cefobid)*	Cefepime (Maxipime)
	Cephalothin (Keflin, Seffin)*	Cefonicid (Monocid)*	Cefotetan (Cefotan)	Cefotaxime* (Claforan)	Cefpirome (Cefrom)*
	Cephapirin (Cefadyl)* Cephradine (Velosef)*	Cefuroxime (Kefurox, Zinacef)	Cefoxitin (Mefoxin)	Ceftazidime (Fortaz) Ceftizoxime (Cefizox)* Ceftriaxone (Rocephin) Moxalactam*	Ceftolozane (combined w tazobactam; CXA-101)
Oral	Cefadroxil (Duricef, Ultracef) Cephalexin (Keflex, Biocef, Keftab) Cephradine (Velosef)*	Cefaclor (Ceclor)* Cefprozil (Cefzil) Cefuroxime axetil (Ceftin) Loracarbef (Lorabid)*		Cefdinir (Omnicef) Cefditoren (Spectracef) Cefixime (Suprax) Cefpodoxime (Vantin) Ceftibuten (Cedax)	

* Not currently available in the United States.

Adapted from Craig WA, Andes DR: Cephalosporins.IN Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 21-1).

Another fifth-generation cephalosporin, *ceftolozane* , is a derivative of ceftazidime with improved activity against *Pseudomonas* spp. It is not stable against most ESBLs or carbapenemases. It is marketed in combination with the β-lactam inhibitor tazobactam, to improve its activity against β-lactamase–producing Enterobacteriaceae. Experience with children is limited.

Table 207.6 lists adverse reactions to cephalosporins.

Table 207.6

Potential Adverse Effects of Cephalosporins

TYPE	SPECIFIC	FREQUENCY
Hypersensitivity	Rash	1–3%
	Urticaria	<1%
	Serum sickness	<1%
	Anaphylaxis	0.01%
Gastrointestinal	Diarrhea	1–19%
	Nausea, vomiting	1–6%
	Transient transaminase elevation	1–7%
	Biliary sludge	20–46%*
Hematologic	Eosinophilia	1–10%
	Neutropenia	<1%
	Thrombocytopenia	<1-3%
	Hypoprothrombinemia	<1%
	Impaired platelet aggregation	<1%
	Hemolytic anemia	<1%
Renal	Interstitial nephritis	<1%
Central nervous system	Seizures	<1%
	Encephalopathy	<1%
False-positive laboratory	Coombs positive	3%
	Glucosuria	Rare
	Serum creatinine	Rare
Other	Drug fever	Rare
	Disulfiram-like reaction †	Rare
	Superinfection	Rare
	Phlebitis	Rare
	Calcium-antibiotic precipitation*	Unknown; can be associated with embolic events

* Ceftriaxone.

† Cephalosporins with thiomethyl tetrazole ring (MTT) side chain.

Adapted from Craig WA, Andes DR: Cephalosporins. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 21-6).

Carbapenems

The carbapenems include imipenem (formulated in combination with cilastatin), meropenem, ertapenem, and doripenem. The basic structure of these agents is similar to that of β-lactam antibiotics, and these drugs have a similar mechanism of action. The carbapenems provide the broadest spectrum of antibacterial activity of any licensed class of antibiotics and are active against gram-positive, gram-negative, and anaerobic organisms. Among the carbapenems, **meropenem** is the only agent licensed for treatment of pediatric meningitis. At this time, ertapenem and doripenem are not approved for pediatric use. Importantly, MRSA and *E. faecium* are *not* susceptible to carbapenems. Carbapenems also tend to be poorly active against *Stenotrophomonas maltophilia,* rendering their use for cystic fibrosis patients who are infected with this organism problematic. Ertapenem is poorly active against *P. aeruginosa* and *Acinetobacter* species and should be avoided when these pathogens are encountered. Although imipenem-cilastatin is the first carbapenem approved for clinical use and the carbapenem with the greatest clinical experience, this antibiotic unfortunately has a propensity to cause seizures in children, particularly in the setting of intercurrent meningitis. Accordingly, meropenem is typically more suitable for pediatric use, where meningitis is commonly a consideration. A new agent called **meropenem-vaborbactam** was licensed. The addition of the β-lactamase inhibitor vaborbactam extends the spectrum of activity of meropenem to include some ESBL- and carbapenemase-producing bacteria. No dosage recommendations exist as yet for pediatric use.

Other carbapenems in various stages of clinical trials include panipenem, biapenem, razupenem, tomopenem, and tebipenem/pivoxil (the first oral carbapenem). Panipenem and biapenem are licensed in Japan, but there is minimal experience with pediatric dosing.

Glycopeptides

Glycopeptide antibiotics include **vancomycin** and **teicoplanin** , the less commonly available analog. These agents are bactericidal and act by inhibition of cell wall biosynthesis. The antimicrobial activity of the glycopeptides is limited to gram-positive organisms, including *S. aureus,* coagulase-negative staphylococci, pneumococcus, enterococci, *Bacillus,* and *Corynebacterium.* Vancomycin is frequently employed in pediatric practice and is of particular value for serious infections, including meningitis, caused by MRSA and penicillin- and cephalosporin-resistant *S. pneumoniae.* Vancomycin is also commonly used for infections in the setting of fever and neutropenia in oncology patients, in combination with other antibiotics (see Chapter 205), and for infections associated with indwelling medical devices (Chapter 206). Oral formulations of vancomycin are occasionally used to treat pseudomembranous colitis caused by *Clostridium difficile* infections; intrathecal therapy may also be used for selected CNS infections. Vancomycin must be administered with care because of its propensity to produce **red man syndrome** , which is a reversible adverse effect that is rare in young children and can typically be readily managed by slowing the rate of drug infusion.

Newer FDA-approved glycopeptide antibiotics include televancin, dalbavancin, and oritavancin; pediatric experience is limited. **Televancin** is indicated for skin and skin structure infections caused by *S. aureus* (including MRSA), group A streptococcus, and *E. faecalis* (vancomycin-susceptible isolates only). It is also approved for hospital-acquired (including ventilator-associated) pneumonia caused by *S. aureus* . The recommended adult dose is 10 mg/kg intravenously (IV) every 24 hr for 7-21 days. Televancin appears to be more nephrotoxic than vancomycin and has been associated with prolongation of the QT interval. **Dalbavancin** 's unique characteristic is its long half-life, 150-250 hr. In adults with normal renal function, the dose is 1000 mg IV, followed 1 wk later by 500 mg IV. This agent can be considered when MRSA is confirmed or strongly suggested. Dalbavancin is not active against vancomycin-resistant *S. aureus* . It is FDA-approved for bacterial skin and soft tissue infections. **Oritavancin** is a vancomycin derivative with indications similar to those of dalbavancin. It has a half-life of approximately 250 hr. The dosage for adults is a single 1200 mg dose, administered IV over 3 hr. The FDA has approved dalbavancin and oritavancin for treatment of acute bacterial skin and skin structure infections caused by gram-positive bacteria, including MRSA.

Aminoglycosides

Aminoglycoside antibiotics include streptomycin, kanamycin, gentamicin, tobramycin, netilmicin, and amikacin. The most commonly used aminoglycosides in pediatric practice are **gentamicin** and **tobramycin** . They exert their mechanism of action by inhibition of bacterial protein synthesis. Although they are most often used to treat gram-negative infections, the aminoglycosides are broad-spectrum agents, with activity against *S. aureus* and synergistic activity against GBS, *L. monocytogenes,* viridans streptococci, corynebacteria JK, *Pseudomonas, Staphylococcus epidermidis,* and *Enterococcus* when co-administered with a β-lactam agent. Aminoglycoside use has decreased with the development of alternatives, but they still play a key role in pediatric practice in the management of neonatal sepsis, UTIs, gram-negative bacterial sepsis, and complicated intraabdominal infections; infections in cystic fibrosis patients (including both parenteral and aerosolized forms of therapy); and in oncology patients with fever and neutropenia. Aminoglycosides, in particular streptomycin, are also important in the management of *Francisella* *tularensis, Mycobacterium tuberculosis,* and atypical mycobacterial infections.

Toxicities of aminoglycoside therapy include nephrotoxicity and ototoxicity (cochlear and/or vestibular), and serum levels as well as renal function and hearing should be monitored in patients on long-term therapy. Toxicities of aminoglycosides may be reduced by the use of once-daily dosing regimens with appropriate monitoring of serum levels. Hypokalemia, volume depletion, hypomagnesemia, and other nephrotoxic drugs may increase the renal toxicity of aminoglycosides. A rare complication of aminoglycosides is **neuromuscular blockade** , which may occur in the presence of other neuromuscular blocking agents and in the setting of infant botulism.

Tetracyclines

The tetracyclines (tetracycline hydrochloride, doxycycline, demeclocycline, and minocycline) are bacteriostatic antibiotics that exhibit their antimicrobial effect by binding to the bacterial 30S ribosomal subunit, inhibiting protein translation. These agents have a broad spectrum of antimicrobial activity against gram-positive and gram-negative bacteria, rickettsia, and some parasites. The oral bioavailability of these agents facilitates oral dosing for many infections, including Rocky Mountain spotted fever, anaplasmosis, ehrlichiosis, Lyme disease, and malaria. Tetracyclines must be prescribed judiciously to children <9 yr old, because they can cause staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in this age-group.

Tigecycline , a semisynthetic derivative of minocycline, is a parenteral agent of a new antibiotic class (**glycylcyclines**) and is licensed in the United States. It has a broader spectrum of activity (bacteriostatic) than traditional tetracyclines but retains the side effect profile of tetracyclines. Tigecycline is active against tetracycline-resistant gram-positive and gram-negative pathogens, including MRSA and possibly VRE, but not *Pseudomonas.* A novel tetracycline derivative, **eravacycline** (a fluorocycline), has completed phase 3 studies but is not yet licensed for use.

Complications of tetracyclines include eosinophilia, leukopenia and thrombocytopenia (tetracycline), pseudotumor cerebri, anorexia, emesis and nausea, candidal superinfection, hepatitis, photosensitivity, and a hypersensitivity reaction (urticaria, asthma exacerbation, facial edema, dermatitis) as well as a systemic lupus erythematosus–like syndrome (minocycline). The FDA issued a “black box” warning regarding tigecycline in

2013 based on a meta-analysis of 10 studies that showed increased mortality among patients receiving this drug.

A salutary side effect of **demeclocycline** has been identified; it is occasionally used as an off-label treatment of hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone.

Sulfonamides

Trimethoprim and the sulfonamides are bacteriostatic agents that inhibit the bacterial folate synthesis pathway, in the process impairing both nucleic acid and protein synthesis. Sulfonamides interfere with the synthesis of dihydropteroic acid from paraaminobenzoic acid, whereas trimethoprim acts at a site further downstream, interfering with synthesis of tetrahydrofolic acid from dihydrofolic acid. The sulfonamides are available in both parenteral and oral formulations. Although there have historically been a large number of sulfonamide antibiotics developed for clinical use, relatively few remain available for pediatric practice. The most important agent is the combination of **trimethoprim-sulfamethoxazole** (TMP-SMX), used for treatment of UTIs. TMP-SMX has also emerged as a commonly prescribed agent for staphylococcal skin and soft tissue infections, since this antibiotic retains activity against MRSA. TMP-SMX also plays a unique role in immunocompromised patients, as a prophylactic and therapeutic agent for *Pneumocystis jiroveci* infection. Other common sulfonamides include **sulfisoxazole** , which is useful in the management of UTIs, and **sulfadiazine** , which is a drug of choice in the treatment of toxoplasmosis.

Macrolides

The macrolide antibiotics most often used in pediatric practice include **erythromycin** , **clarithromycin** , and **azithromycin** . This class of antimicrobials exerts its antibiotic effect through binding to the 50S subunit of the bacterial ribosome, producing a block in elongation of bacterial polypeptides. Clarithromycin is metabolized to 14-hydroxy clarithromycin, and interestingly this active metabolite also has potent antimicrobial activity. The spectrum of antibiotic activity includes many gram-positive bacteria. Unfortunately, resistance to these agents among *S. aureus* and group A streptococcus is fairly widespread, limiting the usefulness of macrolides for many skin and soft-tissue infections and for streptococcal pharyngitis. Azithromycin and clarithromycin have demonstrated efficacy for otitis media. All macrolide members have an important role in the management of pediatric respiratory infections, including atypical pneumonia caused by *M. pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*, as well as infections caused by *Bordetella pertussis*.

Telithromycin , a ketolide antibiotic derived from erythromycin, was initially FDA-approved for the treatment in adults of mild to moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis, having good activity against the agents causing these infections (*S. pneumoniae* , *M. pneumoniae, C. pneumoniae*, and *L. pneumophila* for community-acquired pneumonia; *M. catarrhalis* and *H. influenzae* for sinusitis). Reports of liver failure and myasthenia gravis from telithromycin in particular prompted the withdrawal of drug from the market. **Solithromycin** is a related, next-generation oral and intravenous fluoroketolide in phase 3 clinical development for the treatment of community-acquired pneumonia.

Drug interactions are common with erythromycin and to a lesser extent with clarithromycin. These agents can inhibit the CYP 3A4 enzyme system, resulting in increased levels of certain drugs, such as astemizole, cisapride, statins, pimozide, and theophylline. Itraconazole may increase macrolide levels, whereas rifampin, carbamazepine, and phenytoin may decrease macrolide levels. There are few reported adverse drug interactions with azithromycin. Cross-resistance may develop between a macrolide and the subsequent use of clindamycin.

Lincosamides

The prototype of the lincosamide class of antibiotics is **clindamycin** , which acts at the ribosomal level to exert its antimicrobial effect. The 50S subunit of the bacterial ribosome is the molecular target of this agent. Its spectrum of activity includes gram-positive aerobes and anaerobes. Clindamycin has no significant activity against gram-negative organisms. An important role for clindamycin has emerged in the management of MRSA infections. Because of its outstanding penetration into body fluids (excluding the CNS) and tissues and bone, clindamycin can be used for therapy of serious infections caused by MRSA. Clindamycin is also useful in the management of invasive group A streptococcus infections and in the management of many anaerobic infections, often in combination with a β-lactam. A form of **inducible clindamycin resistance** is exhibited by some strains of MRSA; therefore consultation with the clinical microbiology laboratory is necessary before treating a serious MRSA infection with clindamycin. Pseudomembranous colitis, a common complication of clindamycin therapy in adults, is seldom observed in pediatric patients. Clindamycin also plays an important role in the treatment of malaria and babesiosis (when co-administered with quinine), *P. jiroveci* pneumonia (when co-administered with primaquine), and toxoplasmosis.

Quinolones

The **fluoroquinolones** (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, besifloxacin [ophthalmic suspension], and delafloxacin) are antimicrobials that inhibit bacterial DNA replication by binding to the topoisomerases of the target pathogen, inhibiting the bacterial enzyme DNA gyrase. This class has broad-spectrum activity against both gram-positive and gram-negative organisms. Some fluoroquinolones exhibit activity against penicillin-resistant *S. pneumoniae* as well as MRSA. These agents uniformly show excellent activity against gram-negative pathogens, including the Enterobacteriaceae and respiratory tract pathogens such as *M. catarrhalis* and *H. influenzae*. Quinolones are also very active against pathogens associated with atypical pneumonia, particularly *M. pneumoniae* and *L. pneumophila*.

Although these agents are not approved for use in children, there is a reasonable body of evidence that the fluoroquinolones are generally safe, well tolerated, and effective against a variety of bacterial infections frequently encountered in pediatric practice. Parenteral quinolones are appropriate for critically ill patients with gram-negative infections. The use of oral quinolones in stable outpatients may also be reasonable for treatment of infections that would otherwise require parenteral antibiotics (e.g., *P. aeruginosa* soft tissue infections such as osteochondritis) or selected genitourinary tract infections. However, these agents should be reserved for situations where no other oral antibiotic alternative is feasible. In 2013 the FDA changed the warning labels for the fluoroquinolones to better describe the associated risk of permanent peripheral neuropathy. Additional risks include tendonitis, arrhythmias, and retinal detachment. Moreover, in situations of overuse (e.g., typhoid fever, gonococcal infection), organisms have been demonstrated to rapidly develop resistance. The FDA has advised against the use of quinolones for uncomplicated infections such as sinusitis and bronchitis. Thus, use of fluoroquinolones in pediatric practice should still be approached with continued caution, and consultation with an expert is recommended.

Streptogramins and Oxazolidinones

The emergence of highly resistant gram-positive organisms, in particular VRE, has necessitated development of new classes of antibiotics. One such class especially useful for resistant gram-positive infections is the streptogramins. The currently licensed agent in this category is **dalfopristin-quinupristin,** which is available in a parenteral formulation. It is appropriate for treatment of MRSA, coagulase-negative staphylococci, penicillin-susceptible and penicillin-resistant *S. pneumoniae,* and vancomycin-resistant *E. faecium* but not *E. faecalis.*

Another licensed class of antibiotics for highly resistant gram-positive infections is the oxazolidinone class. The prototype in this group is **linezolid** , available in both oral and parenteral formulations and approved for use in pediatric patients. Its mechanism of action involves inhibition of ribosomal protein synthesis. It is indicated for MRSA, VRE, coagulase-negative staphylococci, and penicillin-resistant *S. pneumoniae* . A related drug, **tedizolid phosphate** , is also FDA-approved for acute bacterial skin and skin structure infections. It is more potent in vitro than linezolid against MRSA and may be associated with less myelosuppression. It is available in both intravenous and oral formulations.

There is little information on streptogramins and oxazolidinones in treatment of CNS infections, and neither class is approved for pediatric meningitis. Linezolid can cause significant anemia and thrombocytopenia and is a monoamine oxidase inhibitor.

Daptomycin

Daptomycin is a novel member of the cyclic lipopeptide class of antibiotics. Its spectrum of activity includes virtually all gram-positive organisms, including *E. faecalis* and *E. faecium* (including VRE) and *S. aureus* (including MRSA). The structure of daptomycin is a 13-member amino acid peptide linked to a 10-carbon lipophilic tail, which results in a novel mechanism of action of disruption of the bacterial membrane through the formation of transmembrane channels. These channels cause leakage of intracellular ions, leading to depolarization of the cellular membrane and inhibition of macromolecular synthesis. A theoretical advantage of daptomycin for serious infections is its bactericidal activity against MRSA and enterococci. It is administered intravenously; experience in children is limited. Myopathy and elevations in creatine phosphokinase have been described. An FDA warning has been issued linking some cases of eosinophilic pneumonitis to the use of daptomycin. Daptomycin is inactivated by surfactant and should not be used to treat pneumonia.

Miscellaneous Agents

Metronidazole , which functions by disruption of DNA synthesis, has a unique role as an antianaerobic agent and also possesses antiparasitic and anthelmintic activity. In 2017 a related drug, **benznidazole** , was approved through the FDA's orphan drug Accelerated Approval Pathway. This antiprotozoal agent inhibits the synthesis of DNA, RNA, and proteins within *Trypanosoma cruzi* and is approved for adult and pediatric use for Chagas disease. **Rifampin** is a rifamycin antibiotic that inhibits bacterial RNA polymerase and has a major role in the management of tuberculosis. It is also of value in the management of other bacterial infections in pediatric patients, usually used as a 2nd (synergistic) agent in the treatment of *S. aureus* infections or to eliminate nasopharyngeal colonization of *H. influenzae* type b or *N. meningitidis*. **Rifabutin** is a related drug that has an off-label indication for treatment of tuberculosis, an orphan drug indication for Crohn disease, and an indication for prevention or treatment of disseminated *Mycobacterium avium* complex disease in patients with HIV or immune deficiency. **Rifaximin** is a *nonabsorbed rifamycin* that has been used as an adjunct agent to treat patients with multiple recurrences of *C. difficile* infection. **Fidaxomicin** is a first-in-class member of a new category of narrow-spectrum macrocyclic antibiotic drugs. It is an RNA polymerase inhibitor with activity against *C. difficile* infection.

The emerging crisis in antimicrobial resistance has also necessitated the rediscovery of antimicrobial agents seldom used in clinical practice in recent decades, such as **colistin** (colistimethate sodium), a member of the polymyxin family of antibiotics (polymyxin E). Polymyxins’ general structure consists of a cyclic peptide with hydrophobic tails. After binding to lipopolysaccharide in the outer membrane of gram-negative bacteria, polymyxins disrupt both outer and inner membranes, leading to cell death. Colistin is broadly active against the Enterobacteriaceae family, including *P. aeruginosa*. It is also active against ESBL- and carbapenemase-producing strains. Toxicities are chiefly renal and neurologic.

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SECTION 4

Gram-Positive Bacterial Infections

OUTLINE

Chapter 208 Staphylococcus
Chapter 209 Streptococcus pneumoniae (Pneumococcus)
Chapter 210 Group A Streptococcus
Chapter 211 Group B Streptococcus
Chapter 212 Non–Group A or B Streptococci
Chapter 213 Enterococcus
Chapter 214 Diphtheria (Corynebacterium diphtheriae)
Chapter 215 Listeria monocytogenes
Chapter 216 Actinomyces
Chapter 217 Nocardia

CHAPTER 208

Staphylococcus

James T. Gaensbauer, James K. Todd

Staphylococci are hardy, aerobic, gram-positive bacteria that grow in pairs and clusters and are ubiquitous as normal flora of humans and present on fomites and in dust. They are resistant to heat and drying and may be recovered from nonbiologic environments weeks to months after contamination. Strains are classified as *Staphylococcus aureus* if they are coagulase positive or as one of the many species of **coagulase-negative staphylococci** (e.g., *Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus haemolyticus*). *S. aureus* has many virulence factors that mediate various serious diseases, whereas coagulase-negative staphylococci tend to be less pathogenic unless an indwelling foreign body (e.g., intravascular catheter) is present. *S. aureus* strains resistant to β-lactam antibiotics, typically referred to as **methicillin-resistant *Staphylococcus aureus* (MRSA)** , have become a significant problem in both community and hospital settings.

208.1

Staphylococcus aureus

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Staphylococcus aureus is the most common cause of pyogenic infection of the skin and soft tissues. **Bacteremia** (primary and secondary) is common and can be associated with or can result in osteomyelitis, suppurative arthritis, pyomyositis, deep abscesses, pneumonia, empyema, endocarditis, pericarditis, and rarely meningitis. **Toxin-mediated diseases** , including food poisoning, staphylococcal scarlet fever, scalded skin syndrome, and toxic shock syndrome (TSS), are caused by certain *S. aureus* strains.

Etiology

Strains of *S. aureus* can be identified and characterized by the virulence factors they produce. These factors tend to play 1 or more of 4 pathogenic roles in human disease: *S. aureus* protecting the organism from host defenses, localizing infection, causing local tissue damage, and affecting noninfected sites through toxin elaboration.

Most strains of *S. aureus* possess factors that protect the organism from host defenses. Many staphylococci produce a loose polysaccharide capsule, or **biofilm** , which may interfere with opsonophagocytosis. Production of clumping factor and coagulase differentiates *S. aureus* from coagulase-negative staphylococci. **Clumping factor** interacts with fibrinogen to create large clumps of organisms, interfering with effective phagocytosis. **Coagulase** causes plasma to clot by interacting with fibrinogen and may have an important role in abscess formation. **Protein A** is located on the outermost coat of the cell wall and can absorb serum immunoglobulins, preventing antibacterial antibodies from acting as opsonins and thus inhibiting phagocytosis. The staphylococcal enzyme **catalase** inactivates hydrogen peroxide, promoting intracellular survival.

Many strains of *S. aureus* produce substances that cause local tissue destruction. A number of immunologically distinct **hemolysins** that act on cell membranes and cause tissue necrosis have been identified (α-toxin, β-hemolysin, δ-hemolysin). Much attention has been given to the **Panton-Valentine leukocidin,** a protein that *S. aureus* combines with phospholipid in the leukocytic cell membrane, producing increased permeability and eventual death of the cell. Strains of *S. aureus* that produce Panton-Valentine leukocidin are associated with more-severe and invasive skin disease, pneumonia, and osteomyelitis. Many strains of *S. aureus* release 1 or more exotoxins. **Exfoliatins A and B** are serologically distinct proteins that produce localized (bullous impetigo) or generalized (scalded skin syndrome, staphylococcal scarlet fever) dermatologic manifestations (see Chapter 685).

S. aureus can produce >20 distinct enterotoxins (types A-V). Ingestion of preformed enterotoxin, particularly types A or B, can result in **food poisoning** , resulting in vomiting and diarrhea and, in some cases, profound hypotension.

Toxic shock syndrome toxin-1 (TSST-1) is associated with **toxic shock syndrome (TSS)** , related to menstruation and focal staphylococcal infection (see Chapter 208.2). TSST-1 is a superantigen that induces production of interleukin (IL)-1 and tumor necrosis factor (TNF), resulting in hypotension, fever, and multisystem involvement. Focal infections associated with enterotoxins A or B also may be associated with nonmenstrual TSS.

S. aureus also possesses intrinsic factors that can contribute to pathogenesis, including proteins that promote adhesion to fibrinogen, fibronectin, collagen, and other human proteins. Expression of proteins that mediate antibiotic resistance is also of critical importance. Although historically sensitive to penicillin, *S. aureus* isolates now almost universally produce **penicillinase** or **β-lactamase** , which inactivates many β-lactamases at the molecular level and represents the major resistance mechanism against many penicillin and cephalosporin antibiotics. Thus, treatment of *S. aureus* with β-lactam antibiotics requires either a penicillinase resistant β-lactam ring or combination with a β-lactamase inhibitor. Production of altered **penicillin-binding proteins (PBPs)** in the bacterial cell wall mediates resistance to penicillinase resistant antibiotics: an **altered PBP-2A** , encoded by the gene *MECA* , is responsible for the methicillin and cephalosporin resistance of MRSA isolates.

Epidemiology

Approximately 20–40% of normal individuals carry at least 1 strain of *S. aureus* in the anterior nares at any given time, with intermittent carriage occurring in up to 70% of individuals. The organisms may be transmitted from the nose to the skin, where colonization is more transient. Persistent umbilical, vaginal, and perianal carriage may also occur. Many neonates are colonized within the 1st week of life, usually by a maternal strain. Rates of colonization with MRSA in the general pediatric population are typically <2% but may be higher in some locales and in children with significant healthcare exposure and chronic medical conditions.

Exposure to *S. aureus* generally occurs by autoinoculation or direct contact with the hands of other colonized individuals. Heavily colonized nasal carriers (often aggravated by a viral upper respiratory tract infection) are particularly effective disseminators. Spread by fomites is rare, although an outbreak occurring in a high school football team was attributed to sharing towels. Infection control policies in healthcare facilities, particularly those emphasizing good hand hygiene, have been shown to decrease rates of nosocomial staphylococcal infection.

Outside the hospital setting, outbreaks of staphylococcal disease, in particular disease caused by methicillin-resistant strains, have been reported among athletes, military personnel, young children, veterinarians, injection drug users, and inmates in correctional facilities. Increased disease frequency is noted among household contacts of a MRSA-colonized or infected individual. Skin infections caused by *S. aureus* are considerably more prevalent among persons living in low socioeconomic circumstances and particularly among those in tropical climates.

The burden of staphylococcal disease is significant. Most important is the role of *S. aureus*, including MRSA, in **hospital-acquired infections** , including infections of the bloodstream, infection of surgical sites, and ventilator-associated pneumonia. *S. aureus* is a significant cause of morbidity and mortality in neonatal intensive care units (NICUs). Community-acquired staphylococcal infections are estimated to result in 14 million annual outpatient healthcare visits. In 2005 an estimated 478,000 hospitalizations were associated with *S. aureu* s infection in the United States, more than half of which were caused by MRSA. Recent evidence shows a decline in rates of invasive MRSA infection in adults, but an opposite trend in U.S. pediatric patients was noted in 2013.

Pathogenesis

Except in the case of food poisoning resulting from ingestion of preformed enterotoxins, disease associated with *S. aureus* typically begins with colonization as previously described. Subsequent disease manifestations in susceptible individuals result either directly from tissue invasion or from injury caused by various toxins and enzymes produced by the organism (Fig. 208.1).

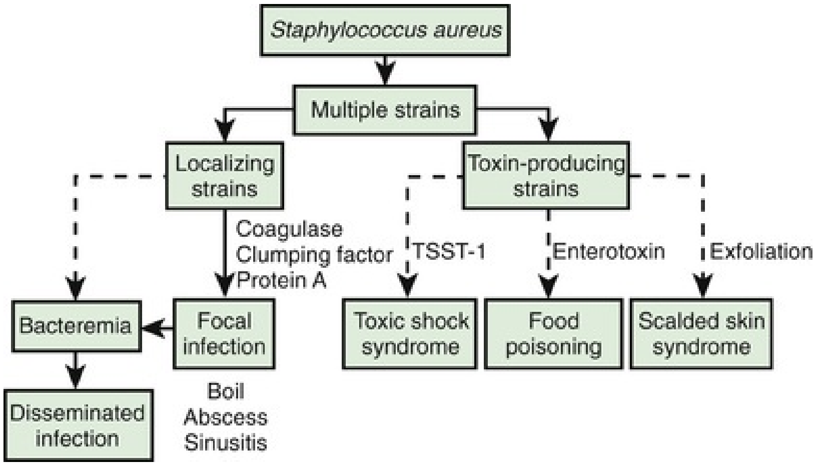
Staphylococcus aureus
Multiple strains
Localizing strains
Toxin-producing strains
Coagulase
Clumping factor
Protein A
TSST-1
Enterotoxin
Exfoliation
Bacteremia
Focal infection
Toxic shock syndrome
Food poisoning
Scalded skin syndrome
Disseminated infection
Boil
Abscess
Sinusitis

FIG. 208.1 **Relationship of virulence factors and diseases associated with *Staphylococcus aureus* . TSST-1, toxic shock syndrome toxin-1.**

The most significant risk factor for the development of infection is **disruption of intact skin** , including breaches from wounds, skin disease such as eczema, epidermolysis bullosa or burns, ventriculoperitoneal shunts, and indwelling intravascular or intrathecal catheters. Additional risk factors include corticosteroid treatment, malnutrition, and azotemia. Antibiotic therapy with a drug to which *S. aureus* is resistant favors colonization and the development of infection. Viral infections of the respiratory tract, especially influenza virus, may predispose to secondary bacterial infection with staphylococci in certain individuals.

Congenital defects in chemotaxis (e.g., Job, Chédiak-Higashi, and Wiskott-Aldrich syndromes) and defective phagocytosis and killing (e.g., neutropenia, chronic granulomatous disease) increase the risk for staphylococcal infections. Patients with HIV infection have neutrophils that are defective in their ability to kill *S. aureus* in vitro. Patients with recurrent staphylococcal infection should be evaluated for immune defects, especially those involving neutrophil dysfunction. Poor mucous clearance in children with cystic fibrosis frequently leads to chronic staphylococcal colonization and persistent inflammation in these patients.

Infants may acquire type-specific humoral immunity to staphylococci transplacentally. Older children and adults develop antibodies to staphylococci as a result of colonization or minor infections. Antibody to the various *S. aureus* toxins appears to protect against those specific toxin-mediated diseases, but humoral immunity does not necessarily protect against focal or disseminated *S. aureus* infection with the same organisms.

Clinical Manifestations

Signs and symptoms vary with the location of the infection, which is usually the skin but may be any tissue. Disease states of various degrees of severity are generally a result of local suppuration, systemic dissemination with metastatic infection, or systemic effects of toxin production.

Newborn

S. aureus is an important cause of neonatal infections (see Chapter 129).

Skin

S. aureus is an important cause of **pyogenic** skin infections, including impetigo contagiosa, ecthyma, bullous impetigo, folliculitis, hydradenitis, furuncles (boils), carbuncles (multiple coalesced boils), and paronychia. **Toxigenic** infection with skin manifestations include staphylococcal scalded skin syndrome and staphylococcal scarlet fever. *S. aureus* is a frequent cause of superinfection of underlying dermatologic conditions, such as eczema or bug bites. Recurrent skin and soft tissue infections often are noted with community-associated MRSA and affect the lower extremities and buttocks. *S. aureus* is also an important cause of traumatic and surgical wound infections and can cause deep soft tissue involvement, including cellulitis and rarely, necrotizing fasciitis.

Respiratory Tract

Infections of the upper respiratory tract (otitis media, sinusitis) caused by *S. aureus* are rare, in particular considering the frequency with which the anterior nares are colonized. *S. aureus* sinusitis is relatively common in children with cystic fibrosis or defects in leukocyte function and may be the only focus of infection in some children with TSS. Suppurative **parotitis** is a rare infection, but *S. aureus* is a common cause. A membranous **tracheitis** that complicates viral croup may result from infection with *S. aureus*, although other organisms may also be responsible. Patients typically have high fever, leukocytosis, and evidence of severe upper airway obstruction. Direct laryngoscopy or bronchoscopy shows a normal epiglottis with subglottic narrowing and thick, purulent secretions within the trachea. Treatment requires careful airway management and appropriate antibiotic therapy.

Pneumonia caused by *S. aureus* may be primary or secondary after a viral infection such as influenza (see Chapter 428). Hematogenous pneumonia may be secondary to septic emboli from right-sided endocarditis or septic thrombophlebitis, with or without intravascular devices. Inhalation pneumonia is caused by alteration of mucociliary clearance, leukocyte dysfunction, or bacterial adherence initiated by a viral infection. Common symptoms and signs include high fever, abdominal pain, tachypnea, dyspnea, and localized or diffuse bronchopneumonia or lobar disease. *S. aureus* often causes a **necrotizing pneumonitis** that may be associated with early development of empyema, pneumatoceles, pyopneumothorax, and bronchopleural fistulas. Chronic pulmonary infection with *S. aureus* contributes to progressive pulmonary dysfunction in children with cystic fibrosis (see Chapter 432).

Sepsis

S. aureus bacteremia and sepsis may be primary or associated with any localized infection. The onset may be acute and marked by nausea, vomiting, myalgia, fever, and chills. Organisms may localize subsequently at any site (usually a single deep focus) but are found especially in the heart valves, lungs, joints, bones, muscles, and deep tissue abscesses.

In some instances, especially in young adolescent males, disseminated *S. aureus* disease occurs, characterized by fever, persistent bacteremia despite antibiotics, and focal involvement of 2 or more separate tissue sites (skin, bone, joint, kidney, lung, liver, heart). These patients often have an endovascular nidus of infection, such as an infected venous thrombosis.

Muscle

Localized staphylococcal abscesses in muscle sometimes without septicemia have been called **pyomyositis.** This disorder is reported most frequently from tropical areas and is termed *tropical pyomyositis,* but also occurs in the United States in otherwise healthy children. Multiple abscesses occur in 30–40% of cases. History may include prior trauma at the site of the abscess. Surgical drainage and appropriate antibiotic therapy are essential.

Bones and Joints

S. aureus is the most common cause of osteomyelitis and suppurative arthritis in children (see Chapters 704 and 705).

Central Nervous System

Meningitis caused by *S. aureus* is uncommon; it is associated with penetrating cranial trauma and neurosurgical procedures (craniotomy, cerebrospinal fluid [CSF] shunt placement), and less frequently with endocarditis, parameningeal foci (epidural or brain abscess), complicated sinusitis, diabetes mellitus, or malignancy. The CSF profile of *S. aureus* meningitis is indistinguishable from that in other forms of bacterial meningitis (see Chapter 621.1).

Heart

S. aureus is a common cause of acute endocarditis on native valves and results in high rates of morbidity and mortality. Perforation of heart valves, myocardial abscesses, heart failure, conduction disturbances, acute hemopericardium, purulent pericarditis, and sudden death may ensue (see Chapter 464).

Kidney

S. aureus is a common cause of renal and perinephric abscess, usually of hematogenous origin. Pyelonephritis and cystitis caused by *S. aureus* are unusual (see Chapter 553).

Toxic Shock Syndrome

S. aureus is the principal cause of TSS, which should be suspected in anyone with fever, shock, and/or a scarlet fever–like rash (see Chapter 208.2).

Intestinal Tract

Staphylococcal enterocolitis may rarely follow overgrowth of normal bowel flora by *S. aureus* , which can result from broad-spectrum oral antibiotic therapy. Diarrhea is associated with blood and mucus. Peritonitis associated with *S. aureus* in patients receiving long-term ambulatory peritoneal dialysis usually involves the catheter tunnel.

Food poisoning may be caused by ingestion of *preformed* enterotoxins produced by staphylococci in contaminated foods (see Chapter 366). The source of contamination is often colonized or infected food workers. Approximately 2-7 hr after ingestion of the toxin, sudden, severe vomiting begins. Watery diarrhea may develop, but fever is absent or low. Symptoms rarely persist >12-24 hr. Rarely, shock and death may occur.

Diagnosis

The diagnosis of *S. aureus* infection depends on isolation of the organism in culture from nonpermissive sites, such as cellulitis aspirates, abscess cavities, blood, bone, or joint aspirates, or other sites of infection. Swab cultures of surfaces are not as useful, because they may reflect surface contamination rather than the true cause of infection. Tissue samples or fluid aspirates in a syringe provide the best culture material. Cellulitic lesions may be cultured using a needle aspirate from the most inflamed area after thorough skin cleansing, inoculated directly into a blood culture bottle; use of injected saline and targeting the leading edge are less effective. Isolation from the nose or skin does not necessarily imply causation because these sites may be normally colonized sites. Because of the high prevalence of MRSA, the increasing severity of *S. aureus* infections, and the fact that bacteremia is not universally present even in severe *S. aureus* infections, it is important to obtain a culture of any potential focus of infection as well as a blood culture before starting antibiotic treatment. The organism can be grown readily in liquid and on solid media. After isolation, identification is made on the basis of Gram stain and coagulase, clumping factor, and protein A reactivity. Increasingly, molecular techniques such as polymerase chain reaction are used to supplement traditional culture methods. Automated PCR systems may allow rapid species identification from positive blood cultures and simultaneously identify genetic patterns associated with methicillin resistance, such as expression of the *MECA* gene produced by MRSA. PCR-based determination of MRSA nasal colonization on admission to hospitals or ICUs aids infection control procedures and identify patients at higher risk of infection.

Diagnosis of *S. aureus* food poisoning is usually made on the basis of epidemiologic and clinical findings. Food suspected of contamination may be cultured and can be tested for enterotoxin.

Differential Diagnosis

Many of the clinical entities previously discussed can also be caused by other bacterial pathogens, and consideration of the differential is particularly important when making empirical antibiotic choices before definitive identification of the offending pathogen. Skin lesions caused by *S. aureus* may be indistinguishable from those caused by group A streptococci, although the former usually expand slowly, while the latter are prone to spread more rapidly and can be very aggressive. Fluctuant skin and soft tissue lesions also can be caused by other organisms, including *Mycobacterium tuberculosis*, atypical mycobacteria, *Bartonella henselae* (cat-scratch disease), *Francisella tularensis*, and various fungi. *S. aureus* pneumonia is often suspected in very ill-appearing children or after failure to improve with standard treatment that does not cover *Staphylococcus* , or on the basis of chest radiographs that reveal pneumatoceles, pyopneumothorax, or lung abscess (Fig. 208.2). Other etiologies of cavitary pneumonias include *Klebsiella pneumoniae* and *M. tuberculosis* . In bone and joint infections, culture is the only reliable way to differentiate *S. aureus* from other, less common etiologies, including group A streptococci and in young children, *Kingella kingae* .

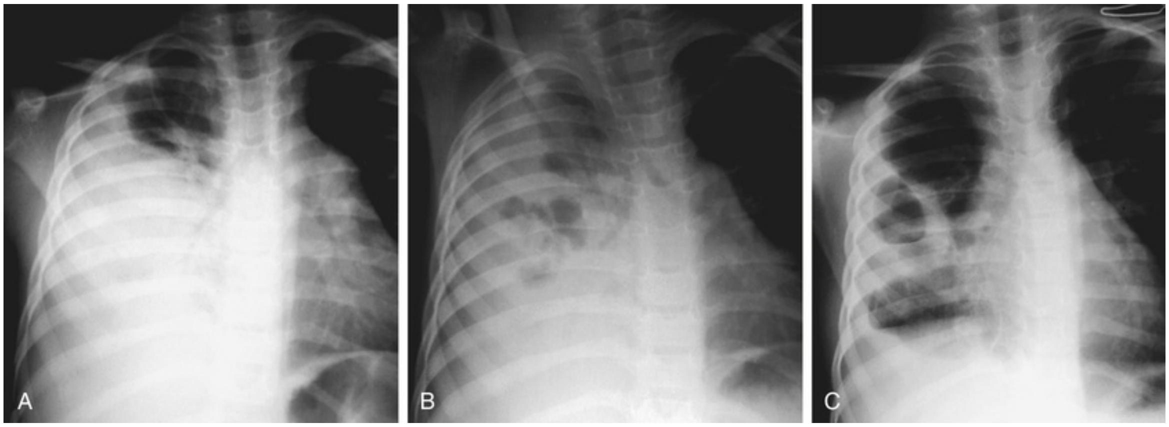

FIG. 208.2 **Pneumatocele formation. A, *Staphylococcus aureus* pneumonia in 5 yr old child initially demonstrated consolidation of the right middle and lower zones. B, Seven days later, multiple lucent areas are noted as pneumatoceles develop. C, Two weeks later, significant resolution is evident, with a rather thick-walled pneumatocele persisting in the right midzone associated with significant residual pleural thickening. (From Kuhn JP, Slovis TL, Haller JO: *Caffey's pediatric diagnostic imaging* , ed 10, Philadelphia, 2004, Mosby, pp 1003–1004.)**

Treatment

Antibiotic therapy alone is rarely effective in individuals with undrained abscesses or with infected foreign bodies. Loculated collections of purulent material should be relieved by incision and drainage. Foreign bodies should be removed, if possible. Therapy always should be initiated with an antibiotic consistent with the local staphylococcal susceptibility patterns as well as the severity of infection. For most patients with serious *S. aureus* infection, intravenous (IV) treatment is recommended until the patient has become afebrile and other signs of infection have improved. Oral therapy is often continued for a time, especially in patients with chronic infection or underlying host defense problems. Serious *S. aureus* infections, with or without abscesses, tend to persist and recur, necessitating prolonged therapy.

Treatment of *S. aureus* osteomyelitis (Chapter 704), meningitis (Chapter 621.1), and endocarditis (Chapter 464) is discussed in the respective chapters on these diagnoses.

Initial treatment for serious infections thought to be caused by **methicillin-susceptible *S. aureus* (MSSA)** should include semisynthetic penicillin (e.g., nafcillin) or a first-generation cephalosporin (e.g., cefazolin). Penicillin and ampicillin are not appropriate, because >90% of all staphylococci isolated, regardless of source, are resistant to these agents. Addition of a β-lactamase inhibitor (clavulanic acid, sulbactam, tazobactam) to a penicillin-based drug also confers antistaphylococcal activity but has no effect on MRSA. The spectrum of these agents (which includes gram-negative bacteria) can be an advantage when broad empirical coverage is needed, but narrower coverage should be selected once *S. aureus* is identified. *Antistaphylococcal penicillins and most cephalosporins do not provide activity against MRSA.*

For initial treatment for penicillin-allergic individuals and those with suspected serious infections caused by MRSA, **vancomycin** is the preferred therapy**.** Serum levels of vancomycin should be monitored, with serum trough concentrations of 10-20 µg/mL, depending on the location and severity of infection. Rare vancomycin intermediate and vancomycin-resistant strains of *S. aureus* have also been reported, mostly in patients being treated with vancomycin. For critically ill patients with suspected *S. aureus* , empirical therapy with both vancomycin and nafcillin should be considered until cultures results are available. *Initial treatment with IV **clindamycin,** followed by a transition to oral clindamycin, has been effective in bone, joint, and soft tissue* *infection; however, not all strains of MSSA or MRSA are susceptible to clindamycin.* Inducible clindamycin resistance in isolates initially reported as susceptible must be ruled out by D-test or molecular methods. Clindamycin is bacteriostatic and should not be used to treat endocarditis, persistent bacteremia, or CNS infections caused by *S. aureus*. Given that the mechanism of action of clindamycin involves inhibition or protein synthesis, many experts use clindamycin to treat *S. aureus* toxin–mediated illnesses (e.g., TSS) to inhibit toxin production.

Although the very-broad- spectrum carbapenems (meropenem, ertapenem, and imipenem) have activity against MSSA, they have no activity against MRSA. As a result, carbapenems are rarely used for empirical therapy of possible staphylococcal infection and are too broad in most cases for use in identified MSSA infections. Quinolone antibiotics have unpredictable activity against MSSA and no activity against MRSA. **Linezolid** and **daptomycin** are useful for serious *S. aureus* infections, particularly those caused by MRSA, when treatment with vancomycin is ineffective or not tolerated.(Table 208.1). A number of novel antistaphylococcal antibiotics have emerged for use in resistant or refractory MSSA and MRSA infection in adults that may be required for pediatric therapy in select patients under the guidance of a pediatric infectious disease specialist. These include **ceftaroline** , a broad-spectrum antistaphylococcal cephalosporin, and **oritavancin** and **dalbavancin** , lipoglycopeptides structurally related to vancomycin with very long half-lives and broad activity against gram-positive organisms. **Rifampin** or **gentamicin** may be added to a β-lactam or vancomycin for synergy in serious infections such as endocarditis, particularly when prosthetic valve material is involved.

Table 208.1

Parenteral Antimicrobial Agent(s) for Treatment of Serious *Staphylococcus aureus* Infections

SUSCEPTIBILITY	ANTIMICROBIALS	COMMENTS
I. INITIAL EMPIRICAL THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)		
Drugs of choice:	Vancomycin + nafcillin or oxacillin	For life-threatening infections (e.g., septicemia, endocarditis, CNS infection); linezolid could be substituted if the patient has received several recent courses of vancomycin
	Vancomycin	For non–life-threatening infection without signs of severe sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and

		infection in the community are substantial
	Cefazolin or nafcillin	For non–life-threatening infection when low likelihood of MRSA is suspected
	Clindamycin	For non–life-threatening infection without signs of severe sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is low
II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT *S. aureus*		
Drugs of choice:	Nafcillin[*]	
Alternatives (depending on susceptibility results):	Cefazolin	
	Clindamycin	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
	Vancomycin	Only for penicillin- and cephalosporin-allergic patients
	Ampicillin + sulbactam	When broader coverage, including gram-negative organisms is required
III. METHICILLIN-RESISTANT *S. aureus* (MRSA)		
Drugs of choice:	Vancomycin[*]	
Alternatives: susceptibility testing results available before alternative drugs are used	Clindamycin (if susceptible)	
	Daptomycin [†]	
	Linezolid [†]	
	Trimethoprim-sulfamethoxazole	

[*] One of the adjunctive agents, gentamicin or rifampin, should be added to the therapeutic regimen for life-threatening infections such as endocarditis or central nervous system (CNS) infection. Consultation with an infectious diseases specialist should be considered to determine which agent to use and duration of use.

[†] Linezolid and daptomycin are agents with activity in vitro and efficacy with multidrug-resistant, gram-positive organisms, including *S. aureus* . Because experience with these agents in children is limited, consultation with an infectious diseases specialist should be considered before use. Daptomycin is ineffective for treatment of pneumonia.

In many infections, oral antimicrobials may be substituted to complete the course of treatment, after an initial period of parenteral therapy and determination of antimicrobial susceptibilities, or can be used as initial treatment in less severe infections. **Dicloxacillin** (50-100 mg/kg/24 hr divided 4 times daily PO) and **cephalexin** (25-100 mg/kg/24 hr divided 3-4 times daily PO) are absorbed well orally (PO) and are effective against MSSA. **Amoxicillin-clavulanate** (40-80 mg amoxicillin/kg/24 hr divided 3 times daily PO) is also effective when a broader spectrum of coverage is required. Clindamycin (30-40 mg/kg/24 hr divided 3-4 times daily PO) is highly absorbed from the intestinal tract and is frequently used for empirical coverage when both MRSA and MSSA are possible, as well as for susceptible MRSA infections or for MSSA in penicillin/cephalosporin-allergic patients**.** Compliance with oral clindamycin may be limited in small children because of poor palatability of oral formulations. **Trimethoprim-sulfamethoxazole** (TMP-SMX) may be an effective oral antibiotic for many strains of both MSSA and MRSA. Oral linezolid is an option for severe MRSA infections that have improved but require ongoing therapy when more common options are not tolerated or are ineffective due to resistance patterns. Despite in vitro susceptibility of *S. aureus* to ciprofloxacin and other quinolone antibiotics, these agents should *not* be used in serious staphylococcal infections, because their use is associated with rapid development of resistance.

The **duration** of oral therapy depends on the response, as determined by the clinical response and in some cases, radiologic and laboratory findings.

Prognosis

Untreated *S. aureus* septicemia is associated with a high fatality rate, which has been reduced significantly by appropriate antibiotic treatment. *S. aureus* pneumonia can be fatal at any age but is more likely to be associated with high morbidity and mortality in young infants or in patients whose therapy has been delayed. Prognosis also may be influenced by numerous host factors, including nutrition, immunologic competence, and the presence or absence of other debilitating diseases. In most cases with abscess formation, surgical drainage is necessary.

Prevention

S. aureus infection is transmitted primarily by direct contact. Strict attention to **hand hygiene** is the most effective measure for preventing the spread of staphylococci from between individuals (see Chapter 198). Use of a hand wash containing chlorhexidine or alcohol is recommended. In hospitals or other institutional settings, all persons with acute *S. aureus* infections should be isolated until they have been treated adequately. There should be constant surveillance for nosocomial *S. aureus* infections within hospitals. When MRSA is recovered, strict isolation of affected patients has been shown to be the most effective method for preventing nosocomial spread of infection. When hospital-acquired infections do occur, clusters of nosocomial cases may be defined by molecular typing, and if associated with a singular molecular strain, it may also be necessary to identify colonized hospital personnel and attempt to eradicate carriage in affected individuals.

A number of protocols are aimed at **decolonization** in patients with recurrent *S. aureus* skin infection, particularly in individuals colonized with MRSA. These often involve various combinations of decontaminating baths (hypochlorite, 1 tsp common bleach solution per gallon of water, or chlorhexidine 4% soap used weekly), an appropriate oral antibiotic, nasal mupirocin twice daily for 1 wk, and cleaning of household linens in hot water. Although success is not universal, recurrent infections may be reduced, particularly when eradication is done in both the patient and frequent or household contacts. Most cases of mild, recurrent disease will resolve in time without these measures.

Because of the potential severity of infections with *S. aureus* and concerns about emerging resistance, much work has focused on developing a staphylococcal vaccine for use in high-risk patients, but to date, clinical trials have been disappointing. Because *S. aureus* is frequently a co-infection in severe influenza infections, an indirect preventive impact against staphylococcal pneumonia and tracheitis may be achieved though annual influenza vaccination.

Food poisoning may be prevented by excluding individuals with *S. aureus* infections of the skin from the preparation and handling of food. Prepared foods should be eaten immediately or refrigerated appropriately to prevent multiplication of *S. aureus* that may have contaminated the food (see Chapter 366).

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208.2

Toxic Shock Syndrome

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Toxic shock syndrome (TSS) is an acute and potentially severe illness characterized by fever, hypotension, erythematous rash with subsequent desquamation on the hands and feet, and multisystem involvement, including vomiting, diarrhea, myalgias, nonfocal neurologic abnormalities, conjunctival hyperemia, and strawberry tongue.

Etiology

TSS is caused by TSST-1–producing and some enterotoxin-producing strains of *S. aureus*, which may colonize the vagina or cause focal sites of staphylococcal infection.

Epidemiology

TSS continues to occur in the United States in men, women, and children, with highest rates in menstruating women 15-25 yr of age. **Nonmenstrual TSS** is associated with *S. aureus* infected nasal packing and wounds, sinusitis, tracheitis, pneumonia, empyema, abscesses, burns, osteomyelitis, and primary bacteremia. Most strains of *S. aureus* associated with TSS are methicillin susceptible because USA300, the predominant isolate of community-acquired MRSA in the United States, does not contain genes expressing the most common TSS superantigens.

Pathogenesis

The primary toxin associated with TSS is TSST-1, although a significant proportion of nonmenstrual TSS is caused by one or more staphylococcal enterotoxins. These toxins act as a **superantigens** , which trigger cytokine release causing massive loss of fluid from the intravascular space and end-organ cellular injury. Epidemiologic and in vitro studies suggest that these toxins are selectively produced in a clinical environment consisting of a neutral pH, a high $P\mathrm{CO}_2$, and an aerobic $P\mathrm{O}_2$, which are the conditions found in abscesses and the vagina with tampon use during menstruation. The risk factors for symptomatic disease include a nonimmune host colonized with a toxin-producing organism, which is exposed to focal growth conditions (menstruation plus tampon use or abscess) that induce toxin production. Some hosts may have a varied cytokine response to exposure to TSST-1, helping to explain a spectrum of severity of TSS that may include staphylococcal scarlet fever. The overall mortality rate of treated patients is 3–5% with early treatment.

Approximately 90% of adults have antibody to TSST-1 without a history of clinical TSS, suggesting that most individuals are colonized at some point with a toxin-producing organism at a site (anterior nares) where low-grade or inactive toxin exposure results in an immune response without disease.

Clinical Manifestations

The diagnosis of TSS is based on clinical manifestations (Table 208.2). Milder cases and those with incomplete clinical characteristics may be common, particularly if the nidus of infection is addressed quickly (e.g., removal of a tampon). The onset of classic TSS is abrupt, with high fever, vomiting, and diarrhea, and is accompanied by sore throat, headache, and myalgias. A diffuse erythematous macular rash (sunburn-like or scarlatiniform) appears within 24 hr and may be associated with hyperemia of pharyngeal, conjunctival, and vaginal mucous membranes. A strawberry tongue is common. Symptoms may include alterations in the level of consciousness, oliguria, and hypotension, which in severe cases may progress to shock and disseminated intravascular coagulation. Complications, including acute respiratory distress syndrome (ARDS), myocardial dysfunction, and renal failure, are commensurate with the degree of shock. Recovery occurs within 7-10 days and is associated with desquamation, particularly of palms and soles; hair and nail loss have also been observed after 1-2 mo. Immunity to the toxins is slow to develop, so recurrences can occur, especially if there is inadequate antibiotic treatment and/or recurrent tampon use. Many cases of apparent scarlet fever without shock may be caused by TSST-1–producing *S. aureus* strains.

Table 208.2

Diagnostic Criteria of Staphylococcal Toxic Shock Syndrome

MAJOR CRITERIA (ALL REQUIRED)
Acute fever; temperature >38.8°C (101.8°F) Hypotension (orthostatic, shock; blood pressure below age-appropriate norms) Rash (erythroderma with convalescent desquamation)
MINOR CRITERIA (ANY 3 OR MORE)
Mucous membrane inflammation (vaginal, oropharyngeal or conjunctival hyperemia, strawberry tongue) Vomiting, diarrhea Liver abnormalities (bilirubin or transaminase greater than twice the upper limit of normal) Renal abnormalities (blood urea nitrogen or creatinine greater than twice the upper limit of normal, or greater than 5 white blood cells per high-power field) Muscle abnormalities (myalgia or creatinine phosphokinase greater than twice the upper limit of normal) Central nervous system abnormalities (alteration in consciousness without focal neurologic signs) Thrombocytopenia ($\leq$100,000/mm^3)
EXCLUSIONARY CRITERIA
Absence of another explanation Negative blood cultures (except occasionally for *Staphylococcus aureus*)

Data from Kimberlin DW, Brady MT, Jackson MA, Long SS, editors*: Red book: 2015 report of the Committee on Infectious Diseases* , ed 30, Elk Grove Village, IL, 2015, American Academy of Pediatrics.

Diagnosis

There is no specific laboratory test, and diagnosis depends on meeting certain clinical and laboratory criteria in the absence of an alternate diagnosis (see Fig. 208.2). Appropriate tests reveal involvement of multiple organ systems, including the hepatic, renal, muscular, gastrointestinal, cardiopulmonary, and central nervous systems. Bacterial cultures of the associated focus (vagina, abscess) before administration of antibiotics usually yield *S. aureus*, although this is not a required element of the definition.

Differential Diagnosis

Group A streptococci can cause a similar TSS-like illness, termed **streptococcal TSS** (see Chapter 210), which is often associated with severe streptococcal sepsis or a focal streptococcal infection such as cellulitis, necrotizing fasciitis, or pneumonia.

Kawasaki disease closely resembles TSS clinically but is usually not as severe or rapidly progressive. Both conditions are associated with fever unresponsive to antibiotics, hyperemia of mucous membranes, and an erythematous rash with subsequent desquamation. However, many of the clinical features of TSS are rare in Kawasaki disease, including diffuse myalgia, vomiting, abdominal pain, diarrhea, azotemia, hypotension, ARDS, and shock (see Chapter 191). Kawasaki disease typically occurs in children <5 yr old. Scarlet fever, Rocky Mountain spotted fever, leptospirosis, toxic epidermal necrolysis, sepsis, and measles must also be considered in the differential diagnosis.

Treatment

Identification and drainage/removal of any focal source of infection (e.g., abscess, tampon, nasal packing), when present, is essential. Recommended antibiotic therapy for TSS should include the combination of a β-lactamase–resistant antistaphylococcal antibiotic (nafcillin, oxacillin, or cefazolin) plus clindamycin to reduce toxin production. Although TSS is most often caused by MSSA, clinicians should consider use of vancomycin in place of the β-lactam in areas where MRSA rates are very high, when hospital acquired MRSA is suspected, and when the clinical picture overlaps with staphylococcal sepsis.

TSS often requires intensive supportive care, including aggressive **fluid replacement** to prevent or treat hypotension, renal failure, and cardiovascular collapse. Inotropic agents may be needed to treat shock; corticosteroids and intravenous immunoglobulin may be helpful in severe cases.

Prevention

The risk for acquiring menstrual TSS is low (1-2 cases/100,000 menstruating women). Changing tampons at least every 8 hr is recommended. If a fever, rash, or dizziness develops during menstruation, any tampon should be removed immediately and medical attention sought. Antistaphylococcal therapy and avoidance of tampon use with subsequent menstrual cycles may also reduce the risk for recurrent menstrual TSS.

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208.3

Coagulase-Negative Staphylococci

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At present, there are approximately 30 species of coagulase-negative staphylococci (**CoNS**) affecting or colonizing humans. *Staphylococcus epidermidis* and, less often, *Staphylococcus hominis, S. haemolyticus,* and others, are widely distributed on the skin and are significant causes of nosocomial infection, particularly in the bloodstream of neonatal and immunocompromised hosts, in surgical patients, and in those with indwelling catheters and other medical devices. *Staphylococcus saprophyticus* is a common cause of urinary tract infection (UTI). *Staphylococcus lugdunensis* has been increasingly recognized as a cause of potentially severe infection.

Epidemiology

In the United States, CoNS may be the most common cause of hospital-acquired infection, particularly in NICUs. In many instances, growth of CoNS from clinical specimens represents contamination from skin rather than a cause of true disease, posing significant challenges for clinicians and infection control specialists. CoNS are normal inhabitants of the human skin, throat, mouth, vagina, and urethra. *S. epidermidis* is the most common and persistent species, representing 65–90% of staphylococci present on the skin and mucous membranes. Colonization, sometimes with strains acquired from hospital staff, precedes infection. Alternatively, direct inoculation during surgery may initiate infection of CSF shunts, prosthetic valves, or indwelling vascular lines. For epidemiologic purposes, CoNS can be identified on the basis of molecular DNA methods.

Pathogenesis

CoNS produce an exopolysaccharide protective biofilm, particularly on indwelling medical devices, that surrounds the organism and may enhance adhesion to foreign surfaces, resist phagocytosis, and impair penetration of antibiotics. However, the low virulence of CoNS usually requires the presence of another factor for development of clinical disease. Of these, the most significant is the presence of an indwelling catheter or other medical device, including central venous catheters (CVCs), hemodialysis shunts and grafts, CSF shunts (meningitis), peritoneal dialysis catheters (peritonitis), pacemaker wires and electrodes (local infection), prosthetic cardiac valves (endocarditis), and prosthetic joints (arthritis). Other risk factors for the development of infection include immature or compromised immunity and significant exposure to antibiotics.

Clinical Manifestations

Bacteremia

CoNS, specifically *S. epidermidis,* are the most common cause of nosocomial bacteremia, usually in association with central vascular catheters. In neonates, CoNS bacteremia, with or without a CVC, may be manifested as apnea, bradycardia, temperature instability, abdominal distention, hematochezia, meningitis in the absence of CSF pleocytosis, and cutaneous abscesses. Persistence of positive blood cultures despite adequate antimicrobial therapy is common, particularly when catheters are not removed. In older children, CoNS bacteremia is indolent and is not usually associated with overwhelming septic shock.

Endocarditis

Infection of native heart valves or the right atrial wall secondary to an infected thrombosis at the end of a central line may produce endocarditis. *S. epidermidis* and other CoNS may rarely produce native valve subacute endocarditis in previously normal patients without a CVC. CoNS is a common cause of prosthetic valve endocarditis, presumably a result of inoculation at surgery. Infection of the valve sewing ring, with abscess formation and dissection, produces valve dysfunction, dehiscence, arrhythmias, or valve obstruction (see Chapter 464). *S. lugdunensis* has been increasingly associated with severe endocardial infection in adults, but its role as a significant pediatric pathogen is unclear.

Central Venous Catheter Infection

CVCs become infected through the exit site and subcutaneous tunnel, which provide a direct path to the bloodstream. *S. epidermidis* is the most frequent pathogen, in part because of its high rate of cutaneous colonization. Line sepsis is usually manifested as fever and leukocytosis; tenderness and erythema may be present at the exit site or along the subcutaneous tunnel. Catheter thrombosis may complicate line sepsis. Disease severity with CoNS is often less severe than other etiologies of line infection.

Cerebrospinal Fluid Shunts

CoNS, introduced at surgery, is the most common pathogen associated with CSF shunt meningitis. Most infections (70–80%) occur within 2 mo of the operation and manifest as signs of meningeal irritation, fever, increased intracranial pressure (headache), or peritonitis from the intraabdominal position of the distal end of the shunt tubing.

Urinary Tract Infection

S. saprophyticus is a common cause of primary UTIs in sexually active females. Manifestations are similar to those characteristics of UTI caused by *Escherichia coli* (see Chapter 553). CoNS also cause asymptomatic UTI in hospitalized patients with urinary catheters and after urinary tract surgery or transplantation.

Diagnosis

Because *S. epidermidis* is a common skin inhabitant and may contaminate poorly collected blood cultures, differentiating bacteremia from contamination is often difficult. True bacteremia should be suspected if blood cultures grow rapidly (within 24 hr), >1 blood culture is positive with the same CoNS strain, cultures from both line and peripheral sites are positive, and clinical and laboratory signs and symptoms compatible with CoNS sepsis are present and subsequently resolve with appropriate therapy. No blood culture that is positive for CoNS in a neonate or patient with an intravascular catheter should be considered contaminated without careful assessment of the foregoing criteria and examination of the patient. Before initiating presumptive antimicrobial therapy in such patients, it is always prudent to draw 2 separate blood cultures to facilitate subsequent interpretation if CoNS is grown. Increasingly, PCR techniques can allow rapid identification of CoNS in positive blood cultures; use of such methods may prevent unnecessary antibiotic exposure.

Treatment

Because most CoNS strains are resistant to methicillin, **vancomycin** is the initial drug of choice. The addition of rifampin to vancomycin may increase antimicrobial efficacy due to good penetration of this antibiotic into biofilms on indwelling medical devices. Other antibiotics with good in vitro activity against CoNS may be considered in certain circumstances. These include linezolid, quinupristin-dalfopristin, and daptomycin. Antibiotics with potential activity include teicoplanin, clindamycin, levofloxacin, and TMP-SMX. Removal of an infected catheter is ideal. However, this is not always possible because of the therapeutic requirements of the underlying disease (e.g., nutrition for short bowel syndrome, chemotherapy for malignancy). A trial of IV vancomycin (potentially with addition of rifampin) is indicated to attempt to preserve the use of the central line, as long as systemic manifestations of infection are not severe. Antibiotic therapy given through an infected CVC (alternating lumens if multiple) and the use of antibiotic locks in conjunction with systemic therapy may increase the likelihood of curing CoNS line sepsis without line removal. Prosthetic heart valves and CSF shunts usually need to be removed to treat the infection adequately.

Peritonitis caused by *S. epidermidis* in patients on continuous ambulatory peritoneal dialysis is an infection that may be treated with IV or intraperitoneal antibiotics without removing the dialysis catheter. If the organism is resistant to methicillin, vancomycin adjusted for renal function is appropriate therapy. Unlike most CoNS, *S. saprophyticus* is usually methicillin susceptible, and UTI can typically be treated with a first-generation cephalosporin (cephalexin), amoxicillin–clavulanic acid, or TMP-SMX.

Prognosis

Most episodes of CoNS bacteremia respond successfully to antibiotics and removal of any foreign body that is present. Poor prognosis is associated with malignancy, neutropenia, and infected prosthetic or native heart valves. CoNS increases morbidity, duration of hospitalization, and mortality among patients with underlying complicated illnesses.

Prevention

Iatrogenic morbidity and resource utilization caused by contaminated blood cultures can be reduced by using gloves, good skin preparatory techniques, and trained, dedicated personnel to draw blood cultures. Prevention of CoNS infection of indwelling lines includes basic techniques such as central line care “bundles,” which incorporate good hand hygiene, decontamination of hubs and ports before access, minimizing frequency of access, and frequent replacement of external connections and infusion materials. In a recent large randomized controlled trial in children, antibiotic-impregnated catheters significantly reduced rates of central line–associated bloodstream infections.

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CHAPTER 209

Streptococcus pneumoniae (Pneumococcus)

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Streptococcus pneumoniae (pneumococcus) is an important pathogen that kills more than 1 million children each year. Childhood pneumococcal disease is prevalent and typically severe, causes numerous clinical syndromes, and is a major cause of life-threatening pneumonia, bacteremia, and meningitis. Antimicrobial resistance in pneumococcus is a major public health problem, with 15–30% of isolates worldwide classified as **multidrug resistant** (**MDR** ; resistant to ≥3 classes of antibiotics). Pneumococcal polysaccharide-protein conjugate vaccines (**PCVs**) developed for infants have been highly successful in the control of disease caused by virulent vaccine-specific serotypes. Epidemiologic surveillance reveals a dynamic pneumococcal ecology with emergence of highly virulent, MDR serotypes. Ongoing vaccine development and distribution efforts remain the best approach to control this threat to childhood health.

Etiology

Streptococcus pneumoniae is a gram-positive, lancet-shaped, polysaccharide encapsulated diplococcus, occurring occasionally as individual cocci or in chains; >90 serotypes have been identified by type-specific capsular polysaccharides. Antisera to some pneumococcal polysaccharides cross-react with other pneumococcal types, defining serogroups (e.g., 6A and 6B). Encapsulated strains cause most serious disease in humans. Capsular polysaccharides impede phagocytosis. Virulence is related in part to capsular size, but pneumococcal types with capsules of the same size can vary widely in virulence.

On solid media, *S. pneumoniae* forms unpigmented, umbilicated colonies surrounded by a zone of incomplete (α) hemolysis. *S. pneumoniae* is bile soluble (i.e., 10% deoxycholate) and optochin sensitive. *S. pneumoniae* is closely related to the viridans groups of *Streptococcus mitis* , which typically overlap phenotypically with pneumococci. The conventional laboratory definition of pneumococci continues to rely on bile and optochin sensitivity, although considerable confusion occurs in distinguishing pneumococci and other α-hemolytic streptococci. Pneumococcal capsules can be microscopically visualized and typed by exposing organisms to type-specific antisera that combine with their unique capsular polysaccharide, rendering the capsule refractile (Quellung reaction). Specific antibodies to capsular polysaccharides confer protection on the host, promoting opsonization and phagocytosis. Additionally, $CD4^+$ T cells have a direct role in antibody-independent immunity to pneumococcal nasopharyngeal colonization. Conjugated PCVs promote T-cell immunity and protect against pneumococcal colonization, in contrast to the pneumococcal polysaccharide vaccine (PPSV23) that is used in adults and certain high-risk pediatric populations and that does not affect nasopharyngeal colonization.

Epidemiology

Most healthy individuals carry various *S. pneumoniae* serotypes in their upper respiratory tract; >90% of children between 6 mo and 5 yr of age harbor *S. pneumoniae* in the nasopharynx at some time. A single serotype usually is carried by a given individual for an extended period (45 days to 6 mo). Carriage does not consistently induce local or systemic immunity sufficient to prevent later reacquisition of the same serotype. Rates of pneumococcal carriage peak during the 1st and 2nd yr of life and decline gradually thereafter. Carriage rates are highest in institutional setting and during the winter, and rates are lowest in summer. Nasopharyngeal carriage of pneumococci is common among young children attending out-of-home care, with rates of 21–59% in point prevalence studies.

Before the introduction of heptavalent pneumococcal conjugate vaccine (**PCV7**) in 2000, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F caused most invasive childhood pneumococcal infections in the United States. The introduction of PCVs resulted in a marked decrease in **invasive pneumococcal**

infections (IPIs) in children. By 2005, however, IPIs began to increase slightly because of an increase in non-PCV7 serotypes, particularly serotype 19A. Serotype replacement can result from expansion of existing nonvaccine serotypes, as well as from vaccine-type pneumococci acquiring the polysaccharide capsule of a nonvaccine serotype (**serotype switching**). Since the introduction of PCV13 in 2010 in the United States, there has been a decline in IPIs caused by new vaccine serotypes, including 19A. Nonetheless, 19A remains an important cause of meningitis. Indirect protection of unvaccinated persons has occurred since PCV introduction, and this *herd protection* is likely a result of decreases in nasopharyngeal carriage of virulent pneumococcal vaccine serotypes.

S. pneumoniae is the most frequent cause of bacteremia, bacterial pneumonia, otitis media, and bacterial meningitis in children. The decreased ability in children <2 yr old to produce antibody against the T-cell–independent polysaccharide antigens and the high prevalence of colonization may explain an increased susceptibility to pneumococcal infection and the decreased effectiveness of polysaccharide vaccines. Children at increased risk of pneumococcal infections include those with sickle cell disease, asplenia, deficiencies in humoral (B-cell) and complement-mediated immunity, HIV infection, certain malignancies (e.g., leukemia, lymphoma), chronic heart, lung, or renal disease (particularly nephrotic syndrome), cerebrospinal fluid (CSF) leak, and cochlear implants. Table 209.1 lists other high-risk groups. Some American Indian, Alaska Native, and African American children may also be at increased risk. Children <5 yr old in out-of-home daycare are at increased risk (approximately 2-fold higher) of experiencing IPIs than other children. Males are more frequently affected than females. Because immunocompetent vaccinated children have had fever episodes of IPI, the proportion of infected children with immunologic risk factors has increased (estimated at 20%).

Table 209.1

Children at Increased Risk of Invasive Pneumococcal Infection

RISK GROUP	CONDITION
Immunocompetent children	Chronic heart disease[*]
	Chronic lung disease [†]
	Diabetes mellitus
	Cerebrospinal fluid leaks

	Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies
	Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasm, leukemia, lymphoma, and Hodgkin disease; or stem cell and solid-organ transplantation
	Congenital immunodeficiency [‡] Toll-like receptor signaling defects (IRAK-4, IKBKG, MyD88) *NEMO* gene defects

[*] Particularly cyanotic congenital heart disease and cardiac failure.

[†] Including asthma if treated with high-dose oral corticosteroid therapy.

[‡] Includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1,C2,C3, and C4 deficiency; and phagocytic disorders, excluding chronic granulomatous disease.

Adapted from Centers for Disease Control and Prevention: Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children: Advisory Committee on Immunization Practices, *MMWR* 59(RR-11):1–18, 2010 (Table 2).

Pneumococcal disease usually occurs sporadically but can be spread from person to person by respiratory droplet transmission. *S. pneumoniae* is an important cause of secondary bacterial pneumonia in patients with influenza. During influenza epidemics and pandemics, most deaths result from bacterial pneumonia, and pneumococcus is the predominant bacterial pathogen isolated in this setting. Pneumococcal copathogenicity may be important in disease caused by other respiratory viruses as well.

Pathogenesis

Invasion of the host is affected by a number of factors. Nonspecific defense mechanisms, including the presence of other bacteria in the nasopharynx, may limit multiplication of pneumococci. Aspiration of secretions containing pneumococci is hindered by the epiglottic reflex and by respiratory epithelial cell cilia, which move infected mucus toward the pharynx. Similarly, normal ciliary flow of fluid from the middle ear through the eustachian tube and sinuses to the nasopharynx usually prevents infection with nasopharyngeal flora, including pneumococci. Interference with these normal clearance mechanisms by allergy, viral infection, or irritants (e.g., smoke) may allow colonization and subsequent infection with these organisms in otherwise normally sterile sites.

Virulent pneumococci are intrinsically resistant to phagocytosis by alveolar macrophages. Pneumococcal disease frequently is facilitated by viral respiratory tract infection, which may produce mucosal injury, diminish epithelial cell ciliary activity, and depress the function of alveolar macrophages and neutrophils. Phagocytosis may be impeded by respiratory secretions and alveolar exudate. In the lungs and other tissues, the spread of infection is facilitated by the antiphagocytic properties of the pneumococcal capsule. Surface fluids of the respiratory tract contain only small amounts of immunoglobulin G and are deficient in complement. During inflammation, there is limited influx of IgG, complement, and neutrophils. Phagocytosis of bacteria by neutrophils may occur, but normal human serum may not opsonize pneumococci and facilitate phagocytosis by alveolar macrophages. In tissues, pneumococci multiply and spread through the lymphatics or bloodstream or, less often, by direct extension from a local site of infection (e.g., sinuses). In bacteremia the severity of disease is related to the number of organisms in the bloodstream and to the integrity of specific host defenses. A poor prognosis correlates with very large numbers of pneumococci and high concentrations of capsular polysaccharide in the blood and CSF.

Invasive pneumococcal disease is 30- to 100-fold more prevalent in children with sickle cell disease and other hemoglobinopathies and in children with congenital or surgical asplenia than in the general population. This risk is greatest in infants <2 yr old, the age when antibody production to most serotypes is poor. The increased frequency of pneumococcal disease in asplenic persons is related to both deficient opsonization of pneumococci and absence of clearance by the spleen of circulating bacteria. Children with sickle cell disease also have deficits in the antibody-independent properdin (alternative) pathway of complement activation, in addition to functional asplenia. Both complement pathways contribute to antibody-independent and antibody-dependent **opsonophagocytosis** of pneumococci. With advancing age (e.g., >5 yr), children with sickle cell disease produce anticapsular antibody, augmenting antibody-dependent opsonophagocytosis and greatly reducing, but not eliminating, the risk of severe pneumococcal disease. Deficiency of many of the complement components (e.g., C2 and C3) is associated with recurrent pyogenic infection, including *S. pneumoniae* infection. The efficacy of phagocytosis also is diminished in patients with B- and T-cell immunodeficiency syndromes (e.g., agammaglobulinemia, severe combined immunodeficiency) or loss of immunoglobulin (e.g., nephrotic syndrome) and is largely caused by a deficiency of opsonic anticapsular antibody. These observations suggest that opsonization of pneumococci depends on the alternative complement pathway in antibody-deficient persons, and that recovery from pneumococcal disease depends on the development of anticapsular antibodies that act as opsonins, enhancing phagocytosis and killing of pneumococci. Children with HIV infection also have high rates of IPI similar to or greater than rates in children with sickle cell disease, although rates of invasive pneumococcal disease decreased after the introduction of highly active antiretroviral therapy (HAART).

Clinical Manifestations

The signs and symptoms of pneumococcal infection are related to the anatomic site of disease. Common clinical syndromes include otitis media (Chapter 658), sinusitis (see Chapter 408), pneumonia (Fig. 209.1) (Chapter 428), and sepsis (Chapter 88). Before routine use of PCVs, pneumococci caused >80% of bacteremia episodes in infants 3-36 mo old with fever without an identifiable source (i.e., occult bacteremia). Bacteremia may be followed by meningitis (Chapter 621), osteomyelitis (Chapter 704), suppurative (septic) arthritis (Chapter 705), endocarditis (Chapter 464), and rarely, brain abscess (Chapter 622). Primary peritonitis (Chapter 398.1) may occur in children with peritoneal effusions caused by nephrotic syndrome and other ascites-producing conditions. Local complications of infection may occur, causing empyema, pericarditis, mastoiditis, epidural abscess, periorbital cellulitis, or meningitis. Hemolytic-uremic syndrome (Chapter 511.04) and disseminated intravascular coagulation also occur as rare complications of pneumococcal infections. Epidemic conjunctivitis caused by nonencapsulated or encapsulated pneumococci occurs as well.

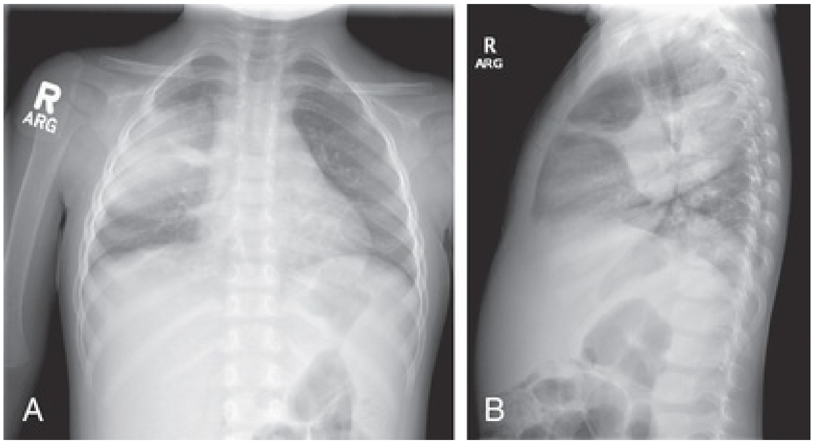

FIG. 209.1 **Bacterial pneumonia. “Round” pneumonia caused by *Streptococcus pneumoniae* in 2 yr old girl with a 2-day history of cough, high fever, leukocytosis, and back pain.**

Diagnosis

The diagnosis of pneumococcal infection is established by recovery of *S. pneumoniae* from the site of infection or the blood/sterile body fluid. Although pneumococci may be found in the nose or throat of patients with otitis media, pneumonia, septicemia, or meningitis, cultures of these locations are generally not helpful for diagnosis, since they are not indicative of causation. Blood cultures should be obtained in children with pneumonia, meningitis, arthritis, osteomyelitis, peritonitis, pericarditis, or gangrenous skin lesions. Because of the implementation of universal vaccination with PCVs, there has been a substantial decrease in the incidence of occult bacteremia, but blood cultures should still be considered in febrile patients with clinical toxicity or significant leukocytosis. Leukocytosis often is pronounced, with total white blood cell counts frequently >15,000/µL. In severe cases of pneumococcal disease, WBC count may be low.

Pneumococci can be identified in body fluids as gram-positive, lancet-shaped diplococci. Early in the course of pneumococcal meningitis, many bacteria may be seen in relatively acellular CSF. With current methods of continuously monitored blood culture systems, the average time to isolation of pneumococcal organisms is 14-15 hr. Pneumococcal latex agglutination tests for urine or other body fluids suffer from poor sensitivity and add little to gram-stained fluids and standard cultures. Multiplex real-time polymerase chain reaction (PCR) assays are specific and more sensitive than culture of pleural fluid, CSF, and blood, particularly in patients who have recently received antimicrobial therapy.

Additional investigational assays, including serotype-specific urinary antigen detection, have not been validated.

Treatment

Antimicrobial resistance among *S. pneumoniae* continues to be a serious healthcare concern, especially for the widely used β-lactams, macrolides, and fluoroquinolones. Serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F are the most common serotypes associated with resistance to penicillin. Consequently, the introduction of the 7- and 13-valent pneumococcal conjugate vaccines (**PCV7** and **PCV13**) has altered antimicrobial resistance patterns.

Resistance in pneumococcal organisms to penicillin and the extended-spectrum cephalosporins cefotaxime and ceftriaxone is defined by the minimum inhibitory concentration (MIC), as well as clinical syndrome. Pneumococci are considered *susceptible*, *intermediate,* or *resistant* to various antibacterial agents based on specific MIC breakpoints. For patients with pneumococcal meningitis, penicillin-susceptible strains have MIC ≤0.06 µg/mL, and penicillin-resistant strains have MIC ≥0.12 µg/mL. For patients with nonmeningeal pneumococcal infections, breakpoints are higher; in particular, penicillin-susceptible strains have MIC ≤2 µg/mL, and penicillin resistant strains have MIC ≥8 µg/mL. For patients with meningitis, cefotaxime- and ceftriaxone-susceptible strains have MIC ≤0.5 µg/mL, and resistant strains have MIC ≥2.0 µg/mL. For patients with nonmeningeal pneumococcal disease, breakpoints are higher, and cefotaxime- and ceftriaxone-susceptible strains have MIC ≤1 µg/mL, and resistant strains have MIC ≥4 µg/mL. In cases when the pneumococcus is resistant to erythromycin but sensitive to clindamycin, *a D-test should be performed* to determine whether clindamycin resistance can be induced; if the D-test is positive, clindamycin should not be used to complete treatment of the patient. More than 30% of pneumococcal isolates are resistant to trimethoprim-sulfamethoxazole (TMP-SMX); levofloxacin resistance is low but has also been reported. All isolates from children with severe infections should be tested for antibiotic susceptibility, given widespread pneumococcal MDR strains. Resistance to vancomycin has not been seen at this time, but vancomycin-tolerant pneumococci that are killed at a slower rate have been reported, and these tolerant pneumococci may be associated with a worse clinical outcome. Linezolid is an oxazolidinone antibacterial with activity against MDR gram-positive organisms, including pneumococcus, and has been used in the treatment of MDR pneumococcal pneumonia, meningitis, and severe otitis. Despite early favorable studies, use of this drug is limited by myelosuppression and high cost, and linezolid resistance in pneumococcus is reported.

Children ≥1 mo old with suspected pneumococcal meningitis should be treated with combination therapy using **vancomycin** (60 mg/kg/24 hr divided every 6 hr IV), and high-dose **cefotaxime** (300 mg/kg/24 hr divided every 8 hr IV) or **ceftriaxone** (100 mg/kg/24 hr divided every 12 hr IV). Proven pneumococcal meningitis can be treated with penicillin alone, or cefotaxime or ceftriaxone alone, if the isolate is penicillin susceptible. If the organism is nonsusceptible (i.e., intermediate or full resistance) to penicillin but susceptible to cefotaxime and ceftriaxone, pneumococcal meningitis can be treated with cefotaxime or ceftriaxone alone. However, if the organism is nonsusceptible to penicillin and to cefotaxime or ceftriaxone, pneumococcal meningitis should be treated with combination vancomycin plus cefotaxime or ceftriaxone, not with vancomycin alone, and consideration should be given to the addition of **rifampin** . Some experts recommend use of corticosteroids in pneumococcal meningitis early in the course of disease, but data demonstrating clear benefit in children are lacking.

The 2011 Infectious Diseases Society of America guidelines recommend **amoxicillin** as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate, uncomplicated community-acquired pneumonia. **Ampicillin** or **penicillin G** may be administered to the fully immunized infant or school-age child admitted to a hospital ward with uncomplicated community-acquired pneumonia, when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae* . Empirical therapy with a parenteral **third-generation cephalosporin** (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents widespread penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia, given the degree of drug resistance currently seen in the United States.

Higher doses of amoxicillin (80-100 mg/kg/24 hr) have been successful in the treatment of otitis media caused by penicillin-nonsusceptible strains. If the patient has failed initial antibiotic therapy, alternative agents should be active against penicillin-nonsusceptible pneumococcus as well as β-lactamase–producing *Haemophilus influenzae* and *Moraxella catarrhalis* . These include high-dose oral amoxicillin-clavulanate (in the 14 : 1 formulation to reduce risk of diarrhea), oral cefdinir, cefpodoxime, or cefuroxime; or a 3-day course of intramuscular (IM) ceftriaxone if patients fail oral therapy. Empirical treatment of pneumococcal disease should be based on knowledge of susceptibility patterns in specific communities.

For individuals with a non–type I allergic reaction to penicillin, cephalosporins (standard dosing) can be used. For type I allergic reactions (immediate, anaphylactic) to β-lactam antibiotics, clindamycin and levofloxacin are preferred alternatives depending on the site of infection (e.g., clindamycin may be effective for pneumococcal infections other than meningitis). TMP-SMX may also be considered for susceptible strains, but erythromycin (or related macrolides; e.g., azithromycin, clarithromycin) should be avoided given high rates of resistance.

Prognosis

Prognosis depends on the integrity of host defenses, virulence and numbers of the infecting organism, age of the host, site and extent of the infection, and adequacy of treatment. The mortality rate for pneumococcal meningitis is approximately 10% in most studies. Pneumococcal meningitis results in sensorineural hearing loss in 20–30% of patients and can cause other serious neurologic sequelae, including paralysis, epilepsy, blindness, and intellectual deficits.

Prevention

The highly successful PCVs have resulted in a marked decrease in IPIs in children. PCVs provoke protective antibody responses in 90% of infants given these vaccines at 2, 4, and 6 mo of age, and greatly enhanced responses (e.g., immunologic memory) are apparent after vaccine doses given at 12-15 mo of age (Table 209.2). In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by up to 97% and to reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent

20% fewer tympanostomy tube placements than unvaccinated children. Following PCV13, a 64% reduction in IPIs caused by vaccine serotypes has been seen, particularly in children <5 yr old. The number of pneumococcal isolates and percentage of isolates with high-level penicillin resistance from cultures taken from children with otitis media or mastoiditis for clinical indications have decreased, largely related to decreases in serotype 19A. Rates of hospitalization for pneumococcal pneumonia among U.S. children decreased after PCV13 introduction. The number of cases of pneumococcal meningitis in children remain unchanged, but the proportion of PCV13 serotypes have decreased significantly. In addition, pneumococcal conjugate vaccines significantly reduce nasopharyngeal carriage of vaccine serotypes. PCVs have significantly decreased rates of invasive pneumococcal disease in children with sickle cell disease, and studies suggest substantial protection for HIV-infected children and splenectomized adults. Adverse events after the administration of PCV have included local swelling and redness and slightly increased rates of fever, when used in conjunction with other childhood vaccines.

Table 209.2

Comparison of Pneumococcal Vaccines Licensed in United States*

CARRIER PROTEIN	PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES	MANUFACTURER
Diphtheria CRM$_{197}$ protein	**4, 6B, 9V, 14, 18C, 19F, 23F**	Wyeth Lederle (PCV7, Prevnar)
Diphtheria CRM$_{197}$ protein	1, 3, **4,** 5, 6A, **6B,** 7F, **9V, 14, 18C,** 19A, **19F, 23F**	Wyeth Lederle (PCV13, Prevnar 13)
None	1, 2, 3, **4,** 5, **6B,** 7F, 8, 9N, **9V,** 10A, 11A, 12F, **14,** 15B, 17F, **18C,** 19A, **19F,** 20, 22F, **23F,** 33F	Sanofi Pasteur MSD (PPSV23, Pneumovax II)

* PCV7 serotypes in **bold** .

Immunologic responsiveness and efficacy after administration of pneumococcal polysaccharide vaccines (PPSV23) is unpredictable in children <2 yr old. PPSV23 contains purified polysaccharide of 23 pneumococcal serotypes responsible for >95% of invasive disease. The clinical efficacy of PPSV23 is controversial, and studies have yielded conflicting results.

Immunization with PCV13 is recommended for all infants on a schedule for primary immunization, in previously unvaccinated infants, and for transition for those partially vaccinated with PCV7 (Table 209.3). High-risk children ≥2 yr old, such as those with asplenia, sickle cell disease, some types of immune deficiency (e.g., antibody deficiencies), HIV infection, cochlear implant, CSF leak, diabetes mellitus, and chronic lung, heart, or kidney disease (including nephrotic syndrome), may benefit also from PPSV23 administered after 2 yr of age following priming with the scheduled doses of PCV13. Thus, it is recommended that children 2 yr of age and older with these underlying conditions receive supplemental vaccination with PPSV23. A 2nd dose of PPSV23 is recommended 5 yr after the 1st dose of PPSV23 for persons ≥2 yr old who are immunocompromised, have sickle cell disease, or functional or anatomic asplenia. Additional recommendations have been made for at-risk children 6-18 yr old (Table 209.4).

Table 209.3

Recommended Routine Vaccination Schedule for 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Among Infants and Children Who Have Not Received Previous Doses of 7-Valent Vaccine (PCV7) or PCV13, by Age at 1st Dose—United States, 2010

AGE AT 1ST DOSE (mo)	PRIMARY PCV13 SERIES*	PCV13 BOOSTER DOSE †
2-6	3 doses	1 dose at age 12-15 mo
7-11	2 doses	1 dose at age 12-15 mo
12-23	2 doses	—
24-59 (healthy children)	1 dose	—
24-71 (children with certain chronic diseases or immunocompromising conditions ‡)	2 doses	—

[*] Minimum interval between doses is 8 wk except for children vaccinated at age <12 mo, for whom minimum interval between doses is 4 wk. Minimum age for administration of 1st dose is 6 wk.

[†] Given at least 8 wk after the previous dose.

[‡] See Table 209.1 .

From Centers for Disease Control and Prevention. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children: Advisory Committee on Immunization Practices, *MMWR* 59(RR-11):1–18 (Table 8); 59:258–261, 2010 (Table 3).

Table 209.4

Medical Conditions or Other Indications for Administration of PCV13,* and Indications for PPSV23 † Administration, and Revaccination for Children Age 6–18 Yr ‡

RISK GROUP	UNDERLYING MEDICAL CONDITION	PCV13 RECOMMENDED	PPSV23 RECOMMENDED	REVACCINATION 5 YR AFTER 1ST DOSE
Immunocompetent persons	Chronic heart disease [§]		✓	
	Chronic lung disease [‖]		✓	
	Diabetes mellitus		✓	
	Cerebrospinal fluid leaks	✓	✓	
	Cochlear implants	✓	✓	
	Alcoholism		✓	
	Chronic liver disease		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease, other hemoglobinopathies	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓
Immunocompromised persons	Congenital or acquired immunodeficiencies [¶]	✓	✓	✓
	HIV infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin disease	✓	✓	✓
	Generalized malignancy	✓	✓	✓
	Iatrogenic immunosuppression[**]	✓	✓	✓
	Solid-organ transplant	✓	✓	✓
	Multiple myeloma	✓	✓	✓

[*] 13-valent pneumococcal conjugate vaccine.

[†] 23-valent pneumococcal polysaccharide vaccine.

[‡] Children age 2-5 yr with chronic conditions (e.g., heart disease, diabetes), immunocompromising conditions (e.g., HIV), functional or anatomic asplenia (including sickle cell disease), cerebrospinal fluid leaks, or cochlear implants, and who have not previously received PCV13, have been recommended to receive PCV13 since 2010.

[§] Including congestive heart failure and cardiomyopathies.

[‖] Including chronic obstructive pulmonary disease, emphysema, and asthma.

[¶] Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).

[**] Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.

From Centers for Disease Control and Prevention: Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices, *MMWR* 62:521–524, 2013.

Immunization with pneumococcal vaccines also may prevent pneumococcal disease caused by nonvaccine serotypes that are serotypically related to a vaccine strain. However, because current vaccines do not eliminate all pneumococcal invasive infections, penicillin prophylaxis is recommended for children at high risk of invasive pneumococcal disease, including children with asplenia or sickle cell disease. Oral penicillin V potassium (125 mg twice daily for children <3 yr old; 250 mg twice daily for children ≥3 yr old) decreases the incidence of pneumococcal sepsis in children with sickle cell disease. Once-monthly IM benzathine penicillin G (600,000 units every 3-4 wk for children weighing <60 lb; 1,200,000 units every 3-4 wk for children weighing ≥60 lb) may also provide prophylaxis. Erythromycin may be used in children with penicillin allergy, but its efficacy is unproved. Prophylaxis in sickle cell disease has been safely discontinued after the 5th birthday in children who have received all recommended pneumococcal vaccine doses and who had not experienced invasive pneumococcal disease. Prophylaxis is often administered for at least 2 yr after splenectomy or up to 5 yr of age. Efficacy in children >5 yr old and adolescents is unproved. If oral antibiotic prophylaxis is used, strict compliance must be encouraged.

Given the rapid emergence of penicillin-resistant pneumococci, especially in children receiving long-term, low-dose therapy, prophylaxis cannot be relied on to prevent disease. High-risk children with fever should be promptly evaluated and treated regardless of vaccination or penicillin prophylaxis history.

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CHAPTER 210

Group A Streptococcus

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Group A streptococcus (**GAS**), also known as *Streptococcus pyogenes*, is a common cause of infections of the upper respiratory tract (pharyngitis) and the skin (impetigo, pyoderma) in children. Less frequently, GAS causes perianal cellulitis, vaginitis, septicemia, pneumonia, endocarditis, pericarditis, osteomyelitis, suppurative arthritis, myositis, cellulitis, omphalitis, and other infections. This organism also causes distinct clinical entities (scarlet fever and erysipelas), as well as streptococcal toxic shock syndrome and monomicrobial necrotizing fasciitis. GAS is also the cause of 2 potentially serious nonsuppurative complications: rheumatic fever (Chapters 210.1 and 465) and acute glomerulonephritis (Chapter 537.4).

Etiology

Group A streptococci are gram-positive, coccoid-shaped bacteria that tend to grow in chains. They are broadly classified by their hemolytic activity on mammalian (typically sheep) red blood cells. The zone of complete hemolysis that surrounds colonies grown on blood agar distinguishes β-hemolytic (complete hemolysis) from α-hemolytic (green or partial hemolysis) and γ (nonhemolytic) species. The β-hemolytic streptococci can be divided into groups by a group-specific polysaccharide (**Lancefield C carbohydrate**) located in the bacterial cell wall. More than 20 serologic groups are identified, designated by the letters A through V. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any of a number of latex agglutination, coagglutination, molecular assays or enzyme immunoassays. Group A strains can also be distinguished from other groups by differences in sensitivity to bacitracin. A disk containing 0.04 unit of bacitracin inhibits the growth of most group A strains, whereas other groups are generally resistant to this antibiotic. This method is approximately 95% accurate. GAS can be subdivided into >220 serotypes on the basis of the **M protein** antigen, which is located on the cell surface and in fimbriae that project from the outer surface of the cell. Currently, a molecular approach to M-typing GAS isolates using the polymerase chain reaction (PCR) is based on sequencing the terminal portion of the *emm* gene of GAS that encodes the M protein. More than 220 distinct M types have been identified using *emm* typing, with excellent correlation between known serotypes and *emm* types. The *emm* types can be grouped into *emm* clusters that share structural and binding properties. Immunity is largely based on type-specific opsonic anti-M antibody.

M/*emm* typing is valuable for epidemiologic studies; specific GAS diseases tend to be associated with certain M types. Types 1, 12, 28, 4, 3, and 2 (in that order) are the most common causes of uncomplicated streptococcal pharyngitis in the United States. M types usually associated with pharyngitis rarely cause skin infections, and the M types associated with skin infections rarely cause pharyngitis. A few **pharyngeal** strains (e.g., M type 12) are associated with glomerulonephritis, but many more **skin** strains (e.g., M types 49, 55, 57, and 60) are considered nephritogenic. Several pharyngeal serotypes (e.g., M types 1, 3, 5, 6, 18, and 29), but no skin strains, are associated with **acute rheumatic fever** in North America. Rheumatogenic potential is not solely dependent on serotype but is likely a characteristic of specific strains within several serotypes.

Epidemiology

Humans are the natural reservoir for GAS. These bacteria are highly communicable and can cause disease in normal individuals of all ages who do not have type-specific immunity against the particular serotype involved. Disease in neonates is uncommon in developed countries, probably because of maternally acquired antibody. The incidence of pharyngeal infections is highest in children 5-15 yr of age, especially in young school-age children. These infections are most common in the northern regions of the United States, especially during winter and early spring. Children with untreated acute pharyngitis spread GAS by airborne salivary droplets and nasal discharge. Transmission is favored by close proximity; therefore schools, military barracks, and homes are important environments for spread. The incubation period for pharyngitis is usually 2-5 days. GAS has the potential to be an important upper respiratory tract pathogen and to produce outbreaks of disease in the daycare setting. Foods contaminated by GAS occasionally cause explosive outbreaks of pharyngotonsillitis. Children are usually no longer infectious within 24 hr of starting appropriate antibiotic therapy. Chronic pharyngeal carriers of GAS rarely transmit this organism to others.

Streptococcal pyoderma (impetigo, pyoderma) occurs most frequently during the summer in temperate climates, or year-round in warmer climates, when the skin is exposed and abrasions and insect bites are more likely to occur (see Chapter 685). Colonization of healthy skin by GAS usually precedes the development of impetigo. Because GAS cannot penetrate intact skin, impetigo and other skin infections usually occur at the site of open lesions (insect bites, traumatic wounds, burns). Although impetigo serotypes may colonize the throat, spread is usually from skin to skin, not via the respiratory tract. Fingernails and the perianal region can harbor GAS and play a role in disseminating impetigo. Multiple cases of impetigo in the same family are common. Both impetigo and pharyngitis are more likely to occur among children living in crowded homes and in poor hygienic circumstances.

The incidence of **severe invasive** GAS infections, including bacteremia, streptococcal toxic shock syndrome, and necrotizing fasciitis, has increased in recent decades. The incidence appears to be highest in very young and elderly persons. Before the routine use of varicella vaccine, varicella was the most commonly identified risk factor for invasive GAS infection in children. Other risk factors include diabetes mellitus, HIV infection, intravenous drug use, and chronic pulmonary or chronic cardiac disease. The portal of entry is unknown in almost 50% of cases of severe invasive GAS infection; in most cases it is believed to be skin or less often mucous membranes. Severe invasive disease rarely follows clinically apparent GAS pharyngitis.

Pathogenesis

Virulence of GAS depends primarily on the M protein, and strains rich in M protein resist phagocytosis in fresh human blood, whereas M-negative strains do not. M protein stimulates the production of protective opsonophagocytic antibodies that are type specific, protecting against infection with a homologous M type but much less so against other M types. Therefore, multiple GAS infections attributable to various M types are common during childhood and adolescence. By adult life, individuals are probably immune to many of the common M types in the environment.

GAS produces a large variety of extracellular enzymes and toxins, including erythrogenic toxins, known as **streptococcal pyrogenic exotoxins** . Streptococcal pyrogenic exotoxins A, C, and SSA, alone or in combination, are responsible for the **rash of scarlet fever** and are elaborated by streptococci that contain a particular bacteriophage. These exotoxins stimulate the formation of specific antitoxin antibodies that provide immunity against the scarlatiniform rash but not against other streptococcal infections. GAS can produce up to 12 different pyrogenic exotoxins, and repeat attacks of scarlet fever are possible. Mutations in genes that are promoters of several virulence genes, including pyrogenic exotoxins, as well as several newly discovered exotoxins, appear to be involved in the pathogenesis of invasive GAS disease, including the streptococcal toxic shock syndrome.

The importance of other streptococcal toxins and enzymes in human disease is not yet established. Many of these extracellular substances are antigenic and stimulate antibody production after an infection. However, these antibodies do not confer immunity. Their measurement is useful for establishing evidence of a recent streptococcal infection to aid in the diagnosis of postinfectious illnesses. Tests for antibodies against streptolysin O (anti–streptolysin O) and DNase B (anti–DNase B) are the most frequently used antibody determinations. Because the immune response to extracellular antigens varies among individuals as well as with the site of infection, it is sometimes necessary to measure other streptococcal antibodies.

Clinical Manifestations

The most common infections caused by GAS involve the respiratory tract and the skin and soft tissues.

Respiratory Tract Infections

GAS is an important cause of acute **pharyngitis** (Chapter 409) and pneumonia (Chapter 428).

Scarlet Fever

Scarlet fever is GAS pharyngitis associated with a characteristic rash, which is caused by an infection with **pyrogenic exotoxin** (erythrogenic toxin)–producing GAS in individuals who do not have antitoxin antibodies. It is now encountered less often and is less virulent than in the past, but the incidence is cyclic, depending on the prevalence of toxin-producing strains and the immune status of the population. The modes of transmission, age distribution, and other epidemiologic features are otherwise similar to those for GAS pharyngitis.

The rash appears within 24-48 hr after onset of symptoms, although it may appear with the first signs of illness (Fig. 210.1A). It often begins around the neck and spreads over the trunk and extremities. The rash is a diffuse, finely papular, erythematous eruption producing bright-red discoloration of the skin, which blanches on pressure. It is often accentuated in the creases of the elbows, axillae, and groin (Pastia lines). The skin has a goose-pimple appearance and feels rough. The cheeks are often erythematous with pallor around the mouth. After 3-4 days, the rash begins to fade and is followed by **desquamation** , initially on the face, progressing downward, and often resembling a mild sunburn. Occasionally, sheetlike desquamation may occur around the free margins of the fingernails, the palms, and the soles. Examination of the pharynx of a patient with scarlet fever reveals essentially the same findings as with GAS pharyngitis. In addition, the tongue is usually coated and the papillae are swollen (Fig. 210.1B). After desquamation, the reddened papillae are prominent, giving the tongue a strawberry appearance (Fig. 210.1C).

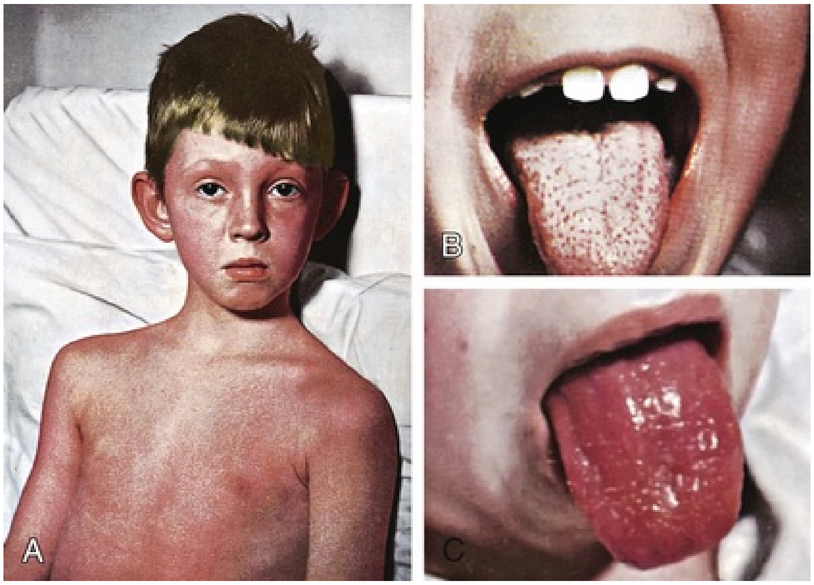

FIG. 210.1 Scarlet fever. A, Punctate, erythematous rash (2nd day). B, White strawberry

tongue (1st day). C, Red strawberry tongue (3rd day). (Courtesy of Dr. Franklin H. Top, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes. From Gershon AA, Hotez PJ, Katz SL: *Krugman's infectious diseases of children,* ed 11, Philadelphia, 2004, Mosby, Plate 53.)

Typical scarlet fever is not difficult to diagnose; the milder form with equivocal pharyngeal findings can be confused with viral exanthems, Kawasaki disease, and drug eruptions. Staphylococcal infections are occasionally associated with a scarlatiniform rash. A history of recent exposure to a GAS infection is helpful. Identification of GAS in the pharynx confirms the diagnosis.

Impetigo

Impetigo (or pyoderma) has traditionally been classified into 2 clinical forms: bullous and nonbullous (see Chapter 685). **Nonbullous impetigo** is the more common form and is a superficial infection of the skin that appears first as a discrete papulovesicular lesion surrounded by a localized area of redness. The vesicles rapidly become purulent and covered with a thick, confluent, amber-colored crust that gives the appearance of having been stuck onto the skin. The lesions may occur anywhere but are most common on the face and extremities. If untreated, nonbullous impetigo is a mild but chronic illness, often spreading to other parts of the body, but occasionally self-limited. Regional **lymphadenitis** is common. Nonbullous impetigo is generally not accompanied by fever or other systemic signs or symptoms. Impetiginized excoriations around the nares are seen with active GAS infections of the nasopharynx, particularly in young children. However, impetigo is rarely associated with overt streptococcal infection of the upper respiratory tract.

Bullous impetigo is less common and occurs most often in neonates and young infants. It is characterized by flaccid, transparent bullae usually <3 cm in diameter on previously untraumatized skin. The usual distribution involves the face, buttocks, trunk, and perineum.

Although *Staphylococcus aureus* has traditionally been accepted as the sole pathogen responsible for bullous impetigo, there has been confusion about the organisms responsible for nonbullous impetigo. In most episodes of nonbullous impetigo, either GAS or *S. aureus* (or both) is isolated. Earlier investigations suggested that GAS was the causative agent in most cases of nonbullous impetigo and that *S. aureus* was only a secondary invader. However, *S. aureus* has emerged as the causative agent in most cases of nonbullous impetigo.

Culture of the lesions is the only way to distinguish nonbullous impetigo caused by *S. aureus* from that caused by GAS.

Erysipelas

Erysipelas is a now relatively rare acute GAS infection involving the deeper layers of the skin and the underlying connective tissue. The skin in the affected area is swollen, red, and very tender. Superficial blebs may be present. The most characteristic finding is a sharply defined, slightly elevated border. At times, reddish streaks of lymphangitis project out from the margins of the lesion. The onset is abrupt, and signs and symptoms of a systemic infection, such as high fever, are often present. Cultures obtained by needle aspirate of the advancing margin of the inflamed area often reveal the causative agent.

Perianal Dermatitis

Perianal dermatitis, also called perianal cellulitis or **perianal streptococcal disease,** is a distinct clinical entity characterized by well-demarcated, perianal erythema associated with anal pruritus, painful defecation, and occasionally blood-streaked stools. Most children are 2-7 yr old (range: 18 days to 12 yr). Physical examination reveals flat, pink to beefy-red perianal erythema with sharp margins extending as far as 2 cm from the anus. Erythema may involve the vulva and vagina. Lesions may be very tender and, particularly when chronic, may fissure and bleed. Systemic symptoms and fever are unusual. Culture or a rapid strep test of a perianal swab will yield group A streptococci or detect antigen.

Vaginitis

GAS is a common cause of vaginitis in prepubertal girls (see Chapter 564). Patients usually have a serous discharge with marked erythema and irritation of the vulvar area, accompanied by discomfort in walking and in urination.

Severe Invasive Disease

Invasive GAS infection is defined by isolation of GAS from a normally sterile body site and includes 3 overlapping clinical syndromes. **GAS toxic shock syndrome (TSS)** is differentiated from other types of invasive GAS infections by the presence of shock and multiorgan system failure early in the course of the infection (Table 210.1). The 2nd syndrome is **GAS necrotizing fasciitis** , characterized by extensive local necrosis of subcutaneous soft tissues and skin. The 3rd syndrome is the group of **focal and systemic infections** that do not meet the criteria for TSS or necrotizing fasciitis and includes bacteremia with no identified focus, meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, suppurative arthritis, myositis, and surgical wound infections. GAS TSS, necrotizing fasciitis, and focal and systemic infections can be present in any combination.

Table 210.1

Definition of Streptococcal Toxic Shock Syndrome

CLINICAL CRITERIA
Hypotension *plus* 2 or more of the following: Renal impairment Coagulopathy Hepatic involvement Adult respiratory distress syndrome Generalized erythematous macular rash Soft tissue necrosis
DEFINITE CASE
Clinical criteria *plus* group A streptococcus from a normally sterile site
PROBABLE CASE
Clinical criteria *plus* group A streptococcus from a nonsterile site

The pathogenic mechanisms responsible for severe, invasive GAS infections, including streptococcal TSS and necrotizing fasciitis, have yet to be defined completely, but an association with streptococcal pyrogenic exotoxins is strongly suspected. At least 2 of the 3 original streptococcal pyrogenic exotoxins (A and C), the newly discovered streptococcal pyrogenic exotoxins, and potentially other as yet unidentified toxins produced by GAS act as **superantigens** , which stimulate intense activation and proliferation of T lymphocytes and macrophages, resulting in the production of large quantities of proinflammatory cytokines. These cytokines are capable of inducing shock and tissue injury and appear to mediate many of the clinical manifestations of severe, invasive GAS infections.

Diagnosis

When deciding whether to perform a diagnostic test on a patient presenting with acute pharyngitis, the clinical and epidemiologic findings should be considered. A history of close contact with a well-documented case of GAS pharyngitis is helpful, as is an awareness of a high prevalence of GAS infections in the community. The signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly to allow the requisite diagnostic precision on clinical grounds alone. The clinical diagnosis of GAS pharyngitis cannot be made with reasonable accuracy even by the most experienced physicians, and laboratory confirmation is required, except for patients with overt viral signs and symptoms (e.g., rhinorrhea, cough, mouth ulcers, hoarseness), who generally do not need a diagnostic test performed.

Culture of a throat swab on a sheep blood agar plate is effective for documenting the presence of GAS and for confirming the clinical diagnosis of acute GAS pharyngitis. When performed correctly, a single throat swab has a sensitivity of 90–95% for detecting the presence of GAS in the pharynx.

The significant disadvantage of culturing a throat swab on a blood agar plate is the delay (overnight or longer) in obtaining the culture result. **Streptococcal rapid antigen detection** tests are available for the identification of GAS directly from throat swabs. Their advantage over culture is the speed in providing results, often <10-15 min. Rapid identification and treatment of patients with streptococcal pharyngitis can reduce the risk for spread of GAS, allowing the patient to return to school or work sooner, and can reduce the acute morbidity of this illness.

Almost all currently available rapid antigen detection tests have excellent specificity of >95% compared with blood agar plate cultures. False-positive test results are quite unusual, and therefore therapeutic decisions can be made with confidence on the basis of a positive test result. Unfortunately, the sensitivity of most of these tests is 80–90%, sometimes lower, when compared with blood agar plate culture. Therefore, a negative rapid test does not completely exclude the presence of GAS, and a confirmatory throat culture should be performed in children and adolescents, but not necessarily in adults, who are at exceptionally low risk for developing acute rheumatic fever. Definitive studies are not available to determine whether some rapid antigen detection tests are significantly more sensitive than others, or whether any of these tests is sensitive enough to be used routinely in children and adolescents without throat culture confirmation of negative test results. Some experts believe that physicians who use a rapid antigen detection test without culture backup should compare the results with that specific test to those of throat cultures to confirm adequate sensitivity in their practice.

Some microbiology laboratories have replaced culture methods with rapid and very sensitive and specific GAS molecular assays. These molecular assays include PCR methods and nucleic acid amplification tests using isothermal loop amplification. The **isothermal loop amplification** methods have been reported to have sensitivity up to 100% and specificity >96% compared to culture or PCR. This very high sensitivity may lead to higher numbers of positive results, which in turn may contribute to identification of more patients with asymptomatic GAS colonization and unnecessary antibiotic therapy. However, the benefit of faster results, sometimes <10 min, ensures more expedited initiation of appropriate antibiotic therapy for patients with GAS pharyngitis.

GAS infection can also be diagnosed retrospectively on the basis of an elevated or increasing streptococcal antibody titer. The **anti–streptolysin O** assay is the streptococcal antibody test most often used. Because streptolysin O also is produced by groups C G streptococci, the test is not specific for group A infection. The anti–streptolysin O response can be feeble after streptococcal skin infection. In contrast, the anti–DNase B responses are generally present after either skin or throat infections. A significant antibody increase is usually defined as an increase in titer of 2 or more dilution increments (≥4-fold rise) between the acute-phase and convalescent-phase specimens, regardless of the actual height of the antibody titer. Physicians frequently misinterpret streptococcal antibody titers because of a failure to appreciate that the normal levels of these antibodies are substantially higher among school-age children than adults. Both the traditional anti–streptolysin O and the anti–DNase B tests are neutralization assays. Newer tests use **latex agglutination** or nephelometric assays. Unfortunately, these newer tests often have not been well standardized against the traditional neutralization assays. Physicians should be aware of these potential problems when interpreting the results of streptococcal serologic testing.

A commercially available **slide agglutination test** for the detection of antibodies to several streptococcal antigens is the Streptozyme test (Wampole Laboratories, Stamford, CT). This test is much less well standardized and less reproducible than other antibody tests, and it should not be used as a test for evidence of a preceding GAS infection.

Differential Diagnosis

Viruses are the most common cause of acute pharyngitis in children. Respiratory viruses such as influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, and respiratory syncytial virus are frequent causes of acute pharyngitis. Other viral causes of acute pharyngitis include enteroviruses and herpes simplex virus. Epstein-Barr virus is a frequent cause of acute pharyngitis that is often accompanied by other clinical findings of infectious mononucleosis (e.g., splenomegaly, generalized lymphadenopathy). Systemic infections with other viral agents, including cytomegalovirus, rubella virus, measles virus, and HIV, may be associated with acute pharyngitis.

GAS is by far the most common cause of bacterial pharyngitis, accounting for 15–30% of cases of acute pharyngitis in children and a lower proportion in adults. Groups C and G β-hemolytic streptococcus also cause acute pharyngitis, typically in teens and young adults (see Chapter 212). *Arcanobacterium haemolyticum* and *Fusobacterium necrophorum* are additional, less common causes. *Neisseria gonorrhoeae* can occasionally cause acute pharyngitis in sexually active adolescents. Other bacteria, such as *Francisella tularensis* and *Yersinia enterocolitica*, as well as mixed infections with anaerobic bacteria (Vincent angina), are rare causes of acute pharyngitis. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have been implicated as causes of acute pharyngitis, particularly in adults. *Corynebacterium diphtheriae* is a serious cause of pharyngitis but is rare because of universal immunization (see Chapter 214). Although other bacteria (e.g., *S. aureus, Haemophilus influenzae, Streptococcus pneumoniae*) are frequently cultured from the throats of children with acute pharyngitis, their etiologic role in pharyngitis has not been established, because they are often isolated in healthy children.

GAS pharyngitis is the only common cause of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore, when confronted with a patient with acute pharyngitis, the clinical decision that usually needs to be made is whether or not the pharyngitis is attributable to GAS.

Treatment

Antibiotic therapy for patients with GAS pharyngitis can prevent **acute rheumatic fever** (RF), shorten the clinical course of the illness, reduce transmission of the infection to others, and prevent suppurative complications.

For the patient with classic scarlet fever, antibiotic therapy should be started immediately, but for the majority of patients, who present with much less distinctive findings, treatment should be withheld until there is laboratory confirmation, by throat culture, molecular assay, or rapid antigen detection test. Rapid antigen detection tests, because of their high degree of specificity, allow initiation of antibiotic therapy immediately for the patient with a positive test result.

GAS is exquisitely sensitive to **penicillin** and **cephalosporins** , and resistant strains have never been encountered. Penicillin or amoxicillin is therefore the drug of choice (except in patients who are allergic to penicillins) for pharyngeal infections as well as for suppurative complications. Oral penicillin V (250 mg/dose 2 or 3 times daily [bid-tid] for children weighing ≤60 lb and 500 mg/dose bid-tid for children >60 lb) is recommended but must be taken for a full **10 days** , even though there is symptomatic improvement within 3-4 days. Penicillin V (phenoxymethylpenicillin) is preferred over penicillin G, because it may be given without regard to mealtime. The major concern with all forms of oral therapy is the risk that the drug will be discontinued before the 10-day course has been completed. Therefore, when oral treatment is prescribed, the necessity of completing a full course of therapy must be emphasized. If the parents seem unlikely to comply with oral therapy because of family disorganization, difficulties in comprehension, or other reasons, parenteral therapy with a single intramuscular (IM) injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for children >60 lb) is the most efficacious and often the most practical method of treatment. Disadvantages include soreness around the site of injection, which may last for several days, and potential for injection into nerves or blood vessels if not administered correctly. The local reaction is diminished when benzathine penicillin G is combined in a single injection with procaine penicillin G, although it is necessary to ensure that an adequate dose of benzathine penicillin G is administered.

In several comparative clinical trials, once-daily amoxicillin (50 mg/kg, maximum: 1,000 mg) for 10 days has been demonstrated to be effective in treating GAS pharyngitis. This somewhat broader-spectrum agent has the advantage of once-daily dosing, which may enhance adherence. In addition, amoxicillin is relatively inexpensive and is considerably more palatable than penicillin V suspension.

A 10-day course of a narrow-spectrum oral cephalosporin is recommended for most **penicillin-allergic** individuals. It has been suggested that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx. Analysis of these data suggests that the difference in eradication is mainly the result of a higher rate of eradication of carriers included unintentionally in these clinical trials. Some penicillin-allergic persons (up to 10%) are also allergic to cephalosporins, and these agents should be avoided in patients with immediate (anaphylactic-type) hypersensitivity to penicillin. Most oral broad-spectrum cephalosporins are considerably more expensive than penicillin or amoxicillin and are more likely to select for antibiotic-resistant flora.

Oral clindamycin is an appropriate agent for treating penicillin-allergic patients, and resistance to clindamycin among GAS isolates in the United States is currently only approximately 1%. An oral **macrolide** (erythromycin or clarithromycin) or **azalide** (azithromycin) is also an appropriate agent for patients allergic to penicillins. Ten days of therapy is indicated except for azithromycin, which is given at 12 mg/kg once daily for 5 days. Erythromycin is associated with substantially higher rates of gastrointestinal side effects than the other agents. In recent years, macrolide resistance rates among pharyngeal isolates of GAS in most areas of the United States have been approximately 5–8%. Sulfonamides and the tetracyclines are not recommended for treatment of GAS pharyngitis. However, studies showed that trimethoprim-sulfamethoxazole (TMP-SMX) is highly active in vitro against GAS and was comparable to IM penicillin for impetigo from GAS in clinical trials.

Most oral antibiotics must be administered for the conventional 10 days to achieve maximal pharyngeal eradication rates of GAS and prevention of RF, but certain newer agents are reported to achieve comparable bacteriologic and clinical cure rates when given for ≤5 days. However, definitive results from comprehensive studies are not available to allow full evaluation of these proposed shorter courses of oral antibiotic therapy, which therefore cannot be recommended at this time. In addition, these antibiotics have a much broader spectrum than penicillin and are generally more expensive, even when administered for short courses.

The majority of patients with GAS pharyngitis respond clinically to antimicrobial therapy, and GAS is eradicated from the pharynx. Posttreatment throat cultures are indicated only in the relatively few patients who remain symptomatic, whose symptoms recur, or who have had RF or rheumatic heart disease and are therefore at unusually high risk for recurrence.

Antibiotic therapy for a patient with nonbullous impetigo can prevent local extension of the lesions, spread to distant infectious foci, and transmission of the infection to others. However, the ability of antibiotic therapy to prevent poststreptococcal glomerulonephritis has not been definitively demonstrated. Patients with a few superficial, isolated lesions and no systemic signs can be treated with topical antibiotics. **Mupirocin** is a safe and effective agent that has become the topical treatment of choice. If there are widespread lesions or systemic signs, oral therapy with coverage for both GAS and *S. aureus* is needed. With the rapid emergence of methicillin-resistant *S. aureus* in many communities, one should consider using clindamycin alone or a combination of TMP-SMX and amoxicillin as first-line therapy. Oral cefuroxime is an effective treatment of perianal streptococcal disease.

Theoretical considerations and experimental data suggest that intravenous **clindamycin** is a more effective agent for the treatment of severe, invasive GAS infections than IV penicillin. However, because approximately 1% of GAS isolates in the United States are resistant to clindamycin, clindamycin initially should be used in combination with penicillin for these infections until susceptibility to clindamycin has been established. If **necrotizing fasciitis** is suspected, immediate surgical exploration or biopsy is required to identify a deep soft-tissue infection that should be debrided immediately. Patients with **streptococcal TSS** require rapid and aggressive fluid replacement, management of respiratory or cardiac failure, if present, and anticipatory management of multiorgan system failure. Limited data suggest that intravenous immune globulin (IVIG) is effective as adjunctive therapy in the management of streptococcal TSS.

Complications

Suppurative complications from the spread of GAS to adjacent structures were extremely common in the preantibiotic era. Cervical lymphadenitis, peritonsillar abscess, retropharyngeal abscess, otitis media, mastoiditis, and sinusitis still occur in children in whom the primary illness has gone unnoticed or in whom treatment of the pharyngitis has been inadequate. GAS pneumonia can also occur.

Acute rheumatic fever (Chapter 210.1) and acute poststreptococcal **glomerulonephritis** (Chapter 537.4) are both nonsuppurative sequelae of infections with GAS that occur after an asymptomatic latent period. They are both characterized by disease remote from the site of the primary GAS infection. Acute RF and acute glomerulonephritis differ in their clinical manifestations, epidemiology, and potential morbidity. In addition, acute glomerulonephritis follows a GAS infection of either the upper respiratory tract or the skin, but acute RF only follows an infection of the upper respiratory tract.

Poststreptococcal Reactive Arthritis

Poststreptococcal reactive arthritis (**PSRA**) describes a syndrome characterized by the onset of acute arthritis following an episode of GAS pharyngitis in a patient whose illness does not fulfill the Jones Criteria for diagnosis of acute RF. It is still unclear whether this entity represents a distinct syndrome or is a variant of acute RF. Although PSRA usually involves the large joints similar to the arthritis of acute RF, it may also involve small peripheral joints, as well as the axial skeleton, and is typically nonmigratory, characteristics distinct from the arthritis of acute RF. The latent period between the antecedent episode of GAS pharyngitis and PSRA may be considerably shorter (usually <10 days) than that typically seen with acute RF (usually 14-21 days). In contrast to the arthritis of acute RF, PSRA does not respond dramatically to therapy with aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs). In addition, fewer patients with PSRA than with acute RF have temperature >38°C (100.4°F). Even though no more than half of PSRA patients with throat culture have GAS isolated, all have serologic evidence of a recent GAS infection. Because a very small proportion of patients with PSRA have been reported to develop valvular heart disease subsequently, these patients should be carefully observed for several months for clinical evidence of **carditis** . Some recommend that these patients receive secondary antistreptococcal prophylaxis for up to 1 yr. If clinical evidence of carditis is not observed, the prophylaxis can be discontinued. If valvular disease is detected, the patient should be classified as having had acute RF and should continue to receive secondary prophylaxis appropriate for RF patients.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus pyogenes*

Pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus pyogenes* (**PANDAS**) is a term proposed for a group of neuropsychiatric disorders (originally obsessive-compulsive disorder (OCD), tic disorder, and Tourette syndrome, or only OCD or feeding abnormality) for which a possible relationship with GAS infections has been hypothesized (see Chapter 37). *This relationship has not been proved.* It has been proposed that this subset of patients with OCDs may produce autoimmune antibodies in response to a GAS infection that cross-react with brain tissue similar to the autoimmune response believed to be responsible for the manifestations of **Sydenham chorea** . It has also been suggested that secondary prophylaxis that prevents recurrences of rheumatic fever, including Sydenham chorea, might also be effective in preventing exacerbations of OCDs in these patients, but clinical trials have not confirmed this. It has also been proposed that these patients may benefit from immunoregulatory therapy such as plasma exchange or IVIG, but these unproven modalities should only be used in a clinical research trial. That PANDAS may represent an extension of the spectrum of acute RF is intriguing, but it should be considered only as a yet-unproven hypothesis. Until carefully designed and well-controlled studies have established a causal relationship between neurobehavioral abnormalities and GAS infections, routine diagnostic laboratory testing for GAS and antistreptococcal antibodies, long-term antistreptococcal prophylaxis, or immunoregulatory therapy (e.g., IVIG, plasma exchange) to treat exacerbations of this disorder clearly are not recommended (see Chapter 37). It has also been suggested that a broad spectrum of infectious agents may have the ability to trigger exacerbations in children with these neurobehavioral disorders.

Prognosis

The prognosis for appropriately treated GAS pharyngitis is excellent, and complete recovery is the rule. When therapy is instituted within 9 days of the onset of symptoms and continued for the full course, acute RF is almost always prevented. There is no comparable evidence that acute poststreptococcal glomerulonephritis can be prevented once pharyngitis or pyoderma with a nephritogenic strain of GAS has occurred. In rare instances, particularly in neonates or in children whose response to infection is compromised, fulminant pneumonia, septicemia, and death may occur despite usually adequate therapy.

Prevention

The only specific indication for long-term use of an antibiotic to prevent GAS infections is for patients with a history of acute RF and/or rheumatic heart disease. Mass prophylaxis is generally not feasible except to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools. Because the ability of antimicrobial agents to prevent GAS infections is limited, a group A streptococcal vaccine offers the possibility of a more effective approach.

Several candidate vaccines are in development, including a 30-valent M protein–based recombinant vaccine, another recombinant vaccine that includes several conserved non–M protein epitopes that induce protective antibody, and an M-protein vaccine that includes an epitope in a very conserved region of M protein to provide broad immunity. All these vaccines are in relatively early stages of development.

210.1

Rheumatic Fever

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Keywords

acute rheumatic fever
carditis
chorea
erythema marginatum
Jones Criteria
minor criteria
migratory polyarthritis
primary prevention
secondary prevention
subcutaneous nodules

Sydenham chorea

Etiology

Considerable evidence supports the link between antecedent GAS pharyngitis and **acute rheumatic fever** (RF) and **rheumatic heart disease** . As many as two thirds of patients with an acute episode of RF have history of an upper respiratory tract infection several weeks before, and the peak age and seasonal incidence of acute RF closely parallel that of GAS pharyngitis. Patients with acute RF almost always have serologic evidence of a recent GAS infection. Their antibody titers are usually *considerably higher* than those seen in patients with uncomplicated GAS infections. Outbreaks of GAS pharyngitis in closed communities, such as boarding schools or military bases, may be followed by outbreaks of acute RF. Antimicrobial therapy that eliminates GAS from the pharynx also prevents initial episodes of acute RF, and long-term, continuous antibiotic prophylaxis that prevents GAS pharyngitis also prevents recurrences of acute RF.

Not all serotypes of GAS can cause rheumatic fever. When some GAS strains (e.g., M type 4) caused acute pharyngitis in a very susceptible rheumatic population, there were no recurrences of RF. In contrast, episodes of pharyngitis caused by other serotypes in the same population led to frequent recurrences of acute RF, suggesting that the latter organisms were rheumatogenic. The concept of *rheumatogenicity* is further supported by the observation that although serotypes of GAS frequently associated with skin infection can be isolated also from the upper respiratory tract, they rarely cause recurrences of RF in individuals with a previous history of RF or first episodes of RF. In addition, certain serotypes of GAS (M types 1, 3, 5, 6, 18, 29) are more frequently isolated from patients with acute RF than are other serotypes.

Epidemiology

The annual incidence of acute rheumatic fever in some developing countries exceeds 50 per 100,000 children, and very high rates are also seen in ethnic minority populations within Australia and New Zealand. Worldwide, **rheumatic heart disease** remains the most common form of acquired heart disease in all age-groups, accounting for up to 50% of all cardiovascular disease and 50% of all cardiac admissions in many developing countries. Striking differences in the incidence of acute RF and rheumatic heart disease among different ethnic groups are often evident within the same country; these differences are partially related to differences in socioeconomic status, and there is a genetic basis for increased susceptibility.

In the United States at the beginning of the 20th century, acute RF was a leading cause of death among children and adolescents, with annual incidence rates of 100-200 per 100,000 population. In addition, rheumatic heart disease was a leading cause of heart disease among adults <40 yr old. At that time, as many as 25% of pediatric hospital beds in the United States were occupied by patients with acute RF or its complications. By the 1940s, the annual incidence of acute RF had decreased to 50 per 100,000 population, and over the next 4 decades, the decline in incidence accelerated rapidly. By the early 1980s, the annual incidence in some areas of the United States was as low as 0.5 per 100,000 population. This sharp decline in the incidence of acute RF has been observed in other industrialized countries as well.

The explanation for this dramatic decline in the incidence of acute RF and rheumatic heart disease in the United States and other industrialized countries is not clear but is likely related in large part to a *decline in circulating rheumatogenic strains causing acute pharyngitis* . Historically, acute RF was associated with poverty and overcrowding, particularly in urban areas. Much of the decline in the incidence of acute RF in industrialized countries during the preantibiotic era was probably the result of improved living conditions. Of the various manifestations of poverty, **crowding** , which facilitates spread of GAS infections, is most closely associated with the incidence of acute RF. The decline in incidence of acute RF in industrialized countries over the past 4 decades is also attributable to the greater availability of medical care and to the widespread use of antibiotics. Antibiotic therapy of GAS pharyngitis is important in preventing initial attacks and, particularly, recurrences of the disease. In addition, the decline in the United States is attributed to a shift in the prevalent strains of GAS causing pharyngitis from mostly rheumatogenic to nonrheumatogenic.

A dramatic outbreak of acute RF in the Salt Lake City, UT, area began in early 1985, and 198 cases were reported by the end of 1989. Other outbreaks were reported between 1984 and 1988 in Columbus and Akron, OH; Pittsburgh, PA; Nashville and Memphis, TN; New York, NY; Kansas City, MO; Dallas, TX; and among Navy recruits in California and Army recruits in Missouri. In virtually all areas of the United States, rates have declined substantially.

Certain rheumatogenic serotypes (types 1, 3, 5, 6, and 18) that were isolated less often during the 1970s and early 1980s dramatically reappeared during rheumatic fever outbreaks, and their appearance in selected communities was probably a major factor. GAS that are associated with rheumatogenicity often form highly mucoid colonies on throat culture plates.

In addition to the specific characteristics of the infecting strain of GAS, the risk of developing acute RF also depends on various host factors. The incidence of both initial attacks and recurrences of acute RF peaks in children 5-15 yr old, the age of greatest risk for GAS pharyngitis. Patients who have had an attack of acute RF tend to have recurrences, and the clinical features of the recurrences tend to mimic those of the initial attack. In addition, there appears to be a genetic predisposition to acute RF. Studies in twins show a higher concordance rate of acute RF in monozygotic than in dizygotic twin pairs.

Pathogenesis

The **cytotoxicity theory** suggests that a GAS toxin is involved in the pathogenesis of acute rheumatic fever and rheumatic heart disease. GAS produces a number of enzymes that are cytotoxic for mammalian cardiac cells, such as streptolysin O, which has a direct cytotoxic effect on mammalian cells in tissue culture. Most proponents of the cytotoxicity theory have focused on this enzyme. However, a major problem with the cytotoxicity hypothesis is its inability to explain the substantial latent period (usually 10-21 days) between GAS pharyngitis and onset of acute RF.

An **immune-mediated pathogenesis** for acute RF and rheumatic heart disease has been suggested by its clinical similarity to other illnesses with an immunopathogenesis and by the latent period between the GAS infection and acute RF. The antigenicity of several GAS cellular and extracellular epitopes and their immunologic cross-reactivity with cardiac antigenic epitopes also lends support to the hypothesis of molecular mimicry. Common epitopes are shared between certain GAS components (e.g., M protein, cell membrane, group A cell wall carbohydrate, capsular hyaluronate) and specific mammalian tissues (e.g., heart valve, sarcolemma, brain, joint). For example, certain rheumatogenic M proteins (M1, M5, M6, and M19) share epitopes with human myocardial proteins such as tropomyosin and myosin. Additionally, the involvement of GAS superantigens such as pyrogenic exotoxins in the pathogenesis of acute RF has been proposed.

Another proposed pathogenetic hypothesis is that the binding of an M-protein N-terminal domain to a region of collagen type IV leads to an **antibody response to the collagen** , resulting in ground substance inflammation, especially in subendothelial areas such as cardiac valves and myocardium.

Clinical Manifestations and Diagnosis

Because no clinical or laboratory finding is pathognomonic for acute rheumatic fever, T. Duckett Jones proposed guidelines in 1944 to aid in diagnosis and to limit overdiagnosis. The **Jones Criteria,** as revised in 2015 by the American Heart Association (AHA), are intended for diagnosis of the initial attack of acute RF and recurrent attacks (Table 210.2). There are **5 major and 4 minor criteria** and a requirement of evidence of recent GAS infection. The 2015 revision includes separate criteria for **Low-Risk populations** (defined as those with incidence ≤2 per 100,000 school-age children per year or all-age rheumatic heart disease prevalence of ≤1 per 1,000 population) and **Moderate/High-Risk populations** (defined as those with higher incidence or prevalence rates). Virtually all of the United States, Canada, and Western Europe are Low-Risk, whereas Moderate/High-Risk populations include Maoris in New Zealand, aborigines in Australia, Pacific Islanders, and most developing countries. Diagnosis of a first attack or recurrent attack of acute RF can be established when a patient fulfills 2 major or 1 major and 2 minor criteria and has evidence of preceding GAS infection. Diagnosis of recurrent acute RF can also be made only in the Moderate/High-Risk population by presence of 3 minor criteria with evidence of preceding GAS infection. In the 2015 Jones Criteria revision, a major change from previous versions expands the definition of the major criterion **carditis** to include *subclinical evidence* (e.g., in the absence of a murmur, echocardiographic evidence of mitral regurgitation [MR] meeting specific criteria to distinguish physiologic from pathologic MR) (see Table 465.1). Areas in which the Jones Criteria differ in Low-Risk from Moderate/High-Risk populations relate to the major criterion of **arthritis** and the minor criteria of arthralgia, definition of fever, and of elevated inflammatory markers (see Table 210.2 and text below). These changes are designed to make it easier to fulfill the Jones Criteria in patients from Moderate/High-Risk populations. Even with strict application of the criteria, overdiagnosis as well as underdiagnosis of acute RF may occur. The diagnosis of acute RF can be made without strict adherence to the Jones Criteria in 3 circumstances: (1) when chorea occurs as the only major manifestation of acute RF, (2) when indolent carditis is the only manifestation in patients who first come to medical attention only months after the apparent onset of acute RF, and (3) in a limited number of patients with recurrence of acute RF in particularly high-risk populations.

Table 210.2

Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)[1-5]

MAJOR MANIFESTATIONS	MINOR MANIFESTATIONS	SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION
Carditis Polyarthritis Erythema marginatum Subcutaneous nodules Chorea	**Clinical features:** Arthralgia Fever	Positive throat culture or rapid streptococcal antigen test Elevated or increasing streptococcal antibody titer
	Laboratory features: Elevated acute-phase reactants:	
	Erythrocyte sedimentation rate	
	C-reactive protein	
	Prolonged P-R interval	

1. **Initial attack** *:* 2 major manifestations, or 1 major and 2 minor manifestations, plus evidence of recent GAS infection. **Recurrent attack** *:* 2 major, or 1 major and 2 minor, or 3 minor manifestations (the latter only in the Moderate/High-Risk population), plus evidence of recent GAS infection (see text).

2. **Low-Risk population** is defined as acute rheumatic fever (ARF) incidence <2 per 100,000 school-age children per year, or all-age rheumatic heart disease (RHD) prevalence of <1 per 1,000 population. **Moderate/High-Risk population** is defined as ARF incidence >2 per 100,000 school-age children per year, or all-age RHD prevalence of >1 per 1,000 population.

3. Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis). See Table 210.3 .

4. Arthritis (major) refers only to polyarthritis in Low-Risk populations, but also to monoarthritis or polyarthralgia in Moderate/High-Risk populations.

5. Minor criteria for Moderate/High-Risk populations only include monoarthralgia (polyarthralgia for Low-Risk populations), fever of >38°C (>38.5°C in Low-Risk populations), ESR >30 mm/hr (>60 mm/hr in Low-Risk populations).

From Gewitz MH, Baltimore RS, Tani LY, et al: Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association, *Circulation* 131(20):1806–1818, 2015.

The 5 Major Criteria

Migratory Polyarthritis

Arthritis occurs in approximately 75% of patients with acute rheumatic fever and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. Involvement of the spine, small joints of the hands and feet, or hips is uncommon. Rheumatic joints are classically hot, red, swollen, and exquisitely tender, with even the friction of bedclothes being uncomfortable. The pain can precede and can appear to be disproportionate to the objective findings. The joint involvement is characteristically migratory in nature; that is, a severely inflamed joint can become normal within 1-3 days without treatment, even as 1 or more other large joints become involved. Severe arthritis can persist for several weeks in untreated patients. Monoarticular arthritis is unusual unless antiinflammatory therapy is initiated prematurely, aborting the progression of the migratory polyarthritis. If a child with fever and arthritis is suspected to have acute RF, it is frequently useful to withhold salicylates and observe for migratory progression. A dramatic response to even low doses of salicylates is another characteristic feature of the arthritis, and the absence of such a response should suggest an alternative diagnosis.

Rheumatic arthritis is almost never deforming. Synovial fluid in acute RF usually has 10,000-100,000 white blood cells/µL with a predominance of neutrophils, protein level of approximately 4 g/dL, normal glucose level, and forms a good mucin clot. Frequently, arthritis is the earliest manifestation of acute RF and may correlate temporally with peak antistreptococcal antibody titers. There is often an inverse relationship between the severity of arthritis and the severity of cardiac involvement. In Moderate/High-Risk populations only, monoarthritis in the absence of prior inflammatory therapies, or even polyarthralgia without frank objective signs of arthritis, can fulfill this major criterion. Before **polyarthralgia** should be considered a major criterion in the Moderate/High-Risk population, other potential causes should be excluded.

Carditis

A major change in the 2015 revision of the Jones Criteria is the acceptance of **subclinical carditis** (defined as without a murmur of valvulitis but with echocardiographic evidence of valvulitis) or **clinical carditis** (with a valvulitis murmur) as fulfilling the major criterion of carditis in all populations. The echocardiographic features of subclinical carditis must meet those included in

Table 465.1 , to distinguish pathologic from physiologic degrees of valve regurgitation. Subclinical (i.e. only echocardiographic) evidence of pathologic mitral regurgitation requires that a jet is seen in at least two views, the jet length is ≥2 cm in at least 1 view, peak jet velocity is >3 meters/second, and the peak systolic jet is in at least 1 envelope. Subclinical pathologic evidence of aortic regurgitation is similar except that the jet length is ≥1 cm in at least 1 view.

Carditis and resultant chronic rheumatic heart disease are the most serious manifestations of acute RF and account for essentially all the associated morbidity and mortality. Rheumatic carditis is characterized by **pancarditis** , with active inflammation of myocardium, pericardium, and endocardium (see Chapter 465). Cardiac involvement during acute RF varies in severity from fulminant, potentially fatal exudative pancarditis to mild, transient cardiac involvement. **Endocarditis** (valvulitis) is a universal finding in rheumatic carditis, whereas the presence of pericarditis or myocarditis is variable. Myocarditis and/or pericarditis without clinical evidence of endocarditis almost never is rheumatic carditis; alternate etiologies (especially viral) need to be sought. Most rheumatic heart disease is isolated mitral valvular disease or combined aortic and mitral valvular disease. Isolated aortic or right-sided valvular involvement is quite uncommon. Serious and long-term illness is related entirely to the severity of valvular heart disease as a consequence of a single attack or recurrent attacks of acute RF. Valvular insufficiency is characteristic of both acute and convalescent stages of acute RF, whereas mitral and/or aortic valvular stenosis usually appears years or even decades after the acute illness. However, in developing countries, where acute RF often occurs at a younger age, mitral stenosis and aortic stenosis may develop sooner after acute RF than in developed countries and can occur in young children.

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without evidence of myocardial or pericardial involvement. Moderate to severe rheumatic carditis can result in cardiomegaly and heart failure with hepatomegaly and peripheral and pulmonary edema. Echocardiographic findings include pericardial effusion, decreased ventricular contractility, and aortic and/or mitral regurgitation. **Mitral regurgitation** is characterized typically by a high-pitched apical holosystolic murmur radiating to the axilla. In patients with significant MR, this may be associated with an apical mid-diastolic murmur of relative mitral stenosis. Aortic insufficiency is characterized by a high-pitched decrescendo diastolic murmur at the left sternal border.

Carditis occurs in approximately 50–60% of all cases of acute RF. Recurrent attacks of acute RF in patients who had carditis with their initial attack are associated with high rates of carditis with increasing severity of cardiac disease. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require valve replacement.

Chorea

Sydenham chorea occurs in approximately 10–15% of patients with acute RF and usually presents as an isolated, frequently subtle, movement disorder. Emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing are characteristic, all exacerbated by stress and disappearing with sleep. Chorea occasionally is unilateral (hemichorea). The latent period from acute GAS infection to chorea is usually substantially longer than for arthritis or carditis and can be months. Onset can be insidious, with symptoms being present for several months before recognition. Clinical maneuvers to elicit features of chorea include (1) demonstration of *milkmaid's grip* (irregular contractions and relaxations of the muscles of the fingers while squeezing the examiner's fingers), (2) spooning and pronation of the hands when the patient's arms are extended, (3) wormian darting movements of the tongue on protrusion, and (4) examination of handwriting to evaluate fine motor movements. Diagnosis is based on clinical findings with supportive evidence of GAS antibodies. However, in the usual patient with a long latent period from the inciting streptococcal infection to onset of chorea, antibody levels have often declined to normal. Although the acute illness is distressing, chorea rarely if ever leads to permanent neurologic sequelae.

Erythema Marginatum

Erythema marginatum is a rare (approximately 1% of patients with acute RF) but characteristic rash of acute RF. It consists of erythematous, serpiginous, macular lesions with pale centers that are not pruritic (Fig. 210.2). It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.

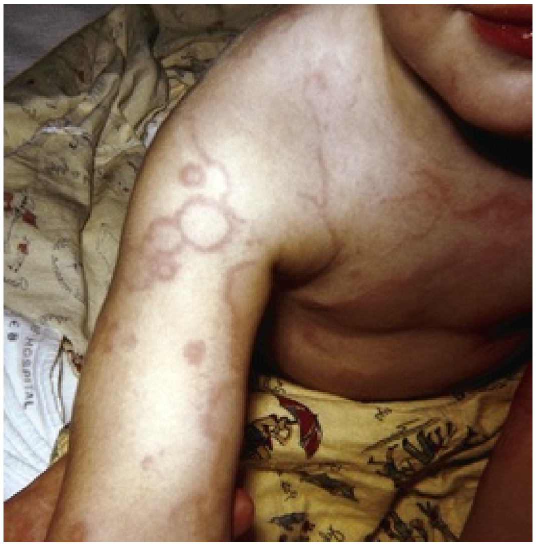

FIG. 210.2 Polycyclic red borders of erythema marginatum in a febrile child with acute rheumatic fever. (From Schachner LA, Hansen RC, editors: *Pediatric dermatology,* ed 3, Philadelphia, 2003, Mosby, p 808.)

Subcutaneous Nodules

Subcutaneous nodules are a rare (≤1% of patients with acute RF) finding and consist of firm nodules approximately 0.5-1 cm in diameter along the extensor surfaces of tendons near bony prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

Minor Criteria

These are more *nonspecific* than major criteria, and the 2015 revised Jones Criteria have included some changes from previous criteria. The 1st of the 2 clinical minor criteria involve joint manifestations (only if arthritis is not used as a major criterion) and is defined as *polyarthralgia* in Low-Risk populations and *monoarthralgia* in Moderate/High-Risk populations. The 2nd clinical minor manifestation is fever, defined as *at least 38.5°C* in Low-Risk populations and *at least 38.0°C* in Moderate/High-Risk populations. The 2 laboratory minor criteria are (1) elevated acute-phase reactants, defined as erythrocyte sedimentation rate (ESR) at least 60 mm/hr and/or C-reactive protein (CRP) at least 3.0 mg/dL (30 mg/L) in Low-Risk populations, and ESR at least 30 mm/hr and/or CRP at least 3.0 mg/dL (30 mg/L) in Moderate/High-Risk populations, and (2) prolonged P-R interval on ECG (unless carditis is a major criterion). However, a prolonged P-R interval alone does not constitute evidence of carditis or predict long-term cardiac sequelae.

Recent Group A Streptococcus Infection

An absolute requirement for the diagnosis of acute RF is supporting evidence of a recent GAS infection. Acute RF typically develops 10-21 days after an acute episode of GAS pharyngitis at a time when clinical findings of pharyngitis are no longer present and when only 10–20% of patients still harbor GAS in the throat. One third of patients with acute RF have no history of an antecedent pharyngitis. Therefore, evidence of an antecedent GAS infection is usually based on elevated or rising serum antistreptococcal antibody titers. A slide agglutination test (Streptozyme) purports to detect antibodies against 5 different GAS antigens. Although this test is rapid, relatively simple to perform, and widely available, it is less standardized and less reproducible than other tests and is not recommended as a diagnostic test for evidence of an antecedent GAS infection. If only a single antibody is measured (usually anti–streptolysin O), only 80–85% of patients with acute RF have an elevated titer; however, 95–100% have an elevation if 3 different antibodies (anti–streptolysin O, anti–DNase B, antihyaluronidase) are measured. Therefore, when acute RF is suspected clinically, multiple antibody tests should be performed. Except for chorea, the clinical findings of acute RF generally coincide with peak antistreptococcal antibody responses. Most patients with chorea have elevation of antibodies to at least 1 GAS antigen. However, in patients with a long latent period from the inciting GAS infection, antibody levels may have declined to within the normal range. The diagnosis of acute RF should *not* be made in those patients with elevated or increasing streptococcal antibody titers who do not fulfill the Jones Criteria.

Differential Diagnosis

The differential diagnosis of rheumatic fever includes many infectious as well as noninfectious illnesses (Table 210.3). When children present with arthritis, a collagen vascular disease must be considered. **Juvenile idiopathic arthritis** (JIA) must be distinguished from acute RF. Children with JIA tend to be younger and usually have less joint pain relative to their other clinical findings than those with acute RF. Spiking fevers, nonmigratory arthritis, lymphadenopathy, and splenomegaly are more suggestive of JIA than acute RF. The response to salicylate therapy is also much less dramatic with JIA than with acute RF.

Systemic lupus erythematosus (SLE) can usually be distinguished from acute RF by antinuclear antibodies in SLE. Other causes of arthritis such as pyogenic arthritis, malignancies, serum sickness, Lyme disease, sickle cell disease, and reactive arthritis related to gastrointestinal infections (e.g., *Shigella, Salmonella, Yersinia*) should also be considered. Poststreptococcal reactive arthritis is discussed earlier (see Chapter 210).

Table 210.3

Differential Diagnosis of Acute Rheumatic Fever

ARTHRITIS	CARDITIS	CHOREA
Juvenile idiopathic arthritis	Viral myocarditis	Huntington chorea
Reactive arthritis (e.g., *Shigella, Salmonella, Yersinia*)	Viral pericarditis	Wilson disease
Serum sickness	Infective endocarditis	Systemic lupus erythematosus
Sickle cell disease	Kawasaki disease	Tic disorder
Malignancy	Congenital heart disease	Hyperactivity
Systemic lupus erythematosus	Mitral valve prolapse	Encephalitis
Lyme disease *(Borrelia burgdorferi)*	Innocent murmurs	
Pyogenic arthritis		
Poststreptococcal reactive arthritis		

When **carditis** is the sole major manifestation of suspected acute RF, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should also be considered. Patients with infective endocarditis may present with both joint and cardiac manifestations. These patients can usually be distinguished from patients with acute RF by blood cultures and the presence of extracardiac findings (e.g., hematuria, splenomegaly, splinter hemorrhages). When **chorea** is the sole major manifestation of suspected acute RF, Huntington chorea, Wilson disease, SLE, and various encephalitides should also be considered.

Treatment

All patients with acute rheumatic fever should be placed on bed rest and monitored closely for evidence of carditis. They can be allowed to ambulate when the signs of acute inflammation have improved. However, patients with carditis require longer periods of bed rest.

Antibiotic Therapy

Once the diagnosis of acute RF has been established and regardless of the throat culture results, the patient should receive 10 days of orally administered penicillin or amoxicillin or a single intramuscular injection of benzathine penicillin to ensure eradication of GAS from the upper respiratory tract. If penicillin allergic, 10 days of erythromycin, 5 days of azithromycin, or 10 days of clindamycin is indicated. After this initial course of antibiotic therapy, long-term antibiotic prophylaxis for secondary prevention should be instituted (see later).

Antiinflammatory Therapy

Antiinflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute RF. Premature treatment with one of these agents may interfere with the development of the characteristic migratory polyarthritis and thus obscure the diagnosis of acute RF. Acetaminophen can be used to control pain and fever while the patient is being observed for more definite signs of acute RF or for evidence of another disease.

Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 50-70 mg/kg/day in 4 divided doses orally (PO) for 3-5 days, followed by 50 mg/kg/day in 4 divided doses PO for 2-3 wk and half that dose for another 2-4 wk. Determination of the serum salicylate level is not necessary unless the arthritis does not respond or signs of salicylate toxicity (tinnitus, hyperventilation) develop. There is no evidence that NSAIDs are more effective than salicylates.

Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive **corticosteroids** . The usual dose of prednisone is 2 mg/kg/day in 4 divided doses for 2-3 wk, followed by half the dose for 2-3 wk and then tapering of the dose by 5 mg/24 hr every 2-3 days. When prednisone is being tapered, aspirin should be started at 50 mg/kg/day in 4 divided doses for 6 wk to prevent rebound of inflammation. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen. The cardiac toxicity of digoxin is enhanced with myocarditis.

Termination of the antiinflammatory therapy may be followed by the reappearance of clinical manifestations or of elevation in ESR and CRP (rebound). It may be prudent to increase salicylates or corticosteroids until near-normalization of inflammatory markers is achieved.

Sydenham Chorea

Because chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease, antiinflammatory agents are usually not indicated. Sedatives may be helpful early in the course of chorea; **phenobarbital** (16-32 mg every 6-8 hr PO) is the drug of choice. If phenobarbital is ineffective, **haloperidol** (0.01-0.03 mg/kg/24 hr divided twice daily PO) or **chlorpromazine** (0.5 mg/kg every 4-6 hr PO) should be initiated. Some patients may benefit from a few-week course of corticosteroids.

Complications

The arthritis and chorea of acute RF resolve completely without sequelae. Therefore, the long-term sequelae of RF are essentially limited to the heart (see Chapter 465).

The AHA has published updated recommendations regarding the use of prophylactic antibiotics to prevent infective endocarditis (see Chapter 464). The AHA recommendations no longer suggest routine endocarditis prophylaxis for patients with rheumatic heart disease who are undergoing dental or other procedures. However, the maintenance of optimal oral healthcare remains an important component of an overall healthcare program. For the relatively few patients with rheumatic heart disease in whom infective endocarditis prophylaxis remains recommended, such as those with a prosthetic valve or prosthetic material used in valve repair, the current AHA recommendations should be followed (see Chapter 464). These recommendations advise using an agent other than a penicillin to prevent infective endocarditis in those receiving penicillin prophylaxis for RF because oral α-hemolytic streptococci are likely to have developed resistance to penicillin.

Prognosis

The prognosis for patients with acute rheumatic fever depends on the clinical manifestations present at the initial episode, the severity of the initial episode, and the presence of recurrences. Approximately 50–70% of patients with carditis during the initial episode of acute RF recover with no residual heart disease; the more severe the initial cardiac involvement, the greater the risk for residual heart disease. Patients without carditis during the initial episode are less likely to have carditis with recurrent attacks, but there is a stepwise increase in cardiac involvement as the number of episodes increases. In contrast, patients with carditis during the initial episode are very likely to have carditis with recurrences, and the risk for permanent heart damage increases with each recurrence. Patients who have had acute RF are susceptible to recurrent attacks following reinfection of the upper respiratory tract with GAS, with approximately 50% risk with each GAS pharyngitis. Therefore, these patients require long-term continuous chemoprophylaxis.

Before antibiotic prophylaxis was available, 75% of patients who had an initial episode of acute RF had 1 or more recurrences in their lifetime. These recurrences were a major source of morbidity and mortality. The risk of recurrence is highest in the 1st 5 yr after the initial episode and decreases with time.

Approximately 20% of patients who present with “pure” chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 yr. Therefore, patients with chorea, even in the absence of other manifestations of RF, require long-term antibiotic prophylaxis (see Table 210.4).

Prevention

Prevention of both initial and recurrent episodes of acute rheumatic fever depends on controlling GAS infections of the upper respiratory tract. Prevention of initial attacks (primary prevention) depends on identification and eradication of GAS causing acute pharyngitis. A New Zealand study in a population with very high rates of acute RF showed that a school-based GAS pharyngitis screening and management program using oral amoxicillin substantially decreased pharyngeal GAS prevalence and rates of acute RF. Individuals who have already suffered an attack of acute RF are particularly susceptible to recurrences of RF with any subsequent GAS upper respiratory tract infection, whether or not they are symptomatic. Therefore, these patients should receive continuous antibiotic prophylaxis to prevent recurrences (secondary prevention).

Primary Prevention

Appropriate antibiotic therapy instituted before the 9th day of symptoms of acute GAS pharyngitis is highly effective in preventing first attacks of acute RF. However, approximately 30% of patients with acute RF do not recall a preceding episode of pharyngitis and did not seek therapy.

Secondary Prevention

Secondary prevention is directed at preventing acute GAS pharyngitis in patients at substantial risk of recurrent acute RF. Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of acute RF has been made and immediately after a full course of antibiotic therapy has been completed. Because patients who have had carditis with their initial episode of acute RF are at higher risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life (Tables 210.4 and 210.5).

Table 210.4

Chemoprophylaxis for Recurrences of Acute Rheumatic Fever (Secondary Prophylaxis)

DRUG	DOSE	ROUTE
Penicillin G benzathine	600,000 IU for children weighing ≤60 lb and 1.2 million IU for children >60 lb, every 4 wk[*]	Intramuscular
or		
Penicillin V	250 mg, twice daily	Oral
or		
Sulfadiazine or sulfisoxazole	0.5 g, once daily for patients weighing ≤60 lb	Oral
	1.0 g, once daily for patients weighing >60 lb	
For People Who Are Allergic to Penicillin and Sulfonamide Drugs		
Macrolide or azalide	Variable	Oral

[*] In high-risk situations, administration every 3 wk is recommended.

Adapted from Gerber MA, Baltimore RS, Eaton CB, et al: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, *Circulation* 119:1541–1551, 2009.

Table 210.5

Duration of Prophylaxis for People Who Have Had Acute Rheumatic Fever: AHA

Recommendations

CATEGORY	DURATION
Rheumatic fever without carditis	5 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis but without residual heart disease (no valvular disease*)	10 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 yr or until 40 yr of age, whichever is longer; sometimes lifelong prophylaxis

* Clinical or echocardiographic evidence.

Adapted from Gerber MA, Baltimore RS, Eaton CB, et al: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association (AHA) Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, *Circulation* 119:1541–1551, 2009.

Patients who did not have carditis with their initial episode of acute RF have a relatively low risk for carditis with recurrences. Antibiotic prophylaxis should continue in these patients until the patient reaches 21 yr of age or until 5 yr have elapsed since the last rheumatic fever attack, whichever is longer. The decision to discontinue prophylactic antibiotics should be made only after careful consideration of potential risks and benefits and of epidemiologic factors such as the risk for exposure to GAS infections.

The regimen of choice for secondary prevention is a single intramuscular injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for those >60 lb) every 4 wk (Table 210.4). In certain high-risk patients, and in certain areas of the world where the incidence of rheumatic fever is particularly high, use of benzathine penicillin G every 3 wk may be necessary because serum concentrations of penicillin may decrease to marginally effective levels after 3 wk. In the United States, administration of benzathine penicillin G every 3 wk is recommended only for those who have recurrent acute RF despite adherence to a 4 wk regimen. In compliant patients, continuous oral antimicrobial prophylaxis can be used. Penicillin V (250 mg twice daily) and sulfadiazine or sulfisoxazole (500 mg for those weighing ≤60 lb or 1,000 mg for those >60 lb, once daily) are equally effective when used in such patients. For the exceptional patient who is allergic to both penicillin and sulfonamides, a macrolide (erythromycin or clarithromycin) or azalide (azithromycin) may be used. Table 210.5 notes the duration of secondary prophylaxis.

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CHAPTER 211

Group B Streptococcus

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Group B streptococcus (**GBS**), or *Streptococcus agalactiae*, is a major cause of **neonatal bacterial sepsis** in the United States. Although advances in prevention strategies have led to a decline in the incidence of neonatal disease, GBS remains a major pathogen for neonates, pregnant women, and nonpregnant adults.

Etiology

Group B streptococci are facultative anaerobic gram-positive cocci that form chains or diplococci in broth and small, gray-white colonies on solid medium. GBS is definitively identified by demonstration of the Lancefield group B carbohydrate antigen, such as with latex agglutination techniques widely used in clinical laboratories. Presumptive identification can be established on the basis of a narrow zone of β-hemolysis on blood agar, resistance to bacitracin and trimethoprim-sulfamethoxazole (TMP-SMX), lack of hydrolysis of bile esculin, and elaboration of CAMP factor (named for the discoverers, Christie, Atkins, and Munch-Petersen), an extracellular protein that, in the presence of the β toxin of *Staphylococcus aureus*, produces a zone of enhanced hemolysis on sheep blood agar. Individual GBS strains are serologically classified according to the presence of 1 of the structurally distinct capsular polysaccharides, which are important virulence factors and stimulators of antibody-associated immunity. Ten GBS capsular types have been identified: types Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX.

Epidemiology

GBS emerged as a prominent neonatal pathogen in the late 1960s. For the next 2 decades, the incidence of neonatal GBS disease remained fairly constant, affecting 1.0-5.4 per 1,000 liveborn infants in the United States. Two patterns of disease were seen: **early-onset disease** , which presents at <7 days of age, and **late-onset disease** , which presents at ≥7 days of age. Since the early 1990s, widespread implementation of **maternal intrapartum chemoprophylaxis** has led to a striking decrease in the incidence of early-onset neonatal GBS disease in the United States, from 1.7 to 0.25 per 1,000 live births in recent years. This strategy has *not* had a significant effect on the incidence of late-onset disease, which has remained stable at approximately 0.3-0.4 per 1,000 live births (Fig. 211.1). The incidence of neonatal GBS disease is higher in premature and low-birthweight infants, although most cases occur in full-term infants. Rates of both early- and late-onset disease are higher in black infants.

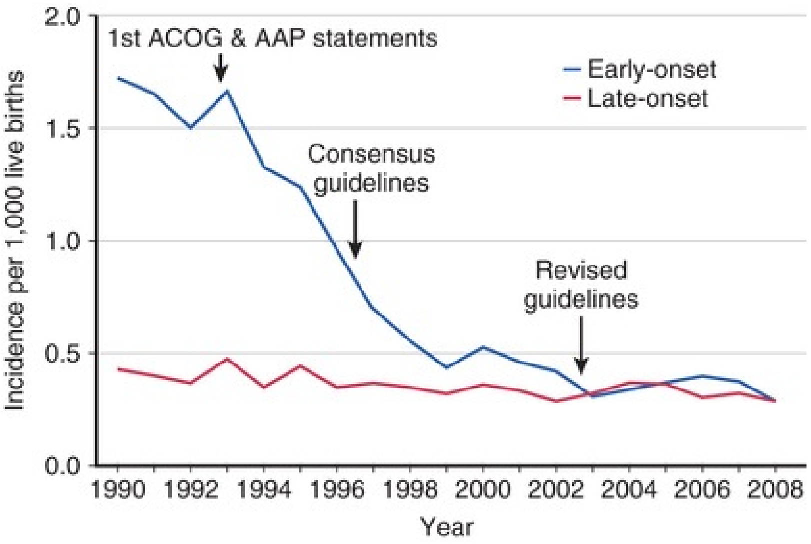

FIG. 211.1 Incidence of early- and late-onset, invasive group B streptococcal (GBS) disease–active bacterial core surveillance areas, 1990–2008, and activities for prevention of GBS disease. AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists. (Adapted from Jordan HT, Farley MM, Craig A, et al: Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease, Pediatr Infect Dis J 27:1057–1064, 2008.)

Colonization by GBS in healthy adults is common. Vaginal or rectal colonization occurs in up to approximately 30% of pregnant women and is the usual source for GBS transmission to newborn infants. In the absence of maternal chemoprophylaxis, approximately 50% of infants born to colonized women acquire GBS colonization, and 1–2% of infants born to colonized mothers develop early-onset disease. Heavy maternal colonization increases the risk for infant colonization and development of early-onset disease. Additional risk factors for early-onset disease include prolonged rupture of membranes, intrapartum fever, prematurity, maternal bacteriuria during pregnancy, or previous delivery of an infant who developed GBS disease. Risk factors for late-onset disease are less well defined. Whereas late-onset disease may follow vertical transmission, horizontal acquisition from nursery or other community sources (family, healthcare providers, placental capsules) has also been described.

GBS is also an important cause of invasive disease in adults. GBS may cause urinary tract infections, bacteremia, endometritis, chorioamnionitis, and wound infection in pregnant and parturient women. In nonpregnant adults, especially those with underlying medical conditions such as diabetes mellitus, cirrhosis, or malignancy, GBS may cause serious infections such as bacteremia, skin and soft tissue infections, bone and joint infections, endocarditis, pneumonia, and meningitis. In the era of maternal chemoprophylaxis, most invasive GBS infections occur in nonpregnant adults. Unlike neonatal disease, the incidence of invasive GBS disease in adults has increased substantially, doubling between 1990 and 2007.

The serotypes most frequently associated with neonatal GBS disease are types Ia, III, and V; Ib and II are less common. Strains of serotype III are isolated in >50% of cases of late-onset disease and of meningitis associated with early- or late-onset disease. The serotype distribution of colonizing and invasive isolates from pregnant women is similar to that from infected newborns. In Japan, serotypes VI and VIII have been reported as common maternal colonizing serotypes, and case reports indicate that type VIII strains may cause neonatal disease indistinguishable from that caused by other serotypes.

Pathogenesis

A major risk factor for the development of early-onset neonatal GBS infection is maternal vaginal or rectal colonization by GBS. Infants acquire GBS by ascending infection or during passage through the birth canal. Fetal aspiration of infected amniotic fluid may occur. The incidence of early-onset GBS infection increases with the duration of rupture of membranes. Infection may also occur through seemingly intact membranes. In cases of late-onset infection, GBS may be vertically transmitted or acquired later from maternal or nonmaternal sources.

Several bacterial factors are implicated in the pathophysiology of invasive GBS disease, primarily the type-specific **capsular polysaccharide** . Strains that are associated with invasive disease in humans elaborate more capsular polysaccharide than do colonizing isolates. All GBS capsular polysaccharides are high-molecular-weight polymers composed of repeating oligosaccharide subunits that include a short side chain terminating in *N* -acetylneuraminic acid (**sialic acid**). Studies in type III GBS show that the sialic acid component of the capsular polysaccharide prevents activation of the alternative complement pathway in the absence of type-specific antibody. Sialylated capsular polysaccharide on the GBS surface also interacts with sialic acid–binding lectins or siglecs on human leukocytes to dampen inflammatory gene activation. Thus, the capsular polysaccharide appears to exert a virulence effect by protecting the organism from opsonophagocytosis in the nonimmune host and by downregulating leukocyte activation. In addition, type-specific virulence attributes are suggested by the fact that type III strains are implicated in most cases of late-onset neonatal GBS disease and meningitis. Type III strains are taken up by brain endothelial cells more efficiently in vitro than are strains of other serotypes, although studies using acapsular mutant strains demonstrate that it is not the capsule itself that facilitates cellular invasion. A single clone of type III GBS is highly associated with late-onset disease and meningitis. This clonal group, ST-17, produces a surface-anchored protein called hypervirulent GBS adhesin (**HvgA**) that is not present in other GBS isolates. HvgA contributes to GBS adherence to intestinal and endothelial cells and mediates invasion into the central nervous system (CNS) in an experimental infection model in mice. Other putative GBS virulence factors include GBS surface proteins, which may play a role in adhesion to host cells; C5a peptidase, which is postulated to inhibit the recruitment of polymorphonuclear cells into sites of infection; β-hemolysin, which has been associated with cell injury in vitro; and hyaluronidase, which has been postulated to act as a spreading factor in host tissues.

In a classic study of pregnant women colonized with type III GBS, those who gave birth to healthy infants had higher levels of capsular polysaccharide–specific antibody than those who gave birth to infants who developed invasive disease. In addition, there is a high correlation of antibody titer to GBS type III in mother–infant paired sera. These observations indicate that transplacental transfer of maternal antibody is critically involved in neonatal immunity to GBS. Optimal immunity to GBS also requires an intact complement system. The classical complement pathway is an important component of GBS immunity in the absence of specific antibody; in addition, antibody-mediated opsonophagocytosis may proceed by the alternative complement pathway. These and other results indicate that anticapsular antibody can overcome the prevention of C3 deposition on the bacterial surface by the sialic acid component of the type III capsule.

The precise steps between GBS colonization and invasive disease remain unclear. In vitro studies showing GBS entry into alveolar epithelial cells and pulmonary vasculature endothelial cells suggest that GBS may gain access to the bloodstream by invasion from the alveolar space, perhaps following intrapartum aspiration of infected fluid. β-Hemolysin/cytolysin may facilitate GBS entry into the bloodstream following inoculation into the lungs. However, highly encapsulated GBS strains, which enter eukaryotic cells poorly in vitro compared with capsule-deficient organisms, are associated with virulence clinically and in experimental infection models.

GBS induces the release of proinflammatory cytokines. The group B antigen and the peptidoglycan component of the GBS cell wall are potent inducers of tumor necrosis factor-α release in vitro, whereas purified type III capsular polysaccharide is not. Even though the capsule plays a central role in virulence through avoidance of immune clearance, the capsule does not directly contribute to cytokine release and the resultant inflammatory response.

The complete genome sequences of hundreds of GBS strains have been reported, emphasizing a genomic approach to better understanding GBS. Analysis of these sequences shows that GBS is closely related to *Streptococcus pyogenes* and *Streptococcus pneumoniae*. Many known and putative GBS virulence genes are clustered in pathogenicity islands that also contain mobile genetic elements, suggesting that interspecies acquisition of genetic material plays an important role in genetic diversity.

Clinical Manifestations

Two syndromes of neonatal GBS disease are distinguishable on the basis of age at presentation, epidemiologic characteristics, and clinical features (Table 211.1). **Early-onset neonatal GBS disease** presents within the 1st 6 days of life and is often associated with maternal obstetric complications, including chorioamnionitis, prolonged rupture of membranes, and premature labor. Infants may appear ill at the time of delivery, and most infants become ill within 24 hr of birth. In utero infection may result in septic abortion or immediate distress after birth. More than 80% of early-onset GBS disease presents as sepsis; pneumonia and meningitis are other common manifestations. Asymptomatic bacteremia is uncommon but can occur. In symptomatic patients, nonspecific signs such as hypothermia or fever, irritability, lethargy, apnea, and bradycardia may be present. Respiratory signs are prominent regardless of the presence of pneumonia and include cyanosis, apnea, tachypnea, grunting, flaring, and retractions. A fulminant course with hemodynamic abnormalities, including tachycardia, acidosis, and shock, may ensue. Persistent fetal circulation may develop. Clinically and radiographically, pneumonia associated with early-onset GBS disease is difficult to distinguish from **respiratory distress syndrome** . Patients with meningitis often present with nonspecific findings, as described for sepsis or pneumonia, with more specific signs of CNS involvement initially absent.

Table 211.1

Characteristics of Early- and Late-Onset Group B Streptococcus Disease

	EARLY-ONSET DISEASE	LATE-ONSET DISEASE
Age at onset	0-6 days	7-90 days
Increased risk after obstetric complications	Yes	No
Common clinical manifestations	Sepsis, pneumonia, meningitis	Bacteremia, meningitis, osteomyelitis, other focal infections
Common serotypes	Ia, Ib, II, III, V	III predominates
Case fatality rate	4.7%	2.8%

Adapted from Schrag SJ, Zywicki S, Farley MM, et al: Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis, *N Engl J Med* 342:15–20, 2000.

Late-onset neonatal GBS disease presents at ≥7 days of life (may be seen in 1st 2-3 mo) and usually manifests as bacteremia (45–65%) and meningitis (25–35%). Focal infections involving bone and joints, skin and soft tissue, the urinary tract, or lungs may also be seen. Cellulitis and adenitis are often localized to the submandibular or parotid regions. In contrast to early-onset disease, maternal obstetric complications are not risk factors for the development of late-onset GBS disease. Infants with late-onset disease are often less severely ill on presentation than infants with early-onset disease, and the disease is often less fulminant.

Invasive GBS disease in children beyond early infancy is uncommon.

Bacteremia without a focus is the most common syndrome associated with childhood GBS disease beyond early infancy. Focal infections may include meningitis, pneumonia, endocarditis, and bone and joint infections.

Diagnosis

A major challenge is distinguishing between respiratory distress syndrome and invasive neonatal GBS infection in preterm infants because the 2 illnesses share clinical and radiographic features. Severe apnea, early onset of shock, abnormalities in the peripheral leukocyte count, and greater lung compliance may be more likely in infants with GBS disease. Other neonatal pathogens, including *Escherichia coli* and *Listeria monocytogenes*, may cause illness that is clinically indistinguishable from that caused by GBS.

The diagnosis of invasive GBS disease is established by isolation and identification of the organism from a normally sterile site, such as blood, urine, or cerebrospinal fluid (CSF). Isolation of GBS from gastric or tracheal aspirates or from skin or mucous membranes indicates colonization and is not diagnostic of invasive disease. CSF should be examined in all neonates suspected of having sepsis, because specific CNS signs are often absent in the presence of meningitis, especially in early-onset disease. Antigen detection methods that use group B polysaccharide–specific antiserum, such as latex particle agglutination, are available for testing of urine, blood, and CSF, but these tests are less sensitive than culture. Moreover, antigen is often detected in urine samples collected by bag from otherwise healthy neonates who are colonized with GBS on the perineum or rectum.

Laboratory Findings

Frequently present are abnormalities in the peripheral white blood cell count, including an increased or decreased absolute neutrophil count, elevated band count, increased ratio of bands to total neutrophils, or leukopenia. Elevated C-reactive protein level has been investigated as a potential early marker of GBS sepsis but is unreliable. Findings on chest radiograph are often indistinguishable from those of respiratory distress syndrome and may include reticulogranular patterns, patchy infiltrates, generalized opacification, pleural effusions, or increased interstitial markings.

Treatment

Penicillin G is the treatment of choice of confirmed GBS infection. Empirical therapy of neonatal sepsis that could be caused by GBS generally includes ampicillin and an aminoglycoside, both for the need for broad coverage pending organism identification and for synergistic bactericidal activity. Once GBS has been definitively identified and a good clinical response has occurred, therapy may be completed with penicillin alone. Especially in patients with meningitis, high doses of penicillin (450,000-500,000 units/kg/day) or ampicillin (300 mg/kg/day) are recommended because of the relatively high mean inhibitory concentration (MIC) of penicillin for GBS as well as the potential for a high initial CSF inoculum. The duration of therapy varies according to the site of infection and should be guided by clinical circumstances (Table 211.2). Extremely ill near-term patients with respiratory failure have been successfully treated with extracorporeal membrane oxygenation.

Table 211.2

Recommended Duration of Therapy for Manifestations of Group B Streptococcus Disease

TREATMENT	DURATION
Bacteremia without a focus	10 days
Uncomplicated meningitis	14 days
Ventriculitis	At least 4 wk
Septic arthritis or osteomyelitis	3-4 wk

Data from the American Academy of Pediatrics: Group B streptococcal infections. In Kimberlin DW, Brady MT, Jackson MA, Long SS, editors: *Red book: 2015 report of the Committee on Infectious Diseases* , ed 30. Elk Grove Village, IL, 2015, American Academy of Pediatrics, pp 746–747.

In patients with GBS meningitis, some experts recommend that additional CSF be sampled at 24-48 hr to determine whether sterility has been achieved. Persistent GBS growth may indicate an unsuspected intracranial focus or an insufficient antibiotic dose.

For **recurrent neonatal GBS disease** , standard intravenous antibiotic therapy followed by attempted eradication of GBS mucosal colonization has been suggested. This suggestion is based on the findings in several studies that invasive isolates from recurrent episodes are usually identical to each other and to colonizing isolates from the affected infant. Rifampin has most frequently been used for this purpose, but one report demonstrates that eradication of GBS colonization in infants is not reliably achieved by rifampin therapy. Optimal management of this uncommon situation remains unclear.

Prognosis

Studies from the 1970s and 1980s showed that up to 30% of infants surviving GBS meningitis had major long-term neurologic sequelae, including developmental delay, spastic quadriplegia, microcephaly, seizure disorder, cortical blindness, or deafness; less severe neurologic complications may be present in other survivors. A study of infants who survived GBS meningitis diagnosed from 1998 through 2006 found that 19% had severe **neurologic impairment** and 25% had mild to moderate impairment at long-term follow-up. Periventricular leukomalacia and severe developmental delay may result from GBS disease and accompanying shock in premature infants, even in the absence of meningitis. The outcome of focal GBS infections outside the CNS, such as bone or soft tissue infections, is generally favorable.

In the 1990s, the case fatality rates associated with early- and late-onset neonatal GBS disease were 4.7% and 2.8%, respectively. Mortality is higher in premature infants; one study reported a case fatality rate of 30% in infants at gestational age <33 wk and 2% in those ≥37 wk. The case fatality rate in children age 3 mo to 14 yr was 9%, and in nonpregnant adults, 11.5%.

Prevention

Persistent morbidity and mortality from perinatal GBS disease despite advances in neonatal care have spurred intense investigation into modes of prevention. Two basic approaches to GBS prevention have been investigated: elimination of colonization from the mother or infant (chemoprophylaxis) and induction of protective immunity (immunoprophylaxis).

Chemoprophylaxis

Administration of antibiotics to pregnant women *before* the onset of labor does not reliably eradicate maternal GBS colonization and is not an effective means of preventing neonatal GBS disease. Interruption of neonatal colonization is achievable through administration of antibiotics to the mother **during labor** .

Infants born to GBS-colonized women with premature labor or prolonged rupture of membranes who were given **intrapartum chemoprophylaxis** had a substantially lower rate of GBS colonization (9% vs 51%) and early-onset disease (0% vs 6%) than did the infants born to women who were not treated. Maternal postpartum febrile illness was also decreased in the treatment group.

In the mid-1990s, guidelines for chemoprophylaxis were issued that specified administration of intrapartum antibiotics to women identified as *high risk* by either culture-based or risk factor–based criteria. These guidelines were revised in 2002 after epidemiologic data indicated the superior protective effect of the **culture-based** approach in the prevention of neonatal GBS disease, and further revised guidelines were issued in 2010. According to current recommendations, vaginorectal GBS screening cultures should be performed for all pregnant women at 35–37 wk gestation, except for those with GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease. Any woman with a positive prenatal screening culture, GBS bacteriuria during pregnancy, or a previous infant with invasive GBS disease should receive intrapartum antibiotics. Women whose culture status is unknown (culture not done, incomplete, or results unknown) and who deliver prematurely (<37 wk gestation), experience prolonged rupture of membranes (≥18 hr), experience intrapartum fever (≥38°C [100.4°F]), or have a positive nucleic acid amplification test for GBS should also receive intrapartum chemoprophylaxis (Figs. 211.2 and 211.3). Routine intrapartum prophylaxis is not recommended for women with GBS colonization undergoing planned cesarean delivery who have not begun labor or had rupture of membranes.

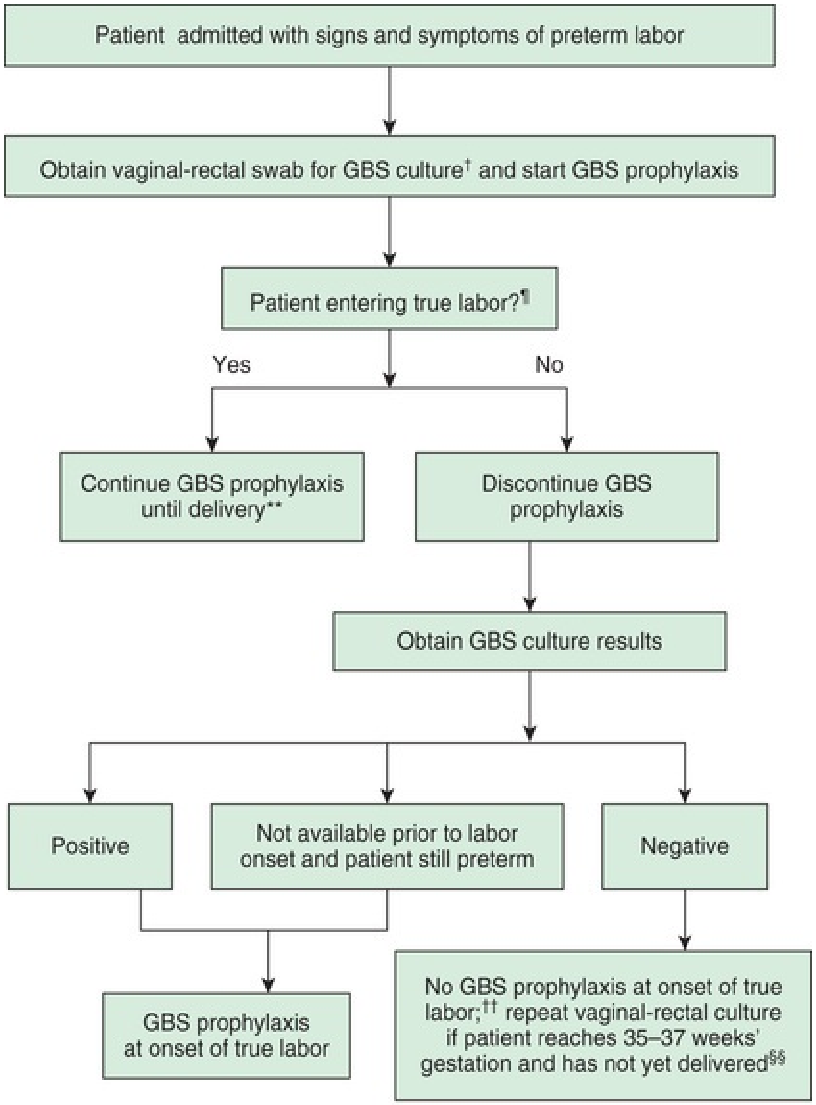
Patient admitted with signs and symptoms of preterm labor
Obtain vaginal-rectal swab for GBS culture† and start GBS prophylaxis
Patient entering true labor?¶
Yes
No
Continue GBS prophylaxis until delivery**
Discontinue GBS prophylaxis
Obtain GBS culture results
Positive
Not available prior to labor onset and patient still preterm
Negative
GBS prophylaxis at onset of true labor
No GBS prophylaxis at onset of true labor;†† repeat vaginal-rectal culture if patient reaches 35–37 weeks' gestation and has not yet delivered§§

[*] At <37 weeks and 0 days' gestation.

[†] If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

[¶] Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis.

[**] If GBS culture results become available prior to delivery and are negative, then discontinue GBS prophylaxis.

[††] Unless subsequent GBS culture prior to delivery is positive.

[§§] A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is re-admitted with signs and symptoms of PTL and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time.

FIG. 211.2 Algorithm for GBS intrapartum prophylaxis for women with preterm labor (PTL). (From Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases, National Center for Immunization and Respiratory

Diseases, Centers for Disease Control and Prevention (CDC): Prevention of perinatal group B streptococcal disease—revised guidelines from CDC 2010, *MMWR Recomm Rep* 59[RR-10]:22, 2010.)

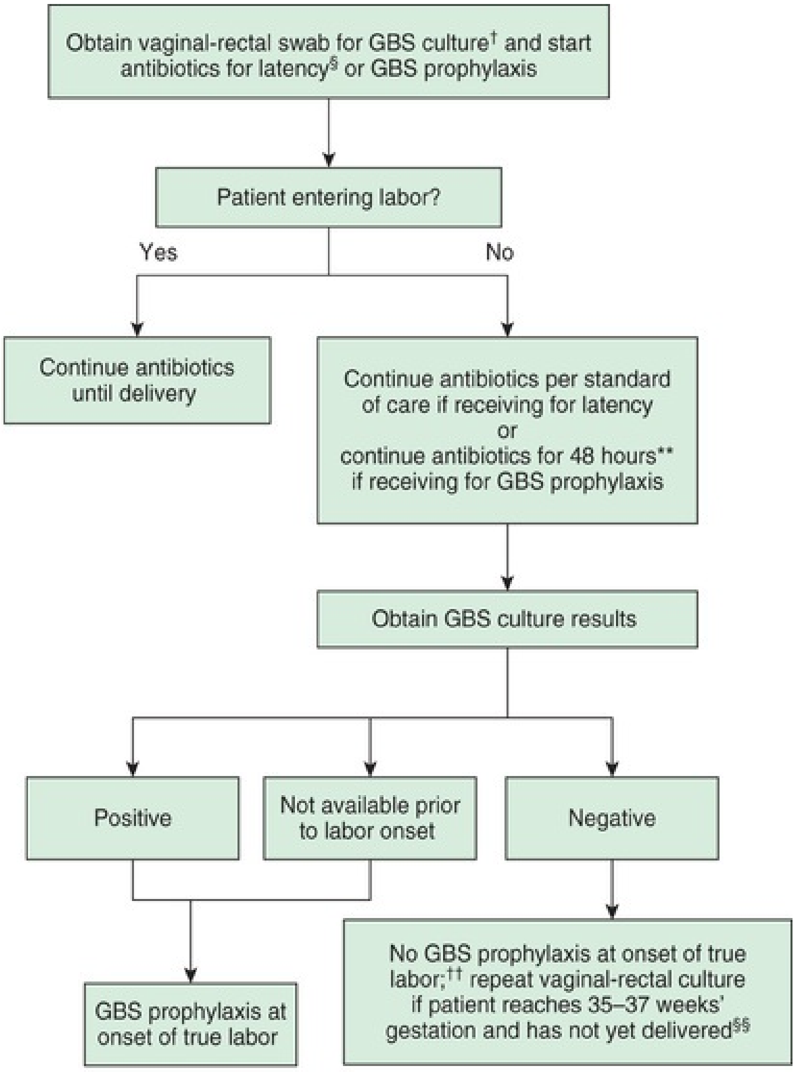

Obtain vaginal-rectal swab for GBS culture[†] and start antibiotics for latency[§] or GBS prophylaxis
Patient entering labor?
Yes
No
Continue antibiotics until delivery
Continue antibiotics per standard of care if receiving for latency or continue antibiotics for 48 hours[**] if receiving for GBS prophylaxis
Obtain GBS culture results
Positive
Not available prior to labor onset
Negative
GBS prophylaxis at onset of true labor
No GBS prophylaxis at onset of true labor;[††] repeat vaginal-rectal culture if patient reaches 35–37 weeks' gestation and has not yet delivered[§§]

[*] At <37 weeks and 0 days' gestation.

[†] If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative.

[§] Antibiotics given for latency in the setting of pPROM that include ampicillin 2 g intravenously (IV) once, followed by 1 g IV every 6 hours for at least 48 hours are adequate for GBS prophylaxis. If other regimens are used, GBS prophylaxis should be initiated in addition.

[**] GBS prophylaxis should be discontinued at 48 hours for women with pPROM who are not in labor. If results from a GBS screen performed on admission become available during the 48-hour period and are negative, GBS prophylaxis should be discontinued at that time.

[††] Unless subsequent GBS culture prior to delivery is positive.

[§§] A negative GBS screen is considered valid for 5 weeks. If a patient with pPROM is entering labor and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time.

FIG. 211.3 Algorithm for screening for group B streptococcal (GBS) colonization and use of intrapartum prophylaxis for women with preterm premature rupture of membranes (pPROM). (From Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases, National Center for

Immunization and Respiratory Diseases, Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC 2010. *MMWR Recomm Rep* 59[RR-10]:22, 2010.)

Penicillin remains the preferred agent for **maternal chemoprophylaxis** because of its narrow spectrum and the universal penicillin susceptibility of GBS isolates associated with human infection. Ampicillin is an acceptable alternative. If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent active against GBS should replace GBS prophylaxis. Occasional GBS isolates have demonstrated reduced in vitro susceptibility to penicillin and other β-lactam antibiotics in association with mutations in penicillin-binding proteins. However, the clinical significance of these higher MIC values is unclear. Because of frequent resistance of GBS to clindamycin (up to 38%), cefazolin should be used in most cases of intrapartum chemoprophylaxis for penicillin-intolerant women. For penicillin-allergic women at high risk for anaphylaxis, clindamycin should be used, if isolates are demonstrated to be susceptible. Vancomycin should be used if isolates are resistant to, or demonstrate inducible resistance to, clindamycin or if clindamycin susceptibility is unknown.

The U.S. Centers for Disease Control and Prevention (CDC) guidelines also provide recommendations for secondary prevention of early-onset GBS disease in newborns (Fig. 211.4). Extent of newborn evaluation and decision to institute empirical antibiotics are guided by clinical evaluation of the infant as well as gestational age, maternal risk factors, and receipt of intrapartum prophylaxis. In the era of maternal chemoprophylaxis, most cases of early-onset disease are seen in infants born to women with negative prenatal screening cultures. Data from a large epidemiologic study indicate that the administration of maternal intrapartum antibiotics does not change the clinical spectrum or delay the onset of clinical signs in infants who developed GBS disease despite maternal prophylaxis.

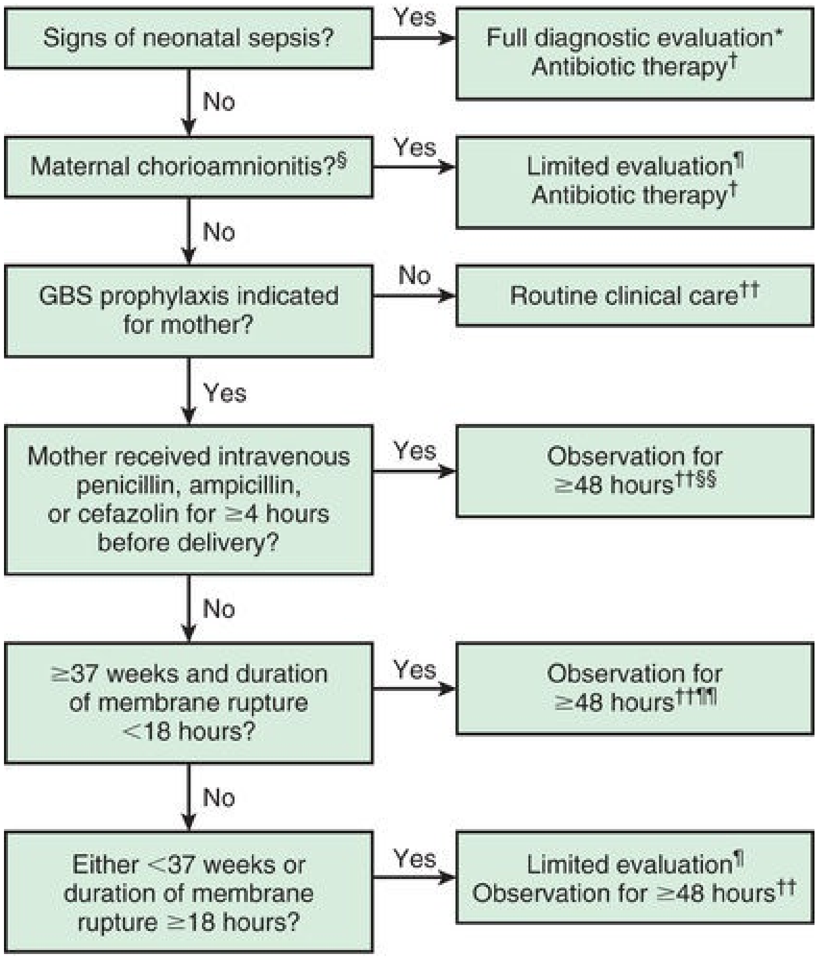
Signs of neonatal sepsis?
Yes
Full diagnostic evaluation*
Antibiotic therapy†
No
Maternal chorioamnionitis?§
Yes
Limited evaluation¶
Antibiotic therapy†
No
GBS prophylaxis indicated for mother?
No
Routine clinical care††
Yes
Mother received intravenous penicillin, ampicillin, or cefazolin for ≥4 hours before delivery?
Yes
Observation for ≥48 hours††§§
No
≥37 weeks and duration of membrane rupture <18 hours?
Yes
Observation for ≥48 hours††¶¶
No
Either <37 weeks or duration of membrane rupture ≥18 hours?
Yes
Limited evaluation¶
Observation for ≥48 hours††

* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

FIG. 211.4 Algorithm for secondary prevention of early-onset group B streptococcal disease among newborns. (From Verani JR, McGee L,

Schrag SJ, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC 2010, *MMWR Recomm Rep* 59[RR-10]:22, 2010.)

A significant concern with maternal intrapartum chemoprophylaxis has been that large-scale antibiotic use among parturient women might lead to increased rates of antimicrobial resistance or infection in infants with organisms other than GBS, but this has not been borne out. In a population-based study of early-onset neonatal infection from 2005–2014, the incidence of early-onset sepsis both overall and caused by *E. coli* remained stable. At present, the substantial decline in early-onset neonatal GBS disease favors continued broad-scale intrapartum chemoprophylaxis, but continued surveillance is required.

A limitation of the maternal chemoprophylaxis strategy is that intrapartum antibiotic use is unlikely to have an impact on late-onset neonatal disease, miscarriages, or stillbirths attributed to GBS, or adult GBS disease. In addition, with wider implementation of maternal chemoprophylaxis, an increasing percentage of early-onset neonatal disease has been in patients born to women with negative cultures, that is, false-negative screens.

Maternal Immunization

Human studies demonstrate that transplacental transfer of naturally acquired maternal antibody to the GBS capsular polysaccharide protects newborns from invasive GBS infection, and that efficient transplacental passage of vaccine-induced GBS antibodies occurs. Conjugate vaccines composed of the GBS capsular polysaccharides coupled to carrier proteins have been produced for human use. In early clinical trials, conjugate GBS vaccines were well tolerated and induced levels of functional antibodies well above the range believed to be protective in >90% of recipients. A vaccine containing type III polysaccharide coupled to tetanus toxoid was safely administered to pregnant women and elicited functionally active type-specific antibody that was efficiently transported to the fetus. Vaccines containing GBS surface proteins have been considered as a means to provide protection against strains of multiple serotypes, and availability of whole genome sequencing has enabled identification of vaccine protein candidates.

A successful GBS maternal vaccine administered before or during pregnancy should lead to transplacental passage of vaccine-induced antibody that protects the fetus and newborn against infection by several GBS serotypes. Such a vaccine would eliminate the need for cumbersome cultures during pregnancy, circumvent the various risks associated with large-scale antibiotic prophylaxis, likely have an impact on both early- and late-onset disease, and provide a prevention strategy in middle and low income countries, where maternal chemoprophylaxis may not be feasible. Intrapartum chemoprophylaxis will likely remain an important aspect of prevention, particularly for women in whom opportunities for GBS immunization are missed and for infants born so early that levels of transplacentally acquired antibodies may not be high enough to be protective.

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CHAPTER 212

Non–Group A or B Streptococci

David B. Haslam

The genus *Streptococcus* is exceptionally diverse and includes the major human pathogens *Streptococcus pyogenes* (group A streptococcus), *Streptococcus agalactiae* (group *B* streptococcus), and *Streptococcus pneumoniae* . Other important pathogens include large-colony species–bearing Lancefield groups C and G antigens and numerous small-colony variants that may or may not express Lancefield carbohydrate antigen among the viridians streptococci (Table 212.1). This chapter focuses on ***Streptococcus dysgalactiae* subspecies *equisimilis,*** commonly known as “group C and G streptococci”; Chapter 209 discusses *S. pneumoniae*, and Chapter 213 discusses enterococci.

Table 212.1

Relationship of Streptococci Identified by Hemolysis and Lancefield Grouping to Sites of Colonization and Disease

	Group A Streptococcus (*S. pyogenes*)	Group B Streptococcus (*S. agalactiae*)	Other β-HEMOLYTIC STREPTOCOCCI	Viridans Streptococci
Hemolysis	β	β	β	α
Lancefield group	A	B	C-H, K-V Especially C and G	
Species or strains	M types (>180)	Serotypes (Ia, Ib, II, III, IV, V, VI, VII, and VIII)		*Streptococcus bovis* *Streptococcus mitis* *Streptococcus mutans* *Streptococcus sanguis* Many others
Normal	Pharynx, skin, anus	Gastrointestinal	Pharynx, skin,	Pharynx,

flora		and genitourinary tract	gastrointestinal and genitourinary tracts	nose, skin, genitourinary tract
Common human diseases	Pharyngitis, tonsillitis, erysipelas, impetigo, septicemia, wound infections, necrotizing fasciitis, cellulitis, meningitis, pneumonia, scarlet fever, toxic shock–like syndrome, rheumatic fever, acute glomerulonephritis	Puerperal sepsis chorioamnionitis, endocarditis, neonatal sepsis, meningitis, osteomyelitis, pneumonia	Wound infections, puerperal sepsis, cellulitis, sinusitis, endocarditis, brain abscess, sepsis, nosocomial infections, opportunistic infections	Endocarditis, human bite infections

α, Partial hemolysis; β, complete hemolysis; γ, no hemolysis (nonhemolytic).

All members of the genus *Streptococcus* are gram-positive, catalase-negative organisms. Lancefield carbohydrate antigen, hemolytic activity, and colony morphology have classically been used to further distinguish and classify streptococci. These features provide a useful framework for the clinician and are still the most commonly used classification schema. However, grouping based on these phenotypic features does not precisely correlate with genetic relatedness, and it is becoming clear that disease propensity is better correlated with sequence homology than with Lancefield grouping or hemolytic activity.

In this chapter, groups C and G streptococci refer exclusively to the large colony-forming organisms, often called “*S. pyogenes*– like,” because their microbiologic and clinical features tend to mimic those of group A streptococcus. Despite their different Lancefield antigens, the group C and G streptococci are almost identical genetically and are placed within the *S. dysgalactiae* subsp. *equisimilis* (**SDSE**) group. Their genome sequences are approximately equidistant between *S. pyogenes* and animal pathogens that bear the group C antigen, which are classified as *S. dysgalactiae* subsp. *dysgalactiae.* These 2 subspecies of *S. dysgalactiae* likely will be split into distinct species in the future, when their sequence-based grouping will reflect their propensity to cause human (represented by subsp. *equisimilis*) and animal (represented by subsp. *dysgalactiae*) infections.

The groups C and G streptococci share a number of virulence factors with *S. pyogenes* , including the production of streptolysin O, M protein, streptococcal pyrogenic exotoxin B, and hyaluronidase. The M protein is similar to that of *S. pyogenes* and may account for postinfectious **glomerulonephritis** that is occasionally seen after infection with these organisms. A toxic shock–like syndrome associated with groups C and G streptococcal infection has been related to M protein type and production of a pyrogenic exotoxin by SDSE.

SDSE organisms are common habitants of the pharynx, detected in up to 5% of asymptomatic children. Other potential sites of colonization include the skin and gastrointestinal tract. Colonization of the vagina is reported and may be the source of occasional SDSE isolated from the umbilicus of healthy neonates.

Clinical manifestations of disease caused by SDSE overlap those of disease caused by *S. pyogenes* . In children, these organisms are implicated most often in **pharyngitis** . The true role of these organisms as a cause of pharyngitis is difficult to determine because asymptomatic colonization is common. Nevertheless, several epidemics of SDSE pharyngitis have been reported, including food-borne outbreaks. A large study in Japan reported the detection of *S. pyogenes* in 15% and SDSE in 2% of children with pharyngitis. The clinical presentation of SDSE is indistinguishable from *S. pyogenes*– associated pharyngitis. Isolated case reports have described SDSE **pneumonia** in children, which is commonly complicated by abscess formation, empyema, and bacteremia. Additional respiratory infections include rare reports of epiglottitis and sinusitis.

SDSE are a significant cause of skin and soft tissue infections. As with *S. pyogenes*, **lymphangitis** can complicate superficial infections caused by SDSE. Musculoskeletal infections, particularly pyogenic arthritis, occasionally are caused by SDSE. Pediatric cases are uncommon but may be increasing in incidence.

Reactive arthritis has been described after SDSE infection; however, unlike the situation with *S. pyogenes* , the association between SDSE infection and acute rheumatic fever has not clearly been defined, and antibiotic prophylaxis is not recommended following reactive arthritis caused by SDSE.

Endocarditis, bacteremia, brain abscess, and toxic shock syndrome caused by SDSE have all been described but are uncommon in children. These infections generally occur in children with immune deficits or in adolescents after delayed recognition of sinusitis.

These organisms can cause neonatal **septicemia** similar to early-onset group B streptococcal disease. Risk factors include prematurity and prolonged rupture of membranes. Respiratory distress, hypotension, apnea, bradycardia, and disseminated intravascular coagulation may be seen, and associated maternal infection is common. Neonatal toxic shock syndrome associated with SDSE has also been described.

Treatment of SDSE infections is similar to that of *S. pyogenes.* These organisms retain susceptibility to penicillin and other β-lactams. Other agents with reliable activity include linezolid, quinupristin-dalfopristin, and vancomycin, although occasional isolates demonstrate tolerance to vancomycin.

Clindamycin and macrolides have poor bactericidal activity against these organisms and are associated with significant resistance rates. Resistance to quinolones is reported, and up to 70% of SDSE cases are resistant to tetracycline.

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CHAPTER 213

Enterococcus

David B. Haslam

Enterococcus has long been recognized as a pathogen in select populations and has become a common and particularly troublesome cause of hospital-acquired infection over the past 2 decades. Formerly classified with *Streptococcus bovis* and *Streptococcus equinus* as Lancefield group D streptococci, enterococci are placed in a separate genus and are notorious for causing hospital-acquired infection and resisting antibiotics.

Etiology

Enterococci are gram-positive, catalase-negative facultative anaerobes that grow in pairs or short chains. Most are nonhemolytic (also called γ-hemolytic) on sheep blood agar, although some isolates have α- or β-hemolytic activity. Enterococci are distinguished from most Lancefield-groupable streptococci by their ability to grow in bile and hydrolyze esculin. They are able to grow in 6.5% NaCl and hydrolyze L -pyrrolidinyl-β-naphthylamide, features used by clinical laboratories to distinguish them from group D streptococcus. Identification at the species level is achieved by differing patterns of carbohydrate fermentation.

Epidemiology

Enterococci are normal inhabitants of the gastrointestinal (GI) tract of humans and organisms throughout the animal kingdom, suggesting they are highly evolved to occupy this niche. Oral secretions and dental plaque, the upper respiratory tract, skin, and vagina may also be colonized by *Enterococcus*. *Enterococcus faecalis* is the predominant organism, with colonization usually occurring in the 1st wk of life. By the time of adulthood, *E. faecalis* colonization is nearly ubiquitous but accounts for a minor fraction of the intestinal microbiota in the normal host. *Enterococcus faecium* colonization is less consistent, although approximately 25% of adults harbor this organism, generally at very low abundance. Disruption of the normal intestinal microbiota by antibiotic exposure or hematopoietic stem cell transplantation greatly enriches for fecal enterococcal abundance and dramatically increases the risk of subsequent bloodstream infection.

E. faecalis accounts for approximately 80% of enterococcal infections, with almost all the remaining infections caused by *E. faecium.* Only rarely are other species, such as *Enterococcus gallinarum* and *Enterococcus casseliflavus,* associated with invasive infection, but these organisms are notable for their intrinsic low-level vancomycin resistance. Whole genome sequencing suggests that the patient's indigenous flora is the source of enterococcal infection in most cases. However, direct spread from person to person or from contaminated medical devices may occur, particularly within newborn nurseries and intensive care units (NICUs), where nosocomial spread has resulted in hospital outbreaks.

Pathogenesis

Enterococci are not aggressively invasive organisms, usually causing disease only in children with damaged mucosal surfaces or impaired immune response. Their dramatic emergence as a cause of nosocomial infection is predominantly a result of their resistance to antibiotics commonly used in the hospital setting. **Hospital-associated enterococci** generally lack CRISPR (clustered regularly interspaced short palindromic repeat) elements. Their diverse antimicrobial resistance repertoire is likely related to deficient CRISPR-mediated defense against phage-mediated horizontal gene transfer. Secreted and cell surface molecules are implicated in pathogenesis. Adhesion-promoting factors such as the surface protein Eps likely account for the propensity of these organisms to cause endocarditis and urinary tract infections (UTIs). The ability to form biofilms likely facilitates the colonization of urinary and vascular catheters. Other proposed virulence factors include cytolysin, aggregation substance, gelatinase, and extracellular superoxide.

Antimicrobial Resistance

Enterococci are *highly resistant* to cephalosporins and semisynthetic penicillins such as nafcillin, oxacillin, and methicillin. They are moderately resistant to extended-spectrum penicillins such as ticarcillin and carbenicillin. Ampicillin, imipenem, and penicillin are the most active β-lactams against these organisms. Some strains of *E. faecalis* and *E. faecium* demonstrate decreased resistance to β-lactam antibiotics because of mutations in penicillin-binding protein 5. In addition, occasional strains of *E. faecalis* produce a plasmid-encoded β-lactamase similar to that found in *Staphylococcus*. These isolates are completely resistant to penicillins, necessitating the combination of a penicillin plus a β-lactamase inhibitor or the use of imipenem or vancomycin. Any active drug may be insufficient if used alone for serious infections where high bactericidal activity is desired (Tables 213.1 and 213.2).

Table 213.1

Intrinsic Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin	Altered binding protein
Aminoglycoside (low level)	Decreased permeability, altered ribosomal binding
Clindamycin	Altered ribosomal binding
Erythromycin	Altered ribosomal binding
Tetracyclines	Efflux pump
Trimethoprim-sulfamethoxazole	Utilize exogenous folate

Table 213.2

Acquired Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin (high level)	Mutation of PBP5
Aminoglycoside (high level)	Enzyme modification
Quinolones	DNA gyrase mutation
Chloramphenicol	Efflux pump
Glycopeptide	Altered cell wall binding
Quinupristin-dalfopristin	Ribosomal modification, efflux pump
Linezolid	Point mutation
Daptomycin	Unknown

All enterococci have intrinsic *low-level resistance* to aminoglycosides because these antibiotics are poorly transported across the *Enterococcus* cell wall. Concomitant use of a cell wall active agent, such as a β-lactam or glycopeptide antibiotic, improves the permeability of the cell wall for the aminoglycosides, resulting in synergistic killing. However, some isolates demonstrate high-level resistance, defined as mean inhibitory concentration (MIC) >2,000 µg/mL, a result of modification or inactivation of aminoglycoside agents. Strains demonstrating high-level resistance and even some moderately resistant isolates are not affected synergistically by aminoglycosides and cell wall–active antibiotics.

Resistance to almost all other antibiotic classes, including tetracyclines, macrolides, and chloramphenicol, has been described among the enterococci, necessitating individual susceptibility testing for these antibiotics when their use is considered. Despite apparent susceptibility in vitro, trimethoprim-sulfamethoxazole (TMP-SMX) has poor activity in vivo and should not be used as the primary agent against *Enterococcus* infections.

Whereas ampicillin and vancomycin continue to have reliable activity against *E. faecalis* , resistance to both antibiotics is prevalent among *E. faecium* . Resistance to vancomycin, defined as MIC >32 µg/mL, and other glycopeptides, including teicoplanin, occurs in >30% of invasive *E. faecium* infections. Rates of vancomycin-resistant *Enterococcus* (**VRE**) have increased >2-fold since 2000 and have become a major challenge in the care of hospitalized patients. Mortality in patients with VRE bloodstream infections is considerable, and treatment is complicated by frequent resistance of VRE to most other antibiotic classes. Both high- and moderate-level resistance are described in *E. faecalis* and *E. faecium.* High-level resistance (MIC ≥64 µg/mL) can be transferred by way of conjugation and usually results from plasmid-mediated transfer of the *vanA* gene. High-level resistance is most common among *E. faecium* but is increasingly seen among *E. faecalis* isolates. Moderate-level resistance (MIC 8-256 µg/mL) results from a chromosomal homolog of *vanA*, known as *vanB.* Isolates that harbor the *vanB* gene are only moderately resistant to vancomycin and initially demonstrate susceptibility to teicoplanin, although resistance can emerge during therapy. Resistance to newer agents, including linezolid and daptomycin, is rare thus far. **Linezolid** resistance is a result of mutations in the 26S ribosomal subunit, whereas **daptomycin** resistance is associated with mutations in genes required for membrane synthesis and repair.

Clinical Manifestations

Enterococcus infections traditionally occurred predominantly in newborn infants; however, infection in older children is increasingly common. Most

Enterococcus infections occur in patients with breakdown of normal physical barriers such as the GI tract, skin, or urinary tract. Other risk factors for *Enterococcus* infection include cancer chemotherapy, prolonged hospitalization, indwelling vascular catheters, prior use of antibiotics, and compromised immunity.

Neonatal Infections

Enterococcus accounts for up to 15% of all neonatal bacteremia and septicemia. As with group B streptococcus infections, *Enterococcus* infections are seen in 2 distinct settings in neonatal patients. Early-onset infection (<7 days of age) may mimic early-onset group B streptococcus septicemia but tends to be milder. Early-onset *Enterococcus* sepsis most often occurs in full-term infants who are otherwise healthy. Late-onset infection (≥7 days old) is associated with risk factors such as extreme prematurity, presence of an intravascular catheter, or **necrotizing enterocolitis** (NEC), or it follows an intraabdominal surgical procedure. Symptoms in late-onset disease are more severe than those in early-onset disease and include apnea, bradycardia, and deteriorating respiratory function. Associated focal infections include scalp abscess and catheter infection. Mortality rates range from 6% in early-onset septicemia to 15% in late-onset infections associated with NEC.

Enterococci are an occasional cause of **meningitis** . In neonates in particular, meningitis usually occurs as a complication of septicemia. Alternatively, the organism may gain access to the central nervous system by way of contiguous spread, such as through a neural tube defect or in association with an intraventricular shunt. *Enterococcus* meningitis can be associated with minimal abnormality of cerebrospinal fluid.

Infections in Older Children

Enterococcus rarely causes UTIs in healthy children but accounts for approximately 15% of cases of nosocomially acquired UTIs in both children and adults. Presence of an indwelling urinary catheter is the major risk factor for nosocomial UTIs. *Enterococcus* is frequently isolated in intraabdominal infections following intestinal perforation or surgery. The significance of enterococci in polymicrobial infections has been questioned, although reported mortality rates are higher when intraabdominal infections include enterococci.

Enterococcus is increasingly common as a cause of nosocomial bacteremia, including catheter-associated bloodstream infections (**CLABSIs**); these organisms accounted for approximately 10% of CLABSIs in children, ranking 3rd after coagulase-negative staphylococci and *Staphylococcus aureus.* Predisposing factors for enterococcal bacteremia and endocarditis include an indwelling central venous catheter, GI surgery, immunodeficiency, and cardiovascular abnormalities. Risk factors for VRE bacteremia include residence on hematology/oncology unit, prolonged mechanical ventilation, immunosuppression, and recent broad-spectrum antibiotic exposure.

Treatment

Treatment of invasive *Enterococcus* infections must recognize that these organisms are resistant to antimicrobial agents frequently used as empirical therapy. In particular, **cephalosporins** should not be relied on in situations where *Enterococcus* is known or suspected to be involved. In general, in the immunocompetent host, minor localized infections caused by susceptible *Enterococcus* can be treated with ampicillin alone. Antibiotics containing β-lactamase inhibitors (clavulanate or sulbactam) provide advantage only for the few organisms whose resistance results from production of β-lactamase. In uncomplicated UTIs, nitrofurantoin is efficacious when the organism is known to be sensitive to this antibiotic.

Invasive infections, such as sepsis, meningitis, and endocarditis, are usually treated with penicillin or ampicillin if the organism is susceptible. Addition of an aminoglycoside has traditionally been suggested but is associated with nephrotoxicity and may not be routinely indicated in uncomplicated enterococcal bloodstream infection. Vancomycin can be substituted for the penicillins in allergic patients but should be used with an aminoglycoside because vancomycin alone is not bactericidal. Endocarditis from strains possessing high-level aminoglycoside resistance may relapse even after prolonged therapy. High-dose or continuous infusion penicillin has been proposed for treatment of these infections in adults, yet ultimately valve replacement may be necessary. In patients with catheter-associated enterococcal bacteremia, the catheter should be removed promptly in most cases, although infected lines have been salvaged with the combined use of ampicillin or vancomycin and an aminoglycoside.

Vancomycin-Resistant Enterococci

The treatment of serious infections caused by multiresistant, vancomycin-resistant strains is particularly challenging. **Linezolid** , an oxazolidinone antibiotic that inhibits protein synthesis, is bacteriostatic against most *E. faecium* and *E. faecalis* isolates, including VRE isolates. Response rates are generally >90%, including cases of bacteremia and sepsis, and this antibiotic has become the preferred agent in treatment of VRE infections in many institutions. Anecdotal reports reveal the success of linezolid in treating meningitis caused by VRE. Unfortunately, as seen with other antibiotics, linezolid resistance is documented, and nosocomial spread of these organisms can occur. Linezolid frequently causes reversible bone marrow suppression after prolonged use and is associated with rare occurrences of lactic acidosis and irreversible peripheral neuropathy. **Serotonin syndrome** may be seen in patients taking concomitant selective serotonin reuptake inhibitor antidepressants. Oxazolidinones in development include **tedizolid** , which has better in vitro activity against enterococci and appears to have favorable pharmacokinetic and toxicity profiles compared to linezolid.

Daptomycin is a cyclic lipopeptide that is rapidly bactericidal against a broad range of gram-positive organisms. This antibiotic inserts into the bacterial cell wall, causing membrane depolarization and cell death. It has been approved for the treatment of adults with serious skin and soft tissue infections, right-sided endocarditis, and bacteremia caused by susceptible organisms. Most strains of VRE (both *E. faecium* and *E. faecalis*) are susceptible to daptomycin in vitro, and its efficacy in adult patients with VRE appears to be similar to that of linezolid. Experience with daptomycin in children is limited, particularly in the setting of *Enterococcus* infections. However, based on the experience with adult patients, daptomycin may be an alternative to linezolid when resistance or side effects limit utility of that antibiotic. Daptomycin dosages may need to be higher in children than adults because of more rapid renal clearance. The antibiotic has unreliable activity in the lung and therefore should not be used as a sole agent to treat pneumonia. Resistance of both *Staphylococcus aureus* and *Enterococcus* to daptomycin has rarely been described, sometimes arising during therapy.

Quinupristin-dalfopristin is a combined streptogramin antibiotic that inhibits bacterial protein synthesis at 2 different stages. It has activity against most *E. faecium* strains, including those with high-level vancomycin resistance. Approximately 90% of *E. faecium* strains are susceptible to quinupristin-dalfopristin in vitro. Notably, it is inactive against *E. faecalis* and therefore should not be used as the sole agent against gram-positive organisms until culture results exclude the presence of *E. faecalis* . Studies in children suggest that this antibiotic is effective and generally well tolerated, although episodes of arthralgia and myalgia during therapy are reported. Emergence of resistance to quinupristin-dalfopristin is rare but has been demonstrated.

Tigecycline is the first clinically available glycylcycline antibiotic, an expended-spectrum derivative of the tetracycline family. The agent inhibits protein synthesis by binding to the 30S ribosome and is bacteriostatic against susceptible organisms. Tigecycline has broad activity against gram-positive, gram-negative, and anaerobic organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE, and is approved for the treatment of adults with skin and soft tissue infections and intraabdominal infections caused by susceptible organisms. Its efficacy in VRE infections has not yet been demonstrated in clinical trials, and there is little published experience with the use of tigecycline in children thus far. As with other tetracycline antibiotics, tigecycline use may cause discoloration of the teeth, and its use in children <8 yr old should generally be avoided. GI side effects are common and may be intolerable.

Ceftaroline , a fifth-generation cephalosporin with activity against MRSA, has activity against many *E. faecalis* strains and may be highly synergistic with daptomycin against daptomycin-nonsusceptible strains. Ceftaroline has poor activity against *E. faecium* and should not be relied on as the sole agent to treat infections caused by this organism.

Prevention

Strategies for preventing enterococcal infections include timely removal of urinary and intravenous catheters and debridement of necrotic tissue. Infection control strategies, including surveillance cultures, patient and staff cohorting, and strict gown and glove isolation, are effective at decreasing colonization rates with VRE. Unfortunately, these organisms may persist on inanimate objects such as stethoscopes, complicating efforts to limit their nosocomial spread. To prevent the emergence and spread of vancomycin-resistant organisms, the U.S. Centers for Disease Control and Prevention (CDC) has developed a series of guidelines for prudent vancomycin use. Antibiotics with broad activity against anaerobic organisms are also thought to contribute to colonization with VRE, suggesting that prudent use of such antibiotics may also help limit spread of VRE. Decolonization strategies have been attempted but are generally ineffective in eradicating skin or GI carriage of VRE. In particular, antimicrobial therapy is not indicated for this purpose. The role of probiotic agents in eliminating VRE colonization is currently unclear but may be a useful adjunct to prudent antimicrobial usage and other infection control interventions in limiting nosocomial spread of VRE.

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CHAPTER 214

Diphtheria (*Corynebacterium diphtheriae*)

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Diphtheria is an acute toxic infection caused by *Corynebacterium* species, typically *Corynebacterium diphtheriae* and, less often, toxigenic strains of *Corynebacterium ulcerans.* Although diphtheria was reduced from a major cause of childhood death to a medical rarity in the Western hemisphere in the early 20th century, recurring reminders of the fragility of this success, particularly in conflict areas, emphasize the need to continue vigorous promotion of those same control principles across the global community.

Etiology

Corynebacteria are aerobic, nonencapsulated, non–spore-forming, mostly nonmotile, pleomorphic, gram-positive bacilli. *C. diphtheriae* is by far the most frequently isolated agent of diphtheria. *C. ulcerans* is more often isolated from animal sources and can cause human disease similar to *C. diphtheriae* . Selective medium (e.g., cystine-tellurite blood agar or Tinsdale agar) that inhibits growth of competing organisms is required for isolation and, when reduced by *C. diphtheriae,* renders colonies gray-black. Differentiation of *C. diphtheriae* from *C. ulcerans* is based on urease activity; *C. ulcerans* is urease-positive. Four *C. diphtheriae* biotypes (*mitis, intermedius, belfanti, gravis*) are capable of causing diphtheria and are differentiated by colony morphology, hemolysis, and fermentation reactions. The ability to produce diphtheritic toxin results from acquisition of a lysogenic corynebacteriophage by either *C. diphtheriae* or *C. ulcerans,* which encodes the diphtheritic toxin gene and confers diphtheria-producing potential on these strains. Thus, indigenous nontoxigenic *C. diphtheriae* can be rendered toxigenic and disease-producing after importation of a toxigenic *C. diphtheriae* . Demonstration of diphtheritic toxin production by the modified Elek test, an agar immunoprecipitin technique, alone or in conjunction with polymerase chain reaction (PCR) testing for carriage of the toxin gene, is necessary to confirm disease. Toxigenic and nontoxigenic strains are indistinguishable by colony type, microscopic features, or biochemical test results.

Epidemiology

Unlike other diphtheroids (coryneform bacteria), which are ubiquitous in nature, *C. diphtheriae* is an exclusive inhabitant of human mucous membranes and skin. Spread is primarily by airborne respiratory droplets, direct contact with respiratory secretions of symptomatic individuals, or exudate from infected skin lesions. Asymptomatic respiratory tract carriage is important in transmission. In areas where diphtheria is endemic, 3–5% of healthy individuals can carry toxigenic organisms, but carriage is exceedingly rare when diphtheria is rare. Skin infection and skin carriage are silent reservoirs of *C. diphtheriae,* and organisms can remain viable in dust or on fomites for up to 6 mo. Transmission through contaminated milk and through an infected food handler has been proved or suspected.

In the 1920s, >125,000 diphtheria cases, with 10,000 deaths, were reported annually in the United States, with the highest fatality rates among very young and elderly persons. The incidence then began to decrease and, with widespread use of diphtheria toxoid in the United States after World War II, declined steadily through the late 1970s. Since then, ≤5 cases have occurred annually in the United States, with no epidemics of respiratory tract diphtheria. Similar decreases occurred in Europe. Despite the worldwide decrease in disease incidence, diphtheria remains endemic in many developing countries with poor immunization rates against diphtheria.

When diphtheria was endemic, it primarily affected children <15 yr old. Since the introduction of toxoid immunization, the disease has shifted to adults who lack natural exposure to toxigenic *C. diphtheriae* in the vaccine era and have low rates of booster immunization. In the 27 sporadic cases of respiratory tract diphtheria reported in the United States in the 1980s, 70% occurred among persons >25 yr old. The largest outbreak of diphtheria in the developed world since the 1960s occurred from 1990–1996 in the newly independent countries of the former Soviet Union, involving >150,000 cases in 14 countries. Of these, >60% of cases occurred in individuals >14 yr old. Case fatality rates ranged from 3–23% by country. Factors contributing to the epidemic included a large population of underimmunized adults, decreased childhood immunization rates, population migration, crowding, and failure to respond aggressively during early phases of the epidemic. Cases of diphtheria among travelers from these endemic areas were transported to many countries in Europe.

Most proven cases of respiratory tract diphtheria in the United States in the 1990s were associated with **importation** of toxigenic *C. diphtheriae,* although clonally related toxigenic *C. diphtheriae* has persisted in this country and Canada for at least 25 yr. World Health Organization (WHO) surveillance reports indicate that most cases of diphtheria worldwide occur in the Southeast Asia and Africa regions. In Europe, increasing reports of respiratory and systemic infections have been attributed to *C ulcerans* ; animal contact is the predominant risk factor.

Cutaneous diphtheria, a curiosity when diphtheria was common, accounted for more than 50% of reported *C. diphtheriae* isolates in the United States by 1975. This indolent local infection, compared with mucosal infection, is associated with more prolonged bacterial shedding, greater contamination of the environment, and increased transmission to the pharynx and skin of close contacts. Outbreaks are associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. It is no longer a tropical or subtropical disease; 1,100 *C. diphtheriae* infections were documented in a neighborhood in Seattle (site of the last major U.S. outbreak), from 1971–1982; 86% were cutaneous, and 40% involved toxigenic strains. Cutaneous diphtheria is an important source for toxigenic *C. diphtheriae* in the United States, and its importation is frequently the source for subsequent sporadic cases of respiratory tract diphtheria. Cutaneous diphtheria caused by *C. ulcerans* from travel to tropical countries or animal contact has been increasingly reported.

Pathogenesis

Both toxigenic and nontoxigenic *C. diphtheriae* cause skin and mucosal infection and can rarely cause focal infection after bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory tract mucosa, inducing local inflammatory reaction. The major virulence of the organism lies in its ability to produce a potent polypeptide exotoxin, which inhibits protein synthesis and causes local tissue necrosis and resultant local inflammatory response. Within the first few days of respiratory tract infection (usually in the pharynx), a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, initially white and advancing to become a gray-brown, leather-like adherent **pseudomembrane** (*diphtheria* is Greek for leather). Removal is difficult and reveals a bleeding edematous submucosa. Paralysis of the palate and hypopharynx is an early local effect of diphtheria toxin. Toxin absorption can lead to systemic manifestations: kidney tubule necrosis, thrombocytopenia, cardiomyopathy, and demyelination of nerves. Because the latter 2 complications can occur 2-10 wk after mucocutaneous infection, the pathophysiology in some cases is suspected to be immunologically mediated.

Clinical Manifestations

The manifestations of *C. diphtheriae* infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin.

Respiratory Tract Diphtheria

In a classic description of 1,400 cases of diphtheria in California (1954), the primary focus of infection was the tonsils or pharynx (94%), with the nose and larynx the next 2 most common sites. After an average incubation period of 2-4 days (range 1-10 days), local signs and symptoms of inflammation develop. Infection of the anterior nares is more common among infants and causes serosanguineous, purulent, erosive rhinitis with membrane formation. Shallow ulceration of the external nares and upper lip is characteristic. In tonsillar and **pharyngeal diphtheria** , sore throat is the universal early symptom. Only half of patients have fever, and fewer have dysphagia, hoarseness, malaise, or headache. Mild pharyngeal injection is followed by unilateral or bilateral tonsillar membrane formation, which can extend to involve the uvula (which may cause toxin-mediated paralysis), soft palate, posterior oropharynx, hypopharynx, or glottic areas (Fig. 214.1). Underlying soft tissue edema and enlarged lymph nodes can cause a bull-neck appearance. The degree of local extension correlates directly with profound prostration, bull-neck appearance, and fatality due to airway compromise or toxin-mediated complications (Fig. 214.2).

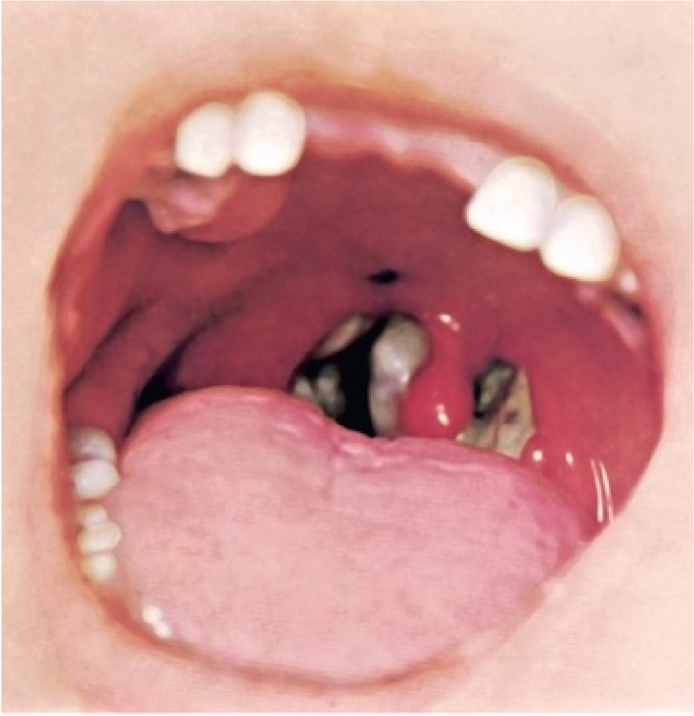

FIG. 214.1 Tonsillar diphtheria. (Courtesy of Franklin H. Top, MD, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes.)

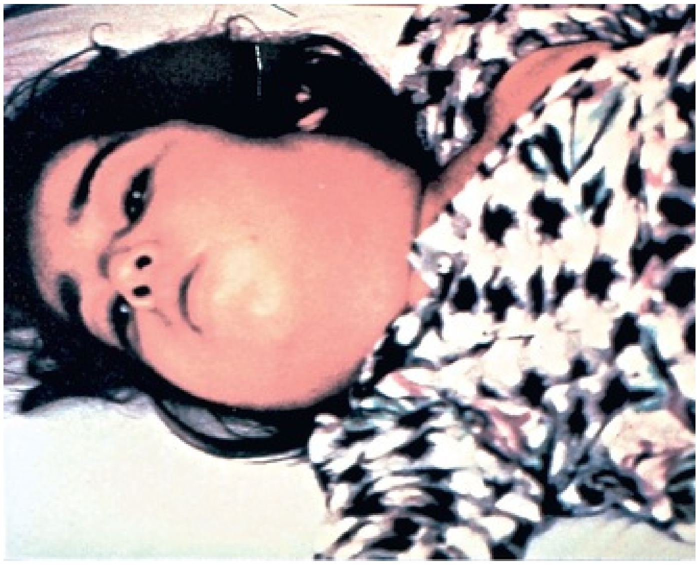

FIG. 214.2 Diphtheria. Bull-neck appearance of diphtheritic cervical lymphadenopathy. (Courtesy of the Centers for Disease Control and Prevention.)

The characteristic adherent membrane, extension beyond the faucial area, dysphagia, and relative lack of fever help differentiate diphtheria from **exudative pharyngitis** caused by *Streptococcus pyogenes* or Epstein-Barr virus. Vincent angina, infective phlebitis with thrombosis of the jugular veins (Lemierre syndrome), and mucositis in patients undergoing cancer chemotherapy are usually differentiated by the clinical setting. Infection of the larynx, trachea, and bronchi can be primary or a secondary extension from the pharyngeal infection. Hoarseness, stridor, dyspnea, and croupy cough are clues. Differentiation from bacterial epiglottitis, severe viral laryngotracheobronchitis, and staphylococcal or streptococcal tracheitis hinges partially on the relative paucity of other signs and symptoms in patients with diphtheria and primarily on visualization of the adherent pseudomembrane at laryngoscopy and intubation.

Patients with laryngeal diphtheria are at significant risk for suffocation because of local soft tissue edema and airway obstruction by the diphtheria membrane, a dense cast of respiratory epithelium, and necrotic coagulum. Establishment of an artificial airway and resection of the pseudomembrane can be lifesaving, but further obstructive complications are common, and systemic toxic complications are inevitable.

Cutaneous Diphtheria

Classic cutaneous diphtheria is an indolent, nonprogressive infection characterized by a superficial, ecthyma-like, nonhealing ulcer with a gray-brown membrane. Diphtheria skin infections cannot always be differentiated from streptococcal or staphylococcal impetigo, and these conditions frequently coexist. In most cases, a primary process, such as dermatosis, laceration, burn, bite, or impetigo, becomes secondarily infected with *C. diphtheriae*. Extremities are more often affected than the trunk or head. Pain, tenderness, erythema, and exudate are typical. Local hyperesthesia or hypesthesia is unusual. Respiratory tract colonization or symptomatic infection with toxic complications occurs in the minority of patients with cutaneous diphtheria. Among infected adults in the Seattle outbreak, 3% with cutaneous infections and 21% with symptomatic nasopharyngeal infection, with or without skin involvement, demonstrated toxic myocarditis, neuropathy, or obstructive respiratory tract complications. All had received at least 20,000 units of equine antitoxin at the time of hospitalization.

Infection at Other Sites

C. diphtheriae occasionally causes mucocutaneous infections at other sites, such as the ear (otitis externa), the eye (purulent and ulcerative conjunctivitis), and the genital tract (purulent and ulcerative vulvovaginitis). The clinical setting, ulceration, membrane formation, and submucosal bleeding help differentiate diphtheria from other bacterial and viral causes. Rare cases of septicemia are described and are universally fatal. Sporadic cases of endocarditis occur, and clusters among intravenous drug users have been reported in several countries; skin was the probable portal of entry, and almost all strains were nontoxigenic. Sporadic cases of pyogenic arthritis, mainly from nontoxigenic strains, have been reported in adults and children. Diphtheroids isolated from sterile body sites should not be routinely dismissed as contaminants without careful consideration of the clinical setting.

Diagnosis

Specimens for culture should be obtained from the nose and throat and any other mucocutaneous lesion. A portion of membrane should be removed and submitted for culture along with underlying exudate. The laboratory must be notified to use selective medium. *C. diphtheriae* survives drying. If obtained in a remote area, a dry swab specimen can be placed in a silica gel pack and sent to the laboratory. Evaluation of a direct smear using Gram stain or specific fluorescent antibody is unreliable. Culture isolates of coryneform organisms should be identified to the species level, and toxigenicity and antimicrobial susceptibility tests should be performed for *C. diphtheriae* isolates. It is recommended that all isolates be sent to a reference laboratory. In the United States, the Centers for Disease Control and Prevention (CDC) Pertussis and Diphtheria Laboratory provides support to local and state health departments needing assistance with isolation, identification, and subtyping of *C. diphtheriae* and *C. ulcerans.*

Complications

Respiratory tract obstruction by pseudomembranes may require bronchoscopy or intubation and mechanical ventilation. Two other tissues usually remote from sites of *C. diphtheriae* infection can be significantly affected by **diphtheritic toxin** : the heart and the nervous system.

Toxic Cardiomyopathy

Toxic cardiomyopathy occurs in 10–25% of patients with respiratory diphtheria and is responsible for 50–60% of deaths. Subtle signs of myocarditis can be detected in most patients, especially the elderly, but the risk for significant complications correlates directly with the extent and severity of exudative local oropharyngeal disease, as well as delay in administration of antitoxin. The first evidence of cardiac toxicity characteristically occurs during the 2nd and 3rd wk of illness as the pharyngeal disease improves, but can appear acutely as early as the 1st wk of illness, a poor prognostic sign, or insidiously as late as the 6th wk. Tachycardia disproportionate to fever is common and may be evidence of cardiac toxicity or autonomic nervous system dysfunction. A prolonged P-R interval and changes in the ST-T wave on an electrocardiographic tracing are relatively frequent findings; dilated and hypertrophic cardiomyopathy detected by echocardiogram has been described. Single or progressive cardiac **dysrhythmias** can occur, including first-, second-, and third-degree heart block. Temporary transvenous pacing may improve outcomes. Atrioventricular dissociation and ventricular tachycardia are also described, the latter having a high associated mortality. Heart failure may appear insidiously or acutely. Elevation of the serum aspartate transaminase concentration closely parallels the severity of myonecrosis. Severe dysrhythmia portends death. Histologic postmortem findings are variable: little or diffuse myonecrosis with acute inflammatory response. Recovery from toxic myocardiopathy is usually complete, although survivors of more severe dysrhythmias can have permanent conduction defects.

Toxic Neuropathy

Neurologic complications parallel the severity of primary infection and are multiphasic in onset. Acutely or 2-3 wk after onset of oropharyngeal inflammation, hypesthesia and local **paralysis** of the soft palate typically occur. Weakness of the posterior pharyngeal, laryngeal, and facial nerves may follow, causing a nasal quality in the voice, difficulty in swallowing, and risk for aspiration. **Cranial neuropathies** characteristically occur in the 5th wk, leading to oculomotor and ciliary paralysis, which can cause strabismus, blurred vision, or difficulty with accommodation. Symmetric demyelinating **polyneuropathy** has onset 10 days to 3 mo after oropharyngeal infection and causes principally motor deficits with diminished deep tendon reflexes. Nerve conduction velocity studies and cerebrospinal fluid findings in diphtheritic polyneuropathy are indistinguishable from those of Guillain-Barré syndrome. Paralysis of the diaphragm may ensue. Complete neurologic recovery is likely, but rarely vasomotor center dysfunction 2-3 wk after onset of illness can cause hypotension or cardiac failure.

Recovery from myocarditis and neuritis is often slow but usually complete. Corticosteroids do not diminish these complications and are not recommended.

Treatment

Specific **antitoxin** is the mainstay of therapy and should be administered on the basis of clinical diagnosis. Because it neutralizes only free toxin, antitoxin efficacy diminishes with elapsed time after the onset of mucocutaneous symptoms. Equine diphtheria antitoxin is available in the United States only from the CDC. Physicians treating a case of suspected diphtheria should contact the CDC Emergency Operations Center (770-488-7100 at all times). Antitoxin is administered as a single empirical dose of 20,000-100,000 units based on the degree of toxicity, site and size of the membrane, and duration of illness. Skin testing must be performed before administration of antitoxin. Patients with positive sensitivity testing or with a history of hypersensitivity reaction to horse equine protein should be desensitized. Antitoxin is probably of no value for local manifestations of cutaneous diphtheria, but its use is prudent because toxic sequelae can occur. Commercially available intravenous immunoglobulin preparations contain low titers of antibodies to diphtheria toxin; their use for therapy of diphtheria is not proved or approved. Antitoxin is not recommended for asymptomatic carriers.

The role of **antimicrobial therapy** is to halt toxin production, treat localized infection, and prevent transmission of the organism to contacts. *C. diphtheriae* is usually susceptible to various agents in vitro, including penicillins, erythromycin, clindamycin, rifampin, and tetracycline. Resistance to erythromycin is common in populations if the drug has been used broadly, and resistance to penicillin has also been reported. Only erythromycin or penicillin is recommended; erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Appropriate therapy is **erythromycin** (40-50 mg/kg/day divided every 6 hr by mouth [PO] or intravenously [IV]; maximum 2 g/day), **aqueous crystalline penicillin G** (100,000-150,000 units/kg/day divided every 6 hr IV or intramuscularly [IM]), or **procaine penicillin** (300,000 units every 12 hr IM for those ≤10 kg in weight; 600,000 units every 12 hr IM for those >10 kg in weight) for 14 days. Once oral medications are tolerated, oral penicillin V (250 mg four times daily) may be used. *Antibiotic therapy is not a substitute for antitoxin therapy.* Some patients with cutaneous diphtheria have been treated for 7-10 days. Elimination of the organism should be documented by negative results of at least 2 successive cultures of specimens from the nose and throat (or skin) obtained 24 hr apart after completion of therapy. Treatment with erythromycin is repeated if either culture yields *C. diphtheriae.*

Supportive Care

Droplet precautions are instituted for patients with pharyngeal diphtheria; for patients with cutaneous diphtheria, **contact precautions** are observed until the results of cultures of specimens taken after cessation of therapy are negative. Cutaneous wounds are cleaned thoroughly with soap and water. Bed rest is essential during the acute phase of disease, usually for ≥2 wk until the risk for symptomatic cardiac damage has passed, with return to physical activity guided by the degree of toxicity and cardiac involvement.

Prognosis

The prognosis for patients with diphtheria depends on the virulence of the organism (subspecies *gravis* has the highest fatality rate), patient age, immunization status, site of infection, and speed of administration of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths. The case fatality rate of almost 10% for respiratory tract diphtheria has not changed in 50 yr; the rate was 8% in a Vietnamese series described in 2004. At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies to diphtheria toxin after infection.

Prevention

Protection against serious disease caused by imported or indigenously acquired *C. diphtheriae* depends on immunization. In the absence of a precisely determined minimum protective level for diphtheria antitoxin, the presumed minimum is 0.01-0.10 IU/mL. In outbreaks, 90% of individuals with clinical disease have had antibody values <0.01 IU/mL, and 92% of asymptomatic carriers have had values >0.1 IU/mL. In serosurveys in the United States and Western Europe, where almost universal immunization during childhood has been achieved, 25% to >60% of adults lack protective antitoxin levels, with typically very low levels in elderly persons.

All suspected diphtheria cases should be reported to local and state health departments. Investigation is aimed at preventing secondary cases in exposed individuals and at determining the source and carriers to halt spread to unexposed individuals. Reported rates of carriage in household contacts of case patients are 0–25%. The risk for development of diphtheria after household exposure to a case is approximately 2%, and the risk after similar exposure to a carrier is 0.3%.

Asymptomatic Case Contacts

All household contacts and people who have had intimate respiratory or habitual physical contact with a patient are closely monitored for illness for 7 days. Cultures of the nose, throat, and any cutaneous lesions are performed. Antimicrobial prophylaxis is presumed effective and is administered regardless of immunization status, using a single injection of benzathine penicillin G

(600,000 units IM for patients <6 yr old, or 1,200,000 units IM for patients >6 yr old) or erythromycin (40-50 mg/kg/day divided qid PO for 10 days; max 2 g/day). Diphtheria toxoid vaccine, in age-appropriate form, is given to immunized individuals who have not received a booster dose within 5 yr. Children who have not received their 4th dose should be vaccinated. Those who have received fewer than 3 doses of diphtheria toxoid or who have uncertain immunization status should be immunized with an age-appropriate preparation on a primary schedule.

Asymptomatic Carriers

When an asymptomatic carrier is identified, antimicrobial prophylaxis is given for 10-14 days and an age-appropriate preparation of diphtheria toxoid is administered immediately if a booster has not been given within 1 yr. Droplet precautions (respiratory tract colonization) or contact precautions (cutaneous colonization only) are observed until at least 2 subsequent cultures obtained 24 hr apart after cessation of therapy have negative results.

Repeat cultures are performed about 2 wk after completion of therapy for cases and carriers; if results are positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed. Susceptibility testing of isolates should be performed, as erythromycin resistance is reported. Neither antimicrobial agent eradicates carriage in 100% of individuals. In one report, a single course of therapy failed in 21% of carriers. Transmission of diphtheria in modern hospitals is rare. Only those who have an unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of the casual contacts of patients and carriers or persons in the community without known exposure has yielded extremely low carriage rates and is not routinely recommended.

Vaccine

Universal immunization with diphtheria toxoid throughout life, to provide constant protective antitoxin levels and to reduce severity of *C. diphtheriae* disease, is the only effective control measure. Although immunization does not preclude subsequent respiratory or cutaneous carriage of toxigenic *C. diphtheriae,* it decreases local tissue spread, prevents toxic complications, diminishes transmission of the organism, and provides herd immunity when at least 70–80% of a population is immunized.

Diphtheria toxoid is prepared by formaldehyde treatment of toxin, standardized for potency, and adsorbed to aluminum salts, enhancing immunogenicity. Two preparations of diphtheria toxoids are formulated according to the *limit of flocculation* (Lf) content, a measure of the quantity of toxoid. The pediatric (6 mo to 6 yr) preparations (i.e., **DTaP** [diphtheria and tetanus toxoids with acellular pertussis vaccine], **DT** [diphtheria and tetanus toxoids vaccine]) contain 6.7-25.0 Lf units of diphtheria toxoid per 0.5 mL dose; the adult preparation (Td; 10% of pediatric diphtheria toxoid dose, Tdap [diphtheria and tetanus toxoids with acellular pertussis vaccine]) contain no more than 2-2.5 Lf units of toxoid per 0.5 mL dose. The *higher-potency* (D) formulation of toxoid is used for primary series and booster doses for children through 6 yr of age because of superior immunogenicity and minimal reactogenicity. For individuals ≥7 yr old, Td is recommended for the primary series and booster doses because the lower concentration of diphtheria toxoid is adequately immunogenic and increasing the content of diphtheria toxoid heightens reactogenicity with increasing age.

For children 6 wk to 6 yr of age, five 0.5 mL doses of diphtheria-containing (D) vaccine (DTaP preferred) are given in the primary series, including doses at 2, 4, and 6 mo of age, and a 4th dose, an integral part of the primary series, at 15-18 mo. A booster dose is given at 4-6 yr of age (unless the 4th primary dose was administered at ≥4 yr). For persons ≥7 yr old not previously immunized for diphtheria, three 0.5 mL doses of *lower-level* diphtheria-containing (d) vaccine are given in a primary series of 2 doses at least 4 wk apart and a 3rd dose 6 mo after the 2nd dose. The 1st dose should be Tdap, and subsequent doses should be Td. The only contraindication to tetanus and diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a prior dose. For children <7 yr old in whom pertussis immunization is contraindicated, DT is used. Those whose immunization is begun with DTaP or DT before 1 yr of age should have a total of five 0.5 mL doses of diphtheria-containing (D) vaccines by 6 yr of age. For those whose immunization is begun at around 1 yr old, the primary series is three 0.5 mL doses of diphtheria-containing (D) vaccine, with a booster given at 4-6 yr, unless the 3rd dose was given after the 4th birthday.

A booster dose, consisting of the adult preparation of Tdap, is recommended at 11-12 yr of age. Adolescents 13-18 yr old who missed the Td or Tdap booster dose at 11-12 yr or in whom it has been ≥5 yr since the Td booster dose also should receive a single dose of Tdap if they have completed the DTP/DTaP series.

There is no association of DT or Td with convulsions. Local adverse effects alone do not preclude continued use. The rare patient who experiences an Arthus-type hypersensitivity reaction or a temperature >39.4°C (103°F) after a dose of Td usually has high serum tetanus antitoxin levels and should not be given Td more frequently than every 10 yr, even if the patient sustains a significant tetanus-prone injury. The DT or Td preparation can be given concurrently with other vaccines. *Haemophilus influenzae* type b (Hib), meningococcal, and pneumococcal conjugate vaccines containing diphtheria toxoid (PRP-D) or the variant of diphtheria toxin, CRM197 protein, are not substitutes for diphtheria toxoid immunization and do not affect reactogenicity.

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CHAPTER 215

Listeria monocytogenes

Thomas S. Murray, Robert S. Baltimore

Listeriosis in humans is caused principally by *Listeria monocytogenes*, 1 of 6 species of the genus *Listeria* that are widely distributed in the environment and throughout the food chain. Human infections can usually be traced to an animal reservoir. Infection usually occurs at the extremes of age. In the pediatric population, perinatal infections predominate and usually occur secondary to maternal infection or colonization. Outside the newborn period, disease is most often encountered in *immunosuppressed* (usually T-cell deficiencies) children and adults and in elderly persons. For most people the major risk for infection with *Listeria* is **food-borne transmission** . In the United States, food-borne outbreaks are caused by improperly processed dairy products and contaminated vegetables and principally affect the same individuals at risk for sporadic disease.

Etiology

Members of the genus *Listeria* are facultatively anaerobic, non–spore-forming, motile, gram-positive bacilli that are catalase positive. In the laboratory, *Listeria* can be distinguished from other gram-positive bacilli by their characteristic tumbling motility and growth at cold temperature (4-10°C [39.2-50°F]). The 6 *Listeria* spp. are divided into 2 genomically distinct groups on the basis of DNA-DNA hybridization studies. One group contains the species *Listeria grayi*, considered nonpathogenic. The 2nd group contains 5 species: the nonhemolytic species *Listeria innocua* and *L. welshimeri* and the hemolytic species *Listeria monocytogenes*, *L. seeligeri*, and *L. ivanovii*. *Listeria ivanovii* is pathogenic primarily in animals, and the vast majority of both human and animal disease is caused by *L. monocytogenes*.

Subtyping of *L. monocytogenes* isolates for epidemiologic purposes has been attempted with the use of heat-stable somatic O and heat-labile flagellar H antigens, phage typing, pulsed-field gel electrophoresis, ribotyping, and multilocus enzyme electrophoresis. Electrophoretic typing demonstrates the clonal structure of populations of *L. monocytogenes* as well as the sharing of populations between human and animal sources. **Subtyping** is an important component of determining whether cases are connected or sporadic but usually requires collaboration with a specialized laboratory.

Selected biochemical tests, together with the demonstration of *tumbling motility* , umbrella-type formation below the surface in semisolid medium, hemolysis, and a typical cyclic adenosine monophosphate test, are usually sufficient to establish a presumptive identification of *L. monocytogenes*.

Epidemiology

Listeria monocytogenes is widespread in nature, has been isolated throughout the environment, and is associated with epizootic disease and asymptomatic carriage in >42 species of wild and domestic animals and 22 avian species. Epizootic disease in large animals (e.g., sheep, cattle) is associated with abortion and "circling disease," a form of basilar meningitis. *L. monocytogenes* is isolated from sewage, silage, and soil, where it survives for >295 days. Human-to-human transmission rarely occurs except in maternal-fetal transmission. The annual incidence of listeriosis decreased by 36% between 1996 and 2004 and has remained level since then. However**, food-borne outbreaks** continue to occur. In 2011, 84 cases and 15 deaths in 19 states were traced to cantaloupes from a single source. The cases were connected by use of pulsed-field gel electrophoresis, which showed that 4 different strains traced to the same source. The rate of *Listeria* infections varies among states. Epidemic human listeriosis has been associated with food-borne transmission in several large outbreaks, especially in association with aged soft cheeses; improperly pasteurized milk and milk products; contaminated raw and ready-to-eat beef, pork, and poultry, and packaged meats and salads; and vegetables both fresh and frozen harvested from farms where the ground is contaminated with the feces of colonized animals. Food-borne outbreaks in 2016 included raw milk, packaged salads, and frozen vegetables. The ability of *L. monocytogene* s to grow at temperatures as low as 4°C (39.2°F) increases the risk for transmission from aged soft cheeses and stored contaminated food. Listeriosis is an uncommon but important recognized etiology of neonatal sepsis and meningitis. Small clusters of nosocomial person-to-person transmission have occurred in hospital nurseries and obstetric suites. Sporadic endemic listeriosis is less well characterized. Likely routes include food-borne infection and zoonotic spread. **Zoonotic transmission** with cutaneous infections occurs in veterinarians and farmers who handle sick animals.

Reported cases of listeriosis are clustered at the extremes of age. Some studies show higher rates in males and a seasonal predominance in the late summer and fall in the Northern hemisphere. Outside the newborn period and during pregnancy, disease is usually reported in patients with underlying immunosuppression, with a 100-300 times increased risk in HIV-infected persons and in the elderly population (Table 215.1). In a recent surveillance study from England, malignancies accounted for one third of cases, with special risk associated with cancer in elderly persons.

Table 215.1

Types of *Listeria monocytogenes* Infections

- Listeriosis in pregnancy
- Neonatal listeriosis
  - Early onset
  - Late onset
- Food-borne outbreaks/febrile gastroenteritis
- Listeriosis in normal children and adults (rare)
- Focal *Listeria* infections (e.g., meningitis, endocarditis, pneumonia, liver abscess, osteomyelitis, septic arthritis)
- Listeriosis in immunocompromised persons
  - Lymphohematogenous malignancies
  - Collagen vascular diseases
  - Diabetes mellitus
  - HIV infection
  - Transplantation
  - Renal failure with peritoneal dialysis
- Listeriosis in elderly persons

The incubation period, which is defined only for common-source food-borne disease, is 21-30 days but in some cases may be longer. Asymptomatic carriage and fecal excretion are reported in 1–5% of healthy persons and 5% of abattoir workers, but duration of excretion, when studied, is short (<1 mo.).

Pathology

One of the major concepts of *Listeria* pathology and pathogenesis is its ability to survive as an intracellular pathogen. *Listeria* incites a mononuclear response and elaboration of cytokines, producing multisystem disease, particularly pyogenic meningitis. Granulomatous reactions and microabscess formation develop in many organs, including liver, lungs, adrenals, kidneys, central nervous system (CNS), and notably the placenta. Animal models demonstrate *translocation* , the transfer of intraluminal organisms across intact intestinal mucosa. Histologic examination of tissues, including the placenta, shows granulomatous inflammation and microabscess formation. Intracellular organisms can often be demonstrated with special stains.

Pathogenesis

Listeria organisms usually enter the host through the gastrointestinal (GI) tract. Gastric acidity provides some protection, and drugs that raise gastric pH may promote infection. Studies of intracellular and intercellular spread of *L. monocytogenes* have revealed a complex pathogenesis. Four pathogenic steps are described: internalization by phagocytosis, escape from the phagocytic vacuole, nucleation of actin filaments, and cell-to-cell spread. **Listeriolysin** , a hemolysin and the best-characterized virulence factor, probably mediates lysis of vacuoles and is responsible for the zone of hemolysis around colonies on blood-containing solid media. In cell-to-cell spread, locomotion proceeds via cytochalasin-sensitive polymerization of actin filaments, which extrude the bacteria in pseudopods, which in turn are phagocytosed by adjacent cells, necessitating escape from a double-membrane vacuole. This mechanism protects intracellular bacteria from the humoral arm of immunity and is responsible for the well-known requirement of T-cell–mediated activation of monocytes by lymphokines for clearance of infection and establishment of immunity. It appears that secretion of cyclic di-adenosine monophosphate by the bacteria induces the host to produce interferon, which activates the immune system to fight the organism. The significant risk for listeriosis in patients with depressed T-cell immunity speaks for the role of this arm of the immune system. The role of opsonizing antibody in protecting against infection is unclear. In addition, siderophores scavenge iron from the host, enhancing growth of the organism and likely explaining the relatively high risk of listeriosis in iron overload syndromes.

Clinical Manifestations

The clinical presentation of listeriosis depends greatly on the age of the patient and the circumstances of the infection.

Listeriosis in Pregnancy

Pregnant women have increased susceptibility to *Listeria* infectious (approximately 20 times higher than nonpregnant women), probably because of a relative impairment in cell-mediated immunity. *L. monocytogenes* has been grown from placental and fetal cultures of pregnancies ending in spontaneous abortion. The usual presentation in the 2nd and 3rd trimesters is a flulike illness that may result in seeding of the uterine contents by bacteremia. Rarely is maternal listeriosis severe, but meningitis in pregnancy has been reported. Recognition and treatment at this stage are associated with normal pregnancy outcomes, but the fetus may not be infected even if listeriosis in the mother is not treated. In other instances, placental listeriosis develops with infection of the fetus that may be associated with stillbirth or premature delivery. Delivery of an infected premature fetus is associated with very high infant mortality. Disseminated disease is apparent at birth, often with a diffuse pustular rash. Infection in the mother usually resolves without specific therapy after delivery, but postpartum fever and infected lochia may occur.

Neonatal Listeriosis

Two clinical presentations are recognized for neonatal listeriosis: early-onset neonatal disease (<5 days, usually within 1-2 days of birth), which is a predominantly **septicemic** form, and late onset neonatal disease (>5 days, mean 14 days of life), which is a predominantly **meningitic** form (Table 215.2). The principal characteristics of the 2 presentations resemble the clinical syndromes described for group B streptococcus (see Chapter 211).

Table 215.2

Characteristic Features of Early- and Late-Onset Neonatal Listeriosis

EARLY ONSET (<5 DAYS)	LATE ONSET (≥5 DAYS)

Positive result of maternal *Listeria* culture	Negative results of maternal *Listeria* culture
Obstetric complications	Uncomplicated pregnancy
Premature delivery	Term delivery
Low birthweight	Normal birthweight
Neonatal sepsis	Neonatal meningitis
Mean age at onset 1.5 days	Mean age at onset 14.2 days
Mortality rate >30%	Mortality rate <10%
	Nosocomial outbreaks

Early-onset disease occurs with milder transplacental or ascending infections from the female genital tract. There is a strong association with recovery of *L. monocytogenes* from the maternal genital tract, obstetric complications, prematurity, and neonatal sepsis with multiorgan involvement, including rash, but without CNS localization (Fig. 215.1). The mortality rate is approximately 20–30%.

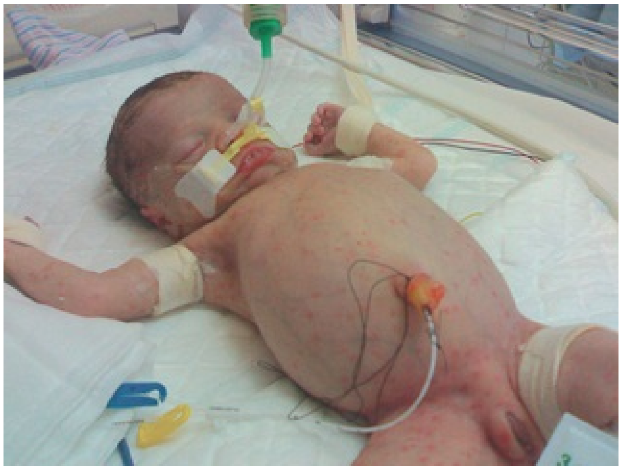

FIG. 215.1 **Listeria monocytogenes. The generalized maculopapular rash present at birth disappeared within a few hours of life. (From Benitez-Segura I, Fiol-Jaume M, Balliu PR, Tejedor M: *Listeria monocytogenes* : generalized maculopapular rash may be the clue, *Arch Dis Child Fetal Neonatal Ed* 98(1):F64, 2013, Fig 1.)**

The epidemiology of **late-onset disease** is poorly understood. Onset is usually after 5 days but before 30 days of age. Affected infants frequently are full-term, and the mothers are culture negative and asymptomatic. The presenting syndrome is usually purulent meningitis with parenchymal brain involvement, which, if adequately treated, has a mortality rate of <20%.

Postneonatal Infections

Listeriosis beyond the newborn period may rarely occur in otherwise healthy children but is most often encountered in association with underlying malignancies (especially lymphomas) or immunosuppression. When associated with food-borne outbreaks, disease may cause GI symptoms or any of the *Listeria* syndromes. The clinical presentation is usually meningitis, less commonly sepsis, and rarely other CNS involvement, such as cerebritis, meningoencephalitis, brain abscess, spinal cord abscess, or a focus outside the CNS, such as suppurative arthritis, osteomyelitis, endocarditis, peritonitis (associated with peritoneal dialysis), or liver abscess. It is not known whether the frequent GI signs and symptoms result from enteric infection, because the mode of acquisition is often unknown.

Diagnosis

Listeriosis should be included in the differential diagnosis of infections in pregnancy, of neonatal sepsis and meningitis, and of sepsis or meningitis in older children who have underlying malignancies (lymphomas), are receiving immunosuppressive therapy, or have undergone transplantation. The diagnosis is established by culture of *L. monocytogenes* from blood or cerebrospinal fluid (CSF). Cultures from the maternal cervix, vagina, lochia, and placenta, if possible, should be obtained when intrauterine infections lead to premature delivery or early-onset neonatal sepsis. Cultures from closed-space infections may also be useful. It is helpful to alert the laboratory to suspected cases so that *Listeria* isolates are not discarded as contaminating diphtheroids.

Histologic examination of the placenta is also useful. Molecular assays are now commercially available to detect *L. monocytogenes* from CNS samples. Serodiagnostic tests have not proved useful.

Differential Diagnosis

Listeriosis is indistinguishable clinically from neonatal sepsis and meningitis caused by other organisms. The presence of increased peripheral blood monocytes suggests listeriosis. Monocytosis or lymphocytosis may be modest or striking. Beyond the neonatal period, *L. monocytogenes* CNS infection is associated with fever, headache, seizures, and signs of meningeal irritation. The brainstem may be characteristically affected. The white blood cell concentration may vary from normal to slightly elevated, and the CSF laboratory findings are variable and less striking than in the more common causes of bacterial meningitis. Polymorphonuclear leukocytes or mononuclear cells may predominate, with shifts from polymorphonuclear to mononuclear cells in sequential lumbar puncture specimens. The CSF glucose concentration may be normal, but a low level mirrors the severity of disease. The CSF protein concentration is moderately elevated. *L. monocytogenes* is isolated from the blood in 40–75% of cases of meningitis caused by the organism. Deep focal infections from *L. monocytogenes*, such as endocarditis, osteomyelitis, and liver abscess, are also indistinguishable clinically from such infections from more common organisms. Cutaneous infections should be suspected in patients with a history of contact with animals, especially products of conception.

Treatment

The emergence of multiantibiotic resistance mandates routine susceptibility testing of all isolates. The recommended therapy is **ampicillin** (100-200 mg/kg/day divided every 6 hr intravenously [IV]; 200-400 mg/kg/day divided every 6 hr IV if meningitis is present) alone or in combination with an **aminoglycoside** (5.0-7.5 mg/kg/day divided every 8 hr IV). The aminoglycoside enhances the bactericidal activity and is generally recommended in cases of endocarditis and meningitis. The adult dose is ampicillin, 4-6 g/day divided every 6 hr, plus an aminoglycoside. The ampicillin dose is doubled if meningitis is present. Special attention to dosing is required for neonates, who require longer dosing intervals because of the longer half-lives of the antibiotics in their bodies. *L. monocytogenes* is not susceptible to the cephalosporins, including third-generation cephalosporins. If these agents are used for empirical therapy for neonatal sepsis or meningitis in a newborn, ampicillin must be added for possible *L. monocytogenes* infection. Vancomycin, vancomycin plus an aminoglycoside, trimethoprim-sulfamethoxazole, and erythromycin are alternatives to ampicillin. The duration of therapy is usually 2-3 wk, with 3 wk recommended for immunocompromised persons and patients with meningitis. A longer course is needed for endocarditis, brain abscess, and osteomyelitis. Antibiotic treatment is unnecessary for gastroenteritis without invasive disease.

Prognosis

Early gestational listeriosis may be associated with abortion or stillbirth, although maternal infection with sparing of the fetus has been reported. There is no convincing evidence that *L. monocytogenes* is associated with repeated spontaneous abortions in humans. The mortality rate is >50% for premature infants infected in utero, 30% for early-onset neonatal sepsis, 15% for late-onset neonatal meningitis, and <10% in older children with prompt institution of appropriate antimicrobial therapy. Mental retardation, hydrocephalus, and other CNS sequelae are reported in survivors of *Listeria* meningitis.

Prevention

Listeriosis can be prevented by pasteurization and thorough cooking of foods. Irradiation of meat products may also be beneficial. Consumption of unpasteurized or improperly processed dairy products should be avoided, especially aged soft cheeses, uncooked and precooked meat products that have been stored at 4°C (39.2°F) for extended periods, and unwashed vegetables (Table 215.3). This avoidance is particularly important during pregnancy and for immunocompromised persons. Infected domestic animals should be avoided when possible. Education regarding risk reduction is aimed particularly at pregnant women and people being treated for cancer.

Table 215.3

Prevention of Food-Borne Listeriosis

GENERAL RECOMMENDATIONS TO PREVENT *LISTERIA* INFECTION
FDA recommendations for washing and handling food:
• Rinse raw produce, such as fruits and vegetables, thoroughly under running tap water before eating, cutting, or cooking. Even if the produce will be peeled, it should still be washed first.
• Scrub firm produce, such as melons and cucumbers, with a clean produce brush.
• Dry the produce with a clean cloth or paper towel.
• Separate uncooked meats and poultry from vegetables, cooked foods, and ready-to-eat foods.
Keep your kitchen and environment cleaner and safer.
• Wash hands, knives, countertops, and cutting boards after handling and preparing uncooked foods.
• Be aware that *Listeria monocytogenes* can grow in foods in the refrigerator. Use an appliance thermometer, such as a refrigerator thermometer, to check the temperature inside your refrigerator. The refrigerator should be 4.5°C (40°F) or lower and the freezer −17.8°C (0°F) or lower.
• Clean up all spills in your refrigerator promptly, especially juices from hot dog and lunch meat packages, raw meat, and raw poultry.
• Clean the inside walls and shelves of your refrigerator with hot water and liquid soap, then rinse.
Cook meat and poultry thoroughly.
• Thoroughly cook raw food from animal sources, such as beef, pork, or poultry to a safe internal temperature. For a list of recommended temperatures for meat and poultry, visit the safe minimum cooking temperatures chart at http://www.FoodSafety.gov .
Store foods safely.

- Use precooked or ready-to-eat food as soon as you can. Do not store the product in the refrigerator beyond the use-by date; follow USDA refrigerator storage time guidelines:
  - Hot dogs: store opened package no longer than 1 wk and unopened package no longer than 2 wk in the refrigerator.
  - Luncheon and deli meat: store factory-sealed, unopened package no longer than 2 wk. Store opened packages and meat sliced at a local deli no longer than 3-5 days in the refrigerator.
- Divide leftovers into shallow containers to promote rapid, even cooling. Cover with airtight lids or enclose in plastic wrap or aluminum foil. Use leftovers within 3-4 days.

Choose safer foods.

- Do not drink raw (unpasteurized) milk, and do not eat foods that have unpasteurized milk in them.

RECOMMENDATIONS FOR PERSONS AT HIGHER RISK *

In addition to the recommendations listed above, include:

Meats

- Do not eat hot dogs, luncheon meats, cold cuts, other deli meats (e.g., bologna), or fermented or dry sausages unless they are heated to an internal temperature of 73.9°C (165°F) or until steaming hot just before serving.
- Avoid getting fluid from hot dog and lunch meat packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli meats.
- Pay attention to labels. Do not eat refrigerated pâté or meat spreads from a deli or meat counter or from the refrigerated section of a store. Foods that do not need refrigeration, such as canned or shelf-stable pâté and meat spreads, are safe to eat. Refrigerate after opening.

Cheeses

- Do not eat soft cheese such as feta, queso blanco, queso fresco, brie, Camembert, blue-veined, or panela (queso panela) unless it is labeled as made with pasteurized milk. Make sure the label says "MADE WITH PASTEURIZED MILK."

Seafood

- Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole, or unless it is a canned or shelf-stable product.
- Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as "nova-style," "lox," "kippered," "smoked," or "jerky."
  - These fish are typically found in the refrigerator section or sold at seafood and deli counters of grocery stores and delicatessens.
- Canned and shelf stable tuna, salmon, and other fish products are safe to eat.

Follow this general FDA advice for melon safety:

- Consumers and food preparers should wash their hands with warm water and soap for at least 20 sec before and after handling any whole melon, such as cantaloupe, watermelon, or honeydew.
- Scrub the surface of melons, such as cantaloupes, with a clean produce brush under running water and dry them with a clean cloth or paper towel before cutting. Be sure that your scrub brush is sanitized after each use, to avoid transferring bacteria between melons.
- Promptly consume cut melon or refrigerate promptly. Keep your cut melon refrigerated ≤4.5°C (40°F) (0-1.1°C [32-34°F] is best), for no more than 7 days.
- Discard cut melons left at room temperature for >4 hr.

* Including pregnant women, persons with weakened immune system, and older adults.

FDA, Food and Drug Administration; USDA, U.S. Department of Agriculture.

Adapted from Centers for Disease Control and Prevention: *Listeria* (listeriosis): prevention. http://www.cdc.gov/listeria/prevention.html .

Careful handwashing is essential to prevent nosocomial spread within obstetric and neonatal units. Immunocompromised patients given prophylaxis with trimethoprim-sulfamethoxazole are protected from *Listeria* infections. Cases and especially outbreaks should be reported immediately to public health authorities so that timely investigation can be initiated in order to interrupt transmission from the contaminated source.

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CHAPTER 216

Actinomyces

Brian T. Fisher

Actinomyces species are anaerobic or microaerophilic, nonsporulating, nonmotile gram-positive bacteria that have a filamentous and branching structure. Infection caused by these bacteria is termed **actinomycosis,** which often presents as an indolent granulomatous, suppurative process with potential for direct extension to contiguous tissue across natural anatomic barriers and formation of draining fistulas and sinus tracts. Organisms from the genus *Actinomyces* can be part of the endogenous flora of the oropharynx, gastrointestinal (GI) tract, or urogenital tract of humans, and thus the site of infection usually is a local process involving the skin or the cervicofacial, abdominal, pelvic, or thoracic regions. However, the infection can disseminate to other locations, including the central nervous system (CNS).

Etiology and Epidemiology

Almost 50 species of *Actinomyces* have been identified using 16S ribosomal RNA sequencing, with more than half these species associated with human infection. *Actinomyces israelii* is the predominant species causing human actinomycosis. Other species associated with infection include, but are not limited to, *Actinomyces odontolyticus, A. meyeri, A. naeslundii, A. gerencseriae,* and *A. viscosus.*

Although actinomycosis occurs worldwide, it is a rare infection. Accordingly, knowledge regarding the epidemiology of actinomycosis is limited to case reports and case series. Based on these reports, this infection appears to affect people of all ages, with no predilection for a particular race, season, or occupation. The infection rate may be higher among males, possibly related to increased trauma or poorer dental hygiene. In a review of 85 cases of actinomycosis, 27% were in persons <20 yr old, and 7% were among children <10 yr old. The youngest patient in this series was 28 days old. Risk factors in children include trauma, dental caries, debilitation, and poorly controlled diabetes mellitus. Although actinomycosis is not a common opportunistic infection, disease has been associated with corticosteroid use, leukemia, renal failure, congenital immunodeficiency diseases, and HIV infection.

Pathogenesis

The 3 most common sites of *Actinomyces* infection are, in order of frequency, cervicofacial, abdominal and pelvic, and thoracic regions, although infection may involve any organ in the body. Actinomycosis typically follows a breach in the local cutaneous or mucosal barrier, such as after a traumatic injury or surgery. Other medical interventions can result in mucosal barrier injuries and predispose to infection, such as the association between intrauterine devices and pelvic actinomycosis. Involvement of the thoracic region has been postulated to present after an aspiration event in patients with poor dentition or a recent dental procedure or after aspiration of a foreign body. Notably, more than one third of patients do not have an identifiable antecedent event that would explain the onset of actinomycosis.

The hallmark of actinomycosis is contiguous spread that fails to respect tissue or fascial planes. Sites of infection show dense cellular infiltrates and suppuration that form many interconnecting abscesses and sinus tracts. These abscesses and sinus tracts may be followed by cicatricial healing from which the organism spreads by burrowing along fascial planes, causing deep, communicating, scarred sinus tracts.

Diagnosis

The presence of **sulfur granules** on macroscopic or microscopic evaluation of involved tissue is highly suggestive of a diagnosis of actinomycosis. On macroscopic appearance, the sulfur granules are typically yellow, accounting for their name, but may be white, gray, or brown. These granules microscopically can appear on hematoxylin-eosin or Gomori methenamine silver stains as a mass of gram-positive branching filamentous rods surrounded by the host immune response inclusive of polymorphonuclear neutrophils and a milieu of eosinophilic staining inert material often referred to as the **Splendore-Hoeppli phenomenon** . Notably, one species, *A. meyeri* , is nonbranching. *Nocardia* is indistinguishable from *Actinomyces* on Gram stain, but *Nocardia* stains with the modified acid-fast stain, contrasting with *Actinomyces* .

Although highly suggestive of actinomycosis, sulfur granules often are not present, and thus additional testing is necessary to make the diagnosis. Patients with actinomycosis in the absence of sulfur granules are typically diagnosed by culturing the organism from tissue procured from the involved site. Cultures on brain-heart infusion agar incubated at 37°C (98.6°F) anaerobically (95% nitrogen and 5% carbon dioxide) and a separate set incubated aerobically reveal organisms within the lines of streak at 24-48 hr. *A. israelii* colonies appear as loose masses of delicate, branching filaments with a characteristic spider-like growth. Colonies of other species, such as *A. naeslundii* and *A. viscosus* may have similar growth characteristics. Unfortunately, even under these conditions, it can be challenging to grow *Actinomyces*, and the yield of different culturing techniques can vary by species. Additionally, conventional biochemical testing for speciation is complex and may result in misclassification of an organism. The evolution of diagnostic tools such as 16S rRNA sequence analysis and matrix-assisted laser desorption/ionization (MALDI) time of flight (TOF) mass spectrometry has improved the accuracy of speciation of cultured organisms and highlighted the potential for detection of *Actinomyces* directly from the involved tissue without culture.

Importantly, actinomycosis is usually, if not always, **polymicrobial** in nature. In a large study of >650 cases, infection with *Actinomyces* was identified in pure culture in only 1 case and was usually identified with other endogenous flora, most notably members of the **HACEK group,** which includes *Aggregatibacter* (formerly *Haemophilus*) *aphrophilus*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae. A. actinomycetemcomitans* is a fastidious, gram-negative bacillus that is part of the oral flora and has been implicated as a pathogen in periodontal disease. Other bacterial species frequently isolated concomitantly in human actinomycosis include *Fusobacterium*, *Bacteroides*, *Capnocytophaga,* and aerobic and anaerobic streptococci.

CT or MRI of the involved area is often employed in the initial patient evaluation. No pathognomonic radiographic findings exist for actinomycosis, but the identification of a process that invades across tissue planes and ignores anatomic boundaries can be highly suggestive of actinomycosis. Furthermore, radiographic imaging can be helpful to establish the extent of the infectious process, guide subsequent diagnostic and therapeutic interventions, and monitor for resolution of infection.

Clinical Manifestations

Cervicofacial Actinomycosis

Cervicofacial actinomycosis in a pediatric patient often manifests as a mass in the neck or submandibular region that persists for weeks to months. Less than half of patients will have associated pain, and fewer than one third of patients will have fever. A minority of patients will report dysphagia or have a draining sinus (Fig. 216.1). Less frequently, cervicofacial actinomycosis manifests clinically as an acute pyogenic infection with a tender, fluctuant mass with trismus, firm swelling, and fistulas with drainage containing the characteristic sulfur granules. Bone is not involved early in the disease, but periostitis, mandibular osteomyelitis, or perimandibular abscess may develop. Infection may spread through sinus tracts to the cranial bones, possibly giving rise to meningitis. The ability of *Actinomyces* to burrow through tissue planes, including the periosteum, is a key difference between actinomycosis and nocardiosis. While predisposing factors for cervicofacial actinomycosis are not well defined for children, adult cases are often preceded by a history of oral trauma, oral surgery, dental procedures, or caries, facilitating entry of organisms into cervicofacial tissues.

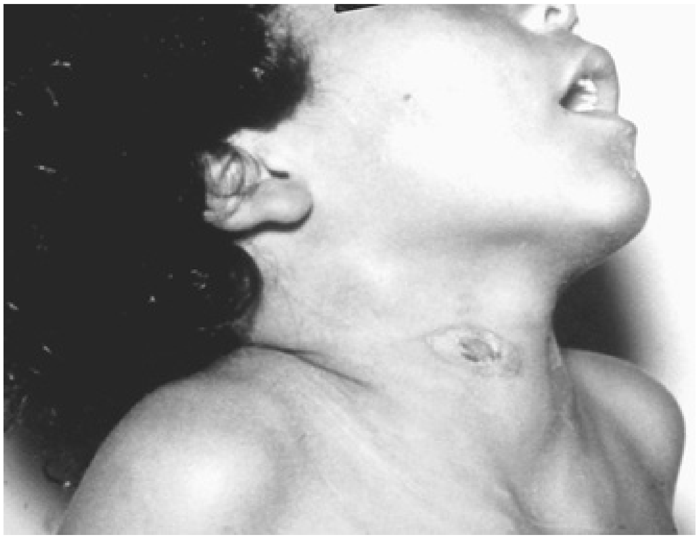

FIG. 216.1 A 2 yr old boy with HIV infection who has cervicofacial actinomycosis and a draining fistula.

Abdominal and Pelvic Actinomycosis

Of all the forms of actinomycosis, delayed diagnosis is most typical for abdominal and pelvic infection. A disruption of the mucosa of the GI tract (e.g., acute GI perforation, abdominal trauma) is often postulated as the inciting event for adult-onset abdominopelvic actinomycosis. In pediatric patients, however, medical history frequently fails to identify prior evidence of mucosal barrier injury. In a contemporary pediatric case series of abdominal and pelvic actinomycosis, prior abdominal surgery (all appendectomies) was reported in only 21% of patients and dental caries in 11%. Most often, a child presents with abdominal pain and a palpable lump or mass on abdominal examination. Fever accompanies the abdominal pain in more than half of cases, with weight loss in almost one third. As with other forms of actinomycosis, abdominopelvic infection can spread across tissue planes by contiguous extension involving any tissue or organ, including muscle, solid abdominopelvic viscera, and walls of the intestinal tract. Likely because of delays in diagnosis, more than one third of pediatric cases present with a draining sinus fistula.

Thoracic Actinomycosis

Thoracic actinomycosis may manifest as an endobronchial infection, a tumor-like lesion, diffuse pneumonia, or a pleural effusion. In a retrospective review of reported pediatric cases of thoracic infection, almost half presented with a chest wall mass. Additional symptoms such as cough, fever, chest pain, and weight loss were reported in <40% of patients. Importantly, thoracic actinomycosis can be found incidentally on radiographs ordered for noninfectious concerns. The variation in presentation and indolent nature of thoracic actinomycosis often delay the diagnosis. Left untreated, the infectious process can dissect along tissue planes and extend through the chest wall or diaphragm, characteristically producing numerous sinus tracts that contain small abscesses and purulent drainage. Other complications include bony destruction of adjacent ribs, sternum, and vertebral bodies. Multiple lobe involvement of the lungs is occasionally found.

Cerebral and Other Forms of Actinomycosis

CNS involvement of *Actinomyces* is often the result of hematogenous spread to the brain parenchyma from a distant site but can also result from contiguous spread from a cervicofacial lesion. The former often results in multiple brain abscesses. **Laryngeal** actinomycosis rarely has been reported in older teenagers. Oropharyngeal colonization with *Actinomyces* may be involved in the development of obstructive tonsillar hypertrophy. Severe forms of **periodontitis,** particularly localized juvenile periodontitis, are associated with *Actinomyces,* especially in children 10-19 yr old. *Actinomyces* has a propensity for infecting heart valves, a process that results in an insidious presentation of endocarditis, with fever present in less than half of cases.

Differential Diagnosis

Actinomycosis has been referred to as a “great imitator” with presentations that mimic appendicitis, pseudoappendicitis caused by *Yersinia enterocolitica,* amebiasis, malignancy, and inflammatory bowel disease. Actinomycosis must be differentiated from other chronic inflammatory infections, including tuberculosis, nocardiosis, polymicrobial bacterial infections, and fungal infections.

Treatment

As with any infection, prompt initiation of antibiotics is important to resolve the infection. Routine susceptibility testing is not typically performed, but most *Actinomyces* spp. are susceptible to penicillin G, which is considered the drug of choice. Because actinomycosis is often found to be polymicrobial in nature, broadening to an agent with a β-lactamase inhibitor, such as ampicillin-sulbactam or amoxicillin-clavulanate, may be warranted, especially if there is an initial poor response. In particular, *A. actinomycetemcomitans* is a **co-pathogen** in at least 30% of actinomycosis infections. Failure to recognize this organism and treat it adequately has resulted in clinical relapse and deterioration in patients with actinomycosis. *A. actinomycetemcomitans* is susceptible to penicillin and ampicillin in vitro, but sensitivity testing does not always correlate with clinical outcome. Transitioning to a cephalosporin, ampicillin-sulbactam, or amoxicillin-clavulanate may be necessary in these patients. Treating actinomycosis in a patient with a penicillin allergy can be challenging, because there is variation in susceptibility by *Actinomyces* spp. to other antibiotic classes. Notably, despite being an anaerobe, a large percentage of *Actinomyces* are not susceptible to metronidazole. It is recommended that an infectious diseases specialist be consulted to help guide antibiotic choices in patients with penicillin allergy or in patients with deep-seated infections such as brain abscesses, endocarditis, or osteomyelitis. Commercially available sensitivity testing methods are available and can be employed in patients with severe disease or poor response to initial therapy.

No definitive comparative effectiveness data exist to guide the optimal route and duration of therapy. Most experts would recommend initial parenteral administration of antibiotics with the opportunity to transition to enteral therapy on clinical improvement. The exception would be for endocarditis or CNS disease, for which parenteral administration should be continued for the entirety of therapy. Given concerns for relapsing infection, antibiotics are often continued for 3-12 mo. The ultimate duration is often dictated by the location of the infection and follow-up clinical exams and imaging. Courses of antibiotic therapy <3 mo have been used in cases of local disease with successful surgical resection.

Traditionally, an adjunctive surgical intervention was thought to be necessary for successful outcome. However, in some case series a subset of patients have responded well to medical management alone. In the setting of significant abscesses and/or sinus tracts, a surgical approach to establish source control and, if possible, completely resect involved issue can hasten clinical improvement.

However, the morbidity of the surgical procedure needs to be weighed against the potential benefits for each patient.

Prognosis

The prognosis is excellent with early diagnosis, prompt initiation of antibiotic therapy, and if necessary, adequate surgical debridement. Actinomycosis often presents in children without a known underlying immunodeficient state. However, disseminated or recalcitrant actinomycosis should raise suspicion for immunodeficiency.

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CHAPTER 217

Nocardia

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A number of *Nocardia* species have been identified as the source of both local and disseminated disease in children and adults. These organisms are primarily opportunistic pathogens infecting immunocompromised persons. Infection caused by these bacteria is termed **nocardiosis** , which consists of acute, subacute, or chronic suppurative infections with a tendency for remissions and exacerbations.

Etiology

Nocardia spp. are obligate aerobes and will grow on a variety of culture media, including simple blood agar, brain-heart infusion agar, and Lowenstein-Jensen media. Colonies can appear as early as 48 hr, but typically growth of *Nocardia* is slower than in other bacteria and may take 1-2 wk. Growth appears as waxy, folded, or heaped colonies at the edges, and yield is best achieved in conditions that include a temperature of 37°C (98.6°F) with 10% carbon dioxide. However, many isolates of *Nocardia* are thermophilic and will grow at temperatures up to 50°C (122°F). Microscopically, *Nocardia* spp. are weakly gram-positive rod-shaped filamentous bacteria. For some isolates, there may be alternating areas of gram-positive and gram-negative staining, giving a beaded appearance often described with *Nocardia*. These organisms are also weakly acid fast, and the modified Kinyoun acid-fast staining technique can be helpful to identify organisms from clinical specimens such as a tissue biopsy or bronchoalveolar lavage (BAL).

Approximately 100 distinct *Nocardia* spp. have been identified, almost 20 of which have been associated with human infection. The distribution of *Nocardia* spp. causing disease varies across observational studies, partly because of variation in taxonomic classification over time. Currently, the predominant species to cause disease are *Nocardia farcinica* , *N. cyriacigeorgica* , *N. abscessus*, and *N. nova* . Species identification can be critical for optimal clinical outcomes because of variability in virulence strategies and antibiotic resistance profiles (see Treatment later). Traditional approaches to speciation require biochemical processing that can be laborious and inefficient. Techniques such as 16S rDNA polymerase chain reaction (PCR) or matrix-assisted laser desorption/ionization (MALDI) time of flight (TOF) mass spectrometry can more efficiently speciate *Nocardia*. Of these, MALDI-TOF technology is likely to become more available in clinical microbiology laboratories in the near future.

Epidemiology

Once thought to be a rare human disease, nocardiosis is being recognized more frequently and has been diagnosed in persons of all ages. Pediatric patients with compromised cellular immunity are at particular risk, including children receiving immune suppression after solid-organ or stem cell transplantation, chemotherapy for malignancy, prolonged corticosteroid therapy, children with poorly controlled HIV infection, or those with a primary immunodeficiency, especially **chronic granulomatous disease** (see Chapter 156). Notably, nocardiosis has been described in patients without an identified immune defect, although in these clinical scenarios, other predisposing factors such as bronchiectasis are often present.

Multiple contemporary retrospective studies have been performed in Australia, France, and Spain to better define the epidemiology of nocardiosis in children and adults. The incidence of nocardiosis has been estimated to be 6 cases per 100,000 hospital admissions. This rate is much higher in susceptible hosts, such as in solid-organ transplant recipients, in whom the rate is as high as 20 per 1000 transplants.

Pathogenesis

Nocardia organisms are environmental saprophytes that are ubiquitous in soil and decaying vegetable matter and have been isolated from soil worldwide. Infection does not result from human to human but typically by inhalation of the organism, presumably from aerosolized dust. Infection can also be acquired by direct cutaneous inoculation, including after arthropod and cat bites. From 70–80% of *Nocardia* infections originate in the pulmonary parenchyma, with 10–25% being primary cutaneous disease.

Nocardia can disseminate from the primary site of infection to any organ or any musculoskeletal location. Dissemination after primary lung infection is common, occurring in 15–50% of patients; those with an underlying immunocompromised condition are more likely to have disseminated disease. The central nervous system (CNS) is the most concerning and most common secondary site of infection, complicating as much as 25% of pulmonary disease. Although rare, isolated CNS disease has been described. Whereas most cases are the result of an environmental exposure, a description of *N. farcinica* sternal wound infections among patients undergoing open heart surgery highlights the possibility of a nosocomial source.

Clinical and Radiographic Manifestations

The clinical presentation can be nonspecific, with fever reported in approximately 60% of patients, cough in 30%, and dyspnea in 25%. Extrapulmonary signs and symptoms can correspond to the site of infection. In particular, neurologic deficit has been reported in up to 25% of all cases and in more than half of patients with CNS involvement. Neurologic complaints can include headache, confusion or altered mental status, weakness, and speech impairment. Renal nocardiosis can cause dysuria, hematuria, or pyuria, and gastrointestinal (GI) involvement may be associated with nausea, vomiting, diarrhea, abdominal distention, or melena. Skin infection manifests as **sporotrichoid nocardiosis** or superficial ulcers (Fig. 217.1). **Mycetoma** is a chronic, progressive infection developing days to months after inoculation, usually on a distal location on the limbs.

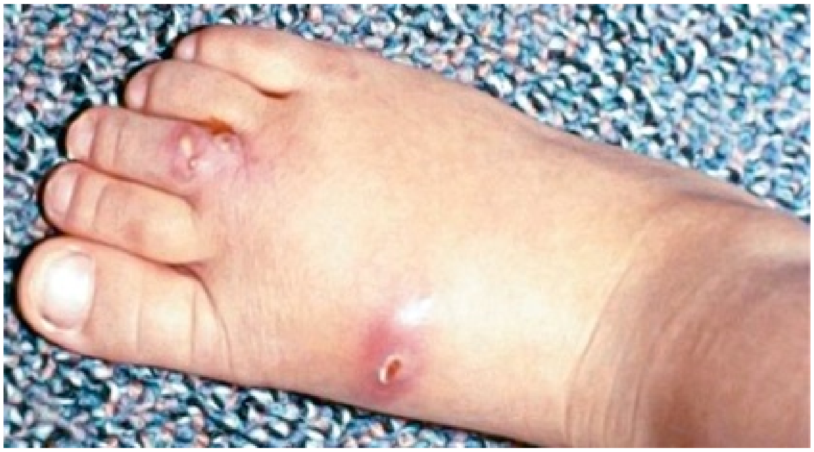

FIG. 217.1 A 2 yr old girl with multiple pustules on the dorsum of the right foot caused by *Nocardia brasiliensis* . (Courtesy of Jaime E. Fergie, MD.)

Given the nonspecific symptoms and signs of nocardiosis (with the exception of cutaneous lesions), radiographic imaging is often necessary to define the location and extent of disease. Pulmonary infection can appear as a consolidation consistent with typical bacterial pneumonia or even as a necrotizing pneumonia with or without a pleural effusion. Single or multiple nodules and cavitary lesions have also been described. Cavitary lesions are more common in patients with an underlying immunocompromising condition. CNS disease can take the form of meningitis or focal lesions. Meningitis presents as neutrophil- or lymphocyte-predominant pleocytosis, elevated cerebrospinal fluid protein, and hypoglycorrhachia. For focal lesions, CT or MRI of the brain often reveals single- or multiple-ring enhancing lesions. Similar to the brain, when other organs or soft tissues are involved, CT or MRI also typically reveals single- or multiple-ring enhancing lesions, suggestive of an abscess or abscesses.

Diagnosis

Microbiologic evidence is necessary to confirm the diagnosis of nocardiosis. An estimated 25% of patients with nocardiosis will be diagnosed by routine blood culture. In the remaining patients, an invasive procedure such as bronchoscopy, tissue biopsy, or abscess aspiration is necessary to procure specimens for diagnostic testing. Histopathologic staining of such material can reveal beaded, weakly gram-positive or modified acid-fast filamentous bacteria. Histopathology can also show delicately branching bacteria with proclivity to fragment. Speciation of *Nocardia* is becoming increasingly reliant on 16S rDNA PCR or

MALDI-TOF technologies. Given that *Nocardia* spp. can colonize the respiratory airway, a sputum or BAL culture that yields a *Nocardia* species is not itself confirmatory of nocardiosis. However, a positive microbiologic test for a *Nocardia* species from one of these specimens in conjunction with the clinical and radiographic findings is strongly supportive of nocardiosis.

When a diagnosis of nocardiosis is made, strong consideration should be given to evaluation for disseminated disease, even in the absence of signs or symptoms, especially in the immunocompromised host. Although data are limited, most experts agree that at the minimum, MRI of the brain should be performed in the immunocompromised host with nocardiosis.

Treatment

The choice, dose, and duration of antimicrobial treatment depend on the site and extent of infection, immune status of the patient, initial clinical response, and species and susceptibility testing of the *Nocardia* isolate. A number of therapeutic options exist for the treatment of nocardiosis; however, there are no comparative effectiveness studies to inform the optimal therapeutic regimen. **Trimethoprim-sulfamethoxazole** (TMP-SMX) is the sulfonamide formulation that is recommended, although sulfadiazine and sulfisoxazole have been used. Increasing recognition of resistance to TMP-SMX across and within *Nocardia* spp. highlights the importance of speciation of *Nocardia* isolates and of performing sensitivity testing in a certified microbiology laboratory. TMP-SMX resistance rates range from 3–10%, with higher rates for specific species. In particular, some reports have identified resistance rates approximating 20% for the commonly identified species of *N. cyriacigeorgica* and *N. farcinica*. Interestingly, administration of TMP-SMX as prophylaxis against *Pneumocystis jiroveci* pneumonia is not always protective against nocardiosis, and thus clinicians should not exclude this diagnosis from the differential in patients receiving TMP-SMX prophylaxis.

Other antibacterial agents with in vitro activity against *Nocardia* spp. include but are not limited to amikacin, amoxicillin-clavulanate, ceftriaxone, ciprofloxacin, clarithromycin, imipenem, linezolid, and minocycline. Large studies reporting on the in vitro resistance of clinical isolates suggest that **linezolid** has the least amount of resistance across all species. Therefore, while awaiting sensitivity testing in patients with *Nocardia* isolated from a clinical specimen, it may be reasonable to administer linezolid empirically. Subsequent therapeutic decisions should be guided by final sensitivity results as well as consideration of the site of infection and pharmacokinetics of the available agents. It is not clear whether parenteral administration is superior to enteral formulations. However, most experts support the use of parenteral therapy for more severe disease, including endocarditis or CNS disease.

In vitro and in vivo animal models have suggested the benefit of combination regimens for the treatment of nocardiosis. There are no clinical data to confirm the need for combination therapy; however, based on the preclinical data, there is expert support for using combination therapy in disseminated disease and in children with an underlying immunocompromising condition. A variety of combination therapies have been suggested in case reports such as amikacin plus ceftriaxone or amikacin plus imipenem. Since data on combination therapy are limited, antibiotic choices should primarily be guided by sensitivity testing of the clinical *Nocardia* isolate.

Surgical drainage of abscesses can be helpful in hastening resolution of nocardiosis. However, no comparative data have documented improvement in overall outcomes with adjunctive surgical intervention, and success has been reported with medical management alone in resolving deep-seated abscesses, even in the CNS. Therefore, the decision to intervene surgically needs to be balanced with the potential consequences of a surgical procedure to drain an abscess.

The necessary duration of therapy for nocardiosis varies by the clinical presentation and the status of the patient. Generally, superficial cutaneous infection requires at least 6-12 wk, pulmonary or systemic nocardiosis is treated for 6-12 mo, and CNS infection for at least 12 mo. These intervals should only be considered as a guide for expected therapeutic durations. The ultimate duration should be dictated by clinical and radiographic resolution of disease.

Prognosis

Historically, nocardiosis has been associated with significant mortality. Fortunately, more recent reports have documented an improved rate of complete cure to approximately 80%. Predictably, attributable case fatality rates vary by disease entity. There is no attributable case fatality associated with cutaneous disease, but 10–20% attributable case fatality has been assigned to disseminated and visceral disease. CNS disease has the highest attributable case fatality rates, reaching 25%. Importantly, much of the data on case fatality rates are informed by predominantly adult cohorts, and thus there may be fewer fatal outcomes in children. Nonetheless, early diagnosis and intervention are important to reduce the morbidity and mortality of nocardiosis, especially in immunocompromised patients at increased risk for disseminated disease.

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SECTION 5

Gram-Negative Bacterial Infections

OUTLINE

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Chapter 219 Neisseria gonorrhoeae (Gonococcus)
Chapter 220 Kingella kingae
Chapter 221 Haemophilus influenzae
Chapter 222 Chancroid (Haemophilus ducreyi)
Chapter 223 Moraxella catarrhalis
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Chapter 225 Salmonella
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CHAPTER 218

Neisseria meningitidis (Meningococcus)

Andrew J. Pollard, Manish Sadarangani

Neisseria meningitidis (the meningococcus) is a commensal of the human nasopharynx in approximately 10% of the population and rarely enters the bloodstream to cause devastating invasive disease such as meningitis and meningococcal septicemia (meningococcemia). Although a rare endemic disease in most countries, the epidemiology of meningococcal disease varies widely over time and in different geographic regions, with both hyperendemic and epidemic disease patterns occurring. Onset of disease in susceptible individuals may be very rapid, within hours, and the case fatality rate is high, especially among those presenting with septic shock, despite access to modern critical care. Individual susceptibility is known to involve a complex relationship among environmental, host, and bacterial factors, and prevention of meningococcal disease through behavior modification (e.g., avoiding tobacco smoke) and vaccination offers the best prospect for control.

Etiology

Neisseria meningitidis is a gram-negative, fastidious, encapsulated, oxidase-positive, aerobic diplococcus. Differences in the chemistry of the polysaccharide capsule allow definition of 12 (previously thought to be 13) serologically distinct meningococcal capsular groups, of which 6, designated A, B, C, W (previously designated W135), X, and Y, are responsible for almost all cases of disease. Meningococcal strains may be subclassified on the basis of antigenic variation in 2 porin proteins found in the outer membrane, **PorB** (serotype) and **PorA** (serosubtype), and **lipopolysaccharide** (immunotype), using serology. Serologic typing is being replaced by molecular typing methods, which target genes under immune selection to provide **antigen sequence typing** (based on amino acid variation in various surface proteins, including PorA and FetA). Sequencing of antigen genes (e.g., *PorA, fHbp, NadA, NHBA*) is set to be an important means of monitoring pressure on meningococcal populations by protein-based vaccines. Because meningococci readily exchange genetic material, typing based on a few antigens cannot provide an accurate picture of relatedness of strains, an important goal in monitoring epidemiology. **Multilocus sequence typing** , which types meningococci using variation in 7 housekeeping genes, has been widely used to map the distribution of genetic lineages of meningococci (http://pubmlst.org/neisseria/) and provides a clearer picture of the genetic and epidemiologic relatedness of strains. To provide still better definition of genetic variation, in some countries, including the United Kingdom, **whole genome sequencing** is used to type meningococci and appears set to replace both antigen and multilocus sequence typing, as costs continue to fall. The application of molecular approaches to epidemiology has established that (1) endemic meningococcal disease is caused by genetically heterogeneous strains, although only a small number of genetic lineages are associated with the majority of cases of invasive disease; and (2) outbreaks are usually clonal, caused by single strains.

Epidemiology

Meningococci are transmitted during close contact through aerosol droplets or exposure to respiratory secretions, as by kissing. The organism does not survive for long periods in the environment. Enhanced rates of mucosal colonization and increased disease risk are associated with activities that increase the likelihood of exposure to a new strain or increase proximity to a carrier, thus facilitating transmission, including kissing, bar patronage, binge drinking, attendance at nightclubs, men having sex with men, and living in freshman college dormitories. Factors that damage the nasopharyngeal mucosa, such as smoking and respiratory viral infection (notably influenza), are also associated with increased rates of carriage and disease, perhaps by driving upregulation of host adhesion molecules that are receptors for meningococci. Carriage is unusual in early childhood and peaks during adolescence and young adulthood.

Meningococcal disease is a global problem, but disease rates vary by a factor of 10-100–fold in different geographic locations at one point in time and in the same location at different times. Most cases of meningococcal disease are sporadic, but small outbreaks (usually in schools or colleges, representing <3% of U.S. cases), **hyperendemic** disease (increased rates of disease persisting for a decade or more as a result of a single clone), and epidemic disease are all recognized patterns. However, over the last decade, rates of meningococcal disease have declined in most industrialized countries, partly through introduction of immunization programs, possibly aided by widespread legislation against smoking in public places. The arrival of hyperinvasive lineages and their eventual decline through development of natural immunity is recognized as a major driver of changes in disease rates over time. The U.S. disease rate was 1.1 cases per 100,000 population in 1999 but had fallen to 0.14 per 100,000 by 2014 (Fig. 218.1). By contrast, the rate of disease in Ireland in 1999 was >12 per 100,000, and rates of 1,000 per 100,000 have been described during epidemic disease in sub-Saharan Africa. Disease caused by dominant hyperendemic clones has been recognized in the last decade in Oregon, United States; Quebec, Canada; Normandy, France; and across New Zealand. Laboratory data underreport meningococcal disease incidence rates, because up to 50% of cases are not culture confirmed, particularly where prehospital antibiotics are recommended for suspected cases. In the United Kingdom, polymerase chain reaction (PCR) methods are used routinely for diagnosis of suspected cases, doubling the number of confirmed cases.

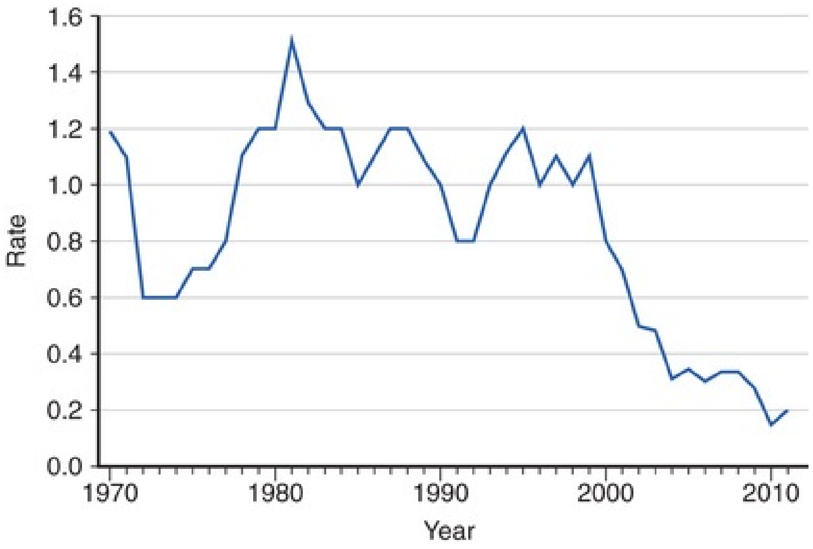

Source: CDC, Unpublished data, National Notifiable Diseases Surveillance System (NNDSS) for 1970–1996 and Active Bacterial Core surveillance (ABCs) system for 1997–2011.

* Per 100,000 population.

† ABCs cases from 1997–2011 estimated to the U.S. population. In 2010, estimated case counts from ABCs were lower than cases reported to NNDSS and might not be representative.

FIG. 218.1 **Rate of meningococcal disease, by year—united states, 1970–2011. (From Cohn AC, MacNeil JR, Clark TA, et al; Centers for Disease Control and Prevention: Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, *MMWR Recomm Rep* 62(RR-2):1–28, 2013.)**

The highest rate of meningococcal disease occurs in infants <1 yr old, probably as a result of *immunologic inexperience* (antibody that recognizes meningococcal antigens is naturally acquired during later childhood), immaturity of the alternative and lectin complement pathways, and perhaps the poor responses made by infants to bacterial polysaccharides. In the absence of immunization, incidence rates decline through childhood, except for a peak of disease among adolescence and young adults, which may be related to increased opportunity for exposure from social activities.

In the United States, most cases of disease in the 1st yr of life are caused by capsular **group B** strains. After age 1 yr, 85% of disease cases are about equally distributed among capsular groups B and C strains, with the remainder caused by **group Y** strains. In most other industrialized countries, capsular group B strains predominate at all ages, in part because of introduction of routine capsular **group C** meningococcal conjugate vaccine among infants and/or toddlers. For reasons not understood, disease in children caused by group Y strains was uncommon in the United States before the 1990s and then began to increase. Rates of disease caused by this capsular group have also increased in several other countries but are declining in the United States. Disease caused by capsular **group W** strains has increased in the United Kingdom as a result of a hyperinvasive clone, which appears to have originated in Latin America.

Large outbreaks of capsular **group A** meningococcal disease occurred during and immediately after the First World War and the Second World War in both Europe and the United States, but since the 1990s, almost all cases caused by capsular group A strains have occurred in Eastern Europe, Russia, and developing countries. The highest incidence of capsular group A disease has occurred in a band across sub-Saharan Africa, the *meningitis belt* , with annual endemic rates of 10-25 per 100,000 population. For more than a century, this region has experienced large capsular group A epidemics every 7-10 yr, with annual rates as high as 1,000 per 100,000 population. The onset of cases in the sub-Saharan region typically begins during the dry season, possibly related to drying and damage to the nasopharyngeal mucosa; subsides with the rainy season; and may reemerge the following dry season. Rates of capsular group A meningococcal disease are currently falling across this region as a result of a mass vaccine implementation targeting strains bearing the A polysaccharide. However, both endemic and epidemic meningococcal disease in this region is also caused by capsular groups C, W, and X strains. Capsular group A and **group X** are infrequent causes of disease in other areas of the world, although both A and W strains have been associated with outbreaks among pilgrims returning from the Hajj.

Pathogenesis and Pathophysiology

Colonization of the nasopharynx by *N. meningitidis* is the first step in either carriage or invasive disease. Disease usually occurs 1-14 days after acquisition of the pathogen. Initial contact of meningococci with host epithelial cells is mediated by pili, which may interact with the host CD46 molecule or an integrin. Close adhesion is then mediated by Opa and Opc binding to carcinoembryonic antigen (CEA) cell adhesion molecule receptors and integrins, respectively. Subsequent internalization of meningococci by epithelial cells is followed by transcytosis through to the basolateral tissues and dissemination into the bloodstream. Immunoglobulin A_1 protease secreted by invasive bacteria degrades secretory IgA on the mucosal surface, circumventing this first-line host defense mechanism.

Once in the bloodstream, meningococci multiply rapidly to high levels to cause septicemia (**meningococcemia**). Patients with a higher bacterial load have a more rapid clinical deterioration and longer period of hospitalization, as well as a higher risk of death and permanent sequelae. Resistance to complement-mediated lysis and phagocytosis is largely mediated by the polysaccharide capsule and **lipopolysaccharide (LPS)** . Outer membrane vesicles released from the surface of the organism contain LPS, outer membrane proteins, periplasmic proteins, and phospholipid, and play a major role in the inflammatory cascade that leads to severe disease.

Much of the tissue damage is caused by host immune mechanisms activated by meningococcal components, in particular LPS. During invasive disease LPS is bound to a circulating plasma protein, known as LPS-binding protein. The host receptor complex for LPS consists of Toll-like receptor (TLR)-4, CD14, and myeloid differentiation protein 2. Binding of LPS to TLR-4, which is upregulated on circulating leukocytes during septicemia, results in activation of a number of different cell types. An intense inflammatory reaction results from secretion of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor, levels of which are closely associated with plasma levels of LPS. The major antiinflammatory cytokines IL-1Rα, IL-2, IL-4, and IL-12 and transforming growth factor-β are present at very low levels. Both high and low levels have been observed for IL-10 and interferon-γ.

The pathophysiologic events that occur during meningococcal septicemia are largely related to microvascular injury. This leads to increased vascular permeability and the capillary leak syndrome, pathologic vasoconstriction and vasodilation, disseminated intravascular coagulation (DIC), and profound myocardial dysfunction. Increased vascular permeability can lead to dramatic fluid loss and severe hypovolemia. **Capillary leak syndrome** with or without aggressive fluid resuscitation (which is essential in severe cases) leads to pulmonary edema and respiratory failure. Initial vasoconstriction is a compensatory mechanism in response to hypovolemia and results in the clinical features of pallor and cold extremities. Following resuscitation, some patients experience **warm shock** , that is, intense vasodilation with bounding pulses and warm extremities, despite persistent hypotension and metabolic acidosis. Virtually all antithrombotic mechanisms appear to be dysfunctional during meningococcal sepsis, leading to a procoagulant state and DIC. All these factors contribute to depressed myocardial function, but there is also a direct negative cytokine effect on myocardial contractility, thought to be largely mediated by IL-6. Hypoxia, acidosis, hypoglycemia, hypokalemia, hypocalcemia, and hypophosphatemia are all common features in severe septicemia and further depress cardiac function. Some patients become unresponsive to the positive inotropic effects of catecholamines and require high levels of inotropic support during intensive care management. These processes result in impairment of microvascular blood flow throughout the body and ultimately lead to **multiorgan failure** , which is responsible for much of the mortality.

Following invasion of the circulation, meningococci may also penetrate the blood-brain barrier and enter the cerebrospinal fluid (CSF), facilitated by pili and possibly Opc. Once there, bacteria continue to proliferate and LPS and other outer membrane products can stimulate a proinflammatory cascade similar to that observed in the blood. This leads to upregulation of specific adhesion molecules and recruitment of leukocytes into the CSF. Central nervous system damage occurs directly by meningeal inflammation and indirectly by circulatory collapse and causes a high rate of neurologic sequelae in affected patients. Death can occur from cerebral edema, which leads to **increased intracranial pressure (ICP)** and cerebral or cerebellar herniation.

Immunity

There is an inverse correlation between the incidence of disease and the prevalence of complement-dependent **serum bactericidal antibody (SBA)** . The level of SBA is highest at birth and among adults and lowest in children between 6 mo and 2 yr of age, when the highest incidence of disease occurs. Such antibodies are naturally elicited by asymptomatic carriage of pathogenic and nonpathogenic *Neisseria* , such as *Neisseria lactamica* , and other antigenically related gram-negative bacteria. A similar relationship was described for capsular groups A, B, and C. Vaccine trials support these earlier findings. For the meningococcal capsular group C conjugate vaccine, an SBA titer ≥1 : 8 correlated strongly with postlicensure vaccine effectiveness. For capsular group B disease the data are less certain, but the proportions of capsular group B vaccine recipients with ≥4-fold rises in SBA after vaccination or SBA titers ≥1 : 4 have been correlated with clinical effectiveness in studies of outer membrane vesicle vaccines. These cutoffs are therefore currently used for regulatory approval of new meningococcal vaccines. The strong association between disease risk and genetic variation in human complement factor H further supports the importance of complement-mediated protection against disease.

There is evidence that mechanisms other than complement-dependent bactericidal antibodies may be important in determining protection against meningococcal disease. Disease in individuals with complement deficiency has a different age distribution, has less severe clinical features, and often involves unusual capsular groups. In particular, complement deficiency does not appear strongly related to an increased risk of capsular group B disease. Alternative surrogate markers of protection include the opsonophagocytic assay and antibody avidity, but no studies have attempted to link these laboratory tests with vaccine efficacy or even population protection, as has been found with SBA.

Host Factors

Host susceptibility is strongly related to age, as previously described, indicating that immunologic responsiveness and/or naïveté in infancy and early childhood are key determinants of risk. **Complement** is a key factor in protection against meningococcal disease. Individuals with inherited deficiencies of properdin, factor D, or terminal complement components have up to a 1,000-fold higher risk for development of meningococcal disease than complement-sufficient people. The risk of meningococcal disease is also increased in patients with acquired complement deficiencies associated with diseases such as nephrotic syndrome, systemic lupus erythematosus (SLE), and hepatic failure and in patients treated with eculizumab, a monoclonal antibody against complement protein C5.

Among those with complement deficiencies, meningococcal disease is more prevalent during late childhood and adolescence, when carriage rates are higher than in children <10 yr old; meningococcal infections in these patients may be recurrent. Although meningococcal disease can occasionally be overwhelming in patients with late complement component deficiency, cases are more typically described as being less severe than in complement-sufficient persons (properdin deficiency being the exception), perhaps reflecting that these cases are often caused by unusual capsular groups. In one study, one third of individuals with meningococcal disease caused by capsular groups X, Y, and W had a complement deficiency. Although protective against early infection, extensive complement activation and bacteriolysis may contribute to the pathogenesis of severe disease once bacterial invasion has occurred.

The sibling risk ratio for meningococcal disease is similar to that for other diseases where susceptibility shows polygenic inheritance, and a number of host genetic factors have now been identified to affect either susceptibility to meningococcal disease or severity of disease. The molecules implicated include proteins on epithelial surfaces, the complement cascade, pattern recognition receptors, clotting factors, and inflammatory mediators. Deficiencies in the complement pathways are consistently associated with an increased risk of meningococcal disease, with specific polymorphisms in mannose-binding lectin and factor H found to be associated with disease susceptibility. A genome-wide association study of 7,522 individuals in Europe identified single nucleotide polymorphisms (SNPs) within genes encoding complement factor H (*CFH*) and CFH-related protein 3 (*CFHR3*), which were associated with host susceptibility to meningococcal disease. Complement-mediated bacteriolysis is known to be extremely important in protection against meningococcal disease, giving these associations biologic plausibility. In particular, factor H attaches to various binding proteins expressed on the bacterial surface, downregulating complement activation and allowing the organism to evade host responses.

In terms of disease severity, a meta-analysis of data from smaller studies found that SNPs in genes encoding plasminogen activator inhibitor 1 (*SERPINE1*), IL-1 receptor antagonist (*IL1RN*), and IL-1β (*IL1B*) are associated with increased mortality from meningococcal disease, as reflected in pathophysiologic changes that occur during invasive disease.

Clinical Manifestations

The most common form of meningococcal infection is asymptomatic carriage of the organism in the nasopharynx. In the rare cases where invasive disease occurs, the clinical spectrum of meningococcal disease varies widely, but the highest proportion of cases present with meningococcal meningitis (30–50%). Other recognized presentations include bacteremia without sepsis, meningococcal septicemia with or without meningitis, pneumonia, chronic meningococcemia, and occult bacteremia. Focal infections in various sites (e.g., myocardium, joints, pericardium, bone, eye, peritoneum, sinuses, middle ear) are well recognized, and all may progress to disseminated disease. Urethritis, cervicitis, vulvovaginitis, orchitis, and proctitis may also occur.

Acute meningococcal septicemia cannot be distinguished from other viral or bacterial infections early after onset of symptoms (Table 218.1). Typical nonspecific early symptoms include fever, irritability, lethargy, respiratory symptoms, refusal to drink, and vomiting. Less frequently, diarrhea, sore throat, and chills/shivering are reported. A maculopapular rash, which is indistinguishable from rashes seen after viral infections, is evident in approximately 10% of cases early in the course of infection (Fig. 218.2). Limb pain, myalgia, or refusal to walk may occur as the primary complaint in 7% of otherwise clinically unsuspected cases. As disease progresses, cold hands or feet and abnormal skin color may be important signs, capillary refill time becomes prolonged, and a nonblanching or petechial rash will develop in >80% of cases. In fulminant meningococcal septicemia, the disease progresses rapidly over several hours from fever with nonspecific signs to septic shock characterized by prominent petechiae and purpura (**purpura fulminans**) with poor peripheral perfusion, tachycardia (to compensate for reduced blood volume resulting from capillary leak), increased respiratory rate (to compensate for pulmonary edema), hypotension (a late sign of shock in young children), confusion, and coma (resulting from decreased cerebral perfusion). Coagulopathy, electrolyte disturbance (especially hypokalemia), acidosis, adrenal hemorrhage, renal failure, and myocardial failure may all develop (Fig. 218.3). Meningitis may be present.

Table 218.1

Prevalence of Symptoms and Signs in Children and Young People With Meningococcal Septicemia, Meningococcal Disease, and Bacterial Meningitis

SYMPTOM OR SIGN	PREVALENCE RANGE (NUMBER OF STUDIES)		
	Bacterial Meningitis	**Meningococcal Disease**	**Meningococcal Septicemia**
Fever	66-97% (10)	58-97% (7)	98% (1)
Vomiting or nausea	18-70% (10)	44-76% (6)	
Rash	9-62% (6)	59-100% (9)	70% (1)
Headache	3-59% (7)	16-49% (5)	40% (1)
Lethargy	13-87% (6)	36-65% (3)	59% (1)
Coughing	N/A (0)	15-27% (2)	33% (1)
Irritable or unsettled	21-79% (8)	36-67% (3)	32% (1)
Runny nose	N/A (0)	24% (1)	31% (1)
Muscle ache or joint pain	23% (1)	7-65% (3)	30% (1)
Refusing food or drink	26-76% (4)	13-60% (3)	27% (1)
Altered mental state*	26-93% (6)	45-81% (3)	N/A (0)
Stiff neck	13-74% (13)	5-71% (6)	N/A (0)
Impaired consciousness	60-87% (4)	10-72% (2)	N/A (0)
Unconsciousness	4-18% (4)	N/A (0)	N/A (0)

Chills or shivering	N/A (0)	39% (1)	N/A (0)
Photophobia	5-16% (2)	2-31% (5)	N/A (0)
Respiratory symptoms	25-49% (4)	16-23% (2)	N/A (0)
Breathing difficulty	13-34% (4)	11% (1)	N/A (0)
Cold hands or feet	N/A (0)	43% (1)	N/A (0)
Shock	8-16% (2)	27-29% (2)	N/A (0)
Seizures	14-38% (12)	7-17% (3)	N/A (0)
Diarrhea	21-29% (2)	7-9% (2)	N/A (0)
Abdominal pain or distention	17% (1)	4% (1)	N/A (0)
Leg pain	N/A (0)	11-37% (2)	N/A (0)
Thirst	N/A (0)	8% (1)	N/A (0)
Sore throat, coryza or throat infection	18% (1)	24% (1)	N/A (0)
Ill appearance	N/A (0)	79% (1)	N/A (0)
Capillary refill time >2 sec	N/A (0)	83% (1)	N/A (0)
Hypotension	N/A (0)	28% (1)	N/A (0)
Abnormal skin color	N/A (0)	19% (1)	N/A (0)
Bulging fontanel [†]	13-45% (4)	N/A (0)	N/A (0)
Ear infection or ear, nose, and throat infections [‡]	18-49% (5)	N/A (0)	N/A (0)
Chest infection	14% (1)	N/A (0)	N/A (0)
Brudzinski sign	11-66% (2)	N/A (0)	N/A (0)
Kernig sign	10-53% (3)	N/A (0)	N/A (0)
Abnormal pupils	10% (1)	N/A (0)	N/A (0)
Cranial nerve pair involvement	4% (1)	N/A (0)	N/A (0)
Toxic or moribund state	3-49% (2)	N/A (0)	N/A (0)
Back rigidity	46% (1)	N/A (0)	N/A (0)
Paresis	6% (1)	N/A (0)	N/A (0)
Focal neurologic deficit	6-47% (3)	N/A (0)	N/A (0)

[*] This includes confusion, delirium, and drowsiness.

[†] The age ranges in the 4 studies are 0-14 yr, 0-2 yr, 0-12 mo, and 0-13 wk.

[‡] One study reported the number of children and young people with ear, nose, and throat infections; the 4 other studies reported the number of ear infections only.

Classification of conditions presented in the table reflects the terminology used in the evidence.

N/A, Not applicable.

Adapted from National Collaborating Center for Women's and Children's Health (UK): Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care, *NICE clinical guidelines, No 102,* London, 2010, RCOG Press.

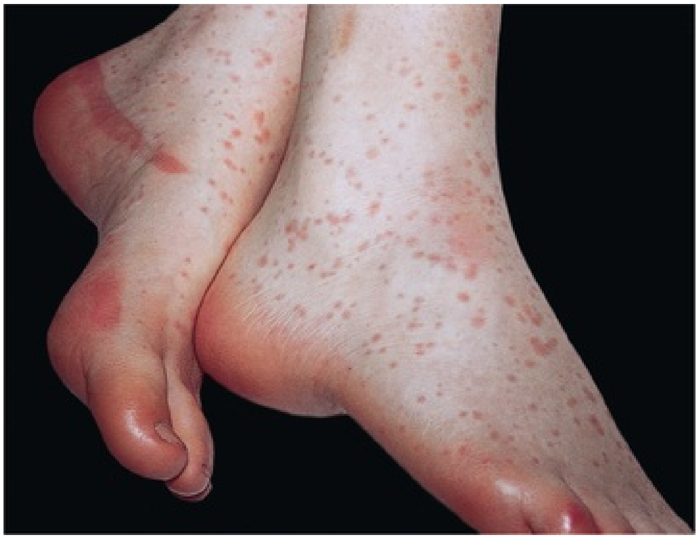

FIG. 218.2 **Meningococcemia. A maculopapular, nonhemorrhagic rash that subsequently became petechial. (From Habif TP: *Clinical dermatology,* ed 6, Philadelphia, 2016, Elsevier, Fig 9-59.)**

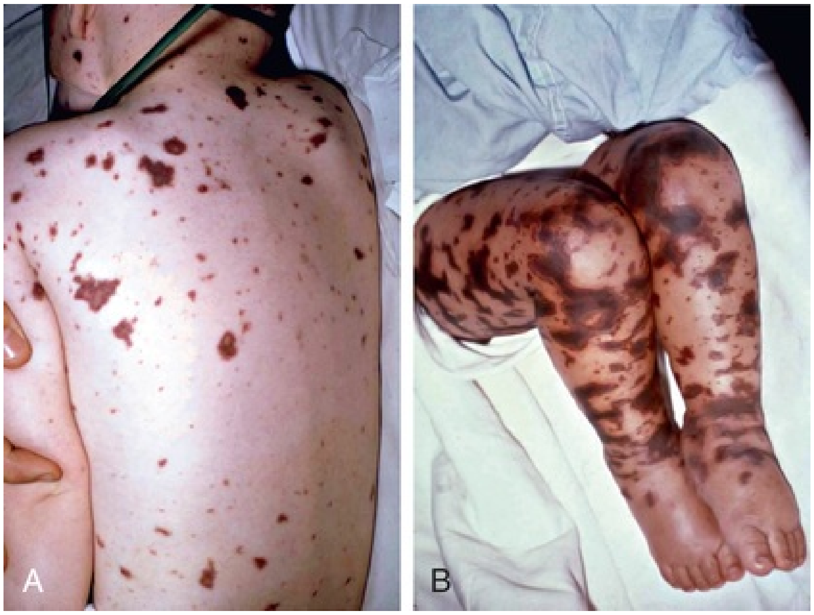

FIG. 218.3 **A,** Purpuric rash in 3 yr old child with meningococcemia. **B,** Purpura fulminans in 11 mo old child with meningococcemia. (From Thompson ED, Herzog KD: Fever and rash. In Zaoutis L, Chiang V, editors: *Comprehensive pediatric hospital medicine,* Philadelphia, 2007, Mosby, Figs 62-6 and 62-7.)

Meningococcal meningitis is indistinguishable from meningitis caused by other bacteria. Nonspecific symptoms and signs (see Table 218.1), including fever and headache, predominate, especially in the young and early in the illness. Children <5 yr old rarely report headache. More specific symptoms of photophobia, nuchal rigidity, bulging of the fontanel, and clinical signs of meningeal irritation may develop but are unusual in infants. Seizures and focal neurologic signs occur less frequently than in patients with meningitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* type b. A meningoencephalitis-like picture can occur, associated with rapidly progressive cerebral edema and death from increased ICP, which may be more common with capsular group A infection.

Occult meningococcal bacteremia manifests as fever with or without associated symptoms that suggest a minor viral infection. Resolution of bacteremia may occur without antibiotics, but sustained bacteremia leads to meningitis in approximately 60% of cases and to distant infection of other tissues.

Chronic meningococcemia, which occurs rarely, is characterized by fever, nontoxic appearance, arthralgia, headache, splenomegaly, and a maculopapular or petechial rash (Fig. 218.4). Symptoms are intermittent, with a mean duration of illness of 6-8 wk. Blood culture results are usually positive, but cultures may initially be sterile. Chronic meningococcemia may spontaneously resolve, but meningitis may develop in untreated cases. Some cases have been associated with complement deficiency and others with sulfonamide therapy. One report indicates that up to 47% of isolates from patients with chronic meningococcemia (vs <10% in acute cases) have a mutation in the *lpxl1* gene, leading to a reduced inflammatory response and the milder course of infection.

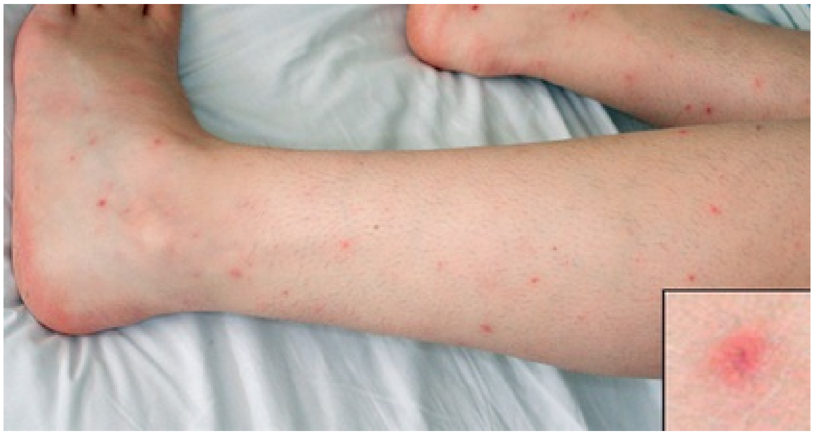

FIG. 218.4 **Rash of chronic meningococcemia. (From Persa OD, Jazmati N, Robinson N, et al: A pregnant woman with chronic meningococcaemia from *Neisseria meningitidis***

with lpxL1-mutations, *Lancet* 384:1900, 2014.).

Diagnosis

The initial diagnosis of meningococcal disease should be made on clinical assessment to avoid delay in implementation of appropriate therapy. Laboratory findings are variable but may include leukocytopenia or leukocytosis, often with increased percentages of neutrophils and band forms, and anemia, thrombocytopenia, proteinuria, and hematuria. Elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may occur, but in patients with rapid onset of disease, these values may be within normal limits at presentation. Increased CRP in the presence of fever and petechiae makes the diagnosis likely. Hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, and metabolic acidosis, often with increased lactate levels, are common in patients with meningococcal septicemia. Patients with coagulopathy have decreased serum concentrations of prothrombin and fibrinogen and prolonged coagulation times.

A confirmed diagnosis of meningococcal disease is established by isolation of *N. meningitidis* from a normally sterile body fluid such as blood, CSF, or synovial fluid. Meningococci may be identified in a Gram stain preparation and/or culture of petechial or purpuric skin lesions, although this procedure is rarely undertaken, and occasionally are seen on Gram stain of the buffy coat layer of a centrifuged blood sample. Although blood culture may be positive in more than two thirds of cases before antibiotic use, culture results often are negative if the patient has been treated with antibiotics prior to collection of the culture specimen; data suggest that <50% are culture positive. Isolation of the organism from the nasopharynx is not diagnostic of invasive disease because the organism is a common commensal.

PCR using primers specific for meningococcal genes (e.g., *ctrA*) has high sensitivity and specificity for detection of meningococci using whole blood samples and has increased confirmation of suspected cases by >40% in the United Kingdom.

Lumbar puncture should be undertaken to establish a diagnosis of meningococcal meningitis in patients without contraindications, including presence of septic shock, coagulopathy, thrombocytopenia, respiratory distress, seizures, increased ICP, or local infection. In patients with meningococcal meningitis, the cellular and chemical characteristics of the CSF are those of acute bacterial meningitis, showing gram-negative diplococci in up to 75% of cases. CSF culture results may be positive in patients with meningococcemia in the absence of CSF pleocytosis or clinical evidence of meningitis; conversely, positive CSF specimens that are gram positive are sometimes culture negative. Overdecolorized pneumococci in Gram stain preparations can be mistaken for meningococci, and therefore empirical therapy should not be narrowed to *N. meningitidis* infection on the basis of Gram stain findings alone.

Detection of capsular polysaccharide antigens using rapid latex agglutination tests on CSF can support the diagnosis in cases clinically consistent with meningococcal disease, but the tests have not performed adequately in clinical practice (poor sensitivity and cross-reactivity of capsular group B test with *Escherichia coli* K1 antigen) and have been replaced by molecular diagnostic methods. Urine antigen testing is insensitive and should not be used. PCR-based assays for detection of meningococci in blood and CSF have been developed, and multiplex PCR assays that detect several bacterial species associated with meningitis, including the meningococcus, are used in some laboratories.

Differential Diagnosis

Meningococcal disease can appear similar to sepsis or meningitis caused by many other gram-negative bacteria, *S. pneumoniae*, *Staphylococcus aureus*, or group A streptococcus; to Rocky Mountain spotted fever, ehrlichiosis, or epidemic typhus; and to bacterial endocarditis. Viral and other infectious etiologies of meningoencephalitis should be considered in some cases.

Petechial **rashes** are common in viral infections (enteroviruses, influenza and other respiratory viruses, measles virus, Epstein-Barr virus, cytomegalovirus, parvovirus) and may be confused with meningococcal disease. Petechial or purpuric rashes are also associated with protein C or S deficiency, platelet disorders (including idiopathic thrombocytopenic purpura), Henoch-Schönlein purpura, connective tissue disorders, drug eruptions, and trauma, including nonaccidental injury. The nonpetechial, blanching maculopapular rash observed in some cases of meningococcal disease, especially early in the course, may initially be confused with a viral exanthem.

Treatment

Antibiotics

Empirical antimicrobial therapy should be initiated immediately after the diagnosis of invasive meningococcal infection is suspected and cultures are obtained, using a **third-generation cephalosporin** to cover the most likely bacterial pathogens until the diagnosis is confirmed. In regions with a high rate of β-lactam–resistant *S. pneumoniae* , empirical *addition* of intravenous (IV) **vancomycin** is recommended (see Chapter 621.1) while awaiting the outcome of bacterial identification and sensitivity, but this is unnecessary in other settings where cephalosporin resistance of pneumococci is very rare (in these settings a risk assessment of each case should be made). Once the diagnosis of β-lactam–sensitive meningococcal disease is confirmed in the laboratory, some authorities recommend a switch to penicillin. Even with no evidence that survival outcomes are different, however, limited evidence from one study indicates that, in meningococcal purpura, necrotic skin lesions are less common among children treated with ceftriaxone than with penicillin. Furthermore, it may be cost-effective by using a once-daily dose of ceftriaxone for therapy in younger children, and this is the recommended practice in the United Kingdom (Table 218.2). No adequate studies have investigated the optimal duration of therapy for children, but the course is generally continued for 5-7 days.

Table 218.2

Treatment of *Neisseria Meningitidis* Invasive Infections

DRUG	ROUTE	DOSE	DOSING INTERVAL (hr)	MAXIMUM DAILY DOSE	NOTES
Penicillin G	IM or IV	300,000 units/kg/day	4-6	12-24 million units	Does not clear carriage, and “prophylaxis” is required at the end of treatment.
Ampicillin	IM or IV	200-400 mg/kg/day	6	6-12 g	Does not clear carriage, and “prophylaxis” is required at the end of treatment.
Cefotaxime	IM or IV	200-300 mg/kg/day	6-8	8-12 g	Recommended in the neonate
Ceftriaxone	IM or IV	100 mg/kg/day	12-24	2-4 g	Preferred treatment as only once or twice daily, and may reduce skin complications.
ALTERNATIVE THERAPY IN THE FACE OF LIFE-THREATENING β-LACTAM ALLERGY					
Chloramphenicol*	IV	50-100 mg/kg/day	6	2-4 g	
Meropenem †	IV	60-120 mg/kg/day	8	1.5-6 g	

[*] Monitor blood levels to avoid toxicity.

[†] Rate of crossreactivity in penicillin-allergic adults is 2–3%.

IM, Intramuscular; IV, intravenous.

Early treatment of meningococcal infections may prevent serious sequelae, but timely early diagnosis is often difficult in the absence of petechial or purpuric skin findings. Among children presenting with petechial rashes, 1–10% may have underlying meningococcal disease, and protocols have been established to ensure that these patients are identified without exposing the >90% of cases without meningococcal disease to unnecessary parenteral antibiotic therapy (Fig. 218.5).

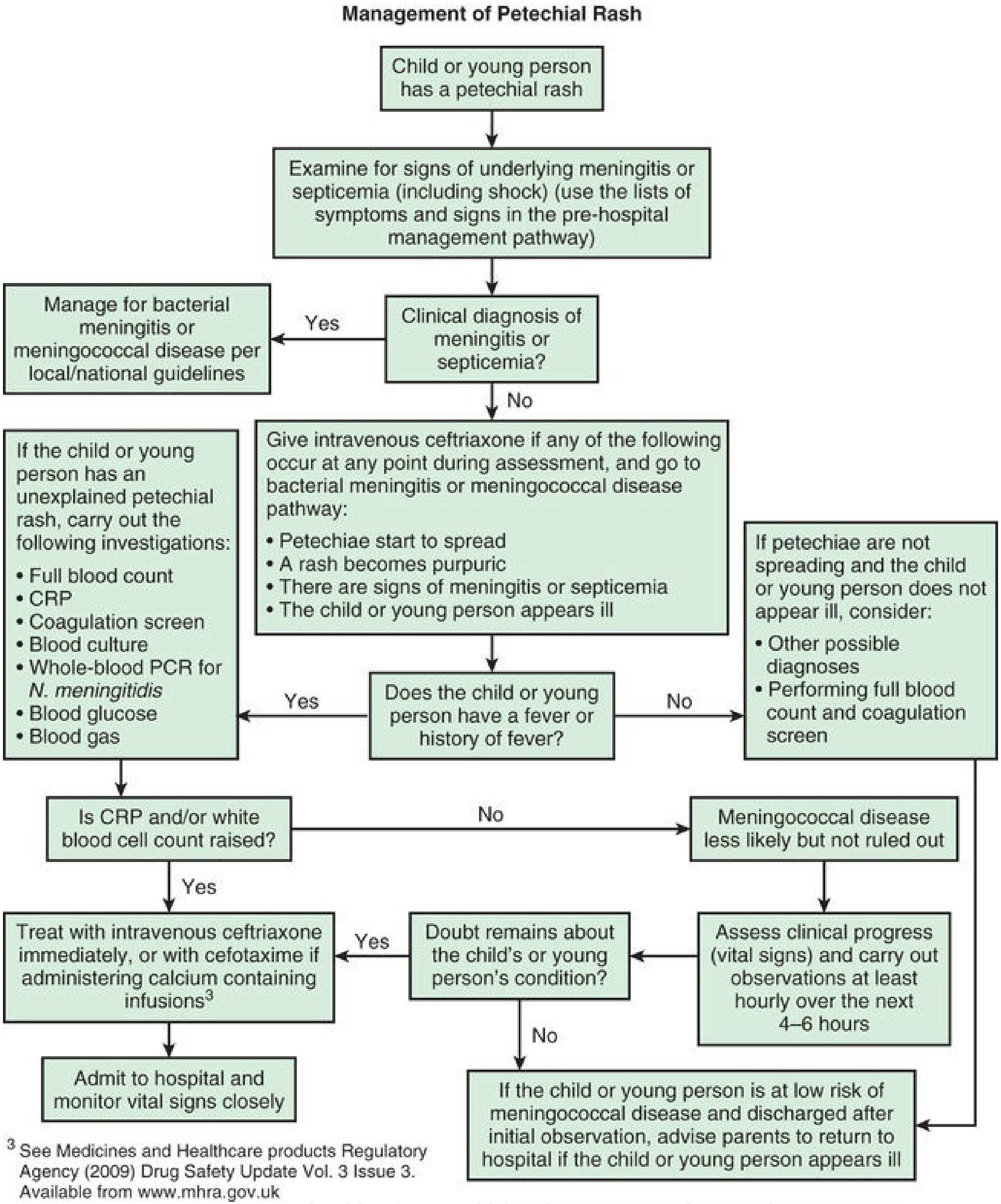
Management of Petechial Rash
Child or young person has a petechial rash
Examine for signs of underlying meningitis or septicemia (including shock) (use the lists of symptoms and signs in the pre-hospital management pathway)
Clinical diagnosis of meningitis or septicemia?
Yes
Manage for bacterial meningitis or meningococcal disease per local/national guidelines
No
Give intravenous ceftriaxone if any of the following occur at any point during assessment, and go to bacterial meningitis or meningococcal disease pathway:
• Petechiae start to spread
• A rash becomes purpuric
• There are signs of meningitis or septicemia
• The child or young person appears ill
If the child or young person has an unexplained petechial rash, carry out the following investigations:
• Full blood count
• CRP
• Coagulation screen
• Blood culture
• Whole-blood PCR for N. meningitidis
• Blood glucose
• Blood gas
Yes
Does the child or young person have a fever or history of fever?
No
If petechiae are not spreading and the child or young person does not appear ill, consider:
• Other possible diagnoses
• Performing full blood count and coagulation screen
Is CRP and/or white blood cell count raised?
No
Meningococcal disease less likely but not ruled out
Yes
Treat with intravenous ceftriaxone immediately, or with cefotaxime if administering calcium containing infusions³
Yes
Doubt remains about the child's or young person's condition?
Assess clinical progress (vital signs) and carry out observations at least hourly over the next 4–6 hours
No
Admit to hospital and monitor vital signs closely
If the child or young person is at low risk of meningococcal disease and discharged after initial observation, advise parents to return to hospital if the child or young person appears ill

[3] See Medicines and Healthcare products Regulatory Agency (2009) Drug Safety Update Vol. 3 Issue 3. Available from www.mhra.gov.uk

FIG. 218.5 **Treatment algorithm for petechial rash. CRP, C-reactive protein; PCR, polymerase chain reaction. (From National Collaborating Center for Women's and Children's Health (UK): Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care, *NICE clinical guidelines,* No 102, London, 2010, RCOG Press.)**

Isolates of *N. meningitidis* with decreased susceptibility to penicillin (minimal inhibitory concentration of penicillin of 0.1-1.0 mg/mL) have been reported from

Europe, Africa, Canada, and the United States (4% of isolates in 2006). Decreased susceptibility is caused at least in part by altered penicillin-binding protein 2 and does not appear to adversely affect the response to therapy. Isolates with reduced susceptibility to third-generation cephalosporins have been described in France, but the level of reduced susceptibility is not likely to affect therapeutic outcomes where these agents are used for treatment.

Supportive Care

Most children with meningococcal disease can be managed with antibiotics and simple supportive care and will improve rapidly. However, with an overall 5–10% case fatality rate, the priority in initiating management of children presenting with meningococcal disease is identification of the life-threatening features of the disease: shock and increased ICP. Delayed initiation of supportive therapy is associated with poor outcome, and protocols have therefore been established to aid clinicians in a step-by-step approach (http://www.meningitis.org). In all children presenting with meningococcal disease, assessment of the airway should be performed, since the airway could be compromised as a result of a depressed level of consciousness (elevated ICP in meningitis or poor cerebral perfusion in shock). In patients with meningococcal septicemia, supplementary oxygen should be used to treat hypoxia, which is caused by pulmonary edema (from capillary leak), and some patients will require endotracheal intubation. Hypovolemia requires both volume replacement and inotropic support to maintain cardiac output. Because ongoing fluid resuscitation may lead to pulmonary edema, endotracheal intubation and ventilation should be initiated in a patient who remains in compensated shock after 40 mL/kg of fluid resuscitation to improve oxygenation and reduce work of breathing. Biochemical and hematologic abnormalities are common in meningococcal septicemia, and protocols recommend anticipation, assessment, and correction of glucose, potassium, calcium, magnesium, phosphate, clotting factors, and anemia.

Children with meningococcal meningitis should be cautiously managed with maintenance fluids (fluid restriction is not recommended and may be harmful), and those with increased ICP should be managed with close attention to maneuvers to maintain normal cerebral perfusion. If there is shock in the presence of elevated ICP, the shock should be carefully corrected to ensure that cerebral perfusion pressure is maintained.

Many adjunctive therapies have been attempted in patients with severe meningococcal septicemia, but few have been subjected to randomized controlled trials (RCTs). Data are insufficient to recommend use of anticoagulant or fibrinolytic agents, extracorporeal membrane oxygenation, plasmapheresis, or hyperbaric oxygen. In well-designed clinical trials, an antibody directed against endotoxin (HA1A) did not confer any benefit in children with meningococcal disease, and although initially promising in adult sepsis, activated protein C was not useful in pediatric sepsis and was associated with an increased risk of bleeding. Recombinant bactericidal permeability increasing protein was studied in an underpowered (survival end-point) trial and showed some potentially beneficial effects against secondary end-points (amputations, transfusions, functional outcome) and requires further investigation.

Although the benefits of **corticosteroids** for adjunctive therapy in pediatric *bacterial* meningitis caused by *H. influenzae* type b (Hib) are accepted, no pediatric data specifically demonstrate benefit in *meningococcal* meningitis. However, some authorities extrapolate from animal data, from experience with Hib, and from compelling data from adult meningitis and recommend corticosteroids as adjunctive therapy in pediatric meningococcal meningitis, given with or soon after the 1st dose of antibiotics. Therapeutic doses of corticosteroids should not be used routinely in meningococcal septicemia. Some intensivists recommend replacement doses of corticosteroids in patients with treatment-refractory septic shock, since severe sepsis caused by meningococcus is associated with adrenal insufficiency resulting from adrenal necrosis or hemorrhage (Waterhouse-Friderichsen syndrome).

Complications

Adrenal hemorrhage, endophthalmitis, arthritis, endocarditis, pericarditis, myocarditis, pneumonia, lung abscess, peritonitis, and renal infarcts can occur during acute infection. Renal insufficiency requiring dialysis may result from prerenal failure. Reactivation of latent herpes simplex virus infections is common during meningococcal infection.

A self-limiting immune complex vasculitis may occur, usually in the 1st 10 days after onset of the disease, resulting in various manifestations, including fever, rash, arthritis, and rarely iritis, pericarditis, or carditis. The arthritis is monoarticular or oligoarticular, involves large joints, and is associated with sterile effusions that respond to nonsteroidal antiinflammatory drugs. Because most patients with meningococcal meningitis become afebrile by the 7th hospital day, persistence or recrudescence of fever after 5 days of antibiotics warrants evaluation for immune complex–mediated complications.

The most common complication of acute severe meningococcal septicemia is focal skin infarction, which typically affects the lower limbs and can lead to substantial scarring and require skin grafting. Distal tissue necrosis in purpura fulminans may require amputation (which should be delayed to allow demarcation) in approximately 2% of survivors. Avascular necrosis of epiphyses and epiphyseal-metaphyseal defects can result from the generalized DIC and may lead to growth disturbance and late skeletal deformities.

Deafness is the most frequent neurologic sequela of meningitis, occurring in 5–10% of children. Cerebral arterial or venous thrombosis with resultant cerebral infarction can occur in severe cases. Meningococcal meningitis is rarely complicated by subdural effusion or empyema or by brain abscess. Other rare neurologic sequelae include ataxia, seizures, blindness, cranial nerve palsies, hemiparesis or quadriparesis, and obstructive hydrocephalus (manifests 3-4 wk after onset of illness). Behavioral and psychosocial complications of the disease are frequently reported.

Prognosis

The case fatality rate for invasive meningococcal disease is 5–10%, with clear differences related to age of the patient and meningococcal genotype. Most deaths occur within 48 hr of hospitalization in children with meningococcemia. Poor prognostic factors on presentation include hypothermia or extreme hyperpyrexia, hypotension or shock, purpura fulminans, seizures, leukopenia, thrombocytopenia (including DIC), acidosis, and high circulating levels of endotoxin and TNF-α. The presence of petechiae for <12 hr before admission, absence of meningitis, and low or normal ESR indicate rapid, fulminant progression and poorer prognosis.

Because complement deficiency is rare following capsular group B infection, screening is unlikely to be useful in detecting cases caused by this group, but some authorities recommend routine screening in these cases. However, with one third or more of cases of disease caused by groups X, Y, and W apparently associated with complement deficiency, it is clearly appropriate to screen after infection with non-B capsular groups.

Prevention

Secondary Prevention

Close contacts of patients with meningococcal disease are at increased risk of infection because such individuals are likely to be colonized with the index case's (hyperinvasive) strain. Antibiotic prophylaxis should be offered as soon as possible to individuals who have been exposed directly to a patient's oral secretions, for whom risk may be 1,000 times the background rate in the population. This includes household, kissing, and close family contacts of cases, as well as childcare and recent preschool contacts in the United States. Up to 30% of cases occur in the 1st wk, but risk persists for up to 1 yr after presentation of the index case. Although prophylaxis is effective in preventing secondary cases, co-primary cases may occur in the days after presentation of the index case, and contacts should be carefully evaluated if they develop symptoms. Advice on management of nonclose contacts, such as those in daycare, nursery settings, or school and other institutions, varies in different countries because the risk of a secondary case in this situation is low and opinion on risk assessment varies. **Ceftriaxone** and **ciprofloxacin** are the most effective agents for prophylaxis, with ciprofloxacin the drug of choice in some countries. **Rifampin** is most widely used but fails to eradicate colonization in 15% of cases (Table 218.3). Prophylaxis is not routinely recommended for medical personnel except those with exposure to aerosols of respiratory secretions, such as through mouth-to-mouth resuscitation, intubation, or suctioning before or in the 24 hr after antibiotic therapy is initiated in the index case.

Table 218.3

Antibiotic Prophylaxis to Prevent *Neisseria Meningitidis* Infection*

AGE-GROUP	DOSE	DURATION	EFFICACY
Rifampin †			
Infants <1 mo	5 mg/kg PO every 12 hr	2 days (4 doses)	
Children ≥1 mo	10 mg/kg PO every 12 hr (max 600 mg)	2 days (4 doses)	90-95%
Adults	600 mg PO every 12 hr	2 days (4 doses)	90-95%
Ceftriaxone			
Children <15 yr	125 mg IM	1 dose	90-95%
Children ≥15 yr	250 mg IM	1 dose	90-95%
Ciprofloxacin			

Children ≥1 mo [†] [‡]	20 mg/kg (max 500 mg) PO	1 dose	90-95%
Azithromycin (Not Recommended Routinely)			
All ages	10 mg/kg (max 500 g) PO	1 dose	90%

[*] Recommended for household and kissing contacts. In the United States, chemoprophylaxis is recommended for:

- Household contact, especially children <2 yr old
- Childcare or preschool contact at any time during 7 days before onset of illness
- Direct exposure to index patient's secretions through kissing, sharing toothbrushes or eating utensils at any time during 7 days before onset of illness
- Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness
- Frequently slept in same dwelling as index patient during 7 days before onset of illness
- Passengers seated directly next to the index case during airline flights lasting >8 hr

[†] Not recommended for pregnant women (ceftriaxone is agent of choice in this setting).

[‡] Not recommended routinely for young people <18 yr old; use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.

IM, Intramuscularly; PO, orally (by mouth).

Neither penicillin nor ampicillin treatment eradicates nasopharyngeal carriage and should not be routinely used for prophylaxis. Patients with meningococcal infection treated solely with penicillin or ampicillin are therefore at risk of relapse or transmission to a close contact and should receive antimicrobial prophylaxis with one of the agents listed in Table 218.3 before hospital discharge. The preference is to use ceftriaxone for *treatment* of the index case, in which case further prophylaxis is not required. Droplet infection control precautions should be observed for hospitalized patients for 24 hr. after initiation of effective therapy. All confirmed or probable cases of meningococcal infection must be reported to the local public health department according to national or regional regulations.

Close contacts of cases could also be immunized to further reduce the risk of secondary infection, as described later.

Vaccination

Meningococcal plain *polysaccharide vaccines* containing capsular polysaccharides from capsular groups A + C or capsular groups A, C, W, Y have been available since the 1960s and used in the control of outbreaks and epidemics and for high-risk groups. However, polysaccharide vaccines are poorly immunogenic in infants, do not induce immunologic memory, and are associated with *immunologic hyporesponsiveness* (reduced response to future doses of polysaccharide). Plain polysaccharide vaccines have been superseded by meningococcal protein-polysaccharide *conjugate vaccines* , which are generally more immunogenic than plain polysaccharides, are immunogenic from early infancy, induce immunologic memory, and are not associated with hyporesponsiveness. The conjugate vaccines contain meningococcal polysaccharides that are chemically conjugated to a carrier protein. Three carrier proteins are used in various meningococcal conjugate vaccines: tetanus toxoid, diphtheria toxoid, and the mutant diphtheria toxin, CRM197. However, although plain polysaccharide vaccines should be considered redundant in most industrialized countries where the new-generation conjugates are available, they may still have a role in some regions where conjugates are not yet available.

The first meningococcal conjugate vaccine used was a monovalent capsular group C meningococcal conjugate vaccine (**MenC**), introduced in the United Kingdom in 1999 and administered to all children and young people <19 yr old in a mass catch-up campaign before establishment in the routine infant immunization schedule. The MenC vaccine has proved highly (>95%) effective in controlling disease through both direct protection of the vaccinated population and induction of herd immunity, protecting the wider population. *Herd immunity* is induced through the impact of conjugate vaccines on colonization, reducing carriage and blocking transmission of meningococci among adolescents and young adults. Monovalent MenC vaccines are used widely in the industrialized countries of Western Europe, Canada, and Australia, where disease caused by capsular group C meningococci has virtually disappeared. However, serologic surveys show that antibody levels wane, especially after infant immunization, and booster doses are now recommended during adolescence to sustain individual and population immunity.

Quadrivalent meningococcal A, C, Y, W conjugate vaccines (**MenACWY**) have been available since 2005 and are routinely used for U.S. adolescents and as a single adolescent booster dose in some countries that had established MenC infant programs more than a decade ago. MenACWY was initially introduced as a single dose at 11 yr of age in the United States, but concerns about waning immunity led to the adoption of a 2nd dose. The initial reports on effectiveness (>80%) of MenACWY in the U.S. program indicates that these vaccines are likely to provide control of disease caused by capsular groups C, W, and Y (capsular group A being unimportant currently), although the program has taken some time to become fully established. As the population of immunized adolescents and young adults in the United States grows, the effects of these vaccines on carriage of meningococci likely will reduce disease among other segments of the population through herd immunity, assuming the transmission dynamics of Y and W meningococci are the same as for capsular group C. Although MenACWY vaccines are not currently recommended in the United States for routine use in younger age-groups in view of the low rate of disease caused by these capsular groups in infancy, they may provide broader protection in countries that are already using MenC vaccines in infant programs. Other combination vaccines containing various conjugates, including Hib-MenC (used in the United Kingdom as 12 mo booster) and Hib-MenCY, may have a role in broadening protection beyond MenC, in early life. Table 218.4 outlines the current U.S. programmatic recommendations.

Table 218.4

Recommendations for Meningococcal Vaccination (United States, 2017)

GENERAL POPULATION			
<2 YR	2-10 YR	11-18 YR	19-55 YR
Not recommended	Not recommended	A single dose of MenACWY-D or MenACWY-CRM at age 11-12 yr with a booster dose at age 16 yr	Not recommended
SPECIAL POPULATIONS AT INCREASED RISK OF MENINGOCOCCAL DISEASE			
RISK FACTOR	**2-18 MONTHS**	**7-23 MONTHS**	**2-55 YR**
Persistent complement deficiencies, functional or anatomic asplenia	4 doses of MenACWY-CRM at 2, 4, 6, and 12-15	2 doses of MenACWY-CRM, with 2nd dose administered at age ≥12 mo and ≥3 mo after 1st dose, or 2 doses of MenACWY-D (not indicated for functional or anatomic asplenia	2 doses of MenACWY-CRM or MenACWY-D 8-12 wk apart* §

	mo[*]	[‡]) at age 9 and 12 mo[*] [†]	*and* MenB vaccine (2 doses of 4CMenB or 3 doses of 2fHbp) [†]
At risk during a community outbreak with a vaccine capsular group covered by the relevant vaccine	4 doses of MenACWY-CRM at 2, 4, 6, and 12-15 mo	2 doses of MenACWY-CRM, with 2nd dose administered at age ≥12 mo and ≥3 mo after 1st dose, or 2 doses of MenACWY-D at age 9 and 12 mo [†]	1 dose of MenACWY-CRM or MenACWY-D MenB vaccine (2 doses of 4CMenB or 3 doses of 2fHbp) depending on capsular group associated with the outbreak [†]
Travel to or resident of countries where meningococcal disease is hyperendemic or epidemic [‖]	4 doses of MenACWY-CRM at 2, 4, 6, and 12-15 mo[*]	2 doses of MenACWY-CRM, with 2nd dose administered at age ≥12 mo and ≥3 mo after 1st dose, or 2 doses of MenACWY-D at 9 and age 12 mo (could be reduced to 8 wk if required for travel)[*] [†]	1 dose of MenACWY-CRM or MenACWY-D[*] [†]
Have HIV	4 doses of MenACWY-CRM at 2, 4, 6, and 12-15 mo[*]	2 doses of MenACWY-CRM or 2 doses of MenACWY-D at age 9-23 mo, 12 wk apart[*] [†]	2 doses of MenACWY-CRM or MenACWY-D 8-12 wk apart[*] [†] [‖]
Other risk factors	—	—	1 dose MenACWY

[*] Booster every 5 yr if ongoing risk (after 3 yr if <7 yr old).

[‡] Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should not be immunized with MenACWY-D before age 2 yr, to avoid interference with the immune response to the pneumococcal conjugate vaccine (PCV).

[§] If MenACWY-D is used, it should be administered at least 4 wk. after completion of all PCV doses.

[‖] For example, visitors to the “meningitis belt” of sub-Saharan Africa. Vaccination also is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

[†] Assuming not previously vaccinated.

Adapted from https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html .

Individuals at high risk of meningococcal disease, such as those with complement deficiency and travelers to regions where there is a risk of epidemic meningococcal disease caused by A or W, should receive MenACWY (see Table 218.4). The risk of disease among close contacts of cases of disease caused by vaccine capsular groups may be further reduced if they are offered MenACWY in addition to antimicrobial prophylaxis. A possible association between MenACWY-diphtheria and Guillain-Barré syndrome, which caused concern early after the vaccine was first used in the United States, has not been substantiated.

A capsular group A meningococcal conjugate vaccine (**MenA**) has been developed for use in the sub-Saharan African meningitis belt, and implementation in 2010 through mass vaccination appears already to have interrupted disease caused by this capsular group. More than 235 million people have been vaccinated since the introduction.

The majority of disease in infants and in most industrialized countries is caused by capsular *group B polysaccharide-bearing meningococci* . This polysaccharide capsule has chemical identity with glycosylated protein antigens in the human fetus and, as a “self” antigen, is therefore not immunogenic in humans and leads to the theoretical risk of induction of autoimmunity. Vaccine development has therefore focused on subcapsular protein antigens. Several countries (e.g., Cuba, Norway, New Zealand) successfully controlled capsular group B epidemics by immunizing with tailor-made outer membrane vesicle vaccines prepared from blebs of outer membrane harvested from the respective epidemic strains. The principal limitation of outer membrane vesicle vaccines is that the bactericidal antibody responses induced by immunization are limited to the vaccine strain, because the response is largely directed against the homologous PorA (serosubtype) protein, and they are therefore not considered for use in endemic settings, including the United States or most other industrialized countries.

Promising approaches for prevention of capsular group B disease have been developed over the past decade. One vaccine that was developed for adolescent immunization was licensed in the United States in 2014 and contains 2 variants of factor H–binding protein (**2fHbp** ; Pfizer vaccines); it appears highly immunogenic in the target population, inducing bactericidal antibodies directed against a panel of strains bearing variants of fHbp. It is currently recommended for use in high-risk groups and during outbreaks (see Table 218.4). Factor H–binding protein appears to be an important virulence determinant, aiding survival of meningococci in blood, and is expressed by virtually all strains.

A 4-component meningococcal vaccine, **4CMenB** (Bexsero, GSK vaccines), is licensed in Europe and North America and available in various other regions. This vaccine contains an outer membrane vesicle (derived from the New Zealand outbreak strain) and 3 recombinant proteins: a single variant of factor H–binding protein, neisserial adhesin A, and neisserial heparin-binding antigen. 4CMenB vaccine induced bactericidal antibodies against strains containing the vaccine antigens in infants, toddlers, and adolescents in clinical trials. The vaccine appears to have a generally favorable safety profile, although induction of fever in infants and pain at the injection site in other age-groups are common.

This vaccine has been used to control university outbreaks of capsular group B meningococcal disease in the United States and Canada and hyperendemic disease in Quebec, Canada. Current recommendations for use in the United States are outlined in Table 218.4 . It was recommended for routine use in the infant immunization program in the United Kingdom in 2014 and deployed from September 2015. Early data indicate a vaccine effectiveness of 82.9% against all capsular group B meningococcal disease following 2 doses at age 2 and 4 mo, but vaccine effectiveness is anticipated to be higher against strains targeted by the vaccine antigens.

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CHAPTER 219

Neisseria gonorrhoeae (Gonococcus)

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Neisseria gonorrhoeae is the causative agent of **gonorrhea** , an infection of the genitourinary tract mucous membranes and of the mucosa of the rectum, oropharynx, and conjunctiva. Gonorrhea transmitted by sexual contact or perinatally is second only to chlamydial infections in the number of cases reported to the U.S. Centers for Disease Control and Prevention (CDC). This high prevalence and the development of antibiotic-resistant strains have led to significant morbidity.

Etiology

Neisseria gonorrhoeae is a nonmotile, aerobic, non–spore-forming, gram-negative diplococcus with flattened adjacent surfaces. Optimal growth occurs at 35-37°C (95-98.6°F) and at pH 7.2-7.6 in an atmosphere of 3–5% carbon dioxide. The specimen should be inoculated immediately onto fresh, moist, modified Thayer-Martin or specialized transport media, because gonococci do not tolerate drying. Thayer-Martin medium contains antimicrobial agents that inhibit hardier normal flora present in clinical specimens from mucosal sites that may otherwise overgrow gonococci. Presumptive identification may be based on colony appearance, Gram stain appearance, and production of cytochrome oxidase. Gonococci are differentiated from other *Neisseria* spp. by the fermentation of glucose but not maltose, sucrose, or lactose. Gram-negative diplococci are seen in infected material, often within polymorphonuclear leukocytes (PMNs).

As with all gram-negative bacteria, *N. gonorrhoeae* possesses a cell envelope composed of an inner cytoplasmic membrane, a middle layer of peptidoglycan, and an outer membrane. The outer membrane contains **lipooligosaccharide** (**LOS** ; also called **endotoxin**), phospholipid, and a variety of proteins that contribute to cell adherence, tissue invasion, and resistance to host defenses. Systems previously used to characterize gonococcal strains included auxotyping and serotyping. **Auxotyping** is based on genetically stable requirements of strains for specific nutrients or cofactors as defined by an isolate's ability to grow on chemically defined media. **Serotyping** systems were based on specific monoclonal antibodies directed against a porin protein called **PorB** (formerly Protein I or PorI), a trimeric outer membrane protein that makes up a substantial part of the gonococcal envelope structure. Changes in PorB proteins present in a community are believed to result, at least in part, from selective immune pressure. DNA-based typing methods have now supplanted auxo- and serotyping. Older gel-based DNA-based typing methods that included restriction fragment length polymorphism (RFLP) analysis of genomic DNA or rRNA (ribotyping), or typing of genes encoding opacity protein (*opa*) were labor intensive and sometimes lacked the ability to accurately discriminate among strains. Methods currently used include the *Neisseria gonorrhoeae* multiantigen sequence typing (**NG-MAST**), which examines the sequences of the variable internal fragments of 2 highly polymorphic *N. gonorrhoeae* genes (*porB* encoding PorB and *tbpB* encoding subunit B of transferrin-binding protein), and multilocus sequence typing (**MLST**), which analyzes the sequences of 7 chromosomal housekeeping genes.

Epidemiology

Since gonorrhea became a nationally notifiable disease in 1944, U.S. rates have ranged between a historic high of 467.7 cases per 100,000 population in 1975 and a historic low of 98.1 per 100,000 in 2009. However, rates have increased almost every year since 2009, with a total of 555,608 cases and a rate of 171.9/100,000 reported in 2017. Rates of reported gonorrhea are also highest in the South (194.0/100,000); among young adults age 20-24 (684.8 cases per 100,000 females age 20-24; 705.2 cases per 100,000 males age 20-24); among males (169.7/100,000 males vs 120.4/100,000 females); and among blacks (548.1/100,000 vs 66.4/100,000 among whites). During 2013–2017, the rate among males increased 86.3% and the rate among females increased 39.4%, suggesting either increased transmission or increased case ascertainment (e.g., through increased extragenital screening) among gay, bisexual, and other men who have sex with men (MSM).

Molecular typing methods (e.g., NG-MAST, MLST) are used to analyze the spread of individual strains of *N. gonorrhoeae* within a community. Maintenance and subsequent spread of gonococcal infections in a community are sustained through continued transmission by asymptomatically infected people and also by a **hyperendemic, high-risk** core group such as commercial sex workers, MSM, or adolescents with multiple sexual partners. This latter observation reflects that most persons who have gonorrhea cease sexual activity and seek care, unless economic need or other factors (e.g., drug addiction) drive persistent sexual activity. Thus, many core transmitters belong to a subset of infected persons who lack or ignore symptoms and continue to be sexually active, underscoring the importance of seeking out and treating the sexual contacts of infected persons who present for treatment. **Oral sex** has a role in sustaining gonorrhea in MSM by providing a pool of untreated asymptomatic pharyngeal infections and may account for as much as one third of symptomatic gonococcal urethritis in MSM.

Gonococcal infection of neonates usually results from peripartum exposure to infected exudate from the cervix of the mother. An acute infection begins 2-5 days after birth. The incidence of neonatal infection depends on the prevalence of gonococcal infection among pregnant women, prenatal screening for gonorrhea, and neonatal ophthalmic prophylaxis.

Pathogenesis and Pathology

N. gonorrhoeae infects primarily columnar epithelium, because stratified squamous epithelium is relatively resistant to invasion. Mucosal invasion by gonococci results in a local inflammatory response that produces a purulent exudate consisting of PMNs, serum, and desquamated epithelium. The gonococcal LOS (endotoxin) exhibits direct cytotoxicity, causing ciliostasis and sloughing of ciliated epithelial cells. Tumor necrosis factor (TNF) and other cytokines are thought to mediate the cytotoxicity of gonococcal infections. LOS activates complement, which also contributes to the acute inflammatory response.

Gonococci may ascend the urogenital tract, causing urethritis or epididymitis in postpubertal males and acute endometritis, salpingitis, and peritonitis (collectively termed **acute pelvic inflammatory disease** or **PID)** in postpubertal females. Dissemination from the fallopian tubes through the peritoneum to the liver capsule results in **perihepatitis** (Fitz-Hugh–Curtis syndrome). Gonococci that invade the lymphatics and blood vessels may cause inguinal lymphadenopathy; perineal, perianal, ischiorectal, and periprostatic abscesses; and **disseminated gonococcal infection** (DGI).

A number of gonococcal virulence and host immune factors are involved in the penetration of the mucosal barrier and subsequent manifestations of local and systemic infection. Selective pressure from different mucosal environments probably leads to changes in the outer membrane of the organism, including expression of variants of pili, opacity or Opa proteins (formerly protein II), and LOS. These changes may enhance gonococcal attachment, invasion, replication, and evasion of the host's immune response.

For infection to occur, the gonococcus must first attach to host cells. Gonococci adhere to the microvilli of nonciliated epithelial cells by hairlike protein structures (pili) that extend from the cell wall. Pili undergo high-frequency antigenic variation that may aid in the organism's escape from the host immune response and may provide specific ligands for different cell receptors. Opacity proteins, most of which confer an opaque appearance to colonies, function as ligands for members of the carcinoembryonic antigen–related cell adhesion molecule (**CEACAM**) family of proteins or heparin sulfate proteoglycans (HSPGs) to facilitate binding to human cells. Interactions between complement receptor 3 (CR3) on cervical epithelial cells and iC3b, pili, and PorB on the gonococcal surface facilitates cellular entry of gonococci in women. In contrast, the interaction between LOS and asialoglycoprotein receptor (ASGP-R) permits gonococcal entry into male urethral epithelial cells. Gonococci that express certain Opa proteins adhere to CEACAM3 and are phagocytosed by human neutrophils in the absence of serum. The interaction of Opa with CEACAM1 on $CD4^+$ T lymphocytes may suppress their activation and proliferation and contribute to the immunosuppression associated with gonorrhea. A gonococcal IgA protease inactivates IgA_1 by cleaving the molecule in the hinge region and could contribute to colonization or invasion of host mucosal surfaces.

Other phenotypic changes that occur in response to environmental stresses allow gonococci to establish infection. Examples include iron-repressible proteins for binding transferrin or lactoferrin, anaerobically expressed proteins, and proteins that are synthesized in response to contact with epithelial cells. Gonococci may grow in vivo under anaerobic conditions or in an environment with a relative lack of iron.

Approximately 24 hr after attachment, the epithelial cell surface invaginates and surrounds the gonococcus in a phagocytic vacuole. This phenomenon is thought to be mediated by the insertion of the gonococcal outer membrane PorB into the host cell, causing alterations in membrane permeability. Subsequently, phagocytic vacuoles begin releasing gonococci into the subepithelial space by means of exocytosis. Viable organisms may then cause local disease (i.e., salpingitis) or disseminate through the bloodstream or lymphatics.

Serum IgG and IgM directed against gonococcal proteins and LOS activate complement on gonococci. Gonococci have evolved several mechanisms to dampen complement activation. Scavenging cytidine monophospho-*N* -acetyl neuraminic acid (CMP-Neu5Ac, the donor molecule for sialic acid) to sialylate its LOS is one such example, which reduces binding of bactericidal antibodies and simultaneously enhances binding of a complement inhibitor called **factor H** (FH). This property is often lost on subculturing gonococci on media that lacks CMP-Neu5Ac and is thus termed “unstable serum resistance.” In contrast, “stable serum resistance”(complement resistance independent of LOS sialylation) is often seen in gonococci that express particular porin proteins (most PorB.1As and select PorB.1Bs),which enables them to bind to complement inhibitors such as FH and C4b-binding protein (C4BP). Such strains are often associated with disseminated disease. *N. gonorrhoeae* differentially subverts the effectiveness of complement and alters the inflammatory responses elicited in human infection. Isolates from cases of DGI typically are “stably” serum resistant, show less C3b deposition on their surface, inactivate C3b more rapidly, generate less C5a, and result in less inflammation at local sites. PID isolates are serum sensitive, deposit more C3b on their surface, inactivate C3b relatively slowly, generate more C5a, and result in more inflammation at local sites. IgG antibody directed against gonococcal reduction-modifiable protein (**Rmp**) blocks complement-mediated killing of *N. gonorrhoeae.* Anti-Rmp blocking antibodies may harbor specificity for outer membrane protein (e.g., OmpA) sequences shared with other *Neisseria* spp. or Enterobacteriaceae, may be directed against a unique Rmp sequence upstream of the OmpA-shared region that includes a cysteine loop, or both. Preexisting antibodies directed against Rmp facilitate transmission of gonococcal infection to exposed women; Rmp is highly conserved in *N. gonorrhoeae,* and the blocking of mucosal defenses may be one of its functions. Gonococcal adaptation also appears to be important in the evasion of killing by neutrophils. Examples include sialylation of LOS, increases in catalase production, and changes in the expression of surface proteins.

Host factors may influence the incidence and manifestations of gonococcal infection. Prepubertal girls are susceptible to vulvovaginitis and rarely experience salpingitis. *N. gonorrhoeae* infects noncornified epithelium, and the thin noncornified vaginal epithelium and alkaline pH of the vaginal mucin predispose this age group to infection of the lower genital tract. Estrogen-induced cornification of the vaginal epithelium in neonates and mature females resists infection. Postpubertal females are more susceptible to salpingitis, especially during menses, when diminished bactericidal activity of the cervical mucus and reflux of blood from the uterine cavity into the fallopian tubes facilitate passage of gonococci into the upper reproductive tract.

Populations at risk for DGI include asymptomatic carriers; neonates; menstruating, pregnant, and postpartum women; MSM; and individuals with defects in complement. The asymptomatic carrier state implies failure of the host immune system to recognize the gonococcus as a pathogen, the capacity of the gonococcus to avoid being killed, or both. **Pharyngeal colonization** has been proposed as a risk factor for DGI. The high rate of asymptomatic infection in pharyngeal gonorrhea may account for this phenomenon. Women are at greater risk for development of DGI during menstruation, pregnancy, and the postpartum period, presumably because of the maximal endocervical shedding and decreased peroxidase bactericidal activity of the cervical mucus during these periods. A lack of neonatal bactericidal IgM antibody is thought to account for the increased susceptibility of neonates to DGI. Persons with terminal complement component deficiencies (C5-C9) are at considerable risk for development of recurrent episodes of DGI.

Clinical Manifestations

Gonorrhea is manifested by a spectrum of clinical presentations from asymptomatic carriage, to the characteristic localized mucosal infections, to disseminated systemic infection (see Chapter 146).

Asymptomatic Gonorrhea

The incidence of asymptomatic gonorrhea in children has not been ascertained. Gonococci have been isolated from the oropharynx of young children who have been abused sexually by male contacts; oropharyngeal symptoms are usually absent. Most genital tract infections produce symptoms in children. However, as many as 80% of sexually mature females with urogenital gonorrhea infections are asymptomatic in settings in which most infections are detected through screening or other case-finding efforts. This situation is in contrast to that in men, who are asymptomatic only 10% of the time. Asymptomatic rectal carriage of *N. gonorrhoeae* has been documented in 26–68% of females with urogenital infection. Most persons with positive rectal culture results are asymptomatic. Most pharyngeal gonococcal infections are asymptomatic, although rarely **acute tonsillopharyngitis** or **cervical lymphadenopathy** can occur. Pharyngeal gonorrhea is easily acquired through fellatio and may account for a significant proportion of urethral gonorrhea in MSM. Pharyngeal gonorrhea is increasingly prevalent, particularly among adolescents and young adults, and associated with overall increasing prevalence of oral sex behaviors.

Uncomplicated, Localized Gonorrhea

Genital gonorrhea has an incubation period of 2-5 days in men and 5-10 days in women. Primary infection develops in the urethra of males, the vulva and vagina of prepubertal females, and the cervix of postpubertal females. Neonatal ophthalmitis (ophthalmia neonatorum) occurs in both sexes.

Urethritis is usually characterized by a purulent discharge and by dysuria without urgency or frequency. Untreated urethritis in males resolves spontaneously in several weeks or may be complicated by epididymitis, penile edema, lymphangitis, prostatitis, or seminal vesiculitis. Gram-negative intracellular diplococci are found in the discharge. In MSM, the rectal mucosa can become infected after receptive anal intercourse. Symptoms range from painless mucopurulent discharge and scant rectal bleeding to overt proctitis with associated rectal pain and tenesmus.

In prepubertal females, **vulvovaginitis** is usually characterized by a purulent vaginal discharge with a swollen, erythematous, tender, and excoriated vulva. Dysuria may occur. Gonococcal infection should be considered in any girl with vaginal discharge, even when sexual abuse is not suspected; sexual abuse must be considered strongly when gonococcal infection is diagnosed in prepubertal children beyond the neonatal period. In postpubertal females, symptomatic gonococcal **cervicitis** and urethritis are characterized by purulent discharge, suprapubic pain, dysuria, intermenstrual bleeding, and dyspareunia. The cervix may be inflamed and tender. In urogenital gonorrhea limited to the lower genital tract, pain is not enhanced by moving the cervix, and the adnexa are not tender to palpation. Purulent material may be expressed from the urethra or ducts of the Bartholin gland. Rectal gonorrhea is often asymptomatic but may cause proctitis with symptoms of anal discharge, pruritus, bleeding, pain, tenesmus, and constipation. Asymptomatic rectal gonorrhea may not be from anal intercourse but may represent translocation of infected secretions from cervicovaginal infection.

Gonococcal **ophthalmitis** may be unilateral or bilateral and may occur in any age group after inoculation of the eye with infected secretions. **Ophthalmia neonatorum** caused by *N. gonorrhoeae* usually appears from 1-4 days after birth (see Chapter 652). Ocular infection in older patients results from inoculation or autoinoculation from a genital site. The infection begins with mild inflammation and a serosanguineous discharge. Within 24 hr, the discharge becomes thick and purulent, and tense edema of the eyelids with marked chemosis occurs. If the disease is not treated promptly, corneal ulceration, rupture, and blindness may follow.

Disseminated Gonococcal Infection

Hematogenous dissemination occurs in 1–3% of all gonococcal infections, more frequently after asymptomatic primary infections than symptomatic infections. Women previously accounted for the majority of cases, with symptoms beginning 7-30 days after infection and within 7 days of menstruation in about one half of cases, but more recent case series describe more male than female cases. The most common manifestations are asymmetric arthralgia, petechial or pustular acral skin lesions, tenosynovitis, suppurative arthritis, and rarely carditis, meningitis, and osteomyelitis. The most common initial symptom is acute onset of **polyarthralgia with fever** . Only 25% of patients complain of skin lesions. Most deny genitourinary symptoms; however, primary mucosal infection is documented by genitourinary cultures. Results of approximately 80–90% of cervical cultures are positive in women with DGI. In males, urethral culture results are positive in 50–60%, pharyngeal culture results are positive in 10–20%, and rectal culture results are positive in 15% of cases.

DGI is classified into 2 clinical syndromes that have some overlapping features. The more common **tenosynovitis-dermatitis syndrome** is characterized by fever, chills, skin lesions, and polyarthralgia predominantly involving the wrists, hands, and fingers. Blood culture results are positive in approximately 30–40% of cases, and results of synovial fluid cultures are almost uniformly negative. In the **suppurative arthritis syndrome** , systemic symptoms and signs are less prominent, and monoarticular arthritis is more common, often involving the knee. A polyarthralgia phase may precede the monoarticular infection. In cases of monoarticular involvement, synovial fluid culture results are positive in approximately 45–55%, and synovial fluid findings are consistent with septic arthritis. Blood culture results are usually negative. DGI in neonates usually occurs as a polyarticular suppurative arthritis.

Dermatologic lesions usually begin as painful, discrete, 1-20 mm, pink or red macules that progress to maculopapular, vesicular, bullous, pustular, or petechial lesions. The typical necrotic pustule on an erythematous base is distributed unevenly over the extremities, including the palmar and plantar surfaces, usually sparing the face and scalp. The lesions number between 5 and 40, and 20–30% may contain gonococci. Although immune complexes may be present in DGI, complement levels are normal, and the role of the immune complexes in pathogenesis is uncertain.

Acute endocarditis is an uncommon (1–3%) but often fatal manifestation of DGI that usually leads to rapid destruction of the aortic valve. **Acute pericarditis** is a rarely described entity in patients with disseminated gonorrhea. **Meningitis** with *N. gonorrhoeae* has been documented, and signs and symptoms are similar to those of any acute bacterial meningitis.

Diagnosis

Laboratory confirmation of gonococcal infection is essential, given the legal implications of potential sexual abuse in children and the need to refer sex partners of adolescents and adults for treatment. Given the advent of highly sensitive and specific nucleic acid amplification tests (NAATs), the use of less sensitive, nonamplified test technologies is no longer justified, such as nucleic acid hybridization/probe tests, nucleic acid genetic transformation tests, or enzyme immunoassays. Culture and susceptibility testing capability still need to be maintained, both because data are insufficient to recommend nonculture tests in cases of sexual assault in prepubescent boys and extragenital anatomic site exposure in prepubescent girls, and because culture is necessary to evaluate suspected cases of gonorrhea treatment failure and to monitor developing resistance to current treatment regimens.

Gram Stain and Culture

Gram stains can be useful in the initial evaluation of patients with suspected gonococcal infection. In males with symptomatic urethritis, a presumptive diagnosis of gonorrhea can be made by identification of gram-negative intracellular diplococci (within leukocytes) in the urethral discharge. A similar finding in females is not sufficient because *Mima polymorpha* and *Moraxella*, which are normal vaginal flora, have a similar appearance. The sensitivity of the Gram stain for diagnosing gonococcal cervicitis and asymptomatic infections is also low. The presence of commensal *Neisseria* spp. in the oropharynx prevents the use of the Gram stain for diagnosis of pharyngeal gonorrhea.

Culture can be performed of any site, including nongenital sites. Advantages of culture include the availability of an isolate for further studies, including antibiotic susceptibility testing. Disadvantages of culture include more stringent transport and growth requirements, lower sensitivity than NAATs, and a delay in availability of results. Material for cervical cultures is obtained as follows. After the exocervix is wiped, a swab is placed in the cervical os and rotated gently for several seconds. Male urethral specimens are obtained by placement of a small swab 2-3 cm into the urethra. Rectal swabs are best obtained by passing of a swab 2-4 cm into the anal canal; specimens that are heavily contaminated by feces should be discarded. For optimal culture results, specimens should be obtained with noncotton swabs (e.g., a urethrogenital calcium alginate–tipped swab [Calgiswab, Puritan Medical Products, Guilford, ME]), inoculated directly onto culture plates, and incubated immediately. The choice of anatomic sites to culture depends on the sites exposed and the clinical manifestations. If symptoms are present, samples from the urethra and rectum can be cultured for men, and samples from the endocervix and rectum can be cultured for all females, regardless of a history of anal intercourse. A pharyngeal culture specimen should be obtained from both men and women if symptoms of pharyngitis are present with a history of recent oral exposure, or oral exposure to a person known to have genital gonorrhea. In a suspected case of **child sexual abuse** , culture remains the recommended method of detection for *N. gonorrhoeae* in urethral specimens from boys and for extragenital sites (conjunctiva, pharynx, and rectum) from all children because NAATs have not yet been sufficiently evaluated for these populations and sample sites. Culture of the endocervix should not be attempted until after puberty.

Specimens from sites that are normally colonized by other organisms (e.g., cervix, rectum, pharynx) should be inoculated on a selective culture medium, such as modified Thayer-Martin medium (fortified with vancomycin, colistin, nystatin, and trimethoprim to inhibit growth of indigenous flora). Specimens from sites that are normally sterile or minimally contaminated (i.e., synovial fluid, blood, cerebrospinal fluid) should be inoculated on a nonselective chocolate agar medium. If DGI is suspected, blood, pharynx, rectum, urethra, cervix, and synovial fluid (if involved) should be cultured. Cultured specimens should be incubated promptly at 35-37°C (95-98.6°F) in 3–5% carbon dioxide. When specimens must be transported to a central laboratory for culture plating, a reduced, nonnutrient holding medium (i.e., Amies-modified Stuart medium) preserves specimens with minimal loss of viability for up to 6 hr. When transport may delay culture plating by >6 hr, it is preferable to inoculate the sample directly onto a culture medium and transport it at an ambient temperature in CO_2 -enriched atmosphere. The Transgrow and JEMBEC (John E. Martin Biological Environmental Chamber) systems of modified Thayer-Martin medium are alternative transport systems.

Nucleic Acid Amplification Tests

The U.S. Food and Drug Administration (FDA) has approved NAATs for use with endocervical swabs, vaginal swabs, male urethral swabs, and female and male first-catch urine. Advantages of using NAATs include less stringent transport conditions, more rapid turnaround time, flexibility in sampling source (providing additional feasibility of testing in settings where physical exam is not done), and patient preference for less invasive sampling. However, NAATs cannot provide antimicrobial susceptibility results, so in cases of persistent gonococcal infection after treatment, clinicians should perform both culture and antimicrobial susceptibility testing. Although urine specimens are acceptable for women, the sensitivity for screening appears to be lower than with vaginal or endocervical swab samples. In contrast, the sensitivity and specificity of urine and urethral swab specimens from men are similar, so first-catch urine is the recommended sample type for urethral screening in men. Product inserts for each NAAT vendor must be carefully examined to assess current indications and allowable specimens. NAATs are not FDA cleared for use with specimens from the rectum, pharynx, conjunctiva, joint fluid, blood, or cerebrospinal fluid. However, most commercial and public health laboratories have established performance specifications to satisfy Centers for Medicare and Medicaid

Services (CMMS) regulations for FDA Clinical Laboratory Improvement Amendments (CLIA) compliance in testing and reporting results for rectal and pharyngeal swab specimens, facilitating their use for clinical management (gonorrhea screening of rectal and pharyngeal sites with NAATs is recommended at least annually in MSM reporting rectal or pharyngeal receptive intercourse).

Data on use of NAATs are limited in children. In a multicenter study of NAATs using strand displacement amplification or transcription-mediated amplification in children being evaluated for sexual abuse, urine from prepubertal girls was a reliable alternative to vaginal culture for detection for *N. gonorrhoeae* . However, culture still remains the recommended method for testing for all other sample sites among prepubertal children. Because of the legal implications of a diagnosis of *N. gonorrhoeae* infection in a child, all positive specimens should be retained for additional confirmatory testing.

Treatment

All patients who are presumed or proven to have gonorrhea should be evaluated for concurrent syphilis, HIV, and *C. trachomatis* infection. The incidence of *Chlamydia* co-infection is 15–25% among males and 35–50% among females. Patients beyond the neonatal period should be treated presumptively for *Chlamydia trachomatis* infection unless a negative chlamydial NAAT result is documented at the time treatment is initiated for gonorrhea. However, if chlamydial test results are not available, or if a non-NAAT result is negative for *Chlamydia* , patients should be treated for both gonorrhea and *Chlamydia* infection (see Chapter 253.2). Persons who receive a diagnosis of gonorrhea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are adequately treated (7 days after receiving treatment and resolution of symptoms, if present). Sexual partners exposed in the preceding 60 days should be examined, specimens collected, and presumptive treatment started.

N. gonorrhoeae has progressively developed resistance to the antibiotics used to treat it over the years. Antimicrobial resistance in *N. gonorrhoeae* occurs as plasmid-mediated resistance to penicillin and tetracycline and chromosomally mediated resistance to penicillins, tetracyclines, spectinomycin, fluoroquinolones, cephalosporins, and azithromycin. Emergence of cephalosporin resistance worldwide has prompted designation of *N. gonorrhoeae* as antibiotic resistance threat level "Urgent" by the CDC. Surveillance data from the CDC Gonococcal Isolate Surveillance Project reveal concerning fluctuations in minimum inhibitory concentration (MIC) for the oral cephalosporin **cefixime** and the injectable third-generation cephalosporin **ceftriaxone** , leading the CDC to revise its U.S. gonorrhea treatment guidelines in 2012 to dual therapy in an attempt to preserve the last commercially available effective treatment. A theoretical basis exists for using 2 antimicrobials with different molecular targets to improve treatment efficacy and potentially delay emergence and spread of resistance to cephalosporins.

Table 219.1 summarizes first-line treatment regimens for neonate, child (weight ≤45 kg), adolescent, and adult gonococcal regimens. Mucosal, localized infections are treatable with single doses; disseminated infections are treated for a minimum of 1 wk. Although dual therapy is not recommended for neonatal and childhood infections, it is recommended for all adult and adolescent infections (inclusive of children >45 kg). The use of **azithromycin** as the 2nd antimicrobial is preferred to doxycycline because of the convenience and compliance advantages of single-dose therapy and the higher prevalence of gonococcal resistance to tetracycline compared to azithromycin among gonococcal surveillance isolates, particularly in strains with elevated MIC to cefixime.

Table 219.1

Recommended Treatment of Gonococcal Infections

	INFECTION	TREATMENT REGIMEN	LENGTH OF THERAPY
Neonates	Ophthalmia neonatorum	Ceftriaxone,* 25-50 mg/kg IV or IM (max 250 mg), plus lavage infected eye frequently until discharge eliminated	Once
	Disseminated infection Scalp abscess Septic arthritis	Ceftriaxone,* 25-50 mg/kg IV or IM qd *or* Cefotaxime, 25-50 mg/kg IV or IM q8–12h †	7 days
	Meningitis	Ceftriaxone,* 25-50 mg/kg IV or IM qd *or* Cefotaxime, 25-50 mg/kg IV or IM q8-12h †	10-14 days
	Endocarditis	Ceftriaxone,* 25-50 mg/kg IV or IM qd *or* Cefotaxime, 25-50 mg/kg IV or IM q8-12h †	Minimum 28 days
Children ≤45 kg	Pharyngeal infection Anorectal infection	Ceftriaxone, 25-50 mg/kg IV or IM (max 250 mg)	Once

	Urogenital infection		
	Conjunctivitis	Ceftriaxone, 50 mg/kg IM (max 1 g) [‡]	Once
	Disseminated infection Septic arthritis	Ceftriaxone, 50 mg/kg IV or IM qd (max 1 g daily)	7 days
	Meningitis	Ceftriaxone, 50 mg/kg IV or IM q12-24h (max 4 g daily)	10-14 days
	Endocarditis	Ceftriaxone, 50 mg/kg IV or IM q12-24h (max 4 g daily)	Minimum 28 days
Adults, adolescents, and children >45 kg	Pharyngeal infection Anorectal infection Urogenital infection	Ceftriaxone, 250 mg IM *plus* Azithromycin, 1 g PO	Once
	Conjunctivitis	Ceftriaxone, 1 g IM *plus* Azithromycin, 1 g PO [‡]	Once
	Disseminated infection Septic arthritis	Ceftriaxone, 1 g IV or IM qd [§] *plus*	7 days
		Azithromycin, 1 g PO	Once
	Meningitis	Ceftriaxone, 1-2 g IV q12-24h *plus*	10-14 days
		Azithromycin, 1 g PO	Once
	Endocarditis	Ceftriaxone, 1-2 g IV q12-24h *plus*	Minimum 28 days
		Azithromycin, 1 g PO	Once

[*] When available, cefotaxime should be substituted for ceftriaxone in neonates with hyperbilirubinemia (particularly those who are premature) and in those <28 days old if receiving calcium-containing intravenous fluids. Consult neonatal dosing references.

[†] Dose and/or dosing frequency change after postnatal age >7 days. Consult neonatal dosing references.

[‡] Plus lavage of the infected eye with saline solution (once).

[§] Ceftriaxone should be continued for 24-48 hr after clinical improvement begins, at which time the switch may be made to an oral agent (e.g., cefixime or a quinolone) if antimicrobial susceptibility is documented by culture. If no organism is isolated and the diagnosis is secure, treatment with ceftriaxone should be continued for at least 7 days.

IM, Intramuscularly; IV, intravenously; PO, orally (by mouth); qd, every day; q8-12h, every 8 to 12 hours.

From Hsu KK, Wangu Z: *Neisseria gonorrhoeae.* In Long SS, Prober CG, Fischer M, editors: *Principles and practice of pediatric infectious diseases,* ed 5, Philadelphia, 2018, Elsevier, Table 126.1.

Alternative regimens exist for adolescents and adults but are extremely limited. For patients with cephalosporin allergy, the combination of gentamicin (240 mg intramuscularly [IM]) plus azithromycin (2 g orally [PO]) cured 100%

of uncomplicated urogenital cases in a trial of U.S. patients age 15-60 yr; the combination of gemifloxacin (320 mg PO) (not licensed for use in those <18 yr old) plus azithromycin (2 g PO) cured >99% of uncomplicated urogenital cases in the same trial but was limited by 8% of patients vomiting within 1 hr of dual–oral drug administration. For patients with azithromycin allergy, doxycycline (100 mg PO twice daily for 7 days) can be used in place of azithromycin as an alternative 2nd antimicrobial. If ceftriaxone is not available, alternative cephalosporins to be used in combination with azithromycin or doxycycline for uncomplicated anorectal and urogenital infection include oral cefixime (400 mg PO), which does not provide as high, or as sustained, bactericidal blood levels as a 250 mg IM dose of ceftriaxone and has limited efficacy for pharyngeal gonorrhea, and other single-dose injectable cephalosporin regimens, such as ceftizoxime (500 mg IM), cefoxitin (2 g IM) with probenecid (1 g PO), or cefotaxime (500 mg IM), none of which offers any advantage over ceftriaxone for urogenital infection, and their efficacy against pharyngeal infection is less certain.

Pregnant women with gonococcal infection should be treated with standard adult dual therapy. If allergy precludes standard treatment, consultation with an infectious disease specialist is recommended. HIV–co-infected patients with gonococcal infection are treated the same as HIV-negative patients.

Follow-up test-of-cure is not recommended for persons diagnosed with uncomplicated urogenital or rectal gonorrhea receiving recommended or alternative regimens. However, any person with pharyngeal gonorrhea who is treated with an alternative regimen should return 14 days after treatment for a test-of cure using culture, NAAT, or both, because pharyngeal gonorrhea is more difficult to eradicate. Symptoms persisting after treatment should be evaluated by culture for *N. gonorrhoeae* (with or without simultaneous NAAT), and any gonococci isolated should be tested for antimicrobial susceptibility. **Treatment failure** should be considered in (1) persons whose symptoms do not resolve within 3–5 days after appropriate treatment and who report no sexual contact during posttreatment follow-up and (2) persons with a positive test-of-cure (i.e., positive culture >72 hr or positive NAAT ≥7 days after receiving recommended treatment) who report no sexual contact during posttreatment follow-up.

Complications

Prompt diagnosis and correct therapy ensure complete recovery from uncomplicated gonococcal disease. Complications of gonorrhea result from the spread of gonococci from a local site of invasion. Complications and permanent sequelae may be associated with delayed treatment, recurrent infection, metastatic sites of infection (meninges, aortic valve), and delayed or topical therapy of gonococcal ophthalmia.

The interval between primary infection and development of a complication is usually days to weeks. In postpubertal females, endometritis may occur, especially during menses, and may progress to salpingitis, tuboovarian abscess, and peritonitis (PID). Manifestations of PID include signs of lower genital tract infection (e.g., vaginal discharge, suprapubic pain, cervical tenderness) and upper genital tract infection (e.g., fever, leukocytosis, elevated erythrocyte sedimentation rate, and adnexal tenderness or mass). The differential diagnosis includes gynecologic diseases (ovarian cyst, ovarian tumor, ectopic pregnancy) and intraabdominal disorders (appendicitis, urinary tract infection, inflammatory bowel disease). Although *N. gonorrhoeae* and *C. trachomatis* are implicated in many cases of PID, this syndrome encompasses a spectrum of infectious diseases of the upper genital tract caused by *N. gonorrhoeae, C. trachomatis,* and endogenous flora (streptococci, anaerobes, gram-negative bacilli). Treatment must therefore be broad. For women with more severe symptoms (inability to exclude surgical emergency, presence of tuboovarian abscess, severe illness, nausea, vomiting or high fever), pregnancy, or lack of response to outpatient therapy within 72 hr, parenteral therapy should be initiated in the hospital. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women, because the clinical response to outpatient treatment is similar among younger and older women.

Recommended parenteral regimens are cefotetan (2 g intravenously [IV] every 12 hr [q12h]) or cefoxitin (2 g IV q6h) plus doxycycline (100 mg PO or IV q12h), or clindamycin (900 mg IV q8h) plus a loading dose of gentamicin (2 mg/kg IV or IM) followed by maintenance gentamicin (1.5 mg/kg q8h). An alternative parenteral regimen is ampicillin-sulbactam (3 g IV q6h) plus doxycycline (100 mg PO or IV q12h). Clinical experience should guide transition to oral therapy, which usually can be initiated within 24 hr of improvement. Thereafter, oral clindamycin (450 mg PO 4 times daily [qid]) or doxycycline (100 mg PO twice daily [bid]) is given to complete 14 days of total therapy, unless tuboovarian abscess is present, in which case clindamycin (450 mg PO qid) or metronidazole (500 mg PO bid) should be added to doxycycline to complete 14 days of therapy with more effective anaerobic coverage.

Parenteral therapy and intramuscular/oral therapy appear to be similar in clinical efficacy for younger and older women with PID of mild to moderate severity. Recommended regimens are as follows: a single dose of ceftriaxone (250 mg IM) plus doxycycline (100 mg PO bid) with or without metronidazole (500 mg PO bid) for 14 days; and single doses of cefoxitin (2 g IM) and probenecid (1 g PO) plus doxycycline (100 mg PO bid) with or without metronidazole (500 mg PO bid) for 14 days.

Once inside the peritoneum, gonococci may seed the liver capsule, causing a perihepatitis with right upper quadrant pain (**Fitz-Hugh–Curtis syndrome**), with or without signs of salpingitis. Perihepatitis may also be caused by *C. trachomatis*. Progression to PID occurs in approximately 20% of cases of gonococcal cervicitis, and *N. gonorrhoeae* is isolated in approximately 40% of cases of PID in the United States. Untreated cases may lead to hydrosalpinx, pyosalpinx, tuboovarian abscess, and eventual sterility. Even with adequate treatment of PID, the risk for sterility from bilateral tubal occlusion approaches 20% after 1 episode of salpingitis and exceeds 60% after 3 or more episodes. The risk for ectopic pregnancy is increased approximately 7-fold after 1 or more episodes of salpingitis. Additional sequelae of PID include chronic pain, dyspareunia, and increased risk for recurrent PID.

Urogenital gonococcal infection acquired during the first trimester of pregnancy carries a high risk for septic abortion. After 16 wk of pregnancy, infection leads to **chorioamnionitis** , a major cause of premature rupture of the membranes and premature delivery.

In males, without treatment, gonococcal urethritis usually resolves spontaneously over several weeks to months. Epididymitis and acute or chronic prostatitis are uncommon complications; most men with gonococcal epididymitis also have overt urethritis. Even more unusual complications include penile edema associated with penile dorsal lymphangitis or thrombophlebitis, periurethral abscess or fistulas, seminal vesiculitis, and balanitis in uncircumcised men.

Prevention

Efforts to develop gonococcal vaccines that confer broad cross-protection have been unsuccessful thus far. A pilus vaccine elicited an antibody response and conferred protection against challenge with the homologous strain but did not protect against disease in a trial involving 3,250 volunteers. The high degree of interstrain and intrastrain antigenic variability of pili poses a formidable barrier to the development of a single effective pilus vaccine. An outer membrane vaccine that was enriched in PorB also elicited an antibody response but failed to protect male volunteers against challenge with the homologous strain, likely because small amounts of Rmp present in the vaccine preparation elicited subversive antibodies. A formalin-killed whole cell vaccine trial in 62 volunteers in an Inuvik population in Canada also failed to provide any protection. Gonococcal surface structures, such as the porin protein (isolated without contaminating Rmp), proteins expressed under various stress conditions that may be encountered in vivo and have been identified by proteomic and transcriptomic approaches, and lipooligosaccharides, may prove more promising as vaccine candidates.

In the absence of a vaccine, prevention of gonorrhea in adolescents and adults can be achieved through **education** , use of **barrier protection** (especially condoms), **screening** of high-risk populations as recommended by the U.S. Preventive Services Task Force (PSTF) and CDC (e.g., sexually active women ≤24 yr old, MSM, individuals previously infected with gonorrhea), and **early identification and treatment** of contacts—all sex partners within the 60 days preceding symptom onset or gonorrhea diagnosis, or, if none, the most recent sex partner, should be examined and treated presumptively. For heterosexual patients, expedited partner therapy (EPT) with cefixime (400 mg) and azithromycin (1 g) can be delivered to partners by the patient, a disease investigation specialist, or a collaborating pharmacy, as permitted by law (https://www.cdc.gov/std/ept/legal/). EPT has been shown to be safe and effective in prevention of reinfection with gonorrhea and is endorsed by the American Academy of Pediatrics, American Academy of Family Physicians, and Society of Adolescent Health and Medicine, as well as other clinical organizations, for use when in-person evaluation and treatment of the partner is impractical or unsuccessful. (Because of the high risk for coexisting undiagnosed sexually transmitted infections such as HIV, EPT is not considered a routine partner management strategy for MSM.)

An infant born to a woman with cervical gonococcal infection has an approximately 30% risk of acquiring ophthalmic infection, compared to a <5% risk if ocular prophylaxis is given. **Gonococcal ophthalmia neonatorum** can be prevented by instilling erythromycin (0.5%) ophthalmic ointment into the conjunctival sac (see Chapter 652). If erythromycin ointment is unavailable, infants at risk for *N. gonorrhoeae* (especially those born to a mother with untreated gonococcal infection or with no prenatal care) can be administered ceftriaxone 25-50 mg/kg IV or IM, not to exceed 250 mg, in a single dose.

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CHAPTER 220

Kingella kingae

Pablo Yagupsky

Kingella kingae is being increasingly recognized as the most common etiology of septic arthritis, osteomyelitis, and spondylodiscitis in young children.

Etiology

Kingella kingae is a fastidious, facultative anaerobic, β-hemolytic member of the Neisseriaceae family that appears as pairs or short chains of gram-negative coccobacilli with tapered ends (Fig. 220.1).

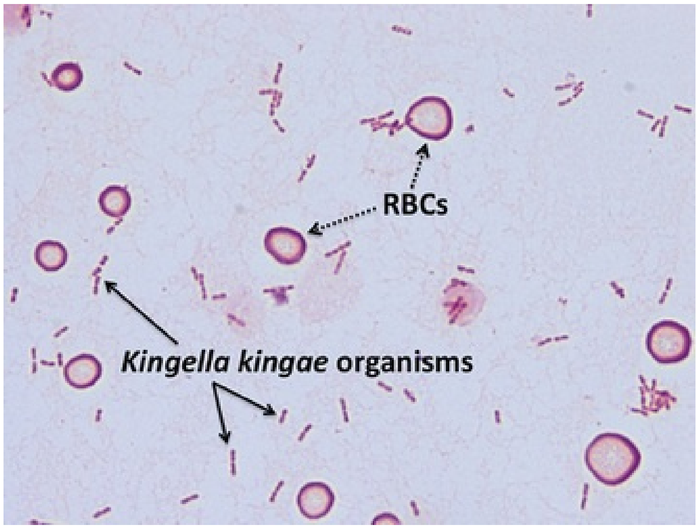

FIG. 220.1 Typical Gram stain of a positive blood culture vial from a child with *K. kingae* bacteremia showing pairs and short chains of plump gram-negative coccobacilli. RBCs, Red blood cells.

Epidemiology

K. kingae is asymptomatically carried in the posterior pharynx. **Colonization** usually starts after age 6 mo, reaches a prevalence of 10% between 12 and 24 mo, and decreases in older children. Pharyngeal colonization plays a crucial role in the **transmission** of the organism through intimate contact between siblings and playmates. Daycare attendance increases the risk for colonization and transmission, and clusters of invasive infection have been reported in childcare facilities.

The species elaborates 4 different polysaccharide capsules (a-d),which appear to represent important virulence factors. Colonizing *K. kingae* strains differ in their invasive potential. Whereas certain clones are commonly found as respiratory colonizers but are seldom isolated from sites of disease, other clones, usually expressing polysaccharide capsule a or b, readily penetrate into the bloodstream and disseminate to the skeletal system or the endocardium, sites for which the organism has a particular tropism.

Invasive *K. kingae* disease is most frequently diagnosed in otherwise healthy children between ages 6 mo and 3 yr, coinciding with the peak prevalence of **pharyngeal carriage** (Fig. 220.2). In contrast, older children and adults with *K. kingae* infections often have underlying chronic diseases, immunosuppressing conditions, malignancy, or cardiac valve pathology. An annual incidence of 9.4 per 100,000 culture-proven invasive infections among Israeli children <5 yr old has been estimated, but because of the suboptimal culture recovery of *K. kingae* organisms, this figure can be considered only a minimal estimate.

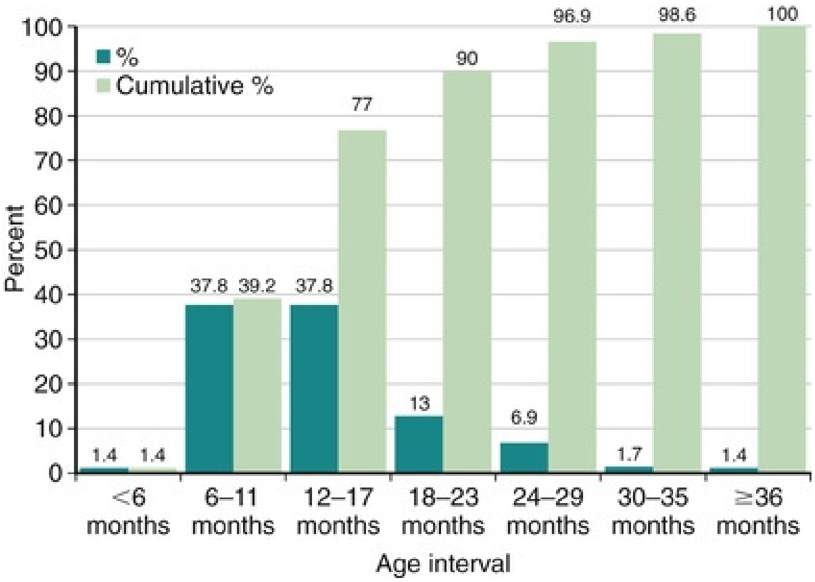

FIG. 220.2 Age distribution of 291 previously healthy children with invasive *K. kingae* infection. (Data from Dubnov-Raz G, Ephros M, Garty BZ, et al: Invasive pediatric *Kingella kingae* infections: a nationwide collaborative study, *Pediatr Infect Dis J* 29:639–643, 2010.)

Pathogenesis

The pathogenesis of *K. kingae* disease begins with adherence of the organism to the pharyngeal epithelium, mediated by pili and a nonpilus adhesin. *K. kingae* secretes a potent Repeats-in-Toxin (RTX) toxin that exhibits deleterious activity to respiratory epithelial cells, macrophages, and synoviocytes, suggesting that it may play a role in disrupting the respiratory mucosa, promoting survival of the bacterium in the bloodstream, and facilitating invasion of skeletal system tissues. Children with *K. kingae* disease frequently present with symptoms of an upper respiratory infection, hand-foot-and-mouth disease, herpetic stomatitis, or buccal aphthous ulcers, suggesting that viral-induced damage to the colonized mucosal surface facilitates invasion of the bloodstream.

Clinical Disease

Septic arthritis is the most common invasive *K. kingae* infection in children, followed by bacteremia, osteomyelitis, and endocarditis (Table 220.1). The organism is the most frequent etiology of skeletal system infections in children 6 mo to 3 yr old in at least some countries. With the exception of patients with endocarditis, the presentation of invasive *K. kingae* infections is frequently mild, and a body temperature <38°C (100.4°F), a normal C-reactive protein (CRP) level, and a normal white blood cell (WBC) count are common, requiring a high index of clinical suspicion.

Table 220.1

Clinical Spectrum and Relative Frequency of *Kingella kingae* Infections

CLINICAL DISEASE	FREQUENCY
SKELETAL SYSTEM	+++
Septic arthritis	+++
Osteomyelitis	++
Spondylodiscitis	+
Tenosynovitis	±
Dactylitis	±
Bursitis	±
Bacteremia with no focus	+++
CARDIAC	+
Endocarditis	+
Pericarditis	±
Meningitis	±
Peritonitis	±
Cellulitis	±
Soft tissue abscesses	±
LOWER RESPIRATORY TRACT	±
Laryngotracheobronchitis	±
Pneumonia	±
Pleural empyema	±
OCULAR	±
Keratitis	±
Corneal abscess	±
Endophthalmitis	±
Eyelid abscess	±

+++, Very common; ++, common; +, infrequent; ±, exceptional.

Septic Arthritis

Although *K. kingae* –driven arthritis especially affects the large, weight-bearing joints, involvement of the small metacarpophalangeal, sternoclavicular, and tarsal joints is not unusual (see Chapter 704). The disease has an acute presentation, and children are brought to medical attention after a median of 3 days. The leukocyte count in the synovial fluid shows <50,000 WBCs/µL in almost 25% of the patients, and the Gram stain of synovial fluid is positive in only a small percentage of cases. Involvement of the hip joint resembles toxic synovitis, and the possibility of a *K. kingae* infection should be always suspected in children <4 yr old presenting with hip pain or a limp.

Osteomyelitis

K. kingae osteomyelitis usually involves the long bones of the extremities (see Chapter 704). The calcaneus, talus, sternum, and clavicle are also frequently affected (and are rarely infected by other bacterial pathogens). Onset of *K. kingae* osteomyelitis is insidious, and the disease is diagnosed after ≥1 wk in 70% of patients. MRI shows mild bone and soft tissue changes. Involvement of the epiphyseal cartilage appears to be specifically associated with the organism. Despite the frequent diagnostic delay, chronic osteomyelitis and functional orthopedic disabilities are unusual.

Spondylodiscitis

K. kingae is currently the 2nd most common bacterium isolated in children <4 yr old with spondylodiscitis. The organism presumably penetrates the rich network of blood vessels that traverse the cartilaginous vertebral endplates and enters the annulus in young children during a bacteremic episode. *K. kingae* spondylodiscitis usually involves the lumbar intervertebral spaces and, with decreasing frequency, the thoracolumbar, thoracic, lumbosacral, and cervical disks. Involvement of multiple disks is uncommon. Patients present with limping, lumbar pain, back stiffness, refusal to sit or walk, neurologic symptoms, or abdominal complaints. Radiography or MRI studies demonstrate narrowing of the intervertebral space. Patients respond well to appropriate antibiotic treatment and recover without complications, although residual narrowing of the intervertebral space may occur.

Occult Bacteremia

Patients with *K. kingae* bacteremia and no focal infection (occult bacteremia) usually present with mild to moderate fever, symptoms suggestive of a viral upper respiratory infection, a mean CRP level of 2.2 mg/dL, and a mean WBC count of 12,700/µL. Children with *K. kingae* bacteremia respond favorably to a short course of antibiotics.

Endocarditis

In contrast to other *K. kingae* infections, endocarditis is also diagnosed in school-age children, adolescents, and adult patients. The disease may affect native as well as prosthetic valves. Predisposing factors include congenital cardiac malformations or rheumatic valvular disease, but some patients have previously normal hearts. Typically, the left side of the heart is involved, usually the mitral valve. Fever and acute-phase reactants are elevated more in patients with endocarditis than in those with uncomplicated bacteremia; no particular cutoff value accurately distinguishes between the 2 conditions. Despite the exquisite susceptibility of *K. kingae* to antibiotics, cardiac failure, septic shock, cerebrovascular accident (stroke), and other life-threatening complications are common, and the mortality rate is high (>10%). Because of the potential severity of *K. kingae* endocarditis, routine echocardiographic evaluation of children with isolated bacteremia is indicated.

Diagnosis

The diagnosis of *K. kingae* disease is established by isolation of the bacterium or by a positive nucleic acid amplification test (NAAT; polymerase chain reaction) from a normally sterile site such as blood, synovial fluid, or bone tissue. Although *K. kingae* grows on routine bacteriologic media, its recovery from exudates is frequently unsuccessful. Detection is enhanced by inoculating synovial fluid specimens into blood culture vials, suggesting that diluting purulent samples in a large volume of nutrient broth reduces the concentration of detrimental factors, improving the isolation of this fastidious bacterium.

Testing bone and joint specimens by NAAT that targets specific *K. kingae* genes, such as *cpn* or those encoding the RTX toxin, results in a 4-fold improvement in the detection of the organism and reduces the fraction of *culture-negative septic arthritis* in young children.

Treatment

K. kingae is usually highly susceptible to penicillin and cephalosporins but exhibits decreased susceptibility to oxacillin. Although β-lactamase production is frequently detected in colonizing *K. kingae* strains, its prevalence among invasive organisms is low and shows wide geographic variation. Testing for β-lactamase production should be routinely performed in all isolates derived from normally sterile body sites.

Because of the lack of specific guidelines for treating *K. kingae* disease, patients have been administered a variety of antibiotic regimens according to protocols developed for infections caused by traditional bacterial pathogens. The first-line therapy for skeletal infections in young children usually consists of intravenous (IV) administration of a second- or third-generation **cephalosporin** , pending culture results. *K. kingae* is always *resistant* to glycopeptide antibiotics, and the majority of isolates are also *resistant* to clindamycin, a serious concern in areas where skeletal infections caused by community-associated methicillin-resistant *S. aureus* are common, and **vancomycin** or **clindamycin** are initially administered to children with presumptive septic arthritis or osteomyelitis. The initial antibiotic regimen is frequently changed to a cephalosporin (e.g., ceftriaxone) once *K. kingae* is identified or to ampicillin after β-lactamase production is excluded. A favorable clinical response and decreasing CRP levels to ≤20 μg/mL are used to guide switching to oral antibiotics and defining duration of therapy. Antibiotic treatment has ranged from 2-3 wk for *K. kingae* arthritis, from 3-6 wk for *K. kingae* osteomyelitis, and from 3-12 wk for *K. kingae* spondylodiscitis. Although some children with septic arthritis have been managed with repeat joint aspirations and lavage, most patients respond promptly to conservative treatment with appropriate antibiotics and do not require invasive surgical procedures.

Children with *K. kingae* bacteremia without focal infection are initially treated with an intravenous β-lactam antibiotic and are subsequently switched to an oral drug once the clinical condition has improved. In most cases, duration of therapy is 1-2 wk.

Patients with *K. kingae* endocarditis are usually treated with an IV β-lactam antibiotic alone or in combination with an aminoglycoside for 4-7 wk. Early surgical intervention is necessary for life-threatening complications unresponsive to medical therapy.

Prevention

Because the risk of asymptomatic pharyngeal carriers for developing an invasive *K. kingae* infection is low (<1% per year), in the absence of clinical disease, there is no indication to eradicate the organism from the colonized mucosal surfaces. Nonetheless, in the reported outbreaks of *K. kingae* infections in child daycare centers, 31 of 199 (15.6%) classmates developed a proven or presumptive infection, including fatal endocarditis, within 1 mo, indicating that the causative strains combined unusual transmissibility and virulence. Under these circumstances, prophylactic antibiotic therapy to eradicate colonization in contacts and prevent further cases of disease has been employed, consisting of either rifampin alone, 10 mg/kg or 20 mg/kg twice daily for 2 days, or rifampin in combination with amoxicillin (80 mg/kg/day) for 2 days or 4 days. The effectiveness of these regimens has ranged between 47% and 80%, indicating that eradication of *K. kingae* from colonized mucosae is difficult to achieve. However, after antibiotic prophylaxis administration, no further cases of disease have been detected, suggesting that reduction of the bacterial density by antibiotics and/or induction of an effective immune response by prolonged carriage is enough to decrease transmissibility and prevent additional cases.

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CHAPTER 221

Haemophilus influenzae

Robert S. Daum

Effective vaccines to prevent ***Haemophilus influenzae* type b (Hib)** disease, introduced in the United States and most other countries, have resulted in a dramatic decrease in the incidence of infections caused by this organism. However, mortality and morbidity from Hib infection remain a problem worldwide, primarily in developing countries. Occasional cases of invasive disease caused by non–type b organisms continue to occur but are infrequent. Nontypeable members of the species are an important cause of otitis media, sinusitis, and chronic bronchitis.

Etiology

Haemophilus influenzae is a fastidious, gram-negative, pleomorphic coccobacillus that requires factor X (hematin) and factor V (phosphopyridine nucleotide) for growth. Some *H. influenzae* isolates are surrounded by a polysaccharide capsule and can be serotyped into 1 of 6 antigenically and biochemically distinct types designated a, b, c, d, e, and f.

Epidemiology

Before the advent of an effective Hib conjugate vaccine in 1988, *H. influenzae* type b was a major cause of serious disease among children. There was a striking age distribution of cases, with >90% in children <5 yr old and the majority in children <2 yr old. The annual attack rate of invasive disease was 64-129 cases per 100,000 children <5 yr old. Invasive disease caused by other capsular serotypes has been much less frequent but continues to occur. The incidence of invasive disease caused by type b and non–type b serotypes has been estimated at approximately 0.08 and 1.02 cases, respectively, per 100,000 children <5 yr old per year in the United States. Nonencapsulated (nontypeable) *H. influenzae* strains also occasionally cause invasive disease, especially in neonates, immunocompromised children, and children in developing countries. The estimated rate of invasive disease caused by nontypeable *H. influenzae* in the United States is 1.88 per 100,000 children <5 yr old per year. Nontypeable isolates are common etiologic agents in otitis media, sinusitis, and chronic bronchitis.

Humans are the only natural hosts for *H. influenzae,* which is part of the normal respiratory flora in 60–90% of healthy children. Most isolates are nontypeable. Before the advent of conjugate vaccine immunization, *H. influenzae* type b could be isolated from the pharynx of 2–5% of healthy preschool and school-age children, with lower rates among infants and adults. Asymptomatic colonization with Hib occurs at a much lower rate in immunized populations.

The continued circulation of the type b organism despite current vaccine coverage levels suggests that elimination of Hib disease may be a formidable task. The few cases of Hib invasive disease in the United States now occur in both unvaccinated and fully vaccinated children. Approximately 50% of cases occur in young infants who are too young to have received a complete primary vaccine series. Among the cases in patients who are old enough to have received a complete vaccine series, the majority are underimmunized. To highlight this point, during a shortage of Hib vaccine, invasive disease developed in 5 children in Minnesota, all of whom were incompletely immunized. Continued efforts are necessary to provide currently available Hib conjugate vaccines to children in developing countries, where affordability remains an important issue.

In the prevaccine era, certain groups and individuals had an increased incidence of invasive Hib disease, including Alaskan Natives, American Indians (Apache, Navajo), and African Americans. Persons with certain chronic medical conditions were also known to be at increased risk for invasive disease, including those with sickle cell disease, asplenia, congenital and acquired immunodeficiencies, and malignancies. Unvaccinated infants with invasive Hib infection are also at increased risk for recurrence, reflecting that they typically do not develop a protective immune response to *H . influenzae.*

Socioeconomic risk factors for invasive Hib disease include childcare outside the home, the presence of siblings of elementary school age or younger, short duration of breastfeeding, and parental smoking. A history of otitis media is associated with an increased risk for invasive disease. Much less is known about the epidemiology of invasive disease caused by non–type b strains, and it is not clear whether the epidemiologic features of Hib disease apply to disease caused by non-Hib isolates.

Among age-susceptible household contacts who have been exposed to a case of invasive Hib disease, there is increased risk for secondary cases of invasive disease in the 1st 30 days, especially in susceptible children <24 mo old. Whether a similar increased risk occurs for contacts of individuals with non-Hib disease is unknown.

The mode of transmission is usually direct contact or inhalation of respiratory tract droplets containing *H. influenzae*. The incubation period for invasive disease is variable, and the exact period of communicability is unknown. Most children with invasive Hib disease are colonized in the nasopharynx before initiation of antimicrobial therapy; 25–40% may remain colonized during the 1st 24 hr of therapy.

With the decline of disease caused by type b organisms, disease caused by other serotypes (a, c-f) and nontypeable organisms has been recognized more clearly. There is no evidence that these non–type b infections have increased in frequency. However, clusters of type a and, less often, type f and type e infections have occurred. Data from Israel suggest that nontypeable *H. influenzae* is the most common case of invasive *H. influenzae* disease in that country.

Pathogenesis

The pathogenesis of Hib disease begins with adherence to respiratory epithelium and colonization of the nasopharynx, which is mediated by pilus and nonpilus adherence factors. The mechanism of entry into the intravascular compartment is unclear but appears to be influenced by cytotoxic factors. Once in the bloodstream, *H. influenzae* type b, and perhaps other encapsulated strains, resist intravascular clearance mechanisms at least in part because of a polysaccharide capsule. In the case of Hib, the magnitude and duration of bacteremia influence the likelihood of dissemination of bacteria to sites such as the meninges and joints.

Noninvasive *H. influenzae* infections such as otitis media, sinusitis, and bronchitis are usually caused by nontypeable strains. These organisms gain access to sites such as the middle ear and sinus cavities by direct extension from the nasopharynx. Factors facilitating spread from the pharynx include eustachian tube dysfunction and antecedent viral infections of the upper respiratory tract.

Antibiotic Resistance

Most *H. influenzae* isolates are susceptible to ampicillin or amoxicillin, but about one-third produce a β-lactamase and are therefore resistant to these antibiotics. β-Lactamase–negative ampicillin-resistant isolates have been identified and manifest resistance by production of a β-lactam–insensitive cell wall synthesis enzyme called PBP3.

Amoxicillin-clavulanate is uniformly active against *H. influenzae* clinical isolates except for the rare β-lactamase–negative ampicillin-resistant isolates. Among macrolides, azithromycin has in vitro activity against a high percentage of *H. influenzae* isolates; in contrast, the activity of erythromycin and clarithromycin against *H. influenzae* clinical isolates is poor. *H. influenzae* resistance to third-generation cephalosporins has not been documented. Resistance to trimethoprim-sulfamethoxazole (TMP-SMX) is infrequent (approximately 10%), and resistance to quinolones is believed to be rare.

Immunity

In the prevaccine era, the most important known element of host defense was antibody directed against the type b capsular polysaccharide polyribosylribitol phosphate (**PRP**). Anti-PRP antibody is acquired in an age-related fashion and facilitates clearance of *H. influenzae* type b from blood, in part related to opsonic activity. Antibodies directed against antigens such as outer membrane proteins or lipopolysaccharide (LPS) may also have a role in opsonization. Both the classical and alternative complement pathways are important in defense against Hib.

Before the introduction of vaccination, protection from Hib infection was presumed to correlate with the concentration of circulating anti-PRP antibody at the time of exposure. A serum antibody concentration of 0.15-1.0 µg/mL was considered protective against invasive infection. Unimmunized infants >6 mo old and young children usually lacked an anti-PRP antibody concentration of this magnitude and were susceptible to disease after encountering Hib. This lack of antibody in infants and young children may have reflected a maturational delay in the immunologic response to thymus-independent type 2 antigens such as unconjugated PRP, presumably explaining the high incidence of type b infections in infants and young children in the prevaccine era.

The conjugate vaccines act as thymus-dependent antigens and elicit serum antibody responses in infants and young children (Table 221.1). These vaccines are believed to prime memory antibody responses on subsequent encounters with PRP. The concentration of circulating anti-PRP antibody in a child primed by a conjugate vaccine may not correlate precisely with protection, presumably because a memory response may occur rapidly on exposure to PRP and provide protection.

Table 221.1

Haemophilus influenzae Type b (Hib) Conjugate Vaccines Available in the United States

VACCINE	TRADE NAME	COMPONENTS	MANUFACTURER
PRP-T	ActHib	PRP conjugated to tetanus toxoid	Sanofi
PRP-T	Hibrix	PRP conjugated to tetanus toxoid	GlaxoSmithKline Biologicals
PRP-OMP	PedvaxHIB	PRP conjugated to OMP	Merck
PRP-T/DTaP-IPV	Pentacel	PRP-T + DTaP-IPV vaccines	Sanofi Pasteur

DTaP, Diphtheria and tetanus toxoids and acellular pertussis vaccine; HepB, hepatitis B vaccine; IPV, trivalent inactivated polio vaccine; OMP, outer membrane protein complex from *Neisseria meningitidis* ; PRP, polyribosylribitol phosphate.

Much less is known about immunity to other *H. influenzae* serotypes or to nontypeable isolates. For nontypeable isolates, evidence suggests that antibodies directed against 1 or more outer membrane proteins are bactericidal and protect against experimental challenge. A variety of antigens have been evaluated in an attempt to identify vaccine candidates for nontypeable *H. influenzae,* including outer membrane proteins (P1, P2, P4, P5, P6, D15, and Tbp A/B), LPS, various adhesins, and lipoprotein D.

Diagnosis

Presumptive identification of *H. influenzae* is established by direct examination of the collected specimen after staining with Gram reagents. Because of its small size, pleomorphism, and occasional poor uptake of stain, as well as the tendency for proteinaceous fluids to have a red background, *H. influenzae* is sometimes difficult to visualize. Furthermore, given that identification of microorganisms on smear by either technique requires at least 10^5 bacteria/mL, failure to visualize them does not preclude their presence.

Culture of *H. influenzae* requires prompt transport and processing of specimens because the organism is fastidious. Specimens should not be exposed to drying or temperature extremes. Primary isolation of *H. influenzae* can be accomplished on chocolate agar or on blood agar plates using the staphylococcus streak technique.

Serotyping of *H. influenzae* is accomplished by slide agglutination with type-specific antisera. Accurate serotyping is essential to monitor progress toward elimination of type b invasive disease. Timely reporting of cases to public health authorities should be ensured.

Clinical Manifestations and Treatment

The initial antibiotic therapy of invasive infections possibly caused by *H. influenzae* should be a parenterally administered antimicrobial agent effective in sterilizing all foci of infection and effective against ampicillin-resistant strains, usually an **extended-spectrum cephalosporin** such as ceftriaxone. These antibiotics have achieved popularity because of their relative lack of serious adverse effects and ease of administration. After the antimicrobial susceptibility of the isolate has been determined, an appropriate agent can be selected to complete the therapy. **Ampicillin** remains the drug of choice for the therapy of infections caused by susceptible isolates. If the isolate is resistant to ampicillin, ceftriaxone can be administered once daily in selected circumstances for outpatient therapy.

Oral antimicrobial agents are sometimes used to complete a course of therapy initiated by the parenteral route and are typically initial therapy for noninvasive infections such as otitis media and sinusitis. If the organism is susceptible, amoxicillin is the drug of choice. An oral second- or third-generation cephalosporin or amoxicillin-clavulanate may be used when the isolate is resistant to ampicillin.

Meningitis

In the prevaccine era, meningitis accounted for more than half of all cases of invasive *H. influenzae* disease. Clinically, meningitis caused by *H. influenzae* type b cannot be differentiated from meningitis caused by *Neisseria meningitidis* or *Streptococcus pneumoniae* (see Chapter 621.1). It may be complicated by other foci of infection such as the lungs, joints, bones, and pericardium.

Antimicrobial therapy should be administered intravenously for 7-14 days for uncomplicated cases. Ceftriaxone, and ampicillin cross the blood-brain barrier during acute inflammation in concentrations adequate to treat *H. influenzae* meningitis. Intramuscular therapy with ceftriaxone may be an alternative in patients with normal organ perfusion.

The prognosis of Hib meningitis depends on the age at presentation, duration of illness before appropriate antimicrobial therapy, cerebrospinal fluid (CSF) capsular polysaccharide concentration, and rapidity with which organisms are cleared from CSF, blood, and urine. Clinically manifested inappropriate secretion of antidiuretic hormone and evidence of focal neurologic deficits at presentation are poor prognostic features. Approximately 6% of patients with Hib meningitis are left with some hearing impairment, probably because of inflammation of the cochlea and the labyrinth. **Dexamethasone** (0.6 mg/kg/day divided every 6 hr for 2 days), particularly when given shortly before or concurrent with the initiation of antimicrobial therapy, decreases the incidence of hearing loss. Major neurologic sequelae of Hib meningitis include behavior problems, language disorders, impaired vision, mental retardation, motor abnormalities, ataxia, seizures, and hydrocephalus.

Cellulitis

Children with Hib cellulitis often have an antecedent upper respiratory tract infection. They usually have no prior history of trauma, and the infection is thought to represent seeding of the organism to the involved soft tissues during bacteremia. The head and neck, particularly the cheek and preseptal region of the eye, are the most common sites of involvement. The involved region generally has indistinct margins and is tender and indurated. **Buccal cellulitis** is classically erythematous with a violaceous hue, although this sign may be absent. *H. influenzae* may often be recovered directly from an aspirate of the leading edge, although this procedure is seldom performed. The blood culture may also reveal the causative organism. Other foci of infection may be present concomitantly, particularly in children <18 mo old. A diagnostic lumbar puncture should be considered at diagnosis in these children.

Parenteral antimicrobial therapy is indicated until patients become afebrile, after which an appropriate oral antimicrobial agent may be substituted. A 7-10 day course is customary.

Preseptal Cellulitis

Infection involving the superficial tissue layers anterior to the orbital septum is termed preseptal cellulitis, which may be caused by *H. influenzae.* Uncomplicated preseptal cellulitis does not imply a risk for visual impairment or direct central nervous system (CNS) extension. However, concurrent bacteremia may be associated with the development of meningitis. *H. influenzae* preseptal cellulitis is characterized by fever, edema, tenderness, warmth of the lid, and, occasionally, purple discoloration. Evidence of interruption of the integument is usually absent. Conjunctival drainage may be associated. *S. pneumoniae, Staphylococcus aureus,* and group A streptococcus cause clinically indistinguishable preseptal cellulitis. The latter 2 pathogens are more likely when fever is absent and the integument is interrupted (e.g., insect bite, trauma).

Children with preseptal cellulitis in whom *H. influenzae* and *S. pneumoniae* are etiologic considerations (young age, high fever, intact integument) should undergo blood culture, and a diagnostic lumbar puncture should be considered.

Parenteral antibiotics are indicated for preseptal cellulitis. Because methicillin-susceptible and methicillin-resistant *S. aureus, S. pneumoniae,* and group A β-hemolytic streptococci are other causes, empirical therapy should include agents active against these pathogens. Patients with preseptal cellulitis without concurrent meningitis should receive parenteral therapy for about 5 days, until fever and erythema have abated. In uncomplicated cases, antimicrobial therapy should be given for 10 days.

Orbital Cellulitis

Infections of the orbit are infrequent and usually develop as complications of acute ethmoid or sphenoid sinusitis. Orbital cellulitis may manifest as lid edema but is distinguished by the presence of proptosis, chemosis, impaired vision, limitation of the extraocular movements, decreased mobility of the globe, or pain on movement of the globe. The distinction between preseptal and orbital cellulitis may be difficult and is best delineated by CT.

Orbital infections are treated with parenteral therapy for at least 14 days. Underlying sinusitis or orbital abscess may require surgical drainage and more prolonged antimicrobial therapy.

Supraglottitis or Acute Epiglottitis

Supraglottitis is a cellulitis of the tissues comprising the laryngeal inlet (see Chapter 412). It has become exceedingly rare since the introduction of conjugate Hib vaccines. Direct bacterial invasion of the involved tissues is probably the initiating pathophysiologic event. This dramatic, potentially lethal condition can occur at any age. Because of the risk of sudden, unpredictable airway obstruction, supraglottitis is a medical emergency. Other foci of infection, such as meningitis, are rare. Antimicrobial therapy directed against *H. influenzae* and other etiologic agents should be administered parenterally, but only after the airway is secured, and therapy should be continued until patients are able to take fluids by mouth. The duration of antimicrobial therapy is typically 7 days.

Pneumonia

The true incidence of *H. influenzae* pneumonia in children is unknown because invasive procedures required to obtain culture specimens are seldom performed (see Chapter 428). In the prevaccine era, type b bacteria were believed to be the usual cause. The signs and symptoms of pneumonia caused by *H. influenzae* cannot be differentiated from those of pneumonia caused by many other microorganisms. Other foci of infection may be present concomitantly.

Children <12 mo old in whom *H. influenzae* pneumonia is suspected should receive parenteral antimicrobial therapy initially because of their increased risk for bacteremia and its complications. Older children who do not appear severely ill may be managed with an oral antimicrobial. Therapy is continued for 7-10 days. Uncomplicated pleural effusion associated with *H. influenzae* pneumonia requires no special intervention. However, if empyema develops, surgical drainage is indicated.

Suppurative Arthritis

Large joints, such as the knee, hip, ankle, and elbow, are affected most often (see Chapter 705). Other foci of infection may be present concomitantly. Although single-joint involvement is the rule, multijoint involvement occurs in approximately 6% of cases. The signs and symptoms of septic arthritis caused by *H. influenzae* are indistinguishable from those of arthritis caused by other bacteria.

Uncomplicated septic arthritis should be treated with an appropriate parenteral antimicrobial for at least 5-7 days. If the clinical response is satisfactory, the remainder of the course of antimicrobial treatment may be given orally. Therapy is typically given for 3 wk for uncomplicated septic arthritis, but it may be continued beyond 3 wk, until the C-reactive protein concentration is normal.

Pericarditis

H. influenzae is a rare cause of pericarditis (see Chapter 467). Affected children often have had an antecedent upper respiratory tract infection. Fever, respiratory distress, and tachycardia are consistent findings. Other foci of infection may be present concomitantly.

The diagnosis may be established by recovery of the organism from blood or pericardial fluid. Gram stain or detection of PRP in pericardial fluid, blood, or urine (when type b organisms are the cause) may aid the diagnosis. Antimicrobials should be provided parenterally in a regimen similar to that used for meningitis (see Chapter 621.1). Pericardiectomy is useful for draining the purulent material effectively and preventing tamponade and constrictive pericarditis.

Bacteremia Without an Associated Focus

Bacteremia caused by *H. influenzae* may be associated with fever without any apparent focus of infection (see Chapter 202). In this situation, risk factors for occult bacteremia include the magnitude of fever (≥39°C [102.2°F]) and the presence of leukocytosis (≥15,000 cells/µL). In the prevaccine era, meningitis developed in approximately 25% of children with occult Hib bacteremia if left untreated. In the vaccine era, this *H. influenzae* infection has become exceedingly rare. When it does occur, the child should be reevaluated for a focus of infection and a 2nd blood culture performed. The child should be hospitalized and given parenteral antimicrobial therapy after a diagnostic lumbar puncture and chest radiograph are obtained.

Miscellaneous Infections

Rarely, *H. influenzae* causes urinary tract infection, epididymoorchitis, cervical adenitis, acute glossitis, infected thyroglossal duct cysts, uvulitis, endocarditis, endophthalmitis, primary peritonitis, osteomyelitis, and periappendiceal abscess.

Invasive Disease in Neonates

Neonates rarely have invasive *H. influenzae* infection. In the infant with illness within the 1st 24 hr of life, especially in association with maternal chorioamnionitis or prolonged rupture of membranes, transmission of the organism to the infant is likely to have occurred through the maternal genital tract, which may be (<1%) colonized with nontypeable *H. influenzae.* Manifestations of neonatal invasive infection include bacteremia with sepsis, pneumonia, respiratory distress syndrome with shock, conjunctivitis, scalp abscess or cellulitis, and meningitis. Less frequently, mastoiditis, septic arthritis, and congenital vesicular eruption may occur.

Otitis Media

Acute otitis media is one of the most common infectious diseases of childhood (see Chapter 658). It results from the spread of bacteria from the nasopharynx through the eustachian tube into the middle ear cavity. Usually, because of a preceding viral upper respiratory tract infection, the mucosa in the area becomes hyperemic and swollen, resulting in obstruction and an opportunity for bacterial multiplication in the middle ear.

The most common bacterial pathogens are *H. influenzae, S. pneumoniae,* and *Moraxella catarrhalis*. Most *H. influenzae* isolates causing otitis media are nontypeable. Ipsilateral conjunctivitis may also be present. Amoxicillin (80-90 mg/kg/day) is a suitable first-line oral antimicrobial agent, because the probability that the causative isolate is resistant to amoxicillin and the risk for invasive potential are sufficiently low to justify this approach. Alternatively, in certain cases, a single dose of ceftriaxone constitutes adequate therapy.

In the case of treatment failure or if a β-lactamase–producing isolate is obtained by tympanocentesis or from drainage fluid, amoxicillin-clavulanate (Augmentin) is a suitable alternative.

Conjunctivitis

Acute infection of the conjunctivae is common in childhood (see Chapter 644). In neonates, *H. influenzae* is an infrequent cause. However, it is an important pathogen in older children. Most *H. influenzae* isolates associated with conjunctivitis are nontypeable, although type b isolates and other serotypes are occasionally found. Empirical treatment of conjunctivitis beyond the neonatal period usually consists of topical antimicrobial therapy with sulfacetamide. Topical fluoroquinolone therapy is to be avoided because of its broad spectrum, high cost, and high rate of emerging resistance among many bacterial species. Ipsilateral otitis media caused by the same organism may be present and requires oral antibiotic therapy.

Sinusitis

H. influenzae is an important cause of acute sinusitis in children, 2nd in frequency only to *S. pneumoniae* (see Chapter 408). Chronic sinusitis lasting >1 yr or severe sinusitis requiring hospitalization is often caused by *S. aureus* or anaerobes such as *Peptococcus*, *Peptostreptococcus*, and *Bacteroides.* Nontypeable *H. influenzae* and viridans group streptococci are also frequently recovered.

For uncomplicated sinusitis, amoxicillin is acceptable initial therapy. However, if clinical improvement does not occur, a broader-spectrum agent, such as amoxicillin-clavulanate, may be appropriate. A 10-day course is sufficient for uncomplicated sinusitis. Hospitalization for parenteral therapy is rarely required; the usual reason is suspicion of progression to orbital cellulitis.

Prevention

Immunization with Hib conjugate vaccine is recommended for all infants. Prophylaxis is indicated if close contacts of an index patient with type b disease are unvaccinated. The contagiousness of non-Hib infections is not known, and prophylaxis is not recommended.

Vaccine

Several Hib conjugate vaccines are currently marketed in the United States, containing either PRP–outer membrane protein (**PRP-OMP**) or PRP–tetanus toxoid (**PRP-T**), which differ in the carrier protein used and the method of conjugating the polysaccharide to the protein (see Table 221.1 and Chapter 197). One of the combination vaccines consists of PRP-OMP combined with hepatitis B vaccine (Comvax, Merck, Whitehouse Station, NJ) and can be used for doses recommended at 2, 4, and 12-15 mo of age. Another consists of PRP-T combined with DTaP vaccine (diphtheria and tetanus toxoids and acellular pertussis) and IPV vaccine (trivalent, inactivated polio vaccine) (Pentacel, Sanofi Pasteur, Swiftwater, PA) and can be used for doses recommended at 2, 4, 6, and 12-15 mo of age. A third consists of PRP-T combined with *N. meningitidis* serogroups C and Y (GlaxoSmithKline Biologicals) and can be used for doses recommended at 2, 4, 6, and 12-15 mo of age for children at increased risk for *N. meningitidis* disease. PRP-T by itself is licensed for doses scheduled for children ≥15 mo old.

The Hib conjugate vaccines stimulate circulating anticapsular antibody and provide long-term immunity through B-cell memory.

Prophylaxis

Unvaccinated children <48 mo old who are in close contact with an index case of invasive Hib infection are at increased risk for invasive infection. The risk for secondary disease for children >3 mo old is inversely related to age. About half the secondary cases among susceptible household contacts occur in the 1st wk after hospitalization of the index case. Because many children are now protected against *H. influenzae* type b by prior immunization, the need for prophylaxis has greatly decreased. When prophylaxis is used, **rifampin** is indicated for all members of the household or close-contact group, including the index patient, if the group includes 1 or more children <48 mo old who are not fully immunized.

Parents of children hospitalized for invasive Hib disease should be informed of the increased risk for secondary infection in other young children in the same household if they are not fully immunized. Parents of children exposed to a single case of invasive Hib disease in a childcare center or nursery school should be similarly informed, although there is disagreement about the need for rifampin prophylaxis for these children.

For prophylaxis, children should be given rifampin orally (0-1 mo old, 10 mg/kg/dose; >1 mo old, 20 mg/kg/dose, not to exceed 600 mg/dose) once daily for 4 consecutive days. The adult dose is 600 mg once daily. Rifampin prophylaxis is not recommended for pregnant women.

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CHAPTER 222

Chancroid *(Haemophilus ducreyi)*

H. Dele Davies

Chancroid is a sexually transmitted disease characterized by painful genital ulceration and inguinal lymphadenopathy.

Etiology and Epidemiology

Chancroid is caused by *Haemophilus ducreyi*, a fastidious gram-negative bacillus. It is prevalent in many developing countries but occurs sporadically in the developed world. Most Western cases occur in returning travelers (90% are male) from endemic areas or occasionally in localized urban outbreaks associated with commercial sex workers. Chancroid is a risk factor for transmission of HIV. Diagnosis of chancroid in infants and children is strong evidence of sexual abuse. Male circumcision lowers the risk for chancroid. The incidence of chancroid has declined significantly since 1981 and remains low in the United States.

Clinical Manifestations

The incubation period is 4-7 days, with a small, inflammatory papule on the preputial orifice or frenulum in men and on the labia, fourchette, or perineal region in women. The lesion becomes pustular, eroded, and ulcerative within 2-3 days. The ulcer edge is classically ragged and undermined. Without treatment, the ulcers may persist for weeks to months. Painful, tender inguinal lymphadenitis occurs in >50% of cases, more often among men. The lymphadenopathy can become fluctuant to form **buboes,** which can spontaneously rupture.

Diagnosis

Diagnosis is usually established by the clinical presentation and the exclusion of both syphilis *(Treponema pallidum)* and herpes simplex virus infections. Gram stain of ulcer secretions may show gram-negative coccobacilli in parallel clusters ("school of fish"). Culture requires expensive, special media and has a sensitivity of only 80%. Polymerase chain reaction (PCR) and indirect immunofluorescence using monoclonal antibodies are available as research tools and are performed by some clinical laboratories using their own in-house Clinical Laboratory Improvement Amendments (CLIA)–verified kits. There are currently no U.S. Food and Drug Administration (FDA)–approved PCR tests for *H. ducreyi* . The ulcer of chancroid is accompanied by concurrent **lymphadenopathy** that is usually unilateral, unlike lymphogranuloma venereum (see Chapter 253.4). Genital herpes is characterized by vesicular lesions with a history of recurrence (see Chapter 279).

Treatment

Most *H. ducreyi* organisms are resistant to penicillin and ampicillin because of plasmid-mediated β-lactamase production. Spread of plasmid-mediated resistance among *H. ducreyi* has resulted in lack of efficacy of previously useful drugs such as sulfonamides and tetracyclines. Chancroid is easy to treat if recognized early. The current treatment recommendation is for **azithromycin** (1 g as a single dose orally [PO]) or **ceftriaxone** (250 mg as a single dose intramuscularly). Alternative regimens include **erythromycin** (500 mg 3 times daily PO for 7 days), which is most often used in developing countries, and ciprofloxacin (500 mg twice daily PO for 3 days, for persons ≥18 yr old). Fluctuant nodes may require drainage. Symptoms usually resolve within 3-7 days. Relapses can usually be treated successfully with the original treatment regimen. Patients with HIV infection may require longer duration of treatment. Persistence of the ulcer and the organism following therapy should raise suspicion of resistance to the prescribed antibiotic.

Patients with chancroid should be evaluated for other sexually transmitted infections, including syphilis, hepatitis B virus, HIV, chlamydia, and gonorrhea; an estimated 10% have concomitant syphilis or genital herpes. If initial HIV or syphilis testing is negative, patients should be tested for again in 3 mo because of the high rates of co-infections. In developing countries, patients with a compatible genital ulcer are treated for both chancroid and syphilis. All sexual contacts of patients with chancroid should be evaluated and treated.

Complications

Complications include **phimosis** in men and secondary bacterial infection. Bubo formation may occur in untreated cases. Genital ulceration as a syndrome increases the risk for transmission of HIV.

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CHAPTER 223

Moraxella catarrhalis

Timothy F. Murphy

Moraxella catarrhalis is an unencapsulated gram-negative diplococcus and is a **human-specific pathogen** that colonizes the respiratory tract beginning in infancy. Patterns of colonization and infection with *M. catarrhalis* are changing in countries where pneumococcal conjugate vaccines are used widely. The most important clinical manifestation of *M. catarrhalis* infection in children is **otitis media** .

Etiology

Moraxella catarrhalis has long been considered to be an upper respiratory tract commensal. Substantial genetic heterogeneity exists among strains of *M. catarrhalis*. Several outer membrane proteins demonstrate sequence differences among strains, particularly in regions of the proteins that are exposed on the bacterial surface. *M. catarrhalis* endotoxin lacks repeating polysaccharide side chains and is thus a lipooligosaccharide (LOS). In contrast to other gram-negative respiratory pathogens, such as *Haemophilus influenzae* and *Neisseria meningitidis*, the LOS of *M. catarrhalis* is relatively conserved among strains; only 3 serotypes (A, B, and C) based on oligosaccharide structure have been identified. Genetic and antigenic differences among strains account for the observation that resolving an infection by one strain does not induce protective immunity to other strains. *M. catarrhalis* causes recurrent infections, which generally represent reinfection by new strains.

Epidemiology

The ecologic niche of *M. catarrhalis* is the human respiratory tract. The bacterium has not been recovered from animals or environmental sources. **Age** is the most important determinant of the prevalence of upper respiratory tract colonization. Common throughout infancy, nasopharyngeal colonization is a dynamic process with active turnover as a result of acquisition and clearance of strains of *M. catarrhalis* . Some geographic variation in rates of colonization is observed. On the basis of monthly or bimonthly cultures, colonization during the 1st yr of life may range from 33–100%. Several factors likely account for this variability among studies, including living conditions, daycare attendance, hygiene, environmental factors (e.g., household smoking), and genetics of the population. The prevalence of colonization steadily decreases with age. Understanding nasopharyngeal colonization patterns is important, because the pathogenesis of otitis media involves migration of the bacterium from the nasopharynx to the middle ear via the eustachian tube.

The widespread use of pneumococcal polysaccharide vaccines in many countries has resulted in alteration of patterns of nasopharyngeal colonization in the population. A relative increase in colonization by nonvaccine pneumococcal serotypes, nontypeable *H. influenzae*, and *M. catarrhalis* has occurred. Whether changes in colonization patterns will result in a true increase in new episodes of otitis media and sinusitis caused by nontypeable *H. influenzae* and *M. catarrhalis* requires continuous surveillance.

Pathogenesis of Infection

Strains of *M. catarrhalis* differ in their virulence properties. The species is composed of complement-resistant and complement-sensitive genetic lineages, the **complement-resistant** strains being more strongly associated with virulence. Strains that cause infection in children differ in several phenotypic characteristics from strains that cause infection in adults, in whom the most common clinical manifestation is lower respiratory tract infection in the setting of chronic obstructive pulmonary disease.

The presence of several **adhesin** molecules with differing specificities for various host cell receptors reflects the importance of adherence to the human respiratory epithelial surface in the pathogenesis of infection. *M. catarrhalis* has long been viewed as an exclusively extracellular pathogen. However, the bacterium is now known to invade multiple cell types, including bronchial epithelial cells, small airway cells, and type 2 alveolar cells. In addition, *M.*

catarrhalis resides intracellularly in lymphoid tissue, providing a reservoir for persistence in the human respiratory tract. As with many gram-negative bacteria, *M. catarrhalis* sheds vesicles from its surface during growth. These vesicles are internalized by respiratory epithelial cells and mediate several virulence mechanisms, including B-cell activation, induction of inflammation, and delivery of β-lactamases. Analysis of genomes reveals modest genetic heterogeneity among strains.

M. catarrhalis forms biofilms in vitro and in the middle ears of children with chronic and recurrent otitis media. **Biofilms** are communities of bacteria encased in a matrix attached to a surface. Bacteria in biofilms are more resistant to antibiotics and to host immune responses than bacteria growing individually in planktonic form.

Clinical Manifestations

M. catarrhalis causes predominantly mucosal infections in children. The mechanism of infection is **migration** of the infecting strains from the nasopharynx to the middle ear in the case of otitis media or to the sinuses in the case of sinusitis. The inciting event for both otitis media and sinusitis is often a preceding viral infection.

Acute Otitis Media

Approximately 80% of children have 1 or more episodes of otitis media by age 3 yr. Otitis media is the most common reason that children receive antibiotics. On the basis of culture of middle ear fluid obtained by tympanocentesis, the predominant causes of acute otitis media are *Streptococcus pneumoniae*, *H. influenzae*, and *M. catarrhalis* . *M. catarrhalis* is cultured from the middle ear fluid in 15–20% of patients with acute otitis media. When more sensitive methods (e.g., PCR) are used, the number of middle ear fluid samples from children with otitis media in which *M. catarrhalis* is detected is substantially greater than by culture alone. The distribution of the causative agents of otitis media is changing as a result of widespread administration of pneumococcal conjugate vaccines, with a relative increase in *H. influenzae* and *M. catarrhalis* .

Acute otitis media caused by *M. catarrhalis* is clinically milder than otitis media caused by *H. influenza* e or *S. pneumoniae*, with less fever and lower prevalence of a red, bulging tympanic membrane. However, substantial overlap in symptoms is seen, making it impossible to predict etiology in an individual child on the basis of clinical features. Tympanocentesis is required to make an etiologic diagnosis but is not performed routinely, and thus, treatment of otitis media is generally empirical.

Recurrent Otitis Media and Otitis Media With Effusion

Otitis media with effusion refers to the presence of fluid in the middle ear in the absence of signs and symptoms of acute infection. Children who experience 4 or more episodes of acute otitis media in a year or who have at least 8 mo of middle ear effusion in a year are defined as **otitis prone** . These children have conductive hearing loss, which may lead to delays in speech and language development. Analysis of middle ear fluid from children with otitis media with effusion using sensitive molecular techniques (e.g., PCR) indicates that bacterial DNA is present in up to 80% of samples from such children. Indeed, *M. catarrhalis* DNA is present, both alone and as a co-pathogen, in a larger proportion of cases of otitis media with effusion than of acute otitis media. Biofilms may account for these observations, although definitive evidence is lacking.

Sinusitis

A small proportion of viral upper respiratory tract infections are complicated by bacterial sinusitis. According to findings of studies that use sinus puncture, *M. catarrhalis* accounts for approximately 20% of cases of acute bacterial sinusitis in children and a smaller proportion in adults. Sinusitis caused by *M. catarrhalis* is clinically indistinguishable from that caused by *S. pneumoniae* or *H. influenzae* .

Bacteremia

M. catarrhalis rarely causes bacteremia or invasive infections in children. When bacteremia occurs, the usual source is the respiratory tract. Some children have underlying immunocompromising conditions, but no particular immunodeficiency is associated with invasive *M. catarrhalis* infections.

Diagnosis

The clinical diagnosis of otitis media is made by demonstration of fluid in the middle ear by pneumatic otoscopy. A tympanocentesis is required to establish an etiologic diagnosis, but this procedure is not performed routinely. Thus, the choice of antibiotic for otitis media is empirical and generally based on guidelines. Management of bacterial sinusitis is also empirical, because determining the etiology of sinusitis requires a **sinus puncture** , also a procedure that is not performed routinely.

The key to making a microbiologic diagnosis is distinguishing *M. catarrhalis* from commensal *Neisseria* organisms that are part of the normal upper respiratory tract flora. Indeed, the difficulty in distinguishing colonies of *M. catarrhalis* from *Neisseria* spp. explains in part why *M. catarrhalis* has been overlooked in the past as a respiratory tract pathogen. *M. catarrhalis* produces round, opaque colonies that can be slid across the agar surface without disruption, the “hockey puck sign.” In addition, after 48 hr, *M. catarrhalis* colonies tend to be larger than *Neisseria* and take on a pink color. A variety of biochemical tests distinguish *M. catarrhalis* from *Neisseria* spp., and commercially available kits based on these tests are available.

Sensitive tests that employ polymerase chain reaction (PCR) to detect respiratory tract bacterial pathogens in human respiratory tract secretions are in development. Their application will likely contribute new information about the epidemiology and disease patterns of *M. catarrhalis* .

Treatment

A proportion of cases of *M. catarrhalis* otitis media resolve spontaneously. Treatment of otitis media is empirical, and clinicians are advised to follow guidelines of the American Academy of Pediatrics (see Chapter 658).

Strains of *M. catarrhalis* rapidly acquired β-lactamase worldwide in the 1970s and 1980s, rendering essentially all strains resistant to amoxicillin. When *M. catarrhalis* is present as a co-pathogen in otitis media, its β-lactamase reduces susceptibility of nontypeable *H. influenzae* and *S. pneumoniae* to amoxicillin. Antimicrobial susceptibility patterns have remained relatively stable for decades. However, strains of *M. catarrhalis* that are resistant to macrolides and fluoroquinolones have been isolated in several centers in Asia. Careful surveillance will be important to track the potential emergence of resistant strains more widely. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, macrolides (azithromycin, clarithromycin), trimethoprim-sulfamethoxazole, and fluoroquinolones.

Prevention

Vaccines to prevent otitis media and other infections caused by *M. catarrhalis* are under development, but none is yet available.

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CHAPTER 224

Pertussis (*Bordetella pertussis* and *Bordetella parapertussis*)

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Pertussis is an acute respiratory tract infection; the term *pertussis* means “intense cough” and is preferable to *whooping cough*, because most infected individuals do not “whoop.”

Etiology

Bordetella pertussis is the cause of epidemic pertussis and the usual cause of sporadic pertussis. *Bordetella parapertussis* is an occasional cause of sporadic pertussis that contributes significantly to total cases of pertussis in Eastern and Western Europe, but increasingly has been detected during regional pertussis outbreaks in the United States. *B. pertussis* and *B. parapertussis* are exclusive pathogens of humans and some primates. *Bordetella holmesii* , first identified as a cause of bacteremia in immunocompromised hosts without cough illness, also is reported to cause pertussis-like cough illness in small outbreaks in healthy persons. *Bordetella bronchiseptica* is a common animal pathogen. Occasional reports in humans describe a variety of body sites involved, and cases typically occur in immunocompromised persons or young children with intense exposure to animals. Protracted coughing (which in some cases is paroxysmal) is attributable sporadically to *Mycoplasma*, parainfluenza viruses, influenza viruses, enteroviruses, respiratory syncytial virus (RSV), or adenoviruses.

Epidemiology

The World Health Organization (WHO) estimated that in 2008, 16 million cases of pertussis and 195,000 childhood deaths occurred worldwide, 95% of which were in developing countries. The WHO also estimated that 82% of infants worldwide received 3 doses of pertussis vaccine and that global vaccination against pertussis averted 687,000 deaths in 2008. Before vaccination was available, pertussis was the leading cause of death from communicable disease among U.S. children <14 yr old, with 10,000 deaths annually. Widespread use of whole cell pertussis vaccine (DTP) led to a >99% decline in cases. After the low U.S. number of 1,010 cases reported in 1976, there was an increase in annual pertussis incidence to 1.2 cases per 100,000 population from 1980 through 1989, with epidemic pertussis in many states in 1989–1990, 1993, and 1996. Since then, pertussis has become increasingly endemic, with shifting burden of disease to young infants, adolescents, and adults. By 2004, the incidence of reported pertussis in the United States was 8.9 cases per 100,000 in the general population and approximately 150 per 100,000 in infants <2 mo old, with 25,827 total cases reported, the highest since 1959. A total of 40 pertussis-related deaths were reported in 2005, and 16 were reported in 2006; >90% of these cases occurred in infants.

Prospective and serologic studies suggested that pertussis is *underrecognized* , especially among adolescents and adults, in whom the actual number of U.S. cases is estimated to be 600,000 annually. A number of studies documented pertussis in 13–32% of adolescents and adults with cough illness for >7 days. Responding to these changes in epidemiology, tetanus toxoid, reduced-content diphtheria toxoid, and acellular pertussis antigens (**Tdap**) was recommended in 2006 for 11-12 yr olds and was aimed to enhance control. With >70% uptake of Tdap in adolescents, the burden of disease in young adolescents fell commensurately, but without evidence of protection of the community (herd) of young infants, older adolescents, and adults. An epidemiologic shift has occurred due to substantial and rapid waning of protection following both DTaP and Tdap in the aging cohort of children and adolescents who were not primed with DTP (whole cell) vaccine, which was no longer used in the United States after 1997. The >42,000 cases of pertussis and 20 deaths reported in 2012 were the highest numbers in >50 yr. A shift in disease burden was observed among 7-10 yr olds in 2010, 13-14 yr olds in 2012, and 14-16 yr olds in 2014, as the cohort of solely DTaP-vaccinated cohort aged.

Neither natural disease nor vaccination provides complete or lifelong immunity against pertussis reinfection or disease. Subclinical reinfection undoubtedly contributed significantly to immunity against disease ascribed previously to both vaccine and prior infection. The resurgence of pertussis can be attributed to a variety of factors, including partial control of pertussis leading to less continuous exposure as well as increased awareness and improved diagnostics. Rapidly waning vaccine-induced immunity and pathogen adaptation are most important currently. Although the DTaP series is protective short-term, vaccine effectiveness wanes rapidly, with estimates of only 10% protection 8.5 yr after the 5th dose. Tdap protection also is short-lived, with efficacy falling from >70% initially to 34% within 2-4 yr. Divergence of circulating strains from vaccine strains began with the introduction of DTP, but with the exclusive use of acellular pertussis vaccines, **pertactin-deficient strains** emerged and have become dominant in countries where these vaccines are used. Pertactin-deficient *B. pertussis* was first reported in the United States from a Philadelphia infant case collection from 2008 to 2011. The Centers for Disease Control and Prevention (CDC) subsequently reported the earliest U.S. isolate from 1994 and rapid dominance of pertactin-deficient strains in the United States since 2010. Despite the role of pertactin as a bacterial virulence factor, illness severity in infants with pertactin-deficient *B. pertussis* is similar to that of pertactin-producing strains. Until development of new pertussis vaccine(s), pertussis will continue to be endemic, with cycling epidemics.

Pathogenesis

Bordetella organisms are small, fastidious, gram-negative coccobacilli that colonize only ciliated epithelium. The exact mechanism of disease symptomatology remains unknown. *Bordetella* species share a high degree of DNA homology among virulence genes. Only *B. pertussis* expresses **pertussis toxin** (PT), the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction). Injection of PT in experimental animals causes lymphocytosis immediately by rerouting lymphocytes to remain in the circulating blood pool but does not cause cough. PT appears to have a central, but not a singular, role in pathogenesis. *B. pertussis* produces an array of other biologically active substances, many of which are postulated to have a role in disease and immunity. After aerosol acquisition, filamentous **hemagglutinin** , some **agglutinogens** (especially fimbriae [Fim] types 2 and 3), and the 69-kDa **pertactin** (Prn) protein are important for attachment to ciliated respiratory epithelial cells. **Tracheal**

cytotoxin, adenylate cyclase, and PT appear to inhibit clearance of organisms. Tracheal cytotoxin, dermonecrotic factor, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptoms and facilitates absorption of PT. Both antibody and cellular immune responses follow infection and immunization. Antibody to PT neutralizes toxin, and antibody to Prn enhances opsonophagocytosis. Disease as well as DTP appear to drive a mixed cellular and antibody (Th1) immunologic response, while DTaP and Tdap drive a narrow antibody-dominant (Th2) response.

Pertussis is *extremely contagious* , with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. High airborne transmission rates were shown in a baboon model of pertussis despite vaccination with the acellular vaccine. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented. After intense exposure as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought, a symptomatic source case can be found for most patients; usually a sibling or related adult.

Clinical Manifestations

Classically, pertussis is a prolonged disease, divided into catarrhal, paroxysmal, and convalescent stages. The **catarrhal stage** (1-2 wk) begins insidiously after an incubation period ranging from 3-12 days with nondistinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion. As initial symptoms wane, coughing marks the onset of the **paroxysmal stage** (2-6 wk). The cough begins as a dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis. A well-appearing, playful toddler with insignificant provocation suddenly expresses an anxious aura and may clutch a parent or comforting adult before beginning a machine-gun burst of uninterrupted cough on a single exhalation, chin and chest held forward, tongue protruding maximally, eyes bulging and watering, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway. **Posttussive emesis** is common, and exhaustion is universal. The number and severity of paroxysms escalate over days to a week and remain at that plateau for days to weeks. At the peak of the paroxysmal stage, patients may have >1 episode hourly. As the paroxysmal stage fades into the **convalescent stage** (≥2 wk), the number, severity, and duration of episodes diminish.

Infants <3 mo old do not display the classic stages. The catarrhal phase lasts only a few days or is unnoticed, and then, after the most insignificant startle from a draft, light, sound, sucking, or stretching, a well-appearing young infant begins to choke, gasp, gag, and flail the extremities, with face reddened. Cough may not be prominent, especially in the early phase, and whoop is infrequent. Apnea and cyanosis can follow a coughing paroxysm, or apnea can occur as the only symptom (without cough). Both are more common with pertussis than with neonatal viral infections. The paroxysmal and convalescent stages in young infants are lengthy. Paradoxically, in infants, cough and whooping may become louder and more classic in convalescence. “Exacerbations” of paroxysmal coughing can occur throughout the 1st yr. of life with subsequent respiratory illnesses; these are not a result of recurrent infection or reactivation of *B. pertussis*.

Adolescents and previously immunized children have foreshortening of all stages of pertussis. Adults have no distinct stages. Classically, adolescents and adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, bursting headache, diminished awareness, and then a gasping breath, usually without a whoop. Posttussive emesis and intermittency of paroxysms separated by hours of well-being are specific clues to the diagnosis. At least 30% of adolescents and adults with pertussis have nonspecific cough illness, distinguished only by duration, which usually is >21 days.

Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are not expected unless complicating secondary bacterial pneumonia is present. Conjunctival hemorrhages and petechiae on the upper body are common.

Diagnosis

Pertussis should be suspected in any individual who has a pure or predominant complaint of cough, especially if the following features *are absent* : fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales. For sporadic cases, a clinical case definition of cough of ≥14 days’ duration with at least 1 associated symptom of paroxysms, whoop, or posttussive vomiting has sensitivity of 81% and specificity of 58% for confirmation of pertussis. Pertussis should be suspected in older children whose cough illness is *escalating* at 7-10 days and whose coughing *is not* continuous, but rather comes in bursts. Pertussis should be suspected in infants <3 mo old with gagging, gasping, apnea, cyanosis, or an apparent life-threatening event. Sudden infant death occasionally is caused by *B. pertussis* .

Adenoviral infections usually are distinguishable by associated features, such as fever, sore throat, and conjunctivitis. *Mycoplasma* causes protracted episodic coughing, but patients usually have a history of fever, headache, and systemic symptoms at the onset of disease as well as more continuous cough and frequent finding of rales on auscultation of the chest. Epidemics of *Mycoplasma* and *B. pertussis* in young adults can be difficult to distinguish on clinical grounds. Although pertussis often is included in the differential diagnosis of young infants with afebrile pneumonia, *B. pertussis* is not associated with staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, rales or wheezes that typify infection by *Chlamydia trachomatis,* or predominant lower respiratory tract signs that typify infection by RSV. Unless an infant with pertussis has secondary pneumonia (and then appears ill), the findings on examination between paroxysms, including respiratory rate, are entirely normal. Foreign body aspiration should be considered in the differential diagnosis.

Leukocytosis (15,000-100,000 cells/µL) caused by *absolute lymphocytosis* is characteristic in the catarrhal stage. Lymphocytes are normal small cells, rather than the large, atypical lymphocytes seen with viral infections. Adults, partially immune children, and occasionally infants may have less impressive lymphocytosis. Absolute increase in neutrophils suggests a different diagnosis or secondary bacterial infection. Eosinophilia is not a manifestation of pertussis. A severe course and death are correlated with rapid-rise and extreme leukocytosis (median peak white blood cell count in fatal vs nonfatal cases, 94,000 vs 18,000/µL, respectively) and thrombocytosis (median peak platelet count in fatal vs nonfatal cases, 782,000 vs 556,000/µL, respectively). Chest radiographic findings are only mildly abnormal in the majority of hospitalized infants, showing perihilar infiltrate or edema (sometimes with a butterfly appearance) and variable atelectasis. Parenchymal consolidation suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and subcutaneous emphysema can be seen occasionally.

Methods for confirmation of infection by *B. pertussis* (culture, PCR, serology) have limitations in sensitivity, specificity, or practicality, and tests' relative values depend on the setting, phase of disease, and purpose of use (e.g., as clinical diagnostic vs epidemiologic tools). Polymerase chain reaction (PCR) testing on nasopharyngeal wash specimens is the laboratory test of choice for *B. pertussis* identification. Both stand-alone and multiplex assays are U.S. Food and Drug Administration (FDA) cleared and available commercially. PCR assays using only single primers (IS*481*) cannot differentiate between some *Bordetella* spp. Multiplex assays using multiple targets can distinguish species. All assays detect pertactin-deficient strains. For **culture** , a specimen is obtained by deep nasopharyngeal aspiration or with the use of a flexible swab (Dacron or calcium alginate–tipped), held in the posterior nasopharynx for 15-30 sec (or until cough occurs). A 1% casamino acid liquid is acceptable for holding a specimen up to 2 hr; Stainer-Scholte broth or Regan-Lowe semisolid transport medium is used for longer transport periods, up to 4 days. The preferred isolation media are Regan-Lowe charcoal agar with 10% horse blood and 5-40 µg/mL cephalexin, and Stainer-Scholte media with cyclodextrin resins. Cultures are incubated at 35-37°C in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Direct fluorescent antibody testing of potential isolates using specific antibody for *B. pertussis* and *B. parapertussis* maximizes recovery rates.

Results of culture and PCR are expected to be positive in unimmunized, untreated children during the catarrhal and early paroxysmal stages of disease. *However, fewer than 20% of culture or PCR tests have positive results in partially or remotely immunized individuals tested in the paroxysmal stage.* Serologic tests for detection of change in antibodies to *B. pertussis* antigens between acute and convalescent samples are the most sensitive tests in immunized individuals and are useful epidemiologically. A single serum sample showing IgG antibody to PT >90 IU/mL (>2 SD above the mean of the immunized population) indicates recent symptomatic infection and usually is positive in the mid-paroxysmal phase. Tests for IgA and IgM pertussis antibody, or antibody to antigens other than PT, are not reliable methods for serologic diagnosis of pertussis.

Treatment

Infants <3 mo old with suspected pertussis usually are hospitalized, as are many 3-6 mo old, unless witnessed paroxysms are not severe, as well as patients of any age if significant complications occur. Prematurely born young infants have a high risk for severe, potentially fatal disease, and children with underlying cardiac, pulmonary, muscular, or neurologic disorders have increased risk of poor outcome beyond infancy. Table 224.1 lists caveats in assessment and care of infants with pertussis. The specific, limited goals of hospitalization are to (1) assess progression of disease and likelihood of life-threatening events at peak of disease; (2) maximize nutrition; (3) prevent or treat complications; and (4) educate parents in the natural history of the disease and in care that will be given at home. Heart rate, respiratory rate, and pulse oximetry are monitored continuously with alarm settings so that paroxysms can be witnessed and recorded by healthcare personnel. Detailed cough records and documentation of feeding, vomiting, and weight change provide data to assess severity. Typical paroxysms that are not life threatening have the following features: duration <45 sec; red but not blue color change; tachycardia, bradycardia (not <60 beats/min in infants), or oxygen desaturation that spontaneously resolves at the end of the paroxysm; whooping or strength for brisk self-rescue at the end of the paroxysm; self-expectorated mucus plug; and posttussive exhaustion but not unresponsiveness. Assessing the need to provide oxygen, stimulation, or suctioning requires skilled personnel who can watchfully observe an infant's ability for self-rescue but who will intervene rapidly and expertly when necessary. The benefit of a quiet, dimly lighted, undisturbed, comforting environment cannot be overestimated or forfeited in a desire to monitor and intervene. Feeding children with pertussis is challenging. The risk of precipitating cough by nipple feeding does not warrant nasogastric, nasojejunal, or parenteral alimentation in most infants. The composition or thickness of formula does not affect the quality of secretions, cough, or retention. Large-volume feedings are avoided.

Table 224.1

Caveats in Assessment and Care of Infants With Pertussis

- Infants with potentially fatal pertussis may appear well between episodes.
- A paroxysm must be witnessed before a decision is made between hospital and home care.
- Only analysis of carefully compiled cough record permits assessment of severity and progression of illness.
- Suctioning of nose, oropharynx, or trachea should not be performed on a “preventive” schedule.
- Feeding in the period following a paroxysm may be more successful than after napping.
- Family support begins at the time of hospitalization with empathy for the child's and family's experience to date, transfer of the burden of responsibility for the child's safety to the healthcare team, and delineation of assessments and treatments to be performed.
- Family education, recruitment as part of the team, and continued support after discharge are essential.

Within 48-72 hr, the direction and severity of disease are obvious from analysis of recorded information. Hospital discharge is appropriate if, over 48 hr, disease severity is unchanged or diminished, intervention is not required during paroxysms, nutrition is adequate, no complication has occurred, and parents are adequately prepared for care at home. Apnea and seizures occur in the incremental phase of illness and in patients with complicated disease. Portable oxygen, monitoring, or suction apparatus should not be needed at home.

Infants who have apnea, paroxysms that lead to life-threatening events, or respiratory failure require escalating respiratory support and frequently require intubation and pharmaceutically induced paralysis.

Antibiotics

An antimicrobial agent always is given when pertussis is suspected or confirmed to decrease contagiousness and to afford possible clinical benefit. ***Azithromycin** is the drug of choice in all age-groups, for treatment or postexposure prophylaxis* (Table 224.2). Macrolide resistance has been reported rarely, and recent isolates have retained susceptibility despite genetic strain adaptations. **Infantile hypertrophic pyloric stenosis (IHPS)** is associated with macrolide use in young infants, especially in those <14 days old, with highest risk in those receiving erythromycin vs azithromycin. Benefits of postexposure prophylaxis or treatment of infants far outweigh risk of IHPS. Young infants should be managed expectantly if projectile vomiting occurs. The FDA also warns of risk of fatal heart rhythms with use of azithromycin in patients already at risk for cardiovascular events, especially those with prolongation of the QT interval. Trimethoprim-sulfamethoxazole (TMP-SMX) is an alternative to azithromycin for infants >2 mo old and children unable to receive azithromycin. Because of limited effectiveness, treatment of *B. parapertussis* is based on clinical judgment and is considered in high-risk populations. Agents are the same as for *B. pertussis* . Treatment of infections caused by other *Bordetella* spp. should be undertaken with consultation of a subspecialist.

Table 224.2

Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis

AGE-GROUP	PRIMARY AGENTS		ALTERNATE AGENT*	
	Azithromycin	Erythromycin	Clarithromycin	TMP-SMX

<1 mo	Recommended agent 10 mg/kg/day in a single dose for 5 days	Not preferred Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis. Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days.	Not recommended (safety data unavailable)	Contraindicated for infants <2 mo of age (risk for kernicterus)
1-5 mo	10 mg/kg/day in a single dose for 5 days	40-50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Contraindicated at age <2 mo For infants age ≥2 mo: TMP 8 mg/kg/day plus SMX 40 mg/kg/day in 2 divided doses for 14 days
Infants age ≥6 mo and children	10 mg/kg in a single dose on day 1 (max 500 mg), then 5 mg/kg/day (max 250 mg) on days 2-5	40-50 mg/kg/day (max 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (max 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMX 40 mg/kg/day in 2 divided doses (max TMP: 320 mg/day) for 14 days
Adults	500 mg in a single dose on day 1, then 250 mg/day on days 2-5	2 g/day in 4 divided doses for 14 days	1 g/day in 2 divided doses for 7 days	TMP 320 mg/day–SMX 1600 mg/day in 2 divided doses for 14 days

[*] Trimethoprim-sulfamethoxazole (TMP-SMX) can be used as an alternative agent to macrolides in patients ≥2 mo old who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis* .

Adapted from Centers for Disease Control and Prevention (CDC): Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines, *MMWR* 54:1–16, 2005.

Adjunct Therapies

No rigorous clinical trial has demonstrated a beneficial effect of β_2 -adrenergic stimulants such as salbutamol and albuterol. Fussing associated with aerosol treatment triggers paroxysms. No randomized, blinded clinical trial of sufficient size has been performed to evaluate the usefulness of corticosteroids in the management of pertussis; their clinical use is not warranted. A randomized, double-blind, placebo-controlled trial of pertussis immunoglobulin intravenous (IGIV) was halted prematurely because of expiration/lack of additional supply of study product; there was no indication of clinical benefit. Standard immunoglobulin has not been studied and should not be used for treatment or prophylaxis.

Isolation

Patients with suspected pertussis are placed in isolation with **droplet precautions** to reduce close respiratory or mucous membrane contact with respiratory secretions. All healthcare personnel should wear a mask on entering the room. Screening for cough should be performed on entrance of patients to emergency departments, offices, and clinics to begin isolation immediately and until 5 days after initiation of azithromycin therapy. Children and staff with pertussis in childcare facilities or schools should be excluded until therapy has been taken for 5 days.

Care of Household and Other Close Contacts

Azithromycin should be given promptly to all household contacts and other close contacts, such as those in daycare, regardless of age, history of immunization, or symptoms (see Table 224.2). The same drugs and age-related doses used for treatment are used for prophylaxis. Visitation and movement of coughing family members in the hospital must be assiduously controlled until therapy has been taken for 5 days. In close contacts <7 yr old who have received <4 doses of DTaP, DTaP should be given to complete the recommended series. Children <7 yr old who received a 3rd DTaP dose >6 mo before exposure, or a 4th dose ≥3 yr before exposure, should be given a booster dose. Individuals ≥9 yr old should be given Tdap. Unmasked healthcare personnel exposed to untreated cases should be evaluated for postexposure prophylaxis and follow-up. Coughing healthcare personnel with or without known exposure to pertussis should be evaluated promptly for pertussis.

Complications

Infants <6 mo old have excessive mortality and morbidity; infants <2 mo old have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), and death (1%). Infants <4 mo old account for 90% of cases of fatal pertussis. Preterm birth and young maternal age are significantly associated with fatal pertussis. Neonates with pertussis have substantially longer hospitalizations, greater need for oxygen, and greater need for mechanical ventilation than neonates with viral respiratory tract infection.

The principal complications of pertussis are **apnea** , **secondary infections** (e.g., otitis media, pneumonia), and **physical sequelae** of forceful coughing. Fever, tachypnea or respiratory distress between paroxysms and absolute neutrophilia are clues to pneumonia. Expected pathogens include *Staphylococcus aureus, Streptococcus pneumoniae,* and bacteria of oropharyngeal flora. Increased intrathoracic and intraabdominal pressure during coughing can result in conjunctival and scleral hemorrhage, petechiae on the upper body, epistaxis, pneumothorax and subcutaneous emphysema, umbilical or inguinal hernia, and rarely hemorrhage in the central nervous system or retina. Laceration of the lingual frenulum occurs occasionally.

The need for intensive care and mechanical ventilation usually is limited to infants <3 mo old and children with underlying conditions. Respiratory failure from apnea may mandate intubation and ventilation through the days when disease peaks; prognosis is good. Progressive **pulmonary hypertension** in very young infants and secondary **bacterial pneumonia** are severe complications of pertussis and are the usual causes of death. Pulmonary hypertension and cardiogenic shock with fatal outcome are associated with extreme elevation of lymphocyte and platelet counts. Autopsies in fatal cases show luminal aggregates of leukocytes in the pulmonary vasculature. Extracorporeal membrane oxygenation of infants with pertussis in whom mechanical ventilation failed has been associated with >80% fatality (questioning the advisability of this procedure). Exchange transfusion or leukapheresis is associated with marked reduction in lymphocyte and platelet counts. Although recovery has been reported in several cases, benefit is unproven. Echocardiography should be performed in critically ill infants with pertussis to detect presence of pulmonary hypertension and to intervene expeditiously.

Acute neurologic events during pertussis almost always are the result of **hypoxemia** or **hemorrhage** associated with coughing or apnea in young infants. Apnea or bradycardia or both may result from apparent laryngospasm or vagal stimulation just before a coughing episode, from obstruction during an episode, or from hypoxemia following an episode. Seizures usually are a result of hypoxemia, but hyponatremia from excessive secretion of antidiuretic hormone during pneumonia can occur. The only neuropathology documented in pertussis is parenchymal hemorrhage and ischemic necrosis.

Bronchiectasis has been reported rarely after pertussis. Children who have pertussis before age 2 yr may have abnormal pulmonary function into adulthood.

Prevention

Universal immunization of children with pertussis vaccine, beginning in infancy with reinforcing dose(s) through adolescence and adulthood, is central to the *control* of pertussis. *Prevention* of pertussis mortality in young infants depends on universal maternal immunization during each pregnancy and focused full immunization of contacts, both children and adults of all ages.

DTaP Vaccines

Several diphtheria and tetanus toxoids combined with acellular pertussis vaccines (**DTaP**) or combination products currently are licensed in the United States for children <7 yr old. Acellular pertussis vaccines all contain inactivated PT and 2 or more additional antigens (filamentous hemagglutinin, Prn, and Fim 2 and 3). Clinical effectiveness immediately at completion of the 5-dose series is approximately 80% for illness defined as "paroxysmal cough" for >21 days. Mild local and systemic adverse events are not uncommon, but more serious events (persistent crying for ≥3 hr, hypotonic hyporesponsive episodes, seizures) are rare. DTaP-containing vaccines can be administered simultaneously with any other vaccines used in the standard schedule for children.

Four doses of DTaP should be administered during the 1st 2 yr of life, generally at ages 2, 4, 6, and 15-18 mo. In high-risk settings, infants may be given DTaP as early as 6 wk of age, with monthly doses through the 3rd dose. The 4th dose may be administered as early as 12 mo of age, provided that 6 mo have elapsed since the 3rd dose. When feasible, the same DTaP product is recommended for all doses of the primary vaccination series. The 5th dose of DTaP is recommended for children at 4-6 yr of age; a 5th dose is not necessary if the 4th dose in the series is administered on or after the 4th birthday.

Local reactions increase modestly in rate and severity with successive doses of DTaP. Swelling of the entire thigh or upper arm, sometimes accompanied by pain, erythema, and fever, has been reported in 2–3% of vaccinees after the 4th or 5th dose of a variety of DTaP products. Limitation of activity is less than might be expected. Swelling subsides spontaneously without sequelae. The pathogenesis is unknown. Extensive limb swelling after the 4th dose of DTaP usually is not associated with a similar reaction to the 5th dose and is not a contraindication to subsequent dose(s) of pertussis vaccines.

Exempting children from pertussis immunization should be considered only within the narrow limits as recommended. Exemptors have significantly increased risk for pertussis and play a role in outbreaks of pertussis among immunized populations. Although well-documented pertussis confers short-term protection, the duration of protection is unknown; immunization should be completed on schedule in children diagnosed with pertussis.

Tdap Vaccines

Two tetanus toxoid, reduced-diphtheria toxoid and acellular pertussis antigen vaccine (Tdap) products were licensed in 2005 and recommended universally in 2006 for adolescents. The preferred age for Tdap vaccination is 11-12 yr. All adolescents and adults of any age (including ≥65 yr) who have not received Tdap should receive a single dose of Tdap promptly, regardless of interval since Td, or at least in place of one Td booster at the 10 yr interval, or when indicated during wound management.

Pregnant women should be given Tdap during every pregnancy to provide passive antibody protection to the infant until administration of DTaP. Although Tdap can be given at any time during pregnancy, optimal administration is early in the period between 27 and 36 wk of gestation to maximize antibody concentration at birth. Safety of Tdap during pregnancy and effectiveness in reducing fatal pertussis in infants are proven. Special effort should be made to ensure that contacts of infants have received DTaP or Tdap as recommended. There is no recommendation for Tdap revaccination of persons other than pregnant women. Although no safety issues are associated with Tdap revaccination, rapidly waning protection following receipt of currently available vaccines does not support cost-effectiveness of universal revaccination.

There is no contraindication to concurrent administration of any other indicated vaccine. When Td is indicated and only Tdap is available, a previously Tdap-immunized person can be given Tdap. A single dose of Tdap is recommended for children 7-10 yr old who had incomplete DTaP vaccination before age 7 yr. Another dose of Tdap can be given in adolescence.

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CHAPTER 225

Salmonella

Jeffrey S. McKinney

Salmonellosis is a common and widely distributed food-borne disease that is a global major public health problem affecting millions of individuals and resulting in significant mortality. **Salmonellae** live in the intestinal tracts of warm- and cold-blooded animals. Some species are ubiquitous, whereas others are specifically adapted to a particular host.

The sequencing of the *Salmonella enterica* serovar Typhi (previously called *Salmonella typhi*) and *Salmonella typhimurium* genomes indicates an almost 95% genetic homology between the organisms. However, the clinical diseases caused by the 2 organisms differ considerably. Orally ingested salmonellae survive at the low pH of the stomach and evade the multiple defenses of the small intestine so as to gain access to the epithelium. Salmonellae preferentially enter M cells, which transport them to the lymphoid cells (T and B) in the underlying Peyer patches. Once across the epithelium, *Salmonella* serotypes that are associated with systemic illness enter intestinal macrophages and disseminate throughout the reticuloendothelial system (RES). By contrast, most **nontyphoidal *Salmonella* (NTS)** serovars induce an early local inflammatory response, which results in the infiltration of polymorphonuclear leukocytes (PMNs) into the intestinal lumen and diarrhea. These NTS serovars cause a gastroenteritis of rapid onset and brief duration, in contrast to **typhoid fever** , which has a considerably longer incubation period and duration of illness and in which systemic illness predominates and only a small proportion of children have diarrhea.

These differences in the manifestations of infection by the 2 groups of pathogens, one predominantly causing intestinal inflammation and the other leading to systemic disease, may be related to specific genetic pathogenicity islands in the organisms. Most NTS serovars seem unable to overcome defense mechanisms that limit bacterial dissemination from the intestine to systemic circulation in immunocompetent individuals and produce a self-limiting **gastroenteritis** . In contrast, *S. typhi* and *S. paratyphi* (i.e., typhoidal strains of *Salmonella*) may possess unique virulence traits that allow them to overcome mucosal barrier functions in immunocompetent hosts, and cause severe systemic illness. Interestingly, the frequencies of typhoid fever in immunocompetent and immunocompromised individuals do not differ. Intriguingly, some invasive NTS strains have been noted in Africa, particularly among HIV-positive adults and among children with HIV, malaria, or malnutrition (see Chapter 225.1). The presentation may resemble typhoid fever more than gastroenteritis.

From a taxonomic, Linnaean, perspective, the genus *Salmonella* belongs to the family Enterobacteriaceae. Two *Salmonella* spp. exist: *Salmonella enterica* and *Salmonella bongori* . The medically relevant species is *Salmonella enterica* , which is further divided into serotypes and often named based on presumed syndromes they cause or where they were discovered geographically.

From a medical perspective, among the salmonellae causing human disease, serotypes are also clinically grouped as either being **typhoidal** or **nontyphoidal** . There are only a few typhoidal Salmonella serotypes, including *Salmonella enterica* var. Typhi, also known as *S.* Typhi, and *Salmonella enterica* var. Paratyphi A. By contrast, there are 1000s of nontyphoidal *Salmonella* serotypes, collectively called **NTS serotypes** . NTS serotypes have a broad host range, whereas *S.* Typhi and *S.* Paratyphi A are restricted to human hosts.

225.1

Nontyphoidal Salmonellosis

Jeffrey S. McKinney

Etiology

Salmonellae are motile, nonsporulating, nonencapsulated, gram-negative rods that grow aerobically and are capable of facultative anaerobic growth. They are resistant to many physical agents but can be killed by heating to 54.4°C (130°F) for 1 hr or 60°C (140°F) for 15 min. They remain viable at ambient or reduced temperatures for days and may survive for weeks in sewage, dried foodstuffs, pharmaceutical agents, and fecal material. As with other members of the family Enterobacteriaceae, *Salmonella* possesses somatic O antigens and flagellar H antigens.

With the exception of a few serotypes that affect only one or a few animal species, such as *Salmonella dublin* in cattle and *S. choleraesuis* in pigs, most serotypes have a broad host spectrum. Typically, such strains cause gastroenteritis that is often uncomplicated and does not need treatment but can be severe in the young, the elderly, and patients with weakened immunity. The causes are typically ***Salmonella* Enteritidis** (*Salmonella enterica* var. Enteritidis) and ***Salmonella* Typhimurium** (*S. enterica* var. Typhimurium), the 2 most important serotypes for salmonellosis transmitted from animals to humans. Nontyphoidal salmonellae have emerged as a major cause of **bacteremia** in Africa, especially among populations with a high incidence of HIV infection.

Epidemiology

Salmonellosis constitutes a major public health burden and represents a significant cost to society in many countries. Typhoid fever caused by this organism is a global problem, with >27 million cases worldwide each year, culminating in an estimated 217,000 deaths. Although there is little information on the epidemiology and the burden of *Salmonella* gastroenteritis in developing countries, *Salmonella* infections are recognized as major causes of childhood diarrheal illness. With the burden of HIV infections and malnutrition in Africa, NTS bacteremic infections have emerged as a major cause of morbidity and mortality among children and adults.

NTS infections have a worldwide distribution, with an incidence proportional to the standards of hygiene, sanitation, availability of safe water, and food preparation practices. In the developed world, the incidence of *Salmonella* infections and outbreaks has increased several-fold over the past few decades, which may be related to modern practices of mass food production that increase the potential for epidemics. Infections with NTS serovars such as *S.* Typhimurium and *S.* Enteritidis cause a significant disease burden, with an estimated 93.8 million cases worldwide and 155,000 deaths each year. Traditionally, *Salmonella* gastroenteritis accounts for more than half of all episodes of bacterial diarrhea in the United States, with incidence peaks at the extremes of ages, among young infants and elderly persons. Most human infections have been caused by *S.* Enteritidis; with *S.* Typhimurium incidence overtaking it in some countries. Recently, however, a surveillance program testing human stool specimens from 10 U.S. sites showed a relative decline in the incidence of *S.* Typhimurium vs other salmonellae, perhaps related to the use of a live-attenuated *S.* Typhimurium vaccine in poultry and more stringent performance standards for *Salmonella* contamination of poultry carcasses.

Salmonella infections in many parts of the world may also be related to intensive **animal husbandry practices** , which selectively promote the rise of certain strains, especially drug-resistant varieties that emerge in response to the use of antimicrobials in food animals. Poultry products were traditionally regarded as a common source of salmonellosis, but consumption of a range of foods is now also associated with outbreaks, including fruits and vegetables, and factory-processed foods such as peanut butter or cookies. It appears that some **multidrug-resistant** (MDR) strains of *Salmonella* are also more virulent than susceptible strains, and that poorer outcome does not simply relate to the delay in treatment response because of empirical choice of an ineffective antibiotic. Strains of MDR *Salmonella*, such as *S.* Typhimurium phage type DT104, harbor a genomic island that contains many of the drug-resistance genes. These *integrons* also contain genes that encode virulence factors.

Several risk factors are associated with outbreaks of *Salmonella* infections. Animals constitute the principal source of human NTS disease, with cases occurring in individuals who have had contact with infected animals, including domestic animals such as cats, dogs, reptiles, pet rodents, and amphibians; **high-risk pets** include turtles, iguanas, bearded dragons, lizards, various snakes, salamanders, and geckos. Specific serotypes may be associated with particular animal hosts; children with *S. enterica* var. Marina typically have exposure to pet lizards. NTS serovars usually cause self-limiting diarrhea, with secondary bacteremia occurring in <10% of patients. The NTS serovars have a broad host range, including poultry and cattle, and NTS infection is usually from food poisoning in developed countries.

Domestic animals probably acquire the infection in the same way that humans do, through oral ingestion. Animal feeds contaminated with *Salmonella* are an important source of infection for animals. Moreover, subtherapeutic concentrations of antibiotics are often added to animal feed to promote growth. Such practices promote the emergence of **antibiotic-resistant bacteria** , including *Salmonella,* in the gut flora of the animals, with subsequent contamination of their meat. There is strong evidence to link resistance of *S.* Typhimurium to fluoroquinolones with the use of this group of antimicrobials in animal feeds. Animal-to-animal transmission can occur, with most infected animals being asymptomatic.

Although almost 80% of *Salmonella* infections are discrete, outbreaks can pose an inordinate burden on public health systems. During 1998–2008, a total of 1,491 outbreaks of *Salmonella* infections were reported to the Foodborne Disease Outbreak Surveillance System, and 80% of these were caused by a single serotype. Of the single-serotype outbreaks, 50% had an implicated food, and 34% could be assigned to a single food commodity. Of the 47 serotypes reported, the 4 most common, causing more than two thirds of the outbreaks, were Enteritidis, Typhimurium, Newport, and Heidelberg. Overall, eggs were the most frequently implicated food, followed by chicken, pork, beef, fruit, and turkey. *Salmonella* infections in chickens increase the risk for contamination of eggs, and both poultry and eggs are regarded as a dominant cause of common-source outbreaks. However, a growing proportion of *Salmonella* outbreaks are also associated with other food sources. The food sources include many fruits and vegetables, such as tomatoes, sprouts, watermelon, cantaloupe, lettuce, and mangoes. Geographically distributed infections are increasingly possible from foods (e.g., peanut butter) processed at a “point source” and then broadly distributed. Contemporary surveillance and reporting networks (e.g., ProMED, FoodNet) may help alert physicians and microbiologists to such events.

In addition to the effect of antibiotic use in animal feeds, the relationship of *Salmonella* infections to prior antibiotic use among children in the previous month is well recognized. This increased risk for infection in people who have received antibiotics for an unrelated reason may be related to alterations in gut microbial ecology, which predispose them to colonization and infection with antibiotic-resistant *Salmonella* isolates. These resistant strains of *Salmonella* can also be more virulent. The Centers for Disease Control and Prevention (CDC) reports resistance to **ceftriaxone** in approximately 3% of NTS tested and some level of resistance to **ciprofloxacin** in 3% of isolates. Approximately 5% of NTS tested by the CDC are resistant to 5 or more types of drugs. Consequently, costs are also expected to be higher for resistant than for susceptible infections because of the severity of the former. These patients are more likely to be hospitalized, and treatment is rendered less effective. The CDC is seeing some level of resistance to ciprofloxacin in two thirds of *S.* Typhi tested. Resistance to ceftriaxone or **azithromycin** has been seen in other parts of the world. *Variation in resistance among different strains makes* Salmonella *microbiologic culture and antibacterial susceptibility testing very important.*

Given the ubiquitous nature of the organism, nosocomial infections with NTS strains can also occur through contaminated equipment and diagnostic or pharmacologic preparations, particularly those of animal origin (pancreatic extracts, pituitary extracts, bile salts, rattlesnake tail). Hospitalized children are at increased risk for severe and complicated *Salmonella* infections, especially with drug-resistant organisms.

Pathogenesis

The estimated number of bacteria that must be ingested to cause symptomatic disease in healthy adults is 10^6 -10^8 *Salmonella* organisms. The gastric acidity inhibits multiplication of salmonellae, and most organisms are rapidly killed at gastric pH ≤2.0. Achlorhydria, buffering medications, rapid gastric emptying after gastrectomy or gastroenterostomy, and a large inoculum enable viable organisms to reach the small intestine. Neonates and young infants have hypochlorhydria and rapid gastric emptying, which contribute to their increased vulnerability to symptomatic salmonellosis. In infants who typically take fluids, the inoculum size required to produce disease is also comparatively smaller because of faster transit through the stomach.

Once they reach the small and large intestines, the ability of *Salmonella* organisms to multiply and cause infection depends on both the infecting dose and competition with normal flora. Prior antibiotic therapy may alter this relationship, as might factors such as co-administration of antimotility agents. The typical intestinal mucosal response to NTS infection is an **enterocolitis** with diffuse mucosal inflammation and edema, sometimes with erosions and microabscesses. *Salmonella* organisms are capable of penetrating the intestinal mucosa, although destruction of epithelial cells and ulcers are usually not found. Intestinal inflammation with PMNs and macrophages usually involves the lamina propria. Underlying intestinal lymphoid tissue and mesenteric lymph nodes enlarge and may demonstrate small areas of necrosis. Such lymphoid hypertrophy may cause interference with the blood supply to the gut mucosa. Hyperplasia of the RES is also found within the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration in almost any organ.

Both *S* . Typhi and NTS possess overlapping and distinct virulence systems

(Fig. 225.1). Although *S.* Typhimurium can cause systemic disease in humans, intestinal infection usually results in a localized enteritis that is associated with a secretory response in the intestinal epithelium. Intestinal infection also induces secretion of interleukin (IL)-8 from the basolateral surface and other chemoattractants from the apical surface, directing recruitment and transmigration of neutrophils into the gut lumen and thus preventing the systemic spread of the bacteria (Fig. 225.2).

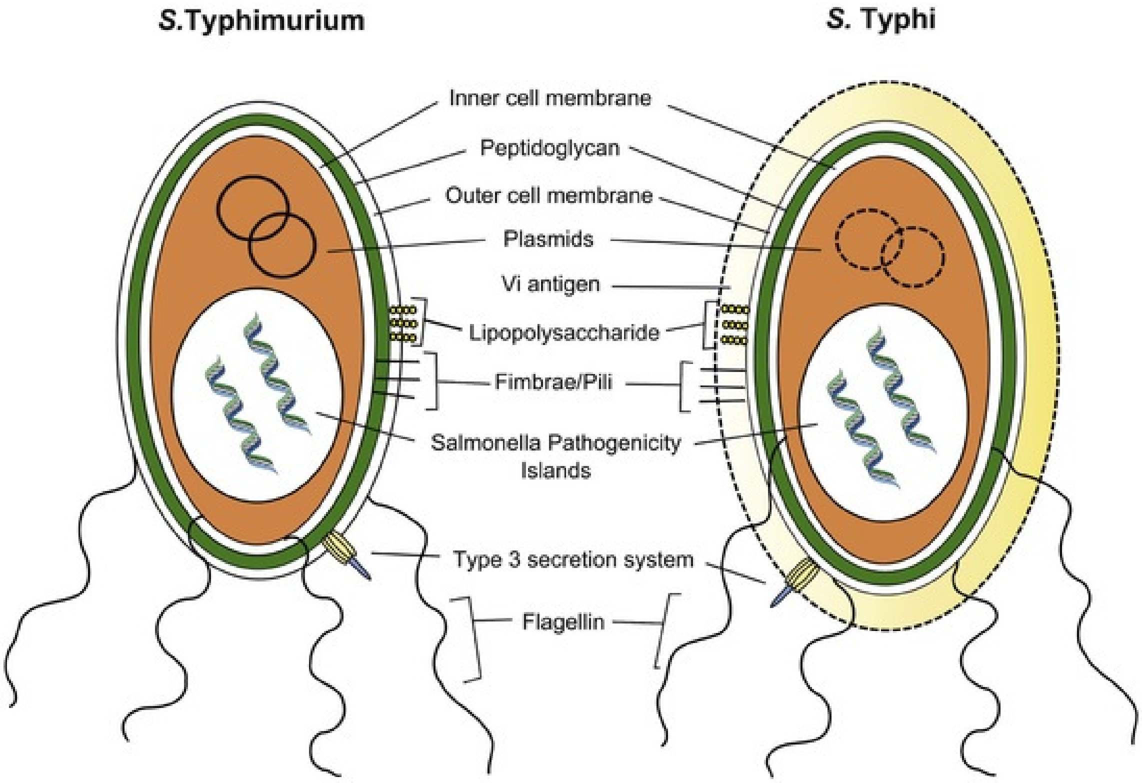
*S.*Typhimurium
S. Typhi
Inner cell membrane
Peptidoglycan
Outer cell membrane
Plasmids
Vi antigen
Lipopolysaccharide
Fimbrae/Pili
Salmonella Pathogenicity Islands
Type 3 secretion system
Flagellin

FIG. 225.1 Overlapping and distinct virulence systems in *Salmonella typhi* and nontyphoidal *Salmonella.* (From de Jong HK, Parry CM, van der Poll T, Wiersinga WJ. Host-pathogen interaction in invasive Salmonellosis. *PLoSPathog* 2012;8(10):e1002933.)

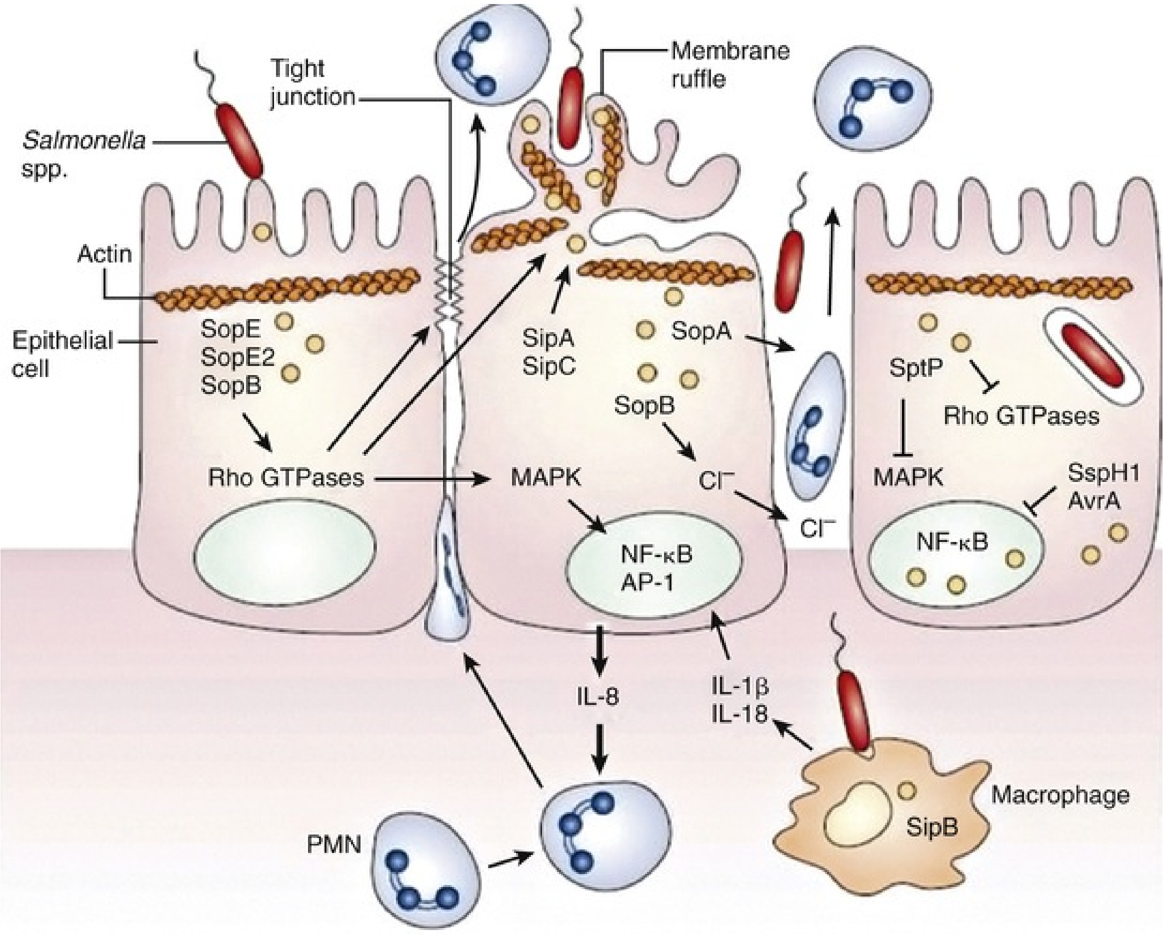
Tight junction
Membrane ruffle
Salmonella spp.
Actin
Epithelial cell
SopE
SopE2
SopB
Rho GTPases
SipA
SipC
SopA
SopB
MAPK
Cl⁻
Cl⁻
SptP
Rho GTPases
MAPK
SspH1
AvrA
NF-κB
AP-1
NF-κB
IL-8
IL-1β
IL-18
Macrophage
SipB
PMN

FIG. 225.2 On contact with the epithelial cell, salmonellae assemble the *Salmonella* pathogenicity island 1–encoded type III secretion system (TTSS-1) and translocate effectors (*yellow spheres*) into the eukaryotic cytoplasm. Effectors such as SopE, SopE2, and SopB then activate host Rho guanosine triphosphatase (GTPase), resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase (MAPK) pathways, and destabilization of tight junctions. Changes in the actin cytoskeleton, which are further modulated by the actin-binding proteins SipA and SipC, lead to bacterial uptake. MAPK signaling activates the transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), which turn on production of the proinflammatory polymorphonuclear leukocyte (PMN) chemokine interleukin (IL)-8. SipB induces caspase-1 activation in macrophages, with the release of IL-1β and IL-18, augmenting the inflammatory response. In addition, SopB stimulates Cl⁻ secretion by its inositol phosphatase activity. The destabilization of tight junctions allows the transmigration of PMNs from the basolateral to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. However, the transmigration of PMNs also occurs in the absence of tight-junction disruption and is further promoted by SopA. The actin cytoskeleton is restored, and MAPK signaling is turned off by the enzymatic activities of SptP. This also results in the downmodulation of inflammatory responses, to which SspH1 and AvrA also contribute by inhibiting activation of NF-κB. (From Haraga A,

Ohlson MB, Miller SI: Salmonellae interplay with host cells, *Nat Rev Microbiol* 6:53–66, 2008.)

Central to *S.* Typhimurium pathogenesis are 2 **type III secretion** systems encoded within the pathogenicity islands **SPI-1** and **SPI-2** , which are responsible for the secretion and translocation of a set of bacterial proteins termed **effectors** into host cells; effectors are able to alter host cell physiology to facilitate bacterial entry and survival. Once delivered by the type III secretion systems, the secreted effectors play critical roles in manipulating the host cell to allow bacterial invasion, induction of inflammatory responses, and assembly of an intracellular protective niche conducive to bacterial survival and replication. The type III secretion system encoded on SPI-1 mediates invasion of the intestinal epithelium, whereas the type III secretion system encoded on SPI-2 is required for survival within macrophages. In addition, the expression of strong agonists of innate pattern recognition receptors (lipopolysaccharide and flagellin) is important for triggering a Toll-like receptor (TLR)–mediated inflammatory response.

Salmonella spp. invade epithelial cells in vitro by a process of bacteria-mediated endocytosis involving cytoskeletal rearrangement, disruption of the epithelial cell brush-border, and subsequent formation of membrane ruffles (Fig. 225.3). An adherent and invasive phenotype of *S.* Enterica is activated under conditions similar to those found in the human small intestine (high osmolarity, low oxygen). The invasive phenotype is mediated in part by SPI-1, a 40-kb region that encodes regulator proteins such as HilA and a variety of other products.

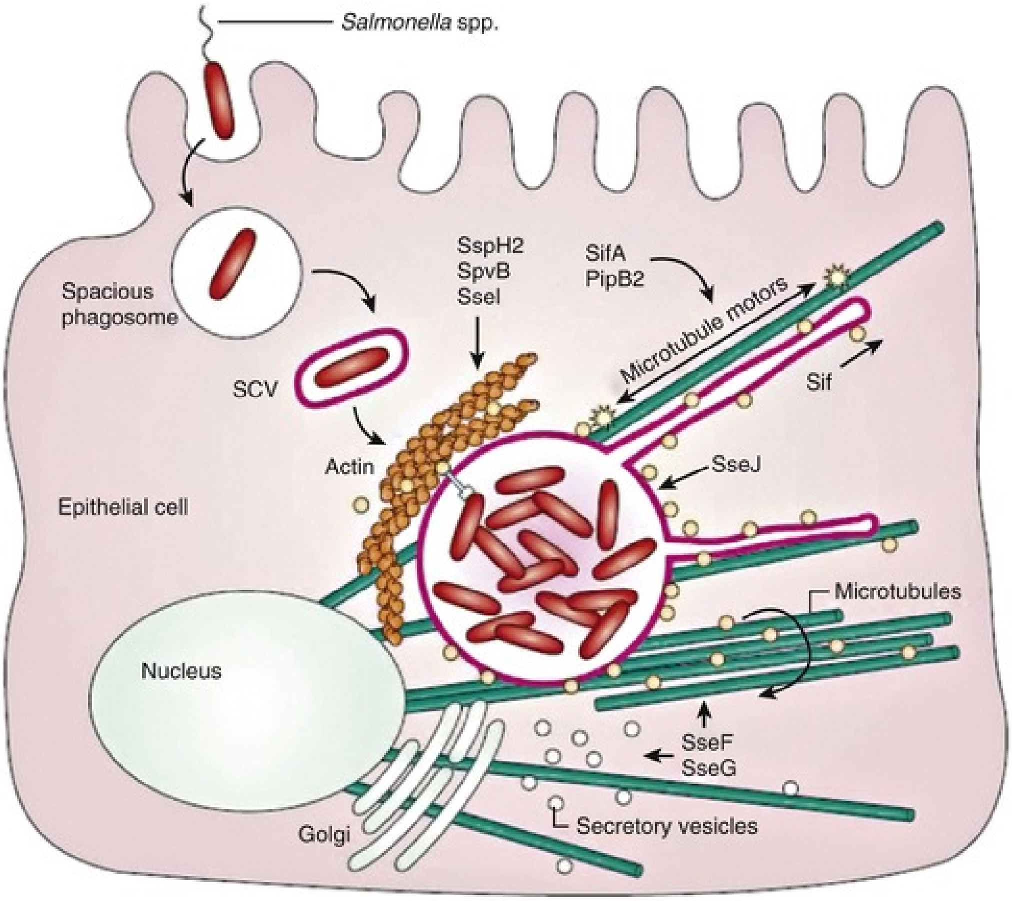
Salmonella spp.
Spacious phagosome
SspH2
SpvB
SseI
SifA
PipB2
Microtubule motors
SCV
Sif
Actin
SseJ
Epithelial cell
Microtubules
Nucleus
SseF
SseG
Golgi
Secretory vesicles

FIG. 225.3 Formation of the *Salmonella* -containing vacuole (SCV) and induction of the *Salmonella* pathogenicity island 2 (SPI-2) type III secretion system (TTSS) within the host cell. Shortly after internalization by macropinocytosis, salmonellae are enclosed in a spacious phagosome that is formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, and is called the SCV. It contains the endocytic marker lysosomal-associated membrane protein 1 (LAMP-1; *purple*). The *Salmonella* SPI-2 is induced within the SCV and translocates effector proteins *(yellow spheres)* across the phagosomal membrane several hours after phagocytosis. The SPI-2 effectors SifA and PipB2 contribute to formation of *Salmonella* -induced filament along microtubules *(green)* and regulate microtubule motor *(yellow star shape)* accumulation on the Sif and the SCV. SseJ is a deacylase that is active on the phagosome membrane. SseF and SseG cause microtubule bundling adjacent to the SCV and direct Golgi-derived vesicle traffic toward the SCV. Actin accumulates around the SCV in an SPI-2–dependent manner, in which SspH2, SpvB, and SseI are thought to have a role. (From Haraga A, Ohlson MB, Miller SI: Salmonellae interplay with host cells, *Nat Rev Microbiol* 6:53–66, 2008.)

Shortly following invasion of the gut epithelium, invasive *Salmonella* organisms encounter macrophages within the gut-associated lymphoid tissue (GALT). The interaction between *Salmonella* and macrophages results in alteration in the expression of a number of host genes, including those encoding proinflammatory mediators (inducible nitric oxide synthase, chemokines, IL-1β), receptors or adhesion molecules (tumor necrosis factor [TNF]-α receptor, CD40, intercellular adhesion molecule 1), and antiinflammatory mediators (transforming growth factor-β1, TGF-β2). Other upregulated genes include those involved in cell death or apoptosis (intestinal epithelial cell protease, TNF-R1, Fas) and transcription factors (early growth response 1, interferon [IFN] regulatory factor 1). *S.* Typhimurium can induce rapid macrophage death in vitro, which depends on the host cell protein caspase-1 and is mediated by the effector protein **SipB** (*Salmonella* invasion protein B). Intracellular *S.* Typhimurium is found within specialized vacuoles that have diverged from the normal endocytic pathway. This ability to survive within monocytes/macrophages is essential for *S.* Typhimurium to establish a systemic infection in the mouse. The mucosal proinflammatory response to *S.* Typhimurium infection and the subsequent recruitment of phagocytic cells to the site may also facilitate systemic spread of the bacteria.

Some virulence traits are shared by all salmonellae, but others are serotype restricted. These virulence traits have been defined in tissue culture and murine models, and it is likely that clinical features of human *Salmonella* infection will eventually be related to specific DNA sequences. With most diarrhea-associated nontyphoidal salmonelloses, the infection does not extend beyond the lamina propria and the local lymphatics. Specific virulence genes are related to the ability to cause bacteremia. These genes are found significantly more often in strains of *S.* Typhimurium isolated from the blood than in strains recovered from stool. Although both *S. dublin* and *S. choleraesuis* have a greater propensity to rapidly invade the bloodstream with little or no intestinal involvement, the development of disease after infection with *Salmonella* depends on the number of infecting organisms, their virulence traits, and several host defense factors. Various host factors may also affect the development of specific complications or clinical syndromes (Table 225.1); of these factors, HIV infections are assuming greater importance in Africa in all age-groups.

Table 225.1

Host Factors and Conditions Predisposing to Development of Systemic Disease with Nontyphoidal *Salmonella* (NTS) Strains

Neonates and young infants (≤3 mo old)
HIV/AIDS
Other immunodeficiencies and chronic granulomatous disease
Defects in interferon γ production or action
Immunosuppressive and corticosteroid therapies
Malignancies, especially leukemia and lymphoma
Hemolytic anemia, including sickle cell disease, malaria, and bartonellosis
Collagen vascular disease
Inflammatory bowel disease
Achlorhydria or use of antacid medications
Impaired intestinal motility
Schistosomiasis, malaria
Malnutrition

Bacteremia is possible with any *Salmonella* serotype, especially in individuals with reduced host defenses and especially in those with altered reticuloendothelial or cellular immune function. Thus, children with HIV infection, chronic granulomatous disease, and leukemia are more likely to develop bacteremia after *Salmonella* infection, although the majority of children with *Salmonella* bacteremia are HIV-negative. Children with *Schistosoma mansoni* infection and hepatosplenic involvement, as well as chronic malarial anemia, are also at a greater risk for development of chronic salmonellosis. Children with sickle cell disease are at increased risk for *Salmonella* septicemia and osteomyelitis. This risk may be related to the presence of numerous infarcted areas in the gastrointestinal (GI) tract, bones, and RES, as well as reduced phagocytic and opsonizing capacity of patients.

Clinical Manifestations

Acute Enteritis

The most common clinical presentation of salmonellosis is acute enteritis. After an incubation period of 6-72 hr (mean: 24 hr), there is an abrupt onset of nausea, vomiting, and crampy abdominal pain, located primarily in the periumbilical area and right lower quadrant, followed by mild to severe watery diarrhea and sometimes by diarrhea containing blood and mucus. A large proportion of children with acute enteritis are febrile, although younger infants may exhibit a normal or subnormal temperature. Symptoms usually subside within 2-7 days in healthy children, and fatalities are rare. However, some children experience severe disease with a septicemia-like picture (high fever, headache, drowsiness, confusion, meningismus, seizures, abdominal distention). The stool typically contains a moderate number of PMNs and occult blood. Mild leukocytosis may be detected.

Bacteremia

Although the precise incidence of bacteremia following *Salmonella* gastroenteritis is unclear, transient bacteremia can occur in 1–5% of children with *Salmonella* diarrhea. Bacteremia can occur with minimal associated symptoms in newborns and very young infants, but in older infants it typically follows gastroenteritis and can be associated with fever, chills, and septic shock. In patients with AIDS, recurrent septicemia appears despite antibiotic therapy, often with a negative stool culture result for *Salmonella* and sometimes with no identifiable focus of infection. NTS GI infections typically cause bacteremia in developing countries.

Nontyphoidal *Salmonella* Bacteremia as Emerging Disease in Africa

In Africa, particularly sub-Saharan, NTS has been increasingly appreciated as among the most common causes of *all* bacteremia cases in febrile adults and children. Bacteremia from NTS in Africa has had an accompanying case fatality rate of 20–25%. Notably, children age 6-36 mo and adults age 30-50 yr are at greatest risk.

Clinical features among children with invasive NTS infections can be confusing, in that diarrhea is often *not* a prominent feature. Furthermore, 60% of children have an apparent lower respiratory tract infection focus (perhaps from co-infection or comorbidity). Fever is present in 95% of cases but may have no apparent focus. Fig. 225.4 summarizes other clinical features. Importantly, the lack of specificity of these clinical features severely compromises the ability of current clinical algorithms to identify invasive NTS infections. Accordingly, blood culture and clinical microbiology systems for bacterial growth, isolation, speciation, and antibacterial drug sensitivity testing are required for diagnosis and well-informed treatment decision-making. Among NTS isolates causing invasive systemic disease, the serotypes *S.* Typhimurium and *S.* Enteritidis have been frequently reported, but several other serotypes can cause invasive disease as well.

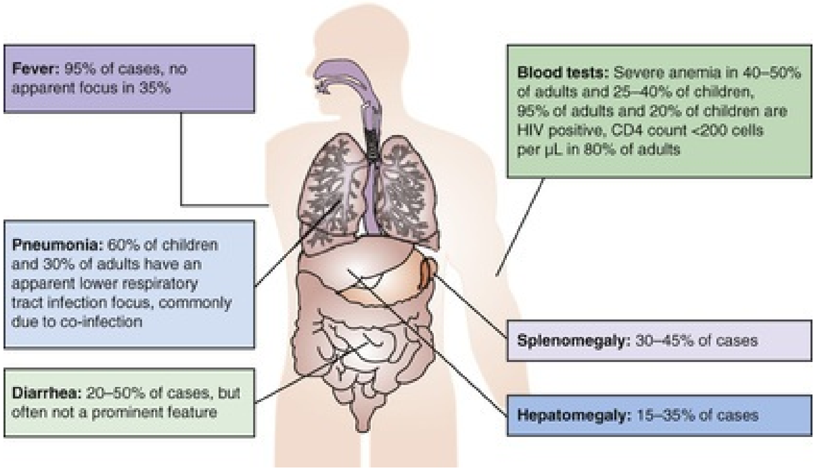
Fever: 95% of cases, no apparent focus in 35%
Pneumonia: 60% of children and 30% of adults have an apparent lower respiratory tract infection focus, commonly due to co-infection
Diarrhea: 20–50% of cases, but often not a prominent feature
Blood tests: Severe anemia in 40–50% of adults and 25–40% of children, 95% of adults and 20% of children are HIV positive, CD4 count <200 cells per μL in 80% of adults
Splenomegaly: 30–45% of cases
Hepatomegaly: 15–35% of cases

FIG. 225.4 Clinical features of invasive nontyphoidal *Salmonella* (NTS) disease in adults and children in Africa. (From Feasey NA, Dougan G, Kingsley RA, et al: Invasive non-typhoidal *Salmonella* disease: an emerging and neglected tropical disease in Africa, *Lancet* 379: 2489–2499, 2012.)

It remains unclear exactly why invasive infections by NTS seem so much more frequent in Africa, compared with the dominance of typhoidal *Salmonellae* in Asia. HIV infection is one identified host risk factor for NTS infection. Indeed, recurrent NTS infection was part of early CDC case definitions for the AIDS. However, only 20% of African children with NTS disease are HIV positive. Other risks for pediatric NTS may include recent or severe malaria infections, sickle cell anemia, active schistosomiasis, and malnutrition.

The epidemiologic patterns thus far appreciated for invasive infections by NTS in Africa suggest epidemics may occur over several years, peaking in the rainy season. However, it remains unclear as to the extent that invasive NTS infections are related to human diarrheal disease or GI carriage. Likewise, obvious food or animal sources of invasive NTS in humans have not been conclusively identified, and the relative role(s) of zoonotic and/or anthroponotic transmission is uncertain. Thus, optimal strategies for interrupting transmission of invasive NTS infections remain unclear. This is particularly problematic, given the emergence of antibacterial drug resistance that has also been noted among NTS organisms, including the multidrug-resistant strain referred to as (DNA multilocus “sequence type”) ST313.

For invasive NTS infections in Africa, resistance to ampicillin, chloramphenicol, and co-trimoxazole may force increasing reliance on more expensive treatment options. Depending on local resistance patterns, drug availability, and patient state, empirical treatments may require third-generation cephalosporins (e.g., ceftriaxone), fluoroquinolones (e.g., ciprofloxacin), or macrolide/azalides (e.g., azithromycin). Of note, while *Salmonella* strains may be killed in culture in vitro by aminoglycosides, this drug class is not appropriate for treatment of invasive salmonellae, because aminoglycosides are not able to penetrate the intracellular niches in hosts that salmonellae so effectively exploit as part of their life cycle.

Nontyphoidal *Salmonella* Bacteremia in Other Geographic Regions

The emergence of invasive, high-mortality NTS infections in sub-Saharan Africa suggests that historical clinical divisions of *Salmonella* infections into typhoidal and nontyphoidal may become problematic oversimplification. Currently, however, in settings outside sub-Saharan Africa, NTS infections still tend to be self-limiting and noninvasive and are low-mortality events for most children who are immunocompetent. Risk factors for systemic spread of NTS include HIV infection, diabetes, sickle cell disease, systemic corticosteroid use, malignancy, chronic liver or kidney disease, chronic granulomatous disease, B-cell deficiencies, and dysfunction of proinflammatory cytokine pathways. Neonates and infants are also at particular risk for disseminated infection and thus warrant more aggressive evaluation and treatment.

Extraintestinal Focal Infections

Following bacteremia, salmonellae have the propensity to seed and cause focal suppurative infection of many organs. The most common focal infections involve the skeletal system, meninges, intravascular sites, and sites of preexisting abnormalities. The peak incidence of *Salmonella* meningitis is in infancy, and the infection may be associated with a florid clinical course, high mortality, and neurologic sequelae in survivors.

Chronic *Salmonella* Carriage

While traditionally viewed primarily as a complication of *Salmonella* infection among adults, *Salmonella* chronic carriage has important medical and epidemiologic implications, and may occur in children. Colonization of the gallbladder by *Salmonella typhi* has long been appreciated, but reports suggest that some nontyphoidal *Salmonella* (e.g., invasive NTS currently in Africa) can also establish long-term asymptomatic carriage states.

Antibacterial treatments of *Salmonella* infections are paradoxical, in that the prospect of becoming a chronic carrier is believed to be increased by exposure to antibacterial agents. Yet, clearance of established chronic carrier status requires prolonged medical treatment using antibacterial agents to which the relevant *Salmonella* strain is susceptible and sometimes requires gallstone or gallbladder removal. Chronic carriers of *Salmonella* may only have intermittently positive stool cultures and are often asymptomatic, which makes approaches to diagnosis and treatment especially complex.

Complications

Salmonella gastroenteritis can be associated with acute dehydration and complications that result from delayed presentation and inadequate treatment. Bacteremia in younger infants and immunocompromised individuals can have serious consequences and potentially fatal outcomes. *Salmonella* organisms can seed many organ systems, including causing osteomyelitis in children, particularly among children with sickle cell disease. Reactive arthritis may follow *Salmonella* gastroenteritis, especially in adolescents with the HLA-B27 antigen.

In certain high-risk groups, especially those with impaired immunity, the course of *Salmonella* gastroenteritis may be more complicated. Neonates, infants <6 mo old, and children with primary or secondary immunodeficiency may have symptoms that persist for several weeks. The course of illness and complications may also be affected by coexisting pathologies. In children with AIDS, *Salmonella* infection frequently becomes widespread and overwhelming, causing multisystem involvement, septic shock, and death. In patients with inflammatory bowel disease, especially active ulcerative colitis, *Salmonella* gastroenteritis may lead to rapid development of toxic megacolon, bacterial translocation, and sepsis. In children with schistosomiasis, the *Salmonella* may persist and multiply within schistosomes, leading to chronic infection unless the schistosomiasis is effectively treated. Prolonged or intermittent bacteremia is associated with low-grade fever, anorexia, weight loss, diaphoresis, and myalgias and may occur in children with RES dysfunction, which can be associated with underlying problems such as hemolytic anemia or malaria.

Diagnosis

Few clinical features are specific to *Salmonella* gastroenteritis to allow differentiation from other bacterial causes of diarrhea. Definitive diagnosis of *Salmonella* infection is based on clinical correlation of the presentation and culture of and subsequent identification of *Salmonella* organisms from feces or other body fluids. In children with gastroenteritis, stool cultures have higher yields than rectal swabs. In children with NTS gastroenteritis, prolonged fever lasting ≥5 days and young age should be recognized as associated with development of bacteremia. In patients with sites of local suppuration, aspirated specimens should be Gram-stained and cultured. *Salmonella* organisms grow well on nonselective or enriched media, such as blood agar, chocolate agar, and nutrient broth, but stool specimens containing mixed bacterial flora require a selective medium, such as MacConkey, xylose-lysine-deoxycholate, bismuth sulfite, or *Salmonella-Shigella* (SS) agar for isolation of *Salmonella* .

Culture-independent diagnostic tests have some utility for screening or epidemiologic studies, but *without susceptibility results,* these tests do not show which drugs will be effective for any given patient.

Treatment

Appropriate therapy relates to the specific clinical presentation of *Salmonella* infection. In children with gastroenteritis, rapid clinical assessment, correction of dehydration and electrolyte disturbances, and supportive care are key. Antibiotics are not generally recommended for the treatment of isolated uncomplicated *Salmonella* gastroenteritis, because they may disrupt normal intestinal flora and prolong the excretion of *Salmonella* and increase the risk for creating a chronic carrier state. However, given the risk for bacteremia in young infants (<3 mo old) and the risk of disseminated infection in high-risk groups with immune compromise (HIV, malignancies, immunosuppressive therapy, sickle cell anemia, immunodeficiency states), these children must receive an appropriate empirically chosen antibiotic until culture results are available (Table 225.2). The *S.* Typhimurium phage type DT104 strain is usually resistant to the following 5 drugs: ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An increasing proportion of *S.* Typhimurium phage type DT104 isolates also have reduced susceptibility to fluoroquinolones. *Given the higher mortality associated with multidrug-resistant* Salmonella i*nfections, it is* *necessary to perform susceptibility tests on all human isolates. Infections with suspected drug-resistant* Salmonella *should be closely monitored and treated with appropriate antimicrobial therapy.*

Table 225.2

Treatment of *Salmonella* Gastroenteritis

ORGANISM AND INDICATION
Salmonella infections in infants <3 mo old or in immunocompromised persons (in addition to appropriate treatment for underlying disorder)
DOSE AND DURATION OF TREATMENT
Cefotaxime, [†] 100-200 mg/kg/day every 6-8 hr for 5-14 days[*] *or* Ceftriaxone, 75 mg/kg/day once daily for 7 days[*] *or* Ampicillin, 100 mg/kg/day every 6-8 hr for 7 days[*] *or* Cefixime, 15 mg/kg/day for 7-10 days[*]

[*] A blood culture should be obtained prior to antibiotic therapy. In a well appearing immunocompetent child without evidence of disseminated disease, a single dose of ceftriaxone may be given followed by oral azithromycin; ampicillin, trimethoprim-sulfamethoxazole, or a fluoroquinolone may be substituted once sensitivities are known.

[†] If available.

Prognosis

Most healthy children with *Salmonella* gastroenteritis recover fully. However, malnourished children and children who do not receive optimal supportive treatment are at risk for development of prolonged diarrhea and complications. Young infants and immunocompromised patients often have systemic involvement, a prolonged course, and extraintestinal foci. In particular, children with HIV infection and *Salmonella* infections can have a florid course.

After infection, NTS are excreted in feces for a median of 5 wk. A prolonged carrier state after nontyphoidal salmonellosis is rare but may be seen in children, particularly those with biliary tract disease and cholelithiasis after chronic hemolysis. During the period of *Salmonella* excretion, the individual may infect others, directly by the fecal-oral route or indirectly by contaminating foods.

Prevention

Control of the transmission of *Salmonella* infections to humans requires control of the infection in the animal reservoir, judicious use of antibiotics in dairy and livestock farming, prevention of contamination of foodstuffs prepared from animals, and use of appropriate standards in food processing in commercial and private kitchens. Because large outbreaks are often related to mass food production, it should be recognized that contamination of just one piece of machinery used in food processing may cause an outbreak; meticulous cleaning of equipment is essential. Clean water supply and education in handwashing and food preparation and storage are critical to reducing person-to-person transmission. *Salmonella* may remain viable when cooking practices prevent food from reaching a temperature >65.5°C (150°F) for >12 min. Parents should be advised of the risk of various pets(classically including reptiles and amphibians but also rodents) and be given recommendations for preventing transmission from these frequently infected hosts (Table 225.3).

Table 225.3

Recommendations for Preventing Transmission of *Salmonella* from Reptiles and Amphibians to Humans

Pet store owners, healthcare providers, and veterinarians should provide information to owners and potential purchasers of reptiles and amphibians about the risks for and prevention of salmonellosis from these pets.
Persons at increased risk for infection or serious complications from salmonellosis (e.g., children <5 yr old, immunocompromised persons) should avoid contact with reptiles and amphibians and any items that have been in contact with reptiles and amphibians.
Reptiles and amphibians should be kept out of households that include children <5 yr old or immunocompromised persons. A family expecting a child should remove any pet reptile or amphibian from the home before the infant arrives.
Reptiles and amphibians should not be allowed in childcare centers.
Persons should always wash their hands thoroughly with soap and water after handling reptiles and amphibians or their cages.
Reptiles and amphibians should not be allowed to roam freely throughout a home or living area.
Pet reptiles and amphibians should be kept out of kitchens and other food preparation areas. Kitchen sinks should not be used to bathe reptiles and amphibians or to wash their dishes, cages, or aquariums. If bathtubs are used for these purposes, they should be cleaned thoroughly and disinfected with bleach.
Reptiles and amphibians in public settings (e.g., zoos, exhibits) should be kept from direct or indirect contact with patrons except in designated “animal contact” areas equipped with adequate handwashing facilities. Food and drink should not be allowed in animal contact areas.

From Centers for Disease Control and Prevention: Reptile-associated salmonellosis—selected states, 1998–2002, *MMWR* 52:1206–1210, 2003.

In contrast to the situation in developed countries, relatively little is known about the transmission of NTS infections in developing countries, and person-to-person transmission may be relatively more important in some settings. Although some vaccines have been used in animals, no human vaccine against NTS infections is currently available. Infections should be reported to public health authorities so that outbreaks can be recognized and investigated. Given the rapid rise of antimicrobial resistance among *Salmonella* isolates, it is imperative that there is rigorous regulation of the use of antimicrobials in animal feeds.

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225.2

Enteric Fever (Typhoid Fever)

Jeffrey S. McKinney

Enteric fever (more commonly termed *typhoid fever*) remains endemic in many developing countries. Given the ease of modern travel, cases are regularly reported from most developed countries, usually from returning travelers.

Etiology

Typhoid fever is caused by *S. enterica* serovar Typhi (*S.* Typhi), a gram-negative bacterium. A very similar but often less severe disease is caused by *Salmonella* Paratyphi A and rarely by *S.* Paratyphi B (Schotmulleri) and *S.* Paratyphi C (Hirschfeldii). The ratio of disease caused by *S.* Typhi to that caused by *S.*

Paratyphi is approximately 10 : 1, although the proportion of *S.* Paratyphi A infections is increasing in some parts of the world, for reasons that are unclear. Although *S.* Typhi shares many genes with *Escherichia coli* and at least 95% of genes with *S.* Typhimurium, several unique gene clusters known as *pathogenicity islands* and other genes have been acquired during evolution. The inactivation of single genes as well as the acquisition or loss of single genes or large islands of DNA may have contributed to host adaptation and restriction of *S.* Typhi.

Epidemiology

It is estimated that >26.9 million typhoid fever cases occur annually, of which 1% result in death. The vast majority of this disease burden is witnessed in Asia. Additionally, an estimated 5.4 million cases caused by paratyphoid occur each year. In 2010, 13.5 million cases of typhoid fever were recorded, and both typhoid and paratyphoid fevers together accounted for >12 million disability-adjusted life-years. The mortality caused by typhoid fever in the same year was found to be 7.2 per 100,000 population for sub-Saharan Africa. Given the paucity of microbiologic facilities in developing countries, these figures may be more representative of the clinical syndrome rather than of culture-proven disease. In most developed countries, the incidence of typhoid fever is <15 cases per 100,000 population, with most cases occurring in travelers. In contrast, the incidence may vary considerably in the developing world, with estimated rates ranging from 100-1,000 cases per 100,000 population. There are significant differences in the age distribution and population at risk. Population-based studies from South Asia also indicate that the age-specific incidence of typhoid fever may be highest in children <5 yr old, in association with comparatively higher rates of complications and hospitalization.

Typhoid fever is notable for the emergence of drug resistance. Following sporadic outbreaks of chloramphenicol-resistant *S.* Typhi infections, many strains of *S.* Typhi have developed plasmid-mediated multidrug resistance to all 3 of the primary antimicrobials: ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. There is also a considerable increase in nalidixic acid–resistant and even ceftriaxone-resistant isolates of *S* . Typhi, as well as the emergence of fluoroquinolone-resistant isolates. Nalidixic acid–resistant isolates first emerged in Southeast Asia and India and now account for the majority of travel-associated cases of typhoid fever in the United States. Given the ongoing global movement of resistant *S.* Typhi, an international awareness of resistance patterns is needed for effective patient care.

S. Typhi is highly adapted to infection of humans to the point that it has lost the ability to cause transmissible disease in other animals. The discovery of the large number of pseudogenes in *S.* Typhi suggests that the genome of this pathogen has undergone degeneration to facilitate a specialized association with the human host. Thus, direct or indirect contact with an infected person (sick or chronic carrier) is a prerequisite for infection. Ingestion of foods or water contaminated with *S.* Typhi from human feces is the most common mode of transmission, although water-borne outbreaks as a consequence of poor sanitation or contamination have been described in developing countries. In other parts of the world, oysters and other shellfish cultivated in water contaminated by sewage and the use of night soil as fertilizer may also cause infection.

Pathogenesis

Enteric fever occurs through the ingestion of the organism, and a variety of sources of fecal contamination have been reported, including street foods and contamination of water reservoirs.

Human volunteer experiments established an infecting dose of about 10^5 -10^9 organisms, with an incubation period ranging from 4-14 days, depending on the inoculating dose of viable bacteria. After ingestion, *S.* Typhi organisms are thought to invade the body through the gut mucosa in the terminal ileum, possibly through specialized antigen-sampling cells known as *M cells* that overlie GALT, through enterocytes, or via a paracellular route. *S.* Typhi crosses the intestinal mucosal barrier after attachment to the microvilli by an intricate mechanism involving membrane ruffling, actin rearrangement, and internalization in an intracellular vacuole. In contrast to NTS, *S.* Typhi expresses virulence factors that allow it to downregulate the pathogen recognition receptor–mediated host inflammatory response. Within the Peyer patches in the terminal ileum, *S.* Typhi can traverse the intestinal barrier through several mechanisms, including the M cells in the follicle-associated epithelium, epithelial cells, and dendritic cells. At the villi, *Salmonella* can enter through the M cells or by passage through or between compromised epithelial cells.

On contact with the epithelial cell, *S.* Typhi assembles type III secretion system encoded on SPI-1 and translocates effectors into the cytoplasm. These effectors activate host Rho guanosine triphosphatases, resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase (MAPK) pathways, and destabilization of tight junctions. Changes in the actin cytoskeleton are further modulated by the actin-binding proteins SipA and SipC and lead to bacterial uptake. MAPK signaling activates the transcription factors activator protein (AP)-1 and nuclear factor (NF)-κB, which turn on production of IL-8. The destabilization of tight junctions allows the transmigration of PMNs from the basolateral surface to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. Shortly after internalization of *S.* Typhi by macropinocytosis, salmonellae are enclosed in a spacious phagosome formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, forming the *Salmonella* -containing vacuole. A 2nd type III secretion system encoded on SPI-2 is induced within the *Salmonella* -containing vacuole and translocates effector proteins SifA and PipB2, which contribute to *Salmonella* -induced filament formation along microtubules.

After passing through the intestinal mucosa, *S.* Typhi organisms enter the mesenteric lymphoid system and then pass into the bloodstream via the lymphatics. This primary bacteremia is usually asymptomatic, and blood culture results are frequently negative at this stage of the disease. The bloodborne bacteria are disseminated throughout the body and are thought to colonize the organs of the RES, where they may replicate within macrophages. After a period of bacterial replication, *S.* Typhi organisms are shed back into the blood, causing a secondary bacteremia that coincides with the onset of clinical symptoms and marks the end of the incubation period (Fig. 225.5).

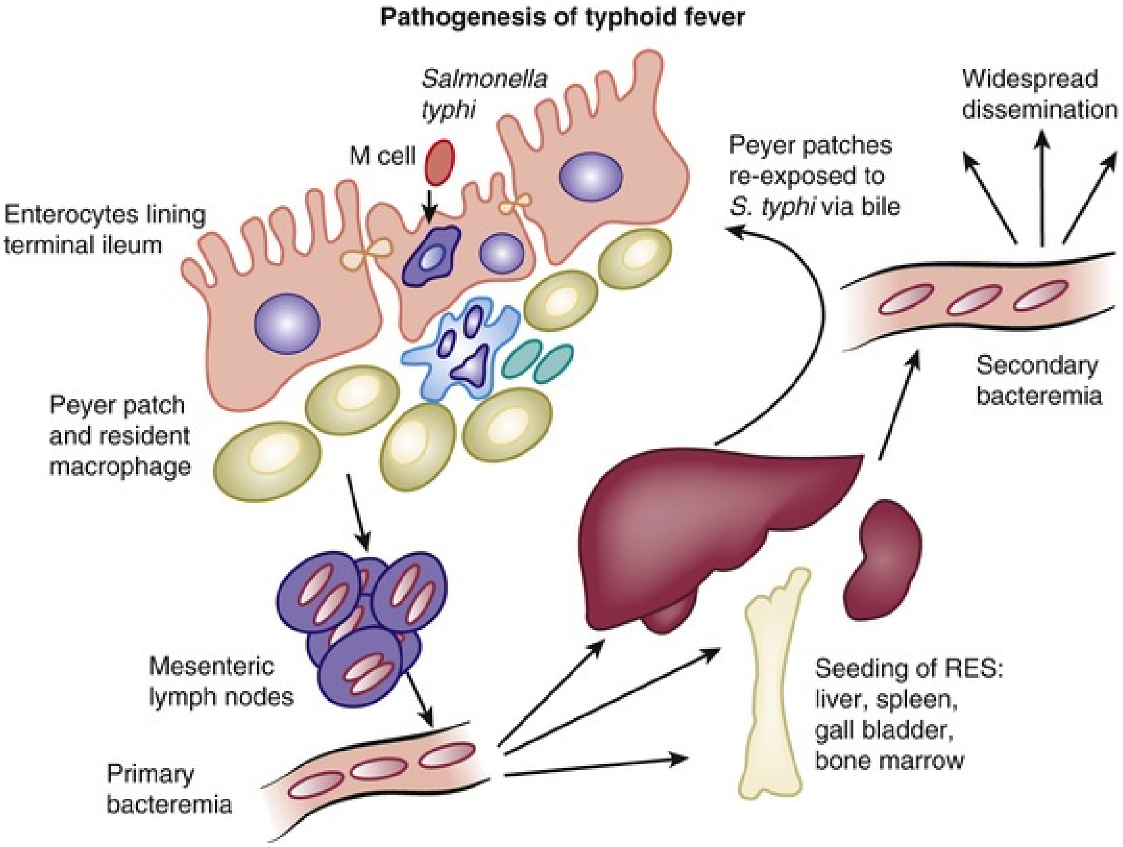
Pathogenesis of typhoid fever
Salmonella typhi
M cell
Enterocytes lining terminal ileum
Peyer patch and resident macrophage
Mesenteric lymph nodes
Primary bacteremia
Peyer patches re-exposed to S. typhi via bile
Widespread dissemination
Secondary bacteremia
Seeding of RES: liver, spleen, gall bladder, bone marrow

FIG. 225.5 Pathogenesis of typhoid fever. *RES,* Reticuloendothelial system. (Adapted from Richens J: Typhoid fever. In Cohen J, Powderly WG, Opal SM, editors: *Infectious diseases* , ed 2, London, 2004, Mosby, pp 1561–1566.)

In vitro studies with human cell lines have shown qualitative and quantitative differences in the epithelial cell response to *S.* Typhi and *S.* Typhimurium with regard to cytokine and chemokine secretion. Thus, perhaps by avoiding the triggering of an early inflammatory response in the gut, *S.* Typhi can instead colonize deeper tissues and organ systems. Infection with *S.* Typhi produces an inflammatory response in the deeper mucosal layers and underlying lymphoid tissue, with hyperplasia of Peyer patches and subsequent necrosis and sloughing of overlying epithelium. The resulting ulcers can bleed but usually heal without scarring or stricture formation. The inflammatory lesion may occasionally penetrate the muscularis and serosa of the intestine and produce perforation. The mesenteric lymph nodes, liver, and spleen are hyperemic and generally have areas of focal necrosis as well. A mononuclear response may be seen in the bone marrow in association with areas of focal necrosis. The morphologic changes of *S.* Typhi infection are less prominent in infants than in older children and adults.

Several virulence factors, including the type III secretion system encoded on

SPI-2, may be necessary for the virulence properties and ability to cause systemic infection. The surface Vi (virulence) polysaccharide capsular antigen found in *S.* Typhi interferes with phagocytosis by preventing the binding of C3 to the surface of the bacterium. The ability of organisms to survive within macrophages after phagocytosis is an important virulence trait encoded by the PhoP regulon and may be related to metabolic effects on host cells. The occasional occurrence of diarrhea may be explained by the presence of a toxin related to cholera toxin and *E. coli* heat-labile enterotoxin. *The clinical syndrome of fever and systemic symptoms is produced by a release of proinflammatory cytokines (IL-6, IL-1β, and TNF-α) from the infected cells.*

Characterization of a toxin, referred to as the **typhoid toxin** , represents a major advance in understanding *Salmonella* biology; with implications for longstanding observations about typhoidal vs nontyphoidal disease features, and the human host restriction of typhoidal infections. Although the exact role of typhoid toxin in disease pathophysiology is still being elucidated, the enzymatically active subunits of typhoid toxin are CdtB and PltA, which are, respectively, a cytothelial distending toxin (a DNase that causes double-stranded breaks in host cell DNA) and a pertussis-like toxin (with ADP-ribosyltransferase activity). These 2 active “A” subunits form a unique A_2 B_5 architecture with a heptomeric set of PltB “B” subunits. The trafficking of the A_2 B_5 typhoid toxin uses an elegant autocrine/paracrine delivery mechanism, which passes through the *Salmonella*- containing vesicle environment, where it is dependent on effectors released by the *Salmonella* pathogenicity island 2–encoded type III secretion system. After assembly in this host intracellular niche so characteristic of *Salmonella* biology, the typhoid exotoxin is exported into the *extracellular* space. Typhoid toxin binds a range of different glycans but has a preference for those with terminal sialic acids, notably sialoglycans terminated in Neu5Ac. Intriguingly, humans have a dominance of these glycans compared with other species. Accordingly, typhoid toxin binding preferences may help explain the human restriction of typhoidal infections and pathophysiology at a molecular level.

Importantly, *S.* Typhi and *S* . Paratyphi both express typhoid toxin, whereas “nontyphoidal” *Salmonella* spp. do not. Not only does this offer the prospect that typhoid toxin may help explain important clinical distinctions between typhoidal and nontyphoidal *Salmonella* infections, it raises hopes for new approaches to disease treatment and diagnostics. For example, antitoxin-based vaccines, therapeutics, or diagnostic tests might finally address the full microbiologic range of typhoid fever(s), because the typhoid toxin is conserved among not only *S.* Typhi but also *S.* Paratyphi isolates.

In addition to the virulence of the infecting organisms, host factors and immunity may also play an important role in predisposition to infection. Patients who are infected with HIV are at significantly higher risk for clinical infection with *S.* Typhi and *S.* Paratyphi. Similarly, patients with *Helicobacter pylori* infection have an increased risk of acquiring typhoid fever.

Clinical Manifestations

The incubation period of typhoid fever is usually 7-14 days but depends on the infecting dose and ranges between 3 and 30 days. The clinical presentation varies from a mild illness with low-grade fever, malaise, and slight, dry cough to a severe clinical picture with abdominal discomfort and multiple complications.

Many factors influence the severity and overall clinical outcome of the infection. They include the duration of illness before the initiation of appropriate therapy, choice of antimicrobial treatment, age, previous exposure or vaccination history, virulence of the bacterial strain, quantity of inoculum ingested, and several host factors affecting immune status.

The presentation of typhoid fever may also differ according to age. Although data from South America and parts of Africa suggest that typhoid may manifest as a mild illness in young children, presentation may vary in different parts of the world. There is emerging evidence from South Asia that the presentation of typhoid may be more dramatic in children <5 yr old, with comparatively higher rates of complications and hospitalization. Diarrhea, toxicity, and complications such as disseminated intravascular coagulation (DIC) are also more common in infancy, resulting in higher case fatality rates. However, some of the other features and complications of typhoid fever seen in adults, such as neurologic manifestations and GI bleeding, are rare in children.

Typhoid fever usually manifests as high-grade fever with a wide variety of associated features, such as generalized myalgia, abdominal pain, hepatosplenomegaly, and anorexia (Table 225.4). In children, diarrhea may occur in the earlier stages of the illness and may be followed by constipation. In the absence of localizing signs, the early stage of the disease may be difficult to differentiate from other endemic diseases, such as malaria and dengue fever. In approximately 25% of cases, a macular or maculopapular rash (“rose spots”) may be visible around the 7th-10th day of the illness, and lesions may appear in crops of 10-15 on the lower chest and abdomen and last 2-3 days (Fig. 225.6). These lesions may be difficult to see in dark-skinned children. Patients managed as outpatients present with fever (99%) but have less emesis, diarrhea, hepatomegaly, splenomegaly, and myalgias than patients who require hospital admission.

Table 225.4

Common Clinical Features of Typhoid Fever in Children*

FEATURE	RATE (%)
High-grade fever	95
Coated tongue	76
Anorexia	70
Vomiting	39
Hepatomegaly	37
Diarrhea	36
Toxicity	29
Abdominal pain	21
Pallor	20
Splenomegaly	17
Constipation	7
Headache	4
Jaundice	2
Obtundation	2
Ileus	1
Intestinal perforation	0.5

* Data collected in Karachi, Pakistan, from 2,000 children.

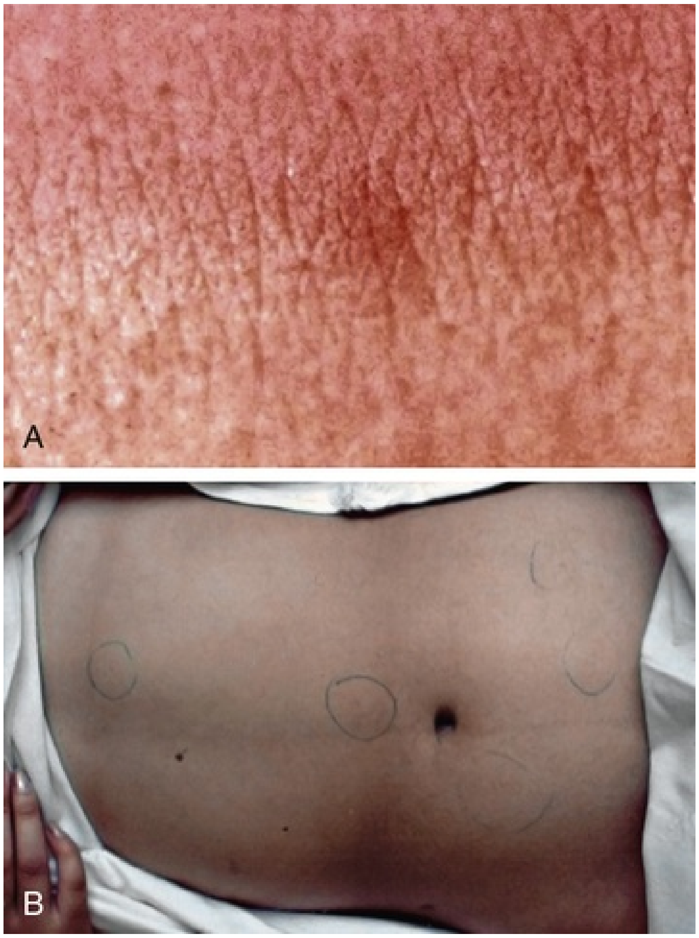

FIG. 225.6 **A,** “Rose spot” in volunteer with experimental typhoid fever. **B,** Small cluster of rose spots is usually located on the abdomen. These lesions may be difficult to identify, especially in dark-skinned people. (From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of *Salmonella enterica* serotype Typhi infection, *Lancet Infect Dis* 5:341–348, 2005.)

The presentation of typhoid fever may be modified by coexisting morbidities and early diagnosis and administration of antibiotics. In malaria-endemic areas and in parts of the world where schistosomiasis is common, the presentation of typhoid may also be atypical. *It is also recognized that multidrug-resistant* (MDR) S. *Typhi infection is a more severe clinical illness with higher rates of toxicity, complications, and case fatality rates, which may be related to the greater virulence as well as higher numbers of circulating bacteria.* The emergence of typhoid infections resistant to nalidixic acid and fluoroquinolones is associated with higher rates of morbidity and treatment failure. These findings may have implications for treatment algorithms, especially in endemic areas with high rates of MDR and nalidixic acid– or fluoroquinolone-resistant typhoid.

If no complications occur, the symptoms and physical findings gradually resolve within 2-4 wk; however, the illness may be associated with malnutrition in a number of affected children. Although enteric fever caused by *S.* Paratyphi organisms has been classically regarded as a milder illness, there have been several outbreaks of infection with drug-resistant *S.* Paratyphi A, suggesting that paratyphoid fever may also be severe, with significant morbidity and complications.

Complications

Although altered liver function is found in many patients with enteric fever, clinically significant hepatitis, jaundice, and cholecystitis are relatively rare and may be associated with higher rates of adverse outcome. Intestinal hemorrhage (<1%) and perforation (0.5–1%) are infrequent among children. Intestinal perforation may be preceded by a marked increase in abdominal pain (usually in the right lower quadrant), tenderness, vomiting, and features of peritonitis. Intestinal perforation and peritonitis may be accompanied by a sudden rise in pulse rate, hypotension, marked abdominal tenderness and guarding, and subsequent abdominal rigidity. A rising white blood cell count with a left shift and free air on abdominal radiographs may be seen in such cases.

Rare complications include toxic myocarditis, which may manifest as arrhythmias, sinoatrial block, or cardiogenic shock (Table 225.5). Neurologic complications are also relatively uncommon among children; they include delirium, psychosis, increased intracranial pressure, acute cerebellar ataxia, chorea, deafness, and Guillain-Barré syndrome. Although case fatality rates may be higher with neurologic manifestations, recovery usually occurs with no sequelae. Other reported complications include fatal bone marrow necrosis, DIC, hemolytic-uremic syndrome, pyelonephritis, nephrotic syndrome, meningitis, endocarditis, parotitis, orchitis, and suppurative lymphadenitis.

Table 225.5

Extraintestinal Infectious Complications of Typhoid Fever Caused by *Salmonella enterica* Serotype Typhi

ORGAN SYSTEM	PREVALENCE (%)	RISK FACTORS	COMPLICATIONS
Central	3-35	Residence in endemic region,	Encephalopathy, cerebral edema,

nervous system		malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, osteomyelitis of skull	subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis
Cardiovascular system	1-5	Cardiac abnormalities—e.g., existing valvular abnormalities, rheumatic heart disease, congenital heart defects	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary system	1-6	Residence in endemic region, past pulmonary infection, sickle cell anemia, alcohol abuse, diabetes, HIV infection	Pneumonia, empyema, bronchopleural fistula
Bone and joint	<1	Sickle cell anemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, extremes of age, corticosteroid use	Osteomyelitis, septic arthritis
Hepatobiliary system	1-26	Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, hemoglobinopathy	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary system	<1	Urinary tract abnormalities, pelvic pathology, systemic abnormalities	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft tissue infections	At least 17 cases reported in English-language literature	Diabetes	Psoas abscess, gluteal abscess, cutaneous vasculitis
Hematologic	At least 5 cases reported in English-language literature		Hemophagocytosis syndrome

From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of *Salmonella enterica* serotype Typhi infection, *Lancet Infect Dis* 5:341–348, 2005.

The propensity to become a carrier follows the epidemiology of gallbladder disease, increasing with patient age and the antibiotic resistance of the prevalent strains. Although limited data are available, rates of chronic carriage are generally lower in children than adults.

Diagnosis

The mainstay of the diagnosis of typhoid fever is a positive result of culture from the blood or another anatomic site. Results of blood cultures are positive in 40–60% of the patients seen early in the course of the disease, and serial blood cultures may be required to identify *Salmonella* bacteremia. Stool and urine culture results may become positive after the 1st wk. The stool culture result is also occasionally positive during the incubation period. The sensitivity of blood cultures in diagnosing typhoid fever in many parts of the developing world is limited. Widespread liberal antibiotic use may render bacteriologic confirmation even more difficult. Bone marrow cultures may increase the likelihood of bacteriologic confirmation of typhoid and may provide a diagnosis for patients with classic fever of unknown origin caused by *Salmonella* . Still, collection of bone marrow specimens is difficult and relatively invasive.

Results of other laboratory investigations are nonspecific. Although blood leukocyte counts are frequently low in relation to the fever and toxicity, there is a wide range in counts; in younger children leukocytosis is common and may reach 20,000-25,000 cells/µL. Thrombocytopenia may be a marker of severe illness and may accompany DIC. Liver function test results may be deranged, but significant hepatic dysfunction is rare.

The classic **Widal test** measures antibodies against O and H antigens of *S.* Typhi but lacks sensitivity and specificity in endemic areas. Because many false-positive and false-negative results occur, diagnosis of typhoid fever by Widal test alone is prone to error. Other relatively newer diagnostic tests using monoclonal antibodies have been developed that directly detect *S.* Typhi–specific antigens in the serum or *S.* Typhi Vi antigen in the urine. However, few have proved sufficiently robust in large-scale evaluations. A nested polymerase chain reaction (PCR) analysis using *H1-d* primers has been used to amplify specific genes of *S.* Typhi in the blood of patients; it is a promising means of making a rapid diagnosis, especially given the low level of bacteremia in enteric fever. Despite these innovations, the mainstay of diagnosis of typhoid remains clinical in much of the developing world, and several diagnostic algorithms have been evaluated in endemic areas.

Differential Diagnosis

In endemic areas, typhoid fever may mimic many common febrile illnesses without localizing signs. In children with multisystem features and no localizing signs, the early stages of enteric fever may be confused with alternative conditions, such as acute gastroenteritis, bronchitis, and bronchopneumonia. Subsequently, the differential diagnosis includes malaria; sepsis with other bacterial pathogens; infections caused by intracellular microorganisms, such as tuberculosis, brucellosis, tularemia, leptospirosis, and rickettsial diseases; and viral infections such as Dengue fever, acute hepatitis, and infectious mononucleosis.

Infection by *Salmonella* in general, and typhoid or paratyphoid fever in particular, should be thoroughly considered in the differential diagnosis and workup for fever in a returned traveler.

Treatment

An early diagnosis of typhoid fever and institution of appropriate treatment are essential. The vast majority of children with typhoid fever can be managed at home with oral antibiotics and close medical follow-up for complications or failure of response to therapy. Patients with persistent vomiting, severe diarrhea, and abdominal distention may require hospitalization and parenteral antibiotic therapy.

There are general principles of typhoid fever management. Adequate rest, hydration, and attention are important to correct fluid and electrolyte imbalance. Antipyretic therapy (acetaminophen 10-15 mg/kg every 4-6 hr PO) should be provided as required. A soft, easily digestible diet should be continued unless the patient has abdominal distention or ileus. Antibiotic therapy is critical to minimize complications (Table 225.6). It has been suggested that traditional therapy with either chloramphenicol or amoxicillin is associated with relapse rates of 5–15% and 4–8%, respectively, whereas use of the azithromycin, quinolones and third-generation cephalosporins is associated with higher cure rates. The antibiotic treatment of typhoid fever in children is also influenced by the prevalence of antimicrobial resistance. Over the past 2 decades, emergence of MDR strains of *S.* Typhi (i.e., isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) has necessitated treatment with **fluoroquinolones** , which are the antimicrobial drug of choice for treatment of salmonellosis in adults, with cephalosporins as an alternative. Some regions are also reporting *S.* Typhi that produce extended-spectrum β-lactamases. Fig. 225.7 shows known worldwide distribution patterns of antimicrobial resistance among *S.* Typhi isolates.

Table 225.6

Treatment of Typhoid Fever in Children

SUSCEPTIBILITY	OPTIMAL THERAPY			ALTERNATIVE EFFECTIVE DRUGS		
	Antibiotic	**Daily Dose (mg/kg/day)**	**Days**	**Antibiotic**	**Daily Dose (mg/kg/day)**	**Days**
UNCOMPLICATED TYPHOID FEVER						
Fully sensitive	Chloramphenicol	50-75	14-21	Fluoroquinolone, e.g., ofloxacin or ciprofloxacin	15	5-7[*]
	Amoxicillin	75-100	14			
Multidrug resistant	Fluoroquinolone	15	5-7	Azithromycin	8-10	7
	or					
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone resistant [†]	Azithromycin	8-10	7	Cefixime	20	7-14
	or					
	Ceftriaxone	75	10-14			
SEVERE TYPHOID FEVER						
Fully sensitive	Fluoroquinolone (e.g., ofloxacin)	15	10-14	Chloramphenicol	100	14-21
				Amoxicillin	100	
Multidrug resistant	Fluoroquinolone	15	10-14	Ceftriaxone	60	10-14
				or		
				Cefotaxime [‡]	80	10-14
Quinolone resistant	Ceftriaxone	60	10-14	Azithromycin	10-20	7
	Cefotaxime [‡]	80	10-14	Fluoroquinolone	20	7-14

[*] A 3-day course is also effective, particularly for epidemic containment.

[†] The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, third-generation cephalosporins, or high-dose fluoroquinolones for 10-14 days is effective.

[‡] If available.

Adapted from World Health Organization: Treatment of typhoid fever. In *Background document: the diagnosis, prevention and treatment of typhoid fever.* Communicable disease surveillance and response: vaccines and biologicals, Geneva, 2003, WHO, pp 19–23. http://whqlibdoc.who.int/hq/2003/WHO_V&B_03.07.pdf .

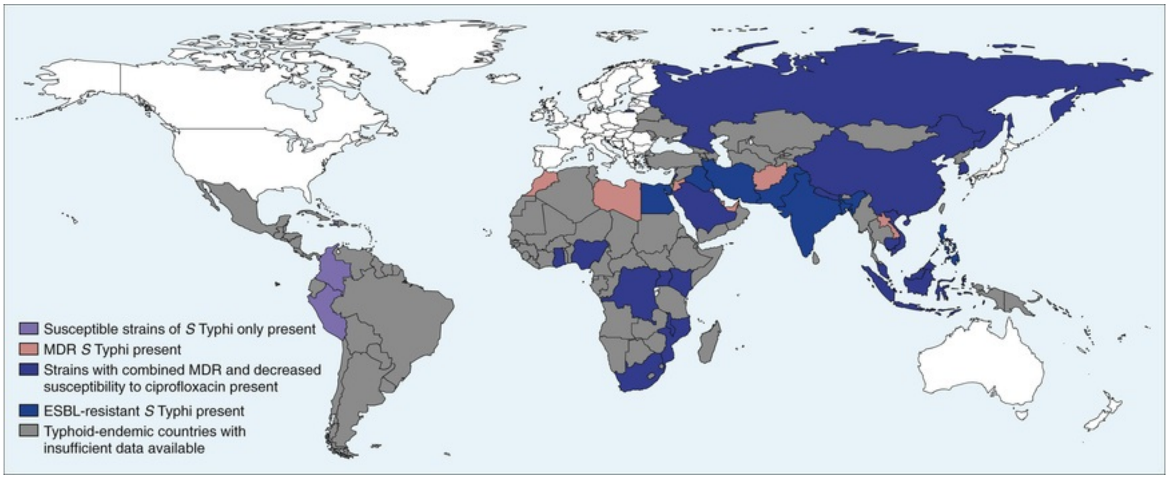
Susceptible strains of S Typhi only present
MDR S Typhi present
Strains with combined MDR and decreased susceptibility to ciprofloxacin present
ESBL-resistant S Typhi present
Typhoid-endemic countries with insufficient data available

FIG. 225.7 Worldwide distribution of antimicrobial drug resistance in *Salmonella enterica* serovar Typhi. Multidrug resistant (MDR) is defined as resistance to the first-line antimicrobial drugs ampicillin, co-trimoxazole, and chloramphenicol. ESBL, Extended-spectrum β-lactamase-producer. (From Wain J, Hendriksen RS, Mikoleit ML et al: Typhoid fever, *Lancet* 385(9973):1136–1145, 2015.)

Given the global movement of humans, foods, and bacteria, contemporary resistance tracking is a highly dynamic and international endeavor. Accordingly, pediatricians should seek to use important updates from reporting networks such as the World Health Organization's **Global Foodborne Infections Network** (WHO-GFN, formerly WHO Salmonella Surveillance Network), PulseNet, and ProMED.

Yet again, a strong microbiology laboratory infrastructure is important for optimal medical decision-making, because *Salmonella* susceptibilities and viable treatment options are often highly dependent on local, and changing, conditions. *Salmonella* strains that are highly resistant to the drugs listed for treatment in Table 225.6 still may have in vitro susceptibility to (notably expensive) newer therapeutics, such as carbapenem class drugs and tigecycline. In some locales, a reemergence of susceptibility to conventional drugs has been noted among some clinical isolates of *S.* Typhi.

Although some investigators suggest that children with typhoid fever should be treated with fluoroquinolones like adults, others question this approach because of the potential development of further resistance to fluoroquinolones and because quinolones are still not approved for widespread use in children. A Cochrane review of the treatment of typhoid fever also indicates that there is little evidence to support the protocolized administration of fluoroquinolones in all cases of typhoid fever. ***Azithromycin*** *may be an alternative antibiotic for* *children with uncomplicated typhoid fever.* The European Committee on Antibiotic Susceptibility Testing has characterized azithromycin susceptible *S.* typhi isolates as those with minimal inhibitory concentration of ≤16 mg/L.

In addition to antibiotics, the importance of supportive treatment and maintenance of appropriate fluid and electrolyte balance must be underscored. Although additional treatment with dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hr for 48 hr) is recommended for severely ill patients with shock, obtundation, stupor, or coma, corticosteroids should be administered only under strict controlled conditions and supervision, because their use may mask signs of abdominal complications.

Prognosis

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and institution of appropriate antibiotic therapy. Other factors are the patient/s, age, general state of health, and nutrition; the causative *Salmonella* serotype; and the appearance of complications. Infants and children with underlying malnutrition and patients infected with MDR isolates are at higher risk for adverse outcomes.

Despite appropriate therapy, 2–4% of infected children may experience relapse after initial clinical response to treatment. Individuals who excrete *S.* Typhi for ≥3 mo after infection are regarded as chronic carriers**.** The risk for becoming a carrier is low in most children (<2% for all infected children) and increases with age. A chronic urinary carrier state can develop in children with schistosomiasis.

Prevention

Of the major risk factors for outbreaks of typhoid fever, **contamination of water supplies** with sewage is the most important. Other risk factors for development of typhoid fever are congestion, contact with another acutely infected individual or a chronic carrier, and lack of water and sanitation services. During outbreaks, central chlorination as well as domestic water purification is important. In endemic situations, consumption of street foods, especially ice cream and cut fruit, is recognized as an important risk factor. The human-to-human spread by chronic carriers is also important, and attempts should be made to target food handlers and high-risk groups for *S.* Typhi carriage screening. Once identified, chronic carriers must be counseled as to the risk for disease transmission and the importance of handwashing.

A variety of vaccines targeting typhoid fever exist, but this remains a disease for which our vaccination protection for children lags, despite that disease risk factors, transmission patterns, and antibacterial drug resistance among salmonellae should make effective immunization an important element of effective control.

The classic heat-inactivated whole cell vaccine for typhoid is associated with an unacceptably high rate of side effects and has been largely withdrawn from public health use.

An oral, live-attenuated preparation of the **Ty21a strain** of *S.* Typhi has efficacy in endemic regions of 67–82% for up to 5 yr. Significant adverse effects are rare, but as a live-attenuated vaccine, Ty21a should not be used by immunocompromised persons. Proguanil, mefloquine, and antibiotics should be stopped from 3 days before until 3 days after the administration of Ty21a.The duration of protection following Ty21a immunization may vary with vaccine dose, and probably with subsequent “booster-like” exposures to *S.* typhi. Indeed, the recommended vaccination schedules for Ty21a vary in different countries.

The Vi capsular polysaccharide can be used in persons ≥2 yr old. It is given as a single intramuscular dose, with a booster every 2 yr, and has a protective efficacy of 70–80%. The vaccines are currently recommended for anyone traveling into endemic areas, but a few countries have introduced large-scale vaccination strategies. Several large-scale projects using the Vi polysaccharide vaccine in Asia have demonstrated protective efficacy against typhoid fever across all age-groups, but the data on protection among young children (<5 yr old) showed intriguing differences between studies.

Protein-conjugated Vi polysaccharide vaccines have been shown to have high efficacy in young children and thus may offer protection in parts of the world where a large proportion of preschool children are at risk for typhoid fever. These conjugated vaccines have been licensed in some countries but are not currently licensed or available in the United States.

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CHAPTER 226

Shigella

Patrick C. Seed

Shigellosis , infection by *Shigella* species, is acute invasive enteric infection clinically manifested by diarrhea that is often bloody. The term **dysentery** describes a syndrome of bloody diarrhea with fever, abdominal cramps, rectal pain, and mucoid stools. **Bacillary dysentery** is a term often used to distinguish dysentery caused by *Shigella* from amebic dysentery caused by *Entamoeba histolytica* .

Etiology

Four species of *Shigella* are responsible for shigellosis: *Shigella dysenteriae* (group A), *Shigella flexneri* (group B), *Shigella boydii* (group C), and *Shigella sonnei* (group D). Serotypes are used to distinguish members of each group: 15, 19, 19, and 1 in groups A-D, respectively. Species/group distributions vary geographically and have important therapeutic implications because of variations in species antimicrobial susceptibility.

Epidemiology

The World Health Organization (WHO) estimates 80-165 million cases of shigellosis each year worldwide and 600,000 deaths annually. *Shigella* spp. are endemic to temperate and tropical climates. Most of these cases and deaths occur in developing countries where public health sanitation and hygiene are inadequate. In the U.S. Foodborne Disease Active Surveillance Network (**FoodNet**), *Shigella* remains the 3rd most important pathogen. In 2016 the top 3 pathogens, *Salmonella* , *Campylobacter* , and *Shigella*, had laboratory-confirmed incidence rates (cases per 100,000 population) of 15.74, 12.82, and 5.39, respectively. Although infection can occur at any age, children <10 yr old have the highest incidence rates, with males having an approximately 1.3-fold higher incidence than females. Approximately 70% of all episodes and 60% of all *Shigella* -related deaths involve children <5 yr old. Infection in the 1st 6 mo of life is rare for reasons that are not clear. Breast milk from women living in endemic areas contains antibodies to both virulence plasmid-coded antigens and lipopolysaccharides, and breastfeeding might partially explain the age-related incidence.

Asymptomatic infection of children and adults occurs frequently in endemic areas. In cases of *Shigella* dysentery, up to 75% of family member contacts may have asymptomatic infection. Infection with *Shigella* occurs most often during the warm months in temperate climates and during the rainy season in tropical climates. In industrialized societies, up to 50% of locally diagnosed cases are associated with international travel; the highest-risk travel designation is Africa, followed by Central America, South America, and parts of Asia. In recent years in the United States, travel to Haiti, the Dominican Republic, and India, in particular, have been associated with antibiotic-resistant (fluoroquinolone) *S. sonnei* infections. Additional risk factors include men who have sex with men (MSM), including recent U.S. outbreaks of azithromycin-resistant *S. sonnei* infections among affected individuals in the Midwest.

In developed countries, *S. sonnei* is the most common cause and *S. flexneri* is the 2nd most common cause of bacillary dysentery; in preindustrial societies, *S. flexneri* is most common, and *S. sonnei* 2nd in frequency. *S. boydii* is found primarily in India. *S. dysenteriae* serotype 1 tends to occur in massive epidemics, but is also endemic in Asia and Africa, where it is associated with high mortality rates (5–15%). The epidemiologic transition has favored the emergence of *S. sonnei* as the dominant serogroup in some countries, although the reason for this epidemiologic shift is not clear.

Contaminated food (often a salad or other item requiring extensive handling of the ingredients) and water are important vectors. Exposure to both contaminated fresh water and contaminated salt water is a risk factor for infection. Rapid spread within families, custodial institutions, and childcare centers demonstrates the ability of *Shigella* to be transmitted from one individual to the next and the requirement for ingestion of very few organisms to cause illness. Human challenge studies have demonstrated the high infectivity and low infectious dose for *Shigella* spp. Ten bacteria of the species *S. sonnei* and *S.*

dysenteriae can cause dysentery. In contrast, ingestion of 10^8 -10^{10} *Vibrio cholerae* is necessary to cause cholera.

Pathogenesis

Shigella has specialized mechanisms to survive the low gastric pH. *Shigella* survives the acid environment in the stomach and moves through the gut to the colon, its target organ. The basic virulence trait shared by all shigellae is the ability to invade colonic epithelial cells by turning on a series of temperature-regulated and host-dependent proteins. This invasion mechanism is encoded on a large (220 kb) plasmid that at body temperature results in synthesis of a group of polypeptides involved in cell invasion and killing. Shigellae that lose the virulence plasmid are no longer pathogenic. **Enteroinvasive** *Escherichia coli* (EIEC) that harbor a closely related plasmid containing these invasion genes behave clinically similar to shigellae (see Chapter 227). The virulence plasmid encodes a type III secretion system required to trigger entry into epithelial cells and apoptosis in macrophages. This secretion system translocates effector molecules from the bacterial cytoplasm to the membrane and cytoplasm of target host cells through a needle-like appendage. The **type III secretion system** is composed of approximately 50 proteins, including the Mxi and Spa proteins involved in assembly and regulation of the type III secretion system, chaperones (IpgA, IpgC, IpgE, and Spa15), transcription activators (VirF, VirB, and MxiE), translocators (IpaB, IpaC, and IpaD), and approximately 30 effector proteins. In addition to the major plasmid-encoded virulence traits, chromosomally encoded factors are also required for full virulence.

The pathologic changes of shigellosis take place primarily in the colon. The changes are most intense in the distal colon, although pancolitis can occur. Shigellae cross the colonic epithelium through M cells in the follicle-associated epithelium overlying the Peyer patches. Grossly, localized or diffuse mucosal edema, ulcerations, friable mucosa, bleeding, and exudate may be seen. Microscopically, ulcerations, pseudomembranes, epithelial cell death, infiltration extending from the mucosa to the muscularis mucosae by PMNs and mononuclear cells, and submucosal edema occur.

After *Shigella* transcytosis through M cells, it encounters resident macrophages and subverts macrophage killing by activating the inflammasome and inducing pyroptosis, apoptosis, and proinflammatory signaling. Free bacteria invade the epithelial cells from the basolateral side, move into the cytoplasm by actin polymerization, and spread to adjacent cells. Proinflammatory signaling by macrophages and epithelial cells further activates the innate immune response involving natural killer cells and attracts polymorphonuclear leukocytes (PMNs). The influx of PMNs disintegrates the epithelial cell lining, which initially exacerbates the infection and tissue destruction by facilitating the invasion of more bacteria. Ultimately, PMNs phagocytose and kill *Shigella* , thus contributing to the resolution of the infection.

Some shigellae make toxins, including Shiga toxin and enterotoxins. **Shiga toxin** is a potent exotoxin that inhibits protein synthesis. It is produced in significant amounts by *S. dysenteriae* serotype 1, by a subset of *E. coli* , which are known as **enterohemorrhagic** *E. coli* (EHEC), or Shiga toxin–producing *E. coli* , and occasionally by other *Shigella* spp. Shiga toxin inhibits protein synthesis to injure vascular endothelial cells and trigger the severe complication of hemolytic-uremic syndrome (see Chapter 227). Targeted deletion of the genes for other enterotoxins *(ShET1* and *ShET2)* decreases the incidence of fever and dysentery in human challenge studies. Lipopolysaccharides are virulence factors for all shigellae; other traits are important for only a few serotypes (e.g., Shiga toxin synthesis by *S. dysenteriae* serotype 1 and *ShET1* by *S. flexneri* 2a).

Immunity

In symptomatic infection, *Shigella* activates an intense innate immune response through triggering extra- and intracellular pathogen recognition systems. The induction of acute inflammation with a massive recruitment of PMNs produces intensive local tissue destruction. In rectal biopsies of infected patients, acute-phase proinflammatory cytokines are induced, including interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α, and TNF-β. Concurrently, antiinflammatory genes encoding IL-10 and transforming growth factor-β are also upregulated to mitigate uncontrolled inflammation. Furthermore, interferon-γ expression is induced during human infection and is required to limit *Shigella* invasion in intestinal epithelial cells and macrophages. *Shigella* -specific immunity elicited upon natural infection is characterized by the induction of a humoral response. Local secretory immunoglobulin A (IgA) and serum IgG are produced against lipopolysaccharide and some protein effectors (Ipas). Protection is thought to be serotype specific. Natural protective immunity arises only after several episodes of infection, is of short duration, and seems to be effective in limiting reinfection, particularly in young children. However, children have delayed and reduced antigen-specific antibody-secreting cells with late and reduced mucosa IgA production against *Shigella* . Less effective adaptive immunity may put children at more risk for increased disease severity, mortality, and recurrences.

Clinical Manifestations and Complications

Shigellae produce intra- and extraintestinal symptoms. *Bacillary dysentery is clinically similar regardless of infecting serotype* . However, different species produce illnesses with different severity and risk for mortality, with *S. dysenteriae* type 1 most likely to produce any single manifestation and with greater severity. Ingestion of shigellae is followed by an incubation period of 12 hr to several days before symptoms ensue. Severe abdominal pain, emesis, anorexia, generalized toxicity, urgency, and painful defecation characteristically occur (Table 226.1). The typically high **fever** with shigellosis distinguishes it from EHEC. The **diarrhea** may be watery and of large volume initially, evolving into frequent, small-volume, bloody mucoid stools. Most children never progress to the stage of bloody diarrhea, but some have bloody stools from the outset. Significant dehydration is related to the fluid and electrolyte losses in feces and emesis. Untreated diarrhea can last 7-10 days; only approximately 10% of patients have diarrhea persisting for >10 days. Persistent diarrhea occurs in malnourished infants, children with AIDS, and occasionally previously normal children. Even nondysenteric disease can be complicated by persistent illness.

Table 226.1

Acute Clinical Manifestations of Shigellosis in Children <5 Yr Old

MANIFESTATION	DYSENTERY ($n = 757$)	WATERY DIARRHEA ($n = 288$)
Fever	607 (80%)	207 (72%)
Abdominal cramps	616 (81%)	137 (48%)
Vomiting	136 (18%)	89 (31%)
WHO-defined dehydration	95 (13%)	134 (47%)
Tenesmus	511 (68%)	32 (11%)
Rectal prolapse	19 (3%)	4 (1%)

From Kotloff KL, Riddle MS, Platts-Mills JA, et al: Shigellosis, *Lancet* 391:801–810, 2018.

Physical examination initially shows abdominal distention and tenderness, hyperactive bowel sounds, and a tender rectum on digital examination. **Rectal prolapse** may be present, particularly in malnourished children. Neurologic findings are among the most common extraintestinal manifestations of bacillary dysentery, occurring in as many as 40% of hospitalized children. EIEC can cause similar neurologic toxicity. Convulsions, headache, lethargy, confusion, nuchal rigidity, or hallucinations may be present before or after the onset of diarrhea. The cause of these neurologic findings is not understood. Infections with Shiga toxin positive and negative strains can lead to neurologic features. **Seizures** sometimes occur when little fever is present, suggesting that simple febrile convulsions do not explain their appearance. Hypocalcemia or hyponatremia may be associated with seizures in a small number of patients. Although symptoms often suggest central nervous system infection, and cerebrospinal fluid pleocytosis with minimally elevated protein levels can occur, meningitis caused by shigellae is rare. Based on animal studies, it has been suggested that proinflammatory mediators, including TNF-α and IL-1β, nitric oxide, and corticotropin-releasing hormone, all play a role in the enhanced susceptibility to *Shigella* -mediated seizures and encephalopathy.

The most common complication of shigellosis is **dehydration** (Table 226.2). Inappropriate secretion of antidiuretic hormone with profound hyponatremia can complicate dysentery, particularly when *S. dysenteriae* is the etiologic agent. Hypoglycemia and protein-losing enteropathy are common and are decreased by early appropriate antibiotic therapy. Severe protein-losing enteropathy is associated with prolonged illness and linear growth shortfalls. **Bacteremia** is uncommon except in girls or women infected with HIV, malnourished children, young infants, and children with *S. dysenteriae* serotype 1 infection. When bacteremia occurs with dysentery (<5%), it is as likely to be caused by other enteric bacteria as by *Shigella* itself. The presence of *E. coli, Klebsiella* , and other enteric bacteria in blood cultures of children with shigellosis may reflect the loss of the barrier function during severe colitis. The mortality rate is high (approximately 20%) when sepsis occurs, with a greater likelihood of occurrence in HIV-infected persons. Other major complications include **disseminated intravascular coagulation** (DIC), particularly in very young, malnourished children. Despite the extent to which the intestinal epithelial barrier is lost, bacteremia and DIC are uncommon.

Table 226.2

Clinical Complications of Shigellosis

INTESTINAL COMPLICATIONS
Rectal prolapse[*]
Toxic megacolon
Intestinal perforation
Intestinal obstruction
Appendicitis
Persistent diarrhea
EXTRAINTESTINAL COMPLICATIONS
Dehydration
Severe hyponatremia (serum sodium <126 mmol/L)[*]
Hypoglycemia
Focal infections (e.g., meningitis, osteomyelitis, arthritis, splenic abscesses, vaginitis)
Sepsis, usually in malnourished or immunocompromised persons
Seizure or encephalopathy
Leukemoid reaction (peripheral leukocytes >40 000/µL)[*]
POSTINFECTIOUS MANIFESTATIONS
Hemolytic-uremic syndrome (HUS)[*]
Reactive arthritis [†]
Irritable bowel syndrome (IBS) [‡]
Malnutrition

[*] Significantly more common in episodes with *Shigella dysenteriae* type 1 than with all other *Shigella* spp. among Bangladeshi children younger than 15 yr during the 1990s (rectal prolapse [52% vs 15%], severe hyponatremia [58% vs 26%], leukemoid reaction [22% vs 2%], and HUS [8% vs 1%]).

[†] Typical acute symptoms include asymmetric oligoarthritis (usually lower limb), enthesitis, dactylitis, and back pain. Extraarticular manifestations include conjunctivitis and uveitis; urethritis and other genitourinary tract manifestations; oral, skin, and nail lesions; and rarely, cardiac abnormalities.

[‡] IBS follows approximately 4% of *Shigella* episodes in studies from high-resource settings.

Adapted from Kotloff KL, Riddle MS, Platts-Mills JA, et al: Shigellosis, *Lancet* 391:801–810, 2018.

Neonatal shigellosis is rare, particularly among the exclusively breastfed. Neonates may have only low-grade fever with mild, nonbloody diarrhea. However, complications occur more often in neonates than in older children and include septicemia, meningitis, dehydration, colonic perforation, and toxic megacolon.

S. dysenteriae serotype 1 infection is frequently complicated by hemolysis, anemia, and **hemolytic-uremic syndrome** . HUS is caused by Shiga toxin–mediated vascular endothelial injury. Shiga- toxin–producing non-*dysenteriae Shigella* and *E. coli* that produce Shiga toxins (e.g., *E. coli* O157:H7, *E. coli* O111:NM, *E. coli* O26:H11, and less often, many other serotypes) also cause HUS (see Chapter 538.5).

Rectal prolapse, toxic megacolon or pseudomembranous colitis (usually associated with *S. dysenteriae*), cholestatic hepatitis, conjunctivitis, iritis, corneal ulcers, pneumonia, arthritis (usually 2-5 wk after enteritis), reactive arthritis, cystitis, myocarditis, and vaginitis (typically with blood-tinged discharge associated with *S. flexneri*) are uncommon events. Although rare, surgical complications of shigellosis can be severe; the most common are intestinal obstruction and appendicitis with and without perforation.

On average, the severity of illness and risk of death are least with disease caused by *S. sonnei* and greatest with infection by *S. dysenteriae* type 1. Risk groups for severe illness and poor outcomes include infants; children who are not breastfed; children with HIV; children recovering from measles; malnourished children and adults; adults >50 yr old; and patients with dehydration, unconsciousness, hypo- or hyperthermia, hyponatremia, or lesser stool frequency who have a history of convulsion when first seen. Death is a rare outcome in well-nourished older children. Multiple factors contribute to death in malnourished children with shigellosis, including illness in the 1st yr of life, altered consciousness, dehydration, hypothermia, thrombocytopenia, anemia, hyponatremia, renal failure, hyperkalemia hypoglycemia, bronchopneumonia, and bacteremia.

The rare syndrome of severe toxicity, convulsions, extreme hyperpyrexia, and headache, followed by brain edema and a rapidly fatal outcome without sepsis or significant dehydration (Ekiri syndrome or “lethal toxic encephalopathy”), is not well understood.

Differential Diagnosis

Although clinical features suggest shigellosis, they are insufficiently specific to allow confident diagnosis. Infection by *Campylobacter jejuni* , *Salmonella* spp., EIEC, Shiga toxin–producing *E. coli* (e.g., *E. coli* O157:H7), *Yersinia enterocolitica* , *Clostridium difficile* , and *Entamoeba histolytica,* as well as inflammatory bowel disease, produce overlapping features and may challenge the clinician.

Diagnosis

Presumptive data supporting a diagnosis of bacillary dysentery include the finding of fecal leukocytes (usually >50 or 100 PMNs per high-power field, confirming the presence of colitis), fecal blood, and demonstration in peripheral blood of leukocytosis with a dramatic left shift (often with more bands than segmented neutrophils). The total peripheral white blood cell count is usually 5,000-15,000 cells/µL, although leukopenia and leukemoid reactions occur.

Culture of both stool and rectal swab specimens optimizes the chance of diagnosing *Shigella* infection. Culture media should include MacConkey agar as well as selective media such as xylose-lysine-deoxycholate and *Salmonella-Shigella* agar. Transport media should be used if specimens cannot be cultured promptly. Appropriate media should be used to exclude *Campylobacter* and *Salmonella* spp. and other agents. Studies of outbreaks and illness in volunteers show that the laboratory is often not able to confirm the clinical suspicion of shigellosis even when the pathogen is present. Multiple fecal cultures improve the yield of *Shigella* .

Culture-based diagnosis of *Shigella* infection, as with other enteric infections, is being displaced by molecular methods, often multiplexed, allowing testing for a panel of potential agents in a single assay. Studies using molecular methods such as polymerase chain reaction (PCR) suggest that culture significantly underestimates the true frequency of infection. Quantitative PCR improves ascertainment of *Shigella* burden in children with moderate to severe diarrhea in low-income countries. The generally **high negative predictive value** (NPV) of many molecular tests for *Shigella* (generally >95–97%) make the tests useful for decisions regarding antibiotic discontinuation and the necessity to test for addition etiologies of diarrhea. The diagnostic inadequacy of cultures makes it incumbent on the clinician to use judgment in the management of clinical syndromes consistent with shigellosis. In children who appear toxic, blood cultures should be obtained, especially in very young or malnourished infants, because of their increased risk of bacteremia.

Treatment

As with gastroenteritis from other causes, the first concern in a child with suspected shigellosis should be for fluid and electrolyte correction and maintenance (see Chapter 366). Drugs that impair intestinal motility (e.g., diphenoxylate hydrochloride with atropine [Lomotil] or loperamide [Imodium]) should not be used because of the risk of prolonging the illness.

Nutrition is a key concern in areas where malnutrition is common. A high-protein and high-caloric diet during convalescence enhances growth in 6 mo after infection. Controlled studies show that cooked green bananas, a food rich in amylase-resistant starches, significantly improves outcome in severe disease. A single large dose of **vitamin A** (200,000 IU) lessens the severity of shigellosis in settings where vitamin A deficiency is common. **Zinc** supplementation (20 mg elemental zinc for 14 days) significantly decreases the duration of diarrhea, improves weight gain during recovery, enhances adaptive immunity to the *Shigella* , and decreases diarrheal disease in malnourished children.

The decision to use **antibiotics** remains challenging (Fig. 226.1). Many experts recommend withholding antibacterial therapy because of the self-limited nature of the infection, the cost of drugs, the risk of emergence of resistant organisms, the risk of prolonging carriage (if *Salmonella* is present), or increasing the risk for HUS (EHEC). However, a counter argument of empirical treatment for all children with suspected shigellosis has validity. Untreated illness can cause a child to have prolonged illness; chronic or recurrent diarrhea can ensue. Malnutrition can develop or worsen during prolonged illness, particularly in children in developing countries. The risk of continued excretion and subsequent infection of family contacts further argues against the strategy of withholding antibiotics.

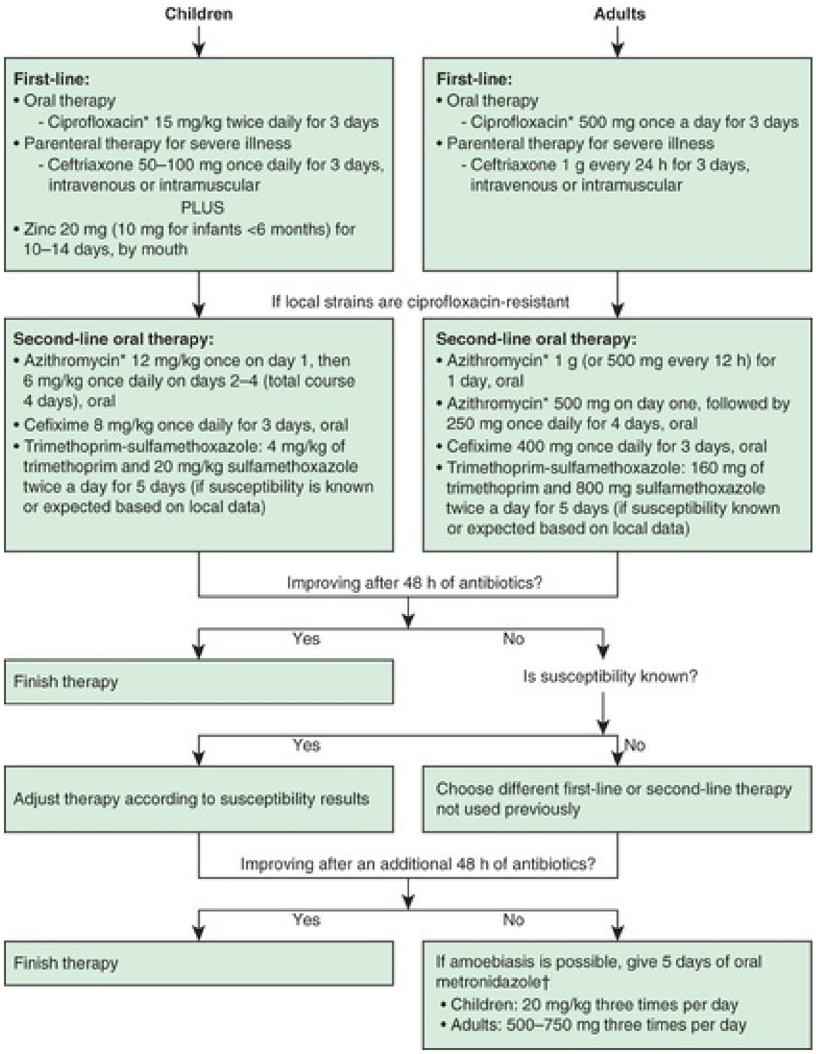
Children
Adults
First-line:
• Oral therapy
- Ciprofloxacin* 15 mg/kg twice daily for 3 days
• Parenteral therapy for severe illness
- Ceftriaxone 50–100 mg once daily for 3 days, intravenous or intramuscular
PLUS
• Zinc 20 mg (10 mg for infants <6 months) for 10–14 days, by mouth
First-line:
• Oral therapy
- Ciprofloxacin* 500 mg once a day for 3 days
• Parenteral therapy for severe illness
- Ceftriaxone 1 g every 24 h for 3 days, intravenous or intramuscular
If local strains are ciprofloxacin-resistant
Second-line oral therapy:
• Azithromycin* 12 mg/kg once on day 1, then 6 mg/kg once daily on days 2–4 (total course 4 days), oral
• Cefixime 8 mg/kg once daily for 3 days, oral
• Trimethoprim-sulfamethoxazole: 4 mg/kg of trimethoprim and 20 mg/kg sulfamethoxazole twice a day for 5 days (if susceptibility is known or expected based on local data)
Second-line oral therapy:
• Azithromycin* 1 g (or 500 mg every 12 h) for 1 day, oral
• Azithromycin* 500 mg on day one, followed by 250 mg once daily for 4 days, oral
• Cefixime 400 mg once daily for 3 days, oral
• Trimethoprim-sulfamethoxazole: 160 mg of trimethoprim and 800 mg sulfamethoxazole twice a day for 5 days (if susceptibility known or expected based on local data)
Improving after 48 h of antibiotics?
Yes
No
Finish therapy
Is susceptibility known?
Yes
No
Adjust therapy according to susceptibility results
Choose different first-line or second-line therapy not used previously
Improving after an additional 48 h of antibiotics?
Yes
No
Finish therapy
If amoebiasis is possible, give 5 days of oral metronidazole†
• Children: 20 mg/kg three times per day
• Adults: 500–750 mg three times per day

FIG. 226.1 **Management algorithm: guidelines for treatment of shigellosis. Empirical therapy should be directed by hospital, clinical laboratory, or public health antibiograms whenever possible. Minimal inhibitory concentrations of 0·12-1·0 μg/mL for ciprofloxacin might be considered susceptible by laboratory standards but could harbor resistance genes known to confer decreased susceptibility. *Azithromycin and fluoroquinolones should be used with caution in patients taking the antimalarial artemether, because these drugs can prolong the QT interval on the electrocardiogram and trigger arrhythmias. † Per WHO recommendations. Another acceptable regimen is a 7-10 day course of metronidazole followed by a luminal agent such as paromomycin or diiodohydroxyquinoline. (From World Health Organization: The selection and use of essential medicines, March, 2017. http://www.who.int/medicines/publications/essentialmedicines/en/ .)**

Shigella antimicrobial susceptibility varies by species and geography. In the United States, strains are frequently resistant to ampicillin (74%) and trimethoprim-sulfamethoxazole (TMP-SMX) (36%). In general, the proportion of antibiotic-resistant isolates is lower in North America and Europe than in Asia or Africa. Previously, *Shigella* was widely regarded as susceptible in vitro to azithromycin, ceftriaxone, cefotaxime, cefixime, nalidixic acid, and quinolones.

However, the CDC reports that 87% of *S. sonnei*– related U.S. cases are ciprofloxacin nonsusceptible, of which only approximately half followed international travel. Among MSM, clusters of shigellosis caused by *S. sonnei* and to a lesser extent *S. flexnerii* were reported with up to 87% azithromycin resistance. International travel increases the risk for antibiotic-resistant infection. For example, Chinese isolates of *S. sonnei* are often resistant to TMP-SMX (94.5%), ampicillin (40.3%), piperacillin (36.5%), and ceftriaxone (12.8%).

Currently, in most developed and developing countries, *Shigella* strains are often resistant to ampicillin and TMP-SMX. Therefore, these drugs should not be used for empirical treatment of suspected shigellosis; they should be instituted only if the strain is known to be susceptible (e.g., in an outbreak caused by a defined strain). Empirical therapy in children with dysentery should be given based on considerations of regional infection cluster data and international travel history. Therapy may include azithromycin, a third-generation cephalosporin, or ciprofloxacin. **Ceftriaxone** (50-100 mg/kg/24 hr as a single daily dose intravenously or intramuscularly) can be used for empirical therapy, especially for small infants. The oral third-generation cephalosporin **cefixime** (8 mg/kg/24 hr divided every 12-24 hr) can also be used; however, oral first- and second-generation cephalosporins are inadequate as alternative drugs despite in vitro susceptibility. **Azithromycin** (12 mg/kg/24 hr orally for the 1st day, followed by 6 mg/kg/24 hr for the next 4 days) has proved to be an effective alternative drug for shigellosis. **Ciprofloxacin** (20-30 mg/kg/24 hr divided into 2 doses) is the drug of choice recommended by WHO for all patients with bloody diarrhea, regardless of age. Concurrent zinc supplementation is recommended with antibiotic therapy.

Although **quinolones** are reported to cause arthropathy in immature animals and are associated with neuropathy, these risks are low in children and are outweighed by the value of these drugs for the treatment of this potentially life-threatening disease. However, some experts recommend that the quinolones be reserved for seriously ill children with bacillary dysentery caused by an organism suspected or known to be resistant to other agents, because overuse of quinolones promotes the development of resistance to these drugs.

Treatment of patients in whom *Shigella* infection is suspected on clinical grounds should be initiated when these patients are first evaluated. Molecular stool testing or culture is obtained to exclude other pathogens and, in the case of culture, to assist in antibiotic changes should a child fail to respond to empirical therapy. A child who has typical dysentery and who responds to initial empirical antibiotic treatment should be continued on that drug for a full 5-day course even if the stool culture is negative, due to the method's low NPV. The logic of this recommendation is based on the proven difficulty of culturing *Shigella* from stools of ill patients during adult volunteer infection studies. In a child who fails to respond to therapy of a dysenteric syndrome in the presence of initially negative stool culture results, additional cultures should be obtained, or molecular testing, where available and cost permissive, should be performed, and the child should be reevaluated for other possible diagnoses. In the child with negative molecular stool testing for shigellae, the high NPV makes the diagnosis less likely, and alternative diagnoses should be considered.

Prevention

Numerous measures have been recommended to decrease the risk of *Shigella* transmission to children. Mothers should be encouraged to *prolong breastfeeding* of infants. Families and daycare personnel should be educated in *proper handwashing* techniques and encouraged to wash hands after using the toilet, changing diapers, or engaging in preparation of foods. They should be taught how to manage potentially contaminated materials such as raw vegetables, soiled diapers, and diaper-changing areas. Children with diarrhea should be excluded from childcare facilities. Children should be supervised when handwashing after they use the toilet. Caretakers should be informed of the risk of transmission if they prepare food when they are ill with diarrhea. Families should be educated regarding danger of swallowing contaminated water from ponds, lakes, or untreated pools. In developing countries, a safe water supply and appropriate sanitation systems are important measures for reducing the risk for shigellosis. There is not yet a vaccine that is effective for preventing infection by *Shigella* . **Measles immunization** can substantially reduce the incidence and severity of diarrheal diseases, including shigellosis. Every infant should be immunized against measles at the recommended age.

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CHAPTER 227

Escherichia coli

Patrick C. Seed

Escherichia coli is an important cause of intraintestinal and extraintestinal infections. **Intraintestinal infections** present as different diarrheal illnesses. **Extraintestinal infections** include disease of the urinary tract (see Chapter 553) and bloodstream (Chapters 129 , 202 , and 203). Intraintestinal **pathogenic** *E. coli* , also called **enteric** *E. coli* , produce diarrheal diseases. *E. coli* causing extra- and intraintestinal infections are highly specialized with unique genetic attributes that encode different sets of virulence factors and genetic programs. Extraintestinal pathogenic *E. coli* increasingly harbor multidrug resistances, including transferrable plasmids resulting in extended-spectrum β-lactamase (ESBL) production. This results in resistance to penicillins, cephalosporins, and aztreonam. Carbapenemase-bearing *E. coli* have also emerged, often in combination with multi–antibiotic class resistance, resulting in highly drug-resistant strains.

Escherichia coli species are members of the Enterobacteriaceae family. They are facultative anaerobic, gram-negative bacilli that usually ferment lactose. Most fecal *E. coli* organisms are commensal, are ubiquitous among humans starting in the 1st mo of life, and do not cause diarrhea. Six major groups of **diarrheagenic** *E. coli* pathotypes have been characterized on the basis of clinical biochemical, and molecular-genetic criteria: enterotoxigenic *E. coli* (ETEC); enteroinvasive *E. coli* (EIEC); enteropathogenic *E. coli* (EPEC); *Shiga* toxin–producing *E. coli* (STEC), also known as enterohemorrhagic *E. coli* (EHEC) or verotoxin-producing *E. coli* (VTEC); enteroaggregative *E. coli* (EAEC or EggEC); and diffusely adherent *E. coli* (DAEC).

E. coli strains can also be categorized by their serogroup, where *O* refers to the lipopolysaccharide (LPS) O-antigen or serotype and *H* refers to the flagellar antigen, for example, *E. coli* O157:H7. However, because each pathotype contains many serotypes (e.g., 117 ETEC serotypes have been identified), and some serotypes can belong to more than 1 pathotype (e.g., O26:H11 can be either EPEC or EHEC, depending on which specific virulence genes are present), serotyping frequently does not provide definitive identification of pathotypes.

Because *E. coli* are normal fecal flora, pathogenicity is defined by demonstration of virulence characteristics and association of those traits with illness (Table 227.1). The mechanism by which *E. coli* produces **diarrhea** typically involves adherence of organisms to a glycoprotein or glycolipid receptor on a target intestinal cell, followed by production of a factor that injures or disturbs the function of intestinal cells. The genes for virulence properties and antibiotic resistance are often carried on transferable plasmids, pathogenicity islands, or bacteriophages. In the developing world, the various diarrheagenic *E. coli* strains cause frequent infections in the 1st years of life; diarrheagenic *E. coli* as a group are responsible for 30-40% of all diarrhea cases in children worldwide. They occur with increased frequency during the warm months in temperate climates and during rainy season months in tropical climates. Most diarrheagenic *E. coli* strains (except STEC) require a large inoculum of organisms to induce disease, thus necessitating exposure to grossly contaminated ingestible materials. Infection is most likely when food-handling or sewage-disposal practices are suboptimal. The diarrheagenic *E. coli* pathotypes are also important in North America and Europe, although their epidemiology is less well defined in these areas than in the developing world. In North America, the various diarrheagenic *E.* coli strains may cause as much as 30% of infectious diarrhea in children <5 yr old.

Table 227.1

Clinical Characteristics, Pathogenesis, and Diagnosis of Diarrheagenic *E. coli*

PATHOGEN	POPULATIONS AT RISK	CHARACTERISTICS OF DIARRHEA			MAIN VIRULENCE FACTORS		DIAGNOSIS
		Watery	**Bloody**	**Duration**	**Adherence Factors**	**Toxins**	
ETEC	>1 yr old and travelers	+++	—	Acute	Colonization factor antigens (CFs or CFAs); ECP	Heat-labile enterotoxin (LT) Heat-stable enterotoxin	Detection of enterotoxins (LT and ST) by enzyme immunoassays

						(ST)	or PCR (*lt*, *st*)
EIEC	>1 yr old	+	++	Acute	Invasion plasmid antigen (IpaABCD)		Detection of invasion plasmid antigen of *Shigella* (*ipaH*) by PCR
EPEC	<2 yr old	+++	+	Acute, prolonged or persistent	A/E lesion, intimin/Tir, EspABD, Bfp	EspF, Map, EAST1, SPATEs (*EspC*)	Detection of intimin gene (*eae*) ± bundle-forming pili (*bfp* A) by PCR, and absence of *Shiga* toxins; HEp-2 cells adherence assay (LA, LLA)
STEC (EHEC/VTEC)	6 mo-10 yr and elderly persons	+	+++	Acute	A/E lesion, intimin/Tir, EspABD	*Shiga* toxins (Stx1, Stx2, and variants of Stx2)	Detection of *Shiga* toxins by enzyme immunoassays or PCR (*Stx* 1, *Stx* 2); stool culture on MacConkey-sorbitol media to detect *E. coli* O157. Simultaneous culture for O157 and nonculture assays to detect *Shiga* toxins
EAEC	<2 yr old, HIV-infected patients, and travelers	+++	+	Acute, prolonged, or persistent	Aggregative adherence fimbriae (AAF)	SPATEs (Pic, Pet), ShET1, EAST1	Detection of *AggR* , AA plasmid, and other virulence genes: *aap* , *aatA* , *astA* , *set1A* by PCR; HEp-2 cells adherence assay (AA)
DAEC	>1 yr old and travelers	++	—	Acute	Afa/Dr, AIDA-I	SPATEs (Sat)	Detection of Dr adhesins (daaC or daaD) and Dr-associated genes by PCR; HEp-2 cells adherence

							assay (DA)

—, Not present; +, present; ++, common; +++, very common; A/E lesion, attaching and effacing lesion; AA, aggregative adherence; Bfp, bundle-forming pili; DA, diffuse adherence; DAEC, diffusely adherent *E. coli;* EAEC, enteroaggregative *E. coli;* EAST1, enteroaggregative heat-stable toxin; ECP, *E. coli* common pilus; EHEC, enterohemorrhagic *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli* ; EspABD, *E. coli* –secreted proteins A, B, and D; ETEC, enterotoxigenic *E. coli;* LA, localized adherence; LLA, localized-like adherence; PCR, polymerase chain reaction; ShET1, *Shigella* enterotoxin 1; SPATEs, serine-protease autotransporter of Enterobacteriaceae; STEC, *Shiga* toxin–producing *E. coli* ; Tir, translocated intimin receptor; VTEC, verotoxin-producing *E. coli.*

Many studies have found diarrheagenic *E. coli* pathotypes in a significant proportion of asymptomatic healthy children living in developing countries. **Fecal contamination** (human and animal), which is common in the low-resource environments where many young children live, facilitates the transmission of pathogens. Also, with modern, highly sensitive microbiologic methods, small numbers of bacteria can be detected in stool samples. Therefore, it is important to assess the prevalence of various enteropathogens in children with and without diarrhea to interpret results. Excretion of enteropathogens by children without diarrhea may be explained by characteristics of the pathogens (virulence heterogeneity), the host (host susceptibility, age, nutritional status, breastfeeding, immunity), and environmental factors (inoculum size).

Enterotoxigenic *Escherichia coli*

ETEC accounts for a sizable fraction of dehydrating infantile diarrhea in the developing world (10–30%) and of **traveler's diarrhea** (20–60% of cases); ETEC is the most common cause of traveler's diarrhea. In the Global Enteric Multicenter Study (GEMS) conducted across Asia and Africa, *heat-stable* enterotoxin (ST)–expressing ETEC (with or without coexpression of *heat-labile* enterotoxin [LT]) was among the most important causes of diarrhea in young children in developing countries and was associated with increased risk of death. The typical signs and symptoms include explosive watery, nonmucoid, nonbloody diarrhea; abdominal pain; nausea; vomiting; and little or no fever. The illness is usually self-limited and resolves in 3-5 days but occasionally lasts >1 wk.

ETEC causes few or no structural alterations in the gut mucosa. Diarrhea follows colonization of the small intestine and elaboration of enterotoxins. ETEC strains secrete an LT and/or an ST. LT, a large molecule consisting of 5 receptor-binding subunits and 1 enzymatically active subunit, is structurally, functionally, and neutralizing antibody cross-reactive with cholera toxin produced by *Vibrio cholerae* . LT stimulates adenylate cyclase, resulting in increased cyclic adenosine monophosphate. ST is a small molecule not related to cholera toxin. ST stimulates guanylate cyclase, resulting in increased cyclic guanosine monophosphate. Each toxin induces ion and water secretion into the intestinal lumen, resulting in profuse watery diarrhea. The genes for these toxins are encoded on plasmids.

Colonization of the intestine requires fimbrial **colonization factor antigens (CFAs)** , which promote adhesion to the intestinal epithelium. Over 25 CFA types exist and can be expressed alone or in combinations. Prevalent colonization factors include CFA/I, CS1-CS7, CS14, and CS17. However, CFAs have not been detected on all ETEC strains. Although 30–50% of ETEC isolates have no characterized CFA by phenotypic screening, novel CFAs continue to be identified. CFAs are highly immunogenic. However, the multiple CFAs and their allelic variants have made the definition of immunity and development of useful vaccines difficult. A large proportion of strains produce a type IV pilus called *longus* , which functions as a colonization factor and is found among several other gram-negative bacterial pathogens. ETEC strains also have the common pilus, produced by commensal and pathogenic *E. coli* strains. Among the nonfimbrial adhesions, TibA is a potent bacterial adhesin that mediates bacterial attachment and invasion of cells. For many years, the O serogroup was used to distinguish pathogenic from commensal *E. coli* . Because the pathogenic *E. coli* are now defined and classified by using probes or primers for specific virulence genes, determining the O serogroup has become less important. Of the >180 *E. coli* serogroups, only a relatively small number typically are ETEC. The most common O groups are O6, O8, O128, and O153, and based on some large retrospective studies, these serogroups account for only half the ETEC strains.

Enteroinvasive *Escherichia coli*

Clinically, EIEC infections present either with watery diarrhea or a dysentery syndrome with blood, mucus, and leukocytes in the stools, as well as fever, systemic toxicity, crampy abdominal pain, tenesmus, and urgency. The illness resembles **bacillary dysentery** because EIEC shares virulence genes with *Shigella* spp. Sequencing of multiple housekeeping genes indicates that EIEC is more related to *Shigella* than to noninvasive *E. coli* . EIEC diarrhea occurs mostly in outbreaks; however, endemic disease occurs in developing countries. In some areas of the developing world as many as 5% of sporadic diarrhea episodes and 20% of bloody diarrhea cases are caused by EIEC (see Chapter 226).

EIEC disease resembles **shigellosis** . EIEC cause colonic lesions with ulcerations, hemorrhage, mucosal and submucosal edema, and infiltration by polymorphonuclear leukocytes (PMNs). EIEC strains behave like *Shigella* in their capacity to invade gut epithelium and produce a dysentery-like illness. The invasive process involves initial entry into cells, intracellular multiplication, intracellular and intercellular spread, and host cell death. All bacterial genes necessary for entry into the host cell are clustered within a 30-kb region of a large virulence plasmid; these genes are closely related to those found on the invasion plasmid of *Shigella* spp. This region carries genes encoding the entry-mediating proteins, including proteins that form a needle-like injection apparatus called type III secretion, required for secreting the invasins (IpaA-D and IpgD). The Ipas are the primary effector proteins of epithelial cell invasion. The type III secretion apparatus is a system triggered by contact with host cells; bacteria use it to transport proteins into the host cell plasma membrane and inject toxins into the host cell cytoplasm.

EIEC encompasses a small number of serogroups (O28ac, O29, O112ac, O124, O136, O143, O144, O152, O159, O164, O167, and some untypeable strains). These serogroups have LPS antigens related to *Shigella* LPS, and as with shigellae, are nonmotile (they lack H or flagellar antigens) and are usually non–lactose fermenting.

Enteropathogenic *Escherichia coli*

EPEC causes acute, prolonged, and persistent diarrhea, primarily in children <2 yr old in developing countries, where the organism may account for 20% of infant diarrhea. In developed countries, EPEC cause occasional daycare center and pediatric ward outbreaks. Profuse watery, nonbloody diarrhea with mucus, vomiting, and low-grade fever are common symptoms. Prolonged diarrhea (>7 days) and persistent diarrhea (>14 days) can lead to **malnutrition** , a potentially mortality-associated outcome of EPEC infection in infants in the developing world. Studies show that breastfeeding is protective against diarrhea caused by EPEC.

EPEC colonization causes blunting of intestinal villi, local inflammatory changes, and sloughing of superficial mucosal cells; EPEC-induced lesions extend from the duodenum through the colon. EPEC induces a characteristic attaching and effacing histopathologic lesion, which is defined by the intimate attachment of bacteria to the epithelial surface and effacement of host cell microvilli. Factors responsible for the attaching and effacing lesion formation are encoded by the *locus of enterocyte effacement* (LEE), a pathogenicity island with genes for a type III secretion system, the translocated intimin receptor (Tir) and intimin, and multiple effector proteins such as the *E. coli* –secreted proteins (EspA-B-D). Some strains adhere to the host intestinal epithelium in a pattern known as *localized adherence* , a trait that is mediated in part by the type IV bundle-forming pilus (Bfp) encoded by a plasmid (the EAF plasmid). After initial contact, proteins are translocated through filamentous appendages forming a physical bridge between the bacteria and the host cell; bacterial effectors (EspB, EspD, Tir) are translocated through these conduits. Tir moves to the surface of host cells, where it is bound by a bacterial outer membrane protein intimin (encoded by the *eae* gene). Intimin-Tir binding triggers polymerization of actin and other cytoskeletal components at the site of attachment. These cytoskeletal changes result in intimate bacterial attachment to the host cell, enterocyte effacement, and pedestal formation.

Other LEE-encoded effectors include Map, EspF, EspG, EspH, and SepZ. Various other effector proteins are encoded outside the LEE and secreted by the type III secretion system (the non–LEE-encoded proteins, or Nle). The contribution of these putative effectors (NleA/EspI, NleB, NleC, NleD, etc.) to virulence is still under investigation. The presence and expression of virulence genes vary among EPEC strains.

The *eae* (intimin) and *bfp* A genes are useful for identifying EPEC and for subdividing this group of bacteria into typical and atypical strains. *E. coli* strains that are *eae* $^{+}$ /*bfp* A^{+} are classified as “typical” EPEC; most of these strains belong to common O:H serotypes. *E. coli* strains that are *eae* $^{+}$ /*bfp* A^{-} are classified as “atypical” EPEC. Typical EPEC has been considered for many years to be a leading cause of infantile diarrhea in developing countries and was considered rare in industrialized countries. However, current data suggest that atypical EPEC are more prevalent than typical EPEC in both developed and developing countries, even in persistent diarrhea cases. Determining which of these heterogeneous strains are true pathogens remains a work in progress. In the GEMS, typical EPEC was the main pathogen associated with increased risk of mortality, particularly in infants in Africa.

The classic EPEC serogroups include strains of 12 O serogroups: O26, O55, O86, O111, O114, O119, O125, O126, O127, O128, O142, and O158. However, various *E. coli* strains defined as EPEC based on the presence of the intimin gene belong to nonclassic EPEC serogroups, especially the atypical strains.

Shiga Toxin–Producing *Escherichia coli*

STEC causes a broad spectrum of diseases. STEC infections may be asymptomatic. Patients who develop intestinal symptoms can have mild diarrhea or severe hemorrhagic colitis. Abdominal pain with initially watery diarrhea that may become bloody over several days characterizes STEC illness. Infrequent fever differentiates STEC disease from the otherwise similar appearance of shigellosis or EIEC disease. Most persons with STEC recover from the infection without further complication. However, 5–10% of children with STEC hemorrhagic colitis go on within a few days to develop systemic complications such as **hemolytic-uremic syndrome** (HUS), characterized by acute kidney failure, thrombocytopenia, and microangiopathic hemolytic anemia (see Chapter 538). Severe illness occurs most often among children 6 mo to 10 yr old. Young children with STEC-associated bloody diarrhea and neutrophilic leukocytosis in the early course of their diarrhea are at risk for HUS progression. Older individuals can also develop HUS or thrombotic thrombocytopenic purpura.

STEC is transmitted person to person (e.g., in families and daycare centers) as well as by food and water; ingestion of a small number of organisms is sufficient to cause disease with some strains. Poorly cooked hamburger is a common cause of food-borne outbreaks, although many other foods (apple cider, lettuce, spinach, mayonnaise, salami, dry fermented sausage, and unpasteurized dairy products) have also been incriminated in STEC transmission.

STEC affects the colon most severely. These organisms adhere to intestinal cells, and most strains that affect humans produce attaching-effacing lesions such as those seen with EPEC and contain related genes (e.g., *intimin, Tir, EspA-D*). Unlike EPEC, STEC produces **Shiga toxins** (Stx; previously called verotoxins and Shiga- like) as key virulence factors. There are 2 major Shiga toxin families, Stx1 and Stx2, with multiple subtypes identified by letters (e.g., Stx2a, Stx2c). Some STEC produce only Stx1, and others produce only 1 of the variants of Stx2; many STEC have genes for several toxins. **Stx1** is essentially identical to Shiga toxin, the protein synthesis–inhibiting exotoxin of *Shigella dysenteriae* serotype 1. **Stx2** and variants of Stx2 are more distantly related to

Shiga toxin, although they share conserved sequences.

These ETEC Shiga toxins are composed of a single A subunit noncovalently associated with a pentamer composed of identical B subunits. The B subunits bind to globotriaosylceramide (Gb_3), a glycosphingolipid receptor on host cells. The A subunit is taken up by endocytosis. The toxin target is the 28S rRNA, which is depurated by the toxin at a specific adenine residue, causing protein synthesis to cease and affected cells to die. These toxins are carried on bacteriophages that are normally inactive (lysogenic) in the bacterial chromosome; when the phages are induced to replicate (e.g., by the stress induced by many antibiotics), they cause lysis of the bacteria and release of large amounts of toxin. Toxin translocation across the intestinal epithelium into the systemic circulation can lead to damage of vascular endothelial cells, resulting in activation of the coagulation cascade, formation of microthrombi, intravascular hemolysis, and ischemia.

The clinical outcome of an STEC infection depends on a strain-specific combination of epithelial attachment and the toxin factors. The Stx2 family of toxins is associated with a higher risk of causing HUS. Strains that make only Stx1 often cause only watery diarrhea and are infrequently associated with HUS.

The most common STEC serotypes are *E. coli* O157:H7, *E. coli* O111:NM, and *E. coli* O26:H11, although several hundred other STEC serotypes have also been described. *E. coli* **O157:H7** is the most virulent serotype and the serotype most frequently associated with HUS; however, other non-O157 serotypes also cause this illness.

Enteroaggregative *Escherichia coli*

EAEC is associated with (1) acute, prolonged and persistent pediatric diarrhea in developing countries, most prominently in children <2 yr old and in malnourished children; (2) acute and persistent diarrhea in HIV-infected adults and children; and (3) acute traveler's diarrhea; EAEC is the 2nd most common cause of traveler's diarrhea after ETEC. Typical EAEC illness is manifested by watery, mucoid, secretory diarrhea with low-grade fever and little or no vomiting. The watery diarrhea can persist for ≥14 days. In some studies, many patients have grossly bloody stools, indicating that EAEC cannot be excluded on stool characteristics. EAEC strains are associated with growth retardation and malnutrition in infants in the developing world.

EAEC organisms form a characteristic biofilm on the intestinal mucosa and induce shortening of the villi, hemorrhagic necrosis, and inflammatory responses. The proposed model of pathogenesis of EAEC infection involves 3 phases: adherence to the intestinal mucosa by way of the aggregative adherence fimbriae or related adhesins; enhanced production of mucus; and production of toxins and inflammation that results in damage to the mucosa and intestinal secretion. Diarrhea caused by EAEC is predominantly secretory. The intestinal inflammatory response (elevated fecal lactoferrin, interleukin [IL]-8 and IL-1β) may be related to growth impairment and malnutrition.

EAEC strains are recognized by adherence to HEp-2 cells in an aggregative, stacked-brick pattern, called *aggregative adherence* (AA). EAEC virulence factors include the AA fimbriae (AAF-I, -II, and -III) that confer the AA phenotype. Some strains produce toxins, including the plasmid-encoded enterotoxin EAST1 (encoded by *ast* A), a homolog of the ETEC ST; an autotransporter toxin called Pet; other STATE toxins; and the chromosomally encoded enterotoxin ShET1 (encoded by *setA* and *setB*). Other virulence factors include outer membrane and secreted proteins, such as dispersin (*aap*), and the dispersin transport complex (aatPABCD). EAEC is a heterogeneous group of *E. coli* . The original diagnostic criteria (HEp-2 cell adherence pattern) identified many strains that are probably not true pathogens; genetic criteria appear to more reliably identify true pathogens. A transcriptional activator called **AggR** controls the expression of plasmid-borne and chromosomal virulence factors. Identification of AggR appears to reliably identify illness-associated pathogenic EAEC strains (“typical” EAEC). EAEC *agg* R-positive strains carrying 1-3 of the genes *aap* , *ast* A, and *set1A* are significantly associated with diarrhea compared with EAEC isolates lacking these genes. Other than the factors AAF and AggR, EAEC strains are genetically diverse and thus display variable virulence. EAEC strains belong to multiple serogroups, including O3, O7, O15, O44, O77, O86, O126, and O127.

Diffusely Adherent *Escherichia coli*

Although the status of DAEC strains as true pathogens has been in doubt, multiple studies in both developed and developing countries have associated these organisms with diarrhea, particularly in children after the 1st 1-2 yr of life. DAEC strains isolated from children and adults seem to represent 2 different bacterial populations. **Age-dependent susceptibility** may explain discrepancies among epidemiologic studies to diarrhea or by the use of inappropriate detection methods. Data suggest that these organisms also cause traveler's diarrhea in adults. DAEC produces acute watery diarrhea that is usually not dysenteric but is often prolonged.

DAEC strains produce diffuse adherence in cultured epithelial cells. They express surface fimbriae (designated F1845) that are responsible for the **diffuse adherence** phenotype in a prototype strain. These fimbriae are homologous with members of the Afa/Dr family of adhesins, which are identified by hybridization with a specific probe, *daaC* , common to operons encoding Afa/Dr adhesions. A 2nd putative adhesin associated with the diffuse adherence pattern phenotype is an outer membrane protein, designated AIDA-I. The contribution of other putative effectors (*icuA, fimH, afa, agg-3A, pap* , *astA, shET1)* to virulence is still under investigation. The only documented secreted factor associated with DAEC infection is the serine-protease autotransporters of Enterobacteriaceae (SPATE) cytotoxin Sat. Bacteria expressing Afa/Dr adhesins interact with membrane-bound receptors, including decay-accelerating factor (DAF). The structural and functional lesions induced by DAEC include loss of microvilli and a decrease in the expression and enzyme activities of functional brush-border–associated proteins. Afa/Dr DAEC isolates produce a secreted autotransporter toxin that induces marked fluid accumulation in the intestine. DAEC strains typically induce IL-8 production in vitro. Serogroups of DAEC strains are less well defined than those of other diarrheagenic *E. coli* .

Enteroaggregative Hemorrhagic *Escherichia coli*

In 2011, a massive outbreak of an unusual O104:H4 strain of diarrheagenic *E. coli* began in Germany. Eventually, >4,000 individuals were sickened with hemorrhagic colitis; the outbreak involved primarily adults (<100 children were reported affected). More than 800 people developed HUS, and >50 of these individuals died. Genomic analysis suggested the outbreak strain was most closely related to EAEC and had acquired a lambdoid bacteriophage with genes for Shiga toxin Stx2a. It was thus a **hybrid** pathogen with colonization mechanisms similar to a typical EAEC strain and toxin production typical of an STEC strain. This outbreak strain carries Pic on the chromosome and a pAA-like plasmid encoding AAF, AggR, Pet, ShET1, and dispersin. A 2nd virulence plasmid encodes multiple antibiotic resistances. The high morbidity and mortality associated with this strain may reflect the stronger adherence of EAEC compared with STEC, delivering more Stx to target cells. Alternative terminology for this strain includes **enteroaggregative hemorrhagic *E. coli*** and **Shiga toxin–producing EAEC** . Whether Shiga toxin production in an EAEC background merits separate classification is unclear. Organisms with Shiga toxin genes in an atypical EPEC background were designated as a separate group (referred to as **STEC** , **EHEC** , or **verotoxin-producing *E. coli***) before the relative importance of the various genes was clear. EPEC strains are a heterogeneous group themselves. The important issue is not the nomenclature but rather the concept that virulence genes can move between *E. coli* , resulting in new variants.

Diagnosis

The features of illness are seldom distinctive enough to allow confident diagnosis strictly on clinical observations, and routine laboratory studies such as blood counts rarely prove effective in the diagnosis. Practical, non–DNA-dependent methods for routine diagnosis of diarrheagenic *E. coli* have been developed primarily for STEC. Serotype O157:H7 is suggested by isolation of an *E. coli* that fails to ferment sorbitol on MacConkey sorbitol medium; latex agglutination confirms that the organism contains O157 LPS. Other STEC strains can be detected in routine hospital laboratories using commercially available enzyme immunoassay or latex agglutination assays to detect Shiga toxins, although the variable sensitivity of commercial immunoassays has limited their value.

Although some STEC (O157:H7 strains) can be detected in routine microbiology laboratories using selective media and appropriate antisera, the diagnosis of other diarrheagenic *E. coli* infection is traditionally made based on tissue culture assays (e.g., HEp-2-cells assay for EPEC, EAEC, DAEC) or identification of specific virulence factors of the bacteria by phenotype (e.g., toxins) or genotype. Multiplex, real-time, or conventional polymerase chain reaction (PCR) can be used for presumptive diagnosis of isolated *E. coli* colonies. The genes commonly used for diagnostic PCR are *lt* and *st* for ETEC; *IpaH* or *iaL* for EIEC; *eae* and *bfp* A for EPEC; *eae, Stx1,* and *Stx2* for STEC; *AggR* or the AA plasmid for EAEC; and *daaC* or *daaD* for DAEC. Commercial assays such as the FilmArray Gastrointestinal Panel and Eurofins Diatherix

Panel now detect genetic markers for EPEC, EAEC, ETEC, STEC, and EIEC, among other pathogen genes, directly from a fecal sample in several hours.

Serotyping does not provide definitive identification of pathotypes (except for selected cases such as O157:H7) because each pathotype contains many serotypes and some serotypes can belong to >1 pathotype. Consequently, serotyping should not be used routinely for diarrheagenic *E. coli* identification in clinical laboratories (e.g., to diagnose EPEC in infantile diarrhea), except during an outbreak investigation.

Other laboratory data are at best *nonspecific* indicators of etiology. Fecal leukocyte examination of the stool is often positive with EIEC or occasionally positive with other diarrheagenic *E. coli* . With EIEC and STEC there may be an elevated peripheral blood PMN count with a left shift. Determination of *Stx2* blood levels in the early, postbloody diarrhea period may be useful to identify children at risk of HUS; however, this method requires further evaluation. Fecal lactoferrin, IL-8, and IL-1β can be used as inflammatory markers. Electrolyte changes are nonspecific, reflecting only fluid loss.

Treatment

The cornerstone of management is appropriate fluid and electrolyte therapy. In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization. Pedialyte and other readily available oral rehydration solutions are acceptable alternatives. After refeeding, continued supplementation with oral rehydration fluids is appropriate to prevent recurrence of dehydration. Early refeeding (within 6-8 hr of initiating rehydration) with breast milk or infant formula or solid foods should be encouraged. Prolonged withholding of feeding can lead to chronic diarrhea and malnutrition. If the child is malnourished, oral zinc should be given to speed recovery and decrease the risk of future diarrheal episodes.

Specific antimicrobial therapy of diarrheagenic *E. coli* is improving with accurate, rapid molecular diagnostic panels using direct fecal samples. However, the unpredictability of antibiotic susceptibilities remains problematic. Treatment is complicated by these organisms often being multiply resistant to antibiotics because of their previous exposure to inappropriate antibiotic therapy. Multiple studies in developing countries have found that diarrheagenic *E. coli* strains typically are resistant to antibiotics such as trimethoprim-sulfamethoxazole (TMP-SMX) and ampicillin (60–70%). Most data come from case series or clinical trials in adults with traveler's diarrhea. ETEC responds to antimicrobial agents such as TMP-SMX when the *E. coli* strains are susceptible. ETEC cases from traveler's diarrhea trials respond to ciprofloxacin, azithromycin, and rifaximin. However, other than for a child recently returning from travel in the developing world, empirical treatment of severe *watery diarrhea* with antibiotics is seldom appropriate.

In resource-poor settings where rapid molecular panel tests are not available, EIEC infections may be treated before culture results are finalized because the clinician suspects shigellosis and has begun empirical therapy. If the organisms prove to be susceptible, TMP-SMX is an appropriate choice. Although treatment of EPEC infection with TMP-SMX intravenously or orally for 5 days may be effective in speeding resolution, the lack of a rapid diagnostic test in the resource-poor setting makes treatment decisions difficult. Ciprofloxacin or rifaximin is useful for EAEC traveler's diarrhea, but pediatric data are sparse. Specific therapy for DAEC has not been defined.

The STEC strains represent a particularly difficult therapeutic dilemma; many antibiotics can induce bacterial stress, toxin production, and phage-mediated bacterial lysis with toxin release. Antibiotics should not be given for STEC infection because they can increase the risk of HUS (see Chapter 538). In settings with rapid molecular diagnostics, a delay in providing antibiotics is rarely consequential and can allow the clinician to more confidently recommend or exclude antibiotics from the therapeutic plan.

Prevention of Illness

In the developing world, prevention of disease caused by pediatric diarrheagenic *E. coli* is probably best done by maintaining prolonged breastfeeding, paying careful attention to personal hygiene, and following proper food- and water-handling procedures. People traveling to these places can be best protected by handwashing, consuming only processed water, bottled beverages, breads, fruit juices, fruits that can be peeled, or foods that are served steaming hot.

Prophylactic antibiotic therapy is effective in adult travelers but has not been studied in children and is not recommended. Public health measures, including sewage disposal and food-handling practices, have made pathogens that require large inocula to produce illness relatively uncommon in industrialized countries. Food-borne outbreaks of STEC are a problem for which no adequate solution has been found. During the occasional hospital outbreak of EPEC disease, attention to enteric isolation precautions and cohorting may be critical.

Protective immunity against diarrheagenic *E. coli* remains an active area of research, and no vaccines are available for clinical use in children. Multiple vaccine candidates based on bacterial toxins and colonization factors have shown promise for prevention of ETEC in adult travelers, but long-term protection with these vaccines has not been optimal, particularly in children.

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CHAPTER 228

Cholera

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Cholera is a dehydrating diarrheal disease that rapidly leads to death in the absence of immediate initiation of appropriate treatment. Worldwide, 1.3 billion people are at risk for cholera, resulting in an estimated 1 to 4 million cases and 95,000 deaths annually. Cholera is highly prone to producing outbreaks, and the ongoing outbreaks in Yemen and Haiti emphasize how cholera and potentially other infectious diseases can easily reemerge in areas that have long been considered free of the disease after a natural disaster or war-related conflicts.

Etiology

Cholera is caused by *Vibrio cholerae* , a gram-negative, comma-shaped bacillus, subdivided into serogroups by its somatic O antigen. Of the >200 serogroups, only serogroups O1 and O139 have been associated with epidemics, although some non-O1, non-O139 *V. cholerae* strains (e.g., O75, O141) are pathogenic and can cause small outbreaks. A flagellar H antigen is present but is not used for species identification. The O1 serogroup is further divided into classical and the El Tor biotypes based on its biochemical characteristics. Since the turn of the 21st century, only **O1 El Tor** has been reported; hybrids and variants of *V. cholerae* O1 El Tor possessing classical genes have been reported worldwide. These hybrid and variant strains have been associated with more severe disease.

Each biotype of *V. cholerae* can be further subdivided into Inaba, Ogawa, and Hikojima serotypes based on the antigenic determinants on the O antigen. **Inaba** strains have A and C antigenic determinants, whereas **Ogawa** strains have A and B antigenic determinants. **Hikojima** strains produce all 3 antigenic determinants but are unstable and rare. Recent studies reveal that serotype switching results from a selection process as yet unidentified.

Epidemiology

The 1st 6 cholera pandemics originated in the Indian subcontinent and were caused by classical O1 *V. cholerae* . The 7th pandemic is the most extensive of all and is caused by *V. cholerae* O1 El Tor. This pandemic began in 1961 in Sulawesi, Indonesia, and has spread to the Indian subcontinent, Southeast Asia, Africa, Oceania, Southern Europe, and the Americas. In 1991, *V. cholerae* O1 El Tor first appeared in Peru before rapidly spreading in the Americas. Cholera becomes **endemic** in areas following outbreaks when a large segment of the population develops immunity to the disease after recurrent exposure. The disease is now endemic in parts of Africa and Asia and in Haiti.

In 1992 the first non-O1 *V. cholerae* that resulted in epidemics was identified in India and Bangladesh and was designated *V. cholerae* **O139** . From 1992–1994, this organism replaced O1 as the predominant cause of cholera in South Asia but has since been an uncommon etiologic agent.

The hybrid El Tor strains were first identified sporadically in Bangladesh. In 2004, during routine surveillance in Mozambique, isolates of *V. cholerae* O1 El Tor carrying classical genes were identified. Since then, hybrid and variant El Tor strains have been reported in other parts of Asia and Africa and have caused outbreaks in India and Vietnam. Although the classical biotype has virtually disappeared, its genes remain within the El Tor biotype. The current circulating strain in Haiti is closely related to the South Asian strain.

Humans are the only known hosts for *V. cholerae*, but free-living and plankton-associated *V. cholerae* exist in the marine environment. The organism thrives best in moderately salty water but can survive in rivers and fresh water if nutrient levels are high, as occurs when there is organic pollution such as human feces. The formation of a biofilm on abiotic surfaces and the ability to enter a viable but nonculturable state have been hypothesized as factors that allow *V. cholerae* to persist in the environment. Surface sea temperature, pH, chlorophyll content, the presence of iron compounds and chitin, and climatic conditions such as amount of rainfall and sea level rise are all important environmental factors that influence the survival of *V. cholerae* in the environment and the expression of cholera toxin, an important virulence determinant.

Consumption of **contaminated water** and ingestion of **undercooked shellfish** are the main modes of transmission, with the latter more often seen in developed countries. In cholera-endemic areas, the incidence is highest among children <2 yr old; however, in epidemics, all age-groups are usually affected. Persons with blood group O, decreased gastric acidity, malnutrition, immunocompromised state, and absence of local intestinal immunity (prior exposure by infection or vaccination) are at increased risk for developing severe disease. Household contacts of cholera-infected patients are at high risk for the disease, because the stools of infected patients contain high concentrations of *V. cholerae* . Moreover, as *V. cholerae* organisms are shed, they enter into a hyperinfective state, requiring an infectious dose that is reduced by one-tenth to one-hundredth compared to organisms that were not shed by humans.

Pathogenesis

Large inocula of bacteria ($>10^8$ colony-forming units) are required for severe cholera to occur; however, for persons whose gastric barrier is disrupted, a much lower dose (10^5 CFUs) is required. After ingestion of *V. cholerae* from the environment, several changes occur in the vibrios as they traverse the human intestine: increased expression of genes required for nutrient acquisition, downregulation of chemotactic response, and expression of motility factors. Together these changes allow the vibrios to reach a hyperinfectious state, leading to lower infectious doses required to secondarily infect other persons. This hyperinfectivity may remain for 5-24 hr after excretion and is believed to be the predominant pathway for person-to-person transmission during epidemics.

If the vibrios survive gastric acidity, they colonize the small intestine through various factors such as toxin–co-regulated pili and motility, leading to efficient delivery of cholera toxin (Fig. 228.1). The cholera toxin consists of 5 binding B subunits and 1 active A subunit. The B subunits are responsible for binding to the GM_1 ganglioside receptors located in the small intestinal epithelial cells. After binding, the A subunit is released into the cell, where it stimulates adenylate cyclase and initiates a cascade of events. An increase in cyclic adenosine monophosphate leads to an increase in chloride secretion by the crypt cells, which in turn leads to inhibition of absorption of sodium and chloride by the microvilli. These events eventually lead to massive purging of electrolyte rich isotonic fluid in the small intestine that exceeds the absorptive capacity of the colon, resulting in rapid dehydration and depletion of electrolytes, including sodium, chloride, bicarbonate, and potassium. Metabolic acidosis and hypokalemia then ensue.

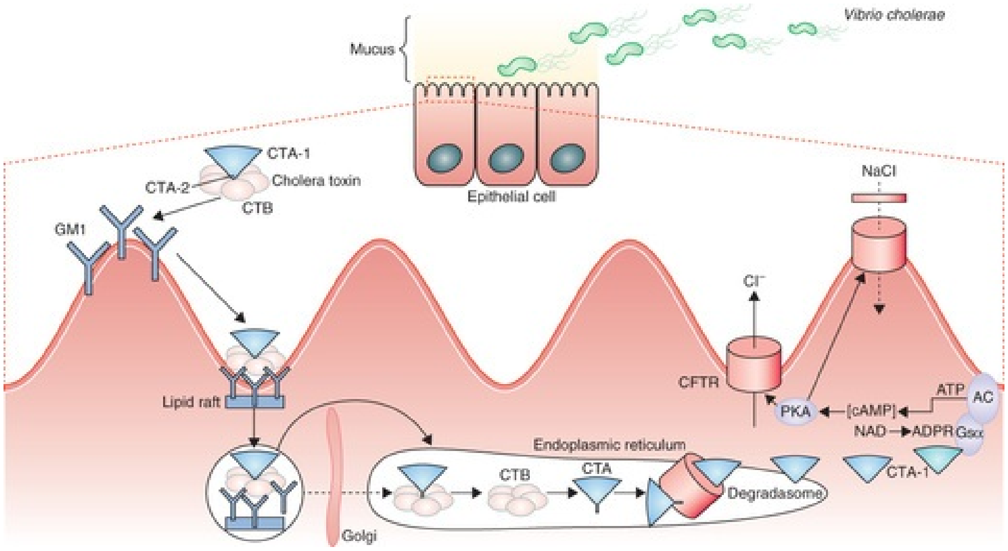

FIG. 228.1 **Cholera pathogenesis and cholera toxin action. After ingestion, *Vibrio cholerae* colonize the small intestine and secrete cholera toxin, which has a doughnut-like structure with a central enzymatic toxic-active A (CTA-1 + CTA-2) subunit associated with a pentameric B subunit (CTB). After binding to GM_1 ganglioside receptors on small intestinal epithelial cells, which are mainly localized in lipid rafts on the cell surface, the cholera toxin is endocytosed and transported to the degradosome via the endoplasmic reticulum (ER) by a retrograde pathway, which, dependent on cell type, may or may not involve passage through the Golgi apparatus. In the ER, CTA dissociates from CTB, allowing CTA-1 to reach the cytosol by being translocated through the degradosome pathway. In the cytosol, CTA-1 subunits rapidly refold and bind to the Gsα subunit of adenylate cyclase (AC) in the cell membrane; on binding, CTA-1 adenosine diphosphate (ADP)-ribosylates the Gsα subunit, which stimulates AC activity, leading to an increase in intracellular concentration of cyclic adenosine monophosphate (cAMP), activation of protein kinase A (PKA), phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR), a major chloride channel, and extracellular secretion of chloride ions (Cl^-) and water. Cholera toxin–induced Cl^- (and bicarbonate ion) secretion is particularly pronounced in intestinal crypt cells, whereas the increased intracellular cAMP concentrations in villus cells mainly inhibit the uptake of sodium chloride (NaCl) and water. (Adapted from Clemens J, Shin S, Sur D, et al: New-generation vaccines against cholera, *Nat Rev Gastroenterol Hepatol* 8:701–710, 2011; by permission of Nature Publishing Group.)**

Clinical Manifestations

Most cases of cholera are mild or inapparent. Among symptomatic individuals, approximately 20% develop severe **dehydration** that can rapidly lead to death. Following an incubation period of 1-3 days (range: several hours to 5 days), acute watery **diarrhea** and **vomiting** ensue. The onset may be sudden, with profuse watery diarrhea, but some patients have a prodrome of anorexia and abdominal discomfort and the stool may initially be brown. Diarrhea can progress to painless purging of profuse *rice-water stools* (suspended flecks of mucus) with a fishy smell, which is the hallmark of the disease (Figs. 228.2 and

228.3). Vomiting with clear watery fluid is usually present at the onset of the disease.

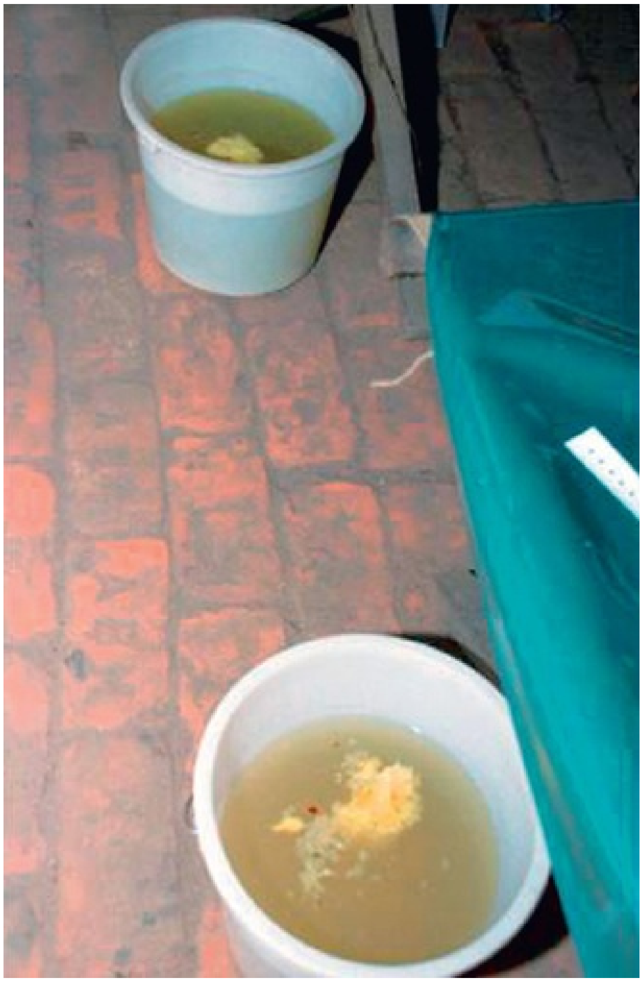

FIG. 228.2 Rice-water stool in a patient with cholera. (Modified from Harris JB, LaRocque RC, Qadri F: Cholera, *Lancet* 379:2466–2474, 2012.)

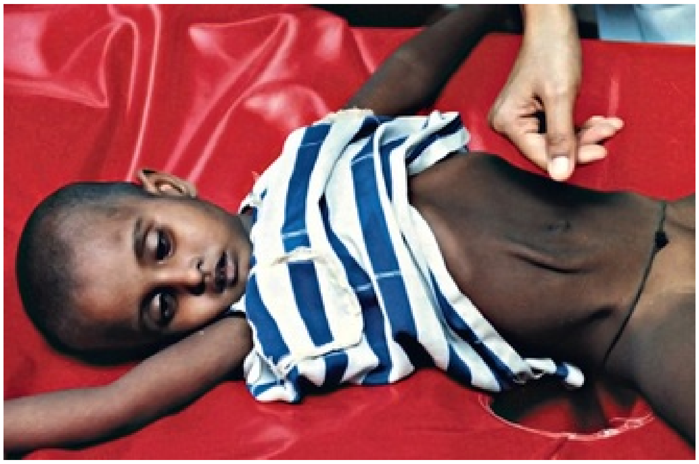

FIG. 228.3 A child, lying on a cholera cot, showing typical signs of severe dehydration from cholera. The patient has sunken eyes, lethargic appearance, and poor skin turgor, but within 2 hr was sitting up, alert, and eating normally. (From Sack DA, Sack RB, Nair GB, et al: Cholera, *Lancet* 363:223–233, 2004.)

Cholera gravis , the most severe form of the disease, results when purging rates of 500-1,000 mL/hr occur. This purging leads to dehydration manifested by decreased urine output, a sunken fontanel (in infants), sunken eyes, absence of tears, dry oral mucosa, shriveled hands and feet ("washerwoman's hands"), poor skin turgor, thready pulse, tachycardia, hypotension, and vascular collapse (Fig. 228.3). Patients with metabolic acidosis can present with typical Kussmaul breathing. Although patients may be initially thirsty and awake, they rapidly progress to obtundation and coma. If fluid losses are not rapidly corrected, death can occur within hours.

Laboratory Findings

Findings associated with dehydration such as elevated urine specific gravity and hemoconcentration are evident. **Hypoglycemia** is a common finding that is caused by decreased food intake during the acute illness. Serum potassium may be initially normal or even high in the presence of metabolic acidosis; however, as the acidosis is corrected, hypokalemia may become evident. Metabolic acidosis due to bicarbonate loss is a prominent finding in severe cholera. Serum sodium and chloride levels may be normal or decreased, depending on the severity of the disease.

Diagnosis and Differential Diagnosis

In children who have acute watery diarrhea with severe dehydration residing in a cholera-endemic area or who have recently traveled to an area known to have cholera, the disease may be suspected pending laboratory confirmation. Cholera differs from other diarrheal diseases in that it often occurs in *large outbreaks affecting both adults and children.* Treatment of dehydration should begin as soon as possible. Diarrhea caused by other etiologic causes (e.g., enterotoxigenic *Escherichia coli* or rotavirus) may be difficult to distinguish from cholera clinically. Microbiologic isolation of *V. cholerae* remains the gold standard for diagnosis. Although definitive diagnosis is not required for treatment to be initiated, laboratory confirmation is necessary for epidemiologic surveillance. *V. cholerae* may be isolated from stools, vomitus, or rectal swabs. Specimens may be transported on Cary-Blair media if they cannot be processed immediately. Selective media such as thiosulfate-citrate–bile salts sucrose agar that inhibit normal flora should be used. Because most laboratories in industrialized countries do not routinely culture for *V. cholerae* , clinicians should request appropriate cultures for clinically suspected cases.

Stool examination reveals few fecal leukocytes and erythrocytes because cholera does not cause inflammation. Dark-field microscopy may be used for rapid identification of typical *darting motility* in wet mounts of rice-water stools, a finding that disappears once specific antibodies against *V. cholerae* O1 or O139 are added. Rapid diagnostic tests are currently available and may be especially useful in areas with limited laboratory capacity, allowing early identification of cases at the onset of an outbreak and facilitating a timely response. Molecular identification with the use of polymerase chain reaction and DNA probes is available but often not used in areas where cholera exists.

Complications

Delayed initiation of rehydration therapy or inadequate rehydration often leads to complications. Renal failure from prolonged hypotension can occur. Unless potassium supplementation is provided, **hypokalemia** can lead to nephropathy and focal myocardial necrosis. Hypoglycemia is common among children and can lead to seizures unless it is appropriately corrected.

Treatment

Rehydration is the mainstay of therapy (see Chapter 69). Effective and timely case management decreases mortality considerably. Children with mild or moderate dehydration may be treated with oral rehydration solution (ORS) unless the patient is in shock, is obtunded, or has intestinal ileus. Vomiting is not a contraindication to ORS. Severely dehydrated patients require intravenous fluid, ideally with lactated Ringer solution. When available, rice-based ORS should be used during rehydration, because this fluid has been shown to be superior to standard ORS in children and adults with cholera. Close monitoring is necessary, especially during the 1st 24 hr of illness, when large amounts of stool may be passed. After rehydration, patients should be reassessed every 1-2 hr, or more frequently if profuse diarrhea is ongoing. Feeding should not be withheld during diarrhea. Frequent, small feedings are better tolerated than less frequent, large feedings.

Antibiotics should only be given in patients with moderately severe to severe dehydration (Table 228.1). As soon as vomiting stops (usually within 4-6 hr after initiation of rehydration therapy), an antibiotic to which local *V. cholerae* strains are sensitive must be administered. Antibiotics shorten the duration of illness, decrease fecal excretion of vibrios, decrease the volume of diarrhea, and reduce the fluid requirement during rehydration. Single-dose antibiotics increase compliance; doxycycline, ciprofloxacin, and azithromycin are effective against cholera. There are increasing reports of resistance to tetracyclines, trimethoprim-sulfamethoxazole, and other drugs. Because of these multidrug-resistant strains, antibiotic treatment must be tailored based on available susceptibility results from the area. The 2013 WHO guidelines recommend cotrimoxazole (4 mg trimethoprim/kg and 20 mg/kg sulfamethoxazole/kg twice daily) and chloramphenicol (20 mg/kg IM every 6 hr for 3 days) as possible alternative antibiotics for treatment. A recent systematic review, however, recommended the use of single-dose azithromycin (20 mg/kg) due to widespread antimicrobial resistance. Cephalosporins and aminoglycosides are not clinically effective against cholera and therefore should not be used, even if in vitro tests show strains to be sensitive.

Table 228.1

Recommended Antimicrobials for Cholera*

RECOMMENDING BODY	ANTIBIOTIC OF CHOICE	ALTERNATIVE
WHO[†] (antibiotics recommended for cases with severe dehydration)	**Adults** Doxycycline, 300 mg given as a single dose orally (PO) *or* Tetracycline, 500 mg 4 times a day × 3 days PO	**Adults** Erythromycin, 250 mg 4 times a day × 3 days PO
	Children Tetracycline, 12.5 mg/kg/dose 4 times a day × 3 days (up to 500 mg/dose × 3 days) PO	**Children** Erythromycin, 12.5 mg/kg/dose 4 times a day × 3 days (up to 250 mg 4 times a day × 3 days) PO
PAHO[‡] (antibiotics recommended for cases with moderate to severe dehydration)	**Adults** Doxycycline, 300 mg PO given as a single dose	**Adults** Ciprofloxacin, 1 g PO single dose *or* Azithromycin, 1 g PO single dose (first line for pregnant women)
	Children Erythromycin, 12.5 mg/kg/dose 4 times a day × 3 days (up to 500 mg/dose × 3 days) *or* Azithromycin, 20 mg/kg as a single dose (up to 1 g)	**Children** Ciprofloxacin, 20 mg/kg PO as a single dose *or* Doxycycline, 2-4 mg/kg PO as a single dose

[*] Antibiotic selection must be based on sensitivity patterns of strains of *Vibrio cholerae* O1 or O139 in the area.

[†] Adapted from World Health Organization: *The treatment of diarrhea: a manual for physicians and other senior health workers* , 4th revision, Geneva, 2005, WHO.

[‡] Adapted from Pan American Health Organization: *Recommendations for clinical management of cholera,* Washington, DC, 2010. http://new.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=10813&Itemid= .

Zinc should be given as soon as vomiting stops . Zinc deficiency is common among children in many developing countries. Zinc supplementation in children <5 yr old shortens the duration of diarrhea and reduces subsequent diarrhea episodes when given daily for 14 days at the time of the illness. Children <6 mo old should receive 10 mg of oral zinc daily for 2 wk, and children >6 mo should receive 20 mg of oral zinc daily for 2 wk.

Prevention

Improved personal hygiene, access to clean water, and sanitation are the mainstays of cholera control. Appropriate case management substantially decreases case fatalities to <1%. Travelers from developed countries often have no prior exposure to cholera and are therefore at risk of developing the disease. Children traveling to cholera-affected areas should avoid drinking potentially contaminated water and eating high-risk foods such as raw or undercooked fish and shellfish. No country or territory requires vaccination against cholera as a condition for entry.

In 2016, a live oral cholera vaccine, CVD 103 Hg-R (Vaxchora, PaxVax), was licensed in the United States for use in adults age 18-64 yr traveling to cholera-affected areas.

Alarmed by the increasing prevalence of cholera, in 2011 the World Health Assembly recommended the use of oral cholera vaccines to complement existing water, sanitation, and hygiene initiatives for cholera control. Older-generation parenteral cholera vaccines have not been recommended by World Health Organization (WHO) because of the limited protection they confer and their high reactogenicity. Oral cholera vaccines are safe, are protective for approximately 2-5 yr duration, and confer moderate herd protection. Three oral cholera vaccines are currently available internationally and recognized by WHO (Table 228.2). An internationally licensed killed whole cell oral cholera vaccine with recombinant B subunit (Dukoral, Crucell) has been available in >60 countries, including the European Union, and provides protection against cholera in endemic areas as well as cross-protection against certain strains of enterotoxigenic *E. coli* . The 2 other vaccines (Shanchol, Shantha Biotech; and Euvichol, Eubiologics) are variants of the 1st vaccine and contain the *V. cholerae* O1 and O139 antigens but do not contain the B subunit. Without the B subunit, these vaccines do not require buffer for administration, thereby reducing administration costs and resources, making them easier to deploy.

Table 228.2

Available Oral Cholera Vaccines*

VACCINE TRADE NAME	CONTENTS	DOSING SCHEDULE
Dukoral (Crucell)	1 mg of recombinant B subunit of cholera toxin plus 2.5 × 10^{10} colony-forming units of the following strains of *V. cholerae* : Formalin-killed El Tor Inaba (Phil 6973) Heat-killed classical Inaba (Cairo 48) Heat-killed classical Ogawa (Cairo 50) Formalin-killed classical Ogawa (Cairo 50)	Children 2-6 yr old: 3 doses, 1-6 wk apart Adults and children >6 yr old: 2 doses, 1-6 wk apart
Shanchol (Shantha Biotech) Euvichol (Eubiologics)	*V. cholerae* O1: 600 EU Formalin-killed El Tor Inaba (Phil 6973) 300 EU Heat-killed classical Inaba (Cairo 48) 300 EU Heat-killed classical Ogawa (Cairo 50) 300 EU Formalin-killed classical Ogawa (Cairo 50)	Adults and children ≥1 yr old: 2 doses, 2 wk apart

	V. cholerae O139-600 EU of Formalin-killed strain 4260B	

[*] WHO-prequalified vaccines.

Oral cholera vaccines have been available for >2 decades, and with the WHO declaration, countries are now using oral cholera vaccines in mass vaccination campaigns where cholera remains a substantial problem. A cholera vaccine stockpile, established by WHO, is now available and can be accessed by countries at risk for cholera, supplementing efforts to lessen the impact of this ongoing cholera scourge.

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CHAPTER 229

Campylobacter

Ericka V. Hayes

Campylobacter , typically *Campylobacter jejuni* and *Campylobacter coli* , are found globally and are among the most common causes of human intestinal infections. Clinical presentation varies by age and underlying conditions.

Etiology

Twenty-six species and 9 subspecies of *Campylobacter* are recognized (as of December 2014). Most of these have been isolated from humans, and many are considered pathogenic. The most significant of these are *C. jejuni* and *C. coli,* which are believed to cause the majority of human enteritis. More than 100 serotypes of *C. jejuni* have been identified. *C. jejuni* has been subspeciated into *C. jejuni* subsp. *jejuni* and *C. jejuni* subsp. *doylei.* Although *C. jejuni* subsp. *doylei* has been isolated from humans, it is much less common, less hardy, and more difficult to isolate. Other species, including *Campylobacter fetus, Campylobacter lari,* and *Campylobacter upsaliensis,* have been isolated from patients with diarrhea, although much less frequently (Table 229.1). Emerging *Campylobacter* spp. have been implicated in acute gastroenteritis, inflammatory bowel disease, and peritonitis, including *C. concisus* , and *C. ureolyticus* . Additional *Campylobacter* spp. have been isolated from clinical specimens, but their roles as pathogens have not been established.

Table 229.1

Campylobacter **Species Associated With Human Disease**

SPECIES	DISEASES IN HUMANS	COMMON SOURCES
C. jejuni	Gastroenteritis, bacteremia, Guillain-Barré	Poultry, raw milk, cats, dogs, cattle, swine,

	syndrome	monkeys, water
C. coli	Gastroenteritis, bacteremia	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, oysters, water
C. fetus	Bacteremia, meningitis, endocarditis, mycotic aneurysm, diarrhea	Sheep, cattle, birds, dogs
C. hyointestinalis	Diarrhea, bacteremia, proctitis	Swine, cattle, deer, hamsters, raw milk, oysters
C. lari	Diarrhea, colitis, appendicitis, bacteremia, UTI	Seagulls, water, poultry, cattle, dogs, cats, monkeys, oysters, mussels
C. upsaliensis	Diarrhea, bacteremia, abscesses, enteritis, colitis, hemolytic-uremic syndrome	Cats, dogs, other domestic pets
C. concisus	Diarrhea, gastritis, enteritis, periodontitis	Human oral cavity, dogs
C. sputorum	Diarrhea, bedsores, abscesses, periodontitis	Human oral cavity, cattle, swine, dogs
C. rectus	Periodontitis	
C. mucosalis	Enteritis	Swine, dogs
C. jejuni subsp. *doylei*	Diarrhea, colitis, appendicitis, bacteremia, UTI	Swine
C. curvus	Gingivitis, alveolar abscess	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water, human oral cavity
C. gracilis	Head and neck abscesses, abdominal abscesses, empyema	Dogs
C. cryaerophila	Diarrhea	Swine

UTI, Urinary tract infection.

Campylobacter organisms are gram-negative, curved, thin (0.2-0.8 µm wide), non–spore-forming rods (0.5-5 µm long) that usually have tapered ends. They are smaller than most other enteric bacterial pathogens and have variable morphology, including short, comma-shaped or S -shaped organisms and long, multispiraled, filamentous, seagull-shaped organisms. Individual organisms are usually motile with a flagellum at one or both poles depending on the species. Such morphology enables these bacteria to colonize the mucosal surfaces of both the gastrointestinal (GI) and respiratory tracts and move through them in a spiraling motion. Most *Campylobacter* organisms are microaerophilic, occasionally partially anaerobic, and oxidase positive. Most can transform into coccoid forms under adverse conditions, especially oxidation.

Epidemiology

Worldwide, *Campylobacter* enteritis is a leading cause of acute diarrhea. Efforts to reduce *Campylobacter* contamination and use of safe handling practices have led to decreased incidence. *Campylobacter* infections can be both food-borne and water-borne and most frequently result from ingestion of contaminated **poultry** (chicken, turkey) or **raw milk** . Less often, the bacteria come from drinking water, household pets (cats, dogs, hamsters), and farm animals. Infections are more common in resource-limited settings, are prevalent year-round in tropical areas, and can exhibit seasonal peaks in temperate regions (late spring with a peak midsummer in most of the United States, with a smaller secondary peak in late fall). In industrialized countries, *Campylobacter* infections peak in early childhood and again in young adulthood (15-44 yr). This 2nd peak is not seen with *Salmonella* and *Shigella* infections. In developing countries, repeated infections are common in childhood, leading to increased immunity and rare disease in adulthood. Each year in the United States, there are an estimated 2.5 million cases of *Campylobacter* infection. Of these, death is rare, with 50-150 reports annually. In The Netherlands, medical record review shows that on average each resident acquires asymptomatic *Campylobacter* colonization every 2 yr, progressing to symptomatic infection in approximately 1% of colonized people.

Food-borne infection is most common and can be seen with the consumption of raw or undercooked meat, as well as by cross-contamination of other foods. Although **chickens** are the classic source of *Campylobacter,* many animal sources of human food can also harbor *Campylobacter,* including seafood. *C. coli* has been linked to swine. Poultry is more likely to be heavily contaminated, whereas red meats often have fewer organisms. Unpasteurized milk products are also a documented source. Additionally, many pets can carry *Campylobacter,* and flies inhabiting contaminated environments can acquire the organism. Shedding from animals can contaminate water sources. Humans can acquire infection from water, although much less frequently than from contaminated food. **Airborne** (droplet) **transmission** of *Campylobacter* has occurred in poultry workers. Use of antimicrobials in animal foods may increase the prevalence of antibiotic-resistant *Campylobacter* isolated from humans.

Human infection can result from exposure to as few as 500 bacteria, although a higher dose (>9,000 bacteria) is often needed to cause illness reproducibly. Inoculum effectiveness is dependent on host factors, including immune status and stomach acidification. *C. jejuni* and *C. coli* spread person to person, perinatally, and at childcare centers where diapered toddlers are present. People infected with *C. jejuni* usually shed the organism for weeks, but some can shed for months, with children tending toward longer shedding. **Handwashing** is critical to preventing spread in these environments.

Pathogenesis

Most *Campylobacter* isolates are acid sensitive and should, in theory, be eradicated in the stomach. Therefore, models for the pathogenesis of *C. jejuni* enteritis include mechanisms to transit the stomach, adhere to intestinal mucosal cells, and initiate intestinal lumen fluid accumulation. Host conditions associated with reduced gastric acidity, such as proton pump inhibitor use, and foods capable of shielding organisms in transit through the stomach may help allow *Campylobacter* to reach the intestine. Once there, *Campylobacter* is able to adhere to and invade intestinal mucosal cells through motility, including use of flagellae, as well as by the use of surface proteins (e.g., PEB1, CadF), large plasmids (e.g., pVir), surface adhesins (e.g., JIpA), and chemotactic factors. Lumen fluid accumulation is associated with direct damage to mucosal cells resulting from bacterial invasion and potentially from an enterotoxin and other cytotoxins. Additionally, *C. jejuni* has mechanisms that enable transit away from the mucosal surface. The factors used depend on the species involved.

Campylobacter spp. differ from other enteric bacterial pathogens in that they have both *N* - and *O* -linked glycosylation capacities. *N* -linked glycosylation is associated with molecules expressed on the bacterial surface, and *O* -linked glycosylation appears limited to flagellae. Slipped-strand mispairing in glycosylation loci results in modified, antigenically distinct surface structures. It is hypothesized that antigenic variation provides a mechanism for immune evasion.

C. fetus possesses a high-molecular-weight S-layer protein that mediates high-level resistance to serum-mediated killing and phagocytosis and is therefore thought to be responsible for the propensity to produce bacteremia. *C. jejuni* and *C. coli* are generally sensitive to serum-mediated killing, but serum-resistant variants exist. Some suggest these serum-resistant variants may be more capable of systemic dissemination.

Campylobacter infections can be followed by **Guillain-Barré syndrome** , **reactive arthritis** , and **erythema nodosum** . Such complications are thought to be from molecular mimicry between nerve, joint, and dermal tissue and *Campylobacter* surface antigens. Most *Campylobacter* infections are not followed by immunoreactive complications, indicating that host conditions as well as other factors, in addition to molecular mimicry, are required for these complications. It is proposed that low-grade inflammation caused by *Campylobacter,* below the threshold that can be detected by endoscopy, results in crosstalk with gut nerves, leading to symptoms.

Clinical Manifestations

There are a variety of clinical presentations of *Campylobacter* infections, depending on host factors such as age, immunocompetence, and underlying conditions. Infection presents most often as gastroenteritis, but also as bacteremia, neonatal infections, and, less often, extraintestinal infections.

Acute Gastroenteritis

Acute gastroenteritis with diarrhea is usually caused by *C. jejuni* (90–95%) or *C. coli,* and rarely by *C. lari, C. hyointestinalis,* or *C. upsaliensis.* Infections with *C. jejuni* and *C. coli* are indistinguishable by clinical presentation. The average incubation period is 3 days (range: 1-7 days). One third of symptomatic patients can have a prodrome with fever, headache, dizziness, and myalgias; 1-3 days later, they develop cramping abdominal pain and loose, watery stools, or, less frequently, mucus-containing bloody stools. In severe cases (approximately 15%), blood appears in the stools 2-4 days after the onset of symptoms. In younger children, >50% may develop blood in their stools. Some patients do not develop diarrhea at all, most often children who are 6-15 yr old. Fever may be the only manifestation initially and is most pronounced in patients >1 yr old. From 60–90% of older children also complain of abdominal pain. The abdominal pain is most frequently periumbilical and sometimes persists after the stools return to normal. The abdominal pain can mimic appendicitis, colitis, or intussusception. Nausea is common, with up to 25% of adults developing vomiting. Vomiting tends to be more common the younger the patient and is most frequent in infants. Infection with species other than *C. jejuni* and *C. coli* may have milder symptoms.

Diarrhea lasts approximately 7 days and will resolve spontaneously. More mild disease can last 1-2 days; 20–30% of patients will have symptoms for 2 wk, and 5–10% are symptomatic for >2 wk. Relapse can occur in 5–10% of patients. Persistent or recurrent *Campylobacter* gastroenteritis has been reported in immunocompetent patients, in patients with hypogammaglobulinemia (both congenital and acquired), and in patients with AIDS. Persistent infection can mimic chronic **inflammatory bowel disease** (IBD); therefore *Campylobacter* infection should also be considered when evaluating for IBD. Some evidence supports that *Campylobacter* infection may also be the trigger for development of IBD. Fecal shedding of the organisms in untreated patients usually lasts for 2-3 wk, with a range from a few days to several months. Shedding tends to occur longer in young children. Acute appendicitis, mesenteric lymphadenitis, and ileocolitis have been reported in patients who have had appendectomy during *C. jejuni* infection.

Bacteremia

Transient bacteremia has been shown in early acute infection in 0.1–1% of patients. With the exception of bacteremia caused by *C. fetus* , bacteremia with *Campylobacter* occurs most often among patients with chronic illnesses or immunodeficiency (e.g., HIV), severe malnutrition, and in extremes of age. However, bacteremia is also well described in patients without underlying disease. The majority of cases of bacteremia are asymptomatic. *C. fetus* causes bacteremia in adults with or without identifiable focal infection, usually in the setting of underlying conditions such as malignancy, immunodeficiency, or diabetes mellitus. When symptomatic, *C. jejuni* bacteremia is associated with fever, headache, malaise, and abdominal pain. Relapsing or intermittent fever is associated with night sweats, chills, and weight loss when the illness is prolonged. Lethargy and confusion can occur, but focal neurologic signs are unusual without cerebrovascular disease or meningitis. Moderate leukocytosis with left shift may be found. Variable presentations have been described, including transient asymptomatic bacteremia, rapidly fatal septicemia, and prolonged bacteremia of 8-13 wk.

Focal Extraintestinal Infections

Focal infections caused by *C. jejuni* are rare and occur mainly among neonates and immunocompromised patients. Multiple sites have been reported, including meningitis, pneumonia, thrombophlebitis, pancreatitis, cholecystitis, ileocecitis, urinary tract infection, arthritis, peritonitis, ileocecitis, pericarditis, and endocarditis. *C. fetus* shows a predilection for vascular endothelium, leading to endocarditis, pericarditis, thrombophlebitis, and mycotic aneurysms. *C. hyointestinalis* has been associated with proctitis, *C. upsaliensis* with breast abscesses, and *C. rectus* with periodontitis.

Perinatal Infections

Perinatal infections are most often acquired at birth from a mother infected with or shedding *Campylobacter.* Maternal *C. fetus* and *C. jejuni* infections may be asymptomatic and can result in abortion, stillbirth, premature delivery, or neonatal infection with sepsis and meningitis. Severe perinatal infections are uncommon and are caused most often by *C. fetus* and rarely by *C. jejuni* . Neonatal infection with *C. jejuni* is associated with diarrhea that may be bloody. Nosocomial infections in nurseries have also been described.

Diagnosis

The clinical presentation of *Campylobacter* enteritis can be similar to that of enteritis caused by other bacterial pathogens. The differential diagnosis includes *Shigella, Salmonella, Escherichia coli* , *Yersinia enterocolitica, Aeromonas, Vibrio parahaemolyticus,* and amebiasis. Fecal leukocytes are found in as many as 75% of cases, and fecal blood is present in 50% of cases (higher in pediatric patients). *Campylobacter* should be considered in patients with bloody stools, fever, and abdominal pain.

The diagnosis of *Campylobacter* enteritis is usually confirmed by identification of the organism in cultures of stool or rectal swabs. Isolation is most likely from selective media such as CAMPY-agar grown in microaerophilic conditions (5–10% oxygen), 1–10% carbon dioxide, with some hydrogen. Some *C. jejuni* grow best at 42°C (107.6°F). Growth on solid media results in small (0.5-1.0 mm), slightly raised, smooth colonies. Organisms can be identified from stool microscopically in approximately 50% of known *Campylobacter* cases. Gram stain is even less sensitive. Stool culture is >90% sensitive and is the standard method of diagnosis. Visible growth on stool culture is most often present in 1-2 days. Visible growth in blood cultures is often not apparent until 5-14 days after inoculation.

Routine culture may be adequate for isolation of *C. jejuni* because of the large numbers of bacteria that are often present. However, because *Campylobacter* organisms grow more slowly under routine conditions than do other enteric bacteria, routine culture can result in failure because of overgrowth of other enteric bacteria. *Campylobacter* culture can be enhanced, when necessary, with selective media. However, selective culture media developed to enhance isolation of *C. jejuni* may inhibit the growth of other *Campylobacter* spp.

Filtration methods are available and can preferentially enrich for *Campylobacter* by selecting for their small size. These methods allow subsequent culture of the enriched sample on antibiotic-free media, enhancing rates of isolation of *Campylobacter* organisms inhibited by the antibiotics included in standard selective media. Isolation of *Campylobacter* from normally sterile sites does not require enhancement procedures. Clinically, it is not necessary to speciate *Campylobacter,* because clinical disease is the same. Speciation can be done, when needed, and specialized laboratories can perform strain typing when required for epidemiologic purposes.

For rapid diagnosis of *Campylobacter* enteritis, direct carbolfuchsin stain of fecal smear, indirect fluorescence antibody test, dark-field microscopy, or latex agglutination were used historically. Polymerase chain reaction testing is more specific and sensitive and is becoming more widely available for rapid testing, often grouped with testing for other bacterial, viral, and parasitic stool pathogens in a multiplex assay. At this time, the recommendation remains to confirm all positive rapid tests with culture, which also allows for susceptibility testing and epidemiologic investigations. Serologic diagnosis is also possible and is most helpful in patients with late-onset reactive arthritis or Guillain-Barré syndrome, since these patients may have negative stool cultures by the time of presentation with these late complications.

Complications

Severe, prolonged *C. jejuni* infection can occur in patients with immunodeficiencies, including hypogammaglobulinemia, malnutrition, and acquired immunodeficiency syndrome (AIDS). In patients with AIDS, increased frequency and severity of *C. jejuni* infection occurs; severity correlates inversely with CD4 count. Complications can include acute complications, as described earlier, and late-onset complications that may present after the acute infection has resolved. The most common late-onset complications include reactive arthritis and Guillain-Barré syndrome.

Reactive Arthritis

Reactive arthritis can accompany *Campylobacter* enteritis in adolescents and adults, especially in patients who are positive for HLA-B27 (see Chapter 182). Reactive arthritis occurs in up to 3% of patients, although up to 13% may have joint symptoms. This manifestation usually appears 1-2 wk after the onset of diarrhea but has been seen 5-40 days later. It involves mainly large joints and resolves without sequelae. The arthritis is typically migratory and occurs without fever. Synovial fluid lacks bacteria. The arthritis responds well to nonsteroidal antiinflammatory drugs and typically resolves after 1 wk to several months. Reactive arthritis with conjunctivitis, urethritis, and rash (including erythema nodosum) also occurs but is less common.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute demyelinating disease of the peripheral nervous system characterized clinically by acute flaccid paralysis and is the most common cause of neuromuscular paralysis worldwide (see Chapter 634). GBS carries a mortality rate of approximately 2%, and approximately 20% of patients develop major neurologic sequelae. *C. jejuni* has been identified as the trigger in up to 40% of patients with GBS and is most closely linked to the serotypes Penner O19 and O41. It has been reported 1-12 wk after *C. jejuni* gastroenteritis in 1 of every 1,000 *C. jejuni* infections. Stool cultures obtained from patients with GBS at the onset of neurologic symptoms have yielded *C. jejuni* in >25% of the cases. Serologic studies suggest that 20–45% of patients with GBS have evidence of recent *C. jejuni* infection. Molecular mimicry between nerve tissue GM_1 ganglioside and *Campylobacter* surface antigens may be the triggering factor in *Campylobacter* -associated GBS. The Miller-Fisher variant, which more often affects cranial nerves, is characterized by ataxia, areflexia, and ophthalmoplegia and is linked to cross-reacting antibodies to the GQ1b ganglioside found in cranial nerve myelin; the most common serotype for this variant is Penner O2. When associated with *Campylobacter,* GBS is more likely to be the axonal form and has a worse prognosis with slower recovery and more neurologic disability. The management of GBS includes supportive care, intravenous immunoglobulin, and plasma exchange.

Other Complications

Immunoglobulin A nephropathy and immune complex glomerulonephritis with *C. jejuni* antigens in the kidneys have been reported. *Campylobacter* infection has also been associated with hemolytic anemia and hemolytic-uremic syndrome.

Treatment

Fluid replacement, correction of electrolyte imbalance, and supportive care are the mainstays of treatment of children with *Campylobacter* gastroenteritis. Antimotility agents are contraindicated because they can cause prolonged or fatal disease. The need for antibiotic therapy in healthy patients with uncomplicated gastroenteritis is controversial. Data suggest a shortened duration of symptoms (by an average of 1.3 days) and intestinal shedding of organisms if antibiotics are initiated early in the disease. Antibiotics are recommended for patients with bloody stools, high fever, or a severe course, as well as for children who are immunosuppressed or have underlying diseases, and individuals at high risk of developing severe disease (e.g., pregnancy). Extraintestinal infections (e.g., bacteremia) should also be treated with antibiotics.

Most *Campylobacter* isolates are susceptible to macrolides, fluoroquinolones, aminoglycosides, chloramphenicol, tetracyclines, and clindamycin (though there is no clinical efficacy data for these last three agents, only in vitro data) and are resistant to cephalosporins, penicillins, and trimethoprim. Resistance to tetracyclines, macrolides, and more often fluoroquinolones has been described. **Antibiotic resistance** among *C. jejuni* has become a serious worldwide problem. Macrolide resistance is increased in areas such as Thailand and Ireland, whereas fluoroquinolone resistance has been reported in Spain, Hungary, and multiple developing countries in >50% of cultured *Campylobacter* . Fluoroquinolone resistance continues to increase in the United States and is related to the use of quinolones in veterinary medicine and food products, as well as acquisition from travelers. Erythromycin-resistant *Campylobacter* isolates are uncommon in the United States; therefore, **azithromycin** is the drug of choice if therapy is required, particularly in pediatric patients. Drug sensitivities should be determined for patients who do not respond to therapy or any patient with invasive or extraintestinal infection. Sepsis is treated with parenteral antibiotics such as meropenem or imipenem, with or without an aminoglycoside. For extraintestinal infection caused by *C. fetus* , prolonged therapy is advised. *C. fetus* isolates resistant to erythromycin and fluoroquinolones have been reported; therefore empirical therapy for serious *C. fetus* infection should avoid these agents pending susceptibilities.

Prognosis

Although *Campylobacter* gastroenteritis is usually self-limited, immunosuppressed children (including children with AIDS) can experience a protracted or severe course. Septicemia in newborns and immunocompromised hosts has a poor prognosis, with an estimated mortality rate of 30–40%. Additional prognosis is based on the secondary sequelae that may develop.

Prevention

Most human *Campylobacter* infections are sporadic and are acquired from infected animals or contaminated foods or water. Interventions to minimize transmission include cooking meats thoroughly, preventing recontamination after cooking by not using the same surfaces, utensils, or containers for both uncooked and cooked food, and avoiding unpasteurized dairy products. Also, it is important to ensure that water sources are not contaminated and that water is kept in clean containers. Contact with infected animals should be avoided. No specific isolation is required; **standard precautions** are sufficient, although in a hospital or clinic setting with an incontinent child, **contact precautions** are indicated. However, children in diapers should be kept out of daycare until the diarrhea resolves. Breastfeeding appears to decrease symptomatic *Campylobacter* disease but does not reduce colonization.

Several approaches at immunization have been studied, including the use of live-attenuated organisms, subunit vaccines, and killed–whole cell vaccines. No vaccine is currently available.

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CHAPTER 230

Yersinia

Ericka V. Hayes

The genus *Yersinia* is a member of the family Enterobacteriaceae and comprises more than 14 named species, 3 of which are established as human pathogens. *Yersinia enterocolitica* is by far the most common *Yersinia* species causing human disease and produces fever, abdominal pain that can mimic appendicitis, and diarrhea. *Yersinia pseudotuberculosis* is most often associated with mesenteric lymphadenitis. *Yersinia pestis* is the agent of **plague** and typically causes an acute febrile lymphadenitis (bubonic plague) and less often occurs as septicemic, pneumonic, pharyngeal, or meningeal plague. Other *Yersinia* species are uncommon causes of infections of humans, and their identification is often an indicator of immunodeficiency.

Yersinia is enzootic and can colonize pets. Infections in humans are incidental and most often result from contact with infected animals or their tissues; ingestion of contaminated water, milk, or meat; or for *Y. pestis*, the bite of infected fleas or inhalation of respiratory droplets (human, dog, cat). Association with human disease is less clear for *Yersinia frederiksenii, Yersinia intermedia, Yersinia kristensenii* , *Yersinia aldovae, Yersinia bercovieri, Yersinia mollaretii, Yersinia rohdei,* and *Yersinia ruckeri*. Some *Yersinia* isolates replicate at low temperatures (1-4°C [33.8-39.2°F]) or survive at high temperatures (50-60°C [122-140°F]). Thus, common food preparation and storage and common pasteurization methods might not limit the number of bacteria. Most are sensitive to oxidizing agents.

230.1

Yersinia enterocolitica

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Keywords

abdominal pain
appendicitis
bacteremia
blood products
chitterlings
diarrhea
enterocolitis
food-borne infection
iron overload
mesenteric lymphadenitis
pharyngitis
pig
pork
water-borne infection

Etiology

Yersinia enterocolitica is a large, gram-negative coccobacillus that exhibits little or no bipolarity when stained with methylene blue and carbolfuchsin. It ferments glucose and sucrose but not lactose, is oxidase negative, and reduces nitrate to nitrite. These facultative anaerobes grow well on common culture media and are motile at 22°C (71.6°F) but not 37°C (98.6°F). Optimal growth temperature is 25-28°C (77-82.4°F); however, the organism can grow at refrigerator temperature. *Y. enterocolitica* includes pathogenic and nonpathogenic members. It has 6 different biotypes (1A, 1B, and 2-5). *Y. enterocolitica* relies on other bacteria for iron uptake, and conditions associated with **iron overload** increase risk of infection.

Epidemiology

Y. enterocolitica is transmitted to humans through food, water, animal contact, and contaminated blood products. Transmission can occur from mother to newborn. *Y. enterocolitica* appears to have a global distribution but is seldom a cause of tropical diarrhea. In 2014, incidence of culture-confirmed *Y. enterocolitica* infection in the United States was 0.28 per 100,000 population (52% decrease from incidence in 1996–1998). Infection may be more common in Northern Europe. Most infections occur among children <5 yr old (incidence: 1.6-1.9 per 100,000 population), with the majority among children <1 yr old. It is estimated that *Y. enterocolitica* accounts for 5% of illnesses secondary to major bacterial enteric pathogens in children <5 yr old in the United States. Cases are more common in colder months and among males.

Natural reservoirs of *Y. enterocolitica* include pigs, rodents, rabbits, sheep, cattle, horses, dogs, and cats, with **pigs** being the major animal reservoir. Direct or indirect contact with animals, including pets, other domesticated animals, and wild animals, may be responsible for <1% of cases of enteric illnesses caused by *Y. enterocolitica* . Culture and molecular techniques have found the organism in a variety of foods and beverages, including vegetable juice, pasteurized milk, carrots, and water. Consumption of contaminated water or food, particularly undercooked pork, is the most common form of transmission to humans. A source of sporadic *Y. enterocolitica* infections is **chitterlings** (pig intestines, “chitlins”), a traditional dish in the southeastern United States as well as Latin America, often in celebration of winter holidays. The infection is often seen in young infants in the household due to contamination of bottle and food preparation when chitterlings are prepared. In one study, 71% of human isolates were indistinguishable from the strains isolated from pigs. *Y. enterocolitica* is an occupational threat to butchers.

In part because of its capacity to multiply at refrigerator temperatures, *Y. enterocolitica* can be transmitted by intravenous injection of contaminated fluids, including blood products.

Patients with conditions leading to iron overload are at higher risk of developing *Yersinia* infections.

Pathogenesis

The *Yersinia* organisms most often enter by the alimentary tract and cause mucosal ulcerations in the ileum. Necrotic lesions of Peyer patches and **mesenteric lymphadenitis** occur. If septicemia develops, suppurative lesions can be found in infected organs. Infection can trigger **reactive arthritis** and **erythema nodosum** , particularly in HLA-B27–positive individuals.

Virulence traits of pathogenic biotypes(1B and 2-5) are encoded by chromosomal genes and a highly conserved 70 kb virulence plasmid (pYV/pCD). The chromosomal genes control the production of heat-stable enterotoxins, and the plasmid allows penetration through the intestinal wall. Adherence, invasion, and toxin production are the essential mechanisms of pathogenesis. The bacteria mainly invade the intestinal epithelium in the Peyer patches of the ileum. After invasion, plasmid-encoded type III secretion of 3 antiphagocytic proteins protects *Yersinia* against the immunologic response of local macrophages. From Peyer patches, bacteria can disseminate to cause local or systemic disease. Motility appears to be required for *Y. enterocolitica* pathogenesis. Serogroups that predominate in human illness are O:3, O:8, O:9, and O:5,27. *Yersinia* does not produce siderophores and uses analogous siderophores from other bacteria or host-chelated iron stores to thrive, placing patients with iron overload, as in hemochromatosis, thalassemia, and sickle cell disease, at higher risk for infection.

Clinical Manifestations

Disease occurs most often as enterocolitis with diarrhea, fever, and abdominal pain. Acute enteritis is more common among younger children, and mesenteric lymphadenitis that can mimic appendicitis may be found in older children and adolescents. Incubation period is usually 4-6 days after exposure (range 1-14 days). Stools may be watery or contain leukocytes and, less often, frank blood and mucus. Duration of diarrhea is often longer for *Y. enterocolitica* than for other causes of acute gastroenteritis, ranging from 12-22 days in several studies. Fever is common. Notably, prominent pharyngitis may be seen in 20% of patients at presentation, which may help distinguish it from other causes of gastroenteritis. *Y. enterocolitica* is excreted in stool for 1-4 wk. Family contacts of a patient are often found to be asymptomatically colonized with *Y. enterocolitica*. *Y. enterocolitica* septicemia is less common and is most often found in very young children (<3 mo old) and immunocompromised persons. Systemic infection can be associated with splenic and hepatic abscesses, osteomyelitis, septic arthritis, meningitis, endocarditis, and mycotic aneurysms.

Exudative pharyngitis, pneumonia, empyema, lung abscess, and acute respiratory distress syndrome occur infrequently.

Reactive complications include erythema nodosum, reactive arthritis, and rarely uveitis. These manifestations may be more common in select populations (northern Europeans), in association with HLA-B27, and in females.

Diagnosis

Diagnosis is made typically through isolation of the organism, usually from the stool. *Y. enterocolitica* is easily cultured from normally sterile sites but requires special procedures for isolation from stool, where other bacteria can outgrow it. *Yersinia* should be cultured on selective agar (CIN, cefsulodin-irgasan-novobiocin) at 25-28°C to increase yield. If O:3 serogroup is suspected, MacConkey agar should be used at 25-28°C. Multiplex polymerase chain reaction (PCR) testing is also available. Many laboratories do not routinely perform the tests required to detect *Y. enterocolitica* ; procedures targeted to this organism must be specifically requested. A history indicating contact with environmental sources of *Yersinia* and detection of fecal leukocytes are helpful indicators of a need to test for *Y. enterocolitica*. The isolation of a *Yersinia* from stool should be followed by tests to confirm that the isolate is a pathogen. Serodiagnosis is not readily available, and utility is limited by cross-reactivity.

Differential Diagnosis

The clinical presentation is similar to other forms of bacterial enterocolitis. The most common considerations include *Shigella, Salmonella, Campylobacter, Clostridium difficile,* enteroinvasive *Escherichia coli, Y. pseudotuberculosis* , and occasionally *Vibrio* -related diarrheal disease. Amebiasis, appendicitis, Crohn disease, ulcerative colitis, diverticulitis, and pseudomembranous colitis should also be considered.

Treatment

Enterocolitis in an immunocompetent patient is a self-limiting disease, and no benefit from antibiotic therapy is established. Patients with systemic infection and very young children (in whom septicemia is common) should be treated.

Yersinia organisms are typically susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, third-generation cephalosporins, and quinolones, although strains resistant to quinolones have been reported. *Y. enterocolitica* produces β-lactamases, which are responsible for resistance to penicillins and first-generation cephalosporins. TMP-SMX is the recommended empirical treatment in children for **enterocolitis** (generally a 5-day course), because it has activity against most strains and is well tolerated. In **severe infections** such as bacteremia, third-generation cephalosporins, with or without aminoglycosides, are effective, and usually a 3 wk course of therapy is administered, with possible transition to oral therapy. Patients on deferoxamine should discontinue iron chelation therapy during treatment for *Y. enterocolitica*, especially if they have complicated gastrointestinal (GI) infection or extraintestinal infection.

Complications

Reactive arthritis, erythema nodosum, erythema multiforme, hemolytic anemia, thrombocytopenia, and systemic dissemination of bacteria have been reported in association with *Y. enterocolitica* infection. Septicemia is more common in younger children, and reactive arthritis is more common in older patients. Arthritis appears to be mediated by immune complexes, which form as a result of antigenic mimicry, and viable organisms are not present in involved joints.

Prevention

Prevention centers on reducing contact with environmental sources of *Yersinia.* Families should be warned of the high risk of chitterling preparation, especially with young infants and children in the household. Breaking or sterilization of the chain from animal reservoirs to humans holds the greatest potential to reduce infections, and the techniques applied must be tailored to the reservoirs in each geographic area. There is no licensed vaccine.

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230.2

Yersinia pseudotuberculosis

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Keywords

appendicitis
erythema nodosum
iron overload

Kawasaki syndrome
mesenteric lymphadenitis
pseudoappendicitis
reactive arthritis
zoonosis

Yersinia pseudotuberculosis has a worldwide distribution; *Y. pseudotuberculosis* disease is less common than *Y. enterocolitica* disease. The most common form of disease is a **mesenteric lymphadenitis** that produces an appendicitis-like syndrome. *Y. pseudotuberculosis* is associated with a Kawasaki syndrome–like illness in approximately 8% of cases.

Etiology

Y. pseudotuberculosis is a small, gram-negative, aerobic and facultative anaerobic coccobacillus. As with *Y. enterocolitica*, it ferments glucose and does not ferment lactose, is oxidase negative, catalase producing, urea splitting, and shares a number of morphologic and culture characteristics. It is differentiated biochemically from *Y. enterocolitica* on the basis of ornithine decarboxylase activity, fermentation of sucrose, sorbitol, and cellobiose, and other tests, although some overlap between species occurs. Antisera to somatic O antigens and sensitivity to *Yersinia* phages can also be used to differentiate the 2 species. Subspecies-specific DNA sequences that allow direct probe- and primer-specific differentiation of *Y. pestis, Y. pseudotuberculosis,* and *Y. enterocolitica* have been described. *Y. pseudotuberculosis* is more closely related phylogenetically to *Y. pestis* than to *Y. enterocolitica.*

Epidemiology

Y. pseudotuberculosis is zoonotic, with reservoirs in wild rodents, rabbits, deer, farm animals, various birds, and domestic animals, including cats and canaries. Transmission to humans is by consumption of or contact with contaminated animals or contact with an environmental source contaminated by animals (often water). Direct evidence of transmission of *Y. pseudotuberculosis* to humans by consumption of lettuce and raw carrots has been reported. The organism has a worldwide distribution; however, infections are more commonly reported in

Europe, in boys, and in the winter. During 1996–2014, FoodNet reported 224 cases of infections secondary to *Y. pseudotuberculosis* in the United States, with an annual average incidence of 0.03 per 100,000 persons. Compared with *Y. enterocolitica* infections, those caused by *Y. pseudotuberculosis* are more likely to be invasive and occur in adolescents and adults. Iron-overloading conditions, AIDS, other immunodeficiencies, and other debilitating diseases (including liver cirrhosis) may predispose to invasive *Y. pseudotuberculosis* infection.

Pathogenesis

Ileal and colonic mucosal ulceration and mesenteric lymphadenitis are hallmarks of the infection. Necrotizing epithelioid granulomas may be seen in the mesenteric lymph nodes, but the appendix is often grossly and microscopically normal. The mesenteric nodes are often the only source of isolation of the organism. *Y. pseudotuberculosis* antigens bind directly to human leukocyte antigen (HLA) class II molecules and can function as **superantigens** , which might account for the clinical illness resembling **Kawasaki syndrome** .

Clinical Manifestations

Pseudoappendicitis and mesenteric lymphadenitis with abdominal pain, right lower quadrant tenderness, fever, and leukocytosis constitute the most common clinical presentation. Enterocolitis and extraintestinal spread are uncommon. Iron overload, diabetes mellitus, and chronic liver disease are often found concomitantly with extraintestinal *Y. pseudotuberculosis* infection. Renal involvement with tubulointerstitial nephritis, azotemia, pyuria, and glucosuria can occur. *Y. pseudotuberculosis* can present as a Kawasaki syndrome–like illness with fever of 1-6 days' duration, strawberry tongue, pharyngeal erythema, scarlatiniform rash, cracked red swollen lips, conjunctivitis, sterile pyuria, periungual desquamation, and thrombocytosis. Some of these children have had coronary changes. Other uncommon manifestations include septic arthritis, massive lower GI bleeding, postaneurysmal prosthetic vascular infection, and acute encephalopathy.

Diagnosis

PCR of involved tissue can be used to identify *Y. pseudotuberculosis* ; isolation by culture can require an extended interval. Involved mesenteric lymph nodes removed at appendectomy can yield the organism by culture. Abdominal CT scan or ultrasound examination of children with unexplained fever and abdominal pain can reveal a characteristic picture of enlarged mesenteric lymph nodes and thickening of the terminal ileum with or without peritoneal findings including appendiceal inflammation and periappendiceal fluid. *Y. pseudotuberculosis* is rarely recovered from stool. Serologic testing is available in specialized labs.

Differential Diagnosis

Appendicitis (most common), inflammatory bowel disease, and other intraabdominal infections should be considered. Kawasaki syndrome, staphylococcal or streptococcal disease, leptospirosis, Stevens-Johnson syndrome, and collagen vascular diseases, including acute-onset juvenile idiopathic arthritis, can mimic the syndrome with prolonged fever and rash. *C. difficile* colitis, meningitis, encephalitis, enteropathic arthropathies, acute pancreatitis, sarcoidosis, toxic shock syndrome, typhoid fever, and ulcerative colitis may also be considered.

Treatment

Uncomplicated mesenteric lymphadenitis caused by *Y. pseudotuberculosis* is a self-limited disease, and antimicrobial therapy is not required. Few data exist on optimal treatment and duration of therapy. Infections with *Y. pseudotuberculosis* can generally be managed the same as those caused by *Y. enterocolitica* . Culture-confirmed bacteremia should be treated with a third-generation cephalosporin with or without an aminoglycoside, TMP-SMX, fluoroquinolones, or chloramphenicol.

Complications

Erythema nodosum and reactive arthritis can follow infection. Coronary aneurysm formation has been described with disease presenting as Kawasaki syndrome–like illness. Rare local complications of GI disease include perforation, obstruction, and intussusception.

Prevention

Avoiding exposure to potentially infected animals and good food-handling practices can prevent infection. The sporadic nature of the disease makes application of targeted prevention measures difficult.

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230.3

Plague *(Yersinia pestis)*

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Keywords

bacteremia
bioterrorism
bubo
bubonic plague
cat
flea bite
plague
pneumonia
postexposure prophylaxis
rat
regional lymphadenitis
septicemia

Etiology

Yersinia pestis is a gram-negative, facultative anaerobe that is a pleomorphic nonmotile, non–spore-forming coccobacillus and a potential agent of bioterrorism. It evolved from *Y. pseudotuberculosis* through acquisition of chromosomal changes and plasmid-associated factors that are essential to its virulence and survival in mammalian hosts and fleas. *Y. pestis* shares bipolar staining appearance with *Y. pseudotuberculosis* and can be differentiated by biochemical reactions, serology, phage sensitivity, and molecular techniques. *Y. pestis* exists in 3 biovars: Antigua (Africa), Medievalis (central Asia), and Orientalis (widespread).

Epidemiology

Plague is endemic in at least 24 countries. Approximately 3,000 cases are reported worldwide per year, with 100-200 deaths. Plague is uncommon in the United States (0-40 reported cases/yr); most of these cases occur west of a line from east Texas to east Montana, with 80% of cases in California, New Mexico, Arizona, and Colorado. In 2015, there was a cluster of 11 cases (with 3 deaths) in 4 mo related to exposure at Yosemite National Park in California's Sierra

Nevada Mountains. The epidemic form of disease killed approximately 25% of the population of Europe in the Middle Ages in one of several epidemics and pandemics. The epidemiology of **epidemic** plague involves extension of infection from the zoonotic reservoirs to urban rats, *Rattus rattus* and *Rattus norvegicus,* and from fleas of urban rats to humans. Epidemics are no longer seen. Selective pressure exerted by plague pandemics in medieval Europe is hypothesized for enrichment of a deletion mutation in the gene encoding CCR5 (CCR5-Δ32). The enhanced frequency of this mutation in European populations endows approximately 10% of European descendants with relative resistance to acquiring HIV-1.

The most common mode of transmission of *Y. pestis* to humans is through **flea bites** . Historically, most human infections are thought to have resulted from bites of fleas that acquired infection from feeding on infected urban rats. Less frequently, infection is caused by contact with infectious body fluids or tissues or inhalation of respiratory secretions of infected animals. Currently, most cases of plague secondary to direct animal contact or inhalation of animal secretions are related to domestic **cats** or **dogs** . Direct transmission from human to human through droplet inhalation is possible but extremely rare. Laboratory transmission of *Y. pestis* has been described as well. **Sylvatic plague** can exist as a stable enzootic infection or as an epizootic disease with high host mortality. Ground squirrels, rock squirrels, prairie dogs, rats, mice, bobcats, cats, rabbits, and chipmunks may be infected. Transmission among animals is usually by flea bite or by ingestion of contaminated tissue. *Xenopsylla cheopis* is the flea usually associated with transmission to humans, but >30 species of fleas have been demonstrated as vector competent, and *Pulex irritans,* the human flea, can transmit plague and might have been an important vector in some historical epidemics. Both sexes are similarly affected by plague, and transmission is more common in colder regions and seasons, possibly because of temperature effects on *Y. pestis* infections in vector fleas.

Pathogenesis

In the most common form of plague, infected fleas regurgitate organisms into a patient's skin during feeding. The bacteria translocate via lymphatics to regional lymph nodes, where *Y. pestis* replicates, resulting in bubonic plague. In the absence of rapidly implemented specific therapy, bacteremia can occur, resulting in purulent, necrotic, and hemorrhagic lesions in many organs. Both plasmid and chromosomal genes are required for full virulence. Pneumonic plague can be secondary to bacteremia or primary when infected material is inhaled. The organism is highly transmissible from persons with pneumonic plague and from domestic cats with pneumonic infection. This high transmissibility and high morbidity and mortality have provided an impetus for attempts to use *Y. pestis* as a biologic weapon.

Clinical Manifestations

Y. pestis infection can manifest as several clinical syndromes; infection can also be subclinical. The 3 principal clinical presentations of plague are bubonic, septicemic, and pneumonic. **Bubonic plague** is the most common form and accounts for 80–90% of cases in the United States. From 2-8 days after a flea bite, lymphadenitis develops in lymph nodes closest to the inoculation site, including the inguinal (most common), axillary, or cervical region. These buboes are remarkable for tenderness. Fever, chills, weakness, prostration, headache, and the development of septicemia are common. The skin might show insect bites or scratch marks. Purpura and gangrene of the extremities can develop as a result of disseminated intravascular coagulation (DIC). These lesions may be the origin of the name Black Death. Untreated plague results in death in >50% of symptomatic patients. Death can occur within 2-4 days after onset of symptoms.

Occasionally, *Y. pestis* establishes systemic infection and induces the systemic symptoms seen with bubonic plague without causing a bubo (**primary septicemic plague**). Because of the delay in diagnosis linked to the lack of the bubo, septicemic plague carries an even higher case fatality rate than bubonic plague. In some regions, bubo-free septicemic plague accounts for 25% of cases.

Pneumonic plague is the least common but most dangerous and lethal form of the disease. Pneumonic plague can result from hematogenous dissemination, or, rarely, as primary pneumonic plague after inhalation of the organism from a human or animal with plague pneumonia or potentially from a biologic attack. Signs of pneumonic plague include severe pneumonia with high fever, dyspnea, and hemoptysis.

Meningitis, tonsillitis, or gastroenteritis can occur. Meningitis tends to be a late complication following inadequate treatment. Tonsillitis and gastroenteritis can occur with or without apparent bubo formation or lymphadenopathy.

Diagnosis

Plague should be suspected in patients with fever and history of exposure to small animals in endemic areas. Thus, bubonic plague is suspected in a patient with a painful swollen lymph node, fever, and prostration who has been potentially exposed to fleas or rodents in the western United States. A history of camping or the presence of flea bites increases the index of suspicion.

Y. pestis is readily transmitted to humans by some routine laboratory manipulations. Thus, it is imperative to clearly notify a laboratory when submitting a sample suspected of containing *Y. pestis*. Laboratory diagnosis is based on bacteriologic culture or direct visualization using Gram, Giemsa, or Wayson stain of lymph node aspirates, blood, sputum, or exudates. Fluorescent antibody staining can also be done on specimens. *Y. pestis* grows slowly under routine culture conditions and best at temperatures that differ from those used for routine cultures in many clinical laboratories. Note some automated blood culture identification systems may misidentify *Y. pestis* . A rapid antigen test detecting *Y. pestis* F1 antigen in sputum and serum samples exists. Suspected isolates of *Y. pestis* should be forwarded to a reference laboratory for confirmation. Special containment shipping precautions are required. Cases of plague should be reported to local and state health departments and the Centers for Disease Control and Prevention (CDC). Serologic testing is also available.

Differential Diagnosis

The Gram stain of *Y. pestis* may be confused with *Enterobacter agglomerans*. Mild and subacute forms of bubonic plague may be confused with other disorders causing localized lymphadenitis and lymphadenopathy, including tularemia and cat-scratch adenitis. Septicemic plague may be indistinguishable from other forms of overwhelming bacterial sepsis.

Pulmonary manifestations of plague are similar to those of anthrax, Q fever, and tularemia, all agents with **bioterrorism** and **biologic warfare** potential. Thus, the presentation of a suspected case, and especially any cluster of cases, requires immediate reporting. Additional information on this aspect of plague and procedures can be found at http://www.bt.cdc.gov/agent/plague/ .

Treatment

Patients with suspected plague should be placed on **droplet isolation** until pneumonia is ruled out, sputum cultures are negative, and antibiotic treatment has been administered for 48 hr. The treatment of choice for bubonic plague historically has been **streptomycin** (30 mg/kg/day, maximum 2 g/day, divided every 12 hr intramuscularly [IM] for 10 days). Intramuscular streptomycin is inappropriate for septicemia because absorption may be erratic when perfusion is poor. The poor central nervous system penetration of streptomycin also makes this an inappropriate drug for meningitis. Furthermore, streptomycin might not be widely and immediately available. **Gentamicin** (children, 7.5 mg/kg IM or intravenously [IV] divided every 8 hr; adults, 5 mg/kg IM or IV once daily) has been shown to be as efficacious as streptomycin; in patients with abscesses, an additional agent may be needed in addition to an aminoglycoside because of poor abscess penetration. Alternative treatments include **doxycycline** (in children who weigh <45 kg: 4.4 mg/kg/day divided every 12 hr IV, maximum 200 mg/day; not recommended for children <8 yr of age; in children who weigh ≥45 kg, 100 mg every 12 hr orally [PO]), c**iprofloxacin** (30 mg/kg/day divided every 12 hr, maximum 400 mg every 12 hr IV), and **chloramphenicol** (100 mg/kg/day IV divided every 6 hr, for children >2 yr; maximum dose 4 g/day; not widely available in the United States). Meningitis is usually treated with chloramphenicol or a fluoroquinolone. Resistance to these agents and relapses are rare. *Y. pestis* is susceptible in vitro to **fluoroquinolones** , which are effective in treating experimental plague in animals. *Y. pestis* is susceptible in vitro to penicillin, but penicillin is ineffective in treatment of human disease. Mild disease may be treated with oral chloramphenicol or tetracycline in children >8 yr old. Clinical improvement is noted within 48 hr of initiating treatment. Typical duration of therapy is 10-14 days, with a switch to oral therapy 2 days after defervescence and clinical improvement. Drainage of suppurative buboes may be needed; material is infectious, and appropriate precautions should be taken intraoperatively.

Postexposure prophylaxis should be given to close contacts of patients with pneumonic plague. Antimicrobial prophylaxis is recommended within 7 days of exposure for persons with direct, close contact with patient with pneumonic plague or those exposed to an accidental or terrorist-induced aerosol. Recommended regimens for children >8 yr old include doxycycline or ciprofloxacin; for children <8 yr old, doxycycline, chloramphenicol and ciprofloxacin are options for a 7-day course at the treatment doses above. Contacts of cases of uncomplicated bubonic plague do not require prophylaxis.

Y. pestis is a potential agent of bioterrorism that can require mass casualty prophylaxis.

Prevention

Avoidance of exposure to infected animals and fleas is the best method of prevention of infection. In the United States, special care is required in environments inhabited by rodent reservoirs of *Y. pestis* and their ectoparasites. Patients with plague should be isolated if they have pulmonary symptoms, and infected materials should be handled with extreme care. There is currently no available licensed vaccine for *Y. pestis* in the United States. Several vaccine development trials are underway, and recombinant subunit vaccines based on rF1 and rV antigens seem to be the most promising. Using baits containing live vaccines for oral immunization of wild animals may be a helpful alternative for control of epidemics.

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CHAPTER 231

Aeromonas and *Plesiomonas*

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Aeromonas and *Plesiomonas* are gram-negative bacilli that include species capable of causing enteritis and, less frequently, skin and soft tissue infections and invasive disease. They are common in fresh water and brackish water and colonize animals and plants in these environments.

231.1

Aeromonas

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Etiology

Aeromonas is a member of the Aeromonadaceae family and includes 2 major groups of isolates: the nonmotile *psychrophilic* organisms that infect cold-blooded animals, most often fish, and the motile *mesophilic* organisms that infect humans and other warm-blooded animals. *Aeromonas* species are oxidase- and catalase-positive, facultatively anaerobic, gram-negative bacilli that ferment glucose. *Aeromonas* is a diverse genus with difficult taxonomy and species differentiation because of high nucleotide variability and has undergone multiple reclassifications of species and taxa in recent years. Eleven species are recognized as clinically significant human pathogens, with *Aeromonas* *hydrophila, Aeromonas veronii* biotype sobria, and *Aeromonas caviae* most frequently associated with human infection. *Aeromonas dhakensis* , which was first isolated from children with diarrhea in Dhaka, Bangladesh and initially classified as a subspecies of *A. hydrophila* , has been recognized as a distinct species and an important cause of human infection.

Epidemiology

Aeromonas organisms are found in fresh and brackish aquatic sources, including rivers and streams, well water, both treated and bottled drinking water, and sewage. These organisms are most often detected in aquatic sources during warm-weather months, when they reach greater population densities. Rates of human infection may also exhibit seasonality depending on local conditions. For example, *Aeromonas* is isolated with increased frequency from May to October in the Northern hemisphere. Some species resist chlorination of water and exhibit tolerance to high salt concentrations. *Aeromonas* has been isolated from meats, milk, seafood, seaweed, and vegetables consumed by humans. Asymptomatic colonization occurs in humans and is more common in inhabitants of tropical regions. Most human infections with *Aeromonas* are associated with exposure to contaminated water but may also be contracted via other routes, including ingestion of contaminated food. A systematic review of cases of traveler's diarrhea worldwide implicated *Aeromonas* in 0.8–3.3% of infections, with highest frequencies in travelers to Southeast Asia and Africa. A study in Bangladesh of >56,000 stool samples from patients with diarrhea found that approximately 25% had a bacterial etiology detected, 13% of which were *Aeromonas* . *Aeromonas* infections have also been acquired at various sites of natural disasters. For example, following the 2004 Thailand tsunami, *Aeromonas* was the leading cause of skin and soft tissue infection among survivors.

Pathogenesis

Clinical and epidemiologic data seem to support that *Aeromonas* organisms are **enteric** pathogens, although this point is not universally accepted. Reasons for uncertainty include a lack of outbreaks with clonally distinct isolates, infrequent person-to-person transmission, absence of a robust animal model, and overlapping prevalence in symptomatic and asymptomatic individuals. In addition, there are conflicting data when comparing the human challenge model with characteristics of suspected outbreaks of *Aeromonas* enteritis, further complicating interpretation.

Aeromonas isolates possess a variety of potential virulence factors, including constitutive *polar* and inducible *lateral* flagella, fimbriae, outer membrane proteins, endotoxin (lipopolysaccharide), capsules, extracellular hydrolytic enzymes, enterotoxins, hemolysins, and multiple secretion systems. The mechanistic role of many of these factors in human pathogenicity remains unclear. Polar flagella provide motility in liquid media, and lateral flagella may act as adhesins. There are numerous hemolysins and heat-labile and heat-stable enterotoxins. *Aeromonas* cytotoxic enterotoxin **(Act/aerolysin)** is secreted by a type II secretion system and is able to lyse erythrocytes, inhibit phagocytosis, and induce cytotoxicity in eukaryotic cells. *Aeromonas* also has a type III secretion system with an effector protein that causes actin reorganization and eventual apoptosis in vitro. A type VI secretion system has been described and functions analogously to a phage tail, with antimicrobial activity.

Aeromonas sobria is the most enterotoxic among clinical isolates, and cytotoxic activity with cytopathic and intracellular effects is found in 89% of isolates. A few strains produce Shiga toxin. Some clinically important species have also been shown to harbor a cholera-like toxin (**Asao toxin**). *Aeromonas* has serine proteases that can cause a cascade of inflammatory mediators, leading to vascular leakage, and in vitro studies show induction of apoptosis in murine macrophages by human isolates of *Aeromonas* . There are limited data on *quorum-sensing* molecules, which coordinate gene expression according to local density and may be involved in biofilm production or population control.

Clinical Manifestations

Aeromonas may colonize humans asymptomatically or cause illness, including enteritis, focal invasive infections, and septicemia. Although apparently immunologically normal individuals may present with any of these manifestations, invasive disease is more common among immunocompromised persons.

Enteritis

The most common clinical manifestation of infection with *Aeromonas* is enteritis, which occurs primarily among children <3 yr old. *Aeromonas* is the 3rd or 4th most common cause of childhood **bacterial diarrhea** and has been isolated from 2–10% of patients with diarrhea and 1–5% of asymptomatic controls. One study demonstrated isolation from hospitalized neonates with diarrhea at rates of 0–19% depending on the season. Isolation from human feces also varies geographically based on food habits, level of sanitation, population demographics, aquaculture and farming practices, and laboratory isolation methods used. *Aeromonas* diarrhea is often watery and self-limited, although a dysentery-like syndrome with blood and mucus in the stool has also been described. Fever, abdominal pain, and vomiting are common in children. Enteritis caused by *A. hydrophila* and *A. sobria* tends to be acute and self-limited, whereas 30% of the patients with *A. caviae* enteritis have chronic or intermittent diarrhea that may last 4-6 wk. *A. sobria* and *A. caviae* are most frequently associated with traveler's diarrhea. Complications of *Aeromonas* enteritis include intussusception, failure to thrive, hemolytic-uremic syndrome, bacteremia, and postinfectious chronic colitis. *Aeromonas* infection may also present as acute segmental colitis, mimicking inflammatory bowel disease or ischemic colitis.

Skin and Soft Tissue Infections

Skin and soft tissue infections are the 2nd most common presentation of *Aeromonas.* Predisposing factors include local trauma and exposure to contaminated fresh water. *Aeromonas* soft tissue infections have been reported following bites from a number of animal species, including alligators, tigers, bears, and snakes, as well as from tick bites. These infections have also been reported after sports injuries and medicinal leech therapy. Antibiotic prophylaxis is generally used in conjunction with leech therapy because of the presence of *A. hydrophila* in the gastrointestinal (GI) tract of leeches, where they aid in the breakdown of ingested red blood cells. The spectrum of skin and soft tissue infections is broad, ranging from a localized skin nodule to life-threatening necrotizing fasciitis, myonecrosis, and gas gangrene. Soft tissue infections are most frequently found on the extremities, are often polymicrobial, and are 3 times more likely in men than in women. *Aeromonas* **cellulitis** , the most common skin manifestation, clinically presents similar to other forms of bacterial cellulitis but should be suspected in wounds after contact with a water source, especially during the summer.

Septicemia

Aeromonas septicemia is the 3rd most common presentation of infection and is associated with a mortality rate of 27–73%, with higher incidence during summer months or during the wet season in the tropics. Patients often present with fever and GI symptoms, including abdominal pain, nausea, vomiting, and diarrhea. From 2–4% of patients may present with ecthyma gangrenosum–like lesions. *Aeromonas* may be the only organism isolated or may be part of a polymicrobial bacteremic illness. Most cases (approximately 80%) occur in immunocompromised adults or those with hepatobiliary disease and in young children in whom the source of infection is probably *Aeromonas* in the GI tract. Less frequently, bacteremia can be secondary to trauma-related myonecrosis or infected burns. In such patients, mortality is often higher than in those with primary bacteremia, because of the underlying trauma. Rarely, *Aeromonas* bacteremia occurs in otherwise healthy adults exposed to fresh water.

Other Infections

Aeromonas is a rare cause of GI infections such as necrotizing gastroenteritis, peritonitis, cholecystitis, appendicitis, and liver and pancreas abscess formation; cardiovascular infections, including endocarditis and septic embolism; and pulmonary infections, including tracheobronchitis, pneumonia, empyema, and lung abscess formation. *Aeromonas* is also associated with musculoskeletal infections, including osteomyelitis, pyogenic arthritis, pyomyositis, and necrotizing fasciitis, as well as ear, nose, and throat infections, including endophthalmitis, keratitis, orbital cellulitis, otitis media, and epiglottitis. Other rare infections include meningitis, urinary tract infection, pelvic inflammatory disease, lymphadenitis, hot tub folliculitis, and surgical wound infections. *Aeromonas* is associated with tracheobronchitis and aspiration pneumonia after near-drowning.

Diagnosis

Diagnosis is established by isolation of *Aeromonas* in culture. The organism is generally grown on standard media when the source material is normally sterile. Isolation and identification of the organism from nonsterile sites are more difficult. Often, *Aeromonas* is not identified by typical laboratory protocols for examining stool specimens. If *Aeromonas* is suspected, the yield may increase if the laboratory is notified before testing, because overnight enrichment in alkaline peptone water and culture on selective agars may be useful. Most strains (approximately 90%) produce β-hemolysis on blood agar. Lactose-fermenting strains of *Aeromonas* may not be identified if the clinical laboratory does not routinely perform oxidase tests on lactose fermenters isolated on MacConkey agar. Aeromonads are resistant to vibriostatic agent O129; however, differentiation of *Aeromonas* from *Vibrio* spp. and identification of *Aeromonas* spp. and subspp. is not reliable using biochemical testing, particularly when commercial identification systems are used. Similarly, classification of *Aeromonas* strains at the species and subspecies level is difficult to achieve by sequencing regions of the 16S rRNA gene. Sequencing of housekeeping genes, such as *gyrB* and *rpoD* , and multilocus sequence typing are accurate for species identification but are time-, cost- and labor-intensive. Increasingly, laboratories use matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry to rapidly identify organisms, because this method is accurate for *Aeromonas* as a genus and for many of the clinically important species.

Treatment

Aeromonas **enteritis** is usually self-limited, and antimicrobial therapy may not be indicated, although some studies suggest that antimicrobial therapy may shorten the course of the illness. Antimicrobial therapy is reasonable to consider in patients with protracted diarrhea, dysentery-like illness, or underlying conditions such as hepatobiliary disease or an immunocompromised state. Antibiotic sensitivity varies among species and also by geography; therefore it is important to perform susceptibility testing. Chromosomally mediated class B, C, and D β-lactamases are found in most species and can be difficult to identify because many are inducible. These include metallo- and AmpC β-lactamases, which can lead to clinical failure if carbapenems or third-generation cephalosporins are used as monotherapy in high-organism-load infections. There is near-uniform resistance to penicillins. **Septicemia** can be treated with a fourth-generation cephalosporin (e.g., cefepime) or ciprofloxacin, with or without an aminoglycoside, although specific therapy should be guided by susceptibility data. Another option for less severe infections includes trimethoprim-sulfamethoxazole (TMP-SMX). Evidence-based recommendations for duration of treatment are lacking, and thus treatment is typically guided by clinical response. In general, diarrhea is treated for 3 days, wound infections for 7-10 days, and bacteremia for 14-21 days, depending on clinical response and host characteristics.

Prevention

Reducing contact with contaminated environmental fresh and brackish water and contaminated foods should reduce the risk for *Aeromonas* infections. Some *Aeromonas* outer membrane proteins are immunogenic and are candidate antigens for preclinical vaccine development.

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231.2

Plesiomonas shigelloides

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Etiology

Plesiomonas shigelloides is a facultatively anaerobic, gram-negative, non–spore-forming bacillus that ferments glucose. It is a catalase-, oxidase-, and indole-positive motile organism with polar flagella. A high level of genetic diversity has been recognized among *P. shigelloides* strains, reflecting frequent homologous recombination.

Epidemiology

P. shigelloides is ubiquitous in fresh water and, because it can tolerate salinity of up to 4%, can be found in estuarine or brackish water, as well as in animal inhabitants of these ecosystems, including fish, shellfish, crustaceans, water mammals, amphibians, reptiles, and other vertebrates. *P. shigelloides* has been recovered from healthy (colonized) and diseased animals, including cats. It can cause both sporadic infections and outbreaks in a range of animals. As a mesophile with optimal growth temperature of 35-39°C (95-102.2°F), *P. shigelloides* has been found most often in tropical waters or during warmer months, although there are increasing reports of isolation from surface water in colder climates. Similarly, most cases of infection occur during the warmer months of the year. *P. shigelloides* is not a usual commensal organism in the human GI tract, and infection of humans is thought to be the result of consumption of contaminated water or raw seafood or possibly through contact with colonized animals. The frequency of isolation of *P. shigelloides* from diarrheal stools in these circumstances has been reported to range from 2% to >10%. Mixed infection with *Salmonella* , *Aeromonas* , rotavirus, or other enteric pathogens may occur in almost one third of patients. The majority of symptomatic patients in North America have a known exposure to potentially contaminated water or seafood (notably oysters) or have traveled abroad. *Plesiomonas* has been reported to be associated with 1.3–5.4% of episodes of traveler's diarrhea, with the highest rates associated with travel to South and Southeast Asia. Other risk factors include immune compromise (in particular HIV infection), blood dyscrasias (including sickle cell disease), and young age. The highest rates of *Plesiomonas* enteritis occur in children <2 yr old. Although *P. shigelloides* has a worldwide distribution, there is unexplained geographic variability in the incidence of enteritis that may be related to water temperatures as well as lack of hygiene and sanitation.

Pathogenesis

Epidemiologic and microbiologic evidence in the form of a series of food-borne outbreaks attributable to *P. shigelloides* indicates that this organism is an **enteropathogen** . However, the pathogenic capacity of *P. shigelloides* has not been confirmed through oral challenge studies, and these organisms have been isolated from the stools of healthy individuals at a low rate. The mechanism of enteritis is not known, but putative virulence factors have been described, including cholera-like toxin, heat-labile and heat-stable enterotoxins, and lipopolysaccharide. Most strains of *P. shigelloides* also secrete a β-hemolysin, which is thought to be a major virulence factor. In vitro studies show that isolates of *P. shigelloides* can invade and induce apoptosis in cells of enteric origin, as well as exhibiting evidence of modulation of host defenses through inhibition of cathepsins involved in antigen processing and presentation.

Clinical Manifestations

Clinical disease in humans generally begins 24-48 hr after exposure to the organism, although incubation periods in excess of 4 days have been reported. Diarrhea can occur in all age-groups, including neonates, is typically secretory, and less often presents as invasive dysentery. Secretory enteritis usually presents as a mild self-limiting disease with watery diarrhea and abdominal pain, but in 13% of cases diarrhea can persist for >2 wk. Dehydration, hypokalemia, and peritonitis are uncommon complications; however, there have been several reports of a cholera-like presentation with severe secretory diarrhea. The frequency of secretory vs dysenteric presentation seems to cluster by individual outbreak, suggesting that either the human populations or the bacterial populations involved are associated with each particular presentation. **Dysentery** presents with macroscopic blood and/or mucus in the stool, significant abdominal pain, and vomiting, with more severe cases also associated with fever. Fatal outcomes have been reported with severe cases of *Plesiomonas* dysentery, although in most of these cases the exact role of *P. shigelloides* is unclear.

Extraintestinal infections, usually bacteremia, are rare and usually occur in patients with underlying immunodeficiency. About 90% of these cases are monomicrobial, and in almost half, *P. shigelloides* is also isolated from a site other than blood. Rarely, bacteremia accompanying enteritis has been documented in apparently otherwise normal children. Septicemia also appears to result from ingestion of contaminated water or seafood and has a high mortality rate in adults. Other extraintestinal diseases include pneumonia, meningitis, osteomyelitis, septic arthritis, reactive arthritis, abscesses, and focal infections of the GI or reproductive tracts. Almost one third of all bacteremias occur in neonates who present with early-onset sepsis and meningitis, and although rare, these make up most of the reported cases of *P. shigelloides* meningitis and have a very high mortality rate (80%). In several cases of neonatal disease, *Plesiomonas* has also been isolated from maternal feces, suggesting intrapartum vertical transmission. Compared to *Aeromonas* and *Vibrio* spp., traumatic wounds sustained in aquatic environments less often contain *P. shigelloides* .

Diagnosis

P. shigelloides is a non–lactose-fermenting organism and grows well on traditional enteric media with optimal growth at 30°C (86°F), although selective techniques may be required to isolate the organism from mixed cultures and to differentiate *P. shigelloides* from *Shigella* spp. If enrichment is necessary, alkaline peptone water or bile peptone broth may be used. Colonies are nonhemolytic on 5% blood agar. Many strains cross-react with *Shigella* on serologic testing but can be differentiated easily as oxidase-positive organisms. *P. shigelloides* has a unique biochemical profile and can generally be identified using commercial kits. Rapid identification systems, including MALDI-TOF, can also be used to identify *P. shigelloides* . *P. shigelloides* is included in at least one U.S. Food and Drug Administration (FDA)–approved commercial panel that detects a range of enteropathogens directly from diarrheal stools (culture independent) by polymerase chain reaction.

Treatment

Enteritis caused by *P. shigelloides* is usually mild and self-limited. In cases associated with dehydration or with a cholera-like disease, patients usually respond favorably to **oral rehydration solution** . Consideration of **antimicrobial therapy** is reserved for patients with prolonged or bloody diarrhea, those who are immunocompromised, the elderly, and the very young. Data from uncontrolled studies suggest that antimicrobial therapy may decrease the duration of symptoms, although no difference was found in an exclusively pediatric study.

P. shigelloides produces a chromosomally encoded, noninducible β-lactamase, which generally renders strains resistant to the penicillins, including broad-spectrum penicillins. *P. shigelloides* is also usually resistant to aminoglycosides and tetracyclines. Most strains of *P. shigelloides* are susceptible to β-lactam/β-lactamase inhibitor combinations as well as to TMP-SMX, some cephalosporins, carbapenems, and fluoroquinolones; however, therapy should be guided by antimicrobial susceptibility testing, since resistance to TMP-SMX, fluoroquinolones, and other agents has been reported.

Severe cases of *P. shigelloides* dysentery should be treated similarly to shigellosis (with empirical azithromycin or a third-generation cephalosporin for children and ciprofloxacin or azithromycin for adults). Antibiotics are essential for therapy of extraintestinal disease. Empirical therapy with a third-generation cephalosporin is often first-line management, because most isolates are susceptible in vitro. Alternatives include imipenem, aztreonam, β-lactam/β-lactamase inhibitor combinations, and quinolones. Definitive therapy should be guided by the susceptibility of the individual isolate. Duration of therapy ranges from 1-2 wk but may be extended depending on underlying chronic conditions and clinical response.

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CHAPTER 232

Pseudomonas, Burkholderia, and *Stenotrophomonas*

232.1

Pseudomonas aeruginosa

Thomas S. Murray, Robert S. Baltimore

Keywords

bacteremia
biofilm
burn wound sepsis
conjunctivitis
cystic fibrosis
ecthyma gangrenosum
immunosuppressed
neutropenia
urinary tract infection
ventilator-associated pneumonia

Etiology

Pseudomonas aeruginosa is a gram-negative rod and is a strict aerobe. It can multiply in a great variety of environments that contain minimal amounts of organic compounds. Strains from clinical specimens do not ferment lactose, are oxidase positive, and may produce β-hemolysis on blood agar. Many strains produce pigments, including pyocyanin, pyoverdine, and pyorubrin, that diffuse into and color the surrounding medium. Strains of *P. aeruginosa* are differentiated for epidemiologic purposes by a variety of genotyping methods, including restriction fragment length polymorphisms using pulsed-field gel electrophoresis, multilocus sequence typing, and more recently, whole genome sequencing.

Epidemiology

P. aeruginosa is a classic “opportunist.” It rarely causes disease in people who do not have a predisposing risk factor. Compromised host defense mechanisms resulting from trauma, neutropenia, mucositis, immunosuppression, or impaired mucociliary transport explain the predominant role of this organism in producing opportunistic infections. In pediatric settings, it is most frequently seen in the respiratory secretions of children with **cystic fibrosis** (CF). *P. aeruginosa* was found in 1% of neonates with fever and bacteremia in a review of 6 U.S. centers. One series of neonatal intensive care unit (NICU) infections reported that 3.8%episodes of neonatal bacteremia from 1989–2003 were caused by *P. aeruginosa* . Another children's hospital reported 232 episodes of *P. aeruginosa* bacteremia over a 10 yr period, with half the infected children diagnosed with an underlying malignancy.

P. aeruginosa and other pseudomonads frequently enter the hospital environment on the clothes, skin, or shoes of patients or hospital personnel, with plants or vegetables brought into the hospital, and in the gastrointestinal (GI) tract of patients. Colonization of any moist or liquid substance may ensue; the organisms may be found growing in any water reservoir, including distilled water, and in hospital kitchen sinks and laundries, some antiseptic solutions, and equipment used for respiratory therapy and urinary procedures. Colonization of skin, throat, stool, and nasal mucosa of patients is low at admission to the hospital but increases to as high as 50–70% with prolonged hospitalization and with the use of broad-spectrum antibiotics, chemotherapy, mechanical ventilation, and urinary catheters. Patients’ intestinal microbial flora may be altered by the broad-spectrum antibiotics, reducing resistance to colonization and permitting *P. aeruginosa* in the environment to populate the GI tract. Intestinal mucosal breakdown associated with medications, especially cytotoxic agents, and nosocomial enteritis may provide a pathway by which *P. aeruginosa* spreads to the lymphatics or bloodstream.

Pathology

The pathologic manifestations of *P. aeruginosa* infections depend on the site and type of infection. Because of its elaboration of toxins and invasive factors, the organism can often be seen invading blood vessels and causing vascular necrosis. In some infections there is spread through tissues with necrosis and microabscess formation. In patients with CF, focal and diffuse bronchitis/bronchiolitis leading to bronchiolitis obliterans has been reported.

Pathogenesis

Invasiveness of *P. aeruginosa* is mediated by a host of virulence factors. Bacterial attachment is facilitated by pili that adhere to epithelium damaged by prior injury or infection. Extracellular proteins, proteases, elastases, and cytotoxins disrupt cell membranes, and in response, host-produced cytokines cause capillary vascular permeability and induce an inflammatory response. Dissemination and bloodstream invasion follow extension of local tissue damage and are facilitated by the antiphagocytic properties of endotoxin, the exopolysaccharide, and protease cleavage of immunoglobulin G. *P. aeruginosa* also produces numerous exotoxins, including exotoxin A, which causes local necrosis and facilitates systemic bacterial invasion. *P. aeruginosa* possesses a type III secretion system composed of a needle structure that inserts into host cell membranes and allows secretion of exotoxins directly into host cells. *P. aeruginosa* strains with the gene encoding the type III secretion system–dependent phospholipase ExoU are associated with increased mortality compared with ExoU-negative strains, in retrospective studies of patients with *P. aeruginosa* **ventilator-associated pneumonia** . The host responds to infection with a robust inflammatory response, recruiting neutrophils to the infection site and producing antibodies to *P. aeruginosa* proteins such as exotoxin A and endotoxin. There is a lack of convincing data that these antibodies are protective against the establishment of infection.

In addition to acute infection, *P. aeruginosa* is also capable of chronic persistence thought to be partly a result of the formation of **biofilms** , organized communities of bacteria encased in an extracellular matrix that protects the organisms from the host immune response and the effects of antibiotics. Biofilm formation requires pilus-mediated attachment to a surface, proliferation of the organism, and production of exopolysaccharide as the main bacterial component of the extracellular matrix. A mature biofilm can persist despite an intense host immune response, is resistant to many antimicrobials, and is difficult to eradicate with current therapies.

Clinical Manifestations

Most clinical patterns are related to opportunistic infections in immunocompromised hosts (see Chapter 205) or are associated with shunts and indwelling catheters (Chapter 206). *P. aeruginosa* may be introduced into a minor wound of a healthy person as a secondary invader, and cellulitis and a localized abscess that exudes green or blue pus may follow. The characteristic skin lesions of *P. aeruginosa*, **ecthyma gangrenosum** , whether caused by direct inoculation or a metastatic focus secondary to septicemia, begin as pink macules and progress to hemorrhagic nodules and eventually to ulcers with ecchymotic and gangrenous centers with eschar formation, surrounded by an intense red areola (Table 232.1 and Fig. 232.1).

Table 232.1

Pseudomonas aeruginosa Infections

INFECTION	COMMON CLINICAL CHARACTERISTICS
Endocarditis	Native right-sided (tricuspid) valve disease with intravenous drug abuse
Pneumonia	Compromised local (lung) or systemic host defense mechanisms; nosocomial (respiratory), bacteremic (malignancy), or abnormal mucociliary clearance (cystic fibrosis) may be pathogenetic; cystic fibrosis is associated with mucoid *P. aeruginosa* organisms producing capsular slime
Central nervous system infection	Meningitis, brain abscess; contiguous spread (mastoiditis, dermal sinus tracts, sinusitis); bacteremia or direct inoculation (trauma, surgery)
External otitis	Swimmer's ear; humid warm climates, swimming pool contamination
Malignant otitis externa	Invasive, indolent, febrile toxic, destructive necrotizing lesion in young infants, immunosuppressed neutropenic patients, or diabetic patients; associated with 7th nerve palsy and mastoiditis
Chronic mastoiditis	Ear drainage, swelling, erythema; perforated tympanic membrane
Keratitis	Corneal ulceration; contact lens keratitis
Endophthalmitis	Penetrating trauma, surgery, penetrating corneal ulceration; fulminant progression
Osteomyelitis/septic arthritis	Puncture wounds of foot and osteochondritis; intravenous drug abuse; fibrocartilaginous joints, sternum, vertebrae, pelvis; open fracture osteomyelitis; indolent pyelonephritis and vertebral osteomyelitis

Urinary tract infection	Iatrogenic, nosocomial; recurrent UTIs in children, instrumented patients, and those with obstruction or stones
Intestinal tract infection	Immunocompromised, neutropenia, typhlitis, rectal abscess, ulceration, rarely diarrhea; peritonitis in peritoneal dialysis
Ecthyma gangrenosum	Metastatic dissemination; hemorrhage, necrosis, erythema, eschar, discrete lesions with bacterial invasion of blood vessels; also subcutaneous nodules, cellulitis, pustules, deep abscesses
Primary and secondary skin infections	Local infection; burns, trauma, decubitus ulcers, toe web infection, green nail (paronychia); whirlpool dermatitis; diffuse, pruritic folliculitis; vesiculopustular or maculopapular, erythematous lesions

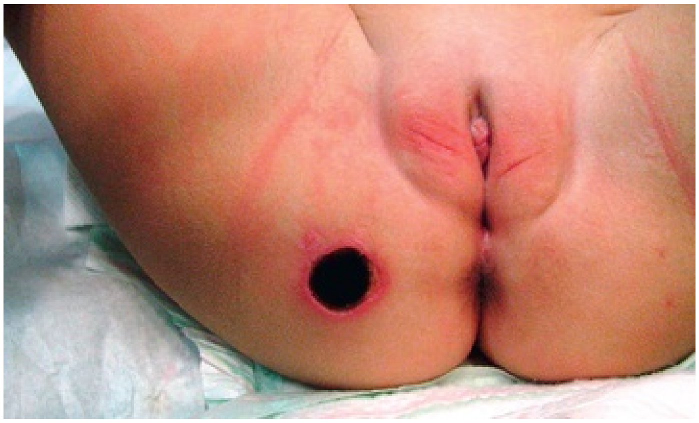

FIG. 232.1 Round, nontender skin lesion on 2 yr old female's buttock. Note the black ulcerated center of the lesion and its red margin. (From Ghanaiem H, Engelhard D: A healthy 2-year-old child with a round black skin lesion, *J Pediatr* 163:1225, 2013.)

Outbreaks of dermatitis and urinary tract infections (UTIs) caused by *P. aeruginosa* have been reported in healthy persons after use of pools or hot tubs. Skin lesions of folliculitis develop several hours to 2 days after contact with these water sources. Skin lesions may be erythematous, macular, papular, or pustular. Illness may vary from a few scattered lesions to extensive truncal involvement. In some children, malaise, fever, vomiting, sore throat, conjunctivitis, rhinitis, and swollen breasts may be associated with dermal lesions. UTIs caused by *P. aeruginosa* are most often nosocomial and are often associated with the presence of an indwelling urinary catheter, urinary tract malformations, and previous antibiotic use. UTIs may be minimized or prevented by prompt removal of the catheter and by early identification and corrective surgery of obstructive lesions when present.

Burns and Wound Infection

The surfaces of burns or wounds are frequently populated by *P. aeruginosa* and other gram-negative organisms; this initial colonization with a low number of adherent organisms is a prerequisite to invasive disease. *P. aeruginosa* colonization of a burn site may develop into **burn wound sepsis** , which has a high mortality rate when the density of organisms reaches a critical concentration. Administration of antibiotics may diminish the susceptible microbiologic flora, permitting strains of relatively resistant *P. aeruginosa* to flourish. Multiplication of organisms in devitalized tissues or associated with prolonged use of intravenous or urinary catheters increases the risk for septicemia with *P. aeruginosa*, a major problem in burned patients (see Chapter 92).

Cystic Fibrosis

P. aeruginosa is common in children with CF, with a prevalence that increases with increasing age and severity of pulmonary disease (see Chapter 432). Initial infection is caused by **nonmucoid environmental strains** of *P. aeruginosa*, but after a variable period, **mucoid strains** of *P. aeruginosa* that produce the antiphagocytic exopolysaccharide alginate, which are rarely encountered in other conditions, predominate. Repeated isolation of mucoid *P. aeruginosa* from the sputum is associated with increased morbidity and mortality. The infection begins insidiously or even asymptomatically, and the progression has a highly variable pace. In children with CF, antibody does not eradicate the organism, and antibiotics are only partially effective; thus, after infection becomes chronic, it cannot be completely eradicated. Repeated courses of antibiotics select for *P. aeruginosa* strains that are resistant to multiple antibiotics.

Immunocompromised Persons

Children with leukemia or other malignancies, particularly those who are receiving immunosuppressive therapy and who are neutropenic, typically with intravascular catheters, are extremely susceptible to septicemia caused by invasion of the bloodstream by *P. aeruginosa* that is colonizing the respiratory or GI tract. Signs of sepsis are often accompanied by a generalized vasculitis, and hemorrhagic necrotic lesions may be found in all organs, including the skin (ecthyma gangrenosum) (see Fig. 232.1). Hemorrhagic or gangrenous perirectal cellulitis or abscesses may occur, associated with ileus and profound hypotension.

Nosocomial Pneumonia

Although not a frequent cause of community-acquired pneumonia in children, *P. aeruginosa* does cause nosocomial pneumonia, especially ventilator-associated pneumonia, in patients of all ages. *P. aeruginosa* has historically been found to contaminate ventilators, tubing, and humidifiers. Such contamination is uncommon now because of disinfection practices and routine changing of equipment. Nevertheless, colonization of the upper respiratory tract and the GI tract may be followed by aspiration of *P. aeruginosa* –contaminated secretions, resulting in severe pneumonia. Prior use of broad-spectrum antibiotics is a risk factor for colonization with antibiotic-resistant strains of *P. aeruginosa*. One of the most challenging situations is distinguishing between colonization and pneumonia in intubated patients. This distinction can often only be resolved by using invasive culture techniques such as quantitative bronchoalveolar lavage.

Infants

P. aeruginosa is an occasional cause of **nosocomial bacteremia** in newborns and accounts for 2–5% of positive blood culture results in NICUs. A frequent focus preceding bacteremia is **conjunctivitis** . Older infants rarely present with community-acquired sepsis caused by *P. aeruginosa*. In the few reports describing community-acquired sepsis, preceding conditions included ecthyma-like skin lesions, virus-associated transient neutropenia, and prolonged contact with contaminated bath water or a hot tub.

Diagnosis

P. aeruginosa infection is rarely clinically distinctive. Diagnosis depends on recovery of the organism from the blood, cerebrospinal fluid (CSF), urine, or needle aspirate of the lung, or from purulent material obtained by aspiration of subcutaneous abscesses or areas of cellulitis. In the appropriate clinical setting, recovery of *P. aeruginosa* from a coughed or suctioned sputum may represent infection; but it also may only represent colonization, and clinical judgment is required. Rarely, skin lesions that resemble *P. aeruginosa* infection may follow septicemia caused by *Aeromonas hydrophila*, other gram-negative bacilli, and

Aspergillus. When *P. aeruginosa* is recovered from nonsterile sites such as skin, mucous membranes, or voided urine, quantitative cultures may be useful to differentiate colonization from invasive infection. In general, ≥100,000 colony-forming units/mL of fluid or gram of tissue is evidence suggestive of invasive infection. Quantitative cultures of tissue and skin are not routine and require consultation with the clinical microbiology laboratory.

Treatment

Systemic infections with *P. aeruginosa* should be treated promptly with an antibiotic to which the organism is susceptible in vitro. Response to treatment may be limited, and prolonged treatment may be necessary for systemic infection in immunocompromised hosts.

Septicemia and other aggressive infections should be treated with either 1 or 2 bactericidal agents. Although the number of agents required is controversial, the evidence continues to suggest that the benefit of adding a 2nd agent is questionable, even when studies have included immunosuppressed patients. Whether the use of 2 agents delays the development of resistance is also controversial, with evidence both for and against. Appropriate antibiotics for single-agent therapy include ceftazidime, cefepime, ticarcillin-clavulanate, and piperacillin-tazobactam. Gentamicin or another aminoglycoside may be used concomitantly for synergistic effect.

Ceftazidime has proved to be extremely effective in patients with CF, at 150-250 mg/kg/day divided every 6-8 hr intravenously (IV) to a maximum of 6 g/day. Piperacillin or piperacillin-tazobactam, 300-450 mg/kg/day divided every 6-8 hr IV to a maximum of 12 g/day, also has proved to be effective therapy for susceptible strains of *P. aeruginosa* when combined with an aminoglycoside. Studies of acute *Pseudomonas* infection in ICUs show that continuous infusions of piperacillin-tazobactam are more effective than the same daily dose given as pulse infusions.

Additional effective antibiotics include imipenem-cilastatin, meropenem, and aztreonam. Ciprofloxacin is an effective outpatient therapy, and while commonly used in children with CF, it is not approved in the United States for persons <18 yr old, except for oral treatment of UTIs or when there are no other agents to which the organism is susceptible. Inhaled therapy with either tobramycin or aztreonam is also used for chronic pulmonary infection, with inhaled colistin reserved for the treatment of resistant pseudomonads. It is important to base continued treatment on the results of susceptibility tests because **antibiotic resistance** of *P. aeruginosa* to 1 or more antibiotics is increasing. Macrolide therapy decreases pulmonary exacerbations in patients with chronic lung disease and *P. aeruginosa* infection. The mechanism likely relates to altering the virulence properties of *P. aeruginosa* rather than direct bacterial killing.

P. aeruginosa displays intrinsic and acquired resistance to antibiotics. It has many mechanisms for resistance to multiple classes of antibiotics, including but not limited to genetic mutation, production of β-lactamases, and drug efflux pumps. Throughout the United States there has been an alarming increase in multidrug-resistant (MDR) *P. aeruginosa* isolates recovered from children, with resistance to at least 3 classes of antibiotics. The rate of MDR *P. aeruginosa* increased to 26% in 2012 from 15.9% in 1999. Also, the rate of carbapenem-resistant *P. aeruginosa* increased from 12% to 20% during the same period. A newer agent with efficacy against many MDR *P. aeruginosa* isolates is ceftazidime/avibactam, a drug that combines ceftazidime with a β-lactamase inhibitor.

Meningitis can occur by spread from a contiguous focus, as a secondary focus when there is bacteremia, or after invasive procedures. *P. aeruginosa* meningitis is best treated with ceftazidime in combination with an aminoglycoside such as gentamicin, both given IV. Concomitant intraventricular or intrathecal treatment with gentamicin may be required when IV therapy fails but is not recommended for routine use.

Supportive Care

P. aeruginosa infections vary in severity from *superficial* to *intense* septic presentations. With severe infections there is often multisystem involvement and a systemic inflammatory response. Supportive care is similar to care for severe sepsis caused by other gram-negative bacilli and requires support of blood pressure, oxygenation, and appropriate fluid management.

Prognosis

The prognosis is dependent primarily on the nature of the underlying factors that predisposed the patient to *P. aeruginosa* infection. In severely immunocompromised patients, the prognosis for patients with *P. aeruginosa* sepsis is poor unless susceptibility factors such as neutropenia or hypogammaglobulinemia can be reversed. The overall mortality rate was 12.3% in one series of 232 children with *P. aeruginosa* bacteremia, with 3% dying within 48 hr of admission. Resistance of the organism to first-line antibiotics also decreases the chance of survival. The outcome may be improved when there is a urinary tract portal of entry, absence of neutropenia or recovery from neutropenia, and drainage of local sites of infection.

P. aeruginosa is recovered from the lungs of most children who die of CF and adds to the slow deterioration of these patients. The prognosis for normal development is poor in the few infants who survive *P. aeruginosa* meningitis.

Prevention

Prevention of infections is dependent on limiting contamination of the healthcare environment and preventing transmission to patients. Effective hospital infection control programs are necessary to identify and eradicate sources of the organism as quickly as possible. In hospitals, infection can be transmitted to children by the hands of personnel, from washbasin surfaces, from catheters and other hospital equipment, and from solutions used to rinse suction catheters.

Strict attention to hand hygiene before and between contacts with patients may prevent or interdict epidemic disease. Meticulous care and sterile procedures in suctioning of endotracheal tubes, insertion and maintenance of indwelling catheters, and removal of catheters as soon as medically reasonable greatly reduce the hazard of extrinsic contamination by *P. aeruginosa* and other gram-negative organisms. Prevention of follicular dermatitis caused by *P. aeruginosa* contamination of whirlpools or hot tubs is possible by maintaining pool water at a pH of 7.2-7.8. Antimicrobial stewardship programs that promote the appropriate use of antibiotics in the hospital setting are critical for reducing the rates of MDR *P. aeruginosa* by limiting unnecessary antibiotic use.

Infections in burned patients may be minimized by protective isolation, debridement of devitalized tissue, and topical applications of bactericidal cream. Administration of intravenous immunoglobulin may be used. Approaches under investigation to prevent infection include development of a *P. aeruginosa* vaccine. No vaccine is currently licensed in the United States.

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232.2

Burkholderia cepacia Complex

Thomas S. Murray, Robert S. Baltimore

Keywords

Burkholderia mallei
Burkholderia pseudomallei
cystic fibrosis
glanders
immune dysfunction
melioidosis

Burkholderia cepacia is a filamentous gram-negative rod now recognized to be a group of related species or **genomovars** (*B. cepacia*, *B. cenocepacia* , *B. multivorans*). It is ubiquitous in the environment but may be difficult to isolate from respiratory specimens in the laboratory, requiring an enriched, selective media oxidation-fermentation base supplemented with polymyxin B–bacitracin-lactose agar (OFPBL) and as long as 3 days of incubation.

B. cepacia is a classic opportunist that rarely infects normal tissue but can be a pathogen for individuals with preexisting damage to respiratory epithelium, especially persons with CF or with immune dysfunction such as chronic granulomatous disease. *B. cepacia* has multiple virulence factors, including lipopolysaccharide, flagella, and a type III secretion system that promotes invasion of respiratory epithelial cells. Resistance to many antibiotics and disinfectants appears to be a factor in the emergence of *B. cepacia* as a nosocomial pathogen. In critical care units it may colonize the tubing used to ventilate patients with respiratory failure. In some patients this colonization may lead to invasive pneumonia and septic shock. Although *B. cepacia* is found throughout the environment, human-to-human spread among CF patients occurs either directly by inhalation of aerosols or indirectly from contaminated equipment or surfaces, accounting for the strict infection control measures for children with CF who are colonized with *B. cepacia* . For example, CF patients colonized with *B. cepacia* are asked not to attend events where other persons with CF will be present. *B. cepacia* infections in persons with CF may represent chronic infection in some patients, but others, especially those with *Burkholderia cenocepacia* , genomovar III, can develop an acute respiratory syndrome of fever, leukocytosis, and progressive respiratory failure, with more rapid decline in pulmonary function and lower survival rate.

Treatment in hospitals should include standard precautions and avoidance of placing colonized and uncolonized patients in the same room. The use of antibiotics is guided by susceptibility studies of a patient's isolates, because the susceptibility pattern of this species is quite variable, and multiply resistant strains are common. Trimethoprim-sulfamethoxazole (TMP-SMX) and doxycycline or minocycline are potential oral therapies for *B. cepacia complex* . For IV therapy, meropenem with a 2nd agent such as TMP-SMX, doxycycline, minocycline, ceftazidime, or amikacin are potential options. Even though there is primary resistance to aminoglycosides, these agents may be useful in combination with other antibiotics. Treatment with 2 or more agents may be necessary to control the infection and avoid the development of resistance. No vaccine is currently available.

Burkholderia mallei (Glanders)

Glanders is a severe infectious disease of horses and other domestic and farm animals that is caused by *Burkholderia mallei,* a nonmotile gram-negative bacillus that is occasionally transmitted to humans. It is acquired by inoculation into the skin, usually at the site of a previous abrasion, or by inhalation of aerosols. Laboratory workers may acquire it from clinical specimens. The disease is relatively common in Asia, Africa, and the Middle East. The clinical manifestations include septicemia, acute or chronic pneumonitis, and hemorrhagic necrotic lesions of the skin, nasal mucous membranes, and lymph nodes. The diagnosis is usually made by recovery of the organism in cultures of affected tissue. Glanders is treated with sulfadiazine, tetracyclines, or chloramphenicol and streptomycin over many months. The disease has been eliminated from the United States, but interest in this organism has increased because of the possibility of its use as a bioterrorism agent (see Chapter 741). Although standard precautions are appropriate when caring for hospitalized infected patients, biosafety level 3 precautions are required for laboratory staff working with *B. mallei.* No vaccine is available.

Burkholderia pseudomallei (Melioidosis)

Melioidosis is an important disease of Southeast Asia and northern Australia and occurs in the United States mainly in persons returning from endemic areas. The causative agent is *Burkholderia pseudomallei,* an inhabitant of soil and water in the tropics. It is ubiquitous in endemic areas, and infection follows inhalation of dust, ingestion, or direct contamination of abrasions or wounds. Human-to-human transmission has only rarely been reported. Serologic surveys demonstrate that asymptomatic infection occurs in endemic areas. The disease may remain latent and appear when host resistance is reduced, sometimes years after the initial exposure. Diabetes mellitus is a risk factor for severe melioidosis.

Melioidosis may present as a **primary skin lesion** (vesicle, bulla, or urticaria) (Fig. 232.2). Pulmonary infection may be subacute and mimic tuberculosis or may present as an acute necrotizing pneumonia. Occasionally, septicemia occurs and numerous abscesses are noted in various organs of the body. Myocarditis, pericarditis, endocarditis, intestinal abscess, cholecystitis, acute gastroenteritis, UTIs, septic arthritis, paraspinal abscess, osteomyelitis, mycotic aneurysm, and generalized lymphadenopathy all have been observed. Melioidosis may also present as an encephalitic illness with fever and seizures. It is also an agent of severe wound infections after contact with contaminated water following a tsunami. Diagnosis is based on visualization of characteristic small, gram-negative rods in exudates or growth on laboratory media such as eosin–methylene blue or MacConkey agar. Serologic tests are available, and diagnosis can be established by a 4-fold or greater increase in antibody titer in an individual with an appropriate syndrome. It has been recognized as a possible agent of bioterrorism (see Chapter 741).

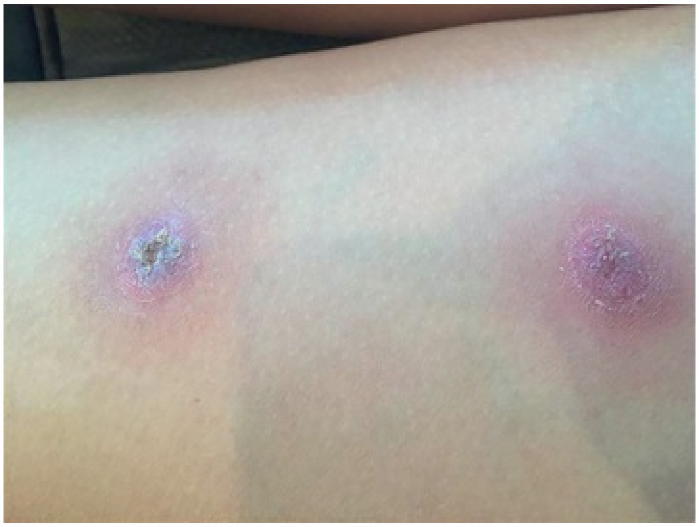

FIG. 232.2 Thigh abscesses at the sites of mosquito bites in 15 yr old Pennsylvania resident who had recently returned from Thailand, July 2016. Photo was taken 7 wk after onset. (From Mitchell PK, Campbell C, Montgomery MP, et al: Notes from the field: travel–associated melioidosis and resulting laboratory exposures—United States, 2016, *MMWR* 66(37):1001–1002, 2017.)

B. pseudomallei is susceptible to many antimicrobial agents, and the U.S. Centers for Disease Control and Prevention (CDC) recommends meropenem or ceftazidime as IV therapies and TMP-SMX or doxycycline as oral therapy. Other choices include aminoglycosides, tetracycline, chloramphenicol, and amoxicillin-clavulanate. Therapy should be guided by antimicrobial susceptibility tests; 2 or 3 agents such as ceftazidime or meropenem plus either TMP-SMX, sulfisoxazole, or an aminoglycoside are usually chosen for severe or septicemic disease. For severe disease, prolonged treatment for 2-6 mo is recommended to prevent relapses. Appropriate antibiotic therapy generally results in recovery.

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232.3

Stenotrophomonas

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Keywords

antimicrobial resistance
neonatal intensive care
nosocomial infection
Stenotrophomonas maltophilia

Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia* or *Pseudomonas maltophilia*) is a short to medium-sized, straight gram-negative bacillus. It is ubiquitous in nature and can be found in the hospital environment, especially in tap water or standing water, and may contaminate sinks and hospital equipment such as nebulizers. Strains isolated in the laboratory may be contaminants, may be a commensal from the colonized surface of a patient, or may represent an invasive pathogen. The species is an opportunist and is often recovered from immunosuppressed patients and patients with CF after multiple courses of antimicrobial therapy. Serious infections usually occur among those requiring intensive care, including neonatal intensive care, typically patients with ventilator-associated pneumonia or catheter-associated infections. Prolonged antibiotic exposure appears to be a frequent factor in nosocomial *S. maltophilia* infections, probably because of its endogenous antibiotic resistance pattern. Common types of infection include pneumonia following airway colonization and aspiration, bacteremia, soft tissue infections, endocarditis, and osteomyelitis. *S. maltophilia* bacteremia is a **nosocomial infection** associated with the presence of a central venous catheter.

Strains vary as to antibiotic susceptibility, and the treatment of *S. maltophilia* can be difficult because of inherent antimicrobial resistance. Data are lacking on whether there is clinical benefit to treat *S. maltophilia* recovered from the respiratory tract of a patient with CF. For invasive infections, **TMP-SMX** is the treatment of choice and is the only antimicrobial for which susceptibility is routinely reported. **Minocycline** monotherapy has recently been shown to be a viable alternative to TMP-SMX with fewer adverse effects and similar clinical outcomes. Mean inhibitory concentration testing is available for other antibiotics, such as ticarcillin-clavulanate, and reserved for TMP-SMX–resistant isolates. For resistant organisms or for patients who cannot tolerate sulfa drugs, other options based on clinical outcome include ciprofloxacin, as well as ceftazidime alone, or in combination with other agents such as aminoglycosides.

Tigecycline is a newer agent reported to have efficacy for treating a highly resistant isolate.

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CHAPTER 233

Tularemia *(Francisella tularensis)*

Kevin J. Downes

Tularemia is a **zoonosis** caused by the gram-negative bacterium *Francisella tularensis.* Tularemia is primarily a disease of wild animals; human disease is incidental and usually results from tick or deer fly bites or contact with infected live or dead wild animals. The illness caused by *F. tularensis* is manifest by multiple clinical syndromes, the most common consisting of an ulcerative lesion at the site of inoculation with regional lymphadenopathy or lymphadenitis. *F. tularensis* is also a potential agent of bioterrorism (see Chapter 741).

Etiology

Francisella tularensis is a small, nonmotile, pleomorphic, catalase-positive gram-negative coccobacillus. It can be classified into 4 main subspecies: *Francisella tularensis* subsp. *tularensis* (type A), *F. tularensis* subsp. *holarctica* (type B), *F. tularensis* subsp. *mediasiatica* , and *F. tularensis* subsp. *novicida* . Type A can be further subdivided into 4 distinct genotypes designated A1a, A1b, A2a, and A2b, with **A1b** appearing to produce more serious disease in humans. Although all subspecies of *F. tularensis* can cause human infections, types A and B are most common and type A is the most virulent. *F. tularensis* is an intracellular organism than can infect a number of host cell types, including macrophages, hepatocytes, and epithelial cells. It is one of the most virulent bacterial pathogens known, with as few as 10 microorganisms causing infections in humans and animals.

Epidemiology

Tularemia is primarily found in the Northern hemisphere. Type A is found predominantly in North America, whereas type B is found throughout the Northern hemisphere, including North America, Europe, and Asia. Human infections with type B are usually milder and have lower mortality rates compared to infections with type A. *F. tularensis* subsp. *mediasiatica* appears to be restricted to central Asia, whereas *F. tularensis* subsp. *novicida* has been isolated in North America, Australia, and Southeast Asia.

According to the Centers for Disease Control and Prevention (CDC), the number of annual reported cases of tularemia in the United States from 2005 to 2015 ranged from 93 to 315 per year. In 2015 the number of cases reported in the United States was the highest it had been over the past 50 years. Tularemia occurs all over the Unites States, with the majority of cases reported from central states (Fig. 233.1). The overall U.S. incidence of tularemia in 2015 was 0.10 per 100,000 residents; Wyoming (3.58/100,000), South Dakota (2.91/100,000), Nebraska (1.32/100,000), Kansas (1.17/100,000), and Colorado (0.95/100,000) were states with the highest incidence.

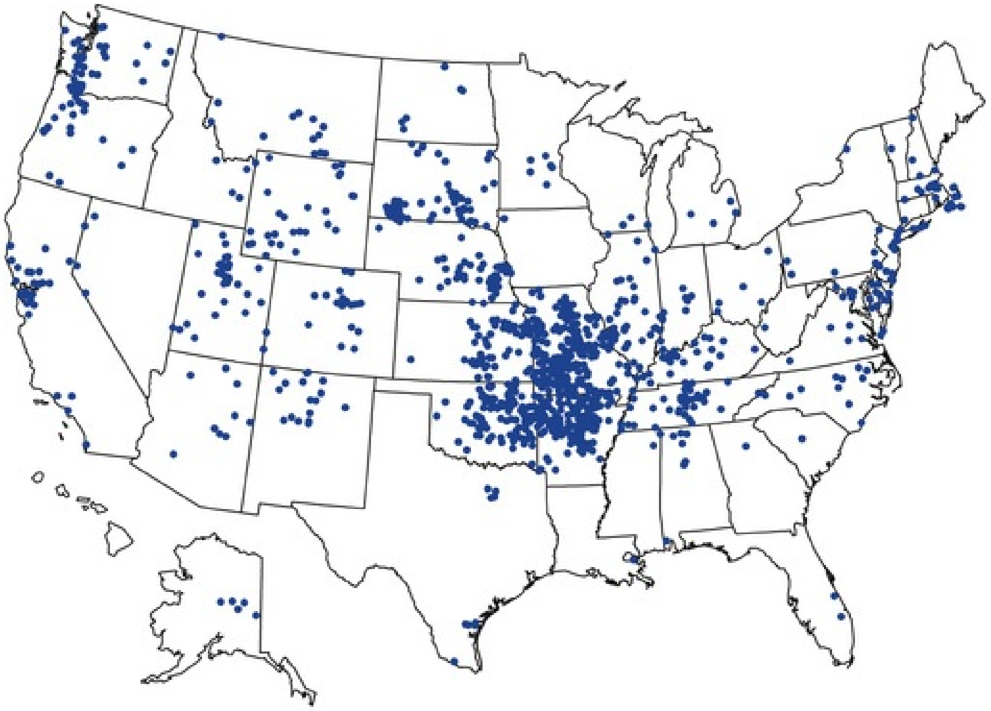

* One dot is placed randomly within county of residence for each reported case.

FIG. 233.1 **Reported cases of tularemia—United States, 2001–2010. (From Centers for Disease Control and Prevention: Tularemia—United States, 2001–2010. *MMWR* 62:963–966, 2013).**

Although cases of tularemia occur all year, most cases and outbreaks occur in warm, summer months (May-August). Tularemia is more common in males, and there is a bimodal distribution based on age, with peaks in childhood (5-9 yr) and later adulthood (65-69 yr), potentially because of greater opportunities for environmental and animal exposures at these ages. Fig. 233.2 shows the distribution of tularemia by age and gender from 2001 to 2010 in the United States.

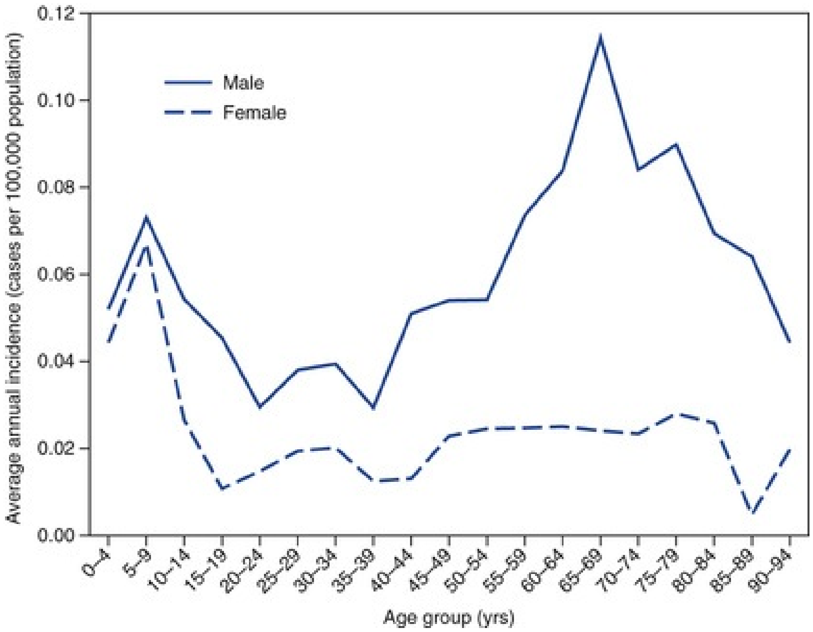

FIG. 233.2 **Incidence of tularemia, by age and gender—United States, 2001–2010. (From Centers for Disease Control and Prevention (CDC): Tularemia—United States, 2001–2010, *MMWR* 62:963–966, 2013).**

Pathogenesis

Of all the zoonotic diseases, tularemia is unusual because of the different modes of transmission of disease. A large number of animals serve as a reservoir for this organism. In the United States, **rabbits** and **ticks** are the principal reservoirs. Dogs may be an intermediate vector. In the United States, *Amblyomma americanum* (lone star tick), *Dermacentor variabilis* (dog tick), and *Dermacentor andersoni* (wood tick) are the most common tick vectors. These ticks usually feed on infected small rodents and later feed on humans. **Deer flies**

(*Chrysops* spp.) can also transmit tularemia and are present in the western United States. *F. tularensis* subsp. *tularensis* is carried by rabbits, ticks, and tabanid flies (e.g., deer flies), whereas subsp. *holarctica* is associated with aquatic habitats and transmitted primarily by mosquitoes, but also aquatic rodents (beavers, muskrats), hares, voles, ticks, tabanid flies, and ingestion of contaminated water (e.g., ponds, rivers).

The organism can penetrate both intact skin and mucous membranes (eyes, mouth, gastrointestinal [GI] tract, or lungs). Transmission can occur through the bite of infected ticks or other biting insects, by contact with infected animals or their carcasses, by consumption of contaminated foods or water, or through inhalation, as might occur in a laboratory setting or if a machine (e.g., lawn mower) runs over infected animal carcasses. However, this organism is not transmitted from person to person. The most common portal of entry for human infection is through the skin or mucous membrane. Hunting or skinning infected wild rodents, such as rabbits or prairie dogs, has been the source of infection in numerous reports. Domesticated animals such as cats and hamsters can also transmit tularemia.

Usually $>10^8$ organisms are required to produce infection if *F. tularensis* bacteria are ingested, but as few as 10 organisms may cause disease if they are inhaled or injected into the skin (i.e., insect bite). Infection with *F. tularensis* stimulates the host to produce antibodies, which have only recently been recognized as important in the immune response to this organism. The *F. tularensis* envelope is largely responsible for virulence and plays major roles in the ability of the organism to evade the immune system, attach to and invade cells, and cause severe disease. The body is most dependent on cell-mediated immunity to contain and eradicate *F. tularensis* . Tularemia is usually followed by specific protection; thus chronic infection or reinfection is unlikely.

Clinical Manifestations

Symptoms of tularemia vary based on the mode of transmission. The average incubation period from infection until clinical symptoms is 3 days (range: 1-21 days). Early symptoms of infection are generally nonspecific: fever, chills, myalgias, arthralgias, headache, and fatigue. Bacteremia may be common in the early stages of infection. A sudden onset of fever is common, and a pulse-temperature dissociation may be present. Findings on physical examination may include lymphadenopathy, hepatosplenomegaly, or skin lesions. Table 233.1

shows the frequency of various symptoms and examination findings.

Table 233.1

Common Clinical Manifestations of Tularemia in Children

SIGN OR SYMPTOM	FREQUENCY
Lymphadenopathy	96%
Fever (>38.3°C [100.9°F])	87%
Ulcer/eschar/papule	45%
Pharyngitis	43%
Myalgias/arthralgias	39%
Nausea/vomiting	35%
Hepatosplenomegaly	35%

The clinical manifestations of tularemia have been divided into 6 major clinical syndromes (Table 233.2). **Ulceroglandular** and **glandular** disease are the 2 most common forms of tularemia diagnosed in children. Infections following the bites of ticks or deer flies take these forms. Mortality with these forms of tularemia is rare, especially with implementation of effective treatment. Glandular disease, which is associated with lymphadenopathy without skin ulceration, may also result from minor skin abrasions. Within 48-72 hr after inoculation of the skin, an erythematous, tender, or pruritic papule may appear at the portal of entry. This papule may enlarge and form an ulcer with a black base. Ulcers are generally erythematous and painful with raised borders and may last several weeks, especially if untreated. Various other skin lesions have been described, including erythema multiforme and erythema nodosum. Approximately 20% of patients may develop a generalized maculopapular rash that occasionally becomes pustular.

Table 233.2

Clinical Syndromes of Tularemia in Children

CLINICAL SYNDROME	CHARACTERISTICS OF SYNDROME	FREQUENCY
Ulceroglandular	Skin ulcer/eschar, painful regional adenopathy	45%
Glandular	Regional adenopathy without detectable skin ulceration	25%
Pneumonia	Nonproductive cough, dyspnea, pleuritic chest pain; multilobar/diffuse infiltrates > lobar infiltrates on chest radiography	14%
Oropharyngeal	Pharyngitis, mucosal ulcers, cervical adenopathy	4%
Oculoglandular	Unilateral, painful, and often purulent conjunctivitis; chemosis; conjunctival ulcers; preauricular adenopathy	2%
Typhoidal	Severe systemic disease (sepsis-like syndrome): high fever, headaches,	2%

	myalgias, arthralgias, neurologic symptoms	

The unifying manifestation of glandular and ulceroglandular forms of tularemia is painful regional **lymphadenopathy** . Adenopathy may develop before, concurrent with, or after skin ulceration in ulceroglandular disease. Cervical or posterior auricular nodes are involved following bites on the head or neck, whereas enlarged axillary or epitrochlear nodes signal exposure on the arms. Nodes may vary in size from 0.5-10 cm ($\frac{1}{5}$-4 inches) and appear singly or in clusters. These affected nodes may become fluctuant and drain spontaneously and are often associated with overlying skin changes. Late suppuration of the involved nodes has been described in 25–30% of patients despite effective therapy. Examination of this material from such lymph nodes usually reveals sterile necrotic material.

Oropharyngeal tularemia results from consumption of poorly cooked meats or contaminated water. This syndrome is characterized by acute pharyngitis, with or without tonsillitis, and cervical lymphadenitis. Infected tonsils may become large and develop a yellowish white membrane that may resemble the membranes associated with diphtheria. GI disease may also occur and usually presents with mild, unexplained diarrhea or emesis but may progress to rapidly fulminant and fatal disease. GI bleeding can develop in more severe forms associated with intestinal ulcers.

Oculoglandular tularemia is uncommon, but when it does occur, the portal of entry is the conjunctiva. Contact with contaminated fingers or debris from crushed insects is the most common mechanism of this form of tularemia. Disease is generally unilateral, and the conjunctiva is painful and inflamed with yellowish nodules and pinpoint ulcerations. Purulent conjunctivitis with ipsilateral preauricular or submandibular lymphadenopathy can develop and is referred to as *Parinaud oculoglandular syndrome* . Corneal ulceration and perforation are uncommon but serious complications of this form of disease.

Typhoidal tularemia is usually associated with a large inoculum of organisms and is a term used to describe severe, bacteremic disease regardless of the mode of transmission or portal of entry. Patients are critically ill, and symptoms mimic those with other forms of sepsis: high fevers, confusion, rigors, myalgias, vomiting, and diarrhea. Clinicians practicing in tularemia-endemic regions must always consider this diagnosis in critically ill children. Complications of bacteremia with *F. tularensis* can include the development of meningitis, pericarditis, hepatitis, peritonitis, endocarditis, skin/soft tissue abscesses, and osteomyelitis. Because of its increased virulence, *F. tularensis* subsp. *tularensis* (type A disease) is more often associated with typhoidal tularemia. Patients with tularemia meningitis usually develop a marked cerebrospinal fluid (CSF) with a monocytic predominance. As with other causes of bacterial meningitis, CSF glucose is low and protein is high.

Pneumonia caused by *F. tularensis* (**pneumonic tularemia**) can develop following inhalation (primary pulmonary infection) or secondary to hematogenous spread in other forms of tularemia, particularly the typhoidal form. Inhalation-related infection has been described in laboratory workers who are working with the organism and results in a relatively high mortality rate. Aerosols from farming activities involving rodent contamination (haying, threshing) or animal carcass destruction with lawn mowers have been reported to cause pneumonia as well. Patients generally complain of a nonproductive cough, dyspnea, or pleuritic chest pain. Chest radiographs of patients with pneumonic tularemia typically reveal diffuse, patchy infiltrates rather than focal areas of consolidation. Pleural effusions may also be present. In pulmonary infections, hilar or mediastinal adenopathy can develop, and in severe forms, necrotizing or hemorrhagic pneumonitis. Mortality with pneumonic tularemia is high if untreated.

Diagnosis

The diagnosis can be delayed since symptoms are often similar to other, more common infections. The history and physical examination of the patient may suggest the diagnosis, especially if the patient has a history of animal or tick exposure. Routine hematologic blood tests are nondiagnostic. Definitive diagnosis is made by growth of *F. tularensis* in culture. *F. tularensis* can be isolated in culture of lymph node biopsies or aspirates, blood, wounds, pharyngeal swabs, pleural fluid, or sputum specimens, although cultures are positive in only approximately 10% of cases. *F. tularensis* can be cultured in the microbiology laboratory on cysteine-glucose–blood agar, but care should be taken to alert the personnel in the laboratory if this is attempted so that they can take the proper precautions to protect themselves from acquiring infection; biosafety level 3 containment is necessary to avoid occupational exposure. Histopathologic findings of involved lymph nodes demonstrate granulomas with central necrosis (early) and caseation (late). Unfortunately, these findings cannot distinguish tularemia from other causes of granulomatous lymphadenitis, such as tuberculosis, cat-scratch disease (*Bartonella henselae* infection), or sarcoidosis.

Polymerase chain reaction of tissue specimens may be more sensitive than culture but is currently only used to make a presumptive diagnosis.

The diagnosis of tularemia is usually established through the use of a standard and highly reliable serum agglutination test. In the standard tube agglutination test, a single titer of ≥1 : 160 in a patient with a compatible history and physical findings can establish the diagnosis. A microagglutination test is also available, and ≥1 : 128 is considered positive. A 4-fold increase in titer from paired serum samples collected >2 wk apart (acute to convalescent phase) can also be considered diagnostic. False-negative serologic responses can be obtained early in the infection or if paired sera are collected too close together. Once infected, patients may have a positive agglutination test result (1 : 20 to 1 : 80) that persists for life. Other testing techniques available include enzyme-linked immunosorbent assay, analysis of urine for tularemia antigen, direct fluorescent antibody, and immunohistochemical staining; these studies have limited roles in establishing the diagnosis of tularemia.

Differential Diagnosis

The differential diagnosis of **ulceroglandular** or **glandular** tularemia is broad and includes infestation with pathogens that cause acute or subacute lymphadenitis: cat-scratch disease *(B. henselae)* , infectious mononucleosis, typical bacterial pathogens (*Staphylococcus aureus,* group A streptococcus), *Mycobacterium tuberculosis,* nontuberculous mycobacteria, *Toxoplasma gondii, Sporothrix schenckii,* plague *(Yersinia pestis)* , anthrax *(Bacillus anthracis)* , melioidosis *(Burkholderia pseudomallei)* , and rat-bite fever *(Streptobacillus moniliformis, Spirillum minus)* . Noninfectious processes such as sarcoidosis and Kawasaki disease can also present similarly. **Oculoglandular** disease may also occur with other infectious agents, such as *B. henselae, Treponema pallidum, Coccidioides immitis,* herpes simplex virus (HSV), adenoviruses, and the bacterial agents responsible for purulent conjunctivitis. **Oropharyngeal** tularemia must be differentiated from the same diseases that cause ulceroglandular/glandular disease and from cytomegalovirus, HSV, adenovirus, and other viral or bacterial etiologies. **Pneumonic** tularemia must be differentiated from the other non–β-lactam–responsive organisms that cause community-acquired pneumonia, such as *Mycoplasma* and *Chlamydophila,* as well as mycobacteria, fungi, and rickettsiae. Inhalation plague, anthrax, and Q fever could present similarly. **Typhoidal** tularemia must be differentiated from other forms of sepsis as well as from enteric fever (typhoid and paratyphoid fever) and brucellosis.

Treatment

Aminoglycosides are the mainstay of treatment of tularemia: gentamicin is the drug of choice for the treatment of tularemia in children and streptomycin is the drug of choice in adults. Table 233.3 displays therapeutic options for treatment of tularemia as well for postexposure prophylaxis. Chloramphenicol and tetracyclines have been used, but the high relapse rate has limited their use in children. They are often used as adjunctive therapy for treatment of tularemia meningitis. Fluoroquinolones (ciprofloxacin) have been successful in mild-moderate cases of illness, especially those caused by subsp. *holarctica* . β-Lactam agents demonstrate poor activity against *F. tularensis* and should not be used.

Table 233.3

Recommended Treatment for Patients With Tularemia

INDICATION	DRUG AND DOSAGE
Moderate-severe disease	Gentamicin, 5 mg/kg/day IV or IM divided every 8-12 hr, *or* Streptomycin, 15 mg/kg/dose IM every 12 hr (max 1 g/dose)
Mild disease	Gentamicin, 5 mg/kg/day IV or IM divided every 8-12 hr, *or* Ciprofloxacin, 15 mg/kg/dose every 12 hr (max 500 mg/dose)
Meningitis	Streptomycin or gentamicin, in doses given for moderate-severe disease, *plus* chloramphenicol, 50-100 mg/kg/day IV divided every 6 hr (max 1000 mg/dose), *or* doxycycline, 2.2 mg/kg/dose IV every 12 hr (max 100 mg/dose)
Postexposure prophylaxis	Doxycycline, 2.2 mg/kg/dose every 12 hr (max 100 mg/dose), *or* Ciprofloxacin, 15 mg/kg/dose every 12 hr (max 500 mg/dose)

IM, Intramuscularly; IV, intravenously.

Therapy with aminoglycosides is typically continued for 7-10 days, but a longer course is needed in more severe disease. In mild cases, 5-7 days may be sufficient. Treatment with chloramphenicol or doxycycline should be continued for 14-21 days because of an increased risk of relapse, likely because of their bacteriostatic nature. Postexposure prophylaxis is generally recommended for 14 days.

Prognosis

Poor outcomes are associated with a delay in appropriate treatment, but with rapid recognition and treatment, fatalities are exceedingly rare. The mortality rate for severe untreated disease (e.g., pneumonia, typhoidal disease) can be as high as 30% in these situations, but in general the overall mortality rate is <1%. Subspecies *tularensis* is associated with more aggressive disease and worse outcomes than subsp. *holarctica* .

Relapses are uncommon if gentamicin or streptomycin is used. Patients typically defervesce within 24-48 hr after starting therapy, although lymphadenopathy can take several weeks to resolve fully. Late suppuration of involved lymph nodes may occur despite adequate therapy. Patients who have not started on appropriate therapy early may respond more slowly to antimicrobial therapy.

Prevention

Prevention of tularemia is based on *avoiding exposure* . Children living in tick-endemic regions should be taught to avoid tick-infested areas. Families should have a tick control plan for their immediate environment and for their pets. Protective clothing should be worn when entering a tick-infested area. Insect repellents can be used safely in infants and children. Children should undergo frequent tick checks during and after their time in tick-infested areas. If ticks are found on the child, **forceps** should be used to pull the tick straight out. The skin should be cleansed before and after this procedure.

Children should also be taught to avoid sick and dead animals. Dogs and cats are most likely to bring these animals to a child's attention. Children should be encouraged to wear gloves, masks, and eye protection while cleaning wild game. Families should cook wild game thoroughly before eating.

Prophylactic antimicrobial agents are not effective in preventing tularemia and should not be used after exposure. No tularemia vaccine is currently available for the general public. **Standard precautions** are adequate for hospitalized children with tularemia, since no cases of person-to-person transmission have been identified.

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CHAPTER 234

Brucella

Kevin J. Downes

Human **brucellosis** is caused by organisms of the genus *Brucella* and continues to be a major public health problem worldwide. Humans are accidental hosts and acquire this zoonosis from direct contact with an infected animal (cattle, sheep, camels, goats, and pigs) or consumption of products of an infected animal. Although brucellosis is widely recognized as an occupational risk among adults working with livestock, much of the brucellosis in children is food-borne and is associated with consumption of unpasteurized dairy products. *Brucella* spp. are also potential agents of bioterrorism (see Chapter 741).

Etiology

Brucella abortus (cattle), *Brucella melitensis* (goats and sheep), *Brucella suis* (swine), and *Brucella canis* (dogs) are the most common organisms responsible for human disease. These organisms are small, aerobic, non–spore-forming, nonmotile, gram-negative coccobacillary bacteria. *Brucella* spp. are fastidious in their growth but can be grown on various laboratory media, including blood and chocolate agars.

Epidemiology

Brucellosis is endemic in many parts of the world and is especially prevalent in the Mediterranean basin, Persian Gulf, Indian subcontinent, and parts of Mexico and Central and South America. There are approximately 500,000 new cases annually worldwide, although accurate estimates of the prevalence of disease are lacking because of underreporting and underdiagnosis. Childhood brucellosis accounts for 10–30% of cases. *B. melitensis* is the most prevalent species causing human brucellosis and is most often carried by sheep, goats, camels, and buffalo. Because of improved sanitation and animal vaccination, brucellosis has become rare in industrialized countries where recreational or occupational exposure to infected animals is a major risk factor for the development of disease. A history of travel to endemic regions or consumption of exotic food or unpasteurized dairy products may be an important clue to the diagnosis of human brucellosis. In the United States, >50% of cases occur in California, Florida, and Texas; hunting **feral swine** in these states is a recently recognized risk factor. All age-groups can be infected by *Brucella*, and infections are more common in males, likely because of more frequent occupational and environmental exposures.

Pathogenesis

Modes of transmission for these organisms include *inoculation* through cuts or abrasions in the skin, inoculation of the conjunctiva, *inhalation* of infectious aerosols, or *ingestion* of contaminated meat or dairy products. **Infected livestock** are the most common source of human infection. In children the primary means of infection is through eating or drinking unpasteurized or raw dairy products. Individuals in endemic areas with occupational exposures to animals, such as farmers and veterinarians, are at highest risk. Laboratory workers are more often exposed to infected aerosols. The risk for infection depends on the nutritional and immune status of the host, the route of inoculum, and the species of *Brucella*. For reasons that remain unclear, it has been suggested that *B. melitensis* and *B. suis* are more virulent than *B. abortus* or *B. canis.*

The major virulence factor for *Brucella* appears to be its cell wall **lipopolysaccharide** (LPS). Strains containing smooth LPS have been demonstrated to have greater virulence and are more resistant to killing by polymorphonuclear leukocytes. These organisms are facultative intracellular pathogens that can survive and replicate within the mononuclear phagocytic cells (monocytes, macrophages) of the reticuloendothelial system. Even though *Brucella* spp. are chemotactic for entry of leukocytes into the body, the leukocytes are less efficient at killing these organisms than other bacteria despite the assistance of serum factors such as complement. *Brucella* spp. possess multiple strategies to evade immune responses and establish and maintain chronic infection. Specifically, during chronic stages of infection, organisms persist within the liver, spleen, lymph nodes, and bone marrow and result in granuloma formation.

Antibodies are produced against the LPS and other cell wall antigens, providing a means of diagnosis and probably playing a role in long-term immunity. The major factor in recovery from infection appears to be development of a cell-mediated response, resulting in macrophage activation and enhanced intracellular killing. Specifically, sensitized T lymphocytes release cytokines (e.g., interferon-γ, tumor necrosis factor-α), which activate the macrophages and enhance their intracellular killing capacity.

Clinical Manifestations

Brucellosis is a systemic illness that can be very difficult to diagnose in children. Symptoms can be acute or insidious in nature and are usually nonspecific. The incubation period is generally 2-4 wk but may be shorter with *B. melitensis* . Fever is present in >75% of cases, and the fever pattern can vary widely. The most common physical complaints are arthralgia, myalgia, and back pain. Systemic symptoms, such as fatigue, sweats, chills, anorexia, headache, weight loss, and malaise, are reported in the majority of adult cases but are less frequent in children. Other associated symptoms include abdominal pain, diarrhea, rash, vomiting, cough, and pharyngitis.

The most common physical manifestation of brucellosis is hepatic and splenic enlargement, which is present in approximately half of cases. Whereas arthralgia is common, arthritis occurs in a minority of cases. Arthritis is typically monoarticular and most often involves the knee or hip in children and the sacroiliac joint in adolescents and adults. A number of skin lesions have been described with brucellosis, but there is no typical rash for this infection. Epididymo-orchitis is more common in adolescents and adults.

In endemic countries, *Brucella* spp. are an important cause of occult bacteremia in young children. Because of the organism's ability to establish chronic infection, hepatic and splenic abscesses may develop. Serious manifestations of brucellosis include endocarditis, meningitis, osteomyelitis, and spondylitis. Although headache, mental inattention, and depression may be demonstrated in patients with uncomplicated brucellosis, invasion of the nervous system occurs in only 1–4% of cases. Neonatal and congenital infections with these organisms have also been described, resulting from transplacental transmission, breast milk, and blood transfusions. The signs and symptoms associated with congenital/neonatal brucellosis are nonspecific.

Hematologic abnormalities are common with brucellosis; thrombocytopenia, leukopenia, anemia, or pancytopenia may occur. Hemolytic complications can include microangiopathic hemolytic anemia, thrombotic microangiopathy, and autoimmune hemolytic anemia. Elevations of liver enzymes occur in approximately half of cases.

Diagnosis

A definitive diagnosis of brucellosis is established by recovering the organisms from the blood, bone marrow, or other tissues. Unfortunately, cultures are insensitive and positive only in a minority of cases. Isolation of the organism may require as long as 4 wk from a blood culture sample unless the laboratory is using an automated culture system such as the lysis-centrifugation method, where the organism can be recovered in 5-7 days. Therefore, it is prudent to alert the clinical microbiology laboratory that brucellosis is suspected so that cultures can be held longer. Bone marrow cultures may be superior to blood cultures when evaluating patients who have received previous antimicrobial therapy.

Because of the low yield of cultures, various serologic tests have been applied to the diagnosis of brucellosis. The serum agglutination test is the most widely used and detects antibodies against *B. abortus, B. melitensis,* and *B. suis*. This method does not detect antibodies against *B. canis* because this species lacks the smooth LPS; *B. canis* –specific antigen is required to diagnose this species. No single titer is ever diagnostic, but most patients with acute infections have titers of ≥1 : 160. Antibodies can generally be detected within 2-4 wk after infection. Low titers may be found early in the course of the illness, requiring the use of acute and convalescent sera testing to confirm the diagnosis: 4-fold increase in titers drawn ≥2 wk apart. Because patients with active infection have both an immunoglobulin M (IgM) and an IgG response and the serum agglutination test measures the total quantity of agglutinating antibodies, the total quantity of IgG is measured by treatment of the serum with 2-mercaptoethanol. This fractionation is important in determining the significance of the antibody titer, because low levels of IgM can remain in the serum for weeks to months after the infection has been treated. IgG titers decrease with effective therapy, and a negative 2-mercaptoethanol test after treatment indicates a favorable response.

It is important to remember that all serologic results must be interpreted in light of a patient's history and physical examination. False-positive results from cross-reacting antibodies to other gram-negative organisms, such as *Yersinia enterocolitica, Francisella tularensis,* and *Vibrio cholerae,* can occur. In addition, the prozone effect can give false-negative results in the presence of high titers of antibody. To avoid this issue, serum that is being tested should be diluted to ≥1 : 320.

The enzyme immunoassay should only be used for suspected cases with negative serum agglutination tests or for the evaluation of patients in the following situations: (1) complicated cases, (2) suspected chronic brucellosis, or (3) reinfection. Polymerase chain reaction assays have been developed but are not available in most clinical laboratories.

Differential Diagnosis

Brucellosis should be considered in the differential diagnosis of fever of unknown origin in endemic areas. It may present similar to other infections such as tularemia, cat-scratch disease, malaria, typhoid fever, histoplasmosis, blastomycosis, and coccidioidomycosis. Infections caused by *Mycobacterium tuberculosis,* atypical mycobacteria, rickettsiae, and *Yersinia* can also present similar to brucellosis.

Treatment

Many antimicrobial agents are active in vitro against *Brucella* spp., but the clinical effectiveness does not always correlate with these results. Agents that provide good intracellular killing are required for elimination of *Brucella* infections. Because of the risk of relapse with monotherapy, combination therapy is generally recommended. In children, **doxycycline** or trimethoprim-sulfamethoxazole (TMP-SMX) in combination with **rifampin** are most often used for uncomplicated (e.g., nonfocal) infections (Table 234.1). While data support that the combination of doxycycline plus an aminoglycoside (streptomycin, gentamicin) is superior to the above oral combination therapies, with fewer treatment failures and relapses, the inconvenience of parenteral therapy may limit this approach in uncomplicated cases, particularly in resource-limited settings. Fluoroquinolones may be a viable alternative to doxycycline or TMP-SMX but have not been studied in children. For uncomplicated infections, a 6 wk course of therapy is recommended.

Table 234.1

Recommended Therapy for Treatment of Brucellosis

AGE/CONDITIONS	ANTIMICROBIAL AGENT	DOSE	ROUTE*	DURATION†
≥8 yr	Doxycycline	4.4 mg/kg/day divided twice daily; max 200 mg/day	PO	≥6 wk
	plus			
	Rifampin	15-20 mg/kg/day in 1 or 2 divided doses; max 600-900 mg/day	PO	≥6 wk
	Alternative:			
	Doxycycline	4.4 mg/kg/day divided twice daily; max 200 mg/day	PO	≥6 wk
	plus			
	Streptomycin	20-40 mg/kg/day in 2-4 divided doses; max 1 g/day	IM	2-3 wk
	or			
	Gentamicin	6-7.5 mg/kg/day in 3 divided doses	IM/IV	1-2 wk
<8 yr	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP (10 mg/kg/day; max 480 mg/day) and SMX (50 mg/kg/day; max 2.4 g/day)	PO	≥6 wk
	plus			
	Rifampin	15-20 mg/kg/day in 1 or 2 divided doses; max 600-900 mg/day	PO	≥6 wk
Meningitis, osteomyelitis/spondylitis endocarditis	Doxycycline	4.4 mg/kg/day divided twice daily; max 200 mg/day	PO	≥4-6 mo
	plus			
	Gentamicin	6-7.5 mg/kg/day in 3 divided doses	IV	1-2 wk
	plus			
	Rifampin	15-20 mg/kg/day in 1 or 2 divided doses; max 600-900 mg/day	PO	≥4-6 mo

[*] PO, Oral (by mouth): IM, intramuscular; IV, intravenous.

[†] Longer courses of therapy may be needed for more severe or complicated cases.

In more serious infections (e.g., endocarditis, meningitis, osteoarticular), 3-drug therapy is advised. An aminoglycoside (streptomycin, gentamicin) should be administered for the 1st 7-14 days along with doxycycline or TMP-SMX plus rifampin, which are then continued for 4-6 mo. Treatment may need to be continued for up to 1 yr in severe cases of central nervous system (CNS) disease.

Although **relapse** occurs in approximately 5–15% of cases, antimicrobial resistance is rare. Relapse is confirmed by isolation of *Brucella* within weeks to months after therapy has ended. Prolonged treatment is the key to preventing disease relapse, and steps should be taken to assure compliance with the long courses of therapy needed to achieve eradication.

Prognosis

The primary indication of clinical response is resolution of symptoms, which may be slow; the average time to defervescence is 4-5 days. The prognosis after therapy is excellent if patients are compliant with the prolonged therapy. Patients should be followed clinically and serologically for 1-2 yr. Before the use of antimicrobial agents, the course of brucellosis was often prolonged and associated with death. Since the institution of specific therapy, most deaths are a result of specific organ system involvement (e.g., endocarditis) in complicated cases. Initiation of antimicrobial therapy may precipitate a Jarisch-Herxheimer–like reaction, presumably because of a large antigen load, but these reactions are rarely associated with serious complications.

Prevention

Prevention of brucellosis depends on effective eradication of the organism from livestock. **Pasteurization** of milk and dairy products for human consumption remains an important aspect of prevention. It should be noted that certification of raw milk does not eliminate the risk of brucellosis acquisition. No vaccine currently exists for use in children, and therefore education of the public continues to have a prominent role in prevention of brucellosis.

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CHAPTER 235

Legionella

Jeffrey S. Gerber

Legionellosis comprises **legionnaires disease** (*Legionella* pneumonia), other invasive extrapulmonary *Legionella* infections, and an acute flulike illness known as **Pontiac fever.** In contrast to the syndromes associated with invasive disease, Pontiac fever is a self-limited illness that develops after aerosol exposure and may represent a toxic or hypersensitivity response to *Legionella*.

Etiology

Legionellaceae are aerobic, non–spore-forming, nonencapsulated, gram-negative bacilli that stain poorly with Gram stain when performed on smears from clinical specimens. Stained smears of *Legionella pneumophila* taken from colonial growth resemble *Pseudomonas*. Unlike other *Legionella* species, *Legionella micdadei* stains acid fast. Although 58 species of the genus have now been identified, the majority (90%) of clinical infections are caused by *L. pneumophila*, and most of the remainder are caused by *L. micdadei*, *Legionella bozemanii*, *Legionella dumoffii*, and *Legionella longbeachae*.

The organisms are fastidious and require L -cysteine, ferric ion, and α-keto acids for growth. Colonies develop within 3-5 days on buffered charcoal yeast extract agar, which may contain selected antibiotics to inhibit overgrowth by other microorganisms; *Legionella* rarely grows on routine laboratory media.

Epidemiology

The environmental reservoir of *Legionella* in nature is fresh water (lakes, streams, thermally polluted waters, potable water), and invasive pneumonia (legionnaires disease) is related to exposure to potable water or to aerosols containing the bacteria. Growth of *Legionella* occurs more readily in warm water, and exposure to warm-water sources is an important risk factor for disease. *Legionella* organisms are facultative intracellular parasites that grow inside protozoa present in biofilms, consisting of organic and inorganic material found in plumbing and water storage tanks and various other bacterial species. Epidemic and sporadic cases of community-acquired legionnaires disease can be attributed to potable water in the local environment of the patient. Risk factors for acquisition of sporadic community-acquired pneumonia include exposure to cooling towers, nonmunicipal water supply, residential plumbing repairs, and lower water heater temperatures, which facilitate growth of bacteria or lead to release of a bolus of biofilm containing *Legionella* into potable water. The mode of transmission may be by inhalation of aerosols or by microaspiration. Outbreaks of legionnaires disease have been associated with protozoa in the implicated water source; replication within these eukaryotic cells presumably amplifies and maintains *Legionella* within the potable-water distribution system or in cooling towers. Outbreaks of community-acquired pneumonia and some nosocomial outbreaks have been linked to common sources, including potable hot-water heaters, evaporative condensers, cooling towers, whirlpool baths, water births, humidifiers, and nebulizers. Travel-associated legionnaires disease and Pontiac fever are increasingly recognized in major outbreaks. Although person-to-person transmission has been reported, if it does occur, it is extremely rare.

Hospital-acquired infections are most often linked to potable water. Exposure may occur through 3 general mechanisms: (1) inhalation of contaminated water vapor through artificial ventilation; (2) aspiration of ingested microorganisms, including those in gastric feedings that are mixed with contaminated tap water; and (3) inhalation of aerosols from showers, sinks, and fountains. Extrapulmonary legionellosis may occur through topical application of contaminated tap water into surgical or traumatic wounds. In contrast to legionnaires disease, Pontiac fever outbreaks have occurred through exposure to aerosols from whirlpool baths and ventilation systems.

The incidence of legionellosis in the United States increased from 1,100 cases in 2000 to >6000 cases in 2015, for a national incidence rate of 1.9 per 100,000 population based on reporting to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Disease Surveillance System. Because this is a passive reporting system, these are likely underestimates of the incidence of disease. An active laboratory-based and population-based surveillance system for tracking *Legionella* infections was recently launched by CDC, which will help to better assess its true incidence and epidemiology. (For up-to-date information, see https://www.cdc.gov/legionella/ .)

Legionellosis demonstrates geographic differences, and the vast majority of cases are classified as legionnaires disease (99.5%), with a small fraction as Pontiac fever (0.5%). *Legionella* infections are reported most frequently in fall and summer, and recent studies show an association with total monthly rainfall and humidity. Approximately 0.5–5.0% of those exposed to a common source develop pneumonia, whereas the attack rate in Pontiac fever outbreaks is very high (85–100%). Although *Legionella* is associated with 0.5–10% of pneumonia cases in adults, it is a rare cause of pneumonia in children, accounting for <1% of cases; however, infrequent testing for *Legionella* might underestimate its prevalence. Acquisition of antibodies to *L. pneumophila* in healthy children occurs progressively over time, although these antibodies presumably reflect subclinical infection or mild respiratory disease or antibodies that cross-react with other bacterial species. Community-acquired legionnaires disease in children is increasingly reported (1.7% of reported cases), and most cases occur in children 15-19 yr old, followed by infants. The incidence in infants is reported to be 0.11 per 100,000. Legionnaires disease is particularly severe in neonates. The epidemiology of hospital-acquired legionnaires disease in children is derived almost exclusively from case reports, so the true incidence of this entity is unknown.

Pathogenesis

Although *Legionella* can be grown on artificial media, the intracellular environment of eukaryotic cells provides the definitive site of growth. *Legionella* organisms are facultative intracellular parasites of eukaryotic cells. In nature, *Legionella* replicate within protozoa found in fresh water. In humans the main target cell for *Legionella* is the alveolar macrophage, although other cell types may also be invaded. After entry, virulent strains of *L. pneumophila* stimulate the formation of a special phagosome that permits bacterial replication to proceed. The phagosome consists of components of the endoplasmic reticulum and escapes the degradative lysosomal pathway. Growth in macrophages occurs to the point of cell death, followed by reinfection of new cells, until these cells are activated and can subsequently kill intracellular microorganisms. Acute, severe infection of the lung provokes an acute inflammatory response and necrosis. Early on, more bacteria are found in extracellular spaces as a result of intracellular replication, lysis, and release of bacteria. Subsequently, macrophage activation and other immune responses produce intense infiltration of tissue by macrophages that contain intracellular bacteria, ultimately leading to control of bacterial replication and killing.

Corticosteroid therapy poses a high risk for infection by interfering with T-cell and macrophage function. Although community-acquired legionnaires disease may occur in healthy, immunocompetent patients without other comorbid conditions, those who have defects in cellular-mediated immunity are at higher risk for infection. As in other diseases caused by facultative intracellular microorganisms, the outcome is critically dependent on the specific and nonspecific immune responses of the host, particularly macrophage and T-cell responses.

Clinical Manifestations

Legionnaires disease was originally believed to cause atypical pneumonia associated with extrapulmonary signs and symptoms, including diarrhea, confusion, hyponatremia, hypophosphatemia, abnormal liver function test results, and renal dysfunction. Although a subset of patients may exhibit these classic manifestations, *Legionella* infection typically causes pneumonia that is indistinguishable from pneumonia produced by other infectious agents. Fever, cough, and chest pain are common presenting symptoms; the cough may be productive of purulent sputum or may be nonproductive. Although the classic chest radiographic appearance demonstrates rapidly progressive alveolar filling infiltrates, the chest radiographic appearance is widely variable, with tumor-like shadows, evidence of nodular infiltrates, unilateral or bilateral infiltrates, or cavitation, although cavitation is rarely seen in immunocompetent patients. This picture overlaps substantially with disease caused by *Streptococcus pneumoniae*. Although pleural effusion is less often associated with legionnaires disease, its frequency varies so widely that neither the presence nor absence of effusion is helpful in the differential diagnosis.

Most reports of nosocomial *Legionella* pneumonia in children demonstrate the following clinical features: rapid onset, temperature >38.5°C (101.3°F), cough, pleuritic chest pain, tachypnea, and dyspnea. Abdominal pain, headache, and diarrhea are also common. Chest radiographs reveal lobar consolidations or diffuse bilateral infiltrates, and pleural effusions may be noted. Usually there is no clinical response to broad-spectrum β-lactam (penicillins and cephalosporins) or aminoglycoside antibiotics. Concomitant infection with other pathogens, including *M. pneumoniae* and *C. pneumoniae* , occurs in 5–10% of cases of legionnaires disease; therefore detection of another potential pulmonary pathogen does not preclude the diagnosis of legionellosis.

Risk factors for legionnaires disease in adults include chronic diseases of the lung (smoking, bronchitis), older age, diabetes and renal failure, immunosuppression associated with organ transplantation, corticosteroid therapy, and episodes of aspiration. In surveys of community-acquired infection, a significant number of adults have no identified risk factors. The number of reported cases of community-acquired legionnaires disease in children is small. Among these, immunocompromised status, especially corticosteroid treatment, coupled with exposure to contaminated potable water, is the major risk factor. Infection in a few children with chronic pulmonary disease without immune deficiency has also been reported, but infection in children lacking any risk factors is uncommon. The modes of transmission of community-acquired disease in children include exposure to mists, fresh water, water coolers, and other aerosol-generating apparatuses. Nosocomial *Legionella* infection has been reported more frequently than community-acquired disease in children and usually occurs in those who are immunocompromised (e.g., stem cell transplants, solid organ transplants), those with structural lung disease, or neonates receiving mechanical ventilation. The modes of acquisition include **microaspiration** , frequently associated with nasogastric tubes, and **aerosol inhalation** . Bronchopulmonary *Legionella* infections are reported in patients with cystic fibrosis and have been associated with aerosol therapy or mist tents. Legionnaires disease is also reported in children with asthma and tracheal stenosis. Chronic corticosteroid therapy for asthma is a reported risk factor for *Legionella* infections in children. Molecular fingerprinting of strains has demonstrated that potable water serves as the major reservoir and source of nosocomial infection.

Pontiac Fever

Pontiac fever in adults and children is characterized by high fever, myalgia, headache, and extreme debilitation, lasting for 3-5 days. Cough, breathlessness, diarrhea, confusion, and chest pain may occur, but there is no evidence for invasive infection. The disease is self-limited without sequelae. Virtually all exposed individuals seroconvert to *Legionella* antigens. A very large outbreak in Scotland that affected 35 children was attributed to *L. micdadei*, which was isolated from a whirlpool spa. The onset of illness was 1-7 days (median: 3 days), and all exposed children developed significant titers of specific antibodies to *L. micdadei*. The pathogenesis of Pontiac fever is not known. In the absence of evidence of true infection, the most likely hypothesis is that this syndrome is caused by a toxic or hypersensitivity reaction to microbial, or protozoan, antigens.

Diagnosis

Culture of *Legionella* from sputum, other respiratory tract specimens, blood, or tissue is the gold standard against which indirect methods of detection should be compared. If present, pleural fluid should be obtained for culture. Specimens obtained from the respiratory tract that are contaminated with oral flora must be treated and processed to reduce contaminants and plated onto selective media. Because these are costly and time-consuming methods, many laboratories do not process specimens for culture.

The urinary antigen assay that detects *L. pneumophila* serogroup I has revolutionized the diagnosis of *Legionella* infection and has 80% sensitivity and 99% specificity. The assay is a useful method in the prompt diagnosis of legionnaires disease caused by this serogroup, which accounts for the majority of symptomatic infections. In the United States, this test is frequently used because it is widely available in reference laboratories. Where available, polymerase chain reaction is used to identify *L. pneumophila* from bronchoscopic lavage and other clinical specimens to the exclusion of other respiratory pathogens. Other methods, including direct immunofluorescence, have low sensitivity and are generally not employed. Retrospective diagnosis can be made serologically using an enzyme immunoassay to detect specific antibody production. Seroconversion may not occur for several weeks after onset of infection, and the available serologic assays do not detect all strains of *L. pneumophila* or all species.

In view of the low sensitivity of direct detection and the slow growth of the microorganism in culture, the diagnosis of legionellosis should be pursued actively when there is suggestive clinical evidence, including the lack of response to usual antibiotics, even when results of other laboratory studies are negative.

Treatment

In community-acquired pneumonia in adults who are hospitalized, guidelines recommend empirical treatment with a broad-spectrum cephalosporin plus a macrolide or quinolone for treatment of atypical microorganisms *(Legionella, Chlamydophila pneumoniae, Mycoplasma pneumoniae)*. Evidence-based guidelines for management of community-acquired pneumonia in children do not yet include *Legionella* in the differential diagnosis or empirical treatment recommendations. Effective treatment of legionnaires disease is based in part on the intracellular concentration of antibiotics. **Azithromycin** , **clarithromycin** , or the **quinolones** (ciprofloxacin and levofloxacin) have generally replaced erythromycin as therapy for patients with diagnosed *Legionella* infection. **Doxycycline** is an acceptable alternative. In serious infections or in high-risk patients, parenteral therapy is recommended initially, although oral conversion if favored when tolerated, particularly due to the generally high bioavailability of oral macrolides, quinolones, and tetracyclines. The duration of antibiotic therapy for legionnaires disease in adults is typically for a minimum of 5 days, although therapy may be continued for 10-14 days in more seriously ill or immunocompromised patients. Treatment of extrapulmonary infections, including prosthetic valve endocarditis and sternal wound infections, may require prolonged therapy. In vitro data and case reports suggest that trimethoprim-sulfamethoxazole (15 mg TMP/kg/day and 75 mg SMX/kg/day) may also be effective. A large, retrospective study of hospitalized adults with *Legionella* pneumonia found no difference in mortality between those treated with azithromycin and with quinolones. The role of combination therapy is unknown.

Prognosis

The mortality rate for community-acquired legionnaires disease in adults who are hospitalized is approximately 15% but may exceed 50% in immunocompromised patients, although reporting bias might inflate these estimates. The prognosis depends on underlying host factors and possibly on the duration of illness before initiation of appropriate therapy. Despite appropriate antibiotic therapy, patients may succumb to respiratory complications, such as acute respiratory distress syndrome. A high mortality rate is noted in case reports of premature infants and children, virtually all of whom have been immunocompromised. Delay in diagnosis is also associated with increased mortality. Consequently, *Legionella* should be considered in the differential diagnosis of both community-acquired and nosocomial pneumonia in children, especially in those refractory to empirical therapy or with epidemiologic risk factors for legionellosis.

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CHAPTER 236

Bartonella

Rachel C. Orscheln

The spectrum of disease resulting from human infection with *Bartonella* species includes the association of **bacillary angiomatosis** and **cat-scratch disease** with *Bartonella henselae.* There are more than 30 validated species of *Bartonella* , but 6 major species are responsible for most human disease: *B. henselae, B.quintana, B. bacilliformis, B. elizabethae, B. vinsonii,* and *B. clarridgeiae* (Table 236.1). The remaining *Bartonella* spp. have been found primarily in animals, particularly rodents and moles. However, zoonotic infections from animal-associated strains of *Bartonella* spp. have been reported. In 2013 a novel *Bartonella* agent with the proposed name *Candidatus* Bartonella ancashi *(Bartonella ancashensis)* was described as a cause of **verruga peruana** .

Table 236.1

Bartonella Species Causing Majority of Human Disease

DISEASE	ORGANISM	VECTOR	PRIMARY RISK FACTOR
Bartonellosis (Carrión disease)	*B. bacilliformis*	Sandfly *(Lutzomyia verrucarum)*	Living in endemic areas (Andes Mountains)
Cat-scratch disease	*B. henselae* *B. clarridgeiae*	Cat	Cat scratch or bite
Trench fever	*B. quintana*	Human body louse	Body louse infestation during outbreak
Bacteremia, endocarditis	*B. henselae* *B. elizabethae* *B. vinsonii* *B. quintana*	Cat for *B. henselae* Rat for *B. elizabethae* Vole for *B. vinsonii* Human body louse for *B. quintana*	Severe immunosuppression
Bacillary angiomatosis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression
Peliosis hepatis	*B. henselae*	Cat for *B. henselae*	Severe immunosuppression

	B. quintana	Human body louse for *B. quintana*	

Members of the genus *Bartonella* are gram-negative, oxidase-negative, fastidious aerobic rods that ferment no carbohydrates. *B. bacilliformis* is the only species that is motile, achieving motility by means of polar flagella. Optimal growth is obtained on fresh media containing ≥5% sheep or horse blood in the presence of 5% carbon dioxide. The use of lysis centrifugation for specimens from blood on chocolate agar for extended periods (2-6 wk) enhances recovery.

236.1

Cat-Scratch Disease *(Bartonella henselae)*

Rachel C. Orscheln

Keywords

Bartonella
B. henselae
CSD
encephalopathy
endocarditis
flea
granuloma
hepatosplenomegaly
inoculation papule
lymphadenitis
Parinaud oculoglandular syndrome
stellate macular retinopathy

The most common presentation of *Bartonella* infection is cat-scratch disease (**CSD**), which is a subacute, regional lymphadenitis caused most frequently by *B. henselae* . It is the most common cause of chronic lymphadenitis that persists for >3 wk.

Etiology

Bartonella henselae can be cultured from the blood of healthy cats. *B. henselae* organisms are the small pleomorphic gram-negative bacilli visualized with Warthin-Starry stain in affected lymph nodes from patients with CSD. Development of serologic tests that showed prevalence of antibodies in 84–100% of cases of CSD, culturing of *B. henselae* from CSD nodes, and detection of *B. henselae* by polymerase chain reaction (PCR) in the majority of lymph node samples and pus from patients with CSD, confirmed the organism as the cause of CSD. Occasional cases of CSD may be caused by other organisms, including *Bartonella clarridgeiae, B. grahamii* , *B. alsatica*, and *B. quintana* .

Epidemiology

CSD is common, with >24,000 estimated cases per year in the United States. It is transmitted most frequently by cutaneous inoculation through the bite or scratch of a cat. However, transmission may occur through other routes, such as flea bites. Most patients (87–99%) have had contact with cats, many of which are kittens <6 mo old, and >50% of patients have a definite history of a cat scratch or bite. Cats have high-level *Bartonella* bacteremia for months without any clinical symptoms; kittens are more frequently bacteremic than adult cats. Transmission between cats occurs through the cat flea, *Ctenocephalides felis*. In temperate zones, most cases occur between September and March, perhaps in relation to the seasonal breeding of domestic cats or to the close proximity of family pets in the fall and winter. In tropical zones, there is no seasonal prevalence. Distribution is worldwide, and infection occurs in all races.

Cat scratches appear to be more common among children, and males are affected more often than females. CSD is a sporadic illness; usually only 1 family member is affected, even though many siblings play with the same kitten. However, clusters do occur, with family cases within weeks of one another. Anecdotal reports have implicated other sources, such as dog scratches, wood splinters, fishhooks, cactus spines, and porcupine quills.

Pathogenesis

The pathologic findings in the primary inoculation **papule** and affected lymph nodes are similar. Both show a central avascular necrotic area with surrounding lymphocytes, giant cells, and histiocytes. Three stages of involvement occur in affected nodes, sometimes simultaneously in the same node. The 1st stage consists of generalized enlargement with thickening of the cortex and hypertrophy of the germinal center and with a predominance of lymphocytes. Epithelioid granulomas with Langerhans giant cells are scattered throughout the node. The 2nd stage is characterized by granulomas that increase in density, fuse, and become infiltrated with polymorphonuclear leukocytes, with beginning central necrosis. In the 3rd stage, necrosis progresses with formation of large, pus-filled sinuses. This purulent material may rupture into surrounding tissue. Similar granulomas have been found in the liver, spleen, and osteolytic lesions of bone when those organs are involved.

Clinical Manifestations

After an incubation period of 7-12 days (range: 3-30 days), 1 or more 3-5 mm red papules develop at the site of cutaneous inoculation, often reflecting a linear cat scratch. These lesions are often overlooked because of their small size but are found in at least 65% of patients when careful examination is performed (Fig. 236.1). Lymphadenopathy is generally evident within 1-4 wk (Fig. 236.2). **Chronic regional lymphadenitis** is the hallmark, affecting the1st or 2nd set of nodes draining the entry site. Affected lymph nodes in order of frequency include the axillary, cervical, submandibular, preauricular, epitrochlear, femoral, and inguinal nodes. Involvement of >1 group of nodes occurs in 10–20% of patients, although at a given site, half the cases involve several nodes.

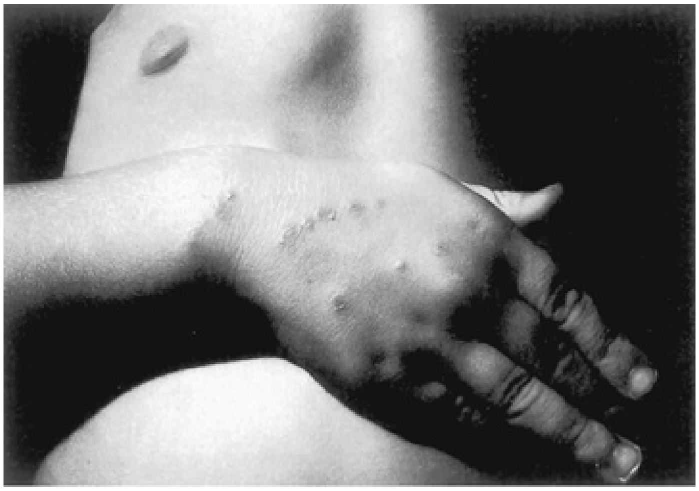

FIG. 236.1 A child with typical cat-scratch disease demonstrating the original scratch injuries and the primary papule that soon thereafter developed proximal to the middle finger. (Courtesy of Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)

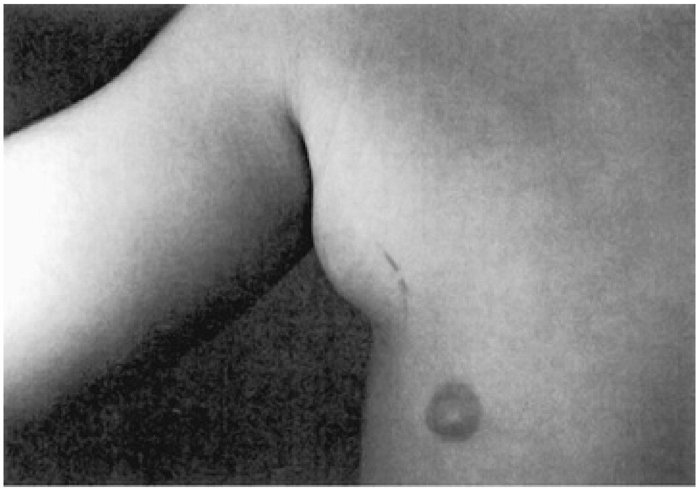

FIG. 236.2 Right axillary lymphadenopathy followed the scratches and development of a primary papule in this child with typical cat-scratch disease. (From Mandell GL, Bennett JE, Dolin R, editors: *Principles and practice of infectious diseases* , ed 6, Philadelphia, 2006, Elsevier, p 2737.)

Nodes involved are usually tender and have overlying erythema but without cellulitis. They usually range between 1 and 5 cm in size, although they can become much larger. From 10–40% eventually suppurate. The duration of enlargement is usually 1-2 mo, with persistence up to 1 yr in rare cases. Fever occurs in approximately 30% of patients, usually 38-39°C (100.4-102.2°F). Other nonspecific symptoms, including malaise, anorexia, fatigue, and headache, affect less than one third of patients. Transient rashes, which may occur in approximately 5% of patients, are mainly truncal maculopapular rashes. Erythema nodosum, erythema multiforme, and erythema annulare are also reported.

CSD is usually a self-limited infection that spontaneous resolves within a few weeks to months. The most common ocular presentation of CSD is **Parinaud oculoglandular syndrome,** which is unilateral conjunctivitis followed by preauricular lymphadenopathy and occurs in 5% of patients with CSD (Fig. 236.3). Direct eye inoculation as a result of rubbing with the hands after cat contact is the presumed mode of spread. A conjunctival granuloma may be found at the inoculation site. The involved eye is usually not painful and has little or no discharge but may be quite red and swollen. Submandibular or cervical lymphadenopathy may also occur.

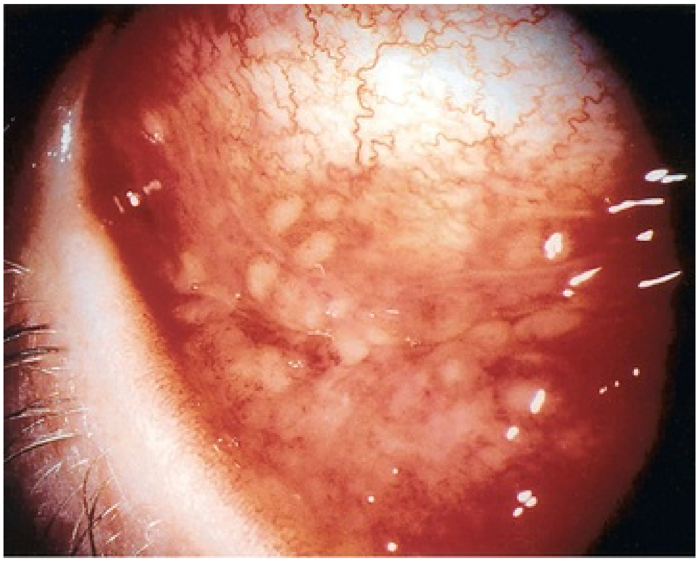

FIG. 236.3 The granulomatous conjunctivitis of Parinaud oculoglandular syndrome is associated with ipsilateral local lymphadenopathy, usually preauricular and less often submandibular. (From Mandell GL, Bennett JE, Dolin R, editors: *Principles and practice of infectious diseases* , ed 6, Philadelphia, 2006, Elsevier, p 2739.)

More severe, disseminated illness occurs up to 14% of patients and is characterized by presentation with high fever, often persisting for several weeks. Other prominent symptoms include significant abdominal pain and weight loss.

Hepatosplenomegaly may occur, although hepatic dysfunction is rare (Fig. 236.4). Granulomatous changes may be seen in the liver and spleen. Another common site of dissemination is bone, with the development of multifocal **granulomatous osteolytic lesions,** associated with localized pain but without erythema, tenderness, or swelling. Other, uncommon manifestations are neuroretinitis with papilledema and stellate macular exudates, encephalitis, endocarditis, and atypical pneumonia.

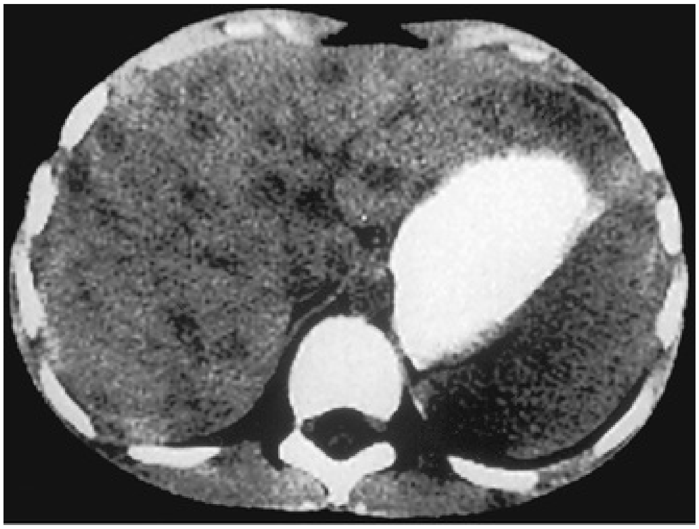

FIG. 236.4 In this CT scan of a patient with hepatic involvement of cat-scratch disease, the absence of enhancement of the multiple lesions after contrast infusion is consistent with the granulomatous inflammation of this entity. Treated empirically with various antibiotics without improvement before establishment of this diagnosis, the patient subsequently recovered fully with no further antimicrobial therapy. (Courtesy of Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)

Diagnosis

In most cases the diagnosis can be strongly suspected on clinical grounds in a patient with history of exposure to a cat. Serologic testing can be used to confirm the diagnosis. Most patients have elevated IgG antibody titers at presentation. However, the IgM response to *B. henselae* has frequently resolved by the time testing is considered. There is cross-reactivity among *Bartonella* spp., particularly *B. henselae* and *B. quintana.*

If tissue specimens are obtained, bacilli may be visualized with Warthin-Starry and Brown-Hopps tissue stains. *Bartonella* DNA can be identified through PCR analysis of tissue specimens. Culturing of the organism is not generally practical for clinical diagnosis.

Differential Diagnosis

The differential diagnosis of CSD includes virtually all causes of lymphadenopathy (see Chapter 517). The more common entities include pyogenic (suppurative) lymphadenitis, primarily from staphylococcal or streptococcal infections, atypical mycobacterial infections, and malignancy. Less common entities are tularemia, brucellosis, and sporotrichosis. Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* infections usually cause more generalized lymphadenopathy.

Laboratory Findings

Routine laboratory tests are not helpful. The erythrocyte sedimentation rate is often elevated. The white blood cell count may be normal or mildly elevated. Hepatic transaminases are often normal but may be elevated in systemic disease. Ultrasonography or CT may reveal many granulomatous nodules in the liver and spleen; the nodules appear as hypodense, round, irregular lesions and are usually multiple. However, CSD presenting as a solitary splenic lesion has been reported.

Treatment

Antibiotic treatment of CSD is not always needed and is not clearly beneficial. For most patients, treatment consists of conservative symptomatic care and observation. Studies show a significant discordance between in vitro activity of antibiotics and clinical effectiveness. For many patients, diagnosis is considered in the context of failure to respond to β-lactam antibiotic treatment of presumed staphylococcal lymphadenitis.

A small prospective study of oral azithromycin (500 mg on day 1, then 250 mg on days 2-5; for smaller children, 10 mg/kg/24 hr on day 1 and 5 mg/kg/24 hr on days 2-5) showed a decrease in initial lymph node volume in 50% of patients during the 1st 30 days, but after 30 days there was no difference in lymph node volume. No other clinical benefit was found. For the majority of patients, CSD is self-limited, and resolution occurs over weeks to months without antibiotic treatment. Azithromycin, clarithromycin, trimethoprim-sulfamethoxazole (TMP-SMX), rifampin, ciprofloxacin, and gentamicin appear to be the best agents if treatment is considered.

Suppurative lymph nodes that become tense and extremely painful should be drained by **needle aspiration** , which may need to be repeated. Incision and drainage of nonsuppurative nodes should be avoided because chronic draining sinuses may result. Surgical excision of the node is rarely necessary.

Children with hepatosplenic CSD appear to respond well to rifampin at a dose of 20 mg/kg for 14 days, either alone or in combination with a 2nd agent such as azithromycin, gentamicin, or TMP-SMX.

Complications

Encephalopathy can occur in as many as 5% of patients with CSD and typically manifests 1-3 wk after the onset of lymphadenitis as the sudden onset of neurologic symptoms, which often include seizures, combative or bizarre behavior, and altered level of consciousness. Imaging studies are generally normal. The cerebrospinal fluid is normal or shows minimal pleocytosis and protein elevation. Recovery occurs without sequelae in almost all patients but may take place slowly over many months.

Other neurologic manifestations include peripheral facial nerve paralysis, myelitis, radiculitis, compression neuropathy, and cerebellar ataxia. One patient has been reported to have encephalopathy with persistent cognitive impairment and memory loss.

Stellate macular retinopathy is associated with several infections, including CSD. Children and young adults present with unilateral or rarely bilateral loss of vision with central scotoma, optic disc swelling, and macular star formation from exudates radiating out from the macula. The findings usually resolve completely, with recovery of vision, generally within 2-3 mo. The optimal treatment for the neuroretinitis is unknown, although treatment of adults with doxycycline and rifampin for 4-6 wk has had good results.

Hematologic manifestations include hemolytic anemia, thrombocytopenic purpura, nonthrombocytopenic purpura, and eosinophilia. **Leukocytoclastic vasculitis,** similar to Henoch-Schönlein purpura, has been reported in association with CSD in one child. A systemic presentation of CSD with pleurisy, arthralgia or arthritis, mediastinal masses, enlarged nodes at the head of the pancreas, and atypical pneumonia also has been reported.

Prognosis

The prognosis for CSD in a normal host is generally excellent, with resolution of clinical findings over weeks to months. Recovery is occasionally slower and may take as long as 1 yr.

Prevention

Person-to-person spread of *Bartonella* infections is not known. Isolation of the affected patient is not necessary. Prevention would require elimination of cats from households, which is not practical or necessarily desirable. Awareness of the risk of cat (and particularly kitten) scratches should be emphasized to parents. Cat scratches or bites should be washed immediately. Cat flea control is helpful.

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236.2

Bartonellosis *(Bartonella bacilliformis)*

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Keywords

B. bacilliformis
Carrión disease
hemolytic anemia
Oroya fever
verruca peruana
sandfly

The first human *Bartonella* infection described was **bartonellosis** , a geographically distinct disease caused by *B. bacilliformis.* There are 2 predominant forms of illness caused by *B. bacilliformis* : **Oroya fever** , a severe, febrile hemolytic anemia, and **verruca peruana** (verruga peruana), an eruption of hemangioma-like lesions. *B. bacilliformis* also causes asymptomatic infection. Bartonellosis is also called **Carrión disease** .

Etiology

Bartonella bacilliformis is a small, motile, gram-negative organism with a brush of ≥10 unipolar flagella, which appear to be important components for invasiveness. An obligate aerobe, it grows best at 28°C (82.4°F) in semisolid nutrient agar containing rabbit serum and hemoglobin.

Epidemiology

Bartonellosis is a zoonosis found only in mountain valleys of the Andes

Mountains in Peru, Ecuador, Colombia, Chile, and Bolivia at altitudes and environmental conditions favorable for the vector, which is the **sandfly** , *Lutzomyia verrucarum.*

Pathogenesis

After the sandfly bite, *Bartonella* organisms enter the endothelial cells of blood vessels, where they proliferate. Found throughout the reticuloendothelial system, they then reenter the bloodstream and parasitize erythrocytes. They bind on the cells, deform the membranes, and then enter intracellular vacuoles. The resultant hemolytic anemia may involve as many as 90% of circulating erythrocytes. Patients who survive this acute phase may or may not experience the cutaneous manifestations, which are nodular hemangiomatous lesions or verrucae ranging in size from a few millimeters to several centimeters.

Clinical Manifestations

The incubation period is 2-14 wk. Patients may be totally asymptomatic or may have nonspecific symptoms such as headache and malaise without anemia.

Oroya fever is characterized by fever with rapid development of anemia. Clouding of the sensorium and delirium are common symptoms and may progress to overt psychosis. Physical examination demonstrates signs of severe hemolytic anemia, including icterus and pallor, sometimes in association with generalized lymphadenopathy.

In the preeruptive stage of **verruca peruana** (Fig. 236.5), patients may complain of arthralgias, myalgias, and paresthesias. Inflammatory reactions such as phlebitis, pleuritis, erythema nodosum, and encephalitis may develop. The appearance of verrucae is pathognomonic of the eruptive phase. Lesions vary greatly in size and number.

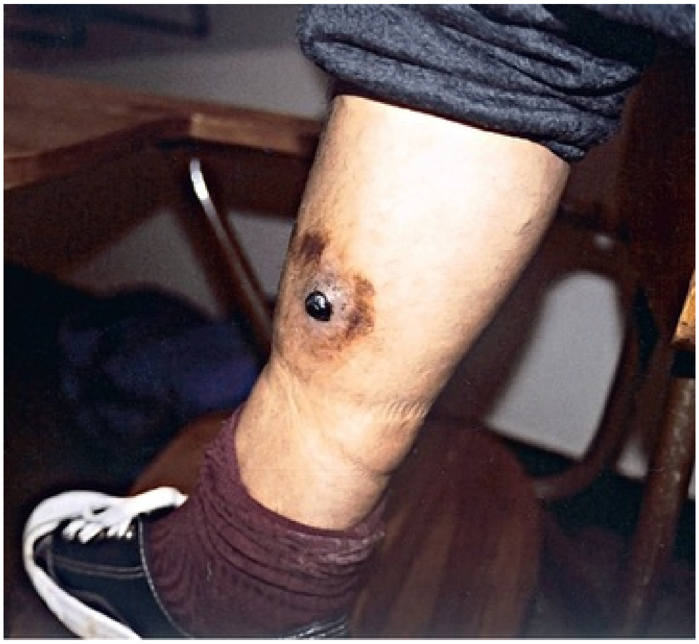

FIG. 236.5 A single, large lesion of verruca peruana on the leg of an inhabitant of the Peruvian Andes. Such lesions are prone to superficial ulceration, and their vascular nature may lead to copious bleeding. Ecchymosis of the skin surrounding the lesion is also evident. (Courtesy of Dr. J.M. Crutcher, Oklahoma State Department of Health, Oklahoma City.)

Diagnosis

The diagnosis of bartonellosis is established on clinical grounds in conjunction with a blood smear demonstrating organisms or with blood culture. The anemia is macrocytic and hypochromic, with reticulocyte counts as high as 50%. *B. bacilliformis* may be seen on Giemsa stain preparation as red-violet rods in the erythrocytes. In the recovery phase, organisms change to a more coccoid form and disappear from the blood. In the absence of anemia, the diagnosis depends on blood cultures. In the eruptive phase, the typical verruca confirms the diagnosis. Antibody testing has been used to document infection.

Treatment

B. bacilliformis is sensitive to many antibiotics, including rifampin, tetracycline, and chloramphenicol. Treatment is very effective in rapidly diminishing fever and eradicating the organism from the blood. **Chloramphenicol** (50-75 mg/kg/day) is considered the drug of choice, because it is also useful in the treatment of concomitant infections such as *Salmonella*. Fluoroquinolones are used successfully as well. Blood transfusions and supportive care are critical in patients with severe anemia. Antimicrobial treatment for verruca peruana is considered when there are >10 cutaneous lesions, if the lesions are erythematous or violaceous, or if the onset of the lesions was <1 mo before presentation. Oral rifampin is effective in the healing of lesions. Surgical excision may be needed for lesions that are large and disfiguring or that interfere with function.

Prevention

Prevention depends on avoidance of the vector, particularly at night, by the use of protective clothing and insect repellents (see Chapter 200)

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236.3

Trench Fever *(Bartonella quintana)*

Rachel C. Orscheln

Keywords

B. quintana
homelessness
human body louse

trench fever

Etiology

The causative agent of trench fever was first designated *Rickettsia quintana,* was then assigned to the genus *Rochalimaea,* and now has been reassigned as *Bartonella quintana.*

Epidemiology

Trench fever was first recognized as a distinct clinical entity during World War I, when more than a million troops in the trenches were infected. Infection with *B. quintana* is currently rare in the United states and primarily occurs in the setting of conditions favorable to body lice infestations, such as homelessness, crowding, and poor sanitation. When pooled samples of head and body lice have been collected from homeless populations, up to 33% of individuals have lice pools that test positive for *B. quintana.*

Humans are the only known reservoir. No other animal is naturally infected, and usual laboratory animals are not susceptible. The **human body louse** , *Pediculus humanus* var. *corporis,* is the vector and is capable of transmission to a new host 5-6 days after feeding on an infected person. Lice excrete the organism for life; transovarian passage does not occur. Humans may have prolonged asymptomatic bacteremia for years.

Clinical Manifestations

The incubation period for trench fever averages about 22 days (range: 4-35 days). The clinical presentation is highly variable. Symptoms can be very mild and brief. About half of infected persons have a single febrile illness with abrupt onset lasting 3-6 days. In other patients, prolonged, sustained fever may occur. More commonly, patients have periodic febrile illness with 3-8 episodes lasting 4-5 days each, sometimes occurring over 1 yr or more. This form is reminiscent of malaria or **relapsing fever** *(Borrelia recurrentis).* Afebrile bacteremia can occur.

Clinical findings usually consist of fever (typically with a temperature of 38.5-40°C [101.3-104°F]), malaise, chills, sweats, anorexia, and severe headache.

Common findings include marked conjunctival injection, tachycardia, myalgias, arthralgias, and severe pain in the neck, back, and legs. Crops of erythematous macules or papules may occur on the trunk on as many as 80% of patients. Splenomegaly and mild liver enlargement may be noted.

Diagnosis

In nonepidemic situations, it is impossible to establish a diagnosis of trench fever on clinical grounds, because the findings are not distinctive. A history of body louse infection or having been in an area of epidemic disease should heighten suspicions. *B. quintana* can be cultured from the blood with modification to include culture on epithelial cells. Serologic tests for *B. quintana* are available, but there is cross-reaction with *B. henselae*.

Treatment

There are no controlled trials of treatment, but bacteremia with *Bartonella* treated with a combination of gentamicin and doxycycline increases the rate of cure compared to other regimens, such as doxycycline or β-lactam antibiotics alone.

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Bacillary Angiomatosis and Bacillary Peliosis Hepatis (*Bartonella henselae* and *Bartonella quintana*)

Rachel C. Orscheln

Keywords

B. henselae
B. quintana
bacillary angiomatosis
bacillary peliosis
bacteremia
endocarditis
epithelioid angiomatosis

Both *B. henselae* and *B. quintana* cause vascular proliferative disease called bacillary angiomatosis and bacillary peliosis in severely immunocompromised persons, primarily adult patients with acquired immunodeficiency syndrome (AIDS) or cancer and organ transplant recipients. Subcutaneous and lytic bone lesions are strongly associated with *B. quintana*, whereas peliosis hepatis is associated exclusively with *B. henselae.*

Bacillary Angiomatosis

Lesions of cutaneous bacillary angiomatosis, also known as **epithelioid angiomatosis** , are the most easily identified and recognized form of *Bartonella* infection in immunocompromised hosts. They are found primarily in patients with AIDS who have very low CD4 counts. The clinical appearance can be quite diverse. The vasoproliferative lesions of bacillary angiomatosis may be cutaneous or subcutaneous and may resemble the vascular lesions (verruca peruana) of *B. bacilliformis* in immunocompetent persons, characterized by erythematous papules on an erythematous base with a collarette of scale. They may enlarge to form large, pedunculated lesions and may ulcerate. Trauma may result in profuse bleeding.

Bacillary angiomatosis may be clinically indistinguishable from Kaposi sarcoma. Other considerations in the differential diagnosis are pyogenic granuloma and verruca peruana *(B. bacilliformis)*. Deep, soft tissue masses caused by bacillary angiomatosis may mimic a malignancy.

Osseous bacillary angiomatosis lesions typically involve the long bones. These lytic lesions are very painful and highly vascular and are occasionally associated with an overlying erythematous plaque. The high degree of vascularity produces a very positive result on a technetium-99m methylene diphosphonate bone scan, resembling that of a malignant lesion.

Lesions can be found in virtually any organ, producing similar vascular proliferative lesions. They may appear raised, nodular, or ulcerative when seen on endoscopy or bronchoscopy. They may be associated with enlarged lymph nodes with or without an obvious local cutaneous lesion. Brain parenchymal lesions have been described.

Bacillary Peliosis

Bacillary peliosis affects the reticuloendothelial system, primarily the liver (**peliosis hepatis**) and less frequently the spleen and lymph nodes. It is a vasoproliferative disorder characterized by random proliferation of venous lakes surrounded by fibromyxoid stroma harboring numerous bacillary organisms. Clinical findings include fever and abdominal pain in association with abnormal liver function test results, particularly a greatly increased alkaline phosphatase level. Cutaneous bacillary angiomatosis with splenomegaly may be associated with thrombocytopenia or pancytopenia. The vascular proliferative lesions in the liver and spleen appear on CT scan as hypodense lesions scattered throughout the parenchyma. The differential diagnosis includes hepatic Kaposi sarcoma, lymphoma, and disseminated infection with *Pneumocystis jirovecii* or *Mycobacterium avium* complex.

Bacteremia and Endocarditis

Bartonella henselae, B. quintana, B. vinsonii, and *B. elizabethae* all are reported to cause bacteremia or endocarditis. They are associated with symptoms such as prolonged fevers, night sweats, and profound weight loss. A cluster of cases in Seattle in 1993 occurred in a homeless population with chronic alcoholism. These patients with high fever or hypothermia were thought to represent *urban trench fever* , but no body louse infestation was associated. Some cases of culture-negative endocarditis may represent *Bartonella* endocarditis. One report described central nervous system involvement with *B. quintana* infection in 2 children.

Diagnosis

Diagnosis of bacillary angiomatosis is made initially by biopsy. The characteristic small-vessel proliferation with mixed inflammatory response and the staining of bacilli by Warthin-Starry silver distinguish bacillary angiomatosis from pyogenic granuloma or Kaposi sarcoma (see Chapter 284). Travel history can usually preclude verruca peruana.

Culture is impractical for CSD but is the diagnostic procedure for suspected bacteremia or endocarditis. Lysis centrifugation technique or fresh chocolate or heart infusion agar with 5% rabbit blood and prolonged incubation may increase the yield of culture. PCR on tissue can also be a useful tool, and positive serologic testing can provide support for the diagnosis.

Treatment

Bartonella infections in immunocompromised hosts caused by both *B. henselae* and *B. quintana* have been treated successfully with antimicrobial agents. Bacillary angiomatosis responds rapidly to erythromycin, azithromycin, and clarithromycin, which are the drugs of choice. Alternative choices are doxycycline or tetracycline. Severely ill patients with peliosis hepatis or patients with osteomyelitis may be treated initially with a macrolide or doxycycline and the addition of rifampin or gentamicin. The use of doxycycline for 6 wk with the addition of an aminoglycoside for a minimum of 2 wk is associated with improved prognosis in endocarditis. A Jarisch-Herxheimer reaction may occur. Relapses may follow, and prolonged treatment for several months may be necessary.

Prevention

Immunocompromised persons should consider the potential risks of cat ownership because of the risks for *Bartonella* infections as well as toxoplasmosis and enteric infections. Those who elect to obtain a cat should adopt or purchase a cat >1 yr old and in good health. Prompt washing of any wounds from cat bites or scratches is essential.

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SECTION 6

Anaerobic Bacterial Infections

OUTLINE

Chapter 237 Botulism (Clostridium botulinum)

Chapter 238 Tetanus (Clostridium tetani)

Chapter 239 Clostridium difficile Infection

Chapter 240 Other Anaerobic Infections

CHAPTER 237

Botulism *(Clostridium botulinum)*

Laura E. Norton, Mark R. Schleiss

There are 3 naturally occurring forms of human botulism, characterized by mode of acquisition: **infant botulism** (intestinal toxemia), **foodborne botulism** , and **wound botulism** . Infant botulism is the most common form in the United States. Under rare circumstances of altered intestinal anatomy, physiology, and microflora, older children and adults may contract infant-type botulism (**adult intestinal toxemia**).Two other forms, both human-made, also occur: **inhalational botulism** , from inhaling accidentally aerosolized toxin, and **iatrogenic botulism,** from overdosage of botulinum toxin used for therapeutic or cosmetic purposes.

Etiology

Botulism is the acute, flaccid paralysis caused by the neurotoxin produced by *Clostridium botulinum* or, infrequently, an equivalent neurotoxin produced by rare strains of *Clostridium butyricum* and *Clostridium baratii. C. botulinum* is a gram-positive, spore-forming, obligate anaerobe whose natural habitat worldwide is soil, dust, and marine sediments. The organism is found in a wide variety of fresh and cooked agricultural products. Spores of some *C. botulinum* strains endure boiling for several hours, enabling the organism to survive efforts at food preservation. In contrast, botulinum toxin is heat labile and easily destroyed by heating at ≥85°C (185°F) for 5 min. **Neurotoxigenic** *C. butyricum* has been isolated from soils near Lake Weishan in China, the site of foodborne botulism outbreaks associated with this organism, as well as from vegetables, soured milk, and cheeses. Although first recognized in China, cases of infant botulism due to *C. butyricum* have now been identified in Japan, Europe, and the

United States. Little is known about the ecology of neurotoxigenic *C. baratii.*

Botulinum toxin is synthesized as a 150-kDa precursor protein that enters the circulation and is transported to the neuromuscular junction. The toxin is only released by actively replicating (vegetative) bacteria and not the spore form. At the neuromuscular junction, toxin binds to the neuronal membrane on the presynaptic side of the neural synapse. It undergoes autoproteolysis to a 100-kDa heavy chain and a 50-kDa light chain. These chains are joined via disulfide bond formation. The heavy chain contains the neuronal attachment sites that mediate binding to presynaptic nerve terminals. It also mediates translocation of the light chain into the cell cytoplasm after binding. The light chain, a key component of the toxin, is a member of the zinc metalloprotease family and mediates cleavage of the fusogenic SNARE protein family member, SNAP-25. Cleavage of this protein precludes release of acetylcholine from axon at the presynaptic terminal, abrogating nerve signaling and producing paralysis. Botulinum toxin is among the most potent poisons known to humankind; indeed, the parenteral human lethal dose is estimated to be on the order of 10^{-6} mg/kg. The toxin blocks neuromuscular transmission and causes death through airway and respiratory muscle paralysis. At least 7 antigenic toxin types, designated by letters A-G, are distinguished serologically, by demonstration of the inability of neutralizing antibody against one toxin type to protect against a different type. Toxin types are further differentiated into subtypes by differences in the nucleotide sequences of their toxin genes. As with the gene for tetanus toxin, the gene for botulinum toxin for some toxin types and subtypes resides on a plasmid.

The toxin types serve as convenient clinical and epidemiologic markers. Toxin types A, B, E, and F are well-established causes of human botulism, whereas types C and D cause illness in other animals. Toxin types A and B cause the majority of cases of infant botulism in the United States. Neurotoxigenic *C. butyricum* strains produce a type E toxin, whereas neurotoxigenic *C. baratii* strains produce a type F toxin. Type G toxin has not been established as a cause of either human or animal disease.

Epidemiology

Infant botulism has been reported from all inhabited continents except Africa. Notably, the infant is the only family member who is ill. The most striking epidemiologic feature of infant botulism is its age distribution, with 95% of cases involving infants 3 wk to 6 mo old, with a broad peak from 2-4 mo old.

Cases have been recognized in infants as young as 1.5 days or as old as 382 days at onset. The male/female ratio of hospitalized cases is approximately 1 : 1, and cases occur in all racial and ethnic groups. Identified risk factors for the illness include breastfeeding, the ingestion of honey, a slow intestinal transit time (<1 stool/day), and ingestion of untreated well water. Although breastfeeding appears to provide protection against fulminant sudden death from infant botulism, cases can occur in breastfed infants at the time of introduction of nonhuman milk for feeding.

Although infant botulism is an uncommon and often unrecognized illness, it is the most common form of human botulism in the United States, with approximately 80-140 hospitalized cases diagnosed annually. The Council of State and Territorial Epidemiologists (CSTE) maintains a **National Botulism Surveillance System** for intensive surveillance for cases of botulism in the United States (https://www.cdc.gov/botulism/surveillance.html). In 2015, 141 confirmed cases of infant botulism were reported to the Centers for Disease Control and Prevention (CDC). There were no deaths. Approximately 56% of infant botulism cases were caused by type B, 43% by type A, and the remainder by other types. Cases were identified in 33 states and the District of Columbia, with California reporting the highest number of cases. Consistent with the known asymmetric soil distribution of *C. botulinum* toxin types, most cases west of the Mississippi River have been caused by type A strains, whereas most cases east of the Mississippi River have been caused by type B strains.

Foodborne botulism results from the ingestion of a food in which *C. botulinum* has multiplied and produced toxin. Although the traditional view of foodborne botulism has been thought of as resulting chiefly from ingestion of home-canned foods, in fact, outbreaks in North America have recently been more often associated with restaurant-prepared foods, including potatoes, sautéed onions, and chopped garlic. Other outbreaks in the United States have occurred from commercial foods sealed in plastic pouches that relied solely on refrigeration to prevent outgrowth of *C. botulinum* spores. Uncanned foods responsible for foodborne botulism cases include peyote tea, hazelnut flavoring added to yogurt, sweet cream cheese, sautéed onions in patty melt sandwiches, potato salad, and fresh and dried fish.

Many types of preserved foods have been implicated in foodborne botulism, but common foods implicated with exposure include low-acid (pH ≥6.0) home-canned foods such as jalapeño peppers, carrots, potatoes, asparagus, olives, and beans. The potential for foodborne botulism exists throughout the world, but outbreaks typically occur in the temperate zones rather than the tropics, where preservation of fruits, vegetables, and other foods is less commonly undertaken.

Approximately 5-10 outbreaks and 15-25 cases of foodborne botulism occur annually in the United States. There were 39 cases of confirmed foodborne botulism reported in the United States in 2015, including a large outbreak of 27 cases associated with a potluck meal in Ohio. Most of the continental U.S. outbreaks resulted from proteolytic type A or type B strains, which produce a strongly putrefactive odor in the food that some people find necessary to verify by tasting, exposing themselves to toxin in the process. In contrast, in Alaska and Canada, most foodborne outbreaks have resulted from nonproteolytic type E strains in Native American foods, such as fermented salmon eggs and seal flippers, which do not exhibit signs of spoilage. A further hazard of type E strains is their ability to grow at the temperatures maintained by household refrigerators (5°C [41°F]).

Wound botulism is an exceptionally rare disease, with <400 cases reported worldwide, but it is important to pediatrics because adolescents and children may be affected. Although many cases have occurred in young, physically active males who are at the greatest risk for traumatic injury, wound botulism also occurs with crush injuries in which no break in the skin is evident. In the past 15 yr, wound botulism from injection has become increasingly common in adult heroin abusers in the western United States and in Europe, not always with evident abscess formation or cellulitis.

A single outbreak of **inhalational botulism** was reported in 1962 in which 3 laboratory workers in Germany were exposed unintentionally to aerosolized botulinum toxin. Some patients in the United States have been hospitalized by accidental overdose of therapeutic or cosmetic botulinum toxin.

Pathogenesis

All forms of botulism produce disease through a final common pathway. Botulinum toxin is carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly, blocking acetylcholine release and causing impaired neuromuscular and autonomic transmission. **Infant botulism** is an infectious disease that results from ingesting the spores of botulinum toxin–producing strains, with subsequent spore germination, multiplication, and production of botulinum toxin in the large intestine. This sequence is distinct from **foodborne botulism** , which is an intoxication that results when preformed botulinum toxin contained in an improperly preserved or inadequately cooked food is swallowed. **Wound botulism** results from spore germination and colonization of traumatized tissue by *C. botulinum;* the pathogenesis of this form of botulism is similar in this respect to that of tetanus. **Inhalational botulism** occurs when aerosolized botulinum toxin is inhaled. A bioterrorist attack could result in large or small outbreaks of inhalational or foodborne botulism (see Chapter 741).

Since botulinum toxin is not a *cytotoxin*, it does not cause overt macroscopic or microscopic pathology. Pathologic changes (pneumonia, petechiae on intrathoracic organs) may be found at autopsy, but these are secondary changes and not primarily attributable to botulinum toxin. No diagnostic technique is available to identify botulinum toxin binding at the neuromuscular junction. Nerve conduction velocity studies are typically normal. Electromyography (EMG) findings are often nonspecific and nondiagnostic (see later). The healing process in botulism consists of sprouting of new terminal unmyelinated motor neurons. Movement resumes when these new nerve terminals locate noncontracting muscle fibers and reinnervate them by inducing formation of a new motor end plate. In experimental animals, this process takes about 4 wk.

Clinical Manifestations

The full clinical spectrum of infant botulism ranges from mild to fulminant sudden death. Botulinum toxin is distributed hematogenously. Because relative blood flow and density of innervation are greatest in the bulbar musculature, all forms of botulism manifest neurologically as a symmetric, descending, flaccid paralysis beginning with the cranial nerve musculature and progressing over hours to days. **Bulbar palsies** may manifest with symptoms as poor feeding, weak suck, feeble cry, drooling, and even obstructive apnea. These clinical clues unfortunately may not be recognized as bulbar in origin (Fig. 237.1). Patients with evolving illness may already have generalized weakness and hypotonia in addition to bulbar palsies when first examined. The brain itself is spared in infant botulism, since botulinum toxin does not cross the blood-brain barrier.

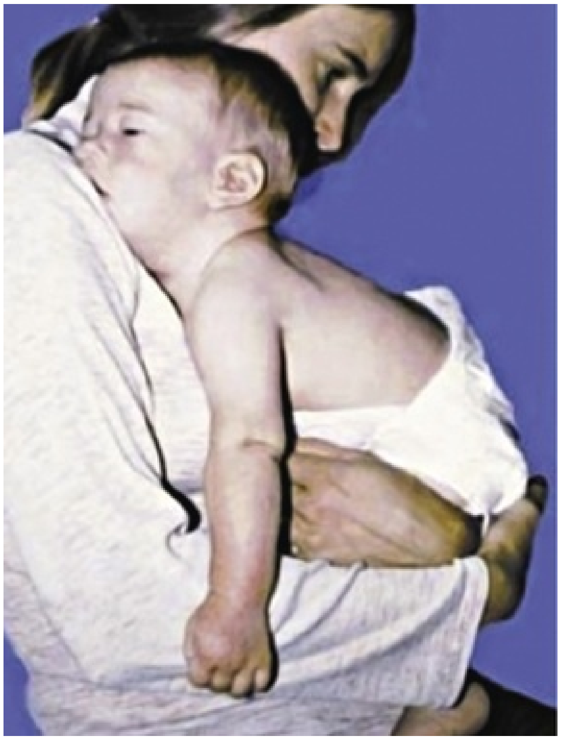

FIG. 237.1 A 3 mo old infant with mild infant botulism showing signs of ptosis, an expressionless face, and hypotonia of the neck, trunk, and limbs. The additional bulbar palsies—ophthalmoplegia, weak cry, weak sucking, and dysphagia (drooling)—are not apparent in the photograph. (From Arnon SS, Schechter R, Maslanka SE, et al: Human botulism immune globulin for the treatment of infant botulism, *N Engl J Med* 354:462–471, 2006.)

In contrast to botulism caused by *C. botulinum,* a majority of the rare cases caused by intestinal colonization with *C. butyricum* are associated with a Meckel diverticulum accompanying abdominal distention, often leading to misdiagnosis as an acute abdomen. The also rare *C. baratii* type F infant botulism cases have been characterized by very young age at onset, rapidity of onset, and greater severity but shorter duration of paralysis.

In older children with **foodborne** or **wound botulism** , the onset of neurologic symptoms follows a characteristic pattern of diplopia, ptosis, dry mouth, dysphagia, dysphonia, and dysarthria, with decreased gag and corneal reflexes. Importantly, because the toxin acts only on motor nerves, paresthesias are not seen in botulism, except when a patient hyperventilates from anxiety. The sensorium remains clear, but this fact may be difficult to ascertain because of the slurred speech.

Foodborne botulism begins with gastrointestinal (GI) symptoms of nausea, vomiting, or diarrhea in approximately 30% of cases. These symptoms are thought to result from metabolic by-products of growth of *C. botulinum* or from the presence of other toxic contaminants in the food, because GI distress is rarely observed in wound botulism. Constipation may occur in foodborne botulism once flaccid paralysis becomes evident. Illness usually begins 12-36 hr after ingestion of the contaminated food but can range from as short as 2 hr to as long as 8 days. The incubation period in **wound botulism** is 4-14 days. Fever may be present in wound botulism but is absent in foodborne botulism unless a secondary infection (often pneumonia) is present. All forms of botulism display a wide spectrum of clinical severity, from the very mild, with minimal ptosis, flattened facial expression, minor dysphagia, and dysphonia, to the fulminant, with rapid onset of extensive paralysis, frank apnea, and fixed, dilated pupils. *Fatigability with repetitive muscle activity* is the clinical hallmark of botulism.

Infant botulism differs in apparent initial symptoms of illness only because the infant cannot verbalize them. Clinical progression can be more rapid and more severe in very young infants. The incubation period in infant botulism is estimated to be 3-30 days. Usually, the first indication of illness is a decreased frequency or even absence of defecation, and indeed constipation may be the chief complaint (although this sign is also frequently overlooked). Parents typically notice inability to feed, lethargy, weak cry, and diminished spontaneous movement. Dysphagia may be evident, and an increase in secretions drooling from the mouth may be noted. Gag, suck, and corneal reflexes all diminish as the paralysis advances. Oculomotor palsies may be evident. Paradoxically, the pupillary light reflex may be unaffected until the child is severely paralyzed, or it may be initially sluggish. Loss of head control is typically a prominent sign. Opisthotonos may be observed. Respiratory arrest may occur suddenly from airway occlusion by unswallowed secretions or from obstructive flaccid pharyngeal musculature. Death from botulism results either from airway obstruction or paralysis of the respiratory muscles. Occasionally, the diagnosis of infant botulism is suggested by a respiratory arrest that occurs after the infant is curled into position for lumbar puncture, or following the administration of an aminoglycoside antibiotic administered for suspected sepsis (see later).

In mild cases or in the early stages of illness, the physical signs of infant botulism may be subtle and easily missed. Eliciting cranial nerve palsies and fatigability of muscular function requires careful examination. Ptosis may not be seen unless the head of the child is kept erect.

Diagnosis

Definitive diagnosis of botulism is made by specialized laboratory testing that requires hours to days to complete. Therefore, clinical diagnosis is the foundation for early recognition of and response to all forms of botulism. Routine laboratory studies, including those of the cerebrospinal fluid (CSF), are normal in botulism unless dehydration, undernourishment (metabolic acidosis and ketosis), or secondary infection is present.

The **classic triad** of botulism is the acute onset of a symmetric flaccid descending paralysis with clear sensorium, no fever, and no paresthesias. Suspected botulism represents a medical and public health emergency that is immediately reportable by telephone in most U.S. health jurisdictions. State health departments (first call) and the CDC (770-488-7100 at any time) can arrange for diagnostic testing, epidemiologic investigation, and provision of equine antitoxin.

The diagnosis of botulism is unequivocally established by demonstration of the presence of botulinum toxin in serum or of *C. botulinum* toxin or organisms in wound material, enema fluid, or feces. *C. botulinum* is not part of the normal resident intestinal flora of humans, and its presence in the setting of acute flaccid paralysis is diagnostic. An epidemiologic diagnosis of foodborne botulism can be established when *C. botulinum* organisms and toxin are found in food eaten by patients.

Electromyography can sometimes distinguish between causes of acute flaccid paralysis, although results may be variable, including normal, in patients with botulism. The distinctive EMG finding in botulism is facilitation (potentiation) of the evoked muscle action potential at high-frequency (50 Hz) stimulation. In infant botulism, a characteristic pattern known as **BSAP** (brief, small, abundant motor unit action potentials), is present only in clinically weak muscles. Nerve conduction velocity and sensory nerve function are normal in botulism.

Infant botulism requires a high index of suspicion for early diagnosis (Table 237.1). Rule out sepsis remains the most common admission diagnosis. If a previously healthy infant (usually 2-4 mo old) demonstrates weakness with difficulty in sucking, swallowing, crying, or breathing, infant botulism should be considered a likely diagnosis. A careful cranial nerve examination is then very helpful. Rare instances of co-infection with *C. difficile* , respiratory syncytial virus, or influenza virus have occurred.

Table 237.1

Diagnoses Considered in Subsequently Laboratory-Confirmed Cases of Infant Botulism

ADMISSION DIAGNOSIS	SUBSEQUENTLY CONSIDERED DIAGNOSES
Suspected sepsis, meningitis	Guillain-Barré syndrome
Pneumonia	Myasthenia gravis
Dehydration	Disorders of amino acid metabolism
Viral syndrome	Hypothyroidism
Hypotonia of unknown etiology	Drug ingestion
	Organophosphate poisoning
Constipation	Brainstem encephalitis
Failure to thrive	Heavy metal poisoning (Pb, Mg, As)
Spinal muscular atrophy type 1 (Werdnig-Hoffmann disease)	Poliomyelitis
	Viral polyneuritis
	Hirschsprung disease
	Metabolic encephalopathy
	Medium-chain acetyl–coenzyme A dehydrogenase deficiency

Differential Diagnosis

Botulism is frequently misdiagnosed, most often as a **polyradiculoneuropathy** (Guillain-Barré or Miller Fisher syndrome), myasthenia gravis, or a central nervous system (CNS) disease (Table 237.2). In the United States, botulism is more likely than **Guillain-Barré syndrome** , intoxication, or poliomyelitis to cause a cluster of cases of acute flaccid paralysis. Botulism differs from other flaccid paralyses in its initial and prominent cranial nerve palsies that are disproportionate to milder weakness and hypotonia below the neck; in its symmetry; and in its absence of sensory nerve damage. Spinal muscular atrophy may closely mimic infant botulism at presentation.

Table 237.2

Conditions Considered in Differential Diagnosis of Foodborne Botulism and Wound Botulism

Acute gastroenteritis
Myasthenia gravis
Guillain-Barré syndrome
Organophosphate poisoning
Meningitis

Encephalitis
Psychiatric illness
Cerebrovascular accident
Poliomyelitis
Hypothyroidism
Aminoglycoside-associated paralysis
Tick paralysis
Hypocalcemia
Hypermagnesemia
Carbon monoxide poisoning
Hyperemesis gravidarum
Laryngeal trauma
Diabetic complications
Inflammatory myopathy
Overexertion

Additional diagnostic procedures may be useful in rapidly excluding botulism as the cause of paralysis. The CSF is unchanged in botulism but is abnormal in many CNS diseases. Although the CSF protein concentration is eventually elevated in Guillain-Barré syndrome, it may be normal early in illness. Imaging of the brain, spine, and chest may reveal hemorrhage, inflammation, or neoplasm. A test dose of edrophonium chloride briefly reverses paralytic symptoms in many patients with myasthenia gravis and, reportedly, in some with botulism, although this is rarely performed in infants. A close inspection of the skin, especially the scalp, may reveal an attached tick that is causing paralysis. Possible organophosphate intoxication should be pursued aggressively, because specific antidotes (oximes) are available and because the patient may be part of a commonly exposed group, some of whom have yet to demonstrate illness. Other tests that require days for results include stool culture for *Campylobacter jejuni* as a precipitant of Guillain-Barré syndrome, spinal muscular atrophy and other genetic (including mitochondrial) disorders, and assays for the autoantibodies that cause myasthenia gravis, Lambert-Eaton syndrome, and Guillain-Barré syndrome.

Treatment

Human botulism immune globulin, given intravenously (BIG-IV, also referred to as BabyBIG), is licensed for the treatment of infant botulism caused by type A or B botulinum toxin. Treatment with BIG-IV consists of a single intravenous infusion of 50-100 mg/kg (see package insert) that should be given as soon as possible after infant botulism is suspected so as to immediately end the toxemia that is the cause of the illness and arrest progression of paralysis. *When the* *diagnosis of infant botulism is suspected, treatment should not be delayed for laboratory confirmation.* In the United States, BIG-IV may be obtained from the California Department of Public Health (24 hr telephone: 510-231-7600; http://www.infantbotulism.org). The use of BIG-IV shortens mean hospital stay from approximately 6 wk to approximately 2 wk. Most of the decrease in hospital stay results from shorter duration of mechanical ventilation and reduced days in intensive care. Hospital costs are reduced by >$100,000 per case (in 2012 U.S. dollars).

Older patients with suspected food, wound, or inhalational botulism may be treated with 1 vial of licensed equine heptavalent (A-G) botulinum antitoxin (HBAT; https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5910a4.htm), available in the United States through the CDC by way of state and local health departments.

Antibiotic therapy is not part of the treatment of uncomplicated infant or foodborne botulism, because the toxin is primarily an intracellular molecule that is released into the intestinal lumen with vegetative bacterial cell death and lysis. Indeed, there is theoretical concern that antibiotics with clostridiocidal activity may increase the amount of free toxin in the large bowel and actually worsen an infant's clinical status. Antibiotic use in infant botulism patients is indicated only for the treatment of secondary infections. In these patients, aminoglycosides should be avoided, since this class of antibiotics can potentiate the action of botulinum toxin at the neuromuscular junction. Wound botulism requires aggressive treatment with antibiotics and antitoxin in a manner analogous to that for tetanus (see Chapter 238) and may require wound debridement to remove the source of the toxin.

Supportive Care

Management of botulism rests on the following 3 principles: (1) fatigability with repetitive muscle activity is the clinical hallmark of the disease; (2) complications are best avoided by anticipating them; and (3) meticulous supportive care is a necessity. The 1st principle applies mainly to feeding and breathing. Correct positioning is imperative to protect the airway and improve respiratory mechanics. The patient should be positioned face-up on a rigid-bottomed crib (or bed), the head of which is tilted at 30 degrees. A small cloth roll is placed under the cervical vertebrae to tilt the head back so that secretions drain to the posterior pharynx and away from the airway. In this tilted position, the abdominal viscera pull the diaphragm down, thereby improving respiratory mechanics. The patient's head and torso should not be elevated by bending the middle of the bed; in such a position, the hypotonic thorax would slump into the abdomen, and breathing would be compromised.

About half of patients with infant botulism require endotracheal intubation, which is best done prophylactically. The indications include diminished gag and cough reflexes and progressive airway obstruction by secretions.

Feeding should be done by a nasogastric or nasojejunal tube until sufficient oropharyngeal strength and coordination enable allow oral feeding by breast or bottle. Expressed breast milk is the most desirable food for infants, in part because of its immunologic components (e.g., secretory IgA, lactoferrin, leukocytes). Tube feeding also assists in the restoration of peristalsis, a nonspecific but probably essential part of eliminating *C. botulinum* from the intestinal flora. Intravenous feeding (hyperalimentation) is discouraged because of the potential for infection and the advantages of tube feeding.

Because sensation and cognitive function remain fully intact, providing auditory, tactile, and visual stimuli is beneficial. Maintaining strong central respiratory drive is essential, so sedatives and CNS depressants should be avoided. Full hydration and stool softeners such as lactulose may mitigate the protracted constipation. Cathartics are not recommended. Patients with foodborne and infant botulism excrete *C. botulinum* toxin and organisms in their feces, often for many weeks, and care should be taken in handling their excreta, with full engagement of hospital infection control staff. When bladder palsy occurs in severe cases, gentle suprapubic pressure with the patient in the sitting position with the head supported may help attain complete voiding and reduce the risk for urinary tract infection (UTI). Families of affected patients may require emotional and financial support, especially when the paralysis of botulism is prolonged.

Complications

Almost all the complications of botulism are *nosocomial,* and a few are iatrogenic (Table 237.3). Some critically ill, toxin-paralyzed patients who must spend weeks or months on ventilators in intensive care units inevitably experience some of these complications. Suspected “relapses” of infant botulism usually reflect premature hospital discharge or an inapparent underlying complication such as pneumonia, UTI, or otitis media.

Table 237.3

Complications of Infant Botulism

Acute respiratory distress syndrome
Aspiration
Clostridium difficile enterocolitis
Hypotension
Inappropriate antidiuretic hormone secretion
Long bone fractures
Misplaced or plugged endotracheal tube
Nosocomial anemia
Otitis media
Pneumonia
Pneumothorax
Recurrent atelectasis
Seizures secondary to hyponatremia
Sepsis
Subglottic stenosis
Tracheal granuloma
Tracheitis
Transfusion reaction
Urinary tract infection

Prognosis

When the regenerating nerve endings have induced formation of a new motor end plate, neuromuscular transmission is restored. In the absence of complications, particularly those related to hypoxia, the prognosis in infant botulism is for full and complete recovery. Hospital stay in untreated infant botulism averages 5.7 wk but differs significantly by toxin type, with patients with untreated type B disease being hospitalized a mean of 4.2 wk and those with untreated type A disease being hospitalized a mean of 6.7 wk.

In the United States, the case fatality ratio for hospitalized cases of infant botulism is <1%. After recovery, patients with untreated infant botulism appear to have an increased incidence of strabismus that requires timely screening and treatment.

The case fatality ratio in foodborne and wound botulism varies by age, with younger patients having the best prognosis. Some adults with botulism have reported chronic weakness and fatigue for >1 yr as sequelae.

Prevention

Foodborne botulism is best prevented by adherence to safe methods of home canning (pressure cooker and acidification), by avoiding suspicious foods, and by heating all home-canned foods to 85°C (185°F) for ≥5 min. Wound botulism is best prevented by not using illicit drugs and by treatment of contaminated wounds with thorough cleansing, surgical debridement, and provision of appropriate antibiotics.

Many patients with infant botulism are presumed to have inhaled and then swallowed airborne clostridial spores; these cases cannot be prevented. However, a clearly identified and avoidable source of botulinum spores for infants is **honey** . *Honey is an unsafe food for any child <1 yr old.* Corn syrups were once thought to be a possible source of botulinum spores, but evidence indicates otherwise. Breastfeeding appears to slow the onset of infant botulism and to diminish the risk for sudden death in infants in whom the disease develops.

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CHAPTER 238

Tetanus *(Clostridium tetani)*

Mark R. Schleiss

Etiology

Tetanus is an acute, spastic paralytic illness caused by a neurotoxin produced by *Clostridium tetani*. Thus, tetanus can be considered more as a toxin-mediated process than an acute infectious process, since there are few, if any, symptoms elicited by the presence of replicating microorganisms or host inflammatory response. Unlike other pathogenic clostridia species, *C. tetani* is not a tissue-invasive organism and instead causes illness through the toxin, **tetanospasmin** , more commonly referred to as **tetanus toxin** . Tetanospasmin is the 2nd most poisonous substance known, surpassed in potency only by botulinum toxin. The human lethal dose of tetanus toxin is estimated to be 10^{-5} mg/kg.

Clostridium tetani is a motile, gram-positive, spore-forming obligate anaerobe. The organism's natural habitat worldwide is soil, dust, and the alimentary tracts of various animals. *C. tetani* forms spores terminally, with a classic morphologic appearance resembling a drumstick or tennis racket microscopically. The formation of spores is a critical aspect of the organism's persistence in the environment. Spores can survive boiling but not autoclaving, whereas the vegetative cells are killed by antibiotics, heat, and standard disinfectants.

Epidemiology

Tetanus occurs worldwide and is endemic in many developing countries, although its incidence varies considerably. Public health efforts in recent years have had an impressive impact on tetanus-associated mortality, although many challenges remain. Approximately 57,000 deaths were caused by tetanus globally in 2015. Of these, approximately 20,000 deaths occurred in neonates and 37,000 in older children and adults. Most mortality from **neonatal (or umbilical) tetanus** occurs in South Asia and Sub-Saharan Africa (Fig. 238.1). Mortality in adults is largely caused by **maternal tetanus,** which results from postpartum, postabortal, or postsurgical wound infection with *C. tetani*. Reported tetanus cases in the United States have declined >95% since 1947, and deaths from tetanus have declined by >99% in that same period. From 2009 through 2015, a total of 197 cases and 16 deaths from tetanus were reported in the United States. The majority of U.S. childhood cases of tetanus have occurred in unimmunized children whose parents objected to vaccination.

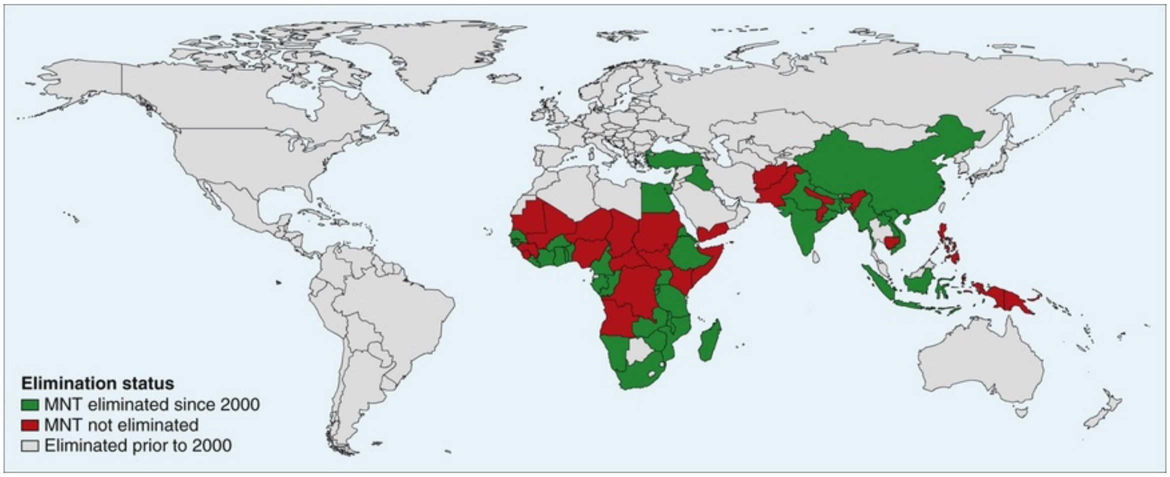

FIG. 238.1 Global elimination status of maternal and neonatal tetanus (MNT). (From World Health Organization: Maternal and neonatal tetanus (MNT) elimination. http://www.who.int/immunization/diseases/MNTE_initiative/en .)

Most non-neonatal cases of tetanus are associated with a traumatic injury, often a penetrating wound inflicted by a dirty object such as a nail, splinter, fragment of glass, or unsterile injection. Tetanus may also occur in the setting of illicit drug injection. The disease has been associated with the use of contaminated suture material and after intramuscular injection of medicines, most notably quinine for chloroquine-resistant falciparum malaria. The disease may also occur in association with animal bites, abscesses (including dental abscesses), ear and other body piercing, chronic skin ulceration, burns, compound fractures, frostbite, gangrene, intestinal surgery, ritual scarification, infected insect bites, and female circumcision. Rarely, cases may present to clinical attention without an antecedent history of trauma.

Pathogenesis

Tetanus typically occurs after spores (introduced by traumatic injury) germinate, multiply, and produce tetanus toxin. A plasmid carries the toxin gene. Toxin is produced only by the vegetative cell, not the spore. It is released after the vegetative phase of replication, with replication occurring under anaerobic conditions. The low oxidation-reduction potential of an infected injury site therefore provides an ideal environment for transition from the spore to the vegetative stage of growth. Following bacterial cell death and lysis, tetanospasmin is produced. The toxin has no known function for clostridia in the soil environment where they normally reside. Tetanus toxin is a 150 kDa simple protein consisting of a heavy (100 kDa) and a light (50 kDa) chain joined by a single disulfide bond. Tetanus toxin binds at the neuromuscular junction and enters the motor nerve by endocytosis, after which it undergoes retrograde axonal transport, facilitated by dyneins, to the cytoplasm of the α-motoneuron. In the sciatic nerve, the transport rate was found to be 3.4 mm/hr. The toxin exits the motoneuron in the spinal cord and next enters adjacent spinal inhibitory interneurons, where it prevents release of the neurotransmitters glycine and γ-aminobutyric acid (GABA). Tetanus toxin thus blocks the normal inhibition of antagonistic muscles on which voluntary coordinated movement depends; as a consequence, affected muscles sustain maximal contraction and cannot relax. This aspect of pathogenesis led to the term **lockjaw** , classically applied to the clinical manifestations of tetanus in the affected individual. The autonomic nervous system is also rendered unstable in tetanus.

The phenomenal potency of tetanus toxin is enzymatic. The 50 kDa light chain (A-chain) of tetanus toxin is a zinc-containing endoprotease whose substrate is synaptobrevin, a constituent protein of the docking complex that enables the synaptic vesicle to fuse with the terminal neuronal cell membrane. The cleavage of synaptobrevin is the final target of tetanus toxin, and even in low doses the neurotoxin will inhibit neurotransmitter exocytosis in the inhibitory interneurons. The blockage of GABA and glycine causes the physiologic effects of tetanus toxin. The 100 kDa heavy chain (B-chain) of the toxin contains its binding and internalization domains. It binds to disialogangliosides (GD2 and GD1b) on the neuronal membrane. The translocation domain aids the movement of the protein across that membrane and into the neuron.

Because *C. tetani* is not an invasive organism, its toxin-producing vegetative cells remain where introduced into the wound, which may display local inflammatory changes and a mixed bacterial flora.

Clinical Manifestations

Tetanus is most often generalized but may also be localized. The incubation period typically is 2-14 days but may be as long as months after the injury. In **generalized tetanus** the presenting symptom in about half of cases is **trismus** (masseter muscle spasm, or lockjaw). Headache, restlessness, and irritability are early symptoms, often followed by stiffness, difficulty chewing, dysphagia, and neck muscle spasm. The so-called sardonic smile of tetanus (**risus sardonicus**) results from intractable spasms of facial and buccal muscles. When the paralysis extends to abdominal, lumbar, hip, and thigh muscles, the patient may assume an arched posture of extreme hyperextension of the body, or **opisthotonos** , with the head and the heels bent backward and the body bowed forward. In severe cases, only the back of the head and the heels of the patient are noted to be touching the supporting surface. Opisthotonos is an equilibrium position that results from unrelenting total contraction of opposing muscles, all of which display the typical boardlike rigidity of tetanus. Laryngeal and respiratory muscle spasm can lead to airway obstruction and asphyxiation. Because tetanus toxin does not affect sensory nerves or cortical function, the patient unfortunately remains conscious, in extreme pain, and in fearful anticipation of the next tetanic seizure. The seizures are characterized by sudden, severe tonic contractions of the muscles, with fist clenching, flexion, and adduction of the arms and hyperextension of the legs. Without treatment, the duration of these seizures may range from a few seconds to a few minutes in length with intervening respite periods. As the illness progresses, the spasms become sustained and exhausting. The smallest disturbance by sight, sound, or touch may trigger a tetanic spasm. Dysuria and urinary retention result from bladder sphincter spasm; forced defecation may occur. Fever, occasionally as high as 40°C (104°F), is common and is caused by the substantial metabolic energy consumed by spastic muscles. Notable autonomic effects include tachycardia, dysrhythmias, labile hypertension, diaphoresis, and cutaneous vasoconstriction. The tetanic paralysis usually becomes more severe in the 1st wk after onset, stabilizes in the 2nd wk, and ameliorates gradually over the ensuing 1-4 wk.

Neonatal tetanus , the infantile form of generalized tetanus, typically manifests within 3-12 days of birth. It presents as progressive difficulty in feeding (sucking and swallowing), associated hunger, and crying. Paralysis or diminished movement, stiffness and rigidity to the touch, and spasms, with or without opisthotonos, are characteristic. The umbilical stump, which is typically the portal of entry for the microorganism, may retain remnants of dirt, dung, clotted blood, or serum, or it may appear relatively benign.

Localized tetanus results in painful spasms of the muscles adjacent to the wound site and may precede generalized tetanus. **Cephalic tetanus** is a rare form of localized tetanus involving the bulbar musculature that occurs with wounds or foreign bodies in the head, nostrils, or face. It also occurs in association with chronic otitis media. Cephalic tetanus is characterized by retracted eyelids, deviated gaze, trismus, risus sardonicus, and spastic paralysis of the tongue and pharyngeal musculature.

Diagnosis

The picture of tetanus is one of the most dramatic in medicine, and the diagnosis may be established clinically. The typical setting is an unimmunized patient (and/or mother) who was injured or born within the preceding 2 wk, who presents with trismus, dysphagia, generalized muscle rigidity and spasm, and a clear sensorium.

Results of routine laboratory studies are usually normal. A peripheral leukocytosis may result from a secondary bacterial infection of the wound or may be stress-induced from the sustained tetanic spasms. The cerebrospinal fluid analysis is normal, although the intense muscle contractions may raise intracranial pressure. Serum muscle enzymes (creatine kinase, aldolase) may be elevated. Neither the electroencephalogram nor the electromyogram shows a characteristic pattern, although EMG may show continuous discharge of motor subunits and shortening, or absence of the silent interval normally observed after an action potential. An assay for antitoxin levels is not readily available, although a serum antitoxin level of ≥0.01 IU/mL is generally considered protective and makes the diagnosis of tetanus less likely. *C. tetani* is not always visible on Gram stain of wound material and is isolated by culture in only approximately 30% of cases. The **spatula test** is a simple diagnostic bedside test that involves touching the oropharynx with a spatula or tongue blade. Normally this maneuver will elicit a gag reflex, as the patient tries to expel the spatula (negative test). If tetanus is present, patients develop a reflex spasm of the masseter muscles and bite the spatula (positive test). This bedside diagnostic maneuver is said to have a high sensitivity and specificity.

Differential Diagnosis

Florid and generalized tetanus is typically not mistaken for any other disease. However, trismus may result from parapharyngeal, retropharyngeal, or dental abscesses or rarely from acute encephalitis involving the brainstem. Either rabies or tetanus may follow an animal bite, and rabies may manifest as trismus with seizures. **Rabies** may be distinguished from tetanus by hydrophobia, marked dysphagia, predominantly clonic seizures, and pleocytosis (see Chapter 300). Although **strychnine poisoning** may result in tonic muscle spasms and generalized seizure activity, it seldom produces trismus, and unlike in tetanus, general relaxation usually occurs between spasms. Hypocalcemia may produce tetany that is characterized by laryngeal and carpopedal spasms, but trismus is absent. Occasionally, epileptic seizures, narcotic withdrawal, or other drug reactions may suggest tetanus.

Treatment

Management of tetanus requires eradication of *C. tetani* , correction of wound environment conditions conducive to its anaerobic replication, neutralization of all accessible tetanus toxin, control of seizures and respiration, palliation, provision of meticulous supportive care, and prevention of recurrences.

Surgical wound excision and debridement are often needed to remove the foreign body or devitalized tissue that created the anaerobic growth conditions necessary for vegetative replication. Surgery should be performed promptly after administration of **human tetanus immunoglobulin** (TIG) and antibiotics. Excision of the umbilical stump in the neonate with tetanus is no longer recommended.

Tetanus toxin cannot be neutralized by TIG after it has begun its axonal ascent to the spinal cord. However, TIG should be given as soon as possible, toward the goal of neutralizing toxin that diffuses from the wound into the circulation before the toxin can bind at distant muscle groups. The optimal dose of TIG has not been determined. Some experts recommend a single intramuscular injection of 500 units of TIG to neutralize systemic tetanus toxin, but total doses as high as 3,000-6,000 U are also recommended. Infiltration of part of the dose of TIG into the wound is recommended by the Red Book Committee of the American

Academy of Pediatrics, although the efficacy of this approach has not been proved. If TIG is unavailable, use of human intravenous immunoglobulin may be necessary. IVIG contains 4-90 U/mL of TIG; the optimal dosage of IVIG for treating tetanus is not known, and its use is not approved for this indication. In parts of the world where it is available, another alternative may be equine-derived tetanus antitoxin (TAT). This product is no longer available in the United States. A dose of 1,500-3,000 U is recommended and should be administered after appropriate testing for sensitivity and desensitization, since up to 15% of patients given the usual dose of TAT will experience serum sickness. The human-derived immunoglobulins are much preferred because of their longer half-life (30 days) and the virtual absence of allergic and serum sickness adverse effects. Results of studies examining the potential benefit of intrathecal administration of TIG are conflicting. The TIG preparation available for use in the United States is neither licensed nor formulated for intrathecal or intravenous use.

Oral (or intravenous) **metronidazole** (30 mg/kg/day, given at 6 hr intervals; maximum dose, 4 g/day) decreases the number of vegetative forms of *C. tetani* and is currently considered the antibiotic of choice. Parenteral penicillin G (100,000 U/kg/day, administered at 4-6 hr intervals, with a daily maximum 12 million U) is an alternative treatment. Antimicrobial therapy for a total duration of 7-10 days is recommended.

Supportive care and pharmacologic interventions targeted at control of tetanic spasms are of critical importance in the management of tetanus. Toward this goal, all patients with generalized tetanus should receive **muscle relaxants** . Diazepam provides both relaxation and seizure control. The initial dose of 0.1-0.2 mg/kg every 3-6 hr intravenously is subsequently titrated to control the tetanic spasms, after which the effective dose is sustained for 2-6 wk before a tapered withdrawal. Magnesium sulfate, other benzodiazepines (midazolam), chlorpromazine, dantrolene, and baclofen are also used. Intrathecal baclofen produces such complete muscle relaxation that apnea often ensues; as with most other agents listed, baclofen should be used only in an intensive care unit setting. Favorable survival rates in generalized tetanus have been described with the use of neuromuscular blocking agents such as vecuronium and pancuronium, which produce a general flaccid paralysis that is then managed by mechanical ventilation. Autonomic instability is regulated with standard α- or β-adrenergic (or both) blocking agents; morphine has also proved useful.

Supportive Care

Meticulous supportive care in a quiet, dark, secluded setting is most desirable. Because tetanic spasms may be triggered by minor stimuli, the patient should be sedated and protected from all unnecessary sounds, sights, and touch, and all therapeutic and other manipulations must be carefully scheduled and coordinated. Endotracheal intubation may not be required, but it should be done to prevent aspiration of secretions before laryngospasm develops. A tracheostomy kit should be immediately at hand for unintubated patients. Endotracheal intubation and suctioning easily provoke reflex tetanic seizures and spasms, so early tracheostomy should be considered in severe cases not managed by pharmacologically induced flaccid paralysis. Therapeutic botulinum toxin has been used to overcome trismus.

Cardiorespiratory monitoring, frequent suctioning, and maintenance of the patient's substantial fluid, electrolyte, and caloric needs are fundamental. Careful nursing attention to mouth, skin, bladder, and bowel function is needed to avoid ulceration, infection, and obstipation. Prophylactic subcutaneous heparin may be of value, but it must be balanced with the risk of hemorrhage. Enoxaparin would be an alternative for the patient for whom deep vein thrombosis prophylaxis is warranted.

Complications

The seizures and the severe, sustained rigid paralysis of tetanus predispose the patient to many complications. Aspiration of secretions with attendant pneumonia is an important complication to consider and may be present at initial diagnosis. Maintaining airway patency often mandates endotracheal intubation and mechanical ventilation with their attendant hazards, including pneumothorax and mediastinal emphysema. The seizures may result in lacerations of the mouth or tongue, in intramuscular hematomas or **rhabdomyolysis** with myoglobinuria and renal failure, or in long-bone or spinal fractures. Venous thrombosis, pulmonary embolism, gastric ulceration with or without hemorrhage, paralytic ileus, and decubitus ulceration are described as complications. Excessive use of muscle relaxants, which are an integral part of care, may produce iatrogenic apnea. Cardiac arrhythmias, including asystole, unstable blood pressure, and labile temperature regulation reflect disordered autonomic nervous system control that may be aggravated by inattention to maintenance of intravascular volume needs.

Prognosis

Recovery in tetanus occurs through regeneration of synapses within the spinal cord that results in restoration of muscle relaxation. Interestingly, an episode of tetanus does not result in the production of toxin-neutralizing antibodies, presumably because the infinitesimally small amounts of toxin required to cause disease are not sufficient to elicit an immune response. Therefore, active immunization with tetanus toxoid during convalescence and/or at discharge, with provision for completion of the primary vaccine series, is mandatory.

The most important factor that influences outcome is the quality of supportive care. Mortality is highest in very young and very old patients. A favorable prognosis is associated with a long incubation period, absence of fever, and localized disease. An unfavorable prognosis is associated with onset of trismus <7 days after injury and onset of generalized tetanic spasms <3 days after onset of trismus. Sequelae of hypoxic brain injury, especially in infants, include cerebral palsy, diminished mental abilities, and behavioral difficulties. Most fatalities occur within the 1st wk of illness. Reported case fatality rates for generalized tetanus are 5–35%, and for neonatal tetanus they extend from <10% with intensive care treatment to >75% without it. Cephalic tetanus has an especially poor prognosis because of breathing and feeding difficulties.

Prevention

Tetanus is an entirely and easily preventable disease. A serum antibody titer of ≥0.01 U/mL is considered protective. Active immunization should begin in early infancy with combined diphtheria toxoid–tetanus toxoid–acellular pertussis (DTaP) vaccine at 2, 4, 6, and 15-18 mo of age, with boosters at 4-6 yr (DTaP) and 11-12 yr (Tdap) of age, and at 10 yr intervals thereafter throughout adult life with tetanus and reduced diphtheria toxoid (Td). Immunization of women with tetanus toxoid prevents neonatal tetanus, and pregnant women should receive 1 dose of reduced diphtheria and pertussis toxoids (Tdap) during each pregnancy, preferably at 27-36 wk of gestation. Recommended immunization schedules are regularly updated (http://www.cdc.gov/vaccines/schedules).

Arthus reactions (type III hypersensitivity reactions), a localized vasculitis associated with deposition of immune complexes and activation of complement, are reported rarely after tetanus vaccination. Mass immunization campaigns in developing countries have occasionally provoked a widespread hysterical reaction.

Wound Management

Tetanus prevention measures after trauma consist of inducing active immunity to tetanus toxin and of passively providing antitoxic antibody (Table 238.1). Tetanus prophylaxis is an essential part of all wound management, but specific measures depend on the nature of the injury and the immunization status of the patient. Prevention of tetanus must be included in planning for the consequences of bombings, natural disasters, and other possible civilian mass-casualty events.

Table 238.1

Tetanus Vaccination and Immune Globulin Use in Wound Management

HISTORY OF ABSORBED TETANUS TOXOID	**CLEAN, MINOR WOUNDS**		**ALL OTHER WOUNDS**[*]	
	DTaP, Tdap, *or* Td[†]	**TIG**[‡]	**DTaP, Tdap, *or* TD**[†]	**TIG**[‡]
Uncertain or <3 doses	Yes	No	Yes	Yes
≥3 doses	No if <10 yr since last dose of tetanus-containing vaccine	No	No if <5 yr since last tetanus-containing vaccine[§]	No
	Yes if ≥10 yr since last dose of tetanus-containing vaccine	No	Yes if ≥5 yr since last tetanus-containing vaccine dose	No

[*] Such as, but not limited to, wounds contaminated with dirt, feces, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.

[†] DTaP is used for children <7 yr old. Tdap is preferred over Td for underimmunized children ≥7 yr old who have not received Tdap previously.

[‡] Intravenous immune globulin should be used when TIG is unavailable.

[§] More frequent boosters are not needed and can accentuate adverse events.

DT, Diphtheria and tetanus toxoid vaccine; DTaP, combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; Td, tetanus toxoid and reduced diphtheria toxoid vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; TIG, tetanus immune globulin.

Data from Tetanus (lockjaw). In Kimberlin DW, Brady MT, Jackson MA, Long SS, editors: *Red book: 2015 report of the Committee on Infectious Diseases,* ed 30, Elk Grove Village, IL, 2015, American Academy of Pediatrics.

Tetanus toxoid should always be given after a dog or other animal bite, even though *C. tetani* is infrequently found in canine mouth flora. Non-minor wounds require human TIG except those in a fully immunized patient (i.e., ≥3 doses of adsorbed tetanus toxoid). In any other circumstances (e.g., patients with an unknown or incomplete immunization history; crush, puncture, or projectile wounds; wounds contaminated with saliva, soil, or feces; avulsion injuries; compound fractures; or frostbite), TIG 250 units should be administered intramuscularly, regardless of the patient's age or weight. If TIG is unavailable, use of human IVIG may be considered. If neither of these products is available, 3,000-5,000 units of equine-derived TAT (in regions of the world where it is available) may be given intramuscularly after testing for hypersensitivity. Serum sickness may occur with this agent.

The wound should undergo immediate, thorough surgical cleansing and debridement to remove foreign bodies and any necrotic tissue in which anaerobic conditions might develop. Tetanus toxoid should be given to stimulate active immunity and may be administered concurrently with TIG (or TAT) if given in separate syringes at widely separated sites. A tetanus toxoid booster (preferably Tdap) is administered to all persons with any wound if the tetanus immunization status is unknown or incomplete. A booster is administered to injured persons who have completed the primary immunization series if (1) the wound is clean and minor but ≥10 yr have passed since the last booster or (2) the wound is more serious and ≥5 yr have passed since the last booster (Table 238.1). Persons who experienced an Arthus reaction after a dose of tetanus toxoid–containing vaccine should not receive Td more frequently than every 10 yr, even for tetanus prophylaxis as part of wound management. In a situation of delayed wound care, active immunization should be started at once.

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CHAPTER 239

Clostridium difficile Infection

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Clostridium difficile infection (**CDI**), also known as pseudomembranous colitis or *C. difficile* –associated diarrhea, refers to gastrointestinal (GI) colonization with *C. difficile* resulting in a diarrheal illness. It is a common cause of **antibiotic-associated diarrhea** and the most common cause of healthcare-associated infections in the United States, accounting for 12% of these infections. An increase in inpatient and outpatient acquisition of CDI has been observed, and new risk factors have been identified, fueling the development of new therapeutic options.

Etiology

Clostridium difficile (which has been renamed *Clostridioides difficile*) is a gram-positive, spore-forming, anaerobic bacillus that is resistant to killing by alcohol. It is acquired from the environment or by the fecal-oral route. Organisms causing symptomatic intestinal disease produce 1 or both of the following: **toxin A** and **toxin B** . These toxins affect intracellular signaling pathways, resulting in inflammation and cell death. The cytotoxic **binary toxin** , an AB toxin, is not present in the majority of strains but has been detected in epidemic strains.

Epidemiology

Once thought to be an infrequent infection of chronically ill and hospitalized patients, the incidence of CDI is increasing in pediatric patients, and the setting of acquisition is changing. The incidence in pediatric patients increased 48%, from 2.5 to 3.7 cases per 1,000 admissions between 2001 and 2006. A population-based cohort study over a similar period found that 75% of cases were community acquired and 16% had no preceding hospitalization or antibiotic exposure. Similar 2011 CDC national data estimate3 cases of community-acquired CDI in children for every healthcare-acquired case. In addition to an overall increase in all strains, a *hypervirulent strain* , denoted **NAP1/BI/027** (also called **BI**), has emerged and is estimated to cause 10–20% of pediatric infections. This strain produces binary toxin and exhibits 16- and 23-fold increases in the production of toxins A and B, respectively. The specific role of this hypervirulent strain in the changing epidemiology of CDI is not completely understood.

Asymptomatic carriage occurs with potentially pathogenic strains and is common in neonates and infants ≤1 yr old. A carrier frequency rate of 50% may occur in children <1 yr old, but the rate declines by age 3 yr. Carriers can infect other susceptible individuals.

Risk factors for CDI include the use of broad-spectrum antibiotics, hospitalization (particularly if the prior room occupant was infected), GI surgery, inflammatory bowel disease (IBD), chemotherapy, enteral tube feeding, proton pump inhibitor (PPI) or H_2 -receptor antagonist use, and chronic illness.

Pathogenesis

Disease is caused by GI infection with a toxin-producing strain. Any process that disrupts normal flora, impairs the acid barrier defense, alters the normal GI immune response (e.g., IBD), or inhibits intestinal motility may lead to infection. Normal bowel flora appears to be protective, conferring colonization resistance.

By affecting intracellular signaling pathways and cytoskeletal organization, toxins induce an inflammatory response and cell death, leading to diarrhea and pseudomembrane formation. Antibodies against toxin A have been shown to confer protection against symptomatic disease, and failure of antibody production occurs in patients with recurrent disease.

Clinical Manifestations

Infection with toxin-producing strains of *C. difficile* leads to a spectrum of disease ranging from mild, self-limited diarrhea to explosive, watery diarrhea with occult blood or mucus, to pseudomembranous colitis, and even death. **Pseudomembranous colitis** describes a bloody diarrhea with accompanying fever, abdominal pain/cramps, nausea, and vomiting. Rarely, small-gut involvement, toxic megacolon, bacteremia, abscess formation, intestinal perforation, and even death can occur.

Symptoms of CDI generally begin <1 wk after colonization and may develop during or weeks after antibiotic exposure. They are generally more severe in certain populations, including patients receiving chemotherapy, patients with chronic GI disease (e.g., IBD), and some patients with cystic fibrosis (CF). CDI-associated **reactive arthritis** is an occasional complication, occurring in approximately 1.4% of children with CDI. Reactive arthritis may begin a median of 10.5 days after initial GI symptoms, often accompanied by fever or rash. Joint involvement may be migratory or polyarticular and may resemble septic arthritis.

Diagnosis

Evaluation for CDI should be reserved for children with **diarrhea** , defined as the passage of at least 3 loose stools within a 24 hr period or bloody diarrhea (Fig. 239.1). CDI is diagnosed by the detection of a *C. difficile* **toxin** in the stool of a symptomatic patient. Most patients present with a history of recent antibiotic use, but the absence of antibiotic exposure should not dissuade the astute clinician from considering this diagnosis and ordering the appropriate test. Conversely, high carriage rates without illness among infants should prompt careful consideration when testing and treating children <3 yr old.

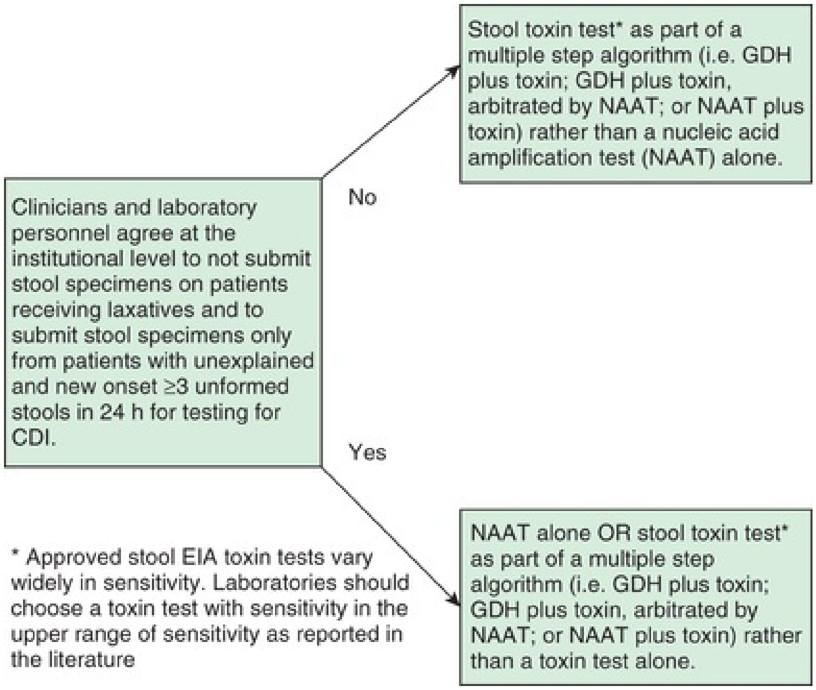

Clinicians and laboratory personnel agree at the institutional level to not submit stool specimens on patients receiving laxatives and to submit stool specimens only from patients with unexplained and new onset ≥3 unformed stools in 24 h for testing for CDI.

Stool toxin test* as part of a multiple step algorithm (i.e. GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a nucleic acid amplification test (NAAT) alone.

NAAT alone OR stool toxin test* as part of a multiple step algorithm (i.e. GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a toxin test alone.

* Approved stool EIA toxin tests vary widely in sensitivity. Laboratories should choose a toxin test with sensitivity in the upper range of sensitivity as reported in the literature

FIG. 239.1 *Clostridium difficile* infection (CDI) laboratory test recommendations based on pre-agreed institutional criteria for patient stool submission. EIA, Enzyme immunoassay; GDH, glutamate dehydrogenase. (From McDonald LC, Gerding DN, Johnson S, et al: Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America [IDSA] and Society for Healthcare Epidemiology of America [SHEA], *Clin Infect Dis* 66(7):e1–e48, 2018, Fig 2.)

The cell culture cytotoxicity assay was replaced as the standard test for toxin detection by **enzyme immunoassay** (EIA), a same-day test for toxin A and/or toxin B with sufficient specificity (94–100%) but less-than-ideal sensitivity (88–93%). Many laboratories use **nucleic acid amplification tests** (NAATs) to supplement or supplant EIA with the goal of improving sensitivity. The sensitivities of the real-time polymerase chain reaction (PCR) assay for toxin A/B were superior compared with EIA for toxin A/B (95% vs 35%, respectively), and the specificity was equal (100%). However, some have questioned the clinical significance of low copy number–positive tests. For example, positive *C. difficile* PCR results occur with similar frequency in patients with IBD with and without an IBD exacerbation. A positive result in a highly sensitive PCR assay that detects low copy numbers of a toxin gene in *C. difficile* may reflect colonization in a subset of patients with IBD, confounding clinical decision-making in managing disease exacerbations. To address this, NAAT-positive tests may be “confirmed” by toxin assays. In addition, eliminating certain high carrier populations from testing (e.g., children under 1 yr of age) will increase the positive predictive value of laboratory testing. Culture for organism isolation is a sensitive test but is labor intensive, taking several days. Culture alone is not specific because it does not differentiate between toxin-producing and non–toxin-producing strains.

Pseudomembranous nodules and characteristic plaques may be seen on colonoscopy or sigmoidoscopy.

Treatment

Initial treatment of CDI involves discontinuation of any nonvital antibiotic therapy and administration of fluid and electrolyte replacement. For mild cases, this treatment may be curative. Persistent symptoms or moderate to severe disease warrant antimicrobial therapy directed against *C. difficile.*

Oral **metronidazole** remains the first-line therapy for mild to moderate CDI in children (Table 239.1). For more severe infection, oral **vancomycin** is approved by the U.S. Food and Drug Administration (FDA) for CDI. Vancomycin exhibits ideal pharmacologic properties for treatment of this enteric pathogen, since it is not absorbed in the gut. Vancomycin is suggested as a first-line agent for severe disease, as manifested by hypotension, peripheral leukocytosis, or severe pseudomembranous colitis. Concerns about cost and the emergence of vancomycin-resistant enterococci limit its use as first-line therapy in mild to moderate disease. **Fidaxomicin** , a second-line agent not yet approved for pediatric use, is a narrow-spectrum macrolide antibiotic with noninferior efficacy to vancomycin but superior recurrence prevention. The cost of a course of fidaxomicin can be twice that of vancomycin and 125-fold higher than metronidazole. Reports have demonstrated high treatment efficacy for donor (unaffected) fecal therapy (transplant).

Table 239.1

Recommendations for the Treatment of *Clostridium difficile* Infection in Children

CLINICAL DEFINITION	RECOMMENDED TREATMENT	PEDIATRIC DOSE	MAXIMUM DOSE	STRENGTH OF RECOMMENDATION/QUALITY OF EVIDENCE
Initial episode,	Metronidazole ×	7.5 mg/kg/dose	500 mg tid or	Weak/Low

nonsevere	10 days PO *or*	tid or qid	qid	
	Vancomycin × 10 days PO	10 mg/kg/dose qid	125 mg qid	Weak/Low
Initial episode, severe/fulminant	Vancomycin × 10 days PO or PR *with or without*	10 mg/kg/dose qid	500 mg qid	Strong/Moderate
	Metronidazole × 10 days IV[*]	10 mg/kg/dose tid	500 mg tid	Weak/Low
First recurrence, nonsevere	Metronidazole × 10 days PO *or*	7.5 mg/kg/dose tid or qid	500 mg tid or qid	Weak/Low
	Vancomycin × 10 days PO	10 mg/kg/dose qid	125 mg qid	Weak/Low
Second or subsequent recurrence	Vancomycin in a tapered and pulsed regimen [†] *or*	10 mg/kg/dose qid	125 mg qid	Weak/Low
	Vancomycin × 10 days, followed by rifaximin [‡] × 20 days *or*	Vancomycin, 10 mg/kg/dose qid; rifaximin: no pediatric dosing	Vancomycin, 500 mg qid; rifaximin, 400 mg tid	Weak/Low
	Fecal microbiota transplantation			Weak/Very low

[*] In cases of severe or fulminant *Clostridium difficile* infection associated with critical illness, consider addition of intravenous metronidazole to oral vancomycin.

[†] Tapered and pulsed regimen: vancomycin, 10 mg/kg with max of 125 mg 4 times daily for 10-14 days, then 10 mg/kg with max of 125 mg twice daily for 1 wk, then 10 mg/kg with max of 125 mg once daily for 1 wk, and then 10 mg/kg with max of 125 mg every 2 or 3 days for 2-8 wk.

[‡] No pediatric dosing for rifaximin; not approved by the U.S. Food and Drug Administration for use in children <12 yr old.

IV, Intravenously; PO, orally; PR, rectally; tid, 3 times daily; qid, 4 times daily.

Adapted from McDonald LC, Gerding DN, Johnson S, et al: Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), *Clin Infect Dis* 66(7):e1–e48, 2018 (Table 2).

Treatment of adults is different (Table 239.2). Because treatment of CDI continues to evolve, adult-based protocols may be relevant to older children and adolescents.

Table 239.2

Recommendations for the Treatment of *Clostridium difficile*

Infection in Adults

CLINICAL DEFINITION	SUPPORTIVE CLINICAL DATA	RECOMMENDED TREATMENT[*]	STRENGTH OF RECOMMENDATION/QUALITY OF EVIDENCE
Initial episode, nonsevere	Leukocytosis with white blood cell count of ≤15,000 cells/mL and serum creatinine level <1.5 mg/dL	VAN, 125 mg qid × 10 days *or*	Strong/High
		FDX, 200 mg bid × 10 days	Strong/High
		Alternate if above agents are unavailable: metronidazole, 500 mg tid PO × 10 days	Weak/High
Initial episode, severe [†]	Leukocytosis with a white blood cell count of ≥15,000 cells/mL or a serum creatinine level >1.5 mg/dL	VAN, 125 mg qid PO × 10 days *or*	Strong/High
		FDX, 200 mg bid × 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	VAN, 500 mg qid PO or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenous metronidazole (500 mg every 8 hr) should be administered with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN) Weak/Low (rectal VAN) Strong/Moderate (intravenous metronidazole)
First recurrence		VAN, 125 mg qid × 10 days, if metronidazole was used for the initial episode *or*	Weak/Low
		Use prolonged tapered and pulsed VAN regimen if standard regimen was used for initial episode (e.g., 125 mg qid for 10-14 days, bid for 1 wk, qd for 1 wk, and then every 2 or 3 days for 2-8 wk) *or*	Weak/Low
		FDX, 200 mg bid ×for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence		VAN in a tapered and pulsed regimen *or*	Weak/Low
		VAN, 125 mg qid PO × 10 days, followed by rifaximin, 400 mg tid × 20 days *or*	Weak/Low
		FDX, 200 mg bid × 10 days *or*	Weak/Low
		Fecal microbiota transplantation [‡]	Strong/Moderate

[*] All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment, and clinicians should consider extending treatment duration to 14 days in those circumstances.

[†] The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future on publication of prospectively validated severity scores for patients with CDI.

[‡] The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried before offering fecal microbiota transplantation.

FDX, Fidaxomicin; VAN, vancomycin; PO, orally (by mouth); qd, once daily; bid, twice daily; tid, 3 times daily; qid, 4 times daily.

Adapted from McDonald LC, Gerding DN, Johnson S, et al: Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), *Clin Infect Dis* 66(7):e1–e48, 2018 (Table 1).

Prognosis

The response rate to initial treatment of CDI is >95%; however, both the treatment failure rate and the recurrence rate have increased since the late 1990s. Additionally, the risk of subsequent reappearance increases with each recurrence.

Initial recurrence rates are 5–20%, are diagnosed clinically, and generally occur within 4 wk of treatment. Some recurrences result from incomplete eradication of the original strain, and others are caused by reinfection with a different strain. Treatment for the initial recurrence involves retreatment with the original antibiotic course.

Recurrences of CDI may be caused by a suboptimal immune response, failure to kill organisms that have sporulated, or failure of delivery of antibiotic to the site of infection, in the case of ileus or toxic megacolon. Subsequent treatment with pulsed or tapered vancomycin decreases recurrence rates. In addition to this approach, other antibiotics (rifaximin or nitazoxanide), toxin-binding polymers (Tolevamer), and probiotics (*Saccharomyces boulardii* or *Lactobacillus* GG) have been used as adjunctive therapy. Although not well studied in children, *S. boulardii* significantly decreases recurrence rates when used as an adjunct to vancomycin therapy in adults. Because failure to manifest an adequate antitoxin immune response is associated with a higher frequency of recurrent CDI, intravenous immune globulin has been used to treat recurrent disease. In the case of ileus or toxic megacolon, an enema of vancomycin may be used to place the antibiotic directly at the site of infection, although most often intravenous therapy is first attempted in this circumstance.

Fecal microbiota transplantation (FMT) has been used to address the disruption in normal gut flora thought to allow colonization with *C. difficile* (see

Table 239.2). FMT involves the instillation of fecal material from a healthy donor into the patient's GI tract by nasoenteric tube, enema, capsules, or colonoscopy. Published FMT results in children with recurrent CDI are limited to case reports and small case series. There are few data to guide clinicians on the indications, route, efficacy, and safety of FMT in children, but investigation is ongoing. Initial reports indicate an overall success rate of approximately 90% in patients with recurrent CDI. Current approaches to FMT are not specific and involve complete reconstitution of the gut microbiome. The gut microbiota has been shown to influence susceptibility to genetic and environmentally acquired conditions. Transplantation of healthy donor fecal material to patients with CDI may reestablish the “normal” composition of the gut microbiota but has the theoretical concern of adding new, microbiome-based susceptibilities derived from the donor microbiome.

It is important to recognize that postinfectious diarrhea may result from other causes, such as postinfectious irritable bowel syndrome, microscopic colitis, and IBD. A test-of-cure is not recommended in the asymptomatic patient, and a positive test for recurrence is not useful until at least 4 wk after the initial test.

Prevention

Currently, the strategies for prevention of CDI include recognition of common sites of acquisition (hospitals, childcare settings, extended-care facilities); effective environmental cleaning (i.e., use of chlorinated cleaning solutions); appropriate antibiotic and PPI prescription practices; cohorting of infected patients; **contact precautions** ; and proper handwashing with soap and water. Moderate evidence shows that probiotics may reduce the incidence of *C. difficile* –associated diarrhea.

Lastly, with the increasing incidence, morbidity, mortality, and rising healthcare costs from CDI, **immunization** to prevent the disease itself could become an effective paradigm. Although a strong immune response against toxins A and B may prevent the development of CDI, it does not prevent colonization of the host by the bacterium. Therefore, surface proteins involved in adherence have been studied as potential vaccine candidates in animals. Vaccines targeting nontoxin antigens will likely be needed to prevent colonization, reduce spore production, and interrupt disease transmission, especially in high-risk populations.

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CHAPTER 240

Other Anaerobic Infections

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Anaerobic bacteria are among the most numerous organisms colonizing humans. Anaerobes are present in soil and are normal inhabitants of all living animals, but infections caused by anaerobes are relatively uncommon. **Obligate anaerobes** are markedly or entirely intolerant of exposure to oxygen. **Facultative anaerobes** can survive in the presence of environmental oxygen but grow better in settings of reduced oxygen tension. This chapter concentrates on conditions associated with obligate anaerobic bacterial infection.

Infections with anaerobes frequently occur adjacent to mucosal surfaces, often as **mixed infections** with aerobes. Conditions of reduced oxygen tension provide the optimal conditions for proliferation of anaerobes. Traumatized areas, devascularized areas, and areas of crush injury are all ideal sites for anaerobic infection. Frequently, both aerobic and anaerobic organisms invade devitalized areas, with local extension and bacteremia most often caused by the more virulent aerobes. Abscess formation evolves over days to weeks and generally involves both aerobes and anaerobes. Examples of such infections include appendicitis and periappendiceal, pelvic, perirectal, peritonsillar, retropharyngeal, parapharyngeal, pulmonary, and dental abscesses. **Septic thrombophlebitis** , as a consequence of appendicitis, chronic sinusitis, pharyngitis, and otitis media, provides a route for hematogenous spread of anaerobic infection to parenchymal organs such as the liver, brain, and lungs.

Anaerobic infection is usually caused by endogenous flora. Combinations of impaired physical barriers to infection, compromised tissue viability, ecologic alterations in normal flora, impaired host immunity, and anaerobic bacterial virulence factors contribute to infection with normal anaerobic inhabitants of mucous membranes. Bacterial virulence factors include capsules, toxins, enzymes, and fatty acids.

Clinical Manifestations

Anaerobic infections occur in a variety of sites throughout the body (Table 240.1). Anaerobes often coexist synergistically with aerobes. Infections with anaerobes are usually polymicrobial, including an aerobic component.

Table 240.1

Infections Associated With Anaerobic Bacteria

SITE AND INFECTION	MAJOR RISK FACTORS	ANAEROBIC BACTERIA*
CENTRAL NERVOUS SYSTEM		
Cerebral abscess	Cyanotic heart disease Cystic fibrosis Penetrating trauma	Polymicrobial *Prevotella* *Porphyromonas* *Bacteroides* *Fusobacterium* *Peptostreptococcus*
Epidural and subdural empyemas, meningitis	Direct extension from contiguous sinusitis, otitis media, mastoiditis, or anatomic defect involving the dura	*Bacteroides fragilis* † *Fusobacterium* *Peptostreptococcus* *Veillonella*
UPPER RESPIRATORY TRACT		
Dental abscess	Poor periodontal hygiene	*Peptostreptococcus*
Ludwig angina (cellulitis of sublingual-submandibular space)	Drugs producing gingival hypertrophy	*Fusobacterium*
Necrotizing gingivitis (Vincent stomatitis)		*Prevotella melaninogenica* *Fusobacterium*
Chronic otitis-mastoiditis-sinusitis	Tympanic perforation Tympanostomy tubes	*Prevotella* *Bacteroides* *Fusobacterium* *Peptostreptococcus*
Peritonsillar abscess Retropharyngeal abscess	Streptococcal pharyngitis Penetrating injury	*Fusobacterium* *Prevotella* *Porphyromonas*
Lemierre syndrome	Preexisting viral or bacterial pharyngitis	*Fusobacterium*
LOWER RESPIRATORY TRACT		
Aspiration pneumonia	Periodontal disease	Polymicrobial *Prevotella* *Porphyromonas* *Fusobacterium* *Peptostreptococcus*
Necrotizing pneumonitis	Bronchial obstruction	*P. melaninogenica*
Lung abscess	Altered gag or consciousness Aspirated foreign body Sequestered lobe Vascular anomaly	*Bacteroides intermedius* *Fusobacterium* *Peptostreptococcus* *Eubacterium*

		B. fragilis *Veillonella*
Septic pulmonary emboli		*Fusobacterium*
INTRAABDOMINAL		
Abscess	Appendicitis	Polymicrobial *B. fragilis* *Bilophila wadsworthia* *Peptostreptococcus* *Clostridium* spp.
Secondary peritonitis	Penetrating trauma (especially of the colon)	*Bacteroides* *Clostridium* *Peptostreptococcus* *Eubacterium* *Fusobacterium*
FEMALE GENITAL TRACT		
Bartholin abscess	Vaginosis	*B. fragilis*
Tuboovarian abscess	Intrauterine device	*Bacteroides bivius*
Endometritis		*Peptostreptococcus*
Pelvic thrombophlebitis		*Clostridium*
Salpingitis		*Mobiluncus*
Chorioamnionitis		*Actinomyces*
Septic abortion		*Clostridium*
SKIN AND SOFT TISSUE		
Cellulitis	Decubitus ulcers	Varies with site and contamination with oral or enteric flora
Perirectal cellulitis	Abdominal wounds	*Clostridium perfringens* (myonecrosis)
Myonecrosis (gas gangrene)	Pilonidal sinus	*Bacteroides* *Clostridium*
Necrotizing fasciitis and synergistic gangrene	Trauma Human and animal bites Immunosuppressed or neutropenic patients Varicella	*Fusobacterium* *Clostridium tertium* *Clostridium septicum* Anaerobic streptococci
BLOOD		
Bacteremia	Intraabdominal infection, abscesses, myonecrosis, necrotizing fasciitis	*B. fragilis* *Clostridium* *Peptostreptococcus* *Fusobacterium*

[*] Infections may also be from or may involve aerobic bacteria as the sole agent or as part of a mixed infection; brain abscess may contain microaerophilic streptococci; intraabdominal infections may contain gram-negative enteric organisms and enterococci; and salpingitis may contain *Neisseria gonorrhoeae* and *Chlamydia trachomatis* .

[†] *Bacteroides fragilis* is usually isolated from infections below the diaphragm except for brain abscesses.

Bacteremia

Anaerobes account for approximately 5% of bloodstream bacterial isolates in adults, but this rate is lower in children. The most common blood isolates of anaerobic bacteria in children are *Bacteroides fragilis* group, *Peptostreptococcus*, *Clostridium,* and *Fusobacterium* spp.

Isolation of anaerobes from the blood is often an indication of a serious primary anaerobic infection. The lower gastrointestinal (GI) tract and wound infections are the 2 most common sources for bacteremia. Risk factors for anaerobic bacteremia include malignancy, hematologic disorders, solid-organ transplant, recent surgery (GI, obstetric, gynecologic), intestinal obstruction, decubiti, dental extraction, early infancy, sickle cell disease, diabetes mellitus, splenectomy, and chemotherapy or other immunosuppressive drug use.

As with certain aerobes, the cell wall of gram-negative anaerobes may contain **endotoxins** , which can be associated with the development of hypotension and shock when present in the circulatory system. Clostridia produce **hemolysins** , and the presence of these organisms in the blood can result in massive hemolysis and cardiovascular collapse.

Central Nervous System

Anaerobic **meningitis** is rare but can occur in neonates as a complication of ear or neck infections or from anatomic defects of meninges (dural sinus tracts). Anaerobic cerebrospinal fluid (CSF) shunt infections may occur when the distal end of the ventriculoperitoneal shunt perforates the intestinal tract.

Brain abscess and subdural empyema are usually polymicrobial, with anaerobes typically involved (see Chapter 622). Brain abscess usually occurs because of spread from infected sinuses, middle ear, or lung and rarely from endocarditis. *Clostridium perfringens* can cause brain abscess and meningitis after head injuries or after intracranial surgery. Brain abscesses may require surgical drainage combined with a prolonged course of antibiotic therapy.

Upper Respiratory Tract

The respiratory tract is colonized by both aerobes and anaerobes. Anaerobic bacteria are involved in chronic sinusitis, chronic otitis media, peritonsillar infections, parapharyngeal and retropharyngeal abscesses, and periodontal infections. The predominant organisms involved are *Prevotella, Porphyromonas, Bacteroides, Fusobacterium,* and *Peptostreptococcus* spp.

Anaerobic periodontal disease is most common in patients with poor dental hygiene or who are receiving drugs that induce gingival hypertrophy. **Vincent**

angina, also known as **acute necrotizing ulcerative gingivitis** or **trench mouth,** is an acute, fulminating, mixed anaerobic bacterial-spirochetal infection of the gingival margin and floor of the mouth. It is characterized by gingival pain, foul breath, and pseudomembrane formation. **Ludwig angina** is an acute, life-threatening cellulitis of dental origin of the sublingual and submandibular spaces. Infection spreads rapidly in the neck and may cause sudden airway obstruction.

Lemierre syndrome, or **postanginal sepsis,** is a suppurative infection of the lateral pharyngeal space, of increasing prevalence, that often begins as pharyngitis (see Chapter 409). It may complicate Epstein-Barr virus or other viral and bacterial infections of the pharynx. It usually manifests as a unilateral septic thrombophlebitis of the jugular venous system with septic pulmonary embolization. Patients present with prolonged pharyngitis, neck pain and fever. Clinical signs include unilateral painful cervical swelling, trismus, and dysphagia, culminating with signs of sepsis and respiratory distress. *Fusobacterium necrophorum* is the most commonly isolated organism, although polymicrobial infection may occur. Metastatic infections involving muscles, bones, internal organs (often lungs), and the brain can occur as a complication of Lemierre syndrome.

Lower Respiratory Tract

Anaerobic lung abscess, empyema, and anaerobic pneumonia are most often encountered in children who have disordered swallowing or seizures or in whom an inhaled foreign body is occluding a bronchus. Infections are usually polymicrobial. Children and adults can aspirate oral or gastric contents during sleep, seizure, or periods of unconsciousness. In most cases, lung cilia and phagocytes clear particulate matter and microbes. If the aspiration is of increased volume or frequency or a foreign body blocks normal ciliary clearance, normal pulmonary clearance mechanisms are overcome and infection ensues. Appropriate cultures need to avoid specimen contamination with oral flora through use of bronchoalveolar lavage, lung biopsy, or thoracentesis.

In unusual cases, particularly in patients with poor dental hygiene, aspirated mouth contents may contain the anaerobe *Actinomyces israelii* , resulting in pulmonary actinomycosis (see Chapter 216). Anaerobic pneumonitis associated with this microorganism is remarkable for the ability of the infection to traverse tissue planes. Affected patients often develop fistulas on their chest walls overlying areas of intrathoracic infection. These may extrude distinctive, pathognomonic particles composed of bacterial colonies, called “sulfur granules.”

Intraabdominal Infection

The entire digestive tract is heavily colonized with anaerobes. The density of organisms is highest in the colon, where anaerobes outnumber aerobes 1,000 : 1. Perforation of the gut leads to leakage of intestinal flora into the peritoneum, resulting in peritonitis involving both aerobes and anaerobes. Secondary sepsis caused by aerobes often occurs early. As the peritoneal infection is walled off, an abscess containing both aerobes and anaerobes often evolves. The predominant aerobic organisms are *Escherichia coli* and *Streptococcus* spp. (including *Enterococcus* spp.), and the anaerobes are the *B. fragilis* group, *Peptostreptococcus* , *Clostridium,* and *Fusobacterium* spp.

Secondary hepatic abscesses may then develop as complications of appendicitis, intestinal perforation, inflammatory bowel disease, or biliary tract disease. In children with malignancy receiving chemotherapy, the intestinal mucosa is often damaged, leading to translocation of bacteria and focal invasion of bowel wall. **Typhlitis** is a mixed infection of the gut wall in neutropenic patients, usually located in the ileocecum and characterized by abdominal pain, diarrhea, fever, and abdominal distention. Similarly, a mixed aerobic-anaerobic infection of the intestinal wall and peritoneum may develop in a small infant as a complication of **necrotizing enterocolitis** , believed to be a result of the relative vascular insufficiency of the gut and hypoxia (see Chapter 123.2).

Genital Tract

Pelvic inflammatory disease and tuboovarian abscesses are frequently caused by mixed aerobic-anaerobic infection. Vaginitis can be caused by overgrowth of anaerobic flora. Anaerobes frequently contribute to chorioamnionitis and premature labor and may result in anaerobic bacteremia of the newborn. Although these bacteremias are often transient, anaerobes occasionally cause invasive disease in the newborn, including central nervous system (CNS) infection.

Skin and Soft Tissue

Anaerobic skin infections occur in the setting of bites, foreign bodies, and skin and tissue ulceration because of pressure necrosis or lack of adequate blood supply. Animal bites and human bites inoculate oral and skin flora into damaged and hypoxic cutaneous tissue. The extent of the infection depends on the depth of the bite and the associated crush injury to the tissues. In immunocompromised patients, unusual oral anaerobes such as *Capnocytophaga canimorsus* can cause life-threatening infection.

Clostridial myonecrosis, or **gas gangrene,** is a rapidly progressive infection of deep soft tissues, primarily muscles, associated with *Clostridium perfringens.* **Necrotizing fasciitis** is a more superficial, polymicrobial infection of the subcutaneous space with acute onset and rapid progression that has significant morbidity and mortality (see Chapter 685.2). Group A streptococcus, known in the lay press as the "flesh-eating bacteria," and *Staphylococcus aureus* are occasionally the causative pathogens. Typically, necrotizing fasciitis is produced by combined infection of *S. aureus* or gram-negative bacilli and anaerobic streptococci, termed **synergistic gangrene** . This infection is often seen as a complication of varicella following secondary infection of a cutaneous vesicle. Diabetic patients may develop a particularly aggressive and destructive synergistic gangrene of the inguinal area and adjacent scrotum or vulva known as **Fournier gangrene** . Early recognition with aggressive surgical debridement and antimicrobial therapy is necessary to limit disfiguring morbidity and mortality.

Other Sites

Occasionally, the bone adjacent to an anaerobic infection becomes infected by direct extension from a contiguous infection in cranial and facial bones or by direct inoculation associated with trauma to tubular bones. Anaerobic septic arthritis is rare, and risk factors include trauma and prosthetic joints. Most infections are monomicrobial, and the organism isolated is related to the route of infection. *Peptostreptococcus* and *P. acnes* are isolated in prosthetic joint infections, *B. fragilis* and fusobacteria in hematogenous infections, and clostridia following trauma.

Anaerobic infections of the kidneys (renal and perirenal abscesses) and heart (pericarditis) are rare. **Enteritis necroticans** ("pigbel") is a rare but often fatal GI infection that can follow ingestion of a large meal in a chronically starved child or adult. It is associated with the consumption of pork and is believed to be caused by *Clostridium welchii* type C (an organism not usually present in the human intestine), the organism being transmitted by contaminated pig meat. Anaerobic **osteomyelitis** , particularly of fingers and toes, can complicate any process capable of producing hypoxic necrosis, including diabetes, neuropathies, vasculopathies, and coagulopathies.

Diagnosis

The diagnosis of anaerobic infection requires a high index of suspicion and the collection of appropriate and adequate specimens for anaerobic culture (Table 240.2). Culture specimens should be obtained in a manner that protects them from contamination with mucosal bacteria and from exposure to ambient oxygen. Swab samples from mucosal surfaces, nasal secretions, respiratory specimens, and stool should *not* be sent for anaerobic culture because these sites normally harbor anaerobic flora. Aspirates of infected sites, abscess material, and biopsy specimens are appropriate for anaerobic culturing. Specimens should be protected from atmospheric oxygen and transported to the laboratory immediately. Anaerobic transport medium is used to increase the likelihood of recovery of obligate anaerobes. Gram staining of abscess fluid from suspected anaerobic infections is useful because even if the organisms do not grow in culture, they can be seen on the smear.

Table 240.2

Clues to Presumptive Diagnosis of Anaerobic Infections*

Infection contiguous to or near a mucosal surface colonized with anaerobic bacteria (oropharynx, intestinal-genitourinary tract)
Putrid odor
Severe tissue necrosis, abscesses, gangrene, or fasciitis
Gas formation in tissues (crepitus on exam or visible on plain radiograph)
Failure to recover organisms using conventional aerobic microbiologic methods, despite the presence of mixed pleomorphic organisms on smears
Failure of organisms to grow after pretreatment with antibiotics effective against anaerobes
Failure of clinical response to antibiotic therapy poorly effective against anaerobic bacteria (e.g., aminoglycosides)
“Sulfur granules” in discharges caused by actinomycosis
Toxin-mediated syndromes: botulism, tetanus, gas gangrene, food poisoning, pseudomembranous colitis
Infections associated with anaerobic bacteria (see Table 240.1)
Septic thrombophlebitis
Septicemic syndrome with jaundice or intravascular hemolysis
Typical appearance on Gram stain:
Bacteroides spp.—small, delicate, pleomorphic, pale, gram-negative bacilli

Fusobacterium nucleatum —thin, gram-negative bacilli with fusiform shape, pointed ends
Fusobacterium necrophorum —pleomorphic gram-negative bacilli with rounded ends
Peptostreptococcus —chained, gram-positive cocci similar to aerobic cocci
Clostridium perfringens —large, short, fat (boxcar-shaped) gram-positive bacilli

[*] Suspicion of anaerobic infection is critical before specimens are sampled for culture, to ensure optimal microbiologic techniques and prompt, appropriate therapy.

Antimicrobial resistance among anaerobes has consistently increased over time, and the susceptibility of anaerobic agents to antimicrobial agents has become less predictable. A rapid and simple screening test for antibiotic susceptibility can be used to detect β-lactamase production and presumptive penicillin resistance. More detailed susceptibility testing, available at reference laboratories, is recommended for isolates recovered from sterile body sites or those that are clinically important and are known to have variable or unique susceptibilities.

Recent advances in direct detection of anaerobes from clinical samples include 16S ribosomal RNA (16S rRNA) gene-based methods, DNA hybridization, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), multiplex PCR, and oligonucleotide array technologies. MALDI-TOF MS has been used as a rapid method to identify infectious agents, including many anaerobes. 16S rRNA gene sequencing can be used for isolates whose identification by MS is unreliable.

Treatment

Treatment of anaerobic infections usually requires adequate drainage and appropriate antimicrobial therapy. Antibiotic therapy varies depending on the suspected or proven anaerobe involved. Many oral anaerobic bacterial species are susceptible to penicillins, although some strains may produce a β-lactamase. Drugs that are active against such strains include metronidazole, penicillins combined with β-lactamase inhibitors (ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam), carbapenems (imipenem, meropenem, doripenem, ertapenem), clindamycin, tigecycline, linezolid, and cefoxitin. Penicillin and vancomycin are active against the gram-positive anaerobes.

Increasing resistance to antimicrobials has been noted among anaerobes, particularly with *Bacteroides* spp. Clindamycin is no longer recommended in the empirical treatment of abdominal infections due to increasing resistance among *Bacteroides.* Aerobes are usually present with the anaerobes, necessitating broad-spectrum antibiotic combinations for empirical therapy. Specific therapy is based on culture results and clinical course.

For **soft tissue infections** , providing adequate perfusion to the area is critical. At times, a muscle flap or skin flap procedure is needed to ensure that nutrients and antimicrobial agents are brought to the affected area and adequate oxygen tension is maintained. Drainage of infected areas is often necessary for cure. Bacteria may survive in abscesses because of high bacterial inoculum, lack of bactericidal activity, and local conditions that facilitate bacterial proliferation. Aspiration is sometimes effective for small collections, whereas incision and drainage may be required for larger abscesses. Extensive debridement and resection of all devitalized tissue are needed to control fasciitis and myonecrosis. Adjunctive **hyperbaric oxygen** (HBO) therapy has been found to be beneficial in a few uncontrolled studies. However, it should be recognized that surgical treatment is critical and should never be delayed for the provision of HBO therapy.

Uncomplicated infections caused by anaerobic organisms are generally treated for 2-4 wk. Some infections, including osteomyelitis and brain abscess, may need longer treatment of 6-8 wk.

Common Anaerobic Pathogens

Clostridium

Strains of *Clostridium* cause disease by proliferation and often by production of toxins. Of the >60 species that have been identified, only a few cause infections in humans. The most frequently implicated *Clostridium* spp. are *C. difficile* (Chapter 239), *C. perfringens* , *C. botulinum* (Chapter 237), *C. tetani* (Chapter 238), *C. butyricum, C. septicum, C. sordellii, C. tertium,* and *C. histolyticum.*

Clostridia can cause unique histotoxic syndromes produced by specific toxins (e.g., gas gangrene, food poisoning) as well as nonsyndromic infections (e.g., abscess, local infections, sepsis).Based on the clinical syndrome produced, clostridial species are categorized into 3 groups: **histotoxic** (*C. perfringens* , *C. ramosum* , *C. novyi* , *C. septicum* , *C. bifermentans* , and *C. sordellii*), **enterotoxigenic** (*C. perfringens* and *C. difficile*), and **neurotoxic** (*C. tetani* and *C. botulinum*).

C. perfringens produces a variety of toxins and virulence factors. Strains of *C. perfringens* are designated A through E. **Alpha toxin** is a phospholipase that hydrolyzes sphingomyelin and lecithin and is produced by all strains. This toxin causes hemolysis, platelet lysis, increased capillary permeability, and hepatotoxicity. **Beta toxin** , produced by strains B and C, causes hemorrhagic necrosis of the small bowel. **Epsilon toxin** is produced by B and D strains and injures vascular endothelial cells, leading to increased vascular permeability, edema, and organ dysfunction. **Iota toxin,** produced by E strains, causes dermal edema. An enterotoxin is produced by type A and some type C and D strains. Hemolysins and a variety of enzymes are produced by many *C. perfringens* strains.

Clostridia can be involved in various other polymicrobial pediatric infections: arthritis, osteomyelitis, skin and soft tissue infections (often after trauma or foreign body penetration), intraabdominal, pulmonary, intracranial, and pelvic infections; abscesses; and panophthalmitis.

Clostridial species invade the bloodstream shortly before, during, or just after death, leading to contamination of tissues that may be donated for transplantation. A large outbreak of *Clostridium* infections in tissue graft recipients was reported in 14 patients who received musculoskeletal grafts processed at a single tissue bank. Because of this outbreak, recommendations for tissue processing now include a processing method that kills bacterial spores.

Myonecrosis (Gas Gangrene)

Clostridium perfringens is the major etiologic cause of myonecrosis, a rapidly progressive anaerobic soft tissue infection. Gas gangrene usually affects muscles compromised by surgery, trauma, or vascular insufficiency that become contaminated with *C. perfringens* spores, usually from foreign material or a medical device. Wounds can be contaminated by *C. perfringens* spores from the skin, dirt, soil, and clothing, especially wounds in the lower trunk.

In immunocompromised persons, especially patients receiving cancer chemotherapy, *C. septicum* is a classic cause of rapidly fatal gas gangrene. A clue to the diagnosis of gas gangrene is pain out of proportion to the clinical appearance of the wound. Infection progresses rapidly with edema, swelling, myonecrosis, and sometimes crepitation of soft tissues. Hypotension, mental confusion, shock, and renal failure are common. A characteristic sweet odor is present in the serosanguineous discharge. The exudate reveals gram-positive bacilli but few leukocytes. Early and complete debridement with excision of necrotic tissue is key to controlling the infection. Repeated, frequent assessment of tissue viability in the operating room is required. High-dose penicillin (250,000 units/kg/day divided every 4-6 hr [q4-6h] intravenously [IV]) or clindamycin (25-40 mg/kg/day divided q6-8h IV) can be employed in pure clostridial infections. If, as is often the case, a mixed bacterial infection is suspected, broader antibiotic coverage is warranted, with an agent such as piperacillin-tazobactam (300 mg/kg/day divided q6hr IV) or meropenem (60 mg/kg/day divided q8h IV). Addition of clindamycin or vancomycin is warranted if staphylococcal or streptococcal co-infection is suspected.

Aggressive supportive care is essential, and amputation of affected limbs is often required. HBO therapy can reduce tissue loss and thus the extent of debridement and has been beneficial in a few studies. However, HBO should only be used as an adjunct to surgical treatment, which is primary.

The prognosis for patients with myonecrosis is poor, even with early, aggressive therapy.

Food Poisoning

Clostridium perfringens type A produces an enterotoxin that causes food poisoning. This intoxication results in the acute onset of watery diarrhea and crampy abdominal pain. The usual foods containing toxin are improperly prepared or stored meats and gravies. A specific etiologic diagnosis is rarely made in children with food poisoning. Therapy consists of rehydration and electrolyte replacement if necessary. The illness resolves spontaneously within 24 hr of onset. Prevention requires the maintenance of hot food at a temperature ≥74°C (165.2°F).

Bacteroides and *Prevotella*

Bacteroides fragilis is one of the more virulent anaerobic pathogens and is most frequently recovered from blood cultures and cultures of tissue or pus. The most common *B. fragilis* infection in children occurs as a complication of **appendicitis** . The organism is part of normal colonic flora but is not common in the mouth or respiratory tract. *B. fragilis* is usually found as part of polymicrobial appendiceal and other intraabdominal abscesses and is often involved in genital tract infections such as pelvic inflammatory disease and tuboovarian abscess. *Prevotella* organisms are normal oral flora, and *Prevotella* infection typically involves gums, teeth, tonsils, and parapharyngeal spaces. Both *B. fragilis* and *Prevotella* may be involved in aspiration pneumonitis and lung abscess.

Strains of *B. fragilis* and *Prevotella melaninogenica* produce β-lactamase and are resistant to penicillins. Recommended treatment is with ticarcillin-clavulanate, piperacillin-tazobactam, cefoxitin, metronidazole, clindamycin, imipenem, or meropenem. Increasing rates of antimicrobial resistance has been seen in *Bacteroides* spp. over the last few decades. *B. fragilis* resistance to clindamycin is increasing worldwide and has reached 40% in some locales. Therefore, clindamycin is no longer recommended as empirical therapy for intraabdominal infections.

Because infections involving *B. fragilis* and *P. melaninogenica* are usually polymicrobial, therapy should include antimicrobial agents active against likely concomitant aerobic pathogens. Drainage of abscesses and debridement of necrotic tissue are often required for control of these infections.

Fusobacterium

Fusobacterium organisms inhabit the intestine, respiratory tract, and female genital tracts. These organisms, which are more virulent than most of the normal anaerobic flora, cause bacteremia and a variety of rapidly progressive infections. **Lemierre syndrome** , bone and joint infections, and abdominal and genital tract infections are most common. Some strains produce a β-lactamase and are resistant to penicillins, requiring therapy with drugs such as ampicillin-sulbactam and clindamycin.

Veillonella

Veillonella spp. are normal flora of the mouth, upper respiratory tract, intestine, and vagina. These anaerobes rarely cause infection. Strains are recovered as part of the polymicrobial flora causing abscess, chronic sinusitis, empyema, peritonitis, and wound infection. *Veillonella* spp. are susceptible to penicillins, cephalosporins, clindamycin, metronidazole, and carbapenems.

Anaerobic Cocci

Peptostreptococcus spp. are normal flora of the skin, respiratory tract, and gut. These organisms are often present in brain abscesses, chronic sinusitis, chronic otitis, and lung abscesses. Such infections are often polymicrobial, and therapy is aimed at the accompanying aerobes as well as the anaerobes. Most of the gram-positive cocci are susceptible to penicillin, cephalosporins, carbapenems, and vancomycin.

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SECTION 7

Mycobacterial Infections

OUTLINE

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CHAPTER 241

Principles of Antimycobacterial Therapy

Stacene R. Maroushek

The treatment of mycobacterial infection and disease can be challenging. Patients require therapy with multiple agents, the offending pathogens commonly exhibit complex drug resistance patterns, and patients often have underlying conditions that affect drug choice and monitoring. Several of the drugs have not been well studied in children, and current recommendations are extrapolated from the experience in adults.

Single-drug therapy of *Mycobacterium tuberculosis* and nontuberculous mycobacteria is not recommended because of the high likelihood of developing antimicrobial resistance. Susceptibility testing of mycobacterial isolates often can aid in therapeutic decision-making.

Agents Used Against *Mycobacterium Tuberculosis*

Commonly Used Agents

Isoniazid

Isoniazid (**INH**) is a hydrazide form of isonicotinic acid and is bactericidal for rapidly growing *M. tuberculosis.* The primary target of INH involves the *INHA* gene, which encodes the enoyl ACP (acyl carrier protein) reductase needed for the last step of the mycolic acid biosynthesis pathway of cell wall production. Resistance to INH occurs following mutations in the *INHA* gene or in other genes encoding enzymes that activate INH, such as *katG* .

INH is indicated for the treatment of *M. tuberculosis*, *M. kansasii*, and *M.*

bovis. The pediatric dosage is 10-15 mg/kg/day orally (PO) in a single dose, not to exceed 300 mg/day. The adult dosage is 5 mg/kg/day PO in a single dose, not to exceed 300 mg/day. Alternative pediatric dosing is 20-30 mg/kg PO in a single dose, not to exceed 900 mg/dose, given twice weekly under **directly observed therapy (DOT)** , in which patients are observed to ingest each dose of antituberculosis medication to maximize the likelihood of completing therapy. The duration of treatment depends on the disease being treated (Table 241.1). INH needs to be taken 1 hr before or 2 hr after meals because food decreases absorption. It is available in liquid, tablet, intravenous (IV; not approved by the FDA), and intramuscular (IM) preparations.

Table 241.1

Recommended Usual Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents

INFECTION/DISEASE CATEGORY	REGIMEN	COMMENTS
LATENT *MYCOBACTERIUM TUBERCULOSIS* INFECTION [a]		
Isoniazid susceptible	12 weeks of isoniazid plus rifapentine, once a week *or*	
	4 mo of rifampin, once a day *or*	Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.
	9 mo of isoniazid, once a day	If daily therapy is not possible, DOT twice a week can be used for 9 mo.
Isoniazid resistant	4 mo of rifampin, once a day	Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.
Isoniazid-rifampin resistant	Consult a tuberculosis specialist.	Moxifloxacin or levofloxacin with or without ethambutol or pyrazinamide.
PULMONARY AND EXTRAPULMONARY INFECTION		
Except meningitis [b]	2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily or twice weekly, followed by 4 mo of isoniazid and rifampin [c] by DOT [d] for drug-susceptible *M. tuberculosis*	Some experts recommend a 3-drug initial regimen (isoniazid, rifampin, and pyrazinamide) if the risk of drug resistance is low. DOT is highly desirable. If hilar adenopathy only and the risk of drug resistance is low, 6 mo course of isoniazid and rifampin is sufficient. Drugs can be given 2 or 3 times/wk under DOT.
	9-12 mo of isoniazid and rifampin for drug-susceptible *Mycobacterium bovis*	

Meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside [e] or ethionamide, once daily, followed by 7-10 mo of isoniazid and rifampin, once daily or twice weekly (9-12 mo total) for drug-susceptible *M. tuberculosis* At least 12 mo of therapy without pyrazinamide for drug-susceptible *M. bovis*	For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin.

[a] Positive TST or IGRA result, no disease. See text for comments and additional acceptable/alternative regimens.

[b] Duration of therapy may be longer for human immunodeficiency virus (HIV)-infected people, and additional drugs and dosing intervals may be indicated

[c] Medications should be administered daily for the 1st 2 wk to 2 mo of treatment and then can be administered 2-3 times/wk by DOT. (Twice-weekly therapy is not recommended for HIV-infected people.)

[d] If initial chest radiograph shows pulmonary cavities, and sputum culture after 2 mo of therapy remains positive, the continuation phase is extended to 7 mo, for a total treatment duration of 9 mo.

[e] Streptomycin, kanamycin, amikacin, or capreomycin.

DOT, Directly observed therapy; IGRA, interferon-γ release assay; TST, tuberculin skin test.

Adapted from American Academy of Pediatrics: *Red book: 2018–2021 report of the Committee on Infectious Diseases,* ed 31, Elk Grove Village, IL, 2018, AAP (Table 3.85).

Major **adverse effects** include hepatotoxicity in 1% of children and approximately 3% of adults (increasing with age) and dose-related peripheral neuropathy. Pyridoxine can prevent the peripheral neuropathy and is indicated for breastfeeding infants and their mothers, children and youth on milk- or meat-deficient diets, pregnant adolescents, and symptomatic HIV-infected children. Minor adverse events include rash, worsening of acne, epigastric pain with occasional nausea and vomiting, decreased vitamin D levels, and dizziness. The liquid formulation of INH contains sorbitol, which often causes diarrhea and stomach upset.

INH is accompanied by significant drug-drug interactions (Table 241.2). The metabolism of INH is by acetylation. Acetylation rates have minimal effect on efficacy, but **slow acetylators** have an increased risk for hepatotoxicity, especially when used in combination with rifampin. Routine baseline liver function testing or monthly monitoring is only indicated for persons with underlying hepatic disease or receiving concomitant hepatotoxic drugs, including other antimycobacterial agents, acetaminophen, or alcohol. Monthly clinic visits while taking INH alone are encouraged to monitor adherence, adverse effects, and worsening of infection.

Table 241.2

Isoniazid Drug-Drug Interactions

DRUG USED WITH ISONIAZID	EFFECTS
Acetaminophen, alcohol, rifampin	Increased hepatotoxicity of isoniazid or listed drugs
Aluminum salts (antacids)	Decreased absorption of isoniazid
Carbamazepine, phenytoin, theophylline, diazepam, warfarin	Increased level, effect, or toxicity of listed drugs due to decreased metabolism
Itraconazole, ketoconazole, oral hypoglycemic agents	Decreased level or effect of listed drugs due to increased metabolism
Cycloserine, ethionamide	Increased central nervous system adverse effects of cycloserine and ethionamide
Prednisolone	Increased isoniazid metabolism

Rifamycins

The rifamycins (rifampin, rifabutin, rifapentine) are a class of macrolide antibiotics developed from *Streptomyces mediterranei.* Rifampin is a synthetic derivative of rifamycin B, and rifabutin is a derivative of rifamycin S. Rifapentine is a cyclopentyl derivative. The rifamycins inhibit the DNA-dependent RNA polymerase of mycobacteria, resulting in decreased RNA synthesis. These agents are generally bactericidal at treatment doses, but they may be bacteriostatic at lower doses. Resistance is from a mutation in the DNA-dependent RNA polymerase gene (*rpoB*) that is often induced by previous incomplete therapy. Cross-resistance between rifampin and rifabutin has been demonstrated.

Rifampin is active against *M. tuberculosis, M. leprae, M. kansasii,* and *M. avium* complex. Rifampin is an integral drug in standard combination treatment of active *M. tuberculosis* disease and can be used as an alternative to INH in the treatment of latent tuberculosis infection in children who cannot tolerate INH. **Rifabutin** has a similar spectrum, with increased activity against *M. avium* complex. **Rifapentine** is undergoing pediatric clinical trials and appears to have activity similar to the activity of rifampin. The pediatric dosage of rifampin is 10-15 mg/ kg/day PO in a single dose, not to exceed 600 mg/day. The adult dosage of rifampin is 5-10 mg/kg/day PO in a single dose, not to exceed 600 mg/day. Commonly used rifampin preparations include 150 and 300 mg capsules and a suspension that is usually formulated at a concentration of 10 mg/mL. The shelf life of rifampin suspension is short (approximately 4 wk), so it should not be compounded with other antimycobacterial agents. An IV form of rifampin is also available for initial treatment of patients who cannot take oral preparations. Dosage adjustment is needed for patients with liver failure. Other rifamycins (rifabutin and rifapentine) have been poorly studied in children and are not recommended for pediatric use.

Rifampin can be associated with **adverse effects** such as transient elevations of liver enzymes; gastrointestinal (GI) upset with cramps, nausea, vomiting, and anorexia; headache; dizziness; and immunologically mediated fever and flulike symptoms. Thrombocytopenia and hemolytic anemias can also occur. Rifabutin has a similar spectrum of toxicities, except for an increased incidence of rash (4%) and neutropenia (2%). Rifapentine has fewer adverse effects but is associated with hyperuricemia and cytopenias, especially lymphopenia and neutropenia. All rifamycins can turn urine and other secretions (tears, saliva, stool, sputum) *orange,* which can stain contact lenses. Patients and families should be warned about this common but otherwise innocuous adverse effect.

Rifamycins induce the hepatic cytochrome P450 (CYP) isoenzyme system and are associated with the increased metabolism and decreased level of several drugs when administered concomitantly. These drugs include digoxin, corticosteroids such as prednisone and dexamethasone, dapsone, fluconazole, phenytoin, oral contraceptives, warfarin, and many antiretroviral agents, especially protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Rifabutin has less of an effect on lowering protease inhibitor levels.

The use of pyrazinamide in combination with rifampin for short-course latent tuberculosis therapy has been associated with serious liver dysfunction and death. This combination has never been well studied or recommended for pediatric patients and should not be used.

No routine laboratory monitoring for rifamycins is indicated unless the patient is symptomatic. In patients with signs of toxicity, complete blood count (CBC) and kidney and liver function tests are indicated.

Pyrazinamide

Pyrazinamide (**PZA**) is a synthetic pyrazide analog of nicotinamide that is bactericidal against intracellular *M. tuberculosis* organisms in acidic environments, such as within macrophages or inflammatory lesions. A bacteria-specific enzyme (pyrazinamidase) converts PZA to pyrazinoic acid, which leads to low pH levels not tolerated by *M. tuberculosis.* Resistance is poorly understood but can arise from bacterial pyrazinamidase alterations.

PZA is indicated for the initial treatment phase of active tuberculosis in combination with other antimycobacterial agents. The pediatric dosage is 15-30 mg/kg/day PO in a single dose, not to exceed 2,000 mg/day. Twice-weekly dosing with directly observed therapy only is with 50 mg/kg/day PO in a single dose, not to exceed 4,000 mg/day. It is available in a 500 mg tablet and can be made into a suspension of 100 mg/mL.

Adverse effects include GI upset (e.g., nausea, vomiting, poor appetite) in approximately 4% of children, dosage-dependent hepatotoxicity, and elevated serum uric acid levels that can precipitate gout in susceptible adults. Approximately 10% of pediatric patients have elevated uric acid levels but with no associated clinical sequelae. Minor reactions include arthralgias, fatigue, and, rarely, fever.

Use of PZA in combination with rifampin for short-course treatment of latent tuberculosis is associated with serious liver dysfunction and death, and this combination should be avoided.

No routine laboratory monitoring for PZA is required, but monthly visits to reinforce the importance of therapy are desirable.

Ethambutol

Ethambutol is a synthetic form of ethylenedi-imino-di-1-butanol dihydrochloride that inhibits RNA synthesis needed for cell wall formation. At standard dosages ethambutol is bacteriostatic, but at dosages >25 mg/kg it has bactericidal activity. The mechanism of resistance to ethambutol is unknown, but resistance develops rapidly when ethambutol is used as a single agent against *M. tuberculosis.*

Ethambutol is indicated for the treatment of infections caused by *M. tuberculosis, M. kansasii, M. bovis,* and *M. avium* complex. Ethambutol should only be used as part of a combination treatment regimen for *M. tuberculosis.* Daily dosing is 15-20 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Twice-weekly dosing is with 50 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Dosage adjustment is needed in renal insufficiency. Ethambutol is available in 100 and 400 mg tablets.

The major adverse effect with ethambutol is **optic neuritis** , and thus ethambutol should generally be reserved for children old enough to have visual acuity and color discrimination reliably monitored. Visual changes are usually dosage dependent and reversible. Other adverse events include headache, dizziness, confusion, hyperuricemia, GI upset, peripheral neuropathy, hepatotoxicity, and cytopenias, especially neutropenia and thrombocytopenia.

Routine laboratory monitoring includes baseline and periodic visual acuity and color discrimination testing, CBC, serum uric acid levels, and kidney and liver function tests.

Less Commonly Used Agents

Aminoglycosides

The aminoglycosides used for mycobacterial infections include streptomycin, amikacin, kanamycin, and capreomycin. **Streptomycin** is isolated from *Streptomyces griseus* and was the first drug used to treat *M. tuberculosis*. **Capreomycin** , a cyclic polypeptide from *Streptomyces capreolus*, and **amikacin** , a semisynthetic derivative of kanamycin, are newer agents that are recommended when streptomycin is unavailable. Aminoglycosides act by binding irreversibly to the 30S subunit of ribosomes and inhibiting subsequent protein synthesis. Streptomycin exhibits concentration-dependent bactericidal activity, and capreomycin is bacteriostatic. Resistance results from mutation in the binding site of the 30S ribosome, by decreased transport into cells, or by inactivation by bacterial enzymes. Cross-resistance between aminoglycosides has been demonstrated.

The aminoglycosides are indicated for the treatment of *M. tuberculosis* and *M. avium* complex. All are considered second-line drugs in the treatment of *M. tuberculosis* and should be used only when resistance patterns are known. Aminoglycosides are poorly absorbed orally and are administered by IM injection. Pediatric dosing ranges for streptomycin are 20 mg/kg/day if given daily and 20-40 mg/kg/day if given twice weekly; dosing is IM in a single daily dose. Capreomycin, amikacin, and kanamycin dosages are 15-30 mg/kg/day IM in a single dose, not to exceed 1 g/day. Dosage adjustment is necessary in renal insufficiency.

Aminoglycosides have **adverse effects** on proximal renal tubules, the cochlea, and the vestibular apparatus of the ear. Nephrotoxicity and ototoxicity account for most of the significant adverse events. Rarely, patients exhibit fever or rash with administration of aminoglycosides. Concomitant use of other nephrotoxic or ototoxic agents should be avoided, because adverse effects may be additive. An infrequent but serious, synergistic, dosage-dependent aminoglycoside effect with nondepolarizing neuromuscular blockade agents can result in respiratory depression or paralysis.

Hearing and kidney function should be monitored at baseline and periodically. Early signs of ototoxicity include tinnitus, vertigo, and hearing loss. Ototoxicity appears to be irreversible, but early kidney damage may be reversible. As with other aminoglycosides, peak and trough drug levels are helpful in dosing and managing early toxicities.

Cycloserine

Cycloserine, derived from *Streptomyces orchidaceus* or *Streptomyces garyphalus*, is a synthetic analog of the amino acid D -alanine that interferes with bacterial cell wall synthesis through competitive inhibition of D -alanine components to be incorporated into the cell wall. It is bacteriostatic, and the mechanism of resistance is unknown.

Cycloserine is used to treat *M. tuberculosis* and *M. bovis* . The dosage is 10-20 mg/kg/day PO divided into 2 doses, not to exceed 1 g/day. It is available in a 250 mg capsule.

The major adverse effect is **neurotoxicity** with significant psychologic disturbance, including seizures, acute psychosis, headache, confusion, depression, and personality changes. The neurotoxic effects are additive with ethionamide and INH. Cycloserine has also been associated with megaloblastic anemia. It must be dosage-adjusted in patients with kidney impairment and should be used with caution in patients with underlying psychiatric illness.

Routine laboratory monitoring includes kidney and hepatic function, CBC, and cycloserine levels. Psychiatric symptoms are less common at blood levels <30 µg/mL.

Ethionamide

Ethionamide is structurally related to INH and is an ethyl derivative of thioisonicotinamide that inhibits peptide synthesis by an unclear mechanism thought to involve nicotinamide adenine dinucleotide and NAD phosphate dehydrogenase disruptions. Ethionamide is bacteriostatic at most therapeutic levels. Resistance develops quickly if ethionamide used as a single-agent therapy, although the mechanism is unknown.

Ethionamide is used as an alternative to streptomycin or ethambutol in the treatment of *M. tuberculosis* and has some activity against *M. kansasii* and *M. avium* complex. A metabolite, ethionamide sulfoxide, is bactericidal against *M. leprae*. Ethionamide has been shown to have good central nervous system (CNS) penetration and has been used as a 4th drug in combination with rifampin, INH, and PZA. The pediatric dosing is 15-20 mg/kg/day PO in 2 divided doses, not to exceed 1 g/day. It is available as a 250 mg tablet.

Gastrointestinal upset is common, and other **adverse effects** include neurologic disturbances (anxiety, dizziness, peripheral neuropathy, seizures, acute psychosis), hepatic enzyme elevations, hypothyroidism, hypoglycemia, and hypersensitivity reaction with rash and fever. Ethionamide should be used with caution in patients with underlying psychiatric or thyroid disease. The psychiatric adverse effects can be potentiated with concomitant use of cycloserine.

In addition to close assessment of mood, routine monitoring includes thyroid and liver function tests. In diabetic patients taking ethionamide, blood glucose levels should be monitored.

Fluoroquinolones

The fluoroquinolones are fluorinated derivatives of the quinolone class of antibiotics. Ciprofloxacin is a first-generation fluoroquinolone, and levofloxacin is the more active l-isomer of ofloxacin. **Moxifloxacin** and **gatifloxacin** are agents with emerging use in pediatric mycobacterial disease. Fluoroquinolones are not indicated for use in children <18 yr old, but studies of their use in pediatric patients continue to indicate that they may be used in special circumstances. Fluoroquinolones are bactericidal and exert their effect by inhibition of DNA gyrase. The alterations in DNA gyrase result in relaxation of supercoiled DNA and breaks in double-stranded DNA. The mechanism of resistance is not well defined but likely involves mutations in the DNA gyrase.

Levofloxacin is an important second-line drug in the treatment of multidrug-resistant (MDR) *M. tuberculosis.* **Ciprofloxacin** has activity against *Mycobacterium fortuitum* complex and against *M. tuberculosis.* The pediatric dosage of ciprofloxacin is 20-30 mg/kg/day PO or intravenously (IV), not to exceed 1.5 mg/day PO or 800 mg/day IV. The adult dosage of ciprofloxacin is 500-750 mg/dose PO in 2 divided doses or 200-400 mg/dose IV every 12 hr. Ciprofloxacin is available in 100, 250, 500, and 750 mg tablets and can be made in 5% (50 mg/mL) or 10% (100 mg/mL) suspensions. The dosage of levofloxacin for children is 5-10 mg/kg/day given once daily either PO or IV, not to exceed 1,000 mg/day, and for adults, 500-1,000 mg/day PO or IV, not to exceed 1,000 mg/day. Levofloxacin is available in 250, 500, and 750 mg tablets, and a 50 mg/mL suspension can be extemporaneously compounded. The suspension has a shelf life of only 8 wk.

The most common adverse effect of fluoroquinolones is **GI upset** , with nausea, vomiting, abdominal pain, and diarrhea, including pseudomembranous colitis. Other, less common adverse effects include bone marrow depression, CNS effects (e.g., lowered seizure threshold, confusion, tremor, dizziness, headache), elevated liver transaminases, photosensitivity, and arthropathies. The potential for arthropathies (e.g., tendon ruptures, arthralgias, tendinitis) is the predominant reason that fluoroquinolones are not recommended for pediatric use. The mechanism of injury appears to involve the disruption of extracellular matrix of cartilage and depletion of collagen, a particular concern related to the bone and joint development of children.

Fluoroquinolones induce the CYP isoenzymes that can increase the concentrations of dually administered theophylline and warfarin. Nonsteroidal antiinflammatory drugs (NSAIDs) can potentiate the CNS effects of fluoroquinolones and should be avoided while taking a fluoroquinolone. Both ciprofloxacin and levofloxacin should be dosage-adjusted in patients with significant renal dysfunction.

While taking fluoroquinolones, patients should be monitored for hepatic and renal dysfunction, arthropathies, and hematologic abnormalities.

Linezolid

Linezolid is a synthetic oxazolidinone derivative. This drug is not currently approved for use against mycobacterial infection in pediatric or adult patients but has activity against some mycobacterial species. Studies on efficacy of treatment of mycobacterial infections are under way. Linezolid inhibits translation by binding to the 23S ribosomal component of the 50S ribosome subunit, preventing coupling with the 70S subunit. Resistance is thought to be from a point mutation at the binding site but is poorly studied because only a few cases of resistance have been reported.

The approved indications for linezolid are for bacterial infections other than mycobacteria, but studies reveal in vitro activity against rapidly growing mycobacteria (*M. fortuitum* complex, *M. chelonae, M. abscessus*), *M. tuberculosis,* and *M. avium* complex. The dosage for 0-11 yr old children is 10 mg/kg/day PO or IV in divided doses every 8-12 hr. For persons >12 yr old, the dosage is 600 mg PO or IV every 12 hr. Linezolid is available in 400 and 600 mg tablets and as a 20 mg/mL suspension.

Adverse effects of linezolid include GI upset (e.g., nausea, vomiting, diarrhea), CNS disturbances (e.g., dizziness, headache, insomnia, peripheral neuropathy), lactic acidosis, fever, myelosuppression, and pseudomembranous colitis. Linezolid is a weak inhibitor of monoamine oxidase A, and patients are advised to avoid foods with high tyramine content. Linezolid should be used cautiously in patients with preexisting myelosuppression.

In addition to monitoring for GI upset and CNS perturbations, routine laboratory monitoring includes CBC at least weekly.

Paraaminosalicylic Acid

Paraaminosalicylic acid (**PAS**) is a structural analog of paraaminobenzoic acid (PABA). It is bacteriostatic and acts by competitively inhibiting the synthesis of folic acid, similar to the action of sulfonamides. Resistance mechanisms are poorly understood.

PAS acts against *M. tuberculosis*. The dosage is 150 mg/kg/day PO in 2 or 3 divided doses. PAS is dispensed in 4 g packets, and the granules should be mixed with liquid and swallowed whole.

Common **adverse effects** include GI upset, and less common events include hypokalemia, hematuria, albuminuria, crystalluria, and elevations of hepatic transaminases. PAS can decrease the absorption of rifampin, and co-administration with ethionamide potentiates the adverse effects of PAS.

In addition to monitoring for weight loss, routine laboratory monitoring includes liver and kidney function tests.

Bedaquiline Fumarate

This oral diarylquinoline has been recommended for the treatment of MDR tuberculosis. Bedaquiline fumarate should be used as part of combination therapy and administered by direct observation. Although approved for patients ≥18 yr old, bedaquiline may be considered for children on a case-by-case basis.

Serious **adverse effects** include hepatotoxicity and a prolonged QT interval.

Delamanid

Delamanid is a dihydro-nitroimidazooxazole derivative recently approved for use in the treatment of MDR tuberculosis. It acts by inhibiting the synthesis of mycobacterial cell wall compounds such as methoxymycolic acid and ketomycolic acid. Limited studies are available in the pediatric population, and delamanid should be used only in conjunction with a tuberculosis specialist.

Adverse effects include nausea, vomiting, dizziness, anxiety, shaking, and QT prolongation.

Agents Used Against *Mycobacterium Leprae*

Dapsone

Dapsone is a sulfone antibiotic with characteristics similar to sulfonamides. Similar to other sulfonamides, dapsone acts as a competitive antagonist of PABA, which is needed for the bacterial synthesis of folic acid. Dapsone is bacteriostatic against *M. leprae*. Resistance is not well understood but is thought to occur after alterations at the PABA-binding site.

Dapsone is used in the treatment of *M. leprae* in combination with other antileprosy agents (rifampin, clofazimine, ethionamide). The pediatric dosage is 1-2 mg/kg/day PO as a single dose, not to exceed 100 mg/day, for a duration of 3-10 yr. The adult dosage is 100 mg/day PO as a single dose. Dapsone is available in 25 and 100 mg scored tablets and as an oral suspension of 2 mg/mL. The dosage should be adjusted in renal insufficiency.

Dapsone has many reported **adverse effects** , including dosage-related hemolytic anemia, especially in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, pancreatitis, renal complications (acute tubular necrosis, acute renal failure, albuminuria), increased liver enzymes, psychosis, tinnitus, peripheral neuropathy, photosensitivity, and a hypersensitivity syndrome with fever, rash, hepatic damage, and malaise. Treatment may produce a *lepra reaction*, which is a nontoxic, paradoxical worsening of lepromatous leprosy with the initiation of therapy. This hypersensitivity reaction is not an indication to discontinue therapy. Dapsone should be used with caution in patients with G6PD deficiency or taking other folic acid antagonists. Dapsone levels can decrease with concomitant rifampin and can increase with concomitant clotrimazole.

Routine laboratory monitoring includes CBC weekly during the 1st mo of therapy, weekly through 6 mo of therapy, and then every 6 mo thereafter. Other periodic assessments include kidney function with creatine levels, urinalysis, and liver function tests.

Clofazimine

Clofazimine is a synthetic phendimetrazine tartrate derivative that acts by binding to the mycobacterial DNA at guanine sites. It has a slow bactericidal activity against *M. leprae*. Mechanisms of resistance are not well studied. No cross-resistance between clofazimine and dapsone or rifampin has been shown.

Clofazimine is indicated as part of a combination therapy for the treatment of *M. leprae*. It appears there may be some activity against other mycobacteria such as *M. avium* complex, although treatment failures are common. Safety and efficacy of clofazimine are poorly studied in children. The pediatric dosage is 1 mg/kg/day PO as a single dose, not to exceed 100 mg/day, in combination with dapsone and rifampin, for 2 yr and then additionally as a single agent for >1 yr. The adult dosage is 100 mg/day PO. Clofazimine should be taken with food to increase absorption.

The most common adverse effect is a dosage-related, reversible, pink to tan-brown discoloration of the skin and conjunctiva. Other **adverse effects** include a dry, itchy skin rash, headache, dizziness, abdominal pain, diarrhea, vomiting, peripheral neuropathy, and elevated hepatic transaminases.

Routine laboratory monitoring includes periodic liver function tests.

Agents Used Against Nontuberculous Mycobacteria

Cefoxitin

Cefoxitin, a cephamycin derivative, is a second-generation cephalosporin that, like other cephalosporins, inhibits cell wall synthesis by linking with penicillin-binding proteins to create an unstable bacterial cell wall. Resistance develops by alterations in penicillin-binding proteins.

Cefoxitin is often used in combination therapy for mycobacterial disease (Table 241.3). Pediatric dosing is based on disease severity, with a range of 80-160 mg/kg/day divided every 4-8 hr, not to exceed 12 g/ day. Adult dosages are 1-2 g/day, not to exceed 12 g/day. Cefoxitin is available in IV and IM formulations. Increased dosing intervals are needed with renal insufficiency.

Table 241.3

Treatment of Nontuberculous Mycobacteria Infections in Children

ORGANISM	DISEASE	INITIAL TREATMENT
SLOWLY GROWING SPECIES		
Mycobacterium avium complex (MAC); *Mycobacterium haemophilum* ; *Mycobacterium lentiflavum*	Lymphadenitis	Complete excision of lymph nodes; if excision incomplete or disease recurs, clarithromycin or azithromycin plus ethambutol and/or rifampin (or rifabutin).
	Pulmonary infection	Clarithromycin or azithromycin plus ethambutol with rifampin or rifabutin (pulmonary resection in some patients who fail to respond to drug therapy). For severe disease, an initial course of amikacin or streptomycin often is included. Clinical data in adults with mild to moderate disease support that 3-times-weekly therapy is as effective as daily therapy, with less toxicity. For patients with advanced or cavitary disease, drugs should be given daily.
Mycobacterium chimaera	Prosthetic valve endocarditis	Valve removal, prolonged antimicrobial therapy based on susceptibility testing.
	Disseminated	See text.
Mycobacterium kansasii	Pulmonary infection	Rifampin plus ethambutol with isoniazid daily. If rifampin resistance is detected, a 3-drug regimen based on drug susceptibility testing should be used.
	Osteomyelitis	Surgical debridement and prolonged antimicrobial therapy using rifampin plus ethambutol with isoniazid.
Mycobacterium marinum	Cutaneous infection	None, if minor; rifampin, TMP-SMX, clarithromycin, or doxycycline* for moderate disease; extensive lesions may require surgical debridement. Susceptibility testing not routinely required.
Mycobacterium ulcerans	Cutaneous and bone infections	Daily intramuscular streptomycin and oral rifampin for 8 wk; excision to remove necrotic tissue, if present; potential response to thermotherapy.
RAPIDLY GROWING SPECIES		
Mycobacterium fortuitum group	Cutaneous infection	Initial therapy for serious disease is amikacin plus meropenem IV, followed by clarithromycin, doxycycline,* TMP-SMX, or ciprofloxacin PO, on the basis of in vitro susceptibility testing; may require surgical excision. Up to 50% of isolates are resistant to cefoxitin.
	Catheter infection	Catheter removal and amikacin plus meropenem IV; clarithromycin, TMP-SMX, or ciprofloxacin, orally, on the basis of in vitro susceptibility testing.
Mycobacterium abscessus	Otitis media; cutaneous infection	There is no reliable antimicrobial regimen because of variability in drug susceptibility. Clarithromycin plus initial course of amikacin plus cefoxitin or imipenem/meropenem; may require surgical debridement on the basis of in vitro susceptibility testing (50% are amikacin resistant).
	Pulmonary infection (in cystic fibrosis)	Serious disease, clarithromycin, amikacin, and cefoxitin or imipenem/meropenem on the basis of susceptibility testing; most isolates have very low MIC to tigecycline; may require surgical resection.
Mycobacterium chelonae	Catheter infection, prosthetic valve endocarditis	Catheter removal; debridement, removal of foreign material; valve replacement; and tobramycin (initially) plus clarithromycin, meropenem, and linezolid.
	Disseminated cutaneous infection	Tobramycin and meropenem or linezolid (initially) plus clarithromycin.

[*] Doxycycline can be used for short durations (i.e., ≤21 days) without regard to patient age, but for longer treatment durations is not recommended for children <8 yr old. Only 50% of isolates of *M.*

marinum are susceptible to doxycycline.

IV, Intravenously; MIC, minimum inhibitory concentration; PO, orally (by mouth); TMP-SMX, trimethoprim-sulfamethoxazole.

From American Academy of Pediatrics: *Red book: 2018–2021 report of the Committee on Infectious Diseases,* ed 31, Elk Grove Village, IL, 2018, AAP (Table 3.90).

Adverse effects are primarily hematologic (eosinophilia, granulocytopenia, thrombocytopenia, hemolytic anemia), GI (nausea, vomiting, diarrhea with possible pseudomembranous colitis), and CNS related (dizziness, vertigo). Potential additive adverse effects can occur when cefoxitin is used with aminoglycosides.

Routine laboratory monitoring with long-term use includes CBC and liver and renal function tests.

Doxycycline

Doxycycline is in the tetracycline family of antibiotics and has limited use in pediatrics. As with other tetracyclines, doxycycline acts to decrease protein synthesis by binding to the 30S ribosome and to transfer RNA. It can also cause alterations to the cytoplasmic membrane of susceptible bacteria.

Doxycycline is used to treat *M. fortuitum* (see Table 241.3). Although it can be used to treat *Mycobacterium marinum*, adult treatment failures have occurred. Pediatric dosing is based on age and weight. For children >8 yr old who weigh <45 kg, the dosage is 4.4 mg/kg/day divided twice daily. Dosing for larger children and adults is 100 mg twice daily. Doxycycline is available as 50 and 100 mg capsules or tablets and in 25 mg/5 mL and 50 mg/5 mL suspensions.

Doxycycline use in children is limited by a **permanent tooth discoloration** , which becomes worse with long-term use. Other **adverse effects** include photosensitivity, liver and kidney dysfunction, and esophagitis, which can be minimized by dosing with large volumes of liquid. Doxycycline can decrease the effectiveness of oral contraceptives. Rifampin, carbamazepine, and phenytoin can decrease the concentration of doxycycline.

Routine laboratory monitoring with long-term use includes kidney and liver function tests as well as CBC.

Macrolides

Clarithromycin and azithromycin belong to the macrolide family of antibiotics. Clarithromycin is a methoxy derivative of erythromycin. Macrolides act by binding the 50S subunit of ribosomes, subsequently inhibiting protein synthesis. Resistance mechanisms for mycobacteria are not well understood but might involve binding site alterations. Clarithromycin appears to have synergistic antimycobacterial activity when combined with rifamycins, ethambutol, or clofazimine.

Clarithromycin is widely used for the prophylaxis and treatment of *M. avium* complex disease and also has activity against *Mycobacterium abscessus*, *M. fortuitum*, and *M. marinum.* Azithromycin has significantly different pharmacokinetics compared with other macrolide agents and has not been studied and is not indicated for mycobacterial infections. The pediatric dosage of clarithromycin for primary prophylaxis of *M. avium* complex infections is 7.5 mg/kg/dose PO given twice daily, not to exceed 500 mg/day. This dosage is used for recurrent *M. avium* complex disease in combination with ethambutol and rifampin. The adult dosage is 500 mg PO twice daily to be used as a single agent for primary prophylaxis or as part of combination therapy with ethambutol and rifampin. Dosage adjustment is needed for renal insufficiency but not liver failure. Clarithromycin is available in 250 and 500 mg tablets and suspensions of 125 mg/5 mL and 250 mg/5 mL.

The primary adverse effect of clarithromycin is **GI upset** , including vomiting (6%), diarrhea (6%), and abdominal pain (3%). Other **adverse effects** include taste disturbances, headache, and QT prolongation if used with inhaled anesthetics, clotrimazole, antiarrhythmic agents, or azoles. Clarithromycin should be used cautiously in patients with renal insufficiency or liver failure.

Routine laboratory monitoring with prolonged use of clarithromycin includes periodic liver enzyme tests. Diarrhea is an early sign of pseudomembranous colitis.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX) is formulated in a fixed ratio of 1 part TMP to 5 parts SMX. SMX is a sulfonamide that inhibits synthesis of dihydrofolic acid by competitively inhibiting PABA, similar to dapsone. TMP blocks production of tetrahydrofolic acid and downstream biosynthesis of nucleic acids and protein by reversibly binding to dihydrofolate reductase. The combination of the 2 agents is synergistic and often bactericidal.

TMP-SMX is often used in combination therapy for mycobacterial disease (see Table 241.3). Oral or IV pediatric dosage for serious infections is TMP 15-

20 mg/kg/day divided every 6-8 hr, and for mild infections, TMP 6-12 mg/kg/day divided every 12 hr. The adult dosage is 160 mg TMP and 800 mg SMX every 12 hr. Dosage reduction may be needed in renal insufficiency. TMP-SMX is available in single-strength tablets (80/400 mg TMP/SMX) and double-strength tablets (160/800 mg TMP/SMX) and in a suspension of 40 mg TMP and 200 mg SMX per 5 mL.

The most common adverse effect with TMP-SMX is **myelosuppression** . It must be used with caution in patients with G6PD deficiency. Other **adverse effects** include renal abnormalities, rash, aseptic meningitis, GI disturbances (e.g., pancreatitis, diarrhea), and prolonged QT interval if co-administered with inhaled anesthetics, azoles, or macrolides.

Routine laboratory monitoring includes monthly CBC and periodic electrolytes and creatinine to monitor renal function.

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CHAPTER 242

Tuberculosis *(Mycobacterium tuberculosis)*

Lindsay Hatzenbuehler Cameron, Jeffrey R. Starke

Tuberculosis has caused human disease for more than 4,000 yr and is one of the most important infectious diseases worldwide.

Etiology

There are 5 closely related mycobacteria in the *Mycobacterium tuberculosis* complex: *M. tuberculosis, M. bovis, M. africanum, M. microti,* and *M. canetti. M. tuberculosis* is the most important cause of tuberculosis (TB) disease in humans. The tubercle bacilli are non–spore-forming, nonmotile, pleomorphic, weakly gram-positive curved rods 1-5 µm long, typically slender and slightly bent. They can appear beaded or clumped under microscopy. They are obligate aerobes that grow in synthetic media containing glycerol as the carbon source and ammonium salts as the nitrogen source (Löwenstein-Jensen culture media). These mycobacteria grow best at 37-41°C (98.6-105.8°F), produce niacin, and lack pigmentation. A lipid-rich cell wall accounts for resistance to the bactericidal actions of antibody and complement. A hallmark of all mycobacteria is **acid fastness** —the capacity to form stable mycolate complexes with arylmethane dyes (crystal violet, carbolfuchsin, auramine, and rhodamine). They resist decoloration with ethanol and hydrochloric or other acids.

Mycobacteria grow slowly, with a generation time of 12-24 hr. Isolation from clinical specimens on solid synthetic media usually takes 3-6 wk, and drug susceptibility testing requires an additional 2-4 wk. Growth can be detected in 1-3 wk in selective liquid medium using radiolabeled nutrients (e.g., BACTEC radiometric system), and drug susceptibilities can be determined in an additional 3-5 days. Once mycobacterial growth is detected, the species of mycobacteria present can be determined within hours using high-pressure liquid chromatography analysis (identifying the mycolic acid fingerprint of each species) or DNA probes. Restriction fragment length polymorphism profiling of mycobacteria is a helpful tool to study the epidemiology of tuberculosis strain relatedness in both outbreaks and routine epidemiology of tuberculosis in a community.

Clinical Stages

There are 3 major clinical stages of tuberculosis: exposure, infection, and disease. **Exposure** means a child has had significant contact (shared the air) with an adult or adolescent with infectious tuberculosis but lacks proof of infection. In this stage, the **tuberculin skin test (TST)** or **interferon-γ release assay (IGRA)** result is negative, the chest radiograph is normal, the physical examination is normal, and the child lacks signs or symptoms of disease. However, the child may be infected and develop TB disease rapidly, since there may not have been enough time for the TST or IGRA to turn positive. **Tuberculosis infection (TBI)** occurs when the individual inhales droplet nuclei containing *M. tuberculosis,* which survive intracellularly within the lung and associated lymphoid tissue. The hallmark of TBI is a positive TST or IGRA result. In this stage the child has no signs or symptoms, a normal physical examination, and the chest radiograph is either normal or reveals only granuloma or calcifications in the lung parenchyma. **Disease** occurs when signs or symptoms or radiographic manifestations caused by *M. tuberculosis* become apparent. Not all infected individuals have the same risk of developing disease. An immunocompetent adult with untreated TBI has approximately a 5–10% lifetime risk of developing disease. In contrast, an infected child <1 yr old has a 40% chance of developing TB disease within 9 mo.

Epidemiology

The World Health Organization (WHO) estimates that since 2015, tuberculosis has surpassed human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) as the leading cause of death from an infectious disease worldwide, and that almost one third of the world's population

(2.5 billion people) is infected with *M. tuberculosis.* Approximately 95% of TB cases occur in the developing world. The highest numbers of cases are in Asia, Africa, and the eastern Mediterranean region. An estimated 10.4 million incident cases and 1.8 million TB-associated deaths occurred worldwide in 2015 (Fig. 242.1). The WHO 2016 Global Tuberculosis Report estimates that in 2015 there were 1 million childhood incident cases, 170,000 TB-associated deaths among non–HIV-infected children, and 40,000 TB-associated deaths among HIV-infected children. The global burden of tuberculosis is influenced by several factors, including: the HIV pandemic; the development of **multidrug-resistant (MDR) tuberculosis** ; and the disproportionately low access of populations in low-resource settings worldwide to both diagnostic tests and effective medical therapy.

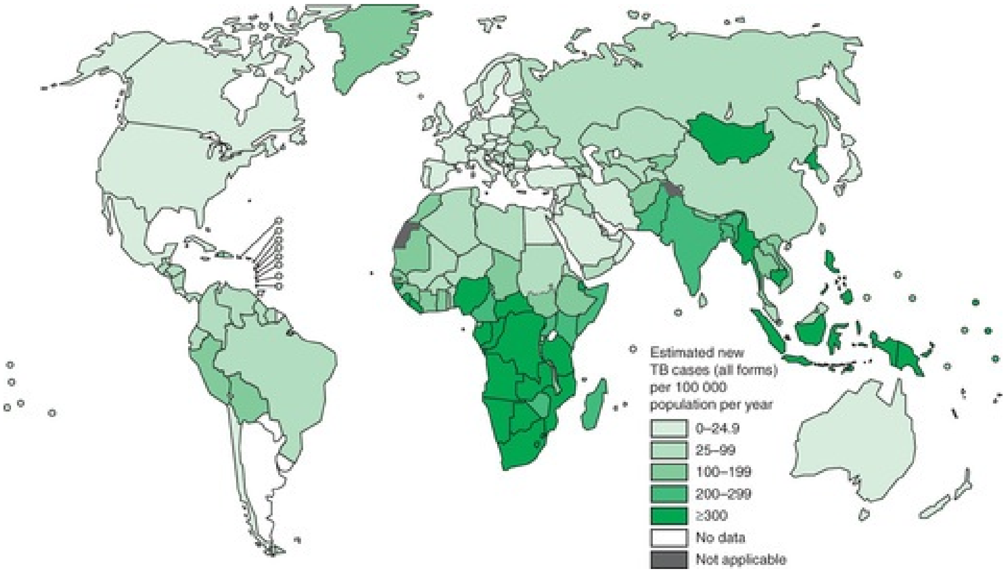
Estimated new TB cases (all forms) per 100 000 population per year
0–24.9
25–99
100–199
200–299
≥300
No data
Not applicable

FIG. 242.1 Estimated 2015 tuberculosis (TB) incidence rates. (From the World Health Organization: *Global tuberculosis report 2016,* Geneva, 2016, WHO.)

In the United States, TB case rates decreased steadily during the 1st half of the 20th century, long before the advent of antituberculosis drugs, as a result of improved living conditions and likely, genetic selection favoring persons resistant to developing disease. A resurgence of tuberculosis in the late 1980s was associated primarily with the HIV epidemic, transmission of the organism in congregate settings including healthcare institutions, disease occurring in recent immigrants, and poor conduct of community TB control. Since 1992, the number of reported TB cases decreased each year until 2015, when it increased by 1.6% from 2014, to 9,557cases (Fig. 242.2). Despite the increase in the number of reported cases in 2015, TB incidence in the United States has remained stable at 3 cases per 100,000 persons. Of the cases in 2015, 439 (4.6%) occurred in children <15 yr old (rate: 1.5/100,000 population), 55% of whom were ≤5 yr old. Racial and ethnic minorities and foreign-born persons, including children in these groups, are disproportionately affected by tuberculosis in the United States. In 2015 the Centers for Disease Control and Prevention (CDC) reported that 87% of all TB cases were among ethnic minority populations. The TB case rate among Asian, non-Hispanic black, and Hispanic children was 27, 13, and 12 times as high, respectively, as among non-Hispanic white children (Fig. 242.3). The TB rate among foreign-born persons in the United States was 13 times higher than among U.S.-born persons and accounted for 66% of all TB cases in 2015 (Fig. 242.4). Foreign-born children accounted for 22% of the total number of childhood TB cases in 2015. Of U.S.-born children with tuberculosis, 66% have at least 1 foreign-born parent, and 75% of all pediatric patients have some international connection through a family member or previous travel or residence in a TB-endemic country.

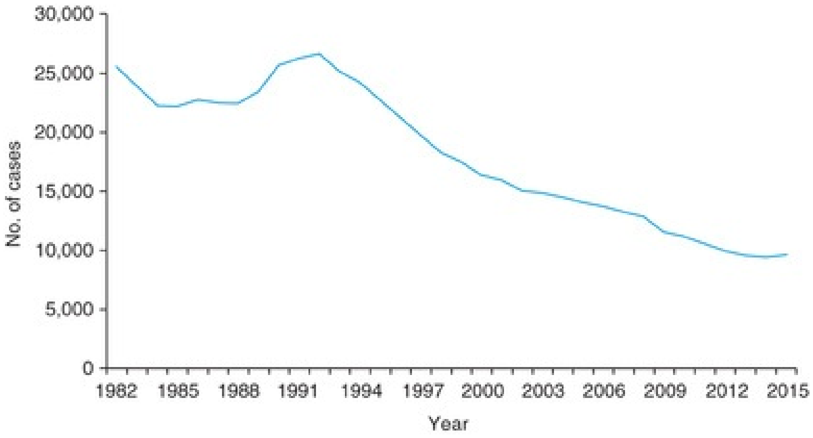

FIG. 242.2 Reported tuberculosis cases in the United States for 1982–2015 (as of June 9, 2016). (From Centers for Disease Control and Prevention: *Reported tuberculosis in the United States, 2015,* Atlanta, 2015, US Department of Health and Human Services.)

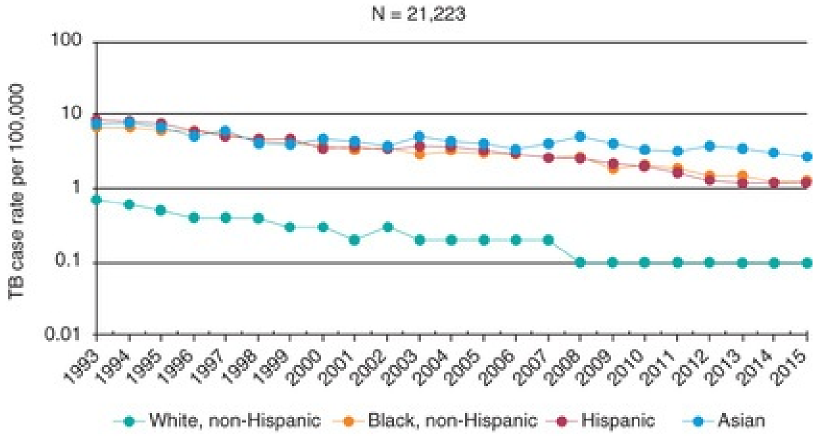

Note: Rates presented in a logarithmic scale
*Rates are per 100,000 persons
Multiple race/ethnicity, American Indian/Alaska Native and Native Hawaiian and other Pacific Islander rate not show because of small denominators

FIG. 242.3 Reported pediatric tuberculosis (TB) cases in the United States by race/ethnicity for the years 1993-2015. (From Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention: *Epidemiology of Pediatric Tuberculosis in United States, 1993-2015* . Atlanta, 2015, U.S. Department of Health and Human Services.)

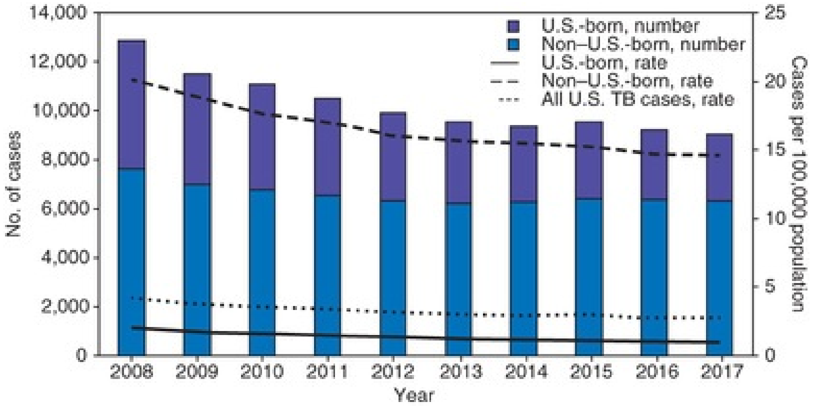

FIG. 242.4 Number of tuberculosis (TB) cases and rate, by national origin —United States, 2008–2017. (From Stewart RJ, Tsang CA, Pratt RH, et al: Tuberculosis—United States, 2017, *MMWR* 67(11):317–322, 2018.)

Most children are infected with *M. tuberculosis* in their home by someone close to them, but outbreaks of childhood tuberculosis also have occurred in elementary and high schools, nursery schools, daycare centers and homes, churches, school buses, and sports teams. HIV-infected adults with tuberculosis can transmit *M. tuberculosis* to children, and children with HIV infection are at increased risk for developing tuberculosis after infection. Specific groups are at high risk for acquiring TBI and progressing to tuberculosis (Table 242.1).

Table 242.1

Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Countries With Low Incidence

RISK FACTORS FOR TUBERCULOSIS INFECTION
Children exposed to high-risk adults
Foreign-born persons from high-prevalence countries
Homeless persons
Persons who inject drugs
Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes
Healthcare workers caring for high-risk patients (if infection control is not adequate)
RISK FACTORS FOR PROGRESSION OF TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE
Infants and children ≤4 yr old, especially those <2 yr old
Adolescents and young adults
Persons co-infected with human immunodeficiency virus
Persons with skin test conversion in the past 1-2 yr
Persons who are immunocompromised, especially in cases of malignancy and solid-organ transplantation, immunosuppressive medical treatments including anti–tumor necrosis factor therapies, diabetes mellitus, chronic renal failure, silicosis, and malnutrition
RISK FACTORS FOR DRUG-RESISTANT TUBERCULOSIS
Personal or contact history of treatment for tuberculosis
Contacts of patients with drug-resistant tuberculosis
Birth or residence in a country with a high rate of drug resistance
Poor response to standard therapy
Positive sputum smears (acid-fast bacilli) or culture ≥2 mo after initiating appropriate therapy

The incidence of **drug-resistant tuberculosis** has increased dramatically throughout the world. **MDR-TB** is defined as resistance to at least isoniazid and rifampin; **extensively drug-resistant tuberculosis** includes MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable drugs (kanamycin, capreomycin, amikacin). In 2015 the estimate for MDR-TB was 3.9% of incident cases, but rates as high as 32% have been reported in countries formerly part of the Soviet Union. In 2015 in the United States, a total of 89 patients with MDR-TB were reported, 70.8% of whom were foreign-born (Fig. 242.5). The CDC reported that among children with culture-confirmed tuberculosis in the United States in 2014, 17.4% had resistance to at least 1 first-line drug, and 0.9% had MDR-TB.

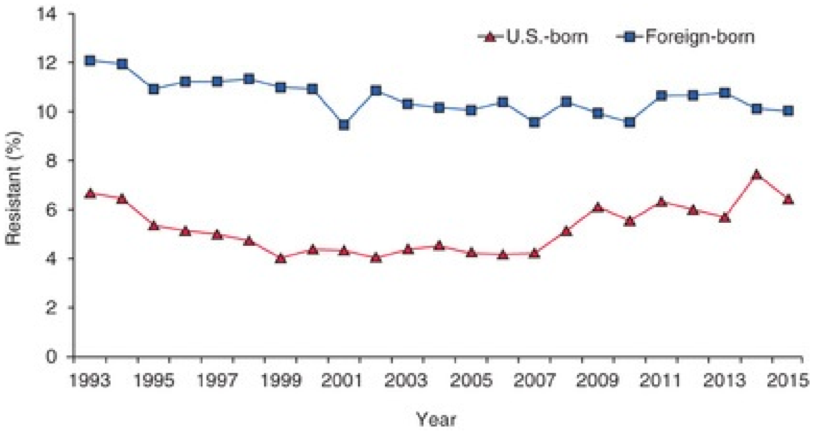

FIG. 242.5 Primary isoniazid resistance in U.S.-born vs foreign-born persons in the United States, 1993–2015 (as of June 9, 2016). Based on initial isolates from persons with no prior history of tuberculosis. (From Centers for Disease Control and Prevention: *Reported tuberculosis in the United States, 2015,* Atlanta, 2015, US Department of Health and Human Services.)

Transmission

Transmission of *M. tuberculosis* is usually by inhalation of airborne mucus droplet nuclei, particles 1-5 µm in diameter that contain *M. tuberculosis.* Transmission rarely occurs by direct contact with an infected discharge or a contaminated fomite. The chance of transmission increases when the patient has a positive acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough. Environmental factors such as poor air circulation enhance transmission. Most adults no longer transmit the organism within several days to 2 wk after beginning adequate chemotherapy, but some patients remain infectious for many weeks. Young children with tuberculosis rarely infect other children or adults. Tubercle bacilli are sparse in the endobronchial secretions of children with pulmonary tuberculosis, and cough is often absent or lacks the tussive force required to suspend infectious particles of the correct size. Children and adolescents with adult-type cavitary or endobronchial pulmonary tuberculosis can transmit the organism.

Airborne transmission of *M. bovis* and *M. africanum* also occurs. *M. bovis* can penetrate the gastrointestinal (GI) mucosa or invade the lymphatic tissue of the oropharynx when large numbers of the organism are ingested. Human infection with *M. bovis* is rare in developed countries as a result of the pasteurization of milk and effective TB control programs for cattle. Approximately 46% of culture-proven childhood TB cases from the San Diego, California, region since 1994 were caused by *M. bovis,* likely acquired by children when visiting Mexico or another country, or consuming dairy products from countries with suboptimal veterinary TB control programs.

Zoonotic transmission is an uncommon source of *M. tuberculosis* that has been reported in adults exposed to elephants and potentially cattle.

Pathogenesis

The **primary complex** (or Ghon complex) of tuberculosis includes local infection at the portal of entry and the regional lymph nodes that drain the area. The lung is the portal of entry in >98% of cases. The tubercle bacilli multiply initially within alveoli and alveolar ducts. Most of the bacilli are killed, but some survive within nonactivated macrophages, which carry them through lymphatic vessels to the regional lymph nodes. When the primary infection is in the lung, the hilar lymph nodes usually are involved, although an upper lobe focus can drain into paratracheal nodes. The tissue reaction in the lung parenchyma and lymph nodes intensifies over the next 2-12 wk as the organisms grow in number and **tissue hypersensitivity** develops. The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation (Fig. 242.6). Occasionally, this portion continues to enlarge, resulting in focal pneumonitis and pleuritis. If caseation is intense, the center of the lesion liquefies and empties into the associated bronchus, leaving a residual cavity.

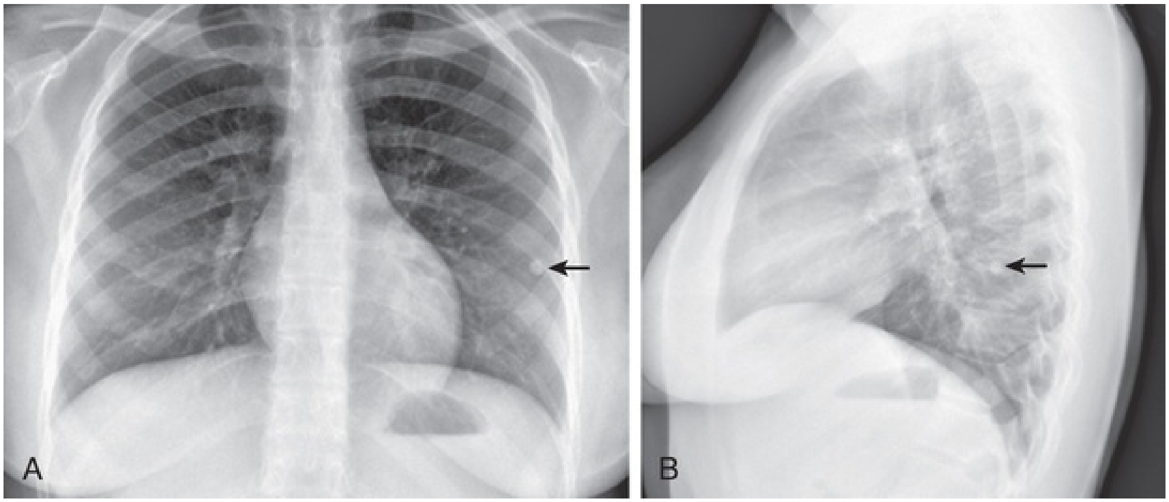

FIG. 242.6 Posteroanterior (**A**) and lateral (**B**) chest radiograph images of an adolescent showing a 7 mm calcified granuloma in the left lower lobe *(arrows)* . (From Lighter J, Rigaud M: Diagnosing childhood tuberculosis: traditional and innovative modalities, *Curr Probl Pediatr Adolesc Health Care* 39:55–88, 2009.)

The foci of infection in the regional lymph nodes develop some fibrosis and encapsulation, but healing is usually less complete than in the parenchymal lesion. Viable *M. tuberculosis* can persist for decades within these foci. In most cases of initial TBI, the lymph nodes remain normal in size. However, hilar and paratracheal lymph nodes that enlarge significantly as part of the host inflammatory reaction can encroach on a regional bronchus (Figs. 242.7 and 242.8). Partial obstruction of the bronchus caused by external compression can cause hyperinflation in the distal lung segment. Complete obstruction results in atelectasis. Inflamed caseous nodes can attach to the bronchial wall and erode through it, causing endobronchial tuberculosis or a fistula tract. The caseum causes complete obstruction of the bronchus. The resulting lesion is a combination of pneumonitis and atelectasis and has been called a **collapse-consolidation lesion** or **segmental lesion** (Fig. 242.9).

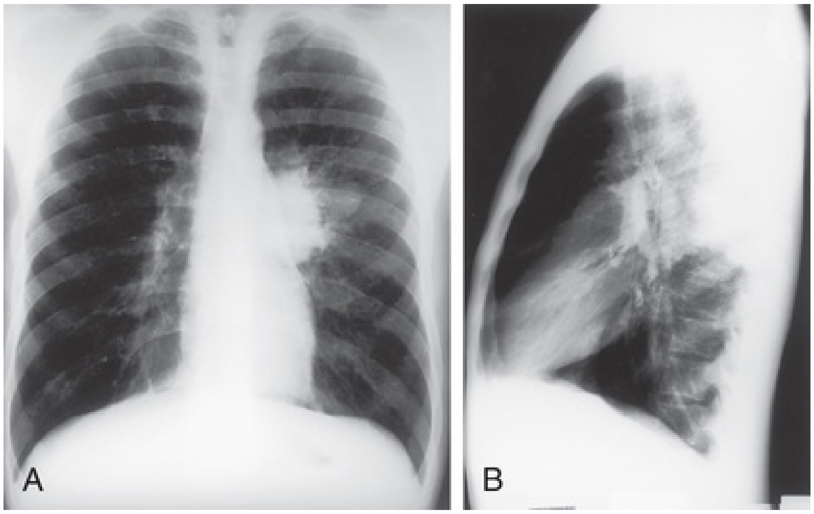

FIG. 242.7 A 14 yr old child with proven primary tuberculosis. Frontal (A) and lateral (B) views of the chest show hyperinflation, prominent left hilar lymphadenopathy, and alveolar consolidation involving the posterior segment of the left upper lobe as well as the superior segment of the left lower lobe. (From Hilton SVW, Edwards DK, editors: *Practical pediatric radiology* , ed 3, Philadelphia, 2003, Saunders, p 334.)

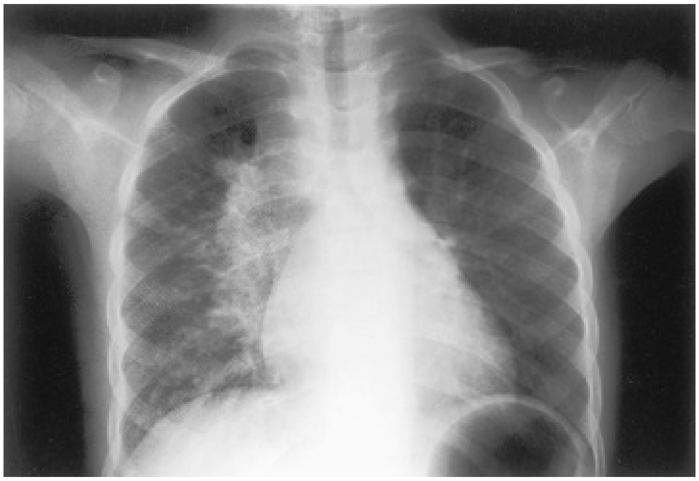

FIG. 242.8 An 8 yr old child with a history of cough. A single frontal view of the chest shows marked right hilar and paratracheal lymphadenopathy with alveolar disease involving the right middle and lower lung fields. This was also a case of primary tuberculosis. (From Hilton SVW, Edwards DK, editors: *Practical pediatric radiology* , ed 3, Philadelphia, 2003, Saunders, p. 335.)

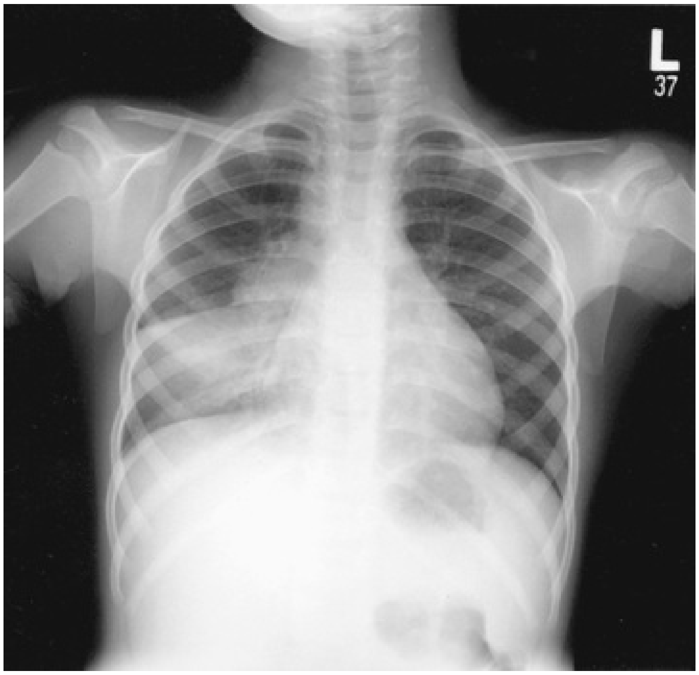

FIG. 242.9 Right-sided hilar lymphadenopathy and collapse-consolidation lesions of primary tuberculosis in a 4 yr old child.

During the development of the primary complex, tubercle bacilli are carried to most tissues of the body through the blood and lymphatic vessels. Although seeding of the organs of the reticuloendothelial system is common, bacterial replication is more likely to occur in organs with conditions that favor their growth, such as the lung apices, brain, kidneys, and bones. **Disseminated tuberculosis** occurs if the number of circulating bacilli is large and the host's cellular immune response is inadequate. More often, the number of bacilli is small, leading to clinically inapparent metastatic foci in many organs. These remote foci usually become encapsulated, but they may be the origin of both **extrapulmonary tuberculosis** and **reactivation pulmonary tuberculosis** .

The time between initial infection and clinically apparent TB disease is variable. Disseminated and meningeal tuberculosis are early manifestations, often occurring within 2-6 mo of acquisition. Significant lymph node or endobronchial tuberculosis usually appears within 3-9 mo. Lesions of the bones and joints take several years to develop, whereas renal lesions become evident decades after infection. Extrapulmonary manifestations are more common in children than adults and develop in 25–35% of children with tuberculosis, vs approximately 10% of immunocompetent adults.

Pulmonary tuberculosis that occurs >1 yr after the primary infection is usually caused by endogenous regrowth of bacilli persisting in partially encapsulated lesions. This reactivation tuberculosis is rare in children but is common among adolescents and young adults. The most common form is an infiltrate or cavity in the apex of the upper lobes, where oxygen tension and blood flow are highest.

The risk for dissemination of *M. tuberculosis* is very high in HIV-infected persons. Reinfection also can occur in persons with advanced HIV or AIDS. In immunocompetent persons the response to the initial infection with *M. tuberculosis* usually provides protection against reinfection when a new exposure occurs. However, exogenous reinfection has been reported to occur in adults and children without immune compromise in highly endemic areas.

Immunity

Conditions that adversely affect cell-mediated immunity predispose to progression from TBI to disease. Rare specific genetic defects associated with deficient cell-mediated immunity in response to mycobacteria include interleukin (IL)-12 receptor B1 deficiency and complete and partial interferon (IFN)-γ receptor 1 chain deficiencies. TBI is associated with a humoral antibody response, which plays little known role in host defense. Shortly after infection, tubercle bacilli replicate in both free alveolar spaces and inactivated alveolar macrophages. Sulfatides in the mycobacterial cell wall inhibit fusion of the macrophage phagosome and lysosomes, allowing the organisms to escape destruction by intracellular enzymes. **Cell-mediated immunity** develops 2-12 wk after infection, along with tissue hypersensitivity (Fig. 242.10). After bacilli enter macrophages, lymphocytes that recognize mycobacterial antigens proliferate and secrete lymphokines and other mediators that attract other lymphocytes and macrophages to the area. Certain lymphokines activate macrophages, causing them to develop high concentrations of lytic enzymes that enhance their mycobactericidal capacity. A discrete subset of regulator helper and suppressor lymphocytes modulates the immune response. Development of specific cellular immunity prevents progression of the initial infection in most persons.

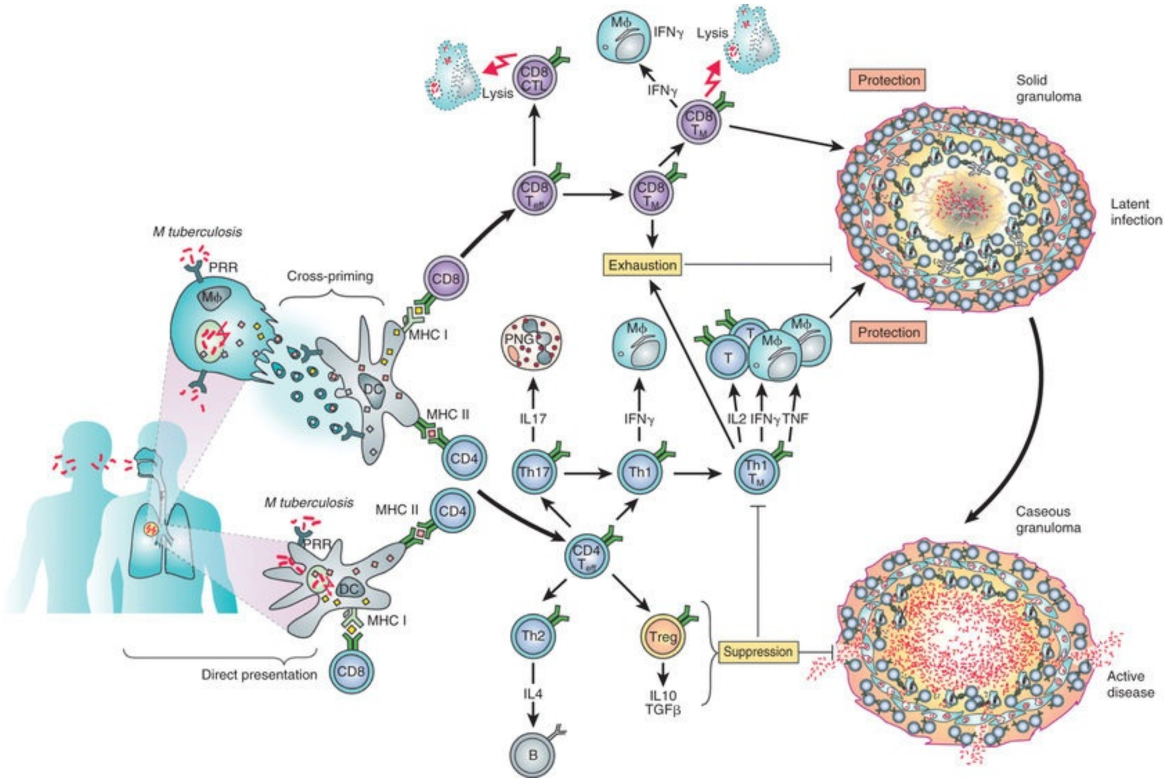
Mϕ
IFNγ
Lysis
CD8 CTL
Lysis
IFNγ
CD8 T_M
Protection
Solid granuloma
CD8 T_{eff}
CD8 T_M
Latent infection
M tuberculosis
PRR
Mϕ
Cross-priming
CD8
Exhaustion
MHC I
DC
PNG
Mϕ
T
T
Mϕ
Mϕ
Protection
MHC II
CD4
IL17
IFNγ
IL2 IFNγ TNF
Th17
Th1
Th1 T_M
M tuberculosis
MHC II
CD4
PRR
DC
CD4 T_{eff}
Caseous granuloma
MHC I
Th2
Treg
Suppression
Active disease
Direct presentation
CD8
IL4
IL10 TGFβ
B

FIG. 242.10 **Overview of the immune response in tuberculosis. Control of *Mycobacterium tuberculosis* is mainly the result of productive teamwork between T-cell populations and macrophages (Mø). *M. tuberculosis* survives within macrophages and dendritic cells (DCs) inside the phagosomal compartment. Gene products of major histocompatibility complex (MHC) class II are loaded with mycobacterial peptides that are presented to CD4 T cells. CD8 T-cell stimulation requires loading of MHC I molecules by mycobacterial peptides in the cytosol, either by egression of mycobacterial antigens into the cytosol or cross-priming, by which macrophages release apoptotic bodies carrying mycobacterial peptides. These vesicles are taken up by DCs and peptides presented. The CD4 T-helper (Th) cells polarize into different subsets. DCs and macrophages express pattern recognition receptors (PRRs), which sense molecular patterns on pathogens. Th1 cells produce interleukin (IL)-2 for T-cell activation, interferon-γ (IFN-γ), or tumor necrosis factor (TNF) for macrophage activation. Th17 cells, which activate polymorphonuclear granulocytes (PNGs), contribute to the early formation of protective immunity in the lung after vaccination. Th2 cells and regulatory T cells (Treg) counterregulate Th1-mediated protection via IL-4, transforming growth factor β (TGF-β), or IL-10. CD8 T cells produce IFN-γ and TNF, which activate macrophages. They also act as cytolytic T lymphocytes (CTL) by secreting perforin and granulysin, which lyse host cells and directly attack *M. tuberculosis* . These effector T cells (Teff) are succeeded by memory T cells (T_M). T_M cells produce multiple cytokines, notably IL2, IFN-γ, and TNF. During active containment in solid granuloma, *M. tuberculosis* recesses into a dormant stage and is immune to attack. Exhaustion of T cells is mediated by interactions between T cells and DCs through members of the programmed death 1 system. Treg cells secrete IL-10 and TGF-β, which suppress Th1. This process allows resuscitation of *M. tuberculosis* , which leads to granuloma caseation and active disease. B, B cell. (From Kaufman SHE, Hussey G, Lambert PH: New vaccines for tuberculosis. *Lancet* 375:2110–2118, 2010.)**

The pathologic events in the initial TBI seem to depend on the balance among the mycobacterial antigen load; cell-mediated immunity, which enhances intracellular killing; and tissue hypersensitivity, which promotes extracellular killing. When the antigen load is small and the degree of tissue sensitivity is high, granuloma formation results from the organization of lymphocytes, macrophages, and fibroblasts. When both antigen load and degree of sensitivity are high, granuloma formation is less organized. Tissue necrosis is incomplete, resulting in formation of caseous material. When the degree of tissue sensitivity is low, as often occurs in infants or immunocompromised persons, the reaction is diffuse and the infection is not well contained, leading to dissemination and local tissue destruction. Tumor necrosis factor (TNF) and other cytokines released by specific lymphocytes promote cellular destruction and tissue damage in susceptible persons.

Clinical Manifestations

Primary Pulmonary Disease

The **primary complex** includes the parenchymal pulmonary focus and the regional lymph nodes. Approximately 70% of lung foci are subpleural, and localized pleurisy is common. The initial parenchymal inflammation usually is not visible on chest radiograph, but a localized, nonspecific infiltrate may be seen before the development of tissue hypersensitivity. All lobar segments of the lung are at equal risk for initial infection. Two or more primary foci are present in 25% of cases. The hallmark of primary tuberculosis in the lung is the relatively large size of the regional lymphadenitis compared with the relatively small size of the initial lung focus (see Figs. 242.7 and 242.8). As delayed-type hypersensitivity develops, the hilar lymph nodes continue to enlarge in some children, especially infants, compressing the regional bronchus and causing obstruction. The usual sequence is *hilar lymphadenopathy, focal hyperinflation,* and then *atelectasis.* The resulting radiographic shadows have been called *collapse-consolidation* or *segmental* tuberculosis (see Fig. 242.9). Rarely, inflamed caseous nodes attach to the endobronchial wall and erode through it, causing endobronchial tuberculosis or a fistula tract. The caseum causes complete obstruction of the bronchus, resulting in extensive infiltrate and collapse. Enlargement of the subcarinal lymph nodes can cause compression of the esophagus and rarely a bronchoesophageal fistula.

Most cases of tuberculous bronchial obstruction in children resolve fully with appropriate treatment. Occasionally, there is residual calcification of the primary focus or regional lymph nodes. The appearance of calcification implies that the lesion has been present for at least 6-12 mo. Healing of the segment can be complicated by scarring or contraction associated with cylindrical bronchiectasis, but this is rare.

Children can have lobar pneumonia without impressive hilar lymphadenopathy. If the primary infection is progressively destructive, liquefaction of the lung parenchyma can lead to formation of a thin-walled primary TB cavity. Rarely, bullous tuberculous lesions occur in the lungs and lead to pneumothorax if they rupture. Erosion of a parenchymal focus of tuberculosis into a blood or lymphatic vessel can result in dissemination of the bacilli and a **miliary** pattern, with small nodules evenly distributed on the chest radiograph (Fig. 242.11).

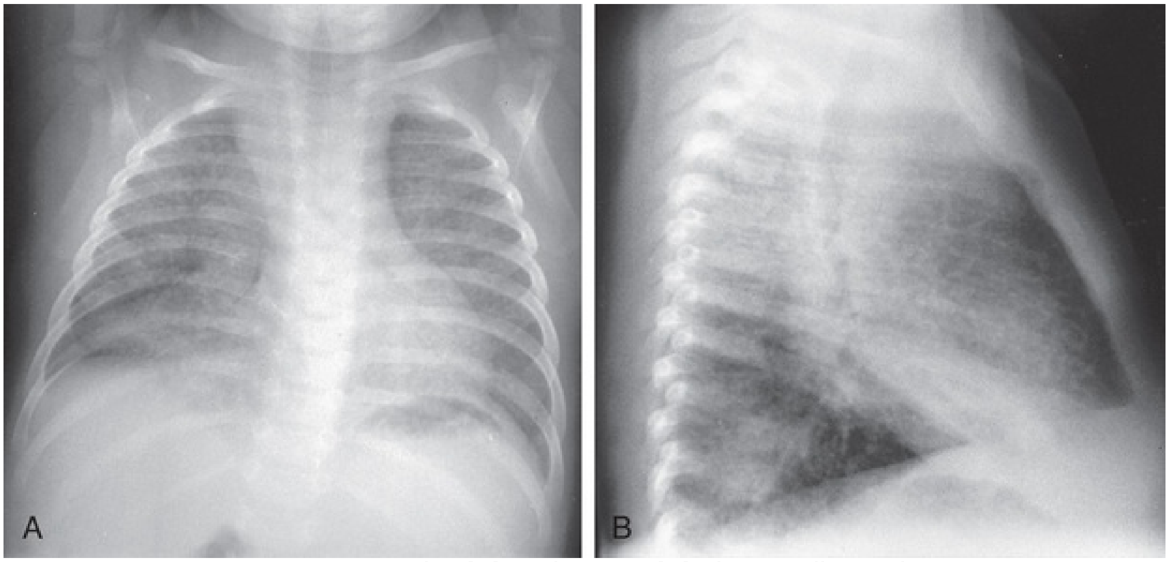

FIG. 242.11 Posteroanterior **(A)** and lateral **(B)** chest radiographs of an infant with miliary tuberculosis. The child's mother had failed to complete treatment for pulmonary tuberculosis twice within 3 yr of this child's birth.

The symptoms and physical signs of primary pulmonary tuberculosis in children are surprisingly meager considering the degree of radiographic changes often present. When active case finding is performed, up to 50% of infants and children with radiographically moderate to severe pulmonary tuberculosis have no physical findings. Infants are more likely to experience signs and symptoms. Nonproductive cough and mild dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. Some infants have difficulty gaining weight or develop a true failure-to-thrive syndrome that often does not improve significantly until several months of effective treatment have been taken. Pulmonary signs are even less common. Some infants and young children with bronchial obstruction have localized wheezing or decreased breath sounds that may be accompanied by tachypnea or, rarely, respiratory distress. These pulmonary symptoms and signs are occasionally alleviated by antibiotics, suggesting bacterial superinfection.

Progressive Primary Pulmonary Disease

A rare but serious complication of tuberculosis in a child occurs when the primary focus enlarges steadily and develops a large caseous center. Liquefaction can cause formation of a primary cavity associated with large numbers of tubercle bacilli. The enlarging focus can slough necrotic debris into the adjacent bronchus, leading to further intrapulmonary dissemination. Significant signs or symptoms are common in locally progressive disease in children. High fever, severe cough with sputum production, weight loss, and night sweats are common. Physical signs include diminished breath sounds, rales, and dullness or egophony over the cavity. The prognosis for full recovery is excellent with appropriate therapy.

Reactivation Tuberculosis

Pulmonary tuberculosis in adults usually represents endogenous reactivation of a site of TBI established previously in the body. This form of tuberculosis is rare in childhood but can occur in adolescence. Children with a healed TBI acquired when they were <2 yr old rarely develop chronic reactivation pulmonary disease, which is more common in those who acquire the initial infection when they are >7 yr old. The most common pulmonary sites are the original parenchymal focus, lymph nodes, or the apical seedings (**Simon foci**) established during the hematogenous phase of the early infection. This form of TB disease usually remains localized in the lungs, because the established immune response prevents further extrapulmonary spread. The most common radiographic findings are extensive infiltrates and thick-walled cavities in the upper lobes.

Older children and adolescents with reactivation tuberculosis are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis, and chest pain than children with primary pulmonary tuberculosis. However, physical examination findings usually are minor or absent, even when cavities or large infiltrates are present. Most signs and symptoms improve within several weeks of starting effective treatment, although the cough can last for several months. This form of tuberculosis may be highly contagious if there is significant sputum production and cough. The prognosis for full recovery is excellent with appropriate therapy.

Pleural Effusion

Tuberculous pleural effusions, which can be local or general, originate in the discharge of bacilli into the pleural space from a subpleural pulmonary focus or caseated lymph node. Asymptomatic local pleural effusion is so common in primary tuberculosis that it is considered as part of the primary complex. Larger and clinically significant effusions occur months to years after the primary infection. Tuberculous pleural effusion is uncommon in children <6 yr old and rare in children <2 yr old. Effusions are usually unilateral but can be bilateral. They are rarely associated with a segmental pulmonary lesion and are uncommon in disseminated tuberculosis. Often the radiographic abnormality is more extensive than would be suggested by physical findings or symptoms (Fig. 242.12).

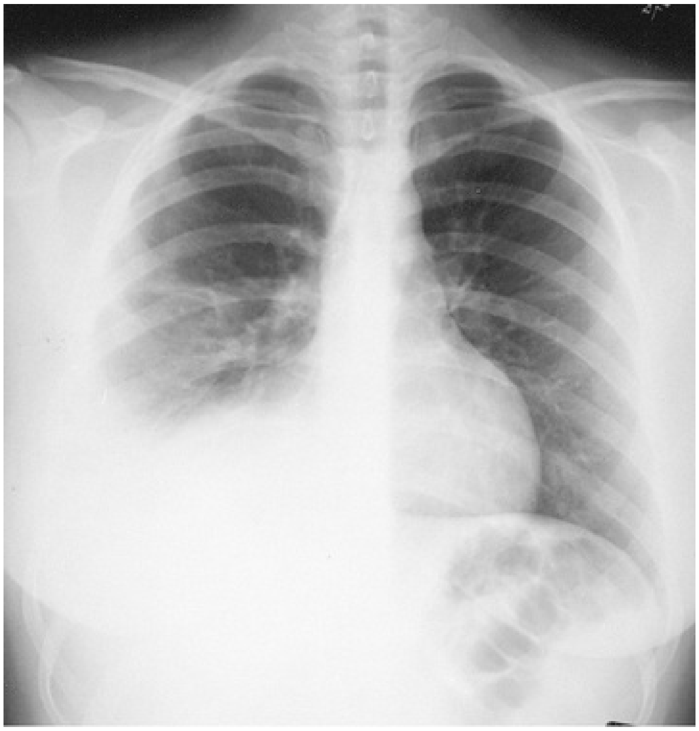

FIG. 242.12 Pleural tuberculosis in 16 yr old girl.

Clinical onset of tuberculous pleurisy is often sudden, characterized by low to high fever, shortness of breath, chest pain on deep inspiration, and diminished breath sounds. The fever and other symptoms can last for several weeks after the start of antituberculosis chemotherapy. The TST is positive in only 70–80% of cases. The prognosis is excellent, but radiographic resolution often takes months. Scoliosis is a rare complication from a long-standing effusion.

Examination of pleural fluid and the pleural membrane is important to establish the diagnosis of tuberculous **pleurisy** . The pleural fluid is usually yellow and only occasionally tinged with blood. The specific gravity is usually 1.012-1.025, the protein level is usually 2-4 g/dL, and the glucose concentration may be low, although it is usually in the low-normal range (20-40 mg/dL). Typically there are several hundred to several thousand white blood cells per microliter (WBCs/μL), with an early predominance of polymorphonuclear leukocytes (PMNs) followed by a high percentage of lymphocytes. Acid-fast smears of the pleural fluid are rarely positive. Cultures of the fluid are positive in <30% of cases. Measurement of adenosine deaminase (ADA) levels may enhance the diagnosis of pleural tuberculosis. Biopsy of the pleural membrane is more likely to yield a positive acid-fast stain or culture, and granuloma formation can be demonstrated.

Pericardial Disease

The most common form of cardiac tuberculosis is **pericarditis** . It is rare, occurring in 0.5–4% of TB cases in children. Pericarditis usually arises from direct invasion or lymphatic drainage from subcarinal lymph nodes. The presenting symptoms are nonspecific, including low-grade fever, malaise, and weight loss. Chest pain is unusual in children. A pericardial friction rub or distant heart sounds with pulsus paradoxus may be present. The pericardial fluid is typically serofibrinous or hemorrhagic. Acid-fast smear of the fluid rarely reveals the organism, but cultures are positive in 30–70% of cases. ADA levels are elevated in TB pericarditis. The culture yield from pericardial biopsy may be higher, and the presence of granulomas often suggests the diagnosis. Partial or complete pericardiectomy may be required when constrictive pericarditis develops.

Lymphohematogenous (Disseminated) Disease

Tubercle bacilli are disseminated to distant sites, including liver, spleen, skin, and lung apices, in all cases of TBI. Lymphohematogenous spread is usually asymptomatic. Rare patients experience protracted hematogenous tuberculosis caused by the intermittent release of tubercle bacilli as a caseous focus erodes through the wall of a blood vessel in the lung. The clinical picture subsequent to lymphohematogenous dissemination depends on the burden of organisms released from the primary focus to distant sites and the adequacy of the host's immune response. Although the clinical picture may be acute, more often it is indolent and prolonged, with spiking fever accompanying the release of organisms into the bloodstream. Multiple organ involvement is common, leading to hepatomegaly, splenomegaly, lymphadenitis in superficial or deep nodes, and papulonecrotic tuberculids appearing on the skin. Bones and joints or kidneys also can become involved. Meningitis occurs only late in the course of the disease. Early pulmonary involvement is surprisingly mild, but diffuse involvement becomes apparent with prolonged infection.

The most clinically significant form of disseminated tuberculosis is miliary disease, which occurs when massive numbers of tubercle bacilli are released into the bloodstream, causing disease in 2 or more organs. **Miliary tuberculosis** usually complicates the primary infection, occurring within 2-6 mo of the initial infection. Although this form of disease is most common in infants and young children, it is also found in adolescents and older adults, resulting from the breakdown of a previously healed primary pulmonary lesion. The clinical manifestations of miliary tuberculosis are protean, depending on the number of organisms that disseminate and where they lodge. Lesions are often larger and more numerous in the lungs, spleen, liver, and bone marrow than other tissues. Because this form of tuberculosis is most common in infants and malnourished or immunosuppressed patients, the host's immune incompetence likely plays a role in pathogenesis.

Rarely, the onset of miliary tuberculosis is explosive, and the patient can become gravely ill in several days. More often, the onset is insidious, with early systemic signs, including anorexia, weight loss, and low-grade fever. At this time, abnormal physical signs are usually absent. Generalized lymphadenopathy and hepatosplenomegaly develop within several weeks in approximately 50% of cases. The fever can then become higher and more sustained, although the chest radiograph usually is normal and respiratory symptoms are minor or absent.

Within several more weeks, the lungs can become filled with tubercles, and dyspnea, cough, rales, or wheezing occur. The lesions of miliary tuberculosis are usually <2-3 mm in diameter when first visible on chest radiograph (see Fig. 242.11). The smaller lesions coalesce to form larger lesions and sometimes extensive infiltrates. As the pulmonary disease progresses, an alveolar air block syndrome can result in frank respiratory distress, hypoxia, and pneumothorax, or pneumomediastinum. Signs or symptoms of meningitis or peritonitis are found in 20–40% of patients with advanced disease. Chronic or recurrent headache in a patient with miliary tuberculosis usually indicates the presence of meningitis, whereas the onset of abdominal pain or tenderness is a sign of tuberculous peritonitis. **Cutaneous lesions** include papulonecrotic tuberculids, nodules, or purpura. Choroid tubercles occur in 13–87% of patients and are highly specific for the diagnosis of miliary tuberculosis. Unfortunately, the TST is nonreactive in up to 40% of patients with disseminated tuberculosis.

Diagnosis of disseminated tuberculosis can be difficult, and a high index of suspicion by the clinician is required. Often the patient presents with fever of unknown origin. Early sputum or gastric aspirate cultures have a low sensitivity. Biopsy of the liver or bone marrow with appropriate bacteriologic and histologic examinations more often yields an early diagnosis. The most important clue is usually history of recent exposure to an adult with infectious tuberculosis.

The resolution of miliary tuberculosis is slow, even with proper therapy. Fever usually declines within 2-3 wk of starting chemotherapy, but the chest radiographic abnormalities might not resolve for many months. Occasionally, corticosteroids hasten symptomatic relief, especially when air block, peritonitis, or meningitis is present. The prognosis is excellent with early diagnosis and adequate chemotherapy.

Upper Respiratory Tract Disease

Tuberculosis of the upper respiratory tract is rare in developed countries but is still observed in developing countries. Children with laryngeal tuberculosis have a croup-like cough, sore throat, hoarseness, and dysphagia. Most children with laryngeal tuberculosis have extensive upper lobe pulmonary disease, but occasional patients have primary laryngeal disease with a normal chest radiograph. Tuberculosis of the middle ear results from aspiration of infected pulmonary secretions into the middle ear or from hematogenous dissemination in older children. The most common signs and symptoms are painless unilateral otorrhea, tinnitus, decreased hearing, facial paralysis, and a perforated tympanic membrane. Enlargement of lymph nodes in the preauricular or anterior cervical chains can accompany this infection. Diagnosis is difficult, because stains and cultures of ear fluid are often negative, and histology of the affected tissue often shows a nonspecific acute and chronic inflammation without granuloma formation.

Lymph Node Disease

Tuberculosis of the superficial lymph nodes, often referred to as **scrofula,** is the most common form of extrapulmonary tuberculosis in children (Figs. 242.13 to 242.15). Historically, scrofula was usually caused by drinking unpasteurized cow's milk laden with *M. bovis.* Most current cases occur within 6-9 mo of initial infection by *M. tuberculosis,* although some cases appear years later. The tonsillar, anterior cervical, submandibular, and supraclavicular nodes become involved secondary to extension of a primary lesion of the upper lung fields or abdomen. Infected nodes in the inguinal, epitrochlear, or axillary regions result from regional lymphadenitis associated with tuberculosis of the skin or skeletal system. The nodes usually enlarge gradually in the early stages of lymph node disease. They are discrete, nontender, and firm but not hard. The nodes often feel fixed to underlying or overlying tissue. Disease is most often **unilateral,** but bilateral involvement can occur because of the crossover drainage patterns of lymphatic vessels in the chest and lower neck. As infection progresses, multiple nodes are infected, resulting in a mass of matted nodes. Systemic signs and symptoms other than a low-grade fever are usually absent. The TST is usually reactive, but the chest radiograph is normal in 70% of cases. The onset of illness is occasionally more acute, with rapid enlargement, tenderness, and fluctuance of lymph nodes and with high fever. The initial presentation is rarely a fluctuant mass with overlying cellulitis or skin discoloration.

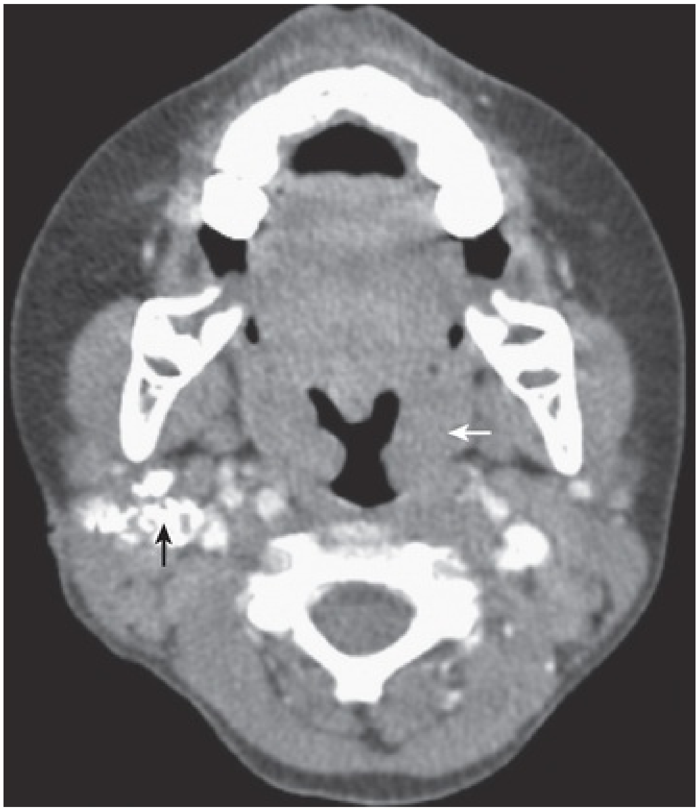

FIG. 242.13 Scrofula. Axial CT image of the neck in 8 yr old boy shows calcified right cervical lymphadenopathy *(black arrow)* with tonsillar swelling *(white arrow)* . (From Lighter J, Rigaud M: Diagnosing childhood tuberculosis: traditional and innovative modalities, *Curr Probl Pediatr Adolesc Health Care* 39:55–88, 2009.)

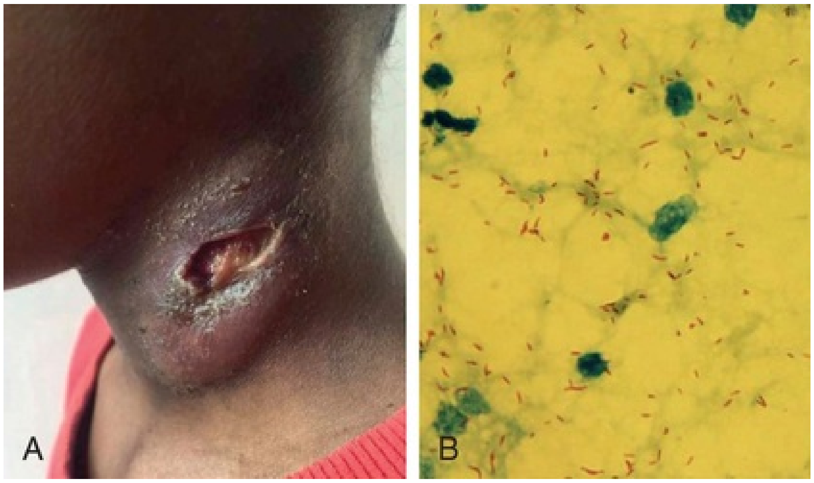

FIG. 242.14 Scrofula. A, Ulcerative lesion 3.2 × 2.1 cm with undermined edges and necrotic base with surrounding induration. B, Acid-fast bacilli. (From Sharawat IK: Scrofula, *J Pediatr* 189:236, 2017).

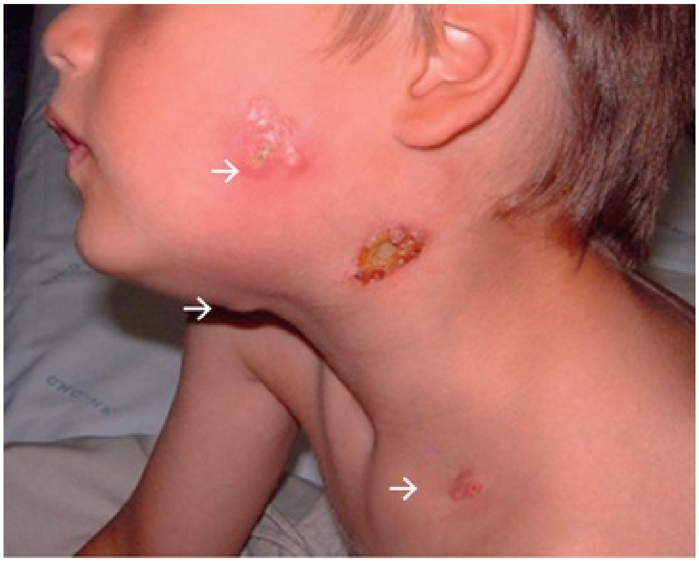

FIG. 242.15 **Scrofula. Tuberculous lymphadenitis with fistula in 4 yr old boy associated with scrofuloderma *(arrows)* . (From Pereira C, Cascais M, Felix M, Salgado M: Scrofula in a child, *J Pediatr* 189:235, 2017).**

Lymph node tuberculosis can resolve if left untreated but more often progresses to caseation and necrosis. The capsule of the node breaks down, resulting in the spread of infection to adjacent nodes. Rupture of the node usually results in a draining sinus tract that can require surgical removal. **Tuberculous lymphadenitis** can usually be diagnosed by fine-needle aspiration (FNA) of the node and responds well to antituberculosis therapy, although the lymph nodes do not return to normal size for months or even years. Surgical removal is not usually necessary and must be combined with antituberculosis medication, because the lymph node disease is only 1 part of a systemic infection.

A definitive diagnosis of tuberculous adenitis usually requires histologic or bacteriologic confirmation, which is best accomplished by FNA for culture, stain, and histology. If FNA is not successful in establishing a diagnosis, excisional biopsy of the involved node is indicated. Culture of lymph node tissue yields the organism in only approximately 50% of cases. Many other conditions can be confused with tuberculous adenitis, including infection caused by **nontuberculous mycobacteria (NTM)** , cat-scratch disease *(Bartonella henselae),* tularemia, brucellosis, toxoplasmosis, pyogenic infection, or noninfectious causes, including tumor, branchial cleft cyst, and cystic hygroma. The most common problem is distinguishing infection caused by *M. tuberculosis* from lymphadenitis caused by NTM in geographic areas where NTM are common. Both conditions are usually associated with a normal chest radiograph and a reactive TST. An important clue to the diagnosis of tuberculous adenitis is an epidemiologic link to an adult with infectious tuberculosis. In areas where both diseases are common, culture of the involved tissue may be necessary to establish the exact cause of the disease.

Central Nervous System Disease

Tuberculosis of the central nervous system (CNS) is the most serious complication in children and is fatal without prompt and appropriate treatment. **Tuberculous meningitis** usually arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops during the lymphohematogenous dissemination of the primary infection. This initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate infiltrates the corticomeningeal blood vessels, producing inflammation, obstruction, and subsequent infarction of cerebral cortex. The brainstem is often the site of greatest involvement, which accounts for the commonly associated dysfunction of cranial nerves III, VI, and VII. The exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular system at the level of the basilar cisterns, leading to a communicating hydrocephalus. The combination of vasculitis, infarction, cerebral edema, and hydrocephalus results in the severe damage that can occur gradually or rapidly. Profound abnormalities in electrolyte metabolism from salt wasting or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) also contribute to the pathophysiology of tuberculous meningitis.

Tuberculous meningitis complicates approximately 0.3% of untreated TBIs in children. It is most common in children 6 mo to 4 yr old. Occasionally, tuberculous meningitis occurs many years after the infection, when rupture of 1 or more of the subependymal tubercles discharges tubercle bacilli into the subarachnoid space. The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression tends to occur more often in infants and young children, who can experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema. More often, the signs and symptoms progress slowly over weeks and are divided into 3 stages.

The **1st stage** typically lasts 1-2 wk and is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal neurologic signs are absent, but infants can experience a stagnation or loss of developmental milestones. The **2nd stage** usually begins more abruptly. The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs. The accelerating clinical illness usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis. Some children have no evidence of meningeal irritation but can have signs of encephalitis, such as disorientation, movement disorders, or speech impairment. The **3rd stage** is marked by coma, hemi- or paraplegia, hypertension, decerebrate posturing, deterioration of vital signs, and eventually death.

The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in the 1st stage have an excellent outcome, whereas most patients in the 3rd stage who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus, or mental retardation. The prognosis for young infants is generally worse than for older children. *It is imperative that antituberculosis treatment be considered for any child who develops basilar meningitis and hydrocephalus, cranial nerve palsy, or stroke with no other apparent etiology.* Often the key to the correct diagnosis is identifying an adult who has infectious tuberculosis and is in contact with the child. Because of the short incubation period of tuberculous meningitis, the illness has not yet been diagnosed in the adult in many cases.

The diagnosis of tuberculous meningitis can be difficult early in its course, requiring a high degree of suspicion on the part of the clinician. The TST is nonreactive in up to 50% of cases, and 20–50% of children have a normal chest radiograph. The most important laboratory test for the diagnosis of tuberculous meningitis is examination and culture of the lumbar CSF. The CSF leukocyte count usually ranges from 10-500 cells/µL. PMNs may be present initially, but lymphocytes predominate in the majority of cases. The CSF glucose is typically <40 mg/dL but rarely <20 mg/dL. The protein level is elevated and may be extremely high (400-5,000 mg/dL) secondary to hydrocephalus and spinal block. Although the lumbar CSF is grossly abnormal, ventricular CSF can have normal chemistries and cell counts because this fluid is obtained from a site proximal to the inflammation and obstruction. During early stage 1, the CSF can resemble that of viral aseptic meningitis, only to progress to the more severe CSF profile over several weeks. The success of the microscopic examination of acid-fast–stained CSF and mycobacterial culture is related directly to the volume of the CSF sample. Examinations or culture of small amounts of CSF are unlikely to demonstrate *M. tuberculosis.* When 5-10 mL of lumbar CSF can be obtained, the acid-fast stain of the CSF sediment is positive in up to 30% of cases and the culture is positive in 50–70% of cases. Polymerase chain reaction (PCR) testing of the CSF and ADA levels can improve diagnosis. Cultures of other body fluids can help confirm the diagnosis.

Radiographic studies can aid in the diagnosis of tuberculous meningitis. CT or MRI of the brain of patients with tuberculous meningitis may be normal during early stages of the disease. As disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia are the most common findings (Fig. 242.16). Some small children with tuberculous meningitis have one or several clinically silent tuberculomas, occurring most often in the cerebral cortex or thalamic regions.

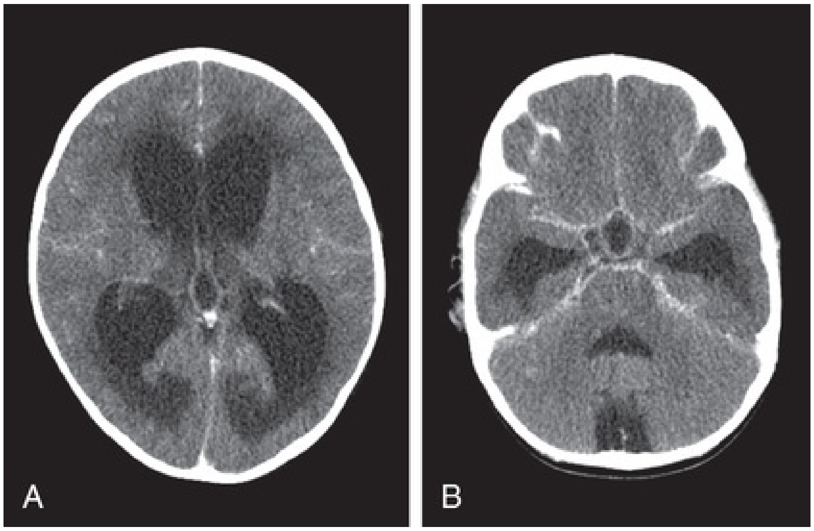

FIG. 242.16 **Tuberculous meningitis in a child. A and B, Postcontrast CT images demonstrate intense enhancement in the suprasellar cistern, sylvian cistern, and prepontine cistern. Dilation of the ventricular system is seen, consistent with associated hydrocephalus. (From Lerner A, Rajamohan A, Shiroishi MS, et al: Cerebral infections and inflammation. In Haaga JR, Boll DT, editors: *CT and MRI of the whole body,* ed 6, Philadelphia, 2017, Elsevier, Fig 10-20.)**

Another manifestation of CNS tuberculosis is the **tuberculoma,** a tumor-like mass resulting from aggregation of caseous tubercles that usually manifests clinically as a brain tumor. Tuberculomas account for up to 30% of brain tumors in some areas of the world but are rare in North America. In adults, tuberculomas are most often supratentorial, but in children they are often infratentorial, located at the base of the brain near the cerebellum (Fig. 242.17).

Lesions are most often singular but may be multiple. The most common symptoms are headache, fever, focal neurologic findings, and convulsions. The TST is usually reactive, but the chest radiograph is usually normal. Surgical excision is sometimes necessary to distinguish tuberculoma from other causes of brain tumor. However, surgical removal is not necessary because most tuberculomas resolve with medical management. Corticosteroids are usually administered during the 1st few wk of treatment or in the immediate postoperative period to decrease cerebral edema. On CT or MRI of the brain, tuberculomas usually appear as discrete lesions with a significant amount of surrounding edema. Contrast medium enhancement is often impressive and can result in a ringlike lesion. Since the advent of CT, the paradoxical development of tuberculomas in patients with tuberculous meningitis who are receiving ultimately effective chemotherapy has been recognized. The cause and nature of these tuberculomas are poorly understood, but they do not represent failure of antimicrobial treatment. This phenomenon should be considered whenever a child with tuberculous meningitis deteriorates or develops focal neurologic findings during treatment. Corticosteroids can alleviate the occasionally severe clinical signs and symptoms that occur. These lesions can persist for months or years.

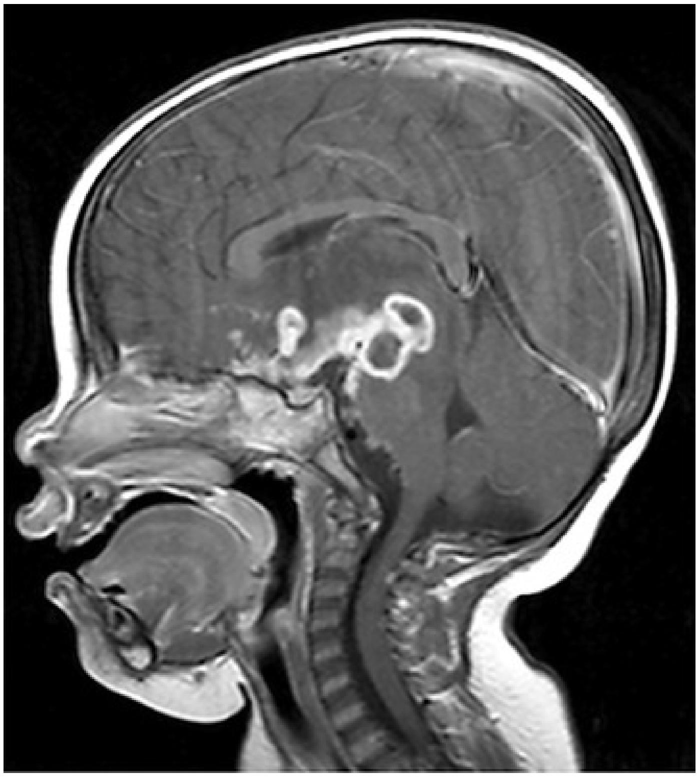

FIG. 242.17 MRI of brain of 3 yr old child showing multiple pontine tuberculomas.

Cutaneous Disease

Cutaneous tuberculosis is rare in the United States but occurs worldwide and accounts for 1–2% of tuberculosis (see Chapter 685).

Bone and Joint Disease

Bone and joint infection complicating tuberculosis is most likely to involve the vertebrae. The classic manifestation of **tuberculous spondylitis** is progression to **Pott disease** , in which destruction of the vertebral bodies leads to gibbus deformity and kyphosis (Fig. 242.18) (see Chapter 699.4). **Skeletal tuberculosis** is a late complication of tuberculosis and has become a rare entity since the availability of antituberculosis therapy, but is more likely to occur in children than in adults. Tuberculous bone lesions can resemble pyogenic and fungal infections or bone tumors. *Multifocal bone involvement can occur.* A bone biopsy is essential to confirm the diagnosis. Surgical intervention is generally not necessary for cure, and prognosis is excellent with adequate medical treatment. A sterile polyarticular (large joints) arthritis may also be noted in patients with active tuberculosis at another site.

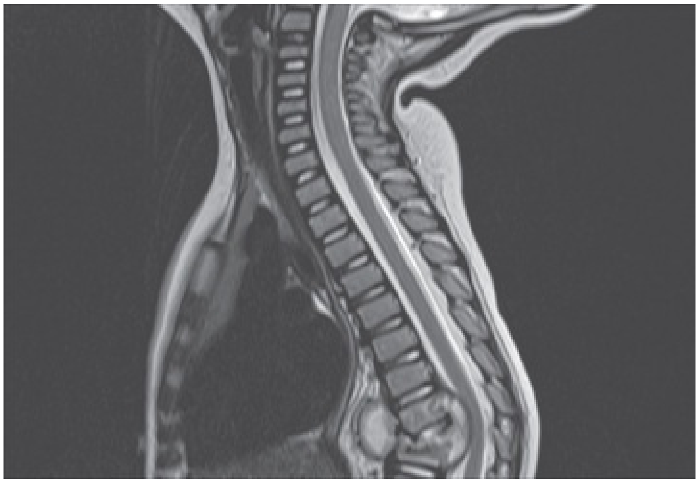

FIG. 242.18 Tuberculosis of the spine in a toddler. (From Feder Jr HM, Rigos L, Teti K: Pott's disease in a Connecticut toddler, *Lancet* 388:504–505, 2016).

Abdominal and Gastrointestinal Disease

Tuberculosis of the oral cavity or pharynx is quite unusual. The most common lesion is a painless ulcer on the mucosa, palate, or tonsil with enlargement of the regional lymph nodes. Tuberculosis of the parotid gland has been reported rarely in endemic countries. Tuberculosis of the esophagus is rare in children but may be associated with a tracheoesophageal fistula in infants. These forms of tuberculosis are usually associated with extensive pulmonary disease and swallowing of infectious respiratory secretions. They can occur in the absence of pulmonary disease, by spread from mediastinal or peritoneal lymph nodes.

Tuberculous peritonitis occurs most often in young men and is uncommon in adolescents and rare in children. Generalized peritonitis can arise from subclinical or miliary hematogenous dissemination. Localized peritonitis is caused by direct extension from an abdominal lymph node, intestinal focus, or genitourinary tuberculosis. Rarely, the lymph nodes, omentum, and peritoneum become matted and can be palpated as a doughy, irregular, nontender mass. Abdominal pain or tenderness, ascites, anorexia, and low-grade fever are typical manifestations. The TST is usually reactive. The diagnosis can be confirmed by paracentesis with appropriate stains and cultures, but this procedure must be performed carefully to avoid entering a bowel that is adherent to the omentum.

Tuberculous enteritis is caused by hematogenous dissemination or by swallowing tubercle bacilli discharged from the patient's own lungs. The jejunum and ileum near Peyer patches and the appendix are the most common sites of involvement. The typical findings are shallow ulcers that cause pain, diarrhea or constipation, weight loss, and low-grade fever. Mesenteric adenitis usually complicates the infection. The enlarged nodes can cause intestinal obstruction or erode through the omentum to cause generalized peritonitis. The clinical presentation of tuberculous enteritis is nonspecific, mimicking other infections and conditions that cause diarrhea. The disease should be suspected in any child with chronic GI complaints and a reactive TST or positive IGRA. Biopsy, acid-fast stain, and culture of the lesions are usually necessary to confirm the diagnosis.

Genitourinary Disease

Renal tuberculosis is rare in children, because the incubation period is several years or longer. Tubercle bacilli usually reach the kidney during lymphohematogenous dissemination. The organisms often can be recovered from the urine in cases of miliary tuberculosis and in some patients with pulmonary tuberculosis in the absence of renal parenchymal disease. In true renal tuberculosis, small caseous foci develop in the renal parenchyma and release *M. tuberculosis* into the tubules. A large mass develops near the renal cortex that discharges bacteria through a fistula into the renal pelvis. Infection then spreads locally to the ureters, prostate, or epididymis. Renal tuberculosis is often clinically silent in its early stages, marked only by sterile pyuria and microscopic hematuria. Dysuria, flank or abdominal pain, and gross hematuria develop as the disease progresses. Superinfection by other bacteria is common and can delay recognition of the underlying tuberculosis. Hydronephrosis or ureteral strictures can complicate the disease. Urine cultures for *M. tuberculosis* are positive in 80–90% of cases, and acid-fast stains of large volumes of urine sediment are positive in 50–70% of cases. The TST is nonreactive in up to 20% of patients. A pyelogram or CT scan often reveals mass lesions, dilation of the proximal ureters, multiple small filling defects, and hydronephrosis if ureteral stricture is present. Disease is most often unilateral.

Genital tract tuberculosis is uncommon in prepubescent boys and girls. This condition usually originates from lymphohematogenous spread, although it can be caused by direct spread from the intestinal tract or bone. Adolescent girls can develop genital tract tuberculosis during the primary infection. The fallopian tubes are most often involved (90–100% of cases), followed by the endometrium (50%), ovaries (25%), and cervix (5%). The most common symptoms are lower abdominal pain and dysmenorrhea or amenorrhea. Systemic manifestations are usually absent, and the chest radiograph is normal in the majority of cases. The TST is usually reactive. Genital tuberculosis in adolescent boys causes epididymitis or orchitis. The condition usually manifests as a painless, unilateral nodular swelling of the scrotum. Involvement of the glans penis is extremely rare. Genital abnormalities and a positive TST in an adolescent boy or girl suggest genital tract tuberculosis.

Pregnancy and the Newborn

Pulmonary and particularly extrapulmonary tuberculosis other than lymphadenitis in a pregnant woman is associated with increased risk for prematurity, fetal growth retardation, low birthweight, and perinatal mortality. **Congenital tuberculosis** is rare because the most common result of female genital tract tuberculosis is infertility. Primary infection in the mother just before or during pregnancy is more likely to cause congenital infection than is reactivation of a previous infection. Congenital transmission usually occurs from a lesion in the placenta through the umbilical vein, when tubercle bacilli infect the fetal liver, where a primary focus with periportal lymph node involvement can occur. Organisms pass through the liver into the main fetal circulation and infect many organs. The bacilli in the lung usually remain dormant until after birth, when oxygenation and pulmonary circulation increase significantly. Congenital tuberculosis can also be caused by aspiration or ingestion of infected amniotic fluid. However, the most common route of infection for the neonate is postnatal airborne transmission from an adult with infectious pulmonary tuberculosis.

Perinatal Disease

Symptoms of congenital tuberculosis may be present at birth but usually begin by the 2nd or 3rd wk of life. The most common signs and symptoms are respiratory distress, fever, hepatic or splenic enlargement, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, failure to thrive, ear drainage, and skin lesions. The clinical manifestations vary in relation to the site and size of the caseous lesions. Many infants have an abnormal chest radiograph, most often with a miliary pattern. Some infants with no pulmonary findings early in the course of the disease later develop profound radiographic and clinical abnormalities. Hilar and mediastinal lymphadenopathy and lung infiltrates are common. Generalized lymphadenopathy and meningitis occur in 30–50% of patients.

The clinical presentation of tuberculosis in newborns is similar to that caused by bacterial sepsis and other congenital infections, such as syphilis, toxoplasmosis, and cytomegalovirus. The diagnosis should be suspected in an infant with signs and symptoms of bacterial or congenital infection whose response to antibiotic and supportive therapy is poor and in whom evaluation for other infections is unrevealing. The most important clue for rapid diagnosis of congenital tuberculosis is a maternal or family **history** of tuberculosis. Often, the mother's disease is discovered only after the neonate's diagnosis is suspected. The infant's TST is negative initially but can become positive in 1-3 mo. A positive acid-fast stain of an early-morning gastric aspirate from a newborn usually indicates tuberculosis. Direct acid-fast stains on middle ear discharge, bone marrow, tracheal aspirate, or tissue biopsy (especially liver) can be useful. The CSF should be examined, cultured, and sent for PCR testing. The mortality rate of congenital tuberculosis remains very high because of delayed diagnosis. Many children have a complete recovery if the diagnosis is made promptly and adequate chemotherapy is started.

Disease in HIV-Infected Children

Most cases of tuberculosis in HIV-infected children are seen in developing countries. However, the rate of TB disease in untreated HIV-infected children is 30 times higher than in non–HIV-infected children in the United States. Establishing the diagnosis of tuberculosis in an HIV-infected child may be difficult, because TST reactivity can be absent (also with a negative IGRA), culture confirmation is difficult, and the clinical features of tuberculosis are similar to many other HIV-related infections and conditions. Tuberculosis in HIV-infected children is often more severe, progressive, and likely to occur in extrapulmonary sites. Radiographic findings are similar to those in children with normal immune systems, but lobar disease and lung cavitation are more common. Nonspecific respiratory symptoms, fever, and weight loss are the most common complaints. Rates of drug-resistant tuberculosis tend to be higher in HIV-infected adults and probably are also higher in HIV-infected children. Recurrent disease and relapse occur more frequently in HIV-infected children. The prognosis generally is good if TB disease is not far advanced at diagnosis and appropriate antituberculosis drugs are available.

The mortality rate of HIV-infected children with tuberculosis is high, especially as the CD4 lymphocyte numbers decrease. In adults the host immune response to TBI appears to enhance HIV replication and accelerate the immune suppression caused by HIV. Increased mortality rates are attributed to progressive HIV infection rather than tuberculosis. Therefore, HIV-infected children with potential exposures and/or recent infection should be promptly evaluated and treated for tuberculosis. Conversely, all children with TB disease should be tested for HIV infection.

Children with HIV infection who are given highly active antiretroviral therapy (HAART) are at high risk of developing **immune reconstitution inflammatory syndrome** . IRIS should be suspected in patients who experience a worsening of TB symptoms during antituberculosis therapy (*paradoxical* IRIS) or who develop new-onset TB symptoms and radiographic findings after initiation of HAART (*unmasking* IRIS). Factors suggesting IRIS are temporal association (within 3 mo of starting HAART), unusual clinical manifestations, unexpected clinical course, exclusion of alternative explanations, evidence of preceding immune restoration (rise in CD4 lymphocyte count), and decrease in HIV viral load. The most common clinical manifestations of IRIS in children are fever, cough, new skin lesions, enlarging lymph nodes in the thorax or neck, and appearance or enlargement of tuberculomas in the brain, with or without accompanying meningitis. The treatment of IRIS in HIV-positive children with tuberculosis should be undertaken by a clinician with specific expertise in TB treatment.

Diagnostic Tools

Tuberculin Skin Testing (TST)

The development of delayed-type hypersensitivity in most persons infected with the *M. tuberculosis* complex organisms makes the TST a useful diagnostic tool. The **Mantoux TST** is the intradermal injection of 0.1 mL purified protein derivative stabilized with Tween 80. T cells sensitized by prior infection are recruited to the skin, where they release lymphokines that induce induration through local vasodilation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area. The amount of induration in response to the test should be measured by a trained person 48-72 hr after administration. In some patients, the onset of induration is >72 hr after placement; this is also a positive result. Immediate hypersensitivity reactions to tuberculin or other constituents of the preparation are short-lived (<24 hr) and not considered a positive result. Tuberculin sensitivity develops 3 wk to 3 mo (most often in 4-8 wk) after inhalation of organisms.

Host-related factors, including very young age, malnutrition, immunosuppression by disease or drugs, viral infections (measles, mumps, varicella, influenza), vaccination with live-virus vaccines, and overwhelming tuberculosis, can depress the skin test reaction in a child infected with *M. tuberculosis*. Corticosteroid therapy can decrease the reaction to tuberculin, but the effect is variable; TST done at the time of initiating corticosteroid therapy is usually reliable. Approximately 10% of immunocompetent children with TB disease (up to 50% of those with meningitis or disseminated disease) do not react initially to purified protein derivative; most become reactive after several months of antituberculosis therapy. False-positive reactions to tuberculin can be caused by cross-sensitization to antigens of NTM, which generally are more prevalent in the environment as one approaches the equator. These cross-reactions are usually transient over months to years and produce <10-12 mm of induration, but larger areas of induration can occur. Previous vaccination with bacille Calmette-Guérin (BCG) also can cause a reaction to a TST, especially if a person has received 2 or more BCG vaccinations. Approximately 50% of the infants who receive a BCG vaccine never develop a reactive TST, and the reactivity usually wanes in 2-3 yr in those with initially positive skin test results. Older children and adults who receive a BCG vaccine are more likely to develop tuberculin reactivity, but most lose the reactivity by 5-10 yr after vaccination. However, some individuals maintain tuberculin reactivity from BCG vaccine for many years. When present, skin test reactivity usually causes <10 mm of induration, although larger reactions occur in some persons.

The appropriate size of induration indicating a positive Mantoux TST result varies with related epidemiologic and risk factors. In children with no TB risk factors, skin test reactions are usually false-positive results. The American Academy of Pediatrics (AAP) and CDC discourage routine testing of all children and recommend targeted tuberculin testing of children at risk identified through periodic screening questionnaires (Table 242.2). Possible exposure to an adult with or at high risk for infectious pulmonary tuberculosis is the most crucial risk factor for children. Reaction size limits for determining a positive TST result vary with the person's risk for infection (Table 242.3). In those at highest risk of progression to TB disease, TST sensitivity is most important, whereas specificity is more important for persons at low risk of progression.

Table 242.2

Tuberculin Skin Test (TST) or Interferon-γ Release Assay (IGRA): Recommendations for Infants, Children, and Adolescents[*]

CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED[†]
Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)
Children with radiographic or clinical findings suggesting tuberculosis disease
Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries from former Soviet Union), including international adoptees
Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries[‡]
Children who should have annual TST or IGRA: • Children infected with human immunodeficiency virus
CHILDREN AT INCREASED RISK FOR PROGRESSION OF TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE
Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies and children receiving tumor necrosis factor (TNF) antagonists deserve special consideration. Without recent exposure, these children are not at increased risk of acquiring tuberculosis infection. Underlying immune deficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered. **An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged corticosteroid administration, organ transplantation, or use of TNF-α antagonists or blockers, or immunosuppressive therapy in any child requiring these treatments.**

[*] Bacille Calmette-Guérin immunization is not a contraindication to a TST.

[†] Beginning as early as 3 mo of age.

[‡] If the child is well and has no history of exposure, the TST or IGRA should be delayed up to 10 wk after return.

From American Academy of Pediatrics: *Red book: 2018 report of the Committee on Infectious Diseases* , ed 30, Elk Grove Village, IL, 2015, AAP, p 831.

Table 242.3

Definitions of Positive Tuberculin Skin Test (TST) Results in Infants, Children, and Adolescents*

INDURATION ≥5 mm

Children in close contact with known or suspected contagious people with tuberculosis disease

Children suspected to have tuberculosis disease:

- Findings on chest radiograph consistent with active or previously tuberculosis disease
- Clinical evidence of tuberculosis disease †

Children receiving immunosuppressive therapy ‡ or with immunosuppressive conditions, including HIV infection

INDURATION ≥10 mm

Children at increased risk of disseminated tuberculosis disease:

- Children <4 yr old
- Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 242.2)

Children with increased exposure to tuberculosis disease:

- Children born in high-prevalence regions of the world
- Children often exposed to adults with HIV infection, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers
- Children who travel to high-prevalence regions of the world

INDURATION ≥15 mm

Children ≥4 yr old without any risk factors

* These definitions apply regardless of previous BCG immunization; erythema at TST site does not indicate a positive test result. Tests should be read at 48-72 hr after placement.

† Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (e.g., meningitis).

‡ Including immunosuppressive doses of corticosteroids or tumor necrosis factor-α antagonists.

BCG, Bacille Calmette-Guérin; HIV, human immunodeficiency virus.

From American Academy of Pediatrics: *Red book: 2015 report of the Committee on Infectious Diseases* , ed 30, Elk Grove Village, IL, 2018, American Academy of Pediatrics, p 830.

Interferon-γ Release Assay (IGRA)

Two blood tests—T-SPOT.*TB* (Oxford Immunotec; Marlborough, MA) and QuantiFERON-TB (QFT, Qiagen; Germantown, MD) detect IFN-γ generation by the patient's T cells in response to specific *M. tuberculosis* antigens (ESAT-6, CFP-10, and TB7.7). The QFT test measures whole blood concentrations of IFN-γ, and the T-SPOT.*TB* test measures the number of lymphocytes/monocytes producing IFN-γ. The test antigens are not present on *M. bovis* –BCG and *Mycobacterium avium* complex, the major group of environmental mycobacteria, so one would expect higher specificity compared with the TST and fewer false-positive results. Both IGRAs have internal positive and negative controls. Internal positive controls allows for detection of an anergic test response, which is useful in children who are young and immunocompromised. Indeterminate (QFT)/invalid (T-SPOT.*TB*) responses occur when the test sample is negative but the positive control has insufficient activity or if the negative control has high background activity. Indeterminate/invalid results are also caused by technical factors (e.g., insufficient shaking of QFT tubes, delayed processing time). Most studies report indeterminate or invalid rates in children of 0–10%, which is influenced by a child's age and immune status. In children <2 yr old, indeterminate rates can be as high as 8.1%, vs 2.7% in older children, although more recent studies generally report much lower rates. *An indeterminate or invalid IGRA result is neither negative nor positive and cannot be used to guide treatment decisions.*

As with the TST, IGRAs cannot differentiate between TBI and TB disease. Two clear advantages of the IGRAs are the need for only one patient encounter (vs two with TST) and the lack of cross-reaction with BCG vaccination and most other mycobacteria, thereby increasing test specificity for TBI. Studies comparing IGRA and TST performance in children have shown comparable sensitivity (85% in culture-confirmed children) between the 2 tests, and superior IGRA specificity (95% vs 49%) in BCG-immunized, low-risk children.

Neither the TST nor the IGRAs perform well in infants and young children who are malnourished, severely immunocompromised, or have disseminated TB disease. Studies have evaluated the use of IGRAs in young children and support their use in children 2-5 yr old. Among immunocompetent children 0-5 yr old with culture-confirmed TB disease, 60% of those <2 yr old had a positive QFT compared to 100% of children 2-5 yr old, rates comparable to the TST.

Additional studies among healthy, exposed children <5 yr old have demonstrated that IGRA and TST agreement reaches 89%, and that IGRA test performance was confirmed to be adequate in children 2-5 yr old. Therefore, most experts support the use of IGRAs for the evaluation of TBI in young children at low risk of infection, especially in those who have received a BCG vaccine. IGRAs are also preferred in children who are unlikely to return for TST. *The use of both TST and IGRA should be considered in children whose initial TST or IGRA testing is negative and who are highly suspect for TB disease or risk of progression from infection to disease,* as well as in those with an indeterminate initial and repeat IGRA testing; those ≥2 yr old who have a positive TST and have received the BCG vaccine; those whose family is reluctant to treat infection based on a TST result alone; and those in whom nontuberculous mycobacterial disease is suspected (Table 242.4). Most studies have shown no consistent, significant difference between the 2 commercially available IGRAs, and the CDC recommends no preference. Because of cost constraints, WHO does not indorse IGRA use in low- and middle-income countries, even in those with a high prevalence of tuberculosis.

Table 242.4

Recommendations for Use of Tuberculin Skin Test (TST) and Interferon-γ Release Assay (IGRA) in Children

TST preferred, IGRA acceptable

- Children <2 yr of age[*]

IGRA preferred, TST acceptable

- Children >2 yr of age who have received BCG vaccine
- Children >2 yr of age who are unlikely to return for TST reading

TST *and* IGRA should be considered when:

The initial and repeat IGRAs are indeterminate or invalid.

The initial test (TST or IGRA) is *negative*, and:

- Clinical suspicion for TB disease is moderate to high. [†]
- The child has TB risk factor and is at high risk of progression and poor outcome (especially therapy with immunomodulating biologic agent, e.g., TNF-α antagonist). [†]

The initial TST is *positive* and:

- >2 yr old and history of BCG vaccination.
- Additional evidence needed to increase adherence with therapy.

[*] Some experts do not use an IGRA for children younger than 2 yr because of a relative lack of data for this age-group and the high risk of progression to disease.

[†] Positive result of either test is considered significant in these groups.

BCG, Bacille Calmette-Guérin; TB, tuberculosis, TNF, tumor necrosis factor.

Adapted from Starke JR, AAP Committee of Infectious Diseases: Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children, *Pediatrics* 134(6):e1771, 2014.

Mycobacterial Sampling, Susceptibility and Culture

The most specific confirmation of pulmonary tuberculosis is isolation of *M. tuberculosis* from a clinical sample. Sputum specimens for culture should be collected from adolescents and older children who are able to expectorate. Induced sputum with a jet nebulizer, inhaled saline, and chest percussion followed by nasopharyngeal suctioning is effective in children as young as 1 yr. Sputum induction provides samples for both culture and acid-fast bacilli staining. The traditional culture specimen in young children is the early-morning gastric acid obtained before the child has arisen and peristalsis has emptied the stomach of the pooled respiratory secretions that have been swallowed overnight. However, even under optimal conditions, 3 consecutive morning gastric aspirates yield the organisms in <50% of cases. The culture yield from bronchoscopy is even lower, but this procedure can demonstrate the presence of endobronchial disease or a fistula. *Negative cultures never exclude the diagnosis of tuberculosis in a child.* The presence of a positive TST or IGRA, an abnormal chest radiograph consistent with tuberculosis, and history of recent exposure to an adult with infectious tuberculosis is highly suggestive of the clinical diagnosis of TB disease. If a likely adult source case has been identified, drug susceptibility test results of the isolate from the adult source usually can be used to determine the best therapeutic regimen for the child, except in very high incidence areas, where the apparent source case might not be the actual one. Cultures should be always obtained from the child whenever the source case is unknown, there are multiple possible source cases, or the source case has possible or confirmed drug-resistant tuberculosis.

Confirmation of extrapulmonary tuberculosis is best achieved with a positive culture. However, for many forms of tuberculosis, the culture yield is only 25–50%, and probable diagnosis is by a combination of clinical signs and symptoms, analysis of body fluids when possible, radiographic or histopathologic evidence of tuberculosis, and elimination of other possible diagnoses.

Nucleic Acid Amplification Tests

The main nucleic acid amplification test (NAAT) studied in children with tuberculosis is PCR, which uses specific DNA sequences as markers for microorganisms. Compared with a clinical diagnosis of pulmonary tuberculosis in children, the sensitivity of PCR has varied from 25–83%, and specificity has varied from 80–100%. A negative PCR result never eliminates the diagnosis of tuberculosis, and the diagnosis is not confirmed by a positive PCR result.

Gene Xpert MTB/RIF (Xpert; Cepheid, Sunnyvale, CA) is a real-time PCR assay for *M. tuberculosis* that simultaneously detects **rifampin resistance** , which is often used as a proxy for MDR tuberculosis. This assay uses a self-contained cartridge system, which yields results from direct specimens in 2 hr and is less operator dependent than traditional PCR detection methods.

Sensitivity and specificity of Xpert have averaged 72–77% and 99% in acid-fast bacilli (AFB) sputum smear–negative adults and 98–99% and 99–100% in AFB sputum smear–positive adults, respectively. Pediatric studies reveal that, compared to culture, the sensitivity and specificity of Xpert is 62% and 98% on induced or expectorated sputa and 66% and 98% on gastric aspirates, respectively. Compared with smear microscopy, Xpert improved the sensitivity of detecting pediatric TB cases by 36–44%. Xpert's sensitivity and specificity to detect rifampin resistance in sputum samples from adults with tuberculosis was 86% and 98%, respectively. Although cartridges for the Xpert system are expensive, it offers advantages in rapid detection of MDR-TB and is especially useful in settings lacking laboratory infrastructure. In low-resource settings, Xpert may replace smear microscopy; however, it should never replace mycobacterial cultures and drug susceptibility studies.

Treatment

The basic principles of management of TB disease in children and adolescents are the same as in adults. Several drugs are used to affect a relatively rapid cure and prevent the emergence of secondary drug resistance during therapy (Tables 242.5 and 242.6). The choice of regimen depends on the extent of TB disease, the host, and the likelihood of drug resistance (see Chapter 241 , Table 241.1). As recommended by WHO and AAP, *the standard therapy of intrathoracic tuberculosis (pulmonary disease and/or hilar lymphadenopathy) in children is a 6 mo regimen of isoniazid and rifampin supplemented in the 1st 2 mo of treatment by pyrazinamide and ethambutol.* Several clinical trials have shown that this regimen yields a success rate approaching 100%, with an incidence of clinically significant adverse reactions of <2%. Nine-month regimens of only isoniazid and rifampin are also effective for drug-susceptible tuberculosis, but the necessary length of treatment, the need for good adherence by the patient, and the relative lack of protection against possible initial drug resistance have led to the favoring of treatment regimens with additional drugs for a short period. Most experts recommend that all drug administration be directly observed, meaning that a healthcare worker watches when the medications are administered to the patients. When **directly observed therapy (DOT)** is used, intermittent (twice or thrice weekly) administration of drugs after an initial period as short as 2 wk of daily therapy is as effective for drug-susceptible tuberculosis in children as daily therapy for the entire course.

Table 242.5

Commonly Used Drugs for Treatment of Tuberculosis in Infants, Children, and Adolescents

DRUG	DOSAGE FORMS	DAILY DOSAGE (mg/kg)	TWICE-WEEKLY DOSAGE (mg/kg/dose)	MAXIMUM DOSE	ADVERSE REACTIONS
Ethambutol	Tablets: 100 mg 400 mg	20	50	2.5 g	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Isoniazid*	Scored tablets: 100 mg 300 mg Syrup: 10 mg/mL	10-15 †	20-30	Daily: 300 mg Twice weekly: 900 mg	Mild hepatic enzyme elevation, hepatitis, † peripheral neuritis, hypersensitivity
Pyrazinamide*	Scored tablets: 500 mg	30-40	50	2 g	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset
Rifampin*	Capsules: 150 mg 300 mg Syrup formulated from capsules	15-20	15-20	600 mg	Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus Oral contraceptives may be ineffective.

* Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (i.e., person weighing >50 kg) daily doses of each drug. Rifater, in the United States, is a capsule containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Isoniazid and rifampin also are available for parenteral administration. Many experts recommend using a daily rifampin dose of 20–30 mg/kg/day for infants and toddlers and for serious forms of tuberculosis such as meningitis and disseminated disease.

† When isoniazid in a dosage exceeding 10 mg/kg/day is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

From American Academy of Pediatrics: *Red book: 2018 report of the Committee on Infectious Diseases* , ed 30, Elk Grove Village, IL, 2015, AAP, p 842.

Table 242.6

Less Commonly Used Drugs for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents*

DRUGS	DOSAGE, FORMS	DAILY DOSAGE (mg/kg)	MAXIMUM DOSE	ADVERSE REACTIONS
	Vials: 500	15-30 (IV or IM	1 g	Auditory and vestibular toxic

Amikacin †	mg, 1 g	administration)		effects, nephrotoxic effects
Bedaquiline	Tablets: 100 mg	Adults and children ≥12 yr, >33 kg: 400 mg for 14 days, then 200 mg 3 times weekly for 22 wk		QTc prolongation, reduced levels with efavirenz co-administration
Capreomycin †	Vials: 1 g	15-30 (IM administration)	1 g	Auditory and vestibular toxicity and nephrotoxic effects
Clofazimine	Gelcaps: 50 mg 100 mg	2-3 mg/kg per day	100 mg	QTc prolongation, reversible skin pigmentation
Cycloserine	Capsules: 250 mg	10-20, given in 2 divided doses	1 g	Psychosis, personality changes, seizures, rash
Delamanid	Tablets: 50 mg 100 mg	Adults and children ≥13 yr, ≥35 kg: 100 mg twice daily Children 6-12 yr, 20-34 kg: 50 mg twice daily		QTc prolongation, adverse events with hypoalbuminemia, avoid if metronidazole allergic
Ethionamide	Tablets: 250 mg	15-20, given in 2-3 divided doses	1 g	GI tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism
Kanamycin	Vials: 75 mg/2 mL 500 mg/2 mL 1 g/3 mL	15-30 (IM or IV administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Levofloxacin	Tablets: 250 mg 500 mg 750 mg Oral solution: 25/mL Vials: 25 mg/mL	Adults: 750-1000 mg (daily) Children: 15-20 mg/kg daily	1 g	Theoretic effect on growing cartilage, joint pain, GI tract disturbances, rash, headache, restlessness, confusion
Linezolid	Tablets: 400 mg 600 mg Syrup: 20 mg/mL	Children ≥12 yr: 10 mg/kg daily Children <12 yr: 10 mg/kg twice daily	600 mg	Bone marrow suppression, peripheral neuropathy, lactic acidosis, potential overlapping toxicity with nucleoside reverse transcriptase inhibitors
Ofloxacin	Tablets: 200 mg 300 mg 400 mg Vials: 20 mg/mL 40 mg/mL	Adults/adolescents: 800 mg Children 15-20 mg/kg daily	800 mg	Arthropathy, arthritis

Moxifloxacin	Tablets: 400 mg IV solution: 400 mg/250 mL in 0.8% saline	Adults/adolescents: 400 mg Children: 7.5-10 mg/kg daily	400 mg	Arthropathy, arthritis
Paraaminosalicylic acid (PAS)	Packets: 3 g	200-300 (2-4 times a day)	10 g	GI tract disturbances, hypersensitivity, hepatotoxic effects
Streptomycin [†]	Vials: 1 g 4 g	20-40 (IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects, rash

[*] These drugs should be used in consultation with a specialist in tuberculosis.

[†] Dose adjustment in renal insufficiency.

GI, Gastrointestinal; IM, intramuscular; IV, intravenous.

From American Academy of Pediatrics: *Red book: 2018 Report of the Committee on Infectious Diseases* , ed 30. Elk Grove Village, IL, 2015, AAP, p 843–844; and Harausz EP, Garcia-Prats AJ, Seddon JA, et al: New/repurposed drugs for pediatric multidrug-resistant tuberculosis: practice-based recommendations, *Am J Respir Crit Care Med* 195(10):1300-1310, 2017.

Extrapulmonary tuberculosis is usually caused by small numbers of mycobacteria. In general, the treatment for most forms of extrapulmonary tuberculosis in children, including cervical lymphadenopathy, is the same as for pulmonary tuberculosis. *Exceptions are bone and joint, disseminated, and CNS tuberculosis, for which there are inadequate data to recommend 6 mo of therapy; these conditions are treated for 9-12 mo.* Surgical debridement in bone and joint disease and ventriculoperitoneal shunting in CNS disease may be necessary adjuncts to medical therapy.

The optimal treatment of tuberculosis in HIV-infected children has not been established. HIV-seropositive adults with tuberculosis can be treated successfully with standard regimens that include isoniazid, rifampin, pyrazinamide, and ethambutol. The total duration of therapy should be 6-9 mo, or 6 mo after culture of sputum becomes sterile, whichever is longer. Data for children are limited to relatively small series. *Most experts believe that HIV-infected children with drug-susceptible tuberculosis should receive the standard 4-drug regimen for the 1st 2 mo followed by isoniazid and rifampin, for a total duration of at least 9 mo. However, all treatment should be daily, not intermittent.* Children with HIV infection appear to have more frequent adverse reactions to antituberculosis drugs and must be monitored closely during therapy. Co-administration of rifampin and some antiretroviral agents results in subtherapeutic blood levels of protease inhibitors and nonnucleoside reverse transcriptase inhibitors and toxic levels of rifampin. Concomitant administration of these drugs is not recommended. Treatment of HIV-infected children is often empirically based on epidemiologic and radiographic information, because the radiographic appearance of other pulmonary complications of HIV in children, such as lymphoid interstitial pneumonitis and bacterial pneumonia, may be similar to that of tuberculosis. Therapy should be considered when tuberculosis cannot be excluded.

Drug-Resistant Tuberculosis

The incidence of drug-resistant tuberculosis is increasing in many areas of the world, including North America. There are 2 major types of drug resistance. **Primary resistance** occurs when a person is infected with *M. tuberculosis* that is already resistant to a particular drug. **Secondary resistance** occurs when drug-resistant organisms emerge as the dominant population during treatment. The major causes of secondary drug resistance are poor adherence to the medication by the patient or inadequate treatment regimens prescribed by the physician. Nonadherence to one drug is more likely to lead to secondary resistance than is failure to take all drugs. Secondary resistance is rare in children because of the small size of their mycobacterial population. Consequently, most drug resistance in children is primary, and patterns of drug resistance among children tend to mirror those found among adults in the same population. The main predictors of drug-resistant tuberculosis among adults are history of previous antituberculosis treatment, co-infection with HIV, and exposure to another adult with infectious drug-resistant tuberculosis.

Treatment of drug-resistant tuberculosis is successful only when at least 2 bactericidal drugs are given to which the infecting strain of M. tuberculosis *is susceptible*. When a child has possible drug-resistant tuberculosis, usually at least 4 or 5 drugs should be administered initially until the susceptibility pattern is determined and a more-specific regimen can be designed. The specific treatment plan must be individualized for each patient according to the results of susceptibility testing on the isolates from the child or the adult source case. *Treatment duration of 9 mo with rifampin, pyrazinamide, and ethambutol is usually adequate for isoniazid-resistant tuberculosis in children. When resistance to isoniazid and rifampin is present, the total duration of therapy often must be extended to 12-24 mo, and intermittent regimens should not be used*. In

2016, WHO endorsed 9-12 mo shorter treatment regimen for adults and children with MDR-TB who were not previously treated with second-line drugs, or in whom resistance to second-line fluoroquinolones or injectable agents is unlikely. This recommendation was based the results of adult observational studies and extrapolated for use in children based on biologic plausibility.

As second-line treatment options for MDR-TB in children, there is increasing use of new antituberculosis medications (bedaquiline and delamanid) and repurposed drugs (linezolid and clofazimine). **Delamanid** is endorsed for use in children ≥6 years and ≥20 kg in whom a 4-drug regimen plus pyrazinamide cannot be used because of drug resistance, in those who experience significant drug intolerance, or those at high risk of treatment failure. There is less evidence to support the use of **bedaquiline** in children. It is considered acceptable in children ≥12 yr old and >33 kg, with the same indications specified for delamanid. A baseline electrocardiogram and QTc monitoring is recommended in patients receiving bedaquiline or delamanid. Both **linezolid** and **clofazimine** are now included as core second-line agents in treatment regimens for children with MDR-TB. Both drugs require close monitoring for adverse effects and toxicity. The prognosis of single-drug–resistant or MDR tuberculosis in children is usually good if the drug resistance is identified early in the treatment, if appropriate drugs are administered under DOT, if adverse reactions from the drugs are minor, and if the child and family are in a supportive environment. The treatment of drug-resistant tuberculosis in children always should be undertaken by a clinician with specific expertise in TB treatment.

Corticosteroids

Corticosteroids are useful in treating some children with TB disease. They are most beneficial when the host inflammatory reaction contributes significantly to tissue damage or impairment of organ function. There is convincing evidence that corticosteroids decrease mortality rates and long-term neurologic sequelae in some patients with **tuberculous meningitis** by reducing vasculitis, inflammation, and ultimately intracranial pressure. Lowering the intracranial pressure limits tissue damage and favors circulation of antituberculosis drugs through the brain and meninges. Short courses of corticosteroids also may be effective for children with **endobronchial tuberculosis** that causes respiratory distress, localized emphysema, or segmental pulmonary lesions. Several randomized clinical trials have shown that corticosteroids can help relieve symptoms and constriction associated with acute tuberculous **pericardial effusion.** Corticosteroids can cause dramatic improvement in symptoms in some patients with tuberculous pleural effusion and shift of the mediastinum. However, the long-term course of disease is probably unaffected. Some children with severe **miliary tuberculosis** have dramatic improvement with corticosteroid therapy if the inflammatory reaction is so severe that alveolocapillary block is present. There is no convincing evidence to support a specific corticosteroid preparation. The most common regimen is **prednisone** , 1-2 mg/kg/day in 1-2 divided doses orally for 4-6 wk, followed by a taper.

Supportive Care

Children receiving treatment should be followed carefully to promote **adherence** to therapy, to monitor for toxic reactions to medications, and to ensure that the tuberculosis is being adequately treated. Adequate **nutrition** is important. Patients should be seen at monthly intervals and should be given just enough medication to last until the next visit. **Anticipatory guidance** with regard to the administration of medications to children is crucial. The physician should foresee difficulties that the family might have in introducing several new medications in inconvenient dosage forms to a young child. The clinician must report all cases of suspected tuberculosis in a child to the local health department to be sure that the child and family receive appropriate care and evaluation.

Nonadherence to treatment is the major problem in TB therapy. The patient and family must know what is expected of them through verbal and written instructions in their primary language. Approximately 30–50% of patients taking long-term treatment are significantly nonadherent with self-administered medications, and clinicians are usually not able to determine in advance which patients will be nonadherent. Preferably, DOT should be instituted by the local health department.

Mycobacterium tuberculosis Infection

The following aspects of the natural history and treatment of TBI, often referred to as *latent tuberculosis infection*, in children must be considered in the formulation of recommendations about therapy: (1) infants and children <5 yr old with TBI have been infected recently; (2) the risk for progression to disease is high; (3) untreated infants with TBI have up to a 40% chance of development of TB disease; (4) the risk for progression decreases gradually through childhood, until adolescence when the risk increases; (5) infants and young children are more likely to have life-threatening forms of tuberculosis, including meningitis and disseminated disease; and (6) children with TBI have more years at risk for development of disease than adults. Because of these factors, and the excellent safety profile of isoniazid, rifampin, and rifapentine in children, there is a tendency to err on the side of overtreatment in infants, young children, and adolescents.

The main TBI treatment regimens used in children include 6-9 mo of **isoniazid** (daily, or twice weekly by DOT), 3 mo of daily **rifampin** and isoniazid, 4-6 mo of daily rifampin, and once-weekly isoniazid and **rifapentine** , for 12 total doses. Isoniazid therapy for TBI appears to be more effective for children than adults, with several large clinical trials demonstrating risk reduction of 70–90%. The risk of isoniazid-related hepatitis is minimal in infants, children, and adolescents, who tolerate the drug better than adults.

Analysis of data from several studies demonstrates that the efficacy decreased significantly if isoniazid was taken for <9 mo. However, the international standard is 6 mo of treatment with isoniazid because of resource considerations. Isoniazid given twice weekly has been used extensively to treat TBI in children, especially schoolchildren and close contacts of case patients. DOT should be considered when it is unlikely that the child and family will adhere to daily self-administration, or if the child is at increased risk for rapid development of disease (newborns and infants, recent contacts, immunocompromised children). For healthy children taking isoniazid but no other potentially hepatotoxic drugs, routine biochemical monitoring and supplementation with pyridoxine are not necessary. A 3 mo daily regimen of rifampin and isoniazid has been used in Europe, with programmatic data suggesting that the regimen is effective, but this regimen is not recommended in the United States. Rifampin alone for 4-6 mo is now frequently used for the treatment of TBI in infants, children, and adolescents. This regimen is most often used when a shorter, self-administered treatment regimen is preferred, when isoniazid cannot be tolerated, or the child has had contact with a source case infected with an isoniazid-resistant but rifamycin-susceptible organism. Rifapentine is a rifamycin with a very long half-life, allowing for weekly administration in conjunction with isoniazid. Studies have demonstrated that 12 doses of once-weekly isoniazid and rifapentine are as effective for treating TBI and as safe as 9 mo of daily isoniazid in children as young as 2 yr. This is becoming the preferred regimen for the treatment of TBI in age-eligible children who are exposed to a contact with presumed pan-susceptible TB. Given the risk of selecting for drug-resistant isolates by missing intermittent doses of rifamycins, this treatment regimen currently is recommended only with DOT under the supervision of local health departments. Studies have revealed that the shorter treatment regimens for TBI in children are equally efficacious as 9 mo of isoniazid and are associated with superior treatment completion rates.

For children with MDR-TB, the regimen will depend on the drug-susceptibility profile of the contract case's organism; an expert in tuberculosis should be consulted.

Few controlled studies have been published regarding the efficacy of any form of treatment for TBI in HIV-infected children. A 9 mo course of daily isoniazid is recommended. Most experts recommend that routine monitoring of serum hepatic enzyme concentrations be performed and pyridoxine be given when HIV-infected children are treated with isoniazid. The optimal duration of rifampin therapy in HIV-infected children with TBI is not known, but many experts recommend at least a 6 mo course.

Isoniazid should be given to children <5 yr old who have a negative TST or IGRA result but who have a known recent exposure to an adult with potentially contagious TB disease. This practice is often referred to as **window prophylaxis** . By the time delayed hypersensitivity develops (2-3 mo), an untreated child already may have developed severe tuberculosis. For these children, tuberculin skin or IGRA testing is repeated 8-10 wk after contact with the source case for tuberculosis has been broken (*broken contact* is defined as physical separation or adequate initial treatment of the source case). If the 2nd test result is positive, the child should complete a treatment course for TBI (either 9 mo of INH or one of the shorter treatment options). If a new TBI treatment course is started (either 4 mo of rifampin or 12 weekly doses of isoniazid and rifapentine), the treatment start date is day one of the new regimen. If the 2nd test result is negative, TBI treatment can be stopped.

Prevention

The highest priority of any TB control program should be case finding and treatment, which interrupts transmission of infection between close contacts. All children and adults with symptoms suggestive of TB disease and those in close contact with an adult with suspected infectious pulmonary tuberculosis should be tested for TBI (by TST or IGRA) and examined as soon as possible. On average, 30–50% of household contacts to infectious cases are infected, and 1% of contacts already have overt disease. This scheme relies on effective and adequate public health response and resources. Children, particularly young infants, should receive high priority during contact investigations, because their risk for infection is high, and they are more likely to rapidly develop severe forms of tuberculosis.

Mass testing of large groups of children for TBI is an inefficient process. When large groups of children at low risk for tuberculosis are tested, the vast majority of TST reactions are actually false-positive reactions because of biologic variability or cross-sensitization with NTM. However, testing of high-risk groups of adults or children should be encouraged, because most of these persons with positive TST or IGRA results have TBI. Testing should take place only if effective mechanisms are in place to ensure adequate evaluation and treatment of the persons who test positive.

Bacille Calmette-Guérin Vaccination

The only available vaccine against tuberculosis is the BCG vaccine. The original vaccine organism was a strain of *M. bovis* attenuated by subculture every 3 wk for 13 yr. This strain was distributed to dozens of laboratories that continued to subculture the organism on different media under various conditions. The result has been production of many BCG vaccines that differ widely in morphology, growth characteristics, sensitizing potency, and animal virulence.

The administration route and dosing schedule for the BCG vaccines are important variables for efficacy. The preferred route of administration is intradermal injection with a syringe and needle, because it is the only method that permits accurate measurement of an individual dose.

The BCG vaccines are extremely safe in immunocompetent hosts. Local ulceration and regional suppurative adenitis occur in 0.1–1% of vaccine recipients. Local lesions do not suggest underlying host immune defects and do not affect the level of protection afforded by the vaccine. Most reactions are mild and usually resolve spontaneously, but chemotherapy is needed occasionally. Surgical excision of a suppurative draining node is rarely necessary and should be avoided if possible. **Osteitis** is a rare complication of BCG vaccination that appears to be related to certain strains of the vaccine that are no longer in wide use. Systemic complaints such as fever, convulsions, loss of appetite, and irritability are extraordinarily rare after BCG vaccination. Profoundly immunocompromised patients can develop disseminated BCG infection after vaccination. Children with HIV infection appear to have rates of local adverse reactions to BCG vaccines that are comparable with rates in immunocompetent children. However, the incidence in these children of disseminated infection months to years after vaccination is currently unknown.

Recommended vaccine schedules vary widely among countries. The official WHO recommendation is a single dose administered during infancy, in populations where the risk for tuberculosis is high. However, *infants with known or suspected HIV infection should not receive a BCG vaccination.* In some countries, repeat vaccination is universal, although no clinical trials support this practice. In others, it is based on either TST or the absence of a typical scar. The optimal age for administration and dosing schedule are unknown because adequate comparative trials have not been performed.

Although dozens of BCG trials have been reported in various human populations, the most useful data have come from several controlled trials. The results of these studies have been disparate. Some demonstrated substantial protection from BCG vaccines, but others showed no efficacy at all. A meta-analysis of published BCG vaccination trials suggested that BCG is 50% effective in preventing pulmonary tuberculosis in adults and children. The protective effect for disseminated and meningeal tuberculosis appears to be slightly higher, with BCG preventing 50–80% of cases. A variety of explanations for the varied responses to BCG vaccines have been proposed, including methodologic and statistical variations within the trials, interaction with NTM that either enhances or decreases the protection afforded by BCG, different potencies among the various BCG vaccines, and genetic factors for BCG response within the study populations. BCG vaccination administered during infancy has little effect on the ultimate incidence of tuberculosis in adults, suggesting waning protection with time.

BCG vaccination has worked well in some situations but poorly in others. Clearly, BCG vaccination has had little effect on the ultimate control of tuberculosis throughout the world, because >5 billion doses have been administered but tuberculosis remains epidemic in most regions. BCG vaccination does not substantially influence the chain of transmission, because cases of contagious pulmonary tuberculosis in adults that can be prevented by BCG vaccination constitute a small fraction of the sources of infection in a population. The best use of BCG vaccination is to prevent life-threatening forms of tuberculosis in infants and young children.

BCG vaccination has never been adopted as part of the strategy for TB control in the United States. Widespread use of the vaccine would render subsequent TSTs less useful. However, BCG vaccination can contribute to TB control in select population groups. BCG is recommended for TST-negative, HIV-negative infants and children who are at high risk for intimate and prolonged exposure to persistently untreated or ineffectively treated adults with infectious pulmonary tuberculosis and who cannot be removed from the source of infection or placed on long-term preventive therapy. It also is recommended for those who are continuously exposed to persons with tuberculosis who have bacilli that are resistant to isoniazid and rifampin. Any child receiving BCG vaccination should have a documented negative TST before receiving the vaccine. After receiving the vaccine, the child should be separated from the possible sources of infection until it can be demonstrated that the child has had a vaccine response, demonstrated by tuberculin reactivity, which usually develops within 1-3 mo.

Active research to develop new TB vaccines has led to the creation and preliminary testing of several vaccine candidates based on attenuated strains of mycobacteria, subunit proteins (H4:IC31), or DNA. The genome of *M. tuberculosis* has been sequenced, allowing researchers to further study and better understand the pathogenesis and host immune responses to tuberculosis.

Prevention of Perinatal Tuberculosis

The most effective way of preventing TB infection and disease in the neonate or young infant is through appropriate testing and treatment of the mother and other family members. High-risk pregnant women should be tested with a TST or IGRA, and those with a positive test result should receive a chest radiograph with appropriate abdominal shielding. If the mother has a negative chest radiograph and is clinically well, no separation of the infant and mother is needed after delivery. The child needs no special evaluation or treatment if the child remains asymptomatic. Other household members should undergo testing for TBI and further evaluation as indicated.

If the mother has suspected tuberculosis at the time of delivery, the newborn should be separated from the mother until the chest radiograph is obtained. If the mother's chest radiograph is abnormal, separation should be maintained until the mother has been evaluated thoroughly, including examination of the sputum. If the mother's chest radiograph is abnormal but the history, physical examination, sputum examination, and evaluation of the radiograph show no evidence of current active tuberculosis, it is reasonable to assume that the infant is at low risk for infection. The mother should receive appropriate treatment, and she and her infant should receive careful follow-up care.

If the mother's chest radiograph or AFB sputum smear shows evidence of current TB disease, additional steps are necessary to protect the infant. Isoniazid therapy for newborns has been so effective that separation of the mother and infant is no longer considered mandatory. Separation should occur only if the mother is ill enough to require hospitalization, has been or is expected to become nonadherent to treatment, or has suspected drug-resistant tuberculosis. Isoniazid treatment for the infant should be continued until the mother is sputum culture negative for ≥3 mo. At that time, a Mantoux TST should be placed on the child. If the test is positive, isoniazid is continued for a total duration of 9-12 mo; if the test is negative, isoniazid can be discontinued. Once the mother and child are taking adequate therapy, it is usually safe for the mother to breastfeed, because the medications, although found in milk, are present in low concentrations. If isoniazid resistance is suspected or the mother's adherence to medication is in question, continued separation of the infant from the mother should be considered. The duration of separation must be at least as long as is necessary to render the mother noninfectious. A TB expert should be consulted if the young infant has potential exposure to the mother or another adult with TB disease caused by an isoniazid-resistant strain of *M. tuberculosis* .

Although isoniazid is not thought to be teratogenic, the treatment of pregnant women who have asymptomatic TBI is often deferred until after delivery. However, symptomatic pregnant women or those with radiographic evidence of TB disease should be appropriately evaluated. Because pulmonary tuberculosis is harmful to both the mother and the fetus and represents a great danger to the infant after delivery, tuberculosis in pregnant women always should be treated. The most common regimen for drug-susceptible tuberculosis is isoniazid, rifampin, and ethambutol. The aminoglycosides and ethionamide should be avoided because of their teratogenic effect. The safety of pyrazinamide in pregnancy has not been established.

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CHAPTER 243

Hansen Disease *(Mycobacterium leprae)*

Cristina Garcia-Mauriño, Asuncion Mejias

Leprosy (Hansen disease) is a heterogeneous, curable infection caused by *Mycobacterium leprae* that primarily affects the upper airway, skin, and peripheral nerves. Disease manifestations are mainly determined by the host's immunologic response to infection, resulting in a wide clinical spectrum. The majority of exposed individuals never develop clinical disease. Hansen disease (**HD**) is currently the accepted designation of leprosy, and contrary to popular folklore, HD is *not* highly transmissible and *is* treatable. In addition, the associated morbidity and disability can be prevented with early diagnosis and appropriate treatment.

Microbiology

Mycobacterium leprae is an obligate intracellular acid-fast gram-positive bacillus of the family Mycobacteriaceae measuring 1-8 µm in length. It grows optimally at 27-33°C (80.6-91.4°F) yet cannot be cultured in vitro. The bacillus multiplies slowly, with a doubling time of 11-13 days. It is the only bacterium known to infect **Schwann cells** of peripheral nerves. Identification of acid-fast bacilli in peripheral nerves is pathognomonic of leprosy.

Epidemiology

The prevalence of leprosy is variable, with the majority of cases being identified in tropical and subtropical areas. The World Health Organization (WHO) goal to eliminate leprosy as a public health problem, defined as a reduction in its prevalence to less than 1 case per 10,000 population, was achieved at the global level in 2000. Despite an overall decline in reported prevalence, HD continues to afflict more than 2 million people worldwide. Approximately 213,899 new cases were reported globally in 2014, with >94% of cases occurring in Southeast Asia (mostly India), Africa, and South America (mostly Brazil). A total of 8.8% of these cases occurred in children. In 2016, WHO released *Global Leprosy Strategy 2016–2020: Accelerating Towards a Leprosy-Free World* .

Since 1984, HD has been a *notifiable disease* in the United States, with 13,950 registered cases by the end of 2015. Of the 178 new U.S. cases reported in 2015, 72% were identified in Texas, Louisiana, Hawaii, California, Florida, New York, and Arkansas. Of the U.S. cases, 57% were identified in immigrants, mainly Asian or South Pacific Islanders; however, over one third of U.S. cases are **autochthonous** and do not report contact with foreign countries or people with leprosy. Less than 3% of U.S. cases in 2015 occurred in children <16 yr old. Younger patients predominate in areas with high endemicity.

The likelihood of developing HD is determined by several variables: age (with 2 incidence peaks: 10-14 yr and 30 yr), gender (male/female ratio 2 : 1, with no differences observed in children), genetics, immune status, type of leprosy (with higher risk in those exposed to patients with multibacillary disease), and possibly through exposure to **armadillos** . Whole genome sequencing has allowed identification of genes and polymorphisms associated with increased susceptibility to leprosy (approximately 5% of people are genetically susceptible to *M. leprae* infection). HD in immunocompromised hosts has been reported in solid-organ and bone marrow transplant recipients and patients receiving tumor necrosis factor (TNF)–blocking monoclonal antibodies. Patients with HIV infection do not appear to be at increased risk of acquiring leprosy, increased disease severity, or poor response to treatment. However, clinicians should be aware that concomitant HIV infection and leprosy can result in worsening of symptoms of leprosy during HIV treatment as a result of an immune reconstitution inflammatory syndrome.

The exact mechanism of transmission is not fully understood but is thought to occur primarily by the respiratory route. Natural infection occurs in humans and armadillos, which are the only recognized nonhuman reservoir. The risk of transmission from armadillos to humans seems low, and again the mechanism is not fully understood. The incubation period between natural infection and overt clinical disease in humans ranges from 3 mo to 20 yr, with a mean of 4 yr for

tuberculoid leprosy and 10 yr for **lepromatous** leprosy. Up to 10^7 viable bacilli per day can be shed in the respiratory secretions of patients with **multibacillary** leprosy. The relative risk for developing disease in household contacts is 8-10 fold for lepromatous disease and 2-4–fold for the tuberculoid form. Transmissions by breast milk, the transplacental route, and through broken skin have been reported. Environmental factors and subclinically infected humans may also play a role in disease transmission. The infectivity of patients with HD becomes negligible within 24 hr of the first administration of effective therapy.

Pathogenesis

In the skin, *M. leprae* shows affinity for keratinocytes, macrophages, and histiocytes, and in peripheral nerves the organism can be found in the Schwann cells. The mechanism of mycobacterial dissemination from the respiratory tract to the skin and nerves is thought to occur hematogenously but has not been completely elucidated. *M. leprae* induces demyelination and binds to the laminin-2 glycoprotein present in the basal lamina of Schwann cells in peripheral nerves, where it replicates slowly over several years. Infection stimulates the dedifferentiation of Schwann cells to immature cells through the activation of the Erk1/2 pathway. This reprogramming of Schwann cells seems to be linked to disease dissemination. In addition to the direct nerve invasion, the immune response to infection also contributes to nerve damage. Schwann cells express human leukocyte antigen (HLA) class II molecules and present mycobacterial peptides to the HLA class II–restricted $CD4^+$ T cells, which initiate an inflammatory response. These events explain the nerve damage seen in paucibacillary disease and in reversal reactions. Swelling within the perineurium leads to ischemia, further nerve damage, and eventually fibrosis and axonal death.

Disease Classification

Disease classification is important to determine potentially infectious cases and prognosis. Based on the cellular immune response and disease dissemination, 2 classification schemes for leprosy are frequently used: the Ridley-Jopling scale and the WHO classification:

A. The **Ridley-Jopling scale** is used in the United States and describes the 5 types of leprosy, according to clinical spectrum of disease, bacillary load, and findings on histopathology.

1. *Tuberculoid form* : Patients usually have a vigorous and specific cellular immune response to *M. leprae* antigens and have a small number of skin lesions, generally, 1-3 well-demarcated macules or plaques with elevated borders (Fig. 243.1) and reduced or absent sensation. The lesions are infiltrated by T-helper 1 (Th1) cells producing abundant interferon (IFN)-γ and TNF-α, forming well-demarcated granulomas, with few, if any bacilli found within the lesions.

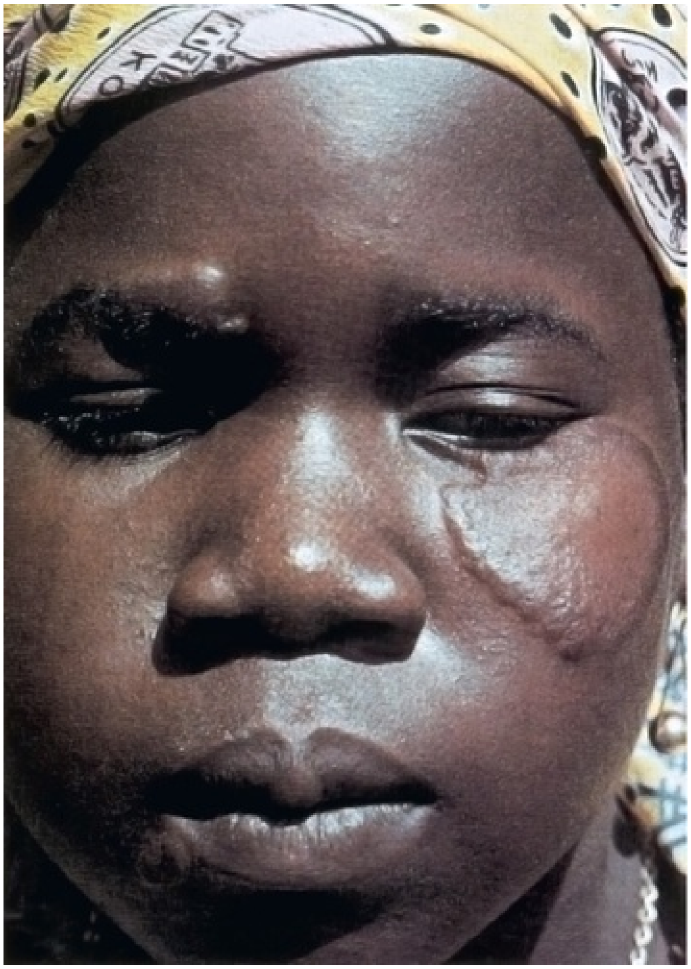

FIG. 243.1 Tuberculous leprosy in a patient who has a single skin lesion with a raised border and flattened center.

2. *Borderline tuberculoid form*
3. *Borderline form*
4. *Borderline lepromatous*
5. *Lepromatous form* : Patients have an absence of specific cellular immunity to *M. leprae* (but intact immunity to *Mycobacterium tuberculosis*) and present the most severe form of disease. They manifest clinically apparent infiltration of

peripheral nerves and skin lesions (usually many lesions and not all hypoesthetic or anesthetic), with a high load of bacilli in the absence of an effective cell-mediated immune response. Skin biopsies reveal extensive infiltration of the skin and nerves, containing messenger RNA for Th2 cytokines such as interleukin (IL)-4 and IL-10, poorly formed granulomas, and uncontrolled proliferation of bacilli within foamy macrophages. A large amount of circulating antibody to *M. leprae* is present but does not confer protective immunity. Over time, patients with the lepromatous form develop a systemic disease with symmetric peripheral nerve involvement and a diffuse infiltrative dermopathy that includes thickening of the facial skin and hair loss of the eyelashes and eyebrows (madarosis), leading to the classic presentation of the *leonine facies* . They also have involvement of the nasal mucosa causing nasal congestion and epistaxis.

The majority of patients will present with a borderline form. From borderline tuberculoid to borderline lepromatous forms, there is a progressive reduction in cellular immune responses, an increase in bacillary load, more frequent hypopigmented skin lesions and nerve involvement, and higher antibody titers (Fig. 243.2). Patients with the extreme forms of the disease (tuberculoid and lepromatous) are considered to have stable cell-mediated immunity, because their disease manifestations do not change much over time. In contrast, patients with borderline disease have unstable cell-mediated immunity and demonstrate changes in their clinical manifestations over time toward the polar forms (downgrade) or present sudden reversal reactions (upgrade). *Indeterminate leprosy* is the earliest form of the disease and is seen most frequently in young children. Patients usually have a single hypopigmented macule with poorly defined borders, without erythema or induration. Anesthesia is minimal or absent, especially if the lesion is on the face. The diagnosis is usually one of exclusion in the setting of a contact investigation. Tissue biopsies show diagnostic evidence of leprosy but do not meet sufficient criteria for classification.

Up to 50–75% of these lesions will heal spontaneously, and the rest will progress to another form of leprosy.

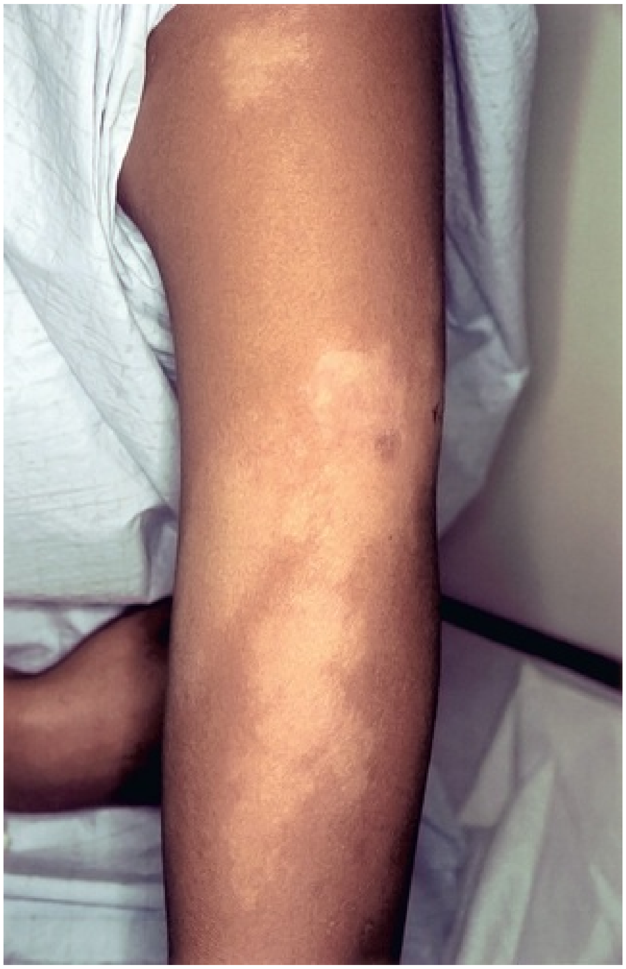

FIG. 243.2 Borderline leprosy in a patient who has numerous, hypopigmented lesions with poorly defined borders.

B. The **WHO classification** can be used when histologic evaluation and confirmatory diagnosis is unavailable, a common scenario in the field. This simplified scheme is based on the number of skin lesions:

1. Paucibacillary (1-5 patches)
2. Multibacillary (>5 patches)

Clinical Manifestations

The host immune response determines the clinical spectrum of leprosy. Skin and serologic studies suggest that up to 90% of infected people develop immunity after exposure, without manifesting clinical disease. In genetically susceptible individuals with sufficient exposure to become infected, the cellular host's immunologic response to infection and unique tropism for peripheral nerves determines the wide spectrum of clinical (and histologic) manifestations. Regardless of the disease subtype, HD affects the skin and peripheral nerves. Leprosy lesions usually do not itch or hurt.

Skin Involvement

The most common skin lesions are **macules** or **plaques** with unclear outer limits, with or without neurologic symptoms. Diffuse infiltrative lesions and subcutaneous nodules are less common. Initial lesions are insidious hypopigmented macules, although they may appear erythematous on pale skin. Lesions may involve any area of the body, are more pronounced in cooler areas (e.g., earlobes, nose), and occur less frequently in the scalp, axillae, or perineum. Approximately 70% of skin lesions have reduced sensation; the degree of hypoesthesia depends on the location and size of the lesion and the degree of Th1 immune response. Examination of the skin should ideally be performed in natural sunlight and be tested for hypoesthesia to light touch, pinprick, temperature, and anhidrosis. Studies in endemic areas in children <15 yr old have shown predominance of **paucibacillary** forms, with predominance of single lesions.

Nerve Involvement

Peripheral nerves are most frequently affected early in the disease and should be palpated for thickness and tenderness (Fig. 243.3), as well as evaluated for both motor and sensory function, particularly temperature and light touch. The posterior tibial nerve (medial malleolus) is the most common nerve affected, followed by the ulnar (elbow), median (wrist), lateral popliteal (fibular neck), and facial nerves. The skin lesions overlying a nerve trunk distribution predict the involvement of nerves in the vicinity. There is a pure **neuritic** form of leprosy, usually occurring in India and Nepal, in which patients present with asymmetric neuropathy, but lack skin lesions.

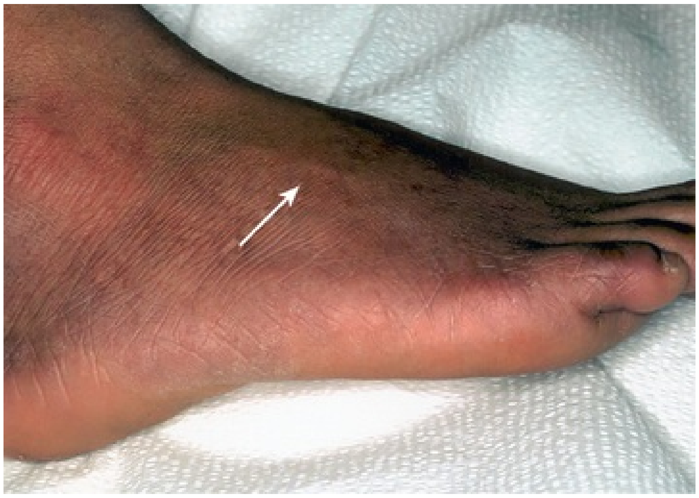

FIG. 243.3 Thickened, superficial peroneal nerve of leprosy.

Other Organ Involvement

Ocular involvement leading to vision loss results from both direct bacillary invasion of the eye and optic nerve damage. **Lagophthalmos** occurs when there is destruction of the facial nerve (cranial nerve VII), and trigeminal nerve (cranial nerve V) destruction causes anesthesia of the cornea and conjunctiva, leading to abrasions. Facial skin lesions are associated with a 10-fold higher risk of facial nerve damage. Systemic involvement of other organs is seen mainly in patients with lepromatous leprosy where a high bacillary burden leads to infiltration of the nasal mucosa, bones, and testes. Renal involvement and amyloidosis are rare findings.

Immunologic Reactions

Leprosy reactions are acute clinical exacerbations reflecting disturbances of the immunologic balance to *M. leprae* infection and occurring in 30–50% of all leprosy patients. These sudden changes occur in patients with borderline and lepromatous leprosy, typically during the initial years after infection (sometimes as the initial presentation), but can occur before, during, or after completion of treatment. There are 2 main types of leprosy reactions, which require immediate treatment so as to prevent long-term complications. In children <15 yr old, leprosy reactions range from 1–30% and are mainly type 1 reactions.

Type 1 reactions (also known as **reversal reactions**) occur in one third of patients with borderline disease. These reactions are characterized by acute edema and increased erythema, warmth, and painful inflammation of preexisting cutaneous plaques or nodules, with acute swelling and tenderness of peripheral nerves that can quickly progress to cause nerve abscesses and necrosis. There may be a peripheral lymphocytosis and an increased cytokine response, but systemic symptoms are uncommon and appear to be associated with an increase in Th1-mediated reactivity to mycobacterial antigens. Increased serum concentrations of CXCL10 have been found in type 1 reactions. Rapid and sustained reversal of the inflammatory process using corticosteroids is essential to prevent continued nerve damage.

Type 2 reactions, or **erythema nodosum leprosum (ENL)** , occur in borderline lepromatous and lepromatous forms, as these patients have the highest levels of *M. leprae* antigens and antibodies, most often in the 1st 2 yr after starting therapy. ENL is distinguished from reversal reactions by the development of new painful, erythematous subcutaneous nodules with an accompanying systemic inflammatory response. ENL is accompanied by high circulating concentrations of TNF-α. Patients develop high fever and signs of systemic toxicity, and in severe cases, ENL can be life threatening, presenting with features similar to septic shock. Deposition of extravascular immune complexes leads to neutrophil infiltration and activation of complement in the skin and other organs. Tender, erythematous dermal papules or nodules (resembling erythema nodosum) occur in clusters, typically on extensor surfaces of the lower extremities and face. Immune complex deposition also contributes to migrating polyarthralgias, painful swelling of lymph nodes and spleen, iridocyclitis, vasculitis, orchitis, and, rarely, nephritis. Patients may present with either a single acute episode, a relapsing form comprised of multiple acute episodes, or a chronic continuous form. Management of type two reactions is usually more complicated because of recurrence and systemic involvement.

Lucio phenomenon (erythema necroticans) is an uncommon, but potentially fatal reaction distinct from type 1 or 2 reactions and occurs in patients with untreated lepromatous leprosy, in patients whose ancestry is from Mexico. It is a necrotizing vasculitis caused by *M. leprae* directly invading the endothelium. Clinically, patients develop violaceous or hemorrhagic plaques, followed by ulcerations in the absence of systemic complaints. Secondary bacterial infections are common.

Diagnosis

The diagnosis of HD requires high clinical suspicion and should be considered in any patient with a hypoesthetic or anesthetic skin lesion that does not respond to standard treatment, especially if there is a history of travel or residence in an endemic region or a history of contact with leprosy patients or armadillos. There are no reliable tests to diagnose subclinical leprosy. Full-thickness skin biopsy and PCR are the main laboratory tests to aid in the diagnosis. Patients are considered to have HD if they have 1 or more of the 3 cardinal signs: loss of sensation in a localized skin lesion, thickened peripheral nerve with loss of sensation or weakness of muscles enervated by that nerve, or the presence of acid-fast bacilli (AFB) on biopsy. The positive predictive value for the diagnosis of leprosy in patients meeting all 3 criteria is 98%.

To confirm the diagnosis and determine the extent of nerve involvement and the type of infiltrate, a full-thickness skin biopsy from the most active lesion should be performed. *M. leprae* is best identified in tissue using the *Fite stain* . Lesions from patients with the lepromatous form reveal numerous AFB in clumps (globi), whereas patients with the tuberculoid form rarely have mycobacteria identified, but the diagnosis can be made by demonstration of well-formed noncaseating granulomas and nerve involvement. The presence of **neural inflammation** differentiates leprosy from other granulomatous disorders. Mycobacterial culture of lesions should be performed to exclude *M. tuberculosis* and nontuberculous cutaneous infections. If no resources are available, slit-skin (skin smear) biopsies represent an alternative. Slit-skin smears have high specificity but low sensitivity; only 30% of adults and 10–30% of children <15 yr old are smear positive (usually patients with the lepromatous form). The bacterial index can range from 0 (no bacilli in 100 oil-immersion fields), as generally seen in paucibacillary disease, to 6+ (>1,000 bacilli/field), as can be seen in multibacillary disease.

Diagnostic and histopathologic consultation in the United States is available through the **National Hansen's Disease Program** (**NHDP** ; http://www.hrsa.gov/hansens or 800-642-2477). Specimens (formalin or paraffin embedded) can be sent to the NHDP for pathologic analysis free of charge. A polymerase chain reaction (PCR) test for *M. leprae* is not readily available in clinical practice but may be performed at the NHDP. In nonendemic areas, PCR may be useful for diagnosis when AFB are discernible in tissue, but clinical and histopathologic features are not typical. *M. leprae* DNA is detectable by PCR in 95% of lepromatous disease (sensitivity >90%) and 55% of tuberculoid lepra (sensitivity of 34–80%). PCR has also allowed detection of the organism in nasal secretions from asymptomatic people. Molecular testing for mutations causing drug resistance is also available through the NHDP and is usually used in the setting of relapse.

Antibodies to *M. leprae* are present in 90% of patients with untreated lepromatous disease, 40–50% of patients with paucibacillary disease, and 1–5% of healthy controls. However, serologic testing is insensitive and is not used for diagnosis.

Treatment

The primary goal of treatment is early antimicrobial therapy to prevent permanent neuropathy. Leprosy is curable. Effective treatment requires multidrug therapy (MDT) with **dapsone** , **clofazimine** , and **rifampin** . Combination therapy is employed to prevent antimicrobial resistance. In the United States, clinical providers considering a diagnosis and treatment of a patient with HD should obtain consultation from the NHDP. The recommended combination MDT can be obtained free of charge from the NHDP (Table 243.1) and in other countries through WHO (Table 243.2). Compared to WHO, the NHDP advocates for a longer duration of treatment and daily rather than monthly administration of rifampin, because shorter antimicrobial regimens have been associated with greater risk of relapse. The recommended duration by the WHO for tuberculoid disease is 6 mo and for lepromatous disease, 12 mo.

Table 243.1

NHDP-Recommended Multidrug Therapy Regimens for Hansen Disease in the United States

TYPE OF LEPROSY	PATIENT POPULATION	ANTIMICROBIAL THERAPY	DURATION OF THERAPY
Multibacillary (LL, BL, BB)	Adult	Dapsone, 100 mg/day, *and* Rifampin, 600 mg/day, *and* Clofazimine, 50 mg/day	24 mo
	Pediatric*	Dapsone, 1 mg/kg/day, *and* Rifampin, 10-20 mg/kg/day, *and* Clofazimine, 1 mg/kg/day †	
Paucibacillary (TT, BT)	Adult	Dapsone, 100 mg/day, *and* Rifampin, 600 mg/day	12 mo
	Pediatric*	Dapsone, 1 mg/kg/day, *and* Rifampin, 10-20 mg/kg/day	

* Daily pediatric mg/kg dose should not exceed adult daily maximum.

† Clofazimine is only available through NHDP Investigational New Drug (IND) program; minimum formulation is 50 mg, and capsules should not be cut. Alternative dosing includes clofazimine, 2 mg/kg every other day, *or* clarithromycin, 7.5 mg/kg/day.

NHDP multidrug therapy is daily and of longer duration than WHO-recommended regimen. All drugs are administered orally.

NHDP, National Hansen's Disease Program; BB, Borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.

Table 243.2

WHO-Recommended Multidrug Therapy (MDT) Regimens for Hansen Disease

TYPE OF LEPROSY	PATIENT POPULATION	ANTIMICROBIAL THERAPY	DURATION OF THERAPY
Multibacillary (LL, BL, BB)	Adult	Rifampicin, 600 mg once monthly, *and* Dapsone, 100 mg/day, *and* Clofazimine, 300 mg once monthly and 50 mg/day	12 mo
	Pediatric*	Rifampicin, 450 mg once monthly, *and* Dapsone, 50 mg/day, *and* Clofazimine, 150 mg once monthly and 50 mg every other day	
Paucibacillary (TT, BT)	Adult	Rifampicin, 600 mg once monthly, *and* Dapsone, 100 mg/day	6 mo
	Pediatric*	Rifampicin, 450 mg once monthly, *and* Dapsone, 50 mg/day	

* In children <10 yr old, MDT dosages should be in mg/kg, not to exceed the adult daily maximum: rifampicin, 10 mg/kg once monthly; dapsone, 2 mg/kg/day; and clofazimine, 1 mg/kg on alternate days.

WHO, World Health Organization; BB, Borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.

Before starting combination MDT, patients should be tested for glucose-6-phosphate dehydrogenase deficiency, have a baseline complete blood cell count and liver function testing, and be evaluated for evidence of active tuberculosis, in which monotherapy with rifampin should be avoided. Response to therapy is seen clinically as flattening or disappearance of skin lesions and improvement in nerve function, usually within 1-2 mo after initiating MDT. Complete resolution or improvement may take 6-12 mo, depending on the severity of infection. Most skin lesions heal without scarring.

Alternative agents to treat HD include minocycline, clarithromycin, and some fluoroquinolones (levofloxacin, ofloxacin, moxifloxacin). Given limited data, these alternative antimicrobials are used in selected cases of intolerance to the routine combination MDT regimen or for documented resistance. It is important to note that some patients who have been adequately treated for HD may later show evidence of chronic reversal reactions and late neuropathies, but these are bacillus negative and thus should not be considered relapses. Neuritis must be treated promptly to minimize nerve injury and disability. Treatment with corticosteroids appears to improve nerve function in two third of patients.

Bone marrow suppression and hepatotoxicity have been reported and should be monitored every 3 mo during therapy. A screening urinalysis should be performed annually. Other reactions, such as methemoglobinemia and hypersensitivity reactions to dapsone, are rare. An ophthalmologic evaluation should routinely be performed in all patients with HD because ocular complications can occur. Given the proclivity for testicular invasion in multibacillary leprosy with resultant testicular dysfunction and infertility, males should be screened for elevated follicle-stimulating hormone or luteinizing hormone concentrations and decreased testosterone levels.

After completion of MDT, annual follow-up for ≥5 yr for paucibacillary and ≥10 yr for multibacillary disease is warranted. Relapse of the disease after completion of MDT is rare (0.01–4.0%) and must be distinguished from the more common leprosy immunologic reactions. Patients who have a bacillary index of ≥4 pre-MDT or ≥3 at the completion of MDT have the highest risk of relapse (approximately 20%). When relapse occurs, it is usually within 5-10 yr of MDT completion and a result of reactivation of drug-susceptible mycobacteria. Thus, patients who are expected to relapse are generally treated with the same MDT regimen. Resistance to dapsone and rifampicin has been documented, although it rarely occurs with combination therapy.

Leprosy Reactions

Immunologic reactions can occur before, during, and years after treatment and should be treated aggressively to prevent peripheral nerve damage. In general, antimycobacterial drugs should be continued. Fatigue, malaise, or fever can be present, and the inflammation associated with these reactions can cause severe nerve injury. Prompt therapy with corticosteroids with or without other antiinflammatory agents, adequate analgesia, and physical support are essential for patients with active neuritis to prevent nerve damage. If corticosteroids are indicated for a prolonged time, the frequency of rifampicin administration should be decreased from daily to monthly administration (to avoid drug interaction).

For **type 1 reactions** , prednisone is recommended, 1 mg/kg/day orally (40-60 mg) with a slow taper (decreasing by 5 mg every 2-4 wk after evidence of improvement over 3-6 mo), in addition to standard MDT. If there is evidence of peripheral nerve deterioration, higher doses and longer tapers may be needed. Nerve function improves after corticosteroid treatment in 30–80% of patients who did not have preexisting neuritis. In patients not responding to corticosteroids, cyclosporine may be used as a second-line agent.

For **type 2 reactions** , prednisone is routinely used at 1 mg/kg/day for 12 wk. However, given the recurrence and chronicity of ENL, corticosteroid-sparing agents should be considered to avoid complications associated with their prolonged use. **Thalidomide** (100-400 mg/daily for 48-72 hr, tapering over 2 wk to 100 mg/daily) is effective in treating these types of reactions. Given the teratogenicity of thalidomide (contraindicated for children <12 yr old and woman of childbearing age), the drug is only available through a restrictive distribution program approved by the U.S. Food and Drug Administration (FDA). Low dose **clofazimine** (50-100 mg 3 times weekly) alone or in combination with corticosteroids (300 mg/day, tapering to <100 mg/day, for 12 mo) has also been useful in managing patients with chronic ENL and is generally used until all signs of the reaction have abated. Other immunosuppressive drugs have been used to treat type-2 reactions with inconsistent results, including cyclosporine, mycophenolate, and methotrexate. Lucio phenomenon is managed with corticosteroids and treatment of underlying infections.

Long-Term Complications

Leprosy is a leading cause of permanent physical disability among communicable diseases worldwide. The major chronic complications and deformities of leprosy are caused by **nerve injury** . Nerve impairment may be purely sensory, motor, or autonomic, or may be a combination. The prognosis for arresting progression of tissue and nerve damage is good if therapy is started early, but recovery of lost sensory and motor function is variable and frequently incomplete. Nerve function impairment can occur before diagnosis, during MDT, or after MDT and can develop without overt signs of skin or nerve inflammation (silent neuropathy). Patients at highest risk of nerve impairment are those with multibacillary leprosy and preexisting nerve damage. These patients should undergo regular monthly surveillance during therapy and for at least 2 yr from the time of diagnosis. In children, deformities can occur in 3–10% of cases and mainly in those with nerve enlargement. Other factors contributing to risk of deformities include increasing age in children, delay in accessing medical care, multiple skin lesions, multibacillary disease, smear positivity, multiple nerve involvement, and leprosy reaction at presentation.

Prevention

In addition to treating active leprosy cases, control measures for HD include the management of **contacts** of index patients. In endemic countries, close monitoring of household contacts of HD patients, particularly HD patients with multibacillary disease, is warranted to ensure that early treatment can be implemented if evidence of early HD develops. These household contacts should be examined at baseline and then yearly for 5 yr. In nonendemic areas, disease presenting in the contacts of patients with HD is rare. A single dose of bacille Calmette-Guérin (BCG) vaccine has variable protective efficacy against leprosy, ranging from 10–80%; an additional dose results in increased protection. Any suspected or newly diagnosed case of leprosy in the United States should be reported to local and state public health departments, the Centers for Disease Control and Prevention (CDC), and NHDP. There are no leprosy vaccines available or recommended for use in the United States. In the hospital setting, **standard precautions** should be implemented. Hand hygiene is recommended for all people in contact with a patient with lepromatous leprosy.

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CHAPTER 244

Nontuberculous Mycobacteria

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Nontuberculous mycobacteria (**NTM**), also referred to as **atypical mycobacteria** and **mycobacteria other than tuberculosis** (MOTT), are all members of the genus *Mycobacterium* and include species other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae* . The NTM constitute a highly diverse group of bacteria that differ from *M. tuberculosis* complex bacteria in their pathogenicity, interhuman transmissibility, nutritional requirements, ability to produce pigments, enzymatic activity, and drug susceptibility. In contrast to the *M. tuberculosis* complex, NTM are acquired from environmental sources and not by person-to-person spread, although the latter is under debate, especially in patients with cystic fibrosis. Their omnipresence in the environment means that the clinical relevance of NTM isolation from clinical specimens is sometimes unclear; a positive culture might reflect occasional presence or contamination rather than true NTM disease. NTM are associated with pediatric lymphadenitis, otomastoiditis, serious lung infections, and, rarely, disseminated disease. Treatment is long-term and cumbersome and often requires adjunctive surgical intervention. Comprehensive guidelines on diagnosis and treatment are provided by the American Thoracic Society (ATS) and British Thoracic Society (BTS).

Etiology

NTM are ubiquitous in the environment all over the world, existing as saprophytes in soil and water (including municipal water supplies, tap water, hot tubs, and shower heads), environmental niches that are the supposed sources of human infections. With the introduction of molecular identification tools such as 16S recombinant DNA gene sequencing, the number of identified NTM species has grown to more than 150; the *clinical relevance* (i.e., percentage of isolates that are causative agents of true NTM disease, rather than occasional contaminants) differs significantly by species.

Mycobacterium avium complex (**MAC** ; i.e., *M. avium* , *Mycobacterium intracellulare*, and several closely related but rarer species) and *Mycobacterium kansasii* are most often isolated from clinical samples, yet the isolation frequency of these species differs significantly by geographic area. MAC bacteria have been frequently isolated from natural and synthetic environments, and cases of MAC disease have been successfully linked to home exposure to shower and tap water. Although the designation *M. avium* suggests that human infections are acquired from birds (Latin *avium*), molecular typing has established that *M. avium* strains that cause pediatric lymphadenitis and adult pulmonary disease represent the *M. avium* hominis suis subgrouping, mainly found in humans and pigs and not in birds.

Some NTM have well-defined ecologic niches that help explain infection patterns. The natural reservoir for *Mycobacterium marinum* is fish and other cold-blooded animals, and the **fish tank granuloma** , a localized skin infection caused by *M. marinum*, follows skin injury in an aquatic environment. *Mycobacterium fortuitum* complex bacteria and *Mycobacterium chelonae* are ubiquitous in water and have caused clusters of nosocomial surgical wound and venous catheter–related infections. *Mycobacterium ulcerans* is associated with severe, chronic skin infections (**Buruli ulcer disease**) and is endemic mainly in West Africa and Australia, although other foci exist. Its incidence is highest in children <15 yr old. *M. ulcerans* had been detected in environmental samples by polymerase chain reaction (PCR) but was only recently recovered by culture from a water strider (an insect of the *Gerris* genus) from Benin.

Epidemiology

Humans are exposed to NTM on a daily basis. In rural U.S. counties, where *M. avium* is common in swamps, the prevalence of asymptomatic infections with *M. avium* complex, as measured by skin test sensitization, approaches 70% by adulthood. Still, the incidence and prevalence of the various NTM disease types remain largely unknown, especially for pediatric NTM disease. In Australian children the overall incidence of NTM infection is 0.84 per 100,000, with lymphadenitis accounting for two thirds of cases. The incidence of pediatric NTM disease in the Netherlands is estimated at 0.77 infections per 100,000 children per year, with lymphadenitis making up 92% of all infections.

In comparison, estimations of the prevalence of NTM from respiratory samples in adults are 5-15 per 100,000 persons per year, with important differences between countries or regions. Because pulmonary NTM disease progresses slowly, over years rather than months, and usually takes several years to cure, the prevalence of pulmonary NTM disease is much higher than incidence rates would suggest.

The paradigm that NTM disease is a rare entity limited to developed countries is changing. In recent studies in African countries with a high prevalence of HIV infection, it has been found that NTM might play a much larger role as a cause of tuberculosis-like disease of children and adults than previously assumed and thus confuse the diagnosis of tuberculosis.

Although it is generally believed that NTM infections are contracted from environmental sources, recent whole genome sequence analysis of *Mycobacterium abscessus* strains of patients in a cystic fibrosis (CF) clinic in the United Kingdom has raised the possibility of nosocomial transmission among CF patients.

Pathogenesis

The histologic appearances of lesions caused by *M. tuberculosis* and NTM are often indistinguishable. The classic pathologic lesion consists of caseating granulomas. Compared to *M. tuberculosis* infections, NTM infections are more likely to result in *granulomas that are noncaseating,* poorly defined (nonpalisading), irregular or serpiginous or even absent, with only chronic inflammatory changes observed. The histology likely reflects the immune status of the patient.

In patients with AIDS and disseminated NTM infection, the inflammatory reaction is usually scant, and tissues are filled with large numbers of histiocytes packed with acid-fast bacilli (AFB). These disseminated NTM infections typically occur only after the number of CD4 T lymphocytes has fallen below 50/µL, suggesting that specific T-cell products or activities are required for immunity to mycobacteria.

The pivotal roles of interferon (IFN)-γ, interleukin (IL)-12, and tumor necrosis factor (TNF)-α in disease pathogenesis are demonstrated by the high incidence of mostly disseminated NTM disease in children with IFN-γ and IL-12 pathway deficiencies and in persons treated with agents that neutralize TNF-α.

Observed differences in pathogenicity, clinical relevance, and spectrum of clinical disease associated with the various NTM species emphasize the importance of bacterial factors in the pathogenesis of NTM disease, although exact virulence factors remain largely unknown.

Clinical Manifestations

Lymphadenitis of the superior anterior cervical or submandibular lymph nodes is the most common manifestation of NTM infection in children (Table 244.1). Preauricular, posterior cervical, axillary, and inguinal nodes are involved occasionally. Lymphadenitis is most common in children 1-5 yr of age and has been related to soil exposure (e.g., playing in sandboxes) and teething, although exact predisposing conditions have not been found. Given the constant environmental exposure to NTM, the occurrence of these infections might also reflect an atypical immune response of a subset of the infected children during or after their first contact with NTM. However, in healthy children with isolated NTM lymphadenitis, immunodeficiency is very rare.

Table 244.1

Major Clinical Syndromes Associated with Nontuberculous Mycobacterial Infection

SYNDROME	MOST COMMON CAUSES	LESS FREQUENT CAUSES*
Chronic nodular disease (adults with bronchiectasis; cystic fibrosis)	MAC (*M. intracellulare, M. avium*), *M. kansasii, M. abscessus*	*M. xenopi, M. malmoense, M. szulgai, M. smegmatis, M. celatum, M. simiae, M. goodii, M. asiaticum, M. heckeshornense, M. branderi, M. lentiflavum, M. triplex, M. fortuitum, M. arupense, M. abscessus* subsp. *bolletii, M. phocaicum, M. aubagnense, M. florentinum, M. abscessus* subsp. *massiliense, M. nebraskense, M. saskatchewanense, M. seoulense, M. senuense, M. paraseoulense, M. europaeum, M. sherrisii, M. kyorinense, M. noviomagense, M. mantenii, M. shinjukuense, M. koreense, M. heraklionense, M. parascrofulaceum, M. arosiense*
Cervical or other lymphadenitis (especially children)	MAC	*M. scrofulaceum, M. malmoense* (northern Europe), *M. abscessus, M. fortuitum, M. lentiflavum, M. tusciae, M. palustre, M. interjectum, M. elephantis, M. heidelbergense, M. parmense, M. bohemicum, M. haemophilum, M. europaeum, M. florentinum, M. triplex, M. asiaticum, M. kansasii, M. heckeshornense*
Skin and soft tissue disease	*M. fortuitum* group, *M. chelonae, M. abscessus, M. marinum, M. ulcerans* (Australia,	*M. kansasii, M. haemophilum, M. porcinum, M. smegmatis, M. genavense, M. lacus, M. novocastrense, M. houstonense, M. goodii, M. immunogenum, M. mageritense, M. abscessus* subsp. *massiliense, M. arupense, M. monacense, M. bohemicum, M. branderi, M. shigaense, M. szulgai, M. asiaticum, M. xenopi, M. kumamotense, M. setense, M. montefiorense* (eels), *M. pseudoshottsii* (fish), *M. shottsii* (fish)

	tropical countries only)	
Skeletal (bone, joint, tendon) infection	*M. marinum*, MAC, *M. kansasii*, *M. fortuitum* group, *M. abscessus*, *M. chelonae*	*M. haemophilum, M. scrofulaceum, M. heckeshornense, M. smegmatis, M. terrae/chromogenicum* complex, *M. wolinskyi, M. goodii, M. arupense, M. xenopi, M. triplex, M. lacus, M. arosiense*
Disseminated infection		*M. genavense, M. haemophilum, M. xenopi*
HIV-seropositive host	*M. avium, M. kansasii*	*M. marinum, M. simiae, M. intracellulare, M. scrofulaceum, M. fortuitum, M. conspicuum, M. celatum, M. lentiflavum, M. triplex, M. colombiense, M. sherrisii, M. heckeshornense*
HIV-seronegative host	*M. abscessus, M. chelonae*	*M. marinum, M. kansasii, M. haemophilum, M. chimaera, M. conspicuum, M. shottsii* (fish), *M. pseudoshottsii* (fish)
Catheter-related infections	*M. fortuitum, M. abscessus, M. chelonae*	*M. mucogenicum, M. immunogenum, M. mageritense, M. septicum, M. porcinum, M. bacteremicum, M. brumae*
Hypersensitivity pneumonitis	Metal workers; hot tub	*M. immunogenum M. avium*

[*] The available information is sparse for selected pathogens such as *M. xenopi, M. malmoense, M. szulgai, M. celatum,* and *M. asiaticum* and the newly described species.

HIV, Human immunodeficiency virus; MAC, *Mycobacterium avium* complex.

From Brown-Elliott BA, Wallace Jr. RJ: Infections caused by nontuberculous mycobacteria other than *Mycobacterium avium* complex. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 254-1).

Affected children usually lack constitutional symptoms and present with a unilateral subacute and slowly enlarging lymph node or group of closely approximated nodes >1.5 cm in diameter that are firm, painless, freely movable, and not erythematous (Fig. 244.1). The involved nodes occasionally resolve without treatment, but most undergo rapid suppuration after several weeks (Fig. 244.2). The center of the node becomes fluctuant, and the overlying skin thins and becomes erythematous and often even violaceous. Eventually, the nodes rupture and can form cutaneous sinus tracts that can drain persistently, reminiscent of scrofula from tuberculosis (Fig. 244.3).

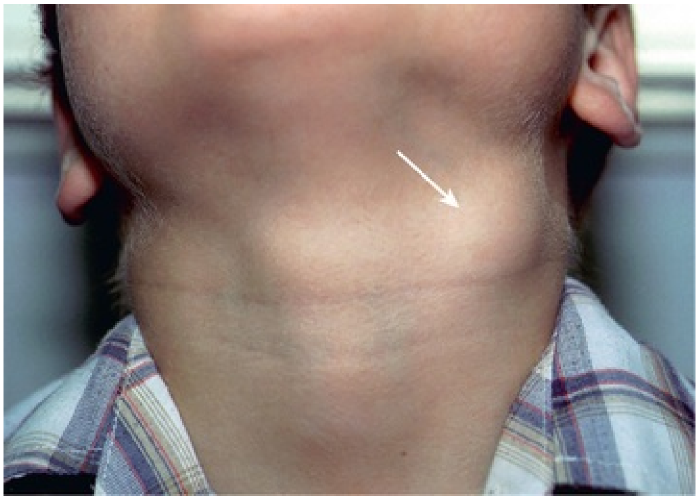

FIG. 244.1 Enlarging cervical lymph node infected with *Mycobacterium avium* complex infection. The node is firm, painless, freely movable, and not erythematous.

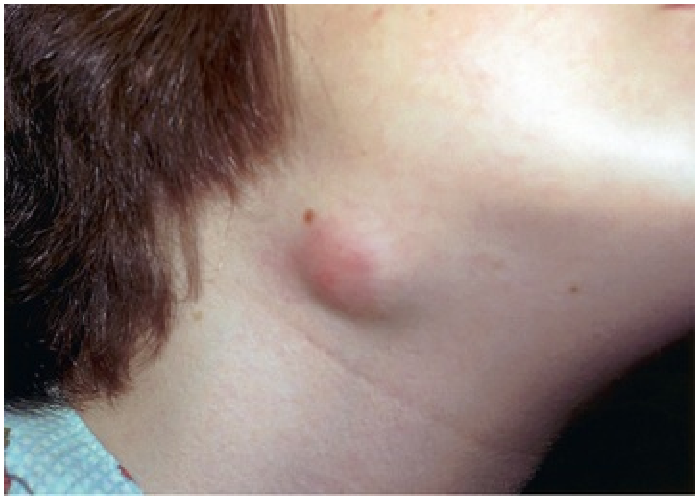

FIG. 244.2 Suppurating cervical lymph node infected with *Mycobacterium avium* complex.

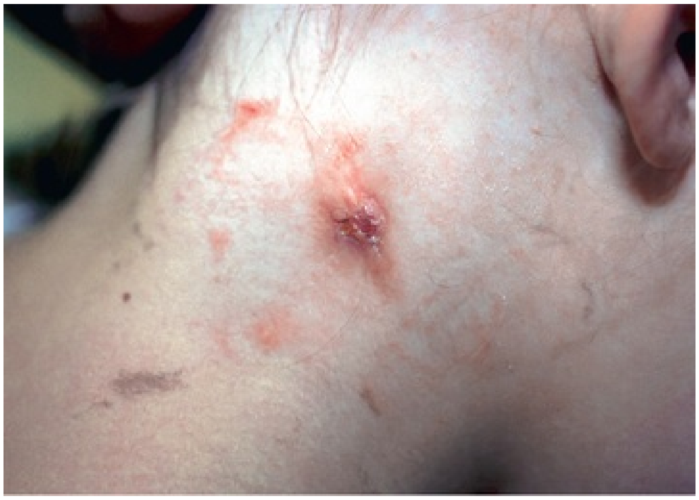

FIG. 244.3 Ruptured cervical lymph node infected with *Mycobacterium avium* complex, which resembles the classic scrofula of tuberculosis.

In the United States and Western Europe, *M. avium* complex accounts for approximately 80% of NTM lymphadenitis in children. *M. kansasii* accounts for most other cases of lymphadenitis in the United States. *Mycobacterium malmoense* and *Mycobacterium haemophilum* have also been described as causative agents of lymphadenitis. *M. malmoense* is only common in Northwestern Europe. For *M. haemophilum* , underestimation of its importance is likely because the bacteria require specific culture conditions (hemin-enriched media, low incubation temperatures). On the basis of PCR analysis of lymph node samples from lymphadenitis cases in The Netherlands, *M. haemophilum* is the 2nd most common cause of this infection, after *M. avium* complex. One study suggests that children with *M. avium* complex lymphadenitis are significantly younger than those infected by *M. haemophilum* , possibly related to age-specific environmental exposures. *Mycobacterium lentiflavum* is also an emerging NTM associated with lymphadenitis.

Cutaneous disease caused by NTM is rare in children (see Table 244.1). Infection usually follows percutaneous inoculation with fresh or salt water contaminated by *M. marinum.* Within 2-6 wk after exposure, an erythematous papule develops at the site of minor abrasions on the elbows, knees, or feet (**swimming pool granuloma**) and on the hands and fingers of fish tank owners, mostly inflicted during tank cleaning (**fish tank granuloma**). These lesions are usually nontender and enlarge over 3-5 wk to form violaceous plaques. Nodules or pustules can develop and occasionally will ulcerate, resulting in a serosanguineous discharge. The lesions sometimes resemble sporotrichosis, with satellite lesions near the site of entry, extending along the superficial lymphatics. Lymphadenopathy is usually absent. Although most infections remain localized to the skin, penetrating *M. marinum* infections can result in tenosynovitis, bursitis, osteomyelitis, or arthritis.

M. ulcerans infection is the 3rd most common mycobacterial infection in immunocompetent patients, after *M. tuberculosis* and *M. leprae* infection, and causes cutaneous disease in children living in tropical regions of Africa, South America, Asia, and parts of Australia. In some communities in West Africa, up to 16% of people have been affected. Children <15 yr old are particularly affected in rural tropical counties, accounting for 48% of infected individuals in Africa. Infection follows percutaneous inoculation from minor trauma, such as pricks and cuts from plants or insect bites. After an incubation period of approximately 3 mo, lesions appear as an erythematous nodule, usually on legs or arms. The lesion undergoes central necrosis and ulceration. The lesion, often called a **Buruli ulcer** after the region in Uganda where a large case series was reported, has a characteristic undermined edge, expands over several weeks, and can result in extensive, deep soft tissue destruction or bone involvement. Lesions are typically painless, and constitutional symptoms are unusual. Lesions might heal slowly over 6-9 mo or might continue to spread, leading to deformities, contractures, and disability.

Skin and soft tissue infections caused by **rapidly growing mycobacteria** , such as *M. fortuitum, M. chelonae,* or *M. abscessus,* are rare in children and usually follow percutaneous inoculation from puncture or surgical wounds, minor abrasions, or tattooing. There has been a large outbreak of *M. fortuitum* furunculosis related to nail salon footbaths. Clinical disease usually arises after a 4-6 wk incubation period and manifests as localized cellulitis, painful nodules, or a draining abscess. *M. haemophilum* can cause painful subcutaneous nodules, which often ulcerate and suppurate in immunocompromised patients, particularly after kidney transplantation.

NTM are an uncommon cause of **catheter-associated infections** but are becoming increasingly recognized in this respect. Infections caused by *M. fortuitum, M. chelonae,* or *M. abscessus* can manifest as bacteremia or localized catheter tunnel infections.

Otomastoiditis , or chronic otitis media, is a rare extrapulmonary NTM disease type that specifically affects children with tympanostomy tubes and a history of topical antibiotic or steroid use. *M. abscessus* is the most common causative agent, followed by *M. avium* complex (see Table 244.1). Patients present with painless, chronic otorrhea resistant to antibiotic therapy. CT can reveal destruction of the mastoid bone with mucosal swelling (Fig. 244.4).

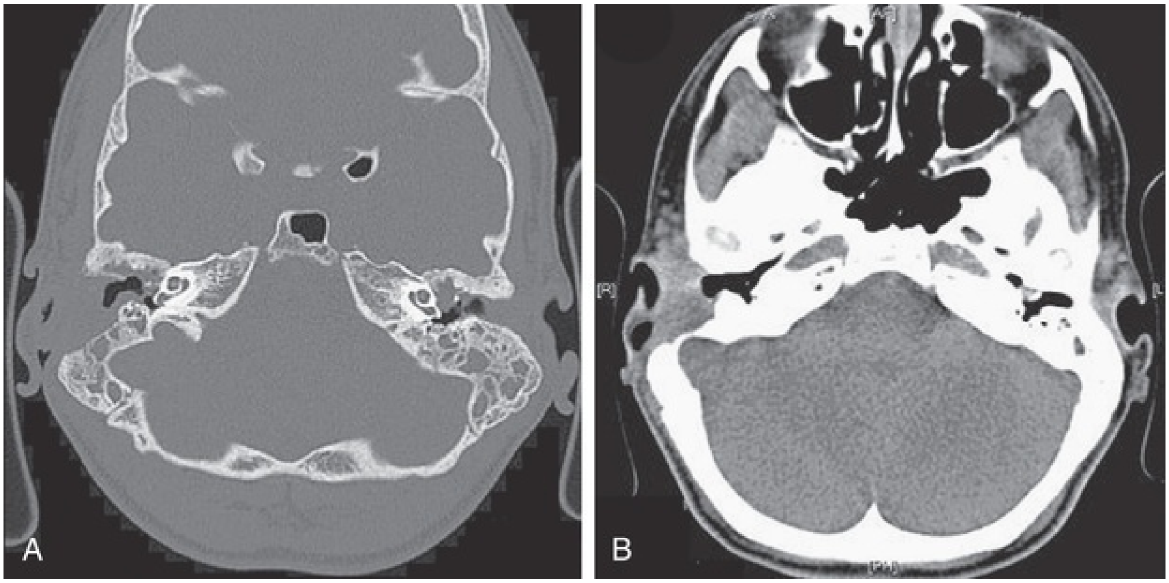

FIG. 244.4 CT images of the middle ear of 6 yr old child infected with *Mycobacterium abscessus,* demonstrating extensive bone destruction in the right mastoid and associated right-sided mucosal swelling. **A,** Bone tissue window setting. **B,** Soft tissue window setting.

Delayed or unsuccessful treatment can result in permanent hearing loss. In unusual circumstances, NTM causes other bone and joint infections that are indistinguishable from those produced by *M. tuberculosis* or other bacterial agents. Such infections usually result from operative incision or accidental puncture wounds. *M. fortuitum* infections from puncture wounds of the foot resemble infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus* .

Pulmonary infections are the most common form of NTM illness in adults but are rare in children. *M. avium* complex bacteria, the most commonly identified organisms (see Table 244.1), are capable of causing acute pneumonitis, chronic cough, or wheezing associated with paratracheal or peribronchial lymphadenitis and airway compression in normal children. Associated constitutional symptoms such as fever, anorexia, and weight loss occur in 60% of these children. Chest radiographic findings are very similar to those for primary tuberculosis, with unilateral infiltrates and hilar lymphadenopathy (Fig. 244.5). Pleural effusion is uncommon. Rare cases of progression to endobronchial granulation tissue have been reported.

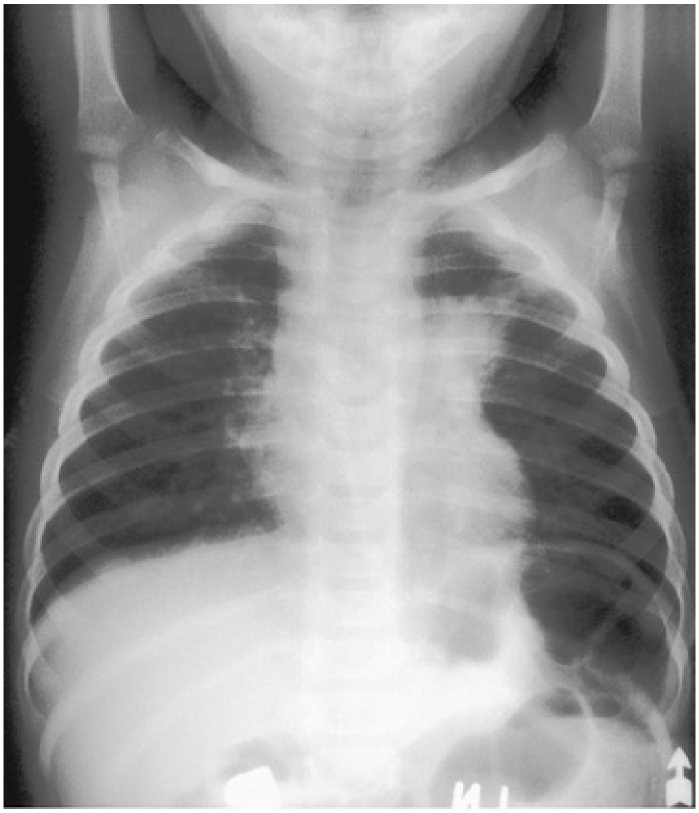

FIG. 244.5 Chest radiograph of 2 yr old child infected with *Mycobacterium avium* complex, demonstrating a left upper lobe infiltrate and left hilar lymphadenopathy.

Pulmonary infections usually occur in adults with underlying chronic lung disease. The onset is insidious and consists of cough and fatigue, progressing to weight loss, night sweats, low-grade fever, and generalized malaise in severe cases. Thin-walled cavities with minimal surrounding parenchymal infiltrates are characteristic, but radiographic findings can resemble those of tuberculosis. A separate disease manifestation occurs in postmenopausal women and is radiologically characterized by bronchiectasis and nodular lesions, often affecting the middle lobe and lingula.

Chronic pulmonary infections specifically affect children with CF and are generally caused by *M. abscessus* and *M. avium* complex. *M. abscessus* primarily affects children, and *M. avium* complex is most common among adults. The percentage of CF patients with at least 1 sputum culture positive for NTM is 6–8.1% overall and increases with age; in CF patients <12 yr old, a prevalence of 3.9% has been reported. The strong representation of *M. abscessus* in these patients is remarkable, because this bacterium is an uncommon isolate in other categories of patients. There are indications that NTM infections in CF patients further accelerate the decline in lung function; antimycobacterial therapy can result in weight gain and improved lung function in affected patients.

Disseminated disease is usually associated with *M. avium* complex infection and occurs in immunocompromised children. The 1st category of patients with disseminated disease includes persons with mutations in genes coding for the interferon-γ receptor (IFNGR) or the IL-12 receptor, or for IL-12 production. Patients with complete **IFNGR deficiency** have severe, difficult-to-treat disease. Those with partial IFNGR deficiency or IL-12 pathway mutations have milder disease that can respond to IFN-γ and antimycobacterial therapy. **Multifocal osteomyelitis** is particularly prevalent in persons with the IFNGR1 818del4 mutation. Recurrences, even years after a course of treatment, and multiple infections are well documented. The 2nd category of patients affected by disseminated disease is patients with acquired immunodeficiency syndrome (**AIDS**). Disseminated NTM disease in patients with AIDS usually appears when CD4 cell counts are <50 cells/µL; in younger children, especially those <2 yr old, these infections occur at higher CD4 cell counts. The most recent estimate of the incidence of disseminated NTM disease is 0.14-0.2 episodes per 100 person-years, a 10-fold decrease from its incidence before highly active antiretroviral therapy (HAART) was available.

Colonization of the respiratory or gastrointestinal (GI) tract probably precedes disseminated *M. avium* complex infections, but screening studies of respiratory secretions or stool samples are not useful to predict dissemination. Continuous high-grade bacteremia is common, and multiple organs are infected, typically including lymph nodes, liver, spleen, bone marrow, and GI tract. Thyroid, pancreas, adrenal gland, kidney, muscle, and brain can also be involved. The most common signs and symptoms of disseminated *M. avium* complex infections in patients with AIDS are fever, night sweats, chills, anorexia, marked weight loss, wasting, weakness, generalized lymphadenopathy, and hepatosplenomegaly. Jaundice, elevated alkaline phosphatase or lactate dehydrogenase levels, anemia, and neutropenia can occur. Imaging studies usually demonstrate massive lymphadenopathy of hilar, mediastinal, mesenteric, or retroperitoneal nodes. The survival in children with AIDS has improved considerably with the availability of HAART.

Disseminated disease in children without any apparent immunodeficiency is exceedingly rare.

Diagnosis

For infections of lymph nodes, skin, bone, and soft tissues, isolation of the causative NTM bacteria by *Mycobacterium* culture, preferably with histologic confirmation of granulomatous inflammation, normally suffices for diagnosis (Table 244.2). The differential diagnosis of NTM lymphadenitis includes acute bacterial lymphadenitis, tuberculosis, cat-scratch disease *(Bartonella henselae)* , mononucleosis, toxoplasmosis, brucellosis, tularemia, and malignancies, especially lymphomas. Differentiation between NTM and *M. tuberculosis* may be difficult, but children with NTM lymphadenitis usually have a Mantoux tuberculin skin test reaction of <15 mm induration, unilateral anterior cervical node involvement, a normal chest radiograph, and no history of exposure to adult tuberculosis. Definitive diagnosis requires excision of the involved nodes for culture and histology. Fine-needle aspiration for PCR and culture can enable earlier diagnosis, before excisional biopsy.

Table 244.2

American Thoracic Society Diagnostic Criteria for Nontuberculous Mycobacteria (NTM) Lung Disease

The **minimum evaluation** of a patient for NTM lung disease should include:

1. Chest radiograph or, when no cavitation is present, HRCT
2. At least 3 sputum or respiratory samples for AFB culture
3. Exclusion of other disease, such as tuberculosis

Clinical diagnosis of NTM is based on pulmonary symptoms, presence of nodules or cavities, as seen on chest radiograph or an HRCT scan, with multifocal bronchiectasis with multiple small nodules, and exclusion of other diagnoses.

Microbiologic diagnosis of NTM:

At least 2 expectorated sputa (or at least 1 bronchial wash or lavage) with positive cultures for NTM, or transbronchial or other lung biopsy showing the presence of granulomatous inflammation or AFB, with 1 or more sputum or bronchial washings that are culture positive for NTM.

AFB, Acid-fast bacilli; HRCT, high-resolution computed tomography.

Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al: An official ATS/IDSA statement: diagnosis, treatment and prevention of nontuberculous mycobacterial diseases, *Am J Respir Crit Care Med* 175:367–416, 2007.

From Brown-Elliott BA, Wallace Jr. RJ: Infections caused by nontuberculous mycobacteria other than *Mycobacterium avium* complex. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 8, Philadelphia, 2015, Elsevier (Table 254-3).

The diagnosis of pulmonary NTM infection in children is difficult because many species of NTM, including *M. avium* complex, are omnipresent in our environment and can contaminate clinical samples or be present but not causative of disease. As a result, isolation of these bacteria from nonsterile specimens (respiratory and digestive tract) does not necessarily reflect true disease. To determine the clinical relevance of isolation of NTM, the ATS/BTS diagnostic criteria are an important support. These criteria take into consideration clinical features and radiologic, pathologic, and microbiologic findings. Their hallmark is the need for multiple positive cultures yielding the same NTM species to make a definitive diagnosis of pulmonary NTM disease. In children, definitive diagnosis often requires invasive procedures such as bronchoscopy and pulmonary or endobronchial biopsy; in CF patients, more aggressive sample pretreatment is necessary to prevent overgrowth by other species, especially *Pseudomonas* . The chance of NTM isolation being clinically relevant differs significantly by species; some species are more likely causative agents of true pulmonary disease (*M. avium* , *M. kansasii* , *M. abscessus* , *M. malmoense*), whereas others are more likely contaminants (*Mycobacterium gordonae* , *M. fortuitum* , *M. chelonae*).

Blood cultures are 90–95% sensitive in AIDS patients with disseminated infection. *M. avium* complex may be detected within 7-10 days of inoculation in almost all patients by automated blood culture systems. In adults, some studies have shown that liver biopsy cultures and stains are more sensitive than blood culture or bone marrow biopsy workup. Commercially available DNA probes differentiate NTM from *M. tuberculosis.* If DNA probes cannot identify the causative mycobacteria, DNA sequencing of bacterial housekeeping genes will always yield a clue to the identity of these NTM. Identification of histiocytes containing numerous AFB from bone marrow and other biopsy tissues provides a rapid presumptive diagnosis of disseminated mycobacterial infection.

Treatment

Therapy for NTM infections is long-term and cumbersome; expert consultation is advised. Therapy involves medical, surgical, or combined treatment (see Chapter 241 , Table 241.3). Isolation of the infecting strain followed by drug-susceptibility testing is ideal, because it provides a baseline for drug susceptibility. Important discrepancies exist between in vitro drug susceptibility and in vivo response to treatment, explained in part by synergism, mainly among first-line antituberculosis drugs. In vitro, **slow growers** (*M. kansasii, M. marinum, Mycobacterium xenopi, M. ulcerans, M. malmoense*) are usually susceptible to the first-line antituberculosis drugs **rifampicin** and **ethambutol** ; *M. avium* complex bacteria are often resistant to these drugs alone but susceptible to the combination and have variable susceptibility to other antibiotics, most importantly the macrolides. **Rapid growers** (*M. fortuitum, M. chelonae, M. abscessus*) are highly resistant to antituberculosis drugs and often have inducible macrolide-resistance mechanisms. Susceptibility to macrolides, aminoglycosides, carbapenems, tetracyclines, and glycylcyclines are most relevant for therapy guidance. In all NTM infections, multidrug therapy (MDT) is essential to avoid development of resistance.

The preferred treatment of NTM lymphadenitis is complete surgical excision. Clinical trials revealed that surgery is more effective than antibiotic treatment (see Table 241.3). Nodes should be removed while still firm and encapsulated. Excision is more difficult if extensive caseation with extension to surrounding tissue has occurred, and complications of facial nerve damage or recurrent infection are more likely in such cases. Incomplete surgical excision is not advised, because chronic drainage can develop. If there are concerns or risk factors for possible *M. tuberculosis* infection, therapy with isoniazid, rifampin, ethambutol, and pyrazinamide should be administered until cultures confirm the cause to be NTM (see Chapter 242). If surgery of NTM lymphadenitis cannot be performed for some reason, or removal of infected tissue is incomplete, or recurrence or chronic drainage develops, a 3 mo trial of chemotherapy is warranted. **Clarithromycin** or **azithromycin** combined with rifabutin or ethambutol are the most common therapy regimens reported (see Table 241.3). Suppuration may still occur on antibiotic therapy. In select patients, a wait-and-see approach can be chosen because the disease can resolve spontaneously, although resolution can take several months.

Posttraumatic cutaneous NTM lesions in immunocompetent patients usually heal spontaneously after incision and drainage without other therapy (see Table 241.3). *M. marinum* is susceptible to rifampin, amikacin, ethambutol, sulfonamides, trimethoprim-sulfamethoxazole, and tetracycline. Therapy with a combination of these drugs, particularly clarithromycin and ethambutol, may be given until 1 mo after the lesion has disappeared. Corticosteroid injections should not be used. Superficial infections with *M. fortuitum* or *M. chelonae* usually resolve after surgical incision and open drainage, but deep-seated or catheter-related infections require removal of infected central lines and therapy with parenteral amikacin plus cefoxitin, ciprofloxacin, or clarithromycin.

Some localized forms of *M. ulcerans* skin disease (Buruli ulcer) can heal spontaneously; for most forms, excisional surgery with primary closure or skin grafting is recommended. Provisional guidelines by the World Health Organization recommend treatment with rifampin and streptomycin, with or without surgery. Currently, all-oral regimens of rifampicin and fluoroquinolones or macrolides are being tested in clinical trials. In clinical experience, a drug treatment duration of 8 wk generally leads to low recurrence levels. **Physiotherapy** after surgery is essential to prevent contractures and functional disabilities.

Pulmonary infections should be treated initially with isoniazid, rifampin, ethambutol, and pyrazinamide pending culture identification and drug-susceptibility testing particularly if their is high suspicion for tuberculosis. For slow-growing NTM, a combination of rifampin or rifabutin, ethambutol, and clarithromycin (or azithromycin) is recommended; exceptions are *M. kansasii* , for which a regimen of isoniazid, rifampicin, and ethambutol is advised, and *M. simiae* , for which no effective regimen is known, and regimens are usually designed on the basis of in vitro drug susceptibilities. After culture conversion, treatment should be continued for at least 1 yr. For pulmonary disease caused by rapidly growing NTM, a combination of macrolides, fluoroquinolones, aminoglycosides, cefoxitin, and carbapenems is the optimal therapy; 3- or 4-drug regimens are selected on drug-susceptibility testing results. In patients with CF, inhaled antibiotics may have a role.

Patients with disseminated *M. avium* complex and IL-12 pathway defects or IFNGR deficiency should be treated for at least 12 mo with clarithromycin or azithromycin combined with rifampin or rifabutin and ethambutol. In vitro susceptibility testing for clarithromycin is important to guide therapy. Once the clinical illness has resolved, lifelong daily prophylaxis with azithromycin or clarithromycin is advisable to prevent recurrent disease. The use of interferon adjunctive therapy is determined by the specific genetic defect.

In children with AIDS, prophylaxis with azithromycin or clarithromycin is indicated to prevent infection with *M. avium* complex. Although few pediatric studies exist, the U.S. Public Health Service recommends either **azithromycin** (20 mg/kg once weekly PO, maximum 1,200 mg/dose; *or* 5 mg/kg once daily PO, maximum 250 mg/dose in patients intolerant of larger dose) or **clarithromycin** (7.5 mg/kg/dose twice daily PO; maximum 500 mg/dose) for

HIV-infected children with significant immune deficiency, as defined by the CD4 count (children ≥6 yr old, CD4 count <50 cells/µL; 2-6 yr old, <75/µL; 1-2 yr old, <500/µL; <1 yr old, <750/µL). Primary prophylaxis may be safely discontinued in children >2 yr old receiving stable HAART for >6 mo and experiencing sustained (>3 mo) CD4 cell recovery well above the age-specific target for initiation of prophylaxis: >100 cells/µL for children ≥6 yr old and >200/µL for children 2-5 yr old. For children <2 yr old, no specific recommendations for discontinuing MAC prophylaxis exist.

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SECTION 8

Spirochetal Infections

OUTLINE

Chapter 245 Syphilis (Treponema pallidum)
Chapter 246 Nonvenereal Treponemal Infections
Chapter 247 Leptospira
Chapter 248 Relapsing Fever (Borrelia)
Chapter 249 Lyme Disease (Borrelia burgdorferi)

CHAPTER 245

Syphilis *(Treponema pallidum)*

Maria Jevitz Patterson, H. Dele Davies

Syphilis is a chronic systemic sexually or vertically (mother to child) transmitted infection that can be easily treated if detected early but manifests with protean clinical symptoms and significant morbidity if left unchecked.

Etiology

Syphilis is caused by *Treponema pallidum*, a delicate, tightly spiraled, motile spirochete with finely tapered ends belonging to the family Spirochaetaceae. The pathogenic members of this genus include *T. pallidum* subspecies *pallidum* (venereal syphilis), *T. pallidum* subspecies *pertenue* (yaws), *T. pallidum* subspecies *endemicum* (bejel or endemic syphilis), and *T. pallidum* subspecies *carateum* (pinta). Because these microorganisms stain poorly and are below the detection limits of conventional light microscopy, detection in clinical specimens requires dark-field, phase contrast microscopy or direct immunofluorescent or silver staining. *T. pallidum* cannot be cultured in vitro. In recent years, advanced detection using nucleic acid amplification testing by polymerase chain reaction (PCR) has been increasingly used by specialized laboratories.

Epidemiology

In addition to presentation at sexually transmitted disease clinics, patients with syphilis are increasingly seen by primary care providers in private practice settings. Two forms of syphilis occur in children and adolescents.

Acquired syphilis is transmitted almost exclusively by sexual contact, including vaginal, anal, and oral exposure. Less-common modes of transmission include transfusion of contaminated blood or direct contact with infected tissues. After an epidemic resurgence of primary and secondary syphilis in the United States that peaked in 1989, the annual rate declined 90% to the lowest ever rate by 2000. The total number of cases of primary and secondary syphilis has subsequently rebounded since 2000, particularly among men who have sex with men and men and women with HIV. Despite a decrease among women for almost a decade, their rates increased every year from 2004 to 2008. Cases of congenital syphilis reached an historic low in 2005 but have subsequently increased, reflecting the rates among women. Since 2012 the rates of congenital syphilis have increased to the highest since 2001 (Fig. 245.1). The increase occurs across every region and all races and ethnicities.

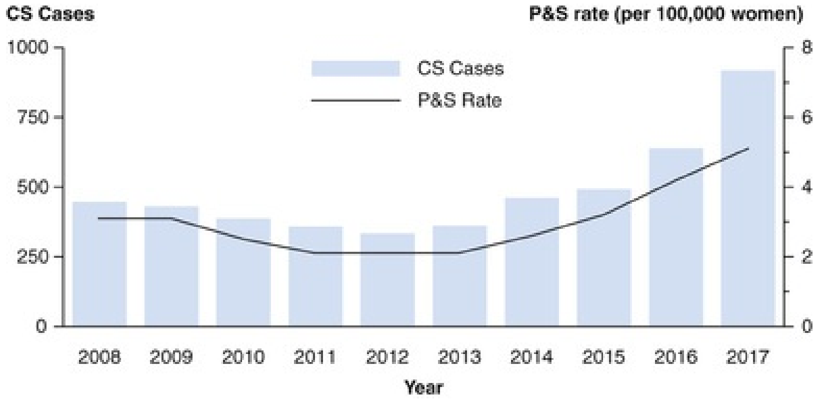

FIG. 245.1 Congenital syphilis—reported cases by year of birth and rates of reported cases of primary and secondary syphilis among women aged 15-44 yr, United States, 2008-2017. *CS* , congenital syphilis; *P&S* , primary and secondary syphilis. (From Centers for Disease Control and Prevention (CDC): *Sexually transmitted disease surveillance 2017* , Atlanta, 2018. US Department of Health and Human Services. Fig. 49. Available at: https://www.cdc.gov/std/stats17/2017-STD-Surveillance-Report_CDC-clearance-9.10.18.pdf .)

Congenital syphilis results from transplacental transmission of spirochetes or occasionally by intrapartum contact with infectious lesions. Women with primary and secondary syphilis and spirochetemia are more likely to transmit infection to the fetus than are women with latent infection. Transmission can occur at any stage of pregnancy, resulting in early fetal loss, preterm or low birthweight infants, stillbirths, neonatal deaths, or infants born with congenital disease. The incidence of congenital infection in offspring of untreated or inadequately treated infected women remains highest during the first 4 yr after acquisition of primary infection, secondary infection, and early latent disease. Maternal factors associated with congenital syphilis include limited access to healthcare, late or no prenatal care, drug use, multiple sex partners, unprotected sexual contact, incarceration, work in the sex trade, and inadequate treatment of syphilis during pregnancy. Congenital syphilis may be seen in the context of untreated, inadequately treated, or undocumented treatment prior to or during pregnancy. In addition, the mother may have been treated appropriately but did not have an adequate serologic response to therapy and the infant was inadequately evaluated or the infant had documented congenital syphilis. Confirmed cases of both acquired and congenital syphilis must be reported to the local health department.

Clinical Manifestations and Laboratory Findings

Many persons infected with syphilis are *asymptomatic for years* or do not recognize the early signs of disease or seek treatment. The Centers for Disease Control and Prevention (CDC) recommends testing all pregnant women and selective testing of adolescents, based on lesions or risk factors (those with other sexually transmitted diseases including HIV, men who have sex with men, incarcerated individuals, or persons who exchange sex for money or drugs). Periods of active clinical disease alternate with periods of latency. **Primary syphilis** is characterized by a chancre and regional lymphadenitis. A **painless papule** (which may be overlooked) appears at the site of entry (usually the genitalia) 2-6 wk after inoculation and develops into a clean, painless, but highly contagious ulcer with raised borders (**chancre)** containing abundant *T. pallidum* . Extragenital chancres can occur at other sites of primary entry and pose a diagnostic challenge. Oral lesions can be mistaken for aphthous ulcers or herpes. Lesions on the nipple can be confused with cellulitis or eczema. Adjacent lymph nodes are generally enlarged and nontender. The chancre heals spontaneously within 4-6 wk, leaving a thin scar.

Untreated patients develop manifestations of **secondary syphilis** related to spirochetemia 2-10 wk after the chancre heals. Manifestations of secondary syphilis include a generalized nonpruritic maculopapular rash, notably involving the palms and soles (Fig. 245.2). Pustular lesions can also develop. **Condylomata lata,** gray-white to erythematous wart-like plaques, can occur in moist areas around the anus, scrotum, or vagina, and white plaques (**mucous patches)** may be found in mucous membranes. Secondary syphilis should be considered in the differential diagnosis of virtually any rash of unknown etiology. A **flu-like illness** with low-grade fever, headache, malaise, anorexia, weight loss, sore throat, myalgias, arthralgias, and generalized lymphadenopathy is often present. Renal, hepatic, or ocular manifestations may be present. Meningitis occurs in 30% of patients with secondary syphilis and is characterized by cerebrospinal fluid (CSF) pleocytosis and elevated protein level. Patients with meningitis might not show neurologic symptoms. Even without treatment, secondary infection becomes **latent** within 1-2 mo after onset of rash. Relapses with secondary manifestations can occur during the 1st yr of latency (the **early latent period). Late syphilis** follows and may be either asymptomatic (**late latent**) or symptomatic (**tertiary**). Tertiary disease follows in about one-third of untreated cases and is marked by neurologic, cardiovascular, and **gummatous lesions** (nonsuppurative granulomas of the skin, bone, and liver, resulting from the host cytotoxic T-cell response). In the pre-antibiotic era, neurologic manifestations of tertiary syphilis (**tabes dorsalis** and **paresis**) were very common. The clinical course of syphilis and its tissue manifestations reflect the immunopathobiology of the host humoral and delayed-type hypersensitivity responses. A robust timeline of progression through the overlapping stages occurs in immunocompromised HIV patients

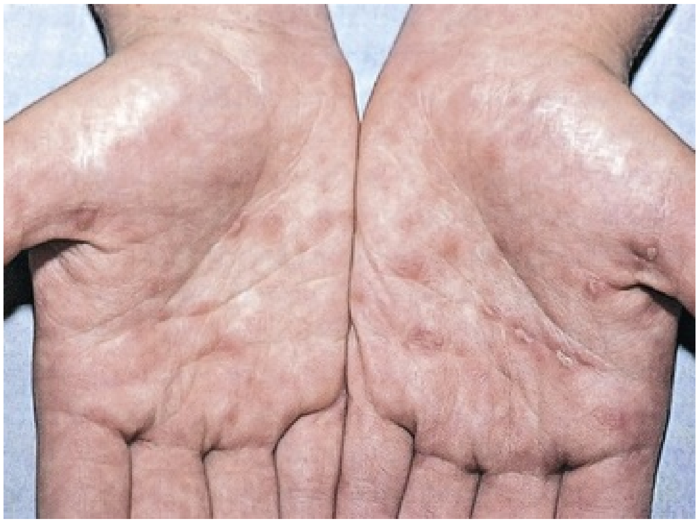

FIG. 245.2 Secondary syphilis. Ham-colored palmar macules on an adolescent with secondary syphilis. (From Weston WL, Lane AT, Morelli JG: *Color textbook of pediatric dermatology,* ed 3, St. Louis, 2002, Mosby.)

Congenital Infection

Untreated syphilis during pregnancy results in a vertical transmission rate approaching 100%, with profound effects on pregnancy outcome, reflecting obliterating endarteritis. Fetal or perinatal death occurs in 40% of affected infants. Premature delivery can also occur. Neonates can also be infected at delivery by contact with an active genital lesion. Most infected infants are asymptomatic at birth, including up to 40% with CSF seeding, and are identified only by routine prenatal screening. In the absence of treatment, symptoms develop within weeks or months. Among infants symptomatic at birth or in the first few months of life, manifestations have traditionally been divided into early and late stages. All stages of congenital syphilis are characterized by a vasculitis, with progression to necrosis and fibrosis. The **early signs** appear during the first 2 yr of life, and the **late signs** appear gradually during the first 2 decades. Early manifestations vary and involve multiple organ systems, resulting from transplacental spirochetemia and are analogous to the secondary stage of acquired syphilis. Hepato-splenomegaly, jaundice, and elevated liver enzymes are common. Histologically, liver involvement includes bile stasis, fibrosis, and extramedullary hematopoiesis. Lymphadenopathy tends to be diffuse and resolve spontaneously, although shotty nodes can persist.

Coombs-negative hemolytic anemia is characteristic. Thrombocytopenia is often associated with platelet trapping in an enlarged spleen. Characteristic **osteochondritis and periostitis** (Fig. 245.3) and a mucocutaneous rash (Fig. 245.4*A* and *B*) manifesting with erythematous maculopapular or vesiculobullous lesions followed by desquamation involving hands and feet (see Fig. 245.4*C*) are common. Mucous patches, persistent rhinitis (**snuffles**), and condylomatous lesions (Fig. 245.5) are highly characteristic features of mucous membrane involvement containing abundant spirochetes. Blood and moist open lesions from infants with congenital syphilis and children with acquired primary or secondary syphilis are infectious until 24 hr of appropriate treatment.

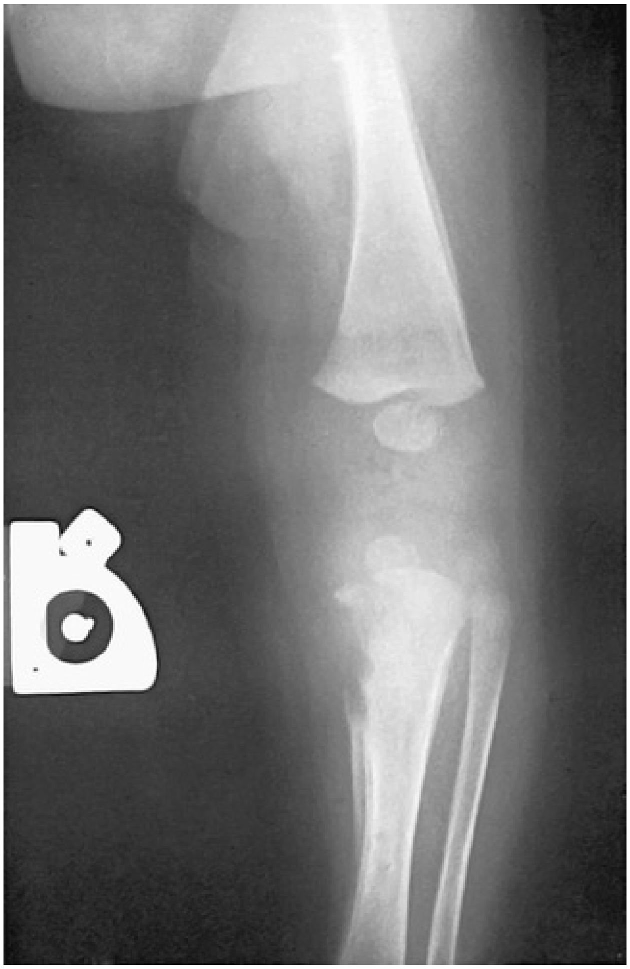

FIG. 245.3 Osteochondritis and periostitis in a newborn with congenital syphilis.

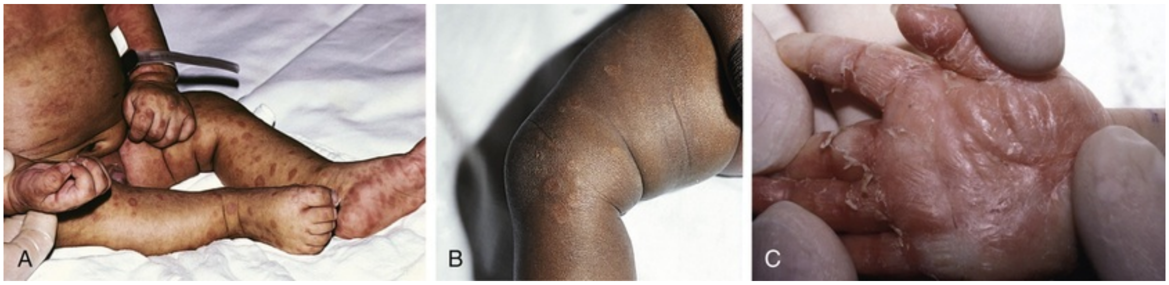

FIG. 245.4 **A** and **B,** Papulosquamous plaques in 2 infants with syphilis. **C,** Desquamation on the palm of a newborn's hand. (**A** and **B** from Eichenfeld LF, Frieden IJ, Esterly NB, editors: *Textbook of neonatal dermatology,* Philadelphia, 2001, WB Saunders, p. 196; **C,** courtesy Dr. Patricia Treadwell.)

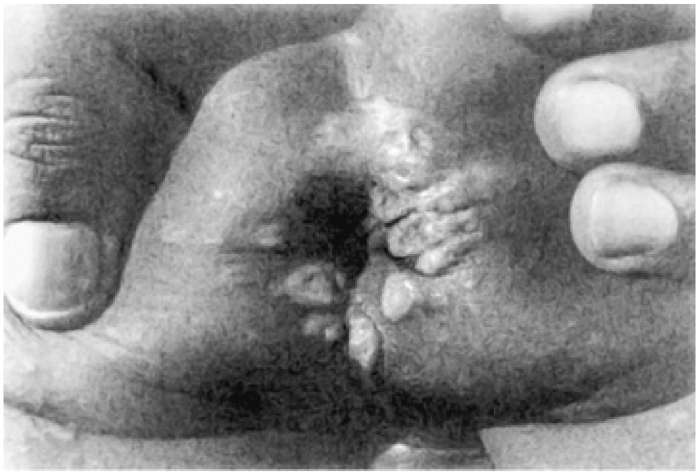

FIG. 245.5 Perianal condylomata lata. (From Karthikeyan K, Thappa DM: Early congenital syphilis in the new millennium, *Pediatr Dermatol* 19:275–276, 2002.)

Bone involvement is common. Roentgenographic abnormalities include **Wimberger lines** (demineralization of the medial proximal tibial metaphysis), multiple sites of osteochondritis at the wrists, elbows, ankles, and knees, and periostitis of the long bones and rarely the skull. The osteochondritis is painful, often resulting in irritability and refusal to move the involved extremity (**pseudoparalysis of Parrot**).

Congenital neurosyphilis is often asymptomatic in the neonatal period, although CSF abnormalities can occur even in asymptomatic infants. Failure to thrive, chorioretinitis, nephritis, and nephrotic syndrome can also be seen. Manifestations of renal involvement include hypertension, hematuria, proteinuria, hypoproteinemia, hypercholesterolemia, and hypocomplementemia, probably related to glomerular deposition of circulating immune complexes. Less-common clinical manifestations of early congenital syphilis include gastroenteritis, peritonitis, pancreatitis, pneumonia, eye involvement (glaucoma and chorioretinitis), nonimmune hydrops, and testicular masses.

Late manifestations (children > 2 yr of age) are rarely seen in developed countries. These result primarily from chronic granulomatous inflammation of bone, teeth, and central nervous system and are summarized in Table 245.1 . Skeletal changes are caused by persistent or recurrent periostitis and associated thickening of the involved bone. Dental abnormalities, such as **Hutchinson teeth** (Fig. 245.6), are common. Defects in enamel formation lead to repeated caries and eventual tooth destruction. **Saddle nose** (Fig. 245.7) is a depression of the nasal root and may be associated with a perforated nasal septum.

Table 245.1

Late Manifestations of Congenital Syphilis

SYMPTOM/SIGN	DESCRIPTION/COMMENTS
Olympian brow	Bony prominence of the forehead caused by persistent or recurrent periostitis
Clavicular or Higoumenaki's sign	Unilateral or bilateral thickening of the sternoclavicular third of the clavicle
Saber shins	Anterior bowing of the midportion of the tibia
Scaphoid scapula	Convexity along the medial border of the scapula
Hutchinson teeth	Peg-shaped upper central incisors; they erupt during 6th yr of life with abnormal enamel, resulting in a notch along the biting surface
Mulberry molars	Abnormal 1st lower (6 yr) molars characterized by small biting surface and excessive number of cusps
Saddle nose*	Depression of the nasal root, a result of syphilitic rhinitis destroying adjacent bone and cartilage
Rhagades	Linear scars that extend in a spoke-like pattern from previous mucocutaneous fissures of the mouth, anus, and genitalia
Juvenile paresis	Latent meningovascular infection; it is rare and typically occurs during adolescence with behavioral changes, focal seizures, or loss of intellectual function
Juvenile tabes	Rare spinal cord involvement and cardiovascular involvement with aortitis
Hutchinson triad	Hutchinson teeth, interstitial keratitis, and 8th nerve deafness
Clutton joint	Unilateral or bilateral painless joint swelling (usually involving knees) from synovitis with sterile synovial fluid; spontaneous remission usually occurs after several weeks
Interstitial keratitis	Manifests with intense photophobia and lacrimation, followed within weeks or months by corneal opacification and complete blindness
8th nerve deafness	May be unilateral or bilateral, appears at any age, manifests initially as vertigo and high-tone hearing loss, and progresses to permanent deafness

* A perforated nasal septum may be an associated abnormality.

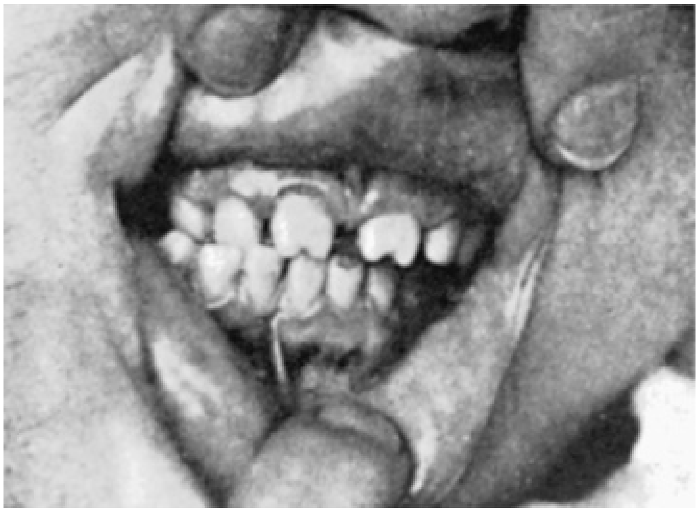

FIG. 245.6 Hutchinson teeth as a late manifestation of congenital syphilis.

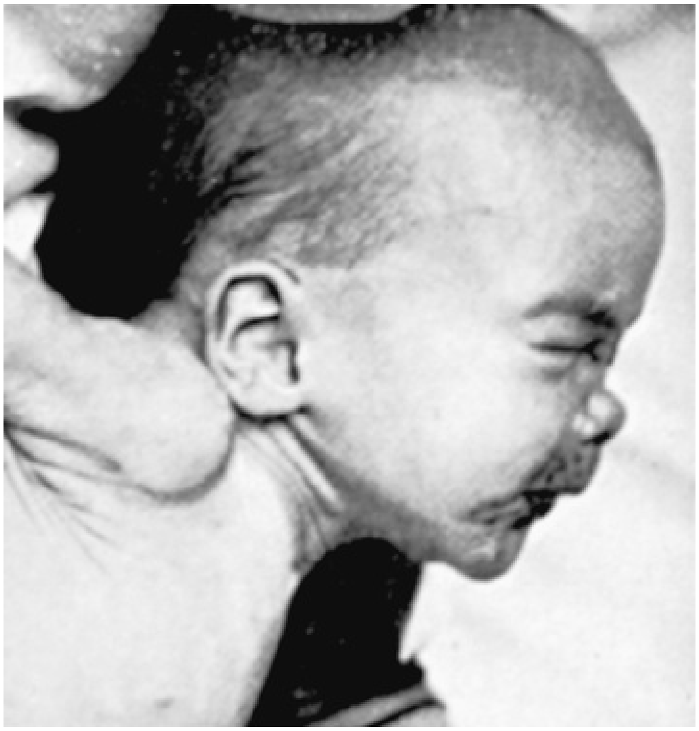

FIG. 245.7 Saddle nose in a newborn with congenital syphilis.

Other late manifestations of congenital syphilis can manifest as hypersensitivity phenomena. These include unilateral or bilateral interstitial keratitis and the **Clutton joint** (see Table 245.1). Other common ocular manifestations include choroiditis, retinitis, vascular occlusion, and optic atrophy. Soft-tissue gummas (identical to those of acquired disease) and paroxysmal cold hemoglobinuria are rare hypersensitivity phenomena.

Diagnosis

Fundamental limitations of the currently available tests for syphilis are vexing, but results must always be interpreted in the context of patient history and physical examination. Physicians should remain aware of their local prevalence rates and treat presumptively when syphilis is suspected by clinical and epidemiologic data. Diagnosis of primary syphilis is confirmed when *T. pallidum* is demonstrated by darkfield microscopy or direct fluorescent antibody testing on specimens from skin lesions, placenta, or umbilical cord. Nucleic acid–based amplification assays, such as PCR, are also used in some specialized laboratories, but are not commercially available. Despite the absence of a true gold standard serologic assay, serologic testing for syphilis remains the principal means for diagnosis and traditionally involves a 2-step screening process with a nontreponemal test followed by a confirmatory treponemal test (Fig. 245.8*A*).

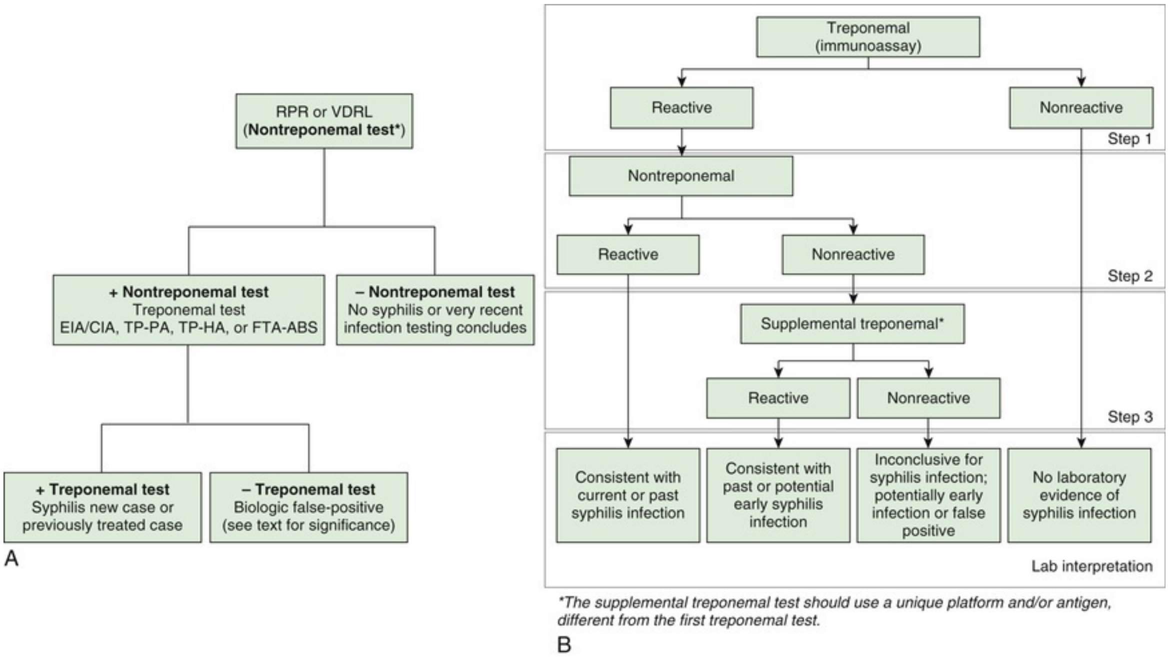
RPR or VDRL
(Nontreponemal test*)
+ Nontreponemal test
Treponemal test
EIA/CIA, TP-PA, TP-HA, or FTA-ABS
– Nontreponemal test
No syphilis or very recent infection testing concludes
+ Treponemal test
Syphilis new case or previously treated case
– Treponemal test
Biologic false-positive (see text for significance)
A
Treponemal (immunoassay)
Reactive
Nonreactive
Step 1
Nontreponemal
Reactive
Nonreactive
Step 2
Supplemental treponemal*
Reactive
Nonreactive
Step 3
Consistent with current or past syphilis infection
Consistent with past or potential early syphilis infection
Inconclusive for syphilis infection; potentially early infection or false positive
No laboratory evidence of syphilis infection
Lab interpretation
B

**The supplemental treponemal test should use a unique platform and/or antigen, different from the first treponemal test.*

FIG. 245.8 **A,** Traditional laboratory testing algorithm for syphilis. **B,** Suggested alternate testing algorithm. *EIA/CIA* , enzyme immunoassay/chemiluminescence immunoassay; *FTA-ABS* , fluorescent treponemal antibody absorption; *RPR* , rapid plasma reagin; *TP-HA* , *Treponema pallidum* hemagglutination; *TP-PA* , *Treponema pallidum* particle agglutination; *VDRL* , Venereal Disease Research Laboratory. *If nontreponemal test is positive qualitatively, a titer is then quantitated. (**A,** Based on data from Workowski KA, Berman S; Centers for Diseases Control and Prevention [CDC]: Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 59[RR-12]:1–110, 26–29, 2010.)

The **Venereal Disease Research Laboratory (VDRL)** and **rapid plasma reagin (RPR)** tests are sensitive *nontreponemal tests* that detect antibodies against phospholipid antigens on the treponeme surface that cross react with cardiolipin-lecithin-cholesterol antigens of damaged host cells. The quantitative results of these tests are helpful both in screening and in monitoring therapy. Titers increase with active disease, including treatment failure or reinfection, and decline with adequate treatment (Fig. 245.9). Nontreponemal tests usually become nonreactive within 1 yr of adequate therapy for primary syphilis and within 2 yr of adequate treatment for secondary disease. 15–20% of patients become **serofast** (nontreponemal titers persisting at low levels for long periods).

In congenital infection, these tests become nonreactive within a few months after adequate treatment. Certain conditions such as infectious mononucleosis and other viral infections, autoimmune diseases, and pregnancy can give false-positive VDRL results. False-positive results are less common with the use of purified cardiolipin-lecithin-cholesterol antigen. All pregnant women should be screened early in pregnancy and at delivery. All positive maternal serologic tests for syphilis, regardless of titer, necessitate thorough investigation. Antibody excess can give a false-negative reading unless the serum is diluted **(prozone effect).** False-negative results can also occur in early primary syphilis, in latent syphilis of long duration, and in late congenital syphilis.

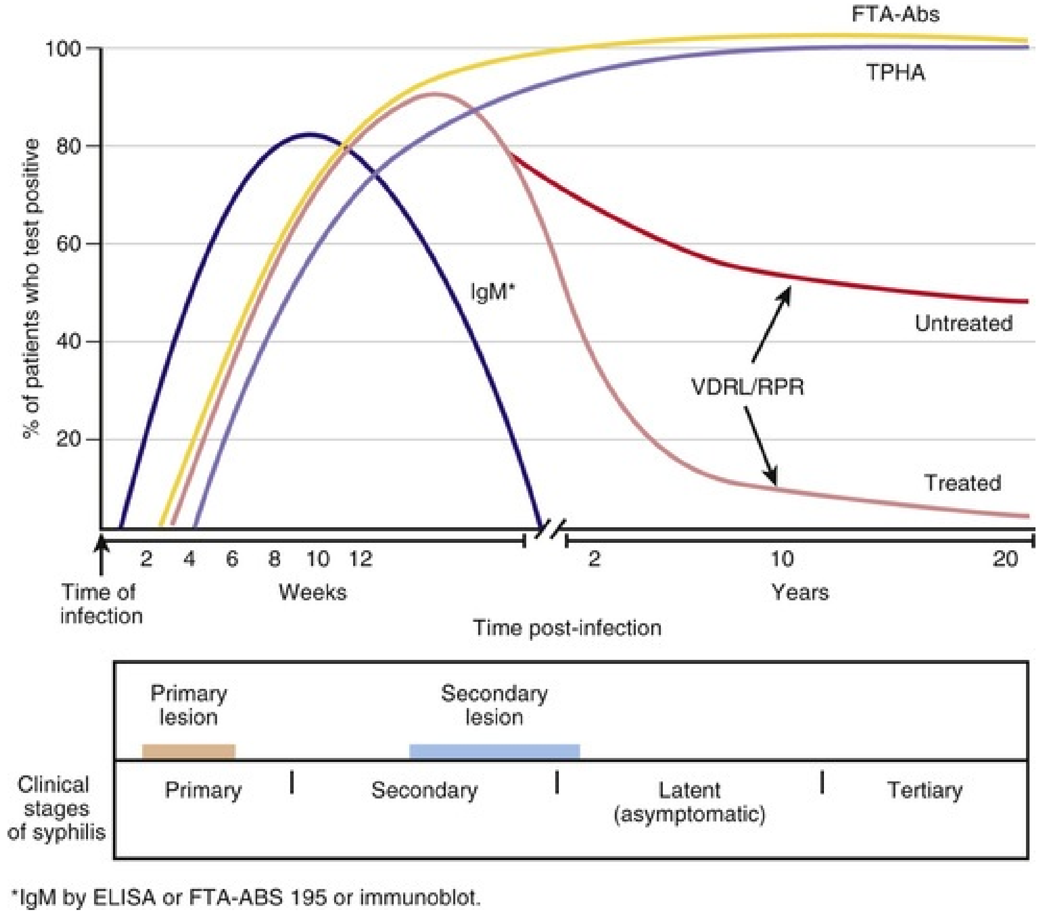

FIG. 245.9 Common patterns of serologic reactivity in syphilis patients. *FTA-Abs* , fluorescent treponemal antibody absorption (test); *RPR* , rapid plasma reagin (test); *TPHA* , *Treponema pallidum* hemagglutination assay; *VDRL* , Venereal Disease Research Laboratory (test). IgM by immunoassay. (From Peeling R, Ye H: Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview. *Bull World Health Organ* 82(6):439–446, 2004.)

Treponemal tests traditionally are used to confirm diagnosis and measure specific *T. pallidum* antibodies (immunoglobulin [Ig] G, IgM, and IgA), which appear earlier than nontreponemal antibodies. These treponemal tests include the *T. pallidum* particle agglutination test, the *T. pallidum* hemagglutination assay, and the fluorescent treponemal antibody absorption test. Treponemal antibody titers become positive soon after initial infection and usually remain positive for life, even with adequate therapy (see Fig. 245.9). These antibody titers do not correlate with disease activity. Traditionally they are useful for diagnosis of a first episode of syphilis and for distinguishing false-positive results of nontreponemal antibody tests but cannot accurately identify length of time of infection, response to therapy, or reinfection.

There is limited cross reactivity of treponemal antibody tests with other spirochetes, including the causative organisms of Lyme disease *(Borrelia burgdorferi),* yaws, endemic syphilis, and pinta. Only venereal syphilis and Lyme disease are found in the United States. *Nontreponemal tests (VDRL, RPR)* are uniformly nonreactive in Lyme disease.

Various enzyme-linked, chemiluminescence, and multiplex flow immunoassays to detect treponemal IgG and IgM have been developed. These assays have increased sensitivity and are amenable to automation and high-volume use. Rapid point-of-care tests are available to allow quality screening programs in resource-limited settings where the World Health Organization otherwise relies on syndromic management of sexually transmitted infections and patients are treated for all likely causes of their constellation of signs and symptoms. In the United States, use of immunoassays has confounded screening because it switches the traditional algorithm: the treponemal-specific testing is done before the nontreponemal testing. Because the former remain positive for life, clinical and epidemiologic data are required to provide guidelines to distinguish cured disease, early syphilis, untreated late latent disease, and true false-positive tests. Benefits of reverse screening are increased detection of transmissible early syphilis and of late latent disease to afford monitoring for tertiary disease. Although the CDC continues to recommend the traditional screen (see Fig. 245.8*A*), they have provided guidelines for interpretation of the reverse screening algorithm (see Fig. 245.8*B*). Interpretation of nontreponemal and treponemal serologic tests in the newborn can be confounded by maternal IgG antibodies transferred to the fetus. Passively acquired antibody is suggested by a neonatal titer at least 4-fold (i.e., a 2 tube dilution) less than the maternal titer. This conclusion can be verified by gradual decline in antibody in the infant, usually becoming undetectable by 3-6 mo of age.

Neurologic involvement can occur at any stage of syphilis. The diagnosis of neurosyphilis remains difficult but is often established by demonstrating pleocytosis and increased protein in the CSF and a positive CSF VDRL test along with neurologic symptoms. The CSF VDRL test is specific but relatively insensitive (22–69%) for neurosyphilis. CSF PCR and IgM immunoblot tests are under development to assist in diagnosis of neurosyphilis.

Darkfield or direct fluorescent antibody microscopy of scrapings from primary lesions or congenital or secondary lesions can reveal *T. pallidum,* often before serology becomes positive, but these modalities are usually not available in clinical practice. Since 2015 different methods of PCR, including routine PCR, nested PCR, reverse-transcriptase PCR, and quantitative PCR targeting different DNA gene sequences have been used by many laboratories as methods to detect *T. pallidum* in primary disease. However, there are currently no commercially available test kits, and each test must be validated for use in each laboratory. Furthermore, these tests are not useful for asymptomatic patients and interpretation may be complicated by the fact that they amplify both dead and living organisms. Placental examination by gross and microscopic techniques can be useful in the diagnosis of congenital syphilis. The disproportionately large placentas are characterized histologically by focal proliferative villitis, endovascular and perivascular arteritis, and focal or diffuse immaturity of placental villi.

Congenital Syphilis

Diagnosis of congenital syphilis requires thorough review of maternal history of syphilis treatment preconception and testing, treatment, and the dynamics of response during the current pregnancy. Regardless of maternal treatment and the presence/absence of symptoms in the infant, proactive evaluation and treatment of exposed neonates is critical (Fig. 245.10 and Table 245.2). Symptomatic infants should be thoroughly evaluated and treated. Fig. 245.10 describes the guidelines for evaluating and managing asymptomatic infants who are considered at risk for congenital syphilis because the maternal nontreponemal and treponemal serology is positive. Internationally adopted, refugee, and immigrant children should also be screened, regardless of history or report of treatment.

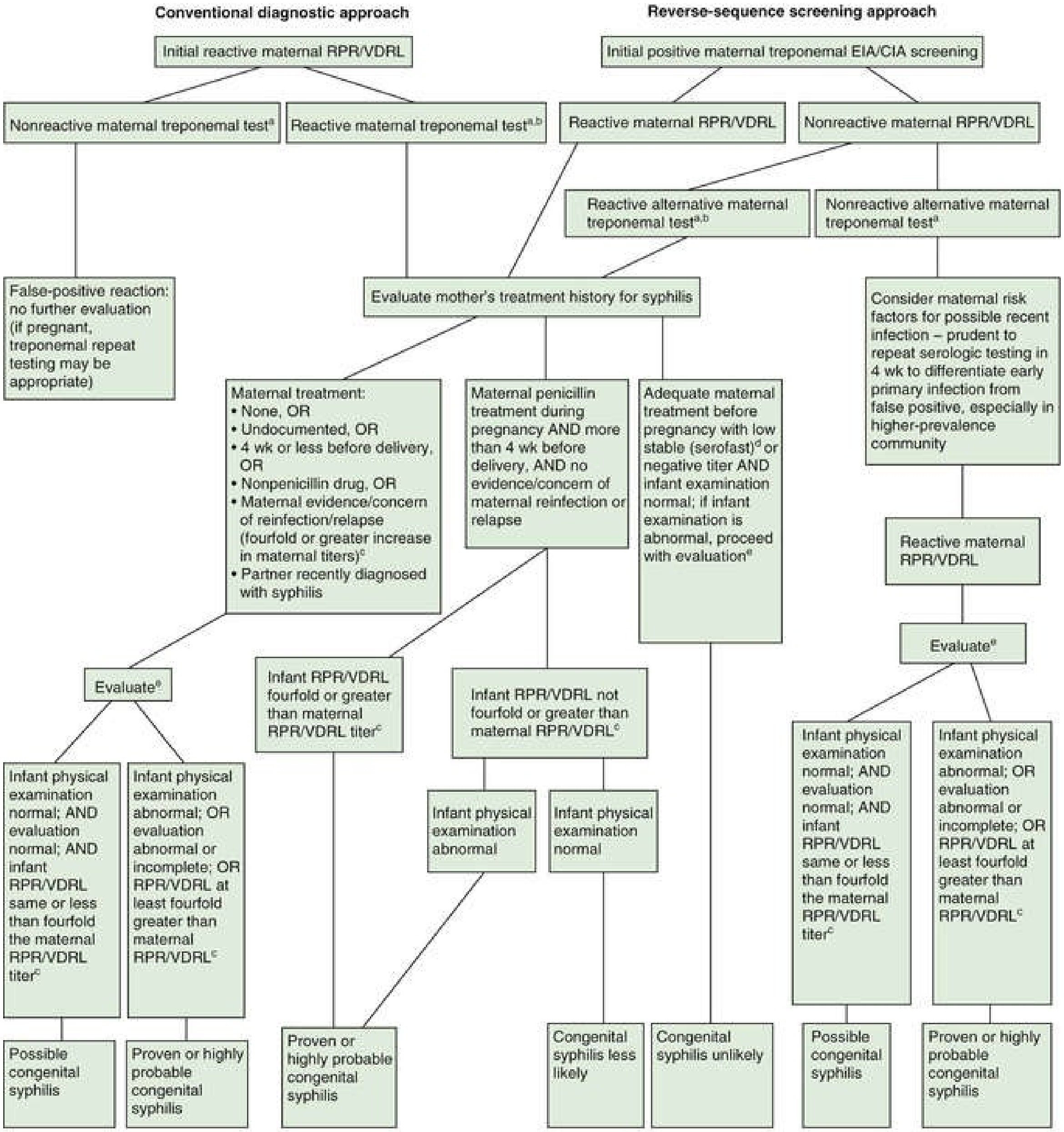
Conventional diagnostic approach
Initial reactive maternal RPR/VDRL
Nonreactive maternal treponemal test[a]
Reactive maternal treponemal test[a,b]
False-positive reaction: no further evaluation (if pregnant, treponemal repeat testing may be appropriate)
Reverse-sequence screening approach
Initial positive maternal treponemal EIA/CIA screening
Reactive maternal RPR/VDRL
Nonreactive maternal RPR/VDRL
Reactive alternative maternal treponemal test[a,b]
Nonreactive alternative maternal treponemal test[a]
Evaluate mother's treatment history for syphilis
Consider maternal risk factors for possible recent infection – prudent to repeat serologic testing in 4 wk to differentiate early primary infection from false positive, especially in higher-prevalence community
Maternal treatment: • None, OR • Undocumented, OR • 4 wk or less before delivery, OR • Nonpenicillin drug, OR • Maternal evidence/concern of reinfection/relapse (fourfold or greater increase in maternal titers)[c] • Partner recently diagnosed with syphilis
Maternal penicillin treatment during pregnancy AND more than 4 wk before delivery, AND no evidence/concern of maternal reinfection or relapse
Adequate maternal treatment before pregnancy with low stable (serofast)[d] or negative titer AND infant examination normal; if infant examination is abnormal, proceed with evaluation[e]
Reactive maternal RPR/VDRL
Evaluate[e]
Evaluate[e]
Infant RPR/VDRL fourfold or greater than maternal RPR/VDRL titer[c]
Infant RPR/VDRL not fourfold or greater than maternal RPR/VDRL[c]
Infant physical examination normal; AND evaluation normal; AND infant RPR/VDRL same or less than fourfold the maternal RPR/VDRL titer[c]
Infant physical examination abnormal; OR evaluation abnormal or incomplete; OR RPR/VDRL at least fourfold greater than maternal RPR/VDRL[c]
Infant physical examination abnormal
Infant physical examination normal
Infant physical examination normal; AND evaluation normal; AND infant RPR/VDRL same or less than fourfold the maternal RPR/VDRL titer[c]
Infant physical examination abnormal; OR evaluation abnormal or incomplete; OR RPR/VDRL at least fourfold greater than maternal RPR/VDRL[c]
Possible congenital syphilis
Proven or highly probable congenital syphilis
Proven or highly probable congenital syphilis
Congenital syphilis less likely
Congenital syphilis unlikely
Possible congenital syphilis
Proven or highly probable congenital syphilis

RPR indicates rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

[a] *Treponema pallidum* particle agglutination (TP-PA) (which is the preferred treponemal test), fluorescent treponemal antibody absorption (FTA-ABS), or microhemagglutination test for antibodies to *T pallidum* (MHA-TP).

[b] Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment for syphilis.

[c] A fourfold change in titer is the same as a change of 2 dilutions. For example, a titer of 1:64 is fourfold greater than a titer of 1:16, and a titer of 1:4 is fourfold lower than a titer of 1:16. When comparing titers, the same type of nontreponemal test should be used (eg, if the initial test was an RPR, the follow-up test should also be an RPR).

[d] Stable VDRL titers 1:2 or less or RPR 1:4 or less beyond 1 year after successful treatment are considered low serofast.

[e] Complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL; other tests as clinically indicated (eg, chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response).

FIG. 245.10 Algorithm for evaluation and treatment of infants born to mothers with reactive serologic tests for syphilis. (From American Academy of Pediatrics: *Red book: 2018-2021 report of the committee on infectious diseases* , ed 31, Elk Grove Village, IL, 2018, American Academy of Pediatrics, Fig. 3.10, p. 779).

Table 245.2

Clues That Suggest a Diagnosis of Congenital Syphilis

EPIDEMIOLOGIC BACKGROUND	CLINICAL FINDINGS
Untreated early syphilis in the mother	Osteochondritis, periostitis
Untreated latent syphilis in the mother	Snuffles, hemorrhagic rhinitis
An untreated mother who has contact with a known syphilitic during pregnancy	Condylomata lata
Mother treated less than 30 days prior to delivery	Bullous lesions, palmar or plantar rash
Mother treated for syphilis during pregnancy with a drug other than penicillin	Mucous patches
Mother treated for syphilis during pregnancy without follow-up to demonstrate 4-fold decrease in titer	Hepatomegaly, splenomegaly
Mother coinfected with HIV	Jaundice
	Nonimmune hydrops fetalis
	Generalized lymphadenopathy
	Central nervous system signs; elevated cell count or protein in cerebrospinal fluid
	Hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia
	Pneumonitis
	Nephrotic syndrome
	Placental villitis or vasculitis (unexplained enlarged placenta)
	Intrauterine growth restriction

Arranged in decreasing order of confidence of diagnosis.

Modified from Remington JS, Klein JO, Wilson CB, et al., editors: *Infectious diseases of the fetus and newborn infant* , ed 6, Philadelphia, 2006, WB Saunders, p. 556.

Diagnosis of neurosyphilis in the newborn with syphilitic infection is confounded by poor sensitivity of the CSF VDRL test in this age group and lack of CSF abnormalities. A positive CSF VDRL test in a newborn warrants treatment for neurosyphilis, even though it might reflect passive transfer of antibodies from serum to CSF. It is now accepted that all infants with a presumptive diagnosis of congenital syphilis should be treated with regimens effective for neurosyphilis because central nervous system involvement cannot be reliably excluded. Diagnosis of syphilis beyond early infancy should lead to consideration of possible child abuse.

For infants with proven or highly probable disease or abnormal physical findings, complete evaluation, including serologic tests (RPR or VDRL), complete blood count with differential and platelet count, liver function tests, long-bone radiographs, ophthalmology examination, auditory brainstem response, and other tests as indicated, should be performed. For infants with a positive VDRL or RPR test result and normal physical examination whose mothers were inadequately treated, further evaluation is not necessary if 10 days of parenteral therapy are administered.

Treatment

The goals of early detection and treatment include treatment of current infection and prevention of both late stage disease and sexual or vertical transmission. *T. pallidum* remains extremely sensitive to penicillin, with no evidence of emerging penicillin resistance, and thus penicillin remains the treatment drug of choice (Table 245.3 and http://www.cdc.gov/std/treatment). Parenteral penicillin G is the only documented effective treatment for congenital syphilis, syphilis during pregnancy, and neurosyphilis. Aqueous crystalline penicillin G is preferred over procaine penicillin, because it better achieves and sustains the minimum concentration of 0.018 µg/mL (0.03 units/mL) needed for 7-10 days to achieve the prolonged treponemicidal levels required for the long dividing time of *T* . *pallidum* . Although nonpenicillin regimens are available to the penicillin-allergic patient, desensitization followed by standard penicillin therapy is the most reliable strategy. Success of treatment also depends upon the integrity of the host immune response. A transient acute systemic febrile reaction called the **Jarisch-Herxheimer reaction** (caused by massive release of endotoxin-like antigens during bacterial lysis) occurs in 15–20% of patients with acquired or congenital syphilis treated with penicillin. It is not an indication for discontinuing penicillin therapy.

Table 245.3

Recommended Treatment for Syphilis in People Older Than 1 Mo

STATUS	CHILDREN	ADULTS
Congenital syphilis	Aqueous crystalline penicillin G, 200,000-300,000 U/kg/day, IV, administered as 50,000 U/kg, every 4-6 hr for 10 days*	
Primary, secondary, and early latent syphilis †	Penicillin G benzathine, ‡ 50,000 U/kg, IM, up to the adult dose of 2.4 million U in a single dose	Penicillin G benzathine, 2.4 million U, IM, in a single dose OR *If allergic to penicillin and not pregnant* , Doxycycline, 100 mg, orally, twice a day for 14 days OR Tetracycline, 500 mg, orally, 4 times/day for 14 days
Late latent syphilis §	Penicillin G benzathine, 50,000 U/kg, IM, up to the adult dose of 2.4 million U, administered as 3 single doses at 1-wk intervals (total 150,000 U/kg, up to the adult dose of 7.2 million U)	Penicillin G benzathine, 7.2 million U total, administered as 3 doses of 2.4 million U, IM, each at 1-wk intervals OR *If allergic to penicillin and not*

		pregnant , Doxycycline, 100 mg, orally, twice a day for 4 wk OR Tetracycline, 500 mg, orally, 4 times/day for 4 wk
Tertiary		Penicillin G benzathine 7.2 million U total, administered as 3 doses of 2.4 million U, IM, at 1-wk intervals *If allergic to penicillin and not pregnant, consult an infectious diseases expert*
Neurosyphilis [‖]	Aqueous crystalline penicillin G, 200,000-300,000 U/kg/day, IV, every 4-6 hr for 10-14 days, in doses not to exceed the adult dose	Aqueous crystalline penicillin G, 18-24 million U per day, administered as 3-4 million U, IV, every 4 hr for 10-14 days [¶] OR Penicillin G procaine, [‡] 2.4 million U, IM, once daily PLUS probenecid, 500 mg, orally, 4 times/day, both for 10-14 days [¶]

[*] If the patient has no clinical manifestations of disease, the cerebrospinal fluid *(CSF)* examination is normal, and the CSF Venereal Disease Research Laboratory *(VDRL)* test result is negative, some experts would treat with up to 3 weekly doses of penicillin G benzathine, 50,000 U/kg, IM. Some experts also suggest giving these patients a single dose of penicillin G benzathine, 50,000 U/kg, IM, after the 10-day course of intravenous aqueous penicillin.

[†] Early latent syphilis is defined as being acquired within the preceding year.

[‡] Penicillin G benzathine and penicillin G procaine are approved for intramuscular administration only.

[§] Late latent syphilis is defined as syphilis beyond 1 yr duration.

[‖] Patients who are allergic to penicillin should be desensitized.

[¶] Some experts administer penicillin G benzathine, 2.4 million U, IM, once per week for up to 3 wk after completion of these neurosyphilis treatment regimens.

IV , intravenously; *IM* , intramuscularly.

From American Academy of Pediatrics: *Red book: 2015 report of the committee on infectious diseases* , ed 30, Elk Grove Village, IL, 2015, American Academy of Pediatrics, Table 3.74.

Acquired Syphilis

Primary, secondary, and early latent disease is treated with a single dose of benzathine penicillin G (50,000 units/kg IM, maximum 2.4 million units). Persons with late latent or tertiary disease require 3 doses at 1 wk intervals. Nonpregnant penicillin-allergic patients without neurosyphilis may be treated with either doxycycline (100 mg PO twice daily for 2 wk) or tetracycline (500 mg PO 4 times daily for 2 wk). Emerging *azalide* and *macrolide resistance* has been documented throughout the U.S. (a 23S rRNA point mutation at position 2058) and more recently worldwide (a 23S rRNA point mutation at position 2059), compromising the effective use of these antibiotics. Careful serologic follow-up is always necessary. Documentation of serologic cure is an essential part of syphilis treatment. Less than a 4-fold decline in titer reflects treatment failure.

The CDC recommends that all persons with syphilis be tested for HIV. Patients coinfected with HIV are at increased risk for neurologic complications and higher rates of treatment failure. CDC guidelines recommend the same treatment of primary and secondary syphilis as for patients who are not infected with HIV, but some experts recommend 3 weekly doses of benzathine penicillin G. HIV-infected patients with late latent syphilis or latent syphilis of unknown duration should have a CSF evaluation for neurosyphilis before treatment.

Sex partners of infected persons of any stage should be evaluated and treated. Persons exposed for 90 days or less preceding diagnosis in a sex partner should be treated presumptively even if seronegative. Persons exposed for more than 90 days before the diagnosis in a sex partner should be treated if seropositive or if serologic tests are not available. Follow-up serology should be performed on treated patients to establish adequacy of therapy, and all patients should be tested for other sexually transmitted diseases, including HIV.

Syphilis in Pregnancy

When clinical or serologic findings suggest active infection or when diagnosis of active syphilis cannot be excluded with certainty, treatment is indicated. The goals of treatment of the pregnant woman include eradication of maternal disease, prevention of mother to child transmission, and treatment of fetal infection. Patients should be treated immediately with the penicillin regimen appropriate for the woman's stage of syphilis. Women who have been adequately treated in the past do not require additional therapy unless quantitative serology suggests evidence of reinfection (**4-fold elevation in titer**). Doxycycline and tetracycline *should not be* administered during pregnancy, and macrolides do not effectively prevent fetal infection. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin.

Congenital Syphilis

Adequate maternal treatment at least 30 days prior to delivery is likely to prevent congenital syphilis. All infants born to mothers with syphilis should be followed until nontreponemal serology is negative. The infant should be treated if there is any uncertainty about the adequacy of maternal treatment. The goal of infant treatment is prevention of organ damage, skeletal deformity, and developmental delay. Any infant at risk of congenital syphilis should be evaluated for HIV.

Congenital syphilis is treated with aqueous penicillin G (100,000-150,000 units/kg/24 hr divided every 12 hr IV for the 1st wk of life, and every 8 hr thereafter) or procaine penicillin G (50,000 units/kg IM once daily) given for 10 days. Both penicillin regimens are recognized as adequate therapy for congenital syphilis, but higher concentrations of penicillin are achieved in the CSF of infants treated with intravenous aqueous penicillin G than in those treated with intramuscular procaine penicillin. Treated infants should be followed every 2-3 mo to confirm at least a 4-fold decrease in nontreponemal titers. Treated infants with congenital neurosyphilis should undergo clinical and CSF evaluation at 6-mo intervals until CSF is normal. At age 2 these infants should receive a full developmental assessment. In a very-low-risk neonate who is asymptomatic and whose mother was treated appropriately, without evidence of relapse or reinfection, but with a low and stable VDRL titer (serofast), no evaluation is necessary. Some specialists would treat such an infant with a single dose of benzathine penicillin G 50,000 units/kg IM.

Prevention

Syphilis, including congenital syphilis, is a reportable disease in all 50 states and the District of Columbia. Testing is indicated at any time for persons with suspicious lesions, a history of recent sexual exposure to a person with syphilis, or diagnosis of another sexually transmitted infection, including HIV infection. The resurgence of syphilis compels clinicians to remain cognizant of its protean manifestations to avoid missed or late diagnosis. Timely treatment lessens risk of community spread. Despite the genome sequencing of *T. pallidum* in 1998, vaccine prevention remains elusive, confounded by the treponeme's ability to evade the immune system.

Congenital Syphilis

Congenital syphilis is a preventable disease, a sentinel event indicating multiple missed opportunities. Primary prevention is tied to prevention of syphilis in women of childbearing age and secondary prevention with early diagnosis and prompt treatment of women and their partners. Access to and use of comprehensive prenatal care is key, with careful history taking (including interim sexual partners) at each visit. Routine prenatal screening for syphilis remains the most important factor in identifying infants at risk for developing congenital syphilis. Screening all women at the beginning of prenatal care is an evidence-based standard of care and legally required in all states. In pregnant women without optimal prenatal care, serologic screening for syphilis should be performed at the time pregnancy is diagnosed. Any woman who is delivered of a stillborn infant at 20 wk or fewer of gestation should be tested for syphilis. In communities and populations with a high prevalence of syphilis and in patients at high risk (women with a history of incarceration, drug use, or multiple or concurrent partners), testing should be performed at least 2 additional times: at the beginning of the 3rd trimester (28 wk) and at delivery. Some states mandate repeat testing at delivery for all women, underscoring the importance of preventive screening. Women at high risk for syphilis should be screened even more frequently, either monthly or pragmatically in the case of inconsistent prenatal care, at every medical encounter because they can have repeat infections during pregnancy or reinfection late in pregnancy. Follow-up serologic testing of all treated women should be done after treatment to document titer decline, relapse, or reinfection.

No newborn should leave the hospital without the mother's syphilis status having been determined at least once during pregnancy or at delivery. In states conducting newborn screening for syphilis, both the mother's and infant's serologic results should be known before discharge. In addition, all previously uninvestigated infants of an infected mother should be screened. Strong linkages between clinicians and public health practitioners remain essential for comprehensive prevention of acquired and congenital syphilis.

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CHAPTER 246

Nonvenereal Treponemal Infections

Stephen K. Obaro, H. Dele Davies

Nonvenereal treponemal infections—yaws, bejel (endemic syphilis), and pinta—are caused by different subspecies of *Treponema pallidum* and occur in tropical and subtropical areas. The causative agents of nonvenereal treponematoses—*T. pallidum pertenue*, *T. pallidum* subspecies *endemicum*, and *Treponema carateum*—cannot be distinguished from *T. pallidum* subspecies *pallidum* by morphologic or serologic tests.

In general, nonvenereal treponematoses have prominent cutaneous manifestations and relapsing courses, as in venereal syphilis, but they are not found in urban centers, they are not sexually transmitted, and they are not congenitally acquired. Transmission is primarily through body contact, poor hygiene, crowded conditions, and poor access to healthcare. Children also serve as the primary reservoirs for these organisms, spreading infection via skin-to-skin and skin-to-mucous membrane contact, and possibly via fomites as well.

Penicillin remains the treatment of choice for syphilis and nonvenereal treponemal infections.

246.1

Yaws *(Treponema pertenue)*

Stephen K. Obaro, H. Dele Davies

Yaws is the most prevalent nonvenereal treponematosis. The causative agent, *Treponema pertenue* , bears very close genomic resemblance to *T. pallidum* subspecies *pallidum* . The overall sequence identity between the genomes of *T. pallidum pertenue* and *T. pallidum* subspecies *pallidum is* 99.8%. Yaws is a contagious, chronic, relapsing infection involving the skin and bony structures caused by the spirochete *T. pertenue,* which is identical to *T. pallidum* microscopically and serologically. It occurs in tropical regions with heavy rainfall and annual temperatures ≥27°C (80°F). Almost all cases occur in children in tropical and subtropical countries. It is also referred to as “framboesia,” “pian,” “parangi,” and “bouba.” A high percentage of the population is infected in endemic areas.

T. pertenue is transmitted by direct contact from an infected lesion through a skin abrasion or laceration. Transmission is facilitated by overcrowding and poor personal hygiene in the rain forest areas of the world. Yaws predominantly affects children, with approximately 75% of cases being reported in children younger than 15 yr of age. This population also constitutes the reservoir for disease transmission. The initial papular lesion, which constitutes **primary yaws** , also described as the **mother yaw,** occurs 2-8 wk after inoculation. This lesion typically involves the buttocks or lower extremities. The papule develops into a raised, raspberry-like papilloma and is often accompanied by regional lymphadenopathy. The skin pathology is very similar to that of venereal syphilis, consisting of epidermal hyperplasia and papillomatosis (Fig. 246.1). Healing of the mother yaw leaves a hypopigmented scar. The **secondary stage** lesions can erupt anywhere on the body before or after the healing of the mother yaw and may be accompanied by lymphadenopathy, anorexia, and malaise. Multiple cutaneous lesions (daughter yaws, pianomas, or frambesias) appear, spread diffusely, ulcerate, and are covered by exudates containing treponemes. Secondary lesions heal without scarring. Recurrent lesions are common within 5 yr after the primary lesion.

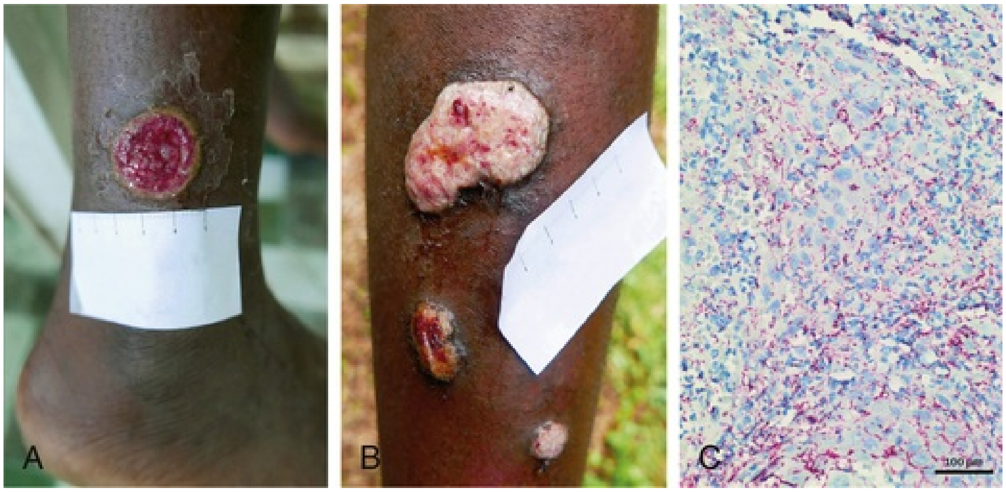

FIG. 246.1 Yaws lesions in a patient with treatment failure associated with macrolide-resistant *T p pertenue* . **A,** Primary lesion (*red* , moist 2.5 cm ulcer) on the left leg of an 11 yr old patient with yaws observed at the 30-mo survey. Lesional swab PCR was positive for *T p pertenue* with wild-type 23S rRNA. **B,** Secondary yaws papillomas (multiple nodules with yellow color granular surface) seen at 36-mo survey. These lesions were PCR positive for *T p pertenue* with A2059G mutation in 23S rRNA. **C,** Photomicrograph of skin biopsy of the larger papilloma lesion in panel **B** with abundant spirochete organisms stained bright red by the *Treponema pallidum* immunohistochemical stain (×400 magnification). *T p pertenue* , *Treponema pallidum* subspecies pertenue. (From Mitja O, Godornes C, Houinei W, et al: Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study, *Lancet* 391:1599–1606, 2018. Fig. 2).

The lesions are often associated with bone pain resulting from underlying periostitis or osteomyelitis, especially of the fingers, nose, and tibia. The initial period of clinical activity is followed by a 5-10 yr period of latency. The appearance of tertiary stage lesions develops in approximately 10% of infected patients, with onset typically at puberty with solitary and destructive lesions. These lesions occur as painful papillomas on the hands and feet, gummatous skin ulcerations, or osteitis. Bony destruction and deformity, juxta-articular nodules, depigmentation, and painful hyperkeratosis **(dry crab yaws)** of the palms and soles are common. Approximately 10% of patients may progress and develop tertiary stage lesions after 5 yr or more of untreated infection, although this outcome is now rare.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Darkfield examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis.

The nontreponemal agglutination tests such as the rapid plasma reagin and Venereal Diseases Research Laboratory tests are positive in untreated cases, and these tests can be used for test of cure, because they revert to negative following treatment. However, the treponemal tests (*T. pallidum* hemagglutination assay, *T. pallidum* particle agglutination assay, and fluorescent treponemal antibody absorption) are more specific and remain positive for life. New immunochromatographic test strips that can be applied for testing both whole blood and serum are simple, cheap, and easy to use and do not require refrigeration. However, they have lower sensitivity compared to the antibody assays and appear to work best in persons with more active disease.

Differential diagnosis includes other conditions with similar cutaneous manifestations such as eczema, psoriasis, excoriated chronic scabies, tungiasis, leishmaniasis, tropical ulcer cutaneous mycoses, and verrucae. Involvement of the bone may mimic dactylitis that is commonly associated with sickle cell disease

Treatment of yaws consists of a single dose of the long-acting benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children < 10 yr) for index patients and all contacts. Patients allergic to penicillin may be treated with erythromycin, doxycycline, or tetracycline at appropriate doses for venereal syphilis (see Chapter 245). One oral dose of azithromycin (30 mg/kg; maximum: 2 g) is as effective as benzathine penicillin. Treatment cures the lesions of active yaws, renders them noninfectious, and prevents relapse. Family members, contacts, and patients with latent infection should receive the same dose as those with active disease. Eradication of yaws from some endemic areas has been accomplished by treating the entire population (mass treatment) with azithromycin, although reemergence has been reported in those who did not receive mass treatment.

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246.2

Bejel (Endemic Syphilis; *Treponema pallidum* endemicum)

Stephen K. Obaro, H. Dele Davies

Bejel, or endemic syphilis, affects children in remote rural communities living in poor hygienic conditions. Unlike yaws, bejel can occur in temperate as well as dry, hot climates. Infection with *T. pallidum* subspecies *endemicum* follows penetration of the spirochete through traumatized skin or mucous membranes. In experimental infections, a primary papule forms at the inoculation site after an incubation period of 3 wk. A primary lesion is almost never visualized in human infections; however, primary ulcers have been described surrounding the nipples of nursing mothers with infected children.

The clinical manifestations of the **secondary stage** typically occur 3-6 mo after inoculation and are confined to the skin and mucous membranes. They consist of highly infectious mucous patches on the oral mucosa and condyloma-like lesions on the moist areas of the body, especially the axilla and anus. These mucocutaneous lesions resolve spontaneously over a period of several months, but recurrences are common. The secondary stage is followed by a variable latency period before the onset of late or tertiary bejel. The tertiary stage can occur as early as 6 mo or as late as several years after resolution of initial symptoms. The lesions in the tertiary stage are identical to those of yaws and include gumma formation in skin, subcutaneous tissue, and bone, resulting in painful destructive ulcerations, swelling, and deformity.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis.

Differentiation from venereal syphilis is extremely difficult in an endemic area. Bejel is distinguished by the absence of a primary chancre and lack of involvement of the central nervous system and cardiovascular system during the late stage.

Treatment of early infection consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children < 10 yr). Late infection is treated with 3 injections of the same dosage at intervals of 7 days. Patients allergic to penicillin may be treated with erythromycin or tetracycline.

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246.3

Pinta *(Treponema carateum)*

Stephen K. Obaro, H. Dele Davies

Pinta is a chronic, nonvenereally transmitted infection caused by *T. pallidum* subsp. *carateum*, a spirochete morphologically and serologically indistinguishable from other human treponemes. This is perhaps the mildest of the nonvenereal treponematoses. The disease is endemic in Mexico, Central America, South America, and parts of the West Indies and largely affects children younger than 15 yr of age.

Infection follows direct inoculation of the treponeme through abraded skin. After a variable incubation period of days, the **primary** lesion appears at the inoculation site as a small asymptomatic erythematous papule resembling localized psoriasis or eczema. The regional lymph nodes are often enlarged. Spirochetes can be visualized on darkfield examination of skin scrapings or from biopsy of the involved lymph nodes. After a period of enlargement, the primary lesion disappears. Unlike primary yaws, the lesion does not ulcerate but can expand with central depigmented resolution. **Secondary** lesions follow within 6-8 mo and consist of small macules and papules on the face, scalp, and other sun-exposed portions of the body. These pigmented, highly infectious lesions are scaly and nonpruritic and can coalesce to form large plaque-like elevations resembling psoriasis. In the late or **tertiary** stage, atrophic and depigmented lesions develop on the hands, wrists, ankles, feet, face, and scalp. Hyperkeratosis of palms and soles is uncommon.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Darkfield examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of cross reactivity, are used to confirm the diagnosis.

Treatment consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children < 10 yr). Tetracycline and erythromycin are alternatives for patients allergic to penicillin. Treatment campaigns and improvement of standards of living are necessary for reduction and elimination of disease.

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CHAPTER 247

Leptospira

H. Dele Davies, Kari A. Simonsen

Leptospirosis is a common and widespread zoonosis caused by aerobic, motile spirochetes of the genus *Leptospira*.

Etiology

Leptospira spp. are thin, helix-shaped members of the phylum Spirochaetes. There are 22 species identified within the genus *Leptospira* , and these are further divided into over 300 serovars. There are at least 10 pathogenic *Leptospira* species, with serovars demonstrating preferential host specificity.

Epidemiology

Leptospirosis has a worldwide distribution, but most human cases occur in tropical and subtropical countries with disease burden disproportionately affecting resource-poor populations. Leptospires survive for days to weeks in warm and damp environmental conditions, including water and moist soil. In the United States, the CDC estimates 100-200 annual cases; Hawaii reports about 50% of US cases, with Pacific coastal and Southern states having higher incidence than the remainder of the country. Leptospires infect many species of animals, including rats, mice, and moles; livestock such as cattle, goats, sheep, horses, and pigs; wild mammals like raccoons or opossums; and domestic dogs. Infected animals excrete spirochetes in their urine for prolonged periods. Globally, most human cases result from exposure to water or soil contaminated with rat urine; however, the major animal reservoir in the United States is the dog. Groups at high risk for leptospirosis include persons exposed occupationally or recreationally to contaminated soil, water, or infected animals. High-risk occupations include agricultural workers, veterinarians, abattoir workers, meat inspectors, rodent control workers, laboratory workers, sewer workers, and military personnel. Exposure to contaminated floodwaters is also a documented source of infection. Transmission via animal bites and directly from person to person has been rarely reported.

Pathology and Pathogenesis

Leptospires enter human hosts through mucous membranes (primarily eyes, nose, and mouth), transdermally through abraded skin, or by ingestion of contaminated water. After penetration, they circulate in the bloodstream, causing endothelial damage of small blood vessels with secondary ischemic damage to end organs.

Clinical Manifestations

The spectrum of human leptospirosis ranges from asymptomatic infection to severe disease (5–10% of infections) with multiorgan dysfunction and death. The onset is usually abrupt, and the illness may follow a monophasic or the classically described biphasic course (Fig. 247.1). The incubation period ranges from 2 to 30 days, following which there is an **initial** or **septicemic phase** lasting 2-7 days, during which leptospires can be isolated from the blood, cerebrospinal fluid (CSF), and other tissues. This phase may be followed by a brief period of well-being before onset of a second symptomatic **immune** or **leptospiruric phase** . This phase is associated with the appearance of circulating IgM antibody, disappearance of organisms from the blood and CSF, and appearance of signs and symptoms associated with localization of leptospires in the tissues. Despite the presence of circulating antibody, leptospires can persist in the kidney, urine, and aqueous humor. The immune phase can last for several weeks. Symptomatic infection may be anicteric or icteric.

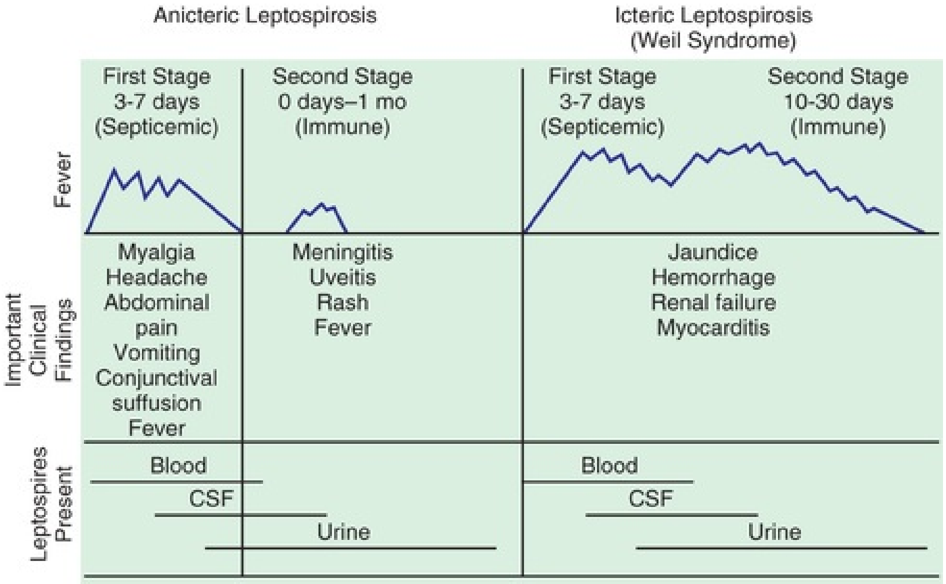
Anicteric Leptospirosis
Icteric Leptospirosis
(Weil Syndrome)
First Stage
3-7 days
(Septicemic)
Second Stage
0 days–1 mo
(Immune)
First Stage
3-7 days
(Septicemic)
Second Stage
10-30 days
(Immune)
Fever
Important Clinical Findings
Myalgia
Headache
Abdominal pain
Vomiting
Conjunctival suffusion
Fever
Meningitis
Uveitis
Rash
Fever
Jaundice
Hemorrhage
Renal failure
Myocarditis
Leptospires Present
Blood
CSF
Urine
Blood
CSF
Urine

FIG. 247.1 Stages of anicteric and icteric leptospirosis. Correlation between clinical findings and presence of leptospires in body fluids, *CSF* , cerebrospinal fluid. (Reprinted with permission from Feigin RD, Anderson DC: Human leptospirosis, *CRC Crit Rev Clin Lab Sci* 5:413–467, 1975. Copyright CRC Press, Inc., Boca Raton, FL.)

Anicteric Leptospirosis

The **septicemic phase** of anicteric leptospirosis has an abrupt onset with flulike signs of fever, shaking chills, lethargy, severe headache, malaise, nausea, vomiting, and severe debilitating myalgia most prominent in the lower extremities, lumbosacral spine, and abdomen. Bradycardia and hypotension can occur, but circulatory collapse is uncommon. Conjunctival suffusion with photophobia and orbital pain (in the absence of chemosis and purulent exudate), generalized lymphadenopathy, and hepatosplenomegaly may also be present. A transient (<24 hr) erythematous maculopapular, urticarial, petechial, purpuric, or desquamating rash occurs in 10% of cases. Rarer manifestations include pharyngitis, pneumonitis, arthritis, carditis, cholecystitis, and orchitis. The **second** or **immune phase** can follow a brief asymptomatic interlude and is characterized by recurrence of fever and aseptic meningitis. Although 80% of infected children have abnormal CSF profiles, only 50% have clinical meningeal manifestations. CSF abnormalities include a modest elevation in pressure, pleocytosis with early polymorphonuclear leukocytosis followed by mononuclear predominance rarely exceeding 500 cells/mm^3 , normal or slightly elevated protein levels, and normal glucose values. Encephalitis, cranial and peripheral neuropathies, papilledema, and paralysis are uncommon. A self-limited unilateral or bilateral uveitis can occur during this phase, rarely resulting in permanent visual impairment. Central nervous system symptoms usually resolve spontaneously within 1 wk, with almost no mortality.

Icteric Leptospirosis (Weil Syndrome)

Weil syndrome is a severe form of leptospirosis seen more commonly in adults (>30 yr) than in children. The initial manifestations are similar to those described for anicteric leptospirosis . The immune phase, however, is characterized by jaundice, acute renal dysfunction, thrombocytopenia, and, in fulminant cases, pulmonary hemorrhage and cardiovascular collapse. Hepatic involvement leads to right upper quadrant pain, hepatomegaly, direct and indirect hyperbilirubinemia, and modestly elevated serum levels of hepatic enzymes. Liver function usually returns to normal after recovery. Patients have abnormal findings on urinalysis (hematuria, proteinuria, and casts), and azotemia is common, often associated with oliguria or anuria. Acute kidney failure occurs in 16–40% of cases. Abnormal electrocardiograms are present in 90% of cases, but congestive heart failure is uncommon. Transient thrombocytopenia occurs in >50% of cases. Rarely, hemorrhagic manifestations occur, including epistaxis, hemoptysis, and pulmonary, gastrointestinal, and adrenal hemorrhage. Patients with pulmonary hemorrhage syndrome may have >50% mortality rate, although the overall mortality rate for severe disease is lower, about 5–15%.

Diagnosis

Leptospirosis should be considered in the differential diagnosis of acute flulike febrile illnesses with a history of direct contact with animals or with soil or water contaminated with animal urine. The disease may be difficult to distinguish clinically from dengue or malaria in endemic areas.

The diagnosis is most often confirmed by serologic testing and less often confirmed by isolation of the infecting organism from clinical specimens. The gold standard diagnostic method is the microscopic agglutination test, a serogroup-specific assay using live antigen suspension of leptospiral serovars and dark-field microscopy for agglutination. A 4-fold or greater increase in titer in paired sera confirms the diagnosis. Agglutinins usually appear by the 12th day of illness and reach a maximum titer by the 3rd wk. Low titers can persist for years. Approximately 10% of infected persons do not have detectable agglutinins, presumably because available antisera do not identify all *Leptospira* serotypes. Additionally, enzyme-linked immunosorbent assay (ELISA) methods, latex agglutination, and immunochromatography are commercially available, and DNA PCR diagnostics have been developed. Phase-contrast and dark-field microscopy are insensitive for spirochete detection, but organisms may be identified using Warthin-Starry silver stain or fluorescent antibody staining of tissue or body fluids. Unlike other pathogenic spirochetes, leptospires can be recovered from the blood or CSF during the first 10 days of illness and from urine after the 2nd wk by repeated culture of small inoculum (i.e., one drop of blood or CSF in 5 mL of medium) on commercially available selective media. However, the inoculum in clinical specimens is small, and growth can take up to 16 wk.

Treatment

Leptospira spp. demonstrate in vitro susceptibility to penicillin and tetracyclines, but in vivo effectiveness of these antibiotics in treating human leptospirosis is unclear due to the naturally high spontaneous recovery rates. Some studies suggest that initiation of treatment before the 7th day shortens the clinical course and decreases the severity of the infection; thus treatment with penicillin G, cefotaxime, ceftriaxone, or doxycycline (in children ≥8 yr of age) should be instituted early when the diagnosis is suspected. There is evidence that a short (<2 wk) course of doxycycline may be safely used in children >2 yr of age. Parenteral penicillin G (6-8 million U/m^2 /day divided every 4 hr IV for 7 days) is recommended, with doxycycline 2 mg/kg/day divided in 2 doses with maximum of 100 mg twice daily as an alternative for patients allergic to penicillin. Cefotaxime, ceftriaxone, and azithromycin have been evaluated in clinical trials and have demonstrated equivalent effectiveness with doxycycline. These antibiotics can be used as alternatives in patients for whom doxycycline is contraindicated. In mild illness, oral doxycycline, amoxicillin, and ampicillin have been used successfully. In severe illness, supportive care with specific attention given to cardiopulmonary status, renal function, coagulopathy, and fluid and electrolyte balance is warranted.

Prevention

Prevention of human leptospirosis infection is facilitated through rodent control measures and avoidance of contaminated water and soil. Immunization of livestock and domestic dogs is recommended as a means of reducing animal reservoirs. Human vaccine development has been challenging due to the diversity of *Leptospira* serovars and their variable geographic distribution. Protective clothing (i.e., boots, gloves, and goggles) should be worn by persons at risk for occupational exposure. In hospital settings, in addition to standard precautions, contact precautions are recommended for potential exposures to infected urine. Leptospirosis was successfully prevented in American soldiers stationed in the tropics by administering prophylactic doxycycline (200 mg PO once a week). This approach may be similarly effective for travelers to highly endemic areas for short periods; however, there are no specific pediatric data to support any prophylaxis regimen.

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CHAPTER 248

Relapsing Fever *(Borrelia)*

H. Dele Davies, Stephen K. Obaro

Relapsing fever is characterized by recurring fevers and flu-like symptoms such as headaches, myalgia, arthralgia, and rigors.

Etiology

Relapsing fever is an arthropod (lice or ticks)-transmitted infection caused by spirochetes of the genus *Borrelia* .

Louse-borne (epidemic) relapsing fever is caused by *Borrelia recurrentis* and is transmitted from person to person by *Pediculus humanus,* the human body louse. Human infection occurs as a result of crushing lice during scratching, facilitating entry of infected hemolymph through abraded or normal skin or mucous membranes.

Tick-borne (endemic) relapsing fever is caused by several species of *Borrelia* and is transmitted to humans by *Ornithodoros* ticks. *Borrelia hermsii* and *Borrelia turicatae* are the common species in the western United States, while *Borrelia dugesii* is the major cause of disease in Mexico and Central America. Human infection occurs when saliva, coxal fluid, or excrement is released by the tick during feeding, thereby permitting spirochetes to penetrate the skin and mucous membranes.

Epidemiology

Louse-borne relapsing fever tends to occur in epidemics associated with war, poverty, famine, and poor personal hygiene, often in association with typhus. This form of relapsing fever is no longer seen in the United States but is endemic in parts of East Africa. Using 16S rRNA polymerase chain reaction assays for molecular detection, up to 20.5% of all unexplained fever in the horn of Africa, including northwestern Morocco where the population traditionally lives in mud huts, is caused by tickborne relapsing fever, making this the most common cause of bacterial infections.

Ornithodoros ticks, which transmit endemic relapsing fever and are distributed worldwide, including in the western United States, prefer warm, humid environments and high altitudes and are found in rodent burrows, caves, and other nesting sites (Fig. 248.1). Rodents (e.g., squirrels and chipmunks) are the principal reservoirs. Infected ticks gain access to human dwellings on the rodent host. Human contact is often unnoticed because these soft ticks have a painless bite and detach immediately after a short blood meal.

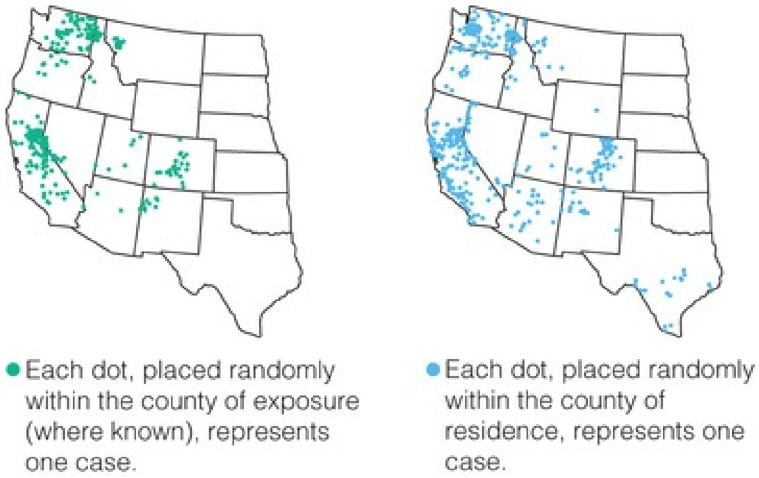
● Each dot, placed randomly within the county of exposure (where known), represents one case.
● Each dot, placed randomly within the county of residence, represents one case.

FIG. 248.1 Cases of tickborne relapsing fever–United States, 1990-2011. During the years 1990-2011, 483 cases of tickborne relapsing fever were reported in the western United States, with infections being transmitted most frequently in California, Washington, and Colorado. (From Centers for Disease Control and Prevention [CDC]: *Tick-borne relapsing fever: distribution* . Available at: http://www.cdc.gov/relapsing-fever/distribution).

Pathology and Pathogenesis

Relapsing fever is cyclical because the *Borrelia* organisms undergo antigenic (phase) variation. Multiple variants evolve simultaneously during the first relapse, with one type becoming predominant. Spirochetes isolated during the primary febrile episode differ antigenically from those recovered during a subsequent relapse. During febrile episodes, spirochetes enter the bloodstream, induce the development of specific immunoglobulin M and G antibodies, and undergo agglutination, immobilization, lysis, and phagocytosis. During remission, *Borrelia* spirochetes may remain in the bloodstream, but spirochetemia is insufficient to produce symptoms. The number of relapses in untreated patients depends on the number of antigenic variants of the infecting strain.

Clinical Manifestations

Relapsing fever is characterized by febrile episodes lasting 2-9 days, separated by afebrile intervals of 2-7 days. Louse-borne disease has an incubation period of 2-14 days, longer periods of pyrexia, fewer relapses, and longer remission periods than tickborne disease. The incubation period of tickborne disease is usually 7 days (range: 2-9 days). Each form of relapsing fever is characterized by sudden onset of high fever, lethargy, headache, photophobia, nausea, vomiting, myalgia, and arthralgia. Additional symptoms may appear later and include abdominal pain, a productive cough, mild respiratory distress, and bleeding manifestations, including epistaxis, hemoptysis, hematuria, and hematemesis. During the end of the primary febrile episode, a diffuse, erythematous, macular, or petechial rash lasting up to 2 days may develop over the trunk and shoulders. There may also be lymphadenopathy, pneumonia, and splenomegaly. Hepatic tenderness associated with hepatomegaly is a common sign, with jaundice in half of affected children. Central nervous system manifestations include lethargy, stupor, meningismus, convulsions, peripheral neuritis, focal neurologic deficits, and cranial nerve paralysis and may be the principal feature of late relapses in tickborne disease. Severe manifestations include myocarditis, hepatic failure, and disseminated intravascular coagulopathy.

The initial symptomatic period characteristically ends with a crisis in 2-9 days, marked by abrupt diaphoresis, hypothermia, hypotension, bradycardia, profound muscle weakness, and prostration. In untreated patients, the 1st relapse occurs within 1 wk, followed by usually 3 but up to 10 relapses, with symptoms during each relapse becoming milder and shorter as the afebrile remission period lengthens.

Diagnosis

Diagnosis depends on demonstration of spirochetes by darkfield microscopy or in thin or thick blood smears stained with Giemsa or Wright stain and by blood culture (Fig. 248.2). During afebrile remissions, spirochetes are not found in the blood. Serologic tests have not been standardized, are generally not available, and produce cross reactions with other spirochetes, including *Borrelia burgdorferi*, the agent of Lyme disease. Molecular methods, including nested polymerase chain reaction or 16S rRNA polymerase chain reaction assays, have been used for detection of tickborne and louse-borne recurrent fever and have been found to have improved sensitivity and specificity compared to blood smears. However, these assays are not yet routinely available for commercial use.

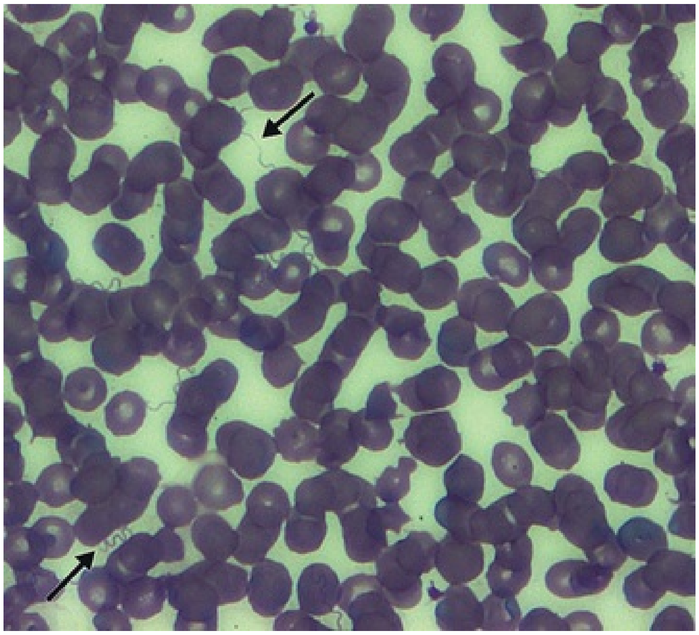

FIG. 248.2 Stained thin smear of a newborn's peripheral blood, showing the presence of numerous spirochetes (indicated by *black arrows*) at ×63 magnification—Colorado, 2011. (From Centers for Disease Control and Prevention [CDC]: Tickborne relapsing fever in a mother and newborn child–Colorado, 2011. *MMWR Morb Mortal Wkly Rep* 61:174–176, 2012.)

Treatment

Oral or parenteral tetracycline or doxycycline is the drug of choice for louse-borne and tickborne relapsing fever. For children older than 8 yr of age and young adults, tetracycline 500 mg PO every 6 hr or doxycycline 100 mg PO every 12 hr for 10 days is effective. Single-dose treatment with tetracycline (500 mg PO) or erythromycin is efficacious in adults, but experience in children is limited. In children younger than 8 yr of age, erythromycin (50 mg/kg/day divided every 6 hr PO) for a total of 10 days is recommended, although there is evidence that doxycycline given for durations of less than 2 wk is safe in children > 2 yr of age. Penicillin and chloramphenicol are also effective.

Resolution of each febrile episode either by natural crisis or as a result of antimicrobial treatment is often accompanied by the Jarisch-Herxheimer reaction, which is caused by massive antigen release. Corticosteroid or antipyretic pretreatment do not prevent the reaction.

Prognosis

With adequate therapy, the mortality rate for relapsing fever is <5%. A majority of patients recover from their illness with or without treatment after the appearance of anti-*Borrelia* antibodies, which agglutinate, kill, or opsonize the spirochete. However, pregnant women and their neonates are at increased risk for tickborne recurrent fever-associated complications, including adult respiratory distress syndrome, Jarisch-Herxheimer reaction, and precipitous or premature delivery. Neonates have up to a 33% case-fatality rate.

Prevention

No vaccine is available. Disease control requires avoidance or elimination of the arthropod vectors. In epidemics of louse-borne disease, good personal hygiene and delousing of persons, dwellings, and clothing with commercially available insecticides can prevent dissemination. The risk for tickborne disease can be minimized in endemic areas by maintaining rodent-free dwellings. Giving prophylactic doxycycline for 4 days after a tick bite may prevent tickborne relapsing fever caused by *Borrelia persica.*

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CHAPTER 249

Lyme Disease *(Borrelia burgdorferi)*

Stephen C. Eppes, Neal D. Goldstein

Lyme disease is the most common vector-borne disease in the United States and is an important public health problem.

Etiology

Lyme disease is caused by the spirochete *Borrelia burgdorferi* sensu lato (broad sense). In North America, *B. burgdorferi* sensu stricto (strict sense) causes almost all cases; a recently discovered species in the upper Midwestern United States, *Borrelia mayonii* (belonging to the group *B. burgdorferi* sensu lato), also causes Lyme disease, but the illness is slightly different, with more diffuse rashes and gastrointestinal symptoms. In Europe, the species *Borrelia afzelii* and *Borrelia garinii* also cause disease. The 3 major outer-surface proteins, called OspA, OspB, and OspC (which are highly charged basic proteins of molecular weights of about 31, 34, and 23 kDa, respectively), and the 41 kDa flagellar protein are important targets for the immune response. Differences in the molecular structure of the different species are associated with differences in the clinical manifestations of Lyme borreliosis in Europe and the United States. These differences include the greater incidence of radiculoneuritis in Europe.

Epidemiology

Lyme disease has been reported from more than 50 countries, predominately distributed in forested areas of Asia; northwestern, central, and eastern Europe; and in the northeastern and midwestern United States. In Europe, most cases occur in the Scandinavian countries and in central Europe, especially Germany, Austria, and Switzerland, while in the United States, 95% of cases occurred in 16 states in 2017: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and Wisconsin (Fig. 249.1).

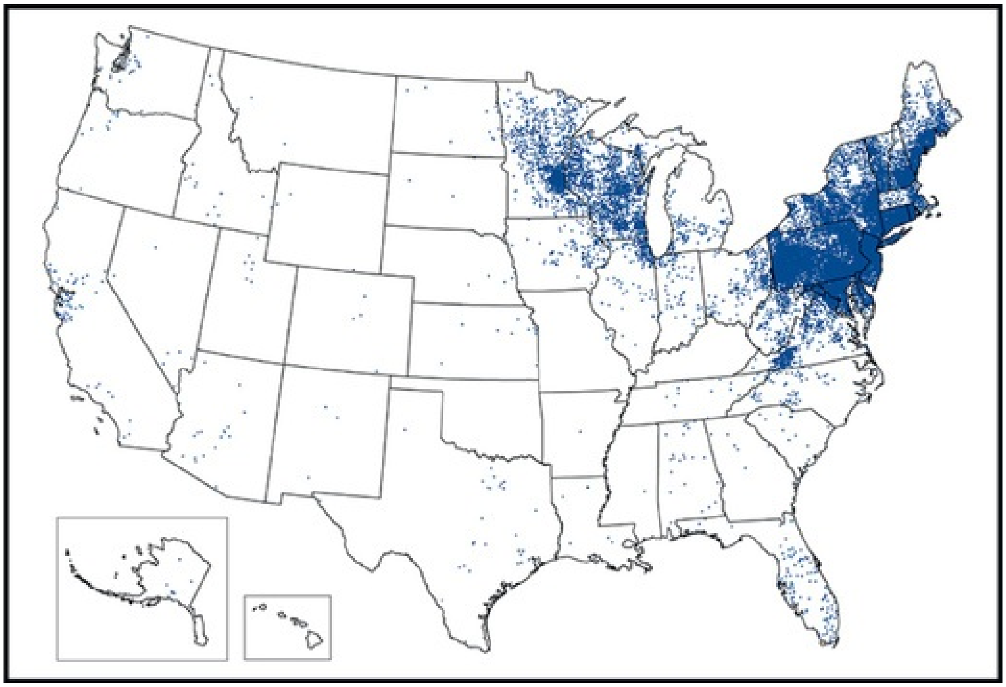

FIG. 249.1 The geographic distribution of Lyme disease cases in the United States. (From the Centers for Disease Control and Prevention [CDC]: *Reported cases of Lyme disease—United States* , 2017. Available at: https://www.cdc.gov/lyme/datasurveillance/maps-recent.html .)

In the United States, in excess of 20,000 confirmed cases have been reported annually to the Centers for Disease Control and Prevention (CDC) over the last decade, and reported cases have trended upward since 1995, with an approximate 9% increase of reported cases in 2017 compared to 2016. In 2017, the most recent year national data are available, more than 29,000 confirmed cases and more than 13,000 probable cases were reported. The 3-yr averaged national incidence is estimated at 8.5 cases per 100,000 population, and for the last decade the national incidence has ranged from a low of 7.0 cases per 100,000 (2012) to a high of 9.8 cases per 100,000 (2009). In endemic areas, the reported annual incidence ranges from 20 to 100 cases per 100,000 population, although this figure may be as high as 600 cases per 100,000 population in hyperendemic areas. The reported incidence of disease is bimodal. There is an initial peak among children 5-14 yr of age followed by a second peak among adults 55-69 yr of age. In the United States, Lyme disease is diagnosed in boys slightly more often than in girls, and 94% of patients are of European descent. Early Lyme disease usually occurs from spring to early fall, corresponding to deer tick activity. Late disease (chiefly arthritis) occurs year round. Among adults, outdoor occupation and leisure activities are risk factors; for children, location of residence in an endemic area is the most important risk for infection.

Lyme disease is designated a nationally notifiable disease by the CDC and Council for State and Territorial Epidemiologists. Healthcare providers, hospitals, laboratories, and other parties are required by law to notify local health departments when a confirmed or probable case of Lyme disease occurs. The local health departments in turn report cases to the state and territorial health departments; it is voluntary in turn for these authorities to report data to the CDC, and therefore the actual number of Lyme disease cases as well as incidence is likely underreported and underestimated. Lyme disease was the 6th most common notifiable disease reported to the CDC in 2017.

Transmission

Lyme disease is a zoonosis caused by the transmission of *B. burgdorferi* to humans through the bite of an infected tick of the *Ixodes* genus. In the eastern and midwestern United States, the vector is ***Ixodes scapularis*** , the black-legged tick that is commonly known as the **deer tick** , which is responsible for most cases of Lyme disease in the United States. The vector on the Pacific Coast is *Ixodes pacificus,* the western black-legged tick. *Ixodes* ticks have a 2-yr, 3-stage life cycle. The larvae hatch in the early summer and are usually uninfected with *B. burgdorferi.* The tick can become infected at any stage of its life cycle by feeding on a host, usually a small mammal such as the white-footed mouse *(Peromyscus leucopus)* , which is a natural reservoir for *B. burgdorferi.* The larvae overwinter and emerge the following spring in the nymphal stage, which is the stage of the tick most likely to transmit the infection. The nymphs molt to adults in the fall, and then adults spend the 2nd winter attached to white-tailed deer *(Odocoileus virginianus)* . The females lay their eggs the following spring before they die, and the 2-yr life cycle begins again.

Several factors are associated with increased risk for transmission of *B. burgdorferi* from ticks to humans. The proportion of infected ticks varies by geographic area and by stage of the tick's life cycle. In endemic areas in the northeastern and midwestern United States, 15–25% of nymphal ticks and 35–50% of adult ticks are infected with *B. burgdorferi*. By contrast, *I. pacificus* often feeds on lizards, which are not a competent reservoir for *B. burgdorferi*, reducing the chance that these ticks will be infected. The risk for transmission of *B. burgdorferi* from infected *Ixodes* ticks is related to the duration of feeding. Experiments in animals show that infected nymphal ticks must feed for 36-48 hr, and infected adults must feed for 48-72 hr, before the risk for transmission of *B. burgdorferi* becomes substantial. If the tick is recognized and removed promptly, transmission of *B. burgdorferi* will not occur. Most patients with Lyme disease do not remember the tick bite that transmitted the infection.

The tick species that carry *B. burgdorferi* may be geographically expanding in the U.S. *I. scapularis* also transmits other microorganisms, namely *Anaplasma phagocytophilum* and *Babesia microti*, as well as a recently described species, *Borrelia miyamotoi*. Simultaneous transmission can result in coinfections with these organisms and *B. burgdorferi*.

Pathology and Pathogenesis

Similar to other spirochetal infections, untreated Lyme disease is characterized by asymptomatic infection, clinical disease that can occur in stages, and a propensity for cutaneous and neurologic manifestations.

The skin is the initial site of infection by *B. burgdorferi*. Inflammation induced by *B. burgdorferi* leads to the development of the characteristic rash, **erythema migrans** . Early disseminated Lyme disease results from the spread of spirochetes through the bloodstream to tissues throughout the body. The spirochete adheres to the surfaces of a wide variety of different types of cells, but the principal target organs are skin, central and peripheral nervous system, joints, heart, and eyes. Because the organism can persist in tissues for prolonged periods, symptoms can appear very late after initial infection.

The symptoms of early disseminated and late Lyme disease are a result of inflammation mediated by interleukin-1 and other lymphokines in response to the presence of the organism. It is likely that relatively few organisms actually invade the host, but cytokines serve to amplify the inflammatory response and lead to much of the tissue damage. Lyme disease is characterized by inflammatory lesions that contain both T and B lymphocytes, macrophages, plasma cells, and mast cells. The refractory symptoms of late Lyme disease can have an immunogenetic basis. Persons with certain HLA-DR allotypes may be genetically predisposed to develop chronic Lyme arthritis. An autoinflammatory response in the synovium can result in clinical symptoms long after the bacteria have been killed by antibiotics.

Clinical Manifestations

The clinical manifestations of Lyme disease are divided into early and late stages (Table 249.1). Early Lyme disease is further classified as early localized or early disseminated disease. Untreated patients can progressively develop clinical symptoms of each stage of the disease, or they can present with early disseminated or with late disease without apparently having had any symptoms of the earlier stages of Lyme disease.

Table 249.1

Clinical Stages of Lyme Disease

DISEASE STAGE	TIMING AFTER TICK BITE	TYPICAL CLINICAL MANIFESTATIONS
Early localized	3-30 days	Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue)
Early disseminated	3-12 wk	Erythema migrans (single or multiple), worse constitutional symptoms, cranial neuritis, meningitis, carditis, ocular disease
Late	>2 mo	Arthritis

Early Localized Disease

The first clinical manifestation of Lyme disease in most patients is erythema migrans (Fig. 249.2). Although it usually occurs 7-14 days after the bite, the onset of the rash has been reported from 3 to 30 days later. The initial lesion occurs at the site of the bite. The rash is generally either uniformly erythematous or a target lesion with central clearing; rarely, there are vesicular or necrotic areas in the center of the rash. Occasionally the rash is itchy or painful, although usually it is asymptomatic. The lesion can occur anywhere on the body, although the most common locations are the axilla, periumbilical area, thigh, and groin. It is not unusual for the rash to occur on the neck or face, especially in young children. Without treatment, the rash gradually expands (hence the name *migrans*) to an average diameter of 15 cm and typically remains present for 1-2 wk. Erythema migrans may be associated with systemic features, including fever, myalgia, headache, or malaise. Coinfection with *B. microti* or *A. phagocytophilum* during early infection with *B. burgdorferi* is associated with more severe systemic symptoms. **Coinfections** should be suspected with unusual features of Lyme disease, poor response to treatment, and prolonged fever, anemia, leukopenia, elevated liver enzymes, or thrombocytopenia.

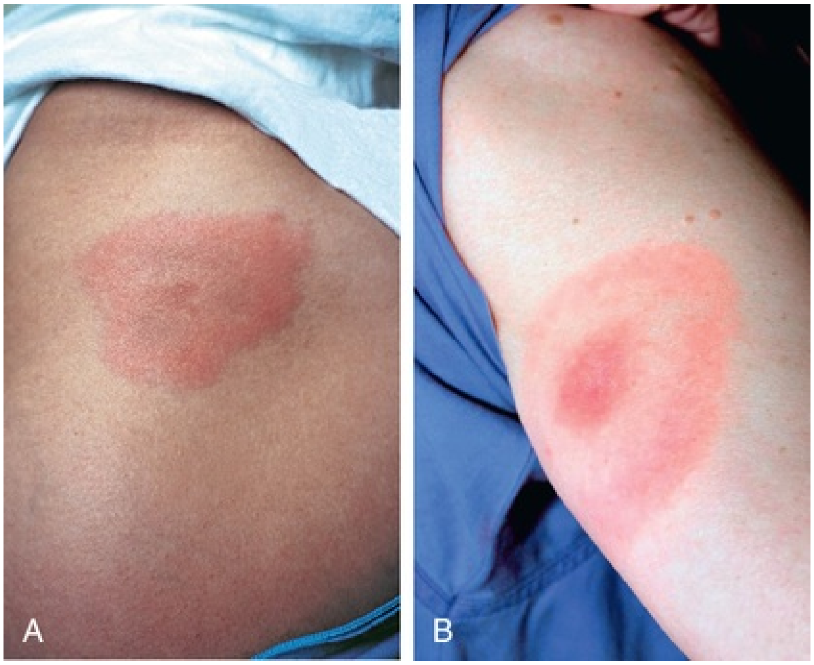

FIG. 249.2 Skin manifestations of Lyme borreliosis. **A,** Erythema migrans on the upper leg, showing central clearing. **B,** Erythema migrans of the arm showing "bulls-eye" appearance. (**A,** from Stanek G, Strle F: Lyme borreliosis, *Lancet* 362:1639–1647, 2003).

Early Disseminated Disease

In the United States, approximately 20% of patients with acute *B. burgdorferi* infection develop secondary (multiple) erythema migrans lesions, a common manifestation of early disseminated Lyme disease, caused by hematogenous spread of the organisms to multiple skin sites (Fig. 249.3). The secondary lesions, which can develop several days or weeks after the first lesion, are usually smaller than the primary lesion and are often accompanied by more-severe constitutional symptoms. The most common early neurologic manifestations are **peripheral facial nerve palsy** and **meningitis** . Lyme meningitis usually has an indolent onset with days to weeks of symptoms that can include headache, neck pain and stiffness, and fatigue. Fever is variably present.

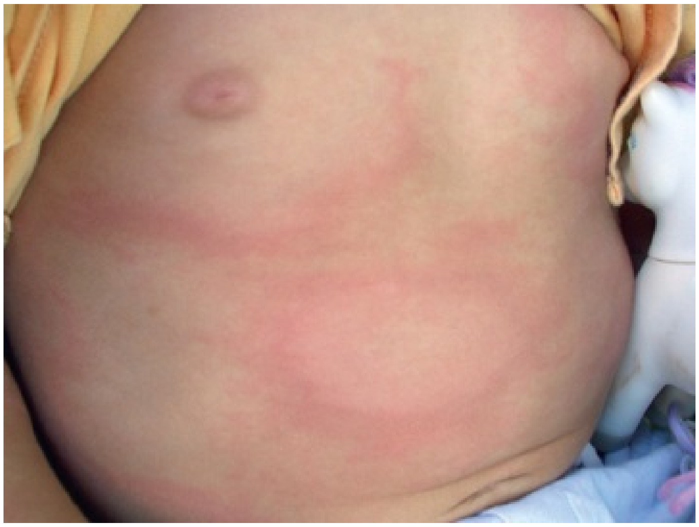

FIG. 249.3 Multiple erythema migrans in a boy with early disseminated Lyme disease.

The clinical findings of papilledema, cranial neuropathy (especially cranial nerve VII), and erythema migrans, which are present individually or together in 90% of cases, help differentiate Lyme meningitis from viral meningitis, in which these findings are rarely present. The aseptic meningitis due to Lyme disease can be accompanied by significant elevations of intracranial pressure, which can sometimes last weeks or even months. All of the cranial nerves except the olfactory have been reported to be involved with Lyme disease, but the most common are VI and especially VII. In endemic areas, Lyme disease is the leading cause of peripheral facial nerve palsy. It is often the initial or the only manifestation of Lyme disease and is sometimes bilateral. Cerebrospinal fluid (CSF) findings indicating meningitis are present in more than half of the cases of peripheral facial nerve palsy. The facial paralysis usually lasts 2-8 wk and resolves completely in most cases. Radiculoneuritis and other peripheral neuropathies can occur but are more common in Europe.

Cardiac involvement occurs in 5–15% of early disseminated Lyme disease and usually takes the form of heart block, which can be 1st, 2nd, or 3rd degree, and the rhythm can fluctuate rapidly. Rarely, myocardial (myocarditis) dysfunction can occur. Patients presenting with suspected or proven early disseminated Lyme disease should have a careful cardiac examination, and electrocardiography should be strongly considered. Lyme carditis is a treatable condition and is the only manifestation of Lyme disease that has been fatal.

Of the ocular conditions reported in Lyme disease, papilledema and uveitis are most common.

Late Disease

Arthritis is the usual manifestation of late Lyme disease and begins weeks to months after the initial infection. Arthritis typically involves the large joints, especially the knee, which is affected in 90% of cases; involvement is usually monoarticular or oligoarticular; occasionally it may be migratory. The hallmark of Lyme arthritis is joint swelling, which is a result of synovial effusion and sometimes synovial hypertrophy. The swollen joint may be only mildly symptomatic or it may be painful and tender, although patients usually do not experience the severe pain and systemic toxicity that are common in pyogenic arthritis. If untreated, the arthritis can last several weeks, resolve, and then be followed by recurrent attacks in the same or other joints.

Late manifestations of Lyme disease involving the central nervous system, sometimes termed *late neuroborreliosis* , are rarely reported in children. In adults, chronic encephalitis and polyneuritis have been attributed to Lyme disease. The term *Lyme encephalopathy* has been used to describe chronic encephalitis (demonstrable by objective measures), but other literature has also used this term in reference to memory loss and other cognitive sequelae after Lyme disease has been treated. At times, the vague and mistaken term *chronic Lyme disease* has been used to describe symptomatology in persons who might have never had well-documented infection with *B. burgdorferi* at all, have serologic evidence of prior infection but current symptoms not consistent with Lyme disease, or have persistent symptoms after having received appropriate antibiotic therapy. Prolonged treatment does not treat the chronic neuropsychiatric symptoms and at times has harmed the patient.

Congenital Lyme Disease

In endemic areas, infection can occur during pregnancy, although congenital infection appears to be a rare event. *B. burgdorferi* has been identified from several abortuses and from a few liveborn children with congenital anomalies; however, the tissues in which the spirochete has been identified usually have not shown histologic evidence of inflammation. Severe skin and cardiac manifestations have been described in a few cases, but no consistent pattern of fetal damage has been identified to suggest a clinical syndrome of congenital infection. Furthermore, studies conducted in endemic areas have indicated that there is no difference in the prevalence of congenital malformations among the offspring of women with serum antibodies against *B. burgdorferi* and the offspring of those without such antibodies.

Laboratory Findings

Standard laboratory tests rarely are helpful in diagnosing Lyme disease because any associated laboratory abnormalities usually are nonspecific. The peripheral white blood cell count may be either normal or elevated. The erythrocyte sedimentation rate (ESR) may be mildly elevated. Liver transaminases are occasionally mildly elevated. In Lyme arthritis, the white blood cell count in joint fluid can range from 25,000 to 100,000/mL, often with a preponderance of polymorphonuclear cells. A lower ESR and C-reactive protein and a peripheral blood absolute neutrophil count of less than 10,000 may help to differentiate Lyme from septic arthritis. When meningitis is present, there usually is a low-grade pleocytosis with a lymphocytic and monocytic predominance. The CSF protein level may be elevated, but the glucose concentration usually is normal. Gram stain and routine bacterial cultures are negative. Imaging of the central nervous system (e.g., MRI and single-photon emission computed tomography) occasionally reveals abnormalities, but there is no definitive pattern in Lyme disease. The main role of imaging is to exclude other diagnoses.

Diagnosis

In the appropriate epidemiologic setting (endemic area, season) typical erythema migrans is pathognomonic . Occasionally, the diagnosis of erythema migrans may be difficult because the rash initially can be confused with nummular eczema, tinea corporis, granuloma annulare, an insect bite, southern tick-associated rash illness, or cellulitis. The relatively rapid expansion of erythema migrans helps distinguish it from these other skin lesions. The other clinical manifestations of Lyme disease are less specific and may be confused with other conditions; the monoarticular or pauciarticular arthritis sometimes is confused with a septic joint or other causes of arthritis in children, such as juvenile idiopathic arthritis or rheumatic fever; the facial nerve palsy caused by Lyme disease is clinically indistinguishable from idiopathic Bell palsy, although bilateral involvement is much more common with Lyme disease; Lyme meningitis generally occurs in the warmer months, the same period that enteroviral meningitis is prevalent. Therefore, for all disease manifestations other than erythema migrans, it is recommended to have laboratory confirmation of infection with *B. burgdorferi*.

Although *B. burgdorferi* has been isolated from blood, skin, CSF, myocardium, and the synovium of patients with Lyme disease, the organism is difficult to isolate in culture (cultivation is largely relegated to research laboratories). Infection is usually identified by the detection of antibody in serum. Although some laboratories offer polymerase chain reaction as a diagnostic test for Lyme disease, its sensitivity may be poor because of the low concentrations of bacteria in many sites, especially CSF. Other antigen-based tests, including a test for *B. burgdorferi* antigens in urine, are unreliable. Clinicians should be aware that some laboratories use alternative diagnostic tests and/or alternative interpretive criteria that are not evidence based, leading to a false diagnosis of Lyme disease. The CDC and the Food and Drug Administration recommend against using these tests.

Serology

Following the transmission of *B. burgdorferi* from a tick bite, specific immunoglobulin (Ig) M antibodies appear first, usually within 2 wk, peak at 6-8 wk, and subsequently decline. Sometimes a prolonged or recurrent elevation of IgM antibodies occurs despite effective antimicrobial treatment. Elevated IgM levels after 6-8 wk are often false positives. Specific IgG antibodies usually appear between 2 and 6 wk, peak after 4-6 mo, and can remain elevated for years, particularly in patients with arthritis. The antibody response to *B. burgdorferi* may be blunted in patients with early Lyme disease who are treated promptly with an effective antimicrobial agent. *Serodiagnosis during the first 4 wk of infection is not sensitive and may need to be repeated.*

By far the most common method used to detect IgG and IgM antibodies is the enzyme-linked immunosorbent assay (ELISA). *This method is sensitive but not optimally specific* . The ELISA sometimes produces false-positive results because of antibodies that cross react with other spirochetal infections (e.g., *B. miyamotoi* , syphilis, leptospirosis, or relapsing fever), or certain viral infections (e.g., Epstein-Barr virus), or that occur in certain autoimmune diseases (e.g., systemic lupus erythematosus). The positive predictive value of the ELISA result depends primarily on the plausibility that the patient has Lyme disease based on the clinical and epidemiologic history and the physical examination (**the pretest probability**). For patients who have been in endemic areas with opportunities for *Ixodes* tick exposure and who have typical clinical manifestations of Lyme disease, the pretest probability is high and positive ELISA results are usually true positives. For patients who are from nonendemic areas and/or who have little risk for *Ixodes* tick exposures and/or have nonspecific symptoms (low pretest probability), rates of false-positive results are high. Infection with *B. miyamotoi* may cause false-positive ELISA tests for Lyme disease. This syndrome of relapsing fever, headache, myalgia, but no rash with neutropenia or thrombocytopenia are uncommon in Lyme disease.

Western immunoblotting is well standardized, and there are accepted criteria for interpretation. Five of 10 IgG bands and 2 of 3 IgM bands are considered reactive. The Western blot is not as sensitive as ELISA, especially in early infection, but is highly specific. Any positive or equivocal ELISA must be confirmed with Western blotting. The CDC recommends using IgM and IgG Western blot confirmation when symptoms have been present ≤30 days and IgG only when symptoms have been present longer than 30 days. This 2-tier testing is the recommended laboratory evaluation of most cases of Lyme disease and is associated with a high degree of sensitivity and specificity when used appropriately. There are discussions to eliminate the second-tier Western blot assay and substitute it with a second-tier ELISA that is easier to perform and interpret.

Clinicians should be aware that Lyme disease might not be the cause of a patient's symptoms despite the presence of antibodies to *B. burgdorferi* . The test result may be falsely positive (as described for ELISA), or the patient might have been infected previously. Antibodies to *B. burgdorferi* that develop with infection can persist for many years despite adequate treatment and clinical cure of the disease. In addition, because some people who become infected with *B. burgdorferi* are asymptomatic, the background rate of seropositivity among patients who have never had clinically apparent Lyme disease may be substantial in endemic areas. Finally, because antibodies against *B. burgdorferi* persist after successful treatment, there is no reason to obtain follow-up serologic tests.

Treatment

Table 249.2 provides treatment recommendations. Most patients can be treated with an oral regimen of antibiotic therapy. Young children are generally treated with amoxicillin. Doxycycline has the advantages of good central nervous system penetration and activity against *A. phagocytophilum* , which may be transmitted at the same time as *B. burgdorferi* in certain geographic areas. In general, children younger than 8 yr of age should not be treated with doxycycline because of the risk of permanent staining of the teeth (although courses of ≤2 wk are usually safe in this regard). Patients who are treated with doxycycline should be alerted to the risk for developing photosensitivity in sun-exposed areas while taking the medication; long sleeves, long pants, and hat are recommended for activities in direct sunlight. The only oral cephalosporin proved to be effective for the treatment of Lyme disease is cefuroxime axetil, which is an alternative for persons who cannot take doxycycline or who are allergic to penicillin. Macrolide antibiotics, including azithromycin, appear to have limited activity.

Table 249.2

Recommended Treatment of Lyme Disease

DRUG	PEDIATRIC DOSING
Amoxicillin	50 mg/kg/day in 3 divided doses (max: 1,500 mg/day)
Doxycycline	4.4 mg/kg/day in 2 divided doses (max: 200 mg/day) (see text regarding doxycycline use in children)
Cefuroxime axetil	30 mg/kg/day in 2 divided doses (max: 1,000 mg/day)
Ceftriaxone (IV)[*] , [†]	50-75 mg/kg/day once daily (max: 2,000 mg/day)
Azithromycin [‡]	10 mg/kg/day once daily ×7 days
RECOMMENDED THERAPY BASED ON CLINICAL MANIFESTATION	
Erythema migrans	Doxycycline ×10 days Amoxicillin ×14 days
Meningitis	Doxycycline ×14 days or Ceftriaxone ×14 days (14-21 for hospitalized patients)
Cranial nerve palsy [§]	Doxycycline ×14 days
Cardiac disease	Oral regimen or ceftriaxone, 14-21 days (see text for specifics)
Arthritis	Oral regimen, 28 days
Persistent arthritis after initial treatment	Oral regimen ×28 days or Ceftriaxone, 14-28 days

[*] Penicillin G is an alternative parenteral agent but requires more frequent dosing.

[†] Doses of 100 mg/kg/day should be used for meningitis.

[‡] For those unable to take amoxicillin or doxycycline.

[§] Treatment is to prevent late disease not to treat the cranial palsy; avoid corticosteroids.

Parenteral therapy is usually recommended for patients with higher degrees of heart block or central nervous system involvement, though oral therapy for meningitis is now considered acceptable for ambulatory patients. Patients with arthritis that fails to resolve after an initial course of oral therapy can be retreated with an oral regimen or can receive intravenous antibiotic therapy. Ceftriaxone is favored because of its excellent anti-*Borrelia* activity, tolerability, and once-daily dosing regimen, which can usually be done on an outpatient basis.

Peripheral facial nerve palsy can be treated using an oral antibiotic. However, these patients may have concomitant meningitis; patients with meningitis may need to receive a parenteral antibiotic. Experts are divided on whether every patient with Lyme-associated facial palsy needs a CSF analysis, but clinicians should consider lumbar puncture for patients with significant headache, neck pain or stiffness, or papilledema.

Patients with symptomatic cardiac disease, 2nd- or 3rd-degree heart block, or significantly prolonged PR interval should be hospitalized and monitored closely. These patients should receive a parenteral antibiotic. Patients with mild 1st-degree heart block can be treated with an oral antibiotic.

Some patients develop a Jarisch-Herxheimer reaction soon after treatment is initiated; this results from lysis of the *Borrelia* . The manifestations of this reaction are low-grade fever and achiness. These symptoms resolve spontaneously within 24-48 hr, although administration of nonsteroidal antiinflammatory drugs often is beneficial. Nonsteroidal antiinflammatory drugs also may be useful in treating symptoms of early Lyme disease and of Lyme arthritis. Coinfections with other pathogens transmitted by *Ixodes* ticks should be treated according to standard recommendations.

Criteria for the post–Lyme disease syndrome have been proposed by the Infectious Disease Society of America. There is no clear evidence that this condition is related to persistence of the organism. Studies in adults show little benefit associated with prolonged or repeated treatment with oral or parenteral antibiotics.

Prognosis

There is a widespread misconception that Lyme disease is difficult to cure and that chronic symptoms and clinical recurrences are common. The most likely reason for apparent treatment failure is an incorrect diagnosis of Lyme disease.

The prognosis for children treated for Lyme disease is excellent. Children treated for erythema migrans rarely progress to late Lyme disease. The long-term prognosis for patients who are treated beginning in the later stages of Lyme disease also is excellent. Although chronic and recurrent arthritis may occur, especially among patients with certain human leukocyte antigen allotypes (an autoimmune process), most children who are treated for Lyme arthritis are cured and have no sequelae. Although there are rare reports of adults who have developed late neuroborreliosis, usually among persons with Lyme disease in whom treatment was delayed for months or years, similar cases in children are rare.

Prevention

The best way to avoid Lyme disease is to avoid tick-infested areas. Children should be examined for deer ticks after known or potential exposure (although many people are not able to identify the species or the stage of the tick). If a tick attachment is noted, the tick should be grasped at the mouthparts with a forceps or tweezers; if these are not available, the tick should be covered with a tissue. The recommended method of tick removal is to pull directly outward without twisting; infection is usually preventable if the tick is removed before 36 hr of attachment; at this time the ticks are flat and non-engorged. The overall risk for acquiring Lyme disease after a tick bite is low (1–3%) in most endemic areas. If the tick is engorged and present for >72 hr (high-risk tick bite), the risk of infection may increase to 25% in hyperendemic areas. Patients and families can be advised to watch the area for development of erythema migrans and to seek medical attention if the rash or constitutional symptoms occur. If infection develops, early treatment of the infection is highly effective. Prophylaxis after a high-risk tick bite with a single dose of doxycycline in adults (200 mg PO) or 4.4 mg/kg in children is effective in reducing the risk of Lyme disease. The routine testing of ticks that have been removed from humans for evidence of *B. burgdorferi* is not recommended, because the value of a positive test result for predicting infection in the human host is unknown.

Personal protective measures that may be effective in reducing the chance of tick bites include wearing protective clothing (long pants tucked into socks, long-sleeved shirts) when entering tick-infested areas, checking for and promptly removing ticks, and using tick repellents such as *N*,*N* -diethyl-3-methylbenzamide (DEET). This chemical can safely be used on pants, socks, and shoes; care must be used with heavy or repeated application on skin, particularly in infants, because of the risk of systemic absorption and toxicity. Permethrin treatment of clothing is also an effective prevention strategy.

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SECTION 9

Mycoplasmal Infections

OUTLINE

Chapter 250 Mycoplasma pneumoniae

Chapter 251 Genital Mycoplasmas (Mycoplasma hominis, Mycoplasma genitalium, and Ureaplasma urealyticum)

CHAPTER 250

Mycoplasma pneumoniae

Asuncion Mejias, Octavio Ramilo

Among the 7 *Mycoplasma* species isolated from the human respiratory tract, *Mycoplasma pneumoniae* remains the most common species causing respiratory infections in school-age children and young adults.

The Organism

Mycoplasmas are the smallest self-replicating prokaryotes known to cause disease in humans. Their size of 150-250 nm is more on the order of viruses than bacteria. *Mycoplasma pneumoniae* is a fastidious double-stranded DNA bacterium that is distinguished by a small genome (~800,000 base pairs) and a long doubling time, which makes culturing it a slow process (5-20 days) compared to other bacteria. *M. pneumoniae* isolates can be classified in 2 major genetic groups (subtype 1 and 2) based on the P1 adhesion protein. Distinguishing these 2 subtypes is important for epidemiologic and clinical purposes. Like other mycoplasmas, *M. pneumoniae* is distinguished by the complete absence of a cell wall that results in (1) their dependence to host cells for obtaining essential nutrients, (2) the intrinsic resistance to β-lactam agents, and (3) their pleomorphic shape and lack of visibility on Gram staining.

Epidemiology

M. pneumoniae infections occur worldwide and throughout the year. This organism is a frequent cause of community-acquired pneumonia (CAP) in children and adults, accounting for ~20% of all CAP in middle and high school children and up to 50% of CAP in college students and military recruits. The proportion of cases increases according to age, as recently shown in a population-based study of CAP conducted in the United States (5% in < 5 yr; 16% in 5-9 yr; and 23% in 10-17 yr).

In contrast to the acute, short-lived epidemics associated with some respiratory viruses, *M. pneumoniae* infection occurs endemically worldwide. Infections tend to occur most commonly during summer or early fall, although mycoplasma infections have been described all year long. Epidemic outbreaks of variable intensity occur every few years and they are likely related to the alternative circulation of the two *M. pneumoniae* subtypes. Transmission occurs through the respiratory route by large droplet spread during close contact with a symptomatic person. Community outbreaks have been described in closed settings (colleges, boarding schools, military bases) and can spread largely through school contacts. Attack rates within families are high, with transmission rates of 40 to > 80% for household adult and children contacts, respectively. In contrast to many other respiratory infections, the incubation period is 2-3 wk; hence, the course of infection in a specific population (family) may last several weeks.

The occurrence of mycoplasma illnesses is related, in part, to age and preexposure immunity. Overt illness is less common before 3 yr of age but can occur. Children younger than 5 yr of age appear to have milder illnesses associated with upper respiratory tract involvement, vomiting, and diarrhea. Immunity after infection is not long lasting, as evidenced by the frequency of reinfections over time. The 2 mycoplasma subtypes are immunologically different, and infection with 1 subtype does not appear to confer immunity against the other. *Asymptomatic carriage* after infection can last up to 4 mo despite antibiotic therapy and may contribute to prolonged outbreaks. Children are often the reservoir from whom mycoplasma spreads. In the clinical setting, there are no available tools yet to differentiate carriage vs. infection.

Pathogenesis

The pathogenicity of *M. pneumoniae* is dependent upon its extracellular attachment and the initiation of the host cell immune response. Cells of the ciliated respiratory epithelium are the target cells of *M. pneumoniae* infection. The organism is an elongated snake-like structure with a one-end organelle, which mediates the attachment to sialic acid receptors in the cilia through a complex set of adhesion proteins (P1, P30, proteins B and C, P116, and HMW1-

3). *M. pneumoniae* rarely invades beyond the respiratory tract basement membrane. Virulent organisms attach to ciliated respiratory epithelial cell surfaces located in the bronchi, bronchioles, alveoli, and possibly upper respiratory tract and burrow down between cells, resulting in ciliostasis and eventual sloughing of the cells. *M. pneumoniae* also causes cytolytic injury to the host cells in part by the production of hydrogen peroxide and possibly through the adenosine diphosphate–ribosylating and vacuolating toxin termed CARDS (community-acquired respiratory distress syndrome). This exotoxin is associated with more severe or even fatal disease. This bacterium facilitates the formation of biofilms, with strain-specific phenotypic differences, which hinder antibiotic penetration and recognition by the immune system.

Once *M. pneumoniae* reaches the lower respiratory tract, it promotes the polyclonal activation of B lymphocytes and CD4+ T cells, and amplifies the immune response with the production of various proinflammatory and antiinflammatory cytokines and chemokines, such as tumor necrosis factor-α, interleukin (IL)-8, IL-1β, Il-6, and IL-10.

Although it is well documented that specific cell-mediated immunity and antibody titers against *M. pneumoniae* increase with age (and therefore probably follow repeated infections), the immune mechanisms that protect against or clear the infection are not well defined. In humans, nasal IgA antibodies correlated with protection after experimental challenge. A distinct aspect of *M. pneumoniae* is its ability to induce the production of cold agglutinins (IgM antibodies) directed against the I antigen expressed in the surface of erythrocytes. Even though antibody responses do not confer complete protection against reinfections, the importance of a robust humoral response is apparent, since patients with congenital antibody deficiencies, such as those with hypogammaglobulinemia, can develop severe and prolonged disease and have a higher risk of extrapulmonary manifestations. In children with sickle cell disease or sickle-related hemoglobinopathies, *M. pneumoniae* is a common infectious trigger of acute chest syndrome. These children and also children with Down syndrome can develop more severe forms of *Mycoplasma* pneumonia. On the other hand, *M. pneumoniae* does not seem to be a common opportunistic agent in patients with AIDS.

M. pneumoniae has been detected by polymerase chain reaction (PCR) in many nonrespiratory sites, including blood, pleural fluid, cerebrospinal fluid (CSF), and synovial fluid. The mechanisms of extrapulmonary disease associated with *M. pneumoniae* are unclear and appear to be different according to the duration of symptoms at the time of presentation: direct invasion vs. immune-mediated.

Clinical Manifestations

Most of the *M. pneumoniae* infections are symptomatic and most of them occur in children and adolescents.

Respiratory Tract Disease

Tracheobronchitis and atypical pneumonia are the most commonly recognized clinical syndromes associated with *M. pneumoniae* . This agent is responsible for up to 20% of all cases of CAP. Although the onset of illness may be abrupt, it is usually characterized by gradual development of headache, malaise, fever, and sore throat, followed by progression of lower respiratory symptoms, including hoarseness and nonproductive cough. The gradual onset in children with atypical pneumonia is in contrast to the sudden onset of lobar pneumonia. Coryza and gastrointestinal complaints are unusual and usually suggest a viral etiology. Although the clinical course in untreated patients is variable, cough, the clinical hallmark of *M. pneumoniae* infection, usually worsens during the 1st wk of illness, and symptoms generally resolve within 2 wk. Cough can last up to 4 wk and may be accompanied by wheezing. Patients generally recover without complications, although some individuals can develop prolonged wheezing.

Chest examination may be unrevealing, even in patients with severe cough. There may be no auscultative or percussive findings or only minimum dry rales. Clinical findings are often less severe than suggested by the patient chest radiograph, explaining why the term walking pneumonia is often used to describe CAP caused by *M. pneumoniae* . Radiographic findings are variable and nonspecific, not allowing differentiation from viral or bacterial pathogens. Pneumonia is usually described as interstitial or bronchopneumonic, and involvement is most common in the lower lobes. Bilateral diffuse infiltrates, lobar pneumonia, or hilar lymphadenopathy can occur in up to 30% of patients. Although unusual, large pleural effusions associated with lobar infiltrates and necrotizing pneumonia have been described in patients with sickle cell disease, immunodeficiencies, Down syndrome, and chronic cardiopulmonary disease. Bronchiolitis obliterans has also been described as a complication of *M. pneumoniae* in otherwise healthy children. The white blood cell and differential counts are usually normal, whereas the erythrocyte sedimentation rate and C-reactive protein are often elevated. Appropriate antibiotics shorten the duration of illness but do not reliably eradicate the bacteria from the respiratory tract.

Other respiratory illnesses caused occasionally by *M. pneumoniae* include undifferentiated upper respiratory tract infections, intractable, nonproductive cough, pharyngitis (usually without marked cervical lymphadenopathy), sinusitis, croup, and bronchiolitis. *M. pneumoniae* is a common trigger of wheezing in asthmatic children and can cause chronic colonization in the airways, resulting in lung dysfunction in adolescents and adult asthmatic patients. Otitis media and bullous myringitis, which also occur with other viral and bacterial infections, have been described but are rare, and their absence should not exclude the diagnosis of *M. pneumoniae* .

Extrapulmonary Disease

Despite the reportedly rare isolation of *M. pneumoniae* from nonrespiratory sites, the improved sensitivity of PCR for *M. pneumoniae* DNA detection has led to increasing identification of this bacterium in nonrespiratory sites, particularly the central nervous system (CNS). Patients with or without respiratory symptoms can have involvement of the skin, CNS, blood, heart, gastrointestinal tract, and joints. Nonrespiratory manifestations of *M. pneumoniae* include:

1. ***CNS disease:*** occurs in 0.1% of all patients with *M. pneumoniae* infection and in 7–16% of those requiring hospitalization. Manifestations include encephalitis, acute disseminated encephalomyelitis (ADEM), transverse myelitis, cerebellar ataxia, aseptic meningitis, Guillain-Barré syndrome, Bell palsy, and peripheral neuropathy. CNS disease manifestations occur 3-23 days (mean: 10 days) after onset of respiratory illness but may not be preceded by any signs of respiratory infection in up to 20% of cases. Studies in children suggest that there are two pathogenic mechanisms for *M. pneumoniae* -associated neurologic disease: the first pattern is characterized by almost absent or no prodromal respiratory symptoms (<7 days) and non-reactive IgM responses. On the other hand, the second pattern is characterized by the presence of respiratory symptoms (most commonly cough) for ≥7 days and reactive IgM in acute serum. In the first group *M. pneumoniae* is usually identified in cerebrospinal fluid by PCR but

not in the respiratory tract, while in children presenting with ≥7 days of respiratory symptoms the opposite is true. These studies suggest that encephalitis occurring more than 7 days after onset of prodromal symptoms is more likely to be caused by an autoimmune response to *M. pneumonia,* while its occurrence early in the course of the disease may be associated with direct bacterial invasion of the CNS. Involvement of the brainstem can result in severe dystonia and movement disorders. The CSF may be normal or have mild mononuclear pleocytosis and/or increase CSF protein concentrations. Diagnosis is confirmed with positive CSF PCR, positive PCR from a throat swab, or demonstration of seroconversion. Findings on MRI include focal ischemic changes, ventriculomegaly, diffuse edema, or multifocal white matter inflammatory lesions consistent with postinfectious ADEM. Long-term sequelae have been reported in 23–64% of cases.

2. ***Dermatologic disease:*** a variety of exanthems have been associated with *M. pneumoniae* , most notably maculopapular rash, urticaria and the mycoplasma associated rash and mucositis syndrome previously called erythema multiforme or Stevens-Johnson syndrome (SJS). Gianotti-Crosti syndrome and erythema nodosum are also associated with *M. pneumoniae* infections. Approximately 10% of children with *M. pneumoniae* CAP will exhibit a maculopapular rash. Mycoplasma-associated rash and mucositis usually develops 3-21 days after initial respiratory symptoms, lasts less than 14 days, and is rarely associated with severe complications (Figs. 250.1 and 250.2). *M. pneumoniae* may also produce an isolated oral mucositis in absence of rash.

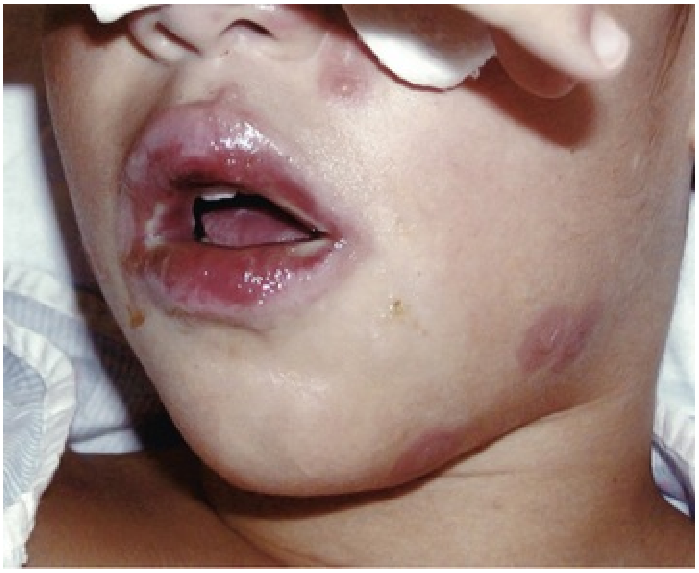

FIG. 250.1 Lip changes found in *Mycoplasma pneumoniae* –associated mucositis.

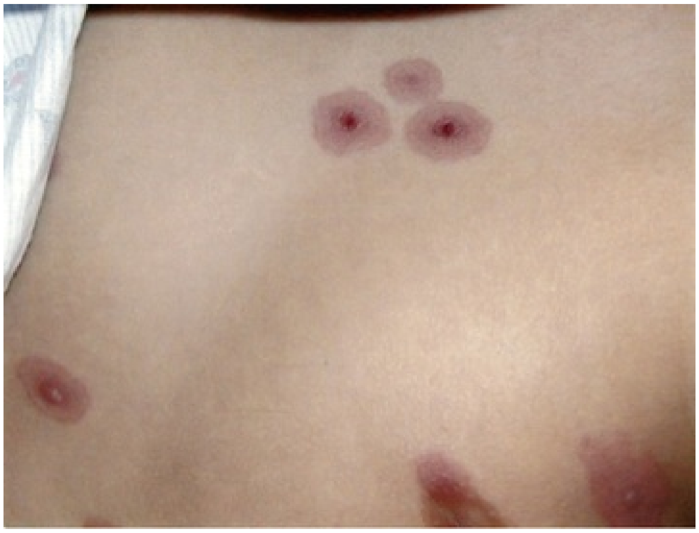

FIG. 250.2 Classic skin lesions found in *Mycoplasma pneumoniae* –associated rash.

3. ***Hematologic abnormalities:*** include mild degrees of hemolysis with a positive Coombs test and minor reticulocytosis 2-3 wk after the onset of illness. Severe hemolysis is associated with high titers of cold hemagglutinins (≥1 : 512) and occurs rarely. Thrombocytopenia, aplastic anemia, and coagulation defects occur occasionally.
4. ***Musculoskeletal:*** arthritis appears to be less common in children than in

adults, but monoarthritis, polyarthritis, and migratory arthritis have been described. Rhabdomyolysis has also been documented, often associated with other organ system manifestations.

5. ***Other conditions,*** such as mild hepatitis, pancreatitis, acute glomerulonephritis, iritis or uveitis, and cardiac complications (pericarditis, myocarditis, and rheumatic fever-like syndrome, most commonly seen in adults) are also described. Fatal *M. pneumoniae* infections are rare.

Diagnosis

No specific clinical, epidemiologic, or laboratory parameters allow for a definite diagnosis of *M. pneumoniae* infection. Nevertheless, pneumonia in school-age children and young adults with a gradual onset and cough as a prominent finding suggests *M. pneumoniae* infection. The best method for diagnosis is a combination of PCR from respiratory samples and serology (acute and convalescent).

Cultures on special media (SP4 agar media) of the throat or sputum might demonstrate the classic *M. pneumoniae* "mulberry" colonies, but growth generally requires incubation for 2-3 wk, and few laboratories maintain the capability of culturing *M. pneumoniae* . The fastidious nutritional requirements of *Mycoplasma* make cultures slow and impractical.

Serologic tests (immunofluorescence tests, enzyme-linked immune assays [EIAs], or complement fixation) to detect serum immunoglobulin (Ig) M and IgG antibodies against *M. pneumoniae* are commercially available. IgM antibodies have a high rate of false-positive and false-negative results. In most cases, IgM antibodies are not detected within the 1st wk after onset of symptoms or in children with recurrent infections and may be positive for up to 6-12 mo after infection. A 4-fold or greater increase in IgG antibody titers against *M. pneumoniae* between acute and convalescent sera obtained 2-4 wk apart is diagnostic.

Cold hemagglutinins (cold-reacting antibodies [IgM] against red blood cells) can be detected in approximately 50% of patients with *M. pneumoniae* pneumonia. These antibodies are nonspecific, especially at titers <1 : 64, as modest increases in cold hemagglutinins can be observed in other viral infections. Cold agglutinin antibodies should not be used for the diagnosis of *M. pneumoniae* infections if other methods are available.

PCR -based tests for *M. pneumoniae* have replaced other diagnostic tests. PCR of a nasopharyngeal or throat swab (the combination of both increases sensitivity) for *M. pneumoniae* genomic DNA carries a sensitivity and a specificity of 80 to >97%. In adults, sputum samples are more likely than nasopharyngeal or throat swabs to yield positive results. Different primers have been used to identify gene sequences of the P1 cytoadhesion protein or the ribosomal (r) 16S RNA. PCR allows a more rapid diagnosis in acutely ill patients and can be positive earlier in the course of infection than serologic tests. Mycoplasma PCR from respiratory samples may be positive in asymptomatic subjects. Nonetheless, identification of *M. pneumoniae* by PCR (or culture) from a patient with compatible clinical manifestations suggests causation.

Other diagnostic methods: The matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) could represent an accurate tool for identification and subtyping of *M. pneumoniae* . However, the need for culture to subsequently be able to perform MALDI-TOF MS limits its applicability in the clinical setting. Silver nanorod array-surface enhanced Raman spectroscopy (NA-SERS) is an investigational system that does not require growth of the bacterium. It appears a promising and sensitive tool for mycoplasma detection and strain characterization.

The diagnosis of extrapulmonary disease associated with *M. pneumoniae* is challenging. Although *M. pneumoniae* has been identified by PCR in the CSF of children with encephalitis, there are currently no reliable tests for the diagnosis of CNS or other nonrespiratory sites associated with *M. pneumoniae* . Since the extrapulmonary manifestations of *M. pneumoniae* may have an immunologic base, measuring acute and convalescent IgM and IgG antibody levels is advisable.

Treatment

M. pneumoniae illness is usually mild, and most cases of pneumonia can be managed without the need for hospitalization. Because mycoplasmas lack a cell wall, they inherently are resistant to β-lactam agents that act by inhibiting the cell wall synthesis. In addition, other drug classes, such as trimethoprim, rifampin, or linezolid are inactive against *M. pneumoniae* . Studies regarding the effectiveness of antimicrobial therapy for *M. pneumoniae* infections in children are contradictory. Nevertheless, empiric treatment is often initiated based on clinical suspicion due to the difficulty of a definitive diagnosis.

Antimicrobial Therapy

M. pneumoniae is typically sensitive to macrolides (erythromycin, clarithromycin, azithromycin), tetracyclines, and quinolones in vitro. Treatment of mycoplasma does not assure eradication. Data from observational studies showed that macrolide treatment of children with *M. pneumoniae* CAP markedly shortened the course of illness. Treatment may be more effective when started within 3-4 days of illness onset. Although macrolides do not have bactericidal activity, they are preferred in children younger than 8 yr of age. Two multicenter studies of pediatric CAP demonstrated comparable clinical and bacteriologic success rates between erythromycin and clarithromycin or azithromycin. However, the newer macrolides were better tolerated. The recommended treatment is clarithromycin (15 mg/kg/day divided into 2 doses PO for 10 days) or azithromycin (10 mg/kg once PO on day 1 and 5 mg/kg once daily PO on days 2-5). In addition to the antibacterial effect, macrolides may have immunomodulatory properties, but the relevance of the antiinflammatory properties of macrolides for the treatment of *M. pneumoniae* CAP is not known. Tetracyclines (doxycycline 100 mg twice a day for 7-14 days) are also effective and may be used for children older than 8 yr of age. Fluoroquinolones such as levofloxacin (750 mg once a day for 7-14 days) are effective and bactericidal but have higher minimum inhibitory concentrations (MIC) compared with macrolides and currently are not recommended as a first-line therapy in children.

Macrolide-resistant strains, mostly associated with mutations in the 23S rRNA, have been increasingly reported in Asia (>90% in Japan and China) and are also present in Europe with great variability from country to country (0% in the Netherlands vs. 26% in Italy). In the United States and Canada, the rates of resistance varied from 3.5 to 13% of cases. Although not routinely performed at clinical laboratories, identification of macrolide-resistant strains can be performed by sequencing and identification of specific mutations in the 23S rRNA gene. The clinical significance of macrolide-resistant infections has not been completely elucidated, however, studies in children indicated that the clinical efficacy of macrolide-susceptible *M. pneumoniae* infections is >4-fold higher compared with infections caused by resistant strains (91% vs. 22% respectively). Thus, for patients with severe infections not responding to macrolide therapy within the first 48 hr of treatment, the possibility of macrolide-resistant *M. pneumoniae* should be considered and switching to a non-macrolide antimicrobial regimen might be prudent. Doxycycline (2-4 mg/kg in one or two divided doses for 10 days; max 200 mg or 100 mg q12h) for children >8 yr, or levofloxacin (10 mg/kg per dose every 12 hr in children <5 yr or once a day in older children) after assessment of risk and benefits of using quinolones in children, are potential alternatives for macrolide-resistant *M. pneumoniae* infections. Other quinolones such as tosufloxacin or garenoxacin are used in Japan. There are new ketolides in development that appear promising.

Adjunctive Therapy

There is no evidence that treatment of upper respiratory tract or nonrespiratory tract disease with antimicrobial agents alters the course of illness. However, patients with severe manifestations of extrapulmonary disease may benefit from antimicrobial treatment, since direct involvement of the bacterium cannot be excluded. Oftentimes antibiotics are administered in combination with immunomodulatory therapy. In this regard, corticosteroids with or without intravenous immunoglobulin are the most commonly used agents for managing severe *M. pneumoniae* extrapulmonary manifestations, particularly for patients with CNS involvement or rash and mucositis. Although definitive data are lacking, case studies suggest the associated clinical benefit of steroids in the management of severe lung disease, SJS, and hemolytic anemia.

Prevention

Trials with inactivated and live attenuated vaccines for *M. pneumoniae* have been conducted with disappointing results. In hospitalized patients standard and droplet precautions are recommended for the duration of symptoms. It is important to emphasize that mycoplasma infection remains contagious as long as cough persists and despite successful antibiotic therapy. Prophylaxis with tetracyclines or azithromycin substantially reduces the secondary attack rates in institutional outbreaks and family close contacts. Antimicrobial prophylaxis is not recommended routinely; however, it can be considered in patients at high risk for severe disease, such as children with sickle cell disease.

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CHAPTER 251

Genital Mycoplasmas (*Mycoplasma hominis, Mycoplasma genitalium* , and *Ureaplasma urealyticum*)

Rosa Rodríguez-Fernández, Asuncion Mejias

Etiology

Mycoplasma species are small pleomorphic bacteria that typically lack a cell wall and are bound by a cell membrane. Many of the biologic properties of mycoplasmas are in fact due to the absence of a rigid cell wall, including resistance to β-lactam antibiotics. These ubiquitous organisms are difficult to cultivate and belong to the family Mycoplasmataceae in the class Mollicutes and represent the smallest self-replicating organisms known to date. The entire genome of many of the *Mycoplasma* species is among the smallest of prokaryotic genomes. The family Mycoplasmataceae is composed of two genera responsible for human infection: *Mycoplasma* and *Ureaplasma*. Of those, *Mycoplasma hominis*, *Mycoplasma genitalium*, and *Ureaplasma* spp., which include *Ureaplasma urealyticum (biovar 2)* and *Ureaplasma parvum (biovar 1)*, are considered human urogenital pathogens and are reviewed in this chapter.

Genital mycoplasmas are often associated with sexually transmitted infections such as cervicitis and nongonococcal urethritis (NGU) or with puerperal infections such as endometritis. *M. hominis* and *Ureaplasma* spp. commonly colonize the female genital tract and can cause chorioamnionitis, colonization of neonates, and perinatal infections. Two other genital *Mycoplasma* species, *Mycoplasma fermentans* and *Mycoplasma penetrans*, have been identified in respiratory or genitourinary secretions primarily in HIV-infected patients.

Epidemiology

M. hominis and *Ureaplasma* spp. are commensal organisms in the lower genital and urinary tract of postpubertal women and men. The prevalence of colonization with these bacteria has been directly associated with low socioeconomic status, hormonal changes, and ethnicity and increases proportionally according to sexual activity, being highest among individuals with multiple sexual partners. Female colonization is greatest in the vagina and lower in the endocervix, urethra, and endometrium, with rates varying from 40% to 80% for *Ureaplasma* spp. and 21–50% for *M. hominis* among sexually active asymptomatic women. *Ureaplasma* is isolated less often from urine than from the cervix, but *M. hominis* is present in the urine and in the cervix with approximately the same frequency. Male colonization is less common and occurs primarily in the urethra. Among prepubertal children and sexually inactive adults, colonization rates are <10%. *M. genitalium* is implicated in approximately 15–20% of NGU cases in men and plays a role in cervicitis and pelvic inflammatory disease in women. Studies using polymerase chain reaction (PCR) show that colonization of the female lower urogenital tract with *M. genitalium* is less common than with *M. hominis* or *Ureaplasma* spp.

Transmission

Genital mycoplasmas are transmitted by sexual contact or by vertical transmission from mother to infant. As with other perinatal infections, vertical transmission can occur through ascending intrauterine infection, hematogenous spread from placental infection, or through a colonized birth canal at the time of delivery. Transmission rates among neonates born to women colonized with *Ureaplasma* spp. range from 18 to 88%. Neonatal colonization rates are higher among infants who weigh <1,000 g, are born in the presence of chorioamnionitis, or are born to mothers of lower socioeconomic status. Neonatal colonization is transient and decreases proportionally with age. Organisms may be recovered from the newborn's throat, vagina, rectum, and, occasionally, conjunctiva for as long as 3 mo after birth.

Pathogenesis

Genital mycoplasmas can cause chronic inflammation of the genitourinary tract and amniotic membranes. These bacteria usually live in a state of adherence to the respiratory or urogenital tract, but can disseminate to other organs when there is a disruption of the mucosa or a weakened or immature immune system, such as in premature infants. *Ureaplasma* spp. can infect the amniotic sac early in gestation without rupturing the amniotic membranes, resulting in a clinically silent, chronic chorioamnionitis characterized by an intense inflammatory response. Attachment to fetal human tracheal epithelium can cause ciliary disarray, clumping, and loss of epithelial cells. *In vitro* studies show that *Ureaplasma* spp. stimulates macrophage production of interleukin (IL)-6 and tumor necrosis factor-α. In addition, high concentrations of proinflammatory cytokines possibly associated with development of bronchopulmonary dysplasia (BPD) of prematurity, such as monocyte chemoattractant protein-1 and IL-8, have been found in tracheal secretions from very-low-birthweight infants colonized with *Ureaplasma* spp. Immunity appears to require serotype-specific antibody. Thus, lack of maternal antibodies might account for a higher disease risk in premature newborns.

Clinical Manifestations

The main syndromes associated with *Ureaplasma* spp., *M. genitalium*, and *M. hominis* are displayed in Table 251.1 .

Table 251.1

Clinical Syndromes and Antibiotic Therapy for Ureaplasmas and Mycoplasmas Infection

	UREAPLASMA SPP.	M. HOMINIS	M. GENITALIUM
INTRAUTERINE AND NEONATAL INFECTIONS			
Chorioamnionitis	++	++	–
Preterm delivery	++	++	++
Postpartum fever	++	+++	UK
BPD	+++	+	UK
CNS infections	+	+	UK
NEC	+	UK	UK
GENITOURINARY INFECTIONS			
NGU (acute/chronic)	++*	–	+++
Cervicitis	–	–	+++
PID	+	++	+++
NON-NEONATAL/NON-GENITOURINARY INFECTIONS			

CNS disease[†]	+	++	–
Bacteremia	+	++	–
Surgical wound infections	++	++	–
Arthritis	+	++	–
TREATMENT			
Macrolides	++	–	++
Quinolones[‡]	+	++	+
Clindamycin	–	++	+
Tetracyclines (doxycycline)	++	+	+

[*] Only *Ureaplasma urealyticum* (not *parvum*).

[†] CNS disease includes: meningitis, brain abscess, subdural empyema, and nonfunctioning CNS shunts.

[‡] The most commonly used quinolones are ciprofloxacin and moxifloxacin.

BPD : bronchopulmonary dysplasia; *CNS* : central nervous system; *NEC* : necrotizing enterocolitis; *NGU* : nongonococcal urethritis; *PID* : pelvic inflammatory disease; *UK* : unknown.

Intrauterine and Neonatal Infections

Chorioamnionitis and Early Onset Infections

Genital mycoplasmas are associated with a variety of fetal and neonatal infections. *Ureaplasma* spp. can cause clinically inapparent chorioamnionitis, resulting in spontaneous abortion, increased fetal death, or premature delivery. The role of *Ureaplasma* in clinical chorioamnionitis is still unclear. The association between preterm birth and ureaplasmas remains uncertain. Studies have shown that women with *Ureaplasma* spp. detected by PCR in amniotic fluid between 12 to 20 wk of gestation have an increased risk of preterm labor and delivery. *Ureaplasma* spp. can also be recovered from tracheal, blood, cerebrospinal fluid (CSF), or lung biopsy specimens in up to 50% of sick infants younger than 34 wk gestation. In a study of 351 mother/infant dyads, isolation of *Ureaplasma* spp. or *M. hominis* from cord blood was documented in 23% of infants born between 23 and 32 wk gestation, and correlated with the development of systemic inflammatory response syndrome.

Bronchopulmonary Dysplasia

The role of these organisms in causing severe respiratory insufficiency, the need for mechanical ventilation, the development of BPD, or death remains controversial. Nevertheless, meta-analyses of published studies have identified respiratory colonization with *Ureaplasma* spp. as an independent risk factor for the development of BPD. However, trials using erythromycin therapy in high-risk preterm infants with tracheobronchial colonization of *U. urealyticum* have failed to show any difference in the development of BPD in treated vs. nontreated infants. To date there is not enough evidence to support the use of antibiotic therapy in preterm infants at-risk or with confirmed *Ureaplasma* spp. infection to prevent the development of BPD.

Central Nervous System Infections

M. hominis and *Ureaplasma* spp. have been isolated from the CSF of premature infants and, less commonly, full-term infants. However, the clinical significance of recovering these bacteria from the CSF is uncertain, simultaneous isolation of other pathogens is unusual, and most infants have no overt signs of CNS disease. These bacteria may represent true pathogens and may be associated with CNS disease based on the host susceptibility/gestational age and bacteria pathogenicity. Overall, CSF pleocytosis is not consistent, and spontaneous clearance of mycoplasmas has been documented without specific therapy. *Ureaplasma* spp. meningitis has been associated with intraventricular hemorrhage and hydrocephalus. Limited data suggest that meningitis caused by *M. hominis* can be associated with significant morbidity and mortality. In a review of 29 reported neonatal cases with *M. hominis* meningitis, 8 (28%) neonates died and 8 (28%) developed neurologic sequelae. The age of onset of meningitis ranges from 1 to 196 days of life, and organisms can persist in the CSF without therapy for days to weeks. Pachymeningitis may be evident on MRI.

Other *: M. hominis* and *Ureaplasma* spp. have also been associated with neonatal conjunctivitis, abscesses (mainly at the scalp electrode site and associated with *M. hominis*), bacteremia, and necrotizing enterocolitis (NEC).

Genitourinary Infections

In sexually active adolescents and adults, genital mycoplasmas are associated with sexually transmitted diseases and are rarely associated with focal infections outside the genital tract. *U. urealyticum* (not *U. parvum*) and *M. genitalium* are recognized etiologic agents of NGU, mainly in men. Approximately 20% of NGU may be caused by these organisms either alone or associated with *Chlamydia trachomatis* . Rare complications of NGU include epididymitis and prostatitis. Salpingitis, cervicitis, pelvic inflammatory disease, and endometritis have been described in women associated with *M. genitalium* and to a lesser extent with *M. hominis.*

Nongenital Infections

Ureaplasma spp. and *M. hominis* infections are rarely described outside the neonatal period. These infections have been reported in both immunocompetent and immunocompromised children, including patients with hypogammaglobulinemia, lymphoma, or solid organ transplant recipients, who appear to be at higher risk of infection.

Cases of *Ureaplasma* spp. pneumonia, osteomyelitis, arthritis, meningitis, mediastinitis, bacteremia, infection of aortic grafts, and post-cesarean wound infections have been reported. Recent data suggest that *Ureaplasma* spp. is associated with post-transplant hyperammonemia syndrome, a rare but potentially fatal complication.

M. hominis is most commonly reported in systemic infections and has been associated with CNS disease (including meningitis, brain abscesses, subdural empyema, and nonfunctioning shunts), surgical wound infections, arthritis (associated in up to 50% of cases with prior manipulation of the GU tract), prosthetic and naïve endocarditis, osteomyelitis, and pneumonia. There are reports of life-threatening mediastinitis, sternal wound infections, pleuritis, peritonitis, and pericarditis, with high mortality rates in patients following organ transplantation. These infections should be suspected in culture-negative systemic or local infections, when samples have been properly collected and before initiation of antibiotic therapy.

Diagnosis

All Mollicutes lack a cell wall and are therefore not visible on Gram stain. *M. hominis* and *Ureaplasma* spp. can grow in cell-free media and require sterols for growth, producing characteristic colonies on agar. Colonies of *M. hominis* are 200-300 μm in diameter with a fried-egg appearance, while colonies of *Ureaplasma* spp. are smaller (16-60 μm in diameter). *M. genitalium* is a fastidious organism and can be isolated with difficulty in cell culture systems. Most hospital diagnostic microbiology laboratories are not prepared to culture these pathogens, and nucleic acid-based tests are the preferred method for diagnosis. PCR-based assays have greater sensitivity and provide a more practical method for detection. Serologic assays have limited value in the clinical setting and are not commercially available for diagnostic purposes.

Genital Tract Infection

Confirmation of genital tract infection is challenging because of the high colonization rates in the vagina and urethra. NGU is typically defined as new-onset urethral discharge or dysuria with Gram stain of urethral discharge showing ≥ 5 polymorphonuclear leukocytes per oil-immersion field in the absence of gram-negative diplococci (i.e., *Neisseria gonorrhoeae*). The lack of cell wall prevents the identification of these bacteria by routine Gram stain. Detection of *Ureaplasma* spp. or *M. hominis* by PCR is available for a variety of specimens, including urine, amniotic fluid, placental tissue, respiratory specimens, synovial fluid, and swabs of the cervix, urethra, and vagina. *M. genitalium* is often identified by nucleic acid amplification test (NAAT) testing of first-void urine specimens in men and vaginal swabs in women.

Neonates

Ureaplasma spp. and *M. hominis* have been isolated from urine, blood, CSF, tracheal aspirates, pleural fluid, abscesses, and lung tissue. Premature neonates who are clinically ill with pneumonitis, focal abscesses, or CNS disease (particularly progressive hydrocephalus with or without pleocytosis) for whom bacterial cultures are negative or in whom there is no improvement with standard antibiotic therapy warrant further work-up to rule out genital mycoplasmas. Isolation requires special media using urea for ureaplasmas and arginine for *M. hominis* , and clinical specimens must be cultured immediately or frozen at −70°C (−94°F) to prevent loss of organisms. When inoculated into broth containing arginine (for *M. hominis*) or urea (for *Ureaplasma* spp.), growth is indicated by an alkaline pH. Identification of *Ureaplasma* spp. on agar requires 1-2 days of growth and visualization with the dissecting microscope, whereas *M. hominis* is apparent to the eye but can require 2-7 days to grow. PCR-based assays are available and will shed light to the causality of these pathogens when sterile sites are tested (CSF, joint fluid, etc.).

Treatment

These organisms lack a cell wall, and thus β-lactam agents are not effective. These bacteria are also resistant to sulfonamides and trimethoprim because they do not produce folic acid. Rifamycins do not have activity against Mollicutes (see Table 251.1).

Unlike other mycoplasmas and ureaplasmas, *M. hominis* is resistant to macrolides but generally susceptible to clindamycin and quinolones. Most *Ureaplasma* spp. are susceptible to macrolides and advanced generation quinolones, such as moxifloxacin, but are often resistant to ciprofloxacin and clindamycin. Susceptibility to tetracyclines is variable for both organisms, with increasing resistance being reported. *M. genitalium* is typically susceptible to macrolides and moxifloxacin, with variable resistance to tetracyclines and clindamycin.

Adolescents and Adults

Recommended treatment for NGU should include antibiotics with activity against *C. trachomatis* with either doxycycline (100 mg PO twice daily for 7 days) or azithromycin (1 g PO as a single dose). Recurrent NGU after completion of treatment suggests the presence of doxycycline or azithromycin-resistant *M. genitalium* . If the initial empiric regimen did not include macrolides, retreatment with azithromycin may be indicated. Azithromycin is also preferred in children younger than 8 yr, and in those with allergy to tetracyclines. On the other hand if patients received azithromycin initially, retreatment with moxifloxacin may be most effective. Before the introduction of azithromycin up to 60% of patients with *M. genitalium* NGU developed recurrent or chronic urethritis despite 1-2 wk of treatment with doxycycline.

Sexual partners should also be treated to avoid recurrent disease in the index case. Nongenital mycoplasmal infections may require surgical drainage and prolonged antibiotic therapy.

Neonates

Treatment of these infections in neonates is challenging. Doxycycline and quinolones are generally avoided at this age due to their associated toxicities. In addition, attributing causality may be difficult. In general, therapy for neonates with genital mycoplasma infections is indicated if infections are associated with pure growth of the organism or if the organism is detected by PCR from a normally sterile site in conjunction with compatible disease manifestations to assure the treatment of an infectious process rather than merely colonization.

Treatment is usually based on predictable antimicrobial sensitivities, because susceptibility testing is not readily available for individual isolates (see Table 251.1). For infants with symptomatic CNS infection, cures have been described with chloramphenicol, doxycycline, and moxifloxacin. The long-term consequences of asymptomatic CNS infection associated with genital mycoplasmas, especially in the absence of pleocytosis, are unknown. Because mycoplasmas can spontaneously clear from the CSF, therapy should involve minimal risks.

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SECTION 10

Chlamydial Infections

OUTLINE

Chapter 252 Chlamydia pneumoniae
Chapter 253 Chlamydia trachomatis
Chapter 254 Psittacosis (Chlamydia psittaci)

CHAPTER 252

Chlamydia pneumoniae

Stephan A. Kohlhoff, Margaret R. Hammerschlag

Chlamydia pneumoniae is a common cause of lower respiratory tract diseases, including pneumonia in children and bronchitis and pneumonia in adults.

Etiology

Chlamydiae are obligate intracellular pathogens that have established a unique niche in host cells. Chlamydiae cause a variety of diseases in animal species at virtually all phylogenic levels. The most significant human pathogens are *C. pneumoniae* and *Chlamydia trachomatis* (see Chapter 253). *Chlamydia psittaci* is the cause of psittacosis, an important zoonosis (see Chapter 254). There are now 9 recognized chlamydial species.

Chlamydiae have a gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both *C. pneumoniae* and *C. trachomatis* encode proteins forming a nearly complete pathway for synthesis of peptidoglycan, including penicillin-binding proteins. Chlamydiae also share a group-specific lipopolysaccharide antigen and use host adenosine triphosphate for the synthesis of chlamydial proteins. Although chlamydiae are auxotrophic for 3 of 4 nucleoside triphosphates, they encode functional glucose-catabolizing enzymes that can be used to generate adenosine triphosphate. As with peptidoglycan synthesis, for some reason these genes are turned off. All chlamydiae also encode an abundant surface-exposed protein called the *major outer membrane protein.* The major outer membrane protein is the major determinant of the serologic classification of *C. trachomatis* and *C. psittaci* isolates.

Epidemiology

C. pneumoniae is primarily a human respiratory pathogen. The organism has also been isolated from nonhuman species, including horses, koalas, reptiles, and amphibians, where it also causes respiratory infection, although the role that these infections might play in transmission to humans is unknown. *C. pneumoniae* appears to affect individuals of all ages. The proportion of community-acquired pneumonias associated with *C. pneumoniae* infection is 2–19%, varying with geographic location, the age group examined, and the diagnostic methods used. Several studies of the role of *C. pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection in 0–18% of patients based on serology or culture for diagnosis. In 1 study, almost 20% of the children with *C. pneumoniae* infection were coinfected with *Mycoplasma pneumoniae. C. pneumoniae* may also be responsible for 10–20% of episodes of acute chest syndrome in children with sickle cell disease, up to 10% of asthma exacerbations, 10% of episodes of bronchitis, and 5–10% of episodes of pharyngitis in children. Asymptomatic infection appears to be common based on epidemiologic studies.

Transmission probably occurs from person to person through respiratory droplets. Spread of the infection appears to be enhanced by close proximity, as is evident from localized outbreaks in enclosed populations, such as military recruits and in nursing homes.

Pathogenesis

Chlamydiae are characterized by a unique developmental cycle (Fig. 252.1) with morphologically distinct infectious and reproductive forms: the elementary body (EB) and reticulate body (RB). Following infection, the infectious EBs, which are 200-400 µm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests a functional interaction with the Golgi apparatus. The EBs then differentiate into RBs that undergo binary fission. After approximately 36 hr, the RBs differentiate into EBs. At approximately 48 hr, release can occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, leaving the host cell intact. Chlamydiae can also enter a persistent state after treatment with certain cytokines such as interferon-γ, treatment with antibiotics, or restriction of certain nutrients. While chlamydiae are in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical, infection is one of the major characteristics of chlamydiae.

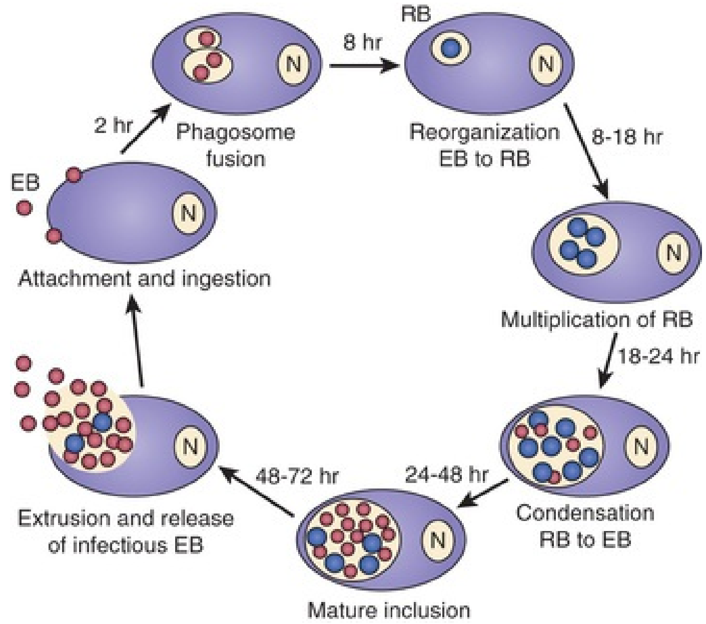
RB
8 hr
N
2 hr
Phagosome fusion
Reorganization EB to RB
8-18 hr
EB
Attachment and ingestion
Multiplication of RB
18-24 hr
48-72 hr
24-48 hr
Extrusion and release of infectious EB
Condensation RB to EB
Mature inclusion

FIG. 252.1 Life cycle of chlamydiae in epithelial cells. *EB,* elementary body; *RB,* reticulate body. (From Hammerschlag MR: Infections due to *Chlamydia trachomatis* and *Chlamydia pneumoniae* in children and adolescents. *Pediatr Rev* 25:43–50, 2004.)

Clinical Manifestations

Infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *M. pneumoniae.* The pneumonia usually occurs as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms, including fever, malaise, headache, cough, and often pharyngitis. Severe pneumonia with pleural effusions and empyema has been described. Milder respiratory infections have been described, manifesting as a pertussis-like illness.

C. pneumoniae can serve as an infectious trigger for asthma, can cause pulmonary exacerbations in patients with cystic fibrosis, and can produce acute chest syndrome in patients with sickle cell anemia. *C. pneumoniae* has been isolated from middle ear aspirates of children with acute otitis media, most of the time as co-infection with other bacteria. Asymptomatic respiratory infection has been documented in 2–5% of adults and children and can persist for 1 yr or longer.

Diagnosis

It is not possible to differentiate *C. pneumoniae* from other causes of atypical pneumonia on the basis of clinical findings. Auscultation reveals the presence of rales and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and can show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of *C. pneumoniae* infection has been based on isolation of the organism in tissue culture. *C. pneumoniae* grows best in cycloheximide-treated HEp-2 and HL cells. The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted swabs in the same manner as that used for *C. trachomatis.* The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. A multiplexed nucleic acid amplification testing assay (Film Array, Biofire Diagnostics, Salt Lake City, UT) received FDA clearance in 2012 for the detection of 17 viruses and *C. pneumoniae* , *M. pneumoniae,* and *Bordetella pertussis.* The Film Array system combines nucleic acid extraction, nested polymerase chain reaction, detection, and data analysis.

Serologic diagnosis can be accomplished using the microimmunofluorescence (MIF) or the complement fixation tests. The complement fixation test is genus specific and is also used for diagnosis of lymphogranuloma venereum (see Chapter 253.4) and psittacosis (see Chapter 254). Its sensitivity in hospitalized patients with *C. pneumoniae* infection and children is variable. The Centers for Disease Control and Prevention (CDC) has proposed modifications in the serologic criteria for diagnosis. Although the MIF test was considered to be the only currently acceptable serologic test, the criteria were made significantly more stringent. Acute infection, using the MIF test, was defined by a 4-fold increase in immunoglobulin (Ig) G titer or an IgM titer of ≥16; use of a single elevated IgG titer was discouraged. An IgG titer of ≥16 was thought to indicate past exposure, but neither elevated IgA titers nor any other serologic marker was thought to be a valid indicator of persistent or chronic infection. Because diagnosis would require paired sera, this would be a retrospective diagnosis. The CDC did not recommend the use of any enzyme-linked immune assay for detection of antibody to *C. pneumoniae* because of concern about the inconsistent correlation of these results with culture results. Studies of *C. pneumoniae* infection in children with pneumonia and asthma show that more than 50% of children with culture-documented infection have no detectable MIF antibody.

Treatment

The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. Most treatment studies have used only serology for diagnosis, and thus microbiologic efficacy cannot be assessed. Prolonged therapy for 2 wk or longer is required for some patients, because recrudescent symptoms and persistent positive cultures have been described following 2 wk of erythromycin and 30 days of tetracycline or doxycycline.

Tetracyclines, macrolides (erythromycin, azithromycin, and clarithromycin), and quinolones show *in vitro* activity. Like *C. psittaci, C. pneumoniae* is resistant to sulfonamides. The results of treatment studies have shown that erythromycin (40 mg/kg/day PO divided twice a day for 10 days), clarithromycin (15 mg/kg/day PO divided twice a day for 10 days), and azithromycin (10 mg/kg PO on day 1, and then 5 mg/kg/day PO on days 2-5) are effective for eradication of *C. pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases.

Prognosis

Clinical response to antibiotic therapy varies. Coughing often persists for several weeks even after therapy.

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CHAPTER 253

Chlamydia trachomatis

Margaret R. Hammerschlag

Chlamydia trachomatis is subdivided into 2 biovars: lymphogranuloma venereum (LGV) and trachoma, which is the agent of human oculogenital diseases other than LGV. Although the strains of both biovars have almost complete DNA homology, they differ in growth characteristics and virulence in tissue culture and animals. In developed countries, *C. trachomatis* is the most prevalent sexually transmitted disease, causing urethritis in men, cervicitis and salpingitis in women, and conjunctivitis and pneumonia in infants.

253.1

Trachoma

Margaret R. Hammerschlag

Keywords

trachoma
mass drug administration
blindness

Trachoma is the most important preventable cause of blindness in the world. It is caused primarily by the A, B, Ba, and C serotypes of *C. trachomatis.* It is endemic in the Middle East and Southeast Asia and among Navajo Indians in the southwestern United States. In areas that are endemic for trachoma, such as Egypt, genital chlamydial infection is caused by the serotypes responsible for oculogenital disease: D, E, F, G, H, I, J, and K. The disease is spread from eye to eye. Flies are a common vector.

Trachoma begins as a **follicular conjunctivitis,** usually in early childhood. The follicles heal, leading to conjunctival scarring that can result in an entropion, with the eyelid turning inward so that the lashes abrade the cornea. It is the corneal ulceration secondary to the constant trauma that leads to scarring and blindness. Bacterial superinfection can also contribute to scarring. Blindness occurs years after the active disease.

Trachoma can be diagnosed clinically. The World Health Organization suggests that at least 2 of 4 criteria must be present for a diagnosis of trachoma: lymphoid follicles on the upper tarsal conjunctivae, typical conjunctival scarring, vascular pannus, and limbal follicles. The diagnosis is confirmed by culture or staining tests for *C. trachomatis* performed during the active stage of disease. Serologic tests are not helpful clinically because of the long duration of the disease and the high seroprevalence in endemic populations.

Poverty and lack of sanitation are important factors in the spread of trachoma. As socioeconomic conditions improve, the incidence of the disease decreases substantially. Endemic trachoma is managed by mass drug administration (MDA) with azithromycin in affected communities. Endemic communities should receive MDA until clinical signs of active disease in children, 1-9 yr of age, falls below 5%. MDA with a single dose of azithromycin to all the residents of a village dramatically reduced the prevalence and intensity of infection. This effect continued for 2 yr after treatment, probably by interrupting the transmission of ocular *C. trachomatis* infection.

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253.2

Genital Tract Infections

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Keywords

cervicitis
urethritis
salpingitis
nucleic acid amplification test

Epidemiology

There are an estimated 3 million new cases of chlamydial sexually transmitted infections each year in the United States. *C. trachomatis* is a major cause of epididymitis and is the cause of 23–55% of all cases of nongonococcal urethritis, although the proportion of chlamydial nongonococcal urethritis has been gradually declining. As many as 50% of men with gonorrhea may be coinfected with *C. trachomatis*. The prevalence of chlamydial cervicitis among sexually active women is 2–35%. Rates of infection among girls 15-19 yr of age exceed 20% in many urban populations but can be as high as 15% in suburban populations as well.

Children who have been sexually abused can acquire anogenital *C. trachomatis* infection, which is usually asymptomatic. However, because perinatally acquired rectal and vaginal *C. trachomatis* infections can persist for 3 yr or longer, the detection of *C. trachomatis* in the vagina or rectum of a young child is not absolute evidence of sexual abuse.

Clinical Manifestations

The trachoma biovar of *C. trachomatis* causes a spectrum of disease in sexually active adolescents and adults. Up to 75% of women with *C. trachomatis* have no symptoms of infection. *C. trachomatis* can cause urethritis (acute urethral syndrome), epididymitis, cervicitis, salpingitis, proctitis, and pelvic inflammatory disease. The symptoms of chlamydial genital tract infections are less acute than those of gonorrhea, consisting of a discharge that is usually mucoid rather than purulent. Asymptomatic urethral infection is common in sexually active men. Autoinoculation from the genital tract to the eyes can lead to concomitant inclusion conjunctivitis.

Diagnosis

Diagnosis of genital chlamydial infection is now accomplished by nucleic acid amplification tests (NAATs). These tests have high sensitivity, perhaps even detecting 10–20% greater than culture, while retaining high specificity. 6 FDA-approved NAATs are commercially available for detecting *C. trachomatis* , including polymerase chain reaction (PCR; Amplicor Chlamydia test, Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (ProbeTec, BD Diagnostic Systems, Sparks, MD), transcription-mediated amplification (Amp CT, Hologic, San Diego, CA), and GeneXpert CT/NG assay (Cepheid, Sunnyvale, CA). PCR and strand displacement amplification are DNA amplification tests that use primers that target gene sequences on the cryptogenic *C. trachomatis* plasmid that is present at approximately 10 copies in each infected cell. Transcription-mediated amplification is a ribosomal RNA amplification assay. GeneXpert is an on-demand qualitative real-time PCR. All these assays are also available as coamplification tests for simultaneously detecting *C. trachomatis* and *Neisseria gonorrhoeae*.

The available commercial NAATs are FDA approved for cervical and vaginal swabs from adolescent girls and women, urethral swabs from adolescent boys and men, and urine from adolescents and adults. Use of urine avoids the necessity for a clinical pelvic examination and can greatly facilitate screening in certain populations, especially adolescents, although several studies have now demonstrated that endocervical specimens and vaginal swabs are superior to urine for NAAT. Self-collected vaginal specimens appear to be as reliable as specimens obtained by a healthcare professional.

Data on use of NAATs for vaginal specimens or urine from children are very limited and insufficient to allow making a recommendation for their use. The CDC recommends that NAATs be used as an alternative to culture only if confirmation is available. Confirmation tests should consist of a second FDA-approved NAAT that targets a different gene sequence from the initial test.

The etiology of most cases of nonchlamydial nongonococcal urethritis is unknown, although *Ureaplasma urealyticum* and possibly *Mycoplasma genitalium* are implicated in up to one-third of cases (see Chapter 251). Proctocolitis may develop in individuals who have a rectal infection with an LGV strain (see Chapter 253.4).

Treatment

The first-line treatment regimens recommended by the CDC for uncomplicated *C. trachomatis* genital infection in men and nonpregnant women include azithromycin (1 g PO as a single dose) and doxycycline (100 mg PO twice a day for 7 days). Alternative regimens are erythromycin base (500 mg PO 4 times a day for 7 days), erythromycin ethylsuccinate (800 mg PO 4 times a day for 7 days), ofloxacin (300 mg PO twice a day for 7 days), and levofloxacin (500 mg PO once daily for 7 days). The high erythromycin dosages might not be well tolerated. Doxycycline and quinolones are contraindicated in pregnant women, and quinolones are contraindicated in persons younger than 18 yr. For pregnant women, the recommended treatment regimen is azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days). Alternative regimens for pregnant women are erythromycin base (250 mg PO 4 times a day for 14 days) and erythromycin ethylsuccinate (800 mg PO 4 times a day for 7 days or 400 mg PO 4 times a day for 14 days).

Empirical treatment without microbiologic diagnosis is recommended only for patients at high risk for infection who are unlikely to return for follow-up evaluation, including adolescents with multiple sex partners. These patients should be treated empirically for both *C. trachomatis* and gonorrhea.

Sex partners of patients with nongonococcal urethritis should be treated if they have had sexual contact with the patient during the 60 days preceding the onset of symptoms. The most recent sexual partner should be treated even if the last sexual contact was more than 60 days from onset of symptoms.

Complications

Complications of genital chlamydial infections in women include perihepatitis (Fitz-Hugh-Curtis syndrome) and salpingitis. Of women with untreated chlamydial infection who develop pelvic inflammatory disease, up to 40% will have significant sequelae; approximately 17% will suffer from chronic pelvic pain, approximately 17% will become infertile, and approximately 9% will have an ectopic (tubal) pregnancy. Adolescent girls may be at higher risk for developing complications, especially salpingitis, than older women. Salpingitis in adolescent girls is also more likely to lead to tubal scarring, subsequent obstruction with secondary infertility, and increased risk for ectopic pregnancy. Approximately 50% of neonates born to pregnant women with untreated chlamydial infection will acquire *C. trachomatis* infection (see Chapter 253.3). Women with *C. trachomatis* infection have a 3-5–fold increased risk for acquiring HIV infection.

Prevention

Timely treatment of sex partners is essential for decreasing risk for reinfection. Sex partners should be evaluated and treated if they had sexual contact during the 60 days preceding onset of symptoms in the patient. The most recent sex partner should be treated even if the last sexual contact was > 60 days. Patients and their sex partners should abstain from sexual intercourse until 7 days after a single-dose regimen or after completion of a 7-day regimen.

Annual routine screening for *C. trachomatis* is recommended for all sexually active female adolescents, for all women 20-25 yr of age, and for older women with risk factors such as new or multiple partners or inconsistent use of barrier contraceptives. Sexual risk assessment might indicate more frequent screening of some women.

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253.3

Conjunctivitis and Pneumonia in Newborns

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Keywords

neonatal conjunctivitis
pneumonia
neonatal ocular prophylaxis

Epidemiology

Chlamydial genital infection is reported in 5–30% of pregnant women, with a risk for vertical transmission at parturition to newborn infants of approximately 50%. The infant may become infected at 1 or more sites, including the conjunctivae, nasopharynx, rectum, and vagina. Transmission is rare following cesarean section with intact membranes. The introduction of systematic prenatal screening for *C. trachomatis* infection and treatment of pregnant women has resulted in a dramatic decrease in the incidence of neonatal chlamydial infection in the United States. However, in countries where prenatal screening is not done, such as the Netherlands, *C. trachomatis* remains an important cause of neonatal infection, accounting for >60% of neonatal conjunctivitis.

Inclusion Conjunctivitis

Approximately 30–50% of infants born to mothers with active, untreated chlamydial infection develop clinical conjunctivitis. Symptoms usually develop 5-14 days after delivery, or earlier in infants born after prolonged rupture of membranes. The presentation is extremely variable and ranges from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva may be very friable and might bleed when stroked with a swab. Chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia, which is sight threatening. At least 50% of infants with chlamydial conjunctivitis also have nasopharyngeal infection.

Pneumonia

Pneumonia caused by *C. trachomatis* can develop in 10–20% of infants born to women with active, untreated chlamydial infection. Only approximately 25% of infants with nasopharyngeal chlamydial infection develop pneumonia. *C. trachomatis* pneumonia of infancy has a very characteristic presentation. Onset usually occurs between 1 and 3 mo of age and is often insidious, with persistent cough, tachypnea, and absence of fever. Auscultation reveals rales; wheezing is uncommon. The absence of fever and wheezing helps to distinguish *C. trachomatis* pneumonia from respiratory syncytial virus pneumonia. A distinctive laboratory finding is the presence of peripheral eosinophilia (>400 cells/µL). The most consistent finding on chest radiograph is hyperinflation accompanied by minimal interstitial or alveolar infiltrates.

Infections at Other Sites

Infants born to mothers with *C. trachomatis* can develop infection in the rectum or vagina. Although infection in these sites appears to be totally asymptomatic, it can cause confusion if it is identified at a later date. Perinatally acquired rectal, vaginal, and nasopharyngeal infections can persist for 3 yr or longer.

Diagnosis

Definitive diagnosis is achieved by isolation of *C. trachomatis* in cultures of specimens obtained from the conjunctiva or nasopharynx. Data on use of NAATs for diagnosis of *C. trachomatis* in children are limited. Limited data suggest that PCR may be equivalent to culture for detecting *C. trachomatis* in the conjunctiva of infants with conjunctivitis. However, NAATs are not currently FDA-cleared for use with conjunctival or nasopharyngeal specimens from infants. Laboratories can do internal validation delineated in the CDC 2014 *C. trachomatis* and *N. gonorrhoeae* laboratory guidelines.

Treatment

The recommended treatment regimens for *C. trachomatis* conjunctivitis or pneumonia in infants are erythromycin (base or ethylsuccinate, 50 mg/kg/day divided 4 times a day PO for 14 days) and azithromycin suspension (20 mg/kg/day once daily PO for 3 days). The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies demonstrate that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10–20%, and some infants require a second course of treatment. Mothers (and their sexual contacts) of infants with *C. trachomatis* infections should be empirically treated for genital infection. An association between treatment with both oral erythromycin and azithromycin and infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 wk of age.

Prevention

Neonatal gonococcal prophylaxis with topical erythromycin ointment does not prevent chlamydial ophthalmia or nasopharyngeal colonization with *C. trachomatis* or chlamydial pneumonia. *The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women.* In 2015, the Canadian Pediatric Society recommended that neonatal ocular prophylaxis be discontinued in Canada and recommended enhanced prenatal screening for chlamydia. The program was implemented in 2016. In the United

States, implementation of prenatal screening and treatment of pregnant women has resulted in a dramatic decrease in perinatal chlamydial infections. For treatment of *C. trachomatis* infection in pregnant women, the CDC currently recommends either azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days) as first-line regimens. Erythromycin base (250 mg PO 4 times a day for 14 days) and erythromycin ethylsuccinate (800 mg 4 times a day for 7 days, or 400 mg PO 4 times a day for 14 days) are listed as alternative regimens. Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner.

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253.4

Lymphogranuloma Venereum

Margaret R. Hammerschlag

Keywords

LGV biovar
proctocolitis

LGV is a systemic sexually transmitted disease caused by the L_1 , L_2 , and L_3 serotypes of the LGV biovar of *C. trachomatis.* Unlike strains of the trachoma biovar, LGV strains have a predilection for lymphoid tissue. Less than 1,000 cases are reported in adults in the United States annually. There has been a resurgence of LGV infections among men who have sex with men in Europe and the United States. Many of the men were HIV infected and used illicit drugs, specifically methamphetamines. The only pediatric case that has been reported since the emergence of the new clusters of HIV-associated cases in 2003 was a 16 yr old boy who presented with LGV proctocolitis after having receptive unprotected anal intercourse with a 30 yr old man he met on the Internet. This history was obtained after the boy was found to be HIV-positive. The diagnosis of LGV, particularly when it presents with proctocolitis, relies on a high index of suspicion that would lead to emphasizing certain aspects of the history and ordering the pertinent diagnostic tests. Many pediatricians and pediatric gastroenterologists might not be very familiar with the entity and might not entertain it as a diagnostic consideration in the pediatric patients. The diagnosis can be further suggested by *C. trachomatis* testing: commonly by NAATs or culturing the organism if culture is available. Currently available NAATs will not differentiate LGV from other *C. trachomatis* serovars. NAATs for *C. trachomatis* are also not FDA-cleared for testing rectal specimens, but laboratories can do an internal validation as recommended in the CDC 2014 *C. trachomatis* and *N. gonorrhoeae* laboratory guidelines. NAATs have been found in several clinical studies to perform well with rectal specimens. Typing of the *C. trachomatis* specimen can be done by sequencing from the NAAT specimen by many state laboratories. Trying to ascertain the *C. trachomatis* serovar for confirmation of LGV has therapeutic implications, as LGV needs to be treated with a 3 wk course of doxycycline; a single-dose of azithromycin will not eradicate the infection.

Clinical Manifestations

The **first stage of LGV** is characterized by the appearance of the primary lesion, a painless, usually transient papule on the genitals. The **second stage** is characterized by usually unilateral femoral or inguinal lymphadenitis with enlarging, painful buboes. The nodes may break down and drain, especially in men. In women, the vulvar lymph drains to the retroperitoneal nodes. Fever, myalgia, and headache are common. The **third stage** is a genitoanorectal syndrome with rectovaginal fistulas, rectal strictures, and urethral destruction. Among men who have sex with men, rectal infection with LGV can produce a severe, acute proctocolitis, which can be confused with inflammatory bowel disease or malignancy.

Diagnosis

LGV can be diagnosed by serologic testing or by culture of *C. trachomatis* or molecular testing for *C. trachomatis* from a specimen aspirated from a bubo. Most patients with LGV have complement-fixing antibody titers of >1:16. Chancroid and herpes simplex virus can be distinguished clinically from LGV by the concurrent presence of painful genital ulcers. Syphilis can be differentiated by serologic tests. However, co-infections can occur.

Treatment

Doxycycline (100 mg PO bid for 21 days) is the recommended treatment. The alternative regimen is erythromycin base (500 mg PO 4 times a day for 21 days). Azithromycin (1 g PO once weekly for 3 wk) may also be effective, but clinical data are lacking. Sex partners of patients with LGV should be treated if they have had sexual contact with the patient during the 30 days preceding the onset of symptoms.

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CHAPTER 254

Psittacosis *(Chlamydia psittaci)*

Stephan A. Kohlhoff, Margaret R. Hammerschlag

Chlamydia psittaci, the agent of psittacosis (also known as **parrot fever** and **ornithosis**), is primarily an animal pathogen and rarely causes human disease. In birds, *C. psittaci* infection is known as *avian chlamydiosis* .

Etiology

C. psittaci affects both psittacine birds (e.g., parrots, parakeets, macaws) and nonpsittacine birds (ducks, turkeys); the known host range includes 130 avian species. The life cycle of *C. psittaci* is the same as for *C. pneumoniae* (see Chapter 252). Strains of *C. psittaci* have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are 7 avian serovars. The organism has also been found in non-avian domestic animals, including cattle, sheep, pigs, goats, and cats. Non-avian *C. psittaci* has rarely caused disease in humans. Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the United States. Each is associated with important host preferences and disease characteristics.

Epidemiology

From 2005 to 2009 there were 66 reported cases of psittacosis in the United States. Of these, 85% of these cases were associated with exposure to birds, including 70% following exposure to caged pet birds, which were usually psittacine birds, including cockatiels, parakeets, parrots, and macaws. Chlamydiosis among caged nonpsittacine birds occurs most often in pigeons, doves, and mynah birds. Persons at highest risk for acquiring psittacosis include bird fanciers and owners of pet birds (43% of cases) and pet shop employees (10% of cases). Reported cases most likely underestimate the number of actual infections owing to a lack of awareness.

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with *C. psittaci* is the primary route of infection. *Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings* . Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. One high-risk activity is cleaning the cage. Several major outbreaks of psittacosis have occurred in turkey-processing plants; workers exposed to turkey viscera are at the highest risk for infection.

Clinical Manifestations

Infection with *C. psittaci* in humans ranges from clinically inapparent to severe disease, including pneumonia and multiorgan involvement. The mean incubation period is 15 days after exposure, with a range of 5-21 days. *Onset of disease is usually abrupt, with fever, cough, headache, myalgia, and malaise.* The fever is high and is often associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Gastrointestinal symptoms are occasionally reported. Crackles may be heard on auscultation. Chest radiographs are usually abnormal and are characterized by the presence of variable infiltrates, sometimes accompanied by pleural effusions. The white blood cell count is usually normal but is sometimes mildly elevated. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common. Nonpulmonary complications include pericarditis, endocarditis, and myocarditis. Mortality occurs in 5% of cases.

Diagnosis

Psittacosis can be difficult to diagnose because of the varying clinical presentations. A history of exposure to birds or association with an active case can be important clues, but as many as 20% of patients with psittacosis have no known contact. Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include routine bacterial and viral respiratory infections as well as *Coxiella burnetii* infection (Q fever), *Mycoplasma pneumoniae* infection, *C. pneumoniae* infection, tularemia, tuberculosis, fungal infections, and Legionnaires disease.

A patient is considered to have a confirmed case of psittacosis if clinical illness is compatible with psittacosis and the case is laboratory confirmed by either isolation of *C. psittaci* from respiratory specimens (e.g., sputum, pleural fluid, or tissue) or blood, or 4-fold or greater increase in antibody (immunoglobulin G) against *C. psittaci* by complement fixation or microimmunofluorescence between paired acute- and convalescent-phase serum specimens obtained at least 2-4 wk apart. A patient is considered to have a probable case of psittacosis if the clinical illness is compatible with psittacosis and 1 of the 2 following laboratory results is present: supportive serology (e.g., *C. psittaci* antibody titer [Immunoglobulin M] ≥ 32 in at least 1 serum specimen obtained after onset of symptoms), or detection of *C. psittaci* DNA in a respiratory specimen (e.g., sputum, pleural fluid, or tissue) via amplification of a specific target by polymerase chain reaction assay.

Although microimmunofluorescence has greater specificity to *C. psittaci* than complement fixation, cross reactions with other *Chlamydia* species can occur. Therefore acute- and convalescent-phase serum specimens should be analyzed at the same time in the same laboratory. False-negative microimmunofluorescence results can occur in acutely ill patients. Early treatment of psittacosis with tetracycline can abrogate the antibody response.

Although *C. psittaci* will grow in the same culture systems used for isolation of *Chlamydia trachomatis* and *C. pneumoniae*, very few laboratories culture for *C. psittaci*, mainly because of the potential biohazard. Real-time polymerase chain reaction assays have been developed for use in the detection of *C. psittaci* in respiratory specimens. These assays can distinguish *C. psittaci* from other chlamydial species and identify different *C. psittaci* genotypes. However, polymerase chain reaction–based tests have not been cleared by the FDA for use as diagnostic tests in human samples.

Treatment

Recommended treatment regimens for psittacosis are doxycycline (100 mg PO twice daily) or tetracycline (500 mg PO 4 times a day) for at least 10-14 days after the fever abates. The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/day divided every 12 hr IV; maximum: 100 mg/dose). Erythromycin (500 mg PO 4 times a day) and azithromycin (10 mg/kg PO day 1, not to exceed 500 mg, followed by 5 mg/kg PO on days 2-5, not to exceed 250 mg) are alternative drugs if tetracyclines are contraindicated (e.g., children < 8 yr of age and pregnant women) but may be less effective. Remission is usually evident within 48-72 hr. Initial infection does not appear to be followed by long-term immunity. Reinfection and clinical disease can develop within 2 mo of treatment.

Prognosis

The mortality rate of psittacosis is 15–20% with no treatment but is <1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

Prevention

Several control measures are recommended to prevent transmission of *C. psittaci* from birds. Bird fanciers should be cognizant of the potential risk. *C. psittaci* is susceptible to heat and to most disinfectants and detergents but is resistant to acid and alkali. Accurate records of all bird-related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30-45 days or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should not be sold or purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

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SECTION 11

Rickettsial Infections

OUTLINE

Chapter 255 Spotted Fever Group Rickettsioses
Chapter 256 Scrub Typhus (Orientia tsutsugamushi)
Chapter 257 Typhus Group Rickettsioses
Chapter 258 Ehrlichiosis and Anaplasmosis
Chapter 259 Q Fever (Coxiella burnetii)

CHAPTER 255

Spotted Fever Group Rickettsioses

J. Stephen Dumler, Megan E. Reller

Rickettsia species were classically divided into *spotted fever* and *typhus* groups based on serologic reactions and the presence or absence of the outer membrane protein A *(ompA)* gene. Sequencing of at least 45 complete genomes has refined distinctions. However, there is controversy regarding phylogeny, and some data suggest that diversity and pathogenicity are the result of gene loss and lateral gene transfer from other prokaryotes or even eukaryotes, which further obscures accurate taxonomic classification. One proposal is to divide existing species into spotted fever and *transitional* groups based on genetic relatedness; both include pathogenic species and species not now known to cause human disease (Table 255.1). Although increasingly more is understood about the molecular basis by which these bacteria cause human illness, an alternative classification system based on pathogenetic mechanisms has not been defined. The list of pathogens and potential pathogens in the spotted fever group has expanded dramatically in recent years. Among them are the tickborne agents *Rickettsia rickettsii,* the cause of Rocky Mountain or Brazilian spotted fever (RMSF); *R. conorii,* the cause of Mediterranean spotted fever (MSF) or boutonneuse fever; *R. sibirica,* the cause of North Asian tick typhus; *R. japonica,* the cause of Oriental spotted fever; *R. honei,* the cause of Flinders Island spotted fever or Thai tick typhus; *R. africae,* the cause of African tick bite fever; *R. akari,* the cause of mite-transmitted rickettsialpox; *R. felis* , the cause of cat flea–transmitted typhus; and *R. australis,* the cause of tick-transmitted Queensland tick typhus. One proposal creates subspecies of *R. conorii* , including subsp. *conorii* (classical MSF), subsp. *indica* (Indian tick typhus), subsp. *caspia* (Astrakhan fever), and subsp. *israelensis* (Israeli spotted fever). The recognition that *R. parkeri* and “*R. philippi* ” (*Rickettsia* 364D) both cause mild spotted fever in North America and the association of high seroprevalence for spotted fever group *Rickettsia* infections in humans where *Amblyomma* ticks frequently contain *R. amblyommatis* suggest that the full range of agents that can cause spotted fever is still to be discerned.

Table 255.1

Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*

GROUP OR DISEASE AGENT		**ARTHROPOD VECTOR, TRANSMISSION HOSTS**		**GEOGRAPHIC DISTRIBUTION**	**PRESENTING CLINICAL FEATURES***
SPOTTED FEVER GROUP					
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor* species (wood tick, dog tick) *Rhipicephalus sanguineus* (brown dog tick)	Dogs Rodents	Western hemisphere	Fever, headache, rash,* emesis, diarrhea, myalgias
Mediterranean spotted fever (boutonneuse fever)	*Rickettsia conorii*	Tick bite: *R. sanguineus* (brown dog tick)	Dogs Rodents	Africa, Mediterranean, India, Middle East	Painless eschar (tache noir) with regional lymphadenopathy, fever, headache, rash,* myalgias
African tick-bite fever	*Rickettsia africae*	Tick bite	Cattle Goats?	Sub-Saharan Africa, Caribbean	Fever, single or multiple eschars, regional lymphadenopathy, rash* (can be vesicular)
Tickborne lymphadenopathy (TIBOLA); Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)	*Rickettsia slovaca, Rickettsia raoultii, Rickettsia sibirica mongolotimonae*	Tick bite: *Dermacentor*	?	Europe	Eschar (scalp), painful lymphadenopathy
Rickettsia sp , 364D genotype	“*Rickettsia philippi* ”	*Dermacentor occidentalis* (Pacific coast tick)		California	Eschar, fever, headache, lymphadenopathy, malaise
Flea-borne spotted fever	*Rickettsia felis*	Flea bite	Opossums Cats Dogs	Western hemisphere, Europe	Fever, rash,* headache
TRANSITIONAL GROUP					
Rickettsialpox	*Rickettsia akari*	Mite bite	Mice	North America, Russia, Ukraine,	Painless eschar, ulcer or papule;

				Adriatic, Korea, South Africa	tender regional lymphadenopathy, fever, headache, rash* (can be vesicular)
Queensland tick typhus	*Rickettsia australis*	*Ixodes holocyclus, I. tasmani*	Bandicoots and Rodents	Australia, Tasmania	Fever, eschar, headache, myalgia lymphadenopathy
TYPHUS GROUP					
Murine typhus	*Rickettsia typhi*	Flea feces	Rats Opossums	Worldwide	Fever, headache, rash,* myalgias, emesis, lymphadenopathy, hepatosplenomega
Epidemic (louse-borne) typhus (recrudescent form: Brill-Zinsser disease)	*Rickettsia prowazekii*	Louse feces	Humans	South America, Central America, Mexico, Africa, Asia, Eastern Europe	Fever, headache, abdominal pain, rash,* CNS involvement
Flying squirrel (sylvatic) typhus	*Rickettsia prowazekii*	Louse feces? Flea feces or bite?	Flying squirrels	Eastern United States	Same as above (often milder)
SCRUB TYPHUS					
Scrub typhus	*Orientia tsutsugamushi*	Chigger bite: *Leptotrombidium*	Rodents?	South Asia, Japan, Indonesia, Korea, China, Russia, Australia	Fever, rash,* headache, painless eschar, hepatosplenomega gastrointestinal symptoms
EHRLICHIOSIS AND ANAPLASMOSIS					
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *Amblyomma americanum* (lone star tick)	Deer Dogs	United States Europe? Africa? Asia?	Fever, headache, malaise, myalgias, rash* ‡ , hepatosplenomega ‡ swollen hands/fe ‡
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *Ixodes* species *Haemaphysalis longicornis*	Rodents Deer Ruminants	United States, Europe, Asia	Fever, headache, malaise, myalgias
Ewingii ehrlichiosis	*Ehrlichia ewingii*	Tick bite: *Amblyomma americanum* (lone star tick)	Dogs Deer	United States (south-central, southeast)	Fever, headache, malaise, myalgias
Ehrlichia muris euclairensis infection	*Ehrlichia muris euclairensis*	*Ixodes scapularis*	?	Minnesota, Wisconsin	Fever, headache, malaise, myalgias
Sennetsu neorickettsiosis	*Neorickettsia sennetsu*	Ingestion of fish helminth?,	fish, trematodes	Japan, Malaysia, Laos	Fever, "mononucleosis"

		ingestion of fermented fish			symptoms, postauricular and posterior cervical lymphadenopathy
Q FEVER					
Q Fever: acute (for chronic, see text)	*Coxiella burnetii*	Inhalation of infected aerosols: contact with parturient animals, abattoir, contaminated cheese and milk, ? ticks	Cattle Sheep Goats Cats Rabbits	Worldwide	Fever, headache, arthralgias, myalgias, gastrointestinal symptoms, cough, pneumonia, rash (children)

[*] Rash is infrequently present at initial presentation but appears during the 1st wk of illness.

[†] Preferred treatment is in **bold** .

[‡] Often present in children but not adults.

ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; DFA, direct fluorescent antibody; IFA, indirect fluorescent antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; IH, immunohistochemistry; PCR, polymerase chain reaction; WBC, white blood cell count.

Infections with other members of the spotted fever and transitional groups are clinically similar to MSF, with fever, maculopapular rash, and eschar at the site of the tick bite. Israeli spotted fever is generally associated with a more severe course, including death, in children. African tick bite fever is relatively mild, can include a vesicular rash, and often manifests with multiple eschars. New potentially pathogenic rickettsial species have been identified, including *R. slovaca*, the cause of tickborne lymphadenopathy or *Dermacentor* -borne necrosis and lymphadenopathy. *R. aeschlimannii, R. heilongjiangensis, R. helvetica, R. massiliae*, and *R. raoultii* are all reported to cause mild to moderate illnesses in humans, although few cases have been described. Fortunately, the vast majority of infections respond well to doxycycline treatment if instituted early in illness; however, this is a significant challenge.

255.1

Rocky Mountain Spotted Fever (*Rickettsia rickettsii)*

Megan E. Reller, J. Stephen Dumler

RMSF is the most frequently identified and most severe rickettsial disease in the United States. It is also the most common vector-borne disease in the United States after Lyme disease. Although considered uncommon, RMSF is believed to be greatly underdiagnosed and underreported. RMSF should be considered in the differential diagnosis of fever, headache, and rash in the summer months, especially after tick exposure. Because fulminant disease and death are associated with delays in treatment, patients in whom the illness is clinically suspected should be treated promptly.

Etiology

RMSF results from systemic infection of endothelial cells by the obligate intracellular bacterium *Rickettsia rickettsii.*

Epidemiology

The term **Rocky Mountain spotted fever** is historical, because the agent was discovered in the Bitterroot Range of the Rocky Mountains of Montana. Few cases are reported from this region. Cases have been reported throughout the continental United States (except Vermont and Maine), southwestern Canada, Mexico, Central America, and South America, but not from outside of the Western Hemisphere. In 2010, the Centers for Disease Control and Prevention (CDC) reporting criteria for Rocky Mountain spotted fever changed to **spotted fever group rickettsiosis,** because serology often does not distinguish *R. rickettsii* from infection by other spotted fever group *Rickettsia* . Additionally, cases detected by enzyme immunoassay were classified as probable. Thus, in 2012, 2,802 confirmed and probable cases of spotted fever rickettsiosis were reported in Morbidity and Mortality Weekly Reports Summary of Notifiable Diseases. Unlike in prior years, most cases were reported from the west south-central states, especially from Arkansas, Oklahoma, and Missouri; high numbers of cases were also reported from North Carolina, Tennessee, Virginia, New Jersey, Georgia, Alabama, and Arizona (Fig. 255.1). The incidence of RMSF cycles over 25-35 yr intervals but has generally increased over the past decades.

The mean number of cases reported each year to the CDC has steadily increased (515 during 1993–1998, 946 during 1999–2004, 2,068 during 2005–2010, and 3,692 during 2011–2016), of which approximately 14% occur in those younger than 19 yr. Habitats favored by ticks, including wooded areas or coastal grassland and salt marshes, and, in the southwestern United States and Mexico, shaded areas where dogs congregate and acquire infected ticks are those that place children at increased risk for infection. Foci of intense risk for infection are found both in rural and urban areas, most recently in Mexico. Clustering of cases within families likely reflects shared environmental exposures. In the United States, 90% of cases occur between April and September, months in which humans spend the most time outdoors. The highest age-specific incidence of RMSF among children is seen in those older than 10 yr of age, with males outnumbering females; however, the highest case fatality rate for RMSF is observed in those less than 10 yr of age.

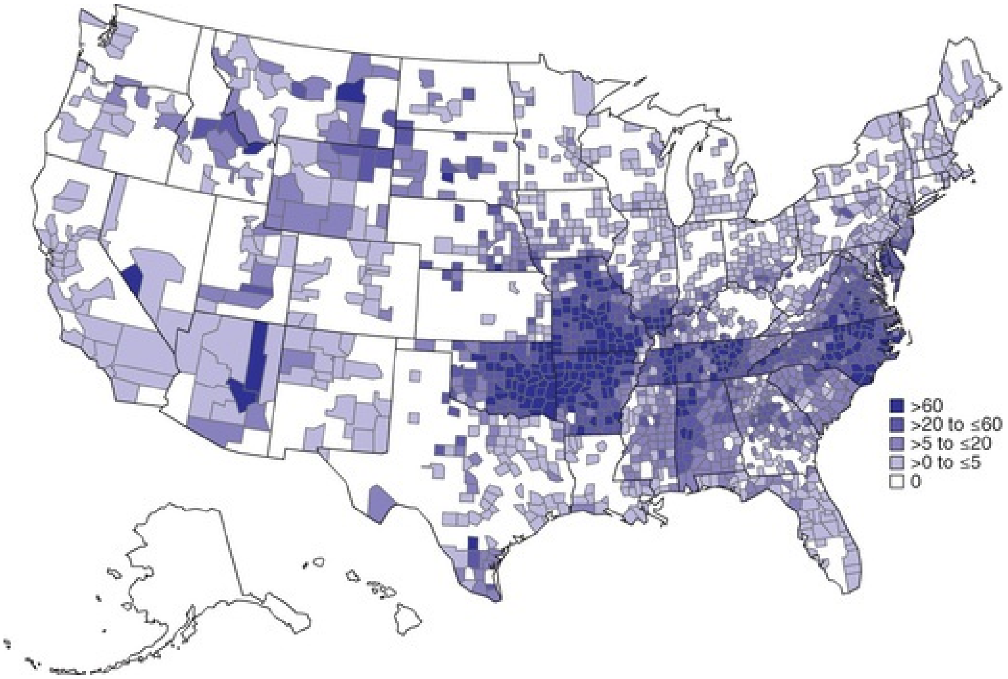

FIG. 255.1 Reported incidence rate* of spotted fever rickettsiosis,[†] by county—United States, 2000–2013. *As reported through national surveillance, per 1,000,000 persons per year. Cases are reported by county of residence, which is not always where the infection was acquired. [†] Includes Rocky Mountain spotted fever (RMSF) and other spotted fever group rickettsioses. In 2010, the name of the reporting category changed from RMSF to spotted fever rickettsiosis. (From Biggs HM, Behravesh CB, Bradley KK, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States, *MMWR Recomm Rep* 65:1–44, 2016, Fig. 1.)

Transmission

Ticks are the natural hosts, reservoirs, and vectors of *R. rickettsii* and maintain the infection in nature by transovarial transmission (passage of the organism from infected ticks to their progeny). Ticks harboring rickettsiae are substantially less fecund than uninfected ticks; thus, horizontal transmission (acquisition of rickettsiae by taking a blood meal from transiently rickettsemic hosts such as small mammals or dogs) contributes to maintenance of rickettsial infections in ticks. Uninfected ticks that simultaneously feed (cofeed) with infected transmitting ticks easily become infected, even if feeding on an immune host and are also likely to be major contributors to natural transmission and maintenance. Ticks transmit the infectious agent to mammalian hosts (including humans) via infected saliva during feeding. The pathogen *R. rickettsii* in ticks becomes virulent after exposure to blood or increased temperature; thus, the longer the tick is attached, the greater the risk of transmission. The principal tick hosts of *R. rickettsii* are *Dermacentor variabilis* (the American dog tick) in the eastern United States and Canada, *Dermacentor andersoni* (the wood tick) in the western United States and Canada, *Rhipicephalus sanguineus* (the common brown dog tick) in the southwestern United States and in Mexico, and *Amblyomma cajennense* and *Amblyomma aureolatum* in Central and South America (Fig. 255.2).

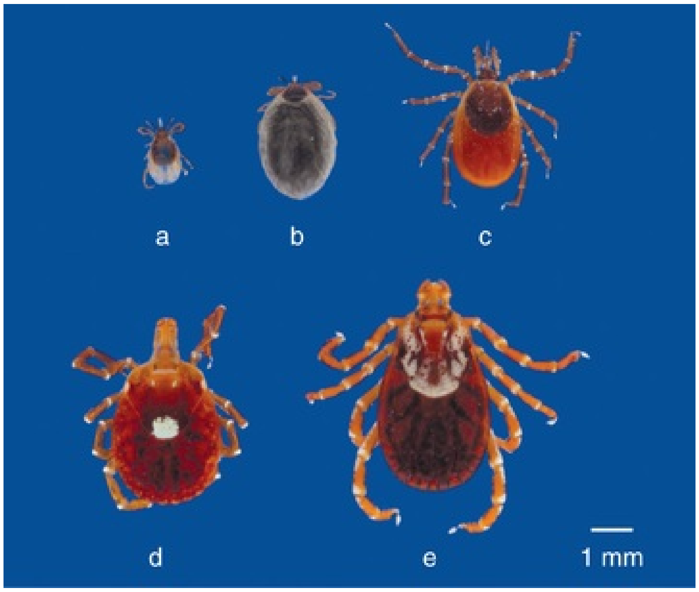

FIG. 255.2 **Tick vectors of agents of human rickettsial diseases. An unengaged nymph (A), engorged nymph (B), and adult female (C) of *Ixodes scapularis (deer tick)* , the vector of *Anaplasma phagocytophilum* and *Ehrlichia muris*– like agent (EMLA), the causes of human granulocytic anaplasmosis and EMLA ehrlichiosis, respectively. An adult female (D) of *Amblyomma americanum* (lone star tick), the vector of *Ehrlichia chaffeensis* and *Ehrlichia ewingii,* the causes of human monocytic ehrlichiosis and ewingii ehrlichiosis, respectively. An adult female (E) of *Dermacentor variabilis* (American dog tick), the vector of *Rickettsia rickettsii,* the cause of Rocky Mountain spotted fever.**

Dogs can serve as reservoir hosts for *R. rickettsii*, can develop RMSF themselves, and can bring infected ticks into contact with humans. Serologic studies suggest that many patients with RMSF likely acquired the illness from ticks carried by the family dog.

Humans can also become infected when trying to remove an attached tick, because *R. rickettsii* –containing tick fluids or feces can be rubbed into the open wound at the bite site or into the conjunctivae by contaminated fingers. Inhalation of aerosolized rickettsiae has caused severe infections and deaths in laboratory workers, highlighting another mechanism of infection.

Pathology and Pathogenesis

Systemic infection is most obvious on the skin (rash), but nearly all organs and tissues are affected. Following inoculation of tick saliva into the dermis, rickettsial outer surface proteins bind to the vascular endothelial cell surface proteins, which signals focal cytoskeletal changes and endocytosis. Thereafter, rickettsia phospholipase-mediated dissolution of the endosomal membranes allows escape into the cytosol. Members of the spotted fever group actively nucleate actin polymerization on 1 pole to achieve directional movement, allowing some rickettsiae to propel into neighboring cells despite minimal initial damage to its host cell. The rickettsiae proliferate and damage the host cells by oxidative membrane alterations, protease activation, or continued phospholipase activity. It is likely that some aspects of intracellular infection are mediated by rickettsial protein effectors delivered into the host cell by bacterial secretion systems.

The histologic correlate of the initial macular or maculopapular rash is perivascular infiltration of lymphoid and histiocytic cells with edema but without significant endothelial damage. Proliferation of rickettsiae within the cytoplasm of infected endothelial cells leads to endothelial injury and **lymphohistiocytic or leukocytoclastic vasculitis** of small venules and capillaries, which allows extravasation of intravascular erythrocytes into the dermis and manifests as a petechial rash (Fig. 255.3). This process is systemic and ultimately results in widespread microvascular leakage, tissue hypoperfusion, and possibly end-organ ischemic injury. Infrequently, inflammation leads to nonocclusive thrombi. Very rarely, small and large vessels become completely obliterated by thrombi, leading to tissue infarction or hemorrhagic necrosis. Interstitial pneumonitis and vascular leakage in the lungs can lead to non-cardiogenic pulmonary edema, and meningoencephalitis can cause significant cerebral edema and herniation.

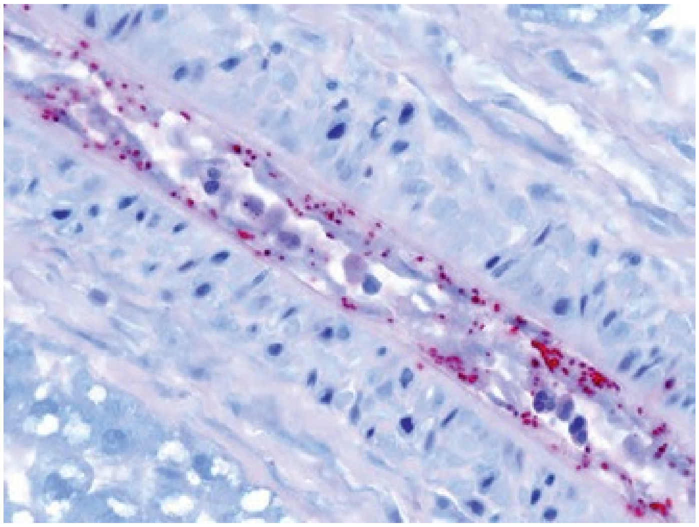

FIG. 255.3 **Immunohistochemical stain demonstrating *Rickettsia (red)* in infection of blood vessel endothelial cells. (From Biggs HM, Behravesh CB, Bradley KK, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—**

United States, *MMWR Recomm Rep* 65:1–44, 2016, Fig. 20.)

The presence of the infectious agent initiates an inflammatory cascade, including release of cytokines and chemokines such as tumor necrosis factor-α, interleukin-1β, interferon-γ, and regulated upon activation, normal T-cell expressed and secreted (RANTES). Infection of endothelial cells by *R. rickettsii* induces surface E-selectin expression and procoagulant activity followed by chemokine recruitment of lymphocytes, macrophages, and, occasionally, neutrophils. Local inflammatory and immune responses are suspected to contribute to the vascular injury; however, the benefits of effective inflammation and immunity are greater. Blockade of tumor necrosis factor-α and interferon-γ action in animal models diminishes survival and increases morbidity; reactive oxygen intermediates, nitric oxide expression, and sequestration of tryptophan from rickettsiae are mechanisms by which rickettsiae are killed within cells. Direct contact of infected endothelial cells with perforin-producing CD8 T lymphocytes and interferon-γ–producing natural killer cells, accompanied by rickettsia antibody, helps control the infection. The timing and balance between rickettsia-mediated increases in vascular permeability and the benefits of induction of innate and adaptive immunity are likely the major determinants of severity and outcome.

Clinical Manifestations

The incubation period of RMSF in children varies from 2 to 14 days (median: 7 days). In 49% of cases, patients or their parents report a history of removing an attached tick, although the site of the tick bite is usually inapparent. Epidemiologic clues include living in or visiting an endemic area, playing or hiking in the woods, typical season, similar illness in family members, and close contact with a dog. In patients presenting for care, the illness is initially nonspecific, and most patients are not diagnosed during their first visit with a healthcare practitioner. Manifestations often (>50%) include fever, rash (frequently involving the palms or soles), nausea and vomiting, and headache, and less often (<50%) myalgias, abdominal pain, diarrhea, conjunctival injection, altered mental status, lymphadenopathy, and peripheral edema. Pain and tenderness of calf muscles are particularly common in children.

The typical **clinical triad of fever, headache, and rash** is observed in 58% of pediatric patients overall, and rash involving soles and palms first appearing after day 3 is associated with significantly higher risk of death among Mexican children. Fever and headache persist if the illness is untreated. Fever can exceed 40°C (104°F) and can remain persistently elevated or can fluctuate dramatically. Headache is severe, unremitting, and unresponsive to analgesics.

Rash usually appears after only 1-2 days of illness, and an estimated 3–5% of children never develop a rash that is recognized. Initially, discrete, pale, rose-red blanching macules or maculopapules appear; characteristically this initial rash is observed on the extremities, including the wrists, ankles, or lower legs (Fig. 255.4). In 65% of patients, the initial rash spreads rapidly to involve the entire body, including the soles and palms. The rash can become petechial or even hemorrhagic, sometimes with palpable purpura.

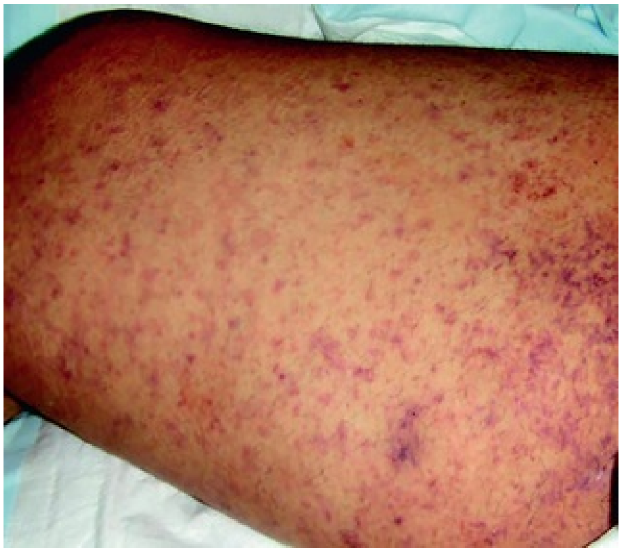

FIG. 255.4 **Maculopapular rash with central petechiae associated with Rocky Mountain spotted fever. (From Biggs HM, Behravesh CB, Bradley KK, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States, *MMWR Recomm Rep* 65:1–44, 2016, Fig. 21.)**

In severe disease, the petechiae can enlarge into ecchymoses, which can become necrotic (Fig. 255.5). Severe vascular obstruction secondary to the rickettsial vasculitis and thrombosis is uncommon but can result in gangrene of the digits, earlobes, scrotum, nose, or an entire limb.

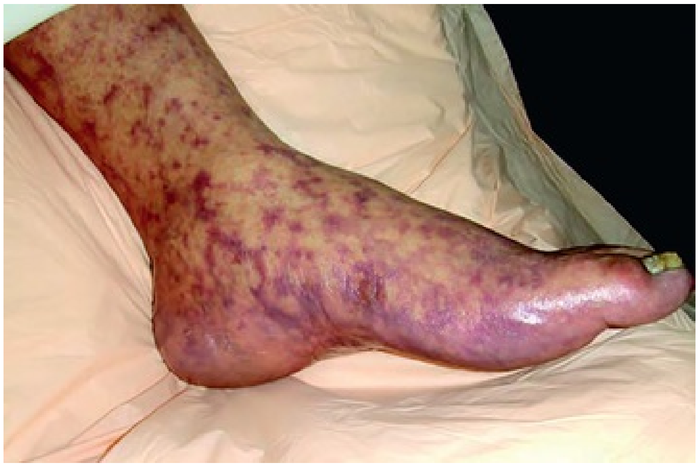

FIG. 255.5 Late-stage petechial purpuric rash involving the sole of the foot in a patient with Rocky Mountain spotted fever. (From Biggs HM, Behravesh CB, Bradley KK, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States, *MMWR Recomm Rep* 65:1–44, 2016, Fig. 22.)

Central nervous system infection usually manifests as changes in mental status (33%) or as photophobia (18%), seizure (17%), or meningismus (16%). Patients can also manifest ataxia, coma, or auditory deficits. Cerebrospinal fluid parameters are usually normal, but one-third have pleocytosis (<10-300 cells/µL), either mononuclear or less often neutrophil-dominated. Some (20%) have elevated protein (<200 mg/dL) in the cerebrospinal fluid; hypoglycorrhachia is rare. Neuroimaging studies often reveal only subtle abnormalities. However, with advanced disease and neurologic signs, a unique but nonspecific “starry sky” appearance may be observed on brain MRI that reflects the same systemic vasculitis observed with skin lesions.

Other

Pulmonary disease occurs more often in adults than in children. However, 33% of children examined have a chest radiograph interpreted as an infiltrate or pneumonia. The clinical presentation in these cases can manifest as rales, infiltrates, and noncardiogenic pulmonary edema. Other findings can include conjunctival suffusion, periorbital edema, dorsal hand and foot edema, and hepatosplenomegaly. Severe disease can include myocarditis, acute renal failure, and vascular collapse.

Persons with glucose-6-phosphate dehydrogenase deficiency are at increased risk for fulminant RMSF, defined as death from *R. rickettsii* infection within 5 days. The clinical course of fulminant RMSF is characterized by profound coagulopathy and extensive thrombosis leading to kidney, liver, and respiratory failure. Features associated with increased risk of death include altered mental status, admission to an intensive care unit, need for inotropic support, coma, and need for rapidly administered intravenous fluid.

Occasionally, clinical signs and symptoms suggest a localized process such as appendicitis or cholecystitis. Thorough evaluation usually reveals evidence of a systemic process, and unnecessary surgical interventions are avoided.

Laboratory Findings

Laboratory abnormalities are common but nonspecific. Thrombocytopenia occurs in 60%, and the total white blood cell count is most often normal, with leukocytosis in 24% and leukopenia in 9%. Other characteristic abnormalities include a left-shifted leukocyte differential, anemia (33%), hyponatremia (<135 mEq/mL in 52%), and elevated serum aminotransferase levels (50%).

Diagnosis

Delays in diagnosis and treatment are associated with severe disease and death. Because no reliable diagnostic test is readily available to confirm RMSF during acute illness, the decision to treat must be based on compatible epidemiologic, clinical, and laboratory features. RMSF should be considered in patients presenting spring through fall with an acute febrile illness accompanied by headache and myalgia (particularly if they report exposure to ticks or contact with a dog or have been in forested or tick-infested rural areas). A history of tick exposure, a rash (especially if on the palms or soles), a normal or low leukocyte count with a marked left shift, a relatively low or decreasing platelet count, and a low serum sodium concentration are all clues that can support a diagnosis of RMSF. In patients without a rash or in dark-skinned patients in whom a rash can be difficult to appreciate, the diagnosis can be exceptionally elusive and delayed. One half of pediatric deaths occur within 9 days of onset of symptoms. Thus, treatment should not be withheld pending definitive laboratory results for a patient with clinically suspected illness. Further, prompt response to early treatment is diagnostically helpful.

If a rash is present, a vasculotropic rickettsial infection can be diagnosed as early as day 1 or 2 of illness with biopsy of a petechial lesion and immunohistochemical or immunofluorescent demonstration of specific rickettsial antigen in the endothelium. Although very specific, the sensitivity of this method is probably 70% at most. Furthermore, it can be adversely influenced by prior antimicrobial therapy, suboptimal selection of skin lesions for biopsy, and examination of insufficient tissue because of the focal nature of the infection. Tissue or blood can also be evaluated for *R. rickettsii* nucleic acids by polymerase chain reaction (PCR) at the CDC and selected public health or reference laboratories; PCR on blood is less sensitive than PCR on tissue and of similar sensitivity to tissue immunohistology, probably because the level of rickettsemia is generally very low (<6 rickettsiae/mL). Since eschars are rare with RMSF, scab scrapings or skin swabs are not useful specimens for the detection of rickettsemia by PCR.

Definitive diagnosis is most often accomplished by serology, which is retrospective, because a rise in titer is not seen until after the 1st wk of illness. The gold standard for the diagnosis of RMSF is a 4-fold increase in immunoglobulin G antibody titer by indirect fluorescent antibody assay between paired acute and convalescent (at 2-4 wk) sera or demonstration of seroconversion with a minimum convalescent titer higher than the positive cutoff (e.g., 128). A single titer is neither sensitive (patients can die before seroconversion) nor specific (an elevated titer can represent prior infection). Despite the historic role of IgM testing, its role in early diagnosis has recently become controversial and cannot be advocated. With current serologic methods, RMSF cannot be reliably distinguished from other spotted fever group rickettsiae infections. Cross reactions with typhus group rickettsiae also occur, but titers may be lower for the typhus group. Cross reactions are not seen with *Ehrlichia* or *Anaplasma* infections. Currently, ELISA serologic methods can only provide “probable” rather than confirmed evidence of infection. Weil-Felix antibody testing should not be performed, because it lacks both sensitivity and specificity. RMSF and other spotted fever group rickettsioses are reportable diseases in the United States.

Differential Diagnosis

Other rickettsial infections are easily confused with RMSF, especially all forms of human ehrlichiosis and murine typhus and novel spotted fever group rickettsioses that result from *R. parkeri* or “*R. philipii* str. 364D” infections. RMSF can also mimic a variety of other diseases, such as meningococcemia and enteroviral infections. Negative blood cultures can exclude meningococcemia. PCR can differentiate enterovirus from *R. rickettsii* in patients with aseptic meningitis and cerebrospinal fluid pleocytosis. Other diseases in the differential diagnosis are typhoid fever, secondary syphilis, Lyme disease, leptospirosis, rat-bite fever, scarlet fever, toxic shock syndrome, rheumatic fever, rubella, parvovirus infection, Kawasaki disease, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura, hemolytic uremic syndrome, aseptic meningitis, acute gastrointestinal illness, acute abdomen, hepatitis, infectious mononucleosis, hemophagocytic and macrophage activation syndromes, dengue fever, and drug reactions.

Treatment

The time-proven effective therapies for RMSF are tetracyclines and chloramphenicol. The treatment of choice for suspected RMSF in patients of all ages, including children under 8 years of age, is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) is an alternative. Chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day) should be reserved for patients with doxycycline allergy and for pregnant women, because chloramphenicol is an independent risk factor for increased mortality vs tetracyclines. If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 µg/mL. Chloramphenicol is preferred for pregnant women because of potential adverse effects of doxycycline on fetal teeth and bone and maternal liver function. RMSF is a life-threatening illness for which prompt therapy is imperative, and multiple recent studies demonstrate a negligible risk for tooth discoloration in children younger than 8 yr of age with the use of doxycycline. Chloramphenicol is rarely associated with aplastic anemia and is no longer available as an oral preparation in the United States. An additional benefit of doxycycline over chloramphenicol is its effectiveness against potential concomitant *Ehrlichia* or *Anaplasma* infection. Sulfonamides should not be used, because they are associated with greater morbidity and mortality with all rickettsial infections. Other antibiotics, including penicillins, cephalosporins, and aminoglycosides, are not effective. The use of alternative antimicrobial agents, such as fluoroquinolones and the macrolides (azithromycin and clarithromycin), has not been evaluated.

Therapy should be continued for a minimum of 5-7 days and until the patient has been afebrile for at least 3 days. Treated patients usually defervesce within 48 hr, so the duration of therapy is usually <10 days.

Supportive Care

Most infections resolve rapidly with appropriate antimicrobial therapy and do not require hospitalization or other supportive care. Among those hospitalized, 36% require intensive care. Particular attention to hemodynamic status is mandatory in severely ill children, because iatrogenic pulmonary or cerebral edema could be easily precipitated owing to diffuse microvascular injury of the lungs, meninges, and brain. Judicious use of corticosteroids for meningoencephalitis has been advocated by some, but no controlled trials have been conducted.

Complications

Complications of RMSF include noncardiogenic pulmonary edema from pulmonary microvascular leakage, cerebral edema from meningoencephalitis, and multiorgan damage (hepatitis, pancreatitis, cholecystitis, epidermal necrosis, and gangrene) mediated by rickettsial vasculitis and/or the accumulated effects of hypoperfusion and ischemia (acute renal failure). Long-term neurologic sequelae can occur in any child with RMSF but are more likely to occur in those hospitalized for ≥2 wk. Examples of neurologic sequelae include speech or swallowing disorders; global encephalopathy; cerebellar, vestibular, and motor dysfunction; hearing loss; and cortical blindness. Learning disabilities and behavioral problems are the most common neurologic sequelae among children who have survived severe disease.

Prognosis

Delays in diagnosis and therapy are significant factors associated with severe illness or death. Before the advent of effective antimicrobial therapy for RMSF, the case fatality rate was 10% for children and 30% for adults. The overall case fatality rate decreased to an historic low (0.3–0.4%) from 2003 to 2012; however, many experts attribute this decrease to detection and reporting of other less virulent emerging forms of spotted fever group rickettsioses that cannot be readily differentiated from RMSF using current serologic tests. The overall case fatality rate of children 5-9 yr of age was 2.4%, and rates as high as 8.5% and 11.8% were documented in Texas (1986–1996) and in Arizona (1999–2007), respectively, and rates as high as 30–40% are now reported from outbreaks in Mexico. Diagnosis based on serology alone underestimates the true mortality of RMSF, because death often occurs within 14 days (before developing a serologic response). Deaths occur despite the availability of effective therapeutic agents, indicating the need for clinical vigilance and a low threshold for early empiric therapy. Even with administration of appropriate antimicrobials, delayed therapy can lead to irreversible vascular or end-organ damage and long-term sequelae or death. Early therapy in uncomplicated cases usually leads to rapid defervescence within 1-3 days and recovery within 7-10 days. A slower response may be seen if therapy is delayed. In those who survive despite no treatment, fever subsides in 2-3 wks.

Prevention

No vaccines are available. Prevention of RMSF is best accomplished by preventing or treating tick infestation in dogs, avoiding areas where ticks reside, using insect repellents containing N, *N* -diethyl-3-methylbenzamide (DEET) or new alternatives (https://www.epa.gov/insect-repellents/find-repellent-right-you), wearing protective clothing, and carefully inspecting children after play in areas where they are potentially exposed to ticks. Recovery from infection yields lifelong immunity.

Prompt and complete removal of attached ticks helps reduce the risk for transmission because rickettsiae in the ticks need to be reactivated to become virulent, and this requires at least several hours to days of exposure to body heat or blood. Contrary to popular belief, the application of petroleum jelly, 70% isopropyl alcohol, fingernail polish, or a hot match are not effective in removing ticks. A tick can be safely removed by grasping the mouth parts with a pair of forceps at the site of attachment to the skin and applying gentle and steady pressure to achieve retraction without twisting, thereby removing the entire tick and its mouth parts. The site of attachment should then be disinfected. Ticks should not be squeezed or crushed, because their fluids may be infectious. The removed tick should be soaked in alcohol or flushed down the toilet, and hands should be washed to avoid accidental inoculation into conjunctivae, mucous membranes, or breaks in skin. Typically, prophylactic antimicrobial therapy is not recommended because tetracyclines and chloramphenicol are only rickettsiastatic; however, the evidence to support this position is meager.

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255.2

Mediterranean Spotted Fever or Boutonneuse Fever *(Rickettsia conorii)*

Megan E. Reller, J. Stephen Dumler

MSF or boutonneuse fever is caused by *R. conorii* and its related subspecies; it is also called by other names, such as Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan fever. It is a moderately severe vasculotropic rickettsiosis in adults but comparatively milder in children, with more frequent lymphadenopathy; often, MSF is initially associated with an eschar at the site of the tick bite. Minor differences in clinical presentation could be associated with genetic diversity of the rickettsial subspecies.

Etiology

MSF is caused by systemic endothelial cell infection by the obligate intracellular bacterium *R. conorii*. Similar species are distributed globally, such as *R. sibirica*, *R. heilongjiangensis*, and *R. mongolotimonae* in Russia, China, Mongolia, and Pakistan; *R. australis* and *R. honei* in Australia; *R. japonica* in Japan; *R. africae* in South Africa; and *R. parkeri* and "*R. philippi* str. 364D" in the Americas (see Table 255.1). Analysis of antigens and related DNA sequences show that all are closely related within a broad genetic clade that includes spotted fever group *Rickettsia* species such as *R. rickettsii* , the cause of RMSF.

Epidemiology

R. conorii is distributed over a large geographic region, including India, Pakistan, Russia, Ukraine, Georgia, Israel, Morocco, southern Europe, Ethiopia, Kenya, and South Africa. Reported cases of MSF in southern Europe have steadily increased since 1980, and the seroprevalence is 11–26% in some areas. The peak in reported cases occurs during July and August in the Mediterranean basin; in other regions it occurs during warm months when ticks are active.

Transmission

Transmission occurs after the bite of the brown dog tick, *R. sanguineus,* or for other *Rickettsia* spp. tick genera such as *Dermacentor, Haemaphysalis, Amblyomma, Hyalomma,* and *Ixodes.* Clustering of human cases of boutonneuse fever, infected ticks, and infected dogs implicate the household dog as a potential vehicle for transmission.

Pathology and Pathogenesis

The underlying pathology seen with MSF is nearly identical to that of RMSF, except that eschars are often present at the site of tick bite where inoculation of rickettsiae occurs. The histopathology of the resultant lesion includes necrosis of dermal and epidermal tissues with a superficial crust; a dermis densely infiltrated by lymphocytes, histiocytes, and scattered neutrophils; and damaged capillaries and venules in the dermis. Immunohistochemical stains and nucleic acid amplification tests confirm that the lesions contain rickettsia-infected endothelial cells, and potentially other cells such as macrophages. The necrosis results from both direct rickettsia-mediated vasculitis and resultant extensive local inflammation. Thus, rickettsiae have ready access to lymphatics and venous blood and disseminate to cause systemic disease.

Clinical Manifestations and Laboratory Findings

Typical findings in children include fever (37–100%), a maculopapular rash that appears 3-5 days after onset of fever (94–100%), hepatosplenomegaly (20–83%), myalgias and arthralgias (10–42%), headache (8–63%), nausea, vomiting, or diarrhea (5–28%), and lymphadenopathy (52–54%). In 60–90% of patients, a **painless eschar** or **tache noire** appears at the site of the tick bite, often on the scalp, with accompanying regional lymphadenopathy (50–60%) (Fig. 255.6). The infection can be severe, mimicking RMSF, although morbidity and fatalities in children are less frequent than in adults. Findings can include seizures, purpuric skin lesions, meningitis and neurologic deficits, respiratory and/or acute renal failure, and severe thrombocytopenia. Even though the case fatality rate can be as high as 10% in adults and severe infections occur in approximately 9% of children, pediatric deaths are rare. As with RMSF, a particularly severe form occurs in patients with glucose-6-phosphate dehydrogenase deficiency and in patients with underlying conditions such as alcoholic liver disease or diabetes mellitus.

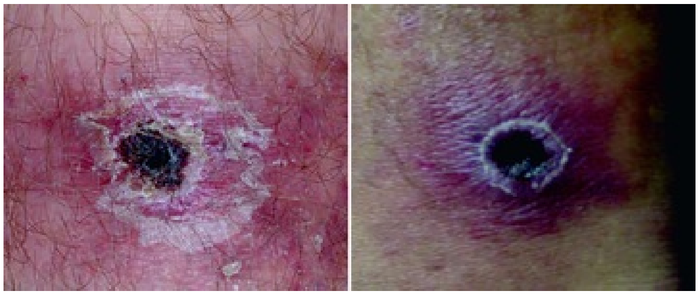

FIG. 255.6 **Various appearances of eschars associated with *Rickettsia parkeri* rickettsiosis. (From Biggs HM, Behravesh CB, Bradley KK, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States, *MMWR Recomm Rep* 65:1–44, 2016, Fig. 24.)**

Diagnosis

Laboratory diagnosis of MSF and related spotted fever group rickettsioses is the same as that for RMSF. Cases can be confirmed by immunohistologic or immunofluorescent or demonstration of or amplification of nucleic acids from rickettsiae in skin biopsies, in vitro cultivation via centrifugation-assisted shell vial tissue culture, or demonstration of seroconversion or accompanied by a 4-fold rise in serum antibody titer to spotted fever group rickettsiae between acute and convalescent sera. Antibodies to spotted fever group antigens cross react, so

RMSF or other spotted fever group rickettsiosis in the United States or MSF in Europe, Africa, and Asia cannot be distinguished by these methods. When eschars are present, biopsy of the eschar with submission of tissue or a swab of the base for PCR provides considerably higher sensitivity than PCR on blood and is advocated, if available. Treatment should not be withheld while waiting for diagnostic test results.

Differential Diagnosis

The differential diagnosis includes conditions also associated with single eschars, such as anthrax, bacterial ecthyma, brown recluse spider bite, rat-bite fever (caused by *Spirillum minus*), and other rickettsioses (such as rickettsialpox, African tick-bite fever, *R. parkeri* or *R. philipii* str. 364D rickettsiosis, and scrub typhus). The spotted fever group rickettsia *R. africae* causes African tick-bite fever, a milder illness than MSF that is often associated with multiple eschars and occasionally a vesicular rash. African tick-bite fever can be contracted in North Africa, where MSF also occurs and is a common infection of travelers to sub-Saharan Africa who encounter bush or high grasslands on safari. *R. parkeri* and *R. philipii* str. 364D rickettsiosis are emerging infections in North and South America and in the U.S. western states, respectively. Both often present with an eschar and milder clinical manifestations similar to those observed with African tick-bite fever.

Treatment and Supportive Care

In adults, MSF is effectively treated with tetracycline, doxycycline, chloramphenicol, ciprofloxacin, ofloxacin, levofloxacin, azithromycin, or clarithromycin. For children, the treatment of choice is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Tetracycline and chloramphenicol are alternatives, as for RMSF. Azithromycin (10 mg/kg/day once daily PO for 3 days), azithromycin (10 mg/kg/day once daily) and clarithromycin (15 mg/kg/day divided twice daily PO for 7 days) are also used. Specific fluoroquinolones regimens effective for children have not been established, although recent reports suggest the use of fluoroquinolones is associated with increased disease severity as compared with doxycycline. Intensive care may be required.

Complications

The complications of MSF are similar to those of RMSF. Overall, the case fatality rate is less than 2%, but fatalities are rare in children. Particularly severe infections have been noted in patients with underlying medical conditions, including glucose-6-phosphate dehydrogenase deficiency and diabetes mellitus.

Prevention

MSF is transmitted by tick bites, and prevention is the same as recommended for RMSF. No vaccine is currently available.

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255.3

Rickettsialpox *(Rickettsia akari)* and Flea-Borne Spotted Fever

Megan E. Reller, J. Stephen Dumler

Rickettsialpox is caused by *R. akari,* a transitional group *Rickettsia* species that is transmitted by the mouse mite, *Allodermanyssus sanguineus.* The mouse host for this mite is widely distributed in cities in the United States, Europe, and Asia. Seroepidemiologic studies suggest a high prevalence of this infection in urban settings. The disease is uncommon and is usually mild. Unlike the situation with most forms of rickettsiosis, the macrophage is an important target cell for *R. akari.*

Rickettsialpox is best known because of its association with a varicelliform rash. In fact, this rash is a modified form of an antecedent typical macular or maculopapular rash like those seen in other vasculotropic rickettsioses and is occasionally seen with other rickettsioses such as African tick-bite fever. Clinical descriptions in children are infrequent. At presentation, most patients have fever, headache, and chills. In up to 90% of cases, there is a painless papular, ulcerative lesion, or eschar, at the initial site of inoculation, which can be associated with tender regional lymphadenopathy. In some patients, the maculopapular rash becomes vesicular, involving the trunk, head, and extremities. The infection generally resolves spontaneously and does not require therapy. However, a short course of doxycycline hastens resolution and is sometimes used in patients older than 8 yr of age and in young children with relatively severe illness. Complications and fatalities are rare; however, clear examples of severe disease in children like that observed with RMSF are described.

Flea-borne spotted fever, caused by *Rickettsia felis* , is often considered within the typhus group because of flea transmission; however, phylogenetic studies place it close to the *Rickettsia* genus spotted fever or within the “transitional” group. Similarly, a related cat flea-associated agent, *R. asembonensis* , was isolated from cat fleas and has been identified in environmental samples over broad geographic regions. Since the discovery of *R. felis* in a febrile patient from Texas by use of molecular amplification methods, and its subsequent isolation from infected cat fleas, molecular and cross-reactive serologic tests have purported to identify human infections globally, some at high rates of prevalence. Clinical isolates have yet to be made from infected humans, and many patients identified by molecular methods lack serologic responses or even clinical signs. Its identification within mosquitoes and in conjunction with malaria further confound its role as a human pathogen. Until many of the discrepant findings observed with *R. felis* are resolved, its role as an important infectious agent in humans remains to be resolved.

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CHAPTER 256

Scrub Typhus *(Orientia tsutsugamushi)*

Megan E. Reller, J. Stephen Dumler

Scrub typhus is an important cause of acute febrile illness in South and East Asia and the Pacific and could be emerging in the Middle East and South America. The causative agent is distinct from, but related to, *Rickettsia* species. The infection is transmitted via chigger (larval mite) bites and involves many antigenically diverse strains of *Orientia tsutsugamushi* , hampering vaccine development.

Etiology

The causative agent of scrub typhus, or tsutsugamushi fever, is *O. tsutsugamushi*, which is distinct from other spotted fever and typhus group rickettsiae (see Table 255.1 in Chapter 255). *O. tsutsugamushi* lacks both lipopolysaccharide and peptidoglycan in its cell wall. Like other vasculotropic rickettsiae, *O. tsutsugamushi* infects endothelial cells and causes vasculitis, the predominant clinicopathologic feature of the disease. However, the organism also infects macrophages and cardiac myocytes. A new *Candidatus* species, *Orientia chuto* , was isolated from a patient in the Middle East, and definitive evidence of infection based on serology and/or PCR amplification of *O. tsutsugamushi* genes from acute phase blood suggests a wider range for scrub typhus and related infections.

Epidemiology

More than 1 million infections occur each year, and it is estimated that more than 1 billion people are at risk. Scrub typhus occurs mostly in Asia, including areas delimited by Korea, Pakistan, and northern Australia. Outside these tropical and subtropical regions, the disease occurs in Japan, the Primorsky of far eastern Russia, Tajikistan, Nepal, and nontropical China, including Tibet. Cases imported to the United States and other parts of the world are reported. Endemic scrub typhus has historically been confined to Asia and Oceania and the tsutsugamushi triangle; however, *Orientia* may be distributed more broadly, with confirmed cases in South America and possible cases in Africa. Most infections in children are acquired in rural areas. In Thailand and Sri Lanka, scrub typhus is the cause of 1–8% of acute fevers of unknown origin. Infections are most common during rainy months, usually June through November. Reported cases in boys are higher than in girls.

Transmission

O. tsutsugamushi is transmitted via the bite of the larval stage (chigger) of a trombiculid mite *(Leptotrombidium)*, which serves as both vector and reservoir. Vertical transovarial transmission (passage of the organism from infected mites to their progeny) is the major mechanism for maintenance in nature. Because only the larval stage takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved, but transmission among co-feeding larval mites is a possibility. Multiple serotypes of *O. tsutsugamushi* are recognized, and some share antigenic cross reactivity; however, they do not stimulate protective cross-immunity.

Pathology and Pathogenesis

The pathogenesis of scrub typhus is uncertain. The process may be stimulated by widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivascular inflammatory lesions observed in histopathologic examinations. In autopsy series, the major result of the vascular injury appears to be hemorrhage. However, data support the concept that vascular injury initiated by the infection is sustained by immune-mediated inflammation that together cause significant vascular leakage. The net result is significant vascular compromise and ensuing end-organ injury, most often manifested in the brain and lungs, as with other vasculotropic rickettsioses.

Clinical Manifestations and Laboratory Findings

Scrub typhus can be mild or severe in children and can affect almost every organ system. Most patients present with fever for 9-11 days (range: 1-30 days) before seeking medical care. Regional or generalized lymphadenopathy is reported in 23–93% of patients, hepatomegaly in about two-thirds, and splenomegaly in about one-third of children with scrub typhus. Gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhea, occur in up to 40% of children at presentation. A **single painless eschar** with an erythematous rim at the site of the chigger bite is seen in 7–68% of cases, and a maculopapular rash is present in less than half; both can be absent. Hemophagocytic lymphohistiocytosis has been described. Leukocyte and platelet counts are most commonly within normal ranges, although thrombocytopenia occurs in one-quarter to one-third of children, and leukocytosis is observed in approximately 40% of children. Clinical manifestations often respond dramatically to appropriate treatment. Adverse outcomes in fetuses and newborn infants of infected mothers have been described, resulting from vertical transmission.

Diagnosis and Differential Diagnosis

Owing to the potential for severe complications, diagnosis and decision to initiate treatment should be based on clinical suspicion and confirmed by *O. tsutsugamushi* serologic tests such as indirect fluorescent antibody. The indirect fluorescent antibody assay is >90% sensitive with 11 days or more of fever, but interpretations vary with prevalence of infection in endemic regions. Although the rickettsiae can be cultivated using tissue culture methods, polymerase chain reaction tests are not highly sensitive, and these diagnostic methods are not widely available. The differential diagnosis includes fever of unknown origin, enteric fever, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue, leptospirosis, malaria, and infectious mononucleosis.

Treatment and Supportive Care

The recommended treatment regimen for scrub typhus is doxycycline (4 mg/kg/day PO or IV divided every 12 hr; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day PO divided every 6 hr; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/24 hr). If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 µg/mL. Alternatives, now supported by data from randomized trials, include azithromycin (10 mg/kg PO on day 1, then 5 mg/kg PO; maximum: 500 mg/day) or clarithromycin (15-30 mg/kg/day PO divided every 12 hr; maximum: 1 g/day). Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid relapse. However, a single dose of oral doxycycline was reported effective for all 38 children treated with this regimen in a large series of children with scrub typhus from Thailand. Most children respond rapidly to doxycycline or chloramphenicol within 1-2 days (range: 1-5 days). Strains of *O. tsutsugamushi* with modestly higher doxycycline minimal inhibitory concentrations are reported in some regions of Thailand. Clinical trials showed that azithromycin could be as effective, and that rifampicin is superior to doxycycline in such cases and could have a role as an alternative therapy, especially for pregnant women. The use of ciprofloxacin in pregnant women resulted in an adverse outcome in 5 of 5 pregnancies among Indian women. Intensive care may be required for hemodynamic management of severely affected patients.

Complications

Serious complications include pneumonitis in 20–35% and meningoencephalitis in approximately 10–25% of children. Acute renal failure, myocarditis, and a septic shock–like syndrome occur much less often. Cerebrospinal fluid examination shows a mild mononuclear pleocytosis with normal glucose levels. Chest radiographs reveal transient perihilar or peribronchial interstitial infiltrates in most children who are examined. Among 883 patients <20 yr of age in 18 published studies, the case fatality rate was 11%; the median for the studies was 1.6–1.8% and ranged as high as 33%.

Prevention

Prevention is based on avoidance of the chiggers that transmit *O. tsutsugamushi*.

Protective clothing is the next most useful mode of prevention. Infection provides immunity to reinfection by homologous but not heterologous strains; however, because natural strains are highly heterogeneous, infection does not always provide complete protection against reinfection. No vaccines are currently available.

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CHAPTER 257

Typhus Group Rickettsioses

Megan E. Reller, J. Stephen Dumler

Members of the typhus group of rickettsiae (see Table 255.1 in Chapter 255) include *Rickettsia typhi*, the cause of murine typhus, and *Rickettsia prowazekii*, the cause of louse-borne or epidemic typhus. *R. typhi* is transmitted to humans by fleas, and *R. prowazekii* is transmitted in the feces of body lice. Louse-borne or epidemic typhus is widely considered to be the most virulent of the rickettsial diseases, with a high case fatality rate even with treatment. Murine typhus is moderately severe and likely underreported worldwide. The genomes of both *R. typhi* and *R. prowazekii* are similar.

257.1

Murine (Endemic or Flea-Borne) Typhus *(Rickettsia typhi)*

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Keywords

murine typhus
endemic typhus

flea-borne typhus

Etiology

Murine typhus is caused by *R. typhi*, a rickettsia transmitted from infected fleas to rats, other rodents, or opossums and back to fleas. Transovarial transmission (passage of the organism from infected fleas to their progeny) in fleas is inefficient. Transmission depends on infection from the flea to uninfected mammals that then sustain transient rickettsemia and serve as sources of the bacterium for uninfected fleas that bite during the period of rickettsemia.

Epidemiology

Murine typhus has a worldwide distribution and occurs especially in warm coastal ports, where it is maintained in a cycle involving rat fleas *(Xenopsylla cheopis)* and rats (*Rattus* species). Peak incidence occurs when rat populations are highest during spring, summer, and fall. Sentinel surveillance studies suggest that travel-acquired murine typhus occurs most often in those visiting Southeast Asia and Africa. In the United States, the disease is recognized most often in south Texas and Southern California. However, seroprevalence studies among children indicate that murine typhus is acquired across the southeast and south-central United States, thus expanding the endemic areas in which pediatricians must be alert for this infection. In the coastal areas of south Texas and in Southern California, the disease is seen predominantly from March through June and is associated with a *sylvatic cycle* involving opossums and cat fleas *(Ctenocephalides felis)* .

Transmission

R. typhi normally cycles between rodents or midsize animals such as opossums and their fleas. Human acquisition of murine typhus occurs when rickettsiae-infected flea feces contaminate flea bite wounds. Direct inoculation via flea bite is possible, but inefficient.

Pathology and Pathogenesis

R. typhi is a vasculotropic rickettsia that causes disease in a manner similar to *Rickettsia rickettsii* (see Chapter 255.1). *R. typhi* organisms in flea feces deposited on the skin as part of the flea feeding reflex are inoculated into the pruritic flea bite wound. After an interval for local proliferation, the rickettsiae spread systemically via lymphatics to the blood, after which they infect the endothelium in many tissues. As with spotted fever group rickettsiae, typhus group rickettsiae infect endothelial cells, but unlike the spotted fever group rickettsiae, they polymerize intracellular actin poorly, have limited intracellular mobility, and probably cause cellular injury by either enzymatic membrane or mechanical lysis after accumulating in large numbers within the endothelial cell cytoplasm. Intracellular infection leads to endothelial cell damage, recruitment of inflammatory cells, and vasculitis. The inflammatory cell infiltrates bring in a number of effector cells, including macrophages that produce proinflammatory cytokines, and CD4, CD8, and natural killer lymphocytes, which can produce immune cytokines such as interferon-γ or participate in cell-mediated cytotoxic responses. Intracellular rickettsial proliferation of typhus group rickettsiae is inhibited by cytokine-mediated mechanisms and nitric oxide–dependent and –independent mechanisms.

Pathologic findings include systemic vasculitis in response to rickettsiae within endothelial cells. This vasculitis manifests as interstitial pneumonitis, meningoencephalitis, interstitial nephritis, myocarditis, and mild hepatitis with periportal lymphohistiocytic infiltrates. As vasculitis and inflammatory damage accumulate, multiorgan damage can ensue.

Clinical Manifestations

In children, murine typhus is a generally a self-limited infection, but can be severe, similar to other vasculotropic rickettsioses. The incubation period varies from 1 to 2 wk. The initial presentation is often nonspecific and mimics typhoid fever; fever of undetermined origin is the most common presentation. Pediatric patients with murine typhus exhibit symptoms classically attributed to other vasculotropic rickettsioses, such as rash (48–80%), myalgias (29–57%), vomiting (29–45%), cough (15–40%), headache (19–77%), and diarrhea or abdominal pain (10–40%). A petechial rash is observed in <15% of children, and the usual appearance is that of macules or maculopapules distributed on the trunk and extremities. The rash can involve both the soles and palms. Among common clinical features, only abdominal pain, diarrhea, and sore throat are more common in children than in adults, underscoring the mild nature of most cases in children. Murine-typhus associated hemophagocytic syndrome was recently described. Although neurologic involvement is a common finding in adults with murine typhus, photophobia, confusion, stupor, coma, seizures, meningismus, and ataxia are seen in <20% of hospitalized children and <6% of infected children treated as outpatients. Poor neonatal outcomes are reported with infection during pregnancy; however, both the frequency and clinical spectrum are not well documented.

Laboratory Findings

Although nonspecific, laboratory findings are less severe than in adults. Helpful findings include mild leukopenia (28–40%) with a moderate left shift, mild to marked thrombocytopenia (30–60%), hyponatremia (20–66%), hypoalbuminemia (30–87%), and elevated aspartate aminotransferase (82%) and alanine aminotransferase (38%). Elevations in serum urea nitrogen are usually a result of prerenal mechanisms.

Diagnosis and Differential Diagnosis

Delays in diagnosis and therapy are associated with increased morbidity and mortality; thus, diagnosis must be based on clinical suspicion. Occasionally, patients present with findings suggesting pharyngitis, bronchitis, hepatitis, gastroenteritis, or sepsis; thus, the differential diagnosis may be extensive.

Confirmation of the diagnosis is usually accomplished by comparing acute and convalescent-phase antibody titers obtained with the indirect fluorescent antibody assay to demonstrate a 4-fold rise in titer. Current objective studies of the diagnostic yield of *R. typhi* nucleic acid amplification from acute-phase whole blood show disappointingly low sensitivity, and rickettsial culture is not readily available. Thus, paired (acute and convalescent) serology to demonstrate a 4-fold rise in IgG antibody titer by IFA remains the standard for confirming acute infection. Use of IgM serologic tests is discouraged for diagnosis of rickettsial infections, because of both limited sensitivity and specificity.

Treatment

A meta-analysis of murine typhus in children reviewed treatment in 261 children, including 54 who received no antimicrobial therapy. Although 15% had complications, there we no deaths. The standard therapy for murine typhus in children was similar to that for adults and focused on use of tetracyclines or chloramphenicol. No controlled trials of other antimicrobial agents have been performed. Quinolones have been used in children, and limited clinical studies show that ciprofloxacin is as effective as doxycycline and chloramphenicol to treat murine typhus; however, treatment failures are reported. In vitro experiments suggest that minimal inhibitory concentrations of azithromycin and clarithromycin for *R. typhi* should be easily achieved.

Therefore, the time-honored recommended treatment for murine typhus remains doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day). Therapy should be for a minimum of 5 days continued until the patient has been afebrile for at least 3 days.

Supportive Care

Although disease is usually mild, 15% of children have complications and 2–7% require intensive care for management of meningoencephalitis, a disseminated intravascular coagulation–like condition, or other conditions. As for other rickettsial infections with significant systemic vascular injury, careful hemodynamic management is mandatory to avoid pulmonary or cerebral edema.

Complications

Complications of murine typhus in pediatric patients are uncommon; however, relapse, stupor, facial edema, dehydration, splenic rupture, and meningoencephalitis are reported. Predominance of abdominal pain has led to surgical exploration to exclude a perforated viscus.

Prevention

Control of murine typhus was dependent on elimination of the flea reservoir and control of flea hosts, and this approach remains important. However, with the recognition of cat fleas as potentially significant reservoirs and vectors, the presence of these flea vectors and their mammalian hosts in suburban areas where close human exposures occur poses increasingly difficult control problems. It is not known with certainty if infection confers protective immunity; reinfection appears to be rare.

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257.2

Epidemic (Louse-Borne) Typhus (*Rickettsia prowazekii*)

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Keywords

epidemic typhus
louse-borne typhus

Etiology

Humans are considered the principal reservoir of *R. prowazekii*, the causative agent of epidemic or louse-borne typhus and its recrudescent form, Brill-Zinsser disease. Another reservoir exists in flying squirrels, their ectoparasites, and potentially ticks, in a sylvatic cycle with small rodents. *R. prowazekii* is the most pathogenic member of the genus *Rickettsia* and multiplies to very large intracellular quantities before rupture of infected endothelial cells.

Epidemiology

The infection is characteristically seen in winter or spring and especially during times of poor hygienic practices associated with crowding, war, famine, extreme poverty, and civil strife. As observed in a recent outbreak among youths at a rehabilitation center in Rwanda, infections in children under these conditions can lead to severe adverse outcomes. *R. prowazekii* has also been associated with sporadic cases of a mild, typhus-like illness in the United States; such cases are associated with exposure to flying squirrels harboring infected lice or fleas. *R. prowazekii* organisms isolated from these squirrels appear to be genetically similar to isolates obtained during typical outbreaks.

Most cases of louse-borne typhus in the developed world are sporadic, but outbreaks have been identified in Africa (Ethiopia, Nigeria, Rwanda, and Burundi), Mexico, Central America, South America, Eastern Europe, Afghanistan, Russia, northern India, and China within the past 25 yr. Following the Burundi Civil War in 1993, 35,000-100,000 cases of epidemic typhus were diagnosed in displaced refugees, resulting in an estimated 6,000 deaths.

Transmission

Human body lice *(Pediculus humanus corporis)* become infected by feeding on persons who have rickettsiae circulating in their blood owing to endothelial infection. The ingested rickettsiae infect the midgut epithelial cells of the lice and are passed into the feces, which, in turn, are introduced into a susceptible human host through abrasions or perforations in the skin, through the conjunctivae, or rarely through inhalation as fomites in clothing, bedding, or furniture.

Clinical Manifestations

Louse-borne typhus can be mild or severe in children. The incubation period is usually <14 days. The typical clinical manifestations include fever, severe headache, abdominal tenderness, and rash in most patients, as well as chills (82%), myalgias (70%), arthralgias (70%), anorexia (48%), nonproductive cough (38%), dizziness (35%), photophobia (33%), nausea (32%), abdominal pain (30%), tinnitus (23%), constipation (23%), meningismus (17%), visual disturbances (15%), vomiting (10%), and diarrhea (7%). However, investigation of recent African outbreaks has shown a lower incidence of rash (25%) and a high incidence of delirium (81%) and cough associated with pneumonitis (70%). The rash is initially pink or erythematous and blanches. In one-third of patients, red, nonblanching macules and petechiae appear predominantly on the trunk. Infections identified during the preantibiotic era typically produced a variety of central nervous system findings, including delirium (48%), coma (6%), and seizures (1%). Estimates of case fatality rates range between 3.5% and 20% in outbreaks.

Brill-Zinsser disease is a form of typhus that becomes recrudescent months to years after the primary infection, thus rarely affecting children. When bacteremic with rickettsiae, these infected patients can transmit the agent to lice, potentially providing the initial event that triggers an outbreak if hygienic conditions permit.

Treatment

Recommended treatment regimens for louse-borne or sylvatic typhus are identical to those used for murine typhus. The treatment of choice is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Alternative treatments include tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr

IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient is afebrile for at least 3 days. Evidence exists that doxycycline as a single 200 mg oral dose (4.4 mg/kg if < 45 kg) is also efficacious.

Prevention

Immediate destruction of vectors with an insecticide is important in the control of an epidemic. Lice live in clothing rather than on the skin; thus, searches for ectoparasites should include examination of clothing. For epidemic typhus, antibiotic therapy and delousing measures interrupt transmission, reduce the prevalence of infection in the human reservoir, and diminish the impact of an outbreak. Dust containing excreta from infected lice is stable and capable of transmitting typhus, and care must be taken to prevent its inhalation. Infection confers solid protective immunity. However, recrudescence can occur years later with Brill-Zinsser disease, implying that immunity is not complete.

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CHAPTER 258

Ehrlichiosis and Anaplasmosis

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Etiology

Ehrlichiosis in humans was 1st described in 1987, when clusters of bacteria confined within cytoplasmic vacuoles of circulating leukocytes (morulae), particularly **mononuclear** leukocytes, were detected in the peripheral blood of a patient with suspected Rocky Mountain spotted fever (RMSF). The etiologic agent, *Ehrlichia chaffeensis*, was cultivated from blood of an infected patient in 1990 and identified as the predominant cause of human ehrlichiosis. Investigations showed that infection by *E. chaffeensis* is transmitted by *Amblyomma americanum* ticks and occurs more often than RMSF in some geographic areas. By 1994, other cases in which morulae were found only in **neutrophils** and lacked serologic evidence for *E. chaffeensis* infection led to the recognition of the species classified as *Anaplasma phagocytophilum* , which encompasses several previously described veterinary pathogens on at least 2 different continents and causing **anaplasmosis** .

Since these 1st discoveries in humans, additional species in the *Anaplasmataceae* family were identified as human pathogens, including (1) *Ehrlichia ewingii* in 1996, a veterinary pathogen of canine neutrophils transmitted by *A. americanum* ticks; (2) the *Ixodes scapularis* –transmitted *Ehrlichia muris* subsp. *euclairensis* in 2009, only present so far in patients from Minnesota and Wisconsin in the United States; (3) infections by *Candidatus* Neoehrlichia mikurensis, presumably *Ixodes* spp. or *Haemaphysalis concinna* tick-transmitted, recognized in 2010 as a cause of sepsis-like infections of immune compromised patients in Europe, and later as a cause of mild febrile illness in healthy individuals in China; (4) Panola Mountain *Ehrlichia* , a bacterium rarely associated with infections in human but present in *A.*

americanum ticks in the United States and with genetic features of the ruminant pathogen *Ehrlichia ruminantium* ; (5) *Ehrlichia canis,* the established canine pathogen that has infected humans in Venezuela; and (6) *Anaplasma capra* , the cause of mild fever after *Ixodes persulcatus* tick bites, so far only identified in China. The latter 5 have not yet been established as causes of infection in children.

Although the infections caused by these various genera have been called ehrlichiosis, further study has identified substantial differences in biology and diagnostic approaches such that the CDC now generally separates these into ehrlichiosis, anaplasmosis, or undetermined ehrlichiosis/anaplasmosis. **Human monocytic ehrlichiosis (HME)** describes disease characterized by infection of predominantly monocytes and is caused by *E. chaffeensis* , **human granulocytic anaplasmosis (HGA)** describes disease related to infection of circulating neutrophils by *Anaplasma phagocytophilum* , and **ewingii ehrlichiosis** is caused by infection of granulocytes by *E. ewingii* (see Table 255.1 in Chapter 255).

All of these organisms are tick-transmitted and are small, obligate intracellular bacteria with gram-negative-type cell walls. *Neorickettsia sennetsu* is another related bacterium that is rarely recognized as a cause of human disease and is not transmitted by ticks. *E. chaffeensis* alters host signaling and transcription once inside the cell. It survives in an endosome that enters a receptor recycling pathway to avoid phagosome-lysosome fusion and growth into a **morula** , an intravacuolar aggregate of bacteria. *A. phagocytophilum* survives in a unique vacuole that becomes decorated by microbial proteins that prevent endosomal trafficking and lysosome fusion. Little is known about the vacuoles in which *E. ewingii* and *E. muris* subsp. *euclairensis* grow. These bacteria are pathogens of phagocytic cells in mammals, and characteristically each species has a specific host cell affinity: *E. chaffeensis* infects mononuclear phagocytes, and *A. phagocytophilum* and *E. ewingii* infect neutrophils. Infection leads to direct modifications in function, in part the result of changes in intracellular signal transduction or modulation of transcription of the host cell that diminishes host defenses toward the bacterium. Yet, host immune and inflammatory reactions are still activated and in part account for many of the clinical manifestations in ehrlichiosis, such as overlaps with macrophage activation or hemophagocytic lymphohistiocytosis syndromes.

Epidemiology

Infections with *E. chaffeensis* occur across the southeastern, south central, and mid-Atlantic states of the United States in a distribution that parallels that of RMSF; cases have also been reported in northern California. Suspected cases with appropriate serologic and occasionally molecular evidence have been reported in Europe, Africa, South America, and the Far East, including China and Korea. Human infections with *E. ewingii* have only been identified in the United States in areas where *E. chaffeensis* also exists, perhaps owing to the shared tick vector. Canine infections are documented in both sub-Saharan Africa and in South America.

Although the median age of patients with HME and HGA is generally older (>51 yr), many infected children have been identified, and for HME the case fatality rate is 4% in those <5 yr of age. Little is known about the epidemiology of *E. ewingii* infections; although infections in children occur, they are recognized at a rate 100-fold less than for *E. chaffeensis* . All infections are strongly associated with tick exposure and tick bites and are identified predominantly during May through September. Although both nymphal and adult ticks can transmit infection, nymphs are more likely to transmit disease, because they are most active during the summer.

Transmission

The predominant tick species that harbors *E. chaffeensis* and *E. ewingii* is *A. americanum*, the Lone Star tick (see Fig. 255.1D in Chapter 255). The tick vectors of *A. phagocytophilum* are *Ixodes* spp. , including *I. scapularis* (black-legged or deer tick) in the eastern United States (see Fig. 255.1 in Chapter 255), *Ixodes pacificus* (western black-legged tick) in the western United States, *Ixodes ricinus* (sheep tick) in Europe, *Ixodes persulcatus* in Eurasia, and *Haemaphysalis concinna* in China. The *Ixodes* spp. ticks also transmit *Borrelia burgdorferi, Borrelia miyamotoi, Babesia microti,* and tick-borne encephalitis-associated flaviviruses in Europe, Powassan viruses, and *E. muris* subsp. *eauclairensis* in North America. Co-infections with these agents and *A. phagocytophilum* are documented in children and adults.

Ehrlichia and *Anaplasma* species are maintained in nature predominantly by horizontal transmission (tick to mammal to tick), because the organisms are not transmitted to the progeny of infected adult female ticks (transovarial transmission). The major reservoir for *E. chaffeensis* is the white-tailed deer *(Odocoileus virginianus)* , which is found abundantly in many parts of the

United States. A reservoir for *A. phagocytophilum* in the eastern United States appears to be the white-footed mouse, *Peromyscus leucopus.* Deer or domestic ruminants can sustain persistent asymptomatic infections, but the genetic variants in these reservoirs might not be infectious for humans. Efficient transmission requires persistent infections of mammals. Although *E. chaffeensis* and *A. phagocytophilum* can cause persistent infections in animals, the documentation of chronic infections in humans is exceedingly rare. Transmission of *Ehrlichia* can occur within hours of tick attachment, in contrast to the 1-2 days of attachment required for transmission of *B. burgdorferi* to occur. Transmission of *A. phagocytophilum* is via the bite of the small nymphal stage of *Ixodes* spp., including *I. scapularis* (see Fig. 255.1*A* in Chapter 255), which is very active during late spring and early summer in the eastern United States.

Pathology and Pathogenesis

Although HME and anaplasmosis often clinically mimic RMSF or typhus, vasculitis is rare. Pathologic findings include mild, diffuse perivascular lymphohistiocytic infiltrates; Kupffer cell hyperplasia and mild lobular hepatitis with infrequent apoptotic hepatocytes and less frequently centrilobular necrosis, cholestasis, and steatosis; infiltrates of mononuclear phagocytes in the spleen, lymph nodes, and bone marrow with occasional hemophagocytosis; granulomas of the liver and bone marrow in patients with *E. chaffeensis* infections; and hyperplasia of 1 or more bone marrow hematopoietic lineages.

The exact pathogenetic mechanisms are poorly understood, but histopathologic examinations suggest diffuse macrophage activation and poorly regulated host immune and inflammatory reactions. This activation results in moderate to profound leukopenia and thrombocytopenia despite a hypercellular bone marrow, and deaths often are related to severe hemorrhage or secondary opportunistic infections. Hepatic and other organ-specific injury occurs by a mechanism that appears to be triggered by the bacterium but more closely related to induction of innate and adaptive immune effectors. Meningoencephalitis with a mononuclear cell pleocytosis in the cerebrospinal fluid (CSF) occurs with HME but is rare with HGA.

Clinical Manifestations

The clinical manifestations of HME, HGA, and ewingii ehrlichiosis are similar. Many well-characterized infections of HME and HGA of variable severity have been reported in children, including deaths. Children with ehrlichiosis are often ill for 4-12 days, shorter than in adults. In series of children with HME, most required hospitalization and many (25%) required intensive care; these statistics might represent preferential reporting of severe cases. However, review of case reports and electronic surveillance of HGA to the Centers for Disease Control and Prevention identified that 42% of patients 5-9 yr of age required hospitalization and the case fatality rate is 4% among children <5 yr of age. Population-based studies document that seroconversion often occurs in children who are well or who have only a mild illness. Many fewer pediatric cases of *E. ewingii* infection are reported, so the clinical manifestations related to this infection are less well characterized. The incubation period (time from last tick bite or exposure) appears to range from 2 days to 3 wk. Nearly 25% of patients do not report a tick bite.

Clinically, ehrlichioses are undifferentiated febrile illnesses. In HME, fever (~100%), headache (77%), and myalgia (77%) are most common, but many patients also report abdominal pain, nausea, and vomiting. Altered mental status accompanied by other signs of central nervous system involvement is present in 36%. Rash is a common feature (~60%) in children. The rash is usually macular or maculopapular, but petechial lesions can occur. Photophobia, conjunctivitis, pharyngitis, arthralgias, and lymphadenopathy can occur but are less consistently present. Lymphadenopathy, hepatomegaly, and splenomegaly are detected in nearly 50% of children with ehrlichiosis. Edema of the face, hands, and feet occurs more commonly in children than in adults, but arthritis is uncommon in both groups.

Similar but less severe manifestations occur with HGA in children, including fever (93%), headache (73%), myalgia (73%), rigors (60%); nausea, vomiting, abdominal pain, and anorexia occur in 30% or less. Cough is present in 20%; rash is very infrequent and most often is erythema migrans that results from concurrent Lyme disease.

Meningoencephalitis with a lymphocyte-predominant CSF pleocytosis is an uncommon but potentially severe complication of HME that appears to be rare with HGA. CSF protein may be elevated, and glucose may be mildly depressed in adults with HME meningoencephalitis, but CSF protein and glucose in affected children are typically normal. In 1 series, 19% of adult patients with central nervous system symptoms and abnormal CSF died despite normal CTs of the brain.

Chronic or persistent disease with low or absent fever is very unlikely to be any form of ehrlichiosis.

Laboratory Findings

Characteristically, most children with HME and HGA present with leukopenia (57–80%) and thrombocytopenia (38–93%); cytopenias reach a nadir several days into the illness. Lymphopenia is common in both HME and HGA, and neutropenia is reported in adults with HGA. Leukocytosis can also occur, but usually after the 1st wk of illness or with effective antimicrobial treatment. Adults with pancytopenia often have a cellular or reactive bone marrow examination, and in nearly 75% of bone marrow specimens from adults with HME, granulomas and granulomatous inflammation are present; this finding is not a feature of adults with HGA. Mild to severely elevated serum hepatic transaminase levels are frequent in both HME (85–92%) and HGA (40–50%). Hyponatremia (<135 mEq/L) is present in most cases. A clinical picture similar to disseminated intravascular coagulopathy has also been reported.

Diagnosis

Any delays in diagnosis or treatment are major contributors to increased morbidity or mortality in adults, where those not started on doxycycline at hospital admission are much more likely to require intensive care and a significantly longer course of illness and hospitalization. Thus treatment must begin as early as possible based on clinical suspicion. Because both HME and anaplasmosis can be fatal, therapy should not be withheld while waiting for the results of confirmatory testing. In fact, prompt response to therapy supports the diagnosis.

While several reports document pediatric patients with *E. chaffeensis* infection diagnosed based on typical *Ehrlichia* morulae in peripheral blood leukocytes (Fig. 258.1A), this finding is too infrequent to be considered a useful diagnostic approach. In contrast, HGA in adults presents with a small but significant percentage (1–40%) of circulating neutrophils (Fig. 258.1B) containing typical morulae in 20–60% of patients.

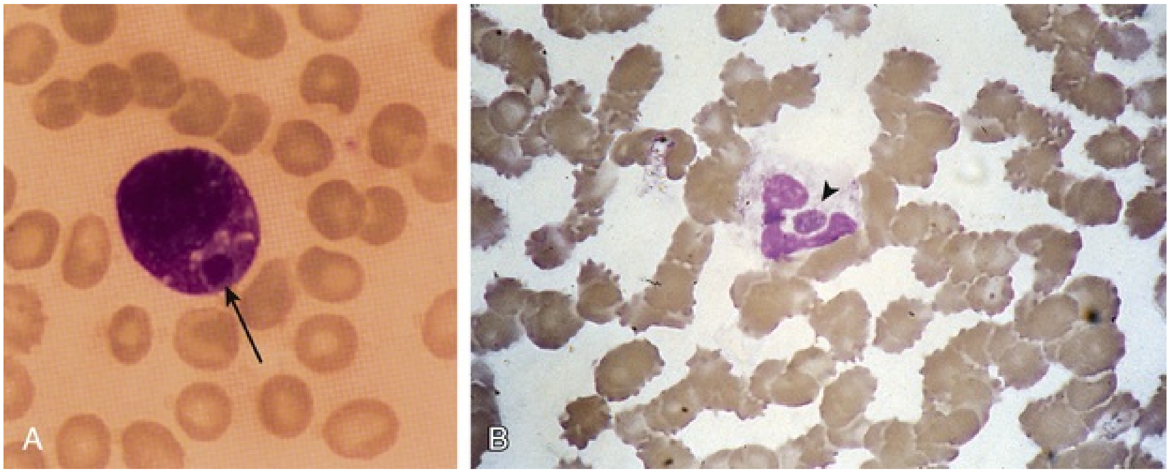

FIG. 258.1 Morulae in peripheral blood leukocytes in patients with human monocytic ehrlichiosis and human granulocytic anaplasmosis. **A,** A morula *(arrow)* containing *Ehrlichia chaffeensis* in a monocyte. **B,** A morula *(arrowhead)* containing *Anaplasma phagocytophilum* in a neutrophil. Wright stains, original magnifications ×1,200. *E. chaffeensis* and *A. phagocytophilum* have similar morphologies but are serologically and genetically distinct.

E. chaffeensis and *A. phagocytophilum* infections can be confirmed by demonstrating a 4-fold change in immunoglobulin G titer by indirect immunofluorescence assay between paired sera. Serologic tests during the acute phase of infection are often negative; consequently, confirmation of acute infection requires demonstration a 4-fold rise in IgG titer in paired samples. Infection can also be established by specific polymerase chain reaction, demonstration of specific antigen in a tissue sample by immunohistochemistry, or isolation of the organism in cell culture. A single specific titer of ≥128 or identification of morulae in monocytes or macrophages for *E. chaffeensis* or in neutrophils or eosinophils for *A. phagocytophilum* by microscopy is suggestive. *E. ewingii* infection can only be confirmed by polymerase chain reaction, because it has not been cultured and serologic antigens are not available. *E. ewingii* antibodies cross react with *E. chaffeensis* in routine serologic tests. Up to 15% of patients with HGA have serologic cross-reactions with *E. chaffeensis* ; thus serodiagnosis depends on testing with both *E. chaffeensis* and *A. phagocytophilum* antigens and demonstrating a 4-fold or higher difference between titers. During the acute phase of illness when antibodies are often not detected, polymerase chain reaction amplification of *E. chaffeensis* or *A. phagocytophilum* DNA is sensitive in >86% of cases. Although *E. chaffeensis* and *A. phagocytophilum* can be cultivated in tissue culture, this method is not timely or widely available.

Differential Diagnosis

Because of the nonspecific presentation, ehrlichiosis mimics other arthropod-borne infections such as RMSF, tularemia, babesiosis, Lyme disease, murine typhus, relapsing fever, and Colorado tick fever. Other potential diagnoses often considered include otitis media, streptococcal pharyngitis, infectious mononucleosis, Kawasaki disease, endocarditis, respiratory or gastrointestinal viral syndromes, hepatitis, leptospirosis, Q fever, collagen–vascular diseases, hemophagocytic syndromes, and leukemia. If rash and disseminated intravascular coagulopathy predominate, meningococcemia, bacterial sepsis, and toxic shock syndrome are also suspected. Meningoencephalitis might suggest aseptic meningitis caused by enterovirus or herpes simplex virus, bacterial meningitis, or RMSF. Severe respiratory disease may be confused with bacterial, viral, and fungal causes of pneumonia. Mounting evidence suggests that ehrlichiosis or anaplasmosis may be precipitating factors for hemophagocytic lymphohistiocytosis.

Treatment

Both HME and HGA are effectively treated with tetracyclines, especially doxycycline, and the majority of patients improve within 48 hr. In vitro tests document that both *E. chaffeensis* and *A. phagocytophilum* have minimal inhibitory concentrations to chloramphenicol above blood levels that can be safely achieved. Therefore, a short course of doxycycline is the recommended regimen. Doxycycline is used safely in children younger than 8 yr of age because tooth discoloration is dose dependent and the need for multiple courses is unlikely; experience has demonstrated that adverse consequences of doxycycline use in children <8 yr of age are extremely rare. Few data exist to recommend alternative therapies; however, both *E. chaffeensis* and *A. phagocytophilum* are susceptible in vitro to rifampin, which has been used successfully to treat HGA in pregnant women and children.

The recommended regimen for patients of all ages with severe or complicated HME and HGA is doxycycline (for those who weigh <45 kg, 4 mg/kg/day PO or IV divided every 12 hr; maximum dose: 100 mg/dose). An alternative regimen is tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum 2 g/day). For children who weigh more than 45 kg, the adult dose, 100 mg twice daily by oral or intravenous route, can be used. Therapy should be continued for ≥5 days and until the patient has been afebrile for ≥2-4 days.

Other broad-spectrum antibiotics, including penicillins, cephalosporins, aminoglycosides, and macrolides, are not effective. In vitro studies suggest that fluoroquinolones are active against *A. phagocytophilum* , although at least 1 patient relapsed when levofloxacin was discontinued. *E. chaffeensis* is naturally resistant to fluoroquinolones owing to a single nucleotide change in *gyrA*, which suggests that *A. phagocytophilum* could also become resistant to fluoroquinolones rapidly.

Complications and Prognosis

Fatal HME is reported in several pediatric patients, where the findings included pulmonary involvement and respiratory failure in patients with or without immune compromise. The pattern of severe pulmonary involvement culminating in diffuse alveolar damage and acute respiratory distress syndrome and secondary nosocomial or opportunistic infections is now well-documented with HME and HGA in adults. One child with HGA died after 3 wk of fever, thrombocytopenia, and lymphadenopathy suspected to be a hematologic malignancy. Patients who are immunocompromised (e.g., HIV infection, high-dose corticosteroid therapy, cancer chemotherapy, immunosuppression for organ transplantation) are at high risk for fulminant *E. chaffeensis* infection, for *E. ewingii* infection, and for severe HGA.

Prevention

HME, HGA, and ewingii ehrlichiosis are tick-borne diseases, and any activity that increases exposure to ticks increases risk. Avoiding tick-infested areas, wearing appropriate light-colored clothing, spraying tick repellents on clothing, carefully inspecting for ticks after exposure, and promptly removing any attached ticks diminish the risk. The interval between tick attachment and transmission of the agents may be as short as 4 hr; thus attached ticks should be removed promptly. A role of prophylactic therapy for ehrlichiosis and anaplasmosis after tick bites has not been investigated. It is not known if infection confers protective immunity; however, reinfection appears to be exceedingly rare.

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CHAPTER 259

Q Fever *(Coxiella burnetii)*

Megan E. Reller, J. Stephen Dumler

Q fever (for query fever, the name given following an outbreak of febrile illness in an abattoir in Queensland, Australia) is rarely reported in children but is probably underdiagnosed. Symptomatic patients can have acute or chronic disease.

Etiology

Although previously classified within the order Rickettsiales, *Coxiella burnetii* (the causative agent of Q fever) is genetically distinct from the genera *Rickettsia, Orientia* , *Ehrlichia*, and *Anaplasma*. Hence, based on small genome analysis, it best aligns within the order Legionellales, family Coxiellaceae. *C. burnetii* is highly infectious for both humans and animals; even a single organism can cause infection. The agent has been nationally notifiable since 1999 and is listed as a Category B agent of bioterrorism by the Centers for Disease Control and Prevention (CDC). Unlike *Rickettsia*, the organism can enter a sporogenic differentiation cycle, which renders it highly resistant to chemical and physical treatments.

C. burnetii resides intracellularly within macrophages. In vitro, the organism undergoes a lipopolysaccharide phase variation similar to that described for smooth and rough strains of Enterobacteriaceae. Unlike *Ehrlichia*, *Anaplasma*, and *Chlamydia*, *C. burnetii* survives and proliferates within acidified phagosomes to form aggregates of >100 bacteria.

Epidemiology

The disease is reported worldwide, except in New Zealand. Although seroepidemiologic studies suggest that infection occurs just as often in children as in adults, children less often present with clinical disease than adults. During the large outbreak of Q fever in the Netherlands in 2007–2009, only 3.5% of those diagnosed with Q fever were age 19 yr or younger. Although infections are recognized more often in men than in women, reported cases in boys and girls are equal. Approximately 60% of infections are asymptomatic, and only 5% of symptomatic patients require hospitalization. Seroprevalence surveys show that 6–70% of children in endemic European and African communities have evidence of past infection. In France, the overall incidence of Q fever is estimated to be 50 cases per 100,000 persons. A similar estimate is not available for Africa, where cases are likely misdiagnosed as malaria. The seroprevalence of Q fever in the United States is estimated to be 3.1%. Reported cases of Q fever in the United States have been received from every state, but 35% are reported from 4 states (California, Texas, Colorado, and Illinois). In the United States, reported Q fever cases increased by greater than 9-fold from 17 cases in 2000 to 167 cases in 2008, reflecting an increase in incidence, increased reporting after September 11, 2001, improved diagnostic tools, or a combination of factors. Cases decreased significantly in 2008–2013 relative to 2007 but returned to previous high levels in 2014 (173 cases, including 147 acute and 39 chronic). Beginning in 2008, reported cases in the United States have been classified as acute or chronic. Between 2002 and 2014, more than 50% of recognized cases in the United States required hospitalization. Reported cases in Asia and Australia have also increased. Most infections in children are identified during the lamb birthing season in Europe (January through June), following farm visits, or after exposure to placentas of dogs, cats, and rabbits. The largest (~4,000 human cases) community outbreak ever described occurred in the Netherlands in 2007–2012 and was associated with intensive farming of dairy goats and dairy sheep. In 2011, the 1st multistate outbreak of Q fever in humans was linked to interstate sale of infected goats; an outbreak of unknown source was also reported. From 2000 to 2010, 60% of cases reported to CDC occurred in individuals without reported exposure to livestock. More than 20% of cases of clinically recognized acute or chronic Q fever occur in immunosuppressed hosts or in persons with prosthetic valves or damaged native valves or vessels. These findings highlight the need for considering Q fever in those with clinically compatible illness, especially but not exclusively in those with likely exposures and in vulnerable hosts. Epidemiologic investigations and control efforts require a One Health approach, with consideration of the interactions between humans, animals, environment, and public health.

Transmission

In contrast to other rickettsial infections, humans usually acquire *C. burnetii* by inhaling infectious aerosols (e.g., contaminated barnyard dust) or ingesting (and likely aspirating) contaminated foods. Ticks are rarely implicated. Cattle, sheep, and goats are the primary reservoirs, but infection in other livestock and domestic pets is also described. Organisms are excreted in milk, urine, and feces of infected animals, but especially in amniotic fluids and the placenta. An increase in incidence is associated with the seasonal mistral winds in France that coincide with lamb birthing season and with consumption of cheese among children in Greece. In Nova Scotia and Maine, exposure to newborn animals, especially kittens, has been associated with small outbreaks of Q fever in families. Exposure to domestic ruminants is the major risk in Europe and Australia, although many urban dwellers in France also acquire Q fever without such an exposure. Person-to-person transmission is possible but rare. Clinical Q fever during pregnancy can result from primary infection or reactivation of latent infection and is associated with miscarriage, intrauterine growth retardation, and premature births. Obstetricians and other related healthcare workers are at risk for acquiring infection because of the quantity of *C. burnetii* sequestered in the placenta. Sexual transmission and cases attributable to blood transfusion or bone marrow transplantation are also reported. Transmission following *live cell therapy* (injected live animal cells) has also been reported.

Pathology and Pathogenesis

The pathology of Q fever depends on the mode of transmission, route of dissemination, specific tissues involved, and course of the infection. When acquired via inhalation, a mild interstitial lymphocytic pneumonitis and macrophage- and organism-rich intraalveolar exudates are often seen. When the liver is involved, a mild to moderate lymphocytic lobular hepatitis can be seen. Inflammatory pseudotumors can develop in the pulmonary parenchyma or other tissues. Classic fibrin-ring (“doughnut”) granulomas, generally associated with acute, self-limited infections, are occasionally identified in liver, bone marrow, meninges, and other organs. Typically, infected tissues are also infiltrated by lymphocytes and histiocytes.

Recovery from symptomatic or asymptomatic acute infection can result in persistent subclinical infection, possibly maintained by dysregulated cytokine responses. The persistence of *C. burnetii* in tissue macrophages at sites of preexisting tissue damage elicits low-grade chronic inflammation and, depending on the site of involvement, can result in irreversible cardiac valve damage, persistent vascular injury, or osteomyelitis. Endocarditis of native or prosthetic valves is characterized by infiltrates of macrophages and lymphocytes in necrotic fibrinous valvular vegetations and an absence of granulomas.

Clinical Manifestations and Complications

Children are less likely to develop symptoms compared with adults. Only approximately 40–50% of people infected with *C. burnetii* develop symptoms. Historically, 2 forms of symptomatic disease have been thought to occur. **Acute Q fever** , now better characterized as **primary Q fever,** is more common and usually manifests as self-limited undifferentiated fever or an influenza-like illness with interstitial pneumonitis. Persistent localized infection with *C. burnetii* can cause what has historically been referred to as **chronic Q fever** . In adults, persistent localized infection usually involves the cardiovascular system—native heart valves, especially those with preexisting valvulopathy, prosthetic valves, or other endovascular prostheses. Q fever osteomyelitis is less common but proportionally more common in children. Less common persistent localized *C. burnetii* infections include lymphadenitis, genital infection, and pericarditis.

Primary (Acute) Q Fever

Acute Q fever develops approximately 3 wk (range: 14-39 days) after exposure to the causative agent. The severity of illness in children ranges from subclinical infection to a systemic illness of sudden onset characterized by high fever, severe frontal headache, nonproductive cough, chest pain, vomiting, diarrhea, abdominal pain, arthralgias, and myalgias. Approximately 40% of children with acute Q fever present with fever, 25% with pneumonia or an influenza-like illness, >10% with meningoencephalitis, and >10% with myocarditis. Other manifestations include pericarditis, hepatitis, hemophagocytosis, rhabdomyolysis, and a hemolytic uremic–like syndrome. Rash, ranging from maculopapular to purpuric lesions, is an unusual finding in adults with Q fever but is observed in approximately 50% of pediatric patients. Rigors and night sweats are common in adults with Q fever and occur less often in children. Prominent clinical findings that can create diagnostic confusion include fatigue, vomiting, abdominal pain, and meningismus. Hepatomegaly and splenomegaly may be detected in some patients.

Routine laboratory investigations in pediatric acute Q fever are usually normal but can reveal mild leukocytosis and thrombocytopenia. Up to 85% of children have modestly elevated serum hepatic transaminase levels that usually normalize within 10 days. Hyperbilirubinemia is uncommon in the absence of complications. C-reactive protein is uniformly elevated in pediatric Q fever. Chest radiographs are abnormal in 27% of all patients; in children, the most common findings include single or multiple bilateral infiltrates with reticular markings in the lower lobes.

Primary Q fever in children is usually a self-limited illness, with fever persisting for only 7-10 days compared with 2-3 wk in adults. However, severe manifestations of acute illness, such as myocarditis requiring cardiac transplantation, meningoencephalitis, pericarditis, hemophagocytosis, thrombosis with antiphospholipid antibody syndrome, as well as a relapsing febrile illness lasting for several months, have been reported.

Persistent Localized Q Fever Infection

The risk for developing persistent localized Q fever infection, historically called *chronic Q fever,* is strongly correlated with advancing age and underlying conditions such as cardiac valve damage or immunosuppression; persistent localized Q fever infection is rarely diagnosed in children. A review identified only 5 cases of Q fever endocarditis and 6 cases of osteomyelitis among children, none of whom had known predisposing immune deficiencies. Four of the 5 cases of endocarditis occurred in children with underlying congenital heart abnormalities and involved the aortic, pulmonary, and tricuspid valves. Four of the 6 children with Q fever osteomyelitis had a prior diagnosis or clinical course consistent with idiopathic chronic recurrent multifocal osteomyelitis. A long interval before diagnosis and lack of high fever are common in pediatric cases of persistent localized Q fever infection—historically chronic Q fever.

Although Q fever endocarditis often results in death (23–65% of cases) in adults, mortality has not been reported for children. Endocarditis associated with persistent or chronic Q fever can occur months to years after acute infection and can occur in the absence of recognized acute Q fever and in the absence of clinically recognized valvulopathy. Chronic hepatitis has also been reported.

Laboratory Findings

Laboratory features in children with chronic Q fever are poorly documented; adult patients often have an erythrocyte sedimentation rate of >20 mm/hr (80% of cases), hypergammaglobulinemia (54%), and hyperfibrinogenemia (67%). In children, the presence of rheumatoid factor in >50% of cases, and circulating immune complexes in nearly 90% suggests an autoimmune process. The presence of antiplatelet antibodies, anti–smooth muscle antibodies, antimitochondrial antibodies, circulating anticoagulants, positive direct Coombs tests, and antiphospholipid antibodies also suggest this possibility.

Diagnosis and Differential Diagnosis

Although uncommonly diagnosed, Q fever in children most often mimics other childhood respiratory infections. It should be considered in children who have an influenza-like illness, lower or upper respiratory tract infection, fever of unknown origin, myocarditis, meningoencephalitis, culture-negative endocarditis, or recurrent osteomyelitis, and who live in rural areas or who are in close contact with domestic livestock, cats, or animal products.

The diagnosis of primary (acute) Q fever is most easily and commonly confirmed by testing acute and convalescent sera (3-6 wk apart), which show a 4-fold increase in indirect fluorescent immunoglobulin G antibody titers to phase II *C. burnetii* antigens. The phase II antibody response to *C. burnetii* appears 1st and is higher than the phase I antibody response. Phase II immunoglobulin G antibodies can remain elevated for months to years, regardless of initial symptoms or lack thereof. In contrast, persistent localized (chronic) Q fever is characterized by a phase I immunoglobulin G antibody titer greater than 800 that is sustained for 6 mo or more, such as occurs with Q fever endocarditis in patients with valvular heart disease. Cross-reactions with antibodies to *Legionella* and *Bartonella* can occur.

Although culture has been considered the gold standard, sensitivity (compared with a composite standard including serology and polymerase chain reaction) is low. *C. burnetii* has been cultivated in tissue culture cells, which can become positive within 48 hr, but isolation and antimicrobial susceptibility testing of *C. burnetii* should be attempted only in specialized biohazard facilities. Testing by polymerase chain reaction can be performed on blood, serum, and tissue samples and is available only in some public health, reference, or research laboratories. Polymerase chain reaction (PCR) has been helpful in patients with equivocal titers, as occurs with early infection. PCR usually remains positive for 7-10 days after acute infection. Sensitivity has been improved by real-time methods and the use of repeated sequences as targets. Immunohistochemical staining has also been used, but is not readily available. PCR should be performed either before or shortly after initiation of treatment. PCR can also confirm a serologic diagnosis of endocarditis in untreated patients. Genotyping has aided epidemiologic investigations to confirm source of infection. The differential diagnosis depends on the clinical presentation. In patients with respiratory disease, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* legionellosis, psittacosis, and Epstein-Barr virus infection should be considered. In patients with granulomatous hepatitis, tuberculous and nontuberculous mycobacterial infections, salmonellosis, visceral leishmaniasis, toxoplasmosis, Hodgkin disease, monocytic ehrlichiosis, granulocytic anaplasmosis, brucellosis, cat scratch disease (*Bartonella henselae*), or autoimmune disorders such as sarcoidosis should be considered. **Culture-negative endocarditis** suggests infection with *Brucella, Bartonella,* HACEK organisms *(Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella)* , partially treated bacterial endocarditis, nonbacterial endocarditis, or potentially noninfectious inflammatory conditions, including chronic recurrent multifocal osteomyelitis and antiphospholipid syndrome.

Treatment

Selection of an appropriate antimicrobial regimen for children is difficult owing to the lack of rigorous studies, the limited therapeutic window for drugs that are known to be efficacious, and the potential length of therapy required to preclude relapse.

Most pediatric patients with Q fever have a self-limited illness that is identified only on retrospective serologic evaluation. However, to prevent potential complications, treatment should be considered for patients who present with acute Q fever within 3 days of onset of symptoms, because therapy started more than 3 days after onset of illness has little effect on the course of acute Q fever. Because confirmatory testing in early acute infection is not possible, and because tetracycline and doxycycline can be associated with tooth discoloration in children younger than 9 yr of age, empirical therapy is warranted in those with clinically suspected Q fever who are 8 yr of age or older or at high risk for severe illness. Doxycycline (4 mg/kg/day PO or IV divided every 12 hr; maximum: 200 mg/day) is the drug of choice; the usual course is 2 wk. Children at high risk include those hospitalized or with severe illness, those diagnosed after prolonged (>2 wk) unremitting symptoms, and those with preexisting valvular heart disease or who are immunocompromised. Because tooth discoloration is both dose and duration dependent and few children require multiple courses, younger children with mild Q fever could be treated with 5 days of doxycycline followed by 14 days of trimethoprim-sulfamethoxazole if symptoms persist. During pregnancy, Q fever is best treated with trimethoprim-sulfamethoxazole. The fluoroquinolones are also effective, and success with a combination of a fluoroquinolone and rifampin is also achieved with prolonged therapy (16-21 days). Macrolides, including erythromycin and clarithromycin, are less-effective alternatives.

For persistent focal Q fever, especially endocarditis and mostly in adults, therapy for 18-36 mo is mandatory. The current recommended regimen for Q fever endocarditis is a combination of doxycycline and hydroxychloroquine for 18 mo or longer. For patients with heart failure, valve replacement could be necessary. Interferon-γ therapy has been used as adjunct therapy for intractable Q fever.

Prevention

Recognition of the disease in livestock or other domestic animals should alert communities to the risk for human infection by aerosol exposures within 15 km. Milk from infected herds must be pasteurized at temperatures sufficient to destroy *C. burnetii*. *C. burnetii* is resistant to significant environmental conditions but can be inactivated with a solution of 1% Lysol, 1% formaldehyde, or 5% hydrogen peroxide. Special isolation measures are not required because person-to-person transmission is rare, except when others are exposed to the placenta of an infected patient. A vaccine is available and provides protection against Q fever for at least 5 yr in abattoir workers. Because the vaccine is strongly reactogenic and no trials in children have been conducted, it should only be used when extreme risk is judged to exist. Clusters of cases resulting from intense natural exposures, such as in slaughterhouses or on farms, are well documented. Clusters of cases that occur in the absence of such an exposure should be investigated as potential sentinel events for bioterrorism.

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SECTION 12

Fungal Infections

OUTLINE

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CHAPTER 260

Principles of Antifungal Therapy

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Invasive fungal infections are a major cause of morbidity and mortality in the growing number of immunocompromised children. Fortunately, the therapeutic armamentarium for invasive fungal infections has markedly increased since the turn of the century (Tables 260.1 and 260.2).

Table 260.1

Suggested Dosing of Antifungal Agents in Children and Neonates

DRUG	FORMULATIONS	SUGGESTED PEDIATRIC DOSAGE	COMMENTS
Amphotericin B deoxycholate	IV	1 mg/kg/day	Generally less toxicity in children than adults; do not start with smaller test doses
Lipid amphotericin B formulations	IV	5 mg/kg/day	Generally, all lipid formulations are dosed the same; there is no clear indication of one formulation over another for clinical efficacy
Fluconazole	IV, PO	12 mg/kg/day	Loading dose (25 mg/kg) is recommended in neonates based on pharmacokinetic simulations and likely suggested in children, but insufficiently studied
Itraconazole	PO	2.5 mg/kg/dose bid	Divide dosage twice daily in children; follow trough levels
Voriconazole	IV, PO	8 mg/kg/dose bid IV maintenance; 9 mg/kg/dose bid oral maintenance	Linear pharmacokinetics in children requires higher dosing than in adults; 9 mg/kg/dose bid IV loading, followed by maintenance dosing; follow trough levels
Posaconazole	IV, PO	Suspected to be 12-24 mg/kg/day divided tid (oral suspension)	Dosage unclear in children at present. In adults, max dosage for oral suspension is 800 mg/day, and optimally divide this into 2 or 3 doses; follow trough levels. Adult dosing for IV and extended-release tablet is 300 mg twice on 1st day,

			then 300 mg once daily.
Isavuconazole	PO, IV	No dosing in children	Adult dosing for IV and tablet is 200 mg 3 times on 1st day, then 200 mg once daily.
Micafungin	IV	2-10 mg/kg/day	Highest dosages in neonates (10 mg/kg/day), and lower dosages in children; >8 yr of age, use adult dosage
Anidulafungin	IV	1.5 mg/kg/day	Loading dose of 3 mg/kg/day
Caspofungin	IV	50 mg/m^2 /day	Load with 70 mg/m^2 /day, then 50/mg/m^2 /day as maintenance dosage

Table 260.2

Suggested Antifungals for Specific More Common Fungal Pathogens

FUNGAL SPECIES	**AMPHOTERICIN B FORMULATIONS**	**FLUCONAZOLE**	**ITRACONAZOLE**	**VORICONAZOLE**	**POSACON**
Aspergillus calidoustus	++	−	−	−	−
Aspergillus fumigatus	+	−	+/−	++	+
Aspergillus terreus	−	−	+	++	+
Blastomyces dermatitidis	++	+	++	+	+
Candida albicans	+	++	+	+	+
Candida glabrata	+	−	+/−	+/−	+/−
Candida krusei	+	−	−	+	+
Candida lusitaniae	−	++	+	+	+
Candida parapsilosis	++	++	+	+	+
Coccidioides immitis	++	+	++	+	++
Cryptococcus spp.	++	+	+	+	+
Fusarium spp.	+/−	−	−	++	+
Histoplasma capsulatum	++	+	++	+	+
Mucor spp.	++	−	+/−	−	+
Scedosporium apiospermum	−	−	+/−	+	+
Scedosporium prolificans	−	−	+/−	+/−	+/−

++ , preferred therapy(ies); +, usually active; +/−, variably active; −, usually not active.

Polyenes

Amphotericin B

The prototype of the oldest antifungal class, the polyene macrolides, is amphotericin B deoxycholate. Amphotericin B was once the preferred treatment for most invasive fungal infections as well as the standard of comparison for all newer antifungal agents. Amphotericin B is so named because it is amphoteric, forming soluble salts in both acidic and basic environments. However, because of its insolubility in water, amphotericin B for clinical use is actually amphotericin B mixed with the detergent deoxycholate. Amphotericin B binds to ergosterol, the major sterol found in fungal cytoplasmic membranes, and acts by creating transmembrane channels. The fungicidal activity is due to a damaged barrier and subsequent cell death through leakage of essential nutrients from the fungal cell.

Amphotericin B is released from its carrier and distributes very efficiently with lipoproteins and is then taken up preferentially by organs of the reticuloendothelial system. Following an initial 24-48 hr distributional half-life there is very slow release and a subsequent terminal elimination half-life of up to 15 days. In addition to conventional amphotericin B deoxycholate, 3 fundamentally different lipid-associated formulations have been developed that offer the advantage of an increased daily dosage of the parent drug, better delivery to the primary reticuloendothelial organs (lungs, liver, spleen), and reduced toxicity. Amphotericin B lipid complex (ABLC) is a tightly packed ribbon-like structure of a bilayered membrane, amphotericin B colloidal dispersion (ABCD) is composed of disk-like structures of cholesteryl sulfate complexed with amphotericin B, and liposomal amphotericin B (L-amphotericin B) consists of small uniformly sized vesicles of a lipid bilayer of amphotericin B. Lipid formulations of amphotericin B generally have a slower onset of action, presumably owing to the required disassociation of free amphotericin B from the lipid vehicle. The ability to safely administer higher daily doses of the parent drugs improves their efficacy, comparing favorably with amphotericin B deoxycholate but with less toxicity. Lipid formulations have the added benefit of increased tissue concentrations compared to conventional amphotericin B, specifically in the liver, lungs, and spleen. However, it is not entirely clear if these higher concentrations in tissue are truly available to the microfoci of infection.

Tolerance to amphotericin B deoxycholate is limited by its acute and chronic toxicities. In addition to interacting with fungal ergosterol, the drug also interacts with cholesterol in human cell membranes, likely accounting for its toxicity. Up to 80% of patients receiving amphotericin B develop either infusion-related toxicity or nephrotoxicity, especially with concomitant therapy with nephrotoxic drugs such as aminoglycosides, vancomycin, cyclosporine, or tacrolimus. Renal function usually returns to normal after cessation of amphotericin B, although permanent renal impairment can occur after larger doses. Amphotericin B nephrotoxicity is generally less severe in infants and children than in adults, likely due to the more rapid clearance of the drug in children. Lipid formulations appear to stabilize amphotericin B in a self-associated state so that it is not available to interact with the cholesterol of human cellular membranes.

Unlike older approaches, there is no total dosage of amphotericin B recommended, and the key to success is to give high dosages in the initial phase of therapy and to reduce the frequency of administration (not necessarily the daily dose) if toxicity develops. There are no data or consensus opinions among authorities indicating improved efficacy of any new amphotericin B lipid formulation over conventional amphotericin B deoxycholate. One exception is that L-amphotericin B has shown fewer infusion-related adverse events than the other lipid formulations or conventional amphotericin B.

Pyrimidine Analogs

5-Fluorocytosine

5-Fluorocytosine (5-FC) is a fluorinated analog of cytosine and has antifungal activity results from the rapid conversion into 5-fluorouracil (5-FU) within susceptible fungal cells. Clinical and microbiologic antifungal resistance develops quickly to 5-FC monotherapy, so clinicians have reserved it for combination approaches to augment other more potent antifungals. Fungistatic 5-FC is thought to enhance the antifungal activity of amphotericin B, especially in anatomic sites where amphotericin B penetration is often suboptimal, such as cerebrospinal fluid (CSF), heart valves, and the vitreal body. 5-FC penetrates well into most body sites because it is small, highly water-soluble, and not bound by serum proteins to any great extent. One explanation for the synergy detected with the combination of amphotericin B plus 5-FC is that the membranepermeabilizing effects of low concentrations of amphotericin B facilitate penetration of 5-FC to the cell interior. 5-FC is only available as an oral formulation in the United States, and the dosage is 150 mg/kg/day in 4 divided doses.

5-FC can exacerbate myelosuppression in patients with neutropenia, and toxic levels can develop when used in combination with amphotericin B, owing to nephrotoxicity of the amphotericin B and decreased renal clearance of 5-FC. Routine serum 5-FC level monitoring is warranted in high-risk patients, and levels should be obtained after 3-5 days of therapy, with a goal to achieve a 2-hr post-dose peak <100 µg/mL (and ideally 30-80 µg/mL). Levels >100 µg/mL are associated with bone marrow aplasia. Toxicities can include azotemia, renal tubular acidosis, leukopenia, thrombocytopenia, and others and appear in approximately 50% of patients in the 1st 2 wk of therapy.

Nearly all clinical studies involving 5-FC are combination antifungal protocols for cryptococcal meningitis, owing to the inherently rather weak antifungal activity of 5-FC monotherapy. The use of 5-FC for *Candida* meningitis in premature neonates is discouraged. A study evaluating risk factors and mortality rates of neonatal candidiasis among extremely premature infants showed that infants with *Candida* meningitis who received amphotericin B in combination with 5-FC had a prolonged time to sterilization of the CSF compared to infants receiving amphotericin B monotherapy.

Azoles

The azole antifungals inhibit the fungal cytochrome $P450_{14DM}$ (also known as lanosterol 14α-demethylase), which catalyzes a late step in fungal cell membrane ergosterol biosynthesis. Of the older 1st-generation, itraconazole has activity against *Aspergillus* but fluconazole is ineffective against *Aspergillus* and other molds. Second-generation triazoles (voriconazole, posaconazole, and isavuconazole) have an expanded antifungal spectrum of activity, including activity against molds, and generally greater *in vitro* antifungal activity.

Fluconazole

Fluconazole is fungistatic, and this activity is not influenced by concentration once the maximal fungistatic concentration is surpassed (concentration independent), in contrast to the concentration-dependent fungicidal activity of amphotericin B. Fluconazole is available as either an oral or intravenous form, and oral administration has a bioavailability of approximately 90% relative to intravenous administration. Fluconazole passes into tissues and fluids very rapidly, probably due to its relatively low lipophilicity and limited degree of binding to plasma proteins. Concentrations of fluconazole are 10-20–fold higher in the urine than blood, making it an ideal agent for treating fungal urinary tract infections. Concentrations in the CSF and vitreous humor of the eye are approximately 80% of those found simultaneously in blood.

Simple conversion of the corresponding adult dosage of fluconazole on a weight basis is inappropriate for pediatric patients. Fluconazole clearance is generally more rapid in children than adults, with a mean plasma half-life of approximately 20 hr in children and approximately 30 hr in adult patients. Therefore, to achieve comparable exposure in pediatric patients, the daily fluconazole dosage needs to be essentially doubled. Correct pediatric fluconazole dosages should be proportionately higher than adult dosages, generally 12 mg/kg/day. In neonates the volume of distribution is significantly greater and more variable than in infants and children, and doubling the dosage for neonatal patients is necessary to achieve comparable plasma concentrations. The increased volume of distribution is thought to be due to the larger amount of body water found in the total body volume of neonates. A pharmacokinetic study in premature infants suggests that maintenance fluconazole dosages of 12 mg/kg/day are necessary to achieve exposures similar to those in older children and adults. In addition, a loading dose of 25 mg/kg in neonates has achieved steady-state concentrations sooner. While this fluconazole loading dose has been studied in adult and neonatal patients, this approach has never been formally studied in children. Side effects of fluconazole are uncommon but generally include gastrointestinal upset (vomiting, diarrhea, nausea) and skin rash.

Fluconazole plays an important role in the treatment of invasive candidiasis. Consensus guidelines suggest that use of the fungistatic fluconazole for invasive candidiasis is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species. Although most isolates of *Candida albicans* remain susceptible to fluconazole, for certain *Candida* species fluconazole is not an ideal agent: *C. krusei* is generally resistant and *C. glabrata* is often resistant. In treating infection caused by these *Candida* species, it is critical to treat with an echinocandin or amphotericin B rather than fluconazole. There is no confirmed role for combination antifungal therapy with fluconazole and another antifungal against invasive candidiasis.

Prophylaxis with fluconazole to prevent neonatal candidiasis remains a controversial topic. In the 1st prospective, randomized double-blind trial of 100 infants with birthweights <1,000 g, infants who received fluconazole for 6 wk had a decrease in fungal colonization and a decrease in the development of invasive fungal infection (0% vs. 20%) compared to placebo. Other studies have yielded similarly encouraging results and have demonstrated that use of fluconazole prophylaxis for 4-6 wk in high-risk infants does not increase the incidence of fungal colonization and infections caused by natively fluconazole-resistant *Candida* species. A more recent large trial studied fluconazole prophylaxis in extremely low birthweight infants in nurseries with a lower incidence of candidiasis and found that fluconazole prophylaxis led to a decreased incidence of candidiasis but had no effect on mortality. The universal implementation of such a strategy across nurseries is discouraged, because the rate of *Candida* infections varies greatly among centers. Consensus guidelines now recommend fluconazole prophylaxis only in centers with high rates (>10%) of neonatal candidiasis.

Itraconazole

Compared to fluconazole, itraconazole has the benefit of antifungal activity against *Aspergillus* species but comes with several practical constraints, such as erratic oral absorption in high-risk patients and significant drug interactions. These pharmacokinetic concerns have been addressed with both an intravenous formulation (now no longer available) and a better-absorbed oral solution to replace the unpredictable capsules used earlier. Itraconazole has a high volume of distribution and accumulates in tissues, and tissue-bound levels are probably more clinically relevant to infection treatment than serum levels. Dissolution and absorption of itraconazole are affected by gastric pH. Patients with achlorhydria or taking H_2 -receptor antagonists might demonstrate impaired absorption, and co-administration of the capsule with acidic beverages such as colas or cranberry juice can enhance absorption. Administration with food significantly increases the absorption of the capsule formulation, but the oral suspension with a cyclodextrin base is better absorbed on an empty stomach.

Side effects are relatively few and include nausea and vomiting (10%), elevated transaminases (5%), and peripheral edema. There have been reports in adults of development of cardiomyopathy. Because of important drug interactions, prior or concurrent use of rifampin, phenytoin, carbamazepine, and phenobarbital should be avoided.

Itraconazole has a role in treating less-serious infections with endemic mycoses (histoplasmosis, coccidioidomycosis, and blastomycosis), as well as use in prophylaxis against invasive fungal infections in high-risk patients. The plethora of drug interactions make itraconazole a concern in complex patients receiving other medications. As with most azole antifungals, monitoring itraconazole serum levels is a key principle in management (generally itraconazole trough levels should be >0.5-1 µg/mL; trough levels >5 µg/mL may be associated with increased toxicity). Concentrations should be checked after 1-2 wk of therapy to ensure adequate drug exposure. When measured by high-pressure liquid chromatography, both itraconazole and its bioactive hydroxy-itraconazole metabolite are reported, the sum of which should be considered in assessing drug levels. Itraconazole is no longer recommended for primary therapy of invasive aspergillosis.

Voriconazole

Voriconazole is a 2nd-generation triazole and a synthetic derivative of fluconazole. Voriconazole generally has the spectrum of activity of itraconazole and the high bioavailability of fluconazole. Importantly, it is fungicidal against *Aspergillus* and fungistatic against *Candida* . It is extensively metabolized by the liver and has approximately 90% oral bioavailability. The cytochrome P-450 2C19 (CYP2C19) enzyme appears to play a major role in the metabolism of voriconazole, and polymorphisms in CYP2C19 are associated with slow voriconazole metabolism. As many as 20% of non-Indian Asians have low CYP2C19 activity and develop voriconazole levels as much as 4-fold higher than those in homozygous subjects, leading to potentially increased toxicity.

Voriconazole is available as an oral tablet, an oral suspension, and an intravenous solution. In adults, voriconazole exhibits nonlinear pharmacokinetics, has a variable half-life of approximately 6 hr with large interpatient variation in blood levels, and achieves good CSF penetration. In contrast to the situation in adults, elimination of voriconazole is linear in children. A multicenter safety, population pharmacokinetic study of intravenous voriconazole dosages in immunocompromised pediatric patients showed that body weight was more influential than age in accounting for the observed variability in voriconazole pharmacokinetics, and voriconazole needs to be dosed higher in pediatric patients than adult patients. Adult patients load with 6 mg/kg/dose and then transition to a maintenance dosage of 4 mg/kg/dose, but children should begin and continue with 9 mg/kg/dose intravenously (see Table 260.1) and continue maintenance dosing at 8 mg/kg/dose. This need for an increased dosage in treating children is crucial to understand and is mandated by the fundamentally different pharmacokinetics of this drug in pediatric patients. Obtaining voriconazole serum levels (to achieve ≥1-2 µg/mL) is critical for therapeutic success. Oral voriconazole is best absorbed on an empty stomach. Generally a trough level greater than the minimum inhibitory concentration (MIC) of the infecting organism is preferred, and very high voriconazole levels have been associated with toxicity (generally >6 µg/mL). However, many studies have shown an inconsistent relationship between dosing and levels, highlighting the need for close monitoring after the initial dosing scheme and then dose adjustment as needed in the individual patient. The main side effects of voriconazole include reversible dosage-dependent visual disturbances (increased brightness, blurred vision) in as many as one-third of treated patients, elevated hepatic transaminases with increasing dosages, and occasional skin reactions likely caused by photosensitization. In some rare long-term (mean of 3 yr of therapy) cases, this voriconazole phototoxicity has developed into cutaneous squamous cell carcinoma. Discontinuing voriconazole is recommended in patients experiencing chronic phototoxicity.

The largest prospective clinical trial of voriconazole as primary therapy for invasive aspergillosis compared initial randomized therapy with voriconazole versus amphotericin B and demonstrated improved response and survival with voriconazole over amphotericin B. *Voriconazole is guideline-recommended as the preferred primary therapy against invasive aspergillosis.* Voriconazole also has a role in treating candidiasis, but its fungistatic nature makes it often less than ideal for treating critically ill or neutropenic patients where the fungicidal echinocandin antifungals are preferred.

Posaconazole

Posaconazole is a 2nd-generation triazole that is a derivative of itraconazole and is currently available as an oral suspension, an intravenous formulation, and an extended release tablet. The antimicrobial spectrum of posaconazole is similar to that of voriconazole; however, the former is active against *Zygomycetes* such as mucormycosis, and voriconazole is not active against these particular mold infections.

Effective absorption of the oral suspension strongly requires taking the medication with food, ideally a high-fat meal; taking posaconazole on an empty stomach will result in approximately one-fourth of the absorption as in the fed state, emphasizing the importance of diet to increase serum levels of oral suspension posaconazole (the opposite of voriconazole). Posaconazole exposure is maximized with acidic beverages, administration in divided doses, and the absence of proton pump inhibitors. The tablet formulation has better absorption due to its delayed release in the small intestine, but absorption will still be slightly increased with food. If the patient can take the large tablets, the extended-release tablet is the preferred form due to the ability to easily obtain higher and more consistent drug levels. Due to the low pH (<5) of IV posaconazole, a central venous catheter is required for administration. The IV formulation contains only slightly lower amounts of the cyclodextrin vehicle than voriconazole, so similar theoretical renal accumulation concerns exist. Posaconazole causes transient hepatic reactions, including mild to moderate elevations in liver transaminases, alkaline phosphatase, and total bilirubin.

The correct pediatric dosage of posaconazole is not known, because initial studies are still ongoing. In adult patients, dosages >800 mg/day do not result in increased serum levels, and division of daily dosing into 3 or 4 doses/day results in greater serum levels than a once- or twice-daily dosing scheme when using the oral suspension. Similar to itraconazole and voriconazole, posaconazole should be monitored with trough levels (to achieve ≥0.7 µg/mL).

In an international randomized, single-blinded study of posaconazole versus fluconazole or itraconazole in neutropenic patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, posaconazole was superior in preventing invasive fungal infections. Fewer patients in the posaconazole group had invasive aspergillosis, and survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole. Another multisite international randomized, double-blinded study in patients with allogeneic hematopoietic stem-cell transplantation and graft versus host disease showed that posaconazole was not inferior to fluconazole in the prevention of invasive fungal infections. *Posaconazole is approved for prophylaxis against invasive fungal infections but has shown great efficacy in clinical experience with recalcitrant mold infections.*

In patients with chronic granulomatous disease (CGD) and proven invasive fungal infection refractory to standard therapy, posaconazole was proved to be well tolerated and quite effective. This agent might prove to be very useful in this patient population where long-term therapy with an oral agent is required.

Isavuconazole

Isavuconazole is triazole that was FDA approved in March 2015 for treatment of invasive aspergillosis and invasive mucormycosis with oral (capsules only) and IV formulations. Isavuconazole has a similar antifungal spectrum as voriconazole and some activity against *Zygomycetes* (yet potentially not as potent against *Zygomycetes* as posaconazole). A phase 3 clinical trial in adult patients demonstrated non-inferiority versus voriconazole against invasive aspergillosis and other mold infections, while another study showed good clinical activity against mucormycosis. Isavuconazole is dispensed as the prodrug isavuconazonium sulfate. Dosing in adult patients is loading with isavuconazole 200 mg (equivalent to 372-mg isavuconazonium sulfate) every 8 hr for 2 days (6 doses), followed by 200 mg once daily for maintenance dosing. The half-life is long (>5 days), there is 98% bioavailability in adults, and there is no reported food effect with oral isavuconazole. Unlike voriconazole, the IV formulation does not contain the vehicle cyclodextrin, possibly making it more attractive in patients with renal failure. Early experience suggests a much lower rate of photosensitivity and skin disorders as well as visual disturbances compared with voriconazole. No specific pediatric dosing data exist for isavuconazole, yet pediatric pharmacokinetic trials are beginning.

Echinocandins

The echinocandins are a class of antifungals that interfere with cell wall biosynthesis by noncompetitive inhibition of 1,3-β-D -glucan synthase, an enzyme present in fungi but absent in mammalian cells. 1,3-β-glucan is an essential cell wall polysaccharide and provides structural integrity for the fungal cell wall. Echinocandins are generally fungicidal in vitro against *Candida* species, although not as rapidly as amphotericin B, and are fungistatic against *Aspergillus.* As a class these agents are not metabolized through the CYP enzyme system, lessening some of the drug interactions and side effects seen with the azole class. The echinocandins appear to have a prolonged and dosage-dependent fungicidal antifungal effect on *C. albicans*, compared to the fungistatic fluconazole. Three compounds in this class (caspofungin, micafungin, and anidulafungin) are FDA approved for use. Owing to the large size of the molecules, the current echinocandins are only available in an intravenous formulation. Because 1,3-β-glucan is a selective target present only in fungal cell walls and not in mammalian cells, drug-related toxicity is minimal, with no apparent myelotoxicity or nephrotoxicity with the agents. *The echinocandins are the preferred primary therapy for invasive candidiasis.*

Caspofungin

At present there is no known maximum tolerated dosage and no toxicity-determined maximum length of therapy for caspofungin. The usual course is to begin with a loading dose followed by a lesser daily maintenance dosage, which is 70 mg followed by 50 mg daily in adult patients. Much of the dosage accumulation is achieved in the 1st wk of dosing, and renal insufficiency has little effect on the pharmacokinetics of caspofungin. Caspofungin has been evaluated at double the recommended dosage (100 mg/day in adults) with no adverse effects, and it is unclear if higher dosage of this relatively safe agent results in greater clinical efficacy.

Pharmacokinetics are slightly different in children, with caspofungin levels lower in smaller children and with a reduced half-life. A study evaluated the pharmacokinetics of caspofungin in children with neutropenia and showed that in patients receiving 50 mg/m^2 /day (maximum, 70 mg/day), the levels were similar to those in adults receiving 50 mg/day and were consistent across age ranges. In this study, weight-based dosing (1 mg/kg/day) was suboptimal when compared to body surface area regimens, so caspofungin should be appropriately dosed in children as a loading dose of 70 mg/m^2 /day, followed by daily maintenance dosing of 50 mg/m^2 /day.

Caspofungin was approved for refractory aspergillosis or intolerance to other therapies and for candidemia and various other sites of invasive *Candida* infections. In the pivotal clinical study, patients with acute invasive aspergillosis underwent salvage therapy after failing primary therapy, and recipients had a 41% favorable response with caspofungin. In a multicenter trial of patients with invasive candidiasis, 73% of patients who received caspofungin had a favorable response at the end of therapy, compared to 62% in the amphotericin B group. Importantly, caspofungin treatment performed equally well to amphotericin B treatment for all the major *Candida* species, but other studies have shown that some infections with *C. parapsilosis* do not potentially clear as effectively with an echinocandin. Caspofungin was also evaluated against L-amphotericin B in the empirical treatment of patients with persistent fever and neutropenia and was not inferior to liposomal amphotericin B in >1,000 patients.

Caspofungin in children has been reported to be safe. Caspofungin pharmacokinetics were evaluated in older infants and toddlers at 50 mg/m^2 /day and found to be similar to adults receiving the standard 50 mg daily dose. Caspofungin in newborns has been used as single or adjuvant therapy for refractory cases of disseminated candidiasis. Neonates with invasive candidiasis are at high risk for central nervous system involvement; it is not known if the dosages of caspofungin studied provide sufficient exposure to penetrate the central nervous system at levels necessary to cure infection. Therefore, caspofungin is not recommended as monotherapy in neonatal candidiasis.

Micafungin

The pharmacokinetics of micafungin have been evaluated in children and young infants. An inverse relation between age and clearance was observed, where mean systemic clearance was significantly greater and mean half-life was significantly shorter in patients 2-8 yr of age compared to patients 9-17 yr of age. Therefore, dosing of micafungin in children is age-related and needs to be higher in children <8 yr old. To achieve micafungin exposures equivalent to exposures in adults receiving 100, 150, and 200 mg daily, as evidenced by simulation profiles, children require dosages >3 mg/kg.

Several pharmacokinetic studies of micafungin in term and preterm infants have shown that micafungin in infants has a shorter half-life and a more rapid rate of clearance compared with published data in older children and adults. These results suggest that young infants should receive 10 mg/kg daily of micafungin if used to treat invasive candidiasis.

The safety profile of micafungin is optimal when compared to other antifungal agents. Clinical trials including those of micafungin used for treatment of localized and invasive candidiasis as well as prophylaxis studies in patients following stem cell transplantation have demonstrated fewer adverse events compared to liposomal amphotericin B and fluconazole. The most common adverse events experienced by these patients are related to the gastrointestinal tract (nausea, diarrhea). Hypersensitivity reactions associated with micafungin have been reported, and liver enzymes are elevated in 5% of patients receiving this agent. Hyperbilirubinemia, renal impairment, and hemolytic anemia related to micafungin use have also been identified in postmarketing surveillance of the drug.

An open-label, noncomparative, multinational study in adult and pediatric patients with a variety of diagnoses evaluated the use of micafungin monotherapy and combination therapy in 225 patients with invasive aspergillosis. Of those only treated with micafungin, favorable responses were seen in 50% of the primary and 41% of the salvage therapy group.

Micafungin at dosages of 100 and 150 mg daily was also noninferior to caspofungin in an international, randomized, double-blinded study of adults with candidemia or invasive candidiasis and was found to be superior to fluconazole in the prevention of invasive fungal infections in a randomized study of adults undergoing hematopoietic stem cell transplantation.

Of the 3 drugs within the echinocandin class, micafungin has been the one most extensively studied in children, including several pharmacokinetic studies in neonates. A pediatric substudy as part of a double-blind, randomized, multinational trial comparing micafungin (2 mg/kg/day) with liposomal amphotericin B (3 mg/kg/day) as 1st-line treatment for invasive candidiasis showed similar success for micafungin and liposomal amphotericin B. In general, micafungin was better tolerated than liposomal amphotericin B as evidenced by fewer adverse events leading to discontinuation of therapy.

Anidulafungin

Anidulafungin has the longest half-life of all the echinocandins (approximately 18 hr). In a study of 25 neutropenic children receiving anidulafungin as empirical therapy, 4 patients in the group receiving 0.75 mg/kg/day experienced adverse events such as facial erythema and rash, elevation in serum blood urea nitrogen, and fever and hypotension. In a pharmacokinetic study in neonates and young infants, anidulafungin exposures comparable to adults were achieved with doses of 1.5 mg/kg/day (3 mg/kg loading dose). One infant in this cohort supported by extracorporeal membrane oxygenation achieved the lowest exposure, which suggests that dose adjustments are required in this population.

A randomized, double-blind study in adult patients without neutropenia with invasive candidiasis showed that anidulafungin was not inferior to fluconazole in the treatment of invasive candidiasis. In this study, the incidence and types of adverse events were similar in the 2 groups, and all-cause mortality was 31% in the fluconazole group and 23% in the anidulafungin group. No clinical studies of anidulafungin in pediatric patients are currently available.

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CHAPTER 261

Candida

Jessica E. Ericson, Daniel K. Benjamin Jr.

Candidiasis encompasses many clinical syndromes that may be caused by several species of *Candida* . Invasive candidiasis (*Candida* infections of the blood and other sterile body fluids) is a leading cause of infection-related mortality in hospitalized immunocompromised patients.

Candida exists in 3 morphologic forms: oval to round **blastospores or yeast cells** (3-6 mm in diameter); double-walled **chlamydospores** (7-17 mm in diameter), which are usually at the terminal end of a pseudohypha; and **pseudomycelium,** which is a mass of pseudohyphae and represents the tissue phase of *Candida.* **Pseudohyphae** are filamentous processes that elongate from the yeast cell without the cytoplasmic connection of a true hypha. *Candida* grows aerobically on routine laboratory media but can require several days of incubation for visible growth.

Candida albicans accounts for most human infections, but *Candida parapsilosis, Candida tropicalis, Candida krusei, Candida lusitaniae, Candida glabrata,* and several other species are commonly isolated from hospitalized children. Species identification and susceptibility testing are important owing to increasing frequency of fluconazole resistance and increasing prevalence of non-albicans *Candida* species. *Candida auris* is an emerging multi-resistant invasive pathogen that has a global presence and affects immunocompromised patients; nosocomial spread has been reported.

Treatment of invasive *Candida* infections is complicated by the emergence of non-*albicans* strains. Amphotericin B deoxycholate is inactive against approximately 20% of strains of *C. lusitaniae.* Fluconazole is useful for many *Candida* infections but is inactive against all strains of *C. krusei* and 5–25% of strains of *C. glabrata.* Susceptibility testing of these clinical isolates is recommended.

261.1

Neonatal Infections

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Keywords

dermatitis
yeast
Candida
fungemia
candidiasis
prophylaxis
amphotericin
fluconazole

Candida is a common cause of oral mucous membrane infections **(thrush)** and perineal skin infections **(*Candida* diaper dermatitis)** in young infants. Rare presentations include **congenital cutaneous candidiasis,** caused by an ascending infection into the uterus during gestation, and **invasive fungal dermatitis,** a postnatal skin infection resulting in positive blood cultures. Invasive candidiasis is a common infectious complication in the neonatal intensive care unit (NICU) because of improved survival of extremely preterm infants.

Epidemiology

Candida species are the third most common cause of bloodstream infection in premature infants. The cumulative incidence is <0.3% among infants >2,500 g birthweight admitted to the NICU. The cumulative incidence increases to 8% for infants <750 g birthweight. In addition, the incidence varies greatly by individual NICU. Among centers in the National Institutes of Health-sponsored Neonatal Research Network, the cumulative incidence of candidiasis among infants <1,000 g birthweight ranges from 2% to 28%. Colonization is associated with a significantly increased risk of future invasive *Candida* infection. Up to 10% of full-term infants are colonized as the result of vertical transmission from the mother at birth, with slightly higher rates of colonization in premature infants. Colonization rates increase to >50% among infants admitted to the NICU by 1 mo of age. Histamine-2 blockers, corticosteroids, and broad-spectrum antibiotics facilitate *Candida* colonization and overgrowth.

Significant risk factors for neonatal invasive candidiasis include prematurity, low birthweight, exposure to broad-spectrum antibiotics, abdominal surgery, endotracheal intubation, and presence of a central venous catheter.

Pathogenesis

Immunologic immaturity along with an underdeveloped layer of skin, need for invasive measures (endotracheal tubes, central venous catheters), and exposure to broad-spectrum antibiotics places preterm infants at great risk for invasive candidiasis. Premature infants are also at high risk for spontaneous intestinal perforations and necrotizing enterocolitis. Both conditions require abdominal surgery, prolonged exposure to broad-spectrum antibiotics, and total parenteral nutrition administration requiring placement of central venous catheters. Each of these factors increases the risk of invasive candidiasis by decreasing the physiologic barriers that protect against invasive infection.

Clinical Manifestations

The manifestations of neonatal candidiasis vary in severity from oral thrush and *Candida* diaper dermatitis (see Chapter 261.2) to invasive candidiasis that can manifest with overwhelming sepsis (see Chapter 261.3). Signs of invasive candidiasis among premature infants are often nonspecific and include temperature instability, lethargy, apnea, hypotension, respiratory distress, abdominal distention, and thrombocytopenia.

Central nervous system involvement is common and is most accurately described as meningoencephalitis. *Candida* infections involving the central nervous system often result in abscesses, leading to unremarkable cerebrospinal fluid parameters (white blood cell count, glucose, protein) even though central nervous system infection is present. Endophthalmitis is an uncommon complication affecting <5% of infants with invasive candidiasis. In addition, candidemia is associated with an increased risk of severe retinopathy of prematurity. Renal involvement commonly complicates neonatal invasive candidiasis. Renal involvement may be limited to candiduria or can manifest with diffuse infiltration of *Candida* throughout the renal parenchyma or the presence of *Candida* and debris within the collecting system. Due to the poor sensitivity of blood cultures for *Candida* , candiduria should be considered a surrogate marker of candidemia in premature infants. Other affected organs include the heart, bones, joints, liver, and spleen.

Diagnosis

Mucocutaneous infections are most often diagnosed by direct clinical exam. Scrapings of skin lesions may be examined with a microscope after Gram staining or suspension in KOH. Definitive diagnosis of invasive disease requires histologic demonstration of the fungus in tissue specimens or recovery of the fungus from normally sterile body fluids. Hematologic parameters are sensitive but not specific. Thrombocytopenia occurs in more than 80% of premature infants with invasive candidiasis, but also occurs in 75% of premature infants with Gram-negative bacterial sepsis and nearly 50% of infants with Gram-positive bacterial sepsis. Blood cultures have very low sensitivity for invasive candidiasis. In a study of autopsy-proven candidiasis in adult patients, the sensitivity of multiple blood cultures for detecting single-organ disease was 28%. Blood culture volumes in infants are often only 0.5-1 mL, making the sensitivity in this population almost certainly lower. Blood culture volume should be maximized as much as possible to increase sensitivity. Fungal-specific media can improve sensitivity when *Candida* is present as a coinfection with bacteria and can also decrease the time to positivity, leading to more rapid diagnosis.

Further assessment of infants in the presence of documented candidemia should include ultrasound or computerized tomography of the head to evaluate for abscesses; ultrasound of the liver, kidney, and spleen; cardiac echocardiography; ophthalmologic exam; lumbar puncture; and urine culture. These tests are necessary to determine if more than 1 body system is infected, which is commonly the case.

Prophylaxis

NICUs with a high incidence of invasive candidiasis should consider prophylaxis with fluconazole in infants <1,000 g birthweight as a cost-effective method of reducing invasive candidiasis. Twice-weekly fluconazole at 3 or 6 mg/kg/dose decreases rates of both colonization with *Candida* species and invasive fungal infections. Use of this dosing strategy has not been shown to increase the frequency of infections caused by fluconazole-resistant strains, but use of an alternative antifungal class for cases of breakthrough infection is suggested.

Treatment

In the absence of systemic manifestations, topical antifungal therapy is the treatment of choice for congenital cutaneous candidiasis in full-term infants. Congenital cutaneous candidiasis in preterm infants can progress to systemic disease, and therefore systemic therapy is warranted.

Every attempt should be made to remove or replace central venous catheters once the diagnosis of candidemia is confirmed. Delayed removal has been consistently associated with increased mortality and morbidity, including poor neurodevelopmental outcomes.

Although no well-powered randomized, controlled trials exist to guide length and type of therapy, 21 days of systemic antifungal therapy from the last positive *Candida* culture is recommended in infants. Antifungal therapy should be targeted based on susceptibility testing. Amphotericin B deoxycholate has been the mainstay of therapy for systemic candidiasis and is active against both yeast and mycelial forms. Nephrotoxicity, hypokalemia, and hypomagnesemia are common, but amphotericin B deoxycholate is better tolerated in infants than in adult patients. *C. lusitaniae* , an uncommon pathogen in infants, is often resistant to amphotericin B deoxycholate. Liposomal amphotericin is associated with worse outcomes in infants and should be used only when urinary tract involvement can reliably be excluded. Fluconazole is often used instead of amphotericin B deoxycholate for treatment of invasive neonatal *Candida* infections because of its effectiveness and low incidence of side effects. It is particularly useful for urinary tract infections, obtaining high concentrations in the urine. A loading dose should be given to obtain therapeutic serum concentrations in a timely manner. Fluconazole is inactive against all strains of

C. krusei and some isolates of *C. glabrata.* Additionally, in centers where fluconazole prophylaxis is used, another agent, such as amphotericin B deoxycholate, should be used for treatment. The echinocandins have excellent activity against most *Candida* species and have been used successfully in patients with resistant organisms or in whom other therapies have failed. Several studies have described the pharmacokinetics of antifungals in infants (Table 261.1).

Table 261.1

Dosing of Antifungal Agents in Infants[*] and Number of Infants Younger Than 1 Yr of Age Studied With Reported Pharmacokinetic Parameters

DRUG	INFANTS STUDIED	SUGGESTED DOSE
Amphotericin B deoxycholate	27	1 mg/kg/day
Amphotericin B lipid complex	28	5 mg/kg/day
Liposomal amphotericin B	17	5 mg/kg/day
Amphotericin B colloidal dispersion	0	5 mg/kg/day
Fluconazole [†]	65	12 mg/kg/day
Micafungin [‡]	138	10 mg/kg/day
Caspofungin [§]	22	50 mg/m^2 /day
Anidulafungin [‡]	15	1.5 mg/kg/day

[*] Voriconazole dosing has not been investigated in the nursery.

[†] A loading dose of 25 mg/kg of fluconazole is necessary to achieve therapeutic serum concentrations in the early days of therapy.

[‡] Micafungin has been studied in infants <120 days of life at this dosage.

[§] Caspofungin and anidulafungin should generally be avoided because dosing sufficient to penetrate brain tissue has not been studied.

Prognosis

Mortality following invasive candidiasis in premature infants has been consistently reported to be around 20% in large studies but can be as high as 50% in infants <1,500 g birthweight. Candidiasis is also associated with poor neurodevelopmental outcomes, chronic lung disease, and severe retinopathy of prematurity.

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261.2

Infections in Immunocompetent Children and Adolescents

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Keywords

Candida
yeast
thrush
dermatitis
vaginitis

Oral Candidiasis

Oral thrush is a superficial mucous membrane infection that affects approximately 2–5% of normal neonates. *C. albicans* is the most commonly isolated species. Oral thrush can develop as early as 7-10 days of age. The use of antibiotics, especially in the 1st yr of life, can lead to recurrent or persistent thrush. It is characterized by pearly white, curdish material visible on the tongue, palate, and buccal mucosa. Oral thrush may be asymptomatic or can cause pain, fussiness, and decreased feeding, leading to inadequate nutritional intake and dehydration. It is uncommon after 1 yr of age but can occur in older children treated with antibiotics. Persistent or recurrent thrush with no obvious predisposing reason, such as recent antibiotic treatment, warrants investigation of an underlying immunodeficiency, especially vertically transmitted HIV infection or a primary congenital immune defect.

Treatment of mild cases might not be necessary. When treatment is warranted, the most commonly prescribed antifungal agent is topical nystatin. For recalcitrant or recurrent infections, a single dose of fluconazole may be useful. In breastfed infants, simultaneous treatment of infant and mother with topical nystatin or oral fluconazole may be indicated.

Diaper Dermatitis

Diaper dermatitis is the most common infection caused by *Candida* (see Chapter 686) and is characterized by a confluent erythematous rash with satellite pustules. *Candida* diaper dermatitis often complicates other noninfectious diaper dermatitides and often occurs following a course of oral antibiotics.

A common practice is to presumptively treat any diaper rash that has been present for longer than 3 days with topical antifungal therapy such as nystatin, clotrimazole, or miconazole. If significant inflammation is present, the addition of hydrocortisone 1% may be useful for the 1st 1-2 days, but topical corticosteroids should be used cautiously in infants because the relatively potent topical corticosteroid can lead to adverse effects. Frequent diaper changes and short periods without diapers are important adjunctive treatments.

Ungual and Periungual Infections

Paronychia and onychomycosis may be caused by *Candida,* although *Trichophyton* and *Epidermophyton* are more common causes (see Chapter 686). *Candida* onychomycosis differs from tinea infections by its propensity to involve the fingernails and not the toenails, and by the associated paronychia. *Candida* paronychia often responds to treatment consisting of keeping the hands dry and using a topical antifungal agent. Psoriasis and immune dysfunction, including HIV and primary immunodeficiencies, predispose to *Candida* ungual infections. Ungual infections often require systemic antifungal therapy. Once-weekly fluconazole for 4-12 mo is an effective treatment strategy with fairly low toxicity.

Vulvovaginitis

Vulvovaginitis is a common *Candida* infection of pubertal and postpubertal female patients (see Chapter 564). Predisposing factors include pregnancy, use of oral contraceptives, and use of oral antibiotics. Prepubertal girls with *Candida* vulvovaginitis usually have a predisposing factor such as diabetes mellitus or prolonged antibiotic treatment. Clinical manifestations can include pain or itching, dysuria, vulvar or vaginal erythema, and an opaque white or cheesy exudate. More than 80% of cases are caused by *C. albicans.*

Candida vulvovaginitis can be effectively treated with either vaginal creams or troches of nystatin, clotrimazole, or miconazole. Oral therapy with a single dose of fluconazole is also effective.

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261.3

Infections in Immunocompromised Children and Adolescents

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Keywords

yeast
Candida
esophagitis
thrush
candidiasis
fungemia

Etiology

Candida albicans is the most common cause of invasive candidiasis among immunocompromised pediatric patients and is associated with higher rates of mortality and end-organ involvement than are non-*albicans* species.

Clinical Manifestations

HIV-Infected Children

Oral thrush and diaper dermatitis are the most common *Candida* infections in HIV-infected children. Besides oral thrush, 3 other types of oral *Candida* infections can occur in HIV-infected children: atrophic candidiasis, which manifests as a fiery erythema of the mucosa or loss of papillae of the tongue; chronic hyperplastic candidiasis, which presents with oral symmetric white plaques; and angular cheilitis, in which there is erythema and fissuring of the angles of the mouth. Topical antifungal therapy may be effective, but systemic treatment with fluconazole or itraconazole is usually necessary. Symptoms of dysphagia or poor oral intake can indicate progression to *Candida* esophagitis, requiring systemic antifungal therapy. In HIV patients, esophagitis can also be caused by cytomegalovirus, herpes simplex virus, reflux, or lymphoma; *Candida* is the most common cause, and *Candida* esophagitis can occur in the absence of thrush.

Candida dermatitis and onychomycosis are more common in HIV-infected children. These infections are generally more severe than they are in immunocompetent children and can require systemic antifungal therapy.

Cancer and Transplant Patients

Fungal infections, especially *Candida* and *Aspergillus* infections, are a significant problem in oncology patients with chemotherapy-associated neutropenia (see Chapter 205). Greater than 5 days of fever during a neutropenic episode is associated with presence of an invasive fungal infection. Accordingly, empirical antifungal therapy should be started if fever and neutropenia persist for 5 or more days. An echinocandin should be used until sensitivity testing results are available. High-risk oncology patients warrant prophylaxis against invasive *Candida* infection. Both fluconazole and echinocandins are used for this indication, typically at lower doses than those used for treatment. If an echinocandin is used for prophylaxis, liposomal amphotericin B should be used if empirical treatment becomes warranted.

Bone marrow transplant recipients have a much higher risk of fungal infections because of the dramatically prolonged duration of neutropenia. Voriconazole prophylaxis decreases the incidence of candidemia in bone marrow transplant recipients with the additional benefit over fluconazole of mold prophylaxis. The use of granulocyte colony-stimulating factor reduces the duration of neutropenia after chemotherapy and is associated with decreased risk for candidemia. When *Candida* infection occurs in this population, the lung, spleen, kidney, and liver are involved in more than 50% of cases.

Solid-organ transplant recipients are also at increased risk for superficial and invasive *Candida* infections. Studies in liver transplant recipients demonstrate the utility of antifungal prophylaxis with amphotericin B deoxycholate, fluconazole, voriconazole, or caspofungin in high-risk patients (those with prolonged surgical time, comorbidities, recent antibiotic exposure, or bile leak).

Catheter-Associated Infections

Central venous catheter infections occur most often in oncology patients but can affect any patient with a central catheter (see Chapter 206). Neutropenia, use of broad-spectrum antibiotics, and parenteral alimentation are associated with increased risk for *Candida* central catheter infection. Treatment typically requires removing or replacing the catheter followed by a 2-3–wk course of systemic antifungal therapy. Removal of the central catheter in place at time of positive blood culture and use of a peripheral IV or enteral support for at least 48 hr prior to obtaining central access is advocated. Removal of the original catheter followed by immediate replacement with a new central catheter in a different anatomic location is acceptable if an interval without central access is not feasible. Delays in catheter removal are associated with increased risks of metastatic complications and death.

Diagnosis

The diagnosis is often presumptive in neutropenic patients with prolonged fever because positive blood cultures for *Candida* occur only in a minority of patients who are later found to have disseminated infection. If isolated, *Candida* grows readily on routine blood culture media, with ≥90% of positive cultures identified within 72 hr. CT may demonstrate findings consistent with invasive fungal infection but also is limited by nonspecific findings and false negatives. The role of screening by CT scan has not been well defined. In high-risk patients, serial serum assays for (1,3)-β-D -glucan, a polysaccharide component of the fungal cell wall, may contribute to the diagnosis of invasive Candida infection. However, this test is not sensitive or specific enough to be used without a careful assessment of the limitations of the assay.

Treatment

Echinocandins are favored as empirical therapy for moderately or severely ill children and for those with neutropenia; fluconazole is acceptable for those who are infected with a susceptible organism and are less critically ill; amphotericin B products are also acceptable. Definitive antifungal selection should be made based on susceptibility testing results. Fluconazole is not effective against *C. krusei* and some isolates of *C. glabrata*. *C. parapsilosis* has occasional resistance to the echinocandins, but the overall rate is still low. Amphotericin B deoxycholate is inactive against approximately 20% of the strains of *C. lusitaniae,* and therefore susceptibility testing should be performed for all strains (Table 261.2). *C. auris* , a species first identified in 2009 that has caused nosocomial infections worldwide, is resistant to most antifungals. An echinocandin should be used until sensitivity results are available.

Table 261.2

Dosing of Antifungal Agents in Children Older Than 1 Yr of Age for Treatment of Invasive Disease

DRUG	SUGGESTED DOSAGE
Amphotericin B deoxycholate	1 mg/kg/day
Amphotericin B lipid complex	5 mg/kg/day
Liposomal amphotericin B	5 mg/kg/day
Amphotericin B colloidal dispersion	5 mg/kg/day
Fluconazole [†]	12 mg/kg/day
Voriconazole[*] , [‡]	8 mg/kg every 12 hr
Micafungin	2-4 mg/kg/day
Caspofungin	50 mg/m^2 /day
Anidulafungin	1.5 mg/kg/day

[*] Use adult dosages in children older than 12 yr of age for voriconazole and older than 8 yr of age

for micafungin.

† Loading doses should be used for fluconazole (25 mg/kg), voriconazole (9 mg/kg q 12 × 24 hr), caspofungin (70 mg/m^2), and anidulafungin (3 mg/kg).

‡ Dosing should be adjusted based on the results of therapeutic drug monitoring.

Primary Immune Defects

Chronic mucocutaneous candidiasis involves *Candida* infections of the oral cavity, esophagus, and/or genital mucosa, as well as involvement of skin and nails, that is recurrent or persistent and difficult to treat. There is a broad spectrum of genetic immune defects associated with chronic mucocutaneous candidiasis mostly related to severe T-cell defects or disorders of interleukin-17 production (see Chapter 151). Genes or disorders associated with chronic mucocutaneous candidiasis include severe combined immunodeficiency syndrome, NEMO or IKBG deficiency, DOCK8 deficiency, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), autoimmune polyendocrinopathy type 1, CARD9 deficiency, *STAT1* gain-of-function mutations, and *IL17RA* mutations.

Primary immunodeficiencies associated with an increased risk of invasive *Candida* infections include severe congenital neutropenia, CARD 9 deficiency, chronic granulomatous disease, and leukocyte adhesion deficiency type 1.

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CHAPTER 262

Cryptococcus neoformans and *Cryptococcus gattii*

David L. Goldman

Etiology

While more than 30 cryptococcal species have been described, 2 species (*Cryptococcus neoformans* and *C. gattii*) are responsible for the vast majority of disease. These species can be further classified by serologic and molecular typing techniques. Both *C. neoformans* and *C. gattii* are encapsulated, facultative intracellular pathogens. There is significant overlap in the disease caused by these pathogens; however, important differences in epidemiology and clinical presentation exist. Cryptococcal disease may rarely also be caused by other species (e.g., *C. laurentii* and *C. albidus*), especially in immunocompromised individuals (including neonates).

Epidemiology

C. neoformans is distributed in temperate climates predominantly in soil contaminated with droppings from certain avian species, including pigeons, canaries, and cockatoos. It may also be found on rotting wood, fruits, and vegetables and may be carried by cockroaches. Disease secondary to *C. neoformans* primarily occurs in immunocompromised individuals and especially in those with defects in cellular immunity, though apparently normal individuals can also be affected. A large increase in the incidence of cryptococcosis was noted in association with the AIDS epidemic, with disease generally occurring with severe immunosuppression ($CD4^+$ T cells < 100/μL). However, since the development of highly active anti-retroviral therapy (HAART), the incidence of AIDS-associated cryptococcosis has decreased dramatically, except in resource-limited areas of the world such as sub-Saharan Africa, where HAART is not readily available.

Other risk factors for cryptococcal infection include immunosuppression associated with organ transplantation, diabetes mellitus, renal failure, cirrhosis, corticosteroids, rheumatologic conditions, chemotherapeutics, and immune modulating monoclonal antibodies (e.g., etanercept, infliximab, and alemtuzumab). In patients who have undergone organ transplantation, cryptococcosis is the third most common fungal infection after candidiasis and aspergillosis. Children with certain primary immunodeficiency diseases may also be at increased risk for cryptococcosis, including those with hyper-IgM syndrome, severe combined immunodeficiency, idiopathic $CD4^+$ lymphopenia, autoantibodies to granulocyte-macrophage colony-stimulating factor or interferon-γ, CD40 ligand deficiency, and monoMAC syndrome (monocytopenia, B and natural killer cell lymphopenia).

C. gattii was initially recognized for its tendency to cause disease in tropical regions, especially among the native peoples of Australasia, where the organism can be found in association with Eucalyptus trees. In these regions, affected individuals are typically immunocompetent. More recently, *C. gattii* disease has been observed outside these tropical regions. An outbreak of *C. gattii* disease involving British Columbia and extending into the Pacific Northwest region of the United States was first recognized in 1999. Affected individuals were typically adults, with disease occurring in both immunocompetent and immunocompromised individuals. Comorbid conditions were often present, with examples including chronic lung and heart disease. A disproportionate fraction of patients (relative to those infected with *C. neoformans*) presented with pulmonary disease. An incubation period ranging from 2 to 12 mo is typical. In the appropriate clinical context, cryptococcosis should be considered in the differential diagnosis of residents of the Pacific Northwest as well as returning travelers.

Overall, cryptococcosis is significantly less common in children than in adults. The basis for this discrepancy is poorly understood but could be related to differences in exposure or immune response. Serologic studies suggest that subclinical infection is common among children living in urban areas after age 2 yr. During the early AIDS epidemic, the incidence of cryptococcosis in the United States was reported to be on the order of 10% in adults and 1% in children. The largest series of pediatric cryptococcosis comes from South Africa and describes 361 cases, accounting for 2% of the cryptococcosis cases over a 2-yr period. More recent series of pediatric cases, including those from Asia, the United States, and Colombia, highlight the potential for Cryptococcus (including *C. neoformans*) to cause disease in immunosuppressed and non-immunosuppressed children.

Pathogenesis

Like many fungi, *C. neoformans* and *C. gattii* survive as saprophytes in the environment. Their virulence characteristics appear to have evolved as an adaptive response to environmental stressors. Several key factors have been identified, including the ability to grow at 37°C, encapsulation, and melanin production. The polysaccharide capsule exhibits a variety of biologic activities that are important in the pathogenesis of disease, including interference with opsonization, inhibition of chemotaxis, and enhancement of non-protective TH2 inflammation. Capsular material is shed by the organism into body tissues and fluids during infection and has been implicated in the development of increased intracranial pressure (ICP), a hallmark of cryptococcal meningoencephalitis. Detection of shed capsular antigen in the serum and CSF are key to the diagnosis of cryptococcal disease. The organism also has the ability to undergo phenotypic variation in response to environmental changes through a variety of mechanisms and can form large giant cells (on the order 20 times its normal size), which are resistant to phagocytosis.

In most cases, infection is acquired by inhalation of desiccated forms of the organism, which upon deposition within the lungs are engulfed by alveolar macrophages. An additional portal of entry can be seen with organ transplantation of infected tissue. Furthermore, direct inoculation can lead to cutaneous or ophthalmic infection. After entry into the respiratory tract, infection can be latent and later progress in the context of immunodeficiency. Alternatively, infection can progress and disseminate to produce symptomatic disease. Cell-mediated immunity that leads to macrophage activation is the most important host defense for producing granulomatous inflammation and containing cryptococcal infection. Entry of the organism into the CNS may occur via several mechanisms, including infected macrophages, through infected endothelial cells, and between the tight junctions of endothelial cells.

Clinical Manifestations

The manifestations of cryptococcal infection reflect the route of inoculation, the infecting strain, and immune status of the host. Sites of infection include lung, CNS, blood, skin, bone, eyes, and lymph nodes.

Meningitis

CNS disease is the most commonly recognized manifestation of cryptococcosis. The disease is characteristically subacute or chronic, and affected patients may develop intracerebral masses, known as cryptococcomas and increased ICP. Importantly meningeal signs and fever (typical of other pediatric meningitides) may be lacking. In a review of pediatric cryptococcosis from Colombia, the most common symptoms were headache (78%), fever (69%), nausea and vomiting (66%), confusion (50%), and meningismus (38%).

Despite antifungal therapy, the mortality rate for cryptococcosis remains high, ranging from 15% to 40%. Most deaths occur within several weeks of diagnosis. Factors associated with a poor prognosis reflect a high fungal burden and poor host response, including altered mentation, high CSF fungal burden, low CSF WBC number (<10 cells/mm^3), and failure to rapidly sterilize the CSF. Increased ICP is a key factor in the morbidity and mortality of cryptococcal meningitis and is especially problematic for patients with *C. gattii* disease. Appropriate management of increased ICP is therefore essential to the appropriate management of cryptococcal meningitis (see below). Post-infectious sequelae are common and include hydrocephalus, decreased visual acuity, deafness, cranial nerve palsies, seizures, and ataxia.

Pneumonia

After CNS disease, pneumonia is the most commonly recognized form of cryptococcosis. As with meningitis, pneumonia occurs in both immunocompetent and immunocompromised individuals. Pulmonary disease can present in isolation or in the context of disseminated disease/meningitis, which is typical among immunocompromised individuals. Along these lines, among adults with AIDS-associated cryptococcal pneumonia, over 90% had concomitant CNS infection. Clinicians should have a high suspicion for cryptococcal meningitis/disseminated disease in patients with cryptococcal pneumonia, especially among immunocompromised individuals.

Cryptococcal pneumonia is often asymptomatic and may be detected because of radiographs performed for other reasons. In this regard, the detection of asymptomatic pulmonary nodules secondary to *C. neoformans* has been described in children with sarcomas, who are being evaluated for metastatic disease. Among symptomatic patients, a wide array of symptoms has been reported, including fever, cough, pleuritic chest pain, and constitutional symptoms like weight loss. In a review of 24 patients with pulmonary cryptococcosis, cough was the most common symptom. Severe disease may result in respiratory failure. The findings of chest radiographs are variable and may demonstrate a poorly localized bronchopneumonia, nodules, masses, or lobar consolidations. However, cavities and pleural effusions are rare. Immunocompromised patients can have alveolar and interstitial infiltrates that mimic *Pneumocystis* pneumonia and usually represent disseminated disease.

Cutaneous Infection

Cutaneous disease most commonly follows disseminated cryptococcosis and rarely local inoculation. Early lesions are erythematous, may be single or multiple, and are variably indurated and tender. Lesions often become ulcerated with central necrosis and raised borders. Cutaneous cryptococcosis in immunocompromised patients can resemble molluscum contagiosum.

Skeletal Infection

Skeletal infection occurs in approximately 5% of patients with disseminated infection but rarely in HIV-infected patients. The onset of symptoms is insidious and chronic. Bone involvement is typified by soft tissue swelling and tenderness, and arthritis is characterized by effusion, erythema, and pain on motion. Skeletal disease is unifocal in approximately 75% of cases. The vertebrae are the most common sites of infection, followed by the tibia, ileum, rib, femur, and humerus. Concomitant bone and joint disease results from contiguous spread.

Sepsis Syndrome

Sepsis syndrome is a rare manifestation of cryptococcosis and occurs almost exclusively among HIV-infected patients. Fever is followed by respiratory distress and multiorgan system disease that is often fatal.

Cryptococcal-associated immune reconstitution inflammatory syndrome (C-IRIS) occurs in the setting of AIDS. Improvement of immune function due to the administration of HAART in AIDS patients (or the reduction of immunosuppression in transplant recipients) may enhance inflammation to the organism, resulting in exacerbation of symptoms. This situation is similar to IRIS seen with other opportunistic pathogens. IRIS may present as a worsening of symptoms in someone with a known diagnosis of cryptococcosis or in someone in whom the diagnosis of cryptococcosis is sub-clinical (unmasking-IRIS). IRIS is particularly problematic in CNS cryptococcosis and may result in worsening of increased ICP. The extent of C-IRIS in pediatric cryptococcosis is not well characterized.

Diagnosis

Recovery of the fungus by culture or demonstration of the fungus in histologic sections of infected tissue or body fluids by India ink staining is definitive. Cryptococci can grow easily on standard fungal and bacterial culture media. Colonies can be seen within 48-72 hr when grown aerobically at standard temperatures. The CSF profile in patients with cryptococcal meningitis may reveal a mild lymphocytosis and elevated protein but is often normal. A latex agglutination test, which detects cryptococcal antigen in serum and CSF, is the most useful diagnostic test. Titers of >1 : 4 in bodily fluid strongly suggest infection, and titers of >1 : 1,024 reflect high burden of yeast, poor host immune response, and greater likelihood of therapeutic failure. Serial monitoring of cryptococcal antigen levels is not useful in guiding therapy, as the polysaccharide antigen is actively shed into the tissue and may persist for prolonged periods. Patients with localized pneumonia typically do not have elevated serum antigen levels (though occasionally low levels of antigen, <1 : 4 may be detected). Higher serum antigen levels in patients with pulmonary disease are indicative of dissemination outside the lungs. A point of care lateral flow assay based on polysaccharide antigen detection has been developed for use in resource limited areas.

Treatment

The choice of treatment depends on the sites of involvement and the host immune status. Treatment regimens have not been rigorously studied in children and generally represent extrapolations from studies done in adults. The immunocompetent patient with asymptomatic or mild disease limited to the lungs should be treated with oral fluconazole (pediatric dose 6-12 mg/kg/day and adult dose 400 mg/day) for 6-12 mo to prevent dissemination of disease. Alternative treatments include itraconazole (pediatric dose 5-10 mg/kg/day divided every 12 hr and adult dose 400 mg/day), voriconazole, and posaconazole. Fluconazole therapy can also be used for immunocompromised individuals with isolated mild-moderate pulmonary disease in the absence of dissemination or CNS disease, as evidenced by unremarkable CSF studies. Longer maintenance therapy with fluconazole to prevent recurrence should be considered in this cohort, especially among AIDS patients if CD4+ T cells remain less than 100/µL. Adjunctive surgical management of pulmonary lesions that are not responsive to surgical management should be considered.

For more severe forms of disease including meningitis and any form of disseminated disease, an initial induction regimen to promote rapid decline in fungal burden is indicated. Induction therapy should consist of amphotericin B (1 mg/kg/day) plus flucytosine (100-150 mg/kg/day divided every 6 hr assuming normal kidney function) for a minimum of 2 wk, keeping serum flucytosine concentrations between 40 and 60 µg/mL. Longer periods of induction (4-6 wk) should be considered in the following scenarios: (1) Immunocompetent patients with cryptococcal meningitis; (2) Meningitis secondary to *C. gattii* ; (3) Neurological complications (including cryptococcomas); and (4) Absence of flucytosine in the induction regimen. Lipid-complex amphotericin B (3-6 mg/kg/day) can be used in place of amphotericin B for patients with underlying renal injury or those receiving nephrotoxic drugs. Following induction, consolidation therapy with oral fluconazole (pediatric dose 10-12 mg/kg/day, adult dose 400-800 mg/day) should be given for 8 wk. In patients with ongoing immunosuppression, maintenance fluconazole should be used to prevent recurrence. In organ transplant recipients, current recommendations are for 6-12 mo of maintenance therapy with fluconazole (pediatric dose 6 mg/kg/day, adult dose 200-400 mg/day). In patients with AIDS, prolonged maintenance therapy should be given. Studies in adults suggest that maintenance therapy can be discontinued once the patient has achieved immune reconstitution (as indicated by $CD4^+$ T cells >100/µL and undetectable or very low HIV RNA level that is sustained for greater than 3 mo). A minimum of 12 mo of antifungal therapy is indicated. Use of adjuvant interferon gamma for patients with refractory cryptococcal meningitis has been described in adults, but not in pediatric patients.

Increased ICP. Increased ICP contributes greatly to the morbidity and mortality of cryptococcal meningitis, and aggressive management of this phenomenon is indicated. Current guidelines indicate that in patients with increased ICP (>25 cm H_2O), CSF should be removed to establish a pressure ≤ 20 cm H_2O or by 50% if ICP is extremely high. Ventriculoperitoneal shunts may be required for patients with persistently elevated increased ICP. Corticosteroids, mannitol, and acetazolamide are generally not indicated in the treatment of increased ICP, though anecdotal reports describe use in association with cryptococcoma and C-IRIS.

C-IRIS. To prevent the development of C-IRIS, most experts recommend delaying the institution of HAART for 4-10 wk after the initiation of antifungal therapy. Recurrence of disease and emergence of antifungal resistance should be excluded in the context of a diagnosis of C-IRIS. Treatment strategies have not been well studied but generally consist of antifungal therapy along with antiinflammatory agents (e.g., NSAIDs and corticosteroids). Reduction of increased ICP through therapeutic lumbar puncture may be necessary.

Prevention

Persons at high risk should avoid exposures such as bird droppings. Effective HAART for persons with HIV infection reduces the risk of cryptococcal disease. Fluconazole prophylaxis is effective for preventing cryptococcosis in patients with AIDS and $CD4^+$ lymphocyte counts <100/µL. An alternative approach involves serial monitoring of serum cryptococcal antigen with pre-emptive antifungal therapy.

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CHAPTER 263

Malassezia

Ashley M. Maranich

Members of the genus *Malassezia* include the causative agents of **tinea versicolor** (also **pityriasis versicolor**) (Fig. 263.1) and are associated with other dermatologic conditions and with fungemia in patients with indwelling catheters. *Malassezia* species are commensal lipophilic yeasts with a predilection for the sebum-rich areas of the skin. They are considered a part of the normal skin flora, with presence established by 3-6 mo of age.

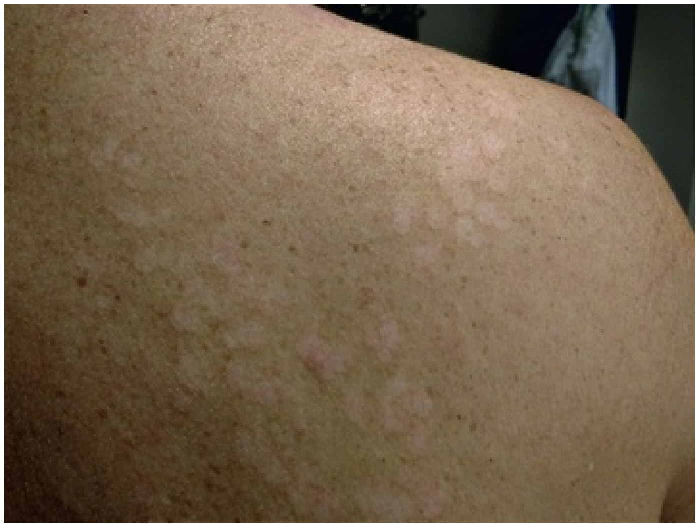

FIG. 263.1 A young adult with tinea versicolor. Notice the characteristic hypopigmented scaling macules. The asymmetric pattern seen in this patient is not characteristic of all patients with this infection. (Courtesy Ashley M Maranich, MD.)

The history of *Malassezia* nomenclature is complex and can be confusing. Because the yeast forms may be oval or round, these organisms were formally designated *Pityrosporum ovale* and *Pityrosporum orbiculare* . Newer technologies have allowed an improved classification system, with 13 recognized species. Only *Malassezia pachydermatis* , a zoophilic yeast that causes dermatitis in dogs, is not lipophilic.

Transformation of the yeast form to a hyphal form facilitates invasive disease. The clusters of thick-walled blastospores together with the hyphae produce the characteristic spaghetti-and-meatballs appearance of *Malassezia* species.

M. globosa , *M. sympodialis* , *M. restricta* , and *M. furfur* are the major causes of tinea versicolor (see Chapter 686). *Malassezia* organisms are also increasingly associated with other dermatologic conditions. *M. sympodialis* and *M. globosa* are implicated in neonatal acne, and *M. globosa* and *M. restricta* are most closely associated with seborrheic dermatitis and dandruff. *Malassezia* are also causally associated with scalp psoriasis, *Pityrosporum* folliculitis, and head and neck atopic dermatitis. *Malassezia* may be isolated from sebum-rich areas of asymptomatic persons, emphasizing that demonstration of the fungus does not equate with infection.

The traditional primary therapy for tinea versicolor is topical selenium sulfide 2.5% applied daily for at least 10 min for a week, followed by weekly to monthly applications for several months to prevent relapse. Additional topical agents that have efficacy include terbinafine, clotrimazole, topical azoles, and tacrolimus. *Malassezia* -associated skin diseases limited to the head and neck can be managed with either 1% ciclopirox, ketoconazole, or zinc pyrithione shampoos.

Oral therapy for tinea versicolor with fluconazole or itraconazole is easier to administer but is more expensive, has higher side effect risks, and may be less effective than topical therapy. Various dosing regimens have been used with success, including fluconazole 300 mg weekly for 2-4 wk, fluconazole as a single 400 mg dose, and itraconazole 200 mg daily for 5-7 days or 100 mg daily for 2 wk. Regardless of the regimen chosen, patients should be encouraged to exercise while taking these medications so as to increase the skin concentration of the drug through sweating.

Despite successful treatment, repigmentation might not occur for several months. Relapses are common and can require repeat or alternative therapies.

M. furfur is the species most commonly causing fungemia, and *M. pachydermatis* has been implicated in several outbreaks in neonatal intensive care units. The use of lipid emulsions containing medium-chain triglycerides inhibits the growth of *Malassezia* and can prevent infection. Infection is most common in premature infants, although immunocompromised patients, especially those with malignancies, can also be infected. Symptoms of catheter-associated fungemia are indistinguishable from other causes of catheter-associated infections but should be suspected in patients, especially neonates, receiving intravenous lipid infusions. Compared with other causes of fungal sepsis, it is unusual for catheter-related *Malassezia* fungemia to be associated with secondary focal infection.

Malassezia species do not grow readily on standard fungal media, and successful culture requires overlaying the agar with olive oil. Recovery of *Malassezia* from blood culture is optimized by supplementing the medium with olive oil or palmitic acid.

Fungemia caused by *M. furfur* or other species can be successfully treated in most cases by immediately discontinuing the lipid infusion and removing the involved catheter. For persistent or invasive infections, amphotericin B (deoxycholate or lipid-complex formulations), fluconazole, and itraconazole are effective. Flucytosine has no activity against *Malassezia* .

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CHAPTER 264

Aspergillus

William J. Steinbach

The aspergilli are ubiquitous fungi whose normal ecological niche is that of a soil saprophyte that recycles carbon and nitrogen. The genus *Aspergillus* contains approximately 250 species, but most human disease is caused by *Aspergillus fumigatus* , *A. flavus* , *A. niger* , *A. terreus*, and *A. nidulans* . Invasive disease is most commonly caused by *A. fumigatus* . *Aspergillus* reproduces asexually via production of spores (conidia). Most cases of *Aspergillus* disease **(aspergillosis)** are due to inhalation of airborne conidia that subsequently germinate into fungal hyphae and invade host tissue. People are likely exposed to conidia on a daily basis. When inhaled by an immunocompetent person, conidia are rarely deleterious, presumably because they are efficiently cleared by phagocytic cells. Macrophage- and neutrophil-mediated host defenses are required for resistance to invasive disease.

Aspergillus is a relatively unusual pathogen in that it can create very different disease states depending on the host characteristics, including allergic (hypersensitivity), saprophytic (noninvasive), chronic, or invasive disease. Immunodeficient hosts are at risk for invasive disease, whereas immunocompetent atopic hosts tend to develop allergic disease. Disease manifestations include primary allergic reactions; colonization of the lungs or sinuses; localized infection of the lung or skin; chronic infection of the lung; invasive pulmonary disease; or widely disseminated disease of the lungs, brain, skin, eye, bone, heart, and other organs. Clinically, these syndromes often manifest with mild, nonspecific, and late-onset symptoms, particularly in the immunosuppressed host, complicating accurate diagnosis and timely treatment.

264.1

Allergic Disease (Hypersensitivity Syndromes)

William J. Steinbach

Keywords

allergic bronchopulmonary aspergillosis
asthma

Asthma

Attacks of atopic asthma can be triggered by inhalation of *Aspergillus* conidia, producing allergic responses and subsequent bronchospasm. Exposure to fungi, especially *Aspergillus* , needs to be considered as a trigger in a patient with an asthma flare, especially in those patients with severe or recalcitrant asthma.

Extrinsic Alveolar Alveolitis

Extrinsic alveolar alveolitis is a hypersensitivity pneumonitis that occurs due to repetitive inhalational exposure to inciting materials, including *Aspergillus* conidia. Symptoms typically occur shortly after exposure and include fever, cough, and dyspnea. Neither blood nor sputum eosinophilia is present. Chronic exposure to the triggering material can lead to pulmonary fibrosis.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hyper-sensitivity disease resulting from immunologic sensitization to *Aspergillus* antigens. It is primarily seen in patients with asthma or cystic fibrosis. Inhalation of conidia produces non-invasive colonization of the bronchial airways, resulting in persistent inflammation and development of hypersensitivity inflammatory responses. Disease manifestations are due to abnormal immunologic responses to *A. fumigatus* antigens and include wheezing, pulmonary infiltrates, bronchiectasis, and even fibrosis.

There are 8 primary diagnostic criteria for ABPA: episodic bronchial obstruction, peripheral eosinophilia, immediate cutaneous reactivity to ***Aspergillus*** antigens, precipitating IgE antibodies to ***Aspergillus*** antigen, elevated total IgE, serum precipitin (specific IgG) antibodies to *A. fumigatus,* pulmonary infiltrates, and central bronchiectasis. Secondary diagnostic criteria include repeated detection of ***Aspergillus*** from sputum by identification of morphologically consistent fungal elements or direct culture, coughing brown plugs or specks. Radiologically, bronchial wall thickening, pulmonary infiltrates, and central bronchiectasis can be seen.

Treatment depends on relieving inflammation via an extended course of systemic corticosteroids. Addition of oral antifungal agents, such as itraconazole or voriconazole, is used to decrease the fungal burden and diminish the inciting stimulus for inflammation. Because disease activity is correlated with serum IgE levels, these levels are used as one marker to define duration of therapy. An area of research interest is the utility of anti-IgE antibody therapy in the management of ABPA.

Allergic *Aspergillus* Sinusitis

Allergic *Aspergillus* sinusitis is thought to be similar in etiology to ABPA. It has been primarily described in young adult patients with asthma and may or may not be seen in combination with ABPA. Patients often present with symptoms of chronic sinusitis or recurrent acute sinusitis, such as congestion, headaches, and rhinitis, and are found to have nasal polyps and opacification of multiple sinuses on imaging. Laboratory findings can include elevated IgE levels, precipitating antibodies to *Aspergillus* antigen, and immediate cutaneous reactivity to *Aspergillus* antigens. Sinus tissue specimens might contain eosinophils, Charcot-Leyden crystals, and fungal elements consistent with *Aspergillus* species. Surgical drainage is an important aspect of treatment, often accompanied by courses of either systemic or inhaled steroids. Use of an antifungal agent may also be considered.

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264.2

Saprophytic (Noninvasive) Syndromes

William J. Steinbach

Keywords

chronic cavitary aspergillosis
aspergilloma

Pulmonary Aspergilloma

Aspergillomas are masses of fungal hyphae, cellular debris, and inflammatory cells that proliferate without vascular invasion, generally in the setting of preexisting cavitary lesions or ectatic bronchi. These cavitary lesions can occur as a result of infections such as tuberculosis, histoplasmosis, or resolved abscesses, or secondary to congenital or acquired defects such as pulmonary cysts or bullous emphysema. Patients may be asymptomatic, with diagnosis made through imaging for other reasons, or they might present with hemoptysis, cough, or fever. On imaging, initially there may be thickening of the walls of a cavity, and later on there is a solid round mass separated from the cavity wall, as the fungal ball develops. Detection of *Aspergillus* antibody in the serum suggests this diagnosis. Treatment is indicated for control of complications, such as hemoptysis. Surgical resection is the definitive treatment but has been associated with significant risks. Systemic antifungal treatment with azole-class agents may be indicated in certain patients.

Chronic Pulmonary Aspergillosis

Chronic aspergillosis can occur in patients with normal immune systems or mild degrees of immunosuppression, including intermittent corticosteroids. Three major categories, each with overlapping clinical features, have been proposed to describe different manifestations of chronic aspergillosis. The first is chronic cavitary pulmonary aspergillosis (CCPA), which is similar to aspergilloma, except that multiple cavities form and expand with occupying fungal balls. The second is chronic fibrosing pulmonary aspergillosis, where the multiple individual lesions progress to significant pulmonary fibrosis. The final is subacute invasive aspergillosis (IA), which was previously called chronic necrotizing pulmonary aspergillosis, a slowly progressive subset found in patients with mild to moderate immune impairment.

Treatment based on new consensus guidelines can sometimes involve surgical resection, although long-term antifungal therapy is often indicated. Management of semi-IA is similar to that of invasive pulmonary aspergillosis; however, the disease is more indolent, and thus there is a greater emphasis on oral therapy. Direct instillation of antifungals into the lesion cavity has been employed with some success.

Sinusitis

Sinus aspergillosis typically manifests with chronic sinus symptoms that are refractory to antibacterial treatment. Imaging can demonstrate mucosal thickening in the case of *Aspergillus* sinusitis or a single mass within the maxillary or ethmoid sinus in the case of sinus aspergilloma. If untreated, sinusitis can progress and extend into the ethmoid sinuses and orbits. Therapy of sinusitis depends on surgical debridement and drainage, including surgical removal of the fungal mass in cases of sinus aspergilloma. Treatment of invasive sinus aspergillosis is identical to treatment of invasive pulmonary aspergillosis.

Otomycosis

Aspergillus can colonize the external auditory canal, with possible extension to the middle ear and mastoid air spaces if the tympanic membrane is disrupted by concurrent bacterial infection. Symptoms include pain, itching, decreased unilateral hearing, or otorrhea. Otomycosis is more often seen in patients with impaired mucosal immunity, such as patients with hypogammaglobulinemia, diabetes mellitus, chronic eczema, or HIV and those using chronic steroids. Treatments have not been well studied, but topical treatment with acetic or boric acid instillations or azole creams as well as oral azoles such as voriconazole, itraconazole, and posaconazole have been described.

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264.3

Invasive Disease

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Keywords

voriconazole
galactomannan
combination antifungal therapy

IA occurs after conidia enter the body, escape immunologic control mechanisms, and germinate into fungal hyphae that subsequently invade tissue parenchyma and vasculature. The invasion of the vasculature can result in thrombosis and localized necrosis and facilitates hematogenous dissemination. The incidence of IA increased over the last several decades, likely due to more use of severely immunosuppressive therapies for a widening array of underlying diseases and better management of other infections found in the at-risk populations. The most common site of primary infection is the lung, but primary invasive infection is also seen in the sinuses and skin and rarely elsewhere. Secondary infection can be seen after hematogenous spread, often to the skin, central nervous system (CNS), eye, bone, and heart.

IA is primarily a disease of immunocompromised hosts, and common risk factors in adults include cancer or chemotherapy-induced neutropenia, particularly if severe and/or prolonged; hematopoietic stem cell transplantation, especially during the initial pre-engraftment phase or if complicated by graft vs. host disease; neutrophil or macrophage dysfunction, as occurs in severe combined immunodeficiency (SCID) or chronic granulomatous disease (CGD); prolonged high-dose steroid use; solid organ transplantation; and rarely HIV. Adults with severe influenza virus pneumonia may also be at risk for IA. Studies in the pediatric age group have identified similar risk factors for IA, but a well-defined incidence of IA among pediatric patients has not been determined to date.

Invasive Pulmonary Aspergillosis

Invasive pulmonary aspergillosis is the most common form of aspergillosis. It plays a significant role in morbidity and mortality in the patient populations mentioned at increased risk for IA. Presenting symptoms can include fever despite initiation of empirical broad-spectrum antibacterial therapy, cough, chest pain, hemoptysis, and pulmonary infiltrates. Patients on high-dose steroids are less likely to present with fever. Symptoms in these immunocompromised patients can be very vague, and thus maintaining a high index of suspicion when confronted with a high-risk patient is essential.

Diagnosis

Imaging can be helpful, although no finding is pathognomonic for invasive pulmonary aspergillosis. Characteristically, multiple, ill-defined nodules can be seen, though lobar or diffuse consolidation is not uncommon and normal chest X-rays do not rule out disease. Classic radiologic signs on CT during neutropenia include the **halo sign,** when angioinvasion produces a hemorrhagic nodule surrounded by ischemia (Fig. 264.1). Early on there is a rim of ground-glass opacification surrounding a nodule. Over time, these lesions evolve into cavitary lesions or lesions with an **air crescent sign** when the lung necroses around the fungal mass, often seen during recovery from neutropenia. Unfortunately, these findings are not specific to invasive pulmonary aspergillosis and can also be seen in other pulmonary fungal infections, as well as pulmonary hemorrhage and organizing pneumonia. In addition, several reviews of imaging results of pediatric aspergillosis cases suggest that cavitation and air crescent formation are less common among these patients than among adult patients. On MRI, the typical finding for pulmonary disease is the **target sign,** a nodule with lower central signal compared to the rim-enhancing periphery.

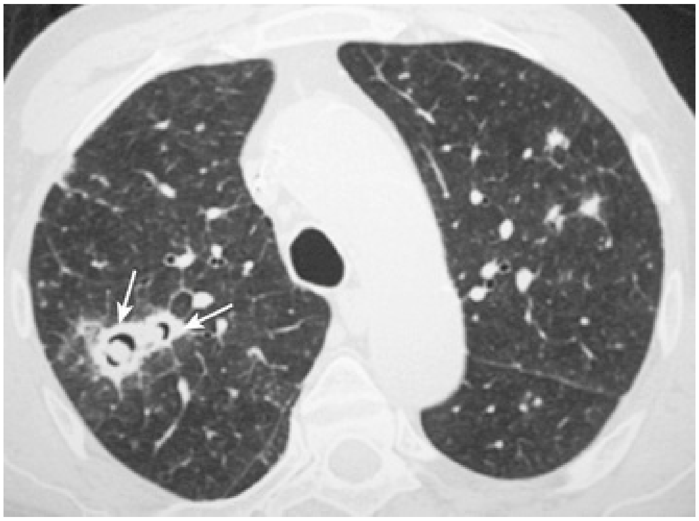

FIG. 264.1 Angioinvasive aspergillosis. CT section at the level of the lower trachea shows a consolidation with an eccentric cavitation and air crescent

sign *(arrows).* This finding in this neutropenic patient is highly diagnostic of angioinvasive aspergillosis. (From Franquet T: Nonneoplastic parenchymal lung disease. In Haaga JR, Boll DT, editors: *CT and MRI of the Whole Body* , ed 6, Philadelphia, 2017, Elsevier, Fig. 36.14.)

Diagnosis of IA can be complicated for a number of reasons. Conclusive diagnosis requires culture of *Aspergillus* from a normally sterile site and histologic identification of tissue invasion by fungal hyphae consistent with *Aspergillus* morphology. However, obtaining tissue specimens is often impractical in critically ill, often thrombocytopenic, patients. In addition, depending on the specimen type, a positive result from culture can represent colonization rather than infection; however, this should be interpreted conservatively in high-risk patients. Isolation of *Aspergillus* from blood cultures is uncommon, likely because fungemia is low-level and intermittent.

Serology can be useful in the diagnosis of allergic ***Aspergillus*** syndromes as well as aspergilloma but is low yield for invasive disease, likely because of deficient immune responses in the high-risk immunocompromised population. Bronchoalveolar lavage (BAL) can be useful, but negative culture results cannot be used to rule out disease, owing to inadequate sensitivity. Addition of molecular biologic assays such as antigen detection and polymerase chain reaction (PCR) can greatly improve the diagnostic yield of BAL for aspergillosis. An enzyme-linked immunosorbent assay (ELISA)-based test for galactomannan, one of the components of the ***Aspergillus*** cell wall, is the molecular biomarker of choice for the diagnosis of IA in serum, BAL fluid, and CSF. This assay is best used in serial monitoring for development of infection and has been shown to be the most sensitive in detecting disease in cancer patients or hematopoietic stem cell transplant recipients, with less utility in solid organ transplant recipients. Earlier reports of increased false-positive reactions in children versus adults have been refuted, and the galactomannan assay is effective in diagnosing IA in children. This test does possess high rates of false negativity in patients with congenital immunodeficiency (e.g., CGD) and invasive ***Aspergillus*** infections. Another molecular assay, the beta-glucan assay, is a nonspecific fungal assay that detects the major component of the fungal cell wall and has been used to diagnose IA. Unlike the galactomannan assay, which is specific for *Aspergillus* , despite some cross-reactivity with other fungi, the beta-glucan assay will not discriminate which fungal infection is infecting the patient. PCR-based assays are in development for the diagnosis of aspergillosis but are still being optimized and are not yet commercially available.

Treatment

Successful treatment of IA hinges on the ability to reconstitute normal immune function and use of effective antifungal agents until immune recovery can be achieved. Therefore, lowering overall immunosuppression, specifically via cessation of corticosteroid use, is vital to improve the ultimate outcome. In 2016, updated treatment guidelines for *Aspergillus* infections were published by the Infectious Diseases Society of America, continuing the shift in management to voriconazole from previous recommendations for amphotericin B. Primary therapy for all forms of IA is the azole-class antifungal voriconazole, based on multiple studies showing both improved response rates and survival in patients receiving voriconazole when compared to amphotericin B. In addition, voriconazole is better tolerated than amphotericin B and can be given orally as well as intravenously. Guideline-recommended alternative therapies include liposomal amphotericin B, isavuconazole, or other lipid formulations of amphotericin B.

Azoles are metabolized through the cytochrome P-450 system, and thus medication interactions can be a significant complication, especially with some chemotherapeutic agents (e.g., vincristine). Other triazole antifungals are also available, including posaconazole, which is approved for antifungal prophylaxis and may be an alternative agent for first-line treatment of IA. Although the dosing of itraconazole and voriconazole has been established for pediatric patients, the pharmacokinetic studies for posaconazole have not yet been completed. Importantly, the dose of voriconazole used in children is higher than that used in adults (see Chapter 260).

The echinocandin class of antifungals may also a play a role in treatment of IA, but to date, these agents are generally employed as second-line medications, particularly for salvage therapy. Combination antifungal therapy has revealed disparate results. Combination primary antifungal therapy with voriconazole plus an echinocandin may be considered in select patients with documented IA but is not recommended. However, it is possible that combination therapy may be beneficial to certain specific patient groups. Importantly, primary therapy with an echinocandin is not recommended, but an echinocandin can be used in the settings in which azole or polyene antifungal are contraindicated. Unfortunately, even with newer antifungals, complete or partial response rates for treatment of IA are only approximately 50%. To augment antifungal therapies, patients have been treated with growth factors to increase neutrophil counts, granulocyte transfusions, interferon-γ, and surgery.

Special Populations

Patients with CGD represent a pediatric population at particular risk for pulmonary aspergillosis. Invasive pulmonary aspergillosis can be the first serious infection identified in these patients, and the lifetime risk of development is estimated to be 33%. Unlike classical IA in cancer patients, the onset of symptoms is often gradual, with slow development of fever, fatigue, pneumonia, and elevated sedimentation rate. The neutrophils of patients with CGD surround the collections of fungal elements but cannot kill them, thereby permitting local invasion with extension of disease to the pleura, ribs, and vertebrae, though angioinvasion is not seen. Imaging in these patients is much less likely to reveal the halo sign, infarcts, or cavitary lesions and instead generally shows areas of tissue destruction due to the ongoing inflammatory processes.

Cutaneous Aspergillosis

Cutaneous aspergillosis can occur as a primary disease or as a consequence of hematogenous dissemination or spread from underlying structures. Primary cutaneous disease classically occurs at sites of skin disruption, such as intravenous access device locations, adhesive dressings, or sites of injury or surgery. Premature infants are at particular risk, given their immature skin and need for multiple access devices. Cutaneous disease in transplant recipients tends to reflect hematogenous distribution from a primary site of infection, often the lungs. Lesions are erythematous indurated papules that progress to painful, ulcerated, necrotic lesions. Treatment depends on the combination of surgical debridement and antifungal therapy, with systemic voriconazole recommended as primary therapy.

Invasive Sinonasal Disease

Invasive *Aspergillus* sinusitis represents a difficult diagnosis, because the clinical presentation tends to be highly variable. Patients can present with congestion, rhinorrhea, epistaxis, headache, facial pain or swelling, orbital swelling, fever, or abnormal appearance of the nasal turbinates. Because noninvasive imaging can be normal, diagnosis rests on direct visualization via endoscopy and biopsy. Sinus mucosa may be pale, discolored, granulating, or necrotic, depending on the stage and extent of disease. The infection can invade adjacent structures, including the eye and brain. This syndrome is difficult to distinguish clinically from other types of invasive fungal disease of the sinuses such as zygomycosis, rendering obtaining specimens for culture and histology extremely important. If the diagnosis is confirmed, treatment should be with voriconazole similar to invasive pulmonary disease. Because voriconazole is not active against mucormycosis, amphotericin B formulations should be considered in invasive fungal sinusitis pending definitive identification.

Central Nervous System

The primary site of *Aspergillus* infection tends to be the lungs, but as the hyphae invade into the vasculature, fungal elements can dislodge and travel through the bloodstream, permitting establishment of secondary infection sites. One of the sites commonly involved in disseminated disease is the CNS. Cerebral aspergillosis can also arise secondary to local extension of sinus disease. The presentation of cerebral aspergillosis is highly variable but can include changes in mental status, seizures, paralysis, coma, and ophthalmoplegia. As the hyphae invade the CNS vasculature, hemorrhagic infarcts develop that convert to abscesses. Biopsy is required for definitive diagnosis, but patients are often too ill to tolerate surgery. Imaging can be helpful for diagnosis, and MRI is preferred. Lesions tend to be multiple, to be located in the basal ganglia, to have intermediate intensity with no enhancement, and to have no mass effect. CT shows hypodense, well-demarcated lesions, sometimes with ring enhancement and edema. Diagnosis often depends on characteristic imaging findings in a patient with known aspergillosis at other sites. Galactomannan assay testing of CSF has been studied and may become a future methodology to confirm the diagnosis. In general, the prognosis for CNS aspergillosis is extremely poor, likely owing to the late onset at presentation. Reversal of immunosuppression is extremely important. Surgical resection of lesions may be useful. Voriconazole, usually at high doses, is the best therapy, and itraconazole, posaconazole, and liposomal formulations of amphotericin B are alternative options.

Eye

Fungal endophthalmitis and keratitis may be seen in patients with disseminated *Aspergillus* infection. Pain, photophobia, and decreased visual acuity may be present, though many patients are asymptomatic. Emergent ophthalmologic evaluation is important when these entities are suspected. Endophthalmitis is treated with intravitreal injection of either amphotericin B or voriconazole along with surgical intervention and systemic antifungal therapy with voriconazole. Keratitis requires topical and systemic antifungal therapy.

Bone

Aspergillus osteomyelitis can occur, most commonly in the vertebrae. Rib involvement occurs owing to extension of disease in patients with CGD and is most often caused by *A. nidulans* . Treatment depends on the combination of surgical debridement and systemic antifungals. Arthritis can develop owing to hematogenous dissemination or local extension, and treatment depends on joint drainage combined with antifungal therapy. Amphotericin B has been the most commonly employed agent in the past, although voriconazole is the preferred first-line therapy.

Heart

Cardiac infection can occur as a result of surgical contamination, secondary to disseminated infection, or as a result of direct extension from a contiguous focus of infection and includes endocarditis, myocarditis, and pericarditis. Treatment requires surgical intervention in the case of endocarditis and pericarditis, along with systemic antifungals, sometimes lifelong due to the possibility of recurrent infection.

Empirical Antifungal Therapy

Because the diagnosis of invasive *Aspergillus* infections is often complicated and delayed, empirical initiation of antifungal therapy is often considered in high-risk patients. At present, antifungal coverage with amphotericin B (conventional or liposomal), voriconazole, itraconazole, or the echinocandin caspofungin should be considered in patients at risk for prolonged neutropenia or with findings suggesting invasive fungal infections. At this time, our ability to diagnose and treat infections due to *Aspergillus* remains suboptimal. Additional study of antigen detection assays based on galactomannan and other *Aspergillus* cell wall components as well as standardization of PCR-based assays will facilitate diagnosis. The optimal treatment remains another challenging question, because current therapeutic regimens tend to produce complete or partial response only approximately half of the time. Novel antifungals currently under development offer a future with hopefully improved survival, but immune reconstitution remains of paramount importance.

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CHAPTER 265

Histoplasmosis (*Histoplasma capsulatum*)

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Etiology

Histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic fungus found in the environment as a saprobe in the mycelial (mold) form and in tissues in the parasitic form as yeast.

Epidemiology

Two varieties of *Histoplasma* cause human histoplasmosis. The most common variety, *H. capsulatum* var. *capsulatum* , is found in soil as the saprotrophic form throughout the midwestern United States, primarily along the Ohio and Mississippi rivers. In parts of Kentucky and Tennessee, almost 90% of the population older than 20 yr of age have positive skin test results for histoplasmin. Sporadic cases have also been reported in nonendemic states in patients without a travel history. Worldwide, *H. capsulatum* var. *capsulatum* is endemic to parts of Central and South America, the Caribbean, China, India, Southeast Asia, and the Mediterranean. The less common variety, *H. capsulatum* var. *duboisii* , is endemic to certain areas of western and central sub-Saharan Africa.

H. capsulatum thrives in soil rich in nitrates such as areas that are heavily contaminated with bird or bat droppings or decayed wood. Fungal spores are often carried on the wings of birds. Focal outbreaks of histoplasmosis have been reported after aerosolization of microconidia resulting from construction in areas previously occupied by starling roosts or chicken coops or by chopping decayed wood or burning bamboo exposed to a blackbird roost. Unlike birds, bats are actively infected with *Histoplasma.* Focal outbreaks of histoplasmosis have also been reported after intense exposure to bat guano in caves and along bridges frequented by bats. Horizontal person-to-person transmission does not occur, although transplacental transmission of *H. capsulatum* has been reported in immunocompromised mothers.

Pathogenesis

Inhalation of microconidia (fungal spores) is the initial stage of human infection. The conidia reach the alveoli, germinate, and proliferate as yeast. Alternatively, spores can remain as mold with the potential for activation. Most infections are asymptomatic or self-limited. When disseminated disease occurs, any organ system can be involved. The initial infection is a bronchopneumonia. As the initial pulmonary lesion ages, giant cells form, followed by formation of caseating or noncaseating granulomas and central necrosis. Granulomas contain viable yeast, and disease can relapse. At the time of spore germination, yeast cells are phagocytosed by alveolar macrophages, where they replicate and gain access to the reticuloendothelial system via the pulmonary lymphatic system and hilar lymph nodes. Dissemination with splenic involvement typically follows the primary pulmonary infection. In normal hosts, specific cell-mediated immunity follows in approximately 2 wk, enabling sensitized T cells to activate macrophages and kill the organism. The initial pulmonary lesion resolves within 2-4 mo but may undergo calcification resembling the Ghon complex of tuberculosis. Alternatively, buckshot calcifications involving the lung and spleen may be seen. Unlike tuberculosis, reinfection with *H. capsulatum* may occur and can lead to exaggerated host responses in some cases.

Children with immune deficiencies, specifically deficiencies involving cell-mediated immunity, are at increased risk for disseminated histoplasmosis. Primary immunodeficiencies involving mutations in the IL-12/IFN-γ pathway have been reported in children with disseminated histoplasmosis, including IL-12Rβ1 deficiency and IFN-γ R1 deficiency. Other primary immunodeficiencies identified in children with disseminated disease include *STAT1* gain-of-function mutations, idiopathic CD4 lymphopenia, AR-DOCK8 deficiency, AD-GATA2 deficiency, and X-linked CD40L deficiency. Children with certain secondary immunodeficiencies (cancer patients, solid organ transplant recipients, children with HIV infection, and children receiving immunomodulatory therapy with

TNF-α inhibitors) are also at increased risk for disseminated disease.

Clinical Manifestations

Exposure to *Histoplasma* is common in endemic areas, although the large majority of infections are subclinical. Less than 1% of those infected display the following clinical manifestations:

Acute pulmonary histoplasmosis follows initial or recurrent respiratory exposure to microconidia. Symptomatic disease occurs more often in young children; in older patients, symptoms follow exposure to large inocula in closed spaces (e.g., chicken coops or caves) or prolonged exposure (e.g., camping on contaminated soil, chopping decayed wood). The median incubation time is 14 days. The prodrome is not specific and usually consists of flu-like symptoms, including headache, fever, chest pain, cough, and myalgias. Hepatosplenomegaly occurs more often in infants and young children. Symptomatic infections may be associated with significant respiratory distress and hypoxia and can require intubation, mechanical ventilation, and steroid therapy. Acute pulmonary disease can also manifest with a prolonged illness (10 days to 3 wk) consisting of weight loss, dyspnea, high fever, asthenia, and fatigue. Children with symptomatic disease typically have a patchy bronchopneumonia; hilar lymphadenopathy is variably present (Fig. 265.1). In young children, the pneumonia can coalesce. Focal or buckshot calcifications are convalescent findings in patients with acute pulmonary infection.

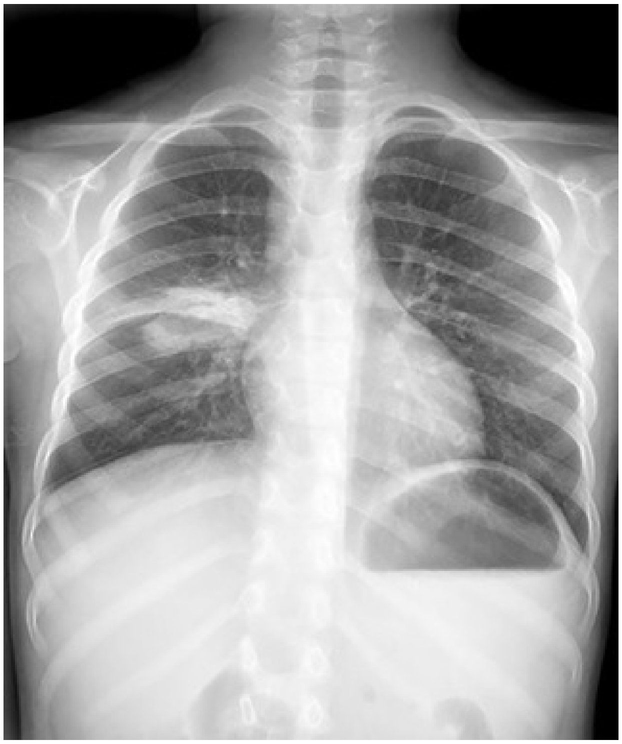

FIG. 265.1 Radiograph of a 5 yr old child with acute pulmonary histoplasmosis showing right perihilar lymphadenopathy.

Complications of pulmonary histoplasmosis occur secondary to exaggerated host responses to fungal antigens within the lung parenchyma or hilar lymph nodes. **Histoplasmomas** are of parenchymal origin and are usually asymptomatic. These fibroma-like lesions are often concentrically calcified and single. Rarely, these lesions produce broncholithiasis associated with "stone spitting," wheezing, and hemoptysis. In endemic regions, these lesions can mimic parenchymal tumors and are occasionally diagnosed at lung biopsy. **Mediastinal granulomas** form when reactive hilar lymph nodes coalesce and mat together. Although these lesions are usually asymptomatic, huge granulomas can compress the mediastinal structures, producing symptoms of esophageal, bronchial, or vena caval obstruction. Local extension and necrosis can produce pericarditis or pleural effusions. **Mediastinal fibrosis** is a rare complication of mediastinal granulomas and represents an uncontrolled fibrotic reaction arising from the hilar nodes. Structures within the mediastinum become encased within a fibrotic mass, producing obstructive symptomatology. Superior vena cava syndrome, pulmonary venous obstruction with a mitral stenosis-like syndrome, and pulmonary artery obstruction with congestive heart failure have been described. Dysphagia accompanies esophageal entrapment, and a syndrome of cough, wheeze, hemoptysis, and dyspnea accompanies bronchial obstruction. Rarely, children develop a sarcoid-like disease with arthritis or arthralgia, erythema nodosum, keratoconjunctivitis, iridocyclitis, and pericarditis. **Pericarditis** , with effusions both pericardial and pleural, is a self-limited benign condition that develops as a result of an inflammatory reaction to adjacent mediastinal disease. The effusions are exudative, and the organism is rarely culturable from fluid. **Progressive disseminated histoplasmosis** can occur in infants as well as children with deficient cell-mediated immunity. Disseminated disease may occur either during the initial acute infection in children with primary or secondary immunodeficiencies affecting T-cell function (see Pathogenesis above), in infants, or as a reactivation of a latent focus of infection within the reticuloendothelial system in children who acquire an immunosuppressive condition years following primary infection. Disseminated histoplasmosis in an HIV-infected patient is an AIDS-defining illness. Fever is the most common finding and can persist for weeks to months before the condition is diagnosed. The majority of patients have hepatosplenomegaly, lymphadenopathy, and interstitial pulmonary disease. Extrapulmonary infection is a characteristic of disseminated disease and can include destructive bony lesions, Addison disease, meningitis, multifocal chorioretinitis, and endocarditis. Some patients develop mucous membrane ulcerations and skin findings such as nodules, ulcers, or molluscum-like papules. A sepsis-like syndrome has been identified in a small number of HIV-infected patients with disseminated histoplasmosis and is characterized by the rapid onset of shock, multiorgan failure, and coagulopathy. Reactive hemophagocytic syndrome has been described in immunocompromised patients with severe disseminated histoplasmosis. Many children with disseminated disease experience transient hyperglobulinemia. Elevated acute-phase reactants and hypercalcemia are typically seen but are nonspecific. Anemia, thrombocytopenia, and pancytopenia are variably present; elevated liver function tests and high serum concentrations of angiotensin-converting enzyme may be observed. Chest radiographs are normal in more than half of children with disseminated disease.

Chronic pulmonary histoplasmosis is an opportunistic infection in adult patients with centrilobular emphysema. **Chronic progressive disseminated histoplasmosis** is a slowly progressive infection due to *Histoplasma* that occurs in older adults without obvious immunosuppression that is uniformly fatal if untreated. These entities are rare in children.

Diagnosis

Optimal diagnosis of suspected histoplasmosis depends on the clinical presentation and underlying immune status of the patient. Utilizing serum and urine antigen tests along with serum antibody tests via complement fixation and immunodiffusion yields a diagnostic sensitivity >90% for acute pulmonary and disseminated forms of histoplasmosis. Diagnostic testing options include:

Antigen detection is the most widely available diagnostic study for patients with suspected pulmonary histoplasmosis or progressive disseminated histoplasmosis. Enzyme immunoassay has replaced radioimmunoassay in many laboratories as the method to detect *H. capsulatum* polysaccharide antigen in urine, blood, bronchoalveolar lavage fluid, and cerebrospinal fluid. In patients at risk for disseminated disease, antigen can be demonstrated in the urine, blood, or bronchoalveolar lavage fluid in more than 90% of cases. Antigenuria has been shown to correlate with severity of disseminated histoplasmosis. Serum, urine, and bronchoalveolar lavage fluid from patients with acute or chronic pulmonary infections are variably antigen positive. In 1 study, antigenuria was present in 83% of patients with acute pulmonary disease and 30% of patients with subacute pulmonary disease. False-positive results on urinary antigen testing can occur in patients with *Blastomyces dermatitidis, Coccidioides immitis, Coccidioides posadasii, Paracoccidioides brasiliensis,* and *Penicillium marneffei* . Testing both urine and serum samples for histoplasma antigen increases the sensitivity compared with testing only the urine or serum alone. Sequential measurement of urinary antigen in patients with disseminated disease is useful for monitoring response to therapy; however, persistent low-level antigenuria may occur in some patients who have completed therapy and have no evidence of active infection.

Antibody tests continue to be useful for the diagnosis of acute pulmonary histoplasmosis, its complications, and chronic pulmonary disease. Serum antibody to yeast and mycelium-associated antigens is classically measured by complement fixation. Although titers of >1 : 8 are found in more than 80% of patients with histoplasmosis, titers of ≥1 : 32 are most significant for the diagnosis of recent infection. Complement-fixation antibody titers are often not significant early in the infection and do not become positive until 4-6 wk after exposure. A 4-fold increase in either yeast or mycelial-phase titers or a single titer of ≥1 : 32 is presumptive evidence of active infection. Complement-fixation titers may be falsely positive in patients with other systemic mycoses such as *B.*

dermatitidis and *C. immitis* and may be falsely negative in immunocompromised patients. Antibody detection by immunodiffusion is less sensitive but more specific than complement fixation and is used to confirm questionably positive complement-fixation titers. The highest sensitivity for antibody testing can be achieved by combining complement fixation and immunodiffusion testing.

Culture sensitivity of tissue or body fluid samples is generally highest for children with progressive disseminated histoplasmosis or acute pulmonary histoplasmosis due to a large inoculum of organisms. *Histoplasma* typically grows within 6 wk on Sabouraud agar at 25°C (77°F). Identification of tuberculate macroconidia allows for only a presumptive diagnosis, because *Sepedonium* species form similar structures. A confirmatory test using a chemiluminescent DNA probe for *H. capsulatum* is necessary to establish a definitive identification. The yeast can be recovered from blood or bone marrow in >90% of patients with progressive disseminated histoplasmosis. Sputum cultures are rarely obtained and are variably positive in normal hosts with acute pulmonary histoplasmosis; cultures of bronchoalveolar lavage fluid appear to have a slightly higher yield than sputum cultures. Blood cultures are sterile in patients with acute pulmonary histoplasmosis, and cultures from any source are typically sterile in patients with the sarcoid form of the disease.

Histological examination can identify yeast forms in tissue from patients with complicated forms of acute pulmonary disease (histoplasmoma and mediastinal granuloma). Tissue should be stained with methenamine silver or periodic acid-Schiff stains, and yeast can be found within or outside of macrophages. In children with disseminated disease, organisms can be identified from bone marrow, liver, and mucocutaneous lesions. In those who are severely ill, Wright stain of peripheral blood can demonstrate fungal elements within leukocytes. Examination of fibrotic tissue from children with mediastinal fibrosis usually demonstrates no organisms.

Real-time polymerase chain reaction has been used on formalin-fixed, paraffin-embedded biopsy tissue and has an analytical sensitivity of at least 6 pg/µL from tissue-extracted DNA and a clinical sensitivity and specificity of 88.9% and 100%, respectively. Although not widely available, molecular methods may ultimately provide a more timely and accurate diagnosis.

Skin testing is useful only for epidemiologic studies, as cutaneous reactivity is lifelong and intradermal injection can elicit an immune response in otherwise seronegative persons. Reagents are no longer commercially available.

Treatment

Acute pulmonary histoplasmosis does not require antifungal therapy for asymptomatic or mildly symptomatic children. Oral itraconazole (4-10 mg/kg/day in 2 divided doses, not to exceed 400 mg daily) for 6-12 wk should be considered in patients with acute pulmonary infections who fail to improve clinically within 1 mo. Although it appears to be less effective, fluconazole may be considered as an alternative therapy in children intolerant to itraconazole. Clinical experience in treating histoplasmosis with the newer azoles (voriconazole and posaconazole) is increasing, although these medications are not currently recommended at this time. *Patients with pulmonary histoplasmosis who become hypoxemic or require ventilatory support* should receive amphotericin B deoxycholate (0.7-1.0 mg/kg/day) or amphotericin B lipid complex (3-5 mg/kg/day) until improved; continued therapy with oral itraconazole for a minimum of 12 wk is also recommended. The lipid preparations of amphotericin are not preferentially recommended in children with pulmonary histoplasmosis, as the classic preparation is generally well tolerated in this patient population. Patients with severe obstructive symptoms caused by granulomatous mediastinal disease may be treated sequentially with amphotericin B followed by itraconazole for 6-12 mo. Patients with milder mediastinal disease may be treated with oral itraconazole alone. Some experts recommend that surgery be reserved for patients who fail to improve after 1 mo of intensive amphotericin B therapy. Sarcoid-like disease with or without pericarditis may be treated with nonsteroidal antiinflammatory agents for 2-12 wk.

Progressive disseminated histoplasmosis usually requires amphotericin B deoxycholate (1 mg/kg/day for 4-6 wk) as the cornerstone of therapy. Lipid preparations of amphotericin may be substituted in patients intolerant to the classic drug preparation. Alternatively, amphotericin B may be given for 2-4 wk followed by oral itraconazole (4-10 mg/kg/day in 2 divided doses) as maintenance therapy for 3 mo, depending on *Histoplasma* antigen status. Longer therapy may be needed in patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. It is recommended to monitor blood levels of itraconazole during treatment, aiming for a concentration of ≥1 µg/mL but <10 µg/mL to avoid potential drug toxicity. It is also recommended to monitor urine antigen levels during therapy and for 12 mo after therapy has ended to ensure cure. Relapses in immunocompromised patients with progressive disseminated histoplasmosis are relatively common. Lifelong suppressive therapy with daily itraconazole (5 mg/kg/day up to adult dose of 200 mg/day) may be required if immunosuppression cannot be reversed. For severely immunocompromised HIV-infected children living in endemic regions, itraconazole (2-5 mg/kg every 12-24 hr) may be used prophylactically. Care must be taken to avoid interactions between antifungal azoles and protease inhibitors.

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CHAPTER 266

Blastomycosis (*Blastomyces dermatitidis* and *Blastomyces gilchristii*)

Gregory M. Gauthier, Bruce S. Klein

Etiology

Blastomyces dermatitidis and *Blastomyces gilchristii* belong to a group of fungi that exhibit thermal dimorphism. In the soil (22-25°C [71.6-77°F]), these fungi grow as mold and produce spores, which are the infectious particles. Following soil disruption, aerosolized mycelial fragments and spores inhaled into the lungs (37°C [98.6°F]) convert into pathogenic yeast and cause infection. In addition to *B. dermatitidis* and *B. gilchristii,* 4 additional species have been recently identified including *B. percursus, B. helicus, B. parvus,* and *B. silverae* .

Epidemiology

B. dermatitidis and *B. gilchristii* cause disease in immunocompetent and immunocompromised children. Only 2–13% of blastomycosis cases occur in the pediatric population (average age: 9.1-11.5 yr; range: 19 days to 18 yr). Blastomycosis of newborns and infants is rare. In North America, the geographic distribution of blastomycosis cases is restricted to the Midwest, south-central, and southeastern United States and parts of Canada bordering the Great Lakes and Saint Lawrence River Valley. In these geographic regions, several areas are hyperendemic for blastomycosis (e.g., Marathon and Vilas Counties, Wisconsin; Washington Parish, Louisiana; central and south-central Mississippi; Kenora, Ontario). Outside of North America, autochthonous infections have been reported from Africa (≈100 cases) and India (<12 cases). *B. dermatitidis* is not considered endemic to the Middle East, Central America, South America, Europe, Asia, or Australia. In North America, *Blastomyces* grows in an ecologic niche characterized by forested, sandy soils with an acidic pH that have decaying vegetation and are near water. Most *Blastomyces* infections are sporadic; however, more than 17 outbreaks have been reported, and most of these outbreaks have involved pediatric patients. Outbreaks are associated with construction or outdoor activities (camping, hiking, fishing, rafting on a river, using a community compost pile); however, some outbreaks have no identifiable risk factors other than geography. The severity of infection is influenced by the size of the inhaled inoculum and the integrity of the patient's immune system. Those immunosuppressed by solid organ transplantation, AIDS, and tumor necrosis factor-α inhibitors are at risk for developing severe or disseminated infection.

Pathogenesis

The ability of mycelial fragments and spores to convert to yeast in the lung is a crucial event in the pathogenesis of infection with *Blastomyces* and other dimorphic fungi. This temperature-dependent morphologic shift, which is known as the phase transition, enables *Blastomyces* to evade the host immune system and establish infection. In the yeast form, the essential virulence factor BAD1 (B*lastomyces* ad*hesin* -1; formerly WI-1) is secreted into the extracellular milieu and binds back to chitin on the fungal cell wall. BAD1 is a multifunctional protein that promotes binding of yeast to alveolar macrophages (via CR3 and CD14 receptors) and lung tissue (via heparan sulfate), blocks the deposition of complement on the yeast surface, binds calcium, suppresses the host's ability to produce cytokines (tumor necrosis factor-α, interleukin-17, interferon-gamma), and inhibits activation of $CD4^+$ T lymphocytes. Deletion of *BAD1* abolishes virulence of *Blastomyces* yeast in a murine model of pulmonary infection.

The phase transition between mold and yeast forms is a complex event that involves alteration in cell wall composition, metabolism, intracellular signaling, and gene expression. The morphologic shift to yeast is regulated in part by a histidine kinase known as DRK1 (*d* imorphism *r* egulating *k* inase-1). This sensor kinase controls not only the conversion of mold to yeast but also spore production, cell wall composition, and *BAD1* expression; the loss of *DRK1* gene expression through gene disruption renders *B. dermatitidis* avirulent in a murine model of pulmonary blastomycosis. The function of DRK1 is conserved in other thermally dimorphic fungi, including *Histoplasma capsulatum* and *Talaromyces marneffei* (formerly *Penicillium marneffei*).

The phase transition is reversible, and following a drop in temperature from 37°C (98.6°F) to 22°C (71.6°F), yeast convert to sporulating mold. Growth as mold promotes survival in the soil, allows for sexual reproduction to enhance genetic diversity, and facilitates transmission to new hosts (via spores and mycelial fragments). The transition from yeast to mold is influenced by SREB (siderophore biosynthesis repressor in *Blastomyces*) and *N* -acetylglucosamine transporters (NGT1, NGT2). Deletion of *SREB* , which encodes a GATA transcription factor, results in the failure of *B. dermatitidis* yeast to complete the conversion to mold at 22°C. *N* -Acetylglucosamine, which polymerizes to form chitin, accelerates the transition to hyphae via NGT1 and NGT2 transporters.

Innate and adaptive immune systems are required to effectively control infection; humoral immunity is dispensable. Macrophages and neutrophils are capable of ingesting and killing *Blastomyces* conidia. In contrast, yeast are poorly killed by nonactivated macrophages, are resistant to reactive oxygen species, and suppress nitric oxide production. Adaptive immunity is mediated by T lymphocytes (Th1 and Th17), which activate macrophages and neutrophils to facilitate clearance of infection. Following infection, cell-mediated immunity against *Blastomyces* can last for at least 2 yr.

Clinical Manifestations

The clinical manifestations of blastomycosis are diverse and include subclinical infection, symptomatic pneumonia, and disseminated disease. Clinical disease develops 3 wk-3 mo following inhalation of spores or mycelial fragments. Asymptomatic or subclinical infections are estimated to occur in 50% of patients.

The most common clinical manifestation of blastomycosis is **pneumonia** , which can range from acute to chronic. Acute symptoms resemble community-acquired pneumonia and include fever, dyspnea, cough, chest pain, and malaise (Fig. 266.1). Respiratory failure, including acute respiratory distress syndrome (ARDS), can occur in patients with an overwhelming burden of infection. Chest imaging typically demonstrates air space consolidation, which can involve the upper or lower lobes. Other radiographic features include nodular, reticulonodular, and miliary patterns. Hilar adenopathy and pleural effusions are uncommon. Because the clinical and radiographic features can mimic bacterial pneumonia, patients can be mistakenly treated with antibiotics, resulting in disease progression, which can result in disseminated disease or respiratory failure, including ARDS. Patients with subacute or chronic pneumonia experience fevers, chills, night sweats, cough, weight loss, hemoptysis, dyspnea, and chest pain. Mass lesions and cavitary disease on chest roentgenography can mimic malignancy and tuberculosis, respectively.

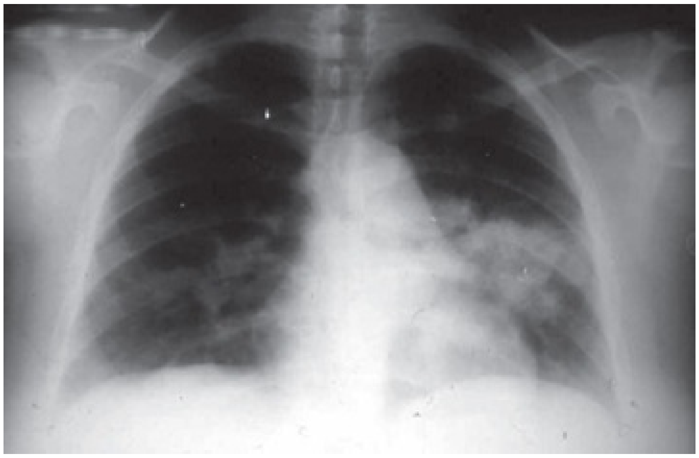

FIG. 266.1 Left lung infection in a patient with symptoms resembling acute bacterial pneumonia. Organisms of *Blastomyces dermatitidis* in sputum seen with potassium hydroxide preparation, and subsequent culture confirmed the diagnosis. (From Bradsher Jr RW: Blastomycoses. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* , ed 8. Philadelphia, 2015, Elsevier, Fig. 266-5.)

Extrapulmonary blastomycosis most often affects the skin or bone but can involve almost any organ. The incidence of **extrapulmonary blastomycosis** in children ranges from 38% to 50%, similar to rates in adult patients (25–40%). The skin is the most common site for extrapulmonary blastomycosis, which is usually the result of hematogenous dissemination. Direct inoculation of *B. dermatitidis* into the skin from trauma or a laboratory accident can result in primary cutaneous blastomycosis. Skin manifestations include plaques, papules, ulcers, nodules, and verrucous lesions. Erythema nodosum is rare in blastomycosis. Dissemination of *B. dermatitidis* to the bone results in lytic destruction, pain, soft tissue swelling, sinus tract formation, and ulceration. The ribs, skull, spine, and long bones are most commonly affected. Patients with osteomyelitis often have pulmonary or cutaneous involvement. Vertebral osteomyelitis can be complicated by paraspinal abscess, psoas abscess, and vertebral body collapse. Extension of long bone osteomyelitis can result in pathologic fracture or septic arthritis. Genitourinary blastomycosis occurs in <10% of adults but is rare in children.

Central nervous system (CNS) blastomycosis (brain abscess, meningitis) occurs in <10% of immunocompetent patients but in up to 40% of persons with AIDS. The majority of patients with CNS blastomycosis have clinically apparent infection at non-CNS sites (e.g., lung, skin). Symptoms of CNS infection include headache, altered mental status, memory loss, seizure, cranial nerve deficits, and focal neurologic deficits. Complications include hydrocephalus, cerebral herniation, infarction, panhypopituitarism, residual weakness, and poor functioning in school. Lumbar puncture demonstrates leukocytosis with a neutrophil or lymphocyte predominance, elevated protein, and low glucose. Growth of *Blastomyces* in culture from cerebral spinal fluid occurs in less than 50% of affected patients.

Blastomycosis can complicate pregnancy, and clinical information is limited to case reports. Disseminated infection involving the lungs, skin, and bone is common. Spread of infection to the placenta has been documented by histopathology; however, the frequency of placental blastomycosis remains unknown. Transmission of *Blastomyces* to the fetus is uncommon and is postulated to occur through transplacental transmission or aspiration of infected vaginal secretions. Although clinical data are limited, blastomycosis during pregnancy does not appear to increase the risk for congenital malformations.

Diagnosis

The diagnosis of blastomycosis requires a high index of suspicion because the clinical and radiographic manifestations can mimic other diseases, including community-acquired pneumonia, tuberculosis, and malignancy. The misdiagnosis of blastomycosis, most often as community-acquired pneumonia, results in delay of therapy and progression of disease including dissemination and respiratory failure. Blastomycosis should be included in the differential diagnosis for patients with pneumonia who (1) live in or visit areas in which this pathogen is endemic; (2) fail to respond to a treatment course of antibiotics; or (3) have concomitant skin lesions or osteomyelitis. A detailed medical history regarding exposure risks (e.g., canoeing, rafting, hiking, fishing, playing in outdoor forts, beaver dam exploration, home remodeling, nearby road or building construction, woodpile for a wood burning stove, and use of a community compost pile) should be obtained. In addition, the health of family pets such as dogs should also be ascertained, as canine disease may be a harbinger of human infection. The incidence of blastomycosis in dogs is 10-fold higher than in humans, and canine infection suggests a common source of environmental *Blastomyces* exposure.

Growth of *Blastomyces* in culture from sputum, skin, bone, or other clinical specimens provides a definitive diagnosis. Sputum specimens should be stained with 10% potassium hydroxide or calcofluor white. Histopathology shows neutrophilic infiltration with noncaseating granulomas (pyogranulomas). *Blastomyces* yeast in tissue samples can be visualized using Gomori methenamine silver or periodic acid–Schiff stains. Yeasts are 8-20 µm in size, have a double refractile cell wall, and are characterized by broad-based budding between mother and daughter cells.

Nonculture diagnostic techniques should be used in conjunction with fungal smears and cultures to facilitate the diagnosis of blastomycosis. The development of a *Blastomyces* antigen test has supplanted insensitive serologic methods such as complement fixation and immunodiffusion. Urine, serum, cerebrospinal fluid, and bronchoalveolar fluid specimens can be collected for the *Blastomyces* antigen test. Sensitivity of the urine antigen test ranges from 76.3% to 92.9% and is influenced by the burden of infection. The antigen test can cross-react with other dimorphic fungi, including *Histoplasma capsulatum, Paracoccidioides brasiliensis,* and *Penicillium marneffei* , decreasing the specificity to 76.9–79%. An antibody test against the BAD1 protein has been developed and has a sensitivity of 87.8% and a specificity of 94–99%; however, this test is not yet commercially available. Combination antigen and BAD1 antibody testing can increase diagnostic sensitivity to 97.6%.

Treatment

Antifungal therapy is influenced by the severity of the infection, involvement of the central nervous system, the integrity of the host's immune system, and pregnancy. All persons diagnosed with blastomycosis should receive antifungal therapy. **Newborns** with blastomycosis should be treated with amphotericin B deoxycholate 1 mg/kg/day. **Children with mild to moderately severe infection** can be treated with itraconazole 10 mg/kg/day (maximum: 400 mg/day) for 6-12 mo. **Children with severe disease, immunodeficiency, or immunosuppression** should be treated with amphotericin B deoxycholate 0.7-1.0 mg/kg/day or lipid amphotericin B 3-5 mg/kg/day until there is clinical improvement, generally 7-14 days, and then itraconazole 10 mg/kg/day (maximum: 400 mg/day) for a total of 12 mo. **Central nervous system blastomycosis** requires therapy with lipid amphotericin B 5 mg/kg/day for 4-6 wk, followed by itraconazole, fluconazole, or voriconazole for ≥12 mo.

All pediatric patients of childbearing age should undergo pregnancy testing prior to initiation of azole antifungals. Itraconazole can increase the risk for spontaneous abortion, and fluconazole can cause craniofacial defects resembling Antley-Bixler syndrome. Voriconazole and posaconazole cause skeletal abnormalities in animal models. Treatment of blastomycosis in **pregnant patients** consists of lipid amphotericin B 3-5 mg/kg/day.

For patients receiving itraconazole, the oral antifungal of choice, *therapeutic drug monitoring* should be performed 14 days into therapy (goal total itraconazole level 1-5 µg/mL), and liver function tests should be monitored periodically. Due to the long half-life of itraconazole, serum drug levels can be obtained at any time of the day, irrespective of when the drug was administered. Total itraconazole level is determined by adding itraconazole and hydroxyitraconazole concentrations; hydroxyitraconazole is a metabolite that possesses antifungal activity. Voriconazole, posaconazole, and isavuconazonium sulfate have activity against *B. dermatitidis* . Clinical experience with these drugs appears promising but remains limited. Therapeutic drug monitoring is needed for voriconazole and posaconazole (goal trough levels 1-5 µg/mL). The echinocandins (caspofungin, micafungin, and anidulafungin) *should not be used* to treat blastomycosis. Serial measurement of urine antigen levels to assess response to therapy can be helpful adjunct in monitoring response to antifungal therapy.

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CHAPTER 267

Coccidioidomycosis (*Coccidioides* Species)

Rebecca C. Brady

Etiology

Coccidioidomycosis (valley fever, San Joaquin fever, desert rheumatism, coccidioidal granuloma) is caused by *Coccidioides* spp., a soil-dwelling dimorphic fungus. *Coccidioides* spp. grow in the environment as spore-bearing (arthroconidia-bearing) mycelial forms. In their parasitic form, they appear as unique, endosporulating spherules in infected tissue. The 2 recognized species, *C. immitis* and *C. posadasii*, cause similar illnesses.

Epidemiology

Coccidioides spp. inhabit soil in arid regions. *C. immitis* is primarily found in California's San Joaquin Valley. *C. posadasii* is endemic to southern regions of Arizona, Utah, Nevada, New Mexico, western Texas, and regions of Mexico and Central and South America.

Population migrations into endemic areas and increasing numbers of immunosuppressed persons have caused coccidioidomycosis to become an important health problem. From 2000 to 2012, there were 3,453 incidents of pediatric coccidioidomycosis cases reported in California, about 9.6% of the total coccidioidomycosis cases. During the same time period, there were 1,301 hospitalizations and 11 deaths associated with coccidioidomycosis in the California pediatric population. Case and hospitalization rates per 100,000 population increased from 0.7 to 3.9 and from 0.2 to 1.2, respectively. These case and hospitalization rates were highest in males, those in the 12-17 age group, and residents of the California endemic region.

Infection results from inhalation of aerosolized spores. Incidence increases during windy, dry periods that follow rainy seasons. Seismic events, archaeologic excavations, and other activities that disturb contaminated sites have caused outbreaks. Person-to-person transmission does not occur. Rarely, infections result from spores that contaminate fomites or grow beneath casts or wound dressings of infected patients. Infection has also resulted from transplantation of organs from infected donors and from mother to fetus or newborn. Visitors to endemic areas can acquire infections, and diagnosis may be delayed when they are evaluated in nonendemic areas. Spores are highly virulent, and *Coccidioides* spp. are potential agents of bioterrorism (see Chapter 741).

Pathogenesis

Inhaled spores reach terminal bronchioles, where they transform into septated spherules that resist phagocytosis and within which many endospores develop. Released endospores transform into new spherules, and the process results in an acute focus of infection. Endospores can also disseminate lymphohematogenously. Eventually, a granulomatous reaction predominates. Both recovery and protection upon reexposure depend on effective cellular immunity.

Children with **congenital primary immunodeficiency** disorders may be at increased risk for infection; these disorders include interleukin-12Rβ1 deficiency, interferon-γR1 deficiency, and *STAT1* gain-of-function mutations.

Clinical Manifestations

The clinical spectrum (Fig. 267.1) encompasses pulmonary and extrapulmonary disease. Pulmonary infection occurs in 95% of cases and can be divided into primary, complicated, and residual infections. Approximately 60% of infections are asymptomatic. Symptoms in children are often milder than those in adults. The incidence of extrapulmonary dissemination in children approaches that of adults.

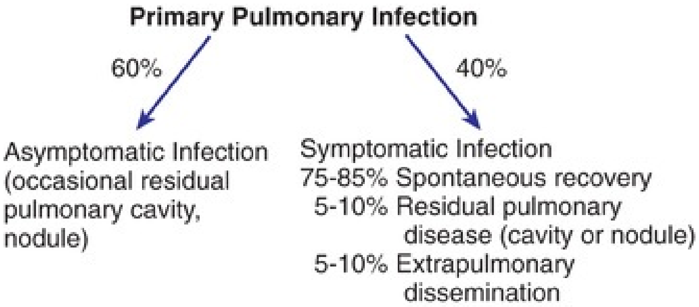
Primary Pulmonary Infection
60%
40%
Asymptomatic Infection (occasional residual pulmonary cavity, nodule)
Symptomatic Infection
75-85% Spontaneous recovery
5-10% Residual pulmonary disease (cavity or nodule)
5-10% Extrapulmonary dissemination

FIG. 267.1 Natural history of coccidioidomycosis.

Primary Coccidioidomycosis

The incubation period is 1-4 wk, with an average of 10-16 days. Early symptoms include malaise, chills, fever, and night sweats. Chest discomfort occurs in 50–70% of patients and varies from mild tightness to severe pain. Headache and/or backache are sometimes reported. An evanescent, generalized, fine macular erythematous or urticarial eruption may be seen within the first few days of infection. Erythema nodosum can occur (more often in women) and is sometimes accompanied by an erythema multiforme rash, usually 3-21 days after the onset of symptoms. The clinical constellation of erythema nodosum, fever, chest pain, and arthralgias (especially knees and ankles) has been termed *desert rheumatism* and *valley fever.* The chest examination is often normal even if radiographic findings are present. Dullness to percussion, friction rub, or fine rales may be present. Pleural effusions can occur and can become large enough to compromise respiratory status. Hilar and mediastinal lymphadenopathy are common (Fig. 267.2).

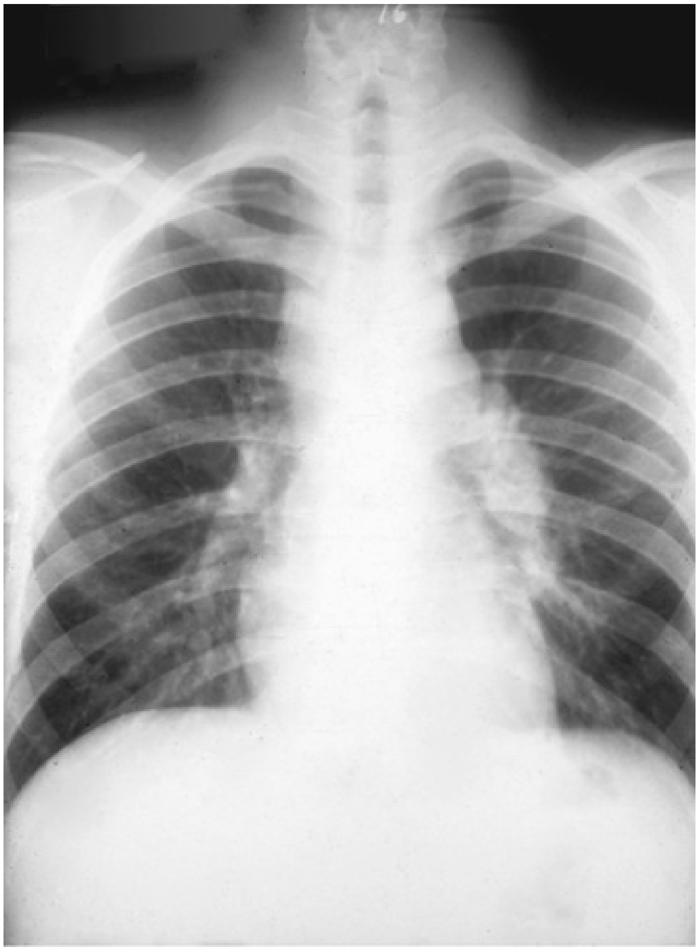

FIG. 267.2 Chest radiograph of a 19 yr old man with acute primary coccidioidomycosis. There is prominent hilar lymphadenopathy and mediastinal widening.

Complicated Pulmonary Infection

Complicated infections include severe and persistent pneumonia, progressive primary coccidioidomycosis, progressive fibrocavitary disease, transient cavities that develop in areas of pulmonary consolidation, and empyema that follows rupture of a cavity into the pleural space. Some cavities persist, are thin walled and peripheral, and cause no symptoms; occasionally there is mild hemoptysis, and rarely there is serious hemorrhage. Rarely, acute respiratory insufficiency occurs following intense exposure; this condition is associated with high mortality rates.

Residual Pulmonary Coccidioidomycosis

Residual pulmonary coccidioidomycosis includes fibrosis as well as persisting pulmonary nodules. Nodules are present in 5–7% of infections and sometimes require differentiation from malignancy in adults.

Disseminated (Extrapulmonary) Infection

Clinically apparent dissemination occurs in 0.5% of patients. Its incidence is increased in infants; men; persons of Filipino, African, and Latin American ancestry; and persons from other Asian backgrounds. Primary or acquired disorders of cellular immunity (Table 267.1) markedly increase the risk of dissemination.

Table 267.1

Risk Factors for Poor Outcome in Patients With Active Coccidioidomycosis

PRIMARY INFECTIONS
Severe, prolonged (≥6 wk), or progressive infection
RISK FACTORS FOR EXTRAPULMONARY DISSEMINATION
Primary or acquired cellular immune dysfunction (including patients receiving tumor necrosis factor inhibitors)
Neonates, infants, the elderly
Male sex (adult)
Filipino, African, Native American, or Latin American ethnicity
Late-stage pregnancy and early postpartum period
Standardized complement fixation antibody titer >1 : 16 or increasing titer with persisting symptoms
Blood group B
Human leukocyte antigen class II allele-DRBI*1301

Symptoms usually occur within 6 mo of primary infection. Prolonged fever, toxicity, skin lesions, subcutaneous and/or osseous cold abscesses, and laryngeal lesions can herald the onset. Organism-specific skin lesions have a predilection for the nasolabial area and appear initially as papules, which evolve to form pustules, plaques, abscesses, and verrucous plaques. Biopsy of these lesions demonstrates spherules. **Basilar meningitis** is the most common manifestation and may be accompanied by ventriculitis, ependymitis, cerebral vasculitis, abscess, and syringomyelia. Headache, vomiting, meningismus, and cranial nerve dysfunction are often present. Untreated meningitis is almost invariably fatal. Bone infections account for 20–50% of extrapulmonary manifestations, are often multifocal, and can affect adjacent structures. Miliary dissemination and peritonitis can mimic tuberculosis.

Diagnosis

Nonspecific tests have limited usefulness. The complete blood count might show an elevated eosinophil count, and marked eosinophilia can accompany dissemination.

Culture, Histopathologic Findings, and Antigen Detection

Although diagnostic, culture is positive in only 8.3% of respiratory tract specimens and in only 3.2% of all other sites. *Coccidioides* is isolated from clinical specimens as the spore-bearing mold form, and thus the laboratory should be informed and use special precautions when the diagnosis is suspected. The observation of endosporulating spherules in histopathologic specimens is also diagnostic.

A quantitative enzyme immunoassay (EIA) (MiraVista Diagnostics) that detects coccidioidal galactomannan in urine, serum, plasma, cerebrospinal fluid, or bronchoalveolar lavage fluid has excellent specificity and is positive in 70% of patients with severe infections. Although the EIA can cross-react with other endemic mycoses, interpretation is often straightforward because there is negligible geographic overlap with areas endemic for other mycoses. In addition, a real-time polymerase chain reaction assay has been developed to directly detect the fungus in tissue samples and is undergoing validation but is not yet commercially available.

Cerebrospinal fluid (CSF) analysis should be performed in patients with suspected dissemination. The findings in meningitis are similar to those seen with tuberculous meningitis (see Chapter 242). Eosinophilic pleocytosis may be present. Fungal stains and culture are usually negative. Volumes of 10 mL in adults have improved the yield of culture.

Serology

Serologic tests provide valuable diagnostic information but may be falsely negative early in self-limited infections and in immunocompromised patients.

Three major methods are used, including EIA, complement fixation (CF), and immunodiffusion. EIA and CF tests are best done in experienced reference laboratories.

Immunoglobulin (Ig) M–specific antibody becomes measurable in 50% of infected patients 1 wk after onset and in 90% of infected patients by 3 wk. EIA is sensitive and can detect IgM and IgG antibody; it is less specific than other methods, and confirmation with immunodiffusion or CF may be needed. IgG antibodies measured by CF appear between the 2nd and 3rd wk but can take several months; follow-up testing is needed if tests are negative and clinical suspicion persists. In the presence of CF titers of 1 : 2 or 1 : 4, a positive immunodiffusion test can help corroborate significance. IgG-specific antibody can persist for months, with titers elevated in proportion to the severity of illness. CF titers >1 : 16 are suggestive of dissemination. Direct comparison of the results of CF (IgG) antibody tests measured by different methodologies should be interpreted with caution. IgG antibody titers used to monitor disease activity should be tested concurrently with serum samples taken earlier in the illness using the same methodology.

C. immitis antibody is present in CSF in 95% of patients with meningitis and is usually diagnostic. Rarely, “spillover” in patients without meningitis but with high IgG titers in serum can be present in CSF. Isolation of *Coccidioides* from CSF culture of patients with meningitis is uncommon, although culture of large volumes of CSF may improve sensitivity.

Imaging Procedures

During primary infection, chest radiography may be normal or demonstrate consolidation, single or multiple circumscribed lesions, or soft pulmonary densities. Hilar and subcarinal lymphadenopathy is often present (see Fig. 267.2). Cavities tend to be thin walled (Fig. 267.3). Pleural effusions vary in size. The presence of miliary or reticulonodular lesions is prognostically unfavorable. Isolated or multiple osseous lesions are usually lytic and often affect cancellous bone. Lesions can affect adjacent structures, and vertebral lesions can impact the spinal cord.

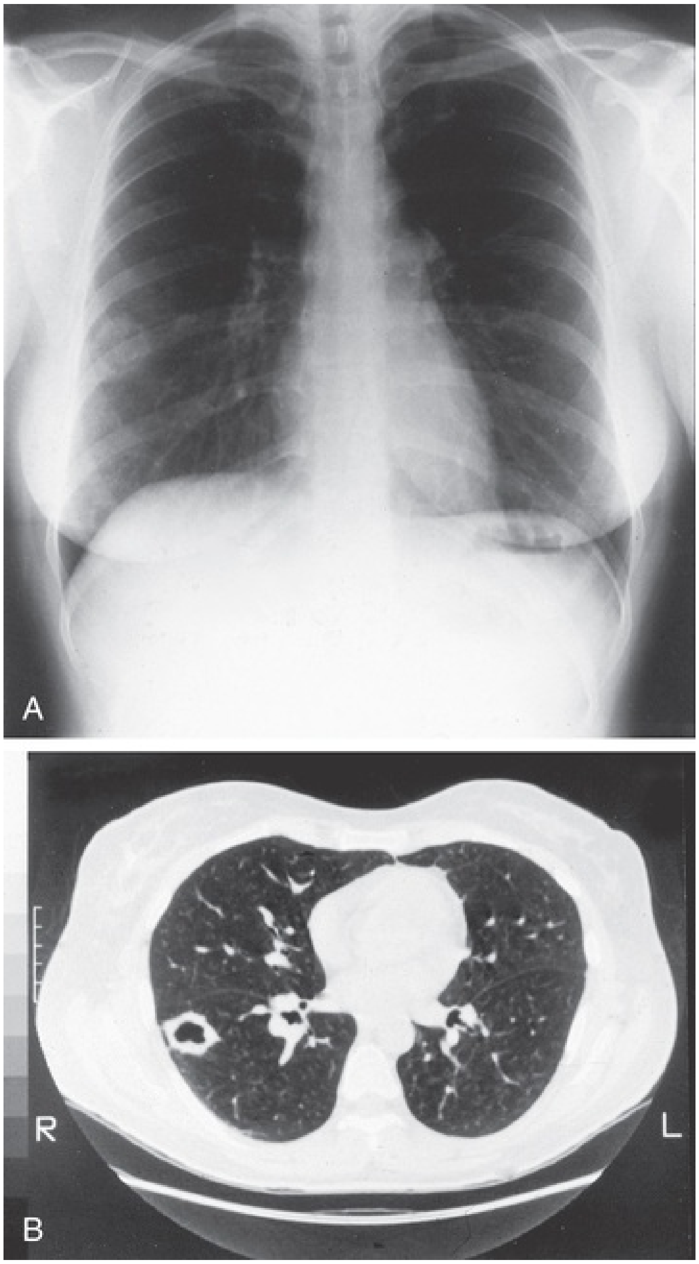

FIG. 267.3 **A,** Chest radiograph revealing a chronic cavitary lesion in the right lung of a woman with coccidioidomycosis. **B,** CT showing the same cavity in the right lung.

Treatment

Based on the few rigorous clinical trials performed in adults and the opinions of experts in the management of coccidioidomycosis, consensus treatment guidelines have been developed (Table 267.2). Consultation with experts in an area of endemicity should be considered when formulating a plan of management.

Table 267.2

Indications for Treatment of Coccidioidomycosis in Adults

INDICATION	TREATMENT
Acute pneumonia, mild	Observe without antifungal treatment at 1-3 mo intervals for 2 yr; some experts recommend antifungal treatment
Weight loss >10%; night sweats >3 wk; infiltrates at least half of 1 lung or parts of both lungs; prominent or persistent hilar lymphadenopathy; complement fixation titers >1 : 16; inability to work, symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1-3 mo intervals for 2 yr
Uncomplicated acute pneumonia, special circumstances: immunosuppression, late pregnancy, Filipino or African ancestry, age >55 yr, other chronic diseases (diabetes, cardiopulmonary disease), symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1-3 mo intervals for 2 yr Treat with amphotericin B if in late pregnancy
Diffuse pneumonia: reticulonodular or miliary infiltrates suggest underlying immunodeficiency and possible fungemia, pain	Treat initially with amphotericin B if significant hypoxia or rapid deterioration, followed by an azole for ≥1 yr In mild cases, an azole for ≥1 yr
Chronic pneumonia	Treat with an azole for ≥1 yr
Disseminated disease, nonmeningeal	Treat with an azole for ≥1 yr except in severe or rapidly worsening cases, for which amphotericin B is recommended
Disseminated disease, meningeal	Treat with fluconazole (some add intrathecal amphotericin B) and treat indefinitely

Patients should be followed closely because late relapse can occur, especially in patients who are immunosuppressed or have severe manifestations. Treatment is recommended for all HIV-infected patients with active coccidioidomycosis and CD4 counts <250/µL. Following successful treatment, antifungals may be stopped if the CD4 count exceeds 250/µL. Treatment should be continued if the CD4 count remains less than 250/µL and should be given indefinitely in all HIV-infected patients with coccidioidal meningitis.

First-line agents include oral and intravenous preparations of fluconazole (12 mg/kg/day IV or PO) and itraconazole (10 mg/kg/day). Serum levels of itraconazole should be monitored.

Amphotericin B is preferred for initial treatment of severe infections. Amphotericin B deoxycholate is less costly than lipid formulations and is often well tolerated in children. Once a daily dose of amphotericin B deoxycholate of

1-1.5 mg/kg/day is achieved, the frequency of administration can be reduced to 3 times weekly. The recommended total dosage ranges from 15 to 45 mg/kg and is determined by the clinical response. Lipid formulations of amphotericin are recommended for patients with impaired renal function, for patients receiving other nephrotoxic agents, or if amphotericin B deoxycholate is not tolerated. Some experts prefer liposomal amphotericin to treat central nervous system infections because it achieves higher levels in brain parenchyma. Amphotericin B preparations do not cross the blood-brain barrier to effectively treat *Coccidioides* spp., but they can mask the signs of meningitis. Infections during pregnancy should be treated with amphotericin B, because the azoles are potentially teratogenic. Voriconazole and posaconazole have been used successfully as salvage therapy in infections failing the standard agents.

Primary Pulmonary Infection

Primary pulmonary coccidioidomycosis resolves in 95% of patients without risk factors for dissemination; antifungal therapy does not lessen the frequency of dissemination or pulmonary residua. When it is elected to defer antifungal therapy, visits are recommended at 1-3 mo intervals for 2 yr and as needed.

Patients with significant or prolonged symptoms are more likely to incur benefit from antifungal agents, but there are no established criteria upon which to base the decision. Table 267.2 summarizes commonly used indicators in adults. A treatment trial in adults with primary respiratory infections examined outcomes of antifungal therapy prescribed on the basis of severity and compared them to an untreated group with less-severe symptoms; complications occurred only in patients in the treatment group and only in those in whom treatment was stopped. If treatment is elected, a 3-6 mo course of fluconazole (12 mg/kg/day) or itraconazole (10 mg/kg/day) is recommended.

Diffuse Pneumonia

Diffuse reticulonodular densities or miliary infiltrates, sometimes accompanied by severe illness, can occur in dissemination or follow exposure to a large fungal inoculum. In this setting, amphotericin B is recommended for initial treatment, followed thereafter by extended treatment with high-dose fluconazole (see Table 267.2).

Disseminated (Extrapulmonary) Infection

For nonmeningeal infection (see Table 267.2), oral fluconazole and itraconazole are effective for treating disseminated coccidioidomycosis that is not extensive, is not progressing rapidly, and has not affected the central nervous system. Some experts recommend higher doses for adults than were used in clinical trials. A subgroup analysis showed a tendency for improved response of skeletal infections that were treated with itraconazole. Amphotericin B deoxycholate is used as an alternative, especially if there is rapid worsening and lesions are in critical locations. Voriconazole has been used successfully as salvage therapy. The optimal duration of therapy with the azoles has not been clearly defined. Late relapses have occurred after lengthy treatment and favorable clinical response.

Meningitis

Therapy with oral or IV fluconazole is currently preferred for coccidioidal meningitis. In adults, a dosage of 400-1,200 mg/day is recommended. For children, the dose is 12 mg/kg/day. Some experts use intrathecal, intraventricular, or intracisternally administered amphotericin B in addition to an azole, believing that the clinical response may be faster. Patients who respond to the azole should continue treatment indefinitely. Hydrocephalus is a common occurrence and is not necessarily a marker of treatment failure. In the event of treatment failure with azoles, intrathecal therapy with amphotericin B deoxycholate is indicated, with or without the azole treatment. Cerebral vasculitis can occur and can predispose to cerebral ischemia, infarction, or hemorrhage. The efficacy of steroids in high dosage is unresolved. Salvage therapy with voriconazole has been found to be effective.

Surgical Management

If a cavity is located peripherally or there is recurrent bleeding or pleural extension, excision may be needed. Infrequently, bronchopleural fistula or recurrent cavitation occurs as a surgical complication; rarely, dissemination can result. Perioperative intravenous therapy with amphotericin B may be considered. Drainage of cold abscesses, synovectomy, and curettage or excision of osseous lesions is sometimes needed. Local and systemic administration of amphotericin B can be used to treat coccidioidal articular disease.

Prevention

Prevention relies on education about ways to reduce exposure. Physicians practicing in nonendemic regions should incorporate careful travel histories when evaluating patients with symptoms compatible with coccidioidomycosis.

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CHAPTER 268

Paracoccidioides brasiliensis

Andrew P. Steenhoff

Etiology

Paracoccidioidomycosis (South American or Brazilian blastomycosis, Lutz-Splendore-Almeida disease) is the most common systemic mycosis in Latin America. It is a fungal infection that is endemic in South America, with cases reported in Central America and Mexico. Brazil accounts for more than 80% of all reported cases. The etiologic agent, *Paracoccidioides brasiliensis,* is a thermally dimorphic fungus found in the environment in the mycelial (mold) form and in tissues as yeast.

Epidemiology

P. brasiliensis is a soil-inhabiting microorganism and is ecologically unique to Central and South America. Endemic outbreaks occur mainly in the tropical rain forests of Brazil, with cases scattered in Argentina, Colombia, and Venezuela. There is an increased incidence in areas with moderately high altitude, with high humidity and rainfall, and where coffee and tobacco are grown. Armadillos appear to be a natural reservoir for *P. brasiliensis.* The most common route of infection is by inhalation of conidia. The disease is not usually thought to be contagious, and person-to-person transmission has not been confirmed. Paracoccidioidomycosis is more common among boys after puberty because of the role of estrogen in preventing the transition of conidia to the yeast form. Children account for <10% of the total number of cases.

Pathogenesis

Invasion of *P. brasiliensis* into the human body is based on a myriad of fungal components and strategies to bypass host defense mechanisms. With the emergence of CRISPR technology and full access to diverse databanks (such as genomes, transcriptomes, proteomes, metabolomes, lipidomes), investigators are poised to better understand the virulence processes of *P. brasiliensis* , hopefully allowing translation into benefits for patients.

The entry route into the body is via the respiratory tract, and the lungs are the site of primary infection, although not all patients have respiratory symptoms. Once the conidia or hyphal fragments reach the alveoli, yeast transformation takes place. The infection then spreads to the mucous membranes of the nose, mouth, and gastrointestinal tract. Cell-mediated immunity, mainly through lymphocytes and the production of Th-1 cytokines, is crucial to containing the infection. Tumor necrosis factor-α and interferon-γ activated macrophages are responsible for intracellular killing of *P. brasiliensis* . If the initial immune response is not successful, the response may shift toward a Th-2 pattern, which is unable to contain the infection, resulting in clinical progression. The yeast can disseminate by the lymphohematogenous route to skin, lymph nodes, and other organs and remain dormant in lymph nodes, producing a latent infection with reactivation occurring later on in life. There are cases of patients who developed disease 30 or more years after leaving an endemic region.

Histopathologically, the yeast-like cells are round, with the parent cell being quite large and surrounded by small buds, giving it the appearance of a ship's wheel. A mixed suppurative and granulomatous inflammatory reaction with areas of necrosis is seen in pulmonary infections. In chronic infections fibrosis and calcification may be seen. Mucocutaneous infections are typified by ulceration and pseudoepitheliomatous hyperplasia.

Clinical Manifestations

There are 2 clinical forms of disease. The **acute** form (juvenile paracoccidioidomycosis) is rare, occurs almost exclusively in children and persons with impaired immunity, and targets the reticuloendothelial system. Pulmonary symptoms may be absent, although chest radiographs often show patchy, confluent, or nodular densities. Patients typically present acutely with fever, malaise, wasting, lymphadenopathy, and abdominal enlargement from intraabdominal lymphadenopathy. Hepatomegaly and splenomegaly are nearly constant. Localized bony lesions have been reported in children and can progress to systemic disease. Multifocal osteomyelitis, arthritis, and pericardial effusions can also occur. Nonspecific laboratory findings include anemia, eosinophilia, and hypergammaglobulinemia. Acute paracoccidioidomycosis has a 25% mortality rate. Hepatic involvement associated with jaundice may confer a worse prognosis.

Adults develop a **chronic,** progressive illness that manifests initially with flu-like symptoms, fever, and weight loss (adult paracoccidioidomycosis). Pulmonary infection develops with dyspnea, cough, chest pain, and hemoptysis. Findings on physical examination are scant, although chest radiographs can show infiltrates that are disproportionate with mild clinical findings. Mucositis involving the mouth and its structures as well as the nose can manifest as localized pain, change in voice, or dysphagia. Lesions can extend beyond the oral cavity onto the skin. Generalized lymphadenopathy, hepatosplenomegaly, and adrenal involvement (seen in 15–50% of cases) can lead to Addison disease. Meningoencephalitis and central nervous system granulomas can occur as presenting or secondary symptoms. Adults with extensive exposure to soil, such as farmers, are most likely to develop the chronic form of the disease.

Diagnosis

Demonstration of the fungus by direct wet mount (potassium hydroxide) preparation of sputum, exudate, or pus supports the diagnosis in many cases. Histopathologic examination of biopsy specimens using special fungal staining techniques is also diagnostic. Immunohistochemistry using monoclonal antibodies to specific glycoproteins can also be done on tissue sections. Culture of the fungus on Sabouraud-dextrose or yeast extract agar confirms the diagnosis. Antibodies to *P. brasiliensis* can be demonstrated in most patients. Serial antibody titers and lymphocyte proliferative responses to fungal antigens are useful for monitoring the response to therapy. The 43 kDa glycoprotein (gp43) is present in sera of more than 90% of patients with paracoccidioidomycosis by immunodiffusion (the most commonly used diagnostic test) and in 100% by immunoblotting. A latex particle agglutination test using pooled crude fungal exoantigens is being developed for the detection of anti–*P. brasiliensis* antibodies and has shown 92% agreement with the double immunodiffusion test. Newer diagnostic methods that might prove to be very useful in the future include polymerase chain reaction, detection of gp43, and capture enzyme-linked immunosorbent assay to detect specific immunoglobulin E in patient sera. Skin testing with paracoccidioidin is not reliable, because 30–50% of patients with active disease are nonreactive initially and a positive test indicates previous exposure but not necessarily active disease.

Treatment

Itraconazole (5-10 mg/kg/day with maximum dose of 200 mg/day) orally for 6 mo is the treatment of choice for paracoccidioidomycosis. Fluconazole has also been used, but high doses (≥600 mg/day) and longer treatment periods are required. A small number of patients have been treated with other azoles, including voriconazole, posaconazole, and isavuconazole. These drugs are potential substitutes for itraconazole but are more costly and can have interactions with other drugs. Terbinafine is an allylamine that has potent in vitro activity against *P. brasiliensis* and has been used for successful treatment of paracoccidioidomycosis. Amphotericin B is recommended for disseminated disease and if other therapies fail. Therapy with sulfonamide compounds, including sulfadiazine, TMP-SMX (trimethoprim 8-10 mg/kg/day to maximum of 160 mg, sulfamethoxazole 40-50 mg/kg/day to maximum of 800 mg), and dapsone, have been used historically and are generally less expensive than the newer azoles and allylamines. The primary disadvantage is that the treatment course is very long, lasting months to years, depending on the agent selected. Relapse can occur following any form of therapy, including with amphotericin B. In selected patients with intense inflammation in sites such as the central nervous system or with lung lesions causing respiratory insufficiency, there is some evidence that use of prednisone for 1-2 wk concomitantly with antifungal therapy reduces inflammation more effectively and may be of benefit. Occasionally children develop paradoxical clinical worsening during treatment, including new lymph node enlargement, fistula formation, fever, and weight loss. In this circumstance, steroids are also recommended.

Two therapies currently under investigation include the use of curcumin, an antioxidant found in the Indian spice turmeric, and the calcineurin inhibitor cyclosporine. Curcumin was found to have more antifungal activity than fluconazole against *P. brasiliensis* when studied in vitro using human buccal epithelial cells. Cyclosporine blocks the thermodimorphism of *P. brasiliensis* . Animal models demonstrate that fungal whole cells, purified antigens, peptides, and DNA vaccines have great potential toward the development of a vaccine for use in humans.

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CHAPTER 269

Sporotrichosis *(Sporothrix schenckii)*

Andrew P. Steenhoff

Etiology

Sporotrichosis is a rare fungal infection that occurs worldwide both sporadically and in outbreaks. The etiologic agent, *Sporothrix schenckii,* exhibits temperature dimorphism, existing as a mold at environmental temperatures (25-30°C [77-86°F]) and as a yeast in vivo (37°C [98.6°F]).

Epidemiology

S. schenckii is found throughout the world, but most cases of sporotrichosis are reported from North America, South America, and Japan. In the United States, the majority of cases have occurred in the Midwest, particularly in areas along the Mississippi and Missouri rivers. The fungus is found in decaying vegetation and has been isolated most commonly from sphagnum moss, rosebushes, barberry, straw, and some types of hay. Sporotrichosis can occur as an occupational disease among farmers, gardeners, veterinarians, and laboratory workers. Transmission from bites and scratches of animals, most commonly cats and armadillos, has occurred. Reports of human-to-human transmission are rare. Sporotrichosis has rarely been reported in infants. The mechanism of transmission in children may be zoonotic but usually is unclear. In 1 endemic area of Peru, the incidence of infection is greater in children than in adults; risk factors for infection in these children are playing in crop fields, living in houses with dirt floors, and owning a cat.

Pathogenesis

Disease in humans usually follows cutaneous inoculation of the fungus into a minor wound. Pulmonary infection can result from the inhalation of large numbers of spores. Disseminated infection is unusual but can occur in immunocompromised patients following ingestion or inhalation of spores. The cellular immune response to *S. schenckii* infection is both neutrophilic and monocytic. Histologically, the coexistence of noncaseating granulomas and microabscess formation is characteristic. T-cell–mediated immunity appears to be important in limiting infection, and antibody does not protect against infection. As a result of the paucity of organisms, it is usually difficult to demonstrate the fungi in biopsy specimens.

Clinical Manifestations

Cutaneous sporotrichosis is the most common form of disease in all age groups. Cutaneous disease may either be lymphocutaneous or fixed cutaneous, the former being much more common (Fig. 269.1). Lymphocutaneous sporotrichosis accounts for more than 75% of reported cases in children and occurs after traumatic subcutaneous inoculation. After a variable and often prolonged incubation period (1-12 wk), an isolated, painless erythematous papule develops at the inoculation site. The initial lesion is usually on an extremity in adults but is often on the face in children. The original papule enlarges and ulcerates. Although the infection might remain limited to the inoculation site (fixed cutaneous form), satellite lesions follow lymphangitic spread and appear as multiple tender subcutaneous nodules tracking along the lymphatic channels that drain the lesion. These secondary nodules are subcutaneous granulomas that adhere to the overlying skin and subsequently ulcerate. Sporotrichosis does not heal spontaneously, and these ulcerative lesions can persist for years if untreated. Systemic signs and symptoms are uncommon.

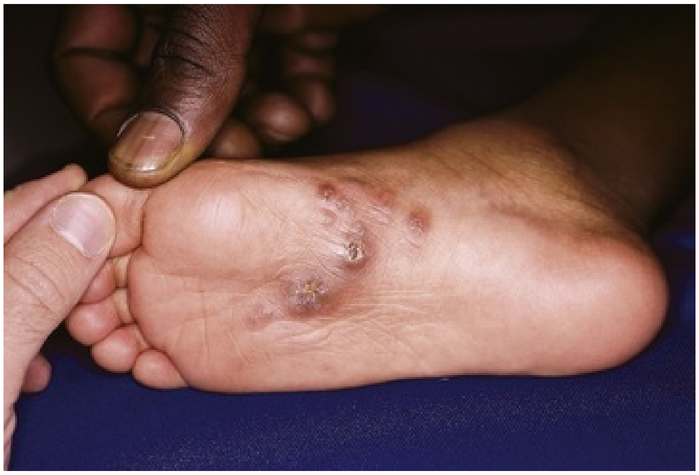

FIG. 269.1 Sporotrichosis. Erythematous papules and nodules on the plantar surface with early lymphangitic (sporotrichoid) spread. (From Paller AS, Mancini AJ: *Hurwitz clinical pediatric dermatology,* ed 5, Philadelphia, 2016, Elsevier, Fig. 17.48.)

Extracutaneous sporotrichosis is rare in children, and most cases are reported in adults with underlying medical conditions, including AIDS and other immunosuppressing diseases. The most common form of extracutaneous sporotrichosis involves infection of the bones and joints. Pulmonary sporotrichosis usually manifests as a chronic pneumonitis similar to the presentation of pulmonary tuberculosis.

Diagnosis

Cutaneous and lymphocutaneous sporotrichosis must be differentiated from other causes of nodular lymphangitis, including atypical mycobacterial infection, nocardiosis, leishmaniasis, tularemia, melioidosis, cutaneous anthrax, and other systemic mycoses, including coccidioidomycosis. Definitive diagnosis requires isolation of the fungus from the site of infection by culture. Special histologic staining such as periodic acid–Schiff and methenamine silver is required to identify yeast forms in tissues, which are typically oval or cigar-shaped. In spite of special staining techniques, diagnostic yield from biopsy specimens is low because of the small number of organisms present in the tissues. In cases of disseminated disease, demonstration of serum antibody against *S. schenckii* – related antigens can be diagnostically useful. Serologic testing is not commercially available but is offered by specialized laboratories, including the Centers for Disease Control and Prevention in the United States.

Treatment

Although comparative trials and extensive experience in children are not available, itraconazole is the recommended treatment of choice for infections outside the central nervous system. The recommended dosage for children is 5-10 mg/kg/day orally, with an initial maximum dose of 200 mg daily, which may be increased up to 400 mg daily if there is no initial response. Alternatively, younger children with cutaneous disease only may be treated with a saturated solution of potassium iodide (1 drop, 3 times daily, increasing as tolerated to a maximum of 1 drop/kg of body weight or 40 to 50 drops, 3 times daily, whichever is lowest). Adverse reactions, usually in the form of nausea and vomiting, should be managed with temporary cessation of therapy and reinstitution at a lower dosage. Therapy is continued 2 to 4 wk after cutaneous lesions have resolved, which usually takes at least 6-12 wk. Terbinafine, an allylamine, has been used successfully to treat cutaneous sporotrichosis but is reported to have lower cure rates and higher relapse rates than itraconazole. Further clinical efficacy data are needed to routinely recommend its use. Amphotericin B is the treatment of choice for pulmonary infections, disseminated infections, central nervous system disease, and infections in immunocompromised persons. Oral fluconazole 12 mg/kg daily (maximum dose, 400-800 mg daily) can be used if other agents are not tolerated. Posaconazole shows promise, but further data are needed.

Therapy with azoles or a saturated solution of potassium iodide should not be used in pregnant women. Amphotericin B can be used safely for cases of pulmonary or disseminated disease in pregnancy. Pregnant patients with cutaneous disease can be treated with local hyperthermia or can have therapy delayed until the pregnancy is completed. Hyperthermia involves heating the affected area to 42-45°C (107.6-113°F) using water baths or heating pads and works by inhibiting growth of the fungus. Dissemination to the fetus does not occur, and the disease is not worsened by pregnancy. Surgical debridement has a role in the treatment of some cases of sporotrichosis, particularly in osteoarticular disease.

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CHAPTER 270

Mucormycosis

Rachel L. Wattier, William J. Steinbach

Etiology

Mucormycosis refers to a group of opportunistic fungal infections caused by fungi of the order Mucorales, which are primitive, fast-growing fungi that are largely saprophytic and ubiquitous. These organisms are found commonly in soil, in decaying plant and animal matter, and on moldy cheese, fruit, and bread. Mucormycosis was previously called zygomycosis, and the causative organisms were referred to as Zygomycetes, but this terminology has been abandoned due to re-classification of organisms from the former phylum Zygomycota using molecular phylogenetic analysis.

The most common disease-causing genera of Mucorales are *Rhizopus, Mucor,* and *Lichtheimia* (formerly *Absidia*). Infections caused by organisms of the genera *Actinomucor, Apophysomyces, Cokeromyces, Cunninghamella, Rhizomucor, Saksenaea*, and *Syncephalastrum* are seen less often. Mucormycosis in humans is characterized by a rapidly evolving course, tissue necrosis, and blood vessel invasion.

Epidemiology

Mucormycosis is primarily a disease of persons with underlying conditions that impair host immunity. Predisposing factors include diabetes, hematologic malignancies, stem cell or organ transplantation, persistent acidosis, corticosteroid or deferoxamine therapy, prematurity, and, less commonly, AIDS. Mucormycosis is the 2nd most common invasive mold infection in immunocompromised hosts, after aspergillosis.

Pathogenesis

The primary route of infection is inhalation of spores from the environment. In immunocompromised persons, if spores are not cleared by macrophages, they germinate into hyphae, resulting in local invasion and tissue destruction. Cutaneous or percutaneous routes of infection can lead to cutaneous and subcutaneous mucormycosis. Ingestion of contaminated food or supplements has been linked to gastrointestinal disease. Typically these infections are characterized by extensive angioinvasion, resulting in thrombosis, infarction, and tissue necrosis, which can limit the delivery of antifungal agents and leukocytes to the site of infection and contribute to dissemination of the infection to other organs.

Macrophages and neutrophils are the main host defense against the Mucorales and other filamentous fungi and provide almost complete immunity against mucormycosis by phagocytosis and oxidative killing of spores, perhaps explaining the predilection for mucormycosis in patients with neutropenia or neutrophil dysfunction. Many of the Mucorales have virulence mechanisms that scavenge iron, an element essential for cell growth, from the host. The iron chelator deferoxamine paradoxically increases iron availability and uptake by members of the Mucorales. Acidosis diminishes the phagocytic and chemotactic ability of neutrophils while increasing the availability of unbound iron, likely explaining the susceptibility to mucormycosis among individuals with uncontrolled acidosis.

Clinical Manifestations

There are no unique signs or symptoms of mucormycosis. It can occur as any of several clinical syndromes, including sinus/rhinocerebral, pulmonary, gastrointestinal, disseminated, or cutaneous or subcutaneous disease.

Sinus and rhinocerebral infection have historically been the most common forms of mucormycosis and occur primarily in persons with diabetes mellitus or who are immunocompromised. Infection typically originates in the paranasal sinuses. Initial symptoms are consistent with sinusitis and include headache, retroorbital pain, fever, and nasal discharge. Infection can evolve rapidly or be slowly progressive. Orbital involvement manifesting as periorbital edema, proptosis, ptosis, and ophthalmoplegia can occur early in the disease. The nasal discharge is often dark and bloody; involved tissues become red, then violaceous, and then black as vessel thrombosis and tissue necrosis occur. Extension beyond the nasal cavity into the mouth is common. Direct bony involvement is common as a result of contiguous pressure effects or because of direct invasion and infarction. Destructive paranasal sinusitis with intracranial extension can be demonstrated by computed tomography (CT) or magnetic resonance imaging (MRI) (Fig. 270.1). Cases complicated by cavernous sinus thrombosis or thrombosis of the internal carotid artery have been reported. Brain abscesses can occur in patients with rhinocerebral infection that extends directly from the nasal cavity and sinuses, usually to the frontal or frontotemporal lobes. In patients with hematogenous disseminated disease, abscesses can involve the occipital lobe or brainstem.

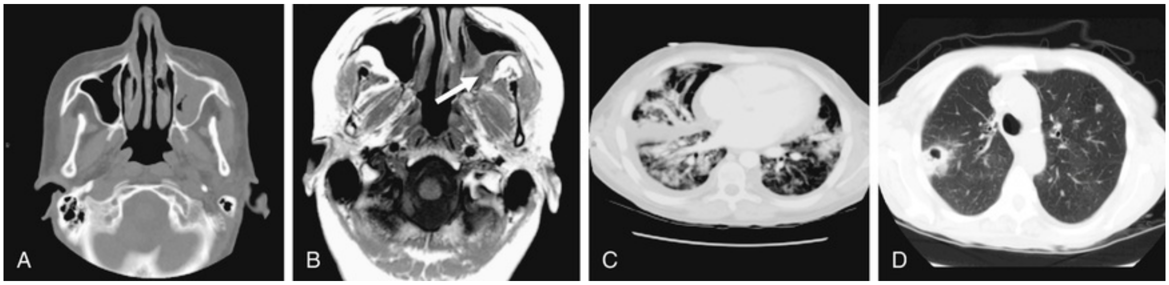

FIG. 270.1 Radiographic findings in sinopulmonary mucormycosis. A, Left maxillary sinus air-fluid level is evident in this computed tomography (CT) scan that is indistinguishable from bacterial sinusitis. B, Magnetic resonance image reveals T2 signal hyperintensity in the left pterygoid musculature *(arrow)* in conjunction with a left maxillary sinus air-fluid level. C, Multiple heterogeneous nodular and consolidative lesions with a large pulmonary vessel infarct *(wedge)* and modest pleural effusions are shown in a cancer patient with cancer and pulmonary mucormycosis. D, Contrast-enhanced CT scan demonstrates a cavity within a dense infiltrate in a patient with acute myelogenous leukemia and pulmonary mucormycosis. (From Konotoyiannis DP, Lewis RE: Agents of mucormycosis and entomophthoramycosis. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* , ed 8, Philadelphia, 2015, Elsevier, Fig. 260-5; courtesy Dr. Edith Marom, University of Texas, MD Anderson Cancer Center, Houston, Texas.)

Pulmonary mucormycosis usually occurs in severely neutropenic patients and has become more common in recent epidemiologic series. It is characterized by fever, tachypnea, and productive cough with pleuritic chest pain and hemoptysis. A wide range of pulmonary radiographic findings, including solitary pulmonary nodule, segmental or lobar consolidation, and cavitary and bronchopneumonic changes, are recognized (see Fig. 270.1). Although the radiographic findings overlap with other pulmonary invasive fungal infections, the presence of multiple nodules (≥10), pleural effusions, or the reversed halo sign are more suggestive of mucormycosis.

Gastrointestinal mucormycosis is uncommon. Often the diagnosis is delayed; only 25% of cases are diagnosed antemortem, and the subsequent mortality is as high as 85%. It can occur as a complication of disseminated disease or as an isolated intestinal infection in individuals with diabetes, immunosuppressed or malnourished children, or preterm infants. Any part of the gastrointestinal tract can be involved, with the stomach followed by colon and ileum being the most commonly affected. Abdominal pain and distention with hematemesis, hematochezia, or melena can occur. Stomach or bowel wall perforation is not uncommon.

Disseminated mucormycosis is associated with a very high mortality rate, especially among immunocompromised persons. Disseminated infection can originate from any of the primary sites of infection but often originates from pulmonary infection. Clinical presentation varies based on the involved sites.

Cutaneous and soft tissue mucormycosis can complicate burns and surgical or traumatic wounds. Primary cutaneous disease may be invasive locally, progressing through all tissue layers, including muscle, fascia, and bone (Fig. 270.2). Necrotizing fasciitis may occur. Infection manifests as an erythematous papule that ulcerates, leaving a black necrotic center. The skin lesions are painful, and affected patients may be febrile. In contrast, secondary cutaneous lesions from hematogenous seeding tend to be nodular, with minimal destruction of the epidermis.

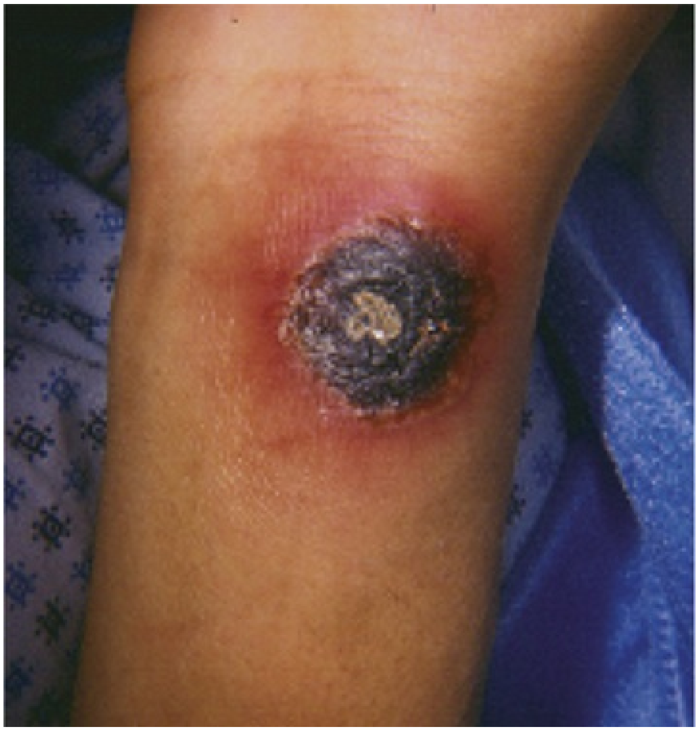

FIG. 270.2 Cutaneous presentation of mucormycosis. Chronic, nonhealing ulcer with necrosis following traumatic inoculation. (From Konotoyiannis DP, Lewis RE: Agents of mucormycosis and entomophthoramycosis. In Bennett JF, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* , ed 8, Philadelphia, 2015, Elsevier, Fig. 260-6A.)

Diagnosis

The diagnosis relies on direct morphologic identification of mycotic elements from culture or tissue biopsy specimens obtained at the site of disease. Mucorales appear as broad (5-25 µm in diameter), infrequently septate, thin-walled hyphae, branching irregularly at right angles when stained with Gomori methenamine silver (GMS) or hematoxylin and eosin. Secondary to their thin-walled structure and lack of regular septation, they often appear twisted, collapsed, or folded. Organisms may be challenging to identify reliably by morphology from tissue specimens; immunohistochemistry or PCR can provide more reliable identification when the morphology is not characteristic. Angioinvasion within tissue is a hallmark of mucormycosis.

Mucorales can be cultured on standard laboratory media from sputum, bronchoalveolar lavage fluid, skin lesions, or biopsy material. Cultures from non-tissue specimens, such as bronchoalveolar lavage fluid, have poor sensitivity. Polymerase chain reaction (PCR)-based methods may improve detection over culture but have not been evaluated on a wide scale. Though Mucorales can be culture contaminants, isolation in a susceptible host should prompt consideration of clinical disease. Noninvasive fungal biomarkers, such as galactomannan, or 1,3-β-D -glucan, do not detect the causative agents of mucormycosis.

Treatment

Most forms of mucormycosis can be aggressive and difficult to treat, with high mortality rates, except for localized cutaneous disease, which has relatively favorable outcomes. The optimal therapy for mucormycosis in children requires early diagnosis and prompt institution of medical therapy combined with extensive surgical debridement of all devitalized tissue. Correction of predisposing factors, such as neutropenia, hyperglycemia, and/or acidosis, if possible, is an essential component of management.

Lipid formulations of amphotericin B, either liposomal amphotericin, or amphotericin B lipid complex, are the mainstay of antifungal therapy for mucormycosis. Doses of at least 5 mg/kg/day and up to 10 mg/kg/day are recommended, though the benefit of increasing up to 10 mg/kg/day is not well defined. The duration of therapy is individualized, depending on clinical response and immune reconstitution.

Other antifungals with activity against the Mucorales include posaconazole and isavuconazole. Importantly, voriconazole is not active against agents of mucormycosis and in some studies has been identified as a predisposing factor for mucormycosis. This association is not completely understood; some studies suggest that it may be a marker for higher-risk patients rather than actually influencing susceptibility. Posaconazole is active against many of the Mucorales and has shown promise when used as salvage therapy, though it has not been evaluated for primary therapy of mucormycosis. Concerns have been raised about its activity against *Rhizopus oryzae* and *Mucor circinelloides* , 2 of the most common causative agents of mucormycosis. Posaconazole is presently not recommended for primary therapy but may be used for salvage therapy or step down from an amphotericin B-based regimen. Isavuconazole was recently licensed for primary therapy of mucormycosis based on a single arm study in which it showed favorable outcomes compared to contemporary response rates with amphotericin B-based therapy. However, there are currently no pediatric dosing data for isavuconazole.

Although the echinocandins lack significant activity against the Mucorales, animal models have demonstrated potential synergy when they are used with amphotericin B in treatment of experimental mucormycosis. Caspofungin has been shown to uncover β-glucan in the cell wall of *Rhizopus*, resulting in an increase in neutrophil activity. However, clinical studies evaluating combination therapy with addition of either an echinocandin or posaconazole to an amphotericin B-based regimen have shown conflicting results. Currently combination therapy is not recommended as primary therapy but may be considered as salvage therapy for refractory disease. Hyperbaric oxygen has been used anecdotally as an adjunctive therapy. Iron chelation with deferasirox has been tried as salvage therapy in refractory mucormycosis but is currently not recommended due to adverse outcomes in a small clinical trial.

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CHAPTER 271

Pneumocystis jirovecii

Francis Gigliotti, Terry W. Wright

Pneumocystis jirovecii pneumonia (interstitial plasma cell pneumonitis) in an immunocompromised person is a life-threatening infection. Primary infection in the immunocompetent person is usually subclinical and goes unrecognized. The disease most likely results from new or repeat acquisition of the organism rather than reactivation of latent organisms. Even in the most severe cases, with rare exceptions, the organisms remain localized to the lungs.

Etiology

P. jirovecii is a common extracellular parasite found worldwide in the lungs of mammals. The taxonomic placement of this organism has not been unequivocally established, but nucleic acid homologies place it closest to fungi despite sharing morphologic features and drug susceptibility with protozoa. Detailed studies of the basic biology of the organism are not possible because of the inability to maintain *P. jirovecii* in culture. Phenotypic and genotypic analyses demonstrate that each mammalian species is infected by a unique strain (or possibly species) of *Pneumocystis.* A biologic correlate of these differences is evidenced by animal experiments that have shown organisms are not transmissible from one mammalian species to another. These observations have led to the suggestion that organisms be renamed, with those infecting humans renamed *P. jirovecii* .

Epidemiology

Serologic surveys show that most humans are infected with *P. jirovecii* before 4 yr. of age. In the immunocompetent child, these infections are usually asymptomatic. *P. jirovecii* DNA can occasionally be detected in nasopharyngeal aspirates of normal infants. Pneumonia caused by *P. jirovecii* occurs almost exclusively in severely immunocompromised hosts, including those with congenital or acquired immunodeficiency disorders, malignancies, or transplanted organs. Patients with primary immunodeficiency diseases at risk for infection include severe combined immunodeficiency disease, X-linked CD40 ligand deficiency, major histocompatibility complex class II deficiency, nuclear factor kappa B essential modulator deficiency, dedicator of cytokinesis 8 deficiency, Wiskott-Aldrich syndrome, and caspase recruitment domain 11 deficiency. Small numbers of *P. jirovecii* can be found in the lungs of infants who have died with the diagnosis of sudden infant death syndrome. This observation could indicate a cause-and-effect relationship or simply that there is overlap in the timing of the primary infection with *P. jirovecii* and sudden infant death syndrome.

Without chemoprophylaxis, approximately 40% of infants and children with AIDS, 70% of adults with AIDS, 12% of children with leukemia, and 10% of patients with organ transplants experience *P. jirovecii* pneumonia. Epidemics that occurred among debilitated infants in Europe during and after World War II are attributed to malnutrition. The use of new biologic immunosuppressive agents has expanded at-risk populations. The addition of tumor necrosis factor-α inhibitors to the management of patients with inflammatory bowel disease has resulted in a demonstrable increase in *P. jirovecii* pneumonia in this patient population, as has the use of rituximab in patients with hematologic malignancies.

The natural habitat and mode of transmission to humans are unknown, but animal studies clearly demonstrate airborne transmission. Animal-to-human transmission is unlikely because of the host specificity of *P. jirovecii* . Thus person-to-person transmission is likely but has not been conclusively demonstrated.

Pathogenesis

Two forms of *P. jirovecii* are found in the alveolar spaces: cysts, which are 5-8 µm in diameter and contain up to 8 pleomorphic intracystic sporozoites (or intracystic bodies), and extracystic trophozoites (or trophic forms), which are 2-5 µm cells derived from excysted sporozoites. The terminology of sporozoite and trophozoite is based on the morphologic similarities to protozoa, because there are no exact correlates for these forms of the organism among the fungi. *P. jirovecii* attaches to type I alveolar epithelial cells, possibly by adhesive proteins such as fibronectin or mannose-dependent ligands.

Control of infection depends on intact cell-mediated immunity. Studies in patients with AIDS show an increased incidence of *P. jirovecii* pneumonia with markedly decreased $CD4^+$ T-lymphocyte counts. The $CD4^+$ cell count provides a useful indicator in both older children and adults of the need for prophylaxis for *P. jirovecii* pneumonia. Although normally functioning $CD4^+$ T cells are central to controlling infection by *P. jirovecii*, the final effector pathway for destruction of *P. jirovecii* is poorly understood but likely depends on alveolar macrophages. A role for $CD4^+$ T cells could be to provide help for the production of specific antibody that is then involved in the clearance of organisms through interaction with complement, phagocytes, or T cells or through direct activation of alveolar macrophages.

In the absence of an adaptive immune response, as can be modeled in severe combined immunodeficient mice, infection with *P. murina* produces little alteration in lung histology or function until late in the course of the disease. If functional lymphocytes are given to severe combined immunodeficient mice infected with *P. murina*, there is rapid onset of an inflammatory response that results in an intense cellular infiltrate, markedly reduced lung compliance, and significant hypoxia, mimicking the characteristic changes of *P. jirovecii* pneumonia in humans. These inflammatory changes are also associated with marked disruption of surfactant function. T-cell subset analysis has shown that $CD4^+$ T cells produce an inflammatory response that clears the organisms but also results in lung injury. $CD8^+$ T cells are ineffective in the eradication of *P. jirovecii*. $CD8^+$ T cells do help to modulate the inflammation produced by $CD4^+$ T cells, but in the absence of $CD4^+$ T cells the ineffectual inflammatory response of $CD8^+$ T cells contributes significantly to lung injury. These various T-cell effects are likely responsible for the variations in presentation and outcome of *P. jirovecii* pneumonia observed in different patient populations.

Pathology

The histopathologic features of *P. jirovecii* pneumonia are of 2 types. The 1st type is infantile interstitial plasma cell pneumonitis, which was seen in epidemic outbreaks in debilitated infants 3-6 mo of age. Extensive infiltration with thickening of the alveolar septum occurs, and plasma cells are prominent. The 2nd type is a diffuse desquamative alveolar pneumonitis found in immunocompromised children and adults. The alveoli contain large numbers of *P. jirovecii* in a foamy exudate with alveolar macrophages active in the phagocytosis of organisms. The alveolar septum is not infiltrated to the extent it is in the infantile type, and plasma cells are usually absent.

Clinical Manifestations

There are at least three distinct clinical presentations of *P. jirovecii* pneumonia. In patients with profound congenital immunodeficiency or in AIDS patients with very few $CD4^+$ T cells, the onset of hypoxia and symptoms is subtle, with tachypnea progressing to nasal flaring, often without fever; intercostal, suprasternal, and infrasternal retractions; and cyanosis in severe cases. In cases of *P. jirovecii* pneumonia occurring in children and adults with immunodeficiency resulting from immunosuppressive medications, the onset of hypoxia and symptoms is often more abrupt, with fever, tachypnea, dyspnea, and cough, progressing to severe respiratory compromise. This type accounts for the majority of cases, although the severity of clinical expression can vary. *Rales are usually not detected on physical examination.* The 3rd pattern of disease is seen in severely immunocompromised patients with *P. jirovecii* pneumonia who appear to be responding to therapy but then have an acute and seemingly paradoxical deterioration thought to be associated with return of immune function. This condition is referred to as *immune reconstitution inflammatory syndrome* and is most commonly seen in patients with newly diagnosed AIDS who present with *P. jirovecii* pneumonia and who have a rapid response to antiretroviral therapy that is instituted at the same time as anti-*Pneumocystis* therapy. It can also occur in stem cell transplant recipients who engraft while infected with *P. jirovecii.*

Laboratory Findings

The chest radiograph reveals bilateral diffuse interstitial or alveolar ground glass infiltrates (Fig. 271.1). The earliest densities are perihilar, and progression proceeds peripherally, sparing the apical areas until last. The arterial oxygen tension (PaO_2) is invariably decreased. The major role of the laboratory in establishing a diagnosis of *P. jirovecii* pneumonia is in identifying organisms in lung specimens by a variety of methods. Once obtained, the specimens are typically stained with 1 of 4 commonly used stains: Grocott-Gomori silver stain and toluidine blue stain for the cyst form, polychrome stains such as Giemsa stain for the trophozoites and sporozoites, and the fluorescein-labeled monoclonal antibody stains for both trophozoites and cysts. Polymerase chain reaction analysis of respiratory specimens offers promise as a rapid diagnostic method, but a standardized system for clinical use has not been established. Serum lactate dehydrogenase levels are often elevated but are not specific.

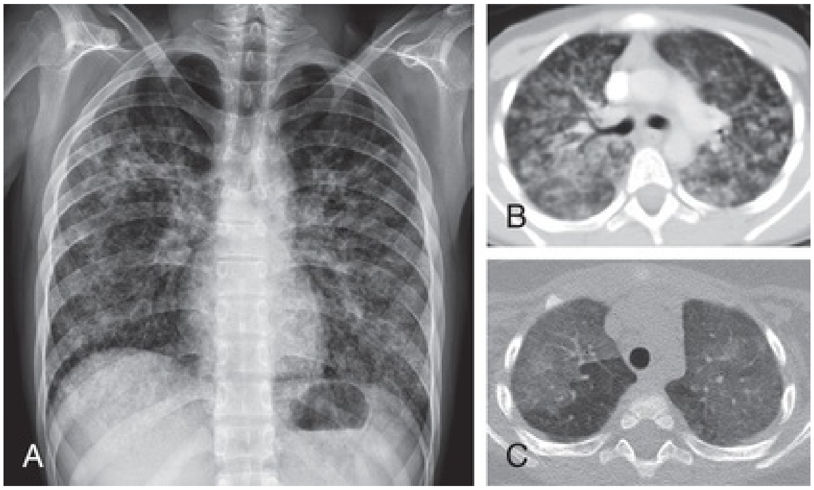

FIG. 271.1 *Pneumocystis jiroveci* infection in a 17 yr old boy with acute lymphoblastic leukemia and immunodeficiency, who presented with dyspnea, fever, nonproductive cough, and decreased white blood cell counts. **A,** The radiograph shows diffuse bilateral interstitial opacity throughout the lungs. **B,** Contrast-enhanced computed tomography *(CT)* confirms the bilateral patchy and ground-glass opacities in both lungs. The diagnosis was confirmed by a positive polymerase chain reaction test from bronchial lavage fluid. **C,** CT in a different patient demonstrates a typical "crazy paving" pattern in both upper lobes. (From Westra SJ, Yikilmaz A, Lee EY: Pulmonary infection. In Coley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 13, Philadelphia, 2019, Elsevier, Fig. 54-30.)

Diagnosis

Definitive diagnosis requires demonstration of *P. jirovecii* in the lung in the presence of clinical signs and symptoms of the infection. Organisms can be detected in specimens collected by bronchoalveolar lavage (BAL), tracheal aspirate, transbronchial lung biopsy, bronchial brushings, percutaneous transthoracic needle aspiration, and open lung biopsy. Hypertonic saline–induced sputum samples are helpful if *P. jirovecii* is found, but the absence of the organisms in induced sputum does not exclude the infection and BAL should be performed. Open lung biopsy is the most reliable method, although BAL is more practical in most cases. Estimates of the diagnostic yield of the various specimens are 20–40% for induced sputum, 50–60% for tracheal aspirate, 75–95% for BAL, 75–85% for transbronchial biopsy, and 90–100% for open lung biopsy.

Treatment

The recommended therapy for *P. jirovecii* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15-20 mg TMP and 75-100 mg SMX/kg/day in 4 divided doses) administered intravenously, or orally if there is mild disease and no malabsorption or diarrhea. The duration of treatment is 3 wk for patients with AIDS and 2 wk for other patients. Unfortunately, adverse reactions often occur with TMP-SMX, especially rash and neutropenia in patients with AIDS. For patients who cannot tolerate or who fail to respond to TMP-SMX after 5-7 days, pentamidine isethionate (4 mg/kg/day as a single dose IV) may be used. Adverse reactions are frequent and include renal and hepatic dysfunction, hyperglycemia or hypoglycemia, rash, and thrombocytopenia. Atovaquone (750 mg twice daily with food, for patients >13 yr of age) is an alternative treatment that has been used primarily in adults with mild to moderate disease. Limited experience is available for younger children. Pharmacokinetic studies of atovaquone show that a dose of 30 mg/kg/day PO in 2 divided doses for children 0-3 mo of age and older than 2 yr of age is adequate and safe; a dose of 45 mg/kg/day PO in 2 divided doses is needed for children between 4 mo and 2 yr of age. Other effective therapies include trimetrexate glucuronate or combinations of trimethoprim plus dapsone or clindamycin plus primaquine.

Some studies in adults suggest that administration of corticosteroids as adjunctive therapy to suppress the inflammatory response increases the chances for survival in moderate and severe cases of *P. jirovecii* pneumonia. The recommended regimen of corticosteroids for adolescents older than 13 yr of age and for adults is oral prednisone, 80 mg/day PO in 2 divided doses on days 1-5, 40 mg/day PO once daily on days 6-10, and 20 mg/day PO once daily on days 11-21. A reasonable regimen for children is oral prednisone, 2 mg/kg/day for the 1st 7-10 days, followed by a tapering regimen for the next 10-14 days.

Supportive Care

Basic supportive care is dictated by the condition of the patient, with careful attention to maintain appropriate hydration and oxygenation. Only 5–10% of AIDS patients require mechanical ventilation compared with 50–60% of patients without AIDS, consistent with the hypothesis that the patient's ability to mount an inflammatory response correlates with severity and outcome. There are anecdotal reports of giving surfactant to children with severe *P. jirovecii* pneumonia, although the use of surfactant to treat adult-type respiratory distress syndrome is controversial.

Complications

Most complications occur as adverse events associated with the drugs used or the mechanical ventilation used for treatment. The most severe pulmonary complication of *P. jirovecii* pneumonia is adult-type respiratory distress syndrome. Rarely, *P. jirovecii* infection affects extrapulmonary sites (e.g., retina, spleen, and bone marrow), but such infections are usually not symptomatic and also respond to treatment.

Prognosis

Without treatment, *P. jirovecii* pneumonitis is fatal in almost all immunocompromised hosts within 3-4 wk of onset. The mortality rate varies with patient population and is related to inflammatory response rather than organism burden. AIDS patients have a mortality rate of 5–10%, and patients with other diseases such as malignancies have mortality rates as high as 20–25%. Patients who require mechanical ventilation have mortality rates of 60–90%. Patients remain at risk for *P. jirovecii* pneumonia as long as they are immunocompromised. Continuous prophylaxis should be initiated or reinstituted at the end of therapy for patients with AIDS (see Chapter 302).

Prevention

Patients at high risk for *P. jirovecii* pneumonia should be placed on chemoprophylaxis. Prophylaxis in infants born to HIV-infected mothers and for HIV-infected infants and children is based on age and CD4 cell counts (see Chapter 302). Because CD4 counts fluctuate rapidly during the first year of life, infants born to HIV-infected mothers should be placed on prophylaxis during the 1st year of life until HIV infection is ruled out. Patients with severe combined immunodeficiency syndrome, patients receiving intensive immunosuppressive therapy for cancer or other diseases, and organ transplant recipients are also candidates for prophylaxis. TMP-SMX (5 mg/kg TMP and 25 mg SMX/kg PO once daily or divided into 2 doses daily) is the drug of choice and may be given for 3 consecutive days each wk, or, alternatively, each day. Alternatives for prophylaxis include dapsone (2 mg/kg/day PO, maximum: 100 mg/dose; or 4 mg/kg PO once weekly, maximum: 200 mg/dose), atovaquone (30 mg/kg/day PO for infants 1-3 mo. and ≥24 mo of age; 45 mg/kg/day for infants and toddlers 4-23 mo of age), and aerosolized pentamidine (300 mg monthly by Respirgard II nebulizer), but all of these agents are inferior to TMP-SMX. Finally, limited clinical experience suggests that pentamidine can be given intravenously once monthly to prevent *P. jirovecii* pneumonia. Prophylaxis must be continued as long as the patient remains immunocompromised. Some AIDS patients who reconstitute adequate immune response during highly active antiretroviral therapy may have prophylaxis withdrawn.

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SECTION 13

Viral Infections

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CHAPTER 272

Principles of Antiviral Therapy

Mark R. Schleiss

Antiviral chemotherapy typically requires a delicate balance between targeting critical steps in viral replication without interfering with host cellular function. Because viruses require cellular functions to complete replication, many antiviral agents exert significant host cellular toxicity, a limitation that has hindered antiviral drug development. In spite of this limitation, a number of agents are licensed for use against viruses, particularly herpesviruses, respiratory viruses, and hepatitis viruses (Table 272.1).

Table 272.1

Currently Licensed Antiviral Drugs

ANTIVIRAL	TRADE NAME	MECHANISM OF ACTION
Acyclovir	Zovirax	Inhibits viral DNA polymerase
Adefovir	Hepsera	Nucleotide reverse transcriptase inhibitor
Amantadine*	Symmetrel	Blocks M2 protein ion channel
Baloxavir	Xofluza	Inhibits polymerase acidic endonuclease, blocking viral replication
Beclabuvir	BMS-791325	Inhibitor of HCV NS5B
Boceprevir †	Victrelis	Inhibitor of HCV NS3 serine protease Active against HCV genotype 1
Cidofovir	Vistide	Inhibits viral DNA polymerase
Daclatasvir	Daklinza	Inhibitor of HCV NS5A Used in varying combinations with sofosbuvir, ribavirin, and interferon
Dasabuvir	Exviera	Inhibitor of HCV NS5B Used together with the combination medication ombitasvir/paritaprevir/ritonavir (Vikiera Pak) Activity limited to HCV genotype 1
Elbasvir	(Zepatier)	Inhibitor of HCV NS5A Used in combination with the NS3/4A protease inhibitor grazoprevir under the trade name Zepatier, either with or without ribavirin

Entecavir	Baraclude	Nucleoside reverse transcriptase inhibitor Active against HBV
Famciclovir	Generic	Inhibits viral DNA polymerase
Fomivirsen ‡	Vitravene	Phosphorothioate oligonucleotide inhibits viral replication via antisense mechanism
Foscarnet	Foscavir	Inhibits viral DNA polymerase and reverse transcriptase at pyrophosphate-binding site
Ganciclovir	Cytovene	Inhibits viral DNA polymerase
Grazoprevir	(Zepatier)	Inhibitor of HCV NS3-4A serine protease Used in combination with elbasvir under the trade name Zepatier, either with or without ribavirin
Idoxuridine	Herplex	Inhibits viral DNA polymerase
Interferon-α	Intro-A (interferon-α2b) Roferon-A (interferon-α2a) Infergen (interferon alfacon-1)	Produces multiple effector proteins that exert antiviral effects; also directly interacts with immune system components
Interferon-α2b plus ribavirin	Rebetron	Not established
Lamivudine (3TC)	Epivir	Inhibits viral DNA polymerase and reverse transcriptase; active against HBV
Ledipasvir	(with Sofosbuvir: Harvoni)	Inhibitor of HCV NS5A
Ombitasvir	(Viekira Pak)	Inhibitor of HCV NS5A Used in combination with paritaprevir, ritonavir and dasabuvir in Viekira Pak Active against HCV genotype 1
Oseltamivir	Tamiflu	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
Paritaprevir	(Viekira Pak) (Technivie/Viekirax)	Inhibitor of HCV NS3-4A serine protease Used in combination with ombitasvir, ritonavir and dasabuvir (Viekira Pak), or in combination with ombitasvir and ritonavir (Technivie/Viekirax)
Pegylated interferon	PEG-Intron (α2b), Pegasys (α2a)	Same as interferon
Penciclovir	Denavir	Inhibits viral DNA polymerase
Peramivir	Rapivab	Neuraminidase inhibitor
Ribavirin	Virazole, Rebetol, Copegus	Interference with viral messenger RNA
Rimantadine*	Flumadine	Blocks M2 protein ion channel
Simeprevir	Olysio	Inhibitor of HCV NS3-4A serine protease Active against genotype 1 ± genotype 4 Used with include sofosbuvir or ribavirin and pegylated interferon-alfa
Sofosbuvir	(Harvoni)	Inhibitor of HCV NS5B Used in combination with Ledipasvir (Harvoni)
Telaprevir	Incivek Incivio	Inhibitor of HCV NS3-4A serine protease Active against HCV genotype 1
Telbivudine	Tyzeka	Interferes with HBV DNA replication
Tenofovir	Viread	Nucleoside reverse transcriptase inhibitor Active against HBV
Trifluridine	Viroptic	Inhibits viral DNA polymerase
Valacyclovir	Valtrex	Same as acyclovir
Valganciclovir	Valcyte	Same as ganciclovir

Velpatasvir	(Epclusa, Sofosvel, Velpanat)	Inhibitor of HCV NS5A Used in combination with sofosbuvir (Epclusa, Sofosvel, Velpanat) Active against all 6 HCV genotypes
Vidarabine	ara-A	Inhibits viral DNA polymerase (and to lesser extent, cellular DNA polymerase)
Zanamivir	Relenza	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
FDA-APPROVED COMBINATION THERAPIES		
Interferon-α2b + ribavirin	Rebetron (Intron-A plus Rebetol)	
Interferon-α2a + ribavirin	Roferon-A + ribavirin	
Pegylated interferon-α2b + ribavirin (3 yr and older)	PEG-Intron + Rebetol	
Pegylated interferon-α2a + ribavirin (5 yr and older)	Pegasys + Copegus	

[*] No longer recommended by Centers for Disease Control and Prevention for treatment of influenza.

[†] No longer marketed in United States.

[‡] No longer available.

In making the decision to commence antiviral drugs, it is important for the clinician to obtain appropriate diagnostic specimens, which can help clarify the antiviral of choice. The choice of a specific antiviral is based on the recommended agent of choice for a particular clinical condition, pharmacokinetics, toxicities, cost, and the potential for development of resistance (Table 272.2). Intercurrent conditions in the patient, such as renal insufficiency, should also be considered. Clinicians must monitor antiviral therapy closely for adverse events or toxicities, both anticipated and unanticipated.

Table 272.2

Antiviral Therapies for Non-HIV Clinical Conditions[*]

VIRUS	CLINICAL SYNDROME	ANTIVIRAL AGENT OF CHOICE	ALTERNATIVE ANTIVIRAL AGENTS
Influenza A and B	Treatment	Oseltamivir (>2 wk old)	Zanamivir (>7 yr old) Peramivir (>2 yr old)
	Prophylaxis	Oseltamivir (>3 mo old)	Zanamivir (>5 yr old)

Respiratory syncytial virus	Bronchiolitis or pneumonia in high-risk host	Ribavirin aerosol	
Adenovirus	In immunocompromised patients: Pneumonia Viremia Nephritis Hemorrhagic cystitis	Cidofovir	
CMV	Congenital CMV infection	Ganciclovir (IV)	Valganciclovir (if oral therapy appropriate; long-term oral valganciclovir investigational but may improve developmental and hearing outcomes)
	Retinitis in AIDS patients	Valganciclovir	Ganciclovir Cidofovir Foscarnet Ganciclovir ocular insert
	Pneumonitis, colitis; esophagitis in immunocompromised patients	Ganciclovir (IV)	Foscarnet Cidofovir Valganciclovir
HSV	Neonatal herpes	Acyclovir (IV)	
	Suppressive therapy following neonatal herpes with central nervous system involvement	Acyclovir (PO)	
	HSV encephalitis	Acyclovir (IV)	
	HSV gingivostomatitis	Acyclovir (PO)	Acyclovir (IV)
	First episode genital infection	Acyclovir (PO)	Valacyclovir
			Famciclovir
			Acyclovir (IV) (severe disease)
	Recurrent genital herpes	Acyclovir (PO)	Valacyclovir
			Famciclovir
	Suppression of genital herpes	Acyclovir (PO)	Valacyclovir
			Famciclovir
	Cutaneous HSV (whitlow, herpes gladiatorum)	Acyclovir (PO)	Penciclovir (topical)
	Eczema herpeticum	Acyclovir (PO)	Acyclovir (IV) (severe disease)
	Mucocutaneous infection in immunocompromised host (mild)	Acyclovir (IV)	Acyclovir (PO) (if outpatient therapy acceptable)
	Mucocutaneous infection in immunocompromised host (moderate to severe)	Acyclovir (IV)	
	Prophylaxis in bone marrow transplant recipients	Acyclovir (IV)	Valacyclovir
	Acyclovir-resistant HSV	Foscarnet	Cidofovir
	Keratitis or keratoconjunctivitis	Trifluridine	Vidarabine
Varicella-zoster virus	Chickenpox, healthy child	Supportive care	Acyclovir (PO)
	Chickenpox, immunocompromised child	Acyclovir (IV)	
	Zoster (not ophthalmic branch	Supportive	Acyclovir (PO)

	of trigeminal nerve), healthy child	care	
	Zoster (ophthalmic branch of trigeminal nerve), healthy child	Acyclovir (IV)	
	Zoster, immunocompromised child	Acyclovir (IV)	Valacyclovir

[*] For antiviral agents for hepatitis B and hepatitis C, see Table 272.1 .

CMV, cytomegalovirus; HSV, herpes simplex virus.

In vitro sensitivity testing of virus isolates to antiviral compounds usually involves a complex tissue culture system. The potency of an antiviral is determined by the **50% inhibitory dose (ID_{50}),** which is the antiviral concentration required to inhibit the growth in cell culture of a standardized viral inoculum by 50%. Because of the complexity of these assays, the results vary widely, and the actual relationship between antiviral sensitivity testing and antiviral therapy outcomes is sometimes unclear. Because these assays are often not readily available and take considerable time to complete, **genotypic analysis** for antiviral susceptibility is increasingly being offered. Such assays may be useful for patients on long-term antiviral therapy.

Clinical context is essential in making decisions about antiviral treatment, along with knowledge of a patient's immune status. For example, antiviral treatment is rarely if ever indicated in an immunocompetent child shedding cytomegalovirus (CMV) but may be lifesaving when administered to an immunocompromised solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) patient. Antivirals can be used with a variety of clinical goals in mind. Antivirals can be used for **treatment** of active end-organ disease, as **prophylaxis** to prevent viral infection or disease, or as **preemptive therapy** aimed at reducing risk of progression to disease (i.e., a positive signal indicating viral replication but in the absence of clinical evidence of end-organ disease). In preemptive therapy, a patient will usually have a positive signal for polymerase chain reaction–based identification of viral nucleic acids in a clinical sample (blood or body fluid) but have no symptoms. However, SOT and HSCT patients are at high risk of developing disease in this setting (particularly due to CMV infection), a scenario that warrants preemptive treatment with an antiviral agent. In contrast, prophylaxis is administered to seropositive patients who are at risk to reactivate latent viral infection but do not yet have evidence of active viral replication or shedding.

A fundamental concept important in the understanding of the mechanism of action of most antivirals is that viruses must use host cell components to replicate. Thus mechanisms of action for antiviral compounds must be selective to virus-specific functions whenever possible, and antiviral agents may have significant toxicities to the host if these compounds impact cellular physiology. Some of the more commonly targeted sites of action for antiviral agents include viral entry, absorption, penetration, and uncoating (amantadine, rimantadine); transcription or replication of the viral genome (acyclovir, valacyclovir, cidofovir, famciclovir, penciclovir, foscarnet, ganciclovir, valganciclovir, ribavirin, trifluridine); viral protein synthesis (interferons) or protein modification (protease inhibitors); and viral assembly, release, or deaggregation (oseltamivir, zanamivir, interferons).

An understudied and underappreciated issue in antiviral therapy is emergence of resistance, particularly in the setting of high viral load, high intrinsic viral mutation rate, and prolonged or repeated courses of antiviral therapy. Resistant viruses are more likely to develop or be selected for in immunocompromised patients because these patients are more likely to have multiple or long-term exposures to an antiviral agent.

Antivirals Used for Herpesviruses

The herpesviruses are important pediatric pathogens, particularly in newborns and immunocompromised children. Most of the licensed antivirals are nucleoside analogs that inhibit viral DNA polymerase, inducing premature chain termination during viral DNA synthesis in infected cells.

Acyclovir

Acyclovir is a safe and effective therapy for herpes simplex virus (HSV) infections. The favorable safety profile of acyclovir derives from its requirement for activation to its active form via phosphorylation by a viral enzyme, thymidine kinase (TK). Thus acyclovir can be activated only in cells already infected with HSV that express the viral TK enzyme, a strategy that maximizes selectivity and reduces the potential for cellular toxicity in uninfected cells. Acyclovir is most active against HSV and is also active against varicella-zoster virus (VZV); therapy is indicated for infections with these viruses in a variety of clinical settings. Activity of acyclovir against CMV is less pronounced, and activity against Epstein-Barr virus is minimal, both in vitro and clinically. Therefore, under most circumstances, acyclovir should not be used to treat CMV or Epstein-Barr virus infections.

The biggest impact of acyclovir in clinical practice is in the treatment of primary and recurrent genital HSV infections. Oral nucleoside therapy plays an important role in the management of acute primary genital herpes, treatment of episodic symptomatic reactivations, and prophylaxis against reactivation. Acyclovir is also indicated in the management of suspected or proven HSV encephalitis in patients of all ages and for treatment of neonatal HSV infection, with or without central nervous system (CNS) involvement. With respect to neonatal HSV infection, the routine empirical use of acyclovir as empiric therapy against presumptive or possible HSV infection in infants admitted with fever and no focus in the 1st 4 wk of life is controversial. Acyclovir should be used routinely in infants born to women with risk factors for primary genital herpes or infants presenting with any combination of vesicular lesions, seizures, meningoencephalitis, hepatitis, pneumonia, or disseminated intravascular coagulation. Some advocate initiation of acyclovir in all febrile neonates. Other experts have argued that a selective approach based on the history and physical exam is more appropriate when making decisions about the use of acyclovir in febrile infants. Given the safety of the drug, prudence would dictate the use of acyclovir in such patients if HSV infection cannot be excluded.

Acyclovir is indicated for the treatment of primary HSV gingivostomatitis and for primary genital HSV infection. Long-term suppressive therapy for genital HSV and for recurrent oropharyngeal infections (herpes labialis) is also effective. Acyclovir is also recommended for less commonly encountered HSV infections, including herpetic whitlow, eczema herpeticum, and herpes gladiatorum. In addition, acyclovir is commonly used for prophylaxis against HSV reactivation in SOT and HSCT patients. Severe end-organ HSV disease, including disseminated infection, is occasionally encountered in immunocompromised or pregnant patients, representing another clinical scenario where acyclovir therapy is warranted.

Acyclovir modifies the course of primary VZV infection, although the effect is modest. Acyclovir or another nucleoside analog should always be used in localized or disseminated VZV infections, such as pneumonia, particularly in immunocompromised patients. Primary VZV infection in pregnancy is another setting where acyclovir is indicated; this is a high-risk scenario and can be associated with a substantial risk of maternal mortality, particularly if pneumonia is present.

Acyclovir is available in topical (5% ointment), parenteral, and oral formulations, including an oral suspension formulation for pediatric use. Topical therapy has little role in pediatric practice and should be avoided in favor of alternative modes of delivery, particularly in infants with vesicular lesions compatible with herpetic infection, where topical therapy should never be used. The bioavailability of oral formulations is modest, with only 15–30% of the oral dose being absorbed. There is widespread tissue distribution following systemic administration, and high concentrations of drug are achieved in the kidneys, lungs, liver, myocardium, and skin vesicles. Cerebrospinal fluid concentrations are approximately 50% of plasma concentrations. Acyclovir crosses the placenta, and breast milk concentrations are approximately 3 times plasma concentrations, although there are no data on efficacy of in utero therapy or impact of acyclovir therapy on nursing infants. Acyclovir therapy in a nursing mother is not a contraindication to breastfeeding. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Hemodialysis also eliminates acyclovir.

Acyclovir has an exceptional safety profile. Toxicity is observed typically only in exceptional circumstances: for example, if administered by rapid infusion to a dehydrated patient or a patient with underlying renal insufficiency, acyclovir can crystallize in renal tubules and produce a reversible obstructive uropathy. High doses of acyclovir are associated with neurotoxicity, and prolonged use can cause neutropenia. The favorable safety profile of acyclovir is underscored by recent studies of its safe use during pregnancy, and suppressive therapy in pregnant women with histories of recurrent genital HSV infection, typically with valacyclovir (see later), has become standard of care among many obstetricians. One uncommon but important complication of long-term use of acyclovir is the selection for acyclovir-resistant HSV strains, which usually occurs from mutations in the HSV TK gene. Resistance is rarely observed in pediatric practice but should be considered in any patient who has been on long-term antiviral therapy and who has an HSV or VZV infection that fails to clinically respond to acyclovir therapy.

Valacyclovir

Valacyclovir is the L -valyl ester of acyclovir and is rapidly converted to acyclovir following oral administration. This agent has a safety and activity profile similar to that of acyclovir but has a bioavailability of >50%, 3-5–fold greater than that of acyclovir. Plasma concentrations approach those observed with intravenous acyclovir. Valacyclovir is available only for oral administration. A suspension formulation is not commercially available, but an oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from 500-mg caplets for use in pediatric patients for whom a solid dosage form is not appropriate. Suppressive therapy with valacyclovir is commonly prescribed in the 2nd and 3rd trimesters of pregnancy in women who have a clinical history of recurrent genital herpes. *It is important to be aware that perinatal transmission of HSV can occur, leading to symptomatic disease in spite of maternal antenatal antiviral prophylaxis.* In such settings, the possibility of emergence of acyclovir-resistant virus should be considered.

Penciclovir and Famciclovir

Penciclovir is an acyclic nucleoside analog that, like acyclovir, inhibits the viral DNA polymerase following phosphorylation to its active form. Compared with acyclovir, penciclovir has a substantially longer intracellular half-life, which in theory can confer superior antiviral activity at the intracellular level; however, there is no evidence that this effect confers clinical superiority. Penciclovir is licensed only as a topical formulation (1% penciclovir cream), and this formulation is indicated for therapy of cutaneous HSV infections. Topical therapy for primary or recurrent herpes labialis or cutaneous HSV infection is an appropriate use of penciclovir in children older than 2 yr of age.

Famciclovir is the prodrug formulation (diacetyl ester) of penciclovir. In contrast to penciclovir, famciclovir may be administered orally and has bioavailability of approximately 70%. Following oral administration, famciclovir is deacetylated to the parent drug, penciclovir. The efficacy of famciclovir for HSV and VZV infections appears equivalent to that of acyclovir, although the pharmacokinetic profile is more favorable. Famciclovir is indicated for oral therapy of HSV and VZV infections. There is currently no liquid or suspension formulation available, and experience with pediatric use is very limited. The toxicity profile is identical to that of acyclovir. In a clinical trial, valacyclovir was found to be superior to famciclovir in prevention of reactivation and reduction of viral shedding in the setting of recurrent genital HSV infection.

Ganciclovir and Valganciclovir

Ganciclovir is a nucleoside analog with structural similarity to acyclovir. Like acyclovir, ganciclovir must be phosphorylated for antiviral activity, which is targeted against the viral polymerase. The gene responsible for ganciclovir phosphorylation is not TK but rather the virally encoded UL97 phosphotransferase gene. Antiviral resistance in CMV can be observed with prolonged use of nucleoside antivirals, and resistance should be considered in patients on long-term therapy who appear to fail to respond clinically and virologically. Ganciclovir is broadly active against many herpesviruses, including HSV and VZV, but is most valuable for its activity against CMV. Ganciclovir was the first antiviral agent licensed specifically to treat and prevent CMV infection. It is indicated for prophylaxis against and therapy of CMV infections in high-risk patients, including HIV-infected patients and SOT or HSCT recipients. Of particular importance is the use of ganciclovir in the management of CMV retinitis, a sight-threatening complication of HIV infection. Ganciclovir is also of benefit for newborns with symptomatic congenital CMV infection and may be of value in partially ameliorating the sensorineural hearing loss and developmental disabilities that are common complications of congenital CMV infection.

Ganciclovir is supplied as parenteral and oral formulations. Ganciclovir ocular implants are also available for the management of CMV retinitis. The bioavailability of oral ganciclovir is poor, <10%, and hence oral ganciclovir therapy has been supplanted by the oral prodrug, valganciclovir, which is well absorbed from the gastrointestinal tract and quickly converted to ganciclovir by intestinal or hepatic metabolism. Bioavailability of ganciclovir (from valganciclovir) is approximately 60% from tablet and solution formulations. Significant concentrations are found in aqueous humor, subretinal fluid, cerebrospinal fluid, and brain tissue (enough to inhibit susceptible strains of CMV). Subretinal concentrations are comparable with plasma concentrations, but intravitreal concentrations are lower. Drug concentrations in the CNS range from 24% to 70% of plasma concentrations. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Dose reduction is proportional to the creatinine clearance. Hemodialysis efficiently eliminates ganciclovir, so administration of additional doses after dialysis is necessary.

Ganciclovir has several important toxicities. Reversible myelosuppression is the most important toxicity associated with ganciclovir therapy and commonly requires either discontinuation of therapy or the intercurrent administration of granulocyte colony–stimulating factor. There are also the theoretical risks for carcinogenicity and gonadal toxicity; although these effects have been observed in some animal models, they have never been observed in patients. The decision to administer ganciclovir to a pediatric patient is complex and should be made in consultation with a pediatric infectious disease specialist.

Foscarnet

Foscarnet has a unique profile, insofar as it is not a nucleoside analog but rather a pyrophosphate analog. The drug has broad activity against most herpesviruses. Like the nucleoside analogs, foscarnet inhibits viral DNA polymerase. On the other hand, foscarnet does not require phosphorylation to exert its antiviral activity, thus differing from the nucleoside analogs. It binds to a different site on the viral DNA polymerase to exert its antiviral effect and therefore retains activity against strains of HSV and CMV that are resistant to nucleoside analogs. Its clinical utility is as a second-line agent for management of CMV infections in high-risk patients who cannot tolerate ganciclovir and as an alternative for patients with persistent or refractory HSV, CMV, or VZV disease with suspected or documented antiviral drug resistance.

Foscarnet is available only as a parenteral formulation and is a toxic agent that must be administered cautiously. Nephrotoxicity is common, and reversible renal insufficiency is often observed, as evidenced by an increase in serum creatinine. Abnormalities in calcium and phosphorus homeostasis are common, and electrolytes and renal function must be monitored carefully during treatment.

Cidofovir

Cidofovir is an acyclic nucleotide analog that requires phosphorylation to its active form, cidofovir diphosphate, to exert its antiviral effect. Analogous to penciclovir, it has an extended intracellular half-life that contributes to its prolonged antiviral activity. Cidofovir is active against HSV, VZV, and CMV. In contrast to most of the other agents with activity against herpesviruses, cidofovir also exhibits broad-spectrum activity against other DNA viruses, most notably the poxviruses. Cidofovir has activity against the BK virus, a polyomavirus, and therapy may be warranted in some settings of BK reactivation post HSCT and post SOT. Cidofovir is useful in the management of adenovirus infections in the immunocompromised host. Cidofovir is also useful in the management of CMV disease caused by strains with documented ganciclovir resistance.

Cidofovir is administered intravenously and is cleared renally by tubular secretion. Extensive prehydration and co-administration of probenecid are recommended. Nephrotoxicity is commonly encountered, even with appropriate prehydration; cidofovir must be co-administered with care with other nephrotoxic medications. Other potential toxicities include reproductive toxicity and carcinogenesis.

Trifluridine

Trifluridine is a pyrimidine nucleoside analog with activity against HSV, CMV, and adenovirus. It is formulated as a 1% ophthalmic solution and approved for topical use in the treatment of HSV keratitis and keratoconjunctivitis. Trifluridine is the treatment of choice for HSV keratitis, a disease that should always be managed in consultation with an ophthalmologist.

Vidarabine

Vidarabine is a nucleoside analog that has activity against HSV. It was the first parenteral antiviral agent for HSV infection, although it is no longer available for intravenous administration. A topical preparation remains available to treat HSV keratitis and is considered a second-line agent for this indication.

Fomivirsen

Fomivirsen is an anti-CMV compound that was used as a second-line agent for CMV retinitis by direct injection into the vitreous space. It is an antisense 21-mer DNA oligonucleotide that binds directly to complementary messenger RNA. This agent is of interest because it was the first antisense antiviral agent approved by the US Food and Drug Administration (FDA). The drug is no longer marketed.

New Agents

There is a major need for development of new, nontoxic antivirals for HSV infection. Two new agents are approaching licensure and will be very useful in the management of HSCT and SOT patients. The oral lipid conjugate prodrug of cidofovir, CMX001, has improved activity against herpesviruses compared with parenterally administered cidofovir and a markedly reduced risk of nephrotoxicity. Another novel agent, letermovir (AIC246), is highly orally bioavailable and has a novel mechanism of action, exerting its antiviral effect by interfering with the viral terminase complex. This agent demonstrates substantial promise as an alternative to more toxic antivirals in patients at high risk for CMV disease, particularly in the transplantation setting. It is also active against BK virus and poxviruses.

Antivirals Used for Respiratory Viral Infections

Antiviral therapies are available for many respiratory pathogens, including respiratory syncytial virus (RSV), influenza A, and influenza B. Antiviral therapy for respiratory viral infections is of particular value for infants, children with chronic lung disease, and immunocompromised children.

Ribavirin

Ribavirin is a guanosine analog that has broad-spectrum activity against a variety of viruses, particularly RNA viruses. Its precise mechanism of action is incompletely understood but is probably related to interference with viral messenger RNA processing and translation. Ribavirin is available in oral, parenteral, and aerosolized formulations. Although intravenous ribavirin is highly effective in the management of Lassa fever and other hemorrhagic fevers, this formulation is not licensed for use in the United States. The only licensed formulations in the United States are an aqueous formulation for aerosol administration (indicated for RSV infection) and an oral formulation that is combined with interferon-α for the treatment of hepatitis C. (For more information about antivirals for hepatitis, see Chapter 385 .) Administration of ribavirin by aerosol should be considered for serious RSV lower respiratory tract disease in immunocompromised children, young infants with serious RSV-associated illness, and high-risk infants and children (children with chronic lung disease or cyanotic congenital heart disease). In vitro testing and uncontrolled clinical studies also suggest efficacy of aerosolized ribavirin for parainfluenza, influenza, and measles infections.

Ribavirin is generally nontoxic, particularly when administered by aerosol.

Oral ribavirin is used in combination with other agents for therapy of hepatitis C (discussed later). There is no role for the use of oral ribavirin in the treatment of community-acquired viral respiratory tract infections. Ribavirin and its metabolites concentrate in red blood cells and can persist for several weeks and, in rare instances, may be associated with anemia. Conjunctivitis and bronchospasm have been reported following exposure to aerosolized drug. Care must be taken when using aerosolized ribavirin in children undergoing mechanical ventilation to avoid precipitation of particles in ventilator tubing; the drug is not formally approved for use in the mechanically ventilated patient, although there is published experience with this approach, which can be considered for mechanically ventilated patients, particularly in a “high-dose, short-duration” regimen (6 g/100 mL water given for a period of 2 hr 3 times a day). Concerns regarding potential teratogenicity from animal studies have not been borne out in clinical practice, although care should be taken to prevent inadvertent exposure to aerosolized drug in pregnant healthcare providers.

Amantadine and Rimantadine

Amantadine and rimantadine are tricyclic amines (adamantanes) that share structural similarity. Both were indicated for prophylaxis and therapy of influenza A. The mechanism of action of the tricyclic amines against influenza A virus was unclear, but they appeared to exert their antiviral effect at the level of uncoating of the virus. Both agents are extremely well absorbed after oral administration and are eliminated via the kidneys (90% of the dose is unchanged), necessitating dosage adjustments for renal insufficiency. The toxicities of the tricyclic amines are modest and include CNS adverse effects such as anxiety, difficulty concentrating, and lightheadedness and gastrointestinal adverse effects such as nausea and loss of appetite.

Although these agents are still manufactured and available, the Centers for Disease Control and Prevention (CDC) no longer recommends the use of the adamantane agents in treatment or prophylaxis against influenza, due to emergence of widespread resistance.

Oseltamivir, Zanamivir, and Peramivir

Oseltamivir and zanamivir are active against both influenza A and B, although the importance of this broader spectrum of antiinfluenza activity in disease control is modest because influenza B infection is typically a much milder illness. Emerging strains of influenza, including H5N1 and the 2009–2010 pandemic strain, H1N1 (swine flu), are susceptible to oseltamivir and zanamivir but resistant to amantadine. Therefore these agents are emerging as the antivirals of choice for influenza infection. Neither agent has appreciable activity against other respiratory viruses. The mechanism of antiviral activity of these agents is via inhibition of the influenza neuraminidase.

Zanamivir has poor oral bioavailability and is licensed only for inhalational administration. With inhaled administration, >75% of the dose is deposited in the oropharynx and much of it is swallowed. The actual amount distributed to the airways and lungs depends on factors such as the patient's inspiratory flow. Approximately 13% of the dose appears to be distributed to the airways and lungs, with approximately 10% of the inhaled dose distributed systemically. Local respiratory mucosal drug concentrations greatly exceed the drug concentration needed to inhibit influenza A and B viruses. Elimination is via the kidneys, and no dosage adjustment is necessary with renal insufficiency, because the amount that is systemically absorbed is low.

Oseltamivir is administered as an esterified prodrug that has high oral bioavailability. It is eliminated by tubular secretion, and dosage adjustment is required for patients with renal insufficiency. Gastrointestinal adverse effects, including nausea and vomiting, are occasionally observed. The drug is indicated for both treatment and prophylaxis. The usual adult dosage for treatment of influenza is 75 mg twice daily for 5 days. Treatment should be initiated within 2 days of the appearance of symptoms. Recommended treatment dosages for children vary by age and weight. The recommended dose for children younger than 1 yr of age is 3 mg/kg/dose twice a day. For children older than 1 yr of age, doses are 30 mg twice a day for children weighing ≤15 kg, 45 mg twice a day for children weighing 15-23 kg, 60 mg twice a day for those weighing 23-40 kg, and 75 mg twice a day for children weighing ≥40 kg. Dosages for chemoprophylaxis are the same for each weight group in children older than 1 yr of age, but the drug should be administered only once daily rather than twice daily. Oseltamivir is FDA approved for therapy of influenza A and B treatment in children 2 wk of age and older, whereas zanamivir is recommended for treatment of children 7 yr of age and older. Current treatment and dosage recommendations for treatment of influenza in children and for chemoprophylaxis are available at: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm . Oseltamivir has been described to produce neuropsychiatric (narcolepsy) and psychologic (suicidal events) side effects in some patient populations; the drug should be discontinued if behavioral or psychiatric side effects are observed. In late 2014 the FDA approved another neuraminidase inhibitor, peramivir, for treatment of influenza. It is available as a single-dose, intravenous option. The drug is currently approved for use in children >2 yr of age. The dose is 12 mg/kg dose, up to 600 mg maximum, via intravenous infusion for a minimum of 15 min in children from 2 to 12 yr of age. Children 13 and older should receive the adult dose (600 mg IV in a single, 1-time dose).

Baloxavir

Oral baloxavir marboxil (Xofluza) is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people ≥12 yr. The safety and efficacy of baloxavir for the treatment of influenza have been established in pediatric patients ≥12 yr and older weighing at least 40 kg. Safety and efficacy in patients <12 yr or weighing less than 40 kg have not been established. Baloxavir efficacy is based on clinical trials in outpatients 12 to 64 yr of age; people with underlying medical conditions and adults >65 yr were not included in the initial published clinical trials. There are no available data for baloxavir treatment of hospitalized patients with influenza.

Antivirals Used for Hepatitis

Seven antiviral agents have been approved by the FDA for treatment of adults with chronic hepatitis B in the United States. These agents are categorized as either interferons (IFN-α2b and peginterferon-α2a) or nucleoside or nucleotide analogs (lamivudine, adefovir, entecavir, tenofovir, telbivudine). Lamivudine is currently considered the first-line therapy in adult patients, but experience in children is limited. In 2012 tenofovir was FDA approved for children with chronic hepatitis B aged 12 yr or older weighing >35 kg. Entecavir was approved in the United States for use in children 2 yr and older with chronic HBV and evidence of active viral replication and disease activity and, with IFN-α, is emerging as a first-line antiviral regimen for children with hepatitis B who are candidates for antiviral therapy.

Adefovir demonstrates a favorable safety profile and is less likely to select for resistance than lamivudine, but virologic response was limited to adolescent patients and was lower than that of lamivudine. Most experts recommend watchful waiting of children with chronic hepatitis B infection, because current therapies are only modestly effective at best and evidence of long-term benefit is scant. Young children are often believed to be immune tolerant of hepatitis B infection (i.e., they have viral DNA present in serum but normal transaminase levels and no evidence of active hepatitis). These children should have transaminases and viral load monitored but are not typically considered to be candidates for antiviral therapy.

Only various combinations of interferons and ribavirin were approved by the FDA to treat adults and children with chronic hepatitis C (see Tables 272.1 and 272.2). The development of novel and highly effective antivirals for HCV has revolutionized the care of hepatitis C patients. These drugs are not yet licensed for pediatric use. Novel drugs include ledipasvir, sofosbuvir, daclatasvir, elbasvir, beclabuvir, grazoprevir, paritaprevir, ombitasvir, velpatasvir, and dasabuvir. Ledipasvir, ombitasvir, daclatasvir, elbasvir, and velpatasvir inhibit the virally encoded phosphoprotein, NS5A, which is involved in viral replication, assembly, and secretion, whereas sofosbuvir is metabolized to a uridine triphosphate mimic, which functions as an RNA chain terminator when incorporated into the nascent RNA by the NS5B polymerase enzyme. Dasabuvir and beclabuvir are also NS5B inhibitors. Paritaprevir and grazoprevir inhibit the nonstructural protein 3 (NS3/4) serine protease, a viral nonstructural protein that is the 70-kDa cleavage product of the hepatitis C virus polyprotein.

Past efforts to treat HCV prior to the advent of these new direct therapies had yielded mixed results. Although only 10–25% of adults treated with interferon had a sustained remission of disease, treatment with a combination of interferon and ribavirin achieves remission in close to half of treated adults. Randomized controlled trials indicated that patients treated with pegylated interferons (so called because they are formulated and stabilized with polyethylene glycol), both as dual therapy with ribavirin and as monotherapy, experienced higher sustained viral response rates than did those treated with nonpegylated interferons. The advent of new, direct therapies has led to permanent remission of HCV disease in adult patients. Data on the use of these agents in infants and children are limited. In early 2017 the combination of sofosbuvir with ribavirin and the fixed-dose combination of sofosbuvir/ledipasvir was approved by the FDA for treatment of children with chronic HCV infection 12 yr of age and older. The only drugs currently approved for children younger than 12 yr remain pegylated interferon and ribavirin. The use of IFN-α2b in combination with ribavirin has been approved by the FDA for chronic hepatitis C in this age group.

There are significant genotype-dependent differences in responsiveness to antiviral therapy; patients with genotype 1 had the lowest levels of sustained virologic response, and patients with genotype 2 or 3 had the highest response. The use of IFN-ααb in combination with ribavirin provides a much more favorable sustained virologic response in children with HCV genotype 2/3 than in those with HCV genotype 1. For genotype 1 hepatitis C treated with pegylated interferons combined with ribavirin, it has been shown that genetic polymorphisms near the human *IL28B* gene, encoding interferon lambda 3, are associated with significant differences in response to the treatment.

Antiviral Immune Globulins

Immune globulins are useful adjuncts in the management of viral disease. However, they are most valuable when administered as prophylaxis against infection and disease in high-risk patients; their value as therapeutic agents in the setting of established infection is less clear. **Varicella-zoster immune globulin (human)** is valuable for prophylaxis against VZV in high-risk children, particularly newborns and immunocompromised children (see Chapter 280). **Cytomegalovirus immune globulin** is warranted for children at high risk for CMV disease, particularly SOT and HSCT patients, and can play a role in preventing injury to the infected fetus when administered to the pregnant patient (see Chapter 282). **Palivizumab,** a monoclonal antibody with anti-RSV activity, is effective for preventing severe RSV lower respiratory tract disease in high-risk premature infants and has replaced **RSV immune globulin** (see Chapter 287). **Hepatitis B immune globulin** is indicated in infants born to hepatitis B surface antigen-positive mothers (see Chapter 385).

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CHAPTER 273

Measles

Wilbert H. Mason, Hayley A. Gans

Measles is highly contagious, but endemic transmission has been interrupted in the United States as a result of widespread vaccination; indigenous or imported cases have occasionally resulted in epidemics in the United States in unimmunized or partially immunized American or foreign-born children (adopted children, refugees, returning tourists). In some areas of the world, measles remains a serious threat to children (Fig. 273.1).

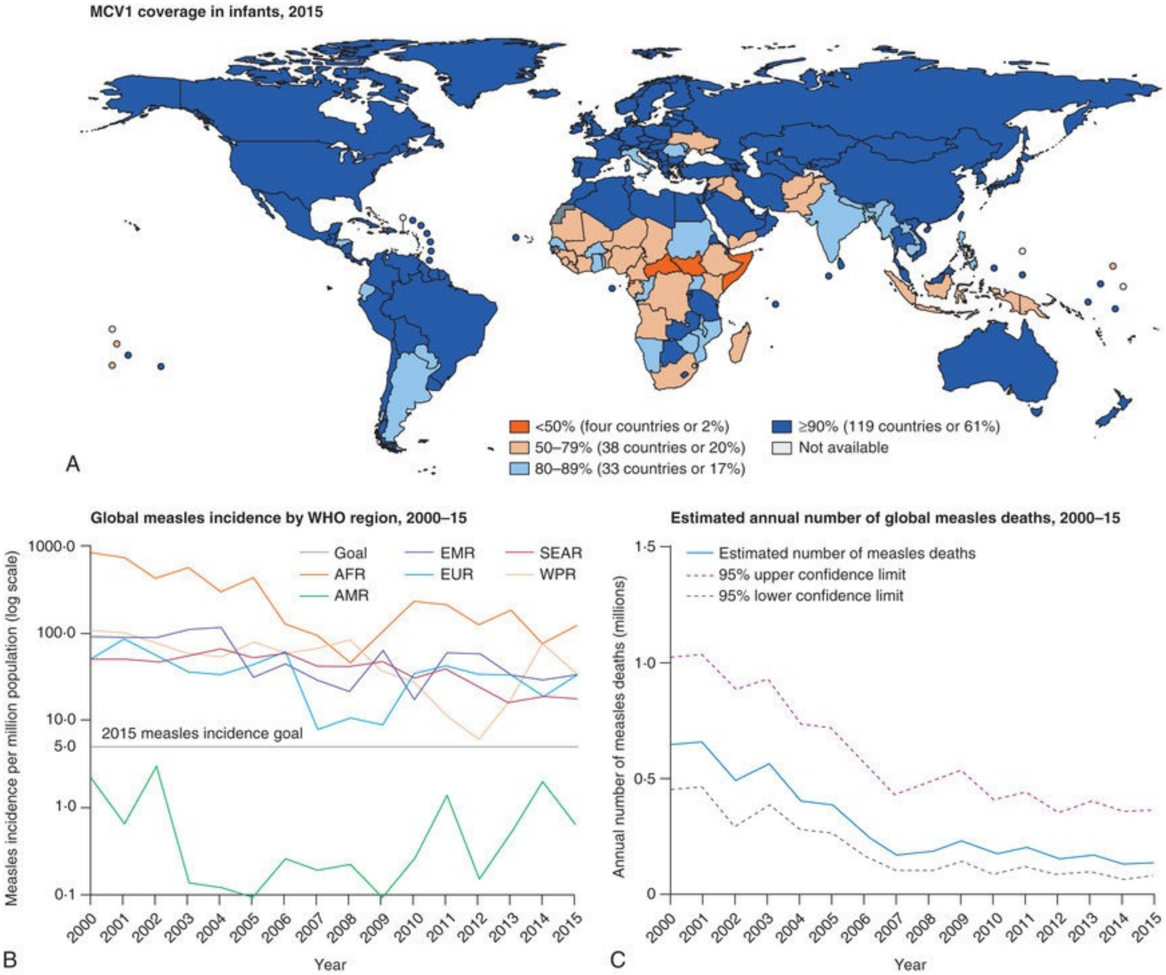

FIG. 273.1 Progress toward achieving global measles milestones for measles vaccine coverage **(A)** , measles incidence **(B)** , and measles mortality **(C)** . **A,** Milestone 1: increase routine coverage with the 1st dose of measles-containing vaccine (MCV1) for children aged 1 yr to ≥90% nationally and ≥80% in every district. Progress: The number of countries with ≥90% MCV1 coverage increased from 84 (44%) in 2000 to 119 (61%) in 2015. Among countries with ≥90% MCV1 coverage nationally, the percentage with ≥80% coverage in every district was only 39% of 119 countries in 2015. **B,** Milestone 2: reduce global measles incidence to less than 5 cases per 1 million population. Progress: reported global annual measles incidence decreased 75% from 2000 to 2015, but only the Region of the Americas achieved the milestone of less than 5 cases per 1 million population. **C,** Milestone 3: reduce global measles mortality by 95% from the 2000 estimate. Progress: the number of estimated global annual measles deaths decreased 79% from 2000 to 2015. AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEAR, South-East Asia Region; WPR, Western Pacific Region. (From Moss WJ: Measles, *Lancet* 390:2490–2502, 2017, Fig. 2, with data from Patel MK, Gacic-Dobo M, Strebel PM, et al: Progress toward regional measles elimination—worldwide, 2000–2015. *MMWR Morb Mortal Wkly Rep* 65:1228–1233, 2016.)

Etiology

Measles virus is a single-stranded, lipid-enveloped RNA virus in the family Paramyxoviridae and genus *Morbillivirus*. Other members of the genus *Morbillivirus* affect a variety of mammals, such as rinderpest virus in cattle and distemper virus in dogs, but humans are the only host of measles virus. Of the 6 major structural proteins of measles virus, the 2 most important in terms of induction of immunity are the hemagglutinin (H) protein and the fusion (F) protein. The neutralizing antibodies are directed against the H protein, and antibodies to the F protein limit proliferation of the virus during infection. Small variations in genetic composition have also been identified that result in no effect on protective immunity but provide molecular markers that can distinguish between viral types. Related genotypes have been grouped by clades, and the World Health Organization recognizes 8 clades, A-H, and 23 genotypes. These markers have been useful in the evaluation of endemic and epidemic spread of measles.

Epidemiology

The measles vaccine has changed the epidemiology of measles dramatically. Once worldwide in distribution, endemic transmission of measles has been interrupted in many countries where there is widespread vaccine coverage. Historically, measles caused universal infection in childhood in the United States, with 90% of children acquiring the infection before 15 yr of age. Morbidity and mortality associated with measles decreased prior to the introduction of the vaccine as a result of improvements in healthcare and nutrition. However, the incidence declined dramatically following the introduction of the measles vaccine in 1963. The attack rate fell from 313 cases per 100,000 population in 1956–1960 to 1.3 cases per 100,000 in 1982–1988.

A nationwide indigenous measles outbreak occurred in the United States in 1989–1991, resulting in more than 55,000 cases, 11,000 hospitalizations, and 123 deaths, demonstrating that the infection had not yet been controlled. This resurgence was attributed to vaccine failure in a small number of school-age children, low coverage of preschool-age children, and more rapid waning of maternal antibodies in infants born to mothers who had never experienced wild-type measles infection. Implementation of the 2-dose vaccine policy and more intensive immunization strategies resulted in interruption of endemic transmission and in 2,000 measles was declared eliminated from the United States. The current rate is <1 case per 1,000,000 population.

Measles continues to be imported into the United States from abroad; therefore continued maintenance of >90% immunity through vaccination is necessary to prevent widespread outbreaks from occurring (see Fig. 273.1).

In 2014 the United States encountered a record number of cases since elimination in 2000, with 667 cases of measles reported to the U.S. Centers for Disease Control and Prevention (CDC). There were 23 outbreaks reported compared with a median of 4 outbreaks reported annually during 2001–2010. The majority of cases were associated with importations from other countries (returning tourists, adoptees, refugees), particularly from the Philippines, with prior year epidemics associated with epidemics in the World Health Organization European Region. Measles cases are largely restricted to unvaccinated individuals. Since 2014, cases continue to result from importations causing multistate outbreaks, but due to increased awareness and vaccination efforts, cases remain <200/annually, with 86 reported in 2016 and 120 to date in 2017.

High levels of measles immunity in a population of ~95% are required to interrupt the endemic spread of measles. In the United States this can be achieved through the current 2-dose immunization strategies when coverage rates are high (>90% 1-dose coverage at 12-15 mo and >95% 2-dose coverage in school-age children). Although measles-mumps-rubella coverage remains high (90–91.5% in children 19-35 mo for 2000–2015), pockets of lower coverage rates exist because of reluctance of parents to vaccinate their children. This variability in vaccination has contributed to outbreaks among school-age children in recent years.

Transmission

The portal of entry of measles virus is through the respiratory tract or conjunctivae following contact with large droplets or small-droplet aerosols in which the virus is suspended. Patients are infectious from 3 days before to up to 4-6 days after the onset of rash. Approximately 90% of exposed susceptible individuals experience measles. Face-to-face contact is not necessary, because viable virus may be suspended in air for as long as 1 hr after the patient with the source case leaves a room. Secondary cases from spread of aerosolized virus have been reported in airplanes, physicians’ offices, and hospitals.

Pathology

Measles infection causes necrosis of the respiratory tract epithelium and an accompanying lymphocytic infiltrate. Measles produces a small-vessel vasculitis on the skin and on the oral mucous membranes. Histology of the rash and exanthem reveals intracellular edema and dyskeratosis associated with formation of epidermal syncytial giant cells with up to 26 nuclei. Viral particles have been identified within these giant cells. In lymphoreticular tissue, lymphoid hyperplasia is prominent. Fusion of infected cells results in multinucleated giant cells, the **Warthin-Finkeldey giant cells** that are pathognomonic for measles, with up to 100 nuclei and intracytoplasmic and intranuclear inclusions.

Pathogenesis

Measles infection consists of 4 phases: incubation period, prodromal illness, exanthematous phase, and recovery. During incubation, measles virus migrates to regional lymph nodes. A primary viremia ensues that disseminates the virus to the reticuloendothelial system. A secondary viremia spreads virus to body surfaces. The prodromal illness begins after the secondary viremia and is associated with epithelial necrosis and giant cell formation in body tissues. Cells are killed by cell-to-cell plasma membrane fusion associated with viral replication that occurs in many body tissues, including cells of the central nervous system. Virus shedding begins in the prodromal phase. With onset of the rash, antibody production begins, and viral replication and symptoms begin to subside. Measles virus also infects $CD4^+$ T cells, resulting in suppression of the Th1 immune response and a multitude of other immunosuppressive effects.

Measles virus attaches to specific cell receptors to infect host cells. Studies in primates show that the initial targets for measles virus are alveolar macrophages, dendritic cells, and lymphocytes. The cell receptor used appears to be the signaling lymphocyte activating molecule or more properly CD150. Subsequently, respiratory epithelial cells become infected but do not express CD150. The mechanism of infection of respiratory tissues is attachment to the PVRL4 receptor (Nectin4) that is expressed on cells in the trachea, oral mucosa, nasopharynx, and lungs. These 2 receptors, CD150 and PVRL4, account for the lymphotropic and epitheliotropic nature of natural measles virus infection and, along with the prolonged immunosuppressive effects of measles, suggest that it is more characteristic of human immunodeficiency virus infection than a respiratory illness.

Clinical Manifestations

Measles is a serious infection characterized by high fever, an enanthem, cough, coryza, conjunctivitis, and a prominent exanthem (Fig. 273.2). After an incubation period of 8-12 days, the prodromal phase begins with a mild fever followed by the onset of conjunctivitis with photophobia, coryza, a prominent cough, and increasing fever. **Koplik spots** represent the enanthem and are the pathognomonic sign of measles, appearing 1-4 days prior to the onset of the rash (Fig. 273.3). They first appear as discrete red lesions with bluish white spots in the center on the inner aspects of the cheeks at the level of the premolars. They may spread to involve the lips, hard palate, and gingiva. They also may occur in conjunctival folds and in the vaginal mucosa. Koplik spots have been reported in 50–70% of measles cases but probably occur in the great majority.

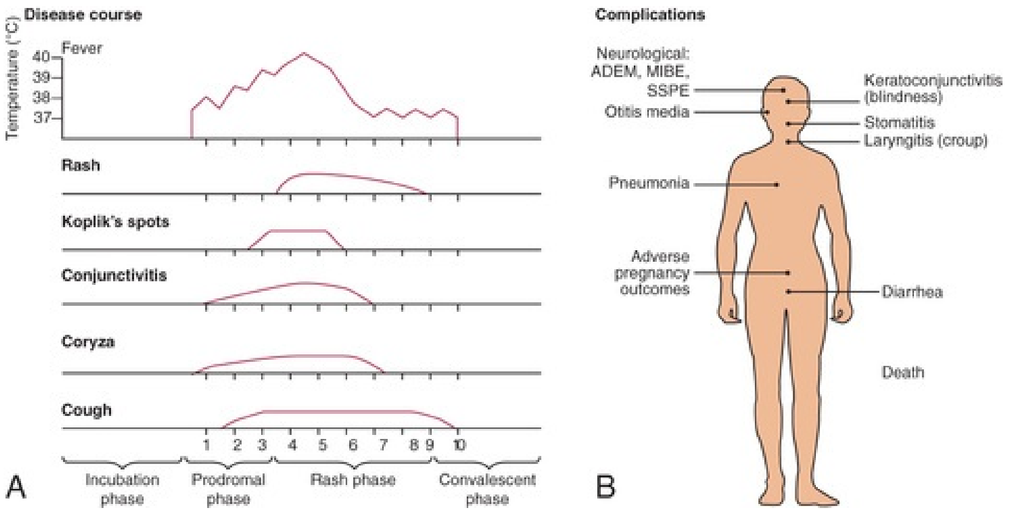
Disease course
Temperature (°C)
Fever
40
39
38
37
Rash
Koplik's spots
Conjunctivitis
Coryza
Cough
1
2
3
4
5
6
7
8
9
10
Incubation phase
Prodromal phase
Rash phase
Convalescent phase
A
Complications
Neurological: ADEM, MIBE, SSPE
Otitis media
Pneumonia
Adverse pregnancy outcomes
Keratoconjunctivitis (blindness)
Stomatitis
Laryngitis (croup)
Diarrhea
Death
B

FIG. 273.2 Measles disease course **(A)** and complications **(B)** . ADEM, acute demyelinating encephalomyelitis; MIBE, measles inclusion body encephalitis; SSPE, subacute sclerosing panencephalitis. (Modified from Moss WJ: Measles, *Lancet* 390:2490–2502, 2017, Fig. 4.)

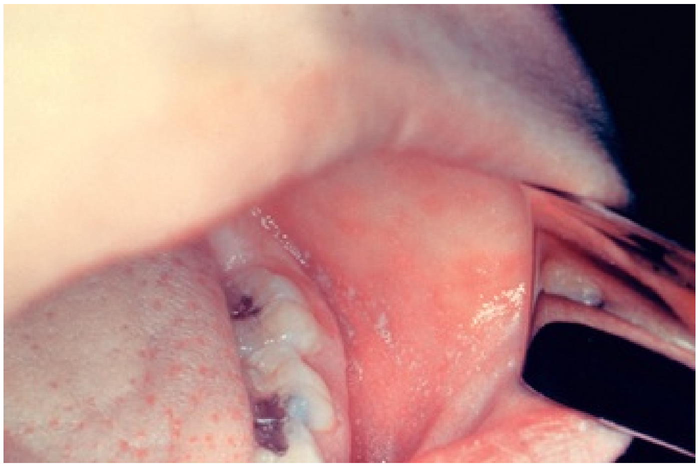

FIG. 273.3 Koplik spots on the buccal mucosa during the 3rd day of rash. (From Centers for Disease Control and Prevention (CDC): *Public health image library* , image #4500. Available at: http://phil.cdc.gov/phil/details.asp .)

Symptoms increase in intensity for 2-4 days until the 1st day of the rash. The rash begins on the forehead (around the hairline), behind the ears, and on the upper neck as a red maculopapular eruption. It then spreads downward to the torso and extremities, reaching the palms and soles in up to 50% of cases. The exanthem frequently becomes confluent on the face and upper trunk (Fig. 273.4).

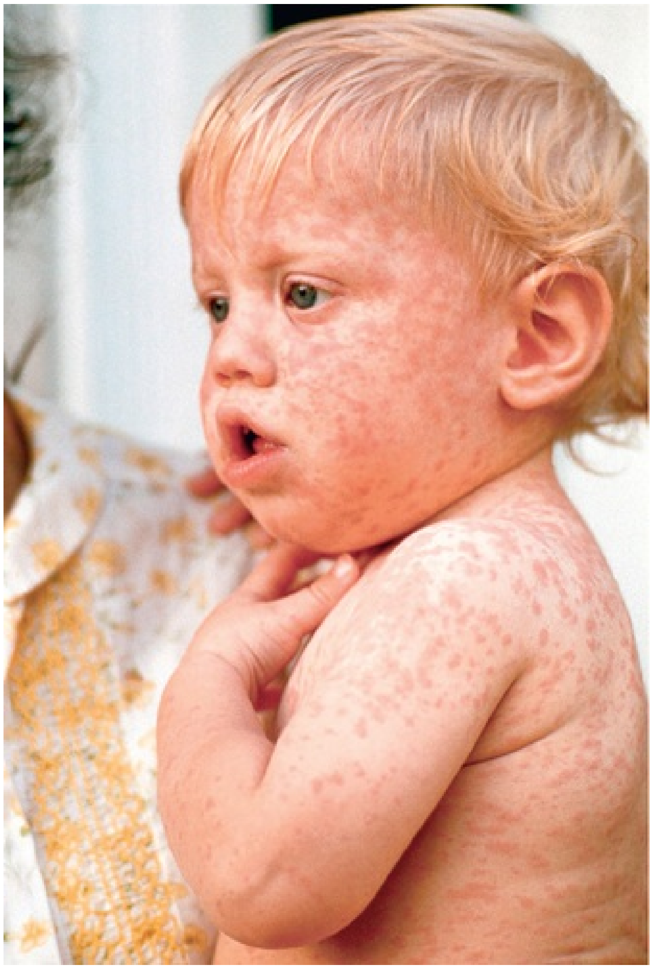

FIG. 273.4 A child with measles displaying the characteristic red blotchy pattern on his face and body. (From Kremer JR, Muller CP: Measles in Europe—there is room for improvement, *Lancet* 373:356–358, 2009.)

With the onset of the rash, symptoms begin to subside. The rash fades over about 7 days in the same progression as it evolved, often leaving a fine desquamation of skin in its wake. Of the major symptoms of measles, the cough lasts the longest, often up to 10 days. In more severe cases, generalized lymphadenopathy may be present, with cervical and occipital lymph nodes especially prominent.

Modified Measles Infection

In individuals with passively acquired antibody, such as infants and recipients of blood products, a subclinical form of measles may occur. The rash may be indistinct, brief, or, rarely, entirely absent. Likewise, some individuals who have received a vaccine, when exposed to measles, may have a rash but few other symptoms. Persons with modified measles are not considered highly contagious.

Laboratory Findings

The diagnosis of measles is almost always based on clinical and epidemiologic findings. Laboratory findings in the acute phase include reduction in the total white blood cell count, with lymphocytes decreased more than neutrophils. However, absolute neutropenia has been known to occur. In measles not complicated by bacterial infection, the erythrocyte sedimentation rate and C-reactive protein level are usually normal.

Diagnosis

In the absence of a recognized measles outbreak, confirmation of the clinical diagnosis is often recommended. Serologic confirmation is most conveniently made by identification of immunoglobulin (Ig) M antibody in serum. IgM antibody appears 1-2 days after the onset of the rash and remains detectable for about 1 mo. If a serum specimen is collected <72 hr after onset of rash and is negative for measles antibody, a 2nd specimen should be obtained. Serologic confirmation may also be made by demonstration of a 4-fold rise in IgG antibodies in acute and convalescent specimens collected 2-4 wk apart. Viral isolation from blood, urine, or respiratory secretions can be accomplished by culture at the CDC or local or state laboratories. Molecular detection by polymerase chain reaction is available through some state and local health departments and through the CDC.

Differential Diagnosis

Typical measles is unlikely to be confused with other illnesses, especially if Koplik spots are observed. Measles in the later stages or modified or atypical infections may be confused with a number of other exanthematous immune-mediated illnesses and infections, including rubella, adenovirus infection, enterovirus infection, and Epstein-Barr virus infection. Exanthem subitum (in infants) and erythema infectiosum (in older children) may also be confused with measles. *Mycoplasma pneumoniae* and group A streptococcus may also produce rashes similar to that of measles. Kawasaki syndrome can cause many of the same findings as measles but lacks discrete intraoral lesions (Koplik spots) and a severe prodromal cough and typically leads to elevations of neutrophils and acute-phase reactants. In addition, the characteristic thrombocytosis of Kawasaki syndrome is absent in measles (see Chapter 191). Drug eruptions may occasionally be mistaken for measles.

Complications

Complications of measles are largely attributable to the pathogenic effects of the virus on the respiratory tract and immune system (Table 273.1 , Fig. 273.2). Several factors make complications more likely. Morbidity and mortality from measles are greatest in individuals younger than 5 yr of age (especially <1 yr of age) and older than 20 yr of age. In developing countries, higher case fatality rates have been associated with crowding, possibly attributable to larger inoculum doses after household exposure. Severe malnutrition in children results in a suboptimal immune response and higher morbidity and mortality with measles infection. Low serum retinol levels in children with measles are associated with higher measles morbidity and mortality in developing countries and in the United States. Measles infection lowers serum retinol concentrations, so subclinical cases of hyporetinolemia may be made symptomatic during measles. Measles infection in immunocompromised persons is associated with increased morbidity and mortality. Among patients with malignancy in whom measles develops, pneumonitis occurs in 58% and encephalitis occurs in 20%.

Table 273.1

Complications by Age for Reported Measles Cases, United States, 1987–2000

COMPLICATION	OVERALL (67,032 CASES WITH AGE INFORMATION)	NO. (%) OF PERSONS WITH COMPLICATION BY AGE GROUP				
		<5 yr (*N* = 28,730)	**5-9 yr (*N* = 6,492)**	**10-19 yr (*N* = 18,580)**	**20-29 yr (*N* = 9,161)**	**<30 yr (*N* = 4,069)**
Any	19,480 (29.1)	11,883 (41.4)	1,173 (18.1)	2,369 (12.8)	2,656 (29.0)	1,399 (34.4)
Death	177 (0.3)	97 (0.3)	9 (0.1)	18 (0.1)	26 (0.3)	27 (0.7)
Diarrhea	5,482 (8.2)	3,294 (11.5)	408 (6.3)	627 (3.4)	767 (8.4)	386 (9.5)

Encephalitis	97 (0.1)	43 (0.2)	9 (0.1)	13 (0.1)	21 (0.2)	11 (0.3)
Hospitalization	12,876 (19.2)	7,470 (26.0)	612 (9.4)	1,612 (8.7)	2,075 (22.7)	1,107 (27.2)
Otitis media	4,879 (7.3)	4,009 (14.0)	305 (4.7)	338 (1.8)	157 (1.7)	70 (1.7)
Pneumonia	3,959 (5.9)	2,480 (8.6)	183 (2.8)	363 (2.0)	554 (6.1)	379 (9.3)

From Perry RT, Halsey NA: The clinical significance of measles: a review, *Clin Infect Dis* 189(Suppl. 1):S4–S16, 2004.

Pneumonia is the most common cause of death in measles. It may manifest as **giant cell pneumonia** caused directly by the viral infection or as superimposed bacterial infection. The most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus* . Following severe measles pneumonia, the final common pathway to a fatal outcome is often the development of bronchiolitis obliterans.

Croup, tracheitis, and bronchiolitis are common complications in infants and toddlers with measles. The clinical severity of these complications frequently requires intubation and ventilatory support until the infection resolves.

Acute otitis media is the most common complication of measles and was of particularly high incidence during the epidemic of the late 1980s and early 1990s because of the relatively young age of affected children. Sinusitis and mastoiditis also occur as complications. Viral and/or bacterial tracheitis is seen and can be life-threatening. Retropharyngeal abscess has also been reported.

Measles infection is known to suppress skin test responsiveness to purified tuberculin antigen. There may be a higher rate of activation of pulmonary tuberculosis in populations of individuals infected with *Mycobacterium tuberculosis* who are then exposed to measles.

Diarrhea and vomiting are common symptoms associated with acute measles, and diffuse giant cell formation is found in the epithelium in the gastrointestinal tract. Dehydration is a common consequence, especially in young infants and children. Appendicitis or abdominal pain may occur from obstruction of the appendiceal lumen by lymphoid hyperplasia.

Febrile seizures occur in <3% of children with measles. Encephalitis following measles is a long-associated complication, often with an unfavorable outcome. Rates of 1-3 per 1,000 cases of measles have been reported, with greater numbers occurring in adolescents and adults than in preschool- or school-age children. Encephalitis is a postinfectious, immunologically mediated process and is not the result of a direct effect by the virus. Clinical onset begins during the exanthem and manifests as seizures (56%), lethargy (46%), coma

(28%), and irritability (26%). Findings in cerebrospinal fluid include lymphocytic pleocytosis in 85% of cases and elevated protein concentrations. Approximately 15% of patients with measles encephalitis die. Another 20–40% of patients suffer long-term sequelae, including cognitive impairment, motor disabilities, and deafness.

Measles encephalitis in immunocompromised patients results from direct damage to the brain by the virus. Subacute measles encephalitis manifests 1-10 mo after measles in immunocompromised patients, particularly those with AIDS, lymphoreticular malignancies, and immunosuppression. Signs and symptoms include seizures, myoclonus, stupor, and coma. In addition to intracellular inclusions, abundant viral nucleocapsids and viral antigen are seen in brain tissue. Progressive disease and death almost always occur.

A severe form of measles rarely seen nowadays is **hemorrhagic measles** or **black measles.** It manifested as a hemorrhagic skin eruption and was often fatal. Keratitis, appearing as multiple punctate epithelial foci, resolved with recovery from the infection. Thrombocytopenia sometimes occurred following measles.

Myocarditis is a rare complication of measles. Miscellaneous bacterial infections have been reported, including bacteremia, cellulitis, and toxic shock syndrome. Measles during pregnancy is associated with high rates of maternal morbidity, fetal wastage, and stillbirths, with congenital malformations in 3% of liveborn infants.

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a chronic complication of measles with a delayed onset and an outcome that is nearly always fatal. It appears to result from a persistent infection with an altered measles virus that is harbored intracellularly in the central nervous system for several yr. After 7-10 yr the virus apparently regains virulence and attacks the cells in the central nervous system that offered the virus protection. This “slow virus infection” results in inflammation and cell death, leading to an inexorable neurodegenerative process.

SSPE is a rare disease and generally follows the prevalence of measles in a population. The incidence in the United States in 1960 was 0.61 cases per million persons younger than age 20 yr. By 1980 the rate had fallen to 0.06 cases per million. Between 1956 and 1982 a total of 634 cases of SSPE had been reported to the national SSPE registry. After 1982 approximately 5 cases/yr were reported annually in the United States, and only 2-3 cases/yr were reported in the early 1990s. However, between 1995 and 2000, reported cases in the United States increased and 13 cases were reported in 2000. Nine of the 13 cases occurred in foreign-born individuals. This “resurgence” may be the result of an increased incidence of measles between 1989 and 1991. Although the age of onset ranges from <1 yr to <30 yr, the illness is primarily one of children and adolescents. Measles at an early age favors the development of SSPE: 50% of patients with SSPE had primary measles before 2 yr of age, and 75% had measles before 4 yr of age. Males are affected twice as often as females, and there appear to be more cases reported from rural than urban populations. Recent observations from the registry indicate a higher prevalence among children of Hispanic origin.

The pathogenesis of SSPE remains enigmatic. Factors that seem to be involved include defective measles virus and interaction with a defective or immature immune system. The virus isolated from brain tissue of patients with SSPE is missing 1 of the 6 structural proteins, the matrix or M protein. This protein is responsible for assembly, orientation, and alignment of the virus in preparation for budding during viral replication. Immature virus may be able to reside, and possibly propagate, within neuronal cells for long periods. The fact that most patients with SSPE were exposed at a young age suggests that immune immaturity is involved in pathogenesis.

Clinical manifestations of SSPE begin insidiously 7-13 yr after primary measles infection. Subtle changes in behavior or school performance appear, including irritability, reduced attention span, and temper outbursts. This initial phase (**stage I**) may at times be missed because of brevity or mildness of the symptoms. Fever, headache, and other signs of encephalitis are absent. The hallmark of the **2nd stage** is massive myoclonus, which coincides with extension of the inflammatory process site to deeper structures in the brain, including the basal ganglia. Involuntary movements and repetitive myoclonic jerks begin in single muscle groups but give way to massive spasms and jerks involving both axial and appendicular muscles. Consciousness is maintained. In the **3rd stage** , involuntary movements disappear and are replaced by choreoathetosis, immobility, dystonia, and lead pipe rigidity that result from destruction of deeper centers in the basal ganglia. The sensorium deteriorates into dementia, stupor, and then coma. The **4th stage** is characterized by loss of critical centers that support breathing, heart rate, and blood pressure. Death soon ensues. Progression through the clinical stages may follow courses characterized as acute, subacute, or chronic progressive.

The diagnosis of SSPE can be established through documentation of a compatible clinical course and at least 1 of the following supporting findings: (1) measles antibody detected in cerebrospinal fluid, (2) characteristic electroencephalographic findings, and (3) typical histologic findings in and/or isolation of virus or viral antigen from brain tissue obtained by biopsy or postmortem examination.

Cerebrospinal fluid analysis reveals normal cells but elevated IgG and IgM antibody titers in dilutions >1 : 8. Electroencephalographic patterns are normal in stage I, but in the myoclonic phase, suppression-burst episodes are seen that are characteristic of, but not pathognomonic for, SSPE. Brain biopsy is no longer routinely indicated for diagnosis of SSPE.

Management of SSPE is primarily supportive and similar to care provided to patients with other neurodegenerative diseases. Clinical trials using isoprinosine with or without interferon suggest significant benefit (30–34% remission rate) compared with patients without treatment (5–10% with spontaneous remissions).

It is recognized that carbamazepine is of significant benefit in the control of myoclonic jerks in the early stages of the illness.

Virtually all patients eventually succumb to SSPE. Most die within 1-3 yr of onset from infection or loss of autonomic control mechanisms. Prevention of SSPE depends on prevention of primary measles infection through vaccination. SSPE has been described in patients who have no history of measles infection and exposure only to the vaccine virus. However, wild-type virus, not vaccine virus, has been found in brain tissue of at least some of these patients, suggesting that they had had subclinical measles previously.

Treatment

Management of measles is supportive because there is no specific antiviral therapy approved for treatment of measles. Maintenance of hydration, oxygenation, and comfort are goals of therapy. Antipyretics for comfort and fever control are useful. For patients with respiratory tract involvement, airway humidification and supplemental oxygen may be of benefit. Respiratory failure from croup or pneumonia may require ventilatory support. Oral rehydration is effective in most cases, but severe dehydration may require intravenous therapy. Prophylactic antimicrobial therapy to prevent bacterial infection is not indicated.

Measles infection in immunocompromised patients is highly lethal. Ribavirin is active in vitro against measles virus. Anecdotal reports of ribavirin therapy with or without intravenous gamma globulin suggest some benefit in individual patients. However, no controlled trials have been performed, and ribavirin is not licensed in the United States for treatment of measles.

Vitamin A

Vitamin A deficiency in children in developing countries has long been known to be associated with increased mortality from a variety of infectious diseases, including measles. In the United States, studies in the early 1990s documented that 22–72% of children with measles had low retinol levels. In addition, 1 study demonstrated an inverse correlation between the level of retinol and severity of illness. Several randomized controlled trials of vitamin A therapy in the developing world and the United States have demonstrated reduced morbidity and mortality from measles. Vitamin A therapy is indicated for all patients with measles. Vitamin A should be administered once daily for 2 days at doses of 200,000 IU for children 12 mo of age or older; 100,000 IU for infants 6 mo through 11 mo of age; and 50,000 IU for infants younger than 6 mo of age.

In children with signs and symptoms of vitamin A deficiency, a 3rd age-appropriate dose is recommended 2-4 wk after the 2nd dose.

Prognosis

In the early 20th century, deaths from measles in the United States varied between 2,000 and 10,000 per year, or about 10 deaths per 1,000 cases of measles. With improvements in healthcare and antimicrobial therapy, better nutrition, and decreased crowding, the death:case ratio fell to 1 per 1,000 cases. Between 1982 and 2002, the CDC estimated that there were 259 deaths caused by measles in the United States, with a death:case ratio of 2.5-2.8 per 1,000 cases of measles. Pneumonia and encephalitis were complications in most of the fatal cases, and immunodeficiency conditions were identified in 14–16% of deaths. In 2011, of the 222 cases reported in the United States, 70 (32%) were hospitalized, including 17 (24%) with diarrhea, 15 (21%) with dehydration, and 12 (17%) with pneumonia. No cases of encephalitis or deaths were reported. In the 1st half of 2015, of 159 reported cases 22 (14%) were hospitalized, with 5 pneumonia cases and no deaths.

Prevention

Patients shed measles virus from 7 days after exposure to 4-6 days after the onset of rash. Exposure of susceptible individuals to patients with measles should be avoided during this period. In hospitals, standard and airborne precautions should be observed for this period. Immunocompromised patients with measles will shed virus for the duration of the illness, so isolation should be maintained throughout the disease.

Vaccine

Vaccination against measles is the most effective and safe prevention strategy. Measles vaccine in the United States is available as a combined vaccine with measles-mumps-rubella vaccine, the last of which is the recommended form in most circumstances (Table 273.2). Following the measles resurgence of 1989-1991, a 2nd dose of measles vaccine was added to the schedule. The current recommendations include a 1st dose at 12-15 mo of age, followed by a 2nd dose at 4-6 yr of age. However, the 2nd dose can be given any time after 30 days following the 1st dose, and the current schedule is a convenience schedule. Seroconversion is slightly lower in children who receive the 1st dose before or at 12 mo of age (87% at 9 mo, 95% at 12 mo, and 98% at 15 mo) because of persisting maternal antibody; however, this is an evolving situation, with children currently as young as 6 mo unprotected from maternal antibodies and susceptible to measles infection. For children who have not received 2 doses by 11-12 yr of age, a 2nd dose should be provided. Infants who receive a dose before 12 mo of age should be given 2 additional doses at 12-15 mo and 4-6 yr of age. Children who are traveling should be offered either primary measles immunization even as young as 6 mo or a 2nd dose even if <4 yr.

Table 273.2

Recommendations for Measles Immunization

CATEGORY	RECOMMENDATIONS
Unimmunized, no history of measles (12-15 mo of age)	MMR or MMRV vaccine is recommended at 12-15 mo of age; a 2nd dose is recommended at least 28 days after the 1st dose (or 90 days for MMRV) and usually is administered at 4 through 6 yr of age
Children 6-11 mo of age in epidemic situations or before international travel	Immunize with MMR vaccine, but this dose is not considered valid, and 2 valid doses administered on or after the 1st birthday are required. The 1st valid dose should be administered at 12-15 mo of age; the 2nd valid dose is recommended at

	least 28 days later and usually is administered at 4 through 6 yr of age. MMRV should not be administered to children <12 mo of age.
Students in kindergarten, elementary, middle, and high school who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the 2nd dose
Students in college and other postsecondary institutions who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the 2nd dose
History of immunization before the 1st birthday	Dose not considered valid; immunize (2 doses)
History of receipt of inactivated measles vaccine or unknown type of vaccine, 1963–1967	Dose not considered valid; immunize (2 doses)
Further attenuated or unknown vaccine administered with IG	Dose not considered valid; immunize (2 doses)
Allergy to eggs	Immunize; no reactions likely
Neomycin allergy, nonanaphylactic	Immunize; no reactions likely
Severe hypersensitivity (anaphylaxis) to neomycin or gelatin	Avoid immunization
Tuberculosis	Immunize; if patient has untreated tuberculosis disease, start antituberculosis therapy before immunizing
Measles exposure	Immunize or give IG, depending on circumstances
HIV infected	Immunize (2 doses) unless severely immunocompromised; administration of IG if exposed to measles is based on degree of immunosuppression and measles vaccine history
Personal or family history of seizures	Immunize; advise parents of slightly increased risk of seizures
Immunoglobulin or blood recipient	Immunize at the appropriate interval

MMR, measles-mumps-rubella vaccine; MMRV, measles-mumps-rubella-varicella vaccine.

From American Academy of Pediatrics: Measles. In Kimberlin DW, Brady MT, Jackson MA, Long SS, editors: *Red book 2018 report of the committee on infectious diseases,* ed 31, Itasca, IL, 2018, American Academy of Pediatrics, Table 3.39, p. 543.

Adverse events from the measles-mumps-rubella vaccine include fever (usually 6-12 days following vaccination), rash in approximately 5% of vaccinated persons, and, rarely, transient thrombocytopenia. Children prone to febrile seizures may experience an event following vaccination, so the risks and benefits of vaccination should be discussed with parents. Encephalopathy and autism have not been shown to be causally associated with the measles-mumps-rubella vaccine or vaccine constituents.

A review of the effect of measles vaccination on the epidemiology of SSPE has demonstrated that measles vaccination protects against SSPE and does not accelerate the course of SSPE or trigger the disease in those already infected with wild measles virus.

Passively administered immune globulin may inhibit the immune response to live measles vaccine, and administration should be delayed for variable amounts of time based on the dose of Ig (Table 273.3).

Table 273.3

Suggested Intervals Between Immunoglobulin Administration and Measles Immunization[*]

INDICATION FOR IMMUNOGLOBULIN	**DOSE**			
	Route	**Units (U) or Milliliters (mL)**	**mg IgG/kg**	**Interval (mo)** [†]
Tetanus (as tetanus Ig)	IM	250 U	10	3
Hepatitis A prophylaxis (as Ig):				
Contact prophylaxis	IM	0.02 mL/kg	3.3	3
International travel	IM	0.06 mL/kg	10	3
Hepatitis B prophylaxis (as hepatitis B Ig)	IM	0.06 mL/kg	10	3
Rabies prophylaxis (as rabies Ig)	IM	20 IU/kg	22	4
Varicella prophylaxis (as VariZIG)	IM	125 U/10 kg (maximum 625 U)	20-40	5
Measles prophylaxis (as Ig):				
Standard	IM	0.50 mL/kg	80	6
Immunocompromised host	IV		400 mg/kg	8
Respiratory syncytial virus prophylaxis (palivizumab monoclonal antibody) [‡]	IM	—	15 mg/kg (monoclonal)	None
Cytomegalovirus immune globulin	IV	3 mL/kg	150	6
Blood transfusion:				
Washed RBCs	IV	10 mL/kg	Negligible	0
RBCs, adenine-saline added	IV	10 mL/kg	10	3
Packed RBCs	IV	10 mL/kg	20-60	6
Whole blood	IV	10 mL/kg	80-100	6
Plasma or platelet products	IV	10 mL/kg	160	7
Replacement (or therapy) of immune deficiencies (as IVIG)	IV	—	300-400	8
ITP (as IVIG)	IV	—	400	8
ITP	IV	—	1,000	10
ITP or Kawasaki disease	IV	—	1,600-2,000	11

[*] Immunization in the form of measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), or monovalent measles vaccine.

[†] These intervals should provide sufficient time for decreases in passive antibodies in all children

to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of Ig or measles vaccine may be indicated after exposure to measles.

[‡] Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.

Ig, immunoglobulin; IgG, immunoglobulin G; ITP, immune (formerly termed “idiopathic”) thrombocytopenic purpura; IVIG, intravenous Ig; RBCs, red blood cells.

From American Academy of Pediatrics: *Red book: 2015 report of the Committee on Infectious Diseases* , ed 30, Elk Grove Village, IL, 2015, American Academy of Pediatrics, Table 1.10, p. 39.

Live vaccines should not be administered to pregnant women or to immunodeficient or immunosuppressed patients. However, patients with HIV who are not severely immunocompromised should be immunized. Because measles virus may suppress the cutaneous response to tuberculosis antigen, skin testing for tuberculosis should be performed before or at the same time as administration of the vaccine. Individuals infected with *M. tuberculosis* should be receiving appropriate treatment at the time of administration of measles vaccine.

Postexposure Prophylaxis

Susceptible individuals exposed to measles may be protected from infection by either vaccine administration or with Ig. The vaccine is effective in prevention or modification of measles if given within 72 hr of exposure. Ig may be given up to 6 days after exposure to prevent or modify infection. Immunocompetent children should receive 0.5 mL/kg (maximum dose in both cases is 15 mL/kg) intramuscularly (IM). For severely immunocompromised children and pregnant woman without evidence of measles immunity, Ig intravenously is the recommended IG at 400 mg/kg. Ig is indicated for susceptible household contacts of measles patients, especially infants younger than 6 mo of age, pregnant women, and immunocompromised persons.

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CHAPTER 274

Rubella

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Rubella (**German measles** or **3-day measles**) is a mild, often exanthematous disease of infants and children that is typically more severe and associated with more complications in adults. Its major clinical significance is transplacental infection and fetal damage as part of the **congenital rubella syndrome (CRS).**

Etiology

Rubella virus is a member of the family Togaviridae and is the only species of the genus *Rubivirus.* It is a single-stranded RNA virus with a lipid envelope and 3 structural proteins, including a nucleocapsid protein that is associated with the nucleus and 2 glycoproteins, E1 and E2, that are associated with the envelope. The virus is sensitive to heat, ultraviolet light, and extremes of pH but is relatively stable at cold temperatures. Humans are the only known host.

Epidemiology

In the prevaccine era, rubella appeared to occur in major epidemics every 6-9 yr, with smaller peaks interspersed every 3-4 yr, and was most common in preschool-age and school-age children. During the rubella epidemic of 1964-1965 there were an estimated 12.5 million cases of rubella associated with 2,000 cases of encephalitis, more than 13,000 abortions or perinatal deaths, and 20,000 cases of CRS. Following introduction of the rubella vaccine in 1969, the incidence of rubella fell 78% and CRS cases fell 69% by 1976 (Fig. 274.1). Further decline in rubella and CRS cases occurred when certain at-risk populations were added to those for whom rubella immunization is indicated, including adolescents and college students. After years of decline, a resurgence of rubella and CRS cases occurred during 1989-1991 in association with the epidemic of measles during that period (see Fig. 274.1). Subsequently, a 2-dose recommendation for rubella vaccine was implemented and resulted in a decrease in incidence of rubella from 0.45 per 100,000 population in 1990 to 0.1 per 100,000 population in 1999 and a corresponding decrease of CRS, with an average of 6 infants with CRS reported annually from 1992 to 2004. Mothers of these infants tended to be young, Hispanic, or foreign born. The number of reported cases of rubella continued to decline through the 1990s and the 1st decade of this century.

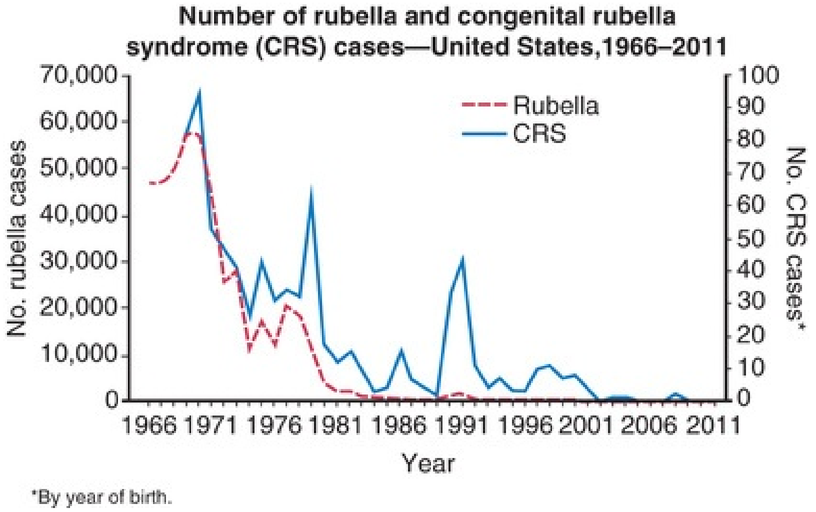

FIG. 274.1 **Number of rubella and congenital rubella syndrome cases—United States, 1966-2011. Rubella and CRS data provided were reported voluntarily to Centers for Disease Control and Prevention from state health departments. (From McLean HQ, Fiebelkorn AP, Temte JL, et al: Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013, *MMWR Recomm Rep* 62[RR-04]:1–34, 2013.)**

The endemic spread of rubella was declared eliminated in the United States in 2004 and eliminated in the Americas in 2015. However, cases of rubella continue to be imported into the United States from countries where it remains endemic, with more than 100,000 cases of CRS annually worldwide. From 2004 to 2016 there were 101 cases of rubella and 11 cases of CRS reported in the United States, all of which were imported cases of unknown source. Three of the CRS cases were acquired in Africa. Worldwide in 2016, 22,106 cases of rubella and 358 cases of CRS were reported, demonstrating that the elimination of rubella internationally has not been achieved and highlighting that continued vigilance and maintenance of high levels of immunity in the United States are necessary.

Pathology

Little information is available on the pathologic findings in rubella occurring postnatally. The few reported studies of biopsy or autopsy material from cases of rubella revealed only nonspecific findings of lymphoreticular inflammation and mononuclear perivascular and meningeal infiltration. The pathologic findings for CRS are often severe and may involve nearly every organ system (Table 274.1).

Table 274.1

Pathologic Findings in Congenital Rubella Syndrome

SYSTEM	PATHOLOGIC FINDINGS
Cardiovascular	Patent ductus arteriosus
	Pulmonary artery stenosis
	Ventriculoseptal defect
	Myocarditis
Central nervous system	Chronic meningitis
	Parenchymal necrosis
	Vasculitis with calcification
Eye	Microphthalmia
	Cataract
	Iridocyclitis
	Ciliary body necrosis
	Glaucoma
	Retinopathy
Ear	Cochlear hemorrhage
	Endothelial necrosis
Lung	Chronic mononuclear interstitial pneumonitis
Liver	Hepatic giant cell transformation
	Fibrosis
	Lobular disarray
	Bile stasis
Kidney	Interstitial nephritis
Adrenal gland	Cortical cytomegaly
Bone	Malformed osteoid
	Poor mineralization of osteoid
	Thinning cartilage
Spleen, lymph node	Extramedullary hematopoiesis
Thymus	Histiocytic reaction
	Absence of germinal centers
Skin	Erythropoiesis in dermis

Pathogenesis

The viral mechanisms for cell injury and death in postnatal or congenital rubella are not well understood. Following infection, the virus replicates in the respiratory epithelium and then spreads to regional lymph nodes (Fig. 274.2). Viremia ensues and is most intense from 10 to 17 days after infection. Viral shedding from the nasopharynx begins approximately 10 days after infection and may be detected up to 2 wk following onset of the rash. The period of highest communicability is from 5 days before to 6 days after the appearance of the rash.

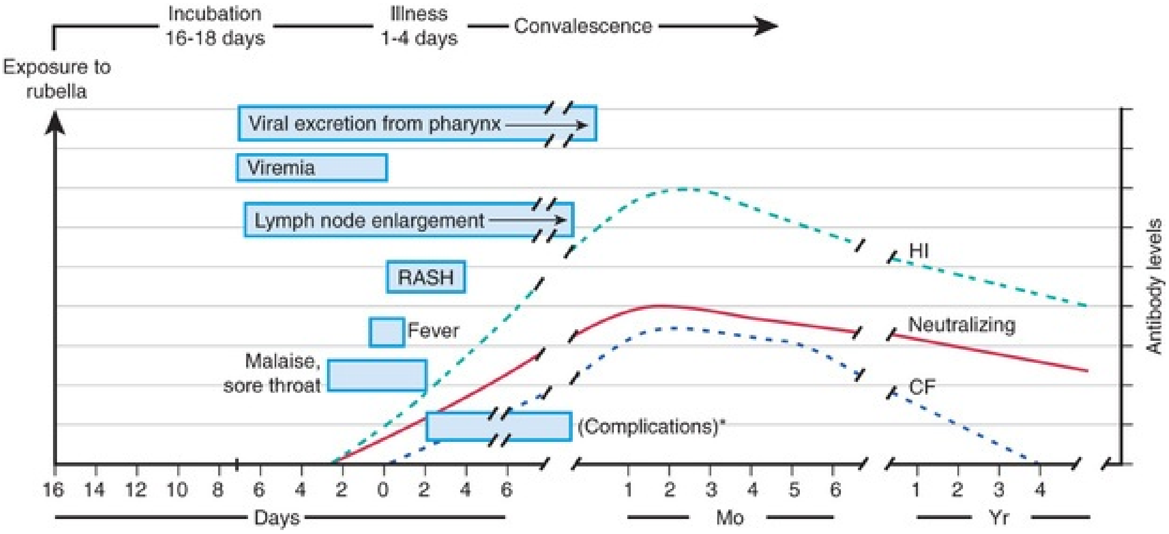

FIG. 274.2 Pathophysiologic events in postnatally acquired rubella virus infection. *Possible complications include arthralgia and/or arthritis, thrombocytopenic purpura, and encephalitis. CF, complement fixation titer; HI, hemagglutination-inhibition titer. (From Lamprecht CL: Rubella virus. In Beshe RB, editor: *Textbook of human virology* , ed 2, Littleton, MA, 1990, PSG Publishing, p. 685.)

Congenital infection occurs during maternal viremia. After infecting the placenta, the virus spreads through the vascular system of the developing fetus and may infect any fetal organ. The most important risk factor for severe congenital defects is the stage of gestation at the time of infection. Maternal infection during the first 8 wk of gestation results in the most severe and widespread defects. The risk for congenital defects has been estimated at 90% for maternal infection before 11 wk of gestation, 33% at 11-12 wk, 11% at 13-14 wk, and 24% at 15-16 wk. Defects occurring after 16 wk of gestation are uncommon, even if fetal infection occurs.

Causes of cellular and tissue damage in the infected fetus may include tissue necrosis due to vascular insufficiency, reduced cellular multiplication time, chromosomal breaks, and production of a protein inhibitor causing mitotic arrests in certain cell types. The most distinctive feature of congenital rubella is chronicity. Once the fetus is infected early in gestation, the virus persists in fetal tissue until well beyond delivery. Persistence suggests the possibility of ongoing tissue damage and reactivation, most notably in the brain.

Clinical Manifestations

Postnatal infection with rubella is a mild disease not easily discernible from other viral infections, especially in children. Following an incubation period of 14-21 days, a prodrome consisting of low-grade fever, sore throat, red eyes with or without eye pain, headache, malaise, anorexia, and lymphadenopathy begins. Suboccipital, postauricular, and anterior cervical lymph nodes are most prominent. In children, the 1st manifestation of rubella is usually the rash, which is variable and not distinctive. It begins on the face and neck as small, irregular pink macules that coalesce, and it spreads centrifugally to involve the torso and extremities, where it tends to occur as discrete macules (Fig. 274.3). About the time of onset of the rash, examination of the oropharynx may reveal tiny, rose-colored lesions (**Forchheimer spots**) or petechial hemorrhages on the soft palate. The rash fades from the face as it extends to the rest of the body so that the whole body may not be involved at any one time. The duration of the rash is generally 3 days, and it usually resolves without desquamation. Subclinical infections are common, and 25–40% of children may not have a rash. Teenagers and adults tend to be more symptomatic and have systemic manifestations, with up to 70% of females demonstrating arthralgias and arthritis.

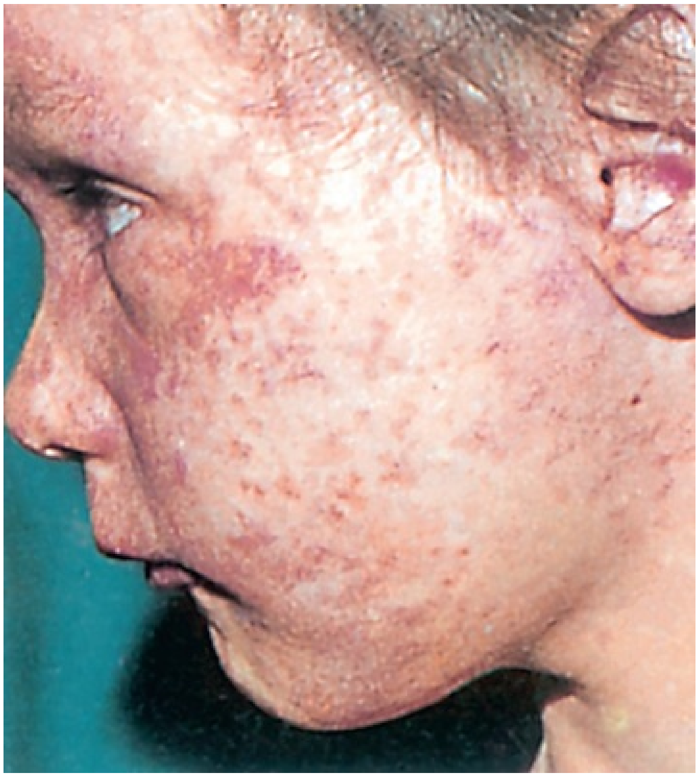

FIG. 274.3 **Rash of rubella.**

Laboratory Findings

Leukopenia, neutropenia, and mild thrombocytopenia have been described during postnatal rubella.

Diagnoses

A specific diagnosis of rubella is important for epidemiologic reasons, for diagnosis of infection in pregnant women, and for confirmation of the diagnosis of congenital rubella. The most common diagnostic test is rubella immunoglobulin (Ig) M enzyme immunosorbent assay, which is typically present about 4 days after the appearance of the rash. As with any serologic test, the positive predictive value of testing decreases in populations with low prevalence of disease and in immunized individuals. Tests should be performed in the context of a supportive history of exposure or consistent clinical findings. The relative sensitivity and specificity of commercial kits used in most laboratories range from 96% to 99% and 86% to 97%, respectively. A caveat for testing of congenitally infected infants early in infancy is that false-negative results may occur owing to competing IgG antibodies circulating in these patients. In such patients, an IgM capture assay, reverse transcriptase polymerase chain reaction (PCR) test, or viral culture should be performed for confirmation. Viral isolation by culture of nasopharyngeal secretions, urine in the newborn, or cord blood or placenta can be used to diagnose congenital infection. PCR testing of amniotic fluid during pregnancy is also an appropriate approach to diagnose congenital infection.

Differential Diagnoses

Rubella may manifest as distinctive features suggesting the diagnosis. It is frequently confused with other infections because it is uncommon, is similar to other viral exanthematous diseases, and demonstrates variability in the presence of typical findings. In severe cases, it may resemble measles. The absence of Koplik spots and a severe prodrome, as well as a shorter course, allow for differentiation from measles. Other diseases frequently confused with rubella include infections caused by adenoviruses, parvovirus B19 (erythema infectiosum), Epstein-Barr virus, enteroviruses, roseola, and *Mycoplasma pneumoniae.*

Complications

Complications following postnatal infection with rubella are infrequent and generally not life threatening.

Postinfectious **thrombocytopenia** occurs in approximately 1 in 3,000 cases of rubella and occurs more frequently among children and in girls. It manifests about 2 wk following the onset of the rash as petechiae, epistaxis, gastrointestinal bleeding, and hematuria. It is usually self-limited.

Arthritis following rubella occurs more commonly among adults, especially women. It begins within 1 wk of onset of the exanthem and classically involves the small joints of the hands. It is self-limited and resolves within weeks without sequelae. There are anecdotal reports and some serologic evidence linking rubella with rheumatoid arthritis, but a true causal association remains speculative.

Encephalitis is the most serious complication of postnatal rubella. It occurs in

2 forms: a postinfectious syndrome following acute rubella and a rare progressive panencephalitis manifesting as a neurodegenerative disorder years following rubella.

Postinfectious encephalitis is uncommon, occurring in 1 in 5,000 cases of rubella. It appears within 7 days after onset of the rash, consisting of headache, seizures, confusion, coma, focal neurologic signs, and ataxia. Fever may recrudesce with the onset of neurologic symptoms. Cerebrospinal fluid may be normal or have a mild mononuclear pleocytosis and/or elevated protein concentration. Virus is rarely, if ever, isolated from cerebrospinal fluid or brain, suggesting a noninfectious pathogenesis. Most patients recover completely, but mortality rates of 20% and long-term neurologic sequelae have been reported.

Progressive rubella panencephalitis (PRP) is an extremely rare complication of either acquired rubella or CRS. It has an onset and course similar to those of the subacute sclerosing panencephalitis associated with measles (see Chapter 273). However, unlike in the postinfectious form of rubella encephalitis, rubella virus may be isolated from brain tissue of the patient with PRP, suggesting an infectious pathogenesis, albeit a slow one. The clinical findings and course are undistinguishable from those of subacute sclerosing panencephalitis and transmissible spongiform encephalopathies (see Chapter 304). Death occurs 2-5 yr after onset.

Other neurologic syndromes rarely reported with rubella include Guillain-Barré syndrome and peripheral neuritis. Myocarditis is a rare complication.

Congenital Rubella Syndrome

In 1941 an ophthalmologist first described a syndrome of cataracts and congenital heart disease that he correctly associated with rubella infections in the mothers during early pregnancy (Table 274.2). Shortly after the first description, hearing loss was recognized as a common finding often associated with microcephaly. In 1964-1965 a pandemic of rubella occurred, with 20,000 cases reported in the United States, leading to more than 11,000 spontaneous or therapeutic abortions and 2,100 neonatal deaths. From this experience emerged the expanded definition of CRS that includes numerous other transient or permanent abnormalities.

Table 274.2

Clinical Manifestations of Congenital Rubella Syndrome in

376 Children Following Maternal Rubella*

MANIFESTATION	RATE (%)
Deafness	67
Ocular	71
Cataracts	29
Retinopathy	39
Heart disease [†]	48
Patent ductus arteriosus	78
Right pulmonary artery stenosis	70
Left pulmonary artery stenosis	56
Valvular pulmonic stenosis	40
Low birthweight	60
Psychomotor retardation	45
Neonatal purpura	23
Death	35

[*] Other findings: hepatitis, linear streaking of bone, hazy cornea, congenital glaucoma, delayed growth.

[†] Findings in 87 patients with congenital rubella syndrome and heart disease who underwent cardiac angiography.

From Cooper LZ, Ziring PR, Ockerse AB, et al: Rubella: clinical manifestations and management, *Am J Dis Child* 118:18–29, 1969.

Nerve deafness is the single most common finding among infants with CRS. Most infants have some degree of intrauterine growth restriction. Retinal findings described as **salt-and-pepper retinopathy** are the most common ocular abnormality but have little early effect on vision. Unilateral or bilateral cataracts are the most serious eye finding, occurring in about a third of infants (Fig. 274.4). Cardiac abnormalities occur in half of the children infected during the first 8 wk of gestation. Patent ductus arteriosus is the most frequently reported cardiac defect, followed by lesions of the pulmonary arteries and valvular disease. Interstitial pneumonitis leading to death in some cases has been reported. Neurologic abnormalities are common and may progress following birth. Meningoencephalitis is present in 10–20% of infants with CRS and may persist for up to 12 mo. Longitudinal follow-up through 9-12 yr of infants without initial retardation revealed progressive development of additional sensory, motor, and behavioral abnormalities, including hearing loss and autism. PRP has also been recognized rarely after CRS. Subsequent postnatal growth retardation and ultimate short stature have been reported in a minority of cases. Rare reports of immunologic deficiency syndromes have also been described.

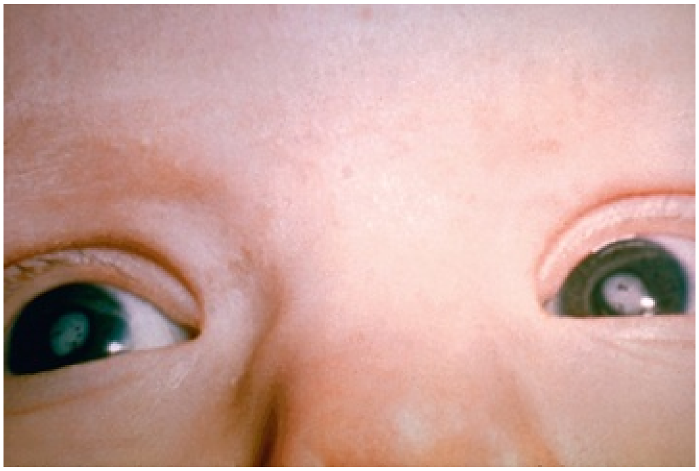

FIG. 274.4 Bilateral cataracts in infant with congenital rubella syndrome.

A variety of late-onset manifestations of CRS have been recognized. In addition to PRP, they include diabetes mellitus (20%), thyroid dysfunction (5%), and glaucoma and visual abnormalities associated with the retinopathy, which had previously been considered benign.

Treatment

There is no specific treatment available for either acquired rubella or CRS.

Supportive Care

Postnatal rubella is generally a mild illness that requires no care beyond antipyretics and analgesics. Intravenous immunoglobulin or corticosteroids can be considered for severe, nonremitting thrombocytopenia.

Management of children with CRS is more complex and requires pediatric, cardiac, audiologic, ophthalmologic, and neurologic evaluation and follow-up because many manifestations may not be readily apparent initially or may worsen with time. Hearing screening is of special importance because early intervention may improve outcomes in children with hearing problems caused by CRS.

Prognosis

Postnatal infection with rubella has an excellent prognosis. Long-term outcomes of CRS are less favorable and somewhat variable. In an Australian cohort evaluated 50 yr after infection, many had chronic conditions but most were married and had made good social adjustments. A cohort from New York from the mid-1960s epidemic had less-favorable outcomes, with 30% leading normal lives, 30% in dependent situations but functional, and 30% requiring institutionalization and continuous care.

Reinfection with wild virus occurs postnatally in both individuals who were previously infected with wild-virus rubella and vaccinated individuals. Reinfection is defined serologically as a significant increase in IgG antibody level and/or an IgM response in an individual who has a documented preexisting rubella-specific IgG above an accepted cutoff. Reinfection may result in an anamnestic IgG response, an IgM and IgG response, or clinical rubella. There are 29 reports in the literature of CRS following maternal reinfection. Reinfection with serious adverse outcomes to adults or children is rare and of unknown significance.

Prevention

Patients with postnatal infection should be isolated from susceptible individuals for 7 days after onset of the rash. Standard plus droplet precautions are recommended for hospitalized patients. Children with CRS may excrete the virus in respiratory secretions up to 1 yr of age, so contact precautions should be maintained for them until 1 yr of age, unless repeated cultures of urine and pharyngeal secretions are negative. Similar precautions apply to patients with CRS with regard to attendance in school and out-of-home childcare.

Exposure of susceptible pregnant women poses a potential risk to the fetus. For pregnant women exposed to rubella, a blood specimen should be obtained as soon as possible for rubella IgG-specific antibody testing; a frozen aliquot also should be saved for later testing. If the rubella antibody test result is positive, the mother is likely immune. If the rubella antibody test is negative, a 2nd specimen should be obtained 2-3 wk later and tested concurrently with the saved specimen. If both of these samples test negative, a 3rd specimen should be obtained 6 wk after exposure and tested concurrently with the saved specimen. If both the 2nd and 3rd specimens test negative, infection has not occurred. A negative first specimen and a positive test result in either the 2nd and 3rd specimen indicate that seroconversion has occurred in the mother, suggesting recent infection. Counseling should be provided about the risks and benefits of termination of pregnancy. The routine use of immunoglobulin for susceptible pregnant women exposed to rubella is not recommended and is considered only if termination of pregnancy is not an option because of maternal preferences. In such circumstances, immunoglobulin 0.55 mL/kg IM may be given with the understanding that prophylaxis may reduce the risk for clinically apparent infection but does not guarantee prevention of fetal infection.

Vaccination

Rubella vaccine in the United States consists of the attenuated Wistar RA 27/3 strain that is usually administered in combination with measles and mumps (MMR) or also with varicella (MMRV) in a 2-dose regimen at 12-15 mo and 4-6 yr of age. It theoretically may be effective as postexposure prophylaxis if administered within 3 days of exposure. Vaccine should not be administered to severely immunocompromised patients (e.g., transplant recipients). Patients with HIV infection who are not severely immunocompromised may benefit from vaccination. Fever is not a contraindication, but if a more serious illness is suspected, immunization should be delayed. Immunoglobulin preparations may inhibit the serologic response to the vaccine (see Chapter 197). Vaccine should not be administered during pregnancy. If pregnancy occurs within 28 days of immunization, the patient should be counseled on the theoretical risks to the fetus. Studies of more than 200 women who had been inadvertently immunized with rubella vaccine during pregnancy showed that none of their offspring developed CRS. Therefore interruption of pregnancy is probably not warranted.

Following a single dose of rubella RA 27/3 vaccine, 95% of persons 12 mo of age and older develop serologic immunity, and after 2 doses 99% have detectable antibody. Rubella RA 27/3 vaccine is highly protective, because 97% of those vaccinated are protected from clinical disease after 1 dose. Detectable antibodies remain for 15 yr in most individuals vaccinated following 1 dose, and 91–100% had antibodies after 12-15 yr after 2 doses. Although antibody levels may wane, especially after 1 dose of vaccine, increased susceptibility to rubella disease does not occur.

Adverse reactions to rubella vaccination are uncommon in children. MMR administration is associated with fever in 5–15% of vaccinees and with rash in approximately 5% of vaccinees. Arthralgia and arthritis are more common following rubella vaccination in adults. Approximately 25% of postpubertal women experience arthralgia, and 10% of postpubertal women experience arthritis. Peripheral neuropathies and transient thrombocytopenia may also occur.

As part of the worldwide effort to eliminate endemic rubella virus transmission and occurrence of CRS, maintaining high population immunity through vaccination coverage and high-quality integrated measles-rubella surveillance have been emphasized as being vital to its success.

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CHAPTER 275

Mumps

Wilbert H. Mason, Hayley A. Gans

Mumps is an acute self-limited infection that was once commonplace but is now uncommon in developed countries because of widespread use of vaccination. It is characterized by fever, bilateral or unilateral parotid swelling and tenderness, and the frequent occurrence of meningoencephalitis and orchitis. Although infrequent in countries with extensive vaccination programs, mumps remains endemic in the rest of the world, warranting continued vaccine protection. Nonetheless, outbreaks of mumps have been reported in highly vaccinated populations in the United States, particularly among students.

Etiology

Mumps virus is in the family Paramyxoviridae and the genus *Rubulavirus*. It is a single-stranded pleomorphic RNA virus encapsulated in a lipoprotein envelope possessing 7 structural proteins. Surface glycoproteins called HN (hemagglutinin-neuraminidase) and F (fusion) mediate absorption of the virus to host cells and penetration of the virus into cells, respectively. Both proteins stimulate production of protective antibodies. Mumps virus exists as a single serotype with up to 12 known genotypes, and humans are the only natural host.

Epidemiology

In the prevaccine era, mumps occurred primarily in young children between the ages of 5 and 9 yr and in epidemics about every 4 yr. Mumps infection occurred more often in the winter and spring months. In 1968, just after the introduction of the mumps vaccine, 185,691 cases were reported in the United States.

Following the recommendation for routine use of mumps vaccine in 1977, the incidence of mumps fell dramatically in young children (Fig. 275.1) and shifted instead to older children, adolescents, and young adults. Outbreaks continued to occur *even in highly vaccinated* populations as a result of primary vaccine failure with 1 dose of vaccine and because of undervaccination of susceptible persons. After implementation of the 2-dose recommendation for the measles-mumps-rubella (MMR) vaccine for measles control in 1989, the number of mumps cases declined further. During 2001-2003, fewer than 300 mumps cases were reported each year. In 2006 the largest mumps epidemic in the past 20 yr occurred in the United States. A total of 6,584 cases occurred, 85% of them in 8 midwestern states. Twenty-nine percent of the cases occurred in patients 18-24 yr old, most of whom were attending college. An analysis of 4,039 patients with mumps seen in the 1st 7 mo of the epidemic indicated that 63% had received more than 2 doses of the MMR vaccine. Subsequently, several outbreaks of mumps have been documented in highly vaccinated populations in the United States, several in school settings including Universities and in Guam. This phenomenon is reported globally as well. The majority of cases in vaccinated persons represent close contact thought to provide intense exposure that may overcome vaccine immunity and perhaps genotype mismatch between circulating mumps genotypes and those in the vaccine.

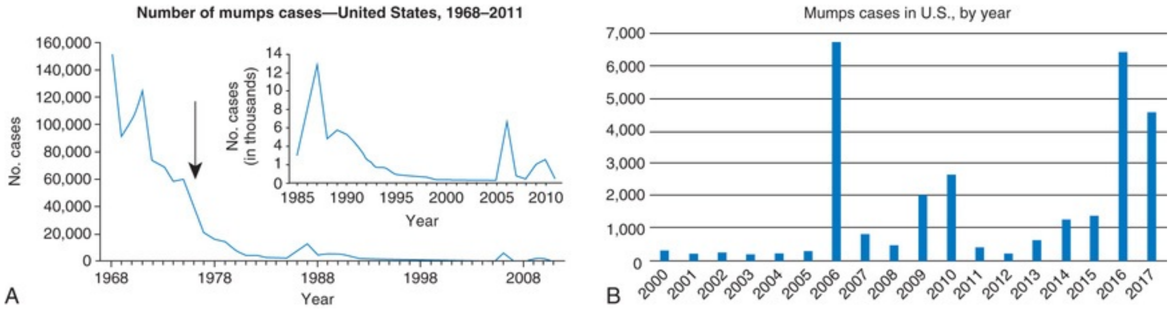

FIG. 275.1 **A,** Mumps cases in the United States from 1968, right after the live mumps vaccine was introduced in 1967, to 2011. There was a steady decline following introduction of the vaccine and recommendation for routine vaccination in 1977 *(arrow).* Note national increases in activity in 1986-1987, 2006. Mumps data provided were reported voluntarily to Centers for Disease Control and Prevention from state health departments. **B,** Mumps cases in the United States from 2000 to 2017 showing the increased activity in 2006, 2009, 2010, and 2014-2017. Mumps data provided were reported voluntarily to Centers for Disease Control and Prevention from state health departments. (**A,** From McLean HQ, Fiebelkorn AP, Temte JL, et al: Prevention of measles, rubella, congenital

rubella syndrome and mumps, *MMWR Recomm Rep* 62[RR-04]:1–34, 2013; **B,** From *Morbidity and Mortality Weekly Report (MMWR)* : Notifiable Diseases and Mortality Tables. https://www.cdc.gov/mumps/outbreaks.html .)

Mumps is spread from person to person by respiratory droplets. Virus appears in the saliva from up to 7 days before to as long as 7 days after onset of parotid swelling. The period of maximum infectiousness is 1-2 days before to 5 days after onset of parotid swelling. Viral shedding before onset of symptoms and in asymptomatic infected individuals impairs efforts to contain the infection in susceptible populations. The U.S. Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Health Infection Control Practices Advisory Committee recommend an isolation period of 5 days after onset of parotitis for patients with mumps in both community and healthcare settings.

Pathology and Pathogenesis

Mumps virus targets the salivary glands, central nervous system (CNS), pancreas, testes, and, to a lesser extent, thyroid, ovaries, heart, kidneys, liver, and joint synovia.

Following infection, initial viral replication occurs in the epithelium of the upper respiratory tract. Infection spreads to the adjacent lymph nodes by the lymphatic drainage, and viremia ensues, spreading the virus to targeted tissues. Mumps virus causes necrosis of infected cells and is associated with a lymphocytic inflammatory infiltrate. Salivary gland ducts are lined with necrotic epithelium, and the interstitium is infiltrated with lymphocytes. Swelling of tissue within the testes may result in focal ischemic infarcts. The cerebrospinal fluid (CSF) frequently contains a mononuclear pleocytosis, even in individuals without clinical signs of meningitis.

Clinical Manifestations

The incubation period for mumps ranges from 12 to 25 days but is usually 16-18 days. Mumps virus infection may result in clinical presentation ranging from asymptomatic (in the prevaccine era 15–24% of infections were asymptomatic, accurate estimates in the postvaccination era are difficult to measure) or nonspecific symptoms to the typical illness associated with parotitis with or without complications involving several body systems. The typical patient presents with a prodrome lasting 1-2 days consisting of fever, headache, vomiting, and achiness. Parotitis follows and may be unilateral initially but becomes bilateral in approximately 70% of cases (Fig. 275.2). The parotid gland is tender, and parotitis may be preceded or accompanied by ear pain on the ipsilateral side. Ingestion of sour or acidic foods or liquids may enhance pain in the parotid area. As swelling progresses, the angle of the jaw is obscured and the ear lobe may be lifted upward and outward (see Figs. 275.2 and 275.3). The opening of the Stensen duct may be red and edematous. The parotid swelling peaks in approximately 3 days and then gradually subsides over 7 days. Fever and the other systemic symptoms resolve in 3-5 days. A morbilliform rash is rarely seen. Submandibular salivary glands may also be involved or may be enlarged without parotid swelling. Edema over the sternum as a result of lymphatic obstruction may also occur. Symptoms in immunized individuals are the same but tend to be less severe, and parotitis may be absent.

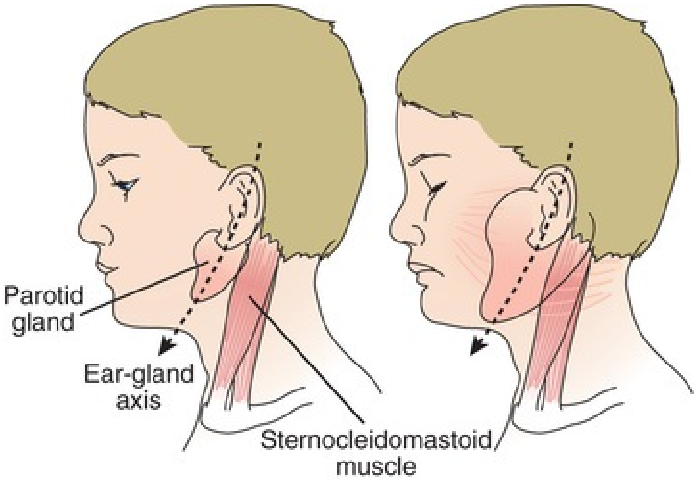

FIG. 275.2 Schematic of a parotid gland infected with mumps *(right)* compared with a normal gland *(left).* An imaginary line bisecting the long axis of the ear divides the parotid gland into 2 equal parts. These anatomic relationships are not altered in the enlarged gland. An enlarged cervical lymph node is usually posterior to the imaginary line. (From Mumps [epidemic parotitis]. In Krugman S, Ward R, Katz SL, editors: *Infectious diseases in children* , ed 6, St. Louis, 1977, Mosby, p. 182.)

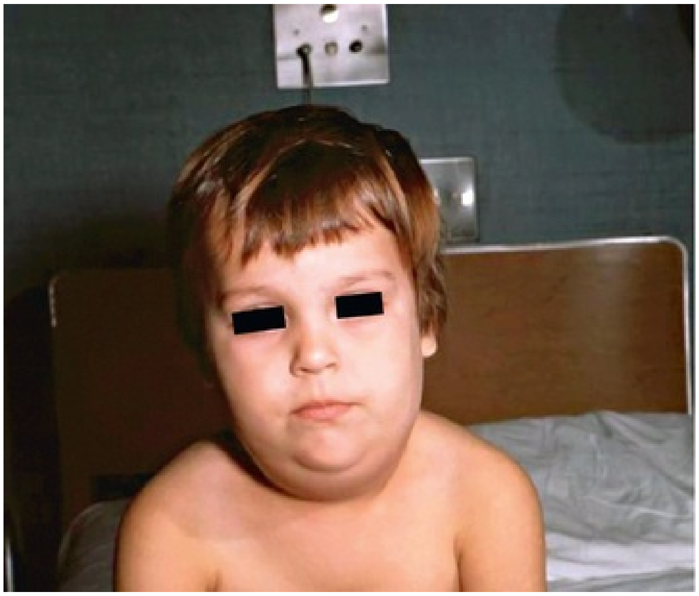

FIG. 275.3 A child with mumps showing parotid swelling. (From the Centers for Disease Control and Prevention [CDC]: Public health image library [PHIL], image #4491. Available at: http://phil.cdc.gov/phil/home.asp .)

Diagnosis

When mumps was highly prevalent, the diagnosis could be made on the basis of a history of exposure to mumps infection, an appropriate incubation period, and development of typical clinical findings. Confirmation of the presence of parotitis could be made with demonstration of an elevated serum amylase value. Leukopenia with a relative lymphocytosis was a common finding. Currently, in highly immunized populations patients with parotitis lasting longer than 2 days and of unknown cause, a specific diagnosis of mumps should be confirmed or ruled out by virologic or serologic means. This step may be accomplished by isolation of the virus in cell culture, detection of viral antigen by direct immunofluorescence, or identification of nucleic acid by reverse transcriptase polymerase chain reaction (PCR). Virus can be isolated from upper respiratory tract secretions (buccal and oropharyngeal [OP] mucosa), CSF, or urine during the acute illness; however, PCR from the OP becomes negative quickly especially in immunized individuals and thus should be run within 3 days of parotid swelling. Serologic testing is usually a more convenient and available mode of diagnosis. A significant increase in serum mumps immunoglobulin G antibody between acute and convalescent serum specimens as detected by complement fixation, neutralization hemagglutination, or enzyme immunoassay tests establishes the diagnosis. Mumps immunoglobulin G antibodies may cross react with antibodies to parainfluenza virus in serologic testing. More commonly, an enzyme immunoassay for mumps immunoglobulin M antibody is used to identify recent infection. All serologic tests are difficult to interpret in immunized individuals, and negative test results do not rule out mumps infection. Skin testing for mumps is neither sensitive nor specific and should not be used.

Differential Diagnosis

Parotid swelling may be caused by many other infectious and noninfectious conditions, especially in sporadic cases. Viruses that cause parotitis include parainfluenza 1 and parainfluenza 3 viruses, influenza A virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, lymphocytic choriomeningitis virus, and HIV. Purulent parotitis, usually caused by *Staphylococcus aureus*, is unilateral, is extremely tender, is associated with an elevated white blood cell count and may involve purulent drainage from the Stensen duct. Submandibular or anterior cervical adenitis from a variety of pathogens may also be confused with parotitis. Other noninfectious causes of parotid swelling include obstruction of the Stensen duct, collagen vascular diseases such as Sjögren syndrome, systemic lupus erythematosus, immunologic diseases, tumor, and drugs.

Complications

The most common complications of mumps are meningitis, with or without encephalitis, and gonadal (orchitis, oophoritis) involvement. Uncommon complications include conjunctivitis, optic neuritis, pneumonia, nephritis, pancreatitis, mastitis, and thrombocytopenia. Complications can occur in the absence of parotitis especially in immunized individuals, and overall complications rates in immunized individuals are lower than in unimmunized and are shifted towards the adult populations.

Maternal infection with mumps during the first trimester of pregnancy results in increased fetal wastage. No fetal malformations have been associated with intrauterine mumps infection. However, perinatal mumps disease has been reported in infants born to mothers who acquired mumps late in gestation.

Meningitis and Meningoencephalitis

Mumps virus is neurotropic and is thought to enter the CNS via the choroid plexus and infect the choroidal epithelium and ependymal cells, both of which can be found in CSF along with mononuclear leukocytes. Symptomatic CNS involvement occurs in 10–30% of infected individuals, but CSF pleocytosis has been found in 40–60% of patients with mumps parotitis. The meningoencephalitis may occur before, along with, or following the parotitis. It most commonly manifests 5 days after the parotitis. Clinical findings vary with age. Infants and young children have fever, malaise, and lethargy, whereas older children, adolescents, and adults complain of headache and demonstrate meningeal signs. In 1 series of children with mumps and meningeal involvement, findings were fever in 94%, vomiting in 84%, headache in 47%, parotitis in 47%, neck stiffness in 71%, lethargy in 69%, and seizures in 18%. In typical cases, symptoms resolve in 7-10 days. CSF in mumps meningitis has a white blood cell pleocytosis of 200-600 µL with a predominance of lymphocytes. The CSF glucose content is normal in most patients, but a moderate hypoglycorrhachia (glucose content 20-40 mg/dL) may be seen in 10–20% of patients. The CSF protein content is normal or mildly elevated.

Less-common CNS complications of mumps include transverse myelitis, acute disseminated encephalomyelitis (**ADEM**), aqueductal stenosis, and facial palsy. Sensorineural hearing loss is rare and has been estimated to occur in 0.5-5.0 in 100,000 cases of mumps. The hearing loss can be transient, with permanent unilateral hearing loss in 1 in 20,000 and bilateral loss occurring rarely. There is some evidence that this sequela is more likely in patients with meningoencephalitis.

Orchitis and Oophoritis

In adolescent and adult males, orchitis is 2nd only to parotitis as a common finding in mumps. Involvement in prepubescent boys is extremely rare, but after puberty, orchitis occurs in 30–40% of males. It begins within days following onset of parotitis in most cases and is associated with moderate to high fever, chills, and exquisite pain and swelling of the testes. In 30% or less of cases, the orchitis is bilateral. Atrophy of the testes may occur, but sterility is rare even with bilateral involvement.

Oophoritis is uncommon in postpubertal females but may cause severe pain and may be confused with appendicitis when located on the right side.

Pancreatitis

Pancreatitis may occur in mumps with or without parotid involvement. Severe disease is rare, but fever, epigastric pain, and vomiting are suggestive. Epidemiologic studies have suggested that mumps may be associated with the subsequent development of diabetes mellitus, but a causal link has not been established.

Cardiac Involvement

Myocarditis has been reported in mumps, and molecular studies have identified mumps virus in heart tissue taken from patients with endocardial fibroelastosis.

Arthritis

Arthralgia, monoarthritis, and migratory polyarthritis have been reported in mumps. Arthritis is seen with or without parotitis and usually occurs within 3 wk of onset of parotid swelling. It is generally mild and self-limited.

Thyroiditis

Thyroiditis is rare following mumps. It has not been reported without parotitis and may occur weeks after the acute infection. Most cases resolve, but some become relapsing and result in hypothyroidism.

Treatment

No specific antiviral therapy is available for mumps. Management should be aimed at reducing the pain associated with meningitis or orchitis and maintaining adequate hydration. Antipyretics may be given for fever.

Prognosis

The outcome of mumps is nearly always excellent, even when the disease is complicated by encephalitis, although fatal cases from CNS involvement or myocarditis have been reported. No mumps deaths have occurred in the recent outbreaks in the United States.

Prevention

Immunization with the live mumps vaccine is the primary mode of prevention used in the United States. It is given as part of the MMR 2-dose vaccine schedule, at 12-15 mo of age for the 1st dose and 4-6 yr of age for the 2nd dose. If not given at 4-6 yr, the 2nd dose should be given before children enter puberty. In those traveling, 2 doses are recommended in individuals older than 12 mo administered at least 28 days apart. Antibody develops in 94% (range: 89–97%) of vaccines after 1 dose. Antibody levels achieved following vaccination are lower than following natural infection.

The median vaccine effectiveness of mumps vaccine after 1 dose of vaccine is 78% (range: 49–92%) and after 2 doses is 88% (range: 66–95%). Duration of effectiveness is ≥10 yr after 1 dose and ≥15 yr after 2 doses.

During outbreaks, *a 3rd MMR dose* administered to the at-risk population was associated with improved outbreak control with significantly fewer cases in those receiving the 3rd dose compared with those not receiving it. Despite these results, modeling supports the current 2-dose schedule without a routine 3rd booster dose because the current regimen significantly controls size of outbreaks, severity of disease, and number of hospitalizations, whereas the 3rd dose appears to be a possible strategy during an outbreak.

As a live-virus vaccine, MMR should not be administered to pregnant women or to severely immunodeficient or immunosuppressed individuals. HIV-infected patients who are not severely immunocompromised may receive the vaccine, because the risk for severe infection with mumps outweighs the risk for serious reaction to the vaccine. Individuals with anaphylactoid reactions to egg or neomycin may be at risk for immediate-type hypersensitivity reactions to the vaccine. Persons with other types of reactions to egg or reactions to other components of the vaccine are not restricted from receiving the vaccine.

In 2006, in response to the multistate outbreak in the United States, evidence of immunity to mumps through vaccination was redefined. Acceptable presumptive evidence of immunity to mumps now consists of 1 of the following: (1) documentation of adequate vaccination at age 12 mo or older, (2) laboratory evidence of immunity, (3) birth before 1957, and (4) documentation of physician-diagnosed mumps. Evidence of immunity through documentation of adequate vaccination is defined as 1 dose of a live mumps virus vaccine for preschool-age children and adults not at high risk and 2 doses for school-age children (i.e., grades K-12) and for adults at high risk (e.g., healthcare workers, international travelers, and students at post–high school educational institutions).

All persons who work in healthcare facilities should be immune to mumps. Adequate mumps vaccination for healthcare workers born during or after 1957 consists of 2 doses of a live mumps virus vaccine. Healthcare workers with no history of mumps vaccination and no other evidence of immunity should receive 2 doses, with >28 days between doses. Healthcare workers who have received only 1 dose previously should receive a 2nd dose. Because birth before 1957 is only presumptive evidence of immunity, healthcare facilities should consider recommending 1 dose of a live mumps virus vaccine for unvaccinated workers born before 1957 who do not have a history of physician-diagnosed mumps or laboratory evidence of mumps immunity. During an outbreak, healthcare facilities should strongly consider recommending 2 doses of a live mumps virus vaccine to unvaccinated workers born before 1957 who do not have evidence of mumps immunity.

Adverse reactions to mumps virus vaccine are rare. Parotitis and orchitis have been reported rarely. There is inadequate information to make a causal relationship to other reactions, such as febrile seizures, deafness, rash, purpura, encephalitis, and meningitis with the strain of mumps vaccine virus used for immunization in the United States. Higher rates of aseptic meningitis following vaccination for mumps are associated with vaccine strains used elsewhere in the world, including the Leningrad 3 and Urabe Am 9 strains. Transient suppression of reactivity to tuberculin skin testing has been reported after mumps vaccination.

In 2005 the quadrivalent measles, mumps, rubella, and varicella (MMRV) vaccine was made available. However, in 2010, studies showed a greater risk of febrile seizures in children 12-23 mo of age 5-12 days following administration of the vaccine. No increased risk of seizures was seen in children receiving the 1st dose of the MMRV at older than 48 mo of age. As a result, the American Academy of Pediatrics currently recommends either the MMR vaccine and separate varicella vaccine or the MMRV vaccine in children 12-47 mo of age. After 48 mo of age, the MMRV is generally preferred.

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CHAPTER 276

Polioviruses

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Etiology

The polioviruses are nonenveloped, positive-stranded RNA viruses belonging to the Picornaviridae family, in the genus *Enterovirus*, species Enterovirus C and consist of 3 antigenically distinct serotypes (types 1, 2, and 3). Polioviruses spread from the intestinal tract to the central nervous system (CNS), where they cause aseptic meningitis and poliomyelitis, or polio. The polioviruses are extremely hardy and can retain infectivity for several days at room temperature.

Epidemiology

The most devastating result of poliovirus infection is paralysis, although 90–95% of infections are inapparent. Despite the absence of symptoms, clinically inapparent infections induce protective immunity. Clinically apparent but nonparalytic illness occurs in approximately 5% of all infections, with paralytic polio occurring in approximately 1 in 1,000 infections among infants to approximately 1 in 100 infections among adolescents. In industrialized countries prior to universal vaccination, epidemics of paralytic poliomyelitis occurred primarily in adolescents. Conversely, in developing countries with poor sanitation, infection early in life results in infantile paralysis. Improved sanitation explains the virtual eradication of polio from the United States in the early 1960s, when only approximately 65% of the population was immunized with the Salk vaccine, which contributed to the disappearance of circulating wild-type poliovirus in the United States and Europe.

Transmission

Humans are the only known reservoir for the polioviruses, which are spread by the fecal-oral route. Poliovirus has been isolated from feces for longer than 2 wk before paralysis to several wk after the onset of symptoms.

Pathogenesis

Polioviruses infect cells by adsorbing to the genetically determined **poliovirus receptor (CD155).** The virus penetrates the cell, is uncoated, and releases viral RNA. The RNA is translated to produce proteins responsible for replication of the RNA, shutoff of host cell protein synthesis, and synthesis of structural elements that compose the capsid. Mature virus particles are produced in 6-8 hr and are released into the environment by disruption of the cell.

In the contact host, wild-type and vaccine strains of polioviruses gain host entry via the gastrointestinal tract. Recent studies in nonhuman primates demonstrate that the primary sites of replication are in the $CD155^+$ epithelial cells lining the mucosa of the tonsil follicle and small intestine, as well as see the macrophages/dendritic cells in the tonsil follicle and Peyer patches. Regional lymph nodes are infected, and primary viremia occurs after 2-3 days. The virus seeds multiple sites, including the reticuloendothelial system, brown fat deposits, and skeletal muscle. Wild-type poliovirus probably accesses the CNS along peripheral nerves. Vaccine strains of polioviruses do not replicate in the CNS, a feature that accounts for the safety of the live-attenuated vaccine. Occasional **revertants** (by nucleotide substitution) of these vaccine strains develop a neurovirulent phenotype and cause **vaccine-associated paralytic poliomyelitis (VAPP).** Reversion occurs in the small intestine and probably accesses the CNS via the peripheral nerves. Poliovirus has almost never been cultured from the cerebrospinal fluid (CSF) of patients with paralytic disease, and patients with aseptic meningitis caused by poliovirus never have paralytic disease. With the 1st appearance of non-CNS symptoms, a secondary viremia probably occurs as a result of enormous viral replication in the reticuloendothelial system.

The exact mechanism of entry into the CNS is not known. However, once entry is gained, the virus may traverse neural pathways and multiple sites within the CNS are often affected. The effect on motor and vegetative neurons is most striking and correlates with the clinical manifestations. Perineuronal inflammation, a mixed inflammatory reaction with both polymorphonuclear leukocytes and lymphocytes, is associated with extensive neuronal destruction. Petechial hemorrhages and considerable inflammatory edema also occur in areas of poliovirus infection. The poliovirus primarily infects motor neuron cells in the spinal cord (**the anterior horn cells**) and the medulla oblongata (the cranial nerve nuclei). Because of the overlap in muscle innervation by 2-3 adjacent segments of the spinal cord, clinical signs of weakness in the limbs develop when more than 50% of motor neurons are destroyed. In the medulla, less-extensive lesions cause paralysis, and involvement of the reticular formation that contains the vital centers controlling respiration and circulation may have a catastrophic outcome. Involvement of the intermediate and dorsal areas of the horn and the dorsal root ganglia in the spinal cord results in hyperesthesia and myalgias that are typical of acute poliomyelitis. Other neurons affected are the nuclei in the roof and vermis of the cerebellum, the substantia nigra, and, occasionally, the red nucleus in the pons; there may be variable involvement of thalamic, hypothalamic, and pallidal nuclei and the motor cortex.

Apart from the histopathology of the CNS, inflammatory changes occur generally in the reticuloendothelial system. Inflammatory edema and sparse lymphocytic infiltration are prominently associated with hyperplastic lymphocytic follicles.

Infants acquire immunity transplacentally from their mothers. Transplacental immunity disappears at a variable rate during the 1st 4-6 mo of life. Active immunity after natural infection is probably lifelong but protects against the infecting serotype only; infections with other serotypes are possible. Poliovirus-neutralizing antibodies develop within several days after exposure as a result of replication of the virus in the tonsils and in the intestinal tract and deep lymphatic tissues. This early production of circulating immunoglobulin (Ig) G antibodies protects against CNS invasion. Local (mucosal) immunity, conferred mainly by secretory IgA, is an important defense against subsequent reinfection of the gastrointestinal tract.

Clinical Manifestations

The incubation period of poliovirus from contact to initial clinical symptoms is usually considered to be 8-12 days, with a range of 5-35 days. Poliovirus infections with wild-type virus may follow 1 of several courses: **inapparent infection,** which occurs in 90–95% of cases and causes no disease and no sequelae; abortive poliomyelitis; nonparalytic poliomyelitis; or paralytic poliomyelitis. Paralysis, if it occurs, appears 3-8 days after the initial symptoms. The clinical manifestations of paralytic polio caused by wild or vaccine strains are comparable, although the incidence of abortive and nonparalytic paralysis with vaccine-associated poliomyelitis is unknown.

Abortive Poliomyelitis

In approximately 5% of patients, a nonspecific influenza-like syndrome occurs 1-2 wk after infection, which is termed *abortive poliomyelitis* . Fever, malaise, anorexia, and headache are prominent features, and there may be sore throat and abdominal or muscular pain. Vomiting occurs irregularly. The illness is short lived, lasting up to 2-3 days. The physical examination may be normal or may reveal nonspecific pharyngitis, abdominal or muscular tenderness, and weakness. Recovery is complete, and no neurologic signs or sequelae develop.

Nonparalytic Poliomyelitis

In approximately 1% of patients infected with wild-type poliovirus, signs of abortive poliomyelitis are present, as are more intense headache, nausea, and vomiting, as well as soreness and stiffness of the posterior muscles of the neck, trunk, and limbs. Fleeting paralysis of the bladder and constipation are frequent. Approximately two thirds of these children have a short symptom-free interlude between the 1st phase (**minor illness**) and the 2nd phase (CNS disease or **major illness**). Nuchal rigidity and spinal rigidity are the basis for the diagnosis of nonparalytic poliomyelitis during the 2nd phase.

Physical examination reveals nuchal-spinal signs and changes in superficial and deep reflexes. Gentle forward flexion of the occiput and neck elicits nuchal rigidity. The examiner can demonstrate head drop by placing the hands under the patient's shoulders and raising the patient's trunk. Although normally the head follows the plane of the trunk, in poliomyelitis it often falls backward limply, but this response is not attributable to true paresis of the neck flexors. In struggling infants, it may be difficult to distinguish voluntary resistance from clinically important true nuchal rigidity. The examiner may place the infant's shoulders flush with the edge of the table, support the weight of the occiput in the hand, and then flex the head anteriorly. True nuchal rigidity persists during this maneuver. When open, the anterior fontanel may be tense or bulging.

In the early stages the reflexes are normally active and remain so unless paralysis supervenes. Changes in reflexes, either increased or decreased, may precede weakness by 12-24 hr. The superficial reflexes, the cremasteric and abdominal reflexes, and the reflexes of the spinal and gluteal muscles are usually the first to diminish. The spinal and gluteal reflexes may disappear before the abdominal and cremasteric reflexes. Changes in the deep tendon reflexes generally occur 8-24 hr after the superficial reflexes are depressed and indicate impending paresis of the extremities. Tendon reflexes are absent with paralysis. Sensory defects do not occur in poliomyelitis.

Paralytic Poliomyelitis

Paralytic poliomyelitis develops in approximately 0.1% of persons infected with poliovirus, causing 3 clinically recognizable syndromes that represent a continuum of infection differentiated only by the portions of the CNS most severely affected. These are (1) spinal paralytic poliomyelitis, (2) bulbar poliomyelitis, and (3) polioencephalitis.

Spinal paralytic poliomyelitis may occur as the 2nd phase of a biphasic illness, the 1st phase of which corresponds to abortive poliomyelitis. The patient then appears to recover and feels better for 2-5 days, after which severe headache and fever occur with exacerbation of the previous systemic symptoms. Severe muscle pain is present, and sensory and motor phenomena (e.g., paresthesia, hyperesthesia, fasciculations, and spasms) may develop. On physical examination the distribution of paralysis is characteristically spotty. Single muscles, multiple muscles, or groups of muscles may be involved in any pattern. Within 1-2 days, *asymmetric flaccid paralysis or paresis occurs* . Involvement of 1 leg is most common, followed by involvement of 1 arm. The proximal areas of the extremities tend to be involved to a greater extent than the distal areas. To detect mild muscular weakness, it is often necessary to apply gentle resistance in opposition to the muscle group being tested. Examination at this point may reveal nuchal stiffness or rigidity, muscle tenderness, initially hyperactive deep tendon reflexes (for a short period) followed by absence or diminution of reflexes, and paresis or flaccid paralysis. In the spinal form, there is weakness of some of the muscles of the neck, abdomen, trunk, diaphragm, thorax, or extremities. *Sensation is intact; sensory disturbances, if present, suggest a disease other than poliomyelitis.*

The paralytic phase of poliomyelitis is extremely variable; some patients progress during observation from paresis to paralysis, whereas others recover, either slowly or rapidly. The extent of paresis or paralysis is directly related to the extent of neuronal involvement; paralysis occurs if >50% of the neurons supplying the muscles are destroyed. The extent of involvement is usually obvious within 2-3 days; only rarely does progression occur beyond this interval. Bowel and bladder dysfunction ranging from transient incontinence to paralysis with constipation and urinary retention often accompany paralysis of the lower limbs.

The onset and course of paralysis are variable in developing countries. The biphasic course is rare; typically the disease manifests in a single phase in which prodromal symptoms and paralysis occur in a continuous fashion. In developing countries, where a history of intramuscular injections precedes paralytic poliomyelitis in approximately 50–60% of patients, patients may present initially with fever and paralysis (**provocation paralysis**). The degree and duration of muscle pain are also variable, ranging from a few days usually to a wk. Occasionally, spasm and increased muscle tone with a transient increase in deep tendon reflexes occur in some patients, whereas in most patients, flaccid paralysis occurs abruptly. Once the temperature returns to normal, progression of paralytic manifestations stops. Little recovery from paralysis is noted in the 1st days or wk, but, if it is to occur, it is usually evident within 6 mo. The return of strength and reflexes is slow and may continue to improve for as long as 18 mo after the acute disease. Lack of improvement from paralysis within the 1st several wk or mo after onset is usually evidence of permanent paralysis. Atrophy of the limb, failure of growth, and deformity are common and are especially evident in the growing child.

Bulbar poliomyelitis may occur as a clinical entity without apparent involvement of the spinal cord. Infection is a continuum, and designation of the disease as bulbar implies only dominance of the clinical manifestations by dysfunctions of the cranial nerves and medullary centers. The clinical findings seen with bulbar poliomyelitis with respiratory difficulty (other than paralysis of extraocular, facial, and masticatory muscles) include (1) nasal twang to the voice or cry caused by palatal and pharyngeal weakness (hard-consonant words such as cookie and candy bring this feature out best); (2) inability to swallow smoothly, resulting in accumulation of saliva in the pharynx, indicating partial immobility (holding the larynx lightly and asking the patient to swallow will confirm such immobility); (3) accumulated pharyngeal secretions, which may cause irregular respirations that appear interrupted and abnormal even to the point of falsely simulating intercostal or diaphragmatic weakness; (4) absence of effective coughing, shown by constant fatiguing efforts to clear the throat; (5) nasal regurgitation of saliva and fluids as a result of palatal paralysis, with inability to separate the oropharynx from the nasopharynx during swallowing; (6) deviation of the palate, uvula, or tongue; (7) involvement of vital centers in the medulla, which manifest as irregularities in rate, depth, and rhythm of respiration; as cardiovascular alterations, including blood pressure changes (especially increased blood pressure), alternate flushing and mottling of the skin, and cardiac arrhythmias; and as rapid changes in body temperature; (8) paralysis of 1 or both vocal cords, causing hoarseness, aphonia, and, ultimately, asphyxia unless the problem is recognized on laryngoscopy and managed by immediate tracheostomy; and (9) the **rope sign,** an acute angulation between the chin and larynx caused by weakness of the hyoid muscles (the hyoid bone is pulled posteriorly, narrowing the hypopharyngeal inlet).

Uncommonly, bulbar disease may culminate in an ascending paralysis (Landry type), in which there is progression cephalad from initial involvement of the lower extremities. Hypertension and other autonomic disturbances are common in bulbar involvement and may persist for a week or more or may be transient. Occasionally, hypertension is followed by hypotension and shock and is associated with irregular or failed respiratory effort, delirium, or coma. This kind of bulbar disease may be rapidly fatal.

The course of bulbar disease is variable; some patients die as a result of extensive, severe involvement of the various centers in the medulla; others recover partially but require ongoing respiratory support, and others recover completely. Cranial nerve involvement is seldom permanent. Atrophy of muscles may be evident, patients immobilized for long periods may experience pneumonia, and renal stones may form as a result of hypercalcemia and hypercalciuria secondary to bone resorption.

Polioencephalitis is a rare form of the disease in which higher centers of the brain are severely involved. Seizures, coma, and spastic paralysis with increased reflexes may be observed. Irritability, disorientation, drowsiness, and coarse tremors are often present with peripheral or cranial nerve paralysis that coexists or ensues. Hypoxia and hypercapnia caused by inadequate ventilation due to respiratory insufficiency may produce disorientation without true encephalitis. The manifestations are common to encephalitis of any cause and can be attributed to polioviruses only with specific viral diagnosis or if accompanied by flaccid paralysis.

Paralytic poliomyelitis with ventilatory insufficiency results from several components acting together to produce ventilatory insufficiency resulting in hypoxia and hypercapnia. It may have profound effects on many other systems. Because respiratory insufficiency may develop rapidly, close continued clinical evaluation is essential. Despite weakness of the respiratory muscles, the patient may respond with so much respiratory effort associated with anxiety and fear that overventilation may occur at the outset, resulting in respiratory alkalosis. Such effort is fatiguing and contributes to respiratory failure.

There are certain characteristic patterns of disease. Pure spinal poliomyelitis with respiratory insufficiency involves tightness, weakness, or paralysis of the respiratory muscles (chiefly the diaphragm and intercostals) without discernible clinical involvement of the cranial nerves or vital centers that control respiration, circulation, and body temperature. The cervical and thoracic spinal cord segments are chiefly affected. Pure bulbar poliomyelitis involves paralysis of the motor cranial nerve nuclei with or without involvement of the vital centers. Involvement of the 9th, 10th, and 12th cranial nerves results in paralysis of the pharynx, tongue, and larynx with consequent airway obstruction. Bulbospinal poliomyelitis with respiratory insufficiency affects the respiratory muscles and results in coexisting bulbar paralysis.

The clinical findings associated with involvement of the respiratory muscles include (1) anxious expression; (2) inability to speak without frequent pauses, resulting in short, jerky, breathless sentences; (3) increased respiratory rate; (4) movement of the ala nasi and of the accessory muscles of respiration; (5) inability to cough or sniff with full depth; (6) paradoxical abdominal movements caused by diaphragmatic immobility caused by spasm or weakness of 1 or both leaves; and (7) relative immobility of the intercostal spaces, which may be segmental, unilateral, or bilateral. When the arms are weak, and especially when deltoid paralysis occurs, there may be impending respiratory paralysis because the phrenic nerve nuclei are in adjacent areas of the spinal cord. Observation of the patient's capacity for thoracic breathing while the abdominal muscles are splinted manually indicates minor degrees of paresis. Light manual splinting of the thoracic cage helps to assess the effectiveness of diaphragmatic movement.

Diagnosis

Poliomyelitis should be considered in any unimmunized or incompletely immunized child with paralytic disease. Although this guideline is most applicable in poliomyelitis endemic countries (Afghanistan, Pakistan, and

Nigeria), the spread of polio in 2013 from endemic countries to many nonendemic countries (Niger, Chad, Cameroon, Ethiopia, Kenya, Somalia, and Syria) and the isolation of wild poliovirus type 1 in Israel in 2014 and circulating type 1 vaccine-associated paralytic polio in Ukraine in 2015 suggest that the diagnosis of polio should be entertained in all countries. VAPP should be considered in any child with paralytic disease occurring 7-14 days after receiving the orally administered polio vaccine (OPV). VAPP can occur at later times after administration and should be considered in any child with paralytic disease in countries or regions where wild-type poliovirus has been eradicated and the OPV has been administered to the child or a contact. The combination of fever, headache, neck and back pain, asymmetric flaccid paralysis without sensory loss, and pleocytosis does not regularly occur in any other illness.

The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strains. In suspected cases of acute flaccid paralysis, 2 stool specimens should be collected 24-48 hr apart as soon as possible after the diagnosis of poliomyelitis is suspected. Poliovirus concentrations are high in the stool in the 1st wk after the onset of paralysis, which is the optimal time for collection of stool specimens. Polioviruses may be isolated from 80–90% of specimens from acutely ill patients, whereas <20% of specimens from such patients may yield virus within 3-4 wk after onset of paralysis. Because most children with spinal or bulbospinal poliomyelitis have constipation, rectal straws may be used to obtain specimens; ideally a minimum of 8-10 g of stool should be collected. In laboratories that can isolate poliovirus, isolates should be sent to either the U.S. Centers for Disease Control and Prevention or to 1 of the WHO-certified poliomyelitis laboratories where DNA sequence analysis can be performed to distinguish between wild poliovirus and neurovirulent, revertant OPV strains. With the current WHO plan for global eradication of poliomyelitis, most regions of the world (the Americas, Europe, and Australia) have been certified wild-poliovirus free; in these areas, poliomyelitis is most often caused by vaccine strains. Hence it is critical to differentiate between wild-type and revertant vaccine-type strains.

The CSF is often normal during the minor illness and typically contains a pleocytosis with 20-300 cells/µL with CNS involvement. The cells in the CSF may be polymorphonuclear early during the course of the disease but shift to mononuclear cells soon afterward. By the 2nd wk of major illness, the CSF cell count falls to near-normal values. In contrast, the CSF protein content is normal or only slightly elevated at the outset of CNS disease but usually rises to 50-100 mg/dL by the 2nd wk of illness. In polioencephalitis, the CSF may remain normal or show minor changes. Serologic testing demonstrates seroconversion or a 4-fold or greater increase in antibody titers from the acute phase of illness to 3-6 wk later.

Differential Diagnosis

Poliomyelitis should be considered in the differential diagnosis of any case of paralysis and is only 1 of many causes of acute flaccid paralysis in children and adults. There are numerous other causes of acute flaccid paralysis (Table 276.1). In most conditions, the clinical features are sufficient to differentiate between these various causes, but in some cases nerve conduction studies and electromyograms, in addition to muscle biopsies, may be required.

Table 276.1

Differential Diagnosis of Acute Flaccid Paralysis

SITE, CONDITION, FACTOR, OR AGENT	CLINICAL FINDINGS	ONSET OF PARALYSIS	PROGRESSION OF PARALYSIS	SENSORY SIGNS AND SYMPTOMS	REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES	RESID PARAI
Anterior Horn Cells of Spinal Cord						
Poliomyelitis (wild and vaccine-associated paralytic poliomyelitis)	Paralysis	Incubation period 7-14 days (range: 4-35 days)	24-48 hr to onset of full paralysis; proximal → distal, asymmetric	No	Yes	Yes
Nonpolio enteroviruses (including EV-A71, EV D68)	Hand-foot-and-mouth disease, aseptic meningitis, acute hemorrhagic conjunctivitis, possibly idiopathic epidemic flaccid paralysis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes
West Nile virus	Meningitis encephalitis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes
Other Neurotropic Viruses						

Rabies virus		Mo–Yr	Acute, symmetric, ascending	Yes	Yes	No
Varicella-zoster virus	Exanthematous vesicular eruptions	Incubation period 10-21 days	Acute, symmetric, ascending	Yes	±	±
Japanese encephalitis virus		Incubation period 5-15 days	Acute, proximal, asymmetric	±	±	±
Guillain-Barré Syndrome						
Acute inflammatory polyradiculo-neuropathy	Preceding infection, bilateral facial weakness	Hr to 10 days	Acute, symmetric, ascending (days to 4 wk)	Yes	Yes	±
Acute motor axonal neuropathy	Fulminant, widespread paralysis, bilateral facial weakness, tongue involvement	Hr to 10 days	1-6 days	No	Yes	±
Acute Traumatic Sciatic Neuritis						
Intramuscular gluteal injection	Acute, asymmetric	Hr to 4 days	Complete, affected limb	Yes	Yes	±
Acute transverse myelitis	Preceding *Mycoplasma pneumoniae, Schistosoma* , other parasitic or viral infection	Acute, symmetric hypotonia of lower limbs	Hr to days	Yes	Yes, early	Yes
Epidural abscess	Headache, back pain, local spinal tenderness, meningismus	Complete		Yes	Yes	±
Spinal cord compression; trauma		Complete	Hr to days	Yes	Yes	±
Neuropathies						
Exotoxin of Corynebacterium diphtheriae	In severe cases, palatal paralysis, blurred vision	Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)		Yes	Yes	
Toxin of Clostridium botulinum	Abdominal pain, diplopia, loss of accommodation, mydriasis	Incubation period 18-36 hr	Rapid, descending, symmetric	±	No	
Tick bite paralysis	Ocular symptoms	Latency period 5-10 days	Acute, symmetric, ascending	No	Yes	
Diseases of the Neuromuscular Junction						
Myasthenia	Weakness,		Multifocal	No	No	No

gravis	fatigability, diplopia, ptosis, dysarthria					
Disorders of Muscle						
Polymyositis	Neoplasm, autoimmune disease	Subacute, proximal → distal	Wk to mo	No	Yes	
Viral myositis		Pseudoparalysis	Hr to days	No	No	
Metabolic Disorders						
Hypokalemic periodic paralysis		Proximal limb, respiratory muscles	Sudden postprandial	No	Yes	±
Intensive Care Unit Weakness						
Critical illness polyneuropathy	Flaccid limbs and respiratory weakness	Acute, following systemic inflammatory response syndrome/sepsis	Hr to days	±	Yes	±

Modified from Marx A, Glass JD, Sutter RW: Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance, *Epidemiol Rev* 22:298–316, 2000.

The possibility of polio should be considered in any case of acute flaccid paralysis, even in countries where polio has been eradicated. The diagnoses most often confused with polio are VAPP, West Nile virus infection, and infections caused by other enteroviruses (including EV-A71 and EV-D68), as well as Guillain-Barré syndrome, transverse myelitis, and traumatic paralysis. In **Guillain-Barré syndrome** , which is the most difficult to distinguish from poliomyelitis, the paralysis is characteristically symmetric, and sensory changes and pyramidal tract signs are common, contrasting with poliomyelitis. Fever, headache, and meningeal signs are less notable, and the CSF has few cells but an elevated protein content. **Transverse myelitis** progresses rapidly over hr to days, causing an acute symmetric paralysis of the lower limbs with concomitant anesthesia and diminished sensory perception. Autonomic signs of hypothermia in the affected limbs are common, and there is bladder dysfunction. The CSF is usually normal. **Traumatic neuritis** occurs from a few hr to a few days after the traumatic event, is asymmetric, is acute, and affects only 1 limb. Muscle tone and deep tendon reflexes are reduced or absent in the affected limb with pain in the gluteus. The CSF is normal.

Conditions causing pseudoparalysis do not present with nuchal-spinal rigidity or pleocytosis. These causes include unrecognized trauma, transient (toxic) synovitis, acute osteomyelitis, acute rheumatic fever, scurvy, and congenital syphilis (pseudoparalysis of Parrot).

Treatment

There is no specific antiviral treatment for poliomyelitis. The management is supportive and aimed at limiting progression of disease, preventing ensuing skeletal deformities, and preparing the child and family for the prolonged treatment required and for permanent disability if this seems likely. Patients with the nonparalytic and mildly paralytic forms of poliomyelitis may be treated at home. All intramuscular injections and surgical procedures are contraindicated during the acute phase of the illness, especially in the 1st wk of illness, because they might result in progression of disease.

Abortive Poliomyelitis

Supportive treatment with analgesics, sedatives, an attractive diet, and bed rest until the child's temperature is normal for several days is usually sufficient. Avoidance of exertion for the ensuing 2 wk is desirable, and careful neurologic and musculoskeletal examinations should be performed 2 mo later to detect any minor involvement.

Nonparalytic Poliomyelitis

Treatment for the nonparalytic form is similar to that for the abortive form; in particular, relief is indicated for the discomfort of muscle tightness and spasm of the neck, trunk, and extremities. Analgesics are more effective when they are combined with the application of hot packs for 15-30 min every 2-4 hr. Hot tub baths are sometimes useful. A firm bed is desirable and can be improvised at home by placing table leaves or a sheet of plywood beneath the mattress. A footboard or splint should be used to keep the feet at a right angle to the legs. Because muscular discomfort and spasm may continue for some wk, even in the nonparalytic form, hot packs and gentle physical therapy may be necessary. Patients with nonparalytic poliomyelitis should also be carefully examined 2 mo after apparent recovery to detect minor residual effects that might cause postural problems in later yr.

Paralytic Poliomyelitis

Most patients with the paralytic form of poliomyelitis require hospitalization with complete physical rest in a calm atmosphere for the 1st 2-3 wk. **Suitable body alignment** is necessary for comfort and to avoid excessive skeletal deformity. A neutral position with the feet at right angles to the legs, the knees slightly flexed, and the hips and spine straight is achieved by use of boards, sandbags, and, occasionally, light splint shells. The position should be changed every 3-6 hr. **Active and passive movements** are indicated as soon as the pain has disappeared. Moist hot packs may relieve muscle pain and spasm. Opiates and sedatives are permissible only if no impairment of ventilation is present or impending. Constipation is common, and fecal impaction should be prevented. When bladder paralysis occurs, a parasympathetic stimulant such as bethanechol may induce voiding in 15-30 min; some patients show no response to this agent, and others respond with nausea, vomiting, and palpitations. Bladder paresis rarely lasts more than a few days. If bethanechol fails, manual compression of the bladder and the psychologic effect of running water should be tried. If catheterization must be performed, care must be taken to prevent urinary tract infections. An appealing diet and a relatively high fluid intake should be started at once unless the patient is vomiting. Additional salt should be provided if the environmental temperature is high or if the application of hot packs induces sweating. Anorexia is common initially. Adequate dietary and fluid intake can be maintained by placement of a central venous catheter. An orthopedist and a physiatrist should see patients as early in the course of the illness as possible and should assume responsibility for their care before fixed deformities develop.

The management of pure bulbar poliomyelitis consists of maintaining the airway and avoiding all risk of inhalation of saliva, food, and vomitus. Gravity drainage of accumulated secretions is favored by using the head-low (foot of bed elevated 20-25 degrees) prone position with the face to 1 side. Patients with weakness of the muscles of respiration or swallowing should be nursed in a lateral or semiprone position. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal aspiration, and soft, flexible catheters may be used for nasopharyngeal aspiration. Fluid and electrolyte equilibrium is best maintained by intravenous infusion because tube or oral feeding in the 1st few days may incite vomiting. In addition to close observation for respiratory insufficiency, the blood pressure should be measured at least twice daily because hypertension is not uncommon and occasionally leads to hypertensive encephalopathy. Patients with pure bulbar poliomyelitis may require tracheostomy because of vocal cord paralysis or constriction of the hypopharynx; most patients who recover have little residual impairment, although some exhibit mild dysphagia and occasional vocal fatigue with slurring of speech.

Impaired ventilation must be recognized early; mounting anxiety, restlessness, and fatigue are early indications for preemptive intervention. Tracheostomy is indicated for some patients with pure bulbar poliomyelitis, spinal respiratory muscle paralysis, or bulbospinal paralysis because such patients are generally unable to cough, sometimes for many months. Mechanical respirators are often needed.

Complications

Paralytic poliomyelitis may be associated with numerous complications. Acute gastric dilation may occur abruptly during the acute or convalescent stage, causing further respiratory embarrassment; immediate gastric aspiration and external application of ice bags are indicated. Melena severe enough to require transfusion may result from single or multiple superficial intestinal erosions; perforation is rare. Mild hypertension for days or weeks is common in the acute stage and probably related to lesions of the vasoregulatory centers in the medulla and especially to underventilation. In the later stages, because of immobilization, hypertension may occur along with hypercalcemia, nephrocalcinosis, and vascular lesions. Dimness of vision, headache, and a lightheaded feeling associated with hypertension should be regarded as premonitory of a frank convulsion. Cardiac irregularities are uncommon, but electrocardiographic abnormalities suggesting myocarditis occur with some frequency. Acute pulmonary edema occurs occasionally, particularly in patients with arterial hypertension. Hypercalcemia occurs because of skeletal decalcification that begins soon after immobilization and results in hypercalciuria, which in turn predisposes the patient to urinary calculi, especially when urinary stasis and infection are present. High fluid intake is the only effective prophylactic measure.

Prognosis

The outcome of inapparent, abortive poliomyelitis and aseptic meningitis syndromes is uniformly good, with death being exceedingly rare and with no long-term sequelae. The outcome of paralytic disease is determined primarily by degree and severity of CNS involvement. In severe bulbar poliomyelitis, the mortality rate may be as high as 60%, whereas in less-severe bulbar involvement and/or spinal poliomyelitis, the mortality rate varies from 5% to 10%, death generally occurring from causes other than the poliovirus infection.

Maximum paralysis usually occurs 2-3 days after the onset of the paralytic phase of the illness, with stabilization followed by gradual return of muscle function. The recovery phase lasts usually about 6 mo, beyond which persisting paralysis is permanent. In general, paralysis is more likely to develop in male children and female adults. Mortality and the degree of disability are greater after the age of puberty. Pregnancy is associated with an increased risk for paralytic disease. Tonsillectomy and intramuscular injections may enhance the risk for acquisition of bulbar and localized disease, respectively. Increased physical activity, exercise, and fatigue during the early phase of illness have been cited as factors leading to a higher risk for paralytic disease. Finally, it has been clearly demonstrated that type 1 poliovirus has the greatest propensity for natural poliomyelitis and type 3 poliovirus has a predilection for producing VAPP.

Postpolio Syndrome

After an interval of 30-40 yr, as many as 30–40% of persons who survived paralytic poliomyelitis in childhood may experience muscle pain and exacerbation of existing weakness or development of new weakness or paralysis. This entity, referred to as postpolio syndrome, has been reported only in persons who were infected in the era of wild-type poliovirus circulation. Risk factors for postpolio syndrome include increasing length of time since acute poliovirus infection, presence of permanent residual impairment after recovery from acute illness, and female sex.

Prevention

Vaccination is the only effective method of preventing poliomyelitis. Hygienic measures help to limit the spread of the infection among young children, but immunization is necessary to control transmission among all age groups. Both the inactivated polio vaccine (IPV), which is currently produced using better methods than those for the original vaccine and is sometimes referred to as enhanced IPV, and the live-attenuated OPV have established efficacy in preventing poliovirus infection and paralytic poliomyelitis. Both vaccines induce production of antibodies against the 3 strains of poliovirus. IPV elicits higher serum IgG antibody titers, but the OPV also induces significantly greater mucosal IgA immunity in the oropharynx and gastrointestinal tract, which limits replication of the wild poliovirus at these sites. Transmission of wild poliovirus by fecal spread is limited in OPV recipients. The immunogenicity of IPV is not affected by the presence of maternal antibodies, and IPV has no adverse effects. Live vaccine may undergo reversion to neurovirulence as it multiplies in the human intestinal tract and may cause VAPP in vaccinees or in their contacts. The overall risk for recipients varies from 1 case per 750,000 immunized infants in the United States to 1 in 143,000 immunized infants in India. The risk for paralysis in the B-cell–immunodeficient recipient may be as much as 6,800 times that in normal subjects. HIV infection has not been found to result in long-term excretion of virus. *As of January 2000, the IPV-only schedule is recommended for routine polio vaccination in the United States.* All children should receive 4 doses of IPV, at 2 mo, 4 mo, 6-18 mo, and 4-6 yr of age.

In 1988 the World Health Assembly resolved to eradicate poliomyelitis globally by 2000, and remarkable progress had been made toward reaching this target. To achieve this goal, the WHO used 4 basic strategies: routine immunization, National Immunization Days, acute flaccid paralysis surveillance, and mop-up immunization. This strategy has resulted in a >99% decline in poliomyelitis cases; in early 2002, there were only 10 countries in the world endemic for poliomyelitis. In 2012 there were the fewest cases of poliomyelitis ever, and the virus was endemic in only 3 countries (Afghanistan, Pakistan, and Nigeria). India has not had a child paralyzed with wild poliovirus type 2 since February 2011. The last case of wild poliovirus type 3 infection occurred in Nigeria in November 2012, and the last case of wild poliovirus type 2 infection occurred in India in October 1999. This progress prompted the WHO assembly, in May 2013, to recommend the development of a *Polio Eradication and Endgame Strategic Plan 2013-2018.* This plan included the withdrawal of trivalent OPV (tOPV) with bivalent OPV (bOPV) in all countries by 2016 and the introduction of initially 1 dose of IPV followed by the replacement of bOPV with IPV in all countries of the world by 2019. As long as the OPV is being used, there is the potential that vaccine-derived poliovirus (VDPV) will acquire the neurovirulent phenotype and transmission characteristics of the wild-type polioviruses. VDPV emerges from the OPV because of continuous replication in immunodeficient persons (iVDPV) or by circulation in populations with low vaccine coverage (cVDPVs). The risk was highest with the type 2 strain. Between 2000 and 2012, 90% of the 750 paralytic cases of cVDPV and 40% of VAPP were caused by type 2 strains. Between 17 April and 1 May 2016, 155 countries and territories in the world switched from the use of tOPV to bOPV. tOPV is no longer used globally in any routine or supplemental immunization activities.

Several countries are global priorities because they face challenges in eradication of the disease. Polioviruses remain endemic in Pakistan, Afghanistan, and Nigeria. For these 3 countries, there are several reasons for the failure to eradicate polio. The rejection of poliovirus vaccine initiatives and campaign quality in security-compromised areas in parts of these countries are still the main difficulties faced in 2019. Following an emergency committee meeting in November 2018 that reviewed data on WPV1 and cVDPV, new recommendations for international travelers to certain countries were made by the WHO and endorsed by the CDC. There has been an increase in WPV1 (21 cases each in Afghanistan and Nigeria and 12 in Pakistan in 2018). In addition, outbreaks of cVDPV2 in Syria, Somalia, Kenya, DR Congo, Niger, and Mozambique, cVDPV1 in Papua New Guinea, and cVDPV3 in Somalia, with spread of cVDPV2 between Somalia and Kenya and between Nigeria and Niger, highlight that routine immunization coverage remains very poor in many areas of these countries. Continuing spread due to poor herd immunity and now international spread pose a significant threat to the eradication effort. The committee recommended that for countries with WPV1, cVDPV1, or cVDPV3 with potential risk of international spread, all residents and long-term visitors (i.e., >4 weeks) of all ages receive a dose of bOPV or IPV between 4 wk and 12 mo before travel to these countries (currently Afghanistan, Pakistan, Nigeria, Papua New Guinea, and Somalia). Such travelers should be provided with an International Certificate of Vaccination of Prophylaxis to record their polio vaccination and service proof of vaccination. These countries have been advised to restrict at the point of departure the international travel of any resident lacking documentation of full vaccination, whether by air, sea, or land. For countries infected with cVDPV2 with potential risk of international spread (DR Congo, Kenya, Nigeria, Niger, and Somalia as of January 2019), visitors should be encouraged to follow these recommendations (not mandated).

In October 2016, cVDPV2 was isolated from the sewage in different parts of India, most probably due to the use of tOPV, which was still being used in private dispensaries and was not destroyed as was mandated. This illustrates the dangers of purely using bOPV. The WHO has mandated that infants in all countries still using bOPV should receive a dose of IPV, to offer protection against polio virus type 2. All countries have complied with this requirement; see Fig. 276.1 for the status as of November 2016. In this regard, recent studies from India have shown that following a course of OPV, IPV boosts serologic and mucosal immunity that lasts for at least 11 mo. It is estimated that between 12 and 24 mo after withdrawal of Sabin poliovirus type 2 vaccine, the world would have eradicated type 2 poliovirus circulation in humans. The switch from bOPV to IPV worldwide is slated to occur soon thereafter. These efforts may be stymied because of the global inability to produce IPV in a large enough volume to cover all the 128 million babies born annually in the world. This problem was a crisis during the global synchronized introduction of bOPV, when several countries (e.g., India) had to use 2 fractional doses of IPV (⅕ dose) administered intradermally. To enhance scale up of IPV production in countries such as India, Brazil, and China, IPV using Sabin strains of poliovirus have been developed in Japan and China. These mitigate the stringent requirements for wild-type poliovirus culture that are normally required for IPV production. Other strategies include developing adjuvants for IPV that could potentially lower the antigen quantities needed for each dose.

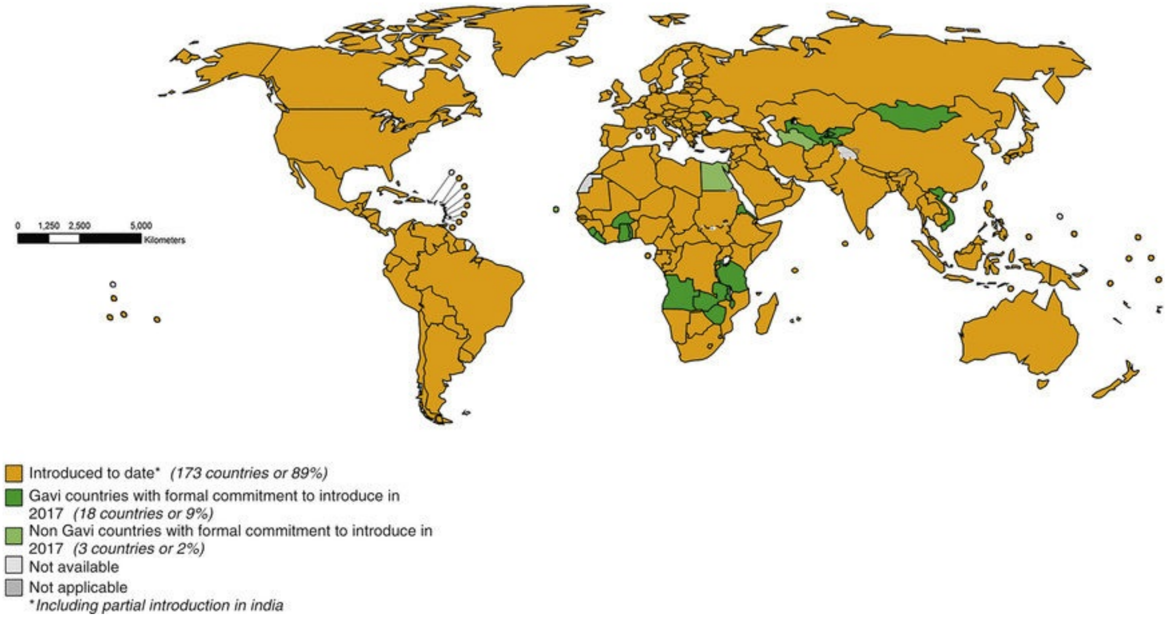
0 1,250 2,500 5,000
Kilometers
Introduced to date* (173 countries or 89%)
Gavi countries with formal commitment to introduce in 2017 (18 countries or 9%)
Non Gavi countries with formal commitment to introduce in 2017 (3 countries or 2%)
Not available
Not applicable
*Including partial introduction in india

FIG. 276.1 Countries identified by the World Health Organization as using IPV vaccine to date and introductions planned according to Gavi eligibility status. WHO/IVB Database as of 7 November 2016. World Health

Organization 2016. (Courtesy World Health Organization. http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/en/ . Accessed June 6, 2017.)

In countries where bOPV is included in routine immunization, it is best if it follows at least 1 dose of IPV or 2 doses of fractional intradermal IPV. This follows the experience in the United States and Hungary that reported no VAPP following a sequential use of IPV followed by OPV. Global synchronous cessation of OPV will need to be coordinated by the WHO, but the recent experiences in the horn of Africa and Israel/West Bank suggest that stopping transmission of wild poliovirus type 1 in the 3 endemic countries is of the utmost urgency, if we are to stop using OPV.

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CHAPTER 277

Nonpolio Enteroviruses

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The genus *Enterovirus* contains a large number of viruses spread via the gastrointestinal and respiratory routes that produce a broad range of illnesses in patients of all ages. Many of the manifestations predominantly affect infants and young children.

Etiology

Enteroviruses are nonenveloped, single-stranded, positive-sense viruses in the Picornaviridae ("small RNA virus") family, which also includes the rhinoviruses, hepatitis A virus, and parechoviruses. The original human enterovirus subgroups —polioviruses (see Chapter 276), coxsackieviruses, and echoviruses—were differentiated by their replication patterns in tissue culture and animals (Table 277.1). Enteroviruses have been reclassified on the basis of genetic similarity into 4 species, human enteroviruses A-D. Specific enterovirus types are distinguished by antigenic and genetic sequence differences, with enteroviruses discovered after 1970 classified by species and number (e.g., enterovirus D68 and A71). Although more than 100 types have been described, 10-15 account for the majority of disease. No disease is uniquely associated with any specific serotype, although certain manifestations are preferentially associated with specific serotypes. *The closely related human parechoviruses can cause clinical presentations similar to those associated with enteroviruses.*

Table 277.1

Classification of Human Enteroviruses

Family	Picornaviridae

Genus	*Enterovirus*
Subgroups*	Poliovirus serotypes 1-3
	Coxsackie A virus serotypes 1-22, 24 (23 reclassified as echovirus 9)
	Coxsackie B virus serotypes 1-6
	Echovirus serotypes 1-9, 11-27, 29-33 (echoviruses 10 and 28 reclassified as non-enteroviruses; echovirus 34 reclassified as a variant of coxsackie A virus 24; echoviruses 22 and 23 reclassified within the genus *Parechovirus*)
	Numbered enterovirus serotypes (enterovirus 72 reclassified as hepatitis A virus)

* The human enteroviruses have been alternatively classified on the basis of nucleotide and amino acid sequences into 4 species (human enteroviruses A-D).

Epidemiology

Enterovirus infections are common, with a worldwide distribution. In temperate climates, annual epidemic peaks occur in summer/fall, although some transmission occurs year-round. Enteroviruses are responsible for 33–65% of acute febrile illnesses and 55–65% of hospitalizations for suspected sepsis in infants during the summer and fall in the United States. In tropical and semitropical areas, enteroviruses typically circulate year-round. In general, only a few serotypes circulate simultaneously. Infections by different serotypes can occur within the same season. Factors associated with increased incidence and/or severity include young age, male sex, exposure to children, poor hygiene, overcrowding, and low socioeconomic status. More than 25% of symptomatic infections occur in children younger than 1 yr of age. Breastfeeding reduces the risk for infection, likely via enterovirus-specific antibodies.

Humans are the only known natural reservoir for human enteroviruses. Virus is primarily spread person to person, by the fecal-oral and respiratory routes, although types causing acute hemorrhagic conjunctivitis may be spread via airborne transmission. Virus can be transmitted vertically prenatally or in the peripartum period, or, possibly, via breastfeeding. Enteroviruses can survive on environmental surfaces, permitting transmission via fomites. Enteroviruses also can frequently be isolated from water sources, sewage, and wet soil. Although contamination of drinking water, swimming pools and ponds, and hospital water reservoirs may occasionally be responsible for transmission, such contamination is often considered the result rather than the cause of human infection. Transmission is common within families (≥50% risk of spread to nonimmune household contacts), daycare centers, playgrounds, summer camps, orphanages, and hospital nurseries; severe secondary infections may occur in nursery outbreaks. Transmission risk is increased by diaper changing and decreased by handwashing. Tickborne transmission has been suggested.

Large enterovirus outbreaks have included meningitis epidemics (echoviruses 4, 6, 9, 13, and 30 commonly); epidemics of hand-foot-and-mouth disease with severe central nervous system (CNS) and/or cardiopulmonary disease caused by enterovirus A71 in Asia and Australia; outbreaks of atypical, severe hand-foot-and-mouth disease caused by coxsackievirus A6 in the United States and United Kingdom; outbreaks of human enterovirus D68 respiratory illness associated with acute flaccid myelitis in the United States and Europe; outbreaks of acute hemorrhagic conjunctivitis caused by enterovirus D70, coxsackievirus A24, and coxsackievirus A24 variant in tropical and temperate regions; and community outbreaks of uveitis. Reverse transcription polymerase chain reaction (RT-PCR) and genomic sequencing help identify outbreaks and demonstrate, depending on the outbreak, commonality of outbreak strains, differences among epidemic strains and older prototype strains, changes in circulating viral subgroups over time, cocirculation of multiple genetic lineages, coinfections with different enterovirus serotypes, and associations between specific genogroups and/or genetic substitutions and epidemiologic and clinical characteristics. Genetic analyses have demonstrated recombination and genetic drift that lead to evolutionary changes in genomic sequence and antigenicity and extensive genetic diversity. For example, emergence of new subgenotypes and genetic lineages of enterovirus A71 may contribute to sequential outbreaks and increases in circulation.

The incubation period is typically 3-6 days, except for a 1-3 day incubation period for acute hemorrhagic conjunctivitis. Infected children, both symptomatic and asymptomatic, frequently shed cultivable enteroviruses from the respiratory tract for <1-3 wk, whereas fecal shedding continues for as long as 7-11 wk. Enterovirus RNA can be shed from mucosal sites for comparable, and, possibly, longer periods.

Pathogenesis

Cell surface macromolecules, including poliovirus receptor, integrin very-late-activation antigen (VLA)-2, decay-accelerating factor/complement regulatory protein (DAF/CD55), intercellular adhesion molecule-1 (ICAM-1), ICAM-5, and coxsackievirus-adenovirus receptor, serve as viral receptors. In addition, respiratory epithelial cell sialic acids serve as receptors for enterovirus D68, enterovirus D70, and coxsackievirus A24 variants, and human scavenger receptor class B2 (SCARB2), human P-selectin glycoprotein ligand-1, and DC-SIGN are receptors for enterovirus A71. After virus attaches to a cell surface receptor, a conformational change in surface capsid proteins expels a hydrophobic pocket factor, facilitating penetration and uncoating with release of viral RNA in the cytoplasm. Translation of the positive-sense RNA produces a polyprotein that undergoes cleavage by proteases encoded in the polyprotein. Several proteins produced guide synthesis of negative-sense RNA that serves as a template for replication of new positive-sense RNA. The genome is approximately 7,500 nucleotides long and includes a highly conserved 5′ noncoding region important for replication efficiency and a highly conserved 3′ polyA region; these flank a continuous region encoding viral proteins. The 5′ end is covalently linked to a small viral protein (VPg) necessary for initiation of RNA synthesis. There is significant variation within genomic regions encoding the structural proteins, leading to variability in antigenicity. Replication is followed by further cleavage of proteins and assembly into 30 nm icosahedral virions. Of the 4 structural proteins (VP1-VP4) in the capsid, VP1 is the most important determinant of serotype specificity. Additional regulatory proteins such as an RNA-dependent RNA polymerase and proteases are also present in the virion. Approximately 10^4 -10^5 virions are released from an infected cell by lysis within 5-10 hr of infection.

Following oral or respiratory acquisition, initial replication for most enteroviruses occurs in the pharynx and intestine, possibly within mucosal M cells. The acid stability of most enteroviruses favors survival in the gastrointestinal tract. Two or more enteroviruses may invade and replicate in the gastrointestinal tract simultaneously, but interference due to replication of 1 type often hinders growth of the heterologous type. Initial replication of most enteroviruses in the pharynx and intestine is followed within days by multiplication in lymphoid tissue such as tonsils, Peyer patches, and regional lymph nodes. A primary, transient viremia (**minor viremia**) results in spread to distant parts of the reticuloendothelial system, including the liver, spleen, bone marrow, and distant lymph nodes. Host immune responses may limit replication and progression beyond the reticuloendothelial system, resulting in subclinical infection. Clinical infection occurs if replication proceeds in the reticuloendothelial system and virus spreads via a secondary, sustained viremia (**major viremia**) to target organs such as the CNS, heart, and skin. *Tropism to target organs is determined in part by the infecting serotype.* Some enteroviruses, such as enterovirus D68, can be acid-labile and bind sialic acid receptors on respiratory epithelial cells in the upper and lower respiratory tract and primarily produce respiratory illness. Cytokine responses may contribute to development of respiratory disease by these viruses. Transient early viremia following respiratory enterovirus D68 infection has also been demonstrated.

Enteroviruses can damage a wide variety of organs and systems, including the CNS, heart, liver, lungs, pancreas, kidneys, muscle, and skin. Damage is mediated by necrosis and the inflammatory response. **CNS infections** are often associated with pleocytosis of the cerebrospinal fluid (CSF), composed of macrophages and activated T lymphocytes, and a mixed meningeal inflammatory response. Parenchymal involvement may affect the cerebral white and gray matter, cerebellum, basal ganglia, brainstem, and spinal cord with perivascular and parenchymal mixed or lymphocytic inflammation, gliosis, cellular degeneration, and neuronophagocytosis. **Encephalitis** during enterovirus A71 epidemics has been characterized by severe involvement of the brainstem, spinal cord gray matter, hypothalamus, and subthalamic and dentate nuclei, and can be complicated by pulmonary edema, pulmonary hemorrhage, and/or interstitial pneumonitis, presumed secondary to brainstem damage, sympathetic hyperactivity, myoclonus, ataxia, autonomic dysfunction, and CNS and systemic inflammatory responses (including cytokine and chemokine overexpression). Immunologic cross-reactivity with brain tissue has been postulated as 1 mechanism responsible for neurologic damage and sequelae following enterovirus A71 infection.

Enterovirus **myocarditis** is characterized by perivascular and interstitial mixed inflammatory infiltrates and myocyte damage, possibly mediated by viral cytolytic (e.g., cleavage of dystrophin or serum response factor) and innate and adaptive immune-mediated mechanisms. Chronic inflammation may persist after viral clearance.

The potential for enteroviruses to cause persistent infection is controversial. Persistent infection in dilated cardiomyopathy and in myocardial infarction has been suggested, but enterovirus RNA sequences and/or antigens have been demonstrated in cardiac tissues in some, but not other, series. Infections with enteroviruses such as coxsackievirus B4, during gestation or subsequently, have been implicated as a trigger for development of β-cell autoantibodies and/or type 1 diabetes in genetically susceptible hosts. Persistent infection in the pancreas, intestine, or peripheral blood mononuclear cells, with downstream immunomodulatory effects, has been suggested, but data are inconsistent. Similarly, persistent infection has been implicated in a variety of conditions, including amyotrophic lateral sclerosis, Sjögren syndrome, chronic fatigue syndrome, and gastrointestinal tumors. Early enterovirus infection was associated with reduced risk of developing lymphocytic and myeloid leukemia in 1 large retrospective Taiwanese cohort study.

Severe **neonatal infections** can produce hepatic necrosis, hemorrhage, inflammation, endotheliitis, and venoocclusive disease; myocardial mixed inflammatory infiltrates, edema, and necrosis; meningeal and brain inflammation, hemorrhage, gliosis, necrosis, and white matter damage; inflammation, hemorrhage, thrombosis, and necrosis in the lungs, pancreas, and adrenal glands; and disseminated intravascular coagulation. In utero infections are characterized by placentitis and infection of multiple fetal organs such as heart, lung, and brain.

Development of type-specific neutralizing antibodies appears to be the most important immune defense, mediating prevention against and recovery from infection. Immunoglobulin (Ig) M antibodies, followed by long-lasting IgA and IgG antibodies, and secretory IgA, mediating mucosal immunity, are produced. Although local reinfection of the gastrointestinal tract can occur, replication is usually limited and not associated with disease. In vitro and animal experiments suggest that heterotypic antibody may enhance disease caused by a different serotype. Evidence also suggests that subneutralizing concentrations of serotype-specific antibody may lead to antibody-dependent enhancement of enterovirus A71 infection. Innate and cellular defenses (macrophages and cytotoxic T lymphocytes) may play important roles in recovery from infection. Altered cellular responses to enterovirus A71, including T lymphocyte and natural killer cell depletion, were associated with severe meningoencephalitis and pulmonary edema.

Hypogammaglobulinemia and *agammaglobulinemia predispose to severe, often chronic enterovirus infections.* Similarly, perinatally infected neonates lacking maternal type-specific antibody to the infecting virus are at risk for severe disease. Enterovirus A71 disease increases after 6 mo of age, when maternal serotype-specific antibody levels have declined. Other risk factors for significant illness include young age, immune suppression (posttransplantation and lymphoid malignancy), and, according to animal models and/or epidemiologic observations, exercise, cold exposure, malnutrition, and pregnancy. Specific human leukocyte antigen genes, immune response gene (e.g., interleukin-10 and interferon-γ) polymorphisms, and low vitamin A levels have been linked to enterovirus A71 susceptibility and severe disease.

Clinical Manifestations

Manifestations are protean, ranging from asymptomatic infection to undifferentiated febrile or respiratory illnesses in the majority, to, less frequently, severe diseases such as meningoencephalitis, myocarditis, and neonatal sepsis. A majority of individuals are asymptomatic or have very mild illness, yet may serve as important sources for spread of infection. Symptomatic disease is generally more common in young children.

Nonspecific Febrile Illness

Nonspecific febrile illnesses are the most common symptomatic manifestations, especially in infants and young children. These are difficult to clinically differentiate from serious infections such as urinary tract infection, bacteremia, and bacterial meningitis, often necessitating hospitalization with diagnostic testing and presumptive antibiotic therapy for suspected bacterial infection in young infants.

Illness usually begins abruptly with fever of 38.5-40°C (101-104°F), malaise, and irritability. Associated symptoms may include lethargy, anorexia, diarrhea, nausea, vomiting, abdominal discomfort, rash, sore throat, and respiratory symptoms. Older children may have headaches and myalgias. Findings are generally nonspecific and may include mild conjunctivitis, pharyngeal injection, and cervical lymphadenopathy. Meningitis may be present, but specific clinical features such as meningeal findings or bulging anterior fontanelle distinguishing those with meningitis are often lacking in infants. Fever lasts a mean of 3 days and occasionally is biphasic. Duration of illness is usually 4-7 days but can range from 1 day to >1 wk. White blood cell (WBC) count and results of routine laboratory tests are generally normal, although transient neutropenia can be seen. Concomitant enterovirus and bacterial infection is rare but has been observed in a small number of infants.

Enterovirus illnesses may be associated with a wide variety of skin manifestations, including macular, maculopapular, urticarial, vesicular, and petechial eruptions. Rare cases of idiopathic thrombocytopenic purpura have been reported. Enteroviruses have also been implicated in cases of pityriasis rosea. In general, the frequency of cutaneous manifestations is inversely related to age. Serotypes commonly associated with rashes are echoviruses 9, 11, 16, and 25; coxsackie A viruses 2, 4, 6, 9, and 16; coxsackie B viruses 3-5; and enterovirus A71. Virus can occasionally be recovered from vesicular skin lesions.

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease, one of the more distinctive rash syndromes, is most frequently caused by coxsackievirus A16, sometimes in large outbreaks, and can also be caused by enterovirus A71; coxsackie A viruses 5, 6, 7, 9, and 10; coxsackie B viruses 2 and 5; and some echoviruses. It is usually a mild illness, with or without low-grade fever. When the mouth is involved, the oropharynx is inflamed and often contains scattered, painful vesicles on the tongue, buccal mucosa, posterior pharynx, palate, gingiva, and/or lips (Fig. 277.1). These may ulcerate, leaving 4-8 mm shallow lesions with surrounding erythema. Maculopapular, vesicular, and/or pustular lesions may occur on the hands and fingers, feet, and buttocks and groin (see Figs. 277.1 and 277.2). Skin lesions occur more commonly on the hands than feet and are more common on dorsal surfaces, but frequently also affect palms and soles. Hand and feet lesions are usually tender, 3-7 mm vesicles that resolve in about 1 wk. Buttock lesions do not usually progress to vesiculation. Disseminated vesicular rashes described as **eczema coxsackium** may complicate preexisting eczema. Coxsackievirus A6, in particular, is responsible for relatively severe, atypical hand-foot-and-mouth disease (and herpangina) affecting adults and children that is characterized by fever, generalized rash (face, proximal extremities, and trunk, in addition to hands, feet, and buttocks), pain, dehydration, and desquamation of palms and soles (Fig. 277.2). **Onychomadesis** (nail shedding) has been observed following coxsackievirus A6 and other coxsackievirus infections. Hand-foot-and-mouth disease caused by enterovirus A71 can be associated with neurologic and cardiopulmonary involvement, especially in young children (see Neurologic Manifestations below). Hand-foot-and-mouth disease caused by coxsackievirus A16 also can occasionally be associated with complications such as encephalitis, acute flaccid paralysis, myocarditis, pericarditis, and shock.

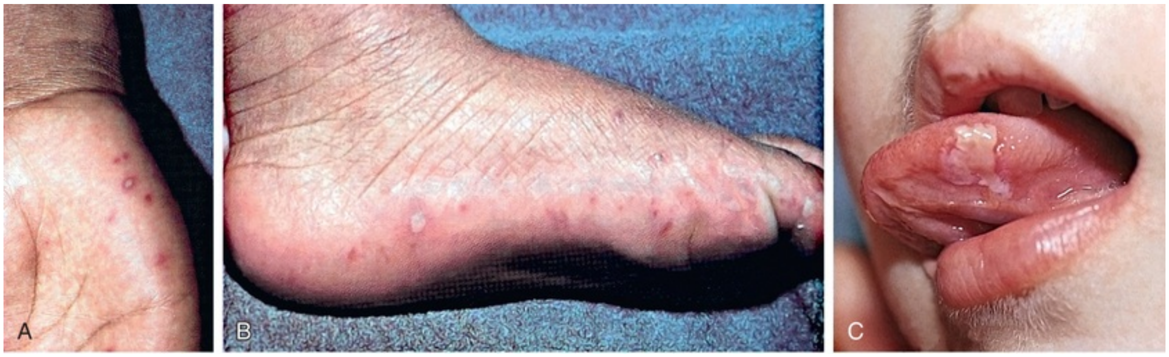

FIG. 277.1 **A,** Oval blisters of the palms in a child with hand-foot-and-mouth disease (coxsackievirus A16 infection). **B,** Oval blisters on the feet of a child with hand-foot-and-mouth disease. **C,** Erosion of the tongue in a child with hand-foot-and-mouth disease. (From Weston WL, Lane AT, Morelli JG: *Color textbook of pediatric dermatology* , ed 3, St. Louis, 2002, Mosby, p. 109.)

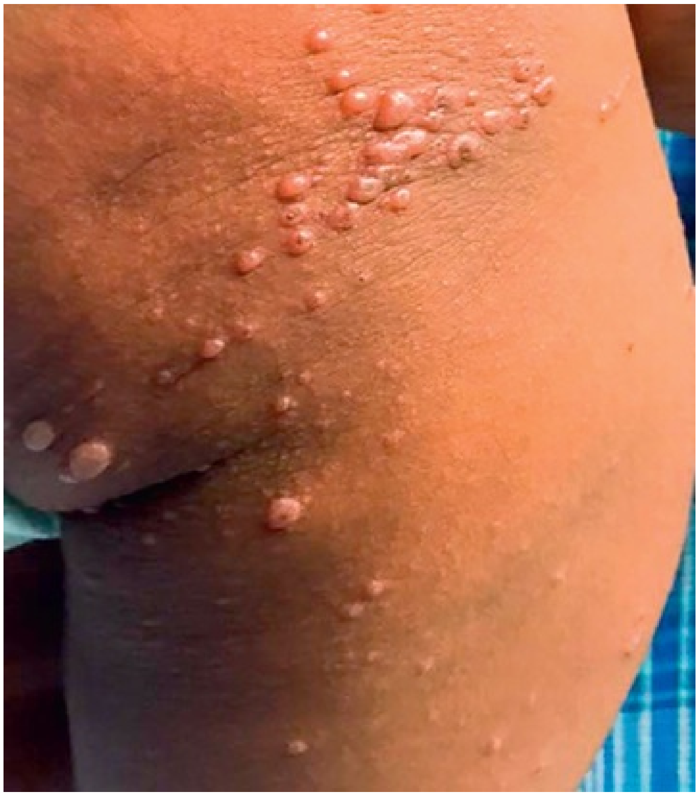

FIG. 277.2 **Atypical hand-foot-and-mouth disease. Vesiculobullous rash on the right buttock and posterior thigh. (From Waldman A, Thomas L, Thacker S, et al: Vesiculobullous eruption as an atypical hand, foot, and mouth presentation. *J Pediatr* 179:273, 2016, Fig. B.)**

Herpangina

Herpangina is characterized by sudden onset of fever, sore throat, dysphagia, and painful lesions in the posterior pharynx. Temperatures range from normal to 41°C (106°F); fever tends to be higher in younger patients. Headache and backache may occur in older children, and vomiting and abdominal pain occur in 25% of cases. Characteristic lesions, present on the anterior tonsillar pillars, soft palate, uvula, tonsils, posterior pharyngeal wall, and, occasionally, the posterior buccal surfaces, are discrete 1-2 mm vesicles and ulcers that enlarge over 2-3 days to 3-4 mm and are surrounded by erythematous rings that vary in size up to 10 mm. The number of lesions can range from 1 to >15, but is most commonly around 5. The remainder of the pharynx appears normal or minimally erythematous. Most cases are mild and have no complications. However, dehydration due to decreased oral intake may occur and some cases are associated with meningitis or more severe illness. Fever generally lasts 1-4 days, and resolution of symptoms occurs in 3-7 days. A variety of enteroviruses cause herpangina, including enterovirus A71, but coxsackie A viruses are implicated most often.

Respiratory Manifestations

Symptoms such as sore throat and coryza frequently accompany and sometimes dominate enterovirus illnesses. Other respiratory findings may include wheezing, exacerbation of asthma, apnea, respiratory distress, pneumonia, otitis media, bronchiolitis, croup, parotitis, and pharyngotonsillitis, which may occasionally be exudative. Lower respiratory tract infection may be significant in immunocompromised patients. Clusters and outbreaks of cases of severe respiratory disease, including pneumonia and wheezing (both in children with a history of asthma and those unaffected by asthma), have been increasingly recognized in association with multiple lineages of enterovirus D68.

Pleurodynia (**Bornholm disease**), caused most frequently by coxsackie B viruses 3, 5, 1, and 2 and echoviruses 1 and 6, is an epidemic or sporadic illness characterized by paroxysmal thoracic pain, due to myositis involving chest and abdominal wall muscles and, possibly, pleural inflammation. In epidemics, which occur every 10-20 yr, children and adults are affected, but most cases occur in persons younger than age 30 yr. Malaise, myalgias, and headache are followed by sudden onset of fever and spasmodic, pleuritic pain in the chest or upper abdomen aggravated by coughing, sneezing, deep breathing, or other movement. During spasms, which last from a few minutes to several hours, pain may be severe and respirations are usually rapid, shallow, and grunting, suggesting pneumonia or pleural inflammation. A pleural friction rub is noted during pain episodes in <10% of patients. Chest radiographs are generally normal but can demonstrate pulmonary infiltrates or pleural effusions. Pain localized to the abdomen may suggest colic, intestinal obstruction, appendicitis, or peritonitis. Pain usually subsides within 3-6 days but can persist for up to weeks. Symptoms may occur in a biphasic or, rarely, recurrent pattern, with less prominent fever during recurrences. Pleurodynia may be associated with meningitis, orchitis, myocarditis, or pericarditis.

Life-threatening noncardiogenic pulmonary edema, hemorrhage, and/or interstitial pneumonitis may occur in patients with enterovirus A71 brainstem encephalitis.

Ocular Manifestations

Epidemics of **acute hemorrhagic conjunctivitis,** primarily caused by enterovirus D70 and coxsackievirus A24/A24 variant, are explosive and marked by high contagiousness, with spread mainly via eye-hand-fomite-eye transmission. School-age children, teenagers, and adults 20-50 yr of age have the highest attack rates. Sudden onset of severe eye pain is associated with photophobia, blurred vision, lacrimation, conjunctival erythema and congestion, lid edema, preauricular lymphadenopathy, and, in some cases, subconjunctival hemorrhages and superficial punctate keratitis. Subconjunctival hemorrhage is the hallmark of enterovirus D70 cases (>70%) but is more rare with coxsackievirus infections. Eye discharge is initially serous but becomes mucopurulent with secondary bacterial infection. Systemic symptoms including fever and headache occur in up to 20% of cases; manifestations suggestive of pharyngoconjunctival fever occasionally occur. Recovery is usually complete within 1-2 wk. Polyradiculoneuropathy or acute flaccid paralysis following enterovirus D70 infection occurs occasionally. Other enteroviruses have occasionally been implicated as causes of keratoconjunctivitis.

Epidemic and sporadic uveitis in infants caused by subtypes of enteroviruses 11 and 19 can be associated with severe complications, including destruction of the iris, cataracts, and glaucoma. Enteroviruses have been implicated in cases of chorioretinitis, uveoretinitis, optic neuritis, and unilateral acute idiopathic maculopathy.

Myocarditis and Pericarditis

Enteroviruses account for approximately 25–35% of cases of myocarditis and pericarditis of proven etiology (see Chapters 466 and 467). Coxsackie B viruses are most commonly implicated, although coxsackie A viruses and echoviruses also may be causative. Adolescents and young adults (especially physically active males) are disproportionately affected. Myopericarditis may be the dominant feature or it may be 1 manifestation of disseminated disease, as in neonates. Disease ranges from relatively mild to severe. Upper respiratory symptoms frequently precede fatigue, dyspnea, chest pain, congestive heart failure, and dysrhythmias. Presentations may mimic myocardial infarction; sudden death may also occur (including apparent sudden infant death syndrome). A pericardial friction rub indicates pericardial involvement. Chest radiography often demonstrates cardiac enlargement and echocardiography may confirm ventricular dilation, reduced contractility, and/or pericardial effusion. Electrocardiography frequently reveals ST segment, T wave, and/or rhythm abnormalities, and serum myocardial enzyme concentrations are often elevated. The acute mortality of enterovirus myocarditis is 0–4%. Recovery is complete without residual disability in the majority of patients. Occasionally, chronic cardiomyopathy, inflammatory ventricular microaneurysms, or constrictive pericarditis may result. The role of persistent infection in chronic dilated cardiomyopathy is controversial. Enteroviruses have also been implicated in late adverse cardiac events following heart transplantation and in acute coronary events, including myocardial infarction, endocarditis, and peripartum cardiomyopathy. Cardiopulmonary dysfunction observed in enterovirus A71 epidemics most commonly occurs without evidence of myocarditis and may be of neurogenic origin; however, true myocarditis has also been described.

Gastrointestinal and Genitourinary Manifestations

Gastrointestinal symptoms such as emesis (especially with meningitis), diarrhea (rarely severe), and abdominal pain are frequent but generally not dominant. Diarrhea, hematochezia, pneumatosis intestinalis, and necrotizing enterocolitis have occurred in premature infants during nursery outbreaks. Enterovirus infection has been implicated in acute and chronic gastritis, intussusception, chronic intestinal inflammation in hypogammaglobulinemic patients, sporadic hepatitis in normal children, severe hepatitis in neonates, and pancreatitis, which may result in transient exocrine pancreatic insufficiency.

Coxsackie B viruses are second only to mumps as causes of orchitis, most commonly presenting in adolescents. The illness is frequently biphasic; fever and pleurodynia or meningitis are followed approximately 2 wk later by orchitis, often with epididymitis. Enteroviruses have also been implicated in cases of nephritis and IgA nephropathy.

Neurologic Manifestations

Enteroviruses are the most common cause of viral **meningitis** in mumps-immunized populations, accounting for up to 90% or more of cases in which a cause is identified. Meningitis is particularly common in infants, especially in those younger than 3 mo of age, often during community epidemics. Frequently implicated serotypes include coxsackie B viruses 2-5; echoviruses 4, 6, 7, 9, 11, 13, 16, and 30; and enteroviruses D70 and A71. Most cases in infants and young children are mild and lack specific meningeal signs, whereas nuchal rigidity is apparent in more than half of children older than 1-2 yr of age. Fever is present in 50–100% and may be accompanied by irritability, malaise, headache, photophobia, nausea, emesis, anorexia, lethargy, hypotonia, rash, cough, rhinorrhea, pharyngitis, diarrhea, and/or myalgia. Some cases are biphasic, with fever and nonspecific symptoms lasting a few days and followed by return of fever with meningeal signs several days later. Fever usually resolves in 3-5 days, and other symptoms in infants and young children usually resolve within 1 wk. In adults, symptoms tend to be more severe and of longer duration. CSF findings include pleocytosis (generally <500 but occasionally as high as 1,000-8,000 WBCs/µL; often predominantly polymorphonuclear cells in the first 48 hr before becoming mostly mononuclear); normal or slightly low glucose content (10% <40 mg/dL); and normal or mildly increased protein content (generally <100 mg/dL). *CSF parameters are normal in up to half of young infants despite detection of enterovirus in CSF and may also be normal in older children early after illness onset.* Acute complications occur in approximately 10% of young children, including simple and complex seizures, obtundation, increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, ventriculitis, transient cerebral arteriopathy, and coma. The long-term prognosis for most children, even in those with acute complications, is good.

Enteroviruses are also responsible for ≥10–20% of cases of **encephalitis** with an identified cause. Frequently implicated serotypes include echoviruses 3, 4, 6, 9, and 11; coxsackie B viruses 2, 4, and 5; coxsackie A virus 9; and enterovirus A71. After initial nonspecific symptoms, there is progression to encephalopathy characterized by confusion, weakness, lethargy, and/or irritability. Symptoms are most commonly generalized, although focal findings, including focal motor seizures, hemichorea, acute cerebellar ataxia, aphasia, extrapyramidal symptoms, and/or focal imaging abnormalities, may occur. Meningeal signs and CSF indices similar to enteroviral meningitis are commonly present, leading to characterization of most cases as **meningoencephalitis** . Severity ranges from mild alteration in mental status to coma and decerebrate status. Long-term sequelae, including epilepsy, weakness, cranial nerve palsy, spasticity, psychomotor retardation, and hearing loss, or death may follow severe disease. Persistent or recurrent cases have been observed rarely.

Neurologic manifestations have been prominent in epidemics in Asia and Australia of enterovirus A71, and, to a lesser extent, coxsackievirus A16 disease. Many affected children have had hand-foot-and-mouth disease, some have had herpangina, and others have had no mucocutaneous manifestations. Neurologic syndromes in a fraction of children have included meningitis, meningoencephalomyelitis, **acute flaccid paralysis** , Guillain-Barré syndrome, transverse myelitis, acute disseminated encephalomyelitis, cerebellar ataxia, opsoclonus-myoclonus syndrome, benign intracranial hypertension, and **brainstem encephalitis** (**rhombencephalitis** involving the midbrain, pons, and medulla). Enterovirus A71 rhombencephalitis is characterized by altered consciousness, myoclonus, vomiting, ataxia, nystagmus, tremor, cranial nerve abnormalities, autonomic dysfunction, and MRI demonstrating lesions in the brainstem, thalamus, and cerebellum. Although the disease has been mild and reversible in some children, others have had rapid progression to noncardiogenic (presumed neurogenic) pulmonary edema and hemorrhage, cardiopulmonary failure, shock, and coma. High mortality rates have been reported in children younger than 5 yr of age, especially in those younger than 1 yr of age. Deficits such as central hypoventilation, bulbar dysfunction, neurodevelopmental delay, cerebellar defects, attention deficit/hyperactivity–related symptoms, persistent limb weakness, and muscle atrophy have been observed among survivors, especially those who experienced cardiopulmonary failure or acute flaccid paralysis during their acute illness. Although the most severe cases have been associated with enterovirus A71, similar clinical pictures have been produced by other enterovirus serotypes (e.g., coxsackieviruses A16 and B5, echovirus 7).

Patients with **antibody or combined immunodeficiencies** (including human immunodeficiency virus infection, acute lymphocytic leukemia, and transplantation) and patients receiving anti-CD20 antibody therapy are at risk for acute or, more commonly, **chronic enterovirus meningoencephalitis.** The latter is characterized by persistent CSF abnormalities, viral detection in CSF or brain tissue for years, and recurrent encephalitis and/or progressive neurologic deterioration, including insidious intellectual or personality deterioration, altered mental status, seizures, motor weakness, and increased intracranial pressure. Although disease may wax and wane, deficits generally become progressive and ultimately are frequently fatal or lead to long-term sequelae. A **dermatomyositis-like syndrome,** hepatitis, arthritis, myocarditis, or disseminated infection may also occur. Chronic enterovirus meningoencephalitis has become less common with prophylactic high-dose intravenous immunoglobulin replacement in agammaglobulinemic patients.

A variety of nonpoliovirus enteroviruses, including enteroviruses D68, D70, A71, coxsackie A viruses 7 and 24, coxsackie B viruses, and several echoviruses, have been associated with acute flaccid paralysis with motor weakness due to spinal cord anterior horn cell involvement. **Acute flaccid myelitis** is used to designate the clinical syndrome of acute flaccid limb weakness with longitudinal magnetic resonance imaging abnormalities in the spinal cord gray matter. Neurologic abnormalities are commonly preceded by a febrile respiratory or gastrointestinal prodromal illness around 1 wk prior to onset. Limb involvement tends to be asymmetric and varies from 1 to all 4 limbs, with severity ranging from mild weakness to complete paralysis. Cranial nerve dysfunction, including bulbar paralysis, and respiratory failure requiring ventilator support, similar to poliovirus poliomyelitis, have been described in acute flaccid myelitis cases associated with enterovirus D68. Sensory involvement, encephalopathy, seizures, and supratentorial imaging changes are uncommon. Functional improvements can be seen over time, but muscle atrophy with limb weakness and some degree of disability frequently persist.

Other neurologic syndromes include cerebellar ataxia; transverse myelitis; Guillain-Barré syndrome (including Miller-Fisher variant) and axonal polyneuropathy; acute disseminated encephalomyelitis; peripheral neuritis; optic neuritis; sudden hearing loss, tinnitus, and inner ear disorders such as vestibular neuritis; and other cranial neuropathies.

Myositis and Arthritis

Although myalgia is common, direct evidence of muscle involvement, including rhabdomyolysis, muscle swelling, focal myositis, and polymyositis, has uncommonly been reported. A dermatomyositis-like syndrome and arthritis can be seen in enterovirus-infected hypogammaglobulinemic patients. Enteroviruses are a rare cause of arthritis in normal hosts.

Neonatal Infections

Neonatal infections are relatively common, with a disease incidence comparable to or greater than that of symptomatic neonatal herpes simplex virus, cytomegalovirus, and group B streptococcus infections. Infection frequently is caused by coxsackie B viruses 2-5 and echoviruses 6, 9, 11, and 19, although many serotypes have been implicated, including coxsackie B virus 1 and echovirus 30 in more recent years. Enteroviruses may be acquired vertically before, during, or after delivery, including possibly via breast milk; horizontally from family members; or by sporadic or epidemic transmission in nurseries. In utero infection can lead to fetal demise, nonimmune hydrops fetalis, or neonatal illness. Additionally, maternal and intrauterine infections have been speculatively linked to congenital anomalies; prematurity, low birthweight, and intrauterine growth restriction; neurodevelopmental sequelae; unexplained neonatal illness and death; and increased risk of type 1 diabetes and schizophrenia.

The majority of neonatal infections are asymptomatic, and symptomatic presentations range from benign febrile illness to severe multisystem disease. Most affected newborns are full term and previously well. Maternal history often reveals a recent viral illness preceding or immediately following delivery, which may include fever and abdominal pain. Neonatal symptoms may occur as early as day 1 of life, with onset of severe disease generally within the first 2 wk of life. Frequent findings include fever or hypothermia, irritability, lethargy, anorexia, rash (usually maculopapular, occasionally petechial or papulovesicular), jaundice, respiratory symptoms, apnea, hepatomegaly, abdominal distention, emesis, diarrhea, and decreased perfusion. Most patients have benign courses, with resolution of fever in an average of 3 days and of other symptoms in about 1 wk. A biphasic course may occur occasionally. A minority have severe disease dominated by any combination of sepsis, meningoencephalitis, myocarditis, hepatitis, coagulopathy, and/or pneumonitis. Meningoencephalitis may be manifested by focal or complex seizures, bulging fontanelle, nuchal rigidity, and/or reduced level of consciousness. Myocarditis, most often associated with coxsackie B virus infection, may be suggested by tachycardia, dyspnea, cyanosis, and cardiomegaly. Hepatitis and pneumonitis are most often associated with echovirus infection, although they may also occur with coxsackie B viruses. Gastrointestinal manifestations may be prominent in premature neonates. Laboratory and radiographic evaluation may reveal leukocytosis, thrombocytopenia, CSF pleocytosis, CNS white matter damage, elevations of serum transaminases and bilirubin, coagulopathy, pulmonary infiltrates, and electrocardiographic changes.

Complications of severe neonatal disease include CNS necrosis and generalized or focal neurologic compromise; arrhythmias, congestive heart failure, myocardial infarction, and pericarditis; hepatic necrosis and failure; coagulopathy with intracranial or other bleeding; adrenal necrosis and hemorrhage; and rapidly progressive pneumonitis and pulmonary hypertension. Myositis, arthritis, necrotizing enterocolitis, inappropriate antidiuretic hormone secretion, hemophagocytic lymphohistiocytosis-like presentation, bone marrow failure, and sudden death are rare events. Mortality with severe disease is significant and is most often associated with hepatitis and bleeding complications, myocarditis, and/or pneumonitis.

Survivors of severe neonatal disease may have gradual resolution of hepatic and cardiac dysfunction, although persistent hepatic dysfunction and residual cardiac impairment, chronic calcific myocarditis, and ventricular aneurysm can occur. Meningoencephalitis may be associated with speech and language impairment; cognitive deficits; spasticity, hypotonicity, or weakness; seizure disorders; microcephaly or hydrocephaly; and ocular abnormalities. However, many survivors appear to have no long-term sequelae. Risk factors for severe disease include illness onset in the first few days of life; maternal illness just prior to or after delivery; prematurity; male sex; infection by echovirus 11 or a coxsackie B virus; positive serum viral culture; absence of neutralizing antibody to the infecting virus; and evidence of severe hepatitis, myocarditis, and/or multisystem disease.

Transplant Recipients and Patients With Malignancies

Enterovirus infections in stem cell and solid organ transplant recipients may be severe and/or prolonged, causing progressive pneumonia, severe diarrhea, pericarditis, heart failure, meningoencephalitis, and disseminated disease. Enterovirus-associated hemophagocytic lymphohistiocytosis, meningitis, encephalitis, and myocarditis have been reported in children with malignancies and patients treated with anti-CD20 monoclonal antibody. Infections in these groups are associated with high fatality rates.

Diagnosis

Clues to enterovirus infection include characteristic findings such as hand-foot-and-mouth disease or herpangina lesions, consistent seasonality, known community outbreak, and exposure to enterovirus-compatible disease. In the neonate, history of maternal fever, malaise, and/or abdominal pain near delivery during enterovirus season is suggestive.

Traditionally, enterovirus infection has been confirmed with viral culture using a combination of cell lines. Sensitivity of culture ranges from 50% to 75% and can be increased by sampling of multiple sites (e.g., CSF plus oropharnyx and rectum in children with meningitis). In neonates, yields of 30–70% are achieved when blood, urine, CSF, and mucosal swabs are cultured. A major limitation is the inability of most coxsackie A viruses to grow in culture. Yield may also be limited by neutralizing antibody in patient specimens, improper specimen handling, or insensitivity of the cell lines used. Culture is relatively slow, with 3-8 days usually required to detect growth. Although cultivation of an enterovirus from any site can generally be considered evidence of recent infection, isolation from the rectum or stool can reflect more remote shedding. Similarly, recovery from a mucosal site may suggest an association with an illness, whereas recovery from a normally sterile site (e.g., CSF, blood, or tissue) is more conclusive evidence of causation. Serotype identification by type-specific antibody staining or neutralization of a viral isolate is generally required only for investigation of an outbreak or an unusual disease manifestation, surveillance, or to distinguish nonpoliovirus enteroviruses from vaccine or wild-type polioviruses.

Direct testing for nucleic acid has replaced culture due to increased sensitivity and more rapid turnaround. RT-PCR detection of highly conserved areas of the enterovirus genome can detect the majority of enteroviruses in CSF; serum; urine; conjunctival, nasopharyngeal, oropharyngeal, tracheal, rectal, and stool specimens; dried blood spots; and tissues such as myocardium, liver, and brain. However, the closely related parechoviruses are not detected by most enterovirus RT-PCR primers. Sensitivity and specificity of RT-PCR are high, with results available in as short as 1 hr. Real-time, quantitative PCR assays and nested PCR assays with enhanced sensitivity have been developed, as have enterovirus-containing multiplex PCR assays, nucleic acid sequence–based amplification assays, reverse transcription-loop-mediated isothermal amplification, culture-enhanced PCR assays, and PCR-based microarray assays. PCR testing of CSF from children with meningitis and from hypogammaglobulinemic patients with chronic meningoencephalitis is frequently positive despite negative cultures. Routine PCR testing of CSF in infants and young children with suspected meningitis during enterovirus season decreases the number of diagnostic tests, duration of hospital stay, antibiotic use, and overall costs. PCR testing of tracheal aspirates of children with myocarditis has good concordance with testing of myocardial specimens. In ill neonates and young infants, PCR testing of serum and urine has higher yields than culture. Viral load in blood of neonates is correlated with disease severity; viral nucleic acid may persist in blood of severely ill newborns for up to 2 mo.

Sequence analysis of amplified nucleic acid can be used for serotype identification and phylogenetic analysis and to establish a transmission link among cases. Serotype-specific (e.g., enterovirus A71, enterovirus D68, and coxsackievirus A16) PCR assays have been developed. For enterovirus A71, the yield of specimens other than CSF and blood (oropharyngeal, nasopharyngeal, rectal, vesicle swabs, and CNS tissue) is greater than the yield of CSF and blood, which are infrequently positive. Enterovirus D68 is more readily detected in respiratory specimens (i.e., nasal wash or nasopharyngeal swab) compared to stool/rectal or CSF specimens. Of note, commercially available multiplex respiratory PCR assays generally are unable to distinguish enteroviruses (including enterovirus D68) from rhinoviruses. Antigen detection assays that target specific serotypes such as enterovirus A71 with monoclonal antibodies have also been developed.

Enterovirus infections can be detected serologically by a rise in serum or CSF of neutralizing, complement fixation, enzyme-linked immunosorbent assay, or other type-specific antibody or by detection of serotype-specific IgM antibody. However, serologic testing requires presumptive knowledge of the infecting serotype or an assay with sufficiently broad cross-reactivity. Sensitivity and specificity may be limiting, and cross-reactivity among serotypes may occur.

Except for epidemiologic studies or cases characteristic of specific serotypes (e.g., enterovirus A71), serology is generally less useful than culture or nucleic acid detection.

Differential Diagnosis

The differential diagnosis of enterovirus infections varies with the clinical presentation (Table 277.2).

Table 277.2

Differential Diagnosis of Enterovirus Infections

CLINICAL MANIFESTATION	BACTERIAL PATHOGENS	VIRAL PATHOGENS
Nonspecific febrile illness	*Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Neisseria meningitidis*	Influenza viruses, human herpesviruses 6 and 7, human parechoviruses
Exanthems/enanthems	Group A streptococcus, *Staphylococcus aureus* , *N. meningitidis*	Herpes simplex virus, adenoviruses, varicella-zoster virus, Epstein-Barr virus, measles virus, rubella virus, human herpesviruses 6 and 7, human parechoviruses
Respiratory illness/conjunctivitis	*S. pneumoniae*, *H. influenzae* (nontypeable and type b), *N. meningitidis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*	Adenoviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, human metapneumovirus, coronaviruses
Myocarditis/pericarditis	*S. aureus*, *H. influenzae* type b, *M. pneumoniae*	Adenoviruses, influenza virus, parvovirus, cytomegalovirus
Meningitis/encephalitis	*S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*, *Mycobacterium tuberculosis* , *Borrelia burgdorferi*, *M. pneumoniae* , *Bartonella henselae*, *Listeria monocytogenes*	Herpes simplex virus, West Nile virus, influenza viruses, adenoviruses, Epstein-Barr virus, mumps virus, lymphocytic choriomeningitis virus, arboviruses, human parechoviruses
Neonatal infections	Group B streptococcus, Gram-negative enteric bacilli, *L. monocytogenes*, *Enterococcus*	Herpes simplex virus, adenoviruses, cytomegalovirus, rubella virus, human parechoviruses

Human parechoviruses , members of the Picornaviridae family, produce many manifestations similar to the nonpolio enteroviruses. They are small RNA viruses that were originally classified as echoviruses. Nineteen parechoviruses have been identified that infect humans; serotypes 1 and 3 are the most common causes of symptomatic infection. Parechovirus epidemics occur in the same season as enterovirus infections, with a biennial pattern of circulation noted in Europe. Outbreaks have been described in the nursery setting. In young infants, parechoviruses can cause a sepsis-like illness similar to enterovirus illness and are a common, underrecognized cause of viral meningoencephalitis. More frequently than with enteroviruses, infants with parechovirus CNS infection often have no CSF pleocytosis. There is also a higher incidence of white matter MRI abnormalities and long-term neurodevelopmental deficits with parechovirus encephalitis compared with enterovirus encephalitis. Rarely, parechoviruses have been identified in cases of hepatitis or myocarditis. Infections in older children are often unrecognized or cause acute, benign febrile, respiratory, or gastrointestinal illnesses with few specific findings.

Infants suspected of having an enterovirus infection should also be considered as possibly having a parechovirus infection, because the 2 may be indistinguishable. A distinctive rash involving the extremities with palm and sole erythema or peripheral leukopenia in the setting of high fever during the summer-fall season are clinical findings that should also prompt consideration of parechovirus infection. The diagnosis of parechovirus infection is confirmed by human parechovirus-specific PCR on CSF, blood, stool, and oropharyngeal or nasopharyngeal specimens.

Treatment

In the absence of a proven antiviral agent for enterovirus infections, supportive care is the mainstay of treatment. Newborns and young infants with nonspecific febrile illnesses and children with meningitis frequently require diagnostic evaluation and hospitalization for presumptive treatment of bacterial and herpes simplex virus infection. Neonates with severe disease and infants and children with concerning disease manifestations (e.g., myocarditis, enterovirus A71 neurologic and cardiopulmonary disease, enterovirus D68 respiratory failure, and acute flaccid myelitis) may require intensive cardiorespiratory support. Milrinone has been suggested as a useful agent in severe enterovirus A71 cardiopulmonary disease. Liver and cardiac transplantation have been performed for neonates with progressive end-organ failure.

Immunoglobulin has been utilized to treat enterovirus infections based on the importance of the humoral immune response to enterovirus infection and the observation that absence of neutralizing antibody is a risk factor for symptomatic infection. Immunoglobulin products contain neutralizing antibodies to many commonly circulating serotypes, although titers vary with serotype and among products and lots. Anecdotal and retrospective, uncontrolled use of intravenous immunoglobulin or infusion of maternal convalescent plasma to treat newborns with severe disease has been associated with varying outcomes. The 1 randomized, controlled trial was too small to demonstrate significant clinical benefits, although neonates who received immunoglobulin containing high neutralizing titers to their own isolates had shorter periods of viremia and viruria. Immunoglobulin has been administered intravenously and intraventricularly to treat hypogammaglobulinemic patients with chronic enterovirus meningoencephalitis and intravenously in transplant and oncology patients with severe infections, with variable success. Intravenous immunoglobulin and corticosteroids have been used for patients with neurologic disease caused by enterovirus A71, enterovirus D68, and other enteroviruses. Modulation of cytokine profiles after administration of intravenous immunoglobulin for enterovirus A71–associated brainstem encephalitis has been demonstrated. High-titer enterovirus A71 immunoglobulin appeared promising in animal models, and clinical trials in regions with epidemic enterovirus A71 disease are ongoing. Anti–enterovirus A71 monoclonal antibodies have also been generated and evaluated in vitro and in animal models. A retrospective study suggested that treatment of presumed viral myocarditis with immunoglobulin was associated with improved outcome; however, virologic diagnoses were not made. Evaluation of corticosteroids and cyclosporine and other immunosuppressive therapy for myocarditis has been inconclusive. Successful treatment of enterovirus myocarditis with interferon-α has been reported anecdotally, and interferon-β treatment was associated with viral clearance, improved cardiac function, and survival in chronic cardiomyopathy associated with persistence of enterovirus (or adenovirus) genome. Activity of interferon-α against enterovirus 71 has been demonstrated in in vitro and animal models, but potency varies with interferon-α type.

Antiviral agents that act at various steps in the enterovirus life cycle—attachment, penetration, uncoating, translation, polyprotein processing, protease activity, replication, and assembly—are being evaluated. Candidates include pharmacologically active chemical compounds, small interfering RNAs and DNA-like antisense agents, purine nucleoside analogs, synthetic peptides, enzyme inhibitors of signal transduction pathways, interferon-inducers, and herbal compounds. Pleconaril, an inhibitor of attachment and uncoating, was associated with benefit in some controlled studies of enterovirus meningitis and picornavirus upper respiratory tract infections, and uncontrolled experience suggested possible benefits in high-risk infections. A randomized, controlled trial of pleconaril in neonates with severe hepatitis, coagulopathy, and/or myocarditis suggested possible virologic and clinical benefits of treatment. Pocapavir, an agent with a similar mechanism of action that is in development for treatment of poliovirus infections, has been used in a small number of cases of severe neonatal enterovirus sepsis. Vapendavir is another attachment inhibitor that is in clinical trials for rhinovirus infections and has in vitro activity against enteroviruses (including enterovirus A71) but has not entered clinical trials for enterovirus infections. Pleconaril, pocapavir, and vapendavir are not currently available for clinical use.

Design and evaluation of candidate agents active against enterovirus A71 and enterovirus D68 are high priorities. Challenges for therapies of enterovirus A71 include limited cross-genotypic activity of candidate compounds and high viral mutagenicity that favors emergence of resistance. Lactoferrin and ribavirin have demonstrated activity in in vitro and/or animal models. The investigational agents rupintrivir and V-7404, which inhibit the 3C-protease conserved among many enteroviruses and essential for infectivity, have broad activity in vitro, including against both enterovirus A71 and enterovirus D68. DAS181 is an investigational, inhaled drug with sialidase activity that has in vitro activity against recently circulating strains of enterovirus D68. The antidepressant fluoxetine interacts with the enterovirus 2C protein and has in vitro activity against group B and D enteroviruses; it has been used anecdotally for chronic enterovirus encephalitis associated with agammaglobulinemia and enterovirus D68-associated acute flaccid myelitis. A retrospective study did not demonstrate a signal of efficacy in the latter condition.

Complications and Prognosis

The prognosis in the majority of enterovirus infections is excellent. Morbidity and mortality are associated primarily with myocarditis, neurologic disease, severe neonatal infections, and infections in immune compromised hosts.

Prevention

The first line of defense is prevention of transmission through good hygiene, such as handwashing, avoidance of sharing utensils and drinking containers and other potential fomites, disinfection of contaminated surfaces, and avoiding community settings where exposures are likely to occur. Chlorination of drinking water and swimming pools may be important. Contact precautions should be used for all patients with enterovirus infections in the hospital setting; droplet precautions should also be included for patients with respiratory syndromes and, possibly, enterovirus A71 infection. Infection control techniques such as cohorting have proven effective in limiting nursery outbreaks. Prophylactic administration of immunoglobulin or convalescent plasma has been used in nursery epidemics; simultaneous use of infection control interventions makes it difficult to determine efficacy.

Pregnant women near term should avoid contact with individuals ill with possible enterovirus infections. If a pregnant woman experiences a suggestive illness, it is advisable not to proceed with emergency delivery unless there is concern for fetal compromise or obstetric emergencies cannot be excluded. Rather, it may be advantageous to extend pregnancy, allowing the fetus to passively acquire protective antibodies. A strategy of prophylactically administering immunoglobulin (or maternal convalescent plasma) to neonates born to mothers with enterovirus infections is untested.

Maintenance antibody replacement with high-dose intravenous immunoglobulin for patients with hypogammaglobulinemia has reduced the incidence of chronic enterovirus meningoencephalitis, although breakthrough infections occur. Inactivated vaccines to prevent enterovirus A71 infections have been demonstrated to be safe and effective (>90% against enterovirus A71 hand-foot-and-mouth disease and >80% against enterovirus A71 serious disease) in phase 3 clinical trials. Inactivated enterovirus A71 vaccines have been approved for prevention of severe hand-foot-and-mouth disease in China and are being studied in other Asian countries. Other vaccine strategies for enterovirus A71, including VP1 capsid protein-based subunit, DNA, and vector vaccines; combined peptide vaccines; live-attenuated vaccines; virus-like particles; breast milk enriched with VP1 capsid protein or lactoferrin; and interferon-γ–expressing recombinant viral vectors, are also under investigation. Circulation of multiple enterovirus A71 types, antigenic drift, viral recombination, and potential immunologic cross-reactivity with brain tissue may pose challenges to development of enterovirus A71 vaccines.

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CHAPTER 278

Parvoviruses

William C. Koch

The parvoviruses are small, single-stranded DNA viruses. They are common infectious agents of a variety of animal species, including mammals, birds, and insects. Parvoviruses as a group include a number of important animal pathogens. There are 5 different types of parvoviruses known to infect humans: the dependoviruses, also called adeno-associated viruses (AAV), parvovirus B19 (B19V), human bocaviruses (HBoV), parvovirus 4 (PARV4), and human bufavirus (HBuV). B19V and HBoV are the only 2 parvoviruses known to be pathogenic in humans. B19V is the most well studied and clinically important of the human parvoviruses and the cause of **erythema infectiosum** or **fifth disease** . *The more recently described human bocavirus is an emerging human pathogen.*

Etiology

The 5 human parvoviruses are distinct enough from each other to represent 5 different genera within the Parvoviridae family. B19V is a member of the genus *Erythroparvovirus* . The virus is composed of an icosahedral protein capsid without an envelope and contains a single-stranded DNA genome of approximately 5.5 kb. It is relatively heat and solvent resistant. It is antigenically distinct from other mammalian parvoviruses and has only 1 known serotype, with 3 distinct genotypes described. The relatively short parvovirus genome does not encode a DNA polymerase, so all parvoviruses require either host cell factors present in late S phase or coinfection with another virus to replicate their DNA. B19V can be propagated effectively in vitro only in CD36+ erythroid progenitor cells derived from human bone marrow, umbilical cord blood, or peripheral blood.

HBoV is a member of the genus *Bocaparvovirus* . HBoV was first isolated from nasopharyngeal specimens from children with respiratory tract infection in 2005. It was identified using random polymerase chain reaction (PCR) amplification and sequencing methods specifically designed to detect previously unknown viral sequences. Analysis of the gene sequences showed similarities to both bovine and canine parvoviruses, and thus the virus was named human bocavirus. Later, 3 other HBoVs were identified in stool samples and named HBoV types 2, 3, and 4, with the initial respiratory isolate called HBoV1. The HBoV capsid structure and genome size are similar to those of B19V, but the genomic organization and replication are different (though not fully characterized to date). HBoVs cannot be propagated in conventional cell culture but have been grown in a pseudostratified human airway epithelial cell culture system.

The AAVs are members of the genus *Dependoparvovirus* and were the first parvoviruses to be found in humans. They were originally identified as contaminants in adenovirus preparations, resulting in the designation AAV. They were later isolated directly from human tissue samples, and now several AAV serotypes are known to commonly infect humans. AAVs have a unique life cycle that can take 1 of 2 paths: (1) a lytic infection with replication of viral DNA and production of new virus, or (2) viral integration into the host cell DNA. In the presence of a "helper" virus, usually an adenovirus or a herpesvirus, AAV can replicate its DNA, produce capsids, and release new virions by cell lysis. In the absence of a helper virus infection, the AAV genome becomes integrated into the host cell DNA. This feature has drawn interest in AAVs as potential vectors for gene therapy. Although human infection with AAVs is common, there is no known disease association and no evidence of pathogenicity, so this virus will not be discussed further in this chapter.

PARV4 was initially identified in 2005 from the blood of an adult patient with acute viral syndrome, who was also an intravenous drug user co-infected with hepatitis C. Subsequently, this virus has been found in blood donors and donated plasma pools in many different countries. It appears to be present in approximately 3% of blood donors in the United States and 4% of plasma pools. There is currently no known disease association or clinical symptomology associated with infection. Likewise, BuV is a parvovirus that has recently been found to infect humans but its role as a pathogen is undetermined. It was first identified in 2012 in the feces from children <5 yr of age with acute diarrhea. BuV is a member of the genus *Protoparvovirus* , and PARV4 has been assigned to a new parvovirus genus, *Tetraparvovirus* . The full epidemiology and clinical relevance of both of these viruses await further study.

Epidemiology

Parvovirus B19

Infections with B19V are common and occur worldwide. Clinically apparent infections, such as the rash illness of erythema infectiosum and transient aplastic crisis, are most prevalent in school-age children (70% of cases occur in patients between 5 and 15 yr of age). Seasonal peaks occur in the late winter and spring, with sporadic infections throughout the year. Seroprevalence increases with age, with 40–60% of adults having evidence of prior infection.

Transmission of B19V is by the respiratory route, presumably via large-droplet spread from nasopharyngeal viral shedding. The transmission rate is 15–30% among susceptible household contacts, and mothers are more commonly infected than fathers. In outbreaks of erythema infectiosum in elementary schools, the secondary attack rates range from 10% to 60%. Nosocomial outbreaks also occur, with secondary attack rates of 30% among susceptible healthcare workers.

Although respiratory spread is the primary mode of transmission, B19V is also transmissible in blood and blood products, as documented among children with hemophilia receiving pooled-donor clotting factor. Given the resistance of the virus to solvents, fomite transmission could be important in childcare centers and other group settings, but this mode of transmission has not been established.

Human Bocaviruses

The majority of published studies have used molecular methods to detect HBoV DNA in respiratory secretions, fecal samples, blood, and other tissues. HBoV DNA (HBoV1) can be found commonly in respiratory secretions from children hospitalized with acute lower respiratory tract infections (LRTIs). It is more prevalent in children younger than 2 yr of age and seems to be associated with wheezing respiratory illness. However, it can be isolated from respiratory secretions from asymptomatic children and can often be found as a coinfection with other common respiratory pathogens of children this age, including respiratory syncytial virus, human metapneumovirus, and rhinoviruses. This has caused some confusion as to the pathogenic role of HBoV in acute LRTI, including whether it can persist in secretions long after a subclinical infection or requires a helper virus. A limited number of seroepidemiologic studies have been performed, and these suggest that infection is common in children younger than 5 yr of age. The most recent studies provide evidence that the virus is in fact pathogenic, especially in children younger than 2 yr with wheezing and LRTI, as HBoV1 is more likely to be the only virus isolated in these patients and more likely to have an acute antibody response when coupled with antibody testing. When quantitative PCR is used, the virus is found to be much higher in titer in these symptomatic cases.

HBoV DNA (HBoV2, HBoV3, and HBoV4) has also been found in fecal samples in studies from various countries, but its role as a cause of viral gastroenteritis is still undetermined.

Pathogenesis

Parvovirus B19

The primary target of B19V infection is the erythroid cell line, specifically erythroid precursors near the pronormoblast stage. Viral infection produces cell lysis, leading to a progressive depletion of erythroid precursors and a transient arrest of erythropoiesis. The virus has no apparent effect on the myeloid cell line. The tropism for erythroid cells is related to the erythrocyte P blood group antigen, which is the primary cell receptor for the virus and is also found on endothelial cells, placental cells, and fetal myocardial cells. Thrombocytopenia and neutropenia are often observed clinically, but the pathogenesis of these abnormalities is unexplained.

Experimental infection of normal volunteers with B19V revealed a biphasic illness. From 7 to 11 days after inoculation, subjects had viremia and nasopharyngeal viral shedding with fever, malaise, and rhinorrhea. Reticulocyte counts dropped to undetectable levels but resulted in only a mild, clinically insignificant fall in serum hemoglobin. With the appearance of specific antibodies, symptoms resolved and serum hemoglobin returned to normal. Several subjects experienced a rash associated with arthralgia 17-18 days after inoculation. Some manifestations of B19 infection, such as transient aplastic crisis, appear to be a direct result of viral infection, whereas others, including the exanthem and arthritis, appear to be **postinfectious phenomena** related to the immune response. Skin biopsy of patients with erythema infectiosum reveals edema in the epidermis and a perivascular mononuclear infiltrate compatible with an immune-mediated process.

Individuals with **chronic hemolytic anemia** and increased red blood cell (RBC) turnover are very sensitive to minor perturbations in erythropoiesis. Infection with B19V leads to a transient arrest in RBC production and a precipitous fall in serum hemoglobin, often requiring transfusion. The reticulocyte count drops to undetectable levels, reflecting the lysis of infected erythroid precursors. Humoral immunity is crucial in controlling infection. Specific immunoglobulin (Ig) M appears within 1-2 days of infection and is followed by anti-B19 IgG, which leads to control of the infection, restoration of reticulocytosis, and a rise in serum hemoglobin.

Individuals with **impaired humoral immunity** are at increased risk for more serious or persistent infection with B19V, which usually manifests as chronic RBC aplasia, although neutropenia, thrombocytopenia, and marrow failure are also described. Children undergoing chemotherapy for leukemia or other forms of cancer, transplant recipients, and patients with congenital or acquired immunodeficiency states (including AIDS) are at risk for chronic B19V infections.

Infections in the **fetus** and **neonate** are somewhat analogous to infections in immunocompromised persons. B19V is associated with nonimmune fetal hydrops and stillbirth in women experiencing a primary infection but does not appear to be teratogenic. Like most mammalian parvoviruses, B19V can cross the placenta and cause fetal infection during primary maternal infection. Parvovirus cytopathic effects are seen primarily in erythroblasts of the bone marrow and sites of extramedullary hematopoiesis in the liver and spleen. Fetal infection can presumably occur as early as 6 wk of gestation, when erythroblasts are first found in the fetal liver; after the 4th mo of gestation, hematopoiesis switches to the bone marrow. In some cases, fetal infection leads to profound fetal anemia and subsequent high-output cardiac failure (see Chapter 124). **Fetal hydrops** ensues and is often associated with fetal death. There may also be a direct effect of the virus on myocardial tissue that contributes to the cardiac failure. However, most infections during pregnancy result in normal deliveries at term. Some of the asymptomatic infants from these deliveries have been reported to have chronic postnatal infection with B19V that is of unknown significance.

Human Bocaviruses

Mechanisms of HBoV replication and pathogenesis are poorly characterized to date. Growth of HBoV1 in tissue culture is difficult, though the virus has been cultured in primary respiratory epithelial cells as noted above. The primary site of viral replication appears to be the respiratory tract, as the virus has been detected most frequently and in highest copy numbers here. HBoV1 has also been found occasionally in the serum, suggesting the potential for systemic spread. HBoV1 has also been detected in stool, but copy numbers are very low. In contrast, HBoV types 2-4 are found predominantly in the stool, but host cell types are not known.

Clinical Manifestations

Parvovirus B19

Many infections are clinically inapparent. Infected children characteristically demonstrate the rash illness of erythema infectiosum. Adults, especially women, frequently experience acute polyarthropathy with or without a rash.

Erythema Infectiosum (Fifth Disease)

The most common manifestation of B19V is erythema infectiosum, also known as *fifth disease* , which is a benign, self-limited exanthematous illness of childhood.

The incubation period for erythema infectiosum is 4-28 days (average: 16-17 days). The prodromal phase is mild and consists of low-grade fever in 15–30% of cases, headache, and symptoms of mild upper respiratory tract infection. The hallmark of erythema infectiosum is the characteristic rash, which occurs in 3 stages that are not always distinguishable. The initial stage is an erythematous facial flushing, often described as a **slapped-cheek appearance** (Fig. 278.1). The rash spreads rapidly or concurrently to the trunk and proximal extremities as a diffuse macular erythema in the second stage. Central clearing of macular lesions occurs promptly, giving the rash a **lacy, reticulated appearance** (Fig. 278.2). The rash tends to be more prominent on extensor surfaces, sparing the palms and soles. Affected children are afebrile and do not appear ill. Some have petechiae. Older children and adults often complain of mild pruritus. The rash resolves spontaneously without desquamation, but tends to wax and wane over 1-3 wk. It can recur with exposure to sunlight, heat, exercise, and stress. Lymphadenopathy and atypical papular, purpuric, vesicular rashes are also described.

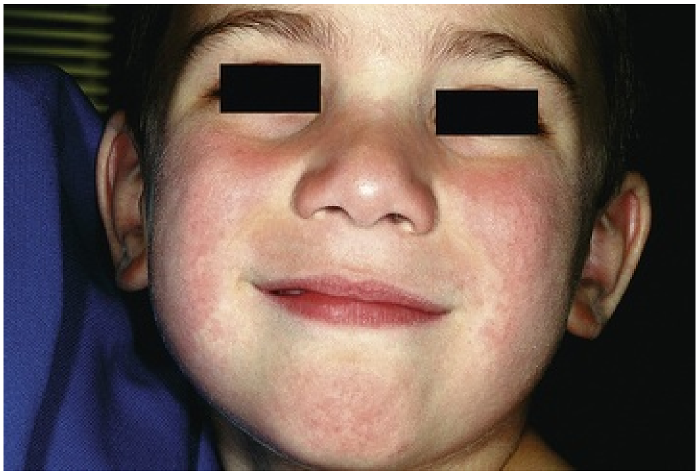

FIG. 278.1 Erythema infectiosum. Erythema of the bilateral cheeks, which has been likened to a "slapped-cheek" appearance. (From Paller AS, Macini AJ: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, WB Saunders, p. 431.)

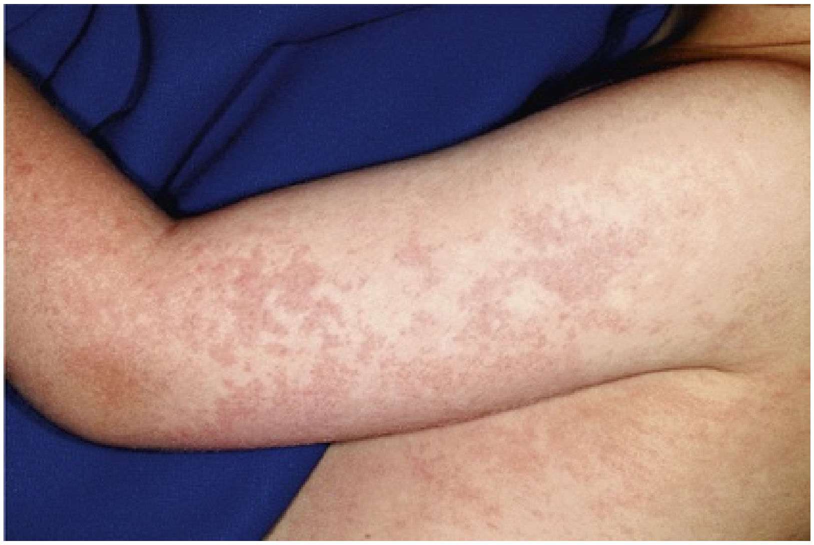

FIG. 278.2 Erythema infectiosum. Reticulate erythema on the upper arm of a patient with erythema infectiosum. (From Paller AS, Macini AJ: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, WB Saunders, p. 431.)

Arthropathy

Arthritis and arthralgia may occur in isolation or with other symptoms. Joint symptoms are much more common among adults and older adolescents with B19V infection. Females are affected more frequently than males. In 1 large outbreak of fifth disease, 60% of adults and 80% of adult women reported joint symptoms. Joint symptoms range from diffuse polyarthralgia with morning stiffness to frank arthritis. The joints most often affected are the hands, wrists, knees, and ankles, but practically any joint may be affected. The joint symptoms are self-limited and, in the majority of patients, resolve within 2-4 wk. Some patients may have a prolonged course of many months, suggesting rheumatoid arthritis. Transient rheumatoid factor positivity is reported in some of these patients but with no joint destruction.

Transient Aplastic Crisis

The transient arrest of erythropoiesis and absolute reticulocytopenia induced by B19V infection leads to a sudden fall in serum hemoglobin in individuals with chronic hemolytic conditions. This B19V-induced RBC aplasia or transient aplastic crisis occurs in patients with all types of chronic hemolysis and/or rapid RBC turnover, including sickle cell disease, thalassemia, hereditary spherocytosis, and pyruvate kinase deficiency. In contrast to children with erythema infectiosum only, patients with aplastic crisis are ill with fever, malaise, and lethargy and have signs and symptoms of profound anemia, including pallor, tachycardia, and tachypnea. Rash is rarely present. The incubation period for transient aplastic crisis is shorter than that for erythema infectiosum because the crisis occurs coincident with the viremia. Children with sickle cell hemoglobinopathies may also have a concurrent vasoocclusive pain crisis, further confusing the clinical presentation.

Immunocompromised Persons

Persons with impaired humoral immunity are at risk for chronic B19V infection. Chronic anemia is the most common manifestation, sometimes accompanied by neutropenia, thrombocytopenia, or complete marrow suppression. Chronic infections occur in persons receiving cancer chemotherapy or immunosuppressive therapy for transplantation and persons with congenital immunodeficiencies, AIDS, and functional defects in IgG production who are thereby unable to generate neutralizing antibodies.

Fetal Infection

Primary maternal infection is associated with nonimmune fetal hydrops and intrauterine fetal demise, with the risk for fetal loss after infection estimated at 2–5%. The mechanism of fetal disease appears to be a viral-induced RBC aplasia at a time when the fetal erythroid fraction is rapidly expanding, leading to profound anemia, high-output cardiac failure, and fetal hydrops. Viral DNA has been detected in infected abortuses. The second trimester seems to be the most sensitive period, but fetal losses are reported at every stage of gestation. If maternal B19V infection is suspected, fetal ultrasonography and measurement of the peak systolic flow velocity of the middle cerebral artery are sensitive, noninvasive procedures to diagnose fetal anemia and hydrops. Most infants infected in utero are born normally at term, including some who have had ultrasonographic evidence of hydrops. A small subset of infants infected in utero may acquire a chronic or persistent postnatal infection with B19V that is of unknown significance. Congenital anemia associated with intrauterine B19V infection has been reported in a few cases, sometimes following intrauterine hydrops. This process may mimic other forms of congenital hypoplastic anemia (e.g., Diamond-Blackfan syndrome). Fetal infection with B19V has been associated with bone lesions but has not been associated with other birth defects. B19V is only 1 of many causes of hydrops fetalis (see Chapter 124.2).

Myocarditis

B19V infection has been associated with myocarditis in fetuses, infants, children, and a few adults. Diagnosis has often been based on serologic findings suggestive of a concurrent B19V infection, but in many cases B19V DNA has been demonstrated in cardiac tissue. B19-related myocarditis is plausible because fetal myocardial cells are known to express P antigen, the cell receptor for the virus. In the few cases in which histology is reported, a predominantly lymphocytic infiltrate is described. Outcomes have varied from complete recovery to chronic cardiomyopathy to fatal cardiac arrest. Although B19-associated myocarditis seems to be a rare occurrence, there appears to be enough evidence to consider B19V as a potential cause of lymphocytic myocarditis, especially in infants and immunocompromised persons.

Other Cutaneous Manifestations

A variety of atypical skin eruptions have been reported with B19V infection. Most of these are petechial or purpuric in nature, often with evidence of vasculitis on biopsy. Among these rashes, the **papular-purpuric gloves-and-socks syndrome (PPGSS)** is well established in the dermatologic literature as distinctly associated with B19V infection (Fig. 278.3). PPGSS is characterized by fever, pruritus, and painful edema and erythema localized to the distal extremities in a distinct gloves-and-socks distribution, followed by acral petechiae and oral lesions. The syndrome is self-limited and resolves within a few weeks. Although PPGSS was initially described in young adults, a number of reports of the disease in children have since been published. In those cases linked to B19V infection, the eruption is accompanied by serologic evidence of acute infection. Generalized petechiae have also been reported.

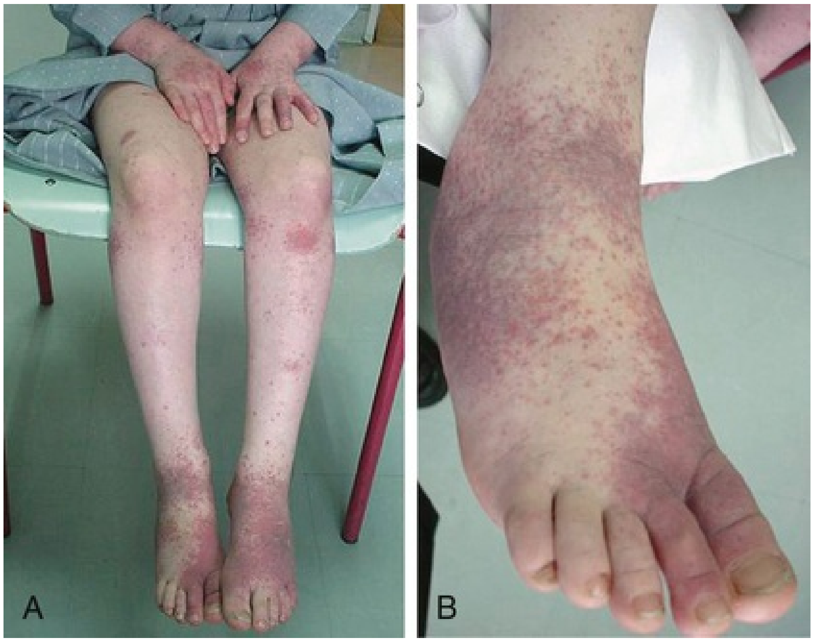

FIG. 278.3 Photographs revealing the petechial rash on the extremities **(A)** that was sharply demarcated on the ankles **(B)** in a 6 yr old child. (From Parez N, Dehee A, Michel Y, et al: Papular-purpuric gloves and socks syndrome associated with B19V infection in a 6-yr-old child. *J Clin Virol* 44:167–169, 2009, Fig. 1.)

Human Bocaviruses

Many studies have reported an association between respiratory tract infection and HBoV1 infection as detected by PCR of respiratory secretions, primarily nasopharyngeal secretions. Clinical manifestations in these studies have ranged from mild upper respiratory symptoms to pneumonia. However, the role of HBoV1 as a pathogen has been challenged by the detection of the virus in asymptomatic children and by the frequent detection of other respiratory viruses in the same samples. Nonetheless, studies that have included some combination of quantitative PCR, serum PCR, and serology have been more convincing about HBoV1 as a human pathogen. The use of a quantitative PCR method also seems to differentiate between HBoV1 infection (and wheezing) and prolonged viral shedding, as patients with higher viral titers were more likely to be symptomatic, to be viremic, and to have HBoV1 isolated without other viruses.

HBoV type 2 DNA has been found in the stool of 3–25% of children with gastroenteritis, but often with another enteric virus. DNA of HBoV types 2, 3, and 4 has also been found in the stool of healthy, asymptomatic individuals. At present, there are few data linking HBoV2, HBoV3, or HBoV4 to gastroenteritis or any clinical illness. Further studies are required to determine if any of the HBoVs are associated with some cases of childhood gastroenteritis.

Diagnosis

Parvovirus B19 Infection

The diagnosis of erythema infectiosum is usually based on clinical presentation of the typical rash and rarely requires virologic confirmation. Similarly, the diagnosis of a typical transient aplastic crisis in a child with sickle cell disease is generally made on clinical grounds without specific virologic testing.

Serologic tests for the diagnosis of B19V infection are available. B19-specific IgM develops rapidly after infection and persists for 6-8 wk. Anti-B19 IgG serves as a marker of past infection or immunity. Determination of anti-B19 IgM is the best marker of recent/acute infection on a single serum sample; seroconversion of anti-B19 IgG antibodies in paired sera can also be used to confirm recent infection. Demonstration of anti-B19 IgG in the absence of IgM, even in high titer, is not diagnostic of recent infection.

Serologic diagnosis is unreliable in immunocompromised persons; diagnosis in these patients requires methods to detect viral DNA. Because the virus cannot be isolated by standard cell culture, methods to detect viral particles or viral DNA, such as PCR and nucleic acid hybridization, are necessary to establish the diagnosis. These tests are not widely available outside of research centers or reference laboratories. Prenatal diagnosis of B19V-induced fetal hydrops can be accomplished by detection of viral DNA in fetal blood or amniotic fluid by these methods.

Human Bocavirus Infections

HBoV1 infections cannot be differentiated from other viral respiratory infections on clinical grounds. HBoV DNA can be readily detected by PCR methods and is now included in several commercially available multiplex respiratory virus PCR assays. Quantitative PCR is useful to differentiate acute infection from persistent viral shedding, as higher viral copy numbers ($>10^4$ HBoV1 genomes/mL) correlate with acute illness, but this test is not widely available. Likewise, serologic methods to detect specific IgM and IgG antibodies have been developed, but these too are not routinely available and there are problems with cross-reactivity among antibodies to the various HBoV types. The most reliable method to diagnose HBoV1 infection would include detection of viral DNA in serum by PCR and in respiratory tract samples by quantitative PCR, with concurrent detection of IgM or a diagnostic IgG response in paired samples.

Differential Diagnosis

Parvovirus B19

The rash of erythema infectiosum must be differentiated from rubella, measles, enteroviral infections, and drug reactions. Rash and arthritis in older children should prompt consideration of juvenile rheumatoid arthritis, systemic lupus erythematosus, serum sickness, and other connective tissue disorders.

Human Bocavirus

Respiratory illness and wheezing caused by HBoV1 cannot be differentiated clinically from other common viral respiratory infections, especially respiratory syncytial virus, human metapneumovirus, rhinoviruses, enterovirus D68, and parainfluenza viruses. HBoV1 infection in young children seems to most closely resemble that of respiratory syncytial virus and human metapneumovirus, as the clinical symptoms and age ranges will overlap.

Treatment

Parvovirus B19

There is no specific antiviral therapy for B19V infection. Commercial lots of intravenous immunoglobulin (IVIG) have been used with some success to treat B19V-related episodes of anemia and bone marrow failure in immunocompromised children. Specific antibody may facilitate clearance of the virus but is not always necessary, because cessation of cytotoxic chemotherapy with subsequent restoration of immune function often suffices. In patients whose immune status is not likely to improve, such as patients with AIDS, administration of IVIG may give only a temporary remission, and periodic reinfusions may be required. In patients with AIDS, clearance of B19V infection has been reported after initiation of highly active antiretroviral therapy (HAART) without the use of IVIG.

No controlled studies have been published regarding dosing of IVIG for B19V-induced RBC aplasia. Multiple case reports and limited clinical series have reported successful treatment of severe anemia secondary to chronic B19V infection utilizing several different IVIG dosing regimens. A starting dose of 400 mg/kg/day for 5 days is usually recommended. The dose and duration of IVIG may be adjusted based on the response to therapy.

B19V-infected fetuses with anemia and hydrops have been managed successfully with intrauterine RBC transfusions, but this procedure has significant attendant risks. Once fetal hydrops is diagnosed, regardless of the suspected cause, the mother should be referred to a fetal therapy center for further evaluation because of the high risk for serious complications (see Chapter 124.2).

Human Bocavirus

There is no specific antiviral therapy available. Appropriate supportive treatment for viral LRTI and pneumonia is recommended, as directed by clinical severity. For children with wheezing illness specifically caused by HBoV1 infection, there are no data examining their response to bronchodilator therapy.

Complications

Parvovirus B19

Erythema infectiosum is often accompanied by arthralgias or arthritis in adolescents and adults that may persist after resolution of the rash. B19V may rarely cause thrombocytopenic purpura. Neurologic conditions, including aseptic meningitis, encephalitis, and peripheral neuropathy, have been reported in both immunocompromised and healthy individuals in association with B19V infection. The incidence of stroke may be increased in children with sickle cell disease following B19V-induced transient aplastic crisis. B19V is also a cause of infection-associated hemophagocytic syndrome, usually in immunocompromised persons.

Human Bocavirus

There are no studies reporting on complications of HBoV1 infection. Complications of wheezing and viral pneumonia would be possible, including hypoxemia and secondary bacterial infection, among others.

Prevention

Parvovirus B19

Children with erythema infectiosum are not likely to be infectious at presentation because the rash and arthropathy represent immune-mediated, postinfectious phenomena. Isolation and exclusion from school or child care are unnecessary and ineffective after diagnosis.

Children with B19V-induced RBC aplasia, including the transient aplastic crisis, are infectious upon presentation and demonstrate a more intense viremia. Most of these children require transfusions and supportive care until their hematologic status stabilizes. They should be isolated in the hospital to prevent spread to susceptible patients and staff. Isolation should continue for at least 1 wk and until fever has resolved. Pregnant caregivers should not be assigned to these patients. Exclusion of pregnant women from workplaces where children with erythema infectiosum may be present (e.g., primary and secondary schools) is not recommended as a general policy because it is unlikely to reduce their risk. There are no data to support the use of IVIG for postexposure prophylaxis in pregnant caregivers or immunocompromised children. No vaccine is currently available, though this is a topic of ongoing research.

Human Bocavirus

There are no studies that have addressed the prevention of transmission of this infection. In the hospital setting, standard precautions should be observed to limit spread of the virus. Since HBoV1 causes respiratory infection and can be detected in respiratory secretions sometimes in very high titer, measures to limit contact with respiratory secretions should be considered, including contact and droplet isolation for severely symptomatic young children. No vaccine is available, and no other preventive measures have been reported.

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CHAPTER 279

Herpes Simplex Virus

Lawrence R. Stanberry

The 2 closely related herpes simplex viruses (HSVs), HSV type 1 (HSV-1) and HSV type 2 (HSV-2), cause a variety of illnesses, depending on the anatomic site where the infection is initiated, the immune state of the host, and whether the symptoms reflect primary or recurrent infection. Common infections involve the skin, eye, oral cavity, and genital tract. Infections tend to be mild and self-limiting, except in the immunocompromised patient and newborn infant, in whom they may be severe and life-threatening.

Primary infection occurs in individuals who have not been infected previously with either HSV-1 or HSV-2. Because these individuals are HSV seronegative and have no preexisting immunity to HSV, primary infections can be severe. **Nonprimary first infection** occurs in individuals previously infected with 1 type of HSV (e.g., HSV-1) who have become infected for the first time with the other type of HSV (in this case, HSV-2). Because immunity to 1 HSV type provides some cross-protection against disease caused by the other HSV type, nonprimary first infections tend to be less severe than true primary infections. During primary and nonprimary initial infections, HSV establishes latent infection in regional sensory ganglion neurons. Virus is maintained in this latent state for the life of the host but periodically can reactivate and cause **recurrent infection.** Symptomatic recurrent infections tend to be less severe and of shorter duration than 1st infections. Asymptomatic recurrent infections are extremely common and cause no physical distress, although patients with these infections are contagious and can transmit the virus to susceptible individuals. Reinfection with a new strain of either HSV-1 or HSV-2 at a previously infected anatomic site (e.g., the genital tract) can occur but is relatively uncommon, suggesting that host immunity, perhaps site-specific local immunity, resulting from the initial infection affords protection against exogenous reinfection.

Etiology

HSVs contain a double-stranded DNA genome of approximately 152 kb that encodes at least 84 proteins. The DNA is contained within an icosadeltahedral capsid, which is surrounded by an outer envelope composed of a lipid bilayer containing at least 12 viral glycoproteins. These glycoproteins are the major targets for humoral immunity, whereas other nonstructural proteins are important targets for cellular immunity. Two encoded proteins, viral DNA polymerase and thymidine kinase, are targets for antiviral drugs. HSV-1 and HSV-2 have a similar genetic composition with extensive DNA and protein homology. One important difference in the 2 viruses is their glycoprotein G genes, which have been exploited to develop a new generation of commercially available, accurate, type-specific serologic tests that can be used to discriminate whether a patient has been infected with HSV-1 or HSV-2 or both.

Epidemiology

HSV infections are ubiquitous, and there are no seasonal variations in risk for infection. The only natural host is humans, and the mode of transmission is direct contact between mucocutaneous surfaces. There are no documented incidental transmissions from inanimate objects such as toilet seats.

All infected individuals harbor latent infection and experience recurrent infections, which may be symptomatic or may go unrecognized and thus are periodically contagious. This information helps explain the widespread prevalence of HSV.

HSV-1 and HSV-2 are equally capable of causing initial infection at any anatomic site but differ in their capacity to cause recurrent infections. HSV-1 has a greater propensity to cause recurrent oral infections, whereas HSV-2 has a greater proclivity to cause recurrent genital infections. For this reason, HSV-1 infection typically results from contact with contaminated oral secretions, whereas HSV-2 infection most commonly results from anogenital contact.

HSV seroprevalence rates are highest in developing countries and among lower socioeconomic groups, although high rates of HSV-1 and HSV-2 infections are found in developed nations and among persons of the highest socioeconomic strata. Incident HSV-1 infections are more common during childhood and adolescence but are also found throughout later life. Data from the U.S. population–based National Health and Nutrition Examination Survey conducted between 1999 and 2004 showed a consistent increase of HSV-1 prevalence with age, which rose from 39% in adolescents 14-19 yr of age to 65% among those 40-49 yr of age. HSV-1 seroprevalence was not influenced by gender, but rates were highest in Mexican-Americans (80.8%), intermediate in non-Hispanic blacks (68.3%), and lowest in non-Hispanic whites (50.1%). The National Health and Nutrition Examination Survey study conducted between 2007 and 2010 found an overall HSV-2 prevalence of 15.5%, with a steady increase with age from 1.5% in the 14-19 yr old age group to 25.6% in the 40-49 yr old group. The rate was higher among females than males (20.3% and 10.6%, respectively) and varied by race and ethnic group, with an overall seroprevalence of 41.8% in non-Hispanic blacks, 11.3% in Mexican-Americans, and 11.3% in whites. Modifiable factors that predict HSV-2 seropositivity include less education, poverty, cocaine use, and a greater lifetime number of sexual partners. Studies show that only approximately 10–20% of HSV-2–seropositive subjects report a history of genital herpes, emphasizing the asymptomatic nature of most HSV infections.

A 3 yr longitudinal study of Midwestern adolescent females 12-15 yr of age found that 44% were seropositive for HSV-1 and 7% for HSV-2 at enrollment. At the end of the study, 49% were seropositive for HSV-1 and 14% for HSV-2. The attack rates, based on the number of cases per 100 person-years, were 3.2 for HSV-1 infection among all females and 4.4 for HSV-2 infection among girls who reported being sexually experienced. Findings of this study indicate that sexually active young women have a high attack rate for genital herpes and suggest that genital herpes should be considered in the differential diagnosis of any young woman who reports recurrent genitourinary complaints. In this study, participants with preexisting HSV-1 antibodies had a significantly lower attack rate for HSV-2 infection, and those who became infected were less likely to have symptomatic disease than females who were HSV seronegative when they entered the study. Prior HSV-1 infection appears to afford adolescent females some protection against becoming infected with HSV-2; in adolescent females infected with HSV-2, the preexisting HSV-1 immunity appears to protect against development of symptomatic genital herpes.

Neonatal herpes is an uncommon but potentially fatal infection of the fetus or more likely the newborn. It is not a reportable disease in most states, and therefore there are no solid epidemiologic data regarding its frequency in the general population. In King County, Washington, the estimated incidence of neonatal herpes was 2.6 cases per 100,000 live births in the late 1960s, 11.9

cases per 100,000 live births from 1978 to 1981, and 31 cases per 100,000 live births from 1982 to 1999. This increase in neonatal herpes cases parallels the increase in cases of genital herpes. The estimated rate of neonatal herpes is 1 per 3,000-5,000 live births, which is higher than reported for the reportable perinatally acquired sexually transmitted infections such as congenital syphilis and gonococcal ophthalmia neonatorum. More than 90% of the cases are the result of maternal-child transmission. The risk for transmission is greatest during a primary or nonprimary first infection (30–50%) and much lower when the exposure is during a recurrent infection (<2%). HSV viral suppression therapy in mothers does not consistently eliminate the possibility of neonatal infection. Infants born to mothers dually infected with HIV and HSV-2 are also at higher risk for acquiring HIV than infants born to HIV-positive mothers who are not HSV-2 infected. It is estimated that approximately 25% of pregnant women are HSV-2 infected and that approximately 2% of pregnant women acquire HSV-2 infection during pregnancy.

HSV is a leading cause of sporadic, fatal encephalitis in children and adults. In the United States the annual hospitalization rate for HSV encephalitis has been calculated to be 10.3 ± 2.2 cases/million in neonates, 2.4 ± 0.3 cases/million in children, and 6.4 ± 0.4 cases/million in adults.

Pathogenesis

In the immunocompetent host the pathogenesis of HSV infection involves viral replication in skin and mucous membranes followed by replication and spread in neural tissue. Viral infection typically begins at a cutaneous portal of entry such as the oral cavity, genital mucosa, ocular conjunctiva, or breaks in keratinized epithelia. Virus replicates locally, resulting in the death of the cell, and sometimes produces clinically apparent inflammatory responses that facilitate the development of characteristic herpetic vesicles and ulcers. Virus also enters nerve endings and spreads beyond the portal of entry to sensory ganglia by intraneuronal transport. Virus replicates in some sensory neurons, and the progeny virions are sent via intraneuronal transport mechanisms back to the periphery, where they are released from nerve endings and replicate further in skin or mucosal surfaces. It is virus moving through this neural arc that is primarily responsible for the development of characteristic herpetic lesions, although most HSV infections do not reach a threshold necessary to cause clinically recognizable disease. Although many sensory neurons become productively infected during the initial infection, some infected neurons do not initially support viral replication. It is in these neurons that the virus establishes a latent infection, a condition in which the viral genome persists within the neuronal nucleus in a largely metabolically inactive state. Intermittently throughout the life of the host, undefined changes can occur in latently infected neurons that trigger the virus to begin to replicate. This replication occurs despite the host's having established a variety of humoral and cellular immune responses that successfully controlled the initial infection. With reactivation of the latent neuron, progeny virions are produced and transported within nerve fibers back to cutaneous sites somewhere in the vicinity of the initial infection, where further replication occurs and causes recurrent infections. Recurrent infections may be symptomatic (with typical or atypical herpetic lesions) or asymptomatic. In either case, virus is shed at the site where cutaneous replication occurs and can be transmitted to susceptible individuals who come in contact with the site or with contaminated secretions. Latency and reactivation are the mechanisms by which the virus is successfully maintained in the human population.

Viremia, or hematogenous spread of the virus, does not appear to play an important role in HSV infections in the immunocompetent host but can occur in neonates, individuals with eczema, and severely malnourished children. It is also seen in patients with depressed or defective cell-mediated immunity, as occurs with HIV infection or some immunosuppressive therapies. Viremia can result in dissemination of the virus to visceral organs, including the liver and adrenals. Hematogenous dissemination of virus to the central nervous system appears to only occur in neonates.

The pathogenesis of HSV infection in newborns is complicated by their relative immunologic immaturity. The source of virus in neonatal infections is typically but not exclusively the mother. Transmission generally occurs during delivery, although it is well documented to occur even with cesarean delivery with intact fetal membranes. The most common portals of entry are the conjunctiva, mucosal epithelium of the nose and mouth, and breaks or abrasions in the skin that occur with scalp electrode use or forceps delivery. With prompt antiviral therapy, virus replication may be restricted to the site of inoculation (the skin, eye, or mouth). However, virus may also extend from the nose to the respiratory tract to cause pneumonia, move via intraneuronal transport to the central nervous system to cause encephalitis, or spread by hematogenous dissemination to visceral organs and the brain. Factors that may influence neonatal HSV infection include the virus type, portal of entry, inoculum of virus to which the infant is exposed, gestational age of the infant, and presence of maternally derived antibodies specific to the virus causing infection. Latent infection is established during neonatal infection, and survivors may experience recurrent cutaneous and neural infections. Persistent central nervous system infection may impact the neurodevelopment of the infant.

Clinical Manifestations

The hallmarks of common HSV infections are skin vesicles and shallow ulcers. Classic infections manifest as small, 2-4 mm vesicles that may be surrounded by an erythematous base. These may persist for a few days before evolving into shallow, minimally erythematous ulcers. The vesicular phase tends to persist longer when keratinized epithelia is involved and is generally brief and sometimes just fleeting when moist mucous membranes are the site of infection. Because HSV infections are common and their natural history is influenced by many factors, including portal of entry, immune status of the host, and whether it is an initial or recurrent infection, the typical manifestations are seldom classic. Most infections are asymptomatic or unrecognized, and nonclassic presentations, such as small skin fissures and small erythematous nonvesicular lesions, are common.

Acute Oropharyngeal Infections

Herpes gingivostomatitis most often affects children 6 mo to 5 yr of age but is seen across the age spectrum. It is an extremely painful condition with sudden onset, pain in the mouth, drooling, refusal to eat or drink, and fever of up to 40.0-40.6°C (104-105.1°F). The gums become markedly swollen, and vesicles may develop throughout the oral cavity, including the gums, lips, tongue, palate, tonsils, pharynx, and perioral skin (Fig. 279.1). The vesicles may be more extensively distributed than typically seen with enteroviral herpangina. During the initial phase of the illness there may be tonsillar exudates suggestive of bacterial pharyngitis. The vesicles are generally present only a few days before progressing to form shallow indurated ulcers that may be covered with a yellow-gray membrane. Tender submandibular, submaxillary, and cervical lymphadenopathy is common. The breath may be foul as a result of overgrowth of anaerobic oral bacteria. Untreated, the illness resolves in 7-14 days, although the lymphadenopathy may persist for several weeks.

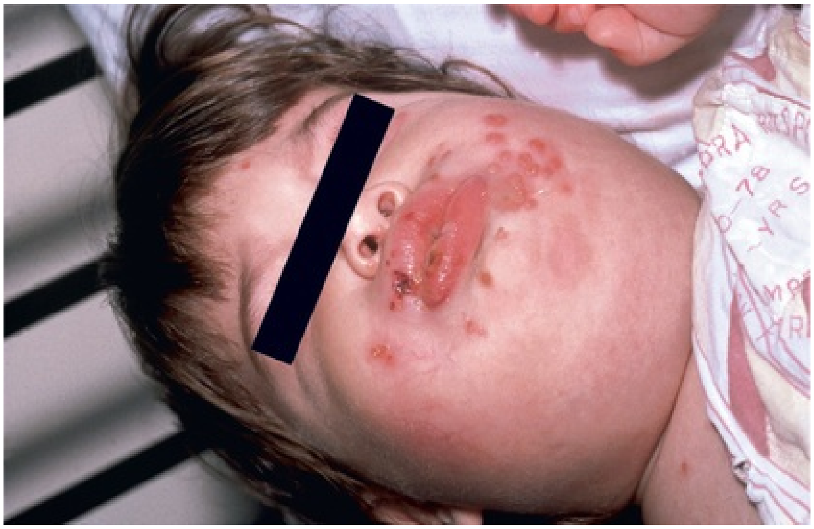

FIG. 279.1 Clustered perioral vesicles and erosions in an infant with primary herpetic gingivostomatitis. (From Schachner LA, Hansen RC, editors: *Pediatric dermatology,* ed 3, Philadelphia, 1988, Mosby, p. 1078.)

In older children, adolescents, and college students, the initial HSV oral infection may manifest as pharyngitis and tonsillitis rather than gingivostomatitis. The vesicular phase is often over by the time the patient presents to a healthcare provider, and signs and symptoms may be indistinguishable from those of streptococcal pharyngitis, consisting of fever, malaise, headache, sore throat, and white plaques on the tonsils. The course of illness is typically longer than for untreated streptococcal pharyngitis.

Herpes Labialis

Fever blisters (cold sores) are the most common manifestation of *recurrent* HSV-1 infections. The most common site of herpes labialis is the vermilion border of the lip, although lesions sometimes occur on the nose, chin, cheek, or oral mucosa. Older patients report experiencing burning, tingling, itching, or pain 3-6 hr (rarely as long as 24-48 hr) before the development of the herpes lesion. The lesion generally begins as a small grouping of erythematous papules that over a few hours progress to create a small, thin-walled vesicle. The vesicles may form shallow ulcers or become pustular. The short-lived ulcer dries and develops a crusted scab. Complete healing without scarring occurs with reepithelialization of the ulcerated skin, usually within 6-10 days. Some patients experience local lymphadenopathy but no constitutional symptoms.

Cutaneous Infections

In the healthy child or adolescent, cutaneous HSV infections are generally the result of skin trauma with macro or micro abrasions and exposure to infectious secretions. This situation most often occurs in play or contact sports such as wrestling (**herpes gladiatorum**) and rugby (**scrum pox**). An initial cutaneous infection establishes a latent infection that can subsequently result in recurrent infections at or near the site of the initial infection. Pain, burning, itching, or tingling often precedes the herpetic eruption by a few hours to a few days. Like herpes labialis, lesions begin as grouped, erythematous papules that progress to vesicles, pustules, ulcers, and crusts and then heal without scarring in 6-10 days. Although herpes labialis typically results in a single lesion, a cutaneous HSV infection results in multiple discrete lesions and involves a larger surface area. Regional lymphadenopathy may occur but systemic symptoms are uncommon. Recurrences are sometimes associated with local edema and lymphangitis or local neuralgia.

Herpes whitlow is a term generally applied to HSV infection of fingers or toes, although strictly speaking it refers to HSV infection of the paronychia. Among children, this condition is most commonly seen in infants and toddlers who suck the thumb or fingers and who are experiencing either a symptomatic or a subclinical oral HSV-1 infection (Fig. 279.2). An HSV-2 herpes whitlow occasionally develops in an adolescent as a result of exposure to infectious genital secretions. The onset of the infection is heralded by itching, pain, and erythema 2-7 days after exposure. The cuticle becomes erythematous and tender and may appear to contain pus, although if it is incised, little fluid is present. Incising the lesion is discouraged, as this maneuver typically prolongs recovery and increases the risk for secondary bacterial infection. Lesions and associated pain typically persist for about 10 days, followed by rapid improvement and complete recovery in 18-20 days. Regional lymphadenopathy is common, and lymphangitis and neuralgia may occur. Unlike other recurrent herpes infections, recurrent herpetic whitlows are often as painful as the primary infection but are generally shorter in duration.

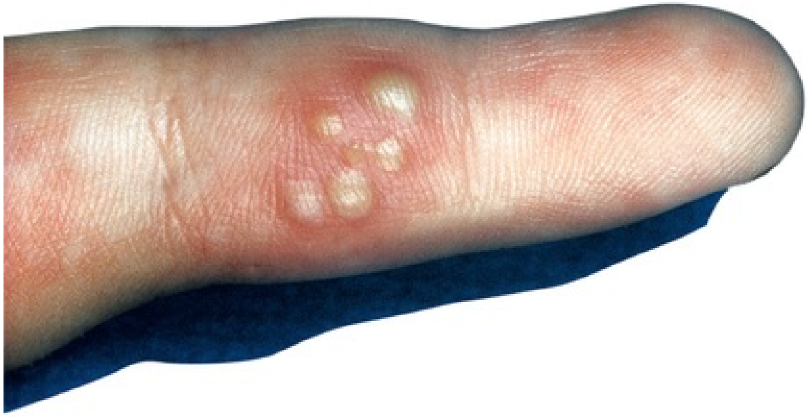

FIG. 279.2 Herpes simplex infection of finger (whitlow). (From Schachner LA, Hansen RC, editors: *Pediatric dermatology,* ed 3, Philadelphia, 1988, Mosby, p. 1079.)

Cutaneous HSV infections can be severe or life-threatening in patients with disorders of the skin such as eczema (eczema herpeticum), pemphigus, burns, and Darier disease and following laser skin resurfacing. The lesions are frequently ulcerative and nonspecific in appearance, although typical vesicles may be seen in adjacent normal skin (Fig. 279.3). If untreated, these lesions can progress to disseminated infection and death. Recurrent infections are common but generally less severe than the initial infection.

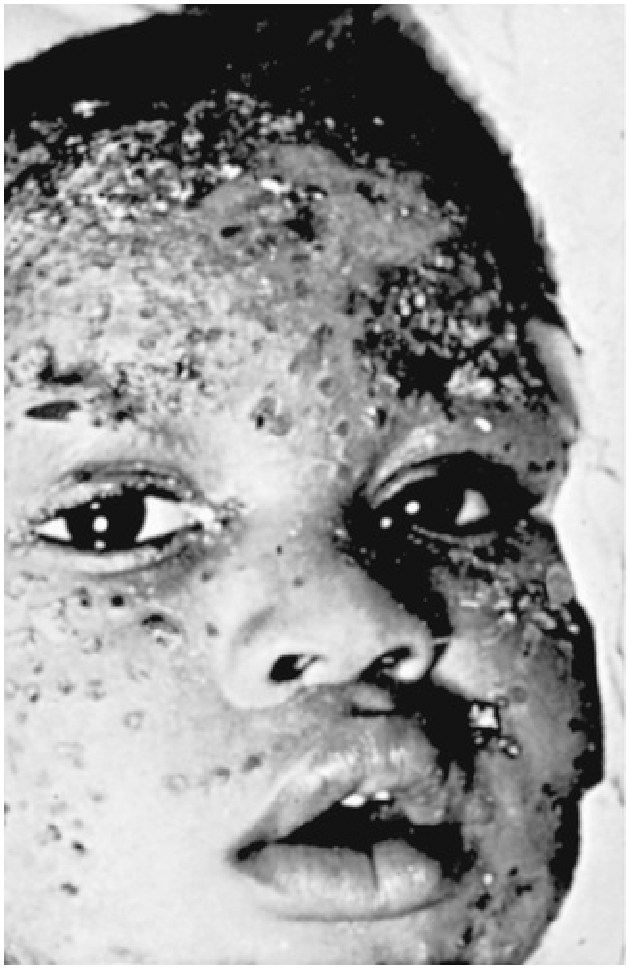

FIG. 279.3 Widespread cutaneous herpes infection in a child with underlying eczema (eczema herpeticum).

Genital Herpes

Genital HSV infection is common in sexually experienced adolescents and young adults, but up to 90% of infected individuals are *unaware* they are infected. Infection may result from genital-genital transmission (usually HSV-2) or oral-genital transmission (usually HSV-1). Symptomatic and asymptomatic individuals periodically shed virus from anogenital sites and hence can transmit the infection to sexual partners or, in the case of pregnant women, to their newborns. Classic primary genital herpes may be preceded by a short period of local burning and tenderness before vesicles develop on genital mucosal surfaces or keratinized skin and sometimes around the anus or on the buttocks and thighs. Vesicles on mucosal surfaces are short lived and rupture to produce shallow, tender ulcers covered with a yellowish gray exudate and surrounded by an erythematous border. Vesicles on keratinized epithelium persist for a few days before progressing to the pustular stage and then crusting.

Patients may experience urethritis and dysuria severe enough to cause urinary retention and bilateral, tender inguinal and pelvic lymphadenopathy. Women may experience a watery vaginal discharge, and men may have a clear mucoid urethral discharge. Significant local pain and systemic symptoms such as fever, headache, and myalgia are common. Aseptic meningitis develops in an estimated 15% of cases. The course of classic primary genital herpes from onset to complete healing is 2-3 wk.

Most patients with symptomatic primary genital herpes experience at least 1 recurrent infection in the following year. Recurrent genital herpes is usually less severe and of shorter duration than the primary infection. Some patients experience a sensory prodrome with pain, burning, and tingling at the site where vesicles subsequently develop. Asymptomatic recurrent anogenital HSV infections are common, and all HSV-2–seropositive individuals appear to periodically shed virus from anogenital sites. *Most sexual transmissions and maternal-neonatal transmissions of virus result from asymptomatic shedding episodes.*

Genital infections caused by HSV-1 and HSV-2 are indistinguishable, but HSV-1 causes significantly fewer subsequent episodes of recurrent infection; hence, knowing which virus is causing the infection has important prognostic value. Genital HSV infection increases the risk for acquiring HIV infection.

Rarely, genital HSV infections are identified in young children and preadolescents. Although genital disease in children should raise concerns about possible sexual abuse, there are documented cases of autoinoculation, in which a child has inadvertently transmitted virus from contaminated oral secretions to his or her own genitalia.

Ocular Infections

HSV ocular infections may involve the conjunctiva, cornea, or retina and may be primary or recurrent. Conjunctivitis or keratoconjunctivitis is usually unilateral and is often associated with blepharitis and tender preauricular lymphadenopathy. The conjunctiva appears edematous but there is rarely purulent discharge. Vesicular lesions may be seen on the lid margins and periorbital skin. Patients typically have fever. Untreated infection generally resolves in 2-3 wk. Obvious corneal involvement is rare, but when it occurs it can produce ulcers that are described as appearing dendritic or geographic. Extension to the stroma is uncommon although more likely to occur in patients inadvertently treated with corticosteroids. When it occurs, it may be associated with corneal edema, scarring, and corneal perforation. Recurrent infections tend to involve the underlying stroma and can cause progressive corneal scarring and injury that can lead to blindness.

Retinal infections are rare and are more likely among infants with neonatal herpes and immunocompromised persons with disseminated HSV infections.

Central Nervous System Infections

HSV encephalitis is the leading cause of sporadic, nonepidemic encephalitis in children and adults in the United States. It is an acute necrotizing infection generally involving the frontal and/or temporal cortex and the limbic system and, beyond the neonatal period, is almost always caused by HSV-1. The infection may manifest as nonspecific findings, including fever, headache, nuchal rigidity, nausea, vomiting, generalized seizures, and alteration of consciousness. Injury to the frontal or temporal cortex or limbic system may produce findings more indicative of HSV encephalitis, including anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations, and focal seizures. The untreated infection progresses to coma and death in 75% of cases. Examination of the cerebrospinal fluid (CSF) typically shows a moderate number of mononuclear cells and polymorphonuclear leukocytes, a mildly elevated protein concentration, a normal or slightly decreased glucose concentration, and often a moderate number of erythrocytes. HSV has also been associated with autoimmune encephalitis (see Chapter 616.4).

HSV is also a cause of aseptic meningitis and is the most common cause of recurrent aseptic meningitis (**Mollaret meningitis**).

Infections in Immunocompromised Persons

Severe, life-threatening HSV infections can occur in patients with compromised immune functions, including neonates, the severely malnourished, those with primary or secondary immunodeficiency diseases (including AIDS), and those receiving some immunosuppressive regimens, particularly for cancer and organ transplantation. Mucocutaneous infections, including mucositis and esophagitis, are most common, although their presentations may be atypical and can result in lesions that slowly enlarge, ulcerate, become necrotic, and extend to deeper tissues. Other HSV infections include tracheobronchitis, pneumonitis, and anogenital infections. Disseminated infection can result in a sepsis-like presentation, with liver and adrenal involvement, disseminated intravascular coagulopathy, and shock.

Perinatal Infections

HSV infection may be acquired in utero, during the birth process, or during the neonatal period. Intrauterine and postpartum infections are well described but occur infrequently. Postpartum transmission may be from the mother or another adult with a nongenital (typically HSV-1) infection such as herpes labialis. Most cases of neonatal herpes result from maternal infection and transmission, usually during passage through an infected birth canal of a mother with asymptomatic genital herpes. Transmission is well documented in infants delivered by cesarean section. Fewer than 30% of mothers of an infant with neonatal herpes have a history of genital herpes. The risk for infection is higher in infants born to mothers with primary genital infection (>30%) than with recurrent genital infection (<2%). Use of scalp electrodes may also increase risk. There also have been rare cases of neonatal herpes associated with Jewish ritual circumcisions, but only with ritual oral contact with the circumcision site.

Neonatal HSV infection is thought to never be asymptomatic. Its clinical presentation reflects timing of infection, portal of entry, and extent of spread. Infants with **intrauterine infection** typically have skin vesicles or scarring, eye findings including chorioretinitis and keratoconjunctivitis, and microcephaly or hydranencephaly that are present at delivery. Few infants survive without therapy, and those who do generally have severe sequelae. Infants infected during delivery or the postpartum period present with 1 of the following 3 patterns of disease: (1) disease localized to the skin, eyes, or mouth; (2) encephalitis with or without skin, eye, and mouth disease; and (3) disseminated infection involving multiple organs, including the brain, lungs, liver, heart, adrenals, and skin (Fig. 279.4). Approximately 20% present between 5 and 9 wk of age.

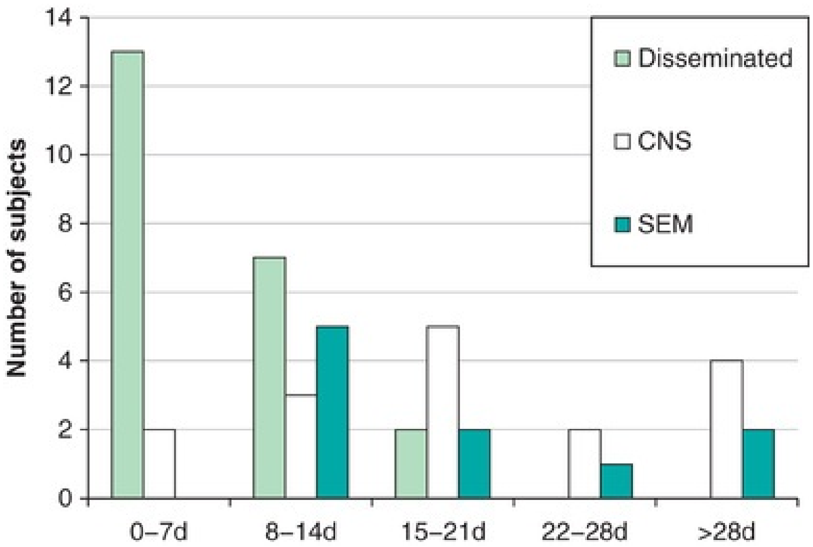

FIG. 279.4 Herpes simplex virus (HSV). Age at presentation by HSV disease type. (From Curfman AL, Glissmeyer EW, Ahmad FA, et al: Initial presentation of neonatal herpes simplex virus infection, *J Pediatr* 172:121–126, 2016, p. 124).

Infants with **skin, eye, and mouth disease** generally present at 5-11 days of life and typically demonstrate a few small vesicles, particularly on the presenting part or at sites of trauma such as sites of scalp electrode placement. If untreated, skin, eye, and mouth disease in infants may progress to encephalitis or disseminated disease.

Infants with encephalitis typically present at 8-17 days of life with clinical findings suggestive of bacterial meningitis, including irritability, lethargy, poor feeding, poor tone, and seizures. Fever is relatively uncommon, and skin vesicles occur in only approximately 60% of cases (Fig. 279.5). If untreated, 50% of infants with HSV encephalitis die and most survivors have severe neurologic sequelae.

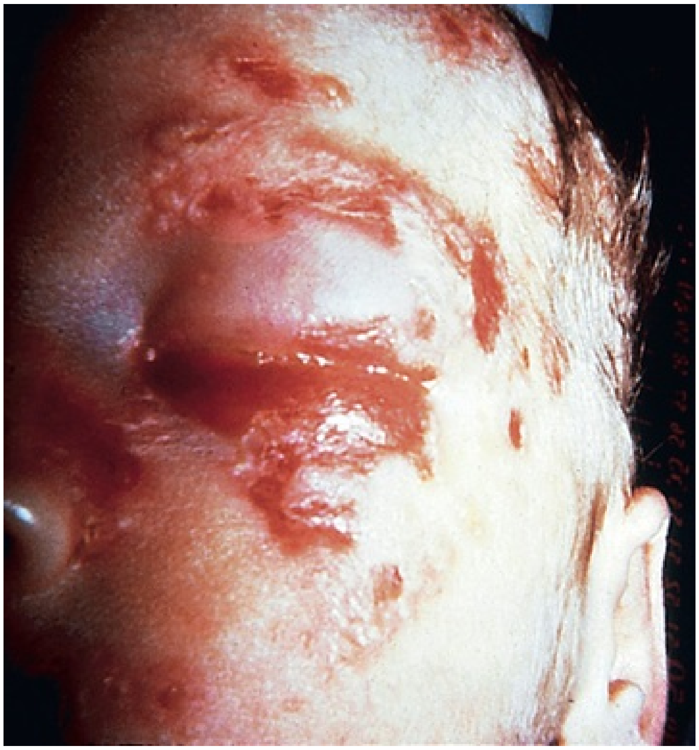

FIG. 279.5 Vesicular-pustular lesions on the face of a neonate with herpes simplex virus infection. (From Kohl S: Neonatal herpes simplex virus infection, *Clin Perinatol* 24:129–150, 1997.)

Infants with disseminated HSV infections generally become ill at 5-11 days of life. Their clinical picture is similar to that of infants with bacterial sepsis, consisting of hyperthermia or hypothermia, irritability, poor feeding, and vomiting. They may also exhibit respiratory distress, cyanosis, apneic spells, jaundice, purpuric rash, and evidence of central nervous system infection; seizures are common. Skin vesicles are seen in approximately 75% of cases. If untreated, the infection causes shock and disseminated intravascular coagulation; approximately 90% of these infants die, and most survivors have severe neurologic sequelae.

Infants with neonatal herpes whose mothers received antiherpes antiviral drugs in the weeks prior to delivery may present later than their untreated counterparts; whether the natural history of the infection in these infants is different is an unanswered question.

Diagnosis

The clinical diagnosis of HSV infections, particularly life-threatening infections and genital herpes, should be confirmed by laboratory test, preferably isolation of virus or detection of viral DNA by polymerase chain reaction (PCR). Histologic findings or imaging studies may support the diagnosis but should not substitute for virus-specific tests. HSV immunoglobulin M tests are notoriously unreliable, and the demonstration of a 4-fold or greater rise in HSV-specific immunoglobulin G titers between acute and convalescent serum samples is useful only in retrospect.

The highest yield for virus cultures comes from rupturing a suspected herpetic vesicle and vigorously rubbing the base of the lesion to collect fluid and cells. Culturing dried, crusted lesions is generally of low yield. Although not as sensitive as viral culture, direct detection of HSV antigens in clinical specimens can be done rapidly and has very good specificity. The use of DNA amplification methods such as PCR for detection of HSV DNA is highly sensitive and specific and in some instances can be performed rapidly. It is the test of choice in examining CSF in cases of suspected HSV encephalitis.

Evaluation of the neonate with suspected HSV infection should include cultures of suspicious lesions as well as eye and mouth swabs and PCR of both CSF and blood. In neonates testing for elevation of liver enzymes may provide indirect evidence of HSV dissemination to visceral organs. Culture or antigen detection should be used in evaluating lesions associated with suspected acute genital herpes. HSV-2 type-specific antibody tests are useful for evaluating sexually experienced adolescents or young adults who have a history of unexplained recurrent nonspecific urogenital signs and symptoms, but these tests are less useful for general screening in populations in which HSV-2 infections are of low prevalence.

Because most HSV diagnostic tests take at least a few days to complete, treatment should not be withheld but rather initiated promptly so as to ensure the maximum therapeutic benefit.

Laboratory Findings

Most self-limited HSV infections cause few changes in routine laboratory parameters. Mucocutaneous infections may cause a moderate polymorphonuclear leukocytosis. In HSV meningoencephalitis there can be an increase in mononuclear cells and protein in CSF, the glucose content may be normal or reduced, and red blood cells may be present. The electroencephalogram and MRI of the brain may show temporal lobe abnormalities in HSV encephalitis beyond the neonatal period. Encephalitis in the neonatal period tends to be more global and not limited to the temporal lobe (Fig. 279.6). Disseminated infection may cause elevated liver enzymes, thrombocytopenia, and abnormal coagulation.

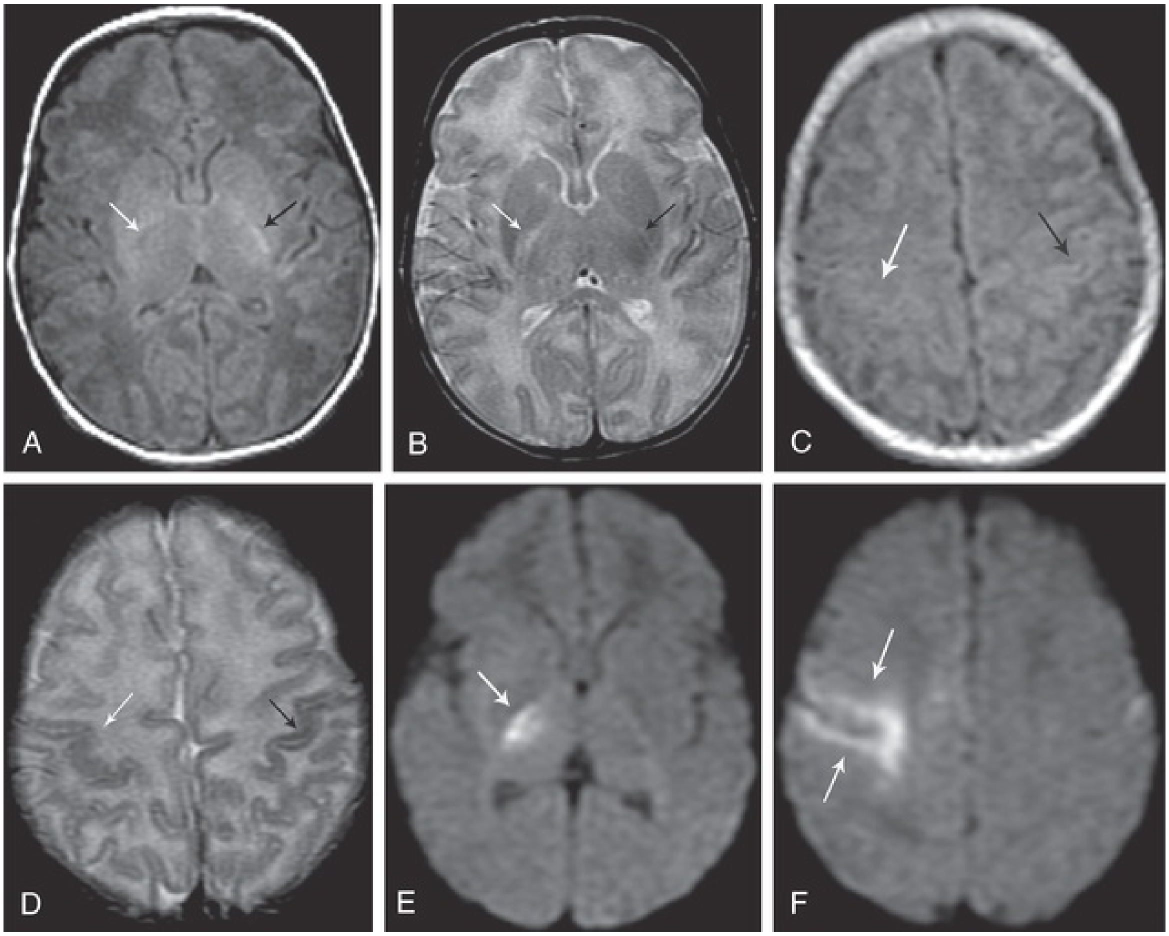

FIG. 279.6 **Involvement of corticospinal tract and thalamus in a 2 wk old infant. A, MRI with axial T1-weighted image demonstrating subtle loss of T1 hyperintensity corresponding to myelination in the posterior limb of the right internal capsule *(white arrow).* T1 hyperintensity in the left posterior limb of the internal capsule is maintained *(black arrow).* B, T2-weighted image showing findings similar to those seen on T1-weighted imaging. C, Axial T1- and (D) T2-weighted images through the vertex demonstrating subtle indistinct margins of the cortex around the right central sulcus *(white arrow)* compared with the normal appearance on the left side *(black arrow).* E and F, Diffusion-weighted images with more extensive diffusion restriction in the posterior limb of the right internal capsule and lateral thalamus *(arrows),* and in the right pre- and postcentral gyrus *(arrows).* (From Bajaj M, Mody S, Natarajan G: Clinical and neuroimaging findings in neonatal herpes simplex virus infection, *J Pediatr* 165:404–407, 2014, Fig. 1.)**

Treatment

See Chapter 272 for more information about principles of antiviral therapy.

Three antiviral drugs are available in the United States for the management of HSV infections, namely acyclovir, valacyclovir, and famciclovir. All 3 are available in oral form, but only acyclovir is available in a suspension form. Acyclovir has the poorest bioavailability and hence requires more frequent dosing. Valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, both have very good oral bioavailability and are dosed once or twice daily. Acyclovir and penciclovir are also available in a topical form, but these preparations provide limited or no benefit to patients with recurrent mucocutaneous HSV infections. Only acyclovir has an intravenous formulation. Early initiation of therapy results in the maximal therapeutic benefit. All 3 drugs have exceptional safety profiles and are safe to use in pediatric patients. *Doses should be modified in patients with renal impairment.*

Resistance to acyclovir and penciclovir is rare in immunocompetent persons but does occur in immunocompromised persons. Virus isolates from immunocompromised persons whose HSV infection is not responding or is worsening with acyclovir therapy should be tested for drug sensitivities. Foscarnet and cidofovir have been used in the treatment of HSV infections caused by acyclovir-resistant mutants.

Topical trifluridine and topical ganciclovir are used in the treatment of herpes keratitis.

Patients with genital herpes also require counseling to address psychosocial issues, including possible stigma, and to help them understand the natural history and management of this chronic infection.

Acute Mucocutaneous Infections

For gingivostomatitis, oral acyclovir (15 mg/kg/dose 5 times a day PO for 7 days; maximum: 1 g/day) started within 72 hr of onset reduces the severity and duration of the illness. Pain associated with swallowing may limit oral intake of infants and children, putting them at risk for dehydration. Intake should be encouraged through the use of cold beverages, ice cream, and yogurt.

For **herpes labialis,** oral treatment is superior to topical antiviral therapy. For treatment of a recurrence in adolescents, oral valacyclovir (2,000 mg bid PO for 1 day), acyclovir (200-400 mg 5 times daily PO for 5 days), or famciclovir

(1,500 mg once daily PO for 1 day) shortens the duration of the episode. Long-term daily use of oral acyclovir (400 mg bid PO) or valacyclovir (500 mg once daily PO) has been used to prevent recurrences in individuals with frequent or severe recurrences.

Anecdotal reports suggest that treatment of adolescents with **herpes gladiatorum** with oral acyclovir (200 mg 5 times daily PO for 7-10 days) or valacyclovir (500 mg bid PO for 7-10 days) at the first signs of the outbreak can shorten the course of the recurrence. For patients with a history of recurrent herpes gladiatorum, chronic daily prophylaxis with valacyclovir (500-1,000 mg daily) has been reported to prevent recurrences.

There are no clinical trials assessing the benefit of antiviral treatment for **herpetic whitlow.** High-dose oral acyclovir (1,600-2,000 mg/day divided in 2-3 doses PO for 10 days) started at the first signs of illness has been reported to abort some recurrences and reduce the duration of others in adults.

A clinical trial in adults has established the effectiveness of oral acyclovir (200 mg 5 times a day PO for 5 days) in the treatment of **eczema herpeticum;** however, serious infections should be treated with intravenous acyclovir. Oral-facial HSV infections can reactivate after cosmetic facial laser resurfacing, causing extensive disease and scarring. Treatment of adults beginning the day before the procedure with either valacyclovir (500 mg twice daily PO for 10-14 days) or famciclovir (250-500 mg bid PO for 10 days) has been reported to be effective in preventing the infections. HSV infections in **burn patients** can be severe or life-threatening and have been treated with intravenous acyclovir (10-20 mg/kg/day divided every 8 hr IV).

Antiviral drugs are not effective in the treatment of HSV-associated **erythema multiforme,** but their daily use as for herpes labialis prophylaxis prevents *reoccurrences* of erythema multiforme.

Genital Herpes

Pediatric patients, usually adolescents or young adults, with suspected first-episode genital herpes should be treated with antiviral therapy. Treatment of the initial infection reduces the severity and duration of the illness but has no effect on the frequency of subsequent recurrent infections. Treatment options for adolescents include acyclovir (400 mg tid PO for 7-10 days), famciclovir (250 mg tid PO for 7-10 days), or valacyclovir (1,000 mg bid PO for 7-10 days). The twice-daily valacyclovir option avoids treatment during school hours. For smaller children, acyclovir suspension can be used at a dose of 10-20 mg/kg/dose 4 times daily not to exceed the adult dose. The 1st episode of genital herpes can be extremely painful, and use of analgesics is generally indicated. All patients with genital herpes should be offered counseling to help them deal with psychosocial issues and understand the chronic nature of the illness.

There are 3 strategic options regarding the management of recurrent infections. The choice should be guided by several factors, including the frequency and severity of the recurrent infections, the psychologic impact of the illness on the patient, and concerns regarding transmission to a susceptible sexual partner. Option 1 is no therapy; option 2 is episodic therapy; and option 3 is long-term suppressive therapy. For **episodic therapy,** treatment should be initiated at the first signs of an outbreak. Recommended choices for episodic therapy in adolescents include famciclovir (1,000 mg bid PO for 1 day), acyclovir (800 mg tid PO for 2 days), or valacyclovir (500 mg bid PO for 3 days or 1,000 mg once daily for 5 days). Long-term suppressive therapy offers the advantage that it prevents most outbreaks, improves patient quality of life in terms of the psychosocial impact of genital herpes, and, with daily valacyclovir therapy, also reduces (but does not eliminate) the risk for sexual transmission to a susceptible sexual partner. Options for **long-term suppressive therapy** are acyclovir (400 mg bid PO), famciclovir (250 mg bid PO), and valacyclovir (500 or 1,000 mg qd PO).

Ocular Infections

HSV ocular infections can result in blindness. Management should involve consultation with an ophthalmologist.

Central Nervous System Infections

Patients older than neonates who have herpes encephalitis should be promptly treated with intravenous acyclovir (10 mg/kg every 8 hr given as a 1 hr infusion for 14-21 days). Treatment for increased intracranial pressure, management of seizures, and respiratory compromise may be required.

Infections in Immunocompromised Persons

Severe mucocutaneous and disseminated HSV infections in immunocompromised patients should be treated with intravenous acyclovir (30 mg/kg per day, in 3 divided doses for 7-14 days) until there is evidence of resolution of the infection. Oral antiviral therapy with acyclovir, famciclovir, or valacyclovir has been used for treatment of less-severe HSV infections and for suppression of recurrences during periods of significant immunosuppression. Drug resistance does occur occasionally in immunocompromised patients, and in individuals whose HSV infection does not respond to antiviral drug therapy, viral isolates should be tested to determine sensitivity. Acyclovir-resistant viruses are often also resistant to famciclovir but may be sensitive to foscarnet or cidofovir.

Perinatal Infections

All infants with proven or suspected neonatal HSV infection should be treated immediately with high-dose intravenous acyclovir (60 mg/kg/day divided every 8 hr IV). Treatment may be discontinued in infants shown by laboratory testing not to be infected. Infants with HSV disease limited to skin, eyes, and mouth should be treated for 14 days, whereas those with disseminated or central nervous system disease should receive 21 days of therapy. Patients receiving high-dose therapy should be monitored for neutropenia.

Suppressive oral acyclovir therapy for 6 mo after completion of the intravenous therapy has been shown to improve the neurodevelopment of infants with central nervous system infection and to prevent cutaneous recurrences in infants regardless of disease pattern. Infants should receive 300 mg/m^2 per dose 3 times daily for 6 mo. The absolute neutrophil count should be measured at weeks 2 and 4 after initiation of treatment and then monthly.

Prognosis

Most HSV infections are self-limiting, last from a few days (for recurrent infections) to 2-3 wk (for primary infections), and heal without scarring. Recurrent oral-facial herpes in a patient who has undergone dermabrasion or laser resurfacing can be severe and lead to scarring. Because genital herpes is a sexually transmitted infection, it can be stigmatizing, and its psychologic consequences may be much greater than its physiologic effects. Some HSV infections can be severe and may have grave consequences without prompt antiviral therapy. Life-threatening conditions include neonatal herpes, herpes encephalitis, and HSV infections in immunocompromised patients, burn patients, and severely malnourished infants and children. Recurrent ocular herpes can lead to corneal scarring and blindness.

Prevention

Transmission of infection occurs through exposure to virus either as the result of skin-to-skin contact or from contact with contaminated secretions. Good handwashing and, when appropriate, the use of gloves provide healthcare workers with excellent protection against HSV infection in the workplace. Healthcare workers with active oral-facial herpes or herpetic whitlow should take precautions, particularly when caring for high-risk patients such as newborns, immunocompromised individuals, and patients with chronic skin conditions. Patients and parents should be advised about good hygienic practices, including handwashing and avoiding contact with lesions and secretions, during active herpes outbreaks. Schools and daycare centers should clean shared toys and athletic equipment such as wrestling mats at least daily after use. Athletes with active herpes infections who participate in contact sports such as wrestling and rugby should be excluded from practice or games until the lesions are completely healed. Genital herpes can be prevented by avoiding genital-genital and oral-genital contact. The risk for acquiring genital herpes can be reduced but not eliminated through the correct and consistent use of condoms. Male circumcision is associated with a reduced risk of acquiring genital HSV infection. The risk for transmitting genital HSV-2 infection to a susceptible sexual partner can be reduced but not eliminated by the daily use of oral valacyclovir by the infected partner.

For **pregnant women** with **active genital herpes** at the time of delivery, the risk for mother-to-child transmission can be reduced but not eliminated by delivering the baby via a cesarean section. The risk for recurrent genital herpes, and therefore the need for cesarean delivery, can be reduced but not eliminated in pregnant women with a history of genital herpes by the daily use of oral acyclovir, valacyclovir, or famciclovir during the last 4 wk of gestation, which is recommended by the American College of Obstetrics and Gynecology. There are documented cases of neonatal herpes occurring in infants delivered by cesarean section, as well as in infants born to mothers who have been appropriately treated with antiherpes antiviral drugs for the last month of gestation. Hence a history of cesarean delivery or antiviral treatment at term does not rule out consideration of neonatal herpes.

Infants delivered vaginally to women with *first-episode* genital herpes are at *very high risk* for acquiring HSV infection. The nasopharynx, mouth, conjunctivae, rectum, and umbilicus should be cultured (some add PCR surface testing) at delivery and 12 to 24 hr after birth. Some also recommend HSV-PCR on blood. Some authorities recommend that these infants receive anticipatory acyclovir therapy for at least 2 wk, and others treat such infants if signs develop or if surface cultures beyond 12-24 hr of life are positive. Infants delivered to women with a history of *recurrent genital herpes* are at low risk for development of neonatal herpes. In this setting, parents should be educated about the signs and symptoms of neonatal HSV infection and should be instructed to seek care without delay at the first suggestion of infection. When the situation is in doubt, infants should be evaluated and tested with surface culture (and PCR) for neonatal herpes as well as with PCR on blood *and* CSF; intravenous acyclovir is begun until culture and PCR results are negative or until another explanation can be found for the signs and symptoms.

Recurrent genital HSV infections can be prevented by the daily use of oral acyclovir, valacyclovir, or famciclovir, and these drugs have been used to prevent recurrences of oral-facial (labialis) and cutaneous (gladiatorum) herpes. Oral and intravenous acyclovir has also been used to prevent recurrent HSV infections in immunocompromised patients. Use of sun blockers is reported to be effective in preventing recurrent oral-facial herpes in patients with a history of sun-induced recurrent disease.

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CHAPTER 280

Varicella-Zoster Virus*

Philip S. LaRussa, Mona Marin, Anne A. Gershon

Varicella-zoster virus (VZV) causes primary, latent, and reactivation infections. The primary infection is manifested as varicella (chickenpox) and results in establishment of a lifelong latent infection of sensory ganglionic neurons. Reactivation of the latent infection causes herpes zoster (shingles). Although often a mild illness of childhood, varicella can cause substantial morbidity and mortality in otherwise healthy children. Morbidity and mortality are higher in immunocompetent infants, adolescents, and adults as well as in immunocompromised persons. Varicella predisposes to severe group A streptococcus and staphylococcus aureus infections. A clinically modified disease can occur among vaccinated persons (breakthrough varicella), usually with milder presentation. Varicella and herpes zoster can be treated with antiviral drugs. Primary clinical disease can be prevented by immunization with live-attenuated varicella vaccine. Two herpes zoster vaccines are available for persons 50 yr of age and older to boost their immunity to VZV and prevent herpes zoster and its major complication, painful postherpetic neuralgia. One is a recombinant subunit (non-live) adjuvanted vaccine, and the other is a live vaccine that contains the same VZV strain used in the varicella vaccine but with a higher potency.

Etiology

VZV is a neurotropic human herpesvirus with similarities to herpes simplex virus. VZV enveloped viruses contain double-stranded DNA genomes that encode 71 proteins, including proteins that are targets of cellular and humoral immunity.

Epidemiology

Before the introduction of varicella vaccine in 1995, varicella was an almost universal communicable infection of childhood in the United States. Most children were infected by 10 yr of age, with fewer than 5% of adults remaining susceptible. This pattern of infection at younger ages remains characteristic in all countries in temperate climates. In contrast, in tropical areas, children acquire varicella at older ages and a higher proportion of young adults remain susceptible, leading to a higher proportion of cases occurring among adults. In the United States, prior to introduction of varicella vaccination, annual varicella epidemics occurred in winter and spring, and there were about 4 million cases of varicella, 11,000-15,000 hospitalizations, and 100-150 deaths every year. Varicella is a more serious disease in young infants, adults, and immunocompromised persons, in whom there are higher rates of complications and deaths than in healthy children. Within households, transmission of VZV to susceptible individuals occurs at a rate of 65–86%; more casual contact, such as occurs in a school classroom, is associated with lower attack rates among susceptible children. Persons with varicella may be contagious 24-48 hr before the rash is evident and until vesicles are crusted, usually 3-7 days after onset of rash, consistent with evidence that VZV is spread by aerosolization of virus in cutaneous lesions; spread from oropharyngeal secretions may occur but to a much lesser extent. Susceptible persons may also acquire varicella after close, direct contact with adults or children who have herpes zoster, again via aerosolization of virus in skin lesions.

Since implementation of the varicella vaccination program in 1996, there have been substantial declines in varicella morbidity and mortality in the United States. By 2006, prior to implementation of the 2-dose program, 1-dose vaccination coverage had reached 90% and varicella incidence had declined 90–91% since 1995 in sites where active surveillance was being conducted; varicella-related hospitalizations had declined 84% from prevaccine years. Varicella-related deaths decreased by 88% from 1990-1994 to 2005-2007; in persons younger than 20 yr of age there was a 97% decline in deaths. Declines in morbidity and mortality were seen in all age groups, including infants younger than 12 mo of age who were not eligible for vaccination, indicating protection from exposure by indirect vaccination effects. Although the age-specific incidence has declined in all age groups, the median age at infection has increased, and cases occur predominantly in children in upper elementary school rather than in the preschool years. This change in varicella epidemiology highlights the importance of offering vaccine to every susceptible child, adolescent, and adult. The continued occurrence of breakthrough infections and of outbreaks in settings with high 1-dose varicella vaccine coverage, together with the evidence that 1 dose is only approximately 85% effective against all varicella, prompted adoption in 2006 of a routine 2-dose childhood varicella vaccination program with catch-up vaccination of all individuals without evidence of immunity. Between 2006 and 2014, varicella incidence declined further by approximately 85% and fewer outbreaks were reported; varicella-related hospitalizations too declined 38% during the 2-dose period (through 2012). Overall, from prevaccine years varicella incidence declined by 97% and hospitalizations by 93% through 2014 and 2012, respectively.

Herpes zoster is caused by the reactivation of latent VZV. It is not common in childhood and shows no seasonal variation in incidence. Zoster is not caused by exposure to a patient with varicella; in fact, exposures to varicella boost the cell-mediated immune response to VZV in individuals with prior infection, decreasing the likelihood of reactivation of latent virus. The lifetime risk for herpes zoster for individuals with a history of varicella is at least 30%, with 75% of cases occurring after 45 yr of age. Herpes zoster is unusual in healthy children younger than 10 yr of age, with the exception of those infected with VZV in utero or in the 1st yr of life, who have an increased risk for development of zoster in the 1st few yr of life. Herpes zoster in otherwise healthy children tends to be milder than herpes zoster in adults, is less frequently associated with acute pain, and is generally not associated with postherpetic neuralgia. In children receiving immunosuppressive therapy for malignancy or other diseases and in those who have HIV infection, herpes zoster occurs more frequently, occasionally multiple times, and may be severe. The attenuated VZV in the varicella vaccine can establish latent infection and reactivate as herpes zoster. However, the risk for development of subsequent herpes zoster is lower after vaccination than after natural VZV infection among both healthy and immunocompromised children. Although the Oka vaccine type VZV is attenuated, the severity of zoster caused by the Oka strain seems to be similar to that caused by the natural or wild type VZV; some reports indicated milder clinical features among vaccine recipients but without being statistically significant. Vaccinated children who do develop zoster may have disease resulting from either vaccine or wild-type VZV, due to breakthrough varicella or subclinical infection of some vaccinees with wild-type VZV occurring at some point after immunization.

Pathogenesis

Primary infection (varicella) results from inoculation of the virus onto the mucosa of the upper respiratory tract and tonsillar lymphoid tissue. During the early part of the 10-21 day incubation period, virus replicates in the local lymphoid tissue and spreads to T lymphocytes, causing a viremia that delivers the virus to skin where innate immunity controls VZV replication for some days. After innate immunity is overcome in skin, widespread cutaneous lesions develop as the incubation period ends. Adaptive host immune responses, especially cellular immunity, limit viral replication and lead to recovery from infection. In the immunocompromised child, the failure of adaptive immunity, especially cellular immune responses, results in continued viral replication that may lead to prolonged and/or disseminated infection with resultant complications of infection in the lungs, liver, brain, and other organs.

Latent infection develops during the incubation period or the disease itself. VZV is transported in a retrograde manner through sensory axons to the dorsal root ganglia throughout the spinal cord and to cranial nerve ganglia. Latency may also develop from viremia, infecting spinal and cranial nerve ganglia as well autonomic ganglia which do not project to the skin, including the enteric nervous system of the intestine. Latency of VZV occurs only in ganglionic neurons. Subsequent **reactivation** of latent VZV causes **herpes zoster,** usually manifested by a vesicular rash that is unilateral and dermatomal in distribution. Reactivation of VZV may also occur without a rash; examples are unilateral dermatomal pain without rash (**zoster sine herpete**), aseptic meningitis, and gastrointestinal illness (enteric zoster). During herpes zoster, necrotic changes may be produced in the neurons and surrounding satellite cells in associated ganglia. The skin lesions of varicella and herpes zoster have identical histopathology, and infectious VZV is present in both. Varicella elicits humoral and cell-mediated immunity that is highly protective against symptomatic reinfection. Suppression of cell-mediated immunity to VZV correlates with an increased risk for VZV reactivation as herpes zoster.

Clinical Manifestations

Varicella is an acute febrile rash illness that was common in children in the United States before the universal childhood vaccination program. It has variable severity but is usually self-limited. It may be associated with severe complications, including bacterial superinfection, especially with staphylococci and group A streptococci, pneumonia, encephalitis, bleeding disorders, congenital infection, and life-threatening perinatal infection. Herpes zoster is not common in children and typically causes localized cutaneous symptoms, but may disseminate in immunocompromised patients.

Varicella in Unvaccinated Individuals

The illness usually begins 14-16 days after exposure, although the incubation period can range from 10 to 21 days. Subclinical varicella is rare; almost all exposed, susceptible persons experience a rash, albeit so mild in some cases that it may go unnoticed. Prodromal symptoms may be present, particularly in older children and adults. Fever, malaise, anorexia, headache, and occasionally mild abdominal pain may occur 24-48 hr before the rash appears. Temperature elevation is usually 37.8-38.9°C (100-102°F) but may be as high as 41.1°C (106°F); fever and other systemic symptoms usually resolve within 2-4 days after the onset of the rash.

Varicella lesions often appear first on the scalp, face, or trunk. The initial exanthem consists of intensely pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles. Clouding and umbilication of the lesions begin in 24-48 hr. While the initial lesions are crusting, new crops form on the trunk and then the extremities; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella (Fig. 280.1). The distribution of the rash is predominantly central or centripetal, with the greatest concentration on the trunk and proximally on the extremities. Ulcerative lesions involving the mucosa of the oropharynx and vagina are also common; many children have vesicular lesions on the eyelids and conjunctivae, but corneal involvement and serious ocular disease are rare. The average number of varicella lesions is about 300, but healthy children may have fewer than 10 to more than 1,500 lesions. In cases resulting from secondary household spread and in older children, more lesions usually occur, and new crops of lesions may continue to develop for more than 7 days. The exanthem may be much more extensive in children with skin disorders, such as eczema or recent sunburn. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children, but severe scarring is unusual unless the lesions were secondarily infected.

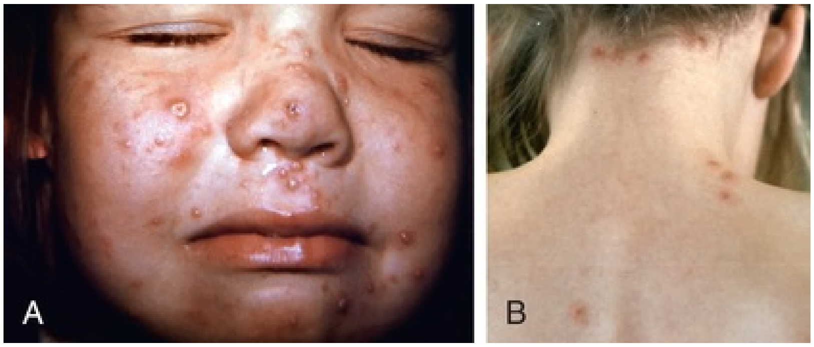

FIG. 280.1 **A,** Varicella lesions in unvaccinated persons display the characteristic "cropping" distribution, or manifest themselves in clusters; the simultaneous presence of lesions in various stages of evolution is characteristic. **B,** Breakthrough varicella lesions are predominantly maculopapular, and vesicles are less common; the illness is most commonly mild with <50 lesions. (**A,** Courtesy Centers for Disease Control and Prevention [CDC]; **B,** courtesy CDC and Dr. John Noble, Jr.)

The differential diagnosis of varicella includes vesicular rashes caused by other infectious agents, such as herpes simplex virus, enterovirus, monkey pox, rickettsial pox, and *S. aureus;* drug reactions; disseminated herpes zoster; contact dermatitis; and insect bites (especially for breakthrough varicella). Severe varicella was the most common illness confused with smallpox before the eradication of smallpox.

Varicelliform Rashes in Vaccinated Individuals

Varicelliform rashes that occur after vaccination could be a result of wild-type VZV, vaccine strain VZV, or other etiologies (e.g., insect bites, coxsackievirus). During days 0-42 after vaccination, the likelihood of rash from wild-type or vaccine strain VZV varies depending on the stage of a country's vaccination program. In the early stages of a vaccine program, rash within 1-2 wk is still most commonly caused by wild-type VZV, reflecting exposure to varicella before vaccination could provide protection. Rash occurring 14-42 days after vaccination is a result of either wild-type or vaccine strains, reflecting exposure and infection before protection from vaccination or an adverse event of vaccination (vaccine-associated rash), respectively. As wild-type varicella continues to decline as a consequence of the vaccination program, wild-type VZV circulation will also decline and rashes in the interval 0-42 days after vaccination will be less commonly caused by wild-type VZV. Spread of vaccine type VZV from a vaccinee with skin lesions has occurred, but is rare. The resulting illness in contacts is either asymptomatic or extremely mild with only a few vesicular lesions. Clinical reversion of the vaccine virus to virulence has not been described.

Breakthrough varicella is disease that occurs in a person vaccinated more than 42 days before rash onset and is caused by **wild-type** virus**.** One dose of varicella vaccine is 98% effective in preventing moderate and severe varicella and is 82% (95% confidence interval [CI]: 79–85%; range: 44–100%) effective in preventing all disease after exposure to wild-type VZV. This means that after close exposure to VZV, as may occur in a household or an outbreak setting in a school or daycare center, about 1 of every 5 children who received 1 dose of vaccine may experience breakthrough varicella. Exposure to VZV may also result in asymptomatic infection in the previously immunized child. The rash in breakthrough disease is frequently atypical and predominantly maculopapular, and vesicles are seen less commonly. The illness is most commonly mild with <50 lesions, shorter duration of rash, fewer complications, and little or no fever. However, approximately 25–30% of breakthrough cases in vaccines who received 1 dose are not mild, with clinical features more similar to those of wild-type infection. Breakthrough cases are overall **less contagious** than wild-type infections within household settings, but contagiousness varies proportionally with the number of lesions; typical breakthrough cases (<50 lesions) is about one-third as contagious as disease in unvaccinated cases, whereas breakthrough cases with ≥50 lesions are as contagious as wild-type cases. Consequently, children with breakthrough disease should be considered potentially infectious and excluded from school until lesions have crusted or, if there are no vesicles present, until no new lesions are occurring. Transmission has been documented to occur from breakthrough cases in household, childcare, and school settings.

Two doses of varicella vaccine provide better protection than a 1-dose schedule. One clinical trial estimated the 2-dose vaccine effectiveness for preventing all disease at 98%; the estimate is 92% (95% CI: 88–95%; range: 84–98%) in conditions of everyday clinical practice. Institution of 2 doses routinely in the United States substantially reduced the school outbreaks that were occurring among children who had received only 1 dose. Breakthrough cases have been reported among 2-dose vaccines; however, recipients of 2 doses of varicella vaccine are less likely to have breakthrough disease than those who received 1 dose. Additionally, data suggest that breakthrough varicella may be further attenuated among 2-dose vaccine recipients.

Neonatal Varicella

Mortality is particularly high in neonates born to susceptible mothers who contract varicella around the time of delivery. Infants whose mothers demonstrate varicella in the period from 5 days prior to delivery to 2 days afterward are at high risk for severe varicella. These infants acquire the infection transplacentally as a result of maternal viremia, which may occur up to 48 hr prior to onset of maternal rash. The infant's rash usually occurs toward the end of the 1st wk to the early part of the 2nd wk of life (although it may be as soon as 2 days). Because the mother has not yet developed a significant antibody response, the infant receives a large dose of virus without the moderating effect of maternal anti-VZV antibody. If the mother demonstrates varicella more than 5 days prior to delivery, she still may pass virus to the soon-to-be-born child, but infection is attenuated because of transmission of maternal VZV-specific antibody across the placenta. This moderating effect of maternal antibody is present if delivery occurs after about 30 wk of gestation, when maternal immunoglobulin (Ig) G is able to cross the placenta in significant amounts. *The recommendations for use of human varicella-zoster immunoglobulin (VZIG) differ based on when the infant is exposed to varicella.* Newborns whose mothers develop varicella during the period of 5 days before to 2 days after delivery should receive VZIG as soon as possible after birth. Although neonatal varicella may occur in about half of these infants despite administration of VZIG, it is milder than in the absence of VZIG administration. All premature infants born < 28 wk of gestation to a mother with active varicella at delivery (even if the maternal rash has been present for >1 wk) should receive VZIG. If VZIG is not available, intravenous immunoglobulin (IVIG) may provide some protection, although varicella-specific antibody titers may vary from lot to lot. Because perinatally acquired varicella may be life threatening, the infant should usually be treated with acyclovir (10 mg/kg every 8 hr IV) when lesions develop. Neonatal varicella can also follow a postpartum exposure of an infant delivered to a mother who was susceptible to VZV, although the frequency of complications declines rapidly in the weeks after birth. Recommendations for VZIG administration for these infants are presented in the postexposure prophylaxis section. Neonates with community-acquired varicella who experience severe varicella, especially those who have a complication such as pneumonia, hepatitis, or encephalitis, should also receive treatment with intravenous acyclovir (10 mg/kg every 8 hr). Infants with neonatal varicella who receive prompt antiviral therapy have an excellent prognosis.

Congenital Varicella Syndrome

In utero transmission of VZV can occur; however, because most adults in temperate climates are immune, pregnancy complicated by varicella is unusual in these settings. When pregnant women do contract varicella early in pregnancy, experts estimate that as many as 25% of the fetuses may become infected. Fortunately, clinically apparent disease in the infant is uncommon: the congenital varicella syndrome occurs in approximately 0.4% of infants born to women who have varicella during pregnancy before 13 wk of gestation and in approximately 2% of infants born to women with varicella between 13 and 20 wk of gestation. Rarely, cases of congenital varicella syndrome have been reported in infants of women infected after 20 wk of pregnancy, the latest occurring at 28 wk of gestation. Before availability of varicella vaccine in the United States, 44 cases of congenital varicella syndrome were estimated to occur each year. The congenital varicella syndrome is characterized by cicatricial skin scarring in a zoster-like distribution; limb hypoplasia; and abnormalities of the neurologic system (e.g., microcephaly, cortical atrophy, seizures, and mental retardation), eye (e.g., chorioretinitis, microphthalmia, and cataracts), renal system (e.g., hydroureter and hydronephrosis), and autonomic nervous system (e.g., neurogenic bladder, swallowing dysfunction, and aspiration pneumonia). Low birthweight is common among infants with congenital varicella syndrome. Most of the stigmata can be attributed to virus-induced injury to the nervous system, although there is no obvious explanation why certain regions of the body are preferentially infected during fetal VZV infection. The characteristic cutaneous lesion has been called a cicatrix, a zigzag scarring, in a *dermatomal* distribution, often associated with atrophy of the affected limb (Fig. 280.2). Many infants with severe manifestations of congenital varicella syndrome (atrophy and scarring of a limb) have significant neurologic deficiencies. Alternatively, there may be neither skin nor limb abnormalities but the infant may show cataracts or even extensive aplasia of the entire brain.

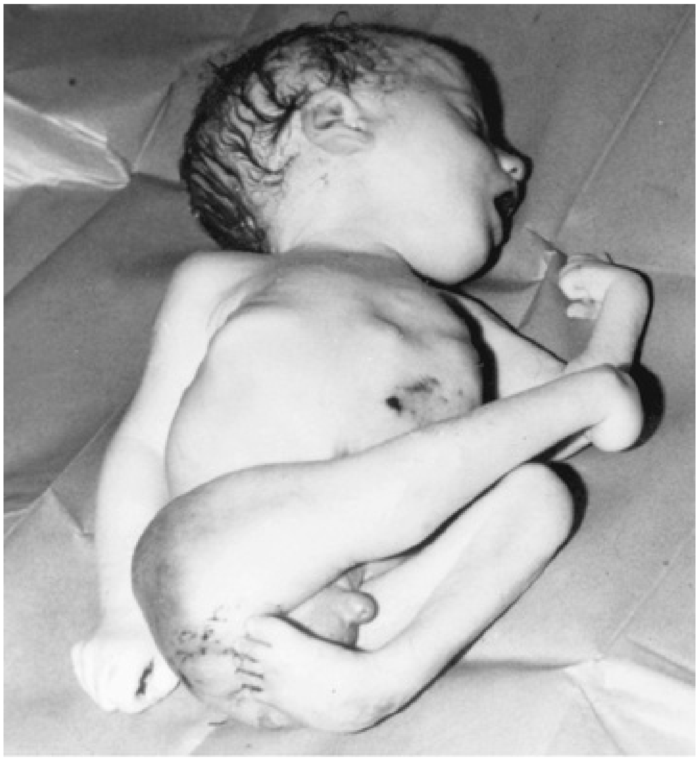

FIG. 280.2 Newborn with congenital varicella syndrome. The infant had severe malformations of both lower extremities and cicatricial scarring over his left abdomen.

There are rare case reports of fetal abnormalities following the development of herpes zoster in the mother; whether or not these cases truly represent the congenital varicella syndrome is unclear. If it does occur, the congenital syndrome acquired as a result of maternal herpes zoster is exceedingly rare. Maternal herpes zoster was associated with typical congenital varicella syndrome in one case, but the mother had disseminated herpes zoster (at 12 wk of gestation).

The diagnosis of VZV fetopathy is based mainly on the history of gestational varicella combined with the presence of characteristic abnormalities in the newborn infant. Virus cannot be cultured from the affected newborn, but viral DNA may be detected in tissue samples by polymerase chain reaction (PCR). Since many infants with congenital varicella syndrome develop zoster before a year of age, it may be possible to isolate VZV from that rash. Alternatively, use of PCR to identify VZV DNA in vesicular fluid or scabs from zoster lesions in such an infant may be diagnostic. VZV-specific IgM antibody is detectable in the cord blood sample in some infants, although the IgM titer drops quickly in the postpartum period and can be nonspecifically positive. Chorionic villus sampling and fetal blood collection for the detection of viral DNA, virus, or antibody have been used in an attempt to diagnose fetal infection and embryopathy. The usefulness of these tests for patient management and counseling has not been defined. Because these tests may not distinguish between infection and disease, their utility may primarily be that of reassurance when the result is negative. Ultrasound may be useful to try to identify limb atrophy, which is common in congenital varicella syndrome. A persistently positive VZV IgG antibody titer at 12-18 mo of age is a reliable indicator of prenatal infection in the asymptomatic child, as is the development of zoster in the 1st yr of life without evidence of postnatal infection.

VZIG has often been administered to the susceptible mother exposed to varicella to modify maternal disease severity; it is uncertain whether this step modifies infection in the fetus, although some evidence suggests that it may be beneficial for the fetus too. Similarly, acyclovir treatment may be given to the mother with severe varicella. A prospective registry of acyclovir use in the 1st trimester demonstrated that the occurrence of birth defects approximates that found in the general population. Acyclovir is a class B drug for pregnancy and should be considered when the benefit to the mother outweighs the potential risk to the fetus. The efficacy of acyclovir treatment of the pregnant woman in preventing or modifying the severity of congenital varicella is not known, but its use should be considered to protect the mother from severe disease. Because the damage caused by fetal VZV infection does not progress in the postpartum period, antiviral treatment of infants with congenital VZV syndrome is not indicated.

Complications

The complications of VZV infection (varicella or zoster) occur more commonly in immunocompromised patients. In the otherwise healthy child, asymptomatic transient varicella hepatitis is relatively common. Mild thrombocytopenia occurs in 1–2% of children with varicella and may be associated with petechiae. Purpura, hemorrhagic vesicles, hematuria, and gastrointestinal bleeding are rare complications that may have serious consequences. Other complications of varicella, some of them rare, include acute cerebellar ataxia, encephalitis, pneumonia, nephritis, nephrotic syndrome, hemolytic-uremic syndrome, arthritis, myocarditis, pericarditis, pancreatitis, orchitis, and acute retinal necrosis. A reduction in the number and rates of varicella-related complications is seen in vaccinated populations. Reports of serious varicella-related complications in vaccinated persons (breakthrough) are rare (meningitis, pneumonia, acute transverse myelitis, encephalitis [1 fatal case in an apparently immunocompetent child], and sepsis). Severe breakthrough varicella can occur among healthy persons, but cases appear to be more common among immunocompromised persons who are usually not recommended to receive varicella vaccine.

Declines in varicella-related hospitalizations and deaths in the United States since implementation of the varicella vaccination program provide supporting evidence that varicella vaccine reduces severe complications from varicella. Approximately 105 deaths (with varicella listed as the underlying cause of death) occurred in the United States annually before the introduction of the varicella vaccine; during 2008-2011 the annual average number of varicella deaths was 17. In both the pre- and postvaccine era, the majority of deaths (>80%) have been among persons without high-risk preexisting conditions.

Bacterial Infections

Secondary bacterial infections of the skin, usually caused by group A streptococcus or *S. aureus*, may occur in children with varicella. These range from impetigo to cellulitis, lymphadenitis, and subcutaneous abscesses. An early manifestation of secondary bacterial infection is erythema of the base of a new vesicle. Recrudescence of fever 3-4 days after the initial exanthem may also herald a secondary bacterial infection. Varicella is a well-described risk factor for serious invasive infections caused by group A streptococcus, which can have a fatal outcome. The more invasive infections, such as varicella gangrenosa, bacterial sepsis, pneumonia, arthritis, osteomyelitis, cellulitis, and necrotizing fasciitis, account for much of the morbidity and mortality of varicella in otherwise healthy children. Bacterial toxin–mediated diseases (e.g., toxic shock syndrome) also may complicate varicella. A substantial decline in varicella-related invasive bacterial infections is associated with the use of the varicella vaccine.

Encephalitis and Cerebellar Ataxia

Encephalitis (1 per 50,000 cases of varicella in unvaccinated children) and acute cerebellar ataxia (1 per 4,000 cases of varicella in unvaccinated children) are well-described neurologic complications of varicella; morbidity from central nervous system complications is highest among patients younger than 5 yr and older than 20 yr. Nuchal rigidity, altered consciousness, and seizures characterize meningoencephalitis. Patients with cerebellar ataxia have a gradual onset of gait disturbance, nystagmus, and slurred speech. Neurologic symptoms usually begin 2-6 days after the onset of the rash but may occur during the incubation period or after resolution of the rash. Clinical recovery is typically rapid, occurring within 24-72 hr, and is usually complete. Although severe hemorrhagic encephalitis, analogous to that caused by herpes simplex virus, is very rare in children with varicella, the consequences are similar to those of herpes simplex virus encephalitis. Reye syndrome (hepatic dysfunction with hypoglycemia and encephalopathy) associated with varicella and other viral illnesses such as influenza is rare now that salicylates are no longer used as antipyretics in these situations (see Chapter 384).

Pneumonia

Varicella pneumonia is a severe complication that accounts for most of the increased morbidity and mortality from varicella in adults and other high-risk populations, but pneumonia may also complicate varicella in young children. Respiratory symptoms, which may include cough, dyspnea, cyanosis, pleuritic chest pain, and hemoptysis, usually begin within 1-6 days after the onset of the rash. Smoking has been described as a risk factor for severe pneumonia complicating varicella. The frequency of varicella pneumonia may be greater in the parturient.

Progressive Varicella

Progressive varicella, with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after 7 days, is a severe complication of primary VZV infection. Severe abdominal pain, which may reflect involvement of mesenteric lymph nodes or the liver, or the appearance of hemorrhagic vesicles in otherwise healthy adolescents and adults, immunocompromised children, pregnant women, and newborns, may herald severe, and potentially fatal, disease. Although rare in healthy children, the risk for progressive varicella is highest in children with congenital cellular immune deficiency disorders and those with malignancy, particularly if chemotherapy, and especially corticosteroids, had been given during the incubation period and the absolute lymphocyte count is <500 cells/µL. The mortality rate for children who acquired varicella while undergoing treatment for malignancy and who were not treated with antiviral therapy approached 7%; varicella-related deaths usually occurred within 3 days after the diagnosis of varicella pneumonia. Children who acquire varicella after organ transplantation are also at risk for progressive VZV infection. Children undergoing long-term, low-dose systemic or inhaled corticosteroid therapy are not considered to be at higher risk for severe varicella, but progressive varicella does occur in patients receiving high-dose corticosteroids. There are case reports in patients receiving inhaled corticosteroids as well as in asthmatic patients receiving multiple short courses of systemic corticosteroid therapy. Unusual clinical findings of varicella, including lesions that develop a hyperkeratotic appearance and continued new lesion formation for weeks or months, have been described in children with untreated, late-stage HIV infection. Immunization of HIV-infected children who have a CD4+ T-lymphocyte percent ≥15%, as well as children with leukemia and solid organ tumors who are in remission and whose chemotherapy can be interrupted for 2 wk around the time of immunization or has been terminated, have reduced frequency of severe disease. Moreover, since the advent of the universal immunization program in the United States, many children who would become immunocompromised later in life because of disease or treatment are protected before the immunosuppression occurs; also, as a result of reductions in varicella incidence, immunocompromised children are less likely to be exposed to varicella.

Herpes Zoster

Herpes zoster manifests as vesicular lesions clustered within 1 or, less commonly, 2 adjacent dermatomes (Fig. 280.3). In the elderly, herpes zoster typically begins with burning pain or itching followed by clusters of skin lesions in a dermatomal pattern. Almost half of the elderly with herpes zoster experience complications; the most frequent complication is postherpetic neuralgia, a painful condition that affects the nerves despite resolution of the skin lesions. Approximately 4% of patients suffer a 2nd episode of herpes zoster; 3 or more episodes are rare. Unlike herpes zoster in adults, zoster in children is infrequently associated with localized pain, hyperesthesia, pruritus, low-grade fever, or complications. In children, the rash is mild, with new lesions appearing for a few days (Fig. 280.4); symptoms of acute neuritis are minimal; and complete resolution usually occurs within 1-2 wk. Unlike in adults, postherpetic neuralgia is unusual in children. An increased risk for herpes zoster early in childhood has been described in children who acquire infection with VZV in utero or in the 1st yr of life.

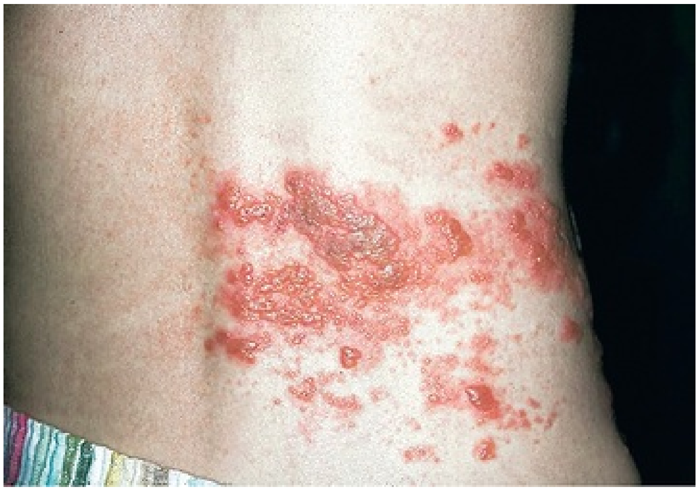

FIG. 280.3 **Herpes zoster involving the lumbar dermatome. (From Mandell GL, Bennett JE, Dolin R, editors: *Principles and practice of infectious diseases* , ed 6, Philadelphia, 2005, Elsevier, p. 1783.)**

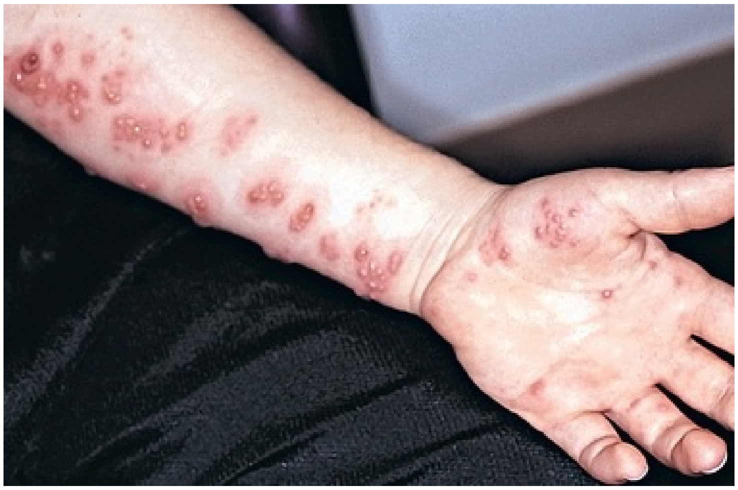

FIG. 280.4 **Many groups of blisters occurring over the arm in a child with herpes zoster. (From Weston WL, Lane AT, Morelli JG: *Color textbook of pediatric dermatology* , ed 3, Philadelphia, 2002, Mosby, Fig. 8-28.)**

Immunocompromised children may have more severe herpes zoster, similar to *the situation in adults, including postherpetic neuralgia.* Immunocompromised patients may also experience disseminated cutaneous disease that mimics varicella, with or without initial dermatomal rash, as well as visceral dissemination with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Severely immunocompromised children, particularly those with advanced HIV infection, may have unusual, chronic, or relapsing cutaneous disease, retinitis, or central nervous system disease without rash. The finding of a lower risk for herpes zoster among vaccinated children with leukemia than in those who have had varicella suggested that the vaccine virus reactivates less commonly than wild-type VZV. A study of HIV-infected vaccinated children found no cases of zoster 4.4 yr after immunization, which was significantly different than the rate in children who had experienced varicella. Studies to date indicate that the risk for herpes zoster in healthy children who have received 1 dose of vaccine is lower than in children who had wild-type varicella. Many more years of follow-up are needed to determine whether this lower risk is maintained among older persons who are at greatest risk for herpes zoster. The risk for herpes zoster in healthy children following 2 doses of varicella vaccine has not been evaluated.

Diagnosis

Varicella and herpes zoster are usually diagnosed primarily by their clinical appearance. Laboratory evaluation has not been considered necessary for diagnosis or management. However, as varicella disease has declined to low levels, laboratory confirmation has become increasingly useful. The atypical nature of breakthrough varicella, with a higher proportion of papular rather than vesicular rashes, poses both clinical and laboratory diagnostic challenges.

Leukopenia is typical during the first 72 hr after onset of rash; it is followed by a relative and absolute lymphocytosis. Results of liver function tests are also usually (75%) mildly elevated. Patients with neurologic complications of varicella or uncomplicated herpes zoster have a mild lymphocytic pleocytosis and a slight to moderate increase in protein content of the cerebrospinal fluid; the cerebrospinal fluid glucose concentration is usually normal.

Rapid laboratory diagnosis of VZV is often important in high-risk patients and can be important for infection control, especially for breakthrough cases that have mild or atypical presentations. Confirmation of VZV infections can be accomplished by many referral hospital laboratories and all state health laboratories. VZV can be identified quickly by direct fluorescence assay of cells from cutaneous lesions (vesicular fluid) in 15-20 min; by PCR amplification testing (vesicular fluid, crusts) in hours to days, depending on availability; and by rapid culture with specific immunofluorescence staining (shell vial technique) in 48-72 hr. In the absence of vesicles or scabs, scrapings of maculopapular lesions can be collected for PCR or direct fluorescence assay testing. Infectious virus may be recovered by means of tissue culture methods; such methods require specific expertise, and virus may take days to weeks to grow. Of available tests, PCR is the most sensitive and allows for differentiation of wild-type and vaccine strains. Direct fluorescence assay is specific and less sensitive than PCR but when available allows for rapid diagnosis. Although multinucleated giant cells can be detected with nonspecific stains (Tzanck smear), they have poor sensitivity and do not differentiate VZV from herpes simplex virus infections. Strain identification (genotyping) can distinguish wild-type VZV from the vaccine strain in a vaccinated child; however, genotyping is available only at specialized reference laboratories. Laboratory tests of lesions cannot be used to distinguish between varicella and disseminated herpes zoster. VZV IgG antibodies can be detected by several methods, and a 4-fold or greater rise in IgG antibodies is confirmatory of acute infection (although this requires a 2-3 wk delay to collect a convalescent specimen); in vaccinated persons, commercially available tests are not sufficiently sensitive to always detect antibody following vaccination and a 4-fold rise in IgG antibody may not occur. VZV IgG antibody tests can also be valuable to determine the immune status of individuals whose clinical history of varicella is unknown or equivocal. However, caution must be taken in interpreting tests for immunity to VZV, especially in immunocompromised patients after a close exposure to VZV. Due to the possibility of false-positive results, it is preferable to rely on clinical rather than laboratory information, and if doubt, assume the individual is susceptible to varicella and proceed accordingly. Testing for VZV IgM antibodies is not useful for routine confirmation or ruling out of varicella because commercially available methods are unreliable and the kinetics of the IgM response have not been well defined. Reliable VZV-specific IgM assays are available in certain reference laboratories, including a capture-IgM assay available at the national VZV laboratory at the Centers for Disease Control and Prevention. Serologic tests are not useful for the initial diagnosis of herpes zoster, but a large rise in IgG titer in convalescent titer in the presence of an atypical zoster rash is confirmatory. As with any laboratory test, a negative varicella test should be considered in the context of the clinical presentation. Clinicians should use clinical judgment to decide on the best course of therapy.

Treatment

Antiviral treatment modifies the course of both varicella and herpes zoster. Antiviral drug resistance is rare for VZV but has occurred, primarily in children with HIV infection and other immunocompromising conditions where frequent relapse of VZV infections has resulted in multiple courses of antiviral therapy. Foscarnet and cidofovir may be useful for the treatment of acyclovir-resistant VZV infections, but consultation of an infectious disease specialist is recommended.

Varicella

The only antiviral drug available in liquid formulation that is licensed for treatment of varicella for pediatric use is acyclovir. Given the safety profile of acyclovir and its demonstrated efficacy in the treatment of varicella, treatment of all children, adolescents, and adults with varicella is acceptable. However, acyclovir therapy is not recommended routinely by the American Academy of Pediatrics for treatment of uncomplicated varicella in the otherwise healthy child because of the marginal benefit, the cost of the drug, and the low risk for complications of varicella. Oral therapy with acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) given as 4 doses/day for 5 days can be used to treat uncomplicated varicella in individuals at increased risk for moderate to severe varicella: nonpregnant individuals older than 12 yr of age and individuals older than 12 mo of age with chronic cutaneous or pulmonary disorders; individuals receiving short-term, intermittent, or aerosolized corticosteroid therapy; individuals receiving long-term salicylate therapy; and possibly secondary cases among household contacts. To be most effective, treatment should be initiated as early as possible, preferably within 24 hr of the onset of the exanthem. There is less clinical benefit if treatment is initiated more than 72 hr after onset of the exanthem. Acyclovir therapy does not interfere with the induction of VZV immunity. Acyclovir has been successfully used to treat varicella in pregnant women. Some experts recommend the use of famciclovir or valacyclovir in older children who can swallow tablets. These drugs are highly active against VZV by the same mechanism as acyclovir and are better absorbed by the oral route than acyclovir. Valacyclovir (20 mg/kg/dose; maximum: 1,000 mg/dose, administered 3 times daily for 5 days) is licensed for treatment of varicella in children 2 to <18 yr of age, and both valacyclovir and famciclovir are approved for treatment of herpes zoster in adults. The oral adult dose of valacyclovir is 1 g TID. Patients receiving these antivirals should be well hydrated, and for prolonged use, renal function and white blood cell counts (especially neutrophils) should be monitored frequently. Common adverse symptoms during valacyclovir treatment are neurologic (headache, agitation, dizziness) and gastrointestinal (nausea, abdominal pain).

Intravenous therapy is indicated for severe disease and for varicella in immunocompromised patients (even if begun more than 72 hr after onset of rash). Any patient who has signs of disseminated VZV, including pneumonia, severe hepatitis, thrombocytopenia, or encephalitis, should receive immediate treatment. IV acyclovir therapy (500 mg/m^2 every 8 hr) initiated within 72 hr of development of initial symptoms decreases the likelihood of progressive varicella and visceral dissemination in high-risk patients. Treatment is continued for 7-10 days or until no new lesions have appeared for 48 hr. Delaying antiviral treatment in high-risk individuals until it is obvious that prolonged new lesion formation is occurring is not recommended because visceral dissemination occurs during the same period.

Acyclovir-resistant VZV has been identified primarily in children infected with HIV. These children may be treated with intravenous foscarnet (120 mg/kg/day divided every 8 hr for up to 3 wk). The dose should be modified in the presence of renal insufficiency. Resistance to foscarnet has been reported with prolonged use. Cidofovir is also useful in this situation. Because of the increased toxicity profile of foscarnet and cidofovir, these 2 drugs should be initiated in collaboration with an infectious disease specialist.

Herpes Zoster

Antiviral drugs are effective for treatment of herpes zoster. In healthy adults, acyclovir (800 mg 5 times a day PO for 5-7 days), famciclovir (500 mg tid PO for 7 days), and valacyclovir (1,000 mg tid PO for 7 days) reduce the duration of the illness but do not prevent development of postherpetic neuralgia. In otherwise healthy children, herpes zoster is a less-severe disease, and postherpetic neuralgia usually does not occur. Therefore, treatment of uncomplicated herpes zoster in the child with an antiviral agent may not always be necessary, although some experts would treat with oral acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) to shorten the duration of the illness. It is important to start antiviral therapy as soon as possible. Delay beyond 72 hr from onset of rash limits its effectiveness.

In contrast, herpes zoster in immunocompromised children can be severe, and disseminated disease may be life-threatening. Patients at high risk for disseminated disease should receive IV acyclovir (500 mg/m^2 or 10 mg/kg every 8 hr). Oral acyclovir, famciclovir, and valacyclovir are options for immunocompromised patients with uncomplicated herpes zoster, who are considered at low risk for visceral dissemination. Neuritis with herpes zoster should be managed with appropriate analgesics.

Use of corticosteroids in the treatment of herpes zoster in children is not recommended.

Prognosis

Primary varicella has a mortality rate of 2-3 per 100,000 cases, with the lowest case fatality rates among children 1-9 yr of age (~1 death per 100,000 cases). Compared with these age groups, infants have a 4 times greater risk of dying and adults have a 25 times greater risk of dying. The most common complications among people who died from varicella were pneumonia, central nervous system complications, secondary infections, and hemorrhagic conditions. The mortality rate of untreated primary infection was 7% in immunocompromised children in the 1960s. In the era of antiviral therapy and improved supportive care, the prognosis has improved with treatment administered early in the course of illness, but deaths have continued to occur.

Herpes zoster among healthy children has an excellent prognosis and is usually self-limited. Severe presentation with complications and sometimes fatalities can occur in immunocompromised children.

Prevention

VZV transmission is difficult to prevent, especially from persons with varicella, because a person with varicella may be contagious for 24-48 hr before the rash is apparent. Herpes zoster is less infectious than varicella; nonetheless, transmission has been reported even in the absence of direct contact with the patient. Infection control practices, including caring for patients with varicella in isolation rooms with filtered air systems, are essential. All healthcare workers should have evidence of varicella immunity (Table 280.1). Unvaccinated healthcare workers without other evidence of immunity who have had a close exposure to VZV should be furloughed for days 8-21 after exposure because they are potentially infectious during this period.

Table 280.1

Evidence of Immunity to Varicella

Evidence of immunity to varicella consists of any of the following:

• Documentation of age-appropriate vaccination with a varicella vaccine:
  • Preschool-age children (i.e., age ≥12 mo): 1 dose
  • School-age children, adolescents, and adults: 2 doses[*]
• Laboratory evidence of immunity[†] or laboratory confirmation of disease
• Birth in the United States before 1980[‡]
• Diagnosis or verification of a history of varicella disease by a healthcare provider[§]
• Diagnosis or verification of a history of herpes zoster by a healthcare provider

[*] For children who received their 1st dose at younger than age 13 yr and for whom the interval between the 2 doses was 28 or more days, the 2nd dose is considered valid.

[†] Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they might yield false-negative results).

[‡] For healthcare personnel, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity.

[§] Verification of history or diagnosis of typical disease can be provided by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, or physician). For persons reporting a history of, or reporting with, atypical or mild cases, assessment by a physician or his/her designee is recommended, and one of the following should be sought: (1) an epidemiologic link to a typical varicella case or to a laboratory-confirmed case or (2) evidence of laboratory confirmation if it was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease, because other diseases might mimic mild atypical varicella.

Vaccine

Varicella is a vaccine-preventable disease. Varicella vaccine contains live, attenuated VZV (Oka strain) and is indicated for subcutaneous administration. In the United States, varicella vaccine is recommended for routine administration as a 2-dose regimen to healthy children at ages 12-15 mo and 4-6 yr. Administration of the 2nd dose earlier than 4-6 yr of age is acceptable, but it must be at least 3 mo after the 1st dose. Catch-up vaccination with the 2nd dose is recommended for children and adolescents who received only 1 dose. Vaccination with 2 doses is recommended for all persons without evidence of immunity. The minimum interval between the 2 doses is 3 mo for persons 12 yr of age or younger and 4 wk for older children, adolescents, and adults. Administration of varicella vaccine within 4 wk of measles-mumps-rubella (MMR) vaccination is associated with a higher risk for breakthrough disease; therefore, it is recommended that the varicella and MMR vaccines either be administered simultaneously at different sites or be given at least 4 wk apart. Varicella vaccine can be administered as a monovalent vaccine (for all healthy persons ≥12 mo of age) or as the quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine (for children age 12 mo through 12 yr only).

Varicella vaccine is contraindicated for persons who have a history of anaphylactic reaction to any component of the vaccine; pregnant women; persons with cell-mediated immune deficiencies, including those with leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic systems; persons receiving immunosuppressive therapy; and persons who have a family history of congenital or hereditary immunodeficiency in 1st-degree relatives unless the immune competence of the potential vaccine recipient is demonstrated. Children with isolated humoral immunodeficiencies may receive varicella vaccine. The monovalent varicella vaccine has been studied in clinical trial settings in children with acute lymphocytic leukemia and certain solid tumors who are in remission but this practice is not recommended except in a research setting. Varicella vaccine can be administered to patients with leukemia, lymphoma, or other malignancies whose disease is in remission, who have restored immunocompetence, and whose chemotherapy has been terminated for at least 3 mo.

The vaccine should be considered for HIV-infected children with a CD4+ T-lymphocyte percentage ≥15%. These children should receive 2 doses of vaccine, 3 mo apart. Specific guidelines for immunizing these children should be reviewed before vaccination. Data indicate that varicella vaccine is highly effective in preventing herpes zoster among children infected with HIV. MMRV should not be administered as a substitute for the component vaccines in HIV-infected children.

Two zoster vaccines are licensed for use for prevention of herpes zoster and to decrease the frequency of postherpetic neuralgia among individuals 50 yr of age and older, with the recombinant vaccine being preferred over the live vaccine.

Zoster vaccines are not indicated for the treatment of zoster or postherpetic neuralgia.

Vaccine-Associated Adverse Events

Varicella vaccine is safe and well tolerated. The incidence of injection site complaints observed ≤3 days after vaccination was slightly higher after dose 2 (25%) than after dose 1 (22%). A mild vaccine-associated varicelliform rash was reported in approximately 1–5% of healthy vaccinees, consisting of 6-10 papular-vesicular, erythematous lesions with peak occurrence 8-21 days after vaccination. Serious adverse reactions confirmed to be caused by the vaccine strain are rare and include pneumonia, hepatitis, meningitis, recurrent herpes zoster, severe rash, and four deaths. Transmission of vaccine virus to susceptible contacts is a very rare event from healthy vaccine recipients (11 instances from 9 vaccinees, all in the presence of a rash in the vaccinee). MMRV vaccine is associated with a greater risk for febrile seizures 5-12 days after the 1st dose among children 12-23 mo of age compared with simultaneous MMR and varicella vaccines (one extra febrile seizure for every 2,500 children vaccinated).

Postexposure Prophylaxis

Vaccine given to healthy children within 3-5 days after exposure (as soon as possible is preferred) is effective in preventing or modifying varicella. Varicella vaccine is now recommended for postexposure use and for outbreak control. Oral acyclovir administered late in the incubation period may modify subsequent varicella in the healthy child; however, its use in this manner is not recommended until it can be further evaluated.

High-titer anti-VZV immune globulin as postexposure prophylaxis is recommended for immunocompromised children, pregnant women, and newborns exposed to varicella. Since 2012 the product licensed for use in the United States is VariZIG. VariZIG is commercially available from a broad network of specialty distributors in the United States (list available at www.varizig.com). The recommended dose is 1 vial (125 units) for each 10 kg increment of body weight (maximum: 625 units), except for infants weighing ≤2 kg who should receive 0.5 vial. VariZIG should be given intramuscularly as soon as possible but may be efficacious up to 10 days after exposure.

Newborns whose mothers have varicella 5 days before to 2 days after delivery should receive VariZIG (0.5 vial for those weighing ≤2 kg and 1 vial for those weighing >2 kg). VariZIG is also indicated for pregnant women and immunocompromised persons without evidence of varicella immunity; hospitalized premature infants born at <28 wk of gestation (or weight <1,000 g) who were exposed to varicella, regardless of maternal varicella immunity; and hospitalized premature infants born at ≥28 wk of gestation who were exposed to varicella and whose mothers have no evidence of varicella immunity. Patients given VariZIG should be monitored closely and treated with acyclovir if necessary once lesions develop.

Close contact between a susceptible high-risk patient and a patient with herpes zoster is also an indication for VariZIG prophylaxis. Passive antibody administration or treatment does not reduce the risk for herpes zoster or alter the clinical course of varicella or herpes zoster when given after the onset of symptoms.

Although licensed pooled IVIG preparations contain anti-VZV antibodies, the titer varies from lot to lot. In situations in which administration of VariZIG is not possible, IVIG can be administered (400 mg/kg administered once within 10 days of exposure). Immunocompromised patients who have received high-dose IVIG (>400 mg/kg) for other indications within 2-3 wk before VZV exposure can be expected to have serum antibodies to VZV.

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[*] The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, US Department of Health and Human Services.

CHAPTER 281

Epstein-Barr Virus

Jason B. Weinberg

Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as glandular fever, it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness.

Etiology

EBV is a double-stranded DNA virus that is a member of the gammaherpesviruses and causes >90% of cases of infectious mononucleosis. Two distinct types of EBV, type 1 and type 2 (also called type A and type B), have been characterized and have 70–85% sequence homology. EBV-1 is more prevalent worldwide, although EBV-2 is more common in Africa than in the United States and Europe. Both types lead to persistent, lifelong, latent infection. Dual infections with both types have been documented among immunocompromised persons. EBV-1 induces in vitro growth transformation of B lymphocytes more efficiently than does EBV-2, but no type-specific disease manifestations or clinical differences have been identified.

As many as 5–10% of infectious mononucleosis–like illnesses are caused by other types of primary infections, particularly cytomegalovirus but also pathogens such as *Toxoplasma gondii*, adenovirus, hepatitis viruses and HIV. In the majority of EBV-negative cases of infectious mononucleosis, the exact cause remains unknown.

Epidemiology

EBV infects more than 95% of the world's population. It is transmitted primarily via oral secretions. Among children, transmission may occur by exchange of saliva from child to child, such as occurs between children in out-of-home childcare. EBV is shed in oral secretions consistently for more than 6 mo after acute infection and then intermittently for life. As many as 20–30% of healthy EBV-infected persons shed virus at any particular time. EBV is also found in male and female genital secretions, and some studies suggest the possibility of spread through sexual contact. Nonintimate contact, environmental sources, and fomites do not contribute to transmission of EBV.

Infection with EBV in developing countries and among socioeconomically disadvantaged populations in developed countries usually occurs during infancy and early childhood. In central Africa, almost all children are infected by 3 yr of age. Among more affluent populations in industrialized countries, half of the population is infected by 6-8 yr of age with approximately 30% of infections occurring during adolescence and young adulthood. In the United States, seroprevalence increases with age, from approximately 54% for 6-8 yr olds to 83% for 18-19 yr olds. Seroprevalence at each age is substantially higher for Mexican-Americans and non-Hispanic blacks than non-Hispanic whites. Large differences are seen by family income, with highest seroprevalence in children of families with lowest income.

The epidemiology of the disease manifestations of infectious mononucleosis is related to the age of acquisition of EBV infection. Primary infection with EBV during childhood is usually asymptomatic or mild and indistinguishable from other childhood infections. Primary EBV infection in adolescents and adults manifests in 30–50% of cases as the **classic triad of fatigue, pharyngitis, and generalized lymphadenopathy** , which constitute the major clinical manifestations of infectious mononucleosis. This syndrome may be seen at all ages but is rarely apparent in children younger than 4 yr of age, when most EBV infections are asymptomatic, or in adults older than 40 yr of age, when most individuals have already been infected by EBV. The true incidence of the syndrome of infectious mononucleosis is unknown but is estimated to occur in 20-70 per 100,000 person-years. In young adults, the incidence increases to approximately 100 per 100,000 person-years. The prevalence of serologic evidence of past EBV infection increases with age; almost all adults in the United States are seropositive.

Pathogenesis

After transmission by saliva to the oral cavity, EBV infects both oral epithelial cells and tonsillar B lymphocytes, although it is unclear which cells are the primary initial targets. Ongoing viral replication leads to viremia and dissemination of infected B lymphocytes into peripheral blood and the lymphoreticular system, including the liver and spleen. Clinical manifestations of infectious mononucleosis, which are due to the host immune response to EBV infection, occur after a 6-wk incubation period following acute infection. The atypical lymphocytes that are frequently detected in patients with infectious mononucleosis are primarily CD8 T lymphocytes. Polyclonal CD8 T lymphocyte activation occurs early during the incubation period following infection, while expansion of EBV-specific CD8 T lymphocytes is detected closer to the time of symptom onset. Natural killer (NK) cells also expand in frequency and number following infection, particularly a $CD56^{dim}$ $CD16^{-}$ NK cell subset that is more effective than other NK cell subsets at recognizing infected cells. The host immune response is effective in rapidly reducing the EBV viral load, although persistent shedding of high levels of virus can be detected in the oropharynx for up to 6 mo. Intermittent shedding from the oropharynx occurs for many years following primary infection.

EBV, like the other herpesviruses, establishes lifelong latent infection after the primary infection. Latent virus persists primarily in memory B lymphocytes. The EBV genome persists as an episome in the nucleus of an infected cell and replicates with cell division. Viral integration into the cell genome is not typical. Only a few viral proteins, including the EBV-determined nuclear antigens (EBNAs), are produced during latency. These proteins are important in maintaining the viral episome during the latent state. Reactivation and new viral replication occurs at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. Reactivation is unlikely to be accompanied by distinctive clinical symptoms.

Clinical Manifestations

The incubation period of infectious mononucleosis in adolescents is 30-50 days. In children, it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. In older patients, the onset of illness is usually insidious and vague. Patients may complain of malaise, fatigue, acute or prolonged (>1 wk) fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1-2 wk. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper quadrant abdominal discomfort and tenderness, which may be the presenting complaint.

The **classic physical examination findings** are generalized lymphadenopathy (90% of cases), splenomegaly (50% of cases), and hepatomegaly (10% of cases). Lymphadenopathy occurs most commonly in the anterior and posterior cervical nodes and the submandibular lymph nodes and less commonly in the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy is particularly suggestive of infectious mononucleosis. Although liver enzymes are often elevated, symptomatic hepatitis or jaundice is uncommon. Splenomegaly to 2-3 cm below the costal margin is typical (15–65% of cases); massive enlargement is uncommon.

The sore throat is often accompanied by moderate to severe pharyngitis with marked tonsillar enlargement, occasionally with exudates (Fig. 281.1). Palatal petechiae at the junction of the hard and soft palate are frequently seen. The pharyngitis is similar to that caused by streptococcal infection. Other clinical findings may include rashes and edema of the eyelids. Rashes are usually maculopapular and have been reported in 3–15% of patients. Patients with infectious mononucleosis who are treated with ampicillin or amoxicillin may experience an **ampicillin rash,** which may also occur with other β-lactam antibiotics (Fig. 281.2). This morbilliform, vasculitic rash is probably immune mediated and resolves without specific treatment. EBV can also be associated with Gianotti-Crosti syndrome, a symmetric rash on the cheeks with multiple erythematous papules, which may coalesce into plaques and persist for 15-50 days. The rash has the appearance of atopic dermatitis and may appear on the extremities and buttocks.

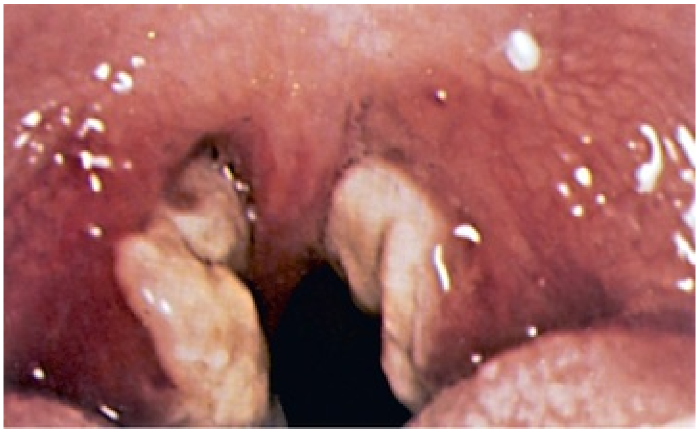

FIG. 281.1 Tonsillitis with membrane formation in infectious mononucleosis. (Courtesy of Alex J. Steigman, MD.)

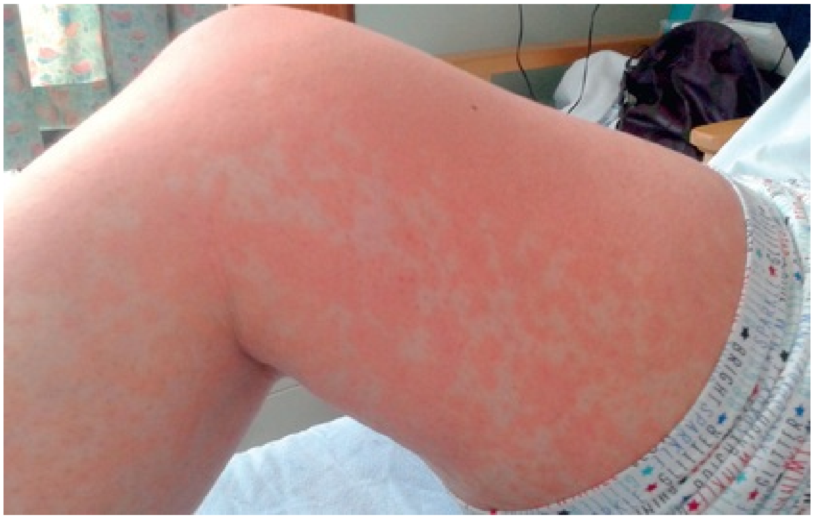

FIG. 281.2 Amoxicillin-induced rash in Epstein-Barr virus infection. Morbilliform maculopapular rash on the leg, which appeared shortly after starting amoxicillin. The rash is typical of that seen in the context of Epstein-Barr virus infection in patients treated with amoxicillin or ampicillin. (From Norman SD, Murray IA, Shetty D, et al: Jaundice, abdominal pain, and fever in a young woman, *Lancet* 390:1713–1714, 2017, Fig. A, p. 1713.)

Diagnosis

A presumptive diagnosis of infectious mononucleosis may be made by the presence of classical clinical symptoms with atypical lymphocytosis in the peripheral blood. The diagnosis is usually confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies.

Differential Diagnosis

EBV is the most common cause of infectious mononucleosis. Infectious mononucleosis–like illnesses may also be caused by primary infection with other pathogens, such as cytomegalovirus, *T. gondii,* adenovirus, and HIV. Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy indistinguishable from that of infectious mononucleosis, but it is not typically associated with hepatosplenomegaly. Approximately 5% of cases of EBV-associated infectious mononucleosis have positive throat cultures for group A streptococcus, representing pharyngeal streptococcal carriage. Failure of a patient with presumed streptococcal pharyngitis to improve within 48-72 hr should evoke suspicion of infectious mononucleosis. Hematologic malignancies should also be considered in a patient with an infectious mononucleosis–like illness, particularly when lymphadenopathy and hepatosplenomegaly are appreciated and the results of an initial laboratory evaluation are not consistent with an infectious etiology.

Laboratory Diagnosis

The majority of patients (>90%) have a leukocytosis of 10,000-20,000 cells/µL, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20–40% of the total number. The atypical cells are mature T lymphocytes that have been antigenically activated. Compared with regular lymphocytes microscopically, **atypical lymphocytes** are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-to-cytoplasm ratio. Although atypical lymphocytosis may be seen with many other infections associated with lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection. Mild thrombocytopenia to 50,000-200,000 platelets/µL occurs in more than 50% of patients but only rarely is associated with purpura. Mild elevation of hepatic transaminases occurs in approximately 75% of uncomplicated cases, but it is usually asymptomatic and without jaundice.

Detection of Heterophile Antibodies

Heterophile antibodies are cross-reactive immunoglobulin M (IgM) antibodies that agglutinate mammalian erythrocytes but are not EBV-specific. Heterophile antibody tests, such as the **monospot** test, are positive in 90% of cases of EBV-associated infectious mononucleosis in adolescents and adults during the second week of illness, but in only up to 50% of cases in children younger than 4 yr of age. Test results can remain positive for up to 12 mo. The false-positive rate is low, generally <10%. A positive heterophile antibody test in a patient with classic clinical manifestations of mononucleosis strongly supports that diagnosis. However, because of the nonspecific nature of heterophile antibody testing, EBV-specific antibody testing should be performed when a precise diagnosis is necessary.

Detection of Epstein-Barr Virus–Specific Antibodies

If the heterophile test result is negative and an EBV infection is suspected, EBV-specific antibody testing is indicated. Measurement of antibodies to EBV proteins including viral capsid antigen (VCA), Epstein-Barr nuclear antigen (EBNA), and early antigen (EA) are used most frequently (Fig. 281.3 and Table 281.1). The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 wk and occasionally up to 3 mo. The IgG response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life.

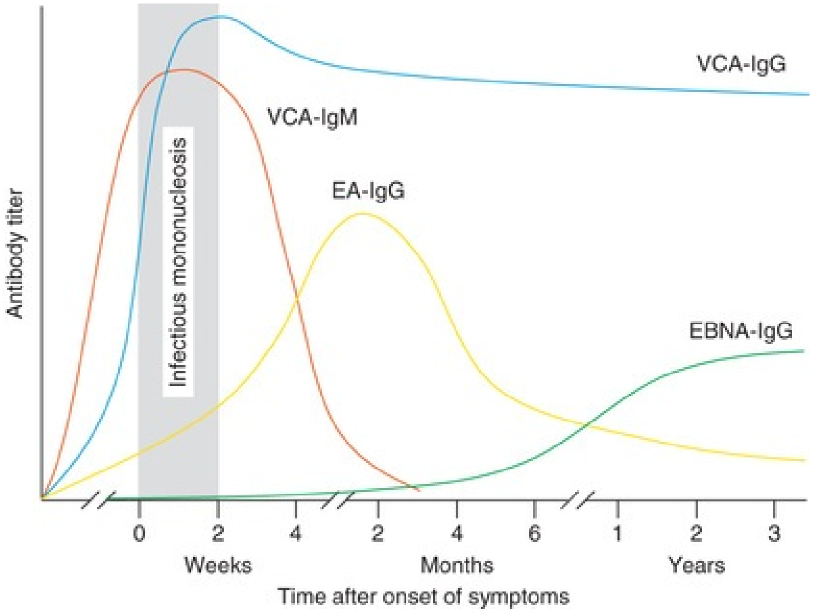

FIG. 281.3 **Kinetics of antibody responses to Epstein-Barr virus (EBV) antigens in infectious mononucleosis. EA, early antigen; EBNA, EBV-determined nuclear antigens; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.**

Table 281.1

Correlation of Clinical Status and Antibody Responses to Epstein-Barr Virus Infection

CLINICAL STATUS	VCA IgM	VCA IgG	EA IgG	EBNA IgG
Susceptible	−	−	−	−
Acute primary infection	+	+	+/−	−
Recent primary infection	+/−	+	+/−	+/−
Past infection	−	+	+/−	+

EA, early antigen (typically the diffuse staining component, or EA-D); EBNA, EBV-determined nuclear antigens; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

Anti-EA IgG antibodies are usually detectable for several months but may persist or be detected intermittently at low levels for many years. Antibodies to the diffuse-staining component of EA (EA-D) are found transiently in 80% of patients during the acute phase of infectious mononucleosis. Antibodies to the cytoplasmic-restricted component of EA (EA-R) emerge transiently in the convalescence from infectious mononucleosis. High levels of antibodies to EA-D or EA-R may be found also in immunocompromised patients with persistent EBV infections and active EBV replication.

Anti-EBNA IgG antibodies are the last to develop in infectious mononucleosis and gradually appear 3-4 mo after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, whereas the presence of anti-EBNA implies infection occurring more than 3-4 mo previously. The wide range of individual antibody responses and the various laboratory methods used can occasionally make interpretation of an antibody profile difficult. The detection of IgM antibody to VCA is the most valuable and specific serologic test for the diagnosis of acute EBV infection and is generally sufficient to confirm the diagnosis.

Detection of Viral DNA

EBV DNA can be detected and viral genome copy number quantified in whole blood, peripheral blood mononuclear cells (PBMC), and plasma using real-time polymerase chain reaction (PCR). EBV DNA can be detected in PBMC and plasma of patients with infectious mononucleosis for a brief period of time after the onset of symptoms and in PBMC for an extended period of time. However, detection of EBV DNA is usually not necessary to diagnose infectious mononucleosis in immunocompetent patients with typical manifestations of disease. In contrast, serial measurements of EBV genome copy number are often used following solid organ or hematopoietic stem cell transplantation as surveillance for posttransplant lymphoproliferative disease (PTLD). Very high or consistently increasing EBV genome copy number suggests an increased risk for PTLD, although definitive diagnosis is typically based on tissue biopsy. The frequency and duration of monitoring EBV genome copy number is determined by the time after transplant and risk factors such as the type of transplant and the degree of immunosuppression. Serial measurement of EBV genome copy number can be useful in monitoring response to therapy for PTLD. Measurement of EBV genome copy number can also be used for screening and to determine prognosis for some EBV-associated malignancies, such as nasopharyngeal carcinoma and Hodgkin lymphoma.

Complications

Severe complications are unusual in patients with infectious mononucleosis. Splenic rupture, either spontaneous or following mild trauma, may occur in approximately 0.1% of cases but is rarely fatal. Airway obstruction due to swelling of oropharyngeal lymphoid tissue occurs in <5% of cases. A variety of neurologic conditions have been associated with EBV infectious mononucleosis. Headache is a common symptom, but symptomatic meningitis or encephalitis is uncommon. More severe neurologic manifestations, such as seizures and ataxia, may occur in 1–5% of cases. Perceptual distortions of sizes, shapes, and spatial relationships, known as the **Alice in Wonderland syndrome (metamorphopsia)** , may be a presenting symptom. Some reports suggest an association between infectious mononucleosis and the possible development of multiple sclerosis. Hematologic abnormalities such as mild hemolytic anemia, thrombocytopenia and neutropenia are relatively common, but aplastic anemia, severe thrombocytopenia, and severe neutropenia are rare. Other rare complications include myocarditis, interstitial pneumonia, pancreatitis, parotitis, and orchitis.

Patients with dysregulated immune responses to primary infection, such as individuals with primary or secondary **hemophagocytic lymphohistiocytosis (HLH)** , can develop severe, life-threatening complications with primary EBV infection. Patients with other primary immunodeficiencies that result in failure to control EBV infection and/or abnormal inflammatory responses to infection are at risk for severe manifestations of EBV infection, often with fulminant infectious mononucleosis, chronic viremia, dysgammaglobulinemia, and lymphoproliferation. Immunodeficiencies most commonly linked to severe EBV infection tend to be those affecting aspects of NK cell, T lymphocyte, and NKT lymphocyte function. Examples include X-linked lymphoproliferative (XLP) syndrome, which is caused by mutations in genes encoding the signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) or X-linked inhibitor of apoptosis (XIAP); X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia (XMEN), caused by mutations in *MAGT1* , which encodes a magnesium transporter protein; and deficiencies in IL-2-inducible T-cell kinase (ITK), CD27, or CD70.

Oncogenesis

Infection with EBV, the first human virus to be associated with malignancy, accounts for up to 2% of cancers worldwide. Manipulation of infected cells by EBV to establish and maintain latency can lead to transformation and oncogenesis. EBV is associated with lymphoid malignancies, such as Burkitt lymphoma, Hodgkin lymphoma, aggressive NK cell leukemia, T- and NK cell lymphoproliferative disorder, and epithelial cell malignancies such as nasopharyngeal carcinoma and gastric carcinoma.

Endemic Burkitt lymphoma is the most common childhood cancer in equatorial East Africa and New Guinea. These regions are holoendemic for *Plasmodium falciparum* malaria and have a high rate of EBV infection early in life. Constant exposure to malaria is thought to act as a B lymphocyte mitogen that contributes to the polyclonal B-lymphocyte proliferation with EBV infection, impairs T lymphocyte surveillance of EBV-infected B lymphocytes, and increases the risk for developing Burkitt lymphoma. Approximately 98% of cases of endemic Burkitt lymphoma contain the EBV genome compared with only 20% of nonendemic (sporadic) Burkitt lymphoma cases in other areas of the world.

The incidence of **Hodgkin lymphoma** peaks in childhood in developing countries and in young adulthood in developed countries. Infection with EBV increases the risk for Hodgkin lymphoma by a factor of 2-4, with the risk of developing Hodgkin lymphoma peaking at 2.4 yr following infectious mononucleosis. EBV is associated with more than half of cases of mixed cellularity Hodgkin lymphoma and approximately one quarter of cases of the nodular sclerosing subtype, but it is rarely associated with lymphocyte-predominant Hodgkin lymphoma. Immunohistochemical studies have localized EBV to the Reed-Sternberg cells and their variants, the pathognomonic malignant cells of Hodgkin lymphoma.

Numerous congenital and acquired immunodeficiency syndromes are associated with an increased incidence of EBV-associated B-lymphocyte lymphoma, especially central nervous system lymphoma and leiomyosarcoma. Congenital immunodeficiencies predisposing to EBV-associated lymphoproliferation include XLP syndrome, common-variable immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. Individuals with acquired immunodeficiencies resulting from anticancer chemotherapy, immunosuppression after solid organ or hematopoietic cell transplantation, or HIV infection have a significantly increased risk for EBV-associated lymphoproliferation. The lymphomas may be focal or diffuse and are usually histologically polyclonal but may become monoclonal. EBV-associated PTLD can occur following solid organ transplantation and, less commonly, allogeneic hematopoietic cell transplantation. The most important risk factors for PTLD are the degree of T lymphocyte immunosuppression and recipient EBV serostatus.

Treatment

There is no specific treatment for infectious mononucleosis. The mainstays of management are rest, adequate fluid and nutrition intake, and symptomatic treatment to manage fever, throat discomfort, and malaise. Bed rest is necessary only when the patient has debilitating fatigue. As soon as there is definite symptomatic improvement, the patient should be encouraged to resume normal activities. Because blunt abdominal trauma may predispose patients to splenic rupture, it is customary and prudent to advise against participation in contact sports and strenuous athletic activities during the first 2-3 wk of illness or while splenomegaly is present.

Antiviral therapy is not recommended. Although nucleoside analogs such as acyclovir inhibit viral replication in vitro and decrease the duration of oropharyngeal viral shedding in patients with infectious mononucleosis, they have not been shown to not provide consistent clinical benefit for patients with infectious mononucleosis or EBV-associated malignancies. Short courses of corticosteroids may be helpful for selected complications of infectious mononucleosis, such as airway obstruction, but there are insufficient data to support the use of corticosteroids to control typical symptoms in patients with infectious mononucleosis. Adoptive immunotherapy involving the infusion of EBV-specific cytotoxic T lymphocytes has shown some promise in early trials for transplant recipients with PTLD and for other patients with EBV-associated malignancies.

Prognosis

The prognosis for complete recovery is excellent. The major symptoms typically last 2-4 wk, followed by gradual recovery within 2 mo of symptom onset. Cervical lymphadenopathy and fatigue may resolve more slowly. Prolonged and debilitating fatigue and malaise may wax and wane for several weeks to 6 mo and are common complaints even in otherwise unremarkable cases. Occasional persistence of fatigue for a few years after infectious mononucleosis is well recognized. There is no convincing evidence linking EBV infection or EBV reactivation to chronic fatigue syndrome.

Prevention

Vaccination against EBV would be appealing strategy to prevent acute disease (infectious mononucleosis) and complications such as EBV-associated malignancies. Early clinical trials using strategies targeting the EBV gp350 envelope glycoprotein demonstrated some protection against symptomatic infectious mononucleosis, although vaccination did not prevent EBV infection. No EBV vaccine is currently approved for clinical use.

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CHAPTER 282

Cytomegalovirus

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Human cytomegalovirus (CMV) is ubiquitous in the population, and individuals who become infected remain persistently infected for life, with intermittent shedding of infectious virus from mucosal surfaces. Although CMV rarely causes symptoms in normal individuals, it is an important cause of morbidity and sometimes death in immunocompromised hosts. CMV remains a well-recognized cause of disease in the newborn infant following intrauterine infection (congenital CMV) and the allograft recipients undergoing posttransplantation immunosuppression. CMV emerged as the most common opportunistic infection in HIV/AIDS patients prior to the advent of effective retroviral therapy. Invasive CMV infections can be observed in patients treated with immunosuppressive biologics such as anti-tumor necrosis factor (TNF) antibodies. In each of these clinical situations, the association of disease with CMV infection has been linked to high levels of virus replication and end organ disease, usually associated with virus dissemination. In contrast, there is likely another group of disease states associated with chronic effects of persistent CMV infection that reflects the robust inflammatory response induced by this virus. Such associations have included coronary artery disease, transplant vasculopathy and cardiac allograft loss, tubular sclerosis and renal allograft loss, exacerbations of inflammatory bowel disease, and possibly some cancers such as glioblastoma. In addition, there continues to be debate surrounding the role of CMV in immune senescence and the decrease in immune responsiveness observed in aging. Whether definitive evidence will eventually directly link CMV to these disease states is uncertain, but it is clear that understanding the complex biology of CMV infections, including the virus-mediated control of ensuing host responses to infection with this virus, will provide new insight into each of these diseases.

The Virus and Its Interaction With the Host

CMV is the largest of the human herpesviruses, with an estimated size of 190 nm. The 230 kb double-stranded DNA genome is about 50% larger than the herpes simplex virus genome and encodes over 200 open reading frames, which include 100 unique virion proteins and an unknown number of nonstructural proteins. Viral DNA replication takes place in the nucleus of the infected cell followed by virus assembly in both the nucleus and cytoplasm. The structure of the virus is typical of herpesviruses and includes a complex envelope composed of host cell–derived membrane studded with virion glycoproteins, an amorphous area between the envelope and the capsid called the tegument layer, and an icosahedral capsid that contains the virion DNA. The tegument layer is highly immunogenic and induces strong adaptive immune responses, including CMV specific CD8+ cytotoxic T lymphocytes that are thought to play a pivotal role in controlling CMV replication in the infected host. Likewise, the protein components of the viral envelope are also immunogenic and believed to induce protective antibody responses that have been correlated with virus neutralization. In vivo, CMV appears to replicate in nearly all tissue and cell types whereas in vitro productive virus replication (production of infectious progeny) occurs in primary cells derived from epithelial tissue and the dermis. Literature from the 1990s suggested that each strain of CMV isolated from epidemiologically unrelated individuals was genetically unique, a finding suggesting that an infinite number of distinct viruses existed in the human population. This observation has been validated with next-generation sequencing technologies, which have provided evidence that CMV exists as genetically diverse forms within an individual. This finding has argued that during replication, CMV DNA synthesis is fraught with error rates that are much higher than previous studies would predict and/or potential recombination events if permissive cells are infected with genetically diverse populations of viruses. Thus repeated exposures to CMV over time could result in an individual acquiring a library of CMVs as reinfection of previously infected individuals with new strains of CMV appears commonplace. These observations have led many investigators to argue that CMV must express an armamentarium of immune evasion functions that allow it to remain hidden from protective host immunity. This relationship between host and virus is best illustrated by the finding that over years a persistently infected individual can maintain a stable virus load, unwavering antiviral antibody responses, and in some individuals, up to 15% of a total peripheral blood CD8+ CTL activity dedicated to recognition of CMV infected cells, suggesting that a détente has been established between virus replication and host innate and adaptive antiviral immunity. Thus CMV efficiently persists in an infected host for a lifetime while inducing chronic immune activation. This latter characteristic of the biology of CMV infection has supported a linkage between CMV and many of the chronic diseases that have been associated with this ubiquitous virus.

Epidemiology

CMV infections are acquired through several settings: (1) community exposure, (2) nosocomial transmission, and (3) intrauterine infection. **Community acquisition** occurs throughout life and is linked by exposure to CMV that is shed from mucosal surfaces such as saliva, genital secretions, and urine. Peaks in exposure occur during childhood and in adolescents and young adults, presumably in the latter cases secondary to sexual activity. Common routes of infection of the very young infant include perinatal exposure to infected genital secretions during birth and ingestion of CMV-containing breast milk. Breastfeeding is the most common route of CMV infection in early childhood. Ingestion of breast milk from seropositive women results in a rate of infection of about 60% in infants. Infection is most common during the first several months of breastfeeding, but the risk continues for the duration of breastfeeding. Infants infected through breast milk excrete virus in the saliva and urine for prolonged periods of time measured in months to years and thus serve as a reservoir of virus for spread to other infants, children, and adults. After this period of intense exposure to CMV during the first year of life, infection in the remainder of childhood and early teenage years depends on specific exposures such as enrollment in group childcare facilities and/or exposure to infected, similarly aged siblings. Up to 50% of young infants and children attending group care facilities can be excreting CMV, a source of virus that can result in infection of children enrolled in the facility and in some cases the adult workers in the facility. Furthermore, once infected at a group care facility, infants can then transmit virus to their parents and siblings, thus providing a mechanism for spread of CMV within the community. Throughout childhood and early adulthood, CMV is transmitted by exposure to saliva and urine. However, as noted above, in adolescence and early adulthood there is a spike in infection presumably associated with sexual exposure. CMV is considered a sexually transmitted infection, and a wealth of data has shown an increased rate of infection in the sexually active population as well as transmission in CMV-discordant couples. In summary, exposure to young children and sexual exposure represent the most consistent risk factors for acquisition of CMV infection.

Nosocomial infections with CMV are well described and are associated with exposure to blood products containing CMV and less commonly through allograft transplantation following transplantation of an organ from a CMV-infected donor. Prior to improvements in blood banking that limited the number of leukocytes in red cell transfusions and that more efficiently identified CMV infected donors, transmission of CMV by blood transfusion was not uncommon and closely related to the volume of blood that was transfused. Transfusion-acquired CMV infections often resulted in symptomatic illness, with laboratory findings including hepatitis and thrombocytopenia in children and adults. In newborn infants lacking antibodies to CMV secondary to being born to women without seroimmunity to CMV or in cases of extreme prematurity, severe and sometimes fatal infections could develop. Similarly, immunocompromised patients who received CMV-containing blood were also at risk for severe infection, regardless of their prior exposure to CMV. Methodologies that more efficiently deplete contaminating leukocytes and the use of blood products from CMV seronegative donors have greatly decreased the incidence of transfusion-associated CMV infections. Finally, CMV transmission through infected allografts is well described and infections arising from CMV transferred in the allograft are a major cause of morbidity in both the early and late period after transplantation. Severe infections and graft loss are more often associated with mismatches between the donor and recipient, as occurs if the donor has a history of CMV infection (donor, CMV positive) and the recipient has not been exposed to CMV (recipient, CMV negative; D+/R− mismatch). Even with effective antiviral therapy to modify CMV infections in the early posttransplant period, CMV infection remains linked to long-term graft dysfunction and graft loss, a particularly important problem in cardiac and lung transplant recipients.

Congenital CMV infection (present at birth) occurs following intrauterine transmission of CMV. Rates of congenital infection between 0.4% and 1.0% have been reported in the United States, with perhaps the best estimate being about 0.4% based on a large multicenter study. Rates as high 2% in some areas in Asia and Africa have also been described. Although the mechanism of transmission remains an active area of investigation, CMV is thought to be transferred to the developing fetus following hematogenous spread of CMV to the placenta, presumably followed by cell-free transfer of virus to the fetal blood system. The rate of transmission to the fetus is about 30% in women with primary infection during pregnancy; in utero infections also occur in previously immune women (nonprimary infection), albeit at a reduced rate that has been suggested to be on the order of 1–2%. This latter rate is an estimate because the number of previously immune women who experience active infection during pregnancy is not known. It is important to note that although the rate of transmission of CMV is more frequent following primary maternal infection, the absolute number of congenitally infected infants born to women with nonprimary infections in most populations outnumber those resulting from primary maternal infection by 3-4-fold. This is particularly true in Africa, South America, and Asia, where maternal seroimmunity to CMV often exceeds 95%. Interestingly, these populations also have the highest rates of congenital CMV infections. The source of nonprimary infection is also somewhat controversial. Older reports suggested that nonprimary infection followed reactivation (recurrence) of virus infection in seroimmune women, whereas more recent literature has demonstrated that reinfection by genetically distinct strains of CMV occurs in previously infected women and these newly acquired viruses can be transmitted to the developing fetus. In some studies, the reinfection rates are about 15–20%, with annualized rates as high as 25%. Thus immunity to CMV is far from protective, although it has been inferred from existing epidemiological data that it can modify the risk of transmission to the developing fetus.

Mechanisms of Disease Associated With Cytomegalovirus Infections

The mechanism(s) of disease associated with CMV infections remains undefined for most clinical syndromes that follow CMV infection. Several reasons have contributed to the overall lack of understanding of the pathogenesis of CMV infections and include: (1) the asymptomatic nature of infections in almost all immunocompetent individuals; (2) the complexity of the underlying disease processes in immunocompromised hosts that often confound the assignment of specific manifestations of CMV infection; (3) the species-specific tropism of human CMV; and perhaps most importantly, (4) limitations inherent in observational studies in humans. The strict species specificity of most CMVs has been a major limitation in the development of animal models that closely recapitulate human CMV infections. However, models have been developed in nonhuman primates, guinea pigs, and rodents to address specific aspects of the biology of CMVs. Although CMV replicates in a limited number of cells types in vitro, CMV inclusions, antigens, and nucleic acids can be demonstrated in almost all organ systems and cell types in individuals with severe, disseminated infections. The virus does not exhibit strict cellular or organ system tropism in vivo. Hematogenous dissemination has been argued to be associated primarily with cell-associated virus, and significant levels of plasma virus are usually detected only in severely immunocompromised hosts with high total-blood viral loads. Virus and viral DNA can be recovered from neutrophils, monocytes, and endothelial cells present in peripheral blood. High levels of virus replication can result in end-organ disease, secondary to direct virus-mediated cellular damage. These manifestations of CMV infections are thought to result from uncontrolled virus replication and dissemination, secondary to deficits in innate and adaptive immune responses to CMV. In some cases, clinical disease has been observed in patients without significant levels of virus replication, a finding suggesting indirect mechanisms of disease such as immunopathologic responses to CMV. Such a mechanism was clearly operative in patients with immune recovery vitritis, a pathological T-lymphocyte–mediated response to CMV in HIV/AIDS patients with CMV retinitis that closely followed the reconstitution of their virus-specific T lymphocyte responses following active retroviral therapy. Likewise, the level of virus replication has not been closely correlated with several chronic diseases thought to be linked to CMV, an observation that is consistent with indirect mechanisms of disease such as immunopathologic responses. These mechanisms are better described in animal models of human CMV disease.

From early observations in patients with invasive CMV infections in allograft recipients it was apparent that immunosuppressive therapies that resulted in altered T lymphocyte function predisposed these patients to severe infections. These observations that were first described in the 1970s were confirmed in multiple studies over the following decade. Definitive evidence consistent with this mechanism was provided by a clinical study that demonstrated that in vitro expanded, CMV-specific cytotoxic T lymphocytes could limit invasive infection in hematopoietic cell transplant recipients. Invasive infections such as retinitis and colitis in HIV/AIDS patients with very low CD4+ T-lymphocyte counts also clearly demonstrated the importance of T lymphocyte responses and invasive

CMV infections. Other studies in solid organ transplant (SOT) recipients have demonstrated that the passive transfer of immune globulins containing high titers of anti-CMV antibodies could provide some degree of protection from invasive disease, a finding that was consistent with the proposed role of antiviral antibodies in limiting CMV dissemination and disease in animal models of invasive CMV infections. The importance of innate immune responses such as natural killer (NK) cells and γδ T lymphocytes in limiting invasive infections have been well documented in representative animal models but definitive evidence for a key role in resistance to CMV infections in humans is limited. Lastly, effector molecules such as γ-interferon appear to a play an important role in controlling local CMV infections in animal models, but evidence of a similar role in humans has not been shown experimentally.

The control of acute CMV infection is clearly dependent on an effective adaptive immune response; however, even a vigorous T lymphocyte response is not sufficient to eliminate CMV from the infected host, as CMV persists for the lifetime of the host either as a low level chronic infection or as a latent infection with limited transcription from specific regions of its genome. The inability of the host to completely clear CMV remains incompletely understood, but the large array of immune evasion functions encoded by this virus likely contributes to the blunted innate and adaptive immune response. These functions include: (1) inhibition of apoptotic and necroptotic functions of infected cells; (2) inhibition of interferon regulated responses; (3) inhibition of NK cell activation; (4) downregulation of class I MHC expression, inhibition of class II MHC function; and (5) mechanisms to limit antibody recognition of envelope proteins such as carbohydrate masking of antibody recognition sites and extensive variation in amino acid sequences in virion envelop proteins. Although each of these functions by itself could potentially have only limited effects on virus clearance secondary to the redundancy of antiviral activities of the host immune system, when acting in concert they likely provide the virus an advantage that leads to its persistence. The importance of these evasion functions has been shown in animal models, and specific immune evasion functions have been shown to facilitate virus dissemination and persistence, reinfection with genetically similar viruses, as well as reinfections with new strains of virus in animals with existing immunity to CMV.

Clinical Manifestations

The clinical manifestations of CMV infection reflect the level of virus replication and the end-organ involvement. The manifestations of invasive CMV infections have been most commonly identified with syndromes that could be associated with a primary infection defined as an infection in an individual without existing immunity to the virus. Chronic CMV infections that have been associated with disease syndromes almost always have concurrent manifestations of the underlying causes of the primary disease, thus confounding the role of CMV in the primary disease process and its contribution to the clinical syndromes in these patients.

Normal Host

In the overwhelming majority of patients with acute CMV infections, there are no specific symptoms or clinical findings. In patients with symptomatic, acute CMV infection, clinical findings most commonly resemble a mononucleosis-like syndrome, with fatigue and occasionally cervical adenopathy. It has been reported that up to 20% of heterophile antibody negative mononucleosis could be attributed to CMV. Laboratory findings could include mild elevation of hepatic transaminases and decreased platelet counts.

Immunocompromised Host

The clinical presentation of CMV infection in immunocompromised hosts often reflects the magnitude of the immunodeficiency. Profoundly immunocompromised hosts such as hematopoietic stem cell transplantation (HSCT) recipients can present with disseminated infection and clinical manifestations reflecting disease in multiple organ systems, including liver, lung, gastrointestinal tract, and, less frequently, the CNS. Organ-threatening and life-threatening disease is not infrequent. In less immunocompromised patients such as most SOT recipients, CMV infection can present with fever, hematological abnormalities including leukopenia and thrombocytopenia, and mild hepatocellular dysfunction. In contrast to renal and liver SOT recipients, heart-lung and lung transplant recipients are at high risk for severe manifestations from CMV infection, presumably because the transplanted organ is a site of virus replication, disease, and life-threatening dysfunction. Prior to widespread use of antivirals for prophylaxis of allograft recipients, clinical disease usually developed between 30 and 60 day posttransplantation. More recently, prolonged antiviral prophylaxis has nearly eliminated CMV disease in the early posttransplant period in most SOTs, but late manifestations of CMV infection often become apparent after discontinuation of antiviral prophylaxis. These late manifestations are most worrisome in HSCT recipients, as they may signal deficits in graft function leading to invasive CMV infections. Finally, long-term graft function has been reported to be influenced by CMV infection. This has been most well studied in the renal allograft recipients and is thought by some investigators to represent a significant cause of chronic graft dysfunction and loss. Perhaps the most dramatic impact of CMV infection late in the posttransplant period can be seen in heart transplant recipients, where CMV is believed to play a major role in transplant vascular sclerosis, a vasculopathy of the coronary arteries in the allograft leading to loss of the transplanted heart.

Congenital Infection

Congenital infection with CMV can present with symptomatic infections (Table 282.1) in about 10% of infected newborns, whereas 90% of infected infants will have *no clinical manifestations* of infection in the newborn period and can be identified only by newborn screening programs. **Severe multiorgan disease** is infrequent and occurs in less than 5% of infants with congenital CMV infections. The clinical findings in infants with symptomatic congenital CMV infections can include hepatosplenomegaly, petechial rashes, jaundice, and microcephaly. These findings were utilized for decades in natural history studies to classify infants has having symptomatic or asymptomatic infections; however, more recently several authors have included intrauterine growth restriction as a finding of symptomatic congenital CMV infection. Laboratory findings are consistent with the clinical findings and include direct hyperbilirubinemia, elevation of hepatic transaminases, thrombocytopenia, and abnormal findings on cranial ultrasonography/computed tomography. If cerebrospinal fluid is obtained, there can be evidence of encephalitis, with elevation of mononuclear cell number and, in some cases, elevation of protein. A small number of symptomatically infected infants (<10%) will be found to have chorioretinitis. Finally, because hearing loss is the most common long-term sequelae associated with congenital CMV infection, the failure of an infant to pass a newborn hearing screening exam should alert caregivers to the possibility of congenital CMV infection. Hearing loss in the older infant and young child should also alert the clinician to the possibility of congenital CMV infection as about 50% of infants with hearing loss associated with congenital CMV infection will pass an initial hearing screening exam but develop hearing loss in later infancy and early childhood. Importantly, hearing loss can be progressive in infants with hearing loss secondary to congenital CMV infections. Lastly, the diagnosis of congenital CMV infection must be made within the first 2-3 wk of life, and congenital CMV infection cannot be assumed to be the cause of hearing loss in older infants without evidence of CMV infection in the newborn period.

Table 282.1

Findings in Infants With Symptomatic Congenital Cytomegalovirus Infection

FINDINGS	% OF INFANTS
CLINICAL FINDINGS	
Prematurity (<37 wk)	24
Jaundice (direct bilirubin >2 mg/dL)	42
Petechiae	54
Hepatosplenomegaly	19
Purpura	3
Microcephaly	35
IUGR	28
1 clinical finding	41
2 clinical findings	59
LABORATORY FINDINGS	
Elevated ALT (>80 IU/mL)	71
Thrombocytopenia (<100,000 k/mm^3)	43
Direct hyperbilirubinemia (>2 mg/dL)	54
Head CT abnormalities	42

Findings in 70 infants with symptomatic congenital CMV infection identified during newborn screening program for infants with congenital CMV infection at the University of Alabama Hospitals over an approximate 20 yr interval.

CMV, cytomegalovirus; IUGR, in utero growth retardation; ALT, alanine aminotransferase.

An organized plan for follow-up is an important component of the clinical management of infants with congenital CMV infection. Because permanent sequelae are limited to disorders of the nervous system, long-term follow-up should include appropriate assessment of development and neuromuscular function in infected infants, with referral to specialized care if necessary. Hearing loss will develop in about 11% of infected infants, and in some infants hearing loss will progress during infancy. Thus audiologic testing and follow-up are mandatory in these patients. Other sequelae such as vision loss are infrequent, but vision testing and comprehensive eye examinations should be included in the care plan of infants with congenital CMV infection.

Perinatal Infection

Perinatal infections can be acquired during birth or following ingestion of CMV-containing breast milk. In almost all cases perinatal infections have not been associated with any clinical manifestations of infection and perhaps more importantly, have not been associated with any long-term sequelae. In rare cases such as is seen in breast milk transmission of CMV to extremely premature infants or infants born to nonimmune women, perinatal infection can result in severe, disseminated infections associated with end-organ disease and death. These more severe infections are thought to develop in infants that lack transplacentally acquired antiviral antibodies, either secondary to extreme prematurity, or as the product of a mother lacking anti-CMV antibodies. However, definitive evidence supporting this explanation is lacking.

Diagnosis

In the nonimmunocompromised individual, diagnosis of CMV infection requires evidence of a primary infection. Serological reactivity for CMV is lifelong following primary infection; therefore the presence of immunoglobulin G (IgG) antibody to CMV does not provide evidence of acute infection. In addition, IgM reactivity for CMV can be detected for prolonged periods after acute infection and cannot be used to reliably estimate the duration of infection. Furthermore, recovery of virus from body fluids such as saliva or urine does not in itself permit diagnosis of CMV infection, because persistently infected individuals can intermittently shed virus. In the immunocompromised host, CMV can frequently be recovered from patients in the absence of evidence of invasive CMV infection. Thus assignment of CMV as a cause of disease in this patient population must be made carefully, and other potential causes of symptoms and clinical findings in these patients must also be considered. Serological assays are of limited value in the transplant recipient secondary to impact of immunosuppression on antibody responses in the allograft recipient. Moreover, IgM antibodies can be produced following a nonprimary infection in these patients. Sequential viral load measurements by polymer chain reaction (PCR) in relevant body fluids such as blood and measurements of CMV DNA in biopsy tissue can be of great value in establishing CMV as a cause of disease in allograft recipients. Histopathological detection of characteristic owl eye inclusion–bearing cells is insensitive but can point to a diagnosis of invasive CMV infection. The addition of immunohistochemistry for the detection of CMV-encoded proteins and/or in situ hybridization for the detection of CMV nucleic acids has greatly improved histologic detection of CMV in tissue specimens.

Congenital Infections

The diagnosis of congenital CMV infections requires the recovery of replicating virus and/or viral nucleic acids within the first 2-3 wk of life. Sources of virus and viral nucleic acids include urine, saliva, and blood. Methods of detection include routine virus culture combined with immunofluorescence and PCR. Although quantification of virus in various specimens can suggest the likelihood of long-term sequelae such as hearing loss for a population of infected newborns, the predictive value for the individual patient remains limited. A considerable amount of effort has been devoted to identifying screening assays that would be suitable for populations of newborn infants. Initial interest centered on dried blood spots, because these samples are routinely collected as a component of newborn screening programs. Unfortunately, studies have indicated that the sensitivity of dried blood spots is too low to be considered useful for screening. In contrast, newborn screening using saliva has proven sensitive and specific and is now standard for newborn screening in some institutions. Identification of an infected infant by screening of saliva requires confirmation, preferably by assaying urine for the presence of CMV.

Early studies suggested that congenitally infected newborn infants could be identified by CMV-specific IgM reactivity and that elevated levels of CMV-specific IgM correlated with severity of disease. Subsequent studies have demonstrated that although this assay was of some value, the limited sensitivity of most assays employed to detect newborn IgM has also limited their clinical utility.

Noncongenital Infections

In nonimmunocompromised patients, demonstration of CMV-specific IgG seroconversion or the presence of CMV-specific IgM antibodies represents evidence of a newly acquired CMV infection. IgM anti-CMV antibody reactivity can persist for months depending on the sensitivity of the particular assay, thus limiting the use of IgM detection to precisely time the acquisition of CMV. The use of the IgG avidity assays in which CMV-specific binding antibodies are eluted with increasing concentrations of chaotropic agents such as urea can be used to estimate the duration of infection. This assay has been used almost exclusively in the management of CMV infections during pregnancy to aid in defining primary maternal infections. Detection of CMV in urine, saliva, blood, and tissue specimens obtained at biopsy can most reliably be accomplished by PCR-based methods, and because findings can be quantified, treatment responses can be monitored. However, conventional culture of CMV using human dermal fibroblasts often combined with immunofluorescence detection of CMV-encoded immediate early antigens also remains standard in many institutions. Routine histological stains allow detection of characteristic nuclear inclusions in tissue specimens (see above).

Treatment

Treatment of *immunocompromised hosts* with invasive CMV disease has been shown to limit both the morbidity and the mortality in the patient with disseminated CMV infections with end-organ disease. This has been shown in allograft transplant recipients and patients with HIV/AIDS. Similarly, antiviral prophylaxis can limit the development of clinically important CMV disease in allograft recipients and is the standard of care in most transplant centers. Several agents are currently licensed for CMV infections, including ganciclovir, foscarnet, and cidofovir, and all have appreciable toxicity. Newer agents such as letermovir have been licensed for use in adults and it is expected that indications for this agent will extend into pediatrics. In some transplant centers, high-titer CMV immunoglobulins have been included as a component of prophylaxis. Early on, when the treatment of CMV infections with antiviral agents was in its infancy, treatment with CMV immunoglobulins was shown to alter the natural history of CMV infection in renal and liver allograft recipients. The effectiveness of antiviral agents when used as prophylaxis in the immediate posttransplant period has resulted in less frequent use of these biologics.

Treatment of **congenitally infected infants** with ganciclovir has been studied in several clinical trials, and a significant number of infected infants have been treated off-label with this agent because of severe CMV infections. Two studies conducted by the Collaborative Antiviral Study Group (CASG) sponsored by the

NIH have suggested that 6 wk of intravenously administered ganciclovir or 6 mo of an oral preparation of ganciclovir could limit hearing loss and possibly improve developmental outcome of infected infants. Long-term outcomes of treated infants are not known; thus it is difficult to definitively interpret these studies. In addition, infants with severe perinatal CMV infection following breast milk ingestion with documented end-organ disease have been successfully treated with ganciclovir. Currently, there are no recommendations for the treatment of infants with congenital CMV infection, although the results from a larger study that will determine the efficacy of treatment in infants with asymptomatic congenital CMV infections may provide sufficient data to firmly establish treatment guidelines.

Prevention

Passive Immunoprophylaxis

As was described in the preceding section, passive transfer of anti-CMV antibodies has been utilized to limit disease but not infection in allograft recipients. A similar approach has also been considered for prevention of intrauterine transmission of CMV and disease based on studies in animal models and limited observational data that suggested a role of antiviral antibodies in limiting disease following CMV infections in the perinatal period. An uncontrolled trial of human immune globulin reported in 2005 provided provocative evidence that passive transfer of anti-CMV antibodies to pregnant women undergoing primary CMV infection could limit transmission and disease. This study was seriously flawed in design, and findings from this trial were controversial. A second study utilizing the same immune globulin preparation failed to demonstrate that immune globulins provided protection from intrauterine transmission or disease. Thus it remains to be determined if passively transferred anti-CMV antibodies can modulate infection and disease following intrauterine exposure to CMV. A larger multicenter trial sponsored by the NIH (NICHD) has been terminated and results of this study should be available in the near future.

Active Immunoprophylaxis

Active immunization for the prevention of congenital CMV infection (and in transplant recipients) has been a goal of biomedical research for over 3 decades. A number of different vaccine platforms have been explored, including replicating attenuated CMV as vaccines, protein-based vaccines, heterologous virus-vectored CMV vaccines, and DNA vaccines. In all cases, some level of immunity has been induced in volunteers. Larger scale trials have been carried out using replication competent, attenuated CMV vaccines and adjuvanted recombinant protein vaccines. Current approaches are directed toward development of an adequately attenuated replicating CMV that retains sufficient immunogenicity to induce protective responses. In contrast to current status of candidate attenuated CMV vaccines, considerable progress has been made in the testing of adjuvanted recombinant viral proteins. An adjuvanted recombinant glycoprotein B, a major protein component of the envelope and target of neutralizing antibodies, has been shown to induce virus neutralizing antibodies and CD4+ T lymphocyte proliferative responses. Moreover, this vaccine reduced virus acquisition by about 50% in a trial carried out in young women. However, closer examination of this vaccine trial revealed that protection was very short-lived and that the effectiveness of the vaccine was not convincingly demonstrated because of the small numbers of subjects in the trial, despite the statistical significance. A follow-up trial in adolescent women using the same vaccine preparation failed to show any statistically significant difference between vaccine and placebo recipients. Finally, a major question that will face all vaccine programs is whether existing immunity in seropositive women can be augmented to a level to prevent damaging infection in their offspring. The maternal population with existing immunity to CMV prior to childbearing age is responsible for the greatest number of congenitally infected infants in almost all regions of the world; thus merely recapitulating naturally acquired adaptive immunity to CMV with a vaccine may not be sufficient to prevent congenital CMV infection and/or limit disease.

Counseling

Studies of the natural history of CMV have repeatedly demonstrated that transmission requires close, often direct contact with infected material such as secretions from the oral or genitourinary tract. Although limited data suggest that CMV can be transmitted on fomites, infectivity can persist for hours on surfaces such as toys. Limiting exposure to such secretions and attention to hygiene such as handwashing can drastically limit acquisition of CMV. Counseling has been shown to be very effective in the prevention of CMV infection in women of childbearing age. In fact, counseling programs have been shown to be more effective in limiting CMV infection during pregnancy than any vaccine that has been tested to date. Sexual transmission is an important route of infection, and CMV is considered to be a sexually transmitted infection. Limiting sexual transmission through education and counseling should be considered in sexually active individuals. Finally, the acquisition of CMV by hospital workers and other healthcare providers has been shown to be less than in age-matched individuals in the general public. Importantly, these studies were carried out prior to universal precautions that are in place in most hospitals today. Thus patient education with an emphasis on describing the sources of infectious virus in communities and attention to general hygiene could dramatically reduce CMV spread in the community, and particularly in women of childbearing age.

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CHAPTER 283

Roseola (Human Herpesviruses 6 and 7)

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Human herpesvirus 6 (HHV-6A and HHV-6B) and human herpesvirus 7 (HHV-7) cause ubiquitous infection in infancy and early childhood. HHV-6B is responsible for the majority of cases of **roseola infantum** (**exanthem subitum** or **sixth disease**) and is associated with other diseases, including encephalitis, especially in immunocompromised hosts. A small percentage of children with roseola have primary infection with HHV-7.

Etiology

HHV-6A, HHV-6B, and HHV-7 are the sole members of the *Roseolovirus* genus in the Betaherpesvirinae subfamily of human herpesviruses. Human cytomegalovirus, the only other β-herpesvirus, shares limited sequence homology with HHV-6 and HHV-7. Morphologically all human herpesviruses are composed of an icosahedral nucleocapsid, protein-dense tegument, and lipid envelope. Within the nucleocapsid, HHV-6 and HHV-7 both contain large, linear, double-stranded DNA genomes that encode more than 80 unique proteins.

Initially, 2 strain groups of HHV-6 were recognized, HHV-6 variant A and HHV-6 variant B. Despite sharing highly conserved genomes with approximately 90% sequence identity, the 2 variants could be distinguished by restriction fragment length polymorphisms, reactivity with monoclonal antibodies, differential cell tropism, and epidemiology. Because of these differences, the two were reclassified as separate species in the genus *Roseolovirus* by the International Committee on the Taxonomy of Viruses in 2012.

HHV-6A detection is quite rare, and HHV-6B is the overwhelmingly predominant virus found in both normal and immunocompromised hosts by both culture and polymerase chain reaction (PCR). Previous reports of HHV-6A detection in children in Africa have not been substantiated in a recent large cohort using a more specific PCR target.

Epidemiology

Primary infection with HHV-6B is acquired rapidly by essentially all children following the loss of maternal antibodies in the 1st few mo of infancy, 95% of children being infected with HHV-6 by 2 yr of age. The peak age of primary HHV-6B infection is 6-9 mo of life, with infections occurring sporadically and without seasonal predilection or contact with other ill individuals. Infection with HHV-7 is also widespread but occurs later in childhood and at a slower rate; only 50% of children have evidence of prior infection with HHV-7 by 3 yr of age. Seroprevalence reaches 75% at 3-6 yr of age. In a small study of children with primary HHV-7 infection, the mean age of the patients was 26 mo, significantly older than that of children with primary HHV-6 infection.

Preliminary data suggest that the majority of children acquire primary infection with HHV-6 from the saliva or respiratory droplets of asymptomatic adults or older children. However, congenital infection with HHV-6 occurs in 1% of newborns. Two mechanisms of vertical transmission of HHV-6 have been identified, transplacental infection and chromosomal integration. HHV-6 is unique among the human herpesviruses in that it is integrated at the telomere end of human chromosomes at a frequency of 0.2–2.2% of the population and is passed from parent to child via the germline. Chromosomal integration of HHV-7 has only been suggested in a single case report thus far. Chromosomal integration has been identified as the major mechanism by which HHV-6 is vertically transmitted, accounting for 86% of congenital infections, with one third resulting from HHV-6A, a percentage much higher than in primary infection in the United States. The clinical consequences of chromosomal integration or transplacental infection with HHV-6 have yet to be determined. However, reactivation of chromosomally integrated HHV-6 virus has been demonstrated following hematopoietic stem cell transplantation (HSCT). In one series of infants identified with HHV-6 congenital infection, no evidence of disease was present in the early neonatal period. Primary infection with HHV-7 is presumed to be spread by the saliva of asymptomatic individuals. DNA of both HHV-6 and HHV-7 has been identified in the cervical secretions of pregnant women, suggesting an additional role for sexual or perinatal transmission of these viruses. Breast milk does not appear to play a role in transmission of either HHV-6 or HHV-7.

Pathology/Pathogenesis

Primary HHV-6B infection causes a viremia that can be demonstrated by co-culture of the patient's peripheral blood mononuclear cells with mitogen-stimulated cord blood mononuclear cells. HHV-6 has a recognizable cytopathic effect, consisting of the appearance of large refractile mononucleated or multinucleated cells with intracytoplasmic and/or intranuclear inclusions. Infected cells exhibit a slightly prolonged life span in culture; however, lytic infection predominates. HHV-6 infection also induces apoptosis of T cells. In vitro, HHV-6 can infect a broad range of cell types, including primary T cells, monocytes, natural killer cells, dendritic cells, and astrocytes. HHV-6 has also been documented to infect B-cell, megakaryocytic, endothelial, and epithelial cell lines. Human astrocytes, oligodendrocytes, and microglia have been infected with HHV-6 ex vivo. The broad tropism of HHV-6 is consistent with the recognition that CD46, present on the surface of all nucleated cells, is a cellular receptor for HHV-6, HHV-6A in particular. CD134, a member of the TNFR superfamily, is the main entry receptor for HHV-6B and may explain some of the differences in tissue tropism noted between HHV-6A and HHV-6B. The CD4 molecule has been identified as a receptor for HHV-7. HHV-7 has been demonstrated to reactivate HHV-6 from latency in vitro, but whether this phenomenon occurs in vivo is not clear.

Primary infection with HHV-6 and HHV-7 is followed by **lifelong latency** or persistence of virus at multiple sites. HHV-6 exists in a true state of viral latency in monocytes and macrophages. The detection of replicating HHV-6 in cultures of primary CD34+ hematopoietic stem cells has also been described, suggesting that cellular differentiation is a trigger of viral reactivation. This observation is clinically significant because HHV-6 may cause either primary or reactivated infection during HSCT. Additionally, HHV-6 and HHV-7 infection may be persistent in salivary glands, and DNA of both HHV-6 and HHV-7 can be routinely detected in the saliva of both adults and children. HHV-7 can also be isolated in tissue culture from saliva, but HHV-6 cannot. HHV-6 DNA has been identified in the cerebrospinal fluid (CSF) of children, both during and subsequent to primary infection, as well as in brain tissue from immunocompetent adults at autopsy, implicating the central nervous system as an additional important site of either viral latency or persistence. HHV-7 DNA has also been found in adult brain tissue but at a significantly lower frequency.

Clinical Manifestations

Roseola infantum (**exanthem subitum** , or **sixth disease**) is an acute, self-limited disease of infancy and early childhood. It is characterized by the abrupt onset of high fever, which may be accompanied by fussiness. The fever usually resolves acutely after 72 hr (crisis) but may gradually fade over a day (lysis) coincident with the appearance of a faint pink or rose-colored, nonpruritic, 2-3 mm morbilliform rash on the trunk (Fig. 283.1). The rash usually lasts 1-3 day but is often described as evanescent and may be visible only for hours, spreading from the trunk to the face and extremities. Because the rash is variable in appearance, location, and duration, it is not distinctive and may be missed. Associated signs are few but can include mild injection of the pharynx, palpebral conjunctivae, or tympanic membranes and enlarged suboccipital nodes. In Asian countries, ulcers at the uvulopalatoglossal junction (**Nagayama spots**) are commonly reported in infants with roseola.

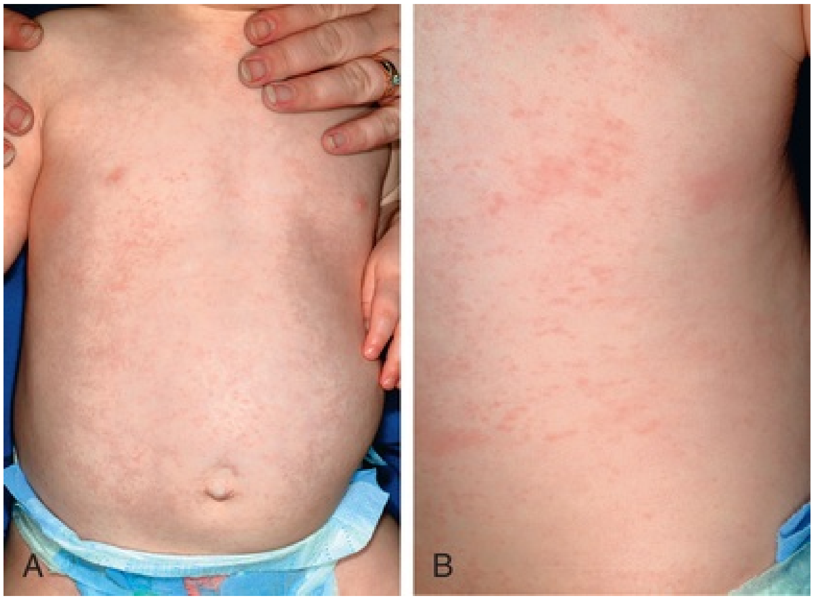

FIG. 283.1 Roseola infantum. Erythematous, blanching macules and papules (A) in an infant who had high fever for 3 days preceding development of the rash. On closer

inspection (B), some lesions reveal a subtle peripheral halo of vasoconstriction. (From Paller AS, Mancinin AJ, editors: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, Elsevier, p. 434.)

High fever (mean: 39.7°C [103.5°F]) is the most consistent finding associated with primary HHV-6B infection. Rash detected either during the illness or following defervescence has been reported in approximately 20% of infected children in the United States. Additional symptoms and signs include irritability, inflamed tympanic membranes, rhinorrhea and congestion, gastrointestinal complaints, and encephalopathy. Symptoms of lower respiratory tract involvement such as cough are identified significantly less frequently in children with primary HHV-6B infection than in children with other febrile illnesses. The mean duration of illness caused by primary HHV-6B infection is 6 days, with 15% of children having fever for 6 or more days. Primary infection with HHV-6B accounts for a significant burden of illness on the healthcare system; one study found that 24% of visits to emergency departments by infants between 6 and 9 mo of age were because of primary HHV-6B infection. A population-based study of primary HHV-6B infection confirmed that 93% of infants had symptoms and were more likely to visit a physician than noninfected infants. Fever was less likely to be present with HHV-6B infection in children younger than 6 mo of age but was significantly more common in older infants and children.

Much less is known about the clinical manifestations of HHV-7 infection. Primary infection with HHV-7 has been identified in a small number of children with roseola in whom the illness is indistinguishable from that caused by HHV-6B. Secondary cases of roseola caused by infection with HHV-7 have also been reported. Additionally, primary infection with HHV-7 may be asymptomatic or may cause a nonspecific febrile illness lasting approximately 3 days.

Laboratory Findings

The most characteristic laboratory findings noted in children with primary HHV-6B infection are lower mean numbers of total white blood cells (8,900/µL), lymphocytes (3,400/µL), and neutrophils (4,500/µL) than in febrile children without primary HHV-6B infection. Similar hematologic findings have been reported during primary infection with HHV-7. Thrombocytopenia, elevated serum transaminase values, and atypical lymphocytes have also been noted sporadically in children with primary HHV-6B infection.

Results of CSF analyses reported in patients with encephalitis thought to be caused by HHV-6 have been normal or demonstrated only minimal CSF pleocytosis with mild elevations of protein, especially early in the course of the disease, which may progress with time. Areas of hyperintense signal on T2-weighted and fluid attenuation inversion recovery images of the hippocampus, uncus, and amygdala have been found on MRI, and increased metabolism within the hippocampus has been observed on positron emission tomography scanning.

Diagnosis

Although roseola is generally a benign self-limited disease, its diagnosis can exclude other, more serious disorders that cause fever and rash. A history of 3 days of high fever in an otherwise nontoxic 10 mo old infant with a blanching maculopapular rash on the trunk suggests a diagnosis of roseola. Likewise, a specific diagnosis of HHV-6 is not usually necessary except in situations in which the manifestations of the infection are severe or unusual and might benefit from antiviral therapy.

The diagnosis of primary infection with either HHV-6 or HHV-7 is confirmed by demonstrating the presence of actively replicating virus in the patient's blood sample coupled with seroconversion. Viral culture is the gold standard method to document active viral replication. Unfortunately, culture is expensive, time consuming, and available only in research laboratories. Two other methods used to identify active HHV-6 replication are the detection of viral DNA by PCR on acellular fluids such as plasma or reverse transcriptase PCR on peripheral blood mononuclear cell samples designed to detect viral transcription and protein production. Quantitative PCR for HHV-6 genome copy numbers on various specimens is also frequently reported and is commercially available. However, the role of this methodology is not clear, as a specific value of DNA that can discriminate between patients with viremia and those who are culture negative has not been determined. Complicating the use of molecular assays for the detection of active replication of HHV-6 is the recognition that individuals with chromosomally integrated HHV-6 have persistent HHV-6 DNA in plasma, peripheral blood mononuclear cells, and CSF in the absence of disease and replicating virus.

Serologic methods such as indirect immunofluorescence assays, enzyme-linked immunosorbent assays, neutralization assays, and immunoblot have been described for the measurement of concentrations of antibodies to HHV-6 and

HHV-7 in serum or plasma and are commercially available. Although immunoglobulin M antibody is produced early in infection with HHV-6, assays designed to measure this response have not proved useful in the diagnosis of primary or reactivated infection. The absence of immunoglobulin G antibody in an infant older than 6 mo of age combined with the presence of replicating virus is strong evidence of primary infection with either HHV-6 or HHV-7. Alternatively, the demonstration of seroconversion between acute and convalescent samples also confirms primary infection but is not clinically useful in the acute care setting. Unfortunately, serologic assays have not been found reliable in the detection of HHV-6 reactivation and cannot be used to differentiate between infection with HHV-6A and infection with HHV-6B. Additionally, limited antibody cross-reactivity has been demonstrated between HHV-6 and HHV-7, complicating the interpretation of serologic assays, especially if low titers are reported.

Differential Diagnosis

Primary infection with either HHV-6B or HHV-7 usually causes an undifferentiated febrile illness that may be very difficult to distinguish from other common viral infections of childhood. This difficulty also applies to the early stages of roseola, before the development of rash. Once the rash is present, roseola may be confused with other exanthematous diseases of childhood, especially measles and rubella. Children with **rubella** often have a prodrome characterized by mild illness with low-grade fever, sore throat, arthralgia, and gastrointestinal complaints, unlike those with roseola. On physical examination, suboccipital and posterior auricular lymph nodes are prominent up to 1 wk before the rash of rubella is evident and persist during the exanthematous phase. Additionally, the rash of rubella usually begins on the face and spreads to the chest, like that in measles. The associated symptoms of **measles** virus infection include cough, coryza, and conjunctivitis, with high fever coincident with the development of rash, unlike in roseola. Roseola may also be confused with scarlet fever, though the latter is rare in children younger than 2 yr of age and causes a characteristic sandpaper-like rash concurrent with fever.

Roseola may be confused with illness caused by **enterovirus infections** , especially in the summer and fall months. Drug hypersensitivity reactions may also be difficult to distinguish from roseola. Antibiotics are frequently prescribed for children with fever from roseola before the appearance of rash. A child who then demonstrates rash after the resolution of fever may erroneously be labeled as being drug allergic.

Complications

Convulsions are the most common complication of roseola and are recognized in up to one third of patients. Seizures are also the most common complication of children with primary HHV-6B infection, occurring in approximately 15%, with a peak age of 12-15 mo. Children with primary HHV-6B infection are also reported to have a higher frequency of partial seizures, prolonged seizures, postictal paralysis, and repeated seizures than are children with febrile seizures not associated with HHV-6. In a study limited to children with primary HHV-6B infection and seizures, 30% of patients had prolonged seizures, 29% had focal seizures, and 38% had repeated seizures. A prospective study of children 2-35 mo of age with suspected encephalitis or severe febrile illness with convulsions found that 17% had primary infection with either HHV-6 or HHV-7, and status epilepticus was the most common presentation. Among children with febrile status epilepticus (FSE), primary or reactivated infection with HHV-6B or HHV-7 has been identified in approximately one third.

An association between recurrent seizures and reactivated or persistent infection of the central nervous system by HHV-6 has also been suggested. Studies evaluating brain tissue specimens implicate HHV-6 in as many as 35% of patients with temporal lobe epilepsy (TLE), high viral loads being found in the hippocampus or lateral temporal lobe regions. HHV-6 protein production has also been identified in a small number of resected tissue specimens. Primary astrocytes obtained from these samples had undetectable levels of a glutamate transporter, suggesting the loss of ability to control glutamate levels as a possible mechanism for the development of recurrent seizures. Additional evidence has demonstrated upregulation of genes related to monocyte chemotaxis in the amygdala of patients with TLE and HHV-6 DNA in specimens. Contrary to these findings, limited clinical data suggest that there may be a decreased risk of recurrent seizures after primary infection with HHV-6 and febrile seizures than of febrile seizures from other causes. Additionally, children with FSE associated with HHV-6B and HHV-7 had similar seizure characteristics and a similar proportion of electroencephalography and MRI hippocampal abnormalities as children with FSE not associated with HHV-6B or HHV-7, suggesting a shared pathogenesis to other etiologies of FSE.

Case reports and small-patient series have described additional complications in children with primary HHV-6B infection, including encephalitis, acute disseminated demyelination, autoimmune encephalitis, acute cerebellitis, hepatitis, and myocarditis. Late-developing long-term sequelae, including developmental disabilities and autistic-like features, are reported rarely in children who have central nervous system symptoms during primary HHV-6B infection.

Reactivation of HHV-6 has been reported in several different populations with and without disease with the use of various methods of detection. The best documentation of HHV-6 reactivation has been in immunocompromised hosts, especially those patients who have undergone HSCT. Such reactivation occurs in approximately 50% of patients, typically at 2-4 wk after transplantation. Many of the clinical complications seen following HSCT have been associated with HHV-6B reactivation, including fever, rash, delayed engraftment of platelets or monocytes, and graft-versus-host disease, with variable degrees of support in the literature for each. HHV-6 reactivation has been associated with worse overall survival compared to HSCT recipients who did not experience reactivation.

HHV-6B reactivation has also been reported as a cause of encephalitis in both normal and immunocompromised hosts. A distinct syndrome of **posttransplant acute limbic encephalitis (PALE)** has been described primarily in patients following HSCT, especially cord blood stem cell transplantation; it is characterized by short-term memory dysfunction, confusion, and insomnia with seizures noted either clinically or on prolonged electroencephalography monitoring. HHV-6B DNA has been identified in the CSF in the majority of these patients, with additional evidence of reactivation by detection of HHV-6B DNA in plasma. HHV-6 proteins were identified in the astrocytes of the hippocampus in one postmortem specimen, consistent with active HHV-6B infection at the time of death. The development of PALE is associated with increased mortality and long-term neurocognitive sequelae.

Treatment

Supportive care is usually all that is needed for infants with roseola. Parents should be advised to maintain hydration and may use antipyretics if the child is especially uncomfortable with the fever. Specific antiviral therapy is not recommended for routine cases of primary HHV-6B or HHV-7 infection. Unusual or severe manifestations of primary or presumed reactivated HHV-6B infection such as encephalitis/PALE, especially in immunocompromised patients, may benefit from treatment. Ganciclovir, foscarnet, and cidofovir all demonstrate inhibitory activity against HHV-6 in vitro, similar to their activity against cytomegalovirus. Case reports suggest that all 3 drugs, alone or in combination, can decrease HHV-6 viral replication, as evidenced by decreased viral loads in plasma and CSF. However, clinical data regarding efficacy are sparse and contradictory, with no randomized trials to guide use. Additionally, in vitro resistance of HHV-6 to all 3 drugs has been described. Despite these drawbacks, treatment with ganciclovir or foscarnet as first-line agents has been recommended for a minimum of 3 wk in patients with PALE. Foscarnet appears to be most likely to have activity against HHV-7 on the basis of in vitro testing, but no clinical data are available.

Prognosis

Roseola is generally a self-limited illness associated with complete recovery. The majority of children with primary infections with HHV-6B and HHV-7 also recover uneventfully without sequelae. Although seizures are a common complication of primary infection with HHV-6B and HHV-7, the risk of recurrent seizures does not appear to be higher than that associated with other causes of simple febrile seizures.

Prevention

Primary infections with HHV-6 and HHV-7 are widespread throughout the human population with no current means of interrupting transmission.

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CHAPTER 284

Human Herpesvirus 8

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Human herpesvirus 8 (HHV-8) is an oncogenic virus identified in tissue specimens from patients with Kaposi sarcoma (KS). Because of this association, it is also known as **Kaposi sarcoma–associated herpesvirus** . HHV-8 is the etiologic agent of two additional lymphoproliferative disorders: **primary effusion–based lymphoma (PEL)** and **multicentric Castleman disease (MCD)** .

Etiology

HHV-8 is a γ_2 -human herpesvirus similar to Epstein-Barr virus. The virus contains a large DNA genome encoding 85-95 unique proteins. Infection is followed by both lytic and latent viral states with different degrees of viral replication associated with distinct disease manifestations.

Epidemiology

The prevalence of infection with HHV-8 varies both geographically and by population and roughly matches the epidemiology of KS. HHV-8 infection is endemic in Africa and parts of South America, with infection rates of up to 30–60% by adolescence. Seroprevalence >20% has also been found in regions bordering the Mediterranean. In contrast, infection rates <5% are noted in North America, central Europe, and Asia. However, within geographic regions, the prevalence of infection varies with risk behaviors, rates of 30–75% being found among men who have sex with men in North America and Europe. HHV-8 DNA can be detected in saliva, blood, semen, and tissues. Based upon large-scale epidemiologic studies and the high prevalence of viral shedding in oral secretions, saliva is believed to be the major mode of transmission. Other less-common routes of HHV-8 transmission include blood transfusion, bone marrow transplantation, and solid organ transplantation. Vertical transmission and transmission via breast milk may occur in regions where HHV-8 is highly endemic, but the risk appears low.

Pathology and Pathogenesis

HHV-8 contains multiple genes that impact cell-cycle regulation and the host immune response. Viral proteins interfere with the function of the tumor suppressor molecules, induce the expression of proangiogenesis factors, and lead to upregulation of the rapamycin pathway target, which is instrumental in the control of cell growth and metabolism. HHV-8 also encodes a homolog of human interleukin-6, which can bind and activate cytokine receptors and serve as a host cell autocrine growth factor. Additionally, viral proteins are associated with the constitutive expression of the transcription factor nuclear factor-κB. All of these proteins may be potential targets for therapeutic intervention.

Clinical Manifestations

Although subclinical infection appears to be common, symptomatic primary HHV-8 infection has been described in immunocompetent children. Patients commonly have fever and a maculopapular rash or a mononucleosis-like syndrome, with full recovery the rule. In immunocompromised patients, primary infection has been associated with fever, rash, splenomegaly, pancytopenia, and lymphoid hyperplasia, and may be quite severe. Additionally, preliminary data suggest that transfusion-associated primary infection with HHV-8 is associated with an increased risk of mortality.

Even in regions with high rates of seroprevalence, the development of KS is uncommon. KS has several different clinical forms; each includes multifocal, angiogenic lesions arising from vascular endothelial cells infected with HHV-8. Classic KS is an indolent disorder seen in elderly men with limited involvement of the skin of the lower extremities. Endemic KS is more aggressive, occurring in children and young people, primarily in Africa, and can include visceral involvement as well as widespread cutaneous lesions (patches, plaques, or nodules). Posttransplantation KS and AIDS-related KS are the most severe forms, with disseminated lesions, often in the gastrointestinal tract and lungs, with or without cutaneous findings.

Primary effusion–based lymphoma is a rare disease caused by HHV-8 that is seen most commonly in HIV-infected individuals. It consists of lymphomatous invasion of the serosal surfaces of the pleura, pericardium, and peritoneum. Similarly, **multicentric Castleman disease** is an unusual lymphoproliferative disorder characterized by anemia, thrombocytopenia, generalized lymphadenopathy, and constitutional symptoms and frequently associated with HHV-8 infection and a high degree of viral replication.

Diagnosis

Serologic assays, including immunofluorescence and enzyme-linked immunosorbent assays, are the primary methods of diagnosing infection with HHV-8. However, testing has limited sensitivity, specificity, and reproducibility and is primarily a research tool with no universally recognized standard assays. Additionally, the loss of antibodies over time, referred to as *seroreversion*, has been described, further complicating serodiagnosis. Immunohistochemistry and molecular methods are available for the detection of HHV-8 in tissue samples and are utilized in the diagnosis of KS, PEL, and MCD, alongside their disease-specific clinical manifestations.

Treatment

Treatment for KS, PEL, and MCD is multifaceted and includes attempts to control malignant proliferations with traditional chemotherapeutic regimens and biologic agents as well as agents aimed at specific cellular pathways targeted by HHV-8 proteins. Combined antiretroviral therapy (ART) is a mainstay of both prevention and therapy for HHV-8 related disease in HIV-infected patients. In HIV-associated KS, treatment with ART alone is often used for the control of mild (i.e., cutaneous) disease, while ART plus chemotherapy is utilized for more severe disease. In transplantation-associated KS, the first line of treatment includes decreasing immunosuppression, often in association with a switch from calcineurin inhibitors to sirolimus (rapamycin) to block the mammalian target of rapamycin pathway. Severe disease frequently requires the use of traditional chemotherapy as well. The role of specific antiherpesvirus antiviral treatment is unclear. Oral valganciclovir decreases the detection of HHV-8 in saliva, and ganciclovir treatment has been associated with decreased rates of development of KS in HIV-infected individuals. However, results of using antivirals in the treatment of established disease have been generally disappointing. The prognosis for PEL tends to be poor despite the use of traditional chemotherapy, while rituximab (anti-CD20)–based therapy has been highly successful for MCD treatment. However, relapse and the development of lymphoma following treatment can still occur. Rituximab treatment may also worsen concurrent KS without additional agents.

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CHAPTER 285

Influenza Viruses*

Fiona P. Havers, Angela J.P. Campbell

Influenza viral infections cause a broad array of respiratory illnesses that are responsible for significant morbidity and mortality in children during **seasonal epidemics** . Influenza A viruses also have the potential to cause **global pandemics** , which can happen when a **new (novel) influenza A virus** emerges and transmits efficiently from person to person.

Etiology

Influenza viruses are large, single-stranded RNA viruses belonging to the family Orthomyxoviridae, which includes three genera (or types): A, B, and C. Influenza A and B viruses are the primary human pathogens causing seasonal epidemics, while influenza virus type C is a sporadic cause of predominantly mild upper respiratory tract illness. Influenza A viruses are further divided into subtypes based on two surface proteins that project as spikes from the lipid envelope, the hemagglutinin (HA) and neuraminidase (NA) proteins (Fig. 285.1). Strain variants are identified by antigenic differences in their HA and NA and are designated by the geographic area from which they were originally isolated, isolate number, and year of isolation—for example, influenza A/Victoria/361/2011(H3N2). The HA and NA antigens from influenza B and C viruses do not receive subtype designations, as there is less variation among influenza B and C antigens. However, influenza B viruses can be further broken down into lineages; currently circulating influenza B viruses belong to the B/Yamagata or B/Victoria lineage.

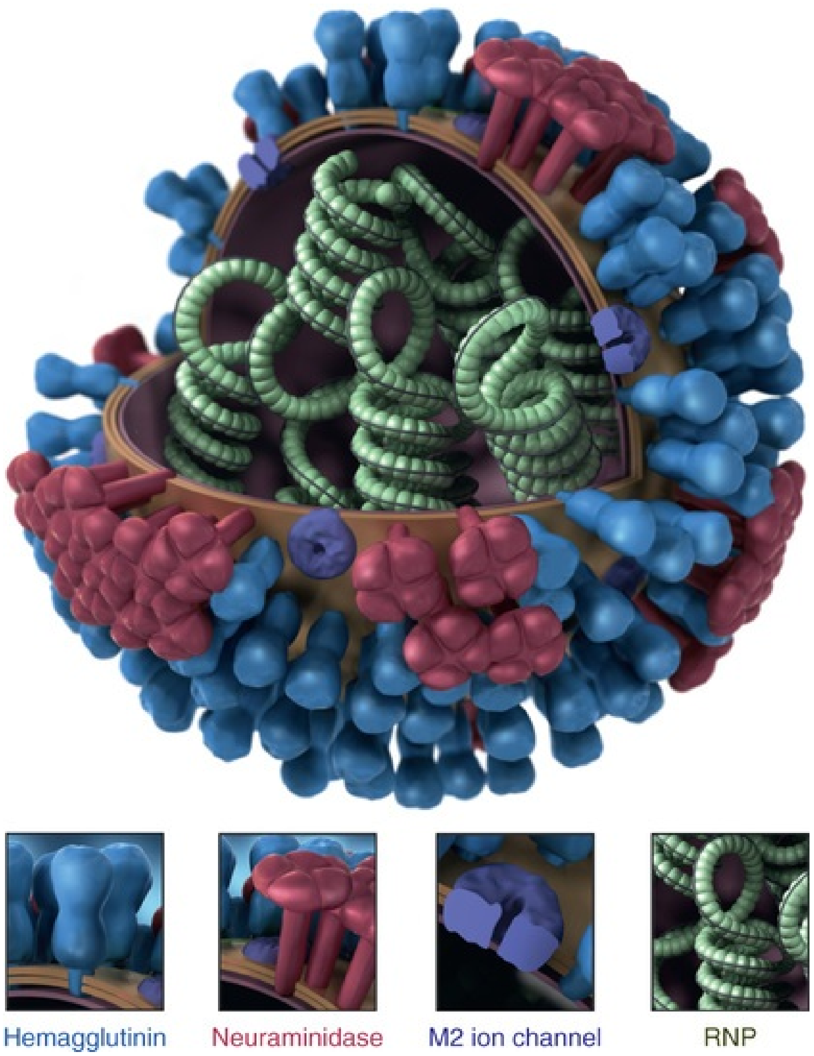

FIG. 285.1 **Graphical representation of influenza virus. The key at bottom identifies the surface protein constituents: the hemagglutinin, neuraminidase, matrix protein 2 (M2) ion channel, and ribonucleoprotein *(RNP)* . (From Centers for Disease Control and Prevention Public Health Image Library, Image ID#11822, Available at https://phil.cdc.gov/phil/details.asp ; courtesy CDC/Douglas Jordan and Dan Higgins, 2009.)**

Epidemiology

Influenza has generally been thought to be transmitted primarily via respiratory droplets, but transmission through contact with secretions and small-particle aerosols may also occur. The typical incubation period ranges from 1 to 4 days, with an average of 2 days. Healthy adults are generally considered potentially infectious from a day before symptoms develop until 5-7 days after becoming ill. Children with primary influenza infection have higher influenza viral loads and more prolonged viral shedding than adults; therefore children may be able to infect others for a longer time. Influenza outbreaks occur commonly in schools and childcare settings. Healthcare-associated influenza infections can also occur in healthcare settings, and outbreaks in long-term care facilities and hospitals may cause significant morbidity.

In the United States, seasonal influenza viruses can be detected year round, but circulating viruses are most common during the fall and winter. Transmission through a community is rapid, with the highest incidence of illness occurring within 2-3 wk of introduction.

Antigenic Variation

Influenza A and B viruses contain a genome consisting of 8 single-stranded RNA segments. Minor changes within a subtype continually occur through point mutations during viral replication, particularly in the HA gene, and result in new influenza strains of the same HA type. This phenomenon, termed **antigenic drift** , occurs in both influenza A and B viruses. Variation in antigenic composition of influenza virus surface proteins occurs almost yearly, which confers a selective advantage to a new strain and contributes to annual epidemics. For this reason, the formulation of the influenza vaccine is reviewed each year and updated as needed.

Less frequent but more dramatic, major changes in virus subtype can occur, resulting in a new influenza A subtype to which most people have little to no immunity. This process is called antigenic shift and can occur through reassortment of viral gene segments when there is simultaneous infection by more than one strain of influenza in a single host, or by direct adaptation of an animal virus to a human host. Antigenic shift occurs in influenza A viruses, which have multiple avian and mammalian hosts acting as reservoirs for diverse strains.

Through the process of **reassortment** , potentially any of 18 HA and 11 NA proteins currently known to reside in influenza A viruses of nonhuman hosts could be introduced into humans, who may have little existing immunologic cross protection to emerging viruses. A global pandemic can result if an influenza A virus with a novel HA or NA enters a nonimmune human population and acquires the capacity for sustained and efficient transmission between people. Four major **global pandemics** have occurred since 1900: in 1918 caused by an influenza A(H1N1) virus, 1957 caused by an influenza A(H2N2) virus, 1968 caused by an influenza A(H3N2) virus, and 2009 caused by an influenza A virus designated A(H1N1)pdm09. The most severe pandemic in recorded history occurred in 1918, when the virus was estimated to have killed at least 50 million people. The 1918 pandemic virus was likely the result of direct adaptation of an avian influenza virus to the human host, rather than from reassortment. The 2009 pandemic virus stemmed from reassortment of genes from swine, avian, and human viruses (Fig. 285.2). This resulted in the emergence of a novel influenza A(H1N1)pdm09 virus that spread quickly from North America across the globe and replaced the previously circulating seasonal H1N1 viruses.

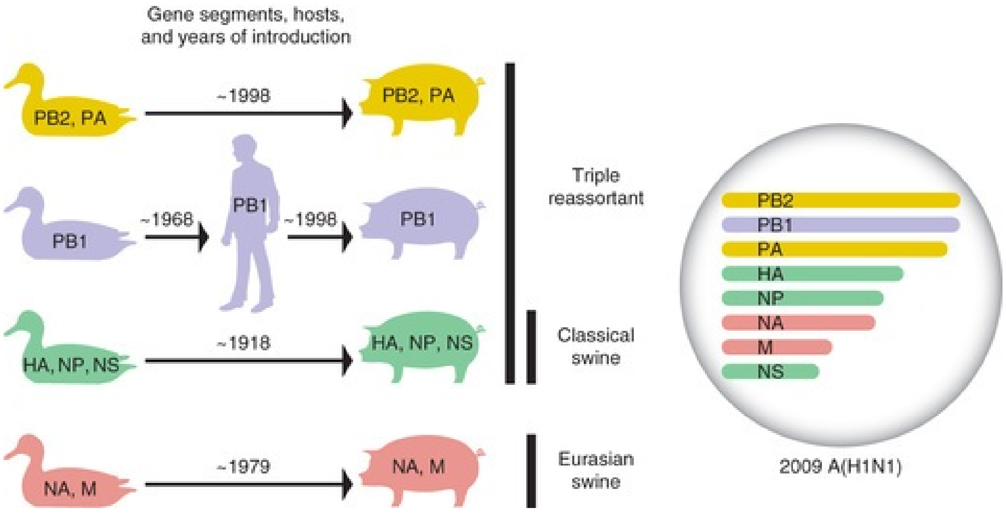

FIG. 285.2 **Host and lineage origins for the gene segments of the 2009 A(H1N1) virus. PB2, polymerase basic 2; PB1, polymerase basic 1; PA, polymerase acidic; HA, hemagglutinin; NP, nucleoprotein; NA, neuraminidase; M, matrix gene; NS, nonstructural gene. Color of gene segment in circle indicates host. (From Garten RJ, Davis CT, Russell CA, et al: Antigenic and genetic characteristics of swine-origin 2009 A(H1N1) influenza viruses circulating in humans, *Science* 325(5937):197–201, 2009.)**

Several novel influenza viruses, all originating in animals, have also caused outbreaks of human infections. Avian influenza A(H5N1), a virulent avian influenza virus that was first identified in 1997, has caused more than 800 documented cases in 16 countries, with a mortality rate over 50%. Another novel avian influenza, A(H7N9) virus, has caused more than 1,300 documented cases and also appears highly virulent. This virus first caused an outbreak of human infections in China during the spring of 2013, with annual epidemics in China occurring in subsequent years. During the first 4 yearly epidemics, infection was fatal in approximately 40% of documented cases.

In addition, novel influenza A variant viruses have caused human infections

(Table 285.1). These include H3N2v viruses, which caused 372 confirmed human infections in the United States from 2011 to 2016 and were primarily transmitted through swine contact at agricultural fairs. Influenza viruses that normally circulate in swine are designated variant (“v”) viruses when detected in humans, and H3N2v and other variant viruses, including H1N1v and H1N2v, have sporadically infected humans. In contrast to avian influenza A(H5N1) and A(H7N9) viruses, variant viruses generally cause mild illness and have been primarily detected in children. However, none of these viruses has exhibited sustained, efficient human-to-human transmission.

Table 285.1

Subtypes of Novel Influenza A Viruses and Clinical Syndromes in Human Infections

	LPAI VIRUSES	HPAI VIRUSES	VARIANT VIRUSES[*]
Conjunctivitis	H7N2, H7N3, H7N7, H10N7	H7N3, H7N7	H1N1v, H3N2v
Upper respiratory tract illness	H6N1, H7N2, H7N3, H7N9, H9N2, H10N7	H5N1, H5N6, H7N7	H1N1v, H1N2v, H3N2v
Lower respiratory tract disease, pneumonia	H7N2, H7N9, H9N2, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v
Respiratory failure, acute respiratory distress syndrome	H7N9, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v
Multiorgan failure	H7N9, H10N8	H5N1, H5N6, H7N7, H7N9	—
Encephalopathy or encephalitis	H7N9	H5N1	—
Fatal outcomes [†]	H7N9, H9N2, H10N8	H5N1, H5N6, H7N7, H7N9	H1N1v, H3N2v

[*] Variant viruses of swine origin.

[†] High mortality in reported cases: about 40% for LPAI H7N9, about 50% for HPAI H5N1, and about 70% for HPAI H5N6.

LPAI, low-pathogenic avian influenza; HPAI, highly pathogenic avian influenza.

From Uyeki TM, Katz JM, Jernigan DB: Novel influenza A viruses and pandemic threats, *Lancet* 389:2172–2174, 2017.

Seasonal Influenza

An estimated 11,000-45,000 children younger than 18 yr of age are hospitalized annually in the United States as a result of seasonal influenza-associated complications, with approximately 6,000-26,000 hospitalizations in children younger than 5 yr of age. Since 2004, the annual number of reported influenza-associated pediatric deaths in the United States has ranged from 37 to 171 during regular influenza seasons (358 were reported to have occurred during the 2009 H1N1 pandemic). Influenza disproportionately affects children with specific chronic conditions, such as underlying pulmonary, cardiac, or neurologic and neuromuscular disorders. Very young children, especially those younger than 2 yr of age, and children with chronic medical conditions are more likely to develop severe influenza-related complications, including viral and bacterial pneumonia, hospitalization, respiratory failure, and death. However, while children with underlying medical conditions are at higher risk of complications, many healthy children are hospitalized with influenza, and nearly half of pediatric influenza-associated deaths are in children that have no known underlying medical condition.

Influenza also causes a substantial burden of disease in outpatient settings. It contributes to an estimated 600,000 to 2,500,000 outpatient medical visits annually in children younger than 5 yr of age, and has been identified in 10–25% of outpatient visits among all children with respiratory symptoms during influenza season. Influenza may also be underdiagnosed. Many who seek medical care for influenza do not have laboratory testing performed and do not receive a diagnosis of influenza. Every year, 3-4 influenza virus types or subtypes typically co-circulate, including influenza A(H3N2), influenza A(H1N1), and B viruses. Although 1 subtype usually predominates in any given season, it is difficult to predict which will be predominant. Thus, the influenza vaccine varies annually and contains 3 or 4 antigens representing the expected circulating types.

Pathogenesis

Influenza viruses infect the respiratory tract epithelium, primarily the ciliated columnar epithelial cells, by using the HA to attach to sialic acid residues. After viral entry into cells, virus replication occurs usually within 4-6 hr, and new virus particles are assembled and released to infect neighboring cells. With primary infection, virus replication continues for 10-14 days. Influenza virus causes a lytic infection of the respiratory epithelium with loss of ciliary function, decreased mucus production, and desquamation of the epithelial layer. These changes permit secondary bacterial invasion, either directly through the epithelium or, in the case of the middle ear space, through obstruction of the normal drainage through the eustachian tube.

The exact immune mechanisms involved in termination of primary infection and protection against reinfection are complex. Induction of cytokines that inhibit viral replication, such as interferon and tumor necrosis factor, as well as other host defenses, such as cell-mediated immune responses and local and humoral antibody defenses, all likely play a role. Secretory immunoglobulin A antibodies produced by the respiratory mucosa are thought to be an effective and immediate response generated during influenza infection. Serum antibody levels inhibiting HA activity can usually be detected by the second week after infection. These antibodies are also generated by vaccines, and high HA inhibition titers correlate with protection.

Clinical Manifestations

The onset of influenza illness is *often abrupt*, with a predominance of systemic symptoms including fever, myalgias, chills, headache, malaise, and anorexia. Coryza, pharyngitis, and dry cough are also usually present at the onset of illness but may be less prominent than systemic symptoms. Respiratory manifestations can include isolated upper respiratory tract illness, including croup, or progression to lower tract disease, such as bronchiolitis or pneumonia. More than other respiratory viruses, influenza virus typically causes systemic manifestations such as high temperature, myalgia, malaise, and headache. Less common clinical manifestations can include parotitis and rash.

Abdominal pain, vomiting, and diarrhea may also occur in children; in some studies, diarrhea was reported to be more often associated with influenza A(H1N1)pdm09 compared with influenza A(H3N2) or influenza B viruses. Influenza is a less distinct illness in younger children and infants. The infected young infant or child may be highly febrile and toxic in appearance, prompting a full diagnostic work-up. The typical duration of the febrile illness is 2-4 days. Cough may persist for longer periods, and evidence of small airway dysfunction is often found weeks later. Owing to the high transmissibility of influenza, other family members or close contacts of an infected person often experience a similar illness.

Complications

Otitis media and pneumonia are common complications of influenza in young children. Acute otitis media may be seen in up to 25% of cases of documented influenza. Pneumonia accompanying influenza may be a primary viral process or a secondary bacterial infection (such as with *Staphylococcus aureus*) facilitated through damaged respiratory epithelium. Influenza may cause acute myositis or rhabdomyolosis marked by muscle weakness and pain, particularly in the calf muscles, and myoglobinuria. Other extrapulmonary complications include acute renal failure, myocarditis, and sepsis. Central nervous system complications, such as encephalitis, myelitis, and Guillain-Barré syndrome, can occur and are seen more commonly in children than adults. Although it has essentially disappeared in the United States, Reye syndrome can result with the use of salicylates during influenza infection (see Chapter 388). Bacterial coinfection may also exacerbate respiratory complications of influenza and lead to sepsis, bacteremia, toxic shock syndrome, and other manifestations.

Influenza is particularly severe in some children, including those with underlying cardiopulmonary disease, including congenital and acquired valvular disease, cardiomyopathy, bronchopulmonary dysplasia, asthma, cystic fibrosis, and neurologic conditions. Pregnant women and adolescent females are at high risk for severe influenza. Children receiving cancer chemotherapy and children with immunodeficiency also have a higher risk of complications and may shed virus for longer periods than immunocompetent children.

Laboratory Findings

The clinical laboratory abnormalities associated with influenza are nonspecific. Chest radiographs may show evidence of atelectasis or infiltrate.

Diagnosis and Differential Diagnosis

The diagnosis of influenza depends on epidemiologic, clinical, and laboratory considerations. In the context of an epidemic, the clinical diagnosis of influenza in a child who has fever, malaise, and respiratory symptoms may be made based on clinical discretion; however, clinical presentation is often indistinguishable from infection with other respiratory viruses, including respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, and even rhinovirus. Confirmation of influenza virus infection by diagnostic testing is not required for clinical decisions to prescribe antiviral medications, and prompt suspicion or diagnosis of influenza may allow for early antiviral therapy to be initiated and may reduce inappropriate use of antibiotics.

A number of diagnostic tests may be used for laboratory confirmation of influenza (Table 285.2). Although rapid influenza diagnostic tests are often employed because of their ease of use and fast results, they can have suboptimal sensitivity to detect influenza virus infection, particularly for novel influenza viruses. Sensitivities of rapid diagnostic tests are generally 50–70% compared to viral culture or reverse-transcription polymerase chain reaction. Specificities are higher, approximately 95–100%. Therefore false-negative results occur more often than false-positive results, particularly when the prevalence of influenza is high (i.e., during peak influenza activity in the community). The interpretation of negative results should take into account the clinical characteristics and the patient's risk for complications. If there is clinical suspicion for influenza in a patient at high risk for complications (Table 285.3), early empiric treatment should be given regardless of a negative rapid diagnostic test result, and another type of test (e.g., reverse-transcription polymerase chain reaction or direct fluorescent antibody testing) may be performed for confirmation.

Table 285.2

Influenza Virus Testing Methods

METHOD	ACCEPTABLE SPECIMENS	TEST TIME	COMMENTS
Rapid Influenza Diagnostic Tests (antigen detection)	Nasopharyngeal (NP) swab, aspirate or wash, nasal swab, aspirate, or wash, throat swab	<15 min	Rapid turnaround; suboptimal sensitivity
Rapid Molecular Assay (influenza nucleic acid amplification)	NP swab, nasal swab	15-30 min	Rapid turnaround, high sensitivity
Immunofluorescence, Direct (DFA) or Indirect (IFA) Fluorescent Antibody Staining (antigen detection)	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hr	Relatively rapid turnaround; requires laboratory expertise and experience
RT-PCR (singleplex and multiplex; real-time and other RNA-based) and other molecular assays (influenza nucleic acid amplification)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varies by assay (generally 1-8 hr)	Excellent sensitivity, relatively rapid turnaround compared with conventional methods
Rapid cell culture (shell vials, cell mixtures; yields live virus)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-3 day	Culture isolates important for strain information and antiviral resistance monitoring
Viral tissue cell culture (conventional;	NP swab, throat swab, NP	3-10 day	Not recommended for

yields live virus)	or bronchial wash, nasal or endotracheal aspirate, sputum		routine patient diagnosis
Serologic tests (antibody detection)	Paired (appropriately timed) acute and convalescent serum specimens	N/A (not performed during acute infection)	Not recommended for routine patient diagnosis, useful for research studies

N/A, not applicable; NP, nucleoprotein; RT-PCR, reverse transcription-polymerase chain reaction.

Modified from Centers for Disease Control and Prevention (CDC): *Influenza virus testing methods.* Available at https://www.cdc.gov/flu/professionals/diagnosis/table-testing-methods.htm in Information for Health Professionals (https://www.cdc.gov/flu/professionals/index.htm); and from 2018 IDSA Clinical Practice Guidelines.

Table 285.3

Children and Adolescents Who Are at Higher Risk for Influenza Complications for Whom Antiviral Treatment is Recommended[*]

Children younger than 2 yr of age[†]
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), and metabolic disorders (including diabetes mellitus); or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Persons with immunosuppression, including that caused by medications or by HIV infection
Adolescents who are pregnant, or postpartum (within 2 wk after delivery)
Persons younger than 19 yr of age who are receiving long-term aspirin- or salicylate-containing medications therapy
American Indians/Alaska Natives
Persons who are extremely obese (body mass index ≥40)
Residents of long-term care facilities
Hospitalized patients at high risk for influenza complications

[*] Antiviral treatment is recommended for high-risk children with confirmed or suspected influenza; antivirals are also recommended for children who are hospitalized or have severe or progressive disease.

[†] Although all children younger than 5 yr of age are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 yr of age, with the highest hospitalization and death rates among infants younger than 6 mo of age.

Current for 2018-2019 influenza season.

Adapted from Centers for Disease Control and Prevention (CDC): *Influenza antiviral medications: summary for clinicians* . Available at https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm . For current details, consult annually updated recommendations at https://www.cdc.gov/flu/professionals/index.htm .

Treatment

Antiviral medications are an important adjunct to influenza vaccination. Three classes of antiviral drugs are licensed for treatment of influenza in children. The neuraminidase inhibitors (NAIs), oral oseltamivir and inhaled zanamivir, may be used for treatment of children from birth and 7 yr, respectively (Table 285.4). In December 2012, the U.S. Food and Drug Administration (FDA) approved the use of oseltamivir for the treatment of influenza in infants as young as 2 wk of age, and the Centers for Disease Control and Prevention (CDC), American Academy of Pediatrics, and the Infectious Diseases Society of America recommend its use in infants of any age. A third NAI, peramivir, is given as an intravenous infusion and is approved for treatment in persons 2 yr of age and older.

Table 285.4

Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis in Children for the 2018-2019 Influenza Season: United States

MEDICATION	TREATMENT DOSING**	CHEMOPROPHYLAXIS DOSING**
ORAL OSELTAMIVIR *		
Adults	75 mg twice daily	75 mg once daily
Children ≥12 mo		
Body wt		
≤15 kg (≤33 lb)	30 mg twice daily	30 mg once daily
>15-23 kg (33-51 lb)	45 mg twice daily	45 mg once daily
>23-40 kg (>51-88 lb)	60 mg twice daily	60 mg once daily
>40 kg (>88 lb)	75 mg twice daily	75 mg once daily
Infants 0-11 mo †	3 mg/kg per dose once daily	3 mg/kg per dose once daily
Term infants ages 0-8 mo †	3 mg/kg per dose twice daily	3 mg/kg per dose once daily for infants 3-8 mo old; not recommended for infants <3 mo old unless situation judged critical because of limited safety and efficacy data in this age group
Preterm infants	See details in footnote ‡	Not recommended
INHALED ZANAMIVIR §		
Adults	10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily
Children (≥7 yr old for treatment; ≥5 yr old for chemoprophylaxis)	10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily

INTRAVENOUS PERAMIVIR		
Adults	600 mg intravenous infusion once given over 15-30 min	Not recommended
Children (2-12 yr old)	One 12 mg/kg dose, up to 600 mg maximum, via intravenous infusion for 15-30 min	Not recommended
Children (13-17 yr old)	One 600 mg dose via intravenous infusion for 15-30 min	Not recommended
ORAL BALOXAVIR [††]		
Adults		
40 to <80 kg	One 40 mg dose	Not recommended
>80 kg	One 80 mg dose	Not recommended
Children		
2-11 yr	Not recommended	Not recommended
12-17 yr, 40 to <80 kg	One 40 mg dose	Not recommended
12-17 yr, >80 kg	One 80 mg dose	Not recommended

[*] Oseltamivir is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available as Tamiflu or as a generic formulation as capsules and as a powder for oral suspension that is reconstituted to provide a final concentration of 6 mg/mL.

[†] Approved by the FDA for children as young as 2 wk of age. Given preliminary pharmacokinetic data and limited safety data, oseltamivir can be used to treat influenza in both term and preterm infants from birth because benefits of therapy are likely to outweigh possible risks of treatment. CDC and US Food and Drug Administration (FDA)–approved dosing is 3 mg/kg per dose twice daily for children aged 9-11 mo; the American Academy of Pediatrics recommends 3.5 mg/kg per dose twice daily. The dose of 3 mg/kg provides oseltamivir exposure in children similar to that achieved by the approved dose of 75 mg orally twice daily for adults, as shown in two studies of oseltamivir pharmacokinetics in children. The AAP has recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants 9-11 mo, on the basis of data that indicated that a higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the CASG 114 study. It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5 mg/kg dose is harmful or causes more adverse events to infants in this age group.

[‡] Oseltamivir dosing for preterm infants. The wt-based dosing recommendation for preterm infants is lower than for term infants. Preterm infants may have lower clearance of oseltamivir because of immature renal function, and doses recommended for term infants may lead to high drug concentrations in this age group. Limited data from the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group provide the basis for dosing preterm infants by using their postmenstrual age (gestational age plus chronological age): 1.0 mg/kg per dose orally twice daily for those <38 wk postmenstrual age; 1.5 mg/kg per dose orally twice daily for those 38-40 wk postmenstrual age; and 3.0 mg/kg per dose orally twice daily for those >40 wk postmenstrual age. For extremely preterm infants (<28 wk), please consult a pediatric infectious diseases physician.

[§] Zanamivir is administered by inhalation by using a proprietary Diskhaler device distributed together with the medication. Zanamivir is a dry powder, not an aerosol, and should not be administered by using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for people with chronic respiratory diseases, such as asthma or chronic obstructive pulmonary disease, which increase the risk of bronchospasm.

[**] Antiviral treatment duration for uncomplicated influenza is 5 days for oral oseltamivir or inhaled zanamivir, and a single dose for intravenous peramivir or oral baloxavir. Recommended post-exposure chemoprophylaxis with oseltamivir or zanamivir in a non-outbreak setting is 7 days after last known exposure.

[††] Oral baloxavir marboxil is approved by the FDA for treatment of acute uncomplicated influenza within 2 days of illness onset in people 12 yr and older. The safety and efficacy of baloxavir for the treatment of influenza have been established in pediatric patients 12 yr and older weighing at least 40 kg. Safety and efficacy in patients <12 yr of age or weighing <40 kg have not been established. Baloxavir efficacy is based on clinical trials in outpatients 12 to 64 yr of age; people with underlying medical conditions and adults >65 yr were not included in the initial published clinical trials (Hayden F et al; *Clin Infect Dis* 2018). There are no available data for baloxavir treatment of hospitalized patients with influenza.

Adapted from Centers for Disease Control and Prevention (CDC): *Influenza antiviral medications: summary for clinicians.* Available at https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm . For current details, consult annually updated recommendations at https://www.cdc.gov/flu/professionals/index.htm ; 2018 IDSA Clinical Practice Guidelines; and from Kimberlin DW, Acosta EP, Prichard MN, et al: National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Oseltamivir pharmacokinetics, dosing, and resistance among children aged <2 yr with influenza, *J Infect Dis* 207(5):709–720, 2013. For current details, consult annually updated recommendations at https://www.cdc.gov/flu/professionals/index.htm .

The second class of drugs is represented by a new influenza antiviral called baloxavir marboxil that was approved by the FDA in October 2018. Baloxavir is active against both influenza A and B viruses but has a different mechanism of action than neuraminidase inhibitors. Baloxavir is a cap-dependent endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication. It is approved for treatment of acute uncomplicated influenza in people 12 yr and older.

The third class of drugs, adamantanes, includes oral amantadine and oral rimantadine, which are effective only against influenza A viruses. Genetic mutations have conferred widespread adamantane resistance among circulating influenza A viruses, including seasonal influenza viruses and many H5N1 and H7N9 avian influenza viruses; *therefore this class of antivirals is not currently recommended for use.*

When initiated early in the course of uncomplicated influenza illness, antiviral agents can reduce the duration of symptoms and the likelihood of complications. Among hospitalized patients, observational studies suggest that early treatment reduces disease severity and mortality. Although most data regarding potential benefit are for adults, a few studies support the use of antiviral agents in children. Antiviral treatment within 2 days of illness onset has been reported to reduce illness duration, the risk of otitis media, and the likelihood of hospitalization in children. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hr of influenza illness onset.

CDC recommends treatment as early as possible for (1) hospitalized patients, (2) patients with complicated or progressive illness, and (3) patients at high risk for influenza complications (see Table 285.3). Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza. Although early treatment is desired, treatment even more than 48 hr from onset may be beneficial and is recommended for these 3 categories of patients.

The recommended treatment course for uncomplicated influenza is 1 dose of an oral oseltamivir or inhaled zanamivir given twice daily for 5 days; intravenous peramivir and oral baloxavir are both given as a single dose. Currently, for hospitalized patients and patients with severe or complicated illness, treatment with oral or enterically administered oseltamivir is recommended. The optimal duration and dose are uncertain for severe or complicated influenza and longer courses of treatment (e.g., 10 days of treatment) may be considered.

Clinical judgment, on the basis of the patient's disease severity, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for outpatients at high risk for complications. Antiviral treatment can also be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hr of illness onset.

It is possible that some influenza viruses may become resistant during antiviral treatment; this has been reported most often for oseltamivir resistance in influenza A(H1N1) viruses. Following treatment with baloxavir, emergence of viruses with molecular markers associated with reduced susceptibility to baloxavir has been observed in clinical trials. Antiviral resistance and reduced susceptibility can also occasionally occur spontaneously with no known exposure to antiviral drugs. It is important to review annual recommendations and updates published by CDC before prescribing influenza antiviral medications (see https://www.cdc.gov/flu/professionals/antivirals/index.htm).

Supportive Care

Adequate fluid intake and rest are important in the management of influenza. Bacterial superinfections are relatively common and should be appropriately treated with antibiotic therapy. Bacterial superinfection should be suspected with recrudescence of fever, prolonged fever, or deterioration in clinical status. With uncomplicated influenza, people should usually start to feel better after the first 48-72 hr of symptoms.

Prognosis

The prognosis for recovery from uncomplicated influenza is generally excellent, although full return to normal level of activity and freedom from cough may require weeks rather than days. Fatigue may also persist for weeks. However, severe influenza disease can be associated with hospitalizations and death, even among previously healthy children.

Prevention

Influenza vaccination is the best means of preventing influenza illness. In studies of children who are fully vaccinated, influenza vaccine is 40% to 60% effective in reducing the risk of laboratory-confirmed influenza illness. Vaccine effectiveness can vary from year to year and among different age and risk groups. Recommendations for use of the influenza vaccine have broadened as the impact of influenza is appreciated in such groups as pregnant women and young infants. Starting in the 2008-2009 influenza season, the United States Advisory Committee on Immunization Practices (ACIP) recommended that all children from 6 mo to 18 yr of age be vaccinated for influenza unless they have a specific contraindication to receiving the vaccine. Since the 2010-2011 season, annual flu vaccination is recommended for everyone 6 mo and older, with rare exception. In 2012, the Department of Health in the United Kingdom extended their influenza vaccination program to include all children between the ages of 2 and 17 yr. To protect infants younger than 6 mo who are too young to receive vaccine, household contacts and out-of-home caregivers are groups for whom additional vaccination efforts should be made. Chemoprophylaxis with antiviral medications is a secondary means of prevention and is not a substitute for vaccination.

Vaccines

There are 2 main categories of seasonal influenza vaccines available for children: inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV). Previously referred to as the trivalent inactivated vaccine, IIV is given intramuscularly; it uses killed virus components. The LAIV vaccine uses weakened influenza virus and is administered as an intranasal spray. Neither IIV nor LAIV can cause influenza. Although in 2014-2015 ACIP and CDC recommended the use of the LAIV nasal spray vaccine for healthy children 2 through 8 yr of age, this preferential recommendation was removed for the 2015-2016 season, and for the 2016-2017 and 2017-2018 seasons, ACIP and CDC made the interim recommendation that LAIV should not be used. This decision was based on concerns regarding low effectiveness against influenza A(H1N1)pdm09 in the United States noted during the 2013-2014 and 2015-2016 seasons. After review of additional data, LAIV containing an updated influenza A(H1N1)pdm09-like vaccine virus, was again recommended by CDC and ACIP as an option for vaccination for the 2018-2019 season. For the 2018-2019 season, ACIP and CDC made the interim recommendation that LAIV4 may be used.

Special vaccination instructions for children 6 mo to 8 yr of age should be followed: children in this age group who have not previously received a total of ≥2 previous doses of trivalent or quadrivalent vaccine require 2 doses (at least 4 weeks apart) of the current season's influenza vaccine to optimize immune response (Fig. 285.3). Influenza vaccines have an excellent safety profile, with the most common side effects being soreness, redness, tenderness, or swelling from the injection, and nasal congestion after the nasal spray.

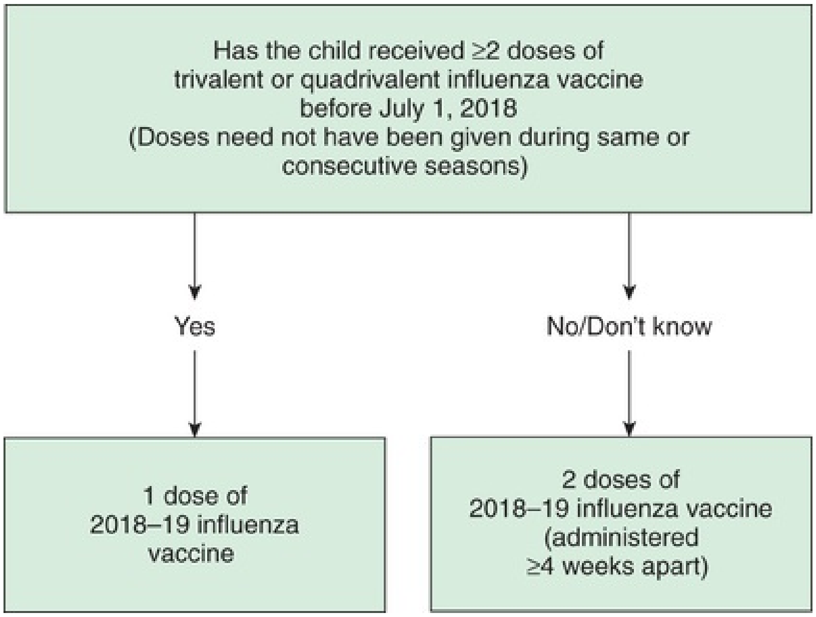
Has the child received ≥2 doses of trivalent or quadrivalent influenza vaccine before July 1, 2018 (Doses need not have been given during same or consecutive seasons)
Yes
No/Don't know
1 dose of 2018–19 influenza vaccine
2 doses of 2018–19 influenza vaccine (administered ≥4 weeks apart)

FIG. 285.3 Influenza vaccine dosing algorithm for children aged 6 mo through 8 yr—Advisory Committee on Immunization Practices, United States, 2018-2019 influenza season. (From Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB: Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices—United States, 2018-19 Influenza Season, *MMWR Recomm Rep* 67 (No. RR-3):1–20, 2018.)

Seasonal influenza vaccines become available in the late summer and early fall each year. The formulation reflects the strains of influenza viruses that are expected to circulate in the coming influenza season. Beginning in the 2013-2014 season, IIVs were available in both trivalent and quadrivalent formulations. The trivalent vaccine (IIV3) contains 2 influenza A strains and 1 influenza B strain; the quadrivalent vaccine (IIV4) contains a second influenza B strain of an antigenically distinct lineage. In addition to IIV and LAIV, a third vaccine category, recombinant hemagglutinin influenza vaccine, became available as a trivalent formulation in the 2013-2014 season but this is not licensed for children.

Ideally, vaccination should be given before the onset of influenza circulation in the community, so that there is time for antibodies to reach protective levels. Healthcare providers should offer vaccination by the end of October, if possible. The ACIP publishes guidelines for vaccine use each year when the vaccines are formulated and released; these should be referred to each season. These guidelines are widely publicized but appear initially in the *Morbidity and Mortality Weekly Report* published by CDC (https://www.cdc.gov/flu/index.htm

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Chemoprophylaxis

Routine use of antiviral medications for chemoprophylaxis is not recommended. Examples for which the use of chemoprophylaxis may be considered to prevent influenza after exposure to an infectious person include (1) unvaccinated persons at high risk of influenza complications, (2) persons for whom vaccine is contraindicated or expected to have low effectiveness, and (3) residents/patients in care facilities during institutional influenza outbreaks. Oral oseltamivir or inhaled zanamivir may be used for chemoprophylaxis of influenza; peramivir and baloxavir are not recommended for chemoprophylaxis because of a lack of data, and adamantanes are not currently recommended because of widespread adamantane resistance. Table 285.4 shows the recommendations for dosage and duration of treatment and chemoprophylaxis for the 2018-2019 influenza season, but updated recommendations from the ACIP and CDC should be consulted every season (https://www.cdc.gov/flu/professionals/antivirals/index.htm).

In general, if chemoprophylaxis can be started within 48 hr of exposure to an infectious person, postexposure chemoprophylaxis for persons at high risk of influenza complications (see Table 285.3) is recommended for 7 days after the last known exposure. An alternative to chemoprophylaxis for some persons after a suspected exposure is close monitoring and early initiation of antiviral treatment if symptoms develop. For control of influenza outbreaks among high-risk persons living in institutional settings, such as long-term care facilities, antiviral chemoprophylaxis is recommended for all vaccinated and unvaccinated residents and for unvaccinated healthcare providers. CDC and the Infectious Diseases Society of America recommend antiviral chemoprophylaxis for a minimum of 2 wk and up to 1 wk after the last known case is identified, whichever is longer.

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[*] Disclaimer: The findings and conclusions in this document are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

CHAPTER 286

Parainfluenza Viruses*

Holly M. Biggs, Angela J.P. Campbell

Human parainfluenza viruses (HPIVs) are common causes of acute respiratory illness in infants and children and are important causes of lower respiratory tract disease in young children and immunocompromised persons. These viruses cause a spectrum of upper and lower respiratory tract illnesses but are particularly associated with **croup** (laryngotracheitis or laryngotracheobronchitis), **bronchiolitis** , and **pneumonia** .

Etiology

HPIVs are members of the Paramyxoviridae family. Four HPIVs cause illness in humans, classified as types 1-4, with diverse manifestations of infection. Type 4 is divided into two antigenic subtypes, 4a and 4b. HPIVs have a nonsegmented, single-stranded RNA genome with a lipid-containing envelope derived from budding through the host cell membrane. The major antigenic moieties are the hemagglutinin neuraminidase (HN) and fusion (F) surface glycoproteins.

Epidemiology

By 5 yr of age, most children have experienced primary infection with HPIV types 1, 2, and 3. HPIV-3 infections generally occur earliest, with half of infants infected by age 1 yr, and over 90% by age 5 yr. HPIV-1 and HPIV-2 are more common after infancy, with approximately 75% infected by age 5 yr. Although HPIV-4 is not recognized as often, about half of children have antibody by the age of 5 yr. In the United States and temperate climates, HPIV-1 has typically been reported to have biennial epidemics in the fall in odd-numbered years (Fig.

286.1). HPIV-2 has been reported to cause yearly outbreaks in the fall, but is less common than HPIV-1 or HPIV-3. HPIV-3 can be endemic throughout the year but typically peaks in late spring. In years with less HPIV-1 activity, the HPIV-3 season has been observed to extend longer or to have a second peak in the fall (see Fig. 286.1). The epidemiology of HPIV-4 is less well defined, because it is difficult to grow in tissue culture and was often excluded from previous studies, but a recent study suggests it may circulate throughout the year and peak in fall of odd-numbered years. National HPIV trends are created from weekly laboratory test result data that are reported on a voluntary basis, and are available at the Centers for Disease Control and Prevention (CDC) National Respiratory and Enteric Virus Surveillance System (NREVSS) website (https://www.cdc.gov/surveillance/nrevss).

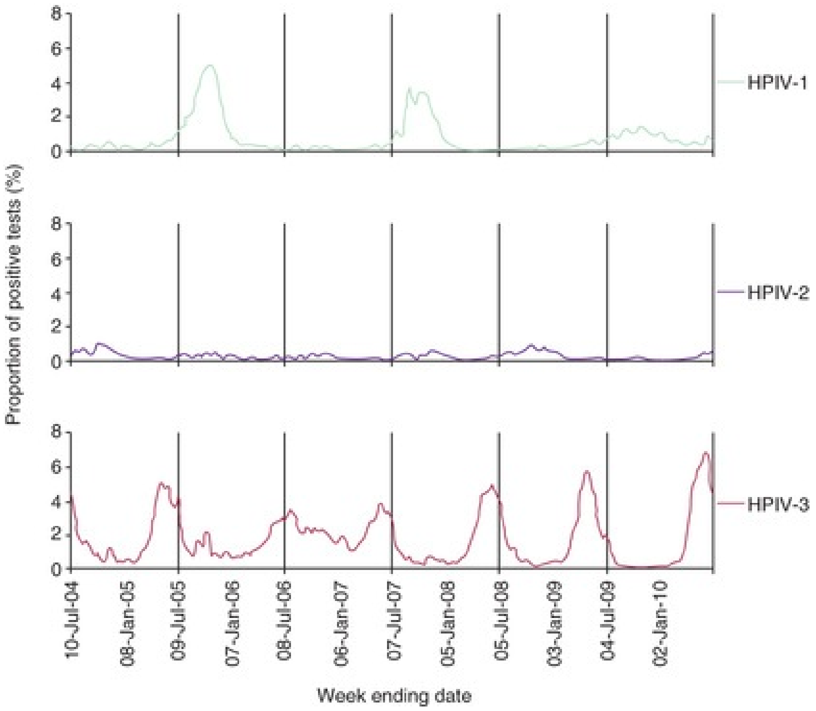

FIG. 286.1 Percentage of antigen tests positive for human parainfluenza virus-1–3 by 3-wk running average from July 2004 to June 2010 reported to the National Respiratory and Enteric Virus Surveillance System. (Data from Abedi GR, Prill MM, Langley GE, et al: Estimates of parainfluenza virus-associated hospitalizations and cost among children aged less than 5 years in the United States, 1998-2010, *J Pediatr Infect Dis Soc* 5:7–13, 2016; Fig. 1.)

HPIVs are spread primarily from the respiratory tract by inhalation of large respiratory droplets or contact with infected nasopharyngeal secretions. HPIVs are notable for causing outbreaks of respiratory illness in hospital wards, clinics, neonatal nurseries, and other institutional settings. The incubation period from exposure to symptom onset may range from 2 to 6 days. Children are likely to excrete virus from the oropharynx for 2-3 wk, but shedding can be more prolonged, especially in immunocompromised children, and may persist for months. Primary infection does not confer permanent immunity, and reinfections are common throughout life. Reinfections are usually mild and self-limited, but can cause serious lower respiratory tract illness, particularly in children with compromised immune systems.

Pathogenesis

HPIVs replicate in the respiratory epithelium. The propensity to cause illness in the upper large airways is presumably related to preferential replication in the larynx, trachea, and bronchi in comparison with other viruses. Some HPIVs induce cell-to-cell fusion. During the budding process, cell membrane integrity is lost, and viruses can induce cell death through the process of apoptosis. In children, the most severe illness generally coincides with the time of maximal viral shedding. However, disease severity is likely related to the host immune response to infection as much as to direct cytopathic effects of the virus. Virus-specific immunoglobulin A antibody levels and serum antibodies to the surface HN and F glycoproteins are able to neutralize HPIV, and both likely contribute to host immunity. Cell-mediated cytotoxicity is also important for controlling and terminating HPIV infection.

Clinical Manifestations

The most common type of illness caused by HPIV infection consists of some combination of low-grade fever, rhinorrhea, cough, pharyngitis, and hoarseness, and may be associated with vomiting or diarrhea. Rarely, HPIV infection is associated with parotitis. HPIVs have also been associated with a variety of skin manifestations, including typical maculopapular viral exanthems, erythema multiforme, and papular acrodermatitis, or Gianotti-Crosti syndrome (see Chapter 687). Although often mild, more serious HPIV illness may result in hospitalization, with common discharge diagnoses of bronchiolitis, fever/possible sepsis, and apnea among younger children, and croup, pneumonia, and asthma among older children (Fig. 286.2). HPIVs account for 50% of hospitalizations for croup and at least 15% of cases of bronchiolitis and pneumonia. HPIV-1, and to a lesser extent HPIV-2, cause more cases of croup, whereas HPIV-3 is more likely to infect the small air passages and cause pneumonia, bronchiolitis, or bronchitis. HPIV-4 causes a similar range of illness as the other types. Any HPIV can cause lower respiratory tract disease, particularly during primary infection or in patients with compromised immune systems. In children and adult patients with hematologic malignancies and undergoing hematopoietic stem cell transplantation, lymphopenia has repeatedly been shown to be an independent risk factor for progression from upper to lower respiratory tract disease.

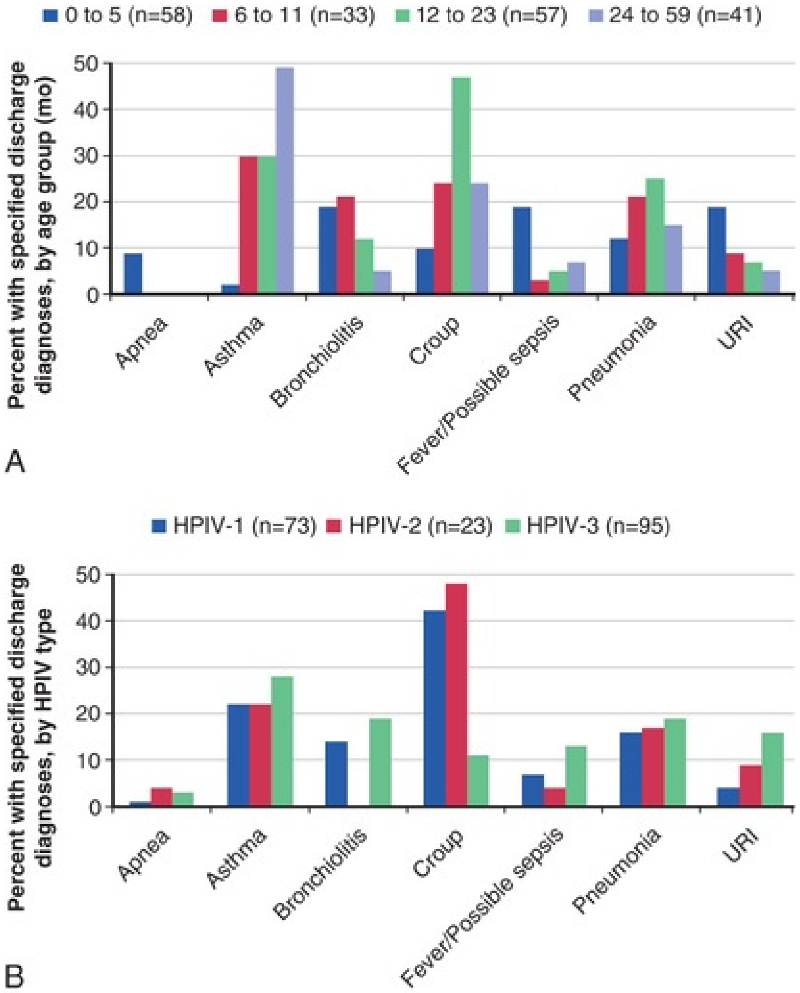

FIG. 286.2 Selected discharge diagnoses of hospitalized children with

parainfluenza (HPIV) infection, by **(A)** age in months and **(B)** virus type. (Data from Weinberg GA, Hall CB, Iwane MK, et al: Parainfluenza virus infection of young children: estimates of the population-based burden of hospitalization, *J Pediatr* 154:694–699, 2009, Table II.)

Diagnosis and Differential Diagnosis

The diagnosis of HPIV infection in children is often based on only clinical and epidemiologic criteria. Croup is a clinical diagnosis and must be distinguished from other diagnoses, including foreign body aspiration, epiglottitis, retropharyngeal abscess, angioedema, and subglottic stenosis or hemangioma. Although the radiographic **steeple sign** , consisting of progressive narrowing of the subglottic region of the trachea, is characteristic of croup, differential considerations include acute epiglottitis, thermal injury, angioedema, and bacterial tracheitis. Manifestation of HPIV lower respiratory tract disease may be similar to that of a number of other respiratory viral infections; therefore identification of virus should be sought by the most sensitive diagnostic means available for certain severe illnesses, such as pneumonia in immunocompromised children.

Sensitive, specific, and rapid molecular assays such as multiplex polymerase chain reaction assays, have become more widely available and greatly increase sensitivity of HPIV detection. For immunocompromised patients, these highly sensitive platforms provide the critical ability to make a prompt diagnosis by detecting a wide range of viral pathogens, including HPIVs, thus allowing for early implementation of infection prevention measures and potential treatment. Conventional laboratory diagnosis is accomplished by HPIV isolation in tissue culture, although time to result can take up to a week or longer; this can be shortened to 1-3 days using a rapid shell viral culture system. Direct immunofluorescent staining is available in some laboratories for rapid identification of virus antigen in respiratory secretions.

Treatment

There are no specific antiviral medications approved for the treatment of HPIV infections. For croup, the possibility of rapid respiratory compromise should influence the level of care and treatment given (see Chapter 412). Humidified air has not been shown to be effective. Corticosteroids, including dexamethasone orally or by injection and less often budesonide via nebulizer, improve symptoms within 6 hr after treatment, lessen the need for other medications, and shorten hospital stays. In general, because of its safety, efficacy, and cost-effectiveness, a single dose of oral dexamethasone (0.6 mg/kg) is the primary treatment for croup in the office or emergency room setting. A single dose of intramuscular dexamethasone or budesonide (2 mg [2 mL solution] via nebulizer) may provide an alternative to dexamethasone for children with severe respiratory distress or vomiting. The dose may be repeated, but this should not be necessary on a routine basis, and there are no guidelines to compare outcomes of single- and multiple-dose treatment schedules. Moderate to severe symptoms that persist for more than a few days should prompt investigation for other causes of airway obstruction.

The severity assessment of croup generally incorporates a number of clinical features, which include the presence and degree of chest wall retractions, whether stridor is present at rest, and evaluation of the child's mental status (e.g., for agitation, anxiety, lethargy). For obstructive airway symptoms associated with moderate to severe croup, nebulized epinephrine (either racemic epinephrine 2.25% solution, 0.05 to 0.1 mL/kg/dose, maximum dose 0.5 mL, diluted, in 3 mL of normal saline; or L -epinephrine, 0.5 mL/kg/dose of 1 : 1,000 solution in normal saline, maximum dose 5 mL) is recommended and may also provide temporary symptomatic improvement. Children should be observed for at least 2 hr after receiving epinephrine treatment for return of obstructive symptoms. Repeated treatments may be provided, depending on the duration of symptoms. Oxygen should be administered for hypoxia, and supportive care with analgesics and antipyretics is reasonable for fever and discomfort associated with HPIV infections. The indications for antibiotics are limited to well-documented secondary bacterial infections of the middle ear(s) or lower respiratory tract.

Ribavirin has some antiviral activity against HPIVs in vitro and in animal models. Inhaled ribavirin has been given to severely immunocompromised children with HPIV pneumonia; however, the majority of data have not shown improved outcomes, and randomized, controlled studies are lacking. Some institutions use intravenous immunoglobulin for HPIV pneumonia in children with hematologic malignancies or who have undergone hematopoietic stem cell transplantation; the impact of this treatment strategy on clinical outcomes is also limited by lack of controlled studies. Use of investigational antiviral DAS181, a novel sialidase fusion protein inhibitor, has shown clinical potential when used for treatment of HPIV lower respiratory tract disease among solid-organ and hematopoietic stem cell transplant recipients, but further study is needed. Other potential strategies for drug development include hemagglutinin-neuraminidase inhibitors, transcription inhibitors, and synthetic small interfering RNAs.

Complications

Eustachian tube obstruction can lead to secondary bacterial invasion of the middle ear space and acute otitis media in 30–50% of HPIV infections. Similarly, obstruction of the paranasal sinuses can lead to sinusitis. The destruction of cells in the upper airways can lead to secondary bacterial invasion and resultant bacterial tracheitis, and antecedent HPIV infection of lower airways may predispose to bacterial pneumonia. Nonrespiratory complications of HPIV are rare but include aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, rhabdomyolysis, myocarditis, and pericarditis.

Prognosis

The prognosis for full recovery from HPIV infection in the immunocompetent child is excellent, with no long-term pulmonary sequelae. Deaths may rarely occur, particularly in immunocompromised children with lower respiratory tract infection.

Prevention

Vaccine development has focused largely on live-attenuated intranasal HPIV-3 vaccines. Candidates include a recombinant human HPIV-3 virus (rcp45) derived from complementary DNA, as well as a complementary DNA–derived chimeric bovine/human HPIV-3 virus; these candidates are well tolerated and immunogenic in infants and young children. Constructs using chimeric bovine/human HPIV-3 virus in addition to the F or both F and G proteins of respiratory syncytial virus are also under investigation. Although at a less advanced state in development, live attenuated candidate HPIV-1 and HPIV-2 vaccines have undergone phase 1 clinical studies (www.clinicaltrials.gov). The measure of protection afforded by vaccines will be difficult to assess, because symptomatic reinfection occurs and the frequency of serious infection in the general population is low. Nonetheless, it is clear that prevention of acute respiratory illness caused by HPIVs, particularly lower respiratory tract infections among infants and young children, is a worthwhile goal.

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* Disclaimer: The findings and conclusions in this document are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

CHAPTER 287

Respiratory Syncytial Virus

James E. Crowe Jr.

Respiratory syncytial virus (RSV) is the major cause of bronchiolitis (see Chapter 418) and viral pneumonia in children younger than 1 yr of age and is the most important respiratory tract pathogen of early childhood.

Etiology

RSV is an enveloped RNA virus with a single-stranded negative-sense genome that replicates entirely in the cytoplasm of infected cells and matures by budding from the apical surface of the cell membrane. Because this virus has a nonsegmented genome, it cannot undergo antigenic shift by reassortment like the influenza viruses do. The virus belongs to the family Pneumoviridae, which comprises large enveloped, negative-sense RNA viruses. This taxon was formerly a subfamily within the Paramyxoviridae but was reclassified in 2016 as a family with two genera, *Orthopneumovirus* (which includes RSV) and *Metapneumovirus* (which includes human metapneumovirus; see Chapter 288). There are two antigenic subgroups of RSV (subgroups A and B), distinguished based primarily on sequence and antigenic variation in one of the two surface proteins, the G glycoprotein that is responsible for attachment to host cells. This antigenic variation, which is caused by point mutations from infidelity of the viral RNA polymerase, may contribute to some degree to the frequency with which RSV reinfects children and adults. However, adult human challenge experiments have shown that the same RSV strain can reinfect in the upper respiratory tract repetitively, suggesting that mucosal immunity in that site is incomplete or short-lived.

RSV replicates in a wide variety of cell line monolayer cultures in the laboratory. In HeLa and HEp-2 cell monolayers, the virus causes cell-to-cell fusion that produces characteristic cytopathology called syncytia (multinucleate enlarged cells), from which the virus derives its name. Identification of syncytia in diagnostic cultures of respiratory secretions is helpful in identifying RSV, but it is not clear whether syncytium formation occurs to any significant degree in the airway epithelium in patients.

Epidemiology

RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over a 4- to 5-mo period. During the remainder of the year, infections are sporadic and much less common. In the Northern hemisphere, epidemics usually peak in January, February, or March, but peaks have been recognized as early as December and as late as June. Some areas in the United States, such as Florida, report a moderate incidence year-round. In the Southern hemisphere, outbreaks also occur during the winter months in that hemisphere. RSV outbreaks often overlap with outbreaks of influenza virus or human metapneumovirus but are generally more consistent from year to year and result in more disease overall, especially among infants younger than 6 mo of age. In the tropics, the epidemic pattern is less clear. The pattern of widespread annual outbreaks and the high incidence of infection during the first 3-4 mo of life are unique among human viruses.

Transplacentally acquired anti-RSV maternal immunoglobulin G (IgG) serum antibodies, if present in high concentration, appear to provide partial protection for the neonate. The age of peak incidence of severe lower respiratory tract disease and hospitalization is about 6 wk. Maternal IgGs may account for the lower severity and incidence of RSV infections during the first 4-6 wk of life, except among infants born prematurely, who receive less maternal immunoglobulin. Breastfeeding provides some protection against severe disease, an effect that may pertain only to female and not male infants. RSV is one of the most contagious viruses that affect humans. Infection is nearly universal among children by their second birthday. Reinfection occurs at a rate of at least 10–20% per epidemic throughout childhood, with a lower frequency among adults. In situations of high exposure, such as daycare centers, attack rates are nearly 100% among previously uninfected infants and 60–80% for second and subsequent infections.

Reinfection may occur as early as a few weeks after recovery but usually takes place during subsequent annual outbreaks. Antigenic variation is not required for reinfection, as shown by the fact that a proportion of adults inoculated repeatedly with the same experimental preparation of wild-type virus could be reinfected multiple times. The immune response of infants is poor in quality, magnitude, and durability. The severity of illness during reinfection in childhood is usually lower than that in first infection and appears to be a function of partial acquired immunity, more robust airway physiology, and increased age.

Asymptomatic RSV infection is unusual in young children. Most infants experience coryza and pharyngitis, often with fever and frequently with otitis media caused by virus in the middle ear or bacterial superinfection following eustachian tube dysfunction. The lower respiratory tract is involved to a varying degree, with bronchiolitis and bronchopneumonia in about a third of children. The hospitalization rate for RSV infection in otherwise healthy infants is typically 0.5–4%, depending on region, gender, socioeconomic status, exposure to cigarette smoke, gestational age, and family history of atopy. The admitting diagnosis is usually bronchiolitis with hypoxia, although this condition is often indistinguishable from RSV pneumonia in infants, and, indeed, the two processes frequently coexist. All RSV diseases of the lower respiratory tract (excluding croup) have their highest incidence at 6 wk to 7 mo of age and decrease in frequency thereafter. The syndrome of bronchiolitis is much less common after the 1st birthday. The terminology used for the diagnosis of virus-associated wheezing illnesses in toddlers can be confusing, because these illnesses are variably termed *wheezing-associated respiratory infection, wheezy bronchitis, exacerbation of reactive airways disease*, or *asthma attack.* Because many toddlers wheeze during RSV infection but do not go on to have lifelong asthma, it is best to use the diagnostic term *asthma* only later in life. Acute viral pneumonia is a recurring problem throughout childhood, although RSV becomes less prominent as the etiologic agent after the first year. RSV plays a causative role in an estimated 40–75% of cases of hospitalized bronchiolitis, 15–40% of cases of childhood pneumonia, and 6–15% of cases of croup.

Bronchiolitis and pneumonia resulting from RSV are more common in males than in females by a ratio of approximately 1.5 : 1. Other risk factors with a similar impact in the United States include one or more siblings in the home, white race, rural residence, maternal smoking, and maternal education < 12 yr. The medical factors in infants associated with the highest risk are chronic lung disease of prematurity, congenital heart disease, immunodeficiency, and prematurity. Still, most infants admitted to the hospital because of RSV infection do not have strong, easily identifiable risk factors. Therefore, any strategy for prophylaxis focused only on individuals with strong risk factors probably could prevent only approximately 10% of hospitalizations, even if the prophylaxis was 100% effective in treated high-risk individuals.

The incubation period from exposure to first symptoms is approximately 3-5 days. The virus is excreted for variable periods, probably depending on the severity of illness and immunologic status. Most infants with lower respiratory tract illness shed infectious viruses for 1-2 wk after hospital admission. Excretion for 3 wk and even longer has been documented. Spread of infection occurs when large, infected droplets, either airborne or conveyed on hands or other fomites, are inoculated in the nasopharynx of a susceptible subject. RSV is probably introduced into most families by young schoolchildren experiencing reinfection. Typically, in the space of a few days, 25–50% of older siblings and one or both parents acquire upper respiratory tract infections, but infants become more severely ill with fever, otitis media, or lower respiratory tract disease.

Nosocomial infection during RSV epidemics is an important concern. Virus is usually spread from child to child on the hands of caregivers or other fomites. Adults experiencing reinfection also have been implicated in the spread of the virus. Contact precautions are sufficient to prevent spread when compliance is meticulous, because the virus is not spread by small particle aerosol to an appreciable degree, and a distance of about 6 ft is likely sufficient to avoid aerosol transmission. However, in practice, adherence to isolation procedures by caregivers often is not complete.

Pathogenesis

Bronchiolitis is caused by obstruction and collapse of the small airways during expiration. Infants are particularly apt to experience small airway obstruction because of the small size of their normal bronchioles; airway resistance is proportional to 1/radius^4 . There has been relatively little pathologic examination of RSV disease in the lower airways of otherwise healthy subjects. Airway narrowing likely is caused by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round-cell infiltration and edema of the surrounding submucosa. These changes result in the formation of mucus plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia, the infiltration is more generalized, and epithelial shedding may extend to both the bronchi and the alveoli. In older subjects, smooth muscle hyperreactivity may contribute to airway narrowing, but the airways of young infants typically do not exhibit a high degree of reversible smooth muscle hyperreactivity during RSV infection.

Several facts suggest that elements of the host response may cause inflammation and contribute to tissue damage. The immune response required to eliminate virus-infected cells (mostly containing cytolytic T cells) is a double-edged sword, reducing the cells producing virus but also causing host cell death in the process. A large number of soluble factors, such as cytokines, chemokines, and leukotrienes, are released in the process, and skewing of the patterns of these responses may predispose some individuals to more severe disease. There is also evidence that genetic factors may predispose to more severe bronchiolitis.

Children who received a formalin-inactivated, parenterally administered RSV vaccine in the 1960s experienced more severe and more frequent bronchiolitis upon subsequent natural exposure to wild-type RSV than did their age-matched controls. Several children died during naturally acquired RSV infections after FI-RSV vaccinations. This event greatly inhibited the progress in RSV vaccine development, because of both an incomplete understanding of the mechanism and a reluctance to test new experimental vaccines that might induce the same type of response.

Some studies have identified the presence of both RSV and human metapneumovirus viral RNA in airway secretions in a significant proportion of infants requiring assisted ventilation and intensive care. It may be that coinfection is associated with more severe disease. Positive results of polymerase chain reaction (PCR) analysis must be interpreted carefully because this positivity can remain for prolonged periods after infection, even when infectious virus can no longer be detected.

It is not clear how often superimposed bacterial infection plays a pathogenic role in RSV lower respiratory tract disease. RSV bronchiolitis in infants is probably exclusively a viral disease, although there is evidence that bacterial pneumonia can be triggered by respiratory viral infection, including with RSV. A large clinical study of pneumococcal vaccine showed that childhood vaccination reduced the incidence of viral pneumonia by approximately 30%, suggesting viral-bacterial interactions that we currently do not fully understand.

Clinical Manifestations

Typically, the first sign of infection in infants with RSV is rhinorrhea. Cough may appear simultaneously but more often does so after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child who experiences bronchiolitis begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse fine inspiratory crackles and expiratory wheezes. Rhinorrhea usually persists throughout the illness, with intermittent fever. Chest radiograph findings at this stage are frequently normal.

If the illness progresses, cough and wheezing worsen and air hunger ensues, with an increased respiratory rate, intercostal and subcostal retractions, hyperexpansion of the chest, restlessness, and peripheral cyanosis. Signs of severe, life-threatening illness are central cyanosis, tachypnea of > 70 breaths/min, listlessness, and apneic spells. At this stage, the chest may be significantly hyperexpanded and almost silent to auscultation because of poor air movement.

Chest radiographs of infants hospitalized with RSV bronchiolitis have normal findings in approximately 30% of cases, with the other 70% showing hyperexpansion of the chest, peribronchial thickening, and interstitial infiltrates. Segmental or lobar consolidation is unusual, and pleural effusion is rare.

In some infants, the course of the illness may resemble that of pneumonia, the prodromal rhinorrhea and cough being followed by dyspnea, poor feeding, and listlessness. Although the clinical diagnosis is pneumonia, wheezing is often present intermittently, and the chest radiographs may show air trapping.

Fever is an inconsistent sign in RSV infection. In young infants, particularly those who were born prematurely, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. Apnea is not necessarily caused by respiratory exhaustion but rather appears to be a consequence of alterations in the central control of breathing.

RSV infections in profoundly immunocompromised hosts may be severe at any age of life. The mortality rates associated with RSV pneumonia in the 1st few weeks after hematopoietic stem cell or solid-organ transplantation in both children and adults are high. RSV infection does not appear to be more severe in HIV-infected patients with reasonable control of HIV disease, although these patients may shed virus in respiratory secretions for prolonged periods.

Diagnosis

Bronchiolitis is a clinical diagnosis. RSV can be suspected with varying degrees of certainty on the basis of the season of the year and the presence of the virus in the community. Other epidemiologic features that may be helpful are the presence of common colds in older household contacts and the age of the child. The other respiratory viruses that attack infants frequently during the first few months of life are human metapneumovirus, influenza viruses, parainfluenza virus type 3, rhinoviruses, enteroviruses, and coronaviruses.

Routine laboratory tests are of minimal diagnostic use in most cases of bronchiolitis or pneumonia caused by RSV. The white blood cell count is normal or elevated, and the differential cell count may be normal with either a neutrophilic or mononuclear predominance. Hypoxemia as measured by pulse oximetry or arterial blood gas analysis is frequent and tends to be more marked than anticipated from the clinical findings. A normal or elevated blood CO_2 value in a patient with a markedly elevated respiratory rate is a sign of respiratory failure.

The most important diagnostic concern is to differentiate viral infection from bacterial or chlamydial infection. When bronchiolitis is not accompanied by infiltrates on chest radiographs, there is little likelihood of a bacterial component. In infants 1-4 mo of age, interstitial pneumonitis may be caused by *Chlamydia trachomatis* (see Chapter 253). With *C. trachomatis* pneumonia, there may be a history of conjunctivitis, and the illness tends to be of subacute onset. Coughing and inspiratory crackles may be prominent; wheezing is not. Fever is usually absent.

Lobar consolidation without other signs or with pleural effusion should be considered of bacterial etiology until proved otherwise. Other signs suggesting bacterial pneumonia are neutrophilia, neutropenia in the presence of severe disease, ileus or other abdominal signs, high temperature, and circulatory collapse. In such instances, antibiotics should be initiated.

The definitive diagnosis of RSV infection is based on the detection in respiratory secretions of live virus by cell culture. Molecular diagnostic tests are more available, however. The presence of viral RNA (detected by a molecular diagnostic test using reverse transcription PCR) or viral antigens (detected by a rapid diagnostic test, usually a membrane blotting test incorporating antibody detection of viral proteins) is strongly supportive in the right clinical setting. The antigen test is less sensitive than virus culture, whereas reverse transcription PCR analysis is more sensitive than culture. An aspirate of mucus or a nasopharyngeal wash from the child's posterior nasal cavity is the optimal specimen. Nasopharyngeal or throat swabs are less preferable but are acceptable. A tracheal aspirate is unnecessary, but endotracheal tube lavage fluid from patients intubated for mechanical ventilation can be tested. The specimen should be placed on ice, taken directly to the laboratory, and processed immediately for culture, antigen detection, or PCR analysis. RSV is thermolabile, so it degrades over relatively short periods of time unless it is frozen at a low temperature such as −80°C (−112°F) in freezers used in research settings.

Treatment

The treatment of uncomplicated cases of bronchiolitis is symptomatic. Many infants are slightly to moderately dehydrated, and therefore fluids should be carefully administered in amounts somewhat greater than those for maintenance. Often, intravenous or tube feeding is helpful when sucking is difficult because of tachypnea. Humidified oxygen and suctioning usually are indicated for hospitalized infants who are hypoxic. High-flow nasal cannula therapy is used for respiratory distress, which is mostly useful for pressure support. Nasal continuous positive airway pressure is used in the intensive care unit for infants who have increased work of breathing, and mechanical ventilation is used for respiratory failure. Heliox (helium blended with oxygen) may improve ventilation in infants who have severe respiratory distress but who do not require large amounts of oxygen.

There is disagreement among experts regarding the usefulness of aerosolized saline or hypertonic saline, epinephrine, or β_2 -agonists in RSV bronchiolitis. Most patients do not receive lasting benefit from prolonged therapy, which is associated with a relatively high frequency of side effects. Corticosteroid therapy is not indicated except in older children with an established diagnosis of asthma, because its use is associated with prolonged virus shedding and is of no proven clinical benefit. The 2014 American Academy of Pediatrics bronchiolitis clinical practice guideline suggests limitations on the use of α- and β-adrenergic agents and corticosteroids.

In nearly all instances of bronchiolitis, antibiotics are not useful, and their inappropriate use contributes to the development of antibiotic resistance. Interstitial pneumonia in infants 1-4 mo old may be caused by *C. trachomatis,* and macrolide therapy may be indicated for that infection.

Ribavirin is an antiviral agent delivered through an oxygen hood, face mask, or endotracheal tube with use of a small-particle aerosol generator most of the day for 3-5 days. Early small trials of its use suggested a modest beneficial effect on the course of RSV pneumonia, with some reduction in the duration of both mechanical ventilation and hospitalization. However, subsequent studies failed to document a clear beneficial effect of ribavirin, and therefore this drug is no longer used for routine therapy of RSV disease. The monoclonal antibody palivizumab is licensed for prophylaxis in high-risk infants during the RSV season and does prevent about half of the expected hospitalizations in that population. Small clinical trials using palivizumab as a therapy during established infection have not shown benefit to date. Next-generation monoclonal antibodies for RSV that are more potent and longer-lasting are in clinical trials.

Prognosis

The mortality rate of hospitalized infants with RSV infection of the lower respiratory tract is very low in the developed world. Almost all deaths occur among young, premature infants or infants with underlying disease of the neuromuscular, pulmonary, cardiovascular, or immunologic system. However, it is estimated that more than 160,000 children worldwide in resource-poor settings die each year from RSV. In addition, thousands of elderly patients die of RSV infection each year in the United States.

There is recurrent wheezing in 30–50% of children who have severe RSV bronchiolitis in infancy, and many older children who are diagnosed with asthma have a history of severe bronchiolitis in infancy. The likelihood of the recurrence of wheezing is increased in the presence of an allergic diathesis (e.g., eczema, hay fever, or a family history of asthma). With a clinical presentation of bronchiolitis in a patient older than 1 yr of age, there is an increasing probability that, although the episode may be virus-induced, the event is likely the first of multiple wheezing attacks that will later be diagnosed as hyperreactive airways disease or asthma. Asthma is difficult to diagnose in the first year of life. It is not fully clear at this time whether early, severe RSV wheezing disease causes some cases of asthma or whether subjects destined to suffer asthma present with symptoms first when provoked by RSV infection during infancy. Results from a long-term follow-up study of infants who received palivizumab prophylaxis suggested that the prevention of severe RSV infection may reduce the incidence of reactive airways disease later in life.

Prevention

In the hospital, the most important preventive measures are aimed at blocking nosocomial spread. During RSV season, high-risk infants should be separated from all infants with respiratory symptoms. Gowns, gloves, and careful handwashing (contact isolation) should be used for the care of all infants with suspected or established RSV infection. A high level of compliance with contact isolation is essential. Viral laboratory tests are adequate for diagnosis in the setting of acute disease when levels of virus are high, but they are not designed to detect low levels of virus. Therefore, contact precaution isolation should be observed for most patients admitted for acute disease assigned for the duration of hospitalization. Rapid antigen tests should not be used to determine whether or not a patient still requires isolation, because low concentrations of virus may be present in respiratory secretions that are infectious for humans but below the lower limit of detection for such assays. Ideally, patients with RSV or metapneumovirus infections are housed separately, because coinfection with the two viruses may be associated with more severe disease.

Passive Immunoprophylaxis

Administration of palivizumab (15 mg/kg intramuscularly once a month), a neutralizing humanized murine monoclonal antibody against RSV, is recommended for protecting high-risk children against serious complications from RSV disease. Immunoprophylaxis reduces the frequency and total days of hospitalization for RSV infections in high-risk infants in about half of cases. Palivizumab is administered monthly from the beginning to the end of the RSV season. Palivizumab prophylaxis may be considered for the following infants and children:

- Infants born before 29 wk of gestation in the first year of life
- Infants born before 32 wk of gestation, who have chronic lung disease of prematurity (required > 21% FIO_2 [fraction of inspired oxygen] for ≥ 28 days after birth), in the first year of life
- Infants younger than 1 yr of age with hemodynamically *significant* congenital heart disease following cardiac transplantation (children < 2 yr age)
- Children 24 mo of age or younger with profound immunocompromising

conditions during RSV season

Infants in the first year of life who have either congenital abnormalities of the airway or neuromuscular disease that compromises the handling of respiratory secretions

Administration in the second year of life is recommended for children who required 28 or more days of oxygen after birth and who have ongoing treatment for chronic pulmonary disease (oxygen, steroids, diuretics)

Recommendations for initiation and termination of prophylaxis reflect current descriptions from the Centers for Disease Control and Prevention of RSV seasonality in different geographic locations within the United States. Initiation in different areas of the United States may be recommended for different months, because of variation in the onset of the season in different regions, with special recommendations for Alaska and Florida. Regardless of the month in which the first dose is administered, the recommendation for a maximal number of five doses for all geographic locations is emphasized for high-risk infants. Categories of infants at increased risk of severe disease include those with hemodynamically significant congenital heart disease, chronic lung disease of prematurity, or birth before 32 wk, 0 days of gestation, congenital anatomic pulmonary abnormalities or neuromuscular disorder, and immunocompromised state; Down syndrome, cystic fibrosis, or Alaska Native infants are at increased risk, but passive immunization is not indicated unless another high-risk condition is present. A second season of palivizumab prophylaxis is recommended only for preterm infants < 32 weeks, 0 days gestation who required at least 28 days of oxygen after birth and who continue to require supplemental oxygen, chronic systemic corticosteroid therapy, or diuretic therapy within 6 mo of the start of the second RSV season.

Vaccine

There is no licensed vaccine against RSV. The challenge for the development of live virus vaccines has been to produce attenuated vaccine strains that infect infants in the nasopharynx after topical inoculation without producing unacceptable symptoms, that remain genetically stable during shedding, and that induce protection against severe disease following reinfection. The most promising live-attenuated virus candidates have been engineered in the laboratory from cold-passaged strains of RSV, according to a basic strategy that yielded the live poliovirus and influenza virus vaccine strains. A variety of nonreplicating experimental vaccines are being tested in early clinical trials. Subunit vaccine candidates are being tested in maternal immunization trials. The rationale of such studies is to test whether boosting the serum level of RSV-neutralizing antibodies in the mother can enhance immunity in neonates following transplacental transfer of those boosted levels of maternal antibodies to the infant.

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CHAPTER 288

Human Metapneumovirus

James E. Crowe Jr.

Etiology

Human metapneumovirus (HMPV) is a respiratory virus that has emerged as one of the most common causes of serious lower respiratory tract illness in children throughout the world.

Etiology

HMPV is an enveloped, single-stranded, nonsegmented, negative-sense RNA genome of the family Pneumoviridae, which comprises large enveloped negative-sense RNA viruses. This taxon was formerly a subfamily within the Paramyxoviridae, but was reclassified in 2016 as a family with two genera, *Metapneumovirus* (which includes HMPV) and *Orthopneumovirus* (which includes respiratory syncytial virus [RSV], see Chapter 287). HMPV and the avian pneumoviruses are highly related and are separated into the separate genus *Metapneumovirus* because the gene order in the nonsegmented genome is slightly altered and because avian pneumoviruses/HMPVs lack the genes for two nonstructural proteins, NS1 and NS2, which are encoded at the 3′ end of RSV genomes. These proteins are thought to counteract host type I interferons. The absence of NS1/NS2 in the metapneumoviruses (compared with RSV) may contribute to an overall slightly reduced pathogenicity relative to wild-type RSV strains.

The HMPV genome encodes nine proteins in the order 3′-N-P-M-F-M2-(orf1 and 2)-SH-G-L-5′. The genome also contains noncoding 3′ leader, 5′ trailer, and intergenic regions, consistent with the organization of most paramyxoviruses, with a viral promoter contained in the 3′ end of the genome. The F (fusion), G (glycosylated), and SH (short hydrophobic) proteins are integral membrane proteins on the surfaces of infected cells and virion particles. The F protein is a classic type I integral membrane viral fusion protein that contains two heptad repeats in the extracellular domain that facilitate membrane fusion. There is a predicted protein cleavage site near a hydrophobic fusion peptide that likely is cleaved by an extracellular protease, activating the F protein for fusion. The predicted attachment (G) protein of HMPV exhibits the basic features of a glycosylated type II mucin-like protein. The HMPV G protein differs from the RSV G protein in that it lacks a cysteine noose structure. This protein may inhibit innate immune responses. The internal proteins of the virus appear similar in function to those of other paramyxoviruses.

Epidemiology

HMPV outbreaks occur in annual epidemics during late winter and early spring in temperate climates, often overlapping with the second half of the annual RSV epidemic (Fig. 288.1). Sporadic infections occur year round. The usual period of viral shedding is likely to be many days or even several weeks after primary infection in infants. The incubation period is approximately 3-5 days. Humans are the only source of virus; there is no known animal or environmental reservoir. Transmission occurs by close or direct contact with contaminated secretions involving large-particle aerosols, droplets, or contaminated surfaces. Nosocomial infections have been reported, and contact isolation with excellent handwashing for healthcare providers is critical in medical settings. This virus also affects the elderly, immunocompromised patients, and patients with reactive airways disease more severely than otherwise healthy individuals.

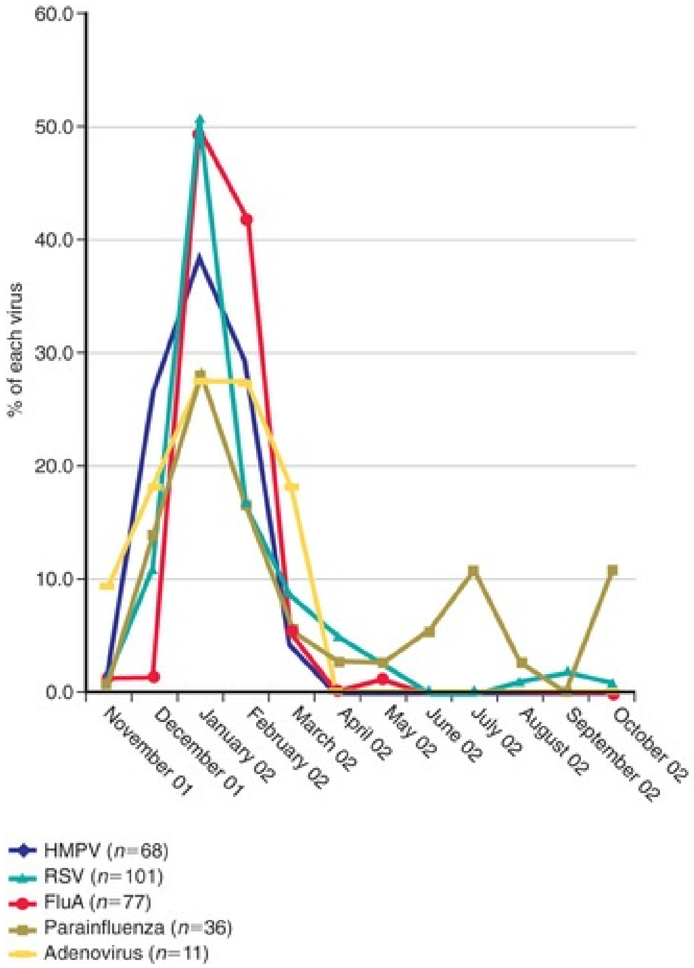

FIG. 288.1 Temporal distribution of respiratory viruses among children hospitalized with lower respiratory tract infections from November 2001 through October 2002. Data are displayed as the proportion of each virus detected monthly. FluA, influenza A; HMPV, human metapneumovirus; RSV, respiratory syncytial virus. (From Wolf DG, Greenberg D, Kalkstein D, et al: Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children, Pediatr Infect Dis J 25:320–324, 2006.)

Pathology

Infection is usually limited to the superficial layer of airway epithelial cells and is associated with a local inflammatory infiltrate consisting of lymphocytes and macrophages. Immunocompromised individuals have evidence of both acute and organizing injuries during prolonged infection.

Pathogenesis

Infection occurs via inoculation of the upper respiratory tract. Infection can spread rapidly to the lower respiratory tract, but it is not clear whether the dissemination is mediated by cell-to-cell spread or by aspiration of infected materials from the upper tract. Severe lower respiratory tract illness, especially wheezing, occurs mainly during the first year of life, at a time when the airways are of a very small diameter and thus a high resistance. Maternal serum-neutralizing antibodies that cross the placenta may afford a relative protection against severe disease for several weeks or months after birth. Once infection is established, it is likely that cytotoxic T cells recognize and eliminate virus-infected cells, thus terminating the infection but also causing some cytopathology. The virus appears to have specific mechanisms for inhibiting T-cell responses during acute infection. Individuals with an underlying predisposition for reactive airways disease (including adults) are susceptible to severe wheezing during reinfection later in life, suggesting that HMPV may cause smooth muscle hyperactivity, inflammation, or increased mucus production in such individuals. Infection in otherwise healthy individuals resolves without apparent long-term consequences in most cases. HMPV infection is associated with exacerbations of asthma later in life.

Clinical Manifestations

HMPV is associated with the common cold (complicated by otitis media in approximately 30% of cases) and with lower respiratory tract illnesses such as bronchiolitis, pneumonia, croup, and exacerbation of reactive airways disease. The profile of signs and symptoms caused by HMPV is very similar to that caused by RSV (Table 288.1). Approximately 5–10% of outpatient lower respiratory tract illnesses in otherwise healthy young children is associated with HMPV infection, which is second in incidence only to RSV. Children with RSV or HMPV infection require supplemental oxygen and medical intensive care at similar frequencies.

Table 288.1

Clinical Manifestations of Human Metapneumovirus in Children

COMMON (>50%)

Fever > 38°C (100.4°F)

Cough

Rhinitis, coryza

Wheezing

Tachypnea, retractions

Hypoxia (O_2 saturation < 94%)

Chest radiograph demonstration of infiltrates or hyperinflation

LESS COMMON

Otitis media

Pharyngitis

Rales

RARE

Conjunctivitis

Hoarseness

Encephalitis

Fatal respiratory failure in immunocompromised children

About half of the cases of HMPV lower respiratory tract illness in children occur in the first 6 mo of life, suggesting that young age is a major risk factor for severe disease. Both young adults and the elderly can have HMPV infection that requires medical care including hospitalization, but severe disease occurs at much lower frequencies in adults than in young children. Severe disease in pediatric and older subjects is most common in immunocompromised patients or those with complications of preterm birth, congenital heart disease, and neuromuscular disease and can be fatal. A significant number of both adult and pediatric patients with asthma exacerbations have HMPV infection; it is not clear whether the virus causes long-term wheezing. RSV and HMPV coinfections have been reported; coinfections may be more severe than infection with a single virus, resulting in pediatric intensive care unit admissions. It is difficult to define true coinfections because these viral RNA genomes can be detected by a reverse transcriptase polymerase chain reaction (PCR) in respiratory secretions for at least several weeks after illness, even when virus shedding has terminated.

Laboratory Findings

The virus can be visualized only with electron microscopy. The virus grows in primary monkey kidney cells or LLC-MK2 cell or Vero cell–line monolayer cultures in reference or research laboratories, but efficient isolation of the virus requires an experienced laboratory technician. Conventional bright-field microscopy of infected cell monolayer cultures often reveals a cytopathic effect only after multiple passages in the cell culture. The characteristics of the cytopathic effect are not sufficiently distinct to allow identification of the virus on this basis alone, even by a trained observer. The most sensitive test for identification of HMPV in clinical samples is reverse transcriptase PCR, usually performed with primers directed to conserved viral genes. Detection by this modality is also available in some multiplex PCR tests for panels of respiratory viruses. Real-time reverse transcriptase PCR tests offer enhanced sensitivity and specificity, including assays designed to detect viruses from the four known genetic lineages. Direct antigen tests for identification of HMPV antigens in nasopharyngeal secretions are available but are less efficient than nucleic acid–based detection. Some laboratories have success with the use of immunofluorescence staining with monoclonal or polyclonal antibodies to detect HMPV in nasopharyngeal secretions and shell vial cultures or in monolayer cultures in which virus has been cultivated, with reported sensitivities varying from about 65% to 90%. A four-fold rise in serum antibody titer to HMPV from the acute to convalescent time point can be used in research settings to confirm infection.

Diagnosis and Differential Diagnosis

In temperate areas, the diagnosis should be suspected during the late winter in infants or young children with wheezing or pneumonia and a negative RSV diagnostic test result. The diseases caused by RSV and HMPV cannot be distinguished clinically. Many other common respiratory viruses, such as parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, enteroviruses, and coronaviruses, can cause similar disease in young children. Some of these viruses can be identified by PCR genetic testing or conventional cell culture means. Chest radiographs are not very specific, mostly showing parahilar opacities, hyperinflation, atelectasis, and, occasionally, consolidation, but not pleural effusion or pneumothorax.

Complications

Bacterial superinfection of the lower airways is unusual but does occur. The local complication of otitis media is common, likely a result of eustachian tube dysfunction caused by the virus.

Treatment

There is no specific treatment at this time for HMPV infection. Management consists of supportive care similar to that used for RSV (see Chapter 287). The rate of bacterial lung infection or bacteremia associated with HMPV infection is not fully defined but is suspected to be low. Antibiotics are usually not indicated in the treatment of infants hospitalized for HMPV bronchiolitis or pneumonia.

Supportive Care

Treatment is supportive and includes careful attention to hydration; monitoring of respiratory status by physical examination and measurement of oxygen saturation; the use of supplemental oxygen, high-flow nasal cannula therapy, and nasal continuous positive airway pressure in an intensive care unit for increased work of breathing; and, if necessary in the case of respiratory failure, mechanical ventilation.

Prognosis

Most infants and children recover from acute HMPV infection without apparent long-term consequences. Many experts believe an association exists between severe HMPV infections in infancy and the risk for recurrent wheezing or the development of asthma; however, it is not clear whether the virus causes these conditions or precipitates their first manifestations.

Prevention

The only method of prevention of HMPV infection is reduction of exposure. Contact precautions are recommended for the duration of HMPV-associated illness among hospitalized infants and young children. Patients known to have HMPV infection should be housed in single rooms or with a cohort of HMPV-infected patients. When feasible, it is wise to care for patients with RSV infection in a separate cohort from HMPV-infected patients, so as to prevent coinfection, which may be associated with more severe disease. Preventive measures include limiting exposure to contagious settings during annual epidemics (such as daycare centers) as much as possible and an emphasis on hand hygiene in all settings, including the home, especially during periods when the contacts of high-risk children have respiratory infections. However, providers should keep in mind that infection is universal in the first several years of life. Therefore, reduction of exposure makes the most sense during the first 6 mo of life, when infants are at the highest risk for severe disease.

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CHAPTER 289

Adenoviruses

Jason B. Weinberg, John V. Williams

Human adenoviruses (HAdVs) are a common cause of human disease. Conjunctivitis is a familiar illness associated with the HAdVs, but these viruses also cause upper and lower respiratory disease, pharyngitis, gastroenteritis, and hemorrhagic cystitis. HAdVs can cause severe disease in immunocompromised hosts. Outbreaks of HAdV infection occur in communities and closed populations, notably the military. No currently approved antiviral drugs are highly effective against HAdVs. Vaccines are available for HAdV types 4 and 7 but are used only for military populations.

Etiology

Adenoviruses are nonenveloped viruses with an icosahedral protein capsid. The double-stranded DNA genome is contained within the particle complexed with several viral proteins. Antigenic variability in surface proteins of the virion and genomic sequencing define at least 70 serotypes grouped into seven species. Species differ in their tissue tropism and target organs, causing distinct clinical infections (Table 289.1). HAdVs can be shed from the gastrointestinal tract for prolonged periods and can establish persistent infection of the tonsils and adenoids.

Table 289.1

Adenovirus Types With Associated Infections

SPECIES	TYPE	PREFERRED SITE OF INFECTION
A	12, 18, 31, 61	Gastrointestinal
B	3, 7, 11, 14, 16, 21, 34, 35, 50, 55, 66	Respiratory; renal/urinary tract

		epithelium
C	1, 2, 5, 6, 57	Respiratory
D	8-10, 13, 15, 17, 19, 20, 22-30, 32, 33, 36-39, 42-49, 51, *53, 54, 56, 58-60, 63-67*	Ocular
E	4	Respiratory
F	40, 41	Gastrointestinal
G	52	Gastrointestinal

Epidemiology

HAdVs circulate worldwide and cause endemic infections year-round in immunocompetent hosts. Asymptomatic infections are also common. Only about one third of all known HAdV types are associated with clinically apparent disease. The most prevalent types in recent surveillance studies are HAdV types 3, 2, 1, and 5. Epidemics of conjunctivitis (often severe), pharyngitis, and respiratory disease occur, especially in schools and military settings. Outbreaks of febrile respiratory illness caused by HAdV-4 and HAdV-7 are a major source of morbidity in military barracks, with attack rates ranging from 25% to > 90%. The spread of HAdV occurs by respiratory and fecal-oral routes. An important factor in HAdV transmission, especially in epidemics, is the ability of the nonenveloped particle to survive on inanimate objects in the environment. Nosocomial outbreaks have been reported.

Pathogenesis

HAdVs bind to cell surface receptors and trigger internalization by endocytosis. Acidification of the endosome induces conformational changes in the capsid, leading to eventual translocation of the genome to the cell nucleus. Viral messenger RNA transcription and genomic replication occur in the nucleus. Progeny virion particles assemble in the nucleus. Lysis of the cell releases new infectious particles and causes damage to epithelial mucosa, sloughing of cell debris, and inflammation. Host responses to HAdV infection include the recruitment of neutrophils, macrophages, and natural killer cells to the site of infection and the elaboration by those cells of a number of cytokines and chemokines. This host immune response is likely to contribute to the symptoms of HAdV infection, but specific mechanisms of pathogenesis are poorly understood. The strict species specificity of the adenoviruses has precluded the development of an animal model for HAdVs, although recent work with HAdV in a humanized mouse model shows promise. Mouse adenovirus has also been used to study adenovirus pathogenesis using a murine model.

Clinical Manifestations

HAdVs cause a variety of common clinical syndromes in both immunocompetent and immunocompromised hosts. These syndromes are difficult to distinguish reliably from similar illnesses caused by other pathogens, such as respiratory syncytial virus, human metapneumovirus, human rhinovirus, rotavirus, group A streptococcus, and other common viral and bacterial pathogens.

Acute Respiratory Disease

Respiratory tract infections are common manifestations of HAdV infections in children and adults. HAdVs cause an estimated 5–10% of all childhood respiratory diseases. Primary infections in infants may manifest as bronchiolitis or pneumonia. HAdV pneumonia may present with features more typical of bacterial disease (lobar infiltrates, high fever, parapneumonic effusions). HAdV-14 has emerged as a significant cause of severe acute respiratory disease in military and civilian populations, in some cases leading to hospitalization and death. Pharyngitis caused by HAdV typically includes symptoms of coryza, sore throat, and fever. The virus can be identified in 15–20% of children with isolated pharyngitis, mostly in preschool children and infants.

Ocular Infections

The common follicular conjunctivitis caused by HAdV is self-limiting and requires no specific treatment. A more severe form called *epidemic keratoconjunctivitis* involves the cornea and conjunctiva. Pharyngoconjunctival fever is a distinct syndrome that includes a high temperature, pharyngitis, nonpurulent conjunctivitis, and preauricular and cervical lymphadenopathy.

Gastrointestinal Infections

HAdV can be detected in the stools of 5–10% of children with acute diarrhea. Most cases of acute diarrhea are self-limiting, although severe disease can occur.

Enteric infection with HAdV is often asymptomatic, and shedding of virus after acute infection can be prolonged, so the causative role in these episodes is frequently uncertain. HAdV may also cause mesenteric adenitis.

Hemorrhagic Cystitis

Hemorrhage cystitis consists of a sudden onset of hematuria, dysuria, frequency, and urgency with negative urine bacterial culture results. Urinalysis may show sterile pyuria in addition to red blood cells. This illness occurs more frequently in young males and typically resolves on its own in 1-2 wk.

Other Complications

Less frequently, HAdVs are associated with myocarditis, hepatitis, or meningoencephalitis in immunocompetent individuals.

Adenoviruses in Immunocompromised Patients

Immunocompromised persons, particularly recipients of hematopoietic stem cell transplants (HSCTs) and solid-organ transplants, are at high risk for severe and fatal disease caused by HAdV. These patients may experience primary HAdV infection. Reactivation of persistent virus in a transplant recipient and transmission of virus from a donor organ may also occur. Organ failure as a consequence of pneumonia, hepatitis, gastroenteritis, and disseminated infection occurs primarily in these patients. HAdV infection in HSCT recipients commonly manifests as pulmonary or disseminated disease and is most likely to occur in the first 100 days after transplantation. Hemorrhagic cystitis caused by HAdV can be severe in HSCT recipients. Infections caused by HAdV in solid-organ transplant recipients usually involve the transplanted organ. Immunocompromised children are at greater risk than immunocompromised adults for complicated HAdV infection, presumably because of a lack of preexisting immunity. Additional risk factors include T-cell–depleted grafts, high-level immunosuppression, and the presence of graft-versus-host disease. Some experts advocate a preemptive screening approach to detect and treat HAdV infection early in immunocompromised patients, with the intent to prevent dissemination and severe illness in this vulnerable population, though no highly effective antiviral therapy exists.

Diagnosis

HAdV may be suspected as the etiology of an illness on the basis of epidemiologic or clinical features, but neither of these categories is specific enough to firmly establish the diagnosis. The frequency of asymptomatic shedding of HAdV makes assigning causality to this pathogen difficult at times. Most HAdV serotypes grow well in culture, although this method requires several days and thus is not helpful for early identification. Cells from respiratory or ocular specimens can be tested using immunofluorescent staining with antibodies to detect HAdV protein. Commercially available enzyme-linked immunoassays can be used to rapidly detect HAdV in patient specimens, usually in stool. Molecular techniques, such as polymerase chain reaction, offer a rapid, sensitive, and specific diagnosis of HAdV infections and are most useful clinically for the management of suspected HAdV infections in immunocompromised hosts. In these patients, measurement of the *HAdV genome copy number* using a quantitative real-time polymerase chain reaction can facilitate the diagnosis, and repeated measurements can aid in assessing a patient's response to treatment. Multiplex molecular assays capable of identifying HAdV in addition to other pathogens are increasingly available and useful for rapid diagnosis. Serology is generally useful only in epidemiologic investigations.

Complications

HAdV pneumonia can lead to respiratory failure requiring mechanical ventilation, especially in immunocompromised patients. Secondary bacterial pneumonia does not appear to be as common following HAdV infection as it is after influenza infection, but data that address this issue are limited. Severe HAdV pneumonia has been linked to chronic lung disease and bronchiolitis obliterans in a minority of cases. Epidemic keratoconjunctivitis is a vision-threatening form of HAdV infection. Nearly any form of HAdV infection can be fatal in an HSCT or solid-organ transplant recipient. Refractory severe anemia requiring repeated blood transfusions can develop in HSCT recipients with hemorrhagic cystitis. Mortality rates of up to 60–80% have been reported in transplant recipients with disseminated HAdV or HAdV pneumonia.

Treatment

Supportive care is the mainstay of HAdV treatment in most cases. Patients with severe HAdV conjunctivitis should be referred for ophthalmologic consultation. No specific antiviral therapy produces a definite clinical benefit against HAdV infection. The nucleoside analog cidofovir has in vitro activity against most HAdV serotypes. Cidofovir is used topically to treat epidemic keratoconjunctivitis, often in conjunction with topical steroids or other immunosuppressive agents to limit the inflammatory component. Cidofovir may be used intravenously for HAdV infections in immunocompromised patients. Cidofovir is highly nephrotoxic; however, prehydration, concomitant administration of probenecid, and weekly dosing may reduce renal toxicity. Clinical studies suggest some benefit from cidofovir, but there are no prospective, randomized controlled trials of cidofovir for HAdV infection. In addition, no formal guidelines or recommendations for treatment exist. The cidofovir derivative brincidofovir is better tolerated than cidofovir and shows promise as an approach to the prevention and treatment of HAdV disease in immunocompromised patients, but experience remains limited. There are anecdotal descriptions of benefit from intravenous immunoglobulin. Adoptive immunotherapy involving the infusion of HAdV-specific T cells may also provide some benefit for immunocompromised patients with life-threatening HAdV infections, but this intervention is not yet considered standard therapy.

Prevention

Environmental and fomite transmission of HAdV occurs readily; therefore, simple measures such as handwashing and cleaning are likely to reduce spread. HAdVs are highly immunogenic and have been used as gene therapy vectors and vaccine vectors for other pathogens, including malaria and HIV, but no HAdV-specific vaccines are available for routine use. Live-attenuated HAdV-4 and HAdV-7 vaccines were used effectively in the United States military from the 1970s until 1999. Cessation of their use led to widespread outbreaks in barracks, and those vaccines were subsequently reintroduced into military use.

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CHAPTER 290

Rhinoviruses

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Human rhinoviruses (HRVs) are the most frequent cause of the **common cold** in both adults and children. Although HRVs were once thought to cause only the common cold, it is now known that they are also associated with lower respiratory infections in adults and children. Many HRVs do not grow in culture. Recent studies using molecular diagnostic tools such as the polymerase chain reaction (PCR) have revealed that HRVs are leading causes of both mild and serious respiratory illnesses in children.

Etiology

HRVs are members of the Picornaviridae family (“pico” = small; “rna” = RNA genome). Traditional methods of virus typing using immune antiserum have identified approximately 100 serotypes, classified into HRVA, HRVB, and, recently, HRVC species on the basis of the genetic sequence similarity. HRVCs can be detected by reverse transcriptase PCR but have been cultured only using highly specialized methods. Virus gene sequence analysis demonstrates that HRVCs are a genetically distinct and diverse species. The increased proportions of HRV reported in recent PCR-based studies are likely the result of detection of these previously unknown HRVC viruses in addition to improved detection of known HRVA and HRVB strains.

Epidemiology

Rhinoviruses are distributed worldwide. There is no consistent correlation between serotypes and epidemiologic or clinical characteristics. Several studies suggest that HRVCs may be more strongly associated with lower respiratory infection and asthma than other HRVs, but the overall disease severity is not increased. Multiple types circulate in a community simultaneously, and particular HRV strains may be isolated during consecutive epidemic seasons, suggesting persistence in a community over an extended period. In temperate climates, the incidence of HRV infection peaks in the fall, with another peak in the spring, but HRV infections occur year-round. HRVC appears to circulate with seasonal variation, exchanging dominance with HRVA. HRVs are the major infectious trigger for asthma among young children, and numerous studies have described a sharp increase in asthmatic attacks in this age-group when school opens in the fall. The peak HRV incidence in the tropics occurs during the rainy season, from June to October.

HRVs are present in high concentrations in nasal secretions and can be detected in the lower airways. HRV particles are nonenveloped and quite hardy, persisting for hours to days in secretions on hands or other surfaces such as telephones, light switches, doorknobs, and stethoscopes. Sneezing and coughing are inefficient methods of transfer. Transmission occurs when infected secretions carried on contaminated fingers are rubbed onto the nasal or conjunctival mucosa. HRVs are present in aerosols produced by talking, coughing, and sneezing. Children are the most important reservoir of these viruses.

Pathogenesis

The majority of HRVs infect respiratory epithelial cells via intercellular adhesion molecule-1, but some HRV strains utilize the low-density lipoprotein receptor. The receptor for HRVC is cadherin-related family member 3 (CDHR3); however, distinct genetic alleles of this protein confer different susceptibility to HRVC infection. Infection begins in the nasopharynx and spreads to the nasal mucosa and, in some cases, to bronchial epithelial cells in the lower airway. There is no direct cellular damage from the virus, and it is thought that many of the pathogenic effects are produced by the host immune response. Infected epithelial cells release a number of cytokines and chemokines, which induce an influx of neutrophils to the upper airway. Both innate and adaptive immune mechanisms are important in HRV pathogenesis and clearance. HRV-specific nasal immunoglobulin (Ig) A can be detected on day 3 after infection, followed by the production of serum IgM and IgG after 7-8 days. Neutralizing IgG to HRVs may prevent or limit the severity of illness following reinfection.

However, cross protection by antibodies to different HRV serotypes is limited in breadth and duration, allowing recurrent infection. Both allergen exposure and elevated IgE values predispose patients with asthma to more severe respiratory symptoms in response to HRV infection. Abnormalities in the host cellular response to HRV infection that result in impaired apoptosis, and increased viral replication, may be responsible for the severe and prolonged symptoms in individuals with asthma.

Clinical Manifestations

Most HRV infections produce clinical symptoms, but many are asymptomatic; however, symptomatic HRV infection induces a much more robust host immune response in the blood than asymptomatic infection. Typical symptoms of sneezing, nasal congestion, rhinorrhea, and sore throat develop following an incubation period of 1-4 days. Cough and hoarseness are present in one third of cases. Fever is less common with HRV than with other common respiratory viruses, including influenza virus, respiratory syncytial virus, and human metapneumovirus. Symptoms are frequently more severe and last longer in children, with 70% of children compared with 20% of adults still reporting symptoms by day 10. Virus can be shed for as long as 3 wk.

HRVs are the most prevalent agents associated with acute wheezing, otitis media, and hospitalization for respiratory illness in children and are an important cause of severe pneumonia and exacerbation of asthma or chronic obstructive pulmonary disease in adults. HRV-associated hospitalizations are more frequent in young infants than in older children and in children with a history of wheezing or asthma. HRV infection in immunocompromised hosts may be life threatening. Certain strains or species of HRV, namely HRVC, may be more pathogenic than others.

Diagnosis

Culturing HRVs is labor intensive and of relatively low yield; HRVC has only been cultivated in a polarized primary airway epithelial cell culture, a highly specialized method. Sensitive and specific diagnostic methods based on reverse transcriptase PCR are commercially available. However, because commercially available reverse transcriptase PCR tests do not identify the HRV types, it can be difficult to distinguish prolonged shedding from newly acquired infection. An important caveat of HRV detection is the fact that HRV infection can be asymptomatic, and thus the presence of the virus does not prove causality in all cases. Serology is impractical because of the great number of HRV serotypes. A presumptive clinical diagnosis based on symptoms and seasonality is not specific, because many other viruses cause similar clinical illnesses. Rapid detection techniques for HRV might lessen the use of unnecessary antibiotics or procedures.

Complications

Possible complications of HRV infection include sinusitis, otitis media, asthma exacerbation, bronchiolitis, pneumonia, and, rarely, death. HRV-associated wheezing during infancy is a significant risk factor for the development of childhood asthma. This effect appears to remain until adulthood, but the mechanisms have not been elucidated. One large study determined that genetic variants at the 17q21 locus were associated with asthma in children who had experienced HRV wheezing illnesses during infancy. A prospective study on a preterm cohort showed that a single nucleotide polymorphism on the gene coding for the vitamin D receptor was associated with development of lower respiratory infection with HRV. Further studies are required to determine the likely multiple genetic and environmental factors that contribute to HRV-related asthma.

Treatment

Supportive care is the mainstay of HRV treatment. The symptoms of HRV infection are commonly treated with analgesics, decongestants, antihistamines, or antitussives. Data are limited on the effectiveness of such nonprescription cold medications for children. If bacterial superinfections are highly suspected or diagnosed, antibiotics may be appropriate. Antibiotics are not indicated for uncomplicated viral upper respiratory infection. Vaccines have not been successfully developed because of the numerous HRV serotypes and limited cross protection between serotypes.

Prevention

Good handwashing remains the mainstay of the prevention of HRV infection and should be reinforced frequently, especially in young children, the predominant “vectors” for disease. A polyvalent inactivated vaccine showed promise in a nonhuman primate model, but there are no licensed vaccines or antivirals.

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CHAPTER 291

Coronaviruses

Kevin W. Graepel, Mark R. Denison

Coronaviruses are increasingly recognized as important human pathogens. They cause up to 15% of common colds and have been implicated in more serious diseases, including croup, asthma exacerbations, bronchiolitis, and pneumonia. Evidence also suggests that coronaviruses may cause enteritis or colitis in neonates and infants and may be underappreciated as agents of meningitis or encephalitis. Four coronaviruses are endemic in humans: human coronaviruses (HCoVs) 229E, OC43, NL63, and HKU1. In addition, two epidemics of previously unknown coronaviruses caused significant respiratory distress and high mortality rates among infected individuals. The discoveries of **SARS-associated coronavirus (SARS-CoV)** , the cause of **severe acute respiratory syndrome (SARS),** and of **Middle East respiratory syndrome coronavirus (MERS-CoV)** support the potential for coronaviruses to emerge from animal hosts such as bats and camels and become important human pathogens.

Etiology

Coronaviruses are enveloped viruses of medium to large size (80-220 nm) that possess the largest known single-stranded positive-sense RNA genomes. These viruses encode the protein nsp14-ExoN, which is the first known RNA proofreading enzyme and is likely responsible for the evolution of the large and complex coronavirus genome. Coronaviruses derive their name from the characteristic surface projections of the spike protein, giving a corona or crown-like appearance on negative-stain electron microscopy. Coronaviruses are organized taxonomically by a lettering system based on genomic phylogenetic relationships. Alphacoronaviruses include HCoV-229E and HCoV-NL63. Betacoronaviruses include four human pathogens and are commonly divided into four lineages, without formal taxonomic recognition. HCoV-OC43 and HCoV-HKU1 are in lineage A, whereas SARS-CoV falls in lineage B. Lineages C and D were exclusively comprised of bat coronaviruses until the discovery of MERS-CoV, which aligns with lineage C. Gammacoronaviruses and deltacoronaviruses presently include exclusively nonhuman pathogens.

Coronaviruses received international attention during the SARS outbreak, which was responsible for more than 800 deaths in 30 countries. SARS-CoV, a novel coronavirus at the time of the epidemic, was found to be the causative agent of SARS. The detection of SARS-like coronaviruses in a live animal market in the Guangdong province in Southern China, along with serologic evidence of exposure in food handlers in the same market, suggest that these markets may have facilitated the spread of SARS-CoV to humans from an animal reservoir. Subsequent studies identified SARS-like coronaviruses in fecal specimens from asymptomatic Chinese horseshoe bats that are very closely related, but not direct precursors to, SARS-CoV and are capable of infecting human cells. Thus, although bats are a reservoir for SARS-CoV-like precursors, the precise antecedent to SARS-CoV remains to be identified.

Another novel coronavirus, **MERS-CoV,** was isolated from a man with acute pneumonia and renal failure in Saudi Arabia. As of March 1, 2017, the WHO had recorded nearly 2000 confirmed cases of MERS, with nearly 700 deaths worldwide (~35% mortality rate). MERS-CoV differs from SARS in that it seems to be less communicable, although human-to-human transmission has been documented. MERS-CoV uses dipeptidyl peptidase 4 and carcinoembryonic antigen–like cell-adhesion molecule 5 as its cellular and co-receptor, respectively; SARS-CoV utilizes ACE-2. With this receptor specificity, MERS-CoV can infect cells from several animal lineages, including human, pig, and bat, suggesting the possibility of movement between multiple species.

Epidemiology

Seroprevalence studies have demonstrated that antibodies against 229E and OC43 increase rapidly during early childhood, so that by adulthood 90–100% of persons are seropositive. Although less information is available for HKU1 and NL63, available studies demonstrate similar patterns of seroconversion to these viruses during early childhood. Although some degree of strain-specific protection may be afforded by recent infection, reinfections are common and occur despite the presence of strain-specific antibodies. Attack rates are similar in different age-groups. Although infections occur throughout the year, there is a peak during the winter and early spring for each of these HCoVs. In the United States, outbreaks of OC43 and 229E have occurred in 2- to 3-yr alternating cycles. Independent studies of viral etiologies of upper and lower respiratory infections during the same period, but from different countries, have confirmed that all known HCoVs have a worldwide distribution. Studies using both viral culture and polymerase chain reaction (PCR) multiplex assays demonstrate that coronaviruses often appear in coinfections with other respiratory viruses, including respiratory syncytial virus, adenovirus, rhinovirus, and human metapneumovirus. Volunteer studies demonstrated that OC43 and 229E are transmitted predominantly through the respiratory route. Droplet spread appears to be most important, although aerosol transmission may also occur.

There have been no identified natural or laboratory-acquired cases of SARS-CoV since 2004, but the mechanisms of introduction, spread, and disease remain important for potential animal-to-human transmission and disease. The primary mode of SARS-CoV transmission occurred through direct or indirect contact of mucous membranes with infectious droplets or fomites. Aerosol transmission was less common, occurring primarily in the setting of endotracheal intubation, bronchoscopy, or treatment with aerosolized medications. Fecal-oral transmission did not appear to be an efficient mode of transmission, but may have occurred because of the profuse diarrhea observed in some patients. The seasonality of SARS-CoV remains unknown. SARS-CoV is not highly infectious, with generally only two to four secondary cases resulting from a single infected adult. During the SARS epidemic, a small number of infected individuals, “superspreaders,” transmitted infection to a much larger number of persons, but the mechanism for this high degree of spread remains unknown. In contrast, persons with mild disease, such as children younger than 12 yr of age, rarely transmitted the infection to others. Infectivity correlated with disease stage; transmission occurred almost exclusively during symptomatic disease. During the 2003 outbreak, most individuals with SARS-CoV infection were hospitalized within 3-4 days of symptom onset. Consequently, most subsequent infections occurred within hospitals and involved either healthcare workers or other hospitalized patients.

As of March 1, 2017, the WHO had recorded cases of MERS-CoV in 27 countries, all of which were linked to exposures in the Arabian peninsula (~80% in Saudi Arabia). Though the route of transmission between animals and humans is not fully understood, MERS-CoV is proposed to have repeatedly entered the human population through contact with respiratory secretions of dromedary camels and possibly with raw camel products (e.g., unpasteurized milk). Antibodies to MERS-CoV are found in dromedaries throughout the Middle East, and strains identical to human MERS-CoV isolates have been found in camels in Egypt, Oman, Qatar, and Saudi Arabia. These strains do not appear to be highly pathogenic or virulent in camels and have likely circulated within dromedaries for > 30 years. Despite well-documented zoonotic transmission, most reported cases occur through linked human-to-human transmission in healthcare settings, including outbreaks in Jordan, South Korea, and Saudi Arabia in 2015 and 2016. Risk factors for nosocomial MERS-CoV outbreaks include overcrowded emergency departments, delayed diagnosis or isolation, and poor infection control practices. Transmission most likely occurs through respiratory droplets and is thus a greater risk during aerosol-generating procedures. Outside of healthcare settings, human-to-human transmission has been infrequently documented and is primarily associated with close contact within households. No sustained human-to-human transmission has yet been reported.

Pathogenesis of SARS and MERS

Severe disease in SARS and MERS likely results from both direct virologic damage and subsequent immunopathology. Studies with SARS-CoV in human airway epithelial cell cultures indicate that ciliated cells are principal targets for infection, whereas MERS-CoV preferentially infects bronchial epithelial cells, type I and II pneumocytes, and vascular endothelial cells. Substantial viral loads can be detected in the lower respiratory tract and in blood for both viruses. However, late progression to severe disease appears independent of the quantity and timing of viremia. Thus, excessive host immune responses likely play an important role in the progression to lower respiratory disease and acute respiratory distress syndrome. CoV infections are associated with massive elaboration of inflammatory cytokines and recruitment of inflammatory cells. The roles for inflammatory cells are controversial, with cytotoxic T cells and macrophages implicated variously in immune protection and immunopathology. Recapitulation of human clinical features in animal models of MERS-CoV infection remains challenging, but promising new models are in development.

Clinical Manifestations

Respiratory Infections

Even though up to 50% of respiratory tract infections with OC43 and 229E are asymptomatic, coronaviruses are still responsible for up to 15% of common colds and can cause fatal disease. Cold symptoms caused by HCoVs are indistinguishable from those caused by rhinoviruses and other respiratory viruses. The average incubation period is 2-4 days, with symptoms typically lasting 4-7 days. Rhinorrhea, cough, sore throat, malaise, and headache are the most common symptoms. Fever occurs in up to 60% of cases. Coronavirus NL63 is a cause of croup in children younger than 3 yr of age. Coronavirus infections are linked to episodes of wheezing in asthmatic children, albeit at a lower frequency and severity than observed with rhinovirus and respiratory syncytial virus infections. Lower respiratory tract infections, including bronchiolitis and pneumonia, are also reported in immunocompetent and immunocompromised children and adults. As with respiratory syncytial virus or rhinovirus, coronavirus detection in upper respiratory infections is frequently associated with acute otitis media and can be isolated from middle ear fluid.

Nonrespiratory Sequelae

There is some evidence to support a role for coronaviruses in human gastrointestinal disease, particularly in young children. Coronavirus-like particles have been detected by electron microscopy in the stools of infants with nonbacterial gastroenteritis. In addition, several outbreaks in neonatal intensive care units of gastrointestinal disease characterized by diarrhea, bloody stools, abdominal distention, bilious gastric aspirates, and classic necrotizing enterocolitis have also been associated with the presence of coronavirus-like particles in stools. In older children and adults, coronavirus-like viruses have been observed with similar frequency in symptomatic and asymptomatic individuals, making it difficult to discern if they are pathogenic in the gastrointestinal tract. Coronaviruses are well-known causes of neurologic disease in animals, including demyelinating encephalitis, but their role in causing human neurologic disease remains unclear. They have been detected by culture, in situ hybridization, and reverse transcriptase PCR (RT-PCR) in brain tissue from a few patients with multiple sclerosis. HCoV-OC43 has been detected by RT-PCR in the spinal fluid, nasopharynx, or brain biopsy specimens of two children with acute encephalomyelitis. However, coronavirus RNA has also been recovered from the spinal fluid and brain tissue of adults without neurologic disease.

Severe Acute Respiratory Syndrome–Associated Coronavirus

SARS-CoV infections in teenagers and adults included a viral replication phase and an immunologic phase. During the viral replication phase, there was a progressive increase in viral load that reached its peak during the second week of illness. The appearance of specific antibodies coincided with peak viral replication. The clinical deterioration that typified the second and third week of illness was characterized by a decline in the viral load and evidence of tissue injury, likely from cytokine-mediated immunity. The explanation for milder clinical disease in children younger than 12 yr of age has not been determined. Seroepidemiologic studies suggest that asymptomatic SARS-CoV infections were uncommon. The incubation period ranged from 1-14 days, with a median of 4-6 days. The clinical manifestations were nonspecific, most commonly consisting of fever, cough, malaise, coryza, chills or rigors, headache, and myalgia. Coryza was more common in children younger than 12 yr of age, whereas systemic symptoms were seen more often in teenagers. Some young children had no respiratory symptoms. Gastrointestinal symptoms, including diarrhea and nausea or vomiting, occurred in up to one third of cases. The clinical course of SARS-CoV infection varied with age. Adults were most severely affected, with initial onset of fever, cough, chills, myalgia, malaise, and headache. Following an initial improvement at the end of the first week, fever recurred and respiratory distress developed, with dyspnea, hypoxemia, and diarrhea. These symptoms progressed in 20% of patients to acute respiratory distress syndrome and respiratory failure. Acute renal failure with histologic acute tubular necrosis was present in 6.9% of patients, likely a result of hypoxic kidney damage. Of SARS patients, 28.8% had abnormal urinalysis, with viral genome detectable by quantitative RT-PCR. In contrast, children younger than 12 yr of age had a relatively mild nonspecific illness, with only a minority experiencing significant lower respiratory tract disease and illness typically lasting less than 5 days. There were no deaths or cases of acute respiratory distress syndrome in children younger than 12 yr of age from SARS-CoV infection. Adolescents manifested increasing severity in direct correlation to increasing age; respiratory distress and hypoxemia were observed in 10–20% of patients, one third of whom required ventilator support. The case fatality rate from SARS-CoV infection during the 2003 outbreak was 10–17%. No pediatric deaths were reported. The estimated case fatality rate according to age varied from < 1% for those younger than 20 yr of age to > 50% for those older than 65 yr of age.

Middle East Respiratory Syndrome Coronavirus

The incubation period of MERS-CoV is between 2-14 days. The syndrome usually presents with nonspecific clinical features typical of acute febrile respiratory illnesses, including low-grade fever, rhinorrhea, sore throat, and myalgia. In mildly symptomatic cases, radiographic findings are typically normal. Severe disease is characterized by the acute respiratory distress syndrome with multilobular airspace disease, ground-glass opacities, and occasional pleural effusions on radiography. The median time between hospitalization and ICU transfer for critical illness is 2 days. Risk factors for severe disease include age > 50 yr and comorbidities such as obesity, diabetes, COPD, end-stage renal disease, cancer, and immunosuppression. Specific host genetic risk factors have not been identified. Variation in clinical outcomes does not appear to be explained by viral strain-specific sequence variability. As with SARS, extrapulmonary manifestations are common in severe MERS disease. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea occur in one third of patients, and acute kidney injury has been documented in half of critically ill patients. Encephalitis-like neurologic manifestations have been observed in three cases. Laboratory analyses typically detect leukopenia and lymphopenia, with occasional thrombocytopenia, anemia, and aminotransferase elevations. The case fatality rate remains at 35%, though the true incidence of MERS-CoV infection is likely underestimated by existing data. Most patients have been adults, although children as young as 9 mo of age have been infected. It is not known whether children are less susceptible to MERS-CoV or present with a different clinical picture.

Diagnosis

In the past, specific diagnostic tests for coronavirus infections were not available in most clinical settings. The use of conserved PCR primers for coronaviruses in multiplex RT-PCR viral diagnostic panels now allows widely available and sensitive detection of the viruses. Virus culture of primary clinical specimens remains a challenge for HCoVs HKU1, OC43, 229E, and NL63, even though both SARS-CoV and MERS-CoV can successfully be grown in culture from respiratory samples. Serodiagnosis with complement fixation, neutralization, hemagglutination inhibition, enzyme immunoassay, and Western blots have been used in the research setting. The diagnosis of SARS-CoV infection can be confirmed by serologic testing, detection of viral RNA using RT-PCR, or isolation of the virus in cell culture. Even though the serology for SARS-CoV has a sensitivity and specificity approaching 100%, antibodies are not detectable until 10 days after the onset of symptoms, and immunoglobulin G seroconversion may be delayed for up to 4 wk. In addition, the SARS epidemic resulted in the inclusion of coronavirus-conserved primers in many diagnostic PCR multiplex assays such that coronaviruses may be more readily detected.

The diagnosis of MERS-CoV should be guided by clinical features and an epidemiologic link. The mainstay for laboratory confirmation of MERS-CoV infection is real-time RT-PCR. Screening should target the region upstream of the envelope gene (upE), followed by confirmation with an assay targeting open reading frame 1a. The best diagnostic sensitivity is achieved from lower respiratory tract samples collected within the first week of infection, though MERS-CoV RNA can be detected in upper respiratory and blood samples. Alternatively, seroconversion can be documented by screening enzyme-linked immunosorbent assays followed by immunofluorescence microscopy. For all known endemic and emerging HCoVs, respiratory specimens (nasopharyngeal swabs or aspirates) are most likely to be positive, but in a setting of a possible novel coronavirus, serum or stool may be positive.

Treatment and Prevention

Coronavirus infections of humans are acute and self-limited, although persistent infection and shedding occurs in multiple animal models in the setting of minimal or no symptoms. There are no available antiviral agents for clinical use against coronaviruses, although strategies targeting conserved coronavirus proteases and coronavirus polymerases have been shown to block replication of the viruses in vitro and are in the drug development pipeline. Thus, treatment of SARS-CoV and MERS-CoV infections is primarily supportive. The role of antiviral and immune-modulating agents remains inconclusive, though several clinical trials are ongoing. Ribavirin was extensively used during the 2003

SARS-CoV outbreak, but is of questionable benefit given its poor in vitro activity against SARS-CoV at clinically relevant concentrations. The identification of the proofreading nsp14-exonuclease in multiple coronaviruses suggests that this activity may be important in resistance to antiviral nucleosides and RNA mutagens such as ribavirin. Systemic corticosteroid therapy may be associated with increased mortality rates in SARS-CoV and MERS-CoV and is thus not recommended unless indicated for another clinical condition. Meta-analysis of observational studies suggests that human convalescent plasma may reduce SARS mortality rates; the use of blood products has not been well-studied in MERS. Several monoclonal antibody preparations have shown positive results against SARS-CoV and MERS-CoV in animal studies.

Challenges for the development of effective vaccines targeted against OC43, 229E, HKU1, and NL63 include the fact that infections are rarely life-threatening and reinfection is the rule, even in the presence of natural immunity from previous infections. The durability of immunity to SARS-CoV and MERS-CoV is poorly understood. Nevertheless, effective vaccines for SARS-CoV and MERS-CoV are highly desirable but not yet available. A potential vaccine target is the viral spike protein, which could be delivered as a recombinant protein or by viral or DNA vectors. This approach appears to be effective against closely related strains of SARS-CoV but not necessarily early animal or human variants. A SARS-CoV vaccine approach that recently has shown success in animal models used a live recombinant SARS-CoV mutant with inactivated ExoN, demonstrating attenuation and protection in aged, immunocompromised mice. Approaches for the rapid development of stably attenuated live viruses or broadly immunogenic and cross-protective protein immunogens continues to be a key area for future research. Although SARS-CoV demonstrated characteristics of symptomatic transmission that made it controllable by public health measures such as quarantine, these characteristics cannot be assumed for future novel HCoVs. The recent discovery of MERS-CoV serves as a reminder that coronavirus emergence is both likely and unpredictable, making it important to continue studies of the replication, emergence, and transmission of coronaviruses. Additionally, strategies for rapid recovery, testing, and development of vaccines and neutralizing human monoclonal antibodies may be essential to prevent the high morbidity and mortality rates associated with previous epidemics.

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CHAPTER 292

Rotaviruses, Caliciviruses, and Astroviruses

Dorsey M. Bass

Diarrhea is a leading cause of childhood death in the world, accounting for 5-10 million deaths per year. In early childhood, the single most important cause of severe dehydrating diarrhea is rotavirus infection. Rotavirus and other gastroenteric viruses are not only major causes of pediatric deaths but also lead to significant morbidity. Children in the United States, before vaccine was available, were estimated to have a risk of hospitalization for rotavirus diarrhea of 1 : 43, corresponding to 80,000 hospitalizations annually.

Etiology

Rotaviruses, astroviruses, caliciviruses such as the Norwalk agent, and enteric adenoviruses are the medically important pathogens of human viral gastroenteritis (see Chapter 366).

Rotaviruses are in the Reoviridae family and cause disease in virtually all mammals and birds. These viruses are wheel-like, triple-shelled icosahedrons containing 11 segments of double-stranded RNA. The diameter of the particles on electron microscopy is approximately 80 nm. Rotaviruses are classified by serogroup (A, B, C, D, E, F, and G) and subgroup (I or II). Rotavirus strains are species specific and do not cause disease in heterologous hosts. Group A includes the common human pathogens as well as a variety of animal viruses. Group B rotavirus is reported as a cause of severe disease in infants and adults in China only. Occasional human outbreaks of group C rotavirus are reported. The other serogroups infect only nonhumans.

Subgrouping of rotaviruses is determined by the antigenic structure of the inner capsid protein, VP6. Serotyping of rotaviruses, described for group A only, is determined by classic cross-neutralization testing and depends on the outer capsid glycoproteins, VP7 and VP4. The VP7 serotype is referred to as the *G type* (for glycoprotein). There are ten G serotypes, of which four cause most illness and vary in occurrence from year to year and region to region. The VP4 serotype is referred to as the P type. There are eleven P serotypes. Although both VP4 and VP7 elicit neutralizing immunoglobulin G antibodies, the relative role of these systemic antibodies compared with that of mucosal immunoglobulin A antibodies and cellular responses in protective immunity remains unclear.

Caliciviruses, which constitute the Caliciviridae family, are small, 27- to 35-nm viruses that are the most common cause of gastroenteritis outbreaks in older children and adults. Caliciviruses also cause a rotavirus-like illness in young infants. They are positive-sense, single-stranded RNA viruses with a single structural protein. Human caliciviruses are divided into two genera, the noroviruses and sapoviruses. Caliciviruses have been named for locations of initial outbreaks: Norwalk, Snow Mountain, Montgomery County, Sapporo, and others. Caliciviruses and astroviruses are sometimes referred to as **small, round viruses** on the basis of appearance on electron microscopy.

Astroviruses, which constitute the Astroviridae family, are important agents of viral gastroenteritis in young children, with a high incidence in both the developing and developed worlds. Astroviruses are positive-sense, single-stranded RNA viruses. They are small particles, approximately 30 nm in diameter, with a characteristic central five- or six-pointed star when viewed on electron microscopy. The capsid consists of three structural proteins. There are eight known human serotypes.

Enteric adenoviruses are a common cause of viral gastroenteritis in infants and children. Although many adenovirus serotypes exist and are found in human stool, especially during and after typical upper respiratory tract infections (see Chapter 289), only serotypes 40 and 41 cause gastroenteritis. These strains are very difficult to grow in tissue culture. The virus consists of an 80-nm–diameter icosahedral particle with a relatively complex double-stranded DNA genome.

Aichi virus is a picornavirus that is associated with gastroenteritis and was initially described in Asia. Several other viruses that may cause diarrheal disease in animals have been postulated but are not well established as human gastroenteritis viruses. These include coronaviruses, toroviruses, and pestiviruses. The **picobirnaviruses** are an unclassified group of small (30-nm), single-stranded RNA viruses that have been found in 10% of patients with HIV-associated diarrhea.

Epidemiology

Worldwide, rotavirus is estimated to cause more than 111 million cases of diarrhea annually in children younger than 5 yr of age. Of these, 18 million cases are considered at least moderately severe, with approximately 500,000 deaths per year. Rotavirus causes 3 million cases of diarrhea, 80,000 hospitalizations, and 20-40 deaths annually in the United States.

Rotavirus infection is most common in winter months in temperate climates. In the United States, the annual winter peak historically spread from west to east. Unlike the spread of other winter viruses, such as influenza, this wave of increased incidence was not caused by a single prevalent strain or serotype. Since widespread adoption of vaccine, this geographic phenomenon has vanished. Typically, several serotypes predominate in a given community for one or two seasons but nearby locations may harbor unrelated strains. Disease tends to be most severe in patients 3-24 mo of age, although 25% of the cases of severe disease occur in children older than 2 yr of age, with serologic evidence of infection developing in virtually all children by 4-5 yr of age. Infants younger than 3 mo are relatively protected by transplacental antibody and possibly breastfeeding. Infections in neonates and in adults in close contact with infected children are generally asymptomatic. Some rotavirus strains have stably colonized newborn nurseries for years, infecting virtually all newborns without causing any overt illness.

Rotavirus and the other gastrointestinal viruses spread efficiently via a fecal-oral route, and outbreaks are common in children's hospitals and childcare centers. The virus is shed in stool at a very high concentration before and for days after the clinical illness. Very few infectious virions are needed to cause disease in a susceptible host.

The epidemiology of **astroviruses** is not as thoroughly studied as that of rotavirus, but these viruses are a common cause of mild to moderate watery winter diarrhea in children and infants and an uncommon pathogen in adults. Hospital outbreaks are common. **Enteric adenovirus** gastroenteritis occurs year-round, mostly in children younger than 2 yr of age. Nosocomial outbreaks occur but are less common than with rotavirus and astrovirus. **Calicivirus** is best known for causing large, explosive outbreaks among older children and adults, particularly in settings such as schools, cruise ships, and hospitals. Often a single food, such as shellfish or water used in food preparation, is identified as a source. Like astrovirus and rotavirus, caliciviruses are also commonly found in winter infantile gastroenteritis.

Pathogenesis

Viruses that cause human diarrhea selectively infect and destroy villus tip cells in the small intestine. Biopsies of the small intestines show variable degrees of villus blunting and round cell infiltrate in the lamina propria. Pathologic changes may not correlate with the severity of clinical symptoms and usually resolve before the clinical resolution of diarrhea. The gastric mucosa is not affected despite the commonly used term *gastroenteritis*, although delayed gastric emptying has been documented during Norwalk virus infection.

In the small intestine, the upper villus enterocytes are differentiated cells, which have both digestive functions, such as hydrolysis of disaccharides, and absorptive functions, such as the transport of water and electrolytes via glucose and amino acid cotransporters. Crypt enterocytes are undifferentiated cells that lack the brush-border hydrolytic enzymes and are net secretors of water and electrolytes. Selective viral infection of intestinal villus tip cells thus leads to (1) decreased absorption of salt and water and an imbalance in the ratio of intestinal fluid absorption to secretion, and (2) diminished disaccharidase activity and malabsorption of complex carbohydrates, particularly lactose. Most evidence supports altered absorption as the more important factor in the genesis of viral diarrhea. It has been proposed that a rotavirus nonstructural protein (NSP4) functions as an enterotoxin.

Viremia may occur often in severe, primary infections, but symptomatic **extraintestinal infection** is extremely rare in immunocompetent persons—although immunocompromised patients may rarely experience central nervous system, hepatic, and renal involvement. The increased vulnerability of infants (compared with older children and adults) to severe morbidity and mortality from gastroenteritis viruses may relate to a number of factors, including decreased intestinal reserve function, lack of specific immunity, and decreased nonspecific host defense mechanisms such as gastric acid and mucus. Viral enteritis greatly enhances intestinal permeability to luminal macromolecules and has been postulated to increase the risk for food allergies.

Clinical Manifestations

Rotavirus infection typically begins after an incubation period of < 48 hr (range: 1-7 days) with mild to moderate fever as well as vomiting, followed by the onset of frequent, watery stools. All three symptoms are present in about 50–60% of cases. Vomiting and fever typically abate during the second day of illness, but diarrhea often continues for 5-7 days. The stool is without gross blood or white blood cells. Dehydration may develop and progress rapidly, particularly in infants. The most severe disease typically occurs among children 4-36 mo of age. Malnourished children and children with underlying intestinal disease, such as short-bowel syndrome, are particularly likely to acquire severe rotavirus diarrhea. Rarely, immunodeficient children experience severe and prolonged illness. Rotavirus has rarely been associated with mild encephalopathy with reversible splenium lesions; this may progress to cerebellitis. Although most newborns infected with rotavirus are asymptomatic, some outbreaks of necrotizing enterocolitis have been associated with the appearance of a new rotavirus strain in the affected nurseries.

The clinical course of **astrovirus** infection appears to be similar to that of rotavirus gastroenteritis, with the notable exception that the disease tends to be milder, with less significant dehydration. **Adenovirus enteritis** tends to cause diarrhea of longer duration, often 10-14 days. The **Norwalk virus** has a short (12-hr) incubation period. Vomiting and nausea tend to predominate in an illness associated with the Norwalk virus, and the duration is brief, usually consisting of 1-3 days of symptoms. The clinical and epidemiologic picture of Norwalk virus often closely resembles so-called food poisoning from preformed toxins such as *Staphylococcus aureus* and *Bacillus cereus.*

Diagnosis

In most cases, a satisfactory diagnosis of acute viral gastroenteritis can be made on the basis of the clinical and epidemiologic features. Many hospitals now offer multiplex PCR stool testing for multiple diarrheal pathogens, including a variety of bacterial and protozoan and all five common viral agents in one test. Enzyme-linked immunosorbent assays, which offer > 90% specificity and sensitivity, are available for the detection of group A rotaviruses, caliciviruses, and enteric adenoviruses in stool samples. Latex agglutination assays are also available for group A rotavirus and are less sensitive than the enzyme-linked immunosorbent assay. Research tools include electron microscopy of stools, RNA polymerase chain reaction analysis to identify G and P antigens, and culture. The diagnosis of viral gastroenteritis should always be questioned in patients with persistent or high fever, blood or white blood cells in the stool, or persistent severe or bilious vomiting, especially in the absence of diarrhea.

Laboratory Findings

Isotonic dehydration with acidosis is the most common finding in children with severe viral enteritis. The stools are free of blood and leukocytes. Although the white blood cell count may be moderately elevated secondary to stress, the marked left shift seen with invasive bacterial enteritis is absent.

Differential Diagnosis

The differential diagnosis includes other infectious causes of enteritis, such as bacteria and protozoa. Occasionally, surgical conditions such as appendicitis, bowel obstruction, and intussusception may initially mimic viral gastroenteritis.

Treatment

Avoiding and treating dehydration are the main goals in the treatment of viral enteritis. A secondary goal is maintenance of the nutritional status of the patient (see Chapters 69 and 366).

There is no routine role for antiviral drug treatment of viral gastroenteritis. Controlled studies show limited benefits for antidiarrheal drugs, and there is a significant risk for serious side effects with these types of agents. Antibiotics are similarly of no benefit. Antiemetics such as ondansetron may help alleviate vomiting in children older than 2 yr. Immunoglobulins have been administered orally to both normal and immunodeficient patients with severe rotavirus and norovirus gastroenteritis, but this treatment is currently considered experimental. Therapy with probiotic organisms such as *Lactobacillus* species has been shown to be helpful only in mild cases and not in dehydrating disease.

Supportive Treatment

Rehydration via the oral route can be accomplished in most patients with mild to moderate dehydration (see Chapters 69 and 366). Severe dehydration requires immediate intravenous therapy followed by oral rehydration. Modern oral rehydration solutions containing appropriate quantities of sodium and glucose promote the optimum absorption of fluid from the intestine. There is no evidence that a particular carbohydrate source (rice) or the addition of amino acids improves the efficacy of these solutions for children with viral enteritis. Other clear liquids, such as flat soda, fruit juice, and sports drinks, are inappropriate for the rehydration of young children with significant stool loss. Rehydration via the oral (or nasogastric) route should be done over 6-8 hr, and feedings should be initiated immediately thereafter. Providing the rehydration fluid at a slow, steady rate, typically 5 mL/min, reduces vomiting and improves the success of oral therapy. Rehydration solution should be continued as a supplement to make up for ongoing excessive stool loss. Initial intravenous fluids are required for the infant in shock or the occasional child with intractable vomiting.

After rehydration has been achieved, resumption of a normal diet for age has been shown to result in a more rapid recovery from viral gastroenteritis. Prolonged (>12 hr) administration of exclusive clear liquids or dilute formula is without clinical benefit and actually prolongs the duration of diarrhea. Breastfeeding should be continued even during rehydration. Selected infants may benefit from lactose-free feedings (such as soy formula and lactose-free cow's milk) for several days, although this step is not necessary for most children. Hypocaloric diets low in protein and fat such as BRAT (*b* ananas, *r* ice, cereal, *a* pplesauce, and *t* oast) have not been shown to be superior to a regular diet.

Prognosis

Most fatalities occur in infants with poor access to medical care and are attributed to dehydration. Children may be infected with rotavirus each year during the first 5 yr of life, but each subsequent infection decreases in severity. Primary infection results in a predominantly serotype-specific immune response, whereas reinfection, which is usually with a different serotype, induces a broad immune response with cross-reactive heterotypic antibody. After the initial natural infection, children have limited protection against subsequent asymptomatic infection (38%) and greater protection against mild diarrhea (73%) and moderate to severe diarrhea (87%). After the second natural infection, protection increases against subsequent asymptomatic infection (62%) and mild diarrhea (75%) and is complete (100%) against moderate to severe diarrhea. After the third natural infection, there is even more protection against subsequent asymptomatic infection (74%) and near-complete protection against even mild diarrhea (99%).

Prevention

Good hygiene reduces the transmission of viral gastroenteritis, but even in the most hygienic societies, virtually all children become infected as a result of the efficiency of infection of the gastroenteritis viruses. Good handwashing and isolation procedures can help control nosocomial outbreaks. The role of breastfeeding in prevention or amelioration of rotavirus infection may be slight, given the variable protection observed in a number of studies. Vaccines offer the best hope for control of these ubiquitous infections.

Vaccines

A trivalent rotavirus vaccine was licensed in the United States in 1998 and was subsequently linked to an increased risk for intussusception, especially during the 3- to 14-day period after the first dose and the 3- to 7-day period after the second dose. The vaccine was withdrawn from the market in 1999. Subsequently, two new live, oral rotavirus vaccines have been approved in the United States after extensive safety and efficacy testing.

A live, oral, pentavalent rotavirus vaccine was approved in 2006 for use in the United States. The vaccine contains five reassortant rotaviruses isolated from human and bovine hosts. Four of the reassortant rotaviruses express one serotype of the outer protein VP7 (G1, G2, G3, or G4), and the fifth expresses the protein P1A (genotype P[8]) from the human rotavirus parent strain. The pentavalent vaccine protects against rotavirus gastroenteritis when administered as a three-dose series at 2, 4, and 6 mo of age. The first dose should be administered between 6 and 12 wk of age, with all three doses completed by 32 wk of age. The vaccine provides substantial protection against rotavirus gastroenteritis, with a primary efficacy of 98% against severe rotavirus gastroenteritis caused by G1-G4 serotypes and 74% efficacy against rotavirus gastroenteritis of any severity through the first rotavirus season after vaccination. It provides a 96% reduction in hospitalizations for rotavirus gastroenteritis through the first 2 yr after the third dose. In a study of more than 70,000 infants, the pentavalent vaccine did not increase the risk for intussusception, although other studies suggest a slight increased risk.

Another new monovalent rotavirus vaccine was licensed in the United States and also appears to be safe and effective. It is an attenuated monovalent human rotavirus and is administered as two oral doses at 2 and 4 mo of age. The vaccine has 85% efficacy against severe gastroenteritis and was found to reduce hospital admissions for all diarrhea by 42%. Despite being monovalent, the vaccine is effective in prevention of all four common serotypes of human rotavirus.

Preliminary surveillance data on the rotavirus incidence from the U.S. Centers for Disease Control and Prevention suggest that rotavirus vaccination greatly reduced the disease burden in the United States during the 2007-2008 rotavirus season and thereafter. Given the incomplete vaccine coverage during this period, the results suggest a degree of “herd immunity” from rotavirus immunization. Studies from several developed countries show greater than 90% protection against severe rotavirus disease. Studies from developing countries show 50–60% protection from severe disease. Vaccine-associated disease has been reported in vaccine recipients who have severe combined immunodeficiency disease (a contraindication). In addition, vaccine-derived virus may undergo reassortment and become more virulent, producing diarrhea in unvaccinated siblings.

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CHAPTER 293

Human Papillomaviruses

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See also Chapter 687 .

Human papillomaviruses (HPVs) cause a variety of proliferative cutaneous and mucosal lesions, including common skin warts, benign and malignant anogenital tract lesions, oral pharyngeal cancers, and life-threatening respiratory papillomas. Most HPV-related infections in children and adolescents are benign (see also Chapter 687).

Etiology

The papillomaviruses are small (55 nm), DNA-containing viruses that are ubiquitous in nature, infecting most mammalian and many nonmammalian animal species. Strains are almost always species specific. Viral DNA is divided into an early region, which encodes proteins associated with viral replication and transcription, and a late region, which encodes capsid proteins necessary for virion assembly. These structural proteins are also the immunodominant antigens leading to type-specific immune responses. More than 100 different types of HPVs have been identified through the comparison of sequence homologies. The different HPV types typically cause disease in specific anatomic sites; more than 30 HPV types have been identified from genital tract specimens.

Epidemiology

HPV infections of the skin are common, and most individuals are probably infected with one or more HPV types at some times. There are no animal reservoirs for HPV; all transmission is presumably from person to person. There is little evidence to suggest that HPV is transmitted by fomites. Common warts, including palmar and plantar warts, are frequently seen in children and adolescents and typically infect the hands and feet, common areas of frequent minor trauma.

Human papillomavirus is also the most prevalent viral sexually transmitted infection in the United States. Up to 80% of sexually active women will acquire HPV through sexual transmission; most have their first infection within 3 yr of beginning sexual intercourse. Thus, HPV disproportionately affects youth, with 75% of new infections occurring in 15- to 24-yr-olds. The greatest risk for HPV in sexually active adolescents is exposure to new sexual partners, but HPV can still be acquired even with a history of one partner, underscoring the ease of transmission of this virus through sexual contact. It is estimated that after 11 acts of sexual intercourse, 100% of all HPV types infecting an individual will be transmitted to the other sexual partner. Couple studies show that there is high concordance in the genital area as well as between the hand and the genital area in the other partner. Whether the DNA detected in the hand is capable of transmitting infectious particles is unknown. Unlike other sexually transmitted infections, female-to-male transmission appears greater than male-to-female transmission. This may be because males in general have superficial transient infections or deposition. In turn, males do not develop an adequate immune response, so reinfections are quite common. The prevalence of HPV in women decreases with time, suggesting immune protection, whereas in men, the prevalence of HPV remains high across all ages.

As with many other genital pathogens, perinatal transmission to newborns can occur. Transmission from caregiver to child during the early childhood years has also been documented. However, both perinatal and early childhood infections appear transient. It remains unclear whether these HPV DNA detections are simply a deposition of caregiver DNA or a true infection. Detection of HPV DNA in older preadolescent children is rare. HPV DNA detection in nonsexually active adolescents has been reported, but a history of sexual activity in adolescents is not always disclosed and is therefore difficult to confirm. While caregivers can spread HPV to young children, if lesions are detected in a child older than 3 yr of age, the possibility of sexual transmission should be raised.

In adolescents, HPV DNA is most commonly detected without evidence of any lesion. Some of these detections are thought to be the result of partner deposition and hence do not represent a true infection. In older women, detection of HPV DNA is more commonly associated with a lesion. This is because the

HPV DNA detected in older women reflects those HPV infections that became established persistent infections. Persistence is now the known necessary prerequisite for the development of significant precancerous lesions and cervical cancer.

Approximately 15–20% of sexually active adolescents have detectable HPV at any given time and have normal cytologic findings. The most common clinically detected lesion in adolescent women is the cervical lesion termed **low-grade squamous intraepithelial lesion (LSIL)** (Table 293.1). LSILs can be found in 25–30% of adolescents infected with HPV. External genital warts are much less common, occurring in < 1% of adolescents, but approximately 10% of individuals will develop genital warts in their lifetime. LSIL is a cytologic and histologic term to reflect the benign changes caused by an active viral infection and is likely present in most, if not all, women with HPV infection. The majority of women, however, have very minute or subtle lesions not easily detected by cytology. As with HPV DNA detection, most LSILs regress spontaneously in young women and do not require any intervention or therapy. Less commonly, HPV can induce more severe cellular changes, termed **high-grade squamous intraepithelial lesions (HSILs)** (see Chapter 568).

Table 293.1

Terminology for Reporting Cervical Cytology and Histology

DESCRIPTIVE DIAGNOSIS OF EPITHELIAL CELL ABNORMALITIES	EQUIVALENT TERMINOLOGY
SQUAMOUS CELL	
Atypical squamous cells of undetermined significance (ASC-US)	Squamous atypia
Atypical squamous cells, cannot exclude HSIL (ASC-H)	
Low-grade squamous intraepithelial lesion (LSIL)	Mild dysplasia, condylomatous atypia, HPV-related changes, koilocytic atypia, cervical intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL)	Moderate dysplasia, CIN 2, severe dysplasia, CIN 3, carcinoma in situ
GLANDULAR CELL	
Endometrial cells, cytologically benign, in a postmenopausal woman **Atypical** Endocervical cells, NOS Endometrial cells, NOS Glandular cells, NOS Endocervical cells, favor neoplastic Glandular cells, favor neoplastic	
Endocervical adenocarcinoma in situ	

Adenocarcinoma Endocervical Endometrial Extrauterine NOS	

NOS, not otherwise specified.

Although HSILs are considered precancerous lesions, they rarely progress to invasive cancer. HSILs occur in approximately 0.4–3% of sexually active women, whereas invasive cervical cancer occurs in 8 cases per 100,000 adult women. In true virginal populations, including children who are not sexually abused, rates of clinical disease are close to zero. In the United States, there are approximately 12,000 new cases and 3,700 deaths from cervical cancer each year. Worldwide, cervical cancer is the second most common cause of cancer deaths among women. HPV is also associated with a range of other anogenital cancers, including an estimated 4,600 cases of anal cancer and 11,100 cases of oropharyngeal cancers in men and women each year.

Some infants may acquire papillomaviruses during passage through an infected birth canal, leading to recurrent **juvenile laryngeal papillomatosis** (also referred to as *respiratory papillomatosis*). Cases also have been reported after cesarean section. The incubation period for emergence of clinically apparent lesions (genital warts or laryngeal papillomas) after perinatally acquired infection is unknown but is estimated to be around 3-6 mo (see Chapter 417.2). It may be that infections can also occur during hygienic care from an infected parent.

Genital warts may represent a sexually transmitted infection even in some very young children. As such, genital warts appearing in childhood should raise suspicion for possible sexual abuse with HPV transmission during the abusive contact. A child with genital warts should therefore be provided with a complete evaluation for evidence of possible abuse (see Chapter 16.1), including the presence of other sexually transmitted infections (see Chapter 146). However, the presence of genital warts in a child does not confirm sexual abuse, because perinatally transmitted genital warts may go undetected until the child is older. Typing for specific genital HPV types in children is not helpful in diagnosis or to confirm sexual abuse status, because the same genital types occur in both perinatal transmission and abuse.

Pathogenesis

Initial HPV infection of the cervix or other anogenital surfaces is thought to begin by viral invasion of the basal cells of the epithelium, a process that is enhanced by disruption of the epithelium caused by trauma or inflammation. It is thought that the virus initially remains relatively dormant because virus is present without any evidence of clinical disease. The life cycle of HPV depends on the differentiation program of keratinocytes. The pattern of HPV transcription varies throughout the epithelial layer as well as through different stages of disease (LSIL, HSIL, invasive cancer). Understanding of HPV transcription enhances understanding of its ability to behave as an oncovirus. Early region proteins, E6 and E7, function as transactivating factors that regulate cellular transformation. Complex interactions between E6- and E7-transcribed proteins and host proteins result in the perturbation of normal processes that regulate cellular DNA synthesis. The perturbations caused by E6 and E7 are primarily disruption of the anti-oncoprotein p53 and retinoblastoma protein (Rb), respectively, contributing to the development of anogenital cancers. Disruption of these proteins results in continued cell proliferation, even under the circumstances of DNA damage, which leads to basal cell proliferation, chromosomal abnormalities, and aneuploidy, hallmarks of squamous intraepithelial lesion (SIL) development.

Evidence of productive viral infection occurs in benign lesions such as external genital warts and LSILs, with the abundant expression of viral capsid proteins in the superficial keratinocytes. The appearance of the HPV-associated koilocyte is a result of the expression of E4, a structural protein that causes collapse of the cytoskeleton. Low-level expression of E6 and E7 proteins results in cell proliferation seen in the basal cell layer of LSILs. LSILs are a manifestation of active viral replication and protein expression. In HSILs, expression of E6 and E7 predominates throughout the epithelium, with little expression of the structural proteins L1 and L2. This results in the chromosomal abnormalities and aneuploidy characteristic of the higher-grade lesions. The critical events that lead to cancer have not been verified; however, several mechanisms are thought to be critical, including viral integration into the host chromosome and activation of telomerase to lengthen chromosomes and avoid physiologic cell senescence. Over 150 HPV types have been documented and are classified by extent of their DNA homology into 5 genera, with the different types having different life-cycle and disease characteristics. The predominant group is α HPV types, which are associated with cutaneous and mucosal anogenital infections and cancers. β, γ, μ, and ν cause predominantly benign cutaneous lesions but can be difficult to manage in severely immunocompromised individuals. Β types are commonly detected on the skin without any apparent lesions but are associated with the development of skin cancers in those with epidermodysplasia verruciformis or other forms of immunodeficiencies. Genital lesions caused by the α HPV types may be broadly grouped into those with little to no malignant potential (low risk) and those with greater malignant potential (high risk). Low-risk HPV types 6 and 11 are most commonly found in genital warts and are rarely found isolated in malignant lesions. High-risk HPV types are those types that are associated with anogenital cancers, specifically cervical cancer. HPV 16 and 18 are thought to be more oncogenic than other HPV types because they comprise 70% of cervical cancers, whereas each of the other 12 high-risk types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73) contributes less than 1–9%. HPV 16 appears to be even more important in anal and HPV-associated oropharyngeal cancers, comprising close to 90% of these cancers. HPV 16 is also commonly found in women without lesions or in those with LSILs, making the connection with cancer confusing. Genital warts and SIL are commonly associated with the detection of multiple HPV types, including a combination of low- and high-risk HPV types. Data show that it is likely that a single lesion arises from a single HPV type. Detection of multiple HPV types reflects the presence of cervical and anal coexisting lesions. Almost all (95%) incident low-risk and high-risk HPV DNA detections, with or without detectable SIL, will spontaneously resolve within 1-3 yr. Although HPV 16 has a slower rate of regression than some of the other high-risk types, the majority of incident HPV 16 detections also will resolve. Data suggest that clearance of an HPV type results in natural immune protection against reinfection with that same type. Redetections of the same type are not common and when found are often associated with a history of a new sexual partner, suggesting that these are not reactivated infections but are due to new exposures. These redetections rarely result in high-grade disease. Persistent high-risk–type infections are associated with increased risk for development of HSILs and invasive cancer. Progression of HSIL to invasive cancer is still rare, with only 5–15% showing progression. Approximately 50% of HPV 16–associated HSILs and 80% of non–HPV 16 HSILs will spontaneously regress in young women. Genital and common warts in general also resolve without therapy but may take years to do so. Genital warts in only extremely rare conditions can become malignant.

Most infants with recognized genital warts are infected with the low-risk types. In contrast, children with a history of sexual abuse have a clinical picture more like that of adult genital warts, consisting of mixed low- and high-risk types. There are rare reports of HPV-associated genital malignancies occurring in preadolescent children and adolescents. On the other hand, precancerous HSILs do occur in sexually active adolescents. There is a concern that younger age of sexual debut has contributed to the increase in invasive cervical cancers seen in women younger than 50 yr of age in the United States, specifically cervical adenocarcinomas. Persistent HPV infections are considered necessary but not sufficient for the development of invasive cancers. Other risk factors for which there is relatively strong suggestive evidence of association include smoking cigarettes, prolonged oral contraceptive use, greater parity, and *Chlamydia trachomatis* and herpes simplex virus infections.

Clinical Manifestations

The clinical findings in HPV infection depend on the site of epithelial infection.

Skin Lesions

The typical HPV-induced lesions of the skin are proliferative, papular, and hyperkeratotic. Common warts are raised circinate lesions with a keratinized surface (Fig. 293.1). Plantar and palmar warts are practically flat. Multiple warts are common and may create a mosaic pattern. Flat warts appear as small (1- to 5-mm), flat, flesh-colored papules.

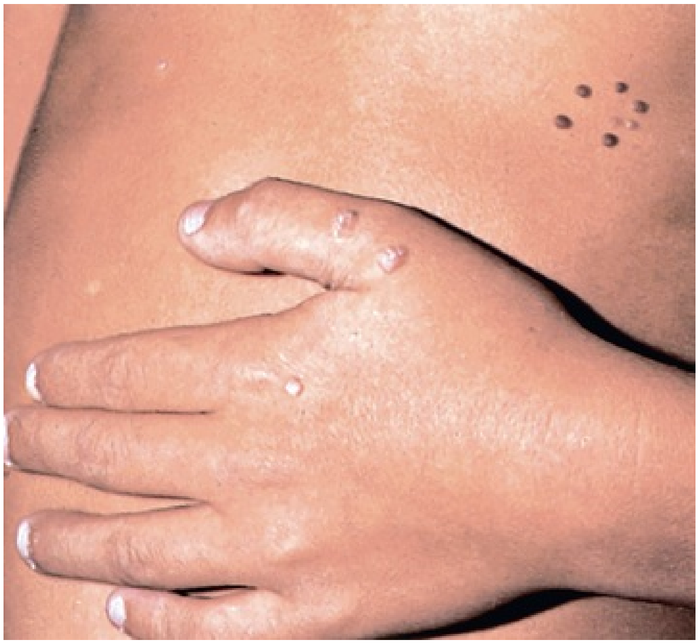

FIG. 293.1 Common warts of the left hand and the chest wall. (From Meneghini CL, Bonifaz E: An Atlas of Pediatric Dermatology, Chicago, 1986, Year Book, p. 45.)

Genital Warts

Genital warts may be found throughout the perineum around the anus, vagina, and urethra, as well as in the cervical, intravaginal, and intraanal areas (Fig. 293.2). Intraanal warts occur predominantly in patients who have had receptive anal intercourse, in contrast with perianal warts, which may occur in men and women without a history of anal sex. Although rare, lesions caused by genital genotypes can also be found on other mucosal surfaces, such as the conjunctivae, tongue, gingivae, and nasal mucosa. They may be single or multiple lesions and are frequently found in multiple anatomic sites, including the cervix. External genital warts can be flat, dome shaped, keratotic, pedunculated, and cauliflower shaped and may occur singly, in clusters, or as plaques. On mucosal epithelium, the lesions are softer. Depending on the size and anatomic location, lesions may be pruritic and painful, may cause burning with urination, may be friable and bleed, or may become superinfected. Adolescents are frequently disturbed by the development of genital lesions. Other rarer lesions caused by HPV of the external genital area include Bowen disease, bowenoid papulosis, squamous cell carcinomas, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

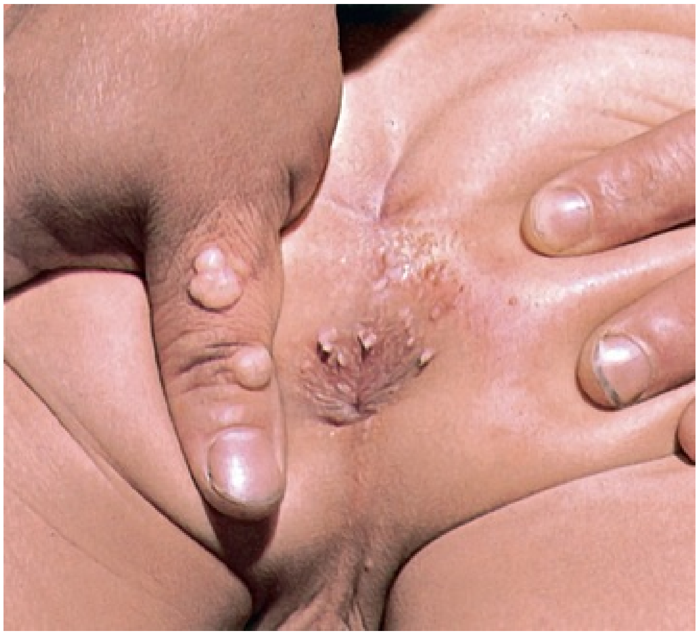

FIG. 293.2 Common warts of the hand in a mother and perianal condylomata acuminata in her son. (From Meneghini CL, Bonifaz E: An Atlas of Pediatric Dermatology, Chicago, 1986, Year Book, p. 44.)

Squamous Intraepithelial Lesions and Cancers

Squamous intraepithelial lesions detected with cytology are usually invisible to the naked eye and require the aid of colposcopic magnification and acetic acid. With aid, the lesions appear white and show evidence of neovascularity. SILs can occur on the cervix, vagina, vulva, penis, and intraanus. HPV-associated squamous cell lesions can also be found in the oropharynx. Invasive cancers tend to be more exophytic, with aberrant-appearing vasculature. These lesions are rarely found in non–sexually active individuals.

Laryngeal Papillomatosis

The median age at diagnosis of recurrent laryngeal papillomatosis is 3 yr. Children present with hoarseness, an altered cry, and sometimes stridor. Rapid growth of respiratory papillomas can occlude the upper airway, causing respiratory compromise. These lesions may recur within weeks of removal, requiring frequent surgery. The lesions do not become malignant unless treated with irradiation.

Diagnosis

The diagnosis of external genital warts and common warts may be reliably determined by visual inspection of a lesion by an experienced observer and does not require additional tests for confirmation. A biopsy should be considered if the diagnosis is uncertain, the lesions do not respond to therapy, or the lesions worsen during therapy.

Screening for cervical cancer in young women begins with cytology, which is either performed by Papanicolaou smear or liquid-based cytology. Screening guidelines, which were updated in 2012 by the American Cancer Society and the U.S. Preventive Services Task Force, recommend starting screening at age 21 yr. Screening earlier is more likely to result in unnecessary referrals for colposcopy, because most lesions, including both LSILs and HSILs in this age-group, are likely to regress. Guidelines recommend screening with cytology every 3 yr. At 30 yr of age, screening can also include co-testing with HPV DNA at an interval of every 5 yr. This is not recommended earlier, because HPV infections are extremely common in young women, resulting in a very low positive-predictive value in this age-group.

The recommended terminology used for cytologic evaluation is based on the Bethesda system (see Table 293.1). Recent updates to the terminology used for histology uses similar terms. Many clinicians still prefer the World Health Organization terminology using cervical intraepithelial neoplasia (CIN) 1, 2, and 3 (see Table 293.1). Although the purpose of screening is to identify CIN 3+ lesions, the majority of CIN lesions are found in women who were referred for **atypical squamous cells of undetermined significance (ASC-US)** or LSILs on cytology. On the other hand, few CIN 3 or cancers exist in women younger than 24 yr of age. Thus, for women 21-24 yr of age, ASC-US and LSILs are treated the same. The current preferred recommendation for young women with ASC-US or LSILs is to repeat cytology every 12 mo for up to 24 mo. For persistent ASC-US or LSILs at 2 yr of follow-up, referral for colposcopy is recommended. Women 21-24 yr of age with HSIL at any visit should be referred for colposcopy and biopsy. In adult women, HSIL can be treated without histologic confirmation. However, this approach should be avoided in those 21-24 yr of age, because HSIL is often misdiagnosed in this group or will resolve spontaneously.

In women older than 21 yr of age, high-risk HPV testing is acceptable to assist in ASC-US triage. This recommendation is based on the observations that adult women with ASC-US and a positive HPV test result for high-risk types are more likely to have CIN 2/3 than women with a negative HPV test result. However, in women with ASC-US and a positive HPV test for high-risk types, repeat cytology is recommended for confirmation. In women 21-24 yr of age referred for colposcopy and found to have no lesion or biopsy-confirmed LSIL after ASC-US or LSIL cytology, repeat cytology is recommended at 12 mo intervals. If ASC-US or LSIL has persisted after 2 yr or if HSIL is present at any time, referral for colposcopy is recommended. In women with biopsy-confirmed LSIL after atypical squamous cells of high grade (ASC-H) or HSIL, observation with cytology and colposcopy is recommended at 6 mo intervals for up to 2 yr. For persistent ASC-H or HSIL at 2 yr or progression at any time, treatment is recommended. Any young woman with histology-confirmed HSIL can be followed by colposcopy and cytology at 6 mo intervals if the patient is compliant. If HSIL continues to persist after 2 yr of follow-up, treatment is recommended. When CIN 3 is specified, treatment is recommended. These guidelines and updates can be found at http://www.asccp.org .

Very sensitive tests for the presence of HPV DNA, RNA, and proteins are becoming generally available, although they are not required for the diagnosis of external genital warts or related conditions. There are no indications for HPV DNA testing in women younger than 21 yr of age or children. HPV DNA testing is not recommended in women 21-30 yr of age but is acceptable for ASC-US triage.

Diagnosis of juvenile laryngeal papillomatosis (JRP) is made based on laryngeal examination.

There are no routine screening recommendations for noncervical or oropharyngeal lesions.

Differential Diagnosis

A number of other conditions should be considered in the differential diagnosis of genital warts, including condyloma latum, seborrheic keratoses, dysplastic and benign nevi, molluscum contagiosum, pearly penile papules, neoplasms, Bowen disease, bowenoid papulosis, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Condyloma latum is caused by secondary syphilis and can be diagnosed with darkfield microscopy and standard serologic tests for syphilis. Seborrheic keratoses are common, localized, hyperpigmented lesions that are rarely associated with malignancy. Molluscum contagiosum is caused by a poxvirus, is highly infectious, and is often umbilicated. Pearly penile papules occur at the penile corona and are normal variants that require no treatment.

Treatment

Most common (plantar, palmar, skin) warts eventually resolve spontaneously (see Chapter 687). Symptomatic lesions should be removed. Removal includes a variety of self-applied therapies, including salicylic acid preparations and provider-applied therapies (cryotherapy, laser therapy, electrosurgery). Genital warts are benign and usually remit, but only over an extended period. It is recommended that genital lesions be treated if the patient or the parent requests therapy. Treatments for genital warts are categorized into self-applied and provider-applied. No one therapy has been shown to be more efficacious than any other. Recommended patient-applied treatment regimens for external genital warts include topical podofilox, imiquimod, and sinecatechins. Podofilox 0.5% solution (using a cotton swab) or gel (using a finger) is applied to visible warts in a cycle of applications twice a day for 3 days followed by 4 days of no therapy, repeated for up to a total of 4 cycles. Imiquimod 5% cream is applied at bedtime, 3 times a week, every other day, for up to 16 wk; the treated area should be washed with mild soap and water 6-10 hr after treatment. Sinecatechins (15% ointment) is a topical product from green tea extract used for external genital wart treatment that can be used 3 times daily for up to 16 wk. Provider-applied therapies include surgical treatments (electrosurgery, surgical excision, laser surgery) and office-based treatment (cryotherapy with liquid nitrogen or a cryoprobe, podophyllin resin 10–25%, and bichloroacetic or trichloroacetic acid). Office-based treatments are usually applied once a week for 3-6 wk. Podophyllin resins have lost favor to other methods because of the variability in preparations. Intralesional interferon is associated with significant adverse effects and is reserved for treatment of recalcitrant cases.

Many therapies are painful, and children should not undergo painful genital treatments unless adequate pain control is provided. Parents and patients should not be expected to apply painful therapies themselves. None of the patient-applied therapies are approved for use during pregnancy, and podophyllin resin is contraindicated in pregnancy. For any of the nonsurgical treatments, prescription is contraindicated in a patient with any history of hypersensitivity to any product constituents.

If HPV exposure as a result of sexual abuse is suspected or known, the clinician should ensure that the child's safety has been achieved and is maintained.

When indicated, the most common treatments for CIN 2/3 are ablative and excisional treatments, including cryotherapy, laser, and loop electrosurgical excisional procedures. Once confirmed by histology with CIN 1, LSILs can be observed indefinitely. The decision to treat a persistent CIN 1 rests between the provider and patient. Risks of treatment, including premature delivery in a future pregnancy, should be discussed prior to any treatment decision. Treatment in pregnancy is not recommended unless invasive cancer is present.

JRP is commonly treated with surgical removal of lesions, but laser and microdebriders are also used. There are also several reports describing the use of adjunctive treatments, including antivirals and the quadrivalent human papillomavirus vaccine. However, the effectiveness of adjunctive therapy is not consistent.

Complications

The presence of HPV lesions in the genital area may be a cause of profound embarrassment to a child or parent. Complications of therapy are uncommon; chronic pain (vulvodynia) or hypoesthesia may occur at the treatment site. Lesions may heal with hypopigmentation or hyperpigmentation and less commonly with depressed or hypertrophic scars. Surgical therapies can lead to infection and scarring. Premature delivery and low birthweight in future pregnancies are complications of excisional therapy for CIN.

It is estimated that 5–15% of untreated CIN 3 lesions will progress to cervical cancer. Most cancer is prevented by early detection and treatment of these lesions. Despite screening, cervical cancer develops rapidly in a few adolescents and young women. The reason for the rapid development of cancer in these rare cases remains unknown, but host genetic defects are likely underlying causes. Juvenile laryngeal papillomas rarely become malignant, unless they have been treated with irradiation. Vulvar condylomas rarely become cancerous. HPV-associated cancers of the vagina, vulva, anus, penis, and oral cavity are much rarer than cervical tumors, and therefore screening for them is not currently recommended. However, anal, vaginal, and vulvar cancers are more common in women with cervical cancer; hence, it is recommended to screen women with cervical cancer for other anogenital or oropharyngeal tumors with visual and/or digital inspection.

Prognosis

With all forms of therapy, genital warts commonly recur, and approximately half of children and adolescents require a second or third treatment. Recurrence is also evident in patients with juvenile laryngeal papillomatosis. Patients and parents should be warned of this likelihood. Combination therapy for genital warts (imiquimod and podofilox) does not improve response and may increase complications. Prognosis of cervical disease is better, with 85–90% cure rates after a single treatment with the loop electrosurgical excision procedure. Cryotherapy has a slightly lower cure rate. Recalcitrant disease should prompt an evaluation and is common in immunocompromised individuals, specifically men and women infected with HIV.

Prevention

The only means of preventing HPV infection is to avoid direct contact with lesions. Condoms may reduce the risk for HPV transmission; condoms also prevent other sexually transmitted infections, which are risk factors associated with SIL development. In addition, condoms appear to hasten the regression of LSILs in women. Avoiding smoking cigarettes is important in preventing cervical cancer. Prolonged oral contraceptive use and parity have been shown to be risks for cervical cancer. However, the mechanisms associated with these factors have not been identified, and consequently no change in counseling is recommended.

HPV vaccines show efficacy against type-specific persistence and development of type-specific disease, including the cervix, vagina, vulva, and anus. A quadrivalent HPV vaccine containing types 6, 11, 16, and 18 was licensed in the United States in 2006, and a bivalent HPV vaccine containing types 16 and 18 was licensed in the United States in 2009. A 9-valent vaccine containing types 6, 11, 16, 18, 31, 33, 45, 52, and 58 was approved in 2014. The types targeted by the nonavalent vaccine account for up to 85% of cervical cancer cases. The efficacy of these vaccines is mediated by the development of neutralizing antibodies. Prelicensure studies demonstrate 90–100% efficacy in the prevention of persistent HPV infection, CIN 2/3, adenocarcinoma in situ, anogenital warts, and precancerous vaginal and vulvar lesions. Since vaccine introduction, data from Sweden and Australia show a decrease in national rates of genital warts within 4 yr of implementing vaccination programs. Recent data from the United States show significant reductions in the prevalence of the HPV types contained in the quadrivalent vaccine among adolescent and young adult females in the years 2009-2012 (postvaccine) compared with 2003-2006 (prevaccine). Additionally, the HPV vaccine–type prevalence was 2.1% in vaccinated compared with 16.9% in unvaccinated 14- to 24-yr-old sexually active females. A systematic review of 20 studies conducted in nine high-income countries showed reductions of at least 68% in the prevalence of HPV 16 and 18 among 13- to 19-yr-olds in countries with HPV vaccination rates > 50%. Available effectiveness data suggest that HPV vaccination confers herd immunity in addition to individual protection.

Vaccination in the United States is recommended routinely for all adolescents at 11-12 yr of age and is administered intramuscularly in the deltoid region in a two-dose series at 0 and 6 -12 mo. A two-dose series was approved and recommended in 2016 for younger adolescents who initiate the HPV vaccine series prior to age 15 yr based upon immunogenicity data showing a comparable immune response among younger adolescents who receive a two-dose series compared with older adolescents who receive a three-dose series. Vaccination is also recommended for adults through age 45 yr if they have not been previously vaccinated.

It is important that vaccination take place in children before they become sexually active, because the rate of HPV acquisition is high shortly after the onset of sexual activity. Vaccine can be given to adolescents as young as 9 yr of age, and a catch-up vaccination is recommended in girls 13-26 yr and in boys 13-21 yr. For males who are gay, bisexual, or have sex with males, who are immunocompromised (including HIV infection), or who are transgender, catch-up vaccination can continue through age 45. For any adolescent who receives his or her first HPV vaccine dose at age 15 or older, a three-dose series at 0, 1-2, and 6 mo is recommended. The three-dose series is also recommended for adolescents and young adults 9-26 yr old who have an immunocompromising condition. Individuals who are already infected with one or more vaccine-related HPV types prior to vaccination are protected from clinical disease caused by the remaining vaccine HPV types. Therefore, a history of prior HPV infection is not a contraindication to vaccine receipt. However, HPV vaccines are not therapeutic.

Postlicensure vaccine safety surveillance has not identified any serious adverse events attributable to HPV vaccine receipt. Three large observational studies and safety monitoring through active and passive surveillance networks among more than 1 million individuals have not identified any association between HPV vaccination and outcomes such as autoimmune disorders, stroke, or venous thrombotic emboli. Vaccination can cause fever in approximately 1 in 60 and discomfort at the injection site for 1 in 30 vaccine recipients. Syncope has also been found to be correlated with vaccine administration in 0.1% of vaccine recipients. Therefore, it is advised that adolescents remain seated for 15 min following vaccination.

Despite an excellent safety and efficacy profile, HPV vaccine uptake has been slow. Immunization rates consistently lag behind rates for the other vaccines included in the adolescent immunization platform. In 2015, only 56.1% of 13- to 17-yr-olds received at least one HPV vaccine dose compared with 81.6% who received at least one dose of the quadrivalent meningococcal vaccine and 86.4% who received Tdap. Reasons for the slow uptake include inconsistent provider recommendation, lack of knowledge about HPV, parental belief that vaccination is not necessary for younger adolescents, and misconceptions about vaccine safety, among others. There is a growing body of literature evaluating interventions to improve HPV vaccine uptake. One important strategy is a strong, consistent recommendation in which HPV vaccines are presented in the same way as Tdap and meningococcal vaccines.

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CHAPTER 294

Arboviral Infections

Scott B. Halstead

The arthropod-borne viral infections are a group of mosquito- or tick-transmitted pathogens of several taxa manifested clinically mostly as neurologic infections, influenza-like illnesses, or acute viral exanthems. In temperate countries, arboviruses are transmitted during warmer weather; however, in tropical and subtropical countries, arboviruses may be transmitted year around either in an urban cycle (human to mosquito to human) or by arthropods that feed on other vertebrate species and then feed on humans.

Etiology

The principal arthropod-borne viral infections in North America are West Nile encephalitis (WNE), St. Louis encephalitis (StLE), Powassan (POW) encephalitis, a complex of California encephalitis group viruses, and, less frequently, western equine encephalitis (WEE), eastern equine encephalitis (EEE), and Colorado tick fever (Fig. 294.1). In 2013, chikungunya virus (CHIK) emerged from its original African zoonosis via Asia into the Western Hemisphere, exposing many residents of the United States who were traveling in the region. A few cases occurred domestically in southern states. In 2015, Zika virus (ZIKV), a flavivirus also maintained in Africa zoonoses, was introduced into the Americas, again from endemic areas in Asia. Limited transmission occurred within the continental United States. The major source of infection among Americans for each of these viruses has been travel to tropical and subtropical countries.

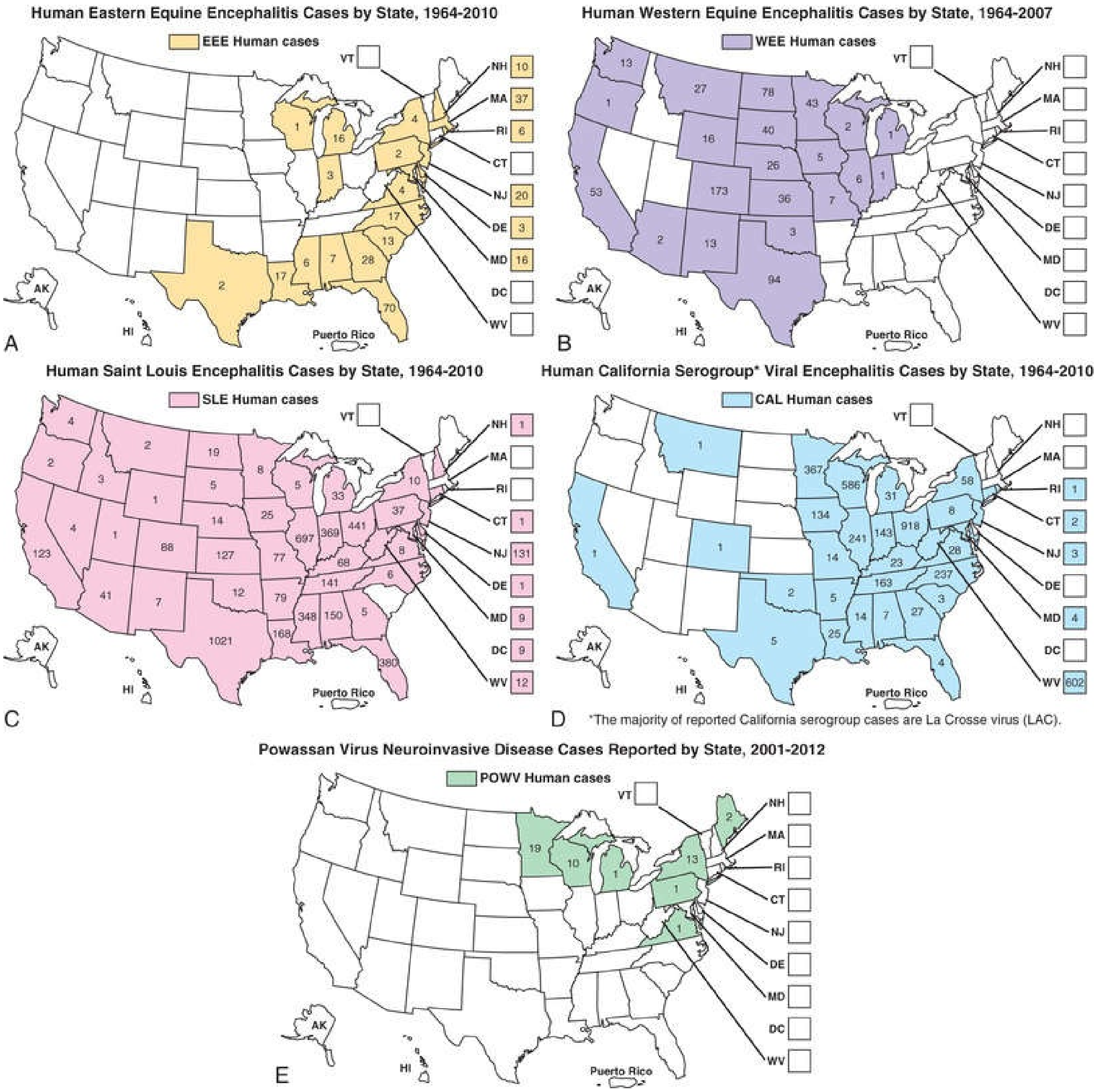

Human Eastern Equine Encephalitis Cases by State, 1964-2010
EEE Human cases
VT
NH 10
MA 37
RI 6
CT
NJ 20
DE 3
MD 16
DC
WV
1
16
3
4
2
4
17
13
28
6
7
17
2
70
AK
HI
Puerto Rico
A
Human Western Equine Encephalitis Cases by State, 1964-2007
WEE Human cases
VT
NH
MA
RI
CT
NJ
DE
MD
DC
WV
13
1
27
78
43
16
40
2
1
5
26
6
1
53
173
36
7
2
13
3
94
AK
HI
Puerto Rico
B
Human Saint Louis Encephalitis Cases by State, 1964-2010
SLE Human cases
VT
NH 1
MA
RI
CT 1
NJ 131
DE 1
MD 9
DC 9
WV 12
4
2
2
19
8
3
5
5
33
10
4
1
14
25
441
37
697
369
123
88
127
77
68
8
141
6
12
79
41
7
348
150
5
1021
168
380
AK
HI
Puerto Rico
C
Human California Serogroup* Viral Encephalitis Cases by State, 1964-2010
CAL Human cases
VT
NH
MA
RI 1
CT 2
NJ 3
DE
MD 4
DC
WV 602
1
367
586
58
31
134
918
8
241
143
1
1
14
23
28
163
237
2
5
3
14
7
27
25
5
4
AK
HI
Puerto Rico
D
*The majority of reported California serogroup cases are La Crosse virus (LAC).
Powassan Virus Neuroinvasive Disease Cases Reported by State, 2001-2012
POWV Human cases
VT
NH
MA
RI
CT
NJ
DE
MD
DC
WV
19
10
1
2
13
1
1
AK
HI
Puerto Rico
E

FIG. 294.1 The distribution and incidence of reported cases of eastern equine encephalitis **(A),** western equine encephalitis **(B),** St. Louis encephalitis **(C),** California serogroup encephalitis **(D),** and Powassan encephalitis; **(E),** reported by state to the Centers for Disease Control and Prevention, 1964 to 2010. (From Division of Vector-Borne Diseases, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/ncidod/dvbid/arbor/arbocase/htm .)

Throughout the world outside North America, there are many arboviruses that pose major health problems (Fig. 294.2). In descending order, these are the dengue viruses (DENV; Chapter 295), transmitted in all subtropical and tropical countries; Japanese encephalitis (JE), transmitted in northern, southern, and Southeast Asia; tick-borne encephalitis (TBE), transmitted across Europe and into northern and eastern Asia; yellow fever (YF; Chapter 296), transmitted from zoonotic cycles in Africa and South America; and Venezuelan equine encephalitis (VEE), transmitted in parts of South and Central America.

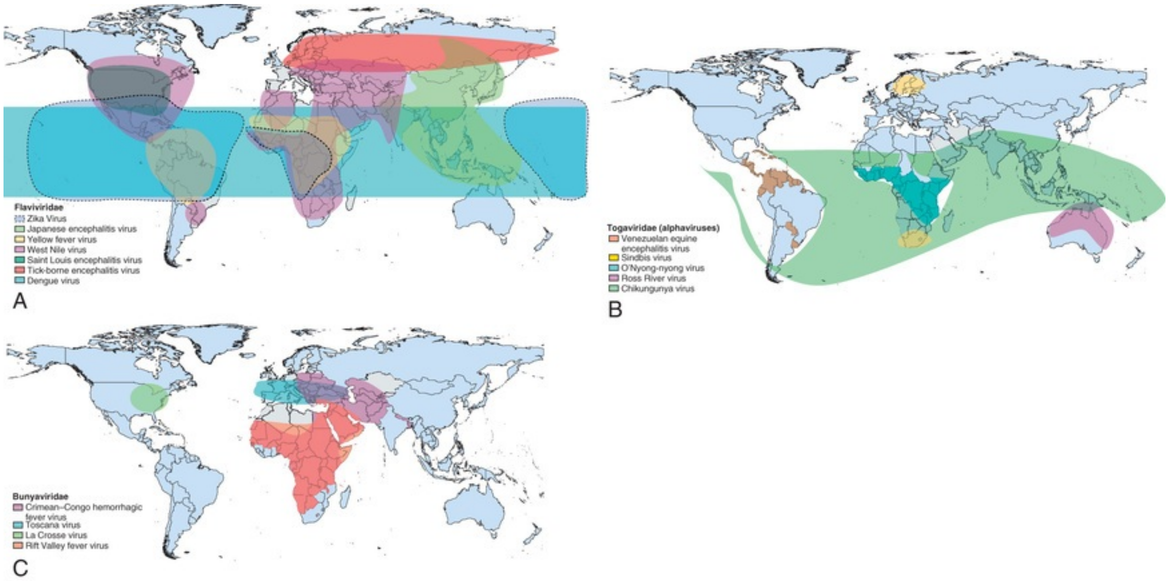
Flaviviridae
Zika Virus
Japanese encephalitis virus
Yellow fever virus
West Nile virus
Saint Louis encephalitis virus
Tick-borne encephalitis virus
Dengue virus
A
Togaviridae (alphaviruses)
Venezuelan equine encephalitis virus
Sindbis virus
O'Nyong-nyong virus
Ross River virus
Chikungunya virus
B
Bunyaviridae
Crimean–Congo hemorrhagic fever virus
Toscana virus
La Crosse virus
Rift Valley fever virus
C

FIG. 294.2 **World distribution of major arbovirus infections. (From Charlier C, Beaudoin MC, Couderc T, et al: Arboviruses and pregnancy: maternal, fetal, and neonatal effects, Lancet Child Adolesc 1:134-146, 2017, Fig. 1.)**

The etiologic agents belong to different viral taxa: *alphaviruses* of the family Togaviridae (CHIK, EEE, VEE, WEE), *flaviviruses* of the family Flaviviridae (DENV, JE, POW, STLE, TBE, WNE, YF, ZIKV), the California complex of the family Bunyaviridae (California encephalitis), and Reoviridae (Colorado tick fever virus). *Alphaviruses* are 69 nm, enveloped, positive-sense RNA viruses. Studies suggest that this group of viruses had a marine origin (specifically the southern ocean) and that they have subsequently spread to both the Old and New Worlds. VEE circulates in nature in six subtypes. Virus types I and III have multiple antigenic variants. Types IAB and IC have caused epizootics and human epidemics. *Flaviviruses* are 40- to 50-nm, enveloped, positive-sense RNA viruses that evolved from a common ancestor. They are mosquito-borne (WNE, STLE, JE, YF, DENV, ZIKV) and tick-borne (POW, TBE) agents, globally distributed, and responsible for many important human viral diseases. The California serogroup, 1 of 16 Bunyavirus groups, are 75- to 115-nm enveloped viruses possessing a three-segment, negative-sense RNA genome. Reoviruses are 60- to 80-nm double-stranded RNA viruses.

Diagnosis

For arboviral infections not described separately, the etiologic diagnosis is established by testing either an acute-phase serum to detect the virus, viral antigen, or viral RNA (influenza-like illnesses or viral exanthems) or by recovery of virus from CNS tissue or CSF. More commonly, the diagnosis is established serologically. Serum obtained ≥ 5 days after the onset of illness is tested for the presence of virus-specific immunoglobulin (Ig) M antibodies using an enzyme-linked immunosorbent assay IgM capture test, an indirect immunofluorescence test, or a precipitin test. Alternatively, acute and convalescent sera can be tested for a four-fold or greater increase in enzyme-linked immunosorbent assay, hemagglutination inhibition, or neutralizing antibody titers. Commercial serologic diagnostic kits are marketed for DENV, CHIK, JE, TBE, WN, YF, or ZIKV viral infections. The serum and CSF should be tested for JE or WN virus–specific IgM. However, IgM may reflect past infection, because it may be present up to 12 mo after infection. For suspected flavivirus infections, including Zika virus, it may be possible to establish infection using a serologic test, calling upon the specificity of neutralizing antibodies. The most common of these is the plaque or focus-reduction neutralizing antibody test. Reference laboratories offer tests for all of the pathogenic flaviviruses. The diagnosis may also be established by the isolation of virus in cell cultures, by identification of viral RNA, or by detection of viral proteins (e.g., dengue NS1) from blood, brain tissue obtained by brain biopsy, or tissues obtained at autopsy.

Prevention

Several vaccines for Japanese encephalitis and tick-borne encephalitis are licensed in endemic and nonendemic countries. An experimental vaccine for VEE is available to protect laboratory workers. Travelers who plan to be in rural areas of Asia during the expected period of seasonal transmission should receive JE vaccine. Similarly, travelers who plan to travel, camp, or picnic in rural areas of Europe and East Asia should consult local health authorities concerning the need to be vaccinated against TBE. An inactivated vaccine manufactured in Japan by intracerebral injection of young mice and available throughout the world has been taken off the market owing to a high incidence of adverse events. In 2008-2009, tissue culture–based JE vaccine (Ixiaro) was licensed in Europe, Australia, and the United States. In the United States, this vaccine is licensed for use in children and adults and is distributed by Novartis (Basel). This vaccine is administered intramuscularly as two doses of 0.5 mL each, 28 days apart. The final dose should be completed at least 1 wk prior to the patient's expected arrival in a JE endemic area. This vaccine contains alum and protamine sulfate and has exhibited only mild adverse events. A highly efficacious live-attenuated single-dose JE vaccine developed in China for children is licensed and marketed in Asian countries. This vaccine can be coadministered with live-attenuated measles vaccine without altering the immune responses to either vaccine. In humans, prior dengue virus infection provides partial protection from clinical JE.

No TBE vaccines are licensed or available in the United States. Two inactivated cell culture–derived TBE vaccines are available in Europe, in adult and pediatric formulations: FSME-IMMUN (Baxter, Austria) and Encepur (Novartis, Germany). The adult formulation of FSME-IMMUN is also licensed in Canada. Two other inactivated TBE vaccines are available in Russia: TBE-Moscow (Chumakov Institute, Russia) and EnceVir (Microgen, Russia). Immunogenicity studies suggest that the European and Russian vaccines should provide cross-protection against all three TBE virus subtypes. For both FSME-IMMUN and Encepur, the primary vaccination series consists of three doses. The specific recommended intervals between doses vary by country and vaccine. Because the routine primary vaccination series requires ≥ 6 mo for completion, most travelers to TBE-endemic areas will find avoiding tick bites to be more practical than vaccination.

For all viral diseases discussed in this chapter, personal measures should be taken to reduce exposure to mosquito or tick bites, especially for short-term residents in endemic areas. These measures include avoiding evening outdoor exposure, using insect repellents, covering the body with clothing, and using bed nets or house screening. Commercial pesticides, widely used by rice farmers, may be useful in reducing populations of vector mosquitoes or ticks. Fenthion, fenitrothion, and phenthoate are effectively adulticidal and larvicidal. Insecticides may be applied from portable sprayers or from helicopters or light aircraft.

294.1

Eastern Equine Encephalitis

Scott B. Halstead

In the United States, EEE is a disease with a very low incidence, with a median of eight cases occurring annually in the Atlantic and Gulf states from 1964 to 2007 (Fig. 294.1). Transmission occurs often in focal endemic areas of the coast of Massachusetts, the six southern counties of New Jersey, and northeastern Florida. In North America, the virus is maintained in freshwater swamps in a zoonotic cycle involving *Culiseta melanura* and birds. Various other mosquito species obtain viremic meals from birds and transmit the virus to horses and humans. Virus activity varies markedly from year to year in response to still unknown ecologic factors. Most infections in birds are silent, but infections in pheasants are often fatal, and epizootics in these species are used as sentinels for periods of increased viral activity. Cases have been recognized on Caribbean islands. The case:infection ratio is lowest in children (1 : 8) and somewhat higher in adults (1 : 29).

EEE virus infections result in fulminant encephalitis with a rapid progression to coma and death in one third of cases. In infants and children, abrupt onset of fever, irritability, and headache are followed by lethargy, confusion, seizures, and coma. High temperature, bulging fontanel, stiff neck, and generalized flaccid or spastic paralysis are observed. There may be a brief prodrome of fever, headache, and dizziness. Unlike most other viral encephalitides, the peripheral white blood cell count usually demonstrates a marked leukocytosis, and the cerebrospinal fluid (CSF) may show marked pleocytosis. Pathologic changes are found in the cortical and gray matter, with viral antigens localized to neurons. There is necrosis of neurons, neutrophilic infiltration, and perivascular cuffing by lymphocytes.

The prognosis in EEE is better for patients with a prolonged prodrome; the occurrence of convulsions conveys a poor prognosis. Patient fatality rates are 33–75% and are highest in the elderly. Residual neurologic defects are common, especially in children.

The diagnosis of encephalitis may be aided by CT or MRI and by electroencephalography. Focal seizures or focal findings on CT or MRI or electroencephalography should suggest the possibility of herpes simplex encephalitis, which should be treated with acyclovir (see Chapter 279).

294.2

Western Equine Encephalitis

Scott B. Halstead

WEE infections occur principally in the United States and Canada west of the Mississippi River (see Fig. 294.1), mainly in rural areas where water impoundments, irrigated farmland, and naturally flooded land provide breeding sites for *Culex tarsalis.* The virus is transmitted in a cycle involving mosquitoes, birds, and other vertebrate hosts. Humans and horses are susceptible to encephalitis. The case:infection ratio varies by age, having been estimated at 1 : 58 in children younger than 4 yr of age and 1 : 1,150 in adults. Infections are most severe at the extremes of life; one third of cases occur in children younger than 1 yr of age. Recurrent human epidemics have been reported from the Yakima Valley in Washington State and the Central Valley of California; the largest outbreak on record resulted in 3,400 cases and occurred in Minnesota, North and South Dakota, Nebraska, and Montana, as well as Alberta, Manitoba, and Saskatchewan, Canada. Epizootics in horses precede human epidemics by several weeks. For the past 20 yr, only three cases of WEE have been reported, presumably reflecting successful mosquito abatement.

In WEE, there may be a prodrome with symptoms of an upper respiratory tract infection. The onset is usually sudden with chills, fever, dizziness, drowsiness, increasing headache, malaise, nausea and vomiting, stiff neck, and disorientation. Infants typically present with the sudden cessation of feeding, fussiness, fever, and protracted vomiting. Convulsions and lethargy develop rapidly. On physical examination, patients are somnolent, exhibit meningeal signs, and have generalized motor weakness and reduced deep tendon reflexes. In infants, a bulging fontanel, spastic paralysis, and generalized convulsions may be observed. On pathologic examination, disseminated small focal abscesses, small focal hemorrhages, and patchy areas of demyelination are distinctive.

Patient fatality rates in WEE are 3–9% and are highest in the elderly. Major neurologic sequelae have been reported in up to 13% of cases and may be as high as 30% in infants. Parkinsonian syndrome has been reported as a residual in adult survivors.

294.3

St. Louis Encephalitis

Scott B. Halstead

Cases of STLE are reported from nearly all states; the highest attack rates occur in the gulf and central states (see Fig. 294.1). Epidemics frequently occur in urban and suburban areas; the largest, in 1975, involved 1,800 persons living in Houston, Chicago, Memphis, and Denver. Cases often cluster in areas where there are ground water or septic systems, which support mosquito breeding. The principal vectors are *Culex pipiens* and *Culex quinquefasciatus* in the central gulf states, *Culex nigripalpus* in Florida, and *C. tarsalis* in California. STLE virus is maintained in nature in a bird–mosquito cycle. Viral amplification occurs in bird species abundant in residential areas (e.g., sparrows, blue jays, and doves). Virus is transmitted in the late summer and early fall. The case:infection ratio may be as high as 1 : 300. Age-specific attack rates are lowest in children and highest in individuals older than age 60 yr. The most recent small outbreaks were in Florida in 1990 and Louisiana in 2001. For the past 15 yr, there have been a mean of 18 cases annually.

Clinical manifestations of STLE vary from a mild flulike illness to fatal encephalitis. There may be a prodrome of nonspecific symptoms with subtle changes in coordination or mentation of several days to 1 wk in duration. Early signs and symptoms include fever, photophobia, headache, malaise, nausea, vomiting, and neck stiffness. About half of patients exhibit an abrupt onset of weakness, incoordination, disturbed sensorium, restlessness, confusion, lethargy, and delirium or coma. The peripheral white blood cell count is modestly elevated, with 100-200 cells/µL found in the CSF. On autopsy, the brain shows scattered foci of neuronal damage and perivascular inflammation.

The principal risk factor for fatal outcome of STLE is advanced age, with patient fatality rates being as high as 80% in early outbreaks. In children, mortality rates are 2–5%. In adults, underlying hypertensive cardiovascular disease has been a risk factor for fatal outcome. Recovery from STLE is usually complete, but the rate of serious neurologic sequelae has been reported to be as high as 10% in children.

294.4

West Nile Encephalitis

Scott B. Halstead

West Nile (WN) virus was imported into the United States in 1999 and survives in a broad enzootic cycle across the United States and Canada. Every state in the continental United States plus nine provinces in Canada have reported mosquito, bird, mammalian, or human WN virus infection, most frequently during the summer or fall months. Through the end of 2015, 43,937 total cases had been reported in the United States, 40–50% of which were neuroinvasive, with 1,911 deaths (Fig. 294.3). WN virus transmission cycles appear to resemble those of Japanese encephalitis with large epizootics and human cases every 5-10 yr. WN virus has entered the blood supply through asymptomatic viremic potential blood donors. Since 2003, blood banks screen for WN virus RNA. During the major outbreak of 2012, 597 viremic potential blood donors were identified and the donation was rejected. WN virus has also been transmitted to humans via the placenta, breast milk, and organ transplantation. Throughout its range, the virus is maintained in nature by transmission between mosquitoes of the *Culex* genus and various species of birds. In the United States, human infections are largely acquired from *C. pipiens*. Horses are the nonavian vertebrates most likely to exhibit disease with WN virus infection. During the 2002 transmission season, 14,000 equine cases were reported, with a mortality rate of 30%. Disease occurs predominantly in individuals >50 yr of age. WN virus has been implicated as the cause of sporadic summertime cases of human encephalitis and meningitis in Israel, India, Pakistan, Romania, Russia, Canada, the United States, and parts of Central and South America. All American WN viruses are genetically similar and are related to a virus recovered from a goose in Israel in 1998.

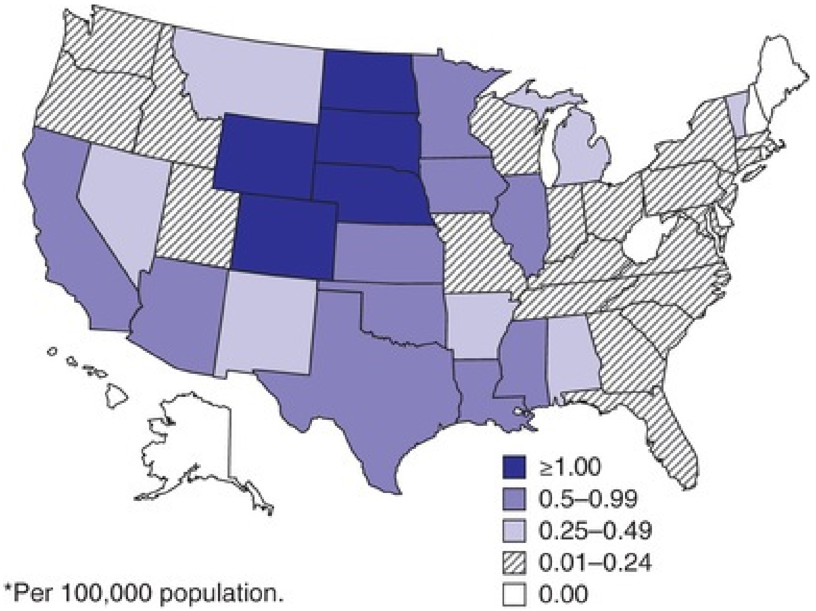

*Per 100,000 population.

FIG. 294.3 Rate (per 100,000 population) of reported cases of West Nile virus neuroinvasive disease, United States, 2016. (From Burakoff A, Lehman J, Fischer M, et al: West Nile virus and other nationally notifiable arboviral diseases, United States, 2016, MMWR 67(1):13-17, 2018.)

West Nile encephalitis (WNE) may be asymptomatic, but when clinical features appear, they include an abrupt onset of high fever, headache, myalgias, and nonspecific signs of emesis, rash, abdominal pain, or diarrhea. Most infections manifest as a flulike febrile illness, whereas a minority of patients demonstrate meningitis or encephalitis, or both. Rarely there may be cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, retinitis, orchitis, pancreatitis, or hepatitis. WN virus disease in the United States has been accompanied by prolonged lymphopenia and an acute asymmetric polio-like paralytic illness with CSF pleocytosis involving the anterior horn cells of the spinal cord. A striking but uncommon feature has been parkinsonism and movement disorders (with tremor and myoclonus). WN virus infections have been shown to lead to chronic kidney disease in a small group of patients.

Cases of WNE and deaths due to the disease occur mainly in the elderly, although many serologic surveys show that persons of all ages are infected. In 2015, among a total of 2,175 human cases, 1,455 were neuroinvasive disease, which resulted in 146 deaths, a 10% mortality rate (see Fig. 294.2). Paralysis may result in permanent weakness.

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294.5

Powassan Encephalitis

Scott B. Halstead

POW virus is transmitted by *Ixodes cookei* among small mammals in eastern Canada and the United States; it has been responsible for 39 deaths in the United States since 2008 (see Fig. 294.1). Other ticks may transmit the virus in a wider geographic area, and there is some concern that *Ixodes scapularis* (also called *Ixodes dammini*), a competent vector in the laboratory, may become involved as it becomes more prominent in the United States.

In a limited experience, POW encephalitis has occurred mainly in adults with vocational or recreational exposure and has a high fatality rate.

POW encephalitis has occurred mostly in adults living in enzootic areas with vocational or recreational exposure; it is associated with significant long-term morbidity and has a case-fatality rate of 10–15%.

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294.6

La Crosse and California Encephalitis

Scott B. Halstead

La Crosse viral infections are endemic in the United States, occurring annually from July to September, principally in the north-central and central states (see Fig. 294.1). Infections occur in peridomestic environments as the result of bites from *Aedes triseriatus* mosquitoes, which often breed in tree holes. The virus is maintained vertically in nature by transovarial transmission and can be spread between mosquitoes by copulation and amplified in mosquito populations by viremic infections in various vertebrate hosts. Amplifying hosts include chipmunks, squirrels, foxes, and woodchucks. A case:infection ratio of 1 : 22-300 has been surmised. La Crosse encephalitis is principally a disease of children, who may account for up to 75% of cases. A mean of 100 cases has been reported annually for the past 10 yr.

The clinical spectrum includes a mild febrile illness, aseptic meningitis, and fatal encephalitis. Children typically present with a prodrome of 2-3 days of fever, headache, malaise, and vomiting. The disease evolves with clouding of the sensorium, lethargy, and, in severe cases, focal or generalized seizures. On physical examination, children are lethargic but not disoriented. Focal neurologic signs, including weakness, aphasia, and focal or generalized seizures, have been reported in 16–25% of cases. CSF shows low to moderate leukocyte counts. On autopsy, the brain shows focal areas of neuronal degeneration, inflammation, and perivascular cuffing.

Recovery from California encephalitis is usually complete. The case fatality rate is approximately 1%.

294.7

Colorado Tick Fever

Scott B. Halstead

Colorado tick fever virus is transmitted by the wood tick *Dermacentor andersoni,* which inhabits high-elevation areas of states extending from the central plains to the Pacific coast. The tick is infected with the virus at the larval stage and remains infected for life. Squirrels and chipmunks serve as primary reservoirs. Human infections typically occur in hikers and campers in indigenous areas during the spring and early summer.

Colorado tick fever begins with the abrupt onset of a flulike illness, including high temperature, malaise, arthralgia and myalgia, vomiting, headache, and decreased sensorium. Rash is uncommon. The symptoms rapidly disappear after 3 days of illness. However, in approximately half of patients, a second identical episode reoccurs 24-72 hr after the first one, producing the typical saddleback temperature curve of Colorado tick fever. Complications, including encephalitis, meningoencephalitis, and a bleeding diathesis, develop in 3–7% of infected persons and may be more common in children younger than 12 yr of age.

Recovery from Colorado tick fever is usually complete. Three deaths have been reported, all in persons with hemorrhagic signs.

294.8

Chikungunya Fever

Scott B. Halstead

Chikungunya virus is enzootic in several species of African subhuman primates but also is endemic in urban *Aedes aegypti* or *Aedes albopictus* transmission cycles in Africa and Asia. Chikungunya exited Africa historically producing Asian pandemics in 1790, 1824, 1872, 1924, 1963, and 2005. In 1827, chikungunya reached the Western Hemisphere, predominantly the Caribbean region, probably brought by the slave trade. In 2005, another Asian pandemic proceeded east from an initial outbreak on Reunion and then traveling to Asia across the Indian Ocean. In 2013, chikungunya virus from this epidemic was introduced into Latin America.

Clinical manifestations begin 3-7 days after a mosquito bite; the onset is abrupt, with high fever and often severe joint symptoms (hands, feet, ankles, wrists) that include symmetric bilateral polyarthralgia or arthritis. Most pediatric patients are relatively asymptomatic, but all ages are vulnerable to classic disease. There may be headache, myalgias, conjunctivitis, weakness, lymphopenia, and a maculopapular rash. Mortality is rare; some individuals develop prolonged joint symptoms (tenosynovitis, arthritis) lasting over a year. The acute episode lasts 7-10 days. The differential diagnosis includes dengue, West Nile, enterovirus diseases, leptospirosis, rickettsial disease, measles, parvovirus disease, rheumatologic diseases, and other alphavirus diseases (e.g., Ross River virus) in endemic areas. Fig. 294.4 lists the diagnostic criteria.

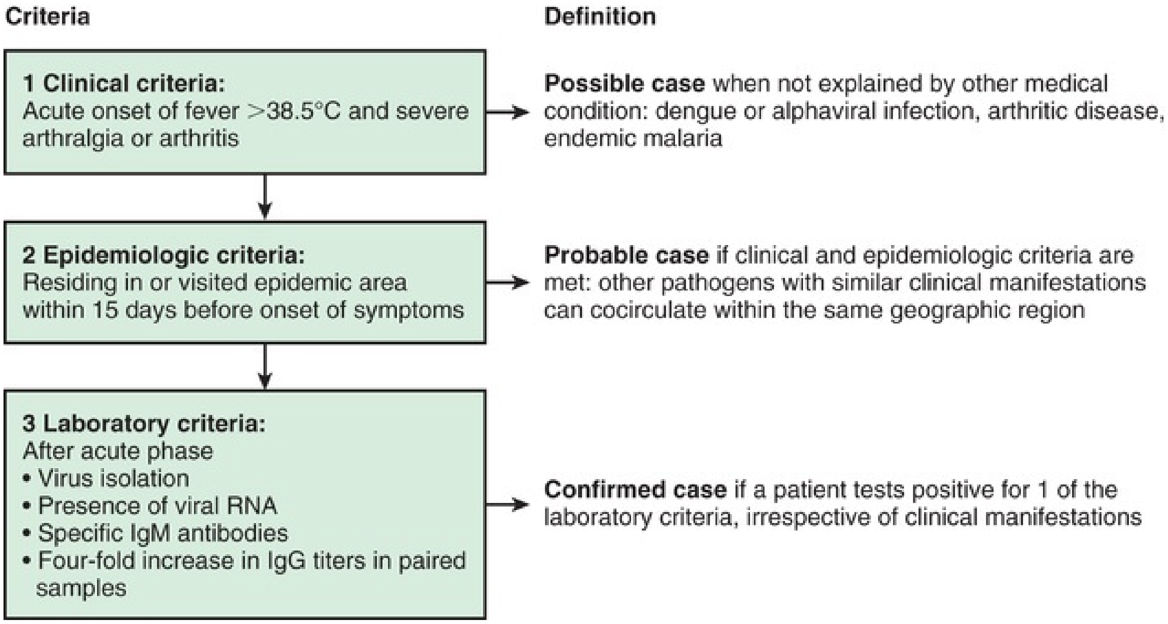
Criteria
Definition
1 Clinical criteria:
Acute onset of fever >38.5°C and severe arthralgia or arthritis
Possible case when not explained by other medical condition: dengue or alphaviral infection, arthritic disease, endemic malaria
2 Epidemiologic criteria:
Residing in or visited epidemic area within 15 days before onset of symptoms
Probable case if clinical and epidemiologic criteria are met: other pathogens with similar clinical manifestations can cocirculate within the same geographic region
3 Laboratory criteria:
After acute phase
• Virus isolation
• Presence of viral RNA
• Specific IgM antibodies
• Four-fold increase in IgG titers in paired samples
Confirmed case if a patient tests positive for 1 of the laboratory criteria, irrespective of clinical manifestations

FIG. 294.4 Diagnostic criteria for chikungunya virus fever. (From Burt FJ, Rolph MS, Rulli NE, et al: Chikungunya: a re-emerging virus, Lancet 379:662-668, 2012, Fig. 6.)

The incidence of febrile convulsions is high in infants. The prognosis is generally good, although in large outbreaks in Africa and India, severe disease and deaths have been attributed to chikungunya infections, predominantly in adults.

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294.9

Venezuelan Equine Encephalitis

Scott B. Halstead

VEE virus was isolated from an epizootic in Venezuelan horses in 1938. Human cases were first identified in 1943. Hundreds of thousands of equine and human cases have occurred over the past 70 yr. During 1971, epizootics moved through Central America and Mexico to southern Texas. After two decades of quiescence, epizootic disease emerged again in Venezuela and Colombia in 1995. Between December 1992 and January 1993, the Venezuelan state of Trujillo experienced an outbreak of this virus. Overall, 28 cases of the disease were reported, along with 12 deaths. June 1993 saw a bigger outbreak, in which 55 humans died, as well as 66 horses. A much larger outbreak in Venezuela and Colombia occurred in 1995. On May 23, 1995, equine encephalitis-like cases were reported in the northwest portion of the country. Eventually, the outbreak spread toward the north, as well as to the south. The outbreak caused about 11,390 febrile cases in humans, as well as 16 deaths. About 500 equine cases were reported with 475 deaths.

The incubation period is 2-5 days, followed by the abrupt onset of fever, chills, headache, sore throat, myalgia, malaise, prostration, photophobia, nausea, vomiting, and diarrhea. In 5–10% of cases, there is a biphasic illness; the second phase is heralded by seizures, projectile vomiting, ataxia, confusion, agitation, and mild disturbances in consciousness. There is cervical lymphadenopathy and conjunctival suffusion. Cases of meningoencephalitis may demonstrate cranial nerve palsy, motor weakness, paralysis, seizures, and coma. Microscopic examination of tissues reveals inflammatory infiltrates in lymph nodes, spleen, lung, liver, and brain. Lymph nodes show cellular depletion, necrosis of germinal centers, and lymphophagocytosis. The liver shows patchy hepatocellular degeneration, the lungs demonstrate a diffuse interstitial pneumonia with intraalveolar hemorrhages, and the brain shows patchy cellular infiltrates.

There is no specific treatment for VEE. The treatment is intensive supportive care (see Chapter 85), including control of seizures (see Chapter 611).

In patients with VEE meningoencephalitis, the fatality rate ranges from 10% to 25%. Sequelae include nervousness, forgetfulness, recurrent headache, and easy fatigability.

Several veterinary vaccines are available to protect equines. VEE virus is highly infectious in laboratory settings, and biosafety level three containment should be used. An experimental vaccine is available for use in laboratory workers. Several vaccine constructs are in the pipeline for potential use in humans.

294.10

Japanese Encephalitis

Scott B. Halstead

JE is a mosquito-borne viral disease of humans, as well as horses, swine, and other domestic animals. The virus causes human infections and acute disease in a vast area of Asia, northern Japan, Korea, China, Taiwan, the Philippines, and the Indonesian archipelago and from Indochina through the Indian subcontinent. *Culex tritaeniorhynchus summarosus,* a night-biting mosquito that feeds preferentially on large domestic animals and birds but only infrequently on humans, is the principal vector of zoonotic and human JE in northern Asia. A more complex ecology prevails in southern Asia. From Taiwan to India, *C. tritaeniorhynchus* and members of the closely related *Culex vishnui* group are vectors. Before the introduction of JE vaccine, summer outbreaks of JE occurred regularly in Japan, Korea, China, Okinawa, and Taiwan. Over the past decade, there has been a pattern of steadily enlarging recurrent seasonal outbreaks in Vietnam, Thailand, Nepal, and India, with small outbreaks in the Philippines, Indonesia, and the northern tip of Queensland, Australia. Seasonal rains are accompanied by increases in mosquito populations and JE transmission. Pigs serve as an amplifying host.

The annual incidence in endemic areas ranges from 1-10 per 10,000 population. Children younger than 15 yr of age are principally affected, with nearly universal exposure by adulthood. The case:infection ratio for JE virus has been variously estimated at 1 : 25 to 1 : 1,000. Higher ratios have been estimated for populations indigenous to enzootic areas. JE occurs in travelers visiting Asia; therefore, a travel history in the diagnosis of encephalitis is critical.

After a 4- to 14-day incubation period, cases typically progress through the following four stages: prodromal illness (2-3 days), acute stage (3-4 days), subacute stage (7-10 days), and convalescence (4-7 wk). The onset may be characterized by an abrupt onset of fever, headache, respiratory symptoms, anorexia, nausea, abdominal pain, vomiting, and sensory changes, including psychotic episodes. Grand mal seizures are seen in 10–24% of children with JE;

parkinsonian-like nonintention tremor and cogwheel rigidity are seen less frequently. Particularly characteristic are rapidly changing central nervous system signs (e.g., hyperreflexia followed by hyporeflexia or plantar responses that change). The sensory status of the patient may vary from confusion through disorientation and delirium to somnolence, progressing to coma. There is usually a mild pleocytosis (100-1,000 leukocytes/µL) in the cerebrospinal fluid, initially polymorphonuclear but in a few days predominantly lymphocytic. Albuminuria is common. Fatal cases usually progress rapidly to coma, and the patient dies within 10 days.

JE should be suspected in patients reporting exposure to night-biting mosquitoes in endemic areas during the transmission season. The etiologic diagnosis of JE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a fourfold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by the polymerase chain reaction.

There is no specific treatment for JE. The treatment is intensive supportive care (see Chapter 85), including control of seizures (see Chapter 611).

Patient fatality rates for JE are 24–42% and are highest in children 5-9 yr of age and in adults older than 65 yr of age. The frequency of sequelae is 5–70% and is directly related to the age of the patient and severity of disease. Sequelae are most common in patients younger than 10 yr at the onset of disease. The more common sequelae are mental deterioration, severe emotional instability, personality changes, motor abnormalities, and speech disturbances.

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294.11

Tick-Borne Encephalitis

Scott B. Halstead

TBE refers to neurotropic tick-transmitted flaviviral infections occurring across the Eurasian land mass. In the Far East, the disease is called *Russian spring-summer encephalitis* ; the milder, often biphasic form in Europe is simply called TBE. TBE is found in all countries of Europe except Portugal and the Benelux countries. The incidence is particularly high in Austria, Poland, Hungary, Czech Republic, Slovakia, former Yugoslavia, and Russia. The incidence tends to be very focal. Seroprevalence is as high as 50% in farm and forestry workers. The majority of cases occur in adults, but even young children may be infected while playing in the woods or on picnics or camping trips. The seasonal distribution of cases is midsummer in southern Europe, with a longer season in Scandinavia and the Russian Far East. TBE can be excreted from the milk of goats, sheep, or cows. Before World War II, when unpasteurized milk was consumed, milk-borne cases of TBE were common.

Viruses are transmitted principally by hard ticks of *Ixodes ricinus* in Europe and *Ixodes persulcatus* in the Far East. Viral circulation is maintained by a combination of transmission from ticks to birds, rodents, and larger mammals and transstadial transmission from larval to nymphal and adult stages. In some parts of Europe and Russia, ticks feed actively during the spring and early fall, giving rise to the name *spring-summer encephalitis.*

After an incubation period of 7-14 days, the European form begins as an acute nonspecific febrile illness that is followed in 5–30% of cases by meningoencephalitis. The Far Eastern variety more often results in encephalitis with higher case fatality and sequelae rates. The first phase of illness is characterized by fever, headache, myalgia, malaise, nausea, and vomiting for 2-7 days. Fever disappears but after 2-8 days may return, accompanied by vomiting, photophobia, and signs of meningeal irritation in children and more severe encephalitic signs in adults. This phase rarely lasts more than 1 wk.

There is no specific treatment for TBE. The treatment is intensive supportive care (see Chapter 85), including control of seizures (see Chapter 611).

The main risk for a fatal outcome is advanced age; the fatality rate in adults is approximately 1%, but sequelae in children are rare. Transient unilateral paralysis of an upper extremity is a common finding in adults. Common sequelae include chronic fatigue, headache, sleep disorders, and emotional disturbances.

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294.12

Zika Virus

Scott B. Halstead

Epidemiology

Zika virus (ZIKV), a member of the *Flavivirus* genus, is maintained in complex African zoonotic cycles, spilling over from time to time into the *Aedes aegypti/Aedes albopictus* urban transmission cycles, possibly over a period of many years (Fig. 294.5). After the virus was discovered in Africa in 1947, human antibodies were found widely dispersed throughout tropical Asia. However, in all these locations, human ZIKV disease was mild and rare until in 2007, when there was an outbreak of a mild febrile exanthem on the Yap Islands in the western Pacific. Soon thereafter, an outbreak on Tahiti in 2013-2014 was followed in 4 wk by a small outbreak of Guillain-Barré syndrome (GBS). In 2015, a massive epidemic in South America was accompanied by focal reports, particularly in Brazil, of ZIKV infections of pregnant women that produced infected and damaged fetuses or newborns. The epidemiology of ZIKV infections is essentially identical to that of the dengue and chikungunya viruses. Residents of urban areas, particularly those without adequate sources of piped water, are at highest risk. *Aedes aegypti,* the principal vector mosquito, is very abundant and widespread throughout South and Central America, Mexico, and the Caribbean region. During the American pandemic, ZIKV was found to infect the male reproductive tract, be secreted in urine and saliva, and be sexually transmitted. By 2017, the ZIKV epidemic in the American tropics appeared to wane. During 2015-2016, large numbers of imported Zika infections, some in pregnant women, were reported in the United States and other temperate-zone developed countries. Small outbreaks of endogenous human Zika infections were reported in South Florida during the summer of 2016.

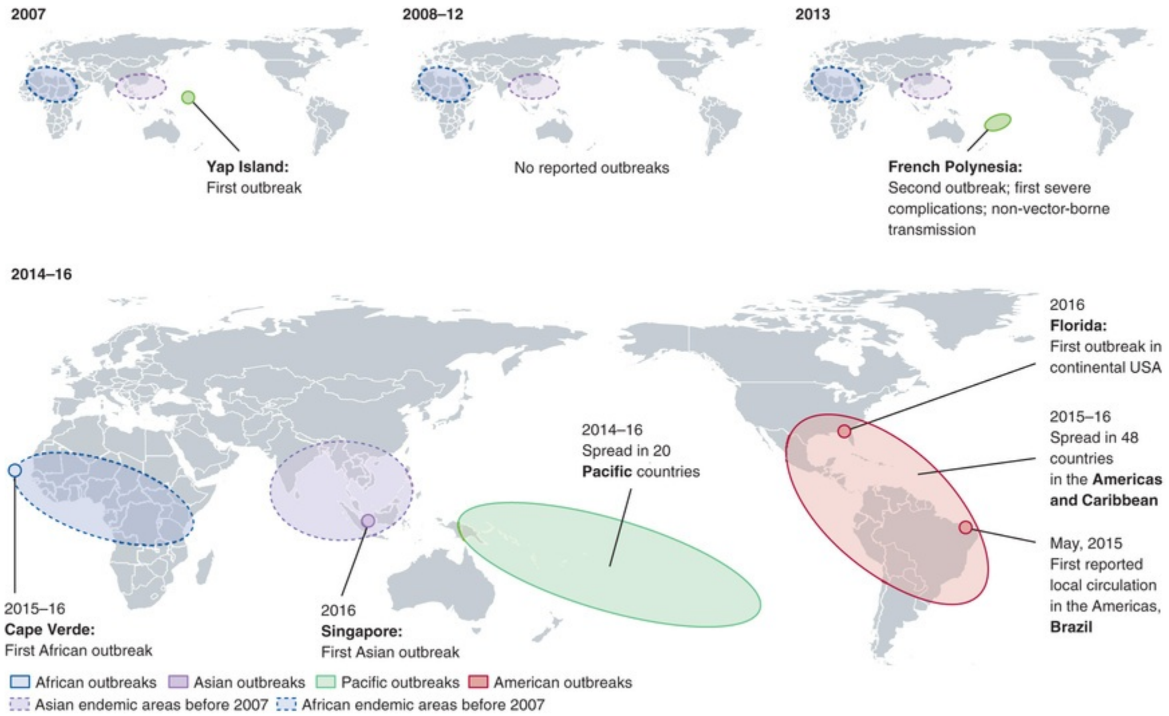
2007
Yap Island:
First outbreak
2008–12
No reported outbreaks
2013
French Polynesia:
Second outbreak; first severe complications; non-vector-borne transmission
2014–16
2016
Florida:
First outbreak in continental USA
2015–16
Spread in 48 countries in the Americas and Caribbean
2014–16
Spread in 20 Pacific countries
May, 2015
First reported local circulation in the Americas, Brazil
2015–16
Cape Verde:
First African outbreak
2016
Singapore:
First Asian outbreak
🟦 African outbreaks 🟪 Asian outbreaks 🟩 Pacific outbreaks 🟥 American outbreaks
⬚ Asian endemic areas before 2007 ⬚ African endemic areas before 2007

FIG. 294.5 Zika virus outbreaks from 2007 to 2016. (From Baud D, Gubler DJ, Schaub B, et al: An update on Zika virus infection, Lancet 390:2099-2109, 2017, Fig. 2.)

From the pediatric perspective, the most important outcome of human ZIKV infection is termed the *congenital Zika syndrome (CZS),* which consists of microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, irritability, seizures, arthrogryposis, ocular abnormalities, and sensorineural hearing loss (Table 294.1). A comprehensive understanding of the precise antecedents to CZS is not known. It appears that the earlier during pregnancy that ZIKV infections occur, the greater the likelihood of and the more severe the CZS. Vertical transmission appears to follow viremia with ZIKV, transiting the uterus to infect the placenta and then the fetus. However, factors that affect the occurrence or severity of CZS, such as age, ethnicity, or prior immune status of the mother, are not known. In vitro studies have demonstrated that dengue antibodies can enhance ZIKV infection in vitro, in Fc-receptor–bearing cells, but, as yet, there is no evidence that a prior dengue infection alters the chance of ZIKV crossing the placenta or increases the risk of CZS. Maternal-fetal transmission of ZIKV can occur during labor and delivery. There are no reports of ZIKV infection acquired by an infant at the time of delivery leading to microcephaly. There are no data to contraindicate breastfeeding, although the virus has been identified in breast milk. Maternal and newborn laboratory testing is indicated during the first 2 wk of life if the mother had relevant epidemiologic exposure within 2 wk of delivery and had clinical manifestations of ZIKV infection (e.g., rash, conjunctivitis, arthralgia, or fever). Infants and children who acquire ZIKV infection postnatally appear to have a mild course, similar to that seen in adults.

Table 294.1

Surveillance Case Classification: Children, Neonate to 2 Years of Age, Born to Mothers With Any Evidence of Zika Virus Infection During Pregnancy

ZIKA-ASSOCIATED BIRTH DEFECTS
Selected structural anomalies of the brain or eyes present at birth (congenital) and detected from birth to age 2 yr. Microcephaly at birth, with or without low birthweight, was included as a structural anomaly. • **Selected congenital brain anomalies:** intracranial calcifications; cerebral atrophy; abnormal cortical formation (e.g., polymicrogyria, lissencephaly, pachygyria, schizencephaly, gray matter heterotopia); corpus callosum abnormalities; cerebellar abnormalities; porencephaly; hydranencephaly; ventriculomegaly/hydrocephaly. • **Selected congenital eye anomalies:** microphthalmia or anophthalmia; coloboma; cataract; intraocular calcifications; chorioretinal anomalies involving the macula (e.g., chorioretinal atrophy and scarring, macular pallor, and gross pigmentary mottling), excluding retinopathy of prematurity; optic nerve atrophy, pallor, and other optic nerve abnormalities. • **Microcephaly at birth:** birth head circumference < 3rd percentile for infant sex and gestational age based on INTERGROWTH-21st online percentile calculator (http://intergrowth21.ndog.ox.ac.uk/).

NEURODEVELOPMENTAL ABNORMALITIES POSSIBLY ASSOCIATED WITH CONGENITAL ZIKA VIRUS INFECTION
Consequences of neurologic dysfunction detected from birth (congenital) to age 2 yr. Postnatal-onset microcephaly was included as a neurodevelopmental abnormality. • **Hearing abnormalities:** Hearing loss or deafness documented by testing, most frequently auditory brainstem response (ABR). Includes sensorineural hearing loss, mixed hearing loss, and hearing loss not otherwise specified. Failed newborn hearing screening is not sufficient for diagnosis. • **Congenital contractures:** Multiple contractures (arthrogryposis) and isolated clubfoot documented at birth. Brain anomalies must be documented for isolated clubfoot but not for arthrogryposis. • **Seizures:** Documented by electroencephalogram or physician report. Includes epilepsy or seizures not otherwise specified; excludes febrile seizures. • **Body tone abnormalities:** Hypertonia or hypotonia documented at any age in conjunction with (1) a failed screen or assessment for gross motor function; (2) suspicion or diagnosis of cerebral palsy from age 1 to 2 yr; or (3) assessment by a physician or other medical professional, such as a physical therapist. • **Movement abnormalities:** Dyskinesia or dystonia at any age; suspicion or diagnosis of cerebral palsy from age 1 to 2 yr. • **Swallowing abnormalities:** Documented by instrumented or noninstrumented evaluation, presence of a gastrostomy tube, or physician report. • **Possible developmental delay:** Abnormal result from most recent developmental screening (i.e., failed screen for gross motor domain or failed screen for two or more developmental domains at the same time point or age); developmental evaluation; or assessment review by developmental pediatrician. Results from developmental evaluation are considered the gold standard if available. • **Possible visual impairment:** Includes strabismus (esotropia or exotropia), nystagmus, failure to fix and follow at age < 1 yr; diagnosis of visual impairment at age ≥ 1 yr. • **Postnatal-onset microcephaly:** Two most recent head circumference measurements reported from follow-up care < 3rd percentile for child's sex and age based on World Health Organization child growth standards; downward trajectory of head circumference percentiles with most recent measurement < 3rd percentile. Age at measurement was adjusted for gestational age in infants born at < 40 wk of gestational age through age 24 mo chronologic age.

From Rice ME, Galang RR, Roth NM, et al: Vital signs: Zika-associated birth defects and neurodevelopmental abnormalities possibly associated with congenital Zika virus infection: US territories and freely associated states, 2018. MMWR 67(31):858-866, 2018.

Clinical Features

Congenital Zika syndrome may be defined in a fetus with diagnostic evidence of ZIKV infection, including (1) severe microcephaly (>3 SD below the mean), partially collapsed skull, overlapping cranial sutures, prominent occipital bone, redundant scalp skin, and neurologic impairment; (2) brain anomalies, including cerebral cortex thinning, abnormal gyral patterns, increased fluid spaces, subcortical calcifications, corpus callosum anomalies, reduced white matter, and cerebellar vermis hypoplasia; (3) ocular findings, such as macular scarring, focal pigmentary retinal mottling, structural anomalies (microphthalmia, coloboma, cataracts, and posterior anomalies), chorioretinal atrophy, or optic nerve hypoplasia/atrophy; (4) congenital contractures, including unilateral or bilateral clubfoot and arthrogryposis multiplex congenita; and (5) neurologic impairment, such as pronounced early hypertonia/spasticity with extrapyramidal symptoms, motor disabilities, cognitive disabilities, hypotonia, irritability/excessive crying, tremors, swallowing dysfunction, vision impairment, hearing impairment, and epilepsy (see Table 294.1).

Acquired Zika virus infection may present with nonspecific viral syndrome–like features. Nonetheless, patients are at increased risk of myelitis and Guillain-Barré syndrome. In addition, the virus may remain present in the blood and body fluids for months after resolution of clinical symptoms.

Management

For infants with confirmed Zika virus infection, close follow-up is necessary. The appropriate follow-up evaluation depends upon whether or not the infant has clinical signs and symptoms of congenital Zika syndrome. All infants should have close monitoring of growth and development, repeat ophthalmologic examinations, and auditory brainstem response testing (see Table 294.1).

Laboratory Diagnosis

Laboratory testing for Zika virus infection in the neonate includes the following: serum and urine for Zika virus RNA via real-time reverse transcription polymerase chain reaction (rRT-PCR) and serum Zika virus immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA). If the IgM is positive, the plaque reduction neutralization test (PRNT) is used to confirm the specificity of the IgM antibodies against Zika virus and to exclude a false-positive IgM result. If CSF is available, it should be tested for Zika virus RNA (via rRT-PCR), as well as Zika virus IgM. CSF specimens need not be collected for the sole purpose of Zika virus testing but may be reasonable for the evaluation of infants with microcephaly or intracranial calcifications. A definitive diagnosis of congenital Zika virus infection is confirmed by the presence of Zika virus RNA in samples of serum, urine, or CSF collected within the first 2 days of life; IgM antibodies may be positive or negative. A negative rRT-PCR result with a positive Zika virus IgM test result indicates probable congenital Zika virus infection.

Fetuses or infants born to mothers who test positive for ZIKV infection should be studied sonographically or for clinical evidence of congenital Zika syndrome, a comprehensive evaluation (including ophthalmologic examination, laboratory tests, and specialist consultation) should be performed prior to hospital discharge.

Prognosis

The prognosis of newborns with congenital Zika syndrome is unclear. Reported acute mortality rates among live-born infants range from 4% to 6%. The combination of Zika virus–related microcephaly and severe cerebral abnormalities generally has a poor prognosis, but little is known about the prognosis for congenitally infected infants with less severe or no apparent abnormalities at birth.

Differential Diagnosis

The differential diagnosis for congenital Zika virus infection includes other congenital infections and other causes of microcephaly.

Prevention

The prevention of the congenital Zika syndrome includes avoidance, if possible, of travel to endemic regions; if travel to endemic regions cannot be avoided, careful contraception (male and female) is essential, especially with the knowledge that Zika virus can persist in semen for months after a primary infection (Table 294.2).

Table 294.2

CDC Recommendations for Preconception Counseling and Prevention of Sexual Transmission of Zika Virus Among Persons With Possible Zika Virus Exposure: United States, August 2018

EXPOSURE SCENARIO	RECOMMENDATIONS (UPDATE STATUS)
Only the male partner travels to an area with risk for Zika virus transmission and couple is planning to conceive	The couple should use condoms or abstain from sex for at least 3 mo after the male partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). **(Updated recommendation)**
Only the female partner	The couple should use condoms or abstain from sex for at least 2 mo after the

travels to an area with risk for Zika virus transmission and couple is planning to conceive	female partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). **(No change in recommendation)** [*]
Both partners travel to an area with risk for Zika virus transmission and couple is planning to conceive	The couple should use condoms or abstain from sex for at least 3 mo from the male partner's symptom onset (if symptomatic) or last possible Zika virus exposure (if asymptomatic). **(Updated recommendation)**
One or both partners have ongoing exposure (i.e., live in or frequently travel to an area with risk for Zika virus transmission) and couple is planning to conceive	The couple should talk with their health care provider about their plans for pregnancy, their risk for Zika virus infection, the possible health effects of Zika virus infection on a baby, and ways to protect themselves from Zika. If either partner develops symptoms of Zika virus infection or tests positive for Zika virus infection, the couple should follow the suggested timeframes listed above before trying to conceive. **(No change in recommendation)** [*]
Men with possible Zika virus exposure whose partner is pregnant	The couple should use condoms or abstain from sex for the duration of the pregnancy. **(No change in recommendation)** [*]

[*] Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al: Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure—United States, September 2016, MMWR Morb Mortal Wkly Rep 65:1077–1081, 2016.

From Polen KD, Gilboa SM, Hills S, et al: Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for men with possible Zika virus exposure: United States, August 2018, MMWR 67(31):868–870, 2018.

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CHAPTER 295

Dengue Fever, Dengue Hemorrhagic Fever, and Severe Dengue

Scott B. Halstead

Dengue fever is a benign syndrome caused by several arthropod-borne viruses and is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia, and lymphadenopathy. **Dengue hemorrhagic fever** (Philippine, Thai, or Singapore hemorrhagic fever; hemorrhagic dengue; acute infectious thrombocytopenic purpura) is a severe, often fatal, febrile disease caused by one of four dengue viruses. It is characterized by capillary permeability, abnormalities of hemostasis, and, in severe cases, a protein-losing shock syndrome **(dengue shock syndrome),** which is thought to have an immunopathologic basis.

A revised case definition adopted by the World Health Organization (WHO) in 2009 includes as **severe dengue** those cases accompanied by fluid loss leading to shock, fluid loss with respiratory distress, liver damage evidenced by elevations of ALT or AST to > 1000 U/L, severe bleeding, and altered consciousness or significant heart abnormalities.

Etiology

There are at least four distinct antigenic types of dengue virus (dengue 1, 2, 3, and 4), members of the family Flaviviridae. In addition, three other arthropod-borne viruses (arboviruses) cause similar dengue fever syndromes with rash (Table 295.1 ; see also Chapter 294).

Table 295.1

Vectors and Geographic Distribution of Dengue-Like

Diseases

VIRUS	GEOGRAPHIC GENUS AND DISEASE	VECTOR	DISTRIBUTION
Togavirus	Chikungunya	*Aedes aegypti*	Africa, India, Southeast Asia, Latin America, United States
		Aedes africanus	
		Aedes albopictus	
Togavirus	O'nyong-nyong	*Anopheles funestus*	East Africa
Flavivirus	West Nile fever	*Culex molestus*	Europe, Africa, Middle East, India
		Culex univittatus	

Epidemiology

Dengue viruses are transmitted by mosquitoes of the Stegomyia family. *Aedes aegypti,* a daytime biting mosquito, is the principal vector, and all four virus types have been recovered from it. Transmission occurs from viremic humans by bite of the vector mosquito where virus multiplies during an extrinsic incubation period and then by bite is passed on to a susceptible human in what is called the urban transmission cycle. In most tropical areas, *A. aegypti* is highly urbanized, breeding in water stored for drinking or bathing and in rainwater collected in any container. Dengue viruses have also been recovered from *Aedes albopictus,* as in the 2001 and 2015 Hawaiian epidemics, whereas outbreaks in the Pacific area have been attributed to several other *Aedes* species. These species breed in water trapped in vegetation. In Southeast Asia and West Africa, dengue virus may be maintained in a cycle involving canopy-feeding jungle monkeys and *Aedes* species, which feed on monkeys.

In the 19th and 20th centuries, epidemics were common in temperate areas of the Americas, Europe, Australia, and Asia. Dengue fever and dengue-like disease are now endemic in tropical Asia, the South Pacific Islands, northern Australia, tropical Africa, the Arabian Peninsula, the Caribbean, and Central and South America (Fig. 295.1). Dengue fever occurs frequently among travelers to these areas. Locally acquired disease has been reported in Florida, Arizona, and Texas, and imported cases in the United States occur in travelers to endemic areas. More than 390 million dengue infections occur annually; approximately 96 million have clinical disease.

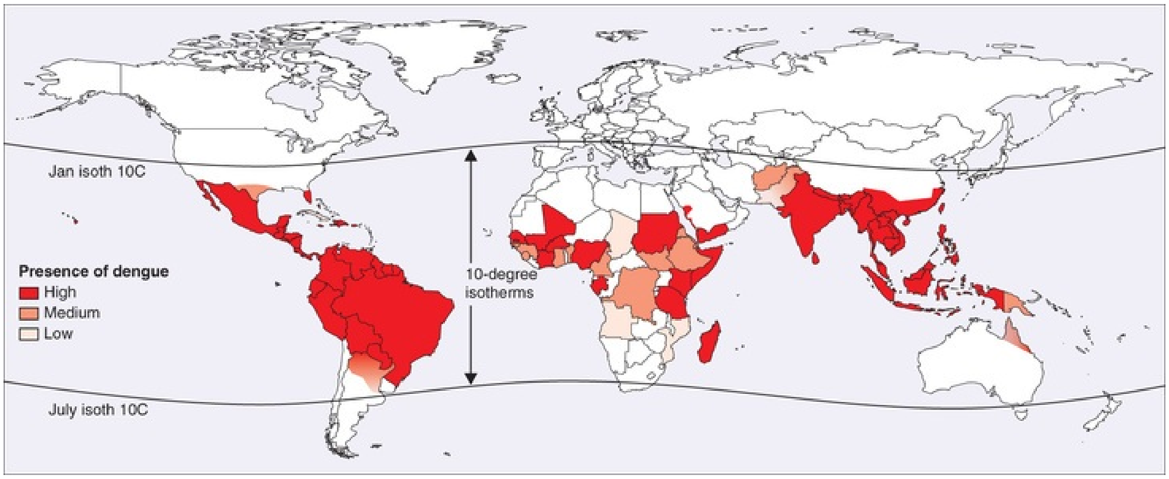

FIG. 295.1 Global dengue burden, 2014. (From Guzman MG, Harris E: Dengue, Lancet 385:453-462, 2015, Fig. 1.)

Dengue outbreaks in urban areas infested with *A. aegypti* may be explosive; in virgin soil epidemics, up to 70–80% of the population may be involved. Most overt disease occurs in older children and adults. Because *A. aegypti* has a limited flight range, spread of an epidemic occurs mainly through viremic human beings and follows the main lines of transportation. Sentinel cases may infect household mosquitoes; a large number of nearly simultaneous secondary infections give the appearance of a contagious disease. Where dengue is highly endemic, children and susceptible foreigners may be the only persons to acquire overt disease, because adults have become immune.

Dengue-Like Diseases

Dengue-like diseases may occur in epidemics. Epidemiologic features depend on the vectors and their geographic distribution (see Chapter 294). Chikungunya virus is enzootic in subhuman primates throughout much of West, Central, and South Africa. Periodic introductions of virus into the urban transmission cycle have led to pandemics, resulting in widespread endemicity in the most populous areas of Asia. In Asia, *A. aegypti* is the principal vector; in Africa, other Stegomyia species may be important vectors. In Southeast Asia, dengue and chikungunya outbreaks occur concurrently in the urban cycle. Outbreaks of o'nyong-nyong fever usually involve villages or small towns, in contrast to the urban outbreaks of dengue and chikungunya. West Nile virus is enzootic in Africa. Chikungunya is now endemic in urban cycles in tropical countries throughout the world. Intense transmission in Caribbean and Central and South

American countries beginning in 2013 results in the emergence of limited chikungunya transmission in the United States.

Dengue Hemorrhagic Fever

Dengue hemorrhagic fever occurs where multiple types of dengue virus are simultaneously or sequentially transmitted. It is endemic in tropical America, Asia, the Pacific Islands, and parts of Africa, where warm temperatures and the practices of water storage in homes plus outdoor breeding sites result in large, permanent populations of *A. aegypti*. Under these conditions, infections with dengue viruses of all types are common. A first infection, referred to as a primary infection, may be followed by infection with a different dengue virus, referred to as a secondary infection. In areas of high endemicity, secondary infections are frequent.

Secondary dengue infections are relatively mild in the majority of instances, ranging from an inapparent infection through an undifferentiated upper respiratory tract or dengue-like disease, but may also progress to dengue hemorrhagic fever. Nonimmune foreigners, both adults and children, who are exposed to dengue virus during outbreaks of hemorrhagic fever have classic dengue fever or even milder disease. The differences in clinical manifestations of dengue infections between natives and foreigners in Southeast Asia are related to immunologic status. Dengue hemorrhagic fever can occur during primary dengue infections, most frequently in infants whose mothers are immune to dengue. Dengue hemorrhagic fever or severe dengue occurs rarely in individuals of African ancestry because of an as yet incompletely described resistance gene that is consistent with the low incidence of severe dengue throughout much of Africa and among African populations in the American tropics despite high rates of dengue infection.

Pathogenesis

The pathogenesis of dengue hemorrhagic fever is incompletely understood, but epidemiologic studies usually associate this syndrome with second heterotypic infections with dengue types 1-4 or in infants born to mothers who have had two or more lifetime dengue infections. Retrospective studies of sera from human mothers whose infants acquired dengue hemorrhagic fever and prospective studies in children acquiring sequential dengue infections have shown that the circulation of infection-enhancing antibodies at the time of infection is the strongest risk factor for development of severe disease. The absence of cross-reactive neutralizing antibodies and presence of enhancing antibodies from passive transfer or active production are the best correlates of risk for dengue hemorrhagic fever. Monkeys that are infected sequentially or are receiving small quantities of enhancing antibodies have enhanced viremias. In humans studied early during the course of secondary dengue infections, viremia levels directly predicted disease severity. When dengue virus immune complexes attach to monocyte/macrophage Fc receptors, a signal is sent that suppresses innate immunity, resulting in enhanced viral production. In the Americas, dengue hemorrhagic fever and dengue shock syndrome have been associated with dengue types 1-4 strains of recent Southeast Asian origin. Outbreaks of dengue hemorrhagic fever in all areas of the world are correlated with secondary dengue infections while recent outbreaks in India, Pakistan, and Bangladesh are related to imported dengue strains.

Early in the acute stage of secondary dengue infections, there is rapid activation of the complement system. Shortly before or during shock, blood levels of soluble tumor necrosis factor receptor, interferon-γ, and interleukin-2 are elevated. C1q, C3, C4, C5-C8, and C3 proactivators are depressed, and C3 catabolic rates are elevated. Circulating viral nonstructural protein 1 (NS1) is a viral toxin that activates myeloid cells to release cytokines by attaching to toll receptor 4. It also contributes to increased vascular permeability by activating complement, interacting with and damaging endothelial cells, and interacting with blood clotting factors and platelets. The mechanism of bleeding in dengue hemorrhagic fever is not known, but a mild degree of disseminated intravascular coagulopathy, liver damage, and thrombocytopenia may operate synergistically. Capillary damage allows fluid, electrolytes, small proteins, and, in some instances, red blood cells to leak into extravascular spaces. This internal redistribution of fluid, together with deficits caused by fasting, thirsting, and vomiting, results in hemoconcentration, hypovolemia, increased cardiac work, tissue hypoxia, metabolic acidosis, and hyponatremia.

Usually no pathologic lesions are found to account for death. In rare instances, death may be a result of gastrointestinal or intracranial hemorrhages. Minimal to moderate hemorrhages are seen in the upper gastrointestinal tract, and petechial hemorrhages are common in the interventricular septum of the heart, on the pericardium, and on the subserosal surfaces of major viscera. Focal hemorrhages are occasionally seen in the lungs, liver, adrenals, and subarachnoid space. The liver is usually enlarged, often with fatty changes. Yellow, watery, and at times blood-tinged effusions are present in serous cavities in approximately 75% of patients at autopsy.

Dengue virus is frequently absent in tissues at the time of death; viral antigens or RNA have been localized to hepatocytes and macrophages in the liver, spleen, lung, and lymphatic tissues.

Clinical Manifestations

Dengue Fever

The incubation period is 1-7 days. The clinical manifestations are variable and are influenced by the age of the patient. In infants and young children, the disease may be undifferentiated or characterized by fever for 1-5 days, pharyngeal inflammation, rhinitis, and mild cough. A majority of infected older children and adults experience sudden onset of fever, with temperature rapidly increasing to 39.4-41.1°C (103-106°F), usually accompanied by frontal or retroorbital pain, particularly when pressure is applied to the eyes. Occasionally, severe back pain precedes the fever (back-break fever). A transient, macular, generalized rash that blanches under pressure may be seen during the first 24-48 hr of fever. The pulse rate may be slow relative to the degree of fever. Myalgia and arthralgia occur soon after the onset of fevers and increase in severity over time. From the second to sixth day of fever, nausea and vomiting are apt to occur, and generalized lymphadenopathy, cutaneous hyperesthesia or hyperalgesia, taste aberrations, and pronounced anorexia may develop.

Approximately 1-2 days after defervescence, a generalized, morbilliform, maculopapular rash appears that spares the palms and soles. It disappears in 1-5 days; desquamation may occur. Rarely there is edema of the palms and soles. About the time this second rash appears, the body temperature, which has previously decreased to normal, may become slightly elevated and demonstrate the characteristic biphasic temperature pattern.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome (DHF/DSS)

The differentiation between dengue fever and dengue hemorrhagic fever is difficult early in the course of illness. A relatively mild first phase with abrupt onset of fever, malaise, vomiting, headache, anorexia, and cough may be followed after 2-5 days by rapid clinical deterioration and collapse. In this second phase, the patient usually has cold, clammy extremities, a warm trunk, flushed face, diaphoresis, restlessness, irritability, midepigastric pain, and decreased urinary output. Frequently, there are scattered petechiae on the forehead and extremities; spontaneous ecchymoses may appear, and easy bruising and bleeding at sites of venipuncture are common. A macular or maculopapular rash may appear, and there may be circumoral and peripheral cyanosis. Respirations are rapid and often labored. The pulse is weak, rapid, and thready, and the heart sounds are faint. The liver may enlarge to 4-6 cm below the costal margin and is usually firm and somewhat tender. Approximately 20–30% of cases of dengue hemorrhagic fever are complicated by shock (dengue shock syndrome). Dengue shock can be subtle, arising in patients who are fully alert, and is accompanied by increased peripheral vascular resistance and raised diastolic blood pressure. Shock is not from congestive heart failure but from venous pooling. With increasing cardiovascular compromise, the diastolic pressure rises toward the systolic level and the pulse pressure narrows. Fewer than 10% of patients have gross ecchymosis or gastrointestinal bleeding, usually after a period of uncorrected shock. After a 24- to 36-hr period of crisis, convalescence is fairly rapid in the children who recover. The temperature may return to normal before or during the stage of shock. Bradycardia and ventricular extrasystoles are common during convalescence.

Dengue With Warning Signs and Severe Dengue

In hyperendemic areas, among Asian children, the DHF/DSS continues to be the dominant life-threatening event, always challenging to an identifying physician using classical WHO diagnostic criteria. When the four dengue viruses spread to the American hemisphere and to South Asia, there were millions of primary and secondary dengue infections, many of them adults of all ages. Dengue disease in these areas presented a wider clinical spectrum resulting in a new diagnostic algorithm and case definitions (see below).

Diagnosis

A clinical diagnosis of dengue fever derives from a high index of suspicion and knowledge of the geographic distribution and environmental cycles of causal viruses (for nondengue causes see Chapter 294). Because clinical findings vary and there are many possible causative agents, the term *dengue-like disease* should be used until a specific diagnosis is established. A case is confirmed by isolation of the virus, viral antigen, or genome by polymerase chain reaction analysis, the detection of IgM dengue antibodies as well as demonstration of a four-fold or greater increase in antibody titers. A probable case is a typical acute febrile illness with supportive serology and occurrence at a location where there are confirmed cases.

The WHO criteria for **dengue hemorrhagic fever** are fever (2-7 days in duration or biphasic), minor or major hemorrhagic manifestations including a positive tourniquet test, thrombocytopenia (≤100,000/µL), and objective evidence of increased capillary permeability (hematocrit increased by ≥ 20%), pleural effusion or ascites (by chest radiography or ultrasonography), or hypoalbuminemia. **Dengue shock syndrome** criteria include those for dengue hemorrhagic fever as well as hypotension, tachycardia, narrow pulse pressure (≤20 mm Hg), and signs of poor perfusion (cold extremities).

In 2009, the WHO promulgated guidelines for the diagnosis of probable dengue, dengue with warning signs, and a category called severe dengue (Fig. 295.2). The presence of warning signs in an individual with probable dengue alerts the physician to the possible need for hospitalization. Severe dengue is a mixture of syndromes associated with dengue infection, including classical DHF/DSS, but also rare instances of encephalitis or encephalopathy, liver damage, or myocardial damage. Severe dengue also includes respiratory distress, a harbinger of pulmonary edema caused by overhydration, an all too common outcome of inexpert treatment (see Treatment and Complications sections).

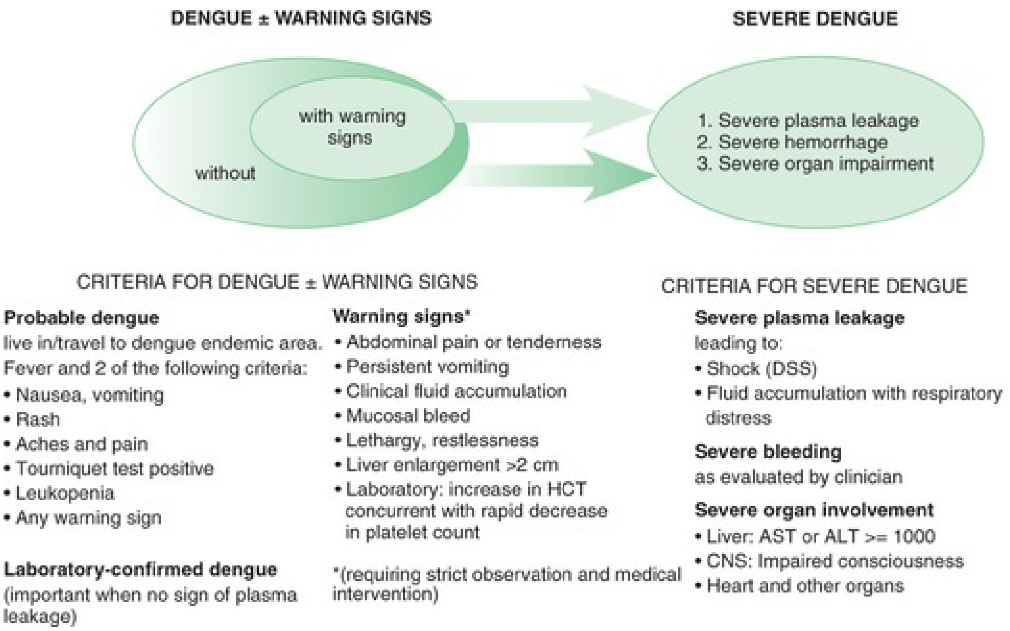

CRITERIA FOR DENGUE ± WARNING SIGNS

Probable dengue
live in/travel to dengue endemic area.
Fever and 2 of the following criteria:

- Nausea, vomiting
- Rash
- Aches and pain
- Tourniquet test positive
- Leukopenia
- Any warning sign

Laboratory-confirmed dengue
(important when no sign of plasma leakage)

Warning signs*

- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargement >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)

CRITERIA FOR SEVERE DENGUE

Severe plasma leakage
leading to:

- Shock (DSS)
- Fluid accumulation with respiratory distress

Severe bleeding
as evaluated by clinician

Severe organ involvement

- Liver: AST or ALT >= 1000
- CNS: Impaired consciousness
- Heart and other organs

FIG. 295.2 Suggested dengue case classification and levels of severity. (From World Health Organization (WHO) and Special Programme for Research and Training in Tropical Diseases (TDR): 2009 Dengue: guidelines for diagnosis, treatment, prevention and control, Fig. 1.4, http://apps.who.int/iris/bitstream/handle/10665/44188/9789241547871_eng.pdf?sequence=1 .)

Virologic diagnosis can be established by serologic tests, by detection of viral proteins or viral RNA, or by the isolation of the virus from blood leukocytes or acute-phase serum. Following primary and secondary dengue infections, there is an appearance of antidengue (immunoglobulin [Ig] M) antibodies. These disappear after 6-12 wk, a feature that can be used to date a dengue infection. In secondary dengue infections, most dengue antibody is of the IgG class. Serologic diagnosis depends on a four-fold or greater increase in IgG antibody titer in paired sera by hemagglutination inhibition, complement fixation, enzyme immunoassay, or neutralization test. Carefully standardized IgM and IgG capture enzyme commercial immunoassays are now widely used to identify acute-phase antibodies from patients with primary or secondary dengue infections in single-serum samples. Usually such samples should be collected not earlier than 5 days and not later than 6 wk after onset. It may not be possible to distinguish the infecting virus by serologic methods alone, particularly when there has been prior infection with another member of the same arbovirus group. Virus can be recovered from acute-phase serum after inoculating tissue culture or living mosquitoes. Viral RNA can be detected in blood or tissues by specific complementary RNA probes or amplified first by polymerase chain reaction or by real-time polymerase chain reaction. A viral nonstructural protein, NS1, is released by infected cells into the circulation and can be detected in acute-stage blood samples using monoclonal or polyclonal antibodies. The detection of NS1 is the basis of commercial tests, including rapid lateral flow tests. These tests offer a reliable point-of-care diagnosis of acute dengue infection.

Differential Diagnosis

The differential diagnosis of dengue fever includes dengue-like diseases, viral respiratory and influenza-like diseases, the early stages of malaria, mild yellow fever, scrub typhus, viral hepatitis, and leptospirosis.

Four arboviral diseases have dengue-like courses but without rash: Colorado tick fever, sandfly fever, Rift Valley fever, and Ross River fever (see Chapter 294). Colorado tick fever occurs sporadically among campers and hunters in the western United States; sandfly fever in the Mediterranean region, the Middle East, southern Russia, and parts of the Indian subcontinent; and Rift Valley fever in North, East, Central, and South Africa. Ross River fever is endemic in much of eastern Australia, with epidemic extension to Fiji. In adults, Ross River fever often produces protracted and crippling arthralgia involving weight-bearing joints.

Because meningococcemia, yellow fever (see Chapter 296), other viral hemorrhagic fevers (see Chapter 297), many rickettsial diseases, and other severe illnesses caused by a variety of agents may produce a clinical picture similar to dengue hemorrhagic fever, the etiologic diagnosis should be made only when epidemiologic or serologic evidence suggests the possibility of a dengue infection.

Laboratory Findings

In dengue fever, pancytopenia may develop after the 3-4 days of illness. Neutropenia may persist or reappear during the latter stage of the disease and may continue into convalescence, with white blood cell counts < 2,000/µL. Platelet counts rarely fall below 100,000/µL. Venous clotting, bleeding and prothrombin times, and plasma fibrinogen values are within normal ranges. The tourniquet test result may be positive. Mild acidosis, hemoconcentration, increased transaminase values, and hypoproteinemia may occur during some primary dengue virus infections. The electrocardiogram may show sinus bradycardia, ectopic ventricular foci, flattened T waves, and prolongation of the P-R interval.

The most common hematologic abnormalities during dengue hemorrhagic fever and dengue shock syndrome are hemoconcentration with an increase of > 20% in the hematocrit, thrombocytopenia, a prolonged bleeding time, and a moderately decreased prothrombin level that is seldom < 40% of control. Fibrinogen levels may be subnormal, and fibrin split-product values are elevated. Other abnormalities include moderate elevations of serum transaminase levels, consumption of complement, mild metabolic acidosis with hyponatremia, occasionally hypochloremia, slight elevation of serum urea nitrogen, and hypoalbuminemia. Roentgenograms of the chest reveal pleural effusions (right > left) in nearly all patients with dengue shock syndrome. Ultrasonography can be used to detect serosal effusions of the thorax or abdomen. Thickening of the gallbladder wall and the presence of perivesicular fluid are characteristic signs of increased vascular permeability.

Treatment

Treatment of uncomplicated dengue fever is supportive. Bed rest is advised during the febrile period. Antipyretics should be used to keep the body temperature < 40°C (104°F). Analgesics or mild sedation may be required to control pain. Aspirin is contraindicated and should not be used because of its effects on hemostasis. Fluid and electrolyte replacement is required for deficits caused by sweating, fasting, thirsting, vomiting, and diarrhea.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Dengue shock syndrome is a medical emergency that may occur in any child who lives in or has a recent travel history to a tropical destination. Management begins with diagnostic suspicion and the understanding that shock often accompanies defervescence. Detailed instructions for case management are available at the Geneva or New Delhi WHO websites: http://www.who.int/csr/don/archive/disease/dengue_fever/dengue.pdf . Management of dengue hemorrhagic fever and dengue shock syndrome includes immediate evaluation of vital signs and degrees of hemoconcentration, dehydration, and electrolyte imbalance. Close monitoring is essential for at least 48 hr because shock may occur or recur precipitously, usually several days after the onset of fever. Patients who are cyanotic or have labored breathing should be given oxygen. Rapid intravenous replacement of fluids and electrolytes can frequently sustain patients until spontaneous recovery occurs. Normal saline is more effective than the more expensive Ringer lactated saline in treating shock. When the pulse pressure is ≤10 mm Hg or when elevation of the hematocrit persists after the replacement of fluids, plasma or colloid preparations are indicated. Oral rehydration of children who are being monitored is useful. Prophylactic platelet transfusions have not been shown to reduce the risk of hemorrhaging or improve low platelet counts and may be associated with adverse effects.

Care must be taken to avoid overhydration, which may contribute to cardiac failure. Transfusions of fresh blood may be required to control bleeding but should not be given during hemoconcentration but only after evaluation of hemoglobin or hematocrit values. Salicylates are contraindicated because of their effect on blood clotting.

Sedation may be required for children who are markedly agitated. Use of vasopressors has not resulted in a significant reduction of mortality rates over that observed with simple supportive therapy. Disseminated intravascular coagulation may require treatment (see Chapter 510). Corticosteroids do not shorten the duration of disease or improve the prognosis in children receiving careful supportive therapy.

Complications

Hypervolemia during the fluid reabsorptive phase may be life-threatening and is heralded by a decrease in hematocrit with wide pulse pressure. Diuretics and digitalization may be necessary.

Primary infections with dengue fever and dengue-like diseases are usually self-limited and benign. Fluid and electrolyte losses, hyperpyrexia, and febrile convulsions are the most frequent complications in infants and young children. Epistaxis, petechiae, and purpuric lesions are uncommon but may occur at any stage. Blood from epistaxis that is swallowed, vomited, or passed by rectum may be erroneously interpreted as gastrointestinal bleeding. In adults and possibly in children, underlying conditions may lead to clinically significant bleeding.

Convulsions may occur during a high temperature. Infrequently, after the febrile stage, prolonged asthenia, mental depression, bradycardia, and ventricular extrasystoles may occur in children.

In endemic areas, dengue hemorrhagic fever should be suspected in children with a febrile illness suggestive of dengue fever who experience hemoconcentration and thrombocytopenia.

Prognosis

Dengue Fever

The prognosis for dengue fever is good. Care should be taken to avoid the use of drugs that suppress platelet activity.

Dengue Hemorrhagic Fever

The prognosis of dengue hemorrhagic fever is adversely affected by a late diagnosis and delayed or improper treatment. Death has occurred in 40–50% of patients with shock, but with adequate intensive care, deaths should occur in < 1% of cases. Infrequently, there is residual brain damage as a consequence of prolonged shock or occasionally of intracranial hemorrhage. Many fatalities are caused by overhydration.

Prevention

Dengue vaccines have been under development continuously since the 1970s. One such vaccine, Dengvaxia, developed by Sanofi Pasteur, is a mixture of four chimeras, DENV structural genes coupled with nonstructural genes of yellow fever 17D. In 2015, Dengvaxia completed phase III per protocol analyses on 32,568 children, vaccinated and controls, ages 2-16 yr. These studies revealed poor protection of seronegatives and good protection of seropositives with a reduction of hospitalization and severe disease in vaccinated children 9 yr old versus controls. Based on these data, this vaccine was endorsed by the WHO for targeted use in individuals 9 yr of age and older, living in countries that are highly endemic for dengue; it now is licensed for use in 14 countries. Other dengue type 1-4 vaccines are under development by the U.S. National Institutes of Health and Instituto Butantan in Sao Paulo, Brazil, and Takeda, Inc.

Dengvaxia seronegative recipients who were incompletely protected were apparently sensitized to experience the enhanced disease of hospitalized dengue.

Prophylaxis in the absence of vaccine consists of avoiding daytime household-based mosquito bites through the use of insecticides, repellents, body covering with clothing, screening of houses, and destruction of *A. aegypti* breeding sites. If water storage is mandatory, a tight-fitting lid or a thin layer of oil may prevent egg laying or hatching. A larvicide, such as Abate (O,O′-[thiodi-*p* -phenylene] O,O,O,O′-tetramethyl phosphorothioate), available as a 1% sand-granule formation and effective at a concentration of 1 ppm, may be added safely to drinking water. Ultra-low-volume spray equipment effectively dispenses the adulticide malathion from trucks or airplanes for rapid intervention during an epidemic. Mosquito repellants and other personal antimosquito measures are effective in preventing mosquito bites in the field, forest, or jungle.

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CHAPTER 296

Yellow Fever

Scott B. Halstead

Yellow fever is an acute infection characterized in its most severe form by fever, jaundice, proteinuria, and hemorrhage. The virus is mosquito-borne and occurs in epidemic or endemic form in South America and Africa. Seasonal epidemics occurred in cities located in temperate areas of Europe and the Americas until 1900, and epidemics continue in West, Central, and East Africa.

Etiology

Yellow fever is the prototype of the *Flavivirus* genus of the family Flaviviridae, which are enveloped single-stranded RNA viruses 35-50 nm in diameter.

Yellow fever circulates zoonotically as five genotypes: type IA in West Central Africa, type IB in South America, type II in West Africa, type III in East Central Africa, and type IV in East Africa. Types IA and IB virus are capable of urban transmission between human beings by *Aedes aegypti*. Sometime in the 1600s, yellow fever virus was brought to the American tropics through the African slave trade. Subsequently, yellow fever caused enormous coastal and riverine epidemics in the Atlantic and Caribbean basins until the 20th century, when the virus and its urban and sylvan mosquito cycles were identified, mosquito control methods were perfected, and a vaccine was developed. The East and East/Central African genotypes have not fully entered the urban cycle and have not spread to the East Coast of Africa or to the countries of Asia.

Epidemiology

Human and nonhuman primate hosts acquire the yellow fever infection by the bite of infected mosquitoes. After an incubation period of 3-6 days, virus appears in the blood and may serve as a source of infection for other mosquitoes. The virus must replicate in the gut of the mosquito and pass to the salivary gland before the mosquito can transmit the virus. Yellow fever virus is transmitted in an urban cycle—human to *A. aegypti* to human—and a jungle cycle—monkey to jungle mosquitoes to monkey. Classic yellow fever epidemics in the United States, South America, the Caribbean, and parts of Europe were of the urban variety. Since 2000, West Africa has experienced five urban epidemics, including in the capital cities of Abidjan (Cote d'Ivoire), Conakry (Guinea), and Dakar (Senegal). In 2012-2013, large outbreaks of East and East/Central yellow fever occurred across a large, predominantly rural area of war-ravaged Darfur in southwestern Sudan and in adjacent areas of northern Uganda. Beginning in 2015 and continuing to mid-2016, there were sharp outbreaks of yellow fever in and around Rwanda, Angola, and the bordering Democratic Republic of Congo, where there were 7,000 reported cases and 500 deaths. Eleven cases were imported into China by workers in Angola. In South America, all of the approximately 200 cases reported each year are jungle yellow fever. In late 2016 and continuing through 2018, a widespread zoonosis resulted in an estimated 2,000 yellow fever cases in Brazil. In colonial times, urban yellow fever attack rates in white adults were very high, suggesting that subclinical infections are uncommon in this age-group. Yellow fever may be less severe in children, with subclinical infection:clinical case ratios ≥ 2:1. In areas where outbreaks of urban yellow fever are common, most cases involve children because many adults are immune. Transmission in West Africa is highest during the rainy season, from July to November.

In tropical forests, yellow fever virus is maintained in a transmission cycle involving monkeys and tree hole–breeding mosquitoes (*Haemagogus* in Central and South America; the *Aedes africanus* complex in Africa). In the Americas, most cases involve tourists, campers, those who work in forested areas, and vacationers exposed to infected mosquitoes. In Africa, enzootic virus is prevalent in moist savanna and savanna transition areas, where other tree hole–breeding *Aedes* vectors transmit the virus between monkeys and humans and between humans.

Pathogenesis

Pathologic changes seen in the liver include (1) coagulative necrosis of hepatocytes in the midzone of the liver lobule, with sparing of cells around the portal areas and central veins; (2) eosinophilic degeneration of hepatocytes **(Councilman bodies);** (3) microvacuolar fatty change; and (4) minimal inflammation. The kidneys show acute tubular necrosis. In the heart, myocardial fiber degeneration and fatty infiltration are seen. The brain may show edema and petechial hemorrhages. Direct viral injury to the liver results in impaired ability to perform functions of biosynthesis and detoxification; this is the central pathogenic event of yellow fever. Hemorrhage is postulated to result from decreased synthesis of vitamin K–dependent clotting factors and, in some cases, disseminated intravascular clotting. However, because the pathogenesis of shock in patients with yellow fever appears similar to that described for dengue shock syndrome and the other viral hemorrhagic fevers, viral damage to platelets and endothelial cells resulting in the release of prohemorrhagic factors may be the central mechanism of hemorrhage in yellow fever. Death and severe disease rates are lower in susceptible subSaharan African blacks than in other racial groups, suggesting existence of a resistance gene.

Renal dysfunction has been attributed to hemodynamic factors (prerenal failure progressing to acute tubular necrosis).

Clinical Manifestations

In Africa, inapparent, abortive, or clinically mild infections are frequent; some studies suggest that children experience a milder disease than do adults. Abortive infections, characterized by fever and headache, may be unrecognized except during epidemics.

In its classic form, yellow fever begins with a sudden onset of fever, headache, myalgia, lumbosacral pain, anorexia, nausea, and vomiting. Physical findings during the early phase of illness, when virus is present in the blood, include prostration, conjunctival injection, flushing of the face and neck, reddening of the tongue at the tip and edges, and relative bradycardia. After 2-3 days, there may be a brief period of remission, followed in 6-24 hr by the reappearance of fever with vomiting, epigastric pain, jaundice, dehydration, gastrointestinal and other hemorrhages, albuminuria, hypotension, renal failure, delirium, convulsions, and coma. Death may occur after 7-10 days, with the fatality rate in severe cases approaching 50%. Some patients who survive the acute phase of illness later succumb to renal failure or myocardial damage. Laboratory abnormalities include leukopenia; prolonged clotting, prothrombin, and partial thromboplastin times; thrombocytopenia; hyperbilirubinemia; elevated serum transaminase values; albuminuria; and azotemia. Hypoglycemia may be present in severe cases. Electrocardiogram abnormalities such as bradycardia and ST-T changes are described.

Diagnosis

Yellow fever should be suspected when fever, headache, vomiting, myalgia, and jaundice appear in residents of enzootic areas or in unimmunized visitors who have recently traveled (within 2 wk Before the onset of symptoms) to endemic areas. There are clinical similarities between yellow fever and dengue hemorrhagic fever. In contrast to the gradual onset of acute viral hepatitis resulting from hepatitis A, B, C, D, or E virus, jaundice in yellow fever appears after 3-5 days of high temperature and is often accompanied by severe prostration. Mild yellow fever is dengue-like and cannot be distinguished from a wide variety of other infections. Jaundice and fever may occur in any of several other tropical diseases, including malaria, viral hepatitis, louse-borne relapsing fever, leptospirosis, typhoid fever, rickettsial infections, certain systemic bacterial infections, sickle cell crisis, Rift Valley fever, Crimean-Congo hemorrhagic fever, and other viral hemorrhagic fevers. Outbreaks of yellow fever always include cases with severe gastrointestinal hemorrhage.

The specific diagnosis depends on the detection of the virus or viral antigen in acute-phase blood samples or antibody assays. The immunoglobulin M enzyme immunoassay is particularly useful. Sera obtained during the first 10 days after the onset of symptoms should be kept in an ultra-low-temperature freezer (−70°C [−94°F]) and shipped on dry ice for virus testing. Convalescent-phase samples for antibody tests are managed by conventional means. In handling acute-phase blood specimens, medical personnel must take care to avoid contaminating themselves or others on the evacuation trail (laboratory personnel and others). The postmortem diagnosis is based on virus isolation from liver or blood, identification of Councilman bodies in liver tissue, or detection of antigen or viral genome in liver tissue.

Treatment

It is customary to keep patients with yellow fever in a mosquito-free area, with use of mosquito nets if necessary. Patients are viremic during the febrile phase of the illness. Although there is no specific treatment for yellow fever, medical care is directed at maintaining the physiologic status with the following measures: (1) sponging and acetaminophen to reduce a high temperature, (2) vigorous fluid replacement of losses resulting from fasting, thirsting, vomiting, or plasma leakage, (3) correcting an acid-base imbalance, (4) maintaining nutritional intake to lessen the severity of hypoglycemia, and (5) avoiding drugs that are either metabolized by the liver or toxic to the liver, kidney, or central nervous system.

Complications

Complications of acute yellow fever include severe hemorrhage, liver failure, and acute renal failure. Bleeding should be managed by transfusion of fresh whole blood or fresh plasma with platelet concentrates if necessary. Renal failure may require peritoneal dialysis or hemodialysis.

Prevention

Yellow fever 17D is a live-attenuated vaccine with a long record of safety and efficacy. It is administered as a single 0.5-mL subcutaneous injection at least 10 days before arrival in a yellow fever–endemic area. YF-VAX, manufactured by Sanofi Pasteur, is licensed for use in the United States. With the exceptions noted later, individuals traveling to endemic areas in South America and Africa should be considered for vaccination, but the length of stay, exact locations to be visited, and environmental or occupational exposure may determine the specific risk and individual need for vaccination. Persons traveling from yellow fever–endemic to yellow fever–receptive countries may be required by national authorities to obtain a yellow fever vaccine (e.g., from South America or Africa to India). Usually, countries that require travelers to obtain a yellow fever immunization do not issue a visa without a valid immunization certificate. Vaccination is valid for 10 yr for international travel certification, although immunity lasts at least 40 yr and probably for life. Immunoglobulin M antibodies circulate for years after administration of yellow fever vaccine.

Since 1996, there have been a number of reports of *yellow fever vaccine–associated viscerotropic disease* with a higher risk in elderly vaccine recipients and a few cases in persons with previous thymectomies. Yellow fever vaccine should not be administered to persons who have symptomatic immunodeficiency diseases, are taking immunosuppressant drugs, have HIV, or have a history of thymectomy. A recent study has shown that individuals taking maintenance corticosteroids may be successfully vaccinated. Although the vaccine is not known to harm fetuses, its administration during pregnancy is not advised. The vaccine virus may be rarely transmitted through breastfeeding. In very young children, there is a small risk of encephalitis and death after yellow fever 17D vaccination. The 17D vaccine should not be administered to infants younger than 6 mo. Residence in or travel to areas of known or anticipated yellow fever activity (e.g., forested areas in the Amazon basin), which puts an individual at high risk, warrants immunization of infants 6-8 mo of age. Immunization of children 9 mo of age and older is routinely recommended before entry into endemic areas. Immunization of persons older than 60 yr of age should be weighed against their risk for sylvatic yellow fever in the American tropics and for urban or sylvatic yellow fever in Africa. Vaccination should be avoided in persons with a history of egg allergy. Alternatively, a skin test can be performed to determine whether a serious allergy exists that would preclude vaccination.

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CHAPTER 297

Ebola and Other Viral Hemorrhagic Fevers

Scott B. Halstead

Viral hemorrhagic fevers are a loosely defined group of clinical syndromes in which hemorrhagic manifestations are either common or especially notable in severe illness. Both the etiologic agents and clinical features of the syndromes differ, but coagulopathy may be a common pathogenetic feature.

Etiology

Six of the viral hemorrhagic fevers are caused by arthropod-borne viruses (arboviruses) (Table 297.1). Four are caused by togaviruses of the family **Flaviviridae:** Kyasanur Forest disease, Omsk hemorrhagic fever, dengue (see Chapter 295), and yellow fever (see Chapter 296) viruses. Three are caused by viruses of the family **Bunyaviridae:** Congo fever, Hantaan fever, and Rift Valley fever (RVF) viruses. Four are caused by viruses of the family **Arenaviridae:** Junin fever, Machupo fever, Guanarito fever, and Lassa fever. Two are caused by viruses in the family **Filoviridae** : Ebola virus and Marburg virus, enveloped, filamentous RNA viruses that are sometimes branched, unlike any other known virus.

Table 297.1

Viral Hemorrhagic Fevers

MODE OF TRANSMISSION	DISEASE	VIRUS
Tick-borne	Crimean-Congo hemorrhagic fever (HF)*	Congo
	Kyasanur Forest disease	Kyasanur Forest disease
	Omsk HF	Omsk

Mosquito-borne [†]	Dengue HF	Dengue (4 types)
	Rift Valley fever	Rift Valley fever
	Yellow fever	Yellow fever
Infected animals or materials to humans	Argentine HF	Junin
	Bolivian HF	Machupo
	Lassa fever[*]	Lassa
	Marburg disease[*]	Marburg
	Ebola HF[*]	Ebola
	HF with renal syndrome	Hantaan

[*] Patients may be contagious; nosocomial infections are common.

[†] Chikungunya virus is associated infrequently with petechiae and epistaxis. Severe hemorrhagic manifestations have been reported in some cases.

Epidemiology

With some exceptions, the viruses causing viral hemorrhagic fevers are transmitted to humans via a nonhuman entity. The specific ecosystem required for viral survival determines the geographic distribution of disease. Although it is commonly thought that all viral hemorrhagic fevers are arthropod borne, seven may be contracted from environmental contamination caused by animals or animal cells or from infected humans (see Table 297.1). Laboratory and hospital infections have occurred with many of these agents. Lassa fever and Argentine and Bolivian hemorrhagic fevers are reportedly milder in children than in adults.

Crimean-Congo Hemorrhagic Fever

Sporadic human infection with Crimean-Congo hemorrhagic fever in Africa provided the original virus isolation. Natural foci are recognized in Bulgaria, western Crimea, and the Rostov-on-Don and Astrakhan regions; disease occurs in Central Asia from Kazakhstan to Pakistan. Index cases were followed by nosocomial transmission in Pakistan and Afghanistan in 1976, in the Arabian Peninsula in 1983, and in South Africa in 1984. In the Russian Federation, the vectors are ticks of the species *Hyalomma marginatum* and *Hyalomma anatolicum,* which, along with hares and birds, may serve as viral reservoirs. Disease occurs from June to September, largely among farmers and dairy workers.

Kyasanur Forest Disease

Human cases of Kyasanur Forest disease occur chiefly in adults in an area of Mysore State, India. The main vectors are two Ixodidae ticks, *Haemaphysalis turturis* and *Haemaphysalis spinigera*. Monkeys and forest rodents may be amplifying hosts. Laboratory infections are common.

Omsk Hemorrhagic Fever

Omsk hemorrhagic fever occurs throughout south-central Russia and northern Romania. Vectors may include *Dermacentor pictus* and *Dermacentor marginatus*, but direct transmission from moles and muskrats to humans seems well established. Human disease occurs in a spring–summer–autumn pattern, paralleling the activity of vectors. This infection occurs most frequently in persons with outdoor occupational exposure. Laboratory infections are common.

Rift Valley Fever

The virus causing RVF is responsible for epizootics involving sheep, cattle, buffalo, certain antelopes, and rodents in North, Central, East, and South Africa. The virus is transmitted to domestic animals by *Culex theileri* and several *Aedes* species. Mosquitoes may serve as reservoirs by transovarial transmission. An epizootic in Egypt in 1977-1978 was accompanied by thousands of human infections, principally among veterinarians, farmers, and farm laborers. Smaller outbreaks occurred in Senegal in 1987, Madagascar in 1990, and Saudi Arabia and Yemen in 2000-2001. Humans are most often infected during the slaughter or skinning of sick or dead animals. Laboratory infection is common.

Argentine Hemorrhagic Fever

Before the introduction of vaccine, hundreds to thousands of cases of Argentine hemorrhagic fever occurred annually from April through July in the maize-producing area northwest of Buenos Aires that reaches to the eastern margin of the Province of Cordoba. Junin virus has been isolated from the rodents *Mus musculus, Akodon arenicola,* and *Calomys laucha*. It infects migrant laborers who harvest the maize and who inhabit rodent-contaminated shelters.

Bolivian Hemorrhagic Fever

The recognized endemic area of Bolivian hemorrhagic fever consists of the sparsely populated province of Beni in Amazonian Bolivia. Sporadic cases occur in farm families who raise maize, rice, yucca, and beans. In the town of San Joaquin, a disturbance in the domestic rodent ecosystem may have led to an outbreak of household infection caused by Machupo virus transmitted by chronically infected *Calomys callosus*, ordinarily a field rodent. Mortality rates are high in young children.

Venezuelan Hemorrhagic Fever

In 1989, an outbreak of hemorrhagic illness occurred in the farming community of Guanarito, Venezuela, 200 miles south of Caracas. Subsequently, in 1990-1991, there were 104 cases reported with 26 deaths caused by Guanarito virus. Cotton rats *(Sigmodon alstoni)* and cane rats *(Zygodontomys brevicauda)* have been implicated as likely reservoirs of Venezuelan hemorrhagic fever.

Lassa Fever

Lassa virus has an unusual potential for human-to-human spread, which has resulted in many small epidemics in Nigeria, Sierra Leone, and Liberia. In 2012, an outbreak of more than 1,000 cases of Lassa fever occurred in east-central Nigeria. Medical workers in Africa and the United States have also contracted the disease. Patients with acute Lassa fever have been transported by international aircraft, necessitating extensive surveillance among passengers and crews. The virus is probably maintained in nature in a species of African peridomestic rodent, *Mastomys natalensis*. Rodent-to-rodent transmission and infection of humans probably operate via mechanisms established for other arenaviruses.

Marburg Disease

Previously, the world experience of human infections caused by Marburgvirus had been limited to 26 primary and 5 secondary cases in Germany and Yugoslavia in 1967 and to small outbreaks in Zimbabwe in 1975, Kenya in 1980 and 1988, and South Africa in 1983. However, in 1999 a large outbreak occurred in the Republic of Congo, and in 2005 a still larger outbreak occurred in Uige Province, Angola, with 252 cases and 227 deaths. In laboratory and clinical settings, transmission occurs by direct contact with tissues of the African green monkey or with infected human blood or semen. A reservoir in bats has been demonstrated. It appears that the virus is transmitted by close contact between fructivorous bats and from bats by aerosol to humans.

Ebola Hemorrhagic Fever

Ebola virus was isolated in 1976 from a devastating epidemic involving small villages in northern Zaire and southern Sudan; smaller outbreaks have occurred subsequently. Outbreaks have initially been nosocomial. Attack rates have been highest in children from birth to 1 yr of age and persons from 15 to 50 yr of age. The virus is in the *Filovirus* family and closely related to viruses of the genus Marburg virus. An Ebola virus epidemic occurred in Kikwit, Zaire, in 1995, followed by scattered outbreaks in Uganda and Central and West Africa. The virus has been recovered from chimpanzees, and antibodies have been found in other subhuman primates, which apparently acquire infection from a zoonotic reservoir in bats. The natural reservoir of Ebola is believed to be fruit bats. Reston virus, related to Ebola virus, has been recovered from Philippine monkeys and pigs and has caused subclinical infections in humans working in monkey colonies in the United States.

In 2014, West Africa experienced the largest outbreak of Ebola virus disease (EVD) in history and the first transmission in a large urban area (Fig. 297.1). Countries primarily affected were Liberia, Sierra Leone, and Guinea, with imported cases reported in Nigeria, Mali, and Senegal, as well as Europe and the United States. The outbreak was caused by the Zaire Ebola virus (species of Ebola virus include the Zaire, Sudan, Bundibugyo, Reston, and Tai Forest species), which has a mortality rate of approximately 55–65%. As of 8 May 2016, the World Health Organization (WHO) and respective governments reported a total of 28,616 suspected cases and 11,310 deaths (39.5%), though the WHO believes that this substantially understates the magnitude of the outbreak. The outbreak had largely subsided by the end of 2015. In 2018, an outbreak occurred in the Democratic Republic of the Congo, affecting more than 500 people (aged 8-80 yr), with a case fatality of approximately 50% (Fig. 297.2).

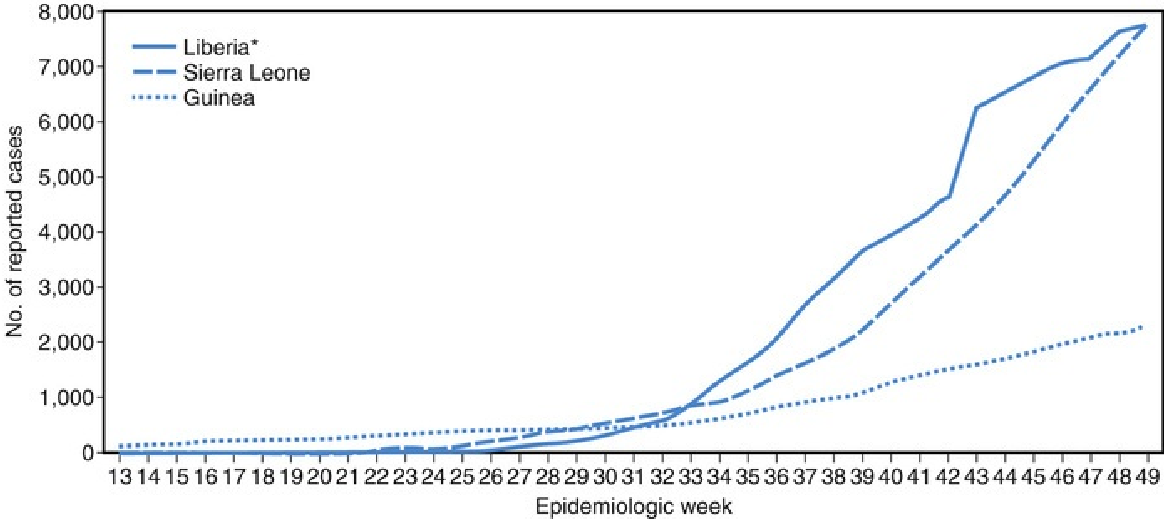

FIG. 297.1 Cumulative number of Ebola virus disease cases reported—three countries, West Africa, April 13, 2016. Reported from Sierra Leone (14,124 cases) and Liberia (10,678), followed by Guinea (3,814). (Data from the number of cases and deaths in Guinea, Liberia, and Sierra Leone during the 2014-2016 West Africa Ebola Outbreak. Accessed at https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html.)

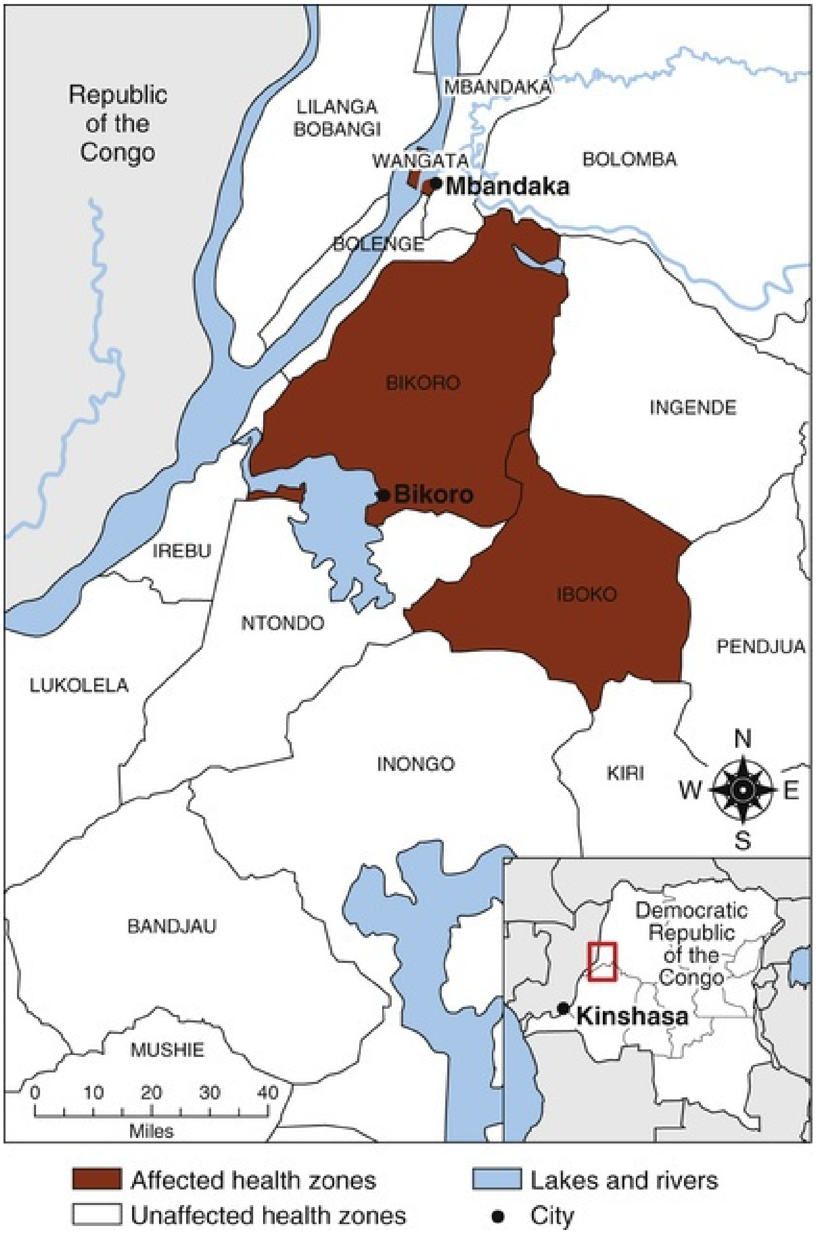
Republic of the Congo
LILANGA BOBANGI
MBANDAKA
WANGATA
Mbandaka
BOLOMBA
BOLENGE
BIKORO
INGENDE
Bikoro
IREBU
IBOKO
NTONDO
PENDJUA
LUKOLELA
INONGO
KIRI
N
W
E
S
BANDJAU
Democratic Republic of the Congo
Kinshasa
MUSHIE
0 10 20 30 40
Miles
Affected health zones
Unaffected health zones
Lakes and rivers
City

FIG. 297.2 Map of Ebola-affected health zones in the Democratic Republic of the Congo (DRC), 2018. (Courtesy of the Centers for Disease Control and Prevention, 2018. Accessed at https://www.cdc.gov/vhf/ebola/outbreaks/drc/drc-map.html .)

EVD may occur following exposure to fruit bats or bushmeat but most often occurs through exposure to body fluids of infected individuals (blood, sweat, saliva, vomitus, diarrhea, and less often human milk or semen) (Table 297.2). Persistent infection after recovery from acute EVD has been well documented, with virus particles present in body fluids such as semen for many months in apparently healthy survivors. Patients are infectious once they are symptomatic;

the incubation period is 2-21 days (mean: 11 days). The age range in the West African epidemic was broad, but most patients were between 15 and 44 yr old.

Table 297.2

Clinical Recommendations for Ebola Virus Infection

RECOMMENDATION	POPULATION	INTERVENTION
1	Oral rehydration	Patients with suspected, probable, or confirmed Ebola virus disease
2	Parenteral administration of fluids	Patients with suspected, probable, or confirmed Ebola virus disease who are unable to drink or who have inadequate oral intake
3	Systematic monitoring and charting of vital signs and volume status	Patients with suspected, probable, or confirmed Ebola virus disease
4	Serum biochemistry	Patients with suspected, probable, or confirmed Ebola virus disease
5	Staffing ratio	Patients with suspected, probable, or confirmed Ebola virus disease
6	Communication with family and friends	Patients with suspected, probable, or confirmed Ebola virus disease
7	Analgesic therapy	Patients with suspected, probable, or confirmed Ebola virus disease who are in pain
8	Antibiotics	Patients with suspected, probable, or confirmed Ebola virus disease with high severity of illness

*Confidence is based on the quality of the evidence for the main outcome.

Modified from Lamontagne F, Fowler RA, Adhikari NK, et al: Evidence-based guidelines for supportive care of patients with Ebola virus disease, Lancet 391:700-708, 2018,Table 2.

Hemorrhagic Fever With Renal Syndrome

The endemic area of hemorrhagic fever with renal syndrome (HFRS), also known as *epidemic hemorrhagic fever* and *Korean hemorrhagic fever,* includes Japan, Korea, far eastern Siberia, north and central China, European and Asian Russia, Scandinavia, Czechoslovakia, Romania, Bulgaria, Yugoslavia, and Greece. Although the incidence and severity of hemorrhagic manifestations and the mortality rates are lower in Europe than in northeastern Asia, the renal lesions are the same. Disease in Scandinavia, **nephropathia epidemica,** is caused by a different although antigenically related virus, Puumala virus, associated with the bank vole, *Clethrionomys glareolus.* Cases occur predominantly in the spring and summer. There appears to be no age factor in susceptibility, but because of occupational hazards, young adult men are most frequently attacked. Rodent plagues and evidence of rodent infestation have accompanied endemic and epidemic occurrences. Hantaan virus has been detected in the lung tissue and excreta of *Apodemus agrarius coreae*. Antigenically related agents have been detected in laboratory rats and in urban rat populations around the world, including Prospect Hill virus in the wild rodent *Microtus pennsylvanicus* in North America and *sin nombre* virus in the deer mouse in the southern and southwestern United States; these viruses are causes of hantavirus pulmonary syndrome (see Chapter 299). Rodent-to-rodent and rodent-to-human transmission presumably occurs via the respiratory route.

Clinical Manifestations

Dengue hemorrhagic fever (see Chapter 295) and yellow fever (see Chapter 296) cause similar syndromes in children in endemic areas.

Crimean-Congo Hemorrhagic Fever

The incubation period of 3-12 days is followed by a febrile period of 5-12 days and a prolonged convalescence. Illness begins suddenly with fever, severe headache, myalgia, abdominal pain, anorexia, nausea, and vomiting. After 1-2 days, the fever may subside until the patient experiences an erythematous facial or truncal flush and injected conjunctivae. A second febrile period of 2-6 days then develops, with a hemorrhagic enanthem on the soft palate and a fine petechial rash on the chest and abdomen. Less frequently, there are large areas of purpura and bleeding from the gums, nose, intestines, lungs, or uterus. Hematuria and proteinuria are relatively rare. During the hemorrhagic stage, there is usually tachycardia with diminished heart sounds and occasionally hypotension. The liver is usually enlarged, but there is no icterus. In protracted cases, central nervous system signs include delirium, somnolence, and progressive clouding of the consciousness. Early in the disease, leukopenia with relative lymphocytosis, progressively worsening thrombocytopenia, and gradually increasing anemia occur. In convalescence there may be hearing and memory loss. The mortality rate is 2–50%.

Kyasanur Forest Disease and Omsk Hemorrhagic Fever

After an incubation period of 3-8 days, both Kyasanur Forest disease and Omsk hemorrhagic fever begin with the sudden onset of fever and headache. Kyasanur Forest disease is characterized by severe myalgia, prostration, and bronchiolar involvement; it often manifests without hemorrhage but occasionally with severe gastrointestinal bleeding. In Omsk hemorrhagic fever, there is moderate epistaxis, hematemesis, and a hemorrhagic enanthem but no profuse hemorrhage; bronchopneumonia is common. In both diseases, severe leukopenia and thrombocytopenia, vascular dilation, increased vascular permeability, gastrointestinal hemorrhages, and subserosal and interstitial petechial hemorrhages occur. Kyasanur Forest disease may be complicated by acute degeneration of the renal tubules and focal liver damage. In many patients, recurrent febrile illness may follow an afebrile period of 7-15 days. This second phase takes the form of a meningoencephalitis.

Rift Valley Fever

Most RVF infections have occurred in adults with signs and symptoms resembling those of dengue fever (see Chapter 295). The onset is acute, with fever, headache, prostration, myalgia, anorexia, nausea, vomiting, conjunctivitis, and lymphadenopathy. The fever lasts 3-6 days and is often biphasic. The convalescence is often prolonged. In the 1977-1978 outbreak, many patients died after showing signs that included purpura, epistaxis, hematemesis, and melena. RVF affects the uvea and posterior chorioretina; macular scarring, vascular occlusion, and optic atrophy occur, resulting in permanent visual loss in a high proportion of patients with mild to severe RVF. At autopsy, extensive eosinophilic degeneration of the parenchymal cells of the liver has been observed.

Argentine, Venezuelan, and Bolivian Hemorrhagic Fevers and Lassa Fever

The incubation period in Argentine, Venezuelan, and Bolivian hemorrhagic fevers and Lassa fever is commonly 7-14 days; the acute illness lasts for 2-4 wk. Clinical illnesses range from undifferentiated fever to the characteristic severe illness. **Lassa fever** is most often clinically severe in white persons. The onset is usually gradual, with increasing fever, headache, diffuse myalgia, and anorexia (Table 297.3). During the first wk., signs frequently include a sore throat, dysphagia, cough, oropharyngeal ulcers, nausea, vomiting, diarrhea, and pains in the chest and abdomen. Pleuritic chest pain may persist for 2-3 wk. In Argentine and Bolivian hemorrhagic fevers and less frequently in Lassa fever, a petechial enanthem appears on the soft palate 3-5 days after onset and at about the same time on the trunk. The tourniquet test may be positive. The clinical course of Venezuelan hemorrhagic fever has not been well described.

Table 297.3

Clinical Stages of Lassa Fever

STAGE	SYMPTOMS
1 (days 1-3)	General weakness and malaise. High fever > 39°C (102.2°F), constant with peaks of 40-41°C (104-105.8°F)
2 (days 4-7)	Sore throat (with white exudative patches) very common; headache; back, chest, side, or abdominal pain; conjunctivitis; nausea and vomiting; diarrhea; productive cough; proteinuria; low blood pressure (systolic < 100 mm Hg); anemia
3 (after 7 days)	Facial edema; convulsions; mucosal bleeding (mouth, nose, eyes); internal bleeding; confusion or disorientation
4 (after 14 days)	Coma and death

From Richmond JK, Baglole DJ: Lassa fever: epidemiology, clinical features, and social consequences, BMJ 327:1271-1275, 2003.

In 35–50% of patients, these diseases may become severe, with persistent high temperature, increasing toxicity, swelling of the face or neck, microscopic hematuria, and frank hemorrhages from the stomach, intestines, nose, gums, and uterus. A syndrome of **hypovolemic shock** is accompanied by pleural effusion and renal failure. **Respiratory distress** resulting from airway obstruction, pleural effusion, or congestive heart failure may occur. A total of 10–20% of patients experience late neurologic involvement, characterized by intention tremor of the tongue and associated speech abnormalities. In severe cases, there may be intention tremors of the extremities, seizures, and delirium. The cerebrospinal fluid is normal. In Lassa fever, nerve deafness occurs in early convalescence in 25% of cases. Prolonged convalescence is accompanied by alopecia and, in Argentine and Bolivian hemorrhagic fevers, by signs of autonomic nervous system lability, such as postural hypotension, spontaneous flushing or blanching of the skin, and intermittent diaphoresis.

Laboratory studies reveal marked leukopenia, mild to moderate thrombocytopenia, proteinuria, and, in Argentine hemorrhagic fever, moderate abnormalities in blood clotting, decreased fibrinogen, increased fibrinogen split products, and elevated serum transaminases. There is focal, often extensive eosinophilic necrosis of the liver parenchyma, focal interstitial pneumonitis, focal necrosis of the distal and collecting tubules, and partial replacement of splenic follicles by amorphous eosinophilic material. Usually bleeding occurs by diapedesis with little inflammatory reaction. The mortality rate is 10–40%.

Marburg Disease and Ebola Hemorrhagic Fever

After an incubation period of 4-7 days, the illness begins abruptly, with severe frontal headache, malaise, drowsiness, lumbar myalgia, vomiting, nausea, and diarrhea. A **maculopapular** eruption begins 5-7 days later on the trunk and upper arms. It becomes generalized and often hemorrhagic and exfoliates during convalescence. The exanthem is accompanied by a dark red enanthem on the hard palate, conjunctivitis, and scrotal or labial edema. Gastrointestinal hemorrhage occurs as the severity of illness increases. Late in the illness, the patient may become tearfully depressed, with marked hyperalgesia to tactile stimuli. In fatal cases, patients become hypotensive, restless, and confused and lapse into coma. Convalescent patients may experience alopecia and may have paresthesias of the back and trunk. There is a marked leukopenia with necrosis of granulocytes. Dysfunction in bleeding and clotting and thrombocytopenia are universal and correlated with the severity of disease; there are moderate abnormalities in concentrations of clotting proteins and elevations of serum transaminases and amylase. Pregnant women and young children are at high risk of severe disease with a fatal outcome. The mortality rate of Marburg disease is 25–85%, and the mortality rate of Ebola hemorrhagic fever 50–90%. High viral loads in acute-phase blood samples convey a poor prognosis. Viral RNA persists in tissues long after symptoms subside, and the virus has been excreted in semen more than 1 yr after recovery.

Manifestations of EVD may come in stages, but most EVD begins with the sudden onset of fever accompanied by fatigue, weakness, myalgias, headache, and sore throat. This is followed by gastrointestinal involvement, including anorexia, nausea, abdominal pain, vomiting, and diarrhea. Hemorrhage (defined by any evidence of bleeding) is seen in more than 50% and is a serious later phase, often accompanied by vascular leakage, multiorgan failure, and death. Those who survive improve on approximately days 6-11 of EVD. One late relapse, producing meningoencephalitis, has been reported.

Hemorrhagic Fever With Renal Syndrome

In most cases, HFRS is characterized by fever, petechiae, mild hemorrhagic phenomena, and mild proteinuria, followed by a relatively uneventful recovery. In 20% of recognized cases, the disease may progress through four distinct phases. The febrile phase is ushered in with fever, malaise, and facial and truncal flushing. It lasts 3-8 days and ends with thrombocytopenia, petechiae, and proteinuria. The hypotensive phase, of 1-3 days, follows defervescence. Loss of fluid from the intravascular compartment may result in marked hemoconcentration. Proteinuria and ecchymoses increase. The oliguric phase, usually 3-5 days in duration, is characterized by a low output of protein-rich urine, increasing nitrogen retention, nausea, vomiting, and dehydration. Confusion, extreme restlessness, and hypertension are common. The diuretic phase, which may last for days or weeks, usually initiates clinical improvement. The kidneys show little concentrating ability, and rapid loss of fluid may result in severe dehydration and shock. Potassium and sodium depletion may be severe. Fatal cases manifest as abundant protein-rich retroperitoneal edema and marked hemorrhagic necrosis of the renal medulla. The mortality rate is 5–10%.

Diagnosis

The diagnosis of these viral hemorrhagic fevers depends on a high index of suspicion in endemic areas. In nonendemic areas, histories of recent travel, recent laboratory exposure, or exposure to an earlier case should evoke suspicion of a viral hemorrhagic fever.

In all viral hemorrhagic fevers, the viral agent circulates in the blood at least transiently during the early febrile stage. Togaviruses and bunyaviruses can be recovered from acute-phase serum samples by inoculation into a tissue culture or living mosquitoes. Argentine, Bolivian, and Venezuelan hemorrhagic fever viruses can be isolated from acute-phase blood or throat washings by intracerebral inoculation into guinea pigs, infant hamsters, or infant mice. Lassa virus may be isolated from acute-phase blood or throat washings by inoculation into tissue cultures. For Marburg disease and Ebola hemorrhagic fever, acute-phase throat washings, blood, and urine may be inoculated into a tissue culture, guinea pigs, or monkeys. The viruses are readily identified on electron microscopy, with a filamentous structure differentiating them from all other known agents. Specific complement-fixing and immunofluorescent antibodies appear during convalescence. The virus of HFRS is recovered from acute-phase serum or urine by inoculation into a tissue culture. A variety of antibody tests using viral subunits is becoming available. The serologic diagnosis depends on the demonstration of seroconversion or a four-fold or greater increase in immunoglobulin G antibody titer in acute and convalescent serum specimens collected 3-4 wk apart. Viral RNA may also be detected in blood or tissues with the use of reverse transcriptase polymerase chain reaction analysis.

The diagnosis of EVD is confirmed by enzyme-linked immunosorbent assay immunoglobulin M and polymerase chain reaction (which may need to be repeated if initially negative) testing. Criteria to aid in the diagnosis of EVD include temperature > 38.6°C (101.5°F) plus symptoms; contact with an affected patient, the patient's body fluids, or the funeral; residence in or travel to an endemic region; or a history of handling bats, rodents, or primates from an endemic area.

Handling blood and other biologic specimens is hazardous and must be performed by specially trained personnel. Blood and autopsy specimens should be placed in tightly sealed metal containers, wrapped in absorbent material inside a sealed plastic bag, and shipped on dry ice to laboratories with biocontainment safety level 4 facilities. Even routine hematologic and biochemical tests should be done with extreme caution.

Differential Diagnosis

Mild cases of hemorrhagic fever may be confused with almost any self-limited systemic bacterial or viral infection. More severe cases may suggest typhoid fever; epidemic, murine, or scrub typhus; leptospirosis; or a rickettsial spotted fever, for which effective chemotherapeutic agents are available. Many of these disorders may be acquired in geographic or ecologic locations endemic for a viral hemorrhagic fever.

The differential diagnosis of EVD includes malaria, typhoid, Lassa fever, influenza infection, and meningococcemia.

Treatment

Ribavirin administered intravenously is effective in reducing mortality rates in Lassa fever and HFRS. Further information and advice about the management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Viral Special Pathogens Branch, Atlanta, Georgia 30333 (470-312-0094).

The therapeutic principle involved in all of these diseases, especially HFRS, is the reversal of dehydration, hemoconcentration, renal failure, and protein, electrolyte, or blood losses (see Table 297.2). The contribution of disseminated intravascular coagulopathy to the hemorrhagic manifestations is unknown, and the management of hemorrhage should be individualized. Transfusions of fresh blood and platelets are frequently given. Good results have been reported in a few patients after the administration of clotting factor concentrates. The efficacy of corticosteroids, ε-aminocaproic acid, pressor amines, and α-adrenergic blocking agents has not been established. Sedatives should be selected with regard to the possibility of kidney or liver damage. The successful management of HFRS may require renal dialysis.

Whole-blood transfusions from Ebola virus–immune donors and administration of Ebola monoclonal antibodies have been shown to be effective in lowering case fatality rates.

Patients suspected of having Lassa fever, Ebola fever, Marburg fever, or Congo-Crimean hemorrhagic fever should be placed in a private room on standard contact and droplet precautions. Caretakers should use barrier precautions to prevent skin or mucous membrane exposure. All persons entering the patient's room should wear gloves and gowns and face shields. Before exiting the patient's room, caretakers should safely remove and dispose of all protective gear and should clean and disinfect shoes. Protocols require two-person clinical care teams, one observer and one caregiver (see CDC website: www.cdc.gov/vhf/ebola).

Treatment of EVD often requires an intensive care unit and management of multiorgan system dysfunction, including correction of hypovolemia, hyponatremia, hypokalemia, hypoalbuminemia, hypocalcemia, and hypoxia, often with renal replacement therapy as well as ventilation support (Table 297.2). Convalescent serum and monoclonal antibodies have been employed on an experimental basis. Strict isolation and appropriate barrier protection of healthcare workers is mandatory. Several vaccines have been shown to be immunogenic, and one used late in the epidemic was protective. Epidemic control measures, isolation, and quarantine have been used to attempt to decrease the spread of the West African epidemic.

Prevention

A live-attenuated vaccine (Candid-I) for Argentine hemorrhagic fever (Junin virus) is highly efficacious. A form of inactivated mouse brain vaccine is reported to be effective in preventing Omsk hemorrhagic fever. Inactivated RVF vaccines are widely used to protect domestic animals and laboratory workers. HFRS inactivated vaccine is licensed in Korea, and killed and live-attenuated vaccines are widely used in China. A vaccinia-vector glycoprotein vaccine provides protection against Lassa fever in monkeys. Single doses of recombinant vesicular stomatitis virus or adenovirus type 3 vaccines containing surface glycoproteins from Ebola and Marburg viruses have been shown to protect monkeys against Ebola virus and Marburg virus disease. The vesicular stomatitis-vectored Ebola vaccine was shown to be effective in preventing Ebola cases in a ring vaccination trial in Guinea and has been used widely in the 2018 Congo outbreak.

Prevention of mosquito-borne and tick-borne infections includes use of repellents, wearing of tight-fitting clothing that fully covers the extremities, and careful examination of the skin after exposure, with removal of any vectors found. Diseases transmitted from a rodent-infected environment can be prevented through methods of rodent control; elimination of refuse and breeding sites is particularly successful in urban and suburban areas.

Patients should be isolated until they are virus-free or for 3 wk after illness. Patient urine, sputum, blood, clothing, and bedding should be disinfected. Disposable syringes and needles should be used. Prompt and strict enforcement of barrier nursing may be lifesaving. The mortality rate among medical workers contracting these diseases is 50%. A few entirely asymptomatic Ebola infections result in strong antibody production.

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CHAPTER 298

Lymphocytic Choriomeningitis Virus

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Lymphocytic choriomeningitis virus (LCMV) is a prevalent human pathogen and an important cause of meningitis in children and adults. Capable of crossing the placenta and infecting the fetus, LCMV is also an important cause of neurologic birth defects and encephalopathy in the newborn.

Etiology

LCMV is a member of the family Arenaviridae, which are enveloped, negative-sense single-stranded RNA viruses. The name of the arenaviruses is derived from *arenosus,* the Latin word for "sandy," because of the fine granularities observed within the virion on ultrathin electron microscopic sections.

Epidemiology

Like all arenaviruses, LCMV utilizes rodents as its reservoir. The common house mouse, *Mus musculus,* is both the natural host and primary reservoir for the virus, which is transferred vertically from one generation of mice to the next via intrauterine infection. Hamsters and guinea pigs are also potential reservoirs. Although heavily infected with LCMV, rodents that acquire the virus transplacentally often remain asymptomatic because congenital infection provides rodents with immunologic tolerance for the virus. Infected rodents shed the virus in large quantities in nasal secretions, urine, feces, saliva, and milk throughout their lives.

Humans typically acquire LCMV by contacting fomites contaminated with infectious virus or by inhaling aerosolized virus. Most human infections occur during the fall and early winter, when mice move into human habitations. Humans can also acquire the virus via organ transplantation. Congenital LCMV infection occurs when a woman acquires a primary LCMV infection during pregnancy. The virus passes through the placenta to the fetus during maternal viremia. The fetus may also acquire the virus during passage through the birth canal from exposure to infected vaginal secretions. Outside of organ transplantation and vertical transmission during pregnancy, there have been no cases of human-to-human transmission of LCMV.

LCMV is prevalent in the environment, has a great geographic range, and infects large numbers of humans. The virus is found throughout the world's temperate regions and probably occurs wherever the genus *Mus* has been introduced (which is every continent but Antarctica). An epidemiologic study found that 9% of house mice are infected and that substantial clustering occurs, where the prevalence is higher. Serologic studies demonstrate that approximately 5% of adult humans possess antibodies to LCMV, indicating prior exposure and infection.

Pathogenesis

LCMV is not a cytolytic virus. Thus, unlike many other nervous system pathogens that directly damage the brain by killing host brain cells, LCMV pathogenesis involves other underlying mechanisms. Furthermore, the pathogenic mechanisms are different in postnatal (acquired) infection than in prenatal (congenital) infection. A critical difference in the pathogenesis of postnatal versus prenatal infection is that the virus infects brain parenchyma in the case of prenatal infection, but is restricted to the meninges and choroid plexus in postnatal cases.

In postnatal infections, LCMV replicates to high titers in the choroid plexus and meninges. Viral antigen within these tissues becomes the target of an acute mononuclear cell infiltration driven by CD8+ T lymphocytes. The presence of lymphocytes in large numbers within the meninges and cerebrospinal fluid leads to the symptoms of meningitis that mark acquired LCMV infection. As the lymphocytes clear the virus from the meninges and cerebrospinal fluid, the density of lymphocytes declines, and the symptoms of meningitis resolve. Thus, symptoms of acquired (postnatal) LCMV infection are immune mediated and are a result of the presence of large numbers of lymphocytes.

Prenatal infection likewise inflames the tissues surrounding the brain parenchyma, and this inflammation leads to some of the signs of congenital LCMV. In particular, within the ventricular system, congenital LCMV infection often leads to ependymal inflammation, which may block the egress of cerebrospinal fluid (CSF) at the cerebral aqueduct and lead to hydrocephalus. However, unlike postnatal cases, prenatal infection with LCMV includes infection of the substance of the brain rather than just the meninges or ependyma. This infection of brain parenchyma leads to the substantial neuropathologic changes typically accompanying congenital LCMV infection. In particular, LCMV infects the mitotically active neuroblasts, located at periventricular sites. Through an unknown mechanism, the presence of the virus kills these periventricular cells, leading to periventricular calcifications, a radiographic hallmark of this disorder. Within the fetal brain, LCMV infection of neurons and glial cells also disrupts neuronal migration, leading to abnormal gyral patterns, and interferes with neuronal mitosis, leading to microcephaly and cerebellar hypoplasia.

Clinical Manifestations

The clinical manifestations of LCMV infection depend on whether the infection occurs prenatally or postnatally. Congenital infection with LCMV is unique, as it involves both the postnatal infection of a pregnant woman and the prenatal infection of a fetus.

Acquired (Postnatal) Lymphocytic Choriomeningitis Virus Infection

LCMV infection during postnatal life (during childhood or adulthood) typically consists of a brief febrile illness, from which the patient fully recovers. The illness classically consists of two clinical phases. In the first phase, the symptoms are those of a nonspecific viral syndrome and include fever, myalgia, malaise, nausea, anorexia, and vomiting. These symptoms usually resolve after several days but are followed by a second phase, consisting of central nervous system disease. The symptoms of this second phase are those of aseptic meningitis, including headache, fever, nuchal rigidity, photophobia, and vomiting. The entire course of the biphasic disease is typically 1-3 wk.

The clinical spectrum of LCMV infection is broad. One third of postnatal infections are asymptomatic. Other patients develop extraneural disease that extends beyond the usual symptoms and may include orchitis, pneumonitis, myocarditis, parotitis, dermatitis, alopecia, and pharyngitis. In others, the neurologic disease may be considerably more severe than usual and may include transverse myelitis, Guillain-Barré syndrome, hydrocephalus, and encephalitis. Recovery from acquired LCMV infection is usually complete, but fatalities occasionally occur.

LCMV infections acquired via solid-organ transplantation always induce severe disease. Several weeks following the transplantation, recipients of infected organs develop fever, leukopenia, and lethargy. Following these nonspecific symptoms, the course of the disease rapidly progresses to multiorgan system failure and shock. These cases are almost always fatal.

Congenital Lymphocytic Choriomeningitis Virus Infection

LCMV infection during pregnancy can kill the fetus and induce spontaneous abortion. Among surviving fetuses, the two clinical hallmarks of congenital LCMV infection are vision impairment and brain dysfunction.

The vision impairment in congenital LCMV infection is a result of **chorioretinitis** and the formation of chorioretinal scars. The scarring is usually bilateral and most commonly located in the periphery of the fundus, but involvement of the macula also occurs.

Although the retinal injuries from congenital LCMV infection are often severe, it is the *brain* effects that cause the greatest disability. Prenatal infection with LCMV commonly induces either macrocephaly or microcephaly. **Macrocephaly** following LCMV infection is almost invariably caused by noncommunicating hydrocephalus, stemming from inflammation within the ventricular system. **Microcephaly** is a result of the virus-induced failure of brain growth. In addition to disturbances of head size, periventricular calcifications are also cardinal features of congenital LCMV infection.

Although hydrocephalus, microencephaly, and periventricular calcifications are by far the most commonly observed abnormalities of the brain in congenital LCMV, other forms of neuropathology, alone or in combination, can also occur. These include periventricular cysts, porencephalic cysts, encephalomalacia, intraparenchymal calcifications, cerebellar hypoplasia, and neuronal migration disturbances.

Infants with congenital LCMV infection typically present during the newborn period with evidence of brain dysfunction. The most common signs are lethargy, seizures, irritability, and jitteriness.

Within the fetus, LCMV has a specific tropism for the brain. Thus, unlike many other congenital infections, LCMV usually does not induce systemic manifestations. Birthweight is typically appropriate for gestational age. Skin rashes and thrombocytopenia, which are common in several other prominent congenital infections, are unusual in congenital LCMV infection. Hepatosplenomegaly is only rarely observed, and serum liver enzyme levels are usually normal. Auditory deficits are unusual.

Laboratory Findings

In acquired (postnatal) LCMV infection, the hallmark laboratory abnormality occurs during the second (central nervous system) phase of the disease and is CSF pleocytosis. The CSF typically contains hundreds to thousands of white blood cells, almost all of which are lymphocytes. However, CSF eosinophilia may also occur. Mild elevations of CSF protein and hypoglycorrhachia are common.

In congenital LCMV infection, laboratory findings in the newborn depend on whether the infant is still infected or not. If the infant still harbors the infection, then examination of the CSF may reveal a lymphocytic pleocytosis. Unlike many other congenital infections, LCMV does not typically induce elevations in liver enzymes, thrombocytopenia, or anemia. In many cases, the most reliably abnormal test is the head CT scan, which typically reveals a combination of microencephaly, hydrocephalus, and periventricular calcifications (Fig. 298.1).

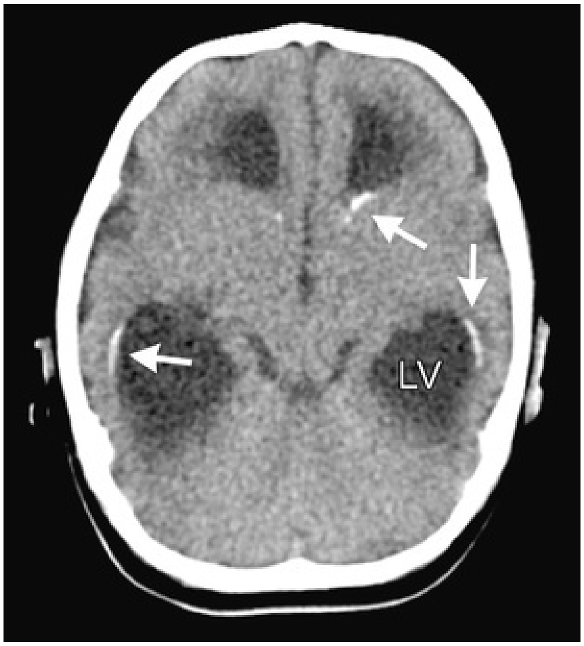

FIG. 298.1 Head CT scan from a 2 mo old microcephalic baby with congenital lymphocytic choriomeningitis virus infection. The scan reveals enlargement of the lateral ventricles *(LV)* and periventricular calcifications *(arrows).*

Diagnosis and Differential Diagnosis

Acute LCMV infections can be diagnosed by isolating the virus from CSF. Polymerase chain reaction has also been used to detect LCMV RNA in patients with active infections. However, by the time of birth, a baby prenatally infected with LCMV may no longer harbor the virus. Thus, congenital LCMV infection is more commonly diagnosed by serologic testing. The immunofluorescent antibody test detects both immunoglobulin (Ig) M and IgG and has greater sensitivity than the more widely available complement fixation method. The immunofluorescent antibody test is commercially available, and its specificity and sensitivity make it an acceptable diagnostic tool. A more sensitive test for detecting congenital LCMV infection is the enzyme-linked immunosorbent assay, which measures titers of LCMV IgG and IgM and is performed at the Centers for Disease Control and Prevention.

For acquired (postnatal) LCMV infection, the principal items in the differential diagnosis are the other infectious agents that can induce meningitis. These include bacteria, fungi, viruses, and some other forms of pathogens. The most common viral causes of meningitis are the enteroviruses, including coxsackieviruses and echoviruses, and the arboviruses, including La Crosse encephalitis virus and equine encephalitis virus. Unlike LCMV, which is most common in winter, the enteroviruses and arboviruses are most commonly acquired in summer and early fall.

The principal items in the differential diagnosis of congenital LCMV infection are the other infectious pathogens that can cross the placenta and damage the developing fetus. These infectious agents are linked by the acronym TORCHS and include *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus, and syphilis. Toxoplasmosis, Zika virus infection, and cytomegalovirus infection are particularly difficult to differentiate from LCMV, because all of these infectious agents can produce microcephaly, intracerebral calcifications, and chorioretinitis. Although clinical clues may aid in distinguishing one congenital infection from another, definitive identification of the causative infectious agent usually requires laboratory data, including cultures and serologic studies.

Complications

Complications in children with congenital LCMV infection are nonspecific and include the medical problems that commonly arise in scenarios, involving ventriculoperitoneal shunts, severe seizure disorders, and static encephalopathy. These complications include shunt failure or infection, aspiration pneumonia, injuries from falls, and joint contractures.

Treatment

There is no specific treatment for acquired or congenital LCMV infection. An effective antiviral therapy for LCMV infection has not yet been developed. Ribavirin is active against LCMV and other arenaviruses in vitro, but its utility in vivo is unproven. Immunosuppressive therapy, if present, should be reduced.

Supportive Care

Children with hydrocephalus from congenital LCMV infection often require placement of a ventriculoperitoneal shunt during infancy for treatment of hydrocephalus. Seizures often begin during early postnatal life, are often difficult to control, and require administration of multiple antiepileptic medications. The mental retardation induced by congenital LCMV infection is often profound. In most cases, affected children should be referred for educational intervention during early life. The spasticity accompanying congenital LCMV infection is often severe. Although physical therapy can help to maintain the range of motion and minimize painful spasms and contractures, implantation of a baclofen pump is often helpful.

Prognosis

The great majority of patients with postnatally acquired LCMV infection have a full recovery with no permanent sequelae. Rarely, postnatal infections induce hydrocephalus and require shunting. Rarer yet, postnatal LCMV infection is fatal.

In contrast to the usual benign outcome of postnatal infections, prenatal infections typically lead to severe and permanent disability. In children with congenital LCMV infection, brain function is nearly always impaired and chorioretinitis is invariably present. Mental retardation, cerebral palsy, ataxia, epilepsy, and blindness are common neurologic sequelae. However, children with congenital LCMV infection have diverse outcomes. All children with the combination of microencephaly and periventricular calcifications are profoundly neurologically impaired. Blindness, medically refractory epilepsy, spastic quadriparesis, and mental retardation are typical of this group. However, other children with congenital LCMV infection who do not have the combination of microencephaly and periventricular calcifications often have a more favorable outcome, with less severe motor, mental, and vision impairments. Children with isolated cerebellar hypoplasia may be ataxic but have only mild or moderate mental retardation and vision loss.

Prevention

No vaccine exists to prevent LCMV infection. However, measures can be taken to reduce the risk of infection. Because rodents, especially house mice, are the principal reservoir of LCMV, people can reduce their risk of contracting LCMV by minimizing their exposure to the secretions and excretions of mice. This can be accomplished most effectively by eliminating cohabitation with mice. Congenital LCMV infection will not occur unless a woman contracts a primary infection with LCMV during pregnancy. Thus, women should be especially careful to avoid contact or cohabitation with mice during pregnancy. Pregnant women should also avoid contact with pet rodents, especially mice and hamsters. These facts should be stressed during prenatal visits.

Acquisition of LCMV from solid-organ transplantation represents a substantial risk to organ recipients. Prospective donors with LCMV meningitis or encephalitis pose a clear risk for transmitting a fatal infection to recipients. Healthcare providers, transplantation centers, and organ procurement organizations should be aware of the risks posed by LCMV and should consider LCMV in any potential donor with signs of aseptic meningitis but no identified infectious agent. The risks and benefits of offering and receiving organs from donors with possible LCMV infection should be carefully considered.

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CHAPTER 299

Hantavirus Pulmonary Syndrome

Scott B. Halstead

The hantavirus pulmonary syndrome (HPS) is caused by multiple closely related hantaviruses that have been identified from the western United States, with sporadic cases reported from the eastern United States (Fig. 299.1) and Canada and important foci of disease in several countries in South America. HPS is characterized by a febrile prodrome followed by the rapid onset of noncardiogenic pulmonary edema and hypotension or shock. Sporadic cases in the United States caused by related viruses may manifest with renal involvement. Cases in Argentina and Chile sometimes include severe gastrointestinal hemorrhaging; nosocomial transmission has been documented in this geographic region only.

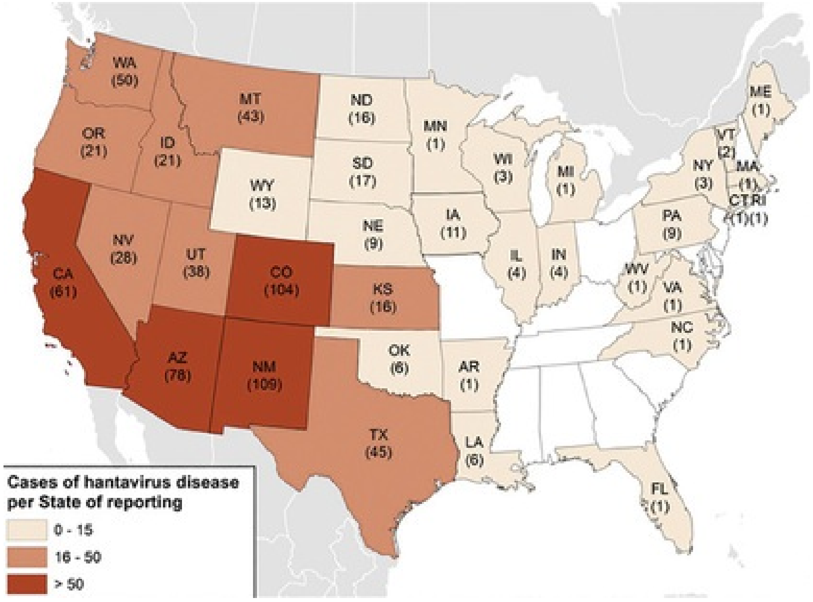
WA (50)
OR (21)
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MT (43)
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MN (1)
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VT (2)
NY (3)
MA (1)
CT (1)
RI (1)
WY (13)
NE (9)
IA (11)
PA (9)
NV (28)
UT (38)
CO (104)
CA (61)
KS (16)
IL (4)
IN (4)
WV (1)
VA (1)
NC (1)
OK (6)
AR (1)
AZ (78)
NM (109)
TX (45)
LA (6)
FL (1)
Cases of hantavirus disease per State of reporting
0 - 15
16 - 50
> 50

FIG. 299.1 Total number of confirmed cases of Hantavirus pulmonary

syndrome, by state reporting, United States, 1993-2016. N = 728 as of January 2017. (From Viral Special Pathogens Branch, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/hantavirus/surveillance/reporting-state.html).

Etiology

Hantaviruses are a genus in the family Bunyaviridae, which are lipid-enveloped viruses with a negative-sense RNA genome composed of three unique segments. Several pathogenic viruses that have been recognized within the genus include Hantaan virus, which causes the most severe form of hemorrhagic fever with renal syndrome (HFRS) seen primarily in mainland Asia (see Chapter 297); Dobrava virus, which causes the most severe form of HFRS seen primarily in the Balkans; Puumala virus, which causes a milder form of HFRS with a high proportion of subclinical infections and is prevalent in northern Europe; and Seoul virus, which results in moderate HFRS and is transmitted predominantly in Asia by urban rats or worldwide by laboratory rats. Prospect Hill virus, a hantavirus that is widely disseminated in meadow voles in the United States, is not known to cause human disease. There are an increasing number of case reports of European hantaviruses causing HPS.

HPS is associated with *sin nombre* virus, isolated from deer mice, *Peromyscus maniculatus*, in New Mexico. Multiple HPS-like agents in the American hemisphere isolated to date belong to a single genetic group of hantaviruses and are associated with rodents of the family Muridae, subfamily Sigmodontinae. These rodent species are restricted to the Americas, suggesting that HPS may be a Western hemisphere disease.

Epidemiology

Persons acquiring HPS generally have a history of recent outdoor exposure or live in an area with large populations of deer mice. Clusters of cases have occurred among individuals who have cleaned houses that were rodent infested. *P. maniculatus* is one of the most common North American mammals and, where found, is frequently the dominant member of the rodent community. About half of the average of 30+ cases seen annually occurs between the months of May and July. Patients are almost exclusively 12-70 yr of age; 60% of patients are 20-39 yr of age. Rare cases are reported in children younger than 12 yr of age. Two thirds of patients are male, probably reflecting their greater outdoor activities. It is not known whether almost complete absence of disease in young children is a reflection of innate resistance or simply lack of exposure. Evidence of human-to-human transmission has been reported in Argentine outbreaks.

Hantaviruses do not cause apparent illness in their reservoir hosts, which remain asymptomatically infected for life. Infected rodents shed virus in saliva, urine, and feces for many weeks, but the duration of shedding and the period of maximum infectivity are unknown. The presence of infectious virus in saliva, the sensitivity of these animals to parenteral inoculation with hantaviruses, and field observations of infected rodents indicate that biting is important for rodent-to-rodent transmission. Aerosols from infective saliva or excreta of rodents are implicated in the transmission of hantaviruses to humans. Persons visiting animal care areas housing infected rodents have been infected after exposure for as little as 5 min. It is possible that hantaviruses are spread through contaminated food and breaks in skin or mucous membranes; transmission to humans has occurred by rodent bites. Person-to-person transmission is distinctly uncommon but has been documented in Argentina.

Pathogenesis

HPS is characterized by sudden and catastrophic pulmonary edema, resulting in anoxia and acute heart failure. The virus is detected in pulmonary capillaries, suggesting that pulmonary edema is the consequence of a T-cell attack on virus-infected capillaries. The disease severity is predicted by the level of acute-phase viremia titer. A useful hamster model of HPS is available.

Clinical Manifestations

HPS is characterized by a prodrome and a cardiopulmonary phase. The mean duration after the onset of prodromal symptoms to hospitalization is 5.4 days. The mean duration of symptoms to death is 8 days (median: 7 days; range: 2-16 days). The most common **prodromal symptoms** are fever and myalgia (100%); cough or dyspnea (76%); gastrointestinal symptoms, including vomiting, diarrhea, and midabdominal pain (76%); and headache (71%). The **cardiopulmonary phase** is heralded by progressive cough and shortness of breath. The most common initial physical findings are tachypnea (100%), tachycardia (94%), and hypotension (50%). Rapidly progressive acute pulmonary edema, hypoxia, and shock develop in most severely ill patients. Pulmonary vascular permeability is complicated by cardiogenic shock associated with increased vascular resistance. The clinical course of the illness in patients who die is characterized by pulmonary edema accompanied by severe hypotension, frequently terminating in sinus bradycardia, electromechanical dissociation, ventricular tachycardia, or fibrillation. Hypotension may be progressive even with adequate oxygenation. HPS virus is excreted in the urine during the acute illness phase, and survivors may demonstrate evidence of chronic renal damage.

Diagnosis

The diagnosis of HPS should be considered in a previously healthy patient presenting with a febrile prodrome, acute respiratory distress, and thrombocytopenia who has had outdoor exposure in the spring and summer months. A specific diagnosis of HPS is made by serologic tests that detect hantavirus immunoglobulin M antibodies. The early appearance of immunoglobulin G antibodies signals probable recovery. Hantavirus antigen can be detected in tissue by immunohistochemistry and amplification of hantavirus nucleotide sequences detected by reverse transcriptase polymerase chain reaction. The state health department or the Centers for Disease Control and Prevention should be consulted to assist in the diagnosis, epidemiologic investigations, and outbreak control.

Laboratory Findings

Laboratory findings include leukocytosis (median: 26,000 cells/µL), an elevated hematocrit resulting from hemoconcentration, thrombocytopenia (median: 64,000 cells/µL), prolonged prothrombin and partial thromboplastin times, elevated serum lactate dehydrogenase concentration, decreased serum protein concentrations, proteinuria, and microscopic hematuria. Patients who die often experience disseminated intravascular coagulopathy including frank hemorrhage and exceptionally high leukocyte counts.

Differential Diagnosis

The differential diagnosis includes adult respiratory distress syndrome, pneumonic plague, psittacosis, severe mycoplasmal pneumonia, influenza, leptospirosis, inhalation anthrax, rickettsial infections, pulmonary tularemia, atypical bacterial and viral pneumonial diseases, legionellosis, meningococcemia, and other sepsis syndromes. The key determinant in the diagnosis of HPS is thrombocytopenia.

Treatment

Management of patients with hantavirus infection requires maintenance of adequate oxygenation and careful monitoring and support of cardiovascular function. The pathophysiology of HPS somewhat resembles that of dengue shock syndrome (see Chapter 295). Pressor or inotropic agents, such as dobutamine, should be administered in combination with judicious volume replacement to treat symptomatic hypotension or shock while avoiding exacerbation of the pulmonary edema. Intravenous ribavirin, which is lifesaving if given early in the course of HFRS and is effective in preventing death in the hamster model, has not yet been demonstrated to be of value in HPS.

Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Viral Special Pathogens Branch, Atlanta, Georgia 30333 (470-312-0094).

Prognosis

In some geographic areas, fatality rates for HPS have been 50%. Severe abnormalities in hematocrit, white blood cell count, lactate dehydrogenase value, and partial thromboplastin time, and a high viral load predict death with high specificity and sensitivity. The early appearance of immunoglobulin G antibodies may signal a hopeful prognosis.

Prevention

Avoiding contact with rodents is the only preventive strategy against HPS. Rodent control in and around the home is important. Barrier nursing is advised, and biosafety level 3 facilities and practices are recommended for laboratory handling of blood, body fluids, and tissues from suspect patients or rodents, because the virus may be aerosolized.

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CHAPTER 300

Rabies

Rodney E. Willoughby Jr.

Rabies virus is a bullet-shaped, negative-sense, single-stranded, enveloped RNA virus from the family Rhabdoviridae, genus *Lyssavirus*. There currently are 14 species of *Lyssavirus*. The classic rabies virus (genotype 1) is distributed worldwide and naturally infects a large variety of animals. The other genotypes are more geographically confined, with none found in the Americas. Seven *Lyssavirus* genotypes are associated with rabies in humans, although genotype 1 accounts for the great majority of cases. Within genotype 1, a number of genetic variants have been defined. Each variant is specific to a particular animal reservoir, although cross-species transmission can occur.

Epidemiology

Rabies is present on all continents except Antarctica. Rabies predominantly afflicts underaged, poor, and geographically isolated populations. Approximately 59,000 cases of human rabies occur in Africa and Asia annually. Theoretically, rabies virus can infect any mammal (which then can transmit disease to humans), but true animal reservoirs that maintain the presence of rabies virus in the population are limited to terrestrial carnivores and bats. Worldwide, transmission from dogs accounts for > 90% of human cases. In Africa and Asia, other animals serve as prominent reservoirs, such as jackals, mongooses, and raccoon dogs. In industrialized nations, canine rabies has been largely controlled through the routine immunization of pets. In the United States, raccoons are the most commonly infected wild animal along the eastern seaboard. Three phylogenies of skunk rabies are endemic in the Midwest (north and south) and California, gray foxes harbor rabies in Arizona and Texas, red foxes and arctic foxes harbor rabies in Alaska, and mongooses carry rabies in Puerto Rico.

Rabies occurs infrequently in livestock. Among American domestic pets, infected cats outnumber infected dogs, probably because cats frequently prowl unsupervised and are not uniformly subject to vaccine laws. Rabies is rare in small mammals, including mice, squirrels, and rabbits; to date, no animal-to-human transmission from these animals has been documented.

The epidemiology of human rabies in the United States is dominated by cryptogenic bat rabies. Bats are migratory in the spring and fall; rabid bats are identified in every state of the union except Hawaii. In one study, the largest proportion of cases of human rabies were infected with a bat variant, and in almost all cases of bat-associated human rabies there was no history of a bat bite. Among inhabitants of the Peruvian Amazon region who have exposure to rabies-infected vampire bats, there are some who have rabies virus–neutralizing antibodies and have survived. Antibody-positive patients remember bat bites but do not recall symptoms of rabies.

In the United States, 30,000 episodes of rabies postexposure prophylaxis (PEP) occur annually. Between one and three endemic human cases are diagnosed annually, half postmortem. There have been five outbreaks of rabies associated with solid-organ and corneal transplantations.

Transmission

Rabies virus is found in large quantities in the saliva of infected animals, and transmission occurs almost exclusively through inoculation of the infected saliva through a bite or scratch from a rabid mammal. Approximately 35–50% of people who are bitten by a known rabies-infected animal and receive no PEP actually contract rabies. The transmission rate is increased if the victim has suffered multiple bites and if the inoculation occurs in highly innervated parts of the body such as the face and the hands. Infection does not occur after exposure of intact skin to infected secretions, but virus may enter the body through intact mucous membranes. Claims that spelunkers may experience rabies after inhaling bat excreta have come under doubt, although inhalational exposure can occur during laboratory accidents.

No case of nosocomial transmission to a healthcare worker has been documented to date, but caregivers of a patient with rabies are advised to use full barrier precautions. The virus is rapidly inactivated in the environment, and contamination of fomites is not a mechanism of spread.

Pathogenesis

After inoculation, rabies virus replicates slowly and at low levels in muscle or skin. This slow initial step likely accounts for the disease's long incubation period. Virus then enters the peripheral motor nerve, utilizing the nicotinic acetylcholine receptor and possibly several other receptors for entry. Once in the nerve, the virus travels by fast axonal transport, crossing synapses roughly every 12 hr. Rapid dissemination occurs throughout the brain and spinal cord before symptoms appear. Infection of the dorsal root ganglia is apparently futile but causes characteristic radiculitis. Infection concentrates in the brainstem, accounting for autonomic dysfunction and relative sparing of cognition. Despite severe neurologic dysfunction with rabies, histopathology reveals limited damage, inflammation, or apoptosis. The pathologic hallmark of rabies, the Negri body, is composed of clumped viral nucleocapsids that create cytoplasmic inclusions on routine histology. Negri bodies can be absent in documented rabies virus infection. Rabies may be a metabolic disorder of neurotransmission; tetrahydrobiopterin deficiency in human rabies causes severe deficiencies in dopamine, norepinephrine, and serotonin metabolism.

After infection of the central nervous system, the virus travels anterograde through the peripheral nervous system to virtually all innervated organs, further exacerbating dysautonomia. It is through this route that the virus infects the salivary glands. Many victims of rabies die from uncontrolled cardiac dysrhythmia.

Deficiency of tetrahydrobiopterin, an essential cofactor for neuronal nitric oxide synthase, is predicted to lead to spasm of the basilar arteries. Onset of vasospasm has been confirmed in a few patients within 5-8 days of the first hospitalization, at about the time coma supervenes in the natural history. Increased intracranial pressure is regularly measured early in rabies in association with elevated *N* -acetylaspartate in cerebrospinal fluid (CSF), but is rarely radiologically apparent. Metabolites in CSF consistent with ketogenesis are associated with demise.

Clinical Manifestations

The incubation period for rabies is 1-3 mo. In severe wounds to the head, symptoms may occur within 5 days after exposure, and occasionally the incubation period can extend to 8 yr. Rabies has two principal clinical forms.

Encephalitic or **furious rabies** begins with nonspecific symptoms, including fever, sore throat, malaise, headache, nausea and vomiting, and weakness. These symptoms are often accompanied by paresthesia and pruritus at or near the site of the bite that then extend along the affected limb. Soon thereafter the patient begins to demonstrate symptoms of encephalitis, with agitation, sleep disturbance, or depressed mentation. Characteristically, patients with rabies encephalitis initially have periods of lucidity alternating with periods of profound encephalopathy. Hydrophobia and aerophobia are the cardinal signs of rabies; they are unique to humans and are not universal or specific. Phobic spasms are manifested by agitation and fear created by being offered a drink or fanning of air in the face, which in turn produce choking and aspiration through spasms of the pharynx, neck, and diaphragm. Seizures are rare and should point to an alternative diagnosis; orofacial dyskinesias and myoclonia may be confused with seizures. The illness is relentlessly progressive. There is a dissociation of electrophysiologic or encephalographic activity with findings of brainstem coma caused by anterograde denervation. Death almost always occurs within 1-2 days of hospitalization in developing countries and by 18 days of hospitalization with intensive care.

A second form of rabies known as **paralytic** or **dumb rabies** is seen much less frequently and is characterized principally by fevers and ascending motor weakness affecting both the limbs and the cranial nerves. Most patients with paralytic rabies also have some element of encephalopathy as the disease progresses subacutely.

Case reports suggest that milder forms of rabies encephalitis may exist, and 28 rabies survivors are known. Rabies should be considered earlier and more frequently than current practice to improve outcomes.

Differential Diagnosis

The differential diagnosis of rabies encephalitis includes all forms of severe cerebral infections, tetanus, and some intoxications and envenomations. Rabies can be confused with autoimmune (anti–*N* -methyl-ᴅ -aspartate receptor, NMDAR) encephalitis, other infectious forms of encephalitis, psychiatric illness, drug abuse, and conversion disorders. Paralytic rabies is frequently confused with Guillain-Barré syndrome. The diagnosis of rabies is frequently delayed in Western countries because of the unfamiliarity of the medical staff with the infection. These considerations highlight the need to pursue a history of contact with an animal belonging to one of the known reservoirs for rabies or to establish a travel history to a rabies-endemic region.

Diagnosis

The Centers for Disease Control and Prevention (CDC) require a number of tests to confirm a clinically suspected case of rabies. Reverse transcription polymerase chain reaction is the most sensitive available assay for the diagnosis of rabies when done iteratively. Rabies virus RNA has been detected in saliva, skin, and brain by the reverse transcription polymerase chain reaction. The virus can be grown both in cell culture and after animal injection, but identification of rabies by these methods is slow. Rabies antigen is detected through immunofluorescence of saliva or biopsies of hairy skin or brain. Corneal impressions are not recommended. Rabies-specific antibody can be detected in serum or CSF samples, but most patients die while seronegative. Antirabies antibodies are present in the sera of patients who have received an incomplete course of the rabies vaccine, precluding a meaningful interpretation in this setting. Recent treatment with intravenous immunoglobulin may result in a false-positive antibody test. Antibody in CSF is rarely detected after vaccination and is considered diagnostic of rabies regardless of immunization status. CSF abnormalities in cell count, glucose, and protein content are minimal and are not diagnostic. MRI findings in the brain are late.

Treatment and Prognosis

Rabies is generally fatal. Conventional critical care yielded 6 survivors from 79 attempts since 1990. Seventeen of 80 patients survived with use of the Milwaukee Protocol (MP) (http://www.mcw.edu/rabies); neurologic outcomes are poor in half of patients. Neither rabies immunoglobulin (RIG) nor rabies vaccine provides benefit once symptoms have appeared. Among 10 survivors of rabies after use of biologics, 7 had poor neurologic outcomes. Among 7 vaccine-naïve survivors, 2 had poor outcomes. Antiviral treatments have not been effective; favipiravir has been administered to 4 patients as compassionate use. Ribavirin and RIG delay the immune response and should be avoided. In contrast, appearance of the normal antibody response by 7 days is associated with clearance of salivary viral load and survival.

Prevention

Primary prevention of rabies infection includes vaccination of domestic animals and education to avoid wild animals, stray animals, and animals with unusual behavior.

Immunization and Fertility Control of Animal Reservoirs

The introduction of routine rabies immunization for domestic pets in the United States and Europe during the middle of the 20th century virtually eliminated infection in dogs. In the 1990s, control efforts in Europe and North America shifted to immunization of wildlife reservoirs of rabies, where rabies was newly emerging. These programs employed bait laced with either an attenuated rabies vaccine or a recombinant rabies surface glycoprotein inserted into vaccinia, distributed by air or hand into areas inhabited by rabid animals. Human contact with vaccine-laden bait has been infrequent. Adverse events after such contact have been rare, but the vaccinia vector poses a threat to the same population at risk for vaccinia itself, namely, pregnant women, immunocompromised patients, and people with atopic dermatitis. Mass culling of endemic reservoirs has never worked; vaccination and fertility control stop outbreaks. Bats are ubiquitous and very important for insect control. Less than 1% of free-flying bats but > 8% of downed bats and bats found in dwellings are rabid.

Postexposure Prophylaxis

The relevance of rabies for most pediatricians centers on evaluating whether an animal exposure warrants PEP (Table 300.1). No case of rabies has been documented in a person receiving the recommended schedule of PEP since introduction of modern cellular vaccines in the 1970s.

Table 300.1

Rabies Postexposure Prophylaxis Guide

ANIMAL TYPE	EVALUATION AND DISPOSITION OF ANIMAL	POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS
Dogs, cats, and ferrets	Healthy and available for 10 days of observation	Prophylaxis only if animal shows signs of rabies*

	Rabid or suspected of being rabid [†]	Immediate immunization and RIG
	Unknown (escaped)	Consult public health officials for advice
Bats, skunks, raccoons, foxes, and most other carnivores; woodchucks	Regarded as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests [†]	Immediate immunization and RIG
Livestock, rodents, and lagomorphs (rabbits, hares, and pikas)	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice and other rodents, rabbits, hares, and pikas almost never require antirabies treatment

[*] During the 10-day observation period, at the first sign of rabies in the biting dog, cat, or ferret, treatment of the exposed person with RIG (human) and vaccine should be initiated. The animal should be euthanized immediately and tested.

[†] The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Immunization is discontinued if the immunofluorescent test result for the animal is negative.

RIG, rabies immunoglobulin.

Given the incubation period for rabies, PEP is a medical urgency, not emergency. Algorithms have been devised to aid practitioners in deciding when to initiate rabies PEP (Fig. 300.1). The decision to proceed ultimately depends on the local epidemiology of animal rabies as determined by active surveillance programs, information that can be obtained from local and state health departments. *In general, bats, raccoons, skunks, coyotes, and foxes should be considered rabid unless proven otherwise through euthanasia and testing of brain tissue*, whereas bites from small herbivorous animals (squirrels, hamsters, gerbils, chipmunks, rats, mice, and rabbits) can be discounted. The response to bites from a pet, particularly a dog, cat, or ferret, depends on local surveillance statistics and on whether the animal is vaccinated and available for observation.

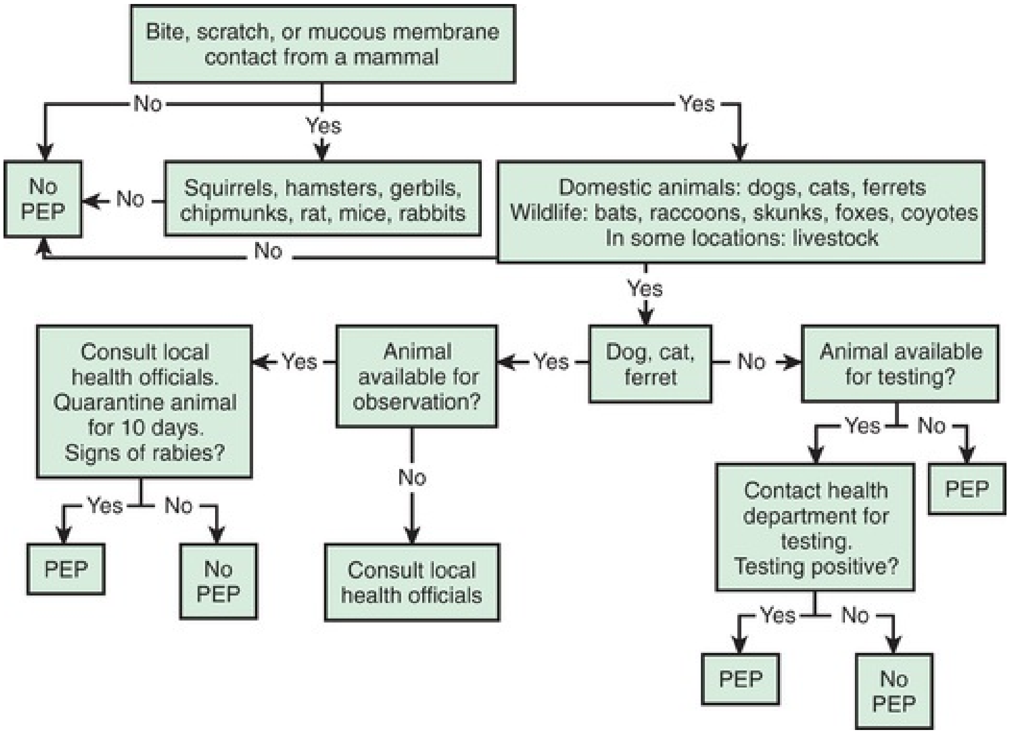

Bite, scratch, or mucous membrane contact from a mammal
No
Yes
Yes
No PEP
No
Squirrels, hamsters, gerbils, chipmunks, rat, mice, rabbits
Domestic animals: dogs, cats, ferrets
Wildlife: bats, raccoons, skunks, foxes, coyotes
In some locations: livestock
No
Yes
Consult local health officials. Quarantine animal for 10 days. Signs of rabies?
Yes
Animal available for observation?
Yes
Dog, cat, ferret
No
Animal available for testing?
Yes
No
No
Contact health department for testing. Testing positive?
PEP
Yes
No
PEP
No PEP
Consult local health officials
Yes
No
PEP
No PEP

FIG. 300.1 Algorithm for evaluating a child for rabies postexposure prophylaxis. This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.

The approach to nonbite bat exposures is controversial. In response to the observation that most cases of rabies in the United States have been caused by bat variants and that the majority of affected patients had no recollection of a bat bite, the CDC has recommended that rabies PEP be considered after any physical contact with bats and when a bat is found in the same room as persons who may not be able to accurately report a bite, assuming that the animal is unavailable for testing. Such people include young children, the mentally disabled, and intoxicated individuals. Other nonbite contacts (e.g., handling a carcass, exposure to an animal playing with a carcass, or coming into contact with blood or excreta from a potentially rabid animal) usually do not require PEP.

In all instances of a legitimate exposure, effort should be made to recover the animal for quarantine and observation or brain examination after euthanasia. Testing obviates the need for PEP more than half the time. In most instances, PEP can be deferred until the results of observation or brain histology are known. In dogs, cats, and ferrets, symptoms of rabies always occur within several days of viral shedding; therefore, in these animals a 10-day observation period is sufficient to eliminate the possibility of rabies.

No duration of time between exposure and onset of symptoms should preclude rabies prophylaxis. Rabies PEP is most effective when applied expeditiously. Nevertheless, the series should be initiated in the asymptomatic person as soon as possible, regardless of the length of time since the bite. *The vaccine and RIG are contraindicated once symptoms develop.*

The first step in rabies PEP is to **cleanse the wound thoroughly.** Soapy water is sufficient to inactivate an enveloped virus, and its effectiveness is supported by broad experience. Other commonly used disinfectants, such as iodine-containing preparations, are virucidal and should be used in addition to soap when available. Probably the most important aspect of this component is that the wound is cleansed with copious volumes of disinfectant. **Primary closure is avoided;** wounds may be bacterially infected as well, so cosmetic repair should follow. Antibiotics and tetanus prophylaxis (see Chapter 238) should be applied with the use of usual wound care criteria.

The second component of rabies PEP consists of passive immunization with RIG. Most failures of PEP are attributed to not using RIG. Human RIG, the formulation used in industrialized countries, is administered at a dose of 20 IU/kg. **As much of the dose is infused around the wound as possible,** and the remainder is injected intramuscularly in a limb distant from the one injected with the killed vaccine. Like other immunoglobulin preparations, RIG interferes with the take of live viral vaccines for at least 4 mo after administration of the RIG dose. Human RIG is not available in many parts of the developing world. Equine RIG serves as a substitute for the human immunoglobulin preparation in some areas. Modern preparations of equine RIG are associated with fewer side effects than prior products composed of crude horse serum. Regrettably, for a large segment of the world's population, no passive immunization product is available at all. Monoclonal antibody products are in clinical trials and may alleviate this deficiency.

The third component of rabies PEP is immunization with inactivated vaccine. In most of the world, cell-based vaccines have replaced previous preparations. Two formulations currently are available in the United States, namely, RabAvert (Chiron Behring Vaccines, Maharashtra, India), a purified chick-embryo cell cultivated vaccine, and Imovax Rabies (Aventis Pasteur, Bridgewater, NJ), cultivated in human diploid cell cultures. In both children and adults, both vaccines are administered intramuscularly in a 1-mL volume in the deltoid or anterolateral thigh on days 0, 3, 7, and 14 after presentation. Injection into the gluteal area is associated with a blunted antibody response, so this area should not be used. The rabies vaccines can be safely administered during pregnancy. In most persons the vaccine is well tolerated; most adverse effects are related to booster doses. Pain and erythema at the injection site occur commonly, and local adenopathy, headache, and myalgias occur in 10–20% of patients. Approximately 5% of patients who receive the human diploid cell vaccine experience an immune complex–mediated allergic reaction, including rash, edema, and arthralgias, several days after a booster dose. The World Health Organization has approved schedules using smaller amounts of vaccine, administered intradermally, that are immunogenic and protective (http://www.who.int/rabies/human/post_exp_prophylaxis/en/), but none is approved for use in the United States. Other cell culture–derived rabies virus vaccines are available in the developing world. A few countries still produce nerve tissue–derived vaccines; these preparations are poorly immunogenic, and cross reactivity with human nervous tissue may occur with their use, producing severe neurologic symptoms even in the absence of rabies infection.

Preexposure Prophylaxis

The killed rabies vaccine can be given to prevent rabies in persons at high risk for exposure to wild-type virus, including laboratory personnel working with rabies virus, veterinarians, and others likely to be exposed to rabid animals as part of their occupation. Preexposure prophylaxis should be considered for persons traveling to a rabies-endemic region where there is a credible risk for a bite or scratch from a rabies-infected animal, particularly if there is likely to be a shortage of RIG or cell culture–based vaccine (see Chapter 200). Rabies vaccine as part of the routine vaccine series is under investigation in some countries. The schedule for preexposure prophylaxis consists of three intramuscular injections on days 0, 7, and 21 or 28. PEP in the patient who has received preexposure prophylaxis or a prior full schedule of PEP consists of two doses of vaccine (one each on days 0 and 3) and does not require RIG. Immunity from preexposure prophylaxis wanes after several years and requires boosting if the potential for exposure to rabid animals recurs.

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CHAPTER 301

Polyomaviruses

Gregory A. Storch

The polyomaviruses are small (45 nm), nonenveloped, circular, double-stranded DNA viruses with genomes of approximately 5,000 bp. Because of the association of animal polyomaviruses with tumors in the animals they infect, there has been concern for a relationship to neoplasia in humans; however, there is strong evidence for an etiologic role in neoplasia only for Merkel cell polyomavirus (see below). Among the other polyomaviruses, the traditional human pathogens are JC virus and BK virus. The number of human polyomaviruses has expanded dramatically, with discovery of up to 12 additional viruses. Two polyomaviruses, designated KI virus and WU virus, can be detected in respiratory samples from children; however, a pathogenic role for these viruses has not been proven to date. Merkel cell polyomavirus is associated with Merkel cell carcinoma, an unusual neuroectodermal tumor of the skin that occurs primarily in elderly and immunocompromised individuals. Clonal integration of Merkel cell polyomavirus DNA is present in Merkel cell carcinoma cells, supporting an etiologic role for the virus in the development of the tumor. Another human polyomavirus has been isolated from patients with the dermatologic condition **trichodysplasia spinulosa** and has been named trichodysplasia spinulosa–associated polyomavirus. Trichodysplasia spinulosa is a condition of the skin that occurs in immunocompromised individuals and involves the development of follicular papules and keratin spines, usually involving the face. Two other viruses, designated human polyomaviruses 6 and 7, have also been found in human skin samples. They have been implicated in pruritic skin rashes in immunocompromised individuals. Human polyomavirus 9 was detected in serum from a renal transplant recipient. Other recently discovered viruses, named Malawi virus and St. Louis virus, were first detected in stool samples, but a role in gastrointestinal or other disease has not been established at this time.

JC and BK viruses are tropic for renal epithelium; JC virus also infects brain oligodendrocytes and is the etiologic agent of **progressive multifocal leukoencephalopathy (PML),** a rare and often fatal demyelinating disease of immunocompromised persons, especially those with AIDS. PML is known to occur in individuals receiving the immunomodulatory agents natalizumab (Tysabri), used to treat multiple sclerosis and Crohn disease, efalizumab (Raptiva), used to treat psoriasis, the anti-CD20 monoclonal antibody rituximab (Rituxan), and the anti-CD52 monoclonal antibody alemtuzumab (Campath), as well as multiple other immunomodulatory agents. BK virus is the cause of **transplant nephropathy** in renal transplant recipients and of hemorrhagic cystitis in hematopoietic stem cell and bone marrow transplant recipients. Several million persons in the United States were exposed to simian virus 40 (SV40), an oncogenic polyomavirus of Asian macaques, from contaminated poliovirus vaccines administered during the years 1955 to 1963. There were no recognized sequelae and no demonstrable increased risk for cancer.

Seroepidemiologic studies have shown that infection with all of the human polyomaviruses appears to be widespread, often occurring during childhood. Primary infection with these viruses is not recognized clinically. Approximately half of children in the United States are infected with BK virus by 3-4 yr of age and with JC virus by 10-14 yr of age, and approximately 60–80% of adults are seropositive for one or both viruses. Infection with polyomaviruses is thought to persist throughout life, with JC and BK viruses remaining latent in renal epithelium, oligodendrocytes, and peripheral blood mononuclear cells. The site of latency of the other human polyomaviruses is not currently known. Approximately 30–50% of healthy persons have detectable BK or JC virus in renal tissue at autopsy. Reactivation and viruria occur with increased frequency with advancing age and are more common in immunocompromised persons. On the basis of polymerase chain reaction results, BK and JC viruria occurs in 2.6% and 13.2%, respectively, of persons younger than 30 yr of age and in approximately 9% and 50%, respectively, of persons older than 60 yr of age.

Reactivation of BK and JC viruses with asymptomatic viruria occurs in 10–50% of hematopoietic stem cell and bone marrow transplant recipients and in 30% of renal transplant recipients. Of those renal transplant recipients who demonstrate BK viruria, approximately one third also have plasma viremia. Recipients with plasma viremia are at risk for development of nephropathy, which can clinically mimic allograft rejection and can result in failure of the allograft. Reduction of immunosuppression has been effective in preventing progression from viremia to nephropathy, and thus posttransplantation monitoring of either urine or plasma by polymerase chain reaction is important. It is particularly important to distinguish BK nephropathy from rejection because the treatments are different—increase in immunosuppression for rejection but decrease in immunosuppression for BK nephropathy.

Polymerase chain reaction is the preferred means for detecting the BK and JC viruses. The high seroprevalence in the general population and lack of clear relationship to clinical illness limit the usefulness of serologic testing, although recent studies suggest that high levels of anti-BK antibodies in renal transplant donors are associated with an increased risk of BK disease in the recipient. There are no proven antiviral treatments for BK or JC virus infection, although cidofovir may be effective in some cases of BK-related transplant nephropathy. Effective treatment of AIDS with antiretroviral therapy can prevent the progression of progressive multifocal leukoencephalopathy. Allogeneic BK virus–specific T cells are a potentially beneficial therapy for PML.

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CHAPTER 302

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Ericka V. Hayes

Advances in research and major improvements in the treatment and management of HIV infection have brought about a substantial decrease in the incidence of new HIV infections and AIDS in children. Globally, from 2000 to 2015, there has been an estimated 70% decline in new infections in children aged 0-14 yr, largely the result of antiretroviral treatment (ART) of HIV-infected pregnant women for the prevention of mother-to-child transmission. Seventy percent of adults and children with HIV infection live in sub-Saharan Africa, where the disease continues to have a devastating impact (Fig. 302.1). Children experience more rapid disease progression than adults, with up to half of untreated children dying within the first 2 yr of life. This rapid progression is correlated with a higher viral burden and faster depletion of infected CD4 lymphocytes in infants and children than in adults. Accurate diagnostic tests and the early initiation of potent drugs to inhibit HIV replication have dramatically increased the ability to prevent and control this disease.

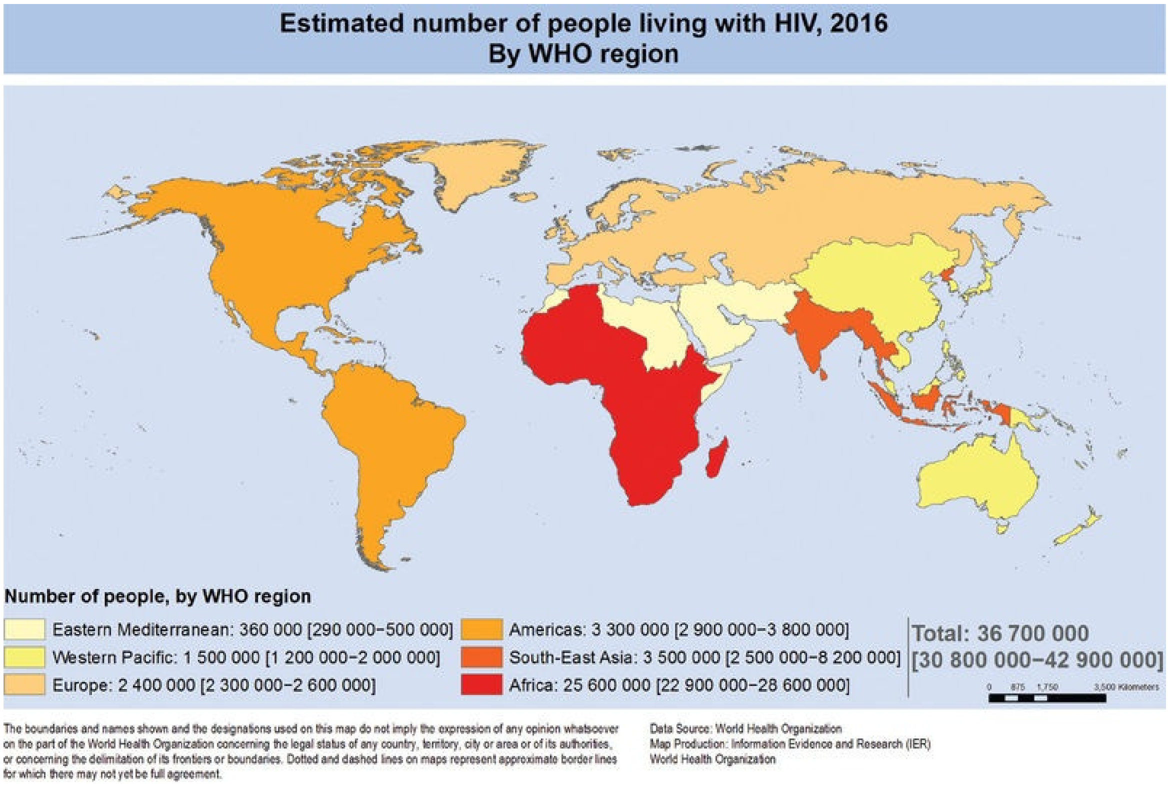
Estimated number of people living with HIV, 2016
By WHO region
Number of people, by WHO region
Eastern Mediterranean: 360 000 [290 000–500 000]
Western Pacific: 1 500 000 [1 200 000–2 000 000]
Europe: 2 400 000 [2 300 000–2 600 000]
Americas: 3 300 000 [2 900 000–3 800 000]
South-East Asia: 3 500 000 [2 500 000–8 200 000]
Africa: 25 600 000 [22 900 000–28 600 000]
Total: 36 700 000
[30 800 000–42 900 000]
0 875 1,750 3,500 Kilometers
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization

FIG. 302.1 Estimated number of people living with HIV in 2016 by WHO region. Data from WHO 2017 report. (Courtesy World Health Organization, 2017. Global Health Observatory (GHO) data. http://www.who.int/gho/hiv/epidemic_status/cases_all/en/ .)

Etiology

HIV-1 and HIV-2 are members of the Retroviridae family and belong to the *Lentivirus* genus, which includes cytopathic viruses causing diverse diseases in several animal species. The HIV-1 genome contains two copies of single-stranded RNA that is 9.2 kb in size. At both ends of the genome there are identical regions, called **long terminal repeats,** which contain the regulation and expression genes of HIV. The remainder of the genome includes three major sections: the **GAG** region, which encodes the viral core proteins (p24 [capsid protein: CA], p17 [matrix protein: MA], p9, and p6, which are derived from the precursor p55); the **POL** region, which encodes the viral enzymes (i.e., reverse transcriptase [p51], protease [p10], and integrase [p32]); and the **ENV** region, which encodes the viral envelope proteins (gp120 and gp41, which are derived from the precursor gp160). Other regulatory proteins, such as transactivator of transcription (tat: p14), regulator of virion (rev: p19), negative regulatory factor (nef: p27), viral protein r (vpr: p15), viral infectivity factor (vif: p23), viral protein u (vpu in HIV-1: P16), and viral protein x (vpx in HIV-2: P15), are involved in transactivation, viral messenger RNA expression, viral replication, induction of cell cycle arrest, promotion of nuclear import of viral reverse transcription complexes, downregulation of the CD4 receptors and class I major histocompatibility complex, proviral DNA synthesis, and virus release and infectivity (Fig. 302.2).

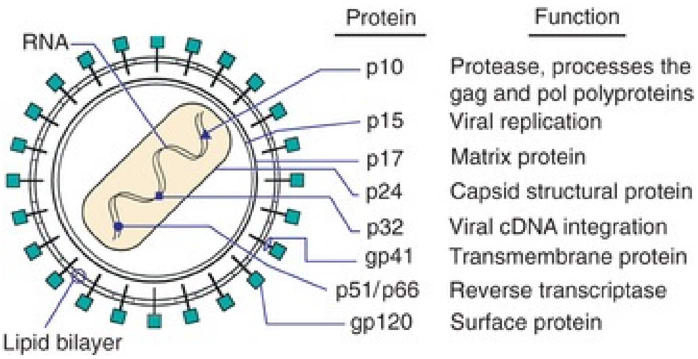

RNA
Lipid bilayer
Protein
Function
p10
Protease, processes the gag and pol polyproteins
p15
Viral replication
p17
Matrix protein
p24
Capsid structural protein
p32
Viral cDNA integration
gp41
Transmembrane protein
p51/p66
Reverse transcriptase
gp120
Surface protein

FIG. 302.2 The human immunodeficiency virus and associated proteins and their functions.

The HIV tropism to the target cell is determined by its envelope glycoprotein (Env). Env consists of two components, namely, the surface, heavily glycosylated subunit, gp120 protein and the associated transmembrane subunit glycoprotein gp41. Both gp120 and gp41 are produced from the precursor protein gp160. The glycoprotein gp41 is very immunogenic and is used to detect HIV-1 antibodies in diagnostic assays; gp120 is a complex molecule that includes the highly variable **V3 loop.** This region is immunodominant for neutralizing antibodies. The heterogeneity of gp120 presents major obstacles in establishing an effective HIV vaccine. The gp120 glycoprotein also carries the binding site for the CD4 molecule, the most common host cell surface receptor of T lymphocytes. This tropism for CD4$^+$ T cells is beneficial to the virus because of the resulting reduction in the effectiveness of the host immune system. Other CD4-bearing cells include macrophages and microglial cells. The observations that CD4$^-$ cells are also infected by HIV and that some CD4$^+$ T cells are resistant to such infections suggests that other cellular attachment sites are needed for the interaction between HIV and human cells. Several chemokines serve as coreceptors for the envelope glycoproteins, permitting membrane fusion and entry into the cell. Most HIV strains have a specific tropism for one of the chemokines, including the fusion-inducing molecule **CXCR-4,** which acts as a coreceptor for HIV attachment to lymphocytes, and **CCR-5,** a β chemokine receptor that facilitates HIV entry into macrophages. Several other chemokine receptors (CCR-3) have also been shown in vitro to serve as virus coreceptors. Other mechanisms of attachment of HIV to cells use nonneutralizing antiviral antibodies and complement receptors. The Fab portion of these antibodies attaches to the virus surface, and the Fc portion binds to cells that express Fc receptors (macrophages, fibroblasts), thus facilitating virus transfer into the cell. Other cell-surface receptors, such as the mannose-binding protein on macrophages or the DC-specific, C-type lectin (DC-SIGN) on dendritic cells, also bind to the HIV-1 envelope glycoprotein and increase the efficiency of viral infectivity. Cell-to-cell transfer of HIV without formation of fully formed particles is a more rapid mechanism of spreading the infection to new cells than is direct infection by the virus.

Following viral attachment, gp120 and the CD4 molecule undergo conformational changes, and gp41 interacts with the fusion receptor on the cell surface (Fig. 302.3). Viral fusion with the cell membrane allows entry of viral RNA into the cell cytoplasm. This process involves accessory viral proteins (nef, vif) and binding of cyclophilin A (a host cellular protein) to the capsid protein (p24). The p24 protein is involved in virus uncoating, recognition by restriction factors, and nuclear importation and integration of the newly created viral DNA. Viral DNA copies are then transcribed from the virion RNA through viral reverse transcriptase enzyme activity, which builds the first DNA strand from the viral RNA and then destroys the viral RNA and builds a second DNA strand to produce double-stranded circular DNA. The HIV-1 reverse transcriptase is error prone and lacks error-correcting mechanisms. Thus, many mutations arise, creating a wide genetic variation in HIV-1 isolates even within an individual patient. Many of the drugs used to fight HIV infection were designed to block the reverse transcriptase action. The circular DNA is transported into the cell nucleus, using viral accessory proteins such as vpr, where it is integrated (with the help of the virus integrase) into the host chromosomal DNA and referred to as the *provirus.* The provirus has the advantage of latency, because it can remain dormant for extended periods, making it extremely difficult to eradicate. The infected $CD4^+$ T cells that survive long enough to revert to resting memory state become the HIV latent reservoir where the virus persists indefinitely even in patients who respond favorably to potent antiretroviral therapy. The molecular mechanisms of this latency are complex and involve unique biologic properties of the latent provirus (e.g., absence of tat, epigenetic changes inhibiting HIV gene expression) and the nature of the cellular host (e.g., absence of transcription factors such as nuclear factor κB). Integration usually occurs near active genes, which allow a high level of viral production in response to various external factors such as an increase in inflammatory cytokines (by infection with other pathogens) and cellular activation. Anti-HIV drugs that block the integrase enzyme activity have been developed. Depending on the relative expression of the viral regulatory genes (tat, rev, nef), the proviral DNA may encode production of the viral RNA genome, which, in turn, leads to production of viral proteins necessary for viral assembly.

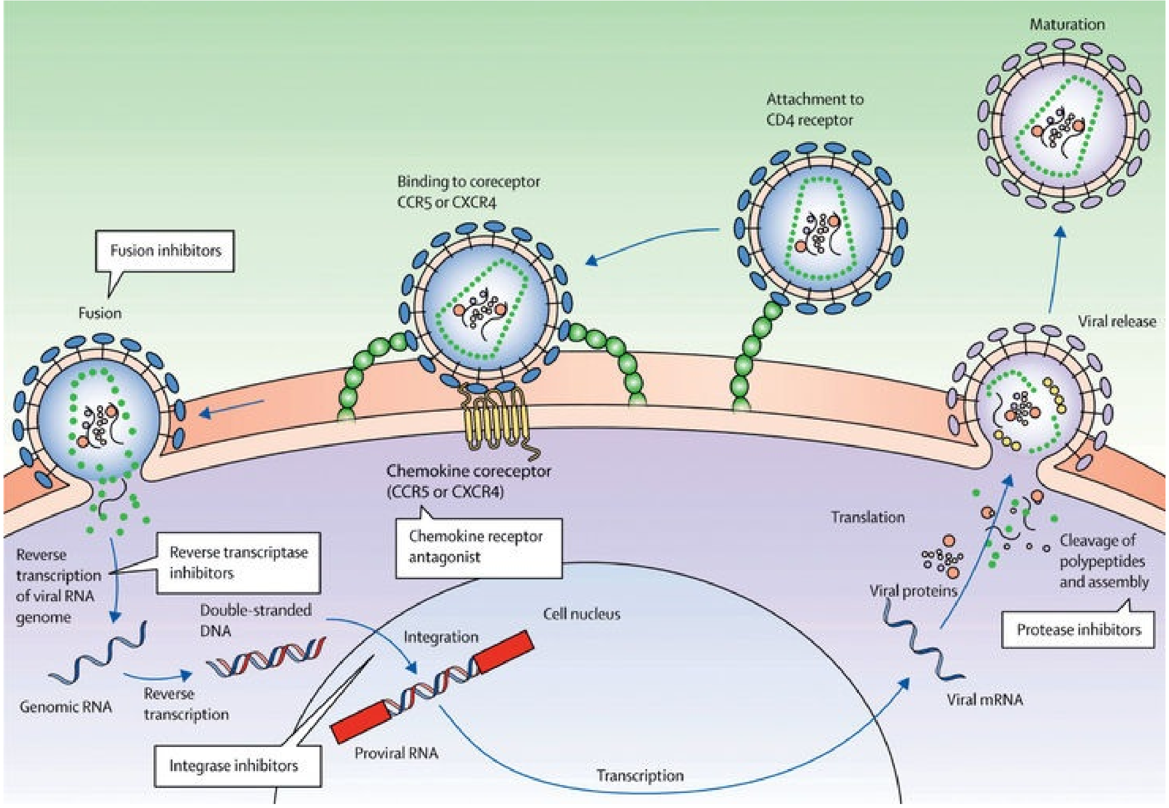
Maturation
Attachment to CD4 receptor
Binding to coreceptor CCR5 or CXCR4
Fusion inhibitors
Fusion
Viral release
Chemokine coreceptor (CCR5 or CXCR4)
Translation
Chemokine receptor antagonist
Reverse transcription of viral RNA genome
Reverse transcriptase inhibitors
Cleavage of polypeptides and assembly
Viral proteins
Cell nucleus
Double-stranded DNA
Integration
Protease inhibitors
Genomic RNA
Reverse transcription
Viral mRNA
Integrase inhibitors
Proviral RNA
Transcription

FIG. 302.3 HIV life cycle showing the sites of action and different classes of antiretroviral drugs. (Adapted from Walker BN, Colledge NR, Ralston SH, Penman I, editors: Davidson's principles and practice of medicine, ed 22, London, 2014, Churchill Livingstone.)

HIV-1 transcription is followed by translation. A capsid polyprotein is cleaved to produce the virus-specific protease (p10), among other products. This enzyme is critical for HIV-1 assembly because it cleaves the long polyproteins into the proper functional pieces. Several HIV-1 antiprotease drugs have been developed, targeting the increased sensitivity of the viral protease, which differs from the cellular proteases. The regulatory protein vif is active in virus assembly and Gag processing. The RNA genome is then incorporated into the newly formed viral capsid that requires zinc finger domains (p7) and the matrix protein (MA: p17). The matrix protein forms a coat on the inner surface of the viral membrane, which is essential for the budding of the new virus from the host cell's surface. As new virus is formed, it buds through specialized membrane areas, known as *lipid rafts*, and is released. The virus release is facilitated by the viroporin vpu, which induces rapid degradation of newly synthesized CD4 molecules that impede viral budding. In addition, vpu counteracts host innate immunity (e.g., hampering natural killer T-cell activity).

Full-length sequencing of the HIV-1 genome demonstrated three different groups (M [main], O [outlier], and N [non-M, non-O]), probably occurring from multiple zoonotic infections from primates in different geographic regions. The same technique identified eight groups of HIV-2 isolates. Group M diversified to nine subtypes (or clades A to D, F to H, J, and K). In each region of the world, certain clades predominate, for example, clade A in Central Africa, clade B in the United States and South America, clade C in South Africa, clade E in Thailand, and clade F in Brazil. Although some subtypes were identified within group O, none was found in any of the HIV-2 groups. Clades are mixed in some patients as a result of HIV recombination, and some crossing between groups (i.e., M and O) has been reported.

HIV-2 has a similar life cycle to HIV-1 and is known to cause infection in several monkey species. Subtypes A and B are the major causes of infection in humans, but rarely cause infection in children. HIV-2 differs from HIV-1 in its accessory genes (e.g., it has no *vpu* gene but contains the *vpx* gene, which is not found in HIV-1). It is most prevalent in western Africa, but increasing numbers of cases are reported from Europe and southern Asia. The diagnosis of HIV-2 infection is more difficult because of major differences in the genetic sequences between HIV-1 and HIV-2. Thus, several of the standard confirmatory assays (immunoblot), which are HIV-1 specific, may give indeterminate results with HIV-2 infection. If HIV-2 infection is suspected, a combination screening test that detects antibody to HIV-1 and HIV-2 peptides should be used. In addition, the rapid HIV detection tests have been less reliable in patients suspected to be dually infected with HIV-1 and HIV-2, because of lower antibody concentrations against HIV-2. HIV-2 viral loads also have limited availability. Notably, HIV-2 infection demonstrates a longer asymptomatic stage of infection and slower declines of CD4+ T-cell counts than HIV-1, as well as is less efficiently transmitted from mother to child, likely related to lower levels of viremia with HIV-2.

Epidemiology

In 2015, the World Health Organization (WHO) estimated that 1.8 million children younger than 15 yr of age worldwide were living with HIV-1 infection; the 150,000 new infections annually in children was a 70% reduction since 2000. Approximately 80% of new infections in this age-group occur in sub-Saharan Africa. These trends reflect the slow but steady expansion of services to prevent perinatal transmission of HIV to infants. Notably, there are still 110,000 deaths worldwide of children < 15 yr of age with HIV. Unfortunately, through 2016, an estimated 16.5 million children have been orphaned by AIDS, defined as having one or both parents die from AIDS.

Globally, the vast majority of HIV infections in childhood are the result of **vertical transmission** from an HIV-infected mother. In the United States, approximately 11,700 children, adolescents, or young adults were reported to be living with perinatally acquired HIV infection in 2014. The number of U.S. children with AIDS diagnosed each year increased from 1984 to 1992 but then declined by more than 95% to < 100 cases annually by 2003, largely from the success of prenatal screening and perinatal antiretroviral treatment of HIV-infected mothers and infants. From 2009 to 2013, there were 497 infants born with perinatally acquired HIV in the United States and Puerto Rico. Children of racial and ethnic minority groups are disproportionately overrepresented, particularly non-Hispanic African-Americans and Hispanics. Race and ethnicity are not risk factors for HIV infection but more likely reflect other social factors that may be predictive of an increased risk for HIV infection, such as lack of educational and economic opportunities. As of 2014, New York, Florida, Texas, Georgia, Illinois, and California are the states with the highest numbers of perinatally acquired cases of HIV in the United States.

Adolescents (13-24 yr of age) constitute an important growing population of newly infected individuals; in 2015, 22% of all new HIV infections occurred in this age-group, with 81% of youth cases occurring in young males who have sex with males (MSM); 8% of cases of AIDS also occurred in this age-group.

Targeted efforts have decreased new cases by 18% among youth MSM from 2008 to 2014. It is estimated than 50% of HIV-positive youth are unaware of their diagnosis, the highest of any age-group. Considering the long latency period between the time of infection and the development of clinical symptoms, reliance on AIDS case definition surveillance data significantly underrepresents the impact of the disease in adolescents. Based on a median incubation period of 8-12 yr, it is estimated that 15–20% of all AIDS cases were acquired between 13 and 19 yr of age.

Risk factors for HIV infection vary by gender in adolescents. For example, 91–93% of males between the ages of 13 and 24 yr with HIV acquire infection through sex with males. In contrast, 91–93% of adolescent females with HIV are infected through heterosexual contact. Adolescent racial and ethnic minority populations are overrepresented, especially among females.

Transmission

Transmission of HIV-1 occurs via sexual contact, parenteral exposure to blood, or vertical transmission from mother to child via exposure to vaginal secretions during birth or via breast milk. The primary route of infection in the pediatric population (<15 yr) is vertical transmission. Rates of transmission of HIV from mother to child have varied in high- and low-resource countries; the United States and Europe have documented transmission rates in untreated women of between 12% and 30%, whereas transmission rates in Africa and Haiti have been higher (25–52%), likely because of more advanced maternal disease and the presence of coinfections. *Perinatal treatment of HIV-infected pregnant women with antiretroviral drugs has dramatically decreased the rate to < 2%.*

Vertical transmission of HIV can occur before delivery **(intrauterine),** during delivery **(intrapartum),** or after delivery **(postpartum** through **breastfeeding).** Although intrauterine transmission has been suggested by identification of HIV by culture or polymerase chain reaction (PCR) in fetal tissue as early as 10 wk, statistical modeling data suggest that the majority of in utero transmissions likely occur in late gestation, when the vascular integrity of the placenta weakens and microtransfusions across the maternal–fetal circulation occur. It is generally accepted that 20–30% of infected newborns are infected in utero, because this percentage of infants has laboratory evidence of infection (positive viral culture or PCR) within the first week of life. Some studies have found that viral detection soon after birth is also correlated with an early onset of symptoms and rapid progression to AIDS, consistent with more long-standing infection during gestation.

A higher percentage of HIV-infected children acquire the virus intrapartum, evidenced by the fact that 70–80% of infected infants do not demonstrate detectable virus until after 1 wk of age. The mechanism of transmission appears to be mucosal exposure to infected blood and cervicovaginal secretions in the birth canal, and intrauterine contractions during active labor/delivery could also increase the risk of late microtransfusions. Breastfeeding is the least-common route of vertical transmission in high resource nations, but is responsible for as much as 40% of perinatal infections in resource-limited countries. Both free and cell-associated viruses have been detected in breast milk from HIV-infected mothers. The risk for transmission through breastfeeding is approximately 9–16% in women with established infection, but is 29–53% in women who acquire HIV postnatally, suggesting that the viremia experienced by the mother during primary infection at least triples the risk for transmission. Where replacement feeding is readily available and safe, it seems reasonable for women to substitute infant formula for breast milk if they are known to be HIV infected or are at risk for ongoing sexual or parenteral exposure to HIV. However, the WHO recommends that in low-resource countries where other diseases (diarrhea, pneumonia, malnutrition) substantially contribute to a high infant mortality rate, the benefit of breastfeeding outweighs the risk for HIV transmission, and HIV-infected women in developing countries should exclusively breastfeed their infants for at least the first 6 mo of life (see Prevention later in this chapter).

Several risk factors influence the rate of vertical transmission: maternal viral load at delivery, preterm delivery (<34 wk gestation), and low maternal antenatal CD4 count. The most important variable appears to be the level of maternal viremia; the odds of transmission may be increased more than two-fold for every $\log_{10}$ increase in viral load at delivery. Elective cesarean delivery was shown to decrease transmission by 87% if used in conjunction with zidovudine therapy in the mother and infant. However, because these data predated the advent of **combined antiretroviral therapy (cART,** also called **HAART),** the additional benefit of cesarean section appears to be negligible if the mother's viral load is < 1,000 copies/mL. It should be noted that rarely (≤0.1%), transmission may occur with maternal viral loads < 50 copies/mL.

Transfusions of infected blood or blood products have accounted for 3–6% of all pediatric AIDS cases. The period of highest risk was between 1978 and 1985, before the availability of HIV antibody–screened blood products. Whereas the prevalence of HIV infection in individuals with hemophilia treated before 1985 was as high as 70%, heat treatment of factor VIII concentrate and HIV antibody screening of donors has virtually eliminated HIV transmission in this population. Donor screening has dramatically reduced, but not eliminated, the risk for blood transfusion–associated HIV infection: nucleic acid amplification testing of minipools (pools of 16-24 donations) performed on antibody-nonreactive blood donations (to identify donations made during the window period before seroconversion) reduced the residual risk of transfusion-transmitted HIV-1 to approximately 1 in 2 million blood units. However, in many resource-limited countries, screening of blood is not uniform, and the risk for transmitting HIV infection via transfusion remains in these settings.

Although HIV can be isolated rarely from saliva, it is in very low titers (<1 infectious particle/mL) and has not been implicated as a transmission vehicle. Studies of hundreds of household contacts of HIV-infected individuals have found that the risk for household HIV transmission is essentially nonexistent. Only a few cases have been reported in which urine or feces (possibly devoid of visible blood) have been proposed as a possible vehicle of HIV transmission, though these cases have not been fully verified.

In the pediatric population, sexual transmission is infrequent, but a small number of cases resulting from sexual abuse have been reported. Sexual contact is a major route of transmission in the adolescent population, accounting for most of the cases.

Pathogenesis

HIV infection affects most of the immune system and disrupts its homeostasis (see Fig. 302.3). In most cases, the initial infection is caused by low amounts of a single virus. Therefore, disease may be prevented by prophylactic drug(s) or vaccine. When the mucosa serves as the portal of entry for HIV, the first cells to be affected are the dendritic cells. These cells collect and process antigens introduced from the periphery and transport them to the lymphoid tissue. HIV does not infect the dendritic cell but binds to its DC-SIGN surface molecule, allowing the virus to survive until it reaches the lymphatic tissue. In the lymphatic tissue (e.g., lamina propria, lymph nodes), the virus selectively binds to cells expressing CD4 molecules on their surface, primarily helper T lymphocytes (CD4$^+$ T cells) and cells of the monocyte-macrophage lineage. Other cells bearing CD4, such as microglia, astrocytes, oligodendroglia, and placental tissue containing villous Hofbauer cells, may also be infected by HIV. Additional factors (coreceptors) are necessary for HIV fusion and entry into cells. These factors include the chemokines CXCR4 (fusion) and CCR5. Other chemokines (CCR1, CCR3) may be necessary for the fusion of certain HIV strains. Several host genetic determinants affect the susceptibility to HIV infection, the progression of disease, and the response to treatment. These genetic variants vary in different populations. A deletion in the CCR5 gene that is protective against HIV infection (CCR5Δ32) is relatively common in whites but is rare in individuals of African descent. Several other genes that regulate chemokine receptors, ligands, the histocompatibility complex, and cytokines also influence the outcome of HIV infection. Usually, $CD4^+$ lymphocytes migrate to the lymphatic tissue in response to viral antigens and then become activated and proliferate, making them highly susceptible to HIV infection. This antigen-driven migration and accumulation of CD4 cells within the lymphoid tissue may contribute to the generalized lymphadenopathy characteristic of the acute retroviral syndrome in adults and adolescents. HIV preferentially infects the very cells that respond to it (HIV-specific memory CD4 cells), accounting for the progressive loss of these cells and the subsequent loss of control of HIV replication. The continued destruction of memory $CD4^+$ cells in the gastrointestinal tract (in the gut-associated lymphoid tissue or GALT) leads to reduced integrity of the gastrointestinal epithelium followed by leakage of bacterial particles into the blood and increased inflammatory response, which cause further $CD4^+$ cell loss. When HIV replication reaches a threshold (usually within 3-6 wk from the time of infection), a burst of plasma viremia occurs. This intense viremia causes acute HIV infection, formerly known as **acute retroviral syndrome** which can present similar to the **flu or mononucleosis** (fever, rash, pharyngitis, lymphadenopathy, malaise, arthralgia, fatigue, elevated liver enzymes) in 50–70% of infected adults. With establishment of a cellular and humoral immune response within 2-4 mo, the viral load in the blood declines substantially, and patients enter a phase characterized by a lack of symptoms and a return of CD4 cells to only moderately decreased levels. Typically, adult patients who are not treated eventually progress to achieve a virologic set point (steady state), usually ranging from 10,000-100,000 during this clinical latency. This is in contrast to untreated infants with vertically acquired HIV who can achieve viral loads that are much higher, resulting in faster CD4 count declines and earlier onset of significant immunodeficiency. HIV rapidly responds to the immune system pressure by developing a genetically complex population (quasispecies) that successfully evades it. In addition, inappropriate use of antiretroviral treatment increases the ability of the virus to diverge even further by selecting for mutants with fitness or resistance advantages in the presence of subtherapeutic drug levels. Early HIV-1 replication in children has no apparent clinical manifestations. Whether tested by virus isolation or by PCR for viral nucleic acid sequences, fewer than 40% of HIV-1–infected infants demonstrate evidence of the virus at birth. The viral load increases by 1-4 mo, and essentially all perinatally HIV-infected infants have detectable HIV-1 in peripheral blood by 4 mo of age, except for those who may acquire infection via ongoing breast feeding.

In adults, the long period of clinical latency (8-12 yr) is not indicative of viral latency. In fact, there is a very high turnover of virus and CD4 lymphocytes (more than a billion cells per day), gradually causing deterioration of the immune system, marked by depletion of CD4 cells. Several mechanisms for the depletion of CD4 cells in adults and children have been suggested, including HIV-mediated single cell killing, formation of multinucleated giant cells of infected and uninfected CD4 cells **(syncytia formation),** virus-specific immune responses (natural killer cells, antibody-dependent cellular cytotoxicity), superantigen-mediated activation of T cells (rendering them more susceptible to infection with HIV), autoimmunity, and programmed cell death (apoptosis). The viral burden is greater in the lymphoid organs than in the peripheral blood during the asymptomatic period. As HIV virions and their immune complexes migrate through the lymph nodes, they are trapped in the network of dendritic follicular cells. Because the ability of HIV to replicate in T cells depends on the state of activation of the cells, the immune activation that takes place within the microenvironment of the lymph nodes in HIV disease serves to promote infection of new CD4 cells, as well as subsequent viral replication within these cells. Monocytes and macrophages can be productively infected by HIV yet resist the cytopathic effect of the virus and, with their long lifespan, explain their role as reservoirs of HIV and as effectors of tissue damage in organs such as the brain. In addition, they reside in anatomic viral sanctuaries where current treatment agents are less effective.

The innate immune system responds almost immediately following HIV infection by recognizing the viral nucleic acids, once the virus fuses to the infected cell, by the toll-like receptor 7. This engagement leads to activation of proinflammatory cytokines and interferon (IFN-α), which blocks virus replication and spread. The virus uses its Nef protein to downregulate the expression of major histocompatibility complex (MHC) and non-MHC ligands to reduce the natural killer (NK) cell–mediated anti-HIV activity. It also modulates NK cell differentiation and maturation, dysregulates cytokine production, and increases apoptosis. Although the mechanism by which the innate system triggers the adaptive immune responses is not yet fully understood, cell-mediated and humoral responses occur early in the infection. CD8 T cells play an important role in containing the infection. These cells produce various ligands (macrophage inflammatory proteins 1α and 1β, RANTES), which suppress HIV replication by blocking the binding of the virus to the coreceptors (CCR5). HIV-specific cytotoxic T lymphocytes (CTLs) develop against both the structural (ENV, POL, GAG) and regulatory (tat) viral proteins. The CTLs appear at the end of the acute infection, as viral replication is controlled by killing HIV-infected cells before new viruses are produced and by secreting potent antiviral factors that compete with the virus for its receptors (CCR5). Neutralizing antibodies appear later in the infection and seem to help in the continued suppression of viral replication during clinical latency. There are at least two possible mechanisms that control the steady-state viral load level during the chronic clinical latency. One mechanism may be the limited availability of activated CD4 cells, which prevent a further increase in the viral load. The other mechanism is the development of an active immune response, which is influenced by the amount of viral antigen and limits viral replication at a steady state. There is no general consensus about which of these two mechanisms is more important. The CD4 cell limitation mechanism accounts for the effect of antiretroviral therapy, whereas the immune response mechanism emphasizes the importance of immune modulation treatment (cytokines, vaccines) to increase the efficiency of immune-mediated control. A group of cytokines that includes tumor necrosis factor TNF-α, TNF-β, interleukin IL-1, IL-2, IL-3, IL-6, IL-8, IL-12, IL-15, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor plays an integral role in upregulating HIV expression from a state of quiescent infection to active viral replication. Other cytokines such as IFN-γ, IFN-β, and IL-13 exert a suppressive effect on HIV replication. Certain cytokines (IL-4, IL-10, IFN-γ, transforming growth factor-β) reduce or enhance viral replication depending on the infected cell type. The interactions among these cytokines influence the concentration of viral particles in the tissues. Plasma concentrations of cytokines need not be elevated for them to exert their effect, because they are produced and act locally in the tissues. The activation of virtually all the cellular components of the immune system (i.e., T and B cells, NK cells, and monocytes) plays a significant role in the pathologic aspects of HIV infection. Further understanding of their interactions during the infection will expand our treatment options. Commonly, HIV isolated during the clinical latency period grows slowly in culture and produces low titers of reverse transcriptase. These isolates from earlier in clinical latency use CCR5 as their coreceptor. By the late stages of clinical latency, the isolated virus is phenotypically different. It grows rapidly and to high titers in culture and uses CXCR4 as its coreceptor. The switch from CCR5 receptor to CXCR4 receptor increases the capacity of the virus to replicate, to infect a broader range of target cells (CXCR4 is more widely expressed on resting and activated immune cells), and to kill T cells more rapidly and efficiently. As a result, the clinical latency phase is over and progression toward AIDS is noted. The **progression of disease** is related temporally to the gradual disruption of lymph node architecture and degeneration of the follicular dendritic cell network with loss of its ability to trap HIV particles. The virus is freed to recirculate, producing high levels of viremia and an increased disappearance of CD4 T cells during the later stages of disease.

The clinical course of HIV infection shows substantial heterogeneity. This variation is determined by both viral and host factors. HIV viruses that use coreceptor CXCR4 in the course of the infection are associated with an accelerated deterioration of the immune system and more rapid progression to AIDS. In addition, several known host genetic determinants (e.g., variants in the human leukocyte antigen region, polymorphisms in the CCR5 region such as CCR5Δ32) were already identified as affecting the disease course. There are likely additional host and viral factors yet to be identified that contribute to the variable course of HIV infection in individuals, as well. **Three distinct patterns of disease** are described in children. Approximately 15–25% of HIV-infected newborns in developed countries present with a **rapid progression** course, with onset of AIDS and symptoms during the first few months of life and a median survival time of 6-9 mo if untreated. In resource-limited countries, the majority of HIV-infected newborns will have this rapidly progressing disease course. It has been suggested that if intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus, the virus could effectively infect the majority of the body's immunocompetent cells. The normal migration of these cells to the marrow, spleen, and thymus would result in efficient systemic delivery of HIV, unchecked by the immature immune system of the fetus. Thus, infection would be established before the normal ontogenic development of the immune system, causing more-severe impairment of immunity. Most children in this group have detectable virus in the plasma (median level: 11,000 copies/mL) in the first 48 hr of life. This early evidence of viral presence suggests that the newborn was infected in utero. The viral load rapidly increases, peaking by 2-3 mo of age (median: 750,000 copies/mL) and staying high for at least the first 2 yr of life.

Sixty percent to 80% of perinatally infected newborns in high resource countries present with a much **slower progression** of disease, with a median survival time of 6 yr representing the second pattern of disease. Many patients in this group have a negative PCR in the first week of life and are therefore considered to be infected intrapartum. In a typical patient, the viral load rapidly increases, peaking by 2-3 mo of age (median: 100,000 copies/mL) and then slowly declines over a period of 24 mo. The slow decline in viral load is in sharp contrast to the rapid decline after primary infection seen in adults. This observation can be explained only partially by the immaturity of the immune system in newborns and infants.

The third pattern of disease occurs in < 5% of perinatally infected children, referred to as **long-term survivors** or **long-term nonprogressors,** who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 yr. Mechanisms for the delay in disease progression include effective humoral immunity and/or CTL responses, host genetic factors (e.g., human leukocyte antigen profile), and infection with an attenuated (defective-gene) virus. A subgroup of the long-term survivors called elite survivors or elite suppressors has no detectable virus in the blood and may reflect different or greater mechanisms of protection from disease progression. Note that both groups warrant long-term close follow-up because later in their course they may begin to progress with their disease.

HIV-infected children have changes in the immune system that are similar to those in HIV-infected adults. Absolute CD4 cell depletion may be less dramatic because infants normally have a relative lymphocytosis. A value of 750 CD4 cells/µL in children younger than 1 yr of age is indicative of severe CD4 depletion and is comparable to < 200 CD4 cells/µL in adults. Lymphopenia is relatively rare in perinatally infected children and is usually only seen in older children or those with end-stage disease. Although cutaneous anergy is common during HIV infection, it is also frequent in healthy children younger than 1 yr of age, and thus its interpretation is difficult in infected infants. The depletion of CD4 cells also decreases the response to soluble antigens such as the in vitro mitogens phytohemagglutinin and concanavalin A.

Polyclonal activation of B cells occurs in most children early in the infection, as evidenced by elevation of immunoglobulins IgA, IgM, IgE, and, particularly, IgG **(hypergammaglobulinemia),** with high levels of anti–HIV-1 antibody. This response may reflect both dysregulation of the T-cell suppression of B-cell antibody synthesis and active CD4 enhancement of the B-lymphocyte humoral response. As a result, the antibody response to routine childhood vaccinations may be abnormal. The B-cell dysregulation precedes the CD4 depletion in many children and may serve as a surrogate marker of HIV infection in symptomatic children in whom specific diagnostic tests (PCR, culture) are not available or are too expensive. Despite the increased levels of immunoglobulins, some children lack specific antibodies or protective antibodies. Hypogammaglobulinemia is very rare (<1%).

Central nervous system (CNS) involvement is more common in pediatric patients than in adults. Macrophages and microglia play an important role in HIV neuropathogenesis, and data suggest that astrocytes may also be involved. Although the specific mechanisms for encephalopathy in children are not yet clear, the developing brain in young infants is affected by at least two mechanisms. The virus itself may directly infect various brain cells or cause indirect damage to the nervous system by the release of cytokines (IL-1α, IL-1β, TNF-α, IL-2) or reactive oxygen damage from HIV-infected lymphocytes or macrophages.

Clinical Manifestations

The clinical manifestations of HIV infection vary widely among infants, children, and adolescents. In most infants, physical examination at birth is normal. Initial symptoms may be subtle, such as lymphadenopathy and hepatosplenomegaly, or nonspecific, such as failure to thrive, chronic or recurrent diarrhea, respiratory symptoms, or oral thrush and may be distinguishable only by their persistence. Whereas systemic and pulmonary findings are common in the United States and Europe, chronic diarrhea, pneumonia, wasting, and severe malnutrition predominate in Africa. Clinical manifestations found more commonly in children than adults with HIV infection include recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis (LIP), and early onset of progressive neurologic deterioration; note that chronic parotid swelling and LIP are associated with a slower progression of disease.

The CDC Surveillance Case Definition for HIV infection is based on the age-specific $CD4^+$ T-lymphocyte count or the $CD4^+$ T-lymphocyte percentage of total lymphocytes (Table 302.1), except when a stage 3–defining opportunistic illness (Table 302.2) supersedes the CD4 data. Age adjustment of the absolute CD4 count is necessary because counts that are relatively high in normal infants decline steadily until age 6 yr, when they reach adult norms. The CD4 count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is unavailable.

Table 302.1

HIV Infection Stage[*] Based on Age-Specific $CD4^+$ T-Lymphocyte Count or $CD4^+$ T-Lymphocyte Percentage of Total Lymphocytes

STAGE	AGE ON DATE OF $CD4^+$ T-LYMPHOCYTE TEST					
	<1 Yr		**1-5 Yr**		**≥6 Yr**	
	CELLS/µL	**%**	**CELLS/µL**	**%**	**CELLS/µL**	**%**
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750-1,499	26-33	500-999	22-29	200-499	14-25
3	<750	<26	<500	<22	<200	<14

[*] Stage is based primarily on the $CD4^+$ T-lymphocyte count. The $CD4^+$ T-lymphocyte count takes precedence over the $CD4^+$ T-lymphocyte percentage, and the percentage is considered only if the count is missing.

From Centers for Disease Control and Prevention: Revised surveillance case definition for HIV infection—United States, 2014, MMWR 63(No RR-3):1-10, 2014.

Table 302.2

Stage 3–Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent[*]
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive [†]
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 mo duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 mo
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV [‡]

Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 mo)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 mo duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii,* disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary,[†] disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci (previously known as *Pneumocystis carinii*) pneumonia
Pneumonia, recurrent[†]
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age > 1 mo
Wasting syndrome attributed to HIV[‡]

[*] Only among children aged < 6 yr.

[†] Only among adults, adolescents, and children aged ≥ 6 yr.

[‡] Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: Centers for Disease Control and Prevention: 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age, MMWR 43(No. RR-12), 1994; Centers for Disease Control and Prevention: 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults, MMWR 41(No. RR-17), 1992.

From Centers for Disease Control and Prevention: Revised surveillance case definition for HIV infection—United States, 2014, MMWR 63(No RR-3):1-10, 2014.

Infections

Approximately 20% of AIDS-defining illnesses in children are recurrent bacterial infections caused primarily by encapsulated organisms such as *Streptococcus pneumoniae* and *Salmonella* as a result of disturbances in humoral immunity. Other pathogens, including *Staphylococcus, Enterococcus, Pseudomonas aeruginosa,* and *Haemophilus influenzae,* and other Gram-positive and Gram-negative organisms may also be seen. The most common serious infections in HIV-infected children are bacteremia, sepsis, and bacterial pneumonia, accounting for more than 50% of infections in these patients. Meningitis, urinary tract infections, deep-seated abscesses, and bone/joint infections occur less frequently. Milder recurrent infections, such as otitis media, sinusitis, and skin and soft tissue infections, are very common and may be chronic with atypical presentations.

Opportunistic infections are generally seen in children with severe depression of the CD4 count. In adults, these infections often represent reactivation of a latent infection acquired early in life. In contrast, young children generally have primary infection and often have a more fulminant course of disease reflecting the lack of prior immunity. In addition, infants < 1 yr of age have a higher incidence of developing stage 3–defining opportunistic infections and mortality rates compared with older children and adults even at higher CD4 counts, reflecting that the CD4 count may overpredict the immune competence in young infants. This principle is best illustrated by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, the most common opportunistic infection in the pediatric population (see Chapter 271). The peak incidence of *Pneumocystis* pneumonia occurs at age 3-6 mo in the setting of undiagnosed perinatally acquired disease, with the highest mortality rate in children younger than 1 yr of age. Aggressive approaches to treatment have improved the outcome substantially. Although the overall incidence of opportunistic infections has markedly declined since the era of combination antiretroviral therapy, opportunistic infections still occur in patients with severe immunodepletion as the result of unchecked viral replication, which often accompanies poor antiretroviral therapy adherence.

The classic clinical presentation of *Pneumocystis* pneumonia includes an acute onset of fever, tachypnea, dyspnea, and marked hypoxemia; in some children, more indolent development of hypoxemia may precede other clinical or x-ray manifestations. In some cases, fever may be absent or low grade, particularly in more indolent cases. Chest x-ray findings most commonly consist of interstitial infiltrates or diffuse alveolar disease, which rapidly progresses. Chest x-ray in some cases can have very subtle findings and can mimic the radiologic appearance of viral bronchiolitis. Nodular lesions, streaky or lobar infiltrates, or pleural effusions may occasionally be seen. The diagnosis is established by demonstration of *P. jiroveci* with appropriate staining of induced sputum or bronchoalveolar fluid lavage; rarely, an open lung biopsy is necessary. Bronchoalveolar lavage and open lung biopsy have significantly improved sensitivity (75–95%) for *Pneumocystis* testing than induced sputum (20–40%), such that if an induced sputum is negative it does not exclude the diagnosis. PCR testing on respiratory specimens is also available and is more sensitive than microscopy but also has less specificity; it is also not widely available.

The first-line therapy for *Pneumocystis* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15-20 mg/kg/day of the TMP component divided every 6 hr intravenously) with adjunctive corticosteroids for moderate to severe disease, usually defined as if the Pa_{O_2} is < 70 mm Hg while breathing room air. After improvement, therapy with oral TMP-SMX should continue for a total of 21 days while the corticosteroids are weaned. An alternative therapy for *Pneumocystis* pneumonia includes intravenous administration of pentamidine (4 mg/kg/day). Other regimens such as TMP plus dapsone, clindamycin plus primaquine, or atovaquone are used as alternatives in adults but have not been widely used in children to date.

Nontuberculous mycobacteria (NTM), with *Mycobacterium avium-intracellulare* complex (MAC) being most common, may cause disseminated disease in HIV-infected children who are severely immunosuppressed. The incidence of MAC infection in antiretroviral therapy–naïve children >6 yr with < 100 CD4 cells/µL is estimated to be as high as 10%, but effective cART that results in viral suppression makes MAC infections rare. Disseminated MAC infection is characterized by fever, malaise, weight loss, and night sweats; diarrhea, abdominal pain, and, rarely, intestinal perforation or jaundice (a result of biliary tract obstruction by lymphadenopathy) may also be present. Labs may be notable for significant anemia. The diagnosis is made by the isolation of MAC from blood, bone marrow, or tissue; the isolated presence of MAC in the stool does not confirm a diagnosis of disseminated MAC. Treatment can reduce symptoms and prolong life but is at best only capable of suppressing the infection if severe CD4 depletion persists. Therapy should include at least two drugs: clarithromycin or azithromycin and ethambutol. A third drug (rifabutin, rifampin, ciprofloxacin, levofloxacin, or amikacin) is generally added to decrease the emergence of drug-resistant isolates. Careful consideration of possible drug interactions with antiretroviral agents is necessary before initiation of disseminated MAC therapy. Drug susceptibilities should be ascertained, and the treatment regimen should be adjusted accordingly in the event of an inadequate clinical response to therapy. Because of the great potential for toxicity with most of these medications, surveillance for adverse effects should be ongoing. Less commonly, NTM infections can also be focal in these patients, including lymphadenitis, osteomyelitis, tenosynovitis, and pulmonary disease.

Oral candidiasis is the most common **fungal infection** seen in HIV-infected children. Oral nystatin suspension (2-5 mL qid) is often effective. Clotrimazole troches or fluconazole (3-6 mg/kg orally qd) are effective alternatives. Oral thrush progresses to involve the esophagus in as many as 20% of children with severe CD4 depletion, presenting with symptoms such as anorexia, dysphagia, vomiting, and fever. Treatment with oral fluconazole for 7-14 days generally results in rapid improvement in symptoms. Fungemia rarely occurs, usually in the setting of indwelling venous catheters, and up to 50% of cases may be caused by non–*albicans* species. Disseminated histoplasmosis, coccidioidomycosis, and cryptococcosis are rare in pediatric patients but may occur in endemic areas.

Parasitic infections such as intestinal cryptosporidiosis and microsporidiosis and rarely isosporiasis or giardiasis are other opportunistic infections that cause significant morbidity. Although these intestinal infections are usually self-limiting in healthy hosts, they cause severe chronic diarrhea in HIV-infected children with low CD4 counts, often leading to malnutrition. Nitazoxanide therapy is partially effective at improving cryptosporidia diarrhea, but immune reconstitution with cART is the most important factor for clearance of the infection. Albendazole has been reported to be effective against most microsporidia (excluding *Enterocytozoon bieneusi*), and TMP-SMX appears to be effective for isosporiasis.

Viral infections, especially with the herpesvirus group, pose significant problems for HIV-infected children. HSV causes recurrent gingivostomatitis, which may be complicated by local and distant cutaneous dissemination. Primary varicella-zoster virus infection (chickenpox) may be prolonged and complicated by bacterial superinfections or visceral dissemination, including pneumonitis. Recurrent, atypical, or chronic episodes of herpes zoster are often debilitating and require prolonged therapy with acyclovir; in rare instances, varicella-zoster virus has developed a resistance to acyclovir, requiring the use of foscarnet. Disseminated cytomegalovirus infection occurs in the setting of severe CD4 depletion (<50 CD4 cells/µL for >6 yr) and may involve single or multiple organs. Retinitis, pneumonitis, esophagitis, gastritis with pyloric obstruction, hepatitis, colitis, and encephalitis have been reported, but these complications are rarely seen if cART is given. Ganciclovir and foscarnet are the drugs of choice and are often given together in children with sight-threatening cytomegalovirus retinitis. Intraocular injections of foscarnet or intraocular ganciclovir implants plus oral valganciclovir have also been efficacious in adults and older children with cytomegalovirus retinitis. Measles may occur despite immunization and may present without the typical rash. It often disseminates to the lung or brain with a high mortality rate in these patients. HIV-infected children with low CD4 counts can also develop extensive cutaneous molluscum contagiosum infection. Respiratory viruses such as respiratory syncytial virus and adenovirus may present with prolonged symptoms and persistent viral shedding. In parallel with the increased prevalence of genital tract human papillomavirus infection, cervical intraepithelial neoplasia and anal intraepithelial neoplasia also occur with increased frequency among HIV-1–infected adult women compared with HIV-seronegative women. The relative risk for cervical intraepithelial neoplasia is 5-10 times higher for HIV-1 seropositive women. Multiple modalities are used to treat human papillomavirus infection (see Chapter 293), although none is uniformly effective and the recurrence rate is high among HIV-1–infected persons.

Appropriate therapy with antiretroviral agents may result in **immune reconstitution inflammatory syndrome (IRIS),** which is characterized by an increased inflammatory response from the recovered immune system to subclinical opportunistic infections (e.g., *Mycobacterium* infection, HSV infection, toxoplasmosis, CMV infection, *Pneumocystis* infection, cryptococcal infection). This condition is more commonly observed in patients with progressive disease and severe CD4$^+$ T-lymphocyte depletion. Patients with IRIS develop fever and worsening of the clinical manifestations of the opportunistic infection or new manifestations (e.g., enlargement of lymph nodes, pulmonary infiltrates), typically within the first few weeks after initiation of antiretroviral therapy. Determining whether the symptoms represent IRIS, worsening of a current infection, a new opportunistic infection, or drug toxicity is often very difficult. If the syndrome does represent IRIS, adding nonsteroidal antiinflammatory agents or corticosteroids may alleviate the inflammatory reaction, although the use of corticosteroids is controversial. The inflammation may take weeks or months to subside. In most cases, continuation of cART while treating the opportunistic infection (with or without antiinflammatory agents) is sufficient. If opportunistic infection is suspected prior to the initiation of antiretroviral therapy, appropriate antimicrobial treatment should be started first.

Central Nervous System

The incidence of CNS involvement in perinatally infected children is as high as 50–90% in resource-limited countries but significantly lower in high income countries, with a median onset at 19 mo of age. Manifestations may range from subtle developmental delay to progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly, and symmetric motor dysfunction. **Encephalopathy** may be the initial manifestation of the disease or may present much later when severe immune suppression occurs. With progression, marked apathy, spasticity, hyperreflexia, and gait disturbance may occur, as well as loss of language and oral, fine, and/or gross motor skills. The encephalopathy may progress intermittently, with periods of deterioration followed by transiently stable plateaus. Older children may exhibit behavioral problems and learning disabilities. Associated abnormalities identified by neuroimaging techniques include cerebral atrophy in up to 85% of children with neurologic symptoms, increased ventricular size, basal ganglia calcifications, and, less frequently, leukomalacia.

Fortunately, since the advent of cART, the incident rate of encephalopathy has dramatically declined to as low as 0.08% in 2006. However, as HIV-infected children progress through adolescence and young adulthood, other subtle manifestations of CNS disease are evident, such as cognitive deficits, attention problems, and psychiatric disorders. Living with a chronic, often stigmatizing, disease; parental loss; and the requirement for lifelong pristine medication adherence compounds these issues, making it challenging for these youth as they inherit responsibility for managing their disease as adults.

Focal neurologic signs and seizures are unusual and may imply a comorbid pathologic process such as a CNS tumor, opportunistic infection, or stroke. **CNS lymphoma** may present with new-onset focal neurologic findings, headache, seizures, and mental status changes. Characteristic findings on neuroimaging studies include a hyperdense or isodense mass with variable contrast enhancement or a diffusely infiltrating contrast-enhancing mass. **CNS toxoplasmosis** is exceedingly rare in young infants but may occur in vertically HIV-infected adolescents and is typically associated with serum antitoxoplasma IgG as a marker of infection. Other opportunistic infections of the CNS are rare and include infection with CMV, JC virus **(progressive multifocal leukoencephalopathy),** HSV, *Cryptococcus neoformans,* and *Coccidioides immitis.* Although the true incidence of cerebrovascular disorders (both hemorrhagic and nonhemorrhagic strokes) is unclear, 6–10% of children from large clinical series have been affected.

Respiratory Tract

Recurrent upper respiratory tract infections such as otitis media and sinusitis are very common. Although the typical pathogens *(S. pneumoniae, H. influenzae, Moraxella catarrhalis)* are most common, unusual pathogens such as *P.*

aeruginosa, yeast, and anaerobes may be present in chronic infections and result in complications such as invasive sinusitis and mastoiditis.

LIP (lymphocytic interstitial pneumonia) is the most common chronic lower respiratory tract abnormality reported to the Centers for Disease Control and Prevention (CDC) for HIV-infected children; historically this occurred in approximately 25% of HIV-infected children, although the incidence has declined in the cART era. LIP is a chronic process with nodular lymphoid hyperplasia in the bronchial and bronchiolar epithelium, often leading to progressive alveolar capillary block over months to years. It has a characteristic chronic diffuse reticulonodular pattern on chest radiography rarely accompanied by hilar lymphadenopathy, allowing a presumptive diagnosis to be made radiographically before the onset of symptoms. There is an insidious onset of tachypnea, cough, and mild to moderate hypoxemia with normal auscultatory findings or minimal rales. Progressive disease presents with symptomatic hypoxemia, which usually resolves with oral corticosteroid therapy, accompanied by digital clubbing. Several studies suggest that LIP is a lymphoproliferative response to a primary Epstein-Barr virus infection in the setting of HIV infection. It is also associated with a slower immunologic decline.

Most symptomatic HIV-infected children experience at least one episode of pneumonia during their disease. *S. pneumoniae* is the most common bacterial pathogen, but *P. aeruginosa* and other Gram-negative bacterial pneumonias may occur in end-stage disease and are often associated with acute respiratory failure and death. Rarely, severe recurrent bacterial pneumonia results in bronchiectasis. *Pneumocystis* pneumonia is the most common opportunistic infection, but other pathogens, including CMV, *Aspergillus*, *Histoplasma,* and *Cryptococcus* can cause pulmonary disease. Infection with common respiratory viruses, including respiratory syncytial virus, parainfluenza, influenza, and adenovirus, may occur simultaneously and have a protracted course and period of viral shedding from the respiratory tract. Pulmonary and extrapulmonary tuberculosis (TB) has been reported with increasing frequency in HIV-infected children in low-resource countries, although it is considerably more common in HIV-infected adults. Because of drug interactions between rifampin and ritonavir-based antiretroviral therapy and poor tolerability of the combination of multiple drugs required, treatment of TB/HIV coinfection is particularly challenging in children.

Cardiovascular System

Cardiac dysfunction, including left ventricular hypertrophy, left ventricular dilation, reduced left ventricular fractional shortening, and/or heart failure occurred in 18–39% of HIV-infected children in the pre-cART era; among those affected, a lower nadir CD4 percentage and a higher viral load were associated with lower cardiac function. However, a more current evaluation of HIV-infected children taking long-term cART found that echocardiographic findings were closer to normal and none had symptomatic heart disease, suggesting that cART has a cardioprotective effect. What is still unclear is whether an increased rate of premature cardiovascular disease that has been seen in adults will be seen in children who have disease- or treatment-related hyperlipidemia, and prospective studies will be needed to assess this risk. Because of this risk, regular monitoring of cholesterol and lipids, as well as education regarding a heart-healthy lifestyle, is an important part of pediatric HIV care.

Gastrointestinal and Hepatobiliary Tract

Oral manifestations of HIV disease include erythematous or pseudomembranous candidiasis, periodontal disease (e.g., ulcerative gingivitis or periodontitis), salivary gland disease (i.e., swelling, xerostomia), and, rarely, ulcerations or oral hairy leukoplakia. Gastrointestinal tract involvement is common in HIV-infected children. A variety of pathogens can cause gastrointestinal disease, including bacteria (*Salmonella*, *Campylobacter, Shigella*, MAC), protozoa *(Giardia*, *Cryptosporidium*, *Isospora*, microsporidia), viruses (CMV, HSV, rotavirus), and fungi *(Candida)*. MAC and the protozoal infections are most severe and protracted in patients with severe CD4 cell depletion. Infections may be localized or disseminated and affect any part of the gastrointestinal tract from the oropharynx to the rectum. Oral or esophageal ulcerations, either viral in origin or idiopathic, are painful and often interfere with eating. AIDS enteropathy, a syndrome of malabsorption with partial villous atrophy not associated with a specific pathogen, has been postulated to be a result of direct HIV infection of the gut. Disaccharide intolerance is common in HIV-infected children with chronic diarrhea.

The most common symptoms of gastrointestinal disease are chronic or recurrent diarrhea with malabsorption, abdominal pain, dysphagia, and failure to thrive. Prompt recognition of weight loss or poor growth velocity in the absence of diarrhea is critical. Linear growth impairment is often correlated with the level of HIV viremia. Supplemental enteral feedings should be instituted, either by mouth or with nighttime nasogastric tube feedings in cases associated with more severe chronic growth problems; placement of a gastrostomy tube for nutritional supplementation may be necessary in severe cases. The wasting syndrome, defined as a loss of > 10% of body weight, is not as common as failure to thrive in pediatric patients, but the resulting malnutrition is associated with a grave prognosis. Chronic liver inflammation evidenced by fluctuating serum levels of transaminases with or without cholestasis is relatively common, often without identification of an etiologic agent. Cryptosporidial cholecystitis is associated with abdominal pain, jaundice, and elevated γ-glutamyltransferase. In some patients, chronic hepatitis caused by CMV, hepatitis B, hepatitis C, or MAC may lead to portal hypertension and liver failure. Several of the antiretroviral drugs or other drugs such as didanosine, protease inhibitors, nevirapine, and dapsone may also cause reversible elevation of transaminases.

Pancreatitis with increased pancreatic enzymes with or without abdominal pain, vomiting, and fever may be the result of drug therapy (e.g., with pentamidine, didanosine, or stavudine) or, rarely, opportunistic infections such as MAC or CMV.

Renal Disease

Nephropathy is an unusual presenting symptom of HIV infection, more commonly occurring in older symptomatic children. A direct effect of HIV on renal epithelial cells has been suggested as the cause, but immune complexes, hyperviscosity of the blood (secondary to hyperglobulinemia), and nephrotoxic drugs are other possible factors. A wide range of histologic abnormalities has been reported, including focal glomerulosclerosis, mesangial hyperplasia, segmental necrotizing glomerulonephritis, and minimal change disease. Focal glomerulosclerosis generally progresses to renal failure within 6-12 mo, but other histologic abnormalities in children may remain stable without significant renal insufficiency for prolonged periods. **Nephrotic syndrome** is the most common manifestation of pediatric renal disease, with edema, hypoalbuminemia, proteinuria, and azotemia with normal blood pressure. Cases resistant to steroid therapy may benefit from cyclosporine therapy. Polyuria, oliguria, and hematuria have also been observed in some patients.

Skin Manifestations

Many cutaneous manifestations seen in HIV-infected children are inflammatory or infectious disorders that are not unique to HIV infection. These disorders tend to be more disseminated and respond less consistently to conventional therapy than in the uninfected child. Seborrheic dermatitis or eczema that is severe and unresponsive to treatment may be an early nonspecific sign of HIV infection. Recurrent or chronic episodes of HSV, herpes zoster, molluscum contagiosum, flat warts, anogenital warts, and candidal infections are common and may be difficult to control.

Allergic drug eruptions are also common, in particular related to nonnucleoside reverse transcription inhibitors; they generally respond to withdrawal of the drug but also may resolve spontaneously without drug interruption; rarely, progression to Stevens-Johnson syndrome has been reported. Epidermal hyperkeratosis with dry, scaling skin is frequently observed, and sparse hair or hair loss may be seen in the later stages of the disease.

Hematologic and Malignant Diseases

Anemia occurs in 20–70% of HIV-infected children, more commonly in children with AIDS. The anemia may be a result of chronic infection, poor nutrition, autoimmune factors, virus-associated conditions (hemophagocytic syndrome, parvovirus B19 red cell aplasia), or the adverse effect of drugs (zidovudine).

Leukopenia occurs in almost 30% of untreated HIV-infected children, and neutropenia often occurs. Multiple drugs used for treatment or prophylaxis for opportunistic infections, such as *Pneumocystis* pneumonia (TMP-SMX), MAC, and CMV (ganciclovir), or antiretroviral drugs (zidovudine) may also cause leukopenia and/or neutropenia. In cases in which therapy cannot be changed, treatment with subcutaneous granulocyte colony-stimulating factor may be necessary.

Thrombocytopenia has been reported in 10–20% of patients. The etiology may be immunologic (i.e., circulating immune complexes or antiplatelet antibodies) or, less commonly, from drug toxicity, or idiopathic. Antiretroviral therapy (cART) may also reverse thrombocytopenia in ART-naïve patients. In the event of sustained severe thrombocytopenia (<10,000 platelets/µL), treatment with intravenous immunoglobulin or anti-D immune globulin offers temporary improvement in most patients already taking cART. If ineffective, a course of steroids may be an alternative, but consultation with a hematologist should be sought. Deficiency of clotting factors (factors II, VII, IX) is not rare in children with advanced HIV disease and is often easy to correct with vitamin K. A novel disease of the thymus has been observed in a few HIV-infected children. These patients were found to have characteristic anterior mediastinal multilocular thymic cysts without clinical symptoms. Histologic examination shows focal cystic changes, follicular hyperplasia, and diffuse plasmacytosis and multinucleated giant cells. Treatment with cART may result in resolution, or spontaneous involution occurs in some cases.

Malignant diseases have been reported infrequently in HIV-infected children, representing only 2% of AIDS-defining illnesses. Non-Hodgkin lymphoma (including Burkitt lymphoma), primary CNS lymphoma, and leiomyosarcoma are the most commonly reported neoplasms among HIV-infected children. Epstein-Barr virus is associated with most lymphomas and with all leiomyosarcomas (see Chapter 281). Kaposi sarcoma, which is caused by human herpesvirus 8, occurs frequently among HIV-infected adults but is exceedingly uncommon among HIV-infected children in resource-rich countries (see Chapter 284).

Diagnosis

All infants born to HIV-infected mothers test antibody-positive at birth because of passive transfer of maternal HIV antibody across the placenta during gestation; therefore, antibody should not be used to establish the diagnosis of HIV in an infant. Most uninfected infants without ongoing exposure (i.e., who are not breastfed) lose maternal antibody between 6 and 18 mo of age and are known as **seroreverters.** Because a small proportion of uninfected infants continue to test HIV antibody-positive for up to 24 mo of age, positive IgG antibody tests, including the rapid tests, cannot be used to make a definitive diagnosis of HIV infection in infants younger than 24 mo. The presence of IgA or IgM anti-HIV in the infant's circulation can indicate HIV infection, because these immunoglobulin classes do not cross the placenta; however, IgA and IgM anti-HIV assays have been both insensitive and nonspecific and therefore are not valuable for clinical use. In any child older than 24 mo of age, demonstration of IgG antibody to HIV by a repeatedly reactive enzyme immunoassay and confirmatory HIV PCR establishes the diagnosis of HIV infection. Breastfed infants should have antibody testing performed 12 wk following cessation of breastfeeding to identify those who became infected at the end of lactation by the HIV-infected mother. Certain diseases (e.g., syphilis, autoimmune diseases) may cause false-positive or indeterminate results. In such cases, specific viral diagnostic tests (see later) have to be done.

Several rapid HIV tests are currently available with sensitivity and specificity better than those of the standard enzyme immunoassay. Many of these tests require only a single step that allows test results to be reported within less than 30 min. Performing rapid HIV testing during delivery or immediately after birth is crucial for the care of HIV-exposed newborns whose mother's HIV status was unknown during pregnancy. A positive rapid test in the mother has to be confirmed by a second different rapid test (testing different HIV-associated antibodies) or by HIV RNA PCR (viral load). Given the earlier detection of fourth-generation HIV ELISA testing (p24 antigen + HIV-1, HIV-2 IgG and IgM antibodies), Western blots are not appropriate to confirm testing, because the fourth generation assays can be positive before the Western blot becomes positive (i.e., in acute infection). In infants who are at risk of exposure to HIV-2 infection (e.g., born to an HIV-infected woman from West Africa or who has an HIV+ partner from West Africa), a rapid test that can detect both HIV-1 and HIV-2 should be used. However, if the HIV testing is negative or the Western blot test reveals an unusual pattern, further diagnostic tests should be considered. In addition, they should be tested with an HIV-2–specific DNA PCR assay; this assay has very limited availability.

Viral diagnostic assays, such as HIV DNA or RNA PCR, are considerably more useful in young infants, allowing a definitive diagnosis in most infected infants by 1-4 mo of age (Table 302.3). By 4 mo of age, HIV PCR testing identifies all infected nonbreastfed infants. Historically, HIV DNA PCR testing was the preferred virologic assay over HIV RNA PCR testing in developed countries for young infants due to what was thought to be a modest advantage in detecting intrapartum acquired infection for DNA PCR in the first month of life. The perinatal use of ART prophylaxis (either single drug or combination) to prevent vertical transmission has not affected the predictive value of viral diagnostic testing. The FDA-approved HIV DNA PCR test is no longer commercially available in the United States, but other assays exist; however, the sensitivity and specificity of noncommercial HIV-1 DNA tests (using individual laboratory reagents) may differ from the sensitivity and specificity of the FDA-approved commercial test. HIV RNA PCR also has increased sensitivity for non-subtype B HIV (rare in the United States). Almost 40% of infected newborns have positive test results in the first 2 days of life, with > 90% testing positive by

2 wk of age. Plasma HIV RNA PCR assays, which detect viral replication, are as sensitive as the DNA PCR for early diagnosis. Either the DNA or RNA PCR is considered acceptable for infant testing. The commercially available HIV-1 assays are not designed for quantification of HIV-2 RNA and thus should not be used to monitor patients with this infection.

Table 302.3

Laboratory Diagnosis of HIV Infection

TEST	COMMENT
HIV DNA PCR	Historically preferred test to diagnose HIV-1 subtype B infection in infants and children younger than 24 mo of age; highly sensitive and specific by 2 wk of age and available; performed on peripheral blood mononuclear cells. False negatives can theoretically occur in non-B subtype HIV-1 infections. Historically had been preferred for testing in young infants.
HIV RNA PCR	Preferred test to identify non–B subtype HIV-1 infections. Similar sensitivity and specificity to HIV DNA PCR in infants and children younger than 24 mo of age

PCR, polymerase chain reaction.

Data from American Academy of Pediatrics, Committee of Pediatric AIDS: Diagnosis of HIV-1 infection in children younger than 18 months in the United States, Pediatrics 120:e1547-e1562, 2007.

Viral diagnostic testing should be performed within the first 12-24 hr of life, particularly for high-risk infants (i.e., those of mothers without sustained virologic suppression, a late cART start, or a diagnosis with acute HIV during the pregnancy); the tests can identify almost 40% of HIV-infected children. It seems that many of these children have a more rapid progression of their disease and deserve more aggressive therapy. Data suggest that if cART treatment starts at this point, the outcome will be much better. In exposed children with negative virologic testing at 1-2 days of life, additional testing should be done at 2-3 wk of age, 4-8 wk of age, and 4-6 mo of age. For higher-risk infants, additional virologic diagnostic testing should be considered at 2 to 4 wk after cessation of ARV prophylaxis (i.e., at 8-10 wk of life) (Fig. 302.4). A positive virologic assay (i.e., detection of HIV by PCR) suggests HIV infection and should be confirmed by a repeat test on a second specimen as soon as possible because false-positive tests can occur. A confirmed diagnosis of HIV infection can be made with two positive virologic test results obtained from different blood samples. HIV infection can be presumptively excluded in nonbreastfed infants with two or more negative virologic tests (one at age ≥ 14 days and one at age ≥ 4 wk) or one negative virologic test (i.e., negative NAT [RNA or DNA]) at age ≥

8 wk or one negative HIV antibody test at age ≥ 6 mo. Definitive exclusion of HIV infection in nonbreastfed infants is based on two or more negative virologic tests, with one obtained at age ≥ 1 mo and one at age ≥ 4 mo, or two negative HIV antibody tests from separate specimens obtained at age ≥ 6 mo. Some experts recommend documentation of seroreversion by testing for antibody at 12-18 mo of age; in low-risk infants with subtype B virus, this is likely not necessary, but antibody testing should be strongly considered in high-risk infants or infants infected with non–subtype B viruses.

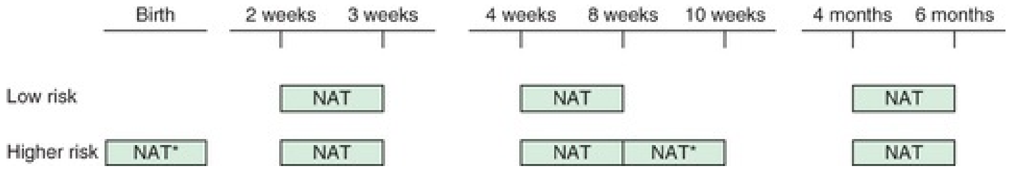

FIG. 302.4 Recommended virologic testing schedules for infants exposed to HIV by perinatal HIV transmission risk. Low Risk: Infants born to mothers who received standard ART during pregnancy with sustained viral suppression (usually defined as a confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and no concerns related to maternal adherence. Higher Risk: Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARVs, received intrapartum ARV drugs only, initiated ART late in pregnancy (late second or third trimester), were diagnosed with acute HIV infection during pregnancy, or had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression. *For higher-risk infants, additional virologic diagnostic testing should be considered at birth and 2-4 wk after cessation of ARV prophylaxis (i.e., at 8-10 wk of life). NAT, nucleic acid test. (From Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf . Accessed 1/13/18, Figure 1.)

Treatment

The currently available therapies do not eradicate the virus and cure the patient; instead they suppress the virus for extended periods of time and changes the course of the disease to a chronic process. Decisions about ART for pediatric HIV-infected patients are based on the magnitude of viral replication (viral load), CD4 lymphocyte count or percentage, and clinical condition. Because cART therapy changes as new drugs become available, decisions regarding therapy should be made in consultation with an expert in pediatric HIV infection. Plasma viral load monitoring and measurement of CD4 values have made it possible to implement rational treatment strategies for viral suppression, as well as to assess the efficacy of a particular drug combination. The following principles form the basis for cART:

1. Uninterrupted HIV replication causes destruction of the immune system and progression to AIDS.
2. The magnitude of the viral load predicts the rate of disease progression, and the CD4 cell count reflects the risk of opportunistic infections and HIV infection complications.
3. cART, which includes at least three drugs with at least two different mechanisms of action, should be the initial treatment. Potent combination therapy that suppresses HIV replication to an undetectable level restricts the selection of ART-resistant mutants; drug-resistant strains are the major factor limiting successful viral suppression and delay of disease progression.
4. The goal of sustainable suppression of HIV replication is best achieved by the simultaneous initiation of combinations of ART to which the patient has not been exposed previously and that are not cross resistant to drugs with which the patient has been treated previously.
5. Drug-related interactions and toxicities should be minimal.
6. Adherence to the complex drug regimens is crucial for a successful outcome.

Increasing data have shown a benefit in adult studies to starting treatment earlier, which has led to recommendations to treat earlier in children, as well. There are strong data to support the treatment of all infants < 12 mo of age, regardless of the clinical symptoms, viral load, or CD4 count from the Children with HIV Early Antiretroviral (CHER) study. Urgent treatment is recommended for older children with stage 3 opportunistic infections or immunologic suppression. Treatment is recommended for all other children, as well. Rarely, treatment may need to be deferred on a case-by-case basis based on clinical or psychosocial factors that may affect adherence with the caregivers and child.

Combination Therapy

As of January 2019, 20 individual ART drugs, with 21 coformulated combination tablets as well as two pharmacokinetic boosters, were approved by the FDA for use in HIV-infected adults and adolescents. Of these, 19 were approved for at least some portion of the pediatric population (0-12 yr of age), with many but not all of them available as a liquid, powder, or small tablet/capsule (Table 302.4). ART drugs are categorized by their mechanism of action, such as preventing viral entrance into $CD4^+$ T cells, inhibiting the HIV reverse transcriptase or protease enzymes, or inhibiting integration of the virus into the human DNA. Within the reverse transcriptase inhibitors, a further subdivision can be made: **nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs)** and **nonnucleoside reverse transcriptase inhibitors (NNRTIs)** (see Fig. 302.3). The NRTIs have a structure similar to that of the building blocks of DNA (e.g., thymidine, cytosine). When incorporated into DNA, they act like chain terminators and block further incorporation of nucleosides, preventing viral DNA synthesis. Among the NRTIs, thymidine analogs (e.g., stavudine, zidovudine) are found in higher concentrations in activated or dividing cells, producing > 99% of the HIV virion population, and nonthymidine analogs (e.g., didanosine, lamivudine) have more activity in resting cells, which account for < 1% of the HIV virions but may serve as a reservoir for HIV. Suppression of replication in both populations is thought to be an important component of long-term viral control. NNRTIs (i.e., nevirapine, efavirenz, etravirine, rilpivirine) act differently than the NRTIs. They attach to the reverse transcriptase and cause a conformational change, reducing the activity of the enzyme. The **protease inhibitors (PIs)** are potent agents that act farther along the viral replicative cycle. They bind to the site where the viral long polypeptides are cut into individual, mature, and functional core proteins that produce the infectious virions before they leave the cell. The virus entry into the cell is a complex process that involves several cellular receptors and fusion. Several drugs have been developed to prevent this process. The **fusion inhibitor** enfuvirtide (T-20), which binds to viral gp41, causes conformational changes that prevent fusion of the virus with the $CD4^+$ cell and entry into the cell. Maraviroc is an example of a selective CCR5 coreceptor antagonist that blocks the attachment of the virus to this chemokine (an essential process in the viral binding and fusion to the $CD4^+$ cells). **Integrase inhibitors (INSTIs)** (i.e., raltegravir, dolutegravir, elvitegravir, bictegravir) block the enzyme that catalyzes the incorporation of the viral genome into the host's DNA.

Table 302.4

Summary of Antiretroviral Therapies Available in 2019

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Lactic acidosis with hepatic steatosis, particularly for older members of the class	
Abacavir (Ziagen, ABC): tablet: 300 mg; oral solution: 20 mg/mL Trizivir: combination of zidovudine (ZDV), lamivudine, ABC (300, 150, 300 mg) Epzicom: combination of lamivudine, ABC (300, 600 mg) Triumeq: combination of ABC, lamivudine, dolutegravir (600, 300, 50 mg)	Children: ≥3 mo to 13 yr: 8 mg/kg/dose bid (maximum dose: 300 mg bid) >25 kg: 300 mg bid Children with stable CD4 counts and undetectable viral load > 6 mo while taking ABC can transition to 16 mg/kg once daily (max: 600 mg) Adolescents and adults: 600 mg once daily Trizivir (>40 kg): 1 tablet bid Epzicom (>25 kg): 1 tablet qd Triumeq: 1 tablet qd	Common: nausea, vomiting, anorexia, fever, headache, diarrhea, rash Less common: hypersensitivity, which can be fatal, Rare: lactic acidosis with hepatic steatosis, pancreatitis, elevated triglycerides, myocardial infarction	Can be given with food Genetic screening for HLAB*5701 must be done prior to initiation of ABC-containing treatment. If test is positive, avoid ABC. Do not restart ABC in patients who had hypersensitivity-like symptoms (e.g., flu-like symptoms)
Didanosine (Videx, ddl): powder for oral solution (prepared with solution containing antacid): 10 mg/mL	2 wk to < 3 mo: 50 mg/m^2 /dose bid 3-8 mo: 100 mg/m^2 /dose bid >8 mo: 120 mg/m^2 /dose (max: 200 mg/dose) bid Adolescents (>13 yr) and adults < 60 kg: 250 mg once daily >60	Common: diarrhea, abdominal pain, nausea, vomiting Less common: pancreatitis, peripheral neuropathy, electrolyte abnormalities, lactic acidosis with hepatic steatosis, hepatomegaly, retinal	Food decreases bioavailability by up to 50%. Take 30 min before or 2 hr after meal. Tablets dissolved in water are stable for 1 hr (4 hr in buffered solution) Drug interactions: antacids/gastric acid antagonists may increase bioavailability; possible decreased absorption of fluoroquinolones, ganciclovir, ketoconazole, itraconazole, dapsone, and some protease inhibitors. Combination with d4T enhances toxicity; also

	kg: 400 mg once daily (to increase adherence)	depigmentation	common if combined with tenofovir. **Note: Due to increased side effects compared with other NRTIs, ddI is no longer recommended for treatment of HIV in children in the US.**
Enteric-coated didanosine (Videx EC): capsule, delayed release: 125, 200, 250, 400 mg; generic: 200, 250, 400 mg	20-25 kg: 200 mg once daily 25-60 kg: 250 mg once daily ≥60 kg: 400 mg once daily	Same as for ddl	Same as for ddl
Emtricitabine (Emtriva, FTC): capsule: 200 mg; oral solution: 10 mg/mL Truvada: combination of FTC, tenofovir disoproxil fumarate (TDF) (200, 300 mg) Truvada Low Strength: combinations of FTC/TDF (100, 150 mg); (133, 200 mg); (167, 250 mg) Atripla: combination of FTC, TDF, efavirenz (EFV) (200, 300, 600 mg) Descovy: combination of FTC, tenofovir disoproxil alafenamide (TAF) (200, 25 mg) Complera: combination of FTC, TDF, rilpivirine (RPV) (200, 300, 25 mg) Odefsey: combination of FTC, TAF, RPV (25, 200, 25 mg) Stribild: combination of FTC, TDF, elvitegravir (EVG), cobicistat (COBI)	Infants: 0-3 mo: 3 mg/kg once daily Children ≥ 3 mo to 17 yr, oral solution: 6 mg/kg (max: 240 mg) once daily >33 kg, adolescents and adults: 200 mg capsule or 240 mg solution once daily Truvada, Descovy, Atripla, Complera, Descovy, Stribild, Genvoya or Biktarvy: adult dose: 1 tablet once daily	Common: headache, insomnia, diarrhea, nausea, skin discoloration Less common: lactic acidosis with hepatic steatosis, neutropenia	Patient should be tested for hepatitis B virus (HBV) because HBV exacerbation can occur when emtricitabine is discontinued. Can be given without regard to food. Oral solution should be refrigerated if temperature above 25°C (77°F) COBI is a pharmacokinetc enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR. Note oral solution is less bioavailable and has a max dose of 240 mg, while the max dose for capsules is 200 mg.

(200, 300, 150, 150 mg) Genvoya: combination of FTC, TAF, EVG, COBI (200, 10, 150, 150 mg) Biktarvy: combination of bictegravir (BIC), FTC, TAF (50, 200, 25 mg)			
Lamivudine (Epivir, Epivir HBV, 3TC): tablet: 150 (scored), 300 mg (Epivir, generic), 100 mg (Epivir HBV); Solution: 5 mg/mL (Epivir HBV), 10 mg/mL (Epivir) Combivir: combination of ZDV, lamivudine (300, 150 mg) Trizivir, Epzicom, and Triumeq combination (see abacavir) Symfi Lo combination of 3TC, TDF, EFV (300, 300, 400 mg)	Neonates (≥32 wk gestational age through 4 wk of age for term infants): 2 mg/kg/dose bid ≥4 wk to <3 mo: 4 mg/kg/dose bid ≥3 mo to <3 yr: 5 mg/kg/dose bid (max 150 mg) ≥3 yr: 5 mg/kg/dose bid (max 150 mg) or 10 mg/kg/dose qd (max 300 mg) For ≥14 kg with scored tablet (150 mg) 14 to <20 kg: 75 mg bid or 150 mg qd (if >3 yr) ≥20 to <25 kg: 75 mg qAM and 150 mg qPM or 225 mg qd (if >3 yr) ≥25 kg: 150 mg bid or 300 mg qd Children should be switched to once-daily dosing of lamivudine (oral solution or tablets) from twice-daily dosing at ≥3 yr if clinically stable for 36 wk with an undetectable viral load and stable CD4 T lymphocyte	Common: headache, nausea Less common: pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, lipodystrophy	No food restrictions Patient should be tested for hepatitis B virus (HBV) because HBV exacerbation can occur when lamivudine is discontinued. M184V mutation for this drug decreases viral fitness and can be advantageous to maintain including inducing AZT hypersusceptibility.

	count Adolescents and adults: Combivir (>30 kg), Trizivir (>40 kg): 1 tablet bid Epzicom (>25 kg): 1 tablet qd Triumeq (>40 kg): 1 tablet qd Symfi Lo (>35 kg): 1 tablet qd		
Stavudine (Zerit, d4T): capsule: 15, 20, 30, 40 mg; solution: 1 mg/mL	≥14 days and < 30 kg: 1 mg/kg/dose bid >30 kg: 30 mg bid	Common: headache, nausea, hyperlipidemia, fat maldistribution Less common: peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis	No food restrictions. Should not be administered with ZDV because of virologic antagonism. Higher incidence of lactic acidosis. Increased toxicity if combined with ddl. **Note: Due to increased side effects compared with other NRTIs, d4T is no longer recommended for treatment of HIV in children in the US.**
Tenofovir disoproxil fumarate (Viread, TDF): tablet: 150, 200, 250, 300 mg; powder: 40 mg/1 g powder Truvada: combination of FTC, TDF (200, 300 mg) Truvada Low Strength: combinations of FTC/TDF (100, 150 mg); (133, 200 mg); (167, 250 mg) Atripla: Combination of FTC, TDF, EFV (200, 300, 600 mg) Complera: combination of FTC, TDF, RPV (200, 300, 25 mg) Stribild: combination of FTC, TDF, EVG, COBI (200, 300, 150, 150 mg)Symfi Lo combination of	2 to <12 yr: 8 mg/kg/dose qd >12 yr and 35 kg, adolescents >12 yr and 35 kg and adults: 300 mg once daily Truvada, Atripla, Complera, Symfi Lo, and Stribild: 1 tablet qd Weight probands for ≥2 yr and ≥17 kg: 17 to <22 kg: 150 mg qd 22 to <28 kg: 200 mg qd 28 to <35 kg: 250 mg qd ≥35 kg: 300 mg qd	Common: nausea, vomiting, diarrhea Less common: lactic acidosis with hepatic steatosis, hepatomegaly, reduced bone density, renal toxicity	High-fat meal increases absorption; coadministration with ddl increased ddl toxicity, decreases atazanavir (ATV) levels (therefore, boosting ATV with ritonavir is required). ATV and lopinavir (LPV) increase TDF levels and potential toxicity. Screen for HBV before TDF is given, because exacerbation of hepatitis may occur when TDF is discontinued

3TC, TDF, EFV (300, 300, 400 mg)			
Tenofovir alafenamide (Vemlidy, TAF) Descovy: combination of TAF, FTC (25, 200 mg) Genvoya: combination of TAF, FTC, EVG, COBI (10, 200, 150, 150 mg) Odefsey: combination of FTC, TAF, RPV (25, 200, 25 mg) Biktarvy: combination of BIC, FTC, TAF (50, 200, 25 mg)	Adolescents (≥13 yr, ≥35 kg): Descovy, Genvoya, or Odefsey: 1 tablet qd Biktarvy: ≥18 yr 1 tablet qd; >12 yr to 18 yr and >35 kg investigational dose 1 tablet qd based on limited data	Common: headache, diarrhea, nausea, increased serum lipids	Newer version of TDF that has less renal and bone toxicity. Screen for HBV before TAF is given, because exacerbation of hepatitis may occur when TAF is discontinued. Concentrates in cells more so than TDF, so is not approved for pregnant women given lack of data.
Zidovudine (Retrovir, AZT, ZDV): capsule: 100 mg; tablet: 300 mg; syrup: 10 mg/mL; intravenous injection: 10 mg/mL (all available generic) Combivir: combination of ZDV, lamivudine (300, 150 mg) Trizivir: Combination of ZDV, lamivudine, ABC (300, 150, 300 mg)	**Low Risk Prophylaxis:** ≥35 wk gestation at birth: *Birth to age 4-6 wk* : 4 mg/kg/dose PO bid (or 3 mg/kg/dose IV q12h) ≥30 to <35 wk gestation at birth: *Birth to age 2 wk* : 2 mg/kg/dose PO bid (or 1.5 mg/kg/dose IV q12h) THEN *Age 2 wk to 4-6 wk* : 3 mg/kg/dose PO bid (or 2.3 mg/kg/dose IV q12h) <30 wk gestation at birth *Birth to age 4-6 wk* : 2 mg/kg/dose PO bid (or 1.5 mg/kg/dose IV q12h)	Common: bone marrow suppression (e.g., macrocytic anemia, neutropenia), headache, nausea, vomiting, anorexia Less common: liver toxicity, lactic acidosis with hepatic steatosis, myopathy, fat redistribution	No food restrictions Drug interactions: should not be given with d4T or doxorubicin. Rifampin may increase metabolism. Cimetidine, fluconazole, valproic acid may decrease metabolism. Ganciclovir, IFN-α, ribavirin increase ZDV toxicity. Only antiretroviral with an IV formulation currently.

	High Risk Prophylaxis and Treatment: ≥35 wk gestation at birth: Birth to age 4 wk: 4 mg/kg/dose PO bid THEN Age >4 wk: 12 mg/kg/dose PO bid ≥30 to <35 wk gestation at birth: Birth to age 2 wk: 2 mg/kg/dose PO bid THEN Age 2 wk to 6-8 wk: 3 mg/kg/dose PO bid THEN Age >6-8 wk: 12 mg/kg/dose PO bid <30 wk gestation at birth: Birth to age 4 wk: 2 mg/kg/dose PO bid THEN Age 4 wk to 8-10 wk: 3 mg/kg/dose PO bid THEN Age >8-10 wk: 12 mg/kg/dose PO bid Infants >4 kg and ≥4 wk post delivery and children: 4 kg to <9 kg: 12 mg/kg/dose PO bid 9 kg to <30 kg: 9 mg/kg/dose PO bid >30 kg, adolescents and adults: 300 mg bid Alternative body surface area dosing: 180-240 mg/m^2 /dose PO		

	bid Combivir *or* Trizivir: 1 tablet bid		
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Rash is mild to severe, usually within first 6 wk. Discontinue the drug if severe rash (with blistering, desquamation, muscle involvement, or fever)	
Efavirenz (Sustiva, EFV): capsule: 50, 200 mg; tablet: 600 mg Atripla: combination of EFV, FTC, TDF (600, 200, 300 mg) Symfi Lo combination of 3TC, TDF, EFV (300, 300, 400 mg)	Children < 3 yr: consult with expert Children ≥ 3 yr: 10 to < 15 kg: 200 mg qd 15 to < 20 kg: 250 mg qd 20 to < 25 kg: 300 mg qd 25 to < 32.5 kg: 350 mg qd 32.5 to < 40 kg: 400 mg qd ≥40 kg: 600 mg qd or 367 mg/m^2 body surface area Atripla (>40 kg, adult dose): 1 tablet qd Symfi Lo (>35 kg, adult dose): 1 tablet qd	Common: skin rashes, CNS abnormalities (e.g., vivid dreams, impaired concentration, insomnia, depression, hallucination) Less common: increased liver enzymes; potentially teratogenic, QTc prolongation (be careful with other QT-prolonging medications), false positives on some cannabinoid and benzodiazepine tests	Capsules can be opened for mixing in food. Administer at bedtime on empty stomach to minimize CNS side effects. Taking with food, especially fatty meal, can increase absorption and CNS side effects. Drug interactions: Efavirenz induces/inhibits CYP3A4 enzymes. Increase clearance of drugs metabolized by this pathway (e.g., antihistamines, sedatives and hypnotics, cisapride, ergot derivatives, warfarin, ethinyl estradiol) and several other ARVs (i.e., protease inhibitors). Drugs that induce CYP3A4 (e.g., phenobarbital, rifampin, rifabutin) decrease efavirenz levels. Clarithromycin levels decrease with EFV, and azithromycin should be considered. Use with caution in female adolescents with reproductive potential because of potential teratogenicity. Avoid using in individuals with a history of past or active psychiatric issues and use with caution in adolescents and young adults owing to possible affective side effects, including increased suicidality.
Etravirine (ETR, Intelence): tablet: 25, 100, 200 mg	Children <6 yr: consult with expert 16 to < 20 kg: 100 mg bid 20 to < 25 kg: 125 mg bid 25 to < 30 kg: 150 mg bid >30 kg, adolescents and adults: 200 mg bid	Common: nausea, rash, diarrhea Less common: hypersensitivity reactions	Always administer following a meal for absorption; taking on empty stomach decreases absorption by 50%. Tablets can be dispersed in water Inducer of CYP3A4 enzymes and inhibitor of CYP2C9 and CYP2C19, causing multiple interactions that should be checked before initiating ETR. Should not be given in combination with TPV, FPV, ATV, or other nonnucleoside reverse transcriptase inhibitors

Nevirapine (Viramune, NVP): tablet: 200 mg; extended-release (XR) tablet: 100, 400 mg; suspension: 10 mg/mL	**High risk Prophylaxis:** 3-dose series for high-risk infants >32 wk gestation at birth (including those born to mothers not taking HAART) NOTE: DOSES ARE A FLAT DOSE, NOT PER KG Dosing intervals: Within 48 hr of birth, 48 hr after first dose, 96 hr after second dose Birth weight 1.5-2 kg: 8 mg/dose PO Birth weight >2 kg: 12 mg/dose PO **Treatment (including higher risk prophylaxis with empiric therapy):** ≥37 wk gestation at birth: Birth to age 4 wk: 6 mg/kg/dose bid THEN Age >4 wk: 200 mg/m^2 /dose bid 34 to <37 wk gestation at birth: Birth to age 1 wk: 4 mg/kg/dose bid Age 1 to 4 wk: 6 mg/kg/dose bid Age >4 wk: 200 mg/m^2 /dose bid Note dose adjustment is optional at 4 wk for empiric HIV therapy for high risk infants with negative testing	Common: skin rash, headache, fever, nausea, abnormal liver function tests Less common: hepatotoxicity (rarely life-threatening), hypersensitivity reactions	No food restrictions Drug interactions: induces hepatic CYP450A enzymes (including CYP3A and CYP2B6) activity and decreases protease inhibitor concentrations (e.g., IND, SQV, LPV). Should not be given with ATV. Reduces ketoconazole concentrations (fluconazole should be used as an alternative). Rifampin decreases nevirapine serum levels. Anticonvulsants and psychotropic drugs using same metabolic pathways as NVP should be monitored. Oral contraceptives may also be affected. XR formulation must be swallowed whole. For children ≤2 yr, some experts start with bid dosing without the 14 day lead-in of qd dosing. Lead-in dosing decreases occurrence of rash by allowing induction of cytochrome p450 metabolizing enzymes.

	≥1 mo to < 8 yr: 200 mg/m^2 once daily for 14 days; then same dose bid (max: 200 mg/dose) ≥8 yr: 120-150 mg/m^2 once daily for 14 days; then bid (max: 200 mg/dose) Adolescents and adults: 200 mg once daily for 14 days; then 200 mg bid *or* XR 400 mg qd (after 14 day lead in)		
Rilpivirine (Edurant, RPV): tablet: 25 mg Complera: combination of RPV, FTC, TDF (25, 200, 300 mg) Odefsey: combination of FTC, TAF, RPV (25, 200, 25 mg) Juluca: combination of RPV, Dolutegravir (DTG) (25, 50 mg)	Pediatric patients: consult with expert Adolescents (>12 yr and 35 kg) and adults: 25 mg PO qd Complera or Odefsey: 1 tablet qd Juluca (>18 yr): 1 tablet qd; only for use in adults with ≥6 mo virologic suppression with no resistance to replace current regimen	Headache, insomnia, rash, depression, mood changes	Given with food only, 500 kcal meal. Do not use with proton pump inhibitors; antacids have to be spaced from dose by 2 h before or 4 h after. Should not be used if viral load > 100,000 copies/µL or drugs that induce CYP3A or with proton pump inhibitors
PROTEASE INHIBITORS		Class adverse effects: Gi side effects, hyperglycemia, hyperlipidemia (except atazanavir and darunavir), lipodystrophy, increased transaminases, increased bleeding disorders in hemophiliacs. Can induce metabolism of ethinyl estradiol; use alternate contraception (other than estrogen-containing oral contraceptives). All of these drugs undergo hepatic metabolism, mostly by CYP3A4, with many drug interactions. Treatment note: except in rare instances, always administer with boosting agent (ritonavir [RTV] or cobicistat [COBI]).	
Atazanavir (Reyataz, ATV): powder packet: 50 mg/packet; capsule: 150, 200, 300 mg (Note: capsules and	Infants and children ≥ 3 mo and ≥ 5 kg: 5 to < 15 kg: ATV 200 mg (4 packets) + RTV	Common: elevation of indirect bilirubin; headache, arthralgia, depression, insomnia, nausea,	Administer with food to increase absorption. Review drug interactions before initiating because ATV inhibits CYP3A4, CYP1A2, CYP2C9, and UGT1A1 enzymes. Use with caution with

packets are *not* interchangeable) Evotaz: combination of ATV, COBI (300, 150 mg)	80 mg qd 15 to < 25 kg: ATV 250 mg (5 packets) + RTV 80 mg qd Note: Capsules are not approved for < 6 yr or < 15 kg Children ≥6 yr and ≥15 kg capsule dosing: 15 to <35 kg: 200 mg + RTV 100 mg ≥35 kg: 300 mg + RTV 100 mg Adolescents and adults: 300 mg + RTV 100 mg Adults (>18 yr): Evotaz: 1 tablet qd	vomiting, diarrhea, paresthesias Less common: prolongation of PR interval on electrocardiogram (ECG); rash, rarely Stevens-Johnson syndrome, diabetes mellitus, nephrolithiasis	cardiac conduction disease or liver impairment. Combination with EFV should not be used in treatment-experienced patients because it decreases ATV levels. TDF, antacids, H_2 -receptor antagonists, and proton-pump inhibitors decrease ATV concentrations. Patients taking buffered ddl should take it at least 2 hr before ATV COBI is a pharmacokinetc enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR.
Darunavir (Prezista, DRV): tablets: 75, 150, 600, 800 mg; suspension: 100 mg/mL Prezcobix: combination DRV, COBI (800, 150 mg)	<3 yr or < 10 kg: do not use 3 to < 12 yr: 10 to < 11 kg: DRV 200 mg + RTV 32 mg bid 11 to < 12 kg: DRV 220 mg + RTV 32 mg bid 12 to < 13 kg: DRV 240 mg + RTV 40 mg bid 13 to < 14 kg: DRV 260 mg + RTV 40 mg bid 14 to < 15 kg: DRV 280 mg + RTV 48 mg bid 15 to < 30 kg: DRB 375 mg + RTV 48 mg bid 30 to < 40 kg: DRV 450 mg + RTV 100 mg bid ≥40 kg: DRV 600 mg + RTV 100 mg bid Adolescents ≥ 40 kg and adults with no DRV mutations: DRV	Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, headache Less common: skin rashes (including Stevens-Johnson syndrome), lipid and liver enzyme elevations, hyperglycemia, fat maldistribution	DRV should be given with food. Contraindicated for concurrent therapy with cisapride, ergot alkaloids, benzodiazepines, pimozide, or any major CYP3A4 substrates. Use with caution in patients taking strong CYP3A4 inhibitors, or moderate/strong CYP3A4 inducers. Adjust dose with concurrent rifamycin therapy. Contains sulfa moiety: potential for cross-sensitivity with sulfonamide class

	800 mg + RTV 100 mg qd Adults (>18 yr) with no DRV mutations: Prezcobix: 1 tablet qd Adolescents ≥ 40 kg and adults *with* DRV mutation(s): DRV 600 mg + RTV 100 mg bid		
Fosamprenavir (Lexiva, FPV): tablet: 700 mg; suspension: 50 mg/mL	6 mo to 18 yr: <11 kg: FPV 45 mg/kg/dose + RTV 7 mg/kg/dose bid 11 to < 15 kg: FPV 30 mg/kg/dose + RTV 3 mg/kg/dose bid 15 to < 20 kg: FPV 23 mg/kg/dose + RTV 3 mg/kg/dose bid >20 kg: FPV 18 mg/kg/dose (max: 700 mg) + RTV 3 mg/kg/dose (max: 100 mg) bid Adolescents > 18 yr and adults: FPV 700 mg + RTV 100 mg bid *or* FPV 1,400 mg + RTV 200 mg qd For protease inhibitor (PI)–experienced, the once-daily dose is not recommended	Common: nausea, vomiting, perioral paresthesias, headache, rash, lipid abnormalities Less common: Stevens-Johnson syndrome, fat redistribution, neutropenia, elevated creatine kinase, hyperglycemia, diabetes mellitus, elevated liver enzymes, angioedema, nephrolithiasis	Should be given with food. FPV is an inhibitor of the CYP450 system and an inducer, inhibitor, and substrate of CYP3A4, which can cause multiple drug interactions. Use with caution in sulfa-allergic individuals.
Indinavir (Crixivan, IDV): capsule: 100, 200, 400 mg	Not approved for use in infants or children Adolescents and adults: IDV 800 mg IDV + RTV (100 mg to 200	Common: nausea, abdominal pain, hyperbilirubinemia, headache, dizziness, lipid abnormalities, nephrolithiasis,	Reduce dose (600 mg IDV every 8 hr) with mild to moderate liver dysfunction. Adequate hydration (at least 48 oz fluid/day in adults) necessary to minimize risk of nephrolithiasis. IDV is cytochrome P450 3A4 inhibitor and substrate,

	mg) bid	metallic taste Less common: fat redistribution, hyperglycemia, diabetes mellitus, hepatitis, acute hemolytic anemia	which can cause multiple drug interactions: rifampin reduces levels; ketoconazole, ritonavir, and other protease inhibitors increase IDV levels. Do not coadminister with EFV, astemizole, cisapride, terfenadine
Lopinavir/Ritonavir (Kaletra, LPV/r): tablet: 100/25 mg, 200/50 mg; solution: 80/20 mg per/mL (contains 42% alcohol, 15% propylene glycol)	14 days to 18 yr: LPV 300 mg/m^2 /dose + RTV 75 mg/m^2 /dose bid In treatment naive children >1 yr a dose of 230 mg/m^2 /dose bid can be used. Adolescents (>18 yr) and adults: LPV 400 mg + RTV 100 mg bid *or* 800 mg LPV + 200 mg RTV qd If taken with NVP, EFV, FPV, or NFV: LPV 600 mg + RTV 150 mg bid	Common: diarrhea, headache, nausea and vomiting, lipid elevation Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation	**Do not administer before postmenstrual age of 42 wk and postnatal age of 14 days owing to potential severe toxicities.** No food restrictions but has better GI tolerability when given with or after a meal. Pills must be swallowed whole. Oral solution should be given with high-fat meal to increase absorption. Poor palatability of oral solution is difficult to mask with flavorings or foods. Once-daily dosing is poorly tolerated in most children, and plasma concentration variability makes qd dosing contraindicated in children. Interacts with drugs using CYP3A4, which can cause multiple drug interactions
Nelfinavir (Viracept, NFV): tablet: 250, 625 mg	<2 yr: not recommended Children 2-13 yr: 45-55 mg/kg/dose bid (max: 1,250 mg/dose) Adolescents and adults: 1,250 mg bid	Common: diarrhea, asthenia, abdominal pain, skin rashes, lipid abnormalities Less common: exacerbation of liver disease, fat redistribution, hyperglycemia, diabetes mellitus, elevation of liver enzymes	Administer with a meal to optimize absorption; avoid acidic food or drink (e.g., orange juice). Tablet can be crushed or dissolved in water to administer as a solution. Nelfinavir inhibits CYP3A4 activity, which may cause multiple drug interactions. Rifampin, phenobarbital, and carbamazepine reduce levels. Ketoconazole, ritonavir, indinavir, and other protease inhibitors increase levels. Do not coadminister astemizole, cisapride, terfenadine. NFV is no longer recommended for treatment for HIV due to inferior potency compared to newer agents and unpredictable pharmacokinetics particularly in adolescents.
Ritonavir (Norvir, RTV): capsule: 100 mg; tablet: 100 mg;	Only use is to enhance other PIs; dose varies (see information for	Common: nausea, headache, vomiting, abdominal pain,	Administration with food enhances bioavailability and reduces gastrointestinal symptoms. RTV solution should

solution: 80 mg/mL (contains 43% alcohol)	specific PI)	diarrhea, taste aversion, lipid abnormalities, perioral paresthesias Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, allergic reactions	not be refrigerated (store at 20-25°C) RTV is potent inhibitor of CYP3A4 and CYP2D6 and inducer of CYP3A4 and CYP1A2 that leads to many drug interactions (e.g., protease inhibitors, antiarrhythmics, antidepressants, cisapride). Use cautiously with inhaled steroids (Cushing syndrome has been reported)
Saquinavir (Invirase, SQV): capsule: 200 mg; tablet: 500 mg	Infants and children < 16 yr: not approved for use Adolescents and adults: SQV 1,000 mg + RTV 100 mg bid	Common: diarrhea, abdominal pain, headache, nausea, skin rashes, lipid abnormalities Less common: exacerbation of chronic liver disease, diabetes mellitus, pancreatitis, elevated liver transaminases, fat maldistribution, increase in both QT and PR in ECG	Administer with a high-fat meal to enhance bioavailability. SQV is metabolized by CYP3A4, which may cause many drug interactions: rifampin, phenobarbital, and carbamazepine decrease serum levels. Saquinavir may decrease metabolism of calcium channel antagonists, azoles (e.g., ketoconazole), macrolides. Pretherapy EKG recommended and contraindicated in patients with prolonged QT interval.
Tipranavir (Aptivus, TPV): capsule: 250 mg; solution: 100 mg/mL (contains 116 IU vitamin E/mL)	<2 yr: not approved 2-18 yr (treatment-experienced only): TPV 375 mg/m^2 /dose + RTV 150 mg/m^2 (max: TPV 500 mg + RTV 200 mg) bid *or* TPV 14 mg/kg/dose + RTV 6 mg/kg/dose (max: same) bid Adolescents (>18 yr) and adult: TPV 500 mg + RTV 200 mg bid	Common: diarrhea, nausea, vomiting, fatigue, headache, skin rashes, elevated liver enzymes, lipid abnormalities Less common: fat redistribution, hepatitis, hyperglycemia, diabetes mellitus, intracranial hemorrhage	No food restrictions. Better tolerated with meal. Can inhibit human platelet aggregation: use with caution in patients at risk for increased bleeding (trauma, surgery, etc.) or in patients receiving concurrent medications that may increase the risk of bleeding. TPV is metabolized by CYP3A4, which may cause many drug interactions. Contraindicated in patients with hepatic insufficiency or in those receiving concurrent therapy with amiodarone, cisapride, ergot alkaloids, benzodiazepines, pimozide. TPV contains sulfonamide moiety, and caution should be taken in patients with sulfonamide allergy
FUSION INHIBITORS			
Enfuvirtide (Fuzeon, ENF): injection:	<6 yr: not approved Children ≥6 yr to	Common: Local injection site reactions in 98%	Must be given subcutaneously. Severity of reactions increased if given intramuscularly. Apply ice after

lyophilized powder of 108 mg reconstituted in 1.1 mL of sterile water delivers 90 mg/mL	16 yr: 2 mg/kg/dose SQ (max: 90 mg) bid Adolescents (>16 yr) and adults: 90 mg SQ bid	(e.g., erythema, induration nodules, cysts, ecchymoses) Less common: increased incidence of bacterial pneumonia, hypersensitivity, fever, nausea, vomiting, chills, elevated liver enzymes, hypotension, immune-mediated reactions (e.g., glomerulonephritis, Guillain-Barré syndrome, respiratory distress)	injection and massage the area to reduce local reactions. Injection sites should be rotated; recommended sites are upper arm, anterior thigh, or abdomen.
ENTRY INHIBITORS			
Maraviroc (Selzentry, MVC): oral solution: 20 mg/mL; tablet: 25, 75, 150, 300 mg	Neonates/infants: not approved ≥2 yr and ≥ 10 kg: Given with CYP3A inhibitors (EVG, RTV, PIs except TPV/r): 10 to < 20 kg: 50 mg bid 20 to < 30 kg: 75 mg bid 30 to < 40 kg: 100 mg bid >40 kg: 150 mg bid Given with NRTIs, T-20, TPV/r, NVP, RAL, or other drugs not affecting CYP3A: 10 to < 30 kg: not recommended 30 to < 40 kg: 300 mg bid >40 kg: 300 mg bid Given with EFV, ETR: not recommended Adolescents > 16 yr and adults:	Common: fever, upper respiratory infection–like symptoms, rash, abdominal pain, musculoskeletal symptoms, dizziness Less common: cardiovascular abnormalities, cholestatic jaundice, rhabdomyolysis, myositis, osteonecrosis	Testing for CCR5-tropic virus required; virus must not have mixed tropism (i.e., CCR5/CXC4) to have efficacy. No food restrictions. MVC is a CYP3A4 and P-glycoprotein (Pgp) substrate, which may cause many drug interactions. Tropism assay to exclude the presence of CXCR4 HIV is required before using MVC. Caution should be used when given to patients with hepatic impairment or cardiac disease or receiving CYP3A4 or P-glycoprotein-modulating drugs.

	150 mg bid if given with potent CYP3A inhibitor (e.g., protease inhibitor except TPV) 300 mg bid if given with not potent CYP3A4 inhibitors (e.g., NRTI, TPV, NVP, ENF, RAL) 600 mg bid if given with potent CYP3A4 inducer (e.g., EFV, ETR, rifampin, phenobarbital)		
INTEGRASE INHIBITORS (INSTI)			
Bictegravir (BIC) Only available as Biktarvy: combination of BIC, TAF, FTC (50, 25, 200 mg) Dolutegravir (Tivicay, DTG): tablet: 10, 25, 50 mg Triumeq: combination of ABC, 3TC, DTG (600, 300, 50 mg) Juluca: combination of RPV, Dolutegravir (DTG) (25, 50 mg)	Biktarvy: ≥18 yr 1 tablet qd; >12 yr to 18 yr and >35 kg: investigational dose 1 tablet qd based on limited data Neonates and infants: not approved ≥30 to < 40 kg: 35 mg qd (ARV-naïve or INSTI-naïve) >12 yr and ≥ 40 kg adolescents and adults: 50 mg qd (INSTI-naïve) If taken with EFV, FPV/RTV, TPV/RTV, or rifampin: 50 mg bid If INSTI-experienced with associated resistance or suspected resistance: 50 mg bid Triumeq: 1 tablet qd (INSTI-naïve, ≥ 40 kg) Juluca (>18 yr):	Diarrhea, nausea, headache Insomnia, headache, neuropsychiatric illness Rare: rash, hepatotoxicity, hypersensitivity reactions	No food restrictions Metabolized by UGT1A1 and CYP450 (CYP) 3A No food restrictions. UGT1A1 and CYP450 (CYP) 3A substrate. Should be taken 2 hr before or 6 hr after taking laxatives, sucralfate, iron or calcium supplements, or buffered medications. DTG decreases tubular secretion of Cr and slightly increases measured Cr but does not affect GFR.

	1 tablet qd; only for use in adults with ≥6 mo virologic suppression with no resistance to replace current regimen		
Elvitegravir (EVG): only found in 2 coformulated fixed-dose combination (FDC) tablets Stribild: combination of EVG, FTC, TDF, COBI (150, 200, 300, 150 mg) Genvoya: combination of FTC, TAF, EVG, COBI (200, 10, 150, 150 mg)	Genvoya: Not approved for <25 kg. Child and Adolescent (Weighing ≥25 kg; Any Sexual Maturity Rating [SMR]) and Adult Dose: 1 tablet qd Stribild: Not approved for <35 kg. Adolescent (Weighing ≥35 kg and SMR 4 or 5) and Adult Dose: 1 tablet qd	Nausea, diarrhea, headache	Administer with food. EVG is metabolized by CYP3A4 and modestly induces CYP2D6 that can cause multiple drug interactions. Cautiously use with nephrotoxic drugs. Do not use Stribild or Genvoya with ritonavir. COBI is a pharmacokinetc enhancer (boosting agent) used to optimize drug levels; it is not interchangeable with ritonavir. It can alter renal tubular secretion of Cr, resulting in elevated Cr with normal GFR.
Raltegravir (Isentress, RAL): film-coated tablet: 400 mg; HD tablet: 600 mg chewable tablet: 25, 100 mg (scored); granules for oral suspension: 100 mg suspended in 10 mL of water for final concentration of 10 mg/mL	**Treatment and high-risk prophylaxis (empiric therapy) for neonates:** >37 wk gestation at birth and >2 kg (oral suspension): Birth to Age 1 wk: approximately 1.5 mg/kg/dose qd 2 to <3 kg: 4 mg qd 3 to <4 kg: 5 mg qd 4 to <5 kg: 7 mg qd If mother on raltegravir in 2-24 h prior to delivery, delay first dose 24 to 48 hr after birth. Start other ART ASAP.	Common: nausea, headache, dizziness, diarrhea, fatigue Less common: itching, creatine phosphokinase elevation, myopathy, rhabdomyolysis, depression, hypersensitivity Rare: rash including Stevens-Johnson, TEN, hypersensitivity reaction	No food restrictions Oral suspension, film-coated tablet and chewable tablet are not interchangeable; chewable tablets and suspension have better oral bioavailability than film-coated tablet; hence, higher-dose film-coated tablet can be taken at 25 kg. RAL is metabolized by UGT1A1 glucuronidation, and inducers of this system (e.g., rifampin, TPV) will reduce RGV levels, whereas inhibitors of this system (e.g., ATV) will increase RGV levels. Do not administer rifampin with once daily raltegravir (HD). Aluminum and magnesium containing antacids should not be co-administered. UGT1A1 metabolism is low at birth and increases rapidly over first 4-6 wk of life. No data for preterm infants.

	Age 1-4 wk: approximately 3 mg/kg/dose bid 2 to <3 kg: 8 mg bid 3 to <4 kg: 10 mg bid 4 to <5 kg: 15 mg bid THEN **Infant and Pediatrics dosing** (Oral suspension) Children aged ≥4 wk and ≥3 kg to <20 kg: approximately 6 mg/kg/dose bid 3 to <4 kg: 25 mg bid 4 to <6 kg: 30 mg bid 6 to <8 kg: 40 mg bid 8 to <11 kg: 60 mg bid 11 to <14 kg: 80 mg bid 14 to <20 kg: 100 mg bid Chewable tablet: 11 to <14 kg: 75 mg bid 14 to <20 kg: 100 mg bid 20 to <28 kg: 150 mg bid 28 to <40 kg: 200 mg bid ≥40 kg: 300 mg bid Child or adolescent ≥ 25 kg and adults: 400 mg film-coated tablet bid Child and Adolescent Weighing ≥50 kg (HD tablet): 1200 mg qd (2 tablets) For treatment-naive or		

	virologically suppressed patients on an initial regimen of 400 mg twice daily (HD tablet): 1200 mg qd (2 tablets)		

Antiretroviral drugs often have significant drug–drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any new medication.

The information in this table is not all-inclusive. Updated and additional information on dosages, drug–drug interactions, and toxicities is available on the AIDSinfo website at http://www.aidsinfo.nih.gov .

Modified from the Guidelines for use of antiretroviral agents in pediatric HIV infection. http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf .

By targeting different points in the viral life cycle and stages of cell activation and by delivering drug to all tissue sites, maximal viral suppression is feasible. Combinations of three drugs consisting of a two-NRTI backbone of (1) a thymidine analog NRTI (abacavir or zidovudine) or tenofovir and (2) a nonthymidine analog NRTI (lamivudine or emtricitabine) to suppress replication in both active and resting cells added to (3) a ritonavir-boosted PI (lopinavir/ritonavir, atazanavir, or darunavir), an NNRTI (efavirenz or nevirapine), or an INSTI (raltegravir or dolutegravir) can produce prolonged suppression of the virus. The use of three drugs from three different classes generally should be avoided but may be necessary in children with highly resistant viruses; the drugs in these regimens should only be chosen by an HIV specialist with pharmacist input. Combination treatment increases the rate of toxicities (see Table 302.4), and complex drug–drug interactions occur among many of the antiretroviral drugs. Many PIs are inducers or inhibitors of the cytochrome P450 system and are therefore likely to have serious interactions with multiple drug classes, including nonsedating antihistamines and psychotropic, vasoconstrictor, antimycobacterial, cardiovascular, anesthetic, analgesic, and gastrointestinal drugs (cisapride). Whenever new medications are added to an antiretroviral treatment regimen, especially a protease inhibitor or cobicistat containing regimen, a pharmacist and/or HIV specialist should be consulted to address possible drug interactions. The inhibitory effect of ritonavir (a PI) on the cytochrome P450 system has been exploited, and small doses of the drug are added to several other protease inhibitors (e.g., lopinavir, atazanavir, darunavir) to slow their metabolism by the P450 system and to improve their pharmacokinetic profile. This strategy provides more effective drug levels with less toxicity and less-frequent dosing. Recently, the development of cobicistat provides an alternative to ritonavir. Although cobicistat is a potent inhibitor of cytochrome P450 3A, it is a weak inhibitor of CYP2D6 and other CYP isoforms (e.g., CYP1A2), making pharmacologic interactions with many drugs more predictable than for ritonavir, which is also active against these isoforms. Preliminary studies with cobicistat suggest that it has a good tolerability profile and less effect on adipocytes (resulting in lesser accumulations of lipid and a milder response to insulin). The better solubility of cobicistat compared with ritonavir has helped the development of more single-tablet combination regimens with cobicistat. However, cobicistat is currently only approved for adolescents and adults; it is not approved for use in pregnancy.

Adherence

Adherence to the medication schedules and dosages is fundamental to cART success. Therefore, assessment of the likelihood of adherence to treatment is an important factor in deciding when to initiate therapy as well as choice of regimen. Numerous studies show that compliance of < 90% results in less-successful suppression of the viral load. In addition, several studies document that almost half of the pediatric patients surveyed were nonadherent to their regimen. Poor adherence to prescribed medication regimens results in subtherapeutic drug concentrations and enhances the development of resistant viruses. Several barriers to adherence are unique to children with HIV infection. Combination antiretroviral regimens are often unpalatable and require extreme dedication on the part of the caregiver and child; a reluctance to disclose the child's disease to others reduces social support; there may be a tendency to skip doses if the caregiver is not around or when the child is in school. Adolescents have other issues that reduce adherence. Denial and/or fear of their infection, an unstructured lifestyle, conduct or emotional disorders, wishing to be the same as their peers, depression, fatigue from taking a lifelong regimen, anxiety, and alcohol and substance abuse are just a few of the barriers to long-term adherence in this growing population. These and other barriers make participation of the family in the decision to initiate therapy essential. Intensive education on the relationship of drug adherence to viral suppression, training on drug administration, frequent follow-up visits, peer support, text messaging, and commitment of the caregiver and the patient (despite the inconvenience of adverse effects or the dosing schedule) are critical for successful antiviral treatment. Multiple methods such as the viral load response, self-reporting of missed doses during the last 3-7 days, and pharmacy/pill counting should be used to assess adherence. Assessing for emergence of resistant virus on sequencing (genotype) can also be a helpful tool.

Initiation of Therapy

The decision on when to initiate cART is evolving. When cART was first introduced, medication regimens had significant side effects. This led to decisions to delay therapy until it would be most beneficial, usually after advanced immunologic suppression had developed. In a large adult cohort, the Strategic Timing of Antiretroviral Treatment (START) trial demonstrated a strong benefit in starting therapy earlier in adults, even before CD4 counts fell into an immunosuppressed range; this became more feasible with the development of safer, better-tolerated medications. In adults, it has also been found that receiving suppressive cART eliminates the risk of the sexual transmission of HIV to others. Current adult guidelines recommend the initiation of cART in all adults with HIV. As with adult guidelines, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV also recommends treatment for all children with HIV. However, the urgency of when to start treatment and the strength of the recommendations vary by age and pretreatment CD4 count. This is due to limited pediatric-specific data, as well as knowing that once pediatric patients are started on medications, treatment will need to continue for life; this means that potential concerns about adherence and toxicities will go on for an extended period. For children < 1 yr of age, the CHER trial has clearly demonstrated the benefit of early immediate ART. Data in older children suggest that mortality rates are lower and growth is more normal in children < 10 yr of age who are started on immediate cART. More studies are needed for confirmation, however.

Children younger than 1 yr of age are at high risk for disease progression, and immunologic and virologic tests to identify those likely to develop rapidly progressive disease are less predictive than in older children. Therefore, HIV-infected infants younger than 1 yr of age should be treated with cART as soon as the diagnosis of HIV infection has been confirmed, regardless of their clinical or immunologic status or viral load. Data suggest that HIV-infected infants who are treated before the age of 3 mo control their HIV infection better than infants whose cART started later than 3 mo of age.

For children 1 yr to under 6 yr of age, urgent treatment is recommended if the children have stage 3–defining opportunistic infections or stage 3 immunodeficiency (CD4 < 500 cells/µL). For children with moderate HIV-related symptoms or CD4 counts of 500-999 cells/µL, treatment is strongly recommended. Treatment is also recommended for asymptomatic or mildly symptomatic children with CD4 counts ≥ 1,000 cells/µL.

For children ≥ 6 yr, urgent treatment is recommended if the children have stage 3–defining opportunistic infections or stage 3 immunodeficiency (CD4 < 200 cells/µL). For children with moderate HIV-related symptoms or CD4 counts of 200-499 cells/µL, treatment is again strongly recommended. Treatment is also recommended for asymptomatic or mildly symptomatic children with CD4 counts ≥ 500 cells/µL. *These guidelines are reviewed yearly, and care providers should check for revisions regularly at http://aidsinfo.nih.gov* .

Dosages

Children are usually treated with higher doses (per kg weight) than adults because of reduced absorption or increased drug metabolism. Data on ART drug dosages for neonates, especially premature infants, are often limited. Because of the immaturity of the neonatal liver, there must often be an increase in the dosing interval of drugs primarily cleared through hepatic glucuronidation.

Adolescents should have ART dosages prescribed on the basis of the Tanner staging of puberty rather than on the basis of age. Pediatric dosing ranges should be used during early puberty (Tanner stages I, II, and III), whereas adult dosing schedules should be followed in adolescents in late puberty (Tanner stages IV and V). Dolutegravir and Efavirenz should be avoided in females who may become pregnant and do not use effective contraception because of potential teratogenicity; however, if an HIV-positive female becomes pregnant while taking a dolutegravir or efavirenz-containing regimen, the regimen can be continued, assuming that virologic suppression is maintained, because by the time the pregnancy is typically determined, the period of teratogenesis has past, specifically for neural tube defects. Because some ART agents may alter the metabolism of some hormonal contraceptives and decrease their effectiveness, interactions should be considered when choosing contraceptive agents. A comprehensive table of interactions of HIV medications with hormonal contraceptives can be found here: https://aidsinfo.nih.gov/guidelines/htmltables/3/5803 . Medroxyprogesterone

(DMPA) is a reasonable choice outside of regimens containing cobicistat. Alternative contraception options, such as use of an intrauterine device, should also be considered.

Changing Antiretroviral Therapy

Therapy should be changed when the current regimen is judged ineffective as evidenced by an increase in viral load, deterioration of the CD4 cell count, or clinical progression. Development of toxicity or intolerance to drugs is another reason to consider a change in therapy. When a change is considered, the patient and family should be reassessed for adherence concerns. Because adherence is a major issue in this population, resistance testing (while the patient is taking antiretroviral medications) is important in identifying adherence issues (e.g., detectable virus sensitive to current drugs suggests a lack of adherence) or the development of resistance (e.g., evidence of resistance mutations to given drugs). In both situations, other contributing factors, such as poor absorption, an incorrect dose, or drug–drug interactions, should be carefully reviewed. While considering possible new drug choices, the potential for cross-resistance should be addressed. In starting a new regimen in a patient with virologic failure, the new regimen should include at least two, but preferably three, fully active antiretroviral medications, with assessment of the anticipated activity based on the treatment history and resistance testing (genotype or phenotype). The goal is to achieve and maintain virologic suppression. If virologic suppression cannot be achieved, the goals of therapy should focus on preserving the immunologic function and preventing further disease progression, as well as preventing the emergence of additional drug resistance (which could limit future treatment options).

Monitoring Antiretroviral Therapy

To ensure proper monitoring, the CD4 cell count, viral load, complete blood count, chemistries, urinalysis, and serum lipids should be obtained before an initiation of or change in cART to have a baseline for comparisons during treatment. At entry into care genotypic resistance testing should be done as well. Children need to be seen within 1-2 wk after initiation of new cART to reinforce and counsel regarding adherence and to screen for potential side effects. Virologic and immunologic surveillance (using the quantitative HIV RNA PCR and CD4 lymphocyte count), as well as clinical assessment, should be performed regularly while on cART. The initial virologic response (i.e., at least a five-fold [0.7 $\log_{10}$] reduction in viral load) should be achieved within 4-8 wk of initiating antiretroviral therapy. The maximum response to therapy usually occurs within 12-16 wk, but may be later (24 wk) in very young infants. Thus, HIV RNA levels should be measured at 4 wk and 3-4 mo after therapy initiation. Once an optimal response has occurred, the viral load should then be measured at least every 3-6 mo. If the response is unsatisfactory, another viral load should be determined as soon as possible to verify the results before a change in therapy is considered. Virologic failure is defined as a repeated plasma viral load ≥200 copies/mL after 6 mo of therapy. The CD4 cells respond more slowly to successful treatment particularly in patients with long standing infection and CD4 suppression. CD4 counts should be monitored every 3-4 mo and potentially can be done less frequently in adolescents and adults with documented virologic suppression. Potential toxicity should be monitored closely for the first 8-12 wk (including complete blood count, serum chemistries), and if no clinical or laboratory toxicity is documented, a follow-up visit every 3-4 mo is adequate. Monitoring for potential toxicity should be tailored to the drugs taken. These toxicities include but are not limited to hematologic complications (e.g., zidovudine); hypersensitivity rash (e.g., efavirenz); lipodystrophy (e.g., redistribution of body fat seen with NRTIs, protease inhibitors, which can take several years to emerge); hyperlipidemia (elevation of cholesterol and triglyceride concentrations); hyperglycemia, and insulin resistance (e.g., protease inhibitors); mitochondrial toxicity leading to severe lactic acidosis (e.g., stavudine, didanosine); electrocardiogram abnormalities (e.g., atazanavir, lopinavir); abnormal bone mineral metabolism (e.g., tenofovir disoproxil fumarate but not tenofovir alafenamide); and hepatic toxicity, including severe hepatomegaly with steatosis. After a patient is on a stable regimen, labs outside of CD4 count and viral load can be done every 6-12 mo. An important part of every visit is ongoing adherence counseling given the need for excellent adherence to cART to avoid the emergence of resistance. *Detailed current guidelines for monitoring HIV-infected children during therapy can be found at http://aidsinfo.nih.gov* .

Resistance to Antiretroviral Therapy

Young children usually are at greater risk than adults for developing resistance because they have higher viral loads than adults and are more limited by which ART options are available. The high mutation rate of HIV (mainly as a result of the absence of error-correcting mechanisms) results in the generation of viruses with multiple mutations everyday in the absence of cART. Failure to reduce the viral load to < 40 copies/mL on cART due to nonadherence resulting in subtherapeutic drug levels increases the risk for developing resistance by selecting those mutant viruses with a competitive advantage (i.e. drug resistance mutations). Even effectively treated patients do not completely suppress all viral replication, and persistence of HIV transcription and evolution of envelope sequences continues in the latent cellular reservoirs, though recent data show that this evolution does not appear to affect the emergence of resistance to cART in virologically suppressed patients. Accumulation of resistance mutations, particularly in nonadherent patients, progressively diminishes the potency of the cART and challenges the physician to find new regimens. For some drugs (e.g., nevirapine, lamivudine), a single mutation is associated with resistance, whereas for other drugs (e.g., zidovudine, lopinavir), several mutations are needed before significant resistance develops. Testing for drug resistance, especially when devising a new regimen, is the standard of care. Two types of tests are available; genotype is most commonly used but the phenotype may be helpful in select patients with complex viral resistance due to exposure to multiple cART regimens.

1. The **phenotype** measures the virus susceptibility in various concentrations of the drug. This allows calculation of the drug concentration that will inhibit the viral replication by 50% (IC_{50}). The ratio of the IC_{50} and a reference virus IC_{50} is reported as the fold resistance change. Note this test is usually combined with a genotype when used but is largely reserved for patients with extremely complex mutations.
2. The **genotype** predicts the virus susceptibility from mutations identified in the HIV genome isolated from the patient and is the more commonly used test. Several online sites (e.g., http://hivdb.stanford.edu) can assist in interpreting the test's results. Several studies show that the treatment success is higher in patients whose cART was guided by genotype or phenotype testing.

Neither method may detect drug resistance if the amount of the resistant virus is < 10% of the circulating population or if it is present only in the latent reservoir. Note that if a patient has not been taking cART for several weeks, the absence of selective drug pressure will make the dominant population of circulating viruses revert to the wild type, and resistance mutations can be missed.

It is recommended to test for drug resistance before initiating therapy and before changing treatment because of virologic failure. When changing therapy, the resistance test results should be considered in the context of previous resistance tests results, if done, and drugs used in previous regimens.

Supportive Care

Even before ART drugs were available, a significant impact on the quality of life and survival of HIV-infected children was achieved when supportive care was given. A multidisciplinary team approach is desirable for successful management. Following the initiation or change of cART, more frequent visits or contacts with the patient/caregivers for support and education will help in their acceptance and adjustment to the new regimen and will contribute to a better adherence. Close attention should be paid to the nutritional status, which is often delicately balanced and may require aggressive supplementation, especially in children with advanced disease. Painful oropharyngeal lesions and dental caries may interfere with eating, and thus routine dental evaluations and careful attention to oral hygiene should be encouraged. Paradoxically, an increasing number of adolescents with perinatally acquired or behavioral risk-acquired disease are obese. Some teens experience ART-related central lipoaccumulation (usually related to older agents), but others have poor dietary habits and inactivity as the cause of their obesity, just as others do who are obese in epidemic numbers in the United States. Their development should be evaluated regularly, with the provision of necessary physical, occupational, and/or speech therapy. Recognition of pain in the young child may be difficult, and effective nonpharmacologic and pharmacologic protocols for pain management should be instituted when indicated.

All HIV-exposed and HIV-infected children should receive standard pediatric immunizations. Live oral polio vaccine should not be given due to poor immunologic response in HIV+ children as well as concern for live vaccination in potentially immunocompromised children (Fig. 302.5). The risk and benefits of rotavirus vaccination should be considered in infants born to HIV-infected mothers. Because < 1% of these infants in resource-rich countries will develop HIV infection, the vaccine should be given. In other situations, the considerable attenuation of the vaccine's strains should be considered, and unless the infant has clinical symptoms of AIDS or a CD4 percentage of < 15%, vaccination is likely appropriate. Other live bacterial vaccines (e.g., bacillus Calmette-Guérin) should be avoided because of the high incidence of bacillus Calmette-Guérin–related disease in HIV-infected infants. Varicella and measles–mumps–rubella vaccines are recommended for children who are not severely immunosuppressed (i.e., CD4 cell percentage ≥ 15%, absolute CD4 count > 500 cells/µL for ages 1-5 yr), but these vaccines should not be given to severely immunocompromised children (i.e., CD4 cell percentage < 15%, absolute CD4 count < 500 cells/µL for age 1-5 yr). Of note, prior immunizations do not always provide protection, as evidenced by outbreaks of measles and pertussis in immunized HIV-infected children. The durability of vaccine-induced titers is often short, especially if vaccines are administered when the child's CD4 cell count is low, and reimmunization when the CD4 count has increased may be indicated. It is recommended that children with HIV receive quadrivalent meningococcal conjugate vaccine at a younger age than the routine schedule. Adolescent vaccines are also important, including the Tdap booster and HPV vaccine. The current recommended annotated vaccine schedule for HIV-infected children is found here: https://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html .

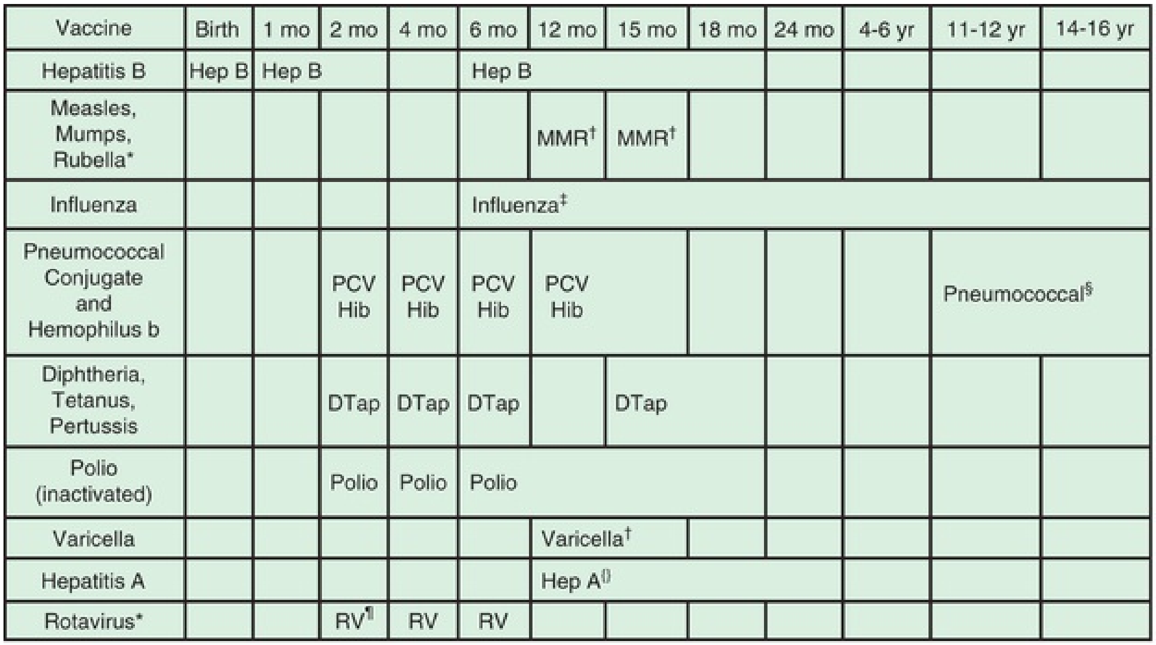

Vaccine	Birth	1 mo	2 mo	4 mo	6 mo	12 mo	15 mo	18 mo	24 mo	4-6 yr	11-12 yr	14-16 yr
Hepatitis B	Hep B	Hep B			Hep B							
Measles, Mumps, Rubella*						MMR†	MMR†					
Influenza					Influenza‡							
Pneumococcal Conjugate and Hemophilus b			PCV Hib	PCV Hib	PCV Hib	PCV Hib					Pneumococcal§	
Diphtheria, Tetanus, Pertussis			DTap	DTap	DTap		DTap					
Polio (inactivated)			Polio	Polio	Polio							
Varicella						Varicella†						
Hepatitis A						Hep A‖						
Rotavirus*			RV¶	RV	RV							

* See text.

† Contraindicated in children with AIDS or CD4⁺ absolute count <500 for age 1-5 yr or <15%. Give 2 doses 1-3 mo apart. In immune reconstituted children on cART, CD4 count has to be sustained above threshold for at least 6 mo before live virus vaccination.

‡ Revaccination is recommended every year. Inactivated vaccine only should be used, not LAIV.

§ Revaccination with pneumococcal polysaccharide vaccine (PPV) every 5 yr.

‖ Two doses at least 6 mo apart.

¶ First dose 6 through 14 wk of age and final dose no later than 8 mo 0 days of age. If using Rotarix, only 2 doses (2 and 4 mo) are needed.

FIG. 302.5 Routine childhood immunization schedule for HIV-infected children.

Prophylactic regimens are integral for the care of HIV-infected children. All infants between 4-6 wk and 1 yr of age who are proven to be HIV-infected should receive prophylaxis to prevent *P. jiroveci* pneumonia regardless of the CD4 count or percentage (Tables 302.5 and 302.6). Infants exposed to HIV-infected mothers should receive the same prophylaxis until they are proven to be noninfected; however, prophylaxis does not have to be initiated if there is strong presumptive evidence of noninfection (i.e., non–breastfed infant with two negative HIV PCR tests at older than 14 days and 4 wk of age, respectively). When the HIV-infected child is older than 1 yr of age, prophylaxis should be given according to the CD4 lymphocyte count (see Table 302.5). The best prophylactic regimen is 150 mg/m^2 /day of TMP and 750 mg/m^2 /day of SMX (maximum: 320/1,600 mg) given as 1-2 daily doses 3 days (consecutively or every other day) per wk. For severe adverse reactions to TMP-SMX, alternative therapies include dapsone, atovaquone, and aerosolized pentamidine.

Table 302.5

Recommendations for PJP Prophylaxis and CD4 Monitoring for HIV-Exposed Infants and HIV-Infected Children, by Age and HIV Infection Status

AGE/HIV INFECTION STATUS	PJP PROPHYLAXIS	CD4 MONITORING
Birth to 4-6 wk, HIV-exposed	No prophylaxis	None
HIV infection reasonably excluded[*]	No prophylaxis	None
<1 yr, HIV-infected or HIV-indeterminate	Prophylaxis regardless of CD4 count or percentage	According to local practice for initiation or follow-up of cART
1-5 yr, HIV-infected	Prophylaxis if CD4 < 500 cells/µL or < 15% [†]	According to local practice for initiation or follow-up of cART
>6 yr, HIV-infected	Prophylaxis if CD4 < 200 cells/µL or < 15% [†] [‡]	According to local practice for initiation or follow-up of cART

[*] See text.

[†] More frequent monitoring (e.g., monthly) is recommended for children whose CD4 counts or percentages are approaching the threshold at which prophylaxis is recommended.

[‡] Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PJP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PJP should receive PJP prophylaxis until their CD4 count is ≥200 cells/mm^3 for patients aged ≥6 yr, CD4 percentage is ≥15% or CD4 count is ≥500 cells/mm^3 for patients aged 1 to <6 yr for >3 consecutive mo after receiving cART for ≥6 mo.

The National Perinatal HIV Hotline (1-888-448-8765) provides consultation on all aspects of perinatal HIV care.

cART, combined antiretroviral therapy; PJP, *Pneumocystis jiroveci* pneumonia.

Table 302.6

Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States[*]

PATHOGEN	PREVENTIVE REGIMEN		
	INDICATION	FIRST CHOICE	ALTERNATIVE
STRONGLY RECOMMENDED AS STANDARD OF CARE			
Pneumocystis pneumonia [†]	HIV-infected or HIV-indeterminate infants aged 1-12 mo; HIV-infected children aged 1-5 yr with CD4 count of < 500 cells/µL or CD4 percentage of < 15%; HIV-infected children aged 6-12 yr with CD4 count of < 200 cells/µL or CD4 percentage of < 15%; >13 yr with CD4 count <200 or	**TMP-SMX** , 150/750 mg/m^2 body surface area per day or 5-10 mg/kg/day (TMP)/25-50 mg/kg/day (SMX) (max: 320/1,600 mg) orally qd or bid 3 times weekly on consecutive days	**Dapsone:** age ≥ 1 mo: 2 mg/kg (max: 100 mg) orally qd; or 4 mg/kg (max: 200 mg) orally once a week **Atovaquone:**

	<15%	*or* qd or bid orally 3 times weekly on alternate days	age 1-3 mo and > 24 mo-12 yr: 30-40 mg/kg orally qd with food; age 4-24 mo: 45 mg/kg orally qd with food; ≥ 13 yr 1500 mg orally qd **Aerosolized pentamidine:** age ≥ 5 yr: 300 mg once a month by Respirgard II (Marquest, Englewood, CO) nebulizer
Malaria	Living or traveling to area in which malaria is endemic	Same for HIV-infected and HIV-uninfected children. Refer to http://www.cdc.gov/malaria/ for the most recent recommendations. **Mefloquine** , 5 mg/kg orally 1 time weekly (max: 250 mg) **Atovaquone/proguanil** (Malarone) qd 11-20 kg: 62.5 mg/25 mg (1 pediatric tablet) 21-30 kg: 2 pediatric tablets 31-40 kg: 3 pediatric tablets >40 kg: 1 adult tablet (250 mg/100 mg)	**Doxycycline,** 2.2 mg/kg body weight (maximum 100 mg) orally qd for children >8 yr **Chloroquine,** 5 mg/kg base (equal 7.5 mg/kg chloroquine phosphate) orally up to 300 mg weekly (only for regions where the parasite is sensitive)
Mycobacterium tuberculosis			
Isoniazid-sensitive	TST reaction ≥ 5 mm or Prior positive TST result without treatment or Close contact with any person who has contagious TB. TB disease must be excluded before start of treatment	**Isoniazid,** 10-15 mg/kg body weight (max: 300 mg) qd for 9 mo *or* 20-30 mg/kg body weight (max: 900 mg) orally 2 times weekly for 9 mo; DOT highly recommended	**Rifampin,** 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo
Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB	**Rifampin,** 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo	Consult TB expert
Multidrug-resistant (isoniazid and rifampin)	Same as previous pathogen; increased probability of exposure to multidrug-resistant TB	Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from	

		source patient	
Mycobacterium avium complex ‡	For children age ≥ 6 yr with CD4 count of < 50 cells/µL; age 2-5 yr with CD4 count of < 75 cells/µL; age 1-2 yr with CD4 count of < 500 cells/µL; age < 1 yr with CD4 count of < 750 cells/µL	**Clarithromycin,** 7.5 mg/kg (max: 500 mg) orally bid *or* **Azithromycin,** 20 mg/kg (max: 1,200 mg) orally once a week	**Azithromycin,** 5 mg/kg body weight (max: 250 mg) orally qd *or* Children age ≥ 5 yr **Rifabutin,** 300 mg orally qd
Varicella-zoster virus §	Exposure to varicella or shingles with no history of varicella or Zoster or seronegative status for VZV or Lack of evidence for age-appropriate vaccination	Varicella-zoster immunoglobulin (VariZIG), 125 IU/10 kg (max: 625 IU) IM, administered ideally within 96 hr after exposure; potential benefit up to 10 days after exposure	If VariZIG is not available and < 96 hr from exposure, **acyclovir** 20 mg/kg (max: 800 mg) 4 times a day for 5-7 days *or* IVIG, 400 mg/kg, administered once
Vaccine-preventable pathogens	Standard recommendations for HIV-exposed and HIV-infected children	Routine vaccinations (see Fig. 302.5)	
USUALLY RECOMMENDED			
Toxoplasma gondii ¶	Seropositive IgG to Toxoplasma and severe immunosuppression: age < 6 yr with CD4 percentage < 15%; age ≥ 6 yr with CD4 count < 100 cells/µL	TMP-SMX, 150/750 mg/m^2 orally qd or divided bid *or* Same dosage qd 3 times weekly on consecutive days *or* bid 3 times weekly on alternate days	**Dapsone,** age ≥ 1 mo: 2 mg/kg or 15 mg/m^2 (max: 25 mg) orally qd plus **Pyrimethamine,** 1 mg/kg (max: 25 mg) orally qd plus **Leucovorin,** 5 mg orally every 3d
Invasive bacterial infections	Hypogammaglobulinemia (i.e., IgG < 400 mg/dL)	IVIG 400 mg/kg body weight every 2-4 wk	
Cytomegalovirus	CMV antibody positivity and severe immunosuppression (CD4 count < 50 cells/µL for >6 yr; CD4 percentage <5% for ≤6 yr) For children aged 4 mo–16 yr, valganciclovir oral solution 50 mg/mL at dose in milligrams = 7 × BSA × CrCl (up to maximum CrCl of 150 mL/min/1.73 m^2) orally qd with food (maximum	**Valganciclovir,** 900 mg orally qd with food for older children who can receive adult dosing	

	dose 900 mg/day)		

[*] Information in these guidelines might not represent FDA approval or FDA-approved labeling for products or indications. Specifically, the terms *safe* and *effective* might not be synonymous with the FDA-defined legal standards for product approval.

[†] Daily trimethoprim-sulfamethoxazole (TMP-SMX) reduces the frequency of certain bacterial infections. Compared with weekly dapsone, daily dapsone is associated with a lower incidence of PCP but higher hematologic toxicity and mortality rates. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need TMP-SMX. TMP-SMX, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine), protect against toxoplasmosis; however, data have not been prospectively collected.

[‡] Substantial drug interactions can occur between rifamycins (i.e., rifampin and rifabutin) and protease inhibitors and nonnucleoside reverse transcriptase inhibitors. A specialist should be consulted.

[§] Children routinely being administered intravenous immunoglobulin (IVIG) should receive VariZIG if the last dose of IVIG was administered more than 21 days before exposure.

[¶] Protection against toxoplasmosis is provided by the preferred anti-*Pneumocystis* regimens and possibly by atovaquone.

CMV, cytomegalovirus; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IM, intramuscularly; IVIG, intravenous immunoglobulin; PCP, *Pneumocystis* pneumonia; TB, tuberculosis; TMP-SMX, trimethoprim-sulfamethoxazole; TST, tuberculin skin test; VZV, varicella-zoster virus.

From Centers for Disease Control and Prevention (CDC): Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children, MMWR Recomm Rep 58(RR-11):127-128, 2009, Table 1.

Prophylaxis against MAC should be offered to HIV-infected children with advanced immunosuppression (i.e., CD4 lymphocyte count < 750 cells/µL in children younger than 1 yr of age, < 500 cells/µL in children 1-2 yr of age, < 75 cells/µL in children 2-5 yr of age, and < 50 cells/µL in children > 6 yr of age) (see Table 302.6). The drugs of choice are azithromycin (20 mg/kg [maximum: 1,200 mg] once a week orally or 5 mg/kg [maximum: 250 mg] once daily orally) or clarithromycin (7.5 mg/kg bid orally). In rare situations, rifabutin 300 mg qd can be an alternative for children older than 6 yr of age though efficacy data in children is very limited.

Based on adult data, primary prophylaxis against most opportunistic infections may be discontinued if patients have experienced sustained (>6 mo duration) immune reconstitution with cART, even if they had previous opportunistic infections such as *Pneumocystis* pneumonia or disseminated MAC. HIV-infected children are at higher risk for TB and thus should have tuberculin skin testing (5 tuberculin units purified protein derivation) or interferon gamma release assay

(IGRA) testing for TB at least once per year; an induration of 5 mm or more should be considered positive for the PPD. If the child is living in close contact with a person with TB, the child should be tested more frequently. Of note, the sensitivity of purified protein derivation and IGRA is reduced in severely immunocompromised patients. The Guidelines for Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children (http://aidsinfo.nih.gov) should be consulted for these and other opportunistic infections that may occur in these populations. To reduce the incidence of opportunistic infections, parents should be counseled about (1) the importance of good hand washing, (2) avoiding raw or undercooked food *(Salmonella)* , (3) avoiding drinking or swimming in lake or river water or being in contact with young farm animals *(Cryptosporidium)* , and (4) the risk of playing with pets (*Toxoplasma* and *Bartonella* from cats, *Salmonella* from reptiles).

Prognosis

The improved understanding of the pathogenesis of HIV infection in children and the availability of more effective antiretroviral drugs has changed the prognosis considerably for children with HIV infection. The earlier cART is started, the better the prognosis. In settings with ready access to early diagnosis and antiretroviral therapy, progression of the disease to AIDS has significantly diminished. Since the advent of cART in the mid-1990s, mortality rates in perinatally infected children have declined more than 90% and many children survive to adolescence and adulthood. Even with only partial reduction of the viral load, children may have both significant immunologic and clinical benefits. In general, the best prognostic indicators are the sustained suppression of the plasma viral load and the restoration of a normal $CD4^+$ lymphocyte count. If determinations of the viral load and CD4 lymphocytes are available, the results can be used to evaluate the prognosis. It is unusual to see rapid progression in an infant with a viral load < 100,000 copies/mL. In contrast, a high viral load (>100,000 copies/mL) over time is associated with a greater risk for disease progression and death. CD4 count is also another prognostic indicator with mortality rate significantly higher in profoundly immunosuppressed individuals. To define the prognosis more accurately, the use of changes in both markers (CD4 lymphocyte percentage and plasma viral load) is recommended.

Even in resource-limited countries where cART and molecular diagnostic tests are less available, the use of cART has had a substantial benefit on the survival of HIV-infected children and has reduced the likelihood of mortality by > 75%. Children with opportunistic infections (e.g., *Pneumocystis* pneumonia, MAC), encephalopathy and regressing developmental milestones, or wasting syndrome, which are all AIDS defining conditions, have the worst prognosis, with 75% dying before 3 yr of age. A higher risk of death was documented in children who did not receive TMP-SMX preventive therapy. Persistent fever and/or oral thrush, serious bacterial infections (meningitis, pneumonia, sepsis), hepatitis, persistent anemia (<8 g/dL), and/or thrombocytopenia (<100,000/µL) also suggest a poor outcome, with > 30% of such children dying before 3 yr of age. In contrast, lymphadenopathy, splenomegaly, hepatomegaly, lymphoid interstitial pneumonitis, and parotitis are associated with a slower progression of disease and a better prognosis. With sustained virologic suppression and maintained immunologic function, life expectancy is quite good. For adults and adolescents acquiring HIV, effective cART can restore life expectancy to near normal.

Prevention

Use of antiretroviral therapy for interruption of perinatal transmission from mother to child has been one of the greatest achievements of HIV research. Maternal cART is documented to decrease the rate of perinatal HIV-1 transmission to < 2%, and to < 1% if the mother's viral RNA level is < 1,000 copies/mL at delivery. Therefore, it is recommended that **all pregnant women** be tested for HIV, and if they are positive, should be treated with a cART regimen, irrespective of the viral load or CD4 count during pregnancy. All infants born to HIV-infected mothers should receive zidovudine prophylaxis for 6 wk; prophylaxis for 4 wk can be done in low-risk infants. Additional ARV therapy should be considered if the risk of acquiring HIV by the newborn is high. High-risk scenarios include infants born to mothers who received neither antepartum nor intrapartum ARV drugs or only intrapartum ARV drugs, infants born to mothers with a significant detectable viral load (>1,000 copies/mL) near delivery despite cART (particularly if it was a vaginal delivery), infants born to mothers of unknown HIV status who test positive at delivery or postpartum, or infants who have a positive HIV antibody test on screening after delivery. In these scenarios, three regimen options can be considered: (1) the addition of three doses of nevirapine (at birth, 48 hr, and 144 hr of life); (2) an empirical HIV therapy regimen of zidovudine, lamivudine, and nevirapine at treatment doses or (3) an empirical HIV therapy regimen of zidovudine, lamivudine, and raltegravir at treatment doses (note treatment doses of raltegravir for neonates are different than for older children with an escalating dose over the 6 wk of therapy due to evolving liver metabolism in neonates). Enthusiasm and support for treatment regimens (particularly option 2) have been driven by a case of an apparent functional cure in an infant in 2013 who went 2 yr without cART with virologic suppression before rebound of the infection occurred (the so-called Mississippi baby), as well as a large cohort of high-risk, exposed infants in Canada. The most experience and data exist for zidovudine, which can cause transient anemia or neutropenia in exposed infants. There is also a strong pool of data supporting the safety of lamivudine. For the remaining drugs for treatment of high risk infants, nevirapine has the the most experience of use but neither has robust data in premature infants. Dosing recommendations exist for nevirapine down to 32 wk but raltegravir can only be used in 37 wk and up. *In high-risk infants, consultation with an experienced HIV specialist is highly recommended. The National Perinatal HIV Hotline (888-448-8765) provides 24-7 support from experienced HIV specialists to help in managing high-risk infants. Guidelines and current recommended doses for prophylaxis in newborns are updated at least yearly and can be accessed at http://www.aidsinfo.nih.gov* . A complete blood count, differential leukocyte count, and platelet count should be performed at 4-8 wk of age to monitor zidovudine toxicity. This should be in conjunction with 4-6 wk of zidovudine prophylaxis for the infant. If the child is found to be HIV infected, baseline laboratory assessment (e.g., CD4 count, HIV RNA, complete blood count, chemistries, lipids, genotype) should be done and cART should be started as soon as possible. The viral load and CD4 lymphocyte counts should be determined at 1 and 3 mo of age and should be repeated every 3 mo. Cesarean section (C-section) as a prevention strategy was examined in a multinational meta-analysis, which showed that the combination of elective C-section and maternal zidovudine treatment reduced transmission by 87%. However, these data were obtained prior to the advent of cART, and the additional benefit of elective C-section to the cART-treated mother whose viral load is < 1,000 copies/mL is negligible. Thus, elective C-section at 38 wk of gestation should be considered only for women whose viral load is > 1,000 copies/mL in late gestation, to further reduce the risk of vertical transmission.

The WHO recommends that all pregnant women receive a cART regimen appropriate for their own health, which should be continued for the remainder of their lives. This approach has the potential to reduce transmission during breastfeeding and future pregnancies, lowers the transmission risk to sexual partners, improves maternal survival, and promotes simplified universal treatment regimens. It is not currently recommended that HIV+ women breastfeed in resource rich countries and there has been a least one case of mother-to-child-transmission via breastfeeding in a virologically suppressed mother.

Although the most effective way to prevent postpartum transmission of HIV is to eliminate breastfeeding altogether and substitute replacement feeding, there is evidence that early weaning may not be safe in resource-limited settings because of the high risk of malnutrition and diarrhea in formula-fed infants without a consistent source of clean water. Furthermore, exclusive breastfeeding (no additional solids or fluids other than water) results in less transmission than mixed feeding. Guidelines have evolved to recommend that HIV-infected mothers living in resource-limited settings should breastfeed their infants until at least 12 mo of age, with exclusive breastfeeding for the first 6 mo, and cART should continue to be provided to the mother. In settings where there are safe alternatives to breastfeeding, formula feeding is recommended. *U.S. guidelines for prevention of mother-to-child transmission are regularly updated at http://aidsinfo.nih.gov/ and the international guidelines are regularly updated at the WHO website (http://www.who.int/hiv/topics/mtct/en/).*

Because perinatal transmission can be reduced dramatically by treating pregnant mothers, prenatal testing and identification of HIV-1 infection as early as possible in the mother is extremely important. The benefit of therapy both for the mother's health and to prevent transmission to the infant cannot be overemphasized. The recommended universal prenatal HIV-1 counseling and HIV-1 testing for all pregnant women has reduced the number of new infections dramatically in many areas of the United States and Europe. For women not tested during pregnancy, the use of rapid HIV antibody testing during labor or on the first day of the infant's life is a way to provide perinatal prophylaxis to an additional group of at-risk infants. Perinatal recommendations also now endorse the testing of pregnant women's partners to identify HIV+ partners who may transmit, leading to acute HIV infection which carries and extremely high risk of mother-to-child transmission.

Prevention of sexual transmission involves avoiding the exchange of bodily fluids. In sexually active adolescents, condoms should be an integral part of programs to reduce sexually transmitted diseases, including HIV-1. Unprotected sex with older partners or with multiple partners and the use of recreational drugs are often associated with acquisition of HIV-1 infection in adolescents and young adults. Educational efforts about avoidance of risk factors are essential for older school-age children and adolescents and should begin before the onset of sexual activity. In addition, promising research for sexually active adults may translate to increased prevention for adolescents. Three African trials demonstrated that male circumcision was associated with a 50–60% reduction in the risk of HIV acquisition in young men. For women, use of a 1% vaginal gel formulation of tenofovir during intercourse was found to reduce HIV acquisition by nearly 40% in one study, though subsequent trials have had variable efficacy; other topical microbicides are being investigated. A double-blind study of preexposure prophylaxis (PrEP) in MSM using once-daily dosing of coformulated tenofovir and emtricitabine resulted in a 44% reduction in the incidence of HIV. The incidence of HIV transmission was reduced by 73% when participants took the drug on 90% or more days. Studies of this regimen in other groups, including serodiscordant heterosexual couples, heterosexual individuals not in committed relationships, and intravenous drug users, showed excellent efficacy, as well (70–92%). All studies to date for PrEP have been in individuals 18 yr and up, however in adolescent patients with sufficiently high risk for acquisition, consideration should be given to using PrEP for HIV prevention. In addition, a large randomized multinational clinical trial of HIV serodiscordant adults demonstrated that effective ARV therapy in the HIV-infected partner reduced secondary transmission to an uninfected sexual partner by 96%. Further trials have confirmed that virologic suppression eliminates sexual transmission in heterosexual partners as well as men who have sex with men, spurning the catchphrase “U=U” or undetectable = untransmittable. The majority of these trials have been in adults, with limited participation by adolescents and young adults. Although much of the efficacy will likely be seen in young people, as well, further studies should be done on efficacy and acceptability in this age-group.

The course and prognosis of HIV infection has been radically improved by cART for all ages, particularly newer agents with less side effects. With good adherence, prolonged virologic suppression can be achieved and immune function can be preserved or reconstituted. However, lifelong adherence and side effects of medications are important challenges to recognize that can prevent patients from achieving good outcomes. Globally, great strides have been made in preventing mother-to-child transmission and increasing access to cART for children and adults, which is important for maintaining health as well as driving down sexual and vertical transmission with virologic suppression. However, there is still much work to be done in order to ensure the end of the global HIV epidemic, including continued advancement of our understanding of the immunology of HIV latency and reservoirs, HIV vaccines, and continued increasing of access to cART worldwide.

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CHAPTER 303

Human T-Lymphotropic Viruses (1 and 2)

Paul Spearman, Lee Ratner

Etiology

Human T-lymphotropic viruses 1 (HTLV-1) and 2 (HTLV-2) are members of the *Deltaretrovirus* genus of the Retroviridae family and are single-stranded RNA viruses that encode reverse transcriptase, an RNA-dependent DNA polymerase that transcribes the single-stranded viral RNA into a double-stranded DNA copy. HTLV-1 was the first human retrovirus discovered, isolated in 1979 by the Gallo laboratory from a cutaneous T-cell lymphoma. The closely related virus HTLV-2 was subsequently identified in 1981. HTLV-1 is associated with adult T-cell leukemia/lymphoma (ATL) and HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP), whereas HTLV-2 is less pathogenic and is rarely associated with leukemia or neurologic diseases.

HTLV-1 and -2 share a genome homology of approximately 65%. The genome contains *gag*, *pol*, and *env* genes and the pX region, which encodes nonstructural proteins. The nonstructural proteins include the Tax and Rex regulatory proteins, the novel proteins essential for virus spread (p30, p12, and p13), and the antisense-encoded HTLV-1 basic leucine zipper factor HBZ. HTLV-1 and -2 infect cells via the ubiquitous glucose transporter type or via Neuropilin-1, which serve as virus receptors. HTLV-1 and -2 can infect a variety of cells, with HTLV-1 most often found in CD4+ T cells and HTLV-2 showing a preference for CD8+ T cells. Following viral entry, reverse transcription produces a double-stranded DNA copy of the RNA genome that is transported into the nucleus and integrated into chromosomal DNA (the provirus), evading the typical mechanisms of immune surveillance and facilitating lifelong infection.

Epidemiology and Modes of Transmission

HTLV-1 infects 15-20 million persons globally. It is endemic in southwestern Japan (where > 10% of adults are seropositive), areas of the Caribbean, including Jamaica and Trinidad (≤6%), and in parts of sub-Saharan Africa (≤5%). Lower seroprevalence rates are found in South America (≤2%) and Taiwan (0.1–1%). There is microclustering with marked variability within geographic regions.

The seroprevalence of HTLV-1 and HTLV-2 in the United States in the general population is 0.01–0.03% for each virus, with higher rates with increasing age. The prevalence of HTLV-1 infection is highest in babies born in endemic areas or in persons who have had sexual contact with persons from endemic areas. The prevalence of HTLV-2 infection is highest in intravenous drug users, with a seroprevalence of 8.8–17.6% in this population.

HTLV-1 and -2 are transmitted as cell-associated viruses from mother to child and transmission through genital secretions, contaminated blood products, and intravenous drug use. **Mother-to-child transmission** during the intrauterine period or peripartum period is estimated to occur in less than 5% of cases but increases to approximately 20% with breastfeeding. A higher maternal HTLV-1 proviral load and prolonged breastfeeding are associated with a greater risk of mother-to-child transmission. In Japan, approximately 20–25% of children born to HTLV-1–infected mothers became infected prior to recommendations that seropositive mothers should avoid breastfeeding, with a marked reduction to 2.5% transmission following restriction of breastfeeding. HTLV-2 may also be transmitted via breastfeeding, but it has a slightly lower reported transmission rate via breast milk of approximately 14%.

Diagnosis

HTLV-1 and HTLV-2 infections are diagnosed by screening using a second-generation enzyme immunoassay, with confirmation by immunoblot, indirect immunofluorescence, or line immunoassays. The polymerase chain reaction can also be used to distinguish HTLV-1 from HTLV-2 infection.

Clinical Manifestations

The lifetime risk of disease associated with HTLV-1 infection is estimated at 5–10% and is highest following vertical transmission. HTLV-1 is associated with ATL and several nonmalignant conditions, including the neurodegenerative disorder HTLV-1–associated myelopathy (HAM), also known as tropical spastic paraparesis and sometimes termed HAM/tropical spastic paraparesis. The geographic epidemiologic characteristics of ATL and HAM are similar. **HTLV-1–associated arthropathy** mimics rheumatoid arthritis, including a positive rheumatoid factor. Treatment is with antiinflammatory agents. **HTLV-1–associated uveitis** may be unilateral or bilateral, is more common among females, and resolves spontaneously, although it often recurs within 1-3 yr. Topical corticosteroids hasten recovery. **HTLV-1–associated infective dermatitis** is a chronic and recurrent eczematous disease occurring during childhood and adolescence, which predisposes to staphylococcal infection. HTLV-1 infection predisposes to disseminated and recurrent *Strongyloides stercoralis* infection, an increased risk of developing tuberculosis disease following latent infection, and severe scabies.

Adult T-Cell Leukemia/Lymphoma

The age distribution of ATL peaks at approximately 50 yr, underscoring the long latent period of HTLV-1 infection. HTLV-1–infected persons remain at risk for ATL even if they move to an area of low HTLV-1 prevalence, with a lifetime risk for ATL of 2–4%. Most cases of ATL are associated with monoclonal integration of the HTLV-1 provirus into the cellular genome of CD4+ T lymphocytes, resulting in unchecked proliferation of CD4 T cells. There is a spectrum of disease that is categorized into different forms: acute, lymphomatous, chronic, primary cutaneous smoldering, and primary cutaneous tumoral. The acute form of ATL comprises 55–75% of all cases. Smoldering, subclinical lymphoproliferation may spontaneously resolve (the outcome in approximately half of cases) or progress to chronic leukemia or lymphomatous or even acute ATL. **Chronic, low-grade, HTLV-1–associated lymphoproliferation (pre-ATL)** may persist for years with abnormal lymphocytes with or without peripheral lymphadenopathy before progressing to the acute form. Acute ATL is characterized by hypercalcemia, lytic bone lesions, lymphadenopathy that spares the mediastinum, hepatomegaly, splenomegaly, cutaneous lymphomas, and opportunistic infections. Leukemia may develop with circulating polylobulated malignant lymphocytes, called flower cells, possessing mature T-cell markers. Antiviral therapy with zidovudine and interferon-α is the standard therapy for leukemic-type ATL in the United States and Europe. In lymphoma-type ATL, response rates may be improved using the anti-CCR4 monoclonal antibody mogamulizumab with chemotherapy. Allogeneic hematopoietic stem cell transplantation is sometimes employed.

Human T-Cell Lymphotropic Virus-1–Associated Myelopathy

HAM is more common in females than in males and has a relatively short incubation period of 1-4 yr after HTLV-1 infection, compared with 40-60 yr for ATL. HAM occurs in up to 4% of persons with HTLV-1 infection, usually developing during middle age. It is characterized by infiltration of mononuclear cells into the gray and white matter of the thoracic spinal cord, leading to severe white matter degeneration and fibrosis. HTLV-1 is found near but not directly within the lesions, suggesting that reactive inflammation is a major mechanism of disease. The cerebrospinal fluid typically shows a mildly elevated protein and a modest monocytic pleocytosis, along with anti–HTLV-1 antibodies. Neuroimaging studies are normal or show periventricular lesions in the white matter. Clinical manifestations include a gradual onset of slowly progressive, symmetric neurologic degeneration of the corticospinal tracts and, to a lesser extent, the sensory system that leads to lower-extremity spasticity or weakness, lower back pain, and hyperreflexia of the lower extremities with an extensor plantar response. The bladder and intestines may become dysfunctional, and men may become impotent. Some patients develop dysesthesias of the lower extremities with diminished sensation to vibration and pain. Upper-extremity function and sensation, cranial nerves, and cognitive function are usually preserved. Treatment regimens have been attempted with corticosteroids, danazol, interferon, plasmapheresis, high-dose vitamin C, and antivirals, all with minimal effects.

Human T-Cell Lymphotropic Virus-2

HTLV-2 was originally identified in patients with hairy cell leukemia, although most patients with hairy cell leukemia are seronegative for HTLV-2 infection. HTLV-2 has been rarely isolated from patients with leukemias or with myelopathies resembling HAM, and there is limited evidence of disease specifically associated with HTLV-2 infection.

Prevention

Routine antibody testing of all blood products for HTLV-1 and -2 is performed in many developed countries and is effective in preventing blood transfusion–associated infections. Unfortunately, this routine testing is not always available in low and middle-income countries with higher endemicity. Prenatal screening and avoidance of breastfeeding by HTLV-1–infected mothers is an effective means of reducing mother-to-child transmission of HTLV-1. Safe sexual practices to avoid sexually transmitted infections, such as condom use and avoiding multiple sexual partners, may reduce transmission of both HTLV-I and HTLV-2. No vaccine is available.

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CHAPTER 304

Transmissible Spongiform Encephalopathies

David M. Asher

The transmissible spongiform encephalopathies (TSEs, prion diseases) are slow infections of the human nervous system, consisting of at least four diseases of humans (Table 304.1): kuru; Creutzfeldt-Jakob disease (CJD) with its variants—sporadic CJD (sCJD), familial CJD (fCJD), iatrogenic CJD (iCJD), and new-variant or variant CJD (vCJD); Gerstmann-Sträussler-Scheinker syndrome (GSS); and fatal familial insomnia (FFI), or the even more rare sporadic fatal insomnia syndrome. TSEs also affect animals; the most common and best-known TSEs of animals are scrapie in sheep, bovine spongiform encephalopathy (BSE or mad cow disease) in cattle, and a chronic wasting disease (CWD) of deer, elk, and moose found in parts of the United States, Canada, Norway, and Finland. All TSEs have similar clinical and histopathologic manifestations, and all are slow infections with very long asymptomatic incubation periods (often years), durations of several months or more, and overt disease affecting only the nervous system. TSEs are relentlessly progressive after illness begins and are invariably fatal. The most striking neuropathologic change that occurs in each TSE, to a greater or lesser extent, is spongy degeneration of the cerebral cortical gray matter.

Table 304.1

Clinical and Epidemiologic Features of Human Transmissible Spongiform Encephalopathies (Prion Diseases)

	CLINICAL	SOURCE OF	GEOGRAPHIC	USEFUL	DURATION

DISEASE	FEATURES	INFECTION	DISTRIBUTION AND PREVALENCE	ANCILLARY TESTS	OF ILLNESS
sCJD	Dementia, myoclonus, ataxia	Unknown	Worldwide; ≈1/1 million/yr; 85–95% of all CJD cases in United States	EEG—PSWCs; CSF 14-3-3; MRI/DWI	1-24 mo (mean: 4-6 mo)
fCJD	Dementia, myoclonus, ataxia	Genetic association (*PRNP* mutations) ?? Possible exogenous source of infection	Worldwide—geographic clusters; >100 known families; 5–15% of CJD cases	Gene testing; EEG—PSWC rare; MRI/DWI (?)	Mean ≈15 mo
iCJD	Incoordination, dementia (late)	Cadaver dural grafts, human pituitary hormones, corneal transplantation, neurosurgical instruments, EEG depth electrodes	≈1% of CJD cases in toto (cadaver dural grafts), > 100 cases (human pituitary hormones), > 100 cases; corneal transplantation, 3 cases; neurosurgical instruments, 6 cases, including 2 from cortical depth electrodes; RBC transfusions, 4 cases of vCJD infection, 3 clinical, 1 preclinical (United Kingdom); human plasma–derived factor VIII, 1 preclinical case of vCJD (United Kingdom)		1 mo-10 yr
vCJD	Mood and behavioral abnormalities, paresthesias, dementia	Linked to BSE in cattle, transfusion plasma products	>230 clinical cases (see iatrogenic vCJD, above): none living, May 2017	Tonsil biopsy may show PrP^{TSE} MRI/FLAIR	8-36 mo (mean 14 mo)
Kuru	Incoordination, ataxia, tremors, dementia (late)	Linked to cannibalism	Fore people of Papua New Guinea (≈2,600 known cases)	EEG—no PSWCs; CSF 14-3-3 often negative; MRI (?)	3-24 mo
GSS	Incoordination, chronic progressive ataxia, corticospinal tract signs, dementia (late), myoclonus (rare)	90% genetic (*PRNP* mutations)	Worldwide; >50 families; ≈1-10/100 million/yr	*PRNP* gene sequencing	2-12 yr (mean ≈ 57 mo)
FFI	Disrupted sleep, intractable insomnia; autonomic hyperactivation; myoclonus, ataxia; corticospinal tract signs; dementia	*PRNP* gene mutation (D 178L); very rare sporadic cases	≈27 families in Europe, United Kingdom, United States, Finland, Australia, China, Japan	EEG—PSWCs only rarely positive; MRI—no DWI abnormalities; CSF 14-3-3 positive in ≈ 50%	8 mo to 6 yr (mean: *PRNP* 129 MM 12 ± 4 mo 129 MV 21 ± 15 mo)

BSE, bovine spongiform encephalopathy; CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; DWI, diffusion-weighted image; EEG, electroencephalography; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FLAIR, fluid attenuation inversion recovery MRI; GSS, Gerstmann-Sträussler-Scheinker syndrome; iCJD, iatrogenic Creutzfeldt-Jakob disease; *PRNP* , prion protein encoding gene; PrP^{TSE} , abnormal prion protein; PSWCs, periodic sharp wave complexes; RBC, red blood cell; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease.

NOTE: PRNP 129 MM, homozygous, encoding the amino acid methionine at both codons 129 of the prion-protein-encoding (PRNP) gene on chromosome 20; 129 MV, heterozygous at PRNP codon 129, encoding methionine on one chromosome 20 and valine on the other.

Modified from Mandell GL, Bennett JE, Dolin R (eds): Principles and practice of infectious diseases, 6e, Philadelphia, 2005, Elsevier, p. 2222; and Love S, Louis DN, Ellison DW (eds): Greenfield's neuropathology, 8e, London, 2008, Hodder Arnold, p. 1239.

Etiology

The TSEs are transmissible to susceptible animals by inoculation of tissues from affected subjects. Although the infectious agents replicate in some cell cultures, they do not achieve the high titers of infectivity found in brain tissues or cause recognizable cytopathic effects in cultures. Most previous studies of TSE agents have used in vivo assays, relying on the transmission of typical neurologic disease to animals as evidence that the agent was present and intact. Inoculation of susceptible recipient animals with small amounts of the infectious TSE agent results, months later, in the accumulation in tissues of large amounts of the agent with the same physical and biologic properties as the original agent. The TSE agents display a spectrum of extreme resistance to inactivation by a variety of chemical and physical treatments that is unknown among conventional pathogens. This characteristic, as well as their partial sensitivity to protein-disrupting treatments and their consistent association with abnormal isoforms of a normal host-encoded protein (prion protein or PrP), stimulated the hypothesis that the TSE agents are probably subviral in size, composed of protein, and devoid of nucleic acid.

The term **prion** (for proteinaceous infectious agent), coined by S.B. Prusiner, is now widely used for such agents. The prion hypothesis proposes that the molecular mechanism by which the pathogen-specific information of TSE agents is propagated involves a self-replicating change in the folding host-encoded PrP associated with a transition from an α-helix–rich structure in the native protease-sensitive conformation (cellular PrP or PrP^{C}) to a β-sheet–rich structure in the protease-resistant conformation associated with infectivity. The existence of a second host-encoded protein—termed protein X—that participates in the transformation was also postulated to explain certain otherwise puzzling findings but has never been identified.

The prion hypothesis is still not universally accepted; it relies on the postulated existence of a genome-like coding mechanism based on differences in protein folding that have not been satisfactorily explained at a molecular level. In addition, it has yet to account convincingly for the many biologic strains of TSE agent that have been observed, although strain-specific differences in the abnormal forms of the PrP have been found and proposed as providing a plausible molecular basis for the coding. It fails to explain why pure PrP uncontaminated with nucleic acid from an infected host has not transmitted a convincingly typical spongiform encephalopathy consistently associated with a serially self-propagating agent. A finding that was also troubling, in several experimental models and human illnesses, was that abnormal PrP and infectivity were not consistently associated. Particularly problematic is the finding that some illnesses associated with mutations in the *PRNP* gene and accompanied by abnormal PrP failed to transmit infection to animals. If the TSE agents ultimately prove to consist of protein and only protein, without any obligatory nucleic acid component, then the term *prion* will indeed be appropriate and the early proponents of the prion hypothesis will prove to have been prescient. If the agents are ultimately found to contain small nucleic acid genomes, then they might better be considered atypical viruses, for which the term *virino* has been suggested. Until the actual molecular structure of the infectious TSE pathogens and the presence or absence of a nucleic acid genome are rigorously established, it seems less contentious to continue calling them TSE agents, although most authorities have accepted the term *prion* (sometimes referring to the agent of a TSE and sometimes to the abnormal protein, even when nontransmissible).

The earliest evidence that abnormal proteins are associated with the TSE was morphologic: Scrapie-associated fibrils were found in extracts of tissues from patients and animals with spongiform encephalopathies but not in normal tissues. Scrapie-associated fibrils resemble but are distinguishable from the amyloid fibrils that accumulate in the brains of patients with Alzheimer disease. A group of antigenically related protease-resistant proteins (PrPs) proved to be components of scrapie-associated fibrils and to be present in the amyloid plaques found in the brains of patients and animals with TSEs. The abnormal forms of PrP are variously designated $\mathrm{PrP}^{\mathrm{Sc}}$ (scrapie-type PrP), PrP-res (protease-resistant PrP), $\mathrm{PrP}^{\mathrm{TSE}}$ (TSE-associated PrP), or $\mathrm{PrP}^{\mathrm{D}}$ (disease-associated PrP) by different authorities.

It remains unclear whether abnormal PrP constitutes the complete infectious particle of spongiform encephalopathies, is a component of those particles, or is a pathologic host protein not usually separated from the actual infectious entity by currently used techniques. The demonstration that PrP is encoded by a normal host gene seemed to favor the last possibility. Several studies suggest that agent-specific pathogenic information can be transmitted and replicated by different conformations of a protein with the same primary amino acid sequence in the absence of agent-specific nucleic acids. Properties of two fungal proteins were found to be heritable without encoding in nucleic acid, although those properties have not been naturally transmitted to recipient fungi as infectious elements. Whatever its relationship to the actual infectious TSE particles, PrP clearly plays a central role in the susceptibility to infection, because the normal PrP must be expressed in mice and cattle if they are to acquire a TSE or to sustain replication of the infectious agents. Furthermore, inherited normal variations in the PrP phenotype are associated with increased susceptibility to vCJD and (to a lesser extent) to sCJD and with occurrence of familial TSEs (fCJD and GSS).

PrPs are glycoproteins; protease-resistant PrPs, when aggregated, have the physical properties of amyloid proteins. The PrPs of different species of animals are very similar in their amino acid sequences and antigenicity but are not identical in structure. The primary structure of PrP is encoded by the host and is not altered by the source of the infectious agent provoking its formation. The function of the ubiquitous protease-sensitive PrP precursor (designated PrP^{C} , for cellular PrP, or PrP-sen, for protease-sensitive PrP) in normal cells is unknown; it binds copper and may play some role in normal synaptic transmission, but it is not required for life or for relatively normal cerebral function in mice and cattle. As noted, animals must express PrP to develop scrapie disease and to support replication of the TSE agents. The degree of homology between amino acid sequences of PrPs in different animal species may correlate with the species barrier that affects the susceptibility of animals of one species to infection with a TSE agent adapted to grow in another species, although the degree of sequence homology does not always predict susceptibility to the same TSE agent.

Attempts to find particles resembling those of viruses or virus-like agents in brain tissues of humans or animals with spongiform encephalopathies have been unsuccessful. Peculiar tubulovesicular structures reminiscent of some viruses have been seen repeatedly in thin sections of TSE-infected brain tissues and cultured cells but not in normal cells. It has never been established that those structures are associated with infectivity.

Epidemiology

Kuru once affected many children of both sexes ≥ 4 yr of age, adolescents, and young adults (mainly females) living in one limited area of Papua New Guinea. The complete disappearance of kuru among people born after 1957 suggests that the practice of ritual cannibalism (thought to have ended that year) was probably the only mechanism by which the infection spread in Papua New Guinea.

CJD, the most common human spongiform encephalopathy, was formerly thought to occur only in older adults; however, iCJD and, much more rarely, sCJD (to date, seven reports in adolescents, one a 14 yr old female) have affected young people. A single case of sporadic fatal insomnia was recognized in a U.S. adolescent. GSS has not been diagnosed in children or adolescents. vCJD has a peculiar predilection for younger people. Of 174 cases of vCJD reported through 2010 in the United Kingdom, all except 23 were in people younger than 40 yr of age and 22 were in people younger than 20 yr of age; the youngest age at onset was 12 yr. sCJD has been recognized worldwide, at yearly rates of 0.25-2 cases/million population (not age-adjusted), with CJD foci of considerably higher incidence among Libyan Jews in Israel, in isolated villages of Slovakia, and in other limited areas. Sporadic CJD has not been convincingly linked to any common exposure, and the source of infection remains unknown. Proponents of the prion hypothesis are convinced that PrP can spontaneously misfold, becoming self-replicating and causing sCJD; skeptics favor infection with some ubiquitous TSE agent, which, fortunately, has a very low attack rate except in persons with certain mutations in the *PRNP* gene. Neither of those possible etiologies has been proven. Person-to-person spread has been confirmed only for iatrogenic cases. Spouses and household contacts of patients are not at risk of acquiring CJD, although two instances of conjugal CJD have been reported. However, medical personnel exposed to brains of patients with CJD may be at some increased risk; at least 20 healthcare workers have been recognized with the disease.

The striking resemblance of CJD to scrapie prompted a concern that infected sheep tissues might be a source of spongiform encephalopathy in humans. No reliable epidemiologic evidence suggests that exposure to potentially scrapie-contaminated animals, meat, meat products, or experimental preparations of the scrapie agent have transmitted a TSE to humans. The potential of the CWD agent to infect human beings has also not been demonstrated but remains under investigation; deer, elk, and moose in 15 U.S. states and 2 Canadian provinces have been naturally infected; cases of CWD were recently detected in wild reindeer and moose (European elk) in Norway and Finland. Consumption of contaminated meat, including venison from animals infected with the CWD agent, has not been implicated as a risk factor for human TSE by epidemiologic studies; however, a recent unpublished study requiring several years yielded evidence that CWD was experimentally transmitted to monkeys fed venison from overtly healthy infected deer, prompting a health advisory from Canadian authorities. The outbreak of BSE among cattle (possibly infected by eating scrapie-agent–contaminated meat-and-bone meal added to feed) was first recognized in the United Kingdom in 1986 and later reported in cattle of 27 other countries, including Canada and the United States. More than 190,000 cases of BSE have been reported to the World Organization for Animal Health (OIE), almost 97% of those from the United Kingdom. Cases in the United Kingdom progressively declined after 1992 and later in other countries; in 2016 only 2 cases worldwide were reported to OIE (from France and Spain) and none from the United Kingdom. The finding of a new TSE in ungulate and feline animals in British zoos and later in domestic cats raised a fear that the BSE agent had acquired a range of susceptible hosts broader than that of scrapie, posing a potential danger for humans. That remains the most plausible explanation for the occurrence of vCJD, first described in adolescents in Britain in 1996 and, as of May 2017, eventually affecting at least 178 people in the United Kingdom. (not counting a disturbing number of people with evidence of possible asymptomatic or “preclinical” vCJD infection) and more than 50 in 11 other countries (total 231 cases worldwide): 27 in France, 5 in Spain, 4 in Ireland, 3 in the Netherlands, 2 each in Italy and Portugal, and single cases in Japan and Saudi Arabia. Variant CJD has also occurred in former U.K. residents (>6 mo) living in Ireland (two cases), France (one case), Canada (one case), Taiwan (one case), and the United States (two cases). Two cases of vCJD—one in the United States and one in Canada—have been reported in former long-time residents of Saudi Arabia, a country that has not recognized BSE but might have imported contaminated meat products from the United Kingdom. A third case of vCJD was previously confirmed in a Saudi citizen residing in Saudi Arabia. The most recent case of vCJD diagnosed in the United States occurred in an immigrant deemed by the CDC to have most likely been infected during early years spent in Kuwait.

No case of vCJD has been confirmed in anyone born in the United Kingdom after 1989. However, examination of resected appendixes in the United Kingdom for evidence of subclinical infection with prions suggested that about 1 in 2,000 people tested had a detectable accumulation of PrP^{TSE} in lymphoid follicles. It remains controversial whether those accumulations resulted from subclinical vCJD or another TSE; none of the subjects to date has presented to medical attention with overt TSE.

Iatrogenic transmissions of CJD have been recognized for more than 30 yr (Table 304.2). Such accidental transmissions of CJD have been attributed to use of contaminated neurosurgical instruments (no case reported since 1980) or operating facilities, use of cortical electrodes contaminated during epilepsy surgery, injections of human cadaveric pituitary growth hormone and gonadotropin (no longer marketed in the United States), and transplantation of contaminated corneas and allografts of human dura mater, still in limited use in the United States as a surgical patching material. Pharmaceuticals and tissue grafts derived from or contaminated with human neural tissues, particularly if obtained from unselected donors and large pools of donors, pose special risks.

Table 304.2

Iatrogenic Transmission of Creutzfeldt-Jakob Disease by Products of Human Origin

PRODUCT	**NO. OF PATIENTS**	**INCUBATION TIME**	
		Mean	**Range**
Cornea	3	17 mo	16-18 mo
Dura mater allograft	>100	7.4 yr	1.3-16 yr
Pituitary extract			
Growth hormone	>100*	12 yr	5-38.5 yr
Gonadotropin	4	13 yr	12-16 yr
Red blood cells	4	? 6 yr	6.3-8.5 yr †
Plasma-derived coagulation factor VIII	1	? > 11 yr ‡	

[*] There have been 28 cases reported among approximately 8,000 recipients of human cadaveric growth hormone in the United States; the remaining cases have been reported in other countries.

[†] The second transfusion-transmitted case of vCJD (Peden AH, Head MW, Ritchie DL, et al: Preclinical vCJD after blood transfusion in a *PRNP* codon 129 heterozygous patient, *Lancet* 364:527-529, 2004) died of unrelated causes about 5 yr after transfusion but was found to have accumulations of abnormal PrP in the spleen and cervical lymph node—a finding unique to vCJD and interpreted as probable preclinical infection.

[‡] The diagnosis of vCJD infection attributed to treatment with human plasma–derived coagulation

factor VIII (UK Health Protection Agency: vCJD abnormal prion protein found in a patient with haemophilia at post mortem, Press release 17 February 2009, http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webw/HPAweb& p=1231252394302) was also supported by immunohistochemical testing for abnormal PrP in the spleen of a person who died of other causes. Both patients with “preclinical” infections are thought to have died during the asymptomatic incubation period of vCJD.

Studies of animals experimentally infected with TSE agents first suggested that blood and blood components from humans with preclinical CJD infections might pose a risk of transmitting disease to recipients, and since the 1980s such blood components have been withdrawn as a precaution in the United States when a donor was later found to have CJD and blood products were still in-date. A surveillance program in the United Kingdom reported vCJD in three recipients of nonleukoreduced red blood cells from donors later diagnosed with vCJD; there was autopsy evidence of a preclinical vCJD infection in a fourth red cell recipient who died of another disease. (vCJD has not occurred in any recipient of leukoreduced red blood cells from a donor who later developed vCJD.) A study conducted over more than 20 yr by the American Red Cross and CDC found no recipient of blood components obtained from donors later diagnosed with sporadic CJD (and from one donor with familial CJD) developed a TSE.

Evidence of a preclinical vCJD infection was found at autopsy in a U.K. patient with hemophilia A treated with a human plasma–derived coagulation factor VIII to which at least one vCJD-infected donor contributed; the coagulation factor involved was never licensed in the United States. U.K. authorities have described two recipients of plasma-derived coagulation factors (both having a history of a transfusion with blood components, as well) who later developed sporadic CJD, concluding that the finding, while of concern, might be coincidental.

Pathogenesis and Pathology

The probable portal of entry for the TSE agent in kuru is thought to have been either through the gastrointestinal tract or lesions in the mouth or integument incidentally exposed to the agent during cannibalism. Patients with vCJD (and animals with BSE and BSE-related TSEs) are thought to have been similarly infected with the BSE agent by consuming contaminated beef products. Except after direct introduction into the nervous system, the first site of replication of TSE agents appears to be in tissues of the reticuloendothelial system. TSE agents have been detected in low titers in the blood of experimentally infected animals (mice, monkeys, hamsters, and sheep and in the blood of persons with vCJD and perhaps sCJD); infectivity was mainly associated with nucleated cells, although the plasma contained a substantial portion of total infectivity in blood. Circulating lymphoid cells seem to be required to infect mice by peripheral routes. Limited evidence suggests that TSE agents also spread to the central nervous system by ascending peripheral nerves. Several research groups claimed to detect the CJD agent in human blood, although other attempts failed.

In human kuru, it seems probable that the only portal of exit of the agent from the body, at least in quantities sufficient to infect others, was through infected tissues exposed during cannibalism. In iatrogenically transmitted CJD, the brains and eyes of patients with CJD have been the probable sources of contamination. Experimental transmission of the agent to animals from the kidney, liver, lung, lymph node, and spleen showed that those tissues as well as the cerebrospinal fluid (CSF) sometimes contain the CJD agent; none of those sources has been implicated in accidental transmission of CJD to humans. At no time during the course of any TSE have antibodies or cell-mediated immunity to the infectious agents been convincingly demonstrated in either patients or animals. However, mice must be immunologically competent to be infected with the scrapie agent by peripheral routes of inoculation.

Typical changes in TSE include vacuolation and loss of neurons with hypertrophy and proliferation of glial cells, most pronounced in the cerebral cortex in patients with CJD and in the cerebellum in those with kuru. The central nervous system lesions are usually most severe in or even confined to gray matter, at least early in the disease. Loss of myelin appears to be secondary to the degeneration of neurons. There generally is no inflammation, but a marked increase in the number and size of astrocytes is usual. Spongiform changes are not a striking autopsy finding in patients with FFI, and neuronal degeneration and gliosis are largely restricted to thalamic nuclei.

Amyloid plaques are found in the brains of all patients with GSS and in at least 70% of those with kuru. These plaques are less common in patients with CJD. Amyloid plaques are most common in the cerebellum but occur elsewhere in the brain, as well. In brains of patients with vCJD, plaques surrounded by halos of vacuoles (described as flower-like or florid plaques) have been a consistent finding. TSE amyloid plaques react with antiserum prepared against PrP. Even in the absence of plaques, extracellular PrP can be detected in the brain parenchyma by immunostaining.

Clinical Manifestations

Kuru, no longer seen, is a progressive degenerative disease of the cerebellum and brainstem with less obvious involvement of the cerebral cortex. The first sign of kuru was usually cerebellar ataxia followed by progressive incoordination. Coarse, shivering tremors were characteristic. Variable abnormalities in cranial nerve function appeared, frequently with impairment in conjugate gaze and swallowing. Patients died of inanition and pneumonia or of burns from cooking fires, usually within 1 yr after onset. Although changes in mentation were common, there was no frank dementia or progression to coma, as in CJD. There were no signs of acute encephalitis, such as fever, headaches, and convulsions.

CJD occurs throughout the world. Patients initially have either sensory disturbances (most often visual) or confusion and inappropriate behavior, progressing over weeks or months to frank dementia, akinetic mutism, and, ultimately, coma. Some patients have cerebellar ataxia early in the disease, and most patients experience myoclonic jerking movements. The mean survival time of patients with sCJD has been < 1 yr from the earliest signs of illness, although approximately 10% live for 2 yr. Variant CJD (Table 304.3) differs from the more common sCJD; patients with vCJD are much younger at onset (as young as 12 yr) and more often present with complaints of dysesthesia and subtle behavioral changes, often mistaken for psychiatric illness. Severe mental deterioration occurs later in the course of vCJD. Patients with vCJD have survived substantially longer than those with sCJD. Attempts have been made to subclassify cases of CJD based on the electrophoretic differences in PrP^{TSE} and variation in its sensitivity to digestion with the proteolytic enzyme proteinase (PK); the different variants are said to have somewhat different clinical features, including the duration of illness, though all are ultimately fatal.

Table 304.3

Clinical and Histopathologic Features of Patients With Variant and Typical Sporadic Creutzfeldt-Jakob Disease

FEATURE	VARIANT CJD (FIRST 10 PATIENTS)	SPORADIC CJD (185 PATIENTS)
Years of age at death* (range)	29 (19-74)	65
Duration of illness, mo	12 (8-23)	4

(range)		
Presenting signs	Abnormal behavior, dysesthesia	Dementia
Later signs	Dementia, ataxia, myoclonus	Ataxia, myoclonus
Periodic complexes on EEG	Rare	Most
PRNP 129 Met/Met	All tested (except one transfusion-transmitted case, one plasma-derivative transmitted case; one possible clinical case in United Kingdom where no tissue was available to confirm)	83%
Histopathologic changes	Vacuolation, neuronal loss, astrocytosis, plaques (100%)	Vacuolation, neuronal loss, astrocytosis, plaques (≤15%)
Florid PrP plaques [†]	100%	0
PrP^{TSE} glycosylation pattern	BSE-like [‡]	Not BSE-like

[*] Median age and duration for variant CJD; averages for typical sporadic CJD.

[†] Dense plaques with a pale periphery of surrounding vacuolated cells.

[‡] Characterized by an excess of high-molecular-mass band (diglycosylated) and 19-kDa nonglycosylated band glycoform of PrP-res (Collinge J, Sidle KC, Meads J, et al: Molecular analysis of prion strain variation and the aetiology of “new variant” CJD, *Nature* 383:685-690, 1996).

BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; EEG, electroencephalogram; Met, codon 129 of one *PRNP* gene encoding for methionine; *PRNP* , prion protein–encoding gene; PrP, prion protein.

Modified from Will RG, Ironside JW, Zeidler M, et al: A new variant of Creutzfeldt-Jakob disease in the UK, Lancet 347:921-925, 1996.

GSS is a familial disease resembling CJD but with more prominent cerebellar ataxia and amyloid plaques. Dementia may appear only late in the course, and the average duration of illness is longer than typical sCJD. Progressively severe insomnia and dysautonomia, as well as ataxia, myoclonus, and other signs resembling those of CJD and GSS, characterize FFI and sporadic fatal insomnia. A case of sporadic **fatal insomnia** has been described in a young adolescent. GSS has not been diagnosed in children or adolescents.

A novel prion disease has been reported that is expressed in several generations with an autosomal dominant pattern associated with a unique mutation in the *PRNP* gene. The affected persons were middle-aged with a history of chronic diarrhea for years plus autonomic neuropathy and modest mental impairment but without full-blown dementia; PK-resistant PrP deposits with amyloid properties occurred in the brain, lymphoid tissues, kidney, spleen, and intestinal tract. The disease was not successfully transmitted to three lines of mice susceptible to several TSEs. It is not clear that such a syndrome—not a spongiform encephalopathy and apparently not associated with an infectious agent—should be lumped together with TSEs. It might well result from the abnormal *PRNP* gene product itself; if so, it would not pose the same potential threat to public health as do the TSEs.

Diagnosis

The diagnosis of spongiform encephalopathies is most often determined on clinical grounds after excluding other diseases. The presence of 14-3-3 protein (see Laboratory Findings) in CSF may aid in distinguishing between CJD and Alzheimer disease—not a consideration in children. Elevations of 14-3-3 protein levels in the CSF are not specific to TSEs and are common in viral encephalitis and other conditions causing rapid necrosis of brain tissue. Brain biopsy may be diagnostic of CJD, but it can be recommended only if a potentially treatable disease remains to be excluded or if there is some other compelling reason to make an antemortem diagnosis. The definitive diagnosis usually requires the microscopic examination of brain tissue obtained at autopsy. The demonstration of protease-resistant PrP in brain extracts augments the histopathologic diagnosis. Accumulation of the abnormal PrP in lymphoid tissues, even before the onset of neurologic signs, is typical of vCJD. Tonsil biopsy may avoid the need for brain biopsy when antemortem diagnosis of vCJD is indicated. To date, no blood-based test has been validated for antemortem testing of either humans or animals. Transmission of disease to susceptible animals by inoculation of brain suspension, while sensitive, specific, and reliable, must be reserved for cases of special research interest.

Laboratory Findings

Virtually all patients with typical sporadic, iatrogenic, and familial forms of CJD have abnormal electroencephalograms (EEGs) as the disease progresses; the background becomes slow and irregular with diminished amplitude. A variety of paroxysmal discharges such as slow waves, sharp waves, and spike-and-wave complexes may also appear, and these may be unilateral or focal or bilaterally synchronous. Paroxysmal discharges may be precipitated by a loud noise. Many patients have typical periodic suppression-burst complexes of high-voltage slow activity on EEG at some time during the illness. Patients with vCJD have had only generalized slowing, without periodic bursts of high-voltage discharges on EEG. The CT or MRI may show cortical atrophy and large ventricles late in the course of CJD. Many patients with vCJD have an increase in density of the pulvinar on MRI. Reliable interpretation of the images is best left to experienced radiologists.

There may be a modest elevation of CSF protein content in patients with TSE. Unusual protein spots were observed in CSF specimens after two-dimensional separation in gels and silver staining; the spots were identified as 14-3-3 proteins, normal proteins (not related to PrP) abundant in neurons but not ordinarily detected in CSF. However, 14-3-3 protein has also been detected in CSF specimens from some patients with acute viral encephalitides and recent cerebral infarctions and is not specific to CJD. Finding the 14-3-3 protein in CSF is neither sensitive nor specific but has been of some help in confirming the diagnosis of vCJD, especially when accompanied by increases in other cellular proteins. The diagnosis usually rests on recognizing the typical constellation of clinical findings, clinical course, and testing (CSF examination, CT or MRI, EEG), confirmed by histopathology and detection of PrP^{TSE} in brain tissues at autopsy (or, less often, by tonsil or brain biopsy). Research techniques that amplify PrP^{TSE} in CSF, nasal brushings, and blood may eventually improve antemortem diagnosis but remain inadequately validated for routine use.

Treatment

No treatment has proven effective. Studies of cell cultures and rodents experimentally infected with TSE agents suggested that treatment with chlorpromazine, quinacrine, and tetracyclines might be of benefit, especially during the incubation period. Results of clinical trials based on those studies have been discouraging, and it seems unlikely that the severe brain damage found in late disease can be reversed by treatment. Infusions with pentosan polysulfate directly into the cerebral ventricles appear to have delayed the progression of vCJD in a least one patient but did not reverse earlier brain damage. Appropriate supportive care should be provided to all CJD patients as for other progressive fatal neurologic diseases. On the basis of experimental studies in animals, several prophylactic postexposure treatment regimens have been suggested, but none has been widely accepted.

Genetic Counseling

TSEs sometimes occur in families in a pattern consistent with an autosomal dominant mode of inheritance. In patients with a family history of CJD, the clinical and histopathologic findings are similar to those seen in sporadic cases. In the United States, only approximately 10% of cases of CJD are familial. GSS and FFI are always familial. In some affected families, approximately 50% of siblings and children of a patient with a familial TSE eventually acquire the disease; in other families, the penetrance of illness may be less.

The gene coding for PrP is closely linked if not identical to that controlling the incubation periods of scrapie in sheep and both scrapie and CJD in mice. The gene encoding PrP in humans is designated the *PRNP* gene and is located on the short arm of chromosome 20. It has an open reading frame of 759 nucleotides (253 codons), in which more than 20 different point mutations and a variety of inserted sequences encoding extra tandem-repeated octapeptides are linked to the occurrence of spongiform encephalopathy in families with a pattern consistent with autosomal dominance of variable penetrance.

The same nucleotide substitution at codon 178 of the *PRNP* gene associated with CJD in some families has been found in all patients with FFI. Homozygosity for valine (V) and especially for methionine (M) at codon 129 seems to increase the susceptibility to iCJD and sCJD. Almost all patients with vCJD to be genotyped have been homozygous for methionine at codon 129 of the *PRNP* gene. A few probable preclinical vCJD infections and two clinically typical cases of vCJD (one confirmed and another not completely evaluated) occurred in persons with the 129 MV heterozygous genotype. It is of interest that when the *PRNP* genes from appendices containing accumulations of what appears to be $\mathrm{PrP}^{\mathrm{TSE}}$ in the UK were sequenced, a surprising number were homozygous for V—the genotype of only approximately 10% of U.K. subjects and never found in a case of vCJD. The significance of this finding is not clear. U.K. authorities have adopted the precautionary assumption that some persons with $\mathrm{PrP}^{\mathrm{TSE}}$ in lymphoid tissues may have latent infections. Whether the blood of such persons is infectious remains unknown.

Although the interpretation of these findings in regard to the prion hypothesis is in dispute, persons from families with CJD or GSS who have the associated mutations in the *PRNP* gene clearly have a high probability of eventually acquiring spongiform encephalopathy. Bearers of TSE-associated mutations have employed a preimplantation genetic diagnosis and in vitro selection of embryos to avoid passing the mutant gene to offspring. The significance of mutations in the *PRNP* genes of individuals from families with no history of spongiform encephalopathy is not known. It seems wise to avoid alarming those from unaffected families who have miscellaneous mutations in the *PRNP* gene, because the implications are not yet clear. In the United States, persons are deferred from donating blood if a blood relative has been diagnosed with a TSE unless the donor does not have a TSE-related mutation.

Prognosis

The prognosis of all spongiform encephalopathies is uniformly poor. Approximately 10% of patients may survive for longer than 1 yr, but the quality of life is poor.

Family Support

The CJD Foundation (http://www.cjdfoundation.org), organized and maintained by family members and friends of patients with CJD and related disorders, working closely with the Centers for Disease Control and Prevention (www.cdc.gov/prions/index.html) and with the National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland (http://www.cjdsurveillance.com), is a support and educational group and a useful source of information regarding available resources for those dealing with the diseases.

Prevention

Exposure to the BSE agent in meat products clearly poses a special danger—now greatly reduced. Authorities in Canada, the United States, and other countries responded by implementing progressively more stringent agricultural and public health measures during the past 20 yr, with elimination of most bovine-derived materials from animal feeds probably the most effective measure. Three cases of BSE in native cattle were recognized in the United States from 2004 through 2012; a case was also found in a Canadian cow imported into the United States in 2003. Canada found 20 native cattle with BSE between 2003 and 2015 (and imported a case from the United Kingdom in

1993). In spite of encouraging epidemiologic studies that failed to implicate exposure to scrapie or CWD agents in human TSEs, it seems prudent to avoid exposing children to meat and other products likely to be contaminated with any TSE agent.

The safety of human blood, blood components, and plasma derivatives in the United States and Canada is protected by deferring those donors with histories suggesting an increased risk of TSEs: persons treated with cadaveric pituitary hormones (no longer used) or dura mater allografts, patients with a family history of CJD (unless sequencing shows that the TSE-affected blood relative or the donor has revealed no TSE-related mutation in either *PRNP* gene), and persons who spent substantial periods of time in specified countries during years when BSE was prevalent. Persons transfused with blood in the United Kingdom and France after 1980 should be deferred from donating blood (similar deferral policies are in place for donors of human cells and tissues). U.K. authorities have warned persons treated with U.K.-sourced pooled coagulation factor concentrates or antithrombin between 1989 and 2001 that they may be “at risk of vCJD for public health purposes” and that “special infection control precautions” apply to them.

In principle, it would be better to identify the few blood and tissue donors actually infected with a TSE rather than deferring all those at increased risk of exposure, because most of them are unlikely to have been infected. Antemortem screening tests that might eventually identify donors with preclinical TSE infections are currently under development though not clinically validated. It is unlikely that any test will be adopted to screen blood donors without simultaneously implementing a highly specific validated confirmatory test to avoid the serious adverse implications of inevitable false-positive screening results.

Standard precautions should be used to handle all human tissues, blood, and body fluids. Materials and surfaces contaminated with tissues or fluids from patients suspected of having CJD must be treated with great care. Whenever possible, discard contaminated instruments by careful packaging and incineration. Contaminated tissues and biologic products probably cannot be completely freed of infectivity without destroying their structural integrity and biologic activity; therefore, the medical and family histories of individual tissue donors should be carefully reviewed to exclude a diagnosis of TSE. Histopathologic examination of brain tissues of cadaveric donors and testing for abnormal PrP might be performed where feasible to provide an additional assurance of safety. Although no method of sterilization can be relied on to remove all infectivity from contaminated surfaces, exposures to moist heat, sodium hydroxide, chlorine bleach, concentrated formic acid, acidified detergent, and guanidine salts markedly reduced infectivity in experimental studies.

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SECTION 14

Antiparasitic Therapy

OUTLINE

Chapter 305 Principles of Antiparasitic Therapy

CHAPTER 305

Principles of Antiparasitic Therapy

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Parasites are divided into three main groups taxonomically: **protozoans,** which are unicellular, and **helminths** and **ectoparasites,** which are multicellular. Chemotherapeutic agents appropriate for one group may not be appropriate for the others, and not all drugs are readily available (Table 305.1). Some drugs are not available in the United States, and some are available only from the manufacturer, specialized compounding pharmacies, or the Centers for Disease Control and Prevention (CDC). Information on the availability of drugs and expert guidance in management can be obtained by contacting the CDC Parasitic Diseases Branch (1-404-718-4745; e-mail parasites@cdc.gov (M-F, 8 AM -4 PM , Eastern time). For assistance in the management of malaria, healthcare providers should call the CDC Malaria Hotline: 1-770-488-7788 or 1-855-856-4713 toll-free (M-F, 9 AM -5 PM , Eastern time). For all emergency consultations after hours, clinicians can contact the CDC Emergency Operations Center at 1-770-488-7100 and request to speak with a CDC Malaria Branch clinician or on-call parasitic diseases physician. Some antiparasitic drugs are not licensed for use in the United States but can be obtained as investigational new drugs (INDs) from the CDC; providers should call the CDC Drug Service, Division of Scientific Resources and Division of Global Migration and Quarantine, at 1-404-639-3670.

Table 305.1

Drugs for Parasitic Infections

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of HIV, physicians anywhere may see infections caused by previously unfamiliar parasites. The table below lists first-choice and alternative drugs for most parasitic infections.

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
***Acanthamoeba* keratitis**			
Drug of choice:	See footnote 1		

Amebiasis *(Entamoeba histolytica)*			
Asymptomatic infection			
Drug of choice:	Iodoquinol (Yodoxin) [2]	650 mg PO tid × 20 days	30-40 mg/kg/day (max 1950 mg) in 3 doses PO × 20 days
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Alternative:	Diloxanide furoate [3]	500 mg tid PO × 10 days	20 mg/kg/day PO in 3 doses × 10 days
Mild to moderate intestinal disease			
Drug of choice:	Metronidazole	500-750 mg tid PO × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole [4]	2 g PO once daily × 3 days	50 mg/kg/day PO (max 2 g) in 1 dose × 3 days
Either followed by:	Iodoquinol [2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Alternative:	Nitazoxanide [5]	500 mg bid × 3 days	1-3 yr: 100 mg bid × 3 days
			4-11 yr: 100 mg bid × 3 days
			12+ yr: use adult dosing
Severe intestinal and extraintestinal disease			
Drug of choice:	Metronidazole	750 mg PO tid × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole [4]	2 g PO once daily × 5 days	50 mg/kg/day PO (max 2 g) × 5 days
Either followed by:	Iodoquinol [2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Amebic meningoencephalitis, primary and granulomatous			
Naegleria fowleri			
Drug of choice:	Amphotericin B deoxycholate [6,7]	1.5 mg/kg/day IV in 2 divided doses × 3 days, then 1 mg/kg daily IV × 11 days	1.5 mg/kg/day IV in 2 divided doses × 3 days, then 1 mg/kg daily IV × 11 days
	plus Amphotericin B deoxycholate [6,7]	1.5 mg/kg intrathecally daily × 2 days, then 1 mg/kg intrathecally every other day × 8 days	1.5 mg/kg intrathecally daily × 2 days, then 1 mg/kg intrathecally every other day × 8 days
	plus Rifampin [7]	10 mg/kg (max 600 mg) IV or PO daily × 28 days	10 mg/kg (max 600 mg) IV or PO daily × 28 days
	plus Fluconazole [7]	10 mg/kg (max 600 mg) IV or PO daily × 28 days	10 mg/kg (max 600 mg) IV or PO daily × 28 days
	plus Azithromycin [7]	500 mg IV or PO daily × 28 days	10 mg/kg (max 500 mg) IV or PO daily × 28 days
	plus Miltefosine [6,7,8]	50 mg PO tid × 28 days	<45 kg: 50 mg bid (max 2.5 mg/kg) × 28 days
			≥45 kg: use adult dosing
	plus Dexamethasone	0.6 mg/kg/day IV in 4 divided doses × 4 days	0.6 mg/kg/day IV in 4 divided doses × 4 days
Acanthamoeba			

Drug of choice:	See footnotes 7 , 8		
Balamuthia mandrillaris			
Drug of choice:	See footnotes 7 , 9a , 9b		
Sappinia diploidea			
Drug of choice:	See footnote 10		
***Ancylostoma caninum* (eosinophilic enterocolitis)**			
Drug of choice:	Albendazole [7]	400 mg PO once	<10 kg/2 yr: [11]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days [12]
or	Pyrantel pamoate (OTC) [7]	11 mg/kg PO (max 1 g) × 3 days	11 mg/kg PO (max 1 g) × 3 days
or	Endoscopic removal		
***Ancylostoma duodenale*, see Hookworm**			
Angiostrongyliasis *(Angiostrongylus cantonensis, Angiostrongylus costaricensis)*			
Drug of choice:	See footnote 13		
Anisakiasis (*Anisakis* spp.)			
Treatment of choice:	Surgical or endoscopic removal		
Alternative:	Albendazole [7, 14]	400 mg PO bid × 6-21 days	<10 kg/2 yr: [11]
			≥2 yr: see adult dosing
Ascariasis (*Ascaris lumbricoides*, roundworm)			
Drug of choice:	Albendazole [7]	400 mg PO once	<10 kg/2 yr: see adult dosing [11]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days or 500 mg PO once	100 mg PO bid × 3 days or 500 mg PO once [12]
or	Ivermectin [7]	150-200 µg/kg PO once	<15 kg: not indicated
			≥15 kg: see adult dosing
Babesiosis *(Babesia microti)*			
Drugs of choice: [15]	Atovaquone [7]	750 mg PO bid × 7-10 days	20 mg/kg (max 750 mg) PO bid × 7-10 days
	plus Azithromycin [7]	500-1000 mg once, then 250 mg daily × 7-10 days. Higher doses (600-1000 mg) and/or prolonged therapy (6 wk or longer) may be required for immunocompromised patients.	10 mg/kg PO on day 1 (max 500 mg/dose), then 5 mg/kg/day (max 250 mg/dose) PO on days 2-10
or	Clindamycin [7]	300-600 mg IV qid or 600 mg tid PO × 7-10 days	20-40 mg/kg/day IV or PO in 3 or 4 doses × 7-10 days (max 600 mg/dose)
	plus Quinine [7]	648 mg tid PO × 7-10 days	10 mg/kg (max 648 mg) PO tid × 7-10 days
***Balamuthia mandrillaris*, see Amebic meningoencephalitis, primary**			
Balantidiasis *(Balantidium coli)*			
Drug of choice:	Tetracycline [7, 16]	500 mg PO qid × 10 days	<8 yr: not indicated
			≥8 yr: 10 mg/kg (max 500 mg) PO qid × 10 days
Alternative:	Metronidazole [7]	750 mg PO tid × 5 days	35-50 mg/kg/day PO in 3 divided doses × 5 days
or	Iodoquinol [2, 7]	650 mg PO tid × 20 days	30-40 mg/kg/day (max 2 g) PO in 3 divided doses × 20 days
or		500 mg PO bid × 3 days	1-3 yr: 100 mg PO bid × 3

	Nitazoxanide [4,7]		days
			4-11 yr: 200 mg PO bid × 3 days
			12+ yr: see adult dosing
Baylisascariasis *(Baylisascaris procyonis)*			
Drug of choice:	Albendazole [7,17]	400 mg PO BID × 10-20 days	<10 kg/2 yr: 25-50 mg/kg/day PO in 1-2 divided doses × 10-20 days [11]
			≥2 yr: 25-50 mg/kg/day PO in 1-2 divided doses × 10-20 days
***Blastocystis hominis* infection**			
Drug of choice:	See footnote [18]		
Capillariasis *(Capillaria philippinensis)*			
Drug of choice:	Mebendazole [7]	200 mg PO bid × 20 days	200 mg PO bid × 20 days [12]
Alternative:	Albendazole [7]	400 mg PO daily × 10 days	<10 kg/2 yr: [11]
			≥2 yr: see adult dosing
Chagas disease, see Trypanosomiasis			
***Clonorchis sinensis,* see Fluke infection**			
Cryptosporidiosis *(Cryptosporidium parvum)*			
Immunocompetent			
Drug of choice:	Nitazoxanide [4]	500 mg PO bid × 3 days	1-3 yr: 100 mg PO bid × 3 days
			4-11 yr: 200 mg PO bid × 3 days
			12+ yr: see adult dosing
HIV infected			
Drug of choice:	See footnote [19]		
Cutaneous larva migrans (*Ancylostoma braziliense, A. caninum,* dog and cat hookworm, creeping eruption)			
Drug of choice:	Albendazole [7,20]	400 mg PO daily × 3-7 days	<10 kg/2 yr: 200 mg PO daily × 3 days [11]
			≥2 yr: see adult dosing
or	Ivermectin [7]	200 µg/kg PO daily × 1-2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
Alternative:	Thiabendazole	Apply topically tid × 7 days	Apply topically tid × 7 days
Cyclosporiasis *(Cyclospora cayetanensis)*			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX) [7,21]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 7-10 days	4-5 mg/kg TMP component (max 160 mg) PO bid × 7-10 days
Cysticercosis, see Tapeworm infection			
Cystoisosporiasis *(Cystoisospora belli,* formerly known as *Isospora)*			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX) [7]	TMP 160 mg/SMX 800 mg (1 DS tablet) PO bid × 10 days	4-5 mg/kg TMP component (max 160 mg) PO bid × 10 days
Alternative:	Pyrimethamine	50-75 mg PO divided bid × 10 days	—
	plus Leukovorin	10-25 mg PO daily × 10 days	—
or	Ciprofloxacin [7]	500 mg PO bid × 7-10 days	—
***Dientamoeba fragilis* infection [22]**			
	Paromomycin [7]	25-35 mg/kg/day PO in 3 doses ×	25-35 mg/kg/day PO in 3

		7 days	divided doses × 7 days
or	Iodoquinol [2]	650 mg PO tid × 20 days	30-40 mg/kg/day PO (max 2 g) in 3 divided doses × 20 days
or	Metronidazole [7]	500-750 mg tid × 10 days	35-50 mg/kg/day in 3 divided doses × 10 days
***Diphyllobothrium latum*, see Tapeworm infection**			
***Dracunculus medinensis* (guinea worm) infection**			
Treatment of choice:	Slow mechanical extraction of worm [23]		
***Echinococcus*, see Tapeworm infection**			
***Entamoeba histolytica*, see Amebiasis**			
***Enterobius vermicularis* (pinworm) infection** [24]			
Drug of choice:	Albendazole [7]	400 mg PO once; repeat in 2 wk	<10 kg/2 yr: 200 mg PO once; repeat in 2 wk [11] ≥2 yr: see adult dosing
or	Mebendazole	100 mg PO once; repeat in 3 wk	100 mg PO once; repeat in 3 wk [12]
or	Pyrantel pamoate (OTC)	11 mg/kg base PO once (max 1 g); repeat in 2 wk	11 mg/kg base PO once (max 1 g); repeat in 2 wk
***Fasciola hepatica*, see Fluke infection**			
Filariasis [25]			
Lymphatic filariasis *(Wuchereria bancrofti, Brugia malayi, Brugia timori)*			
Drug of choice: [26]	Diethylcarbamazine [27], [28]	6 mg/kg once or 6 mg/kg PO in 3 divided doses × 12 days [29]	<18 mo: no indication ≥18 mo: see adult dosing
Loa loa			
<8,000 microfilaria/mL [28]			
Drug of choice:	Diethylcarbamazine [27], [28]	9 mg/kg PO in 3 doses × 14 days [29]	<18 mo: no indication ≥18 mo: see adult dosing
Alternative:	Albendazole [27]	200 mg PO bid × 21 days	<10 kg/2 yr: [11] ≥2 yr: see adult dosing
≥8,000 microfilaria/mL [28], [30]			
Treatment of choice:	Apheresis		
or	Albendazole [27]	200 mg PO bid × 21 days	<10 kg/2 yr: [11] ≥2 yr: see adult dosing
Either followed by:	Diethylcarbamazine [27], [28]	8-10 mg/kg PO in 3 doses × 21 days [29]	<18 mo: no indication ≥18 mo: see adult dosing
Mansonella ozzardi			
Drug of choice:	See footnote 31		
Mansonella perstans			
Drug of choice:	Doxycycline [7], [16], [32]	100 mg bid PO × 6 wk	4 mg/kg/day in 2 doses PO × 6 wk
Mansonella streptocerca [33]			
Drug of choice:	Diethylcarbamazine	6 mg/kg/day PO × 14 days	6 mg/kg/day PO × 14 days
or	Ivermectin [7]	150 µg/kg PO once	<15 kg: not indicated ≥15 kg: see adult dosing
Tropical pulmonary eosinophilia (TPE) [34]			
Drug of choice:	Diethylcarbamazine [27]	6 mg/kg once or 6 mg/kg PO in 3 divided doses × 14-21 days [26]	<18 mo: no indication ≥18 mo: see adult dosing

***Onchocerca volvulus* (river blindness)**			
Drug of choice:	Ivermectin[35]	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic	<15 kg: not indicated ≥15 kg: see adult dosing
Fluke, hermaphroditic, infection			
***Clonorchis sinensis* (Chinese liver fluke)**			
Drug of choice:	Praziquantel	25 mg/kg PO tid × 2 days	25 mg/kg PO tid × 2 days[36]
or	Albendazole[7]	10 mg/kg PO × 7 days	<10 kg/2 yr: [11] ≥2 yr: see adult dosing
***Fasciola hepatica* (sheep liver fluke)**			
Drug of choice:	Triclabendazole[7,37,38]	10 mg/kg PO once or twice	10 mg/kg PO once or twice
Alternative:	Nitazoxanide[7]	500 mg PO bid × 7 days	1-3 yr: 100 mg PO bid 4-11 yr: 200 mg PO bid ≥12 yr: see adult dosing
or	Bithionol[3,7]	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
***Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai* (intestinal flukes)**			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 1 day	25 mg/kg PO tid × 1 day[36]
***Metorchis conjunctus* (North American liver fluke)**[39]			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 1 day	25 mg/kg PO tid × 1 day[36]
Nanophyetus salmincola			
Drug of choice:	Praziquantel[7]	20 mg/kg PO tid × 1 day	20 mg/kg PO tid × 1 day[36]
***Opisthorchis viverrini* (Southeast Asian liver fluke), *O. felineus* (cat liver fluke)**			
Drug of choice:	Praziquantel	25 mg/kg PO tid × 2 days	25 mg/kg PO tid × 2 days[36]
or	Albendazole[7]	10 mg/kg PO × 7 days	<10 kg/2 yr: [11] ≥2 yr: see adult dosing
***Paragonimus westermani* (lung fluke)**			
Drug of choice:	Praziquantel[7]	25 mg/kg PO tid × 2 days	25 mg/kg PO tid × 2 days[36]
or	Triclabendazole[7,40]	10 mg/kg PO bid × 1 day or 5 mg/kg daily × 3 days	10 mg/kg PO bid × 1 day or 5 mg/kg daily × 3 days
or	Bithionol[3,7]	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
Giardiasis *(Giardia intestinalis*, also known as *G. duodenalis* or *G. lamblia)*			
Drug of choice:	Metronidazole[7]	250 mg PO tid × 5 days	5 mg/kg (max 250 mg) PO tid × 5 days
or	Nitazoxanide[5]	500 mg PO bid × 3 days	1-3 yr: 100 mg PO every 12 hr × 3 days 4-11 yr: 200 mg PO every 12 hr × 3 days 12+ yr: see adult dosing
or	Tinidazole[4]	2 g PO once	50 mg/kg PO once (max 2 g)
Alternative:[41]	Paromomycin[7,42]	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
or	Furazolidone[3]	100 mg PO qid × 7-10 days	6 mg/kg/day PO in 4 doses × 7-10 days
or	Quinacrine[2]	100 mg PO tid × 5 days	2 mg/kg tid PO × 5 days (max 300 mg/day)

Gnathostomiasis *(Gnathostoma spinigerum)*			
Treatment of choice: [43]	Albendazole [7]	400 mg PO bid × 21 days	<10 kg/2 yr: [11]
			≥2 yr: see adult dosing
or	Ivermectin [7]	200 µg/kg/day PO × 2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
±	Surgical removal		
Gongylonemiasis (*Gongylonema* sp.) [44]			
Treatment of choice:	Surgical removal		
or	Albendazole [7]	400 mg PO daily × 3 days	10 mg/kg/day PO × 3 days
Hookworm infection *(Ancylostoma duodenale, Necator americanus)*			
Drug of choice:	Albendazole [7]	400 mg PO once	<10 kg/2 yr: [11]
			≥2 yr: see adult dosing
or	Mebendazole	100 mg PO bid × 3 days or 500 mg once	100 mg PO bid × 3 days or 500 mg once [12]
or	Pyrantel pamoate (OTC) [7]	11 mg/kg (max 1 g) PO × 3 days	11 mg/kg (max 1 g) PO × 3 days
Hydatid cyst, see Tapeworm infection			
***Hymenolepis nana*, see Tapeworm infection**			
***Leishmania* infection** [45]			
Visceral [46]			
Drug of choice:	Liposomal amphotericin B (AmBisome) [47], [48]	3 mg/kg/day IV on days 1-5, 14, and 21 (total dose 21 mg/kg)	3 mg/kg/day IV on days 1-5, 14, and 21 (total dose 21 mg/kg)
or	Miltefosine [49]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5 mg/kg daily × 28 days [7]
		≥45 kg: 50 mg PO tid × 28 days	12 yr: see adult dosing
or	Sodium stibogluconate (Pentostam) [27], [50]	20 mg/kg/day IV or IM × 28 days	20 mg/kg/day IV or IM × 28 days
or	Amphotericin B deoxycholate [7]	1 mg/kg IV daily or every 2 days for 15-20 doses	1 mg/kg IV daily or every 2 days for 15-20 doses
Alternative:	Meglumine antimoniate [3], [50]	20 mg pentavalent antimony/kg/day IV or IM × 28 days	20 mg pentavalent antimony/kg/day IV or IM × 28 days
or	Pentamidine [7]	4 mg/kg IV or IM daily or every 2 days for 15-30 doses	4 mg/kg IV or IM daily or every 2 days for 15-30 doses
Cutaneous [51], [52]			
Drug of choice:	Sodium stibogluconate [27], [50]	20 mg/kg/day IV or IM × 20 days	20 mg/kg/day IV or IM × 20 days
or	Liposomal amphotericin B (AmBisome) [7]	3 mg/kg/day IV on days 1-5 and 10 or 1-7 (total dose 18-21 mg/kg)	3 mg/kg/day IV on days 1-5 and 10 or 1-7 (total dose 18-21 mg/kg)
or	Amphotericin B deoxycholate [7]	0.5-1 mg/kg IV daily or every 2 days (total dose 15-30 mg/kg)	0.5-1 mg/kg IV daily or every 2 days (total dose 15-30 mg/kg)
or	Miltefosine [49]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5 mg/kg daily × 28 days [7]
		≥45 kg: 50 mg PO tid × 28 days	12 yr: see adult dosing
Alternatives:	Meglumine antimoniate [3,50]	20 mg pentavalent antimony/kg/day IV or IM × 20	20 mg pentavalent antimony/kg/day IV or IM

		days	× 20 days
or	Pentamidine [7, 53]	3-4 mg/kg IV or IM every 2 days × 3-4 doses	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses
or	Paromomycin [7, 54]	Topically 2×/day × 10-20 days	Topically 2×/day × 10-20 days
or	Ketoconazole [7]	600 mg daily × 28 days	
or	Fluconazole [7]	200 mg daily × 6 wk	
or	Local therapy, including cryotherapy, thermotherapy, intralesional Sb^V, topical paromomycin, photodynamic or laser therapy		
Mucosal [54, 55]			
Drug of choice:	Sodium stibogluconate [27, 50]	20 mg/kg/day IV or IM × 28 days	20 mg/kg/day IV or IM × 28 days
or	Liposomal amphotericin B (AmBisome) [7]	3 mg/kg/day IV × 10 days or 4 mg/kg on days 1-5, 10, 17, 24, 31, and 38 (total dose 20-60 mg/kg)	2-4 mg/kg/day IV × 10 days or 4 mg/kg on days 1-5, 10, 17, 24, 31, and 38 (total dose 20-60 mg/kg)
or	Amphotericin B deoxycholate [7]	0.5-1 mg/kg IV daily or every 2 days (total dose 20-45 mg/kg)	0.5-1 mg/kg IV daily or every 2 days (total dose 20-45 mg/kg)
or	Miltefosine [49]	30-44 kg: 50 mg PO bid × 28 days	<12 yr: 2.5 mg/kg daily × 28 days [7]
		≥45 kg: 50 mg PO tid × 28 days	12 yr: see adult dosing
Alternative:	Meglumine antimoniate [3, 50]	20 mg pentavalent antimony/kg/day IV or IM × 28 days	20 mg pentavalent antimony/kg/day IV or IM × 28 days
Lice (head and body) infestation *(Pediculus humanus capitis, Pediculus humanus humanus)*			
Drug of choice:	0.5% Malathion (Ovide) [56]	Topically 2x, 1 wk apart	Topically 2x, 1 wk apart, approved for ≥ 6 yr
or	1% Permethrin (Nix) (OTC) [56]	Topically 2x, 1 wk apart	Topically 2x, 1 wk apart, approved for ≥ 2 mo
or	Pyrethrins with piperonyl butoxide (A-200, Pronto, R&C, Rid, Triple X) (OTC) [57]	Topically 2x, 1 wk apart	Topically 2x, 1 wk, approved for ≥ 2 yr
or	0.5% Ivermectin lotion (Sklice)	Topically, once	Topically once, approved for ≥ 6 mo
or	0.9% Spinosad suspension (Natroba)	Topically once, 2nd dose in 1 wk if live adult lice seen	Topically once, 2nd dose in 1 wk if live adult lice seen, approved for ≥ 6 mo
or	Ivermectin [7, 58]	200-400 µg/kg PO 2x, 1 wk apart	<15 kg: not indicated
			≥15 kg: see adult dosing
or	5% Benzyl alcohol lotion (Ulesfia)	Topically 2x, 1 wk apart	Topically 2x, 1 wk apart
Lice (pubic) infestation *(Phthirus pubis)* [59]			
Drug of choice:	1% Permethrin (Nix) (OTC) [56]	Topically 2x, 1 wk apart	Topically 2x, 1 wk apart, approved for ≥ 2 mo
or	Pyrethrins with piperonyl butoxide (A-200, Pronto, R&C, Rid, Triple X) (OTC) [52]	Topically 2x, 1 wk apart	Topically 2x, 1 wk apart, approved for ≥ 2 yr
or	0.5% Malathion (Ovide) [56]	Topically 2x, 1 wk apart	Topically 2x, 1 wk apart, approved for ≥ 6 yr

or	0.5% Ivermectin lotion (Sklice)	Topically, once	Topically once, approved for ≥ 6 mo
or	Ivermectin [7, 58]	200-400 µg/kg PO 2x, 1 wk apart	<15 kg: not indicated ≥15 kg: see adult dosing
***Loa loa*, see Filariasis**			
Malaria *(Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax,* and *Plasmodium malariae)* Treatment			
Uncomplicated infection due to *P. falciparum* or species not identified acquired in areas of chloroquine resistance or unknown resistance [60]			
Drug of choice: [61]	Atovaquone/proguanil (Malarone) Adult tablets: 50 mg atovaquone/100 mg proguanil Pediatric tablets: 62.5 mg atovaquone/25 mg proguanil [62]	4 adult tablets PO once daily or 2 adult tablets PO bid × 3 days [63]	<5 kg: not indicated 5-8 kg: 2 pediatric tablets PO daily × 3 days 9-10 kg: 3 pediatric tablets PO daily × 3 days 11-20 kg: 1 adult tablet PO daily × 3 days 21-30 kg: 2 adult tablets PO daily × 3 days 31-40 kg: 3 adult tablets PO daily × 3 days >40 kg: 4 adult tablets PO daily × 3 days
or	Coartem (artemether-lumefantrine) Fixed dose of 20 mg artemether and 120 mg lumefantrine per tablet	4 tablets per dose. A 3- day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. These 6 doses should be administered over 3 days at 0, 8, 24, 36, 48, and 60 h5.	5 to < 15 kg: 1 tablet PO per dose 15 to < 25 kg: 2 tablets PO per dose 25 to < 35 kg: 3 tablets per dose ≥35 kg: 4 tablets PO per dose
or	Quinine sulfate	648 mg salt PO tid × 3-7 days [63]	10 mg salt/kg PO tid × 3-7 days [64]
	plus Doxycycline [7, 16]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus Tetracycline [7, 16]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus Clindamycin [7, 65]	20 mg/kg/day PO in 3 divided doses × 7 days [66]	20 mg/kg/day PO in 3 doses × 7 days
Alternative:	Mefloquine [67, 68]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
Uncomplicated infection due to *P. falciparum* or species not identified acquired in areas of chloroquine sensitivity or uncomplicated *P. malariae* or *P. knowlesi*			
Drug of choice:	Chloroquine phosphate (Aralen)	600 mg base PO, then 300 mg base PO at 6, 24, and 48 hr	10 mg/kg base PO, then 5 mg/kg base PO at 6, 24, and 48 hr
or	Hydroxychloroquine (Plaquenil) [71]	620 mg base PO, then 310 mg base PO at 6, 24, and 48 hr	10 mg/kg base PO, then 5 mg/kg base PO at 6, 24, and 48 hr
Uncomplicated infection with *P. vivax* acquired in areas of chloroquine resistance [68]			
Drug of choice:	Atovaquone/proguanil (Malarone) Adult tablets: 50 mg atovaquone/100 mg proguanil	4 adult tablets PO once daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tablets PO daily × 3 days 9-10 kg: 3 pediatric tablets

	Pediatric tablets: 62.5 mg atovaquone/25 mg proguanil [62]		PO daily × 3 days
			11-20 kg: 1 adult tablet PO daily × 3 days
			21-30 kg: 2 adult tablets PO daily × 3 days
			31-40 kg: 3 adult tablets PO daily × 3 days
			>40 kg: 4 adult tablets PO daily × 3 days
	plus Primaquine [70]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Quinine sulfate	648 mg salt PO tid × 3-7 days [63]	10 mg salt/kg PO tid × 3-7 days [57]
	plus Doxycycline [7, 16]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus Tetracycline [7, 16]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus Clindamycin [7, 65]	20 mg/kg/day PO in 3 divided doses × 7 days [66]	20 mg/kg/day PO in 3 doses × 7 days
	plus Primaquine [69]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Mefloquine [67]	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
	plus Primaquine [70]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
Uncomplicated infection with *P. ovale* and *P. vivax* acquired in areas without chloroquine resistance [68]			
Drug of choice:	Chloroquine phosphate (Aralen)	600 mg base PO, then 300 mg base PO at 6, 24, and 48 hr	10 mg/kg base PO, then 5 mg/kg base PO at 6, 24, and 48 hr
	plus Primaquine [70]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Hydroxychloroquine (Plaquenil) [71]	620 mg base PO, then 310 mg base PO at 6, 24, and 48 hr	10 mg/kg base PO, then 5 mg/kg base PO at 6, 24, and 48 hr
	plus Primaquine [70]	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
Severe malaria due to all *Plasmodium* spp.			
Drug of choice: [72]	Quinidine gluconate [73]	10 mg salt/kg IV in normal saline loading dose (max 600 mg) over 1-2 hr, followed by continuous infusion of 0.02 mg salt/kg/min until PO therapy can be started	10 mg salt/kg IV in normal saline loading dose (max 600 mg) over 1-2 hr, followed by continuous infusion of 0.02 mg salt/kg/min until PO therapy can be started
	plus Doxycycline [7, 16]	100 mg PO or IV bid × 7 days	4 mg/kg/day PO or IV in 2 doses × 7 days
	or plus Tetracycline [7, 16]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus Clindamycin [7, 65]	20 mg/kg/day PO in 3 divided doses × 7 days or 10 mg/kg IV loading dose, then 5 mg/kg tid until able to take PO [60]	20 mg/kg/day PO in 3 divided doses × 7 days or 10 mg/kg IV loading dose, then 5 mg/kg tid until able to take PO [60]
Alternative:	Artesunate [27, 74]	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and

Followed by:	Atovaquone-proguanil, doxycycline, clindamycin, or mefloquine as above		72 hr
Prevention of relapses: *P. vivax* and *P. ovale* only			
Drug of choice:	Primaquine phosphate [70]	30 mg base/day PO × 14 days	0.6 mg base/kg/day PO × 14 days
Malaria: Prevention [75]			
Chloroquine-sensitive areas [60]			
Drug of choice	Chloroquine phosphate [76, 77, 78]	500 mg salt (300 mg base), PO once/wk beginning 1-2 wk before travel to malarious area and 4 wk after leaving	5 mg/kg base once/wk, up to adult dose of 300 mg base beginning 1-2 wk before travel to malarious area and 4 wk after leaving
or	Hydroxychloroquine (Plaquenil) [71]	400 mg (310 mg base) PO once/wk beginning 1-2 wk before travel to malarious area and 4 wk after leaving	5 mg/kg base once/wk, up to adult dose of 310 mg base beginning 1-2 wk before travel to malarious area and 4 wk after leaving
Chloroquine-resistant areas [60]			
Drug of choice:	Atovaquone/proguanil [62, 77, 79, 80]	1 adult tablet PO q day beginning 1-2 days before travel to malarious area and 7 days after leaving	11-20 kg: 1 pediatric tablet PO/day
			21-30 kg: 2 pediatric tablets PO/day
			31-40 kg: 3 pediatric tablets PO/day
			>40 kg: 1 adult tablet PO/day
or	Mefloquine [67, 77, 78, 81]	1 adult tablet PO q day beginning 1-2 wk before travel to malarious area and 4 wk after leaving	<9 kg: 5 mg/kg salt once/wk
			9-19 kg: ¼ tablet once/wk
			19-30 kg: ½ tablet once/wk
			31-45 kg: ¾ tablet once/wk
			>45 kg: 1 tablet once/wk
or	Doxycycline [7, 82]	100 mg PO daily	≥8 yr: 2 mg/kg/day, up to 100 mg/day
Alternative for areas with primarily *P. vivax:*	Primaquine [7, 83]	30 mg base PO daily beginning 1-2 days before travel to malarious area and 7-14 days after leaving	0.5 mg/kg base (max 30 mg) daily beginning 1-2 days before travel to malarious area and 7-14 days after leaving
Malaria: Presumptive self-treatment [84]			
Drug of choice:	Atovaquone/proguanil (Malarone) Adult tablets: 50 mg atovaquone/100 mg proguanil Pediatric tablets 62.5 mg atovaquone/25 mg proguanil [62]	4 adult tablets PO once daily × 3 days	<5 kg: not indicated
			5-8 kg: 2 pediatric tablets PO daily × 3 days
			9-10 kg: 3 pediatric tablets PO daily × 3 days
			11-20 kg: 1 adult tablet PO daily × 3 days
			21-30 kg: 2 adult tablets PO daily × 3 days
			31-40 kg: 3 adult tablets PO daily × 3 days
			>40 kg: 4 adult tablets PO

			daily × 3 days
or	Quinine sulfate[63]	648 mg salt PO tid × 3-7 days	10 mg salt/kg PO tid × 3-7 days
	plus Doxycycline[7,16]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 divided doses × 7 days
or	Mefloquine[67,68]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
Microsporidiosis			
Ocular *(Encephalitozoon hellem, Encephalitozoon cuniculi, Vittaforma corneae [Nosema corneum])*			
Drug of choice:	Albendazole[7,85]	400 mg PO bid	<10 kg/2 yr:[11]
			≥2 yr: see adult dosing
	plus Fumagillin[86]		
Intestinal *(Enterocytozoon bieneusi, Encephalitozoon [Septata] intestinalis)*			
***E. bieneusi*[87]**			
Drug of choice:	Fumagillin	60 mg/day PO × 14 days in 3 divided doses	
E. intestinalis			
Drug of choice:	Albendazole[7,85]	400 mg PO bid × 21 days	<10 kg/2 yr:[11]
			≥2 yr: see adult dosing
Disseminated *(E. hellem, E. cuniculi, E. intestinalis, Pleistophora* sp., *Trachipleistophora* sp., and *Brachiola vesicularum)*			
Drug of choice:[88]	Albendazole[7,85]	400 mg PO bid	<10 kg/2 yr:[11]
			≥2 yr: see adult dosing
Mites, see Scabies			
***Moniliformis moniliformis* infection**			
Drug of choice:	Pyrantel pamoate (OTC)[7]	11 mg/kg PO once, repeat twice, 2 wk apart	11 mg/kg PO once, repeat twice, 2 wk apart
***Naegleria* species, see Amebic meningoencephalitis, primary**			
***Necator americanus*, see Hookworm infection**			
Oesophagostomum bifurcum			
Drug of choice:	See footnote 89		
***Onchocerca volvulus*, see Filariasis**			
***Opisthorchis viverrini*, see Fluke infection**			
***Paragonimus westermani*, see Fluke infection**			
***Pediculus capitis, Pediculus humanus, Phthirus pubis*, see Lice**			
Pinworm, see *Enterobius*			
***Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia (PCP)[90]**			
Moderate to severe disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	15-20 mg/kg/day TMP component IV in 3-4 divided doses × 21 days (change to PO after clinical improvement)	15-20 mg/kg/day TMP component IV in 3-4 divided doses × 21 days (change to PO after clinical improvement)
Alternative:	Pentamidine	3-4 mg IV daily × 21 days	3-4 mg IV daily × 21 days
or	Primaquine	30 mg base PO daily × 21 days	0.3 mg/kg base PO (max 30 mg) daily × 21 days
	plus Clindamycin[7]	600-900 mg IV tid or qid × 21 days, or 300-450 mg PO tid or qid × 21 days (change to PO after clinical improvement)	15-25 mg/kg IV tid or qid × 21 days, or 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days (change to PO after clinical improvement)

Mild to moderate disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	320 mg/1600 mg (2 DS tablets) PO tid × 21 days	TMP 15-20 mg/kg/day PO in 3 or 4 doses × 21 days
Alternatives:	Dapsone	100 mg PO daily × 21 days	2 mg/kg/day (max 100 mg) PO × 21 days
	plus Trimethoprim	15 mg/kg/day PO in 3 doses	15 mg/kg/day PO in 3 doses
or	Primaquine	30 mg base PO daily × 21 days	0.3 mg/kg base PO daily (max 30 mg) × 21 days
	plus Clindamycin	300-450 mg PO tid or qid × 21 days	10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days
or	Atovaquone	750 mg PO bid × 21 days	1-3 mo: 30 mg/kg/day PO in 2 doses × 21 days
Primary and secondary prophylaxis [91]			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	1 tablet (single strength or greater) PO daily or 1 DS tablet PO 3 days/wk	TMP 150 mg/m [2] in 1-2 doses daily or on 3 consecutive days per wk [92]
Alternatives: [91]	Dapsone [7]	50 mg PO bid, or 100 mg PO daily	2 mg/kg/day (max 100 mg) PO or 4 mg/kg (max 200 mg) PO each wk
or	Dapsone [7]	50 mg PO daily or 200 mg PO each wk	
	plus Pyrimethamine [93]	50 mg PO or 75 mg PO each wk	
or	Pentamidine aerosol	300 mg inhaled monthly via Respirgard II nebulizer	≥5 yr: 300 mg inhaled monthly via Respirgard II nebulizer
or	Atovaquone [7]	1,500 mg/day PO in 1 or 2 doses	1-3 mo: 30 mg/kg/day PO 4-24 mo: 45 mg/kg/day PO in 2 doses × 21 days >24 mo: 30 mg/kg/day PO in 2 doses × 21 days
Roundworm, see Ascariasis			
***Sappinia diploidea*, see Amebic meningoencephalitis, primary**			
Scabies *(Sarcoptes scabiei)*			
Drug of choice:	5% Permethrin [94]	Topically, 2× at least 1 wk apart	Topically 2x, 1 wk apart, approved for ≥ 2 mo
Alternative: [94], [95]	Ivermectin [7], [94], [96]	200 µg/kg PO x2 at least 1 wk apart	<15 kg: not indicated ≥15 kg: see adult dosing
	10% Crotamiton	Topically overnight on days 1, 2, 3, 8	Topically overnight on days 1, 2, 3, 8
Schistosomiasis *(Bilharziasis)*			
Schistosoma haematobium* or *S. intercalatum			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day [36]
Schistosoma japonicum* or *S. mekongi			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day [36]
Schistosoma mansoni			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day [36]

Alternative:	Oxamniquine [97], [98]	15 mg/kg PO once	20 mg/kg/day PO in 2 doses × 1 day
Sleeping sickness, see Trypanosomiasis			
Strongyloidiasis *(Strongyloides stercoralis)*			
Drug of choice: [99]	Ivermectin	200 µg/kg/day PO × 2 days	<15 kg: not indicated
			≥15 kg: see adult dosing
Alternative:	Albendazole [7], [100]	400 mg PO bid × 7 days	<10 kg/2 yr: [11]
			≥2 yr: see adult dosing
Tapeworm infection			
Adult (intestinal stage)			
***Diphyllobothrium latum* (fish), *Taenia saginata* (beef), *Taenia solium* (pork), *Dipylidium caninum* (dog)**			
Drug of choice:	Praziquantel [7]	5-10 mg/kg PO once	5-10 mg/kg PO once [36]
Alternative:	Niclosamide	2 g PO once	50 mg/kg PO once
***Hymenolepis nana* (dwarf tapeworm)**			
Drug of choice:	Praziquantel [7]	25 mg/kg PO once	25 mg/kg PO once [36]
Alternative:	Niclosamide [101]	2 g PO daily × 7 days	11-34 kg: 1 g PO on day 1, then 500 mg/day PO × 6 days
			>34 kg: 1.5 g PO on day 1, then 1 g/day PO × 6 days
Larval (tissue stage)			
***Echinococcus granulosus* (hydatid disease cystic echinococcosis)**			
Drug of choice: [102]	Albendazole [7]	400 mg PO bid × 1-6 mo	<10 kg/2 yr: 5-7.5 mg/kg PO bid (max 400 mg) [11]
			≥2 yr: 5-7.5 mg/kg PO bid (max 400 mg) × 1-6 mo
***Echinococcus multilocularis* (alveolar echinococcosis)**			
Treatment of choice:	See footnote 103		
***Taenia solium* (cysticercosis)**			
Treatment of choice: [104]	Albendazole	400 mg bid PO × 8-30 days; can be repeated as necessary	<10 kg/2 yr: 7.5 mg/kg PO bid × 8-30 days; can be repeated as necessary [11]
			≥2 yr: 7.5 mg/kg PO (max 400 mg) bid × 8-30 days; can be repeated as necessary
	plus Steroids		
Alternative:	Praziquantel [7]	50 mg/kg/day PO in 3 divided doses × 15 days	50 mg/kg/day PO in 3 divided doses × 15 days [36]
or	Surgical removal		
Toxocariasis, see Visceral larva migrans			
Toxoplasmosis *(Toxoplasma gondii)* [105]			
Drug of choice: [106], [107]	Pyrimethamine [108]	200 mg PO × 1, then 50-75 mg/day × 3-6 wk	2 mg/kg/day × 3 days, then 1 mg/kg/day (max 25 mg/day) × 3-6 wk [109]
	plus Sulfadiazine	1.5 g PO qid × 3-6 wk	100-200 mg/kg/day in 4 divided doses × 3-6 wk
	or plus Clindamycin	1.8-2.4 g/day IV or PO in 3-4 doses × 3-6 wk	5-7.5 mg/kg IV or PO tid or qid (max 600 mg/dose) × 3-6 wk
	or plus Atovaquone	1,500 mg PO bid	1,500 mg PO bid

Alternative:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7]	15-20 mg/kg/day TMP component PO or IV in 3-4 divided doses × 3-6 wk	15-20 mg/kg TMP component PO or IV in 3 or 4 doses × 3-6 wk
Trichinellosis *(Trichinella spiralis)*			
Drug of choice:	Steroids for severe symptoms	Prednisone 30-60 mg PO daily × 10-15 days	
	plus Albendazole[7]	400 mg PO bid × 8-14 days	<10 kg/2 yr:[11]
			≥2 yr: see adult dosing
Alternative:	Mebendazole[7]	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days[12]
Trichomoniasis *(Trichomonas vaginalis)*			
Drug of choice:[110]	Metronidazole	2 g PO once or 500 mg PO bid × 7 days	15 mg/kg/day PO in 3 doses × 7 days
or	Tinidazole[4]	2 g PO once	50 mg/kg PO once (max 2 g)
***Trichostrongylus* infection**			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg base PO once (max 1 g)	11 mg/kg PO once (max 1 g)
Alternative:	Mebendazole[7]	100 mg PO bid × 3 days	100 mg PO bid × 3 days[12]
or	Albendazole[7]	400 mg PO once	<10 kg/2 yr:[11]
			≥2 yr: 15 mg/kg/day PO (max 800 mg) × 1-6 mo
Trichuriasis (*Trichuris trichiura*, whipworm)			
Drug of choice:	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days[12]
Alternative:	Albendazole[7]	400 mg PO × 3 days	<10 kg/2 yr:[11]
			≥2 yr: see adult dosing
or	Ivermectin[7]	200 µg/kg PO daily × 3 days	<15 kg: not indicated
			≥15 kg: see adult dosing
Trypanosomiasis[111]			
***Trypanosoma cruzi* (American trypanosomiasis, Chagas disease)**			
Drug of choice:	Benznidazole[27]	5-7 mg/kg/day PO in 2 divided doses × 60 days	≤12 yr: 5-7.5 mg/kg/day PO in 2 divided doses × 60 days
			>12 yr: see adult dosing
Alternative:	Nifurtimox[27, 112]	8-10 mg/kg/day PO in 3-4 doses × 90 days	≤10 yr: 15-20 mg/kg/day PO in 3-4 doses × 90 days
			11-16 yr: 12.5-15 mg/kg/day in 3-4 doses × 90 days
			>16 yr: see adult dosing
***Trypanosoma brucei gambiense* (West African trypanosomiasis, sleeping sickness)**			
Hemolymphatic stage			
Drug of choice:[113]	Pentamidine isethionate[7]	4 mg/kg/day IM × 7-10 days	4 mg/kg/day IM or IV × 7-10 days
Alternative:	Suramin[27]	100 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	2 mg/kg (test dose) IV, then 20 mg/kg IV on days 1, 3, 7, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Eflornithine[27, 114]	100 mg/kg IV qid × 14 days	100 mg/kg IV qid × 14 days
Alternative:	Melarsoprol[27, 115]	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased	2-3.6 mg/kg (max 200 mg) daily IV (progressively

		during series) × 3 days. After 7 days, 3.6 mg/kg daily × 3 days. After 7 days, give a 3rd series of 3.6 mg/kg daily × 3 days.	increased during series) × 3 days. After 7 days, 3.6 mg/kg daily × 3 days. After 7 days, give a 3rd series of 3.6 mg/kg daily × 3 days.
***Trypanosoma brucei rhodesiense* (East African trypanosomiasis, sleeping sickness)**			
Hemolymphatic stage			
Drug of choice:	Suramin [27]	100 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	2 mg/kg (test dose), then 20 mg/kg IV on days 1, 3, 7, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol [27, 114]	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days. After 7 days, 3.6 mg/kg daily × 3 days. After 7 days, give a 3rd series of 3.6 mg/kg daily × 3 days.	2-3.6 mg/kg (max 200 mg) daily IV (progressively increased during series) × 3 days. After 7 days, 3.6 mg/kg daily × 3 days. After 7 days, give a 3rd series of 3.6 mg/kg daily × 3 days.
Visceral larva migrans (Toxocariasis) [116]			
Drugs of choice:	Albendazole [7]	400 mg PO bid × 5 days	<10 kg/2 yr: [11] ≥2 yr: see adult dosing
or	Mebendazole [7]	100-200 mg PO bid × 5 days	100-200 mg PO bid × 5 days [12]
Whipworm, see Trichuriasis			
***Wuchereria bancrofti*, see Filariasis**			

[1] For treatment of keratitis caused by *Acanthamoeba,* 0.02% topical polyhexamethylene biguanide (PHMB) and 0.02% chlorhexidine have been successfully used individually and in combination in a large number of patients (Tabin G, et al: *Cornea* 20:757, 2001; Wysenbeek YS, et al: *Cornea* 19:464, 2000). The expected treatment course is 6-12 mo. PHMB is no longer available from Leiter's Park Avenue Pharmacy but is available from the O'Brien Pharmacy (1-800-627-4360; distributes in many states) and the Greenpark Pharmacy (1-713-432-9855; Texas only). Combinations with either 0.1% propamidine isethionate (Brolene) or hexamidine (Desmodine) have been used (Seal DV: *Eye* 17:893, 2003) successfully, but these are not available in the United States. Neomycin is no longer recommended due to high levels of resistance (*Acanthamoeba* keratitis: Treatment guidelines from The Medical Letter 143, 8/1/2013). In addition, the combination of chlorhexidine, natamycin (pimaricin), and debridement also has been successful (Kitagawa K, et al: *Jpn J Ophthalmol* 47:616, 2003).

[2] The drug is not available commercially but can be compounded by Expert Compounding Pharmacy, 6744 Balboa Blvd, Lake Balboa, CA 91406 (1-800-247-9767 or 1-818-988-7979 or info@expertpharmacy.org).

[3] The drug is not available commercially in the United States.

[4] A nitroimidazole similar to metronidazole, tinidazole was approved by the FDA in 2004 and appears to be as effective and better tolerated than metronidazole. It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist may crush the tablets and mix them with cherry syrup (Humco, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use. Ornidazole, a similar drug, is also used outside the United States.

[5] Nitazoxanide is FDA approved as a pediatric oral suspension for treatment of *Cryptosporidium* in

immunocompetent children ≥ 1 yr of age. It has also been used in some small studies for *Balantidium coli* infection. It may also be effective for mild to moderate amebiasis (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003; Rossignol JF, et al: *Trans R Soc Trop Med Hyg* 101:1025, 2007). Nitazoxanide is available in 500 mg tablets and an oral suspension; it should be taken with food.

[6] *Naegleria* infection has been treated successfully with IV and intrathecal use of both amphotericin B and miconazole plus rifampin and with amphotericin B, rifampin, and ornidazole (Seidel J, et al: *N Engl J Med* 306:346, 1982; Jain R, et al: *Neurol India* 50:470, 2002). Other reports of successful therapy are less-well documented.

[7] An approved drug, but usage is considered off-label for this condition by the FDA.

[8] If you have a patient with suspected free-living amoeba infection, please contact the CDC Emergency Operations Center at 1-800-CDC-INFO to consult with a CDC expert regarding the use of this drug. Miltefosine has been reported to successfully treat primary amebic meningoencephalitis due to *Naegleria fowleri,* although controlled trials have not been conducted (Linam M, et al: *Pediatrics* 135:e744-e748, 2015).

[9a] Strains of *Acanthamoeba* isolated from fatal granulomatous amebic encephalitis are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and (less so) amphotericin B. Chronic *Acanthamoeba* meningitis has been successfully treated in two children with a combination of oral trimethoprim-sulfamethoxazole, rifampin, and ketoconazole (Singhal T, et al: *Pediatr Infect Dis J* 20:623, 2001), and in an AIDS patient with fluconazole, sulfadiazine, and pyrimethamine combined with surgical resection of the CNS lesion (Seijo Martinez M, et al: *J Clin Microbiol* 38:3892, 2000). Disseminated cutaneous infection in an immunocompromised patient has been treated successfully with IV pentamidine isethionate, topical chlorhexidine, and 2% ketoconazole cream, followed by oral itraconazole (Slater CA, et al: *N Engl J Med* 331:85, 1994).

[9b] A free-living leptomyxid ameba that causes subacute to fatal granulomatous CNS disease. Several cases of *Balamuthia* encephalitis have been successfully treated with flucytosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin (phenothiazines were also used) combined with surgical resection of the CNS lesion (Deetz TR, et al: *Clin Infect Dis* 37:1304, 2003; Jung S, et al: *Arch Pathol Lab Med* 128:466, 2004). Case reports and in vitro data suggest miltefosine may have some antiamebic activity (Aichelburg AC, et al: *Emerg Infect Dis* 14:1743, 2008; Martinez DY, et al: *Clin Infect Dis* 51:e7, 2010; Schuster FL, et al: *J Eukaryot Microbiol* 53:121, 2006). Miltefosine (Impavido) is now commercially available. Contact the Centers for Disease Control/Agency for Toxic Substances Disease Registry at 1-770-488-7100 or 1-800-232-4636 (main number) for guidance on treatment.

[10] A free-living ameba not previously known to be pathogenic to humans. It has been successfully treated with azithromycin, IV pentamidine, itraconazole, and flucytosine combined with surgical resection of the CNS lesion (Gelman BB, et al: *J Neuropathol Exp Neurol* 62:990, 2003).

[11] Limited data in children < 2 yr but has been used successfully for treatment of cutaneous larva migrans in children as young as 8 mo at a dose of 200 mg daily × 3 days (Black MD, et al: *Australas J Dermatol* 51:281-284, 2010). The WHO also recommends albendazole in children < 2 yr for treatment of taeniasis, strongyloidiasis, filariasis, hookworms, roundworms, pinworms, and threadworms.

[12] Limited safety data in children < 2 yr of age.

[13] Most patients have a self-limited course and recover completely. Analgesics, corticosteroids,

and careful removal of CSF at frequent intervals can relieve symptoms from increased intracranial pressure (Lo Re V III, Gluckman SJ: *Am J Med* 114:217, 2003). No anthelmintic drug is proven to be effective, and some patients have worsened with therapy (Slom TJ, et al: *N Engl J Med* 346:668, 2002). Mebendazole or albendazole and a corticosteroid appeared to shorten the course of infection (Sawanyawisuth K, Sawanyawisuth K: *Trans R Soc Trop Med Hyg* 102:990, 2008; Chotmongkol V, et al: *Am J Trop Med Hyg* 81:443, 2009).

[14] (Repiso Ortega A, et al: *Gastroenterol Hepatol* 26:341, 2003.) Successful treatment of a patient with anisakiasis with albendazole has been reported (Moore DA, et al: *Lancet* 360:54, 2002).

[15] Exchange transfusion has been used in severely ill patients and those with high (>10%) parasitemia (Hatcher JC, et al: *Clin Infect Dis* 32:1117, 2001). Clindamycin and quinine is the preferred therapy for severely ill patients. In patients who were not severely ill, combination therapy with atovaquone and azithromycin was as effective as clindamycin and quinine and may have been better tolerated (Krause PJ, et al: *N Engl J Med* 343:1454, 2000). Highly immunosuppressed patients should be treated for a minimum of 6 wk and at least 2 wk past the last positive smear (Krause PJ, et al: *Clin Infect Dis* 46:370, 2008). High doses of azithromycin (600-1,000 mg) have been used in combination with atovaquone for the treatment of immunocompromised patients (Weiss LM, et al: *N Engl J Med* 344:773, 2001). Resistance to atovaquone plus azithromycin has been reported in immunocompromised patients treated with a single subcurative course of this regimen (Wormser GP, et al: *Clin Infect Dis* 50:381, 2010). Most asymptomatic patients do not require treatment unless parasitemia persists > 3 mo (Wormser GP, et al: *Clin Infect Dis* 43:1089-1134, 2006).

[16] Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old.

[17] No drugs have been consistently demonstrated to be effective. The combination of albendazole 37 mg/kg/day PO and high-dose steroids has been used successfully (Peters JM, et al: *Pediatrics* 129:e806, 2012; Haider S: *Emerg Infect Dis* 18:347, 2012). Albendazole 25 mg/kg/day PO × 20 days started as soon as possible (up to 3 days after possible infection) might prevent clinical disease and is recommended for children with known exposure, as in the setting of ingestion of raccoon stool or contaminated soil (Murray WJ, Kazacos KR: *Clin Infect Dis* 39:1484, 2004). Mebendazole, levamisole, or ivermectin could be tried if albendazole is not available. Ocular baylisascariasis has been treated successfully using laser photocoagulation therapy to destroy the intraretinal larvae.

[18] Clinical significance of these organisms is controversial; metronidazole 750 mg tid × 10 days, iodoquinol 650 mg tid × 20 days, or trimethoprim-sulfamethoxazole 1 DS tablet bid × 7 days has been reported to be effective (Stenzel DJ, Borenam PFL: *Clin Microbiol Rev* 9:563, 1996; Ok UZ, et al: *Am J Gastroenterol* 94:3245, 1999). Metronidazole resistance may be common (Haresh K, et al: *Trop Med Int Health* 4:274, 1999). Nitazoxanide has been effective in children (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003).

[19] Nitazoxanide has not consistently been shown to be superior to placebo in HIV-infected patients (Amadi B, et al: *Lancet* 360;1375, 2002). For HIV-infected patients, potent antiretroviral therapy (ART) is the mainstay of treatment. Nitazoxanide 500-1,000 mg for 14 days, paromomycin 500 mg 4 times daily × 14-21 days, or a combination of paromomycin and azithromycin may be tried to decrease diarrhea and recalcitrant malabsorption of antimicrobial drugs, which can occur with chronic cryptosporidiosis (Pantenburg B, et al: *Expert Rev Anti Infect Ther* 7:385, 2009).

[20] Albanese G, et al: *Int J Dermatol* 40:67, 2001.

[21] HIV-infected patients may need a higher dosage and long-term maintenance (Kansouzidou A,

et al: *J Trav Med* 11:61, 2004).

[22] Norberg A, et al: *Clin Microbiol Infect* 9:65, 2003.

[23] Treatment of choice is slow extraction of worm combined with wound care (*MMWR Morbid Mortal Wkly Rep* 60:1450, 2011). Instructions for this can be found at https://www.cdc.gov/parasites/guineaworm/treatment.html . Ten days of treatment with metronidazole 250 mg tid in adults and 25 mg/kg/day in 3 doses in children is not curative, but it decreases inflammation and facilitates removal of the worm. Mebendazole 400-800 mg/day × 6 days has been reported to kill the worm directly.

[24] Because all family members are usually infected, treatment of the entire household is recommended.

[25] Antihistamines or corticosteroids may be required to decrease allergic reactions due to disintegration of microfilariae from treatment of filarial infections, especially those caused by *Loa loa.* Endosymbiotic *Wolbachia* bacteria may have a role in filarial development and host response and may represent a new target for therapy. Treatment with doxycycline 100 or 200 mg/day × 4-6 wk in lymphatic filariasis and onchocerciasis has resulted in substantial loss of *Wolbachia* with subsequent blocking of microfilariae production and absence of microfilaria when followed for 24 mo after treatment (Hoerauf A, et al: *Med Microbiol Immunol* 192:211, 2003; Hoerauf A, et al: *BMJ* 326:207, 2003).

[26] Most symptoms caused by adult worm. Single-dose combination of albendazole (400 mg) with either ivermectin (200 µg/kg) or diethylcarbamazine (6 mg/kg) is effective for reduction or suppression of *Wuchereria bancrofti* microfilaria but does not kill the adult forms (Addiss D, et al: *Cochrane Database Syst Rev* (1):CD003753, 2004).

[27] This drug is not FDA approved and not commercially available but is available under IND application through the CDC Drug Service (CDC Drug Service, Division of Scientific Resources, telephone at 1-404-639-3670.

[28] DEC is contraindicated in patients coinfected with *Oncocerca volvulus* due to risk of a life-threatening Mazzotti reaction and in patients with *Loa loa* infection and microfilaria levels ≥ 8,000 mm^3 due to risk of encephalopathy and renal failure. Some experts use a cutoff of ≥ 2,500 mm^3 .

[29] For patients with microfilaria in the blood, *Medical Letter* consultants would start with a lower dosage and scale up: day 1, 50 mg; day 2, 50 mg tid; day 3, 100 mg tid; day 4-14, 6 mg/kg in 3 doses (for *Loa loa,* day 4-14, 9 mg/kg in 3 doses). Multidose regimens have been shown to provide more rapid reduction in microfilaria than single-dose diethylcarbamazine, but microfilaria levels are similar 6-12 mo after treatment (Andrade LD, et al: *Trans R Soc Trop Med Hyg* 89:319, 1995; Simonsen PE, et al: *Am J Trop Med Hyg* 53:267, 1995). A single dose of 6 mg/kg is used in endemic areas for mass treatment (Figueredo-Silva J, et al: *Trans R Soc Trop Med Hyg* 90:192, 1996; Noroes J, et al: *Trans R Soc Trop Med Hyg* 91:78, 1997).

[30] In heavy infections with *Loa loa,* rapid killing of microfilariae can provoke an encephalopathy. Apheresis has been reported to be effective in lowering microfilarial counts in patients heavily infected with *Loa loa* (Ottesen ES: *Infect Dis Clin North Am* 7:619, 1993). Albendazole or ivermectin has also been used to reduce microfilaremia; albendazole is preferred because of its slower onset of action and lower risk for encephalopathy (Klion AD, et al: *J Infect Dis* 168:202, 1993; Kombila M, et al: *Am J Trop Med Hyg* 58:458, 1998). Albendazole may be useful for treatment of loiasis when diethylcarbamazine is ineffective or cannot be used, but repeated courses may be necessary (Klion AD, et al: *Clin Infect Dis* 29:680, 1999). Diethylcarbamazine,

300 mg once/wk, has been recommended for prevention of loiasis (Nutman TB, et al: *N Engl J Med* 319:752, 1988).

[31] Diethylcarbamazine has no effect. Ivermectin 200 µg/kg once has been effective.

[32] Doxycycline is preferred for strains that carry *Wolbachia* bacteria. Combination therapy with diethylcarbamazine and mebendazole and monotherapy with mebendazole have been used successfully in strains that do not carry *Wolbachia.* Evidence is limited, and optimal therapy is uncertain. Ivermectin and albendazole appear to be ineffective.

[33] Diethylcarbamazine is potentially curative because of activity against both adult worms and microfilariae. Ivermectin is only active against microfilariae. (*The Medical Letter:* Drugs for parasitic infections, vol 11, 2013.)

[34] Relapse occurs and can be treated with diethylcarbamazine.

[35] Annual treatment with ivermectin, 150 µg/kg, can prevent blindness from ocular onchocerciasis (Mabey D, et al: *Ophthalmology* 103:1001, 1996). Ivermectin kills only the microfilaria but not the adult worms; emerging evidence suggests doxycycline is effective in killing adult worms and sterilizing females. The recommended regimen from the CDC is doxycycline 100-200 mg PO daily for 6 wk begun 1 wk after a dose of ivermectin is given to reduce the microfilaria burden. Diethylcarbamazine and suramin were formerly used for treatment of this disease but should no longer be used owing to the availability of less toxic therapies.

[36] Limited safety data in children < 4 yr old but has been used in mass prevention campaigns with no reported adverse effects.

[37] Unlike infections with other flukes, *Fasciola hepatica* infections do not respond to praziquantel. Triclabendazole may be safe and effective, but data are limited (Graham CS, et al: *Clin Infect Dis* 33:1, 2001). In the United States, the drug is not approved by the FDA and is not yet commercially available. However, it is available to U.S.-licensed physicians through the CDC Drug Service, under a special protocol, which requires that both the CDC and FDA agree that the drug is indicated for treatment of a particular patient. Providers should contact the CDC Drug Service, Division of Scientific Resources, at 1-404-639-3670. It is available from Victoria Pharmacy, Zurich, Switzerland (www.pharmaworld.com). The drug should be given with food for better absorption. A single study has found that nitazoxanide has limited efficacy for treating fascioliasis in adults and children (Favennec L, et al: *Aliment Pharmacol Ther* 17:265, 2003).

[38] Richter J, et al: *Curr Treat Options Infect Dis* 4:313, 2002.

[39] MacLean JD, et al: *Lancet* 347:154, 1996.

[40] Triclabendazole may be effective in a dosage of 5 mg/kg once/day × 3 days or 10 mg/kg bid × 1 day (Calvopiña M, et al: *Trans R Soc Trop Med Hyg* 92:566, 1998). In the United States, it is not approved by the FDA and is not yet commercially available. However, it is available to U.S.-licensed physicians through the CDC Drug Service, under a special protocol, which requires both the CDC and FDA to agree that the drug is indicated for treatment of a particular patient. Providers should contact the CDC Drug Service, Division of Scientific Resources, at 1-404-639-3670. The drug is available from Victoria Pharmacy, Zurich, Switzerland; Phone, 41 43 344 60 60; FAX, 41 43 344 60 69; http://www.pharmaworld.com ; e-mail, info@pharmaworld.com .

[41] Albendazole 400 mg daily × 5 days alone or in combination with metronidazole may also be effective (Hall A, Nahar Q: *Trans R Soc Trop Med Hyg* 87:84, 1993; Dutta AK, et al: *Indian J Pediatr* 61:689, 1994; Cacopardo B, et al: *Clin Ter* 146:761, 1995). Combination treatment with

standard doses of metronidazole and quinacrine given for 3 wk has been effective for a small number of refractory infections (Nash TE, et al: *Clin Infect Dis* 33:22, 2001). In one study, nitazoxanide was used successfully in high doses to treat a case of *Giardia* infection resistant to metronidazole and albendazole (Abboud P, et al: *Clin Infect Dis* 32:1792, 2001).

[42] Not absorbed; may be useful for treatment of giardiasis in pregnancy.

[43] de Gorgolas M, et al: *J Travel Med* 10:358, 2003. All patients should be treated with a medication regardless of whether surgery is attempted.

[44] Eberhard ML, Busillo C: *Am J Trop Med Hyg* 61:51, 1999; Wilson ME, et al: *Clin Infect Dis* 32:1378, 2001.

[45] Consultation with physicians experienced in management of this disease is recommended. To maximize effectiveness and minimize toxicity, the choice of drug, dosage, and duration of therapy should be individualized based on the region of disease acquisition, likely infecting species, number, significance and location of lesions, and host factors such as immune status (Murray HW: *Lancet* 366:1561, 2005; Aronson N, et al: *Clin Infect Dis* 63:202, 2016). Some of the listed drugs and regimens are effective only against certain *Leishmania* species/strains and only in certain areas of the world (Sundar S, Chakravarty J: *Expert Opin Pharmacother* 14:53, 2013).

[46] Visceral infection is most commonly caused by the Old World species *Leishmania donovani* (kala-azar) and *Leishmania infantum* and the New World species *Leishmania chagasi.* Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired. Liposomal amphotericin B is the treatment of choice in the IDSA leishmaniasis guidelines (Aronson N, et al: *Clin Infect Dis* 63:202, 2016).

[47] Three lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *Leishmania infantum,* the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis (Meyerhoff A: *Clin Infect Dis* 28:42, 1999). Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) have also been used with good results but are considered investigational for this condition by the FDA.

[48] The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day on days 1-5 and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration. (Russo R, Nigro LC, Minniti S, et al: Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B [AmBisome], *J Infect* 32:133-137, 1996).

[49] For treatment of kala-azar in adults in India, oral miltefosine 100 mg/day (~205 mg/kg/day) for 3-4 wk was 97% effective after 6 mo (Jha TK, et al: *N Engl J Med* 341:1795, 1999; Sangraula H, et al: *J Assoc Physicians India* 51:686, 2003). GI adverse effects are common, and the drug is contraindicated in pregnancy. The dose of miltefosine in an open-label trial in children in India was 2.5 mg/kg/day × 28 days (Bhattacharya SK, et al: *Clin Infect Dis* 38:217, 2004). Miltefosine (Impavido) has been FDA approved for treatment of leishmaniasis due to *Leishmania donovani;* cutaneous leishmaniasis due to *L. braziliensis* , *L. guyanensis* , and *L. panamensis;* and mucosal leishmaniasis due to *L. braziliensis* since 2014 and is now commercially available.

[50] May be repeated or continued; a longer duration may be needed for some patients (Herwaldt BL: *Lancet* 354:1191, 1999).

[51] Cutaneous infection is most commonly caused by the Old World species *Leishmania major* and *Leishmania tropica* and the New World species *Leishmania mexicana, Leishmania (Viannia)*

braziliensis, and others. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[52] In a placebo-controlled trial in patients 12 yr old and older, oral miltefosine was effective for the treatment of cutaneous leishmaniasis caused by *Leishmania (Viannia) panamensis* in Colombia but not *L. (V.) braziliensis* in Guatemala at a dosage of about 2.5 mg/kg/day for 28 days. “Motion sickness,” nausea, headache, and increased creatinine were the most frequent adverse effects (Soto J, et al: *Clin Infect Dis* 38:1266, 2004). For treatment of *L. major* cutaneous lesions, a study in Saudi Arabia found that oral fluconazole, 200 mg once/day × 6 wk, appeared to speed healing (Alrajhi AA, et al: *N Engl J Med* 346:891, 2002).

[53] At this dosage, pentamidine has been effective against leishmaniasis in Colombia, where the likely organism was *L. (V.) panamensis* (Soto-Mancipe J, et al: *Clin Infect Dis* 16:417, 1993; Soto J, et al: *Am J Trop Med Hyg* 50:107, 1994); its effect against other species is not well established. Updated based on *Leishmania* practice guidelines (Aronson N, et al: *Clin Infect Dis* 63:202-264, 2016).

[54] Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread. A formulation of 15% paromomycin/12% methylbenzethonium chloride (Leshcutan) in soft white paraffin for topical use has been reported to be partially effective in some patients against cutaneous leishmaniasis due to *L. major* in Israel and against *L. mexicana* and *L. (V.) braziliensis* in Guatemala, where mucosal spread is very rare (Arana BA, et al: *Am J Trop Med Hyg* 65:466, 2001). The methylbenzethonium is irritating to the skin; lesions may worsen before they improve.

[55] Mucosal infection is most commonly due to the New World species *L. (V.) braziliensis, L. (V.) panamensis,* or *L. (V.) guyanensis.* Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired

[56] Yoon KS, et al: *Arch Dermatol* 139:994, 2003.

[57] A second application is recommended 1 wk later to kill hatching progeny. Lice are increasingly demonstrating resistance to pyrethrins and permethrin (Meinking TL, et al: *Arch Dermatol* 138:220, 2002). Ivermectin lotion 0.5% was approved by the FDA in 2012 for treatment of head lice in persons 6 mo of age and older. It is not ovicidal, but it appears to prevent nymphs from surviving. It is effective in most patients when given as a single application on dry hair without nit combing (www.cdc.gov/parasites/lice/head/treatment.html).

[58] Ivermectin is effective against adult lice but has no effect on nits (Jones KN, English JC III: *Clin Infect Dis* 36:1355, 2003).

[59] For infestation of eyelashes with *Phthirus pubis* lice, use petrolatum; TMP-SMX has also been used (Meinking TL: *Curr Probl Dermatol* 24:157, 1996). For pubic lice, treat with 5% permethrin or ivermectin as for scabies. TMP-SMX has also been effective, together with permethrin for head lice (Hipolito RB, et al: *Pediatrics* 107:E30, 2001).

[60] Chloroquine-resistant *P. falciparum* occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Haiti, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia, and Iran). For treatment of multidrug-resistant *P. falciparum* in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, artesunate plus mefloquine, or artemether plus mefloquine may be used (Luxemburger JC, et al: *Trans R Soc Trop Med Hyg* 88:213, 1994; Karbwang J, et al: *Trans R Soc Trop Med Hyg* 89:296, 1995).

[61] Uncomplicated or mild malaria may be treated with oral drugs.

[62] To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown, and use is generally not recommended. In a few small studies, outcomes were normal in women treated with the combination in the second and third trimesters (Paternak B, et al: *Arch Intern Med* 171:259, 2011; Boggild AK, et al: *Am J Trop Med Hyg* 76:208, 2007). The drug should not be given to patients with severe renal impairment (creatinine clearance < 30 mL/min). There have been isolated case reports of resistance in *P. falciparum* in Africa, but *Medical Letter* consultants do not believe there is a high risk for acquisition of Malarone-resistant disease (Schwartz E, et al: *Clin Infect Dis* 37:450, 2003; Farnert A, et al: *BMJ* 326:628, 2003; Kuhn S, et al: *Am J Trop Med Hyg* 72:407, 2005; Happi C, et al: *Malar J* 5:82, 2006).

[63] Although approved for once-daily dosing, *Medical Letter* consultants usually divide the dose into 2 doses to decrease nausea and vomiting.

[64] In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7 days.

[65] For use in pregnancy.

[66] Lell B, Kremsner PG: *Antimicrob Agents Chemother* 46:2315, 2002.

[67] At this dosage, adverse effects, including nausea, vomiting, diarrhea, dizziness, a disturbed sense of balance, toxic psychosis, and seizures can occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option, because of an increased risk for stillbirth (Nosten F, et al: *Clin Infect Dis* 28:808, 1999). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric illness. Mefloquine can be given to patients taking β blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine, quinidine, or halofantrine, and caution is required in using quinine, quinidine, or halofantrine to treat patients with malaria who have taken mefloquine for prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[68] *P. falciparum* with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[69] *P. vivax* with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia, and Peru.

[70] Primaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is most common in African, Asian, and Mediterranean peoples. Patients should be screened for G6PD deficiency before treatment. Primaquine should not be used during pregnancy.

[71] If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of

hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.

[72] Exchange transfusion has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema, or renal complications (Miller KD, et al: *N Engl J Med* 321:65, 1989).

[73] Continuous ECG, blood pressure, and glucose monitoring is recommended, especially in pregnant women and young children. For problems with quinidine availability, call the manufacturer (Eli Lilly, 1-800-545-5979) or the CDC Malaria Hotline (1-770-488-7788). Quinidine may have greater antimalarial activity than quinine. The loading dose should be decreased or omitted in those patients who have received quinine or mefloquine. If more than 48 hr of parenteral treatment is required, the quinine or quinidine dose should be reduced by 30–50%.

[74] Oral artesunate is not available in the United States; the IV formulation is available through the CDC Malaria Branch under an investigational new drug (IND) for patients with severe disease who do not have timely access or cannot tolerate, or fail to respond to, IV quinidine (*Med Lett Drugs Ther* 50:37, 2008). To avoid the development of resistance, adults treated with artesunate must also receive oral treatment doses of either atovaquone/proguanil, doxycycline, clindamycin, or mefloquine; children should take either atovaquone/proguanil, clindamycin, or mefloquine (Nosten F, et al: *Lancet* 356:297, 2000; van Vugt M: *Clin Infect Dis* 35:1498, 2002; Smithuis F, et al: *Trans R Soc Trop Med Hyg* 98:182, 2004). If artesunate is given IV, oral medication should be started when the patient is able to tolerate it (SEAQUAMAT group, *Lancet* 366:717, 2005; Duffy PE, Sibley CH: *Lancet* 366:1908, 2005). Reduced susceptibility to artesunate characterized by slow parasitic clearance has been reported in Cambodia (Rogers WO, et al: *Malar J* 8:10, 2009; Dundorp AM, et al: *N Engl J Med* 361:455, 2009).

[75] No drug regimen guarantees protection against malaria. If fever develops within a year (particularly within the first 2 mo) after travel to malarious areas, travelers should be advised to seek medical attention. Insect repellents, insecticide-impregnated bed nets, and proper clothing are important adjuncts for malaria prophylaxis (*Med Lett* 45:41, 2003). Malaria in pregnancy is particularly serious for both mother and fetus; therefore, prophylaxis is indicated if exposure cannot be avoided.

[76] In pregnancy, chloroquine prophylaxis has been used extensively and safely.

[77] For prevention of attack after departure from areas where *P. vivax* and *P. ovale* are endemic, which includes almost all areas where malaria is found (except Haiti), some experts prescribe in addition primaquine phosphate 30 mg base/day or, for children, 0.6 mg base/kg/day during the last 2 wk of prophylaxis. Others prefer to avoid the toxicity of primaquine and rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 69 .

[78] Beginning 1-2 wk before travel and continuing weekly for the duration of stay and for 4 wk after leaving malarious zone. Most adverse events occur within 3 doses. Some *Medical Letter* consultants favor starting mefloquine 3 wk prior to travel and monitoring the patient for adverse events; this allows time to change to an alternative regimen if mefloquine is not tolerated. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz of water. For pediatric doses less than 1/2 tablet, it is advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There are no data for use in children weighing < 5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.

[79] Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after

leaving. In one study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (Overbosch D, et al: *Clin Infect Dis* 33:1015, 2001).

[80] Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving malarious zone. In one study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (Overbosch D, et al: *Clin Infect Dis* 33:1015, 2001). The protective efficacy of Malarone against *P. vivax* is variable, ranging from 84% in Indonesian New Guinea (Ling J, et al: *Clin Infect Dis* 35:825, 2002) to 100% in Colombia (Soto J, et al: *Am J Trop Med Hyg* 75:430, 2006). Some *Medical Letter* consultants prefer alternate drugs if traveling to areas where *P. vivax* predominates.

[81] Mefloquine has not been approved for use during pregnancy. However, it has been reported to be safe for prophylactic use during the second or third trimester of pregnancy and possibly during early pregnancy, as well. Mefloquine is not recommended for patients with cardiac conduction abnormalities, and patients with a history of depression, seizures, psychosis, or psychiatric disorders should avoid mefloquine prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders; in these areas, atovaquone/proguanil or doxycycline should be used for prophylaxis.

[82] Beginning 1-2 days before travel and continuing for the duration of stay and for 4 wk after leaving. Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old. Doxycycline can cause GI disturbances, vaginal moniliasis, and photosensitivity reactions.

[83] Studies have shown that daily primaquine beginning 1 day before departure and continued until 3-7 days after leaving the malaria area provides effective prophylaxis against chloroquine-resistant *P. falciparum* (Baird JK, et al: *Clin Infect Dis* 37:1659, 2003). Some studies have shown less efficacy against *P. vivax.* Nausea and abdominal pain can be diminished by taking with food.

[84] A traveler can be given a course of atovaquone/proguanil, mefloquine, or quinine plus doxycycline for presumptive self-treatment of febrile illness. The drug given for self-treatment should be different from that used for prophylaxis. This approach should be used only in very rare circumstances when a traveler cannot promptly get to medical care.

[85] For HIV-infected patients, continue until resolution of ocular symptoms and until CD4 count > 200 cells/µL for > 6 mo after initiation of antiretroviral therapy.

[86] Ocular lesions caused by *E. hellem* in HIV-infected patients have responded to fumagillin eyedrops prepared from Fumidil-B (bicyclohexyl ammonium fumagillin) used to control a microsporidial disease of honey bees (Diesenhouse MC: *Am J Ophthalmol* 115:293, 1993), available from Leiter's Park Avenue Pharmacy (San Jose, CA; 1-800-292-6773; www.leiterrx.com). For lesions caused by *V. corneae,* topical therapy is generally not effective and keratoplasty may be required (Davis RM, et al: *Ophthalmology* 97:953, 1990).

[87] Oral fumagillin (Sanofi Recherche, Gentilly, France) has been effective in treating *E. bieneusi* (Molina J-M, et al: *N Engl J Med* 346:1963, 2002), but it has been associated with thrombocytopenia. HAART may lead to microbiologic and clinical response in HIV-infected patients with microsporidial diarrhea (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004). Octreotide (Sandostatin) has provided symptomatic relief in some patients with large-volume diarrhea.

[88] Molina J-M, et al: *J Infect Dis* 171:245, 1995. There is no established treatment for

Pleistophora. For disseminated disease caused by *Trachipleistophora* or *Brachiola,* itraconazole 400 mg PO once/day plus albendazole may also be tried (Coyle CM, et al: *N Engl J Med* 351:42, 2004).

[89] Albendazole or pyrantel pamoate may be effective (Ziem JB, et al: *Ann Trop Med Parasitol* 98:385, 2004).

[90] *Pneumocystis* has been reclassified as a fungus. In severe disease with room air $PO_2 \leq 70$ mm Hg or $A\text{-}aO_2$ gradient ≥ 35 mm Hg, prednisone should also be used (Gagnon S, et al: *N Engl J Med* 323:1444, 1990; Caumes E, et al: *Clin Infect Dis* 18:319, 1994).

[91] Primary/secondary prophylaxis in patients with HIV can be discontinued after the CD4 count increases to $> 200 \times 10^6$ /L for longer than 3 mo.

[92] An alternative trimethoprim-sulfamethoxazole regimen is 1 DS tablet 3×/wk. Weekly therapy with sulfadoxine 500 mg/pyrimethamine 25 mg/leucovorin 25 mg was effective for *Pneumocystis carinii* pneumonia (PCP) prophylaxis in liver transplant patients (Torre-Cisneros J, et al: *Clin Infect Dis* 29:771, 1999).

[93] Plus leucovorin 25 mg with each dose of pyrimethamine.

[94] In some cases, treatment may need to be repeated in 10-14 days (Currie BJ, McCarthy JS: *N Engl J Med* 362:717, 2010). A second ivermectin dose taken 2 wk later increased the cure rate to 95%, which is equivalent to that of 5% permethrin (Usha V, et al: *J Am Acad Dermatol* 42:236, 2000). Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P: *Curr Opin Infect Dis* 15:123, 2004).

[95] Lindane (γ-benzene hexachloride; Kwell) should be reserved as a second-line agent. The FDA has recommended it should not be used for immunocompromised patients, young children, the elderly, and patients who weigh < 50 kg.

[96] Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P: *Curr Opin Infect Dis* 15:123, 2004). The safety of oral ivermectin in pregnancy and young children has not been established.

[97] Oxamniquine has been effective in some areas in which praziquantel is less effective (Stelma FF, et al: *J Infect Dis* 176:304, 1997). Oxamniquine is contraindicated in pregnancy.

[98] In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/day × 2 days. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (Shekhar KC: *Drugs* 42:379, 1991).

[99] In immunocompromised patients or disseminated disease, it may be necessary to prolong or repeat therapy or to use other agents. Veterinary parenteral and enema formulations of ivermectin have been used in severely ill patients unable to take oral medications (Chiodini PL, et al: *Lancet* 355:43, 2000; Orem J, et al: *Clin Infect Dis* 37:152, 2003; Tarr PE: *Am J Trop Med Hyg* 68:453, 2003).

[100] Albendazole must be taken with food; a fatty meal increases oral bioavailability.

[101] Niclosamide must be thoroughly chewed or crushed and swallowed with a small amount of water. Nitazoxanide may be an alternative (Ortiz JJ, et al: *Trans R Soc Trop Med Hyg* 96:193, 2002; Chero JC, et al: *Trans R Soc Trop Med Hyg* 101:203, 2007; Diaz E, et al: *Am J Trop Med*

Hyg 68:384, 2003).

[102] Optimal treatment depends on multiple factors, including size, location, and number of cysts and presence of complications. In some patients, medical therapy alone is preferred, but some patients may benefit from surgical resection or percutaneous drainage of cysts. Praziquantel is useful preoperatively or in case of spillage of cyst contents during surgery. Percutaneous aspiration-injection-reaspiration (PAIR) with ultrasound guidance plus albendazole therapy has been effective for management of hepatic hydatid cyst disease (Smego RA Jr, et al: *Clin Infect Dis* 37:1073, 2003).

[103] Surgical excision is the only reliable means of cure. Reports have suggested that in nonresectable cases, the use of albendazole or mebendazole can stabilize and sometimes cure infection (Craig P: *Curr Opin Infect Dis* 16:437, 2003). Medical treatment is prolonged up to 2 yr or more.

[104] Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with antiseizure medication. Treatment of parenchymal cysticerci with albendazole or praziquantel is controversial (Maguire JM: *N Engl J Med* 350:215, 2004). Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids (6 mg dexamethasone or 40-60 mg prednisone daily) and an antiseizure medication (Garcia HH, et al: *N Engl J Med* 350:249, 2004). Some recent studies have shown improved outcomes with combination albendazole and praziquantel (Garcia HH, et al: *Lancet Infect Dis* 14:687, 2014). Patients with subarachnoid cysts or giant cysts in the fissures should be treated for at least 30 days (Proaño JV, et al: *N Engl J Med* 345:879, 2001). Surgical intervention or CSF diversion is indicated for obstructive hydrocephalus; prednisone 40 mg/day may be given with surgery. Arachnoiditis, vasculitis, or cerebral edema is treated with prednisone 60 mg/day or dexamethasone 4-6 mg/day together with albendazole or praziquantel (White Jr AC: *Annu Rev Med* 51:187, 2000). Any cysticercocidal drug may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are used. An ophthalmic exam should always precede treatment to rule out intraocular cysts.

[105] In ocular toxoplasmosis with macular involvement, corticosteroids are recommended in addition to antiparasitic therapy for an antiinflammatory effect.

[106] To treat CNS toxoplasmosis in HIV-infected patients, some clinicians have used pyrimethamine 50-100 mg/day (after a loading dose of 200 mg) with sulfadiazine and, when sulfonamide sensitivity developed, have given clindamycin 1.8-2.4 g/day in divided doses instead of the sulfonamide. Atovaquone plus pyrimethamine appears to be an effective alternative in sulfa-intolerant patients (Chirgwin K, et al: *Clin Infect Dis* 34:1243, 2002). Treatment is followed by chronic suppression with lower-dosage regimens of the same drugs. For primary prophylaxis in HIV patients with $< 100 \times 10^6$ /L CD4 cells, either trimethoprim-sulfamethoxazole, pyrimethamine with dapsone, or atovaquone with or without pyrimethamine can be used. Primary or secondary prophylaxis may be discontinued when the CD4 count increases to $> 200 \times 10^6$ /L for more than 3 mo (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004).

[107] Women who develop toxoplasmosis during the first trimester of pregnancy can be treated with spiramycin (3-4 g/day). After the first trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started (Montoya JG, Liesenfeld O: *Lancet* 363:1965,

2004). Pyrimethamine is a potential teratogen and should be used only after the first trimester.

[108] Plus leucovorin 10-25 mg with each dose of pyrimethamine.

[109] Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for about 1 yr (Remington JS, Klein JO, editors: *Infectious Disease of the Fetus and Newborn Infant,* ed 5, Philadelphia, 2001, WB Saunders, p. 290).

[110] Sexual partners should be treated simultaneously. Metronidazole-resistant strains have been reported and can be treated with higher doses of metronidazole (2-4 g/day × 7-14 days) or with tinidazole (Hager WD: *Sex Transm Dis* 31:343, 2004).

[111] Barrett MP, et al: *Lancet* 362:1469, 2003.

[112] The addition of γ-interferon to nifurtimox for 20 days in experimental animals and in a limited number of patients appears to shorten the acute phase of Chagas disease (McCabe RE, et al: *J Infect Dis* 163:912, 1991).

[113] For treatment of *T. b. gambiense,* pentamidine and suramin have equal efficacy but pentamidine is better tolerated.

[114] Eflornithine is highly effective in *T. b. gambiense* but not against *T. b. rhodesiense* infections. It is available in limited supply only from the WHO and the CDC. Eflornithine dose may be reduced to 400 mg/kg IV in 2 doses for 7 days when used in conjunction with nifurtimox at a dose of 5 mg/kg PO tid × 10 days (Priotto G, et al: *Lancet* 374:56, 2009).

[115] In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy (Pepin J, et al: *Trans R Soc Trop Med Hyg* 89:92, 1995). Up to 20% of patients with *T. b. gambiense* fail to respond to melarsoprol (Barrett MP: *Lancet* 353:1113, 1999). Consultation with experts at the CDC is recommended.

[116] Optimum duration of therapy is not known; some consultants would treat for 20 days. For severe symptoms or eye involvement, corticosteroids can be used in addition.

CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; DS, double strength; ECG, electrocardiography; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HAART, highly active antiretroviral therapy; SMX, sulfamethoxazole; TMP, trimethoprim; WHO, World Health Organization.

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Selected Antiparasitic Drugs for Protozoans

Nitazoxanide (Alinia)

Nitazoxanide is a nitrothiazole benzamide, initially developed as a veterinary anthelmintic. Nitazoxanide inhibits pyruvate-ferredoxin oxidoreductase, which is an enzyme necessary for anaerobic energy metabolism. In humans, nitazoxanide is effective against many **protozoans** and **helminths.** Nitazoxanide is approved for the treatment of diarrhea caused by *Cryptosporidium parvum* and *Giardia intestinalis* in patients 1 yr of age and older.

Nitazoxanide is available as a tablet and an oral suspension (100 mg/5 mL), which has a pink color and strawberry flavor. The bioavailability of the suspension is ~ 70% compared with the tablet. The drug is well absorbed from the gastrointestinal tract but should be taken with food due to approximately two-fold higher absorption. One third is excreted in urine, and two thirds is excreted in feces as the active metabolite, tizoxanide. Although in vitro metabolism studies have not demonstrated cytochrome P450 enzyme effects, no pharmacokinetic studies have been performed yet in patients with compromised renal or hepatic function. In addition, no studies have been performed in pregnant or lactating women. Common adverse effects include abdominal pain, diarrhea, nausea, and urine discoloration. Rare side effects include anorexia, flatulence, increased appetite, fever, pruritus, and dizziness. Intriguingly, nitazoxanide has in vitro activity against multiple other pathogens, including influenza virus, rotavirus, and hepatitis C virus, although the clinical use of the agent against these viruses remains investigational.

Tinidazole (Tindamax)

Tinidazole is a synthetic nitroimidazole with a chemical structure similar to metronidazole. It is approved by the Food and Drug Administration (FDA) for patients 3 yr of age and older and for treatment of trichomoniasis, giardiasis, and amebiasis. In the treatment of giardiasis, it has the advantages of very few side effects and only requiring a single dose. It is available as a tablet, which can be crushed and administered with food. Its mechanism of action against *Trichomonas* may be secondary to the generation of free nitro radicals by the **protozoan.** The mechanism of action against *Giardia lamblia* and *Entamoeba histolytica* is unknown. Like metronidazole, it can cause a disulfiram-like reaction if combined with alcohol. After oral administration, tinidazole is rapidly and completely absorbed and is distributed into almost all tissues and body fluids; it can cross the blood–brain barrier and placental barrier. It is excreted via urine and feces. Hemodialysis increases clearance of the drug. No studies have been performed for patients undergoing peritoneal dialysis or for patients with compromised hepatic function. Tinidazole carries a pregnancy category C classification and can be detected in breast milk. Breastfeeding should be interrupted during treatment and for 3 days after treatment.

Atovaquone/Proguanil (Malarone)

Atovaquone is a hydroxynaphthoquinone and has been used in the past predominantly against *Pneumocystis* pneumonia in AIDS patients. Its mechanism of action is via disruption of the mitochondria membrane potential through interaction with cytochrome B. However, atovaquone can also effectively inhibit liver stages of all *Plasmodium* species, and in 2000 the FDA approved atovaquone/proguanil for the prevention and treatment of acute, uncomplicated *Plasmodium falciparum* malaria in adults and children ≥ 11 kg. Atovaquone alone and in combination with proguanil is the only drug to completely inhibit the liver stage, which provides the advantage of only needing to use the drug for 7 days after departing a malaria-endemic area (compared with several weeks).

Proguanil inhibits the parasite dihydrofolate reductase enzyme by the active form, cycloguanil. When used alone, it has poor efficacy for prophylaxis, but when administered with atovaquone, it acts in synergy on the cytochrome B enzyme in *Plasmodia* mitochondria, though the exact mechanism of synergy is unknown.

Two double-blind, randomized clinical trials assessing malaria prophylaxis demonstrated that atovaquone/proguanil was at least comparable to (and perhaps better than) chloroquine plus proguanil, and that atovaquone/proguanil was comparable to mefloquine. Atovaquone/proguanil was better tolerated than chloroquine plus proguanil and mefloquine. Atovaquone/proguanil treatment of acute uncomplicated *P. falciparum* infection has demonstrated higher or comparable cure rates when compared with other *P. falciparum* treatment drugs. Compared with other antimalarial therapies, atovaquone/proguanil has the highest cost.

Artemisinin Derivatives (Artemether, Artesunate) and Combination Therapies (Artemether/Lumefantrine or Coartem)

Artemisinin is a sesquiterpene lactone isolated from the weed *Artemisia annua*. It was developed in China, where it is known as qinghaosu. Artemisinin and its derivatives act very rapidly against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant *P. falciparum.* Artemisinins are also rapidly eliminated. Resistance to artemisinins has been documented in Cambodia, Laos, Myanmar, Thailand, and Vietnam. Coartem is the first artemisinin-containing drug approved for use by the FDA for patients ≥ 5 kg. It is a fixed-dose combination of two novel antimalarials, artemether (20 mg) and lumefantrine (120 mg). It is a highly effective 3-day malaria treatment, with cure rates of > 96%, even in areas of multidrug resistance. Artesunate is available from the CDC through an IND protocol as an intravenous (IV) treatment for severe malaria.

Selected Antiparasitic Drugs for Helminths and Ectoparasites

Albendazole (Albenza)

Albendazole is a benzimidazole carbamate structurally related to mebendazole and has similar anthelmintic activity. Its absorption from the gastrointestinal tract is poor but improved with a concomitant high-fat meal. Albendazole sulfoxide, the principal metabolite with anthelmintic activity, has a plasma half-life of 8.5 hr. It is widely distributed in the body, including the bile and cerebrospinal fluid. It is eliminated in bile. Albendazole is FDA approved for treatment of two cestode (tapeworm) infections: neurocysticercosis and hydatid diseases *(Echinococcus granulosus).* It is used off-label for numerous other **helminth** infections, including cutaneous larva migrans *(Ancylostoma caninum* and *Ancylostoma braziliense),* ascariasis *(Ascaris lumbricoides),* Chinese liver fluke *(Clonorchis sinensis),* pinworm *(Enterobius vermicularis),* lymphatic filariasis *(Wuchereria bancrofti, Brugia malayi, Brugia timori),* gnathostomiasis (*Gnathostoma* spp.), hookworms *(Ancylostoma duodenale* and *Necator americanus),* microsporidiosis, and visceral larva migrans *(Toxocara canis* and *Toxocara cati).* Albendazole is generally well tolerated. Common adverse effects include headache, nausea, vomiting, and abdominal pain. Serious adverse effects include elevated liver enzymes and leukopenia, which have occurred in a few patients with treatment of hydatid disease. Rare adverse effects include acute renal failure, pancytopenia, granulocytopenia, and thrombocytopenia. Despite the fact that albendazole and other antiparasitic drugs, including mebendazole, praziquantel, and pyrimethamine, have been in use for decades, the number of manufacturers is small and costs have risen in recent years.

Ivermectin (Stromectol, Mectizan)

Ivermectin is a semisynthetic derivative of one of the avermectins, which is a group of macrocyclic lactones produced by *Streptomyces avermitilis.* After oral administration, ivermectin has peak plasma concentrations after approximately 4 hr and a plasma elimination half-life of approximately 12 hr. It is excreted as metabolites over a 2-wk period via feces. It is FDA approved for treatment of two nematode (roundworm) infections: onchocerciasis and intestinal strongyloidiasis. It may have some effect in treating a broad range of other **helminths** and **ectoparasites,** including cutaneous larva migrans *(Ancylostoma braziliense),* ascariasis *(Ascaris lumbricoides),* loiasis, pinworm *(Enterobius vermicularis),* whipworm *(Trichuris trichiura),* gnathostomiasis *(Gnathostoma spinigerum), Mansonella* infections, lice *(Pediculus humanus* and *Phthirus pubis),* mites (*Demodex* spp.), and scabies. Combination therapies of ivermectin with albendazole or diethylcarbamazine are being used to treat lymphatic filariasis. Combination therapy with albendazole and the off-label use of veterinary injectable formulations have been used to treat complicated *Strongyloides* infections, including disseminated disease and hyperinfection syndrome. Common adverse events include dizziness, headache, pruritus, and gastrointestinal effects. Serious adverse events include **Mazzotti reactions** in patients with onchocerciasis, including arthralgia, synovitis, enlarged lymph nodes, rash, and fever secondary to microfilaria death. A topical formulation is available for treatment of head lice, which are increasingly becoming very resistant to over-the-counter medications such as permethrins.

Praziquantel (Biltricide)

Praziquantel achieves its antiparasitic activity via the pyrazino isoquinoline ring system and was originally synthesized as a potential tranquilizer. After oral administration, praziquantel is rapidly absorbed, with peak levels in 1-2 hr and a plasma half-life of about 1-3 hr. Elimination via the urine and feces is > 80% complete after 24 hr. Praziquantel is metabolized in the liver by the microsomal cytochrome P450 (especially 2B1 and 3A). Bioavailability of praziquantel is increased with concomitant administration of agents that inhibit cytochrome

P450. Praziquantel is FDA approved for treatment of several species of trematodes (flatworms) including the Chinese liver fluke *(Clonorchis sinensis),* Southeast Asian liver fluke *(Opisthorchis viverrini),* and schistosomiasis. It is used off-label for treatment of additional trematode pathogens, including the North American liver fluke *(Metorchis conjunctus), Nanophyetus salmincola,* intestinal flukes *(Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai),* and lung flukes *(Paragonimus westermani , Paragonimus kellicotti).* It is also used off-label for multiple cestode (tapeworm) infections. Adverse effects can be seen in 30–60% of patients, although most are mild and disappear within 24 hr. Common adverse effects include headache, abdominal pain, dizziness, and malaise. Serious but rare adverse effects include arrhythmias, heart block, and convulsions.

SECTION 15

Protozoan Diseases

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CHAPTER 306

Primary Amebic Meningoencephalitis

Matthew D. Eberly

Naegleria, Acanthamoeba, Balamuthia, and *Sappinia* are small, free-living amebae that cause human amebic meningoencephalitis, which has two distinct clinical presentations. The more common is an acute, fulminant, and usually fatal **primary amebic meningoencephalitis** (PAM) caused by *Naegleria fowleri* that occurs in previously healthy children and young adults. **Granulomatous amebic meningoencephalitis,** which is caused by *Acanthamoeba, Balamuthia,* and *Sappinia,* is a more indolent infection that typically occurs in immunocompromised hosts and may also present with a disseminated form of the disease.

Etiology

Naegleria is an ameboflagellate that can exist as cysts, trophozoites, and transient flagellate forms. Temperature and environmental nutrient and ion concentrations are the major factors that determine the stage of the ameba. Trophozoites are the only stages that are invasive, although cysts are potentially infective, because they can convert to the vegetative form very quickly under the proper environmental stimuli. Although there are some 30 species of *Naegleria,* only *Naegleria fowleri* has been shown to be pathogenic for humans.

Acanthamoeba exists in cyst and motile trophozoite forms; only the trophozoite form is invasive. Cases of *Acanthamoeba* **keratitis** usually follow incidents of trivial corneal trauma followed by flushing with contaminated tap water. Infections can also occur among contact lens wearers who come into contact with contaminated water during swimming or use contact lenses cleaned or stored in contaminated tap water. Granulomatous amebic encephalitis from *Acanthamoeba* occurs worldwide and is associated with an immunocompromising condition such as HIV infection, diabetes mellitus, chronic liver disease, renal failure, immunosuppressive therapy, or radiation therapy.

Balamuthia mandrillaris has been implicated as an etiology of granulomatous amebic encephalitis. Although the clinical presentation is similar to infection with *Acanthamoeba,* most patients are not immunocompromised.

Other free-living amebae can also cause infection, as illustrated by a case report of *Sappinia pedata* granulomatous encephalitis.

Epidemiology

The free-living amebae have a worldwide distribution. *Naegleria* species have been isolated from a variety of freshwater sources, including ponds and lakes, domestic water supplies, hot springs and spas, thermal discharge of power plants, groundwater, and, occasionally, from the nasal passages of healthy children. *Acanthamoeba* species have been isolated from soil, mushrooms, vegetables, brackish water, and seawater, as well as most of the freshwater sources for *Naegleria.* It can also be found in tap water, because chlorination does not kill *Acanthamoeba. Balamuthia* is present in soil and may be transmitted by inhalation or contamination of preexisting skin lesions.

Naegleria meningoencephalitis has been reported from every continent except Antarctica. Most of the cases occur during the summer months in previously healthy individuals who have a history of swimming in or contact with freshwater lakes and rivers before their illness. Between 1962 and 2017, 143 cases of primary amebic meningoencephalitis (PAM) were reported in the United States. Most of the reports have come from the southern and southwestern states, particularly Florida and Texas, but infections have occurred in Kansas, Indiana, and even Minnesota. Of note, two cases from Louisiana in 2011 were linked to sinus irrigation with neti pots, which contained contaminated tap water. In 2013, a boy also from Louisiana developed PAM from an exposure to a lawn water slide, which derived its tap water from a treated public drinking water system. In 2015, a 21 yr old female developed *N. fowleri* meningoencephalitis possibly from a swimming pool supplied by an overland water pipe.

Pathogenesis

The free-living amebae enter the nasal cavity by inhalation or aspiration of dust or water contaminated with trophozoites or cysts. *Naegleria* gains access to the central nervous system through the olfactory epithelium and migrates via the olfactory nerve to the olfactory bulbs located in the subarachnoid space and bathed by the cerebrospinal fluid (CSF). This space is richly vascularized and is the route of spread to other areas of the central nervous system. Grossly, there is widespread cerebral edema and hyperemia of the meninges. The olfactory bulbs are necrotic, hemorrhagic, and surrounded by a purulent exudate. Microscopically, the gray matter is the most severely affected, with severe involvement in all cases. Fibrinopurulent exudate may be found throughout the cerebral hemispheres, brainstem, cerebellum, and upper portions of the spinal cord. Pockets of trophozoites may be seen in necrotic neural tissue, usually in the perivascular spaces of arteries and arterioles.

The route of invasion and penetration in cases of granulomatous amebic meningoencephalitis caused by *Acanthamoeba* and *Balamuthia* may be by direct spread through olfactory epithelium or hematogenous spread from a primary focus in the skin or lungs. Pathologic examination reveals granulomatous encephalitis, with multinucleated giant cells mainly in the posterior fossa structures, basal ganglia, bases of the cerebral hemispheres, and cerebellum. Both trophozoites and cysts may be found in the central nervous system lesions, primarily located in the perivascular spaces and invading blood vessel walls. The olfactory bulbs and spinal cord are usually spared. The single case of *Sappinia* encephalitis followed a sinus infection, and evaluation revealed a solitary 2 cm temporal lobe mass with mild ring enhancement.

Clinical Manifestations

The incubation of ***Naegleria* infection** may be as short as 2 days or as long as 15 days. Symptoms have an acute onset and progress rapidly. Infection is characterized by a sudden onset of severe headache, fever, pharyngitis, nasal congestion or discharge, and nausea and vomiting, followed by altered mental status, nuchal rigidity, photophobia, confusion, somnolence, seizures, and ultimately coma. Most cases end in death within 3-10 days after onset of symptoms.

Granulomatous amebic meningoencephalitis may occur weeks to months after the initial infection. The presenting signs and symptoms are often those of single or multiple central nervous system space-occupying lesions and include hemiparesis, ataxia, personality changes, seizures, and drowsiness. Altered mental status is often a prominent symptom. Headache and fever occur only sporadically, but stiff neck is seen in a majority of cases. Cranial nerve palsies, especially of cranial nerves III and VI, may be present. There is also one report of acute hydrocephalus and fever with *Balamuthia*. Granulomatous amebic meningoencephalitis is usually fatal after 4-6 wk of illness. Results of neuroimaging studies of the brain usually demonstrate multiple low-density lesions resembling infarcts or enhancing lesions of granulomas (Fig. 306.1).

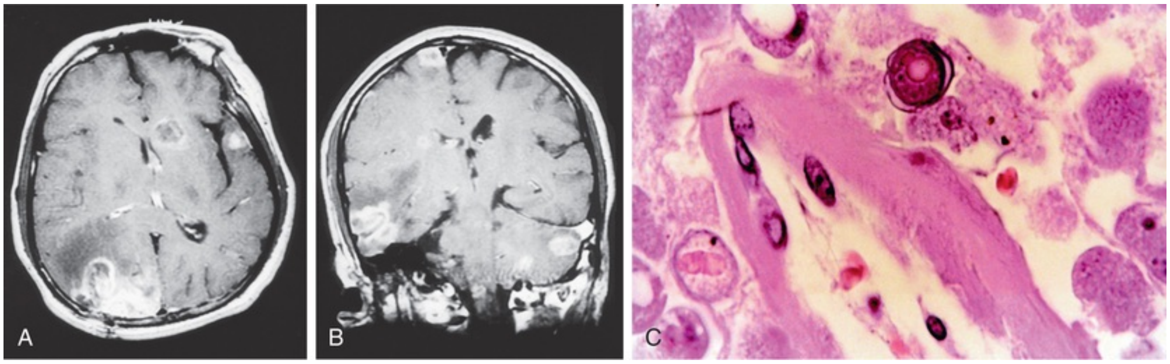

FIG. 306.1 **A** and **B,** MRIs of the brain of a patient with *Balamuthia mandrillaris* granulomatous amebic encephalitis. Multiple enhancing lesions are seen in the right hemisphere, left cerebellum, midbrain, and brainstem. **C,** Photomicrograph of the brain lesion from the same patient showing perivascular amebic trophozoites. A round amebic cyst with a characteristic double wall is seen in the top center (hematoxylin-and-eosin, original magnification ×100). (From Deol I, Robledo L, Meza A, et al: Encephalitis due to a free-living amoeba [Balamuthia mandrillaris]: case report with literature review, Surg Neurol 53:611-616, 2000.)

Diagnosis

The CSF in *Naegleria* infection may mimic that of herpes simplex encephalitis early in the disease and that of acute bacterial meningitis later in the disease, with a neutrophilic pleocytosis, elevated protein level, and hypoglycorrhachia. *Motile amebae may be visualized on a wet mount of freshly drawn CSF using Wright or Giemsa stains*, but they are often mistaken for lymphocytes or macrophages. Because *Naegleria* are the only amebae that differentiate into the flagellate state in a hypotonic environment, placing a drop of fresh CSF in 1 mL of distilled water and watching for the development of swimming flagellates after 1-2 hr can confirm the diagnosis of *Naegleria. Naegleria* can also be grown on a nonnutrient agar plate coated with *Escherichia coli,* on which they feed.

The diagnosis of granulomatous amebic meningoencephalitis relies on the isolation or histologic identification of *Acanthamoeba* trophozoites or cysts from brain tissue specimens. The CSF findings of granulomatous meningoencephalitis reveal lymphocytic pleocytosis, moderately elevated protein, and low glucose concentrations. However, motile trophozoites of *Acanthamoeba* are more difficult to isolate than *Naegleria,* and the CSF is typically sterile. *Acanthamoeba* may be cultured from the same agar used for growing *Naegleria,* but *Balamuthia* must be grown on mammalian cell cultures. Pediatric cases of *Balamuthia* meningoencephalitis have been diagnosed antemortem by brain biopsy as well as postmortem. Immunofluorescence staining of brain tissue can differentiate *Acanthamoeba* and *Balamuthia.* An indirect fluorescent antibody test from the serum is also available for *Balamuthia.*

Treatment

Naegleria infection is nearly always fatal, but early recognition and treatment are crucial to survival. Until 2013, there had been only two known survivors in North America, with treatment regimens of amphotericin B, either alone or in combination with other agents such as rifampin, chloramphenicol, fluconazole, ketoconazole, and dexamethasone. In 2013, however, the U.S. Centers for Disease Control and Prevention (CDC) made available the antileishmanial drug **miltefosine** for the treatment of PAM. That summer, two children who contracted *Naegleria* both survived; both patients received oral miltefosine as part of their treatment, and one underwent external ventricular drain placement and therapeutic hypothermia. The recommended drug treatment for primary amebic meningoencephalitis by the CDC includes intravenous and intrathecal amphotericin B, oral miltefosine, along with azithromycin, fluconazole, rifampin, and dexamethasone. Early identification, early initiation of combination therapy, and aggressive management of increased intracranial pressure remain key elements for a successful outcome. For suspected cases, clinicians should contact the CDC Emergency Operations Center at (770) 488-7100 for assistance.

The optimal therapy for granulomatous amebic meningoencephalitis is uncertain. However, miltefosine has likewise been used to successfully treat patients with *Balamuthia* and disseminated *Acanthamoeba* infections. Strains of

Acanthamoeba isolated from fatal cases are usually susceptible in vitro to pentamidine, ketoconazole, and flucytosine, and less so to amphotericin B. One patient was successfully treated with sulfadiazine and fluconazole, and another was successfully treated with intravenous pentamidine followed by oral itraconazole. *Acanthamoeba* keratitis responds to long courses of topical propamidine–polymyxin B sulfate or topical polyhexamethylene biguanide or chlorhexidine gluconate, and antifungal azoles plus topical steroids. Limited success has been demonstrated in *Balamuthia* infection with systemic azole therapy combined with flucytosine. More recently, the combination of flucytosine, pentamidine, fluconazole, sulfadiazine, azithromycin, and phenothiazines resulted in the survival of two patients with *Balamuthia* meningoencephalitis, although both were left with mild neuromotor and cognitive impairment. Corticosteroids prior to initiating effective therapy appear to have a detrimental effect, contributing to rapid progression of disease.

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CHAPTER 307

Amebiasis

Edsel Maurice T. Salvana, Robert A. Salata

Entamoeba species infect or colonize up to 10% of the world's population, particularly in resource-limited settings. In most infected individuals, *Entamoeba histolytica* or a related species parasitizes the lumen of the gastrointestinal tract and causes few symptoms or sequelae. Although *E. histolytica* is the only invasive species, other *Entamoeba* species have been implicated in human disease, and molecular epidemiology is helping to detail the role that these diverse protozoans play in human health. Invasive *E. histolytica* infection can lead to **amebic colitis, amebic liver abscess,** and, less commonly, abscesses in other extraintestinal sites.

Etiology

Four morphologically identical but genetically distinct species of *Entamoeba* are known to infect humans. *Entamoeba dispar,* the most prevalent species, does not cause symptomatic disease. *Entamoeba moshkovskii,* previously thought to be nonpathogenic, has increasingly been shown to cause diarrhea in infants and children, and asymptomatic infection with *E. moshkovskii* may be as common as *E. dispar* infection in some communities. *E. histolytica,* the main pathogenic species, causes a spectrum of disease and can become invasive in 4–10% of infected patients. Patients previously described as asymptomatic carriers of *E. histolytica* based on microscopy findings were likely harboring *E. dispar* or *E. moshkovskii.* A fourth species, *E. bangladeshi,* was discovered in 2012, but more studies are needed to ascertain its human pathogenicity. Four other species of nonpathogenic *Entamoeba* are known to colonize the human gastrointestinal tract: *E. coli, E. hartmanni, E. gingivalis,* and *E. polecki.*

Infection is usually acquired through the ingestion of parasite cysts, which measure 10-18 μm in diameter and contain four nuclei. Cysts are resistant to harsh environmental conditions, including chlorine concentrations commonly used in water purification, but can be killed by heating to 55°C (131°F). Cysts are resistant to gastric acidity and digestive enzymes and germinate in the small intestine to form trophozoites. These large, actively motile organisms colonize the lumen of the large intestine and may invade the mucosal lining. Some eventually transform to cysts and are passed out in the stool to infect other hosts anew.

Epidemiology

Prevalence of infection with *E. histolytica* varies greatly by region and socioeconomic status. Early prevalence studies did not distinguish between *E. histolytica* and *E. dispar,* but more recent estimates show that infection with *E. histolytica* causes 100 million cases of symptomatic disease and 2,000 to 17,000 deaths annually. Prospective studies have shown that 4–10% of individuals infected with *E. histolytica* develop amebic colitis and that < 1% of infected individuals develop disseminated disease, including amebic liver abscess. These numbers vary by region; for example, in South Africa and Vietnam, liver abscesses form a disproportionately large number of the cases of invasive disease due to *E. histolytica.* Amebic liver abscesses occur equally in male and female children but are generally rare in childhood. Peak abscess formation occurs between 30 to 60 years old and is 10-12 times more prevalent in adult males than females, possibly due to an inhibitory effect of testosterone on innate immune mechanisms.

Amebiasis causes its largest burden of disease in Africa, Southeast Asia, and the Eastern Mediterranean. In the United States, amebiasis is seen most frequently in travelers to and immigrants from developing countries. Residents of mental health institutions and men who have sex with men are at increased risk for invasive amebiasis. Food or drink contaminated with *Entamoeba* cysts and oral-anogenital sex are the most common means of infection. Untreated water and night soil (human feces used as fertilizer) are important sources of infection in resource-limited settings. Food handlers shedding amebic cysts play a role in spreading infection.

Pathogenesis

Trophozoites are responsible for tissue invasion and destruction. Hypersecretion of mucus by colonic goblet cells is induced by secreted amebic cysteine protease 5, which eventually leads to degradation of the mucus layer, exposing colonic epithelial cells. Amebae then attach using a galactose and *N* -acetyl-ᴅ -galactosamine–specific lectin. This lectin also provides resistance to complement-mediated lysis, and its intermediate subunit has been found to have hemagglutinating, hemolytic, and cytolytic activity. Once attached to the colonic mucosa, trophozoites penetrate the epithelial layer, destroying host cells by cytolysis and induction of apoptosis. Cytolysis is mediated by trophozoite release of amebapores (pore-forming proteins), phospholipases, and hemolysins. Trogocytosis, where amebae ingest pieces of living cells and induce intracellular calcium elevation leading to apoptosis, was recently described as a mechanism for direct host cell killing by amebae.

Once host cells are partially digested by amebic proteases, the degraded material is internalized through phagocytosis. Early invasive amebiasis produces significant inflammation, owing in part to parasite-mediated activation of nuclear factor-κB. Once *E. histolytica* trophozoites invade the intestinal mucosa, the organisms multiply and spread laterally underneath the intestinal epithelium to produce the characteristic *flask-shaped ulcers.* Amebae produce similar lytic lesions if they reach the liver. These lesions are commonly called *abscesses,* although they contain no granulocytes. Well-established ulcers and amebic liver abscesses demonstrate little local inflammatory response.

Immunity to infection is associated with a mucosal secretory IgA response against the galactose/*N* -acetyl-ᴅ -galactosaminelectin. Neutrophils appear to be important in the initial host defense, but *E. histolytica* –induced epithelial cell damage releases neutrophil chemoattractants, and *E. histolytica* is able to kill neutrophils, which then release mediators that further damage epithelial cells. The disparity between the extent of tissue destruction by amebae and the absence of a local host inflammatory response in the presence of systemic humoral (antibody) and cell-mediated responses may reflect both parasite-mediated apoptosis and the ability of the trophozoite to kill not only epithelial cells but neutrophils, monocytes, and macrophages. Leptin receptor polymorphisms have been implicated as host genetic factors that affect the susceptibility to infection by *E. histolytica.* The chemotactic effect of leptin is decreased in individuals with an arginine polymorphism in position 223 of the leptin receptor, and this polymorphism also decreases host STAT-3 gene expression leading to enhanced induction of host cell apoptosis by amebae.

The *E. histolytica* genome is functionally tetraploid, and there is evidence of lateral gene transfer from bacteria. The amebapore-A (Ap-A) gene, along with other important genes, can be epigenetically silenced using plasmids with specifically engineered sequences or short hairpin RNAs. Transcriptional profiling using proteomics and microarrays has identified multiple virulence factors, including cysteine proteases, which modulate lysosome and phagosome function, and a total of 219 excretory-secretory proteins. The bacterial microbiome has also been shown to influence *E. histolytica* pathogenicity by affecting lectin expression, with increased *Prevotella copri* populations associated with higher rates of diarrhea in infected children.

Clinical Manifestations

Clinical presentations range from asymptomatic cyst passage to amebic colitis, amebic dysentery, ameboma, and extraintestinal disease. Up to 10% of infected persons develop invasive disease within a year, and asymptomatic carriers should be treated. Severe disease is more common in young children, pregnant women, malnourished individuals, and persons taking corticosteroids, and invasive disease is more common in men. Extraintestinal disease usually involves the liver, but less common extraintestinal manifestations include amebic brain abscess, pleuropulmonary disease, ulcerative skin, and genitourinary lesions.

Amebic Colitis

Amebic colitis may occur within 2 wk of infection or may be delayed for months. The onset is usually gradual, with colicky abdominal pains and frequent bowel movements (6-8/day). Diarrhea is frequently associated with tenesmus. Almost all stool is heme-positive, but most patients do not present with grossly bloody stools. Generalized constitutional symptoms and signs are characteristically absent, with fever documented in only one third of patients. Amebic colitis affects all age-groups, but its incidence is strikingly common in children 1-5 yr of age. Severe amebic colitis in infants and young children tends to be rapidly progressive, with more frequent extraintestinal involvement and high mortality rates, particularly in tropical countries. Amebic dysentery can result in dehydration and electrolyte disturbances.

Amebic Liver Abscess

Amebic liver abscess, a serious manifestation of disseminated infection, is uncommon in children. Although diffuse liver enlargement has been associated with intestinal amebiasis, liver abscesses occur in < 1% of infected individuals and may appear in patients with no clear history of intestinal disease. Amebic liver abscess may occur months to years after exposure, so obtaining a careful travel history is critical. In children, fever is the hallmark of amebic liver abscess and is frequently associated with abdominal pain, distention, and enlargement and tenderness of the liver. Changes at the base of the right lung, such as elevation of the diaphragm and atelectasis or effusion, may also occur.

Laboratory Findings

Laboratory examination findings are often unremarkable in uncomplicated amebic colitis. Laboratory findings in amebic liver abscess are a slight leukocytosis, moderate anemia, high erythrocyte sedimentation rate, and elevations of hepatic enzyme (particularly alkaline phosphatase) levels. Stool examination for amebae is negative in more than half of patients with documented amebic liver abscess. Ultrasonography, CT, or MRI can localize and delineate the size of the abscess cavity (Fig. 307.1). The most common finding is a single abscess in the right hepatic lobe.

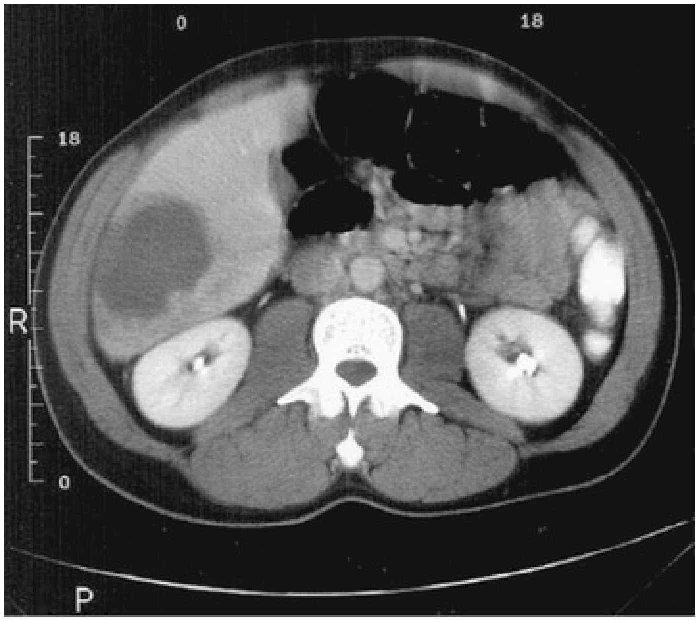

FIG. 307.1 Abdominal CT scan of a patient with an amebic liver abscess. (From Miller Q, Kenney JM, Cotlar AM: Amebic abscess of the liver presenting as acute cholecystitis, Curr Surg 57:476-479, 2000, Fig. 1, p. 477.)

Diagnosis and Differential Diagnosis

A diagnosis of amebic colitis is made in the presence of compatible symptoms with detection of *E. histolytica* either by stool antigen testing or PCR. This approach has a greater than 95% sensitivity and specificity, and when it is coupled with a positive serology test, it is the most accurate means of diagnosis in developed countries. Several approved stool antigen kits are commercially available in the United States, but most cannot distinguish between *E. histolytica* and *E. dispar.* Microscopic examination of stool samples has a sensitivity of 60%. Sensitivity can be increased to 85–95% by examining three stools. Microscopy cannot differentiate between *E. histolytica* and *E. dispar* unless phagocytosed erythrocytes (specific for *E. histolytica*) are seen. Endoscopy and biopsies of suspicious areas should be performed when stool sample results are negative and suspicion remains high.

Various serum antibody tests are available. Serologic results are positive in 70–80% of patients with invasive disease (colitis or liver abscess) at presentation and in > 90% of patients after 7 days. The most sensitive serologic test, indirect hemagglutination, yields a positive result years after invasive infection.

Therefore, many uninfected adults and children in highly endemic areas demonstrate antibodies to *E. histolytica*. Conventional and real-time multiplex PCR performed on stool is the most sensitive and preferred method for distinguishing *E. histolytica* from nonpathogenic *E. dispar* and *E. moshkovskii*. Different multiplex formats have also been developed, including enteric pathogen panels with varying sensitivities and specificities. Isothermal nucleic acid methods using recombinase and loop-mediated amplification (LAMP) in point-of-care diagnostics are promising and will greatly facilitate treatment, especially in developing countries.

The **differential diagnosis** for amebic colitis includes colitis due to bacterial, mycobacterial, and viral pathogens, as well as noninfectious causes such as inflammatory bowel disease. Pyogenic liver abscess due to bacterial infection, hepatoma, and echinococcal cysts are in the differential diagnosis for amebic liver abscess. However, echinococcal cysts are rarely associated with systemic symptoms such as fever, unless there is cyst rupture or leakage.

Complications

Complications of amebic colitis include acute necrotizing colitis, ameboma, toxic megacolon, extraintestinal extension, or local perforation and peritonitis. Less commonly, a chronic form of amebic colitis develops, often recurring over several years. Amebomas are nodular foci of proliferative inflammation that sometimes develop in the wall of the colon. Amebiasis should be excluded before initiating corticosteroid treatment for inflammatory bowel disease, because this is associated with high mortality rates.

An amebic liver abscess may rupture into the peritoneum, pleural cavity, skin, and pericardium. Cases of amebic abscesses in extrahepatic sites, including the lung and brain, have been reported.

Treatment

Invasive amebiasis is treated with a nitroimidazole such as metronidazole or tinidazole and then a luminal amebicide (Table 307.1). Tinidazole has similar efficacy to metronidazole, with shorter and simpler dosing, and is better tolerated. Adverse effects include nausea, abdominal discomfort, and a metallic taste that disappears after completion of therapy. Therapy with a nitroimidazole should be followed by treatment with a luminal agent, such as paromomycin (which is preferred) or iodoquinol. Diloxanide furoate can also be used in children > 2 yr of age, but it is no longer available in the United States. Paromomycin should not be given concurrently with metronidazole or tinidazole, because diarrhea is a common side effect of paromomycin and may confuse the clinical picture. Asymptomatic intestinal infection with *E. histolytica* should be treated, preferably with paromomycin or alternatively with either iodoquinol or diloxanide furoate. For fulminant cases of amebic colitis, some experts suggest adding dehydroemetine (1 mg/kg/ day subcutaneously or intramuscularly, never intravenously), available only through the Centers for Disease Control and Prevention. Patients should be hospitalized for monitoring if dehydroemetine is administered. Dehydroemetine should be discontinued if tachycardia, T-wave depression, arrhythmia, or proteinuria develops.

Table 307.1

Drug Treatment for Amebiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
INVASIVE DISEASE		
Metronidazole	Colitis or liver abscess: 750 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days
Or		
Tinidazole	Colitis: 2 g once daily for 3 days	Colitis: 50 mg/kg/day once daily for 3 days
	Liver abscess: 2 g once daily for 3-5 days	Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days
Or		
Diloxanide furoate †	500 mg tid for 10 days	20 mg/kg/day in 3 divided doses for 7 days
Or		
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in 3 divided doses for 20 days
ASYMPTOMATIC INTESTINAL COLONIZATION		
Paromomycin (preferred)	As for invasive disease	As for invasive disease
Or		
Diloxanide furoate †		
Or		
Iodoquinol		

* All pediatric dosages are up to a maximum of the adult dose.

† Not available in the United States.

Broad-spectrum antibiotic therapy may be indicated in fulminant colitis to cover possible spillage of intestinal bacteria into the peritoneum and translocation into the bloodstream. Intestinal perforation and toxic megacolon are indications for surgery. In amebic liver abscess, image-guided aspiration of large lesions or left lobe abscesses may be necessary if rupture is imminent or if the patient shows a poor clinical response 4-6 days after administration of amebicidal drugs. A Cochrane meta-analysis comparing metronidazole and metronidazole plus aspiration in uncomplicated amebic liver abscess showed that there is insufficient evidence to make any recommendation for or against this approach. Chloroquine, which concentrates in the liver, may also be a useful adjunct to nitroimidazoles in the treatment of amebic liver abscess or in cases of treatment failure or intolerance. To confirm cure, stool examination should be repeated every 2 wk following completion of therapy until clear.

Auranofin, a gold-containing antirheumatologic drug that inhibits *E. histolytica* thioredoxin reductase, has been shown to be active against amebic trophozoites and shows promise as a broad-spectrum antiparasitic agent. Phase one clinical trials were recently completed.

Prognosis

Most infections evolve to either an asymptomatic carrier state or eradication. Extraintestinal infection carries about a 5% mortality rate.

Prevention

Control of amebiasis can be achieved by exercising proper sanitation and hygiene. Regular examination of food handlers and thorough investigation of diarrheal episodes may help identify the source of infection. No prophylactic drug or vaccine is available. Immunization with a combination of galactose/*N* -acetyl-D -galactosamine lectin and CpG oligodeoxynucleotides has been shown to be protective in animals, and an intranasal galactose-lectin subunit vaccine has been shown to be protective in baboons. Recent work has shown that the C-terminal fragment of the biologically active intermediate subunit of the galactose/*N* -acetyl-D -galactosamine is a promising vaccine candidate and may also prevent the development of liver abscesses.

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CHAPTER 308

Giardiasis and Balantidiasis

308.1

Giardia duodenalis

Chandy C. John

Giardia duodenalis is a flagellated protozoan that infects the duodenum and jejunum. Infection results in clinical manifestations that range from asymptomatic colonization to acute or chronic diarrhea and malabsorption. Infection is more prevalent in children than in adults. *Giardia* is endemic in areas of the world with poor levels of sanitation. It is also an important cause of morbidity in developed countries, where it is associated with urban childcare centers, residential institutions for the developmentally delayed, and waterborne and foodborne outbreaks. *Giardia* is a particularly significant pathogen in children with malnutrition and certain immunodeficiencies (IgA deficiency, common variable immunodeficiency, X-linked hypogammaglobulinemia).

Etiology

The life cycle of *G. duodenalis* (also known as *Giardia lamblia* or *Giardia intestinalis*) is composed of two stages: trophozoites and cysts. *Giardia* infects humans after ingestion of as few as 10-100 cysts, which measure 8-10 µm in diameter. Each ingested cyst produces two trophozoites in the duodenum. After excystation, trophozoites colonize the lumen of the duodenum and proximal jejunum, where they attach to the brush border of the intestinal epithelial cells and multiply by binary fission. The body of the trophozoite is teardrop shaped, measuring 10-20 µm in length and 5-15 µm in width. *Giardia* trophozoites contain two oval nuclei anteriorly, a large ventral disk, a curved median body posteriorly, and four pairs of flagella. As detached trophozoites pass down the intestinal tract, they encyst to form oval cysts that contain four nuclei. Cysts are passed in stools of infected individuals and may remain viable in water for as long as 2 mo. Their viability often is not affected by the usual concentrations of chlorine used to purify water for drinking.

Giardia strains that infect humans are diverse biologically, as shown by differences in antigens, restriction endonuclease patterns, DNA fingerprinting, isoenzyme patterns, and pulsed-field gel electrophoresis. Studies suggest that different *Giardia* genotypes may cause unique clinical manifestations, but these findings appear to vary according to the geographic region tested.

Epidemiology

Giardia occurs worldwide and is the most common intestinal parasite identified in public health laboratories in the United States, where it is estimated that up to 2 million cases of giardiasis occur annually. *Giardia* infection usually occurs sporadically, but *Giardia* is a frequently identified etiologic agent of outbreaks associated with drinking water. The age-specific prevalence of giardiasis is high during childhood and begins to decline after adolescence. The asymptomatic carrier rate of *G. lamblia* in the United States is as high as 20–30% in children younger than 36 mo of age attending childcare centers. Asymptomatic carriage may persist for several months.

Transmission of *Giardia* is common in certain high-risk groups, including children and employees in childcare centers, consumers of contaminated water, travelers to certain areas of the world, men who have sex with men, and persons exposed to certain animals. The major reservoir and vehicle for spread of *Giardia* appears to be water contaminated with *Giardia* cysts, but foodborne transmission occurs. The seasonal peak in age-specific case reports coincides with the summer recreational water season and may be a result of the extensive use of communal swimming venues by young children, the low infectious dose, and the extended periods of cyst shedding that can occur. In addition, *Giardia* cysts are relatively resistant to chlorination and to ultraviolet light irradiation. Boiling is effective for inactivating cysts.

Person-to-person spread also occurs, particularly in areas of low hygiene standards, frequent fecal-oral contact, and crowding. Individual susceptibility, lack of toilet training, crowding, and fecal contamination of the environment all predispose to transmission of enteropathogens, including *Giardia*, in childcare centers. Childcare centers play an important role in transmission of urban giardiasis, with secondary attack rates in families as high as 17–30%. Children in childcare centers may pass cysts for several months. Campers who drink untreated stream or river water, particularly in the western United States, and residents of institutions for the developmentally delayed are also at increased risk for infection.

Humoral immunodeficiencies, including common variable immunodeficiency and X-linked agammaglobulinemia, predispose humans to chronic symptomatic *Giardia* infection, suggesting the importance of humoral immunity in controlling giardiasis. Selective immunoglobulin A deficiency is also associated with *Giardia* infection. Although many individuals with AIDS have relatively mild *Giardia* infections, *Giardia* infection refractory to treatment may occur in a subset of individuals with AIDS. A higher incidence of *Giardia* infection in patients with cystic fibrosis was reported in 1988, particularly in older children and adults, but there have been no subsequent confirmations of this risk. Human milk contains glycoconjugates and secretory immunoglobulin A antibodies that may provide protection to nursing infants against *Giardia* .

Clinical Manifestations

The incubation period of *Giardia* infection usually is 1-2 wk but may be longer. A broad spectrum of clinical manifestations occurs, depending on the interaction between *G. lamblia* and the host. Children who are exposed to *G. lamblia* may experience asymptomatic excretion of the organism, acute infectious diarrhea, or chronic diarrhea with persistent gastrointestinal tract signs and symptoms, including failure to thrive and abdominal pain or cramping. *Giardia* was the cause of 15% of nondysenteric diarrheal illnesses in children examined in U.S. outpatient clinics in one study. Most infections in children and adults are asymptomatic. There is usually no extraintestinal spread, but occasionally trophozoites may migrate into bile or pancreatic ducts.

Symptomatic infections occur more frequently in children than in adults. Most symptomatic patients usually have a limited period of acute diarrheal disease with or without low-grade fever, nausea, and anorexia; in a small proportion of patients, an intermittent or more protracted course characterized by diarrhea, abdominal distention and cramps, bloating, malaise, flatulence, nausea, anorexia, and weight loss develops (Table 308.1). Stools initially may be profuse and watery and later become greasy and foul smelling and may float. Stools do not contain blood, mucus, or fecal leukocytes. Varying degrees of malabsorption may occur. Abnormal stool patterns may alternate with periods of constipation and normal bowel movements. Malabsorption of sugars, fats, and fat-soluble vitamins is well documented and may be responsible for substantial weight loss. *Giardia* has been associated with iron deficiency in internationally adopted children. Extraintestinal manifestations of *Giardia* appear to be more common in adults than children and include arthritis and, in one report after an outbreak, chronic fatigue syndrome. Giardiasis in children has been associated with growth stunting, and repeated *Giardia* infections correlate with a decrease in cognitive function in children in endemic areas.

Table 308.1

Clinical Signs and Symptoms of Giardiasis

SYMPTOM	FREQUENCY (%)
Diarrhea	64-100
Malaise, weakness	72-97
Abdominal distention	42-97
Flatulence	35-97
Abdominal cramps	44-81
Nausea	14-79
Foul-smelling, greasy stools	15-79
Anorexia	41-73
Weight loss	53-73
Vomiting	14-35
Fever	0-28
Constipation	0-27

Diagnosis

Giardiasis should be considered in children who have acute nondysenteric diarrhea, persistent diarrhea, intermittent diarrhea and constipation, malabsorption, chronic crampy abdominal pain and bloating, failure to thrive, or weight loss. It should be particularly high in the differential diagnosis of children in child care, children in contact with an index case, children with a history of recent travel to an endemic area, and children with humoral immunodeficiencies. Testing for giardiasis should be standard for internationally adopted children from *Giardia* -endemic areas, and screening for iron deficiency should be considered in internationally adopted children with giardiasis.

Stool enzyme immunoassay (EIA) or direct fluorescent antibody tests for *Giardia* antigens have been tests of choice for giardiasis. EIA is less reader dependent and more sensitive for detection of *Giardia* than microscopy. Some studies report that a single stool is sufficiently sensitive for detection of *Giardia* by EIA, whereas others suggest that sensitivity is increased with testing of two samples. A diagnosis of giardiasis was traditionally established by microscopy documentation of trophozoites or cysts in stool specimens, but three stool specimens are required to achieve a sensitivity of > 90% using this approach. In patients in whom other parasitic intestinal infections are in the differential diagnosis, microscopy examination of stool allows evaluation for these infections in addition to *Giardia.*

Polymerase chain reaction and gene probe–based detection systems specific for *Giardia* have been used in environmental monitoring and clinical testing. Multiplex polymerase chain reaction testing for multiple parasitic pathogens is a viable option for testing.

In patients with chronic symptoms in whom giardiasis is suspected but in whom testing of stool specimens for *Giardia* yields a negative result, aspiration or biopsy of the duodenum or upper jejunum should be considered. In a fresh specimen, trophozoites usually can be visualized by direct wet mount. An alternate method of directly obtaining duodenal fluid is the commercially available Entero-Test (Hedeco Corp, Mountain View, CA), but this method is less sensitive than aspiration or biopsy. The biopsy can be used to make touch preparations and tissue sections for identification of *Giardia* and other enteric pathogens and also to visualize changes in histology. Biopsy of the small intestine should be considered in patients with characteristic clinical symptoms, negative stool and duodenal fluid specimen findings, and one or more of the following: abnormal radiographic findings (such as edema and segmentation in the small intestine); an abnormal lactose tolerance test result; an absent secretory immunoglobulin A level; hypogammaglobulinemia; or achlorhydria. Duodenal biopsy may show findings consistent with chronic inflammation, including eosinophilic infiltration of the lamina propria.

Radiographic contrast studies of the small intestine may show nonspecific findings such as irregular thickening of the mucosal folds. Blood cell counts usually are normal. Giardiasis is not tissue invasive and is not associated with peripheral blood eosinophilia.

Treatment

Children with acute diarrhea in whom *Giardia* organisms are identified should receive therapy. In addition, children who manifest failure to thrive or exhibit malabsorption or gastrointestinal tract symptoms such as chronic diarrhea should be treated.

Asymptomatic excreters generally are not treated, except in specific instances such as outbreak control, prevention of household transmission by toddlers to pregnant women and patients with hypogammaglobulinemia or cystic fibrosis, and situations requiring oral antibiotic treatment where *Giardia* may produce malabsorption of the antibiotic.

The FDA has approved tinidazole and nitazoxanide for the treatment of *Giardia* in the United States. Both medications have been used to treat *Giardia* in thousands of patients in other countries and have excellent safety and efficacy records against *Giardia* (Table 308.2). Tinidazole has the advantage of single-dose treatment and very high efficacy (>90%), while nitazoxanide has the advantage of a suspension form, high efficacy (80–90%), and very few adverse effects. Metronidazole, though never approved by the FDA for treatment of *Giardia*, is also highly effective (80–90% cure rate), and the generic form is considerably less expensive than tinidazole or nitazoxanide. Frequent adverse effects are seen with metronidazole therapy, and it requires 3-times-a-day dosing for 5-7 days. Suspension forms of tinidazole and metronidazole must be compounded by a pharmacy; neither drug is sold in suspension form.

Table 308.2

Drug Treatment for Giardiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL) *
RECOMMENDED		
Tinidazole	2 g once	>3 yr: 50 mg/kg once
Nitazoxanide	500 mg bid for 3 days	1-3 yr: 100 mg (5 mL) bid for 3 days
		4-11 yr: 200 mg (10 mL) bid for 3 days
		>12 yr: 500 mg bid for 3 days
Metronidazole	250 mg tid for 5-7 days	15 mg/kg/day in 3 divided doses for 5-7 days
ALTERNATIVE		
Albendazole	400 mg once a day for 5 days	>6 yr: 400 mg once a day for 5 days
Paromomycin	25-35 mg/kg/day in 3 divided doses for 5-10 days	Not recommended
Quinacrine †	100 mg tid for 5-7 days	6 mg/kg/day in 3 divided doses for 5 days

* All pediatric dosages are up to a maximum of the adult dose.

[†] Not commercially available. Can be compounded by Medical Center Pharmacy in New Haven, CT (203-688-8970) or Panorama Compounding Pharmacy in Van Nuys, CA (818-988-7979).

Second-line alternatives for the treatment of patients with giardiasis include albendazole, paromomycin, and quinacrine (see Table 308.2). Albendazole may be of similar efficacy to metronidazole. Albendazole has few adverse effects and is effective against many helminths, making it useful for treatment when multiple intestinal parasites are identified or suspected. Paromomycin is a nonabsorbable aminoglycoside and is less effective than other agents but is recommended for treatment of pregnant women with giardiasis because of the potential teratogenic effects of other agents. Quinacrine is effective and inexpensive but is not available commercially and must be obtained from compounding pharmacies (see Table 308.2). Quinacrine can also rarely have serious side effects, including hallucinations and psychosis. Refractory cases of giardiasis have been successfully treated with a number of regimens including nitazoxanide, prolonged courses of tinidazole, or combination therapy, most commonly a 3 wk course of metronidazole and quinacrine.

Prognosis

Symptoms recur in some patients in whom reinfection cannot be documented and in whom an immune deficiency such as an immunoglobulin abnormality is not present, despite use of appropriate therapy. Several studies have demonstrated that variability in antimicrobial susceptibility exists among strains of *Giardia*, and in some instances resistant strains have been demonstrated. Combined therapy may be useful for infection that persists after single-drug therapy, assuming reinfection has not occurred and the medication was taken as prescribed.

Prevention

Infected persons and persons at risk should practice strict handwashing after any contact with feces. This point is especially important for caregivers of diapered infants in childcare centers, where diarrhea is common and *Giardia* organism carriage rates are high.

Methods to purify public water supplies adequately include chlorination, sedimentation, and filtration. Inactivation of *Giardia* cysts by chlorine requires the coordination of multiple variables such as chlorine concentration, water pH, turbidity, temperature, and contact time. These variables cannot be appropriately controlled in all municipalities and are difficult to control in swimming pools. Individuals, especially children in diapers, should avoid swimming if they have diarrhea. Individuals should also avoid swallowing recreational water and drinking untreated water from shallow wells, lakes, springs, ponds, streams, and rivers.

Travelers to endemic areas are advised to avoid uncooked foods that might have been grown, washed, or prepared with water that was potentially contaminated. Purification of drinking water can be achieved by a filter with a pore size of < 1 μm or that has been rated by the National Sanitation Foundation for cyst removal, or by brisk boiling of water for at least 1 min. Treatment of water with chlorine or iodine is less effective but may be used as an alternate method when boiling or filtration is not possible.

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308.2

Balantidiasis

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Balantidium coli is a ciliated protozoan and is the largest protozoan that parasitizes humans. Both trophozoites and cysts may be identified in feces. Disease caused by this organism is uncommon in the United States and generally is reported where there is a close association of humans with pigs, which are the natural hosts of *B. coli.* Because the organism infects the large intestine, symptoms are consistent with large bowel disease, similar to those associated with amebiasis and trichuriasis, and include nausea, vomiting, lower abdominal pain, tenesmus, and bloody diarrhea. Symptoms associated with chronic infection include abdominal cramps, watery diarrhea with mucus, occasionally bloody diarrhea, and colonic ulcers similar to those associated with *Entamoeba histolytica*. Extraintestinal spread of *B. coli* is rare and usually occurs only in immunocompromised patients. Most infections are asymptomatic.

Diagnosis using direct saline mounts is established by identification of trophozoites (50-100 µm long) or spherical or oval cysts (50-70 µm in diameter) in stool specimens. Trophozoites usually are more numerous than cysts.

The recommended treatment regimen is metronidazole (45 mg/kg/day divided tid PO; maximum: 750 mg/dose) for 5 days, or tetracycline (40 mg/kg/day divided qid PO; maximum: 500 mg/dose) for 10 days for persons older than 8 yr of age. An alternative is iodoquinol (40 mg/kg/day divided tid PO; maximum: 650 mg/dose) for 20 days.

Prevention of contamination of the environment by pig feces is the most important means for control.

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CHAPTER 309

Cryptosporidium, *Cystoisospora*, *Cyclospora*, and Microsporidia

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The spore-forming intestinal protozoa *Cryptosporidium*, *Cystoisospora* (formerly *Isospora*), and *Cyclospora* are important intestinal pathogens in both immunocompetent and immunocompromised hosts. *Cryptosporidium*, *Cystoisospora*, and *Cyclospora* are coccidian parasites that predominantly infect the epithelial cells lining the digestive tract. Microsporidia were formerly considered spore-forming protozoa but have been reclassified as fungi. Microsporidia are ubiquitous, obligate intracellular parasites that infect many other organ systems in addition to the gastrointestinal tract and cause a broader spectrum of disease.

Cryptosporidium

Cryptosporidium is recognized as a leading protozoal cause of diarrhea in children worldwide and is a common cause of outbreaks in childcare centers; it is also a significant pathogen in immunocompromised patients.

Etiology

Cryptosporidium hominis and *Cryptosporidium parvum* cause most cases of cryptosporidiosis in humans. Disease is initiated by ingestion of infectious oocysts that were excreted in the feces of infected humans and animals. The oocysts are immediately infectious to other hosts or can reinfect the same host. The ingested oocysts release sporozoites that attach to and invade the intestinal epithelial cells.

Epidemiology

Cryptosporidiosis is associated with diarrheal illness worldwide and is more prevalent in developing countries and among children younger than 2 yr of age. It has been implicated as an etiologic agent of persistent diarrhea in the developing world and as a cause of significant morbidity and mortality from malnutrition, including permanent effects on growth.

Transmission of *Cryptosporidium* to humans can occur by close association with infected animals, via person-to-person transmission, or from environmentally contaminated water and food. Although zoonotic transmission, especially from cows, occurs in persons in close association with animals, person-to-person transmission is probably responsible for cryptosporidiosis outbreaks within hospitals and childcare centers, where transmission rates as high as 67% have been reported. Recommendations to prevent outbreaks in childcare centers include exclusion of children with diarrhea from attending, strict handwashing, elimination of water play or swimming activities, use of protective clothes or diapers capable of retaining liquid diarrhea, and separation of diapering and food-handling areas and responsibilities.

Outbreaks of cryptosporidial infection are associated with contaminated community water supplies and recreational waters, including lakes and chlorinated swimming pools. Wastewater in the form of raw sewage and runoff from dairies and grazing lands can contaminate both drinking and recreational water sources. It is estimated that *Cryptosporidium* oocysts are present in 65–97% of the surface water in the United States. The organism's small size (4-6 µm in diameter), resistance to chlorination, and ability to survive for long periods outside a host create problems in public water supplies.

Clinical Manifestations

The incubation period is 2-10 days (average, 7 days) after infection. *Cryptosporidium* infection is associated with profuse, watery, nonbloody diarrhea that can be accompanied by diffuse crampy abdominal pain, nausea, vomiting, and anorexia. Although less common in adults, vomiting occurs in more than 80% of children with cryptosporidiosis. Nonspecific symptoms such as myalgia, weakness, and headache also may occur. Fever occurs in 30–50% of cases. Malabsorption, lactose intolerance, dehydration, weight loss, and malnutrition often occur in severe cases. The clinical spectrum and disease severity have been linked with both the infecting species and host human leukocyte antigen class I and class II alleles.

In immunocompetent persons, the disease is usually self-limiting, typically 5-10 days, although diarrhea may persist for several weeks and oocyst shedding may persist for many weeks after symptoms resolve. Chronic diarrhea is common in individuals with immunodeficiency, such as congenital hypogammaglobulinemia or HIV infection. Symptoms and oocyst shedding can continue indefinitely and may lead to severe malnutrition, wasting, anorexia, and even death.

Cryptosporidiosis in **immunocompromised hosts** is often associated with biliary tract disease, characterized by fever, right upper quadrant pain, nausea, vomiting, and diarrhea. It also is associated with pancreatitis. Respiratory tract disease, with symptoms of cough, shortness of breath, wheezing, croup, and hoarseness, is very rare.

Diagnosis

Infection can be diagnosed by microscopy using modified acid-fast stain or polymerase chain reaction, but immunodetection of antigens on the surface of the organism in stool samples using monoclonal antibody–based assays is the current diagnostic method of choice. Multiplex molecular test panels for gastrointestinal pathogens that include *Cryptosporidium* are available and are a standard test.

In stool, oocysts appear as small, spherical bodies (2-6 μm) and stain red with modified acid-fast staining. Because *Cryptosporidium* does not invade below the epithelial layer of the mucosa, fecal leukocytes are not found in stool specimens. Oocyst shedding in feces can be intermittent, and several fecal specimens (at least three for an immunocompetent host) should be collected for microscopic examination. Serologic diagnosis is not helpful in acute cryptosporidiosis.

In tissue sections, *Cryptosporidium* organisms can be found along the microvillus region of the epithelia that line the gastrointestinal tract. The highest concentration usually is detected in the jejunum. Histologic section results reveal villus atrophy and blunting, epithelial flattening, and inflammation of the lamina propria.

Treatment

Often the diarrheal illness attributable to cryptosporidiosis is self-limited in *immunocompetent* patients and requires no specific antimicrobial therapy. Treatment should focus on supportive care, including rehydration orally or, if fluid losses are severe, intravenously. Nitazoxanide (100 mg bid PO for 3 days for children 1-3 yr of age; 200 mg bid PO for children 4-11 yr of age; 500 mg bid PO for children ≥ 12 yr of age) is approved for treatment of diarrhea caused by *Cryptosporidium.* Clinical studies have not definitively demonstrated that nitazoxanide is superior to placebo in trials of HIV-infected (with low CD4 counts) or immunocompromised patients. However, given the severity of the infection in these populations, nitazoxanide treatment is usually initiated. In patients with HIV infection, treatment with combination antiretroviral therapy should also be administered to improve immune function. Other agents that have been suggested for treatment in clinical reports or small studies include orally administered human serum immunoglobulin or bovine colostrum, paromomycin, spiramycin, azithromycin, and roxithromycin or a combination of antibiotics.

Cystoisospora

Like *Cryptosporidium, Cystoisospora belli* is implicated as a cause of diarrhea in institutional outbreaks and in travelers and has also been linked with contaminated water and food. *Cystoisospora* appears to be more common in tropical and subtropical climates and in developing areas, including South America, Africa, and Southeast Asia. *Cystoisospora* has not been associated with animal contact. It is also an infrequent cause of diarrhea in patients with AIDS in the United States but may infect up to 15% of AIDS patients in Haiti.

The life cycle and pathogenesis of infection with *Cystoisospora* species are similar to those of *Cryptosporidium* organisms except that oocysts excreted in the stool are not immediately infectious and must undergo further maturation at temperatures below 37°C (98.6°F). Thus, direct person-to-person transmission is unlikely. The most common clinical manifestation is watery, nonbloody diarrhea. Symptoms of infection are indistinguishable from those of cryptosporidiosis, although fever may be a more common finding. Eosinophilia may be present in up to 50% of cases, contrasting with other enteric protozoan infections. The diagnosis is established by detecting the oval, 22- to 33-µm long by 10- to 19-µm wide oocysts by using modified acid-fast staining of the stool. Each oocyst contains two sporocysts, each with four sporozoites. Fecal leukocytes are not detected. Oocysts are shed in low numbers, underscoring the need for repeated stool examinations. The presence of oocysts in the gastrointestinal track is almost always associated with clinical symptoms. The histologic appearance of the gastrointestinal epithelium reveals blunting and atrophy of the villi, acute and chronic inflammation, and crypt hyperplasia.

Isosporiasis responds promptly to treatment with oral trimethoprim-sulfamethoxazole (TMP-SMX: 5 mg TMP and 25 mg SMX/kg/dose; [maximum: 160 mg TMP and 800 mg SMX/dose] bid for 10 days). In patients with AIDS, relapses are common and often necessitate higher doses of TMP/SMX and/or maintenance therapy. Combination antiretroviral therapy associated with immune recovery may also result in improved symptoms. Ciprofloxacin or a regimen of pyrimethamine alone or with folinic acid is effective in patients intolerant of sulfonamide drugs.

Cyclospora

Cyclospora cayetanensis is a coccidian parasite similar to but larger than *Cryptosporidium.* The organism infects both immunocompromised and immunocompetent individuals and is more common in children younger than 18 mo of age. The pathogenesis and pathologic findings of cyclosporiasis are similar to those of isosporiasis. Asymptomatic carriage of the organism has been found, but travelers who harbor the organism almost always have diarrhea. Outbreaks of cyclosporiasis are linked with contaminated food and water. Implicated foods include raspberries, lettuce, snow peas, basil, and other fresh food items. After fecal excretion, the oocysts must sporulate outside the host to become infectious. This finding explains the lack of person-to-person transmission.

The clinical manifestations of cyclosporiasis are similar to those of cryptosporidiosis and isosporiasis and follow an incubation period of approximately 7 days. Moderate *Cyclospora* illness is characterized by a median of 6 stools/day with a median duration of 10 days (range: 3-25 days). The duration of diarrhea in immunocompetent persons is characteristically longer in cyclosporiasis than in the other intestinal protozoan illnesses. Associated symptoms frequently include anorexia; fatigue; abdominal bloating or gas; abdominal cramps or pain; nausea; muscle, joint, or body aches; low-grade fever; chills; headache; and weight loss. Vomiting may occur. Bloody stools are uncommon. Biliary disease has been reported. Intestinal pathology includes inflammation with villus blunting.

The diagnosis is established by identification of oocysts in the stool or molecular diagnostic testing. Oocysts are wrinkled spheres, measure 8-10 μm in diameter, and resemble large *Cryptosporidium* organisms. Each oocyst contains two sporocysts, each with two sporozoites. The organisms can be seen by using modified acid-fast, auramine-phenol, or modified trichrome staining, but stain less consistently than *Cryptosporidium.* They can also be detected with phenosafranin stain and by autofluorescence using strong green or intense blue under ultraviolet epifluorescence. Multiple stool samples enhance identification of the pathogen. Fecal leukocytes are not present. Commercially available multiplex molecular test panels for gastrointestinal pathogens that include *Cyclospora* are now available and may become the new standard.

The treatment of choice for cyclosporiasis is TMP-SMX (5 mg TMP and 25 mg SMX/kg/dose bid PO for 7 days; maximum: 160 mg TMP and 800 mg SMX/dose). Ciprofloxacin or nitazoxanide is effective in patients intolerant of sulfonamide drugs.

Microsporidia

Microsporidia are ubiquitous and infect most animal groups, including humans. They are classified as fungi, and multiple species of the phylum Microsporidia have been linked with human disease in both immunocompetent and immunocompromised hosts. The species most commonly associated with gastrointestinal disease are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis.*

Although still not definitive, the source of human infections is likely zoonotic. Like *Cryptosporidium,* there is concern for waterborne transmission through occupational and recreational contact with contaminated water sources. There is also the potential for foodborne outbreaks; the organisms have been identified on vegetables as a consequence of contaminated irrigation water. Vector-borne transmission is hypothesized because one species, *Brachiola algerae,* typically infects mosquitoes. Finally, transplacental transmission has been reported in animals but not in humans. Once infected, intracellular division produces new spores that can spread to nearby cells, disseminate to other host tissues, or be passed into the environment via feces. Spores also have been detected in urine and respiratory epithelium, suggesting that some body fluids may also be infectious. Once in the environment, microsporidial spores remain infectious for up to 4 mo.

Initially, microsporidial intestinal infection had been almost exclusively reported in patients with AIDS, but there is increasing evidence that immunocompetent individuals are also commonly infected. Microsporidia-associated diarrhea is intermittent, copious, watery, and nonbloody. Abdominal cramping and weight loss may be present; fever is unusual. Stromal keratitis and encephalitis may also be associated with microsporidia infections. Disseminated disease involving most organs, including liver, heart, kidney, bladder, biliary tract, lung, bone, skeletal muscle, and sinuses, has been reported.

Microsporidia stain with modified trichrome, hematoxylin-eosin, Giemsa, Gram, periodic acid–Schiff, and acid-fast stains, but are often overlooked because of their small size (1-5 µm) and the absence of associated inflammation in surrounding tissues. Electron microscopy remains the reference method of detection. An immunofluorescence assay is available. The Centers for Disease Control and Prevention offer a molecular identification of *Enterocytozoon bieneusi, Encephalitozoon intestinalis, Encephalitozoon hellem,* and *Encephalitozoon cuniculi* using species-specific polymerase chain reaction (PCR) assays.

There is no proven therapy for microsporidial intestinal infections. Albendazole (adult dose 400 mg bid PO for 3 wk; for children, 7.5 mg/kg body weight [maximum 400 mg/dose] bid PO) is usually effective against *E. intestinalis* infection, but is ineffective against infection caused by some microsporidial species. Fumagillin (adult dose 20 mg tid PO for 2 wk) was effective in a small controlled study of adults with *E. bieneusi* infection, and topical therapy with this agent was also demonstrated to be effective in HIV-infected adults with keratoconjunctivitis. Fumagillin is not currently available in the United States. Supportive care with hydration, correction of electrolyte imbalances, and nutrition should be used in gastrointestinal infection when clinically indicated. Improvement in underlying HIV infection with combination antiretroviral therapy also improves microsporidiosis symptoms.

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CHAPTER 310

Trichomoniasis *(Trichomonas vaginalis)*

Edsel Maurice T. Salvana, Robert A. Salata

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. It is the second most common sexually transmitted infection worldwide. Vulvovaginitis is the symptomatic disease form, but *T. vaginalis* has been implicated in pelvic inflammatory disease, pregnancy loss, chronic prostatitis, and an increased risk of HIV transmission.

Epidemiology

Over 276 million new cases of trichomoniasis occur annually, making it the most common nonviral sexually transmitted infection globally. Most men and up to 30% of women are asymptomatic. Although the disease is easily treated, sequelae of untreated infection remain a significant cause of morbidity because of high reinfection rates from untreated partners, underrecognition of asymptomatic cases, and insensitive diagnostics.

Trichomoniasis is the most common parasitic infection in the United States, with a total of 3.7 million cases and approximately 1.1 million new infections per year. *T. vaginalis* is recovered from > 60% of female partners of infected men and 70% of male sexual partners of infected women. Vaginal trichomoniasis is rare until menarche. Its presence in a younger child should raise the possibility of **sexual abuse.**

Trichomoniasis may be transmitted to neonates during passage through an infected birth canal. Infection in this setting is usually self-limited, but rare cases of neonatal vaginitis and respiratory infection have been reported.

Pathogenesis

T. vaginalis is an anaerobic, flagellated protozoan parasite. Infected vaginal secretions contain 10^1 to 10^5 or more protozoa/mL. *T. vaginalis* is pear shaped and exhibits characteristic twitching motility in wet mount (Fig. 310.1). Reproduction is by binary fission. It exists only as vegetative cells; cyst forms have not been described. Many types of adhesion molecules allow attachment of *T. vaginalis* to host cells. Tv lipoglycan is a surface glycoconjugate that binds human galectin-1 and -3 and plays a major role in adhesion, pathogenesis, and immune modulation. In addition, hundreds of putative membrane proteins, BspA proteins, and tetraspanins are involved in cellular attachment. Some of these proteins are contained in exosome vesicles, along with a large concentration of RNA oligonucleotides, which seem to further enhance adhesion. Adhesion is a prerequisite to cytolysis, and once attached the parasite secretes hydrolases, proteases, and cytotoxic molecules that destroy or impair the integrity of host cells. *Trichomonas* is highly dependent on iron for its growth and metabolism, and cysteine proteinase mRNAs have been shown to interact with other parasite proteins for posttranscriptional regulation in the absence of iron-regulatory proteins, which are present in other eukaryotes. This dependence on iron may partially explain the propensity of *T. vaginalis* to infect women due to a higher iron state during menses. The *T. vaginalis* genome is very large, with multiple repetitive sequences and transposable elements making up over 60,000 genes, as well as apparently nonfunctional but transcribed pseudogenes. This unusually large number of genetic elements is thought to have an adaptive function, with differential gene expression occurring in response to differing conditions, giving the organism flexibility for survival.

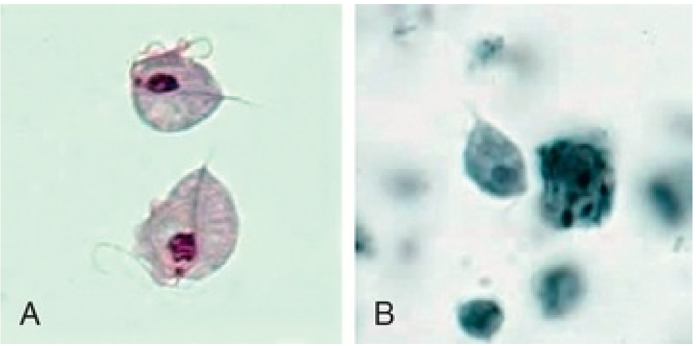

FIG. 310.1 *Trichomonas vaginalis* trophozoites stained with Giemsa **(A)**

and iron hematoxylin **(B).** (From the Centers for Disease Control and Prevention: Laboratory identification of parasites of public health concern. Trichomoniasis (website). https://www.cdc.gov/dpdx/trichomoniasis/index.html .)

Macrophage migration and cytokine production have been shown to be downregulated by the parasite in successful infection. Parasite-specific antibodies and lymphocyte priming occur in response to infection, but durable protective immunity does not occur, possibly also owing to degradation of antibodies by parasitic cysteine proteases.

Clinical Manifestations

The incubation period in females is 5-28 days. Symptoms may begin or worsen with menses. Most infected women eventually develop symptoms, although up to one third remain asymptomatic. Common signs and symptoms include a copious malodorous gray, frothy vaginal discharge, vulvovaginal irritation, dysuria, and dyspareunia. Physical examination may reveal a frothy discharge with vaginal erythema and cervical hemorrhages (strawberry cervix). The discharge usually has a pH of > 4.5. Abdominal discomfort is unusual and should prompt evaluation for pelvic inflammatory disease (see Chapter 146).

Most infections in males are asymptomatic. Symptomatic males usually have dysuria and scant urethral discharge. Trichomonads occasionally cause epididymitis, prostatic involvement, and superficial penile ulceration. Infection is often self-limited, spontaneously resolving in 36% of men. *Trichomonas* has been implicated as a cause of recurrent or relapsing urethritis and can be isolated in 3–20% of men with nongonococcal urethritis. Treatment failures with standard therapy for gonorrhea and *Chlamydia* are frequently treated with antitrichomonal therapy.

Diagnosis

Trichomonads may be recognized in vaginal secretions by wet mount microscopy. This has a sensitivity of approximately 35–60% compared with culture and nucleic acid techniques. Although *Trichomonas* is sometimes seen on Pap smears and urine microscopy, these methods are not considered reliable tests for disease. Culture of the organism used to be the gold standard for detection, but this is increasingly being replaced by nucleic acid amplification tests, which are at least as sensitive. The APTIMA TV (Hologic/Gen-Probe, Inc., Marlborough, MA) assay and the BD Probe Tec TV Q^x Amplified DNA Assay (Becton Dickinson, Franklin Lakes, NJ) are U.S. Food and Drug Administration (FDA) cleared commercial NAATs for testing of samples from men and women. Xpert TV (Cepheid Inc., Sunnyvale, CA) is a cartridge-based nucleic acid test that is FDA-cleared but only for use on urine, endocervical, and vaginal swabs in women. Two point-of-care kits for rapid testing, Affirm VP III (BD Diagnostic Systems, Sparks, MD) and OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), are also FDA-cleared for use in women and yield results in 45 min and 10 min, respectively. Patients with *T. vaginalis* should be screened for other sexually transmitted infections. Multiplex nucleic acid formats for rapid diagnosis of multiple sexually transmitted diseases including *Trichomonas* have also been developed and are in clinical trials.

Complications

Untreated trichomoniasis has been associated with pelvic inflammatory disease, premature delivery, low birthweight, endometritis, salpingitis, and vaginal cuff cellulitis. The association between trichomoniasis and infertility is relatively weak, but there is some evidence that coinfection with other STIs increases the overall risk of PID. *T. vaginalis* infection increases the risk of acquisition and transmission of HIV. In HIV-infected individuals, trichomoniasis is associated with higher viral loads in cervical secretions and semen, as well as higher levels of infected lymphocytes in urogenital fluids.

Treatment

In the United States, metronidazole and tinidazole are used; in other countries, ornidazole is also used. Both metronidazole (single-dose regimen of 2 g orally as a single dose for adolescents and adults; alternative regimen, 500 mg orally bid for 7 days) and tinidazole (single 2 g dose orally in adolescents and adults) are used as first-line treatments. For children infected prior to adolescence, the recommended regimen is metronidazole 15 mg/kg/day divided in 3 doses orally for 7 days; tinidazole is not approved for dosing in younger children. For HIV-infected patients, the 7-day course of metronidazole is superior to and recommended over the single dose regimen. Topical metronidazole gel is not efficacious as monotherapy but may decrease symptoms in severe infection in conjunction with oral therapy. Sexual partners should be treated simultaneously to prevent reinfection. Multiple head-to-head trials comparing the efficacy between single-dose/short courses of metronidazole and single-dose tinidazole have shown either noninferiority or superior efficacy for tinidazole. Tinidazole is more expensive than metronidazole and is generally reserved for treatment failures or intolerance. A small number of patients with severe nitroimidazole hypersensitivity have been treated with intravaginal suppositories of boric acid, nitazoxanide, and paromomycin with varying degrees of success.

Treatment failures have been reported with metronidazole, although a poor response can usually be overcome by higher doses. Second-line treatment is either a 7-day course of metronidazole 500 mg twice daily or a single dose of tinidazole. If this approach fails, either metronidazole or tinidazole at 2 g daily for 5 days is recommended. Further treatment failure should be referred to an infectious diseases specialist and may require susceptibility testing, which is available from the Centers for Disease Control and Prevention. Metronidazole has not been shown to be teratogenic but is currently classified as a category C drug. A Cochrane metanalysis previously showed an association between premature births with metronidazole treatment of asymptomatic *T. vaginalis* infection in pregnancy. Other studies have shown no harm from metronidazole treatment in this setting. Treatment of trichomoniasis in pregnancy should always be considered, especially in symptomatic patients, and may decrease the risk of perinatal transmission.

Prevention

Prevention of *T. vaginalis* infection is best accomplished by treatment of all sexual partners of an infected person, and by programs aimed at prevention of all sexually transmitted infections (see Chapter 146). No vaccine is available, and drug prophylaxis is not recommended.

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CHAPTER 311

Leishmaniasis *(Leishmania)*

Peter C. Melby

The leishmaniases are a diverse group of diseases caused by intracellular protozoan parasites of the genus *Leishmania*, which are transmitted by phlebotomine sandflies. Multiple species of *Leishmania* are known to cause human disease involving the skin and mucosal surfaces and the visceral reticuloendothelial organs (Table 311.1). Cutaneous disease is usually localized and mild but may cause cosmetic disfigurement. Rarely, cutaneous infection can disseminate or involve the skin diffusely. Mucosal and visceral forms of leishmaniasis are associated with significant morbidity and mortality.

Table 311.1

Clinical and Epidemiologic Characteristics of Main *Leishmania* spp.

	SUBGENUS	CLINICAL FORM	MAIN CLINICAL FEATURES	NATURAL PROGRESSION	RISK GROUPS	MAIN RESERVO
Leishmania donovani *	*Leishmania*	VL, PKDL	Persistent fever, splenomegaly, weight loss, and anemia in VL; multiple painless macular, papular, or nodular lesions in PKDL	VL is fatal within 2 yr; PKDL lesions self-heal in up to 85% of cases in Africa but rarely in Asia	Predominantly adolescents and young adults for VL; young children in Sudan and no clearly established risk factors for PKDL	Humans
Leishmania tropica *	*Leishmania*	CL, LR, rarely VL	Ulcerating dry lesions,	CL lesions often self-heal within 1	No well-defined risk groups	Humans, bu zoonotic fo

			painless, and frequently multiple	yr		exist
Leishmania aethiopica *	*Leishmania*	CL, DCL, DsCL, oronasal CL	Localized cutaneous nodular lesions; occasionally oronasal; rarely ulcerates	Self-healing, except for DCL, within 2-5 yr	Limited evidence; adolescents	Hyraxes
Leishmania major *	*Leishmania*	CL	Rapid necrosis, multiple wet sores, severe inflammation	Self-healing in >50% of cases within 2-8 mo; multiple lesions slow to heal, and severe scarring	No well-defined risk groups	Rodents
Leishmania infantum *	*Leishmania*	VL, CL	Persistent fever and splenomegaly in VL; typically single nodules and minimal inflammation in CL	VL is fatal within 2 yr; CL lesions self-heal within 1 yr and confers individual immunity	Children <5 yr old and immunocompromised adults for VL; older children and young adults for CL	Dogs, hares humans
Leishmania mexicana †	*Leishmania*	CL, DCL, DsCL	Ulcerating lesions, single or multiple	Often self-healing in 3-4 mo	No well-defined risk groups	Rodents, marsupials
Leishmania amazonensis †	*Leishmania*	CL, DCL, DsCL	Ulcerating lesions, single or multiple	Not well described	No well-defined risk groups	Possums, rodents
Leishmania braziliensis †	*Viannia*	CL, MCL, DCL, LR	Ulcerating lesions can progress to mucocutaneous form; local lymph nodes are palpable before and early on in the onset of the lesions	Might self-heal in 6 mo; 2.5% of cases progress to MCL	No well-defined risk groups	Dogs, humans, rodents, horses
Leishmania guyanensis †	*Viannia*	CL, DsCL, MCL	Ulcerating lesions, single or multiple that can progress to	Might self-heal within 6 mo	No well-defined risk groups	Possums, sloths, anteaters

			mucocutaneous form; palpable lymph nodes			

[*] Old World leishmaniasis.

[†] New World leishmaniasis.

[‡] Estimates are of all New World leishmaniases, with *Leishmania braziliensis* comprising the vast majority of these cases.

CL, Cutaneous leishmaniasis; DCL, diffuse cutaneous leishmaniasis; DsCL, disseminated cutaneous leishmaniasis; LR, leishmaniasis recidivans; MCL, mucocutaneous leishmaniasis; PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.

Adapted from Burza S, Croft SL, Boelaert ML: Leishmaniasis, *Lancet* 392:951–966, 2018 (Table 1).

Etiology

Leishmania organisms are members of the Trypanosomatidae family and include 2 subgenera, *Leishmania (Leishmania)* and *Leishmania (Viannia)* . The parasite is dimorphic, existing as a flagellate promastigote in the insect vector and as an aflagellate amastigote that resides and replicates within mononuclear phagocytes of the vertebrate host. Within the **sandfly** vector, the promastigote changes from a noninfective procyclic form to an infective metacyclic stage (Fig. 311.1). Fundamental to this transition are changes that take place in the terminal polysaccharides of the surface **lipophosphoglycan** , which allow forward migration of the infective parasites to be inoculated in the host skin during a blood meal. Metacyclic lipophosphoglycan also plays an important role in the entry and survival of *Leishmania* in the host cells. Once within the macrophage, the promastigote transforms to an amastigote and resides and replicates within a phagolysosome. The parasite is resistant to the acidic, hostile environment of the macrophage and eventually ruptures the cell and goes on to infect other macrophages. Infected macrophages have a diminished capacity to initiate and respond to an inflammatory response, thus providing a safe haven for the intracellular parasite.

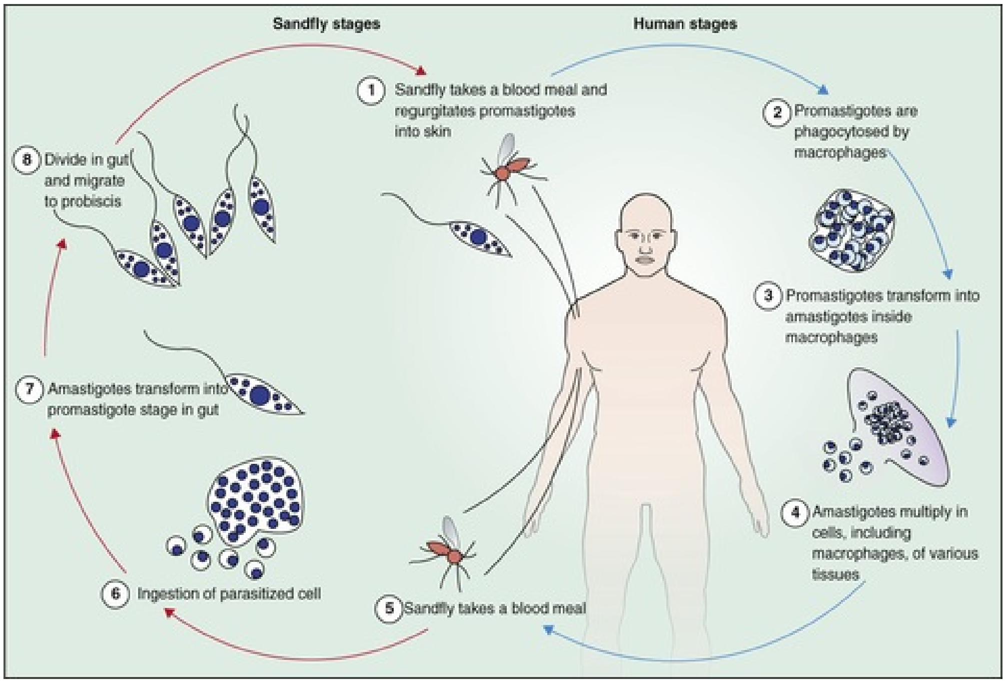
Sandfly stages
Human stages
1 Sandfly takes a blood meal and regurgitates promastigotes into skin
2 Promastigotes are phagocytosed by macrophages
3 Promastigotes transform into amastigotes inside macrophages
4 Amastigotes multiply in cells, including macrophages, of various tissues
5 Sandfly takes a blood meal
6 Ingestion of parasitized cell
7 Amastigotes transform into promastigote stage in gut
8 Divide in gut and migrate to probiscis

FIG. 311.1 ***Leishmania*** **life cycle. (From Reithinger R, Dujardin JC, Louzir H, et al: Cutaneous leishmaniasis, *Lancet Infect Dis* 7:581–596, 2007, Fig 5.)**

Epidemiology

The leishmaniases are estimated to affect 10-20 million people in endemic tropical and subtropical regions on all continents except Australia and Antarctica (Fig. 311.2). The different forms of the disease are distinct in their causes, epidemiologic characteristics, transmission, and geographic distribution. The leishmaniases may occur sporadically throughout an endemic region or may occur in epidemic waves. With only rare exceptions, the *Leishmania* organisms that primarily cause cutaneous disease do not cause visceral disease.

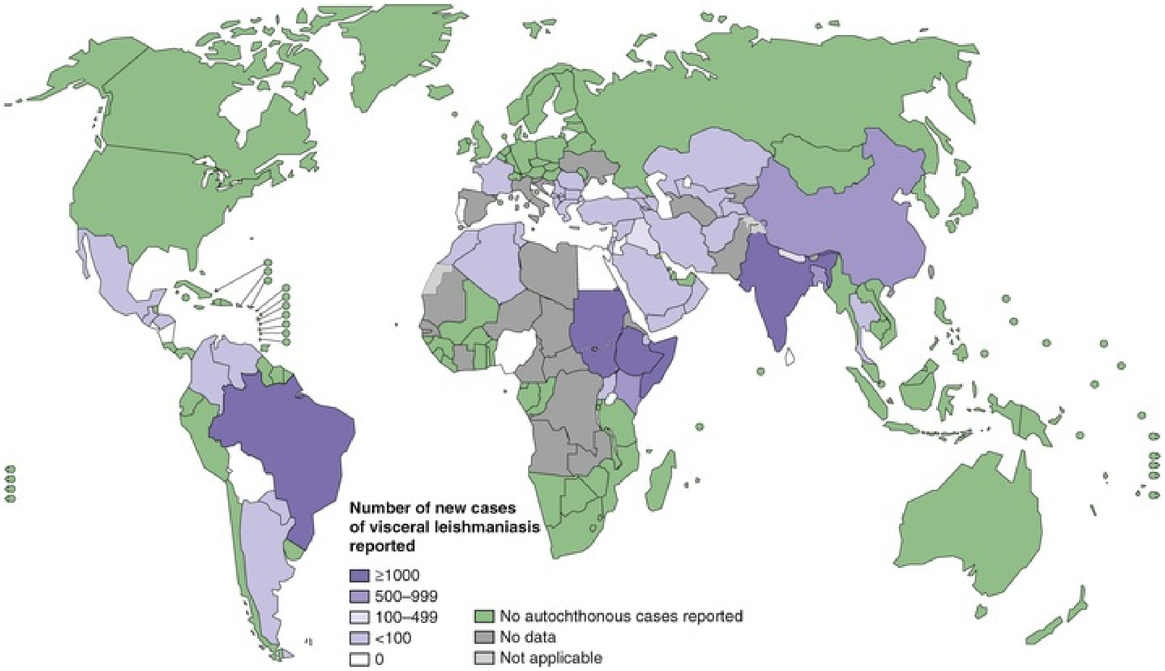
Number of new cases of visceral leishmaniasis reported
≥1000
500–999
100–499
<100
0
No autochthonous cases reported
No data
Not applicable

FIG. 311.2 **Status of endemicity of visceral leishmaniasis worldwide in 2016. (From World Health Organization: *Recognizing neglected tropical diseases through changes on the skin: a training guide for front-line health workers,* Geneva, 2018, WHO.)**

Localized cutaneous leishmaniasis (LCL) in the Old World is caused by *L. (Leishmania) major* and *L. (L.) tropica* in North Africa, the Middle East, Central Asia, and the Indian subcontinent. *L. (L.) aethiopica* is a cause of LCL and **diffuse cutaneous leishmaniasis (DCL)** in Kenya and Ethiopia. In the New World, *L. (L.) mexicana* causes LCL in a region stretching from southern Texas through Central America. *L. (L.) amazonensis*, *L. (L.) pifanoi*, *L. (L.) garnhami*, and *L. (L.) venezuelensis* cause LCL in South America, the Amazon basin, and northward. These parasites can also cause DCL. Members of the *Viannia* subgenus (*L. [V.] braziliensis, L. [V.] panamensis, L. [V.] guyanensis,* and *L. [V.] peruviana*) cause LCL and **mucosal leishmaniasis (ML)** from the northern highlands of Argentina northward to Central America. Some species, particularly *L. (V.) braziliensis,* rarely cause **disseminated leishmaniasis (DL)** . **Visceral leishmaniasis (VL)** in the Old World is caused by *L. (L.) donovani* in Kenya, Sudan, India, Pakistan, and China and by *L. (L.) infantum* in the Mediterranean basin, Middle East, and central Asia. *L. tropica* also has been recognized as an uncommon cause of visceral disease in the Middle East and India. VL in the New World is caused by *L. (L.) infantum* (formerly also called *L. chagasi*), which is distributed from Mexico (rare) through Central and South America. *L. infantum* can also cause LCL in the absence of visceral disease in this same geographic distribution.

The maintenance of *Leishmania* in most endemic areas is through a **zoonotic** transmission cycle. In general, the dermotropic strains in both the Old and the New World are maintained in rodent reservoirs, and the domestic dog is the usual reservoir for *L. infantum.* The transmission between reservoir and sandfly is highly adapted to the specific ecologic characteristics of the endemic region. Human infections occur when human activities bring them in contact with the zoonotic cycle. **Anthroponotic** transmission, in which humans are the presumed reservoir for vector-borne transmission, occurs with *L. tropica* in some urban areas of the Middle East and Central Asia, and with *L. donovani* in India and Sudan. Congenital transmission of *L. donovani* or *L. infantum* has been reported.

There is a resurgence of leishmaniasis in long-standing endemic areas as well as in new foci. Tens of thousands of cases of LCL occurred in outbreaks in Syria and Kabul, Afghanistan; severe epidemics with >100,000 deaths from VL have occurred in India and Sudan. VL is most prevalent among the poorest of the poor, with substandard housing contributing to the vector-borne transmission and undernutrition leading to increased host susceptibility. The emergence of the leishmaniases in new areas is the result of (1) movement of a susceptible population into existing endemic areas, usually because of agricultural or industrial development or timber harvesting; (2) increase in vector and/or reservoir populations as a result of agriculture development projects or climate change; (3) increase in anthroponotic transmission resulting from rapid urbanization in some focuses; and (4) increase in sandfly density resulting from a reduction in vector control programs.

Pathology

Histopathologic analysis of the skin lesions of LCL and DL show intense chronic granulomatous inflammation involving the epidermis and dermis with relatively few amastigotes. Occasionally, neutrophils and even microabscesses can be seen. The lesions of DCL are characterized by dense infiltration with vacuolated macrophages containing abundant amastigotes. ML is characterized by an intense granulomatous reaction with prominent tissue necrosis, which may include adjacent cartilage or bone. In VL there is prominent reticuloendothelial cell hyperplasia in the liver, spleen, bone marrow, and lymph nodes. Amastigotes are abundant in the histiocytes and Kupffer cells. Late in the course of disease, splenic infarcts are common, centrilobular necrosis and fatty infiltration of the liver occur, the normal marrow elements are replaced by parasitized histiocytes, and erythrophagocytosis is present.

Pathogenesis

Cellular immune mechanisms determine resistance or susceptibility to infection with *Leishmania*. Resistance is mediated by interleukin (IL)-12–driven generation of a T helper 1 (Th1) cell response, with interferon (IFN)-γ inducing classic macrophage (M1) activation and parasite killing. Susceptibility is associated with expansion of IL-4–producing Th2 cells and/or the production of IL-10 and transforming growth factor (TGF)-β, which are inhibitors of macrophage-mediated parasite killing, and the generation of regulatory T cells and alternatively activated (M2) macrophages. Patients with ML exhibit a hyperresponsive cellular immune reaction that may contribute to the prominent tissue destruction seen in this form of the disease. Patients with DCL or active VL demonstrate reduced or altered *Leishmania* -specific cellular immune responses, with prominent generation of IL-10, but these responses recover after successful therapy.

Within endemic areas, people who have had a subclinical infection can be identified by a positive delayed-type hypersensitivity skin response to leishmanial antigens **(Montenegro skin test**) or by antigen-induced production of IFN-γ in a whole blood assay. Subclinical infection occurs considerably more frequently than does active cutaneous or visceral disease. **Host** factors (genetic background, concomitant disease, nutritional status), **parasite** factors (virulence, size of the inoculum), and possibly **vector** -specific factors (vector genotype, immunomodulatory salivary constituents) influence the expression as either subclinical infection or active disease. Within endemic areas, the prevalence of skin test positivity increases with age, and the incidence of clinical disease decreases with age, indicating that immunity is acquired in the population over time. Individuals with prior active disease or subclinical infection are usually immune to a subsequent clinical infection; however, latent infection can lead to active disease if the patient is immunosuppressed.

Clinical Manifestations

The different forms of the disease are distinct in their causes, epidemiologic features, transmission, and geographic distribution.

Localized Cutaneous Leishmaniasis

LCL (**Oriental sore**) can affect individuals of any age, but children are the primary victims in many endemic regions. It may present as 1 or a few papular, nodular, plaque-like, or ulcerative lesions that are usually located on exposed skin, such as the face and extremities (Fig. 311.3). Rarely, >100 lesions have been recorded. The lesions typically begin as a small papule at the site of the sandfly bite, which enlarges to 1-3 cm in diameter and may ulcerate over the course of several weeks to months. The shallow ulcer is usually nontender and surrounded by a sharp, indurated, erythematous margin. There is no drainage unless a bacterial superinfection develops. Lesions caused by *L. major* and *L. mexicana* usually heal spontaneously after 3-6 mo, leaving a depressed scar. Lesions on the ear pinna caused by *L. mexicana,* called **chiclero ulcer** because they were common in chicle harvesters in Mexico and Central America, often follow a chronic, destructive course. In general, lesions caused by *L. (Viannia)* species tend to be larger and more chronic. Regional lymphadenopathy and palpable subcutaneous nodules or lymphatic cords, the so-called sporotrichoid appearance, are also more common when the patient is infected with organisms of the *Viannia* subgenus. If lesions do not become secondarily infected, there are usually no complications aside from the residual cutaneous scar.

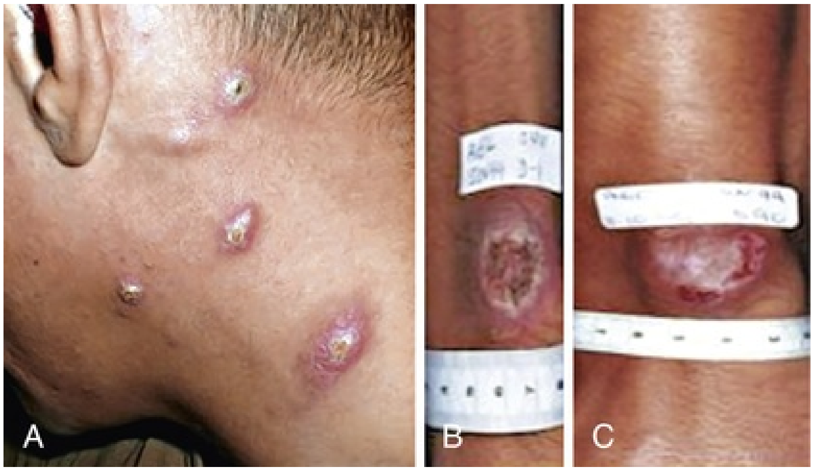

FIG. 311.3 Cutaneous disease. A, Old World infection *(Leishmania major)* acquired in Iraq; note 5 papular and nodular lesions on neck. B, New World infection *(Leishmania panamensis)* in Colombia; purely ulcerative lesion is characteristic of New World disease. C, Healed infection in patient shown in B 70 days after 20 days of meglumine antimonate treatment; note paper-thin scar tissue over flat reepithelialized skin. (*A,* courtesy of P. Weina; *B,* courtesy of J. Soto. *A-C,* modified from Murray HW, Berman JD, Davies CR, et al: Advances in leishmaniasis, *Lancet* 366:1561–1577, 2005.)

Diffuse Cutaneous Leishmaniasis

DCL is a rare form of leishmaniasis caused by organisms of the *L. mexicana* complex in the New World and *L. aethiopica* in the Old World. DCL manifests as large, nonulcerating macules, papules, nodules, or plaques that often involve large areas of skin and may resemble lepromatous leprosy. The face and extremities are most often involved. Dissemination from the initial lesion usually takes place over several years. These patients are anergic to the Montenegro skin test, and it is thought that an immunologic defect underlies this severe form of cutaneous leishmaniasis.

Disseminated Leishmaniasis

In rare cases, parasites can spread (likely by the hematogenous route) in an immunocompetent host from a primary lesion to cause DL. This is defined as >10 lesions (usually in the hundreds) involving at least 2 noncontiguous areas of the skin. DL has been most often attributed to *L. (V.) braziliensis* . The lesions are typically inflammatory papules or ulcers, in contrast to the nodular and plaque-like lesions of DCL, and about one third of patients have mucosal involvement.

Mucosal Leishmaniasis

ML (**espundia**) is an uncommon but serious manifestation of leishmanial infection resulting from hematogenous spread of parasites to the nasal or oropharyngeal mucosa from a cutaneous infection. It is usually caused by parasites in the *L. (Viannia)* complex. Approximately half of the patients with mucosal lesions have had active cutaneous lesions within the preceding 2 yr, but ML may not develop until many years after resolution of the primary lesion. ML occurs in <5% of individuals who have, or have had, LCL caused by *L. (V.) braziliensis.* Patients with ML typically have nasal mucosal involvement and present with nasal congestion, discharge, and recurrent epistaxis. Oropharyngeal and laryngeal involvement is less common but associated with severe morbidity. Marked soft tissue, cartilage, and even bone destruction occurs late in the course of disease and may lead to visible deformity of the nose or mouth, nasal septal perforation, and tracheal narrowing with airway obstruction.

Visceral Leishmaniasis

VL (**kala-azar**) typically affects children <5 yr old in the New World and Mediterranean region (*L. infantum*) and older children and young adults in Africa and Asia (*L. donovani*). After inoculation of the organism into the skin by the sandfly, the child may have a completely asymptomatic infection or an oligosymptomatic illness that either resolves spontaneously or evolves into active kala-azar. Children with **asymptomatic** infection are transiently seropositive but show no clinical evidence of disease. Children who are **oligosymptomatic** have mild constitutional symptoms (malaise, intermittent diarrhea, poor activity tolerance) and intermittent fever; most will have a mildly enlarged liver. In most of these children the illness will resolve without therapy, but in approximately 25% it will evolve to active kala-azar within 2-8 mo. Extreme incubation periods of several years have rarely been described. During the 1st few wk to mo of disease evolution, the fever is intermittent, there is weakness and loss of energy, and the spleen begins to enlarge. The classic clinical features of high fever, marked splenomegaly, hepatomegaly, and severe cachexia typically develop 3-6 mo after the onset of the illness, but a rapid clinical course over 1 mo has been noted in up to 20% of patients in some series (Fig. 311.4). At the terminal stages of kala-azar, the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascites may be present. Anemia may be severe enough to precipitate heart failure. Bleeding episodes, especially epistaxis, are frequent. The late stage of the illness is often complicated by secondary bacterial infections, which frequently are a cause of death. A younger age at the time of infection, HIV co-infection, and underlying malnutrition are risk factors for the development and more rapid evolution of active VL. Death occurs in >90% of patients without specific antileishmanial treatment and in 4–10% of treated patients. VL is a known cause of **hemophagocytic lymphohistiocytosis** in endemic areas.

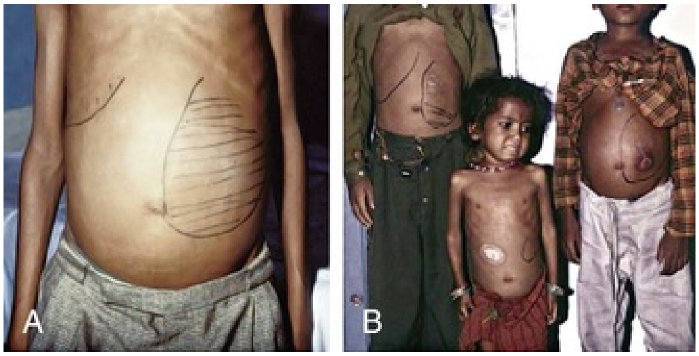

FIG. 311.4 Visceral leishmaniasis *(Leishmania donovani)* in Bihar State, India. A, Hepatosplenomegaly and wasting in a young man. B, Children with burn marks over enlarged spleen or liver—local shaman's unsuccessful remedy. (*A,* Courtesy of D. Sacks; *B,* courtesy of R. Kenney; *A* and *B,* adapted from Murray HW, Berman JD, Davies CR, et al: Advances in leishmaniasis, *Lancet* 366:1561–1577, 2005.)

VL is an opportunistic infection associated with **HIV infection** . Most cases have occurred in southern Europe and Brazil, often as a result of needle sharing associated with illicit drug use, with the potential for many more cases as the endemic regions for HIV and VL converge. Leishmaniasis may also result from reactivation of a long-standing subclinical infection. Frequently there is an atypical clinical presentation of VL in HIV-infected individuals with prominent involvement of the gastrointestinal tract and absence of the typical hepatosplenomegaly.

A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as **post–kala-azar dermal leishmaniasis.** These lesions may appear during or shortly after therapy (Africa) or up to several years later (India). The lesions of post–kala-azar dermal leishmaniasis are hypopigmented, erythematous, or nodular and usually involve the face and torso. They may persist for several months or for many years.

Laboratory Findings

Patients with cutaneous leishmaniasis or ML generally do not have abnormal laboratory results unless the lesions are secondarily infected with bacteria. Laboratory findings associated with classic kala-azar include anemia (hemoglobin, 5-8 mg/dL), thrombocytopenia, leukopenia (2,000-3,000 cells/µL), elevated hepatic transaminase levels, and hyperglobulinemia (>5 g/dL) that is mostly immunoglobulin G.

Differential Diagnosis

Diseases that should be considered in the differential diagnosis of LCL include sporotrichosis, blastomycosis, chromomycosis, lobomycosis, cutaneous tuberculosis, atypical mycobacterial infection, leprosy, ecthyma, syphilis, yaws, and neoplasms. Infections such as syphilis, tertiary yaws, histoplasmosis, and paracoccidioidomycosis, as well as sarcoidosis, granulomatosis with polyangiitis, midline granuloma, and carcinoma, may have clinical features similar to those of ML. VL should be strongly suspected in the patient with prolonged fever, weakness, cachexia, marked splenomegaly, hepatomegaly, cytopenias, and hypergammaglobulinemia who has had potential exposure in an endemic area. The clinical picture may also be consistent with that of malaria, typhoid fever, miliary tuberculosis, schistosomiasis, brucellosis, amebic liver abscess, infectious mononucleosis, lymphoma, and leukemia.

Diagnosis

The development of 1 or several slowly progressive, nontender, nodular, or ulcerative lesions in a patient who had potential exposure in an endemic area should raise suspicion of LCL.

Serologic tests for diagnosis of cutaneous or mucosal disease generally have low sensitivity and specificity and offer little for diagnosis. Serologic testing by enzyme immunoassay, indirect fluorescence assay, or direct agglutination is very useful in VL because of the very high level of antileishmanial antibodies. An immunochromatographic strip test using a recombinant antigen (K39) has a diagnostic sensitivity and specificity for VL of 80–90% and 95%, respectively. Serodiagnostic tests have positive findings in only about half the patients co-infected with HIV.

Definitive diagnosis of leishmaniasis is established by the demonstration of amastigotes in tissue specimens or isolation of the organism by culture. **Amastigotes** can be identified in Giemsa-stained tissue sections, aspirates, or impression smears in about half the cases of LCL but only rarely in the lesions of ML. **Culture** of a tissue biopsy or aspirate, best performed by using Novy-McNeal-Nicolle biphasic blood agar medium, yields a positive finding in only approximately 65% of cases of cutaneous leishmaniasis. Identification of parasites in impression smears, histopathologic sections, or culture medium is more readily accomplished in DCL than in LCL. In patients with VL, smears or cultures of material from splenic, bone marrow, or lymph node aspirations are usually diagnostic. In experienced hands, **splenic aspiration** has a higher diagnostic sensitivity, but it is rarely performed in the United States because of the risk for bleeding complications. A positive culture result allows speciation of the parasite, usually by isoenzyme analysis by a reference laboratory, which may have therapeutic and prognostic significance.

Treatment

Specific antileishmanial therapy is not routinely indicated for uncomplicated LCL caused by strains that have a high rate of spontaneous resolution and self-healing *(L. major, L. mexicana)*. Lesions that are extensive, severely inflamed, or located where a scar would result in disability (near a joint) or cosmetic disfigurement (face or ear), that involve the lymphatics, or that do not begin healing within 3-4 mo should be treated. Cutaneous lesions suspected or known to be caused by members of the *Viannia* subgenus (New World) should be treated because of the low rate of spontaneous healing and the potential risk for development of mucosal or disseminated disease. Similarly, patients with lesions caused by *L. tropica* (Old World), which are typically chronic and nonhealing, should be treated. All patients with VL or ML should receive therapy.

The pentavalent **antimony compounds** (sodium stibogluconate [Pentostam, GlaxoSmithKline, Uxbridge, UK] and **meglumine antimoniate** [Glucantime, Aventis, Strasbourg, France]) have been the mainstay of antileishmanial chemotherapy for >40 yr. These drugs have similar efficacies, toxicities, and treatment regimens. Currently, for **sodium stibogluconate** (available in the United States from the Centers for Disease Control and Prevention, Atlanta, GA), the recommended regimen is 20 mg/kg/day intravenously (IV) or intramuscularly (IM) for 20 days (for LCL and DCL) or 28 days (for ML and VL). Repeated courses of therapy may be necessary in patients with severe cutaneous lesions, ML, DCL, DL, or VL. An initial clinical response to therapy usually occurs in the 1st wk of therapy, but complete clinical healing (reepithelialization and scarring for LCL and ML, and regression of splenomegaly and normalization of cytopenias for VL) is usually not evident for weeks to a few months after completion of therapy. Cure rates with this regimen of 90–100% for LCL, 50–70% for ML, and 80–100% for VL were common in the 1990s, but treatment failures, especially in children, have become common in parts of India, East Africa, and Latin America.

Relapses are common in patients who do not have an effective antileishmanial cellular immune response (DCL or HIV co-infection). Adverse effects of antimony therapy are dose and duration dependent and include fatigue, arthralgias and myalgias (50%), abdominal discomfort (30%), elevated hepatic transaminase level (30–80%), elevated amylase and lipase levels (almost 100%), mild hematologic changes (slightly decreased leukocyte count, hemoglobin level, and platelet count) (10–30%), and nonspecific T-wave changes on electrocardiography (30%). Sudden death from cardiac toxicity has rarely been reported with use of very high doses of pentavalent antimony.

Amphotericin B desoxycholate and the amphotericin lipid formulations are very useful in the treatment of VL, ML or DL, and in some regions have replaced antimony as first-line therapy, especially in HIV-infected patients. However, the prohibitively high cost of these drugs precludes their use in many resource-poor regions of the world. Amphotericin B desoxycholate at doses of 0.5-1.0 mg/kg every day or every other day for 14-20 doses achieved a cure rate for VL of close to 100%, but the renal toxicity associated with amphotericin B was common. The lipid formulations of amphotericin B are especially attractive for treatment of leishmaniasis because the drugs are concentrated in the reticuloendothelial system and are less nephrotoxic. Liposomal amphotericin B is highly effective, with a 90–100% cure rate for VL in immunocompetent children, some of whom were refractory to antimony therapy. **Liposomal amphotericin B** (AmBisome, Gilead Sciences, Foster City, CA) is approved by the U.S. Food and Drug Administration (FDA) for treatment of VL at a recommended dose for *immunocompetent patients* of 3 mg/kg on days 1-5, 14, and 21 (total dose 21 mg/kg) and should be considered for first-line therapy in the United States. Therapy for *immunocompromised patients* should be prolonged (recommended total dose 40 mg/kg). A single high dose of liposomal amphotericin B (10 mg/kg) was found to be effective in India (approximately 95% efficacy) but was less effective in East Africa (58% efficacy).

Parenteral treatment of VL with the aminoglycoside **paromomycin** (aminosidine) has efficacy (95%) similar to that of amphotericin B in India. A dose-sparing regimen of the combination of sodium stibogluconate and paromomycin is effective and used in East Africa. **Miltefosine** , a membrane-activating alkylphospholipid, has been approved as the first oral treatment for VL and has a cure rate of 80–90% in Indian patients with VL when administered orally at 50-100 mg/day (or 2.5 mg/kg for children <12 yr old) for 28 days. Miltefosine is indicated for cutaneous infection caused by *L. braziliensis* , *L.*

guyanensis, and *L. panamensis* ; ML caused by *L. braziliensis* ; and VL caused by *L. donovani* . Gastrointestinal adverse effects were frequent but did not require discontinuation of the drug. An increased rate of relapse (up to 20%) has been seen in children treated with miltefosine. Dose-sparing combination regimens are being actively investigated for treatment of VL. Treatment of LCL with oral drugs has had only modest success. Ketoconazole has been effective in treating adults with LCL caused by *L. major, L. mexicana,* and *L. panamensis,* but not *L. tropica* or *L. braziliensis* . Fluconazole in high doses (up to 8 mg/kg/day) for 4-8 wk was demonstrated to be effective in treating LCL in studies in both the Old and New World; however, the experience in young children is limited. Miltefosine, 2.5 mg/kg/day orally for 20-28 days, was effective in 70–90% of patients with LCL in the Americas. Topical treatment of LCL with paromomycin ointment has been effective in selected areas in the both the Old and the New World. Enhanced drug development efforts and clinical trials of new drugs are clearly needed, especially in children.

Prevention

Personal protective measures should include avoidance of exposure to the nocturnal sandflies and, when necessary, the use of insect repellent and permethrin-impregnated mosquito netting. Where peridomiciliary transmission is present, community-based residual insecticide spraying has had some success in reducing the prevalence of leishmaniasis, but long-term effects are difficult to maintain. Control or elimination of infected reservoir hosts (e.g., seropositive domestic dogs) has had limited success. Where anthroponotic transmission is thought to occur, as in south Asia, early recognition, diagnosis, and treatment of cases and vector control measures are essential for progress toward elimination. Several vaccines have been demonstrated to have efficacy in experimental models, and vaccination of humans or domestic dogs may have a role in the control of the leishmaniases in the future.

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CHAPTER 312

African Trypanosomiasis (Sleeping Sickness; *Trypanosoma brucei* Complex)

Edsel Maurice T. Salvana, Robert A. Salata

Sixty million people in 36 countries are at risk for infection with *Trypanosoma brucei* complex, the causative agent of sleeping sickness. Also known as **human African trypanosomiasis (HAT)** , this disease is restricted to sub-Saharan Africa, the range of the tsetse fly vector. It is a disease of extreme poverty, with the highest disease burden observed in remote rural areas. HAT comes in 2 geographically and clinically distinct forms. *Trypanosoma brucei gambiense* causes a chronic infection and affects people who live in western and central Africa (**West African sleeping sickness** , **Gambian trypanosomiasis**). *Trypanosoma brucei rhodesiense* is a zoonosis that presents as an acute illness lasting several weeks and usually occurs in residents or travelers from eastern and southern Africa (**East African sleeping sickness** , **Rhodesian trypanosomiasis**).

Etiology

HAT is a vector-borne disease caused by parasitic, extracellular, flagellated kinetoplastid protozoans of 2 subspecies of *Trypanosoma brucei* . It is transmitted to humans through the bite of *Glossina* , commonly known as the **tsetse fly** .

Humans usually contract East African HAT when they venture from towns to rural areas to visit woodlands or livestock, highlighting the importance of zoonotic reservoirs in this disease. West African HAT is contracted closer to settlements and only requires a small vector population, making it difficult to eradicate. Animal reservoirs occur, but the main source of infection remains chronically infected human hosts.

Life Cycle

Trypanosoma brucei undergoes several stages of development in the insect and mammalian host. On ingestion with a blood meal, nonproliferative **short stumpy (SS)** forms of the parasite transform into procyclic forms in the insect's midgut. These procyclic forms proliferate and undergo further development into epimastigotes, which then become infective metacyclic forms that migrate to the insect's salivary glands. The life cycle within the tsetse fly takes 15-35 days. On inoculation into the mammalian host, the metacyclic stage transforms into proliferative **long slender (LS)** forms in the bloodstream and the lymphatics, eventually penetrating the central nervous system (CNS). LS forms appear in waves in the peripheral blood, with each wave followed by a febrile crisis and heralding the formation of a new antigenic variant. Once a critical density of LS forms is reached, a quorum-sensing mechanism causes most of these to transform into nonproliferative SS forms that are ingested by *Glossina* and start the cycle anew. Some LS forms remain to maintain the infection in the human host.

Direct transmission to humans has been reported, either vertically to infants or mechanically through contact with tsetse flies with viable LS forms on their mouthparts from a recent blood meal from an infected host.

Epidemiology

HAT remains a major public health problem in sub-Saharan Africa. It occurs in the region between latitudes 14 degrees north and 29 degrees south, where the annual rainfall creates optimal climatic conditions for *Glossina* . In 2009, because of intensive control efforts spearheaded by the World Health Organization (WHO), the number of new HAT cases annually fell below 10,000. In 2015, this further fell to 2,804 cases, with 84% of cases coming from the Democratic Republic of Congo. Gambian trypanosomiasis is targeted for sustainable elimination as a public health problem by 2030.

T. brucei rhodesiense infection is restricted to the eastern third of the endemic area in tropical Africa, stretching from Ethiopia to the northern boundaries of South Africa. *T. brucei gambiense* , which accounts for 98% of HAT cases, occurs mainly in the western half of the continent's endemic region. Rhodesian HAT, which has an acute and often fatal course, greatly reduces chances of transmission to tsetse flies. The ability of *T. brucei rhodesiense* to multiply rapidly in the bloodstream and infect other species of mammals helps maintain its life cycle.

Pathogenesis

At the site of the *Glossina* bite, tsetse fly salivary antigens, peptides, and proteins promote an immune-tolerant microenvironment that facilitates parasite invasion. Injected metacyclic parasites transform into LS forms, which rapidly divide by binary fission. The parasites, along with the attendant inflammation, cellular debris, and metabolic products, may give rise to a hard, painful, red nodule known as a **trypanosomal chancre** . Dissemination into the blood and lymphatic systems follows, with subsequent localization to the CNS. Histopathologic findings in the brain are consistent with meningoencephalitis, with lymphocytic infiltration and perivascular cuffing of the membranes. The appearance of **morula** cells of Mott (large, strawberry-like cells, supposedly derived from plasma cells) is a characteristic finding in chronic disease.

Mechanisms underlying virulence in HAT are still incompletely understood but seem to be mediated by a complex interplay of trypanosomal, human, and *Glossina* factors. *T. brucei gambiense* secretes a specific glycoprotein, TgsGP, while *T. brucei rhodesiense* expresses a protein known as serum resistance–associated protein (SRA), which counteracts trypanolytic apolipoprotein L-1 (ApoL1) in human serum. Trypanosomes also secrete a host of biologically active molecules that can dampen immune responses. For example, *T. brucei* adenylate cyclase (TbAdC) is hyperproduced when a trypanosome is phagocytosed by responding macrophages, causing a spike in cyclic adenosine monophosphate (cAMP), which then activates the macrophage's protein kinase and shuts down TNF-α production, acting as a Trojan horse and downregulating the immune response. Another molecule, *T. brucei* –derived kinesin heavy chain (TbKHC1), downregulates host nitrogen oxide production, dampening the proinflammatory response and causing an increase in production of host polyamines, which are essential nutrients for the parasite. Other parasite-derived molecules are involved in modulating B cell and macrophage responses, especially in chronic infection, resulting in an immune-tolerant condition that allows parasite proliferation without killing the host. Although antigenic variation of **variant surface glycoprotein (VSG)** on the trypanosome surface has long been recognized as a major factor in evading acquired immunity during infection, VSG also inhibits complement activation and antibody-mediated aggregation, facilitating establishment and maintenance of infection. Soluble VSG is hypersecreted, especially at the peak of parasitemia, and may serve as a decoy for antibodies and complement factor, diverting immune responses away from trypanosomes.

Clinical Manifestations

Clinical presentations vary not only because of the 2 subspecies of organisms but also because of differences in host response in the indigenous population of endemic areas and in newcomers or visitors. Visitors usually suffer more from the acute symptoms, but if untreated, death usually follows for natives and visitors alike. Symptoms usually occur within 2-3 wk of infection. The clinical syndromes of HAT are trypanosomal chancre, hemolymphatic stage, and meningoencephalitic stage.

Trypanosomal Chancre

The site of the tsetse fly bite may be the first presenting feature. A nodule or chancre (3-4 cm) develops in 2-3 days and becomes a painful, hard, red nodule surrounded by an area of erythema and swelling within 1 wk. Nodules are typically seen on the lower limbs and sometimes also on the head. They subside spontaneously in about 2 wk., leaving no permanent scar.

Hemolymphatic Stage (Stage 1)

The most common presenting features of acute HAT occur at the time of invasion of the bloodstream by the parasites, 2-3 wk after infection. Patients usually present with irregular episodes of fever, each lasting up to 7 days, accompanied by headache, sweating, and generalized lymphadenopathy. Attacks may be separated by symptom-free intervals of days or even weeks. Painless, nonmatted **lymphadenopathy** , most often of the posterior cervical and supraclavicular nodes, is one of the most constant signs, particularly in the

Gambian form. A common feature of trypanosomiasis in Caucasians is the presence of blotchy, irregular, nonpruritic, erythematous **macules** , which may appear any time after the first febrile episode, usually within 6-8 wk. The majority of macules have a normal central area, giving the rash a circinate outline. This **rash** is seen mainly on the trunk and is evanescent, fading in one place only to appear at another site. Examination of the blood during this stage may show anemia, leukopenia with relative monocytosis, and elevated levels of IgM. Cardiac manifestations of HAT have also been reported but are generally limited to nonspecific ST-T wave electrocardiographic abnormalities. Histopathologic characterization shows a lymphomonohistiocytic infiltrate in the interstitium, with no penetration of the myocardial cells, unlike that for American trypanosomiasis (see Chapter 313). The perimyocarditis is usually self-limited and does not typically progress to congestive heart failure.

Meningoencephalitic Stage (Stage 2)

Neurologic symptoms and signs are nonspecific, including irritability, insomnia, and irrational and inexplicable anxieties with frequent changes in mood and personality. Neurologic symptoms may precede invasion of the CNS by the organisms. In untreated *T. brucei rhodesiense* infections, CNS invasion occurs within 3-6 wk and is associated with recurrent bouts of headache, fever, weakness, and signs of acute toxemia. Death occurs in 6-9 mo as a result of secondary infection or cardiac failure.

In Gambian HAT, cerebral symptoms appear within 2 yr after the acute symptoms. An increase in drowsiness during the day and insomnia at night reflect the continuous progression of infection and may be accompanied by anemia, leukopenia, and muscle wasting. The chronic, diffuse meningoencephalitis without localizing symptoms is the form referred to as **sleeping sickness** . Drowsiness and an uncontrollable urge to sleep are the major features of this stage and become almost continuous in the terminal stages. Tremor or rigidity with stiff and ataxic gait suggest involvement of the basal ganglia. Psychotic changes occur in one third of untreated patients. While most untreated disease is fatal, in rare cases, individuals remain asymptomatic, clear parasitemia, and become seronegative.

Diagnosis

Definitive diagnosis can be established during the early stages by examination of a fresh, thick blood smear, which permits visualization of the motile active forms (Fig. 312.1). HAT can also be detected from blood using a variety of sensitive techniques, such as quantitative buffy coat smears and mini anion exchange resins. The **card agglutination trypanosomiasis test** (CATT) is of value for epidemiologic purposes and for screening for *T. brucei gambiense* . Dried, Giemsa-stained smears should be examined for the detailed morphologic features of the organisms. If a thick blood or buffy coat smear is negative, concentration techniques may help. Aspiration of an enlarged lymph node can also be used to obtain material for parasitologic examination. If positive, cerebrospinal fluid (CSF) should also be examined for the organisms. The presence of trypanosomes, or ≥5 white blood cells (WBCs)/µL, or both, is indicative of stage 2 disease. If trypanosomes are absent in the CSF, some authorities use a count of 10 to 20 WBCs/µL as a cutoff for diagnosing late-stage disease. Polymerase chain reaction–based tests have been shown to be highly sensitive and specific, but these tests require advanced laboratory facilities. Field-based loop-mediated isothermal amplification tests have been developed and validated. Low cost, stable, but highly specific rapid tests such as the HAT Sero-Strip and HAT Sero-K-SeT, which detect trypanosome-specific antibodies, have been developed and may prove to be useful for point-of-care diagnosis as the focus shifts from control to elimination. Other areas of active research for diagnostics include new biomarkers, cytokine profiles, proteomics, and polysomnography, which are being used not only to identify disease but to differentiate disease stages.

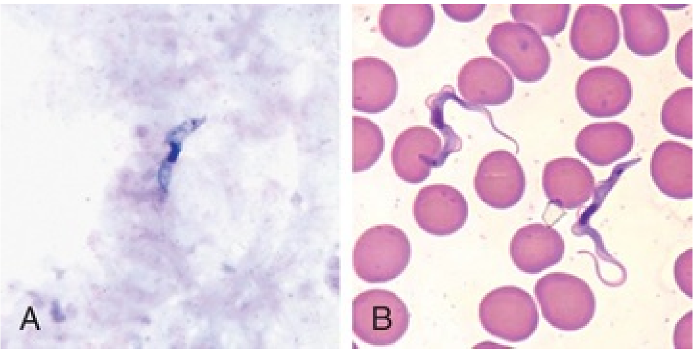

FIG. 312.1 *Trypanosoma brucei* sp. trypomastigotes in thick blood smear stained with Giemsa (**A**) and thin blood smear stained with Wright-Giemsa (**B**). (From Centers for Disease Control and Prevention: Laboratory identification of parasites of public health concern. Trypanosomiasis,

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Treatment

The choice of chemotherapeutic agents for treatment depends on the stage of the infection and the causative organisms.

Stage 1 Treatment

Hematogenous forms of both Rhodesian and Gambian HAT can be treated with either suramin or pentamidine, which are better tolerated than drugs for stage 2 or CNS disease but are associated with substantial risks of toxicity. **Suramin** is a polysulphonated symmetric naphthalene derivative given as a 10% solution for intravenous (IV) administration. A **test dose** (10 mg for children; 100-200 mg for adults) is initially administered to detect rare idiosyncratic reactions of shock and collapse. The dose for subsequent IV injections is 20 mg/kg (maximum 1 g) administered on days 1, 3, 7, 14, and 21. Suramin is nephrotoxic, and thus a urinalysis should be performed before each dose. Marked proteinuria, blood, or casts is a contraindication to continuation of suramin. Resistance is rare but has been reported.

Pentamidine isethionate (4 mg/kg/day intramuscularly [IM] daily or on alternate days for 7-10 days) concentrates to high levels in trypanosomes and is highly trypanocidal. It is better tolerated than suramin but carries significant risk of hypoglycemia, nephrotoxicity, hypotension, leukopenia, and liver enzyme elevation. Because of its potency, long half-life, and toxicity, short-course treatment is desirable and is being investigated.

Stage 2 Treatment

The treatment of late-stage *T. brucei gambiense* has substantially changed because of programmatic efforts of the WHO and the donation of large quantities of trypanosomicidal drugs, including eflornithine, pentamidine, suramin, and nifurtimox. Combination **eflornithine and nifurtimox** (NECT) is the treatment of choice for *T. brucei gambiense* CNS infection. This regimen is noninferior to eflornithine monotherapy, and the duration of treatment is shorter. For combination therapy, eflornithine is given at 400 mg/kg/day intravenously (IV) divided every 12 hr for 7 days, along with nifurtimox, 15 mg/kg/day orally divided every 8 hr for 10 days. If nifurtimox is unavailable, eflornithine monotherapy can be given at 400 mg/kg/day IV divided every 6 hr for 14 days. Adverse reactions to these regimens include fever, hypertension, and seizures, with NECT having less frequent events.

Melarsoprol is an arsenical compound and is the only effective treatment for late *T. brucei rhodesiense* disease. Treatment of children is initiated at 0.36 mg/kg IV once daily, with gradually escalating doses every 1-5 days to 3.6 mg/kg once daily; treatment is usually 10 doses (18-25 mg/kg total dose). Treatment of adults is with melarsoprol 2-3.6 mg/kg IV once daily for 3 days; and after 1 wk, 3.6 mg/kg once daily for 3 days, which is repeated after 10-21 days. An alternative regimen is 2.2 mg/kg once daily for 10 days. Guidelines recommend 18-25 mg/kg total over 1 mo. Reactions such as fever, abdominal pain, and chest pain are rare but may occur during or shortly after administration. Serious toxic effects include encephalopathy and exfoliative dermatitis.

Difficulty in administering IV medications, severe side effects, and the emergence of drug resistance have led to the search for better antitrypanosomal agents. Two oral drugs, **fexinidazole** and **benzoxaborole** , are very promising and are currently in clinical trials. Efforts to decrease the toxicity of melarsoprol by making it more water soluble are also being studied.

Prevention

A vaccine or consistently effective prophylactic therapy is not available and is particularly challenging because of the antigenic variation caused by VSGs. A single injection of pentamidine (3-4 mg/kg IM) provides protection against Gambian trypanosomiasis for at least 6 mo, but the effectiveness against the Rhodesian form is uncertain.

Vector control programs against *Glossina* have been essential in controlling disease, coupled with the use of screens, traps, insecticides, and sanitary measures. Control of infection in animal reservoirs with mass administration of trypanocidal drugs in cattle has met with some success. Neutral-colored clothing may reduce tsetse fly bites. Mobile medical surveillance of the population at risk by specialized staff has been done, and strong collaboration among WHO, Medecins sans Frontieres, and African governments has shifted the burden of treatment to well-organized and well-funded national control programs.

Transgenic techniques, including using **endosymbiotic bacteria** that confer trypanosome resistance to *Glossina,* are being developed and considered.

The full genome of *T. brucei* with about 9,000 genes has been sequenced. Approximately 10% of these genes encode VSGs. This advance has helped identify genes relevant to the disease and its possible prevention, as well as the design of new antitrypanosomal drugs, including those that target specific metabolic pathways.

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CHAPTER 313

American Trypanosomiasis (Chagas Disease; *Trypanosoma cruzi*)

Edsel Maurice T. Salvana, Robert A. Salata

American trypanosomiasis or Chagas disease is caused by the protozoan *Trypanosoma cruzi* . Its natural vectors are the reduviid insects, specifically **triatomines** , variably known as wild bedbugs, assassin bugs, or kissing bugs. It can also be transmitted orally from contaminated food, vertically from mother to child, and through blood transfusion or organ transplantation. Signs and symptoms of acute Chagas disease are usually nonspecific, whereas chronic disease may manifest as cardiomyopathy or severe gastrointestinal (GI) dilation and dysfunction.

Etiology

American trypanosomiasis is caused by *Trypanosoma cruzi* , a parasitic, flagellated kinetoplastid protozoan. The main vectors for *T. cruzi* are insects of the family Reduviidae, subfamily Triatominae, which includes *Triatoma infestans, Rhodnius prolixus,* and *Panstrongylus megistus.*

Life Cycle

T. cruzi has 3 recognizable morphogenetic phases: amastigotes, trypomastigotes, and epimastigotes (Figs. 313.1 and 313.2). **Amastigotes** are intracellular forms found in mammalian tissues that are spherical and have a short flagellum but form clusters of oval shapes (pseudocysts) within infected tissues. **Trypomastigotes** are spindle-shaped, extracellular, nondividing forms that are found in blood and are responsible for both transmission of infection to the insect vector and cell-to-cell spread of infection. **Epimastigotes** are found in the midgut of the vector insect and multiply in the midgut and rectum of arthropods, differentiating into metacyclic forms. **Metacyclic trypomastigotes** are the infectious form for humans and are released onto the skin of a human when the insect defecates close to the site of a bite, entering through the damaged skin or mucous membranes. Once in the host, these multiply intracellularly as amastigotes, which then differentiate into bloodstream trypomastigotes and are released into the circulation when the host cell ruptures. Bloodborne trypomastigotes circulate until they enter another host cell or are taken up by the bite of another insect, completing the life cycle.

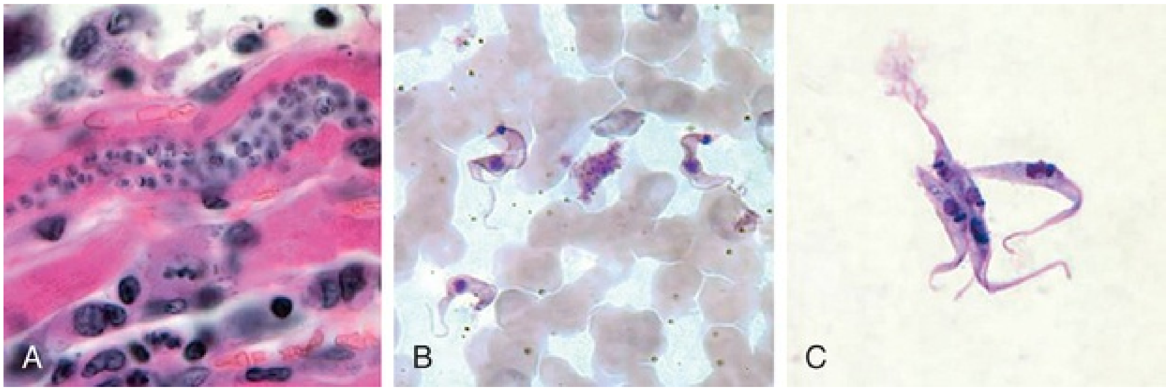

FIG. 313.1 Stages of *Trypanosoma cruzi* . A, Amastigote; B, trypomastigote; C, epimastigote. (From Centers for Disease Control and Prevention: Laboratory identification of parasites of public health concern. Trypanosomiasis, American [website], 2018. https://www.cdc.gov/dpdx/trypanosomiasisamerican/index.html .)

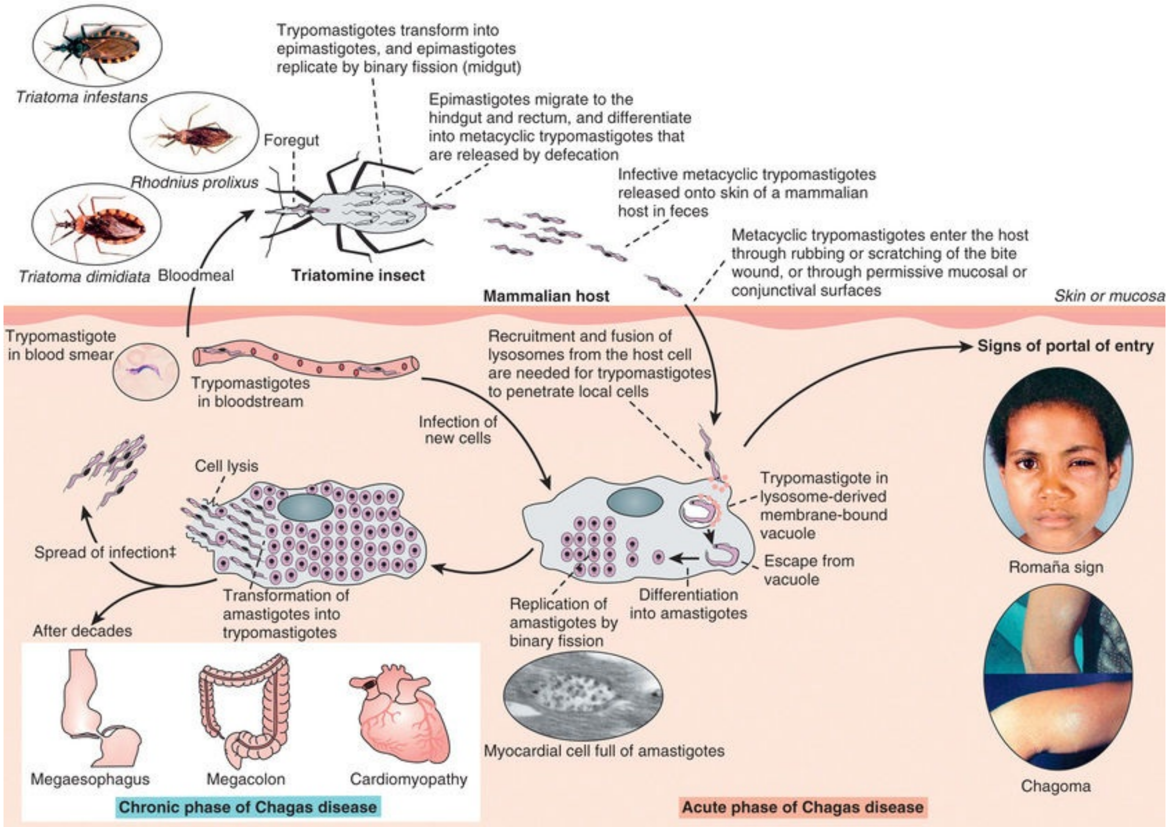
Triatoma infestans
Rhodnius prolixus
Triatoma dimidiata
Bloodmeal
Foregut
Trypomastigotes transform into epimastigotes, and epimastigotes replicate by binary fission (midgut)
Epimastigotes migrate to the hindgut and rectum, and differentiate into metacyclic trypomastigotes that are released by defecation
Triatomine insect
Infective metacyclic trypomastigotes released onto skin of a mammalian host in feces
Metacyclic trypomastigotes enter the host through rubbing or scratching of the bite wound, or through permissive mucosal or conjunctival surfaces
Mammalian host
Skin or mucosa
Trypomastigote in blood smear
Trypomastigotes in bloodstream
Recruitment and fusion of lysosomes from the host cell are needed for trypomastigotes to penetrate local cells
Signs of portal of entry
Infection of new cells
Cell lysis
Spread of infection‡
Trypomastigote in lysosome-derived membrane-bound vacuole
Escape from vacuole
Romaña sign
Transformation of amastigotes into trypomastigotes
Replication of amastigotes by binary fission
Differentiation into amastigotes
After decades
Megaesophagus
Megacolon
Cardiomyopathy
Myocardial cell full of amastigotes
Chagoma
Chronic phase of Chagas disease
Acute phase of Chagas disease

FIG. 313.2 **Vector-borne transmission and life cycle of *Trypanosoma cruzi* . (From Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease, *Lancet* 375:1388–1400, 2010, Fig 1.)**

Epidemiology

Natural transmission of Chagas disease occurs in North and South America, most frequently in continental Latin America. The disease may arise elsewhere because of migration and transmission through contaminated blood. World Health Organization (WHO) and Pan-American Health Organization–led efforts in large-scale vector control, blood donor screening to prevent transmission through transfusion, and case finding and treatment of chronically infected mothers and newborn infants have effectively halted transmission in a number of areas of South America. The number of cases has dropped from a peak of 24 million in 1984 to a current estimate of 6-7 million, with about 10,000 deaths annually. Overall vectorial transmission continues to drop, although challenges remain, including the emergence of disease in new areas thought to be Chagas free, along with reemergence in previously controlled areas.

Infection is divided into 2 main phases: acute and chronic (Table 313.1). **Acute infection** is asymptomatic in up to 95% of infected individuals, but can manifest as fever, lymphadenopathy, organomegaly, myocarditis, and meningoencephalitis. **Chronic infection** in 60–70% of patients is *indeterminate,* meaning the patient is asymptomatic but has a positive antibody titer. Approximately 30% of infected persons proceed to chronic determinate or symptomatic *T. cruzi* infection. The *T. cruzi* genome has been fully sequenced and contains 12,000 genes, the most widely expanded among trypanosomatids, and may reflect its ability to invade a wide variety of host tissues. Significant variability has been also found, along with extensive epigenetic modification of surface proteins, which may contribute to immune evasion. Six *discrete typing units* (DTUs) are recognized, referred to as TcI to TcVI. A newly described 7th type called Tcbat has recently been identified. DTUs may differ in geographic distribution, predominant vector, and hosts and may also differ in disease manifestations and response to treatment.

Table 313.1

Clinical Features and Diagnosis of Chagas Disease

	GEOGRAPHIC DISTRIBUTION	CLINICAL SIGNS/SYMPTOMS	DIAGNOSIS
ACUTE FORMS *			
Vectorial	Endemic countries	Incubation period: 1-2 wk Signs of portal of entry: indurated cutaneous lesion (chagoma) or palpebral edema (Romaña sign) Most cases are mild disease (95–99%) and unrecognized. Persistent fever, fatigue, lymphadenopathy, hepatomegaly, splenomegaly, morbilliform rash, edema In rare cases, myocarditis or meningoencephalitis Anemia, lymphocytosis, elevated AST/ALT concentrations Risk of mortality: 0.2–0.5%	Direct parasitological methods: patent parasitemia up to 90 days Microscopic examination of fresh blood, Giemsa-stained thin and thick blood films, or buffy coat Concentration methods: microhematocrit and Strout method PCR techniques Serology is not useful.
Congenital	Endemic and nonendemic countries	Incubation period: birth to several weeks Most are asymptomatic or have mild disease. Prematurity, low birthweight, abortion,	Direct parasitological methods Concentration

		neonatal death Fever, jaundice, edema, hepatomegaly, splenomegaly, respiratory distress syndrome, myocarditis, meningoencephalitis Anemia and thrombocytopenia Risk of mortality: <2%	methods: microhematocrit, Strout method Direct microscopy also useful PCR: most sensitive technique Serology: after 9 mo or later
Oral	Restricted areas of endemic countries (Amazon basin) and local outbreaks	Incubation period: 3-22 days Fever, vomiting, periocular edema, dyspnea, fever, myalgia, prostration, cough, splenomegaly, hepatomegaly, chest pain, abdominal pain, digestive hemorrhage Risk of mortality: 1–35%	Same as for vectorial.
Transfusion and transplant	Endemic and nonendemic countries	Incubation period: 8-160 days; persistent fever Clinical characteristics similar to those of vectorial cases (excluding portal of entry signs) Risk of mortality is variable and depends on the severity of baseline disease.	Same as for vectorial. PCR techniques usually yield positive results days to weeks before trypomastigotes are detectable in blood. Tissue samples are needed in some circumstances.
Reactivation in HIV-infected patients	Endemic and nonendemic countries	Behaves as other opportunistic infections Reactivation with <200 CD4 cells per µL (mostly with <100) Affects CNS (75–90%) as single or multiple space-occupying lesions or as severe necrohemorrhagic meningoencephalitis Cardiac involvement (10–55%): myocarditis, pericardial effusion or worsening of previous cardiomyopathy Risk of mortality: 20%	Direct parasitological methods, as in vectorial cases. Parasite can be found in CSF, other body fluids, and tissue samples. PCR: not useful for diagnosis of reactivation Serology: indicative of chronic infection and helpful in cases of suspected disease
Reactivation in other immunosuppressed patients	Endemic and nonendemic countries	Reactivation after transplantation or in patients with hematologic malignancies Clinical characteristics similar to those of patients who undergo transfusion and those with panniculitis and other skin disorders Risk of mortality is variable and depends on severity of baseline disease and prompt diagnosis.	Direct parasitological methods, as in vectorial cases. Parasite can be found in tissue samples. PCR: increasing parasite load detected with real-

			time PCR in serial specimens could be indicative of a high risk of reactivation.
CHRONIC FORMS			
Indeterminate	Endemic and nonendemic countries	Asymptomatic Normal chest radiograph and 12-lead ECG.	Serology: detection of IgG PCR: low sensitivity
Cardiac and gastrointestinal	Endemic and nonendemic countries	Cardiac manifestations: fatigue, syncope, palpitations, dizziness, stroke; late manifestations: chest pain (atypical), dyspnea, edema, left ventricular dysfunction, congestive heart failure; alterations in 12-lead ECG, echocardiography, or other heart function tests Gastrointestinal: dysphagia, regurgitation, severe constipation (dilated esophagus or colon); alterations in esophageal manometry, barium swallow, or barium enema	Serology: detection of IgG PCR: low sensitivity

[*] Including reactivation in immunosuppressed patients.

ALT, Alanine transaminase; AST, aspartate transaminase; CNS, central nervous system; CSF, cerebrospinal fluid; ECG, electrocardiogram; PCR, polymerase chain reaction.

From Pérez-Molina J, Molina I: Chagas disease, *Lancet* 391:82–92, 2018 (Table 2).

T. cruzi infection is primarily a zoonosis, and humans are incidental hosts. *T. cruzi* has a large sylvan reservoir and has been isolated from numerous animal species. The presence of reservoirs and vectors of *T. cruzi* and the socioeconomic and educational levels of the population are the most important risk factors for vector-borne transmission to humans. Insect vectors are found in rural, wooded areas and acquire infection through ingestion of blood from humans or animals with circulating trypomastigotes.

Housing conditions are very important in the transmission chain. Incidence and prevalence of infection depend on the adaptation of the triatomines to human dwellings, as well as the vector capacity of the species. Animal reservoirs of reduviid bugs include dogs, cats, rats, opossum, guinea pigs, monkeys, bats, and raccoons. Humans often become infected when land in enzootic areas is developed for agricultural or commercial purposes. An estimated 238,000 immigrants from endemic countries living in the United States are likely infected with *T. cruzi* . Increasing cases of **autochthonous** transmission in the United States have also been reported and confirmed with molecular typing, particularly from California, Louisiana, Texas, and Georgia, although these numbers remain small. One study found that 5.2% of Latin America immigrants in Los Angeles with conduction abnormalities on electrocardiogram (ECG) were seropositive for *T. cruzi* .

Humans can be infected transplacentally, occurring in 10.5% of infected mothers and causing congenital Chagas disease. Transplacental infection is associated with premature birth, fetal wastage, and placentitis. Disease transmission can occur through blood transfusions in endemic areas from asymptomatic blood donors. Seropositivity rates in endemic areas are as high as 20%. The risk for transmission through a single blood transfusion from a chagasic donor is 13–23%. Blood screening for Chagas disease in the United States was started in 2006 and has detected >2,200 seropositive cases since February 2017 (www.aabb.org). Percutaneous injection as a result of laboratory accidents is also a documented mode of transmission. Oral transmission through **contaminated food** is an increasingly important method of transmission as vector transmission is successfully interrupted by control programs. Although breastfeeding is an uncommon mode of transmission, women with acute infections should not nurse until they have been treated.

Pathogenesis

Acute Disease

At the site of entry or puncture site, neutrophils, lymphocytes, macrophages, and monocytes infiltrate. *T. cruzi* organisms are engulfed by macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, and replicate. A local tissue reaction, the **chagoma** , develops, and the process extends to a local lymph node (see Fig. 313.2). Blood forms appear, and the process disseminates. Immune evasion and dissemination seem to be facilitated by secretory products from parasite microvesicles and host cell–derived exosomes. These include molecules that facilitate host-parasite adhesion; small tRNAs that increase susceptibility of the host cell to infection; *cruzipain,* which digests human IgG subclasses and facilitates host cell invasion; and other molecules with different functions that make up hundreds of substances found in the microvesicles and exosomes. CCR5 seems to play a dual role in disease severity, helping control infection in the acute phase, but contributing to increased inflammation and myocardial tissue damage when upregulated in chronic infection. The interplay of these cytokines and associated receptors results in a wide variability in disease manifestations and progression to chronic disease. Acute myocarditis likely occurs in all patients with acute disease but is frequently asymptomatic and may only be apparent on biopsy.

Chronic Disease

The pathophysiology of chronic Chagas disease is incompletely understood, but significant progress has recently been made using highly sensitive, quantitative polymerase chain reaction (PCR) methods and real-time bioluminescent markers in animal models. The major driver of cardiac pathology is likely caused by sporadic and repeated bouts of **tissue invasion** from a persistent source, likely the gut, causing lymphocytic infiltration and cumulative fibrosis. Molecular mimicry of host antigens by the parasite and consequent autoimmune stimulation of neurologic receptors were previously thought to be the main driver of cardiomyopathy, but this phenomenon does not seem to occur outside concomitant infection.

T. cruzi demonstrates tropism for certain tissues. It is **myotropic** and invades smooth, skeletal, and heart muscle cells. Attachment is mediated by specific receptors that attach to complementary glycoconjugates on the host cell surface. Attachment to cardiac muscle results in inflammation of the endocardium and myocardium, edema, focal necrosis in the contractile and conducting systems, periganglionitis, and lymphocytic inflammation. The heart becomes enlarged, and endocardial thrombosis or aneurysm may result. Right bundle branch block (RBBB) is common. Parasites also attach to neural cells and reticuloendothelial cells. In patients with gastrointestinal tract involvement, myenteric plexus destruction leads to pathologic organ dilation. Antibodies involved with resistance to *T. cruzi* are related to the phase of infection. IgG antibodies, probably to several major surface antigens, mediate immunophagocytosis of *T. cruzi* by macrophages. Conditions that depress cell-mediated immunity increase the severity of *T. cruzi* infection. There is increasing evidence that host genetic factors play a significant role in progression and severity of chronic disease.

Clinical Manifestations

Acute Chagas disease in children is usually asymptomatic or is associated with mild febrile illness characterized by malaise, facial edema, and lymphadenopathy (see Table 313.1). Infants often demonstrate local signs of inflammation at the site of parasite entry, which is then referred to as a **chagoma** . Approximately 50% of children come to medical attention with the **Romaña sign** (unilateral, painless eye swelling), conjunctivitis, and preauricular lymphadenitis. Patients complain of fatigue and headache. Fever can persist for 4-5 wk. More severe systemic presentations can occur in children <2 yr old and may include lymphadenopathy, hepatosplenomegaly, and meningoencephalitis. A cutaneous morbilliform eruption can accompany the acute syndrome. Anemia, lymphocytosis, hepatitis, and thrombocytopenia have also been described.

The heart, central nervous system (CNS), peripheral nerve ganglia, and reticuloendothelial system are often heavily parasitized. The heart is the primary target organ. The intense parasitism can result in acute inflammation and in 4-chamber cardiac dilation. Diffuse myocarditis and inflammation of the conduction system can lead to the development of fibrosis. Histologic examination reveals the characteristic **pseudocysts** , which are the intracellular aggregates of amastigotes.

Intrauterine infection in pregnant women can cause spontaneous abortion or premature birth. In children with congenital infection, severe anemia, hepatosplenomegaly, jaundice, and seizures can mimic congenital cytomegalovirus infection, toxoplasmosis, and erythroblastosis fetalis. *T. cruzi* can be visualized in the cerebrospinal fluid in cases of meningoencephalitis. Children usually undergo spontaneous remission in 8-12 wk and enter indeterminate chronic phase with lifelong low-grade parasitemia and development of antibodies to many *T. cruzi* cell surface antigens. In acute disease, mortality is 5–10%, with deaths caused by acute myocarditis, with resultant heart failure, or meningoencephalitis. Acute Chagas disease should be differentiated from malaria, schistosomiasis, visceral leishmaniasis, brucellosis, typhoid fever, and infectious mononucleosis.

Autonomic dysfunction and peripheral neuropathy can occur. CNS involvement in Chagas disease is uncommon. If granulomatous encephalitis occurs in the acute infection, it is usually fatal.

Chronic Chagas disease may be asymptomatic or symptomatic. The most common presentation of chronic *T. cruzi* infection is **cardiomyopathy** , manifested by congestive heart failure, arrhythmia, and thromboembolic events. ECG abnormalities include partial or complete atrioventricular block and RBBB. Left bundle branch block is unusual. Myocardial infarction has been reported and may be secondary to left apical aneurysm embolization or necrotizing arteriolitis of the microvasculature. Left ventricular apical aneurysms are pathognomonic of chronic chagasic cardiomyopathy.

Gastrointestinal manifestations of chronic Chagas disease occur in 8–10% of patients and involve a diminution in the Auerbach and the Meissner plexus. There are also preganglionic lesions and a reduction in the number of dorsal motor nuclear cells of the vagus nerve. Characteristically, this involvement presents clinically as megaesophagus and megacolon. Sigmoid dilation, volvulus, and fecalomas are often found in **megacolon** . Loss of ganglia in the esophagus results in abnormal dilation; the esophagus can reach up to 26 times its normal weight and hold up to 2 L of excess fluid. **Megaesophagus** presents as dysphagia, odynophagia, and cough. Esophageal body abnormalities occur independently of lower esophageal dysfunction. Megaesophagus can lead to esophagitis and cancer of the esophagus. Aspiration pneumonia and pulmonary tuberculosis are also more common in patients with megaesophagus.

Immunocompromised Persons

T. cruzi infections in immunocompromised persons may be caused by **transmission** from an asymptomatic donor of blood products or **reactivation** of prior infection. Organ donation to allograft recipients can result in a devastating form of the illness. Cardiac transplantation for Chagas cardiomyopathy has resulted in reactivation, despite prophylaxis and postoperative treatment with benznidazole. HIV infection also leads to reactivation in about 20% of cases; cerebral lesions are more common in these patients and can mimic *Toxoplasma* encephalitis. Myocarditis is also frequently observed, and secondary prophylaxis may be of benefit in some HIV–co-infected patients. In immunocompromised patients at risk for reactivation, serologic testing and close monitoring are necessary.

Diagnosis

A careful history with attention to geographic origin and travel is important. A peripheral blood smear or a Giemsa-stained smear during the acute phase of illness may show motile trypanosomes, which is diagnostic for Chagas disease (see Fig. 313.1). These are only seen in the 1st 6-12 wk of illness. Buffy coat smears may improve yield.

Most persons seek medical attention during the chronic phase of the disease, when parasites are not found in the bloodstream and clinical symptoms are not diagnostic. Serologic testing is used for diagnosis, most commonly enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination, and indirect fluorescent antibody testing. No single serology test is sufficiently reliable to make the diagnosis, so repeat or parallel testing using a different method or antigen is required to confirm the result of an initial positive serologic test, and in the case of discordant results, a 3rd test may be employed. Two tests, the Ortho *T. cruzi* ELISA Test System and the Abbott Prism Chagas Assay, are approved by the U.S. Food and Drug Administration (FDA) for screening of blood donors but not for clinical samples. For clinical samples in suspected Chagas cases in the USA, contact the Centers for Disease Control and Prevention (CDC) for further guidance. Confirmatory tests used typically include the radiologic immunoprecipitation assay (Chagas RIPA, used as an unlicensed confirmatory test in U.S. blood donors from 2006 to 2014) and Western blot assays based on trypomastigote excreted-secreted antigens (TESA-WB). Since 2014, the Abbott Enzyme Strip Assay Chagas using recombinant *T. cruzi* antigens has been FDA-approved and used for confirmation in blood donors.

Nonimmunologic methods of diagnosis are available. Mouse inoculation and **xenodiagnosis** (allowing uninfected reduviid bugs to feed on a patient's blood and examining the intestinal contents of those bugs 30 days after the meal) are cumbersome and not routinely performed. Parasites can be cultured in Novy-MacNeal-Nicolle (NNN) media. PCR tests of nuclear and kinetoplast DNA sequences have been developed and can be highly sensitive in acute disease, but are less reliable in chronic disease. PCR is not sufficiently sensitive for blood screening and was positive in only 1 of 22 RIPA-confirmed donors in the United States. Moreover, there is significant variability among methods and parasite strains. Diagnosis of congenital transmission in newborns cannot be made at birth with serology because of the presence of maternal antibodies in the 1st 6 mo of life. Microscopic examination, parasite culture, or PCR can be used. However, a serologic test at 6-12 mo is recommended to exclude infection definitively.

Treatment

Biochemical differences between the metabolism of American trypanosomes and that of mammalian hosts have been exploited for chemotherapy. Trypanosomes are very sensitive to oxidative radicals and do not possess catalase or glutathione reductase/glutathione peroxidase, which are key enzymes in scavenging free radicals. All trypanosomes also have an unusual reduced nicotinamide adenine dinucleotide phosphate (NADPH)–dependent disulfide reductase. Drugs that stimulate hydrogen peroxide (H_2O_2) generation or prevent its utilization are potential trypanosomicidal agents. Other biochemical pathways that have been targeted include ergosterol synthesis using azole compounds and the hypoxanthine-guanine phosphoribosyltransferase pathway using allopurinol.

Drug treatment for T. cruzi infection is currently limited to nifurtimox and benznidazole. Both are effective against trypomastigotes and amastigotes and have been used to eradicate parasites in the acute stages of infection. Treatment responses vary according to the phase of Chagas disease, duration of treatment, dose, age of the patient, and geographic origin of the patient. For acute disease, the average cure rate is about 60–80%. Cure of chronic disease is difficult to assess due to the different definitions of cure, whether with a negative serology or quantitative polymerase chain reaction. In recent trials, benznidazole has shown a cure rate of about 30% using ELISA, and 46–90% using PCR. A trial for chronic disease efficacy with nifurtimox is ongoing. Neither drug is safe in pregnancy. Recent trials with posaconazole, fexinidazole, and E1224 (a prodrug of ravuconazole) for chronic disease have been disappointing.

Benznidazole is a nitroimidazole derivative that may be slightly more effective than nifurtimox. Recent work in metabolomics has shown that benznidazole's primary mechanism of action involves covalent binding with trypanosomal protein thiols and low-molecular-weight thiols, resulting in depletion of these molecules and disruption of the parasite metabolism. The recommended treatment regimen for children <12 yr old is 10 mg/kg/day orally (PO) divided twice daily (bid) for 60 days, and for those >12 yr old, 5-7 mg/kg/day PO bid for 60 days. This drug is associated with significant toxicity, including rash, photosensitivity, peripheral neuritis, granulocytopenia, and thrombocytopenia.

Nifurtimox generates highly toxic oxygen metabolites through the action of nitroreductases, which produce unstable nitroanion radicals, which in turn react with oxygen to produce peroxide and superoxide free radicals. The treatment regimen for children 1-10 yr old is 15-20 mg/kg/day PO divided 4 times daily (qid) for 90 days; for children 11-16 yr, 12.5-15 mg/kg/day PO qid for 90 days; and for children >16 yr, 8-10 mg/kg/day PO divided 3-4 times daily for 90-120 days. Nifurtimox has been associated with weakness, anorexia, gastrointestinal disturbances, toxic hepatitis, tremors, seizures, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.

With the adoption by WHO of control and elimination strategies for Chagas disease, both acute and chronic disease should be treated. Serologic conversion is seen as an appropriate treatment response for chronic disease, although some patients who achieve this still eventually develop symptoms. One study reported cure rates as high as 97% for chronic disease in patients <16 yr old and supports early and aggressive case finding and treatment. Continuing efforts for elimination will necessitate development of more accurate diagnostics and more effective drugs, particularly for chronic disease. Treatment of congestive heart failure is generally in line with recommendations for management of dilated cardiomyopathy from other causes. β-Adrenergic blockers have been validated in the management of these patients. Digitalis toxicity occurs frequently in patients with Chagas cardiomyopathy. Pacemakers may be necessary in cases of severe heart block. Although cardiac transplantation has been used successfully in chagasic patients, it is reserved for those with the most severe disease manifestations. Plasmapheresis to remove antibodies with adrenergic activity has been proposed for refractory patients; this approach has worked in patients with dilated cardiomyopathy from other causes, but its application to Chagas disease is unproved.

A light, balanced diet is recommended for **megaesophagus** . Surgery or dilation of the lower esophageal sphincter treats megaesophagus; pneumatic dilation is the superior mode of therapy. Nitrates and nifedipine have been used to reduce lower esophageal sphincter pressure in patients with megaesophagus. Treatment of **megacolon** is surgical and symptomatic. Treatment of meningoencephalitis is also supportive.

In accidental infection when parasitic penetration is certain, treatment should be immediately initiated and continued for 10-15 days. Blood is usually collected and serologic samples tested for seroconversion at 15, 30, and 60 days.

Prevention

Massive coordinated vector control programs under the auspices of WHO and the Pan-American Health Organization and the institution of widespread blood donor screening and targeted surveillance of chronically infected mothers and infants at risk have effectively eliminated or at least drastically reduced transmission in most endemic countries. Chagas disease remains linked to poverty, and thus improvement of living conditions is likewise essential to successful control and eradication. Education of residents in endemic areas, use of bed nets, use of insecticides, and destruction of adobe houses that harbor reduviid bugs are effective methods to control the bug population. Synthetic pyrethroid insecticides help keep houses free of vectors for up to 2 yr and have low toxicity for humans. Paints incorporating insecticides have also been used. A therapeutic vaccine composed of bivalent recombinant *T. cruzi* antigens has been shown to be effective in preclinical proof-of-concept animal models and is currently undergoing further development.

Blood transfusions in endemic areas are a significant risk. **Gentian violet** , an amphophilic cationic agent that acts photodynamically, has been used to kill the parasite in blood. Photoirradiation of blood containing gentian violet and ascorbate generates free radicals and superoxide anions that are trypanosomicidal. **Mepacrine** and **maprotiline** have also been used to eradicate the parasite in blood transfusions.

Because immigrants can carry this disease to nonendemic areas, serologic testing should be performed in blood and organ donors from endemic areas. Potential seropositive donors can be identified by determining whether they have been or have spent extensive time in an endemic area. Questionnaire-based screening of potentially infected blood and organ donors from areas endemic for infection can reduce the risk for transmission. Seropositivity should be considered a contraindication to organ donation, particularly for heart transplantation.

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CHAPTER 314

Malaria *(Plasmodium)*

Chandy C. John

Malaria is an acute illness characterized by paroxysms of fever, chills, sweats, fatigue, anemia, and splenomegaly. It has played a major role in human history, causing harm to more people than perhaps any other infectious disease. Although substantial progress has been made in combating malaria in endemic areas, with a 37% reduction in malaria incidence and 60% reduction in malaria mortality, malaria remains one of the leading causes of morbidity and mortality worldwide, with an estimated 214 million cases and 438,000 deaths in 2015. Malarial deaths in areas of high malaria transmission occur primarily in children <5 yr of age, but in areas of low transmission, a large percentage of deaths may occur in older children and adults. Although malaria is not endemic in the United States, 1,500-2,000 imported cases are seen in the United States each year. Physicians practicing in nonendemic areas should consider the diagnosis of malaria in any febrile child who has returned from a malaria-endemic area within the previous year, because delay in diagnosis and treatment can result in severe illness or death.

Etiology

Malaria is caused by intracellular *Plasmodium* protozoa transmitted to humans by female *Anopheles* mosquitoes. Before 2004, only 4 species of *Plasmodium* were known to cause malaria in humans: *P. falciparum, P. malariae, P. ovale* , and *P. vivax* . In 2004, *P. knowlesi* (a primate malaria species) was also shown to cause human malaria, and cases of *P. knowlesi* infection have been documented in Malaysia, Indonesia, Singapore, and the Philippines. Malaria also can be transmitted through blood transfusion and use of contaminated needles and transplacentally from a pregnant woman to her fetus. The risk for blood transmission is low in the United States, but may occur through transfusion of whole blood, packed red blood cells (RBCs), platelets, and leukocytes and through organ transplantation.

Epidemiology

Malaria is a major worldwide problem, occurring in 95 countries that comprise approximately half the world's population (Fig. 314.1). The principal areas of transmission are Africa, Asia, and South America. *P. falciparum* and *P. malariae* are found in most malarious areas. *P. falciparum* is the predominant species in Africa, Haiti, and New Guinea. *P. vivax* predominates in Bangladesh, Central America, India, Pakistan, and Sri Lanka. *P. vivax* and *P. falciparum* predominate in Southeast Asia, South America, and Oceania. *P. ovale* is the least-common species and is transmitted primarily in Africa. Transmission of malaria has been eliminated in most of North America (including the United States), Europe, and most of the Caribbean, as well as Australia, Chile, Israel, Japan, Lebanon, and Taiwan.

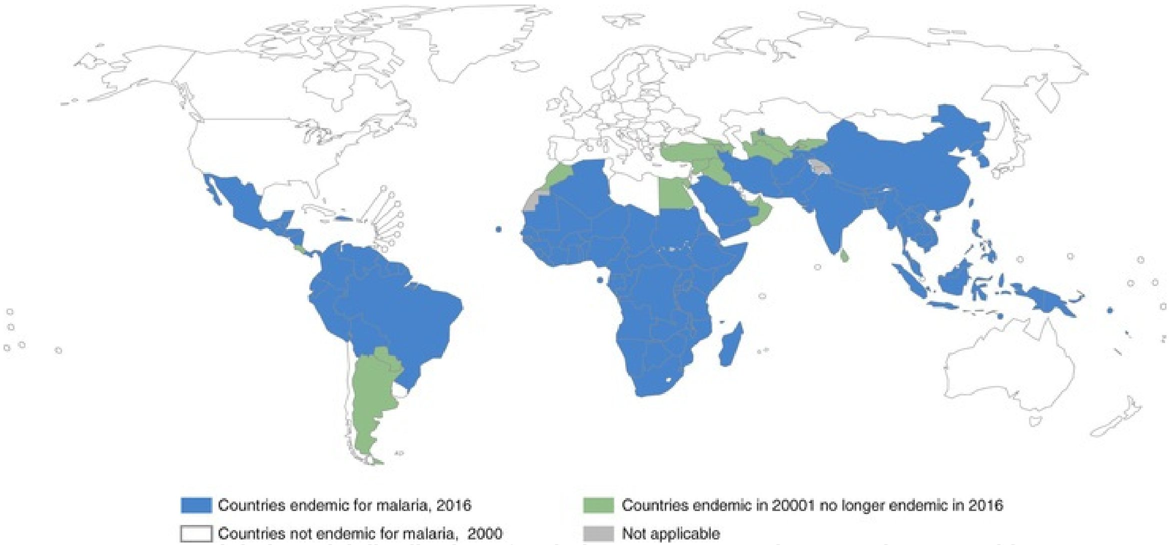
Countries endemic for malaria, 2016
Countries endemic in 20001 no longer endemic in 2016
Countries not endemic for malaria, 2000
Not applicable

FIG. 314.1 **Global spatial distribution of malaria, 2000 compared to 2016. (From World Malaria Report 2016. Geneva: World Health Organization; 2016. License: CC BY-NC-SA 3.0 IGO.)**

Most cases of malaria in the United States occur among previously infected visitors to the United States from endemic areas and among U.S. citizens who travel to endemic areas without appropriate chemoprophylaxis. The most common regions of acquisition of the approximately 1,700 cases of malaria reported to the Centers for Disease Control and Prevention (CDC) among U.S. citizens in 2013 were Africa (82%), Asia (11%), and the Caribbean and Central or South America (7%). Although only 17% of malaria cases occurred in children (<18 yr old), children <5 yr old were more likely to develop severe malaria (37%) than were persons ≥5 yr old (15%). All the 10 deaths from malaria were caused by *P. falciparum* . Rare cases of apparent locally transmitted malaria have been reported since the 1950s. These cases may result from transmission from untreated and often asymptomatic infected individuals from malaria-endemic countries who travel to the United States and infect local mosquitoes or from infected mosquitoes from malaria-endemic areas that are transported to the United States on airplanes.

Pathogenesis

Plasmodium species exist in a variety of forms and have a complex life cycle that enables them to survive in different cellular environments in the human host (asexual phase) and the mosquito (sexual phase) (Fig. 314.2). A marked amplification of *Plasmodium* , from approximately 10^2 to as many as 10^{14} organisms, occurs during a 2-step process in humans, with the 1st phase in hepatic cells (exoerythrocytic phase) and the 2nd phase in the RBCs (erythrocytic phase). The **exoerythrocytic phase** begins with inoculation of sporozoites into the bloodstream by a female *Anopheles* mosquito. Within minutes, the sporozoites enter the hepatocytes of the liver, where they develop and multiply asexually as a **schizont** . After 1-2 wk, the hepatocytes rupture and release thousands of merozoites into the circulation. The tissue schizonts of *P. falciparum, P. malariae,* and apparently *P. knowlesi* rupture once and do not persist in the liver. There are 2 types of tissue schizonts for *P. ovale* and *P. vivax* . The primary type ruptures in 6-9 days, and the secondary type remains dormant in the liver cell for weeks, months, or as long as 5 yr before releasing merozoites and causing relapse of infection. The **erythrocytic phase** of *Plasmodium* asexual development begins when the merozoites from the liver penetrate erythrocytes. Once inside the erythrocyte, the parasite transforms into the **ring form** , which then enlarges to become a **trophozoite** . These latter 2 forms can be identified with Giemsa stain on blood smear, the primary means of confirming the diagnosis of malaria (Fig. 314.3). The trophozoite multiplies asexually to produce a number of small erythrocytic **merozoites** that are released into the bloodstream when the erythrocyte membrane ruptures, which is associated with fever. Over time, some of the merozoites develop into male and female gametocytes that complete the *Plasmodium* life cycle when they are ingested during a blood meal by the female anopheline mosquito. The male and female gametocytes fuse to form a **zygote** in the stomach cavity of the mosquito. After a series of further transformations, sporozoites enter the salivary gland of the mosquito and are inoculated into a new host with the next blood meal.

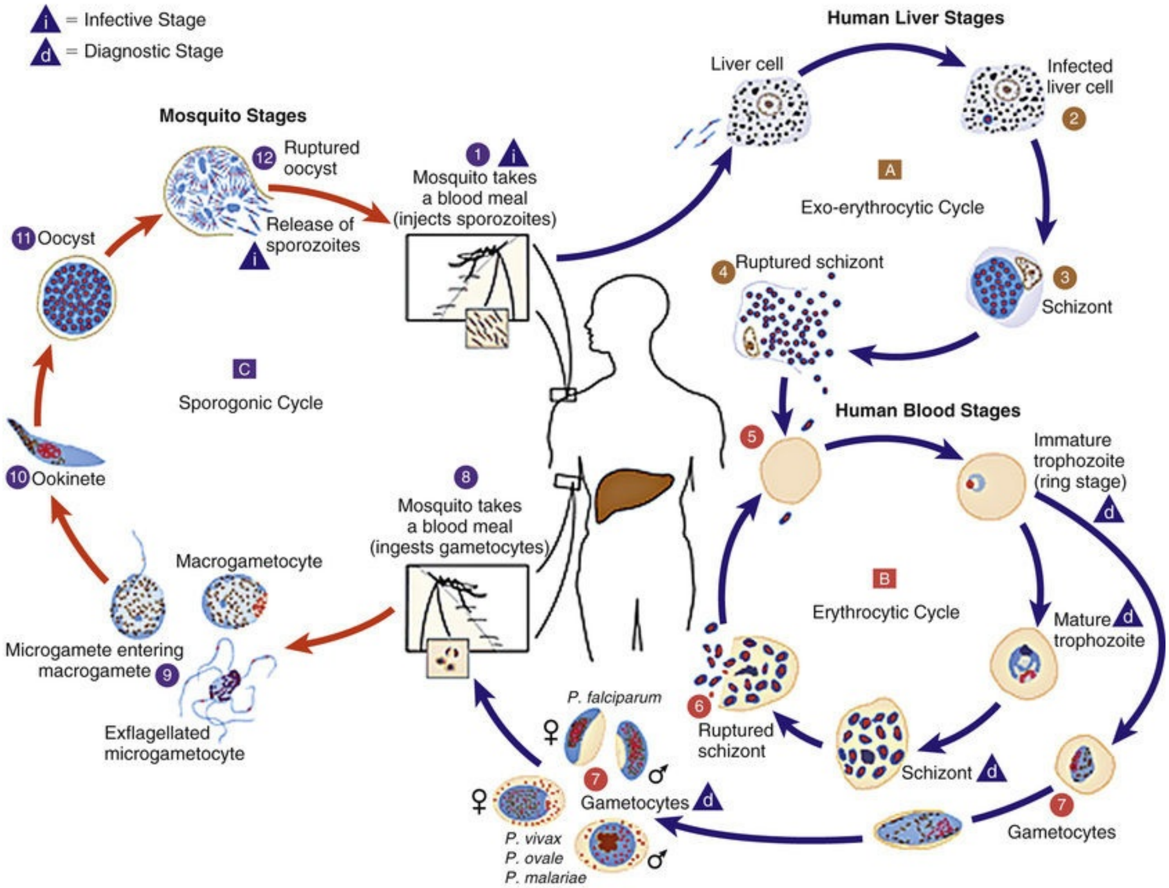
i = Infective Stage
d = Diagnostic Stage
Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
4 Ruptured schizont
3 Schizont
Mosquito Stages
12 Ruptured oocyst
Release of sporozoites i
1 i Mosquito takes a blood meal (injects sporozoites)
11 Oocyst
C
Sporogonic Cycle
10 Ookinete
Human Blood Stages
5
Immature trophozoite (ring stage) d
B
Erythrocytic Cycle
Mature trophozoite d
8 Mosquito takes a blood meal (ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete 9
Exflagellated microgametocyte
P. falciparum
♀
♂
7 Gametocytes d
6 Ruptured schizont
Schizont d
7 Gametocytes
♀
P. vivax
P. ovale
P. malariae
♂

FIG. 314.2 **Life cycle of *Plasmodium* spp. (From Centers for Disease Control and Prevention: Laboratory diagnosis of malaria: *Plasmodium* spp. https://www.cdc.gov/dpdx/malaria/index.html .)**

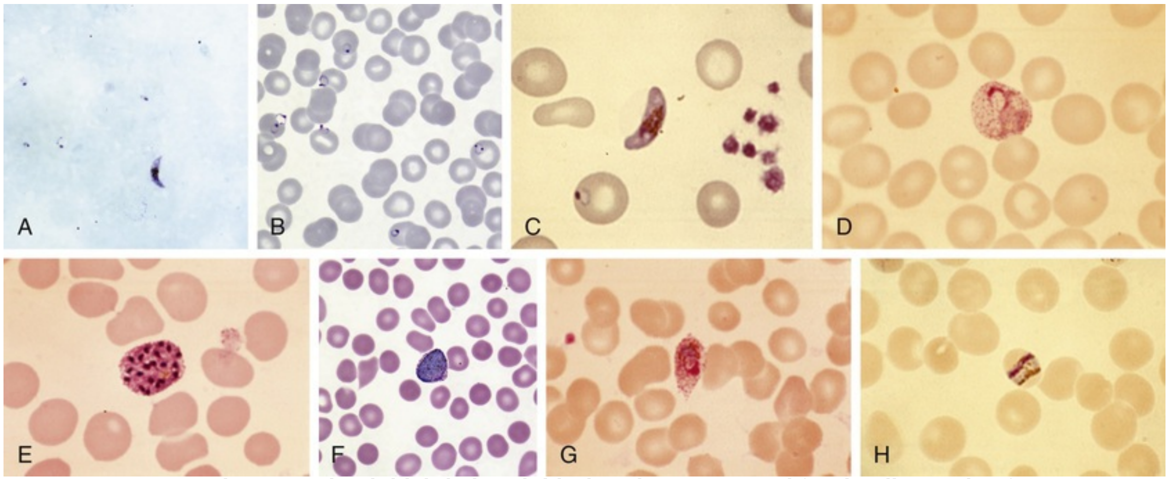

FIG. 314.3 Giemsa-stained thick (A) and thin (B-H) smears used for the diagnosis of malaria and the speciation of *Plasmodium* parasites. A, Multiple signet-ring *Plasmodium falciparum* trophozoites, which are visualized outside erythrocytes. B, A multiply infected erythrocyte containing signet-ring *P. falciparum* trophozoites, including an accolade form positioned up against the inner surface of the erythrocyte membrane. C, Banana-shaped gametocyte unique to *P. falciparum.* D, Ameboid trophozoite characteristic of *Plasmodium vivax.* Both *P. vivax*– and *Plasmodium ovale* –infected erythrocytes exhibit Schüffner dots and tend to be enlarged compared with uninfected erythrocytes. E, *P. vivax* schizont. Mature *P. falciparum* parasites, by contrast, are rarely seen on blood smears because they sequester in the systemic microvasculature. F, *P. vivax* spherical gametocyte. G, *P. ovale* trophozoite. Note Schüffner dots and ovoid shapes of the infected erythrocyte. H, Characteristic band-form trophozoite of *Plasmodium malariae,* containing intracellular pigment hemozoin. (*A, B,* and *F,* From Centers for Disease Control and Prevention: DPDx: laboratory identification of parasites of public health concern. https://www.cdc.gov/dpdx/malaria/index.html ; *C, D, E, G,* and *H,* courtesy of David Wyler, Newton Centre, MA.)

Physiology and pathogenesis in malaria differ according to species. Infection with all species leads to **fever** , caused by the host immune response when erythrocytes rupture and release merozoites into the circulation, and **anemia** , caused by hemolysis and bone marrow suppression. Severe malaria is more common in *P. falciparum* because of several process, including higher-density parasitemia, which may lead to excessive production of proinflammatory cytokines; cytoadherence of *P. falciparum* -infected erythrocytes to the vascular endothelium; and polyclonal activation, resulting in both hypergammaglobulinemia and the formation of immune complexes. **Cytoadherence** of infected erythrocytes to vascular endothelium can lead to obstruction of blood flow and capillary damage, with resultant vascular leakage of blood, protein, and fluid and tissue anoxia. Parasite anaerobic metabolism may also lead to hypoglycemia and metabolic acidosis. The cumulative effects of these pathologic processes may lead to cerebral, cardiac, pulmonary, renal, and hepatic failure.

Immunity after *Plasmodium* sp. infection is incomplete, preventing severe disease but still allowing future infection. In some cases, parasites circulate in small numbers for a long time but are prevented from rapidly multiplying and causing severe illness. Repeated episodes of infection occur because the parasite has developed a number of immune-evasive strategies, such as intracellular replication, vascular cytoadherence that prevents infected erythrocytes from circulating through the spleen, rapid antigenic variation, and alteration of the host immune system resulting in partial immune suppression. The human host response to *Plasmodium* infection includes natural immune mechanisms that prevent infection by other *Plasmodium* spp., such as those of birds or rodents, as well as several alterations in erythrocyte physiology that prevent or modify malarial infection. Erythrocytes containing **hemoglobin S** (sickle erythrocytes) resist malaria parasite growth, erythrocytes lacking Duffy blood group antigen are relatively resistant to *P. vivax* , and erythrocytes containing **hemoglobin F** (fetal hemoglobin) and ovalocytes are resistant to *P. falciparum* . In hyperendemic areas, newborns rarely become ill with malaria, in part because of passive maternal antibody and high levels of fetal hemoglobin. Children 3 mo to 2-5 yr of age have little specific immunity to malaria species and therefore suffer yearly attacks of debilitating and potentially fatal disease. Immunity is subsequently acquired, and severe cases of malaria become less common. Severe disease may occur during pregnancy, particularly first pregnancies or after extended residence outside the endemic region. Both T-cell and antibody responses are important in development of biologic and clinical immunity to *Plasmodium* spp.

Clinical Manifestations

Children and adults are asymptomatic during the initial phase of infection, the incubation period of malaria infection. The usual incubation periods are 9-14 days for *P. falciparum* , 12-17 days for *P. vivax* , 16-18 days for *P. ovale*, and 18-40 days for *P. malariae* . The incubation period can be as long as 6-12 mo for *P. vivax* and can also be prolonged for patients with partial immunity or incomplete chemoprophylaxis. A prodrome lasting 2-3 days is noted in some patients before parasites are detected in the blood. Prodromal symptoms include headache, fatigue, anorexia, myalgia, slight fever, and pain in the chest, abdomen, and joints.

Children with malaria often lack the typical paroxysms in adults (high fever, followed by shaking chills and then diaphoresis) and may have nonspecific symptoms, including fever (may be low-grade but is often >40°C [104°F]), headache, drowsiness, anorexia, nausea, vomiting, and diarrhea. While the rupture of schizonts that occurs every 48 hr with *P. vivax* and *P. ovale* and every 72 hr with *P. malariae* can result in a classic pattern of fevers every other day (*P. vivax* and *P. ovale*) or every 3rd day (*P. malariae*), periodicity is less apparent with *P. falciparum,* and mixed infections and may not be apparent early on in infection, when parasite broods have not yet synchronized. Patients with primary infection, such as travelers from nonendemic regions, also may have irregular symptomatic episodes for 2-3 days before regular paroxysms begin, so most travelers presenting with malaria lack a classic malaria fever pattern. Distinctive physical signs may include splenomegaly (common), hepatomegaly, and pallor as a consequence of anemia. Typical laboratory findings include anemia, thrombocytopenia, and a normal or low leukocyte count. The erythrocyte sedimentation rate is often elevated.

P. falciparum is the most severe form of malaria and is associated with higher-density parasitemia and a number of complications (Fig. 314.4). The most common serious complication is severe **anemia** , which also is associated with other malaria species. Serious complications that appear unique to *P. falciparum* include cerebral malaria, respiratory distress from metabolic acidosis, acute renal failure, hypotension, and bleeding diatheses (Table 314.1) (see later, Complications of *Plasmodium falciparum* Malaria). The diagnosis of *P. falciparum* malaria in a nonimmune individual constitutes a medical emergency. Severe complications and death can occur if appropriate therapy is not instituted promptly. In contrast to malaria caused by *P. ovale, P. vivax,* and *P. malariae,* which usually result in parasitemias of <2%, malaria caused by *P. falciparum* can be associated with parasitemia levels as high as 60%. The differences in parasitemia reflect that *P. falciparum* infects both immature and mature erythrocytes, whereas *P. ovale* and *P. vivax* primarily infect immature erythrocytes and *P. malariae* infects only mature erythrocytes. Like *P. falciparum, P. knowlesi* has a 24 hr replication cycle and can also lead to very-high-density parasitemia.

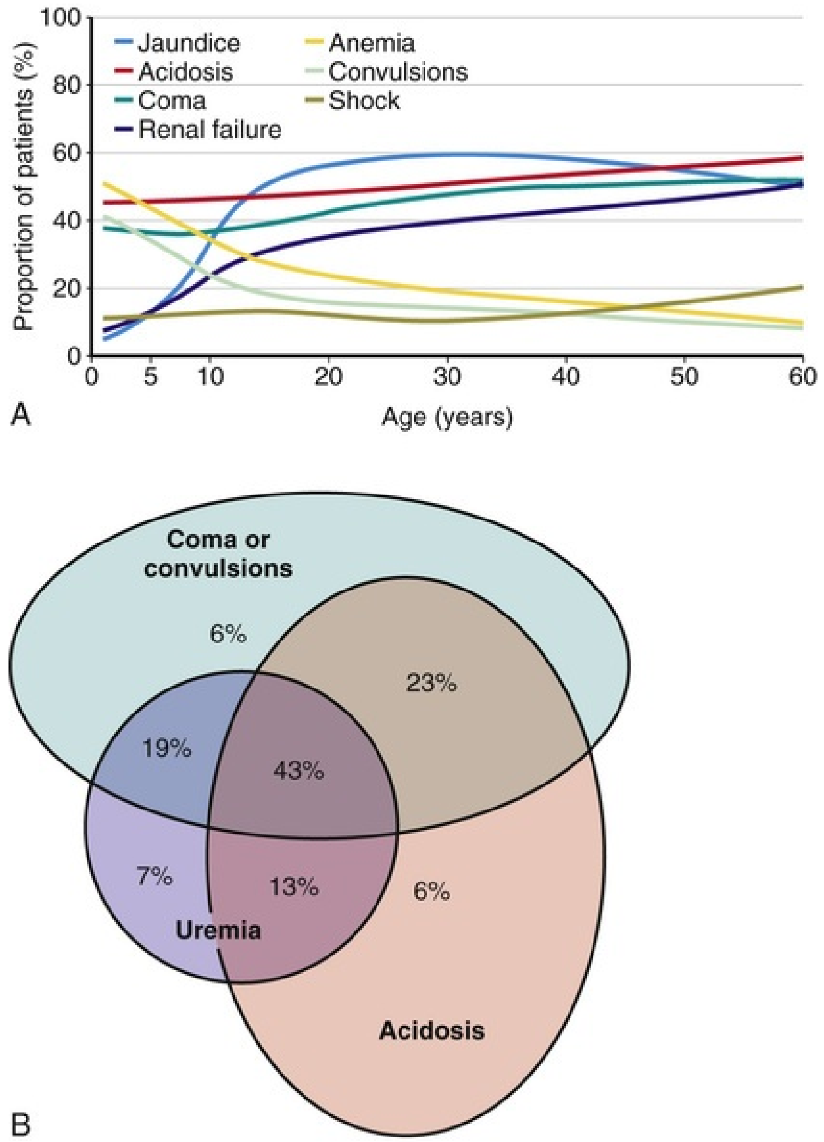

FIG. 314.4 Manifestations of severe falciparum malaria by age (**A**) and mortality in children associated with central nervous system involvement, acidosis, and uremia (**B**). Data from 3,228 prospectively studied African children with severe falciparum malaria. *Uremia* here is defined as a blood urea nitrogen >7.14 mmol/L. Surface areas denote the relative prevalence of the different severity signs, which frequently coexist. The percentages denote the observed mortality associated with the presenting signs. (From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria, *Lancet* 383:723–735, 2014; based on data from von Seidlein L, Olaosebikan R, Hendriksen ICE, et al: Predicting the clinical outcome of severe falciparum malaria in African children: findings from a large randomized trial. *Clin Infect Dis* 54:1080–1090, 2012.)

Table 314.1

World Health Organization Criteria for Severe Malaria, 2000

- Impaired consciousness
- Prostration
- Respiratory distress
- Multiple seizures
- Jaundice
- Hemoglobinuria
- Abnormal bleeding
- Severe anemia
- Circulatory collapse
- Pulmonary edema

P. vivax malaria has long been considered less severe than *P. falciparum* malaria, but recent reports suggest that in some areas it is as frequent a cause of severe disease and death as *P. falciparum* . Severe disease and death from *P. vivax* are usually caused by severe anemia and sometimes splenic rupture. *P. ovale* malaria is the least common type of malaria. It is similar to *P. vivax* malaria and usually is found in conjunction with *P. falciparum* malaria. *P. malariae* is the mildest and most chronic of all malaria infections. **Nephrotic syndrome** is a rare complication of *P. malariae* infection that is not observed with any other human malaria species. Nephrotic syndrome associated with *P. malariae* infection is poorly responsive to corticosteroids. Low-level, undetected *P. malariae* infection may be present for years and is sometimes unmasked by immunosuppression or physiologic stress such as splenectomy or corticosteroid treatment. *P. knowlesi* malaria is most often uncomplicated but can lead to severe malaria and death if high-density parasitemia is present.

Recrudescence after a primary attack may occur from the survival of erythrocyte forms in the bloodstream. Long-term relapse is caused by release of merozoites from an exoerythrocytic source in the liver, which occurs with *P. vivax* and *P. ovale* , or from persistence within the erythrocyte, which occurs with *P. malariae* and rarely with *P. falciparum* . A history of typical symptoms in a person >4 wk after return from an endemic area is therefore more likely to be *P. vivax, P. ovale,* or *P. malariae* infection than *P. falciparum* infection. In the most recent survey of malaria in the United States (2013) by the CDC, among individuals in whom a malaria species was identified, 61% of cases were caused by *P. falciparum,* 14% by *P. vivax,* 2% by *P. malariae,* 4% by *P. ovale* , and 2% by mixed-species infection; 94% of *P. falciparum* infections were diagnosed within 30 days of arrival in the United States, and 99% within 90 days of arrival. In contrast, 54% of *P. vivax* cases occurred >30 days after arrival in the United States.

Congenital malaria is acquired from the mother prenatally or perinatally but is rarely reported in the United States. Congenital malaria usually occurs in the offspring of a nonimmune mother with *P. vivax* or *P. malariae* infection, although it can be observed with any of the human malaria species. The first sign or symptom typically occurs between 10 and 30 days of age (range: 14 hr to several months of age). Signs and symptoms include fever, restlessness, drowsiness, pallor, jaundice, poor feeding, vomiting, diarrhea, cyanosis, and hepatosplenomegaly. **Malaria in pregnancy** is a major health problem in malaria endemic countries, can be severe, and is associated with adverse outcomes in the fetus or neonate, including intrauterine growth restriction and low birthweight, even in the absence of transmission from mother to child.

Diagnosis

Any child who presents with fever or unexplained systemic illness and has traveled or resided in a malaria-endemic area within the previous year should be evaluated for malaria. Malaria should be considered regardless of the use of chemoprophylaxis. Important criteria that suggest *P. falciparum* malaria include symptoms occurring <1 mo after return from an endemic area, >2% parasitemia, ring forms with double-chromatin dots, and erythrocytes infected with>1 parasite.

The diagnosis of malaria is established by identification of organisms on Giemsa-stained smears of peripheral blood (see Fig. 314.3) or by rapid immunochromatographic assay (rapid diagnostic test). Giemsa stain is superior to Wright stain or Leishman stain. Both thick and thin blood smears should be examined. The concentration of erythrocytes on a **thick smear** is 20-40 times that on a thin smear and is used to quickly scan large numbers of erythrocytes. The **thin smear** allows for positive identification of the malaria species and determination of the percentage of infected erythrocytes and is useful in following the response to therapy. Identification of the species is best made by an experienced microscopist and checked against color plates of the various *Plasmodium* spp. (see Fig. 314.3). Morphologically, it is impossible to distinguish *P. knowlesi* from *P. malariae* , so polymerase chain reaction (PCR) detection by a reference laboratory or the CDC is required. Although *P. falciparum* is most likely to be identified from blood just after a febrile paroxysm, most children with malaria will have a positive blood smear regardless of the time the smear is obtained. Most guidelines recommend at least

3 negative blood smears to rule out malaria in children in whom malaria is strongly suspected, because low-level parasitemia could potentially go undetected early in the illness. However, few data are available on the utility of repeated blood smears for malaria detection, and most case reports and series document a positive initial smear.

The BinaxNOW Malaria test is approved by the U.S. Food and Drug Administration (FDA) for rapid diagnosis of malaria. This immunochromatographic test for *P. falciparum* histidine-rich protein (HRP2) and aldolase is approved for testing for *P. falciparum* and *P. vivax*. **Aldolase** is present in all 5 of the malaria species that infect humans. Thus, a positive result for *P. vivax* could be because of *P. ovale* or *P. malariae* infection. Sensitivity and specificity for *P. falciparum* (94–99% and 94–99%, respectively) and *P. vivax* (87–93% and 99%, respectively) are good, but sensitivity for *P. ovale* and *P. malariae* is lower. Sensitivity for *P. falciparum* decreases at lower levels of parasitemia, so microscopy is still advised in areas where expert microscopy is available. The test is simple to perform and can be done in the field or laboratory in 10 min. PCR is more sensitive than microscopy but is technically more complex. It is available in some reference laboratories and can be useful for confirmation and for diagnosis of multiple species of malaria, but the time delay in availability of results generally precludes its use for acute diagnosis of malaria. PCR detection may detect asymptomatic parasitemia in children with very-low-level parasitemia (e.g., internationally adopted children from malaria-endemic areas), with greater sensitivity than microscopy, and may be the preferred method of detection in these children, who, since asymptomatic, do not require immediate treatment.

Differential Diagnosis

The differential diagnosis of malaria is broad and includes viral infections such as influenza and hepatitis, sepsis, pneumonia, meningitis, encephalitis, endocarditis, gastroenteritis, pyelonephritis, babesiosis, brucellosis, leptospirosis, tuberculosis, relapsing fever, typhoid fever, yellow fever, viral hemorrhagic fevers, amebic liver abscess, neoplasm, and collagen vascular disease.

Treatment

Physicians caring for patients with malaria or traveling to endemic areas need to be aware of current information regarding malaria because resistance to antimalarial drugs has complicated therapy and prophylaxis. The best source for such information is the CDC Malaria webpage (https://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf),which provides up-to-date guidelines for malaria treatment, and an algorithm for an approach to malaria treatment (Fig. 314.5). In cases where treatment is unclear or complex, the CDC Malaria Hotline is an excellent resource and is available to physicians 24 hr a day (844-856-4713, from 9 AM to 5 PM Eastern Time Monday-Friday, and 770-488-7100 at all other times and on holidays; request to speak to the CDC Malaria Branch Expert).

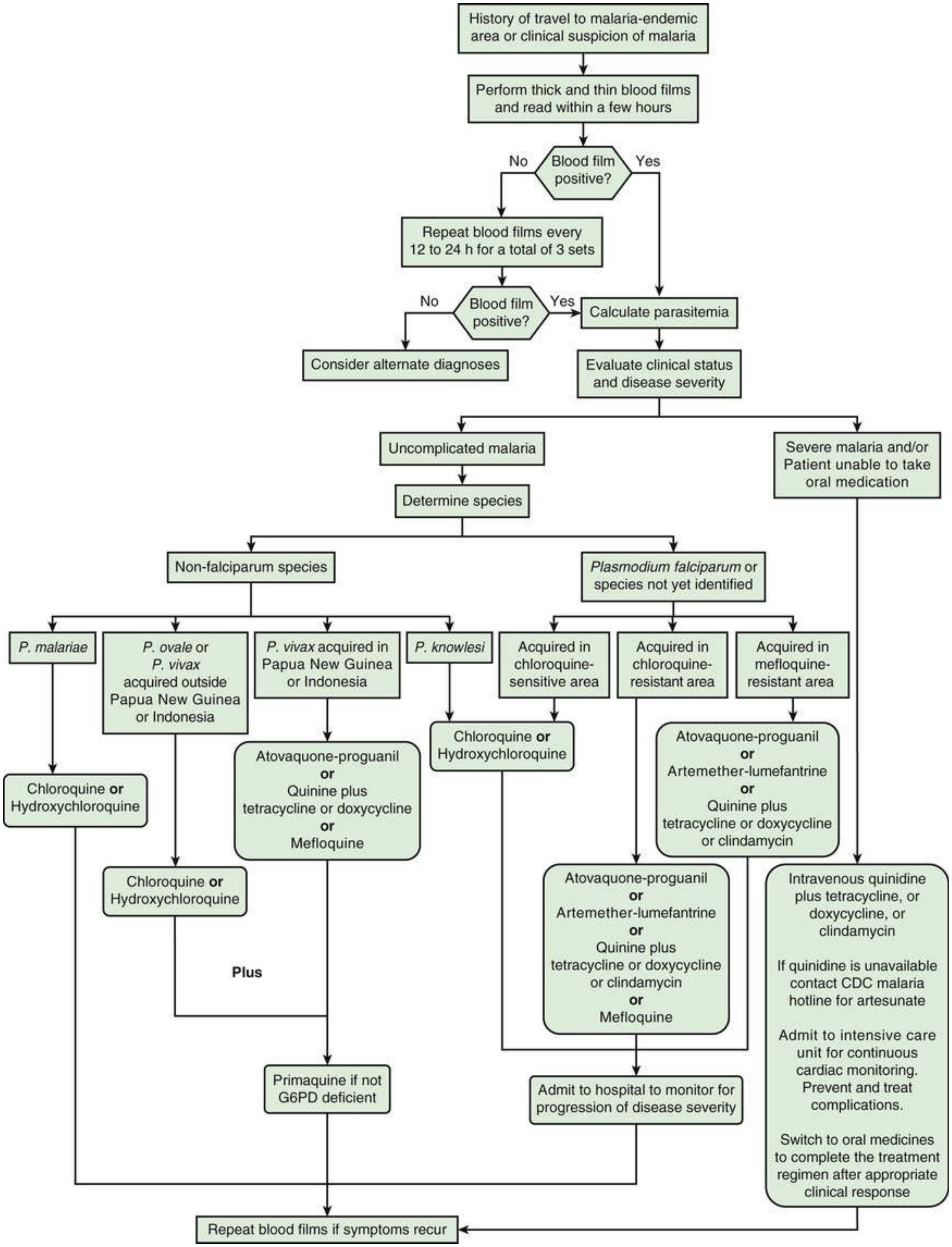
History of travel to malaria-endemic area or clinical suspicion of malaria
Perform thick and thin blood films and read within a few hours
No
Blood film positive?
Yes
Repeat blood films every 12 to 24 h for a total of 3 sets
No
Blood film positive?
Yes
Calculate parasitemia
Consider alternate diagnoses
Evaluate clinical status and disease severity
Uncomplicated malaria
Severe malaria and/or Patient unable to take oral medication
Determine species
Non-falciparum species
Plasmodium falciparum or species not yet identified
P. malariae
P. ovale or *P. vivax* acquired outside Papua New Guinea or Indonesia
P. vivax acquired in Papua New Guinea or Indonesia
P. knowlesi
Acquired in chloroquine-sensitive area
Acquired in chloroquine-resistant area
Acquired in mefloquine-resistant area
Chloroquine **or** Hydroxychloroquine
Atovaquone-proguanil **or** Quinine plus tetracycline or doxycycline **or** Mefloquine
Chloroquine **or** Hydroxychloroquine
Atovaquone-proguanil **or** Artemether-lumefantrine **or** Quinine plus tetracycline or doxycycline or clindamycin
Chloroquine **or** Hydroxychloroquine
Atovaquone-proguanil **or** Artemether-lumefantrine **or** Quinine plus tetracycline or doxycycline or clindamycin **or** Mefloquine
Intravenous quinidine plus tetracycline, or doxycycline, or clindamycin
If quinidine is unavailable contact CDC malaria hotline for artesunate
Admit to intensive care unit for continuous cardiac monitoring. Prevent and treat complications.
Switch to oral medicines to complete the treatment regimen after appropriate clinical response
Plus
Primaquine if not G6PD deficient
Admit to hospital to monitor for progression of disease severity
Repeat blood films if symptoms recur

FIG. 314.5 **Algorithm for approach to patient with malaria in the United States. (From Centers for Disease Control and Prevention. http://www.cdc.gov/malaria/resources/pdf/algorithm.pdf .)**

Fever without an obvious cause in any patient who has left a P. falciparum–*endemic area within 30 days and is nonimmune should be considered a medical emergency. Thick and thin blood smears should be obtained immediately, and all children with symptoms of severe disease should be hospitalized.* If negative, blood films should be repeated every 12 hr until 3 smears are documented as negative. If the patient is severely ill, antimalarial therapy should be initiated immediately. Outpatient therapy generally is not given to nonimmune children but may be considered in immune or semi-immune children who have low-level parasitemia (<1%), no evidence of complications defined by the World Health Organization (WHO), no vomiting, and a lack of toxic appearance; who are able to contact the physician or emergency department at any time; and in whom follow-up within 24 hr is ensured.

Plasmodium Falciparum Malaria

Malarious regions considered chloroquine-sensitive include Central America west of the Panama Canal, Haiti, the Dominican Republic, and most of the Middle East except Iran, Oman, Saudi Arabia, and Yemen. The CDC website (http://www.cdc.gov/MALARIA/) should be consulted for updated information on chloroquine susceptibility in an area, and current treatment options. Individuals traveling from areas with chloroquine-susceptible *P. falciparum* can be treated with **chloroquine** if they do not have severe malaria. *Malaria acquired in* P. falciparum *areas with chloroquine resistance or where there is any doubt about chloroquine sensitivity after conferring with the CDC should be treated with drugs other than chloroquine.* Trials in Asia and Africa have definitively proved that artesunate treatment of severe malaria is associated with decreased mortality compared to quinine treatment. However, artesunate is still not FDA-approved in the United States for treatment of malaria, or available outside of special-request indications from the CDC, so intravenous (IV) **quinidine gluconate** remains first-line therapy for severe malaria in the United States (Table 314.2). Monotherapy with artesunate agents should never be used because of the development of resistance and treatment failures. Nonetheless, in endemic countries, artesunate derivatives in combination with other antimalarial agents have become the treatment of choice (Tables 314.3 and 314.4). *Children with severe malaria should be admitted to the intensive care unit for monitoring of complications, plasma quinidine levels, and adverse effects during quinidine administration.* During administration of quinidine, blood pressure monitoring for hypotension and cardiac monitoring for widening of the QRS complex or lengthening of the QTc interval should be performed continuously, and blood glucose monitoring for hypoglycemia should be performed periodically. Cardiac adverse events may require temporary discontinuation of the drug or slowing of the IV infusion. *Parenteral therapy should be continued until the parasitemia is <1%, which usually occurs within 48 hr, and the patient can tolerate oral medication.* **Quinidine gluconate** (United States) or **quinine sulfate** (other countries) is administered for a total of 3 days for malaria acquired in Africa or South America and for 7 days for malaria acquired in Southeast Asia. Doxycycline, tetracycline, or clindamycin is then given orally to complete the therapeutic course (see Tables 314.2 and 314.4). Although there are no data to support the use of quinidine followed by **atovaquone-proguanil** or **artemether-lumefantrine** , the difficulty of maintaining compliance with oral quinine has led many clinicians to complete oral therapy after IV quinine with a complete course of atovaquone-proguanil or artemether-lumefantrine.

Table 314.2

CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)

(CDC Malaria Hotline: [770] 488-7788 or [855] 856-4713 toll-free Monday-Friday 9 AM to 5 PM EST; [770] 488-7100 after hours, weekends, and holidays)

CLINICAL DIAGNOSIS/ *PLASMODIUM* spp.	**REGION INFECTION ACQUIRED**	**RECOMMENDED DRUG AND ADULT DOSE** [1]	**RECOMMENDED DRUG AND PEDIATRIC DOSE** [1]**; PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE**
Uncomplicated malaria/*P. falciparum* *or* Species not identified If “species not identified” is subsequently diagnosed as *P. vivax* or *P. ovale:* see *P. vivax* and *P. ovale* (below)	**Chloroquine-resistant or unknown resistance** [2] (All malarious regions except those specified as “chloroquine-sensitive,” listed below)	**Atovaquone-proguanil (Malarone)** [3] **Adult tab = 250 mg atovaquone/100 mg proguanil** 4 adult tabs PO qd × 3 days	**Atovaquone-proguanil (Malarone)** [3] **Adult tab = 250 mg atovaquone/100 mg proguanil** **Pediatric (ped) tab = 62.5 mg atovaquone/25 mg proguanil** 5-8 kg: 2 ped tabs PO qd × 3 days 9-10 kg: 3 ped tabs PO qd × 3 days

regarding treatment with primaquine			11-20 kg: 1 adult tab PO qd × 3 days 21-30 kg: 2 adult tabs PO qd × 3 days 31-40 kg: 3 adult tabs PO qd × 3 days >40 kg: 4 adult tabs PO qd × 3 days
		Artemether-lumefantrine (Coartem) [3] 1 tablet = 20 mg artemether and 120 mg lumefantrine A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by 2nd dose 8 hr later, then 1 dose PO bid for the following 2 days 5-<15 kg: 1 tablet per dose 15-<25 kg: 2 tablets per dose 25-<35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose	
		Quinine sulfate plus 1 of the following: doxycycline, tetracycline, or clindamycin Quinine sulfate: 542 mg base (=650 mg salt) [4] PO tid × 3 or 7 days [5] Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg base/kg/day PO divided tid × 7 days	Quinine sulfate [4] plus 1 of the following: doxycycline, [6] tetracycline, [6] or clindamycin Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg) PO tid × 3 or 7 days [5] Doxycycline: 2.2 mg/kg PO every 12 hr × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg base/kg/day PO divided tid × 7 days
		Mefloquine (Lariam and generics) [7] 684 mg base (=750 mg salt) PO as initial dose, followed by 456 mg base (=500 mg salt) PO given 6-12 hr after initial dose Total dose = 1,250 mg salt	Mefloquine (Lariam and generics) [7] 13.7 mg base/kg (=15 mg salt/kg) PO as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) PO given 6-12 hr after initial dose. Total dose = 25 mg salt/kg
Uncomplicated malaria/*P. falciparum* *or* Species not identified	Chloroquine-sensitive (Central America west of Panama Canal; Haiti;	Chloroquine phosphate (Aralen and generics) [8] 600 mg base (=1,000 mg salt) PO immediately, followed by 300 mg base (=500 mg salt) PO at 6, 24, and 48 hr	Chloroquine phosphate (Aralen and generics) [8] 10 mg base/kg PO immediately, followed by 5 mg

	the Dominican Republic; and most of the Middle East)	Total dose: 1,500 mg base (=2,500 mg salt) *or* Hydroxychloroquine (Plaquenil and generics) 620 mg base (=800 mg salt) PO immediately, followed by 310 mg base (=400 mg salt) PO at 6, 24, and 48 hr Total dose: 1,550 mg base (=2,000 mg salt)	base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg *or* Hydroxychloroquine (Plaquenil and generics) 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg
Uncomplicated malaria/*P. malariae* or *P. knowlesi*	All regions	Chloroquine phosphate [8] : treatment as above *or* Hydroxychloroquine: treatment as above	Chloroquine phosphate: [8] treatment as above *or* Hydroxychloroquine: treatment as above
Uncomplicated malaria/*P. vivax* or *P. ovale*	All regions NOTE : for suspected chloroquine-resistant *P. vivax*, see row below	Chloroquine phosphate [8] plus primaquine phosphate [9] Chloroquine phosphate: treatment as above Primaquine phosphate: 30 mg base PO qd × 14 days *or* Hydroxychloroquine plus primaquine phosphate [9] Hydroxychloroquine: treatment as above Primaquine phosphate: 30 mg base PO qd × 14 days	Chloroquine phosphate [8] plus primaquine phosphate [9] Chloroquine phosphate: treatment as above Primaquine: 0.5 mg base/kg PO qd × 14 days *or* Hydroxychloroquine plus primaquine phosphate [9] Hydroxychloroquine: treatment as above Primaquine phosphate: 0.5 mg base/kg PO qd × 14 days
Uncomplicated malaria/*P. vivax*	Chloroquine-resistant [10] (Papua New Guinea and Indonesia)	Quinine sulfate plus either doxycycline or tetracycline plus primaquine phosphate [9] Quinine sulfate: treatment as above Doxycycline or tetracycline: treatment as above Primaquine phosphate: treatment as above	Quinine sulfate plus either doxycycline [6] or tetracycline [6] plus primaquine phosphate [9] Quinine sulfate: treatment as above Doxycycline or tetracycline: treatment as above Primaquine

			phosphate: treatment as above
		Atovaquone-proguanil plus primaquine phosphate [9] **Atovaquone-proguanil:** treatment as above **Primaquine phosphate:** treatment as above	**Atovaquone-proguanil plus primaquine phosphate** [9] **Atovaquone-proguanil:** treatment as above **Primaquine phosphate:** treatment as above
		Mefloquine plus primaquine phosphate [9] **Mefloquine:** treatment as above **Primaquine phosphate:** treatment as above	**Mefloquine plus primaquine phosphate** [9] **Mefloquine:** treatment as above **Primaquine phosphate:** treatment as above
Uncomplicated malaria: alternatives for pregnant women [11-13]	**Chloroquine-sensitive** (See uncomplicated malaria sections above for chloroquine-sensitive species by region)	**Chloroquine phosphate:** treatment as above *or* **Hydroxychloroquine:** treatment as above	Not applicable
	Chloroquine-resistant (See sections above for regions with chloroquine-resistant ***P. falciparum*** and ***P. vivax*** **)**	**Quinine sulfate plus clindamycin** **Quinine sulfate:** treatment as above **Clindamycin:** treatment as above *or* **Mefloquine:** treatment as above	Not applicable
Severe malaria [14-16]	**All regions**	**Quinidine gluconate** [14] **plus 1 of the following: doxycycline, tetracycline, or clindamycin** **Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hr, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hr. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hr, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hr every 8 hr, starting 8 hr after the loading dose (see package insert).	**Quinidine gluconate** [14] **plus 1 of the following: doxycycline,** [4] **tetracycline,** [4] **or clindamycin** **Quinidine gluconate:** same mg/kg dosing and recommendations as for adults **Doxycycline:** treatment as above. If patient not able to

		Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America **Doxycycline:** treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hr and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days **Tetracycline:** treatment as above **Clindamycin:** treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days ***Investigational new drug (contact CDC for information):*** **Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), doxycycline (clindamycin in pregnant women), or mefloquine. Artemether-lumefantrine is not included in CDC treatment table but may also be given as follow-up drug after artesunate if available.**	take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hr and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children >45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days **Tetracycline:** treatment as above **Clindamycin:** treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug (contact CDC for information):*** **Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), clindamycin, or mefloquine. Artemether-lumefantrine is not included in CDC treatment table but may also be given as follow-up drug after artesunate if available.**

[1] If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use 1 of the other options instead.

[2] NOTE : There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum* . Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

[3] Take with food or whole milk. If patient vomits within 30 min of taking a dose, patient should repeat the dose.

[4] U.S.-manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult because of unavailability of noncapsule forms of quinine.

[5] For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

[6] Doxycycline and tetracycline are not indicated for use in children <8 yr old. For children <8 yr old with chloroquine-resistant *P. falciparum* , atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children <8 yr old with chloroquine-resistant *P. vivax,* mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

[7] Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia as a consequence of drug resistance.

[8] When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.

[9] Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally 1 time per week for 8 wk; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

[10] NOTE : There are 3 options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax.* High treatment failure rates as a result of chloroquine-resistant *P. vivax* are well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* are also documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections*,* options A, B, and C are equally recommended.

[11] For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

[12] Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the 1st trimester because of a lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

[13] For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

[14] Persons with a positive blood smear *or* history of recent possible exposure and no other recognized pathology who have 1 or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum.*

[15] Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an IV loading dose of quinidine unless they have received >40 mg/kg of quinine in the preceding 48 hr or if they have received mefloquine within the preceding 12 hr. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.

[16] Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

IV, Intravenous(ly); PO, orally (by mouth); qd, once daily; bid, twice daily; tid, 3 times daily; qid, 4 times daily.

From US Centers for Disease Control and Prevention. http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf .

Table 314.3

Treatment of Uncomplicated Malaria in Malaria Endemic Areas

Treatment of Uncomplicated Malaria in Malaria Endemic Areas

REGIMENS	
All *Plasmodium falciparum* malaria	Artemether-lumefantrine, 1.5 mg/kg–9 mg/kg twice daily for 3 days with food or milk Artesunate, 4 mg/kg daily for 3 days, and mefloquine, 25 mg base per kg (8 mg/kg/daily for 3 days[*])[†] Dihydroartemisinin-piperaquine, 2.5 mg/kg–20 mg/kg daily for 3 days
Sensitive *P. falciparum* malaria	Artesunate, 4 mg/kg daily for 3 days, and a single dose of sulfadoxine-pyrimethamine, 25 mg/kg–1.25 mg/kg Artesunate, 4 mg/kg, and amodiaquine,[*] 10 mg base per kg daily for 3 days
Chloroquine-sensitive *Plasmodium vivax,*[‡] *Plasmodium malariae,*[‡] *Plasmodium ovale,*[‡] *Plasmodium knowlesi*[‡]	Chloroquine, 10 mg base per kg immediately, followed by 10 mg/kg at 24 hr and 5 mg/kg at 48 hr

[*] World Health Organization prequalified fixed dose formulations are preferable to loose tablets. A taste masked dispersible pediatric tablet formulation of artemether-lumefantrine is available.

[†] High failure rates with artesunate-mefloquine have been reported on the Thailand–Myanmar border.

[‡] Any of the artemisinin combination treatments can be given except for artesunate-sulfadoxine-pyrimethamine where *P. vivax* is resistant. Patients with *P. vivax* or *P. ovale* infections should also be given a 14-day course of primaquine to eradicate hypnozoites (radical cure). However, severe glucose-6-phosphate dehydrogenase deficiency is a contraindication because a 14-day course of primaquine can cause severe hemolytic anemia in this group.

From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria, *Lancet* 383:723–732, 2014.

Table 314.4

Treatment of Severe Malaria in Adults and Children in Malaria-Endemic Areas

- Artesunate, 2.4 mg/kg by intravenous or intramuscular[*] injection, followed by 2.4 mg/kg at 12 hr and 24 hr; continue injection once daily if necessary[†]
- Artemether, 3.2 mg/kg by immediate intramuscular[*] injection, followed by 1.6 mg/kg daily
- Quinine dihydrochloride, 20 mg salt per kg infused during 4 hr, followed by maintenance of 10 mg salt per kg infused during 2-8 hr every 8 hr (can also be given by intramuscular injection[*] when diluted to 60-100 mg/mL)

Artesunate is the treatment of choice. Artemether should only be used if artesunate is unavailable. Quinine dihydrochloride should be given only when artesunate and artemether are unavailable.

[*] Intramuscular injections should be given to the anterior thigh.

[†] Young children with severe malaria have lower exposure to artesunate and its main biologically active metabolite dihydroartemisinin than do older children and adults. Revised dose regimens to ensure similar drug exposures have been suggested.

From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria, *Lancet* 383:723–732, 2014.

Parenteral artesunate or artemether can be substituted for quinine for treatment of severe malaria in children and adults (see Table 314.2). **Artesunate** is now available on special request from the CDC (770-488-7788) for treatment of severe malaria but requires a specific indication such as adverse reaction to quinidine, contraindication to quinidine, or lack of availability of quinidine. Empirical therapy should not be delayed while awaiting delivery of artesunate. Children who receive artesunate can follow up with artemether-lumefantrine oral therapy. Oral and rectal administration of these artemisinin-based antimalarial drugs is effective in treatment of malaria, but such formulations are not indicated or approved in the United States.

Patients from areas with chloroquine-resistant *P. falciparum* who have mild infection, parasitemia <1%, no evidence of complications, and no vomiting and who can take oral medication can be considered for oral therapy with either oral atovaquone-proguanil (**Malarone**), oral artemether-lumefantrine (**Coartem**), or oral quinine plus doxycycline, tetracycline, or clindamycin (see Table 314.2). However, as noted in Fig. 314.5 , all children with clinical (symptomatic) malaria, even those started on oral therapy, should be admitted to evaluate for progression of disease. Semi-immune children have been treated as outpatients, but there is limited data on the safety of this approach. Coartem is FDA-approved for the treatment of uncomplicated malaria and is an appealing choice because it is highly effective and well-tolerated. Pediatric dosing is well established, but pediatric dispersible tablets, available in some other countries, are not yet available in the United States. Coartem should not be used in children with known QT interval prolongation. Patients who acquire *P. falciparum* in Thailand, Myanmar, or Cambodia should receive Coartem or Malarone in preference to quinine. **Mefloquine** is contraindicated for use in patients with a known hypersensitivity to mefloquine or with a history of epilepsy or severe psychiatric disorders. Mefloquine is not recommended for persons with cardiac conduction abnormalities but may be administered to persons who are concurrently receiving β-blockers if they have no underlying arrhythmia. Quinidine or quinine may exacerbate the adverse effects of mefloquine and should generally not be given to patients who have received mefloquine unless there are no other alternatives.

Patients with uncomplicated *P. falciparum* malaria acquired in areas without chloroquine resistance should be treated with oral **chloroquine phosphate** . If the parasite count does not drop rapidly (within 24-48 hr) and become negative after 4 days, chloroquine resistance should be assumed, and the patient should be started on a different antimalarial regimen.

Supportive therapy is important and may include RBC transfusion(s) to maintain the hematocrit at >20%, supplemental oxygen and ventilatory support for pulmonary edema or cerebral malaria, careful IV rehydration for severe malaria, IV glucose for hypoglycemia, anticonvulsants for cerebral malaria with seizures, and dialysis for renal failure. Exchange transfusion has been advocated for children and adults with parasitemia >10% and evidence of severe complications (e.g., severe malarial anemia, cerebral malaria), but no randomized clinical trial has been conducted to assess its utility, and some groups, including the CDC, no longer advocate its use for severe malaria. Corticosteroids are not recommended for cerebral malaria because they do not improve outcomes.

Plasmodium Vivax, P. Ovale, P. Malariae, or *P. Knowlesi* Malaria

Uncomplicated infection caused by *P. vivax* , *P. ovale* , or *P. malariae* can usually be treated with **chloroquine** , except in areas with chloroquine resistance (Papua New Guinea and Indonesia, see Table 314.2). Chloroquine remains the initial drug of choice for *P. vivax* malaria in the absence of good data on drug alternatives. Indications for using alternative therapy are worsening or new symptoms, persistent *P. vivax* parasitemia after 72 hr, and possibly acquisition of infection in Oceania or India. Patients with *P. vivax* or *P. ovale* malaria should also be given **primaquine** once daily for 14 days to prevent relapse from the **hypnozoite** forms that remain dormant in the liver. Some strains may require 2 courses of primaquine. *Testing for glucose-6-phosphate dehydrogenase deficiency must be performed before initiation of primaquine, because it can cause hemolytic anemia in such patients* . Unfortunately, no alternatives to primaquine currently exist for eradication of the hypnozoite forms of *P. vivax* or *P. ovale* . Patients with any type of malaria should be monitored for possible recrudescence because it may occur >90 days after therapy with low-grade resistant organisms. If vomiting precludes oral administration, chloroquine can be given by nasogastric tube. Based on limited evidence, chloroquine plus sulfadoxine-pyrimethamine should be used to treat *P. knowlesi* infections. For cases of severe malaria caused by any *Plasmodium* spp., IV quinidine or quinine with a 2nd drug (clindamycin, doxycycline, or tetracycline) should be used, as for *P. falciparum* . Patients with any type of malaria must be monitored for possible recrudescence with repeat blood smears at the end of therapy, because recrudescence may occur >90 days after therapy with low-grade resistant organisms. For children living in endemic areas, mothers should be encouraged to seek evaluation for malaria any time the child has a fever, because many clinics in endemic areas now have accurate rapid diagnostic tests available. If such children are severely ill, they should be given the same therapy as nonimmune children.

Complications of *Plasmodium Falciparum* MALARIA

WHO has identified 10 complications of *P. falciparum* malaria that define severe malaria (see Table 314.1 and Fig. 314.4). The most common complications in children are severe anemia, impaired consciousness (including cerebral malaria), respiratory distress (a result of metabolic acidosis), multiple seizures, prostration, and jaundice.

Severe malarial anemia (hemoglobin level <5 g/dL) is the most common severe complication of malaria in children and is the leading cause of anemia leading to hospital admission in African children. Anemia is associated with hemolysis, but removal of infected erythrocytes by the spleen and impairment of erythropoiesis likely play a greater role than hemolysis in the pathogenesis of severe malarial anemia. The primary treatment for severe malarial anemia is blood transfusion. With appropriate and timely treatment, severe malarial anemia usually has a relatively low mortality (approximately 1%).

Cerebral malaria is defined as the presence of coma in a child with *P. falciparum* parasitemia and an absence of other reasons for coma. Children with altered mental status who are not in coma fall into the larger category of *impaired consciousness* . Cerebral malaria is most common in children in areas of midlevel transmission and in adolescents or adults in areas of very low transmission. It is less frequently seen in areas of very high transmission. Cerebral malaria often develops after the patient has been ill for several days but may develop precipitously. Cerebral malaria has a fatality rate of 15–40% and is associated with long-term cognitive impairment in children. Repeated seizures are frequent in children with cerebral malaria. Hypoglycemia is common, but children with true cerebral malaria fail to arouse from coma even after receiving a dextrose infusion that normalizes their glucose level. Physical findings may include high fever, seizures, muscular twitching, rhythmic movement of the head or extremities, contracted or unequal pupils, retinal hemorrhages, hemiplegia, absent or exaggerated deep tendon reflexes, and a positive Babinski sign. Lumbar puncture reveals increased pressure and mildly increased cerebrospinal fluid protein, typically with no CSF pleocytosis and a normal CSF glucose. Studies suggest that funduscopic findings of **malaria retinopathy** (retinal hemorrhages, peripheral whitening, macular whitening, vessel changes) are relatively specific for cerebral malaria, so children with cerebral malaria who do not have malaria retinopathy should be carefully assessed for other causes of coma. However, they should still be treated for cerebral malaria because a growing body of evidence suggests that even in these children, *P. falciparum* is a contributor to their comatose state. Treatment of cerebral malaria other than antimalarial medications is largely supportive and includes evaluation of and treatment of seizures and hypoglycemia. A study using MRI to assess children with cerebral malaria documented that cerebral edema with increased intracranial pressure is the leading cause of death in children with cerebral malaria, but treatment with mannitol and corticosteroids has not improved outcomes in these children.

Respiratory distress is a poor prognostic indicator in severe malaria and appears to be caused by **metabolic acidosis** rather than intrinsic pulmonary disease. To date, no successful interventions for treatment of metabolic acidosis in children with severe malaria have been described, and primary therapy of malaria appears to be the most effective way to address acidosis.

Seizures are a common complication of severe malaria, particularly cerebral malaria. Benzodiazepines are first-line therapy for seizures, and intrarectal diazepam has been used successfully in children with malaria and seizures. Many seizures resolve with a single dose of diazepam. For persistent seizures, phenobarbital or phenytoin are the standard medications used. Phenytoin may be preferred for seizure treatment, particularly in hospitals or clinics where ventilatory support is not available. However, no comparative trials of the 2 drugs have been performed. There are currently no drugs recommended for seizure prophylaxis in children with severe malaria. Phenobarbital prophylaxis decreased seizure activity but increased mortality in one major study of children with severe malaria, probably because the respiratory depression associated with phenobarbital may have been exacerbated by benzodiazepine therapy.

Hypoglycemia is a complication of malaria that is more common in children, pregnant women, and patients receiving quinine therapy. Patients may have a decreased level of consciousness that can be confused with cerebral malaria. Any child with impaired consciousness and malaria should have a glucose level checked, and if glucometers are not immediately available, an empirical bolus of dextrose should be given. Hypoglycemia is associated with increased mortality and neurologic sequelae.

Circulatory collapse (algid malaria) is a rare complication that manifests as hypotension, hypothermia, rapid weak pulse, shallow breathing, pallor, and vascular collapse. It is most likely caused by bacterial superinfection, since up to 15% of children in endemic areas with severe malaria may have concurrent bacteremia. Death may occur within hours. Any child with severe malaria and hypotension or hypoperfusion should have a blood culture obtained and should be treated empirically for bacterial sepsis.

Long-term cognitive impairment occurs in 25% of children with cerebral malaria and also in children with repeated episodes of uncomplicated disease. Prevention of attacks in these children may improve educational attainment.

Hyperreactive malarial splenomegaly (HMS) is a chronic complication of *P. falciparum* malaria in which massive splenomegaly persists after treatment of acute infection. Major criteria include splenomegaly (>10 cm), IgM > 2 SD above local mean, high levels of antibodies to a blood-stage *P. falciparum* antigen, and a clinical response to an antimalarial drug. HMS occurs exclusively in children in endemic areas with repeated exposure to malaria and is thought to be caused by an impaired immune response to *P. falciparum* antigens. Prolonged antimalarial prophylaxis (for at least 1 yr, typically with chloroquine, quinine, or mefloquine) is required to treat this syndrome if the child remains in a malaria-endemic area. Spleen size gradually regresses on antimalarial prophylaxis but often increases again if prophylaxis is stopped.

Other complications in children include **acute kidney injury** and **jaundice** , both of which are associated with a worse outcome and prostration. A growing literature demonstrates that although renal failure requiring dialysis is rare in children with severe malaria, acute kidney injury is common and is associated with increased mortality. **Prostration** is defined as the inability to sit, stand, or eat without support, in the absence of impaired consciousness. Prostration has also been associated with increased mortality in some studies, but the pathophysiology of this process is not well understood. Uncommon complications include hemoglobinuria, abnormal bleeding, and pulmonary edema. Of note, pulmonary edema is more frequent in adolescents and adults.

Prevention

Malaria prevention consists of reducing exposure to infected mosquitoes and chemoprophylaxis. The most accurate and current information on areas in the world where malaria risk and drug resistance exist can be obtained by contacting local and state health departments or the CDC or consulting *Health Information for International Travel* , which is published by the U.S. Public Health Service.

Travelers to endemic areas should remain in well-screened areas from dusk to dawn, when the risk for transmission is highest. They should sleep under permethrin-treated mosquito netting and spray insecticides indoors at sundown. During the day, travelers should wear clothing that covers the arms and legs, with trousers tucked into shoes or boots. Mosquito repellent should be applied to thin clothing and exposed areas of the skin, with applications repeated as noted on the repellent instructions, and at least every 4 hr. A child should not be taken outside from dusk to dawn, but if at risk for exposure, a solution with 25–35% *N*, diethyltoluamide (DEET) (not >40%) should be applied to exposed areas, except for the eyes, mouth, or hands. Hands are excluded because they are often placed in the mouth. DEET should then be washed off as soon as the child comes back inside. The American Academy of Pediatrics recommends that DEET solutions be avoided in children <2 mo old. Adverse reactions to DEET include rashes, toxic encephalopathy, and seizures, but these reactions occur almost exclusively with inappropriate application of high concentrations of DEET. **Picaridin** is an alternative and sometimes better-tolerated repellent. Even with these precautions, a child should be taken to a physician immediately if the child develops illness when traveling to a malarious area.

Chemoprophylaxis is necessary for all visitors to and residents of the tropics who have not lived there since infancy, including children of all ages (Table 314.5). Healthcare providers should consult the latest information on resistance patterns before prescribing prophylaxis for their patients. Chloroquine is given in the few remaining areas of the world free of chloroquine-resistant malaria strains. In areas where chloroquine-resistant *P. falciparum* exists, atovaquone-proguanil, mefloquine, or doxycycline may be given as chemoprophylaxis. **Atovaquone-proguanil** is generally recommended for shorter trips (up to 2 wk) because it must be taken daily. Pediatric tablets are available and are generally well tolerated, although the taste is sometimes unpleasant to very young children. For longer trips, **mefloquine** is preferred, since it is given only once a week. Mefloquine does not have a pediatric formulation and has an unpleasant taste that usually requires that the cut tablet be disguised in another food, such as chocolate syrup. Mefloquine should not be given to children if they have a known hypersensitivity to mefloquine, are receiving cardiotropic drugs, have a history of convulsive or certain psychiatric disorders, or travel to an area where mefloquine resistance exists (the borders of Thailand with Myanmar and Cambodia, western provinces of Cambodia, and eastern states of Myanmar). Atovaquone-proguanil is started 1-2 days before travel, and mefloquine is started 2 wk before travel. It is important that these doses are given, both to allow therapeutic levels of the drugs to be achieved and to be sure that the drugs are tolerated. **Doxycycline** is an alternative for children >8 yr old. It must be given daily and should be given with food. Side effects of doxycycline include photosensitivity and vaginal yeast infections. **Primaquine** is a daily prophylaxis option for children who cannot tolerate any of the other options, but it should be provided in consultation with a travel medicine specialist if needed, and all children should be checked for glucose-6-phosphate dehydrogenase deficiency before prescribing this medication, because it is contraindicated in children with G6PD deficiency. Provision of medication can be considered in individuals who refuse to take prophylaxis or will be in very remote areas without accessible medical care. Provision of medication for self-treatment of malaria should be done in consultation with a travel medicine specialist, and the medication provided should be different than that used for prophylaxis.

Table 314.5

Chemoprophylaxis of Malaria for Children

AREA	DRUG	DOSAGE (ORAL)	ADVANTAGES	DISADVANTAGES	BEST USE
Chloroquine-resistant area	Mefloquine* †	<10 kg: 4.6 mg base (5 mg salt)/kg/wk 10-19 kg: ¼ tab/wk 20-30 kg: ½ tab/wk 31-45 kg: ¼ tab/wk >45 kg: 1 tab/wk (228 mg base)	Once weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria-endemic area for ≥4 wk Children unlikely to take daily medication
	Doxycycline ‡	2 mg/kg daily	Inexpensive	Cannot give to	Children going

		(max 100 mg)		children <8 yr Daily dosing Must take with food or causes stomach upset Photosensitivity	to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone/proguanil [§] (Malarone)	Pediatric tabs: 62.5 mg atovaquone/ 25 mg proguanil Adult tabs: 250 mg proguanil/ 100 mg proguanil	Pediatric formulation Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria-endemic area for <4 wk
		5-8 kg: pediatric tab once daily (off-label)			
		9-10 kg: pediatric tab once daily (off-label)			
		11-20 kg: 1 pediatric tab once daily			
		21-30 kg: 2 pediatric tabs once daily			
		31-40 kg: 3 pediatric tabs once daily			
		>40 kg: 1 adult tab once daily			
Chloroquine-susceptible area	Chloroquine phosphate	5 mg base/kg/wk (max: 300 mg base)	Once weekly dosing Inexpensive Generally well tolerated	Bitter taste No pediatric formulation	Best medication for children traveling to areas with *Plasmodium falciparum* or *Plasmodium vivax* that is chloroquine susceptible
	Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas				

[*] Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.

[†] Mefloquine resistance exists in western Cambodia and along the Thailand-Cambodia and Thailand-Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.

[‡] Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children younger than 8 yr of age or in pregnant women.

[§] Atovaquone/proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children weighing <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

A number of other efforts are currently underway to prevent malaria in malaria-endemic countries. Some have been highly successful, leading to a significant decrease in malaria incidence in many countries in Africa, Asia, and South America in the last decade. These interventions include the use of insecticide-treated bed nets (which have decreased all-cause mortality in children <5 yr old in several highly malaria endemic areas by approximately 20%), indoor residual spraying with long-lasting insecticides, and the use of **artemisinin-combination therapy** for first-line malaria treatment. The first malaria vaccine to have any degree of efficacy is the **RTS,S vaccine** , which is based on the circumsporozoite protein of *P. falciparum* . In various clinical trials, this vaccine has shown an efficacy of 17–56% against uncomplicated malaria and 38–50% against severe malaria in young children in malaria-endemic areas for as long as48 mo after vaccination. Given the relatively low efficacy of this vaccine, it is still unclear if it will be implemented as part of a combination strategy that includes the already successful interventions mentioned. Numerous other vaccines are also in current clinical trials, and it is hoped that future vaccines will improve on the efficacy of the RTS,S vaccine. There is currently no vaccine with sufficient efficacy to be considered for prevention of malaria in travelers.

Intermittent prevention treatment during infancy has been particularly successful in reducing the incidence of malaria in sub Saharan Africa. **Sulfadoxine-pyrimethamine** given to infants at the 2nd and 3rd doses of the diphtheria, tetanus toxoid, and pertussis vaccine is safe and relatively effective. Intermittent prevention treatment has also been given to pregnant women; 3 doses of sulfadoxine-pyrimethamine have resulted in a reduction of low-birthweight infants.

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CHAPTER 315

Babesiosis *(Babesia)*

Peter J. Krause

Babesiosis is a malaria-like disease caused by intraerythrocytic protozoa that are transmitted by hard body (**ixodid**) ticks. The clinical manifestations of babesiosis range from subclinical illness to fulminant disease resulting in death.

Etiology

More than 100 species of *Babesia* infect a wide variety of wild and domestic animals throughout the world. Only a few of these species have been reported to infect humans, including *Babesia crassa* -like pathogen, *Babesia divergens, Babesia duncani, Babesia microti, Babesia venatorum,* and *Babesia* sp. XXB/HangZhou, and KO1.

Epidemiology

Babesia organisms are transmitted to humans from vertebrate reservoir hosts by the *Ixodes ricinus* family of ticks. *B. microti* is the most common cause of babesiosis in humans. The primary reservoir for *B. microti* in the United States is the white-footed mouse, *Peromyscus leucopus* , and the primary vector is *Ixodes scapularis* , the black-legged tick. *I. scapularis* ticks also transmit the causative agents of **Lyme disease** , human granulocytic anaplasmosis, *Borrelia miyamotoi* infection, *Ehrlichia muris* –like agent ehrlichiosis, and Powassan virus encephalitis and may simultaneously transmit 2 or more microorganisms. White-tailed deer *(Odocoileus virginianus)* serve as the host on which adult ticks most abundantly feed but are incompetent reservoirs. Babesiosis may be transmitted through blood transfusion, and *B. microti* is the most frequently reported transfusion-transmitted microbial agent in the United States. Rarely, babesiosis is acquired by transplacental transmission.

In the United States, human *B. microti* infection is endemic in the Northeast and Upper Midwest (Fig. 315.1). Most cases occur in June, July, and August. *B. duncani* infects humans along the Pacific coast. *B. divergens* –like infections have been described in Kentucky, Missouri, and Washington State. In Europe, human babesiosis caused by *B. divergens, B. microti,* and *B. venatorum* occurs sporadically. In Asia, *B. venatorum* is endemic in northeastern China. Cases of *B. microti* infection have been described in Taiwan, mainland China, and Japan. Cases of *Babesia crassa* and *Babesia* sp. XXB/HangZhou have been reported in China and KO1 in Korea. Human babesiosis also has been documented in Africa, Australia, Canada, India, and South America.

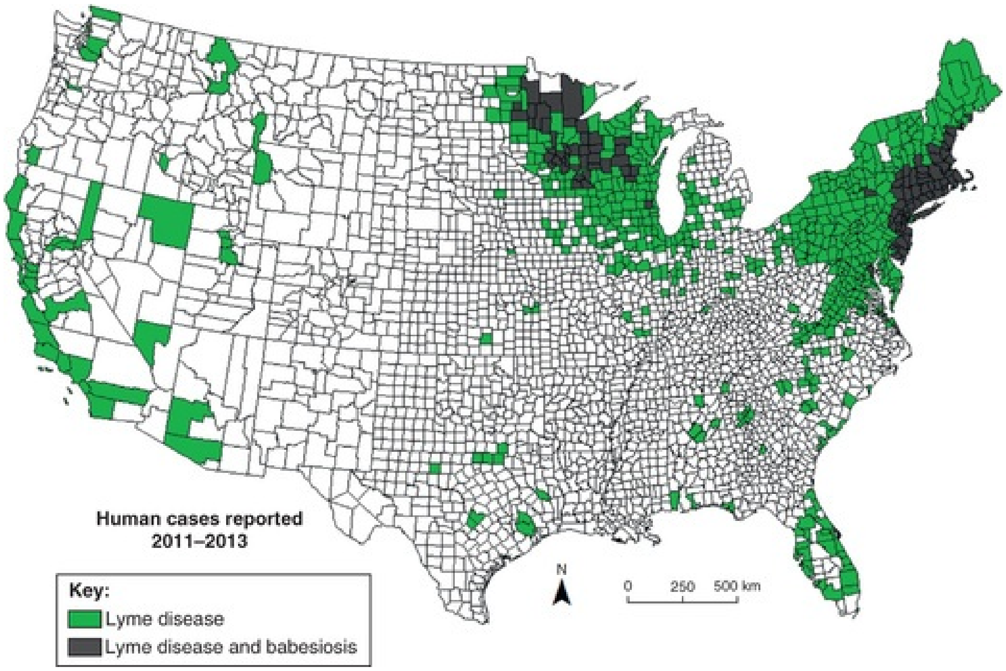

FIG. 315.1 **Human babesiosis emerging in areas endemic for Lyme disease. This U.S. map is based on data obtained from the Centers for Disease Control and Prevention that recorded the names of counties that reported cases of Lyme disease and/or babesiosis from 2011 to 2013. Counties with ≥3 cases of Lyme disease but <3 cases of babesiosis are depicted in *green.* Counties with ≥3 cases of Lyme disease and ≥3 cases of babesiosis are depicted in *gray* . No county reported ≥3 cases of babesiosis but <3 cases of Lyme disease. (Adapted from Diuk-Wasser M, Vannier E, Krause PJ: Coinfection by *Ixodes* tick-borne pathogens: ecological, epidemiological, and clinical consequences, *Trends Parasitol* 32:30–42, 2016.)**

In certain sites and in certain years of high transmission, babesiosis constitutes a significant public health burden. On Nantucket Island, case rates as high as 280 per 100,000 population have been recorded, placing the community burden of disease in a category with gonorrhea as “moderately common.” Comparable incidence rates have been described elsewhere on the southern New England coast.

Pathogenesis

The pathogenesis of human babesiosis is not well understood. Lysis of infected erythrocytes with resultant anemia and the excessive production of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 may account for most of the clinical manifestations and complications of the disease. The spleen has an important role in clearing parasitemia, as do T and B cells, macrophages, polymorphonuclear leukocytes, cytokines, antibody, and complement.

Clinical Manifestations

The clinical severity of babesiosis ranges from subclinical infection to fulminant disease and death. In clinically apparent cases, symptoms of babesiosis begin after an incubation period of 1-9 wk from the beginning of tick feeding or 1 wk to 6 mo after transfusion. Typical symptoms in moderate to severe infection include intermittent fever to as high as 40°C (104°F) accompanied by any combination of chills, sweats, headache, and myalgias. Less common are arthralgias, sore throat, abdominal pain, nausea, vomiting, emotional lability, hyperesthesia, conjunctival injection, photophobia, weight loss, and nonproductive cough. The findings on physical examination generally are minimal, often consisting only of fever. Splenomegaly, hepatomegaly, or both are noted occasionally, but rash seldom is reported. Abnormal laboratory findings include moderately severe hemolytic anemia, elevated reticulocyte count, thrombocytopenia, proteinuria, and elevated bilirubin, blood urea nitrogen, and creatinine levels. The leukocyte count is normal to slightly decreased, often with neutropenia. Complications include respiratory failure, disseminated intravascular coagulation, congestive heart failure, renal failure, liver failure, coma, and death. Babesiosis symptoms usually last for 1-2 wk, although prolonged recovery of up to ≥1 yr may occur in highly immunocompromised hosts who experience relapsing infection. Such patients include those with cancer and asplenia, those receiving immunosuppressive therapy, or those with HIV/AIDS, even though they receive multiple courses of antibabesial therapy. More than one fifth of these patients died, while the remainder were cured after an average of 3 mo (range: 1-24 mo) of antibabesial therapy.

Risk factors for severe disease include aging, neonatal prematurity, anatomic or functional asplenia, malignancy, HIV/AIDS, immunosuppressive drugs, acquisition of infection through blood transfusion, or organ transplantation. Concurrent babesiosis and Lyme disease has been reported in 3–11% of patients experiencing Lyme disease, depending on location in the United States. Such co-infection results in more severe Lyme disease illness. Moderate to severe babesiosis may occur in children, but infection generally is less severe than in adults. About half of infected children are asymptomatic or experience minimal symptoms. Neonates may develop severe illness and usually are infected from blood transfusion.

Diagnosis

Diagnosis of *B. microti* infection in human hosts is confirmed by microscopic demonstration of the organism using Giemsa-stained thin blood films. Parasitemia may be exceedingly low, especially early in the course of illness. Thick blood smears may be examined, but the organisms may be mistaken for stain precipitate or iron inclusion bodies. The polymerase chain reaction is a sensitive and specific test for detection of *Babesia* DNA and can be used in addition to or instead of blood smear to confirm the diagnosis. Subinoculation of blood into hamsters or gerbils and in vitro cultivation are too specialized for all but the most experienced laboratories. Serologic testing is useful, particularly for diagnosing *B. microti* infection. The indirect immunofluorescence serologic assay for both IgG and IgM antibodies is sensitive and specific and can support a diagnosis of babesiosis, although may reflect past infection rather than acute disease. The diagnosis of babesiosis is most reliably made in patients who have lived or traveled in an area where babesiosis is endemic, who experience viral infection–like symptoms, and who have identifiable parasites on blood smear or amplifiable *Babesia* DNA in blood and antibabesial antibody in serum. The diagnosis of active babesial infection based on seropositivity alone is suspect.

Treatment

The combination of **clindamycin** (7-10 mg/kg given intravenously [IV] or orally [PO] every 6-8 hr, up to maximum of 600 mg/dose) and **quinine** (8 mg/kg PO every 8 hr, up to maximum of 650 mg/dose) for 7-10 days was the first effective therapeutic combination for the treatment of babesiosis. However, adverse reactions are common, especially tinnitus and abdominal distress. The combination of **atovaquone** (20 mg/kg PO every 12 hr, up to maximum of 750 mg/dose) and **azithromycin** (10 mg/kg/day PO once on day 1, up to maximum of 500 mg/dose, and 5 mg/kg once daily thereafter, up to maximum of 250 mg/dose) for 7-10 days is as effective as clindamycin and quinine but has far fewer adverse effects. Atovaquone with azithromycin has been used successfully to treat babesiosis in infants and should be used initially in all children experiencing babesiosis. Clindamycin with quinine is an alternative choice. Treatment failure with atovaquone-azithromycin and clindamycin-quinine may occur in highly immunocompromised hosts. Consultation with an infectious diseases expert is recommended in these cases. Exchange blood transfusion can decrease parasitemia rapidly and remove toxic by-products of infection. Partial or complete exchange transfusion is recommended for children with high-grade parasitemia (≥10%), severe anemia (hemoglobin <10 g/dL) or pulmonary, renal, or hepatic compromise.

Prognosis

Moderate to severe disease is frequently observed in some highly endemic areas. The babesiosis case fatality rate was estimated at 5% in a retrospective study of 136 New York cases but may be as high as 21% in immunocompromised hosts and those who acquire babesiosis through blood transfusion. Immunity is sometimes incomplete, with low-level asymptomatic parasitemia persisting for as long as 26 mo after symptoms have resolved, or with relapsing symptomatic disease in immunocompromised hosts.

Prevention

Prevention of babesiosis can be accomplished by avoiding areas where ticks, deer, and mice are known to thrive. Use of clothing that covers the lower part of the body and that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin (Permanone) is recommended for those who travel in the foliage of endemic areas. DEET can be applied directly to the skin. A search for ticks should be carried out and the ticks removed using tweezers. Prospective blood donors with a history of babesiosis are excluded from giving blood to prevent transfusion-related cases.

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CHAPTER 316

Toxoplasmosis *(Toxoplasma gondii)*

Rima McLeod, Kenneth M. Boyer

Toxoplasma gondii, an obligate, intracellular, apicomplexan protozoan, is acquired perorally, transplacentally, or rarely parenterally in laboratory accidents, transfusions, or from a transplanted organ. In immunologically normal children, acute acquired infection most often is asymptomatic or unrecognized, but may cause lymphadenopathy or affect almost any organ. *Once acquired, latent encysted organisms persist in the host throughout life.* In immunocompromised persons, initial acquisition or recrudescence of latent organisms can cause signs or symptoms related to the central nervous system (CNS) or result in systemic disease, as in bone marrow transplant recipients. If untreated, congenital infection usually causes disease that manifests either perinatally or later in life, most frequently chorioretinitis and CNS lesions. Other manifestations, such as intrauterine growth restriction, prematurity, cognitive and motor deficits, fever, lymphadenopathy, rash, hearing loss, pneumonitis, hepatitis, thrombocytopenia, and cerebrospinal fluid (CSF) inflammatory changes may also occur. Unrecognized congenital toxoplasmosis in infants with HIV infection may be fulminant.

Etiology

Toxoplasma gondii is a coccidian protozoan that multiplies only in living cells. It is descended from an ancient, free-living, single-celled extracellular parasite called *Colpodella* that shares some ultrastructural features with *T. gondii* . Tachyzoites, the pathogenic form of the parasite in active infections, are oval or crescent-like, measuring 2-4 × 4-7 µm. Tissue cysts, which are 10-100 µm in diameter, may contain 1000s of latent parasites called **bradyzoites** and will remain in tissues, especially the CNS and skeletal and heart muscle, for the life of the host. *Toxoplasma* can multiply in all tissues of mammals and birds.

Oocysts , another form of the parasite, are formed in the cat intestine. Newly infected, nonimmune cats and other Felidae species are the definitive hosts of *T. gondii*, in which genetic exchange occurs during a sexual cycle. *Toxoplasma* organisms are transmitted to cats when the cat ingests infected meat containing encysted bradyzoites or ingests oocysts containing sporozoites excreted by other recently infected cats. The parasites then multiply through schizogonic and gametogonic cycles in the distal ileal epithelium of the cat intestine. Oocysts containing 2 sporocysts are excreted, and, under proper conditions of temperature and moisture, each sporocyst matures into 4 sporozoites. For approximately 2 wk the cat excretes 10^5 -10^7 oocysts daily, which may retain their viability for >1 yr in a suitable environment. Oocysts sporulate 1-5 days after excretion and are then infectious. Oocysts are killed by drying or boiling but not exposure to bleach. Oocysts have been isolated from soil and sand frequented by cats, and outbreaks associated with contaminated food and water have been reported. Oocysts and tissue cysts are sources of animal and human infections (Fig. 316.1*A* and *B*). There are genetically distinct genetic types of *T. gondii* that have different virulence for mice (and likely for humans) and form different numbers of cysts in the brain of outbred mice. In the United States, there are 4 predominant clonal lineages called **types I** , **II** , **III** , and **IV** (haplogroup XII) in addition to atypical, recombinant types (Fig. 316.1*C*). There is 1 predominant clonal type (type II) in France, Austria, and Poland, and nonarchetypal parasites are prevalent in Brazil, Guyana, French Guiana, and Central America (Fig. 316.1*D*). Secreted molecules are primary virulence factors that differ between genetic lineages called **strains** (Fig. 316.1*E*).

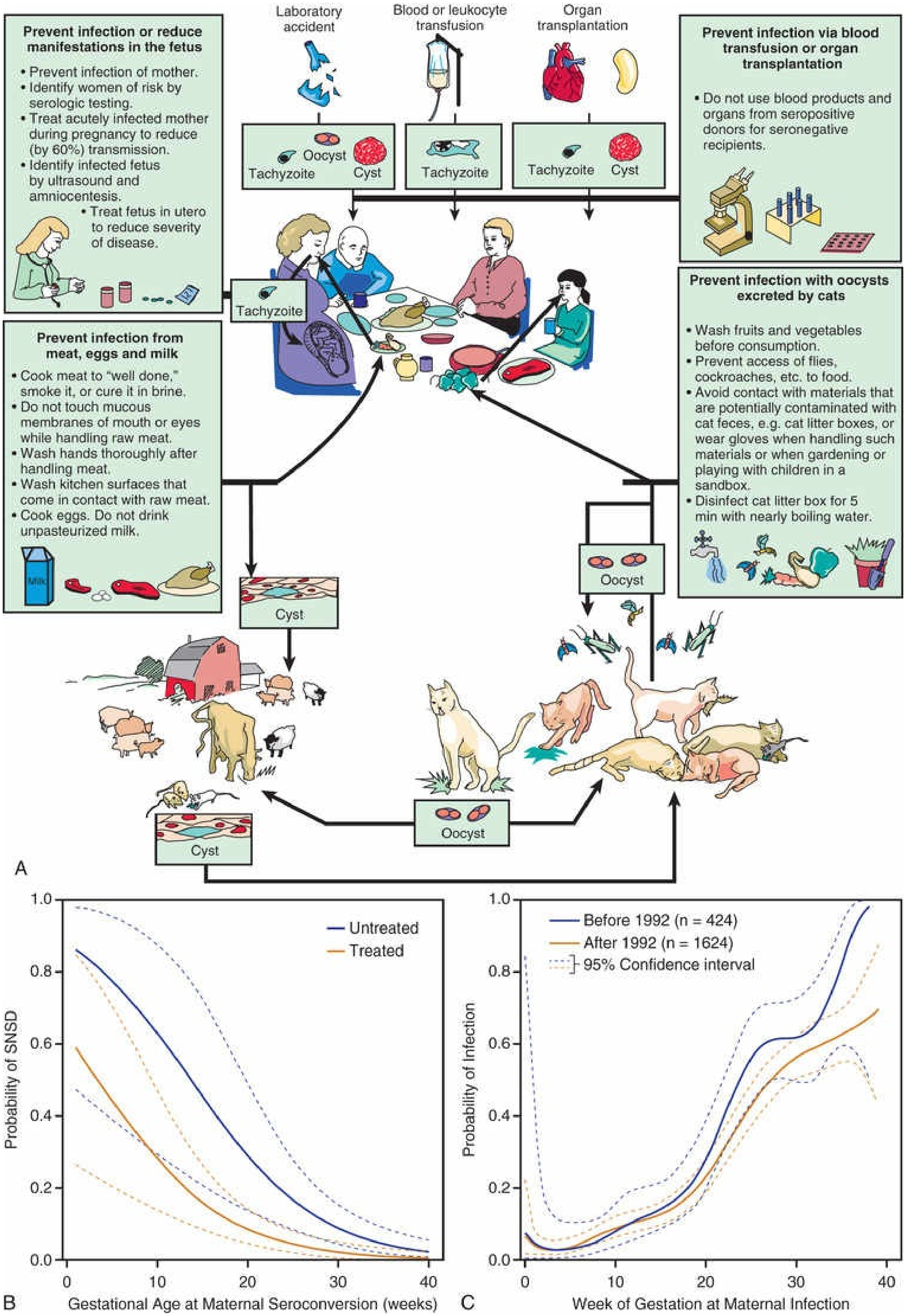

Prevent infection or reduce manifestations in the fetus

- Prevent infection of mother.
- Identify women of risk by serologic testing.
- Treat acutely infected mother during pregnancy to reduce (by 60%) transmission.
- Identify infected fetus by ultrasound and amniocentesis.
- Treat fetus in utero to reduce severity of disease.

Prevent infection via blood transfusion or organ transplantation

- Do not use blood products and organs from seropositive donors for seronegative recipients.

Prevent infection from meat, eggs and milk

- Cook meat to “well done,” smoke it, or cure it in brine.
- Do not touch mucous membranes of mouth or eyes while handling raw meat.
- Wash hands thoroughly after handling meat.
- Wash kitchen surfaces that come in contact with raw meat.
- Cook eggs. Do not drink unpasteurized milk.

Prevent infection with oocysts excreted by cats

- Wash fruits and vegetables before consumption.
- Prevent access of flies, cockroaches, etc. to food.
- Avoid contact with materials that are potentially contaminated with cat feces, e.g. cat litter boxes, or wear gloves when handling such materials or when gardening or playing with children in a sandbox.
- Disinfect cat litter box for 5 min with nearly boiling water.

Laboratory accident
Blood or leukocyte transfusion
Organ transplantation
Oocyst
Tachyzoite
Cyst
Tachyzoite
Tachyzoite
Cyst
Tachyzoite
Milk
Cyst
Oocyst
Oocyst
Cyst
A
1.0
0.8
0.6
0.4
0.2
0.0
Probability of SNSD
Untreated
Treated
0
10
20
30
40
Gestational Age at Maternal Seroconversion (weeks)
B
1.0
0.8
0.6
0.4
0.2
0.0
Probability of Infection
Before 1992 (n = 424)
After 1992 (n = 1624)
95% Confidence interval
0
10
20
30
40
Week of Gestation at Maternal Infection
C

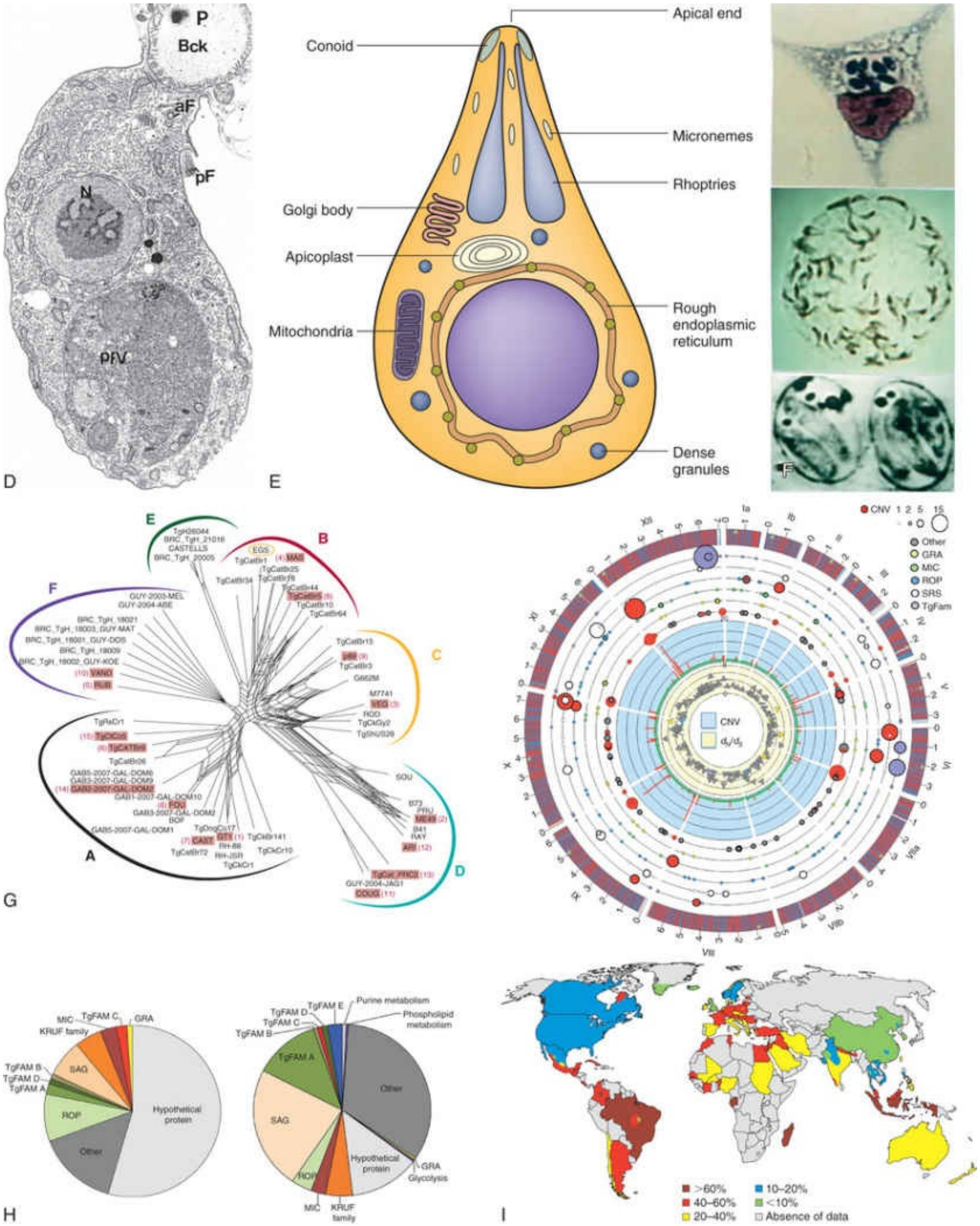
P
Bck
aF
pF
N
PFV
D
Apical end
Conoid
Micronemes
Rhoptries
Golgi body
Apicoplast
Mitochondria
Rough endoplasmic reticulum
Dense granules
E
F
E
TgH26044
BRC_TgH_21016
CASTELLS
BRC_TgH_20005
B
EGS
TgCatBr1
(4) MAS
TgCatBr25
TgCatBr34
TgCatBr18
TgCatBr44
TgCatBr5 (8)
TgCatBr10
TgCatBr64
F
GUY-2003-MEL
GUY-2004-ABE
BRC_TgH_18021
BRC_TgH_18003_GUY-MAT
BRC_TgH_18001_GUY-DOS
BRC_TgH_18009
BRC_TgH_18002_GUY-KOE
(10) VAND
(5) RUB
C
TgCatBr15
p89 (9)
TgCatBr3
G662M
M7741
VEG (3)
ROD
TgCkGy2
TgShUS28
TgRsCr1
(15) TgCkCr5
(6) TgCATBr9
TgCatBr26
GAB5-2007-GAL-DOM6
GAB3-2007-GAL-DOM9
(14) GAB2-2007-GAL-DOM2
GAB1-2007-GAL-DOM10
(6) FOU
GAB3-2007-GAL-DOM2
BOF
GAB5-2007-GAL-DOM1
TgDogCo17
(7) CAST
GT1 (1)
TgCkBr141
RH-88
RH-JSR
TgCatBr72
TgCkCr10
TgCkCr1
A
SOU
B73
PRU
ME49 (2)
B41
RAY
ARI (12)
TgCat_PRC2 (13)
GUY-2004-JAG1
COUG (11)
D
G
CNV 1 2 5 15
Other
GRA
MIC
ROP
SRS
TgFam
CNV
d_N/d_S
Ia
Ib
II
III
IV
V
VI
VIIa
VIIb
VIII
IX
X
XI
XII
MIC
TgFAM C
GRA
KRUF family
TgFAM B
TgFAM D
TgFAM A
SAG
ROP
Other
Hypothetical protein
TgFAM E
Purine metabolism
TgFAM D
TgFAM C
Phospholipid metabolism
TgFAM B
TgFAM A
Other
SAG
Hypothetical protein
ROP
GRA
Glycolysis
MIC
KRUF family
H
>60%
40–60%
20–40%
10–20%
<10%
Absence of data
I

FIG. 316.1 **The parasite: *Toxoplasma* life cycle, ancient ancestor, ultrastructure, life cycle stages affecting humans, genetic variation, and global seroprevalence. A, Life cycle of *Toxoplasma gondii* and prevention of toxoplasmosis by interruption of transmission to humans. B, Risk of severe neurologic disease or death (SNDD) in children with congenital toxoplasmosis (CT) according to antepartum treatment. Probability of SNDD according to imputed gestational age at seroconversion and 95% bayesian credible limits. *Dotted lines* denote treated pregnancies; *solid lines* denote**

untreated pregnancies. (SNDD is a composite outcome comprising a pediatric report at any age of microcephaly; insertion of an intraventricular shunt; an abnormal or suspicious neurodevelopmental examination that resulted in referral to a specialist; seizures during infancy or at an older age that required anticonvulsant therapy; severe bilateral visual impairment [visual acuity of Snellen ≤6/60 in both eyes assessed after 3 yr]; cerebral palsy; or death from any cause before age 2 yr, including termination of pregnancy [consistency of SSND findings was checked through multiple assessments].) Severe neurologic sequelae were assessed at a median of 4 yr follow-up, death was assessed by age 2 yr, and severe bilateral visual impairment was included in the composite outcome of severe neurologic sequelae. C, Probability of fetal infection according to gestational age at the time of maternal infection before (*n* = 451) and after (*n* = 1624) mid-1992, Lyon cohort (1987–2008). D, *Colpodella vorax,* an ancient progenitor to the apicomplexans. E, Ultrastructure of *T. gondii* tachyzoite. F, Light micrographs of *top to bottom,* tachyzoite, bradyzoite, and sporozoite stages of *T. gondii.* G, Genetic characterization of EGS strain. Genetic relationship of *T. gondii* isolate strain *(left)* and positions on chromosomes *(right)* . H, Composition of *T. gondii* genome. I, Global status of *T. gondii* seroprevalence. (*B,* From Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment of serious neurologic sequelae of congenital toxoplasmosis: an observational prospective cohort study, *PLoS Med* 7:e1000351, 2010; *C,* from Wallon M, Peyron F, Cornu C, et al: Congenital toxoplasmosis infection: monthly prenatal screening decreases transmission rate and improves clinical outcome at age 3 years, *Clin Infect Dis* 56:1229, 2013; *D,* from Brugerolle G: *Colpodella vorax* : ultrastructure, predation, life-cycle, mitosis, and phylogenetic relationships, *Eur J Protistol* 38(2):113–125, 2002; *E,* from Wheeler K: Characterization of *Toxoplasma gondii* dense granule protein 1: genetic, functional, and mechanistic analyses (Undergraduate Honors thesis), Kelsey Wheeler; *F,* from Dubey JP, Miller N, Frenkel JK: The *Toxoplasma gondii* oocyst from cat feces, *J Exp Med* 132(4):636-662, 1970; *G,* from McPhillie M, Zhou Y, El Bissati K, et al: New paradigms for understanding and step changes in treating active and chronic, persistent apicomplexan infections, *Sci Rep* 6(1), 2016; *H,* from Lorenzi H, Khan A, Behnke M, et al: Local admixture of amplified and diversified secreted pathogenesis determinants shapes mosaic *Toxoplasma gondii* genomes, *Nat Commun* 7:10147, 2016; *I,* from Pappas G, Roussos N, Falagas ME: Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis, *Int J Parasitol* 39(12):1385–1394, 2009.)

Epidemiology

Toxoplasma infection is ubiquitous in animals and is one of the most common latent infections of humans throughout the world, infecting, and remaining in, approximately 2 billion people. Prevalence varies considerably among people and animals in different geographic areas. In different areas of the world, approximately 3–35% of pork, 7–60% of lamb, and 0–9% of beef contain *T. gondii* organisms. Significant antibody titers are detected in 50–80% of residents of some localities, such as France, Brazil, and Central America, and in <5% in other areas. The current prevalence estimate in the United States is 10%, but prevalence varies in differing demographies. For example, in the study of Lancaster County pregnant women in an Amish community, prevalence was 50%.There appears to be a higher prevalence of infection in some warmer, more humid climates. Non type II parasites are more common in mothers of congenitally infected infants in warm, moist southern climates, in rural areas, in those with lower socioeconomic status, and with Hispanic ethnicity in the United States. Non–type II parasites are more often associated with prematurity and severe congenital infection in the United States.

Human infection in older children and adults is usually acquired orally by eating undercooked or raw meat that contains cysts or food (e.g., salad greens) or other material contaminated with oocysts from acutely infected cats. Freezing meat to −20°C (−4°F) or heating meat to 66°C (150.8°F) renders the tissue cysts noninfectious. Outbreaks of acute acquired infection have occurred in families, at social gatherings, and in restaurants where people have consumed the same infected food or water. *Toxoplasma* organisms are not known to be transmitted from person to person except for transplacental infection from mother to fetus and, rarely, by organ transplantation or transfusion. *T. gondii* has been noted in the prostate gland and sperm of nonhuman animals, but no sexual transmission between humans has been proved.

Seronegative transplant recipients who receive an organ or bone marrow from seropositive donors have experienced life-threatening illness requiring therapy. Seropositive recipients who receive an infected donor organ may have increased serologic titers without recognized, associated disease. Laboratory accidents have resulted in infections, including fatalities.

Congenital Toxoplasmosis

Transmission to the fetus usually follows acquisition of primary infection by an immunologically normal pregnant woman during gestation. Congenital transmission from mothers infected before pregnancy is extremely rare except for immunocompromised women who are chronically infected. The estimated incidence of congenital infection in the United States ranges from 1 in 1,000 to 1 in 8,000 live births. An estimated 15 million people are living with congenital toxoplasmosis worldwide. The incidence of infection among pregnant women depends on the general risk for infection in the specific locale and the proportion of the population that has not been infected previously.

Pathogenesis

T. gondii is acquired by children and adults from ingesting food that contains cysts or that is contaminated with oocysts from acutely infected cats. Oocysts also may be transported to food by flies and cockroaches. They may be carried to people on the fur of dogs. When the organism is ingested, bradyzoites are released from cysts or sporozoites from oocysts. The organisms enter gastrointestinal (GI) cells, where they multiply, rupture cells, infect contiguous cells, enter the lymphatics and blood, and disseminate lymphohematogenously throughout the body. **Tachyzoites** proliferate, producing necrotic foci surrounded by a cellular reaction. With development of a normal immune response that is both humoral and cell mediated, tachyzoites disappear from tissues. In immunocompromised persons and also some apparently immunocompetent persons, acute infection progresses and may cause potentially lethal disease, including pneumonitis, myocarditis, or encephalitis.

Alterations of T-lymphocyte populations during acute *T. gondii* infection are common and include lymphocytosis, increased $CD8^+$ T-cell count, and decreased $CD4^+$ /$CD8^+$ ratio. Characteristic histopathologic changes in lymph nodes during acute infection include reactive follicular hyperplasia with irregular clusters of epithelioid histiocytes that encroach on and blur margins of germinal centers, and focal distention of sinuses with monocytoid cells. Depletion of $CD4^+$ T cells in patients with AIDS predisposes to severe manifestations of toxoplasmosis.

Cysts form as early as 7 days after infection and remain for the life of the host. During latent infection they produce little or no inflammatory response but can cause recrudescent disease in immunocompromised persons. **Recrudescent chorioretinitis** can occur in children and adults with postnatally acquired infection and in older children and adults with congenitally acquired infection. Host and parasite genetics influence outcomes.

Congenital Toxoplasmosis

When a mother acquires infection during gestation, organisms may disseminate hematogenously to the placenta. Infection may be transmitted to the fetus transplacentally or during vaginal delivery. Of untreated maternal infections acquired in the first trimester, approximately 17% of fetuses are infected, usually with severe disease. Of untreated maternal infection acquired in the third trimester, approximately 65% of fetuses are infected, usually with disease that is milder or inapparent at birth. These different rates of transmission and outcomes are most likely related to placental blood flow, virulence, inoculum of *T. gondii,* and immunologic capacity of the mother and fetus to limit parasitemia.

Examination of the placenta of infected newborns may reveal chronic inflammation and cysts. Tachyzoites can be seen with Wright or Giemsa stains but are best demonstrated with immunoperoxidase technique. Tissue cysts stain well with periodic acid–Schiff and silver stains as well as with the immunoperoxidase technique. Gross or microscopic areas of necrosis may be present in many tissues, especially the CNS, choroid and retina, heart, lungs, skeletal muscle, liver, and spleen. Areas of calcification occur in the brain.

Almost all congenitally infected individuals who are not treated manifest signs or symptoms of infection, such as chorioretinitis, by adolescence. Some severely involved infants with congenital infection appear to have *Toxoplasma* antigen–specific cell-mediated hyporesponsiveness, which may be important in the pathogenesis of disease.

Clinical Manifestations

Manifestations of primary infection with *T. gondii* are highly variable and are influenced primarily by host immunocompetence. There may be no signs or symptoms or severe disease. Reactivation of previously asymptomatic congenital toxoplasmosis usually manifests as ocular toxoplasmosis.

Acquired Toxoplasmosis

Immunocompetent children who acquire infection postnatally generally do not have clinically recognizable symptoms. When clinical manifestations are apparent, they may include almost any combination of fever, stiff neck, myalgia, arthralgia, maculopapular rash that spares the palms and soles, localized or generalized lymphadenopathy, hepatomegaly, hepatitis, reactive lymphocytosis, meningitis, brain abscess, encephalitis, confusion, malaise, pneumonia, polymyositis, pericarditis, pericardial effusion, and myocarditis. **Chorioretinitis** occurs in approximately 1% of U.S. cases and in 20% of cases in epidemics in Brazil at 2 years after infection. Approximately 10% of mothers of congenitally infected infants have eye lesions on dilated indirect ophthalmoscopic examinations. Postnatally acquired chorioretinal lesions cannot be distinguished from congenitally acquired lesions based on appearance. In some areas of Brazil, 80% of the population is infected, 20% of whom have retinal involvement, with 50% of those >50 yr old. Symptoms and signs of active ocular infection may be present for a few weeks only or may persist for many months.

The most common manifestation of acute acquired toxoplasmosis is enlargement of 1 or a few cervical lymph nodes. Cases of *Toxoplasma* **lymphadenopathy** can resemble infectious mononucleosis, lymphoma, or other lymphadenopathies (see Chapter 517). Pectoral, mediastinal, mesenteric, and retroperitoneal lymph nodes may be involved. Involvement of intraabdominal lymph nodes may be associated with fever, mimicking appendicitis. Nodes may be tender but do not suppurate. Lymphadenopathy may wax and wane for as long as 1-2 yr. However, almost all patients with lymphadenopathy recover spontaneously without antimicrobial therapy. Significant organ involvement in immunologically normal persons is uncommon, although some individuals have significant morbidity, including rare cases of encephalitis, brain abscesses, hepatitis, myocarditis, pericarditis, and polymyositis. In persons acquiring *T . gondii* in Guyana near the Maroni River, and along Amazon tributaries, a severe form of life-threatening, multivisceral involvement with fever has occurred.

Ocular Toxoplasmosis

In the United States and Western Europe, *T. gondii* is estimated to cause 35% of cases of **chorioretinitis** (Fig. 316.2). In Brazil, *T. gondii* retinal lesions are common. Clinical manifestations include blurred vision, visual floaters, photophobia, epiphora, and, with macular involvement, loss of central vision. Ocular findings of **congenital toxoplasmosis** also include strabismus, microphthalmia, microcornea, cataracts, anisometropia, nystagmus, glaucoma, optic neuritis, and optic atrophy. Episodic recurrences are common, but precipitating factors have not been defined. Recurrent, active disease usually occurs at school-entry age and during adolescence. Anecdotally, stress or trauma seems to precipitate symptoms. Recurrences are most common closest to the time of acquisition of infection, and treatment leads to resolution of activity.

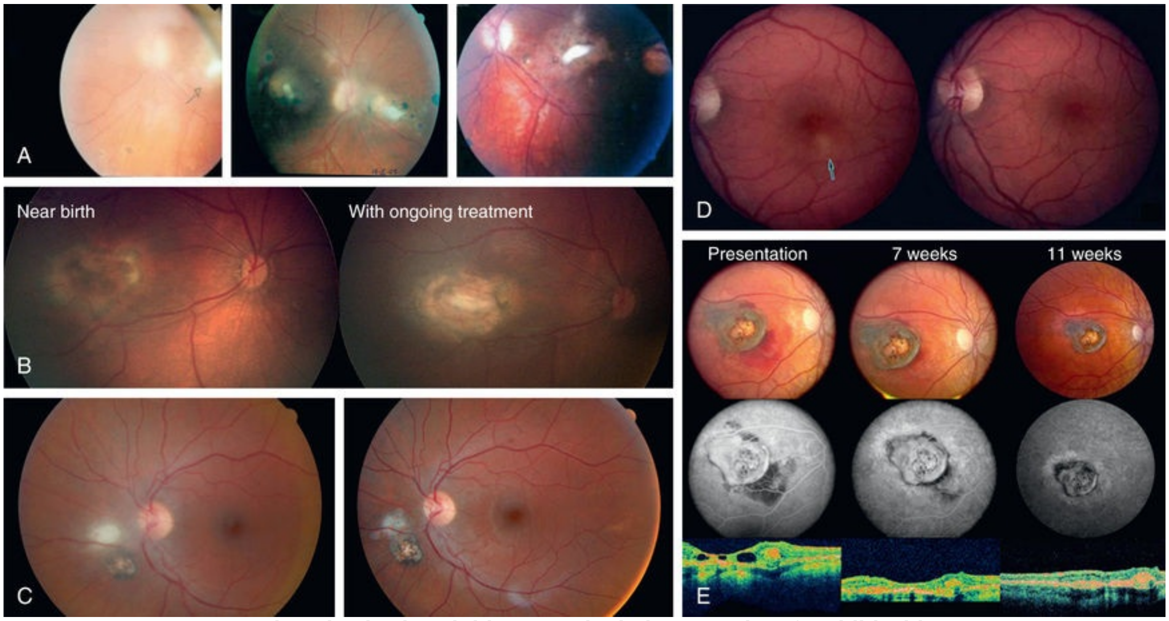

FIG. 316.2 Toxoplasmic chorioretinitis. A, Retinal photographs of a child with severe vitreitis that is less intense than the classic "headlight in fog" appearance *(left).* Resolving vitreitis caused by underlying active lesion *(middle).* Resolved healed lesion without vitreitis *(right).* B, Retina photographs for a newborn infant with active vitreitis (*left,* "near birth") with clearing of vitreitis and marked, but not complete, resolution of activity of the lesion 3 wk later (*right,* "with ongoing treatment"). C, Retinal photographs of a child showing an active lesion at presentation *(left),* and scarred lesion *(right).* D, Retinal photographs showing an active retinal lesion before treatment *(left)* and a completely resolved normal appearing retina within 1 mo of initiating treatment *(right).* E, Active choroidal neovascular membranes (CNVMs) in a child. Fundus photographs *(top row),* fluorescein angiogram (FA; *middle row*), and ocular coherence tomography (OCT; *bottom row*) of a child at presentation *(first column),* 7 wk after first ranibizumab (Lucentis, antibody to VEGF) injection *(second column)* , and 11 wk after first ranibizumab injection *(third column).* (*A-D,* Adapted from Delair E, Latkany P, Noble AG, et al: Clinical manifestations of ocular toxoplasmosis, *Ocul Immunol Inflamm* 19:91–102, 2011; *E,* adapted from Benevento JD, Jager RD, Noble AG, et al: Toxoplasmosis-associated neovascular lesions treated successfully with ranibizumab and antiparasitic therapy, *Arch Ophthalmol* 126:1152–1156, 2008.)

Immunocompromised Persons

Disseminated *T. gondii* infection among older children who are **immunocompromised** by AIDS, malignancy, cytotoxic therapy, corticosteroids, or immunosuppressive drugs given for organ transplantation involves the CNS in 50% of cases and may also involve the heart, lungs, and GI tract. Stem cell transplant recipients present a special problem, because active infection is difficult to diagnose serologically. After transplantation, *T. gondii* –specific antibody levels may remain the same, increase, or decrease, and can even become undetectable. Toxoplasmosis in transplantation patients almost always results from transplantation from a seropositive donor to a seronegative recipient. Thus, knowledge of the serologic status of the donor and recipient is essential. Active infection is often fulminant and rapidly fatal without treatment. Following blood PCR can establish diagnosis and monitor efficacy of treatment.

Congenital *T. gondii* infection in infants with HIV infection is rare in the United States but can be a severe and fulminant disease with substantial CNS involvement. Alternatively, it may be more indolent in presentation, with focal neurologic deficits or systemic manifestations such as pneumonitis occurring with progressive CD4 depletion in the highly active antiretroviral therapy (HAART)–untreated infant.

From 25–50% of persons with *T. gondii* antibodies and HIV infection without antiretroviral treatment eventually experience **toxoplasmic encephalitis** , which is fatal if not treated. HAART and trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis to prevent *Pneumocystis* have diminished the incidence of toxoplasmosis in patients with HIV infection, but toxoplasmic encephalitis remains a presenting manifestation in some adult patients with AIDS. Typical findings include fever, headache, altered mental status, psychosis, cognitive impairment, seizures, and focal neurologic defects, including hemiparesis, aphasia, ataxia, visual field loss, cranial nerve palsies, and dysmetria or movement disorders. In adult patients with AIDS, toxoplasmic retinal lesions are often large with diffuse necrosis and contain many organisms but little inflammatory cellular infiltrate. Diagnosis of presumptive toxoplasmic encephalitis based on neuroradiologic studies in patients with AIDS necessitates a prompt therapeutic trial of medications effective against *T. gondii.* Clear clinical improvement within 7-14 days and improvement of neuroradiologic findings within 3 wk make the presumptive diagnosis almost certain.

Congenital Toxoplasmosis

Congenital toxoplasmosis usually occurs when a woman acquires primary infection while pregnant. Most often, maternal infection is asymptomatic or without specific symptoms or signs. As with other adults with acute toxoplasmosis, lymphadenopathy is the most commonly identified physical finding.

In monozygotic twins the clinical pattern of involvement is most often similar, whereas in dizygotic twins the manifestations often differ, including cases of congenital infection in only 1 twin. The major histocompatibility complex class II gene DQ3 appears to be more common than DQ1 among HIV-infected persons seropositive for *T. gondii* who develop toxoplasmic encephalitis, as well as in children with congenital toxoplasmosis who develop hydrocephalus. These findings suggest that the presence of HLA-DQ3 is a risk factor for severity of toxoplasmosis. Other allelic variants of genes, including *COL2A* , *ABC4R* , *P2X7R* , *NALP1* , *ALOX12*, *TLR9* , and *ERAAP* , are also associated with increased susceptibility.

Congenital infection may present as a mild or severe neonatal disease. It may also present with sequelae or relapse of a previously undiagnosed and untreated infection later in infancy or even later in life. There is a wide variety of manifestations of congenital infection, ranging from hydrops fetalis and perinatal death to small size for gestational age, prematurity, peripheral retinal scars, persistent jaundice, mild thrombocytopenia, CSF pleocytosis, and the characteristic triad of chorioretinitis, hydrocephalus, and cerebral calcifications. More than 50% of congenitally infected infants are considered normal in the perinatal period, but almost all such children will develop ocular involvement later in life if they are not treated during infancy. Neurologic signs such as convulsions, setting-sun sign with downward gaze, and hydrocephalus with increased head circumference may be associated with substantial cerebral damage or with relatively mild inflammation obstructing the aqueduct of Sylvius. If affected infants are treated and shunted promptly, signs and symptoms may resolve, and development may be normal.

The spectrum and frequency of neonatal manifestations of 210 newborns with congenital *Toxoplasma* infection identified by a serologic screening program of pregnant women in France were described in 1984. In this study, 10% had severe congenital toxoplasmosis with CNS involvement, eye lesions, and general systemic manifestations; 34% had mild involvement with normal clinical examination results other than retinal scars on dilated indirect exams or isolated intracranial calcifications in brain CT scans; and 55% had no detectable manifestations. These numbers represent an *underestimation* of the incidence of severe congenital infection for several reasons: the most severe cases, including most who died, were not referred; therapeutic abortion sometimes was performed when acute acquired infection of the mother was diagnosed early during pregnancy; in utero **spiramycin** therapy prevented or diminished the severity of infection; only 13 of the 210 congenitally infected newborns had brain CT, and only 77% of these 210 infants had a CSF examination. Routine newborn examinations often yield normal findings for congenitally infected infants, but more careful evaluations may reveal significant abnormalities. A

2012 analysis of the **National Collaborative Chicago-Based Congenital Toxoplasmosis Study** (NCCCTS, 1981–2009) data found that 72% of children at or near birth had chorioretinal scars, 70% had CNS calcifications, 12% microcephaly, 37% hydrocephalus, 41% thrombocytopenia, 39% hepatomegaly, 32% splenomegaly, and 41% were born prematurely (Fig. 316.3). In one study of 28 infants in New England, identified by a universal state-mandated serologic screening program for *T. gondii* –specific IgM, 26 (93%) had normal findings on routine newborn examination, but 14 (50%) had significant abnormalities detected with more careful evaluation. The abnormalities included retinal scars (7 infants), active chorioretinitis (3 infants), and CNS abnormalities (8 infants). In Fiocruz, Belo Horizonte, Brazil, infection is common, affecting 1 in 600 live births. Half these infected infants have active chorioretinitis at birth. When the infection is acquired in utero and the fetus is treated by drug therapy of the pregnant woman with **pyrimethamine** , **sulfadiazine** , and **leucovorin** , signs and symptoms in the infant may be prevented. The newborn infant may appear normal with no CSF abnormalities and no brain or eye disease. In utero therapy initiated rapidly results in a reduction of ocular and neurologic sequelae.

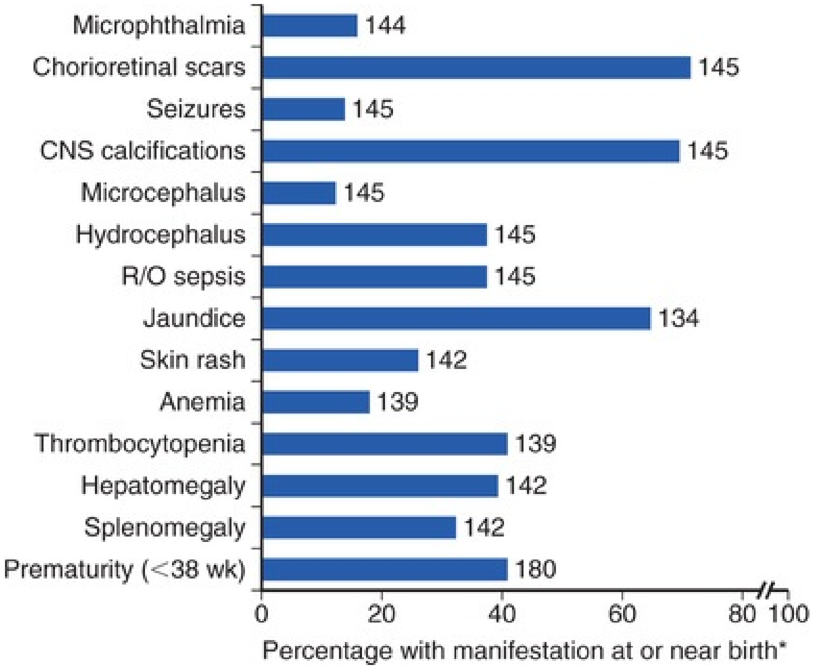

FIG. 316.3 Congenital toxoplasmosis: manifestations at presentation. National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS, 1981–2009). *Infants diagnosed with congenital toxoplasmosis in the newborn period and referred to the NCCCTS during the 1st yr of life. Numbers adjacent to histogram bars represent number of infants with this manifestation and is based on information in birth records;

R/O, rule out sepsis. Sample size dependent on available birth records/diagnoses at birth. (Adapted from McLeod R, Boyer KM, Lee D, et al: Prematurity and severity are associated with *Toxoplasma gondii* alleles [NCCCTS, 1981–2009], *Clin Infect Dis* 54:1595–1605, 2012.)

There is also a wide spectrum of symptoms of untreated congenital toxoplasmosis that presents later in the 1st yr of life (Table 316.1). These children may have IQ scores of <70, and have convulsions and severely impaired vision.

Table 316.1

Signs and Symptoms Occurring Before Diagnosis or During the Course of Untreated Acute Congenital Toxoplasmosis in 152 Infants (A) and in 101 of These Same Children After They Had Been Followed ≥4 Yr (B)

SIGNS AND SYMPTOMS	**FREQUENCY OF OCCURRENCE IN PATIENTS WITH**	
	“Neurologic” Disease*	**“Generalized” Disease †**
A. INFANTS	**108 PATIENTS (%)**	**44 PATIENTS (%)**
Chorioretinitis	102 (94)	29 (66)
Abnormal cerebrospinal fluid	59 (55)	37 (84)
Anemia	55 (51)	34 (77)
Convulsions	54 (50)	8 (18)
Intracranial calcification	54 (50)	2 (4)
Jaundice	31 (29)	35 (80)
Hydrocephalus	30 (28)	0 (0)
Fever	27 (25)	34 (77)
Splenomegaly	23 (21)	40 (90)
Lymphadenopathy	18 (17)	30 (68)
Hepatomegaly	18 (17)	34 (77)
Vomiting	17 (16)	21 (48)
Microcephaly	14 (13)	0 (0)
Diarrhea	7 (6)	11 (25)
Cataracts	5 (5)	0 (0)
Eosinophilia	6 (4)	8 (18)
Abnormal bleeding	3 (3)	8 (18)
Hypothermia	2 (2)	9 (20)
Glaucoma	2 (2)	0 (0)
Optic atrophy	2 (2)	0 (0)
Microphthalmia	2 (2)	0 (0)
Rash	1 (1)	11 (25)
Pneumonitis	0 (0)	18 (41)
B. CHILDREN ≥4 YR OLD	**70 PATIENTS (%)**	**31 PATIENTS (%)**
Intellectual impairment	62 (89)	25 (81)
Convulsions	58 (83)	24 (77)
Spasticity and palsies	53 (76)	18 (58)

Severely impaired vision	48 (69)	13 (42)
Hydrocephalus or microcephaly	31 (44)	2 (6)
Deafness	12 (17)	3 (10)
Normal	6 (9)	5 (16)

[*] Patients with otherwise undiagnosed central nervous system disease in the 1st yr of life.

[†] Patients with otherwise undiagnosed nonneurologic diseases during the 1st 2 mo of life.

Adapted from Eichenwald H: A study of congenital toxoplasmosis. In Slim JC, editor: *Human toxoplasmosis* , Copenhagen, 1960, Munksgaard, pp. 41–49. Study performed in 1947. The most severely involved institutionalized patients were not included in the later study of 101 children.

Systemic Signs

From 25% to >50% of infants with clinically apparent disease at birth are born prematurely. Parasite clonal types other than type II are more often associated with prematurity and more-severe disease. Intrauterine growth restriction, low Apgar scores, and temperature instability are common. Other manifestations may include lymphadenopathy, hepatosplenomegaly, myocarditis, pneumonitis, nephrotic syndrome, vomiting, diarrhea, and feeding problems. Bands of metaphyseal lucency and irregularity of the line of provisional calcification at the epiphyseal plate may occur without periosteal reaction in the ribs, femurs, and vertebrae. Congenital toxoplasmosis may be confused with erythroblastosis fetalis resulting from isosensitization, although the Coombs test result is usually negative with congenital *T. gondii* infection.

Skin

Cutaneous manifestations among newborn infants with congenital toxoplasmosis include rashes and jaundice and/or petechiae secondary to thrombocytopenia, but ecchymoses and large hemorrhages secondary to thrombocytopenia also occur. Rashes may be fine punctate, diffuse maculopapular, lenticular, deep blue-red, sharply defined macular, or diffuse blue and papular. Macular rashes involving the entire body including the palms and soles, exfoliative dermatitis, and cutaneous calcifications have been described. **Jaundice** with hepatic involvement and/or hemolysis, cyanosis due to interstitial pneumonitis from congenital infection, and edema secondary to myocarditis or nephrotic syndrome may be present. Jaundice and conjugated hyperbilirubinemia may persist for months.

Endocrine Abnormalities

Endocrine abnormalities may occur secondary to hypothalamic or pituitary involvement or end-organ involvement but are not common. Occasionally reported endocrinopathies include myxedema, persistent hypernatremia with vasopressin-sensitive diabetes insipidus, sexual precocity, and partial anterior hypopituitarism.

Central Nervous System

Neurologic manifestations of congenital toxoplasmosis vary from massive acute encephalopathy to subtle neurologic syndromes. Toxoplasmosis should be considered as a potential cause of any undiagnosed neurologic disease in children <1 yr old, especially if retinal lesions are present.

Hydrocephalus may be the sole clinical neurologic manifestation of congenital toxoplasmosis and almost always requires shunt placement. Hydrocephalus may present prenatally and progress during the perinatal period or, much less often, may present later in life. Patterns of seizures are protean and have included focal motor seizures, petit and grand mal seizures, muscular twitching, opisthotonos, and hypsarrhythmia. Spinal or bulbar involvement may be manifested by paralysis of the extremities, difficulty swallowing, and respiratory distress. **Microcephaly** usually reflects severe brain damage, but some children with microcephaly caused by congenital toxoplasmosis who have been treated have normal or even superior cognitive function. Untreated congenital toxoplasmosis that is symptomatic in the 1st yr of life can cause substantial diminution in cognitive function and developmental delay. Intellectual impairment also occurs in some children with subclinical infection without or despite treatment with pyrimethamine and sulfonamides. Seizures and focal motor defects may become apparent after the newborn period, even when infection is subclinical at birth.

CSF abnormalities occur in at least 50% of infants with congenital toxoplasmosis. A CSF protein level >1 g/dL is characteristic of severe CNS toxoplasmosis and is usually accompanied by hydrocephalus. Local production of *T. gondii* –specific IgG and IgM antibodies may be demonstrated. CT of the brain is useful to detect calcifications, determine ventricular size, and demonstrate porencephalic cystic structures (Fig. 316.4). **Calcifications** occur throughout the brain, but there is a propensity for development of calcifications in the caudate nucleus and basal ganglia, choroid plexus, and subependyma. MRI and contrast-enhanced CT brain scans are useful for detecting active inflammatory lesions. MRI that requires<45 sec or ultrasonography may be useful for following ventricular size. Medical treatment in utero and in the 1st yr of life results in improved neurologic outcomes and, in many cases, diminution or disappearance of calcifications.

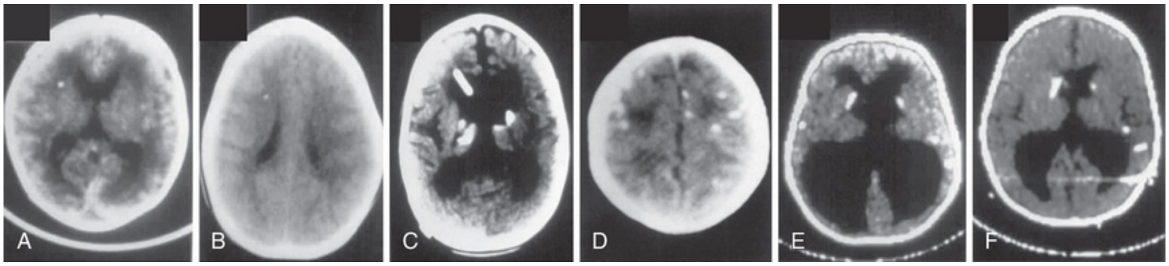

FIG. 316.4 Head CT scans of infants with congenital toxoplasmosis. A, CT scan at birth that shows areas of hypolucency, mildly dilated ventricles, and small calcifications. B, CT scan of the same child at 1 yr of age (after antimicrobial therapy for 1 yr). This scan is normal with the exception of 2 small calcifications. This child's Mental Development Index (MDI) at 1 yr old was 140 by the Bayley Scale of Infant Development. C, CT scan from a 1 yr old infant who was normal at birth. His meningoencephalitis became symptomatic in the 1st few wk of life but was not diagnosed correctly and remained untreated during his 1st 3 mo of life. At 3 mo old, development of hydrocephalus and bilateral macular chorioretinitis led to the diagnosis of congenital toxoplasmosis, and antimicrobial therapy was initiated. This scan shows significant residual atrophy and calcifications. This child had substantial motor dysfunction, development delays, and visual impairment. D, CT scan obtained during the 1st mo of life of a microcephalic child. Note the numerous calcifications. This child's IQ scores using the Stanford-Binet Intelligence Scale for children when she was 3 yr old and Wechsler Preschool and Primary Scale Intelligence when 5 yr old were 100 and 102, respectively. She received antimicrobial therapy during her 1st yr of life. E, CT scan with hydrocephalus caused by aqueductal obstruction, before shunt. F, Scan from the same patient as the scan in E , after shunt. This child's IQ scores using the Stanford-Binet Intelligence Scale for children were approximately 100 when she was 3 and 6 yr old. (A-F, Adapted from McAuley J, Boyer K, Patel D, et al: Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial, *Clin Infect Dis* 18:38–72, 1994.)

Eyes

Almost all untreated congenitally infected infants develop **chorioretinal lesions** by adulthood and may have severe visual impairment. *T. gondii* causes a **focal necrotizing retinitis** in congenitally infected individuals (see Fig. 316.2). Retinal detachment may occur. Any part of the retina may be involved, either unilaterally or bilaterally, including the maculae. The optic nerve may be involved, and toxoplasmic lesions that involve projections of the visual pathways in the brain or the visual cortex also may lead to visual impairment. In association with severe retinal lesions and vitritis, secondary anterior uveitis may develop and occasionally lead to erythema of the external eye. Other ocular findings include cells and protein in the anterior chamber, large keratic precipitates, posterior synechiae, nodules on the iris, and neovascular formation on the surface of the iris, sometimes with increased intraocular pressure and glaucoma. Rarely, the extraocular musculature may also be involved directly. Other manifestations include strabismus, nystagmus, visual impairment, and microphthalmia. Enucleation has been required for a blind, phthisic, painful eye. The **differential diagnosis** of ocular toxoplasmosis includes congenital coloboma and inflammatory lesions caused by cytomegalovirus, lymphocytic choriomeningitis virus, *Bartonella henselae* , *Toxocara canis* , *Treponema pallidum*, *Mycobacterium tuberculosis* , varicella-zoster virus, Zika virus, or vasculitis. Ocular toxoplasmosis may be a recurrent and progressive disease that requires multiple courses of therapy. Limited data suggest that occurrence of lesions in the early years of life may be prevented by instituting **antimicrobial treatment** with pyrimethamine and sulfonamides during the 1st yr of life, and that treatment of the infected fetus in utero followed by treatment in the 1st yr of life with pyrimethamine, sulfadiazine, and leucovorin further reduces the incidence and the severity of the retinal disease.

Ears

Sensorineural hearing loss, both mild and severe, may occur. It is not known whether this is a static or progressive disorder. Treatment in the 1st yr of life is associated with decreased frequency of hearing loss.

Diagnosis

Diagnosis of acute *Toxoplasma* infection can be established by a number of methods (Table 316.2): isolation of *T. gondii* from blood or body fluids; identification of tachyzoites in sections or preparations of tissues and body fluids, amniotic fluid, or placenta; identification of cysts in the placenta or tissues of a fetus or newborn; and characteristic lymph node histologic features. Serologic tests are very useful for diagnosis. Polymerase chain reaction (PCR) is useful to identify *T. gondii* DNA in CSF and amniotic fluid and has been reported to be useful with infant peripheral blood and urine to establish the diagnosis definitively and in immunocompromised patients for diagnosis and monitoring treatment.

Table 316.2

Generalizations Concerning Clinical Presentations, *Toxoplasma* -Specific Diagnostic Tests, and Treatment

CLINICAL SETTING & MANIFESTATION	SAMPLE SOURCE	*TOXOPLASMA* -SPECIFIC DIAGNOSTIC TESTS								TREATMENT	
		G	M	A	E	Av	AC/HS	PCR	Subinoculation	Sp	PSL*
PRENATAL											
Acute infection in pregnant woman ≤18 wk gestation *and* no clinical evidence of fetal infection	Mother	+	+	+	+	L	Acute	AF (17-18 wk)	NS	+	+ † No P 1st trimester
Acute infection in pregnant woman ≤18 wk gestation *and* signs of fetal infection	Mother	+	+	+	+	L	Acute	AF (may not be necessary)	NS		+ † No P 1st trimester
Acute infection in pregnant woman at >21 wk gestation	Mother	+	+	+	+	L	Acute	AF	NS		+
Congenital infection in infant	Infant	+	+	+	+	L	Acute	Placenta/buffy coat	Placenta/buffy coat		+
POSTNATAL											
Acute, symptomatic Acute, self-limited symptoms	Child	+	+	+	+	L	Acute	NS	NS		+
Chronic, asymptomatic	Child	+	−	−	−	H	Chronic	NS	NS		
Acute, severely symptomatic	Child	+	+	+	+	L	Acute	§	Body fluids/buffy coat		+
Immune compromised ¶	Child	+/−	+/−	+/−	+/−	+/−	+/−	§	Body fluids/buffy coat		
Laboratory accident ‖	Child	+/−	+/−	+/−	+/−	+/−	+/−	NS	NS		+
Eye Disease											
Quiescent scar**	Child	+	+/−	+/−	+/−	+/−	+/−	NS	NS		
Active chorioretinitis**	Child	+	+/−	+/−	+/−	+/−	+/−	NS	NS		+
Active CNVM**	Child	+	+/−	+/−	+/−	+/−	+/−	NS	NS		+

[*] Pyrimethamine and leucovorin should be adjusted for granulocytopenia; complete blood counts, including platelets, should be monitored each Monday and Thursday. If there is sulfonamide allergy, alternative medicines include clindamycin, azithromycin, or clarithromycin in place of sulfadiazine.

[†] *Do not* use pyrimethamine in the 1st 14 wk of gestation.

[‡] Occasionally, corticosteroids (prednisone) have been used when CSF protein is ≥1 g/dL or when active chorioretinitis threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

[§] Utility of PCR depends on clinical setting. For example, the following may be useful to establish the diagnosis: PCR of body fluids such as amniotic fluid or CSF; cells from bronchoalveolar lavage from a patient with pneumonia; or tissue such as placenta where presence of parasites or parasite DNA would support a diagnosis of infection.

[¶] In some cases, in immunocompromised persons, there is no detectable serologic response to *T. gondii* . However, if clinical presentation is indicative of infection in the absence of positive serologic results, CSF, buffy coat of peripheral blood, histopathology of tissue samples, or body fluids tested with PCR or subinoculation may be useful. If PCR demonstrates the presence of *T. gondii* DNA in the sample, it is useful for diagnosis. However, the sensitivity of PCR has been variable in this setting. In some circumstances, presumptive treatment may be warranted.

[||] Whether a person should be treated for a laboratory accident depends on the nature of the accident, the serology of the person before the accident, and other factors. When there is risk of infection, treatment is given.

[**] Serologic results depend on whether infection is acute (recently acquired) or chronic. When testing serum from persons with ocular toxoplasmosis, *T. gondii* –specific IgG may be demonstrable only in an undiluted serum sample.

[††] Corticosteroids (prednisone) are used if inflammation or edema caused by infection threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

+, Positive; −, negative; +/−, equivocal; A, *T. gondii*– specific IgA; AC/HS, direct agglutination; AF, amniotic fluid; Av, *T. gondii*– specific IgG avidity; CNVM, choroidal neovascular membrane; Co, corticosteroids (prednisone); CSF, cerebrospinal fluid; E, *T. gondii*– specific IgE; G, *T. gondii*– specific IgG; IG, immunoglobulin; Lu, Lucentis (antibody to vascular endothelial growth factor); M, *T. gondii*– specific IgM; NS, not standard to obtain; PCR, polymerase chain reaction; PSL, pyrimethamine, sulfadiazine, leucovorin (folinic acid); Sp, spiramycin.

Adapted from Remington JS, McLeod R, et al: Toxoplasmosis. In Remington JS, Klein JO, editors: *Infectious diseases of the fetus and newborn infant* , ed 6, Philadelphia, 2006, Saunders.

Isolation

Organisms can be isolated by inoculation of body fluids, leukocytes, or tissue specimens into mice or tissue cultures. Body fluids should be processed and inoculated immediately, but *T. gondii* has been isolated from tissues and blood that have been stored overnight or even for 4-5 days at 4°C (39.2°F). Freezing or treatment of specimens with formalin kills *T. gondii*. From 6-10 days after inoculation into mice, or earlier if mice die, peritoneal fluids should be examined for tachyzoites. If inoculated mice survive for 6 wk and seroconvert, definitive diagnosis is made by visualization of *Toxoplasma* cysts in mouse brain. If cysts are not seen, **subinoculation** of mouse tissue into other mice are performed. Treatment of mice that receive subinoculated tissues with corticosteroid appears to enhance ability to isolate the parasite.

Microscopic examination of tissue culture inoculated with *T. gondii* shows necrotic, heavily infected cells with numerous extracellular tachyzoites. Isolation of *T. gondii* from blood or body fluids reflects acute infection. Except in the fetus or neonate, it is usually not possible to distinguish acute from past infection by isolation of *T. gondii* from tissues (e.g., skeletal muscle, lung, brain, eye) obtained by biopsy or at autopsy.

Diagnosis of acute infection can be established by visualization of tachyzoites in biopsy tissue sections, bone marrow aspirate, or body fluids (e.g., CSF, amniotic fluid). Immunofluorescent antibody and immunoperoxidase staining techniques may be necessary, because it is often difficult to distinguish the tachyzoite using ordinary stains. Tissue cysts are diagnostic of infection but do not differentiate between acute and chronic infection, although the presence of many cysts suggests recent acute infection. Cysts in the placenta or tissues of the newborn infant establish the diagnosis of congenital infection. Characteristic histologic features strongly suggest the diagnosis of toxoplasmic lymphadenitis.

Serologic Testing

Serologic tests are useful in establishing the diagnosis of congenital or acutely acquired *Toxoplasma* infection. Each laboratory that reports serologic test results must have established values for their tests that diagnose infection in specific clinical settings, provide interpretation of their results, and ensure appropriate quality control before therapy is based on serologic test results. Serologic test results used as the basis for therapy should ideally be confirmed in a reference laboratory.

The **Sabin-Feldman dye test** is sensitive and specific. It measures primarily IgG antibodies. Results should be expressed in international units (IU/mL), based on international standard reference sera available from the World Health Organization (WHO).

The **IgG indirect fluorescent antibody (IgG-IFA) test** measures the same antibodies as the dye test, and the titers tend to be parallel. These antibodies usually appear 1-2 wk after infection, reach high titers (≥1 : 1,000) after 6-8 wk, and then decline over months to years. Low titers (1 : 4 to 1 : 64) usually persist for life. Antibody titer does not correlate with severity of illness.

An **agglutination test** (Bio-Mérieux, Lyon, France) available commercially in Europe uses formalin-preserved whole parasites to detect IgG antibodies. This test is accurate, simple to perform, and inexpensive.

The **IgM-IFA test** is useful for the diagnosis of acute acquired infection with *T. gondii* in the older child because IgM antibodies appear earlier, often by 5 days after infection, and diminish more quickly than IgG antibodies. In most instances, IgM antibodies rise rapidly (1 : 50 to <1 : 1,000) and then fall to low titers (1 : 10 or 1 : 20) or disappear after weeks or months. However, some patients continue to have positive IgM results with low titers for several years. The IgM-IFA test detects *Toxoplasma* -specific IgM in only approximately 25% of congenitally infected infants at birth. IgM antibodies may not be present in sera of immunocompromised patients with acute toxoplasmosis or in patients with reactivation of ocular toxoplasmosis. The IgM-IFA test may yield false-positive results as a result of rheumatoid factor.

The **double-sandwich IgM enzyme-linked immunosorbent assay (IgM-ELISA)** is also useful for detection of *Toxoplasma* IgM antibodies. In the older child, serum IgM-ELISA *Toxoplasma* antibodies of >2 (a value of one reference laboratory; each laboratory must establish its own value for positive results) indicates that *Toxoplasma* infection most likely has been acquired recently. The IgM-ELISA identifies approximately 50–75% of infants with congenital infection. IgM-ELISA avoids both the false-positive results from rheumatoid factor (RF) and the false-negative results from high levels of passively transferred maternal IgG antibody in fetal serum, as may occur in the IgM-IFA test. Results obtained with commercial kits must be interpreted with caution, because false-positive reactions can occur. Care must also be taken to determine whether kits have been standardized for diagnosis of infection in specific clinical settings, such as in the newborn infant. The **IgA-ELISA** also is a sensitive test for detection of maternal and congenital infection, and results may be positive when those of the IgM-ELISA are not.

The **immunosorbent agglutination assay (ISAGA)** combines trapping of a patient's IgM to a solid surface and use of formalin-fixed organisms or antigen-coated latex particles. It is read as an agglutination test. There are no false-positive results from RF or antinuclear antibodies (ANAs). **IgM-ISAGA** is more sensitive than and may detect specific IgM antibodies before and for longer periods than IgM-ELISA.

At present, IgM-ISAGA and IgA-ELISA are the most useful tests for diagnosis of congenital infection in the newborn but are not positive in all infected infants. The IgE-ELISA and IgE-ISAGA are also sometimes useful in establishing the diagnosis of congenital toxoplasmosis or acute acquired *T. gondii* infection. The presence of IgM antibodies in the older child or adult can never be used alone to diagnose acute acquired infection.

The **differential agglutination test (HS/AC)** compares antibody titers obtained with formalin-fixed tachyzoites (**HS antigen**) with titers obtained using acetone-fixed tachyzoites (**AC antigen**) to differentiate recent and remote infections in adults and older children. This method may be particularly useful in differentiating remote infection in pregnant women, because levels of IgM and IgA antibodies detectable by ELISA or ISAGA may remain elevated for months to years in adults and older children.

The **avidity test** can be helpful to establish time of acquisition of infection. A high-avidity test result indicates that infection began >12-16 wk earlier, which is especially useful in determining time of acquisition of infection in the 1st or final 16 wk of gestation. A low-avidity test result may be present for many months or even years and does not definitively identify recent acquisition of infection.

A relatively higher level of *Toxoplasma* antibody in the aqueous humor or in CSF demonstrates local production of antibody during active ocular or CNS toxoplasmosis. This comparison is performed, and a coefficient [C] is calculated as follows:

$$C = \frac{\text{Antibody titer in body fluid}}{\text{Antibody titer in serum}} \times \frac{\text{Concentration of IgG in serum}}{\text{Concentration of IgG in body fluid}}$$

Significant coefficients [C] are >8 for ocular infection, >4 for CNS for congenital infection, and >1 for CNS infection in patients with AIDS. If the serum dye test titer is >300 IU/mL, it is not possible to demonstrate significant local antibody production using this formula with either the dye test or the IgM-IFA test titer. IgM antibody may be detectable in CSF.

Comparative **Western immunoblot** tests of sera from a mother and infant may detect congenital infection. Infection is suspected when the mother's serum and her infant's serum contain antibodies that react with different *Toxoplasma* antigens.

The **enzyme-linked immunofiltration assay** using micropore membranes permits simultaneous study of antibody specificity by immunoprecipitation and characterization of antibody isotypes by immunofiltration with enzyme-labeled antibodies. This method able to detect 85% of cases of congenital infection in the 1st few days of life.

Serologic tests in development include multiplex antibody tests for IgG, IgM, and IgA-specific antibodies, as well as point-of-care tests designed to provide accurate and rapid identification of recent infection or seroconversion in pregnant women.

PCR is used to amplify the DNA of *T. gondii,* which then can be detected by using a DNA probe. Detection of repetitive *T. gondii* genes, the B1 or 529 bp, 300 copy gene, in amniotic fluid is the PCR target of choice for establishing the diagnosis of congenital *Toxoplasma* infection in the fetus. Sensitivity and specificity of this test in amniotic fluid obtained to diagnose infections acquired between 17 and 21 wk of gestation are approximately 95%. Before and after that time, PCR with the 529 bp, 300 copy repeat gene as the template is 92% sensitive and 100% specific for detection of congenital infection. PCR of vitreous or aqueous fluids also has been used to diagnose ocular toxoplasmosis. PCR of peripheral white blood cells, CSF, and urine has been reported to detect congenital infection.

Point-of-care tests such as the *Toxoplasma* ICT IgG-IgM test or a nanogold test will lower the cost of and increase the ease of rapid testing.

Lymphocyte blastogenesis to *Toxoplasma* antigens has been used to diagnose congenital toxoplasmosis when the diagnosis is uncertain and other test results are negative. However, a negative result does not exclude the diagnosis because peripheral blood lymphocytes of infected newborns may not respond to *T. gondii* antigens because of immune tolerance testing in specific circumstances.

Acquired Toxoplasmosis

Recent infection is diagnosed by seroconversion from a negative to a positive IgG antibody titer (in the absence of transfusion); a 2-tube increase in *Toxoplasma* -specific IgG titer when serial sera are obtained 3 wk apart and tested in parallel; or the detection of *Toxoplasma* -specific IgM antibody in conjunction with other tests, but never alone.

Ocular Toxoplasmosis

IgG antibody titers of 1 : 4 to 1 : 64 are usual in older children with active *Toxoplasma* chorioretinitis. Even the presence of antibodies measurable only when serum is tested undiluted is helpful in establishing the diagnosis. The diagnosis is likely with characteristic retinal lesions and positive serologic tests. PCR of aqueous or vitreous fluid has been used to diagnose ocular toxoplasmosis but is infrequently performed because of the risks associated with obtaining intraocular fluid.

Immunocompromised Persons

IgG antibody titers may be low, and *Toxoplasma* -specific IgM is often absent in immunocompromised stem cell transplant recipients, but not in kidney or heart transplant recipients with toxoplasmosis. Demonstration of *Toxoplasma* DNA by PCR in serum, blood, and CSF may identify disseminated *Toxoplasma* infection in immunocompromised persons. Resolution of CNS lesions during a therapeutic trial of pyrimethamine and sulfadiazine has been useful to diagnose toxoplasmic encephalitis in patients with AIDS. Brain biopsy has been used to establish the diagnosis if there is no response to a therapeutic trial and to exclude other possible diagnoses such as CNS lymphoma.

Congenital Toxoplasmosis

Fetal ultrasound examination, performed every 2 wk during gestation, beginning at diagnosis of acute acquired infection in a pregnant woman, and PCR analysis of amniotic fluid are used for prenatal diagnosis. *T. gondii* may also be isolated from the placenta at delivery.

Serologic tests are also useful in establishing a diagnosis of congenital toxoplasmosis. Either persistent or rising titers in the dye test or IFA test, or a positive IgM-ELISA or IgM-ISAGA result, is diagnostic of congenital toxoplasmosis. The half-life of IgM is approximately 2 days, so if there is a placental leak, the level of IgM antibodies in the infant's serum decreases significantly, usually within 1 wk. Passively transferred maternal IgG antibodies may require many months to a year to disappear from the infant's serum, depending on the magnitude of the original titer. The half-life of passively transferred maternal IgG is approximately 30 days, so the titer diminishes by half each 30 days. Synthesis of *Toxoplasma* antibody is usually demonstrable by the 3rd mo of life if the infant is untreated, although the rate of IgG synthesis varies considerably in infants <1 yr old. If the infant is treated, synthesis may be delayed for as long as the 9th mo of life and, infrequently, may not occur at all. When an infant begins to synthesize IgG antibody, infection may be documented serologically even without demonstration of IgM antibodies by an increase in the ratio of specific serum IgG antibody titer to the total IgG, whereas the ratio will decrease if the specific IgG antibody has been passively transferred from the mother.

Newborns suspected of having congenital toxoplasmosis should be evaluated by general, ophthalmologic, and neurologic examinations; head CT scan; and some or ideally all of the following tests: an attempt to isolate *T. gondii* from the placenta and infant's leukocytes from peripheral blood buffy coat; measurement of serum *Toxoplasma* -specific IgG, IgM, IgA, and IgE antibodies, and the levels of total serum IgM and IgG; lumbar puncture, including analysis of CSF for cells, glucose, protein, *Toxoplasma* -specific IgG and IgM antibodies, and level of total IgG; and testing of CSF for *T. gondii* by PCR and inoculation into mice. Presence of *Toxoplasma* -specific IgM in CSF that is not contaminated with blood, or confirmation of local antibody production of *Toxoplasma* -specific IgG antibody in CSF, establishes the diagnosis of congenital *Toxoplasma* infection.

Many manifestations of congenital toxoplasmosis are similar to findings that occur in other perinatal infections, especially congenital cytomegalovirus infection. Since neither cerebral calcification nor chorioretinitis is pathognomonic, a negative urine culture or PCR for CMV soon after birth is a useful adjunctive test. The clinical picture in the newborn infant may also be compatible with sepsis, aseptic meningitis, syphilis, or hemolytic disease. Some children <5 yr old with chorioretinitis have postnatally acquired *T. gondii* infection.

Treatment

Pyrimethamine and **sulfadiazine** act synergistically against *Toxoplasma*, and combination therapy is indicated for many of the forms of toxoplasmosis. Use of pyrimethamine is contraindicated during the first trimester of pregnancy. **Spiramycin** should be used to attempt to prevent vertical transmission of infection to the fetus of acutely infected pregnant women. Pyrimethamine inhibits the enzyme dihydrofolate reductase, and thus the synthesis of folic acid, and therefore produces a dose-related, reversible, and usually gradual depression of the bone marrow. Neutropenia is most common, but rarely treatment has been reported to result in thrombocytopenia and anemia as well. **Reversible neutropenia** is the most common adverse effect in treated infants. All patients treated with pyrimethamine should have leukocyte counts twice weekly. Seizures may occur with overdosage of pyrimethamine. Potential toxic effects of sulfonamides (e.g., crystalluria, hematuria, rash) should be monitored. Hypersensitivity reactions occur, especially in patients with AIDS. Folinic acid, as calcium **leucovorin** , should always be administered concomitantly and for 1 wk after treatment with pyrimethamine is discontinued to prevent bone marrow suppression.

Acquired Toxoplasmosis

Patients with acquired toxoplasmosis and lymphadenopathy usually do not need specific treatment unless they have severe and persistent symptoms or evidence of damage to vital organs (see Table 316.2). If such signs and symptoms occur, treatment with pyrimethamine, sulfadiazine, and leucovorin should be initiated. Patients who appear to be immunocompetent but have severe and persistent symptoms or damage to vital organs (e.g., chorioretinitis, myocarditis) need specific therapy until these specific symptoms resolve, followed by therapy for an additional 2 wk. Therapy often is administered for at least 4-6 wk. The optimal duration of therapy is unknown. A loading dose of pyrimethamine for older children is 2 mg/kg/day divided twice daily (maximum 50 mg bid), given for the 1st 2 days of treatment. The maintenance dose begins on the 3rd day and is 1 mg/kg/day (maximum 50 mg/day). Sulfadiazine is administered at 100 mg/kg/day bid (maximum 4 g/day). Leucovorin is administered orally (PO) at 5-20 mg 3 times weekly (or even daily depending on the leukocyte count).

Ocular Toxoplasmosis

Patients with active ocular toxoplasmosis are treated with pyrimethamine, sulfadiazine, and leucovorin (see Table 316.2). They are treated while disease is active and then for approximately 1 wk after the lesion has developed a quiescent appearance (i.e., sharp borders, pigmentation at margins of the lesion, and resolution of associated inflammatory cells in the vitreous), which usually occurs in 2-4 wk when treatment is initiated promptly. Within 7-10 days, the borders of the retinal lesions sharpen, and visual acuity usually returns to that noted before development of the acute lesion. Systemic corticosteroids have been administered concomitantly with antimicrobial treatment when lesions involve the macula, optic nerve head, or papillomacular bundle. Corticosteroids must never be given alone but may be initiated after loading doses of pyrimethamine and sulfadiazine have been administered (2 days). With recurrences, new lesions often appear contiguous to old ones. Very rarely, vitrectomy and removal of the lens are needed to restore visual acuity. Active choroidal neovascular membranes as a result of toxoplasmic chorioretinitis have been treated successfully in children with intravitreal injection of antibody to vascular endothelial growth factor in addition to oral anti-*Toxoplasma* medicines. Suppressive treatment has prevented frequent recurrences of vision-threatening lesions.

Immunocompromised Persons

Serologic evidence of acute infection in an immunocompromised patient, regardless of whether signs and symptoms of infection are present or tachyzoites are demonstrated in tissue, are indications for therapy similar to that described for immunocompetent persons with symptoms of organ injury (see Table 316.2). It is important to establish the diagnosis as rapidly as possible and institute treatment early. In immunocompromised patients other than those with AIDS, therapy should be continued for at least 4-6 wk beyond complete resolution of all signs and symptoms of active disease and, if possible, resolution of cause for immune suppression. Careful follow-up of these patients is imperative because relapse may occur, requiring prompt reinstitution of therapy. Relapse was once common in AIDS patients without antiretroviral treatment, and suppressive therapy with pyrimethamine and sulfonamides, or TMP-SMX, was continued for life. Now it is possible to discontinue maintenance therapy when the CD4 count remains at >200 cells/µL for 4 mo and all lesions have resolved. Therapy usually induces a beneficial response clinically but does not eradicate cysts. Treatment of *T. gondii* –seropositive patients with AIDS should be continued as long as CD4 counts remain at <200/µL. Prophylactic TMP-SMX therapy for *Pneumocystis jirovecii* pneumonia significantly reduces the incidence of toxoplasmosis in AIDS patients.

Congenital Toxoplasmosis

All fetuses and newborns infected with *T. gondii* should be treated regardless of whether they have clinical manifestations of infection, because treatment may be effective in interrupting acute disease that damages vital organs (Fig. 316.5 ; see Table 316.2). The fetus is treated by treating the pregnant woman with pyrimethamine and sulfadiazine (with leucovorin). Infants should be treated for 1 yr with pyrimethamine (2 mg/kg/day PO bid for 2 days, then beginning on the 3rd day, 1 mg/kg/day for 2 or 6 mo, and then 1 mg/kg given on Monday, Wednesday, and Friday), sulfadiazine (100 mg/kg/day PO bid), and leucovorin (5-10 mg PO given on Monday, Wednesday, and Friday, or more often depending on neutrophil count). The relative efficacy in reducing sequelae of infection and the safety of treatment with 2 mo vs 6 mo of the higher dosage of pyrimethamine are being compared in the U.S. National Collaborative Study. (Updated information about this study and these regimens is available from Dr. Rima McLeod, 773-834-4131.) Pyrimethamine and sulfadiazine are available only in tablet form but can be prepared as suspensions. **Prednisone** (1 mg/kg/day PO bid) has been used in addition when active chorioretinitis involves the macula or otherwise threatens vision, or when the CSF protein is >1,000 mg/dL at birth, but the efficacy of this adjunctive therapy is not established. Prednisone is continued only for as long as the active inflammatory process in the posterior pole of the eye is vision threatening or CSF protein is >1,000 mg/dL, then tapered rapidly if the duration of treatment has been brief.

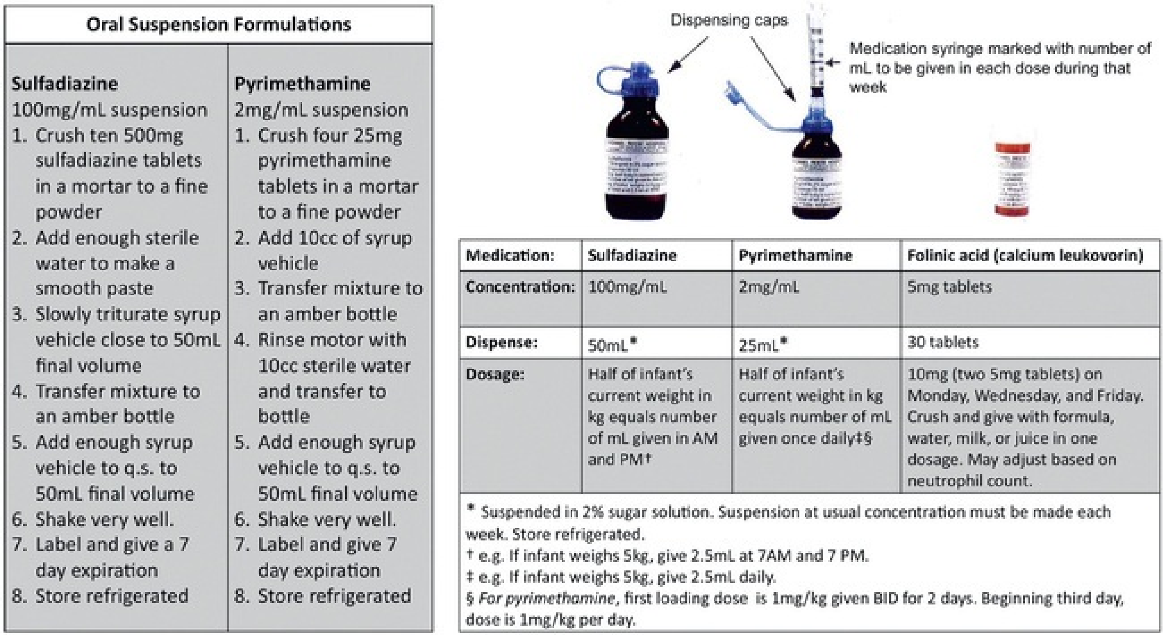

Dispensing caps
Medication syringe marked with number of mL to be given in each dose during that week

Oral Suspension Formulations	
Sulfadiazine 100mg/mL suspension 1. Crush ten 500mg sulfadiazine tablets in a mortar to a fine powder 2. Add enough sterile water to make a smooth paste 3. Slowly triturate syrup vehicle close to 50mL final volume 4. Transfer mixture to an amber bottle 5. Add enough syrup vehicle to q.s. to 50mL final volume 6. Shake very well. 7. Label and give a 7 day expiration 8. Store refrigerated	**Pyrimethamine** 2mg/mL suspension 1. Crush four 25mg pyrimethamine tablets in a mortar to a fine powder 2. Add 10cc of syrup vehicle 3. Transfer mixture to an amber bottle 4. Rinse motor with 10cc sterile water and transfer to bottle 5. Add enough syrup vehicle to q.s. to 50mL final volume 6. Shake very well. 7. Label and give 7 day expiration 8. Store refrigerated

Medication:	Sulfadiazine	Pyrimethamine	Folinic acid (calcium leukovorin)
Concentration:	100mg/mL	2mg/mL	5mg tablets
Dispense:	50mL*	25mL*	30 tablets
Dosage:	Half of infant's current weight in kg equals number of mL given in AM and PM†	Half of infant's current weight in kg equals number of mL given once daily‡§	10mg (two 5mg tablets) on Monday, Wednesday, and Friday. Crush and give with formula, water, milk, or juice in one dosage. May adjust based on neutrophil count.

* Suspended in 2% sugar solution. Suspension at usual concentration must be made each week. Store refrigerated.

† e.g. If infant weighs 5kg, give 2.5mL at 7AM and 7 PM.

‡ e.g. If infant weighs 5kg, give 2.5mL daily.

§ *For pyrimethamine*, first loading dose is 1mg/kg given BID for 2 days. Beginning third day, dose is 1mg/kg per day.

FIG. 316.5 Compounding and administration of medications to treat congenital toxoplasmosis in infants. (Adapted from Remington JS, McLeod R, et al: Toxoplasmosis. In Remington JS, Klein JO, editors: *Infectious diseases of the fetus and newborn infant,* ed 6, Philadelphia, 2006, Saunders; and McAuley J, Boyer K, Patel D, et al: Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial, *Clin Infect Dis* 18:38–72, 1994.)

Pregnant Women With *Toxoplasma gondii* Infection

The immunologically normal pregnant woman who acquired *T. gondii* >6 mo before conception does not need treatment to prevent congenital infection of her fetus. Although data are not available to allow for a definitive time interval, if infection occurs during or shortly before the pregnancy, it is reasonable to evaluate the fetus by PCR with amniotic fluid and ultrasonography and treat to prevent congenital infection in the fetus (see Table 316.2).

Treatment of a pregnant woman who acquires infection at any time during pregnancy reduces the chance of congenital infection in her infant. **Spiramycin** (1 g PO every 8 hr without food) is recommended for prevention of fetal infection if the mother develops acute toxoplasmosis during pregnancy. Spiramycin is available in the United States on an “emergency use” request by a physician through the FDA Division of Anti-Infective Drugs (301-796-1400) after the diagnosis of acute infection is confirmed in a reference laboratory (Palo Alto Medical Facility Toxoplasma Serology Lab, 650-853-4828). With this approval, the physician can then contact the spiramycin manufacturer, Sanofi Pasteur (1-800-822-2463), to obtain spiramycin for the patient. Adverse reactions are infrequent and include paresthesia, rash, nausea, vomiting, and diarrhea.

For treatment of the pregnant woman whose fetus has a confirmed or probable infection, in the second or third trimester, the combination of pyrimethamine, sulfadiazine, and leucovorin is recommended. Following a loading dose of pyrimethamine (50 mg bid) for 2 days, beginning on the 3rd day, pyrimethamine is administered at 50 mg once daily. Beginning on the 1st day of treatment with pyrimethamine, sulfadiazine (1.5-2.0 g PO bid), and leucovorin (10 mg PO once daily) are also given. In the first trimester, when there is definite infection, **sulfadiazine** alone is recommended because pyrimethamine is potentially teratogenic at that time. Spiramycin treatment is used for infection acquired early in gestation when fetal infection is uncertain. Treatment of the mother of an infected fetus with pyrimethamine and sulfadiazine reduces infection in the placenta and the severity of disease in the newborn. Delay in maternal treatment during gestation results in greater brain and eye disease in the infant. Diagnostic amniocentesis should be performed at >17-18 wk of gestation in pregnancies when there is high suspicion of fetal infection. Overall sensitivity of PCR for amniotic fluid is at 85% between 17 and 21 wk of gestation. The sensitivity of PCR using amniotic fluid for diagnosis of fetal infection is 92% in early and late gestation when amniotic fluid is tested for presence of the 529 bp, 300 copy gene. After 24 wk gestation, incidence of transmission is relatively high, and all pregnant women who are infected acutely after that time are treated with pyrimethamine and sulfadiazine to treat the fetus.

The approach in France to congenital toxoplasmosis includes systematic serologic screening of all women of childbearing age and for those who are sero-negative again intrapartum each month during gestation beginning at ≤11 wk gestational age, at birth, and 1 mo after birth. Mothers with acute infection early in gestation and without evidence of involvement of the fetus are treated with spiramycin, which decreases the transmission. Ultrasonography and amniocentesis for PCR at approximately 17-18 wk of gestation are used for fetal diagnosis and have 97% sensitivity and 100% specificity. Confidence intervals for sensitivity are larger early and late in gestation. Fetal infection is treated with pyrimethamine and sulfadiazine. Termination of pregnancy is very rare at present. Prompt initiation of treatment with pyrimethamine and sulfadiazine during pregnancy usually has an excellent outcome, with normal development of children. Only 19% have subtle findings of congenital infection, including intracranial calcifications (13%) and chorioretinal scars (6%), although 39% may have chorioretinal scars detected at follow-up later in childhood. Several studies have demonstrated improved outcomes with shorter times between diagnosis and initiation of treatment. In Germany, for seroconverting women who are between 15 and 17 weeks' gestation and before amniocentesis, administration of pyrimethamine, sulfadiazine, and leukovorin results in good outcomes for infants but sometimes sulfadiazine hypersensitivity for mothers.

Chronically infected pregnant women who are immunocompromised have transmitted *T. gondii* to their fetuses. Such women should be treated with spiramycin throughout gestation. The optimal management for prevention of congenital toxoplasmosis in the fetus of a pregnant woman with HIV infection, a CD4 count <200 cells/µL, and inactive *T. gondii* infection is unknown. Fortunately, this situation now is rarely encountered in the United States. If the pregnancy is not terminated, some investigators suggest that the mother should be treated with spiramycin or sulfadiazine alone during the 1st 14 wk of gestation and thereafter with pyrimethamine and sulfadiazine until term. There are no universally accepted guidelines at present. In a study of adult patients with AIDS and toxoplasmic encephalitis, pyrimethamine (75 mg PO once daily) combined with high dosages of intravenous clindamycin (1,200 mg every 6 hr) appeared equal in efficacy to sulfadiazine and pyrimethamine in the treatment of the toxoplasmic encephalitis. Other experimental agents include the macrolides clarithromycin and azithromycin.

Prognosis

Early institution of specific treatment for congenitally infected infants usually rapidly controls the active manifestations of toxoplasmosis, including active chorioretinitis, meningitis, encephalitis, hepatitis, splenomegaly, and thrombocytopenia. Rarely, hydrocephalus resulting from aqueductal obstruction may develop or become worse during therapy. Treatment appears to reduce the incidence of some sequelae, such as diminished cognitive and abnormal motor function. Without therapy and in some treated patients as well, chorioretinitis often recurs. Children with extensive involvement at birth may function normally later in life or have mild to severe impairment of vision, hearing, cognitive function, and other neurologic functions. Delays in diagnosis and therapy, perinatal hypoglycemia, hypoxia, hypotension, repeated shunt infections, and severe visual impairment are associated with a poorer prognosis. The prognosis is not necessarily poor for infected babies. Currently available treatments do not eradicate encysted parasites.

Studies in Lyon and Paris, France, demonstrated that outcome of treated fetal toxoplasmosis, even when infection is acquired early in gestation, is usually favorable if no hydrocephalus is detected on ultrasound, and treatment with pyrimethamine and sulfadiazine is initiated promptly. The **Systematic Review on Congenital Toxoplasmosis** (SYROCOT) study in Europe indicated that neurologic outcome is improved with shorter times between diagnosis and initiation of treatment of fetal toxoplasmosis. Work in Lyon has indicated a low incidence of recurrent eye disease in children with congenital toxoplasmosis who had been treated in utero and in their 1st yr of life. The NCCCTS (1981–2004) in the United States found that neurologic, developmental, audiologic, and ophthalmologic outcomes are considerably better for most, but not all, children who were treated in the 1st yr of life with pyrimethamine and sulfadiazine (with leucovorin) compared to children who had not been treated or were treated for only 1 mo in earlier decades described in the literature.

Prevention

Counseling pregnant women about the methods of preventing transmission of *T. gondii* (see Fig. 316.1) during pregnancy can reduce acquisition of infection during gestation. Women who do not have specific antibody to *T. gondii* before pregnancy should only eat well-cooked meat during pregnancy and avoid contact with oocysts excreted by cats. Cats that are kept indoors, maintained on prepared food, and not fed fresh, uncooked meat should not contact encysted *T. gondii* or shed oocysts. Serologic screening, ultrasound monitoring, and treatment of pregnant women during gestation can also reduce the incidence and manifestations of congenital toxoplasmosis. No protective vaccine is yet available for human use.

Point-of-care testing to facilitate gestational screening, recent developments in medicines for treatment of active and chronic infections, and progress toward vaccines to prevent infections in humans and oocyst shedding by cats are all recent advances with promise to prevent or improve outcomes for *Toxoplasma gondii* infections.

Acknowledgment

We gratefully acknowledge the participant families, physicians, and other personnel of the National Collaborative Congenital Toxoplasmosis Study (NCCTS), and colleagues, for helping to create the understanding and knowledge in this chapter; and Cornwell Mann family, Taking out Toxo (TOT), TRI, and NIH, NIAID/DMID ROI AI27530 and RO1 AI071319-01 for support.

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SECTION 16

Helminthic Diseases

OUTLINE

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Chapter 318 Hookworms (Necator americanus and Ancylostoma spp.)

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CHAPTER 317

Ascariasis *(Ascaris lumbricoides)*

Arlene E. Dent, James W. Kazura

Etiology

Ascariasis is caused by the nematode, or **roundworm** , *Ascaris lumbricoides*. Adult worms of *A. lumbricoides* inhabit the lumen of the small intestine. The reproductive potential of *Ascaris* is prodigious; a gravid female worm produces 200,000 eggs per day. The fertile ova are oval in shape with a thick, mammillated covering measuring 45-70 µm in length and 35-50 µm in breadth (Fig. 317.1). After passage in the feces, the eggs embryonate and become infective in 5-10 days under favorable environmental conditions. Adult worms can live for 12-18 mo (Fig. 317.2).

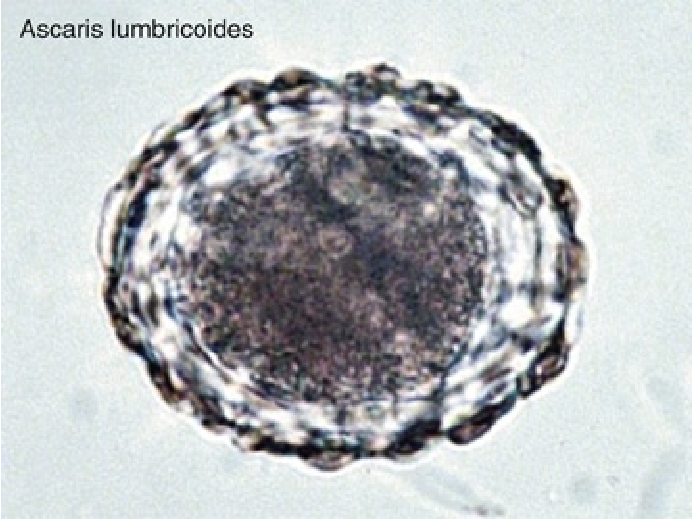

FIG. 317.1 Soil-transmitted helminth eggs *(A. lumbricoides)* . (From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm, *Lancet* 367:1521–1532, 2006.)

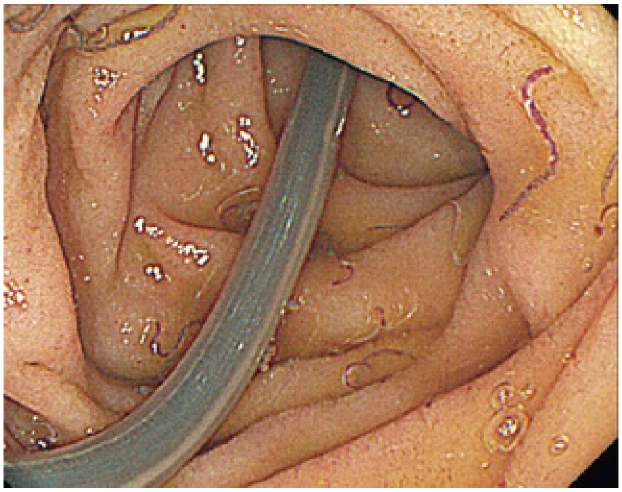

FIG. 317.2 Endoscopic image of intestinal *Ascaris lumbricoides* and hookworm co-infection. The ascaris worm is large in relation to the lumen and multiple blood-filled hookworms. (Courtesy of Dr. Kunimitsu Inoue, Almeida Hospital, Oita, Japan.)

Epidemiology

Ascariasis occurs globally and is the most prevalent human **helminthiasis** in the world. It is most common in tropical areas (South America, Africa, Asia) where environmental conditions are optimal for maturation of ova in the soil. Approximately 1 billion persons are estimated to be infected. Although the number of cases in the United States is not known precisely, the highest prevalence is thought to be in high-poverty areas of the South and Appalachia. Pig farming in Maine is also associated with *Ascaris* species. Key factors linked with a higher prevalence of infection include poor socioeconomic conditions, use of human feces as fertilizer, and geophagia. Even though infection can occur at any age, the highest rate is in preschool or early school-age children. Transmission is primarily hand to mouth but may also involve ingestion of contaminated raw fruits and vegetables. Transmission is enhanced by the high output of eggs by fecund female worms and resistance of ova to the outside environment. *Ascaris* eggs can remain viable at 5-10°C (41-50°F) for as long as 2 yr.

Pathogenesis

Ascaris ova hatch in the small intestine after ingestion by the human host. Larvae are released, penetrate the intestinal wall, and migrate to the lungs by way of the venous circulation. The parasites then cause **pulmonary ascariasis** as they enter into the alveoli and migrate through the bronchi and trachea (Fig. 317.3). They are subsequently swallowed and return to the intestines, where they mature into adult worms. Female *Ascaris* begin depositing eggs in 8-10 wk.

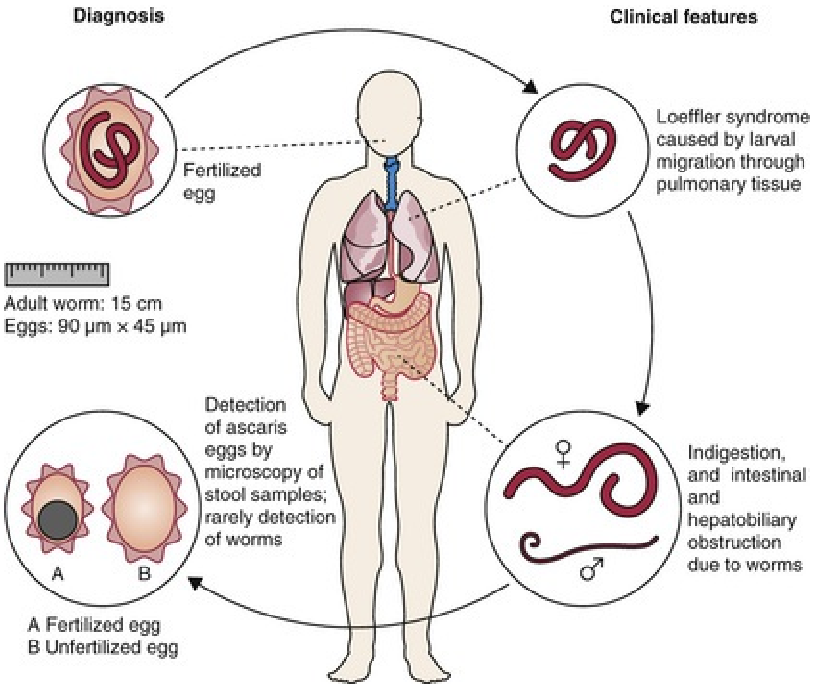
Diagnosis
Clinical features
Fertilized egg
Loeffler syndrome caused by larval migration through pulmonary tissue
Adult worm: 15 cm
Eggs: 90 µm × 45 µm
Detection of ascaris eggs by microscopy of stool samples; rarely detection of worms
Indigestion, and intestinal and hepatobiliary obstruction due to worms
♀
♂
A
B
A Fertilized egg
B Unfertilized egg

FIG. 317.3 **Transmission of *Ascaris lumbricoides* : diagnosis and clinical features. (From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG: Soil-transmitted helminth infections, *Lancet* 391:252–262, 2018, Fig 2A.)**

Clinical Manifestations

The clinical presentation depends on the intensity of infection and the organs involved. Most individuals have low to moderate worm burdens and have no symptoms or signs. The most common clinical problems are from **pulmonary disease** and **obstruction of the intestinal or biliary tract** . Larvae migrating through these tissues may cause allergic symptoms, fever, urticaria, and granulomatous disease. The pulmonary manifestations resemble Loeffler syndrome and include transient respiratory symptoms such as cough and dyspnea, pulmonary infiltrates, and blood eosinophilia. Larvae may be observed in the sputum. Vague abdominal complaints have been attributed to the presence of adult worms in the small intestine, although the precise contribution of the parasite to these symptoms is difficult to ascertain. A more serious complication occurs when a large mass of worms leads to acute bowel obstruction. Children with heavy infections may present with vomiting, abdominal distention, and cramps. In some cases, worms may be passed in the vomitus or stools. *Ascaris* worms occasionally migrate into the biliary and pancreatic ducts, where they cause cholecystitis or pancreatitis. Worm migration through the intestinal wall can lead to peritonitis. Dead worms can serve as a nidus for stone formation. Studies show that chronic infection with *A. lumbricoides* (often coincident with other helminth infections) impairs growth, physical fitness, and cognitive development.

Diagnosis

Microscopic examination of fecal smears can be used for diagnosis because of the high number of eggs excreted by adult female worms (see Fig. 317.1). A high index of suspicion in the appropriate clinical context is needed to diagnose pulmonary ascariasis or obstruction of the gastrointestinal tract. Ultrasound examination of the abdomen is capable of visualizing intraluminal adult worms.

Treatment

Although several chemotherapeutic agents are effective against ascariasis, none has documented utility during the pulmonary phase of infection. Treatment options for gastrointestinal ascariasis include **albendazole** (400 mg orally once, for all ages), **mebendazole** (100 mg orally twice daily for 3 days or 500 mg once, for all ages), or **ivermectin** (150-200 µg/kg orally once). **Piperazine citrate** (75 mg/kg/day for 2 days; maximum dose: 3.5 g/day), which causes neuromuscular paralysis of the parasite and rapid expulsion of the worms, is the treatment of choice for intestinal or biliary obstruction and is administered as syrup through a nasogastric tube. Surgery may be required for cases with severe obstruction. **Nitazoxanide** (100 mg orally twice per day for 3 days for children

1-3 yr old; 200 mg twice per day for 3 days for children 4-11 yr; 500 mg twice per day for 3 days for adolescents and adults) produces cure rates comparable to single-dose albendazole. Drug resistance has not been reported, but repeated treatment for ascariasis may be necessary because reinfection is common.

Prevention

Although ascariasis is the most prevalent worm infection in the world, little attention has been given to its control (Table 317.1). **Anthelmintic chemotherapy programs** can be implemented in 1 of 3 ways: (1) offering universal treatment to all individuals in an area of high endemicity; (2) offering treatment targeted to groups with high frequency of infection, such as children attending primary school; or (3) offering individual treatment based on intensity of current or past infection. Improving education about and practices of sanitary conditions and sewage facilities, discontinuing the practice of using human feces as fertilizer, and education are the most effective long-term preventive measures.

Table 317.1

Clinical and Public Health Control of Soil-Transmitted Helminthiasis

	CLINICAL DIAGNOSIS AND MANAGEMENT	PUBLIC HEALTH CONTROL
Diagnosis	Individual	Community level (e.g., in select schools)
Diagnostic criteria	Parasitological	Residence in an area with soil-transmitted helminthiasis prevalence >20%
Treatment approach	Single dose or multiple dose	Single-dose periodic mass treatment
Threshold for treatment	Travel history, symptoms and signs, positive laboratory test	Estimated prevalence of infection in target population
Treatment objective	Parasitological cure	Decreased worm burden; reduction in transmission
Ancillary treatment	Based on clinical signs and symptoms	Typically, only if included in mass treatment (e.g., vitamin A supplementation)
Follow-up	Parasitological test of cure; improvement in associated health conditions	Not usually done
Health education (sanitation/hygiene)	Recommended	Recommended

From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG: Soil-transmitted helminth infections, *Lancet* 391:252–262, 2018 (Table 1).

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CHAPTER 318

Hookworms (*Necator americanus* and *Ancylostoma* spp.)

Peter J. Hotez

Etiology

Two major genera of hookworms, which are nematodes, or roundworms, infect humans. *Necator americanus,* the only representative of its genus, is a major **anthropophilic** hookworm and is the most common cause of human hookworm infection. Hookworms of the genus *Ancylostoma* include the anthropophilic hookworm *Ancylostoma duodenale,* which also causes classic hookworm infection, and the less common **zoonotic** species *Ancylostoma ceylanicum* (restricted mostly to Southeast Asia). Human zoonotic infection with the dog hookworm *Ancylostoma caninum* is associated with an eosinophilic enteritis syndrome. The larval stage of *Ancylostoma braziliense,* whose definitive hosts include dogs and cats, is the principal cause of cutaneous larva migrans.

The infective larval stages of the anthropophilic hookworms live in a developmentally arrested state in warm, moist soil. Larvae infect humans either by penetrating through the skin (*N. americanus* and *A. duodenale*) or when they are ingested *(A. duodenale).* Larvae entering the human host by skin penetration undergo **extraintestinal migration** through the venous circulation and lungs before they are swallowed, whereas orally ingested larvae may undergo extraintestinal migration or remain in the gastrointestinal (GI) tract (Figs. 318.1 and 318.2). Larvae returning to the small intestine undergo 2 molts to become adult, sexually mature, male and female worms ranging in length from 5-13 mm. The buccal capsule of the adult hookworm is armed with cutting plates *(N. americanus)* or teeth *(A. duodenale)* to facilitate attachment to the mucosa and submucosa of the small intestine. Hookworms can remain in the intestine for 1-5 yr, where they mate and produce eggs. Although up to 2 mo is required for the larval stages of hookworms to undergo extraintestinal migration and develop into mature adults, *A. duodenale* larvae may remain developmentally arrested for many months before resuming development in the intestine. Mature *A. duodenale* female worms produce about 30,000 eggs per day; daily egg production by *N. americanus* is <10,000/day (Fig. 318.3). The eggs are thin shelled and ovoid, measuring approximately 40-60 µm. Eggs that are deposited on soil with adequate moisture and shade develop into first-stage larvae and hatch. Over the ensuing several days and under appropriate conditions, the larvae molt twice to the **infective** stage. Infective larvae are developmentally arrested and nonfeeding. They migrate vertically in the soil until they either infect a new host or exhaust their lipid metabolic reserves and die.

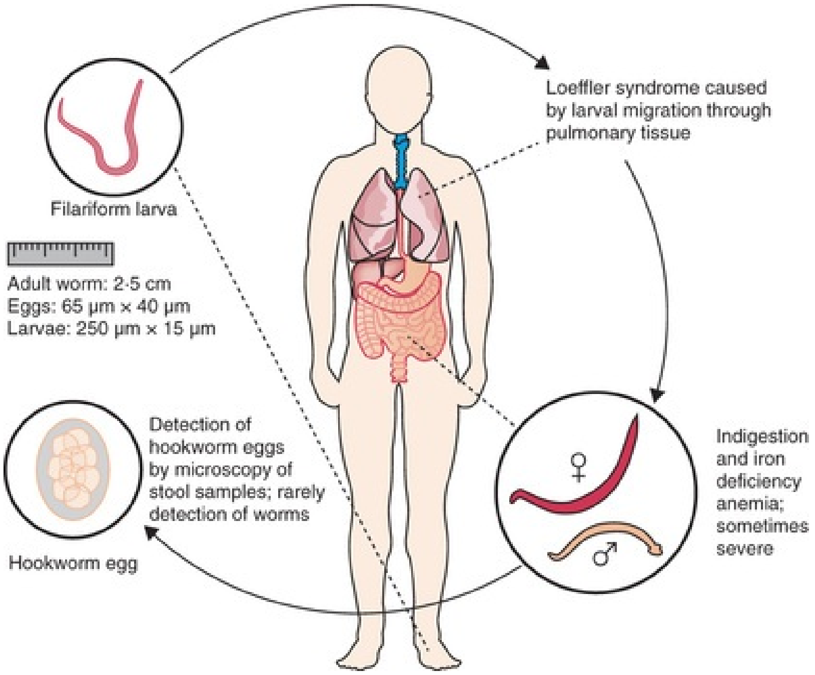
Loeffler syndrome caused by larval migration through pulmonary tissue
Filariform larva
Adult worm: 2-5 cm
Eggs: 65 µm × 40 µm
Larvae: 250 µm × 15 µm
Detection of hookworm eggs by microscopy of stool samples; rarely detection of worms
Hookworm egg
♀
♂
Indigestion and iron deficiency anemia; sometimes severe

FIG. 318.1 **Transmission of hookworm (*Ancylostoma duodenale* and *Necator americanus*): diagnosis and clinical features. (From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG: Soil-transmitted helminth infections, *Lancet* 391:252–262, 2018, Fig 2C.)**

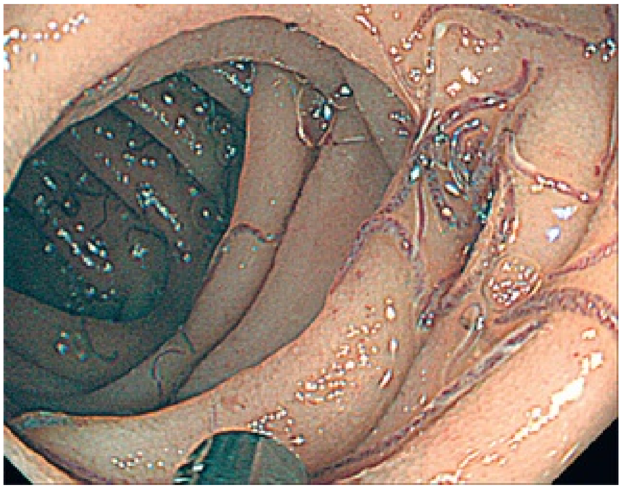

FIG. 318.2 Endoscopic images of intestinal hookworm infection. (Courtesy of Dr. Kunimitsu Inoue, Almeida Hospital, Oita, Japan.)

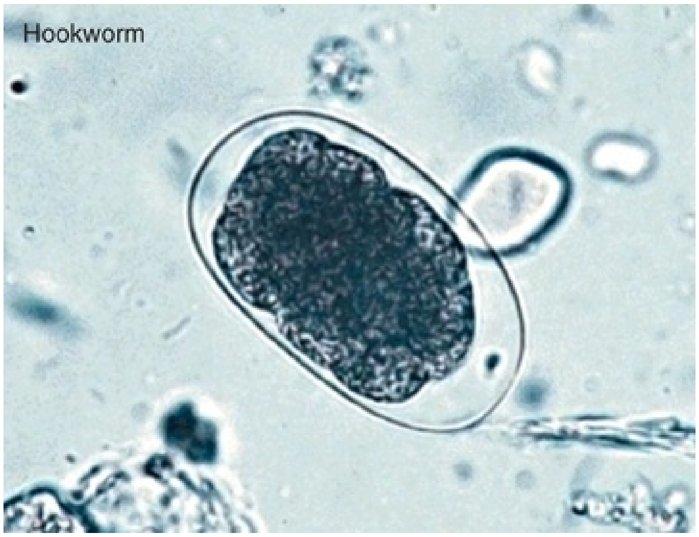

FIG. 318.3 Soil-transmitted hookworm helminth eggs. (From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm, *Lancet* 367:1521–1532, 2006.)

Epidemiology

Hookworm infection is one of the most prevalent infectious diseases of humans. The Global Burden of Disease Study 2015 reported that approximately 428 million people are infected with hookworms, with further estimates indicating that hookworm infection globally results in 4.1 million disability-adjusted life-years, possibly leading all **neglected tropical diseases** in years lost through disability. In the case of hookworm infection, all the years lost through disability are attributed to anemia from intestinal blood loss. There is also a massive socioeconomic impact from hookworm infection, with estimates that hookworm can cause up to $139 billion in losses from diminished productivity.

Because of the requirement for adequate soil moisture, shade, and warmth, hookworm infection is usually confined to rural areas, especially where human feces are used for fertilizer or where sanitation is inadequate. Hookworm is an infection associated with *economic underdevelopment and poverty* throughout the tropics and subtropics. Sub-Saharan Africa, East Asia, and tropical regions of the Americas have the highest prevalence of hookworm infection. High rates of infection are often associated with cultivation of certain agricultural products, such as tea in India; sweet potato, corn, cotton, and mulberry trees in China; coffee in Central and South America; and rubber in Africa. It is not uncommon to find dual *N. americanus* and *A. duodenale* infections. *N. americanus* predominates in Central and South America as well as in southern China and Southeast Asia, whereas *A. duodenale* predominates in North Africa, in northern India, in China north of the Yangtze River, and among aboriginal people in Australia. The ability of *A. duodenale* to withstand somewhat harsher environmental and climatic conditions may reflect its ability to undergo arrested development in human tissues. *A. ceylanicum* infection occurs in India and Southeast Asia.

Eosinophilic enteritis caused by *A. caninum* was first described in Queensland, Australia, with 2 reported cases in the United States. Because of its global distribution in dogs, it was initially anticipated that human *A. caninum* infections would be identified in many locales, but this has not been found.

Pathogenesis

The major morbidity of human hookworm infection is a direct result of **intestinal blood loss** . Adult hookworms adhere tenaciously to the mucosa and submucosa of the proximal small intestine by using their cutting plates or teeth and a muscular esophagus that creates negative pressure in their buccal capsules. At the attachment site, host inflammation is downregulated by the release of antiinflammatory polypeptides by the hookworm. Rupture of capillaries in the lamina propria is followed by blood extravasation, with some of the blood ingested directly by the hookworm. After ingestion, the blood is anticoagulated, the red blood cells are lysed, and the hemoglobin released and digested. Each adult *A. duodenale* hookworm causes loss of an estimated 0.2 mL of blood/day; blood loss is less for *N. americanus*. Individuals with light infections have minimal blood loss and thus may have hookworm infection but not hookworm disease. There is a direct correlation between the number of adult hookworms in the gut and the volume of fecal blood loss. Hookworm disease results only when individuals with moderate and heavy infections experience sufficient blood loss to develop iron deficiency and anemia. Hypoalbuminemia and consequent edema and anasarca from the loss of intravascular oncotic pressure can also occur. These features depend heavily on the dietary reserves of the host.

Clinical Manifestations

Chronically infected children with moderate and heavy hookworm infections suffer from intestinal blood loss that results in **iron deficiency** and can lead to anemia as well as protein malnutrition. Prolonged iron deficiency associated with hookworms in childhood can lead to physical growth retardation and cognitive and intellectual deficits.

Anthropophilic hookworm larvae elicit dermatitis sometimes referred to as **ground itch** when they penetrate human skin. The vesiculation and edema of ground itch are exacerbated by repeated infection. Infection with a zoonotic hookworm, especially *A. braziliense*, can result in lateral migration of the larvae to cause the characteristic cutaneous tracts of **cutaneous larva migrans** (see Chapter 318.1). Cough subsequently occurs in *A. duodenale* and *N. americanus* hookworm infection when larvae migrate through the lungs to cause laryngotracheobronchitis, usually about 1 wk after exposure. Pharyngitis also can occur. The onset of eosinophilia coincides with the entry of hookworm larvae into the GI tract. Upper abdominal pain can occur during this period, but it eventually subsides.

Chronic intestinal hookworm infection is not typically associated with specific GI complaints, although pain, anorexia, and diarrhea have been attributed to the presence of hookworms. The major clinical manifestations are related to intestinal blood loss. Heavily infected children exhibit all the signs and symptoms of **iron-deficiency anemia** and **protein malnutrition** . In some cases, children with chronic hookworm disease acquire a yellow-green pallor known as **chlorosis.**

An infantile form of **ancylostomiasis** resulting from heavy *A. duodenale* infection has been described. Affected infants experience diarrhea, melena, failure to thrive, and profound anemia. Infantile ancylostomiasis has significant mortality.

Eosinophilic enteritis caused by *A. caninum* is associated with colicky abdominal pain that begins in the epigastrium and radiates outward and is usually exacerbated by food. Extreme cases may mimic acute appendicitis.

Diagnosis

Children with hookworm release eggs that can be detected by direct fecal examination (see Fig. 318.3). Quantitative methods are available to determine whether a child has a heavy **worm burden** that can cause hookworm disease. The eggs of *N. americanus* and *A. duodenale* are morphologically indistinguishable. Species identification typically requires egg hatching and differentiation of third-stage infective larvae; methods using polymerase chain reaction (PCR) methods have been developed but are not generally used in clinical practice.

In contrast, eggs are generally not present in the feces of patients with eosinophilic enteritis caused by *A. caninum.* Eosinophilic enteritis is often diagnosed by demonstrating ileal and colonic ulcerations by colonoscopy in the presence of significant blood eosinophilia. An adult canine hookworm may occasionally be recovered during colonoscopic biopsy. Patients with this syndrome develop IgG and IgE serologic responses.

Treatment

The goal of **deworming** is removal of the adult hookworms with an **anthelmintic** drug. The **benzimidazole** anthelmintics, mebendazole and albendazole, are effective at eliminating hookworms from the intestine, although multiple doses are sometimes required. **Albendazole** (400 mg orally [PO] once, for all ages) often results in cure, although *N. americanus* adult hookworms are sometimes more refractory and require additional doses. **Mebendazole** (100 mg PO twice daily [bid] for 3 days, for all ages) is also effective. In many developing countries, mebendazole is administered as a single dose of 500 mg; however, the cure rates with this regimen can be as low as 10% or less.

According to the World Health Organization (WHO), children should be encouraged to chew tablets of albendazole or mebendazole, because forcing very young children to swallow large tablets may cause choking or asphyxiation. Mebendazole is recommended for *A. caninum* –associated eosinophilic enteritis, although recurrences are common. Because the benzimidazoles have been reported to be embryotoxic and teratogenic in laboratory animals, their safety during pregnancy and in young children is a potential concern, and the risks vs benefits must be carefully considered. WHO currently supports the use of benzimidazoles in infected children ≥1 yr old but at a reduced dose (200 mg for albendazole) in the youngest age-group (1-2 yr old). In some countries, **pyrantel pamoate** (11 mg/kg PO once daily for 3 days; maximum dose: 1 g) is available in liquid form and is an effective alternative to the benzimidazoles. A newer drug known as **tribendimidine** is still under clinical development and may be available in the future. Replacement therapy with oral iron is not usually required to correct hookworm-associated iron deficiency in children.

Prevention

In 2001, the World Health Assembly urged its member states to implement programs of periodic deworming so as to control the morbidity of hookworm and other soil-transmitted helminth infections (see Table 317.1 in Chapter 317). Although anthelmintic drugs are effective at eliminating hookworms from the intestine, the high rates of drug failure from single-dose mebendazole or albendazole and posttreatment reinfection among children suggest that mass drug administration alone is not effective for controlling hookworm in highly endemic areas. Moreover, data suggest that the efficacy of mebendazole decreases with frequent, periodic use, leading to concerns about the possible emergence of **anthelmintic drug resistance** . To reduce the reliance exclusively on anthelmintic drugs, a recombinant human hookworm vaccine has been developed and is undergoing clinical testing. Economic development and associated improvements in sanitation, health education, and avoidance of human feces as fertilizer remain critical for reducing hookworm transmission and endemicity.

318.1

Cutaneous Larva Migrans

Peter J. Hotez

Keywords

A. braziliense
creeping eruption

Etiology

Cutaneous larva migrans (**creeping eruption**) is caused by the larvae of several nematodes, primarily hookworms, which are not usually parasitic for humans. *A. braziliense,* a hookworm of dogs and cats, is the most common cause, but other animal hookworms may also produce the disease.

Epidemiology

Cutaneous larva migrans is usually caused by *A. braziliense,* which is endemic to the southeastern United States and Puerto Rico. Travelers account for a significant percentage of the cases. Recently, autochthonous cases have been reported from Europe.

Clinical Manifestations

After penetrating the skin, larvae localize at the epidermal-dermal junction and migrate in this plane, moving at a rate of 1-2 cm/day. The response to the parasite is characterized by raised, erythematous, serpiginous tracks, which occasionally form bullae (Fig. 318.4). These lesions may be single or numerous and are usually localized to an extremity, although any area of the body may be affected. As the organism migrates, new areas of involvement may appear every few days. Intense localized pruritus, without any systemic symptoms, may be associated with the lesions. Bacterial superinfection can occur.

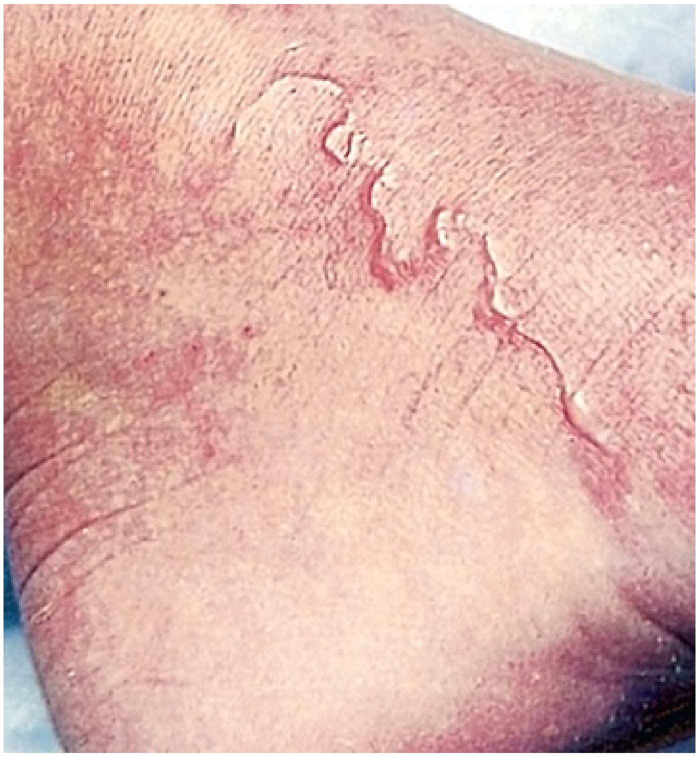

FIG. 318.4 **Creeping eruption of cutaneous larva migrans. (From Korting GW: *Hautkrankheitenbeikindern und jugendlichen* , Stuttgart, Germany, 1969, FK Schattauer Verlag.)**

Diagnosis

Cutaneous larva migrans is diagnosed by clinical examination of the skin. Patients are often able to recall the exact time and location of exposure, because the larvae produce intense itching at the site of penetration. Eosinophilia may occur but is uncommon.

Treatment

If left untreated, the larvae die, and the syndrome resolves within a few weeks to several months. Treatment with **ivermectin** (200 µg/kg PO daily for 1-2 days; considered drug of choice by some investigators), **albendazole** (400 mg PO daily for 3 days, for all ages), or topical **thiabendazole** hastens resolution, if symptoms warrant treatment. The U.S. Food and Drug Administration has not approved these drugs for cutaneous larva migrans. The safety of ivermectin in young children (weighing <15 kg) and pregnant women remains to be established. Albendazole should be taken with a fatty meal.

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CHAPTER 319

Trichuriasis *(Trichuris trichiura)*

Arlene E. Dent, James W. Kazura

Etiology

Trichuriasis is caused by the **whipworm** , *Trichuris trichiura,* a nematode, or roundworm, that inhabits the cecum and ascending colon. The principal hosts of *T. trichiura* are humans, who acquire infection by ingesting embryonated, barrel-shaped eggs (Fig. 319.1). The larvae escape from the shell in the upper small intestine and penetrate the intestinal villi. The worms slowly move toward the cecum, where the anterior three-quarters whiplike portion remains within the superficial mucosa and the short posterior end is free in the lumen (Fig. 319.2). In 1-3 mo, the adult female worm begins producing 5,000-20,000 eggs per day. After excretion in the feces, embryonic development occurs in 2-4 wk with optimal temperature and soil conditions. The adult worm life span is approximately 2 yr.

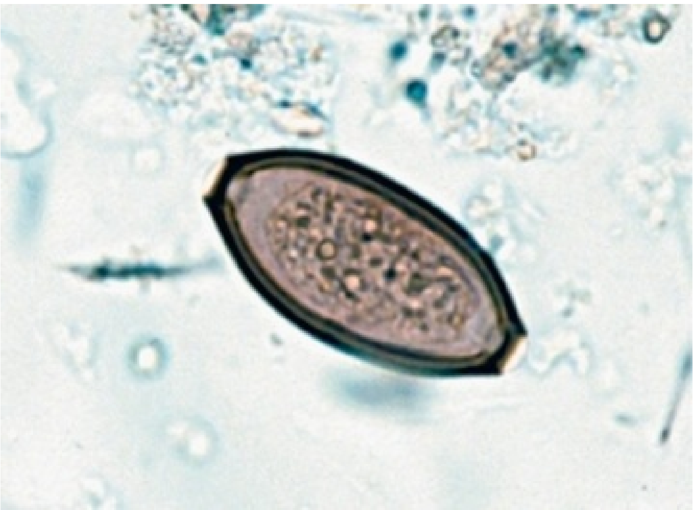

FIG. 319.1 **Trichuris trichiura. Soil-transmitted helminth eggs. (From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm, *Lancet* 367:1521–1532, 2006.)**

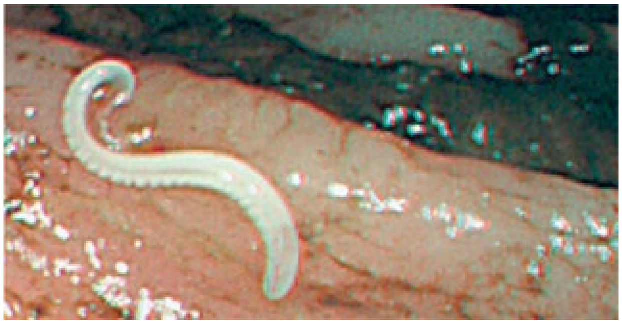

FIG. 319.2 ***Trichuris trichiura* infection. (Courtesy of Dr. Kunimitsu Inoue, Almeida Hospital, Oita, Japan).**

Epidemiology

Trichuriasis occurs throughout the world and is especially common in poor rural communities with inadequate sanitary facilities and soil contaminated with human or animal feces. Trichuriasis is one of the most prevalent human helminthiases, with an estimated 1 billion infected individuals worldwide. In many parts of the world, where protein-energy malnutrition and anemia are common, the prevalence of *T. trichiura* infection can be as high as 95%. Although trichuriasis occurs in the rural southeastern United States, its prevalence has not been reported. The highest rate of infection occurs among children 5-15 yr old. Infection develops after ingesting embryonated ova by direct contamination of hands, food (raw fruits and vegetables fertilized with human feces), or drink (Fig. 319.3). Transmission can also occur indirectly through flies or other insects.

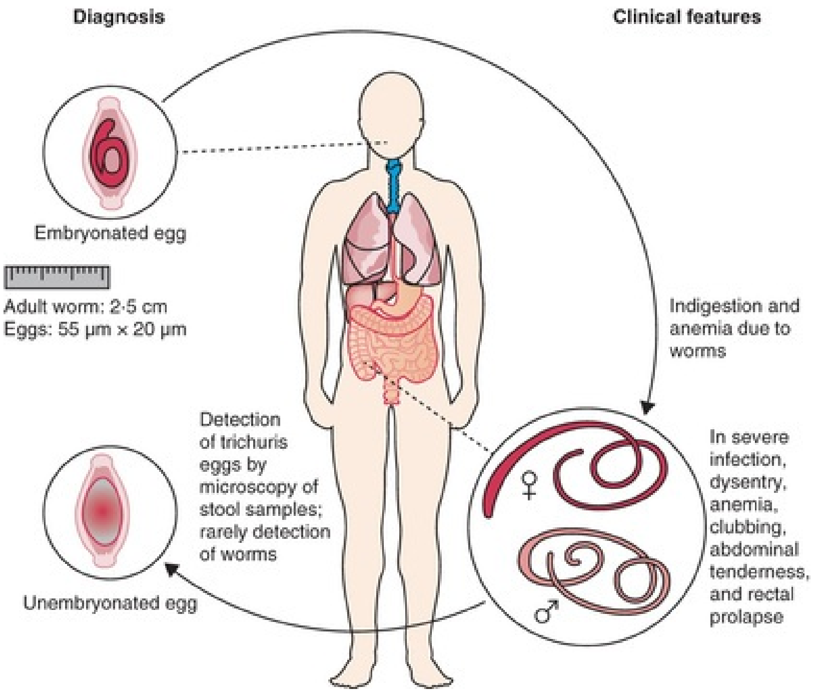
Diagnosis
Clinical features
Embryonated egg
Adult worm: 2·5 cm
Eggs: 55 μm × 20 μm
Indigestion and anemia due to worms
Detection of trichuris eggs by microscopy of stool samples; rarely detection of worms
In severe infection, dysentry, anemia, clubbing, abdominal tenderness, and rectal prolapse
♀
♂
Unembryonated egg

FIG. 319.3 **Transmission of *Trichuris trichiura* : diagnosis and clinical features. (From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG: Soil-transmitted helminth infections, *Lancet* 391:252–262, 2018, Fig 2B.)**

Clinical Manifestations

Most persons harbor low worm burdens and do not have symptoms. Some individuals may have a history of right lower quadrant or vague periumbilical pain. Adult *Trichuris* ingest approximately 0.005 mL of blood per worm per day. Children, who are most likely to be heavily infected, frequently suffer from disease. Clinical manifestations include chronic dysentery, rectal prolapse, anemia, poor growth, as well as developmental and cognitive deficits. There is no significant eosinophilia, even though a portion of the worm is embedded in the mucosa of the large bowel.

Diagnosis

Because egg output is so high, fecal smears frequently reveal the characteristic barrel-shaped ova of *T. trichiura.*

Treatment

Albendazole (400 mg orally for 3 days, for all ages) is the drug of choice and is safe and effective, in part because it is poorly absorbed from the gastrointestinal tract. It reduces egg output by 90–99% and has cure rates of 70–90%, although reinfection and resumption of egg production by live worms that presumably survive after treatment may occur. Alternatives include **mebendazole** (100 mg orally twice daily for 3 days) and **ivermectin** (200 µg/kg orally for 3 days). Single-day treatment with albendazole, nitazoxanide, or albendazole plus nitazoxanide lead to cure rates that are low and short-lived. Combination treatment with **oxantel pamoate** (20 mg/kg) plus 400 mg albendazole on consecutive days may have the highest cure rate.

Prevention

Disease can be prevented by personal hygiene, improved sanitary conditions, and eliminating the use of human feces as fertilizer (see Table 317.1 in Chapter 317).

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CHAPTER 320

Enterobiasis *(Enterobius vermicularis)*

Arlene E. Dent, James W. Kazura

Etiology

The cause of enterobiasis, or **pinworm** infection, is *Enterobius vermicularis,* which is a small (1 cm in length), white, threadlike nematode, or roundworm, that typically inhabits the cecum, appendix, and adjacent areas of the ileum and ascending colon. Gravid females migrate at night to the perianal and perineal regions, where they deposit up to 15,000 eggs. Ova are convex on one side and flattened on the other and have diameters of approximately 30 × 60 µm. Eggs embryonate within 6 hr and remain viable for 20 days. Human infection occurs by the fecal-oral route typically by ingestion of embryonated eggs that are carried on fingernails, clothing, bedding, or house dust. After ingestion, the larvae mature to form adult worms in 36-53 days.

Epidemiology

Enterobiasis infection occurs in individuals of all ages and socioeconomic levels. It is prevalent in regions with temperate climates and is the most common helminth infection in the United States. It infects 30% of children worldwide, and humans are the only known host. Infection occurs primarily in institutional or family settings that include children. The prevalence of pinworm infection is highest in children 5-14 yr of age. It is common in areas where children live, play, and sleep close together, thus facilitating egg transmission. Because the life span of the adult worm is short, chronic parasitism is likely caused by repeated cycles of reinfection. **Autoinoculation** can occur in individuals who habitually put their fingers in their mouth.

Pathogenesis

Enterobius infection may cause symptoms by mechanical stimulation and irritation, allergic reactions, and migration of the worms to anatomic sites where they become pathogenic. *Enterobius* infection has been associated with concomitant *Dientamoeba fragilis* infection, which causes diarrhea.

Clinical Manifestations

Pinworm infection is innocuous and rarely causes serious medical problems. The most common complaints include itching and restless sleep secondary to nocturnal perianal or **perineal pruritus** . The precise cause and incidence of pruritus are unknown but may be related to the intensity of infection, psychologic profile of the infected individual and the family, or allergic reactions to the parasite. Eosinophilia is not observed in most cases, because tissue invasion does not occur. Aberrant migration to ectopic sites occasionally may lead to appendicitis, chronic salpingitis, pelvic inflammatory disease, peritonitis, hepatitis, and ulcerative lesions in the large or small bowel.

Diagnosis

A history of nocturnal **perianal pruritus** in children strongly suggests enterobiasis. Definitive diagnosis is established by identification of parasite eggs or worms. Microscopic examination of adhesive cellophane tape pressed against the perianal region early in the morning frequently demonstrates eggs (Fig. 320.1). Repeated examinations increase the chance of detecting ova; 1 examination detects 50% of infections, 3 examinations 90%, and 5 examinations 99%. Worms seen in the perianal region should be removed and preserved in 75% ethyl alcohol until microscopic examination can be performed. Digital rectal examination may also be used to obtain samples for a wet mount. Routine stool samples rarely demonstrate *Enterobius* ova.

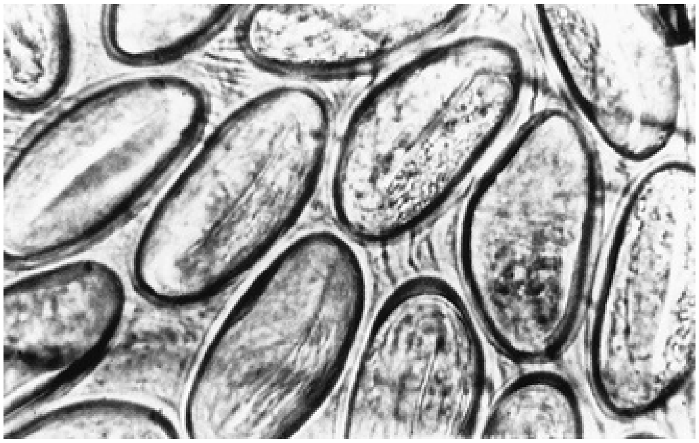

FIG. 320.1 Eggs of *Enterobius vermicularis* . (From Guerrant RL, Walker DH, Weller PF, et al: *Tropical infectious diseases* , Philadelphia, 2006, Churchill Livingstone, p 1248.)

Treatment

Anthelmintic drugs should be administered to infected individuals and their family members. **Albendazole** (400 mg orally with a repeat dose 2 wk later for all age-groups) is the treatment of choice and results in cure rates exceeding 90%. Alternatives include **mebendazole** (100 mg orally with a repeat dose 2 wk later) and **pyrantel pamoate** (11 mg/kg base orally 3 times for 1 day up to a maximum of 1 g; repeat at 2 wk). Morning bathing removes a large portion of eggs. Frequent changing of underclothes, bedclothes, and bedsheets decreases environmental egg contamination and may decrease the risk for autoinfection.

Prevention

Household contacts can be treated at the same time as the infected individual. Repeated treatments every 3-4 mo may be required in circumstances with repeated exposure, such as with institutionalized children. Good hand hygiene is the most effective method of prevention.

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CHAPTER 321

Strongyloidiasis *(Strongyloides stercoralis)*

Arlene E. Dent, James W. Kazura

Etiology

Strongyloidiasis is caused by the nematode, or roundworm, *Strongyloides stercoralis*. Only adult female worms inhabit the small intestine. The nematode reproduces in the human host by parthenogenesis and releases eggs containing mature larvae into the intestinal lumen. **Rhabditiform** larvae immediately emerge from the ova and are passed in feces, where they can be visualized by stool examination. Rhabditiform larvae either differentiate into free-living adult male and female worms or metamorphose into the infectious **filariform** larvae. Sexual reproduction occurs only in the free-living stage. Humans are usually infected through skin contact with soil contaminated with infectious larvae (Fig. 321.1). Larvae penetrate the skin, enter the venous circulation and then pass to the lungs, break into alveolar spaces, and migrate up the bronchial tree. They are then swallowed and pass through the stomach, and adult female worms develop in the small intestine. Egg deposition begins approximately 28 days after initial infection.

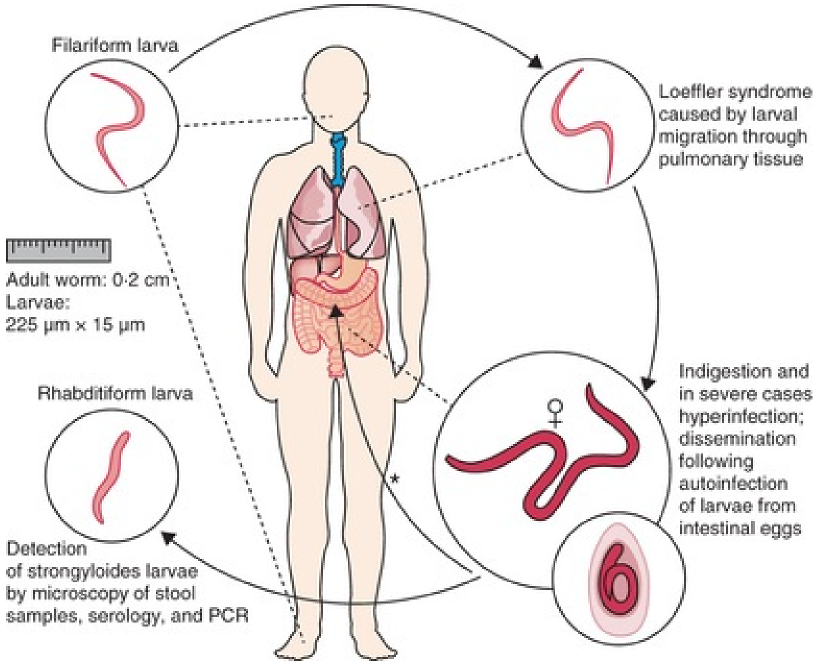
Filariform larva
Loeffler syndrome caused by larval migration through pulmonary tissue
Adult worm: 0·2 cm
Larvae:
225 μm × 15 μm
Rhabditiform larva
♀
Indigestion and in severe cases hyperinfection; dissemination following autoinfection of larvae from intestinal eggs
*
Detection of strongyloides larvae by microscopy of stool samples, serology, and PCR

FIG. 321.1 Transmission of *Strongyloides stercoralis* : diagnosis and clinical features. (From Jourdan PM, Lamberton PHL, Fenwick A, Addiss DG: Soil-transmitted helminth infections, *Lancet* 391:252–262, 2018, Fig 2D.)

The **hyperinfection syndrome** occurs when large numbers of larvae transform into infective organisms during their passage in feces and then reinfect (**autoinfect**) the host by way of the lower gastrointestinal (GI) tract or perianal region. This cycle may be accelerated in immunocompromised persons, particularly those with depressed T-cell function.

Epidemiology

S. stercoralis infection is prevalent in tropical and subtropical regions of the world and is endemic in several areas of Europe, the southern United States, and Puerto Rico. Transmission requires appropriate environmental conditions, particularly warm, moist soil. Poor sanitation and crowded living conditions are conducive to high levels of transmission. Dogs and cats can act as reservoirs. The highest prevalence of infection in the United States (4% of the general population) is in impoverished rural areas of Kentucky and Tennessee. Infection may be especially common among residents of mental institutions, veterans who were prisoners of war in areas of high endemicity, and refugees and immigrants. Because of internal autoinfection, individuals may remain infected for decades. Infection may be transmitted by organ transplantation. Individuals with hematologic malignancies, autoimmune diseases, malnutrition, and drug-induced immunosuppression (especially corticosteroids) are at high risk for the hyperinfection syndrome. Patients with AIDS may experience a rapid course of disseminated strongyloidiasis with a fatal outcome.

Pathogenesis

The initial host immune response to infection is production of immunoglobulin E and eosinophilia in blood and tissues, which presumably prevents dissemination and hyperinfection in the immunocompetent host. Adult female worms in otherwise healthy and asymptomatic individuals may persist in the GI tract for years. If infected persons become immunocompromised, the reduction in cellular and humoral immunity may lead to an abrupt and dramatic increase in parasite load with systemic dissemination.

Clinical Manifestations

Approximately 30% of infected individuals are asymptomatic. The remaining patients have symptoms that correlate with the 3 stages of infection: invasion of the skin, migration of larvae through the lungs, and parasitism of the small intestine by adult worms. **Larva currens** is the manifestation of an allergic reaction to filariform larvae that migrate through the skin, where they leave pruritic, tortuous, urticarial tracks. The lesions may recur and are typically found over the lower abdominal wall, buttocks, or thighs, resulting from larval migration from defecated stool. Pulmonary disease secondary to larval migration through the lung rarely occurs and may resemble **Loeffler syndrome** (cough, wheezing, shortness of breath, transient pulmonary infiltrates accompanied by eosinophilia). GI strongyloidiasis is characterized by indigestion, crampy abdominal pain, vomiting, diarrhea, steatorrhea, protein-losing enteropathy, protein-caloric malnutrition, and weight loss. Edema of the duodenum with irregular mucosal folds, ulcerations, and strictures can be seen radiographically. Infection may be chronic in nature and is associated with **eosinophilia** .

Strongyloidiasis is potentially lethal because of the ability of the parasite to replicate within the host and cause overwhelming hyperinfection in immunocompromised persons. The **hyperinfection syndrome** is characterized by an exaggeration of the clinical features that develop in symptomatic immunocompetent individuals. The onset is usually sudden, with generalized abdominal pain, distention, and fever. Multiple organs can be affected as massive numbers of larvae disseminate throughout the body and introduce bowel flora. The latter may result in bacteremia and septicemia. Cutaneous manifestations may include petechiae and purpura. Cough, wheezing, and hemoptysis are indicative of pulmonary involvement. Whereas eosinophilia is a prominent feature of strongyloidiasis in immunocompetent persons, this sign may be absent in immunocompromised persons. Because of the low incidence of strongyloidiasis in industrialized countries, it is often misdiagnosed, resulting in a significant delay in treatment.

Diagnosis

Intestinal strongyloidiasis is diagnosed by examining feces or duodenal fluid for the characteristic larvae (Fig. 321.2). Several stool samples should be examined by direct smear, the Koga agar plate method, or the Baermann test. Alternatively, duodenal fluid can be sampled by the **enteric string test** (Entero-Test) or aspiration via endoscopy. In children with the hyperinfection syndrome, larvae may be found in sputum, gastric aspirates, and rarely in small intestinal biopsy specimens. An enzyme-linked immunosorbent assay for IgG antibody to *Strongyloides* may be more sensitive than parasitological methods for diagnosing intestinal infection in the immunocompetent host. The utility of the assay in diagnosing infection in immunocompromised patients with the hyperinfection syndrome has not been determined. Eosinophilia is common.

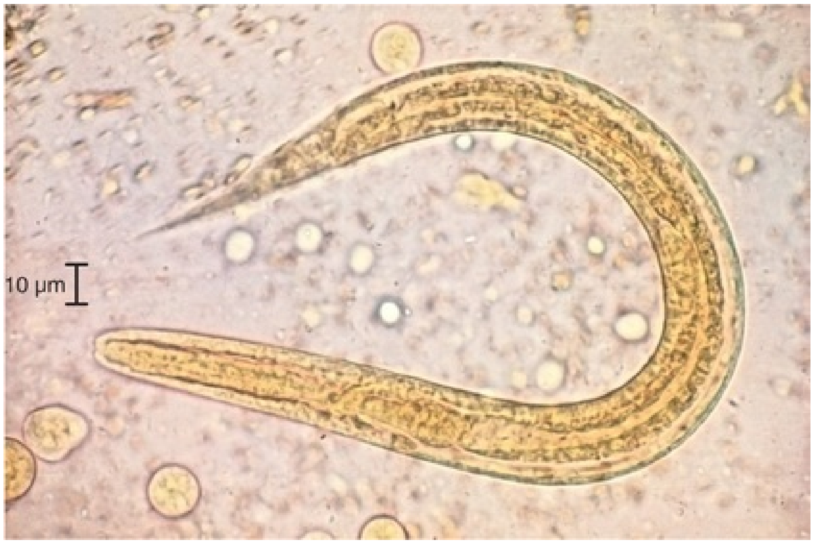

FIG. 321.2 **Larvae of intestinal strongyloidiasis.**

Treatment

Treatment is directed at eradication of infection. **Ivermectin** (200 µg/kg/day once daily orally for 2 days) is the drug of choice for uncomplicated strongyloidiasis. Alternatively, **albendazole** (400 mg orally twice daily for 7 days) may be used. Patients with the hyperinfection syndrome should be treated with ivermectin for 7-10 days and may require repeated courses. Reducing the dose of immunosuppressive therapy and treatment of concomitant bacterial infections are essential in the management of the **hyperinfection syndrome** . Close follow-up with repeated stool examination is necessary to ensure complete elimination of the parasite. *Strongyloides* antibodies decrease within 6 mo after successful treatment.

Prevention

Sanitary practices designed to prevent soil and person-to-person transmission are the most effective control measures (see Table 317.1). Wearing **shoes** is a main preventive strategy. Reducing transmission in institutional settings can be achieved by decreasing fecal contamination of the environment, such as by the use of clean bedding. Because infection is uncommon in most settings, case detection and treatment are advisable. Individuals who will be given prolonged high-dose corticosteroids, immunosuppressive drugs before organ transplantation, or cancer chemotherapy should have a screening examination for *S. stercoralis*. If infected, they should be treated before immunosuppression is initiated.

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CHAPTER 322

Lymphatic Filariasis (*Brugia malayi, Brugia timori*, and *Wuchereria bancrofti*)

Arlene E. Dent, James W. Kazura

Etiology

The filarial worms *Brugia malayi* (**Malayan filariasis**), *Brugia timori*, and *Wuchereria bancrofti* (**bancroftian filariasis**) are threadlike nematodes that cause similar infections. Infective larvae are introduced into humans during blood feeding by the **mosquito** vector. Over 4-6 mo, the larval forms develop into sexually mature adult worms. Once an adequate number of male and female worms accumulate in the afferent lymphatic vessels, adult female worms release large numbers of microfilariae that circulate in the bloodstream. The life cycle of the parasite is completed when mosquitoes ingest microfilariae in a blood meal, which molt to form infective larvae over 10-14 days. Adult worms have a 5-7 yr life span.

Epidemiology

More than 120 million people living in tropical Africa, Asia, and Latin America are infected; approximately 10–20% of these individuals have clinically significant morbidity attributable to filariasis. *W. bancrofti* is transmitted in Africa, Asia, and Latin America and accounts for 90% of lymphatic filariasis. *B. malayi* is restricted to the South Pacific and Southeast Asia, and *B. timori* is restricted to several islands of Indonesia. Travelers from nonendemic areas of the world who spend brief periods in endemic areas are rarely infected. Global elimination has been targeted for 2020.

Clinical Manifestations

The clinical manifestations of *B. malayi, B. timori,* and *W. bancrofti* infection are similar; manifestations of acute infection include transient, recurrent lymphadenitis and lymphangitis. The early signs and symptoms include episodic fever, lymphangitis of an extremity, lymphadenitis (especially the inguinal and axillary areas), headaches, and myalgias that last a few days to several weeks. These symptoms are caused by an acute inflammatory response triggered by death of adult worms. Initial damage to lymphatic vessels may remain subclinical for years. The syndrome is most frequently observed in persons 10-20 yr old. Manifestations of chronic lymphatic filariasis occur mostly in adults ≥30 yr old and result from anatomic and functional obstruction to lymph flow. This obstruction results in lymphedema of the legs, arms, breasts, and/or genitalia. Male genital involvement, such as hydrocele, is very common in *W. bancrofti* infection, but uncommon in *Brugia* spp. infection. Chronic lymphedema predisposes affected extremities to bacterial superinfections, sclerosis, and verrucous skin changes, resulting in **elephantiasis** , which may involve 1 or more limbs, the breasts, or genitalia. It is uncommon for children to have overt signs of chronic filariasis.

Tropical Pulmonary Eosinophilia

The presence of microfilariae in the body has no apparent pathologic consequences except in persons with tropical pulmonary eosinophilia, a syndrome of filarial etiology in which microfilariae are found in the lungs and lymph nodes but not the bloodstream. It occurs only in individuals who have lived for years in endemic areas. Men 20-30 yr old are most likely to be affected, although the syndrome occasionally occurs in children. The presentation includes paroxysmal nocturnal cough with dyspnea, fever, weight loss, and fatigue. Rales and rhonchi are found on auscultation of the chest. The x-ray findings may occasionally be normal, but increased bronchovascular markings, discrete opacities in the middle and basal regions of the lung, or diffuse miliary lesions are usually present (Fig. 322.1). Recurrent episodes may result in interstitial fibrosis and chronic respiratory insufficiency in untreated individuals. Hepatosplenomegaly and generalized lymphadenopathy are often seen in children. The **diagnosis** is suggested by residence in a filarial endemic area, eosinophilia (>2,000/µL), compatible clinical symptoms, increased serum IgE (>1,000 IU/mL), and high titers of antimicrofilarial antibodies in the absence of microfilaremia. Although microfilariae may be found in sections of lung or lymph node, biopsy of these tissues is unwarranted in most situations. The clinical response to **diethylcarbamazine** (2 mg/kg/dose orally 3 times daily for 12-21 days) is the final criterion for diagnosis; the majority of patients improve with this therapy. If symptoms recur, a 2nd anthelmintic course should be administered. Patients with chronic symptoms are less likely to show improvement than those who have been ill for a short time.

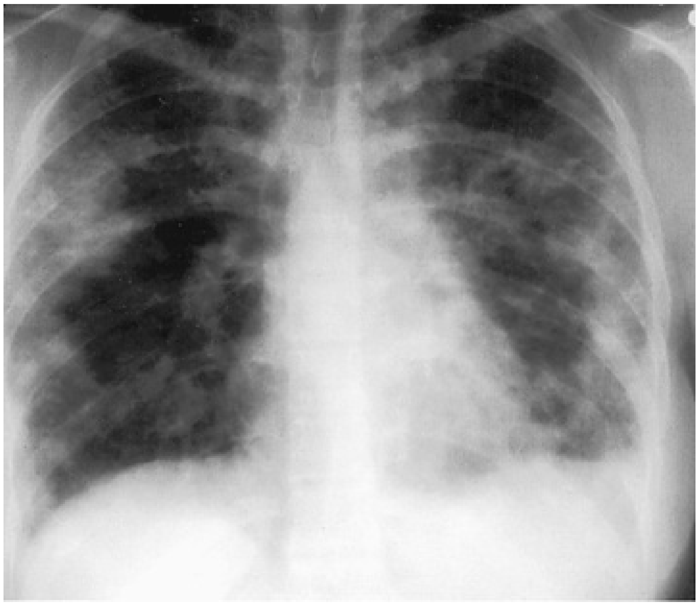

FIG. 322.1 **Chest radiograph of a woman with tropical pulmonary eosinophilia. Reticulonodular opacities are scattered throughout both lungs. (From Mandell GL, Bennett JE, Dolin R, editors: *Principles and practice of infectious diseases* , ed 6, Philadelphia, 2006, Elsevier, p 3274.)**

Diagnosis

Demonstration of microfilariae in the blood is the primary means for confirming the diagnosis of lymphatic filariasis. Because microfilaremia is **nocturnal** in most cases, blood samples should be obtained between 10 PM and 2 AM . Anticoagulated blood is passed through a Nuclepore filter that is stained and examined microscopically for microfilariae. Adult worms or microfilariae can be identified in tissue specimens obtained at biopsy. Infection with *W. bancrofti* in the absence of bloodborne microfilariae may be diagnosed by detection of parasite antigen in the serum. Adult worms in lymphatic vessels can be visualized by ultrasonography.

Treatment

The use of antifilarial drugs in the management of acute lymphadenitis and lymphangitis is controversial. No controlled studies demonstrate that administration of drugs such as diethylcarbamazine modifies the course of acute lymphangitis. Diethylcarbamazine may be given to asymptomatic microfilaremic persons to lower the intensity of parasitemia. The drug also kills a proportion of the adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypotension, and even death may occur, especially with high microfilarial levels, the dose of **diethylcarbamazine** should be increased gradually (*children* : 1 mg/kg orally as a single dose on day 1, 1 mg/kg 3 times daily on day 2, 1-2 mg/kg 3 times daily on day 3, and 2 mg/kg 3 times daily on days 4-14; *adults* : 50 mg orally on day 1, 50 mg 3 times daily on day 2, 100 mg 3 times daily on day 3, and 2 mg/kg 3 times daily on days 4-14). For patients with no microfilaria in the blood, the full dose (2 mg/kg/day orally divided 3 times daily) can be given beginning on day 1. Repeat doses may be necessary to further reduce the microfilaremia and kill lymph-dwelling adult parasites. *W. bancrofti* is more sensitive than *B. malayi* to diethylcarbamazine.

Global programs to control and ultimately eradicate lymphatic filariasis from endemic populations currently recommend a single annual dose of diethylcarbamazine (6 mg/kg orally once) in combination with **albendazole** (400 mg orally once) for 5 yr (mass drug administration). In coendemic areas of filariasis and **onchocerciasis** , mass drug applications with single-dose **ivermectin** (150 µg/kg orally once) and albendazole are used because of severe adverse reactions with diethylcarbamazine in onchocerciasis-infected individuals. Five years of annual mass treatment is thought to be necessary to stop transmission. Adjuvant medicines (e.g., doxycycline) that target endosymbiont bacteria *(Wolbachia)* in filarial parasites may accelerate eradication.

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CHAPTER 323

Other Tissue Nematodes

Arlene E. Dent, James W. Kazura

Onchocerciasis *(Onchocerca Volvulus)*

Infection with *Onchocerca volvulus* leads to onchocerciasis or **river blindness** . Onchocerciasis occurs primarily in West Africa but also in Central and East Africa and is the world's 2nd leading infectious cause of blindness. There have been scattered foci in Central and South America, but the infection is now thought to be eliminated in the Americas. *O. volvulus* larvae are transmitted to humans by the bite of *Simulium* black flies that breed in fast-flowing streams. The larvae penetrate the skin and migrate through the connective tissue and eventually develop into adult worms that can be found tangled in fibrous tissue. Adult worms can live in the human body for up to 14 yr. Female worms produce large numbers of microfilariae that migrate through the skin, connective tissue, and eye. Most infected individuals are asymptomatic. In heavily infected individuals, clinical manifestations are a result of localized host inflammatory reactions to dead or dying microfilariae and subcutaneous adult worms surrounded by a palpable fibrous capsule. Cutaneous and ocular reactions to microfilariae produce pruritic dermatitis, punctate keratitis, corneal pannus formation, and chorioretinitis. Adult worms in subcutaneous nodules are not painful and tend to occur over bony prominences of the hip. The **diagnosis** can be established by obtaining snips of skin covering the scapulae, iliac crests, buttocks, or calves. The snips are immersed in saline for several hours and examined microscopically for microfilariae that have emerged into the fluid. The diagnosis can also be established by demonstrating microfilariae in the cornea or anterior chamber on slit-lamp examination or finding adult worms on a nodule biopsy specimen. Ophthalmology consultation should be obtained before treatment of eye lesions.

A single dose of **ivermectin** (150 µg/kg orally) is the drug of choice and clears *O. volvulus* microfilariae from the skin for several months but has no effect on the adult worm. Treatment with ivermectin should be repeated every 6-12 mo until the patient is asymptomatic or has no evidence of eye infection. Adverse effects of ivermectin therapy include fever, urticaria, and pruritus, which are more frequent in individuals not born in endemic areas who acquired the infection following periods of intense exposure, such as Peace Corps volunteers. Patients with concurrent high-density microfilaremia from loiasis may develop potentially fatal encephalopathy with ivermectin therapy. Treatment with ivermectin should be withheld until *Loa loa* microfilaremia can be reduced. **Moxidectin** is a promising new agent. Personal protection includes avoiding areas where biting flies are numerous, wearing protective clothing, and using insect repellent. Programs of mass treatment with ivermectin have been implemented in Africa in an effort to reduce the prevalence of onchocerciasis.

The World Health Organization (WHO) set goals for onchocerciasis elimination by 2020 using mass drug administration with ivermectin. Elimination can be declared only after 3 yr of posttreatment surveillance without microfilaria detection in skin biopsies.

Nodding syndrome , a form of epilepsy in African children living in focal areas of Uganda and South Sudan, was epidemiologically associated with onchocerciasis, but an etiologic link was not established. Recently, researchers identified neurotoxic autoantibodies that cross-react with *O. volvulus* proteins, which were found more frequently in people with nodding syndrome than in those in the same village without the syndrome. Nodding syndrome may be an autoimmune epileptic disorder triggered by *O. volvulus* infection.

Loiasis *(Loa Loa)*

Loiasis is caused by infection with the tissue nematode *Loa loa*. The parasite is transmitted to humans by diurnally biting flies *(Chrysops)* that live in the rain forests of West and Central Africa. Migration of adult worms through skin, subcutaneous tissue, and subconjunctival area can lead to transient episodes of pruritus, erythema, and localized edema known as **Calabar swellings** , which are nonerythematous areas of subcutaneous edema 10-20 cm in diameter typically found around joints such as the wrist or the knee (Fig. 323.1). They resolve over several days to weeks and may recur at the same or different sites. Lifelong residents of *L. loa* –endemic regions may have microfilaremia and eosinophilia but are often asymptomatic. In contrast, travelers to endemic regions may have a hyperreactive response to *L. loa* infection characterized by frequent recurrences of swelling, high level eosinophilia, debilitation, and serious complications such as glomerulonephritis and encephalitis. **Diagnosis** is usually established on clinical grounds, often assisted by the infected individual reporting a worm being seen crossing the conjunctivae. Microfilariae may be detected in blood smears collected between 10 AM and 2 PM . Adult worms should be surgically excised when possible.

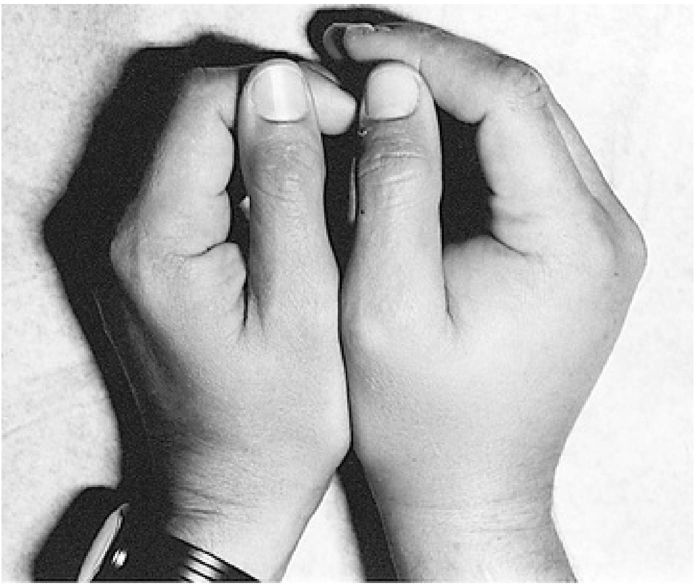

FIG. 323.1 **Calabar swelling of the right hand. (From Guerrant RL, Walker DH, Weller PF, et al: *Tropical infectious diseases* , Philadelphia, 2006, Churchill Livingstone, p 1165.)**

Diethylcarbamazine is the agent of choice for eradication of microfilaremia, but the drug does not kill adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypertension, and even death may occur, especially with high microfilaria levels, the dose of diethylcarbamazine should be increased gradually in such cases (*children* : 1 mg/kg orally on day 1, 1 mg/kg 3 times daily on day 2, 1-2 mg/kg three times daily on day 3, 2 mg/kg three times daily on days 4-21; *adults* : 50 mg orally on day 1, 50 mg three times daily on day 2, 100 mg three times daily on day 3, 2 mg/kg three times daily on days 4-21). Full doses can be instituted on day 1 in persons without microfilaremia (3 mg/kg orally three times daily for 12 days). A 3 wk course of **albendazole** can also be used to slowly reduce *L. loa* microfilarial levels as a result of embryotoxic effects on the adult worms. Antihistamines or corticosteroids may be used to limit allergic reactions secondary to killing of microfilariae. Personal protective measures include avoiding areas where biting flies are present, wearing protective clothing, and using insect repellents. Diethylcarbamazine (300 mg orally once weekly) prevents infection in travelers who spend prolonged periods in endemic areas. *L. loa* do not harbor *Wolbachia* endosymbionts, and therefore doxycycline has no effect on infection.

Infection With Animal Filariae

The most commonly recognized zoonotic filarial infections are caused by members of the genus *Dirofilaria.* The worms are introduced into humans by the bites of mosquitoes containing third-stage larvae. The most common filarial zoonosis in the United States is *Dirofilaria tenuis,* a parasite of raccoons. In Europe, Africa, and Southeast Asia, infections are usually caused by the dog parasite *Dirofilaria repens.* The **dog heartworm** , *Dirofilaria immitis,* is the second most frequently encountered filarial zoonosis worldwide. Other genera, including *Dipetalonema* -like worms, *Onchocerca,* and *Brugia,* are rare causes of zoonotic filarial infections.

Animal filariae do not undergo normal development in the human host. The clinical manifestations and pathologic findings correspond to the anatomic site of infection and can be categorized into 4 major groups: subcutaneous, lung, eye, and lymphatic. Pathologic examination of affected tissue reveals a localized foreign body reaction around a dead or dying parasite. The lesion consists of granulomas with eosinophils, neutrophils, and tissue necrosis. *D. tenuis* does not leave the subcutaneous tissues, whereas *Brugia beaveri* eventually localizes to superficial lymph nodes. Infections may be present for up to several months. *D. immitis* larvae migrate for several months in subcutaneous tissues and most frequently result in a well-circumscribed, coinlike lesion in a single lobe of the lung. The chest radiograph typically reveals a solitary pulmonary nodule 1-3 cm in diameter. Definitive **diagnosis** and cure depend on surgical excision and identification of the nematode within the surrounding granulomatous response. *D. tenuis* and *B. beaveri* infections present as painful, rubbery, 1-5 cm nodules in the skin of the trunk, of the extremities, and around the orbit. Patients often report having been engaged in activities predisposing to exposure to infected mosquitoes, such as working or hunting in swampy areas. Management is by

surgical excision .

Angiostrongylus Cantonensis

Angiostrongylus cantonensis, the **rat lungworm,** is the most common cause of **eosinophilic meningitis** worldwide. Rats are the definitive host. Human infection follows ingestion of third-stage larvae in raw or undercooked intermediate hosts such as snails and slugs, or transport hosts such as freshwater prawns, frogs, and fish. Most cases are sporadic, but clusters have been reported, including clusters related to consumption of lettuce contaminated with intermediate or transport hosts. Even though most infections have been described in Southeast Asia, the South Pacific, and Taiwan, shipboard travel of infected rats has spread the parasite to Madagascar, Africa, the Caribbean, and most recently Australia and North America. Larvae penetrate the vasculature of the intestinal tract and migrate to the meninges, where they usually die but induce eosinophilic aseptic meningitis. Patients present 2-35 days after ingestion of larvae with severe headache, neck pain or nuchal rigidity, hyperesthesias and paresthesias (often migrating), fatigue, fever, rash, pruritus, nausea, and vomiting. Neurologic involvement varies from asymptomatic to paresthesias, severe pain, weakness, and focal neurologic findings such as cranial nerve palsies. Symptoms can last for several weeks to months, especially headache. Coma and death from hydrocephalus occur rarely in heavy infections. Peripheral blood eosinophilia is not always present on initial examination but peaks about 5 wk after exposure, often when symptoms are improving. Cerebrospinal fluid (CSF) analysis reveals pleocytosis with >10% eosinophils in more than half of patients, with mildly elevated protein, a normal glucose level, and an elevated opening pressure. Head CT or MRI is usually unremarkable. The **diagnosis** is established clinically with supporting travel and diet history. A sensitive and specific enzyme-linked immunosorbent assay (ELISA) is available on a limited basis from the Centers for Disease Control and Prevention (CDC) for testing CSF or serum.

Treatment is primarily supportive because the majority of infections are mild, and most patients recover within 2 mo without neurologic sequelae. Analgesics should be given for headache. Careful, repeated lumbar punctures should be performed to relieve hydrocephalus. Anthelmintic drugs have not been shown to influence the outcome and may exacerbate neurologic symptoms. The use of corticosteroids may shorten the duration of persistent and severe headaches.

There is a higher incidence of permanent neurologic sequelae and mortality among children than among adults. Infection can be avoided by not eating raw or undercooked crabs, prawns, or snails.

Angiostrongylus Costaricensis

Angiostrongylus costaricensis is a nematode that infects several species of rodents and causes abdominal **angiostrongyliasis** , which has been described predominantly in Latin America and the Caribbean. The mode of transmission to humans, who are accidental hosts, is unknown. It is speculated that infectious larvae from a molluscan intermediate host, such as the slug *Vaginulus plebeius*, contaminate water or vegetation that is inadvertently consumed (chopped up in salads or on vegetation contaminated with the slug's mucus secretions). Although this slug is not indigenous to the continental United States, it has been found on imported flowers and produce. The incubation period for abdominal angiostrongyliasis is unknown, but limited data suggest that it ranges from 2 wk to several months after ingestion of larvae. Third-stage larvae migrate from the gastrointestinal tract to the mesenteric arteries, where they mature into adults. These eggs degenerate and elicit an eosinophilic granulomatous reaction. The clinical findings of abdominal angiostrongyliasis mimic **appendicitis,** although the former are typically more indolent. Children can have fever, right lower quadrant pain, a tumor-like mass, abdominal rigidity, and a painful rectal examination. Most patients have leukocytosis with eosinophilia. Radiologic examination may show bowel wall edema, spasticity, or filling defects in the ileocecal region and the ascending colon. Examination of stool for ova and parasites is not useful for *A. costaricensis* but is useful for evaluating the presence of other intestinal parasites. An ELISA is available for **diagnosis** on a limited basis from the CDC, but the test has a low specificity and is known to cross react with *Toxocara, Strongyloides,* and *Paragonimus.*

Many patients undergo laparotomy for suspected appendicitis and are found to have a mass in the terminal ileum to the ascending colon. *No specific treatment is known for abdominal angiostrongyliasis.* Even though the use of anthelmintic therapy has not been studied systematically, thiabendazole or diethylcarbamazine has been suggested. The prognosis is generally good. Most cases are self-limited, although surgery may be required in some patients. Cornerstones of **prevention** include avoidance of slugs and not ingesting raw food and water that may be contaminated with imperceptible slugs or slime from slugs. Rat control is also important in preventing the spread of infection.

Dracunculiasis *(Dracunculus Medinensis)*

Dracunculiasis is caused by the guinea worm, *Dracunculus medinensis.* WHO has targeted dracunculiasis for eradication. As of 2016, the transmission of the infection was confined to Chad, Ethiopia, Mali, and South Sudan. Humans become infected by drinking contaminated stagnant water that contains immature forms of the parasite in the gut of tiny crustaceans (copepods or water fleas). Larvae are released in the stomach, penetrate the mucosa, mature, and mate. Approximately 1 yr later, the adult female worm (1-2 mm in diameter and up to 1 m long) migrates and partially emerges through the human host skin, usually of the legs. Thousands of immature larvae are released when the affected body part is immersed in the water. The cycle is completed when larval forms are ingested by the crustaceans. Infected humans have no symptoms until the worm reaches the subcutaneous tissue, causing a **stinging papule** that may be accompanied by urticaria, nausea, vomiting, diarrhea, and dyspnea. The lesion vesiculates, ruptures, and forms a painful ulcer in which a portion of the worm is visible. **Diagnosis** is established clinically. Larvae can be identified by microscopic examination of the discharge fluid.

Metronidazole (25 mg/kg/day orally divided into 3 doses for 10 days; maximum dose: 750 mg) decreases local inflammation. Although the drug does not kill the worm, it facilitates its removal. The worm must be physically removed by rolling the slowly emerging 1 m–long parasite onto a thin stick over a week. Topical corticosteroids shorten the time to complete healing while topical antibiotics decrease the risk of secondary bacterial infection. Dracunculiasis can be prevented by boiling or chlorinating drinking water or passing the water through a cloth sieve before consumption. Eradication is dependent on behavior modification and education.

Gnathostoma Spinigerum

Gnathostoma spinigerum is a dog and cat nematode endemic to Southeast Asia, Japan, China, Bangladesh, and India, but has been identified in Mexico and parts of South America. Infection is acquired by ingesting intermediate hosts containing larvae of the parasite, such as raw or undercooked freshwater fish, chickens, pigs, snails, or frogs. Penetration of the skin by larval forms and prenatal transmission has also been described. Nonspecific signs and symptoms such as generalized malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric pain develop 24-48 hr after ingestion of *G. spinigerum*. Ingested larvae penetrate the gastric wall and migrate through soft tissue for up to 10 yr. Moderate to severe eosinophilia can develop. Cutaneous **gnathostomiasis** manifests as intermittent episodes of localized, migratory nonpitting edema associated with pain, pruritus, or erythema. Central nervous system involvement in gnathostomiasis is suggested by focal neurologic findings, initially neuralgia followed within a few days by paralysis or changes in mental status. Multiple cranial nerves may be involved, and CSF may be xanthochromic but typically shows an eosinophilic pleocytosis. **Diagnosis** of gnathostomiasis is based on clinical presentation and epidemiologic background. Brain and spinal cord lesions may be seen on CT or MRI. Serologic testing varies in sensitivity and specificity and is available through the CDC.

There is no well-documented effective chemotherapy, although **albendazole** (400 mg orally twice daily for 21 days) as first-line therapy or **ivermectin** (200 µg/kg for 2 days) as an alternative is recommended without or with surgical removal. Multiple courses may be needed. Corticosteroids have been used to relieve focal neurologic deficits. **Surgical resection** of the *Gnathostoma* is the major mode of therapy and the treatment of choice. Blind surgical resection of subcutaneous areas of diffuse swelling is not recommended because the worm can rarely be located. **Prevention** through the avoidance of ingestion of poorly cooked or raw fish, poultry, or pork should be emphasized for individuals living in or visiting endemic areas.

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CHAPTER 324

Toxocariasis (Visceral and Ocular Larva Migrans)

Arlene E. Dent, James W. Kazura

Etiology

Most cases of human toxocariasis are caused by the **dog roundworm** , *Toxocara canis.* Adult female *T. canis* worms live in the intestinal tracts of young puppies and their lactating mothers. Large numbers of eggs are passed in the feces of dogs and embryonate under optimal soil conditions. *Toxocara* eggs can survive relatively harsh environmental conditions and are resistant to freezing and extremes of moisture and pH. Humans ingest embryonated eggs contaminating soil, hands, or fomites. The larvae hatch and penetrate the intestinal wall and travel via the circulation to the liver, lung, and other tissues. Humans do not excrete *T. canis* eggs because the larvae are unable to complete their maturation to adult worms in the intestine. The **cat roundworm** , *Toxocara cati,* is responsible for far fewer cases of **visceral larva migrans (VLM)** than *T. canis.* Ingestion of infective larvae of the raccoon ascarid *Baylisascaris procyonis* rarely leads to VLM but can cause **neural larva migrans** , resulting in fatal eosinophilic meningitis. Ingestion of larvae from the opossum ascarid *Lagochilascaris minor* leads to VLM rarely.

Epidemiology

Human *T. canis* infections have been reported in almost all parts of the world, primarily in temperate and tropical areas where dogs are popular household pets. Young children are at highest risk because of their unsanitary play habits and tendency to place fingers in the mouth. Other behavioral risk factors include

pica , contact with puppy litters, and institutionalization. In North America, the highest prevalences of infection are in the southeastern United States and Puerto Rico, particularly among socially disadvantaged African American and Hispanic children. In the United States, serosurveys show that 4.6–7.3% of children are infected. Assuming an unrestrained and untreated dog population, toxocariasis is prevalent in settings where other **geohelminth infections** , such as ascariasis, trichuriasis, and hookworm infections, are common.

Pathogenesis

T. canis larvae secrete large amounts of immunogenic glycosylated proteins. These antigens induce immune responses that lead to eosinophilia and polyclonal and antigen-specific immunoglobulin E production. The characteristic histopathologic lesions are granulomas containing eosinophils, multinucleated giant cells (histiocytes), and collagen. Granulomas are typically found in the liver but may also occur in the lungs, central nervous system (CNS), and ocular tissues. Clinical manifestations reflect the intensity and chronicity of infection, anatomic localization of larvae, and host granulomatous responses.

Clinical Manifestations

Three major clinical syndromes are associated with human toxocariasis: VLM, **ocular larva migrans (OLM)** , and **covert toxocariasis** (Table 324.1). The classic presentation of VLM includes eosinophilia, fever, and hepatomegaly and occurs most often in toddlers with a history of pica and exposure to puppies. The findings include fever, cough, wheezing, bronchopneumonia, anemia, hepatomegaly, leukocytosis, eosinophilia, and positive *Toxocara* serology. Cutaneous manifestations such as pruritus, eczema, and urticaria can be present. OLM tends to occur in older children without signs or symptoms of VLM. Presenting symptoms include unilateral visual loss, eye pain, white pupil, or strabismus that develops over weeks. Granulomas occur on the posterior pole of the retina and may be mistaken for retinoblastoma. Serologic testing for *Toxocara* has allowed the identification of individuals with less obvious or covert symptoms of infection. These children may have nonspecific complaints that do not constitute a recognizable syndrome. Common findings include hepatomegaly, abdominal pain, cough, sleep disturbance, failure to thrive, and headache with elevated *Toxocara* antibody titers. Eosinophilia may be present in 50–75% of cases. The prevalence of positive *Toxocara* serology in the general population supports that most children with *T. canis* infection are asymptomatic and will not develop overt clinical sequelae over time. A correlation between positive *Toxocara* serology and allergic asthma has also been described.

Table 324.1

Clinical Syndromes of Human Toxocariasis

SYNDROME	CLINICAL FINDINGS	AVERAGE AGE	INFECTIOUS DOSE	INCUBATION PERIOD	LABORATORY FINDINGS	ELISA
Visceral larva migrans	Fevers, hepatomegaly, asthma	5 yr	Moderate to high	Weeks to months	Eosinophilia, leukocytosis, elevated IgE	High (≥1 : 16)
Ocular larva migrans	Visual disturbances, retinal granulomas, endophthalmitis, peripheral granulomas	12 yr	Low	Months to years	Usually none	Low
Covert toxocariasis	Abdominal pain, gastrointestinal symptoms, weakness, hepatomegaly, pruritus, rash	School-age to adult	Low to moderate	Weeks to years	± Eosinophilia ± Elevated IgE	Low to moderate

ELISA, Enzyme-linked immunosorbent assay; IgE, immunoglobulin E; ±, with or without.

Adapted from Liu LX: Toxocariasis and larva migrans syndrome. In Guerrant RL, Walker DH, Weller PF, editors: *Tropical infectious diseases: principles, pathogens & practice,* Philadelphia, 206, Churchill-Livingstone, p 1209.

Diagnosis

A presumptive diagnosis of toxocariasis can be established in a young child with **eosinophilia** (>20%), leukocytosis, hepatomegaly, fevers, wheezing, and a history of geophagia and exposure to puppies or unrestrained dogs. Supportive laboratory findings include hypergammaglobulinemia and elevated isohemagglutinin titers to A and B blood group antigens. Most patients with VLM have an absolute eosinophil count >500/µL. Eosinophilia is less common in patients with OLM. Biopsy confirms the diagnosis. When biopsies cannot be obtained, an enzyme-linked immunosorbent assay using excretory-secretory proteins harvested from *T. canis* larvae maintained in vitro is the standard serologic test used to confirm toxocariasis. A titer of 1 : 32 is associated with a sensitivity of approximately 78% and a specificity of approximately 92%. The sensitivity for OLM is significantly less. The diagnosis of OLM can be established in patients with typical clinical findings of a retinal or peripheral pole granuloma or endophthalmitis with elevated antibody titers. Vitreous and aqueous humor fluid anti-*Toxocara* titers are usually greater than serum titers. The diagnosis of covert toxocariasis should be considered in individuals with chronic weakness, abdominal pain, or allergic signs with eosinophilia and increased IgE. In temperate regions of the world, nonparasitic causes of eosinophilia that should be considered in the differential diagnosis include allergies, drug hypersensitivity, lymphoma, vasculitis, and **idiopathic hypereosinophilic syndrome** (see Chapter 155).

Treatment

Most patients do not require treatment because signs and symptoms are mild and subside over weeks to months. Several anthelmintic drugs have been used for symptomatic cases, often with adjunctive corticosteroids to limit inflammatory responses that presumably result from release of *Toxocara* antigens by dying parasites. **Albendazole** (400 mg orally twice daily for 5 days for all ages) has demonstrated efficacy in both children and adults. **Mebendazole** (100-200 mg PO twice daily for 5 days for all ages) is also useful. Anthelmintic treatment of CNS and ocular disease should be extended (3-4 wk). Even with no clinical trials on OLM therapy, a course of oral corticosteroids such as **prednisone** (1 mg/kg/day PO for 2-4 wk) has been recommended to suppress local inflammation while treatment with anthelmintic agents is initiated.

Prevention

Transmission can be minimized by public health measures that prevent dog feces from contaminating the environment. These include keeping dogs on leashes and excluding pets from playgrounds and sandboxes that toddlers use. Children should be discouraged from putting dirty fingers in their mouth and eating dirt. Vinyl covering of sandboxes reduces the viability of *T. canis* eggs. Widespread veterinary use of broad-spectrum anthelmintics effective against *Toxocara* may lead to a decline in parasite transmission to humans.

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CHAPTER 325

Trichinellosis *(Trichinella spiralis)*

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Etiology

Human trichinellosis (also called **trichinosis**) is caused by consumption of meat containing encysted larvae of *Trichinella spiralis,* a tissue-dwelling nematode with a worldwide distribution. After ingestion of raw or inadequately cooked meat from pigs (or other commercial meat sources such as horses) containing viable *Trichinella* larvae, the organisms are released from the cyst by acid-pepsin digestion of the cyst walls in the stomach and then pass into the small intestine. The larvae invade the small intestine columnar epithelium at the villi base and develop into adult worms. The adult female worm produces about 500 larvae over 2 wk and is then expelled in the feces. The larvae enter the bloodstream and seed striated muscle by burrowing into individual muscle fibers. Over a period of 3 wk, they coil as they increase about 10 times in length and become capable of infecting a new host if ingested. The larvae eventually become encysted and can remain viable for years. **Sylvatic** *Trichinella* spp. (*T. brivoti, T. nativa, T. pseudospiralis,* and *T. murrelli*) present in traditional native foods such as walrus meat, and **game meat** may also cause disease similar to that caused by *T. spiralis* .

Epidemiology

Despite public health efforts to control trichinellosis by eliminating the practice of feeding garbage to domestic swine, epidemics and isolated cases of *Trichinella* spp. infection continue to be a health problem in many areas of the world. It is most common in Asia, Latin America, and Central Europe. Swine fed with garbage may become infected when given uncooked trichinous scraps, usually pig meat, or when the carcasses of infected wild animals such as rats are eaten. Prevalence rates of *T. spiralis* in domestic swine range from 0.001% in the United States to ≥25% in China. The resurgence of this disease can be attributed to translocations of animal populations, human travel, and export of food as well as ingestion of sylvatic *Trichinella* through game meat. In the United States from 1997 to 2001, wild game meat (especially bear or walrus meat) was the most common source of infection. Most outbreaks occur from the consumption of *T. spiralis* –infected pork (or horse meat in areas of the world where horse is eaten) obtained from a single source.

Pathogenesis

During the 1st 2-3 wk after infection, pathologic reactions to infection are limited to the gastrointestinal (GI) tract and include a mild, partial villous atrophy with an inflammatory infiltrate of neutrophils, eosinophils, lymphocytes, and macrophages in the mucosa and submucosa. Larvae are released by female worms and disseminate over the next several weeks. Skeletal muscle fibers show the most striking changes with edema and basophilic degeneration. The muscle fiber may contain the typical coiled worm, the cyst wall derived from the host cell, and the surrounding lymphocytic and eosinophilic infiltrate.

Clinical Manifestations

The development of symptoms depends on the number of viable larvae ingested. Most infections are asymptomatic or mild, and children often show milder symptoms than adults who consumed the same amount of infected meat. Watery diarrhea is the most common symptom corresponding to maturation of the adult worms in the GI tract, which occurs during the 1st 1-2 wk after ingestion. Patients may also complain of abdominal discomfort and vomiting. Fulminant **enteritis** may develop in individuals with extremely high worm burdens. The classic symptoms of facial and periorbital edema, fever, weakness, malaise, and myalgia peak approximately 2-3 wk after the infected meat is ingested, as the larvae migrate and then encyst in the muscle. Headache, cough, dyspnea, dysphagia, subconjunctival and splinter hemorrhages, and a macular or petechial rash may occur. Patients with high-intensity infection may die from myocarditis, encephalitis, or pneumonia. In symptomatic patients, **eosinophilia** is common and may be dramatic.

Diagnosis

The Centers for Disease Control and Prevention (CDC) diagnostic criteria for trichinellosis require positive serology or muscle biopsy for *Trichinella* with 1 or more compatible clinical symptoms (eosinophilia, fever, myalgia, facial or periorbital edema). To declare a discrete outbreak, at least 1 person must have positive serology or muscle biopsy. Antibodies to *Trichinella* are detectable approximately 3 wk after infection. Severe muscle involvement results in elevated serum creatine phosphokinase and lactic dehydrogenase levels. Muscle biopsy is not usually necessary, but if needed, a sample should be obtained from a tender swollen muscle. A history of eating undercooked meat supports the diagnosis. The cysts may calcify and may be visible on radiograph.

Treatment

Recommended treatment of trichinellosis diagnosed at the GI phase is **albendazole** (400 mg orally twice daily for 8-10 days for all ages) to eradicate the adult worms if a patient has ingested contaminated meat within the previous 1 wk. An alternative regimen is mebendazole (200-400 mg PO 3 times daily for 3 days followed by 400-500 mg three times daily for 10 days). There is no consensus for treatment of muscle-stage trichinellosis. Corticosteroids may be used, although evidence for efficacy is anecdotal.

Prevention

Trichinella larvae can be killed by cooking meat (≥55°C [131°F]) until there is no trace of pink fluid or flesh, or by storage in a freezer (−15°C [5°F]) for ≥3 wk. Freezing to kill larvae should only be applied to pork meat, because larvae in horse, wild boar, or game meat can remain viable even after 4 wk of freezing. Smoking, salting, and drying meat are unreliable methods of killing *Trichinella*. Strict adherence to public health measures, including garbage feeding regulations, stringent rodent control, prevention of exposure of pigs and other livestock to animal carcasses, constructing barriers between livestock, wild animals, and domestic pets, and proper handling of wild animal carcasses by hunters, can reduce infection with *Trichinella*. Current meat inspection for trichinellosis is by direct digestion and visualization of encysted larvae in meat samples. Serologic testing does not have a role in meat inspection.

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CHAPTER 326

Schistosomiasis *(Schistosoma)*

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The term **schistosomiasis (bilharzia)** encompasses the acute and chronic inflammatory disorders caused by human infection with *Schistosoma* spp. parasites. Disease is related to both the systemic and the focal effects of schistosome infection and its consequent host immune responses triggered by parasite eggs deposited in the tissues. For the affected individuals, this frequently manifests as disabling chronic morbidity.

Etiology

Schistosoma organisms are the trematodes, or **flukes** , that parasitize the bloodstream. Five schistosome species infect humans: *Schistosoma haematobium, S. mansoni, S. japonicum, S. intercalatum,* and *S. mekongi* . Humans are infected through contact with water contaminated with *cercariae* , the free-living infective stage of the parasite. These motile, forked-tail organisms emerge from infected snails and are capable of penetrating intact human skin. As they reach maturity, adult worms migrate to specific anatomic sites characteristic of each schistosome species: *S. haematobium* adults are found in the perivesical and periureteral venous plexus, *S. mansoni* in the inferior mesenteric veins, and *S. japonicum* in the superior mesenteric veins. *S. intercalatum* and *S. mekongi* are usually found in the mesenteric vessels. Adult schistosome worms (1-2 cm long) are clearly adapted for an intravascular existence. The female accompanies the male in a groove formed by the lateral edges of its body. On fertilization, female worms begin oviposition in the small venous tributaries. The eggs of the 3 main schistosome species have characteristic morphologic features: *S. haematobium* has a terminal spine, *S. mansoni* has a lateral spine, and *S.*

japonicum has a smaller size with a short, curved spine (Fig. 326.1). Parasite eggs provoke a significant granulomatous inflammatory response that allows them to ulcerate through host tissues to reach the lumen of the urinary tract or the intestines. They are carried to the outside environment in urine or feces (depending on the species), where they will hatch if deposited in freshwater. Motile miracidia emerge, infect specific freshwater snail intermediate hosts, and divide asexually. After 4-12 wk, the infective cercariae are released by the snails into the contaminated water.

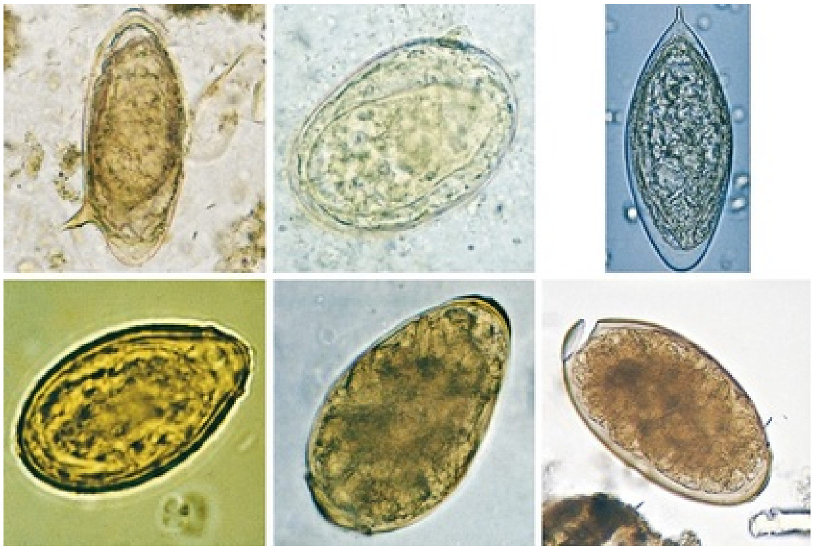

FIG. 326.1 Eggs of common human trematodes. Clockwise from upper left: *Schistosoma mansoni, S. japonicum, S. haematobium, Clonorchis sinensis, Paragonimus westermani* , and *Fasciola hepatica* (note the partially open operculum). (From Centers for Disease Control and Prevention: DPDx: laboratory identification of parasites of public health concern. http://www.cdc.gov/dpdx/az.html .)

Epidemiology

Schistosomiasis infects more than 300 million people worldwide and puts more than 700 million people at risk, primarily children and young adults. There are 3.3 million disability-adjusted life-years (DALYs) attributed to schistosomiasis, making it the 2nd most disabling parasitic disease after malaria. Prevalence is increasing in many areas as population density increases and new irrigation projects provide broader habitats for vector **snails** . Humans are the main definitive hosts for the 5 clinically important species of schistosomes, although

S. japonicum is also a zoonosis, infecting animals such as dogs, rats, pigs, and cattle. *S. haematobium* is prevalent in Africa and the Middle East; *S. mansoni* is prevalent in Africa, the Middle East, the Caribbean, and South America; and *S. japonicum* is prevalent in China, the Philippines, and Indonesia, with some sporadic foci in parts of Southeast Asia. The other 2 species are less prevalent. *S. intercalatum* is found in West and Central Africa, and *S. mekongi* is found only along the upper Mekong River in the Far East.

Transmission depends on water contamination by human excreta, the presence of specific intermediate snail hosts, and the patterns of water contact and social habits of the population (Fig. 326.2). The distribution of infection in endemic areas shows that prevalence increases with age, to a peak at 10-20 yr old. Exposure to infected water starts early in life for children living in endemic areas. Passive water contact by infants (accompanying mothers in their daily household activities) evolves to more active water contact as preschool and school-age children pursue recreational activities such as swimming and wading.

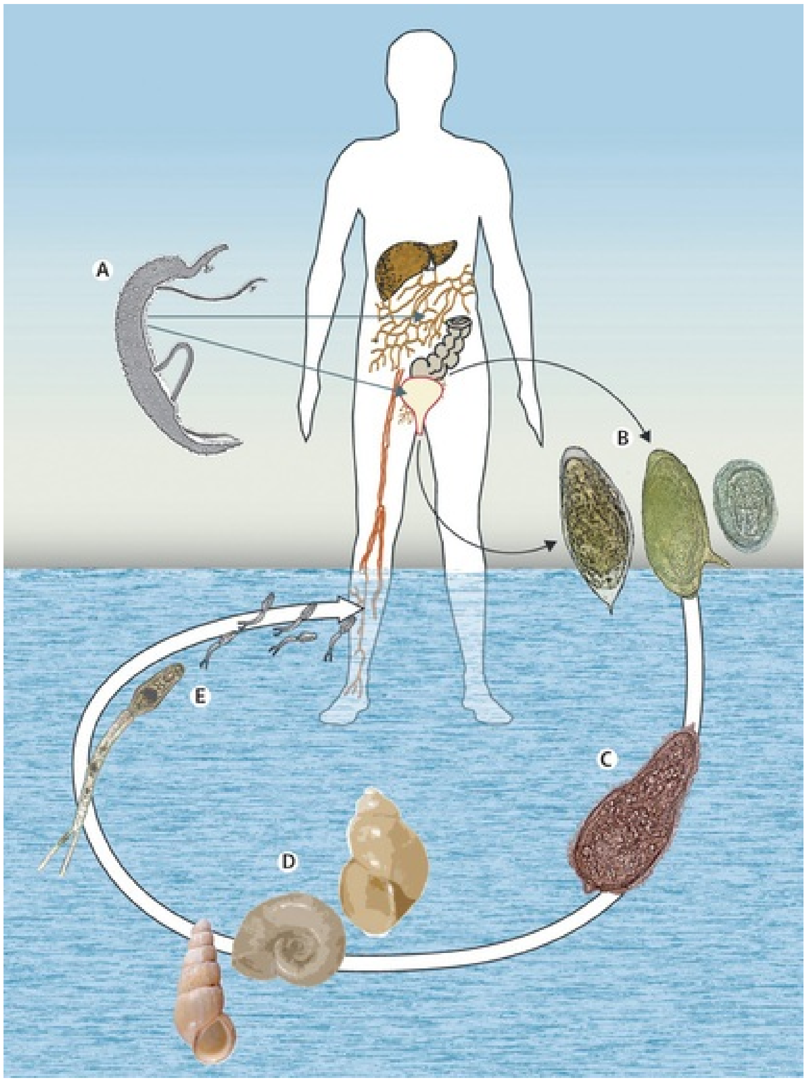

FIG. 326.2 Life cycle of *Schistosoma mansoni, S. haematobium,* and *S. japonicum* . *A,* Paired adult worms (larger male enfolding slender female). *B,* Eggs (left to right, *S. haematobium, S. mansoni, S. japonicum)* . *C,* Ciliated miracidium. *D,* Intermediate host snails (left to right, *Oncomelania, Biomphalaria, Bulinus)* . *E,* Cercariae. (From Colley DG, Bustinduy AL, Secor WE, King CH: Human schistosomiasis, *Lancet* 383:2253–2264, 2014, Fig 1.)

Measuring intensity of infection (by quantitative egg count in urine or feces) demonstrates that the heaviest worm loads are found in school-age and adolescent children. Even though schistosomiasis is most prevalent and most severe in older children and young adults, who are at maximal risk for suffering from its acute and chronic sequelae, preschool children can also exhibit significant disease manifestations.

Pathogenesis

Both early and late manifestations of schistosomiasis are immunologically mediated. *Acute* schistosomiasis, known as **snail fever** or **Katayama syndrome**, is a febrile illness that represents an immune complex disease associated with early infection and oviposition. The major pathology of infection occurs later, with *chronic* schistosomiasis, in which retention of eggs in the host tissues is associated with chronic granulomatous injury. Eggs may be trapped at sites of deposition (urinary bladder, ureters, intestine) or may be carried by the bloodstream to other organs, most frequently the liver and less often the lungs and central nervous system (CNS). The host response to these eggs involves local as well as systemic manifestations. The cell-mediated immune response leads to granulomas composed of lymphocytes, macrophages, and eosinophils that surround the trapped eggs and add significantly to the degree of tissue destruction. Granuloma formation in the bladder wall and at the ureterovesical junction results in the major disease manifestations of schistosomiasis haematobia: hematuria, dysuria, and obstructive uropathy. Intestinal as well as hepatic granulomas underlie the pathologic sequelae of the other schistosome infections: ulcerations and fibrosis of intestinal wall, hepatosplenomegaly, and portal hypertension caused by presinusoidal obstruction of blood flow. In terms of systemic disease, antischistosome inflammation increases circulating levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, associated with elevated levels of C-reactive protein. These responses are associated with hepcidin-mediated inhibition of iron uptake and use, leading to anemia of chronic inflammation. Schistosomiasis-related undernutrition may be the result of similar pathways of chronic inflammation. Acquired partial protective immunity against schistosomiasis has been demonstrated in some animal species and may occur in humans.

Clinical Manifestations

Two main chronic clinical syndromes arise from *Schistosoma* spp. infection: **urogenital schistosomiasis** caused by *S. haematobium* and **intestinal schistosomiasis** caused by *S. mansoni* or *S. japonicum.* Most chronically infected individuals experience mild symptoms and may not seek medical attention; the more severe symptoms of schistosomiasis occur mainly in those who are heavily infected or who have been infected over longer periods. In addition to organ-specific morbidities, infected patients frequently demonstrate anemia, chronic pain, diarrhea, exercise intolerance, and chronic undernutrition manifesting as growth stunting. Cercarial penetration of human skin may result in a papular pruritic rash known as **schistosomal dermatitis** or **swimmer's itch** . It is more pronounced in previously exposed individuals and is characterized by edema and intense cellular infiltrates in the dermis and epidermis. Acute schistosomiasis (Katayama syndrome) may occur, particularly in heavily infected individuals, 4-8 wk after exposure; this is a serum sickness–like syndrome manifested by the acute onset of fever, cough, chills, sweating, abdominal pain, lymphadenopathy, hepatosplenomegaly, and eosinophilia. Acute schistosomiasis typically presents in first-time visitors to endemic areas who experience primary infection at an older age.

Symptomatic children with chronic urogenital schistosomiasis usually complain of frequency, dysuria, and hematuria. Urine examination shows erythrocytes, parasite eggs, and occasional eosinophiluria. In endemic areas, moderate to severe pathologic lesions have been demonstrated in the urinary tract of >20% of infected children. The extent of disease correlates with the intensity of infection, but significant morbidity can occur even in lightly infected children. The advanced stages of urogenital schistosomiasis are associated with chronic renal failure, secondary infections, and squamous carcinoma of the bladder.

An important complication of *S. haematobium* infection is **female genital schistosomiasis** . Eggs migrate from the vesical plexus to lodge in the female genital tract where they induce a granulomatous inflammatory response that can manifest as contact bleeding, pain, and eventual infertility. Symptoms start as early as 10 yr of age, with an apparent 3-4–fold greater risk of HIV transmission. Pathognomonic lesions can be visualized in the cervix by photocolposcopy. **Male genital schistosomiasis** can also present with hematospermia, pain, and lumpy semen.

Children with chronic schistosomiasis mansoni, japonica, intercalatum, or mekongi may have intestinal symptoms; colicky abdominal pain and bloody diarrhea are the most common. However, the intestinal phase may remain subclinical, and the late syndrome of hepatosplenomegaly, portal hypertension, ascites, and hematemesis may then be the first clinical presentation. Liver disease is caused by granuloma formation and subsequent **periportal fibrosis** ; no appreciable liver cell injury occurs, and hepatic function may be preserved for a long time. Schistosome eggs may escape into the lungs, causing **pulmonary hypertension** and cor pulmonale. *S. japonicum* worms may migrate to the brain vasculature and produce localized lesions that cause seizures.

Transverse myelitis , spinal compression, and other CNS involvement (meningoencephalitis) are rare but well-known complications in children or young adults with either acute or chronic *S. haematobium* or *S. mansoni* infection.

Although end-organ scarring is pathognomonic, affected children may also have persistent long-term systemic effects of infection, including poor growth, anemia, decreased aerobic capacity, and cognitive impairment.

Diagnosis

Schistosome eggs are found in the excreta of infected individuals; quantitative methods should be used to provide an indication of the burden of infection. For diagnosis of *S. haematobium* infection, a volume of 10 mL of urine should be collected around midday, the time of maximal egg excretion, and filtered for microscopic examination. Stool examination by the Kato-Katz thick smear procedure and detection of parasite antigen in patient serum or urine are the methods of choice for diagnosis and quantification of other schistosome infections (*S. mansoni* and *S. japonicum*). The unique schistosome antigens *circulating anodic antigen* (CAA) and *circulating cathodic antigen* (CCA) may also be detected in the urine or plasma.

Treatment

Treatment of children with schistosomiasis should be based on an appreciation of the intensity of infection and the extent of disease. The recommended treatment for schistosomiasis is **praziquantel** (40 mg/kg/day orally [PO] divided twice daily [bid] for 1 day for schistosomiasis haematobia, mansoni, and intercalatum; 60 mg/kg/day PO divided 3 times daily [tid] for 1 day for schistosomiasis japonica and mekongi). Children <5 yr old with *S. mansoni* may need up to 60 mg/kg/day PO tid for 1 day to achieve clearance. A 2nd treatment 4-6 wk after the 1st course may help in eliminating residual infection.

Prevention

Transmission in endemic areas may be decreased by reducing the parasite load in the human population. The availability of oral, single-dose, effective chemotherapeutic agents may help achieve this goal. When added to national drug-based control programs, other measures such as improved sanitation, antiparasitic treatment given at well-child visits, focal application of molluscicidals, and animal vaccination may prove useful in breaking the cycle of transmission. Ultimately, control of schistosomiasis is closely linked to economic and social development.

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CHAPTER 327

Flukes (Liver, Lung, and Intestinal)

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Several different **trematodes** , or flukes, can parasitize humans and cause disease. Flukes are endemic worldwide but are more prevalent in the less developed parts of the world. They include *Schistosoma*, or the blood flukes (see Chapter 326), as well as fluke species that cause infection in the human biliary tree, lung tissue, and intestinal tract. These latter trematodes are characterized by complex life cycles (Fig. 327.1). Sexual reproduction of adult worms in the definitive host produces eggs that are passed in the stool. Larvae, called **miracidia** , develop in freshwater. These in turn infect certain species of mollusks (aquatic snails or clams), in which asexual multiplication by parasite larvae produces cercariae. Cercariae then seek a 2nd intermediate host, such as an insect, crustacean, or fish, or attach to vegetation to produce infectious **metacercariae** . Humans acquire liver, lung, and intestinal fluke infections by eating uncooked, lightly cooked, pickled, or smoked foods containing these infectious parasite cysts. The “alternation of generations” requires that flukes parasitize more than 1 host (often 3) to complete their life cycle. Because parasitic flukes are dependent on these nonhuman species for transmission, the distribution of human fluke infection closely matches the ecologic range of the flukes’ intermediate hosts. As a group, these parasites are commonly referred to as **food-borne trematodes** .

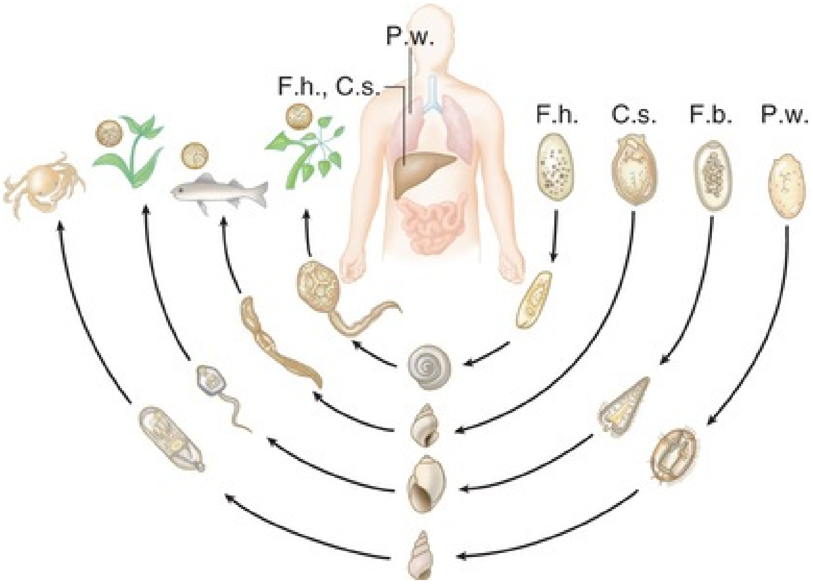

FIG. 327.1 **Life cycle of parasitic liver, lung, and intestinal flukes. C.s., *Clonorchis sinensis* ; F.b., *Fasciolopsis buski* ; F.h., *Fasciola hepatica* ; P.w., *Paragonimus westermani.* (Adapted from Mandell GL, Bennett JE, Dolin R, editors: *Principles and practice of infectious diseases* , ed 7, Philadelphia, 2010, Elsevier, Fig 289-2.)**

Liver Flukes

Fascioliasis *(Fasciola hepatica)*

Fasciola hepatica, the sheep liver fluke, infects cattle, other ungulates, and occasionally humans. This infection affects approximately 17 million people worldwide and has been reported in many different parts of the world, particularly South America, Europe, Africa, China, Australia, and Cuba. Although *F. hepatica* is enzootic in North America, reported cases are extremely rare. Humans are infected by ingestion of metacercariae attached to vegetation, especially wild watercress, lettuce, and alfalfa. In the duodenum, the parasites excyst and penetrate the intestinal wall, liver capsule, and parenchyma. They wander for a few weeks before entering the bile ducts, where they mature. Adult *F. hepatica* (1-2.5 cm) commence oviposition approximately 12 wk after infection; the eggs are large (75-140 µm) and operculated. They pass to the intestines with bile and exit the body in the feces (see Fig. 327.1). On reaching freshwater, the eggs mature and hatch into miracidia, which infect specific snail intermediate hosts to multiply into many cercariae. These then emerge from infected snails and encyst on aquatic grasses and plants.

Clinical manifestations usually occur either during the liver migratory phase of the parasites or after their arrival at their final habitat in upper bile ducts. Fever, right upper quadrant pain, and hepatosplenomegaly characterize the 1st phase of illness. Peripheral blood eosinophilia is usually marked. As the worms enter bile ducts, most of the acute symptoms subside. On rare occasions, patients may have obstructive jaundice or biliary cirrhosis, with signs of cholestasis, ascending cholangitis, cholelithiasis and jaundice and increased liver enzymes, direct bilirubin, and γ-glutamyl transpeptidase. *F. hepatica* infection is diagnosed by identifying the characteristic eggs in fecal smears or duodenal aspirates. **Diagnosis** can be suggested by positive serology and imaging that reveals acute, hypodense liver lesions that change over time. Presentation can be dramatic in children, with features including generalized edema, hepatic cirrhosis with esophageal varices, and in severe cases, death from generalized organ failure.

The recommended **treatment** of fascioliasis is triclabendazole (10 mg/kg orally [PO] once or twice) or bithionol (30-50 mg/kg PO once daily on alternate days for a total of 10-15 doses). In the United States, bithionol is not generally available, but may be available from compounding pharmacies.

Clonorchiasis *(Clonorchis sinensis)*

Infection of bile passages with *Clonorchis sinensis*, the Chinese or oriental liver fluke, is endemic in China, South Korea, northern Vietnam, and parts of Russia and Japan, affecting more than 15 million people. Humans acquire infection by ingestion of raw or inadequately cooked freshwater fish carrying the encysted metacercariae of the parasite under their scales or skin. Metacercariae excyst in the duodenum and pass through the ampulla of Vater to the common bile duct and bile capillaries, where they mature into hermaphroditic adult worms (3-15 mm). *C. sinensis* worms deposit small operculated eggs (14-30 µm), which are discharged through the bile duct to the intestine and feces (see Fig. 327.1). The eggs mature and hatch outside the body, releasing motile miracidia into local freshwater streams, rivers, or ponds. If these are taken up by the appropriate snails, they develop into cercariae, which are in turn released from the snail to encyst under the skin or scales of freshwater fish.

Most individuals with *C. sinensis* infection, particularly those with few organisms, are minimally symptomatic. Among heavily infected individuals, who tend to be older (>30 yr), localized obstruction of a bile duct results from repeated local trauma and inflammation. In these patients, cholangitis and cholangiohepatitis may lead to liver enlargement and jaundice. In Hong Kong, Korea, and other parts of Asia, cholangiocarcinoma is associated with chronic *C. sinensis* infection.

Clonorchiasis is diagnosed by examination of feces or duodenal aspirates for the parasite eggs. The recommended **treatment** of clonorchiasis is praziquantel (75 mg/kg/day PO divided 3 times daily [tid] for 2 days). An alternative, used in adults, is albendazole (10 mg/kg once daily PO for 7 days). Tribendimidine (400 mg PO for 3 days) has been recently used in China with good cure rates.

Opisthorchiasis (*Opisthorchis* spp.)

Infections with species of *Opisthorchis* are clinically similar to those caused by *C. sinensis. Opisthorchis felineus* and *Opisthorchis viverrini* are liver flukes of cats and dogs that infect humans through ingestion of metacercariae in freshwater fish. Infection with *O. felineus* is endemic in Eastern Europe and Southeast Asia, and *O. viverrini* is found mainly in Thailand, affecting an estimated 10 million people. Most individuals are minimally symptomatic; liver enlargement, relapsing cholangitis, and jaundice may occur in heavily infected individuals. Diagnosis is based on recovering eggs from stools or duodenal aspirates. The recommended **treatment** of opisthorchiasis is praziquantel (75 mg/kg/day PO tid for 2 days).

Lung Flukes

Paragonimiasis (*Paragonimus* spp.)

Human infection by the lung fluke *Paragonimus westermani,* and less frequently other species of *Paragonimus,* occurs throughout the Far East, in localized areas of West Africa, and in several parts of Central and South America, affecting approximately 20 million people. The highest incidence of paragonimiasis occurs in older children and adolescents 11-15 yr of age. Although *P. westermani* is found in many carnivores, human cases are relatively rare and seem to be associated with specific dietary habits, such as eating raw freshwater crayfish or crabs. These crustaceans contain the infective metacercariae in their tissues. After ingestion, the metacercariae excyst in the duodenum, penetrate the intestinal wall, and migrate to their final habitat in the lungs. Adult worms (5-10 mm) encapsulate within the lung parenchyma and deposit brown operculated eggs (60-100 µm) that pass into the bronchioles and are expectorated by coughing (see Fig. 327.1). Ova can be detected in the sputum of infected individuals or in their feces. If eggs reach freshwater, they hatch and undergo asexual multiplication in specific snails. The cercariae encyst in the muscles and viscera of crayfish and freshwater crabs.

Most individuals infected with *P. westermani* harbor low or moderate worm loads and are minimally symptomatic. The clinical manifestations include cough, production of rust-colored sputum, and hemoptysis (mimicking tuberculosis), which is the principal manifestation and occurs in 98% of symptomatic children. There are no characteristic physical findings, but laboratory examination usually demonstrates marked eosinophilia. Chest radiographs often reveal small, patchy infiltrates or radiolucencies in the middle lung fields; however, radiographs may appear normal in one fifth of infected individuals. In rare circumstances, lung abscess, pleural or pericardial effusion, or bronchiectasis may develop. Extrapulmonary localization of *P. westermani* in the brain, peritoneum, intestines, or pericardium may rarely occur. Cerebral paragonimiasis occurs primarily in heavily infected individuals living in highly endemic areas of the Far East. The clinical presentation resembles jacksonian epilepsy or the symptoms of cerebral tumors.

Definitive diagnosis of paragonimiasis is established by identification of eggs in fecal or sputum smears. The recommended **treatment** of paragonimiasis is praziquantel (75 mg/kg/day PO tid for 2 days). Triclabendazole can also be used (10 mg/kg PO daily for 1-2 days).

Intestinal Flukes

Several wild and domestic animal intestinal flukes, including *Fasciolopsis buski*, *Nanophyetus salmincola*, and *Heterophyes heterophyes*, may accidentally infect humans who eat uncooked or undercooked fish or water plants. For example, *F. buski* is endemic in the Far East, where humans who ingest metacercariae encysted on aquatic plants become infected. These develop into large flukes (1-5 cm) that inhabit the duodenum and jejunum. Mature worms produce operculated eggs that pass with feces; the organism completes its life cycle through specific snail intermediate hosts. Individuals with *F. buski* infection are usually asymptomatic; heavily infected patients complain of abdominal pain and diarrhea and show signs of malabsorption. Diagnosis of fasciolopsiasis and other intestinal fluke infections is established by fecal examination and identification of the eggs (see Fig. 327.1). As for other fluke infections, praziquantel (75 mg/kg/day PO tid for 2 days) is the drug of choice.

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CHAPTER 328

Adult Tapeworm Infections

Philip R. Fischer, A. Clinton White Jr

Tapeworms are adult forms of **cestodes** , multicellular helminth parasites, that live in human intestines and cause non–life-threatening illness. Invasive larval forms of cestodes are associated with cysts that lead to severe human disease such as neurocysticercosis (*Taenia solium* ; see Chapter 329) and echinococcosis (mostly *Echinococcus granulosa* and *E. multilocularis* ; Chapter 330). The adult worms themselves are flat and multisegmented, varying in length from 8 mm to 10 meters (m). Table 328.1 summarizes the key features of tapeworms that affect children.

Table 328.1

Key Features of Common Tapeworms in Children

PARASITE SPECIES	GEOGRAPHY	SOURCE	SYMPTOMS	TREATMENT
Taenia saginata	Asia, Africa, Latin America	Cysts in beef	Abdominal discomfort, motile proglottid migration, passing segments	Praziquantel *or* niclosamide, possibly nitazoxanide
Taenia solium	Asia, Africa, Latin America	Cysticerci in pork	Minimal, proglottids in stool	Praziquantel *or* niclosamide, possibly nitazoxanide
Taenia asiatica	Asia	Pigs	Minimal	Praziquantel *or* niclosamide, possibly nitazoxanide
Diphyllobothrium spp.	Worldwide, often northern areas	Plerocercoid cysts in freshwater fish	Usually minimal; with prolonged or heavy infection with *D. latum* , vitamin B_{12} deficiency	Praziquantel *or* niclosamide
Hymenolepis	Worldwide, often northern	Infected humans,	Mild abdominal discomfort	Praziquantel, niclosamide, *or*

	areas	rodents		nitazoxanide
Dipylidium caninum	Worldwide	Domestic dogs and cats	Proglottids in stool, anal pruritus confused with pinworm	Praziquantel *or* niclosamide

Etiology

The **beef tapeworm** *(Taenia saginata)* , the **pork tapeworm** *(T. solium)*, and the Asian tapeworm *(Taenia asiatica)* are long worms (4-10 m) named for their intermediate hosts (*T. saginata* , *T. solium*) or geographic distribution (*T. asiatica* ; larval host is the pig). The adult worms are found only in the human intestine. As with the adult stage of all tapeworms, their body is a series of 100s or 1000s of flattened segments (**proglottids**) with an anterior attachment organ **(scolex)** that anchors the parasite to the bowel wall. New segments arise from the distal aspect of the scolex with progressively more mature segments attached distally. The gravid terminal segments contain 50,000-100,000 eggs, and the eggs or even detached intact proglottids pass out of the child through the anus (with or separate from defecation). These tapeworms differ most significantly in that the intermediate stage of the pork tapeworm (**cysticercus**) can also infect humans and cause significant morbidity (see Chapter 329), whereas the larval stage of *T. saginata* does not cause human disease. *T. asiatica* is similar to and often confused with the beef tapeworm.

Epidemiology

The pork and beef tapeworms are distributed worldwide, with the highest risk for infection in Latin America, Africa, India, Southeast Asia, and China, where the relevant intermediate host is raised domestically. The prevalence in adults may not reflect the prevalence in young children, because cultural practices may dictate how well meat is cooked and how much is served to children.

Pathogenesis

When children ingest raw or undercooked meat containing larval cysts, gastric acid and bile facilitate release of immature scolices that attach to the lumen of the small intestine. The parasite grows, adding new segments at the base of the scolex. The terminal segments mature and after 2-3 mo produce eggs that are released in stool. The surface of proglottids serves as an absorptive organ to “steal” nutritional elements from the child's small bowel for use by the parasite. There is sometimes a transient eosinophilia before the parasite matures enough to release eggs.

Clinical Manifestations

Nonspecific abdominal symptoms have been reported with beef and pork tapeworm infections, but the most bothersome symptom is the psychologic distress caused by seeing proglottids in the stool or undergarments. The released segments of the worms are motile (especially those of *T. saginata*) and sometimes lead to anal pruritus. The adult beef and pork tapeworms are only rarely associated with other symptoms.

Diagnosis

Identification of the infecting tapeworm species facilitates understanding of risk for invasive disease. Carriers of adult pork tapeworms are at increased risk for transmitting eggs with the pathogenic intermediate stage (cysticercus) to themselves or others, whereas children infected with the beef tapeworm or *T. asiatica* are a risk only to livestock. Because proglottids are generally passed intact, visual examination for gravid proglottids in the stool is a sensitive test; these segments may be used to identify species. Eggs, by contrast, are often absent from stool and cannot distinguish between *T. saginata* and *T. solium* (Fig. 328.1). If the parasite is completely expelled, the scolex of each species is diagnostic. The scolex of *T. saginata* has only a set of 4 anteriorly oriented suckers, whereas *T. solium* is armed with a double row of hooks in addition to suckers. The proglottids of *T. saginata* have >20 branches from a central uterine structure, and the proglottids of *T. solium* have ≤10 branches. Expelled proglottid segments are usually approximately 0.5 × 1-2 × 0.1 cm in size. Molecular methods can distinguish *T. saginata* from *T. asiatica* . Antigen detection tests are increasingly available.

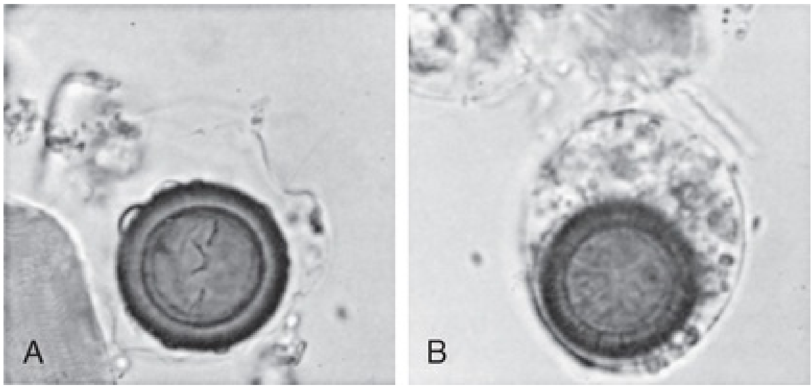

FIG. 328.1 Eggs of *Taenia saginata* recovered from feces (original magnification ×400). A and B, The eggs are generally bile-stained, dark, and prismatic. There is occasionally some surrounding cellular material from the proglottid in which the egg develops, which is more evident in B than in A. The larva within the egg shows 3 pairs of hooklets (A), which may occasionally be observed in motion.

Differential Diagnosis

Anal pruritus may mimic symptoms of pinworm *(Enterobius vermicularis)* infection. *Diphyllobothrium latum* and *Ascaris lumbricoides* (a long round worm) may be mistaken for *T. saginata* or *T. solium* in stools.

Treatment

Infections with all adult tapeworms respond to praziquantel (25 mg/kg orally [PO] once). When available, an alternative treatment for **taeniasis** is niclosamide (50 mg/kg PO once for children; 2 g PO once for adults). Nitazoxanide is sometimes effective as well. The parasite is usually expelled on the day of administration. Treatment with electrolyte–polyethylene glycol bowel preparations can increase the yield of passage of scolices.

Prevention

Prolonged freezing or thorough cooking of beef and pork kills the larval cystic forms of the parasite. Appropriate human sanitation can interrupt transmission by preventing infection in livestock.

Diphyllobothriasis (*Diphyllobothrium*

Spp.)

Etiology

The **fish tapeworms** of the genus *Diphyllobothrium* are the longest human tapeworms, reaching >10 m in length, and have an anatomic organization similar to that of other adult cestodes. An elongated scolex, equipped with slits (**bothria**) along each side but no suckers or hooks, is followed by 1000s of segments looped in the small bowel. Gravid terminal proglottids detach periodically but tend to disintegrate before expulsion, thus releasing eggs rather than intact worm segments in the feces. In contrast to taeniids, the life cycle of *Diphyllobothrium* spp. requires 2 intermediate hosts. Small, freshwater crustaceans (copepods) take up the larvae that hatch from parasite eggs. The parasite passes up the food chain as small fish eat the copepods and are in turn eaten by larger fish. In this way, the juvenile parasite becomes concentrated in pike, walleye, perch, burbot, and perhaps salmon associated with aquaculture. Consumption of raw or undercooked fish leads to human infection with adult fish tapeworms.

Epidemiology

The fish tapeworm is most prevalent in the temperate climates of Europe, North America, and Asia but may be found along the Pacific coast of South America and in Africa. In North America the prevalence is highest in Alaska, Canada, and northern areas of continental United States. The tapeworm is found in fish from those areas that are then taken to market. Persons who prepare raw fish for home or commercial use or who sample fish before cooking are particularly at risk for infection.

Pathogenesis

The adult worm of *Diphyllobothrium latum* (found in northern Europe) has high-affinity receptors and efficiently scavenges vitamin B_{12} for its own use in the constant production of large numbers of segments and as many as 1 million eggs per day. As a result, diphyllobothriasis causes **megaloblastic anemia** in 2–9% of infections. Interestingly, other *Diphyllobothrium* spp. do not out-compete the host for vitamin B_{12} . Children with other causes of vitamin B_{12} or folate deficiency, such as chronic infectious diarrhea, celiac disease, or congenital malabsorption, are more likely to develop symptomatic infection.

Clinical Manifestations

Infection is largely asymptomatic. Segments may be noted in stool. Those who develop vitamin B_{12} or folate deficiency present with megaloblastic anemia with leukopenia, thrombocytopenia, glossitis, and/or signs of spinal cord posterior column dysfunction (loss of vibratory sense, proprioception, and coordination).

Diagnosis

Parasitological examination of the stool is useful because eggs are abundant in the feces and have morphology distinct from that of all other tapeworms. The eggs are ovoid and have an **operculum** , which is a cap structure at one end that opens to release the embryo (Fig. 328.2). The worm itself has a distinct scolex and proglottid morphology; however, these are not likely to be passed spontaneously.

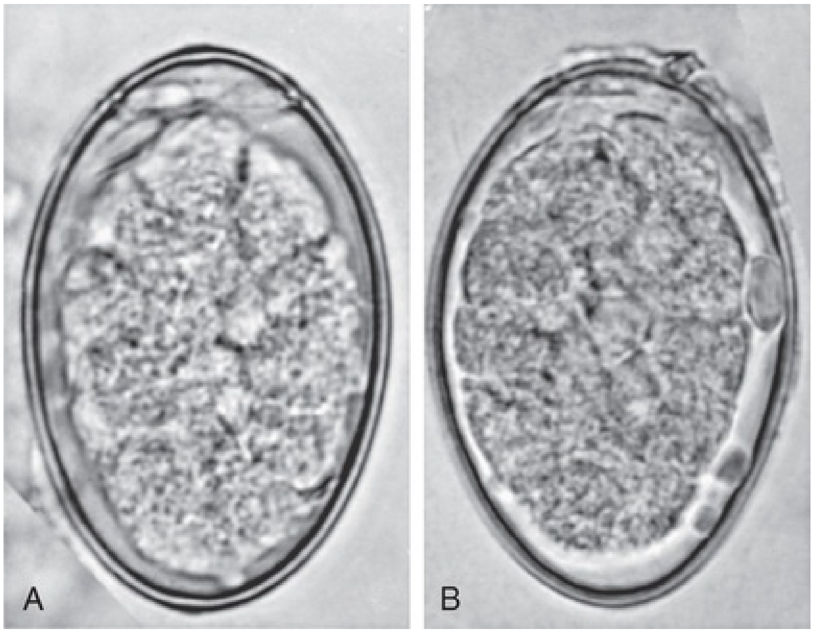

FIG. 328.2 **Eggs of *Diphyllobothrium latum* as seen in feces (original magnification ×400). A and B, The caplike operculum is at the upper end of the eggs here.**

Differential Diagnosis

A segment or a whole section of the worm might be confused with *Taenia* or *Ascaris* after it is passed. Pernicious anemia, bone marrow toxins, and dietary restriction may contribute to or mimic the nutritional deficiencies associated with diphyllobothriasis.

Treatment

As with all adult tapeworms, *D. latum* infections respond to praziquantel (5-10 mg/kg PO once). Niclosamide (50 mg/kg PO in a single dose) is also effective.

Prevention

The intermediate stage is easily killed by brief cooking or prolonged freezing of fish before ingestion. Because humans are the major reservoir for adult worms, health education is one of the most important tools for preventing transmission, together with improved human sanitation.

Hymenolepiasis *(Hymenolepis)*

Infection with *Hymenolepis nana,* the **dwarf tapeworm,** is very common in developing countries. Most cases are asymptomatic. However, heavy infection has been associated with diarrhea, weight loss, fever, and eosinophilia. The intermediate stage of *Hymenolepis diminuta* develops in various hosts (e.g., rodents, ticks, fleas), but the entire life cycle of *H. nana* is completed in humans. Therefore, hyperinfection with 1000s of small adult worms in a single child may occur. A similar infection may occur less often with *H. diminuta*. Eggs but not segments may be found in the stool. *H. nana* infection responds to praziquantel (25 mg/kg PO once). Nitazoxanide is effective in about three fourths of children (100 mg PO twice daily [bid] for 3 days for children 1-3 yr old, 200 mg bid for 3 days for children 4-11 yr old, and 500 mg bid for 3 days for older children).

Dipylidiasis *(Dipylidium Caninum)*

Dipylidium caninum is a common tapeworm of domestic dogs and cats. Human infection is relatively rare. Direct transmission between pets and humans does not occur; human infection requires ingestion of the parasite's intermediate host, the dog or cat flea. Infants and small children are particularly susceptible because of their level of hygiene, generally more intimate contact with pets, and activities in areas where fleas can be encountered. Thus, children are most at risk of inadvertent ingestion of fleas infected with the larvae. The most common symptom is passage of proglottids in stool. The proglottids are similar in size and shape to white rice grains. Anal pruritus, vague abdominal pain, and diarrhea have at times been associated with dipylidiasis, which is thus sometimes confused with pinworm *(E. vermicularis).* Dipylidiasis responds to treatment with praziquantel (5-10 mg/kg PO once) and niclosamide (50 mg/kg PO as a single dose). **Deworming** of pets and **flea control** are the best preventive measures.

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CHAPTER 329

Cysticercosis

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Etiology

Taenia solium, also known as the **pork tapeworm** , causes 2 different infections in children. In its normal life cycle, children can acquire the tapeworm form by ingestion of undercooked pork containing the larval cysts (see Chapter 328). In the intestines, the cyst converts into the tapeworm form. Children are also susceptible to infection by the eggs shed by tapeworm carriers. After the eggs are ingested, the larvae are released from the eggs, invade through the intestines, and migrate through the bloodstream to the muscles (and other organs), where they form tissue cysts (0.2-2.0 cm fluid-filled bladders containing a single invaginated **scolex**). Infection with the cystic form is termed **cysticercosis** , and involvement of the central nervous system (CNS) is termed **neurocysticercosis.** The tapeworm form only develops after ingestion of undercooked pork. Ingestion of pork is not necessary to develop cysticercosis, but individuals harboring an adult worm may infect themselves with the eggs by the fecal-oral route.

Epidemiology

The pork tapeworm is widely distributed wherever pigs are raised and have contact with human fecal material. Intense transmission occurs in Central and South America, southern and Southeast Asia, and much of sub-Saharan Africa. In these areas, approximately 30% of cases of seizures may be a result of cysticercosis. Most cases of cysticercosis in the United States are imported; however, local transmission has been documented.

Pathogenesis

Living, intact cystic stages usually suppress the host immune and inflammatory responses. Intact cysts can be associated with disease when they obstruct the flow of cerebrospinal fluid. Most cysts remain asymptomatic for a few years. Symptoms typically develop as the cysticerci begin to degenerate, associated with a host inflammatory response. The natural history of cysts is eventually to resolve by complete resorption or calcification, but this process may take years. Cysticerci can also present as subcutaneous nodules, ocular infection, or spinal lesions with myelopathy or radiculopathy.

Clinical Manifestations

Seizures are the presenting finding in the vast majority of children with neurocysticercosis. Less common manifestations include hydrocephalus, diffuse cerebral edema, or focal neurologic findings. It is important to classify neurocysticercosis as parenchymal, intraventricular, subarachnoid, spinal, or ocular on the basis of anatomic location, clinical presentation, and radiologic appearance, since the prognosis and management vary with location.

Parenchymal neurocysticercosis typically presents with seizures. The seizures are usually focal, but often generalize. Children may present with a single seizure or recurrent epilepsy. Mild neurocognitive defects have been documented from cysticerci alone but are more commonly associated with poorly controlled seizures. A fulminant encephalitis-like presentation may rarely occur after a massive initial infection associated with cerebral edema. **Intraventricular** neurocysticercosis (up to 20% of cases) is associated with obstructive hydrocephalus and acute, subacute, or intermittent signs of increased intracranial pressure, usually without localizing signs. **Subarachnoid** neurocysticercosis is rare in children. It can be associated with basilar arachnoiditis that can present with signs of meningeal irritation, communicating hydrocephalus, cerebral infarction, or **spinal** disease with radiculitis or transverse myelitis. Cysticerci in the tissues may present with focal findings from mass effect. **Ocular** neurocysticercosis causes decreased visual acuity because of cysticerci in the retina or vitreous, retinal detachment, or iridocyclitis.

Diagnosis

Neurocysticercosis should be suspected in a child with onset of seizures or hydrocephalus and who also has a history of residence in an endemic area and/or a care provider from an endemic area. The most useful diagnostic study for parenchymal disease is MRI of the head. MRI provides the most information about cyst location, cyst viability, and associated inflammation. The **protoscolex** is sometimes visible within the cyst, which provides a pathognomonic sign for cysticercosis (Fig. 329.1*A*). The MRI also better detects basilar arachnoiditis (Fig. 329.1*B*), intraventricular cysts (Fig. 329.1*C*), and cysts in the spinal cord. CT is best for identifying calcifications. A solitary parenchymal cyst, with or without contrast enhancement, or CNS calcifications are the most common findings in children (Fig. 329.2). Plain films may reveal calcifications in muscle or brain consistent with cysticercosis. In children from endemic regions, the presentation with a single enhancing lesion that is round and <2 cm in diameter, absence of symptoms or signs of other diseases (e.g., no fever or lymph nodes), no focal findings, and no evidence of increased intracranial pressure is highly specific for neurocysticercosis.

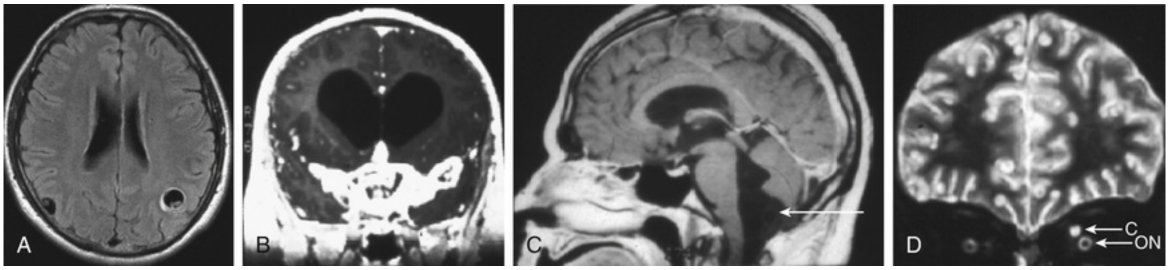

FIG. 329.1 Neurocysticercosis. A, MRI (T1 weighted) demonstrating 2 parenchymal cysts with protoscoleces. B, MRI (T1 weighted) of cysticercal basilar arachnoiditis. C, MRI (T1 weighted) showing a cyst below the fourth ventricle *(arrow).* D, MRI (T2 weighted) showing a cysticercus (C) above the optic nerve (ON).

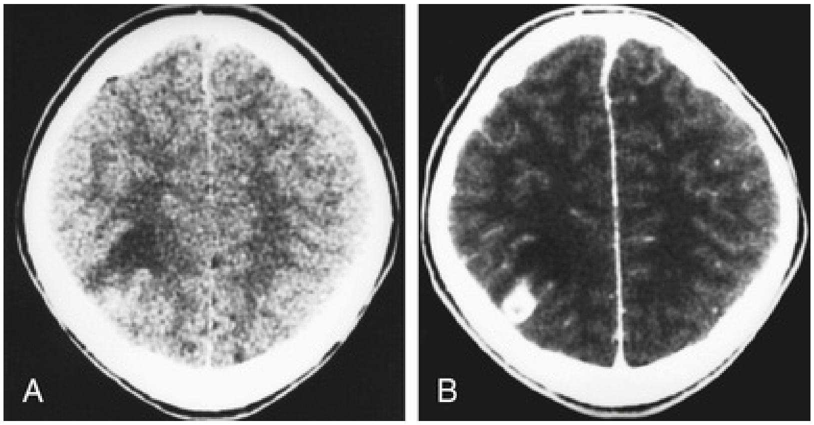

FIG. 329.2 Neurocysticercosis. CT image of a solitary lesion with (A) and without (B) contrast, showing contrast enhancement. (Courtesy of Dr. Wendy G. Mitchell and Dr. Marvin D. Nelson, Children's Hospital, Los Angeles.)

Serologic diagnosis using the enzyme-linked immunotransfer blot is available commercially in the United States and through the Centers for Disease Control and Prevention (CDC). Serum antibody testing is highly specific but is frequently negative in children with single lesions or just calcifications. Antigen-detection assays and polymerase chain reaction assays show promise as diagnostic procedures but currently are not commercially available in the United States.

Differential Diagnosis

Neurocysticercosis is often confused clinically with other seizure disorders. Clinical suspicion is based on travel history, a history of contact with an individual who might carry an adult tapeworm, or suggestive imaging studies. The imaging appearance can be confused with brain abscess, granulomas (including tuberculomas, fungal infections, Langerhans histiocytosis, and toxoplasmosis), and tumors.

Treatment

The initial management of cysticercosis should focus on symptomatic therapy for seizures and/or hydrocephalus. Seizures can usually be controlled using standard antiepileptic drugs. If the lesions resolve, antiepileptic drugs can often be tapered and stopped. Frequent seizures or the development of calcified lesions are risk factors for recurrent seizures and indications for prolonged or lifelong antiepileptic therapy.

The natural history of **parenchymal** lesions is to resolve spontaneously, with or without antiparasitic drugs, but this process is often prolonged (months to years). Solitary parenchymal cysts resolve slightly more rapidly with antiparasitic therapy. Antiparasitic drugs also decrease the frequency of recurrent seizures. Other forms of the disease are less common in children. In adults with cystic lesions, randomized controlled trials suggested an overall 2-fold decrease in recurrence of generalized seizures with albendazole treatment. The benefit to children was significantly less, perhaps because most of these infections were with only 1-2 cysts. Corticosteroids likely also decrease seizure frequency.

The most commonly used antiparasitic is **albendazole** (15 mg/kg/day orally [PO] divided twice daily [bid]). It can be taken with a fatty meal to improve absorption. The most common duration of therapy is 7 days for single parenchymal lesions. However, longer duration (months), higher doses (up to 30 mg/kg/day), or combination therapy with praziquantel is often required for multiple lesions or subarachnoid disease. For example, in adults with more than 2 cysticerci, recent trials note improved resolution with combination therapy with albendazole, praziquantel, and corticosteroids. **Praziquantel** (50-100 mg/kg/day PO divided 3 times daily [tid] for 28 days) can be used with albendazole or as an alternative to it. First-pass metabolism is common with corticosteroids or antiepileptic drugs. **Cimetidine** can be used in conjunction with praziquantel to blunt the first-pass metabolism. A worsening of symptoms can follow the use of either drug based on the host's inflammatory response to the dying parasite. Patients should be medicated with prednisone (1-2 mg/kg/day) or oral dexamethasone (0.15 mg/kg/day) beginning before the 1st dose of antiparasitic drugs and continuing for at least 2 wk. **Methotrexate** can be used as a steroid-sparing agent in patients requiring prolonged antiinflammatory therapy.

Most patients with hydrocephalus require neurosurgical interventions. Some cases require emergent placement of a ventriculostomy, but most can be managed by cystectomy alone. For obstructive hydrocephalus caused by ventricular cysticercosis, many patients can be cured by minimally invasive surgery. **Neuroendoscopy** is the preferred approach to cysticerci in the lateral or 3rd ventricle. Cysticerci in the 4th ventricle can be removed by a suboccipital craniotomy. There are also reports of endoscopic removal of 4th ventricular cysticerci using flexible neuroendoscopy. Adherent cysticerci that cannot be removed can be treated by placement of a ventriculoperitoneal shunt (VPS).

However, there is a high rate of shunt failure, which can be minimized somewhat by treatment with antiparasitic drugs plus corticosteroids.

Subarachnoid disease has a poor prognosis. The prognosis is much improved by aggressive therapy, including antiparasitic drugs, antiinflammatory treatment, and neurosurgical procedures for hydrocephalus (e.g., VPS placement). However, the duration of antiparasitic and antiinflammatory therapy often needs to be prolonged. **Ocular** cysticercosis is usually treated surgically, although there are reports of cure using medical therapy alone.

Prevention

In areas with evolved public health systems, cysticercosis can largely be eliminated by meat inspection, condemnation of infected meat, and thorough cooking of pork. This approach has not worked in countries where most meat is butchered informally. Mass chemotherapy for tapeworm carriers, mass treatment of pigs, and improved personal hygiene have decreased or eliminated transmission in some areas. Screening family members and those preparing food for index cases for cysticercosis has a very low yield, in part because of the poor sensitivity of current tests. Those who have noted passing material consistent with taeniasis should be treated with praziquantel regardless of the results of stool studies. Veterinary vaccines for several cestode infections have a high degree of efficacy and have a potential role in decreasing parasite transmission.

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CHAPTER 330

Echinococcosis (*Echinococcus granulosus* and *Echinococcus multilocularis*)

Miguel M. Cabada, Philip R. Fischer, A. Clinton White Jr.

Etiology

Echinococcosis (**hydatid disease** or **hydatidosis**) is a widespread, serious human cestode infection (Fig. 330.1). Two major *Echinococcus* groups of species are responsible for distinct clinical presentations. *Echinococcus granulosus* and related species cause **cystic hydatid disease, and** *Echinococcus multilocularis* causes **alveolar hydatid disease** . The adult parasites are small (2-7 mm) tapeworms with only 2-6 segments that inhabit the intestines of canines such as dogs, wolves, dingoes, jackals, coyotes, and foxes. Canines are infected by ingesting contaminated viscera from ungulates (*E. granulosus*) or mice (*E. multilocularis*). These carnivores pass the eggs in their stool, which contaminates the soil, pasture, and water, as well as their own fur. Domestic animals, such as sheep, goats, cattle, and camels, ingest *E. granulosus* complex eggs while grazing. Some species of *E. granulosus* complex have a **sylvatic** cycle involving wild cervids such as moose, elk, and deer. For *E. multilocularis* , the main intermediate hosts are small rodents. Humans are infected by consuming eggs by direct contact with infected canines or from ova in the environment. In Europe, contamination of gardens by fox excrement is a major risk factor for transmission. The larvae hatch, penetrate the gut, and are carried by the vascular or lymphatic systems to the liver, lungs, and less frequently, bones, kidney, brain, or heart in *E. granulosus* infection. *E. multilocularis* larvae infect the liver almost exclusively.

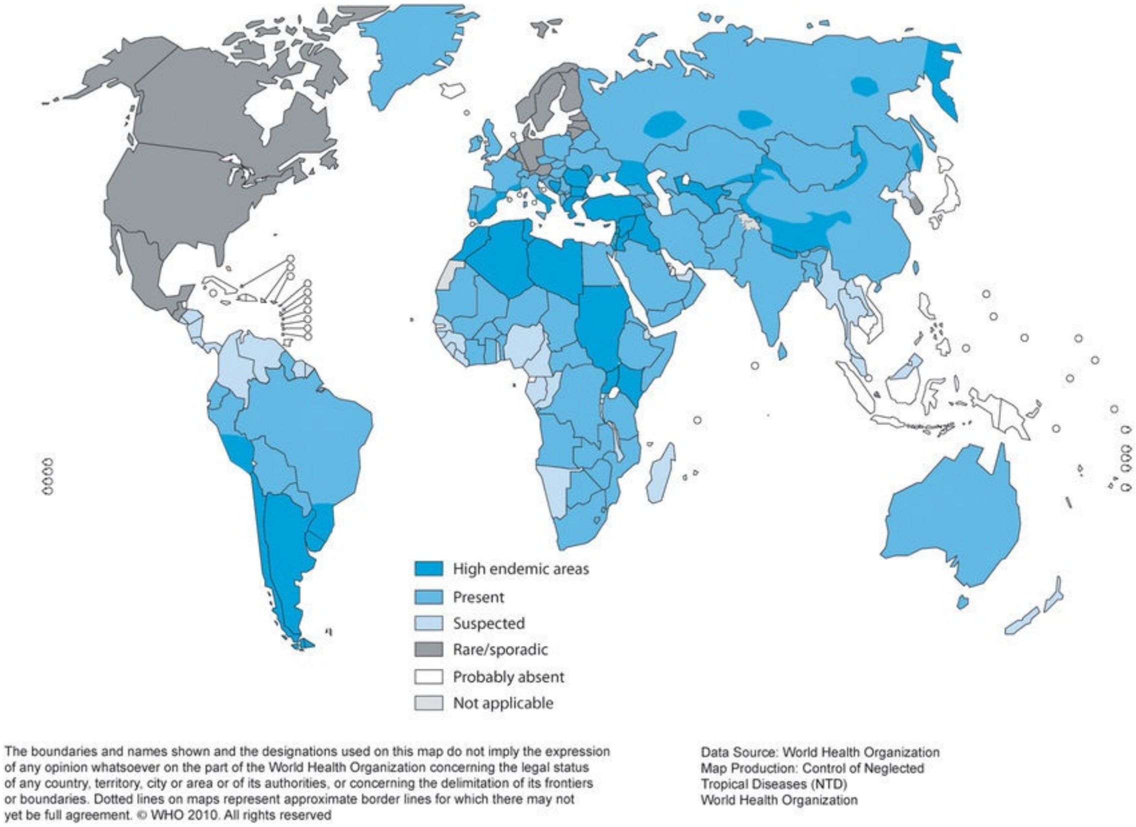
High endemic areas
Present
Suspected
Rare/sporadic
Probably absent
Not applicable
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2010. All rights reserved
Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

FIG. 330.1 **Worldwide distribution of *Echinococcus granulosus* and cystic echinococcosis (hydatidosis), 2009. (From Control of Neglected Tropical Diseases. © World Health Organization, 2011. http://gamapserver.who.int/mapLibrary/Files/Maps/Global_echinococcosis_2009.png.)**

Echinococcus granulosus complex comprises several recognized species previously arranged in genotype groups. These are *E. granulosussensustricto* (G1-G3), *E. equinus* (G4), *E. ortleppi* (G5), and *E. canadensis* (G6-G10). The species within the *E. granulosus* complex show significant variation not only in genetics but also in ecology. While *E. granulosussensustricto* is mainly found in domesticated ovines and dogs around the world, *E. canadensis* is found in a sylvatic wolf/moose cycle in North America and Siberia and has been identified in bovines and swine in South America.

Epidemiology

There is potential for transmission of *E. granulosus* to humans wherever dogs are allowed to ingest the entrails of herd animals. Cysts have been detected in up to 10% of the human population in northern Kenya and western China. Disease is highly endemic in the Middle East and Central Asia. In South America, the disease is prevalent in sheepherding areas of the Andes, the beef-herding areas of the Brazilian/Argentine Pampas, and Uruguay. Among developed countries, the disease is recognized in Italy, Greece, Portugal, Spain, and Australia, and is reemergent in dogs in Great Britain. In North America, transmission rarely occurs through a sylvatic cycle in the Arctic, as well as in foci of the domestic cycle in sheep-raising areas of western United States.

Transmission of *E. multilocularis* occurs primarily in Western China, Central Europe, Siberia, and Turkey. Transmission is now rare in the Arctic regions of North America. Ingestion of infected rodents by dogs or foxes facilitates transmissions to children. Separate species, *E. vogeli* and *E. oligarthrus* , have mainly a sylvatic cycle involving canines and felines that causes polycystic disease in northern South America.

Pathogenesis

E. granulosus complex parasites are often acquired in childhood, but cysts require many years to become large enough to be detected or cause symptoms. In children the lung is a common site, whereas in adults up to 70% of cysts develop in the liver. Cysts can also develop in bone, the genitourinary system, spleen, subcutaneous tissues, and brain. The host surrounds the primary cyst with a tough, fibrous capsule. Inside this capsule, the parasite produces a thick lamellar layer with the consistency of a soft-boiled egg white. Inside the lamellar layer is the thin germinal layer of cells responsible for production of 1000s of protoscoleces that remain attached to the wall or float free in the cyst fluid (Video 330.1 ▶). Smaller internal daughter cysts may develop within the primary cyst capsule. The fluid in a healthy cyst is clear, colorless, and watery. Rupture of the cyst, which can occur spontaneously, with trauma, or during surgery, can be associated with immediate hypersensitivity reactions, including anaphylaxis. Protoscoleces released into the tissues can also develop into new cysts.

E. multilocularis almost always involves the liver. The lesions grow very slowly and rarely present in children. The secondary reproductive units bud externally and are not confined within a single, well-defined structure. Thus the lesions are invasive and often confused with a malignancy. Furthermore, the cyst tissues are poorly demarcated from those of the host, making surgical removal difficult. The secondary cysts are also capable of distant metastatic spread. The growing cyst mass eventually replaces a significant portion of the liver and compromises adjacent tissues and structures.

Clinical Manifestations

In the liver, cysts may remain asymptomatic, may regress spontaneously, or may produce nonspecific symptoms. Symptomatic cysts can cause increased abdominal girth, hepatomegaly, a palpable mass, vomiting, or abdominal pain. In the lung, cysts produce chest pain, chronic cough, or hemoptysis. Expectorated fluid from ruptured lung cysts is often described as "salty." Mass effects can be noted in the brain and bone. Serious complications result from compression of adjacent structures or spillage of cyst contents. **Anaphylaxis** can occur with cyst rupture or spontaneous spillage, from trauma or intraoperatively. Cyst fluid may cause hypersensitivity pneumonitis after rupture. Spillage can also be catastrophic long-term, because each protoscolex can form a new cyst and fill up the abdominal cavity or rarely the pleural space. Jaundice from cystic hydatid disease is rare.

Alveolar hydatid disease may be diagnosed incidentally, but often the proliferating mass may compromise the biliary system and/or hepatic tissue, causing progressive obstructive jaundice and hepatic failure. Symptoms also occur from expansion of extrahepatic foci.

Diagnosis

Ultrasonography is the most valuable tool for both the diagnosis and treatment of cystic hydatid disease of the liver. The World Health Organization (WHO) standardized ultrasound criteria for classification of liver cystic echinococcosis have been shown to be reliable with excellent inter/intraobserver reliability. Ultrasonography staging has a direct use in defining optimal therapy (Fig. 330.2). Chest radiographs frequently reveal characteristic rounded masses in lung hydatid disease (Fig. 330.3). Alveolar disease resembles a diffuse solid tumor. CT findings are similar to those of ultrasonography and may at times be useful in distinguishing alveolar from cystic hydatid disease in geographic regions where both occur (Fig. 330.4). CT or MRI is also important in planning a surgical intervention.

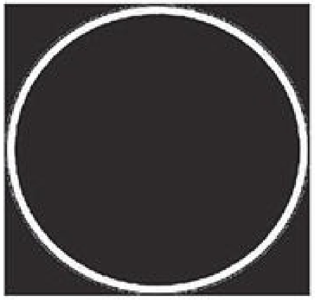
CE1 (type I)

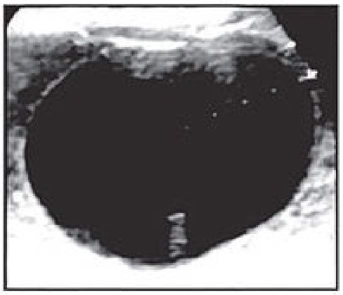
Fluid collection (hyaline)

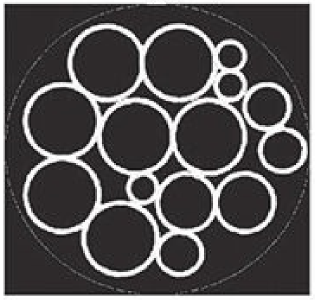
CE2 (type II)

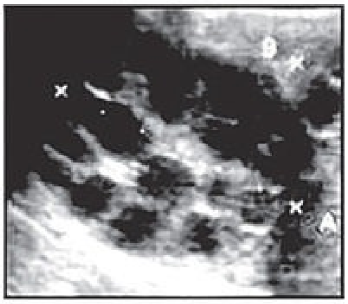
Multivescular

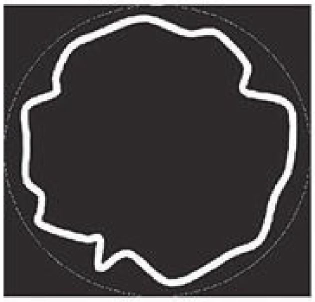
CE3 (type III)

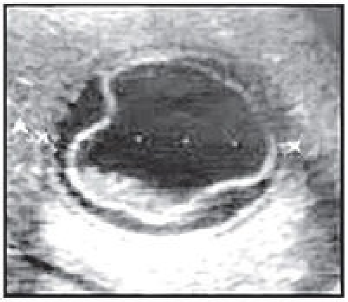
Fluid collection with split wall

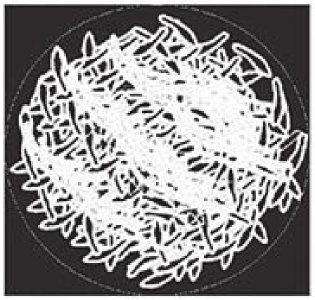
CE4 (type IV)

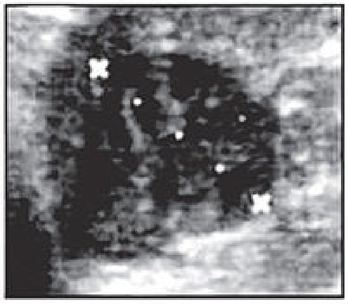
Heterogeneous pattern

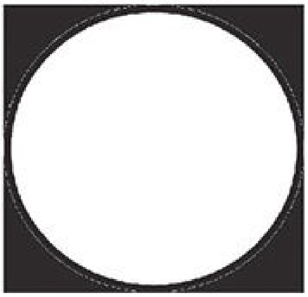
CE5 (type V)

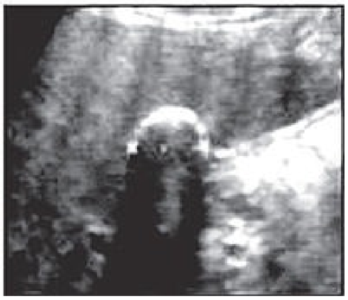
Calcified

FIG. 330.2 Ultrasound classification of cystic echinococcosis (CE) cysts. The WHO informal working group on echinococcosis classification differs from that of Gharbi and colleagues by the addition of a "cystic lesion" (CL) stage (undifferentiated) *(not shown),* and by reversing the order of CE types 2 and 3. CE3 transitional cysts may be differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles). CE1 and CE3a are early-stage cysts and CE4 and CE5 late-stage cysts. (From McManus DP, Gray DJ, Zhang W, Yang Y: Diagnosis, treatment, and management of echinococcosis, *BMJ* 344:e3866, 2012, Fig 4.)

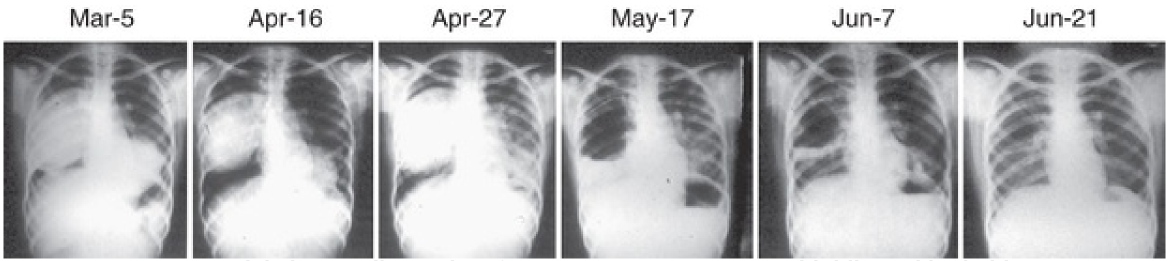

FIG. 330.3 Serial chest radiographs of a young Kenyan woman with bilateral hydatid cysts. After 2 mo of albendazole therapy, sudden rupture of the right cyst was associated with massive aspiration and acute respiratory distress.

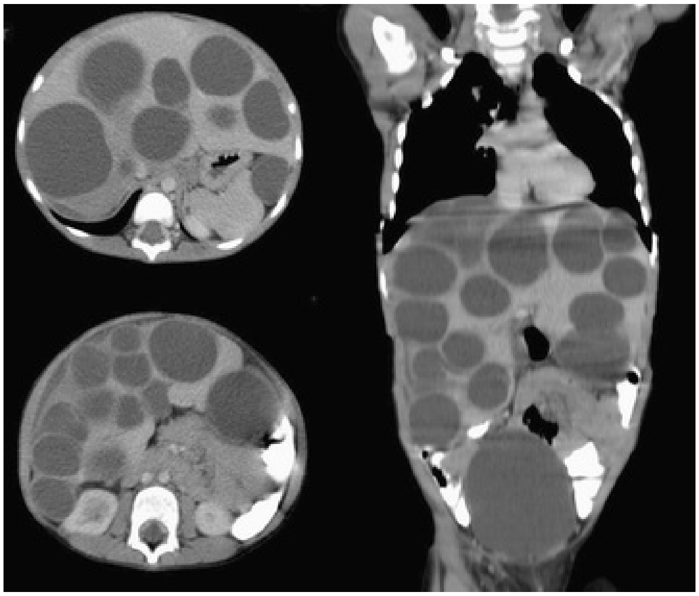

FIG. 330.4 Liver cystic echinococcosis (hydatid disease). Abdominal CT revealed hepatomegaly and multiple (>20) liver cysts. (From Ben-Shimol S, Zelcer I: Liver hydatid cysts, *J Pediatr* 163:1792, 2013.)

Serologic studies are used to confirm the diagnosis of cystic echinococcosis.

However, most of the antibody detection tests available use crude hydatid fluid antigens, which include epitopes that cross-react with other helminths. Cross-reaction has been reported with other noninfectious illness as well. In addition, some children with active cystic echinococcosis may not have circulating levels of specific antibody. Thus the sensitivity and specificity of the enzyme-linked immunosorbent assay to diagnose cystic echinococcosis may vary from 50–100% and 40–100%, respectively, depending on the antigen used and cyst stage, location, number, and viability. The sensitivity is higher for hepatic or bone disease, but the false-negative rate may be >50% with pulmonary or central nervous system (CNS) infection.

Differential Diagnosis

Benign hepatic cysts are common but can be distinguished from cystic hydatid disease by the absence of a distinct 3-layer wall, internal membranes, and hydatid sand. The density of bacterial hepatic abscesses is distinct from the watery cystic fluid characteristic of *E. granulosus* infection, but hydatid cysts may also be complicated by secondary bacterial infection. Alveolar echinococcosis is often confused with hepatoma or metastatic tumor.

Treatment

Management of cystic hydatid disease should be individualized and guided by disease stage and location. Approaches range from surgical resection for disease that tends to respond poorly to drugs and complicated cysts to watchful waiting for cysts that have already degenerated. For cystic echinococcosis (**CE**) types 1 or 3a (see Fig. 330.2) that are <5 cm in diameter, **albendazole** chemotherapy alone (15 mg/kg/day orally divided twice daily for 1-6 mo; maximum 800 mg/day) may result in a high rate of cure. Adverse effects include occasional alopecia, mild gastrointestinal disturbance, and elevated transaminases on prolonged use. Because of leukopenia, the U.S. Food and Drug Administration (FDA) recommends that blood counts be monitored at the beginning and every 2 wk during therapy. Medical treatment with albendazole may also be used for cysts that are not suitable for interventions such as **PAIR** (percutaneous, aspiration, instillation, and reaspiration) or surgery, but response rates are low.

For larger CE1 and CE3a lesions, ultrasound- or CT-guided PAIR is the preferred therapy. Compared with surgical treatment alone, PAIR plus albendazole results in similar cyst disappearance with fewer adverse events and fewer days in the hospital. Spillage with PAIR is uncommon, but prophylactic albendazole therapy is routinely administered at least 1 wk before PAIR and 1 mo afterward. PAIR is contraindicated in pregnancy and for bile-stained cysts, which may indicate the presence of a biliary fistula. The scolicidal agents instilled during PAIR may increase risk for biliary complications in these patients. Surgery with albendazole treatment is the recommended approach for CE2 and CE3b cysts of the liver. In experienced centers, cysts with thick internal septation (CE2) can be managed using a trocar to break up the membranes and external drainage. CE4 and CE5 cysts do not require immediate interventions and are followed ultrasonographically for signs of reactivation.

Surgery is the treatment of choice for complicated **cysts** , including ruptured cysts, cysts communicating with the biliary tract, large pulmonary cysts, or cysts of the CNS or bones. Small thoracic cysts may resolve with chemotherapy, but most cysts require operative removal.

For conventional surgery, the inner cyst wall (only laminate and germinal layers are of parasite origin) can be easily peeled from the fibrous layer, although some studies suggest that removal of the whole capsule has a better outcome in terms of recurrent disease. Considerable care must be taken to avoid spillage of cyst contents, and surgical drapes should be soaked in hypertonic saline because cyst fluid contains viable protoscoleces, each capable of producing secondary cysts. An additional risk is anaphylaxis because of spilled cyst fluid, making it useful to employ a surgeon experienced in this surgery. For hepatic cysts, patients should begin therapy with albendazole (ideally in combination with praziquantel) for several days to weeks preoperatively. Antiparasitic drugs should be continued for 4-12 wk postoperatively.

Alveolar hydatidosis frequently requires radical surgery, including partial hepatectomy, lobectomy, or liver transplantation. Medical therapy with albendazole should be continued for 2 yr after presumably curative surgery. In patients who are not operative candidates or whose lesions are not amenable to surgical cure, albendazole long-term suppressive therapy should be used to slow the progression, but the infection generally recurs if albendazole is stopped.

Prognosis

Factors predictive of success with chemotherapy are age of the cyst (<2 yr), low internal complexity of the cyst, and small size. The site of the cyst is not important, although cysts in bone respond poorly. For alveolar hydatidosis, if surgical removal is unsuccessful, the average mortality is 92% by 10 yr after diagnosis.

Prevention

Important measures to interrupt transmission include, above all, thorough **handwashing** , avoiding contact with dogs in endemic areas, boiling or filtering water when camping, and proper disposal of animal carcasses. Strict procedures for proper disposal of refuse from slaughterhouses must be instituted and followed so that dogs and wild carnivores do not have access to entrails. Other useful measures are control or treatment of the feral dog population and regular praziquantel treatment of pets and working dogs in endemic areas. Vaccines have been developed to prevent infection in grazing animals but are not widely used.

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PART XVII

The Digestive System

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SECTION 1

Clinical Manifestations of Gastrointestinal Disease

OUTLINE

Chapter 331 Normal Digestive Tract Phenomena
Chapter 332 Major Symptoms and Signs of Digestive Tract Disorders

CHAPTER 331

Normal Digestive Tract Phenomena

Asim Maqbool, Chris A. Liacouras

Gastrointestinal function varies with maturity; what is a physiologic event in a newborn or infant might be a pathologic symptom at an older age. A fetus can swallow amniotic fluid as early as 12 wk of gestation, but nutritive sucking in neonates first develops at about 34 wk of gestation. The coordinated oral and pharyngeal movements necessary for swallowing solids develop within the first few mo of life. Before this time, the tongue thrust is upward and outward to express milk from the nipple, instead of a backward motion, which propels solids toward the esophageal inlet. By 1 mo of age, infants appear to show preferences for sweet and salty foods. Infants' interest in solids increases at approximately 4 mo of age. The recommendation to begin solids at 6 mo of age is based on nutritional and cultural concepts rather than maturation of the swallowing process (see Chapter 56). Infants swallow air during feeding, and burping is encouraged to prevent gaseous distention of the stomach.

A number of normal anatomic variations may be noted in the mouth. A **short lingual frenulum** ("tongue-tie") may be worrisome to parents but only rarely interferes with nursing, bottle feeding, eating, or speech, generally requiring no treatment. **Surface furrowing** of the tongue (a geographic or scrotal tongue) is usually a normal finding. A **bifid uvula** may be isolated or associated with a submucous cleft of the soft palate (Fig. 331.1).

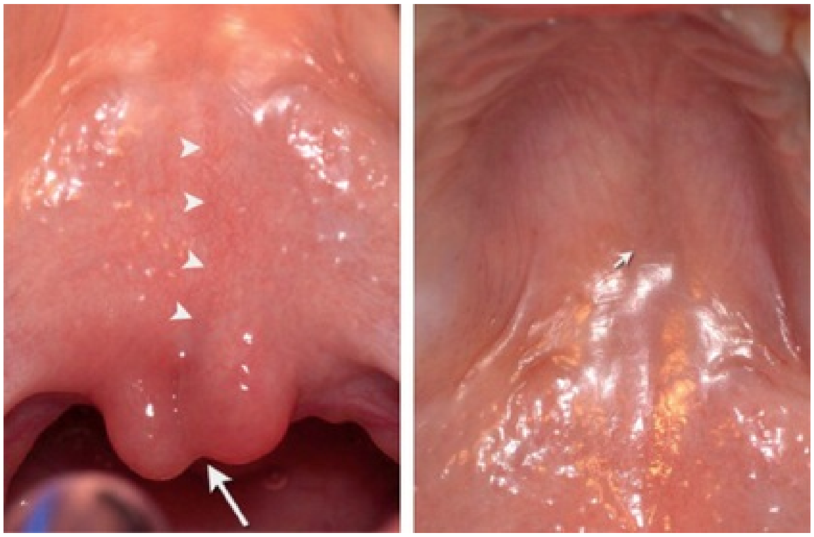

FIG. 331.1 Classic submucous cleft palate with triad of bifid uvula *(large arrow)* , furrow along the midline of the soft palate *(arrowheads)* , and a notch in the posterior margin of the hard palate *(small arrow)* . The midline furrow is sometimes referred to as the zona pellucida, reflecting the translucent nature of this area in some patients. (From Hasan A, Gardner A, Devlin M, Russell C: Submucous cleft palate with bifid uvula. *J Pediatr* 165:872, 2014.)

Regurgitation, the result of gastroesophageal reflux, occurs commonly in the 1st yr of life. Effortless regurgitation can dribble out of an infant's mouth but also may be forceful. In an otherwise healthy infant with regurgitation, volumes of emesis are commonly approximately 15-30 mL but occasionally are larger. Most often, the infant remains happy, although possibly hungry, after an episode of regurgitation. Episodes can occur from one to several times per day. Regurgitation gradually resolves in 80% of infants by 6 mo of age and in 90% by 12 mo. If complications develop or regurgitation persists, gastroesophageal reflux is considered pathologic rather than merely developmental and deserves further evaluation and treatment. Complications of gastroesophageal reflux include failure to thrive, pulmonary disease (apnea or aspiration pneumonitis), and esophagitis with its sequelae (see Chapters 349 and 350).

Infants and young children may be erratic eaters; this may be a worry to parents. A toddler might eat insatiably or refuse to consume food during a meal. Toddlers and young children also tend to eat only a limited variety of foods. Parents should be encouraged to view nutritional intake over several days and not be overly concerned about individual meals. Infancy and adolescence are periods of rapid growth; high nutrient requirements for growth may be associated with voracious appetites. The reduced appetite of toddlers and preschool children is often a worry to parents who are used to the relatively greater dietary intake during infancy. Demonstration of age-appropriate growth on a growth curve is reassuring.

The number, color, and consistency of stools can vary greatly in the same infant and between infants of similar age, without apparent explanation. The earliest stools after birth consist of meconium, a dark, viscous material that is normally passed within the 1st 48 hr of life. With the onset of feeding, meconium is replaced by green-brown transition stools, often containing curds, and, after 4-5 days, by yellow-brown milk stools. **Stool frequency** is extremely variable in normal infants and can vary from none to 7 per day. Breastfed infants can have frequent small, loose stools early (transition stools), and then after 2-3 wk can have very infrequent soft stools. Some nursing infants might not pass any stool for 1-2 wk and then have a normal soft bowel movement. The color of stool has little significance except for the presence of blood or absence of bilirubin products (white-gray rather than yellow-brown). The presence of vegetable matter, such as peas or corn, in the stool of an older infant or toddler ingesting solids is normal and suggests poor chewing and not malabsorption. A pattern of intermittent loose stools, known as **toddler's diarrhea,** occurs commonly between 1 and 3 yr of age. These otherwise healthy growing children often drink excessive carbohydrate-containing beverages. The stools typically occur during the day and not overnight. The volume of fluid intake is often excessive; limiting sugar and unabsorbable carbohydrate-containing beverages and increasing fat in the diet often lead to resolution of the pattern of loose stools.

A protuberant abdomen is often noted in infants and toddlers, especially after large feedings. This can result from the combination of weak abdominal musculature, relatively large abdominal organs, and lordotic stance. In the first yr of life, it is common to palpate the liver 1-2 cm below the right costal margin. The normal liver is soft in consistency and percusses to normal size for age. A Riedel lobe is a thin projection of the right lobe of the liver that may be palpated low in the right lateral abdomen. A soft spleen tip might also be palpable as a normal finding. In thin young children, the vertebral column is easily palpable, and an overlying structure may be mistaken for a mass. Pulsation of the aorta can be appreciated. Normal stool can often be palpated in the left lower quadrant in the descending or sigmoid colon.

Blood loss from the gastrointestinal tract is never normal, but swallowed blood may be misinterpreted as gastrointestinal bleeding. Maternal blood may be ingested at the time of birth or later by a nursing infant if there is bleeding near the mother's nipple. Nasal or oropharyngeal bleeding is occasionally mistaken for gastrointestinal bleeding (see Chapter 124.4). Red dyes in foods or drinks can turn the stool red but do not produce a positive test result for occult blood.

Jaundice is common in neonates, especially among premature infants, and usually results from the inability of an immature liver to conjugate bilirubin, leading to an elevated indirect component (see Chapter 123.3). Persistent elevation of indirect bilirubin levels in nursing infants may be a result of breast milk jaundice, which is usually a benign entity in full-term infants. An elevated direct bilirubin is not normal and suggests liver disease, although in infants it may be a result of extrahepatic infection (urinary tract infection). The direct bilirubin fraction should account for no more than 15–20% of the total serum bilirubin. Elevations in direct bilirubin levels can follow indirect hyperbilirubinemia as the liver converts excessive indirect to direct bilirubin and the rate-limiting step in bilirubin excretion shifts from the glucuronidation of bilirubin to excretion of direct bilirubin into the bile canaliculus. Indirect hyperbilirubinemia, which occurs commonly in normal newborns, tends to tint the sclerae and skin golden yellow, whereas direct hyperbilirubinemia produces a greenish yellow hue. The degree of jaundice does not always directly correlate with serum bilirubin levels. An elevated total serum bilirubin warrants closer examination, fractionation of bilirubin (direct and indirect), and ongoing surveillance. The American Academy of Pediatrics has issued guidelines on the evaluation and management of jaundice in the newborn and on how to follow elevated bilirubin levels, to identify causes of atypical bilirubin elevations, and how to prevent complications. Atypical elevations of unconjugated bilirubin are associated with risk for encephalopathy and kernicterus. Elevations in conjugated bilirubin are reviewed in the chapter on cholestasis (see Chapter 383.1).

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CHAPTER 332

Major Symptoms and Signs of Digestive Tract Disorders

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Disorders of organs outside the gastrointestinal (GI) tract can produce symptoms and signs that mimic digestive tract disorders and should be considered in the differential diagnosis (Table 332.1). In children with normal growth and development, treatment may be initiated without a formal evaluation based on a presumptive diagnosis after taking a history and performing a physical examination. Poor weight gain or weight loss is often associated with a significant pathologic process and usually necessitates a more formal evaluation.

Table 332.1

Some Nondigestive Tract Causes of Gastrointestinal Symptoms in Children

ANOREXIA
Systemic disease: inflammatory, neoplastic
Cardiorespiratory compromise
Iatrogenic: drug therapy, unpalatable therapeutic diets
Depression
Anorexia nervosa
VOMITING
Inborn errors of metabolism
Medications: erythromycin, chemotherapy, nonsteroidal antiinflammatory drugs, marijuana
Increased intracranial pressure
Brain tumor
Infection of the urinary tract
Labyrinthitis
Adrenal insufficiency
Pregnancy
Psychogenic
Abdominal migraine
Poisoning/toxins

Renal disease
DIARRHEA
Infection: otitis media, urinary tract infection Uremia Medications: antibiotics, cisapride Tumors: neuroblastoma Pericarditis Adrenal insufficiency
CONSTIPATION
Hypothyroidism Spina bifida Developmental delay Dehydration: diabetes insipidus, renal tubular lesions Medications: narcotics Lead poisoning Infant botulism
ABDOMINAL PAIN
Pyelonephritis, hydronephrosis, renal colic Pneumonia (lower lobe) Pelvic inflammatory disease Porphyria Fabry disease Angioedema Endocarditis Abdominal migraine Familial Mediterranean fever Sexual or physical abuse Systemic lupus erythematosus School phobia Sickle cell crisis Vertebral disk inflammation Psoas abscess Pelvic osteomyelitis or myositis Medications
ABDOMINAL DISTENTION OR MASS
Ascites: nephrotic syndrome, neoplasm, heart failure Discrete mass: Wilms tumor, hydronephrosis, neuroblastoma, mesenteric cyst, hepatoblastoma, lymphoma Pregnancy
JAUNDICE
Hemolytic disease Urinary tract infection Sepsis Hypothyroidism Panhypopituitarism

Dysphagia

Difficulty in swallowing is termed *dysphagia*. Painful swallowing is termed **odynophagia** . **Globus** is the sensation of something stuck in the throat without a clear etiology. Swallowing is a complex process that starts in the mouth with mastication and lubrication of food that is formed into a bolus. The bolus is pushed into the pharynx by the tongue. The pharyngeal phase of swallowing is rapid and involves protective mechanisms to prevent food from entering the airway. The epiglottis is lowered over the larynx while the soft palate is elevated against the nasopharyngeal wall; respiration is temporarily arrested while the upper esophageal sphincter opens to allow the bolus to enter the esophagus. In the esophagus, peristaltic coordinated muscular contractions push the food bolus toward the stomach. The lower esophageal sphincter relaxes shortly after the upper esophageal sphincter, so liquids that rapidly clear the esophagus enter the stomach without resistance.

Dysphagia is classified as oropharyngeal dysphagia and esophageal dysphagia. **Oropharyngeal dysphagia** occurs when the transfer of the food bolus from the mouth to the esophagus is impaired (also termed *transfer dysphagia*). The striated muscles of the mouth, pharynx, and upper esophageal sphincter are affected in oropharyngeal dysphagia. Neurologic and muscular disorders can give rise to oropharyngeal dysphagia (Table 332.2). Chiari malformations, Russell-Silver syndrome, and cri du chat may present with upper esophageal sphincter dysfunction, manifest by dysphagia with solids. The most serious complication of oropharyngeal dysphagia is life-threatening aspiration.

Table 332.2

Causes of Oropharyngeal Dysphagia

NEUROMUSCULAR DISORDERS
Cerebral palsy Brain tumors Cerebrovascular disease/stroke Chiari malformation Polio and postpolio syndromes Multiple sclerosis Myositis Dermatomyositis Myasthenia gravis Muscular dystrophies Acquired or inherited dystonia syndrome Dysautonomia
METABOLIC AND AUTOIMMUNE DISORDERS
Hyperthyroidism Systemic lupus erythematosus Sarcoidosis Amyloidosis
INFECTIOUS DISEASE
Meningitis

Botulism Diphtheria Lyme disease Neurosyphilis Viral infection: polio, coxsackievirus, herpes, cytomegalovirus
STRUCTURAL LESIONS
Inflammatory: abscess, pharyngitis Congenital web Cricopharyngeal bar Dental problems Bullous skin lesions Plummer-Vinson syndrome Zenker diverticulum Extrinsic compression: osteophytes, lymph nodes, thyroid swelling, aberrant right subclavian artery (dysphagia lusoria)
OTHER
Corrosive injury Side effects of medications After surgery After radiation therapy

Adapted from Gasiorowska A, Faas R: Current approach to dysphagia. *Gastroenterol Hepatol* 5(4):269–279, 2009.

A complex sequence of neuromuscular events is involved in the transfer of foods to the upper esophagus. Abnormalities of the muscles involved in the ingestion process and their innervation, strength, or coordination are associated with transfer dysphagia in infants and children. In such cases, an oropharyngeal problem is usually part of a more generalized neurologic or muscular problem (botulism, diphtheria, neuromuscular disease). Painful oral lesions, such as acute viral stomatitis or trauma, occasionally interfere with ingestion. If the nasal air passage is seriously obstructed, the need for respiration causes severe distress when suckling. Although severe structural, dental, and salivary abnormalities would be expected to create difficulties, ingestion proceeds relatively well in most affected children if they are hungry.

Esophageal dysphagia occurs when there is difficulty in transporting the food bolus down the esophagus. Esophageal dysphagia can result from neuromuscular disorders or mechanical obstruction (Table 332.3). Primary motility disorders causing impaired peristaltic function and dysphagia are rare in children. Eosinophilic esophagitis can present with esophageal dysphagia. Achalasia is an esophageal motility disorder with associated inability of relaxation of the lower esophageal sphincter, and it rarely occurs in children. Motility of the distal esophagus is disordered after surgical repair of tracheoesophageal fistula or achalasia. Abnormal motility can accompany collagen vascular disorders. Mechanical obstruction can be intrinsic or extrinsic.

Intrinsic structural defects cause a fixed impediment to the passage of food bolus because of a narrowing within the esophagus, as in a stricture, web, or tumor. Extrinsic obstruction is caused by compression from vascular rings, mediastinal lesions, or vertebral abnormalities. Structural defects typically cause more problems in swallowing solids than liquids. In infants, esophageal web, tracheobronchial remnant, or vascular ring can cause dysphagia. An esophageal stricture secondary to esophagitis (chronic gastroesophageal reflux, eosinophilic esophagitis, chronic infections) occasionally has dysphagia as the first manifestation. An esophageal foreign body or a stricture secondary to a caustic ingestion also causes dysphagia. A Schatzki ring, a thin ring of mucosal tissue near the lower esophageal sphincter, is another mechanical cause of recurrent dysphagia, and again is rare in children.

Table 332.3

Causes of Esophageal Dysphagia

NEUROMUSCULAR
Eosinophilic esophagitis Achalasia cardia Diffuse esophageal spasm Scleroderma
GERD
INTRINSIC LESIONS
Foreign bodies including pills Esophagitis: GERD, eosinophilic esophagitis, infections Stricture: corrosive injury, pill induced, peptic Esophageal webs Esophageal rings Esophageal diverticula Neoplasm Chagas disease
EXTRINSIC LESIONS
Vascular compression Mediastinal lesion Cervical osteochondritis Vertebral abnormalities

GERD , Gastroesophageal reflux disease.

Adapted from Gasiorowska A, Faas R: Current approach to dysphagia. *Gastroenterol Hepatol* 5(4):269–279, 2009.

When dysphagia is associated with a delay in passage through the esophagus, the patient may be able to point to the level of the chest where the delay occurs, but esophageal symptoms are usually referred to the suprasternal notch. When a patient points to the suprasternal notch, the impaction can be found anywhere in the esophagus.

Regurgitation

Regurgitation is the effortless movement of stomach contents into the esophagus and mouth. It is not associated with distress, and infants with regurgitation are often hungry immediately after an episode. The lower esophageal sphincter prevents reflux of gastric contents into the esophagus. Regurgitation is a result of gastroesophageal reflux through an incompetent or, in infants, immature lower esophageal sphincter. This is often a developmental process, and regurgitation or “spitting” resolves with maturity. Regurgitation should be differentiated from vomiting, which denotes an active reflex process with an extensive differential diagnosis (Table 332.4).

Table 332.4

Differential Diagnosis of Emesis During Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Gastroenteritis Gastroesophageal reflux Overfeeding Anatomic obstruction[*] Systemic infection [†] Pertussis syndrome Otitis media	Gastroenteritis Systemic infection Gastritis Toxic ingestion/poisoning Pertussis syndrome Medication Reflux (GERD) Sinusitis Otitis media Anatomic obstruction[*] Eosinophilic esophagitis	Gastroenteritis GERD Systemic infection Toxic ingestion/poisoning/marijuana Gastritis Sinusitis Inflammatory bowel disease Appendicitis Migraine Pregnancy Medications Ipecac abuse, bulimia Concussion
RARE		
Adrenogenital syndrome Inborn errors of metabolism Brain tumor (increased intracranial pressure) Subdural hemorrhage Food poisoning Rumination Renal tubular acidosis Ureteropelvic junction obstruction Pseudoobstruction	Reye syndrome Hepatitis Peptic ulcer Pancreatitis Brain tumor Increased intracranial pressure Middle ear disease/labyrinthitis Chemotherapy Achalasia	Reye syndrome Hepatitis Peptic ulcer Pancreatitis Cholecystitis Brain tumor Increased intracranial pressure Concussion Middle ear disease/labyrinthitis Chemotherapy Cyclic vomiting (migraine)

	Cyclic vomiting (migraine) Esophageal stricture Duodenal hematoma Inborn error of metabolism Pseudoobstruction Gastroparesis	Biliary colic Renal colic Porphyria Diabetic ketoacidosis Adrenal insufficiency Pseudoobstruction Intestinal tumor Gastroparesis Achalasia Superior mesentery artery syndrome Distal intestinal obstruction syndrome

[*] Includes malrotation, pyloric stenosis, intussusception, Hirschsprung disease, adhesions, hernias.

[†] Meningitis, sepsis.

GERD , Gastroesophageal reflux disease, inguinal hernia.

Anorexia

Anorexia means prolonged lack of appetite. Hunger and satiety centers are located in the hypothalamus; it seems likely that afferent nerves from the GI tract to these brain centers are important determinants of the anorexia that characterizes many diseases of the stomach and intestine (see Chapter 47). Satiety is stimulated by distention of the stomach or upper small bowel, the signal being transmitted by sensory afferents, which are especially dense in the upper gut. Chemoreceptors in the intestine, influenced by the assimilation of nutrients, also affect afferent flow to the appetite centers. Impulses reach the hypothalamus from higher centers, possibly influenced by pain or the emotional disturbance of an intestinal disease. Other regulatory factors include hormones, ghrelin, leptin, and plasma glucose, which, in turn, reflect intestinal function (see Chapter 47).

Vomiting

Vomiting is a highly coordinated reflex process that may be preceded by increased salivation and begins with involuntary retching. Violent descent of the diaphragm and constriction of the abdominal muscles with relaxation of the gastric cardia actively force gastric contents back up the esophagus. This process is coordinated in the medullary vomiting center, which is influenced directly by afferent innervation and indirectly by the chemoreceptor trigger zone and higher central nervous system (CNS) centers. Many acute or chronic processes can cause vomiting (see Tables 332.1 and 332.4).

Vomiting caused by obstruction of the GI tract is probably mediated by intestinal visceral afferent nerves stimulating the vomiting center (Table 332.5). If obstruction occurs below the second part of the duodenum, vomitus is usually bile stained. Emesis can also become bile stained with repeated vomiting in the absence of obstruction when duodenal contents are refluxed into the stomach. Nonobstructive lesions of the digestive tract can also cause vomiting; this includes diseases of the upper bowel, pancreas, liver, or biliary tree. CNS or metabolic derangements and cyclic vomiting syndrome (Table 332.6) can lead to severe, persistent emesis. Marijuana use among teens has also led to cannabis hyperemesis syndrome (see Chapter 140.3).

Table 332.5

Causes of Gastrointestinal Obstruction

ESOPHAGUS
Congenital
Esophageal atresia Vascular rings Schatzki ring Tracheobronchial remnant
Acquired
Esophageal stricture Foreign body Achalasia Chagas disease Collagen vascular disease
STOMACH
Congenital
Antral webs Pyloric stenosis
Acquired
Bezoar, foreign body Pyloric stricture (ulcer) Chronic granulomatous disease of childhood Eosinophilic gastroenteritis Crohn disease Epidermolysis bullosa
SMALL INTESTINE
Congenital
Duodenal atresia Annular pancreas Malrotation/volvulus Malrotation/Ladd bands

Ileal atresia Meconium ileus Meckel diverticulum with volvulus or intussusception Inguinal hernia Internal hernia Intestinal duplication Pseudoobstruction
Acquired
Postsurgical adhesions Crohn disease Intussusception Distal ileal obstruction syndrome (cystic fibrosis) Duodenal hematoma Superior mesenteric artery syndrome
COLON
Congenital
Meconium plug Hirschsprung disease Colonic atresia, stenosis Imperforate anus Rectal stenosis Pseudoobstruction Volvulus Colonic duplication
Acquired
Ulcerative colitis (toxic megacolon) Chagas disease Crohn disease Fibrosing colonopathy (cystic fibrosis)

Table 332.6

Criteria for Cyclic Vomiting Syndrome

All of the criteria must be met for the consensus definition of cyclic vomiting syndrome:

- At least 5 attacks in any interval, or a minimum of 3 episodes during a 6-mo period
- Recurrent episodes of intense vomiting and nausea lasting 1 hr to 10 days and occurring at least 1 wk apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during episodes occurs ≥4 times/hr for ≥1 hr
- Return to baseline health between episodes
- Not attributed to another disorder

From Li, B UK, Lefevre F, Chelimsky GG, et al: North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr* 47:379–393, 2008.

Potential complications of emesis are noted in Table 332.7 . Broad management strategies for vomiting in general and specific causes of emesis are noted in Tables 332.8 and 332.9 .

Table 332.7

Complications of Vomiting

COMPLICATION	PATHOPHYSIOLOGY	HISTORY, PHYSICAL EXAMINATION, AND LABORATORY STUDIES
Metabolic	Fluid loss in emesis	Dehydration
	HCl loss in emesis	Alkalosis; hypochloremia
	Na, K loss in emesis	Hyponatremia; hypokalemia
	Acidosis	Dehydration
Nutritional	Emesis of calories and nutrients Anorexia for calories and nutrients	Malnutrition; "failure to thrive"
Mallory-Weiss tear	Retching → tear at lesser curve of gastroesophageal junction	Forceful emesis → hematemesis
Esophagitis	Chronic vomiting → esophageal acid exposure	Heartburn; Hemoccult + stool
Aspiration	Aspiration of vomitus, especially in context of obtundation	Pneumonia; neurologic dysfunction
Shock	Severe fluid loss in emesis or in accompanying diarrhea	Dehydration (accompanying diarrhea can explain acidosis?)
	Severe blood loss in hematemesis	Blood volume depletion
Pneumomediastinum, pneumothorax	Increased intrathoracic pressure	Chest x-ray
Petechiae, retinal hemorrhages	Increased intrathoracic pressure	Normal platelet count

From Kliegman RM, Greenbaum LA, Lye PS, editors: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, Elsevier, p 318.

Table 332.8

Pharmacologic Therapies for Vomiting Episodes

DISORDER/THERAPEUTIC DRUG CLASS	DRUG	DOSAGE
REFLUX		
Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg PO or IV qid
GASTROPARESIS		
Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg PO or IV qid
Motilin agonist	Erythromycin	3-5 mg/kg PO or IV tid-qid
INTESTINAL PSEUDOOBSTRUCTION		
Stimulation of intestinal migratory myoelectric complexes	Octreotide (Sandostatin)	1 μg/kg SC bid-tid
CHEMOTHERAPY		
Dopamine antagonist	Metoclopramide	0.5-1.0 mg/kg IV qid, with antihistamine prophylaxis of extrapyramidal side effects
Serotoninergic 5-HT_3 antagonist	Ondansetron (Zofran)	0.15-0.3 mg/kg IV or PO tid
Phenothiazines (extrapyramidal, hematologic side effects)	Prochlorperazine (Compazine)	≈0.3 mg/kg PO bid-tid

	Chlorpromazine (Thorazine)	>6 mo of age: 0.5 mg/kg PO or IV tid-qid
Steroids	Dexamethasone (Decadron)	0.1 mg/kg PO tid
Cannabinoids	Tetrahydrocannabinol (Nabilone)	0.05-0.1 mg/kg PO bid-tid
POSTOPERATIVE		
	Ondansetron, phenothiazines	See under chemotherapy
MOTION SICKNESS, VESTIBULAR DISORDERS		
Antihistamine	Dimenhydrinate (Dramamine)	1 mg/kg PO tid-qid
Anticholinergic	Scopolamine (Transderm Scop)	Adults: 1 patch/3 days
ADRENAL CRISIS		
Steroids	Cortisol	2 mg/kg IV bolus followed by 0.2-0.4 mg/kg/hr IV (±1 mg/kg IM)

ECG , Electrocardiogram; *GI* , gastrointestinal.

From Kliegman RM, Greenbaum LA, Lye PS, editors: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, Elsevier, p 317.

Table 332.9

Supportive and Nonpharmacologic Therapies for Vomiting Episodes

DISEASE	**THERAPY**
All	Treat cause • Obstruction: operate • Allergy: change diet (±steroids) • Metabolic error: Rx defect • Acid peptic disease: H2RAs, PPIs, etc.
COMPLICATIONS	
Dehydration	IV fluids, electrolytes
Hematemesis	Transfuse, correct coagulopathy
Esophagitis	H_2 RAs, PPIs
Malnutrition	NG or NJ drip feeding useful for many chronic conditions
Meconium ileus	Gastrografin enema
DIOS	Gastrografin enema; balanced colonic lavage solution (e.g., GoLYTELY)
Intussusception	Barium enema; air reduction enema
Hematemesis	Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocautery for selected upper GI tract lesions
Sigmoid volvulus	Colonoscopic decompression
Reflux	Positioning; dietary measures (infants: rice cereal, 1 tbs/oz of formula)
Psychogenic components	Psychotherapy; tricyclic antidepressants; anxiolytics (e.g., diazepam: 0.1 mg/kg PO tid-qid)

DIOS , Distal intestinal obstruction syndrome; *GI* , gastrointestinal; *H_2 RA* , H_2 -receptor antagonist; *NG* , nasogastric; *NJ* , nasojejunal; *PPIs* , proton pump inhibitors; *tbs* , tablespoon.

From Kliegman RM, Greenbaum LA, Lye PS, editors: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, Elsevier, p 319.

Diarrhea

Diarrhea is best defined as excessive loss of fluid and electrolyte in the stool. Acute diarrhea is defined as sudden onset of excessively loose stools of >10 mL/kg/day in infants and >200 g/24 hr in older children, which lasts <14 days. When the episode lasts longer than 14 days, it is called *chronic* or *persistent diarrhea.*

Normally, a young infant has approximately 5 mL/kg/day of stool output; the volume increases to 200 g/24 hr in an adult. The greatest volume of intestinal water is absorbed in the small bowel; the colon concentrates intestinal contents against a high osmotic gradient. The small intestine of an adult can absorb 10-11 L/day of a combination of ingested and secreted fluid, whereas the colon absorbs approximately 0.5 L. Disorders that interfere with absorption in the small bowel tend to produce voluminous diarrhea, whereas disorders compromising colonic absorption produce lower-volume diarrhea. **Dysentery** (small-volume, frequent bloody stools with mucus, tenesmus, and urgency) is the predominant symptom of colitis.

The basis of all diarrheas is disturbed intestinal solute transport and water absorption. Water movement across intestinal membranes is passive and is determined by both active and passive fluxes of solutes, particularly sodium, chloride, and glucose. The pathogenesis of most episodes of diarrhea can be explained by secretory, osmotic, or motility abnormalities or a combination of these (Table 332.10).

Table 332.10

Mechanisms of Diarrhea

PRIMARY MECHANISM	DEFECT	STOOL EXAMINATION	EXAMPLES	COMMENT
Secretory	Decreased absorption, increased secretion, electrolyte transport	Watery, normal osmolality with ion gap <100 mOsm/kg	Cholera, toxigenic *Escherichia coli* ; carcinoid, VIP, neuroblastoma, congenital chloride diarrhea, *Clostridium difficile* , cryptosporidiosis (AIDS)	Persists during fasting; bile salt malabsorption can also increase intestinal water secretion; no stool leukocytes

Osmotic	Maldigestion, transport defects ingestion of unabsorbable substances	Watery, acidic, and reducing substances; increased osmolality with ion gap >100 mOsm/kg	Lactase deficiency, glucose-galactose malabsorption, lactulose, laxative abuse	Stops with fasting; increased breath hydrogen with carbohydrate malabsorption; no stool leukocytes
Increased motility	Decreased transit time	Loose to normal-appearing stool, stimulated by gastrocolic reflex	Irritable bowel syndrome, thyrotoxicosis, postvagotomy dumping syndrome	Infection can also contribute to increased motility
Decreased motility	Defect in neuromuscular unit(s) stasis (bacterial overgrowth)	Loose to normal-appearing stool	Pseudoobstruction, blind loop	Possible bacterial overgrowth
Decreased surface area (osmotic, motility)	Decreased functional capacity	Watery	Short bowel syndrome, celiac disease, rotavirus enteritis	Might require elemental diet plus parenteral alimentation
Mucosal invasion	Inflammation, decreased colonic reabsorption, increased motility	Blood and increased WBCs in stool	*Salmonella, Shigella* infection; amebiasis; *Yersinia, Campylobacter* infection	Dysentery evident in blood, mucus, and WBCs

VIP , Vasoactive intestinal peptide; *WBC* , white blood cell.

From Kliegman RM, Greenbaum LA, Lye PS, editors: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, Elsevier, p 274.

Secretory diarrhea occurs when the intestinal epithelial cell solute transport system is in an active state of secretion. It is often caused by a secretagogue, such as cholera toxin, binding to a receptor on the surface epithelium of the bowel and thereby stimulating intracellular accumulation of cyclic adenosine monophosphate or cyclic guanosine monophosphate. Some intraluminal fatty acids and bile salts cause the colonic mucosa to secrete through this mechanism. Diarrhea not associated with an exogenous secretagogue can also have a secretory component (congenital microvillus inclusion disease). Secretory diarrhea is usually of large volume and persists even with fasting. The stool osmolality is predominantly indicated by the electrolytes and the ion gap is 100 mOsm/kg or less. The ion gap is calculated by subtracting the concentration of electrolytes from total osmolality:

$$\text{Ion gap} = \text{Stool osmalality} - [(\text{Stool Na} + \text{stool K}) \times 2]$$

Osmotic diarrhea occurs after ingestion of a poorly absorbed solute. The solute may be one that is normally not well absorbed (magnesium, phosphate, lactulose, or sorbitol) or one that is not well absorbed because of a disorder of the small bowel (lactose with lactase deficiency or glucose with rotavirus diarrhea). Malabsorbed carbohydrate is fermented in the colon, and short-chain fatty acids are produced. Although short-chain fatty acids can be absorbed in the colon and used as an energy source, the net effect is increase in the osmotic solute load. This form of diarrhea is usually of lesser volume than a secretory diarrhea and stops with fasting. The osmolality of the stool will not be explained by the electrolyte content, because another osmotic component is present and so the anion gap is >100 mOsm.

Motility disorders can be associated with rapid or delayed transit and are not generally associated with large-volume diarrhea. Slow motility can be associated with bacterial overgrowth leading to diarrhea. The differential diagnosis of common causes of acute and chronic diarrhea is noted in Table 332.11 .

Table 332.11

Differential Diagnosis of Diarrhea

INFANT	CHILD	ADOLESCENT
ACUTE		
Common		
Gastroenteritis (viral > bacterial > protozoal) Systemic infection Antibiotic associated Overfeeding	Gastroenteritis (viral > bacterial > protozoal) Food poisoning Systemic infection Antibiotic associated	Gastroenteritis (viral > bacterial > protozoal) Food poisoning Antibiotic associated
Rare		
Primary disaccharidase deficiency Hirschsprung toxic colitis Adrenogenital syndrome Neonatal opiate withdrawal	Toxic ingestion Hemolytic uremic syndrome Intussusception	Hyperthyroidism Appendicitis
CHRONIC		
Common		
Postinfectious secondary lactase deficiency Cow's milk or soy protein intolerance (allergy) Chronic nonspecific diarrhea of infancy Excessive fruit juice (sorbitol) ingestion Celiac disease Cystic fibrosis AIDS enteropathy	Postinfectious secondary lactase deficiency Irritable bowel syndrome Celiac disease Cystic fibrosis Lactose intolerance Excessive fruit juice (sorbitol) ingestion Giardiasis Inflammatory bowel disease AIDS enteropathy	Irritable bowel syndrome Inflammatory bowel disease Lactose intolerance Giardiasis Laxative abuse (anorexia nervosa) Constipation with encopresis
Rare		

Primary immune defects Autoimmune enteropathy IPEX and IPEX-like syndromes Glucose-galactose malabsorption Microvillus inclusion disease (microvillus atrophy) Congenital transport defects (chloride, sodium) Primary bile acid malabsorption Factitious syndrome by proxy Hirschsprung disease Shwachman syndrome Secretory tumors Acrodermatitis enteropathica Lymphangiectasia Abetalipoproteinemia Eosinophilic gastroenteritis Short bowel syndrome	Primary and acquired immune defects Secretory tumors Pseudoobstruction Sucrase-isomaltase deficiency Eosinophilic gastroenteritis Secretory tumors	Secretory tumor Primary bowel tumor Parasitic infections and venereal diseases Appendiceal abscess Addison disease

IPEX, Immunodysregulation polyendocrinopathy enteropathy X-linked.

From Kliegman RM, Greenbaum LA, Lye PS, editors: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, Elsevier, p 272.

Constipation

Any definition of constipation is relative and depends on stool consistency, stool frequency, and difficulty in passing the stool. A normal child might have a soft stool only every second or third day without difficulty; this is not constipation. A hard stool passed with difficulty every third day should be treated as constipation. Constipation can arise from defects either in filling or emptying the rectum (Table 332.12).

Table 332.12

Causes of Constipation

NONORGANIC (FUNCTIONAL)—RETENTIVE
Anatomic
Anal stenosis, atresia with fistula Imperforate anus Anteriorly displaced anus Intestinal stricture (postnecrotizing enterocolitis) Anal stricture
Abnormal Musculature
Prune-belly syndrome Gastroschisis Down syndrome Muscular dystrophy

Intestinal Nerve or Muscle Abnormalities
Hirschsprung disease Pseudoobstruction (visceral myopathy or neuropathy) Intestinal neuronal dysplasia Spinal cord lesions Tethered cord Autonomic neuropathy Spinal cord trauma Spina bifida Chagas disease
Drugs
Anticholinergics Narcotics Methylphenidate Phenytoin Antidepressants Chemotherapeutic agents (vincristine) Pancreatic enzymes (fibrosing colonopathy) Lead, arsenic, mercury Vitamin D intoxication Calcium channel blocking agents
Metabolic Disorders
Hypokalemia Hypercalcemia Hypothyroidism Diabetes mellitus, diabetes insipidus Porphyria
Intestinal Disorders
Celiac disease Cow's milk protein intolerance Cystic fibrosis (meconium ileus equivalent) Inflammatory bowel disease (stricture) Tumor Connective tissue disorders Systemic lupus erythematosus Scleroderma
Psychiatric Diagnosis
Anorexia nervosa

A nursing infant might have very infrequent stools of normal consistency; this is usually a normal pattern. True constipation in the neonatal period is most likely secondary to Hirschsprung disease, intestinal pseudoobstruction, or hypothyroidism.

Defective rectal filling occurs when colonic peristalsis is ineffective (in cases of hypothyroidism or opiate use and when bowel obstruction is caused either by a structural anomaly or by Hirschsprung disease). The resultant colonic stasis leads to excessive drying of stool and a failure to initiate reflexes from the rectum that normally trigger evacuation. Emptying the rectum by spontaneous evacuation depends on a defecation reflex initiated by pressure receptors in the rectal muscle. Therefore stool retention can also result from lesions involving these rectal muscles, the sacral spinal cord afferent and efferent fibers, or the muscles of the abdomen and pelvic floor. Disorders of anal sphincter relaxation can also contribute to fecal retention.

Constipation tends to be self-perpetuating, whatever its cause. Hard, large stools in the rectum become difficult and even painful to evacuate; thus more retention occurs and a vicious circle ensues. Distention of the rectum and colon lessens the sensitivity of the defecation reflex and the effectiveness of peristalsis. Fecal impaction is common and leads to other problems. Eventually, watery content from the proximal colon might percolate around hard retained stool and pass per rectum unperceived by the child. This involuntary **encopresis** may be mistaken for diarrhea. Constipation itself does not have deleterious systemic organic effects, but urinary tract stasis with increased risk of urinary tract infections can accompany severe long-standing cases and constipation can generate anxiety, having a marked emotional impact on the patient and family.

Abdominal Pain

There is considerable variation among children in their perception and tolerance for abdominal pain. This is one reason the evaluation of chronic abdominal pain is difficult. A child with **functional abdominal pain** (no identifiable organic cause) may be as uncomfortable as one with an organic cause. It is very important to distinguish between organic and nonorganic (functional) abdominal pain because the approach for the management is based on this. Normal growth and physical examination (including a rectal examination) and the absence of anemia or hematochezia are reassuring in a child who is suspected of having functional pain.

A specific cause may be difficult to find, but the nature and location of a pain-provoking lesion can usually be determined from the clinical description. Two types of nerve fibers transmit painful stimuli in the abdomen. In skin and muscle, A fibers mediate sharp localized pain; C fibers from viscera, peritoneum, and muscle transmit poorly localized, dull pain. These afferent fibers have cell bodies in the dorsal root ganglia, and some axons cross the midline and ascend to the medulla, midbrain, and thalamus. Pain is perceived in the cortex of the postcentral gyrus, which can receive impulses arising from both sides of the body. In the gut, the usual stimulus provoking pain is tension or stretching. Inflammatory lesions can lower the pain threshold, but the mechanisms producing pain or inflammation are not clear. Tissue metabolites released near nerve endings probably account for the pain caused by ischemia. Perception of these painful stimuli can be modulated by input from both cerebral and peripheral sources. Psychologic factors are particularly important. Tables 332.13 and 332.14 list features of abdominal pain. Pain that suggests a potentially serious organic etiology is associated with age younger than 5 yr; fever; weight loss; bile- or blood-stained emesis; jaundice; hepatosplenomegaly; back or flank pain or pain in a location other than the umbilicus; awakening from sleep in pain; referred pain to shoulder, groin or back; elevated erythrocyte sedimentation rate, white blood cell count, or C-reactive protein; anemia; edema; hematochezia; or a strong family history of inflammatory bowel disease or celiac disease.

Table 332.13

Chronic Abdominal Pain in Children

DISORDER	CHARACTERISTICS	KEY EVALUATIONS
NONORGANIC		
Functional abdominal pain	Nonspecific pain, often periumbilical	Hx and PE; tests as indicated
Irritable bowel syndrome	Intermittent cramps, diarrhea, and constipation	Hx and PE
Nonulcer dyspepsia	Peptic ulcer–like symptoms without abnormalities on evaluation of the upper GI tract	Hx; esophagogastroduodenoscopy
GASTROINTESTINAL TRACT		
Chronic constipation	Hx of stool retention, evidence of constipation on examination	Hx and PE; plain x-ray of abdomen
Lactose intolerance	Symptoms may be associated with lactose ingestion; bloating, gas, cramps, and diarrhea	Trial of lactose-free diet; lactose breath hydrogen test
Parasite infection (especially *Giardia*)	Bloating, gas, cramps, and diarrhea	Stool evaluation for O&P; specific immunoassays for *Giardia*
Excess fructose or sorbitol ingestion	Nonspecific abdominal pain, bloating, gas, and diarrhea	Large intake of apples, fruit juice, or candy or chewing gum sweetened with sorbitol
Crohn disease	See Chapter 362	
Peptic ulcer	Burning or gnawing epigastric pain; worse on awakening or before meals; relieved with antacids	Esophagogastroduodenoscopy, upper GI contrast x-rays, or MRI enteroscopy
Esophagitis	Epigastric pain with substernal burning	Esophagogastroduodenoscopy
Meckel diverticulum	Periumbilical or lower abdominal pain; may have blood in stool (usually painless)	Meckel scan or enteroclysis
Recurrent intussusception	Paroxysmal severe cramping abdominal pain; blood may be present in stool with episode	Identify intussusception during episode or lead point in intestine between episodes with contrast studies of GI tract
Internal, inguinal, or abdominal wall hernia	Dull abdomen or abdominal wall pain	PE, CT of abdominal wall

Chronic appendicitis or appendiceal mucocele	Recurrent RLQ pain; often incorrectly diagnosed, may be rare cause of abdominal pain	Barium enema, CT
GALLBLADDER AND PANCREAS		
Cholelithiasis	RUQ pain, might worsen with meals	Ultrasound of gallbladder
Choledochal cyst	RUQ pain, mass ± elevated bilirubin	Ultrasound or CT of RUQ
Recurrent pancreatitis	Persistent boring pain, might radiate to back, vomiting	Serum amylase and lipase ± serum trypsinogen; ultrasound, CT, or MRI-ERCP of pancreas
GENITOURINARY TRACT		
Urinary tract infection	Dull suprapubic pain, flank pain	Urinalysis and urine culture; renal scan
Hydronephrosis	Unilateral abdominal or flank pain	Ultrasound of kidneys
Urolithiasis	Progressive, severe pain; flank to inguinal region to testicle	Urinalysis, ultrasound, IVP, CT
Other genitourinary disorders	Suprapubic or lower abdominal pain; genitourinary symptoms	Ultrasound of kidneys and pelvis; gynecologic evaluation
MISCELLANEOUS CAUSES		
Abdominal migraine	See text; nausea, family Hx migraine	Hx
Abdominal epilepsy	Might have seizure prodrome	EEG (can require >1 study, including sleep-deprived EEG)
Gilbert syndrome	Mild abdominal pain (causal or coincidental?); slightly elevated unconjugated bilirubin	Serum bilirubin
Familial Mediterranean fever	Paroxysmal episodes of fever, severe abdominal pain, and tenderness with other evidence of polyserositis	Hx and PE during an episode, DNA diagnosis
Sickle cell crisis	Anemia	Hematologic evaluation
Lead poisoning	Vague abdominal pain ± constipation	Serum lead level
Henoch-Schönlein purpura	Recurrent, severe crampy abdominal pain, occult blood in stool, characteristic rash, arthritis	Hx, PE, urinalysis
Angioneurotic edema	Swelling of face or airway, crampy pain	Hx, PE, upper GI contrast x-rays, serum C1 esterase inhibitor
Acute intermittent porphyria	Severe pain precipitated by drugs, fasting, or infections	Spot urine for porphyrins
Anterior cutaneous nerve entrapment syndrome (ACNES)	Exquisite localized (~2 × 2 cm) tenderness that is replicable, most often right lower quadrant	Pain relief within 15 min of abdominal wall injection of local anesthetic; may need surgery

ERCP, Endoscopic retrograde cholangiopancreatography.*EEG* , Electroencephalogram; *GI* , gastrointestinal; *Hx* , history; *IVP* , intravenous pyelography; *O&P* , ova and parasites; *PE* , physical exam; *RLQ* , right lower quadrant; *RUQ* , right upper quadrant.

Table 332.14

Distinguishing Features of Acute Abdominal Pain in Children

DISEASE	ONSET	LOCATION	REFERRAL	QUALITY	COMMENTS
Pancreatitis	Acute	Epigastric, left upper quadrant	Back	Constant, sharp, boring	Nausea, emesis, tenderness

Intestinal obstruction	Acute or gradual	Periumbilical-lower abdomen	Back	Alternating cramping (colic) and painless periods	Distention, obstipation, emesis, increased bowel sounds
Appendicitis	Acute (1-3 days)	Periumbilical, then localized to lower right quadrant; generalized with peritonitis	Back or pelvis if retrocecal	Sharp, steady	Anorexia, nausea, emesis, local tenderness, fever with peritonitis
Intussusception	Acute	Periumbilical-lower abdomen	None	Cramping, with painless periods	Hematochezia, knees in pulled-up position
Urolithiasis	Acute, sudden	Back (unilateral)	Groin	Sharp, intermittent, cramping	Hematuria
Urinary tract infection	Acute	Back	Bladder	Dull to sharp	Fever, costovertebral angle tenderness, dysuria, urinary frequency
Pelvic inflammatory disease	Acute	Pelvis, lower quadrant	Upper thigh	Aching, peritoneal signs	Vaginal discharge, fever
Small bowel obstruction	Acute to subacute	Periumbilical	None	Cramping diffuse	Emesis and obstipation
Ruptured ectopic pregnancy	Acute sudden	Pelvis, lower quadrant	None	Sharp, intense, localized	Vaginal bleeding, shock

Visceral pain tends to be dull and aching and is experienced in the dermatome from which the affected organ receives innervations. So, most often, the pain and tenderness are not felt over the site of the disease process. Painful stimuli originating in the liver, pancreas, biliary tree, stomach, or upper bowel are felt in the epigastrium; pain from the distal small bowel, cecum, appendix, or proximal colon is felt at the umbilicus; and pain from the distal large bowel, urinary tract, or pelvic organs is usually suprapubic. The pain from the cecum, ascending colon, and descending colon sometimes is felt at the site of the lesion because of the short mesocecum and corresponding mesocolon. The pain caused by appendicitis is initially felt in the periumbilical region, and pain from the transverse colon is usually felt in the supra pubic region. The shifting (localization) of pain is a pointer toward diagnosis; for example, periumbilical pain of a few hours localizing to the right lower quadrant suggests appendicitis. Radiation of pain can be helpful in diagnosis; for example, in biliary colic the radiation of pain is toward the inferior angle of the right scapula, pancreatic pain radiated to the back, and the renal colic pain is radiated to the inguinal region on the same side.

Somatic pain is intense and usually well localized. When the inflamed viscus comes in contact with a somatic organ such as the parietal peritoneum or the abdominal wall, pain is localized to that site. Peritonitis gives rise to generalized abdominal pain with rigidity, involuntary guarding, rebound tenderness, and cutaneous hyperesthesia on physical examination.

Referred pain from extraintestinal locations, from shared central projections with the sensory pathway from the abdominal wall, can give rise to abdominal pain, as in pneumonia when the parietal pleural pain is referred to the abdomen.

Gastrointestinal Hemorrhage

Bleeding can occur anywhere along the GI tract, and identification of the site may be challenging (Table 332.15). Bleeding that originates in the esophagus, stomach, or duodenum can cause **hematemesis.** When exposed to gastric or intestinal juices, blood quickly darkens to resemble coffee grounds; massive bleeding is likely to be red. Red or maroon blood in stools, **hematochezia,** signifies either a distal bleeding site or massive hemorrhage above the distal ileum. Moderate to mild bleeding from sites above the distal ileum tends to cause blackened stools of tarry consistency **(melena);** major hemorrhages in the duodenum or above can also cause melena.

Table 332.15

Differential Diagnosis of Gastrointestinal Bleeding in Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Bacterial enteritis Milk protein allergy intolerance Intussusception Swallowed maternal blood Anal fissure Lymphonodular hyperplasia	Bacterial enteritis Anal fissure Colonic polyps Intussusception Peptic ulcer/gastritis Swallowed epistaxis Prolapse (traumatic) gastropathy secondary to emesis Mallory-Weiss syndrome	Bacterial enteritis Inflammatory bowel disease Peptic ulcer/gastritis Prolapse (traumatic) gastropathy secondary to emesis Mallory-Weiss syndrome Colonic polyps Anal fissure
RARE		
Volvulus Necrotizing enterocolitis Meckel diverticulum Stress ulcer, gastritis Coagulation disorder (hemorrhagic disease of newborn) Esophagitis	Esophageal varices Esophagitis Meckel diverticulum Lymphonodular hyperplasia Henoch-Schönlein purpura Foreign body Hemangioma, arteriovenous malformation	Hemorrhoids Esophageal varices Esophagitis Pill ulcer Telangiectasia-angiodysplasia Graft versus host disease Duplication cyst • Angiodysplasia

	Sexual abuse Hemolytic-uremic syndrome Inflammatory bowel disease Coagulopathy Duplication cyst • Angiodysplasia • Angiodysplasia with von Willebrand disease • Blue rubber bleb nevus syndrome	• Angiodysplasia with von Willebrand disease • Blue rubber bleb nevus syndrome

Erosive damage to the mucosa of the GI tract is the most common cause of bleeding, although variceal bleeding secondary to portal hypertension occurs often enough to require consideration. Prolapse gastropathy producing subepithelial hemorrhage and Mallory-Weiss lesions secondary to mucosal tears associated with emesis are causes of upper intestinal bleeds. Vascular malformations are a rare cause in children; they are difficult to identify (Figs. 332.1 and 332.2). Upper intestinal bleeding is evaluated with esophagogastroduodenoscopy. Evaluation of the small intestine is facilitated by capsule endoscopy. The capsule-sized imaging device is swallowed in older children or placed endoscopically in younger children. Lower GI bleeding is investigated with a colonoscopy. In brisk intestinal bleeding of unknown location, a tagged red blood cell scan is helpful in locating the site of the bleeding, although CT angiography is usually diagnostic. Occult blood in stool is usually detected by using commercially available fecal occult blood testing cards, which are based on a chemical reaction between the chemical guaiac and oxidizing action of a substrate (hemoglobin), giving a blue color. The guaiac test is very sensitive, but random testing can miss chronic blood loss, which can lead to iron-deficiency anemia. GI hemorrhage can produce hypotension and tachycardia but rarely causes GI symptoms; brisk duodenal or gastric bleeding can lead to nausea, vomiting, or diarrhea. The breakdown products of intraluminal blood might tip patients into hepatic coma if liver function is already compromised and can lead to elevation of serum bilirubin.

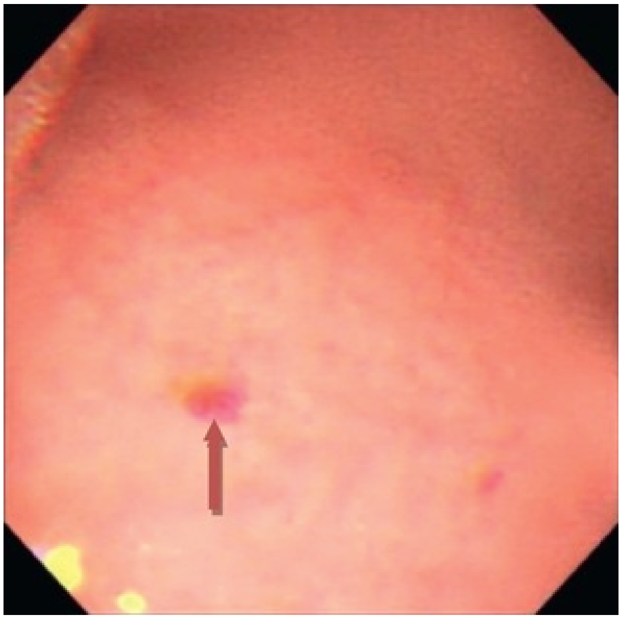

FIG. 332.1 A 7 yr old boy had tarry stool for days. Panendoscopy showed multiple cherry red flat spots in the gastric mucosa, compatible with the findings of angiodysplasia in computed tomographic angiography. (From Chuang F, Lin JS, Yeung C, et al: Intestinal angiodysplasia: an uncommon cause of gastrointestinal bleeding in children. *Pediatr Neonatol* 52:214–218, 2011. Fig. 2.)

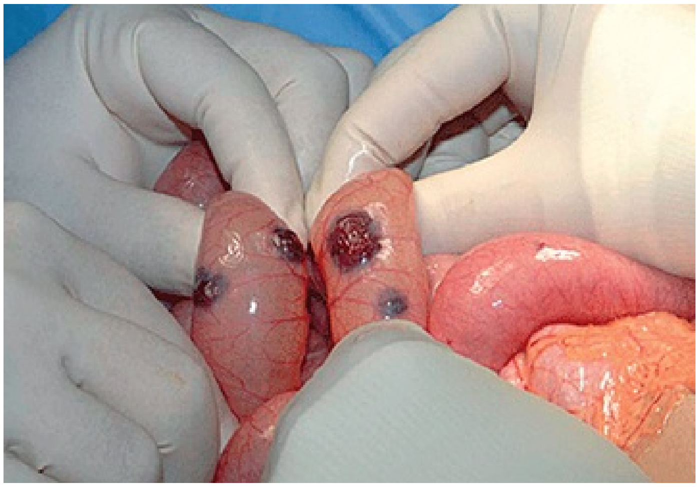

FIG. 332.2 Operative features of blue rubber bleb nevus syndrome: these lesions are similar to cutaneous lesions. (From Hasosah MY, Abdul-Wahab AA, Bin-Yahab SA, et al: Blue rubber bled nevus syndrome: extensive small bowel vascular lesions responsible for gastrointestinal bleeding. *J Pediatr Child Health* 46:63–65, 2010. Fig 3.)

Abdominal Distention and Abdominal Masses

Enlargement of the abdomen can result from diminished tone of the wall musculature or from increased content: fluid, gas, or solid. Ascites, the accumulation of fluid in the peritoneal cavity, distends the abdomen both in the flanks and anteriorly when it is large in volume. This fluid shifts with movement of the patient and conducts a percussion wave. Ascitic fluid is usually a transudate with a low protein concentration resulting from reduced plasma colloid osmotic pressure of hypoalbuminemia and/or from raised portal venous pressure. In cases of portal hypertension, the fluid leak probably occurs from lymphatics on the liver surface and from visceral peritoneal capillaries, but ascites does not usually develop until the serum albumin level falls. Sodium excretion in the urine decreases greatly as the ascitic fluid accumulates, and thus additional dietary sodium goes directly to the peritoneal space, taking with it more water. When ascitic fluid contains a high protein concentration, it is usually an exudate caused by an inflammatory or neoplastic lesion.

When fluid distends the gut, either obstruction or imbalance between absorption and secretion should be suspected. The factors causing fluid accumulation in the bowel lumen often cause gas to accumulate too. The result may be audible gurgling noises. The source of gas is usually swallowed air, but endogenous flora can increase considerably in malabsorptive states and produce excessive gas when substrate reaches the lower intestine. Gas in the peritoneal cavity (pneumoperitoneum) is usually caused by a perforated viscus and can cause abdominal distention depending on the amount of gas leak. A tympanitic percussion note, even over solid organs such as the liver, indicates a large collection of gas in the peritoneum.

An abdominal organ can enlarge diffusely or be affected by a discrete mass. In the digestive tract, such discrete masses can occur in the lumen, wall, omentum, or mesentery. In a constipated child, mobile, nontender fecal masses are often found. Congenital anomalies, cysts, or inflammatory processes can affect the wall of the gut. Gut wall neoplasms are extremely rare in children. The pathologic enlargement of liver, spleen, bladder, and kidneys can give rise to abdominal distention.

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SECTION 2

The Oral Cavity

OUTLINE

Chapter 333 Development and Developmental Anomalies of the Teeth

Chapter 334 Disorders of the Oral Cavity Associated With Other Conditions

Chapter 335 Malocclusion

Chapter 336 Cleft Lip and Palate

Chapter 337 Syndromes With Oral Manifestations

Chapter 338 Dental Caries

Chapter 339 Periodontal Diseases

Chapter 340 Dental Trauma

Chapter 341 Common Lesions of the Oral Soft Tissues

Chapter 342 Diseases of the Salivary Glands and Jaws

Chapter 343 Diagnostic Radiology in Dental Assessment

CHAPTER 333

Development and Developmental Anomalies of the Teeth

Vineet Dhar

Newborn infants do not have teeth for about first 6 mo after birth (predentate period). At this stage, the upper and lower alveolar ridges in the mouth, also known as gum pads, house the primary (deciduous) and some permanent tooth buds. The primary dentition period starts with eruption of the first primary tooth; all 20 primary teeth erupt by 3 yr of age. The permanent teeth start erupting around age of 6 yr, and the transition to full permanent dentition is completed by 13 yr of age. The transition time between primary and permanent dentition, when a mix of primary and permanent teeth are present, is referred to as mixed dentition.

Development of Teeth

Initiation

The primary teeth form in dental crypts that arise from a band of epithelial cells incorporated into each developing jaw. By 12 wk of fetal life, each of these epithelial bands **(dental laminae)** has 5 areas of rapid growth on each side of the maxilla and the mandible, seen as rounded, budlike enlargements. Organization of adjacent mesenchyme takes place in each area of epithelial growth, and the 2 elements together are the beginning of a tooth.

After the formation of these crypts for the 20 primary teeth, another generation of tooth buds forms lingually (toward the tongue); these will develop into the succeeding permanent incisors, canines, and premolars that eventually replace the primary teeth. This process takes place from approximately 5 mo of gestation for the central incisors to approximately 10 mo of age for the second premolars. On the other hand, the permanent first, second, and third molars arise from extension of the dental laminae distal to the second primary molars; buds for these teeth develop at approximately 4 mo of gestation, 1 yr of age, and 4-5 yr of age, respectively.

Histodifferentiation–Morphodifferentiation

As the epithelial bud proliferates, the deeper surface invaginates and a mass of mesenchyme becomes partially enclosed. The epithelial cells differentiate into the ameloblasts that lay down an organic matrix that forms enamel; the mesenchyme forms the dentin and dental pulp.

Calcification

After the organic matrix has been laid down, the deposition of the inorganic mineral crystals takes place from several sites of calcification that later coalesce. The characteristics of the inorganic portions of a tooth can be altered by disturbances in formation of the matrix, decreased availability of minerals, or the incorporation of foreign materials. Such disturbances can affect the color, texture, or thickness of the tooth surface. Calcification of primary teeth begins at 3-4 mo in utero and concludes postnatally at approximately 12 mo, with mineralization of the second primary molars (Table 333.1).

Table 333.1

Calcification, Crown Completion, and Eruption

TOOTH	FIRST EVIDENCE OF CALCIFICATION	CROWN COMPLETED	ERUPTION
PRIMARY DENTITION			
Maxillary			
Central incisor	3-4 mo in utero	4 mo	7.5 mo
Lateral incisor	4.5 mo in utero	5 mo	8 mo
Canine	5.5 mo in utero	9 mo	16-20 mo
First molar	5 mo in utero	6 mo	12-16 mo
Second molar	6 mo in utero	10-12 mo	20-30 mo
Mandibular			
Central incisor	4.5 mo in utero	4 mo	6.5 mo
Lateral incisor	4.5 mo in utero	4¼ mo	7 mo
Canine	5 mo in utero	9 mo	16-20 mo
First molar	5 mo in utero	6 mo	12-16 mo
Second molar	6 mo in utero	10-12 mo	20-30 mo
PERMANENT DENTITION			

Maxillary			
Central incisor	3-4 mo	4-5 yr	7-8 yr
Lateral incisor	10 mo	4-5 yr	8-9 yr
Canine	4-5 mo	6-7 yr	11-12 yr
First premolar	1.5- 1¾ yr	5-6 yr	10-11 yr
Second premolar	2- 2¼ yr	6-7 yr	10-12 yr
First molar	At birth	2.5-3 yr	6-7 yr
Second molar	2.5-3 yr	7-8 yr	12-13 yr
Third molar	7-9 yr	12-16 yr	17-21 yr
Mandibular			
Central incisor	3-4 mo	4-5 yr	6-7 yr
Lateral incisor	3-4 mo	4-5 yr	7-8 yr
Canine	4-5 mo	6-7 yr	9-10 yr
First premolar	1¾ -2 yr	5-6 yr	10-12 yr
Second premolar	2¼ -2.5 yr	6-7 yr	11-12 yr
First molar	At birth	2.5-3 yr	6-7 yr
Second molar	2.5-3 yr	7-8 yr	11-13 yr
Third molar	8-10 yr	12-16 yr	17-21 yr

Modified from Logan WHG, Kronfeld R: Development of the human jaws and surrounding structures from birth to age 15 years. *J Am Dent Assoc* 20:379, 1993.

Eruption

At the time of tooth bud formation, each tooth begins a continuous movement toward the oral cavity. Table 333.1 lists the times of eruption of the primary and permanent teeth.

Anomalies Associated With Eruption Pattern: Delayed eruption of the 20 primary teeth can be familial or indicate systemic or nutritional disturbances such as hypopituitarism, hypothyroidism, cleidocranial dysplasia, trisomy 21, and multiple other syndromes. Failure of eruption of single or small groups of teeth can arise from local causes such as malpositioned teeth, supernumerary teeth, cysts, or retained primary teeth. Premature *loss* of primary teeth is most commonly caused by premature *eruption* of the permanent teeth. If the entire dentition is advanced for age and sex, precocious puberty or hyperthyroidism should be considered.

Natal teeth are observed in approximately 1 in 2,000 newborn infants, usually in the position of the mandibular central incisors. Natal teeth are present at birth, whereas **neonatal teeth** erupt in the first mo of life. Attachment of natal and neonatal teeth is generally limited to the gingival margin, with little root formation or bony support. They may be a supernumerary or a prematurely erupted primary tooth. A radiograph can easily differentiate between the 2 conditions. Natal teeth are associated with cleft palate, Pierre Robin syndrome, Ellis-van Creveld syndrome, Hallermann-Streiff syndrome, pachyonychia congenita, and other anomalies. A family history of natal teeth or premature eruption is present in 15–20% of affected children.

Natal or neonatal teeth occasionally result in pain and refusal to feed and can produce maternal discomfort because of abrasion or biting of the nipple during nursing. If the tooth is mobile, there is a danger of detachment, with aspiration of the tooth. Because the tongue lies between the alveolar processes during birth, it can become lacerated (**Riga-Fede disease**). Decisions regarding extraction of prematurely erupted primary teeth must be made on an individual basis.

Exfoliation failure occurs when a primary tooth is not shed before the eruption of its permanent successor. Most often the primary tooth exfoliates eventually, but in some cases the primary tooth needs to be extracted. This occurs most commonly in the mandibular incisor region.

Anomalies Associated With Tooth Development

Both failures and excesses of tooth initiation are observed. Developmentally missing teeth can result from environmental insult, a genetic defect involving only teeth, or the manifestation of a syndrome.

Anomalies of Number: Anodontia, or absence of teeth, occurs when no tooth buds form (ectodermal dysplasia, or familial missing teeth) or when there is a disturbance of a normal site of initiation (the area of a palatal cleft). The teeth that are most commonly absent are the third molars, the maxillary lateral incisors, and the mandibular second premolars.

If the dental lamina produces more than the normal number of buds, **supernumerary teeth** occur, most often in the area between the maxillary central incisors. Because they tend to disrupt the position and eruption of the adjacent normal teeth, their identification by radiographic examination is important. Supernumerary teeth also occur with cleidocranial dysplasia (see Chapter 337) and in the area of cleft palates.

Anomalies of Size: Twinning, in which 2 teeth are joined together, is most often observed in the mandibular incisors of the primary dentition. It can result from gemination, fusion, or concrescence. **Gemination** is the result of the division of one tooth germ to form a bifid crown on a single root with a common pulp canal; an extra tooth appears to be present in the dental arch. **Fusion** is the joining of incompletely developed teeth that, owing to pressure, trauma, or crowding, continue to develop as 1 tooth. Fused teeth are sometimes joined along their entire length; in other cases a single wide crown is supported on 2 roots. **Concrescence** is the attachment of the roots of closely approximated adjacent teeth by an excessive deposit of cementum. This type of twinning, unlike the others, is found most often in the maxillary molar region.

Disturbances during differentiation can result in alterations in dental morphology, such as **macrodonti** a (large teeth) or **microdontia** (small teeth). The maxillary lateral incisors can assume a slender, tapering shape **(peg-shaped laterals).**

Anomalies of Shape: Dens in Dente or **Dens Invaginatus** presents as *tooth within tooth* appearance, which results from invagination of inner enamel epithelium caused by disruption during morphodifferentiation,

Dens Evaginatus presents as an extra cusp on anterior or posterior teeth, which contains enamel, dentin, and sometimes even pulp tissue. In the anterior teeth the cusp is talon shaped and presents in the cingulum area.

Taurodontism is more common in permanent molars and is characterized by elongated pulp chamber with short stunted roots due to failure or late invagination of Hertwig epithelial root sheath. It may be associated with several syndromic conditions such as Down syndrome, trichodento-osseous syndrome, ectodermal dysplasia (hypohidrotic), and amelogenesis imperfecta (hypomaturation-hypoplastic type).

Dilaceration is an abnormal bend or curve in root possibly due to trauma. It may be subsequent to injury to the primary predecessor tooth.

Anomalies of Structure: Amelogenesis imperfecta represents a group of hereditary conditions that manifest in enamel defects of the primary and permanent teeth without evidence of systemic disorders (Fig. 333.1). The teeth are covered by only a thin layer of abnormally formed enamel through which the yellow underlying dentin is seen. The primary teeth are generally affected more than the permanent teeth. Susceptibility to caries is low, but the enamel is subject to destruction from abrasion. Complete coverage of the crown may be indicated for dentin protection, to reduce tooth sensitivity, and for improved appearance.

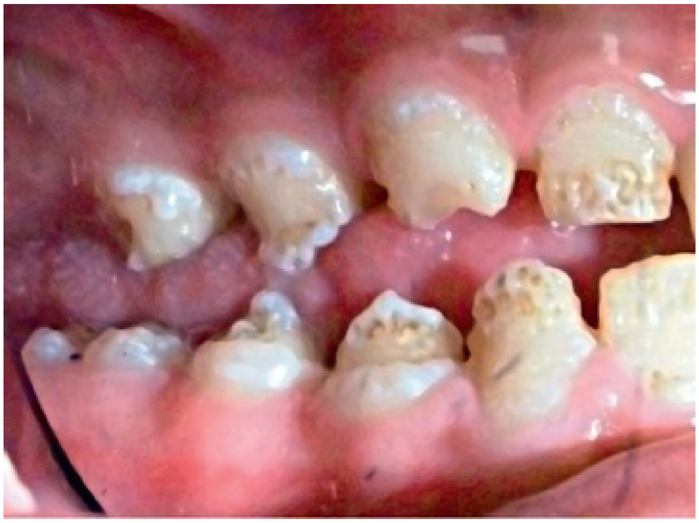

FIG. 333.1 **Amelogenesis imperfecta, hypoplastic type. The enamel defect results in areas of missing or thin enamel, as well as grooves and pits.**

Dentinogenesis imperfecta, or hereditary opalescent dentin, is a condition analogous to amelogenesis imperfecta in which the odontoblasts fail to differentiate normally, resulting in poorly calcified dentin (Fig. 333.2). This autosomal dominant disorder can also occur in patients with **osteogenesis imperfecta.** The enamel-dentin junction is altered, causing enamel to break away. The exposed dentin is then susceptible to abrasion, in some cases worn to the gingiva. The teeth are opaque and pearly, and the pulp chambers are generally obliterated by calcification. Both primary and permanent teeth are usually involved. If there is excessive wear of the teeth, selected complete coverage of the teeth may be indicated to prevent further tooth loss and improve appearance.

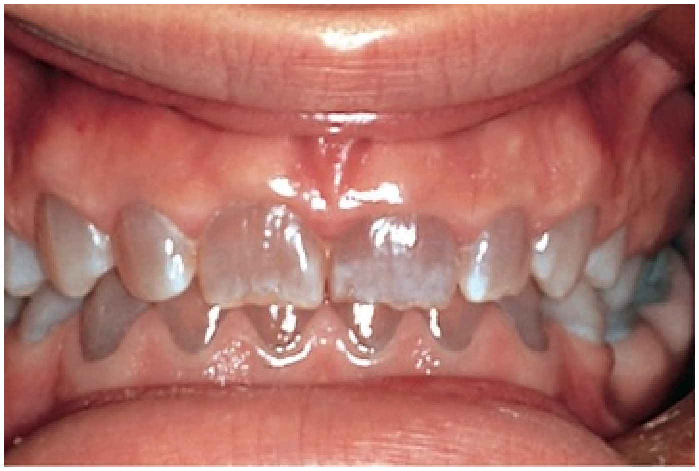

FIG. 333.2 Dentinogenesis imperfecta. The bluish, opalescent sheen on several of these teeth results from genetically defective dentin. This condition may be associated with osteogenesis imperfecta. (From Nazif MM, Martin BS, McKibben DH, et al: Oral disorders. In Zitelli BJ, Davis HW, editors: *Atlas of pediatric physical diagnosis,* ed 4, Philadelphia, 2002, Mosby, p 703.)

Localized disturbances of calcification that correlate with periods of illness, malnutrition, premature birth, or birth trauma are common. **Hypocalcification** appears as opaque white patches or horizontal lines on the tooth; **hypoplasia** is more severe and manifests as pitting or areas devoid of enamel. Systemic conditions, such as renal failure and cystic fibrosis, are associated with enamel defects. Local trauma to the primary incisors can also affect calcification of permanent incisors.

Fluorosis (mottled enamel) can result from systemic fluoride consumption >0.05 mg/kg/day during enamel formation. This high fluoride consumption can be caused by residing in an area of high fluoride content of the drinking water (>2.0 ppm), swallowing excessive fluoridated toothpaste, or inappropriate fluoride prescriptions. Excessive fluoride during enamel formation affects ameloblastic function, resulting in inconspicuous white, lacy patches on the enamel to severe brownish discoloration and hypoplasia. The latter changes are usually seen with fluoride concentrations in the drinking water >5.0 ppm.

Anomalies of Color: Discolored teeth can result from incorporation of foreign substances into developing enamel. Neonatal hyperbilirubinemia can produce blue to black discoloration of the primary teeth. Porphyria produces a red-brown discoloration. Tetracyclines are extensively incorporated into bones and teeth and, if administered during the period of formation of enamel, can result in brown-yellow discoloration and hypoplasia of the enamel. Such teeth fluoresce under ultraviolet light. The period at risk extends from approximately 4 mo of gestation to 7 yr of life. Repeated or prolonged therapy with tetracycline carries the highest risk.

Teething is associated with primary tooth eruption and may manifest with benign symptoms such as gingival hyperemia, irritability, sucking fingers, and drooling; some infants have no symptoms or symptoms not identified by their parents. Low-grade fever is an inconsistent finding. The treatment of symptoms of teething is often unnecessary but could include oral analgesics and iced teething rings. “Natural” (homeopathic) teething remedies may contain toxic additives and should be avoided.

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CHAPTER 334

Disorders of the Oral Cavity Associated With Other Conditions

Vineet Dhar

Disorders of the teeth and surrounding structures can occur in isolation or in combination with other systemic conditions (Table 334.1). Most commonly, medical conditions that occur during tooth development can affect tooth formation or appearance. Damage to teeth during their development is permanent.

Table 334.1

Dental Problems Associated With Selected Medical Conditions

MEDICAL CONDITION	COMMON ASSOCIATED DENTAL OR ORAL FINDINGS
Cleft lip and palate	Missing teeth, extra (supernumerary) teeth, shifting of arch segments, feeding difficulties, speech problems
Kidney failure	Mottled enamel (permanent teeth), facial dysmorphology
Cystic fibrosis	Stained teeth with extensive medication, mottled enamel
Immunosuppression	Oral candidiasis with potential for systemic candidiasis, cyclosporine-induced gingival hyperplasia
Low birthweight	Palatal groove, narrow arch with prolonged oral intubation; enamel defects of primary teeth
Heart defects with susceptibility to bacterial endocarditis	Bacteremia from dental procedures or trauma
Neutrophil chemotactic deficiency	Aggressive periodontitis (loss of supporting bone around teeth)
Diabetes mellitus type I (uncontrolled)	Aggressive periodontitis
Neuromotor dysfunction	Oral trauma from falling; malocclusion (open bite); gingivitis from lack of hygiene
Prolonged illness (generalized) during tooth formation	Enamel hypoplasia of crown portions forming during illness
Seizures	Gingival enlargement if phenytoin is used
Maternal infections	Syphilis: abnormally shaped teeth
Vitamin D–dependent rickets	Enamel hypoplasia

CHAPTER 335

Malocclusion

Vineet Dhar

The oral cavity is essentially a masticatory instrument. The purpose of the anterior teeth is to bite off large portions of food. The posterior teeth reduce foodstuff to a soft, moist bolus. The cheeks and tongue force the food onto the areas of tooth contact. Establishing a proper relationship between the mandibular and maxillary teeth is important for both physiologic and cosmetic reasons.

Variations in Growth Patterns

Growth patterns are classified into 3 main types of occlusion, determined when the jaws are closed and the teeth are held together (Fig. 335.1). According to the Angle classification of malocclusion, in **class I occlusion** (normal), the cusps of the posterior mandibular teeth interdigitate ahead of and inside of the corresponding cusps of the opposing maxillary teeth. This relationship provides a normal facial profile.

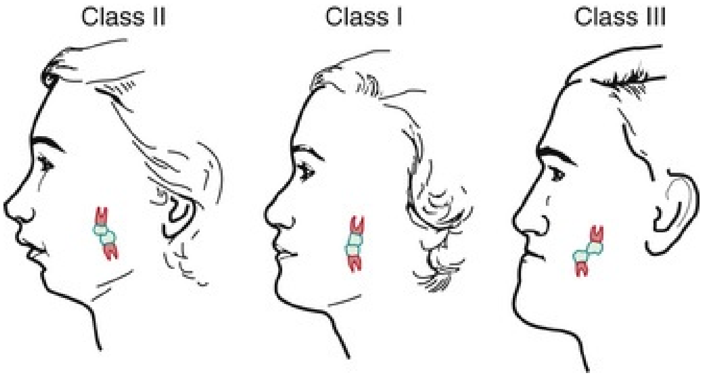

FIG. 335.1 **Angle classification of occlusion. The typical correspondence between the facial-jaw profile and molar relationship is shown. (Data from Borrie FR, Bearn DR,**

Innes NP, Iheozor-Ejiofor Z: Interventions for the cessation of non-nutritive sucking habits in children. *Cochrane Database Syst Rev* 31(3):CD008694, 2015. doi: 10.1002/14651858.CD008694.pub2.)

In **class II malocclusion,** *buck teeth* , the cusps of the posterior mandibular teeth are behind and inside the corresponding cusps of the maxillary teeth. This common occlusal disharmony is found in approximately 45% of the population. The facial profile can give the appearance of a *receding chin* (retrognathia) (mandibular deficiency) or protruding front teeth. The resultant increased space between upper and lower anterior teeth encourage finger sucking and tongue-thrust habits. In addition, children with pronounced class II malocclusions are at greater risks of damage to the incisors as a consequence of trauma. Treatment includes orthodontic retraction of the maxilla or stimulation of the mandible.

In **class III malocclusion,** *underbite* , the cusps of the posterior mandibular teeth interdigitate a tooth or more ahead of their opposing maxillary counterparts. The anterior teeth appear in crossbite with the mandibular incisors protruding beyond the maxillary incisors. The facial profile gives the appearance of a *protruding chin* **(prognathia)** with or without an appearance of maxillary deficiency. If necessary, treatment includes mandibular excess reduction osteotomy or orthodontic maxillary facial protrusion.

Crossbite

Normally, the mandibular teeth are in a position just inside the maxillary teeth, so that the outside mandibular cusps or incisal edges meet the central portion of the opposing maxillary teeth. A reversal of this relation is referred to as a crossbite. Crossbites can be anterior, involving the incisors; can be posterior, involving the molars; or can involve single or multiple teeth.

Open and Closed Bites

If the posterior mandibular and maxillary teeth make contact with each other, but the anterior teeth are still apart, the condition is called an *open bite*. Open bites can result from skeletal growth pattern or digit sucking. If digit sucking is terminated before skeletal and dental growth is complete, the open bite might resolve naturally. If mandibular anterior teeth occlude inside the maxillary anterior teeth in an overclosed position, the condition is referred to as a *closed* or *deep bite*.

Treatment of open and closed bites consists of orthodontic correction, generally performed in the preteen or teenage years. Some cases require orthognathic surgery to position the jaws optimally in a vertical direction.

Dental Crowding

Overlap of incisors can result when the jaws are too small or the teeth are too large for adequate alignment of the teeth. Growth of the jaws is mostly in the posterior aspects of the mandible and maxilla, and therefore inadequate space for the teeth at 7 or 8 yr of age will not resolve with growth of the jaws. Spacing in the primary dentition is normal and favorable for adequate alignment of successor teeth.

Digit Sucking

Various and conflicting etiologic theories and recommendations for correction have been proposed for digit sucking in children. Prolonged digit sucking can cause flaring of the maxillary incisor teeth, an open bite, and a posterior crossbite. The prevalence of digit sucking decreases steadily from the age of 2 yr to approximately 10% by the age of 5 yr. The earlier the habit is discontinued after the eruption of the permanent maxillary incisors (age 7-8 yr), the greater the likelihood that there will be lessening effects on the dentition.

A variety of treatments have been suggested, from behavioral modification to insertion of an appliance with extensions that serves as a reminder when the child attempts to insert the digit. Unfortunately, a systematic review has found only low-quality evidence of the effectiveness of interventions such as orthodontic appliances and psychological interventions. The greatest likelihood of success occurs in cases in which the child desires to stop. Stopping of the habit will not rectify a malocclusion caused by a prior deviant growth pattern.

CHAPTER 336

Cleft Lip and Palate

Vineet Dhar

Clefts of the lip and palate are distinct entities which are closely related embryologically, functionally, and genetically. It is thought that cleft of the lip appears because of hypoplasia of the mesenchymal layer, resulting in a failure of the medial nasal and maxillary processes to join. Cleft of the palate results from failure of palatal shelves to approximate or fuse.

Incidence and Epidemiology

The incidence of cleft lip with or without cleft palate is approximately 1 in 750 white births; the incidence of cleft palate alone is approximately 1 in 2,500 white births. Clefts of the lip are more common in males. Possible causes include maternal drug exposure, a syndrome-malformation complex, or genetic factors. Although clefts of lips and palates appear to occur sporadically, the presence of susceptible genes appears important. There are approximately 400 syndromes associated with cleft lip and palates. There are families in which a cleft lip or palate, or both, is inherited in a dominant fashion (**van der Woude syndrome**), and careful examination of parents is important to distinguish this type from others, because the recurrence risk is 50%. Ethnic factors also affect the incidence of cleft lip and palate; the incidence is highest among Asians (~1 in 500) and Native Americans (~1 in 300) and lowest among blacks (~1 in 2,500). Cleft lip may be associated with other cranial facial anomalies, whereas cleft palate may be associated with central nervous system anomalies.

Clinical Manifestations

Cleft lip can vary from a small notch in the vermilion border to a complete separation involving skin, muscle, mucosa, tooth, and bone. Clefts of the lip may be unilateral (more often on the left side) or bilateral and can involve the alveolar ridge (Fig. 336.1).

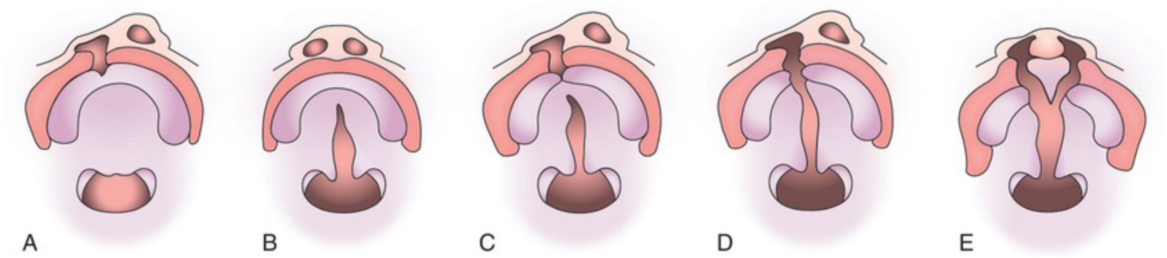

FIG. 336.1 **Nonsyndromic orofacial clefts. A, Cleft lip and alveolus. B, Cleft palate. C, Incomplete unilateral cleft lip and palate. D, Complete unilateral cleft lip and palate. E, Complete bilateral cleft lip and palate. (From Shaw WC: *Orthodontics and occlusal management* . Oxford, UK, 1993, Butterworth-Heinemann.)**

Isolated cleft palate occurs in the midline and might involve only the uvula or can extend into or through the soft and hard palates to the incisive foramen. When associated with cleft lip, the defect can involve the midline of the soft palate and extend into the hard palate on one or both sides, exposing one or both of the nasal cavities as a unilateral or bilateral cleft palate. The palate can also have a **submucosal cleft** indicated by a bifid uvula, partial separation of muscle with intact mucosa, or a palpable notch at the posterior of the palate (see Fig. 336.1).

Treatment

A complete program of habilitation for the child with a cleft lip or palate can require years of special treatment by a team consisting of a pediatrician, plastic surgeon, otolaryngologist, oral and maxillofacial surgeon, pediatric dentist, prosthodontist, orthodontist, speech therapist, geneticist, medical social worker, psychologist, and public health nurse.

The immediate problem in an infant born with a cleft lip or palate is feeding. Although some advocate the construction of a plastic obturator to assist in feedings, most believe that, with the use of soft artificial nipples with large openings, a squeezable bottle, and proper instruction, feeding of infants with clefts can be achieved.

Surgical closure of a cleft lip is usually performed by 3 mo of age, when the infant has shown satisfactory weight gain and is free of any oral, respiratory, or systemic infection. Modification of the Millard rotation–advancement technique is the most commonly used technique; a staggered suture line minimizes notching of the lip from retraction of scar tissue. The initial repair may be revised at 4 or 5 yr of age. Corrective surgery on the nose may be delayed until adolescence. Nasal surgery can also be performed at the time of the lip repair. Cosmetic results depend on the extent of the original deformity, healing potential of the individual patient, absence of infection, and the skill of the surgeon.

Because clefts of the palate vary considerably in size, shape, and degree of deformity, the timing of surgical correction should be individualized. Criteria such as width of the cleft, adequacy of the existing palatal segments, morphology of the surrounding areas (width of the oropharynx), and neuromuscular function of the soft palate and pharyngeal walls affect the decision. The goals of surgery are the union of the cleft segments, intelligible and pleasant speech, reduction of nasal regurgitation, and avoidance of injury to the growing maxilla.

In an otherwise healthy child, closure of the palate is usually done before 1 yr of age to enhance normal speech development. When surgical correction is delayed beyond the 3rd yr, a contoured speech bulb can be attached to the posterior of a maxillary denture so that contraction of the pharyngeal and velopharyngeal muscles can bring tissues into contact with the bulb to accomplish occlusion of the nasopharynx and help the child to develop intelligible speech.

A cleft palate usually crosses the alveolar ridge and interferes with the formation of teeth in the maxillary anterior region. Teeth in the cleft area may be displaced, malformed, or missing. Missing teeth or teeth that are nonfunctional are replaced by prosthetic devices.

Postoperative Management

During the immediate postoperative period, special nursing care is essential. Gentle aspiration of the nasopharynx minimizes the chances of the common complications of atelectasis or pneumonia. The primary considerations in postoperative care are maintenance of a clean suture line and avoidance of tension on the sutures. The infant is fed with a specially designed bottle and the arms are restrained with elbow cuffs. A fluid or semifluid diet is maintained for 3 wk. The patient's hands, toys, and other foreign bodies must be kept away from the surgical site.

Sequelae

Recurrent otitis media and subsequent hearing loss are frequent with cleft palate. Displacement of the maxillary arches and malposition of the teeth usually require orthodontic correction. Misarticulations and velopharyngeal dysfunction are often associated with cleft lip and palate and may be present or persist because of physiologic dysfunction, anatomic insufficiency, malocclusion, or inadequate surgical closure of the palate. Such speech is characterized by the emission of air from the nose and by a hypernasal quality with certain sounds, or by compensatory misarticulations (glottal stops). Before and sometimes after palatal surgery, the speech defect is caused by inadequacies in function of the palatal and pharyngeal muscles. The muscles of the soft palate and the lateral and posterior walls of the nasopharynx constitute a valve that separates the nasopharynx from the oropharynx during swallowing and in the production of certain sounds. If the valve does not function adequately, it is difficult to build up enough pressure in the mouth to make such explosive sounds as p, b, d, t, h, y, or the sibilants s, sh, and ch, and such words as “cats,” “boats,” and “sisters” are not intelligible. After operation or the insertion of a speech appliance, speech therapy is necessary.

Velopharyngeal Dysfunction

The speech disturbance characteristic of the child with a cleft palate can also be produced by other osseous or neuromuscular abnormalities where there is an inability to form an effective seal between oropharynx and nasopharynx during swallowing or phonation. In a child who has the potential for abnormal speech, adenoidectomy can precipitate overt hypernasality. If the neuromuscular function is adequate, compensation in palatopharyngeal movement might take place and the speech defect might improve, although speech therapy is necessary. In other cases, slow involution of the adenoids can allow gradual compensation in palatal and pharyngeal muscular function. This might explain why a speech defect does not become apparent in some children who have a submucous cleft palate or similar anomaly predisposing to palatopharyngeal incompetence.

Clinical Manifestations

Although clinical signs vary, the symptoms of velopharyngeal dysfunction are similar to those of a cleft palate. There may be hypernasal speech (especially noted in the articulation of pressure consonants such as p, b, d, t, h, v, f, and s); conspicuous constricting movement of the nares during speech; inability to whistle, gargle, blow out a candle, or inflate a balloon; loss of liquid through the nose when drinking with the head down; otitis media; and hearing loss. Oral inspection might reveal a cleft palate or a relatively short palate with a large oropharynx; absent, grossly asymmetric, or minimal muscular activity of the soft palate and pharynx during phonation or gagging; or a submucous cleft.

Velopharyngeal dysfunction may also be demonstrated radiographically. The head should be carefully positioned to obtain a true lateral view; one film is obtained with the patient at rest and another during continuous phonation of the vowel u as in “boom.” The soft palate contacts the posterior pharyngeal wall in normal function, whereas in velopharyngeal dysfunction such contact is absent.

In selected cases of velopharyngeal dysfunction, the palate may be retropositioned or pharyngoplasty may be performed using a flap of tissue from the posterior pharyngeal wall. Dental speech appliances have also been used successfully. The type of surgery used is best tailored to the findings on nasoendoscopy.

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CHAPTER 337

Syndromes With Oral Manifestations

Vineet Dhar

Many syndromes have distinct or accompanying facial, oral, and dental manifestations (see Apert syndrome, Chapter 609.11 ; Crouzon disease, Chapter 609.11 ; Down syndrome, Chapter 98.2).

Osteogenesis imperfecta is often accompanied by effects on the teeth, termed **dentinogenesis imperfecta** (see Chapter 333 , Fig. 333.2). Depending on the severity of presentation, treatment of the dentition varies from routine preventive and restorative monitoring to covering affected posterior teeth with stainless steel crowns, to prevent further tooth loss and improve appearance. Dentinogenesis imperfecta can also occur in isolation without the bony effects.

Another syndrome, **cleidocranial dysplasia,** has orofacial features such as frontal bossing, hypoplastic maxilla, and supernumerary teeth. The primary teeth can be overretained, and the permanent teeth remain unerupted. Supernumerary teeth are common, especially in the premolar area. Extensive dental rehabilitation may be needed to correct severe tooth crowding and unerupted and supernumerary teeth.

Ectodermal dysplasias are a heterogeneous group of conditions in which oral manifestations range from little or no involvement (the dentition is completely normal) to cases in which the teeth can be totally or partially absent or malformed (Chapter 668). Because alveolar bone does not develop in the absence of teeth, the alveolar processes can be either totally or partially absent, and the resultant overclosure of the mandible causes the lips to protrude. Facial development is otherwise not disturbed. Teeth, when present, can range from normal to small and conical. If aplasia of the buccal and labial salivary glands is present, dryness and irritation of the oral mucosa can occur. People with ectodermal dysplasia might need partial or full dentures, even at a very young age. The vertical height between the jaws is thus restored, improving the position of the lips and facial contours, as well as restoring masticatory function.

Pierre Robin syndrome consists of micrognathia and is usually accompanied by a high arched or cleft palate (Fig. 337.1). The tongue is usually of normal size, but the floor of the mouth is foreshortened. The air passages can become obstructed, particularly on inspiration, usually requiring treatment to prevent suffocation. The infant should be maintained in a prone or partially prone position so that the tongue falls forward to relieve respiratory obstruction. Some patients require tracheostomy. Mandibular distraction procedures in the neonate can improve mandibular size, enhance respiration, and facilitate oral feedings.

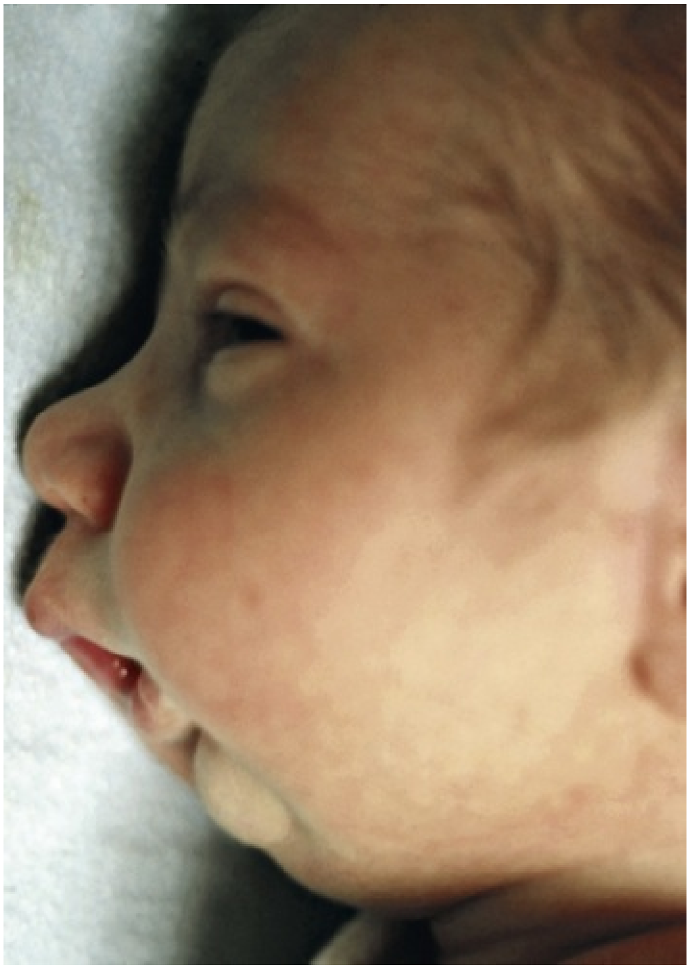

FIG. 337.1 Pierre Robin syndrome. (From Clark DA: *Atlas of neonatology,* ed 7, Philadelphia, 2000, WB Saunders, p 144.)

Sufficient spontaneous mandibular growth can take place within a few months to relieve the potential airway obstruction. Often the growth of the mandible achieves a normal profile in 4-6 yr. Of children with Pierre Robin syndrome, 30–50% have **Stickler syndrome** (types I-VI), an autosomal dominant condition that includes other findings such as prominent joints, arthritis, hypotonia, hypermobile joints, mitral valve prolapse, hearing loss, spine problems (scoliosis, kyphosis, platyspondyly), and ocular problems (high myopia, glaucoma, cataracts, retinal detachment). Symptoms may vary greatly even with a family. Mutations are noted in the genes that produce collagen (*COL2A1* in most; *COL11A1* in others) in many, but not all, patients with Stickler syndrome. Other syndromes are associated with Pierre Robin syndrome, including 22Q11.2 deletion syndrome (velocardiofacial syndrome).

Mandibulofacial dysostosis (Treacher Collins syndrome or Franceschetti syndrome) is an autosomal dominant syndrome that primarily affects the face. The facial appearance varies but is characterized by downward-sloping palpebral fissures, colobomas of the lower eyelids, sunken cheekbones, blind fistulas opening between the angles of the mouth and the ears, deformed pinnae, atypical hair growth extending toward the cheeks, receding chin, and large mouth. Facial clefts, abnormalities of the ears, and deafness are common. The mandible is usually hypoplastic; the ramus may be deficient, and the coronoid and condylar processes are flat or even aplastic. The palatal vault may be either high or cleft. Dental malocclusions are common. The teeth may be missing, hypoplastic, or displaced or be in an open bite position. Initially, the primary concern is breathing and feeding problems. Surgery to restore normal structure of the face can be performed, which may include repair of cleft palate, zygomatic and orbit reconstruction, reconstruction of the lower eyelid, external ear reconstruction, and orthognathic surgery.

Hemifacial microsomia presentation can be quite variable but is usually characterized by unilateral hypoplasia of the mandible and can be associated with partial paralysis of the facial nerve, underdeveloped ear, and blind fistulas between the angles of the mouth and the ears. Severe facial asymmetry and malocclusion can develop because of the absence or hypoplasia of the mandibular condyle on the affected side. Congenital condylar deformity tends to increase with age. Early craniofacial surgery may be indicated to minimize the deformity. This disorder can be associated with ocular and vertebral anomalies (oculoauriculovertebral spectrum, including Goldenhar syndrome); therefore radiographs of the vertebrae and ribs should be considered to determine the extent of skeletal involvement.

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CHAPTER 338

Dental Caries

Vineet Dhar

Etiology

The development of dental caries depends on interrelationships among the tooth surface, dietary carbohydrates, and specific oral bacteria. Organic acids produced by bacterial fermentation of dietary carbohydrates reduce the pH of dental plaque adjacent to the tooth to a point where demineralization occurs. The initial demineralization appears as an opaque **white spot lesion** on the enamel, and with progressive loss of tooth mineral, cavitation of the tooth occurs (Fig. 338.1).

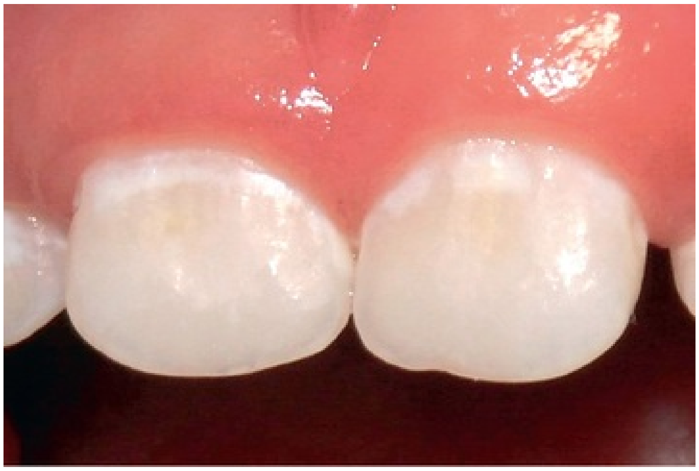

FIG. 338.1 Initial carious lesions (white spot lesions) around the necks of the maxillary central incisors.

The group of microorganisms, mutans streptococci, is associated with the development of dental caries. These bacteria have the ability to adhere to enamel, produce abundant acid, and survive at low pH. Once the enamel surface cavitates, other oral bacteria (lactobacilli) can colonize the tooth, produce acid, and foster further tooth demineralization. Demineralization from bacterial acid production is determined by the frequency of carbohydrate consumption and by the type of carbohydrate. Sucrose is the most cariogenic sugar because one of its by-products during bacterial metabolism is glucan, a polymer that enables bacteria to adhere more readily to tooth structures. Dietary behaviors, such as consuming sweetened beverages in a nursing bottle or frequently consuming sticky candies, increase the cariogenic potential of foods because of the long retention of sugar in the mouth.

Epidemiology

As per the 2011–2012 National Health and Nutrition Examination Survey (NHANES), approximately 15% of children ranging from 2 to 8 yr of age had one or more primary teeth affected by dental caries (Fig. 338.2). In the permanent dentition, over 10% of children aged 12-15 yr had dental caries and one-fourth of children were affected by age 16-19 yr (Fig. 338.3).

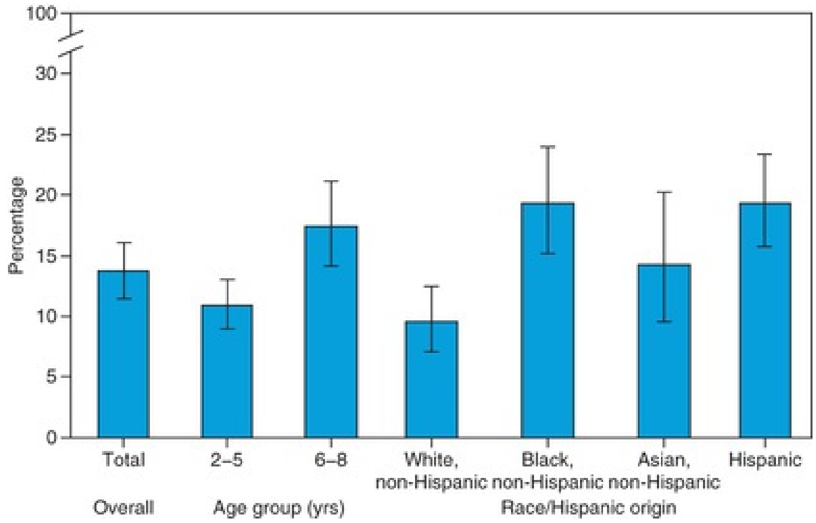

FIG. 338.2 Prevalence* of untreated dental caries† in primary teeth§ among children aged 2-8 yr, by age group and race/Hispanic origin—National Health and Nutrition Examination Survey, 2011-2014. *With 95% confidence intervals indicated with error bars. † Untreated dental caries is defined as tooth decay (dental cavities) that have not received appropriate treatment. Data were collected by dentists in the mobile examination center

as part of the oral health component of the National Health and Nutrition Examination Survey. [§] Primary teeth are the first teeth (baby teeth), which are shed and replaced by permanent teeth. (From Centers for Disease Control and Prevention: Prevalence of untreated dental caries in primary teeth among children aged 2-8 years, by age group and race/Hispanic origin—National Health and Nutrition Examination Survey, 2011–2014. *MMWR* 66(9):261, 2017.)

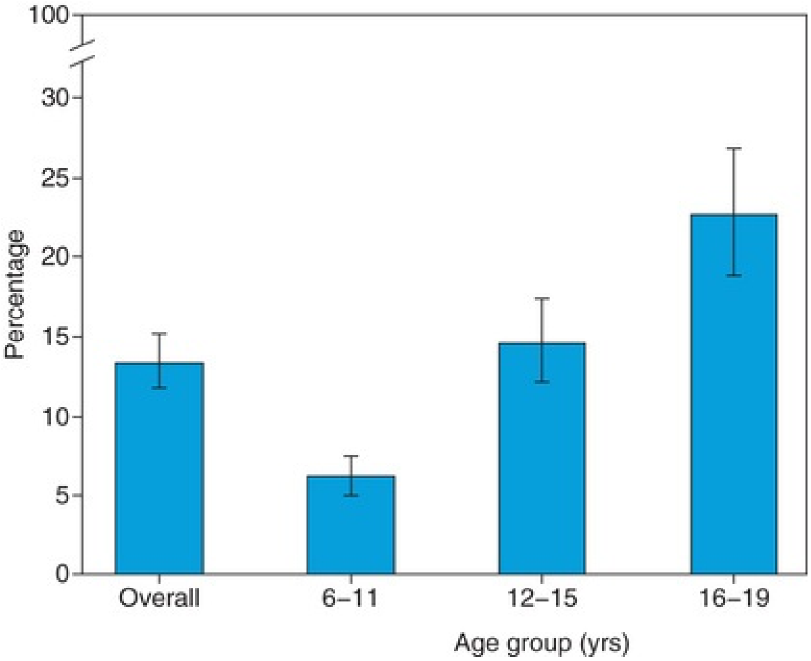

FIG. 338.3 Prevalence* of untreated dental caries[†] in permanent teeth among children and adolescents aged 6-19 yr, by age group—National Health and Nutrition Examination Survey, United States, 2011-2014. *With 95% confidence intervals indicated with error bars. [†] Untreated dental caries (i.e., dental cavities) are defined as tooth decay that has not received appropriate treatment. Data were collected by dentists in the mobile examination center as part of the oral health component of the National Health and Nutrition Examination Survey. (From Centers for Disease Control and Prevention: Prevalence of untreated dental caries in permanent teeth among children and adolescents aged 6-19 years, by age group—National Health and Nutrition Examination Survey, United States, 2011–2014. *MMWR* 66(1):36, 2017.)

Clinical Manifestations

Dental caries of the primary dentition usually begins in the pits and fissures.

Small lesions may be difficult to diagnose by visual inspection, but larger lesions are evident as darkened or cavitated lesions on the tooth surfaces (Fig. 338.4). Rampant dental caries in infants and toddlers, referred to as **early childhood caries** , is the result of early colonization of the child with cariogenic bacteria and the frequent ingestion of sugar, either in the bottle or in solid foods. The carious process in this situation is initiated earlier and consequently can affect the maxillary incisors first and then progress to the molars as they erupt.

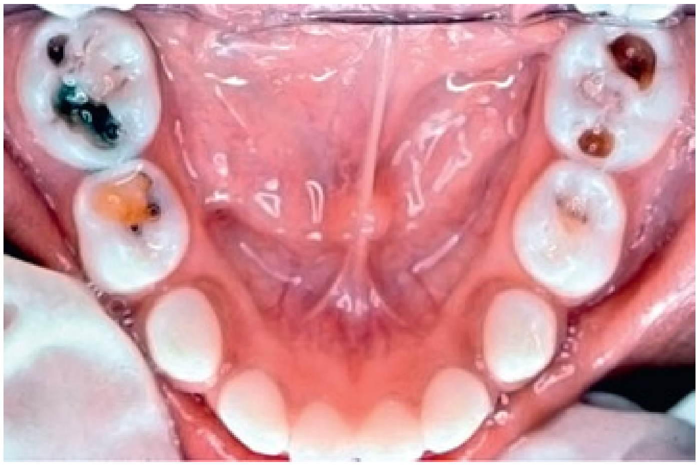

FIG. 338.4 **Rampant caries in a 3 yr old child. Note darkened and cavitated lesions on the fissure surfaces of mandibular molars.**

The prevalence of untreated caries was significantly higher in children between 3 and 9 yr of age living at or below 100% of federal poverty level compared with those above the poverty level. Besides high frequency of sugar consumption and colonization with cariogenic bacteria, other enabling factors include low socioeconomic status of the family, other family member with carious teeth, recent immigrant status of the child, and the visual presence of dental plaque on the child's teeth. Children who develop caries at a young age are known to be at high risk for developing further caries as they get older. Therefore the appropriate prevention of early childhood caries can result in the elimination of major dental problems in toddlers and less decay in later childhood.

Among adolescents, the prevalence of dental caries experience was higher in age group 16-19 yr (67%) compared with age group 12-15 yr (50%). Overall, the caries experience did not significantly differ by race, Hispanic origin, and poverty levels.

Complications

Left untreated, dental caries usually destroy most of the tooth and invade the dental pulp (Fig. 338.5), leading to an inflammation of the pulp **(pulpitis)** and significant pain. Pulpitis can progress to pulp necrosis, with bacterial invasion of the alveolar bone causing a **dental abscess** (Fig. 338.6). Red flags for serious spreading of dental infection are noted in Table 338.1 . Infection of a primary tooth can disrupt normal development of the successor permanent tooth. In some cases, this process leads to spread of infection to other facial spaces (Fig. 338.7).

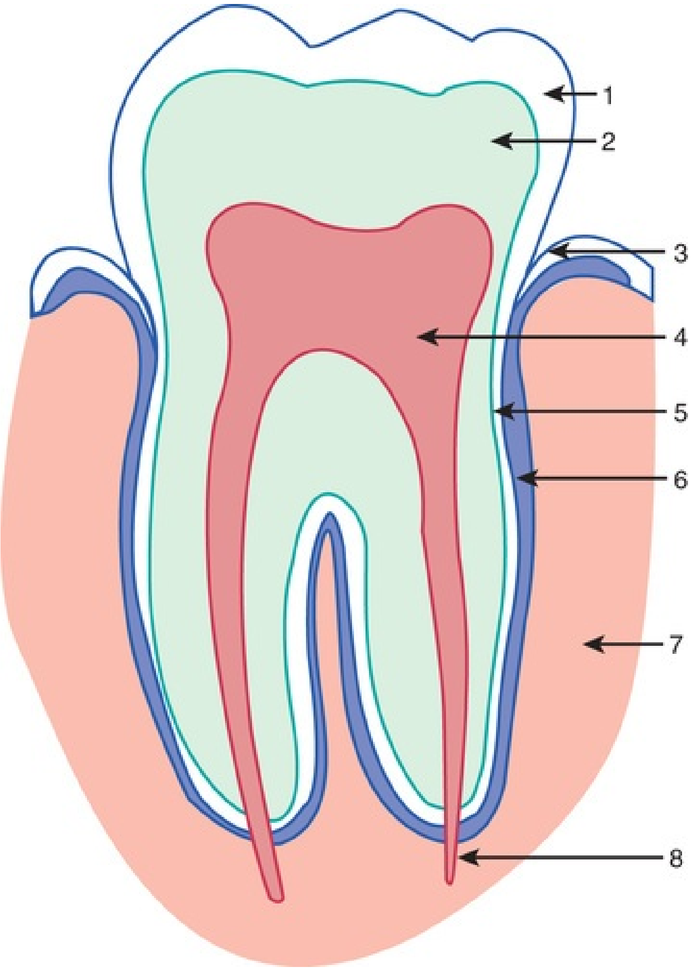

FIG. 338.5 Basic dental anatomy: *1,* enamel; *2,* dentin; *3,* gingival margin; *4,* pulp; *5,* cementum; *6,* periodontal ligament; *7,* alveolar bone; *8,* neurovascular bundle.

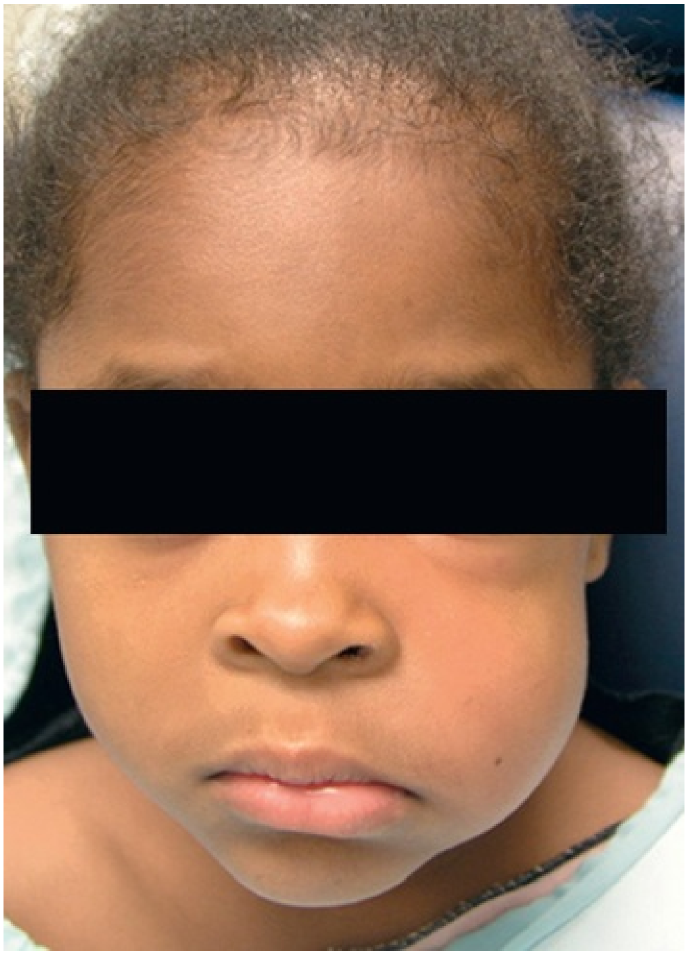

FIG. 338.6 **Facial swelling from an abscessed primary molar. Resolution of the inflammation can be achieved by a course of antibiotics, followed by either extraction or root canal of the offending tooth.**

Table 338.1

Red Flags Suggestive of a Spreading Dental Infection

• Pyrexia
• Tachycardia or tachypnea
• Trismus; may be relative due to pain or absolute due to a collection within the muscle causing muscle spasm in cases of masticator space involvement
• Raised tongue and floor of mouth, drooling
• Periorbital cellulitis
• Difficulty with speaking, swallowing, and breathing
• Hypotension
• Increased white blood cell count
• Lymphadenopathy
• Dehydration

From Robertson DP, Keys W, Rautemaa-Richardson R, et al: Management of severe acute dental infections. *BMJ* 350:h1300, 2015 (Box 3, p. 151).

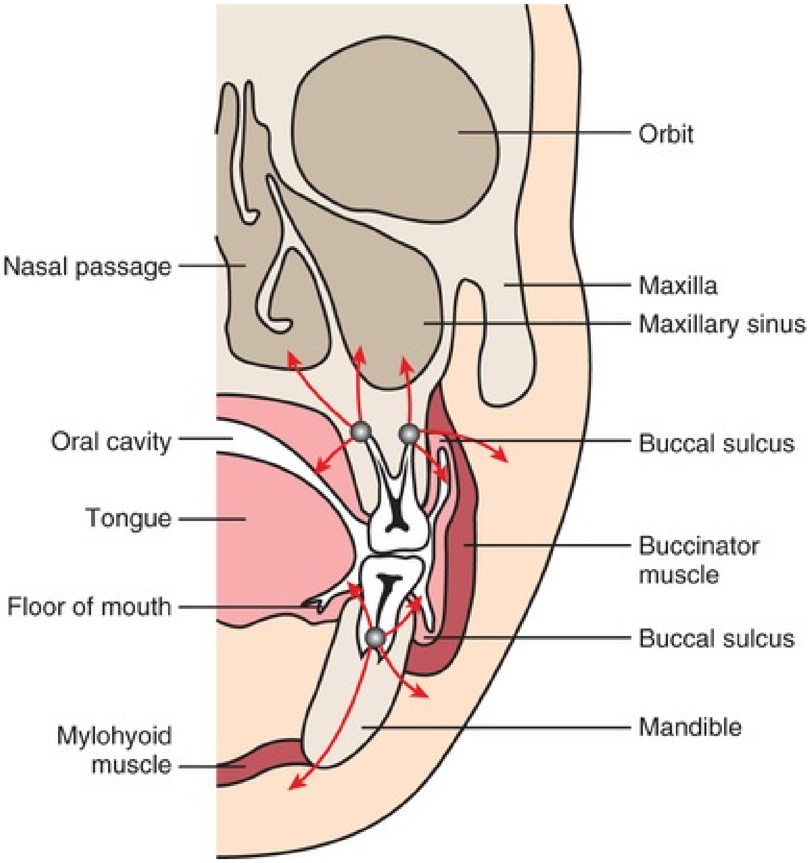
Orbit
Nasal passage
Maxilla
Maxillary sinus
Oral cavity
Buccal sulcus
Tongue
Buccinator muscle
Floor of mouth
Buccal sulcus
Mandible
Mylohyoid muscle

FIG. 338.7 Spread of infection in the maxillofacial region is complicated by the variety of vital structures. Routes of spread are determined by fascial planes and this affects the presentation and management of each subdivision of cervicofacial infection. (From Robertson DP, Keys W, Rautemaa-Richardson R, et al: Management of severe acute dental infections. *BMJ* 350:h1300, 2015. Fig. 3, p. 151.)

Treatment

The age at which dental caries occurs is important in dental management. Children younger than 3 yr of age lack the developmental ability to cooperate with dental treatment and often require sedation or general anesthesia to repair carious teeth. After age 4 yr, children can generally cope with dental restorative care with the use of local anesthesia. Children with neurologic impairment or developmental delay may require general anesthesia for dental procedures at older ages.

Dental treatment, using silver amalgam, plastic composite, or stainless-steel crowns, can restore most teeth affected with dental caries. If caries involves the dental pulp, a partial removal of the pulp (pulpotomy) or complete removal of the pulp (pulpectomy) may be required. If a tooth requires extraction, a space maintainer may be indicated to prevent migration of teeth, which subsequently leads to malposition of permanent successor teeth.

Clinical management of the pain and infection associated with untreated dental caries varies with the extent of involvement and the medical status of the patient. Dental infection localized to the dentoalveolar unit can be managed by local measures (extraction, pulpectomy). Oral antibiotics are indicated for dental infections associated with fever, cellulitis, and facial swelling or if it is difficult to anesthetize the tooth in the presence of inflammation. Penicillin is the antibiotic of choice, except in patients with a history of allergy to this agent. Clindamycin and erythromycin are suitable alternatives. Oral analgesics, such as ibuprofen, are usually adequate for pain control.

Prevention

Dental caries screening, risk assessment, and preventive management in young children needs to be part of the scope of medical providers because children younger than 3 yr often are not under the care of a dentist. Prevention of early childhood caries is critical because, if primary dental care is not initiated or does not succeed, teeth may develop dental caries requiring restorative care. Dental restorative care to treat caries in young children may require the use of sedation or general anesthesia with its associated high costs and possible health risks, and there is high recurrence of carious lesions once they develop.

Because they are seeing infants and toddlers on a periodicity schedule, physicians have an important role in screening children younger than 3 yr of age for dental caries; providing preventive instructions; applying preventive measures, such as fluoride varnish; and referring the child to a dentist if problems exist.

Fluoride

The most effective preventive measure against dental caries is communal water supplies with optimal fluoride content. Water fluoridation at the level of 0.7-1.2

mg fluoride per liter (ppm F) was introduced in the United States in the 1940s. Because fluoride from water supplies is now one of several sources of fluoride, the Department of Health and Human Services proposes to not have a fluoride range, but instead to limit the recommendation to the lower limit of 0.7 ppm F. The rationale is to balance the benefits of preventing dental caries with reducing the chance of fluorosis. Children who reside in areas with fluoride-deficient water supplies or who consume primarily bottled water, and are at risk for caries, benefit from dietary fluoride supplements (Table 338.2). If the patient uses a private water supply, it is necessary to get the water tested for fluoride levels before prescribing fluoride supplements. To avoid potential overdoses, no fluoride prescription should be written for more than a total of 120 mg of fluoride. However, because of confusion regarding fluoride supplements among practitioners and parents, association of supplements with fluorosis, and lack of parent compliance with the daily administration, supplements may no longer be the first-line approach for preventing caries in preschool-aged children.

Table 338.2

Supplemental Fluoride Dosage Schedule

AGE	FLUORIDE IN HOME WATER		
	<0.3 (PPM)	**0.3-0.6 (PPM)**	**>0.6 (PPM)**
6 mo-3 yr	0.25*	0	0
3-6 yr	0.50	0.25	0
6-16 yr	1.00	0.50	0

* Milligrams of fluoride per day.

Topical fluoride on a daily basis can be achieved by using fluoridated toothpaste. Supervised use of less than a *pea-sized* amount of toothpaste (approximately 0.25 g) on the toothbrush in children between 3 and 6 yr of age reduces the risk of fluorosis. Children younger than 3 yr of age should brush with less than a *smear or grain-sized* amount of fluoridated toothpaste. Professional topical fluoride applications performed semiannually reportedly reduce caries by approximately 30%. Fluoride varnish is ideal for professional applications in preschool children because of ease of use, even with non–dental health providers, and its safety because of single-dose dispensers. Products that are available come in containers of 0.25, 0.4, or 0.6 mL of varnish, corresponding to 5.6, 9.0, and 13.6 mg fluoride, respectively. Fluoride varnish should be administered twice a year for preschool children at moderate caries risk and 4 times a year for children at high caries risk.

Oral Hygiene

Daily brushing, especially with fluoridated toothpaste, helps to prevent dental caries. Most children younger than 8 yr of age do not have the coordination required for adequate tooth brushing. Accordingly, parents should assume responsibility for the child's oral hygiene, with the degree of parental involvement appropriate to the child's changing abilities.

Diet

Frequent consumption of sweetened fruit drinks is not generally recognized by parents for its high cariogenic potential. Consuming sweetened beverages in a nursing bottle or sippy cup should be discouraged and special efforts made to instruct parents that their child should consume sweetened beverages only at meal times and not exceed 6 oz/day.

Dental Sealant

Plastic dental sealants have been shown to be effective in preventing caries on the pit and fissure of the primary and permanent molars. Sealants are most effective when placed soon after teeth erupt and used in children with deep grooves and fissures in the molar teeth. Sealants have been shown to reduce caries incidence by 85% over 7 yr.

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CHAPTER 339

Periodontal Diseases

Vineet Dhar

The periodontium includes the gingiva, alveolar bone, cementum, and periodontal ligament (see Fig. 338.5).

Gingivitis

Poor oral hygiene results in the accumulation of dental plaque at the tooth-gingival interface that activates an inflammatory response, expressed as localized or generalized reddening and swelling of the gingiva. More than half of American school children experience gingivitis. In severe cases, the gingiva spontaneously bleeds and there is oral malodor. Treatment is proper oral hygiene (careful tooth brushing and flossing); complete resolution can be expected. Fluctuations in hormonal levels during the onset of puberty can increase inflammatory responses to plaque. Gingivitis in healthy children is unlikely to progress to periodontitis (inflammation of the periodontal ligament resulting in loss of alveolar bone).

Aggressive Periodontitis in Children (Prepubertal Periodontitis)

Periodontitis in children before puberty is a rare disease that often begins between the time of eruption of the primary teeth and the age of 4 or 5 yr. The disease occurs in localized and generalized forms. There is rapid bone loss, often leading to premature loss of primary teeth. It is often associated with systemic problems, including neutropenia, leukocyte adhesion or migration defects, hypophosphatasia, Papillon-Lefèvre syndrome, leukemia, and Langerhans cell histiocytosis. However, in many cases, there is no apparent underlying medical problem. Nonetheless, diagnostic workups are necessary to rule out underlying systemic disease.

Treatment includes aggressive professional teeth cleaning, strategic extraction of affected teeth, and antibiotic therapy. There are few reports of long-term successful treatment to reverse bone loss surrounding primary teeth.

Aggressive Periodontitis in Adolescents

Localized aggressive periodontitis (LAgP) in adolescents is characterized by rapid attachment and alveolar bone loss, on at least 2 first molars and incisors. Overall prevalence in the United States is <1%, but the prevalence among African Americans is reportedly 2.5%. This form of periodontitis is associated with a strain of *Aggregatibacter (Actinobacillus)* bacteria. In addition, the neutrophils of patients with aggressive periodontitis can have chemotactic or phagocytic defects. If left untreated, affected teeth lose their attachment and can exfoliate. Treatment varies with the degree of involvement. Patients whose disease is diagnosed at onset are usually managed by surgical or nonsurgical debridement in conjunction with antibiotic therapy. Prognosis depends on the degree of initial involvement and compliance with therapy.

Generalized aggressive periodontitis (GAgP) occurs more in adolescents and young adults and is characterized by generalized interproximal attachment loss and bone loss, including 3 teeth that are not first molars and incisors.

Cyclosporine- or Phenytoin-Induced Gingival Overgrowth

The use of cyclosporine to suppress organ rejection or phenytoin for anticonvulsant therapy, and in some cases calcium channel blockers, is associated with generalized enlargement of the gingiva. Phenytoin and its metabolites have a direct stimulatory action on gingival fibroblasts, resulting in accelerated synthesis of collagen. Phenytoin induces less gingival hyperplasia in patients who maintain meticulous oral hygiene.

Gingival hyperplasia occurs in 10–30% of patients treated with phenytoin. Severe manifestations can include gross enlargement of the gingiva, sometimes covering the teeth; edema and erythema of the gingiva; secondary infection, resulting in abscess formation; migration of teeth; and inhibition of exfoliation of primary teeth and subsequent impaction of permanent teeth. Treatment should be directed toward prevention and, if possible, discontinuation of cyclosporine or phenytoin. Patients undergoing long-term treatment with these drugs should receive frequent dental examinations and oral hygiene care. Severe forms of gingival overgrowth are treated by gingivectomy, but the lesion recurs if drug use is continued.

Acute Pericoronitis

Acute inflammation of the flap of gingiva that partially covers the crown of an incompletely erupted tooth is common in mandibular permanent molars. Accumulation of debris and bacteria between the gingival flap and tooth precipitates the inflammatory response. A variant of this condition is a gingival abscess caused by entrapment of bacteria because of orthodontic bands or crowns. Trismus and severe pain may be associated with the inflammation. Untreated cases can result in facial space infections and facial cellulitis.

Treatment includes local debridement and irrigation, warm saline rinses, and antibiotic therapy. When the acute phase has subsided, resection of the gingival flap prevents recurrence. Early recognition of the partial impaction of mandibular 3rd molars and their subsequent extraction prevents these areas from developing pericoronitis.

Necrotizing Periodontal Disease (Acute Necrotizing Ulcerative Gingivitis)

Necrotizing periodontal disease, in the past sometimes referred to as “trench mouth,” is a distinct periodontal disease associated with oral spirochetes and fusobacteria. However, it is not clear whether bacteria initiate the disease or are secondary. It rarely develops in healthy children in developed countries, with a prevalence in the United States of <1%, but is seen more often in children and adolescents from developing areas of Africa, Asia, and South America. In certain African countries, where affected children usually have protein malnutrition, the lesion can extend into adjacent tissues, causing necrosis of facial structures (cancrum oris, or noma).

Clinical manifestations of necrotizing periodontal disease include necrosis and ulceration of gingiva between the teeth, an adherent grayish pseudomembrane over the affected gingiva, oral malodor, cervical lymphadenopathy, malaise, and fever. The condition may be mistaken for acute herpetic gingivostomatitis. Dark-field microscopy of debris obtained from necrotizing lesions demonstrates dense spirochete populations.

Treatment of necrotizing periodontal disease is divided into an acute management with local debridement, oxygenating agents (direct application of 10% carbamide peroxide in anhydrous glycerol qid), and analgesics. Dramatic resolution usually occurs within 48 hr. If a patient is febrile, antibiotics (penicillin or metronidazole) may be an important adjunctive therapy. A second phase of treatment may be necessary if the acute phase of the disease has caused irreversible morphologic damage to the periodontium. The disease is not contagious.

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CHAPTER 340

Dental Trauma

Vineet Dhar

Traumatic oral injuries may be categorized into 3 groups: injuries to teeth, injuries to soft tissue (contusions, abrasions, lacerations, punctures, avulsions, and burns), and injuries to jaw (mandibular and/or maxillary fractures).

Injuries to Teeth

Approximately 10% of children between 18 mo and 18 yr of age sustain significant tooth trauma. Oral injuries are second most common, covering 18% of all somatic injuries in the age group 0-6 yr. Among oral injuries, injuries to teeth are most common, followed by soft tissue injuries. There appear to be 3 age periods of greatest predilection: toddlers (1-3 yr), usually from falls or child abuse; school-age children (7-10 yr), usually from bicycle and playground accidents; and adolescents (16-18 yr), often the result of fights, athletic injuries, and automobile accidents. Injuries to teeth are more common among children with protruding front teeth. Children with craniofacial abnormalities or neuromuscular deficits are also at increased risk for dental injury. Injuries to teeth can involve the hard dental tissues, the dental pulp (nerve), and injuries to the periodontal structure (surrounding bone and attachment apparatus) (Fig. 340.1 ; Table 340.1).

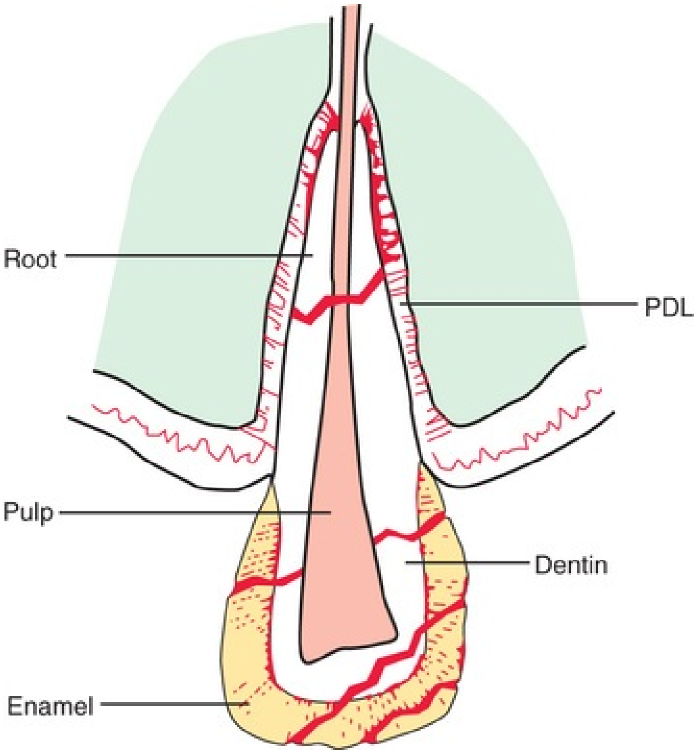

FIG. 340.1 Tooth fractures can involve enamel, dentin, or pulp and can occur in the crown or root of a tooth. *PDL,* periodontal ligament. (From Pinkham JR: *Pediatric dentistry: infancy through adolescence,* Philadelphia, 1988, WB Saunders, p. 172.)

Table 340.1

Injuries to Crowns of Teeth

TYPE OF TRAUMA	DESCRIPTION	TREATMENT AND REFERRAL
Enamel infraction (crazing)	Incomplete fracture of enamel without loss of tooth structure	Initially might not require therapy but should be assessed periodically by dentist
Enamel fractures	Fracture of only the tooth enamel	Tooth may be smoothed or treated to replace fragment
Enamel and dentin fracture	Fracture of enamel and dentinal layer of the tooth. Tooth may be sensitive to cold or air. Pulp may become necrotic, leading to periapical abscess	Refer as soon as possible. Area should be treated to preserve the integrity of the underlying pulp
Enamel, dentin fracture involving the pulp	Bacterial contamination can lead to pulpal necrosis and periapical abscess. The tooth might have the appearance of bleeding or might display a small red spot	Refer immediately. The dental therapy of choice depends on the extent of injury, the condition of the pulp, the development of the tooth, time elapsed from injury, and any other injuries to the supporting structures. Therapy is directed toward minimizing contamination in an effort to improve the prognosis

From Josell SD, Abrams RG: Managing common dental problems and emergencies. *Pediatr Clin North Am* 38:1325–1342, 1991.

Fractures of teeth may be uncomplicated (confined to the hard dental tissues) or complicated (involving the pulp). Exposure of the pulp results in its bacterial contamination, which can lead to infection and pulp necrosis. Such pulp exposure complicates therapy and can lower the likelihood of a favorable outcome.

The teeth most often affected are the maxillary incisors. Uncomplicated crown fractures are treated by covering exposed dentin and by placing an aesthetic restoration. Complicated crown fractures involving the tooth pulp usually require **endodontic therapy** (root canal). Crown-root fractures and root fractures usually require extensive dental therapy. Such injuries in the primary dentition can interfere with normal development of the permanent dentition, and therefore significant injuries of the primary incisor teeth are usually managed by extraction.

Traumatic oral injuries should be referred to a dentist as soon as possible. Even when the teeth appear intact, a dentist should promptly evaluate the patient. Baseline data (radiographs, mobility patterns, responses to specific stimuli) enable the dentist to assess the likelihood of future complications.

Injuries to Periodontal Structures

Trauma to teeth with associated injury to periodontal structures that hold the teeth usually manifests as mobile or displaced teeth. Such injuries are more common in the primary than in the permanent dentition. Categories of trauma to the periodontium include concussion, subluxation, intrusive luxation, extrusive luxation, and avulsion.

Concussion

Injuries that produce minor damage to the periodontal ligament are termed *concussions*. Teeth sustaining such injuries are not mobile or displaced but react markedly to percussion (gentle hitting of the tooth with an instrument). This type of injury usually requires no therapy and resolves without complication. Primary incisors that sustain concussion can change color, indicating pulpal degeneration, and should be evaluated by a dentist.

Subluxation

Subluxated teeth exhibit mild to moderate horizontal mobility and/or vertical mobility. Hemorrhage is usually evident around the neck of the tooth at the gingival margin. There is no displacement of the tooth. Many subluxated teeth need to be immobilized by splints to ensure adequate repair of the periodontal ligament. Some of these teeth develop pulp necrosis.

Intrusion

Intruded teeth are pushed up into their socket, sometimes to the point where they are not clinically visible. Intruded primary incisors can give the false appearance of being avulsed (knocked out). To rule out avulsion, a dental radiograph is indicated (Figs. 340.2 and 340.3).

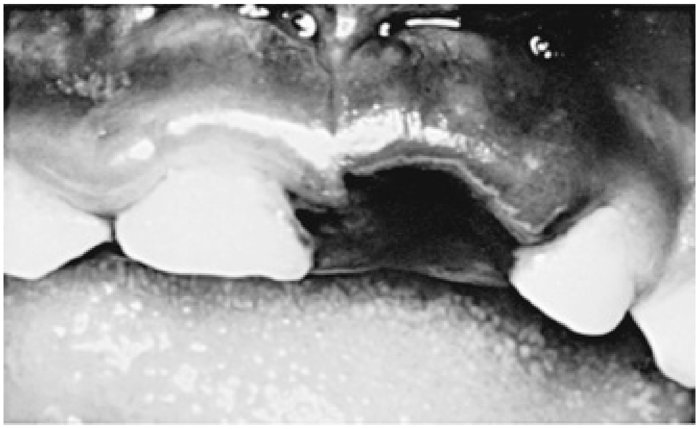

FIG. 340.2 Intruded primary incisor that appears avulsed (knocked out).

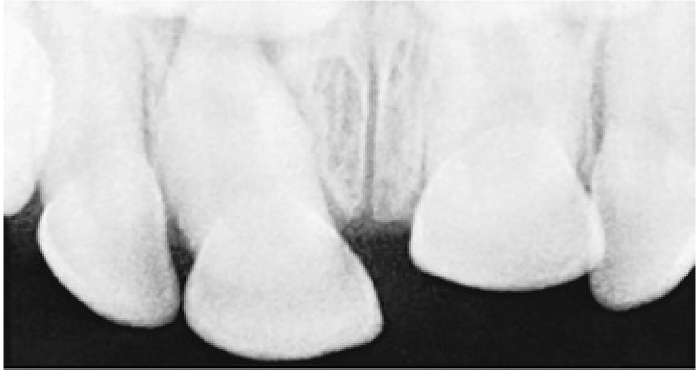

FIG. 340.3 Occlusal radiograph documents intrusion of "missing tooth" presented in Fig. 340.2 .

Extrusion

Extrusion injury is characterized by displacement of the tooth from its socket. The tooth is usually displaced to the lingual (tongue) side, with fracture of the wall of the alveolar socket. These teeth need immediate treatment; the longer the delay, the more likely the tooth will be fixed in its displaced position. Therapy is directed at reduction (repositioning the tooth) and fixation (splinting). The pulp of such teeth often becomes necrotic and requires endodontic therapy. Extrusive luxation in the primary dentition is usually managed by extraction because complications of reduction and fixation can result in problems with development of permanent teeth.

Avulsion

If avulsed permanent teeth are replanted as soon as possible after injury, there is a good chance that normal reattachment will follow and the tooth will have a good prognosis. However, if the tooth is in a dry environment for longer than 1 hr, the ligament that holds the tooth in place has little chance for survival and failure (root resorption, ankylosis) is common. Parents confronted with this emergency situation can be instructed to do the following:

◆ Find the tooth.
◆ Briefly rinse the tooth. (Do not scrub the tooth. Do not touch the root. After plugging the sink drain, hold

the tooth by the crown and rinse it under running tap water.)

- Insert the tooth into the socket. (Gently place it back into its normal position. Do not be concerned if the tooth extrudes slightly. If the parent or child is too apprehensive for replantation of the tooth, the tooth should be placed in cold cow's milk or other cold isotonic solution.)
- Go directly to the dentist. (In transit, the child should hold the tooth in its socket with a finger. The parent should place the child in an age-appropriate child seat, buckle a seatbelt around the child, and drive safely.)

After the tooth is replanted, it must be immobilized to facilitate reattachment; endodontic therapy is always required. The initial signs of complications associated with replantation can appear as early as 1 wk after trauma or as late as several years later. Close dental follow-up is indicated for at least 1 yr.

Prevention

To minimize the likelihood of dental injuries:

- Every child or adolescent who engages in contact sports should wear a **mouth guard** , which may be constructed by a dentist or purchased at any athletic goods store.
- Helmets with face guards should be worn by children or adolescents with neuromuscular problems

or seizure disorders to protect the head and face during falls.

- Helmets should also be used during biking, skiing, skating, and skateboarding.
- All children or adolescents with protruding incisors should be evaluated by a pediatric dentist or orthodontist.

Additional Considerations

Children who experience dental trauma might also have sustained head or neck trauma, and therefore neurologic assessment is warranted. Tetanus prophylaxis should be considered with any injury that disrupts the integrity of the oral tissues. The possibility of child abuse should always be considered.

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CHAPTER 341

Common Lesions of the Oral Soft Tissues

Vineet Dhar

Oropharyngeal Candidiasis

Oropharyngeal infection with *Candida albicans* (thrush, moniliasis) (see Chapter 261.1) is common in neonates from contact with the organism in the birth canal or contact with the breast during breastfeeding. The lesions of oropharyngeal candidiasis (OPC) appear as white plaques covering all or part of the oropharyngeal mucosa. These plaques are removable from the underlying surface, which is characteristically inflamed and has pinpoint hemorrhages. The diagnosis is confirmed by direct microscopic examination on potassium hydroxide smears and culture of scrapings from lesions. OPC is usually self-limited in the healthy newborn infant, but topical application of nystatin to the oral cavity of the baby and to the nipples of breastfeeding mothers will hasten recovery.

OPC is also a major problem during myelosuppressive therapy. **Systemic candidiasis** , a major cause of morbidity and mortality during myelosuppressive therapy, develops almost exclusively in patients who have had prior oropharyngeal, esophageal, or intestinal candidiasis. This observation implies that prevention of OPC should reduce the incidence of systemic candidiasis. The use of oral rinses of 0.2% chlorhexidine gluconate solution along with systemic antifungals may be effective in preventing OPC, systemic candidiasis, or candidal esophagitis.

Aphthous Ulcers

The aphthous ulcer (canker sore) is a distinct oral lesion (Fig. 341.1), prone to recurrence; Table 341.1 notes the differential diagnosis. Aphthous ulcers are reported to develop in 20% of the population. Their etiology is unclear, but allergic or immunologic reactions, emotional stress, genetics, and injury to the soft tissues in the mouth have been implicated. Aphthous-like lesions may be associated with inflammatory bowel disease, Behçet disease, gluten-sensitive enteropathy, periodic fever-aphthae-pharyngitis-adenitis syndrome, Sweet syndrome, HIV infection (especially if ulcers are large and slow to heal), and cyclic neutropenia. Clinically, these ulcers are characterized by well-circumscribed, ulcerative lesions with a white necrotic base surrounded by a red halo. The lesions generally last 10-14 days and heal without scarring. Nonprescription palliative therapies, such as benzocaine and topical lidocaine, are effective, as are topical steroids. Tetracycline has benefit with severe outbreaks, but caution is necessary in pregnant women, since it is classified as FDA pregnancy category D. In younger children (≤8 yr), tetracycline can affect developing teeth and cause permanent staining of the teeth.

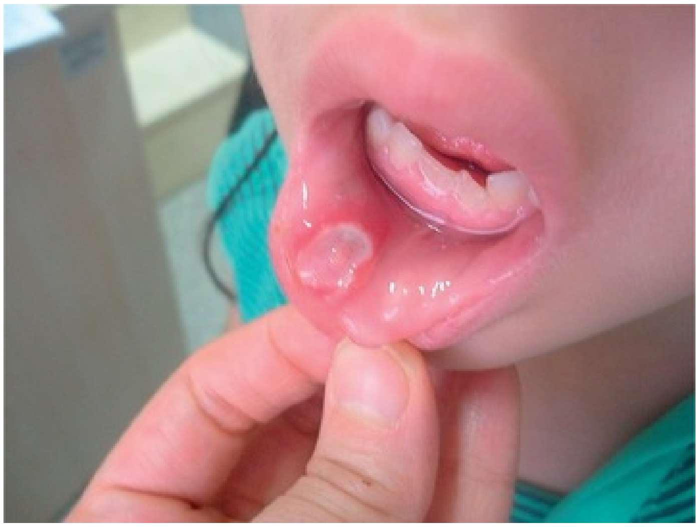

FIG. 341.1 **Major aphthous in a child. (From Gürkan A, Özlü SG, Altiaylik-Özer P, et al: Recurrent aphthous stomatitis in childhood and adolescence: a single-center experience. *Pediatr Dermatol* 32(4):476–480, 2015. Fig. 1.)**

Table 341.1

Differential Diagnosis of Oral Ulceration

CONDITION	COMMENT
Common	
Aphthous ulcers (canker sores)	Painful circumscribed lesions; recurrences
Traumatic ulcers	Accidents, chronic cheek biter, after dental local anesthesia
Hand, foot, and mouth disease	Painful; lesions on tongue, anterior oral cavity, hands, and feet
Herpangina	Painful; lesions confined to soft palate and oropharynx
Herpetic gingivostomatitis	Vesicles on mucocutaneous borders; painful, febrile
Recurrent herpes labialis	Vesicles on lips; painful
Chemical burns	Alkali, acid, aspirin; painful
Heat burns	Hot food, electrical
Uncommon	
Neutrophil defects	Agranulocytosis, leukemia, cyclic neutropenia; painful
Systemic lupus erythematosus	Recurrent; may be painless
Behçet syndrome	Resembles aphthous lesions; associated with genital ulcers, uveitis
Necrotizing ulcerative gingivostomatitis	Vincent stomatitis; painful
Syphilis	Chancre or gumma; painless
Oral Crohn disease	Aphthous-like; painful
Histoplasmosis	Lingual
Pemphigus	May be isolated to the oral cavity
Stevens-Johnson syndrome	May be isolated to or appear initially in the oral cavity

Herpetic Gingivostomatitis

After an initial incubation period of approximately 1 wk, the primary infection with herpes simplex virus manifests as fever and malaise, usually in a child younger than 5 yr (see Chapter 279). The oral cavity can show various expressions, including the gingiva becoming erythematous, mucosal hemorrhages, and clusters of small vesicles erupting throughout the mouth. There is often involvement of the mucocutaneous margin and perioral skin (Fig. 341.2). The oral symptoms generally are accompanied by fever, lymphadenopathy, and difficulty eating and drinking. The symptoms usually regress within 2 wk without scarring. Fluids should be encouraged because the child may become dehydrated. Analgesics and anesthetic rinses can make the child more comfortable. Oral acyclovir, if taken within the first 3 days of symptoms in immunocompetent patients, is beneficial in shortening the duration of symptoms. Caution should be exercised to prevent autoinoculation, especially of the eyes.

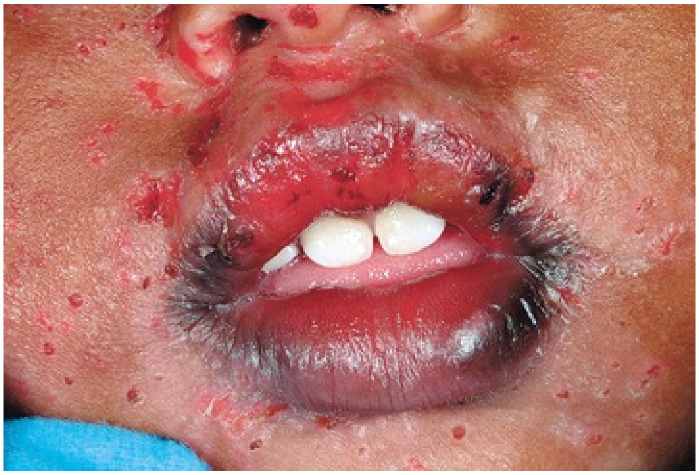

FIG. 341.2 Herpetic gingivostomatitis. Lip erosions with multiple perioral herpetic lesions involving the mucotaneous borders. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology,* ed 3, Philadelphia, 2006, WB Saunders, p. 398.)

Recurrent Herpes Labialis

Approximately 90% of the worldwide population develops antibodies to herpes simplex virus. In periods of quiescence, the virus is thought to remain latent in sensory neurons. Unlike primary herpetic gingivostomatitis which manifests as multiple painful vesicles on the lips, tongue, palate, gingiva, and mucosa, recurrent herpes is generally limited to the lips. Other than the annoyance of causing pain and being a cosmetic issue, recurrent episodes generally do not involve systemic symptoms. Reactivation of the virus is thought to be the result of exposure to ultraviolet light, tissue trauma, stress, or fevers. There is little advantage of antiviral therapy over palliative therapies in an otherwise healthy patient affected by recurrent herpes.

Parulis

The parulis (gum boil) is a soft reddish papule located adjacent to the root of a chronically abscessed tooth. It occurs at the end-point of a draining dental sinus tract. Treatment consists of diagnosing which tooth is abscessed and extracting it or performing root canal treatment on the offending tooth.

Cheilitis

Cheilitis, dryness of the lips followed by scaling and cracking and accompanied by a characteristic burning sensation, is common in children. Cheilitis may be caused by sensitivity to contact substances, lip licking, vitamin deficiency, weakened immune system, or fungal or bacterial infections, and often occurs in association with fever. Treatment may include antifungal or antibacterial agents and frequent application of petroleum jelly.

Ankyloglossia

Ankyloglossia, or tongue-tie, is characterized by an abnormally short lingual frenum that can hinder the tongue movement, but rarely interferes with feeding or speech. It is possible that the frenum could spontaneously lengthen as the child gets older. If, in the rare event that the extent of the ankyloglossia is severe, speech may be affected and surgical correction may be indicated.

Geographic Tongue

Geographic tongue (migratory glossitis) is a benign and asymptomatic lesion that is characterized by one or more smooth bright red patches, often showing a yellow, gray, or white membranous margin on the dorsum of an otherwise normally roughened tongue. The condition has no known cause, and no treatment is indicated (see Chapter 684).

Fissured Tongue

The fissured tongue (scrotal tongue) is a malformation manifested clinically by numerous small furrows or grooves on the dorsal surface (see Chapter 684). If the tongue is painful, brushing the tongue or irrigating with water can reduce the bacteria in the fissures.

Developmental (Normal) Variations

Bohn Nodules

Bohn nodules are small developmental anomalies located along the buccal and lingual aspects of the mandibular and maxillary ridges and in the hard palate of the neonate. These lesions arise from remnants of mucous gland tissue. Treatment is not necessary as the nodules usually disappear within a few weeks.

Dental Lamina Cysts

Dental lamina cysts are small cystic lesions located along the crest of the mandibular and maxillary ridges of the neonate. These lesions arise from epithelial remnants of the dental lamina. Treatment is not necessary; they disappear within a few weeks.

Epstein Pearls

Epstein pearls are small developmental lesions located in the median palatal raphe region due to entrapment of epithelial remnants along the line of fusion of the palatal halves. Treatment is not necessary as these slough off on their own within a few weeks.

Fordyce Granules

Fordyce granules are common and almost 80% of adults have these yellow-white granules in clusters or plaque-like areas on the oral mucosa, most commonly on the buccal mucosa or lips. They are aberrant sebaceous glands. The glands are present at birth, but they can undergo hypertrophy and first appear as discrete yellowish papules during the preadolescent period in approximately 50% of children. No treatment is necessary.

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CHAPTER 342

Diseases of the Salivary Glands and Jaws

Vineet Dhar

With the exception of mumps (see Chapter 275), diseases of the salivary glands are rare in children. Bilateral enlargement of the submaxillary glands can occur in HIV/AIDS, cystic fibrosis, Epstein-Barr virus infection, malnutrition, and transiently during acute asthmatic attacks. Chronic vomiting can be accompanied by enlargement of the parotid glands. Benign salivary gland hypertrophy has been associated with endocrinopathies: thyroid disease, diabetes, and Cushing syndrome. Infiltrative disease or tumors are uncommon; red flags include facial nerve palsy, rapid growth, fixed skin, paresthesias, ulceration, or a history of radiation to the head or neck region.

Parotitis

Acute parotitis is often caused by blockage, with further inflammation due to bacterial infection. The blockage may be due to a salivary stone or mucous plug. Stones can be removed by physical manipulation, surgery, or lithotripsy. **Recurrent parotitis** is an idiopathic swelling of the parotid gland that can occur in otherwise healthy children. The swelling is usually unilateral, but both glands can be involved simultaneously or alternately. There is little pain; the swelling is limited to the gland and usually lasts 2-3 wk. Treatment may include local heat, massaging the gland, and antibiotics. **Suppurative parotitis** is usually caused by *Staphylococcus aureus* . It is usually unilateral and may be accompanied by fever. The gland becomes swollen, tender, and painful. Suppurative parotitis responds to antibacterial therapy based on culture obtained from the Stensen duct or by surgical drainage. Viral causes of parotitis include mumps (often in epidemics), Epstein-Barr virus, human herpesvirus 6, enteroviruses, and HIV.

Ranula

A ranula is a cyst associated with a major salivary gland in the sublingual area. It is a large, soft, mucus-containing swelling in the floor of the mouth. It occurs at any age, including infancy. The cyst should be excised, and the severed duct should be exteriorized.

Mucocele

Mucocele is a salivary gland lesion caused by a blockage of a salivary gland duct. It is most common on the lower lip and has the appearance of a fluid-filled vesicle, or a fluctuant nodule with the overlying mucosa being normal in color. Treatment is surgical excision, with removal of the involved accessory salivary gland.

Congenital Lip Pits

Congenital lip pits are caused by fistulous tracts that lead to embedded mucous glands in the lower lip. They leak saliva, especially with salivary stimulation. Lip pits can be isolated anomalies, or they can be found in patients with cleft lip or palate. Treatment is surgical excision of the glandular tissue.

Eruption Cyst

Eruption cyst is a smooth painless swelling over the erupting tooth. If bleeding occurs in the cyst space, it may appear blue or blue-black. In most cases, no treatment is indicated and the cyst resolves with the full eruption of the tooth.

Xerostomia

Also known as dry mouth, xerostomia may be associated with fever, dehydration, anticholinergic drugs, chronic graft-versus-host disease, Mikulicz disease (leukemic infiltrates), Sjögren syndrome, or tumoricidal doses of radiation when the salivary glands are within the field. Long-term xerostomia is a high-risk factor for dental caries.

Salivary Gland Tumors

See Chapter 527 .

Histiocytic Disorders

See Chapter 534 .

Tumors of the Jaw

Ossifying fibroma is a common benign tumor of the jaw. It is often asymptomatic, being discovered on routine radiographic examinations. Treatment is resection due to the possibility of recurrence. **Central giant cell granuloma** is another common lesion thought to be reactive, rather than neoplastic. Although usually asymptomatic, it can be expansile, with or without resorption of the roots of teeth and perforation of the cortical plate. Treatment is complete curettage or surgical excision. **Dentigerous cysts** are common lesions associated with the crown of an impacted or unerupted tooth. Although usually asymptomatic, they can become large and destructive. Treatment is surgical removal.

The malignant primary tumors of the jaw in children include Burkitt lymphoma, osteogenic sarcoma, lymphosarcoma, ameloblastoma, and, more rarely, fibrosarcoma.

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CHAPTER 343

Diagnostic Radiology in Dental Assessment

Vineet Dhar

Diagnostic dental radiology in children follows the As Low As Reasonably Achievable (ALARA) principle. In children, intraoral radiographs such as bitewings and select periapical radiographs are taken during routine dental visits, and repeated every 6 mo to 2 yr based on the caries risk assessment. Additional radiographs such as panoramic views, cephalometric radiographs, and dental cone beam computed tomography (CBCT) are taken when indicated. In general, the cumulative radiation exposure due to routine dental radiographs is minimal. In addition, precautions such as use of high-speed film, collimated beam, protective aprons and thyroid collars, proper technique, and minimizing number of exposures, are all taken to keep radiation exposure minimal.

Intraoral dental radiographs are highly detailed, direct-exposure films that demonstrate sections of the child's teeth and supporting bone structures. The film or image receptor is placed lingual to the teeth, and the x-ray beam is directed through the teeth and supporting structures. The resulting images are used to detect dental caries, loss of alveolar bone (periodontal disease), abscesses at the roots of the teeth, and trauma to the teeth and alveolar bone. These radiographs are also used to demonstrate the developmental status of permanent teeth within the bone.

The **panoramic radiograph** provides a single tomographic image of the upper and lower jaw, including all teeth and supporting structures. The x-ray tube rotates about the patient's head with reciprocal movement of the film or image receptor during the exposure. The panoramic image shows the teeth, mandibular bodies, rami, and condyles; maxillary sinuses; and a majority of the facial buttresses. Such images are used to show abnormalities of tooth number, development and eruption pattern, cystic and neoplastic lesions, bone infections, and fracture, as well as dental caries and periodontal disease (see Fig. 343.1).

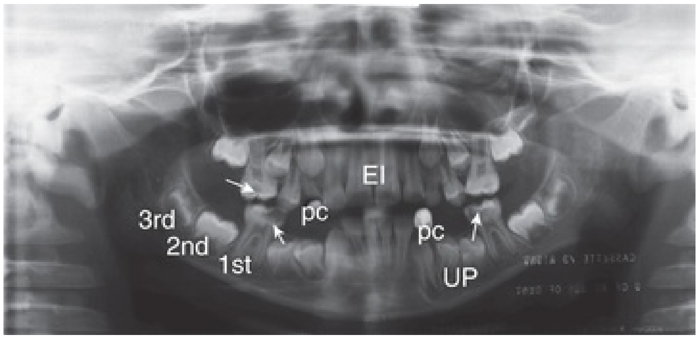

FIG. 343.1 **A panoramic radiograph of a 10 yr old child showing extensive dental caries of the 1st permanent molars *(arrows),* as well as normal structures: erupted 1st permanent molar, unerupted 2nd molar, and unerupted 3rd molar; erupted incisors *(EI)* , unerupted premolars *(UP),* and erupted primary canines *(pc).***

Cephalometric radiographs are posteroanterior and lateral skull films that are taken using a **cephalostat** (head positioner) and employ techniques that clearly demonstrate the facial skeleton and soft facial tissues. Similar protocols for positioning children are used throughout the world. From these images, cranial and facial points and planes can be determined and compared with standards derived from thousands of images. A child's facial growth can be assessed serially when cephalometric radiographs are taken sequentially. Relationships among the maxilla, mandible, cranial base, and facial skeleton can be determined in a quantitative manner. Additionally, the alignment of the teeth and the relation of the teeth to the supporting bone can be serially measured.

Dental CBCT is a variation of traditional computed tomography (CT), used mainly to evaluate oral and maxillofacial regions and teeth. Dental CBCT generally delivers lower radiation exposure than traditional CT, but higher than conventional dental radiography. There are several indications for CBCT, such as evaluation of oral-maxillofacial pathologies, diagnosis of dental trauma, endodontic treatment, visualization of abnormal teeth, orthodontic assessment, or cleft palate assessment, among others.

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SECTION 3

The Esophagus

OUTLINE

Chapter 344 Embryology, Anatomy, and Function of the Esophagus

Chapter 345 Congenital Anomalies

Chapter 346 Obstructing and Motility Disorders of the Esophagus

Chapter 347 Dysmotility

Chapter 348 Hiatal Hernia

Chapter 349 Gastroesophageal Reflux Disease

Chapter 350 Eosinophilic Esophagitis, Pill Esophagitis, and Infective Esophagitis

Chapter 351 Esophageal Perforation

Chapter 352 Esophageal Varices

Chapter 353 Ingestions

CHAPTER 344

Embryology, Anatomy, and Function of the Esophagus

Seema Khan, Sravan Kumar Reddy Matta

The esophagus is a hollow muscular tube, separated from the pharynx above and the stomach below by two tonically closed sphincters. Its primary function is to convey ingested material from the mouth to the stomach. Largely lacking digestive glands and enzymes, and exposed only briefly to nutrients, it has no active role in digestion.

Embryology

The esophagus develops from the postpharyngeal foregut and can be distinguished from the stomach in the 4 wk old embryo. At the same time, the trachea begins to bud just anterior to the developing esophagus; the resulting laryngotracheal groove extends and becomes the lung. Disturbance of this stage can result in congenital anomalies such as **tracheoesophageal fistula.** The length of the esophagus is 8-10 cm at birth and doubles in the first 2-3 yr of life, reaching approximately 25 cm in the adult. The abdominal portion of the esophagus is as large as the stomach in an 8 wk old fetus but gradually shortens to a few millimeters at birth, attaining a final length of approximately 3 cm by a few years of age. This intraabdominal location of both the distal esophagus and the **lower esophageal sphincter** (LES) is an important antireflux mechanism, because an increase in intraabdominal pressure is also transmitted to the sphincter, augmenting its defense. Swallowing can be seen in utero as early as 16-20 wk of gestation, helping to circulate the amniotic fluid; **polyhydramnios** is a hallmark of lack of normal swallowing or of esophageal or upper gastrointestinal tract obstruction. Sucking and swallowing are not fully coordinated before 34 wk of gestation, a contributing factor for feeding difficulties in premature infants.

Anatomy

The luminal aspect of the esophagus is covered by thick, protective, nonkeratinized stratified squamous epithelium, which abruptly changes to simple columnar epithelium at the stomach's upper margin at the **gastroesophageal junction (GEJ).** This squamous epithelium is relatively resistant to damage by gastric secretions (in contrast to the ciliated columnar epithelium of the respiratory tract), but chronic irritation by gastric contents can result in morphometric changes (thickening of the basal cell layer and lengthening of papillary ingrowth into the epithelium) and subsequent metaplasia of the cells lining the lower esophagus from squamous to columnar. Deeper layers of the esophageal wall are composed successively of lamina propria, muscularis mucosae, submucosa, and the two layers of muscularis propria (circular surrounded by longitudinal). The two delimiting sphincters of the esophagus, the **upper esophageal sphincter (UES)** at the cricopharyngeus muscle and the **LES** at the **GEJ,** constrict the esophageal lumen at its proximal and distal boundaries. The muscularis propria of the upper third of the esophagus is predominantly striated, and that of the lower two-thirds is smooth muscle. Clinical conditions involving striated muscle (cricopharyngeal dysfunction, cerebral palsy) affect the upper esophagus, whereas those involving smooth muscle (achalasia, reflux esophagitis) affect the lower esophagus. The muscular LES and the mucosal “Z-line” of the GEJ may be discrepant up to several centimeters.

Function

The esophagus can be divided into 3 areas: the UES, the esophageal body, and the LES. At rest, the tonic LES pressure is normally approximately 20 mm Hg; values <10 mm Hg are usually considered abnormal, although it seems that competence against retrograde flow of gastric material is maintained if the LES pressure is >5 mm Hg. The LES pressure rises during intragastric pressure amplifications, whether caused by gastric contractions, abdominal wall muscle contractions (“straining”), or external pressure applied to the abdominal wall. It also rises in response to cholinergic stimuli, gastrin, gastric alkalization, and certain drugs (bethanechol, metoclopramide, cisapride). The UES pressure is more variable and often higher than that of the LES; it decreases almost to zero during deep sleep and it increases markedly during stress and straining. The UES and LES relax briefly to allow material to pass through during swallowing, belching, reflux, and vomiting. They can contract in response to subthreshold levels of reflux (esophagoglottal closure reflex).

Swallowing is initiated by elevation of the tongue, propelling the bolus into the pharynx. The larynx elevates and moves anteriorly, pulling open the relaxing UES, while the opposed aryepiglottic folds close. The epiglottis drops back to cover the larynx and direct the bolus over the larynx and into the UES. The soft palate occludes the nasopharynx. The primary peristalsis thus initiated is a contraction originating in the oropharynx that clears the esophagus aborally (Fig. 344.1). Oropharyngeal swallowing related dysfunction may occur at multiple levels (Table 344.1). The LES, tonically contracted as a barrier against gastroesophageal reflux (GER), relaxes as swallowing is initiated, at nearly the same time as the UES relaxation. The LES relaxation persists considerably longer, until the peristaltic wave traverses it and closes it. The normal esophageal peristaltic speed is approximately 3 cm/sec; the wave takes 4 sec or longer to traverse the 12 cm esophagus of a young infant and considerably longer in a larger child. Facial stimulation by a puff of air can induce swallowing and esophageal peristalsis in healthy young infants, a reflex termed the **Santmyer swallow.**

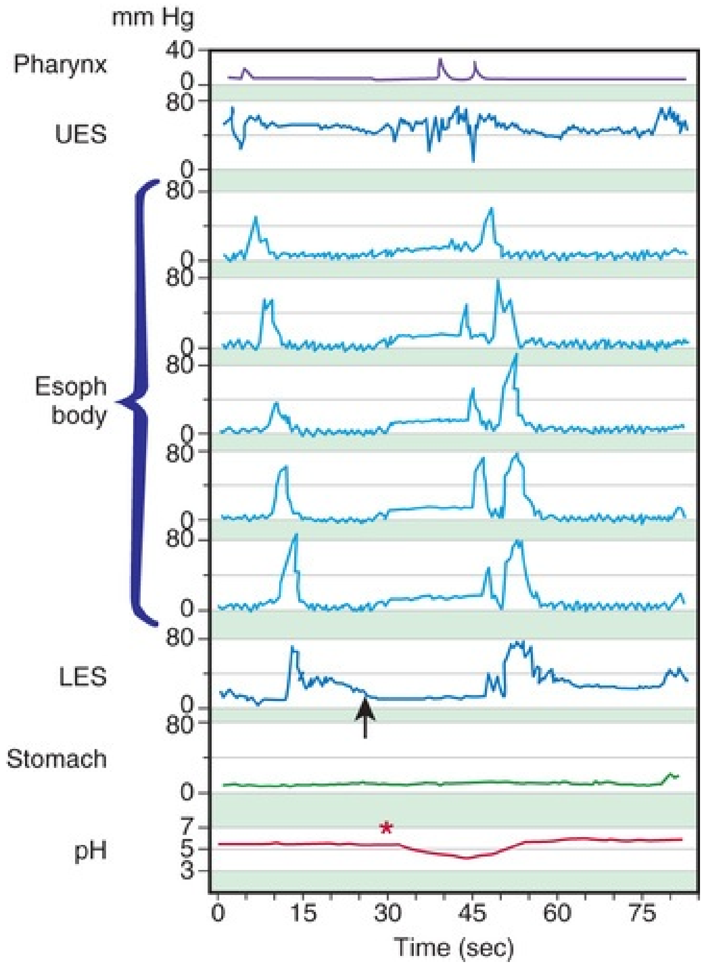

FIG. 344.1 A continuous tracing of esophageal motility showing 2 swallows, as indicated by the pharyngeal contraction associated with relaxation of the upper esophageal sphincter *(UES)* and followed by peristalsis in the body of the esophagus. The lower esophageal sphincter *(LES)* also displays a transient relaxation *(arrow)* unassociated with a swallow. There is an episode of gastroesophageal reflux *(*)* recorded by a *pH* probe at the time of the transient *LES* relaxation. (Courtesy John Dent, FRACP, PhD and Geoffrey Davidson, MD.)

Table 344.1

Mechanical Events of the Oropharyngeal Swallow and Evidence of Dysfunction

MECHANICAL EVENT	EVIDENCE OF DYSFUNCTION
Nasopharyngeal closure	Nasopharyngeal regurgitation Nasal voice
Laryngeal closure	Aspiration during bolus transit
Upper esophageal sphincter opening	Dysphagia Post-swallow residue/aspiration Diverticulum formation

Tongue loading and bolus propulsion	Sluggish misdirected bolus
Pharyngeal clearance	Post-swallow residue in hypopharynx/aspiration

Modified from Pandolfino JE, Kahrilas PJ: Esophageal neuromuscular function and motility disorders. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, New York, 2016, Elsevier (Table 43.1).

In addition to relaxing to move swallowed material past the GEJ into the stomach, the LES normally relaxes to vent swallowed air or to allow retrograde expulsion of material from the stomach. Perhaps as an extension of these functions, the normal LES also permits physiologic reflux episodes, brief events that occur approximately 5 times in the first postprandial hour, particularly in the awake state, but are otherwise uncommon. **Transient LES relaxation,** not associated with swallowing, is the major mechanism underlying **pathologic reflux** (see Fig. 344.1).

The close linkage of the anatomy of the upper digestive and respiratory tracts has mandated intricate functional protections of the respiratory tract during retrograde movement of gastric contents as well as during swallowing. The protective functions include the LES tone, the bolstering of the LES by the surrounding diaphragmatic crura, and the *backup protection* of the UES tone. Secondary peristalsis, akin to primary peristalsis but without an oral component, originates in the upper esophagus, triggered mainly by GER, and thereby also clears refluxed gastric contents from the esophagus. Another protective reflex is the *pharyngeal swallow* (initiated above the esophagus, but without lingual participation). Multiple levels of protection against aspiration include the rhythmic coordination of swallowing and breathing and a series of protective reflexes with esophagopharyngeal afferents and efferents that close the UES or larynx. These reflexes include the esophago-UES contractile reflex, the pharyngo-UES contractile reflex, the esophagoglottal closure reflex, and 2 pharyngoglottal adduction reflexes. The last 2 reflexes have chemoreceptors on the laryngeal surface of the epiglottis and mechanoreceptors on the aryepiglottic folds as their sites of stimulus. It is likely that interactions between the esophagus and the respiratory tract, which cause extraesophageal manifestations of gastroesophageal reflux disease (GERD), will be explained by subtle abnormalities in these protective reflexes.

344.1

Common Clinical Manifestations and Diagnostic Aids

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Keywords

dysphagia
radionuclide scintigraphy
high-resolution esophageal manometry
common clinical manifestations

Manifestations of esophageal disorders include pain, obstruction or difficulty swallowing, abnormal retrograde movement of gastric contents (reflux, regurgitation, or vomiting), or bleeding; esophageal disease can also engender respiratory symptoms. Pain in the chest unrelated to swallowing **(heartburn)** can be a sign of esophagitis, but similar pain might also represent cardiac, pulmonary, or musculoskeletal disease or visceral hyperalgesia. Pain during swallowing **(odynophagia)** localizes the disease more discretely to the pharynx and esophagus and often represents inflammatory mucosal disease. Complete esophageal obstruction can be produced acutely by esophageal foreign bodies, including food impactions; can be congenital, as in esophageal atresia; or can evolve over time as a peptic stricture occludes the esophagus. Difficulty swallowing **(dysphagia)** can be produced by incompletely occlusive esophageal obstruction (by extrinsic compression, intrinsic narrowing, or foreign bodies) but can also result from dysmotility of the esophagus (whether primary/idiopathic or secondary to systemic disease). Inflammatory lesions of the esophagus without obstruction or dysmotility are a third cause of dysphagia; eosinophilic esophagitis, most often afflicting older boys, is relatively common.

The most common esophageal disorder in children is **GERD,** which is from retrograde return of gastric contents into the esophagus. **Esophagitis** can be caused by GERD, by eosinophilic disease, by infection, or by caustic substances.

Esophageal **bleeding** can result from severe esophagitis that produces erosions or ulcerations and can manifest as anemia or Hemoccult-positive stools. More acute or severe bleeding can be from ruptured **esophageal varices.** The resulting hematemesis must be differentiated from more distal bleeding (gastric ulcer) and from more proximal bleeding (a nosebleed or hemoptysis). Respiratory symptoms of esophageal disease can result from luminal contents incorrectly being directed into the respiratory tract or to reflexive respiratory responses to esophageal stimuli.

Diagnostic Aids

The esophagus can be evaluated by radiography, endoscopy, histology, scintigraphy, manometry, pH-metry (linked as indicated with other polysomnography), and multichannel intraluminal impedance. Contrast (usually barium) radiographic study of the esophagus usually incorporates fluoroscopic imaging over time so that motility and anatomy can be assessed. Although most often requested to evaluate for GERD, it is neither sensitive nor specific for this purpose; it can detect complications of GERD (stricture) or conditions mimicking GERD (pyloric stenosis or malrotation with intermittent volvulus), or concurrent hiatal hernia complicating GERD.

Barium fluoroscopy is optimal for evaluating for structural anomalies, such as duplications, strictures, hiatal hernia, congenital esophageal stenosis or external esophageal compression by an aberrant blood vessel, or for causes of dysmotility, such as achalasia. Modifications of the routine barium fluoroscopic study are used in special situations. When an *H-type* tracheoesophageal fistula is suspected, the test is most sensitive if the radiologist, with the patient prone, distends the esophagus with barium via a nasogastric tube. The videofluoroscopic evaluation of swallowing performed with varying consistencies of barium (modified barium swallow, oropharyngeal videoesophagram, or cookie swallow) optimally evaluates children with dysphagia by demonstrating incoordination of the pharyngeal and esophageal phases of swallowing and any associated aspiration.

In some centers, fiberoptic endoscopic evaluation of swallowing uses nasopharyngeal endoscopy to visualize the pharynx and larynx during swallowing of dye-enhanced foods when dysphagia, laryngeal penetration, or aspiration is suspected. This is often combined with sensory testing of the laryngeal adductor reflex in response to a calibrated puff of air through the endoscope to the arytenoids, generating the composite fiberoptic endoscopic evaluation of swallowing sensory testing that examines the mechanisms of any aspiration that is present. Endoscopy allows direct visualization of esophageal mucosa and helps therapeutically in the removal of foreign bodies and treatment of esophageal varices. Endoscopy also allows biopsy samples to be taken, thus improving the diagnosis of **endoscopy-negative GERD** , differentiating GERD from eosinophilic esophagitis, and identifying viral or fungal causes of esophagitis.

Radionuclide scintigraphy scans are helpful in evaluating the efficiency of peristalsis and demonstrating reflux episodes. They can be specific, although not very sensitive, for aspiration and can quantify gastric emptying, thus hinting at a cause for GERD. The related radionuclide salivagram can demonstrate aspiration of even minute amounts of saliva.

Esophageal manometry evaluates for dysmotility from the pharynx to the stomach; by synchronized quantitative pressure measurements along the esophagus, it detects and characterizes dysfunctions sometimes missed radiographically. Manometry is often challenging in young infants, and sphincters are optimally evaluated with special Dent sleeves, rather than the simple ports available for the esophageal body. High-resolution esophageal manometry (HRM) along with video fluoroscopic swallowing study (VFSS) to evaluate UES relaxation, pharyngeal and peristaltic pressures is now available at a few centers of expertise.

Extended pH monitoring of the distal esophagus is a sensitive test for acidic GER episodes that can quantify duration and degree of acidity, but not volume, of the reflux episodes. It is linked with polysomnography (a pneumogram) when GER is suspected to cause apnea or similar symptoms. Multichannel intraluminal impedance is a method for pH-independent detection of bolus movements in the esophagus; with a pH probe incorporated, it can distinguish between acid and nonacid liquid and gaseous reflux, the proximal extent of reflux, and several aspects of esophageal function, such as direction of bolus flow, duration of bolus presence, and bolus clearance.

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CHAPTER 345

Congenital Anomalies

345.1

Esophageal Atresia and Tracheoesophageal Fistula

Seema Khan, Sravan Kumar Reddy Matta

Keywords

VACTERL
polyhydramnios

Esophageal atresia (EA) is the most common congenital anomaly of the esophagus, with a prevalence of 1.7 per 10,000 live births. Of these, >90% have an associated tracheoesophageal fistula (TEF). In the most common form of EA, the upper esophagus ends in a blind pouch and the TEF is connected to the distal esophagus (type C). Fig. 345.1 shows the types of EA and TEF and their relative frequencies. The exact cause is still unknown; associated features include advanced maternal age, European ethnicity, obesity, low socioeconomic status, and tobacco smoking. This defect has survival rates of >90%, owing largely to improved neonatal intensive care, earlier recognition, and appropriate intervention. Infants weighing <1,500 g at birth and those with severe associated cardiac anomalies have the highest risk for mortality. Fifty percent of infants are nonsyndromic without other anomalies, and the rest have associated anomalies, most often associated with the vertebral, anorectal, (cardiac), tracheal, esophageal, renal, radial, (limb) (VACTERL) syndrome. Cardiac and vertebral anomalies are seen in 32% and 24%, respectively. VACTERL is generally associated with normal intelligence. Despite low concordance among twins and the low incidence of familial cases, genetic factors have a role in the pathogenesis of TEF in some patients as suggested by discrete mutations in syndromic cases: Feingold syndrome *(N-MYC)*, CHARGE syndrome (*c* oloboma of the eye; *c* entral nervous system anomalies; *h* eart defects; *a* tresia of the choanae; *r* etardation of growth and/or development; *g* enital and/or urinary defects [hypogonadism]; *e* ar anomalies and/or deafness) *(CHD7)*, and anophthalmia-esophageal-genital syndrome *(SOX2)*.

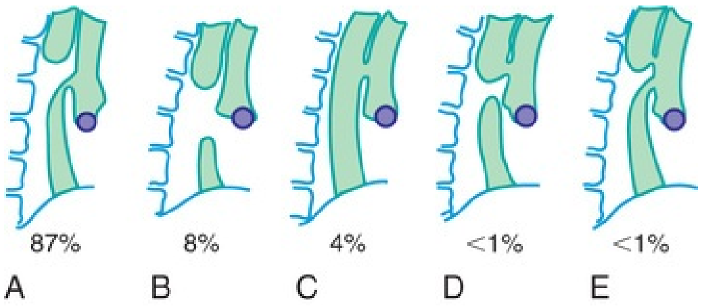

FIG. 345.1 Diagrams of the 5 most commonly encountered forms of esophageal atresia and tracheoesophageal fistula, shown in order of frequency.

Presentation

The neonate with EA typically has frothing and bubbling at the mouth and nose after birth as well as episodes of coughing, cyanosis, and respiratory distress. Feeding exacerbates these symptoms, causes regurgitation, and can precipitate aspiration. Aspiration of gastric contents via a distal fistula causes more damaging pneumonitis than aspiration of pharyngeal secretions from the blind upper pouch. The infant with an isolated TEF in the absence of EA (“H-type” fistula) might come to medical attention later in life with chronic respiratory problems, including refractory bronchospasm and recurrent pneumonias.

Diagnosis

In the setting of early-onset respiratory distress, the inability to pass a nasogastric or orogastric tube in the newborn suggests EA. Imaging findings of absence of the fetal stomach bubble and maternal polyhydramnios might alert the physician to EA before birth. Plain radiography in the evaluation of respiratory distress might reveal a coiled feeding tube in the esophageal pouch and/or an air-distended stomach, indicating the presence of a coexisting TEF (Fig. 345.2). Conversely, pure EA can manifest as an airless scaphoid abdomen. In isolated TEF (H type), an esophagogram with contrast medium injected under pressure can demonstrate the defect (Fig. 345.3). Alternatively, the orifice may be detected at bronchoscopy or when methylene blue dye injected into the endotracheal tube during endoscopy is observed in the esophagus during forced inspiration. The differential diagnosis of congenital esophageal lesions is noted in Table 345.1 .

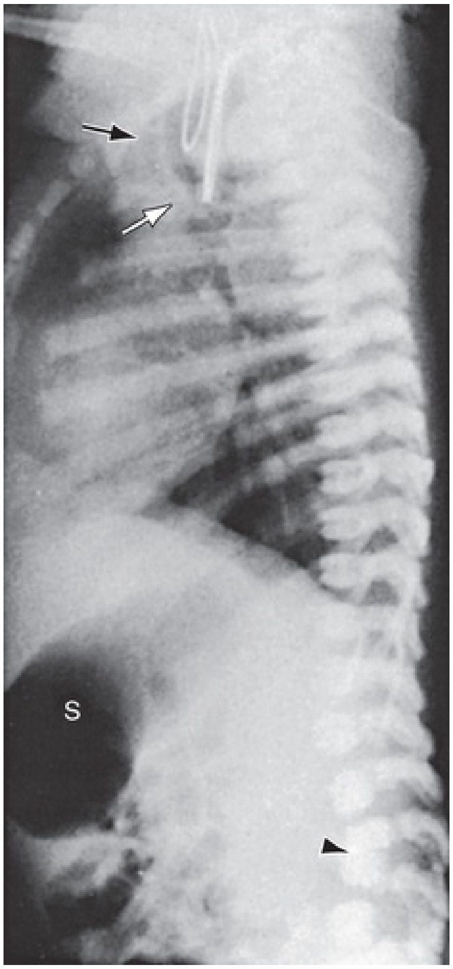

FIG. 345.2 Tracheoesophageal fistula. Lateral radiograph demonstrating a nasogastric tube coiled *(arrows)* in the proximal segment of an atretic esophagus. The distal fistula is suggested by gaseous dilation of the stomach *(S)* and small intestine. The *arrowhead* depicts vertebral fusion, whereas a heart murmur and cardiomegaly suggest the presence of a ventricular septal defect. This patient demonstrated elements of the vertebral, anorectal, tracheal, esophageal, renal, and radial anomalad. (From Balfe D, Ling D, Siegel M: The esophagus. In Putman CE, Ravin CE, editors: *Textbook of diagnostic imaging,* Philadelphia, 1988, WB Saunders.)

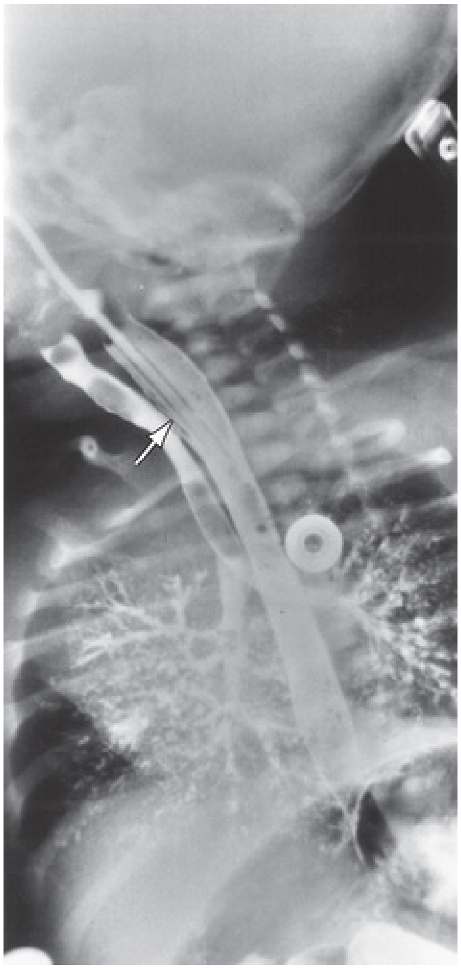

FIG. 345.3 H-type fistula *(arrow)* demonstrated in an infant after barium swallow on frontal-oblique chest x-ray. The tracheal aspect of the fistula is characteristically superior to the esophageal aspect. Barium is seen to outline the tracheobronchial tree. (From Wyllie R, Hyams JS, editors: *Pediatric gastrointestinal and liver disease,* ed 3, Philadelphia, 2006, Saunders Elsevier, p. 299.)

Table 345.1

Clinical Aspects of Esophageal Developmental Anomalies

ANOMALY	AGE AT PRESENTATION	PREDOMINANT SYMPTOMS	DIAGNOSIS	TREATMENT
Isolated atresia	Newborns	Regurgitation of feedings Aspiration	Esophagogram* Plain film: gasless abdomen	Surgery
Atresia + distal TEF	Newborns	Regurgitation of feedings Aspiration	Esophagogram* Plain film: gas-filled abdomen	Surgery
H-type TEF	Infants to adults	Recurrent pneumonia	Esophagogram*	Surgery

		Bronchiectasis	Bronchoscopy [†]	
Esophageal stenosis	Infants to adults	Dysphagia Food impaction	Esophagogram[*] Endoscopy [†]	Dilation [‡] Surgery [§]
Duplication cyst	Infants to adults	Dyspnea, stridor, cough (infants) Dysphagia, chest pain (adults)	EUS[*] MRI/CT [†]	Surgery
Vascular anomaly	Infants to adults	Dyspnea, stridor, cough (infants) Dysphagia (adults)	Esophagogram[*] Angiography [†] MRI/CT/EUS	Dietary modification [‡] Surgery [§]
Esophageal ring	Children to adults	Dysphagia	Esophagogram[*] Endoscopy [†]	Dilation [‡] Endoscopic incision [§]
Esophageal web	Children to adults	Dysphagia	Esophagogram[*] Endoscopy [†]	Bougienage

[*] Diagnostic test of choice.

[†] Confirmatory test.

[‡] Primary therapeutic approach.

[§] Secondary therapeutic approach.

TEF, tracheoesophageal fistula.

From Madanick R, Orlando RC: Anatomy, histology, embryology, and developmental anomalies of the esophagus. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, New York, 2016, Elsevier, Table 42.2.

Management

Initially, maintaining a patent airway, pre-operative proximal pouch decompression to prevent aspiration of secretions, and use of antibiotics to prevent consequent pneumonia are paramount. Prone positioning minimizes movement of gastric secretions into a distal fistula, and esophageal suctioning minimizes aspiration from a blind pouch. Endotracheal intubation with mechanical ventilation is to be avoided if possible because it can worsen distention of the stomach. Surgical ligation of the TEF and primary end-to-end anastomosis of the esophagus via right-sided thoracotomy constitute the current standard surgical approach. In the premature or otherwise complicated infant, a primary closure may be delayed by temporizing with fistula ligation and gastrostomy tube placement. If the gap between the atretic ends of the esophagus is >3 to 4 cm (>3 vertebral bodies), primary repair cannot be done; options include using gastric, jejunal, or colonic segments interposed as a neoesophagus. Careful search must be undertaken for the common associated cardiac and other anomalies. Thoracoscopic surgical repair is feasible and associated with favorable long-term outcomes.

Outcome

The majority of children with EA and TEF grow up to lead normal lives, but complications are often challenging, particularly during the first 5 yr of life. Complications of surgery include anastomotic leak, refistulization, and anastomotic stricture. Gastroesophageal reflux disease, resulting from intrinsic abnormalities of esophageal function, often combined with delayed gastric emptying, contributes to management challenges in many cases. Gastroesophageal reflux disease contributes significantly to the respiratory disease **(reactive airway disease)** that often complicates EA and TEF and also worsens the frequent anastomotic strictures after repair of EA.

Many patients have an associated tracheomalacia that improves as the child grows. Hence, it is important to target on prevention of long-term complications using appropriate surveillance techniques (endoscopy, pH-Impedance).

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345.2

Laryngotracheoesophageal Clefts

Seema Khan, Sravan Kumar Reddy Matta

Laryngotracheoesophageal clefts are uncommon anomalies that result when the septum between the esophagus and trachea fails to develop fully, leading to a common channel defect between the pharyngoesophagus and laryngotracheal lumen, thus making the laryngeal closure incompetent during swallowing or reflux. Other developmental anomalies, such as EA and TEF, are seen in 20% of patients with clefts. The severity of presenting symptoms depends on the type of cleft; they are commonly classified as four types (I-IV) according to the inferior extent of the cleft. Early in life, the infant presents with stridor, choking, cyanosis, aspiration of feedings, and recurrent chest infections. The diagnosis is difficult and usually requires direct endoscopic visualization of the larynx and esophagus. When contrast radiography is used, material is often seen in the esophagus and trachea. Treatment is surgical repair, which can be complex if the defects are long.

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345.3

Congenital Esophageal Stenosis

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Keywords

total bronchial remnants (TBR)
bougie dilations

Congenital esophageal stenosis (CES) is a rare anomaly of the esophagus with clinical significance. Though the original incidence is not known, it is estimated to affect 1 : 25,000 to 50,000 live births. The defect results from incomplete separation of respiratory tract from the primitive foregut at 25th day of fetal life. CES is differentiated by histology into 3 types: esophageal membrane/web, total bronchial remnants (TBR), and fibromuscular remnants (FMR). Symptoms vary depending on the location and severity of the defect. Higher lesions present with respiratory symptoms and lower lesions present with dysphagia and vomiting. Esophagogram (Fig. 345.4), MRI, CT, and endoscopic ultrasound are used for diagnosis. Endoscopy (Fig. 345.5) is done to evaluate mucosal abnormalities like strictures, foreign bodies, and esophagitis. Treatment option (surgical correction, bougie dilation) is chosen based on the location, severity, and type of stenosis.

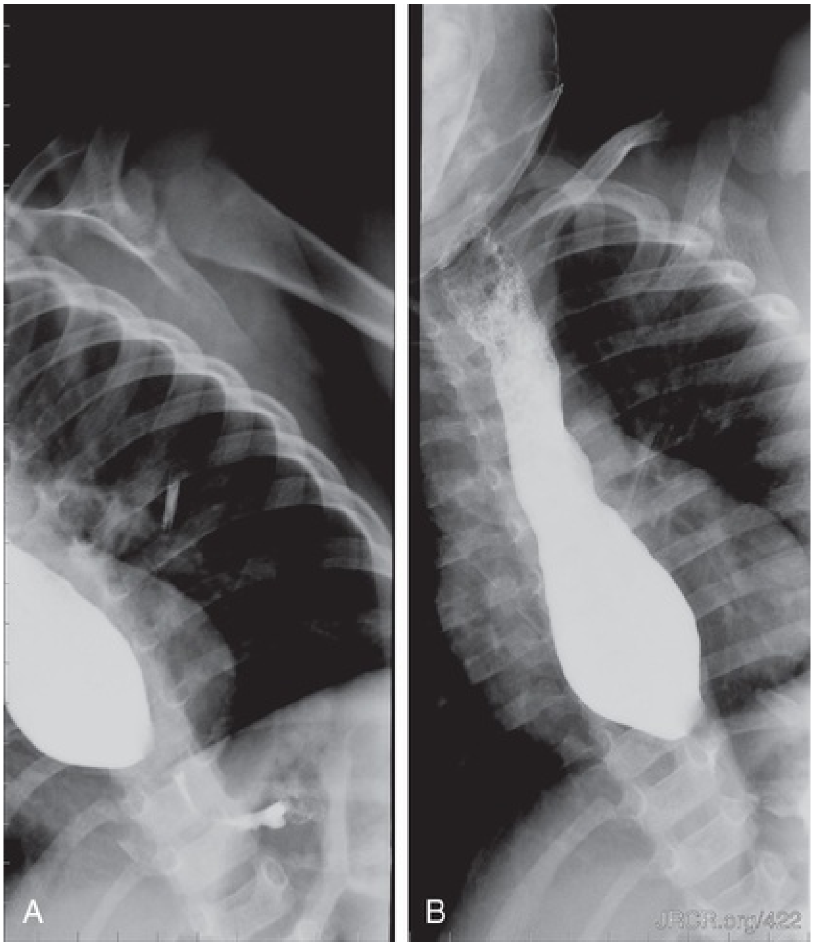

FIG. 345.4 An 18-month-old male with congenital esophageal stenosis. Esophagogram using barium as contrast media, shows an AP projection (A) and an unsuccessful attempt to obtain a lateral projection (B) , due to poor collaboration of the patient. An asymmetric short narrowing of the distal esophagus is observed, as well as proximal dilatation of the esophagus. Gastroesophageal reflux was not identified. (From Serrao E, Santos, A, Gaivao A: Congenital esophageal stenosis: a rare case of dysphagia, *J Radiol Case Rep* 4(6):8–14, 2010. Fig. 2).

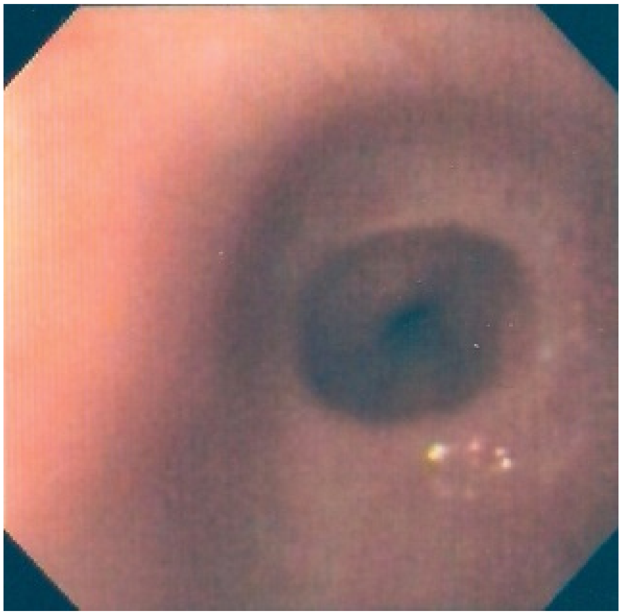

FIG. 345.5 An 18-month-old male with congenital esophageal stenosis. Esophagoscopy showed a circumferential, slightly non-central narrowing at the distal esophagus, 2 cm proximal to the esophagogastric junction. (From Serrao E, Santos, A, Gaivao A: Congenital esophageal stenosis: a rare case of dysphagia, *J Radiol Case Rep* 4(6):8–14, 2010. Fig. 3).

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CHAPTER 346

Obstructing and Motility Disorders of the Esophagus

Seema Khan, Sravan Kumar Reddy Matta

Obstructing lesions classically produce **dysphagia** to *solids* earlier and more noticeably than to liquids and can manifest when the infant liquid diet begins to incorporate solids; this contrasts to **dysphagia** from **dysmotility,** in which swallowing of *liquids* is affected as early as, or earlier than, solids. In most instances of dysphagia, evaluation begins with fluoroscopy, which may include videofluoroscopic evaluation of swallowing, particularly if aspiration is a primary symptom. Secondary studies are often endoscopic if intrinsic obstruction is suspected or manometric if dysmotility is suspected; other imaging studies may be used in particular cases. Congenital lesions can require surgery, whereas webs and peptic strictures might respond adequately to endoscopic (or bougie) dilation. Peptic strictures, once dilated, should prompt consideration of fundoplication for ongoing prophylaxis.

Extrinsic

Esophageal duplication cysts are the most commonly encountered foregut duplications (see Table 345.1). These cysts are lined by intestinal epithelium, have a well-developed smooth muscle wall, and are attached to the normal gastrointestinal tract. Most of these affect the distal half of the esophagus on the right side. The most common presentation is respiratory distress caused by compression of the adjacent airways. Dysphagia is a common symptom in older children. Upper gastrointestinal bleeding can occur as a result of acid-secreting gastric mucosa in the duplication wall. **Neuroenteric cysts** might contain glial elements and are associated with **vertebral anomalies.** Diagnosis is made using modalities, such as barium swallow, chest CT, and MRI, or endosonography. Treatment is surgical; laparoscopic approach to excision is also possible.

Enlarged mediastinal or subcarinal **lymph nodes,** caused by infection (tuberculosis, histoplasmosis) or neoplasm (lymphoma), are the most common external masses that compress the esophagus and produce obstructive symptoms. **Vascular anomalies** can also compress the esophagus; *dysphagia lusoria* is a term denoting the dysphagia produced by a developmental vascular anomaly, which is often an aberrant right subclavian artery or right-sided or double aortic arch (see Chapter 459.1).

Intrinsic

Intrinsic narrowing of the esophageal lumen can be congenital or acquired. The etiology is suggested by the location, the character of the lesion, and the clinical situation. The lower esophagus is the most common location for peptic strictures, which are generally somewhat ragged and several cm long. Thin membranous rings, including the **Schatzki ring** at the squamocolumnar junction, can also occlude this area. In the midesophagus, congenital narrowing may be associated with the esophageal atresia–tracheoesophageal fistula complex, in which some of the lesions might incorporate cartilage and might be impossible to dilate safely; alternatively, reflux esophagitis can induce a ragged and extensive narrowing that appears more proximal than the usual peptic stricture, often because of an associated hiatal hernia. Congenital webs or rings can narrow the upper esophagus. The upper esophagus can also be narrowed by an inflammatory stricture occurring after a caustic ingestion or due to epidermolysis bullosa. Cricopharyngeal achalasia can appear radiographically as a cricopharyngeal bar posteriorly in the upper esophagus. **Eosinophilic esophagitis** is one of the most common causes for esophageal obstructive symptoms. Although the pathogenesis of obstructive eosinophilic esophagitis is not yet completely explained and seems to vary among individual patients, endoscopy or radiology demonstrates stricture formation in some children with eosinophilic esophagitis, and in others a noncompliant esophagus is evident, with thickened wall layers demonstrable by ultrasonography.

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CHAPTER 347

Dysmotility

Seema Khan, Sravan Kumar Reddy Matta

Upper Esophageal and Upper Esophageal Sphincter Dysmotility (Striated Muscle)

Cricopharyngeal **achalasia** signifies a failure of complete relaxation of the upper esophageal sphincter (UES), whereas cricopharyngeal **incoordination** implies full relaxation of the UES but incoordination of the relaxation with the pharyngeal contraction. These entities are usually detected on videofluoroscopic evaluation of swallowing (sometimes accompanied by visible cricopharyngeal prominence, termed a *bar*), but often the most precise definition of the dysfunction is obtained with manometry. A self-limited form of cricopharyngeal incoordination occurs in infancy and remits spontaneously in the 1st yr of life if nutrition is maintained despite the dysphagia. In children, treatment options for non-self-limited cricopharyngeal achalasia consist of dilation, Botox injection, and transcervical myotomy. It is important to evaluate such children thoroughly, including cranial MRI to detect **Arnold-Chiari malformations,** which can manifest in this way but are best treated by cranial decompression rather than esophageal surgery. Cricopharyngeal spasm may be severe enough to produce posterior pharyngeal (**Zenker**) **diverticulum** above the obstructive sphincter; this entity occurs rarely in children.

Systemic causes of swallowing dysfunction that can affect the oropharynx, UES, and upper esophagus include cerebral palsy, Arnold-Chiari malformations, syringomyelia, bulbar palsy or cranial nerve defects (Möbius syndrome, transient infantile paralysis of the superior laryngeal nerve), transient pharyngeal muscle dysfunction, spinal muscular atrophy (including Werdnig-Hoffmann disease), muscular dystrophy, multiple sclerosis, infections (botulism, tetanus, poliomyelitis, diphtheria), inflammatory and autoimmune diseases (dermatomyositis, myasthenia gravis, polyneuritis, scleroderma), and familial dysautonomia. All of these can produce dysphagia. Medications (nitrazepam, benzodiazepines) and tracheostomy can adversely affect the function of the UES and thereby produce dysphagia.

Lower Esophageal and Lower Esophageal Sphincter Dysfunction (Smooth Muscle)

Causes of dysphagia resulting from more distal primary esophageal dysmotility include achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive lower esophageal sphincter (LES); all but achalasia are rare in children. Secondary causes include Hirschsprung disease, pseudoobstruction, inflammatory myopathies, scleroderma, and diabetes.

Achalasia is a primary esophageal motor disorder of unknown etiology characterized by loss of LES relaxation and loss of esophageal peristalsis, both contributing to a functional obstruction of the distal esophagus. Degenerative, autoimmune (antibodies to Auerbach plexus), and infectious (Chagas disease caused by *Trypanosoma cruzi*) factors are possible causes. In rare cases, achalasia is familial or part of the achalasia, alacrima, and adrenal insufficiency, known as triple A syndrome or **Allgrove syndrome** . *Pseudoachalasia* refers to achalasia caused by various forms of cancer via obstruction of the gastroesophageal junction, infiltration of the submucosa and muscularis of the LES, or as part of the paraneoplastic syndrome with formation of anti-Hu antibodies. Pathologically, in achalasia, inflammation surrounds ganglion cells, which are decreased in number. There is selective loss of postganglionic inhibitory neurons that normally lead to sphincter relaxation, leaving postganglionic cholinergic neurons unopposed. This imbalance produces high basal LES pressures and insufficient LES relaxation. The loss of esophageal peristalsis can be a secondary phenomenon.

Achalasia manifests with regurgitation and dysphagia for solids and liquids and may be accompanied by undernutrition or chronic cough; retained esophageal food can produce esophagitis. *The presentations of chronic* *regurgitation/vomiting with weight loss, and chronic cough have led to misdiagnoses of anorexia nervosa and asthma, respectively.* The mean age in children is 8.8 yr, with a mean duration of symptoms before diagnosis of 23 mo; it is uncommon before school age. Chest radiograph shows an air–fluid level in a dilated esophagus. **Barium fluoroscopy** reveals a smooth tapering of the lower esophagus leading to the closed LES, resembling a bird's beak (Fig. 347.1). Loss of primary peristalsis in the distal esophagus with retained food and poor emptying are often present. **Manometry** is the most sensitive diagnostic test and helps differentiate the three types of achalasia; it reveals the defining features of aperistalsis in the distal esophageal body and incomplete or absent LES relaxation, often accompanied by high-pressure LES and low-amplitude esophageal body contractions (Fig. 347.2).

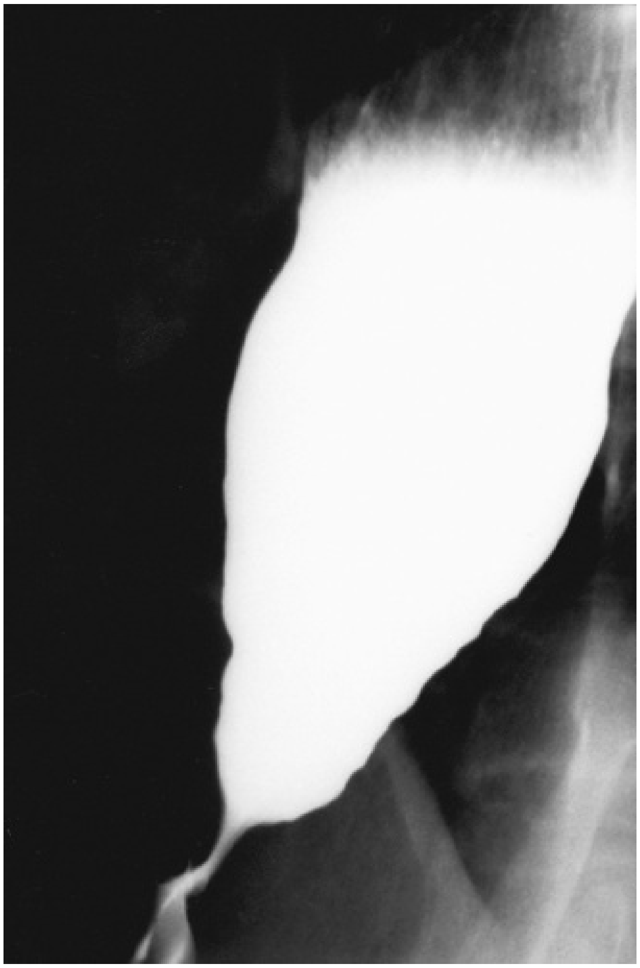

FIG. 347.1 Barium esophagogram of a patient with achalasia demonstrating dilated esophagus and narrowing at the lower esophageal

sphincter. Note retained secretions layered on top of barium in the esophagus.

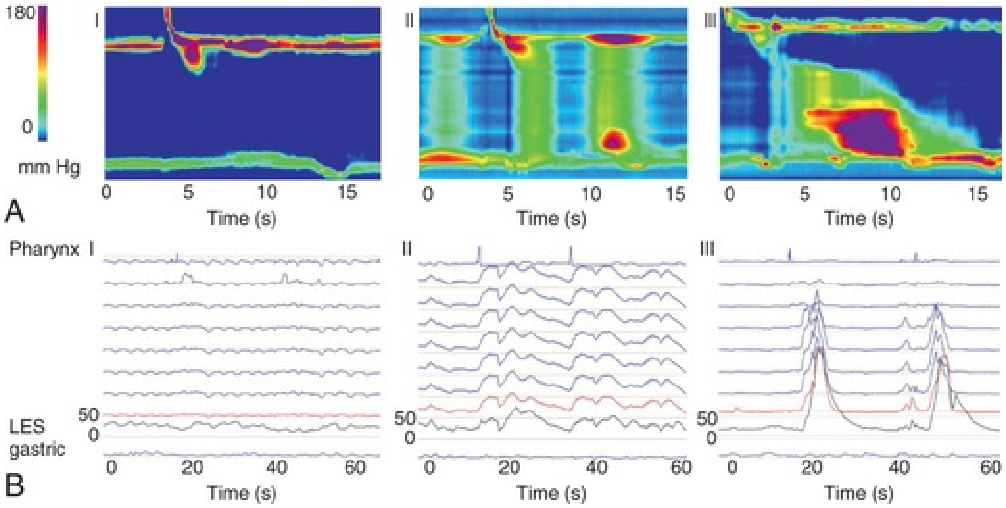

FIG. 347.2 **Based on the residual wave type on HRM, 3 subtypes of achalasia can be determined. A, No distal pressurization is observed in type I (AI), whereas panesophageal pressurizations and spastic contractions are observed in type II (AII) and type III (AIII), respectively. B, A similar classification can be made when conventional manometry is used. Note that pressure recordings in type II achalasia are similar in every line tracing, compatible with panesophageal pressurization. (From Rohof WO, Salvador R, Annese V: Outcomes of treatment for achalasia depend on manometric subtype. *Gastroenterology* 144(4): 718–725, 2013. Fig. 1).**

The goals of achalasia therapy are relief of symptoms, improvement of esophageal emptying, and prevention of megaesophagus. The two most effective treatment options are pneumatic dilation and laparoscopic or surgical (Heller) myotomy. Pneumatic dilation is the initial treatment of choice and does not preclude a future myotomy. Surgeons often supplement a myotomy with an antireflux procedure to prevent the gastroesophageal reflux disease that otherwise often ensues when the sphincter is rendered less competent. Laparoscopic myotomy is a particularly effective procedure in adolescent and young adult males. Peroral endoscopic myotomy (POEM) may be a feasible, safe, and an effective alternative to the laparoscopic method. Calcium channel blockers (nifedipine) and phosphodiesterase inhibitors offer temporary relief of dysphagia. Endoscopic injection of the LES with **botulinum toxin** counterbalances the selective loss of inhibitory neurotransmitters by inhibiting the release of acetylcholine from nerve terminals and may be an effective therapy. Botulinum toxin is effective in 50–65% of patients and is expensive;

half the patients might require a repeat injection within 1 yr. Most eventually require dilation or surgery.

Diffuse esophageal spasm causes chest pain and dysphagia and affects adolescents and adults. It is diagnosed **manometrically** and can be treated with nitrates or calcium-channel-blocking agents.

Gastroesophageal reflux disease constitutes the most common cause of nonspecific abnormalities of esophageal motor function, probably through the effect of the esophageal inflammation on the musculature.

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CHAPTER 348

Hiatal Hernia

Seema Khan, Sravan Kumar Reddy Matta

Herniation of the stomach through the esophageal hiatus can occur as a common sliding hernia (type 1), in which the gastroesophageal junction slides into the thorax, or it can be paraesophageal (type 2), in which a portion of the stomach (usually the fundus) is insinuated next to the esophagus inside the gastroesophageal junction in the hiatus (Figs. 348.1 and 348.2). A combination of sliding and paraesophageal types (type 3) is present in some patients. Sliding hernias are often associated with gastroesophageal reflux, especially in developmentally delayed children. The relationship to hiatal hernias in adults is unclear. Diagnosis is usually made by an upper gastrointestinal series and upper endoscopy. Medical treatment is not directed at the hernia but at the gastroesophageal reflux, unless failure of medical therapy prompts correction of the hernia at the time of fundoplication.

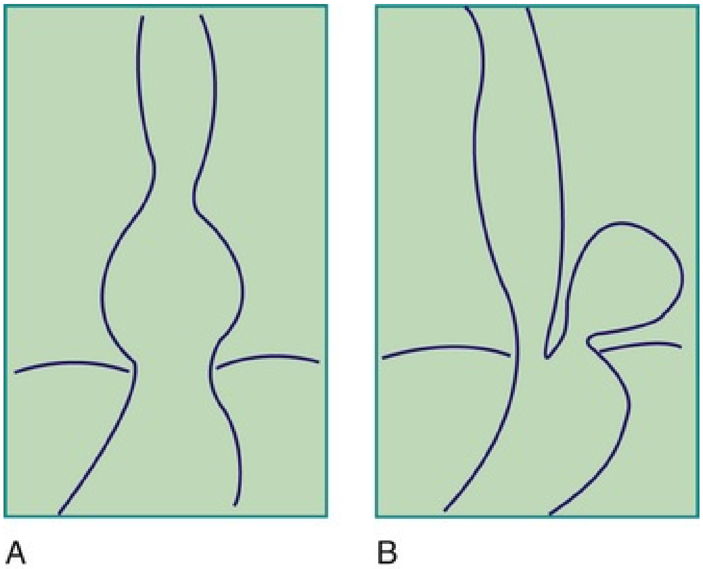

FIG. 348.1 **Types of esophageal hiatal hernia. A, Sliding hiatal hernia, the most common type. B, Paraesophageal hiatal hernia.**

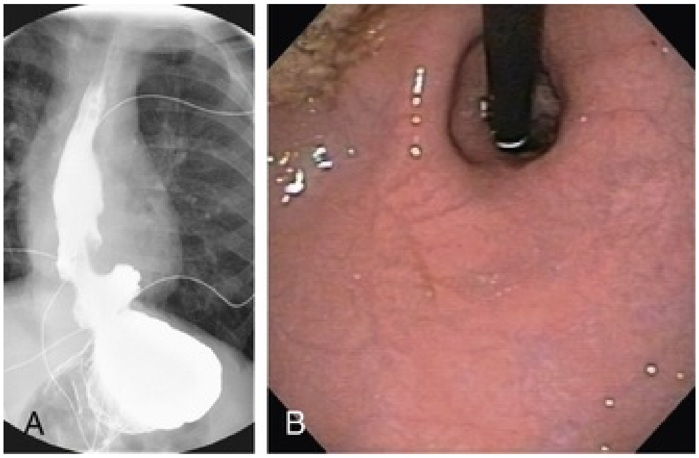

FIG. 348.2 **A,** An upper gastrointestinal series shows a large hiatal hernia that extends above the diaphragm and impedes the exit of contrast from the esophagus into the stomach. Contrast is also noted to reflux to the upper esophagus. **B,** A retroflexed view of the hernia from the stomach during an upper endoscopy.

A paraesophageal hernia can be an isolated congenital anomaly or associated with gastric volvulus, or it may be encountered after fundoplication for gastroesophageal reflux, especially if the edges of a dilated esophageal diaphragmatic hiatus have not been approximated. Fullness after eating and upper abdominal pain are the usual symptoms. Infarction of the herniated stomach is rare.

CHAPTER 349

Gastroesophageal Reflux Disease

Seema Khan, Sravan Kumar Reddy Matta

Gastroesophageal reflux disease (GERD) is the most common esophageal disorder in children of all ages. Gastroesophageal reflux (GER) signifies the retrograde movement of gastric contents across the lower esophageal sphincter (LES) into the esophagus, which occurs physiologically every day in all infants, older children, and adults. Physiologic GER is exemplified by the effortless regurgitation of normal infants. The phenomenon becomes **pathologic GERD** in infants and children who manifest or report bothersome symptoms because of frequent or persistent GER, producing esophagitis-related symptoms, or extra-esophageal presentations, such as respiratory symptoms or nutritional effects.

Pathophysiology

Factors determining the esophageal manifestations of reflux include the duration of esophageal exposure (a product of the frequency and duration of reflux episodes), the causticity of the refluxate, and the susceptibility of the esophagus to damage. The LES, defined as a high-pressure zone by manometry, is supported by the crura of the diaphragm at the gastroesophageal junction, together with valve-like functions of the esophagogastric junction anatomy, form the antireflux barrier. In the context of even the normal intraabdominal pressure augmentations that occur during daily life, the frequency of reflux episodes is increased by insufficient LES tone, by abnormal frequency of LES relaxations, and by hiatal herniation that prevents the LES pressure from being proportionately augmented by the crura during abdominal straining. Normal intraabdominal pressure augmentations may be further exacerbated by straining or respiratory efforts. The duration of reflux episodes is increased by lack of swallowing (e.g., during sleep) and by defective esophageal peristalsis. Vicious cycles ensue because chronic esophagitis produces esophageal peristaltic dysfunction (low-amplitude waves, propagation disturbances), decreased LES tone, and inflammatory esophageal shortening that induces hiatal herniation, all worsening reflux.

Transient LES relaxation (TLESR) is the primary mechanism allowing reflux to occur, and is defined as simultaneous relaxation of both LES and the surrounding crura. TLESRs occur independent of swallowing, reduce LES pressure to 0-2 mm Hg (above gastric), and last 10-60 sec; they appear by 26 wk of gestation. A vagovagal reflex, composed of afferent mechanoreceptors in the proximal stomach, a brainstem pattern generator, and efferents in the LES, regulates TLESRs. Gastric distention (postprandially, or from abnormal gastric emptying or air swallowing) is the main stimulus for TLESRs. Whether GERD is caused by a higher frequency of TLESRs or by a greater incidence of reflux during TLESRs is debated; each is likely in different persons. Straining during a TLESR makes reflux more likely, as do positions that place the gastroesophageal junction below the air–fluid interface in the stomach. Other factors influencing gastric pressure–volume dynamics, such as increased movement, straining, obesity, large-volume or hyperosmolar meals, gastroparesis, a large sliding hiatal hernia, and increased respiratory effort (coughing, wheezing) can have the same effect.

Epidemiology and Natural History

Infant reflux becomes evident in the first few mo of life, peaks at 4 mo, and resolves in up to 88% by 12 mo and in nearly all by 24 mo. *Happy spitters* are infants who have recurrent regurgitation *without* exhibiting discomfort or refusal to eat and failure to gain weight. Symptoms of GERD in **older children** tend to be chronic, waxing and waning, but completely resolving in no more than half, which resembles adult patterns (Table 349.1). The histologic findings of esophagitis persist in infants who have naturally resolving symptoms of reflux. GERD likely has genetic predispositions: family clustering of GERD symptoms, endoscopic esophagitis, hiatal hernia, Barrett esophagus, and adenocarcinoma have been identified. As a continuously variable and common disorder, complex inheritance involving multiple genes and environmental factors is likely. Genetic linkage is indicated by the strong evidence of GERD in studies with monozygotic twins. A pediatric autosomal dominant form with otolaryngologic and respiratory manifestations has been located to chromosome 13q14, and the locus is termed GERD1.

Table 349.1

Symptoms According to Age

MANIFESTATIONS	INFANTS	CHILDREN	ADOLESCENTS AND ADULTS
Impaired quality of life	+++	+++	+++
Regurgitation	++++	+	+
Excessive crying/irritability	+++	+	–
Vomiting	++	++	+
Food refusal/feeding disturbances/anorexia	++	+	+
Persisting hiccups	++	+	+
Failure to thrive	++	+	–
Abnormal posturing/Sandifer syndrome	++	+	–
Esophagitis	+	++	+++
Persistent cough/aspiration pneumonia	+	++	+
Wheezing/laryngitis/ear problems	+	++	+
Laryngomalacia/stridor/croup	+	++	–
Sleeping disturbances	+	+	+
Anemia/melena/hematemesis	+	+	+
Apnea/BRUE/desaturation	+	–	–
Bradycardia	+	?	?
Heartburn/pyrosis	?	++	+++
Epigastric pain	?	+	++
Chest pain	?	+	++
Dysphagia	?	+	++
Dental erosions/water brush	?	+	+
Hoarseness/globus pharyngeus	?	+	+
Chronic asthma/sinusitis	–	++	+
Laryngostenosis/vocal nodule problems	–	+	+
Stenosis	–	(+)	+
Barrett/esophageal adenocarcinoma	–	(+)	+

+++ , Very common; ++ common; + possible; (+) rare; − absent; ? unknown; *BRUE* , brief resolved unexplained event; previously called as *ALTE* , apparent life-threatening event.

From Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease,* ed 4, Philadelphia, 2011, WB Saunders, Table 22.3, p. 235.

Clinical Manifestations

Most of the common clinical manifestations of esophageal disease can signify the presence of GERD and are generally thought to be mediated by the pathogenesis involving acid GER (Table 349.2). Although less noxious for the esophageal mucosa, nonacid reflux events are recognized to play an important role in extraesophageal disease manifestations. **Infantile reflux** manifests more often with regurgitation (especially postprandially), signs of esophagitis (irritability, arching, choking, gagging, feeding aversion), and resulting failure to thrive; symptoms resolve spontaneously in the majority of infants by 12-24 mo. **Older children** can have regurgitation during the preschool years; this complaint diminishes somewhat as children age, and complaints of abdominal and chest pain supervene in later childhood and adolescence. Occasional children present with food refusal or neck contortions (arching, turning of head) designated **Sandifer syndrome.** The respiratory presentations are also age dependent: GERD in infants may manifest as obstructive apnea or as stridor or lower airway disease in which reflux complicates primary airway disease such as laryngomalacia or bronchopulmonary dysplasia. Otitis media, sinusitis, lymphoid hyperplasia, hoarseness, vocal cord nodules, and laryngeal edema have all been associated with GERD. Airway manifestations in older children are more commonly related to asthma or to otolaryngologic disease such as laryngitis or sinusitis. Despite the high prevalence of GERD symptoms in asthmatic children, data showing direction of causality are conflicting.

Table 349.2

Symptoms and Signs That May Be Associated With Gastroesophageal Reflux

SYMPTOMS
Recurrent regurgitation with or without vomiting
Weight loss or poor weight gain
Irritability in infants
Ruminative behavior
Heartburn or chest pain
Hematemesis
Dysphagia, odynophagia
Wheezing
Stridor
Cough
Hoarseness
SIGNS
Esophagitis
Esophageal stricture
Barrett esophagus
Laryngeal/pharyngeal inflammation
Recurrent pneumonia
Anemia
Dental erosion
Feeding refusal
Dystonic neck posturing (Sandifer syndrome)

Apnea spells
Apparent life-threatening events

From Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease,* ed 4, Philadelphia, 2011, WB Saunders, Table 22.1, p. 235.

Neurologically challenged children are one group that is recognized to be at an increased risk for GERD. It is not well established if the greater risk is conferred due to inadequate defensive mechanisms and/or inability to express symptoms. A low clinical threshold is important in the early identification and prompt treatment of GERD symptoms in these individuals.

Diagnosis

For most of the typical GERD presentations, particularly in older children, a thorough history and physical examination suffice initially to reach the diagnosis. This initial evaluation aims to identify the pertinent positives in support of GERD and its complications and the negatives that make other diagnoses unlikely. The history may be facilitated and standardized by questionnaires (e.g., the Infant Gastroesophageal Reflux Questionnaire, the I-GERQ, and its derivative, the I-GERQ-R), which also permit quantitative scores to be evaluated for their diagnostic discrimination and for evaluative assessment of improvement or worsening of symptoms. The clinician should be alerted to the possibility of other important diagnoses in the presence of any *alarm or warning signs* : bilious emesis, frequent projectile emesis, gastrointestinal bleeding, lethargy, organomegaly, abdominal distention, micro- or macrocephaly, hepatosplenomegaly, failure to thrive, diarrhea, fever, bulging fontanelle, and seizures. The important differential diagnoses to consider in the evaluation of an infant or a child with chronic vomiting are milk and other food allergies, eosinophilic esophagitis, pyloric stenosis, intestinal obstruction (especially malrotation with intermittent volvulus), nonesophageal inflammatory diseases, infections, inborn errors of metabolism, hydronephrosis, increased intracranial pressure, rumination, and bulimia. Focused diagnostic testing, depending on the presentation and the differential diagnosis, can then supplement the initial examination.

Most of the esophageal tests are of some use in particular patients with suspected GERD. **Contrast (usually barium) radiographic** study of the esophagus and upper gastrointestinal tract is performed in children with vomiting and dysphagia to evaluate for achalasia, esophageal strictures and stenosis, hiatal hernia, and gastric outlet or intestinal obstruction (Fig. 349.1). It has poor sensitivity and specificity in the diagnosis of GERD as a result of its limited duration and the inability to differentiate physiologic GER from GERD. Furthermore, contrast radiography neither accurately assesses mucosal inflammation nor correlates with severity of GERD.

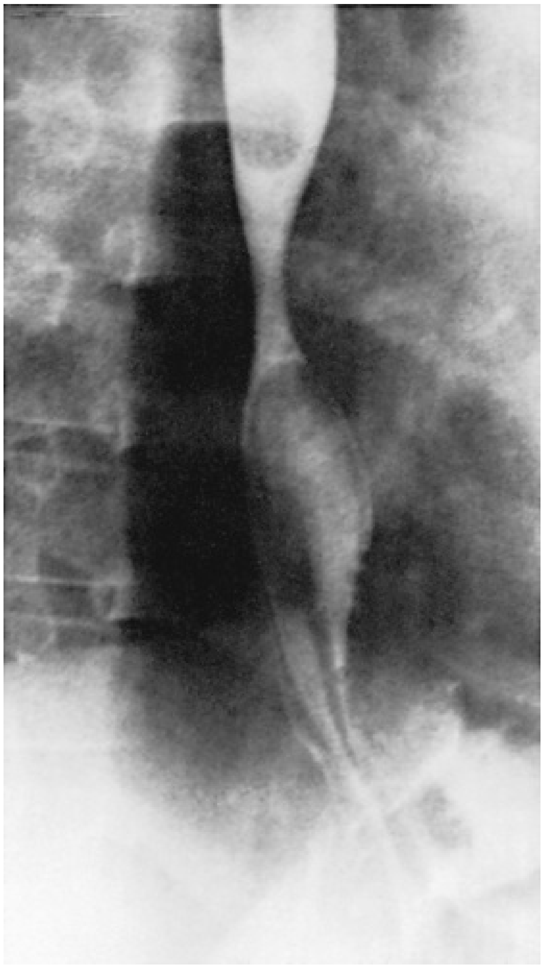

FIG. 349.1 **Barium esophagogram demonstrating free gastroesophageal reflux. Note stricture caused by peptic esophagitis. Longitudinal gastric folds above the diaphragm indicate the unusual presence of an associated hiatal hernia.**

Extended esophageal pH monitoring of the distal esophagus, no longer considered the *sine qua non* of a GERD diagnosis, provides a quantitative and sensitive documentation of acidic reflux episodes, the most important type of reflux episodes for pathologic reflux. The distal esophageal pH probe is placed at a level corresponding to 87% of the nares-LES distance, based on regression equations using the patient's height, on fluoroscopic visualization, or on manometric identification of the LES. Normal values of distal esophageal acid exposure (pH <4) are generally established as <5 to 8% of the total monitored time, but these quantitative normals are insufficient to establish or disprove a diagnosis of pathologic GERD. The most important indications for esophageal pH monitoring are for assessing efficacy of acid suppression during treatment, evaluating apneic episodes in conjunction with a pneumogram and perhaps impedance, and evaluating atypical GERD presentations such as chronic cough, stridor, and asthma. Dual pH probes, adding a proximal esophageal probe to the standard distal one, are used in the diagnosis of extraesophageal GERD, identifying upper esophageal acid exposure times of 1% of the total time as threshold values for abnormality.

Endoscopy allows diagnosis of erosive esophagitis (Fig. 349.2) and complications such as strictures or Barrett esophagus; esophageal biopsies can diagnose histologic reflux esophagitis in the absence of erosions while simultaneously eliminating allergic and infectious causes. Endoscopy is also used therapeutically to dilate reflux-induced strictures. Radionucleotide scintigraphy using technetium can demonstrate aspiration and delayed gastric emptying when these are suspected.

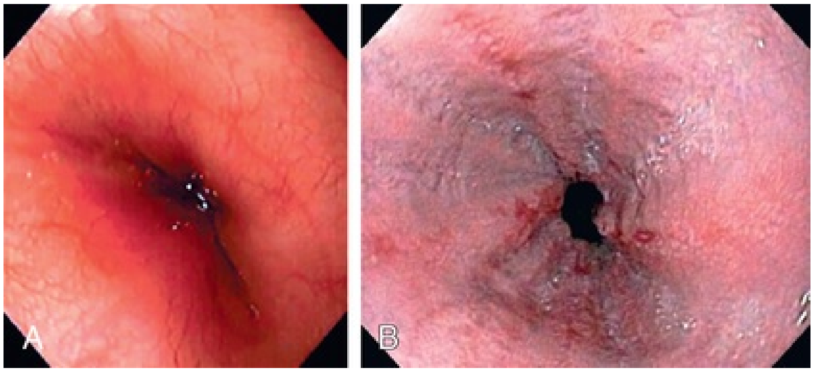

FIG. 349.2 Endoscopic image of a normal esophagus **(A)** and erosive peptic esophagitis **(B)** .

The multichannel **intraluminal impedance** is a cumbersome test, but with potential applications both for diagnosing GERD and for understanding esophageal function in terms of bolus flow, volume clearance, and (in conjunction with manometry) motor patterns associated with GERD. Owing to the multiple sensors and a distal pH sensor, it is possible to document acidic reflux (pH <4), weakly acidic reflux (pH 4-7), and weakly alkaline reflux (pH

>7) with multichannel intraluminal impedance. It is an important tool in those with respiratory symptoms, particularly for the determination of nonacid reflux, but must be cautiously applied in routine clinical evaluation because of limited evidence-based parameters for GERD diagnosis and symptom association.

Esophageal manometry is not useful in demonstrating gastroesophageal reflux but might be of use to evaluate transient LES relaxations and pressures.

Laryngotracheobronchoscopy evaluates for visible airway signs that are associated with extraesophageal GERD, such as posterior laryngeal inflammation and vocal cord nodules; it can permit diagnosis of silent aspiration (during swallowing or during reflux) by bronchoalveolar lavage with subsequent quantification of lipid-laden macrophages in airway secretions. Detection of pepsin in tracheal fluid is a marker of reflux-associated aspiration of gastric contents. Esophageal manometry permits evaluation for dysmotility, particularly in preparation for antireflux surgery.

Empirical antireflux therapy, using a time-limited trial of high-dose proton pump inhibitor (PPI), is a cost-effective strategy for diagnosis in adults; although not formally evaluated in older children, it has also been applied to this age group. Failure to respond to such empirical treatment, or a requirement for the treatment for prolonged periods, mandates formal diagnostic evaluation.

Management

Conservative therapy and lifestyle modifications that form the foundation of GERD therapy can be effectively implemented through education and reassurance for parents. Dietary measures for infants include normalization of any abnormal feeding techniques, volumes, and frequencies. Thickening of feeds or use of commercially prethickened formulas increases the percentage of infants with no regurgitation, decreases the frequency of daily regurgitation and emesis, and increases the infant's weight gain. However, caution should be exercised when managing preterm infants because of the possible association between xanthan gum-based thickened feeds and necrotizing enterocolitis. The evidence does not clearly favor 1 type of thickener over another; the addition of a Tbsp of rice or oat cereal per oz of formula results in a greater caloric density (30 kcal/oz) and reduced crying time, although it might not modify the number of nonregurgitant reflux episodes. Caution must be exercised while using rice cereal, as studies show increased risk of arsenic exposure in children with rice and rice product consumption. A short trial (2 wk) of a hypoallergenic diet in infants may be used to exclude milk or soy protein allergy before pharmacotherapy. A combination of modified feeding volumes, hydrolyzed infant formulas, proper positioning, and avoidance of smoke exposure satisfactorily improve GERD symptoms in 24–59% of infants with GERD. Older children should be counseled to avoid acidic or reflux-inducing foods (tomatoes, chocolate, mint) and beverages (juices, carbonated and caffeinated drinks, alcohol). Weight reduction for obese patients and elimination of smoke exposure are other crucial measures at all ages.

Positioning measures are particularly important for infants, who cannot control their positions independently. Seated position worsens infant reflux and should be avoided in infants with GERD. Esophageal pH monitoring demonstrates more reflux episodes in infants in supine and side positions compared with the prone position, but evidence that the supine position reduces the risk of sudden infant death syndrome has led the American Academy of Pediatrics and the North American Society of Pediatric Gastroenterology and Nutrition to recommend supine positioning during sleep. When the infant is awake and observed, prone position and upright carried position can be used to minimize reflux. Lying in the flat supine position and semi-seated positions (e.g., car seats, infant carriers) in the postprandial period are considered provocative positions for GER and therefore should be avoided. The efficacy of positioning for older children is unclear, but some evidence suggests a benefit to left side position and head elevation during sleep. The head should be elevated by elevating the head of the bed, rather than using excess pillows, to avoid abdominal flexion and compression that might worsen reflux.

Pharmacotherapy is directed at ameliorating the acidity of the gastric contents or at promoting their aboral movement and should be considered for those symptomatic infants and children who are either highly suspected or proven to have GERD. Antacids are the most commonly used antireflux therapy and are readily available over the counter. They provide rapid but transient relief of symptoms by acid neutralization. The long-term regular use of antacids cannot be recommended because of side effects of diarrhea (magnesium antacids) and constipation (aluminum antacids) and rare reports of more serious side effects of chronic use.

Histamine-2 receptor antagonists (H2RAs: cimetidine, famotidine, nizatidine, and ranitidine) are widely used antisecretory agents that act by selective inhibition of histamine receptors on gastric parietal cells. There is a definite benefit of H2RAs in treatment of mild-to-moderate reflux esophagitis.

H2RAs have been recommended as first-line therapy because of their excellent overall safety profile, but they are superseded by PPIs in this role, as increased experience with pediatric use and safety, FDA approval, and pediatric formulations and dosing are available.

PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) provide the most potent antireflux effect by blocking the hydrogen–potassium adenosine triphosphatase channels of the final common pathway in gastric acid secretion. PPIs are superior to H2RAs in the treatment of severe and erosive esophagitis. Pharmacodynamic studies indicate that children require higher doses of PPIs than adults on a per-weight basis. The use of PPIs to treat infants and children deemed to have GERD on the basis of symptoms is common, however an important systematic review of the efficacy and safety of PPI therapy in pediatric GERD reveals no clear benefit for PPI over placebo use in suspected infantile GERD (crying, arching behavior). Limited pediatric data are available to draw definitive conclusions about potential complications implicated with PPI use, such as respiratory infections, *Clostridium difficile* infection, bone fractures (noted in adults), hypomagnesemia, and kidney damage.

Prokinetic agents available in the United States include metoclopramide (dopamine-2 and 5-HT$_3$ antagonist), bethanechol (cholinergic agonist), and erythromycin (motilin receptor agonist). Most of these increase LES pressure; some improve gastric emptying or esophageal clearance. None affects the frequency of TLESRs. The available controlled trials *have not* demonstrated much efficacy for GERD. In 2009, the FDA announced a black box warning for metoclopramide, linking its chronic use (longer than 3 mo) with tardive dyskinesia, the rarely reversible movement disorder. Baclofen is a centrally acting γ-aminobutyric acid agonist that decreases reflux by decreasing TLESRs in healthy adults and in a small number of neurologically impaired children with GERD. Other agents of interest include peripherally acting γ-aminobutyric acid agonists devoid of central side effects, and metabotropic glutamate receptor 5 antagonists that are reported to reduce TLESRs but are as yet inadequately studied for this indication in children.

Cisapride is a serotonergic-receptor agonist with prokinetic effect that is only available in the United States through a limited access program because of its cardiac side effects (QT prolongation, dysrhythmias).

Surgery, usually **fundoplication,** is effective therapy for intractable GERD in children, particularly those with refractory esophagitis or strictures and those at risk for significant morbidity from chronic pulmonary disease. It may be combined with a gastrostomy for feeding or venting. The availability of potent acid-suppressing medication mandates more-rigorous analysis of the relative risks (or costs) and benefits of this relatively irreversible therapy in comparison to long-term pharmacotherapy. Some of the risks of fundoplication include a wrap that is *too tight* (producing dysphagia or gas-bloat) or *too loose* (and thus incompetent). Surgeons may choose to perform a *tight* (360 degrees, Nissen) or variations of a *loose* (<360 degrees, Thal, Toupet, Boix-Ochoa) wrap, or to add a gastric drainage procedure (pyloroplasty) to improve gastric emptying, based on their experience and the patient's disease. Preoperative accuracy of diagnosis of GERD and the skill of the surgeon are two of the most important predictors of successful outcome. Long-term studies suggest that fundoplications often become incompetent in children, as in adults, with reflux recurrence rates of up to 14% for Nissen and up to 20% for loose wraps (the rates may be highest with laparoscopic procedures); this fact currently combines with the potency of PPI therapy that is available to shift practice toward long-term pharmacotherapy in many cases. Fundoplication procedures may be performed as open operations, by laparoscopy, or by endoluminal (gastroplication) techniques. Pediatric experience is limited with endoscopic application of radiofrequency therapy (Stretta procedure) to a 2-3 cm area of the LES and cardia to create a high-pressure zone to reduce reflux.

Total esophagogastric dissociation is performed in selective neurologically impaired children with repeated failed fundoplications and with severe life-threatening gastroesophageal reflux disease.

349.1

Complications of Gastroesophageal Reflux Disease

Seema Khan, Sravan Kumar Reddy Matta

Keywords

brief resolved unexplained event (BRUE)
Barrett's esophagitis

Esophageal: Esophagitis and Sequelae—Stricture, Barrett Esophagus, Adenocarcinoma

Esophagitis can manifest as irritability, arching, and feeding aversion in infants; chest or epigastric pain in older children; and, rarely, as hematemesis, anemia, or Sandifer syndrome at any age. Erosive esophagitis is found in approximately 12% of children with GERD symptoms and is more common in boys, older children, neurologically challenged children, children with severe chronic respiratory disease, and in those with hiatal hernia. Prolonged and severe esophagitis leads to formation of strictures, generally located in the distal esophagus, producing dysphagia, and requiring repeated esophageal dilations and often fundoplication. Long-standing esophagitis predisposes to metaplastic transformation of the normal esophageal squamous epithelium into intestinal columnar epithelium, termed **Barrett esophagus,** a precursor of esophageal adenocarcinoma. A large multicenter prospective study of 840 consecutive children who underwent elective endoscopies reported a 25.7% prevalence for reflux esophagitis, and a mere 0.12% for Barrett esophagus in children without neurologic disorders or tracheoesophageal anomalies. Both Barrett esophagus and adenocarcinoma occur more in white males and in those with increased duration, frequency, and severity of reflux symptoms. This transformation increases with age to plateau in the fifth decade; adenocarcinoma is rare in childhood. Barrett esophagus, uncommon in children, warrants periodic surveillance biopsies, aggressive pharmacotherapy, and fundoplication for progressive lesions.

Nutritional

Esophagitis and regurgitation may be severe enough to induce failure to thrive because of caloric deficits. Enteral (nasogastric or nasojejunal, or percutaneous gastric or jejunal) or parenteral feedings are sometimes required to treat such deficits.

Extraesophageal: Respiratory (“Atypical”) Presentations

GERD should be included in the differential diagnosis of children with unexplained or refractory otolaryngologic and respiratory complaints. GERD can produce respiratory symptoms by direct contact of the refluxed gastric contents with the respiratory tract (aspiration, laryngeal penetration, or microaspiration) or by reflexive interactions between the esophagus and respiratory tract (inducing laryngeal closure or bronchospasm). Often, GERD and a primary respiratory disorder, such as asthma, interact and a vicious cycle between them worsens both diseases. Many children with these extraesophageal presentations do not have typical GERD symptoms, making the diagnosis difficult. These atypical GERD presentations require a thoughtful approach to the differential diagnosis that considers a multitude of primary otolaryngologic (infections, allergies, postnasal drip, voice overuse) and pulmonary (asthma, cystic fibrosis) disorders. Therapy for the GERD must be more intense (usually incorporating a PPI) and prolonged (usually at least 3-6 mo). In these cases a multidisciplinary approach involving otolaryngology, pulmonary for airway disease and gastroenterology for reflux disease is often warranted for specialized diagnostic testing and for optimizing intensive management.

Apnea and Stridor

These upper airway presentations have been linked with GERD in case reports and epidemiologic studies; temporal relationships between them and reflux episodes have been demonstrated in some patients by esophageal pH–multichannel intraluminal impedance studies, and a beneficial response to therapy for GERD provides further support in a number of case series. An evaluation of 1,400 infants with apnea attributed the apnea to GERD in 50%, but other studies have failed to find an association. Apnea and brief resolved unexplained event-like presentation (previously called an “apparent life-threatening event”) caused by reflux is generally obstructive, owing to laryngospasm that may be conceived of as an abnormally intense protective reflex. At the time of such apnea, infants have often been provocatively positioned (supine or flexed seated), have been recently fed, and have shown signs of obstructive apnea, with unproductive respiratory efforts. *The evidence suggests that for the large majority of infants presenting with apnea and a brief resolved unexplained event, GERD is not causal.* Stridor triggered by reflux generally occurs in infants anatomically predisposed toward stridor (laryngomalacia, micrognathia). Spasmodic croup, an episodic frightening upper airway obstruction, can be an analogous condition in older children. Esophageal pH probe studies might fail to demonstrate linkage of these manifestations with reflux owing to the buffering of gastric contents by infant formula and the episodic nature of the conditions. Pneumograms can fail to identify apnea if they are not designed to identify obstructive apnea by measuring nasal airflow.

Reflux laryngitis and other otolaryngologic manifestations (also known as laryngopharyngeal reflux) can be attributed to GERD. **Hoarseness,** voice fatigue, throat clearing, chronic cough, pharyngitis, sinusitis, otitis media, and a sensation of globus have been cited. Laryngopharyngeal signs of GERD include edema and hyperemia (of the posterior surface), contact ulcers, granulomas, polyps, subglottic stenosis, and interarytenoid edema. The paucity of well-controlled evaluations of the association contributes to the skepticism with which these associations may be considered. Other risk factors irritating the upper respiratory passages can predispose some patients with GERD to present predominantly with these complaints.

Many studies have reported a strong association between asthma and reflux as determined by history, pH–multichannel intraluminal impedance, endoscopy, and esophageal histology. GERD symptoms are present in an average of 23% (19–80%) of children with asthma as observed in a systematic review of 19 studies examining the prevalence of GERD in asthmatics. The review also reported abnormal pH results in 63%, and esophagitis in 35% of asthmatic children. However, this association does not clarify the direction of causality in individual cases and thus does not indicate which patients with asthma are likely to benefit from anti-GERD therapy. Children with asthma who are particularly likely to have GERD as a provocative factor are those with symptoms of reflux disease, those with refractory or steroid-dependent asthma, and those with nocturnal worsening of asthma. Endoscopic evaluation that discloses esophageal sequelae of GERD provides an impetus to embark on the aggressive (high dose and many months’ duration) therapy of GERD.

Dental erosions constitute the most common oral lesion of GERD, the lesions being distinguished by their location on the lingual surface of the teeth. The severity seems to correlate with the presence of reflux symptoms and the presence of an acidic milieu as the result of reflux in the proximal esophagus and oral cavity. The other common factors that can produce similar dental erosions are juice consumption and bulimia.

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CHAPTER 350

Eosinophilic Esophagitis, Pill Esophagitis, and Infective Esophagitis

Seema Khan

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic esophageal disorder characterized by esophageal dysfunction and infiltration of the esophageal epithelium by ≥15 eosinophils per high-power field. The diagnostic criteria has recently been updated as a result of the consensus conference on Appraisal of Guidelines for Research and Evaluation (AGREE). The diagnosis of EoE should be considered in the clinical presentation of esophageal dysfunction, associated with esophageal epithelial infiltration of at least 15 eosinophils (eos) per high power field (hpf) or ~60 eos per mm^2 , and after a careful evaluation of non-EoE disorders. Proton pump inhibitors should be considered as another treatment option rather than a diagnostic criterion to differentiate from GERD. EoE is a global disease, with incidence and prevalence rates in children 5 and 29.5 per 100,000. While infants and toddlers present commonly with vomiting, feeding problems, and poor weight gain, older children and adolescents usually experience solid food dysphagia with occasional food impactions (Fig. 350.1) or strictures and may complain of heartburn, chest or epigastric pain. Most patients are male. The mean age at diagnosis is 7 yr (range: 1-17 yr), and the duration of symptoms is 3 yr. Many patients have other atopic diseases (or a positive family history) and associated food allergies; laboratory abnormalities can include peripheral eosinophilia and elevated immunoglobulin E (IgE) levels. The pathogenesis involves mainly T-helper type 2 cytokine-mediated (interleukin 5 and 13) pathways leading to production of a potent eosinophil chemoattractant, eotaxin-3, by esophageal epithelium. The eosinophilic esophagitis endoscopic reference score (**EREFS**), based on commonly observed features of edema (E), rings (R; Fig. 350.2), exudates (E; see Fig. 350.2), furrows (F; Fig. 350.3), strictures (S), has utility in diagnosis and monitoring response to treatment. Esophageal histology reveals profound eosinophilia, with a currently acceptable cutoff for diagnosis chosen at ≥15 to 20/high-power field. Up to 30% children with EoE have grossly normal esophageal mucosa. EoE is differentiated from gastroesophageal reflux disease by concurrent atopic diseases, its general lack of erosive esophagitis, its greater eosinophil density, and its normal esophageal pH-multichannel intraluminal impedance results. A favorable response to proton pump inhibitor therapy should no longer be considered diagnostic of gastroesophageal reflux disease, as approximately two-thirds of children with EoE also demonstrate histologic response and constitute a proton pump inhibitor–responsive EoE (PPI-REF) group. Observations in children and adults with EoE are notable for striking similarities between PPI responders and PPI non-responders with regard to symptoms, histology, molecular signature, and mechanistic features. This response may be because of an acid suppressive action or down regulation of Th-2 allergic cell pathway, an antieosinophil effect of the PPI class that is mediated by inhibition of eotaxin-3 secretion. Evaluation of EoE should include a search for food (aerodigestive) and environmental allergies via skin prick (IgE mediated) and patch (non–IgE mediated) tests to guide decisions regarding dietary elimination and future food challenges.

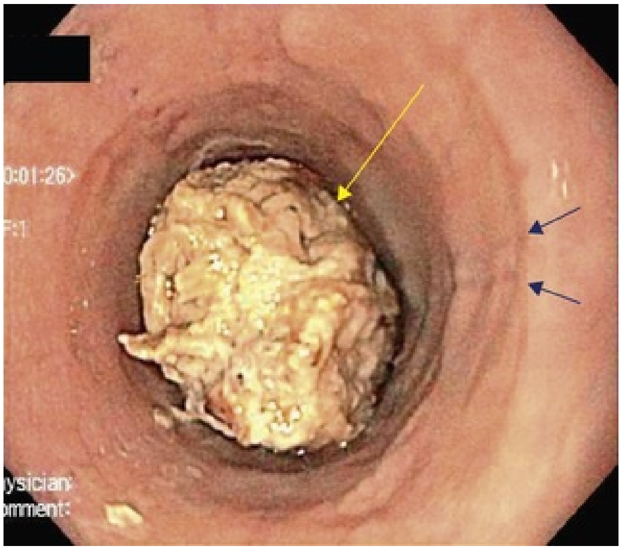

FIG. 350.1 Endoscopic visualization of esophageal food impaction *(yellow arrow)* and mucosal rings *(blue arrows)* .

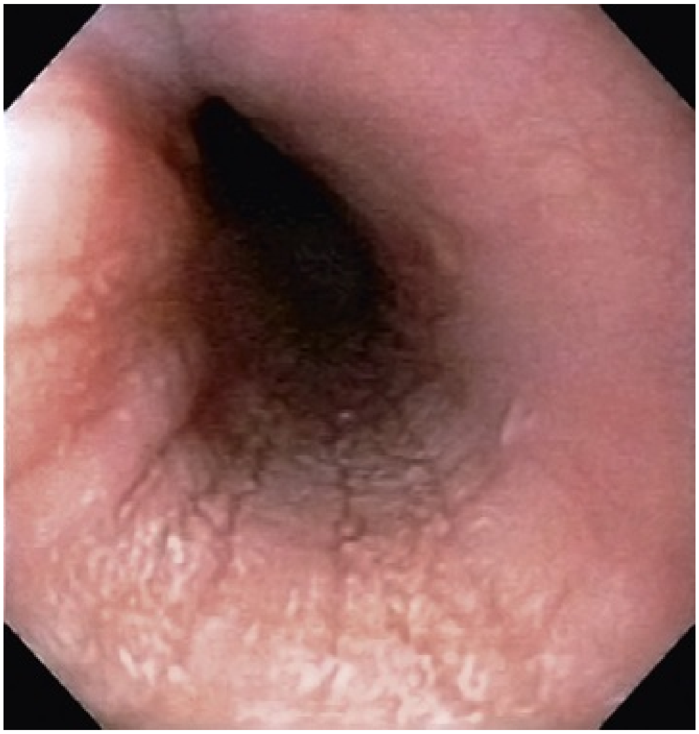

FIG. 350.2 Endoscopic image of eosinophilic esophagitis with characteristic mucosal appearance of furrowing and white specks.

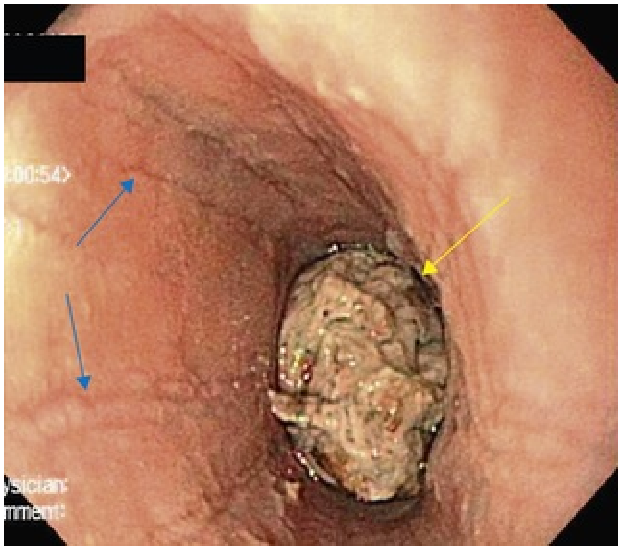

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FIG. 350.3 Endoscopy photograph showing mucosal furrowing *(blue arrows)* characteristic of Eosinophilic esophagitis in a patient with food impaction *(yellow arrow)* .

Treatment involves dietary restrictions that take one of 3 forms: elimination diets guided by circumstantial evidence and food allergy test results; “6 food elimination diet” removing the major food allergens (milk, soy, wheat, egg, peanuts and tree nuts, seafood); and elemental diet composed exclusively of an amino acid-based formula. Elimination diets are generally successful, with highest histologic response observed in nearly 91% on elemental diet and in 72% to empiric dietary elimination. Targeted elimination diets guided by multimodal allergy testing are comparable to empiric food elimination and hence lead to the argument against rigorous testing. The major drawbacks of dietary therapy lie in its cost, difficult access, and lower quality of life, any or all of which influence adherence and outcome.

Topically acting swallowed corticosteroids (fluticasone without spacer, viscous budesonide suspension) have been used successfully for those who refuse, fail to adhere, or have a poor response to restricted diets. Histologic remission is observed in 65-77% children and adults treated with fluticasone for 3 mo. Histologic recurrence after discontinuation of fluticasone is common, and emphasizes the need for maintenance therapy, and an approach that would carefully balance the risks of adrenocortical insufficiency as well as, bone demineralization and fungal infections against the risk of EoE evolution from an inflammatory to fibrostenotic disease producing esophageal stenosis and strictures. Therapies under investigation include anti-interleukin-5 antibodies (mepolizumab, reslizumab). Patients require periodic endoscopy and histologic reassessment for the most reliable monitoring of response to treatment, particularly given a significant disconnect between symptoms and histology in the evolution of the disease. Expert clinical guidelines stress long-term studies to develop systematic treatment and best follow-up protocols.

Infective Esophagitis

Uncommon, and most often affecting immunocompromised children, infective esophagitis is caused by fungal agents, such as *Candida* albicans and *Torulopsis glabrata;* viral agents, such as herpes simplex, cytomegalovirus, HIV, and varicella zoster; and, rarely, bacterial infections, including diphtheria and tuberculosis, or parasites. The typical presenting signs and symptoms are odynophagia, dysphagia, and retrosternal or chest pain; there may also be fever, nausea, and vomiting. Candida is the leading cause of infective esophagitis in immunocompetent and immunocompromised children and presents with concurrent oropharyngeal infection in the majority of immunocompromised patients. It may also be an incidental finding in asymptomatic patients, notably in those with EoE receiving topical swallowed corticosteroids. Esophageal viral infections can also manifest in immunocompetent hosts as an acute febrile illness. Infectious esophagitis, like other forms of esophageal inflammation, occasionally progresses to esophageal stricture. Diagnosis of infectious esophagitis is made by endoscopy, usually notable for white plaques in candida, multiple superficial ulcers or *volcano ulcers* in herpes simplex virus, and single deep ulcer in cytomegalovirus. Histopathologic examination solidifies the diagnosis with the detection of yeast and pseudohyphae in Candida; tissue invasion distinguishes esophagitis from mere colonization. Multinucleated giant cells with intranuclear Cowdry type A (eosinophilic) and type B (ground glass appearance) inclusions in HSV, and both intranuclear and intracytoplasmic inclusions producing an *owl's eye* appearance in CMV are typically described. Adding polymerase chain reaction, tissue-viral culture, and immunocytochemistry enhances the diagnostic sensitivity and precision. Treatment is with appropriate antimicrobial agents; azole therapy, particularly oral fluconazole for Candida; oral acyclovir for HSV, and oral valganciclovir for CMV, or alternatively intravenous ganciclovir in severe CMV disease.

Pill Esophagitis

This acute injury is produced by contact with a damaging agent. Medications implicated in pill esophagitis include tetracycline, doxycycline, potassium chloride, ferrous sulfate, nonsteroidal antiinflammatory medications, cloxacillin, and alendronate (Table 350.1). Most often the offending tablet is ingested at bedtime with inadequate water. This practice often produces acute discomfort followed by progressive retrosternal pain, odynophagia, and dysphagia. Endoscopy shows a focal lesion often localized to one of the anatomic narrowed regions of the esophagus or to an unsuspected pathologic narrowing (Fig. 350.4). Treatment is supportive; lacking much evidence, sucralfate, antacids, topical anesthetics, and bland or liquid diets are often used. The offending pill may be restarted after complete resolution of symptoms, if deemed necessary, though with clear emphasis on ingestion with adequate volume of water, usually at least 4 oz.

Table 350.1

Medications Commonly Associated With Esophagitis or Esophageal Injury

ANTIBIOTICS
Clindamycin
Doxycycline
Penicillin
Rifampin
Tetracycline
ANTIVIRAL AGENTS
Nelfinavir
Zalcitabine
Zidovudine
BISPHOSPHONATES
Alendronate
Etidronate
Pamidronate
CHEMOTHERAPEUTIC AGENTS
Bleomycin
Cytarabine
Dactinomycin
Daunorubicin
5-Fluorouracil
Methotrexate
Vincristine
NSAIDs
Aspirin
Ibuprofen
Naproxen
OTHER MEDICATIONS
Ascorbic acid
Ferrous sulfate
Lansoprazole
Multivitamins
Potassium chloride
Quinidine
Theophylline

From Katzka DA: Esophageal disorders caused by medications, trauma, and infection. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, 2016, Box 46.1.

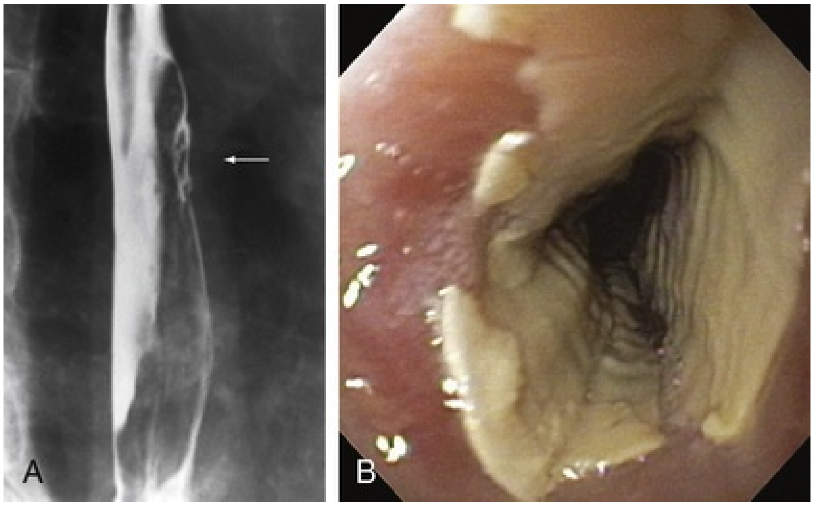

FIG. 350.4 **(A)** Barium esophagogram showing esophageal ulceration secondary to tetracycline, with the *arrow* pointing to an area of ulcerations. **(B)** Endoscopic image of a tetracycline-induced esophageal burn. (From Katzka DA: Esophageal disorders caused by medications, trauma, and infection. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, 2016. Fig. 46.1).

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CHAPTER 351

Esophageal Perforation

Seema Khan

The majority of esophageal perforations in children are from blunt trauma (automobile injury, gunshot wounds, child abuse) or are iatrogenic. Cardiac massage, the Heimlich maneuver, nasogastric tube placement, traumatic laryngoscopy or endotracheal intubation, excessively vigorous postpartum suctioning of the airway during neonatal resuscitation, difficult upper endoscopy, sclerotherapy of esophageal varices, esophageal compression by a cuffed endotracheal tube, and dilation for therapy of achalasia and strictures have all been implicated. Esophageal rupture has followed forceful vomiting in patients with anorexia and has followed esophageal injury due to caustic ingestion, foreign body ingestion, food impactions, pill esophagitis, or eosinophilic esophagitis. Drinking cold, carbonated beverages rapidly is also known to cause esophageal perforation.

Spontaneous esophageal rupture **(Boerhaave syndrome)** is less common and is associated with sudden increases in intraesophageal pressure wrought by situations such as vomiting, coughing, or straining at stool. Children and adults with eosinophilic esophagitis have also been described with Boerhaave syndrome in the setting of forceful emesis in the aftermath of esophageal food impaction. In older children, as in adults, the tear occurs on the distal left lateral esophageal wall, because the smooth muscle layer here is weakest; in neonates (neonatal Boerhaave syndrome), spontaneous rupture is on the right.

Symptoms of esophageal perforation include pain, neck tenderness, dysphagia, subcutaneous crepitus, fever, and tachycardia; several patients with cervical perforations have displayed cold water polydipsia in an attempt to soothe pain in the throat. Imaging studies are important for a rapid and accurate diagnosis. Perforations in the proximal thoracic esophagus tend to create signs (pneumothorax, effusions) in the left chest, whereas the signs of distal tears are more often on the right. Plain radiography (posteroanterior and lateral views) and computed tomography of the neck and chest are often used, with the latter as more sensitive and accurate in diagnosis. Signs of perforation include pneumomediastinum, mediastinal widening, subcutaneous emphysema, pneumothorax, hydrothorax, pleural effusion, and lung collapse. If these x-rays are normal, an esophagogram using water-soluble contrast media should be performed, but esophagograms miss >30% of cervical perforations. Therefore, a negative water-soluble contrast esophagogram should be followed by a barium study; the greater density of barium can better demonstrate a small defect, although with a higher risk of inflammatory mediastinitis. Endoscopy may also be useful but carries a 30% false-negative rate.

Treatment must be individualized. Small tears in contained perforations with minimal mediastinal contamination in hemodynamically stable patients can be treated conservatively with broad-spectrum antibiotics, nothing given orally, gastric drainage, and parenteral nutrition. Endoscopic techniques, considered less invasive and morbid, are now being used more frequently and include clips for defects <2 cm, and placement of stents and suturing for larger defects. Chest exploration and direct surgical repair is infrequently indicated these days. Mortality rates range between 20% and 28%, with poor prognosis correlated with delayed diagnosis and interventions.

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CHAPTER 352

Esophageal Varices

Seema Khan

Esophageal varices form in adults with portal hypertension with hepatic venous pressure gradient above 10 mm Hg and pose a risk for bleeding at above 12 mm Hg (see Chapter 394). Spontaneous decompression of this hypertension through portosystemic collateral circulation via the coronary vein, in conjunction with the left gastric veins, gives rise to esophageal varices. Most esophageal varices are *uphill varices* ; less commonly, those that arise in the absence of portal hypertension and with superior vena cava obstruction are *downhill varices* . Their treatment is directed at the underlying cause of the superior vena cava abnormality. Hemorrhage from esophageal varices is the major cause of morbidity and mortality from portal hypertension. Presentation is with significant hematemesis and melena; whereas most patients have liver disease, some children with extrahepatic portal venous obstruction might have been previously asymptomatic. Any child with hematemesis and splenomegaly should be presumed to have esophageal variceal bleeding until proved otherwise. The leading causes of pediatric portal hypertension, biliary atresia, and extrahepatic portal vein obstruction are uniquely distinct from diseases encountered in adults. Hence, children tend to tolerate variceal bleeding better due to generally well compensated liver disease, with studies reporting mortality risk <1% after initial variceal bleed.

Upper endoscopy is the preferred diagnostic test for esophageal varices, as it provides definitive diagnosis and delineation of details that aid in predicting the risk for bleeding, as well as enabling therapy for acute bleeding episodes via either sclerotherapy or band ligation. A report comprising a large series of children with biliary atresia and portal hypertension described endoscopic findings of large varices, red marks, and the presence of gastric varices as predictive of bleeding. Noninvasive methods of evaluating varices include barium contrast studies, ultrasound, computerized tomography, magnetic resonance, and elastography, but they are not recommended for routine diagnostic evaluation because of suboptimal accuracy compared to endoscopy.

Primary prophylaxis with the goal of preventing an initial hemorrhage can decrease the incidence of esophageal bleeding; the various modalities used are nonselective β blockade (e.g., propranolol or nadolol), sclerotherapy, ligation, and portosystemic shunt surgery. A recent expert consensus based on a large review of the available evidence has proposed that MesoRex bypass surgery should be offered to children with EHPVO as both primary and secondary prophylaxis in the appropriate context. Due to insufficient evidence, the same cannot be recommended regarding endoscopic therapies and nonselective beta blockers for primary prophylaxis in children. In contrast, adults do have a reduced risk of first-time variceal bleeding with endoscopic variceal ligation when compared with untreated controls as well as patients treated with β blockade; a decrease in mortality is only noted in comparison to the control group (see Chapter 394). The management of acute variceal bleeding must include attention to hemodynamic stability through blood transfusion, vasoactive drugs (e.g., octreotide), short-term antibiotic use, and endoscopy to perform ligation or sclerotherapy, as needed. Transjugular intrahepatic portosystemic shunt should be considered for variceal bleeding refractory to medical and endoscopic therapy. Secondary prophylaxis to reduce recurrence of bleeding uses nonselective β blockade and obliteration of varices through serial treatment via ligation or sclerotherapy. The only randomized controlled pediatric study has shown superiority of ligation over sclerotherapy in reducing the risk for rebleeding and complications.

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CHAPTER 353

Ingestions

353.1

Foreign Bodies in the Esophagus

Seema Khan

The majority (80%) of accidental foreign-body ingestions occur in children, most of whom are 5 yr of age or younger. Older children and adolescents with developmental delays and those with psychiatric disorders are also at increased risk. The presentation of a foreign body lodged in the esophagus constitutes an emergency and is associated with significant morbidity and mortality because of the potential for perforation and sepsis. Coins are by far the most commonly ingested foreign body, followed by small toy items. Food impactions are less common in children than in adults and usually occur in children in association with eosinophilic esophagitis *(diagnosed in 92% of those presenting with food impactions and dysphagia)*, repair of esophageal atresia, and Nissen fundoplication. Most esophageal foreign bodies lodge at the level of the cricopharyngeus (upper esophageal sphincter), the aortic arch, or just superior to the diaphragm at the gastroesophageal junction (lower esophageal sphincter).

At least 30% of children with esophageal foreign bodies may be totally asymptomatic, so any history of foreign body ingestion should be taken seriously and investigated. An initial bout of choking, gagging, and coughing may be followed by excessive salivation, dysphagia, food refusal, emesis, or pain in the neck, throat, or sternal notch regions. Respiratory symptoms such as stridor, wheezing, cyanosis, or dyspnea may be encountered if the esophageal foreign body impinges on the larynx or membranous posterior tracheal wall. Cervical swelling, erythema, or subcutaneous crepitations suggest perforation of the oropharynx or proximal esophagus.

Evaluation of the child with a history of foreign body ingestion starts with plain anteroposterior radiographs of the neck, chest, and abdomen, along with lateral views of the neck and chest. The flat surface of a coin in the esophagus is seen on the anteroposterior view and the edge on the lateral view (Fig. 353.1). The reverse is true for coins lodged in the trachea; here, the edge is seen anteroposteriorly and the flat side is seen laterally. Disk-shaped button batteries can look like coins and be differentiated by the double halo and step-off on anteroposterior and lateral views, respectively (Fig. 353.2). The use of button batteries has been increasingly popular, leading to a sharp rise in accidental ingestions, and critical in the increase in morbidity and mortality. The latter is thought to be due to both an increase in diameter and a change to lithium cells. Children younger than 5 yr of age with ingestion of batteries ≥20 mm are considered to have the highest risk for catastrophic events such as necrosis, tracheoesophageal fistula, perforation, stricture, vocal cord paralysis, mediastinitis, and aortoenteric fistula (Fig. 353.3). Materials such as plastic, wood, glass, aluminum, and bones may be radiolucent; failure to visualize the object with plain films in a symptomatic patient warrants urgent endoscopy. Computed tomography (CT) scan with 3-dimensional reconstruction may increase the sensitivity of imaging a foreign body. Although barium contrast studies may be helpful in the occasional asymptomatic patient with negative plain films, their use is to be discouraged because of the potential of aspiration, as well as making subsequent visualization and object removal more difficult.

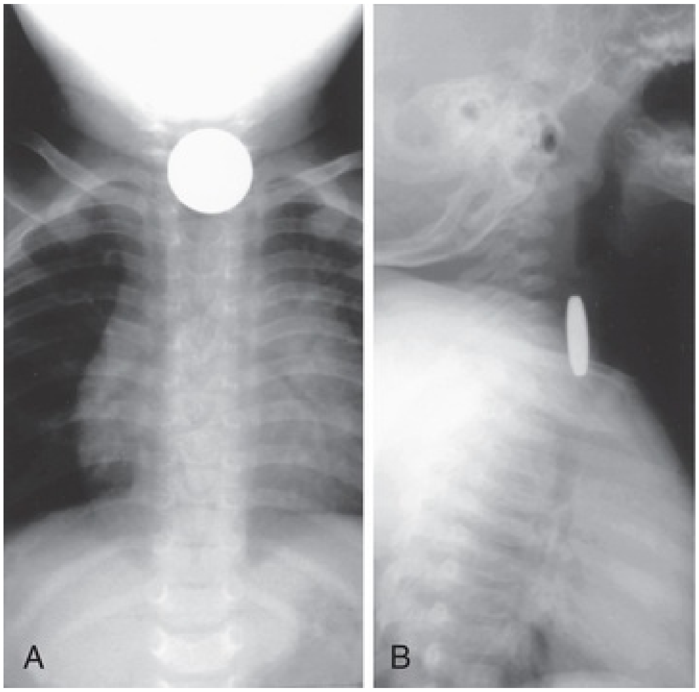

FIG. 353.1 Radiographs of a coin in the esophagus. When foreign bodies lodge in the esophagus, the flat surface of the object is seen in the anteroposterior view (A) and the edge is seen in the lateral view (B) . The reverse is true for objects in the trachea. (Courtesy Beverley Newman, MD.)

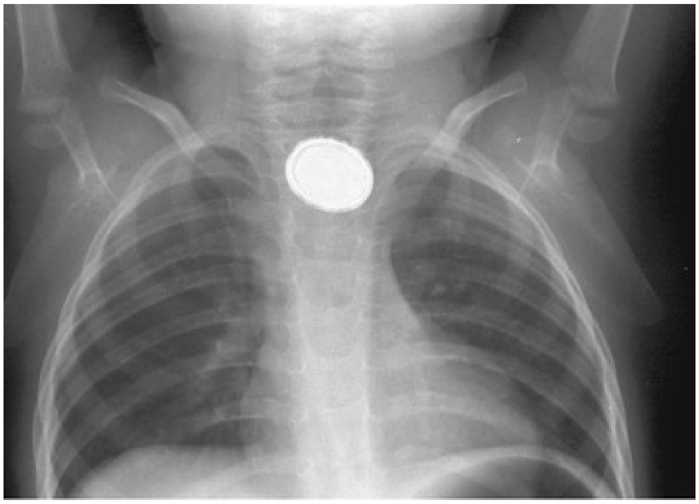

FIG. 353.2 Disk battery impacted in esophagus. Note the double rim. (From Wyllie R, Hyams JS, editors: *Pediatric gastrointestinal and liver disease,* ed 3, Philadelphia, 2006, Saunders.)

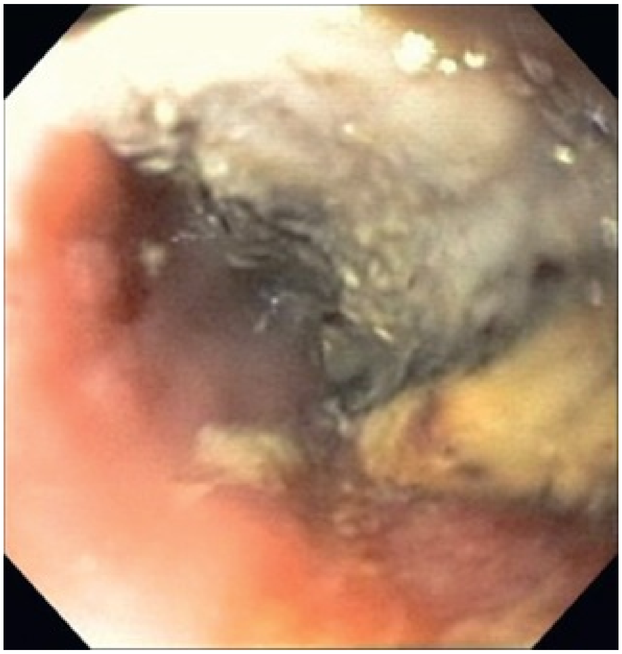

FIG. 353.3 Severe esophageal injury at site of button battery (BB) removal, with necrosis and eschar. (From Leinwand K, Brumbaugh DE, Kramer RE: Button battery ingestion in children—a paradigm for management of severe pediatric foreign body ingestions, *Gastrointest Endoscopy Clin N Am* 26:99–118, 2016, Fig. 1.)

In managing the child with an esophageal foreign body, it is important to assess risk for airway compromise and to obtain a chest CT scan and surgical consultation in cases of suspected airway perforation. Treatment of esophageal foreign bodies usually merits endoscopic visualization of the object and underlying mucosa and removal of the object using an appropriately designed foreign body–retrieving accessory instrument through the endoscope and with an endotracheal tube protecting the airway. Sharp objects in the esophagus, multiple magnets or single magnet with a metallic object, or foreign bodies associated with respiratory symptoms mandate urgent removal within 12 hr of presentation. Button batteries, in particular, must be emergently removed within 2 hr of presentation regardless of the timing of patient's last oral intake because they can induce mucosal injury in as little as 1 hr of contact time and involve all esophageal layers within 4 hr (see Figs. 353.3 and 353.4). Asymptomatic blunt objects and coins lodged in the esophagus can be observed for up to 24 hr in anticipation of passage into the stomach. If there are no problems in handling secretions, meat impactions can be observed for up to 24 hr. In patients without prior esophageal surgeries, glucagon (0.05 mg/kg intravenously [IV]) can sometimes be useful in facilitating passage of distal esophageal food boluses by decreasing the lower esophageal sphincter pressure. The use of meat tenderizers or gas-forming agents can lead to perforation and are not recommended. An alternative technique for removing esophageal coins impacted for <24 hr, performed most safely by experienced radiology personnel, consists of passage of a Foley catheter beyond the coin at fluoroscopy, inflating the balloon, and then pulling the catheter and coin back simultaneously with the patient in a prone oblique position. Concerns about the lack of direct mucosal visualization and, when tracheal intubation is not used, the lack of airway protection prompt caution in the use of this technique. Bougienage of esophageal coins toward the stomach in selected uncomplicated pediatric cases has been suggested to be an effective, safe, and economical modality where endoscopy might not be routinely available.

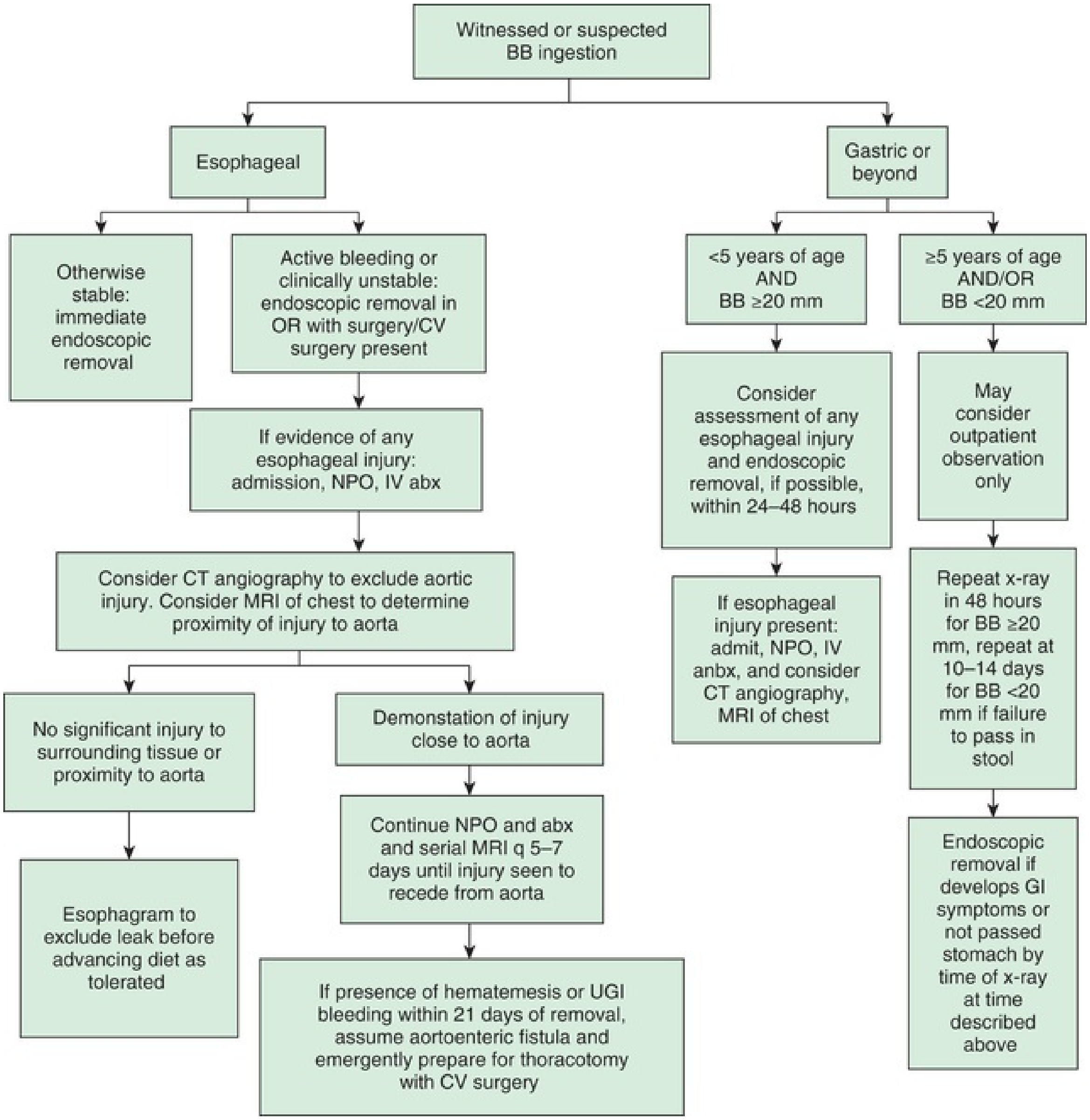
Witnessed or suspected BB ingestion
Esophageal
Gastric or beyond
Otherwise stable: immediate endoscopic removal
Active bleeding or clinically unstable: endoscopic removal in OR with surgery/CV surgery present
If evidence of any esophageal injury: admission, NPO, IV abx
Consider CT angiography to exclude aortic injury. Consider MRI of chest to determine proximity of injury to aorta
No significant injury to surrounding tissue or proximity to aorta
Esophagram to exclude leak before advancing diet as tolerated
Demonstation of injury close to aorta
Continue NPO and abx and serial MRI q 5–7 days until injury seen to recede from aorta
If presence of hematemesis or UGI bleeding within 21 days of removal, assume aortoenteric fistula and emergently prepare for thoracotomy with CV surgery
<5 years of age AND BB ≥20 mm
Consider assessment of any esophageal injury and endoscopic removal, if possible, within 24–48 hours
If esophageal injury present: admit, NPO, IV anbx, and consider CT angiography, MRI of chest
≥5 years of age AND/OR BB <20 mm
May consider outpatient observation only
Repeat x-ray in 48 hours for BB ≥20 mm, repeat at 10–14 days for BB <20 mm if failure to pass in stool
Endoscopic removal if develops GI symptoms or not passed stomach by time of x-ray at time described above

FIG. 353.4 Proposed management algorithm for ingestion of button battery *(BB)* in children. Abx, antibiotics; BB, button battery; CT, computed tomography; CV, cardiovascular; GI, gastrointestinal; IV, intravenous; MRI, magnetic resonance imaging; NPO, nil per os; OR, operating room; Q, every; UGI, upper gastrointestinal series. (From Kramer RE, Lerner DG, Lin T, et al: Management of ingested foreign bodies in children: a clinical report of the NASPGHAN endoscopy committee, *J Pediatr Gastroenterol Nutr* 60(4):562–574, 2015, Fig. 1.)

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353.2

Caustic Ingestions

Seema Khan

Keywords

esophageal foreign body
magnet
button battery
caustic ingestion
endoscopy.

Ingestion of caustic substances is a worldwide public health problem accounting for a significant burden on healthcare resources. According to an inpatient database of U.S. pediatric hospital discharges in 2009, the estimated number of caustic ingestions was 807 (95% confidence interval [CI], 731-882) cases, amounting to $22,900,000 in total hospital charges. The medical sequelae of caustic ingestions are esophagitis, necrosis, perforation, and stricture formation (see Chapter 77). Most cases (70%) are accidental ingestions of liquid alkali substances that produce severe, deep liquefaction necrosis; drain decloggers are most common, and because they are tasteless, more is ingested (Table 353.1). **Acidic agents** (20% of cases) are bitter, so less may be consumed; they produce coagulation necrosis and a somewhat protective thick eschar. They can produce severe gastritis, and volatile acids can result in respiratory symptoms. Children younger than 5 yr of age account for half of the cases of caustic ingestions, and boys are far more often involved than girls.

Table 353.1

Ingestible Caustic Materials Around the House

CATEGORY	MOST DAMAGING AGENTS	OTHER AGENTS
Alkaline drain cleaners, milking machine pipe cleaners	Sodium or potassium hydroxide	Ammonia Sodium hypochlorite Aluminum particles
Acidic drain openers	Hydrochloric acid Sulfuric acid	
Toilet cleaners	Hydrochloric acid Sulfuric acid Phosphoric acid Other acids	Ammonium chloride Sodium hypochlorite
Oven and grill cleaners	Sodium hydroxide Perborate (borax)	
Denture cleaners	Persulfate (sulfur) Hypochlorite (bleach)	
Dishwasher detergent • Liquid • Powdered • Packaged	Sodium hydroxide Sodium hypochlorite Sodium carbonate	
Bleach	Sodium hypochlorite	Ammonia salt
Swimming pool chemicals	Acids, alkalis, chlorine	
Battery acid (liquid)	Sulfuric acid	
Disk batteries	Electric current	Zinc or other metal salts
Rust remover	Hydrofluoric, phosphoric, oxalic, and other acids	
Household delimers	Phosphoric acid Hydroxyacetic acid Hydrochloric acid	
Barbeque cleaners	Sodium and potassium hydroxide	
Glyphosate surfactant (RoundUp) acid	Glyphosate herbicide	Surfactants
Hair relaxer	Sodium hydroxide	
Weed killer	Dichlorophenoxyacetate, ammonium phosphate, propionic acid	

From Wylie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease* , ed 4, Philadelphia, 2011, WB Saunders, Table 19.1, p. 198.

Source: National Library of Medicine: *Health and safety information on household products* (website). http://householdproducts.nlm.nih.gov/

Caustic ingestions produce signs and symptoms such as vomiting, drooling, refusal to drink, oral burns, dysphagia, dyspnea, abdominal pain, hematemesis, and stridor. Twenty percent of patients develop esophageal strictures. Absence of oropharyngeal lesions does not exclude the possibility of significant esophagogastric injury, which can lead to perforation or stricture. The absence of symptoms is usually associated with no or minimal lesions; hematemesis, respiratory distress, or presence of at least 3 symptoms predicts severe lesions. An upper endoscopy is recommended as the most efficient means of rapid identification of tissue damage and must be undertaken in all symptomatic children.

Dilution by water or milk is recommended as acute treatment, but neutralization, induced emesis, and gastric lavage are contraindicated. Treatment depends on the severity and extent of damage (Table 353.2 , Fig. 353.5). Stricture risk is increased by circumferential ulcerations, white plaques, and sloughing of the mucosa and is reported to occur in 70–100% of grade IIB and grade III caustic esophagitis. Strictures can require treatment with dilation, and in some severe cases, surgical resection and colon or small bowel interposition are needed. Silicone stents (self-expanding) placed endoscopically after a dilation procedure can be an alternative and conservative approach to the management of strictures. Rare late cases of superimposed esophageal carcinoma are reported. The role of corticosteroids is controversial; they are not recommended in grade 1 burns, but they can reduce the risk of strictures in more-advanced caustic esophagitis. Many centers also use proton pump inhibitors as well as antibiotics in the initial treatment of caustic esophagitis on the premise that reducing superinfection in the necrotic tissue bed will, in turn, lower the risk of stricture formation. Studies examining the role of antibiotics in caustic esophagitis have not reported a clinically significant benefit even in those with grade 2 or greater severity of esophagitis.

Table 353.2

Classification of Caustic Injury

GRADE	VISIBLE APPEARANCE	CLINICAL SIGNIFICANCE
Grade 0	History of ingestion but no visible damage or symptoms	Able to take fluids immediately
Grade 1	Edema, loss of normal vascular pattern, hyperemia, no transmucosal injury	Temporary dysphagia, able to swallow within 0-2 days, no long-term sequelae
Grade 2a	Transmucosal injury with friability, hemorrhage, blistering, exudate, scattered superficial ulceration	Scarring, no circumferential damage (no stenosis), no long-term sequelae
Grade 2b	Grade 2a plus discrete ulceration and/or circumferential	Small risk of perforation, scarring that may

	ulceration	result in later stenosis
Grade 3a	Scattered deep ulceration with necrosis of the tissue	Risk of perforation, high risk of later stenosis
Grade 3b	Extensive necrotic tissue	High risk of perforation and death, high risk of stenosis

From Wylie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease* , ed 4, Philadelphia, 2011, WB Saunders, Table 19.2, p. 199.

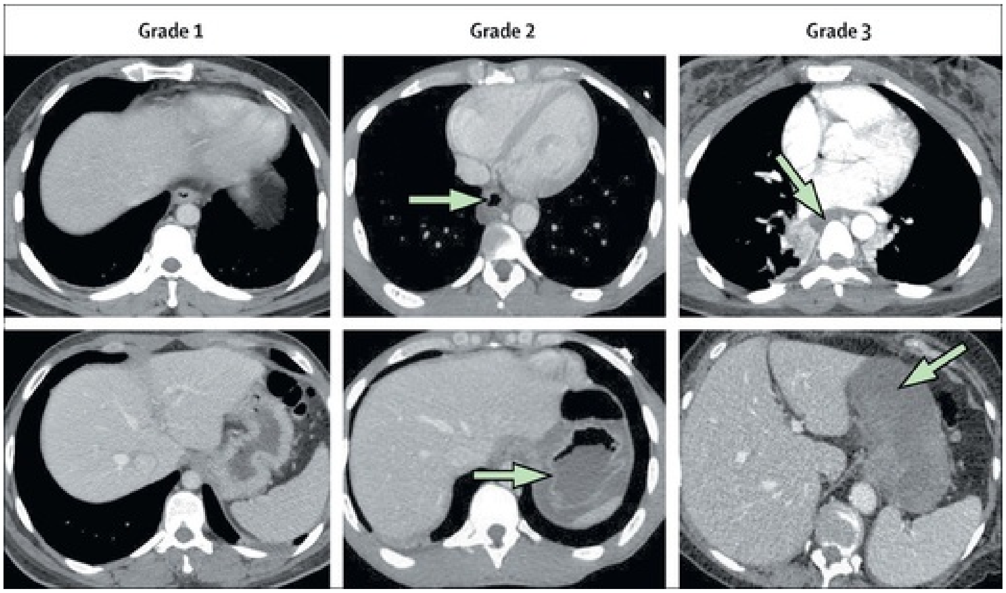

FIG. 353.5 Computed Tomography (CT) Grading of Corrosive Injuries of the Esophagus and the Stomach. Grade 1, normal appearance; grade 2, wall and soft tissue edema, increased wall enhancement *(arrow)* ; grade 3, transmural necrosis with absent wall enhancement *(arrow)* . (From Chirica M, Bonavina L, Kelly MD, et al: Caustic ingestion, *Lancet* 389:2041–2050, 2017, Fig. 1.)

There may be an increase of esophageal (not gastric) carcinoma following a caustic ingestion.

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SECTION 4

Stomach and Intestines

OUTLINE

Chapter 354 Normal Development, Structure, and Function of the Stomach and Intestines

Chapter 355 Pyloric Stenosis and Other Congenital Anomalies of the Stomach

Chapter 356 Intestinal Atresia, Stenosis, and Malrotation

Chapter 357 Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct

Chapter 358 Motility Disorders and Hirschsprung Disease

Chapter 359 Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions

Chapter 360 Foreign Bodies and Bezoars

Chapter 361 Peptic Ulcer Disease in Children

Chapter 362 Inflammatory Bowel Disease

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Chapter 364 Disorders of Malabsorption

Chapter 365 Intestinal Transplantation in Children With Intestinal Failure

Chapter 366 Acute Gastroenteritis in Children

Chapter 367 Chronic Diarrhea

Chapter 368 Functional Gastrointestinal Disorders

Chapter 369 Cyclic Vomiting Syndrome

Chapter 370 Acute Appendicitis

Chapter 371 Surgical Conditions of the Anus and Rectum

Chapter 372 Tumors of the Digestive Tract

Chapter 373 Inguinal Hernias

CHAPTER 354

Normal Development, Structure, and Function of the Stomach and Intestines

Asim Maqbool, Chris A. Liacouras

Development

The primitive gut is recognizable by the 4th wk of gestation and is composed of the foregut, midgut, and hindgut. The **foregut** gives rise to the upper gastrointestinal tract, which includes the esophagus, stomach, and duodenum to the level of the insertion of the common bile duct. The **midgut** gives rise to the rest of the small bowel and the large bowel to the level of the midtransverse colon. The **hindgut** forms the remainder of the colon and upper anal canal. The rapid growth of the midgut causes it to protrude out of the abdominal cavity through the umbilical ring during fetal development. The midgut subsequently returns to the peritoneal cavity and rotates counterclockwise until the cecum lies in the right lower quadrant. The process is normally complete by the 8th wk of gestation.

The liver derives from the hepatic diverticulum that evolves into parenchymal cells, bile ducts, vascular structures, and hematopoietic and Kupffer cells. The extrahepatic bile ducts and gallbladder develop first as solid cords that canalize by the 3rd mo of gestation. The dorsal and ventral pancreatic buds grow from the foregut by the 4th wk of gestation. The two buds fuse by the 6th wk. Exocrine secretory capacity is present by the 5th mo.

Cis -regulatory genomic sequences govern gene expression during development. Modules of *cis* sequences are linked and allow a cascade of gene regulation that controls functional development. Extrinsic factors have the capacity to influence gene expression. In the gut, several growth factors, including growth factor-β, insulin-like growth factor, and growth factors found in human colostrum (human growth factor and epidermal growth factor), influence gene expression.

Propulsion of food down the gastrointestinal tract relies on the coordinated action of muscles in the bowel wall. The contractions are regulated by the enteric nervous system under the influence of a variety of peptides and hormones. The enteric nervous system is derived from neural crest cells that migrate in a cranial to caudal fashion. Migration of the neural crest tissue is complete by the 24th wk of gestation. Interruption of the migration results in **Hirschsprung disease** . Newborn bowel motor patterns are different from adults. Normal fasting upper gastrointestinal motility is characterized by a triphasic pattern known as the migrating motor complex. Migrating motor complexes occur less often in neonates, and they have more nonmigrating phasic activity. This leads to ineffective propulsion, particularly in premature infants. Motility in the fed state consists of a series of ring contractions that spread caudad over variable distances.

Digestion and Absorption

The wall of the stomach, small bowel, and colon consists of four layers: the mucosa, submucosa, muscularis, and serosa. Eighty-five percent of the gastric mucosa is lined by oxyntic glands containing cells that secrete hydrochloric acid, pepsinogen, and intrinsic factor, and mucous and endocrine cells that secrete peptides having paracrine and endocrine effects. Pepsinogen is a precursor of the proteolytic enzyme pepsin, and intrinsic factor is required for the absorption of vitamin B_{12} . Pyloric glands are located in the antrum and contain gastrin-secreting cells. Acid production and gastrin levels are inversely related to each other except in pathologic secretory states. Acid secretion is low at birth but increases dramatically by 24 hr. Acid and pepsin secretions peak in the first 10 days and decrease from 10 to 30 days after birth. Intrinsic factor secretion rises slowly in the first 2 wk of life.

The small bowel is approximately 270 cm long at birth in a term neonate and grows to an adult length of 450-550 cm by 4 yr of age. The mucosa of the small intestine is composed of villi, which are finger-like projections of the mucosa into the bowel lumen that significantly expand the absorptive surface area. The mucosal surface is further expanded by a brush border containing digestive enzymes and transport mechanisms for monosaccharides, amino acids, dipeptides and tripeptides, and fats. The cells of the villi originate in adjacent crypts and become functional as they migrate from the crypt up the villus. The small bowel mucosa is completely renewed in 4-5 days, providing a mechanism for rapid repair after injury, but in young infants or malnourished children, the process may be delayed. Crypt cells also secrete fluid and electrolytes. The villi are present by 8 wk of gestation in the duodenum and by 11 wk in the ileum.

Disaccharidase activities are measurable at 12 wk, but lactase activity does not reach maximal levels until 36 wk. Even premature infants usually tolerate lactose-containing formulas because of carbohydrate salvage by colonic bacteria. In children of African and Asian ethnicity, lactase levels may begin to fall at 4 yr of age, leading to intolerance to mammalian milk. Mechanisms to digest and absorb protein, including pancreatic enzymes and mucosal mechanisms to transport amino acids, dipeptides, and tripeptides, are in place by the 20th wk of gestation.

Carbohydrates, protein, and fat are normally absorbed by the upper half of the small intestine; the distal segments represent a vast reserve of absorptive capacity. Most of the sodium, potassium, chloride, and water are absorbed in the small bowel. Bile salts and vitamin B_{12} are selectively absorbed in the distal ileum, and iron is absorbed in the duodenum and proximal jejunum. Intraluminal digestion depends on the exocrine pancreas. Secretin and cholecystokinin stimulate synthesis and secretion of bicarbonate and digestive enzymes, which are released by the upper intestinal mucosa in response to various intraluminal stimuli, among them components of the diet.

Carbohydrate digestion is normally an efficient process that is completed in the distal duodenum. Starches are broken down to glucose, oligosaccharides, and disaccharides by pancreatic amylase. Residual glucose polymers are broken down at the mucosal level by glucoamylase. Lactose is broken down at the brush border by lactase, forming glucose and galactose; sucrose is broken down by sucrase-isomaltase to fructose and glucose. Galactose and glucose are primarily transported into the cell by a sodium- and energy-dependent process, whereas fructose is transported by facilitated diffusion.

Proteins are hydrolyzed by pancreatic enzymes, including trypsin, chymotrypsin, elastase, and carboxypeptidases, into individual amino acids and oligopeptides. The pancreatic enzymes are secreted as proenzymes, which are activated by release of the mucosal enzyme enterokinase. Oligopeptides are further broken down at the brush border by peptidases into dipeptides, tripeptides, and amino acids. Protein can enter the cell by separate noncompetitive carriers that can transport individual amino acids or dipeptides and tripeptides similar to those in the renal tubule. The human gut is capable of absorbing antigenic intact proteins in the first few wk of life because of *leaky* junctions between enterocytes. Entry of potential protein antigens through the mucosal barrier might have a role in later food- and microbe-induced symptoms.

Fat absorption occurs in two phases. Dietary triglycerides are broken down into monoglycerides and free fatty acids by pancreatic lipase and colipase. The free fatty acids are subsequently emulsified by bile acids, forming micelles with phospholipids and other fat-soluble substances, and are transported to the cell membrane, where they are absorbed. The fats are reesterified in the enterocyte, forming chylomicrons that are transported through the intestinal lymphatics to the thoracic duct. Medium-chain fats are absorbed more efficiently and can directly enter the cell. They are subsequently transported to the liver via the portal system. Fat absorption can be affected at any stage of the digestion and absorption process. Decreased pancreatic enzymes occur in cystic fibrosis, cholestatic liver disease leads to poor bile salt production and micelle formation, celiac disease affects mucosal surface area, abnormal chylomicron formation occurs in abetalipoproteinemia, and intestinal lymphangiectasia affects transport of the chylomicrons.

Fat absorption is less efficient in the neonate compared with adults. Premature infants can lose up to 20% of their fat calories compared with up to 6% in the adult. Decreased synthesis of bile acids and pancreatic lipase and decreased efficiency of ileal absorption are contributing factors. Fat digestion in the neonate is facilitated by lingual and gastric lipases. Bile salt–stimulated lipase in human milk augments the action of pancreatic lipase. Infants with malabsorption of fat are usually fed with formulas that have a greater percentage of medium-chain triglycerides, which are absorbed independently of bile salts.

The colon is a 75-100 cm sacculated tube formed by three strips of longitudinal muscle called *taenia coli* that traverse its length and fold the mucosa into haustra. Haustra and taenia appear by the 12th wk of gestation. The most common motor activity in the colon is nonpropulsive rhythmic segmentation that acts to mix the chyme and expose the contents to the colonic mucosa. Mass movement within the colon typically occurs after a meal. The colon extracts additional water and electrolytes from the luminal contents to render the stools partially or completely solid. The colon also acts to scavenge by-products of bacterial degradation of carbohydrates. Stool is stored in the rectum until distention triggers a defecation reflex that, when assisted by voluntary relaxation of the external sphincter, permits evacuation.

CHAPTER 355

Pyloric Stenosis and Other Congenital Anomalies of the Stomach

355.1

Hypertrophic Pyloric Stenosis

Asim Maqbool, Chris A. Liacouras

Hypertrophic pyloric stenosis occurs in 1-3/1,000 infants in the United States. It is more common in whites of northern European ancestry, less common in blacks, and rare in Asians. Males (especially firstborns) are affected approximately 4-6 times as often as females. The offspring of a mother and, to a lesser extent, the father who had pyloric stenosis are at higher risk for pyloric stenosis. Pyloric stenosis develops in approximately 20% of the male and 10% of the female descendants of a mother who had pyloric stenosis. The incidence of pyloric stenosis is increased in infants with B and O blood groups. Pyloric stenosis is occasionally associated with other congenital defects, including tracheoesophageal fistula and hypoplasia or agenesis of the inferior labial frenulum.

Etiology

The cause of pyloric stenosis is unknown, but many factors have been implicated. Pyloric stenosis is usually not present at birth and is more concordant in monozygotic than dizygotic twins. It is unusual in stillbirths and probably develops after birth. Pyloric stenosis has been associated with eosinophilic gastroenteritis, Apert syndrome, Zellweger syndrome, trisomy 18, Smith-Lemli-Opitz syndrome, and Cornelia de Lange syndrome. An association has been found with the use of erythromycin in neonates with highest risk if the medication is given within the first 2 wk of life. There have also been reports of higher incidence of pyloric stenosis among mostly female infants of mothers treated with macrolide antibiotics during pregnancy and breastfeeding. Abnormal muscle innervation, elevated serum levels of prostaglandins, and infant hypergastrinemia have been implicated. Reduced levels of neuronal nitric oxide synthase have been found with altered expression of the neuronal nitric oxide synthase exon 1c regulatory region, which influences the expression of the neuronal nitric oxide synthase gene. Reduced nitric oxide might contribute to the pathogenesis of pyloric stenosis.

Clinical Manifestations

Non-bilious vomiting is the initial symptom of pyloric stenosis. The vomiting may or may not be projectile initially but is usually progressive, occurring immediately after a feeding. Emesis might follow each feeding, or it may be intermittent. The vomiting usually starts after 3 wk of age, but symptoms can develop as early as the first wk of life and as late as the 5th mo. Approximately 20% have intermittent emesis from birth that then progresses to the classic picture. After vomiting, the infant is hungry and wants to feed again. As vomiting continues, a progressive loss of fluid, hydrogen ion, and chloride leads to *hypochloremic metabolic alkalosis* . Awareness of pyloric stenosis has led to earlier identification of patients with fewer instances of chronic malnutrition and severe dehydration and at times a subclinical self-resolving hypertrophy.

Hyperbilirubinemia is the most common clinical association of pyloric stenosis, also known as *icteropyloric syndrome* . Unconjugated hyperbilirubinemia is more common than conjugated and usually resolves with surgical correction of the pyloric stenosis. It may be associated with a decreased level of glucuronyl transferase as seen in approximately 5% of affected infants; mutations in the bilirubin uridine diphosphate glucuronosyltransferase gene *(UGT1A1)* have also been implicated. If conjugated hyperbilirubinemia is a part of the presentation, other etiologies need to be investigated. Other coexistent clinical diagnoses have been described, including eosinophilic gastroenteritis, hiatal hernia, peptic ulcer, congenital nephrotic syndrome, congenital heart disease, and congenital hypothyroidism.

The diagnosis has traditionally been established by palpating the pyloric mass. The mass is firm, movable, approximately 2 cm in length, olive shaped, hard, best palpated from the left side, and located above and to the right of the umbilicus in the mid epigastrium beneath the liver's edge. The olive is easiest palpated after an episode of vomiting. After feeding, there may be a visible gastric peristaltic wave that progresses across the abdomen (Fig. 355.1).

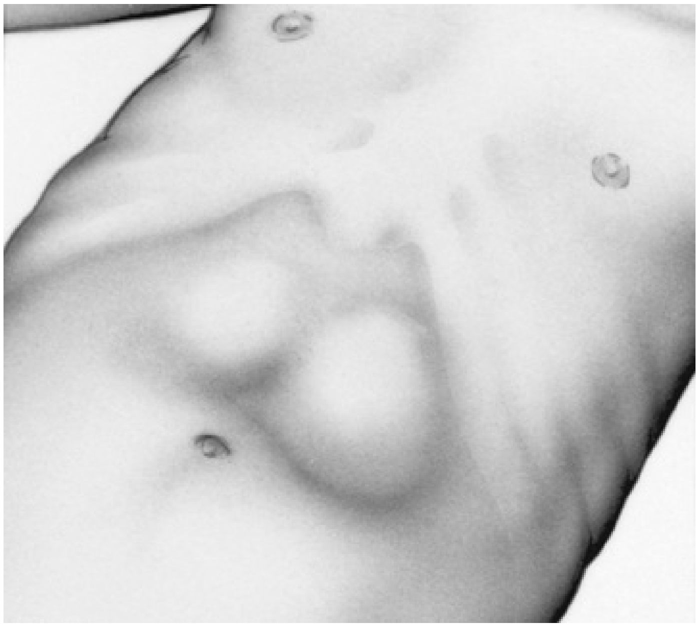

FIG. 355.1 **Gastric peristaltic wave in an infant with pyloric stenosis.**

Two imaging studies are commonly used to establish the diagnosis. Ultrasound examination confirms the diagnosis in the majority of cases. Criteria for diagnosis include pyloric thickness 3-4 mm, an overall pyloric length 15-19 mm, and pyloric diameter of 10-14 mm (Fig. 355.2). Ultrasonography has a sensitivity of approximately 95%. When contrast studies are performed, they demonstrate an elongated pyloric channel (string sign), a bulge of the pyloric muscle into the antrum (shoulder sign), and parallel streaks of barium seen in the narrowed channel, producing a “double tract sign” (Fig. 355.3).

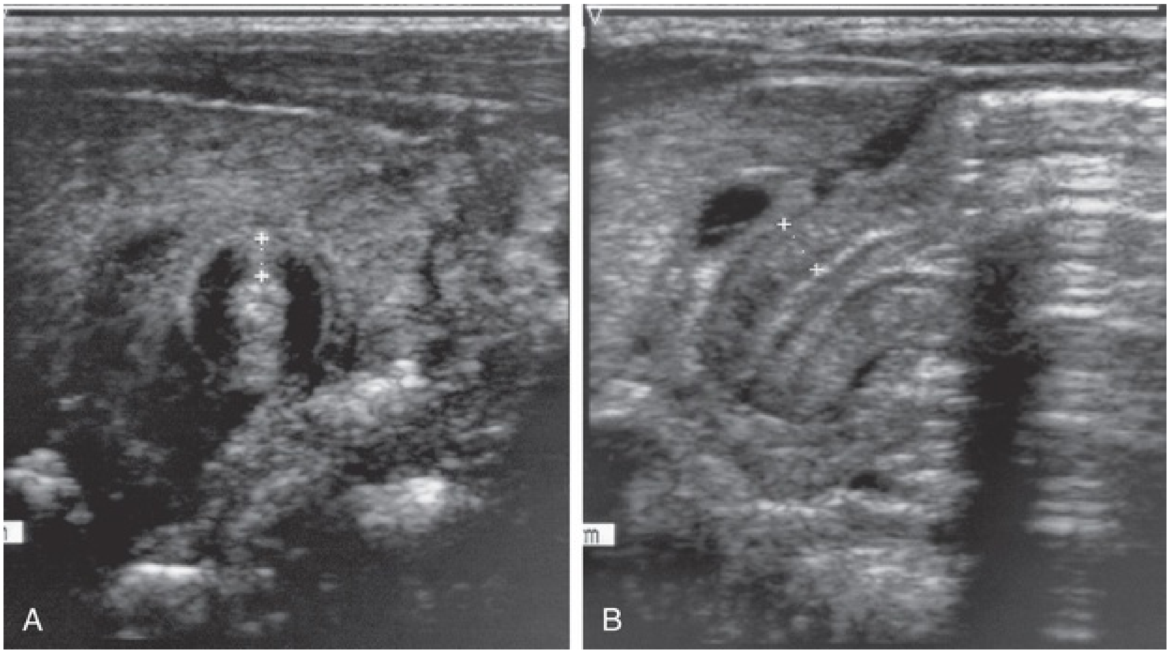

FIG. 355.2 **A,** Transverse sonogram demonstrating a pyloric muscle wall thickness of >4 mm (distance between *crosses*). **B,** Horizontal image demonstrating a pyloric channel length >14 mm (wall thickness outlined between *crosses*) in an infant with pyloric stenosis.

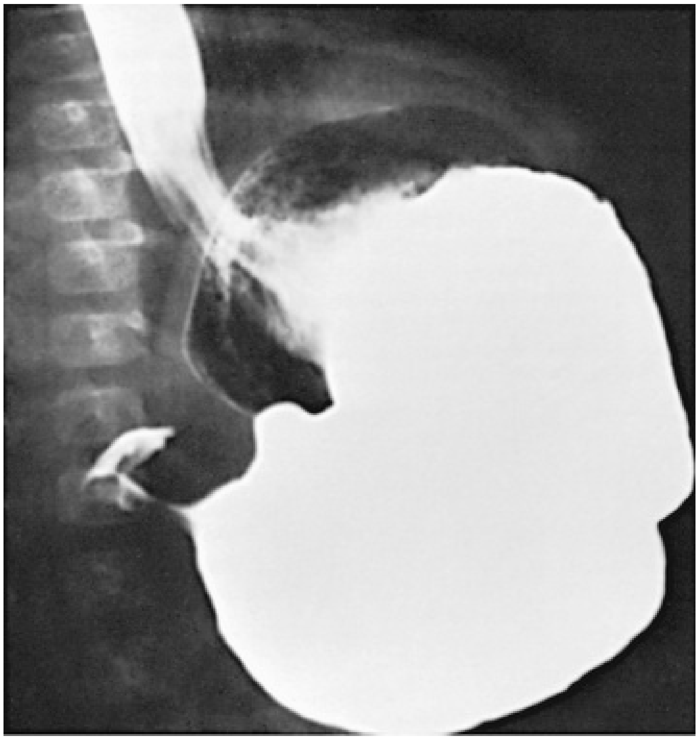

FIG. 355.3 **Barium in the stomach of an infant with projectile vomiting. The attenuated**

pyloric canal is typical of congenital hypertrophic pyloric stenosis.

Differential Diagnosis

Gastric waves are occasionally visible in small, emaciated infants who do not have pyloric stenosis. Infrequently, gastroesophageal reflux, with or without a hiatal hernia, may be confused with pyloric stenosis. Gastroesophageal reflux disease can be differentiated from pyloric stenosis by radiographic studies. Adrenal insufficiency from the adrenogenital syndrome can simulate pyloric stenosis, but the absence of a metabolic acidosis and elevated serum potassium and urinary sodium concentrations of adrenal insufficiency aid in differentiation (see Chapter 594). Inborn errors of metabolism can produce recurrent emesis with alkalosis (urea cycle) or acidosis (organic acidemia) and lethargy, coma, or seizures. Vomiting with diarrhea suggests gastroenteritis, but patients with pyloric stenosis occasionally have diarrhea. Rarely, a pyloric membrane or pyloric duplication results in projectile vomiting, visible peristalsis, and, in the case of a duplication, a palpable mass (Table 355.1). Duodenal stenosis proximal to the ampulla of Vater results in the clinical features of pyloric stenosis but can be differentiated by the presence of a pyloric mass on physical examination or ultrasonography.

Table 355.1

Anomalies of the Stomach

ANOMALY	INCIDENCE	AGE AT PRESENTATION	SYMPTOMS AND SIGNS	TREATMENT
Stomach				
Gastric, antral, or pyloric atresia	3/100,000, when combined with webs	Infancy	Nonbilious emesis	Gastroduodenostomy, gastrojejunostomy
Pyloric or antral membrane (web)	As above	Any age	Failure to thrive, emesis	Incision or excision, pyloroplasty
Microgastria	Rare	Infancy	Emesis, malnutrition	Continuous-drip feedings or jejunal reservoir pouch
Gastric diverticulum	Rare	Any age	Usually asymptomatic	Usually unnecessary
Gastric duplication	Rare; male:female, 1 : 2	Any age	Abdominal mass, emesis, hematemesis; peritonitis if ruptured	Excision or partial gastrectomy

Gastric teratoma	Rare	Any age	Upper abdominal mass	Resection
Gastric volvulus	Rare	Any age	Emesis, refusal to feed	Reduction of volvulus, anterior gastropexy
Pyloric stenosis (infantile hypertrophic and adult forms)	United States, 3/1,000 (range, 1-8/1,000 in various regions); male:female, 4 : 1	Infancy	Non-bilious emesis	Pyloromyotomy
Congenital absence of the pylorus	Rare	Childhood, adulthood	Dyspepsia, if symptomatic	Usually unnecessary

Modified from Semrin MG, Russo MA: Anatomy, histology, and developmental anomalies of the stomach and duodenum. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, Philadelphia, Saunders, 2015, Table 48.1.

Treatment

The preoperative treatment is directed toward correcting the fluid, acid–base, and electrolyte losses. Correction of the alkalosis is essential to prevent postoperative apnea, which may be associated with anesthesia. Most infants can be successfully rehydrated within 24 hr. Vomiting usually stops when the stomach is empty, and only an occasional infant requires nasogastric suction.

The surgical procedure of choice is pyloromyotomy. The traditional Ramstedt procedure is performed through a short transverse skin incision. The underlying pyloric mass is cut longitudinally to the layer of the submucosa, and the incision is closed. Laparoscopic technique is equally successful and in one study resulted in a shorter time to full feedings and discharge from the hospital as well as greater parental satisfaction. The success of laparoscopy depends on the skill of the surgeon. Postoperative vomiting occurs in half the infants and is thought to be secondary to edema of the pylorus at the incision site. In most infants, feedings can be initiated within 12-24 hr after surgery and advanced to maintenance oral feedings within 36-48 hr after surgery. Persistent vomiting suggests an incomplete pyloromyotomy, gastritis, gastroesophageal reflux disease, or another cause of the obstruction. The surgical treatment of pyloric stenosis is curative, with an operative mortality of 0–0.5%. Endoscopic balloon dilation has been successful in infants with persistent vomiting secondary to incomplete pyloromyotomy.

Conservative management with nasoduodenal feedings is advisable in patients who are not good surgical candidates. Oral and intravenous atropine sulfate (pyloric muscle relaxant) has also been described when surgical expertise is not available with 80% success rate described in some studies. In conservative protocols, atropine is administered intravenously at a dose of 0.01 mg/kg 6 times a day 5 min before feeding. During atropine infusion, the heart rate needs to be continuously monitored by electrocardiography. Oral feeding is started at a volume of 10 mL formula, 6 times a day. The volume is increased day by day until patients tolerate 150 mL/kg/day unless vomiting occurs more than twice a day. When patients are able to tolerate the full volume of formula without vomiting more than twice a day, 0.02 mg/kg atropine is administered orally 6 times a day before feeding. As the conservative management takes longer and oral feedings may not be tolerated at first, worsening of the nutrition status may occur and total parenteral nutrition may be required. It was also postulated that surgical management is more time and cost effective.

Acknowledgment

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355.2

Congenital Gastric Outlet Obstruction

Asim Maqbool, Chris A. Liacouras

Gastric outlet obstruction resulting from pyloric atresia and antral webs is uncommon and accounts for <1% of all the atresias and diaphragms of the alimentary tract (see Table 355.1). The cause of the defects is unknown. Pyloric atresia has been associated with **epidermolysis bullosa** and usually presents in early infancy. The gender distribution is equal.

Clinical Manifestations

Infants with pyloric atresia present with nonbilious vomiting, feeding difficulties, and abdominal distention during the first day of life. **Polyhydramnios** occurs in most cases, and low birth weight is common. The gastric aspirate at birth is large (>20 mL fluid) and should be removed to prevent aspiration. Rupture of the stomach may occur as early as the first 12 hr of life. Infants with antral web may present with less dramatic symptoms, depending on the degree of obstruction. Older children with antral webs present with nausea, vomiting, abdominal pain, and weight loss.

Diagnosis

The diagnosis of congenital gastric outlet obstruction is suggested by the finding of a large, dilated stomach on abdominal plain radiographs or in utero ultrasonography. Upper gastrointestinal (GI) contrast series is usually diagnostic and demonstrates a pyloric dimple. When contrast studies are performed, care must be taken to avoid possible aspiration. An antral web may appear as a thin septum near the pyloric channel. In older children, endoscopy has been helpful in identifying antral webs.

Treatment

The treatment of all causes of gastric outlet obstruction in neonates starts with the correction of dehydration and hypochloremic alkalosis. Persistent vomiting should be relieved with nasogastric decompression. Surgical or endoscopic repair should be undertaken when a patient is stable.

355.3

Gastric Duplication

Asim Maqbool, Chris A. Liacouras

Gastric duplications are uncommon cystic or tubular structures that usually occur within the wall of the stomach (see Table 355.1). They account for 2–7% of all GI duplications. They are most commonly located on the greater curvature. Most are <12 cm in diameter and do not usually communicate with the stomach lumen; however, they do have common blood supply. Associated anomalies occur in as many as 35% of patients. Several hypotheses for the etiology of the duplication cysts have been developed including the splitting notochord theory, diverticulation, canalization defects, and caudal twinning.

The most common clinical manifestations are associated with partial or complete gastric outlet obstruction. In 33% of patients, the cyst may be palpable. Communicating duplications can cause gastric ulceration and be associated with hematemesis or melena.

Radiographic studies usually show a paragastric mass displacing stomach. Ultrasound can show the inner hyperechoic mucosal and outer hypoechoic muscle layers that are typical of GI duplications. Surgical excision is the treatment for symptomatic gastric duplications.

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355.4

Gastric Volvulus

Asim Maqbool, Chris A. Liacouras

The stomach is tethered longitudinally by the gastrohepatic, gastrosplenic, and gastrocolic ligaments. In the transverse axis, it is tethered by the gastrophrenic ligament and the retroperitoneal attachment of the duodenum. A volvulus occurs when one of these attachments is absent or elongated, allowing the stomach to rotate around itself. In some children, other associated defects are present, including intestinal malrotation, diaphragmatic defects, hiatal hernia, or adjacent organ abnormalities such as asplenia. Volvulus can occur along the longitudinal axis, producing organoaxial volvulus, or along the transverse axis, producing mesenteroaxial volvulus. Combined volvulus occurs if the stomach rotates around both organoaxial and mesenteroaxial axes.

The clinical presentation of gastric volvulus is nonspecific and suggests high intestinal obstruction. Gastric volvulus in infancy is usually associated with nonbilious vomiting and epigastric distention. It has also been associated with episodes of dyspnea and apnea in this age group. Acute volvulus can advance rapidly to strangulation and perforation. Chronic gastric volvulus is more common in older children; the children present with a history of emesis, abdominal pain and distention, early satiety, and failure to thrive.

The diagnosis is suggested in plain abdominal radiographs by the presence of a dilated stomach. Erect abdominal films demonstrate a double fluid level with a characteristic “beak” near the lower esophageal junction in mesenteroaxial volvulus. The stomach tends to lie in a vertical plane. In organoaxial volvulus, a single air–fluid level is seen without the characteristic beak with stomach lying in a horizontal plane. Upper GI series has also been used to aid the diagnosis.

Treatment of acute gastric volvulus is emergent surgery once a patient is stabilized. Laparoscopic gastropexy is the most common surgical approach. In selected cases of chronic volvulus in older patients, endoscopic correction has been successful.

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355.5

Hypertrophic Gastropathy

Asim Maqbool, Chris A. Liacouras

Hypertrophic gastropathy in children is uncommon and, in contrast to that in adults (Ménétrier disease), is usually a transient, benign, and self-limited condition.

Pathogenesis

The condition is most often secondary to cytomegalovirus (CMV) infection, but other agents, including herpes simplex virus, *Giardia*, and *Helicobacter pylori*, are also implicated. The pathophysiologic mechanisms underlying the clinical picture are not completely understood but might involve widening of gap junctions between gastric epithelial cells with resultant fluid and protein losses. There is an association with increased expression of transforming growth factor-α in gastric mucosal tissue shown in CMV-induced gastropathy. *H. pylori* infection can cause the elevation of serum glucagon-like peptide-2 levels, a mucosal growth-inducing gut hormone.

Clinical Manifestations

Clinical manifestations include vomiting, anorexia, upper abdominal pain, diarrhea, edema (hypoproteinemic protein-losing enteropathy), ascites, and, rarely, hematemesis if ulceration occurs.

Diagnosis and Differential Diagnosis

The mean age at diagnosis is 5 yr (range: 2 days to 17 yr); the illness usually lasts 2-14 wk. Endoscopy with biopsy and tissue CMV polymerase chain reaction is diagnostic. Endoscopy shows characteristic enlarged gastric folds. The upper GI series might show thickened gastric folds. The differential diagnosis includes eosinophilic gastroenteritis, gastric lymphoma or carcinoma, Crohn disease, and inflammatory pseudotumor.

Treatment

Therapy is supportive and should include adequate hydration, antisecretory agents (H_2 receptor blockade, acid suppression with proton pump inhibitors), and albumin replacement if the hypoalbuminemia is symptomatic. When *H. pylori* are detected, appropriate treatment is recommended. Ganciclovir in CMV-positive gastropathy is indicated only in severe cases. There are no official guidelines as far as the length of treatment. In practice, IV therapy is initiated for the 1st 24-48 hr. Treatment is continued with oral valganciclovir for a total of 3 wk. Complete recovery is the rule. Hypertrophic gastropathy should be considered in a previously healthy child with new onset edema and no other causes of protein losses. This is not a chronic condition in children, and the disease tends to have much more severe course in adult patients.

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CHAPTER 356

Intestinal Atresia, Stenosis, and Malrotation

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Approximately 1 in 1,500 children is born with intestinal obstruction. Obstruction may be partial or complete, and it may be characterized as simple or strangulating. Luminal contents fails to progress in an aboral direction in simple obstruction, whereas blood flow to the intestine is also impaired in strangulating obstruction. If strangulating obstruction is not promptly relieved, it can lead to bowel infarction and perforation.

Intestinal obstruction can be further classified as either intrinsic or extrinsic based on underlying etiology. Intrinsic causes include inherent abnormalities of intestinal innervation, mucus production, or tubular anatomy. Among these, congenital disruption of the tubular structure is most common and can manifest as obliteration (**atresia**) or narrowing (**stenosis**) of the intestinal lumen. More than 90% of intestinal stenosis and atresia occurs in the duodenum, jejunum, and ileum. Rare cases occur in the colon, and these may be associated with more proximal atresias.

Extrinsic causes of congenital intestinal obstruction involve compression of the bowel by vessels (e.g., preduodenal portal vein), organs (e.g., annular pancreas), and cysts (e.g., duplication, mesenteric). Abnormalities in intestinal rotation during fetal development also represent a unique extrinsic cause of congenital intestinal obstruction. Malrotation is associated with inadequate mesenteric attachment of the intestine to the posterior abdominal wall, which leaves the bowel vulnerable to auto obstruction as a result of intestinal twisting or volvulus. Malrotation is commonly accompanied by congenital adhesions that can compress and obstruct the duodenum as they extend from the cecum to the right upper quadrant.

Obstruction is typically associated with bowel distention, which is caused by an accumulation of ingested food, gas, and intestinal secretions proximal to the point of obstruction. As the bowel dilates, absorption of intestinal fluid is decreased and secretion of fluid and electrolytes is increased. This shift results in isotonic intravascular depletion, which is usually associated with hypokalemia. Bowel distention also results in a decrease in blood flow to the obstructed bowel. As blood flow is shifted away from the intestinal mucosa, there is loss of mucosal integrity. Bacteria proliferate in the stagnant bowel, with a predominance of coliforms and anaerobes. This rapid proliferation of bacteria, coupled with the loss of mucosal integrity, allows bacteria to translocate across the bowel wall and potentially lead to endotoxemia, bacteremia, and sepsis.

The clinical presentation of intestinal obstruction varies with the cause, level of obstruction, and time between the obstructing event and the patient's evaluation. Classic symptoms of obstruction in the neonate include vomiting, abdominal distention, and obstipation. Obstruction high in the intestinal tract results in large-volume, frequent, bilious emesis with little or no abdominal distention. Pain is intermittent and is usually relieved by vomiting. Obstruction in the distal small bowel leads to moderate or marked abdominal distention with emesis that is progressively feculent. Both proximal and distal obstructions are eventually associated with obstipation. However, meconium stools can be passed initially if the obstruction is in the upper part of the intestinal tract or if the obstruction developed late in intrauterine life.

The diagnosis of congenital bowel obstruction relies on a combination of history, physical examination, and radiologic findings. In certain cases, the diagnosis is suggested in the prenatal period. Routine prenatal ultrasound can detect polyhydramnios, which often accompanies high intestinal obstruction. The presence of polyhydramnios should prompt aspiration of the infant's stomach immediately after birth. Aspiration of more than 15-20 mL of fluid, particularly if it is bile stained, is highly indicative of proximal intestinal obstruction.

In the postnatal period, a plain radiograph is the initial diagnostic study and can provide valuable information about potential associated complications. With completely obstructing lesions, plain radiographs reveal bowel distention proximal to the point of obstruction. Upright or crosstable lateral views typically demonstrate a series of air–fluid levels in the distended loops. Caution must be exercised in using plain films to determine the location of intestinal obstruction. Because colonic haustra are not fully developed in the neonate, small and large bowel obstructions may be difficult to distinguish with plain films. In these cases, contrast studies of the bowel or computed tomography images may be indicated. Oral or nasogastric contrast medium may be used to identify obstructing lesions in the proximal bowel, and contrast enemas may be used to diagnose more-distal entities. Indeed, enemas may also play a therapeutic role in relieving distal obstruction caused by meconium ileus or meconium plug syndrome.

Initial treatment of infants and children with bowel obstruction must be directed at fluid resuscitation and stabilizing the patient. Nasogastric decompression usually relieves pain and vomiting. After appropriate cultures, broad-spectrum antibiotics are usually started in ill-appearing neonates with bowel obstruction and those with suspected strangulating infarction. Patients with strangulation must have immediate surgical relief before the bowel infarcts, resulting in gangrene and intestinal perforation. Extensive intestinal necrosis results in short bowel syndrome (see Chapter 364.7). Nonoperative conservative management is usually limited to children with suspected adhesions or inflammatory strictures that might resolve with nasogastric decompression or antiinflammatory medications. If clinical signs of improvement are not evident within 12-24 hr, then operative intervention is usually indicated.

356.1

Duodenal Obstruction

Asim Maqbool, Chris A. Liacouras

Congenital duodenal obstruction occurs in 2.5-10/100,000 live births. In most cases, it is caused by atresia, an intrinsic defect of bowel formation. It can also result from extrinsic compression by abnormal neighboring structures (e.g., annular pancreas, preduodenal portal vein), duplication cysts, or congenital bands associated with malrotation. Although intrinsic and extrinsic causes of duodenal obstruction occur independently, they can also coexist. Thus a high index of suspicion for more than one underlying etiology may be critical to avoiding unnecessary reoperations in these infants.

Duodenal atresia complicates 1/10,000 live births and accounts for 25–40% of all intestinal atresias. In contrast to more-distal atresias, which likely arise from prenatal vascular accidents, duodenal atresia results from failed recanalization of the intestinal lumen during gestation. Throughout the 4th and 5th wk of normal fetal development, the duodenal mucosa exhibits rapid proliferation of epithelial cells. Persistence of these cells, which should degenerate after the 7th wk of gestation, leads to occlusion of the lumen (atresia) in approximately two-thirds of cases and narrowing (stenosis) in the remaining one-third. Duodenal atresia can take several forms, including a thin membrane that occludes the lumen, a short fibrous cord that connects two blind duodenal pouches, or a gap that spans two nonconnecting ends of the duodenum. The membranous form is most common, and it almost invariably occurs near the ampulla of Vater. In rare cases, the membrane is distensible and is referred to as a *windsock web* . This unusual form of duodenal atresia causes obstruction several centimeters distal to the origin of the membrane.

Approximately 50% of infants with duodenal atresia are premature. Concomitant congenital anomalies are common and include congenital heart disease (30%), malrotation (20–30%), annular pancreas (30%), renal anomalies (5–15%), esophageal atresia with or without tracheoesophageal fistula (5–10%), skeletal malformations (5%), and anorectal anomalies (5%). Of these anomalies, only complex congenital heart disease is associated with increased mortality. Annular pancreas is associated with increased late complications, including gastroesophageal reflux disease, peptic ulcer disease, pancreatitis, gastric outlet and recurrent duodenal obstruction, and gastric cancer. Thus long-term follow-up of these patients into adulthood is warranted. Nearly half of patients with duodenal atresia have chromosome abnormalities; trisomy 21 is identified in up to one-third of patients.

Clinical Manifestations and Diagnosis

The hallmark of duodenal obstruction is bilious vomiting without abdominal distention, which is usually noted on the first day of life. Peristaltic waves may be visualized early in the disease process. A history of polyhydramnios is present in half the pregnancies and is caused by inadequate absorption of amniotic fluid in the distal intestine. This fluid may be bile stained because of intrauterine vomiting. Jaundice is present in one-third of the infants.

The diagnosis is suggested by the presence of a *double-bubble* sign on a plain abdominal radiograph (Fig. 356.1). The appearance is caused by a distended and gas-filled stomach and proximal duodenum, which are invariably connected. Contrast studies are occasionally needed to exclude malrotation and volvulus because intestinal infarction can occur within 6-12 hr if the volvulus is not relieved. Contrast studies are generally not necessary and may be associated with aspiration. Prenatal diagnosis of duodenal atresia is readily made by fetal ultrasonography, which reveals a sonographic double-bubble. Prenatal identification of duodenal atresia is associated with decreased morbidity and fewer hospitalization days.

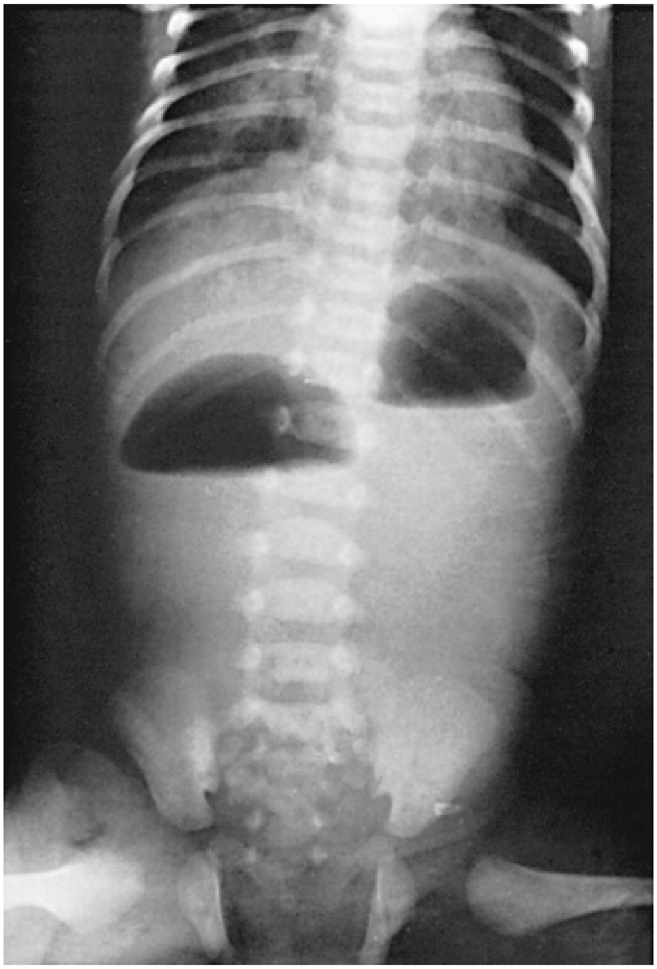

FIG. 356.1 Abdominal radiograph of a newborn infant held upright. Note the "double-bubble" gas shadow above and the absence of gas in the distal bowel in this case of congenital duodenal atresia.

Treatment

The initial treatment of infants with duodenal atresia includes nasogastric or orogastric decompression and intravenous fluid replacement. Echocardiography, renal ultrasound, and radiology of the chest and spine should be performed to evaluate for associated anomalies. Definitive correction of the atresia is usually postponed until life-threatening anomalies are evaluated and treated.

The typical surgical repair for duodenal atresia is duodenoduodenostomy. This procedure is also preferred in cases of concomitant or isolated annular pancreas. In these instances, the duodenoduodenostomy is performed without dividing the pancreas. The dilated proximal bowel might have to be tapered to improve peristalsis. Postoperatively, a gastrostomy tube can be placed to drain the stomach and protect the airway. Intravenous nutritional support or a transanastomotic jejunal tube is needed until an infant starts to feed orally. Long-term prognosis is excellent, approaching 90% survival in most series.

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356.2

Jejunal and Ileal Atresia and Obstruction

Asim Maqbool, Chris A. Liacouras

The primary etiologies of congenital small bowel obstruction involve intrinsic abnormalities in anatomic development (jejunoileal stenosis and atresia), mucus secretion (meconium ileus), and bowel wall innervation (long-segment Hirschsprung disease).

Jejunoileal atresias are generally attributed to intrauterine vascular accidents, which result in segmental infarction and resorption of the fetal intestine. Underlying events that potentiate vascular compromise include intestinal volvulus, intussusception, meconium ileus, and strangulating herniation through an abdominal wall defect associated with gastroschisis or omphalocele. Maternal behaviors that promote vasoconstriction, such as cigarette smoking and cocaine use, might also have a role. Only a few cases of familial inheritance have been reported. In these families, multiple intestinal atresias have occurred in an autosomal recessive pattern. Jejunoileal atresias have been linked with multiple births, low birthweight, and prematurity. Unlike atresia in the duodenum, they are not commonly associated with extraintestinal anomalies.

Five types of jejunal and ileal atresias are encountered (Fig. 356.2). In type I, a mucosal web occludes the lumen, but continuity is maintained between the proximal and distal bowel. Type II involves a small-diameter solid cord that connects the proximal and distal bowel. Type III is divided into two subtypes. Type IIIa occurs when both ends of the bowel end in blind loops, accompanied by a small mesenteric defect. Type IIIb is similar, but it is associated with an extensive mesenteric defect and a loss of the normal blood supply to the distal bowel. The distal ileum coils around the ileocolic artery, from which it derives its entire blood supply, producing an “apple-peel” appearance. This anomaly is associated with prematurity, an unusually short distal ileum, and significant foreshortening of the bowel. Type IV involves multiple atresias. Types II and IIIa are the most common, each accounting for 30-35% of cases. Type I occurs in approximately 20% of patients. Types IIIb and IV account for the remaining 10–20% of cases, with IIIb being the least-common configuration.

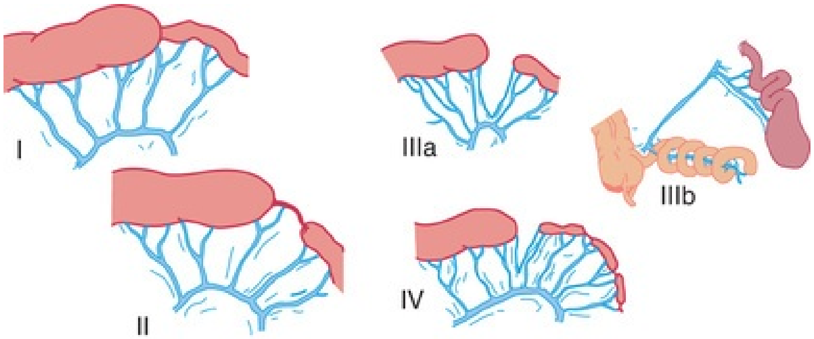

FIG. 356.2 Classification of intestinal atresia. *Type I:* Mucosal obstruction caused by an intraluminal membrane with intact bowel wall and mesentery. *Type II:* Blind ends are separated by a fibrous cord. *Type IIIa:* Blind ends are separated by a V-shaped mesenteric defect. *Type IIIb:* "Apple-peel" appearance. *Type IV:* Multiple atresias. (From Grosfeld J: Jejunoileal atresia and stenosis. In Welch KJ, Randolph JG, Ravitch MM, editors: *Pediatric surgery,* ed 4, Chicago, 1986, Year Book Medical Publishers.)

Meconium ileus occurs primarily in newborn infants with cystic fibrosis, an exocrine gland defect of chloride transport that results in abnormally viscous secretions (Chapter 432). Approximately 80–90% of infants with meconium ileus have cystic fibrosis, but only 10–15% of infants with cystic fibrosis present with meconium ileus. In simple cases, the distal 20-30 cm of ileum is collapsed and filled with pellets of pale stool. The proximal bowel is dilated and filled with thick meconium that resembles sticky syrup or glue. Peristalsis fails to propel this viscid material forward, and it becomes impacted in the ileum. In complicated cases, a volvulus of the dilated proximal bowel can occur, resulting in intestinal ischemia, atresia, and/or perforation. Perforation in utero results in meconium peritonitis, which can lead to potentially obstructing adhesions and calcifications.

Both intestinal atresia and meconium ileus must be distinguished from long-segment Hirschsprung disease. This condition involves congenital absence of ganglion cells in the myenteric and submucosal plexuses of the bowel wall. In a small subset (5%) of patients, the aganglionic segment includes the terminal ileum in addition to the entire length of the colon. Infants with long-segment Hirschsprung disease present with a dilated small intestine that is ganglionated but has hypertrophied walls, a funnel-shaped transitional hypoganglionic zone, and a collapsed distal aganglionic bowel.

Clinical Manifestation and Diagnosis

Distal intestinal obstruction is less likely than proximal obstruction to be detected in utero. Polyhydramnios is identified in 20–35% of jejunoileal atresias, and it may be the first sign of intestinal obstruction. Abdominal distention is rarely present at birth, but it develops rapidly after initiation of feeds in the first 12-24 hr. Distention is often accompanied by vomiting, which is often bilious. Up to 80% of infants fail to pass meconium in the first 24 hr of life. Jaundice, associated with unconjugated hyperbilirubinemia, is reported in 20–30% of patients.

In patients with obstruction caused by jejunoileal atresia or long-segment Hirschsprung disease, plain radiographs typically demonstrate multiple air–fluid levels proximal to the obstruction in the upright or lateral decubitus positions (Fig. 356.3). These levels may be absent in patients with meconium ileus because the viscosity of the secretions in the proximal bowel prevents layering. Instead, a typical hazy or ground-glass appearance may be appreciated in the right lower quadrant. This haziness is caused by small bubbles of gas that become trapped in inspissated meconium in the terminal ileal region. If there is meconium peritonitis, patchy calcification may also be noted, particularly in the flanks. Plain films can reveal evidence of pneumoperitoneum due to intestinal perforation. Air may be seen in the subphrenic regions on the upright view and over the liver in the left lateral decubitus position.

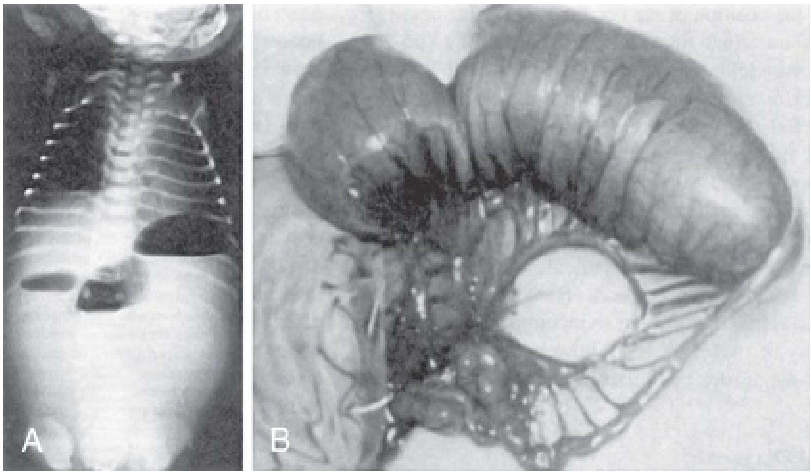

FIG. 356.3 **A,** Abdominal radiograph in a neonate with bilious vomiting shows a few loops of dilated intestine with air–fluid levels. **B,** At laparotomy, a type I (mucosal) jejunal atresia was observed. (From O'Neill JA Jr, Grosfeld JL, Fonkalsrud EW, et al, editors: *Principles of pediatric surgery,* ed 2, St. Louis, 2003, Mosby, p. 493.)

Because plain radiographs do not reliably distinguish between small and large bowel in neonates, contrast studies are often required to localize the obstruction. Water-soluble enemas (Gastrografin, Hypaque) are particularly useful in differentiating atresia from meconium ileus and Hirschsprung disease. A small *microcolon* suggests disuse and the presence of obstruction proximal to the ileocecal valve. Abdominal ultrasound may be an important adjunctive study, which can distinguish meconium ileus from ileal atresia and also identify concomitant intestinal malrotation.

Treatment

Patients with small bowel obstruction should be stable and in adequate fluid and electrolyte balance before operation or radiographic attempts at disimpaction unless volvulus is suspected. Documented infections should be treated with appropriate antibiotics. Prophylactic antibiotics are usually given before surgery.

Ileal or jejunal atresia requires resection of the dilated proximal portion of the bowel followed by end-to-end anastomosis. If a simple mucosal diaphragm is present, jejunoplasty or ileoplasty with partial excision of the web is an acceptable alternative to resection. In uncomplicated meconium ileus, Gastrografin enemas diagnose the obstruction and wash out the inspissated material. Gastrografin is hypertonic, and care must be taken to avoid dehydration, shock, and bowel perforation. The enema may have to be repeated after 8-12 hr. Resection after reduction is not needed if there have been no ischemic complications.

Approximately 50% of patients with simple meconium ileus do not adequately respond to water-soluble enemas and need laparotomy. Operative management is indicated when the obstruction cannot be relieved by repeated attempts at nonoperative management and for infants with complicated meconium ileus. The extent of surgical intervention depends on the degree of pathology. In simple meconium ileus, the plug can be relieved by manipulation or direct enteral irrigation with *N* -acetylcysteine following an enterotomy. In complicated cases, bowel resection, peritoneal lavage, abdominal drainage, and stoma formation may be necessary. Total parenteral nutrition is generally required.

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356.3

Malrotation

Asim Maqbool, Chris A. Liacouras

Malrotation is incomplete rotation of the intestine during fetal development and involves the intestinal nonrotation or incomplete rotation around the superior mesenteric artery. The gut starts as a straight tube from stomach to rectum. Intestinal rotation and attachment begin in the 5th wk of gestation when the midbowel (distal duodenum to midtransverse colon) begins to elongate and progressively protrudes into the umbilical cord until it lies totally outside the confines of the abdominal cavity. As the developing bowel rotates in and out of the abdominal cavity, the superior mesenteric artery, which supplies blood to this section of gut, acts as an axis. The duodenum, on reentering the abdominal cavity, moves to the region of the ligament of Treitz, and the colon that follows is directed to the left upper quadrant. The cecum subsequently rotates counterclockwise within the abdominal cavity and comes to lie in the right lower quadrant. The duodenum becomes fixed to the posterior abdominal wall before the colon is completely rotated. After rotation, the right and left colon and the mesenteric root become fixed to the posterior abdomen. These attachments provide a broad base of support to the mesentery and the superior mesenteric artery, thus preventing twisting of the mesenteric root and kinking of the vascular supply. Abdominal rotation and attachment are completed by the 12th wk of gestation.

Nonrotation occurs when the bowel fails to rotate after it returns to the abdominal cavity. The first and second portions of the duodenum are in their normal position, but the remainder of the duodenum, jejunum, and ileum occupy the right side of the abdomen and the colon is located on the left. The most common type of malrotation involves failure of the cecum to move into the right lower quadrant (Fig. 356.4). The usual location of the cecum is in the subhepatic area. Failure of the cecum to rotate properly is associated with failure to form the normal broad-based adherence to the posterior abdominal wall. The mesentery, including the superior mesenteric artery, is tethered by a narrow stalk, which can twist around itself and produce a midgut volvulus. Bands of tissue **(Ladd bands)** can extend from the cecum to the right upper quadrant, crossing, and possibly obstructing, the duodenum.

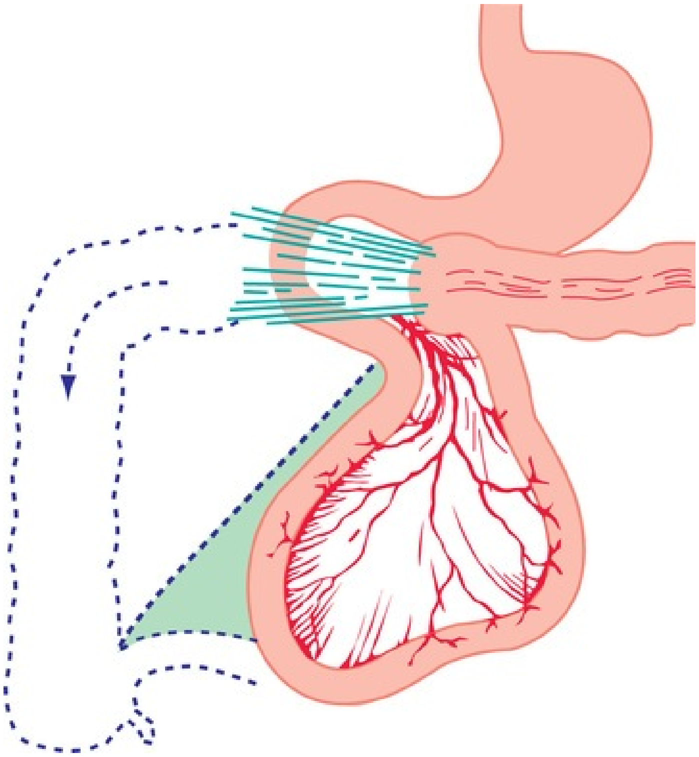

FIG. 356.4 **The mechanism of intestinal obstruction with incomplete rotation of the midgut (malrotation). The *dotted lines* show the course the cecum should have taken. Failure to rotate has left obstructing bands across the duodenum and a narrow pedicle for the midgut loop, making it susceptible to volvulus. (From Nixon HH, O'Donnell B: *The essentials of pediatric surgery,* Philadelphia, 1961, JB Lippincott.)**

Malrotation and nonrotation are often associated with other anomalies of the abdominal wall such as diaphragmatic hernia, gastroschisis, and omphalocele. Malrotation is also associated with the **heterotaxy syndrome** , which is a complex of congenital anomalies including congenital heart malformations, malrotation, biliary atresia, and either asplenia or polysplenia (see Chapter 458.11).

Clinical Manifestations

The reported incidence of malrotation is approximately 1 in 500 infants. The majority, about 75–85% of patients, present in the first yr of life, and more than 50% present within the first mo of life, with symptoms of acute or chronic obstruction. Vomiting is the most common symptom in this age group. Infants often present in the first wk of life with **bilious emesis** and acute bowel obstruction. Older infants present with episodes of recurrent abdominal pain that can mimic colic and suggest intermittent volvulus. Malrotation in older children can manifest with recurrent episodes of vomiting and/or abdominal pain. Patients occasionally present with **malabsorption** or **protein-losing enteropathy** associated with bacterial overgrowth. Symptoms are caused by intermittent volvulus or duodenal compression by Ladd bands or other adhesive bands affecting the small and large bowel. Approximately 25–50% of adolescents with malrotation are asymptomatic. Adolescents who become symptomatic present with acute intestinal obstruction or history of recurrent episodes of abdominal pain or postprandial bloating and occasional vomiting. Patients of any age with a rotational anomaly can develop acute bowel-threatening volvulus without preexisting symptoms.

An acute presentation of small bowel obstruction in a patient without previous bowel surgery can be the result of **volvulus** associated with malrotation. This is a life-threatening complication of malrotation, which resembles an acute abdomen or sepsis and is the main reason that symptoms suggesting malrotation should always be investigated. Volvulus occurs when the small bowel twists around the superior mesenteric artery leading to vascular compromise of the bowel. The diagnosis may be suggested by ultrasound but is confirmed by contrast radiographic studies. The abdominal plain film is usually nonspecific but might demonstrate a gasless abdomen or evidence of duodenal obstruction with a double-bubble sign. Upper gastrointestinal series is the imaging test of choice and the gold standard in the evaluation and diagnosis of malrotation and volvulus. Normal rotation is indicated by the duodenal C-loop crossing the midline and a duodenojejunal junction located to the left of the spine. Upper gastrointestinal series is the best exam to visualize the malposition of the ligament of Treitz and can also reveal a corkscrew appearance of the small bowel or a duodenal obstruction with a *bird's beak* appearance of the duodenum. Barium enema usually demonstrates malposition of the cecum but is normal in up to 20% of patients. Ultrasonography can demonstrate the inversion of the superior mesenteric artery and vein. A superior mesenteric vein located to the left of the superior mesenteric artery suggests malrotation. Malrotation with volvulus is suggested by duodenal obstruction, thickened bowel loops to the right of the spine, the superior mesenteric vein coiling around the superior mesenteric artery, and free peritoneal fluid.

Treatment

Surgical intervention is recommended for any patient with a significant rotational abnormality, regardless of age. If a volvulus is present, surgery is done immediately as an acute emergency, the volvulus is reduced, and the duodenum and upper jejunum are freed of any bands and remain in the right abdominal cavity. The colon is freed of adhesions and placed in the right abdomen with the cecum in the left lower quadrant, usually accompanied by incidental appendectomy. The Ladd procedure may be done laparoscopically for malrotation without volvulus and if gut ischemia is not present, but it is generally done as an open procedure if volvulus is present. The purpose of surgical intervention is to minimize the risk of subsequent volvulus rather than to return the bowel to a normal anatomic configuration. Extensive intestinal ischemia from volvulus can result in short bowel syndrome (see Chapter 364.7).

Acknowledgment

Melissa Kennedy, MD contributed to the prior version of this chapter.

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CHAPTER 357

Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct

357.1

Intestinal Duplication

Asim Maqbool, Chris A. Liacouras

Duplications of the intestinal tract are rare anomalies that consist of well-formed tubular or spherical structures firmly attached to the intestine with a common blood supply. The lining of the duplications resembles that of the gastrointestinal (GI) tract. Duplications are located on the mesenteric border and can communicate with the intestinal lumen. Duplications can be classified into three categories: localized duplications, duplications associated with spinal cord defects and vertebral malformations, and duplications of the colon. Occasionally (10–15% of cases), multiple duplications are found.

Localized duplications can occur in any area of the GI tract but are most common in the ileum and jejunum. They are usually cystic or tubular structures within the wall of the bowel. The cause is unknown, but their development has been attributed to defects in recanalization of the intestinal lumen after the solid stage of embryologic development. Duplication of the intestine occurring in association with **vertebral and spinal cord anomalies** (hemivertebra, anterior spina bifida, band connection between lesion and cervical or thoracic spine) is thought to arise from splitting of the notochord in the developing embryo.

Duplication of the colon is usually associated with anomalies of the urinary tract and genitals. Duplication of the entire colon, rectum, anus, and terminal ileum can occur. The defects are thought to be secondary to caudal twinning, with duplication of the hindgut, genital, and lower urinary tracts.

Clinical Manifestations

Symptoms depend on the size, location, and mucosal lining. Duplications can cause bowel obstruction by compressing the adjacent intestinal lumen, or they can act as the lead point of an intussusception or a site for a volvulus. If they are lined by acid-secreting mucosa, they can cause ulceration, perforation, and hemorrhage of or into the adjacent bowel. Patients can present with abdominal pain, vomiting, palpable mass, or acute GI hemorrhage. Intestinal duplications in the thorax **(neuroenteric cysts)** can manifest as respiratory distress. Duplications of the lower bowel can cause constipation or diarrhea or be associated with recurrent prolapse of the rectum.

The diagnosis is suspected on the basis of the history and physical examination. Radiologic studies such as barium studies, ultrasonography, CT, and MRI are helpful but usually nonspecific, demonstrating cystic structures or mass effects. Radioisotope technetium scanning can localize ectopic gastric mucosa. The treatment of duplications is surgical resection and management of associated defects.

357.2

Meckel Diverticulum and Other Remnants of the Omphalomesenteric Duct

Melissa A. Kennedy, Asim Maqbool, Chris A. Liacouras

Meckel diverticulum is the most common congenital anomaly of the GI tract and is caused by the incomplete obliteration of the omphalomesenteric duct during the 7th wk of gestation. The omphalomesenteric duct connects the yolk sac to the gut in a developing embryo and provides nutrition until the placenta is established. Between the 5th and 7th wk of gestation, the duct attenuates and separates from the intestine. Just before this involution, the epithelium of the yolk sac develops a lining similar to that of the stomach. Partial or complete failure of involution of the omphalomesenteric duct results in various residual structures. Meckel diverticulum is the most common of these structures and is the most common congenital GI anomaly, occurring in 2–3% of all infants. A typical Meckel diverticulum is a 3-6 cm outpouching of the ileum along the antimesenteric border 50-75 cm (approximately 2 feet) from the ileocecal valve (Fig. 357.1). The distance from the ileocecal valve depends on the age of the patient. Meckel diverticulum has been conveniently referred to by the “rule of 2s,” which explains the classic presentation of this congenital anomaly. Meckel diverticulum are found in approximately 2% of the general population, are usually located 2 feet proximal to the ileocecal valve and are approximately 2 inches in length, can contain 2 types of ectopic tissue (pancreatic or gastric), generally present before the age of 2 yr, and are found twice as commonly in females. Although intraabdominal in location, a rare presentation of a Meckel diverticulum is entrapment in an inguinal, umbilical, or femoral hernia (Littre hernia). Other omphalomesenteric duct remnants occur infrequently, including a persistently patent duct, a solid cord, or a cord with a central cyst or a diverticulum associated with a persistent cord between the diverticulum and the umbilicus.

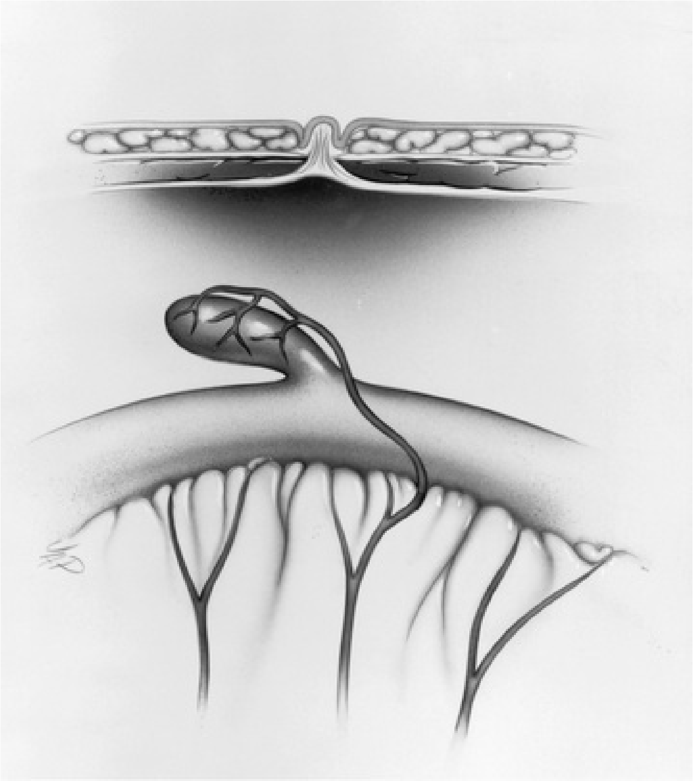

FIG. 357.1 Typical Meckel diverticulum located on the antimesenteric border.

Clinical Manifestations

Symptoms of a Meckel diverticulum usually arise in the first or second yr of life (average: 2.5 yr), but initial symptoms can occur in the first decade. The majority of symptomatic Meckel diverticula are lined by an ectopic mucosa, including an acid-secreting mucosa that causes intermittent painless rectal bleeding by ulceration of the adjacent normal ileal mucosa. This ectopic mucosa is most commonly of gastric origin, but it can also be pancreatic, jejunal, or a combination of these tissues. Unlike the upper duodenal mucosa, the acid is not neutralized by pancreatic bicarbonate.

The stool is typically described as brick colored or currant jelly colored. Bleeding can cause significant anemia but is usually self-limited because of contraction of the splanchnic vessels, as patients become hypovolemic. Bleeding from a Meckel diverticulum can also be less dramatic, with melanotic stools.

Less often, a Meckel diverticulum is associated with partial or complete bowel obstruction. The most common mechanism of obstruction occurs when the diverticulum acts as the lead point of an intussusception. The mean age of onset of obstruction is younger than that for patients presenting with bleeding. Obstruction can also result from intraperitoneal bands connecting residual omphalomesenteric duct remnants to the ileum and umbilicus. These bands cause obstruction by internal herniation or volvulus of the small bowel around the band. A Meckel diverticulum occasionally becomes inflamed **(diverticulitis)** and manifests similarly to acute appendicitis. These children are older, with a mean of 8 yr of age. Diverticulitis can lead to perforation and peritonitis.

Diagnosis

The diagnosis of omphalomesenteric duct remnants depends on the clinical presentation. If an infant or child presents with significant painless rectal bleeding, the presence of a Meckel diverticulum should be suspected because Meckel diverticulum accounts for 50% of all lower GI bleeds in children younger than 2 yr of age.

Confirmation of a Meckel diverticulum can be difficult. Plain abdominal radiographs are of no value, and routine barium studies rarely fill the diverticulum. The most sensitive study is a Meckel radionuclide scan, which is performed after intravenous infusion of technetium-99m pertechnetate. The mucus-secreting cells of the ectopic gastric mucosa take up pertechnetate, permitting visualization of the Meckel diverticulum (Fig. 357.2). The uptake can be enhanced with various agents, including cimetidine, ranitidine, glucagon, and pentagastrin. The sensitivity of the enhanced scan is approximately 85%, with a specificity of approximately 95%. A false-negative scan may be seen in anemic patients; although false-positive results are uncommon, they have been reported with intussusception, appendicitis, duplication cysts, arteriovenous malformations, and tumors. Other methods of detection include radiolabeled tagged red blood cell scan (the patient must be actively bleeding), abdominal ultrasound, superior mesenteric angiography, abdominal CT scan, or exploratory laparoscopy. In patients who present with intestinal obstruction or a picture of appendicitis with omphalomesenteric duct remnants, the diagnosis is rarely made before surgery.

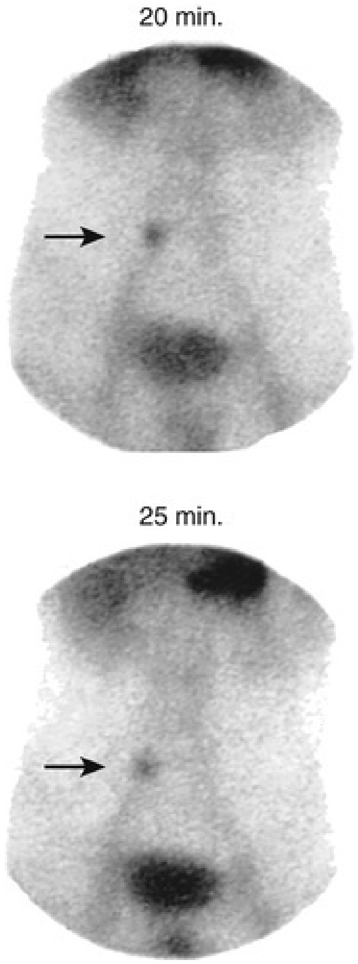

FIG. 357.2 Meckel scan demonstrating accumulation of technetium in the stomach superior bladder (inferior) and in the acid-secreting mucosa of a Meckel diverticulum.

The treatment of a symptomatic Meckel diverticulum is surgical excision. A diverticulectomy can be performed safely as either a laparoscopic or open procedure, although most continue to be performed as open procedures. There is significant debate regarding the proper management of an asymptomatic Meckel diverticulum and whether excision vs observation is appropriate. However, the risk of serious complications does seem to exceed the operative risk in children younger than 8 yr old.

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CHAPTER 358

Motility Disorders and Hirschsprung Disease

358.1

Chronic Intestinal Pseudoobstruction

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Chronic intestinal pseudoobstruction (CIPO) comprises a group of primary and secondary disorders characterized as a motility disorder with the dominant defect of impaired peristalsis; symptoms are consistent with intestinal obstruction in the absence of mechanical obstruction (Table 358.1). The natural history of primary pseudoobstruction is that of a progressive disorder, although there are occasional cases of secondary pseudoobstruction caused by conditions that can transiently or permanently alter bowel motility. The most common cause of acute pseudoobstruction is Ogilvie syndrome (acute pseudoobstruction of the colon). Pseudoobstruction represents a wide spectrum of pathologic disorders from abnormal myoelectric activity to abnormalities of the nerves (intestinal neuropathy) or musculature (intestinal myopathy) of the gut. The organs involved can include the entire gastrointestinal tract or be limited to certain components, although almost always include the small bowel. The distinctive pathologic abnormalities are considered together because of their clinical similarities. For these reasons, CIPO may be thought of more as a clinical syndrome at times.

Table 358.1

Causes of Secondary Chronic Intestinal Pseudoobstruction in Children

- Autoimmune
- Autoimmune myositis
- Autoimmune ganglionitis
- Scleroderma
- Endocrine
- Diabetes mellitus
- Hypoparathyroidism
- Hypothyroidism
- Gastrointestinal
  - Celiac disease
  - Eosinophilic gastroenteritis
  - Inflammatory bowel disease
- Hematology/oncology
  - Multiple myeloma
  - Paraneoplastic syndromes
  - Pheochromocytoma
  - Sickle cell disease
- Infection
  - Chagas disease
  - Cytomegalovirus
  - Epstein-Barr virus
  - Herpes zoster
  - JC virus
  - Kawasaki disease
  - Postviral neuropathy
- Medications and toxins
  - Chemotherapy
  - Cyclopentolate and phenylephrine eye drops
  - Diltiazem and nifedipine
  - Fetal alcohol syndrome
  - Jellyfish envenomation
  - Opioid medications
  - Postanesthesia
  - Radiation injury
- Mitochondrial disorders
  - Mitochondrial neurogastrointestinal encephalomyopathy
- Musculoskeletal disorders
  - Ehlers-Danlos syndrome
  - Myotonic dystrophy
  - Duchenne muscular dystrophy
- Rheumatology
  - Amyloidosis
  - Dermatomyositis
  - Polymyositis
  - Systemic lupus erythematous

From Bitton S, Markowitz JF: Ulcerative colitis in children and adolescents. In Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease,* 5th ed, Elsevier, 2016, Philadelphia, Box. 44.3, p. 548.

Most congenital forms of primary pseudoobstruction occur sporadically, although autosomal dominant *(SOX10),* autosomal recessive *(RAD2I, SGOL1, TYMP, POLG),* X-linked *(FLNA, L1CAM),* and familial patterns of inheritance have been identified. Patients with autosomal dominant forms of pseudoobstruction have variable expressions of the disease. Patients with mutations in *TYMP* and *POLG* genes present with mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE); MELAS syndrome is another mitochondrial disorder associated with CIPO. MNGIE is characterized by intestinal dysmotility, abdominal pain and distention, emesis, cachexia, ptosis, leukoencephalopathy, peripheral neuropathy (paresthesia, pain), and myopathy. Sixty percent have symptoms (often subtle) before age 20 yr (see Chapter 358.2). *Acquired* pseudoobstruction can follow episodes of acute gastroenteritis, presumably resulting in injury to the myenteric plexus.

In *congenital* pseudoobstruction, abnormalities of the muscle or nerves can be demonstrated in most cases. In myopathies, the smooth muscle is involved, in which the outer longitudinal muscle layer is replaced by fibrous material. These manifestations of visceral myopathies may be primary or secondary phenomenon. The enteric nervous system is usually altered in neuropathies and may involve disorganized ganglia, hypoganglionosis, or hyperganglionosis. Abnormalities in the interstitial cells of Cajal, the intestinal pacemaker, are classified as mesenchymopathies. In others, mitochondrial defects have been identified.

Clinical Manifestations

More than half the children with congenital pseudoobstruction experience symptoms in the first few mo of life (Table 358.2). Two-thirds of the infants presenting in the first few days of life are born prematurely, and approximately 40% have malrotation of the intestine. In 75% of all affected children, symptoms occur in the first year of life, while the remainder are usually symptomatic within the next several years. Females present with CIPO more than males do during the first year of life, with equal sex distribution in older children. The most common symptoms are abdominal distention (85–95% of patients) and vomiting (55–90%). Constipation, growth failure, and abdominal pain occur in approximately 60% of patients and diarrhea in 25–30%. The symptoms wax and wane in most patients; poor nutrition, psychologic stress, and intercurrent illness tend to exacerbate symptoms. Urinary tract and bladder involvement occurs in 80% of children with myopathic pseudoobstruction and in 20% of those with neuropathic disease. Symptoms can manifest as recurrent urinary tract infection, megacystis, or obstructive symptoms. Megacystis-microcolon–intestinal hypoperistalsis syndrome is a prenatal or neonatal manifestation of CIPO.

Table 358.2

Main Similarities and Differences in Chronic Intestinal Pseudoobstruction in Children, Adolescents, and Young Adults

	CHILDREN	ADOLESCENTS—YOUNG ADULTS
Etiology	Mainly idiopathic	Half of cases are secondary to acquired diseases
Histopathology	Myopathies and neuropathies	Mainly neuropathies
Symptom onset	In utero, from birth or early infancy with 65–80% of patients symptomatic by 12 mo of age	Median age of onset at 17 yr
Clinical features	Occlusive symptoms at birth and/or chronic symptoms without free intervals Urologic involvement is commonly encountered ranging from 36% to 100% pediatric case series High risk of colonic and small bowel volvulus secondary to severe gut dilation, dysmotility, congenital bridles, or concurrent malrotation	Chronic abdominal pain and distension with superimposed acute episodes of pseudoobstruction Urinary bladder involvement not so often reported
Natural history	Myopathic CIPO, urinary involvement and concurrent intestinal malrotation are poor prognostic factors	The ability to restore oral feeding and the presence of symptoms <20 yr of age is associated with a low mortality; while, systemic sclerosis and severe/diffuse esophageal and intestinal dysmotility are associated with a high mortality
Diagnostic approach	Specialized tests (e.g., intestinal manometry) often difficult to perform; noninvasive, radiation-free imaging tests are warranted	Various methodologic approaches usually starting from endoscopy and radiological tests up to more sophisticated functional exams
Nutritional therapy	To ensure normal growth extensively hydrolyzed and elemental formulas are often empirically used to facilitate intestinal absorption	To improve nutritional status and prevent malnutrition
Pharmacologic therapy	Small number/sample size-controlled trials	Small number/sample-size controlled trials; few conclusions can be drawn for most drugs
Surgical therapy	Venting ostomies (although characterized by high complication rates) possibly helpful; surgery as a “bridge” to transplantation may be indicated in highly selected cases	Venting ostomies can be helpful; resective surgery may be indicated in accurately selected patients (i.e., cases with proven segmental gut dysfunction)

From Di Nardo G, Di Lorenzo C, Lauro A, et al: Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options, *Neurogastroenterol Motil* 29:e12945, 2017, Table 2.

Diagnosis

The diagnosis of pseudoobstruction is based on the presence of compatible symptoms in the absence of mechanical obstruction (Fig. 358.1). Plain abdominal radiographs demonstrate air-fluid levels in the intestine. Neonates with evidence of obstruction at birth may have a microcolon. Contrast studies demonstrate slow passage of barium; water-soluble agents should be considered. Esophageal motility is abnormal in about half the patients. Antroduodenal (small intestinal) motility and gastric emptying studies have abnormal results if the upper gut is involved (Table 358.3). The clinical manifestations depend in large part to the areas of the gastrointestinal tract that are involved, with milder forms more common in older children. Although counterintuitive, older children with CIPO may present with both abdominal distention and diarrhea, related to *small bowel bacterial overgrowth* because of altered motility. Other presentations may include constipation and bilious emesis, as well as failure to thrive, as a consequence of decreased enteral feeding tolerance.

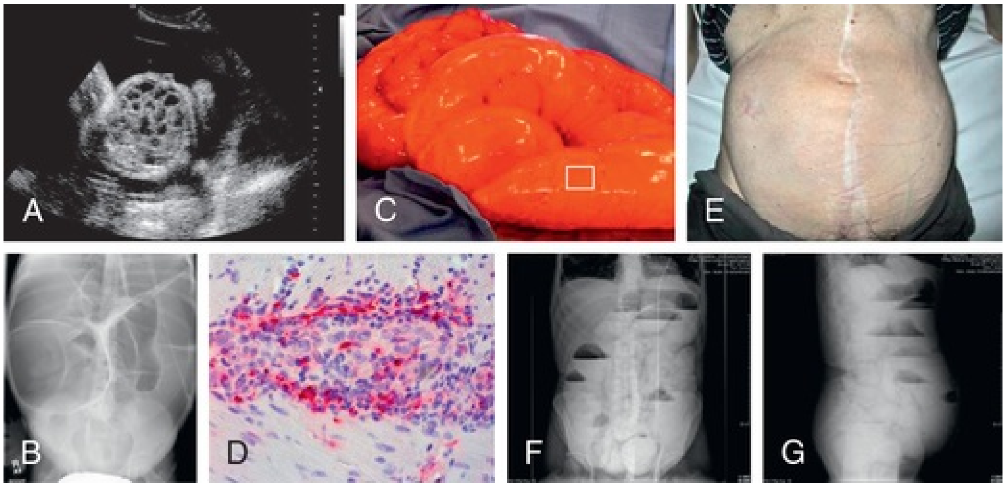

FIG. 358.1 Synoptic view of the chronic intestinal pseudoobstruction (CIPO) spectrum. A and B, The most severe pediatric cases with antenatal (in utero) evidence of multivisceral dilation—often gut (B) and urinary system—commonly associated with an extremely poor prognosis. C and D, CIPO phenotype with rapid progression to intestinal dilation (± ureter/bladder) and failure, often occurring as a result of an anamnestically reported gastroenteritis. Massive bowel dilation (C) and associated histopathology (D ; corresponds to white squared area in C) revealed an intense inflammatory (mainly lymphocytic) neuropathy (hence, myenteric ganglionitis). Alkaline phosphatase antialkaline phosphatase immunohistochemical technique using specific anti-CD8 monoclonal antibodies was used to identify a subset of T lymphocytes. E and G, Examples of another phenotype of the syndrome that may be seen in patients who have more insidious mild and nonspecific symptoms progressing to a classic CIPO over time. E, Markedly distended abdomen of a 32 yr old man who presented with subocclusive episodes after years of unspecific (dyspeptic-/irritable bowel syndrome–

like) symptoms. Note the evident air-fluid levels detectable in upright position in anteroposterior (F) and laterolateral (G) plain abdominal radiographs. (A, From Shen O, Schimmel MS, Eitan R, et al: Prenatal diagnosis of intestinal pseudo-obstruction, *Ultrasound Obstet Gynecol* 29:229–231, 2007. B–G, From Di Nardo G, Di Lorenzo C, Lauro A, et al: Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options, *Neurogastroenterol Motil* 29:e12945, 2017.)

Table 358.3

Findings in Pseudoobstruction

GI SEGMENT	FINDINGS*
Esophageal motility	Abnormalities in approximately half of CIPO, although in some series up to 85% demonstrate abnormalities
	Decreased LES pressure
	Failure of LES relaxation
	Esophageal body: low-amplitude waves, poor propagation, tertiary waves, retrograde peristalsis, occasionally aperistalsis
Gastric emptying	May be delayed
EGG	Tachygastria or bradygastria may be seen
ADM	Postprandial antral hypomotility is seen and correlates with delayed gastric emptying
	Myopathic subtype: low-amplitude contractions, <10-20 mm Hg
	Neuropathic subtype: contractions are uncoordinated, disorganized
	Absence of fed response
	Fasting MMC is absent, or MMC is abnormally propagated
Colonic	Absence of gastrocolic reflex because there is no increased motility in response to a meal
ARM	Normal rectoanal inhibitory reflex

[*] Findings can vary according to the segment(s) of the GI tract that are involved.

ADM, antroduodenal manometry; ARM, anorectal manometry; CIPO, chronic intestinal pseudoobstruction; EGG, electrogastrography; GI, gastrointestinal; LES, lower esophageal sphincter; MMC, migrating motor complex.

From Steffen R: Gastrointestinal motility. In Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease,* ed 3, Philadelphia, 2006, WB Saunders, p. 66.

The initial focus is to rule out anatomic obstruction and to assess for bladder involvement, because that is a frequent and significant extraintestinal manifestation of concern. Manometric evidence of a normal migrating motor complex and postprandial activity should redirect the diagnostic evaluation. CIPO due to an intestinal myopathy may demonstrate manometry evidence of low-amplitude contractions, whereas CIPO due to enteric neuropathy demonstrates normal amplitude but poorly organized contractions (nonperistaltic or tonic). Anorectal motility is normal and differentiates pseudoobstruction from Hirschsprung disease. Full-thickness intestinal biopsy might show involvement of the muscle layers or abnormalities of the intrinsic intestinal nervous system.

The differential diagnosis is broad and includes such etiologies as Hirschsprung disease, mitochondrial neurogastrointestinal encephalomyopathy, mechanical obstruction, psychogenic constipation, neurogenic bladder, and superior mesenteric artery syndrome. Secondary causes of ileus or pseudoobstruction that should be considered include medication side effects, infectious etiologies, metabolic disturbances, immunologic disorders, oncologic processes, vasculitides, neuropathies, and myopathies (see Table 358.1). Examples include use of opiates hypokalemia, hypothyroidism, hypokalemia, diabetic neuropathy, porphyria, amyloidosis, Chagas disease, scleroderma, hereditary angioedema, mitochondrial disorders, and radiation, and these must be excluded. Other causes of abdominal distention such as small bowel bacterial overgrowth and aerophagia may present similarly and should be considered. *Small bowel bacterial overgrowth is a complication of CIPO.*

Treatment

Nutritional support is the mainstay of treatment for pseudoobstruction. Thirty to 50% of patients require partial or complete parenteral nutrition. Some patients can be treated with intermittent enteral supplementation, whereas others can maintain themselves on selective oral diets. Prokinetic drugs are generally used, although studies have not shown definitive evidence of their efficacy. Isolated gastroparesis can follow episodes of viral gastroenteritis and spontaneously resolves, usually in 6-24 mo. Erythromycin, a motilin receptor agonist, and cisapride, a serotonin 5-HT_4 receptor agonist, may enhance gastric emptying and proximal small bowel motility and may be useful in this select group of patients. Metoclopramide, a prokinetic and antinausea agent, is effective in gastroparesis, although side effects, such as tardive dyskinesia, limit its use. Domperidone, an antidopaminergic agent, is a prokinetic agent that can be considered. Pain management is difficult and requires a multidisciplinary approach.

Symptomatic small bowel bacterial overgrowth is usually treated with rotated nonabsorbable oral antibiotics and/or probiotics. Bacterial overgrowth can be associated with steatorrhea and malabsorption. Octreotide, a long-acting somatostatin analog, has been used in low doses to treat small bowel bacterial overgrowth. Patients with acid peptic symptoms are generally treated with acid suppression. Many patients with CIPO benefit from a gastrostomy, and some benefit from decompressive enterostomies (Fig. 358.2). Colectomy with ileorectal anastomosis is beneficial if the large bowel is the primary site of the motility abnormality. Bowel transplantation may benefit selected patients with CIPO. The prognosis is better for patients without urinary tract involvement and for those with neuropathic etiologies over myopathic disorders.

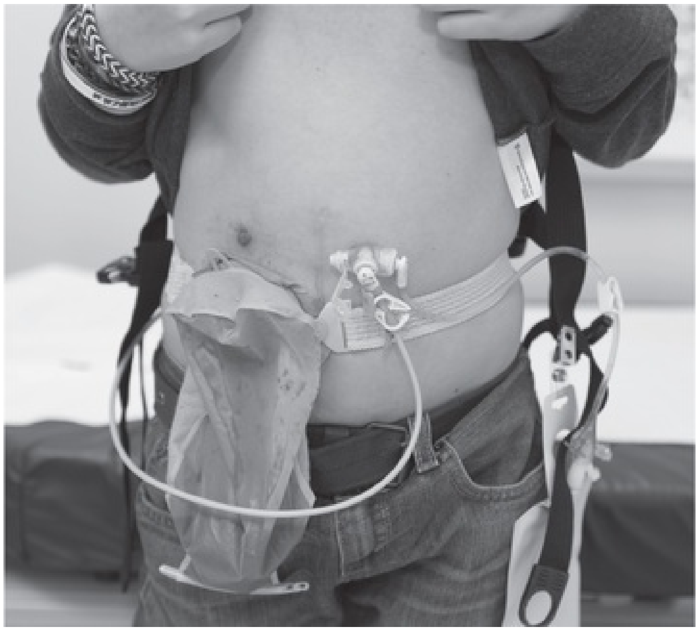

FIG. 358.2 Photograph of a child with chronic intestinal pseudoobstruction who improved clinically after ileostomy creation. He receives enteral feeding through his jejunal feeding tube, whereas his gastrostomy tube remains to straight drain. (From Bitton S, Markowitz JF: Ulcerative colitis in children and adolescents. In Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease* , ed 5, Philadelphia, 2016, Elsevier, Fig. 44.3).

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358.2

Mitochondrial Neurogastrointestinal Encephalomyopathy

Asim Maqbool, Chris A. Liacouras

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a multisystem autosomal recessive disease that initially presents with severe gastrointestinal disturbances; the neurologic manifestations usually occur later in the illness and may initially be subtle or asymptomatic.

MNGIE is caused by a mutation in the nuclear DNA *TYMP* gene encoding thymidine phosphorylase that results in abnormalities in intergenomic communication with resulting instability of mitochondrial DNA (some patients have mutations on *POLG1*). There are at least 50 individual mutations with a poor genotype-phenotype correlation and varying manifestations within each family. Consanguinity is present in 30% of families.

MNGIE affects both males and females and is usually diagnosed in the 2nd and 3rd decade (average age: 18 yr; range: 5 mo-35 yr). Onset is usually around age 12 yr, but there is often a 5- to 10-yr delay in the diagnosis.

MNGIE *initially* presents with gastrointestinal symptoms. Severe intestinal dysmotility and gastroparesis are associated with early satiety, postprandial emesis, episodic pseudoobstruction, diarrhea, constipation, and abdominal pain and cramping, which leads to significant cachexia. Because of the age of onset, emesis, early satiety, and cachexia patients are often misdiagnosed with an eating disorder.

Most often, following the onset of gastrointestinal manifestations, ptosis, progressive external ophthalmoplegia, hearing loss, myopathy, and peripheral neuropathy may develop. The neuropathy is either demyelinating or a mixed axonal demyelinating type and manifests as weakness, decreased or absent deep tendon reflexes, and paresthesias. Leukoencephalopathy is initially asymptomatic and noted on MRI as patchy lesions predominantly in the cortex but also in the basal ganglia and brainstem. Eventually the central nervous system lesions become diffuse and confluent. A small number of patients develop cognitive impairment or dementia.

The diagnosis is suggested by the constellation of gastrointestinal and neurologic symptoms, lactic acidosis, ragged red fibers, and cytochrome C oxidase–deficient fibers seen in most patients on muscle biopsy. Reduced activity of thymidine phosphorylase enzyme and elevated plasma levels of thymidine and deoxyuridine are often diagnostic; genetic testing for the mutation or other genes *(POLG1)* is recommended.

Treatment is focused on providing sufficient nutritional support and avoidance of infectious complications and of nutritional deficiencies. Domperidone has been used for nausea and emesis, antibiotics for small bowel bacterial overgrowth, amitriptyline or gabapentin for neuropathic pain, and parenteral alimentation for nutritional support. Opiates and any medications that affect intestinal motility or mitochondrial function must be avoided. Stem cell transplantation has been successful in a small number of patients.

Overall the prognosis is poor, with few surviving into the 4th or 5th decade.

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358.3

Encopresis and Functional Constipation

Asim Maqbool, Chris A. Liacouras

Constipation is defined as a delay or difficulty in defecation present for >1 month and significant enough to cause distress to the patient. Another approach to the definition is the Rome criteria, outlined in Tables 358.4 and 358.5 . Functional constipation, also known as idiopathic constipation or fecal withholding, can usually be differentiated from constipation secondary to organic causes based on a history and physical examination. Unlike anorectal malformations and Hirschsprung disease, functional constipation typically starts after the neonatal period. Usually, there is an intentional or subconscious withholding of stool. An acute episode usually precedes the chronic course. This acute event could include a social stressor such as initiation of toilet training, birth of a sibling, starting daycare, or abuse. The acute episode may be a dietary change from human milk to cow's milk, secondary to the change in the protein and carbohydrate ratio or an allergy to cow's milk. Although iron has been suspected of causing issues with cow's milk–related constipation, this has not been consistently demonstrated or substantiated. The stool becomes firm, smaller, and difficult to pass, resulting in anal irritation and often an anal fissure. In toddlers, coercive or inappropriately early toilet training is a factor that can initiate a pattern of stool retention. In older children, retentive constipation can develop after entering a situation that makes stooling inconvenient such as school. Because the passage of bowel movements is painful, voluntary withholding of feces to avoid the painful stimulus develops.

Table 358.4

Rome IV Diagnostic Criteria for Defecatory Disorders in Neonates and Toddlers

FGID	AGE RANGE	CRITERIA REQUIREMENTS	CRITERIA ELEMENTS
Functional constipation	All pediatric age groups	Must include 1 month of ≥2 of the following in infants up to 4 months of age: In toilet trained children, the following additional criteria may be used:	• 2 or fewer defections weekly • History of excessive stool retention • History of hard/painful bowel movements • History of large-diameter stools • Presence of a large fecal mass in the rectum • At least 1 weekly episode of incontinence after being toilet trained • History of large-diameter stools that may clog the toilet

FGID, Functional gastrointestinal disorders.

Modified from Benninga MA, Faure C, Hyman PE, et al. Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 150:1443–1455, 2016.

Table 358.5

Rome IV Diagnostic Criteria for Defecatory Disorders in Children and Adolescents

	AGE RANGE	CRITERIA REQUIREMENTS	CRITERIA ELEMENTS
Functional Constipation	Developmental age ≥4 yr	Must include ≥2 of the following ≥1/wk for 1 ≥1 mo with insufficient criteria to diagnose irritable bowel syndrome	• ≤ 2 defecations in the toilet per week • ≥1 episode of fecal incontinence per week • History of retentive posturing or excessive volitional stool retention • History of painful or hard bowel movements • Presence of a large fecal mass in the rectum • History of large diameter stools that can obstruct the toilet • After appropriate evaluation, symptoms cannot be fully explained by another medical condition
Nonretentive Fecal Incontinence	developmental age ≥4 yr	≥1-mo history of the following symptoms:	• Defecation into places inappropriate to the sociocultural context • No evidence of fecal retention • After appropriate evaluation, symptoms cannot be fully explained by another medical condition

Modified from Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150:1456–1468, 2016.

Clinical Manifestations

When children have the urge to defecate, typical behaviors include contracting the gluteal muscles by stiffening the legs while lying down, holding onto furniture while standing, or squatting quietly in corners, waiting for the call to stool to pass. The urge to defecate passes as the rectum accommodates to its contents. A vicious cycle of retention develops, as increasingly larger volumes of stool need to be expelled. Caregivers may misinterpret these activities as straining, but it is withholding behavior. There is often a history of blood in the stool noted with the passage of a large bowel movement. Findings suggestive of underlying pathology include failure to thrive, weight loss, abdominal pain, vomiting, or persistent anal fissure or fistula.

In functional constipation, daytime encopresis is common. **Encopresis** is defined as voluntary or involuntary passage of feces into inappropriate places at least once a mo for 3 consecutive months once a chronologic or developmental age of 4 yr has been reached. Encopresis is not diagnosed when the behavior is exclusively the result of the direct effects of a substance (e.g., laxatives) or a general medical condition (except through a mechanism involving constipation). Subtypes include retentive encopresis (with constipation and overflow incontinence), representing 65–95% of cases, and nonretentive encopresis (without constipation and overflow incontinence). **Nonretentive fecal incontinence** is defined as no evidence of fecal retention (impaction), ≥1 episodes per week in the previous 1 mo, or defecation in places inappropriate to the social context in a child who has been previously toilet trained and without evidence of anatomic, inflammatory, metabolic, endocrine, or neoplastic process that could explain the symptoms. Encopresis can persist from infancy onward (primary) or can appear after successful toilet training (secondary). The updated Rome criteria (IV) differentiate between infants/toddlers and older children who have been toilet trained versus not toilet trained, for practical assessment purposes.

Diagnosis

The physical examination often demonstrates a large volume of stool palpated in the suprapubic area; rectal examination demonstrates a dilated rectal vault filled with guaiac-negative stool. Children with encopresis often present with reports of underwear soiling, and many parents initially presume that diarrhea, rather than constipation, is the cause. In **retentive encopresis** , associated complaints of difficulty with defecation, abdominal or rectal pain, impaired appetite with poor growth, and urinary (day and/or night) incontinence are common. Children often have large bowel movements that obstruct the toilet. There may also be retentive posturing or recurrent urinary tract infections. **Nonretentive encopresis** is more likely to occur as a solitary symptom and have an associated primary underlying psychological etiology. Children with encopresis can present with poor school performance and attendance that is triggered by the scorn and derision from schoolmates because of the child's offensive odor.

The location of the anus relative to perineal anatomic landmarks by sex also needs to be considered. This is expressed as the **anogenital index** , and it can be calculated when necessary. This is determined by the distance in centimeters from the vagina or scrotum to the anus, divided by the distance from the vagina or scrotum to the coccyx. The normal anogenital index in females is 0.39 ± 0.09, whereas 0.56 ± 0.2 is normal for males. The presence of a hair tuft over the spine or spinal dimple, or failure to elicit a cremasteric reflex or anal wink suggests spinal pathology. A tethered cord is suggested by decreased or absent lower leg reflexes. **Spinal cord lesions** can occur with overlying skin anomalies. Urinary tract symptoms include recurrent urinary tract infection and enuresis. Children with no evidence of abnormalities on physical examination rarely require radiologic evaluation.

In refractory patients (intractable constipation), specialized testing should be considered to rule out conditions such as hypothyroidism, hypocalcemia, lead toxicity, celiac disease, and disorders of neuromuscular gastrointestinal pathology (Table 358.6). Colonic transit studies using radiopaque markers or scintigraphy techniques may be useful. Selected children can benefit from MRI of the spine to identify an intraspinal process, motility studies to identify underlying myopathic or neuropathic bowel abnormalities, or a contrast enema to identify structural abnormalities. In patients with severe functional constipation, water-soluble contrast enema reveals the presence of a mega rectosigmoid (Fig. 358.3). Anorectal motility studies can demonstrate a pattern of paradoxical contraction of the external anal sphincter during defecation, which can be treated by behavior modification and biofeedback. Colonic motility can guide therapy in refractory cases, demonstrating segmental problems that might require surgical intervention.

Table 358.6

London Classification of Gastrointestinal Neuromuscular Pathology

- 1. Neuropathies
  - 1.1 Absent neurons
    - 1.1.1 Aganglionosis[*]
  - 1.2 Decreased numbers of neurons
    - 1.2.1 Hypoganglionosis
  - 1.3 Increased numbers of neurons
    - 1.3.1 Ganglioneuromatosis[†]
    - 1.3.2 IND, type B[‡]
  - 1.4 Degenerative neuropathy[§]
  - 1.5 Inflammatory neuropathies
    - 1.5.1 Lymphocytic ganglionitis[¶]
    - 1.5.2 Eosinophilic ganglionitis
  - 1.6 Abnormal content in neurons
    - 1.6.1 Intraneuronal nuclear inclusions
    - 1.6.2 Megamitochondria
  - 1.7 Abnormal neurochemical coding[**]
  - 1.8 Relative immaturity of neurons
  - 1.9 Abnormal enteric glia
    - 1.9.1 Increased numbers of enteric glia

- 2. Myopathies
  - 2.1 Muscularis propria malformations [††]
  - 2.2 Muscle cell degeneration
    - 2.2.1 Degenerative leiomyopathy/ [‡‡]
    - 2.2.2 Inflammatory leiomyopathy
      - 2.2.2.1 Lymphocytic leiomyositis
      - 2.2.2.2 Eosinophilic leiomyositis
  - 2.3 Muscle hyperplasia/hypertrophy
    - 2.3.1 Muscularis mucosae hyperplasia
  - 2.4 Abnormal content in myocytes
    - 2.4.1 Filament protein abnormalities
      - 2.4.1.1 Alpha-actin myopathy [§§]
      - 2.4.1.2 Desmin myopathy
    - 2.4.2 Inclusion bodies
      - 2.4.2.1 Polyglucosan bodies
      - 2.4.2.2 Amphophilic
      - 2.4.2.3 Megamitochondria [¶¶]
  - 2.5 Abnormal supportive tissue
    - 2.5.1 Atrophic desmosis[***]
- 3. ICC abnormalities (enteric mesenchymopathy)
  - 3.1 Abnormal ICC networks [†††]

[*] Can include rare cases of non-Hirschsprung disease severe hypoplastic hypoganglionosis with long interganglionic intervals (zonal aganglionosis).

[†] Although neurons have not been formally quantified, gross increases of disorganized neurons are evident.

[‡] Can include retarded neuronal maturation.

[§] May occur with or without neuronal loss but is best regarded as a separate entity.

[¶] May occur with neuronal degeneration and/or loss; lymphocytic epithelioganglionitis is a variant.

[**] Includes neurotransmitter loss (e.g., reduced or absent expression) or loss of a neurochemically defined functional subset of nerves (see text).

[††] Includes absence, fusion, or additional muscle coats.

[‡‡] Hollow visceral myopathy may be diagnosed in familial cases with other characteristic phenotypic features; myopathy with autophagic activity and pink blush myopathy with nuclear crowding are rare variants in which degenerative findings are less overt.

[§§] Smooth muscle alpha-actin deficiency is best described, although deficiencies of other proteins related to the contractile apparatus of myocytes have been reported.

[¶¶] Mitochondrial neurogastrointestinal encephalomyopathy causes a degenerative appearance predominantly in the longitudinal muscle.

[***] Absent connective tissue scaffold has been almost exclusively described in the colon.

[†††] Generally reduced or absent ICC, although abnormal morphology also reported.

ICC, interstitial cells of Cajal; IND, intestinal neuronal dysplasia.

From Knowles CH, De Giorgio R, Kapur RP, et al: The London classification of gastrointestinal neuromuscular pathology: report on behalf of the Gastro 2009 International Working Group, *Gut*

59:882–887, 2010, Table 1, p. 883.

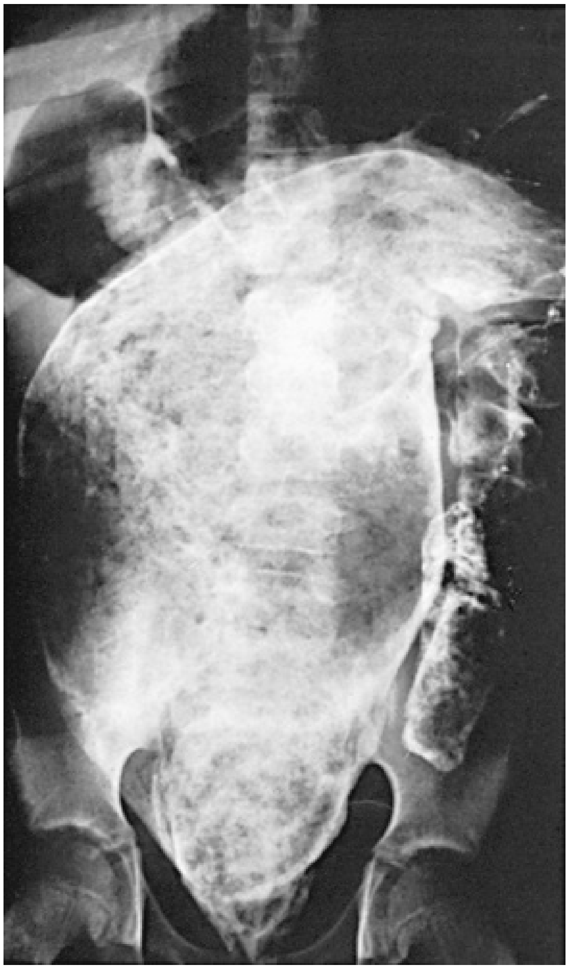

FIG. 358.3 Barium enema in a 14 yr old boy with severe constipation. The enormous dilation of the rectum and distal colon is typical of acquired functional megacolon.

Complications of retentive encopresis include day and night urinary incontinence, urinary retention, urinary tract infection, megacystis, and rarely toxic megacolon.

Treatment

Therapy for functional constipation and encopresis includes patient education, relief of impaction, and softening of the stool. Caregivers must understand that soiling associated with overflow incontinence is associated with loss of normal sensation and not a willful act. There needs to be a focus on adherence with regular postprandial toilet sitting and adoption of a balanced diet. In addition, caregivers should be instructed not to respond to soiling with retaliatory or punitive measures, because children are likely to become angry, ashamed, and resistant to intervention. From the outset, parents should be actively encouraged to reward the child for adherence to a healthy bowel regimen and to avoid power struggles.

If an impaction is present on the initial physical examination, an enema is usually required to clear the impaction while stool softeners are started as maintenance medications. Typical regimens include the use of polyethylene glycol preparations, lactulose, or mineral oil (Tables 358.7 and 358.8). Prolonged use of stimulants such as senna or bisacodyl should be avoided.

Table 358.7

Suggested Medications and Dosages for Disimpaction

MEDICATION	AGE	DOSAGE
RAPID RECTAL DISIMPACTION		
Glycerin suppositories	Infants and toddlers	
Phosphate enema	<1 yr	60 mL
	>1 yr	6 mL/kg body weight, up to 135 mL twice
SLOW ORAL DISIMPACTION IN OLDER CHILDREN		
Over 2-3 Days		
Polyethylene glycol with electrolytes		25 mL/kg body weight/hr, up to 1,000 mL/hr until clear fluid comes from the anus
Over 5-7 Days		
Polyethylene without electrolytes		1.5 g/kg body weight/day for 3 days
Milk of magnesia		2 mL/kg body weight twice/day for 7 days
Mineral oil		3 mL/kg body weight twice/day for 7 days
Lactulose or sorbitol		2 mL/kg body weight twice/day for 7 days

From Loening-Baucke V: Functional constipation with encopresis. In Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease* , ed 3, Philadelphia, 2006, WB Saunders, p. 183.

Table 358.8

Suggested Medications and Dosages for Maintenance Therapy of Constipation

MEDICATION	AGE	DOSE
TYPICAL DOSES FOR LONG-TERM TREATMENT (YEARS)		

Milk of magnesia	>1 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Mineral oil	>12 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Lactulose or sorbitol	>1 mo	1-3 mL/kg body weight/day, divided into 1-2 doses
Polyethylene glycol 3350 (MiraLAX)	>1 yr	0.7 g/kg body weight/day (max 17.5 g/day)
FOR SHORT-TERM TREATMENT (MONTHS)		
Senna (Senokot) syrup, tablets	1-5 yr	5 mL (1 tablet) with breakfast, max 15 mL daily
	5-15 yr	2 tablets with breakfast, maximum 3 tablets daily
Glycerin enemas	>10 yr	20-30 mL/day (½ glycerin and ½ normal saline)
Bisacodyl suppositories	>10 yr	10 mg daily

From Loening-Baucke V: Functional constipation with encopresis. In Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease* , ed 3, Philadelphia, 2006, WB Saunders, p. 185.

Compliance can wane, and failure of this standard treatment approach sometimes requires more intensive intervention. In cases where behavioral or psychiatric problems are evident, involvement of a psychologist or behavioral management (e.g., behavior programs and/or biofeedback) is recommended. Maintenance therapy is generally continued until a regular bowel pattern has been established and the association of pain with the passage of stool is abolished.

For children with chronic diarrhea and/or irritable bowel syndrome where stress and anxiety play a major role, stress reduction and learning effective coping strategies can play an important role in responding to the encopresis. Relaxation training, stress inoculation, assertiveness training, and/or general stress management procedures can be helpful, and the participation of behavioral health specialists is valuable.

Neurostimulation (transcutaneous or sacral implantation) and pelvic physiotherapy are novel approaches used in patients with medication refractory constipation. Children with spinal problems can be successfully managed with low volumes of fluid through a cecostomy or sigmoid tube.

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358.4

Congenital Aganglionic Megacolon (Hirschsprung Disease)

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Hirschsprung disease, or congenital aganglionic megacolon, is a developmental disorder (neurocristopathy) of the enteric nervous system, characterized by the absence of ganglion cells in the submucosal and myenteric plexus. It is the most common cause of lower intestinal obstruction in neonates, with an overall incidence of 1 in 5,000 live births. The male:female ratio for Hirschsprung disease is 4 : 1 for short-segment disease and approximately 2 : 1 with total colonic aganglionosis. Prematurity is uncommon.

There is an increased familial incidence in long-segment disease. Hirschsprung disease may be associated with other congenital defects, including trisomy 21, Joubert syndrome, Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, Shah-Waardenburg syndrome, cartilage-hair hypoplasia, multiple endocrine neoplasm 2 syndrome, neurofibromatosis, neuroblastoma, congenital hypoventilation (Ondine's curse), and urogenital or cardiovascular abnormalities. Hirschsprung disease has been seen in association with microcephaly, mental retardation, abnormal facies, autism, cleft palate, hydrocephalus, and micrognathia.

Pathology

Hirschsprung disease is the result of an absence of ganglion cells in the bowel wall, extending proximally and continuously from the anus for a variable distance. The absence of neural innervation is a consequence of an arrest of neuroblast migration from the proximal to distal bowel. Without the myenteric and submucosal plexus, there is inadequate relaxation of the bowel wall and bowel wall hypertonicity, which can lead to intestinal obstruction.

Hirschsprung disease is usually sporadic, although dominant and recessive patterns of inheritance have been demonstrated in family groups. Genetic defects have been identified in multiple genes that encode proteins of the RET signaling pathway (*RET, GDNF,* and *NTN*) and involved in the endothelin (EDN) type B receptor pathway (*EDNRB, EDN3,* and *EVE-1*). Syndromic forms of Hirschsprung disease have been associated with the *L1CAM, SOX10,* and *ZFHX1B* (formerly *SIP1*) genes.

The aganglionic segment is limited to the rectosigmoid in 80% of patients. Approximately 10–15% of patients have long-segment disease, defined as disease proximal to the sigmoid colon. Total bowel aganglionosis is rare and accounts for approximately 5% of cases. Observed histologically is an absence of Meissner's and Auerbach's plexuses and hypertrophied nerve bundles with high concentrations of acetylcholinesterase between the muscular layers and in the submucosa.

Clinical Manifestations

Hirschsprung disease is usually diagnosed in the neonatal period secondary to a distended abdomen, failure to pass meconium, and/or bilious emesis or aspirates with feeding intolerance. In 99% of healthy full-term infants, meconium is passed within 48 hr of birth. Hirschsprung disease should be suspected in any full-term infant (the disease is unusual in preterm infants) with delayed passage of stool. Some neonates pass meconium normally but subsequently present with a history of chronic constipation. Failure to thrive with hypoproteinemia from protein-losing enteropathy is a less common presentation because Hirschsprung disease is usually recognized early in the course of the illness but has been known to occur. Breastfed infants might not present as severely as formula-fed infants.

Failure to pass stool leads to dilation of the proximal bowel and abdominal distention. As the bowel dilates, intraluminal pressure increases, resulting in decreased blood flow and deterioration of the mucosal barrier. Stasis allows proliferation of bacteria, which can lead to enterocolitis (*Clostridium difficile, Staphylococcus aureus,* anaerobes, coliforms) with associated diarrhea, abdominal tenderness, sepsis, and signs of bowel obstruction. *Red flags* in the neonatal period then include neonatal intestinal obstruction, bowel perforation, delayed passage of meconium, abdominal distention relieved by digital rectal stimulation or enemas, chronic severe constipation, and enterocolitis. Early recognition of Hirschsprung disease before the onset of enterocolitis is essential in reducing morbidity and mortality.

Hirschsprung disease in older patients must be distinguished from other causes of abdominal distention and chronic constipation (see Tables 358.6 and 358.9 and Figs. 358.4 and 358.5). The history often reveals constipation starting in infancy that has responded poorly to medical management. Failure to thrive is not uncommon. Fecal incontinence, fecal urgency, and stool-withholding behaviors are usually not present. Significant abdominal distention is unusual in non-Hirschsprung related constipation, as is emesis. The abdomen is tympanitic and distended, with a large fecal mass palpable in the left lower abdomen. Rectal examination demonstrates a normally placed anus that easily allows entry of the finger but feels snug. The rectum is usually empty of feces, and when the finger is removed, there may be an explosive discharge of foul-smelling feces and gas. The stools, when passed, can consist of small pellets, be ribbon-like, or have a fluid consistency, unlike the large stools seen in patients with functional constipation. Intermittent attacks of intestinal obstruction from retained feces may be associated with pain and fever. Urinary retention with enlarged bladder or hydronephrosis can occur secondary to urinary compression.

Table 358.9

Distinguishing Features of Hirschsprung Disease and

Functional Constipation

VARIABLE	FUNCTIONAL	HIRSCHSPRUNG DISEASE
HISTORY		
Onset of constipation	After 2 yr of age	At birth
Encopresis	Common	Very rare
Failure to thrive	Uncommon	Possible
Enterocolitis	None	Possible
Forced bowel training	Usual	None
EXAMINATION		
Abdominal distention	Uncommon	Common
Poor weight gain	Rare	Common
Rectum	Filled with stool	Empty
Rectal examination	Stool in rectum	Explosive passage of stool
Malnutrition	None	Possible
INVESTIGATIONS		
Anorectal manometry	Relaxation of internal anal sphincter	Failure of internal anal sphincter relaxation
Rectal biopsy	Normal	No ganglion cells, increased acetylcholinesterase staining
Barium enema	Massive amounts of stool, no transition zone	Transition zone, delayed evacuation (>24 hr)

From Imseis E, Gariepy C: Hirschsprung disease. In Walker WA, Goulet OJ, Kleinman RE, et al, editors: *Pediatric gastrointestinal disease* , ed 4, Hamilton, ON, 2004, BC Decker, p. 1035.

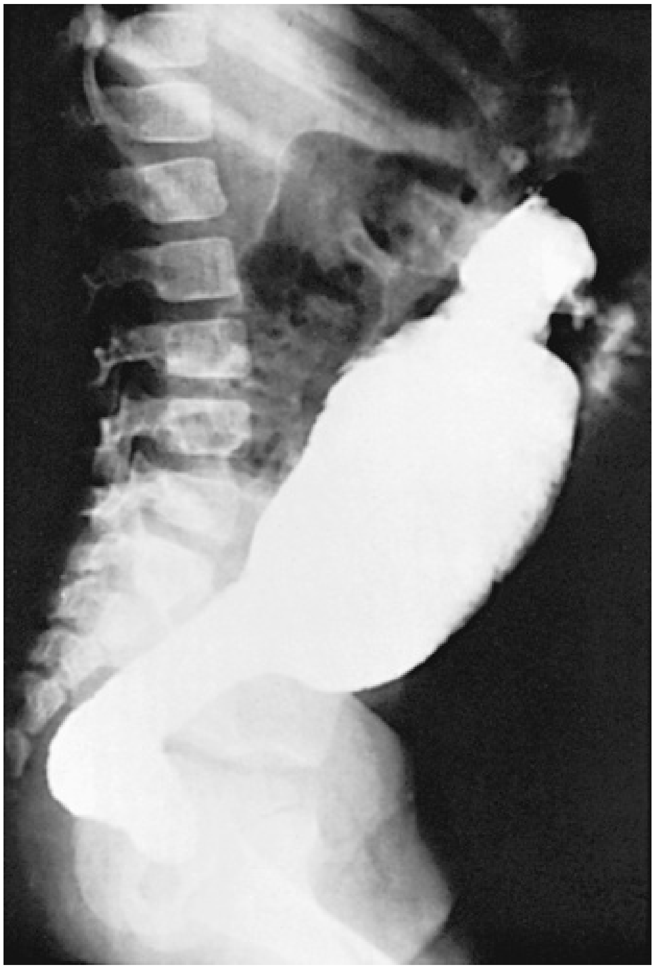

FIG. 358.4 Lateral view of a barium enema in a 3 yr old girl with Hirschsprung disease. The aganglionic distal segment is narrow, with distended normal ganglionic bowel above it.

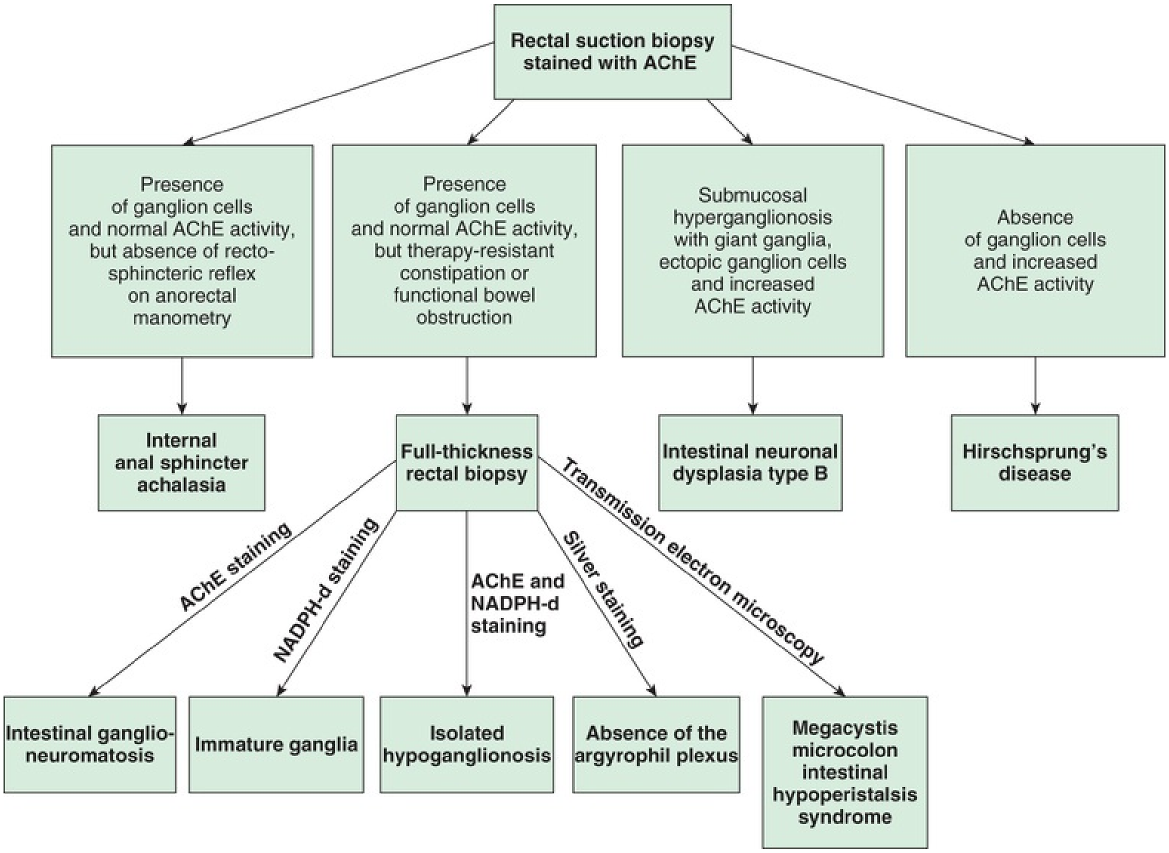
Rectal suction biopsy stained with AChE
Presence of ganglion cells and normal AChE activity, but absence of recto-sphincteric reflex on anorectal manometry
Presence of ganglion cells and normal AChE activity, but therapy-resistant constipation or functional bowel obstruction
Submucosal hyperganglionosis with giant ganglia, ectopic ganglion cells and increased AChE activity
Absence of ganglion cells and increased AChE activity
Internal anal sphincter achalasia
Full-thickness rectal biopsy
Intestinal neuronal dysplasia type B
Hirschsprung's disease
AChE staining
NADPH-d staining
AChE and NADPH-d staining
Silver staining
Transmission electron microscopy
Intestinal ganglio-neuromatosis
Immature ganglia
Isolated hypoganglionosis
Absence of the argyrophil plexus
Megacystis microcolon intestinal hypoperistalsis syndrome

FIG. 358.5 Diagnostic algorithm for investigating chronic constipation and functional bowel obstruction in newborn infants and young children. *AChE,* Acetylcholinesterase; *NADPH-d,* nicotinamide adenine dinucleotide phosphate diaphorase. (From Friedmacher F, Puri P: Classification and diagnostic criteria of variants of Hirschsprung's disease, *Pediatr Surg Int* 29:855–872, 2013, Fig. 1.)

In neonates, Hirschsprung disease must be differentiated from meconium plug syndrome, meconium ileus, and intestinal atresia. In older patients, the **Currarino triad** must be considered, which includes anorectal malformations (ectopic anus, anal stenosis, imperforate anus), sacral bone anomalies (hypoplasia, poor segmentation), and presacral anomaly (anterior meningoceles, teratoma, cyst).

Diagnosis

Rectal suction biopsy is the "gold standard" for diagnosing Hirschsprung disease (see Fig. 358.5). The biopsy material should contain an adequate amount of submucosa to evaluate for the presence of ganglion cells. To avoid obtaining biopsies in the normal area of hypoganglionosis, which ranges from 3 to 17 mm in length, the suction rectal biopsy should be obtained no closer than 2 cm above the dentate line. The biopsy specimen should be stained for acetylcholinesterase to facilitate interpretation. Patients with aganglionosis demonstrate a large number of hypertrophied nerve bundles that stain positively for acetylcholinesterase with an absence of ganglion cells. Calretinin staining may provide a diagnosis of Hirschsprung disease when acetylcholinesterase staining may not be sufficient.

Anorectal manometry evaluates the internal anal sphincter while a balloon is distended in the rectum. In healthy individuals, rectal distention initiates relaxation of the internal anal sphincter in response to rectal distention (known as the rectoanal inhibitory reflux [RAIR]). In patients with Hirschsprung disease, the internal anal sphincter fails to relax in response to rectal distention, and there is absence of the RAIR. Although the sensitivity and specificity can vary widely, in experienced hands, the test can be quite sensitive. However, the test can be technically difficult to perform in young infants. A normal response in the course of manometric evaluation precludes a diagnosis of Hirschsprung disease; an equivocal or paradoxical response requires a repeat motility or rectal biopsy. The sensitivity and specificity of anorectal manometry are both >90%.

An unprepared contrast enema is most likely to aid in the diagnosis in children older than 1 mo of age because the proximal ganglionic segment might not be significantly dilated in the first few wk of life. Classic findings are based on the presence of an abrupt narrow transition zone between the normal dilated proximal colon and a smaller-caliber obstructed distal aganglionic segment. In the absence of this finding, it is imperative to compare the diameter of the rectum to that of the sigmoid colon, because a rectal diameter that is the same as or smaller than the sigmoid colon suggests Hirschsprung disease. Radiologic evaluation should be performed without prior preparation (i.e., *unprepped contrast enema study*) to prevent transient dilation of the aganglionic segment. As many as 10% of newborns with Hirschsprung disease have a normal contrast study. This diagnostic test is most valuable in the disease that involves the distal colon, and specifically, the rectosigmoid. A transition zone may not be readily identifiable in total bowel aganglionosis. Twenty-four-hour delayed films are helpful in showing retained contrast (see Fig. 358.4). If significant barium is still present in the colon, it increases the suspicion of Hirschsprung disease even if a transition zone is not identified. Barium enema examination is useful in determining the extent of aganglionosis before surgery and in evaluating other diseases that manifest as lower bowel obstruction in a neonate. The sensitivity (~70%) and specificity (50–80%) of barium enema studies diagnosing

Hirschsprung disease is lower than other methodologies. Full-thickness rectal biopsies can be performed at the time of surgery to confirm the diagnosis, level of involvement and to differentiate other disorders (see Fig. 358.5).

Treatment

Once the diagnosis is established, the definitive treatment is operative intervention. Previously, a temporary ostomy was placed, and definitive surgery was delayed until the child was older. Currently, many infants undergo a primary pull-through procedure unless there is associated enterocolitis or other complications, when a decompressing ostomy is usually required.

There are essentially three surgical options. The first successful surgical procedure, described by Swenson, was to excise the aganglionic segment and anastomose the normal proximal bowel to the rectum 1-2 cm above the dentate line. The operation is technically difficult and led to the development of two other procedures. Duhamel described a procedure to create a neorectum, bringing down normally innervated bowel behind the aganglionic rectum. The neorectum created in this procedure has an anterior aganglionic segment with normal sensation and a posterior ganglionic segment with normal propulsion. The endorectal pull-through procedure described by Soave involves stripping the mucosa from the aganglionic rectum and bringing normally innervated colon through the residual muscular cuff, thus bypassing the abnormal bowel from within. Advances in techniques have led to successful laparoscopic single-stage endorectal pull-through procedures, which are the treatment of choice.

In **ultrashort-segment Hirschsprung disease** , also known as **anal achalasia** , the aganglionic segment is limited to the internal sphincter. The clinical symptoms are similar to those of children with functional constipation. Ganglion cells are present on rectal suction biopsy, but the anorectal manometry is abnormal, with failure of relaxation of the internal anal sphincter in response to rectal distention. Current treatment, although controversial, includes anal botulism injection to relax the anal sphincter and anorectal myectomy if indicated.

Long-segment Hirschsprung disease involving the entire colon and, at times, part of the small bowel presents a difficult problem. Anorectal manometry and rectal suction biopsy demonstrate findings of Hirschsprung disease, but radiologic studies are difficult to interpret because a colonic transition zone cannot be identified. The extent of aganglionosis can be determined accurately by biopsy at the time of laparotomy. When the entire colon is aganglionic, often together with a length of terminal ileum, ileal-anal anastomosis is the treatment of choice, preserving part of the aganglionic colon to facilitate water absorption, which helps the stools to become firm.

The prognosis of surgically treated Hirschsprung disease is generally satisfactory; the great majority of patients achieve fecal continence. Long-term postoperative problems include constipation, recurrent enterocolitis, stricture, prolapse, perianal abscesses, and fecal soiling. Some children require myectomy or a redo pull-through procedure.

Hirschsprung disease–associated **enterocolitis** can occur at any time prior to or following surgery and is the leading cause of death in these patients. Dysmotility related to partial obstruction, underlying disease, impaired immune function, and the intestinal microbiome may all contribute to this pathophysiologic process. Explosive, foul-smelling and/or bloody diarrhea, abdominal distention, explosive discharge of rectal contents on digital examination, diminished peripheral perfusion, lethargy, and fever are all ominous signs. Management principles include hydration, decompression from above and below (nasogastric Salem Sump, rectal tube, rectal irrigation), and the use of broad-spectrum antibiotics.

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358.5

Intestinal Neuronal Dysplasia

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Intestinal neuronal dysplasia (IND) describes different quantitative (hypoganglionosis or hyperganglionosis) and qualitative (immature or heterotropic ganglion cells) abnormalities of the myenteric and/or submucosal plexus. The typical histology is that of hyperganglionosis and giant ganglia. Type A occurs very rarely and is characterized by congenital aplasia or hypoplasia of the sympathetic innervation. Patients present early in the neonatal period with episodes of intestinal obstruction, diarrhea, and bloody stools. This type B, which accounts for more than 95% of cases, is characterized by malformation of the parasympathetic submucous and myenteric plexus with giant ganglia and thickened nerve fibers, increased acetylcholinesterase staining, and isolated ganglion cells in the lamina propria. IND type B mimics Hirschsprung disease, and patients present with chronic constipation (see Table

358.6 and Fig. 358.5). Clinical manifestations include abdominal distention, constipation, and enterocolitis. Various lengths of bowel may be affected from segmental to the entire intestinal tract. IND has been observed in an isolated form and proximal to an aganglionic segment. Other intraintestinal and extraintestinal manifestations are present in patients with IND. It has been reported in all age groups, most commonly in infancy, but is also seen in adults who have had constipation not dating back to childhood.

Associated diseases and conditions include Hirschsprung disease, prematurity, small left colon syndrome, and meconium plug syndrome. Studies have identified a deficiency in substance P in patients with IND. Type A IND may be inherited in a familial, autosomal recessive pattern. Most cases of IND type B are sporadic, with few familial clusters, suggesting autosomal dominant inheritance.

Management includes that for functional constipation, and, if unsuccessful, surgery is indicated.

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358.6

Superior Mesenteric Artery Syndrome (Wilkie Syndrome, Cast Syndrome, Arteriomesenteric Duodenal Compression Syndrome)

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Superior mesenteric artery syndrome results from compression of the third duodenal segment by the artery against the aorta. Malnutrition or catabolic states may cause mesenteric fat depletion, which collapses the duodenum within a narrowed aortomesenteric angle. Other etiologies include extraabdominal compression (e.g., body cast) and mesenteric tension, as can occur from ileoanal pouch anastomosis. Rapid weight loss and immobilization are risk factors.

Symptoms include intermittent epigastric pain, anorexia, nausea, and vomiting. Risk factors include thin body habitus, prolonged bed rest, abdominal surgery, and exaggerated lumbar lordosis. Onset can be within weeks of a trigger, but some patients have chronic symptoms that evade diagnosis. A classic example is an underweight adolescent who begins vomiting 1-2 wk following scoliosis surgery or spinal fusion. Recognition may be delayed in the context of an eating disorder.

The diagnosis is established radiologically by demonstrating a duodenal cutoff just right of midline along with proximal duodenal dilation, with or without gastric dilation. Although the upper gastrointestinal series remains a mainstay, modalities including CT, MR angiography, or ultrasound may be more appropriate if there is concern for other etiologies such as malignancy. Upper endoscopy should be considered to rule out intraluminal pathology.

Treatment focuses on obstructive relief, nutritional rehabilitation, and correction of associated fluid and electrolyte abnormalities. Lateral or prone positioning can shift the duodenum away from obstructing structures and allow resumption of oral intake. If repositioning is unsuccessful, patients require nasojejunal enteral nutrition past the obstruction or parenteral nutrition if this is not tolerated. This management is successful in the vast majority of cases, with eventual withdrawal of tube feeding once weight has been regained and enteral feeding tolerance orally has been gradually and fully restored. Patients with refractory courses may require surgery to bypass the obstruction.

Acknowledgment

Andrew Chu contributed to the previous version of this chapter.

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CHAPTER 359

Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions

359.1

Ileus

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Ileus is the failure of intestinal peristalsis caused by loss of coordinated gut motility without evidence of mechanical obstruction. In children, it is most often associated with abdominal surgery or infection (gastroenteritis, pneumonia, peritonitis). Ileus also accompanies metabolic abnormalities (e.g., uremia, hypokalemia, hypercalcemia, hypermagnesemia, acidosis) or administration of certain drugs, such as opiates, vincristine, and antimotility agents such as loperamide when used during gastroenteritis.

Ileus manifests with nausea, vomiting, feeding intolerance, abdominal distention with associated pain, and delayed passage of stool and bowel gas. Bowel sounds are minimal or absent, in contrast to early mechanical obstruction, when they are hyperactive. Abdominal radiographs demonstrate multiple air-fluid levels throughout the abdomen. Serial radiographs usually do not show progressive distention as they do in mechanical obstruction. Contrast radiographs, if performed, demonstrate slow movement of barium through a patent lumen. Ileus after abdominal surgery generally resolves in within 72 hr.

Treatment involves correcting the underlying abnormality, supportive care of comorbidities, and mitigation of iatrogenic contributions. Electrolyte abnormalities should be identified and corrected, and narcotic agents, when used, should be weaned as tolerated. Nasogastric decompression can relieve recurrent vomiting or abdominal distention associated with pain; resultant fluid losses should be corrected with isotonic crystalloid solution. Prokinetic agents such as erythromycin are not routinely recommended. Selective peripheral opioid antagonists such as methylnaltrexone hold promise in decreasing postoperative ileus, but pediatric data are lacking.

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359.2

Adhesions

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Adhesions are fibrous tissue bands that result from peritoneal injury. They can constrict hollow organs and are a major cause of postoperative small bowel obstruction. Most remain asymptomatic, but problems can arise any time after the 2nd postoperative wk to yr after surgery, regardless of surgical extent. In one study, the 5-yr readmission risk because of adhesions varied by operative region (2.1% for colon to 9.2% for ileum) and procedure (0.3% for appendectomy to 25% for ileostomy formation/closure). The overall risk was 5.3% excluding appendectomy and 1.1% when appendectomy was included.

The diagnosis is suspected in patients with abdominal pain, constipation, emesis, and a history of intraperitoneal surgery. Nausea and vomiting quickly follow onset of pain. Initially, bowel sounds are hyperactive, and the abdomen is flat. Subsequently, bowel sounds disappear, and bowel dilation can cause abdominal distention. Fever and leukocytosis suggest bowel necrosis and peritonitis. Plain radiographs demonstrate obstructive features, and a CT scan or contrast studies may be needed to define the etiology.

Management includes nasogastric decompression, intravenous fluid resuscitation, and broad-spectrum antibiotics in preparation for surgery. Nonoperative intervention is contraindicated unless a patient is stable with obvious clinical improvement. In children with repeated obstruction, fibrin-glued plication of adjacent small bowel loops can reduce the risk of recurrent problems. Long-term complications include female infertility, failure to thrive, and chronic abdominal and/or pelvic pain.

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Andrew Chu, MD contributed to the prior version of this chapter.

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359.3

Intussusception

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Intussusception occurs when a portion of the alimentary tract is telescoped into an adjacent segment. It is the most common cause of intestinal obstruction between 5 mo and 3 yr of age and the most common abdominal emergency in children younger than 2 yr of age. Sixty percent of patients are younger than 1 yr of age and 80% of the cases occur before age 24 mo; it is rare in neonates. The incidence varies from 1 to 4 per 1,000 live births. The male:female ratio is 3 : 1.

Many small bowel–small bowel and a few small bowel–colonic intussusceptions reduce spontaneously; if left untreated, ileal-colonic intussusception may lead to intestinal infarction, perforation, peritonitis, and death.

Etiology and Epidemiology

Approximately 90% of cases of intussusception in children are idiopathic. The seasonal incidence has peaks in fall and winter. Correlation with prior or concurrent respiratory adenovirus (type C) infection has been noted, and the condition can complicate otitis media, gastroenteritis, Henoch-Schönlein purpura, or other upper respiratory tract infections. A slight increase in intussusception has been noted to occur within 3 wk of the rotavirus vaccine (especially after the first dose), but this is a very rare side effect.

It is postulated that gastrointestinal infection or the introduction of new food proteins results in swollen Peyer patches in the terminal ileum. Lymphoid nodular hyperplasia is another related risk factor. Prominent mounds of lymph tissue lead to mucosal prolapse of the ileum into the colon, thus causing an intussusception. In 2–8% of patients, **recognizable lead points** for the intussusception are found, such as a Meckel diverticulum, intestinal polyp, neurofibroma, intestinal duplication cysts, inverted appendix stump, leiomyomas, hamartomas, ectopic pancreatic tissue, anastomotic suture line, enterostomy tube, posttransplant lymphoproliferative disease, hemangioma, or malignant conditions such as lymphoma or Kaposi sarcoma. Gastrojejunal and jejunostomy tubes can also serve as lead points for intussusception. Lead points are more common in children older than 2 yr of age; the older the child, the higher the risk of a lead point. In adults, lead points are present in 90%. Intussusception can complicate mucosal hemorrhage, as in Henoch-Schönlein purpura, idiopathic thrombocytopenic purpura, or hemophilia. Cystic fibrosis, celiac disease, and Crohn disease are other risk factors. Postoperative intussusception is ileoileal and usually occurs within several days of an abdominal operation. Anterograde intussusception may occur rarely following bariatric surgery with a Roux-en-Y gastric bypass and is noteworthy that there does not seem to be a *lead point* in these cases. Intrauterine intussusception may be associated with the development of intestinal atresia. Intussusception in premature infants is rare.

Ileal-ileal intussusception may be more common than previously believed, is often idiopathic or associated with Henoch-Schönlein purpura, and usually resolves spontaneously.

Pathology

Intussusceptions are most often ileocolic, less commonly cecocolic, and occasionally ileal. Very rarely, the appendix forms the apex of an intussusception. The upper portion of bowel, the **intussusceptum,** invaginates into the lower, the **intussuscipiens,** pulling its mesentery along with it into the enveloping loop. Constriction of the mesentery obstructs venous return; engorgement of the intussusceptum follows, with edema, and bleeding from the mucosa leads to a bloody stool, sometimes containing mucus. The apex of the intussusception can extend into the transverse, descending, or sigmoid colon, even to and through the anus in neglected cases. This presentation must be distinguished from rectal prolapse. Most intussusceptions do not strangulate the bowel within the first 24 hr but can eventuate in intestinal gangrene and shock.

Clinical Manifestations

In typical cases, there is sudden onset, in a previously well child, of severe paroxysmal colicky pain that recurs at frequent intervals and is accompanied by straining efforts with legs and knees flexed and loud cries. The infant may initially be comfortable and play normally between the paroxysms of pain, but if the intussusception is not reduced, the infant becomes progressively weaker and lethargic. At times, the **lethargy** is often disproportionate to the abdominal signs. With progression, a shock-like state, with fever and peritonitis, can develop. The pulse becomes weak and thready, the respirations become shallow and grunting, and the pain may be manifested only by moaning sounds. Vomiting occurs in most cases and is usually more frequent in the early phase. In the later phase, the vomitus becomes bile stained. Stools of normal appearance may be evacuated in the first few hr of symptoms. After this time, fecal excretions are small or more often do not occur, and little or no flatus is passed. Blood is generally passed in the first 12 hr but at times not for 1-2 days and infrequently not at all; 60% of infants pass a stool containing red blood and mucus, the currant jelly stool. Some patients have only irritability and alternating or progressive lethargy. The classic triad of pain, a palpable sausage-shaped abdominal mass, and bloody or currant jelly stool is seen in <30% of patients with intussusception. The combination of paroxysmal pain, vomiting, and a palpable abdominal mass has a positive predictive value of >90%; the presence of rectal bleeding increases this to approximately 100%.

Palpation of the abdomen usually reveals a slightly tender sausage-shaped mass, sometimes ill defined, which might increase in size and firmness during a paroxysm of pain and is most often in the right upper abdomen, with its long axis cephalocaudal. If it is felt in the epigastrium, the long axis is transverse. Approximately 30% of patients do not have a palpable mass. The presence of bloody mucus on rectal examination supports the diagnosis of intussusception. Abdominal distention and tenderness develop as intestinal obstruction becomes more acute. On rare occasions, the advancing intestine prolapses through the anus. *This prolapse can be distinguished from prolapse of the rectum by the separation between the protruding intestine and the rectal wall, which does not exist in prolapse of the rectum.*

Ileoileal intussusception in children younger than 2 yr can have a less-typical clinical picture, the symptoms and signs being chiefly those of small intestinal obstruction; these often resolve without treatment. **Recurrent intussusception** is noted in 5–8% and is more common after hydrostatic than surgical reduction. Chronic intussusception, in which the symptoms exist in milder form at recurrent intervals, is more likely to occur with or after acute enteritis and can arise in older children as well as in infants.

Diagnosis

When the clinical history and physical findings suggest intussusception, an ultrasound is typically performed. A plain abdominal radiograph might show a density in the area of the intussusception. Screening ultrasounds for suspected intussusception increases the yield of diagnostic or therapeutic enemas and reduces unnecessary radiation exposure in children with negative ultrasound examinations. The diagnostic findings of intussusception on ultrasound include a tubular mass in longitudinal views and a doughnut or target appearance in transverse images (Fig. 359.1). Ultrasound has a sensitivity of approximately 98–100% and a specificity of approximately 98% in diagnosing intussusception. Air, hydrostatic (saline), and, less often, water-soluble contrast enemas have replaced barium examinations. Contrast enemas demonstrate a filling defect or cupping in the head of the contrast media where its advance is obstructed by the intussusceptum (Fig. 359.2). A central linear column of contrast media may be visible in the compressed lumen of the intussusceptum, and a thin rim of contrast may be seen trapped around the invaginating intestine in the folds of mucosa within the intussuscipiens (coiled-spring sign), especially after evacuation. Retrogression of the intussusceptum under pressure and visualized on x-ray or ultrasound documents successful reduction. Air reduction is associated with fewer complications and lower radiation exposure than traditional contrast hydrostatic techniques.

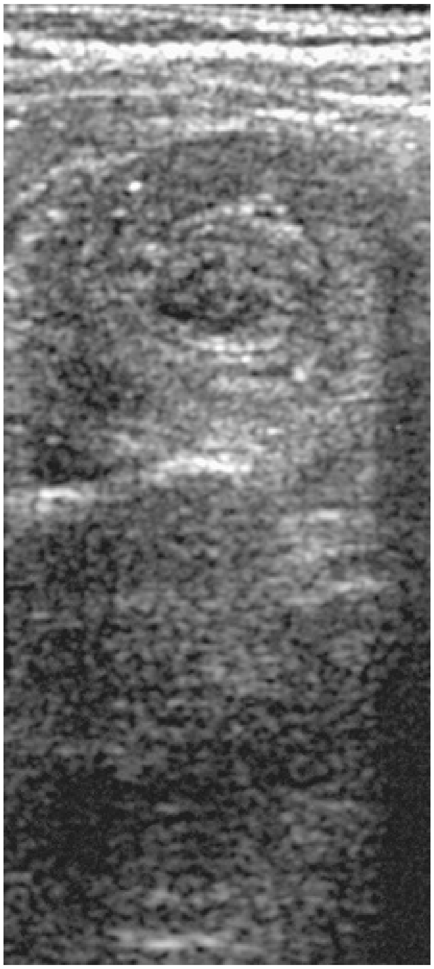

FIG. 359.1 Transverse image of an ileocolic intussusception. Note the loops within the loops of bowel.

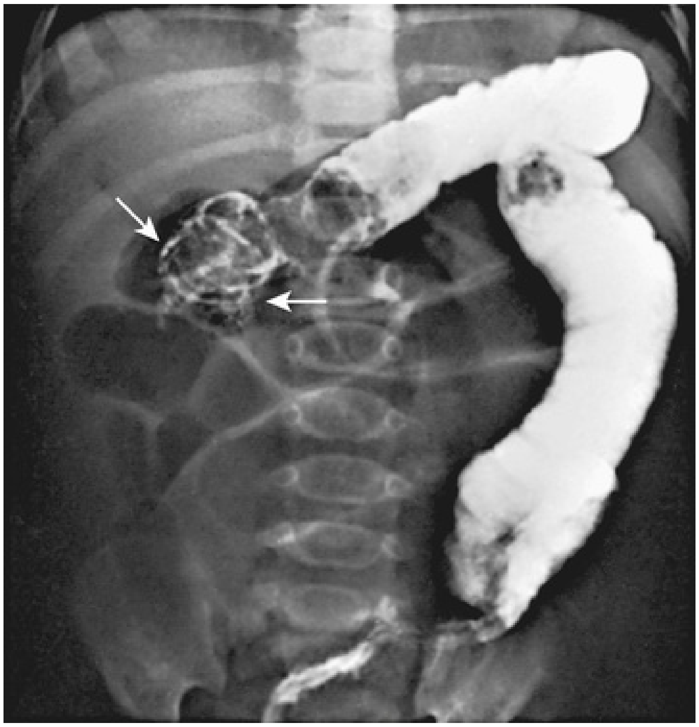

FIG. 359.2 Intussusception in an infant. The obstruction is evident in the proximal transverse colon. Contrast material between the intussusceptum and the intussuscipiens (arrows) is responsible for the coiled-spring appearance.

Differential Diagnosis

It may be particularly difficult to diagnose intussusception in a child who already has gastroenteritis; a change in the pattern of illness, in the character of pain, or in the nature of vomiting or the onset of rectal bleeding should alert the physician. The bloody stools and abdominal cramps that accompany enterocolitis can usually be differentiated from intussusception because in enterocolitis the pain is less severe and less regular, there is diarrhea, and the infant is recognizably ill between pains. Bleeding from a Meckel diverticulum is usually painless. Joint symptoms, purpura, or hematuria usually but not invariably accompany the intestinal hemorrhage of Henoch-Schönlein purpura. Because intussusception can be a complication of this disorder, ultrasonography may be needed to distinguish the conditions.

It is important in patients with cystic fibrosis to distinguish intussusception from distal intestinal obstruction syndrome. Distal intestinal obstruction syndrome requires antegrade treatment, which would be harmful if there was an intussusception.

Treatment

Reduction of an acute intussusception is an emergency procedure and should be performed immediately after diagnosis in preparation for possible surgery. In patients with prolonged intussusception and signs of shock, peritoneal irritation, intestinal perforation, or pneumatosis intestinalis, hydrostatic reduction should not be attempted.

The success rate of radiologic hydrostatic reduction under fluoroscopic or ultrasonic guidance is approximately 80–95% in patients with ileocolic intussusception. Spontaneous reduction of intussusception occurs in approximately 4–10% of patients. Bowel perforations occur in 0.5–2.5% of attempted barium and hydrostatic (saline) reductions. The perforation rate with air reduction is 0.1–0.2%. Surgical reduction is indicated in the presence of refractory shock, suspected bowel necrosis or perforation, peritonitis, and multiple recurrences (suspected lead point).

An **ileoileal intussusception** is best demonstrated by abdominal ultrasonography. Reduction by instillation of contrast agents, saline, or air might not be possible. Such intussusceptions can develop insidiously after bowel surgery and require reoperation if they do not spontaneously reduce. Ileoileal disease is common with Henoch-Schönlein purpura and other unidentifiable disorders and usually resolves without the need for any specific treatment. If manual operative reduction is impossible or the bowel is not viable, resection of the intussusception is necessary, with end-to-end anastomosis.

Prognosis

Untreated ileal-colonic intussusception in infants is usually fatal; the chances of recovery are directly related to the duration of intussusception before reduction. Most infants recover if the intussusception is reduced in the first 24 hr, but the mortality rate rises rapidly after this time, especially after the 2nd day. Spontaneous reduction during preparation for operation is not uncommon.

The **recurrence rate** after reduction of intussusceptions is approximately 10%, and after surgical reduction it is 2–5%; none has recurred after surgical resection. Most recurrences occur within 72 hr of reduction. Corticosteroids may reduce the frequency of recurrent intussusception but are rarely used for this purpose. Repeated reducible episodes caused by lymphonodular hyperplasia may respond to treatment of identifiable food allergies if present. A single recurrence of intussusception can usually be reduced radiologically. In patients with multiple ileal-colonic recurrences, a lead point should be suspected and laparoscopic surgery considered. It is unlikely that an intussusception caused by a lesion such as lymphosarcoma, polyp, or Meckel diverticulum will be successfully reduced by radiologic intervention. With adequate surgical management, laparoscopic reduction carries a very low mortality.

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359.4

Closed-Loop Obstructions

Asim Maqbool, Chris A Liacouras

Closed-loop obstructions (i.e., **internal hernia**) result from bowel loops that enter windows created by mesenteric defects or adhesions and become trapped. Vascular engorgement of the strangulated bowel results in intestinal ischemia and necrosis unless promptly relieved. Prior abdominal surgery is an important risk factor. Symptoms include abdominal pain, distention, and bilious emesis. Symptoms can be intermittent if the herniated bowel slides in and out of the defect. Peritoneal signs suggest ischemic bowel. Plain radiographs demonstrate signs of small bowel obstruction or free air if the bowel has perforated. CT scan can identify and delineate internal hernias. Supportive management includes intravenous fluids, antibiotics, and nasogastric decompression. Prompt surgical relief of the obstruction is indicated to prevent bowel necrosis.

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CHAPTER 360

Foreign Bodies and Bezoars

360.1

Foreign Bodies in the Stomach and Intestine

Asim Maqbool, Chris A. Liacouras

Once in the stomach, 95% of all ingested objects pass without difficulty through the remainder of the gastrointestinal tract. Perforation after ingestion of a foreign body is estimated to be <1% of all objects ingested. Perforation tends to occur in areas of physiologic sphincters (pylorus, ileocecal valve), acute angulation (duodenal sweep), congenital gut malformations (webs, diaphragms, diverticula), or areas of previous bowel surgery.

Most patients who ingest foreign bodies are between the ages of 6 mo and 6 yr. Coins are the most commonly ingested foreign body in children, and meat or food impactions are the most common accidental foreign body in adolescents and adults. Patients with nonfood foreign bodies often describe a history of ingestion. Young children might have a witness to ingestion. Immediate concerns are what the foreign body is, the location of the foreign body, the size of the foreign body, and the time that the ingestion occurred. Approximately 90% of foreign bodies are opaque. Radiologic examination is routinely performed to determine the type, number, and location of the suspected objects. Contrast radiographs may be necessary to demonstrate some objects, such as plastic parts or toys.

Conservative management is indicated for most foreign bodies that have passed through the esophagus and entered the stomach. Most objects pass though the intestine in 4-6 days, although some take as long as 3-4 wk. While waiting for the object to pass, parents are instructed to continue a regular diet and to observe the stools for the appearance of the ingested object. Cathartics should be avoided. Exceptionally long or sharp objects are usually monitored radiologically. Parents or patients should be instructed to report abdominal pain, vomiting, persistent fever, and hematemesis or melena immediately to their physicians. Failure of the object to progress within 3-4 wk seldom implies an impeding perforation but may be associated with a congenital malformation or acquired bowel abnormality.

Certain objects pose more risk than others. In cases of sharp foreign bodies, such as straight pins, weekly assessments are required. Surgical removal is necessary if the patient develops symptoms or signs of obstruction or perforation or if the foreign body fails to progress for several weeks. Small magnets used to secure earrings or parts of toys are associated with bowel perforation. Whereas a single magnet in the stomach may not require intervention in an asymptomatic child, a magnet in the esophagus requires immediate removal. When the *multiple* magnets disperse after ingestion, they may be attracted to each other across bowel walls, leading to pressure necrosis and perforation (Fig. 360.1). Inexpensive toy medallions containing lead can lead to **lead toxicity.** Newer coins can also decompose when subjected to prolonged acid exposure. Unless multiple coins are ingested, the metals released are unlikely to pose a clinical risk.

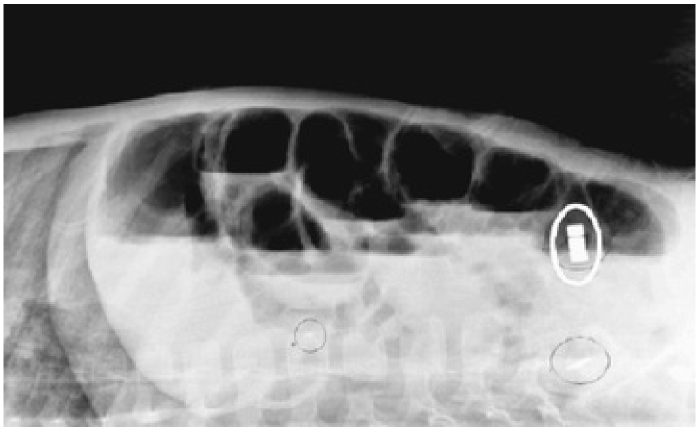

FIG. 360.1 Abdominal radiograph of a boy aged 3 yr, noting three attached magnets that resulted in volvulus (i.e., twisting of the bowel) and multiple

bowel perforations. (Courtesy U.S. Consumer Product Safety Commission. From Centers for Disease Control and Prevention: Gastrointestinal injuries from magnet ingestion in children—United States, 2003–2006. *MMWR Morb Mortal Wkly Rep* 55:1296–1300, 2006.)

Ingestion of batteries rarely leads to problems, but symptoms can arise from leakage of alkali or heavy metal (mercury) from battery degradation in the gastrointestinal tract. Batteries can also generate electrical current and thereby cause low-voltage electrical burns to the intestine. If patients experience symptoms such as vomiting or abdominal pain, if a large-diameter battery (>20 mm in diameter) remains in the stomach for longer than 48 hr, or if a lithium battery is ingested, the battery should be removed. Batteries larger than 15 mm that do not pass the pylorus within 48 hr are less likely to pass spontaneously and generally require removal. In children younger than 6 yr of age, batteries larger than 15 mm are not likely to pass spontaneously and should be removed endoscopically. If the patient develops peritoneal signs, surgical removal is required. Batteries beyond the duodenum pass per rectum in 85% within 72 hr. The battery should be identified by size and imprint code or by evaluation of a duplicate measurement of the battery compartment. The National Button Battery Ingestion Hotline (202-625-3333) can be called for help in identification. The Poison Control Center (800-222-1222) can be called as well for ingestion of batteries and caustic materials. Lithium batteries result in more severe injury than a button alkali battery, with damage occurring in minutes. Button batteries in a symptomatic child should be removed, or if there are multiple batteries, they should be removed.

In older children and adults, oval objects larger than 5 cm in diameter or 2 cm in thickness tend to lodge in the stomach and should be endoscopically retrieved. Thin long objects >6 cm in length fail to negotiate the pylorus or duodenal sweep and should also be removed. In infants and toddlers, objects >3 cm in length or >20 mm in diameter do not usually pass through the pylorus and should be removed. An open safety pin presents a major problem and requires urgent endoscopic removal if within reach. Razor blades can be managed with a rigid endoscope by pulling the blade into instrument. The endoscopist can alternatively use a rubber hood on the head of the endoscope to protect the esophagus. Other sharp objects (needles, bones, pins) usually pass the stomach, but complications may be as high as 35%; if possible, they should be removed by endoscope if in the stomach or proximal duodenum. If sharp objects are not able to be removed but no progress is observed in location during 3 days, surgical removal is indicated. Drugs (aggregated iron pills, cocaine) may have to be surgically removed; initial management can include oral polyethylene glycol lavage. Drug body packing (heroin, cocaine) is usually seen on kidneys-ureters-bladder or CT imaging and often passes without incident. Endoscopic procedures may rupture the material, causing severe toxicity. Surgery is indicated if toxicity develops, if the packages fail to progress, or if there are signs of obstruction.

Ingestion of magnets poses a danger to children. The number of magnets is thought to be critical. If a single magnet is ingested, there is the least likelihood of complications. If 2 or more magnets are ingested, the magnetic poles are attracted to each other and create the risk of obstruction, fistula development, and perforation. Endoscopic retrieval is emergent after films are taken when multiple magnets are ingested. Abdominal pain or peritoneal signs require urgent surgical intervention. If all magnets are located in the stomach, immediate endoscopic removal is indicated. If the ingestion occurred greater than 12 hr prior to evaluation, or if the magnets are beyond the stomach and the patient is symptomatic, general surgery should be consulted. If the patient is asymptomatic, endoscopic or colonoscopic removal may be considered, along with a surgical evaluation.

Lead-based foreign bodies can cause symptoms from lead intoxication. Early endoscopic removal is indicated of an object suspected to contain lead. A lead level should be obtained.

Water-absorbing polymer balls (beads) can expand to approximately 400 times their starting size and if ingested may produce intestinal obstruction. Initially of a small diameter, they pass the pylorus only to rapidly enlarge in the small intestine. Surgical removal is indicated.

Children occasionally place objects in their rectum. Small blunt objects usually pass spontaneously, but large or sharp objects typically need to be retrieved. Adequate sedation is essential to relax the anal sphincter before attempting endoscopic or speculum removal. If the object is proximal to the rectum, observation for 12-24 hr usually allows the object to descend into the rectum.

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360.2

Bezoars

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A bezoar is an accumulation of exogenous matter in the stomach or intestine. They are predominantly composed of food or fiber. Most bezoars have been found in females with underlying personality problems or in neurologically impaired persons. Patients who have undergone abdominal surgery are at higher risk for the development of bezoars. The peak age at onset of symptoms is the 2nd decade of life.

Bezoars are classified on the basis of their composition. **Trichobezoars** are composed of the patient's own hair. It is most frequently a complication of the psychiatric disorder trichotillomania, and the most severe form is known as Rapunzel syndrome (hair bezoar extending beyond the stomach to the small intestine). **Phytobezoars** are composed of a combination of plant and animal material, and gastric phytobezoars are the most common in patients with poor motility. **Lactobezoars** were previously found most often in premature infants and can be attributed to the high casein or calcium content of some premature formulas. Swallowed chewing gum can occasionally lead to a bezoar.

Trichobezoars can become large and form casts of the stomach; they can enter into the proximal duodenum. They manifest as symptoms of gastric outlet or partial intestinal obstruction, including vomiting, anorexia, and weight loss. Patients might complain of abdominal pain, distention, and severe halitosis. Physical examination can demonstrate patchy baldness and a firm mass in the left upper quadrant. Patients occasionally have iron-deficiency anemia, hypoproteinemia, or steatorrhea caused by an associated chronic gastritis. Phytobezoars manifest in a similar manner. Detached segments of the bezoar or trichobezoar can migrate to the small intestine as a “satellite masses” and result in small bowel obstruction.

An abdominal plain film can suggest the presence of a bezoar, which can be confirmed on ultrasound or CT examination. On CT a bezoar appears a nonhomogeneous, nonenhancing mass within the lumen of the stomach or intestine. Oral contrast circumscribes the mass.

Bezoars in the stomach can usually be removed endoscopically. If endoscopy is unsuccessful, surgical intervention may be needed. Lactobezoars usually resolve when feedings are withheld for 24-48 hr. Coca-Cola has been used as a dissolution therapy for gastric phytobezoar and has been shown to be effective when used with endoscopy. Trichobezoars almost always require surgical removal.

Sunflower seed bezoars are reported to cause rectal pain and constipation as a result of the seed shells being associated with fecal impaction. Endoscopic removal is indicated, as these bezoars are refractory to enema or lavage management.

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CHAPTER 361

Peptic Ulcer Disease in Children

Samra S. Blanchard, Steven J. Czinn

Peptic ulcer disease, resulting from inflammation caused by an imbalance between cytoprotective and cytotoxic factors in the stomach and duodenum, manifests with varying degrees of gastritis or frank ulceration. The pathogenesis of peptic ulcer disease is multifactorial, but the final common pathway for the development of ulcers is the action of acid and pepsin-laden contents of the stomach on the gastric and duodenal mucosa and the inability of mucosal defense mechanisms to allay those effects. Abnormalities in the gastric and duodenal mucosa can be visualized on endoscopy, with or without histologic changes. Deep mucosal lesions that disrupt the muscularis mucosa of the gastric or duodenal wall define **peptic ulcers.** Gastric ulcers are generally located on the lesser curvature of the stomach, and 90% of duodenal ulcers are found in the duodenal bulb. While there are no large population-based pediatric studies, rates of peptic ulcer disease in childhood appear to be low. Large pediatric centers anecdotally report an incidence of 5-7 children with gastric or duodenal ulcers per 2,500 hospital admissions each year.

Ulcers in children can be classified as **primary** peptic ulcers, which are chronic and more often duodenal, or **secondary,** which are usually more acute in onset and are more often gastric (Table 361.1). Primary ulcers are most often associated with *Helicobacter pylori* infection; idiopathic primary peptic ulcers account for up to 20% of duodenal ulcers in children. Secondary peptic ulcers can result from stress caused by sepsis, shock, or an intracranial lesion (Cushing ulcer), or in response to a severe burn injury (Curling ulcer). Secondary ulcers are often the result of using aspirin or nonsteroidal antiinflammatory drugs (NSAIDs); hypersecretory states like Zollinger-Ellison syndrome (see Chapter 361.1), short bowel syndrome, and systemic mastocytosis are rare causes of peptic ulceration.

Table 361.1

Etiologic Classification of Peptic Ulcers

- Positive for *Helicobacter pylori* infection
- Drug (NSAID)-induced
- *Helicobacter pylori* and NSAID-positive
- *H. pylori* and NSAID-negative*
- Acid hypersecretory state (Zollinger-Ellison syndrome)
- Anastomosis ulcer after subtotal gastric resection
- Tumors (cancer, lymphoma)
- Rare specific causes
- Crohn disease of the stomach or duodenum
- Eosinophilic gastroduodenitis
- Systemic mastocytosis
- Radiation damage
- Viral infections (cytomegalovirus or herpes simplex infection, particularly in immunocompromised patients)
- Colonization of stomach with *Helicobacter heilmannii*
- Severe systemic disease
- Cameron ulcer (gastric ulcer where a hiatal hernia passes through the diaphragmatic hiatus)
- True idiopathic ulcer

* Requires search for other specific causes. *NSAID,* nonsteroidal antiinflammatory drug. (From Vakil N, Megraud F: Eradication therapy for *Helicobacter pylori, Gastroenterology* 133:985–1001, 2007.)

Pathogenesis

Acid Secretion

By 3-4 yr of age, gastric acid secretion approximates adult values. Acid initially secreted by the oxyntic cells of the stomach has a pH of approximately 0.8, whereas the pH of the stomach contents is 1-2. Excessive acid secretion is associated with a large parietal cell mass, hypersecretion by antral G cells, and increased vagal tone, resulting in increased or sustained acid secretion in response to meals and increased secretion during the night. The secretagogues that promote gastric acid production include acetylcholine released by the vagus nerve, histamine secreted by enterochromaffin cells, and gastrin released by the G cells of the antrum. Mediators that decrease gastric acid secretion and enhance protective mucin production include prostaglandins.

Mucosal Defense

A continuous layer of mucous gel that serves as a diffusion barrier to hydrogen ions and other chemicals covers the gastrointestinal (GI) mucosa. Mucus production and secretion are stimulated by prostaglandin E_2 . Underlying the mucous coat, the epithelium forms a second-line barrier, the characteristics of which are determined by the biology of the epithelial cells and their tight junctions. Another important function of epithelial cells is to secrete chemokines when threatened by microbial attack. Secretion of bicarbonate into the mucous coat, which is regulated by prostaglandins, is important for neutralization of hydrogen ions. If mucosal injury occurs, active proliferation and migration of mucosal cells occurs rapidly, driven by epithelial growth factor, transforming growth factor-α, insulin-like growth factor, gastrin, and bombesin, and covers the area of epithelial damage.

Clinical Manifestations

The presenting symptoms of peptic ulcer disease vary with the age of the patient. Hematemesis or melena is reported in up to half of the patients with peptic ulcer disease. School-age children and adolescents more commonly present with epigastric pain and nausea, similar to the presentation generally seen in adults. Dyspepsia, epigastric abdominal pain, and fullness are also seen in older children. Infants and younger children usually present with feeding difficulty, vomiting, crying episodes, hematemesis, or melena. In the neonatal period, gastric perforation can be the initial presentation.

The classic symptom of peptic ulceration, epigastric pain alleviated by the ingestion of food, is present only in a minority of children. Many pediatric patients present with poorly localized abdominal pain, which may be periumbilical. The vast majority of patients with periumbilical or epigastric pain or discomfort do not have a peptic ulcer, but rather a functional GI disorder, such as irritable bowel syndrome or nonulcer (functional) dyspepsia. Patients with peptic ulceration rarely present with acute abdominal pain from perforation or symptoms and signs of pancreatitis from a posterior penetrating ulcer. Occasionally, bright red blood per rectum may be seen if the rate of bleeding is brisk and the intestinal transit time is short. Vomiting can be a sign of gastric outlet obstruction.

The pain is often described as dull or aching, rather than sharp or burning, as in adults. It can last from minutes to hours; patients have frequent exacerbations and remissions lasting from weeks to months. Nocturnal pain waking the child is common in older children. A history of typical ulcer pain with prompt relief after taking antacids is found in <33% of children. Rarely, in patients with acute or chronic blood loss, penetration of the ulcer into the abdominal cavity or adjacent organs produces shock, anemia, peritonitis, or pancreatitis. If inflammation and edema are extensive, acute or chronic gastric outlet obstruction can occur. *In a child with a normal diet for age, iron deficiency anemia may suggest peptic ulceration.* Other gastric causes of iron deficiency anemia include autoimmune gastritis, gastric hyperplasia, and possible Jervell and Lange-Nielson syndrome (*KCNQ1* mutations).

Diagnosis

Esophagogastroduodenoscopy is the method of choice to establish the diagnosis of peptic ulcer disease. It can be safely performed in all ages by experienced pediatric gastroenterologists. Endoscopy allows the direct visualization of esophagus, stomach, and duodenum, identifying the specific lesions. Biopsy specimens must be obtained from the esophagus, stomach, and duodenum for histologic assessment as well as to screen for the presence of *H. pylori* infection. Endoscopy also provides the opportunity for hemostatic therapy including clipping, injection, and the use of thermal coagulation.

Primary Ulcers

Helicobacter pylori Gastritis

H. pylori is among the most common bacterial infections in humans. *H. pylori* is a Gram-negative, S -shaped rod that produces urease, catalase, and oxidase, which might play a role in the pathogenesis of peptic ulcer disease. The mechanism of acquisition and transmission of *H. pylori* is unclear, although the most likely mode of transmission is fecal–oral or oral–oral. Viable *H. pylori* organisms can be cultured from the stool or vomitus of infected patients. Risk factors such as low socioeconomic status in childhood or affected family members also influence the prevalence. All children infected with *H. pylori* develop histologic chronic active gastritis but are often asymptomatic. In children, *H. pylori* infection can manifest with abdominal pain or vomiting and, less often, refractory iron deficiency anemia or growth retardation. *H. pylori* can be associated, though rarely, with chronic autoimmune thrombocytopenia.

Chronic colonization with *H. pylori* can predispose children to a significantly increased risk of developing a duodenal ulcer, gastric cancer such as adenocarcinoma, or mucosa-associated lymphoid tissue lymphomas. The relative risk of gastric carcinoma is 2.3-8.7 times greater in infected adults as compared to uninfected subjects. *H. pylori* is classified by the World Health Organization as a group I carcinogen.

Anemia, idiopathic thrombocytopenic purpura, short stature, and sudden infant death syndrome (SIDS) have also been reported as possible extragastric manifestations of *H. pylori* infection. In one published study, *H. pylori* infection has been correlated with cases of SIDS, but there is no evidence to suggest that *H. pylori* plays a role in the pathogenesis of SIDS.

The **diagnosis** of *H. pylori* infection is made histologically by demonstrating the organism in the biopsy specimens (Fig. 361.1). The most recent consensus report recommends against using antibody-based tests (IgG, IgA) for *H pylori* in serum, whole blood, urine, and saliva in the clinical setting.[13] C-urea breath tests and stool antigen tests are reliable noninvasive methods of detecting *H. pylori* infection in patients who do not require endoscopic evaluation. Patients should stop proton pump inhibitor (PPI) therapy 2 wk prior to testing as negative results on therapy may represent false negatives. Nonetheless, for symptomatic children with suspected *H. pylori* infection, an initial upper endoscopy is recommended to evaluate and confirm *H. pylori* disease. The range of endoscopic findings in children with *H. pylori* infection varies from being grossly normal to the presence of nonspecific gastritis with prominent rugal folds, nodularity (Fig. 361.2), or ulcers. Because the antral mucosa appears to be endoscopically normal in a significant number of children with primary *H. pylori* gastritis, gastric biopsies should always be obtained from the body and antrum of the stomach regardless of the endoscopic appearance. If *H. pylori* is identified, even in a child with no symptoms, eradication therapy should be offered (Tables 361.2 and 361.3). Successful *H pylori* eradication is associated with cure of peptic ulcer disease and very low risk of relapse. Therefore, monitoring the success of therapy is mandatory in these patients 4-6 wk after stopping antibiotics and at least 2 wk after stopping PPI therapy. Eradication can be tested with the 13C-urea breath (13C-UBT) test or stool antigen test. If there is an eradication failure, the patient should receive rescue therapy (Fig. 361.3). Because of a significant incidence of *H. pylori* resistance to clarithromycin, other treatment options are recommended if the community resistance rate is >15% or if it is unknown.

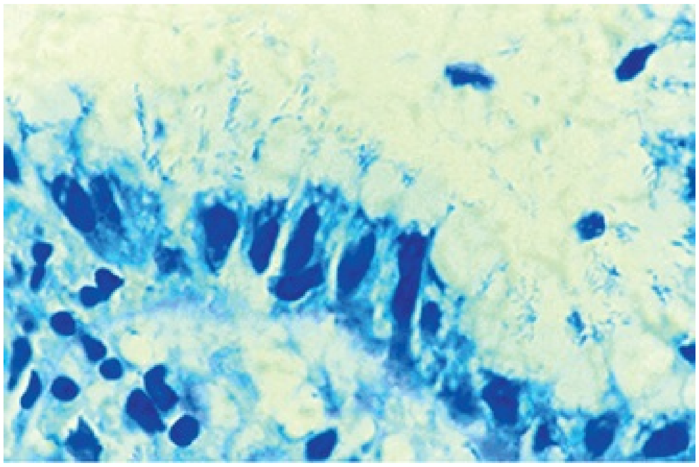

FIG. 361.1 Appearance of *Helicobacter pylori* on the gastric mucosal surface with Giemsa stain (high-power view). (From Campbell DI, Thomas JE: *Helicobacter pylori* infection in paediatric practice, *Arch Dis Child Educ Pract Ed* 90:ep25–ep30, 2005.)

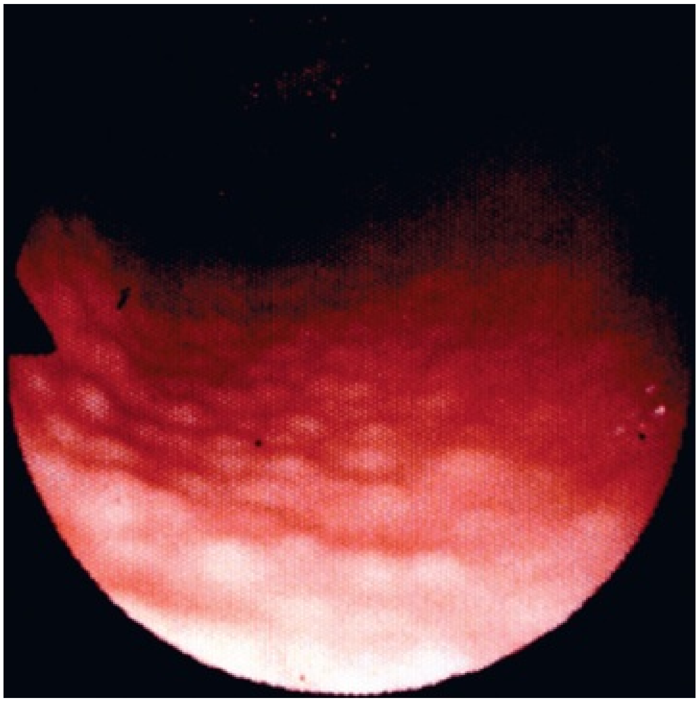

FIG. 361.2 Endoscopic view of lymphoid modular hyperplasia of the gastric antrum. (From Campbell DI, Thomas JE: *Helicobacter pylori* infection in paediatric practice, *Arch Dis Child Educ Pract Ed* 90:ep25–ep30, 2005.)

Table 361.2

Recommended Eradication Therapies for *Helicobacter pylori* –Associated Disease in Children

MEDICATIONS	DOSE		DURATION OF TREATMENT
Proton pump inhibitor	1 mg/kg/dose twice a day		1 mo
ANTIBIOTICS	**WEIGHT**	**DOSE**	**DURATION OF TREATMENT**
Amoxicillin	15-24 kg	500 mg twice a day	14 days
	25-34 kg	750 mg twice a day	
	>35 kg	1,000 mg twice a day	
Clarithromycin	15-24 kg	250 mg twice a day	14 days
	25-34 kg	500 mg in AM , 250 mg in PM	
	>35 kg	500 mg twice a day	
Metronidazole	15-24 kg	250 mg twice a day	14 days
	25-34 kg	500 mg in AM , 250 mg in PM	
	>35 kg	500 mg twice a day	

Depending on previous antibiotic use history, recommended combinations are Amoxicillin + Clarithromycin + PPI OR Amoxicillin + Metronidazole + PPI OR Clarithromycin + Metronidazole + PPI. (Modified from Jones NL, Koletzko S, Goodman K, et al: Joint ESPGHAN/NASPGHAN Guidelines for the Management of Helicobacter pylori in Children and Adolescents, *J Pediatr Gastroenterol Nutr* 64(6):991–1003, 2017.)

Table 361.3

Antisecretory Therapy With Pediatric Dosages

MEDICATION	PEDIATRIC DOSE	HOW SUPPLIED
H_2 RECEPTOR ANTAGONISTS		
Ranitidine	4-10 mg/kg/day Divided 2 or 3 × a day	Syrup: 75 mg/5 mL Tablets: 75, 150, 300 mg
Famotidine	1-2 mg/kg/day Divided twice a day	Syrup: 40 mg/5 mL Tablets: 20, 40 mg
Nizatidine	5-10 mg/kg/day divided twice a day Older than 12 yr: 150 mg twice a day	Solution: 15 mg/mL Capsule 150, 300 Tablet: 75 mg
PROTON PUMP INHIBITORS		
Omeprazole	1.0-3.3 mg/kg/day weigh < 20 kg: 10 mg/day weigh > 20 kg: 20 mg/day Approved for use in those older than 2 yr	Capsules: 10, 20, 40 mg
Lansoprazole	0.8-4 mg/kg/day weigh < 30 kg: 15 mg/day weigh > 30 kg: 30 mg/day Approved for use in those older than 1 yr	Capsules: 15, 30 mg Powder packet: 15, 30 mg SoluTab: 15, 30 mg
Rabeprazole	1-11 yr (weigh < 15 kg): 5 mg/day 1-11 yr (weigh > 15 kg): 10 mg/day >12 yr: 20 mg tablet	Delayed release capsule: 5, 10 mg Delayed release tablet: 20 mg
Pantoprazole	1-5 yr: 0.3-1.2 mg/kg/day (limited data) >5 yr of age:	Tablet: 20, 40 mg Powder pack: 40 mg

	weigh > 15 kg to < 40 kg: 20 mg/day weigh > 40 kg: 40 mg/day	
Esomeprazole	1 mo - < 1 yr old weigh 3 kg to 5 kg: 2.5 mg weigh > 5 kg to 7.5 kg: 5 mg weigh > 7.5 kg to 12 kg: 10 mg 1-11 yr old weigh < 20 kg: 10 mg weigh > 20 kg: 20 mg Approved for use 1 mo and older	Capsules: 20, 40 Delayed release single dose packs: 2.5, 5, 10, 20 mg
Dexlansoprazole	12-17 yr: 30-60 mg Approved for use in 12-17 yr	Capsules: 30, 60
Omeprazole sodium bicarbonate	Not approved for use < 18 yr at time of publication	Capsules: 20, 40 Powder for oral suspension: 20 mg, 40 mg
CYTOPROTECTIVE AGENTS		
Sucralfate	40-80 mg/kg/day	Suspension: 1,000 mg/5 mL Tablet: 1,000 mg

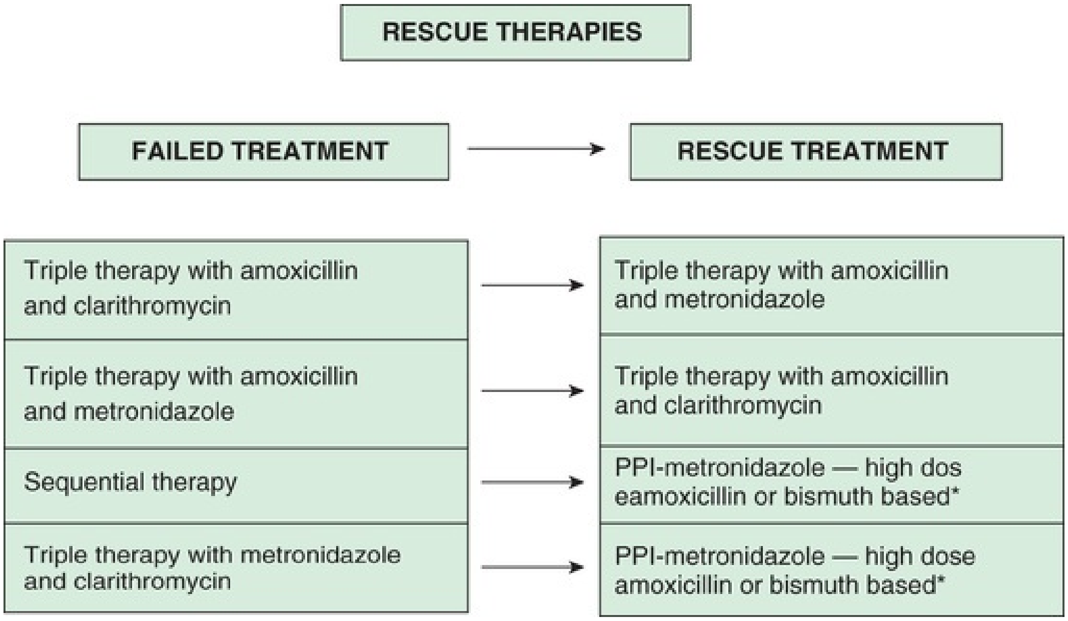
RESCUE THERAPIES
FAILED TREATMENT
RESCUE TREATMENT
Triple therapy with amoxicillin and clarithromycin
Triple therapy with amoxicillin and metronidazole
Triple therapy with amoxicillin and metronidazole
Triple therapy with amoxicillin and clarithromycin
Sequential therapy
PPI-metronidazole — high dos eamoxicillin or bismuth based*
Triple therapy with metronidazole and clarithromycin
PPI-metronidazole — high dose amoxicillin or bismuth based*

FIG. 361.3 Rescue therapy for failed eradication of *H. pylori* . *Bismuth-based therapy with tetracycline instead of amoxicillin if patients >8 yr. Bismuth dose is 262 mg four times a day for patients 8–10 yr and 524 mg four times a day for those >10 yr. (See Tables 361.2 and 361.3 .) In adolescents, levofloxacin or tetracycline can be considered. High-dose amoxicillin ranges from 750 mg twice a day for body weight 15–24 kg, 1000 mg twice a day for 25–34 kg, and 1500 mg twice a day for >35 kg. (Adapted from Jones NL, Koletzko S, Goodman K, et al: Joint ESPGHAN/NASPGHAN guidelines for the management of *Helicobacter pylori* in children and adolescents, *J Pediatr Gastroenterol Nutr* 64:991–1003, 2017.)

Idiopathic Ulcers

H. pylori –negative peptic ulcers in children who have no history of taking NSAIDs represent 15–20% of pediatric peptic ulcers. The pathogenesis of idiopathic ulcer remains uncertain. These patients do not have nodularity in the gastric antrum or histologic evidence of gastritis. In idiopathic ulcers, acid suppression *alone* is the preferred effective treatment. Either PPIs or H_2 receptor antagonists may be used. Idiopathic ulcers have a high recurrence rate after discontinuing antisecretory therapy. These children should be followed closely, and if symptoms recur, antisecretory therapy should be restarted. It is also important to consider uncommon but possible conditions like Crohn disease, cytomegalovirus (CMV), and Zollinger-Ellison syndrome.

Secondary Ulcers

Aspirin and Other Nonsteroidal Antiinflammatory Drugs

NSAIDs produce mucosal injury by direct local irritation and by inhibiting cyclooxygenase (COX) and prostaglandin formation. Prostaglandins enhance mucosal resistance to injury; therefore a decrease in prostaglandin production increases the risk of mucosal injury. The severe erosive gastropathy produced by NSAIDs can ultimately result in bleeding ulcers or gastric perforations. The location of these ulcers is more common in the stomach than in the duodenum, and usually in the antrum. Use of COX-2-selective NSAIDs can also cause ulcerations in the GI tract.

“Stress” Ulceration

Stress ulceration usually occurs within 24 hr of onset of a critical illness in which physiologic stress is present. In many cases, the patients bleed from gastric erosions, rather than ulcers. Approximately 25% of the critically ill children in a pediatric intensive care unit have macroscopic evidence of gastric bleeding. Preterm and term infants in the neonatal intensive care unit can also develop gastric mucosal lesions and can present with upper GI bleeding or perforated ulcers. Although prophylactic measures to prevent stress ulcers in children are not standardized, drugs that inhibit gastric acid production are often used in the pediatric intensive care unit to reduce the rate of gastric erosions or ulcers.

Treatment

The management of acute hemorrhage includes serial monitoring of pulse, blood pressure, and hematocrit to ensure hemodynamic stability and avoid significant hypovolemia and anemia. Normal saline can be used to resuscitate a patient who has poor intravascular volume status. This can be followed by packed red blood cell transfusions for significant symptomatic anemia. The patient's blood should be typed and cross matched, and a large-bore catheter should be placed for fluid or blood replacement. A nasogastric tube should be placed to determine if the bleeding has stopped. Significant anemia can occur after fluid resuscitation as a consequence of equilibration or continued blood loss (which can also cause shock). In adults, a conservative threshold for transfusion (<7 g/dL vs. 9 g hemoglobin) resulted in improved survival and fewer episodes of rebleeding. Fortunately, most acute peptic ulcer bleeding stops spontaneously.

Patients with suspected peptic ulcer hemorrhage should receive high-dose intravenous (IV) PPI therapy, which lowers the risk of rebleeding. Some centers also use octreotide, which lowers splanchnic blood flow and gastric acid production; others use a prokinetic agent to improve endoscopic visualization.

Once the patient is hemodynamically stable, endoscopy within 24 hr is indicated to identify the source of bleeding and to treat a potential bleeding site. Methods used to achieve hemostasis include mechanical devices (clipping), injection therapy (diluted epinephrine 1:10,000), and thermal therapy (heater probe). Ulcer therapy has two goals: ulcer healing and elimination of the primary cause. Other important considerations are relief of symptoms and prevention of complications. The first-line drugs for the treatment of gastritis and peptic ulcer disease in children are PPIs and H_2 receptor antagonists (see Table 361.3). PPIs are more potent in ulcer healing. Cytoprotective agents can also be used as adjunct therapy if mucosal lesions are present. Antibiotics in combination with a PPI must be used for the treatment of *H. pylori* -associated ulcers (see Table 361.2 and Fig. 361.3).

H_2 -receptor antagonists (ranitidine, famotidine, nizatidine) competitively inhibit the binding of histamine at the H_2 subtype receptor of the gastric parietal cell. PPIs block the gastric parietal cell H^+ /K^+ –adenosine triphosphatase pump in a dose-dependent fashion, reducing basal and stimulated gastric acid secretion. Seven PPIs are available in the United States: omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, dexlansoprazole, and omeprazole/sodium bicarbonate. Apart from the last 2, they are all approved in children and adolescents. They are well tolerated with only minor adverse effects, such as diarrhea (1–4%), headache (1–3%), and nausea (1%). When one considers therapeutic efficacy, the evidence suggests that all PPIs have comparable efficacy in treatment of peptic ulcer disease using standard doses and are superior to H_2 -receptor antagonists. PPIs have their greatest effect when given before a meal. Pantoprazole and esomeprazole are the only PPI available in IV form in United States. IV PPI should be used in acute upper GI bleeding. Twice-a-day IV PPI is as effective as continuous infusion and the current recommendation is to start with IV PPI and change to the oral form after evaluating their rebleeding risk at the time of endoscopy. Long-term PPI therapy may result in hypomagnesemia and the risk of QT prolongation, as well as vitamin B12 and iron deficiencies and small bowel bacterial overgrowth. Conflicting results from multiple studies suggest a possible increased risk of community-acquired and ventilator-associated pneumonias as well as *Clostridium difficile* infection.

Treatment of *Helicobacter pylori* –Related Peptic Ulcer Disease

In pediatrics, antibiotics and bismuth salts have been used in combination with PPIs to treat H. pylori infection (see Table 361.2). Eradication rates in children range from 68 to 92% when the dual or triple therapy is used for 4-6 wk. The ulcer healing rate ranges from 91 to 100%. Triple therapy yields a higher cure rate than dual therapy. The optimal regimen for the eradication of *H. pylori* infection in children has yet to be established, but the use of a PPI in combination with clarithromycin and amoxicillin or metronidazole for 2 wk is a well-tolerated and recommended triple therapy (see Table 361.2). Although children younger than 5 yr of age can become reinfected, the most common reason for treatment failure is poor compliance or antibiotic resistance. *H. pylori* has become more resistant to clarithromycin or metronidazole because of the extensive use of these antibiotics for other infections. In the case of resistant *H. pylori* infection, sequential treatment or rescue therapy with different antibiotics are acceptable options (see Fig. 361.3). The sequential treatment regimen is a 10-day treatment consisting of a PPI and amoxicillin (both twice daily) administered for the first 5 days followed by triple therapy consisting of a PPI, clarithromycin, and metronidazole for the remaining 5 days. Levofloxacin, rifabutin, or furazolidone can be used with amoxicillin and bismuth as a rescue therapy depending on the age of the patient. Knowledge of the community's *H. pylori* resistance pattern to clarithromycin or metronidazole might help choose the initial or rescue therapy; if it is unknown, one should assume resistance.

Surgical Therapy

Since the discovery of *H. pylori* and the availability of modern medical management, peptic ulcer disease requiring surgical treatment has become extremely rare. The indications for surgery remain uncontrolled bleeding, perforation, and obstruction. Since the introduction of H_2 -receptor antagonists, the recognition and treatment of *H. pylori,* and the use of PPIs, the incidence of surgery for bleeding and perforation has decreased dramatically.

361.1

Zollinger-Ellison Syndrome

Samra S. Blanchard, Steven J. Czinn

Zollinger-Ellison syndrome is a rare syndrome characterized by refractory, severe peptic ulcer disease caused by gastric hypersecretion due to the autonomous secretion of gastrin by a neuroendocrine tumor, a gastrinoma. Clinical presentations are similar to those of peptic ulcer disease with the addition of diarrhea. The diagnosis is suspected by the presence of recurrent, multiple, or atypically located ulcers. More than 98% of patients have elevated fasting gastrin levels. Zollinger-Ellison syndrome is common in patients with

multiple endocrine neoplasia 1 and rare with **neurofibromatosis** and **tuberous sclerosis** . Prompt and effective management of increased gastric acid secretion is essential in the management. **PPIs are the drug of choice due to their long duration of action and potency.** H_2 -receptor antagonists are also effective, but higher doses are required than those used in peptic ulcer disease.

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CHAPTER 362

Inflammatory Bowel Disease

Ronen E. Stein, Robert N. Baldassano

The term *inflammatory bowel disease* (IBD) is used to represent 2 distinctive disorders of idiopathic chronic intestinal inflammation: Crohn disease and ulcerative colitis. Their respective etiologies are poorly understood, and both disorders are characterized by unpredictable exacerbations and remissions. The most common time of onset of IBD is during the preadolescent/adolescent era and young adulthood. A bimodal distribution has been shown with an early onset at 10-20 yr of age and a second, smaller peak at 50-80 yr of age. Approximately 25% of patients present before 20 yr of age. IBD may begin as early as the 1st yr of life, and an increased incidence among young children has been observed since the turn of the 20th century. Children with early-onset IBD are more likely to have colonic involvement. In developed countries, these disorders are the major causes of chronic intestinal inflammation in children beyond the first few yr of life. A third, less-common category, *indeterminate colitis* , represents approximately 10% of pediatric patients.

Genetic and environmental influences are involved in the pathogenesis of IBD. The prevalence of Crohn disease in the United States is much lower for Hispanics and Asians than for whites and blacks. The risk of IBD in family members of an affected person has been reported in the range of 7–30%; a child whose parents both have IBD has a >35% chance of acquiring the disorder. Relatives of a patient with ulcerative colitis have a greater risk of acquiring ulcerative colitis than Crohn disease, whereas relatives of a patient with Crohn disease have a greater risk of acquiring this disorder; the 2 diseases can occur in the same family. The risk of occurrence of IBD among relatives of patients with Crohn disease is somewhat greater than for patients with ulcerative colitis.

The importance of genetic factors in the development of IBD is noted by a higher chance that both twins will be affected if they are monozygotic rather than dizygotic. The concordance rate in twins is higher in Crohn disease (36%) than in ulcerative colitis (16%). Genetic disorders that have been associated with IBD include Turner syndrome, the Hermansky-Pudlak syndrome, glycogen storage disease type Ib, and various immunodeficiency disorders. In 2001, the first IBD gene, *NOD2*, was identified through association mapping. A few months later, the IBD 5 risk haplotype was identified. These early successes were followed by a long period without notable risk factor discovery. Since 2006, the year of the first published genome-wide array study on IBD, there has been an exponential growth in the set of validated genetic risk factors for IBD (Table 362.1).

Table 362.1

Selection of Most Important Genes Associated With Inflammatory Bowel Disease and the Most Commonly Associated Physiological Functions and Pathways

	GENE NAME	ASSOCIATED DISEASE	GENE FUNCTION AND ASSOCIATED PATHWAYS	PHYSIOLOGICAL FUNCTION
NOD2	Nucleotide-binding oligomerization domain-containing protein 2	Crohn disease	Bacterial recognition and response, NFκB activation and autophagy and apoptosis	Innate mucosal defense
IL10	Interleukin 10	Crohn disease	Antiinflammatory cytokine, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL10RA	Interleukin 10 receptor A	Crohn disease	Antiinflammatory cytokine receptor, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL10RB	Interleukin 10 receptor B	Crohn disease	Antiinflammatory cytokine receptor, NFκB inhibition, JAK-STAT regulation	Immune tolerance
IL23R	Interleukin 23 receptor	Crohn disease and ulcerative colitis	Immune regulation, proinflammatory pathways—JAK-STAT regulation	Interleukin 23/T helper 17
TKY2	Tyrosine kinase 2	Crohn disease and ulcerative colitis	Inflammatory pathway signaling (interleukin 10 and 6 etc) through intracellular activity	Interleukin 23/T helper 17
IRGM	Immunity related GTPase M	Crohn disease	Autophagy and apoptosis in cells infected with bacteria	Autophagy
ATG16L1	Autophagy related 16 like 1	Crohn disease	Autophagy and apoptotic pathways	Autophagy
SLC22A4	Solute carrier family 22 member 4	Crohn disease	Cellular antioxidant transporter	Solute transporters
CCL2	C-C motif chemokine ligand 2	Crohn disease	Cytokine involved in chemotaxis for monocytes	Immune cell recruitment
CARD9	Caspase recruitment domain family member 9	Crohn disease and ulcerative colitis	Apoptosis regulation and NFκB pathway activation	Oxidative stress

IL2	Interleukin 2	Ulcerative colitis	Cytokine involved in immune cell activation	T-cell regulation
MUC19	Mucin 19	Crohn disease and ulcerative colitis	Gel-forming mucin protein	Epithelial barrier

JAK-STAT, Janus kinase-signal transducers and activators of transcription; *NFκB,* nuclear factor κ-light chain enhancer of activated B cells.

From Ashton JJ, Ennis S, Beattie RM: Early-onset paediatric inflammatory bowel disease, *Lancet* 1:147–158, 2017, Table 1, p 148.

A perinuclear antineutrophil cytoplasmic antibody is found in approximately 70% of patients with ulcerative colitis compared with <20% of those with Crohn disease and is believed to represent a marker of genetically controlled immunoregulatory disturbance. Approximately 55% of those with Crohn disease are positive for anti–*Saccharomyces cerevisiae* antibody. Since the importance of these were first described, multiple other serologic and immune markers of Crohn disease and ulcerative colitis have been recognized.

IBD is caused by dysregulated or inappropriate immune response to environmental factors in a genetically susceptible host. An abnormality in intestinal mucosal immunoregulation may be of primary importance in the pathogenesis of IBD, involving activation of cytokines, triggering a cascade of reactions that results in bowel inflammation. These cytokines are recognized as known or potential targets for IBD therapies.

Multiple environmental factors are recognized to be involved in the pathogenesis of IBD, none more critical than the gut microbiota. The increasing incidence of IBD over time is likely in part attributable to alterations in the microbiome. Evidence includes association between IBD and residence in or immigration to industrialized nations, a *Western diet* , increased use of antibiotics at a younger age, high rates of vaccination, and less exposure to microbes at a young age. While gut microbes likely play an important role in the pathogenesis of IBD, the exact mechanism needs to be elucidated further. Some environmental factors are disease specific; for example, cigarette smoking is a risk factor for Crohn disease but paradoxically protects against ulcerative colitis.

It is usually possible to distinguish between ulcerative colitis and Crohn disease by the clinical presentation and radiologic, endoscopic, and histopathologic findings (Table 362.2). It is not possible to make a definitive diagnosis in approximately 10% of patients with chronic colitis; this disorder is called *indeterminate colitis*. Occasionally, a child initially believed to have ulcerative colitis on the basis of clinical findings is subsequently found to have Crohn colitis. This is particularly true for the youngest patients, because Crohn disease in this patient population can more often manifest as exclusively colonic inflammation, mimicking ulcerative colitis. The medical treatments of Crohn disease and ulcerative colitis overlap.

Table 362.2

Comparison of Crohn Disease and Ulcerative Colitis

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Rectal bleeding	Sometimes	Common
Diarrhea, mucus, pus	Variable	Common
Abdominal pain	Common	Variable
Abdominal mass	Common	Not present
Growth failure	Common	Variable
Perianal disease	Common	Rare
Rectal involvement	Occasional	Universal
Pyoderma gangrenosum	Rare	Present
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Thrombosis	Less common	Present
Colonic disease	50–75%	100%
Ileal disease	Common	None except backwash ileitis
Stomach–esophageal disease	More common	Chronic gastritis can be seen
Strictures	Common	Rare
Fissures	Common	Rare
Fistulas	Common	Rare
Toxic megacolon	None	Present
Sclerosing cholangitis	Less common	Present
Risk for intestinal cancers	Increased	Greatly increased
Discontinuous (skip) lesions	Common	Not present
Transmural involvement	Common	Unusual
Crypt abscesses	Less common	Common
Granulomas	Common	None
Linear ulcerations	Uncommon	Common
Perinuclear antineutrophil cytoplasmic antibody–positive	<20%	70%

Extraintestinal manifestations occur slightly more commonly with Crohn disease than with ulcerative colitis (Table 362.3). Growth retardation is seen in 15–40% of children with Crohn disease at diagnosis. Decrease in height velocity occurs in nearly 90% of patients with Crohn disease diagnosed in childhood or adolescence. Of the extraintestinal manifestations that occur with IBD, joint, skin, eye, mouth, and hepatobiliary involvement tend to be associated with colitis, whether ulcerative or Crohn. The presence of some manifestations, such as peripheral arthritis, erythema nodosum, and anemia, correlates with activity of the bowel disease. Activity of pyoderma gangrenosum correlates less well with activity of the bowel disease, whereas sclerosing cholangitis, ankylosing spondylitis, and sacroiliitis do not correlate with intestinal disease. Arthritis occurs in 3 patterns: migratory peripheral arthritis involving primarily large joints, ankylosing spondylitis, and sacroiliitis. The peripheral arthritis of IBD tends to be nondestructive. Ankylosing spondylitis begins in the 3rd decade and occurs most commonly in patients with ulcerative colitis who have the human leukocyte antigen B27 phenotype. Symptoms include low back pain and morning stiffness; back, hips, shoulders, and sacroiliac joints are typically affected. Isolated sacroiliitis is usually asymptomatic but is common when a careful search is performed. Among the skin manifestations, erythema nodosum is most common. Patients with erythema nodosum or pyoderma gangrenosum have a high likelihood of having arthritis as well. Glomerulonephritis, uveitis, and a hypercoagulable state are other rare manifestations that occur in childhood. Cerebral thromboembolic disease has been described in children with IBD.

Table 362.3

Extraintestinal Complications of Inflammatory Bowel Disease

MUSCULOSKELETAL
Peripheral arthritis Granulomatous monoarthritis Granulomatous synovitis Rheumatoid arthritis Sacroiliitis Ankylosing spondylitis Digital clubbing and hypertrophic osteoarthropathy Periostitis Osteoporosis, osteomalacia Rhabdomyolysis Pelvic osteomyelitis Recurrent multifocal osteomyelitis Relapsing polychondritis
SKIN AND MUCOUS MEMBRANES
Oral lesions Cheilitis Aphthous stomatitis, glossitis Granulomatous oral Crohn disease Inflammatory hyperplasia fissures and cobblestone mucosa Peristomatitis vegetans
DERMATOLOGIC
Erythema nodosum Pyoderma gangrenosum Sweet syndrome Metastatic Crohn disease Psoriasis

Epidermolysis bullosa acquisita Perianal skin tags Polyarteritis nodosa Melanoma and nonmelanoma skin cancers
OCULAR
Conjunctivitis Uveitis, iritis Episcleritis Scleritis Retrobulbar neuritis Chorioretinitis with retinal detachment Crohn keratopathy Posterior segment abnormalities Retinal vascular disease
BRONCHOPULMONARY
Chronic bronchitis with bronchiectasis Chronic bronchitis with neutrophilic infiltrates Fibrosing alveolitis Pulmonary vasculitis Small airway disease and bronchiolitis obliterans Eosinophilic lung disease Granulomatous lung disease Tracheal obstruction
CARDIAC
Pleuropericarditis Cardiomyopathy Endocarditis Myocarditis
MALNUTRITION
Decreased intake of food • Inflammatory bowel disease • Dietary restriction Malabsorption • Inflammatory bowel disease • Bowel resection • Bile salt depletion • Bacterial overgrowth
Intestinal losses • Electrolytes • Minerals • Nutrients Increased caloric needs • Inflammation • Fever
HEMATOLOGIC/ONCOLOGIC
Anemia: iron deficiency (blood loss) Vitamin B12 (ileal disease or resection, bacterial overgrowth, folate deficiency) Anemia of chronic inflammation Anaphylactoid purpura (Crohn disease) Hyposplenism Autoimmune hemolytic anemia Coagulation abnormalities Increased activation of coagulation factors Activated fibrinolysis Anticardiolipin antibody

Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions Systemic lymphoma (nonenteric)
RENAL AND GENITOURINARY
Metabolic • Urinary crystal formation (nephrolithiasis, uric acid, oxylate) Hypokalemic nephropathy Inflammation • Retroperitoneal abscess • Fibrosis with ureteral obstruction • Fistula formation Glomerulitis Membrane nephritis Renal amyloidosis, nephrotic syndrome
PANCREATITIS
Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition) Ampullary Crohn disease Granulomatous pancreatitis Decreased pancreatic exocrine function Sclerosing cholangitis with pancreatitis
HEPATOBILIARY
Primary sclerosing cholangitis Small duct primary sclerosing cholangitis (pericholangitis) Carcinoma of the bile ducts Fatty infiltration of the liver Cholelithiasis Autoimmune hepatitis
ENDOCRINE AND METABOLIC
Growth failure, delayed sexual maturation Thyroiditis Osteoporosis, osteomalacia
NEUROLOGIC
Peripheral neuropathy Meningitis Vestibular dysfunction Pseudotumor cerebri Cerebral vasculitis Migraine

Modified from Kugathasan S: Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, editors: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, WB Saunders, p 285.

362.1

Chronic Ulcerative Colitis

Ronen E. Stein, Robert N. Baldassano

Keywords

incidence
extraintestinal manifestations
fulminant colitis
5-aminosalicylate
immunomodulator
biologic corticosteroid
surgery

Ulcerative colitis, an idiopathic chronic inflammatory disorder, is localized to the colon and spares the upper gastrointestinal (GI) tract. Disease usually begins in the rectum and extends proximally for a variable distance. When it is localized to the rectum, the disease is ulcerative proctitis, whereas disease involving the entire colon is pancolitis. Approximately 50–80% of pediatric patients have extensive colitis, and adults more commonly have distal disease. Ulcerative *proctitis* is less likely to be associated with systemic manifestations, although it may be less responsive to treatment than more-diffuse disease. Approximately 30% of children who present with ulcerative proctitis experience proximal spread of the disease. Ulcerative colitis has rarely been noted to present in infancy. Dietary protein intolerance can easily be misdiagnosed as ulcerative colitis in this age group. Dietary protein intolerance (cow's milk protein) is a transient disorder; symptoms are directly associated with the intake of the offending antigen.

The incidence of ulcerative colitis has increased but not to the extent of the increase in Crohn disease; incidence varies with country of origin. The age-specific incidence rates of pediatric ulcerative colitis in North America is 2/100,000 population. The prevalence of ulcerative colitis in northern European countries and the United States varies from 100 to 200/100,000 population. Men are slightly more likely to acquire ulcerative colitis than are women; the reverse is true for Crohn disease.

Clinical Manifestations

Blood, mucus, and pus in the stool as well as diarrhea are the typical presentation of ulcerative colitis. Constipation may be observed in those with proctitis. Symptoms such as tenesmus, urgency, cramping abdominal pain (especially with bowel movements), and nocturnal bowel movements are common. The mode of onset ranges from insidious with gradual progression of symptoms to acute and fulminant (Table 362.4 and Figs. 362.1 and 362.2). Fever, severe anemia, hypoalbuminemia, leukocytosis, and more than 5 bloody stools per day for 5 days define **fulminant colitis** . Chronicity is an important part of the diagnosis; it is difficult to know if a patient has a subacute, transient infectious colitis or ulcerative colitis when a child has had 1-2 wk of symptoms. Symptoms beyond this duration often prove to be secondary to IBD. Anorexia, weight loss, and growth failure may be present, although these complications are more typical of Crohn disease.

Table 362.4

Montreal Classification of Extent and Severity of Ulcerative Colitis

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): 4 or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): 4 stools per day, minimum signs of systemic symptoms
- S3 (severe): 6 or more bloody stools per day, pulse rate of ≥90 beats/min, temperature ≥37.5°C (99.5°F), hemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/hr

E, extent; *S,* severity.

From Ordàs I, Eckmann L, Talamini M, et al: Ulcerative colitis, *Lancet* 380:1606–1616, 2012, Panel 2, p 1610.

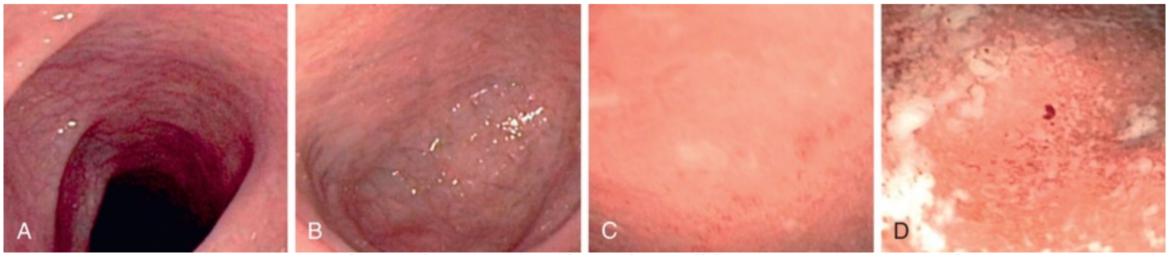

FIG. 362.1 **Mayo endoscopic score for ulcerative colitis. A, Score 0 = normal; endoscopic remission. B, Score 1 = mild; erythema, decreased vascular pattern, mild friability. C, Score 2 = moderate; marked erythema, absent vascular pattern, friability, erosions. D, Score 3 = severe; spontaneous bleeding, ulceration. (Images courtesy Elena Ricart. From Ordàs I, Eckmann L, Talamini M, et al: Ulcerative colitis, *Lancet* 380:1606–1616, 2012, Fig. 2, p 1610.)**

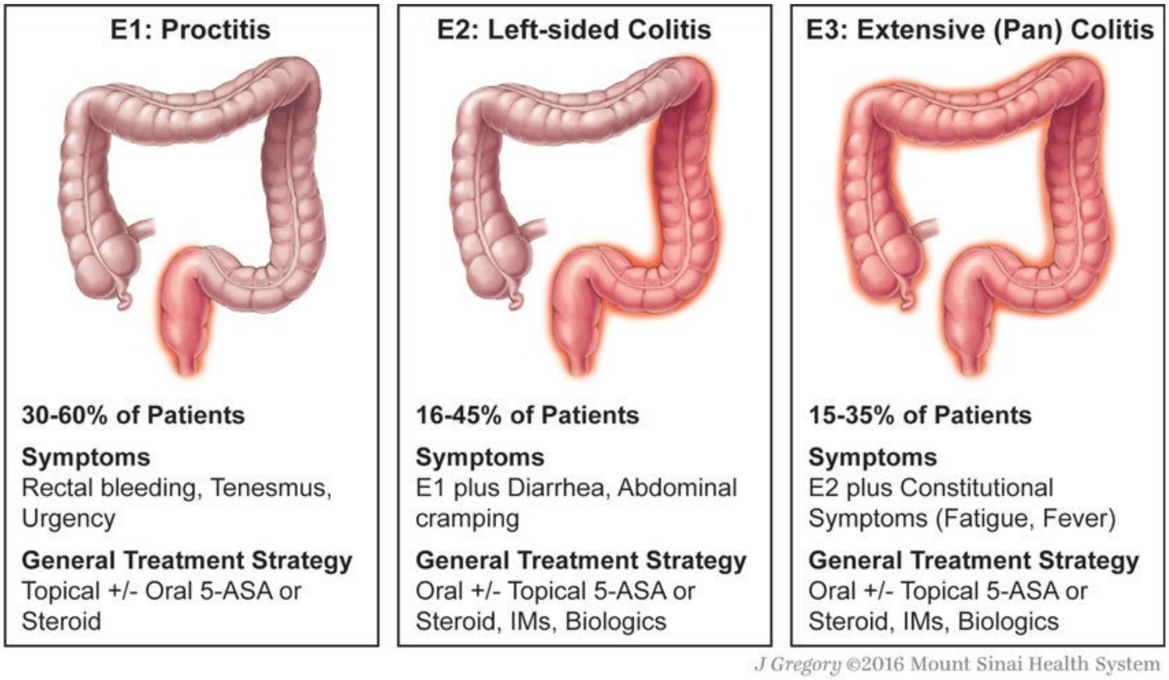
E1: Proctitis
30-60% of Patients
Symptoms
Rectal bleeding, Tenesmus, Urgency
General Treatment Strategy
Topical +/- Oral 5-ASA or Steroid
E2: Left-sided Colitis
16-45% of Patients
Symptoms
E1 plus Diarrhea, Abdominal cramping
General Treatment Strategy
Oral +/- Topical 5-ASA or Steroid, IMs, Biologics
E3: Extensive (Pan) Colitis
15-35% of Patients
Symptoms
E2 plus Constitutional Symptoms (Fatigue, Fever)
General Treatment Strategy
Oral +/- Topical 5-ASA or Steroid, IMs, Biologics
J Gregory ©2016 Mount Sinai Health System

FIG. 362.2 Ulcerative colitis phenotypes by Montreal Classification. Symptoms and treatment strategy can differ based on extent of disease. (Illustration by Jill Gregory. Printed with permission of ©Mount Sinai Health System.)

Extraintestinal manifestations that tend to occur more commonly with ulcerative colitis than with Crohn disease include pyoderma gangrenosum, sclerosing cholangitis, chronic active hepatitis, and ankylosing spondylitis. Iron deficiency can result from chronic blood loss as well as decreased intake. Folate deficiency is unusual but may be accentuated in children treated with sulfasalazine, which interferes with folate absorption. Chronic inflammation and the elaboration of a variety of inflammatory cytokines can interfere with erythropoiesis and result in the anemia of chronic disease. Secondary amenorrhea is common during periods of active disease.

The clinical course of ulcerative colitis is marked by remission and relapse, often without apparent explanation. After treatment of initial symptoms, approximately 5% of children with ulcerative colitis have a prolonged remission (longer than 3 yr). Approximately 25% of children presenting with severe ulcerative colitis require colectomy within 5 yr of diagnosis, compared with only 5% of those presenting with mild disease. It is important to consider the possibility of enteric infection with recurrent symptoms; these infections can mimic a flare-up or actually provoke a recurrence. The use of nonsteroidal antiinflammatory drugs is considered by some to predispose to exacerbation.

It is generally believed that the risk of colon cancer begins to increase after 8-10 yr of disease and can then increase by 0.5–1% per yr. The risk is delayed by approximately 10 yr in patients with colitis limited to the descending colon. Proctitis alone is associated with virtually no increase in risk over the general population. Because colon cancer is usually preceded by changes of mucosal dysplasia, it is recommended that patients who have had ulcerative colitis for longer than 8-10 yr be screened with colonoscopy and biopsies every 1-2 yr. Although this is the current standard of practice, it is not clear if morbidity and mortality are changed by this approach. Two competing concerns about this plan of management remain unresolved. The original studies may have overestimated the risk of colon cancer and, therefore, the need for surveillance has been overemphasized; and screening for dysplasia might not be adequate for preventing colon cancer in ulcerative colitis if some cancers are not preceded by dysplasia.

Differential Diagnosis

The major conditions to exclude are infectious colitis, allergic colitis, and Crohn colitis. Every child with a new diagnosis of ulcerative colitis should have stool cultured for enteric pathogens, stool evaluation for *Clostridium difficile*, ova and parasites, and perhaps serologic studies for amebae (Table 362.5). Cytomegalovirus infection can mimic ulcerative colitis or be associated with an exacerbation of existing disease, usually in immunocompromised patients. The most difficult distinction is from Crohn disease because the colitis of Crohn disease can initially appear identical to that of ulcerative colitis, particularly in younger children. The gross appearance of the colitis or development of small bowel disease eventually leads to the correct diagnosis; this can occur years after the initial presentation.

Table 362.5

Infectious Agents Mimicking Inflammatory Bowel Disease

AGENT	MANIFESTATIONS	DIAGNOSIS	COMMENTS
BACTERIAL			
Campylobacter jejuni	Acute diarrhea, fever, fecal blood, and leukocytes	Culture	Common in adolescents, may relapse
Yersinia enterocolitica	Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood, and leukocytes Extraintestinal manifestations, mimics Crohn disease	Culture	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
Clostridium difficile	Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay	May be nosocomial Toxic megacolon possible
Escherichia coli O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing	Hemolytic uremic syndrome
Salmonella	Watery → bloody diarrhea, foodborne, fecal leukocytes, fever, pain, cramps	Culture	Usually acute
Shigella	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture	Dysentery symptoms
Edwardsiella tarda	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
Aeromonas hydrophila	Cramps, diarrhea, fecal blood	Culture	May be chronic Contaminated drinking water
Plesiomonas shigelloides	Diarrhea, cramps	Culture	Shellfish source
Tuberculosis	Rarely bovine, now Mycobacterium tuberculosis Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy	Can mimic Crohn disease
PARASITES			
Entamoeba histolytica	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
Giardia lamblia	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	“Owl”-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
AIDS-ASSOCIATED ENTEROPATHY			
Cryptosporidium	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease

Isospora belli	As in Cryptosporidium		Tropical location
Cytomegalovirus	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

At the onset, the colitis of hemolytic uremic syndrome may be identical to that of early ulcerative colitis. Ultimately, signs of microangiopathic hemolysis (the presence of schistocytes on blood smear), thrombocytopenia, and subsequent renal failure should confirm the diagnosis of hemolytic-uremic syndrome. Although Henoch-Schönlein purpura can manifest as abdominal pain and bloody stools, it is not usually associated with colitis. Behçet disease can be distinguished by its typical features (see Chapter 186). Other considerations are radiation proctitis, viral colitis in immunocompromised patients, and ischemic colitis (Table 362.6). In infancy, dietary protein intolerance can be confused with ulcerative colitis, although the former is a transient problem that resolves on removal of the offending protein, and ulcerative colitis is extremely rare in this age group. Hirschsprung disease can produce an enterocolitis before or within months after surgical correction; this is unlikely to be confused with ulcerative colitis.

Table 362.6

Chronic Inflammatory Bowel-Like Intestinal Disorders Including Monogenetic Diseases

INFECTION (see Table 362.5)
AIDS-Associated
Toxin
Immune–Inflammatory
Severe combined immunodeficiency diseases Agammaglobulinemia Chronic granulomatous disease Wiskott-Aldrich syndrome Common variable immunodeficiency diseases Acquired immunodeficiency states Dietary protein enterocolitis Autoimmune polyendocrine syndrome type 1 Behçet disease Lymphoid nodular hyperplasia Eosinophilic gastroenteritis Omenn syndrome Graft-versus-host disease IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndromes Interleukin-10 signaling defects Autoimmune enteropathy* Microscopic colitis

Hyperimmunoglobulin M syndrome
Hyperimmunoglobulin E syndromes
Mevalonate kinase deficiency
Familial Mediterranean fever
Phospholipase Cγ_2 defects
IL10RA mutation
Familial hemophagocytic lymphohistiocytosis type 5
X-linked lymphoproliferative syndromes types 1, 2 (*XIAP* gene)
Congenital neutropenias
TRIM22 mutation
Leukocyte adhesion deficiency 1
VASCULAR–ISCHEMIC DISORDERS
Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)
Henoch-Schönlein purpura
Hemolytic uremic syndrome
Granulomatosis with angiitis
OTHER
Glycogen storage disease type 1b
Dystrophic epidermolysis bullosa
X-linked ectodermal dysplasia and immunodeficiency
Dyskeratosis congenita
ADAM-17 deficiency
Prestenotic colitis
Diversion colitis
Kindler syndrome
Radiation colitis
Neonatal necrotizing enterocolitis
Typhlitis
Sarcoidosis
Hirschsprung colitis
Intestinal lymphoma
Laxative abuse
Endometriosis
Hermansky-Pudlak syndrome
Trichohepatoenteric syndrome
Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome

[*] May be the same as IPEX.

Diagnosis

The diagnosis of ulcerative colitis or ulcerative proctitis requires a typical presentation in the absence of an identifiable specific cause (see Tables 362.5 and 362.6) and typical endoscopic and histologic findings (see Tables 362.2 and 362.4). One should be hesitant to make a diagnosis of ulcerative colitis in a child who has experienced symptoms for <2-3 wk until infection has been excluded. When the diagnosis is suspected in a child with subacute symptoms, the physician should make a firm diagnosis only when there is evidence of chronicity on colonic biopsy. Laboratory studies can demonstrate evidence of anemia (either iron deficiency or the anemia of chronic disease) or hypoalbuminemia. Although the sedimentation rate and C-reactive protein are often elevated, they may be normal even with fulminant colitis. An elevated white blood cell count is usually seen only with more-severe colitis. Fecal calprotectin levels are usually elevated and are increasingly recognized to be a more sensitive and specific marker of GI inflammation than typical laboratory parameters. Barium enema is suggestive but not diagnostic of acute (Fig. 362.3) or chronic burned-out disease (Fig. 362.4).

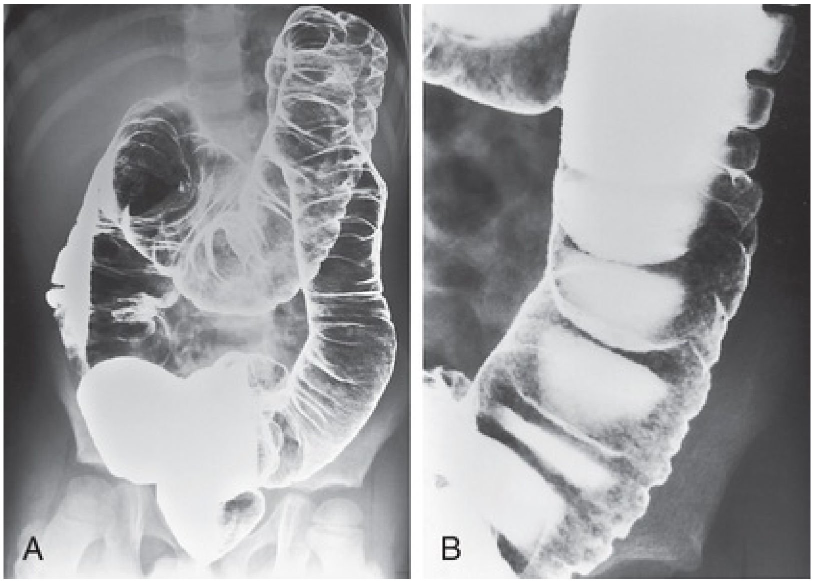

FIG. 362.3 Ulcerative colitis. Double-contrast barium enema in a 5 yr old boy who had had intermittent intestinal and extraintestinal symptoms since the age of 3 yr. A, Small ulcerations are distributed uniformly about the colonic circumference and continuously from the rectum to the proximal transverse colon. This pattern of involvement is typical of ulcerative colitis. B, In this coned view of the sigmoid in the same patient, small ulcerations are represented by fine spiculation of the colonic contour in tangent and by fine stippling of the colon surface en face. (From Hoffman AD: The child with diarrhea. In Hilton SW, Edwards DK, editors: *Practical pediatric radiology,* ed 2, Philadelphia, 1994, WB Saunders, p 260.)

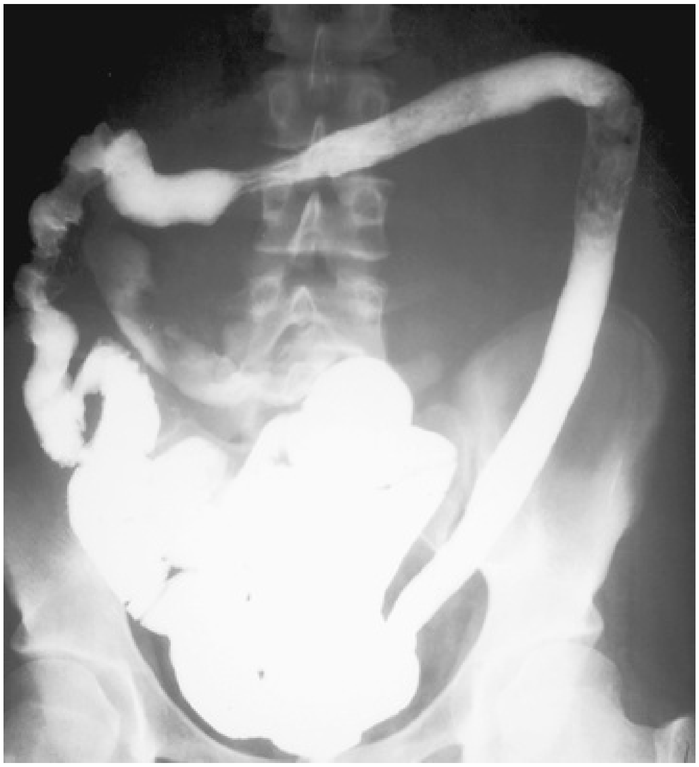

FIG. 362.4 Ulcerative colitis: late changes. This single-contrast barium enema shows the late changes of ulcerative colitis in a 15 yr old girl. The colon is featureless, reduced in caliber, and shortened. Dilation of the terminal ileum (backwash ileitis) is present. (From The child with diarrhea. In Hoffman AD, Hilton SW, Edwards DK, editors: *Practical pediatric radiology,* ed 2, Philadelphia, 1994, WB Saunders, p 262.)

The diagnosis of ulcerative colitis must be confirmed by endoscopic and histologic examination of the colon (see Fig. 362.1). Classically, disease starts in the rectum with a gross appearance characterized by erythema, edema, loss of vascular pattern, granularity, and friability. There may be a *cutoff* demarcating the margin between inflammation and normal colon, or the entire colon may be involved. There may be some variability in the intensity of inflammation even in those areas involved. Flexible sigmoidoscopy can confirm the diagnosis; colonoscopy can evaluate the extent of disease and rule out Crohn colitis. A colonoscopy should not be performed when fulminant colitis is suspected because of the risk of provoking *toxic megacolon* or causing a perforation during the procedure. The degree of colitis can be evaluated by the gross appearance of the mucosa. One does not generally see discrete ulcers, which would be more suggestive of Crohn colitis. The endoscopic findings of ulcerative colitis result from microulcers, which give the appearance of a diffuse abnormality. With very severe chronic colitis, pseudopolyps may be seen. Biopsy of involved bowel demonstrates evidence of acute and chronic mucosal inflammation. Typical histologic findings are cryptitis, crypt abscesses, separation of crypts by inflammatory cells, foci of acute inflammatory cells, edema, mucus depletion, and branching of crypts. The last finding is not seen in infectious colitis. Granulomas, fissures, or full-thickness involvement of the bowel wall (usually on surgical rather than endoscopic biopsy) suggest Crohn disease.

Perianal disease , except for mild local irritation or anal fissures associated with diarrhea, should make the clinician think of Crohn disease. Plain radiographs of the abdomen might demonstrate loss of haustral markings in an air-filled colon or marked dilation with toxic megacolon. With severe colitis, the colon may become dilated; a diameter of >6 cm, determined radiographically, in an adult suggests toxic megacolon. If it is necessary to examine the colon radiologically in a child with severe colitis (to evaluate the extent of involvement or to try to rule out Crohn disease), it is sometimes helpful to perform an upper GI contrast series with small bowel follow-through and then look at delayed films of the colon. A barium enema is contraindicated in the setting of a potential toxic megacolon.

Treatment

Medical

A medical *cure* for ulcerative colitis is not available; treatment is aimed at controlling symptoms and reducing the risk of recurrence, with a secondary goal of minimizing steroid exposure. The intensity of treatment varies with the severity of the symptoms.

The first drug class to be used with mild or mild-to-moderate colitis is an aminosalicylate. Sulfasalazine is composed of a sulfur moiety linked to the active ingredient 5-aminosalicylate (5-ASA). This linkage prevents the premature absorption of the medication in the upper GI tract, allowing it to reach the colon, where the 2 components are separated by bacterial cleavage. The dose of sulfasalazine is 30-100 mg/kg/24 hr (divided into 2-4 doses). Generally, the dose is not more than 2-4 g/24 hr. Hypersensitivity to the sulfa component is the major side effect of sulfasalazine and occurs in 10–20% of patients. Because of poor tolerance, sulfasalazine is used less commonly than other, better tolerated 5-ASA preparations (mesalamine, 50-100 mg/kg/day; balsalazide 2.25-6.75 g/day). Sulfasalazine and the 5-ASA preparations effectively treat active ulcerative colitis and prevent recurrence. It is recommended that the medication be continued even when the disorder is in remission. These medications might also modestly decrease the lifetime risk of colon cancer.

Approximately 5% of patients have an *allergic reaction* to 5-ASA, manifesting as rash, fever, and bloody diarrhea, which can be difficult to distinguish from symptoms of a flare of ulcerative colitis. 5-ASA can also be given in enema or suppository form and is especially useful for proctitis. Hydrocortisone enemas are used to treat proctitis as well, but they are probably not as effective. A combination of oral and rectal 5-ASA as well as monotherapy with rectal preparation has been shown to be more effective than just oral 5-ASA for distal colitis. Extended release budesonide may also induce remission in patients with mild-to-moderate ulcerative colitis.

Probiotics are effective in adults for maintenance of remission for ulcerative colitis, although they do not induce remission during an active flare. The most promising role for probiotics has been to prevent pouchitis, a common complication following colectomy and ileal–pouch anal anastomosis surgery.

Children with moderate to severe pancolitis or colitis that is unresponsive to 5-ASA therapy should be treated with corticosteroids, most commonly prednisone. The usual starting dose of prednisone is 1-2 mg/kg/24 hr (40-60 mg maximum dose). This medication can be given once daily. With severe colitis, the dose can be divided twice daily and can be given intravenously. Steroids are considered an effective medication for acute flares, but they are not appropriate maintenance medications because of loss of effect and side effects, including growth retardation, adrenal suppression, cataracts, osteopenia, aseptic necrosis of the head of the femur, glucose intolerance, risk of infection, mood disturbance, and cosmetic effects.

For a hospitalized patient with persistence of symptoms despite intravenous steroid treatment for 3-5 days, escalation of therapy or surgical options should be considered. The validated pediatric ulcerative colitis activity index can be used to help determine current disease severity based on clinical factors and help determine who is more likely to respond to steroids and those who will likely require escalation of therapy (Table 362.7).

Table 362.7

Pediatric Ulcerative Colitis Activity Index

ITEM	POINTS

(1) Abdominal Pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) Rectal Bleeding	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) Stool Consistency of Most Stools	
Formed	0
Partially formed	5
Completely unformed	10
(4) Number of Stools Per 24 hr	
0-2	0
3-5	5
6-8	10
>8	15
(5) Nocturnal Stools (Any Episode Causing Wakening)	
No	0
Yes	10
(6) Activity Level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of Index (0-85)	

With medical management, most children are in remission within 3 mo; however, 5–10% continue to have symptoms unresponsive to treatment beyond 6 mo. Many children with disease requiring frequent corticosteroid therapy are started on immunomodulators such as azathioprine (2.0-2.5 mg/kg/day) or 6-mercaptopurine (1-1.5 mg/kg/day). Uncontrolled data suggest a corticosteroid-sparing effect in many treated patients. This is not an appropriate choice in a steroid nonresponsive patient with acute severe colitis because of longer onset of action. Lymphoproliferative disorders are associated with thiopurine use. Cyclosporine, which is associated with improvement in some children with severe or fulminant colitis, is rarely used owing to its high side-effect profile, its inability to change the natural history of disease, and the increasing use of infliximab, a chimeric monoclonal antibody to tumor necrosis factor (TNF)-α, which is also effective in cases of fulminant colitis. Infliximab is effective for induction and maintenance therapy in children and adults with moderate to severe disease. TNF blocking agents are associated with an increased risk of infection (particularly tuberculosis) and malignancies (lymphoma, leukemia). Adalimumab is also approved for treatment of moderate to severe ulcerative colitis in adults. Vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the GI tract, is approved for the treatment of ulcerative colitis in adults. Tofacitinib, an oral Janus kinase inhibitor, is also approved for treatment of moderate to severe adult ulcerative colitis. A specific combination of 3-4 wide-spectrum oral antibiotics given over 2-3 wk may be effective in treating severe pediatric ulcerative colitis refractory to other therapies but is being further studied in children.

Surgical

Colectomy is performed for intractable disease, complications of therapy, and fulminant disease that is unresponsive to medical management. No clear benefit of the use of total parenteral nutrition or a continuous enteral elemental diet in the treatment of severe ulcerative colitis has been noted. Nevertheless, parenteral nutrition is used if oral intake is insufficient so that the patient will be nutritionally ready for surgery if medical management fails. With any medical treatment for ulcerative colitis, the clinician should always weigh the risk of the medication or therapy against the fact that colitis can be successfully treated surgically.

Surgical treatment for intractable or fulminant colitis is total colectomy. The optimal approach is to combine colectomy with an endorectal pull-through, where a segment of distal rectum is retained and the mucosa is stripped from this region. The distal ileum is pulled down and sutured at the internal anus with a J pouch created from ileum immediately above the rectal cuff. This procedure allows the child to maintain continence. Commonly, a temporary ileostomy is created to protect the delicate anastomosis between the sleeve of the pouch and the rectum. The ileostomy is usually closed within several months, restoring bowel continuity. At that time, stool frequency is often increased but may be improved with loperamide. The major complication of this operation is *pouchitis,* which is a chronic inflammatory reaction in the pouch, leading to bloody diarrhea, abdominal pain, and, occasionally, low-grade fever. The cause of this complication is unknown, although it is more common when the ileal pouch has been constructed for ulcerative colitis than for other indications (e.g., familial polyposis coli). Pouchitis is seen in 30–40% of patients who had ulcerative colitis. It commonly responds to treatment with oral metronidazole or ciprofloxacin. Probiotics have also been shown to decrease the rate of pouchitis as well as the recurrence of pouchitis following antibiotic therapy.

Support

Psychosocial support is an important part of therapy for this disorder. This may include adequate discussion of the disease manifestations and management between patient and physician, psychologic counseling for the child when necessary, and family support from a social worker or family counselor. Patient support groups have proved helpful for some families. Children with ulcerative colitis should be encouraged to participate fully in age-appropriate activities; however, activity may need to be reduced during periods of disease exacerbation.

Prognosis

The course of ulcerative colitis is marked by remissions and exacerbations. Most children with this disorder respond initially to medical management. Many children with mild manifestations continue to respond well to medical management and may stay in remission on a prophylactic 5-ASA preparation for long periods. An occasional child with mild onset, however, experiences intractable symptoms later. Beyond the 1st decade of disease, the risk of development of colon cancer begins to increase rapidly. The risk of colon cancer may be diminished with surveillance colonoscopies beginning after 8-10 yr of disease. Detection of significant dysplasia on biopsy would prompt colectomy.

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362.2

Crohn Disease (Regional Enteritis, Regional Ileitis, Granulomatous Colitis)

Ronen E. Stein, Robert N. Baldassano

Keywords

incidence
extraintestinal manifestations
growth
enteral nutritional therapy
5-aminosalicylate
corticosteroid
immunomodulator
biologic
surgery

Crohn disease, an idiopathic, chronic inflammatory disorder of the bowel, involves any region of the alimentary tract from the mouth to the anus. Although there are many similarities between ulcerative colitis and Crohn disease, there are also major differences in the clinical course and distribution of the disease in the GI tract (see Table 362.2). The inflammatory process tends to be eccentric and segmental, often with skip areas (normal regions of bowel between inflamed areas). Although inflammation in ulcerative colitis is limited to the mucosa (except in toxic megacolon), GI involvement in Crohn disease is often *transmural* .

Compared to adult-onset disease, pediatric Crohn disease is more likely to have extensive anatomic involvement. At initial presentation, more than 50% of patients have disease that involves ileum and colon (ileocolitis), 20% have exclusively colonic disease, and upper GI involvement (esophagus, stomach, duodenum) is seen in up to 30% of children. Isolated small bowel disease is much less common in the pediatric population compared to adults. Isolated colonic disease is common in children younger than 8 yr of age and may be indistinguishable from ulcerative colitis. Anatomic location of disease tends to extend over time in children.

Crohn disease tends to have a bimodal age distribution, with the first peak beginning in the teenage years. The incidence of Crohn disease has been increasing. In the United States, the reported incidence of pediatric Crohn disease is 4.56/100,000 and the pediatric prevalence is 43/100,000 children.

Clinical Manifestations

Crohn disease can be characterized as inflammatory, stricturing, or penetrating. Patients with small bowel disease are more likely to have an obstructive pattern (most commonly with right lower quadrant pain) characterized by fibrostenosis, and those with colonic disease are more likely to have symptoms resulting from inflammation (diarrhea, bleeding, cramping). Disease phenotypes often change as duration of disease lengthens (inflammatory becomes structuring and/or penetrating) (Figs. 362.5 and 362.6).

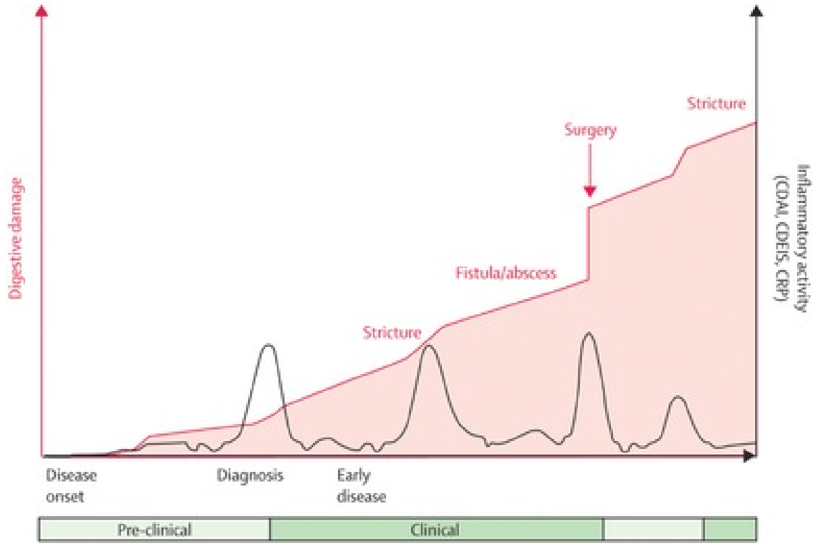

FIG. 362.5 The Lémann Score. Exemplary visualization of the Lémann score, a new technique to score and study intestinal damage in Crohn

disease. *CDAI,* Crohn disease activity index; *CDEIS,* Crohn disease of endoscopic severity; *CRP,* C-reactive protein. (From Baumgart DC, Sandborn WJ: Crohn's disease, *Lancet* 380:1590–1602, 2012, Fig. 5, p 1596.)

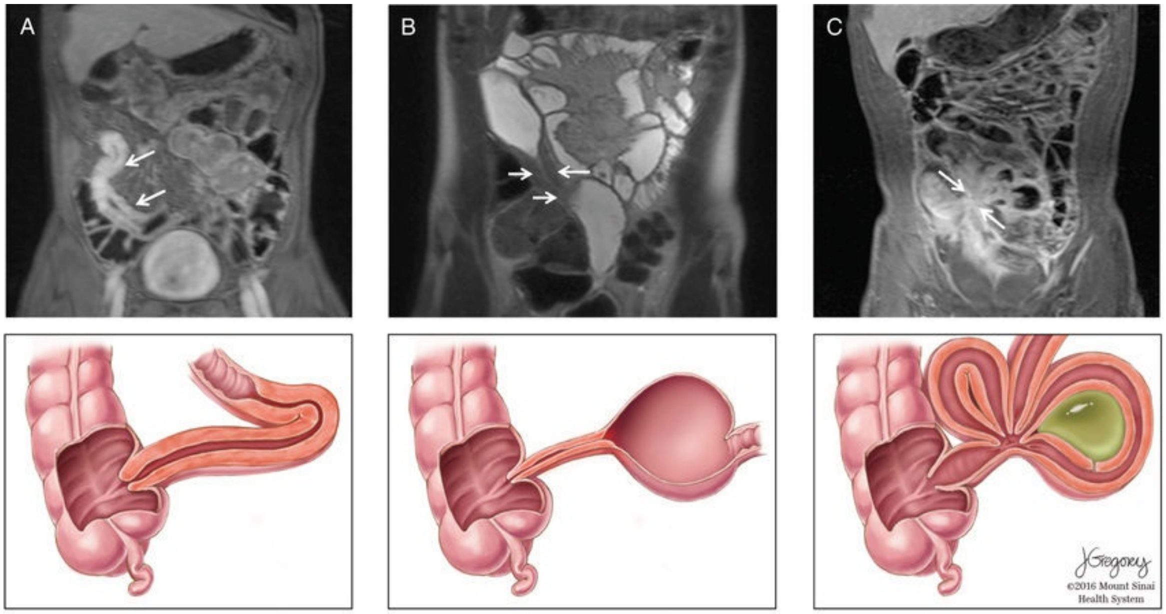

- Diarrhea
- Abdominal pain
- Weight loss
- Low-grade fever
- Fatigue
- Growth retardation
- Malnourishment

- Postprandial pain
- Bloating
- Nausea and vomiting
- Occlusion/subocclusion

- Symptoms depend on the location of fistulae
- Enterourinary fistula: fecaluria, pneumaturia, recurrent UTI
- Rectovaginal fistula: dispareunia, stool discharge through the vagina
- Enteroenteric fistula: asymptomatic, abdominal abscesses

FIG. 362.6 Behavior of CD as per Montreal classification represented in MRE and illustrated with typical symptoms **A,** T1-weighted MRE imaging with fat saturation after injection of gadolinium chelates shows mural thickening and enhancement in the distal ileum *(arrows)* in a patient with active CD. **B,** T2-weighted MRE imaging shows a narrowed luminal segment with thickened wall and upstream dilation *(arrows)* , suggesting the presence of a stricture. **C,** T1-weighted MRE imaging with fat saturation after injection of gadolinium chelates shows multiple converging enhancing loops of small bowel suggestive of enteroenteric fistulas *(arrows)* . Lower illustration shows a deep and transmural fissure or ulcer leading to the formation of an abscess. *CD,* Crohn disease; *MRE,* magnetic resonance enterography; *UTI,* urinary tract infection. (Illustration by Jill Gregory. Printed with permission of ©Mount Sinai Health System. From Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L: Crohn's disease, *Lancet* 389:1741–1754, 2017, Fig. 1, p 1744.)

Systemic signs and symptoms are more common in Crohn disease than in ulcerative colitis. Fever, malaise, and easy fatigability are common. Growth failure with delayed bone maturation and delayed sexual development can precede other symptoms by 1 or 2 yr and is at least twice as likely to occur with Crohn disease as with ulcerative colitis. Children can present with growth failure as the only manifestation of Crohn disease. Decreased height velocity occurs in about 88% of prepubertal patients diagnosed with Crohn disease, and this often precedes GI symptoms. Causes of growth failure include inadequate caloric intake, suboptimal absorption or excessive loss of nutrients, the effects of chronic inflammation on bone metabolism and appetite, and the use of corticosteroids during treatment. Primary or secondary amenorrhea and pubertal delay are common. In contrast to ulcerative colitis, perianal disease is common (tag, fistula, deep fissure, abscess). Gastric or duodenal involvement may be associated with recurrent vomiting and epigastric pain. Partial small bowel obstruction, usually secondary to narrowing of the bowel lumen from *inflammation* or *stricture* , can cause symptoms of cramping abdominal pain (especially with meals), borborygmus, and intermittent abdominal distention (Figs. 362.7 and 362.8). Stricture should be suspected if the child notes relief of symptoms in association with a sudden sensation of gurgling of intestinal contents through a localized region of the abdomen. Inflammatory obstruction versus fibrotic stricture-induced obstruction may be distinguished by positron emission tomography/magnetic resonance imaging (PET/MRI), which will direct specific therapy (Fig. 362.9).

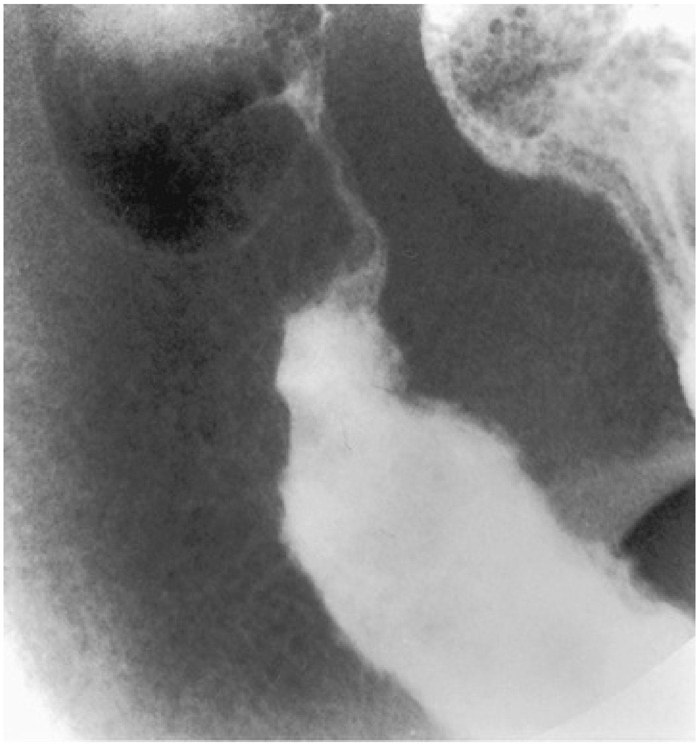

FIG. 362.7 Stenotic Crohn disease. Severe stenosis of the terminal ileum is present in this 16 yr old boy. Inflammatory effacement of the mucosal folds and small ulcerations characterize the proximal nonstenotic segment. (From Hoffman AD: The child with diarrhea. In Hilton SW, Edwards DK, editors: *Practical pediatric radiology,* ed 2, Philadelphia, 1994, WB Saunders, p 267.)

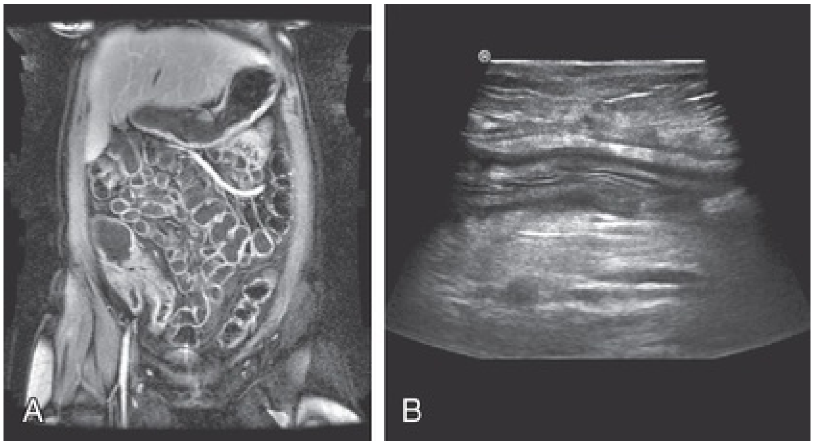

FIG. 362.8 Stenosis in Crohn disease. **A,** Magnetic resonance enterography of Crohn disease restricted to the terminal ileum (Montreal category L1) with inflammatory stenosis. **B,** Ultrasound image of an intestinal stenosis in Crohn disease. (From Baumgart DC, Sandborn WJ:

Crohn's disease, *Lancet* 380:1590–1602, 2012, Fig. 4, p 1596.)

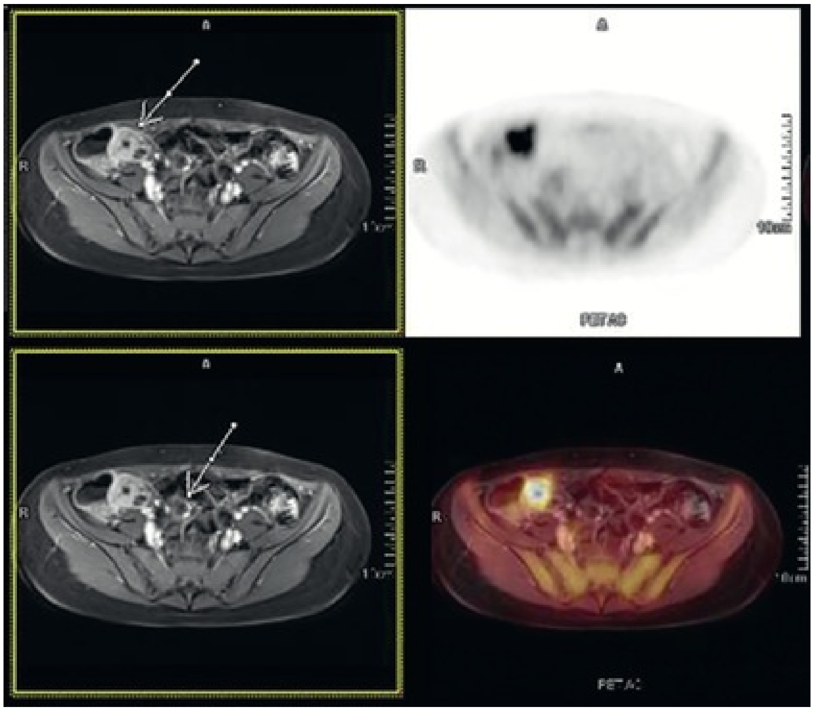

FIG. 362.9 PET/MR (PET, positron emission tomography; MR, magnetic resonance) co-registration and fusion *(right image in the bottom row)* showing a fibrotic stricture of the last bowel loop *(top, arrow)* with active inflammation, and concomitant inflammation of the ileocolic mesentery *(bottom, arrow)* . (From Pellino G, Nicolai E, Catalano OA, et al: PET/MR versus PET/CT imaging: impact on the clinical management of small-bowel Crohn's disease, *J Crohn Colitis* 10(3):277–285, 2017, Fig. 3.)

Penetrating disease is demonstrated by fistula formation. Enteroenteric or enterocolonic fistulas (between segments of bowel) are often asymptomatic but can contribute to malabsorption if they have high output or result in bacterial overgrowth (Fig. 362.10). Enterovesical fistulas (between bowel and urinary bladder) originate from ileum or sigmoid colon and appear as signs of urinary infection, pneumaturia, or fecaluria. Enterovaginal fistulas originate from the rectum, cause feculent vaginal drainage, and are difficult to manage. Enterocutaneous fistulas (between bowel and abdominal skin) often are caused by prior surgical anastomoses with leakage. Intraabdominal abscess may be associated with fever and pain but might have relatively few symptoms. Hepatic or splenic abscess can occur with or without a local fistula. Anorectal abscesses often originate immediately above the anus at the crypts of Morgagni. The patterns of perianal fistulas are complex because of the different tissue planes. Perianal abscess is usually painful, but perianal fistulas tend to produce fewer symptoms than anticipated. Purulent drainage is commonly associated with perianal fistulas. Psoas abscess secondary to intestinal fistula can present as hip pain, decreased hip extension (psoas sign), and fever.

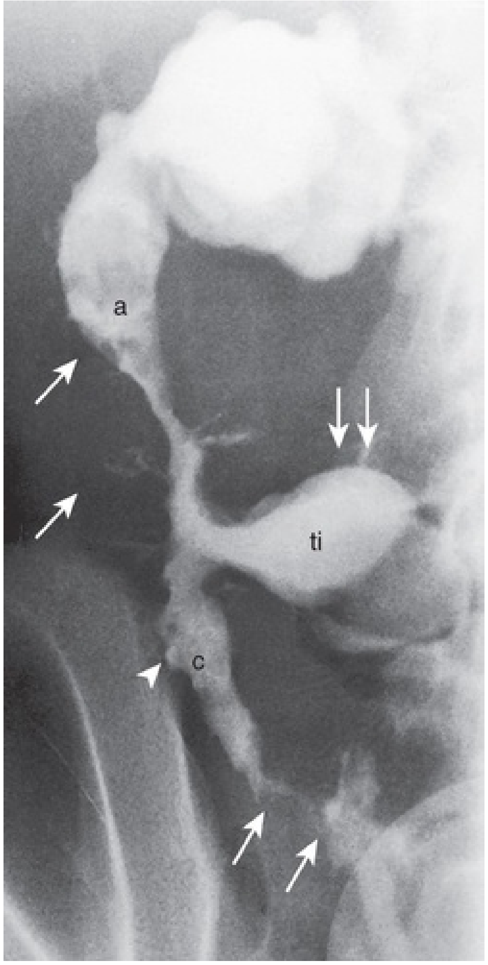

FIG. 362.10 Crohn disease: sinuses and fistula. Severe ileocolitis has resulted in an ileocecal fistula *(single arrows, lower)* and sinus formation in the ascending colon *(a) (arrows on platform). c,* Cecum *(arrowhead); ti,* terminal ileum *(paired arrows).* (From The child with diarrhea. In Hoffman AD, Hilton SW, Edwards DK, editors: *Practical pediatric radiology* , ed 2, Philadelphia, 1994, WB Saunders, p 268.)

Extraintestinal manifestations occur more commonly with Crohn disease than with ulcerative colitis; those that are especially associated with Crohn disease include oral aphthous ulcers, peripheral arthritis, erythema nodosum, digital clubbing, episcleritis, renal stones (uric acid, oxalate), and gallstones. Any of the extraintestinal disorders described in the section on IBD can occur with Crohn disease (see Table 362.3). The peripheral arthritis is nondeforming. The occurrence of extraintestinal manifestations usually correlates with the presence of colitis.

Extensive involvement of small bowel, especially in association with surgical resection, can lead to short bowel syndrome, which is rare in children. Complications of terminal ileal dysfunction or resection include bile acid malabsorption with secondary diarrhea and vitamin B_{12} malabsorption, with possible resultant deficiency. Chronic steatorrhea can lead to oxaluria with secondary renal stones. Increasing calcium intake can actually decrease the risk of renal stones secondary to ileal inflammation. The risk of cholelithiasis is also increased secondary to bile acid depletion.

A disorder with this diversity of manifestations can have a major impact on an affected child's lifestyle. Fortunately, the majority of children with Crohn disease are able to continue with their normal activities, having to limit activity only during periods of increased symptoms.

Differential Diagnosis

The most common diagnoses to be distinguished from Crohn disease are the infectious enteropathies (in the case of Crohn disease: acute terminal ileitis, infectious colitis, enteric parasites, and periappendiceal abscess) (see Tables 362.5 , 362.6 , and 362.8). *Yersinia* can cause many of the radiologic and endoscopic findings in the distal small bowel that are seen in Crohn disease. The symptoms of bacterial dysentery are more likely to be mistaken for ulcerative colitis than for Crohn disease. Celiac disease and *Giardia* infection have been noted to produce a Crohn-like presentation including diarrhea, weight loss, and protein-losing enteropathy. GI tuberculosis is rare but can mimic Crohn disease. Foreign-body perforation of the bowel (toothpick) can mimic a localized region with Crohn disease. Small bowel lymphoma can mimic Crohn disease but tends to be associated with nodular-filling defects of the bowel without ulceration or narrowing of the lumen. Bowel lymphoma is much less common in children than is Crohn disease. Recurrent functional abdominal pain can mimic the pain of small bowel Crohn disease. *Lymphoid nodular hyperplasia* of the terminal ileum (a normal finding) may be mistaken for Crohn ileitis. Right lower quadrant pain or mass with fever can be the result of periappendiceal abscess. This entity is occasionally associated with diarrhea as well.

Table 362.8

Differential Diagnosis of Presenting Symptoms of Crohn Disease

PRIMARY PRESENTING SYMPTOM	DIAGNOSTIC CONSIDERATIONS
Right lower quadrant abdominal pain, with or without mass	Appendicitis, infection (e.g., *Campylobacter, Yersinia* spp.), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst
Chronic periumbilical or epigastric abdominal pain	Irritable bowel syndrome, constipation, lactose intolerance, peptic disease
Rectal bleeding, no diarrhea	Fissure, polyp, Meckel diverticulum, rectal ulcer syndrome
Bloody diarrhea	Infection, hemolytic-uremic syndrome, Henoch-Schönlein purpura, ischemic bowel, radiation colitis
Watery diarrhea	Irritable bowel syndrome, lactose intolerance, giardiasis, *Cryptosporidium* infection, sorbitol, laxatives
Perirectal disease	Fissure, hemorrhoid (rare), streptococcal infection, condyloma (rare)
Growth delay	Endocrinopathy
Anorexia, weight loss	Anorexia nervosa
Arthritis	Collagen vascular disease, infection
Liver abnormalities	Chronic hepatitis

From Kugathasan S: Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, editors: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, WB Saunders, p 287.

Growth failure may be the only manifestation of Crohn disease; other disorders such as growth hormone deficiency, gluten-sensitive enteropathy (celiac disease), Turner syndrome, or anorexia nervosa must be considered. If arthritis precedes the bowel manifestations, an initial diagnosis of juvenile idiopathic arthritis may be made. Refractory anemia may be the presenting feature and may be mistaken for a primary hematologic disorder. Chronic granulomatous disease of childhood can cause inflammatory changes in the bowel as well as perianal disease. Antral narrowing in this disorder may be mistaken for a stricture secondary to Crohn disease. Other immunodeficiencies or autoinflammatory conditions and monogenetic disorders may present with GI symptoms suggestive of IBD, particularly in very early or infant/toddler onset of disease (see Table 362.6).

Diagnosis

Crohn disease can manifest as a variety of symptom combinations (see Fig.

362.6). At the onset, symptoms may be subtle (growth retardation, abdominal pain alone); this explains why the diagnosis might not be made until 1 or 2 yr after the start of symptoms. The diagnosis of Crohn disease depends on finding typical clinical features of the disorder (history, physical examination, laboratory studies, and endoscopic or radiologic findings), ruling out specific entities that mimic Crohn disease, and demonstrating chronicity. The history can include any combination of abdominal pain (especially right lower quadrant), diarrhea, vomiting, anorexia, weight loss, growth retardation, and extraintestinal manifestations. Only 25% initially have the triad of diarrhea, weight loss, and abdominal pain. Most do not have diarrhea, and only 25% have GI bleeding.

Children with Crohn disease often appear chronically ill. They commonly have weight loss and growth failure, and they are often malnourished. The earliest sign of growth failure is decreased height velocity, which can be present in up to 88% of prepubertal patients with Crohn disease and typically precedes symptoms. Children with Crohn disease often appear pale, with decreased energy level and poor appetite; the latter finding sometimes results from an association between meals and abdominal pain or diarrhea. There may be abdominal tenderness that is either diffuse or localized to the right lower quadrant. A tender mass or fullness may be palpable in the right lower quadrant. Perianal disease, when present, may be characteristic. Large anal skin tags (1-3 cm diameter) or perianal fistulas with purulent drainage suggest Crohn disease. Digital clubbing, findings of arthritis, and skin manifestations may be present.

A complete blood cell count commonly demonstrates anemia, often with a component of iron deficiency, as well as thrombocytosis. Although the erythrocyte sedimentation rate and C-reactive protein are often elevated, they may be unremarkable. The serum albumin level may be low, indicating small bowel inflammation or protein-losing enteropathy. Fecal calprotectin and lactoferrin are increasingly being used as more sensitive and specific markers of bowel inflammation as compared to serologic parameters, and these are often elevated. Multiple serologic, immune, and genetic markers can also be abnormal, although the best utilization of these remains to be determined.

The small and large bowel and the upper GI tract should be examined by both endoscopic and radiologic studies in the child with suspected Crohn disease. Esophagogastroduodenoscopy and ileocolonoscopy should be performed to properly assess the upper GI tract, terminal ileum, and entire colon. Findings on colonoscopy can include patchy, nonspecific inflammatory changes (erythema, friability, loss of vascular pattern), aphthous ulcers, linear ulcers, nodularity, and strictures. Findings on biopsy may be only nonspecific chronic inflammatory changes. Noncaseating granulomas, similar to those of sarcoidosis, are the most characteristic histologic findings, although often they are not present. Transmural inflammation is also characteristic but can be identified only in surgical specimens.

Radiologic studies are necessary to assess the entire small bowel and investigate for evidence of structuring or penetrating disease. A variety of findings may be apparent on radiologic studies. Plain films of the abdomen may be normal or might demonstrate findings of partial small bowel obstruction or thumbprinting of the colon wall. An upper GI contrast study with small bowel follow-through might show aphthous ulceration and thickened, nodular folds as well as narrowing or stricturing of the lumen. Linear ulcers can give a cobblestone appearance to the mucosal surface. Bowel loops are often separated as a result of thickening of bowel wall and mesentery. Other manifestations on radiographic studies that suggest more-severe Crohn disease are fistulas between bowel (enteroenteric or enterocolonic), sinus tracts, and strictures (see Figs. 362.7 , 362.8 , and 362.10).

An upper GI contrast examination with small bowel follow-through has typically been the study of choice for imaging of the small bowel, but CT and magnetic resonance (MR) enterography and small bowel ultrasound are increasingly being used. MR and ultrasound have the advantage of not exposing the patient to ionizing radiation. CT and MR enterography can also assess for extraluminal findings such as abscesses and phlegmons. MR of the pelvis is also useful for delineating the extent of perianal involvement. PET/MRI may help define obstructing lesions as either inflammatory or fibrotic (see Fig. 362.9).

Video capsule endoscopy is another modality that allows for evaluation of the small bowel. This study can uncover mucosal inflammation or ulceration that might not have been detected by traditional imaging. However, video capsule endoscopy is contraindicated in the presence of stricturing disease, as surgical intervention would be required to remove a video capsule that is unable to pass through the bowel because a stricture. If there is concern for stricturing disease, a patency capsule can be swallowed prior to video capsule endoscopy to assess for passage through the GI tract.

Treatment

Crohn disease cannot be *cured* by medical or surgical therapy. The aim of treatment is to relieve symptoms and prevent complications of chronic inflammation (anemia, growth failure), prevent relapse, minimize corticosteroid exposure, and, if possible, effect mucosal healing.

Medical

The specific therapeutic modalities used depend on geographic localization of disease, severity of inflammation, age of the patient, and the presence of complications (abscess). Traditionally, a *step-up* treatment paradigm has been used in the treatment of pediatric Crohn disease, whereby early disease is treated with steroids and less immunosuppressive medications. Escalation of therapy would occur if disease severity increased, the patient was refractory to current medications, or for steroid dependence. A *top-down* approach has also been espoused, particularly in adults after multiple studies demonstrated superior efficacy. With this approach, patients with moderate to severe Crohn disease are treated initially with stronger, disease-modifying agents, with the goal of achieving mucosal healing, or deep remission, early in the disease course. This is thought to increase the likelihood of long-term remission while decreasing corticosteroid exposure. Improvements in remission and growth have been shown using a top-down approach in pediatrics and this treatment approach is being increasingly used among children. However, the precise role for this approach in pediatrics is still being determined.

5-Aminosalicylates

For mild terminal ileal disease or mild Crohn disease of the colon, an initial trial of mesalamine (50-100 mg/kg/day, maximum 3-4 g) may be attempted. Specific pharmaceutical preparations have been formulated to release the active 5-ASA compound throughout the small bowel, in the ileum and colon, or exclusively in the colon. Rectal preparations are used for distal colonic inflammation.

Antibiotics/Probiotics

Antibiotics such as metronidazole (10-22.5 mg/kg/day) are used for infectious complications and are first-line therapy for perianal disease (although perianal disease usually recurs when antibiotic is discontinued). Additionally, at low doses antibiotics may be effective for treatment of mild to moderate Crohn disease. To date, probiotics have not been shown to be effective in induction or maintenance of remission for pediatric Crohn disease.

Corticosteroids

Corticosteroids are used for acute exacerbations of pediatric Crohn disease because they effectively suppress acute inflammation, rapidly relieving symptoms (prednisone, 1-2 mg/kg/day, maximum 40-60 mg). The goal is to taper dosing as soon as the disease becomes quiescent. Clinicians vary in their tapering schedules, and the disease can flare during this process. There is no role for continuing corticosteroids as maintenance therapy because, in addition to their side effects, tolerance develops, and steroids do not change disease course or promote healing of mucosa. A special controlled ileal-release formulation of budesonide, a corticosteroid with local antiinflammatory activity on the bowel mucosa and high hepatic first-pass metabolism, is also used for mild to moderate ileal or ileocecal disease (adult dose: 9 mg daily). Ileal-release budesonide appears to be more effective than mesalamine in the treatment of active ileocolonic disease but is less effective than prednisone. Although less effective than traditional corticosteroids, budesonide does cause fewer steroid-related side effects.

Immunomodulators

Approximately 70% of patients require escalation of medical therapy within the 1st yr of pediatric Crohn disease diagnosis. Immunomodulators such as azathioprine (2.0-2.5 mg/kg/day) or 6-mercaptopurine (1.0-1.5 mg/kg/day) may be effective in some children who have a poor response to prednisone or who are steroid dependent. Because a beneficial effect of these drugs can be delayed for 3-4 mo after starting therapy, they are not helpful acutely. The early use of these agents can decrease cumulative prednisone dosages over the first 1-2 yr of therapy. Genetic variations in an enzyme system responsible for metabolism of these agents (thiopurine *S* -methyltransferase) can affect response rates and potential toxicity. Lymphoproliferative disorders have developed from thiopurine use in patients with IBD. Other common toxicities include hepatitis, pancreatitis, increased risk of skin cancer, increased risk of infection, and slightly increased risk of lymphoma.

Methotrexate is another immunomodulator that is effective in the treatment of active Crohn disease and has been shown to improve height velocity in the 1st yr of administration. The advantages of this medication include once-weekly dosing by either subcutaneous or oral route (15 mg/m^2 , adult dose 25 mg weekly) and a more-rapid onset of action (6-8 wk) than azathioprine or 6-

mercaptopurine. Folic acid is usually administered concomitantly to decrease medication side effects. Administration of ondansetron prior to methotrexate has been shown to diminish the risk of the most common side effect of nausea. The most common toxicity is hepatitis. The immunomodulators are effective for the treatment of perianal fistulas.

Biologic Therapy

Therapy with antibodies directed against mediators of inflammation is used for patients with Crohn disease. Infliximab, a chimeric monoclonal antibody to TNF-α, is effective for the induction and maintenance of remission and mucosal healing in chronically active moderate to severe Crohn disease, healing of perianal fistulas, steroid sparing, and preventing postoperative recurrence. Pediatric data additionally support improved growth with the administration of this medication. The onset of action of infliximab is quite rapid and it is initially given as 3 infusions over a 6 wk period (0, 2, and 6 wk), followed by maintenance dosing beginning every 8 wk. The durability of response to infliximab is variable and dose escalation (higher dose and/or decreased interval) is often necessary. Measurement of serum trough infliximab level prior to an infusion can help guide dosing decisions. Side effects include infusion reactions, increased incidence of infections (especially reactivation of latent tuberculosis), increased risk of lymphoma, and the development of autoantibodies. The development of antibodies to infliximab is associated with an increased incidence of infusion reactions and decreased durability of response. Regularly scheduled dosing of infliximab, as opposed to episodic dosing on an as-needed basis, is associated with decreased levels of antibodies to infliximab. A purified protein derivative test for tuberculosis should be done before starting infliximab.

Adalimumab, a subcutaneously administered, fully humanized monoclonal antibody against TNF-α, is effective for the treatment of chronically active moderate to severe Crohn disease in adults and children. After a loading dose, this is typically administered once every 2 wk, although dose escalation is sometimes required with this medication. Vedolizumab, a humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the GI tract, is approved for the treatment of Crohn disease in adults. Like infliximab, vedolizumab is initially given as 3 infusions over a 6 wk period followed by maintenance dosing beginning every 8 wk. However, the onset of action for vedolizumab is slower compared to infliximab and adalimumab. Therefore, concomitant therapies may be needed until response is demonstrated.

Dose escalation to every 4 wk may be necessary in some patients with loss-of-response but is being further studied. Ustekinumab, a monoclonal antibody against interleukins 12 and 23, was recently approved for treatment of chronically active moderate to severe Crohn disease in adults. A loading dose is given intravenously followed by maintenance dosing administered subcutaneously every 8 wk. New antiselective adhesion molecules and small molecule treatments, such as an oral SMAD7 antisense oligonucleotide that targets TGF-β signaling, are currently being tested.

Enteral Nutritional Therapy

Exclusive enteral nutritional therapy, whereby all of a patient's calories are delivered via formula, is an effective primary as well as adjunctive treatment. The enteral nutritional approach is as rapid in onset of response and as effective as the other treatments. Pediatric studies have suggested similar efficacy to prednisone for improvement in clinical symptoms, but enteral nutritional therapy is superior to steroids for actual healing of mucosa. Because affected patients have poor appetite and these formulas are relatively unpalatable, they are often administered via a nasogastric or gastrostomy infusion, usually overnight. The advantages are that it is relatively free of side effects, avoids the problems associated with corticosteroid therapy, and simultaneously addresses the nutritional rehabilitation. Children can participate in normal daytime activities. A major disadvantage of this approach is that patients are not able to eat a regular diet because they are receiving all of their calories from formula. A novel approach where 80–90% of caloric needs are provided by formula, allowing children to have some food intake, has been successful. For children with growth failure, this approach may be ideal, however.

High-calorie oral supplements, although effective, are often not tolerated because of early satiety or exacerbation of symptoms (abdominal pain, vomiting, or diarrhea). Nonetheless, they should be offered to children whose weight gain is suboptimal even if they are not candidates for exclusive enteral nutritional therapy. The continuous administration of nocturnal nasogastric feedings for chronic malnutrition and growth failure has been effective with a much lower risk of complications than parenteral hyperalimentation.

Surgery

Surgical therapy should be reserved for very specific indications. Recurrence rate after bowel resection is high (>50% by 5 yr); the risk of requiring additional surgery increases with each operation. Potential complications of surgery include development of fistula or stricture, anastomotic leak, postoperative partial small bowel obstruction secondary to adhesions, and short bowel syndrome. Surgery is the treatment of choice for localized disease of small bowel or colon that is unresponsive to medical treatment, bowel perforation, fibrosed stricture with symptomatic partial small bowel obstruction, and intractable bleeding. Intraabdominal or liver abscess sometimes is successfully treated by ultrasonographic or CT-guided catheter drainage and concomitant intravenous antibiotic treatment. Open surgical drainage is necessary if this approach is not successful. Growth retardation was once considered an indication for resection; without other indications, trial of medical and/or nutritional therapy is currently preferred.

Perianal abscess often requires drainage unless it drains spontaneously. In general, perianal fistulas should be managed by a combined medical and surgical approach. Often, the surgeon places a seton through the fistula to keep the tract open and actively draining while medical therapy is administered, to help prevent the formation of a perianal abscess. A severely symptomatic perianal fistula can require fistulotomy, but this procedure should be considered only if the location allows the sphincter to remain undamaged.

The surgical approach for Crohn disease is to remove as limited a length of bowel as possible. There is no evidence that removing bowel up to margins that are free of histologic disease has a better outcome than removing only grossly involved areas. The latter approach reduces the risk of short bowel syndrome. Laparoscopic approach is increasingly being used, with decreased postoperative recovery time. One approach to symptomatic small bowel stricture has been to perform a strictureplasty rather than resection. The surgeon makes a longitudinal incision across the stricture but then closes the incision with sutures in a transverse fashion. This is ideal for short strictures without active disease. The reoperation rate is no higher with this approach than with resection, whereas bowel length is preserved. Postoperative medical therapy with agents such as mesalamine, metronidazole, azathioprine, and, more recently, infliximab, is often given to decrease the likelihood of postoperative recurrence.

Severe perianal disease can be incapacitating and difficult to treat if unresponsive to medical management. Diversion of fecal stream can allow the area to be less active, but on reconnection of the colon, disease activity usually recurs.

Support

Psychosocial issues for the child with Crohn disease include a sense of being different, concerns about body image, difficulty in not participating fully in age-appropriate activities, and family conflict brought on by the added stress of this disease. Social support is an important component of the management of Crohn disease. Parents are often interested in learning about other children with similar problems, but children may be hesitant to participate. Social support and individual psychologic counseling are important in the adjustment to a difficult problem at an age that by itself often has difficult adjustment issues. Patients who are socially "connected" fare better. Ongoing education about the disease is an important aspect of management because children generally fare better if they understand and anticipate problems. The Crohn and Colitis Foundation of America has local chapters throughout the United States and supports several regional 1-wk camps for children with Crohn disease.

Prognosis

Crohn disease is a chronic disorder that is associated with high morbidity but low mortality. Symptoms tend to recur despite treatment and often without apparent explanation. Weight loss and growth failure can usually be improved with treatment and attention to nutritional needs. Up to 15% of patients with early growth retardation secondary to Crohn disease have a permanent decrease in linear growth. Osteopenia is particularly common in those with chronic poor nutrition and frequent exposure to high doses of corticosteroids. Dual energy x-ray absorptiometry can help identify patients at risk for developing osteopenia. Steroid-sparing agents, weight bearing exercise, and improved nutrition, including supplementation with vitamin D and calcium, can improve bone mineralization. Some of the extraintestinal manifestations can, in themselves, be major causes of morbidity, including sclerosing cholangitis, chronic active hepatitis, pyoderma gangrenosum, and ankylosing spondylitis.

The region of bowel-involved and complications of the inflammatory process tend to increase with time and include bowel strictures, fistulas, perianal disease, and intraabdominal or retroperitoneal abscess. Most patients with Crohn disease eventually require surgery for one of its many complications; the rate of reoperation is high. Surgery is unlikely to be curative and should be avoided except for the specific indications noted previously. An earlier, most aggressive medical treatment approach, with the goal of exacting mucosal healing may improve long-term prognosis, and this is an active area of investigation. The risk of colon cancer in patients with long-standing Crohn colitis approaches that associated with ulcerative colitis, and screening colonoscopy after 8-10 yr of colonic disease is indicated.

Despite these complications, most children with Crohn disease lead active, full lives with intermittent flare-up in symptoms.

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362.3

Very Early Onset Inflammatory Bowel Disease

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Keywords

immunodeficiency
monogenic
indeterminate colitis
Crohn disease
ulcerative colitis
infant
toddler

IBD may be classified according to age at onset: pediatric onset (<17 yr), early onset (<10 yr), very early onset (<6 yr), infant/toddler onset (0-2 yr), and neonatal onset IBD (<28 days). The incidence of pediatric IBD is rising with the greatest rates of increase occurring among young children. Very early onset IBD (VEO-IBD) accounts for up to 15% of pediatric onset IBD with an estimated prevalence of 14/100,000 children. Approximately 1% of children with IBD are diagnosed below the age of 2 yr.

Although IBD is a complex disorder with genetics, the immune system, the microbiome, and environmental factors each contributing to its development, children with VEO-IBD are more likely to have a *monogenic* cause for their disease. Advances in genetic testing have led to the identification of novel genetic pathways linked to the development of VEO-IBD. Many of these pathways contain genes associated with primary immunodeficiencies (see Tables 362.1 and 362.6). Family history of IBD among first-degree relatives occurs more frequently in children diagnosed at a younger age. Approximately 44% of children diagnosed with ulcerative colitis under the age of 2 will have a first-degree relative with IBD compared to 19% of older children with IBD.

VEO-IBD has a distinct clinical phenotype characterized by a higher likelihood for extensive colonic involvement and a greater tendency for a more aggressive disease course that is refractory to conventional therapies. However, there is a spectrum of clinical presentations within this population, including patients with milder forms of the disease and a more traditional disease course. Younger patients with IBD can present with any combination of diarrhea, abdominal pain, vomiting, and growth failure. Severe perirectal disease can be present and is often associated with monogenic forms of VEO-IBD, including those caused by interleukin 10 receptor gene mutations.

Diagnosis of IBD is ultimately confirmed by upper endoscopy and ileocolonoscopy. Classic histological findings of IBD can be seen, although atypical findings, such as the presence of extensive epithelial apoptosis, could indicate the presence of monogenic disease. Most children with VEO-IBD will have isolated colonic inflammation on ileocolonoscopy. However, the inflammation can be extensive and involve the entire colon making it challenging to differentiate between Crohn disease and ulcerative colitis; 11–22% of patients with VEO-IBD are diagnosed with *indeterminate colitis* at diagnosis. Additionally, an initial diagnosis of ulcerative colitis occurs in approximately 60% of VEO-IBD patients. However, because children with VEO-IBD are more likely to have disease extension over time, a number of patients felt to have indeterminate colitis or ulcerative colitis at diagnosis may eventually be reclassified as having Crohn disease later in life.

The differential diagnosis of VEO-IBD is similar to older children and adults including infectious and allergic colitis (see Table 362.5). However, primary immunodeficiencies, such as chronic granulomatous disease, common variable immunodeficiency, severe combined immunodeficiency, Wiskott-Aldrich Syndrome and immunodysregulation, polyendocrinopathy, and enteropathy, X-linked are higher on the differential (see Table 362.6). Therefore, immunological evaluation is a critical component of diagnosis and management. History of autoimmunity, atypical infections, recurrent infections, skin disorders, and/or hair abnormalities could indicate an underlying immunodeficiency. Laboratory evaluation could include dihydrorhodamine cytometric testing, quantitative immunoglobulins, vaccine titers, as well as testing of B and T cell function. More targeted immunological testing is guided by clinical history. Genetic testing modalities, such as whole exome sequencing, are helpful in identifying rare monogenic pathways responsible for development of the disease.

There are no official consensus guidelines regarding treatment of children with VEO-IBD. Younger children are more likely to fail conventional therapies, such as 5-ASA, immunomodulators, and biologics, and require surgical intervention. Surgical decisions must be made with caution in very young children as disease extension from the colon to the small intestine can occur with time. More extensive and severe disease at presentation could explain the higher rates of treatment failure among younger children. However, other children may fail conventional therapies if the inflammation is being driven by a monogenic disease process that is not targeted by conventional therapies. Therefore, for children with an underlying primary immunodeficiency or a novel monogenic disease process, the specific disease pathway involved may influence treatment choices. In some cases, bone marrow transplantation may be a necessary treatment for the underlying disease process.

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CHAPTER 363

Eosinophilic Gastroenteritis

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Eosinophilic gastroenteritis consists of a group of rare and poorly understood disorders that have in common gastric and small intestine infiltration with eosinophils and peripheral eosinophilia. The esophagus and large intestine may also be involved. Tissue eosinophilic infiltration can be seen in mucosa, muscularis, or serosa. The mucosal form is most common and is diagnosed by identifying large numbers of eosinophils in biopsy specimens of gastric antrum or small bowel. Endoscopy may reveal gastritis or colitis, ulceration, and thickened mucosal folds as well as nodules. This condition clinically overlaps the dietary protein hypersensitivity disorders of the small bowel and colon. Peripheral eosinophilia may be absent. The differential diagnosis also includes celiac disease, chronic granulomatous disease, connective tissue disorders and vasculitides (eosinophilic granulomatosis with polyangiitis), multiple infections (particularly parasites), hypereosinophilic syndrome, early inflammatory bowel disease, medications (tacrolimus, enalapril, naproxen, interferon, rifampicin, azathioprine), and rarely malignancy. Many patients have allergies to multiple foods, seasonal allergies, atopy, eczema, and asthma. Serum immunoglobulin E is commonly elevated. Laboratory abnormalities may include hypoalbuminemia, iron deficiency anemia, and elevated liver enzymes.

The presentation of eosinophilic gastroenteritis is nonspecific. Clinical symptoms often correlate with which layers of the gastrointestinal tract are affected. Mucosal involvement can produce nausea, vomiting, diarrhea, abdominal pain, gastrointestinal bleeding, protein-losing enteropathy, or malabsorption. Involvement of the muscularis can produce obstruction (especially of the pylorus) or intussusception, whereas serosal activity produces abdominal distention and eosinophilic ascites. Presentation in infants can be similar to pyloric stenosis. Laboratory testing often reveals peripheral eosinophilia, elevated serum immunoglobulin E levels, hypoalbuminemia, and anemia.

The disease usually runs a chronic, debilitating course with sporadic severe exacerbations. Although almost always effective for the treatment of isolated eosinophilic esophagitis (see Chapter 350), elemental diets are not always successful for the treatment of eosinophilic gastroenteritis. Orally administered cromolyn sodium and montelukast are sometimes successful. Many patients require treatment for acute disease exacerbations with systemic corticosteroids, which are often effective. Systemic corticosteroids may also be needed long-term. Oral budesonide, a corticosteroid with local anti-inflammatory activity on the bowel mucosa and limited systemic absorption due to high hepatic first-pass metabolism, can be attempted for long-term therapy.

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CHAPTER 364

Disorders of Malabsorption

Raanan Shamir

All disorders of malabsorption are associated with diminished intestinal absorption of one or more dietary nutrients. Malabsorption can result from a defect in the nutrient **digestion** in the intestinal lumen or from defective mucosal **absorption.** Malabsorption disorders can be categorized into generalized mucosal abnormalities usually resulting in malabsorption of multiple nutrients (Table 364.1) or malabsorption of specific nutrients (carbohydrate, fat, protein, vitamins, minerals, and trace elements) (Table 364.2). Almost all the malabsorption disorders are accompanied by chronic diarrhea, which further worsens the malabsorption (Chapter 367).

Table 364.1

Malabsorption Disorders and Chronic Diarrhea Associated With Generalized Mucosal Defect

MUCOSAL DISORDERS
Gluten-sensitive enteropathy (celiac disease) Cow's milk and other protein-sensitive enteropathies Eosinophilic enteropathy
PROTEIN-LOSING ENTEROPATHY
Lymphangiectasia (congenital and acquired) Disorders causing bowel mucosal inflammation, Crohn disease
CONGENITAL BOWEL MUCOSAL DEFECTS
Microvillous inclusion disease Tufting enteropathy Carbohydrate-deficient glycoprotein syndrome Enterocyte heparan sulfate deficiency Enteric anendocrinosis (*NEUROG 3*, *PCSK1* mutations) Tricho-hepatic-enteric syndrome
IMMUNODEFICIENCY DISORDERS
Congenital immunodeficiency disorders Selective immunoglobulin A deficiency (can be associated with celiac disease)

  - Severe combined immunodeficiency
  - Agammaglobulinemia
  - X-linked hypogammaglobulinemia
  - Wiskott-Aldrich syndrome
  - Common variable immunodeficiency disease
  - Chronic granulomatous disease

ACQUIRED IMMUNE DEFICIENCY

- HIV infection
- Immunosuppressive therapy and post–bone marrow transplantation

AUTOIMMUNE ENTEROPATHY

- IPEX (*i* mmune dysregulation, *p* olyendocrinopathy, *e* nteropathy, *X* -linked inheritance)
- IPEX-like syndromes
- Autoimmune polyglandular syndrome type 1

MISCELLANEOUS

- Immunoproliferative small intestinal disease
- Short bowel syndrome
- Blind loop syndrome
- Radiation enteritis
- Protein–calorie malnutrition
- Crohn disease
- Pseudoobstruction

Table 364.2

Classification of Malabsorption Disorders and Chronic Diarrhea Based on the Predominant Nutrient Malabsorbed

CARBOHYDRATE MALABSORPTION

- Lactose malabsorption
- Congenital lactase deficiency
- Hypolactasia (adult type)
- Secondary lactase deficiency
- Congenital sucrase isomaltase deficiency
- Glucose galactose malabsorption

FAT MALABSORPTION

- Exocrine pancreatic insufficiency
  - Cystic fibrosis
  - Shwachman-Diamond syndrome
  - Johanson-Blizzard syndrome
  - Pearson syndrome
- Secondary exocrine pancreatic insufficiency
  - Chronic pancreatitis
  - Protein–calorie malnutrition
  - Decreased pancreozymin/cholecystokinin secretion
- Isolated enzyme deficiency
  - Enterokinase deficiency
  - Trypsinogen deficiency
  - Lipase/colipase deficiency
- Disrupted enterohepatic circulation of bile salts
  - Cholestatic liver disease
  - Bile acid synthetic defects
  - Deconjugation of bile acids (bacterial overgrowth)

- Bile acid malabsorption (terminal ileal disease)
- Intestinal brush border disorders
  - Allergic enteropathy
  - Autoimmune enteropathy
  - Disorders in formation and transport of chylomicrons by enterocytes to the lymphatics
  - Abetalipoproteinemia
  - Homozygous hypobetalipoproteinemia
  - Chylomicron retention disease (Anderson disease)
- Disorders of lymph flow
  - Lymphangiectasia primary/secondary

PROTEIN/AMINO ACID MALABSORPTION

- Lysinuric protein intolerance (defect in dibasic amino acid transport)
- Hartnup disease (defect in free neutral amino acids)
- Blue diaper syndrome (isolated tryptophan malabsorption)
- Oasthouse urine disease (defect in methionine absorption)
- Lowe syndrome (lysine and arginine malabsorption)
- Enterokinase deficiency
- Protein-losing enteropathy
  - *DGAT1* mutation
  - Congenital disorders of glycosylation
  - CD55 deficiency

MINERAL AND VITAMIN MALABSORPTION

- Congenital chloride diarrhea
- Congenital sodium absorption defect
- Acrodermatitis enteropathica (zinc malabsorption)
- Menkes disease (copper malabsorption)
- Vitamin D–dependent rickets
- Folate malabsorption
- Congenital
- Secondary to mucosal damage (celiac disease)
- Vitamin B_{12} malabsorption
- Autoimmune pernicious anemia
- Decreased gastric acid (H_2 blockers or proton pump inhibitors)
- Terminal ileal disease (e.g., Crohn disease) or resection
- Inborn errors of vitamin B_{12} transport and metabolism
- Primary hypomagnesemia

DRUG INDUCED

- Sulfasalazine: folic acid malabsorption
- Cholestyramine: calcium and fat malabsorption
- Anticonvulsant drugs such as phenytoin (causing vitamin D deficiency and folic acid and calcium malabsorption)
- Gastric acid suppression: vitamin B_{12}
- Methotrexate: mucosal injury

Clinical Approach

The clinical features depend on the extent and type of the malabsorbed nutrient. The common presenting features, especially in toddlers with malabsorption, are diarrhea, abdominal distention, and failure to gain weight, with a fall in growth chart percentiles. Physical findings include abdominal distention, muscle wasting, and the disappearance of the subcutaneous fat, with subsequent loose skinfolds (Fig. 364.1). The nutritional consequences of malabsorption are more dramatic in toddlers because of the limited energy reserves and higher proportion of calorie intake being used for weight gain and linear growth. In older children, malnutrition can result in growth retardation, as is commonly seen in children with late diagnosis of celiac disease (CD). If malabsorption is left untreated, linear growth slows, and with prolonged malnutrition, death can follow (see Chapter 57). This extreme outcome is usually restricted to children living in the developing world, where resources to provide enteral and parenteral nutrition support may be limited. Nonetheless, monogenetic causes often produce failure to thrive in all countries. Specific findings on examination can guide toward a specific disorder; edema is usually associated with protein-losing enteropathy (PLE), digital clubbing with cystic fibrosis and CD, perianal excoriation and gaseous abdominal distention with carbohydrate malabsorption, perianal and circumoral rash with acrodermatitis enteropathica, abnormal hair with Menkes syndrome, tricho-hepato-enteric syndrome (THE) and the typical facial features diagnostic of the Johanson-Blizzard syndrome.

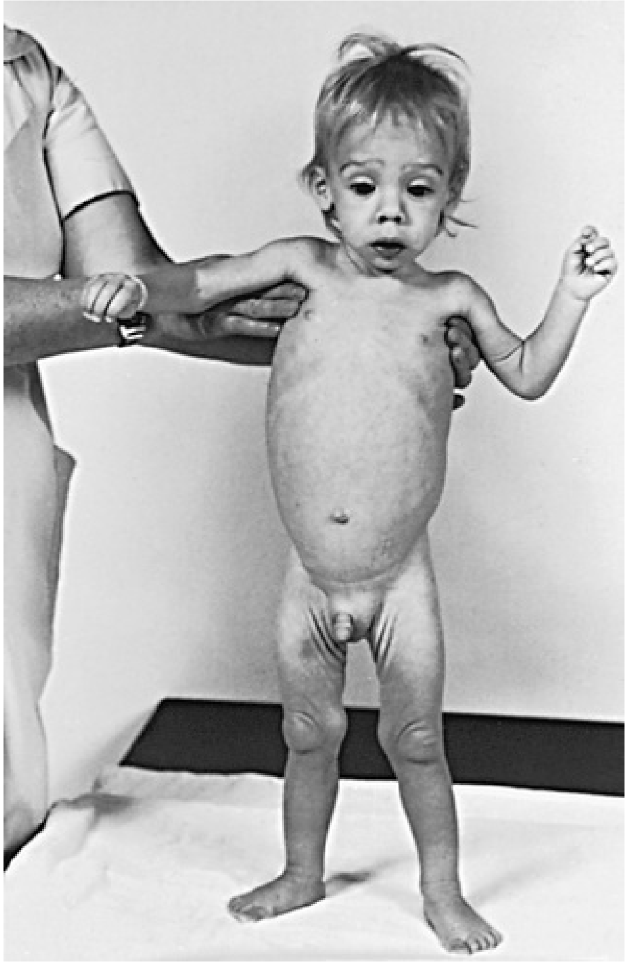

FIG. 364.1 An 18 mo old boy with active celiac disease. Note the loose skinfolds, marked proximal muscle wasting, and distended abdomen. The child looks ill.

Many children with malabsorption disorders have a good appetite as they try to compensate for the fecal protein and energy losses. In exocrine pancreatic insufficiency, fecal losses of up to 40% of ingested protein and energy do not lead to malnutrition, as long as they are compensated by an increased appetite. In conditions associated with villous atrophy or inflammation (CD, postinfectious enteropathy), fecal protein and energy losses are usually modest, but associated anorexia and reduced food intake results in malnutrition.

The nutritional assessment is an important part of clinical evaluation in children with malabsorptive disorders (see Chapter 55). Long-term calcium and vitamin D malabsorption can lead to reduced bone mineral density and metabolic bone disease (often resistant to oral vitamin D), with increased risk of bone fractures. Vitamin K malabsorption, irrespective of the underlying mechanism (fat malabsorption, mucosal atrophy), can result in coagulopathy.

Severe PLE is often associated with malabsorption syndromes (CD, congenital disorders of glycosylation, intestinal lymphangiectasia) and causes hypoalbuminemia and edema. Other nutrient deficiencies include iron malabsorption causing microcytic anemia and low reticulocyte count, low serum folate levels in conditions associated with mucosal atrophy, especially in the proximal part of the small intestinal tract and low serum vitamin A and vitamin E concentrations in fat malabsorption.

The evaluation of a child with malabsorption should be proceed in a stepwise manner. Clinical history alone might not be sufficient to make a specific diagnosis, but it can direct the pediatrician toward a more structured and rational investigative approach. Diarrhea is the main clinical expression of malabsorption. The onset of diarrhea in early infancy suggests a congenital defect (Table 364.3). In secretory diarrhea caused by disorders such as congenital chloride diarrhea (CCD) and microvillus inclusion disease (MVID), the stool is watery and voluminous and can be mistaken for urine (see Chapter 367). The onset of symptoms after the introduction of a particular food into a child's diet can provide diagnostic clues, such as with sucrose in sucrase-isomaltase deficiency. The nature of the diarrhea may be helpful: explosive watery diarrhea suggests carbohydrate malabsorption; loose, bulky stools are associated with CD; and pasty and yellowish offensive stools suggest an exocrine pancreatic insufficiency. Stool color is usually not helpful; green stool with undigested “peas and carrots” can suggest rapid intestinal transit in toddler's diarrhea, which by itself is a self-limiting condition unassociated with failure to thrive.

Table 364.3

Diarrheal Diseases Appearing in the Neonatal Period

CONDITION	CLINICAL FEATURES
Congenital enteropathy	
Microvillus inclusion disease Tufting enteropathy	Secretory diarrhea Secretory diarrhea
Congenital intestinal transport defect	
Congenital glucose–galactose malabsorption Congenital bile acid malabsorption Congenital chloride diarrhea Congenital sodium diarrhea (*GUCY2C* mutation)	Acidic diarrhea Steatorrhea Secretory diarrhea, metabolic alkalosis Hydramnion, secretory diarrhea
Congenital isolated enzyme deficiency	
Congenital lactase deficiency Congenital enterokinase deficiency Congenital trypsinogen deficiency	Acidic diarrhea Failure to thrive, edema Failure to thrive, edema

Congenital lipase and/or colipase deficiency	Failure to thrive, oily stool
Enteric anendocrinosis (*NEUROG 3* mutation)	Hyperchloremic acidosis, failure to thrive
Immunodeficiency and autoinflammatory diseases (see Table 362.6)	Failure to thrive, opportunistic infections, eczema

Following medical history, physical examination and laboratory testing (see next Chapter 364.1), intestinal biopsies may assist in the diagnosis. This is usually done for chronic rather than acute diseases (that can be self-limited). Generalized mucosal villous atrophy (flat mucosa) may be associated with malabsorption of multiple *macronutrients* and *micronutrients* and has a wide range of differential diagnoses (see Chapter 364.2).

364.1

Evaluation of Children With Suspected Intestinal Malabsorption

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Keywords

Steatorrhea
protein-losing enteropathy
carbohydrate malabsorption

The investigation is guided by the history and physical examination. In a child presenting with chronic or recurrent diarrhea, the initial work-up should include stool cultures and antibody tests for parasites; stool microscopy for ova and parasites such as *Giardia* ; and fecal leukocytes and calprotectin or lactoferrin to exclude inflammatory disorders. Stool pH and reducing substances for carbohydrate malabsorption, stool osmolality to differentiate between osmotic and secretory diarrhea and quantitative stool fat examination and α_1 -antitrypsin to demonstrate fat and protein malabsorption, respectively, should also be determined. Fecal stool elastase-1 can determine exocrine pancreatic insufficiency.

A complete blood count, including peripheral smear for microcytic anemia, lymphopenia (lymphangiectasia), neutropenia (Shwachman syndrome), and acanthocytosis (abetalipoproteinemia) is useful. If CD is suspected, serum immunoglobulin (Ig) A and tissue transglutaminase (TG2) antibody levels should be determined. Depending on the initial test results, more specific investigations can be planned.

Investigations for Carbohydrate Malabsorption

The measurement of carbohydrate in the stool for pH and the amount of reducing substances is a simple screening test when available. An acidic stool with >2+ reducing substance suggests carbohydrate malabsorption. Sucrose or starch in the stool is not recognized as a reducing sugar until after hydrolysis with hydrochloric acid, which converts them to reducing sugars.

Breath hydrogen test is used to identify the specific carbohydrate that is malabsorbed. After an overnight fast, the suspected sugar (lactose, sucrose, fructose, or glucose) is administered as an oral solution (carbohydrate load up to 2 g/kg, maximum total of 25 g, depending on the specific carbohydrate type). In malabsorption, the sugar is not digested or absorbed in the small bowel; it passes on to the colon and is metabolized by the normal gut microflora. One of the products of this process is hydrogen gas, which is absorbed through the colon mucosa and excreted in the breath. Increased hydrogen concentration in the breath samples suggests carbohydrate malabsorption. A rise in breath hydrogen of 20 ppm above the baseline preferably with associated symptoms is considered a positive test. The child should not be on antibiotics at the time of the test, because colonic flora is essential for fermenting the sugar.

Small bowel mucosal biopsies can measure mucosal disaccharidase (lactase, sucrase, maltase, palatinase) concentrations directly. In primary enzyme deficiencies the mucosal enzyme levels are low and small bowel mucosal morphology is normal. Primary enzymatic deficiencies can be diagnosed by genetic testing (see Chapters 364.9 and 367). Partial or total villous atrophy due to disorders such as CD, or following acute rotavirus gastroenteritis can result in secondary disaccharidase deficiency and transient lactose intolerance (see Chapter 364.2 for differential diagnosis of villous atrophy). The disaccharidase levels revert to normal after mucosal healing.

Investigations for Fat Malabsorption

The presence of fat globules in the stool suggests fat malabsorption. The ability to assimilate fat varies with age; a premature infant can absorb only 65–75% of dietary fat, a full-term infant absorbs almost 90%, and an older child absorbs more than 95% of fat while on a regular diet. Quantitative determination of fat malabsorption requires a 3-day stool collection for evaluation of fat excretion and determination of the coefficient of fat absorption:

$$\text{Coefficient of fat absorption } \% = (\text{fat intake} - \text{fecal fat losses}/\text{fat intake}) \times 100$$

where fat intake and fat losses are in grams. Because fecal fat balance studies are cumbersome, expensive, and unpleasant to perform, simpler tests are often preferred. Among these stool tests, the acid steatocrit test is the most reliable. When BA deficiency is suspected of being the cause of fat malabsorption, the evaluation of BA levels in duodenal fluid aspirate may be useful. Intestinal mucosal abnormalities affect not only fat absorption, but also steatorrhea, and are usually far less severe in intestinal mucosal disorders (CD, cow's milk protein enteropathy) than in exocrine pancreatic insufficiency.

Exocrine pancreatic insufficiency and other fat malabsorption disorders (see Table 364.2) are usually associated with deficiencies of fat-soluble vitamins A, D, E, and K. Serum concentrations of vitamins A, D, and E can be measured. A prolonged prothrombin time is an indirect test to assess vitamin K malabsorption and subsequent deficiency.

Investigations for Protein-Losing Enteropathy

Dietary and endogenous proteins secreted into the bowel are almost completely absorbed and minimal amounts of protein from these sources passes into the colon. The majority of the stool nitrogen is derived from gut bacterial proteins. Excessive bowel protein loss usually manifests as hypoalbuminemia. Because the most common cause of hypoalbuminemia in children is a renal disorder, urinary protein excretion must be determined. Other potential causes of hypoalbuminemia include acute infection, liver disease (reduced production) and inadequate protein intake. Very rarely hypoalbuminemia can result from an extensive skin disorder (burns) causing protein loss via the skin. Measurement of stool α_1 -antitrypsin is a useful screening test for PLE. This serum protein has a molecular weight similar to albumin; however, unlike albumin it is resistant to digestion in the gastrointestinal (GI) tract. Excessive α_1 -antitrypsin excretion in the stool should prompt further investigations to identify the specific cause of gut or stomach (Menetrier disease) protein loss.

Investigations for Exocrine Pancreatic Function

Cystic fibrosis (Chapter 432) is the most common cause of exocrine pancreatic insufficiency in children; therefore, a sweat chloride test must be performed before embarking on invasive tests to investigate possible exocrine pancreatic insufficiency (Fig. 364.2). Many cases of cystic fibrosis are detected by neonatal genetic screening programs; occasional rare mutations are undetected.

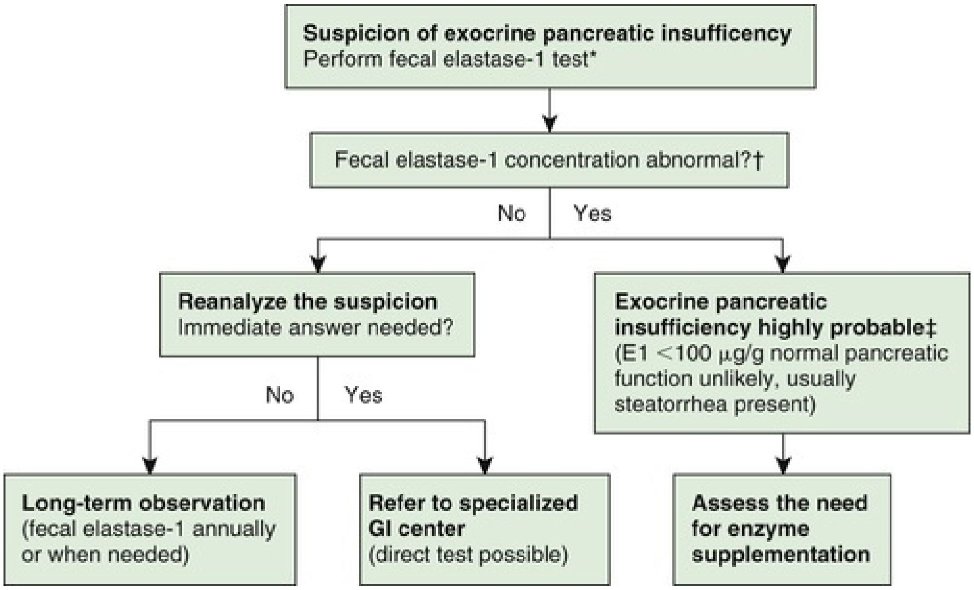
Suspicion of exocrine pancreatic insuffiency
Perform fecal elastase-1 test*
Fecal elastase-1 concentration abnormal?†
No
Yes
Reanalyze the suspicion
Immediate answer needed?
No
Yes
Exocrine pancreatic insufficiency highly probable‡
(E1 <100 µg/g normal pancreatic function unlikely, usually steatorrhea present)
Long-term observation
(fecal elastase-1 annually or when needed)
Refer to specialized GI center
(direct test possible)
Assess the need for enzyme supplementation

FIG. 364.2 **Algorithm for assessment of exocrine pancreatic function. *If not available, use another test. Perform appropriate imaging studies of the pancreas. †In case of borderline values, consider repeating the test with 3 independent samples. ‡Consider differential diagnosis (especially consider mucosal villous atrophy and dilution effect of watery stool).** ***GI*** **, Gastrointestinal. (Modified from Walkowiak J, Nousia-Arvanitakis S, Henker J, et al: Indirect pancreatic function tests in children,** ***J Pediatr Gastroenterol Nutr*** **40[2]:107–114, 2005.)**

Fecal elastase-1 estimation is a sensitive test to assess exocrine pancreatic function in chronic cystic fibrosis and pancreatitis. Elastase-1 is a stable endoprotease unaffected by exogenous pancreatic enzymes. One disadvantage of the fecal elastase-1 test is the lack of full differentiation between primary exocrine pancreatic insufficiency and exocrine pancreatic dysfunction secondary to intestinal villous atrophy. The proximal small bowel is the site for pancreozymin/cholecystokinin production; the latter is the hormone that stimulates enzyme secretion from the exocrine pancreas. Mucosal atrophy can lead to diminished pancreozymin/cholecystokinin secretion and subsequently to exocrine pancreatic insufficiency. Fecal elastase-1 can also give a false-positive result during acute episodes of diarrhea.

Serum trypsinogen concentration can also be used as a screening test for exocrine pancreatic insufficiency. In cystic fibrosis, the levels are greatly elevated early in life, and then they gradually fall, so that by 5-7 yr of age, most patients with cystic fibrosis with pancreatic insufficiency have subnormal levels. Patients with cystic fibrosis and adequate exocrine pancreatic function tend to have normal or elevated levels. In such patients, observing the trend in serial serum trypsinogen estimation may be useful in monitoring exocrine pancreatic function. In Shwachman syndrome, another condition associated with exocrine pancreatic insufficiency, the serum trypsinogen level is low.

Other tests for pancreatic insufficiency (nitroblue tetrazolium–paraaminobenzoic acid test and pancreolauryl test) measure urine or breath concentrations of substances released and absorbed across the mucosal surface following pancreatic digestion. These tests lack specificity and are rarely used in clinical practice.

The gold standard test for exocrine pancreatic function is direct analysis of duodenal aspirate for volume, bicarbonate, trypsin, and lipase upon secretin, and pancreozymin/cholecystokinin stimulation. This involves duodenal intubation (see Chapter 375).

Investigations for Intestinal Mucosal Disorders

Establishing a specific diagnosis for malabsorption often requires histologic examination of small bowel mucosal biopsies. These are obtained during endoscopy, which allows multiple biopsies to be performed, because mucosal involvement can be patchy, especially in CD. Periodic acid–Schiff (PAS) staining of mucosal biopsies and electron microscopy are necessary in congenital diarrhea to assess congenital microvillus atrophy. Bowel mucosal lesions can also be segmental in cases of IL. In these situations, radiographic small bowel series, repeated ultrasonographies or lymphoscintigraphy can identify a region of thickened bowel responsible for protein loss. Intestinal biopsies can detect infectious agents such as *Giardia lamblia* . During endoscopy, mucosal biopsies can be obtained to measure mucosal disaccharidase activities. Duodenal aspirates can be performed to measure pancreatic enzyme concentration as well as quantitative bacterial cultures.

Imaging Procedures

Plain radiographs and barium contrast studies might suggest a site and cause of intestinal motility disorders. Although flocculations of barium and dilated bowel with thickened mucosal folds have been attributed to diffuse malabsorptive lesions such as CD, these abnormalities are nonspecific. Diffuse fluid-filled bowel loops during sonography also suggest malabsorption.

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364.2

Celiac Disease

Riccardo Troncone, Raanan Shamir

Keywords

celiac disease
gluten
prolamines
HLA DQ2
DQ8
tissue transglutaminase
small bowel biopsy
gluten free diet

Etiology and Epidemiology

CD is an immune-mediated systemic disorder elicited by gluten in wheat and related prolamines from rye and barley in genetically susceptible individuals, and is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD–specific antibodies, human leukocyte antigen (HLA)-DQ2 or DQ8 haplotypes, and enteropathy. CD–specific antibodies comprise autoantibodies against TG2 including endomysial antibodies (EMAs), and antibodies against deamidated forms of gliadin peptides.

CD is a common disorder with about 1% prevalence of biopsy-proven disease. It is thought to be rare in Central Africa and East Asia. Although CD develops in genetically susceptible individuals, environmental factors might affect the risk of developing CD or the timing of its presentation. Neither breastfeeding during gluten introduction nor any breastfeeding has been shown to reduce the risk of CD. The earlier introduction of gluten is associated with the earlier development of CD autoimmunity (positive serology) and CD, but the cumulative incidence of each in later childhood is not affected. It is advised to introduce gluten into the infant's diet anytime between 4 and 12 mo of age. Infectious agents have been hypothesized to play a causative role as frequent rotavirus infections were shown to be associated with an increased risk of developing CD. It is plausible that the contact with gliadin at a time when there is an ongoing intestinal inflammation alters intestinal permeability, and the enhanced antigen presentation can increase the risk of developing CD, at least in a subset of persons. The mode of delivery, socioeconomic status, season of birth, and the use of drugs have been associated with the risk of developing CD, but the evidence is contradictory.

Genetics and Pathogenesis

A genetic predisposition is suggested by the family aggregation and the concordance in monozygotic twins, which approaches 100%. The strongest association is with HLA-DQ2.5 (1 or 2 copies encoded by DQA1 *05 [for the alpha] and DQB1*02 genes [for the beta chain]). Such a DQ molecule has been found to be present in more than 90% of CD patients. The highly homologous DQ2.2 molecule confers a much lower risk, while the data available on DQ2-negative CD patients indicate that they almost invariably are HLA-DQ8–positive (DQA1*0301/DQB1*0302). A gene dosage effect has been proved in prospective studies, and a molecular hypothesis for such a phenomenon has been proposed, based on the impact of the number and quality of the HLA-DQ2 molecules on gluten peptide presentation to T cells. The HLA locus is the most significant and dominant gene associated with CD; however, other loci known to contribute to CD have been documented. Most have been found to be associated with other autoimmune diseases such as type 1 diabetes. Interestingly, very few polymorphisms associated with CD are in coding regions, as they often are in binding sites for transcription factors, then affecting gene expression.

CD is a T-cell–mediated chronic inflammatory disorder with an autoimmune component. Altered processing by intraluminal enzymes, changes in intestinal permeability and activation of innate immunity mechanisms precede the activation of the adaptive immune response. Immunodominant epitopes from gliadin are highly resistant to intraluminal and mucosal digestion; incomplete degradation favors the immunostimulatory and toxic effects of these sequences. Some gliadin peptides (p31-43) activate innate immunity, in particular they induce interleukin (IL)-15. The latter, but also type 1 interferons, may alter the tolerogenic phenotype of dendritic cells, resulting in lamina propria T-cell activation by other peptides presented in the context of HLA-DQ2 or HLA-DQ8 molecules. Gliadin-specific T-cell responses are enhanced by the action of TG2: the enzyme converts particular glutamine residues into glutamic acid, which results in higher affinity of these gliadin peptides for HLA-DQ2 or HLA-DQ8.

The pattern of cytokines produced following gliadin activation is dominated by interferon-γ (T-helper type 1 skewed); IL-21 is also upregulated. In downstream T-cell activation a complex remodeling of the mucosa takes place, involving increased levels of metalloproteinases and growth factors, which leads to the classical histologic finding of a flat mucosa. A severe impairment of intraepithelial lymphocytes (IELs) homeostasis is present in CD. IL-15 is implicated in the expression of natural killer receptors CD94 and NKG2D, as well as in epithelial expression of stress molecules, thus enhancing cytotoxicity, cell apoptosis, and villous atrophy. The most evident expression of autoimmunity is the presence of serum antibodies to TG2. However, the mechanisms leading to autoimmunity are largely unknown, as well as their pathogenetic significance. *Potential* CD, in which TG2 antibodies can be detected in situ without any histologic abnormality, shows that the production of antibodies does not necessarily lead to intestinal damage. The finding that IgA deposits on extracellular TG2 are not limited to the intestine but can be found in the liver, lymph nodes, and muscles indicates that TG2 is accessible to the gut-derived autoantibodies, turning CD into a systemic disease.

Clinical Presentation and Associated Disorders

Clinical features of CD vary considerably. Intestinal symptoms are more common in children whose disease is diagnosed *within the first 2 yr of life* ; failure to thrive, chronic diarrhea, vomiting, abdominal distention, muscle wasting, anorexia, and irritability are present in most cases (Fig. 364.3). Occasionally there is constipation, with cases presenting with intussusception. As the age at presentation of the disease shifts to later in childhood, and with the more extensive use of serologic screening tests, extraintestinal manifestations, without any accompanying digestive symptoms, have increasingly become recognized, affecting almost all organs (Table 364.4). One of the most common extraintestinal manifestation of CD is iron-deficiency anemia, which is usually unresponsive to iron therapy. Osteoporosis may be present; in contrast to adults, it can be reversed by a gluten-free diet, with restoration of normal peak bone densitometric values. Other extraintestinal manifestations include short stature, delayed puberty, arthritis and arthralgia, epilepsy with bilateral occipital calcifications, peripheral neuropathies, isolated hypertransaminasemia, dental enamel hypoplasia, and aphthous stomatitis. The mechanisms responsible for the severity and the variety of clinical presentations remain obscure. Nutritional deficiencies or abnormal immune responses have been advocated. Silent CD is recognized, mainly in asymptomatic first-degree relatives of CD patients and in subjects affected by diseases associated with CD (Table 364.5). Small bowel biopsy in silent/subclinical CD reveals severe mucosal damage consistent with CD. Potential CD is defined when patients have positive CD–specific antibodies, but without documented small bowel damage (Table 364.6).

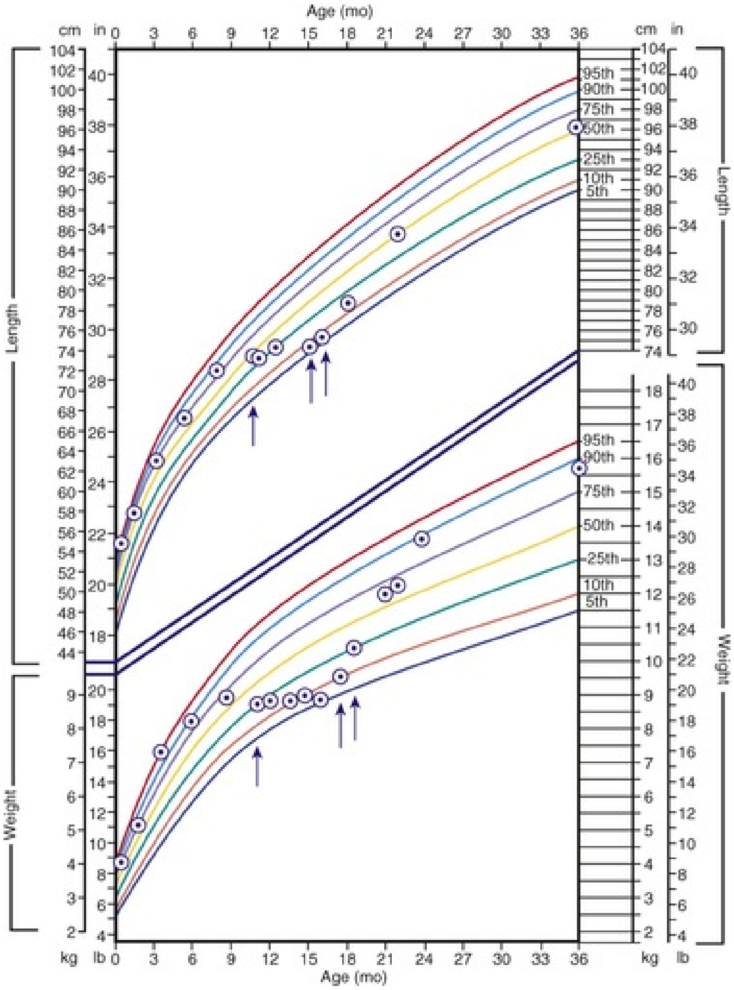

FIG. 364.3 Gluten-sensitive enteropathy. Growth curve demonstrates initial normal growth from 0 to 9 mo, followed by onset of poor appetite with intermittent vomiting and diarrhea after initiation of gluten-containing diet *(single arrow)* . After biopsy conformed diagnosis and treatment with gluten-free diet *(double arrow)* , growth improves.

Table 364.4

Extraintestinal Manifestations of Celiac Disease

MANIFESTATION	PROBABLE CAUSE(S)
CUTANEOUS	
Ecchymoses and petechiae	Vitamin K deficiency; rarely, thrombocytopenia
Edema	Hypoproteinemia
Dermatitis herpetiformis	Epidermal (type 3) tTG autoimmunity
Follicular hyperkeratosis and dermatitis	Vitamin A malabsorption, vitamin B complex malabsorption
ENDOCRINOLOGIC	
Amenorrhea, infertility, impotence, delayed puberty	Malnutrition, hypothalamic-pituitary dysfunction, immune dysfunction
Secondary hyperparathyroidism	Calcium and/or vitamin D malabsorption with hypocalcemia
HEMATOLOGIC	
Anemia	Iron, folate, vitamin B_{12} , or pyridoxine deficiency
Hemorrhage	Vitamin K deficiency; rarely, thrombocytopenia due to folate deficiency
Thrombocytosis, Howell-Jolly bodies	Hyposplenism
HEPATIC	
Elevated liver biochemical test levels Autoimmune hepatitis	Lymphocytic hepatitis Autoimmunity
MUSCULAR	
Atrophy	Malnutrition due to malabsorption
Tetany	Calcium, vitamin D, and/or magnesium malabsorption
Weakness	Generalized muscle atrophy, hypokalemia
NEUROLOGIC	
Peripheral neuropathy	Deficiencies of vitamin B_{12} and thiamine; immune-based neurologic dysfunction
Ataxia	Cerebellar and posterior column damage
Demyelinating central nervous system lesions	Immune-based neurologic dysfunction
Seizures	Unknown
SKELETAL	
Osteopenia, osteomalacia, and osteoporosis	Malabsorption of calcium and vitamin D, secondary hyperparathyroidism, chronic inflammation
Osteoarthropathy	Unknown
Pathologic fractures	Osteopenia and osteoporosis
OTHER	
Enamel hypoplasia	Vitamin D, calcium malabsorption
Anxiety, schizophrenia	Unknown, uncertain
Pulmonary hemosiderosis	Unknown, uncertain
Aphthous stomatitis	Unknown

tTG , tissue transglutaminase.

Modified from Kelly CP: Celiac disease. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, Philadelphia, 2016, Elsevier. Table 107.1.

Table 364.5

National Institute for Health and Care Excellence Guidelines on the Indications That Should Prompt Testing for Celiac Disease

CELIAC TESTING RECOMMENDED
• Persistent unexplained abdominal or gastrointestinal symptoms • Faltering growth • Prolonged fatigue • Unexpected weight loss • Severe or persistent mouth ulcers • Unexplained iron, vitamin B12, or folate deficiency • Type 1 diabetes • Autoimmune thyroid disease • Irritable bowel syndrome • First degree relatives of people with coeliac disease • Dermatitis herpetiformis
CELIAC TESTING SHOULD BE CONSIDERED
• Metabolic bone disorders (reduced bone mineral density or osteomalacia) • Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia) • Unexplained subfertility or recurrent miscarriage • Persistently increased concentrations of liver enzymes with unknown cause • Dental enamel defects • Down syndrome • Turner syndrome • William syndrome • Selective IgA deficiency

IgA , immunoglobulin-A.

From Downey L, Houten R, Murch S, Longson D for the Guideline Development Group: Recognition, assessment, and management of coeliac disease: summary of updated NICE guidance, *BMJ* 351: h4513, 2015.

Table 364.6

Clinical Spectrum of Celiac Disease

SYMPTOMATIC
Frank malabsorption symptoms and signs (e.g., chronic diarrhea, failure to thrive, weight loss) Extraintestinal symptoms and signs (e.g., anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis)
SILENT
No apparent symptoms in spite of histologic evidence of villous atrophy In most cases identified by serologic screening in at-risk groups (see Table 364.1)
LATENT
Subjects who have a normal intestinal histology, but at some other time have shown a gluten-dependent enteropathy
POTENTIAL

Subjects with positive celiac disease serology but without evidence of altered intestinal histology. Patients may or may not have symptoms and signs of disease and may or may not develop a gluten-dependent enteropathy later

Some diseases—many with an autoimmune pathogenesis—are found with a higher-than-normal incidence in CD patients. Among these are type 1 diabetes, autoimmune thyroid disease, Addison disease, Sjögren syndrome, rheumatoid arthritis, autoimmune cholangitis, autoimmune hepatitis, and primary biliary cholangitis. Such associations have been interpreted as a consequence of the sharing of identical HLA haplotypes, but a direct role of gluten in promoting autoimmunity cannot be excluded. The relation between CD and other autoimmune diseases is poorly defined; once those diseases are established, they are not influenced by a gluten-free diet. Other associated conditions include selective IgA deficiency and Down, Turner, and Williams syndromes.

Diagnosis

The diagnosis of CD is based on a combination of symptoms, antibodies, HLA status, and duodenal histology. The initial approach to symptomatic patients is to test for anti-TG2 IgA antibodies and for total IgA in serum to exclude IgA deficiency. If IgA anti-TG2 antibodies are negative, and serum total IgA is normal for age, CD is unlikely to be the cause of the symptoms. If anti-TG2 antibody testing is positive the patients should be referred to a pediatric gastroenterologist for further diagnostic workup, which depends on the serum antibody levels.

IgA anti-TG2 decline if the patient is on a gluten free diet. In patients with selective IgA deficiency, testing is recommended with IgG antibodies to TG2.

Patients with positive anti-TG2 antibody levels <10 times the upper limit of normal should undergo upper endoscopy with multiple biopsies. In patients with positive anti-TG2 antibody levels at or >10 times the upper limit of normal, blood should be drawn for HLA and EMA testing. If the patient is positive for EMA antibodies and positive for DQ2 or DQ8 HLA testing, the diagnosis of CD is confirmed, a life-long gluten-free diet is started and the patient is followed for the improvement of symptoms and the decline of antibodies. HLA testing is almost always positive; thus, it is possible that HLA testing will not be necessary in the future to establish diagnosis. In the rare case of negative results for HLA and/or anti-EMA in a child with TG2 antibody titers >10 times the upper limits of normal, the diagnostic workup should be extended, including repeated testing and duodenal biopsies (Fig. 364.4). In asymptomatic persons belonging to high-risk groups, CD should always be diagnosed using duodenal biopsies (Fig. 364.5). When biopsies are indicated, at least 4 fragments should be obtained from the descending part of the duodenum and at least 1 from the duodenal bulb. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten-free diet. CD is not the only cause for villous atrophy (Table 364.7). Gluten challenge and biopsies will only be necessary in selected cases in which diagnostic uncertainty remains.

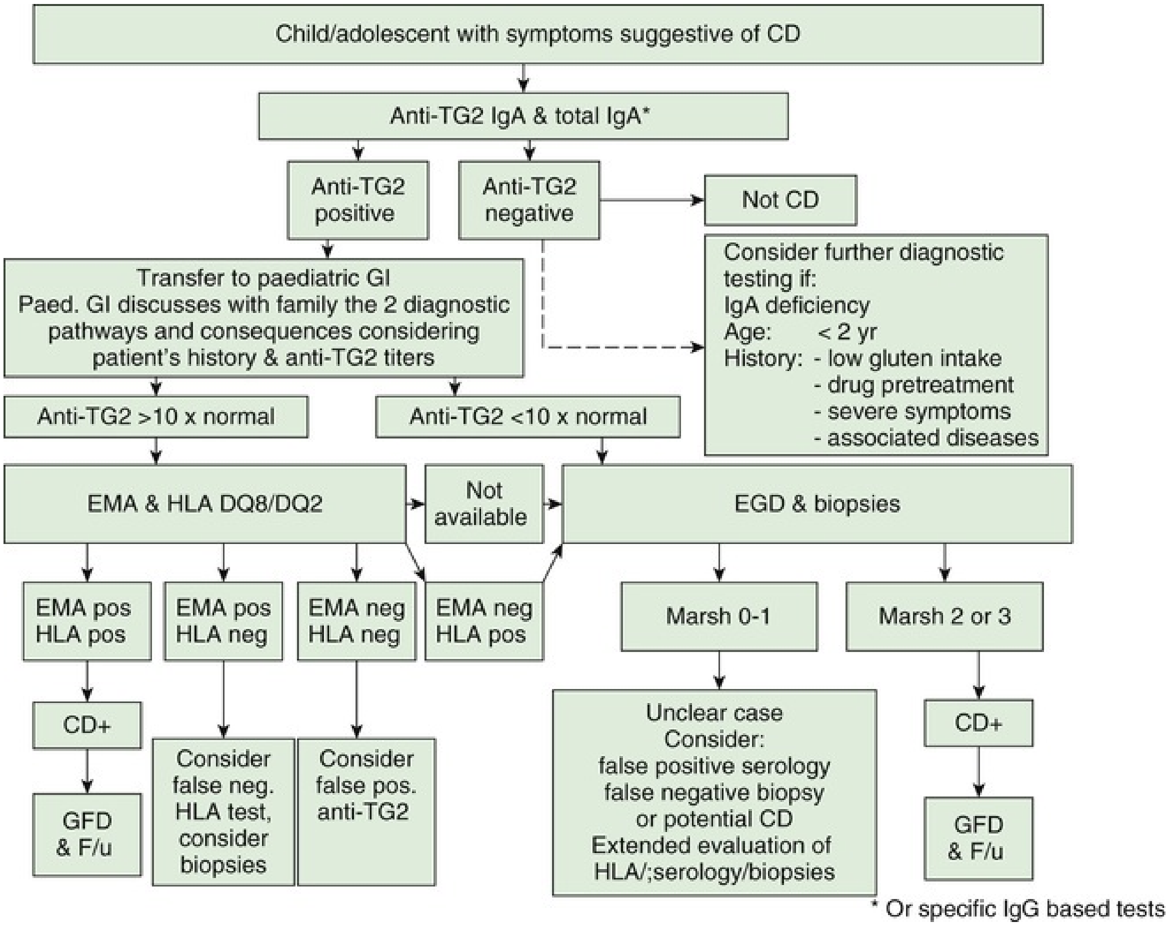
Child/adolescent with symptoms suggestive of CD
Anti-TG2 IgA & total IgA*
Anti-TG2 positive
Anti-TG2 negative
Not CD
Consider further diagnostic testing if:
IgA deficiency
Age: < 2 yr
History: - low gluten intake
- drug pretreatment
- severe symptoms
- associated diseases
Transfer to paediatric GI
Paed. GI discusses with family the 2 diagnostic pathways and consequences considering patient's history & anti-TG2 titers
Anti-TG2 >10 x normal
Anti-TG2 <10 x normal
EMA & HLA DQ8/DQ2
Not available
EGD & biopsies
EMA pos HLA pos
EMA pos HLA neg
EMA neg HLA neg
EMA neg HLA pos
Marsh 0-1
Marsh 2 or 3
CD+
GFD & F/u
Consider false neg. HLA test, consider biopsies
Consider false pos. anti-TG2
Unclear case
Consider:
false positive serology
false negative biopsy
or potential CD
Extended evaluation of HLA/;serology/biopsies
CD+
GFD & F/u
* Or specific IgG based tests

FIG. 364.4 Diagnostic algorithm for celiac disease in symptomatic children/adolescents, according to ESPGHAN. *CD* , Celiac disease; *EGD,* esophagogastroduodenoscopy; *EMA* , endomysial antibodies; *GFD* , gluten-free diet; *GI* , gastrointestinal; *HLA* , human leukocyte antigen; *Ig* , immunoglobulin. (Modified from Husby S, Koletzko S, Korponay-Szabò IR, et al: European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for the diagnosis of celiac disease, *J Pediatr Gastroenterol Nutr* 54[1]:136–160, 2012. Fig. 1.)

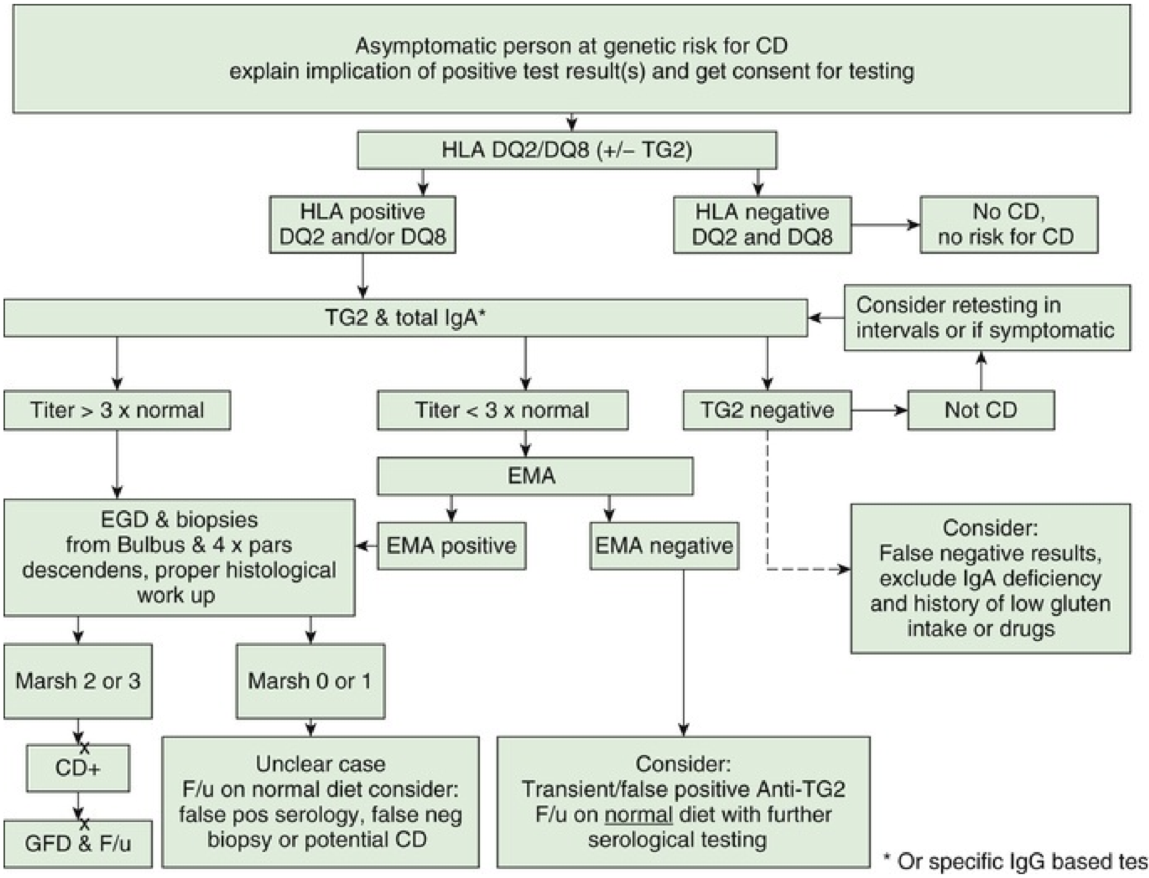
Asymptomatic person at genetic risk for CD
explain implication of positive test result(s) and get consent for testing
HLA DQ2/DQ8 (+/– TG2)
HLA positive DQ2 and/or DQ8
HLA negative DQ2 and DQ8
No CD, no risk for CD
TG2 & total IgA*
Consider retesting in intervals or if symptomatic
Titer > 3 x normal
Titer < 3 x normal
TG2 negative
Not CD
EMA
EGD & biopsies from Bulbus & 4 x pars descendens, proper histological work up
EMA positive
EMA negative
Consider: False negative results, exclude IgA deficiency and history of low gluten intake or drugs
Marsh 2 or 3
Marsh 0 or 1
CD+
GFD & F/u
Unclear case F/u on normal diet consider: false pos serology, false neg biopsy or potential CD
Consider: Transient/false positive Anti-TG2 F/u on normal diet with further serological testing

* Or specific IgG based tests

FIG. 364.5 Diagnostic algorithm for celiac disease *(CD)* in asymptomatic children/adolescents belonging to at-risk groups, according to ESPGHAN. *EGD,* Esophagogastroduodenoscopy; *EMA* , endomysial antibodies; *Ig* , immunoglobulin; *HLA* , human leukocyte antigen; *TG2* , transglutaminase. (Modified from Husby S, Koletzko S, Korponay-Szabò IR, et al: European Society for Pediatric Gastroenterology, Hepatology and Nutrition Guidelines for the diagnosis of celiac disease, *J Pediatr Gastroenterol Nutr* 54[1]:136–160, 2012. Fig. 2.)

Table 364.7

Other Causes of Flat Mucosa

Autoimmune enteropathy
Tropical sprue
Giardiasis
HIV enteropathy
Bacterial overgrowth
Crohn disease
Eosinophilic gastroenteritis
Cow's milk enteropathy
Food allergy
Primary immunodeficiency

Graft-versus-host disease
Chemotherapy and radiation
Protein energy malnutrition

Treatment

The only treatment for CD is lifelong strict adherence to a gluten-free diet. This requires a wheat-, barley-, and rye-free diet (Tables 364.8 and 364.9). Despite evidence that oats are safe for most patients with CD, there is concern regarding the possibility of contamination of oats with gluten during harvesting, milling, and shipping. Nevertheless, it seems wise to add oats to the gluten-free diet only when the latter is well established, so that possible adverse reactions can be readily identified. There is a consensus that all CD patients should be treated with a gluten-free diet regardless of the presence of symptoms. However, whereas it is relatively easy to assess the health improvement after treatment of CD in patients with clinical symptoms of the disease, it proves difficult in persons with asymptomatic CD. The nutritional risks, particularly osteopenia and increased risk for other autoimmune disorders, are those mainly feared for subjects who have silent CD and continue on a gluten-containing diet. Little is known about the health risks in untreated patients with potential CD.

Table 364.8

Principles of Initial Dietary Therapy for Patients With Celiac Disease

Avoid all foods containing wheat, rye, and barley gluten (pure oats usually safe).
Avoid malt unless clearly labeled as derived from corn.
Use only rice, corn, maize, buckwheat, millet, amaranth, quinoa, sorghum, potato or potato starch, soybean, tapioca, and teff, bean, and nut flours.
Wheat starch and products containing wheat starch should only be used if they contain <20 ppm gluten and are marked “gluten free.”
Read all labels and study ingredients of processed foods.
Beware of gluten in medications, supplements, food additives, emulsifiers, or stabilizers.
Limit milk and milk products initially if there is evidence of lactose intolerance.
Avoid all beers, lagers, ales, and stouts (unless labeled gluten free).
Wine, most liqueurs, ciders, and spirits, including whiskey and brandy, are allowed.

ppm , Parts per million.

Table 364.9

Some Potential Sources of Hidden Gluten

- Beers, ales, other fermented beverages (distilled beverages acceptable)
- Bouillon and soups
- Candy
- Communion wafers
- Drink mixes
- Gravy and sauces
- Herbal tea
- Imitation meat and seafood
- Nutritional supplements
- Play-Doh
- Salad dressings and marinades
- Self-basting turkeys
- Soy sauce

From Kelly CP. Celiac disease. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, Philadelphia, Elsevier, 2016. Box 107.3.

Some patients do not respond to a gluten free diet; *refractory or nonresponsive CD* requires a systematic approach to determine the correct diagnosis, compliance, and therapeutic options (Fig. 364.6).

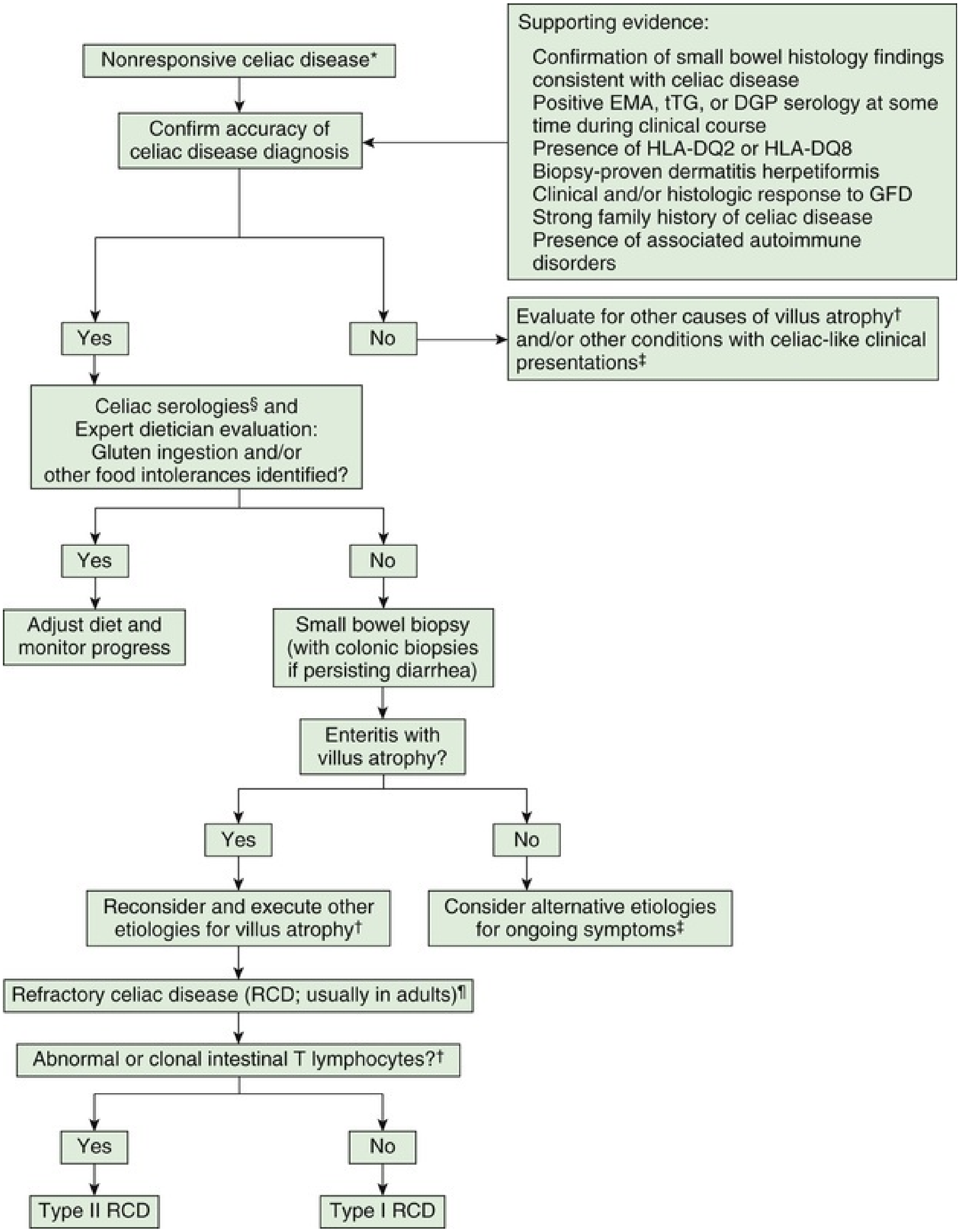
Nonresponsive celiac disease*
Confirm accuracy of celiac disease diagnosis
Supporting evidence:
Confirmation of small bowel histology findings consistent with celiac disease
Positive EMA, tTG, or DGP serology at some time during clinical course
Presence of HLA-DQ2 or HLA-DQ8
Biopsy-proven dermatitis herpetiformis
Clinical and/or histologic response to GFD
Strong family history of celiac disease
Presence of associated autoimmune disorders
Yes
No
Evaluate for other causes of villus atrophy† and/or other conditions with celiac-like clinical presentations‡
Celiac serologies§ and Expert dietician evaluation: Gluten ingestion and/or other food intolerances identified?
Yes
No
Adjust diet and monitor progress
Small bowel biopsy (with colonic biopsies if persisting diarrhea)
Enteritis with villus atrophy?
Yes
No
Reconsider and execute other etiologies for villus atrophy†
Consider alternative etiologies for ongoing symptoms‡
Refractory celiac disease (RCD; usually in adults)¶
Abnormal or clonal intestinal T lymphocytes?†
Yes
No
Type II RCD
Type I RCD

FIG. 364.6 Diagnostic algorithm for the approach to patients with nonresponsive celiac disease. **Nonresponsive celiac disease* may be defined as persistent symptoms and signs despite 6-12 mo of dietary gluten avoidance. Abnormal TTG can last even 2-3 yr. † Causes of non-celiac small intestinal villus atrophy that may be misdiagnosed as celiac disease include autoimmune enteropathy, tropical sprue, SIBO, hypogammaglobulinemia, combined variable immunodeficiency, collagenous sprue, eosinophilic enteritis, Crohn disease, and peptic duodenitis. ‡ Conditions that present clinically in a fashion similar to celiac disease but where villus atrophy is not evident

include IBS, food intolerances, SIBO, eosinophilic enteritis, Crohn disease, and microscopic colitis. § Positive serologic testing for celiac disease despite 12 mo of treatment with a GFD suggest that there may be ongoing gluten ingestion. ‖ *Refractory celiac disease (RCD)* is defined as persistent or recurrent malabsorptive symptoms and signs, with small intestinal villus atrophy despite a strict GFD for more than 12 mo and in the absence of other disorders including overt lymphoma. ¶ Abnormal intestinal lymphocytes may be identified by immunohistochemistry of intraepithelial lymphocytes or by flow cytometry showing an increased number of CD3-positive cells that lack CD8 or by the identification of clonal T-cell receptor gene rearrangement by molecular analysis. *EMA* , Endomysial antibody; *DGP* , deamidated gliadin peptide; *GFD* , gluten-free diet; *HLA* , human leukocyte antigen; *tTGA* , tissue transglutaminase antibody. (Adapted from Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease. *Gut* 59:547–57, 2010; and Rubio-Tapia A, Hill ID, Kelly CP, et al. ACG clinical guidelines: Diagnosis and management of celiac disease. *Am J Gastroenterol* 108:656–76, 2013.)

The Codex Alimentarius Guidelines define gluten-free food item for food containing <20 ppm (equivalent to 20 mg gluten in 1 kg of product); however, although analytical methods for gluten detection have reached a satisfactory degree of sensitivity, more information is needed on the daily gluten amount that may be tolerated by CD patients. The data available so far seem to suggest that the threshold should be set to <50 mg/day, although individual variability makes it difficult to set a universal threshold.

It is important that an experienced dietician with specific expertise in CD counseling educates the family and the child about dietary restriction. Compliance with a gluten-free diet can be difficult, especially in adolescents. It is recommended that children with CD be monitored with periodic visits for assessment of symptoms, growth, physical examination, complete blood count, thyroid diseases, and adherence to the gluten-free diet. Periodic measurements of TG2 antibody levels to document reduction in antibody titers can be helpful as indirect evidence of adherence to a gluten-free diet, although they are insensitive to slight dietary transgressions. If compliance is uncertain, bone health should be assessed.

The Spectrum of Gluten-Related Disorders

CD is not the only disorder related to gluten ingestion. Symptoms in IgE-mediated wheat allergy are usually immediate (urticaria, angioedema, asthma, exercise-induced anaphylaxis). Diagnosis is based on dietary challenge, in vitro assay for specific IgE and skin testing.

Non-celiac gluten sensitivity (NCGS) is a poorly understood condition.

Diagnosis is suspected in patients who do not have CD or wheat allergy, and yet show GI and non-GI symptoms upon ingestion of gluten- or wheat-containing food. In the general population, the incidence of self-reported gluten avoidance varies from 0.5 to 13%. Similar symptoms are often experienced by patients with irritable bowel syndrome (IBS), and some patients with IBS respond positively to a gluten-free diet.

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364.3

Other Malabsorptive Syndromes

Corina Hartman, Raanan Shamir

Keywords

Microvillus inclusion disease
Secretory diarrhea
Congenital tufting enteropathy
Tricho-hepatic-enteric syndrome
Enteric anendocrinosis
Proprotein convertase 1/3
Mitchell-Riley syndrome
Autoimmune enteropathy
Abetalipoproteinemia
Steatorrhea
Hypobetalipoproteinemia
Chylomicron retention disease
DGAT1
Wolman disease
Adrenal calcification
Lysosomal acid lipase
Tangier disease
Sitosterolemia

Primary bile acids malabsorption
Congenital diarrhea
Protein-losing enteropathy
Intestinal lymphangiectasia

Defects of Enterocyte Differentiation and Polarization

This group mainly includes 2 conditions characterized by typical histological and ultrastructural lesions in the intestinal biopsies, microvillus inclusion disease (MVID) and congenital tufting enteropathy (CTE). Tricho-hepato-enteric syndrome (THE) or syndromic/phenotypic diarrhea is also usually classified in this group.

Microvillus Inclusion Disease (Congenital Microvillus Atrophy)

MVID is an autosomal recessive disorder, which manifests at birth with profuse watery *secretory diarrhea* . A late-onset variant, with onset 2-3 mo postnatal has also been described. It is the most severe cause of congenital diarrhea involving the development of the intestinal mucosa. Light microscopy of the small bowel mucosa demonstrates diffuse thinning of the mucosa, with hypoplastic villus atrophy and no inflammatory infiltrate. Diagnosis is performed with light microscopy using PAS and CD10 staining, which shows a very thin or absent brush border, together with positive PAS and CD10 intracellular inclusions. Electron microscopy shows enterocytes with absent or sparse microvilli. The apical cytoplasm of the enterocytes contains electron-dense secretory granules; the hallmark is the presence of microvilli within involutions of the apical membrane (Fig. 364.7). Polyhydramnios is observed on prenatal sonography, and neonates usually present very early onset of severe watery diarrhea (up to 200-330 mL/kg/day) causing dehydration and failure to thrive. Despite parenteral nutrition, diarrhea continues, and initial fluid management is difficult. MVID and Fanconi syndrome that have been described in two patients may complicate management because of the additional features of a renal tubular acidosis, phosphaturia, rickets, and renal fluid losses. Mutations of the *MYO5B* gene coding for a nonconventional motor protein, myosin Vb, are associated with MVID in a cohort of patients suffering from early-onset MVID.

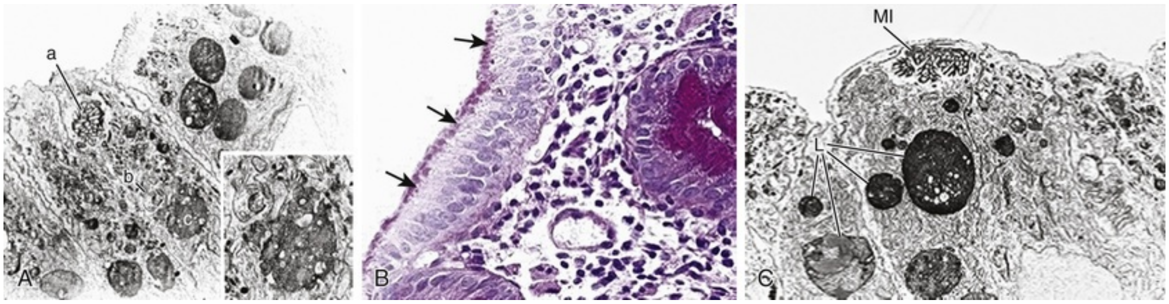

FIG. 364.7 **Microvillus inclusion disease. A, From top to bottom: microvillus inclusion *(a)* , a granule with few microvilli *(b)* , and a lysosome *(c)* detected in the same enterocyte. *Inset:* Higher magnification of *b* and *c* ×11,000, inset ×21,500. B, Microvillus inclusion disease. Periodic acid-Schiff (PAS) staining highlights abundant PAS-positive material *(arrows)* in the apical part of the enterocyte cytoplasm. C, Microvillus inclusion disease. The villous enterocyte lack brush-border microvilli, whereas their apical cytoplasm contains a microvillus inclusion *(MI)* and numerous lysosomes *(L)* ×5,500. (*A,* From Morroni M, Cangiotti AM, Guarino A, et al: Unusual ultrastructural features in microvillous inclusion disease: a report of two cases, *Virchows Arch* 448[6]:805–810, 2006.)**

MYO5B mutations result in mislocalization of apical proteins and disrupted enterocyte polarization, leading to MVID. Another gene, the t-SNARE syntaxin3 *(STX3)* , has been described in patients with MVID and a milder phenotype. Patients with mutations in the STX3 binding protein *STXBP2/Munc18-2* , causing familial hemophagocytic lymphohistiocytosis type 5, also show microvillus atrophy and histologic findings reminiscent of MVID. Loss of STX3 or Munc18-2 inhibits the fusion of vesicles with the apical membrane, resulting in the intracellular retention of apical proteins. *MYO5B* mutations have also been identified in several patients with progressive familial intrahepatic cholestasis (PFIC)-like phenotype with normal serum gamma-glutamyl transferase activity and without intestinal disease.

Tufting Enteropathy (Congenital Tufting Enteropathy)

CTE (intestinal epithelial dysplasia) manifests in the first few weeks of life with persistent watery diarrhea. CTE accounts for a small fraction of infants with *intractable diarrhea of infancy* . The distinctive feature on small intestinal mucosal biopsy is focal epithelial tufts (teardrop-shaped groups of closely packed enterocytes with apical rounding of the plasma membrane) involving 80–90% of the epithelial surface. The typical pathology does not appear immediately after birth; other enteropathies may show tufts on the epithelial surface.

CTE is a phenotypic and genetic heterogenous condition. Genetic studies identified mutations in epithelial cell adhesion molecule *(EPCAM)* gene in 73% of patients and mutations in hepatocyte growth factor activator inhibitor type 2 *SPINT2/HAI2* gene in 21%. No identified mutations are identified in a minority of patients. The phenotype associated with mutations of *EPCAM* is usually an isolated congenital diarrhea without associated extra digestive symptoms, except late-onset arthritis or superficial punctuate keratitis. In the *syndromic* form of CTE, diarrhea is associated with 1 or more of these same anomalies: superficial punctate keratitis (100%), choanal atresia (50%), esophageal or intestinal atresia, anal imperforation, hair dysplasia, skin hyperlaxity, bone abnormalities, hexadactylia, and facial dysmorphism.

No specific treatment exists, thus, as for MVID, management requires permanent parenteral nutrition (PN) with possible intestinal transplantation (see Chapter 365).

Tricho-Hepato-Enteric Syndrome (Syndromic Diarrhea)

THE, also known as *syndromic diarrhea* (SD), is a congenital enteropathy manifesting with early onset of severe diarrhea. Patients are born small for gestational age and present with diarrhea starting in the first 6 mo of life. They have an abnormal phenotype, including facial dysmorphism with prominent forehead, broad nose, and hypertelorism with a distinct abnormality of hair, **trichorrhexis nodosa** . Hairs are woolly, easily removed, and poorly pigmented. Abnormal cutaneous lesions including café-au-lait on the lower limbs may be observed. Liver disease affects about half of the patients with extensive fibrosis or cirrhosis. Cardiac abnormalities and colitis have been reported sporadically, as well as one case involving polyhydramnios, placental abnormalities, and congenital hemochromatosis. Patients may have defective antibody responses despite normal serum Ig levels and defective antigen-specific skin tests despite positive proliferative responses in vitro. Patients with THE can also present as very-early-onset inflammatory bowel disease (IBD). Small bowel biopsies show nonspecific villus atrophy with or without mononuclear cell infiltration of the lamina propria, and without specific histologic abnormalities involving the epithelium. Mutations in either tetratricopeptide repeat domain 37 *(TTC37)* gene (60%) or *SKIV2L* (40%) have been identified as cause of THE syndrome. Enterocytes with *TTC37* mutations, show reduced expression of brush-border-associated NHE-2 and -3, aquaporin-7, the Na+/I- symporter, and the H+/K+-ATPase or mislocalization relative to their normal pattern. Prognosis of this type of intractable diarrhea of infancy is poor. The long-term follow-up of these children reported that at 15 years about 50% of patients were alive or have been weaned off PN. The main complications are liver disease and infections. Most of the children achieve short final stature and half are slightly developmentally delayed.

Defects in Enteroendocrine Cells Differentiation

This class of congenital diarrheas is characterized by abnormal enteroendocrine cells development or function. The genes causing these disorders encode either transcription factors essential for the development of all or a subset of enteroendocrine cells, or cellular proteins/endopeptidases that are required for the production of active hormones from prohormones. The conditions manifest with *osmotic* diarrhea and in some, additional systemic endocrine disorders. The treatment is nutritional support and hormonal replacement if needed. Four genes have been associated with the diseases classified in this group: *NEUROG3*, *RFX6*, *ARX*, and *PCSK1* .

Enteric Anendocrinosis

NEUROG3 is a key transcription factor that controls the fate of endocrine cells in both the pancreas and intestine. Mutations of the *NEUROG3* gene produce generalized mucosal malabsorption, vomiting, diarrhea, failure to thrive, dehydration, and a hyperchloremic metabolic acidosis. Oral alimentation with anything other than water produces diarrhea. Villus-crypt architecture in small bowel biopsies is normal, but staining for neuroendocrine cells (e.g., employing antichromogranin antibodies) demonstrates a complete absence of this secretory cell lineage with the preservation of goblet cells and Paneth cells.

Proprotein Convertase 1/3 Deficiency

Autosomal recessive proprotein convertase 1/3 (PC1/3) deficiency, caused by mutations in the *PCSK1* gene, is characterized by severe congenital malabsorptive diarrhea, early-onset obesity, and other endocrine abnormalities. All functional hormones produced by endocrine cells, including those in the gut, are processed by a specific Ca2+-dependent serine endoprotease named proprotein convertase 1/3 (also known as neuroendocrine convertase 1). Chronic watery, neonatal onset diarrhea is described in infants with hyperinsulinism, hypoglycemia, hypogonadism, and hypoadrenalism. A small bowel biopsy reveals a nonspecific enteropathy.

Growth hormone deficiency, adrenal insufficiency, central diabetes insipidus, and hypogonadism are commonly observed.

Mitchell-Riley Syndrome

Mitchell-Riley syndrome is a complex clinical phenotype that includes severe intrauterine growth restriction, neonatal diabetes, GI anomalies (annular pancreas, intestinal malrotation, gallbladder agenesis, abnormal biliary tract) and chronic *osmotic* diarrhea. Several probands previously reported with Mitchell-Riley syndrome had *RFX6* mutations. DNA-binding protein RFX6 (regulatory factor X6; encoded by *RFX6*) is a winged helix transcription factor downstream of neurogenin-3 signal required for islet cell development and enteroendocrine cell function. Immunofluorescence staining in RFX6 knockout mice shows that pancreatic endocrine cells are present, but do not express the islet cell hormones including insulin, glucagon, somatostatin, or ghrelin.

Aristaless-Related Homeobox Gene Mutations

Aristaless-related homeobox (Arx) gene encodes a homeodomain containing a transcription factor required for the normal development of mouse and human enteroendocrine cells. *Arx* expression is detected in a subset of neurogenin3-

positive endocrine progenitors and is also found in a subset of hormone-producing cells. In mice, removal of *Arx* from the developing endoderm results in a decrease of some enteroendocrine cell types, such as gastrin, glucagon/GLP-1, CCK, secretin secreting cells and an increase of somatostatin-expressing cells. Mutations in the *ARX* gene are associated with a complex clinical phenotype of X-linked intellectual disability, seizures, lissencephaly, abnormal genitalia, and occasionally congenital diarrhea.

Autoimmune Enteropathy

The term autoimmune enteropathy describes a subgroup of infants with severe, protracted diarrhea, no response to dietary restriction, the presence of circulating gut autoantibodies and/or associated autoimmune diseases and the lack of severe immunodeficiency. Symptoms of autoimmune enteropathy usually occur after the first 6 mo of life, presenting with chronic diarrhea, PLE, malabsorption, and failure to thrive. The diagnosis is based on the endoscopic and histologic identification of inflammation mainly of the *small bowel* but also of the colon. Histologic findings in the small bowel include partial or complete villus atrophy, crypt hyperplasia, and an increase in chronic inflammatory cells in the lamina propria. Marked intraepithelial lymphocytosis reminiscent of CD can be present in a subset of patients. Cryptitis and crypt abscesses can also be seen and may obscure the presence of apoptosis. Immunologic analyses indicate the presence of autoantibodies including *anti–enterocyte antibodies (present in ∼85% of patients)* , as well as *anti–autoimmune enteropathy-related 75 kDa antigen* .

The differential diagnosis of pediatric autoimmune enteropathy includes other immune-mediated disorders, such as food sensitivity enteropathies (e.g., cow milk intolerance and celiac disease), Crohn disease and graft-versus-host disease. It is essential to exclude an underlying primary immune deficiency, particularly in boys with other autoimmune features because some have **IPEX syndrome** (see Chapter 152.5). Different phenotypes of IPEX syndrome patients, as well as IPEX-like forms of autoimmune enteropathy that are *FOXP3* -independent are described involving females with or without extraintestinal autoimmune disorders.

Treatment options are limited and are based on nutritional support, including parenteral nutrition and glucocorticoids followed by immunosuppressive drugs. Hematopoietic stem cell transplantation is indicated in patients with a known molecular defect, such as IPEX syndrome.

Autoimmune Polyglandular Syndrome Type 1

See Chapter 151 .

Defects in Lipids Transport and Metabolism)

See Chapter 104.3 .

After uptake from the lumen, fatty acids and monoacylglycerol are transported to the endoplasmic reticulum (ER). In the ER they are converted to triglycerides in several metabolic steps, the last of which is dependent on acyl CoA:diacylglycerol acyltransferase 1 (DGAT1). Apolipoprotein B (ApoB) and microsomal triglycerides transfer protein (MTTP) act in concert to incorporate triglycerides into chylomicrons. The newly formed chylomicrons bud from the ER in a prechylomicron transport vesicle (PCTV), which subsequently fuses with the Golgi, a process that is dependent on Sar1b. The chylomicron is then transported in a vesicle to the basal membrane, where it exits the cell.

Abetalipoproteinemia

Abetalipoproteinemia (Bassen-Kornzweig syndrome) is a rare autosomal recessive disorder of lipoprotein metabolism associated with severe fat malabsorption/steatorrhea from birth (see Chapter 104.3). Children fail to thrive during the 1st yr of life, have stools that are pale, foul smelling, and bulky. The abdomen is distended, and deep tendon reflexes are absent because of peripheral neuropathy, which is secondary to vitamin E deficiency. Intellectual development tends to be slow. After 10 yr of age, intestinal symptoms are less severe, ataxia may develop, with loss of position and vibration sensation, and the onset of intention tremors. These latter symptoms reflect involvement of the posterior columns, cerebellum, and basal ganglia. In adolescence, in the absence of adequate supplement of vitamin E, atypical retinitis pigmentosa develops.

The diagnosis is suggested by the presence of acanthocytes in the peripheral blood smear and extremely low plasma levels of cholesterol (<50 mg/dL); triglycerides are also very low (<20 mg/dL). Chylomicrons and very-low-density lipoproteins are not detectable, and the low-density lipoprotein (LDL) fraction is virtually absent from the circulation. Marked triglyceride accumulation in villus enterocytes occurs in the duodenal mucosa. Patients with abetalipoproteinemia have mutations of the *MTTP* gene. MTTP catalyzes the transfer of triglycerides to nascent ApoB particles in the ER.

Specific treatment is not available. Nutritional support and large supplements of the fat-soluble vitamins A, D, E, and K should be given. Vitamin E (100-200 mg/kg/24 hr) appears to arrest neurologic and retinal degeneration. Limiting long-chain fat intake can alleviate intestinal symptoms; medium-chain triglycerides (MCTs) can be used to supplement fat intake.

Homozygous Hypobetalipoproteinemia

Homozygous hypobetalipoproteinemia (see Chapter 104.3) is a dominantly inherited condition associated with mutations in the *APOB* gene, encoding ApoB, the apolipoprotein of the nascent chylomicron. The homozygous form is indistinguishable from abetalipoproteinemia. The parents of these patients, as heterozygotes, have reduced plasma LDL and apoprotein-B concentrations, whereas the parents of patients with abetalipoproteinemia have normal levels. On transmission electron microscopy of small bowel biopsies, the size of lipid vacuoles in enterocytes differentiates between abetalipoproteinemia and hypobetalipoproteinemia: many small vacuoles are present in hypobetalipoproteinemia, and larger vacuoles are seen in abetalipoproteinemia.

Chylomicron Retention Disease (Anderson Disease)

Chylomicron retention disease (CRD) is a rare autosomal recessive disorder caused by mutations in the *SAR1B* gene. *SAR1B* mutations result in defective trafficking of nascent chylomicrons in pre-chylomicron transport vesicles between the ER and the Golgi apparatus, interfering with the successful assembly of chylomicrons and their delivery to the lamina propria. The patients with CRD have steatorrhea, chronic diarrhea, and failure to thrive. Acanthocytosis is rare and neurologic manifestations are less severe than those observed in abetalipoproteinemia. Plasma cholesterol levels are moderately reduced (<75 mg/dL) and fasting triglycerides are normal, but the fat-soluble vitamins, particularly A and E, are very low. Treatment is early aggressive therapy with fat-soluble vitamins and modification of dietary fat intake, as in the treatment of abetalipoproteinemia.

DGAT1 Mutation

DGAT1 encodes for diacyl CoA:diacylglycerol acyl transferase (DGAT) that converts diacylglycerides to triglycerides by adding an acyl CoA moiety. In the small intestine, DGAT1 helps to reassemble the triglycerides, whereas in the liver it produces triglycerides from fatty acids synthesized de novo or taken up from the circulation. The mechanism by which *DGAT1* mutations causes diarrhea is unclear but is likely to involve the build-up of DGAT1 lipid substrates in the enterocytes or in the gut lumen. Mutations in *DGAT1* gene have been reported in patients presenting with failure to thrive, PLE, hypoalbuminemia, early-onset diarrhea, and oral vitamin D refractory rickets.

Wolman Disease

Wolman disease is a rare, lethal lipid storage disease that leads to lipid accumulation in multiple organs, including the small intestine. In addition to vomiting, severe diarrhea, and hepatosplenomegaly, patients have steatorrhea as a result of lymphatic obstruction. Insufficient free cholesterol available for steroidogenesis in adrenal glands results in adrenal insufficiency; a characteristic pattern of subcapsular adrenal calcification represents a distinctive marker of disease. Deficiency of lysosomal acid lipase (LAL) is the underlying cause of disease (see Chapter 104.4). LAL is a lysosomal enzyme that hydrolyzes cholesteryl esters and triglycerides within endo-lysosomes. Loss-of-function mutations in the *LIPA* gene are associated with variable phenotypes. Homozygous and compound heterozygous mutations, resulting in complete LAL deficiency, cause Wolman disease. Mutations associated with residual LAL activity cause cholesteryl ester storage disease, a less severe disorder exhibiting a variable phenotype. Common features in infants, children, and adults include elevated serum aminotransferase levels, dyslipidemia, hepatomegaly, liver fibrosis, and cirrhosis. Wolman disease may also present with neonatal cholestasis and severe liver disease as its main feature already in infancy. Hemophagocytic lymphohistiocytosis has been reported in few infants with Wolman disease. The hallmark of the disease is the presence of *adrenal calcification* seen on imaging, and definite diagnosis is done genetically.

Hematopoietic stem cell transplantation has been reported in few patients with variable outcome. A recombinant human enzyme-replacement therapy for LAL deficiency is approved for use in patients suffering from LAL deficiency. This treatment has allowed a small number of infants with Wolman disease to achieve a relatively normal growth rate and to improve survival. In older children and adults, the enzyme has corrected their dyslipidemia and produced significant improvement in markers of hepatic function.

Tangier Disease

See Chapter 104 .

Cellular free cholesterol is mobilized, along with phospholipid, through the export pump ABCA1, resulting in the transfer to an extracellular ApoA-I acceptor and the formation of discoidal high-density lipoprotein (HDL) cholesterol. Loss-of-function mutations in *ABCA1* genes in patients with Tangier disease cause cholesterol accumulation in the intestine, spleen, tonsils, relapsing neuropathy, orange-brown spots on the colon and ileum, and diarrhea in association with decreased plasma cholesterol levels (ApoA-I and A-II), with virtually no detectable plasma HDL. Specific therapy for Tangier disease has not yet been established.

Sitosterolemia

See Chapter 104.4 .

Sitosterol and other sterols are preferentially secreted back into the intestinal lumen through the sterol pump, paired half-transporters ABCG5/G8. Mutations of the *ABCG5* (sterolin-1) and *ABCG8* (sterolin-2) transporters result in the defective efflux of sterol and leads to the increased absorption of dietary sterols. The disorder is associated with tendon xanthomas, increased atherosclerosis, and hemolysis. Plasma levels of phytosterols (mainly sitosterol) are typically >10 mg/dL.

Bile Acid Malabsorption

Bile acids (BA) are detergent compounds secreted by and excreted from the liver, and are responsible for the solubilization of the dietary lipids, aiding in their digestion and absorption. Approximately 95% of BAs are reabsorbed in the terminal ileum and transported back to the liver, the enterohepatic circulation. The apical Na+-dependent bile salt transporter (ASBT) or ileal BA transporter (IBAT) is responsible for the active reuptake of BAs in the terminal ileum. Mutation in the *ASBT/SLC10A2* gene are very rare and are responsible for *primary* BA malabsorption, a disease associated with congenital diarrhea, steatorrhea, and reduced plasma cholesterol levels. Unabsorbed BA stimulate chloride excretion in the colon, resulting in diarrhea. *Secondary* BA malabsorption can result from ileal disease, such as in Crohn disease, and following ileal resection. The diagnosis of BA malabsorption is typically based on reduced BA retention of radiolabeled ^{75} Selenium-homocholic acid taurine (^{75} SeHCAT), increased BA synthesis (serum C4) or increased fecal BA loss. In clinical practice, diagnosis is often based on the response to BA sequestrants (e.g., cholestyramine or colesevelam), which are also the treatment of choice for this disorder.

Chronic neonatal-onset diarrhea has also been described in autosomal recessive cerebrotendinous xanthomatosis, which is caused by an inborn error of BA synthesis resulting from 27-hydroxylase deficiency. These children also present with juvenile-onset cataracts and developmental delay. Neonatal cholestasis has also been described as a presenting feature. Tendon xanthomas develop in the 2nd and 3rd decades of life. The diagnosis is important to establish, because treatment is effective when employing oral chenodeoxycholic acid.

Protein-Losing Enteropathy

PLE is a rare entity caused by a variety of intestinal and extraintestinal disorders and characterized by excessive enteric loss of plasma proteins. The clinical presentation of patients with PLE is variable and depends upon the underlying cause, but generally includes edema and hypoproteinemia. Impaired synthesis (malnutrition, liver disease), protein loss through other organs (kidney or skin) or redistribution (septic states) have to be excluded before considering PLE. The disorders causing PLE can be divided into those due to protein loss from an inflamed or abnormal mucosal surface or from derangements in intestinal lymphatics, such as in primary or secondary **IL** (Table 364.10).

Table 364.10
Causes of Protein-Losing Enteropathy

PROTEIN-LOSING ENTEROPATHY		**AGENT, DISEASES (*GENE*)**
Gastrointestinal infections	Viral infections Bacterial and parasitic diseases Gastrointestinal infestations	CMV, rotavirus *Salmonella, Shigella, Campylobacter, Clostridium difficile, Helicobacter pylori, Whipple disease* Small bowel bacterial overgrowth *Giardiasis* *Strongyloides stercoralis*
Gastrointestinal inflammatory disorders	Gastric diseases Gastrointestinal disorders	Menetrier disease Eosinophilic gastroenteropathy Food induced enteropathy Celiac disease, Crohn disease, Ulcerative colitis, Tropical sprue Radiation enteritis GVHD, NEC
Gastrointestinal malignancies	Adenocarcinomas Lymphomas Kaposi sarcoma	Esophageal, gastric, colonic
Vasculitic disorders	Henoch Schönlein purpura Systemic lupus erythematosus	
Drugs	NSAIDs	
Metabolic/genetic	Congenital disorders of glycosylation (CDG) Mutations in *DGAT1* gene Mutations in CD55	CDG-Ib (*MPI)* Congenital enterocyte heparan sulphate deficiency (*ALG6)*
Intestinal lymphangiectasia	Congenital/ Primary IL • Syndromal/genetic/ metabolic	Turner, Noonan, Klippel–Trenaunay–Weber Hennekam syndrome *(CCBE1, FAT4)* PLE with skeletal dysplasia (*FGFR3*) Generalized lymphatic dysplasia (*PIEZO1)*
	Secondary • Infection • Inflammation • Radiotherapy • Neoplastic disorders • Cardiac disorders	Abdominal tuberculosis Crohn disease, sarcoidosis Retroperitoneal fibrosis Retroperitoneal malignancies, lymphoma Constrictive pericarditis, after Fontan operation, congestive heart failure

CDG , Carbohydrate deficient glycoprotein; *CMV* , cytomegalovirus; *GVHD* , graft versus host disease; *IL* , intestinal lymphangiectasia; *NEC* , *NSAIDs* , nonsteroidal anti-inflammatory drugs; *PLE* , protein-losing enteropathy.

IL is characterized by diffuse or local dilatation of the enteric lymphatics and is located in the mucosa, submucosa, or subserosa. Lymph rich in proteins, lipids, and lymphocytes leak into the bowel lumen, resulting in PLE, steatorrhea, and lymphocyte depletion. Hypoalbuminemia, hypogammaglobulinemia, edema, lymphopenia, malabsorption of fat and fat-soluble vitamins, and chylous ascites often occur. IL can also manifest with ascites, peripheral edema, and a low serum albumin. The etiology of *primary* IL is unknown. Several genes, including vascular endothelial growth factor receptor 3 *(VEGFR3)* , prospero-related homeobox-transcriptional factor *(PROX1)* , forkhead transcriptional factor *(FOXC2)* , and SRY (sex determining region Y)-Box 18 *(SOX18)* , are involved in the development of the lymphatic system and have been shown to have altered expression in the duodenal mucosa in patients with IL. Recently, mutation in CD55, a regulator of complement activation, was described as a cause for primary PLE. The diagnosis of PLE is suggested by the typical clinical and laboratory findings in association with an elevated fecal α_1 -antitrypsin clearance. Radiologic findings of uniform, symmetric thickening of mucosal folds throughout the small intestine are characteristic but nonspecific. Small bowel mucosal biopsy in patients with IL can show dilated lacteals with distortion of villi and no inflammatory infiltrate. A patchy distribution and deeper mucosal involvement on occasion causes false-negative results on small bowel histology. Video capsule endoscopy may reveal similar lesions (Figs. 364.8 and 364.9).

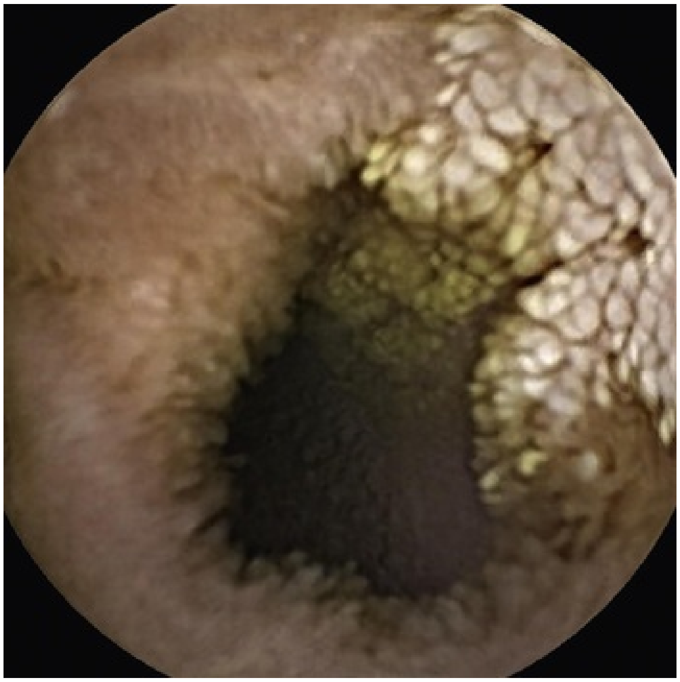

FIG. 364.8 Swollen villi detected by video capsule endoscopy in the proximal ileum. (From Gortani G, Maschio M, Ventura A: A child with edema, lower limb deformity, and recurrent diarrhea, *J Pediatr* 161:1177, 2012, Fig. 1.)

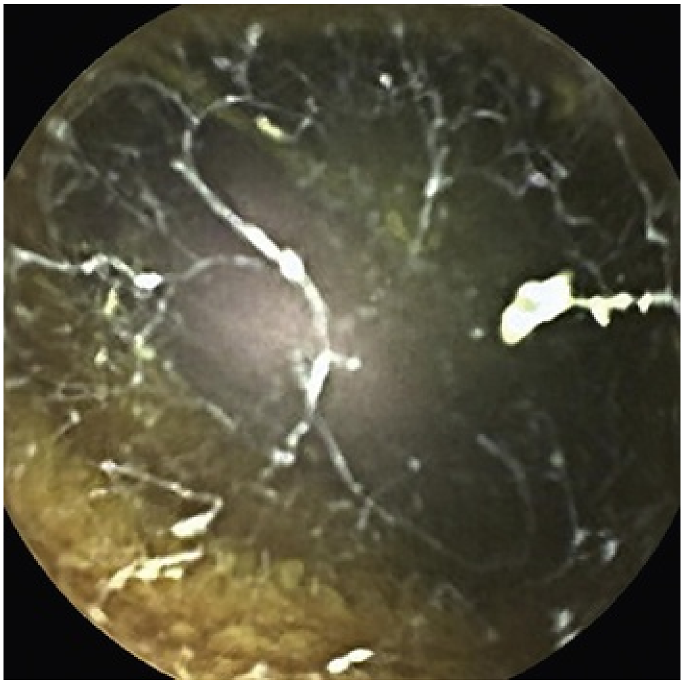

FIG. 364.9 Protein-rich lymphatic fluid aggregates detected by video capsule endoscopy in the intestinal lumen. (From Gortani G, Maschio M, Ventura A: A child with edema, lower limb deformity, and recurrent diarrhea, *J Pediatr* 161:1177, 2012, Fig. 2.)

Treatment of PLE is generally supportive and consists of a low fat and high-protein diet. In patients with IL, a low-fat and high-protein diet supplemented with MCTs is recommended. Besides dietary adjustments, appropriate treatment for the underlying etiology is necessary, as well as supportive care to avoid complications of edema. Rarely, parenteral nutrition is required. If only a portion of the intestine is involved, surgical resection may be considered. Few patients with lymphatic malformation and generalized lymphatic anomalies were successfully treated with propranolol. Successful use of mTOR inhibitor, everolimus, in a patient with primary IL has been reported. Prognosis depends upon the severity and treatment options of the underlying disease.

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364.4

Intestinal Infections and Infestations Associated With Malabsorption

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Keywords

Postinfectious diarrhea
Environmental enteropathy
Tropical sprue
Proximal intestinal bacterial overgrowth
Whipple disease

Malabsorption is a rare consequence of primary intestinal infection and infestation in immunocompetent children, but is relatively common in malnourished children and is associated with significant mortality. Often malabsorption is associated with diarrhea and triggers a vicious circle with wasting and growth failure. For children living in developing countries, malabsorption is associated with long-term growth failure leading to stunting within a peculiar condition defined as environmental enteropathy, in which diarrhea is not always present. Generally, malabsorption is associated with a duration of an intestinal infection longer than expected. *Prolonged* diarrhea is an acute-onset diarrhea that lasts >7 days, whereas *chronic* diarrhea lasts >14 days (some use 30 days to define chronic).

Postinfectious Diarrhea

In infants and toddlers, chronic diarrhea can appear following infectious enteritis, regardless of the nature of the pathogen. The pathogenesis of the diarrhea is not always clear and may be related to persistent infection or re-infection, secondary lactase deficiency, food protein allergy, antibiotic-associated diarrhea or a combination of these. In some cases, postinfectious diarrhea may be the initial manifestation of functional diarrhea, in which case is not associated with malabsorption.

Treatment of postinfectious diarrhea is supportive and may include a lactose-free diet in the presence of secondary lactase deficiency; infants might require a semi-elemental diet. The beneficial effect of specific probiotic products may be indicated in selected conditions.

Proximal Intestinal Bacterial Overgrowth

Bacteria are normally present in large numbers in the colon (10^{11}-10^{13} colony-forming units [CFU]/g of feces) and have a symbiotic relationship with the host, providing nutrients and protecting the host from pathogenic organisms. Bacteria are usually present only in a small number in the stomach and small bowel; excessive numbers of bacteria in the stomach or small bowel are harmful. Bacterial overgrowth can result from clinical conditions that alter the gastric pH or small bowel motility, including disorders such as partial bowel obstruction, diverticula, intestinal failure, intestinal duplications, diabetes mellitus, idiopathic intestinal pseudoobstruction syndrome, and scleroderma, as well as proton pump inhibitor use. Prematurity, immunodeficiency, and malnutrition are other factors associated with bacterial overgrowth of the small bowel.

The diagnosis of bacterial overgrowth is often difficult and can be made by culturing small bowel aspirate ($>10^5$ CFU/mL) or by a lactulose hydrogen breath test. Lactulose is a synthetic disaccharide, which is not digested by mucosal brush border enzymes but can be fermented by bacteria. High baseline breath hydrogen and a quick rise in hydrogen in expired breath samples support the diagnosis of bacterial overgrowth; false-positive tests are common.

Bacterial overgrowth leads to inefficient intraluminal processing of dietary fat with steatorrhea due to bacterial deconjugation of bile salts, vitamin B_{12} malabsorption, and microvillus brush border injury with further malabsorption. Bacterial consumption of vitamin B_{12} and enhanced synthesis of folate result in decreased vitamin B_{12} and increased folate serum levels. Overproduction of *D-lactate* (the isomer of L-lactate) can cause stupor, neurologic dysfunction, and shock from D-lactic acidosis. Lactic acidosis should be suspected in children at risk of bacterial overgrowth, who show signs of neurologic deterioration and a high anion gap metabolic acidosis not explained by measurable acids such as L-lactate. Measurement of D-lactate is required because standard lactate assay only measures the L-isomer.

The treatment of bacterial overgrowth focuses on the correction of underlying causes such as partial obstruction. Oral metronidazole can provide relief for many months, but is not always effective. The cycling of antibiotics, including azithromycin, trimethoprim-sulfamethoxazole, ciprofloxacin, and metronidazole, may be required. Other alternatives are oral nonabsorbable antibiotics such as aminoglycosides, nitazoxanide, or rifaximin. Occasionally, antifungal therapy is required to control fungal overgrowth of the bowel.

Environmental Enteropathy (Tropical Sprue)

This is the result of the interactions between enteric pathogens, enteropathy, and malnutrition, and is associated with a peculiar intestinal histology (enteropathy) occurring in several developing countries. It is similar or overlaps with tropical sprue and is associated with evident or subclinical malabsorption. It is a frequent cause of death in childhood in endemic regions, particularly in Asian areas, such as south India, and in several African countries. In developing countries selected pathogens including rotavirus, shigella, cryptosporidium, and enterotoxigenic *Escherichia coli* cause the majority of intestinal infections leading to moderate to severe diarrhea and often trigger a vicious circle with malnutrition. This tends to progress to wasting and stunting with or without a clear association with diarrhea.

In addition to a high risk of death, environmental enteropathy impairs normal growth and brain development, and impacts productivity. The etiology of this disorder is unclear because it follows outbreaks of acute diarrheal disease and improves with antibiotic therapy; therefore an infectious etiology is suspected. Nevertheless, environmental enteropathy includes inter-related mechanisms such as intestinal malabsorption, increased permeability, loss of intestinal mass, inflammation, increased bacterial translocation, and impairment of immune response. The incidence is decreasing worldwide, largely because of an improvement in hygiene and access to nutrients. Clinical symptoms include fever and malaise followed by diarrhea. After about a week the acute features subside, and anorexia, intermittent diarrhea, and chronic malabsorption result in severe malnutrition characterized by glossitis, stomatitis, cheilosis, night blindness, hyperpigmentation, and edema, reflecting the various nutrient deficiencies. Muscle wasting is often marked, and the abdomen is often distended. Megaloblastic anemia results from folate and vitamin B_{12} deficiencies.

Diagnosis is made by small bowel biopsy, which shows villous flattening with crypt hyperplasia and mild intestinal inflammation, with lipid accumulation in the surface epithelium.

Treatment requires nutritional supplementation, including supplementation of folate and vitamin B_{12} . To prevent recurrence, 6 mo of therapy with oral folic acid (5 mg) and antibiotics are recommended. Relapses occur in 10–20% of patients who continue to reside in an endemic tropical region. The scale-up of infrastructure, particularly the improvement in hygiene conditions and access to food in association with people empowerment through educational interventions, are the key to prevention rather than medical interventions in individual cases.

Whipple Disease

Whipple disease is a chronic systemic infectious disorder. It is a rare disease, especially in childhood caused by *Tropheryma whipplei,* which can be cultured from a lymph node in the involved tissue.

The most common symptoms in Whipple disease are diarrhea, abdominal pain, weight loss, and joint pains. Malabsorption, lymphadenopathy, skin hyperpigmentation, and neurologic symptoms are also common. Involvement of other organs, such as eyes, heart, and kidneys, has been reported.

Diagnosis requires a high index of suspicion and is made upon demonstration of PAS-positive macrophage inclusions in the biopsy material, usually a duodenal biopsy. Positive identification using polymerase chain reaction for *T. whipplei confirms the diagnosis.*

Treatment requires antibiotics, such as trimethoprim sulfamethoxazole, for 1-2 yr. A 2-wk course of intravenous ceftriaxone or meropenem, followed by trimethoprim sulfamethoxazole for 1 yr, is recommended.

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364.5

Immunodeficiency Disorders

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Keywords

Diarrhea
hypogammaglobulinemia
immunoglobulins

GI disorders are present in 5–50% of patients with primary immune deficiencies driven by the fact that the gut is the largest lymphoid organ in the body. Malabsorption due to either intestinal inflammation or infection is common with primary immunodeficiency disorders; chronic diarrhea with failure to thrive is often the mode of presentation. Defects of humoral and or cellular immunity may be involved, including selective IgA deficiency, agammaglobulinemia, common variable immunodeficiency disease (CVID), severe combined immunodeficiency (SCID), hyper IgM syndrome, Wiskott-Aldrich syndrome, or chronic granulomatous disease. Although most patients with selective IgA deficiency are asymptomatic, malabsorption caused by giardiasis or nonspecific enteropathy with bacterial overgrowth can occur. Malabsorption syndrome or chronic noninfectious diarrhea manifesting as sprue-like enteropathy with villous atrophy has been reported in 60% of children with CVID. Malabsorption has also been reported in approximately 10% of patients with late-onset CVID, often secondary to giardiasis. Malabsorption as a result of infectious diarrhea—most commonly related to giardia, salmonella, campylobacter, cryptosporidium, and enteroviruses—is a well-recognized complication of X-linked agammaglobulinemia. Cryptosporidium is the most common pathogen causing diarrhea and malabsorption in hyper-IgM syndrome patients. SCID-affected children develop severe diarrhea and malabsorption early in life involving viral and opportunistic infections, especially chronic rotavirus infection, cytomegalovirus, and adenovirus. Malabsorption associated with immunodeficiency is exacerbated by villus atrophy and secondary disaccharidase deficiency. In chronic granulomatous disease, phagocytic function is impaired and granulomas develop throughout the GI tract, mimicking Crohn disease. In addition to failure to thrive, it is important to consider that malabsorption associated with immunodeficiency is often complicated by micronutrient deficiencies, including vitamins A, E, and B_{12} , and calcium, zinc, and iron.

Immunodeficiencies in children are more often secondary to other conditions such as cancer and chemotherapy. Malnutrition, diarrhea, and failure to thrive are common in untreated children with HIV infection. The risk of GI infection is related to the depression of the CD4 count. Opportunistic infections include *Cryptosporidium parvum*, cytomegalovirus, *Mycobacterium avium-intracellulare*, *Isospora belli*, *Enterocytozoon bieneusi*, *Candida albicans*, astrovirus, calicivirus, adenovirus, and the usual bacterial enteropathogens. In these patients, *Cryptosporidium* can cause a chronic secretory diarrhea.

Cancer chemotherapy can damage the bowel mucosa, leading to secondary malabsorption of disaccharides such as lactose. After bone marrow transplantation, mucosal damage from graft-versus-host disease can cause diarrhea and malabsorption. Small bowel biopsies show nonspecific villus atrophy, mixed inflammatory cell infiltrates, and increased apoptosis. Cancer chemotherapy and bone marrow transplantation are associated with pancreatic damage, which may lead to exocrine pancreatic insufficiency.

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364.6

Immunoproliferative Small Intestinal Disease

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Keywords

IPSID (**immunoproliferative small intestinal disease**)
MALT (**mucosa associated lymphoid-tissue lymphoma**)
Antibiotic treatment

Lymphoma (Chapter 523) is the most common small bowel malignancy in the pediatric age group. Malignant lymphomas of the small intestine are categorized into 3 subtypes: Burkitt lymphoma, non-Hodgkin lymphomas, and Mediterranean lymphoma. Burkitt lymphoma, the most common form in children, characteristically involves the terminal ileum with extensive abdominal involvement. The relatively uncommon *Western* type of non-Hodgkin lymphomas (usually large B-cell type), can involve various regions of the small intestine. **Mediterranean lymphoma** (termed by The World Health Organization as *immunoproliferative small intestinal disease [IPSID]* or α-heavy chain disease) is a rare extra-nodal marginal zone B-cell lymphoma occurring primarily in the proximal small intestine. It is a variant of **mucosa-associated lymphoid-tissue lymphoma (MALT)** described in young adults from the developing world, and is characterized by lymphoplasmacytic intestinal infiltrates with monotypic α-heavy chain expression.

IPSID occurs most often in the proximal small intestine in older children and young adults in the Mediterranean basin, Middle East, Asia, and Africa. Poverty and frequent episodes of gastroenteritis during infancy are antecedent risk factors. The initial clinical presentation is intermittent diarrhea and abdominal pain. Later, chronic diarrhea with malabsorption, PLE, weight loss, digital clubbing, and growth failure ensue. Intestinal obstruction, abdominal masses, and ascites are common in advanced stages.

In contrast to primary nonimmunoproliferative small intestinal lymphomas, in which the pathology in the intestine is usually focal, involving specific segments of the intestine and leaving the segments between the involved areas free of disease, the pathology in IPSID is diffuse, with a mucosal cellular infiltrate involving large segments of the intestine and sometimes the entire length of the intestine, thus producing malabsorption. Molecular and immunohistochemical studies demonstrated an association with *Campylobacter jejuni* infection. The differential diagnosis includes chronic enteric infections (parasites, tropical sprue), CD, and other lymphomas. Radiologic findings include multiple filling defects, ulcerations, strictures, and enlarged mesenteric lymph nodes on CT scan.

The diagnosis is usually established by endoscopic biopsies and/or laparotomy. Upper endoscopy shows thickening, erythema, and nodularity of the mucosal folds in the duodenum and proximal jejunum. Capsule endoscopy may be helpful in the diagnosis. As the disease progresses, tumors usually appear in the proximal small intestine and rarely in the stomach. The diagnosis requires multiple duodenal and jejunal mucosal biopsies showing dense mucosal infiltrates, consisting of centrocyte-like and plasma cells. Progression to higher-grade large-cell lymphoplasmacytic and immunoblastic lymphoma is characterized by increased plasmocytic atypia with formation of aggregates and later sheets of dystrophic plasma cells and immunoblasts invading the submucosa and muscularis propria. A serum marker of IgA, a heavy-chain paraprotein, is present in most cases.

Treatment of early-stage IPSID with antibiotics results in complete remission in 30–70% of cases (tetracycline, ampicillin, or metronidazole) and some patients achieving durable remission that may last several years, but they should be monitored closely for relapse. However, the majority of untreated IPSID cases progress to lymphoplasmacytic and immunoblastic lymphoma invading the intestinal wall and mesenteric lymph nodes, which can metastasize to distant organs, requiring aggressive treatment with surgery and/or chemotherapy.

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364.7

Short Bowel Syndrome

Yaron Avitzur, Raanan Shamir

Keywords

Intestinal failure
adaptation
stoma
total parenteral nutrition
enteral nutrition

enteral autonomy
complications
central line infection
intestinal failure associated liver disease
small bowel bacterial overgrowth
lengthening procedure
intestinal transplantation

Short bowel (or short gut) syndrome results from congenital malformations or resection of the small bowel (Table 364.11). Its incidence increases with low birth weight and earlier gestational age and is estimated at 7/1,000 live births in U.S. infants with birth weight <1,500 mg. Loss of >50% of the small bowel, with or without a portion of the large intestine, can result in symptoms of generalized malabsorptive disorder or in specific nutrient deficiencies, depending on the region of the bowel resected. At birth, the length of small bowel is 200-250 cm; by adulthood, it grows to 300-800 cm. Bowel resection in an infant has a better prognosis than in an adult because of the potential for intestinal growth and adaptation. An infant with as little as 15 cm of bowel with an ileocecal valve, or 20 cm without, has the potential to survive and be eventually weaned from parenteral nutrition.

Table 364.11

Causes of Short Bowel Syndrome

CONGENITAL
Congenital short bowel syndrome Intestinal atresia Gastroschisis
BOWEL RESECTION
Necrotizing enterocolitis Volvulus with or without malrotation Long segment Hirschsprung disease Meconium peritonitis Crohn disease Trauma

In addition to the length of the bowel, the anatomic location of the resection is also important. The proximal 100-200 cm of jejunum is the main site for carbohydrate, protein, iron, and water-soluble vitamin absorption, whereas fat absorption occurs over a longer length of the small bowel. Depending on the region of the bowel resected, specific nutrient malabsorption can result. Vitamin B_{12} and bile salts are only absorbed in the distal ileum (Fig. 364.10). Jejunal resections are generally tolerated better than ileal resections because the ileum, unlike the jejunum, can adapt to absorb nutrients and fluids. Net sodium and water absorption is relatively much higher in the ileum. Ileal resection has a profound effect on fluid and electrolyte absorption due to malabsorption of sodium and water by the remaining ileum; ileal malabsorption of bile salts stimulates increased colonic secretion of fluid and electrolytes. The presence of a colon in continuity is better tolerated and improves absorption and enteral autonomy.

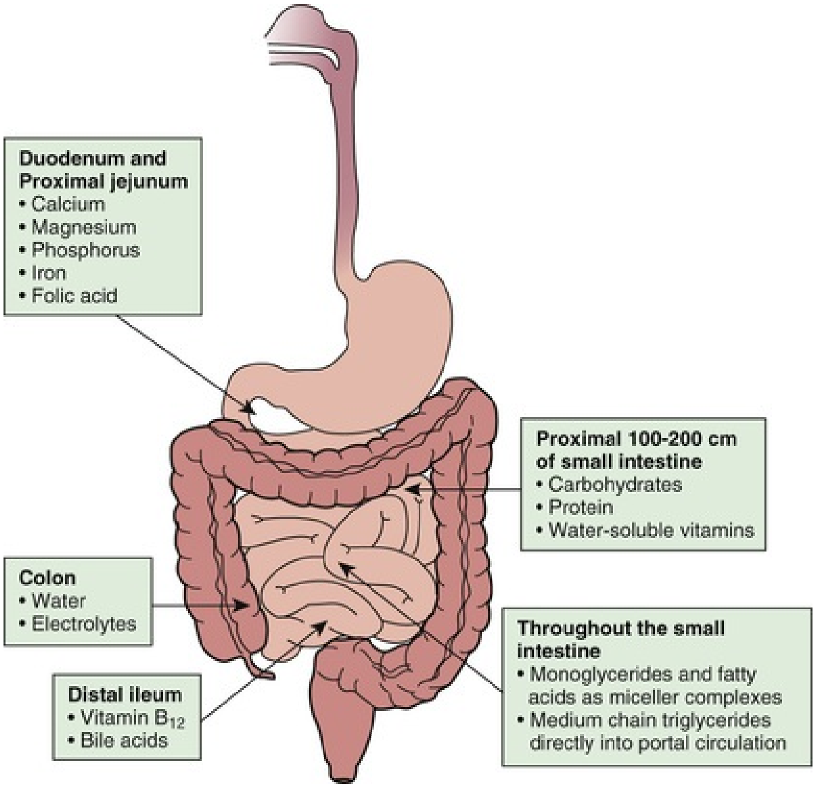
Duodenum and Proximal jejunum
• Calcium
• Magnesium
• Phosphorus
• Iron
• Folic acid
Proximal 100-200 cm of small intestine
• Carbohydrates
• Protein
• Water-soluble vitamins
Colon
• Water
• Electrolytes
Throughout the small intestine
• Monoglycerides and fatty acids as miceller complexes
• Medium chain triglycerides directly into portal circulation
Distal ileum
• Vitamin B_{12}
• Bile acids

FIG. 364.10 **Absorption of nutrients in the small bowel varies with the region.**

Treatment

After bowel resection, treatment of short bowel syndrome is initially focused on repletion of the massive fluid and electrolyte losses while the bowel initially accommodates to absorb these losses. Proton pump inhibitors are usually added to reduce gastric secretions and to improve fluid balance. Nutritional support is often provided via parenteral nutrition. A central venous catheter should be inserted to provide parenteral fluid and nutrition support. The ostomy or stool output should be measured, and fluid and electrolyte losses adequately replaced. Measurement of urinary Na^+ to assess body Na^+ stores is useful to prevent Na^+ depletion. Maintaining urinary Na^+ higher than 20 mmol/L ensures that Na^+ intake is adequate. Early introduction of even a small amount of enteral feeding by mouth or tube feeding is essential and enhances bowel adaptation.

After the initial few weeks following resection, fluid and electrolyte losses stabilize, and the focus of therapy shifts to bowel rehabilitation with a gradual increase in the volume of enteral feeds. Continuous or bolus small-volume enteral feeding should be promoted with an extensively or partially hydrolyzed protein with MCT-enriched formula if the colon is in continuation. Breast milk is preferable over formula and its use should be encouraged as it stimulates gut hormones and promotes mucosal growth. Enteral feeding also increases pancreatobiliary flow and reduces parenteral nutrition-induced hepatotoxicity. Infant should be given a small amount of formula or mother's milk by mouth as early as possible to maintain an interest in oral feeding and to minimize or avoid the development of oral aversion. As intestinal adaptation occurs, enteral feeding increases, and parenteral supplementation decreases. The bowel mucosa proliferates, and the bowel lengthens with growth.

Approximately 60% of patients with short bowel syndrome achieve **enteral autonomy** within 5 yr of bowel resection and the majority achieve it in the first 2-3 yr after resection. In addition to bowel length, the presence of the ileocecal valve, a diagnosis of necrotizing enterocolitis, and care by an intestinal rehabilitation program increase the likelihood of achieving enteral autonomy.

Patients may require repeat surgeries for obstruction or bowel lengthening procedures (longitudinal lengthening, serial transverse enteroplasties or both) to optimize the bowel absorptive capacity. The bowel lengthening procedure is indicated in patients with dilated bowel who are unable to progress towards enteral autonomy or those with refractory bacterial overgrowth.

Vitamin and micronutrient deficiencies are common and worsen over time. The management of specific micronutrient and vitamin deficiencies and the treatment of transient problems, such as postinfectious mucosal malabsorption, are required. GI infections or small bowel bacterial overgrowth can cause setbacks in the progression to full enteral feeding in patients with marginal absorptive function. Marked increase in stool output or evidence of carbohydrate malabsorption (stool pH <5.5 and positive test for reducing substances) contraindicate further increases in enteral feeds. Slow advancement of continuous or bolus enteral feeding rates continues until all nutrients are provided enterally.

In patients with large stool output, the addition of soluble fiber and antidiarrheal agents, such as loperamide and anticholinergics, can be beneficial, although these drugs can increase the risk of bacterial overgrowth. Cholestyramine can be beneficial for patients with distal ileal resection, but its potential depletion of the BA pool can increase steatorrhea. Bacterial overgrowth is common in infants with a short bowel and can delay progression of enteral feedings. Empirical treatment with metronidazole or other antibiotics (nitazoxanide, rifaximin) is often useful. Diets high in fat and without simple sugars may be helpful in reducing bacterial overgrowth as well as enhancing adaptation.

Complications

Long-term complications of short bowel syndrome include those of parenteral nutrition: central catheter infection, thrombosis, intestinal failure associated liver disease (IFALD), and gallstones. Appropriate care of the central line to prevent infection and catheter-related thrombosis is extremely important. Sepsis is a leading cause of death, can occur any time after treatment is initiated (months to years later), and is most often bacterial (single organism more common than polymicrobial), although fungal infection may be noted in 20–25% of septic episodes. The use of an ethanol lock or Taurolidine lock can reduce the incidence of central catheter infections and prevent infections.

Some patients need long-term parenteral nutritional support, and lack of central line access is potentially life threatening; inappropriate removal or frequent changes of central lines in the neonatal period should be avoided. **IFALD** can lead to cholestasis, cirrhosis, and liver failure, and is a common reason for death or need the for transplantation. The incidence and severity of IFALD has significantly reduced over the last decade, probably due to the reduced use of soy-based lipid emulsions and the positive effect of omega–3-based lipid emulsions on cholestasis. Other complications of terminal ileal resection include vitamin B_{12} deficiency, which might not appear until 1-2 yr after parenteral nutrition is withdrawn. Long-term monitoring for deficiencies of vitamin B_{12} , folate, iron, fat-soluble vitamins, and trace minerals, such as zinc and copper, is important. Renal stones can occur as a result of hyperoxaluria secondary to steatorrhea (calcium binds to the excess fat and not to oxalate, so more oxalate is absorbed and excreted in the urine). Venous thrombosis and vitamin deficiency have been associated with hyperhomocysteinemia in short bowel syndrome. Bloody diarrhea secondary to patchy, mild colitis can rarely develop during the progression of enteral feedings. The pathogenesis of this *feeding colitis* is unknown, but it is usually benign and can improve with a hypoallergenic diet or treatment with mesalamine.

In some children with life-threatening complications of parenteral nutrition, especially progressive liver failure and loss of vascular access, small intestine and liver transplantation becomes the preferred therapy (see Chapter 365).

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364.8

Chronic Malnutrition

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Keywords

Acute malnutrition
chronic malnutrition
severe malnutrition
anthropometry
diarrhea
refeeding syndrome

Primary malnutrition is very common in developing countries and is directly related to increased disease burden and mortality. In developed countries, the etiology, clinical course, and outcomes are different. The American Society for Parenteral and Enteral Nutrition (ASPEN) defined pediatric malnutrition in developed countries as an imbalance between nutrient requirements and intake that results in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes. Malnutrition can be classified as *illness related* (caused by disease/trauma) or *non-illness–related* (caused by environmental/behavioral factors). It can be further classified into *acute* malnutrition (<3 mo; short duration, weight loss without stunting) or *chronic* malnutrition (>3 mo; weight loss and stunting) that may differ in their etiology, growth patterns, and outcome. Chronic malnutrition occurs mainly as a result of decreased food intake, malabsorption syndromes, and increased nutritional needs in children with chronic diseases. Malnutrition is diagnosed in 11–50% of hospitalized children and reports from Europe suggest a prevalence of close to 20% in chronically ill children. Child neglect and improper preparation of formula can result in severe malnutrition. Malnutrition can be identified by evaluating dietary intake, by medical history (anorexia, vomiting, dysphagia, mood and behavioral changes, abdominal pain, diarrhea), by anthropometric measurements (e.g., reduced weight per age and weight per height, body mass index <5th percentile, mid upper arm circumference <−1 z score), by clinical signs of nutrient deficiencies (atrophic tongue in iron deficiency; anemia or alopecia in zinc deficiency) and by laboratory tests assessing vitamin and micronutrient deficiencies. Screening tools for malnutrition are used in adults to provide a simple and fast way of diagnosing those patients at risk for malnutrition. Few such screening tools for the pediatric population were developed to assess children at risk, but their use in clinical practice is still questionable.

Malnourished children suffer from impaired immunity, chronic enteropathy, poor wound healing, muscle weakness, and diminished psychologic drive. Malnutrition has short-term consequences (increased disability, morbidity, and mortality) and long-term consequences (final adult size, developmental deficiencies, economic productivity). Undernutrition in hospitalized children is associated with increased infectious complications, delayed recovery, increased length of stay and costs, increased readmission rate, and increased mortality.

Nutritional rehabilitation in malnourished children is discussed in Chapter 58
.

Chronic malnutrition complicated by diarrheal dehydration is a commonly observed phenomenon. Infectious diarrhea is common in tropical and subtropical countries, in the setting of poor hygiene practices and water quality, in immunocompromised hosts (e.g., HIV, congenital immunodeficiency), and when impairment of the immune response is due to chronic malnutrition itself. In children with chronic disorders, diarrhea may be related to the underlying disease that should be sought for. Examples include noncompliance with a gluten-free diet in CD, noncompliance with pancreatic enzyme treatment in cystic fibrosis, and cholestatic liver disease with fat malabsorption. Malnutrition per se can lead to exocrine pancreatic insufficiency, which, in turn, aggravates malabsorption and diarrhea.

In infants and children with severe malnutrition, many of the signs normally used to assess the state of hydration or shock are unreliable. Severe malnutrition might be accompanied by sepsis; thus, children with septic shock might not have diarrhea, thirst, or sunken eyes but may be hypothermic, hypoglycemic, or febrile. Cardiac reserve is lowered, and heart failure is a common complication.

Despite clinical signs of dehydration, urinary osmolality may be low in the chronically malnourished child. Renal acidifying ability is also limited in patients with malnutrition.

Management of the diarrhea in chronically malnourished children is based on 3 principles: oral rehydration to correct dehydration, rapid resumption of feeds with avoidance of periods of nothing by mouth, and treating the etiology of the diarrhea.

When treating the dehydration, it must be remembered that in dehydrated and malnourished infants there appears to be overexpansion of the extracellular space accompanied by extracellular and presumably intracellular hypoosmolality. Thus reduced or hypotonic osmolarity oral rehydration solutions are indicated in this setting. When oral rehydration is not possible, the route of choice is nasogastric, and intravenous therapy should be avoided if possible.

Initial intravenous therapy in profound dehydration is designed to improve the circulation and expand extracellular volume. For patients with edema, the quality of fluid and the rate of administration might need to be readjusted from recommended levels to avoid overhydration and pulmonary edema. Blood should be given if the patient is in shock and severely anemic. Potassium salts can be given early if urine output is good. Clinical improvement may be more rapid with magnesium therapy.

Children with chronic malnutrition are at risk for the refeeding syndrome (see

Chapter 58). Therefore initial calorie provision should not exceed the previous daily intake and is usually begun at 50–75% of estimated resting energy expenditure, with rapid increase to caloric goals once there are no severe abnormalities in sodium, potassium, phosphorus, calcium, or magnesium. Correction of malnutrition and catch-up growth are not part of the primary treatment of these children, but a nutrition rehabilitation plan is necessary.

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364.9

Enzyme Deficiencies

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Keywords

Carbohydrate malabsorption
lactase deficiency
sucrase-isomaltase deficiency
Hypolactasia
lactose intolerance
fructose malabsorption
glucose-galactose malabsorption
exocrine pancreatic insufficiency
autoimmune polyendocrinopathy syndrome type 1
enterokinase deficiency
trehalase deficiency
trypsinogen deficiency

Carbohydrate Malabsorption

Symptoms of carbohydrate malabsorption include loose watery diarrhea, flatulence, abdominal distention, and pain. Some children are asymptomatic unless the mal-absorbed carbohydrate is consumed in large amounts. Disaccharidases are present on the brush border membrane of the small bowel. **Disaccharidase deficiency** can be caused by a genetic defect or secondary to damage to the small bowel epithelium, as occurs with infection or inflammatory disorders.

Unabsorbed carbohydrates enter the large bowel and are fermented by intestinal bacteria, producing organic acids and gases such as methane and hydrogen. The gases can cause discomfort and the unabsorbed carbohydrates and the organic acids cause osmotic diarrhea characterized by an acidic pH and the presence of either reducing or nonreducing sugars in the stool. Hydrogen gas can be detected in the breath as a sign of fermentation of unabsorbed **carbohydrates (H_2 -breath test).**

Lactase Deficiency

Congenital lactase deficiency is rare and is associated with symptoms occurring on exposure to lactose in milk. Fewer than 50 cases have been reported worldwide. In patients with congenital lactase deficiency, 5 distinct mutations in the coding region of the *LCT* gene were found. In most patients (84%), homozygosity for a nonsense mutation, 4170T-A (Y1390X; OMIM 223000), designated Fin (major), was found.

Primary adult type-hypolactasia is caused by a physiologic decline in lactase actively that occurs following weaning in most mammals. The brush-border lactase is expressed at low levels during fetal life; activity increases in late fetal life and peaks from term to 3 yr, after which levels gradually decrease with age. This decline in lactase levels varies between ethnic groups. Lactase deficiency occurs in approximately 15% of white adults, 40% of Asian adults, and 85% of African-American adults in the United States. Lactase is encoded by a single gene *(LCT)* of approximately 50 kb located on chromosome 2q21. C/T (−13910) polymorphisms of the *MCM6* gene were found to be related to adult-type hypolactasia in most European populations. In 3 African populations—Tanzanians, Kenyans, and Sudanese—3 single-nucleotide polymorphisms, G/C(−14010), T/G(−13915), and C/G(−13907), were identified with lactase persistence and have derived alleles that significantly enhance transcription from the lactase gene promoter in vitro.

Secondary lactose intolerance follows small bowel mucosal damage (CD, acute severe gastroenteritis) and is usually transient, improving with mucosal healing. Lactase deficiency can be diagnosed by H_2 -breath test (2 g/kg up to 25 g) or by measurement of lactase activity in mucosal tissue retrieved by small bowel biopsy. Diagnostic testing is not mandatory, and often simple dietary changes that reduce or eliminate lactose from the diet relieve symptoms.

Treatment of lactase deficiency consists of a milk-free diet. A lactose-free formula (based on either soy or cow's milk) can be used in infants. In older children, low-lactose milk can be consumed. The addition of lactase to dairy products usually abbreviates the symptoms.

Live-culture yogurt contains bacteria that produce lactase enzymes and is therefore tolerated in most patients with lactase deficiency. Hard cheeses and cottage cheeses have a small amount of lactose and are generally well tolerated.

Fructose Malabsorption

Children consuming a large quantity of juice rich in fructose, corn syrup, or natural fructose in fruit juices can present with diarrhea, abdominal distention, and slow weight gain. Restricting the amount of juice in the diet resolves the symptoms and helps avoid unnecessary investigations. A fructose H_2 breath test can be helpful in the diagnosis of fructose malabsorption. The reason for fructose malabsorption is the reduced abundance of GLUT-5 transporter on the surface of the intestinal brush-border membrane, which occurs in approximately 5% of the population.

Sucrase-Isomaltase Deficiency

Sucrase-isomaltase (SI) deficiency is a rare autosomal recessive disorder with a complete absence of sucrase and reduced maltase digestive activity. The SI complex is composed of 1,927 amino acids encoded by a 3,364 bp messenger RNA. The gene locus on chromosome 3 has 30 exons spanning 106.6 kb. The majority of SI mutations result in a lack of enzyme protein synthesis (null mutation). Posttranslational processing defects are also identified.

Approximately 2% of Europeans and Americans are mutant heterozygote. Sucrase deficiency is especially common in indigenous Greenlanders (estimated 5%) in whom it is often accompanied by lactase deficiency. Gene variants of the SI are found to have some implications in IBS, because they were found more often in patients with IBS than in controls.

Symptoms of SI deficiency usually begin when the infant is exposed to sucrose or a glucose polymer diet. This can occur with ingestion of non–lactose-based infant formula or on the introduction of pureed food, especially fruits and sweets. Diarrhea, abdominal pain, and poor growth are observed. Occasionally, patients present with symptoms in late childhood or even adult life, but careful history often indicates that symptoms appeared earlier. Diagnosis of sucrase-isomaltase malabsorption requires acid hydrolysis of stool for reducing substances because sucrase is a nonreducing sugar. Alternatively, a diagnosis can be achieved with a hydrogen breath test, a direct enzyme assay of small bowel biopsy, or genetic testing.

The mainstay of treatment is lifelong dietary restriction of sucrose-containing foods, although symptoms may diminish with age. Enzyme replacement with a purified yeast enzyme, sacrosidase (Sucraid), is a highly effective adjunct to dietary restriction.

Glucose-Galactose Malabsorption

More than 30 different mutations of the sodium/glucose cotransporter gene *(SGLT1)* are identified. These mutations cause a rare autosomal recessive disorder of intestinal glucose and galactose/Na^+ cotransport system that leads to osmotic diarrhea. Because most dietary sugars are polysaccharides or disaccharides with glucose or galactose moieties, diarrhea follows the ingestion of glucose, breast milk, or conventional lactose-containing formulas. Dehydration and acidosis can be severe, resulting in death.

The stools are acidic and contain sugar. Patients with the defect have normal absorption of fructose, and their small bowel function and structure are normal in all other aspects. Intermittent or permanent glycosuria after fasting, or after a glucose load, is a common finding because of the transport defect also being present in the kidney. The presence of reducing substances in watery stools and slight glycosuria despite low blood sugar levels is highly suggestive of glucose-galactose malabsorption. Malabsorption of glucose and galactose is easily identified using the breath hydrogen test. It is safe to perform the 1st test with a dose of 0.5 g/kg of glucose; if necessary, a 2nd test can be performed using 2 g/kg. Breath H_2 will rise more than 20 ppm. The small intestinal biopsy is useful to document a normal villous architecture and normal disaccharidase activities. The identification of mutations of *SGLT1* makes it possible to perform prenatal screening in families at risk for the disease.

Treatment consists of rigorous restriction of glucose and galactose. Fructose, the only carbohydrate that can be given safely, should be added to a carbohydrate-free formula at a concentration of 6–8%. Diarrhea immediately ceases when infants are given such a formula. Although the defect is permanent, later in life, limited amounts of glucose, such as starches or sucrose, may be tolerated.

Exocrine Pancreatic Insufficiency

Chapter 376 discusses disorders of exocrine pancreatic insufficiency. Cystic fibrosis is the most common congenital disorder associated with exocrine pancreatic insufficiency. Although rare, the next most common cause of pancreatic insufficiency in children is Shwachman-Diamond syndrome. Other rare disorders causing exocrine pancreatic insufficiency are Johanson-Blizzard syndrome (severe steatorrhea, aplasia of alae nasi, deafness, hypothyroidism, scalp defects) Pearson bone marrow syndrome (sideroblastic anemia, variable degree of neutropenia, thrombocytopenia), and isolated pancreatic enzyme deficiency (lipase, colipase and lipase-colipase, trypsinogen, amylase). Deficiency of enterokinase—a key enzyme that is produced in the proximal small bowel and is responsible for the activation of trypsinogen to trypsin—manifests clinically as exocrine pancreatic insufficiency.

Autoimmune polyendocrinopathy syndrome type 1 , a rare autosomal recessive disorder, is caused by mutation in the autoimmune regulator gene (AIRE). Chronic mucocutaneous candidiasis is associated with failure of the parathyroid gland, adrenal cortex, pancreatic β cells, gonads, gastric parietal cells, and thyroid gland. Pancreatic insufficiency and steatorrhea are associated with this condition.

Enterokinase (Enteropeptidase) Deficiency

Enterokinase (enteropeptidase) is a brush-border enzyme of the small intestine. It is responsible for the activation of trypsinogen into trypsin. Deficiency of this enzyme results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemic edema after birth.

The diagnosis can be established by measuring the enzyme level in intestinal tissue or by genetic testing, as enterokinase deficiency is caused by mutation in the serine protease-7 gene *(PRSS7)* on chromosome 21q21. Treatment of this rare autosomal recessive disorder consists of replacement with pancreatic enzymes and administration of a protein hydrolyzed formula with added MCT oil in infancy.

Trehalase Deficiency

The disaccharide trehalose is mainly present in mushrooms and has been approved to add to dried food. It is hydrolyzed by the intestinal trehalase into 2 molecules of glucose. Trehalase deficiency has been reported in 8% of Greenlanders, otherwise only 3 cases of this deficiency have been reported elsewhere. In untreated celiac disease the intestinal trehalase activity is reduced as those of other disaccharidases and recovers after introduction of a gluten-free diet.

Trypsinogen Deficiency

Trypsinogen deficiency is a rare syndrome with symptomatology similar to that of enterokinase deficiency. Enterokinase catalyzes the conversion of trypsinogen to trypsin, which, in turn, activates the various pancreatic proenzymes, such as chymotrypsin, procarboxypeptidase, and proelastase, for their active forms. Deficiency of trypsinogen results in severe diarrhea, malabsorption, failure to thrive, and hypoproteinemic edema soon after birth.

The trypsinogen gene is encoded on chromosome 7q35. Treatment is the same as for enterokinase deficiency, with pancreatic enzymes and protein hydrolysate formula with added MCT oil in infancy.

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364.10

Liver and Biliary Disorders Causing Malabsorption

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Keywords

Cholestasis
Nutrition

Liver disease
malabsorption
vitamin deficiency

Absorption of lipids and lipid-soluble vitamins depend to a great extent on adequate bile flow delivering BA to the small intestine that help mixed micelle formation of lipid droplets. Most of the liver and biliary disorders lead to impairment of the bile flow, contributing to malabsorption of long-chain fatty acids and vitamins such as A, D, E, and K. Liver disorders that are associated with significant malabsorption and failure to thrive are mainly due to these categories:

PFIC syndromes and BA synthesis defects. PFIC type 1 is also associated with chronic diarrhea caused by bile transport defect in the gut. It is not uncommon for these children to have symptomatic fat-soluble vitamin deficiencies and suffer from pathologic fractures and peripheral neuropathy.

Children with storage disorders (e.g., **Wolman disease**) also manifest with severe failure to thrive and multiple vitamin deficiencies.

Children with biliary disorders such as biliary atresia after porto-enterostomy surgery (Kasai portoenterostomy), cystic fibrosis, neonatal sclerosing cholangitis, Alagille syndrome, and sclerosing cholangitis constitute another major group of disorders with reduced bile flow where malabsorption could be a significant challenge

Chronic liver disease of any etiology could also lead to lipid malabsorption from the above described mechanisms. In addition, severe portal hypertension can lead to portal hypertensive enteropathy, resulting in poor absorption of the nutrients.

Decompensated liver disease leads to anorexia and increased energy expenditures, further widening the gap between calorie intake and net absorption, leading to severe malnutrition. Adequate management of nutrition is essential to improve the outcome with or without liver transplantation. This is usually achieved by using MCT-rich milk formula, supplemental vitamins, and continuous or bolus enteral feed where oral intake is poor.

Vitamin D deficiency is commonly observed on biochemical tests, and children can present with pathologic fractures. Simultaneous administration of vitamin D with the water-soluble vitamin E preparation (TPGS 1,000 succinate) enhances absorption of vitamin D as well. In young infants with **cholestasis** , **oral vitamin D_3 is given** at a dose of 1,000 IU/kg/24 hr. After 1 mo, if the serum

25-hydroxyvitamin D level is low, intramuscular administration of 10,000 units/kg or maximum of 60,000 is recommend. Three 6 mo, 25-hydroxy vitamin D blood level monitoring is suggested in children with severe cholestasis.

Vitamin E deficiency in patients with chronic cholestasis is not usually symptomatic, but it can manifest as a progressive neurologic syndrome, which includes peripheral neuropathy (manifesting as loss of deep tendon reflexes and ophthalmoplegia), cerebellar ataxia, and posterior column dysfunction. Early in the course, findings are partially reversible with treatment; late features might not be reversible. It may be difficult to identify vitamin E deficiency because the elevated blood lipid levels in cholestatic liver disease can falsely elevate the serum vitamin E level. Therefore it is important to measure the ratio of serum vitamin E to total serum lipids; the normal level for patients younger than 12 yr of age is >0.6, and for patients older than 12 yr it is >0.8. The neurologic disease can be prevented with the use of an oral water-soluble vitamin E preparation (TPGS, Liqui-E) at a dose of 25-50 IU/day in neonates and 15-25 IU/kg/day in children.

Vitamin K deficiency can occur as a result of cholestasis and poor fat absorption. In children with liver disease it is very important to differentiate between the coagulopathy related to vitamin K malabsorption and one secondary to the synthetic failure of the liver. A single dose of vitamin K administered intravenously does not correct the prolonged prothrombin time in liver failure, but the deficiency state responds within a few hours. Easy bruising may be the first sign. In neonatal cholestasis, coagulopathy as a result of vitamin K deficiency can manifest with intracranial bleeds with devastating consequences, and prothrombin time should be routinely measured to monitor for deficiency in children with cholestasis. All children with cholestasis should receive regular vitamin K supplementation.

Vitamin A deficiency is rare and is associated with night blindness, xerophthalmia, and increased mortality if patients contract measles. Serum vitamin A levels should be monitored and adequate supplementation considered; caution should be observed as high levels of vitamin A can cause liver damage.

364.11

Rare Inborn Defects Causing

Malabsorption

Corina Hartman, Raanan Shamir

Keywords

Fanconi-Bickel syndrome
Cystinuria
Lysinuric protein intolerance
Hartnup disease
Blue diaper syndrome
Iminoglycinuria
Dicarboxylic aminoaciduria
Vitamin B_{12}
Cobalamin malabsorption
Megaloblastic anemia
Imerslund-Grasbeck syndrome
Folate
Folate malabsorption
Congenital chloride diarrhea
Secretory diarrhea
Congenital sodium diarrhea
Acrodermatitis enteropathica
Menkes disease
Occipital horn syndrome
Familial hypomagnesemia
Intestinal iron absorption
Hemochromatosis
Refractory iron-deficiency anemia

Congenital (primary) malabsorption disorders originate from multitude types of defects including structural or functional defects of enterocytes or disorders involving other cellular lineages of the GI tract such as enteroendocrine or immune cells (see Chapter 364.3 and 367). Integral membrane proteins, which fulfill a transport function as receptor or channel across the apical or basolateral membrane of enterocytes for nutritional components, are another class of disorders associated with primary disorders of malabsorption. Histologic examination of the small and large bowel is typically normal. Most of these disorders are inherited in an autosomal recessive pattern. Most are rare, and patients present with a broad phenotypic heterogeneity as a result of modifier genes and nutritional and other secondary factors.

Disorders of Carbohydrate Absorption

These are described in Chapter 364.9 .

Patients with **Fanconi-Bickel syndrome** present with tubular nephropathy; rickets; hepatomegaly; glycogen accumulation in liver, kidney, and small bowel; failure to thrive; fasting hypoglycemia and postprandial hyperglycemia. The disorder is caused by homozygous mutations of GLUT2 *(SLC2A2),* the facilitative monosaccharides transporter at the basolateral membrane of enterocytes, hepatocytes, renal tubules, pancreatic islet cells, and cerebral neurons. The patients exhibit postprandial hyperglycemia secondary to low insulin secretion (impaired glucose-sensing mechanisms in beta-cells) and fasting hypoglycemia due to altered glucose transport out of the liver. The increased intracellular glucose level inhibits glycogen degradation leading to glycogen accumulation and hepatomegaly. Similarly, altered monosaccharides transport out of enterocytes may be responsible for the putative glycogen accumulation and as a consequence, for diarrhea and malabsorption observed in some patients. Therapy includes the substitution of electrolyte losses and vitamin D, and supplying uncooked cornstarch to prevent hypoglycemia. Patients who present in the neonatal period need frequent small meals and galactose-free milk.

Disorders of Amino Acid and Peptide Absorption

Protein digestion and absorption in the intestine is accomplished by a combination of proteases, peptidases, and peptide and amino acid transporters. Amino acid transporters are essential for the absorption of amino acids from nutrients, mediate the inter-organ, intercellular transfer of amino acids and the transport of amino acids between cellular compartments. Owing to their ontogenic origins, enterocytes and renal tubules share similar amino acid transporters. Their highest intestinal transporter activity is found in the jejunum. The transporters causing Hartnup disease, cystinuria, iminoglycinuria, and dicarboxylic aminoaciduria are located in the apical membrane, and those causing lysinuric protein intolerance (LPI) and blue diaper syndrome are anchored in the basolateral membrane of the intestinal epithelium.

Dibasic amino acids, including cystine, ornithine, lysine, and arginine are taken up by the Na-independent SLC3A1/SLC7A9, which is defective in cystinuria. Cystinuria is the most common primary inherited aminoaciduria. This disorder is not associated with any GI or nutritional consequences because of compensation by an alternative transporter. However, hypersecretion of cystine in the urine leads to recurrent cystine stones, which account for up to 6–8% of all urinary tract stones in children. Ample hydration, urine alkalinization, and cystine-binding thiol drugs can increase the solubility of cystine. Cystinuria type I *(SLC3A1)* is inherited as an autosomal recessive trait, whether the transmission of non-type I cystinuria *(SLC7A9)* is autosomal dominant with incomplete penetrance. Cystinuria type I has been described in association with 2p21 deletion syndrome and hypotonia-cystinuria syndrome.

LPI is the second most common disorder of amino acids transport (see Chapter 103.14). LPI is caused by y^+ LAT-1 (SLC7A7) carrier at the basolateral membrane of the intestinal and renal epithelium and the failure to deliver cytosolic dibasic cationic amino acids into the paracellular space. This defect is not compensated by the SLC3A1/SLC7A9 transporter at the apical membrane. The symptoms of LPI, which appear after weaning, include diarrhea, failure to thrive, hepatosplenomegaly, nephritis, respiratory insufficiency, alveolar proteinosis, pulmonary fibrosis, and osteoporosis. Abnormalities of bone marrow have also been described in a subgroup of LPI patients. The disorder is characterized by low plasma concentrations of dibasic amino acids (in contrast to high levels of citrulline, glutamine, and alanine) and massive excretion of lysine (as well as orotic acid, ornithine, and arginine in moderate excess) in the urine. Hyperammonemia and coma usually develop after episodic attacks of vomiting, after fasting, or following the administration of large amounts of protein (or alanine load), possibly because of a deficiency of intramitochondrial ornithine. Some patients show moderate retardation. Cutaneous manifestations can include alopecia, perianal dermatitis, and sparse hair. Some patients avoid protein-containing food. Immune dysfunction potentially attributable to nitric oxide overproduction secondary to arginine intracellular trapping might be the pathophysiological route explaining many LPI complications, including hemophagocytic lymphohistiocytosis, various autoimmune disorders, and an incompletely characterized immune deficiency. Treatment includes dietary protein restriction (<1.5 g/kg/day), orally administered citrulline (100 mg/kg/day), which is well absorbed from the intestine and carnitine supplementation.

Hartnup disease is characterized by the malabsorption of all neutral amino acids (except proline), including the essential amino acid tryptophan. It is characterized by aminoaciduria, photosensitive pellagra-like rash, headaches, cerebellar ataxia, delayed intellectual development, and diarrhea. The clinical spectrum ranges from asymptomatic patients to severely affected patients with progressive neurodegeneration leading to death by adolescence. SLC6A19, which is the major luminal sodium-dependent neutral amino acid transporter of small intestine and renal tubules, has been identified as the defective protein. Its association with collectrin and angiotensin-converting enzyme II is likely to be involved in the phenotypic heterogeneity of Hartnup disorder. Tryptophan is a precursor of nicotinamide adenine dinucleotide phosphate biosynthesis; therefore, the disorder can be treated by nicotinamide in addition to a diet of 4 g protein/kg. The use of lipid-soluble esters of amino acids and tryptophan ethyl ester has also been reported.

Defects in specific, basolateral tryptophan transporter (SLC16A10) are the cause of **blue diaper syndrome** (indicanuria, Drummond syndrome). Intestinal bacteria convert the unabsorbed tryptophan to indican, which is responsible for the bluish discoloration of the urine after its hydrolysis and oxidation. Symptoms can include digestive disturbances such as vomiting, constipation, poor appetite, failure to thrive, hypercalcemia, nephrocalcinosis, fever, irritability, and ocular abnormalities.

The underlying defect of **iminoglycinuria** is the malabsorption of proline, hydroxyproline, and glycine as a consequence of the proton amino acid transporter SLC36A2 defect, with a possible participation of modifier genes, one of which (SLC6A20) is present in the intestinal epithelium. This disorder is usually benign, but sporadic cases with encephalopathy, mental retardation, deafness, blindness, kidney stones, hypertension, and gyrate atrophy have been described.

The neuronal glutamate transporter EAAT3 (SLC1A1) is affected in **dicarboxylic aminoaciduria** . This carrier is present in the small intestine, kidney, and brain, and transports the anionic acids L -glutamate, L - and D -aspartate, and L -cysteine. There are single case reports indicating that this disorder could be associated with hyperprolinemia and neurologic symptoms such as POLIP (polyneuropathy, ophthalmoplegia, leukoencephalopathy, intestinal pseudoobstruction) syndrome.

Disorders of Fat Transport

These are described in Chapter 104.3 and 364.3 .

Disorders of Vitamin Absorption

Transporters and receptors of the intestinal epithelium have been described for water-soluble but not fat-soluble vitamins, the latter being absorbed primarily into enterocytes by passive diffusion after the emulsification of fats by bile salts. Transfer proteins (retinol-binding protein, RBP4, and α-tocopherol transfer protein, TTP1) have been involved in deficiency states of vitamins E (spinocerebellar ataxia) and A (ophthalmologic signs), respectively.

Vitamin B_{12} (cobalamin) is synthesized exclusively by microorganisms and is acquired mostly from meat and milk (see Chapter 481.2). Its absorption starts with the removal of cobalamin from dietary protein by gastric acidity and its binding to haptocorrin. In the duodenum, pancreatic proteases hydrolyze the cobalamin-haptocorrin complex, allowing the binding of cobalamin to intrinsic factor (IF), which originates from parietal cells. The receptor of the cobalamin-IF complex (Cbl-IF) is located at the apical membrane of the ileal enterocytes, and represents a heterodimer consisting of cubilin (CUBN) and amnionless (AMN). After endocytic uptake into endosomes, the Cbl-IF and its receptor binds to megalin and forms a cobalamin–transcobalamin-2 complex (after cleavage of IF) for further transcytosis. Vitamin B_{12} exits the lysosome via LMBD1 and ABCD4, and is released to the blood stream most likely through the basolateral transporter multifunctional multidrug resistance protein 1 (MRP1). Biologically available circulating vitamin B_{12} is bound to transcobalamin (TC), a nonglycosylated protein that carries 10–30% of the total vitamin B_{12} . TC-vitamin B_{12} complexes enter the cells via 2 members of the LDL receptor gene family, CD320 and renal Lrp2/Megalin. As a cofactor for methionine synthase, cobalamin converts homocysteine to methionine. Cobalamin deficiency can be caused by inadequate intake of the vitamin (e.g., breastfeeding by mothers on a vegan diet), primary or secondary achlorhydria including autoimmune gastritis, exocrine pancreatic insufficiency, bacterial overgrowth (see Chapter 364.4), ileal disease (Crohn disease, see Chapter 362.2), ileal (or gastric) resection, infections (fish tapeworm), and Whipple disease (see Chapter 367).

Clinical signs of congenital cobalamin malabsorption, which usually appear from a few months to more than 10 yr, are pancytopenia including **megaloblastic anemia** , fatigue, failure to thrive, and neurologic symptoms, including developmental delay. Recurrent infections and bruising may be present. Laboratory evaluation indicates low serum cobalamin, hyperhomocysteinemia, methylmalonic acidemia, and mild proteinuria. The Schilling test is useful to differentiate between a lack of IF and the malabsorption of cobalamin. Several rare autosomal recessive disorders of congenital cobalamin deficiency affect absorption and transport of cobalamin (in addition to 7 other inherited defects of cobalamin metabolism). These include mutations of the gastric IF *(GIF)* gene with absence of IF (but normal acid secretion and lack of autoantibodies against IF or parietal cells), mutations of the *AMN* and *CUBN* genes subunits of the Cbl-IF receptor in ileum (**Imerslund-Grasbeck syndrome**), and mutations in the TC 2 cDNA. Two new inborn defects were identified recently in the genes encoding LMBD1 and ABCD4 transporters, and are responsible for the rare Cbl-lF inborn defect resulting in the trapping of free vitamin B_{12} in lysosomes. These disorders require long-term parenteral cobalamin treatment: intramuscular injections of cobalamin. High-dose substitution with oral cyanocobalamin (1 mg biweekly) does not seem to be sufficient for all patients with congenital cobalamin deficiency.

Folate is an essential vitamin required to synthesize methionine from homocysteine. It is found mainly in green leafy vegetables, legumes, and oranges. After its uptake by enterocytes, folate is converted to 5-methyltetrahydrofolate. Secondary folate deficiency is caused by insufficient folate intake, villous atrophy (e.g., CD, IBD), treatment with phenytoin, and trimethoprim, among others (see Chapter 481.1). Several inherited disorders of folate metabolism and transport have been described.

Three mammalian folate transporter systems have been described to date in a variety of tissues: (1) the bidirectional reduced folate carrier 1 (RFC1, SLC19A1), (2) the glycosyl-phosphatidylinositol-anchored folate receptors (FOLR1, FOLR2, and FOLR4) responsible for folate-receptor mediated endocytosis, and (3) the human proton-coupled folate transporter (PCFT). Hereditary **folate malabsorption** is characterized by a defect of the PCFT of the brush-border, leading to impaired absorption of folate in the upper small intestine as well as impaired transport of folate into the central nervous system. Symptoms of congenital folate malabsorption are diarrhea, failure to thrive, megaloblastic anemia (in the first few mo of life), glossitis, infections *(Pneumocystis jiroveci)* with hypoimmunoglobulinemia, and neurologic abnormalities (seizures, intellectual impairment, and basal ganglia calcifications). Macrocytosis, with or without neutropenia, multilobulated polymorphonuclear cells, increased lactate dehydrogenase and bilirubin, increased saturation of transferrin, and decreased cholesterol can be found. Low levels of folate are present in serum and cerebrospinal fluid. Plasma homocysteine concentrations as well as urine excretion of formiminoglutamic acid and orotic acid are elevated. Long-lasting deficiency is best documented using red cell folate. Therapy involves large doses of oral (up to 100 mg/day) or systemic (intrathecal) folate. Sulfasalazine and methotrexate are potent inhibitors of PCFT. Therefore, folate deficiency may develop during treatment with these drugs. Although the RFC1 is ubiquitously expressed, including the brush-border membrane in the small intestine, involvement of RFC1 in intestinal folate uptake has not been confirmed.

The molecular basis of intestinal transport of other water-soluble vitamins such as vitamin C (Na^+ -dependent vitamin C transporters 1 and 2), pyridoxine/vitamin B_6 , and biotin/vitamin B_5 (Na^+ -dependent multivitamin transporter) have been described; congenital defects of these transporter systems have not yet been found in humans. A **thiamine/vitamin B_1 -responsive megaloblastic anemia** syndrome, which is associated with early-onset type 1 diabetes mellitus and sensorineural deafness, is caused by mutations of the thiamine transporter protein, THTR-1 (SLC19A2), present in the brush-border.

Disorders of Electrolyte and Mineral Absorption

Congenital chloride diarrhea (CCD) belongs to the more common causes of severe congenital diarrhea, with prevalence in Finland of 1 : 20,000. It is caused by a defect of the *SLC26A3* gene, which encodes a Na^+ -independent Cl^- /HCO_3

$^-$ exchanger within the apical membrane of ileal and colonic epithelium. Founder mutations have been described in Finnish, Polish, and Arab patients: V317del, I675-676ins, and G187X, respectively. The Cl^- /HCO_3 $^-$ exchanger absorbs chloride originating from gastric acid and the cystic fibrosis transmembrane conductance regulator and secretes bicarbonate into the lumen, neutralizing the acidity of gastric secretion.

Prenatally, CCD is characterized by maternal polyhydramnios, dilated fetal bowel loops and preterm birth. Newborns with CCD present with severe life-threatening *secretory diarrhea* during the first few weeks of life. Volvulus has been reported in few patients with CCD. Laboratory findings are metabolic alkalosis, hypochloremia, hypokalemia, and hyponatremia (with high plasma renin and aldosterone activities). Fecal chloride concentrations are >90 mmol/L and exceed the sum of fecal sodium and potassium. Early diagnosis and aggressive lifelong enteral substitution of KCl in combination with NaCl (chloride doses of 6-8 mmol/kg/day for infants and 3-4 mmol/kg/day for older patients) prevent mortality and long-term complications (such as urinary infections, hyperuricemia with renal calcifications, renal insufficiency, and hypertension) and allow normal growth and development. Orally administered proton pump inhibitors, cholestyramine, and butyrate can reduce the severity of diarrhea. The diarrheal symptoms usually tend to regress with age. However, febrile diseases are likely to exacerbate symptoms as a consequence of severe dehydration and electrolyte imbalances. (See Chapter 71 for fluid and electrolyte management.)

The classic form of **congenital sodium diarrhea** (CSD) manifests with polyhydramnios, massive *secretory diarrhea* , severe metabolic acidosis, alkaline stools (fecal $pH > 7.5$) and hyponatremia because of fecal losses of Na^+ (fecal $Na^+ > 70$ mmol/L). Urinary secretion of sodium is low to normal. CSD is clinically and genetically heterogeneous. A syndromic form of CSD with superficial punctate keratitis, choanal or anal atresia, hypertelorism, and corneal erosions has been related to mutations of *SPINT2,* encoding a serine–protease inhibitor, whose pathophysiologic action on intestinal Na^+ absorption is unclear. This form of CSD is also referred to as **CTE** (intestinal epithelial dysplasia), as it often shows clustered enterocytes that form “tufts” with branching crypts on histology (described in Chapter 364.3). Two genetic defects have been identified so far in several patients with the non-syndromic form of CSD. Dominant activating mutations in receptor guanylate cyclase C *(GUCY2C)* were found to cause a spectrum of secretory diarrheas including nonsyndromic CSD in 4 patients. These mutations were associated with elevated intracellular cyclic guanosine monophosphate (cGMP) levels that induced inhibition of NHE3 exchanger via its phosphorylation by cGMP kinase II. Mutations in *SLC9A3* , the gene encoding the Na^+ /H^+ antiporter 3 (NHE3), the major intestinal brush-border Na^+ /H^+ exchanger, were identified in 9 patients with non-syndromic CSD. IBD developed in a number of patients with dominant GC-C mutations, and also in 2 of 9 patients with recessive SLC9A3 mutations, implicating NHE3 in the pathogenesis of IBD in a subset of patients. The congenital form of **acrodermatitis enteropathica** manifests with severe deficiency of body zinc soon after birth in bottle-fed children, or after weaning from breastfeeding. Clinical signs of this disorder are anorexia, diarrhea, failure to thrive, humoral and cell-mediated immunodeficiency (poor wound healing, recurrent infections), male hypogonadism, skin lesions (vesicobullous dermatitis on the extremities and perirectal, perigenital, and perioral regions, and alopecia), and neurologic abnormalities (tremor, apathy, depression, irritability, nystagmus, photophobia, night blindness, and hypogeusia). The genetic defect of acrodermatitis enteropathica is caused by a mutation in the Zrt-Irt-like protein 4 (ZIP4, SLC39A4), normally expressed on the apical membrane, which enables the uptake of zinc into the cytosol of enterocytes. The zinc-dependent alkaline phosphatase and plasma zinc levels are low. Paneth cells in the crypt of the small intestinal mucosa show inclusion bodies. Acrodermatitis enteropathica requires long-term treatment with elemental zinc at 1 mg/kg/day. Maternal zinc deficiency impairs embryonic, fetal, and postnatal development. Chapter 67 describes the *acquired* forms of zinc deficiency. Transient neonatal zinc deficiency is an autosomal dominant disorder with similar manifestations as AE. The disease is caused by mutations in ZnT2, the transporter responsible for supplying human milk with zinc.

Menkes disease and **occipital horn syndrome** are both caused by mutations in the gene encoding Cu^{2+} transporting adenosine triphosphatase (ATPase), α-polypeptide (ATP7A), also called Menkes or MNK protein. ATP7A is mainly expressed by enterocytes, placental cells, and the central nervous system, and is localized in the *trans* -Golgi network for copper transfer to enzymes in the secretory pathway or to endosomes to facilitate copper efflux. Copper values in liver and brain are low in contrast to an increase in mucosal cells, including enterocytes and fibroblasts. Plasma copper and ceruloplasmin levels decline postnatally. Clinical features of Menkes disease are progressive cerebral degeneration (convulsions), feeding difficulties, failure to thrive, hypothermia, apnea, infections (urinary tract), peculiar facies, hair abnormalities (kinky hair), hypopigmentation, bone changes, and cutis laxa. Patients with the classic form of Menkes disease usually die before the age of 3 yr. A therapeutic trial with copper-histidinase should start before the age of 6 wk. In contrast to Menkes disease, occipital horn syndrome usually manifests during adolescence with borderline intelligence, craniofacial abnormalities, skeletal dysplasia (short clavicles, pectus excavatum, genu valgum), connective tissue abnormalities, chronic diarrhea, orthostatic hypotension, obstructive uropathy, and osteoporosis. It should be differentiated from Ehlers-Danlos syndrome type V.

Active calcium absorption is mediated by the transient receptor potential channel 6 (TRPV6) at the brush border membrane, calbindin, and the Ca-ATPase, or the Na^+ -Ca^{++} exchanger for calcium efflux at the basolateral membrane within the proximal small bowel. A congenital defect of these transporters has not yet been described.

Intestinal absorption of dietary magnesium, which occurs via the transient receptor potential channel TRPM6 at the apical membrane, is impaired in familial **hypomagnesemia with secondary hypocalcemia** , which manifests with neonatal seizures and tetany.

Intestinal iron absorption consists of several complex regulated processes starting with the uptake of heme-containing iron by heme carrier protein 1 (HCP1) and Fe^{2+} (after luminal reduction of oxidized Fe^{3+}) by the divalent metal transporter 1 (DMT1) at the apical membrane, followed by the efflux of Fe^{2+} by ferroportin 1 (also called the iron-regulated transporter) at the basolateral membrane of duodenal enterocytes. Hepatic hormone hepcidin has a key role in iron homeostasis by interacting with ferroportin. When it binds to ferroportin, hepcidin induces phosphorylation of the iron exporter, causing its internalization and degradation. A decrease in the ferroportin protein level on the cell surface inhibits iron export from intracellular pools. Thus, hepcidin controls plasma iron levels by reducing iron absorption in the gut, lowering iron release from hepatocytes, and preventing iron recycling by macrophages Hepcidin deficiency causes iron overload in hereditary hemochromatosis and iron-loading anemias, whereas hepcidin excess causes or contributes to the development of iron-restricted anemia in inflammatory diseases, infections, some cancers, and chronic kidney disease. Mutations of the ferroportin 1 gene have been found in the autosomal dominant form of **hemochromatosis** type 4. Mutations within the hemochromatosis (HFE) gene (Cys282 Tyr, His63Asn, Ser65Cys) of classic hemochromatosis reduce the endocytic uptake of diferric transferrin by the transferrin receptor-1 at the basolateral membrane of the intestinal epithelium. Hepcidin is the defective gene of juvenile hemochromatosis (type 2, subtype B). Elevated hepcidin results in hypoferremia and insufficient supply of iron for erythropoiesis, leading to different types of anemia. The underlying causes of hepcidin elevation in iron-restricted anemias are varied. An example of a genetic cause of hepcidin increase is the familial **iron-refractory iron deficiency anemia** (IRIDA), an autosomal recessive disorder caused by a mutation in matriptase-2 *(TMPRSS6)* , a negative regulator of hepcidin expression. This anemia is characterized by very low plasma iron levels, unresponsiveness to oral iron therapy and partial correction by parenteral iron. Mutations in DMT1 transporter *(SLC11A2)* are another cause of **IRIDA** . The development of severe microcytic, hypochromic anemia typifies these patients; however, surprisingly, some of them load iron in the liver.

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CHAPTER 365

Intestinal Transplantation in Children With Intestinal Failure

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The introduction of tacrolimus and the development of the abdominal multiorgan procurement techniques allowed the tailoring of various types of intestine grafts that can contain other intraabdominal organs, such as the liver, pancreas, and stomach. The understanding that the liver protects the intestine against rejection demonstrates the interaction between recipient and donor immunocytes (host-versus-graft and graft-versus-host) which under the cover of immunosuppression allows varying degrees of graft acceptance and eventual minimization of drug therapy. Over the past several years the number of patients placed on the list for and those undergoing intestinal transplantation has decreased, which may be a result of (1) improvements in the care of patients with intestinal failure under a multidisciplinary intestinal care team management, (2) the introduction of new lipid management strategies for the treatment of cholestatic liver disease, and (3) corrective surgery enhancing absorptive surface and motility, which has led to increased survival and decreased morbidity.

Indications for Intestinal Transplant

Intestinal failure describes a patient who has lost the ability to maintain nutritional support and adequate fluid requirements, needed to sustain growth, with their own intestine and is permanently dependent on total parenteral nutrition (TPN). The majority of these patients have short bowels as a result of a congenital deficiency or acquired condition (see Chapter 364.07). In others, the cause of intestinal failure is a functional disorder of motility or absorption (Table 365.1). Rarely do patients receive intestinal transplants for benign neoplasms.

The complications of intestinal failure include loss of venous access, life-threatening infections, and TPN-induced cholestatic liver disease.

Table 365.1

Causes of Intestinal Failure in Children Requiring Transplantation

SHORT BOWEL
• Congenital disorders • Volvulus • Gastroschisis • Necrotizing enterocolitis • Intestinal atresia • Trauma
INTESTINAL DYSMOTILITY
• Intestinal pseudoobstruction • Intestinal aganglionosis (Hirschsprung disease)
ENTEROCYTE DYSFUNCTION
• Microvillus inclusion disease • Tufting enteropathy • Autoimmune disorders • Crohn disease
TUMORS
• Familial polyposis • Inflammatory pseudotumor

Paucity of Venous Access

Administration of TPN requires the insertion of a centrally placed venous catheter, there being only 6 readily accessible sites (bilateral internal jugulars, subclavians, iliac veins). The loss of venous access generally occurs in the setting of recurrent catheter sepsis and thrombosis; clinical convention suggests that loss of 50% of these venous access sites places the patient at risk of not being able to be treated with TPN.

Life-Threatening Infections

Life-threatening infections are usually catheter-related; the absence of significant lengths of intestine may be associated with abnormal motility of the residual bowel (producing both delayed or rapid emptying), with varying degrees of bacterial overgrowth and possible bacterial or fungal translocation as a consequence of loss of intestinal barrier function and/or loss of gut immunity.

This situation can produce cholestatic liver disease, multisystem organ failure, and metastatic infectious foci in lungs, kidneys, liver, and the brain.

Liver Disease

The development of cholestatic liver disease is the most serious complication of intestinal failure and may be a consequence of the toxic drug effects of TPN on hepatocytes, a disruption of bile flow and bile acid metabolism, and the frequent occurrence of bacterial translocation and sepsis with endotoxin release into the portal circulation. This complication varies in frequency depending on the patient's age and the etiology of the intestinal failure; it is most common in neonates with extreme short gut. The effects on the liver include fatty transformation, steatohepatitis and necrosis, fibrosis, and then cholestasis. The development of clinical jaundice (total bilirubin > 3 mg/dL) and thrombocytopenia are significant risk factors for poor outcome, because these changes portend the development of portal hypertensive gastroenteropathy, hypersplenism, coagulopathy, and uncontrollable bleeding.

Transplantation Operation

Donor Selection

Intestinal grafts are usually procured from hemodynamically stable, ABO-identical brain-dead donors who have minimal clinical or laboratory evidence suggesting intraabdominal ischemia; size matching varies according to age of the recipients; present surgical techniques allow for significant reductions of the graft in order to achieve abdominal closure. Human leukocyte antigen has been random, and cross matching has not been a determinant of graft acceptance. Exclusion criteria include a history of malignancy and intraabdominal evidence of infection; systemic viral or bacterial infections are not excluded. Donor preparation has been limited to the administration of systemic and enteral antibiotics. Prophylaxis for graft-versus-host disease with graft pretreatment using irradiation or a monoclonal antilymphocyte antibody has varied over time. Grafts have been preserved with the University of Wisconsin solution, as is the case with other types of abdominal organs.

Types of Intestinal Grafts

Intestinal allografts are used in various forms, either alone (as an **isolated intestine graft**) or as a composite graft, which can include the liver, duodenum, and pancreas (**liver–intestine graft**); when this composite graft includes the stomach, and the recipient operation requires the removal of all of the patient's gastrointestinal tract (as with intestinal pseudoobstruction) and liver, then this replacement graft is known as a **multivisceral graft** .

The procurement of these various types of grafts focuses on the preservation of the arterial vessels of celiac and/or superior mesenteric arteries, as well as appropriate venous outflow, which would include the superior mesenteric vein or the hepatic veins in the composite grafts. The larger composite grafts inherently retain the celiac and superior mesenteric arteries; this includes multivisceral grafts, liver plus small bowel grafts, and *modified multivisceral grafts* in which the liver is excluded but the entire gastrointestinal tract is replaced, including the stomach. The isolated intestine graft retains the superior mesenteric artery and vein; this graft can be accomplished with preservation of the vessels going to the pancreas, when that organ has been allocated to another recipient. The graft that is to be used in a particular recipient is dissected out in situ and then removed after cardiac arrest of the donor, with core cooling of the organs, using an infusion of preservation solution (Fig. 365.1).

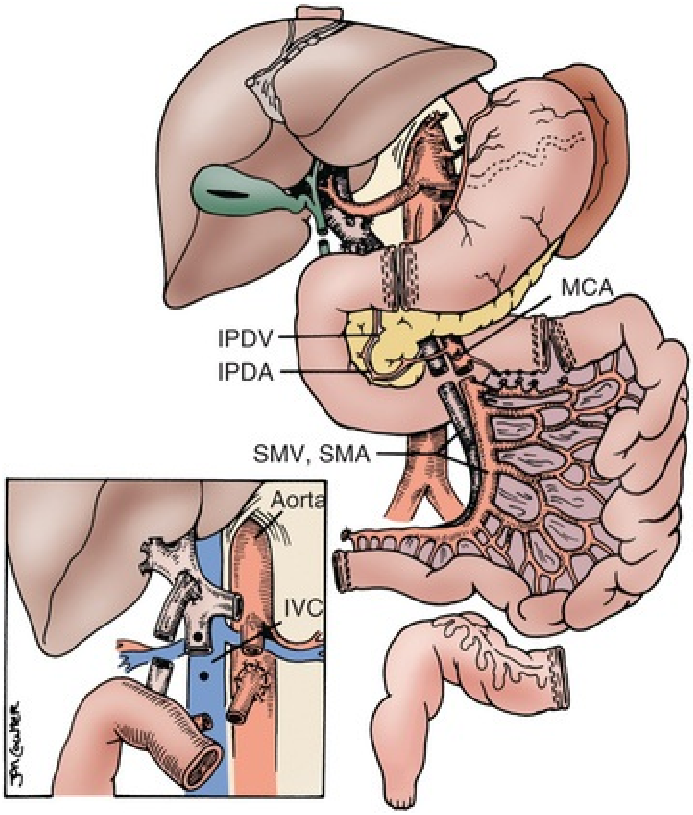

FIG. 365.1 The various abdominal organs can be dissected in situ, providing isolated or composite grafts to fit the individual patient's needs. Separation of intestine and pancreas is feasible, with preservation of the inferior pancreaticoduodenal artery *(IPDA)* and vein *(IPDV).* The use of vascular grafts from the donor allow connections to the superior mesenteric pedicle (artery *[SMA]* and vein *[SMV]*) to aorta and inferior vena cava *(IVC)* or portal vein *(inset). MCA,* Major coronary artery. (From Abu-Elmagd K, Fung J, Bueno J, et al: Logistics and technique for procurement of intestinal, pancreatic and hepatic grafts from the same donor, *Ann Surg* 232:680–697, 2000.)

Various modifications in these grafts have included the preservation of visceral ganglia at the base of the arteries, the inclusion of donor duodenum and pancreas for the liver and intestine graft, the inclusion of colon, the reduction of the liver graft (into left or right side) and variable reduction of the intestine graft, and the development of living donor intestine grafts.

The Recipient Operation

Because many children have had multiple previous abdominal operations, intestinal transplantation can be a formidable technical challenge; most children require replacement of the liver because of TPN-induced disease and often present with advanced liver failure. Transplantation of an isolated intestinal allograft involves exposure of the lower abdomen, infrarenal aorta, and inferior vena cava. Placement of vascular homografts using donor iliac artery and vein to these vessels allows arterialization and venous drainage of the intestinal graft. In patients who have retained their intestine and then undergo an enterectomy at the time of transplantation, use of the native superior mesenteric vessels is feasible.

Transplantation of a larger composite graft requires the removal and replacement of the native liver in the liver with intestine transplant, and complete abdominal exenteration in the multivisceral transplant. In a similar fashion, the infrarenal aorta is exposed for placement of an arterial conduit graft (donor thoracic aorta) for arterialization of the graft. The venous drainage is achieved to the retained hepatic veins, which are fashioned to a single conduit for anastomosis to the allograft liver.

The intestinal anastomosis to native proximal and distal bowel is performed, leaving an enterostomy of distal allograft ileum; this will be used for routine posttransplantation surveillance endoscopy and biopsy. This ostomy is closed 3-6 mo after transplantation (Fig. 365.2).

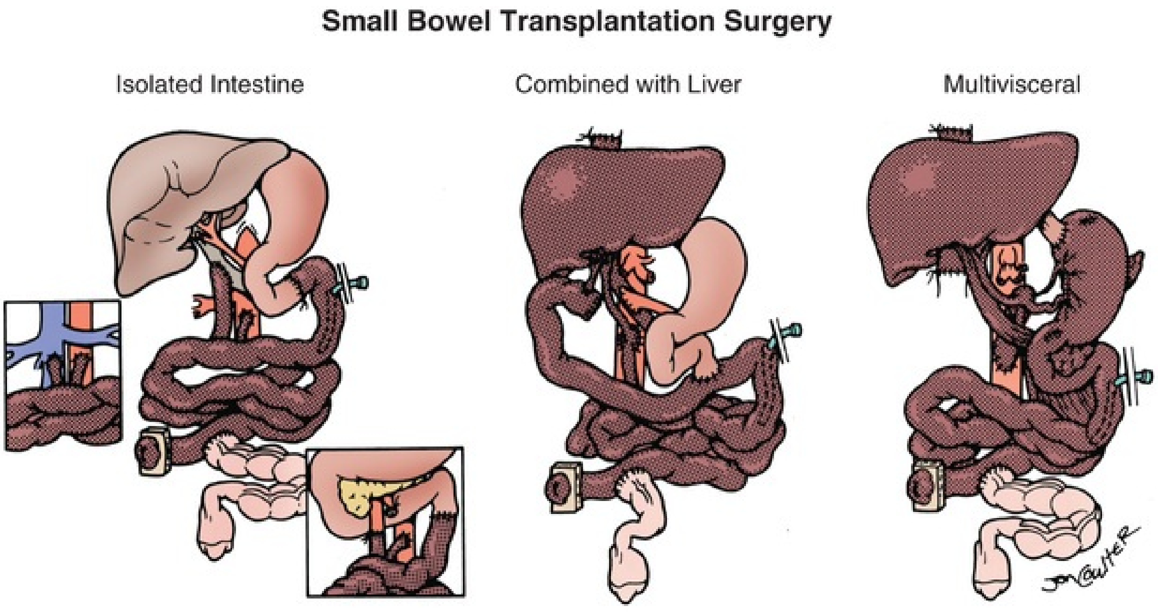

FIG. 365.2 **The three basic intestinal transplant procedures (the graft is *shaded*). With the isolated intestine, the venous outflow may be to the recipient portal vein *(main figure),* inferior vena cava *(inset left),* or superior mesenteric vein *(inset right).* With the composite grafts, which include the liver, the arterialization is from the aorta with venous drainage out from the liver graft to the recipient inferior vena cava.**

Postoperative Management

Immunosuppression

Successful immunosuppression for intestinal transplantation is initiated with tacrolimus and corticosteroids. This required high levels of tacrolimus (in the nephrotoxic range), and although initial success rates were high they were followed by rejection rates of > 80%, infection, and late drug toxicities, resulting in a gradual loss of grafts and patients. The next generation of protocols incorporated the addition of other agents, such as azathioprine, cyclophosphamide, induction with an interleukin-2 antibody antagonist, mycophenolate mofetil, and rapamycin. This modification resulted in a decreased incidence in the severity of initial rejection; the ability to decrease immunosuppression later did not allow for stabilization of long-term survival. The introduction of *recipient pretreatment* using antilymphocyte antibodies and the elimination of recipient therapy with steroids have resulted in improved transplant survival as a result of a significant decrease in the incidence of rejection and infection, permitting the gradual decrease of immunosuppressive drug therapy within 3 mo, and a decline in drug toxicity events. The most common induction regimen used is T cell depleting agents followed by -2 receptor antagonists (Fig. 365.3). A mainstay of maintenance immunosuppression is tacrolimus and prednisone dual therapy. By 1 yr the majority of patients are on tacrolimus monotherapy (Fig. 365.4).

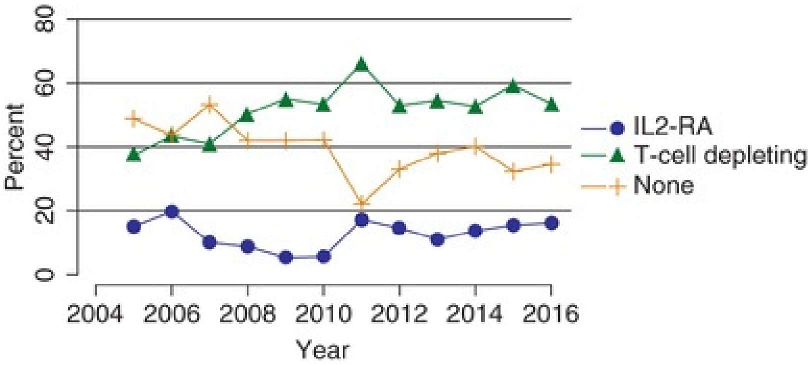

FIG. 365.3 **Induction agents used in intestinal transplant recipients. Immunosuppression at transplant reported to the OPTN. *IL2-RA* , interleukin-2 receptor antagonist. (From Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2016 Annual Data Report. Fig IN28. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration; 2018. Available at https://srtr.transplant.hrsa.gov/annual_reports/Default.aspx)**

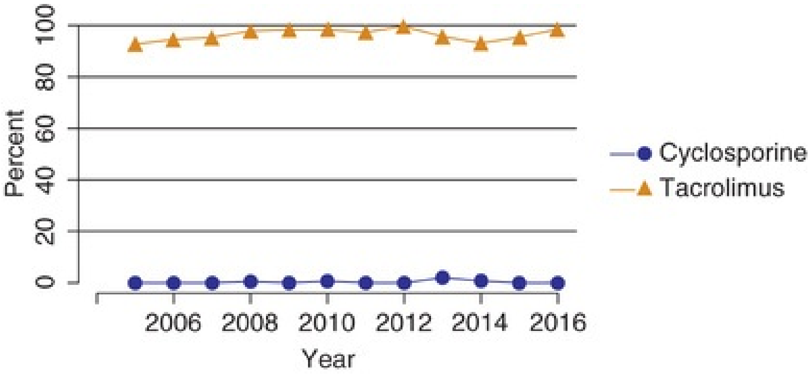

FIG. 365.4 **Calcineurin inhibitor use in intestine transplant recipients. Immunosuppression at transplant reported to the OPTN. (From Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2016 Annual Data Report. Fig IN29. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration; 2018. Available at https://srtr.transplant.hrsa.gov/annual_reports/Default.aspx)**

Allograft Assessment

There are no simple laboratory tools that allow assessment of the intestinal allograft. The gold standard for diagnosis of intestinal allograft rejection has been serial endoscopic surveillance and biopsies through the allograft ileostomy. Clinical signs and symptoms of rejection or infection of the allograft can overlap and mimic each other, producing either rapid diarrhea or complete ileus with pseudoobstruction syndromes, or gastrointestinal bleeding. Any changes in clinical status should warrant thorough evaluation for rejection with endoscopic biopsies and an evaluation for opportunistic infection, malabsorption, and other enteral infections.

The diagnosis of *acute rejection* is based on seeing destruction of crypt epithelial cells from apoptosis, in association with a mixed lymphocytic infiltrate. These histologic findings may or may not correlate with endoscopic evidence of injury, which varies from diffuse erythema and friability to ulcers and, in cases of severe rejection, exfoliation of the intestinal mucosa. *Chronic rejection* of the allograft can be diagnosed only through full-thickness sampling of the intestine, which shows the typical vasculopathy that can result in progressive ischemia of the allograft.

Rejection and Graft-Versus-Host Disease

Acute rejection rates for the intestinal allograft are significantly higher than with any other organ, in the range of 80–90%, and severe rejection requiring the use of antilymphocyte antibody preparations may be as high as 30%. Triple-drug regimens and the use of interleukin-2 antibody inhibitors have resulted in significant decreases in rejection rates; nonetheless, the amount of immunosuppression was incompatible with improvements in long-term patient and graft survival. Rejection rates of 40% are achievable with the use of antilymphocyte globulin. These protocols induce varying degrees of *proper tolerance* , which can eventually allow for minimization of immunosuppression, thus reducing the risk of drug toxicity and infection. Vascular rejection has been an uncommon occurrence, and chronic rejection has been seen in approximately 15% of cases.

Graft-versus-host disease is infrequent but potentially life-threatening; the mortality rate exceeds 80% and most recipients die from infectious complications from bone marrow failure. The incidence seen in intestinal transplantation is 5–6%. Although no standard treatment is available, early diagnosis, prevention of infection, and initiation of treatment as soon as possible may improve outcomes.

Infections

Infectious complications are the most significant cause of morbidity and mortality after intestinal transplantation. The most common infections (bacterial, fungal, polymicrobial) occur as a result of the continuing need for venous catheter placement for as long as 1 yr posttransplantation. Infections as a consequence of immunosuppressive drug management are from cytomegalovirus (CMV) infection (22% incidence), Epstein-Barr virus (EBV)–induced infections (21% incidence), and adenovirus enteritis (40% incidence). Despite improvements in monitoring and preventative measures, CMV remains the most common viral infection postintestinal transplantation. CMV may be acquired from blood transfusions, reactivation of endogenous viruses, or the donated allograft. The highest-risk recipients for CMV infection are those who are immunologically naïve and receive an allograft from a donor who is seropositive. The 2 CMV prevention strategies commonly employed are universal prophylaxis and preemptive therapy. Consensus guidelines recommend prophylaxis treatment for high-risk patients (donor+/recipient−). The preferred drugs for CMV prophylaxis are ganciclovir and oral valganciclovir.

Patients at the highest risk for EBV infection are those who are seronegative at the time of transplantation and those requiring a high-burden immunosuppressive therapy to maintain their graft. EBV disease varies from asymptomatic viremia to posttransplant lymphoproliferative disorder (PTLD). The incidence of EBV-related PTLD is highest in patients receiving intestinal allografts compared to liver, heart, or kidney. Children have a higher incidence of PTLD compared to adults, and are most likely to have EBV+PTLD. Early diagnosis and prevention of PTLD is essential and the mainstay of therapy is to reduce immunosuppression, although some patients have required chemotherapy. The use of anti–B-cell monoclonal antibodies, such as the anti-CD20 antibody rituximab, in PTLD has been successful as noted in anecdotal reports. Successful management of these viral infections is achieved through early detection and preemptive therapy, for both CMV and EBV, before the development of a serious life-threatening infection. This approach has improved outcomes for CMV, eliminating the mortality in the pediatric patient population (see Chapters 205 , 281 , and 282).

Outcomes

Intestinal transplantation is the standard of care for children with intestinal failure who have significant complications of TPN and can no longer tolerate such therapy. Data from the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) Annual Report 2015, and center-specific data reports have documented significant improvements with short- and long-term survivals for transplantations occurring principally in the last 10 yr; isolated intestinal transplantation graft failure rates for deceased donor transplants in 2013-2014 were 24.5% at 1 yr, 42.4% at 3 yr for transplants in 2011-2012, and 54% at 5 yr for transplants in 2009-2010 (Fig. 365.5). For liver-intestine recipients during the same time period graft failure rates were 27% at 1 yr, 33.3% at 3 yr, 48.7% at 5 yr, and 51% at 10 yr for transplants 2003-2004 (Fig. 365.6). It is hoped that with the minimization strategies currently used the long-term survival will plateau as occurs with other organ transplants; rehabilitation and quality-of-life studies have shown that more than 80% of survivors reach total independence from TPN and have meaningful life activities. Consequently, there has been a shift in efforts to improve long-term outcomes and quality of life.

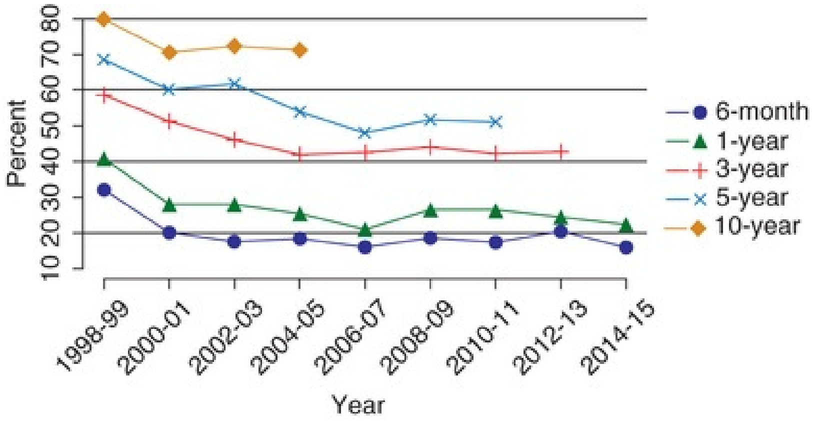

FIG. 365.5 Graft failure among transplant recipients of intestine without liver. All recipients of deceased donor intestines, including multiorgan transplants. Patients are followed until the earliest of retransplant, graft failure, death, or December 31, 2016. Estimates computed with Cox proportional hazards models adjusted for age, sex, and race. (From Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2016 Annual Data Report. Fig IN37. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration; 2018. Available at https://srtr.transplant.hrsa.gov/annual_reports/Default.aspx)

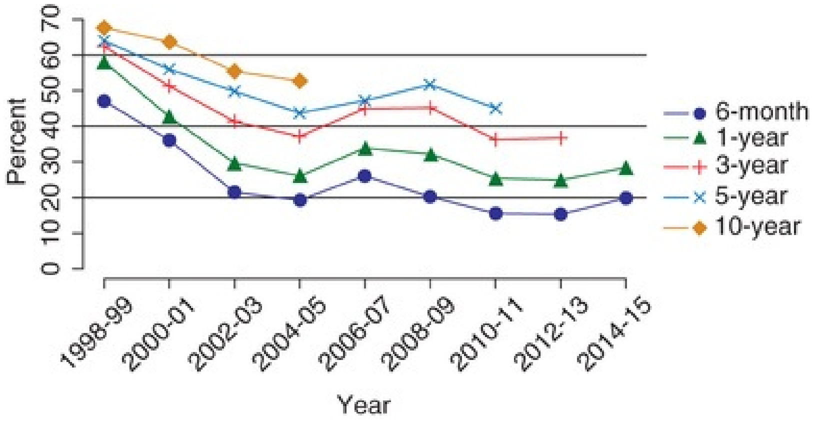

FIG. 365.6 Graft failure among transplant recipients of intestine with liver. All recipients of deceased donor intestines, including multiorgan transplants. Patients are followed until the earliest of retransplant, graft failure, death, or December 31, 2016. Estimates computed with Cox proportional hazards models adjusted for age, sex, and race. (From Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2016 Annual Data Report. Fig IN38. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration; 2018. Available at https://srtr.transplant.hrsa.gov/annual_reports/Default.aspx)

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CHAPTER 366

Acute Gastroenteritis in Children

Karen L. Kotloff

The term *gastroenteritis* denotes inflammation of the gastrointestinal tract, most commonly the result of infections with bacterial, viral, or parasitic pathogens (Tables 366.1 to 366.3). Many of these infections are foodborne illnesses (Table 366.4). Several clinical syndromes are often described because they have different (albeit overlapping) etiologies, outcomes, and treatments. **Acute gastroenteritis** (AGE) captures the bulk of infectious cases of diarrhea. The most common manifestations are diarrhea and vomiting, which can also be associated with systemic features such as abdominal pain and fever. **Dysentery** refers to a syndrome characterized by frequent small stools containing visible blood, often accompanied by fever, tenesmus, and abdominal pain. This should be distinguished from bloody diarrhea (larger volume bloody stools with less systemic illness) because the etiologies may differ. **Prolonged** (lasting 7-13 days) and **persistent diarrhea** (lasting 14 days or longer) are important because of their impact on growth and nutrition.

Table 366.1

Etiologies of Viral Gastroenteritis

ETIOLOGY	INCUBATION PERIOD	ACUTE SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTORS	COMMERCIA AVAILABLE DIAGNOSTIC TEST
Caliciviruses (including noroviruses and sapoviruses)	12-48 hr	Nausea, vomiting, abdominal cramping, diarrhea, fever, myalgia, and some	1-3 days	Person-to-person (fecal-oral and aerosolized vomit), and food, water, and fomites contaminated with human feces.	Very contagious (chlorine and heat resistant); produces large outbreaks in	No. Testing stool or vom using real ti reverse transcriptas (RT)- quantitative PCR is the

		headache			closed settings such as cruise ships, and restaurants.	preferred method, available in public healt laboratories Immunoass for norovir have poor sensitivity. FDA-clear multiplex P assays are available to detect these organisms. Norovirus genotyping and GII) is performed CDC.
Rotavirus (groups A-C), astrovirus, and enteric adenovirus (serotypes 40 and 41)	2-4 days	Often begins with vomiting, followed by watery diarrhea, low-grade fever	3-8 days	Person-to-person (fecal-oral), fomites. Aerosol transmission of rotavirus may be possible.	Nearly all infants and children worldwide were infected by 2 yr of age before vaccine introduction.	Yes. Rotavirus: immunoassay (preferred), late agglutination, a immune-chromatography stool. Enteric adenovirus: immunoassay. cleared multipl PCR assays are available to det these organisms

CDC, Centers for Disease Control and Prevention.

Modified from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

Table 366.2

Etiologies of Bacterial Gastroenteritis

ETIOLOGY	INCUBATION PERIOD	ACUTE SIGNS AND SYMPTOMS	DURATION OF ILLNESS	PRINCIPAL VEHICLE AND TRANSMISSION	RISK FACTOR
Bacillus cereus (preformed emetic toxin)	1-6 hr	Sudden onset of severe nausea and vomiting; diarrhea may be present	24 hr	Soil and water	Improperly refrigerated coo or fried rice, me
Bacillus cereus (enterotoxins formed in vivo)	8-16 hr	Abdominal cramps, watery diarrhea; nausea and vomiting	1-2 days	Soil and water	Meats, stews, gravies, vanilla sauce

		may be present			
Campylobacter jejuni	1-5 days	Diarrhea, (10–20% of episodes are prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised	5-7 days (sometimes >10 days) usually self-limiting	Wild and domestic animals and animal products, including pets	Raw and undercooked poultry, unpasteurized m untreated surfac water
Clostridium difficile toxin	Unknown—can appear weeks after antibiotic cessation	Mild to moderate watery diarrhea that can progress to severe, pseudomembranous colitis with systemic toxicity.	Variable	Person-person (fecal-oral), mostly within healthcare facilities	Immunosuppres intestinal diseas surgery, prolong hospitalization, antibiotics
Clostridium perfringens toxin	8-16 hr	Watery diarrhea, nausea, abdominal cramps; fever is rare	1-2 days	Environment, human and animal intestines	Meats, poultry, gravy, dried or precooked foods with poor temperature cont
Enterohemorrhagic *Escherichia coli* (EHEC) including *E. coli* O157:H7 and other *Shiga* toxin–producing *E. coli* (STEC)	1-9 days (usually 3-4 days)	Watery diarrhea that becomes bloody in 1-4 days in ~40% of infections; in contrast to dysentery, bloody stools are large volume and fever/toxicity are minimal. More common in children <4 yr old.	4-7 days	Food and water contaminated with feces from ruminants; infected people and animals (fecal-oral); predominantly high-resource countries	Undercooked be especially hamburger, unpasteurized m and juice, raw fr and petting zoos recreational swimming, dayc Antimotility age and antibiotics increase risk of hemolytic uremi syndrome
Enterotoxigenic *E. coli* (ETEC)	1-5 days	Watery diarrhea, abdominal cramps, some vomiting	3-7 days	Water or food contaminated with human feces	Infants and youn children in LMI and travelers
Salmonella , nontyphoidal	1-5 days	Diarrhea, (10–20% prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised	5-7 days (sometimes >10 days) usually self-limiting	Domestic poultry, cattle, reptiles, amphibians, birds	Ingestion of raw undercooked foo improper food handling, travele immunosuppres hemolytic anemi achlorhydria, contact with infected animal
Shigella spp.	1-5 days (up to 10 days for *S. dysenteriae* type 1)	Abdominal cramps, fever, diarrhea Begins with watery stools that can be the only	5-7 days	Infected people or fecally contaminated surfaces (fecal-oral)	Poor hygiene an sanitation, crowding, travel daycare, MSM, prisoners

		manifestation or proceed to dysentery.			
Staphylococcus aureus (preformed enterotoxin)	1-6 hr	Sudden onset of severe nausea and vomiting Abdominal cramps Diarrhea and fever may be present	1-3 days	Birds, mammals, dairy, and environment	Unrefrigerated o improperly refrigerated mea potato and egg salads, cream pastries
Vibrio cholerae O1 and O139	1-5 days	Watery diarrhea and vomiting, that can be profuse and lead to severe dehydration and death within hours.	3-7 days	Food and water contaminated with human feces	Contaminated w fish, shellfish, street-vended fo from endemic or epidemic setting blood group O, vitamin A deficiency
Vibrio parahaemolyticus	2-48 hr	Watery diarrhea, abdominal cramps, nausea, vomiting. Bacteremia and wound infections occur uncommonly, especially in high-risk patients, e.g., with liver disease and diabetes.	2-5 days	Estuaries and marine environments; currently undergoing pandemic spread	Undercooked or seafood, such as fish, shellfish
Vibrio vulnificus	1-7 days	Vomiting, diarrhea, abdominal pain. Bacteremia and wound infections, particularly in patients with chronic liver disease (presents with septic shock and hemorrhagic bullous skin lesions)	2-8 days	Estuaries and marine environments	Undercooked or shellfish, especia oysters, other contaminated seafood, and ope wounds exposed seawater
Yersinia enterocolitica and *Yersinia pseudotuberculosis*	1-5 days	Diarrhea, (10–20% prolonged), cramps, fever, and vomiting; bloody diarrhea, bacteremia, extraintestinal infections, severe disease in immunocompromised; pseudoappendicitis occurs primarily in older children.	5-7 days (sometimes >10 days) usually self-limiting	Swine products, occasionally person-to-person and animal-to-humans, water-borne, bloodborne (can multiply during refrigeration)	Undercooked po improper food handling, unpasteurized m tofu, contaminat water, transfusio from a bacterem person, cirrhosis chelation therap

[†] FDA-cleared multiplex PCR assays are available but generally not recommended for diagnosis in individual patients because of inability to determine antimicrobial susceptibility to guide treatment or speciate the organism for outbreak investigation.

FDA, Food and Drug Administration; *LMIC,* low and middle-income countries; *MSM,* men who have sex with men; *PCR,* polymerase chain reaction; *TCBS,* thiosulfate-citrate-bile salts-sucrose.

Modified from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

Table 366.3

Etiologies of Parasitic Gastroenteritis

ETIOLOGY	**INCUBATION PERIOD**	**ACUTE SIGNS AND SYMPTOMS**	**DURATION OF ILLNESS**	**PRINCIPAL VEHICLE AND TRANSMISSION**	**RISK FACTORS**	**CO AV DI TE**
Cryptosporidium	1-11 days	Diarrhea (usually watery), bloating, flatulence, cramps, malabsorption, weight loss, and fatigue may wax and wane. Persons with AIDS or malnutrition have more severe disease.	1-2 wk; may be remitting and relapsing over weeks to months	Person-to-person (fecal-oral), Contaminated food and water (including municipal and recreational water contaminated with human feces.	Infants 6-18 mo of age living in endemic settings in LMIC, patients with AIDS, childcare settings, drinking unfiltered surface water, MSM, IgA deficiency	Re mi exa wit (di ant pre mc for Im PC ser mi
Cyclospora cayetanensis	1-11 days	Same as *Cryptosporidium*	Same as *Cryptosporidium*	Fresh produce (imported berries, lettuce)	Travelers, consumption of fresh produce imported from the tropics.	
Entamoeba histolytica	2-4 wk	Gradual onset of cramps, watery diarrhea and often dysentery with cramps but rarely fever. Can wax and wane with weight loss.	Variable; may be protracted (several weeks to several months)	Fecal-oral transmission Any uncooked food or food contaminated by an ill food handler after cooking;	Persons living in or traveling to LMIC, institutionalized persons, MSM.	

		Dissemination to live and other organs can occur.		drinking water		
Giardia intestinalis	1-4 wk	Diarrhea, stomach cramps, gas, weight loss; symptoms may wax and wane.	2-4 wk	Any uncooked food or food contaminated by an ill food handler after cooking; drinking water	Hikers drinking unfiltered surface water, persons living in or traveling to LMIC, MSM, IgA deficiency	Mi exa for ma sar im mc Mu

[†] FDA-cleared multiplex PCR assays are available.

IgA, Immunoglobulin A; *LMID,* low- and middle-income countries; *MSM,* men who have sex with men; *PCR,* polymerase chain reaction.

Modified from Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

Table 366.4

Incidence of Bacterial and Parasitic Food-Borne Infections in 2017 and Percentage Change Compared With 2014-2016 Average Annual Incidence by Pathogen FoodNet Sites,[*] 2014-2017 [†]

PATHOGEN	**2017**		**2017 VERSUS 2014-2016**	
	NO. OF CASES	**INCIDENCE RATE** [§]	**% CHANGE** [¶]	**(95% CI)**
Bacteria				
Campylobacter	9,421	19.1	10	(2 to 18)
Salmonella	7,895	16.0	−5	(−11 to 1)
Shigella	2,132	4.3	−3	(−25 to 25)
Shiga toxin–producing *E. coli* [**]	2,050	4.2	28	(9 to 50)
Yersinia	489	1.0	166	(113 to 234)
Vibrio	340	0.7	54	(26 to 87)
Listeria	158	0.3	26	(2 to 55)
Parasites				
Cryptosporidium	1,836	3.7	10	(−16 to 42)
Cyclospora	163	0.3	489	(253 to 883)

[*] Connecticut, Georgia, Maryland, Minnesota, New Mexico, Oregon, Tennessee, and selected counties in California, Colorado, and New York.

[†] Data for 2017 are preliminary.

[§] Per 100,000 population.

[¶] Percentage change reported as increase or decrease.

[**] For Shiga toxin–producing *E. coli* , all serogroups were combined because it is not possible to distinguish between serogroups using culture-independent diagnostic tests. Reports that were only Shiga toxin–positive from clinical laboratories and were Shiga toxin–negative at a public health laboratory were excluded (n = 518). When these were included, the incidence rate was 5.2, which was a 57% increase (CI = 33–85%).

CI, confidence interval; *FoodNet,* CDC's Foodborne Diseases Active Surveillance Network.

From Marder EP, Griffin PM, Cieslak PR, et al: Preliminary incidence and trends of infections with pathogens transmitted commonly through food—foodborne diseases active surveillance network, 10 U.S. sites, 2006-2017, *MMWR* 67(11):324–328, 2018 (Table 1, p. 325).

Burden of Childhood Diarrhea

Although global mortality due to diarrheal diseases has declined substantially (39%) during the past 2 decades, it remains unacceptably high. In 2015, diarrheal disease caused an estimated 499,000, or 8.6% of all childhood deaths, making it the 4th most common cause of child mortality worldwide. Over the same period, a smaller decline (10%) was observed in the incidence of diarrhea disease among children younger than 5 yr. Almost 1.0 billion episodes occurred in 2015 worldwide, resulting in an estimated 45 million childhood disability-adjusted life years. Approximately 86% of the episodes occurred in Africa and South Asia (63% and 23%, respectively). The decline in diarrheal mortality, despite the lack of significant changes in incidence, is the result of preventive rotavirus vaccination and improved case management of diarrhea, as well as improved nutrition of infants and children. These interventions have included widespread home- and hospital-based oral rehydration solution (ORS) therapy and improved nutritional management of children with diarrhea.

In addition to the risk of mortality, high rates of diarrhea can be associated with long-term adverse outcomes. Diarrheal illnesses, especially episodes among young children that are recurrent, prolonged, or persistent, can be associated with malnutrition, stunting, micronutrient deficiencies, and significant deficits in psychomotor and cognitive development.

Pathogens

Rotavirus is the most common cause of AGE among children throughout the world. Several other viruses occur less frequently. Norovirus and sapovirus are the 2 genera of *Caliciviruses* that cause AGE. Norovirus genogroup II, genotype

4 (GII.4) has predominated globally during the past decade. Among the more than 50 serotypes of adenovirus, 40 and 41 are most often associated with diarrhea. Astroviruses are identified less often (see Table 366.1).

The major bacterial pathogens that cause AGE are nontyphoidal *Salmonella* (NTS), *Shigella, Campylobacter* , and *Yersinia* (see Table 366.2). Five pathotypes of *Escherichia coli* infect humans: Shiga toxin–producing (STEC), also known as enterohemorrhagic (EHEC), enterotoxigenic (ETEC), enteropathogenic (EPEC), enteroaggregative (EAEC), and enteroinvasive (EIEC). Two serogroups of *Vibrio cholerae* (O1 and O139) produce epidemic cholera and cause nearly all sporadic cases. *Clostridium difficile* disease can be both nosocomial and community acquired in children. Bacterial pathogens that cause foodborne illness due to their ability to produce emetic and/or enterotoxins include *Bacillus cereus* , *Clostridium perfringens* , and *Staphylococcus aureus.* The significance of isolating *Aeromonas* and *Plesiomonas* in a diarrheal stool remains uncertain.

Giardia intestinalis, Cryptosporidium spp., *Cyclospora cayetanensis* , and *Entamoeba histolytica* are the most common parasites that cause diarrhea in the United States (see Table 366.3). At least 13 species of *Cryptosporidium* are associated with human disease, but *C. hominis* and to a less extent *C. parvum* are most common. The genus *Entamoeba* comprises 6 species that colonize humans, but only *E. histolytica* is considered a human pathogen. *G. intestinalis* (formerly *G. lamblia* and *G. duodenalis*) is a flagellate protozoan that infects the small intestine and biliary tract. Other protozoa that uncommonly cause AGE are *Isospora belli* (now designated *Cystoisospora belli*) and *Blastocystic hominis.*

Epidemiology in the United States and Other Middle- and High-Income Countries

Risk Factors Related to Economic Development. Insufficient access to adequate hygiene, sanitation, and clean drinking water are the main factors leading to the heavy burden of AGE in developing countries. Nonetheless, infectious AGE remains ubiquitous in middle- and high- income countries, although the severe consequences have become uncommon. In fact, economic development poses its own risks for transmission of enteric pathogens. The ability to mass-produce and widely distribute food has led to large multistate outbreaks of AGE due to NTS, STEC, and other agents. Globalization has cultivated a taste for tropical fruits and vegetables, creating a mechanism for importation of novel pathogens. The increasing frequency of antimicrobial resistance among bacteria that causes AGE has been linked to the use of antibiotics as growth-promotors for animals bred for food. Recreational swimming facilities and water treatment systems have provided a vehicle for massive outbreaks of *Cryptosporidium* , a chlorine-resistant organism. Venues serving catered food to large groups of people, such as hotels and cruise ships, are conducive to outbreaks, as are institutions where hygiene is compromised, such as daycare centers, prisons, and nursing homes. Hospitalization and modern medical therapy have created a niche for nosocomial *C. difficile* toxin infection (Table 366.5).

Table 366.5

Exposure or Condition Associated With Pathogens Causing Diarrhea

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EXPOSURE OR CONDITION	**PATHOGEN(S)**
FoodBorne	
Foodborne outbreaks in hotels, cruise ships, resorts, restaurants, catered events	Norovirus, nontyphoidal *Salmonella* , *Clostridium perfringens* , *Bacillus cereus* , *Staphylococcus aureus* , *Campylobacter* spp., ETEC, STEC, *Listeria* , *Shigella* , *Cyclospora cayetanensis* , *Cryptosporidium* spp.
Consumption of unpasteurized milk or dairy products	*Salmonella* , *Campylobacter* , *Yersinia enterocolitica* , *S. aureus* toxin, *Cryptosporidium* , and STEC. *Listeria* is infrequently associated with diarrhea, *Brucella* (goat milk cheese), *Mycobacterium bovis* , *Coxiella burnetii*
Consumption of raw or undercooked meat or poultry	STEC (beef), *C. perfringens* (beef, poultry), *Salmonella* (poultry), *Campylobacter* (poultry), *Yersinia* (pork, chitterlings), *S. aureus* (poultry), and *Trichinella* spp. (pork, wild game meat)
Consumption of fruits or unpasteurized fruit juices, vegetables, leafy greens, and sprouts	STEC, nontyphoidal *Salmonella* , *Cyclospora* , *Cryptosporidium* , norovirus, hepatitis A, and *Listeria monocytogenes*
Consumption of undercooked eggs	*Salmonella* , *Shigella* (egg salad)
Consumption of raw shellfish	*Vibrio* species, norovirus, hepatitis A, *Plesiomonas*
Exposure or Contact	
Swimming in or drinking untreated fresh water	*Campylobacter* , *Cryptosporidium* , *Giardia* , *Shigella* , *Salmonella* , STEC, *Plesiomonas shigelloides*
Swimming in recreational water facility with treated water	*Cryptosporidium* and other potentially waterborne pathogens when disinfectant concentrations are inadequately maintained
Healthcare, long-term care,	Norovirus, *Clostridium difficile* , *Shigella* , *Cryptosporidium* , *Giardia* , STEC,

prison exposure, or employment	rotavirus
Childcare center attendance or employment	Rotavirus, *Cryptosporidium* , *Giardia* , *Shigella* , STEC
Recent antimicrobial therapy	*C. difficile* , multidrug-resistant *Salmonella*
Travel to resource-challenged countries	*Escherichia coli* (enteroaggregative, enterotoxigenic, enteroinvasive), *Shigella* , typhi and nontyphoidal *Salmonella* , *Campylobacter* , *Vibrio cholerae* , *Entamoeba histolytica* , *Giardia* , *Blastocystis* , *Cyclospora* , *Cystoisospora* , *Cryptosporidium*
Exposure to house pets with diarrhea	*Campylobacter* , *Yersinia*
Exposure to pig feces in certain parts of the world	*Balantidium coli*
Contact with young poultry or reptiles	Nontyphoidal *Salmonella*
Visiting a farm or petting zoo	STEC, *Cryptosporidium* , *Campylobacter*
Exposure or Condition	
Age group	Rotavirus (6-18 mo of age), nontyphoidal *Salmonella* (infants from birth to 3 mo of age and adults >50 yr with a history of atherosclerosis), *Shigella* (1-7 yr of age), *Campylobacter* (young adults)
Underlying immunocompromising condition	Nontyphoidal *Salmonella* , *Cryptosporidium* , *Campylobacter* , *Shigella* , *Yersinia*
Hemochromatosis or hemoglobinopathy	*Y. enterocolitica* , *Salmonella*
AIDS, immunosuppressive therapies	*Cryptosporidium* , *Cyclospora* , *Cystoisospora* , microsporidia, *Mycobacterium avium* –intercellulare complex, cytomegalovirus
Anal-genital, oral-anal, or digital-anal contact	*Shigella* , *Salmonella* , *Campylobacter* , *E. histolytica* , *Giardia lamblia* , *Cryptosporidium*

ETEC, enterotoxigenic *Escherichia coli* ; *STEC,* Shiga toxin–producing *Escherichia coli* .

From Shane AL, Mody RK, Crump JA, et al: 2017 Infectious Diseases Society for America clinical practice guidelines for the diagnosis and management of infectious diarrhea, *Clin Infect Dis* 65(12):e45–80, 2017 (Table 2, p. e48).

Endemic Diarrhea. In the United States, rotavirus was the most common cause of medically attended AGE among children younger than 5 yr until the introduction of rotavirus vaccine for routine immunization of infants. Annual epidemics swept across the country beginning in the southwest in November and reaching the northeast by May, affecting nearly every child by the age of 2 yr. Since vaccine introduction, healthcare utilization for AGE has decreased markedly. Norovirus is the leading cause of AGE among children in the United States seeking healthcare, followed by sapovirus, adenovirus 40 and 41, and astrovirus (see Table 366.1).

Foodborne Transmission. The most comprehensive resource for describing the burden of bacterial and protozoal diarrhea in the United States is the Foodborne Diseases Active Surveillance Network (FoodNet) maintained by the Centers for Disease Control and Prevention (CDC) (see Table 366.4). FoodNet performs active laboratory-based surveillance of 9 bacterial and protozoal enteric infections commonly transmitted by food. Among children 0-19 yr of age in 2015, NTS was most common, followed by *Campylobacter* and *Shigella* , then STEC and *Cryptosporidium* . *Vibrio, Yersinia, and Cyclospora* were the least common (see Table 366.5). Children younger than 5 yr have the highest incidence of disease, and the elderly have the highest frequency of hospitalization and death. Only 5% of these infections are associated with recognized outbreaks.

Noninfectious agents may also cause foodborne gastrointestinal symptoms due to a direct toxic effect of the food (mushrooms) or contamination (heavy metals) (Table 366.6).

Table 366.6

Foodborne Noninfectious Illnesses

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREAT
Antimony	5 min-8 hr usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Support
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine Can cause eosinophilia	Gastric BAL (dimerc
Cadmium	5 min-8 hr usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Support
Ciguatera fish poisoning (ciguatera toxin)	2-6 hr	GI: abdominal pain, nausea, vomiting, diarrhea	Days to weeks to months	A variety of large reef fish: grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Sup care mar Chil mor vulr
	3 hr	Neurologic: paresthesias, reversal of hot or cold, pain, weakness				
	2-5 days	Cardiovascular: bradycardia, hypotension, increase in T-wave				

		abnormalities				
Copper	5 min-8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Support
Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma Pregnant women and the developing fetus are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Support
Mushroom toxins, short-acting (muscimol, muscarine, psilocybin, *Coprinus atramentaria* , ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction, confusion, visual disturbance	Self-limited	Wild mushrooms (cooking might not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Support
Mushroom toxins, long-acting (amanitin)	4-8 hr diarrhea; 24-48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Support care, lif threaten may ne support
Nitrite poisoning	1-2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate-brown blood	Usually self-limited	Cured meats, any contaminated foods, spinach exposed to excessive nitrification	Analysis of the food, blood	Support care, m blue
Pesticides (organophosphates or carbamates)	Few minutes to few hours	Nausea, vomiting, abdominal cramps, diarrhea,	Usually self-limited	Any contaminated food	Analysis of the food, blood	Atropin PAM (pralido used w atropine

		headache, nervousness, blurred vision, twitching, convulsions, salivation, meiosis				able to sympto rarely necessa carbama poisoni
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4-6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threaten may ne respirat support
Scombroid (histamine)	1 min-3 hr	Flushing, rash, burning sensation of skin, mouth and throat, dizziness, urticaria, paresthesias	3-6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi	Demonstration of histamine in food or clinical diagnosis	Support care, antihist
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning: 30 min-2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	Hours to 2-3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Support care, ge self-lim
	Neurotoxic shellfish poisoning: few minutes to hours	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning: 24-48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				Elderly especial sensitiv amnesi shellfis poisoni
Shellfish toxins (paralytic shellfish	30 min-3 hr	Diarrhea, nausea,	Days	Scallops, mussels, clams,	Detection of toxin in food or	Life-threaten

poisoning)		vomiting leading to paresthesias of mouth and lips, weakness, dysphasia, dysphonia, respiratory paralysis		cockles	water where fish are located; high-pressure liquid chromatography	may nee respirat support
Sodium fluoride	Few minutes to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with NaF-containing insecticides and rodenticides	Testing of vomitus or gastric washings Analysis of the food	Support
Thallium	Few hours	Nausea, vomiting, diarrhea, painful paresthesias, motor polyneuropathy, hair loss	Several days	Contaminated food	Urine, hair	Support
Tin	5 min-8 hr usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of the food	Support
Vomitoxin	Few minutes to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of the food	Support
Zinc	Few hours	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of the food, blood and feces, saliva or urine	Support

BAL, bronchoalveolar lavage; *GI,* gastrointestinal.

From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

Diarrhea Outbreaks. The U.S. Foodborne Disease Outbreak Surveillance System quantifies enteric infections associated with foodborne outbreaks. In 2015, among all age groups, norovirus was the most common agent (46%), followed by NTS (23%). Less common are *C* . *perfringens* (6%), STEC (5%), *Campylobacter* (5%), and *S* . *aureus* (2%), followed much less often (each 1%) by *B* . *cereus* , *Clostridium botulinum, Shigella, Cryptosporidium, Yersinia, Listeria, Vibrio parahaemolyticus,* and *Shigella* . Outbreaks of enteric pathogens propagated by direct person-to-person contact are most often caused by norovirus and *Shigella* species; other pathogens include NTS, rotavirus, *Giardia* , *Cryptosporidium* , *C . difficile*, and *C. jejuni.*

Nosocomial Diarrhea. *C. difficile* is the most common cause of healthcare-associated infection in the United States. Severe disease occurs most often in those with predisposing conditions (e.g., recent antibiotics, gastric acid suppression, immunosuppression, gastrointestinal comorbidities). In contrast to adults, rates of colostomy and in-hospital mortality have not increased in children despite increasing rates of community and hospital-acquired *C. difficile* infection, suggesting that *C. difficile* may be less pathogenic in children. Moreover, high rates of asymptomatic carriage (and presence of toxin) among children younger than 2 yr creates diagnostic uncertainty, so testing and treatment should be reserved for those with supporting clinical evidence (see Table 366.2).

Zoonotic Transmission. Many diarrheal pathogens are acquired from animal reservoirs (see Tables 366.1 to 366.3 , 366.5). The ability of NTS to undergo transovarian passage in hens allows infection of intact grade A pasteurized eggs, a source of multiple large outbreaks. Although *Campylobacter* is prevalent in poultry, its lower outbreak potential has been attributed to its lack of transovarian spread in hens and stringent growth requirements, which limit its ability to replicate in foods. On the other hand, *Campylobacter* has an extensive reservoir in domestic and wild animals and remains a major cause of sporadic bacterial foodborne disease in industrialized countries, usually from consumption of contaminated chicken, meat, beef, and milk. Its ubiquitous animal reservoir also has resulted in widespread contamination of surface waters, resulting in diarrhea among hikers and campers who drink from streams, ponds, and lakes in wilderness areas. The predilection for STEC to asymptomatically colonize the intestines of ruminant animals explains why unpasteurized dairy products, fruits harvested from fields where cattle graze, and undercooked hamburger are common vehicles. The major animal reservoir for *Yersinia* is pigs, so ingestion of raw or undercooked pork products is an important risk factor. Pets can be the source of NTS (asymptomatic young birds, amphibians, and reptiles), *Campylobacter* , and *Yersinia* (puppies and kittens that are usually ill with diarrhea).

Seasonality. Seasonality provides a clue to implicate specific pathogens, although patterns may differ in tropical and temperate climates. Rotavirus and norovirus peak in cool seasons, whereas enteric adenovirus infections occur throughout the year, with some increase in summer. *Salmonella, Shigella,* and

Campylobacter favor warm weather, whereas the tendency for *Yersinia* to tolerate cold manifests as a winter seasonality, with higher prevalence in northern countries, and ability to survive in contaminated blood products during refrigeration.

Epidemiology in Low- and Middle-Income Countries

The Global Enteric Multicenter Study (GEMS) evaluated children younger than 5 yr living in 7 low-income countries in sub-Saharan Africa and South Asia and seeking healthcare for moderate-to-severe diarrhea (Fig. 366.1). Although a broad array of pathogens were identified, most episodes of moderate-to-severe diarrhea were attributed to 4 pathogens: rotavirus, *Cryptosporidium, Shigella* , and ETEC producing heat-stable toxin (ST) either alone or in combination with heat-labile toxin (LT), herein termed ST-ETEC, and, to less extent, adenovirus 40 and 41. On the other hand, several etiologic agents that are common causes of AGE in high-resource settings are notable for their low frequency in resource-limited settings: NTS, STEC, norovirus, and *C. difficile* toxin. The 3 agents associated with most deaths among children under 5 yr are rotavirus (29%), *Cryptosporidium* (12%), and *Shigella* (11%). The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project (MAL-ED) was a study of less severe, community-based diarrhea. Viral causes predominated (36.4% of the overall incidence), but *Shigella* had the single highest attributable incidence (26.1 attributable episodes per 100 child-years).

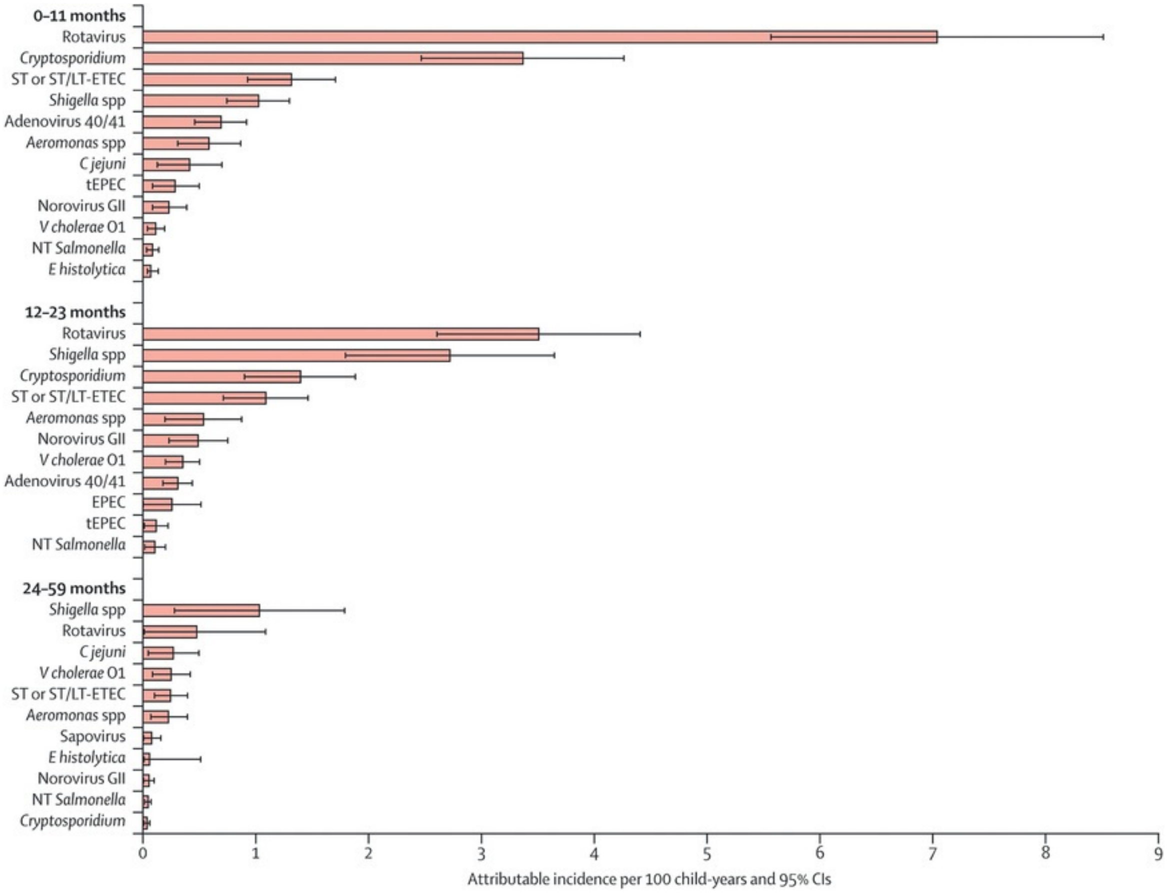

FIG. 366.1 Attributable incidence of pathogen-specific moderate-to-severe diarrhea per 100 child-yr by age stratum, all sites combined. The *bars* show the incidence rates, and the *error bars* show the 95% confidence intervals. *EPEC* , enteropathogenic; *ETEC* , enterotoxigenic; *LT* , labile toxin; *NT* , Nontyphoidal; *ST* , stable toxin. (Modified from Kotloff KL, Nataro JP, Blackwelder WC, et al: Burden and aetiology of diarrhoeal disease in infants and young children in developing countries [the Global Enteric Multicenter Study, GEMS]: a prospective, case-control study, *Lancet* 382[9888]:209–222, 2013, Fig. 4.)

Host Risk Factors

Most pathogens show an age predilection. The incidence of rotavirus and NTS are highest in infancy. Endemic shigellosis peaks in 1-4 yr olds, whereas *Campylobacter* and *Cryptosporidium* show a bimodal distribution with the greatest number of reported cases in infants and young children a secondary peak in adolescents and young adults. Pandemic *V. cholerae* and *S. dysenteriae* type 1 produce high attack rates and mortality in all age groups and often afflict displaced persons in emergency settings. Some agents (e.g., NTS, *Shigella*, *Campylobacter, Yersinia* , and *Cryptosporidium*) are more frequent and more severe when the host is immunocompromised or malnourished.

Additional risks factors for AGE include immunodeficiency, measles, malnutrition, and lack of exclusive or predominant breastfeeding. Malnutrition increases the risk of diarrhea and associated mortality, and moderate to severe stunting increases the odds of diarrhea-associated mortality. The fraction of such infectious diarrhea deaths that are attributable to nutritional deficiencies varies with the prevalence of deficiencies; the highest attributable fractions are in sub-Saharan Africa, South Asia, and Andean Latin America. The risks are particularly high with malnutrition, particularly when associated with micronutrient deficiency. Vitamin A deficiency accounts for 157,000 deaths from diarrhea, measles, and malaria. Zinc deficiency is estimated to cause 116,000 deaths from diarrhea and pneumonia. Table 366.7 summarizes some of the key risk factors associated with childhood diarrhea globally, especially in the presence of micronutrient deficiency.

Table 366.7

Proven Risk Factors With Direct Biologic Links to Diarrhea: Relative Risks or Odds Ratios and 95% Confidence Intervals

	DIARRHEAL MORBIDITY	**DIARRHEAL MORTALITY**
No breastfeeding (0-5 mo)	RR = 2.7 (1.7-4.1) compared with exclusive breastfeeding	RR = 10.5 (2.8-39.6) compared with exclusive breastfeeding
No breastfeeding (6-23 mo)	RR = 1.3 (1.1-1.6) compared with any breastfeeding	RR = 2.2 (1.1-4.2) compared with any breastfeeding
Underweight	(compared with ≥2 WAZ)	(compared with ≥1 WAZ)
−2 to ≤1 WAZ		OR = 2.1 (1.6-2.7)
−3 to ≤2 WAZ	RR = 1.2 (1.1-1.4)	OR = 3.4 (2.7-4.4)
≤3 WAZ		OR = 9.5 (5.5-16.5)
Stunted		
−2 to ≤1 HAZ		OR = 1.2 (0.9-1.7)
−3 to ≤2 HAZ		OR = 1.6 (1.1-2.5)
<−3 HAZ		OR = 4.6 (2.7-14.7)
Wasted		
−2 to ≤1 WHZ		OR = 1.2 (0.7-1.9)
−3 to ≤2 WHZ		OR = 2.9 (1.8-4.5)
≤3 WHZ		OR = 6.3 (2.7-14.7)
Vitamin A deficiency (vs. not deficient)		RR = 1.5 (1.3-1.8)

Zinc deficiency (vs. not deficient)	RR = 1.2 (1.1-1.2)	RR = 1.2 (1.0-1.6)

HAZ, height-for-age Z-score; *OR,* odds ratio; *RR,* relative risk; *WAZ,* weight-for-age Z score; *WHZ,* weight-for-height Z-score.

Modified from Walker CL, Rudan I, Liu L, et al: Global burden of childhood pneumonia and diarrhoea, *Lancet* 381:1405–1416, 2013.

Pathogenesis of Infectious Diarrhea

Intrinsic properties of the organism help to define the mode of transmission and incubation period (Table 366.8). Enteropathogens that are infectious in small inocula (*Shigella,* STEC, norovirus, rotavirus, *G. intestinalis, Cryptosporidium* spp., *C. difficile, E. histolytica*) are readily transmitted by person-to-person contact via the fecal-oral route. Pathogens with larger infectious doses, such as cholera, NTS, ETEC, and *Campylobacter* , generally require food or water vehicles (see Tables 366.1 to 366.3). Pathogens that produce preformed toxins (*S. aureus, B. cereus* emetic toxin) have shorter incubation periods (1-6 hr) compared with 8-16 hr for those that must elaborate enterotoxins in situ (e.g., *C. perfringens* and *B. cereus enterotoxin*). Incubation periods of 1-5 days are seen with pathogens that attach to the epithelium and elaborate enterotoxins (e.g., *V. cholerae* , ETEC) or cytotoxins (e.g., *S* . *dysenteriae* type 1 and STEC) or those that invade and disrupt the intestinal epithelium (*Shigella* , NTS, *Campylobacter* , and *Yersinia*). The requirement for protozoa to progress through a life cycle to trigger pathogenic processes results in a more extended incubation period. Other properties affecting transmissibility are bioavailability as conferred by a copious and/or prolonged fecal shedding, extended infectivity in the environment, and resistance to disinfection (all exhibited by norovirus and *Cryptosporidium*), or a large environmental or animal reservoir (e.g., *Campylobacter*). The ability to circumvent immune surveillance by frequent antigenic changes resulting from recombinational events (e.g., norovirus) or a large serotype diversity (e.g., *Shigella*) maintains a susceptible host population.

Table 366.8

Comparison of 3 General Pathogenic Mechanisms of Enteric Infection

TYPE OF INFECTION

PARAMETER	**I**	**II**	**III**
Mechanism	Noninflammatory (enterotoxin or adherence/superficial invasion)	Inflammatory, epithelial destruction (invasion, cytotoxin)	Penetrating
Location	Proximal small bowel	Colon	Distal small bowel
Illness	Watery diarrhea	Dysentery	Enteric fever
Stool examination	No fecal leukocytes Mild or no ↑ lactoferrin	Fecal polymorphonuclear leukocytes ↑↑ Lactoferrin	Fecal mononuclear leukocytes
Examples	*Vibrio cholerae* ETEC *Clostridium perfringens* *Bacillus cereus* *Staphylococcus aureus* Also [†] : *Giardia intestinalis* *Rotavirus* Noroviruses *Cryptosporidium* spp. EPEC, EAEC *Cyclospora cayetanensis*	*Shigella* EIEC STEC NTS *Vibrio parahaemolyticus* *Clostridium difficile* *Campylobacter jejuni* *Entamoeba histolytica* [*]	*Yersinia enterocolitica* *Salmonella* Typhi, *S.* Paratyhpi, and occasionally NTS, *Campylobacter*, and *Yersinia*

[*] Although amebic dysentery involves tissue inflammation, the leukocytes are characteristically pyknotic or absent, having been destroyed by the virulent amebae.

[†] Although not typically enterotoxic, these pathogens alter bowel physiology via adherence, superficial cell entry, cytokine induction, or toxins that inhibit cell function.

EAEC, enteroaggregative *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *Escherichia coli;* ETEC, enterotoxigenic *Escherichia coli* ; *NTS,* nontyphoidal *Salmonella; STEC,* Shiga toxin–producing *Escherichia coli* .

Modified from Mandell GL, Bennett JE, Dolin R, editors: *Principles and practices of infectious diseases* , ed 7, Philadelphia, 2010, Churchill Livingstone.

Viral AGE causes a cytolytic infection of the small intestinal villus tips resulting in decreased absorption of water, disaccharide malabsorption, inflammation, and cytokine activation. The rotavirus protein NSP4 acts as a viral enterotoxin that produces secretory diarrhea. In addition, rotavirus activates the enteric nervous system causing decreased gastric emptying and increased intestinal mobility. There is a genetic susceptibility to both rotavirus and norovirus infection that is mediated by histo-blood group antigens on the epithelial cell surface and in mucus secretions (Fig. 366.2).

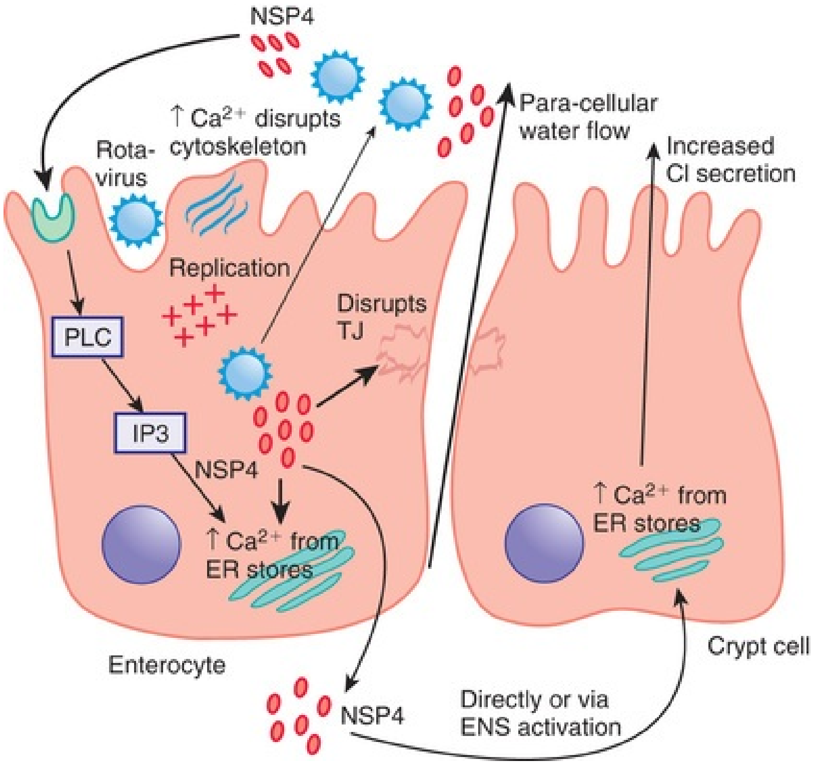
NSP4
↑ Ca²⁺ disrupts cytoskeleton
Rota-virus
Para-cellular water flow
Increased Cl secretion
Replication
Disrupts TJ
PLC
IP3
NSP4
↑ Ca²⁺ from ER stores
↑ Ca²⁺ from ER stores
Enterocyte
Crypt cell
NSP4
Directly or via ENS activation

FIG. 366.2 **Pathogenesis of rotavirus infection and diarrhea. *ENS,* Enteric nervous system; *ER,* endoplasmic reticulum; *NSP4,* non-structural protein 4; *PLC,* phospholipase C; *TJ,* tight junction. (Modified from Ramig RF: Pathogenesis of intestinal and systemic rotavirus infection, *J Virol* 78:10213–10220, 2004.)**

Pathogens primarily manifesting as secretory diarrhea attach to the surface of the epithelium and stimulate secretion of water and electrolytes by activating adenylate cyclase and raising intracellular cAMP (*V. cholerae* and heat- LT–producing ETEC) and/or cGMP (ETEC producing heat-ST) (Figs. 366.3 and 366.4). The diarrheagenic phenotype of *C. difficile* is attributed to production of toxins A (an enterotoxin) and B (an enterotoxin and cytotoxin). The epidemic hypervirulent NAP1 *C. difficile* also makes binary toxin, which may enhance colonization and augment toxin production.

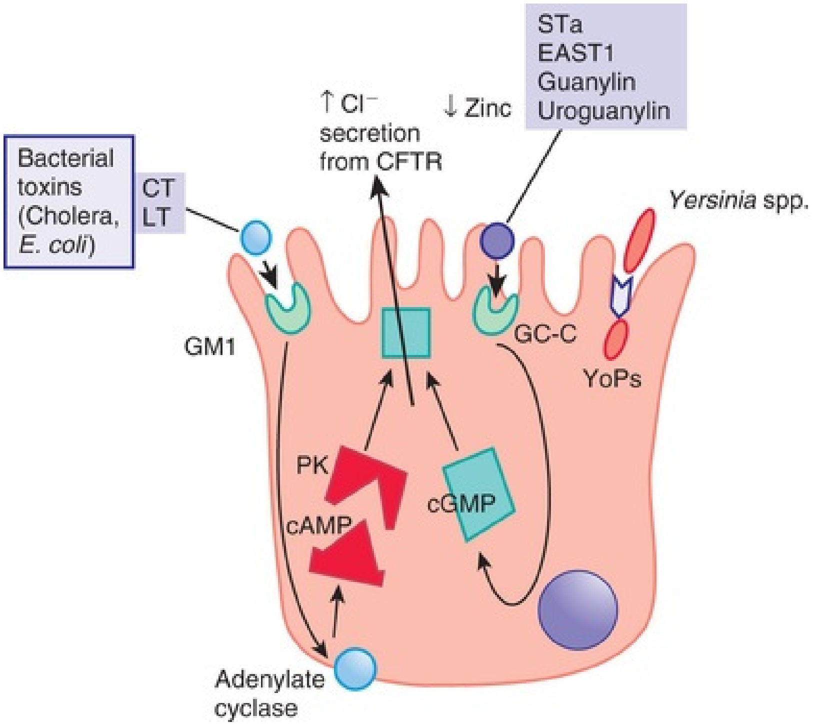
STa
EAST1
Guanylin
Uroguanylin
↑ Cl⁻ secretion from CFTR
↓ Zinc
Bacterial toxins (Cholera, *E. coli*)
CT
LT
Yersinia spp.
GM1
GC-C
YoPs
PK
cAMP
cGMP
Adenylate cyclase

FIG. 366.3 **Mechanism of secretory and penetrating diarrhea. *cAMP,* Cyclic adenosine monophosphate; *CFTR,* cystic fibrosis transmembrane conductance regulator through which chloride is secreted; *cGMP,* cyclic guanosine monophosphate; *YoPs, Yersinia* outer proteins that alter host cell functions to promote disease; *CT,* cholera toxin; *EAST 1,* enteroaggregative *E. coli* ST; *GC-C,* guanylate cyclase, the transmembrane receptor for STa and other toxins; *GM1,* a ganglioside containing one sialic acid residue that serves as the receptor for CT and LT; *LT,* heat labile toxin; *PK,* protein kinase; *STa,* heat stable toxin a. (Modified from Thapar M, Sanderson IR: Diarrhoea in children: an interface between developing and developed countries, *Lancet* 363:641–653, 2004; and Montes M, DuPont HL: Enteritis, enterocolitis and infectious diarrhea syndromes. In Cohen J, Powderly WG, Opal SM, et al, editors: *Infectious diseases,* ed 2, London, 2004, Mosby, pp. 31–52.)**

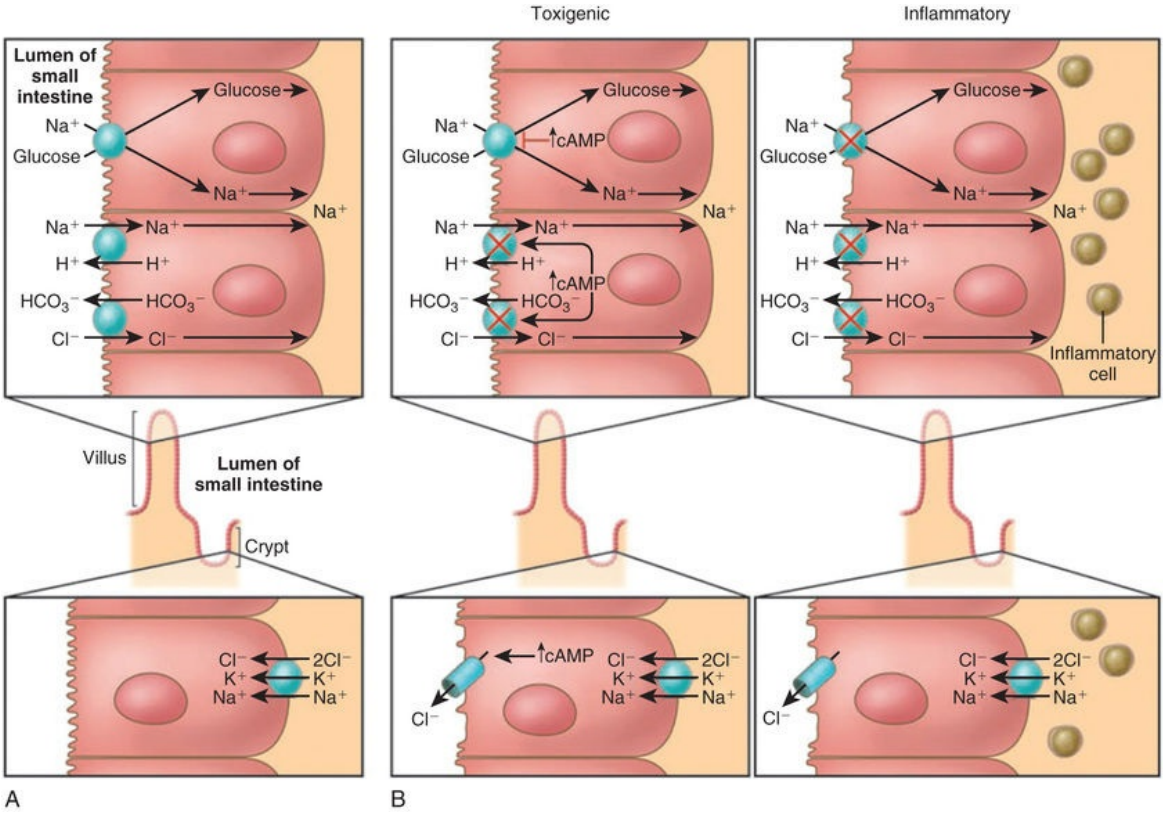
Toxigenic
Inflammatory
Lumen of small intestine
Glucose
Na+
Glucose
Na+
Na+
Na+
Na+
H+
H+
HCO3−
HCO3−
Cl−
Cl−
cAMP
Inflammatory cell
Villus
Lumen of small intestine
Crypt
Cl−
K+
Na+
2Cl−
K+
Na+
cAMP
Cl−
A
B

FIG. 366.4 Movement of Na^+ and Cl^- in the small intestine. A, Movement in normal subjects. Na^+ is absorbed by 2 different mechanisms in absorptive cells from villi: glucose-stimulated absorption and electroneutral absorption (which represents the coupling of Na^+/H^+ and Cl^-/HCO_3^- exchanges). B, Movement during diarrhea caused by a toxin and inflammation. (From Petri WA, Miller M, Binder HJ, et al: Enteric infections, diarrhea and their impact on function and development, *J Clin Invest* 118:1277–1290, 2008.)

Shigella , NTS, *Campylobacter* , and *Yersinia* all possess an invasive phenotype and elicit diarrhea by a variety of mechanisms that generally involves elicitation of inflammatory cytokines with or without associated toxin production (Fig. 366.5). The pathogenesis of *Shigella* , the most common cause of bacillary dysentery, has been characterized in greatest detail. Following invasion, *Shigella* induces extensive destruction and inflammation of the intestinal epithelium producing ulcers and microabscesses that manifest with diarrheal stools containing blood and pus. Production of enterotoxins contributes to secretory diarrhea, which can be seen early in shigellosis or as the sole manifestation. A single serotype of *Shigella* , *S* . *dysenteriae* type 1, elaborates the Shiga toxin which increases the severity of illness and is responsible for development of hemolytic uremic syndrome (HUS).

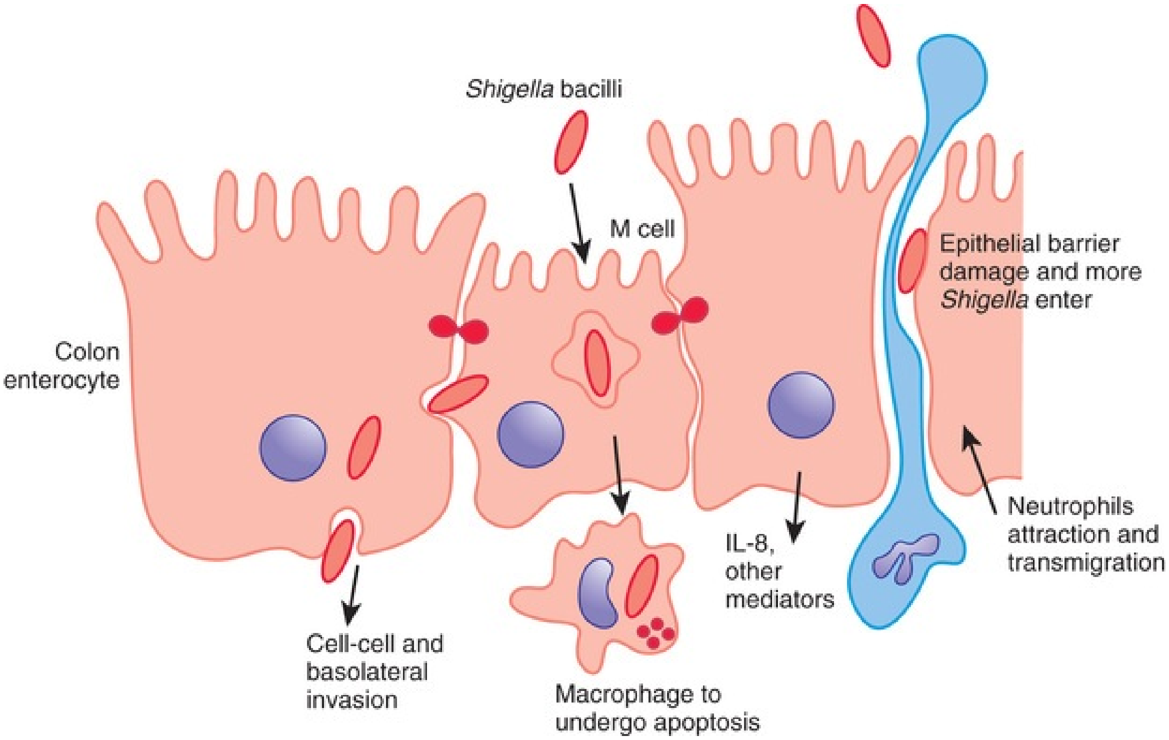
Shigella bacilli
M cell
Colon enterocyte
Epithelial barrier damage and more *Shigella* enter
Neutrophils attraction and transmigration
IL-8, other mediators
Cell-cell and basolateral invasion
Macrophage to undergo apoptosis

FIG. 366.5 **Pathogenesis of shigella infection and diarrhea. *IL-8,* interleukin-8. (Modified from Opal SM, Keusch GT: Host responses to infection. In Cohen J, Powderly WG, Opal SM, et al, editors: *Infectious diseases,* ed 2, London, 2004, Mosby, pp. 31–52.)**

Cryptosporidia sporozoites released from ingested cysts penetrate intestinal epithelial cells and develop into trophozoites within the intracellular, but extracytoplasmic, environment. After undergoing asexual multiplication and sexual development, they are released in the colon as infectious oocysts capable of causing autoinfection. Host factors, in particular T-cell function, play a critical role in disease severity. *Cyclospora* cysts are not infectious in freshly passed stools but must sporulate in the environment for 1-2 wk to become infectious; they are usually transmitted in contaminated produce and water (see Table 366.4).

Clinical Manifestation of Diarrhea

General Findings. Diarrhea is usually defined as the passage of 3 or more abnormally loose or liquid stools per day. Frequent passage of formed stools is not diarrhea, nor is the passing of loose, pasty stools by breastfed babies. Clinical clues to the possible etiology of gastroenteritis are noted in Table 366.9 .

Table 366.9

Clinical Presentations Suggestive of Infectious Diarrhea Etiologies

FINDING	LIKELY PATHOGENS
Persistent or chronic diarrhea	*Cryptosporidium* spp., *Giardia lamblia* , *Cyclospora cayetanensis* , *Entamoeba histolytica* , non-typhoidal *Salmonella*, *Yersinia,* and *Campylobacter* spp.
Visible blood in stool	STEC, *Shigella* , *Salmonella* , *Campylobacter* , *Entamoeba histolytica* , noncholera *Vibrio parahaemolyticus* , *Yersinia* , *Balantidium coli* , and *Aeromonas*
Fever	Not highly discriminatory—viral, bacterial, and parasitic infections can cause fever. In general, higher temperatures are suggestive of bacterial etiology or *E. histolytica* . Patients infected with STEC usually are not febrile at time of presentation
Abdominal pain	STEC, *Salmonella* , *Shigella* , *Campylobacter* , *Yersinia* , noncholera *Vibrio* species, *Clostridium difficile*
Severe abdominal pain, often grossly bloody stools (occasionally nonbloody), and minimal or no fever	STEC, *Salmonella* , *Shigella* , *Campylobacter* , and *Yersinia enterocolitica*
Persistent abdominal pain and fever	*Y. enterocolitica and Y. pseudotuberculosis* ; may mimic appendicitis
Nausea and vomiting lasting ≤24 hr	Ingestion of *Staphylococcus aureus* enterotoxin or *Bacillus cereus* (short-incubation emetic syndrome)
Diarrhea and abdominal cramping lasting 1-2 days	Ingestion of *Clostridium perfringens* or *Bacillus cereus* (long-incubation emetic syndrome)
Vomiting and nonbloody diarrhea	Norovirus (low-grade fever usually present during the first 24 hr in 40% of infections); diarrhea usually lasts 2-3 days or less; other viral diarrheas (e.g., rotavirus, enteric adenovirus, sapovirus, astrovirus) usually last 3-8 days.
Chronic watery diarrhea, often lasting a year or more	Brainerd diarrhea (epidemic secretory diarrhea, etiologic agent has not been identified); postinfectious irritable bowel syndrome

STEC, Shiga toxin–producing *Escherichia coli* .

From Shane AL, Mody RK, Crump JA, et al: 2017 Infectious Diseases Society for America clinical practice guidelines for the diagnosis and management of infectious diarrhea, *Clin Infect Dis* 65(12):e45–80, 2017 (Table 3, p. e54).

In the past, many guidelines divided patients into subgroups for mild (3–5%), moderate (6–9%), and severe (≥10%) dehydration. However, it is difficult to distinguish between mild and moderate dehydration based on clinical signs alone. Therefore most guidelines now combine mild and moderate dehydration and simply use none, some, and severe dehydration. The individual signs that best predict dehydration are prolonged capillary refill time >2 sec, abnormal skin turgor, hyperpnea (deep, rapid breathing suggesting acidosis), dry mucous membranes, absent tears, and general appearance (including activity level and thirst). As the number of signs increases, so does the likelihood of dehydration. Tachycardia, altered level of consciousness, and cold extremities with or without hypotension suggest severe dehydration.

Viral Diarrhea. Symptoms of rotavirus AGE usually begin with vomiting followed by frequent passage of watery nonbloody stools, associated with fever in about half the cases (see Table 366.1). The diarrhea lacks fecal leukocytes, but stools from 20% of cases contain mucus. Recovery with complete resolution of symptoms generally occurs within 7 days. Although disaccharide malabsorption is found in 10–20% of episodes, it is rarely clinically significant.

Other viral agents elicit similar symptoms and cannot be distinguished from rotavirus based on clinical findings. In an outbreak setting, the pattern of a brief incubation period (12-48 hr), short duration of illness, and clustering of cases is shared by caliciviruses and preformed bacterial toxin. However, unlike preformed toxins, caliciviruses cause secondary infections, which confirm the contagious nature of the outbreak. Diarrheal illnesses caused by enteric adenovirus infections tend to be more prolonged than rotavirus (7 to 10 days), whereas astroviruses cause a shorter course (~5 days) usually without significant vomiting.

Bacterial Diarrhea. Although there is considerable overlap, fever >40°C, overt fecal blood, abdominal pain, no vomiting before diarrhea onset, and high stool frequency (>10 per day) are more common with bacterial pathogens (see Tables 366.2 and 366.9). Although high fever and overt fecal blood are often absent in bacterial enteritis, when present, there is a high probability of a bacterial etiology. The classical bacterial agents, NTS, *Shigella, Campylobacter,* and *Yersinia*, present with 1 of 5 syndromes.

1. Acute diarrhea, the most common presentation, may be accompanied by fever and vomiting. Clinically silent bacteremia associated with uncomplicated NTS AGE can be seen among otherwise healthy children younger than 2 yr living in industrialized countries.
2. Bloody diarrhea or frank dysentery is classically caused by *Shigella* . Watery diarrhea typically precedes dysentery and is often the sole clinical manifestation of mild infection. Progression to dysentery indicates colitis and may occur within hours to days. Patients with severe infection may pass more than 20 dysenteric stools in 1 day. Dysenteric illnesses due to *Campylobacter* have been confused with inflammatory bowel disease.
3. Invasive, nonfocal disease (**enteric fever**) is a febrile illness associated with bacteremia without localized infection. Diarrhea may be minimal or absent. Although classically the result of *S.* Typhi or Paratyphi A and B, enteric fever can result from systemic spread of the classical bacterial enteropathogens. Although enteric fever caused by *S.* Typhi or Paratyphi

A and B primarily affect preschool and school-age children in endemic countries, other bacterial enteropathogens most often cause disease in infants (particularly <3 mo), the immunocompromised, and children with malnutrition. Additional risk factors include hemolytic anemia and intravascular lesions for NTS, and iron overload, cirrhosis, and chelation therapy for *Yersinia* sepsis. The distinct clones of NTS that have arisen in sub-Saharan Africa described earlier are causing enteric fever–type illnesses often in the absence of AGE. *Shigella* sepsis is rare and is seen most often in malnourished and immunocompromised hosts.

4. Extraintestinal invasive infections can result from either local invasion or bacteremic spread (Table 366.10). Examples of local invasion include mesenteric adenitis, appendicitis, and rarely cholecystitis, mesenteric venous thrombosis, pancreatitis, hepatic, or splenic abscess. Bacteremic spread may result in pneumonia, osteomyelitis, meningitis (3 conditions seen most commonly with NTS), abscesses, cellulitis, septic arthritis, and endocarditis. *Shigella* can cause noninvasive contiguous infections such as vaginitis and urinary tract infections.

Table 366.10

Intestinal and Extraintestinal Complications of Enteric Infections

COMPLICATION	ASSOCIATED ENTERIC PATHOGEN(S)
Intestinal Complications	
Persistent diarrhea	All causes
Recurrent diarrhea (usually immunocompromised persons)	*Salmonella, Shigella* , *Yersinia* , *Campylobacter, Clostridium difficile* , *Entamoeba histolytica* , *Cryptosporidium, Giardia*
Toxic megacolon	*Shigella* , *C. difficile* , *E. histolytica*
Intestinal perforation	*Shigella* , *Yersinia, C. difficile* , *E. histolytica*
Rectal prolapse	*Shigella* , STEC, *C. difficile*
Enteritis necroticans–jejunal hemorrhagic necrosis	*Clostridium perfringens* type C beta toxin
Extraintestinal Complications	
Dehydration, metabolic abnormalities, malnutrition, micronutrient deficiency	All causes
Bacteremia with systemic spread of bacterial pathogens, including endocarditis, osteomyelitis, meningitis, pneumonia, hepatitis, peritonitis,	Nontyphoidal *Salmonella, Shigella, Yersinia, Campylobacter*

chorioamnionitis, soft tissue infection, and septic thrombophlebitis	
Local spread (e.g., vulvovaginitis and urinary tract infection) Pseudoappendicitis Exudative pharyngitis, cervical adenopathy Rhabdomyolysis and hepatic necrosis	*Shigella* *Yersinia, Campylobacter* (occasionally) *Yersinia* *Bacillus cereus* emetic toxin
Postinfectious Complications	
Reactive arthritis	*Salmonella, Shigella, Yersinia, Campylobacter, Cryptosporidium, C. difficile*
Guillain-Barré syndrome	*Campylobacter*
Hemolytic uremic syndrome	STEC, *Shigella dysenteriae* 1
Glomerulonephritis, myocarditis, pericarditis	*Shigella, Campylobacter, Yersinia*
Immunoglobulin A (IgA) nephropathy	*Campylobacter*
Erythema nodosum	*Yersinia, Campylobacter, Salmonella*
Hemolytic anemia	*Campylobacter, Yersinia*
Intestinal perforation	*Salmonella, Shigella, Campylobacter, Yersinia, Entamoeba histolytica*
Osteomyelitis, meningitis, aortitis	*Salmonella, Yersinia, Listeria*

STEC, Shiga toxin–producing *Escherichia coli.*

From Centers for Disease Control and Prevention: Managing acute gastroenteritis among children, *MMWR Recomm Rep* 53:1–33, 2004.

5. Vertical transmission of *Shigella* , NTS, and *Campylobacter* can produce perinatal infection resulting in a spectrum of illness from isolated diarrhea or hematochezia to fulminant neonatal sepsis. One species of *Campylobacter, C. fetus,* is particularly virulent in pregnant women and can result in chorioamnionitis, abortion, and neonatal sepsis and meningitis.

Crampy abdominal pain and nonbloody diarrhea are the first symptoms of STEC infection, sometimes with vomiting. Within several days, diarrhea becomes bloody and abdominal pain worsens. Bloody diarrhea lasts between 1 and 22 days (median 4 days). In contrast to dysentery, the stools associated with STEC hemorrhagic colitis are large volume and rarely accompanied by high fever. ETEC produce a secretory watery diarrhea that affects infants and young children in developing countries and is the major causative agents of travelers' diarrhea, accounting for about half of all episodes in some studies. EPEC remains a leading cause of persistent diarrhea associated with malnutrition among infants from developing countries. EIEC, which are genetically, biochemically, and clinically nearly identical to *Shigella* , causes rare foodborne outbreaks in industrialized countries. EAEC has been associated with persistent diarrhea in immunocompromised persons and sporadic diarrhea in infants in countries with varying levels of economic development; however, some other studies have not found an association with disease.

C. difficile toxin is associated with several clinical syndromes. The most common is mild to moderate watery diarrhea, low-grade fever, and mild abdominal pain. Occasionally, the illness will progress to full-blown *pseudomembranous colitis* characterized by diarrhea, abdominal cramps, and fever. The colonic mucosa contains 2-5 mm raised, yellowish plaques. Fatal cases are associated with toxic megacolon, systemic toxicity, and multisystem organ failure, possibly related to systemic absorption of toxin. A vomiting illness is associated with *S. aureus* and *B. cereus* emetic toxin, while diarrhea is the major manifestation of *C. perfringens* and *B. cereus* enterotoxins.

Protozoal Diarrhea. Illnesses due to intestinal protozoa tend to be more prolonged, sometimes for 2 wk or more, but usually self-limited in the otherwise healthy host (see Table 366.3). In general, the duration and severity of *Cryptosporidium* diarrhea is strongly influenced by the immune and nutritional status of the host. A protozoal etiology should be suspected when there is a prolonged diarrheal illness characterized by episodes of sometimes-explosive diarrhea with nausea, abdominal cramps, and abdominal bloating. The stools are usually watery but can be greasy and foul smelling due to concomitant malabsorption of fats, which is more likely to occur if the parasite load is high. Occasionally diarrhea may alternate with constipation.

In addition to diarrhea, *E. histolytica* causes a range of other syndromes. Amebic dysentery is characterized by bloody or mucoid diarrhea, which may be profuse and lead to dehydration or electrolyte imbalances. Hepatic amebiasis is limited to abscess formation in the liver, which may occur with or without intestinal disease.

Intestinal and Extraintestinal Complications

The major complications from diarrhea from any cause are dehydration, electrolyte, or acid-base derangements, which can be life-threatening (see Table 366.10). Avoiding delays in diagnosis and treatment, and appropriate supportive care using either oral, enteral, or intravenous hydration can prevent or treat most of these conditions. Children who experience frequent episodes of acute diarrhea or prolonged or persistent episodes (seen especially in low resource settings) are at risk for poor growth and nutrition and complications such as secondary infections and micronutrient deficiencies (iron, zinc, vitamin A). Ensuring continued nutritional support during diarrheal episodes is important because prolonged limitation of the diet may extend diarrheal symptoms. Reestablishing a normal diet generally restores villous anatomy and function with resolution of loose stools.

Viral AGE illnesses are usually self-limited and resolve after several days. Rarely, **intussusception** is triggered by lymphoid hyperplasia associated with viral AGE. Complications of bacterial AGE may be the result of local or systemic spread of the organism; in malnourished children and HIV-infected populations, associated **bacteremia** is well-recognized. Toxic megacolon, intestinal perforation, and rectal prolapse can occur, particularly in association with *Shigella* in developing countries and *C. difficile* . The most dreaded complication of pediatric diarrhea in the United States is **HUS** , the leading cause of acquired renal failure in children, developing in 5–10% of patients infected with STEC. It is usually diagnosed 2-14 days after the onset of diarrhea. HUS is unlikely to occur once diarrhea has remained resolved for 2 or 3 days with no evidence of hemolysis. Risk factors include age 6 mo to 4 yr, bloody diarrhea, fever, elevated leukocyte count, and treatment with antibiotics and antimotility agents. Two-thirds of patients no longer excrete the organism at the time they develop HUS (Chapter 538.5).

Pseudoappendicitis secondary to mesenteric adenitis is a notable complication of *Yersinia* , and sometimes *Campylobacter* . Older children and adolescents are most often affected. It typically presents with fever and abdominal pain with tenderness localized to the right lower quadrant, with or without diarrhea, and can be confused with appendicitis. CT scan or sonogram may be helpful to distinguish true appendicitis.

Immune-mediated complications that are thought to result from immunologic cross reactivity between bacterial antigens and host tissues are more often seen in adults than children. These include reactive arthritis following infection with the classical bacterial enteropathogens and Guillain-Barré syndrome following *Campylobacter* infection.

Protozoan illnesses, when persistent, can lead to poor weight gain in the young and immunocompromised individuals, weight loss, malnutrition, or vitamin deficiencies. Infection with *Entamoeba* can cause severe ulcerating colitis, colonic dilation, and perforation. The parasite may spread systemically, most commonly causing liver abscesses. In high-risk settings, it is critical to exclude *Entamoeba* infection and tuberculosis before initiating corticosteroids for presumed ulcerative colitis.

Differential Diagnosis

The physician should also consider noninfectious diseases that can present with bright red blood per rectum or hematochezia (Table 366.11). In an infant or young child without systemic symptoms, these may include anal fissures, intermittent intussusception, juvenile polyps, and Meckel diverticulum. Necrotizing enterocolitis can cause lower gastrointestinal bleeding in infants, especially premature neonates. Inflammatory bowel disease should be considered in older children. Examples of noninfectious causes of nonbloody diarrhea include congenital secretory diarrheas, endocrine disorders (hyperthyroidism), neoplasms, food intolerance, and medications (particularly antibiotics). Noninfectious causes of chronic or relapsing diarrhea include cystic fibrosis, celiac disease, milk protein intolerance, and congenital or acquired disaccharidase deficiency. Significant abdominal pain should raise suspicion of other infectious processes in the abdomen such as appendicitis and pelvic inflammatory disease. Prominent vomiting with or without abdominal pain can be a manifestation of pyloric stenosis, intestinal obstruction, pancreatitis, appendicitis, and cholecystitis.

Table 366.11

Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis

Specific Infectious Processes
• Bacillary dysentery *(Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Shigella boydii; invasive Escherichia coli)* • Campylobacteriosis *(Campylobacter jejuni)* • Amebic dysentery *(Entamoeba histolytica)* • Ciliary dysentery *(Balantidium coli)* • Bilharzial dysentery *(Schistosoma japonicum, Schistosoma mansoni)* • Other parasitic infections *(Trichinella spiralis)* • Vibriosis *(Vibrio parahaemolyticus)* • Salmonellosis *(Salmonella typhimurium)*

• Typhoid fever *(Salmonella typhi)* • Enteric fever *(Salmonella choleraesuis, Salmonella paratyphi)* • Yersiniosis *(Yersinia enterocolitica)* • Spirillar dysentery *(Spirillum spp.)*
Proctitis
• Gonococcal *(Neisseria gonorrhoeae)* • Herpetic (herpes simplex virus) • Chlamydial *(Chlamydia trachomatis)* • Syphilitic *(Treponema pallidum)*
Other Syndromes
• Necrotizing enterocolitis of the newborn • Enteritis necroticans • Pseudomembranous enterocolitis *(Clostridium difficile)* • Typhlitis
Chronic Inflammatory Processes
• Enteropathogenic and enteroaggregative *E. coli* • Gastrointestinal tuberculosis • Gastrointestinal mycosis • Parasitic enteritis
Syndromes Without Known Infectious Cause
• Idiopathic ulcerative colitis • Celiac disease • Crohn disease • Radiation enteritis • Ischemic colitis • Immune deficiency including HIV infection • Allergic enteritis

From Mandell GL, Bennett JE, Dolin R, editors: *Principles and practices of infectious diseases* , ed 7, Philadelphia, 2010, Churchill Livingstone.

Clinical Evaluation of Diarrhea

In the initial evaluation of all patients with AGE, the physician should focus on the patient's hydration status and electrolyte balance, as well as evidence of sepsis or invasive bacterial infection, which could complicate bacterial AGE (Fig. 366.6). Once the patient is stabilized, the history and physical examination can focus on detecting risk factors and exposures, as well as the clinical features that may suggest specific etiologic agents (see Tables 366.5 and 366.6).

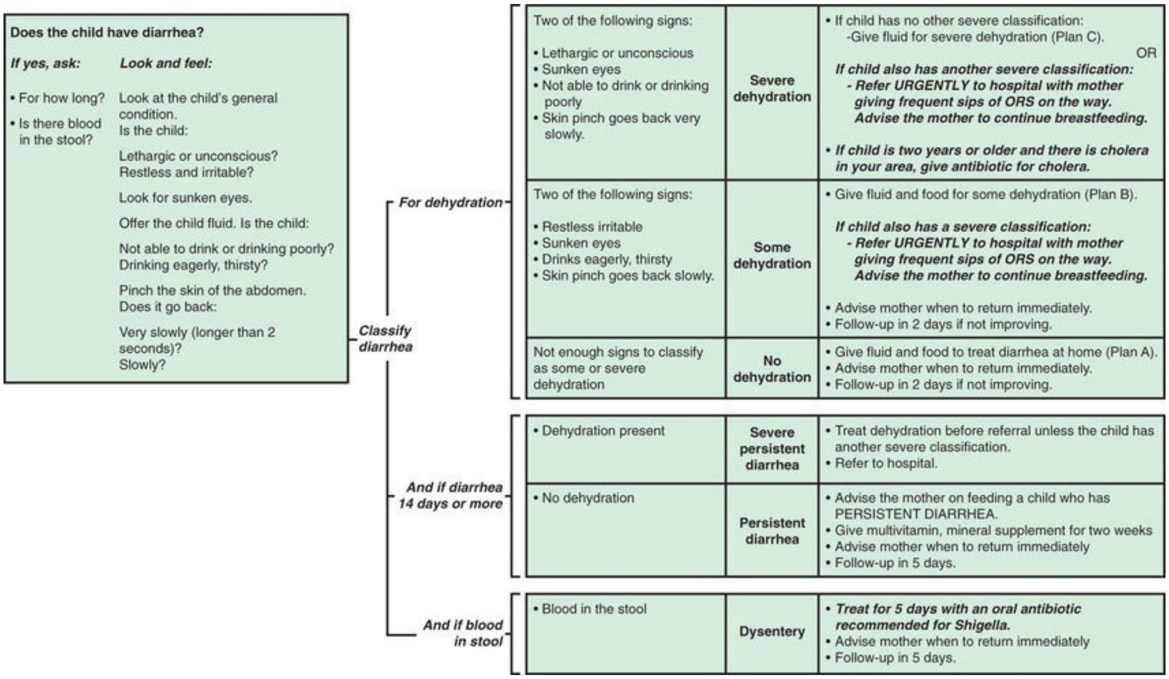
Does the child have diarrhea?
If yes, ask:
Look and feel:
• For how long?
• Is there blood in the stool?
Look at the child's general condition.
Is the child:
Lethargic or unconscious?
Restless and irritable?
Look for sunken eyes.
Offer the child fluid. Is the child:
Not able to drink or drinking poorly?
Drinking eagerly, thirsty?
Pinch the skin of the abdomen.
Does it go back:
Very slowly (longer than 2 seconds)?
Slowly?
Classify diarrhea
For dehydration
Two of the following signs:
• Lethargic or unconscious
• Sunken eyes
• Not able to drink or drinking poorly
• Skin pinch goes back very slowly.
Severe dehydration
• If child has no other severe classification:
-Give fluid for severe dehydration (Plan C).
OR
If child also has another severe classification:
- Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way.
Advise the mother to continue breastfeeding.
• If child is two years or older and there is cholera in your area, give antibiotic for cholera.
Two of the following signs:
• Restless irritable
• Sunken eyes
• Drinks eagerly, thirsty
• Skin pinch goes back slowly.
Some dehydration
• Give fluid and food for some dehydration (Plan B).
If child also has a severe classification:
- Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way.
Advise the mother to continue breastfeeding.
• Advise mother when to return immediately.
• Follow-up in 2 days if not improving.
Not enough signs to classify as some or severe dehydration
No dehydration
• Give fluid and food to treat diarrhea at home (Plan A).
• Advise mother when to return immediately.
• Follow-up in 2 days if not improving.
And if diarrhea 14 days or more
• Dehydration present
Severe persistent diarrhea
• Treat dehydration before referral unless the child has another severe classification.
• Refer to hospital.
• No dehydration
Persistent diarrhea
• Advise the mother on feeding a child who has PERSISTENT DIARRHEA.
• Give multivitamin, mineral supplement for two weeks
• Advise mother when to return immediately
• Follow-up in 5 days.
And if blood in stool
• Blood in the stool
Dysentery
• Treat for 5 days with an oral antibiotic recommended for Shigella.
• Advise mother when to return immediately
• Follow-up in 5 days.

FIG. 366.6 Integrated Management of Childhood Illnesses protocol for the recognition and management of diarrhea in developing countries. *ORS,* oral rehydration solution.

Important elements of the medical history include the duration of diarrhea and a description of stools (frequency, amount, presence of blood or mucus), fever (duration, magnitude), vomiting (onset, amount and frequency), and the amount and type of solid and liquid oral intake. Clinical signs of dehydration should be evaluated (Table 366.12): urine output (number of wet diapers per day and time since the last urination), whether eyes appear sunken, whether the child is active, whether the child drinks vigorously, and the date and value of the most recent weight measurement. A documented weight loss can be used to calculate the fluid deficit. The past medical history should identify comorbidities that might increase the risk or severity of AGE.

Table 366.12

Clinical Signs Associated With Dehydration

SYMPTOM	MINIMAL OR NO DEHYDRATION	SOME DEHYDRATION	SEVERE DEHYDRATION
Mental status	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most

			severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing	Normal	Normal; fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skinfold	Instant recoil	Recoil in <2 sec	Recoil in >2 sec
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output	Normal to decreased	Decreased	Minimal

Modified from Duggan C, Santosham M, Glass RI: The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy, *MMWR Recomm Rep* 41(RR-16):1–20, 1992; and World Health Organization: *The treatment of diarrhoea: a manual for physicians and other senior health workers,* Geneva, 1995, World Health Organization; and Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, *MMWR* 53(RR-4):1–33, 2004.

Certain physical signs are best assessed before approaching the child directly, so he/she remains calm, including general appearance (activity, response to stimulation) and respiratory patterns. Skin turgor is assessed by pinching a small skin fold on the lateral abdominal wall at the level of the umbilicus. If the fold does not promptly return to normal after release, the recoil time is quantified as delayed slightly or ≥2 sec. Excess subcutaneous tissue and hypernatremia may produce a false negative test and malnutrition can prolong the recoil time. To measure capillary refill time, the palmar surface of the child's distal fingertip is pressed until blanching occurs, with the child's arm at heart level. The time elapsed until restoration of normal color after release usually exceeds 2 sec in the presence of dehydration. Mucous membrane moisture level, presence of tears, and extremity temperature should be assessed.

Laboratory Diagnosis

Most cases of AGE do not require diagnostic laboratory testing. Stool specimens could be examined for mucus, blood, neutrophils or fecal lactoferrin, a neutrophil product. The finding of more than 5 leukocytes per high-power field or a positive lactoferrin assay in an infant not breastfeeding suggests an infection with a classical bacterial enteropathogen; patients infected with STEC and *E. histolytica* usually have negative tests.

Laboratory diagnosis of viral AGE may be helpful when an outbreak is suspected, cases are linked to a suspected outbreak, or when cohorting of patients is considered to limit the spread of infection. The preferred method of testing norovirus is real-time reverse transcription quantitative polymerase chain reaction (RT-qPCR), available at most public health and virology laboratories. Commercial tests are available for the diagnosis of rotavirus and enteric adenoviruses but not for astrovirus in the United States (see Table 366.1).

Stool cultures for detection of bacterial agents are costly, so requests should be restricted to patients with clinical features predictive of bacterial AGE, have moderate or severe disease, are immunocompromised, in outbreaks with suspected hemolytic-uremic syndrome, or have a highly suggestive epidemiologic history. To optimize recovery of pathogens, stool specimens for culture need to be transported and plated quickly; if the latter is not quickly available, specimens might need to be transported in special transport media. If the child has not passed a stool and antibiotics will be administered, a rectal swab should be collected promptly. After dipping the cotton tip into the medium that will be used for transport, it is gently inserted into the child's rectum and rotated 360 degrees. A properly collected rectal swab is stained or covered with fecal material. Standard stool culture methods performed in clinical microbiology laboratories recover *Shigella* and *Salmonella* species. If *Campylobacter* , *Yersinia* , or *Vibrio* species are suspected, the laboratory should be notified unless media are routinely used for their detection. All bloody stools should also be inoculated into media specific for detection of *E. coli* 0157:H7 or directly tested for the presence of Shiga-like toxin (or both). Except for *C. difficile* , nosocomial acquisition of a bacterial enteric pathogen is very unlikely. Hence stool microbiologic assays are generally not indicated for patients in whom diarrhea develops more than 3 days after admission unless the patient is immunocompromised or to investigate a hospital outbreak (see Table 366.2). Stool can also be tested for bacterial pathogens by nucleic acid amplification test (NAAT); if the NAAT is positive, the sample should automatically be cultured to determine antimicrobial sensitivities.

For children older than 2 yr who have recently received antibiotics or have other risk factors, evaluation for *C. difficile* infection may be appropriate. The cytotoxin assay detects toxin B, but testing for toxin A is also available in some laboratories; however, this test is laborious. Several tests are commercially available to detect toxin-producing *C. difficile* in stool, including enzyme immunoassays for toxins A and B, cell culture cytotoxicity assay, and PCR. The sensitivities of cell culture and PCR are superior to that of immunoassay. Testing for *C . difficile* toxin in children younger than 2 yr is discouraged because the organism and its toxins are commonly detected in asymptomatic infants (see Table 366.2).

Evaluation for intestinal protozoa that cause diarrhea is usually indicated in patients who recently traveled to an endemic area, have contact with untreated water, and manifest suggestive symptoms. The most commonly used method is direct microscopy of stool for cysts and trophozoites. However, this approach is time consuming and lacks sensitivity, in part because shedding can be intermittent. Analyzing 3 specimens from separate days is optimal, and fecal concentration techniques provide some benefit. The sensitivity and specificity of microscopy are substantially improved using immunofluorescence antibodies that are commercially available for visualization of *Cryptosporidium* and *Giardia* cysts. In addition, enzyme immunoassays are available for *Cryptosporidium, Giardia*, and *Entamoeba* that are more sensitive and specific than direct microscopy and provide a useful diagnostic tool (not all commercial kits distinguish between pathogenic *E. histolytica* and nonpathogenic *E. dispar*). Molecular methods (NAAT) are also available.

Several culture-independent *rapid multiplex molecular panels* for detection of viral, bacterial, and protozoal gastrointestinal pathogens directly from stool samples are FDA approved, including xTag GPP (14 pathogens), Verigene EP (9 pathogens), and the FirmArray GI (22 pathogens). These methods offer several advantages over conventional diagnostics, including reduced sample volume requirements, broad coverage without the need to select specific tests, enhanced ability to detect coinfections, increased sensitivity, and rapid turnaround. However, their use is controversial because the available tests do not provide strain specificity or antimicrobial susceptibility testing to assist with outbreak detection and treatment decisions.

Most episodes of diarrheal dehydration are isonatremic and do not warrant serum electrolyte measurements. Electrolyte measurements are most useful in children with severe dehydration, when intravenous fluids are administered, when there is a history of frequent watery stools, yet the skin pinch feels doughy without delayed recoil, which suggests hypernatremia, or when inappropriate rehydration fluids have been administered at home. A suspicion for HUS prompts a complete blood count with review of the peripheral smear, platelets, serum electrolytes, and renal function tests. Patients with shigellosis can demonstrate bandemia or even a leukemoid reaction. Blood culture should be obtained if there is concern for systemic bacterial infection. This includes infants and children with fever and/or blood in the stool who are younger than 3 mo, are immunocompromised, or have hemolytic anemia or other risk factors. If diarrhea persists with no cause identified, endoscopic evaluation may be indicated. Biopsy specimens help in diagnosing inflammatory bowel disease or identifying infecting agents that may mimic it. A sweat test is warranted if cystic fibrosis is suspected.

Treatment

The broad principles of management of AGE in children include rehydration and maintenance ORS plus replacement of continued losses in diarrheal stools and vomitus after rehydration, continued breastfeeding, and refeeding with an age-appropriate, unrestricted diet as soon as dehydration is corrected. Zinc supplementation is recommended for children in developing countries.

Hydration

Children, especially infants, are more susceptible than adults to dehydration because of the greater basal fluid and electrolyte requirements per kilogram and because they are dependent on others to meet these demands (Table 366.13). *Dehydration must be evaluated rapidly and corrected in 4-6 hr according to the degree of dehydration and estimated daily requirements*. When there is emesis, small volumes of ORS can be given initially by a dropper, teaspoon, or syringe, beginning with as little as 5 mL at a time. The volume is increased as tolerated. The low-osmolality World Health Organization (WHO) ORS containing 75 mEq of sodium, 64 mEq of chloride, 20 mEq of potassium, and 75 mmol of glucose per liter, with total osmolarity of 245 mOsm/L, is now the global standard of care and more effective than home fluids. Soda beverages, fruit juices, tea, and other home fluids are not suitable for rehydration or maintenance therapy because they have inappropriately high glucose concentration and osmolalities and low sodium concentrations. Tables 366.12 and 366.13 outline a clinical evaluation plan and management strategy for children with moderate to severe diarrhea. Replacement for emesis or stool losses is noted in Table 366.13 . Oral rehydration can also be given by a nasogastric tube if needed; this is not the usual route.

Table 366.13

Fluid and Nutritional Management of Diarrhea

DEGREE OF DEHYDRATION[*]	REHYDRATION THERAPY	REPLACEMENT OF LOSSES DURING MAINTENANCE [†]
Some dehydration	Infants [‡] and children: ORS, 50-100 mL/kg over 3-4 hr. Continue breast feeding. After 4 hr, give food every 3-4 hr for children who normally receive solid foods.	Infants and children: <10 kg body weight: 50-100 mL ORS for each diarrheal stool or vomiting episode, up to ~500 mL/day >10 kg body weight: 100-200 mL ORS for each diarrheal stool or vomiting episode; up to ~1 L/day Replace losses as above as long as diarrhea or vomiting continues
Severe dehydration	Malnourished infants may benefit from smaller-volume, frequent boluses of 10 mL/kg body weight due to reduced capacity to increase cardiac output with larger volume resuscitation. Infants (<12 months) and children (12 mo to 5 yr) without malnutrition: Give 20-30 mL/kg boluses of intravenous isotonic crystalloid solution (e.g., normal saline solution) over 30-60 min. Repeat boluses as necessary to restore adequate perfusion. Then give 70 mL/kg over 2.5-5 hr. (Note the slower infusion times are for infants.) Reassess the infant or child frequently and adjust infusion rate if needed. Switch to ORS, breast milk, and feed as described for some dehydration, when the child can drink, perfusion is adequate, and mental status is normal. Adjust electrolytes and administer dextrose based on chemistry values.	Infants and children: <10 kg body weight: 50-100 mL ORS for each diarrheal stool or vomiting episode, up to ~500 mL/day >10 kg body weight: 100-200 mL ORS for each diarrheal stool or vomiting episode; up to ~1 L/day Adolescents and adults: Ad libitum, up to ~2 L/day Replace losses as above as long as

		diarrhea or vomiting continue. If unable to drink, administer either through a nasogastric tube or give 5% dextrose 0.25 normal saline solution with 20 mEq/L potassium chloride intravenously.

[*] A variety of scales are available to grade the severity of dehydration in young children, but no single, standard, validated method exists. Note that signs of dehydration may be masked when a child is hypernatremic. The World Health Organization defines some dehydration as the presence of two or more of the following signs: restlessness/irritability, sunken eyes, drinks eagerly, thirsty, and skin pinch goes back slowly. Severe dehydration is defined as two or more of the following signs: lethargy/unconsciousness, sunken eyes, unable to drink/drinks poorly, and skin pinch goes back very slowly (>2 sec).

[†] After rehydration is complete, maintenance fluids should be resumed along with an age-appropriate normal diet offered every 3-4 hr. Children previously receiving a lactose-containing formula can tolerate the same product in most instances. Diluted formula does not appear to confer any benefit.

[‡] Breastfed infants should continue nursing throughout the illness.

Low-osmolarity ORS can be given to all age groups, with any cause of diarrhea. It is safe in the presence of hypernatremia, as well as hyponatremia (except when edema is present). Some commercially available formulations that can be used as ORS include Pedialyte Liters (Abbott Nutrition), CeraLyte (Cero Products), and Enfalac Lytren (Mead Johnson). Popular beverages that should not be used for rehydration include apple juice, Gatorade, and commercial soft drinks.

ORS, oral rehydration solution.

Modified from Centers for Disease Control and Prevention: Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 52(RR-16):1–16, 2003; and World Health Organization. Pocket book of hospital care for children: Guidelines for the management of common childhood illnesses, ed 2 (http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/).

A small minority of children, including those with severe dehydration or unable to tolerate oral fluids, require initial intravenous rehydration, but oral rehydration is the preferred mode of rehydration and replacement of ongoing losses. Signs of severe dehydration that might necessitate intravenous resuscitation are shown in Table 366.13 . Limitations to ORS include shock, decreased level of consciousness, an ileus, intussusception, carbohydrate intolerance (rare), severe emesis, and high stool output (>10 mL/kg/hr).

Enteral Feeding and Diet Selection

Continued breastfeeding and refeeding with an age-appropriate, unrestricted diet as soon as dehydration is improving or resolved aids in recovery from the episode. Foods with complex carbohydrates (rice, wheat, potatoes, bread, and cereals), fresh fruits, lean meats, yogurt, and vegetables should be reintroduced while ORS is given to replace ongoing losses from emesis or stools and for maintenance. Fatty foods or foods high in simple sugars (juices, carbonated sodas) should be avoided. The usual energy density of any diet used for the therapy of diarrhea should be around 1 kcal/g, aiming to provide an energy intake of a minimum of 100 kcal/kg/day and a protein intake of 2-3 g/kg/day. In selected circumstances when adequate intake of energy-dense food is problematic, the addition of amylase to the diet through germination techniques can also be helpful.

If the normal diet includes infant formula, it should not be diluted, or changed to a lactose-free preparation unless lactose malabsorption is evident. With the exception of acute lactose intolerance in a small subgroup, most children with diarrhea are able to tolerate milk and lactose-containing diets. *Withdrawal of milk and replacement with specialized lactose-free formulations are unnecessary.* Although children with persistent diarrhea are not lactose intolerant, administration of a lactose load exceeding 5 g/kg/day may be associated with higher purging rates and treatment failure. Alternative strategies for reducing the lactose load while feeding malnourished children who have prolonged diarrhea include addition of milk to cereals and replacement of milk with fermented milk products such as yogurt.

Rarely, when dietary intolerance precludes the administration of cow's milk–based formulations or whole milk, it may be necessary to administer specialized milk-free diets such as a comminuted or blenderized chicken-based diet or an elemental formulation. Although effective in some settings, the latter are unaffordable in most developing countries. In addition to rice-lentil formulations, the addition of green banana or pectin to the diet has also been shown to be effective in the treatment of persistent diarrhea. Fig. 366.7 gives an algorithm for managing children with prolonged diarrhea in developing countries.

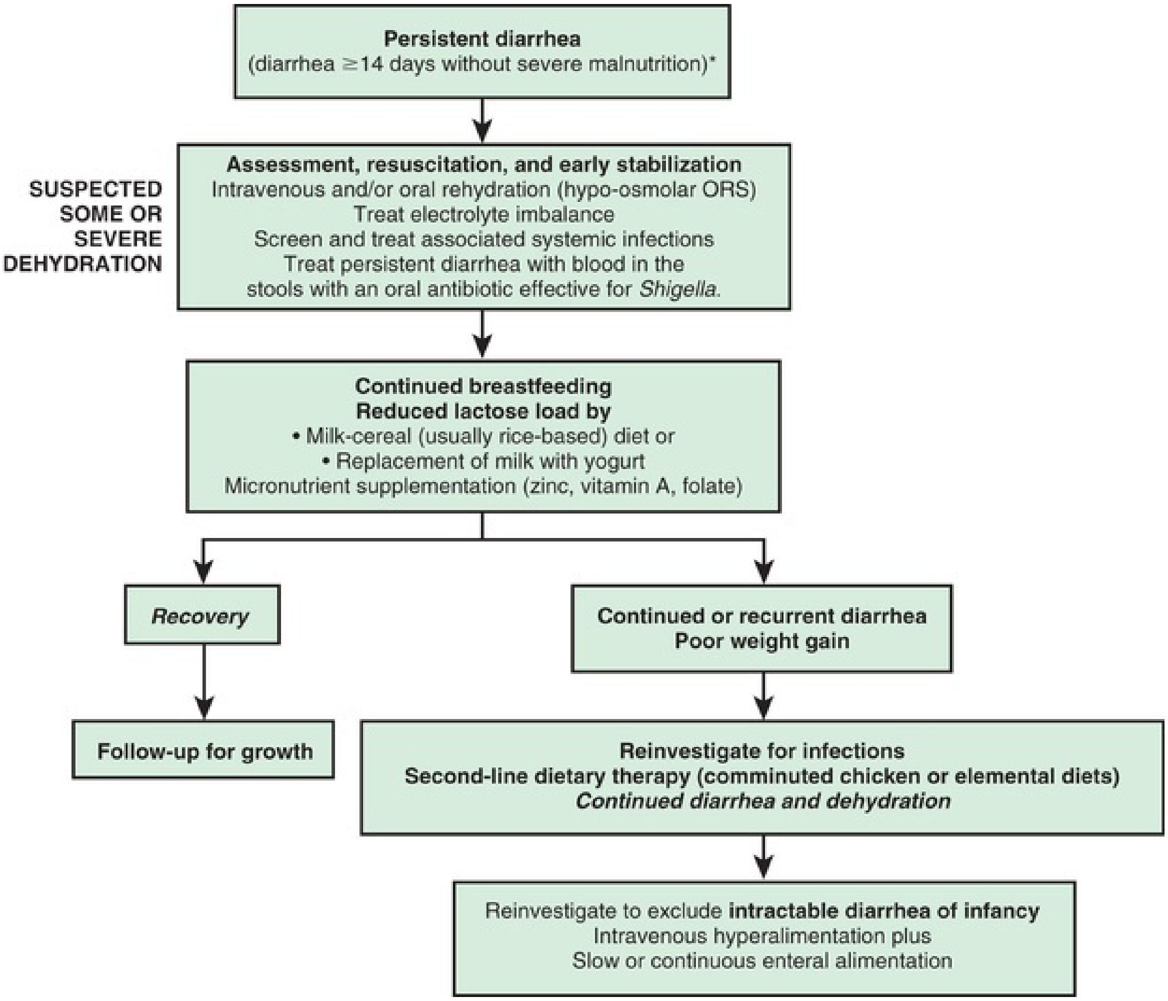
Persistent diarrhea
(diarrhea ≥14 days without severe malnutrition)*
SUSPECTED SOME OR SEVERE DEHYDRATION
Assessment, resuscitation, and early stabilization
Intravenous and/or oral rehydration (hypo-osmolar ORS)
Treat electrolyte imbalance
Screen and treat associated systemic infections
Treat persistent diarrhea with blood in the stools with an oral antibiotic effective for Shigella.
Continued breastfeeding
Reduced lactose load by
• Milk-cereal (usually rice-based) diet or
• Replacement of milk with yogurt
Micronutrient supplementation (zinc, vitamin A, folate)
Recovery
Follow-up for growth
Continued or recurrent diarrhea
Poor weight gain
Reinvestigate for infections
Second-line dietary therapy (comminuted chicken or elemental diets)
Continued diarrhea and dehydration
Reinvestigate to exclude intractable diarrhea of infancy
Intravenous hyperalimentation plus
Slow or continuous enteral alimentation

FIG. 366.7 Management of persistent diarrhea. *IV,* intravenous; *NG,* nasogastric tube; *ORS,* oral rehydration solution. *Severely malnourished children require urgent referral for hospitalization and specific treatment.

Among children in low- and middle-income countries, where the dual burden of diarrhea and malnutrition is greatest and where access to proprietary formulas and specialized ingredients is limited, the use of locally available age-appropriate foods should be promoted for the majority of acute diarrhea cases. Even among those children for whom lactose avoidance may be necessary, nutritionally complete diets composed of locally available ingredients can be used at least as effectively as commercial preparations or specialized ingredients. These same conclusions may also apply to the dietary management of children with persistent diarrhea, but the evidence remains limited.

Zinc Supplementation

Zinc supplementation in children with diarrhea in developing countries leads to reduced duration and severity of diarrhea and could potentially prevent a large proportion of cases from recurring. Zinc administration for diarrhea management can significantly reduce all-cause mortality by 46% and hospital admission by 23%. In addition to improving diarrhea recovery rates, administration of zinc in community settings leads to increased use of ORS and reduction in the inappropriate use of antimicrobials. All children older than 6 mo of age with acute diarrhea in at-risk areas should receive oral zinc (20 mg/day) in some form for 10-14 days during and continued after diarrhea. The role of zinc in well nourished, zinc replete populations in developed countries is less certain.

Additional Therapies

The use of probiotic nonpathogenic bacteria for prevention and therapy of diarrhea has been successful in some settings, although the evidence does not support a recommendation for their use in all settings. A variety of organisms *(Lactobacillus, Bifidobacterium)* have a good safety record; therapy has not been standardized and the most effective (and safe) organism has not been identified. *Saccharomyces boulardii* is effective in antibiotic-associated and in *C. difficile* diarrhea, and there is some evidence that it might prevent diarrhea in daycare centers. Two large randomized placebo-controlled trials evaluating the efficacy of two *Lactobacillus* -based probiotic formulations failed to reduce a clinical severity score in Canadian infants and preschool children with acute gastroenteritis. *Lactobacillus rhamnosus GG* or a combination probiotic product containing *L. rhamnosus* R0011 and *L. helveticus* R0052 is has shown variable efficacy; reduction is more evident in cases of childhood rotavirus diarrhea.

Ondansetron (oral mucosal absorption preparation) reduces the incidence of emesis, thus permitting more effective oral rehydration and is well-established in emergency management of AGE in high-resource settings, reducing intravenous fluid requirements and hospitalization. Because persistent vomiting can limit ORS, a single sublingual dose of an oral dissolvable tablet of ondansetron (4 mg for children 4-11 yr old and 8 mg for children older than 11 yr [generally 0.2 mg/kg]) may be given. However, most children do not require specific antiemetic therapy; careful ORS is usually sufficient. Antimotility agents (loperamide) are contraindicated in children with dysentery and probably have no role in the management of acute watery diarrhea in otherwise healthy children. Similarly, antiemetic agents, such as the phenothiazines, are of little value and are associated with potentially serious side effects (lethargy, dystonia, malignant hyperpyrexia).

Antibiotic Therapy

Judicious antibiotic therapy for suspected or proven bacterial infections can reduce the duration and severity of illness and prevent complications (Table 366.14). Several factors justify limited use. First, most episodes of AGE are self-limited among otherwise healthy children. Second, the increasing prevalence of antibiotic resistance has prompted restricted use of these drugs. Third, antibiotics may worsen outcome, because some studies have shown that antibiotic therapy of STEC infection increases the risk of HUS and prolongs excretion of NTS without improving clinical outcome. Therefore antibiotics are used primarily to treat severe infections, prevent complications in high-risk hosts, or to limit the spread of infection. Microbiologic (culture) confirmation of the etiology and susceptibility testing should be sought prior to treatment if possible.

Table 366.14

Antibiotic Therapy for Infectious Diarrhea

ORGANISM	INDICATION FOR THERAPY	DOSAGE AND DURATION OF TREATMENT
Shigella spp.	In high-income countries, judicious treatment is recommended to curtail growing antibiotic resistance because most shigellosis is self-limited. Treatment should be reserved for moderate to severe disease (require hospitalization, have systemic disease or complications), immunocompromised, or to prevent or mitigate outbreaks in certain settings (e.g., childcare or food handling). Also consider treating patients with significant discomfort, intestinal comorbidities, institutional settings, or household exposure to high-risk individuals. WHO recommends empiric antibiotics for all children in developing countries with dysentery assuming that most cases are caused by *Shigella*.	*First line:* • Ciprofloxacin* 15 mg/kg/day PO bid × 3 days; OR • Ceftriaxone 50-100 mg/kg/day IV or IM, qd × 3 days for severe illness requiring parenteral therapy; OR • Azithromycin* 12 mg/kg once on 1st day, then 6 mg/kg once daily on days 2 through 4 (total course: 4 days) *Second line:* • Cefixime 8 mg/kg once daily for 3 days; OR • Trimethoprim-sulfamethoxazole 4 mg/kg/day of TMP and 20 mg/kg/day SMX twice a day for 5 days (if susceptibility known or likely based on local data)
ETEC	Watery diarrhea in a traveler returning from an endemic area that interferes with planned activities or is persistent.	*First line:* • Azithromycin* 12 mg/kg once on first day, then 6 mg/kg once

		daily on days 2 and 3 (total course: 3 days) *Second line:* • Ciprofloxacin* 15 mg/kg/day PO bid × 3 days
STEC	Avoid antimicrobials and anti-motility drugs	
Salmonella , non-typhoidal	Antibiotics for uncomplicated gastroenteritis in normal host are ineffective and may prolong excretion and are not recommended Treatment should be reserved for infection in infants younger than 3 mo, and patients with immunocompromise, malignancy, chronic GI disease, severe colitis hemolytic anemia, or HIV infection. Most strains are resistant to multiple antibiotics	See treatment of *Shigella.* Patients without bacteremia can be treated orally for 5-7 days. Patients with bacteremia (proven or until blood culture results are available in a high-risk host) should be treated parenterally for 10-14 days. Focal or disseminated invasive infections (e.g., osteomyelitis, meningitis) and bacteremic patients with HIV/AIDS should be treated parenterally for 4-6 wk.
Yersinia spp.	Antibiotics are not usually required for diarrhea, which is usually self-limited and clinical benefits of antibiotics are not established. Bacteremia and focal invasive infections should be treated. Deferoxamine therapy should be withheld for severe infections or associated bacteremia	For bacteremia or focal invasive infections, use third generation cephalosporins. Can also consider carbapenem, doxycycline (for children ≥8 yr) plus aminoglycoside, TMP-SMX, or fluoroquinolone at doses recommended for sepsis. Begin IV then switch to oral when clinically stable, for a total course of 2-6 wk.
Campylobacter spp.	Dysentery, moderate and severe gastroenteritis or at risk for severe disease (e.g., elderly, pregnant, or immunocompromised), and bacteremia or focal invasive infection should be treated. Treatment of gastroenteritis appears effective if given within 3 days of onset of illness.	*For gastroenteritis or dysentery:* • Erythromycin PO 40 mg/kg/day divided qid × 5 days; OR • Azithromycin PO 10 mg/kg/day × 3 days *For bacteremia or focal invasive infection:* • Consider parenteral macrolides or carbapenems pending susceptibility results. Fluoroquinolone resistance is >50% in some areas of the world.
Clostridium difficile	Colitis • Discontinue inciting antibiotics if possible; • Infectious disease consult suggested if disease is persistent or recurrent.	*First line (mild-moderate colitis):* • Metronidazole PO 30 mg/kg/day divided tid or qid × 10 days; max 500 mg/dose; OR • Vancomycin PO 40 mg/kg/day divided qid × 10 days, max 125 mg/dose *Second line (severe colitis):* • Vancomycin PO 40 mg/kg/day divided qid × 10 days, max 500

		mg/dose; OR • If ileus, give same dose PR as 500 mg/100 mL normal saline by retention enema with or without plus metronidazole IV 30 mg/kg/day divided tid × 10 days; max 500 mg/dose • Fidaxomicin not yet approved for children; see text
Entamoeba histolytica	Treat the following conditions: • Asymptomatic cyst excretors • Mild to moderate intestinal disease • Severe intestinal or extraintestinal disease (including liver abscess)	*Asymptomatic cyst excretors:* • Iodoquinol PO 30-40 mg/kg/day, max 2 g, divided tid × 20 days; OR • Paromomycin PO 25-35 mg/kg/d divided tid × 7 days; *Mild to moderate intestinal disease and severe intestinal or extra-intestinal disease:* • Metronidazole PO 30-40 mg/kg/day divided tid × 7-10 days; OR • Tinidazole PO 50 mg/kg, single dose, max 2 g (for children ≥ 3 yr old) × 3 days, OR 5 days for severe disease EITHER FOLLOWED BY (to prevent relapse) • Iodoquinol PO 30-40 mg/kg/day tid × 20 days; OR • Paromomycin PO 25-35 mg/kg/day tid × 7 days
Giardia intestinalis	Persistent symptoms	• Tinidazole PO 50 mg/kg, single dose, max 2 g (for children ≥ 3 yr old); OR • Nitazoxanide PO; OR – Age 1-3 yr: 100 mg bid × 3 days – Age 4-11 yr: 200 mg bid × 3 days – Age over 11 yr: 500 mg bid × 3 days • Metronidazole PO 30-40 mg/kg/day divided tid × 7 days (max 250 mg per dose)
Cryptosporidium spp.	Treat immunocompromised and HIV-infected hosts, although efficacy is equivocal Treatment may not be needed in normal hosts	*Immunocompetent children:* • Nitazoxanide, as for *Giardia* *Solid organ transplants:* • Nitazoxanide, as for *Giardia* , × ≥14 days; reduce immunosuppression if possible and consider paromomycin combined with azithromycin for severe symptoms or treatment failure

		HIV-infected children: • Combined antiretroviral therapy is the primary treatment • Nitazoxanide, as for *Giardia* , generally for 3-14 days while awaiting CD4 cell recovery; OR • Consider paromomycin alone or combined with azithromycin in severe disease or treatment failure
Cyclospora spp *Isospora belli* (now designated *Cystoisospora belli*).	All symptomatic children	TMP 5 mg/kg/day and SMX 25 mg/kg/day PO bid × 7-10 days (HIV-infected children may need longer courses)
Blastocystis hominis	The significance of *B. hominis* as a cause of disease is controversial, so treatment should be reserved for those with suggestive symptoms and no other pathogen that could be the cause.	• Metronidazole PO 30-40 mg/kg/day divided tid × 7-10 days; OR • Nitazoxanide, as for *Giardia* ; OR TMP-SMX as for *Cyclospora* ; OR Tinidazole, as for *Giardia*

[*] Azithromycin and fluoroquinolones should be avoided in patients taking the antimalarial artemether. These drugs can prolong the QT interval on the electrocardiogram and trigger arrhythmias.

EIEC, enteroinvasive *Escherichia coli* ; *EPEC,* enteropathogenic *E. coli* ; *ETEC,* enterotoxigenic *E. coli* ; *GI,* gastrointestinal; *IV,* intravenous; *IM* , intramuscular; *max,* maximum; *SMX,* sulfamethoxazole; *TMP,* trimethoprim; *WHO* , World Health Organization.

Treatment of *C. difficile* infection warrants special consideration. Removal of the offending antibiotic, if possible, is the first step. Antibiotic therapy directed against *C. difficile* should be instituted if the symptoms are severe or persistent. Testing for *C. difficile* is discouraged for children with diarrhea who are <2 yr unless there is strong evidence to implicate *C. difficile* as the etiologic agent. This recommendation is based on the high rates of asymptomatic infection with toxigenic and nontoxigenic strains and the rarity of characteristic clinical manifestations not attributed to other pathogens in this age group. Oral vancomycin and metronidazole for 7-14 days (first line agents) displayed equivalent efficacy in a prospective randomized trial; however, metronidazole is preferred because of lower cost and decreased potential for inducing vancomycin-resistant enterococci. Twenty percent of adults treated for *C. difficile* diarrhea have a relapse, but the frequency in children is not known. The first relapse should be treated with another course of antibiotics based on severity of illness. For recurrent disease, tapering and/or pulsed regimen of oral vancomycin over a 4- to 6-wk period has been proposed. In the absence of ongoing symptoms, a test of cure is not necessary. The role of probiotics in the prevention of *C. difficile* -associated diarrhea in children has not been established. Fecal transplant is being explored to treat persistent or recurrent *C. difficile* colitis. *Fidaxomicin* is an alternate agent approved for patients ≥18 yr of age; it is recommended for the initial episode (severe and nonsevere) and recurrences. The adult dose is 200 mg BID for 10 days by mouth. *Bezlotoxumab,* a monoclonal antibody against *C. difficile* toxins A and B, has been shown to reduce the recurrence rate.

Antibiotic therapy for parasitic infections is shown in Table 366.14 .

Prevention

Promotion of Exclusive Breastfeeding and Vitamin A

Exclusive breastfeeding (administration of no other fluids or foods for the first 6 mo of life) protects young infants from diarrheal disease through the promotion of passive immunity and through reduction in the intake of potentially contaminated food and water. In developing countries, exclusive breastfeeding for the first 6 mo of life is widely regarded as one of the most effective interventions to reduce the risk of premature childhood mortality and has the potential to prevent 12% of all deaths of children younger than 5 yr of age. Vitamin A supplementation reduces all-cause childhood mortality by 25% and diarrhea-specific mortality by 30%.

Rotavirus Immunization

Three live oral **rotavirus** vaccines are licensed: the 3-dose pentavalent G1, G2, G3, G4, P[8] human-bovine vaccine (RotaTeq), the 2-dose monovalent human G1P[8] vaccine (ROTARIX), and the 3-dose monovalent human-bovine 116E G6P[11] vaccine (Rotavax). The result has been substantial reductions in rotavirus-associated and all-cause hospitalizations for diarrheal disease in both vaccinated infants (direct protection) and unvaccinated individuals (indirect, or herd protection), as well as reductions in-office visits for less severe rotavirus diarrhea. Reductions in all-cause diarrhea deaths have been demonstrated in some countries.

Programmatic uptake has lagged in low-resource settings where most severe disease and death occurs; however, Gavi, the Vaccine Alliance, has supported introduction of rotavirus vaccine into more than 40 countries to date. Even though vaccine efficacy against severe rotavirus AGE is lower (50–64%) in low- compared with high-resource countries, the number of severe rotavirus AGE prevented per vaccinated child is higher because of the substantially greater baseline rate of severe rotavirus gastroenteritis in developing countries. Vaccine (live virus) associated rotavirus infection has been reported in children with severe combined immunodeficiency disease, but the vaccine has been shown to be safe in HIV-infected populations.

Two licensed, efficacious 2-dose oral inactivated **cholera** vaccines (Dukoral for children 2 yr and older and ShanChol for children 1 yr or older) are available in many countries but currently have no specific indication in endemic and epidemic settings where they could potentially reduce the burden of severe diarrhea and mortality in young children. For travelers, a single-dose live oral cholera vaccine (Vaxchora) was recently licensed for adults in the United States. In addition, 2 forms of typhoid fever vaccine are available: a polysaccharide vaccine delivered intramuscularly that can be administered to children older than 2 yr (Vivotif) and an oral, live attenuated vaccine that can be administered to children over 6 yr of age (Typhim Vi). Conjugate polysaccharide typhoid vaccines that could be used in children younger than 2 yr have recently become available. In 2018, the World Health Organization issued a recommendation for the use of this vaccine in infants and children 6 mo of age or older living in endemic areas, with catch-up vaccination campaigns, if possible, for children up to 15 yr old. The vaccine is not yet available in the United States or Europe.

Improved Water and Sanitary Facilities and Promotion of Personal and Domestic Hygiene

Much of the reduction in diarrhea prevalence in the developed world is the result of improvement in standards of hygiene, sanitation, and water supply. Strikingly, an estimated 88% of all diarrheal deaths worldwide can be attributed to unsafe water, inadequate sanitation, and poor hygiene. Handwashing with soap and safe excreta disposal can reduce the risk of diarrhea by 48% and 36%, respectively, and a 17% reduction is estimated as a result of improvements in water quality.

366.1

Traveler's Diarrhea

Karen L. Kotloff

Keywords

Diarrhea
traveler's diarrhea
gastroenteritis

Traveler's diarrhea is a common complication of visitors to developing countries and is caused by a variety of pathogens, in part depending on the season and the region visited. It is the most common (28%) travel-associated health problem in children. Traveler's diarrhea can manifest with watery diarrhea or as dysentery. Without treatment, 90% will have resolved within a week and 98% within a month of onset. Some individuals develop more severe or persistent diarrhea and become dehydrated or unwell and may experience complications such as bacteremia and intestinal perforation. Children younger than 2 yr are at higher risk for traveler's diarrhea, as well as more severe disease. According to the FoodNet, the pathogens identified most commonly in travelers in the United States were *Campylobacter* (42%), NTS (32%), and *Shigella* (13%). ETEC and intestinal protozoa (*G. intestinalis* and *E. histolytica*) are also important.

Treatment

For infants and children, rehydration, as discussed in Chapter 366, is appropriate, followed by a standard diet. Adolescents and adults should increase their intake of electrolyte-rich fluids. Kaolin-pectin, anticholinergic agents, *Lactobacillus,* and bismuth salicylate are not effective therapies. Loperamide, an antimotility and antisecretory agent, reduces the number of stools in older children with watery diarrhea and improves outcomes when used in combination with antibiotics in traveler's diarrhea. However, loperamide should not be used in febrile or toxic patients with dysentery, in those with bloody diarrhea, and in children younger than 6 yr.

The effectiveness of antibiotics depends on the pathogen and its susceptibility profile. In forming a treatment plan, the potential side effects should be weighed against the treatment need for a short-lasting and self-limiting disease such as traveler's diarrhea. Antibiotics are not recommended for mild diarrhea that is tolerable, is not distressing, and does not interfere with planned activities. When empiric therapy is required abroad, azithromycin is suggested for young children. Fluoroquinolones are recommended for older children and adults and as second line therapy for younger children. Short-duration (3 days) therapy is effective. Travelers should be reminded that diarrhea can be a symptom of other severe diseases, such as malaria. Therefore, if diarrhea persists or additional symptoms such as fever occur, travelers should seek medical advice. For up-to-date information on local pathogens and resistant patterns, see www.cdc.gov/travel .

If the patient has returned home with diarrhea, a microbiologic evaluation can be obtained before initiating antibiotic therapy. Prolonged diarrhea should prompt further investigation into possible parasitic infections or NTS. Prophylactic antibiotics for travelers are not recommended.

Prevention

In the pretravel visit, caregivers should be advised about diarrhea prevention, the signs, symptoms, and management of dehydration, and the use of ORS. ORS and age-appropriate antibiotics should be included in a routine health packet. Travelers should drink bottled or canned beverages or boiled water. They should avoid ice, salads, and fruit they did not peel themselves. Food should be eaten hot, if possible. Raw or poorly cooked seafood is a risk, as is eating in a restaurant rather than a private home. Swimming pools and other recreational water sites can also be contaminated.

Chemoprophylaxis is not routinely recommended for previously healthy children or adults. Nonetheless, travelers should bring azithromycin (younger than 16 yr of age) or ciprofloxacin (older than 16 yr of age) and begin antimicrobial therapy if diarrhea develops.

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CHAPTER 367

Chronic Diarrhea

Anat Guz-Mark, Raanan Shamir

Definition of Epidemiology

Chronic diarrhea is defined as stool volume of more than 10 g/kg/day in toddlers/infants and greater than 200 g/day in older children that lasts for 4 wk or more. **Persistent** diarrhea began acutely but lasts longer than 14 days. In practice, this usually means having loose or watery stools more than 3 times a day. *Awakening at night to pass stool is often a sign of an organic cause of diarrhea.* The epidemiology has 2 distinct patterns. In *developing* countries, chronic diarrhea is, in many cases, the result of an intestinal infection that persists longer than expected. This syndrome is often defined as **protracted (persistent) diarrhea** , but there is no clear distinction between protracted (persistent) and chronic diarrhea. In countries with higher socioeconomic conditions, chronic diarrhea is less frequent, and the etiology often varies with age. The outcome of diarrhea depends on the cause and ranges from benign, self-limited conditions, such as toddler's diarrhea, to severe congenital diseases, such as microvillus inclusion disease, that may lead to progressive intestinal failure.

Pathophysiology

The mechanisms of diarrhea are generally divided into **secretory** and **osmotic** , but often diarrhea is a *combination of both mechanisms* . In addition, *inflammation* and *motility disorders* may contribute to diarrhea. Secretory diarrhea is usually associated with large volumes of watery stools and persists when oral feeding is withdrawn. Osmotic diarrhea is dependent on oral feeding, and stool volumes are usually not as massive as in secretory diarrhea (Fig. 367.1).

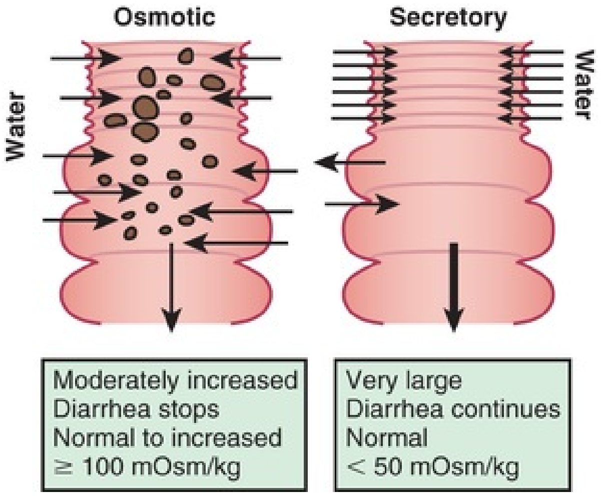

FIG. 367.1 Pathways of osmotic and secretory diarrhea. Osmotic diarrhea is caused by functional or structural damage of intestinal epithelium. Nonabsorbed osmotically active solutes drive water into the lumen. Stool osmolality and ion gap are generally increased. Diarrhea stops in children when not eating. In secretory diarrhea, ions are actively pumped into the intestine by the action of exogenous and endogenous secretagogues. Usually there is no intestinal damage. Osmolality and ion gap are within normal levels. Large volumes of stools are lost independent of food ingestion.

Secretory diarrhea is characterized by active electrolyte and water fluxes toward the intestinal lumen, resulting from either the inhibition of neutral NaCl absorption in villous enterocytes or an increase in electrogenic chloride secretion in secretory crypt cells as a result of the opening of the cystic fibrosis transmembrane regulator (CFTR) chloride channel or both. The result is more secretion from the crypts than absorption in the villous that persists during fasting. The other components of the enterocyte ion secretory machinery are (1) the Na-K 2Cl cotransporter for the electroneutral chloride entrance into the enterocyte; (2) the Na-K pump, which decreases the intracellular Na^+ concentration, determining the driving gradient for further Na^+ influx; and (3) the K^+ selective channel, that enables K^+ , once it has entered the cell together with Na^+ , to return to the extracellular fluid.

Electrogenic secretion is induced by an increase of intracellular concentration of cyclic adenosine monophosphate, cyclic guanosine monophosphate, or calcium in response to microbial enterotoxins, or to endogenous endocrine or nonendocrine molecules, including inflammatory cytokines. Another mechanism of secretory diarrhea is the inhibition of the electroneutral NaCl-coupled pathway that involves the Na^+ /H^+ and the $Cl^- /HCO_3{}^-$ exchangers. Defects in the genes of the Na^+ /H^+ and the $Cl^- /HCO_3{}^-$ exchangers are responsible for congenital Na^+ and Cl^- diarrhea, respectively.

Osmotic diarrhea is caused by nonabsorbed nutrients in the intestinal lumen as a result of one or more of the following mechanisms: (1) intestinal damage (e.g., enteric infection); (2) reduced absorptive surface area (e.g., active celiac disease); (3) defective digestive enzyme or nutrient carrier (e.g., lactase deficiency); (4) decreased intestinal transit time (e.g., functional diarrhea); and (5) nutrient overload, exceeding the digestive capacity (e.g., overfeeding, sorbitol in fruit juice). Whatever the mechanism, the osmotic force generated by nonabsorbed solutes drives water into the intestinal lumen. A very common example of osmotic diarrhea is lactose intolerance. Lactose, if not absorbed in the small intestine, reaches the colon, where it is fermented to short-chain organic acids, releasing hydrogen that is detected in the lactose breath test, and generating an osmotic overload. Another risk for chronic osmotic diarrhea often noted in patients with diarrhea-associated irritable bowel syndrome are foods containing FODMAPs (fermentable oligo-di-monosaccharides and polyols).

In many children chronic diarrhea may be caused by the combination of multiple mechanisms.

Etiology

Table 367.1 summarizes the main etiologies of chronic diarrhea in infants and children.

Table 367.1

Main Etiologies of Chronic Diarrhea in Children Older and Younger Than 2 Yr of Age

ETIOLOGY	YOUNGER THAN 2 YR	OLDER THAN 2 YR
Infections	+++	+++
Postenteritis syndrome	+++	+++
Immune deficiency	++	Rare
Celiac disease	+++ (after gluten introduction)	+++
Food allergy	+++	+
Inflammatory bowel disease	+ (rare)	+++
Pancreatic insufficiency	++	++
Cholestasis and insufficient bile acids	++	++
Cystic fibrosis	++	+
Lactose intolerance	++ (mostly postinfectious)	+++
Intestinal lymphangiectasia	+	+
Motility disorders	++	Rare

Short bowel syndrome	+++	+
Toddler's and functional diarrhea	++	++
Excessive intake of fruit juices and fluids	++	++
Congenital diarrheal disorders, including structural enterocyte defects and enzymatic or transport malabsorption syndromes	++	Unlikely

Infectious

Enteric infections are by far the most frequent cause of persistent or chronic diarrhea, both in developing and industrialized countries, however outcomes are often very different. In the former, comorbid conditions, such as HIV/AIDS, malaria, or tuberculosis, result in malnutrition that impairs the child's immune response, thereby potentiating the likelihood of prolonging diarrhea or acquiring another enteric infection. In children with HIV/AIDS, the viral infection itself impairs immune function and may trigger a vicious circle with malnutrition. Sequential infections with the same or different pathogens may also be responsible for chronic diarrhea. In *developing* countries, enteroadherent *Escherichia coli* and *Giardia lamblia* have been implicated in chronic diarrhea, whereas, in *developed* countries, chronic infectious diarrhea usually runs a more benign course and the etiology is often viral, with a major role of rotavirus and norovirus (Table 367.2).

Table 367.2

A Comparative List of Prevalent Agents and Conditions in Children With Persistent Infectious Diarrhea in Industrialized and Developing Countries

AGENT/DISEASE	
INDUSTRIALIZED COUNTRIES	**DEVELOPING COUNTRIES**
Clostridium difficile Enteroaggregative *Escherichia coli*	Enteroaggregative *E. coli* Atypical *E. coli* Shigella Heat stable/heat labile enterotoxin-producing *E. coli*
Astrovirus Norovirus Rotavirus[*] Small intestinal bacterial overgrowth (SIBO) Postenteritis diarrhea syndrome	Rotavirus[*] Cryptosporidium *Giardia lamblia* Tropical sprue

[*] More frequent in industrialized than in developing countries as agent of chronic diarrhea.

Chronic diarrhea in travelers to or expatriates from developing countries may depend on the country of origin. Nonetheless, common pathogens include giardia, *E. coli* , shigella, campylobacter, salmonella, and enteric viruses. Less common pathogens include amebiasis, strongyloides, and tropical spruce.

Opportunistic microorganisms induce diarrhea exclusively, more severely, or for more prolonged periods, in specific populations, such as immunocompromised children. Specific agents cause chronic diarrhea or exacerbate diarrhea in many chronic diseases. *Clostridium difficile* or cytomegalovirus act as opportunistic agents in oncologic patients as well as in patients with inflammatory bowel diseases. *Cryptosporidium* may induce severe and protracted diarrhea in AIDS patients.

Small intestinal bacterial overgrowth results in chronic diarrhea by either a direct interaction between the microorganism and the enterocyte, or the consequence of deconjugation and dihydroxylation of bile salts and hydroxylation of fatty acids due to an increased proliferation of bacteria in the proximal intestine.

Postenteritis diarrhea syndrome (Chapter 364.4) is a clinicopathologic condition in which small intestinal mucosal damage persists after acute gastroenteritis. Sensitization to food antigens, secondary disaccharidase deficiency, persistent infections, reinfection with an enteric pathogen, or side effects of medication may be responsible for causing postenteritis diarrhea syndrome, thought to be related to dysregulation of the intestinal microbiota. Functional diarrhea which may be related to the pathogenesis of irritable bowel syndrome may be caused by complications of an acute gastroenteritis.

Inflammatory/Immunologic

Celiac disease (Chapter 364.2) is a genetically determined permanent gluten intolerance that affects about 1 in 100 individuals, depending on geographic origin. In the genetically susceptible host, gliadin, the major protein of gluten, reacts with the immune system to cause villous atrophy. A reduction of intestinal absorptive surface is responsible for the diarrhea in celiac disease, which is reversible upon restriction of gluten from the diet.

Food allergy (mainly cow milk protein allergy Chapter 176) may present during infancy with chronic diarrhea. An abnormal immune response to food proteins can cause a proctitis/colitis or an enteropathy. **Eosinophilic gastroenteritis** is characterized by eosinophilic infiltration of the intestinal wall and is strongly associated with atopy. However, whereas diarrhea in food allergy responds to withdrawal of the responsible food, this does not always occur in eosinophilic gastroenteritis, in which immune suppression may be needed.

Inflammatory bowel diseases, including Crohn disease, ulcerative colitis, and inflammatory bowel disease–undetermined, cause chronic diarrhea that is often associated with abdominal pain, elevated inflammatory markers, and increased concentrations of fecal calprotectin or lactoferrin (see Chapter 362). The age of onset of inflammatory bowel disease is broad, with rare cases described in the 1st few mo of life, but the peak incidence in childhood occurs in adolescence. The severity of the symptoms is highly variable with a pattern characterized by long periods of well-being followed by exacerbations.

Autoimmune processes may target the intestinal epithelium, alone or in association with extraintestinal symptoms. **Autoimmune enteropathy** is associated with the production of antienterocyte and antigoblet cell antibodies, primarily immunoglobulin A, but also immunoglobulin G, directed against components of the enterocyte brush-border or cytoplasm and by a cell-mediated autoimmune response with mucosal T-cell activation. An X-linked immune-dysregulation, polyendocrinopathy, and enteropathy (**IPEX syndrome**) is associated with variable gene mutations and phenotypes of chronic diarrhea (more on autoimmune enteropathy and IPEX syndrome is available on Chapter 364.3).

Immune deficiency can present as chronic diarrhea in children. In these cases (for example, severe combined immunodeficiency or AIDS) the child can be infected by an opportunistic pathogen; can exhibit a persistent diarrhea due to a pathogen usually causing an acute gastroenteritis; or be infected by multiple and recurrent different pathogens causing mucosal damage to the intestines. Other immunoregulatory defects, found in patients with agammaglobulinemia, isolated immunoglobulin A deficiency, and common variable immunodeficiency disorder, may result in mild persistent infectious diarrhea.

Pancreatic Deficiency

Chronic diarrhea may be the manifestation of maldigestion caused by exocrine pancreatic disorders (see Chapters 376 and 378.2). In most patients with **cystic fibrosis** , exocrine pancreatic insufficiency results in steatorrhea and protein malabsorption. In **Shwachman-Diamond syndrome** , exocrine pancreatic hypoplasia may be associated with neutropenia, bone changes, and intestinal protein-losing enteropathy. Specific isolated pancreatic enzyme defects, such as lipase deficiency, result in fat and/or protein malabsorption. Familial pancreatitis, associated with a mutation in the trypsinogen gene, may be associated with exocrine pancreatic insufficiency and chronic diarrhea. Mutations in *CFTR* , *CTRC* , *PRSS1* , *PRSS2* , *SPINK 1* , and *SPINK 5* are associated with hereditary pancreatitis.

Liver and Bile Acids Disorders

Liver disorders and **cholestasis** may lead to a reduction in the bile salts pool resulting in fat malabsorption causing chronic diarrhea in the form of steatorrhea. Bile acid loss may be associated with diseases affecting the terminal ileum, such as Crohn disease, or following ileal resection. In **primary bile acid malabsorption** , neonates and young infants present with chronic diarrhea and fat malabsorption caused by mutations of ileal bile transporter. In addition to the fat malabsorption, the bile acid loss from the intestinal lumen is a form of secretory diarrhea by itself (called **cholorrheic diarrhea** , which is usually associated with significant diaper dermatitis).

Carbohydrate Malabsorption

Rare genetic mutations (Chapters 364.9 and 364.11) can cause carbohydrate malabsorption. More commonly, **lactose intolerance** is *secondary* to lactase deficiency caused by intestinal mucosal damage (usually as part of postenteritis syndrome, which is a self-limited process). Depending on ethnicity, a progressive, age-related, loss of lactase activity may begin around 7 yr of age and affects approximately 80% of the non-white population, and acquired hypolactasia may be responsible for chronic diarrhea in older children receiving cow’s milk (adult-type lactase deficiency).

Similarly, **fructose malabsorption** is common in Western countries with estimates as high as 40% of the population. These individuals cannot absorb fructose and often develop bloating, abdominal pain, diarrhea, and flatulence. Typically, they do not have liver disease. This is in contrast to **hereditary fructose intolerance** , a rare genetic disorder with incidence estimated to be 1 in 20,000-30,000. This disease is associated with mutations in the *ASDOB* gene that encodes for the aldolase B enzyme that is found primarily in the liver and is involved in the metabolism of fructose. Individuals with hereditary fructose intolerance may have nausea, abdominal pain/bloating, vomiting, diarrhea, and hypoglycemia. Continued ingestion of fructose results in *hepatomegaly* and eventually cirrhosis.

Protein-Losing Enteropathy

Chronic diarrhea can be the manifestation of obstructed intestinal lymphatic drainage, causing protein-losing enteropathy with steatorrhea, diarrhea, and lymphopenia. Besides **intestinal lymphangiectasia** , many diseases that cause intestinal mucosal injury can also result in protein-losing enteropathy, characterized by low serum protein levels and elevated fecal α_1 -antitrypsin (see Chapter 364.3).

Motility Disorders

Disorders of intestinal motility include abnormal development and function of the enteric nervous system, such as in **Hirschsprung disease** and **chronic intestinal pseudoobstruction** (which encompass both the neurogenic and the myogenic forms). Other motility disorders may be secondary to extraintestinal disorders, such as in *hyperthyroidism* and *scleroderma* . Motility disorders are associated with either constipation or diarrhea or both, with the former usually dominating the clinical picture.

Short Bowel Syndrome

Short bowel syndrome is the single most frequent etiology of intestinal failure in children (Chapter 364.7). Many intestinal abnormalities such as stenosis, segmental atresia, gastroschisis, and malrotation may require surgical resection, but the most frequent primary cause of short bowel is necrotizing enterocolitis. Rarely, a child can be born with congenitally short small bowel. In these conditions, the residual intestine may be insufficient to carry on its digestive–absorptive functions, resulting in severe chronic diarrhea, malnutrition, and failure to thrive, requiring long-term treatment with parenteral nutrition.

Nonspecific Diarrhea, Including Toddler's Diarrhea

The most benign and common etiology of chronic diarrhea is nonspecific diarrhea that encompasses **functional diarrhea** (or **toddler's diarrhea**) in children younger than 4 yr of age and **irritable bowel syndrome** in those 5 yr of age and older. It is the leading cause of chronic diarrhea in an otherwise well child. Toddler's diarrhea is defined by the daily painless recurrent passage of 4 or more large unformed stools, for 4 or more wk, with onset in infancy or preschool years. Nighttime defecation is usually absent. The child appears unperturbed by the diarrhea, there is no evidence of failure to thrive, and the symptoms resolve spontaneously by school age.

Diarrhea may also be the result of an **excessive intake of fluid and nonabsorbable carbohydrate** . If the child's fluid intake were > 150 mL/kg/24 hr, fluid intake should be reduced not to exceed 90 mL/kg/24 hr in order to decrease the stool frequency and volume. If the dietary history suggests that the child is ingesting significant amounts of fruit juice, especially apple juice, then the consumption of juice should be decreased. *Sorbitol, which is a nonabsorbable sugar, is found in apple, pear, and prune juices, and often causes diarrhea in toddlers.* Moreover, apple and pear juices contain higher amounts of fructose than glucose, a feature postulated to cause diarrhea in toddlers. In older children, irritable bowel syndrome is often associated with abdominal pain and may be related to anxiety, depression, and other psychological disturbances (Chapter 368). When the cause of the diarrhea remains undetermined and the clinical course is inconsistent with organic disorders, **factitious** disorder by proxy should be considered.

Congenital Diarrheal Disorders

The most severe etiology of chronic diarrhea includes a number of heterogeneous congenital conditions leading to syndromes often referred to as **intractable or protracted diarrhea** . This is the result of a permanent defect in the structure or function of the enterocyte, leading to progressive, potentially irreversible intestinal failure. The genetic and molecular basis of many causes of protracted diarrhea has been identified recently and a new classification of **congenital diarrheal disorders (CDDs)** has been proposed (Table 367.3). CDDs are a group of rare but severe enteropathies, with a similar clinical presentation despite a different pathogenesis and outcome. The diarrhea can be either secretory or osmotic, depending on the specific defect. Often severe diarrhea presents at birth or shortly thereafter, but in milder forms diarrhea may go unrecognized for years. CDDs can be classified in 4 groups: defects of digestion, absorption and transport of nutrients and electrolytes; defects of enterocyte differentiation and polarization; defects of enteroendocrine cell differentiation; and defects of modulation of intestinal immune response.

Table 367.3

Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES				
DISEASE	**GENE NAME**	**GENE LOCATION**	**TRANSMISSION AND INCIDENCE**	**MECHANISM**
GENES ENCODING BRUSH-BORDER ENZYMES				
Congenital lactase deficiency (LD)	*LCT*	2q21.3	AR, 1 in 60,000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	*SI*	3q26.1	AR, 1 in 5,000; higher incidence in Greenland, Alaska, and Canada	Osmotic
Congenital maltase-glucoamylase deficiency (MGD)	Not defined	—	Few cases described	Osmotic
GENES ENCODING MEMBRANE CARRIERS				
Glucose-galactose malabsorption (GGM)	*SLC5A1*	22q13.1	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	Not defined	—	Up to 40%	Osmotic
Fanconi-Bickel syndrome (FBS)	*SLC2A2*	3q26.2	AR, rare, higher frequency in consanguineous	Osmotic
Acrodermatitis enteropathica (ADE)	*SLC39A4*	8q24.3	AR, 1 in 500,000	Osmotic
Congenital chloride diarrhea (CCD, DIAR 1)	*SLC26A3*	7q31.1	AR, sporadic; frequent in some ethnicities	Osmotic
Lysinuric protein intolerance (LPI)	*SLC7A7*	14q11.2	AR, about 1 in 60,000 in Finland and Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	*SLC10A2*	13q33.1	AR	Secretory
Cystic fibrosis (CF)	*CFTR*	7q31.2	AR, 1 in 2,500	Osmotic
GENES ENCODING PANCREATIC ENZYMES				
Enterokinase deficiency (EKD)	*PRSS7*	21q21	AR	Osmotic
Hereditary pancreatitis (HP)	*PRSS1* *PRSS2* *SPINK1* *CTRC*	7q34 7q34 5q32 1p36.21	AD, cases with compound mutations in different genes; SPINK1 mutations may also cause tropical pancreatitis	Osmotic
Congenital absence of pancreatic lipase (APL)	*PNLIP*	10q25.3	AR	Osmotic
GENES ENCODING PROTEINS OF LIPOPROTEIN METABOLISM				
Abetalipoproteinemia (ALP)	*MTP*	4q27	AR, about 100 cases described; higher frequency among Ashkenazi	Osmotic

			Jews	
Hypobetalipoproteinemia (HLP)	*APOB*	2p24.1	Autosomal codominant	Osmotic
Chylomicron retention disease (CRD)	*SAR1B*	5q31.1	AR, about 40 cases described	Osmotic
GENES ENCODING OTHER TYPES OF PROTEINS				
Congenital sodium diarrhea (CSD)	*SPINT2* (only syndromic CSD) *SLC9A3*	19q13.2 5p15.33	AR	Osmotic
Shwachman-Diamond syndrome (SDS)	*SBDS*	7q11	AR	Osmotic
Activating guanylate cyclase-C mutation	*GUCY2C*	12p12.3	AD	Secretory
GENES ENCODING FOR OTHER ENZYMES				
Defect in triglyceride synthesis	*DGAT1*	8q24.3	AR	Protein-losing enteropathy
DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION				
Microvillous inclusion disease (MVID, DIAR 2)	*MYO5B*	18q21.1	AR; rare; higher frequency among Navajo	Secretory
Congenital tufting enteropathy (CTE, DIAR 5)	*EPCAM*	2p21	AR; 1 in 50,000-100,000; higher among Arabians	Secretory
Trichohepatoenteric syndrome (THE)	*TTC37* *SKIV2L*	5q15 6p21.33	AR; 1 in 400,000	Secretory
DEFECTS OF ENTEROENDOCRINE CELL DIFFERENTIATION				
Congenital malabsorptive diarrhea (CMD, DIAR 4)	*NEUROG3*	10q22.1	AR; few cases described	Osmotic
Proprotein convertase 1/3 deficiency (PCD)	*PCSK1*	5q15	AR	Osmotic
DEFECTS OF MODULATION OF INTESTINAL IMMUNE RESPONSE				
Autoimmune polyglandular syndrome type 1 (APS1)	*AIRE*	21q22.3	AR; AD (1 family)	Secretory
Immune dysfunction, polyendocrinopathy, X-linked (IPEX)	*FOXP3*	Xp11.23	X-linked (autosomal cases described), very rare	Secretory
IPEX-like syndrome	Not defined	—	Not X-linked	Secretory

AD , autosomal dominant; *AR* , autosomal recessive.

Although CDDs are rare diseases, in most specific disorders the genetic defect and transmission are known. The incidence of genetic disorders associated with CDD can range from 1 in 2,500 for cystic fibrosis, 1 in 5,000 for sucrose-isomaltase deficiency, 1 in 60,000 for congenital lactase deficiency, to 1 in 400,000 for trichohepatoenteric syndrome. For most CDDs, such as IPEX syndrome or autoimmune polyglandular syndrome type 1, the clinical application of exome sequencing is likely to increase identification of more patients with these rare causes of chronic diarrhea. Selected CDDs are more frequent in ethnic groups where consanguineous marriages are common, or in some geographic areas because of founder effects. Congenital lactase deficiency is more common in Finland; lysinuric protein intolerance has a higher incidence either in Finland and in Japan because of founder effect, and a specific mutation is typically found in each of the 2 ethnic groups. A defect in the *DGAT1* gene was identified using whole-exome sequencing in an Ashkenazi Jewish family and associated with the early onset of vomiting and nonbloody diarrhea with protein-losing enteropathy. For specific CDDs see Chapters 364.3 and 364.11 .

Most cases of protracted diarrhea syndrome are not easily treated. The natural history of protracted diarrhea is related to the primary intestinal disease and the specific defect in nutrient absorption. Treatment is more favorable for motility disorders and autoimmune enteropathy than for structural enterocyte defects. Children with motility disorders may have persistent symptoms, but they are rarely fatal, whereas children with structural enterocyte defects have a more severe course, poorer prognosis, and are more likely to be candidates for intestinal transplantation (see Chapter 365). Some late-onset CDDs may be relatively mild and are recognized only later in life.

Evaluation of Patients

Because of the spectrum of etiologies, the medical approach should be based on diagnostic algorithms that begin with assessment for infectious causes, and then consider the age of the child, growth, and clinical and epidemiologic factors. Early onset in the neonatal period is rare and may suggest a congenital or severe condition (see also Table 364.3), however infections and food allergy are more frequent in this age group, and together with gastrointestinal (GI) malformations should be high on the differential diagnosis. In later infancy and up to 2 yr of age, infections and allergies are the most common; inflammatory diseases are more frequent in older children and adolescents. Celiac disease as well as functional nonspecific diarrhea should always be considered independently of age because of their relatively high frequency at all ages.

Specific clues in the family and personal history may provide useful indications, suggesting a congenital, allergic, or inflammatory etiology. A history of *polyhydramnios* is consistent with congenital chloride-sodium diarrhea (where a typical sonographic finding of dilated fetal bowel loops is present), cystic fibrosis, and other CDDs, as well as a family history of a chronic or intractable diarrhea in a relative presenting in the 1st mo of life, as well as *consanguinity* .

An acute onset of diarrhea that runs a protracted course suggests postenteritis diarrhea, secondary lactase deficiency, small intestinal overgrowth, or the onset of chronic nonspecific diarrhea (toddler's diarrhea). The association of diarrhea with specific foods may indicate a nutrient basis, such as intolerance to selected nutrients (fructose). Anthropometric evaluation is essential to understand if diarrhea has affected weight gain and growth, providing estimation of the severity of diarrhea. Normal weight and growth strongly support functional diarrhea that may respond to simple dietary management. It should be noted that a child with functional diarrhea may be inappropriately “treated” with a diluted hypocaloric diet in an effort to reduce the diarrhea, resulting in impaired growth.

Initial clinical examination should include the evaluation of general and nutritional status. Dehydration, marasmus, or kwashiorkor require prompt supportive interventions to stabilize the patient. Nutritional evaluation should start with the evaluation of the weight and height curves, and of the weight-for-height index to determine the impact of diarrhea on growth. Weight is generally impaired before height, but with time, linear growth also becomes affected, and both parameters may be equally abnormal in the long term. Assessment of nutritional status includes a dietary history, physical examination, and biochemical testing including nutritional investigations. Caloric intake should be quantitatively determined, energy requirements determined, and the relationship between weight modifications and energy intake should be carefully considered. Assessment of body composition may be performed by measuring mid-arm circumference and triceps skinfold thickness or by bioelectrical impedance analysis, dual-emission x-ray absorptiometry scans, or air plethysmography. Biochemical markers including albumin, prealbumin, retinol binding protein, serum iron, and transferrin may assist in grading malnutrition, as the half-life of serum proteins may distinguish between short- and long-term malnutrition. Evaluation of micronutrient concentrations should always be considered. Zinc, magnesium, vitamin A, and folate deficiency are associated with chronic diarrhea and should be provided if needed.

In infants with chronic diarrhea, feeding history must be carefully obtained, providing clues for allergy or specific food intolerance, such as cow's-milk protein allergy or sucrose-isomaltase deficiency. Associated symptoms and selected investigations provide important diagnostic clues. Signs of general inflammation such as fever, mucoid or bloody stools, and abdominal pain may suggest inflammatory bowel disease. The presence of eczema or asthma is associated with an allergic disorder, whereas specific extraintestinal manifestations (arthritis, diabetes, thrombocytopenia, etc.) may suggest an autoimmune disease. Specific skin lesions may be suggestive of **acrodermatitis enteropathica** that might respond to zinc supplementation. Typical facial abnormalities and woolly hair are associated with phenotypic diarrhea.

Investigations

Microbiologic investigation should include a thorough list of intestinal bacterial, viral, and protozoan pathogens. Proximal intestinal bacterial overgrowth may be determined using the lactulose hydrogen breath test, but false-positive tests are common (see Chapter 364.4).

Initial investigations of a child with chronic diarrhea should always include an assessment of intestinal inflammation using fecal calprotectin or lactoferrin, and serology for celiac disease (see Chapter 364.2). The role of a mucosal biopsy is determined by the noninvasive diagnostic evaluation in consultation with a pediatric gastroenterologist.

Noninvasive assessment of digestive-absorptive function and of intestinal inflammation plays a key role in the diagnostic workup (Table 367.4). Abnormalities in the digestive-absorptive function tests suggest small bowel involvement, whereas intestinal inflammation, as demonstrated by increased fecal calprotectin or lactoferrin, supports colitis.

Table 367.4

Noninvasive Tests for Intestinal Digestive–Absorptive Function and Inflammation

TEST	NORMAL VALUES	IMPLICATION
α_1 -Antitripsin concentration	<0.9 mg/g	Increased intestinal permeability/protein loss
Steatocrit	<2.5% (older than 2 yr) fold increase over age-related values (younger than 2 yr)	Fat malabsorption
Fecal-reducing substances	Absent	Carbohydrate malabsorption
Elastase concentration	>200 µg/g	Pancreatic function
Chymotrypsin concentration	>7.5 units/g >375 units/24 hr	Pancreatic function
Fecal occult blood	Absent	Blood loss in the stools/inflammation
Fecal calprotectin concentration	<100 µg/g (in children to 4 yr of age) <50 µg/g (older than 4 yr)	Intestinal inflammation
Fecal leukocytes	<5/microscopic field	Colonic inflammation
Fecal lactoferrin	Absent	Inflammation
Nitric oxide in rectal dialysate	<5 µM of NO_2^- /NO_3^-	Rectal inflammation

Dual sugar (cellobiose/mannitol) absorption test	Urine excretion ratio: 0.010 ± 0.018	Increased intestinal permeability
Xylose oral load	25 mg/dL	Reduced intestinal surface

Determining the osmotic versus secretory nature of the diarrhea in neonates and infants with protracted diarrhea is especially important. The **stool osmolar gap** , sometimes called stool ion gap, is calculated as 290 mOsm/kg (or measured stool osmolality) minus [2 × (stool Na + stool K)]. If the osmolar gap is above 100 mOsm/kg, fecal osmolality is derived from ingested or nonabsorbed osmotically active solutes or nonmeasured ions. In contrast, a low gap (<50 mOsm/kg) is typically observed in secretory diarrhea. It is also important to measure Cl^- concentration in the stool to rule out CCD, which is characterized by low osmolar gap due to high Cl^- fecal loss (>90 mmol/L).

Whereas most etiologies of chronic diarrhea can be exaggerated by feeding and have osmotic or mixed nature to the stool, secretory diarrhea necessitates investigation for congenital defects in enterocytes, defects in the intestinal immune response (IPEX and autoimmune enteropathy), and disorders of bile acid malabsorption. Because of the overlap between secretory and osmotic features of the diarrhea in many diseases, a classification based on the response to bowel rest was also introduced. Severe diarrhea that persists at bowel rest is characteristic of **congenital enteropathies** (microvillous inclusion disease, tufting enteropathy, syndromic diarrhea). Diarrhea that disappears at bowel rest can imply carbohydrate or fat malabsorptive syndromes, as well as defects in enteroendocrine cells. In most other etiologies the diarrhea can decrease significantly, but not disappear, in response to bowel rest, including some congenital diseases as well as acquired inflammatory and other enteropathies.

Histology is important in establishing mucosal involvement, noting changes in the epithelial cells, or in identifying specific intracellular inclusion bodies caused by pathogens, such as cytomegalovirus, or the presence of parasites. Electron microscopy is essential to detect subcellular structural abnormalities such as microvillous inclusion disease. Immunohistochemistry allows the study of mucosal immunity as well as of other cell types (smooth muscle cells and enteric neuronal cells).

Imaging has a major role in the diagnostic approach. Abdominal ultrasound may help in detecting liver and pancreatic abnormalities or an increase in distal ileal wall thickness that suggests inflammatory bowel disease. A preliminary plain abdominal x-ray is useful for detection of abdominal distention, suggestive of intestinal obstruction, or increased retention of colonic feces. Intramural or portal gas may be seen in necrotizing enterocolitis or intussusception. Structural abnormalities such as diverticula, malrotation, stenosis, blind loop, and congenital short bowel, as well as motility disorders, may be investigated through a barium meal and a small bowel follow-through. Capsule endoscopy can be done when the patient weighs more than 10 kg and allows the exploration of the entire intestinal tract searching for structural changes, inflammation, or bleeding; the new SmartPill measures pressure, pH, and temperature as it moves through the GI tract, assessing motility.

Specific investigations should be carried out for specific diagnostic indications. Prick and patch test may support a diagnosis of food allergy. However, an elimination diet with withdrawal of the suspected harmful food from the diet and subsequent challenge is the most reliable strategy by which to establish a diagnosis. Bile malabsorption may be explored by the retention of the bile acid analog ^{75}Se-homocholic acid-taurine (^{75}SeHCAT) in the enterohepatic circulation. A scintigraphic examination, with radio-labeled octreotide is indicated in suspected APUD cell neoplastic proliferation. In other diseases, specific imaging techniques such as computed tomography, or nuclear magnetic resonance endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography, may have important diagnostic value.

Once infectious agents have been excluded and nutritional assessment performed, a stepwise approach to the child with chronic diarrhea may be applied. The main causes of chronic diarrhea should be investigated, based on the features of the diarrhea and the specific nutrient(s) that is (are) affected. The use of whole-exome sequencing or specific molecular analysis may be especially essential in children suspected of having CDD. A step-by-step diagnostic approach is important to minimize the unnecessary use of invasive procedures as well as the cost, while optimizing the yield of the diagnostic evaluation (Table 367.5).

Table 367.5

Stepwise Diagnostic Approach to Children and Infants With Chronic Diarrhea

INITIAL EVALUATION	
• Personal and family history: Prenatal sonography; feeding history; family history of protracted diarrhea; consanguinity	• Infectious workup: Stool cultures; parasites; viruses • Allergic workup: Elimination diet trial

• Physical examination: Dysmorphism; skeletal abnormalities; organomegaly; dermatitis	
⇩	
LABORATORY TESTS	
• Stool analysis: *Stool volume following fasting; stool electrolytes and ion gap; pH and reducing substances; steatocrit; fecal leukocytes and calprotectin; fecal elastase;* α_1 *-antitrypsin*	• Blood and serum analysis: Serum electrolytes; lipid profile; albumin and pre-albumin; amylase and lipase; inflammatory markers; ammonia; celiac serology
⇩	
IMAGING	
• Abdominal ultrasound: Bowel wall thickening; liver and bile disorders	• X-ray and contrast studies: Congenital malformation; signs of motility disorders
⇩	
ENDOSCOPIES AND INTESTINAL HISTOLOGY	
Endoscopy and standard jejunal/colonic histology* ; morphometry; PAS staining; intestinal immunohistochemistry; electron microscopy	
⇩	
GENETIC INVESTIGATION	
• Specific molecular analysis	• Whole-exome sequencing
⇩	
OTHER SPECIAL INVESTIGATIONS	
Sweat test; specific carbohydrates breath tests; ^{75} SeHCAT measurement; antienterocyte antibodies; metabolic diseases workup; motility studies; neuroendocrine tumor markers	

* The decision to perform an upper or a lower endoscopy may be supported by noninvasive tests.

PAS , Periodic acid–Schiff; ^{75} *SeHCAT* , ^{75} Se-homocholic acid-taurine.

Treatment

Chronic diarrhea associated with impaired nutritional status should always be considered a serious disease, and therapy should be started promptly. Treatment includes general supportive measures, nutritional rehabilitation, elimination diet, and medications. The latter include therapies for specific etiologies as well as interventions aimed at counteracting fluid secretion and/or promoting restoration of disrupted intestinal epithelium. Because death in most instances is caused by dehydration, replacement of fluid and electrolyte losses is the most important early intervention.

Nutritional rehabilitation is often essential and is based on clinical and biochemical assessment. In moderate to severe malnutrition, caloric intake should be carefully advanced to avoid the development of refeeding syndrome and may be progressively increased to 50% or more above the recommended dietary allowances. The intestinal absorptive capacity should be monitored by digestive function tests. In children with steatorrhea, medium-chain triglycerides may be the main source of lipids. A lactose-free diet should be started in all children with chronic diarrhea and is recommended by the World Health Organization. Lactose is generally replaced by maltodextrin or a combination of complex carbohydrates. A sucrose-free formula is indicated in sucrase-isomaltase deficiency. Semi-elemental or elemental diets have the dual purpose of overcoming food intolerance, which may be the primary cause of chronic diarrhea, particularly in infancy and early childhood, and facilitating nutrient absorption. The sequence of elimination should begin from less to more restricted diets, that is, cow's-milk protein hydrolysate to amino-acid–based formulas, depending on the child's situation. In severely compromised infants, it may be prudent to start with amino-acid–based feeding.

When oral nutrition is not feasible or fails, enteral or parenteral nutrition should be considered. Enteral nutrition may be provided via nasogastric or gastrostomy tube and is indicated in a child who is not able to be fed orally, either because of inability to tolerate nutrient requirements or because of extreme weakness. In extreme wasting and in cases of significant intestinal mucosal damage or dysfunction, enteral nutrition may not be tolerated, and **parenteral nutrition** is required.

Micronutrient and vitamin supplementation are part of nutritional rehabilitation, especially in malnourished children in developing countries. Zinc supplementation is important in both prevention and therapy of chronic diarrhea, since it promotes ion absorption, restores epithelial proliferation, and stimulates immune response. Nutritional rehabilitation has a general beneficial effect on the patient's general condition, intestinal function, and immune response.

Functional diarrhea in children may benefit from a diet based on the “4 F” principles (reduce fructose and fluids, increase fat and fiber). The use of probiotics in persistent infectious and postinfectious diarrhea in children appear to hold promise as adjunctive therapy with reduction in symptom duration, but there is still insufficient evidence to recommend their routine use.

Pharmacologic therapy includes, based on the etiology, anti-infectious drugs, immune suppression, and drugs that may inhibit fluid loss and promote cell growth. If a bacterial agent is detected, specific antibiotics should be prescribed. Empiric antibiotic therapy may be used in children with either small bowel bacterial overgrowth or with suspected infectious diarrhea. Table 367.6 summarizes the antimicrobial treatment of infectious persistent diarrhea. Immune suppression should be considered in selected conditions such as autoimmune enteropathy and inflammatory bowel disease.

Table 367.6

Antimicrobial Treatment for Persistent Diarrhea

	DRUG	INDICATIONS	DOSAGE	DURATION
Antibiotics	Trimethoprim-sulfamethoxazole	*Salmonella* spp., *Shigella* spp.	6-12 mg/kg/day (of Trimethoprim) in 2 divided doses–daily os	5-7 days
	Azithromycin	*Shigella* spp., *Campylobacter*	1 day: 12 mg/kg/day once–daily os 2-5 days: 6 mg/kg/day once–daily os *alternative: 10 mg/kg/day once–daily os, for 3 days	5 days
	Ciprofloxacin	*Shigella* spp.	20-30 mg/kg/day in 2 divided doses–os or IV	3 days
	Ceftriaxone	*Shigella* spp.	50-100 mg/kg/day once–IM or IV	2-5 days
	Metronidazole	*Giardia*, *Amebiasis* , *Blastocystis* , *Clostridium difficile*	15-35 mg/kg/day in 2-3 divided doses–os	7-10 days
	Paromomycin	*Amebiasis*	25-35 mg/kg/day in 3 divided doses–os	7 days
	Vancomycin	*Clostridium difficile*	40 mg/kg/day in 4 divided doses–os	10 days
Antiparasitic	Nitazoxanide	*Amebiasis* , *Giardiasis* , *Blastocystis*, *Cryptosporidiosis*	100 mg every 12 hr for children ages 12-47 mo 200 mg every 12 hr for children ages 4-11 yr 500 mg every 12 hr for children older than 11 yr	3 days
	Albendazole	*Ascaris*, *Hookworm*, and *Pinworm* infection	400 mg	Once

Depends on local susceptibility profile. *IM* , intramuscular; *IV* , intravenous; *os* , by mouth.

Treatment may be also directed at modifying specific pathophysiologic processes. Secretion of ions may be reduced by antisecretory agents, such as the enkephalinase inhibitor racecadotril. Some benefit from absorbents, such as diosmectite, has been described, with reduction of diarrhea duration in infectious diarrhea. In diarrhea caused by neuroendocrine tumors (NETs), microvillus inclusion disease and enterotoxin-induced severe diarrhea, a trial of somatostatin analog octreotide may be considered. Zinc promotes both enterocyte growth and ion absorption and may be effective when intestinal atrophy and ion secretion are associated. However, when therapeutic attempts and other nutritional support have failed, the only option to treat children with intestinal failure, while maintaining adequate growth and development, may be long-term parenteral nutrition or eventually intestinal transplantation.

367.1

Diarrhea From Neuroendocrine Tumors

Shimon Reif, Raanan Shamir

KeyWords

Neuroendocrine tumor (NET)
multiple endocrine neoplasia (MEN)
carcinoid
carcinoid syndrome
VIP
VIPoma
somatostatin
octreotide

The incidence of neuroendocrine tumors (NET) originating in the gastrointestinal (GI) tract is increasing globally. The commonly perceived notion of NETs is of slow-growing malignancies with a benign course. Indeed, well-differentiated GI-NETs may exhibit indolent clinical behavior, but recent studies indicate that they are frequently already metastatic at diagnosis. The most common tumor in children is **carcinoid** and mostly it is a low-grade tumor especially when it is small, that is <1 cm. It is equally distributed between the small and large intestine and can commonly be found in the appendix. Most carcinoids are found incidentally and are asymptomatic, especially those that are located in the appendix. Some NET patients (around 10%) will develop secretory diarrhea requiring symptom control to optimize quality of life and clinical outcomes. Such patients are defined as having carcinoid syndrome, characterized by excessive production of one or more peptides, which, when released into the circulation, exert their endocrine effects and can be measured by radioimmunologic methods (in the plasma or as their urinary metabolites). These peptides therefore also act as tumor markers. In clinically functioning tumors, the secreted peptides cause a recognizable syndrome that can include watery diarrhea. Compared to carcinoid, vasoactive intestinal polypeptide (VIP)omas are much less frequent. Because it secretes VIP, a more potent vasoactive peptide, it induces more profuse diarrhea, with up to 70% of patients having volumes greater than 3 L/day. Though rare as a cause of watery diarrhea, a NET should be considered in the differential diagnosis when diarrhea is unusually severe or takes a chronic course (resulting in electrolyte and fluid depletion). GI-NETs may be associated with flushing, palpitations, or bronchospasm. Furthermore, patients may have a positive family history of multiple endocrine neoplasia MEN 1 or 2 syndromes. (Table 367.7).

Table 367.7

Diarrhea Caused by Neuroendocrine Tumors

TUMOR AND CELL TYPE	SITE	MARKERS	SIGNS OF HORMONE HYPERSECRETION	THERAPY
Carcinoid	Intestinal argentaffin cells, typically midgut, also foregut and hindgut, ectopic bronchial tree	**Serotonin (5-HT), urine 5-HIAA** * (diagnostic) Also produce substance P, neuropeptide K, somatostatin, VIP Chromogranin A	Secretory diarrhea, crampy abdominal pain, flushing, wheezing (and cardiac valve damage if foregut site)	Resection Somatostatin analog, (palliative) Genetic MEN-1
Gastrinoma, Zollinger-Ellison syndrome	Pancreas, small bowel, liver, and spleen	**Gastrin**	Multiple peptic ulcers, secretory diarrhea	H_2 -blockers, PPI, tumor resection, (gastrectomy) Genetic MEN-1
Mastocytoma	Cutaneous, intestine, liver, spleen	**Histamine** , **VIP**	Pruritus, flushing, apnea If VIP, diarrhea	H_1 - and H_2 -blockers, steroids, resection if solitary
Medullary carcinoma	Thyroid C-cells	**Calcitonin** , **VIP** , **prostaglandins**	Secretory diarrhea	Radical thyroidectomy ± lymphadenectomy (genetic MEN-2A/B, familial MTC)
Ganglioneuroma, pheochromocytoma,	Chromaffin cells; abdominal > other	**Metanephrines** and	Hypertension, tachycardia,	Perioperative α-adrenergic (BP)

ganglioneuroblastoma, neuroblastoma	sites; extraadrenal or adrenal	**catecholamines** , **VIP** VMA, HMA in neuroblastoma	paroxysmal palpitations, sweating, anxiety, watery diarrhea [†]	and β-adrenergic blockade with volume support tumor resection Genetic MEN-2 (*RET* gene), VHL, NF-1, SDH
Somatostatinoma	Pancreas	**Somatostatin**	Secretory diarrhea, steatorrhea, cholelithiasis, diabetes	Resection Genetic MEN-1
VIPoma	Pancreas	**VIP** , **prostaglandins**	Secretory diarrhea, achlorhydria, hypokalemia	Somatostatin analogs, resection Genetic MEN-1

[*] Bold indicates major markers.

[†] Diarrhea has been reported only in adult patients with pheochromocytoma.

BP , blood pressure; H_1 , histamine receptor type 1; H_2 , histamine receptor type 2; *HMA* , homovanillic acid; *MEN-1* , multiple endocrine neoplasia type 1; *MTC* , medullary thyroid carcinoma; *NF-1* , neurofibromatosis type 1; *PPI* , proton pump inhibitor; *SDH* , succinate dehydrogenase; *VHL* , von Hippel-Lindau disease; *VIP* , vasoactive intestinal polypeptide; *VMA* , vanillylmandelic acid.

(Modified from Spoudeas HA, editor: *Paediatric endocrine tumors. A multidisciplinary consensus statement of best practice from a working group convened under the auspices of the British Society of Paediatric Endocrinology and Diabetes (BSPED) and the United Kingdom Children's Cancer Study Group (UKCCSG)* , Crawley, West Sussex, 2005, Novo Nordisk.)

Baseline tests should include plasma chromogranin A and urinary 5-hydroxyindoloacetic acid (metabolite of serotonin) and other specific biochemistry being guided by the suspected syndrome (see Table 367.7). Localization of any NET is best achieved using a multimodality approach. Whole-body CT, MRI, and somatostatin receptor scintigraphy may be required (because nearly all NETs express membrane receptors for small peptides, e.g., somatostatin), with gallium-68 positron emission tomography. Therapeutic interventions to be considered include surgical, pharmacological, and radioisotope therapy. Details to be considered when making therapeutic decisions include disease extent and location, tumor grade, pace of disease progression, symptoms, and co-morbidities.

Tumor resection is the treatment of choice when the tumor is small and localized. However, resection is potentially hazardous as it can precipitate life-threatening adrenergic crises. When arising in the appendix, carcinoid tumors less than 2 cm in size can be managed by simple appendectomy. When greater than 2 cm in size or arising from the base of the appendix, a right hemicolectomy is indicated. Fortunately, in pediatric patients, metastases (most frequently to the liver) are rare. Tumor histochemistry will confirm the NET type and classification. Pharmacologic treatment may include the use of long-acting somatostatin analogues. This usually results in a pronounced improvement of symptoms including diarrhea. However, the improvement is mostly temporary with many patients becoming resistant to somatostatin. An oral medication, Everolimus, a more specific target of Rapamycin (mTOR)-inhibitor, has been reported as add-on treatment to octreotide mainly in adult patients. Data suggest a positive effect of ondansetron, a serotonin-3-receptor antagonist, on diarrhea. Peptide receptor radioisotope therapy also has been reported as a therapeutic modality.

The diagnosis of NET in children should prompt a genetic referral to exclude a familial tumor predisposition syndrome.

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CHAPTER 368

Functional Gastrointestinal Disorders

Asim Maqbool, Chris A. Liacouras

Functional gastrointestinal disorders (FGIDs) comprise a group of conditions that relate to the gastrointestinal (GI) tract. These disorders cannot be completely explained by anatomical or biochemical abnormalities (infectious, inflammatory). FGIDs commonly afflict children across a broad range of manifestations and are defined primarily by symptoms. The symptom-based criteria employed to classify FGIDs have been developed by expert consensus and opinion under the auspices of the Rome Foundation, and are referred to as Rome IV Criteria. FGIDs pose diagnostic challenges as there is no anatomical or laboratory-based testing that is used to define them. FGID defining criteria strive not to be entirely based on diagnoses of exclusion, but rather aim to be based on objective, unambiguous, and accurate criteria derived from the presentation as elicited during obtaining the medical history and performing a clinical examination. These criteria strive to be uniform, reliable, reproducible, and to minimize unnecessary evaluations/testing with low diagnostic yield or relevance. FGIDs often coexist across the spectrum of GI disorders, such as inflammatory bowel disease, celiac disease, or irritable bowel syndrome (IBS). FGIDs may be influenced by psychosocial stressors, or a result of an otherwise benign episode of abdominal pain. The brain–gut axis likely plays a prominent role in the pathophysiology of many FGIDs. Some FGID manifestations may relate to dysbiosis and the intestinal microbiota. There may be a genetic basis to some of these disorders as well. Early life physical or psychologic stressors may manifest later as FGID. Maladaptive responses or lack of adequate coping skills may complicate the treatment of FGIDs but may also allow for a valuable approach to management using behavioral therapies.

FGIDs encompass 2 age groups: infants and toddlers or children and adolescents. Aerophagia, functional constipation, and cyclical vomiting span both age groups (Fig. 368.1).

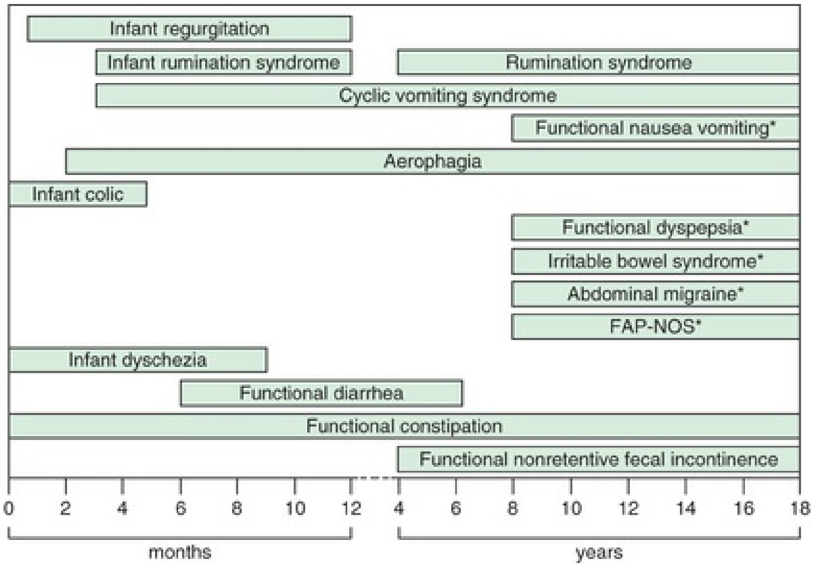

FIG. 368.1 Age distribution of functional gastrointestinal disorders in infants, toddlers, children, and adolescents. *History may not be reliable below this age. *FAP-NOS* , Functional abdominal pain—not otherwise specified. (Modified from Benninga MA, Nurko S, Faure C, et al: Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 150[6]:1443–1455.e2, 2016.)

Infant regurgitation implies effortless retrograde and involuntary passage of gastric contents from the stomach cephalad and is more commonly referred to as gastroesophageal reflux (Table 368.1). When refluxate reaches the oropharynx and is visible, it is labelled as regurgitation. This phenomenon is normal for healthy infants, unless there are complications associated with the process, such as esophageal inflammation, dysphagia, feeding difficulties, inadequate oral intake to meet needs leading to failure to thrive, or the inability to protect the airway with risk for aspiration; in this setting gastroesophageal reflux *disease* is the correct designation (Chapter 349). Unlike vomiting, regurgitation does not include the forceful expulsion of gastric contents via the mouth. Rumination is a different phenomenon, in that previously ingested and swallowed food is brought back up to the oral cavity, remasticated and subsequently reswallowed.

Table 368.1

Diagnostic Criteria for Infant Regurgitation

Must include both of the following in otherwise healthy infants 3 wk to 12 mo of age:
1. Regurgitation 2 or more times per day for 3 or more wk
2. No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing

From Benninga MA, Nurko S, Faure C, et al: Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 150(6):1443–1455.e2, 2016.

Infant rumination is defined as a habitual regurgitation of gastric contents into the oropharynx to allow for remastication and reswallowing (Table 368.2). It is thought to be a form of self-stimulation and may occur in the setting of emotional or sensory deprivation. The regurgitation of gastric contents is effortless and can be remasticated and reswallowed versus expulsion from the oropharynx. Infant rumination occurs between 3 and 8 mo of age and does not respond to measures used to manage regurgitation. This phenomenon does not occur during socialization/interaction with individuals, does not occur during sleep, and is not associated with distress. Empathy and nurturing lay the foundation for management. Behavior management is important to achieve resolution of this phenomenon.

Table 368.2

Diagnostic Criteria for Infant Rumination Syndrome

Must include all of the following for at least 2 mo:

1. Repetitive contractions of the abdominal muscles, diaphragm, and tongue
2. Effortless regurgitation of gastric contents, which are either expelled from the mouth or rechewed and reswallowed
3. Three or more of the following:
    a. Onset between 3 and 8 mo
    b. Does not respond to management for gastroesophageal reflux disease and regurgitation
    c. Unaccompanied by signs of distress
    d. Does not occur during sleep and when the infant is interacting with individuals in the environment

From Benninga MA, Nurko S, Faure C, et al: Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 150(6):1443–1455.e2, 2016.

Infant colic (Chapter 22.1) is a normal developmental process associated with fussiness, irritability, and difficultly consoling the infant (Table 368.3). A trigger is not identifiable. This phenomenon usually occurs between 1 and 4 mo of age. The typical behavior usually leads to consultation with a pediatrician or a pediatric gastroenterologist out of suspicion for abdominal pain. Patients are often unnecessarily treated for gastroesophageal reflux, gas, or suspected cow-milk protein or soy allergy leading to dietary changes and the use of medications for the management of acidity or gas. Probiotics have been investigated as a possible treatment. Probiotics may be more beneficial for breast versus cow-milk-fed infants. Soothing in a quiet, tranquil space may also be effective. Providing reassurance, education, support, and ensuring adequate coping skills and support for family members are key. This is a self-limited phenomenon that resolves on its own.

Table 368.3

Diagnostic Criteria for Infant Colic

For clinical purposes, must include all of the following:
1. An infant who is < 5 mo of age when the symptoms start and stop
2. Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers
3. No evidence of infant failure to thrive, fever, or illness
“Fussing” refers to intermittent distressed vocalization and has been defined as “[behavior] that is not quite crying but not awake and content either.” Infants often fluctuate between crying and fussing, so that the 2 symptoms are difficult to distinguish in practice.
For clinical research purposes, a diagnosis of infant colic must meet the preceding diagnostic criteria and also include both of the following:
1. Caregiver reports infant has cried or fussed for 3 or more hr per day during 3 or more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician
2. Total 24-hr crying plus fussing in the selected group of infants is confirmed to be 3 hr or more when measured by at least 1 prospectively kept, 24-hr behavior diary

From Benninga MA, Nurko S, Faure C, et al: Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 150(6):1443–1455.e2, 2016.

Functional diarrhea is often also referred to as *toddler's diarrhea* (Table 368.4). This condition excludes steatorrhea. Excessive fruit juice with nonabsorbable carbohydrates (i.e., sorbitol) intake coupled with a low-fat diet drive this osmotic process. An evaluation of the diet for possible other etiologies as well as assessment for infections, inflammation, antibiotic, and laxative use is important. In addition, assessments of growth as well as ruling out fecal impaction and encopresis via digital rectal examination are important. The diarrhea is usually stool colored, painless, liquid-watery, and may contain undigested foods. Growth is usually not affected. Dietary changes such as reducing fruit juice intake as well as fructose are helpful in resolving symptoms.

Table 368.4

Diagnostic Criteria for Functional Diarrhea

Must include all of the following:
1. Daily painless, recurrent passage of 4 or more large, unformed stools

2. Symptoms last more than 4 wk
3. Onset between 6 and 60 mo of age
4. No failure to thrive if caloric intake is adequate

From Benninga MA, Nurko S, Faure C, et al: Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 150(6):1443–1455.e2, 2016.

Infant dyschezia is manifested by infants straining prior to defecation associated with visible distress, crying, a red/purple facial discoloration, with symptoms persisting for 10-20 min alleviated by the passage in stools, limited to infants < 9 mo of age. There is no associated obstruction or anal anomaly; stools are passed several times daily and are not associated with other health problems. Dyschezia is thought to represent discoordinated intraabdominal musculature contraction with pelvic floor relaxation. A good medical history and neurological and digital rectal examinations to rule out anatomical or neuromuscular abnormalities are key. Normal growth is to be expected. Reassurance provides the basis of management. Laxative, suppository, or digital manipulation is not required and may be counterproductive.

Functional constipation (Chapter 358.3) is associated with withholding behaviors, which in turn may relate to social stressors or changes in social situations (Table 368.5). These often occur at the time of diet changes in infants and at the initiation of toilet training for toddlers. Painful passage of hard, large caliber stools < 2 times/wk in the setting of withholding behaviors is noted. For those children who have previously been toilet trained, fecal incontinence or encopresis is often observed. Large-caliber stools that obstruct the toilet are also noted frequently. Abdominal examination may reveal a palpable mass, and digital rectal examination may reveal a large rectal stool mass. The differential diagnosis for constipation is extensive, with functional constipation and slow transit constipation common. Dietary factors may play a role. Anorectal malformations, neuromuscular and motility issues may also present as such. Hirschsprung disease is on the differential diagnosis. The evaluation and management are based on a detailed history and thorough physical examination. A defecation history extending to the first 1-2 days of life is particularly important, as almost all children pass their first bowel movement within the first 48 hr of life. Assessment for associated signs and symptoms and growth trends are important. Red flags are noted in Table 368.6 . Imaging plays a role, and rectal suction biopsy or even full thickness rectal biopsy may be required to rule out Hirschsprung disease in cases with high index of suspicion. Management encompasses dietary and lifestyle changes, and medications to soften stool with osmotic laxatives over stimulant laxatives. The goal is to achieve painless defection and resolve fear and withholding revolving around defecation. Behavior modification including reassurance and positive incentive reward systems are useful. Avoidance of toilet training until symptoms resolve and the child shows interest or willingness to proceed are generally advocated.

Table 368.5

Diagnostic Criteria for Functional Constipation

Must include 1 mo of at least 2 of the following in infants up to 4 yr of age:
1. Two or fewer defecations per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large-diameter stools
5. Presence of a large fecal mass in the rectum
In toilet-trained children, the following additional criteria may be used:
6. At least 1 episode/wk of incontinence after the acquisition of toileting skills
7. History of large-diameter stools that may obstruct the toilet

From Benninga MA, Nurko S, Faure C, et al: Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 150(6):1443–1455.e2, 2016.

Table 368.6

Potential Alarm Features in Constipation

Passage of meconium >48 hr in a term newborn
Constipation starting in the 1st mo of life
Family history of Hirschsprung disease
Ribbon stools
Blood in the stools in the absence of anal fissures
Failure to thrive
Bilious vomiting
Severe abdominal distension
Abnormal thyroid gland
Abnormal position of the anus
Absent anal or cremasteric reflex
Decreased lower extremity strength/tone/reflex
Sacral dimple
Tuft of hair on spine
Gluteal cleft deviation
Anal scars

From Hyams JS, Di Lorenzo C, Saps M, et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150(6):1456–1468.e2, 2016 (Table 3, p. 1465).

Functional Gastrointestinal Disorders in Children and Adolescents

Functional nausea and functional vomiting may coexist or may occur independently of one another (Table 368.7). These conditions occur without coincident abdominal pain. The presentation may accompany *autonomic symptoms* such as diaphoresis, pallor, tachycardia, and dizziness. The differential diagnosis includes anatomical, inflammatory, infectious, and motility etiologies. Anxiety and other behavioral conditions can be present with these FGIDs and should be evaluated for and managed accordingly. Cyproheptadine may be effective in the management of nausea.

Table 368.7

Diagnostic Criteria* for Functional Nausea and Functional Vomiting

FUNCTIONAL NAUSEA
Must include all of the following fulfilled for the last 2 mo:
1. Bothersome nausea as the predominant symptom, occurring at least twice per week, and generally not related to meals
2. Not consistently associated with vomiting
3. After appropriate evaluation, the nausea cannot be fully explained by another medical condition
FUNCTIONAL VOMITING
Must include all of the following:
1. On average, 1 or more episodes of vomiting per week
2. Absence of self-induced vomiting or criteria for an eating disorder or rumination
3. After appropriate evaluation, the vomiting cannot be fully explained by another medical condition

[*] Criteria fulfilled for at least 2 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150(6):1456–1468, 2016 (p. 1457).

Rumination in *older* children and adolescents may be associated with an unpleasant sensation or discomfort such as abdominal pressure or burning (Table 368.8). Repeated regurgitation and remastication or oral repulsion of regurgitated gastric contents occurs soon after ingesting foodstuffs and does not occur during sleep. It is not preceded by active expulsion of gastric contents/retching and cannot be explained by any other medical condition. *Eating disorders* may also present and must be considered. There is no expectation that older children and adolescents need to be treated for or fail to respond to treatment for gastroesophageal reflux for this diagnosis to be made. A triggering event can be identified prior to symptoms, which may occur following resolution of an infectious illness or with psychosocial stress. Other GI issues to be considered include anatomical, infectious, inflammatory, and motility disorders. An important distinction between rumination and other GI etiologies of emesis includes effortless versus forceful regurgitation, and the time course, which is usually immediately following ingestion of foodstuffs. Given the significant behavioral component in this behavior, psychologic-behavioral therapy is key in management.

Table 368.8

Diagnostic Criteria* for Rumination Syndrome in Children

Must include all of the following:

1. Repeated regurgitation and rechewing or expulsion of food that:
    a. Begins soon after ingestion of a meal
    b. Does not occur during sleep
2. Not preceded by retching
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition. An eating disorder must be ruled out

* Criteria fulfilled for at least 2 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150(6):1456–1468, 2016 (p. 1458).)

Aerophagia is often seen in patients with impairments in neurocognition. Air swallowing is described as excessive, occurring throughout the day with progressive abdominal distention and with repetitive passage of gas via belching and/or flatus. Symptoms may be more severe in those children who cannot belch. Chewing gum and gulping down liquids may be risk factors in cognitively normal children. Symptoms are not attributable to any other causes such as partial obstructions, small bowel bacterial overgrowth, GI dysmotility (pseudoobstruction), or to malabsorptive disorders. Abdominal pain, nausea, and early satiety are reported associated GI symptoms; sleeping difficulty, headaches, and dizziness are also reported. Anxiety is a frequent comorbidity and may contribute to the behavior. Treatment is multidisciplinary and may include behavioral therapy and medications to relieve anxiety.

Functional Abdominal Pain Disorders

Functional Dyspepsia

Functional dyspepsia includes postprandial fullness and early satiety as well as epigastric pain or burning that is exclusive of defecation and not fully explainable by another or an underlying medical condition (Table 368.9). Subtypes may include *postprandial distress syndrome* (symptoms may preclude finishing a meal or be manifest by bloating, nausea, and excessive belching following a meal) as well as *epigastric pain syndrome* (epigastric pain/burning sufficient to preclude or disrupt normal activities, with pain not generalizable or localizable to other abdominal or chest regions, and not relieved by defecation or passage of flatus). An impaired gastric accommodation reflex, food allergy, delayed gastric emptying, or post viral gastroparesis has been implicated. Increased visceral hypersensitivity has also been suspected. The differential diagnosis includes GI etiologies of epigastric pain. Causes for concern can be guided by the family history and by the nature of symptoms including abdominal pain and other alarm features (Tables 368.10 and 368.11). Evaluation is based on symptoms. Initial treatment measures include a trial of diet (avoiding spicy foods, coffee, NSAID) and lifestyle changes if food triggers can be identified, and gastric acid reduction therapy. Assessment by a pediatric gastroenterologist and upper endoscopy/esophagogastroduodenoscopy are often performed. Further treatment with cyproheptadine to improve gastric accommodation or to decrease visceral hypersensitivity can be attempted. Use of amitriptyline or prokinetic medications can be considered. Electrical stimulation of the stomach (or percutaneous) is a potential option for patients refractory to standard therapy.

Table 368.9

Diagnostic Criteria* for Functional Dyspepsia

Must include 1 or more of the following bothersome symptoms at least 4 days/mo:
1. Postprandial fullness
2. Early satiation
3. Epigastric pain or burning not associated with defecation
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.
Within FD, the following subtypes are now adopted:
1. Postprandial distress syndrome includes bothersome postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching.
2. Epigastric pain syndrome, which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (a) burning quality of the pain but without a retrosternal component and (b) the pain commonly induced or relieved by ingestion of a meal but may occur while fasting.

[*] Criteria fulfilled for at least 2 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150(6):1456–1468, 2016 (p. 1460).

Table 368.10

Alarm Symptoms Usually Needing Further Investigations in Children With Chronic Abdominal Pain

- Pain that wakes up the child from sleep
- Persistent right upper or right lower quadrant pain
- Significant vomiting (bilious vomiting, protracted vomiting, cyclical vomiting, or worrisome pattern to the physician)
- Unexplained fever
- Genitourinary tract symptoms
- Dysphagia
- Odynophagia
- Chronic severe diarrhea or nocturnal diarrhea
- Gastrointestinal blood loss
- Involuntary weight loss
- Deceleration of linear growth
- Delayed puberty
- Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease

Table 368.11

Alarm Signs Usually Needing Further Investigations in Children With Chronic Abdominal Pain

- Localized tenderness in the right *upper* quadrant
- Localized tenderness in the right *lower* quadrant
- Localized fullness or mass
- Hepatomegaly
- Splenomegaly
- Jaundice
- Costovertebral angle tenderness
- Arthritis
- Spinal tenderness
- Perianal disease
- Abnormal or unexplained physical findings
- Hematochezia
- Anemia

Pediatric IBS

Pediatric IBS can be classified into 4 groups: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with constipation and diarrhea, and unspecified IBS. IBS includes findings of abdominal pain ≥ 4 days/mo associated with defecation and/or a change in frequency of stool from baseline and/or a change in form/appearance of stool (Table 368.12). It is noteworthy that pain does not resolve following resolution of constipation; if it does, it is then reclassified as functional constipation. In fact, IBS-C is often confused with functional constipation. IBS cannot be explained by another or underlying medical condition. The pathophysiology of IBS is thought to involve the brain-gut axis and includes a psychosocial stressor component. Visceral hypersensitivity may be attenuated or amplified by psychosocial stressors. Abdominal or rectal pain may occur. A *postinfectious* IBS phenomenon is known to occur in children, adolescents, and adults and may be driven by inflammatory cytokines. Perturbations in the intestinal microbiota or by dysbiosis may be coincident, with causality or consequence not yet established. The GI differential diagnosis includes anatomical, infectious, inflammatory, and motility disorders as well as conditions associated with malabsorption. Differentiation between those GI disorders and IBS is guided by the history and physical, and markers of inflammation particularly in the stool such as fecal calprotectin are clinically useful (see Tables 368.10 and 368.11). Management of symptoms can include dietary modification to reduce or restrict foods that may provoke symptoms or cause gas (see fiber section and FODMAPS [fermentable oligo-di-monosaccharides and polyols] discussion Chapter 57). Altering microbiota by use of probiotics has been effective; drug therapy for IBS is noted in Table 368.13 . Peppermint oil has been shown to reduce pain in children with IBS. Cognitive behavioral therapy is important to identify possible psychosocial stressors and to help identify coping mechanisms. Preliminary data suggests that transcutaneous neurostimulation may also be of value.

Table 368.12

Diagnostic Criteria* for Irritable Bowel Syndrome

Must include all of the following:

1. Abdominal pain at least 4 days/mo associated with one or more of the following:
    a. Related to defecation
    b. A change in frequency of stool
    c. A change in form (appearance) of stool
2. In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
3. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

* Criteria fulfilled for at least 2 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150(6):1456–1468, 2016 (p. 1461).

Table 368.13

Recommendations for Treatment of Irritable Bowel Syndrome

RECOMMENDATIONS FOR TREATMENT OF IBS
• Mild symptoms often respond to dietary changes. • Antispasmodics can be used as needed for abdominal pain or postprandial symptoms. • Antidepressants can improve abdominal pain and global symptoms. They may be considered for patients with moderate to severe symptoms.
IBS WITH CONSTIPATION (IBS-C)
• Fiber may relieve constipation in patients with mild symptoms. • Polyethylene glycol can increase the frequency of bowel movements, but may not improve overall symptoms or abdominal pain. • Lubiprostone or linaclotide can be tried in patients whose symptoms have not responded to polyethylene glycol.
IBS WITH DIARRHEA (IBS-D)
• Taken as needed, loperamide can reduce postprandial urgency and stool frequency, but it does not improve global symptoms. • Rifaximin and eluxadoline have been modestly more effective than placebo in relieving symptoms. • Alosetron should be reserved for women with severe, chronic IBS-D that is unresponsive to other drugs.

IBS , Irritable bowel syndrome.

From Drugs for irritable bowel syndrome, *The Medical Letter* 58(1504):121–126, 2016 (p. 121).

Abdominal Migraine

Abdominal migraine shares some features with cyclic vomiting syndrome. Stereotypical patterns and symptoms afflict the patient, and are typically of acute onset, intense, lasting for at least an hour, being either periumbilical or generalized, and usually debilitating during a bout (Table 368.14). Episodes can include anorexia, nausea, emesis, headaches, photophobia, and pallor. Episodes are separated by weeks to months, with bouts occurring over at least a 6-mo period. Between bouts, patients return to baseline functioning and are symptom free. *Triggers* include sleep hygiene disruption, fatigue, travel, and are usually alleviated by sleep. The differential diagnosis includes anatomical, infectious, or inflammatory conditions, as well as hepatobiliary and pancreatic disorders, neurological and metabolic conditions, and psychiatric disorders. Anatomical obstruction of the GI or urological tract should be included in the differential diagnosis. Preventing exposure to known triggers once identified is important.

Similar to prophylaxis for cyclic vomiting syndrome, cyproheptadine, propranolol, and amitriptyline may be effective. Oral pizotifen (antiserotonin, antihistamine) is an effective prophylactic agent. Anti-migraine therapies such as triptans may be effective in aborting bouts. This disorder shares many features with both cyclic vomiting syndrome and migraine headaches and may evolve into migraine headaches in adulthood.

Table 368.14

Diagnostic Criteria* for Abdominal Migraine

Must include all of the following occurring at least twice:

1. Paroxysmal episodes of intense, acute periumbilical, midline, or diffuse abdominal pain lasting 1 hr or more (should be the most severe and distressing symptom)
2. Episodes are separated by weeks to months.
3. The pain is incapacitating and interferes with normal activities
4. Stereotypical pattern and symptoms in the individual patient
5. The pain is associated with 2 or more of the following:
    a. Anorexia
    b. Nausea
    c. Vomiting
    d. Headache
    e. Photophobia
    f. Pallor
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

* Criteria fulfilled for at least 6 mo before diagnosis.

From Hyams JS, Di Lorenzo C, Saps M, et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150(6):1456–1468, 2016 (p. 1462).

Functional Abdominal Pain Not Otherwise Specified

Functional abdominal pain not otherwise specified occurs at least 4 times/mo with either intermittent or continuous abdominal pain not associated with a particular activity or coincident to *another physiologic event* such as menses or eating, cannot be explained by any other or underlying medical condition, and is of ≥2 mo duration. In many ways, it is a FGID of exclusion, as it does not meet criteria for IBS, functional dyspepsia, or abdominal migraine. Psychosocial stressors may play a role. There may be increased coincidence with postural orthostatic hypotension. Behavioral approaches may be helpful to identify and manage stressors and exacerbators.

Functional Defecation Disorders

Functional Constipation

Functional constipation in children and adolescents may have onset revolving around a social stressor, change in social situation, and peaks at the time of toilet training, when withholding behaviors emerge (Table 368.15). Encopresis may occur without sensation if the rectum is chronically distended sufficiently. Anorexia, abdominal distention, and pain are often coincident. The diagnosis is based on medical history and physical examination, including digital rectal examination. An abdominal x-ray is not required to make the diagnosis if a digital rectal examination can be performed to appreciate the fecal mass. The differential diagnosis for constipation in children and adolescents is similar to that as for infants and toddlers and is the approach to the evaluation and management of constipation (see Table 368.6). Management includes disimpaction followed by dietary and lifestyle approaches, osmotic laxatives to soften stools, and behavioral approaches similar to those employed for younger children discussed previously (Chapter 358.3).

Table 368.15

Diagnostic Criteria for Functional Constipation in Children With Chronic Abdominal Pain

Must include 2 or more of the following occurring at least once per week for a minimum of 1 mo with insufficient criteria for a diagnosis of irritable bowel syndrome:
1. Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 yr
2. At least 1 episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large diameter stools that can obstruct the toilet
After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

From Hyams JS, Di Lorenzo C, Saps M, et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 150(6):1456–1468, 2016 (p. 1464).

Nonretentive Fecal Incontinence

Nonretentive fecal incontinence occurs in the setting of not having fecal retention, occurring in inappropriate settings for a specific society and culture, without evidence of another or underlying medical condition, and occurring for ≥1 mo in a child of ≥4 yr of age. These patients otherwise have normal defecatory patterns and function, differentiating and distinguishing them from functional constipation. An emotional disturbance or disorder should be suspected in these cases. A thorough medical history and physical examination are required to fully appreciate what factors are involved in this condition. A rectal examination is important to differentiate this condition from functional constipation and encopresis. Given the significant comorbidity of behavior and emotional axis issues, involvement of behavioral health professionals is essential to the evaluation and management of this condition.

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CHAPTER 369

Cyclic Vomiting Syndrome

Asim Maqbool, B U.K. Li, Chris A. Liacouras

Cyclic vomiting syndrome (CVS) is an idiopathic disorder manifested as episodic vomiting, usually of sudden onset and high intensity/frequency (4/hr:12-15 episodes/day) of vomiting, with eventual resolution and return to a normal baseline between attacks. Typical bouts last for 24-48 hr, and usually respond promptly to hydration. To meet the criteria for CVS, identifiable organic disorders are excluded following an appropriate workup (Table 369.1).

Table 369.1

Consensus Definition for Diagnostic Criteria and Red Flags for Cyclic Vomiting Syndrome

DIAGNOSTIC CRITERIA
• Episodic (≥2 or more) attacks of intense nausea and paroxysmal vomiting lasting hours to days within a 6-mo period
• Stereotypical pattern and symptoms in the individual patient
• Episodes are separated by weeks to months
• Return to baseline between episodes
• Not attributable to another disorder
RED FLAGS
• Bilious emesis, abdominal tenderness, and/or severe abdominal pain
• Attacks precipitated by an intercurrent illness, fasting, and/or a high protein meal
• Neurological abnormalities (mental status changes, ophthalmic abnormalities asymmetry/focal changes, ataxia)
• Atypical pattern or progression/deterioration from a typical presentation for the individual patient to a more continuous or chronic pattern

Modified from the Rome IV Criteria: Li BU, Lefevre F, Chelimsky GG, et al: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome, *J Pediatr Gastroenterol Nutr* 47(3):379–393, 2008.

The prevalence of CVS in children is estimated at ~2% in predominantly Caucasian populations, although it does occur in those of African or Asian descent, and Hispanic ethnicity. There is a slight female predominance. The median age of onset is 5 yr, but it can begin in infancy and adolescence. Typically, there is a delay of 2.5 yr in making the diagnosis despite multiple episodes and emergency room visits. The natural history of CVS is that most children outgrow it during preadolescence or adolescence, and of those, many will develop migraines. There are also later pediatric-onset (mean age 13) and adult-onset (mean age 32) subgroups indicating that in a minority it can begin or persist in adulthood.

One key clinical feature of CVS is its consistent and stereotypical pattern of presentation within individuals. Typically, symptoms start at the same time, often during early morning hours, lasting the same duration and demonstrating identical autonomic symptoms of pallor and listlessness, unrelenting nausea, abdominal pain, and in less than half, headaches and photophobia. CVS bouts occur at a minimum 5 times, or 3 times over a 6-mo period. About half of cases occur on a cycle as often as monthly; some cycle as infrequently as every 3-4 mo. The other patients have unpredictable sporadic bouts that may be associated with a specific trigger. Potential triggers include infectious illnesses, stress and especially excitement (holidays), sleep deprivation (sleepovers), dietary triggers (chocolate, monosodium glutamate), food allergy, onset of menses, and weather changes. Typically, vomiting bouts are particularly intense, with greater than 4 bouts of emesis per hour at the peak, and can include gastric contents or frequent dry heaves. While most attacks last 2 days, an episode can last anywhere from hours and rarely up to 10 days. CVS attacks are debilitating, often necessitating IV rehydration, and resulting in hospitalization. Seasonal variation apparently occurs in approximately a third of patients, with more attacks in winter, fewer during summer. In some adolescent patients, a *coalescent form* develops with daily nausea between episodes of emesis (which becomes less frequent).

Multiple *comorbid* disorders can further comprise quality of life between episodes; these include anxiety, constipation-predominant irritable bowel syndrome, chronic fatigue or limited stamina, sleep disorders, postural orthostatic tachycardia syndrome, daily nausea, and complex regional pain syndrome.

In all cases of CVS, an underlying causative etiology (anatomical, infectious, inflammatory, neoplastic, and metabolic or endocrine) cannot be identified. There is typically a positive family history of migraines in children with CVS; attacks of both conditions share many clinical features. Although the pathophysiology is not fully known, there is suggestive evidence that an overresponsive hypothalamic-pituitary-adrenal axis (including corticotropin-releasing factor), autonomic nervous system dysregulation (sympathetic predominance), mitochondrial dysfunction (16519T and 3010A), and nuclear mutations *(RYR2)* may play contributory roles. Although the role of cannabis is unknown in CVS, *cannabis-induced hyperemesis syndrome* shares many features with CVS, including the relief of symptoms by hot showers (Chapter 140.3).

Patients with chronic vomiting should always be evaluated for potential etiologies other than CVS. The differential diagnosis includes GI anomalies (malrotation, duplication cysts, choledochal cysts, recurrent intussusceptions), CNS disorders (neoplasm, epilepsy, vestibular pathology), nephrolithiasis, cholelithiasis, hydronephrosis, metabolic-endocrine disorders (urea cycle, mitochondrial disorders, fatty acid metabolism, Addison disease, porphyria, hereditary angioedema, familial Mediterranean fever), chronic appendicitis, and inflammatory bowel disease. Laboratory evaluation is based on a careful history and physical examination and may include, if indicated, endoscopy, contrast GI radiography, brain MRI, and metabolic studies (lactate, organic acids, ammonia). Bilious emesis usually suggests a small bowel obstruction and is considered a red flag; however, children with CVS may have bile stained emesis. A tender abdomen is also unusual for CVS and warrants further workup. Acute and chronic appendicitis can mimic CVS. Prior abdominal surgery may increase risk for adhesion-related partial bowel obstructions (see Table 369.1).

Non-gastrointestinal causes of frequent vomiting include renal, metabolic, endocrine, and neurological disorders. Renal abnormalities to consider include acute or chronic ureteropelvic junction (UPJ) obstruction presenting with hydronephrosis (Dietl crisis) and nephrolithiasis. The clinician must also consider metabolic disorders, especially in the infant or toddler less than 2 yr of age. Fasting or high protein meals that provoke emesis raise a red flag for metabolic disorders, such as disorders of fatty acid oxidation, organic acidemias, or partial ornithine transcarbamylase deficiency. Acute intermittent porphyria can present in the adolescent triggered by alcohol or medications. Endocrine disorders, including diabetic ketoacidosis, Addison disease, and pheochromocytoma, can mimic CVS episodes. Although an atypical presentation, CNS tumors can have episodic vomiting and papilledema; altered mental status and focal neurological findings are red flags requiring neuroimaging. Pregnancy can present with CVS-like symptoms.

Children who meet the diagnostic criteria for CVS and have no red flags should have simple screening tests for electrolyte abnormalities, acidosis, hypoglycemia, and renal dysfunction during episodes, and an UGI radiograph to exclude malrotation. Presenting with gastrointestinal (bilious emesis, abdominal tenderness), metabolic (fasting or meal-induced), and neurological (papilledema, altered mental status) red flags warrants further evaluation (see Table 369.1).

In the management of acute episodes, early and aggressive hydration (especially with dextrose) may shorten episodes in addition to correcting fluid losses. Reducing extraneous sensory stimulation, similar to the management approach for migraines, may also be beneficial (Table 369.2). Regardless of intervention, episodes will eventually spontaneously resolve with return to a normal baseline. Triptans can be used as an *abortive medication* in patients with a family history of migraines, at the onset of symptoms. Ondansetron may reduce nausea and emesis. Sedation may reduce severity or stop a CVS episode; drugs include antihistamines such as diphenhydramine and promethazine. Lorazepam or rectal diazepam can be also used. These measures are empiric; a lack of evidence base limits our understanding of efficacy. For rare but severe refractory cases, general anesthetics have been used. A dramatic change in presentation of attacks suggests a red flag such as acute hydronephrosis or small bowel obstruction from volvulus.

Table 369.2

Supportive Care and Abortive Treatment Approaches in Cyclic Vomiting Syndrome

SUPPORTIVE CARE		
Fluid and electrolyte management	Dextrose containing fluid (D10) and normal saline as a single infusion or as a Y infusion	
Nutrition	• Resume enteral nutrition as soon as possible. • If unable to tolerate enteral nutrition and meets criteria, start parenteral nutrition after 3-4 days.	
Medications	Antiemetics	Ondansetron • 0.3-0.4 mg/kg/dose IV every 4-6 hr (maximum 16 mg/dose) • Side effect: constipation, QTc prolongation Alternative: Granisetron
	Sedatives	Diphenhydramine • 1-1.25 mg/kg/dose IV every 6 hr Lorazepam 0.05-0.1 mg/kg/dose IV every 6 hr • Side effects: respiratory depression, hallucinations Chlorpromazine 0.5-1 mg/kg/dose every 6-8 hr + diphenhydramine IV
	Analgesics	Ketorolac 0.5 mg/kg/dose IV every 6 hr (maximum dose 30 mg)
Treatment of specific signs and symptoms	Epigastric pain • Acid reduction therapy with an H_2 RA or a PPI Diarrhea	

	• Antidiarrheals Hypertension • Short-acting ACE inhibitors such as captopril
Treatment of specific complications	• Dehydration and electrolyte deficits: replace calculated deficits • Metabolic acidosis: determine etiology and rectify • SIADH: restrict free water intake • Hyperemesis: IV acid reduction • Weight loss: enteral or parenteral nutrition
ABORTIVE CARE	
Antimigraine (triptans)	Sumatriptan • 20 mg intranasally at episode onset • Side effects: neck pain/burning, coronary vasospasm • Contraindications: basilar artery migraine
RECOVERY AND REFEEDING	
• Feed ad libitum when the child declares that the episode is over	

Medications listed above are for off-label use.

Modified from Li BU, Lefevre F, Chelimsky GG, et al: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome, *J Pediatr Gastroenterol Nutr* 47(3):379–393, 2008.

Prophylactic management begins with lifestyle measures (maintenance fluid intake, adequate calories, sleep hygiene, and exercise), including avoidance of known triggering foods (allergens, chocolate, aged cheese, monosodium glutamate; Table 369.3). Recommendations for prophylactic regimens include cyproheptadine in patients less than 5 yr of age and amitriptyline in patients ≥5 yr; propranolol serves as a secondary agent in both age groups. Supplements such as coenzyme Q10 and L-carnitine have occasionally been reported to be useful adjuncts. When standard care fails, the addition of anticonvulsants such as topiramate has been implemented. For those with catamenial CVS, low-dose estrogen oral contraceptives or Depo-Provera may prevent episodes. Treatment of *comorbid disorders* , especially anxiety (cognitive behavioral therapy, antianxiety agents) and postural orthostatic tachycardia syndrome (fluids, salt, fludrocortisone), may be needed for effective management of CVS.

Table 369.3

Prophylactic Lifestyle Changes and Pharmacological Options for Cyclic Vomiting Syndrome

LIFESTYLE MEASURES	
Reassurance and anticipatory Guidance	• Episodes are not intentional. • The natural history of CVS is that it will resolve with time.
Avoidance of triggers	• Identify dietary triggers (“vomit diary”) and avoid precipitating factors. • Triggering foods may include chocolate, cheese, monosodium glutamate. • Fasting a common trigger

	• Excitement a potential trigger • Excessive activity/exhaustion • Avoid sleep deprivation and practice good sleep hygiene	
Managing triggers	• Provide supplemental energy as carbohydrates for fasting induced episodes. • Provision of snacks between meals, before sleep and before exertion	
Migraine headache type lifestyle interventions	• Aerobic exercise and avoidance of overexertion • Regular mealtime schedule—avoid skipping meals • Avoid/moderate caffeine intake	
PROPHYLACTIC PHARMACOLOGICAL APPROACHES		
	Age <5 yr	Age ≥5 yr
	Antihistamines: • Cyproheptadine • 0.25-0.5 mg/kg/day in 2 daily divided doses or as a single dose qhs • Side effects of increased appetite, weight gain, and sedation • Pizotifen β-blockers: (2nd choice) • Propranolol • 0.25-1 mg/kg/day, most often 10 mg 2-3×/day. • Side effects include lethargy and reduced exercise tolerance. • Contraindicated in asthma, diabetes, heart disease, depression • Taper over 1-2 wk to discontinue	Tricyclic antidepressants: • Amitriptyline • Begin at 0.25-0.5 mg/kg qhs and increase weekly by 5-10 mg until achieve 1-1.5 mg/kg • Monitor EKG for prolonged QTc interval at baseline before initiation and 10 days after peak dose achieved • Side effects: constipation, sedation, arrhythmias, behavioral changes Alternatives: nortriptyline β-blockers: (2nd choice): • Propranolol Other agents: Anticonvulsants: • Phenobarbital 2 mg/kg qhs • Side effects: sedation, cognitive impairment Alternatives: • Topiramate, valproic acid, gabapentin, levetiracetam
DIETARY SUPPLEMENTS		
	• L-Carnitine 50-100 mg/kg/day divided 2-3×/day, maximum dose of 2 g 2×/day • Coenzyme Q10 200 mg 2×/day divided 2-3×/day, maximum dose 100 mg 3×/day	

Medications listed above are for off-label use. *CVS* , cyclic vomiting syndrome.

Modified from Li BU, Lefevre F, Chelimsky GG, et al: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome, *J Pediatr Gastroenterol Nutr* 47(3):379–393, 2008.

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CHAPTER 370

Acute Appendicitis

John J. Aiken

Acute appendicitis remains the most common acute surgical condition in children and a major cause of childhood morbidity and health care costs, mostly associated with complicated/perforated appendicitis (PA). The peak incidence of acute appendicitis occurs in children in the second decade, and approximately 100,000 children are treated in children's hospitals for appendicitis each year. The broad spectrum of clinical presentation in acute appendicitis has been associated with significant practice variation in evaluation, diagnostic measures, and treatment of abdominal pain and suspected appendicitis. The traditional strategy of the liberal use of computed tomography (CT) to avoid misdiagnosis and early surgery to avoid progression to perforation has lacked validation in large reviews and resulted in high negative appendectomy rates and excessive radiation exposure. Perforation rates have remained around 40% and negative appendectomy rates as high as 10–20% in the past several decades. In current practice, most centers have adopted clinical practice guidelines (CPGs) combining history, physical examination findings, laboratory data, and appendicitis risk scoring systems to standardize care, improve diagnostic accuracy and outcomes, and direct cost-conscious resource utilization. Appendiceal ultrasound has emerged as a highly sensitive and specific imaging modality for diagnosis and led to a significant decrease in the use of CT and radiation exposure in the initial evaluation of children presenting with abdominal pain and possible suspected appendicitis. While prompt appendectomy remains the standard treatment in acute appendicitis, advances in imaging techniques, improved antibiotic regimens, increased use of percutaneous drainage procedures by interventional radiologists, and emerging data on high success rates with initial antibiotic treatment alone have led to an increase in the initial nonoperative management of both simple and complicated (abscess, phlegmon) appendicitis. Laparoscopic appendectomy (LA, minimally invasive technique) has emerged as the preferred surgical approach for both simple and PA, with an open surgical approach reserved as an alternative for selected cases or when attempted LA is technically difficult and/or deemed unsafe.

Epidemiology

The incidence of acute appendicitis increases with age, from a rate of 1-2 per 10,000 children from birth to 4 yr of age, to a rate of 19-28 per 10,000 children younger than age 14 yr annually. Children have a lifetime risk of 7–9% and appendicitis is diagnosed in 1–8% of children presenting to the emergency department (ED) for evaluation of abdominal pain. Appendicitis is most common in older children, with peak incidence between the ages of 10 and 18 yr; it is rare in children younger than 5 yr of age (<5% of cases) and extremely rare (<1% of cases) in children younger than 3 yr of age.

Infants with appendicitis are often misdiagnosed with sepsis and because of the diagnostic delay, they present in advanced stages of the disease. Most infant cases are primary, but some may be associated with Hirschsprung disease, cystic fibrosis, inguinal hernia, prematurity, meconium plug syndrome, or complex multiorgan syndromes.

Incidence rates for acute appendicitis are higher in males, whites, and Hispanics compared to African Americans and Asians; Hispanics, Asians, and patients with nonprivate insurance have higher odds of perforation. There is a peak incidence of appendicitis in the third quarter between July and September and the incidence is higher in the West and North Central regions compared with the Mid-Atlantic States. The reasons for these ethnic, geographic, and socioeconomic disparities remain unclear with possibilities including cultural differences in interaction with the medical system, limitations in access to care, or differences in disease progression by race.

Mortality is low (<1%), but morbidity remains high, mostly in association with PA. Up to 40% of children have PA at presentation, and perforation rates approach 90% in young children (<3 yr). Children with simple (nonperforated) appendicitis typically recover easily, with a low complication rate and rapid return to premorbid state and full activities. In contrast, PA is associated with substantial postoperative morbidity including readmission rates estimated at 12.8%, postoperative intraabdominal abscess rate ∼20%, surgical site infection (SSI) rate ∼20%, prolonged length of stay (LOS), need for prolonged antibiotic exposure, increased postoperative use of CT, and significant delay in return to wellness and normal activities. The Healthcare Cost and Utilization Project estimated that appendicitis with peritonitis accounted for 25,410 pediatric hospital admissions in 2012, with a mean LOS of 5.2 days and mean costs of $13,076.

Pathophysiology

The clinical entity of acute appendiceal inflammation followed by perforation, abscess formation, and peritonitis is most likely a disease of multiple etiologies, the final common pathway of which involves invasion of the appendiceal wall by bacteria. Genetic, environmental, and infectious etiologies (bacterial, viral, fungal, and parasitic) have all been implicated in acute appendicitis. Family history confers a nearly threefold increased risk for appendicitis. One pathway to acute appendicitis begins with luminal obstruction; inspissated fecal material, lymphoid hyperplasia, ingested foreign body, parasites, and tumors have been described. Obstruction of the appendiceal lumen initiates a progressive cascade involving increasing intraluminal pressure, lymphatic and venous congestion and edema, impaired arterial perfusion, ischemia of the appendiceal wall, bacterial proliferation and invasion of the wall, and necrosis. This sequence correlates with the clinical disease progression from simple appendicitis to gangrenous appendicitis and, thereafter, appendiceal perforation.

Because the appendix has the highest concentration of gut-associated lymphoid tissue (GALT) in the intestine, some have hypothesized that the appendix may have an immune function similar to that of the thymus or bursa of Fabricius. Submucosal lymphoid follicles, which can obstruct the appendiceal lumen, are few at birth but multiply steadily during childhood, reaching a peak in number during the teen years, when acute appendicitis is most common.

Enteric infection likely plays a role in many cases of acute appendicitis in association with mucosal ulceration and invasion of the appendiceal wall by bacteria. Bacteria such as *Yersinia* , *Salmonella*, and *Shigella* spp., and viruses such as infectious mononucleosis, mumps, coxsackievirus B, and adenovirus, are implicated. In addition, case reports demonstrate the occurrence of appendicitis from ingested foreign bodies, in association with carcinoid tumors of the appendix, *Ascaris* infestation and rarely, following blunt abdominal trauma. Children with cystic fibrosis have an increased incidence of appendicitis; the cause is believed to be the abnormal thickened mucus. Appendicitis in neonates is rare and warrants diagnostic evaluation for cystic fibrosis and Hirschsprung disease.

Appendectomy decreases the risk of ulcerative colitis and increases the risk of recurrent *Clostridium difficile-associated colitis.* Appendicoliths and appendicitis are more common in developed countries with refined, low-fiber diets than in developing countries with a high-fiber diet; no causal relationship has been established between lack of dietary fiber and appendicitis. In a large database analysis for genetic inheritability of appendicitis one locus had genome-wide significance, and a candidate gene *(PITX2)* was identified which was associated with a protective risk of appendicitis. A family history is associated with a nearly threefold increased appendicitis risk and genetic factors may account for 30% of appendicitis risk.

Clinical Features

Appendicitis in children has an immensely broad spectrum of clinical presentation; <50% of cases have the classic presentation. The signs and symptoms in acute appendicitis can vary depending on the timing of presentation, patient age, the abdominal/pelvic location of the appendix, and most importantly, individual variability in the evolution of the disease process. Children early in the disease process can appear well and demonstrate mild symptoms, minimal findings on physical examination, and normal laboratory studies, while those with perforation and advanced peritonitis can demonstrate severe illness with bowel obstruction, renal failure, and septic shock. Most patients with appendicitis demonstrate an insidious onset of illness characterized by generalized nonspecific malaise or anorexia in the first 12 hr, and a steady, escalating progression in severity of signs and symptoms over 2-3 days with increasing abdominal pain, vomiting, fever, and tachycardia; perforation is common beyond 48 hr of illness. Thus, the opportunity for diagnosis before perforation in acute appendicitis in children is most often brief (48-72 hr) and a high percentage of patients are perforated at presentation.

Abdominal pain is consistently the *primary* symptom in acute appendicitis; beginning shortly (hours) after the onset of illness. As with other visceral organs, there are no somatic pain fibers within the appendix; therefore, early appendiceal inflammation results in pain which is vague, poorly localized, unrelated to activity or position, often colicky, and periumbilical in location as a result of visceral inflammation from a distended appendix. Progression of the inflammatory process in the next 24 hr leads to involvement of the adjacent parietal peritoneal surfaces, resulting in somatic pain localized to the right lower quadrant (RLQ); *thus, the classic description of periumbilical mid-abdominal pain migrating to the RLQ. The position of the appendix is a critical factor affecting interpretation of presenting signs and symptoms and accurate diagnosis.* When the appendix is in a retrocecal or pelvic position, a slower progression of illness is typical and clinical presentation is likely to be delayed. Localized pain in the RLQ leads to spasm in the overlying abdominal wall muscles and now the pain is predictably exacerbated by movement. The child often describes marked discomfort with the bumpy car ride to the hospital, moves cautiously, and has difficulty getting onto the examining room stretcher. Nausea and vomiting occur in more than half the patients, and typically *follow* the onset of abdominal pain by several hours. Anorexia is a classic and consistent finding in acute appendicitis, but occasionally affected patients are hungry. Diarrhea and urinary symptoms are also common, particularly in cases of PA when there is likely inflammation near the rectum and possible abscess in the pelvis. Painful voiding may not be from dysuria, but pressure transmitted to an inflamed peritoneum. As it progresses, appendicitis is often associated with adynamic ileus, leading to the complaint of constipation and possible misdiagnosis.

Because enteric infections can cause appendicitis, diarrhea may be a manifestation and gastroenteritis may be the assumed diagnosis. In contrast to gastroenteritis, the abdominal pain in early appendicitis is *constant* (not cramping or relieved by defecation), the emesis may become bile stained and persistent, and the clinical course worsens steadily rather than demonstrating a waxing and waning pattern often seen in viral gastroenteritis. Fever is common in appendicitis and typically low-grade unless perforation has occurred. Most patients demonstrate at least mild tachycardia, likely secondary to pain and dehydration. The temporal progression of symptoms from vague, mild pain, malaise, and anorexia to severe localized pain, fever, and vomiting typically occurs rapidly (24-48 hr) in the majority of cases. If the diagnosis is delayed beyond 48 hr, perforation is likely (>65%). When several days have elapsed in the progression of appendicitis, patients typically develop signs and symptoms evidencing advanced disease, including worsening and diffuse pain, abdominal distension, and bilious emesis suggestive of developing small bowel obstruction. The retrocecal appendix can demonstrate symptoms suggestive of septic arthritis of the hip or a psoas muscle abscess.

A primary focus in the management of appendicitis is the avoidance of sepsis and the infectious complications leading to increased morbidity, mostly seen with PA.

Bacteria can be cultured from the serosal surface of the appendix before microscopic or gross perforation and bacterial invasion of the mesenteric veins (pylephlebitis) can result (rarely) in thrombosis and possible liver abscess or portal hypertension. A period after perforation of lessened abdominal pain and acute symptoms has been described, presumably with the elimination of pressure within the appendix. If, following perforation, the omentum or adjacent intestine is able to wall off the fecal contamination, the evolution of illness is less predictable and delay in presentation is likely. If perforation leads to diffuse peritonitis, the child generally has escalating diffuse abdominal pain and rapid development of toxicity evidenced by dehydration and signs of sepsis including hypotension, oliguria, acidosis, and high-grade fever. Young children have a poorly developed omentum and are often unable to control the spread of infection. Perforation and abscess formation with appendicitis can lead to intestinal fistula formation, scrotal cellulitis and abscess through a patent processus vaginalis (indirect inguinal hernia), or small bowel obstruction. The most likely diagnosis in children who present with signs and symptoms of mechanical small bowel obstruction who have not had prior abdominal surgery is complicated appendicitis.

Physical Examination

Although the hallmark of diagnosing acute appendicitis remains a careful and thorough history and physical examination, all clinicians know the arcane nature of acute appendicitis, the consistent or typical clinical features are not present in all patients, and the diagnosis can be a humbling experience even for the most experienced clinicians. A primary focus of the initial assessment is attention to the *temporal evolution* of the illness in relation to specific presenting signs and symptoms. In some patients, the diagnosis can be made on history and physical examination alone; in current practice the selective use of advanced imaging has improved diagnostic accuracy and resulted in significant progress in lowering of negative appendectomy rates.

Physical examination begins with inspection of the child's demeanor as well as the appearance of the abdomen. Because appendicitis most often has an insidious onset, children rarely present <12 hr from the onset of illness. Children with early appendicitis (18-36 hr) typically appear mildly ill and move tentatively, hunched forward and, often, with a slight limp favoring the right side. Supine, they often lie quietly on their right side with their knees pulled up to relax the abdominal muscles, and when asked to lie flat or sit up, they move cautiously and might use a hand to protect the RLQ. Early in appendicitis, the abdomen is typically flat; abdominal distention suggests more advanced disease characteristic of perforation or developing small bowel obstruction. Auscultation can reveal normal or hyperactive bowel sounds in early appendicitis, which are replaced by hypoactive bowel sounds as the disease progresses to perforation. *The judicious use of morphine analgesia to relieve abdominal pain does not change diagnostic accuracy or interfere with surgical decision making, and patients should receive adequate pain control.* Localized abdominal tenderness is the single most reliable finding in the diagnosis of acute appendicitis. McBurney described the classic point of localized tenderness in acute appendicitis, which is the junction of the lateral and middle thirds of the line joining the right anterior–superior iliac spine and the umbilicus, but the tenderness can also localize to any of the aberrant locations of the appendix. Localized tenderness is a later and less-consistent finding when the appendix is retrocecal in position (>50% of cases). In cases of an appendix localized entirely in the pelvis, tenderness on abdominal examination may be minimal. A gentle touch on the child's arm at the beginning of the examination with the reassurance that the abdominal examination will be similarly gentle can help to establish trust and increase the chance for a reliable and reproducible examination. The examination is best initiated in the left lower abdomen, so that the immediate part of the exam is not uncomfortable and conducted in a counterclockwise direction moving gently to the left upper abdomen, right upper abdomen, and, lastly, the right lower abdomen. This should alleviate anxiety, allow relaxation of the abdominal musculature, and enhance trust. The examiner makes several circles of the abdomen with sequentially more pressure. A soft, compressible, nontender abdominal wall is reassuring. In appendicitis, any abdominal wall movement, including coughing (Dunphy sign), may elicit pain. A consistent finding in acute appendicitis is guarding—rigidity of the overlying abdominal wall muscles in the RLQ. This rigidity may be voluntary, to protect the area of tenderness from the examiner's hand, or involuntary, if the inflammation has progressed to peritonitis causing spasm of the overlying muscle.

Abdominal tenderness may be vague or even absent early in the course of appendicitis and is often diffuse after rupture. Rebound tenderness and referred tenderness (Rovsing sign) are also consistent findings in acute appendicitis, but not always present. Rebound tenderness is elicited by deep palpation of the abdomen followed by the sudden release of the examining hand. This is often very painful to the child and has demonstrated poor correlation with peritonitis, so it should be avoided. Gentle finger percussion is a better test for peritoneal irritation. Similarly, digital rectal examination is uncomfortable and unlikely to contribute to the evaluation of appendicitis in most cases of appendicitis in children. Psoas and obturator internus signs are pain with passive stretch of these muscles. The psoas sign is elicited with active right thigh flexion or passive extension of the hip and typically positive in cases of a retrocecal appendix. The obturator sign is demonstrated by adductor pain after internal rotation of the flexed thigh and typically positive in cases of a pelvic appendix. Physical examination may demonstrate a mass in the RLQ representing an inflammatory mass (phlegmon) around the appendix or a localized intraabdominal abscess (fluid collection).

Appendicitis Risk Scoring Systems

Several risk scoring systems have become commonly used tools to promote standardization of the approach to the child with abdominal pain and suspected appendicitis. The clear aim is to maximize diagnostic accuracy in acute appendicitis, and guide imaging evaluation and resource utilization. They all combine the predictive value of consistent symptoms, physical examination findings, and laboratory data yielding a numerical score. The systems most widely utilized are the Alvarado score and the Pediatric Appendicitis Score (PAS). The PAS combines elements of history (migration of pain, anorexia, nausea, vomiting) with physical examination findings (RLQ tenderness, rebound tenderness, fever) and laboratory data (white blood cell [WBC] >10,000, polymorphonuclear neutrophils >75%) to assign a risk score in the low, intermediate, or high-risk range for acute appendicitis (Table 370.1). Scores of ≤4 suggest a very low likelihood of appendicitis, whereas scores ≥8 are highly sensitive and specific for appendicitis. Intermediate scores, between 4 and 7 on the PAS, are considered inconclusive and typically trigger advanced imaging studies. Targeted (appendiceal) ultrasound has demonstrated high sensitivity and specificity (∼90%) in the diagnosis of acute appendicitis in centers experienced with the technique and has become the initial imaging study of choice for suspected appendicitis. The notable benefits of ultrasound compared to CT scan include that it is well-tolerated, non-invasive, and lacks ionizing radiation exposure. CT is reserved for cases of nonvisualization of the appendix on ultrasound, or when the ultrasound findings are inconclusive.

Table 370.1

Pediatric Appendicitis Scores

FEATURE	SCORE
Fever > 38°C (100.4°F)	1
Anorexia	1
Nausea/vomiting	1
Cough/percussion/hopping tenderness	2
Right lower quadrant tenderness	2
Migration of pain	1
Leukocytosis > 10,000 (10^9 /L)	1
Polymorphonuclear-neutrophilia > 7,500 (10^9 /L)	1
Total	10

From Acheson J, Banerjee J: Management of suspected appendicitis in children, *Arch Dis Child Educ Pract Ed.* 95:9–13, 2010.

The use of appendicitis risk scoring systems, in conjunction with clinical judgment, have demonstrated high sensitivity and specificity for acute appendicitis (80–90%) and their application has reduced practice variability, improved diagnostic accuracy, decreased preoperative radiation exposure, and enabled efficient resource utilization—all important elements of current quality improvement and safety initiatives. Their greatest value to date appears to be in predicting patients that have a low likelihood of the diagnosis of appendicitis (negative predictive value) and can avoid imaging studies, and particularly ionizing radiation exposure.

Laboratory Findings

A variety of laboratory tests have been used in the evaluation of children with suspected appendicitis. Individually, none are very sensitive or specific for appendicitis, but collectively they can affect the clinician's level of suspicion and decision-making to proceed with pediatric surgery consultation, discharge, or imaging studies.

A complete blood count with differential and urinalysis are obtained. The leukocyte count in early appendicitis may be normal, and typically is only mildly elevated (11,000-16,000/mm^3) with a left shift as the illness progresses in the initial 24-48 hr. Whereas a normal WBC count never completely eliminates appendicitis, a count <8,000/mm^3 in a patient with a history of illness longer than 48 hr should be viewed as highly suspicious for an alternative diagnosis. The leukocyte count may be markedly elevated (>20,000/mm^3) in PA and rarely in nonperforated cases; a markedly elevated WBC count, other than in cases of advanced PA, should raise suspicion of an alternative diagnosis. Urinalysis often demonstrates a few white or red blood cells as a result of the proximity of the inflamed appendix to the ureter or bladder, but it should be free of bacteria. The urine is often concentrated and contains ketones from diminished oral intake and vomiting. Gross hematuria is uncommon, and in association with purpuric skin lesions and arthritis may indicate Henoch-Schönlein purpura.

Electrolytes and liver chemistries are generally normal unless there has been a delay in diagnosis, leading to severe dehydration and/or sepsis. Amylase and liver enzymes are only helpful to exclude alternative diagnoses such as pancreatitis and cholecystitis and are not commonly obtained if appendicitis is the strongly suspected diagnosis. C-reactive protein (CRP) increases in proportion to the degree of appendiceal inflammation. It has not demonstrated high sensitivity or specificity in the diagnosis of appendicitis; some studies have demonstrated an association between disease severity (PA and abscess formation) and elevated CRP levels. In this context, CRP may have a role in identifying patients with complicated appendicitis, which may be managed initially nonoperatively with antibiotics and drainage of fluid collections.

Imaging Studies

Following a thorough initial evaluation including history, physical examination, review of vital signs, and laboratory studies, if the diagnosis is uncertain, radiographic studies can substantially improve diagnostic accuracy.

Plain Radiographs

In the majority of cases, appendiceal ultrasound and CT scan have become the predominant studies in inconclusive cases of acute appendicitis. Plain abdominal radiographs may be helpful in rare select cases of abdominal pain/suspected appendicitis. Plain abdominal x-rays may demonstrate several findings suggestive of acute appendicitis, including sentinel loops of bowel and localized ileus, scoliosis from psoas muscle spasm, a colonic air–fluid level above the right iliac fossa (colon cutoff sign), an RLQ soft tissue mass, or a calcified appendicolith (5–10% of cases); they are normal in 50% of patients, have a low sensitivity, and are not generally recommended (Fig. 370.1). Plain films are most helpful in evaluating complicated cases in which small bowel obstruction or free air is suspected.

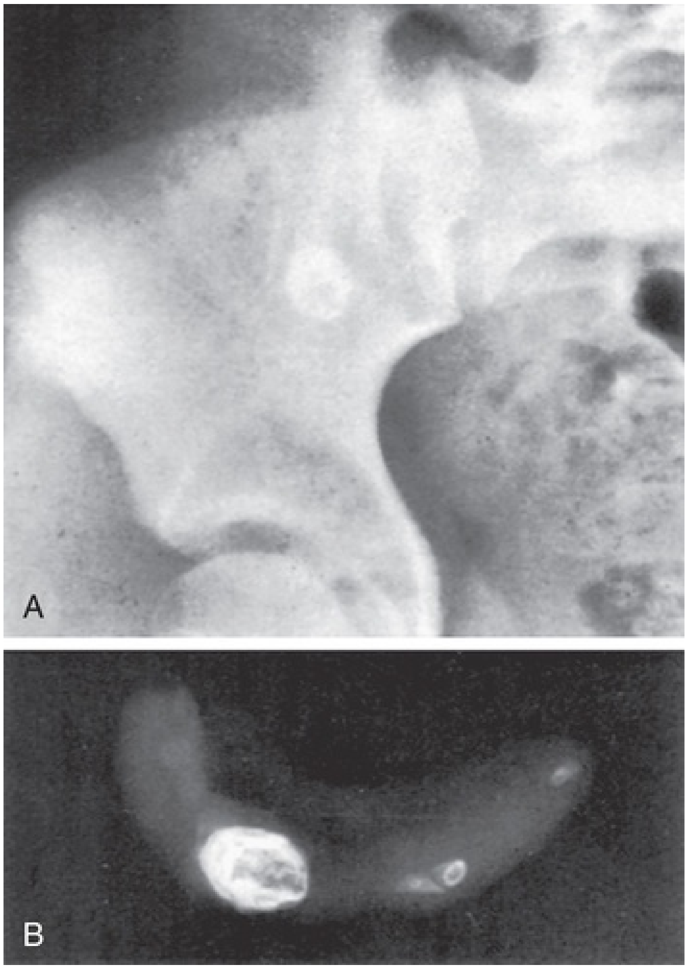

FIG. 370.1 Calcified appendicoliths are seen in a coned-down anteroposterior view of the right lower quadrant **(A)** and in the resected appendix of a 10 yr old girl with acute appendicitis **(B)** . (From Kuhn JP, Slovis TL, Haller JO: *Caffrey's pediatric diagnostic imaging,* vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1682.)

Ultrasound

Ultrasound has emerged as the first-choice tool for children requiring an imaging study in the evaluation of suspected acute appendicitis. Ultrasound has demonstrated sensitivity and specificity approaching 90% in pediatric centers experienced with the technique, and has substantial advantages including low cost, ready availability, rapidity, and avoidance of sedation, contrast agents, and radiation exposure. Ultrasound can be particularly helpful in adolescent females, a group with a high negative appendectomy rate (normal appendix found at surgery), because of its ability to evaluate for ovarian pathology without ionizing radiation. Graded abdominal compression is used to displace the cecum and ascending colon and identify the appendix, which has a typical target appearance (Fig. 370.2). The ultrasound criteria for appendicitis include wall thickness ≥6 mm, luminal distention, lack of compressibility, a complex mass in the RLQ, or an appendicolith. The visualized appendix usually coincides with the site of localized pain and tenderness. In addition, ultrasound may identify PA on *initial evaluation* ; initial management of PA has increasingly moved toward percutaneous drainage procedures, broad spectrum antibiotics, and nonoperative treatment. An enlarged appendix (>6 mm), hyperemia, noncompressibility of the appendiceal wall, localized tenderness, and associated mesenteric fat stranding or fluid are all consistent with acute appendicitis. Findings that suggest advanced appendicitis on ultrasound include asymmetric wall thickening, abscess formation, associated free intraabdominal/pelvic fluid, surrounding tissue edema, and decreased local tenderness to compression. *The main limitation of ultrasound is an inability to visualize the appendix, which is reported in 25–60% of cases*. It has been postulated that a normal appendix must be visualized to exclude the diagnosis of appendicitis by ultrasound; however, one report concluded that in patients with a nonvisualized appendix on ultrasound imaging and no evidence of secondary inflammatory changes, the likelihood of appendicitis was <2%. Certain conditions predictably decrease the sensitivity and reliability of ultrasound for appendicitis, including obesity, bowel distention, and uncontrolled pain.

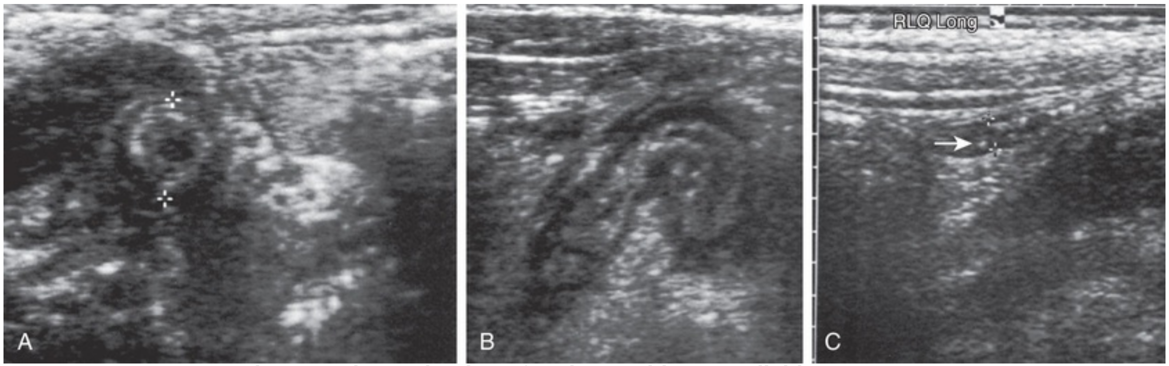

FIG. 370.2 Ultrasound examination of patients with appendicitis. A, Transverse ultrasound scan of the appendix demonstrates the characteristic “target sign.” In this case, the innermost portion is sonolucent, compatible with fluid or pus. B, Longitudinal view of another patient demonstrates the alternating hyperechoic and hypoechoic layers with an outermost hypoechoic layer, suggesting periappendiceal fluid. C, Longitudinal ultrasound scan of the right lower quadrant demonstrates a dilated, non-compressible appendix. The bright echo within the appendix represents an appendicolith with acoustic shadowing *(arrow).* (From Kuhn JP, Slovis TL, Haller JO: *Caffrey's pediatric diagnostic imaging,* vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1684.)

Computed Tomography

CT scan has been the gold standard imaging study for evaluating children with suspected appendicitis, and has sensitivity of 97%, specificity 99%, positive predictive value 98%, and negative predictive value 98% (Figs. 370.3 and 370.4). The advantages of CT imaging include ready availability, rapid acquisition time, and lack of operator dependency. CT carries the significant negative effects of exposure of children to ionizing radiation and increased costs. The exam can be performed using intravenous and enteral (oral or rectal) contrast; however, the administration of enteral contrast has several drawbacks including increasing abdominal distension, risk of emesis and aspiration, and increasing radiation exposure without demonstrable improvement in accuracy of diagnosis. The use of oral contrast should be reserved for patients in whom alternative diagnoses are suspected, particularly Crohn disease. Because the finding of fat stranding in surrounding tissues is a key component of CT evaluation for appendicitis, CT is less reliable in thin children with minimal body fat.

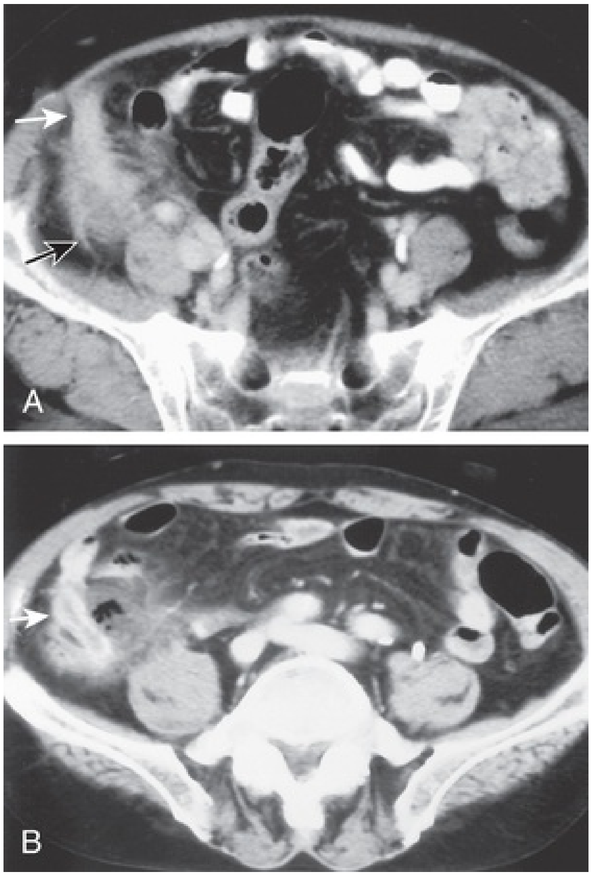

FIG. 370.3 **A,** Phlegmon *(open arrow)* is noted around the enlarged appendix *(solid arrow)* in perforated appendicitis. **B,** Extraluminal air is shown adjacent to the wall-enhanced appendix *(arrow)* in perforated appendicitis. (From Yeung KW, Chang MS, Hsiao CP: Evaluation of perforated and non-perforated appendicitis with CT, *Clin Imaging* 28(6):422–427, 2004.)

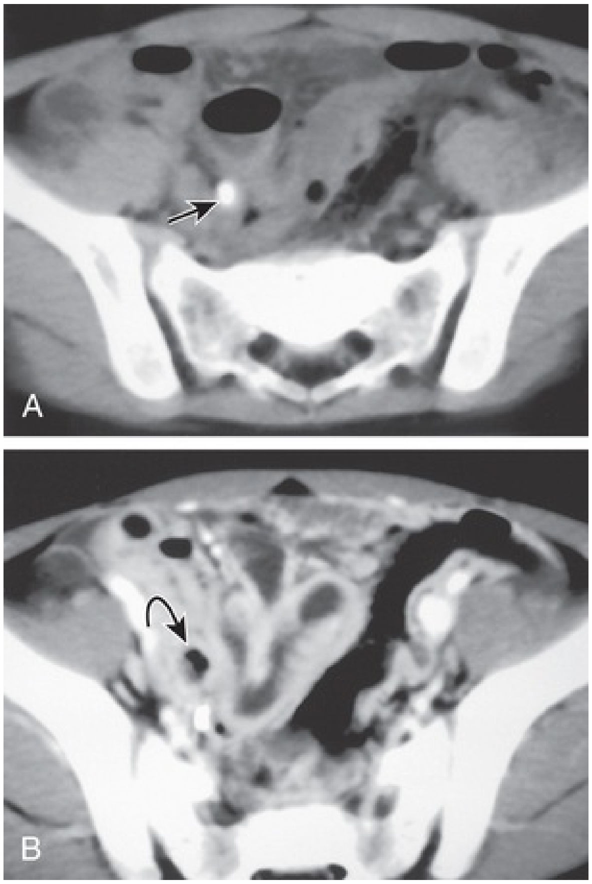

FIG. 370.4 **A,** Precontrast-enhanced CT reveals an appendicolith *(arrow)* in perforated appendicitis. **B,** Postcontrast-enhanced CT (1 cm below the level in **A**) reveals intraluminal air in the appendix *(curved arrow)* associated with ileal wall enhancement in perforated appendicitis. (From Yeung KW, Chang MS, Hsiao CP: Evaluation of perforated and non-perforated appendicitis with CT, *Clin Imaging* 28(6):422–427, 2004.)

The avoidance of enteral contrast, targeted CT imaging, and the use of pediatric specific protocols can significantly lower radiation dosages without sacrificing diagnostic accuracy. The use of appendicitis risk scoring systems, in conjunction with CPGs, and increasing experience with appendiceal ultrasound have led to a decreased use of CT scans (<6.6% in most reports), without negatively affecting time to appendectomy or negative appendectomy rates.

Magnetic Resonance Imaging and White Blood Cell Scans

MRI is at least equivalent to CT in diagnostic accuracy for appendicitis and does not involve ionizing radiation; however, its use in the evaluation of appendicitis is limited because it is less available, associated with higher costs, often requires sedation, and does not offer equivalent access for drainage of fluid collections. MRI may prove most useful in adolescent females when ultrasound imaging is equivocal. Radionuclide-labeled WBC scans have also been used in some centers in evaluating atypical cases of possible appendicitis in children and demonstrated a high sensitivity (97%) but only modest specificity (80%).

Diagnosis and Treatment

Acute appendicitis is believed to be a time-sensitive condition, thus, any delay in diagnosis or treatment may lead to an increased risk of perforation and its attendant morbidity. The misdiagnosis of appendicitis is second only to meningitis as a cause of medical malpractice suits in pediatric emergency care. A careful history and physical examination remains primary in the initial assessment of a child presenting with abdominal symptoms. The classic history in acute appendicitis, although possibly not most common, is a 24-hr history of diffuse mid-abdominal pain which migrates and becomes localized to the RLQ. Patients should have a WBC count with differential analysis, as this is a component of most appendicitis risk scoring systems. A urinalysis is also typically obtained and a pregnancy test in appropriately selected patients. CPGs have become common practice in many centers for evaluation of patients with abdominal pain and suspected appendicitis to reduce practice variability and improve diagnostic accuracy and resource utilization. CPGs have been shown to have a high positive and negative predictive value (∼95%), and to decrease both LOS and costs without increasing morbidity or complications. These guidelines combine initial history, physical examination, and laboratory data with predictive risk scoring systems to cohort patients into low, intermediate, and high risk for the diagnosis of acute appendicitis. In general, low-risk patients can be discharged without imaging studies, high-risk patients would have pediatric surgical consultation, and the inconclusive or intermediate risk group would most predictably benefit from a period of observation or proceeding with advanced imaging studies. If the initial assessment leads to a high level of suspicion for appendicitis, pediatric surgical consultation should be the next step, with the likelihood of an appendectomy without further studies. In patients with a low concern for appendicitis, the child may be discharged with family education regarding the natural history and progression of acute appendicitis and advice to return for repeat evaluation if the child is not improving on liquids and a bland diet in the next 24 hr. The group of patients with an intermediate risk score would proceed with targeted ultrasound of the appendix if the center has experience with the technique. If the ultrasound study is unable to visualize the appendix, or the appendix is visualized but the findings inconclusive, the next options would include admission for a period of observation and planned reassessment, CT imaging, or diagnostic laparoscopy.

The use of observation units, where the child may be observed with intravenous fluids, serial vital signs, and planned re-examinations is another strategy. At the end of a period of observation, typically 12-24 hr, the clinician decides on discharge based on reassuring clinical status, proceeds to diagnostic laparoscopy and appendectomy, or proceeds with advanced imaging evaluation. The period of observation can occur at home provided the patient is physiologically well; a hospital-based observational unit has the advantage of being able to provide intravenous fluids. An observation strategy seems most useful in patients who present with a brief history of illness (<12 hr) when advanced imaging studies predictably have lower sensitivity and specificity. If observed patients remain equivocal, advanced imaging should be more reliable further into the disease process.

Differential Diagnosis

The list of illnesses that can mimic acute appendicitis is extensive because many gastrointestinal, gynecologic, and inflammatory disorders can manifest with similar illness history, signs, and symptoms. Differential diagnosis, even limited to common conditions, includes gastroenteritis, mesenteric adenitis, Meckel diverticulitis, intussusception, inflammatory bowel disease, diabetes mellitus, sickle cell disease, streptococcal pharyngitis, lower lobe pneumonia, cholecystitis, pancreatitis, urinary tract infection (UTI), infectious enteritis, and, in females, ovarian torsion, ectopic pregnancy, ruptured/hemorrhagic ovarian cysts, and pelvic inflammatory disease (including tuboovarian abscess). *Epiploic appendagitis* , an inflammation of the fat-filled structures on the antimesenteric surface of the colon, may present with acute lower quadrant abdominal pain after torsion, thrombosis, and ischemic injury to the structure. Viral infections, bacterial infections, and parasitic infections can all closely mimic acute appendicitis. Intestinal tract lymphoma, tumors of the appendix (carcinoid in children), and ovarian tumors are rare but can also masquerade as acute appendicitis. Henoch-Schönlein purpura can initially present as severe abdominal pain. Urinary tract causes of abdominal pain include UTI, nephrolithiasis, and pyelonephritis. In patients with pyelonephritis, the fever and WBC count are likely much higher, symptoms of dysuria will be present, and the tenderness is located more in the flank or costovertebral angle. Rarely, appendicitis may recur in the stump of a previous appendectomy. *Children younger than 3 yr of age and adolescent girls have historically proven to be at particularly high risk for an incorrect diagnosis* .

Viral illnesses are common in children, often are associated with abdominal pain and vomiting, and thus mimic acute appendicitis. The classic patient with acute appendicitis describes abdominal pain as the preeminent symptom, and in general, symptoms of systemic illness such as headache, chills, and myalgias are infrequent in appendicitis and common when viral illness is the correct diagnosis.

The diagnosis of appendicitis in adolescent females is especially challenging, and some series report negative appendectomy rates as high as 30–40%. Ovarian cysts are often acutely painful as a result of rupture, rapid enlargement, or hemorrhage. Rupture of an ovarian follicle associated with ovulation often causes mid-cycle lateralizing pain (mittelschmerz), but there is no progression of symptoms and systemic illness is absent. Ovarian tumors and torsion can also mimic acute appendicitis, although ovarian torsion is typically characterized by the acute onset of severe pain and is associated with more frequent and forceful nausea and vomiting than is typically seen in early appendicitis. In pelvic inflammatory disease, the pain is typically suprapubic, bilateral, and of longer duration. The need for accurate urgent diagnosis in females is influenced by concern that PA can predispose the patient to future ectopic pregnancy or tubal infertility, although data have not consistently demonstrated increased incidence of infertility after PA. For these reasons, adjunct diagnostic studies (ultrasound, CT, MRI, or diagnostic laparoscopy) should be used more liberally in females to keep negative appendectomy rates low.

Torsion of an undescended testis and epididymitis are common but should be discovered on physical exam. Meckel's diverticulitis is an infrequent condition, but the clinical presentation closely mimics appendicitis. The diagnosis is rarely made before surgery. Primary spontaneous peritonitis (PSP) is classically seen in prepubertal females or patients with either nephrotic syndrome or cirrhosis and is frequently mistaken for appendicitis.

Atypical presentations of appendicitis are expected in association with other conditions such as pregnancy, Crohn disease, steroid treatment, and immunosuppressive therapy. Appendicitis in association with Crohn disease often has a protracted presentation with an atypical pattern of recurring but localized abdominal pain. It should be recognized that *missed* appendicitis is the most common cause of small bowel obstruction in children without history of prior abdominal surgery.

Antibiotics

Antibiotics should be initiated promptly once the diagnosis of appendicitis is made or highly suspected. Antibiotics substantially lower the incidence of postoperative wound infections, SSIs and intraabdominal abscesses—the source of the majority of the substantial morbidity and costs in PA. Many believe the time from onset of illness to the initiation of antibiotics has more impact on postoperative complication rates, LOS, and overall costs than time from diagnosis to surgery.

The antibiotic regimen should be directed against the typical bacterial flora found in the appendix, including anaerobic organisms (*Bacteroides, Clostridia,* and *Peptostreptococcus* spp.) and Gram-negative aerobic bacteria (*Escherichia coli, Pseudomonas aeruginosa, Enterobacter,* and *Klebsiella* spp.). Many antibiotic combinations have demonstrated equivalent efficacy in controlled trials in terms of wound infection rate, resolution of fever, LOS, and incidence of complications. Historically, a triple-antibiotic regimen consisting of ampicillin, gentamicin, and clindamycin was standard. Exhaustive studies of different antibiotic regimens have been performed, mostly aimed at lowering costs and frequency of dosing while maintaining efficacy. Both piperacillin/tazobactam and cefoxitin have demonstrated equivalent effectiveness and may decrease LOS and pharmaceutical costs compared to the triple-antibiotic regimen.

For simple (nonperforated) appendicitis, one preoperative dose of a single broad-spectrum agent (Zosyn) or equivalent is sufficient. In PA, the antibiotic is continued intravenously for 2-3 days postoperatively until the child is afebrile (≥24 hr), tolerating a general diet, and ready for discharge. Some centers prefer to add metronidazole in PA to augment coverage of anaerobes. The decision to discharge patients with PA managed with upfront appendectomy on a course of oral antibiotics (typically 3-5 days) remains controversial. The literature does not support improved outcomes with PA if antibiotics are extended beyond a 4- to 5-day course.

Surgical Intervention

Once the diagnosis of appendicitis is confirmed or highly suspected, the standard treatment for acute appendicitis, both simple and complicated, in current practice is most often prompt appendectomy. LA (minimally invasive technique) is the preferred surgical approach (65–70%) in both simple and PA, with open appendectomy markedly declining in the past decade. The laparoscopic approach has demonstrated slight improvement in clinical outcome measures (wound infection rate, intraabdominal abscess, analgesic requirements, wound cosmesis, and return to full activity), however, costs can be higher. The laparoscopic approach (diagnostic laparoscopy/LA) has particular advantages for obese patients, when alternative diagnoses are suspected, and in adolescent females to evaluate for ovarian pathology and alternative diagnoses while avoiding the ionizing radiation associated with CT imaging. The operation should proceed semi-electively within 12-24 hr of diagnosis. Children with appendicitis are typically at least mildly dehydrated and should receive supportive care prior to surgery, including fluid resuscitation to correct hypovolemia and electrolyte abnormalities, antipyretics to lower fever, and broad-spectrum antibiotics. These important fundamentals of care ensure safe anesthesia and optimize outcomes. In most cases, preoperative management can be accomplished during the period of diagnostic evaluation and prompt appendectomy can be performed. Pain management begins even before a definitive diagnosis is made, and consultation of a pain service, if available, is appropriate. Emergency surgery (middle of the night) *is rarely* indicated in acute appendicitis and should only be performed in the rare circumstance when physiologic resuscitation requires urgent control of advanced intraabdominal sepsis not amenable to percutaneous drainage by IR, or when this is not available. No correlation has been demonstrated between timing of surgery and perforation rates or postoperative morbidity when the operation proceeds within 24 hr of diagnosis. When comparing emergent appendectomy (within 5 hr of admission) with urgent appendectomy (within 17 hr of admission), no difference in PA, operative time, readmission rate, postoperative complications, LOS, or hospital charges have been noted. In addition, occasionally unexpected pathology (appendiceal tumors, intestinal lymphoma, congenital renal anomalies, Crohn disease) is discovered at operation, and intraoperative consultation with other specialists and/or frozen section evaluation may be required. The laparoscopic approach, in conjunction with standardized, expedited postoperative recovery protocols, and improved (single drug) and shorter duration antibiotic regimens have led to decreased LOS in both simple and complicated (perforated) appendicitis. The average LOS in most centers is approximately 24 hr for simple appendicitis and 4-5 days for perforated cases that recover without postoperative complications. In simple appendicitis, some centers have initiated same-day discharge.

Perforated Appendicitis

A major area of focus and challenge in the management of acute appendicitis is the group of patients with delayed presentation (>48 hr of symptoms). In most busy centers, because acute appendicitis often has an insidious onset of generalized malaise, as many as 40–50% of patients have delayed presentation. This cohort of patients has a high incidence of PA at presentation (40–59%) and a 56% greater LOS stay than those presenting within ≤24 hr of the onset of symptoms. The risk for development of postoperative complications (SSI, intraabdominal abscess, small bowel obstruction) approaches 20–30% for children with PA versus an approximately 3% risk of complications in patients with simple appendicitis.

Management options for children presenting with PA include upfront appendectomy following a brief period of stabilization with intravenous fluids and antibiotics, antibiotics alone, and antibiotics in conjunction with percutaneous drainage of intraabdominal fluid collections/abscesses. The past decade has witnessed a substantial trend toward nonoperative management in children with delayed presentation and suspected PA to avoid the high complication rate in these patients and the potential technical challenges of operative treatment in the setting of marked intraabdominal inflammation/peritonitis. Based on patient status, findings on imaging studies, and availability of experienced interventional radiologists, initial nonoperative management of PA with percutaneous drainage of fluid collections, intravenous fluids and broad-spectrum antibiotics has demonstrated success in >80% of patients. Antibiotics are initiated and typically continued intravenously for 1-2 days along with pain control. If the child demonstrates clinical recovery by resolution of fever and pain, and the patient can tolerate a general diet, the child is converted to oral antibiotics and discharged to complete an outpatient antibiotic course (typically 7-10 days of ciprofloxacin/Flagyl). A patient who fails to demonstrate clinical recovery proceeds to prompt appendectomy. This nonoperative management, and particularly the transition to oral antibiotics, has contributed to a decreased LOS and costs in the management of PA. Patients who do not have upfront appendectomy will require a decision regarding interval appendectomy (IA) in 4-6 wk, provided she/he does not fail nonoperative management after discharge by recurrence of pain, fever, or vomiting.

Nonoperative Management of Uncomplicated Appendicitis

Multiple studies in adults have demonstrated highly effective treatment of appendicitis with antibiotics alone. In addition, other conditions similar to appendicitis, such as diverticulitis, intraabdominal abscess in Crohn disease, and tubo-ovarian abscess, are primarily treated with antibiotics alone, with surgery reserved for failures of medical management. These outcomes have led many centers to evaluate initial nonoperative management of acute (simple) appendicitis in children and currently several randomized controlled studies are ongoing. Previous studies demonstrated a success rate for nonoperative management of simple appendicitis in children of 75–80%, with no increased rates of PA in patients who fail initial nonoperative management. Advantages of the antibiotic alone/nonoperative approach in acute appendicitis include avoidance of surgical complications and the risk of general anesthesia, and an operative procedure that may not be necessary. In some children's centers, the nonoperative approach is being offered on experimental protocol. Selection criteria for nonoperative management typically include <48-hr duration of symptoms, age >7 yr, imaging confirmation of acute non-PA, appendiceal diameter <1.2 cm, *absence* of appendicolith, abscess, or phlegmon, WBC >5,000, and <18,000 cells/µL. The clinical pathway for children enrolled consists of an initial 1-2 days of intravenous broad-spectrum antibiotics and pain control. If the child demonstrates clinical recovery by resolution of pain and fever and is tolerating a general diet, he/she is discharged to complete 7-10 days of oral antibiotics. If the child does not demonstrate clinical recovery, prompt appendectomy is performed. Early nonoperative trials found that predictors of failure of nonoperative management included pain >48 hr duration, presence of an appendicolith, inflammatory mass or abscess on imaging, and elevated laboratory values (WBC > 18,000, CRP > 4 mg/dL). Reports of this approach suggest a more rapid return to full activities and lower costs associated with the hospitalization for nonoperative management; however, others have reported that patients with nonoperative management had more subsequent ED visits, advanced imaging studies, and hospitalizations compared with those managed operatively at the first visit.

Recurrent Appendicitis

Prospective studies of the incidence of early recurrent appendicitis (within 1 yr) describe a range between 10 to 20% in patients initially managed nonoperatively. The lifetime risk of recurrent appendicitis in children treated nonoperatively is unknown. Controversies remain in the initial nonoperative management of PA. Most studies have reported significantly fewer overall complications (wound infections, intraabdominal abscesses, bowel obstruction, re-operations) in patients with initial nonoperative management of PA compared to patients with PA managed with upfront appendectomy; other reviews have supported early appendectomy in PA because initial nonoperative management and delayed appendectomy was associated with a significantly longer time to return to normal activities and an adverse event rate of 30% versus 55% in the initial nonoperative cohort. The initial nonoperative management and delayed appendectomy patients also incurred higher costs. Currently under review is the need for delayed appendectomy IA in patients with complicated appendicitis initially managed nonoperatively. While the trend in cases of PA at presentation is toward initial nonoperative management, the data remains uncertain, and there is no convincing data to recommend one approach in all patients.

Interval Appendectomy

In patients with PA initially treated nonoperatively, the decision to proceed with IA, typically in 4-6 wk, is another area of management lacking consensus. Traditionally, most surgeons recommended IA to avoid recurrent appendicitis and to confirm the original diagnosis, citing reports which demonstrated an incidence of unexpected pathology in 30% of IA specimens. This has been questioned with nonoperative management of simple appendicitis gaining acceptance and many debating the risk of recurrent appendicitis (5–20%), believing it to be lower. The lifetime risk of recurrent appendicitis is unknown. Decision-making for IA must be individualized to balance the risks of recurrent appendicitis with the risks of anesthesia and comorbid conditions such as obesity, congenital heart disease, chronic respiratory conditions, and others.

Incidental Appendicoliths

The question of the incidental appendicolith is an intriguing one for pediatric practitioners. These are patients who do not have appendicitis but are found to have an appendicolith on imaging studies. An appendicolith is defined as a calcification within the appendiceal lumen. In adults, incidental appendicoliths identified by CT scans vary in incidence from <1% to as high as 10%. They have a characteristic dense and laminated appearance when compared to other lower abdominal calcifications, including phleboliths (venous calcifications) and, in females, ovarian calcifications, most commonly seen in ovarian tumors. They can be appreciated on plain film, ultrasound, and CT scan. When an appendicolith is noted in the evaluation of a child with abdominal pain and suspected appendicitis, the finding of the appendicolith confirms the diagnosis; surgical consultation and prompt appendectomy is indicated. Appendicoliths may be noted in the evaluation of patients who have no signs of appendicitis, such as imaging obtained after trauma or for nonspecific abdominal complaints in patients with low likelihood of appendicitis. The concern in this setting is that the appendicolith may increase the eventual development of acute appendicitis. In addition, there is the concern that should appendicitis develop in association with an appendicolith, there may be a rapidly escalating course and early perforation. Some physicians believe that a persistent appendicolith may be associated with recurrent RLQ/iliac fossa pain.

Incidental appendicoliths may be transient and in most short-term follow-up studies have a low risk of subsequent acute appendicitis. In addition, the lifetime risk for the development of appendicitis in patients with an incidental appendicolith is approximately 5%, which is not different from the normal population. The risk of subsequent appendicitis may be higher in those presenting with abdominal pain or those younger than 19 yr of age. Radiographically detected incidental appendicoliths are usually managed with observation, planned follow-up, and patient education for signs of acute appendicitis. After discussing the risks and benefits with the family, and persistence of the appendicolith, an individualized approach is best between the physician and family relative to elective appendectomy.

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CHAPTER 371

Surgical Conditions of the Anus and Rectum

371.1

Anorectal Malformations

Christina M. Shanti

Keywords

Imperforate anus
Perineal fistula
Fourchette fistula
Rectovaginal fistula
Cloaca
Rectourethral fistula
Caudal regression
Anal stenosis
Anterior ectopic anus
Rectal atresia
Currarino triad
Tethered Cord
PSARP: Posterior sagittal anorectoplasty
Fecal continence
ACE Antegrade continence enema

MACE Malone antegrade continence enema

To fully understand the spectrum of anorectal anomalies, it is necessary to consider the importance of the sphincter complex, a mass of muscle fibers surrounding the anorectum (Fig. 371.1). This complex is the combination of the puborectalis, levator ani, external and internal sphincters, and the superficial external sphincter muscles, all meeting at the rectum. Anorectal malformations are defined by the relationship of the rectum to this complex and include varying degrees of stenosis to complete atresia. The incidence is 1/3,000 live births. Significant long-term concerns focus on bowel control and urinary and sexual functions.

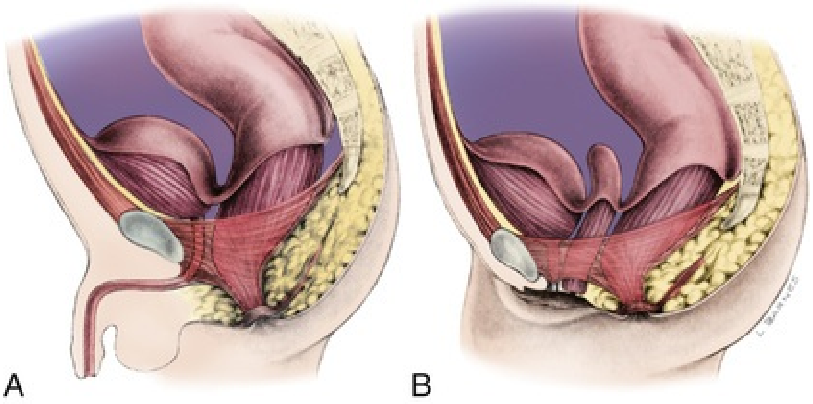

FIG. 371.1 **Normal anorectal anatomy in relation to pelvic structures. A, Male. B, Female. (From Peña A: *Atlas of surgical management of anorectal malformations* , New York, 1989, Springer-Verlag, p 3.)**

Embryology

The hindgut forms early as the part of the primitive gut tube that extends into the tail fold in the 2nd wk of gestation. At about day 13, it develops a ventral diverticulum, the allantois, or primitive bladder. The junction of allantois and hindgut becomes the cloaca, into which the genital, urinary, and intestinal tubes empty. This is covered by a cloacal membrane. The urorectal septum descends to divide this common channel by forming lateral ridges, which grow in and fuse by the middle of the 7th wk. Opening of the posterior portion of the membrane (the anal membrane) occurs in the 8th wk. Failures in any part of these processes can lead to the clinical spectrum of anogenital anomalies.

Imperforate anus can be divided into low lesions, where the rectum has descended through the sphincter complex, and high lesions, where it has not. Most patients with imperforate anus have a fistula. There is a spectrum of malformation in males and females. In males, low lesions usually manifest with meconium staining somewhere on the perineum along the median raphe (Fig. 371.2*A*). Low lesions in females also manifest as a spectrum from an anus that is only slightly anterior on the perineal body to a fourchette fistula that opens on the moist mucosa of the introitus distal to the hymen (Fig. 371.3*A*). A high imperforate anus in a male has no apparent cutaneous opening or fistula, but it usually has a fistula to the urinary tract, either the urethra or the bladder (see Fig. 371.2*B*). Although there is occasionally a rectovaginal fistula, in females, high lesions are usually cloacal anomalies in which the rectum, vagina, and urethra all empty into a common channel or cloacal stem of varying length (see Fig. 371.3*B*). The interesting category of males with imperforate anus and no fistula occurs mainly in children with trisomy 21. The most common lesions are the rectourethral bulbar fistula in males and the rectovestibular fistula in females; the 2nd most common lesion in both sexes is the perianal fistula (Fig. 371.4).

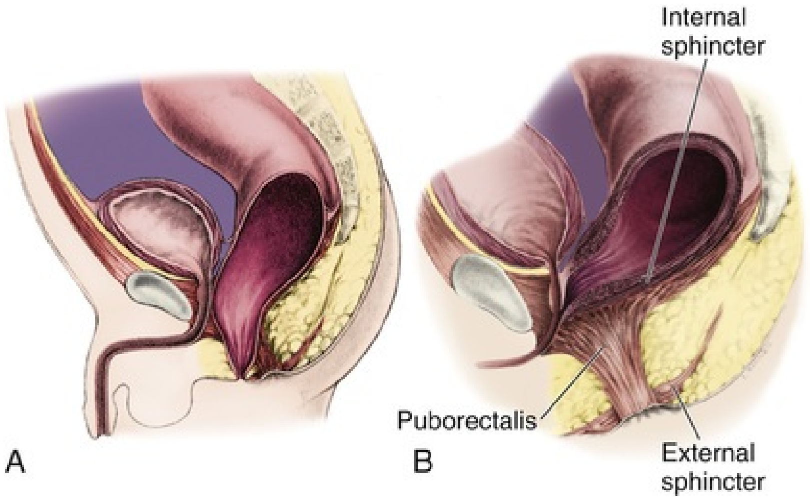

FIG. 371.2 **Imperforate anus in males. A, Low lesions. B, High lesions. (From Peña A: *Atlas of surgical management of anorectal malformations* , New York, 1989, Springer-Verlag, pp 7, 26.)**

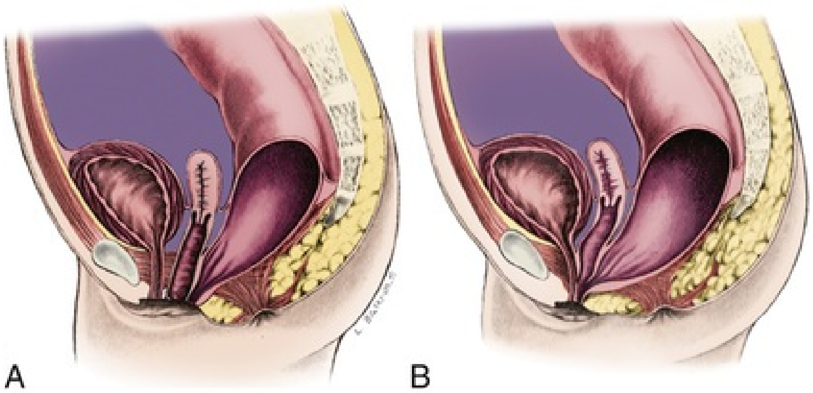

FIG. 371.3 Imperforate anus in females. A, Vestibular fistula. B, Cloaca. (From Peña A: *Atlas of surgical management of anorectal malformations* , New York, 1989, Springer-Verlag, pp 50, 60.)

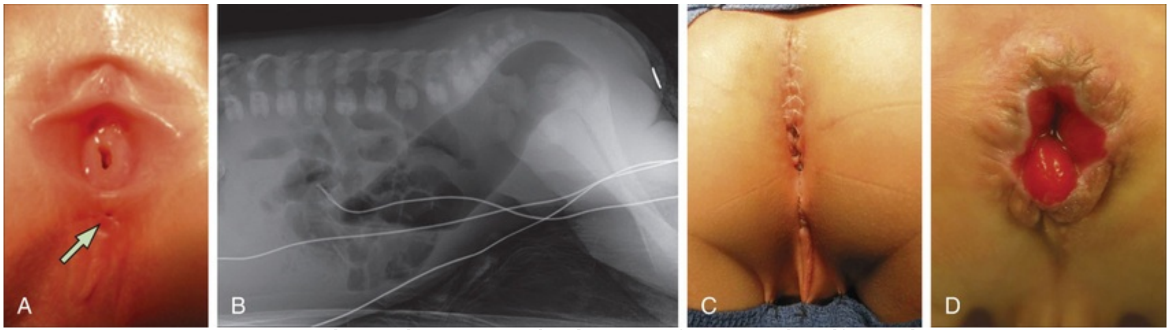

FIG. 371.4 Preoperative and postoperative images of anorectal malformations. A, Preoperative rectoperineal fistula. B, Radiograph with cross table lateral film showing neonate in prone position and gas below the coccyx. C, Postoperative appearance after a posterior sagittal anorectoplasty. D, Postoperative large, patulous, and prolapsed anoplasty. (From Bischoff A, Bealer J, Pená A: Controversies in anorectal malformations, *Lancet Child/Adolesc* 1:323–330, 2017, Fig. p. 324).

Associated Anomalies

There are many anomalies associated with anorectal malformations (Table 371.1). The most common are anomalies of the kidneys and urinary tract in conjunction with abnormalities of the sacrum. This complex is often referred to as *caudal regression syndrome* . Males with a rectovesical fistula and patients with a persistent cloaca have a 90% risk of urologic defects. Other common associated anomalies are cardiac anomalies and esophageal atresia with or without tracheoesophageal fistula. These can cluster in any combination in a patient. When combined, they are often accompanied by abnormalities of the radial aspect of the upper extremity and are termed the VACTERL (*v* ertebral, *a* nal, *c* ardiac, *t* racheal, *e* sophageal, *r* enal, *l* imb) anomalad.

Table 371.1

Associated Malformations

GENITOURINARY
• Vesicoureteric reflux • Renal agenesis • Renal dysplasia • Ureteral duplication • Cryptorchidism • Hypospadias • Bicornuate uterus • Vaginal septa
VERTEBRAL
• Spinal dysraphism • Tethered chord • Presacral masses • Meningocele • Lipoma • Dermoid • Teratoma
CARDIOVASCULAR
• Tetralogy of Fallot • Ventricular septal defect • Transposition of the great vessels • Hypoplastic left-heart syndrome
GASTROINTESTINAL
• Tracheoesophageal fistula • Duodenal atresia • Malrotation • Hirschsprung disease
CENTRAL NERVOUS SYSTEM
• Spina bifida • Tethered cord

Anorectal malformations, particularly anal stenosis and rectal atresia, can also present as Currarino triad, which includes sacral agenesis, presacral mass, and anorectal stenosis. These patients present with a funnel appearing anus, have sacral bony defects on plain x-ray, and have a presacral mass (teratoma, meningocele, dermoid cyst, enteric cyst) on exam or imaging. It is an autosomal dominant disorder due in most patients to a mutation in the *MNX1* gene.

A good correlation exists between the degree of sacral development and future function. Patients with an absent sacrum usually have permanent fecal and urinary incontinence. Spinal abnormalities and different degrees of dysraphism are often associated with these defects. Tethered cord occurs in approximately

25% of patients with anorectal malformations. Untethering of the cord can lead to improved urinary and rectal continence in some patients, although it seldom reverses established neurologic defects. The diagnosis of spinal defects can be screened for in the first 3 mo of life by spinal ultrasound, although MRI is the imaging method of choice if a lesion is suspected. In older patients, MRI is needed.

Manifestations and Diagnosis

Low Lesions

Examination of a newborn includes the inspection of the perineum. The absence of an anal orifice in the correct position leads to further evaluation. Mild forms of imperforate anus are often called *anal stenosis* or *anterior ectopic anus* . These are typically cases of an imperforate anus with a perineal fistula. The normal position of the anus on the perineum is approximately halfway (0.5 ratio) between the coccyx and the scrotum or introitus. Although symptoms, primarily constipation, have been attributed to anterior ectopic anus (ratio: <0.34 in females, <0.46 in males), many patients have no symptoms.

If no anus or fistula is visible, there may be a low lesion or *covered anus* . In these cases, there are well-formed buttocks and often a thickened raphe or *bucket handle* . After 24 hr, meconium bulging may be seen, creating a blue or black appearance. In these cases, an immediate perineal procedure can often be performed, followed by a dilation program.

In a male, the perineal (cutaneous) fistula can track anteriorly along the median raphe across the scrotum and even down the penile shaft. This is usually a thin track, with a normal rectum often just a few millimeters from the skin. Extraintestinal anomalies are seen in <10% of these patients.

In a female, a low lesion enters the vestibule or fourchette (the moist mucosa outside the hymen but within the introitus). In this case, the rectum has descended through the sphincter complex. Children with a low lesion can usually be treated initially with perineal manipulation and dilation. Visualizing these low fistulas is so important in the evaluation and treatment that one should avoid passing a nasogastric tube for the first 24 hr to allow the abdomen and bowel to distend, pushing meconium down into the distal rectum.

High Lesions

In a male with a high imperforate anus, the perineum appears flat. There may be air or meconium passed via the urethra when the fistula is high, entering the bulbar or prostatic urethra, or even the bladder. In *rectobulbar urethral fistulas* (the most common in males), the sphincter mechanism is satisfactory, the sacrum may be underdeveloped, and an anal dimple is present. In *rectoprostatic urethral fistulas* , the sacrum is poorly developed, the scrotum may be bifid, and the anal dimple is near the scrotum. In *rectovesicular fistulas* , the sphincter mechanism is poorly developed, and the sacrum is hypoplastic or absent. In males with trisomy 21, all the features of a high lesion may be present, but there is no fistula, the sacrum and sphincter mechanisms are usually well developed, and the prognosis is good.

In females with high imperforate anus, there may be the appearance of a rectovaginal fistula. A true rectovaginal fistula is rare. Most are either the fourchette fistulas described earlier or are forms of a cloacal anomaly.

Persistent Cloaca

In persistent cloaca, the embryologic stage persists in which the rectum, urethra, and vagina communicate in a common orifice, the cloaca. It is important to realize this, because the repair often requires repositioning the urethra and vagina as well as the rectum. Children of both sexes with a high lesion require a colostomy before repair.

Rectal Atresia

Rectal atresia is a rare defect occurring in only 1% of anorectal anomalies. It has the same characteristics in both sexes. The unique feature of this defect is that affected patients have a normal anal canal and a normal anus. The defect is often discovered while rectal temperature is being taken. An obstruction is present approximately 2 cm above the skin level. These patients need a protective colostomy. The functional prognosis is excellent because they have a normal sphincteric mechanism (and normal sensation), which resides in the anal canal.

Approach to the Patient

Evaluation includes identifying associated anomalies (see Table 371.1). Careful inspection of the perineum is important to determine the presence or absence of a fistula. If the fistula can be seen there, it is a low lesion. The invertogram or upside-down x-ray is of little value, but a prone crosstable lateral plain x-ray at 24 hr of life (to allow time for bowel distention from swallowed air) with a radiopaque marker on the perineum can demonstrate a low lesion by showing the rectal gas bubble <1 cm from the perineal skin (see Fig. 371.4). A plain x-ray of the entire sacrum, including both iliac wings, is important to identify sacral anomalies and the adequacy of the sacrum. An abdominal-pelvic ultrasound and voiding cystourethrogram must be performed. The clinician should also pass a nasogastric tube to identify esophageal atresia and should obtain an echocardiogram. In males with a high lesion, the voiding cystourethrogram often identifies the rectourinary fistula. In females with a high lesion, more invasive evaluation, including vaginogram and endoscopy, is often necessary for careful detailing of the cloacal anomaly.

Good clinical evaluation and a urinalysis provide enough data in 80–90% of male patients to determine the need for a colostomy. Voluntary sphincteric muscles surround the most distal part of the bowel in cases of perineal and rectourethral fistulas, and the intraluminal bowel pressure must be sufficiently high to overcome the tone of those muscles before meconium can be seen in the urine or on the perineum. The presence of meconium in the urine and a flat bottom are considered indications for the creation of a colostomy. Clinical findings consistent with the diagnosis of a perineal fistula represent an indication for an anoplasty without a protective colostomy. Ultrasound is valuable not only for the evaluation of the urinary tract, but it can also be used to investigate spinal anomalies in the newborn and to determine how close to the perineum the rectum has descended.

More than 90% of the time, the diagnosis in females can be established on perineal inspection. The presence of a single perineal orifice is a cloaca. A palpable pelvic mass (hydrocolpos) reinforces this diagnosis. A vestibular fistula is diagnosed by careful separation of the labia, exposing the vestibule. The rectal orifice is located immediately in front of the hymen within the female genitalia and in the vestibule. A perineal fistula is easy to diagnose. The rectal orifice is located somewhere between the female genitalia and the center of the sphincter and is surrounded by skin. Less than 10% of these patients fail to pass meconium through the genitalia or perineum after 24 hr of observation. Those patients can require a prone crosstable lateral film.

Operative Repair

Sometimes a perineal fistula, if it opens in good position, can be treated by simple dilation. Hegar dilators are employed, starting with a No. 5 or 6 and letting the baby go home when the mother can use a No. 8. Twice-daily dilatations are done at home, increasing the size every few weeks until a No. 14 is achieved. By 1 yr of age, the stool is usually well formed and further dilation is not necessary. By the time No. 14 is reached, the examiner can usually insert a little finger. If the anal ring is soft and pliable, dilation can be reduced in frequency or discontinued.

Occasionally, there is no visible fistula, but the rectum can be seen to be filled with meconium bulging on the perineum, or a covered anus is otherwise suspected. If confirmed by plain x-ray or ultrasound of the perineum that the rectum is <1 cm from the skin, the clinician can do a minor perineal procedure to perforate the skin and then proceed with dilation or do a simple perineal anoplasty.

When the fistula orifice is very close to the introitus or scrotum, it is often appropriate to move it back surgically. This also requires postoperative dilation to prevent stricture formation. This procedure can be done any time from the newborn period to 1 yr. It is preferable to wait until dilatations have been done for several weeks and the child is bigger. The anorectum is a little easier to dissect at this time. The posterior sagittal approach of Peña is used, making an incision around the fistula and then in the midline to the site of the posterior wall of the new location. The dissection is continued in the midline, using a muscle stimulator to be sure there is adequate muscle on both sides. The fistula must be dissected cephalad for several centimeters to allow posterior positioning without tension. If appropriate, some of the distal fistula is resected before the anastomosis to the perineal skin.

In children with a high lesion, a double-barrel colostomy is performed. This effectively separates the fecal stream from the urinary tract. It also allows the performance of an augmented pressure colostogram before repair to identify the exact position of the distal rectum and the fistula. The definitive repair or posterior sagittal anorectoplasty (PSARP) is performed at about 1 yr of age. A midline incision is made, often splitting the coccyx and even the sacrum. Using a muscle stimulator, the surgeon stays strictly in the midline and divides the sphincter complex and identifies the rectum. The rectum is then opened in the midline and the fistula is identified from within the rectum. This allows a division of the fistula without injury to the urinary tract. The rectum is then dissected proximally until enough length is gained to suture it to an appropriate perineal position. The muscles of the sphincter complex are then sutured around (and especially behind) the rectum.

Other operative approaches (such as an anterior approach) are used, but the most popular procedure is by laparoscopy. This operation allows division of the fistula under direct visualization and identification of the sphincter complex by transillumination of perineum. Other imaging techniques in the management of anorectal malformations include 3D endorectal ultrasound, intraoperative MRI, and colonoscopy-assisted PSARPs, which may help perform a technically better operation. None of these other procedures or innovations has demonstrated improved outcomes.

A similar procedure can be done for female high anomalies with variations to deal with separating the vagina and rectum from within the cloacal stem. When the stem is longer than 3 cm, this is an especially difficult and complex procedure.

Usually the colostomy can be closed 6 wk or more after the PSARP. Two weeks after any anal procedure, twice-daily dilatations are performed by the family. By doing frequent dilatations, each one is not so painful and there is less tissue trauma, inflammation, and scarring.

Outcome

The ability to achieve rectal continence depends on both motor and sensory elements. There must be adequate muscle in the sphincter complex and proper positioning of the rectum within the complex. There must also be intact innervation of the complex and of sensory elements, as well as the presence of these sensory elements in the anorectum. Patients with low lesions are more likely to achieve true continence. They are also, however, more prone to constipation, which leads to overflow incontinence. It is very important that all these patients are followed closely, and that the constipation and anal dilation are well managed until toilet training is successful. Tables 371.2 and 371.3 outline the results of continence and constipation in relation to the malformation encountered.

Table 371.2

Types of Anorectal Malformation by Sex

MALE (PERCENTAGE CHANCE OF BOWEL CONTROL [*])
• Rectoperineal fistula (100%)
• Rectourethral bulbar fistula (85%)
• Imperforate anus without fistula (90%)
• Rectourethral prostatic fistula (65%)
• Rectobladder neck fistula (15%)
FEMALE (PERCENTAGE CHANCE OF BOWEL CONTROL [*])
• Rectoperineal fistula (100%)
• Rectovestibular fistula (95%)
• Imperforate anus without fistula (90%)
• Rectovaginal fistula (rare anomaly) [†]
• Cloaca (70%) [‡]

[*] Provided patients have a normal sacrum, no tethered cord, and they receive a technically correct operation without complications.

[†] Rectovaginal anomalies are extremely unusual; usually their prognosis is like rectovestibular fistula.

[‡] Cloaca represents a spectrum; those with a common channel length <3 cm have the best functional prognosis.

From Bischoff A, Bealer J, Pená A: Controversies in anorectal malformations, *Lancet Child/Adolesc* 1:323–330, 2017 (Panel p. 323).

Table 371.3

Constipation and Type of Anogenital Malformation

TYPE	PERCENTAGE
Vestibular fistula	61
Bulbar urethral fistula	64
Rectal atresia/stenosis	50
Imperforate with no fistula	55
Perineal fistula	57
Long cloaca	35
Prostatic fistula	45
Short cloaca	40
Bladder neck fistula	16

Modified from Levitt MA, Peña A: Outcomes from the correction of anorectal malformations, *Curr Opin Pediatr* 17:394–401, 2005.

Children with high lesions, especially males with rectoprostatic urethral fistulas and females with cloacal anomalies, have a poorer chance of being continent, but they can usually achieve a socially acceptable defecation (without a colostomy) pattern with a bowel management program. Often, the bowel management program consists of a daily enema to keep the colon empty and the patient clean until the next enema. If this is successful, an *antegrade continence enema* (ACE) procedure, sometimes called the Malone or Malone antegrade continence enema (MACE) procedure, can improve the patient's quality of life. These procedures provide access to the right colon either by bringing the appendix out the umbilicus in a nonrefluxing fashion or by putting a plastic button in the right lower quadrant to access the cecum. The patient can then sit on the toilet and administer the enema through the ACE, thus flushing out the entire colon. Antegrade regimens can produce successful 24 hr cleanliness rates of up to 95%. Of special interest is the clinical finding that most patients improve their control with growth. Patients who wore diapers or pull-ups to primary school are often in regular underwear by high school. Some groups have taken advantage of this evidence of psychologic influences to initiate behavior modification early with good results.

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371.2

Anal Fissure

Christina M. Shanti

Keywords

Anal fissure
Skin tag
Sphincterotomy
Botulinum toxin
Calcium channel blockers

Anal fissure is a laceration of the anal mucocutaneous junction. It is an acquired lesion of unknown etiology. While likely secondary to the forceful passage of a hard stool, it is mainly seen in infants younger than 1 yr of age when the stool is frequently quite soft. Fissures may be the consequence and not the cause of constipation.

Clinical Manifestations

A history of constipation is often described, with a recent painful bowel movement corresponding to the fissure formation after passing of hard stool. The patient then voluntarily retains stool to avoid another painful bowel movement, exacerbating the constipation, resulting in harder stools. Complaints of pain on defecation and bright red blood on the surface of the stool are often elicited.

The diagnosis is established by inspection of the perineal area. The infant's hips are held in acute flexion, the buttocks are separated to expand the folds of the perianal skin, and the fissure becomes evident as a minor laceration. Often a small skin appendage is noted peripheral to the lesion. This *skin tag* represents epithelialized granulomatous tissue formed in response to chronic inflammation. Findings on rectal examination can include hard stool in the ampulla and rectal spasm.

Treatment

The parents must be counseled as to the origin of the laceration and the mechanism of the cycle of constipation. The goal is to ensure that the patient has soft stools to avoid overstretching the anus. The healing process can take several weeks or even several months. A single episode of impaction with passing of hard stool can exacerbate the problem. Treatment requires that the primary cause of the constipation be identified. The use of dietary and behavioral modification and a stool softener is indicated. Parents should titrate the dose of the stool softener based on the patient's response to treatment. Stool softening is best done by increasing water intake or using an oral polyethylene glycolate such as MiraLAX or GlycoLax. Surgical intervention, including stretching of the anus, “internal” anal sphincterotomy, or excision of the fissure, is not indicated or supported by scientific evidence.

Chronic anal fissures in older patients are associated with constipation, prior rectal surgery, Crohn disease, and chronic diarrhea. They are managed initially like fissures in infants, with stool softeners with the addition of sitz baths. Topical 0.2% glyceryl trinitrate reduces anal spasm and heals fissures, but it is often associated with headaches. Calcium channel blockers, such as 2% diltiazem ointment and 0.5% nifedipine cream, are more effective and cause fewer headaches than glyceryl trinitrate. Injection of botulinum toxin from 1.25 to 25 units is also effective and probably chemically replicates the action of internal sphincterotomy, which is the most effective treatment in adults, although seldom used in children.

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371.3

Perianal Abscess and Fistula

Christina M. Shanti

Keywords

Cryptitis
Anal fistula
Seton
Fistulotomy
Fistulectomy
Crohn's disease

Perianal abscesses usually manifest in infancy and are of unknown etiology. Fistula appears to be secondary to the abscess rather than a cause. Links to congenitally abnormal crypts of Morgagni have been proposed, suggesting that deeper crypts (3-10 mm rather than the normal 1-2 mm) lead to trapped debris and cryptitis (Fig. 371.5).

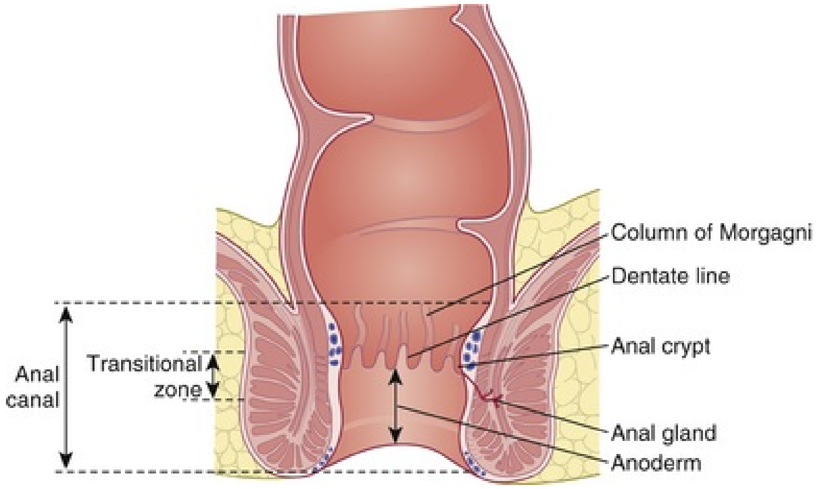

FIG. 371.5 **Anatomy of the anal canal. (Adapted from Brunicardi FC, Anderson DK, Billar TR, et al: *Schwartz's principles of surgery* , ed 8, New York, 2004, McGraw-Hill.)**

Conditions associated with the risk of an anal fistula include Crohn disease, tuberculosis, pilonidal disease, hidradenitis, HIV, trauma, foreign bodies, dermal cysts, sacrococcygeal teratoma, actinomycosis, lymphogranuloma venereum, and radiotherapy.

The most common organisms isolated from perianal abscesses are mixed aerobic *(Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus)* and anaerobic (*Bacteroides* spp., *Clostridium*, *Veillonella*) flora. A total of 10–15% yield pure growth of *E. coli, S. aureus,* or *Bacteroides fragilis.* There is a strong male predominance in those affected who are younger than 2 yr of age. This imbalance corrects in older patients, where the etiology shifts to associated conditions such as inflammatory bowel disease, leukemia, or immunocompromised states.

Clinical Manifestations

In younger patients, symptoms are usually mild and can consist of low-grade fever, mild rectal pain, and an area of perianal cellulitis. Often these spontaneously drain and resolve without treatment. In older patients with underlying predisposing conditions, the clinical course may be more serious. A compromised immune system can mask fever and allow rapid progression to toxicity and sepsis. Abscesses in these patients may be deeper in the ischiorectal fossa or even supralevator in contrast to those in younger patients, which are usually adjacent to the involved crypt.

Progression to fistula in patients with perianal abscesses occurs in up to 85%

of cases and usually manifests with drainage from the perineal skin or multiple recurrences. Similar to abscess formation, fistulas have a strong male predominance. Histologic evaluation of fistula tracts typically reveals an epithelial lining of stratified squamous cells associated with chronic inflammation. It might also reveal an alternative etiology such as the granulomas of Crohn disease or even evidence of tuberculosis.

Treatment

Treatment is rarely indicated in infants with no predisposing disease because the condition is often self-limited. Even in cases of fistulization, conservative management (observation) is advocated because the fistula often disappears spontaneously. In one study, 87% of fistulas (in 97/112 infants) closed after a mean of 5 mo of observation and conservative management. Antibiotics are not useful in these patients. When dictated by patient discomfort, abscesses may be drained under local anesthesia. Fistulas requiring surgical intervention may be treated by fistulotomy (unroofing or opening), fistulectomy (excision of the tract leaving it open to heal secondarily), or placement of a seton (heavy suture threaded through the fistula, brought out the anus and tied tightly to itself). In patients with inflammatory bowel disease, topical tacrolimus has been effective.

Older children with predisposing diseases might also do well with minimal intervention. If there is little discomfort and no fever or other sign of systemic illness, local hygiene and antibiotics may be best. The danger of surgical intervention in an immunocompromised patient is the creation of an even larger, nonhealing wound. There certainly are such patients with serious systemic symptoms who require more aggressive intervention along with treatment of the predisposing condition. Broad-spectrum antibiotic coverage must be administered, and wide excision and drainage are mandatory in cases involving sepsis and expanding cellulitis.

Fistulas in older patients are mainly associated with Crohn disease, a history of pull-through surgery for the treatment of Hirschsprung disease, or, in rare cases, tuberculosis. Those fistulas are often resistant to therapy and require treatment of the predisposing condition.

Complications of treatment include recurrence and, rarely, incontinence.

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371.4

Hemorrhoids

Christina M. Shanti

Keywords

Hemorrhoids
Portal hypertension
Thrombosed hemorrhoid
Internal hemorrhoid

External hemorrhoid

Hemorrhoidal disease occurs in both children and adolescents, often related to a diet deficient in fiber and poor hydration. In younger children, the presence of hemorrhoids should also raise the suspicion of portal hypertension. A third of patients with hemorrhoids require treatment.

Clinical Manifestations

Presentation depends on the location of the hemorrhoids. External hemorrhoids occur below the dentate line (see Figs. 371.5 and 371.6) and are associated with extreme pain and itching, often due to acute thrombosis. Internal hemorrhoids are located above the dentate line and manifest primarily with bleeding, prolapse, and occasional incarceration.

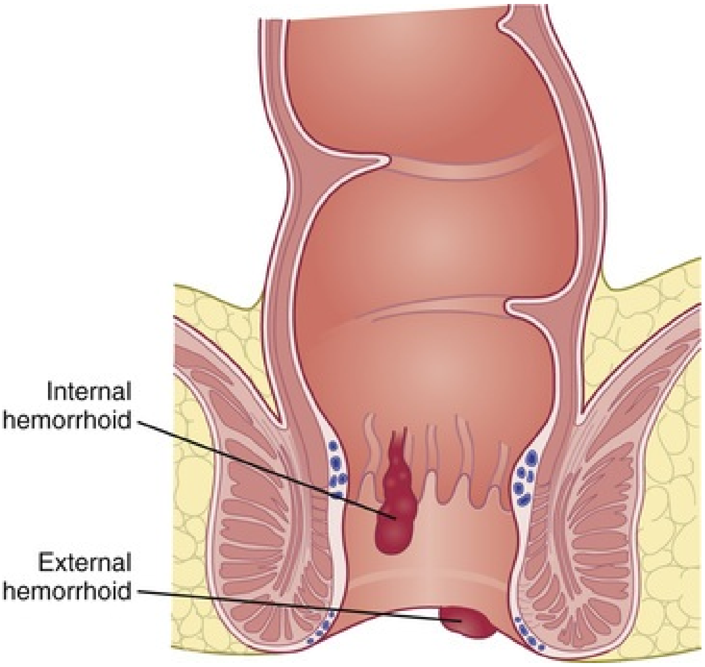

FIG. 371.6 **Formation of hemorrhoids.**

Treatment

In most cases, conservative management with dietary modification, decreased straining, and avoidance of prolonged time spent sitting on the toilet results in resolution of the condition. Discomfort may be treated with topical analgesics or anti-inflammatories such as Anusol (pramoxine) and Anusol-HC (hydrocortisone) and sitz baths. The natural course of thrombosed hemorrhoid involves increasing pain, which peaks at 48-72 hr, with gradual remission as the thrombus organizes and involutes over the next 1-2 wk. In cases where the patient with external hemorrhoids presents with excruciating pain soon after the onset of symptoms, thrombectomy may be indicated. This is best accomplished with local infiltration of bupivacaine 0.25% with epinephrine 1:200,000, followed by incision of the vein or skin tag and extraction of the clot. This provides immediate relief; recurrence is rare and further follow-up is unnecessary.

Internal hemorrhoids can become painful when prolapse leads to incarceration and necrosis. Pain usually resolves with reduction of hemorrhoidal tissue. Surgical treatment is reserved for patients failing conservative management. Techniques described in adults include excision, rubber banding, stapling, and excision using the LigaSure device. Complications are rare (<5%) and include recurrence, bleeding, infection, nonhealing wounds, and fistula formation.

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371.5

Rectal Mucosal Prolapse

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Keywords

Rectal prolapse
Procidentia
Rectocele
Ehler-Danlos Syndrome
Cystic fibrosis
Imperforate anus
Delorme resection
Thiersch procedure
Rectopexy
Altemeier resection

Rectal mucosal prolapse is the exteriorization of the rectal mucosa through the anus. In the unusual occurrence when all the layers of the rectal wall are included, it is called *procidentia* or *rectocele* . Most cases of rectal tissue protruding through the anus are prolapse and not polyps, hemorrhoids, intussusception, or other tissue.

Most cases of prolapse are idiopathic. The onset is often between 1 and 5 yr of age. It usually occurs when the child begins standing and then resolves by approximately 3-5 yr of age when the sacrum has taken its more adult shape and the anal lumen is oriented posteriorly. Thus the entire weight of the abdominal viscera is not pushing down on the rectum, as it is earlier in development.

Other predisposing factors include intestinal parasites (particularly in endemic areas), malnutrition, diarrhea, ulcerative colitis, pertussis, Ehlers-Danlos syndrome, meningocele (more often associated with procidentia owing to the lack of perineal muscle support), cystic fibrosis, and chronic constipation. Patients treated surgically for imperforate anus can also have varying degrees of rectal mucosal prolapse. This is particularly common in patients with poor sphincteric development. Rectal prolapse is also seen with higher incidence in patients with mental issues and behavior problems. These patients are particularly difficult to manage and are more likely to fail medical treatment.

Clinical Manifestations

Rectal mucosal prolapse usually occurs during defecation, especially during toilet training. Reduction of the prolapse may be spontaneous or accomplished manually by the patient or parent. In severe cases, the prolapsed mucosa becomes congested and edematous, making it more difficult to reduce. Rectal prolapse is usually painless or produces mild discomfort. If the rectum remains prolapsed after defecation, it can be traumatized by friction with undergarments, with resultant bleeding, wetness, and potentially ulceration. The appearance of the prolapse varies from bright red to dark red and resembles a beehive. It can be as long as 10-12 cm. See Chapter 372 for a distinction from a prolapsed polyp.

Treatment

Initial evaluation should include tests to rule out any predisposing conditions, especially cystic fibrosis and sacral root lesions. Reduction of protrusion is aided by pressure with warm compresses. An easy method of reduction is to cover the finger with a piece of toilet paper, introduce it into the lumen of the mass, and gently push it into the patient's rectum. The finger is then immediately withdrawn. The toilet paper adheres to the mucous membrane, permitting release of the finger. The paper, when softened, is later expelled.

Conservative treatment consists of careful manual reduction of the prolapse after defecation, attempts to avoid excessive pushing during bowel movements (with patient's feet off the floor), use of laxatives and stool softeners to prevent constipation, avoidance of inflammatory conditions of the rectum, and treatment of intestinal parasitosis when present. If all this fails, surgical treatment may be indicated. Existing surgical options are associated with some morbidity, and therefore medical treatment should always be attempted first.

Sclerosing injections have been associated with complications such as neurogenic bladder. We have found linear cauterization effective and with few complications other than recurrence. In the operating room, the prolapse is recreated by traction on the mucosa. Linear burns are made through nearly the full thickness of the mucosa using electrocautery. One can usually make 8 linear burns on the outside and 4 on the inside of the prolapsed mucosa. In the immediate postoperative period, prolapse can still occur, but in the next several weeks, the burned areas contract and keep the mucosa within the anal canal. The Delorme mucosal sleeve resection addresses mucosal prolapse via a transanal approach by incising, prolapsing, and amputating the redundant mucosa. The resulting mucosal defect is then approximated with absorbable suture.

For patients with procidentia or full-thickness prolapse or intussusception of the rectosigmoid (usually from myelodysplasia or other sacral root lesions), other, more invasive options exist. Those most commonly in use by pediatric surgeons today include the following: A modification of the Thiersch procedure involves placing a subcutaneous suture to narrow the anal opening. Complications include obstruction, fecal impaction, and fistula formation. Laparoscopic rectopexy is effective and can be performed as an outpatient. The Altemeier perineal rectosigmoidectomy is a transanal, full-thickness resection of redundant bowel with a primary anastomosis to the anus.

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371.6

Pilonidal Sinus and Abscess

Christina M. Shanti

Keywords

Pilonidal sinus
Pilonidal abscess
Sacral dimple

The etiology of pilonidal disease remains unknown; 3 hypotheses explaining its origin have been proposed. The first states that trauma, such as can occur with prolonged sitting, impacts hair into the subcutaneous tissue, which serves as a nidus for infection. The second suggests that in some patients, hair follicles exist in the subcutaneous tissues, perhaps the result of some embryologic abnormality, and that they serve as a focal point for infection, especially with secretion of hair oils. The third speculates that motion of the buttocks disturbs a particularly deep midline crease and works bacteria and hair beneath the skin. This theory arises from the apparent improved short-term and long-term results of operations that close the wound off the midline, obliterating the deep natal cleft.

Pilonidal disease usually manifests in adolescents or young adults with significant hair over the midline sacral and coccygeal areas. It can occur as an acute abscess with a tender, warm, flocculent, erythematous swelling or as draining sinus tracts. This disease does not resolve with nonoperative treatment. An acute abscess should be drained and packed open with appropriate anesthesia. Oral broad-spectrum antibiotics covering the usual isolates (*S. aureus* and *Bacteroides* species) are prescribed, and the patient's family withdraws the packing over the course of a week. When the packing has been totally removed, the area can be kept clean by a bath or shower. The wound usually heals completely in 6 wk. Once the wound is healed, most pediatric surgeons feel that elective excision should be scheduled to avoid recurrence. There are some reports, however, this is only necessary if the disease recurs. Usually, patients who present with sinus tracts are managed with a single elective excision.

Most surgeons carefully identify the extent of each sinus tract and excise all skin and subcutaneous tissue involved to the fascia covering the sacrum and coccyx. Some close the wound in the midline; others leave it open and packed for healing by secondary intention. This method has been modified by the application of a vacuum-assisted (VAC sponge) dressing. This is a system that applies continuous suction to a porous dressing. It is usually changed every 3 days and can be done at home with the assistance of a nurse. Some marsupialize the wound by suturing the skin edges down to the exposed fascia covering the sacrum and coccyx. There appears to be improved success with excision and closure in such a way that the suture line is not in the midline. Currently there appears to be enthusiasm for the less radical methods that Bascom has introduced, treating simple sinus tracts with small local procedures and limiting excision to only diseased tissues, while still keeping the incision off the midline. Recurrence or wound-healing problems are relatively common, occurring in 9–27% of cases. The variety of treatments and procedures currently being described indicates that all are associated with significant complications and delays in return to normal activity. Still, it is rare for problems to persist beyond 1-2 yr. Recalcitrant cases are treated by a large, full-thickness gluteal flap or skin grafting.

A simple dimple located in the midline intergluteal cleft, at the level of the coccyx, is seen relatively commonly in normal infants. No evidence indicates that this little sinus provokes any problems for the patient. An open dermal sinus is an asymptomatic, benign condition that does not require operative intervention.

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CHAPTER 372

Tumors of the Digestive Tract

Danielle Wendel, Karen F. Murray

Tumors of the digestive tract in children are mostly polypoid. They are also commonly syndromic tumors and tumors with known genetic identification (Table 372.1). They usually manifest as painless rectal bleeding, but when large they can cause obstruction or serve as lead points for intussusception. Most intestinal tumors can be generally classified into 2 groups: hamartomatous or adenomatous.

Table 372.1

General Features of the Inherited Colorectal Cancer Syndromes

SYNDROME	POLYP DISTRIBUTION	AGE OF ONSET	RISK OF COLON CANCER	GENETIC LESION	CLINICAL MANIFESTATIONS	ASSOCI LESION
HAMARTOMATOUS POLYPS						
Juvenile polyposis	Large and small intestine, gastric polyps	1st decade	~10–50%	*PTEN, SMAD4, BMPR1A* Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Congenit abnormal 20% of t nonfamil type, clu AV malforma
Peutz-Jeghers syndrome	Small and large intestine	1st decade	Increased	*LKB1/STK11* Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Orocutan melanin pigment
Cowden syndrome	Colon	2nd decade	Not increased	*PTEN* gene	Macrocephaly, breast/thyroid/endometrial cancers, developmental delay	
Bannayan-Riley-Ruvalcaba syndrome	Colon	2nd decade	Not increased	*PTEN* gene	Macrocephaly, speckled penis, thyroid/breast cancers, hemangiomas, lipomas	

ADENOMATOUS POLYPS						
Familial adenomatous polyposis (FAP)	Large intestine, often >100	16 yr (range: 8-34 yr)	100%	5q (*APC* gene), autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Desmoid CHRPE, GI polyp osteoma, hepatobla thyroid c
Attenuated familial adenomatous polyposis (AFAP)	Colon (fewer in number)	>18 yr	Increased	*APC* gene	Same as FAP	Fewer associate lesions
MYH-associated polyposis	Colon	>20 yr	High risk	*MYH* autosomal recessive	Same as FAP	May be confused sporadic AFAP; fe extrainte findings
Gardner syndrome	Large and small intestine	16 yr (range: 8-34 yr)	100%	5q (*APC* gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoid tumors, multiple osteomas fibromas epidermo cysts
Hereditary nonpolyposis colon cancer, (Lynch syndrome)	Large intestine	40 yr	30%	DNA mismatch repair genes *(MMR)* Autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Other tur (e.g., ova ureter, pa stomach)

APC, adenomatous polyposis coli; *AV* , arteriovenous; *CHRPE* , congenital hypertrophy of the retinal pigment epithelium; *GI,* gastrointestinal; *PTEN* , phosphatase and tensin homolog.

Hamartomatous Tumors

Hamartomas are benign tumors composed of tissues that are normally found in an organ but that are not organized normally. Juvenile, retention, or inflammatory polyps are hamartomatous polyps, which represent the most common intestinal tumors of childhood, occurring in 1–2% of children. Patients generally present in the 1st decade, most often at ages 2-5 yr, and rarely at younger than 1 yr. Polyps may be found anywhere in the gastrointestinal (GI) tract, most commonly in the rectosigmoid colon; they are often solitary but may be multiple.

Histologically, juvenile polyps are composed of hamartomatous collections of mucus-filled glandular and stromal elements with inflammatory infiltrate, covered with a thin layer of epithelium. These polyps are often bulky, vascular, and prone to bleed as their growth exceeds their blood supply with resultant mucosal ulceration, or autoamputation with bleeding from a residual central artery.

Patients often present with painless rectal bleeding after defecation. Bleeding is generally scant and intermittent; rarely presenting findings can include iron deficiency anemia and/or hypoalbuminemia. Extensive bleeding can occur but is generally self-limited, requiring supportive care until the bleeding stops spontaneously after autoamputation. Occasionally endoscopic polypectomy is required for control of bleeding. Abdominal pain or cramps are uncommon unless associated with intussusception. Patients can present with prolapse, with a dark, edematous, pedunculated mass protruding from the rectum. Mucus discharge and pruritus are associated with prolapse.

Patients presenting with rectal bleeding require a thorough workup; differential diagnosis includes anal fissure, other intestinal polyposis syndromes, Meckel diverticulum, inflammatory bowel disease, intestinal infections, Henoch-Schönlein purpura, or coagulopathy.

Diagnosis and therapy are best accomplished via endoscopy. Polyps may be visualized via ultrasound or cross-sectional imaging, but this provides no therapeutic advantage. Colonoscopy affords opportunity for biopsy, polypectomy by snare cautery, and visualization of synchronous lesions; up to 50% of children have one or more additional polyps, and approximately 20% may have more than 5 polyps. Retrieved polyps should be sent for histologic evaluation for definitive diagnosis.

Juvenile Polyposis Syndrome

Patients with juvenile polyposis syndrome (JPS) present with multiple juvenile polyps, ≥5 but typically 50-200. Polyps may be isolated to the colon or distributed throughout the GI tract. There is often a family history (20–50%) with an autosomal dominant pattern of variable penetrance. Alterations in transforming growth factor-β pathways have been identified in some JPS patients and families; mutations in *SMAD4* or *BMPR1A* are found in 50–60% of patients with JPS. Genetic testing is available for both of these mutations. Clinical diagnosis of JPS is established by presence of one of the following: a lifetime total of 5 or more juvenile polyps in the colon, juvenile polyps outside the colon, or any number of juvenile polyps in a patient with a family history of

JPS.

Histologically, these polyps are identical to solitary juvenile polyps; however, the GI malignancy risk is greatly increased (10–50%). Most malignancy is colorectal, although gastric, upper GI, and pancreatic tumors have been described. The risk of malignancy is greater in patients with increased polyp burden and a positive family history. These patients should therefore undergo routine esophagogastroduodenoscopy, colonoscopy, and upper GI contrast studies. Serial polypectomy or polyp biopsy should be undertaken if possible. If dysplasia or malignant degeneration is found, a total colectomy is indicated.

Juvenile polyposis of infancy is characterized by early polyp formation (younger than 2 yr of age) and may be associated with protein-losing enteropathy, hypoproteinemia, anemia, failure to thrive, and intussusception. Early endoscopic or surgical intervention may be needed.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder (incidence: ~1 : 120,000 total population) characterized by mucocutaneous pigmentation and extensive GI hamartomatous polyposis. Macular pigmented lesions may be dark brown to dark blue and are found primarily around the lips and oral mucosa, although these lesions may also be found on the hands, feet, or perineum. Lesions can fade by puberty or adulthood.

Polyps are primarily found in the small intestine (in order of prevalence: jejunum, ileum, duodenum) but may also be colonic or gastric. Histologically, polyps are defined by normal epithelium surrounding bundles of smooth muscle arranged in a branching or frond-like pattern. Symptoms arising from GI polyps in PJS are similar to those of other polyposis syndromes—namely bleeding and abdominal cramping from obstruction or recurrent intussusception. Patients can require repeated laparotomies and intestinal resections.

The diagnosis of PJS is made clinically in patients with histologically proven hamartomatous polyps if 2 of 3 conditions are met: positive family history with an autosomal dominant inheritance pattern, mucocutaneous hyperpigmentation, and small bowel polyposis. Genetic testing can reveal mutations in *LKB1/STK11* (19p13.3), a serine-threonine kinase that acts as a tumor-suppressor gene. Up to 94% of patients with clinical characteristics of PJS have a mutation at this locus. Only 50% of patients with PJS have an affected family member, suggesting a high rate of spontaneous mutations.

Patients with PJS have increased risk of GI and extraintestinal malignancies. Lifetime cancer risk has been reported to be in the range of 47–93%. Colorectal, breast, and reproductive tumors are most common. GI surveillance should begin in childhood (by age 8 yr or when symptoms occur) with upper and lower endoscopy. The small bowel may be evaluated radiographically, with magnetic resonance enterography, endoscopically with balloon or push enteroscopy, or with video capsule endoscopy. Polyps larger than 1.5 cm should be removed, although resection does not lower the cancer risk and is mainly to avoid complications. Screening for breast, gynecologic, and testicular cancers should be routine after age 18 yr.

Phosphatase and Tensin Homolog Hamartoma Tumor Syndromes

Mutations in the tumor-suppressor gene protein tyrosine phosphatase and tensin homolog *(PTEN)* are associated with several rare autosomal dominant syndromes, including Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. These patients present with multiple hamartomas in skin (99%), brain, breast, thyroid, endometrium, and GI tract (60%). Other extraintestinal manifestations include macrocephaly, developmental delay, lipomas, and genital pigmentation. Patients are at increased risk for breast and thyroid malignancies; the risk of GI cancer does not appear to be elevated.

Adenomatous Tumors

Adenomatous Polyposis Coli-Associated Polyposis Syndromes

Familial adenomatous polyposis (FAP) is the most common genetic polyposis syndrome (incidence 1 : 5,000 to 1 : 17,000 persons) and is characterized by numerous adenomatous polyps throughout the colon, as well as extraintestinal manifestations. FAP and related syndromes (attenuated FAP; Gardner and Turcot syndromes) are linked to mutations in the adenomatous polyposis coli *(APC)* gene, a tumor suppressor mapped to 5q21. *APC* regulates degradation of β-catenin, a protein with roles in regulation of the cytoskeleton, tissue architecture organization, cell migration and adherence, and numerous other functions.

Intracellular accumulation of β-catenin may be responsible for colonic epithelial cell proliferation and adenoma formation. More than 400 APC mutations have been described, and up to 30% of patients present with no family history (spontaneous mutations).

Polyps generally develop late in the 1st decade of life or in adolescence (mean age of presentation is 16 yr). At the time of diagnosis, 5 or more adenomatous polyps are present in the colon and rectum. By young adulthood, the number typically increases to hundreds or even thousands. Adenomatous polyps (or adenomas) are precancerous lesions within the surface epithelium of the intestine, displaying various degrees of dysplasia. Without intervention, the risk of developing colon cancer is 100% by the 5th decade of life (average age of cancer diagnosis is 40 yr). Other GI adenomas can develop, particularly in the stomach and duodenum (50–90%). The risk of periampullary or duodenal carcinoma is significantly elevated (4–12% lifetime risk). Extraintestinal malignancies occur at an increased rate in FAP, including hepatoblastoma in young patients (1.6% before age 5 yr) and follicular or papillary thyroid cancer in teens.

Extraintestinal manifestations of FAP may be present from birth or develop in early childhood. Lesions include congenital hypertrophy of retinal pigment epithelium, desmoid tumors, epidermoid cysts, osteomas, fibromas, and lipomas. Many of these benign soft-tissue tumors appear before intestinal polyps develop. Expression of extraintestinal findings can depend on location of mutation on the *APC* gene.

Other syndromes associated with *APC* mutations include *Gardner syndrome* , classically characterized by multiple colorectal polyps, desmoid tumors, and soft-tissue tumors, including fibromas, osteomas (typically mandibular), epidermoid cysts, and lipomas. Once thought to be a distinct clinical entity, Gardner syndrome shares many characteristics with FAP. Up to 20% of FAP patients present with the classic extraintestinal manifestations once associated with Gardner syndrome. Some (but not all) cases of *Turcot syndrome* are also related to *APC.* These patients present with colorectal polyposis and primary brain tumors (medulloblastoma). Attenuated FAP is characterized by a significantly increased risk of colorectal cancer but fewer polyps than classic FAP (average: 30 polyps). The average age of cancer diagnosis in this form of FAP is 50-55 yr. Upper GI tumors and extraintestinal manifestations may be present but are less common.

The clinical presentation of FAP is variable. Polyps are generally sessile, of variable size, and initially asymptomatic. If symptoms develop, they can include rectal bleeding (possibly with secondary anemia), cramping, and diarrhea. The presence of symptoms at presentation does not correlate with malignant changes. Diagnosis should be suspected from family history, and ensuing colonoscopy is confirmatory. Histologic examination of biopsied polyps reveals adenomatous architecture (as opposed to inflammatory or hamartomatous polyps found in other polyposis syndromes) with varying degrees of dysplasia. Genetic testing for *APC* mutations is clinically available, and index patients should be tested. If a mutation is identified, affected family members should be screened and appropriate genetic counseling should be provided. If the index patient does not demonstrate a defined mutation, family members may undergo genetic testing, which might identify novel *APC* mutations. Children with identified *APC* mutations must undergo careful surveillance, with colonoscopy every 1-2 yr. Once polyps are identified, colonoscopy should be performed annually. Patients should also have upper endoscopy after development of colonic polyps to monitor for gastric and especially duodenal lesions.

Treatment of FAP requires prophylactic proctocolectomy to prevent cancer. Ileoanal pull-through procedures restore bowel continuity, with acceptable functional outcomes. Resection should be done once polyposis has become extensive (>20-30) or by the midteens. Nonsteroidal anti-inflammatory agents, such as sulindac, and cyclooxygenase-2 inhibitors, such as celecoxib, might inhibit polyp progression. No guidelines have been established, however, and their efficacy in preventing malignant transformation of existing polyps is unknown.

Carcinoma

Primary carcinomas of the small bowel or colon are extremely rare in children. Development of adenocarcinoma in adolescence or early adulthood may be associated with a genetic predisposition or syndrome such as FAP, hereditary nonpolyposis colon carcinoma, PJS, radiation exposure, or inflammatory bowel disorders such as Crohn disease or ulcerative colitis.

Colorectal carcinoma, though rare (reported incidence of 1 case per 1,000,000 persons younger than 19 yr of age), is the most common primary GI carcinoma in children. Many cases are spontaneous (i.e., not associated with a genetic predisposition or syndrome). Histologically, tumors tend to be poorly differentiated and pathologically aggressive. Patients may be asymptomatic, or they present with nonspecific signs and symptoms such as abdominal pain, constipation, and vomiting. Delay in diagnosis is common. Many patients present with advanced-stage disease, with microscopic or gross metastases at the time of diagnosis. Surgical resection is the primary treatment modality, although with delayed presentation and advanced-stage disease, complete resection may not be possible. Chemotherapy and radiation have a limited role in patients with metastatic disease.

Other Gastrointestinal Tumors

Lymphoma

Lymphoma is the most common GI malignancy in the pediatric population. Approximately 30% of children with non-Hodgkin lymphoma present with abdominal tumors. Immunocompromised patients have an increased incidence of lymphoma. Predisposing conditions include HIV/AIDS, agammaglobulinemia, long-standing celiac disease, and bone marrow or solid-organ transplantation. Lymphoma can occur anywhere in the GI tract, but it most commonly occurs in distal small bowel and ileocecal region. Presenting symptoms include crampy abdominal pain, vomiting, obstruction, bleeding, or palpable mass. Lymphoma should be considered in patients older than 3 yr of age who present with intussusception. Treatment consists of a combination of surgical resection and chemotherapy, depending on the extent of the tumor burden.

Nodular Lymphoid Hyperplasia

Lymphoid follicles in the lamina propria and submucosa of the gut normally aggregate in Peyer patches, most prominently in the distal ileum. These follicles can become hyperplastic, forming nodules that protrude into the lumen of the bowel during times of developmental lymphoid proliferation such as early childhood and adolescence. Some suggested etiologies are infectious (classically *Giardia*), allergic, or immunologic. Nodular lymphoid hyperplasia has been described in infants with enterocolitis secondary to dietary protein sensitivity. This phenomenon has also been described in patients with inflammatory bowel disease and Castleman disease. Patients may be asymptomatic or, especially in cases of immunodeficiency, may present with abdominal pain, rectal bleeding, diarrhea, or intussusception. Nodular lymphoid hyperplasia usually resolves spontaneously. The use of anti-inflammatory medications or elimination diets is unlikely to change the clinical course, although in cases with severe pain or bleeding, corticosteroids may be effective.

Carcinoid Tumor

Carcinoids are neuroendocrine tumors of enterochromaffin cells, which can occur throughout the GI tract, but in children they are typically found in the appendix. This is often an incidental diagnosis at the time of appendectomy. Complete resection of small tumors (<1 cm) with clear surgical margins is curative. Appendiceal tumors >2 cm mandate further bowel resection, typically a right hemicolectomy. Carcinoid tumors outside the appendix (small intestine, rectum, stomach) are more likely to metastasize. Metastatic carcinoid tumor within the liver can give rise to the carcinoid syndrome. Serotonin, 5-hydroxytryptophan, or histamine is elaborated by the tumor, and elevated serum levels cause cramps, diarrhea, vasomotor disturbances (flushing), bronchoconstriction, and right-heart failure. The diagnosis is confirmed by elevated urinary 5-hydroxyindoleacetic acid. Symptomatic relief of carcinoid symptoms may be achieved with administration of somatostatin analogs (octreotide).

Leiomyoma

Leiomyomas are rare benign tumors that can arise anywhere in the GI tract, although most often in the stomach, jejunum, or distal ileum. Age of presentation is variable, from the newborn period through adolescence. Patients may be asymptomatic or can present with an abdominal mass, obstruction, intussusception, volvulus, or pain and bleeding from central necrosis of the tumor. Surgical resection is the treatment of choice. Pathologically, these tumors may be difficult to distinguish from malignant leiomyosarcomas. Smooth muscle tumors occur with increased incidence in children with HIV or those requiring immunosuppression after transplantation.

Gastrointestinal Stromal Cell Tumors

Gastrointestinal stromal cell tumors (GISTs) are intestinal mesenchymal tumors that probably arise from interstitial cells of Cajal or their precursors. Historically, these may have been diagnosed as tumors of smooth muscle or neural cell origin. The World Health Organization recognized GIST in 1990 as a distinct neoplasm. Typically GISTs arise in adults, after the 3rd decade of life. Cases have also been reported in the pediatric population, generally in adolescents with a female predominance. In the pediatric population, tumors are most commonly found in the stomach, though they can occur anywhere in the GI tract or even the mesentery or omentum. Many patients (~45%) present with metastatic disease primarily to the lymph nodes, although metastases to the peritoneum or liver occur as well. Patients may be asymptomatic for years to decades or can present with an abdominal mass, lower GI bleeding, or obstruction. Treatment consists of surgical resection of local disease. Recurrence rates are high, and early postoperative surveillance is recommended. GISTs occurring in adults are typically associated with mutation in the *KIT* oncogene. This mutation is less commonly found in pediatric GISTs (~15%). Adjuvant therapy for *KIT* $^+$ lesions is imatinib or sunitinib, tyrosine kinase inhibitors that are available as oral therapy. Patients with persistent disease or metastases might benefit from treatment.

Vascular Tumors

Vascular malformations and hemangiomas are rare in children. The usual presentation is painless rectal bleeding, which may be chronic or acute, with massive or even fatal hemorrhage. There are usually no associated symptoms, although intussusception has been described. Half of patients have associated cutaneous hemangiomas or telangiectasia. These lesions may be associated with blue rubber bleb nevus syndrome, hereditary hemorrhagic telangiectasia, as well as other syndromes. About half of these lesions are in the colon and can be identified on colonoscopy. During acute bleeding episodes, bleeding can be localized via nuclear medicine bleeding scans, mesenteric angiography, or endoscopy. Colonic bleeding may be controlled by endoscopic means. Surgical intervention is required occasionally for isolated lesions.

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CHAPTER 373

Inguinal Hernias

John J. Aiken

Inguinal hernias are one of the most common conditions seen in pediatric practice, with an overall incidence of 0.8–4.5% in term infants and children and increasing to nearly 30% in premature and low birthweight (<1 kg) infants. The repair of congenital inguinal hernia is the most common surgical procedure performed in pediatric surgical practice. The frequency of this condition, along with its potential morbidity of ischemic injury to the intestine, testis, or ovary, makes proper diagnosis and management an important aspect of daily practice for pediatric practitioners and pediatric surgeons. Most inguinal hernias in infants and children are **congenital indirect** hernias (99%) because of a patent processus vaginalis (PV), an evagination of peritoneum in the inguinal area important in testicular descent. There is rarely any defect/deficiency in the abdominal wall musculature in congenital indirect inguinal hernia. Inguinal hernias are more common in males compared with females (8 : 1 ratio), but females have a higher incidence of bilateral inguinal hernias (~25%) compared with males (~12%). Two other types of inguinal hernia are seen rarely in children: **direct** (acquired) hernia (0.5–1.0%) and **femoral** hernia (<0.5%). Femoral hernias are substantially more common in females (2 : 1 ratio). Approximately 50% of inguinal hernias manifest clinically in the 1st yr of life, most in the first 6 mo. The incidence of incarceration in untreated hernias varies between 6% and 18% across ages. The risk of incarceration is greatest in infancy, with some reports of incarceration rates of 30–40% in the 1st yr of life, mandating prompt identification and operative repair to minimize morbidity and complications related to incarceration and strangulation. Laparoscopic hernia (LH) repair has increasingly emerged in many pediatric centers as an effective alternative to traditional open hernia (OH) repair.

Embryology and Pathogenesis

Indirect inguinal hernias in infants and children are congenital and result from an arrest of embryologic development—failure of obliteration of the PV rather than a weakness in the abdominal wall musculature. The pertinent developmental anatomy of indirect inguinal hernia relates to development of the gonads and descent of the testis through the inguinal canal and into the scrotum late in gestation. The testes descend from the urogenital ridge in the retroperitoneum to the area of the internal ring by about 28 wk of gestation. The final descent of the testes into the scrotum occurs late in gestation, between weeks 28 and 36, guided by the PV and the gubernaculum. The PV, an outpouching of peritoneum in the inguinal region, is present in the developing fetus at 12 wk gestation. The PV develops lateral to the deep inferior epigastric vessels and descends anteriorly along the spermatic cord within the cremasteric fascia through the internal inguinal ring. The testis accompanies the PV as it exits the abdomen and descends into the scrotum. The gubernaculum testis forms from the mesonephros (developing kidney), attaches to the lower pole of the testis, and directs the testis through the internal ring, inguinal canal and into the scrotum. The testis passes through the inguinal canal in a few days but takes about 4 wk to migrate from the external ring to its final position in the scrotum. The cordlike structures of the gubernaculum occasionally pass to ectopic locations (perineum or femoral region), resulting in ectopic testes.

In the last few weeks of gestation or shortly after birth, the layers of the PV normally fuse together and obliterate the patency from the peritoneal cavity through the inguinal canal to the testis. The PV also obliterates distally just above the testes, and the portion of the PV that envelops the testis becomes the tunica vaginalis. In females, the PV obliterates earlier, at approximately 7 mo of gestation, and may explain why females demonstrate a much lower incidence of inguinal hernia. Proper closure of the PV effectively *seals off* the opening from the abdominal cavity into the inguinal region, containing the abdominal viscera within the abdominal cavity. Failure of the PV to close permits fluid or abdominal viscera to escape the abdominal cavity into the extra-abdominal inguinal canal and accounts for a variety of inguinal–scrotal abnormalities commonly seen in infancy and childhood. Involution of the left-sided PV precedes that of the right, which is consistent with the increased incidence of indirect inguinal hernias on the right side (60%).

The ovaries descend into the pelvis from the urogenital ridge but do not exit from the abdominal cavity. The cranial portion of the gubernaculum in females differentiates into the ovarian ligament, and the inferior aspect of the gubernaculum becomes the round ligament, which passes through the internal ring and terminates in the labia majora. The PV in females is also known as the canal of Nuck.

Androgenic hormones produced by the fetal testis, adequate end-organ receptors, and mechanical factors such as increased intraabdominal pressure combine to regulate complete descent of the testis. The testes and spermatic cord structures (spermatic vessels and vas deferens) are located in the retroperitoneum but are affected by increases in intraabdominal pressure as a consequence of their intimate attachment to the descending PV. The genitofemoral nerve also has an important role: it innervates the cremaster muscle, which develops within the gubernaculum, and experimental division or injury to both nerves in the fetus prevents testicular descent. Failure of regression of smooth muscle (present to provide the force for testicular descent) has also been postulated to play a role in the development of indirect inguinal hernias. Several studies have investigated genes involved in the control of testicular descent for their role in closure of the patent PV—for example, hepatocyte growth factor and calcitonin gene-related peptide. Unlike in adult hernias, there does not appear to be any deficiency in collagen synthesis associated with inguinal hernia in children (Fig. 373.1).

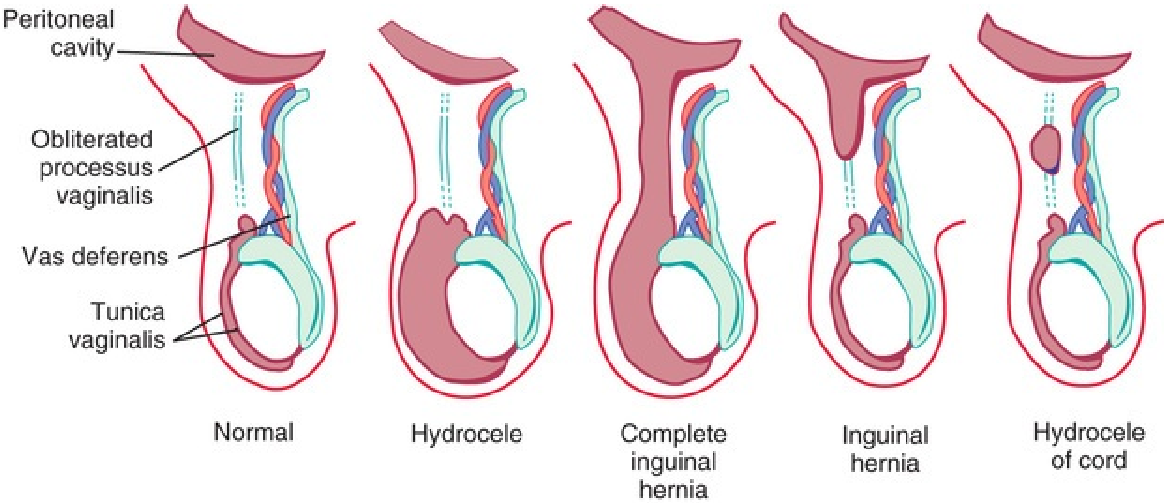

FIG. 373.1 **Hernia and hydroceles. (Modified from Scherer LR III, Grosfeld JL: Inguinal and umbilical anomalies, *Pediatr Clin North Am* 40:1121–1131, 1993.)**

A **direct inguinal hernia** results from a weakness in the abdominal wall musculature in the inguinal region, specifically the transverses abdominis muscle, which forms the floor of the inguinal canal. A direct inguinal hernia originates **medial** to the deep inferior epigastric vessels and is external to the cremasteric fascia; the hernia sac protrudes directly through the posterior wall of the inguinal canal and does not protrude through the external ring. A **femoral hernia** originates medial to the femoral vein and descends inferior to the inguinal ligament along the femoral canal.

Incidence

The incidence of congenital indirect inguinal hernia in full-term newborn infants is estimated at 3.5–5.0%. The incidence of hernia in preterm and low birthweight infants is considerably higher, ranging from 9% to 11%, and approaches 30% in very-low birthweight infants (<1,000 g) and preterm infants (<28 wk of gestation). Inguinal hernia is much more common in males than females, with a male-to-female ratio of approximately 8 : 1. Approximately 60% of inguinal hernias occur on the right side, 30% are on the left side, and 10% are bilateral. The incidence of bilateral hernias is higher in females (20–40%) and young children (<2 yr). An increased incidence of congenital inguinal hernia has been documented in twins and in family members of patients with inguinal hernia. There is a history of another inguinal hernia in the family in 11.5% of patients. The sisters of affected females are at the highest risk, with a relative risk of 17.8. In general, the risk of brothers of a sibling is approximately 4-5, as is the risk of a sister of an affected brother. Both a multifactorial threshold model and autosomal dominance with incomplete penetrance and sex influence have been suggested as an explanation for this pattern of inheritance.

Inguinal hernia, scrotal hydrocele (communicating and noncommunicating), and hydrocele of the spermatic cord are conditions resulting from varying degrees of failure of closure of the PV. Closure of the PV is often incomplete at birth and continues postnatally; the rate of patency is inversely proportional to the age of the child. It has been estimated that the patency rate of the PV is as high as 80% at birth and decreases to ≈40% during the 1st yr of life, and that ≈20% of males have a persistent patency of the PV at 2 yr of age. Patency of the PV after birth is an opening from the abdominal cavity into the inguinal region and therefore a potential hernia, but not all patients will develop a clinical hernia. An inguinal hernia occurs clinically when intraabdominal contents escape the abdominal cavity and enter the inguinal region through the PV patency. Depending on the extent of patency of the PV, the hernia may be confined to the inguinal region or pass down into the scrotum. Complete failure of obliteration of the PV, mostly seen in infants, predisposes to a complete inguinal hernia characterized by a protrusion of abdominal contents into the inguinal canal and extending into the scrotum. Obliteration of the PV distally (around the testis) with patency proximally results in the classic indirect inguinal hernia with a bulge in the inguinal canal.

A **hydrocele** occurs when only fluid enters the patent PV; the swelling may exist only in the scrotum (scrotal hydrocele), only along the spermatic cord in the inguinal region (hydrocele of the spermatic cord), or extend from the scrotum through the inguinal canal and even into the abdomen (abdominal–scrotal hydrocele). A hydrocele is termed a **communicating hydrocele** if it demonstrates fluctuation in size, often increasing in size after activity and, at other times, being smaller when the fluid decompresses into the peritoneal cavity often after laying recumbent. Occasionally, hydroceles develop in older children following trauma, inflammation, torsion of the appendix testes, or in association with tumors affecting the testis.

Although reasons for failure of closure of the PV are unknown, it is more common in cases of testicular nondescent (cryptorchidism) and prematurity. In addition, persistent patency of the PV is twice as common on the right side, presumably related to later descent of the right testis and interference with obliteration of the PV from the developing inferior vena cava and external iliac vein. Table 373.1 lists the risk factors identified as contributing to failure of closure of the PV and to the development of clinical inguinal hernia. The incidence of inguinal hernia in patients with cystic fibrosis is approximately 15%, believed to be related to an altered embryogenesis of the wolffian duct structures, which leads to an absent vas deferens and infertility in males with this condition. There is also an increased incidence of inguinal hernia in patients with **testicular feminization syndrome** and other disorders of sexual development. The rate of recurrence after repair of an inguinal hernia in patients with a connective tissue disorder approaches 50%, and often the diagnosis of connective tissue disorders in children results from investigation following development of a recurrent inguinal hernia.

Table 373.1

Predisposing Factors for Hernias

- Prematurity

- Urogenital
  - Cryptorchidism
  - Exstrophy of the bladder or cloaca
  - Ambiguous genitalia
  - Hypospadias/epispadias
- Increased peritoneal fluid
  - Ascites
  - Ventriculoperitoneal shunt
  - Peritoneal dialysis catheter
- Increased intraabdominal pressure
  - Repair of abdominal wall defects
  - Severe ascites (chylous)
  - Meconium peritonitis
- Chronic respiratory disease
  - Cystic fibrosis
- Connective tissue disorders
  - Ehlers-Danlos syndrome
  - Hunter-Hurler syndrome
  - Marfan syndrome
  - Mucopolysaccharidosis

Clinical Presentation and Diagnosis

An inguinal hernia typically appears as an intermittent, asymptomatic bulge or mass in the inguinal region or scrotum, most often noted on routine physical examination or by a parent; after bathing or urination are classic presentations. In females, the mass typically occurs in the upper portion of the labia majora. The bulge or mass is most visible at times of irritability or increased intraabdominal pressure (crying, straining, coughing). Most inguinal hernias present clinically in young children, approximately 50% in the 1st yr, and most are asymptomatic or minimally symptomatic. The classic history from the parents is of intermittent groin, labial, or scrotal swelling that spontaneously reduces but that is gradually enlarging or is more persistent and is becoming more difficult to reduce. The **hallmark signs** of an inguinal hernia on physical examination are a smooth, firm mass that emerges through the external inguinal ring lateral to the pubic tubercle and enlarges with increased intraabdominal pressure. When the child relaxes, the hernia typically reduces spontaneously or can be reduced by gentle pressure, 1st posteriorly to free it from the external ring and then upward toward the peritoneal cavity. In males, the hernia sac contains intestines; female infants often have an ovary and fallopian tube in the hernia sac.

The diagnosis of inguinal hernia is clinical and generally is made by history and physical examination. Methods used to demonstrate the hernia on examination vary depending on the age of the child. A quiet infant can be made to strain the abdominal muscles by stretching the infant out supine on the bed with legs extended and arms held straight above the head. Most infants struggle to get free, thus increasing the intraabdominal pressure and pushing out the hernia. Older children can be asked to perform the Valsalva maneuver by blowing up a balloon or coughing. The older child should be examined while standing, and examination after voiding also can be helpful. With increased intraabdominal pressure, the protruding mass is obvious on inspection of the inguinal region or can be palpated by an examining finger invaginating the scrotum to palpate at the external ring. Another subtle and less definitive test is the *silk glove sign,* which describes the feeling of the layers of the hernia sac as they slide over the spermatic cord structures with rolling of the spermatic cord beneath the index finger at the pubic tubercle. In the absence of a bulge, the finding of increased thickness of the inguinal canal structures on palpation also suggests the diagnosis of an inguinal hernia. It is important on examination to note the position of the testes because retractile testes are common in infants and young males and can mimic an inguinal hernia with a bulge in the region of the external ring. Because in the female patient approximately 20–25% of inguinal hernias are **sliding** hernias (the contents of the hernia sac are adherent within the sac and therefore not reducible), a fallopian tube or ovary can be palpated in the inguinal canal as a firm, slightly mobile, nontender mass in the labia or inguinal canal. A **femoral** hernia appears as a protrusion on the medial aspect of the thigh, below the inguinal region, and does not enter the scrotum or labia.

Because most young child hernias reduce spontaneously, the physical examination in the office can be equivocal. Infants and children with a strong history suggestive of inguinal hernia and an equivocal clinical examination may be offered ultrasound or referral to a pediatric surgeon. Diagnostic laparoscopy has been increasingly used to evaluate for suspected inguinal hernia; particularly in infants where the risk of incarceration and potential injury to the intestines or testis is high. In an older child with low risk of incarceration, the parents can be reassured and educated relative to the low risk of incarceration and morbidity. If an inguinal hernia is present, it will predictably become increasingly observed. A plan for a period of observation is thoughtful and safe, and the parents can be asked to take a digital image at home if the bulge is noted.

Evaluation of Acute Inguinal–Scrotal

Swelling

Commonly in pediatric practice, an inguinal–scrotal mass appears suddenly in an infant or child and is associated with pain/discomfort. The differential diagnosis includes incarcerated inguinal hernia, acute hydrocele, torsion of an undescended testis, infection (epididymitis/orchitis), and suppurative inguinal lymphadenitis. Differentiating between the incarcerated inguinal hernia and the acute hydrocele is probably the most difficult. The infant or child with an incarcerated inguinal hernia is likely to have associated findings suggesting intestinal obstruction, such as colicky abdominal pain, abdominal distention, vomiting, and cessation of stool, and may appear ill. Plain radiographs, if obtained, typically demonstrate distended intestines with multiple air–fluid levels. The infant with an acute hydrocele may have discomfort but is consolable and tolerates feedings without signs or symptoms suggesting intestinal obstruction.

On examination of the child with the acute scrotal hydrocele, the clinician may note that the mass is somewhat mobile. In addition, the inguinal region is flat and the mass confined to the scrotum. With the incarcerated hernia, there is a lack of mobility of the groin mass and marked swelling or mass extending from the scrotal mass through the inguinal area and up to and including the internal ring. An experienced clinician can selectively use a bimanual examination to help differentiate groin abnormalities. The examiner palpates the internal ring per rectum, with the other hand placing gentle pressure on the inguinal region over the internal ring. In cases of an indirect inguinal hernia, intraabdominal viscera can be palpated extending through the internal ring.

Another method used in diagnostic evaluation is **transillumination** to ascertain if the mass contains only fluid (hydrocele) versus intestine (hernia); however, it must be noted that transillumination can be misleading because the thin wall of the infant's intestine can approximate that of the hydrocele wall and both may transilluminate. This is also the reason aspiration to assess the contents of a groin mass is discouraged. **Ultrasonography** can help distinguish between a hernia, a hydrocele, and lymphadenopathy, and is a simple and well-tolerated test. An expeditious diagnosis is important to avoid the potential complications of an incarcerated hernia, which can develop rapidly. Diagnostic laparoscopy is an effective and reliable tool in this setting by pediatric surgeons but requires general anesthesia.

The occurrence of suppurative adenopathy in the inguinal region can be confused with an incarcerated inguinal hernia. Examination of the watershed area of the inguinal lymph nodes might reveal a superficial infected or crusted skin lesion. In addition, the swelling associated with inguinal lymphadenopathy is typically located more inferior and lateral than the mass of an inguinal hernia, and there may be other associated enlarged nodes in the area. Torsion of an undescended testis can manifest as a painful erythematous mass in the groin. The absence of a gonad in the scrotum in the ipsilateral side should clinch this diagnosis. Infectious etiologies typically demonstrate swelling and tenderness of the testis, but often there is associated urinary symptoms and the swelling is confined to the scrotum and does not extend into the inguinal canal.

Incarcerated Hernia

Incarceration is a common consequence of untreated inguinal hernia in infants and presents as a *nonreducible* mass in the inguinal canal, scrotum, or labia. Contained structures can include small bowel, appendix, omentum, colon, bladder, or, rarely, Meckel diverticulum. In females, the ovary, fallopian tube, or both are commonly incarcerated. Rarely, the uterus in infants can also be pulled into the hernia sac. A **strangulated hernia** is one that is tightly constricted in its passage through the inguinal canal, and as a result, the hernia contents have become ischemic or gangrenous. The incidence of incarceration of an inguinal hernia is between 6% and 18% throughout childhood years, and two thirds of incarcerated hernias occur in the 1st yr of life. The greatest risk is in infants younger than 6 mo of age, with reported incidences of incarceration between 25% and 30%. Reports vary, but many believe a history of prematurity imparts an increased risk of incarceration in the 1st yr of life.

Although incarceration may be tolerated in adults for years, most nonreducible inguinal hernias in children, unless treated, rapidly progress to *strangulation* with potential infarction of the hernia contents or intestinal obstruction. Initially, pressure on the herniated viscera leads to impaired lymphatic and venous drainage. This leads to swelling of the herniated viscera, which further increases the compression in the inguinal canal, ultimately resulting in total occlusion of the arterial supply to the trapped viscera. Progressive ischemic changes take place, culminating in gangrene and/or perforation of the herniated viscera. The testis is at risk of ischemia because of compression of the testicular blood vessels by the strangulated hernia. In females, herniation/incarceration of the ovary places it at risk of torsion with resultant ischemia.

The symptoms of an incarcerated hernia are irritability, feeding intolerance, and abdominal distention in the infant; pain presents in the older child. Within a few hours, the infant becomes inconsolable; lack of flatus or stool signals complete intestinal obstruction. A somewhat tense, nonfluctuant mass is present in the inguinal region and can extend down into the scrotum or labia. The mass is well defined, firm, and does not reduce. With the onset of ischemic changes, the pain intensifies, and the vomiting becomes bilious or feculent. Blood may be noted in the stools. The mass is typically markedly tender, and there is often edema and erythema of the overlying skin. The testes may be normal, demonstrate a reactive hydrocele, or may be swollen and hard on the affected side because of venous congestion resulting from compression of the spermatic veins and lymphatic channels at the inguinal ring by the tightly strangulated hernia mass. Abdominal radiographs demonstrate features of partial or complete intestinal obstruction, and gas within the incarcerated bowel segments may be seen below the inguinal ligament or within the scrotum.

Ambiguous Genitalia

Infants with disorders of sexual development commonly present with inguinal hernias, often containing a gonad, and require special consideration. In female infants with inguinal hernias, particularly if the presentation is bilateral inguinal masses, **testicular feminization syndrome** should be suspected (>50% of patients with testicular feminization have an inguinal hernia; see Chapter 606). Conversely, the true incidence of testicular feminization in all female infants with inguinal hernias is difficult to determine but is approximately 1%. In phenotypic females, if the diagnosis of testicular feminization is suspected preoperatively, the child should be screened with a buccal smear for Barr bodies and appropriate genetic evaluation before proceeding with the hernia repair. The diagnosis of testicular feminization is occasionally made at the time of operation by identifying an abnormal gonad (testis) within the hernia sac or absence of the uterus on laparoscopy or rectal exam. In the normal female infant, the uterus is easily palpated as a distinct midline structure beneath the symphysis pubis on rectal examination. Preoperative diagnosis of testicular feminization syndrome or other disorders of sexual development such as mixed gonadal dysgenesis and selected pseudohermaphrodites enables the family to receive genetic counseling, and gonadectomy can be accomplished at the time of the hernia repair if indicated.

Indications for Surgery

The presence of an inguinal hernia in the pediatric age group constitutes the indication for operative repair. An inguinal hernia does not resolve spontaneously, and prompt repair eliminates the risk of incarceration and the associated potential complications, particularly in the 1st 6-12 mo of life. The timing of operative repair depends on several factors, including age, general condition of the patient, and comorbid conditions. In full-term, healthy infants (younger than 1 yr) with an inguinal hernia, repair should proceed promptly (within 2-3 wk) following diagnosis because as many as 70% of incarcerated inguinal hernias requiring emergency operation occur in infants younger than 11 mo. In addition, the incidence of complications associated with elective hernia repair (intestinal injury, testicular atrophy, recurrent hernia, wound infection) are low (≈1%), but rise to as high as 18–20% when repair is performed emergently at the time of incarceration. The incidence of testicular atrophy after incarceration in infants younger than 3 mo of age has been reported as high as 30%. Therefore, an approach emphasizing prompt elective repair in infants is warranted; anesthetic risks must be considered when determining timing of elective surgery for inguinal hernia repair. The risk factors for apnea following general anesthesia include prematurity, multiple congenital anomalies, history of apnea and bradycardia, chronic lung disease, postconceptual age <60 wk at the time of surgery, and anemia. Unfortunately, while this group of patients would be ideal for inguinal hernia repair under regional (spinal/caudal) anesthesia, inguinal hernia repair in this group is often remarkably technically challenging even for experienced pediatric surgeons, and success is elusive under regional techniques. The outcome advantage of a regional technique is lost if additional intravenous sedation is required. Full-term infants <3 mo of age and preterm infants <60 wk postconceptual age should be observed following repair for a minimum of 12 hr postoperatively and potentially overnight following general anesthesia for the development of apnea and bradycardia.

In children older than 1 yr, the risk of incarceration is less, and the repair can be scheduled with less urgency. For the routine reducible hernia, the operation should be carried out electively shortly after diagnosis. Elective inguinal hernia repair in healthy children can be safely performed in an outpatient setting with an expectation for full recovery within 48 hr. A regional caudal block or local inguinal nerve block using local anesthetic is useful to diminish perioperative pain and optimize recovery. Prophylactic antibiotics are not routinely used except for associated conditions, such as congenital heart disease or the presence of a ventriculoperitoneal shunt. *The operation should be performed at a facility with the ability to admit the patient to an inpatient unit as needed should concerns or complications arise.*

There is controversy as to the optimal timing of inguinal herniorrhaphy in preterm and low-birth-weight infants. In the past 2 decades, most pediatric surgeons have planned hernia repair shortly before discharge from the neonatal intensive care unit. This group has a high rate of incarceration, but also a high risk of anesthesia related postoperative complications with elective surgery, such as apnea, bradycardia, inability to extubate, hemodynamic instability (5–10%), and even cardiopulmonary arrest. In addition, this group also has an increased rate of postoperative surgical-related complications such as wound infection (5–10%) and recurrent hernia (10%). At present, studies to develop evidence-based data for timing of inguinal hernia repair in premature infants are ongoing, but there is a lack of consensus and patients should be individualized, with important consultation with both neonatology and pediatric anesthesia. The operation for inguinal hernia repair is most often performed under general anesthesia, but it can be performed under spinal/caudal anesthesia in selected high-risk infants in whom avoidance of intubation is preferable (e.g., because of chronic lung disease or bronchopulmonary dysplasia). In this setting, open repair (OH) is preferable to the laparoscopic approach, as it can be performed under local/regional techniques.

An incarcerated, irreducible hernia without evidence of strangulation in a clinically stable patient should initially be managed nonoperatively, unless there is evidence of bowel obstruction, peritonitis, or hemodynamic instability, because 70–95% of incarcerated inguinal hernias are successfully reduced. Manual reduction is performed using a surgical technique called taxis, first with traction caudad and posteriorly to free the mass from the external inguinal ring, and then upward to reduce the contents back into the peritoneal cavity. Reduction attempts usually require sedation (intravenous) and analgesics, and thus appropriate experience with monitoring and airway management are critical concerns. In addition, if reduction of the incarcerated hernia is successful, the infant may rapidly become somnolent and apneic, requiring important supportive measures by skilled personnel. Other techniques advocated to assist in the nonoperative reduction of an incarcerated inguinal hernia include elevation of the lower torso and legs. Ice packs should be avoided in infants because of the risk of hypothermia but may be used for brief periods in the older child. If reduction is successful but difficult, the patient should be observed (several hours) to ensure that feedings are tolerated and there is no concern that necrotic intestine was reduced; fortunately, this is an uncommon occurrence. Given the risk of early recurrent incarceration after a successful reduction, it is recommended that herniorrhaphy be performed following a brief period (1-4 days), by which time there is less edema, handling of the sac is easier, and the risk of complications is reduced.

If the inguinal hernia is unable to be reduced, or there is concern for an incomplete reduction, then operative reduction should be performed emergently. In addition, for any patient who presents with a prolonged history of incarceration of an inguinal hernia, signs of peritoneal irritation, or small bowel obstruction, surgery and operative reduction and repair of the hernia should be urgently performed. Initial management includes nasogastric intubation, intravenous fluids, and administration of broad-spectrum antibiotics. When fluid and electrolyte imbalance has been corrected and the child's condition is satisfactory, exploration is undertaken. In current practice, the laparoscopic approach may have advantages, as the abdominal cavity insufflation expands the internal ring, potentially aiding reduction of the incarcerated viscera as well as enabling visualization of the viscera for possible ischemic injury and/or perforation. The risk of postoperative complications such as testicular atrophy, bowel ischemia, wound infections, and recurrence of hernia is increased following emergency inguinal hernia repair, 4.5–33% compared with 1% in elective hernia repairs in healthy, full-term infants.

A common presentation in female patients is an irreducible ovary in the inguinal hernia in an otherwise asymptomatic patient. The inguinal mass is soft and nontender to gentle exam, and there is no swelling or edema; thus there are no findings suggesting strangulation. This represents a *sliding* hernia with the fallopian tube and ovary fused to the wall of the hernia sac preventing reduction to the abdominal cavity. Overzealous attempts to reduce the hernia are unwarranted and potentially harmful to the tube and ovary. The risk that incarceration, most often resulting from torsion of the ovary in this setting, will lead to strangulation is not known. Most pediatric surgeons recommend elective repair of the hernia within 24-48 hr.

The appearance of necrotic ovaries and testes at the time of operation does not consistently evidence irreversible damage or predict future functionality. Multiple studies report that even when ovaries appear persistently ischemic after relief of incarceration and detorsion, most ovaries, if preserved, will recover and demonstrate evidence of follicular development. Similarly, ischemic appearing testes following relief of incarceration survive in as much as 50% of cases. Testicular atrophy occurs in 2.5–15% of incarcerated hernias. Given the potential for retained functionality, the current recommendation is to avoid testicular resection unless there is frank necrosis present.

Open Inguinal Hernia Repair

The open technique for elective inguinal hernia repair in infants and children has been the standard of care since its introduction more than 50 yr ago. The operation is performed through a small (2-3 cm) inguinal skin crease incision. The procedure involves the opening of the inguinal canal, reduction of the contents of the hernia sac if present, careful separation of the hernia sac from the cremasteric muscle fibers, spermatic cord vessels, and vas deferens to avoid injury to these structures in the inguinal canal, division of the hernia sac, and high ligation of the hernia sac at the internal ring, thus preventing protrusion of abdominal contents into the inguinal canal. A communicating hydrocele is approached with the same technique, separation of the spermatic cord structures from the hernia sac, high ligation of the proximal portion of the hernia sac, and opening of the distal sac to relieve the hydrocele. In older children with a noncommunicating hydrocele, the approach may be through a scrotal incision with avoidance of manipulation of the spermatic cord vessels and vas deferens. Open inguinal hernia repair has a low rate of recurrence, vas deferens injury, and testicular atrophy (~1–2%).

In females, surgical repair is technically simpler because the hernia sac and round ligament can be ligated without concern for injury to the ovary and its blood supply, which generally remain within the abdomen. The hernia sac and round ligament are divided from their distal attachment in the labia majora, proximal dissection away from the cremasteric muscle fibers to the internal ring, and high ligation at the internal ring. In female infants, opening of the sac to visualize the ovary and fallopian tube may help avoid injury to these structures during suture ligation of the sac and also rule out testicular feminization syndrome. If the ovary and fallopian tube are within the sac and not reducible, the sac is suture ligated distal to these structures, and the internal ring is closed after reducing the sac and its contents to the abdominal cavity.

Laparoscopic Inguinal Hernia Repair

Although the classic open inguinal hernia repair is most commonly performed, laparoscopic repair (LH) is used by most pediatric surgeons. There are several techniques described, both transperitoneal and pre-peritoneal, depending on surgeon preference. Like the open technique, the laparoscopic technique is fundamentally a high ligation of the indirect inguinal hernia sac (PV) at the internal ring to prevent protrusion of abdominal viscera into the inguinal canal. The laparoscopic technique affords confirmation of the diagnosis, as well as inspection of the contralateral side for the presence of a hernia or a patent PV (potential hernia). Reported advantages of laparoscopic repair (LR) compared with open repair (OH) include better cosmesis, shorter length of stay (LOS), faster recovery, and greater ability to visualize and repair a contralateral hernia.

In LH, the inguinal canal is not explored, and the spermatic cord structures are not manipulated, which may portend reduced risk to the testicular blood supply or vas deferens, particularly in younger patients. Disadvantages of LH in infants and younger children are the increased risk associated with general anesthesia, the potential hemodynamic effects of abdominal insufflation (acidosis), and technical challenges of the LH technique. Operative times have been similar for the OH and LH approaches; however, there is wide variability with the LH technique based on the experience of the surgeon and surgical team. Laparoscopic procedures in infants should always be performed expeditiously and with low insufflations pressure to avoid the risk of cardiorespiratory compromise and development of acidosis. Postoperative pain in both techniques is managed with oral acetaminophen for 24-48 hr; older children may require a brief period of postoperative narcotics. In a prospective, randomized study, the laparoscopic approach was associated with decreased pain, parental perception of faster recovery, and parental perception of better wound cosmesis. At present, outcomes, recurrence rates, recovery metrics, complications, and family satisfaction appears similar for both approaches (OH and LH), and evidence is lacking to recommend one approach over the other.

Contralateral Inguinal Exploration

Most children (85%) present with a unilateral inguinal hernia. Controversy exists regarding when to proceed with contralateral groin exploration. The only purpose of contralateral exploration is to avoid the occurrence of a hernia on that side at a later date. The advantages of contralateral exploration include avoidance of parental anxiety and possibly a 2nd anesthesia, the cost of additional surgery, and the risk of contralateral incarceration. The disadvantages of exploration include potential injury to the spermatic cord vessels, vas deferens, and testis; increased operative and anesthesia time; and the fact that, in many infants, it is an unnecessary procedure.

With the introduction of minimally invasive techniques and laparoscopy, much of the debate over contralateral inguinal exploration has been resolved, as laparoscopy enables assessment of the contralateral side without risk of injury to the spermatic cord structures or testis. When performing OH repair, the laparoscope can be introduced through an umbilical incision or by passing a 30-degree or 70-degree oblique scope through the OH sac prior to ligation of the hernia sac on the involved side. If patency of the contralateral side is demonstrated, the surgeon can proceed with bilateral hernia repair, and if the contralateral side is properly obliterated, exploration and potential complications are avoided. When performing LH, visualization of the contralateral side is easily performed. The downside of this approach includes the risks associated with laparoscopy, and that laparoscopy cannot differentiate between a patent PV and a true hernia (Figs. 373.2 and 373.3). Infants and children with risk factors for development of an inguinal hernia or with medical conditions that increase the risk of general anesthesia should be approached with a low threshold for routine contralateral exploration.

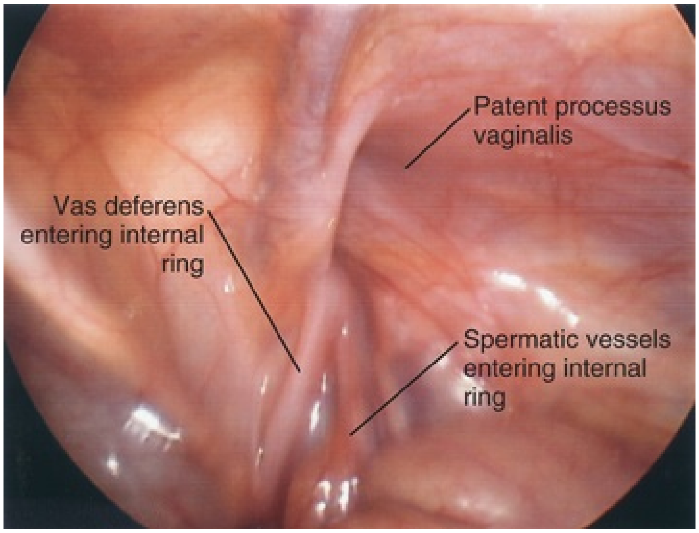
Patent processus vaginalis
Vas deferens entering internal ring
Spermatic vessels entering internal ring

FIG. 373.2 Image on laparoscopy of patent processus vaginalis on right side.

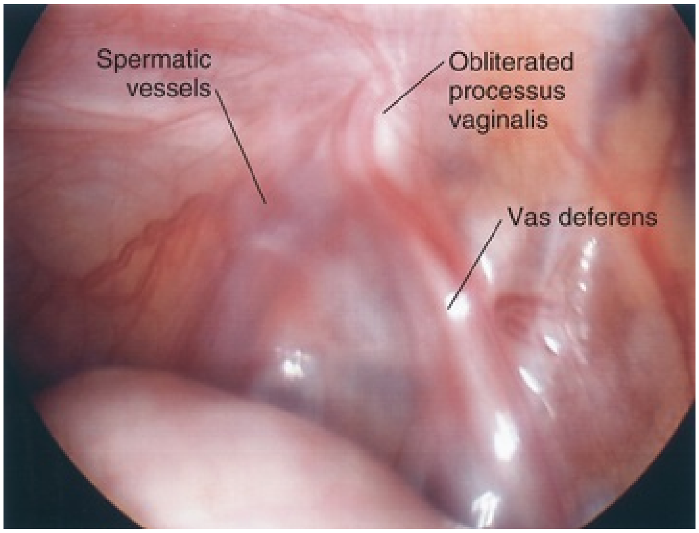

FIG. 373.3 Image on diagnostic laparoscopy of obliterated processus vaginalis on left side.

Direct Inguinal Hernia

Direct inguinal hernias are rare in children, approximately 0.5–1%. Direct hernias appear as groin masses that extend toward the femoral vessels with exertion or straining. The etiology is from a muscular defect or weakness in the floor of the inguinal canal *medial* to the epigastric vessels. Thus direct inguinal hernias in children are generally considered an acquired problem. In one third of cases, the patient has a history of a prior indirect hernia repair on the side of the direct hernia, which suggests a possible missed direct hernia at the initial surgery, or injury to the floor muscles of the inguinal canal at the time of the 1st herniorrhaphy. Patients with **connective tissue disorders** such as Ehlers-Danlos syndrome or Marfan syndrome and mucopolysaccharidosis such as Hunter-Hurler syndrome are at increased risk for the development of direct inguinal hernias either independently or after indirect inguinal hernia repair.

Operative repair of a direct inguinal hernia involves strengthening of the floor of the inguinal canal, and many standard techniques have been described, similar to repair techniques used in adults. The repair can be performed through a single limited incision, and therefore LR does not offer significant advantage. Recurrence after repair, in contrast to that in adults, is extraordinarily rare. Because typically the area of muscular weakness is small and pediatric tissues have greater elasticity, primary repair is usually possible. Prosthetic material (mesh) for direct hernia repair or other approaches, such as preperitoneal repair, are rarely required in the pediatric age group. The older child with a direct inguinal hernia and a connective tissue disorder may be the exception, and a laparoscopic approach and prosthetic material in such a case can be useful for repair.

Femoral Hernia

Femoral hernias are rare in children (<1% of groin hernias in children). They are more common in females than males, (2 : 1 ratio). They are extremely rare in infancy and occur typically in older children, believed to most often be an acquired defect. Femoral hernias represent a protrusion through the femoral canal. The bulge of a femoral hernia is located below the inguinal ligament and typically projects on the medial aspect of the proximal thigh. Femoral hernias are more often missed clinically than direct hernias on physical examination or at the time of indirect hernia repair. Repair of a femoral hernia involves closure of the defect at the femoral canal, generally suturing the inguinal ligament to the pectineal ligament/fascia.

Complications

Complications after elective inguinal hernia repair are uncommon (≈1.5%) but significantly higher in association with incarceration (≈10%). The major risk of elective inguinal hernia repair in infants and children relates to the need for general anesthesia, and spinal/caudal anesthesia should be considered based on the experience of the surgeon and anesthesia team. Surgical complications can be related to technical factors (recurrence, iatrogenic cryptorchidism or *trapped testicle* , inadvertent injury to the vas deferens or spermatic vessels), or to the underlying process, such as bowel ischemia, gonadal infarction, and testicular atrophy following incarceration. The most critical surgical complication of inguinal hernia repair involves injury to the testicular vessels, vas deferens, testicular atrophy, or iatrogenic cryptorchidism (trapped testicle). Since LH repair generally does not involve inguinal exploration or manipulation of the testicular vessels or vas deferens, the risk of injury is potentially lower, but supportive data are unavailable at present.

Wound Infection

Wound infection occurs in <1% of elective inguinal hernia repairs in infants and children, but the incidence increases to 5–7% in association with incarceration and emergent repair. The patient typically develops fever and irritability 3-5 days after the surgery, and the wound demonstrates warmth, erythema, and fluctuance. Management consists of opening and draining the wound, a short course of antibiotics, and a daily wound dressing. The most common organisms are Gram-positive (*Staphylococcus* and *Streptococcus* spp.), and consideration should be given to coverage of methicillin-resistant *Staphylococcus aureus*. The wound generally heals in 1-2 wk with low morbidity and a good cosmetic result.

Recurrent Hernia

The recurrence rate of inguinal hernias after elective inguinal hernia repairs is generally reported as 0.5–1.0%, with rates as high as 2% for premature infants. The rate of recurrence after emergency repair of an incarcerated hernia is much higher, reported as 3–6% in most large series. The true incidence of recurrence is most certainly even higher, given the problem of accurate long-term follow-up. In the group of patients who develop recurrent inguinal hernia, the recurrence occurs in 50% within 1 yr of the initial repair and in 75% by 2 yr. Recurrence of an indirect hernia may be the result of a technical problem in the original procedure, such as failure to identify the sac properly, failure to perform high ligation of the sac at the level of the internal ring, or a tear in the sac that leaves a strip of peritoneum along the cord structures. Recurrence as a direct hernia can result from injury to the inguinal floor (transversalis fascia) during the original procedure or, more likely, failure to identify a direct hernia during the original exploration. Patients with *connective tissue disorders* (collagen deficiency) or conditions that cause *increased intraabdominal pressure* (ventriculoperitoneal shunts, ascites, chronic lung disease, peritoneal dialysis) are at increased risk for recurrence.

Iatrogenic Cryptorchidism (Trapped Testicle)

Iatrogenic cryptorchidism describes malposition of the testis after inguinal hernia repair. This complication is usually related to disruption of the testicular attachment in the scrotum at the time of hernia repair or failure to recognize an undescended testis during the original procedure, allowing the testes to retract, typically to the region of the external ring. At the completion of inguinal hernia repair, the testis should be placed in a dependent intrascrotal position. If the testis will not remain in this position, proper fixation in the scrotum should be performed at the time of the hernia repair.

Incarceration

Incarceration of an inguinal hernia can result in injury to the intestines, the fallopian tube and ovary, or the ipsilateral testis. The incidence of incarceration of a congenital indirect inguinal hernia is reported as 6–18% throughout childhood and as high as 30% for infants younger than 6 mo of age. Intestinal injury requiring bowel resection is uncommon, occurring in only 1–2% of incarcerated hernias. In cases of incarceration in which the hernia is reduced nonoperatively, the likelihood of intestinal injury is low; however, these patients should be observed closely for 6-12 hr following reduction of the hernia persistent for signs and symptoms of intestinal obstruction, such as fever, vomiting, abdominal distention, or bloody stools. Laparoscopy affords the opportunity to inspect the reduced viscera for injury or necrosis in select cases.

The reported incidence of testicular infarction and subsequent testicular atrophy with incarceration is 4–12%, with higher rates among the irreducible cases requiring emergency operative reduction and repair. The testicular insult can be caused by compression of the gonadal vessels by the incarcerated hernia mass or as a result of damage incurred during operative repair. Young infants are at highest risk, with testicular infarction rates reported as high as 30% in infants younger than 2-3 mo of age. These problems underscore the need for prompt reduction of incarcerated hernias and early repair once the diagnosis is known to avoid repeat episodes of incarceration.

Injury to the Vas Deferens and Male Fertility

Similar to the gonadal vessels, the vas deferens can be injured as a consequence of compression from an incarcerated hernia or during operative repair. This injury is almost certainly underreported because it is unlikely to be recognized until adulthood and, even then, possibly only if the injury is bilateral. Although the vulnerability of the vas deferens has been documented in many studies, no good data exist as to the actual incidence of this complication. One review reported an incidence of injury to the vas deferens of 1.6% based on pathology demonstrating segments of the vas deferens in the hernia sac specimen; this may be overstated, because others have shown that small glandular inclusions found in the hernia sac can represent müllerian duct remnants and are of no clinical importance. The relationship between male fertility and previous inguinal hernia repair is also unknown. There appears to be an association between infertile males with testicular atrophy and abnormal sperm count and a previous hernia repair. A relationship has also been reported between infertile males with spermatic autoagglutinating antibodies and previous inguinal hernia repair. The proposed etiology is that operative injury to the vas deferens during inguinal hernia repair might result in obstruction of the vas with diversion of spermatozoa to the testicular lymphatics, and this breach of the blood–testis barrier produces an antigenic challenge, resulting in formation of spermatic autoagglutinating antibodies.

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SECTION 5

Exocrine Pancreas

OUTLINE

Chapter 374 Embryology, Anatomy, and Physiology of the Pancreas

Chapter 375 Pancreatic Function Tests

Chapter 376 Disorders of the Exocrine Pancreas

Chapter 377 Treatment of Pancreatic Insufficiency

Chapter 378 Pancreatitis

Chapter 379 Pancreatic Fluid Collections

Chapter 380 Pancreatic Tumors

CHAPTER 374

Embryology, Anatomy, and Physiology of the Pancreas

Steven L. Werlin, Michael Wilschanski

The human pancreas develops from the ventral and dorsal domains of the primitive duodenal endoderm beginning at about the 5th wk of gestation (Fig. 374.1). The larger dorsal anlage, which develops into the tail, body, and part of the head of the pancreas, grows directly from the duodenum. The smaller ventral anlage develops as 1 or 2 buds from the primitive liver and eventually forms the major portion of the head of the pancreas. At about the 17th wk of gestation, the dorsal and ventral anlagen fuse as the buds develop and the gut rotates. The ventral duct forms the proximal portion of the major pancreatic duct of Wirsung, which opens into the ampulla of Vater. The dorsal duct forms the distal portion of the duct of Wirsung and the accessory duct of Santorini, which empties independently in approximately 5% of people. Variations in fusion might account for pancreatic developmental anomalies. Pancreatic agenesis has been associated with a base pair deletion in the insulin promoter factor 1-*HOX* gene, *PDX1 (PAGEN1)* , *PTF1A (PAGEN 2), GATA 6 haploinsufficiency* and *FS123TER* genes. Other genes involved in pancreatic organogenesis include the *IHH* , *SHH* or sonic hedgehog gene, *SMAD2* , and transforming growth factor-1β genes.

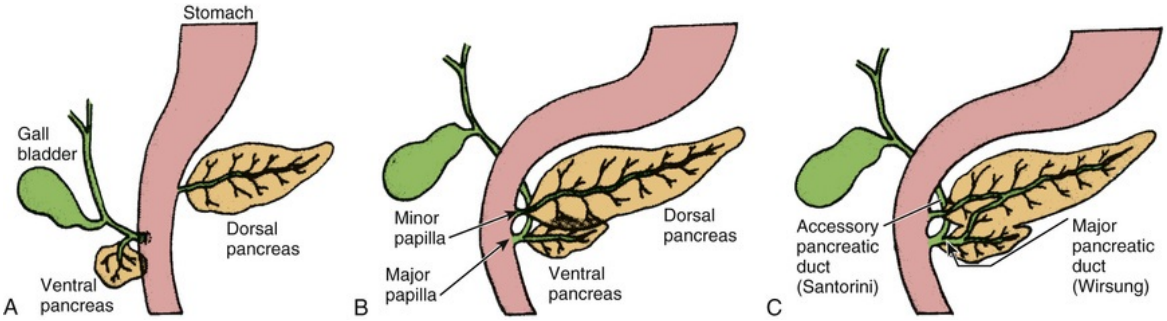
Stomach
Gall bladder
Dorsal pancreas
Ventral pancreas
A
Minor papilla
Major papilla
Dorsal pancreas
Ventral pancreas
B
Accessory pancreatic duct (Santorini)
Major pancreatic duct (Wirsung)
C

FIG. 374.1 **Development of the exocrine pancreas. A, Gestational age 6 wk. B, Gestational age 7-8 wk. The ventral pancreas has rotated but has not yet fused with the dorsal pancreas. C, The ventral and dorsal pancreatic ductal systems have fused. (From Werlin SL: The exocrine pancreas. In Kelly VC, editor: *Practice of pediatrics,* vol 3, Hagerstown, MD, 1980, Harper and Row, Fig. 16.1.)**

The pancreas lies transversely in the upper abdomen between the duodenum and the spleen in the retroperitoneum (Fig. 374.2). The head, which rests on the vena cava and renal vein, is adherent to the C loop of the duodenum and surrounds the distal common bile duct. The tail of the pancreas reaches to the left splenic hilum and passes above the left kidney. The lesser sac separates the tail of the pancreas from the stomach.

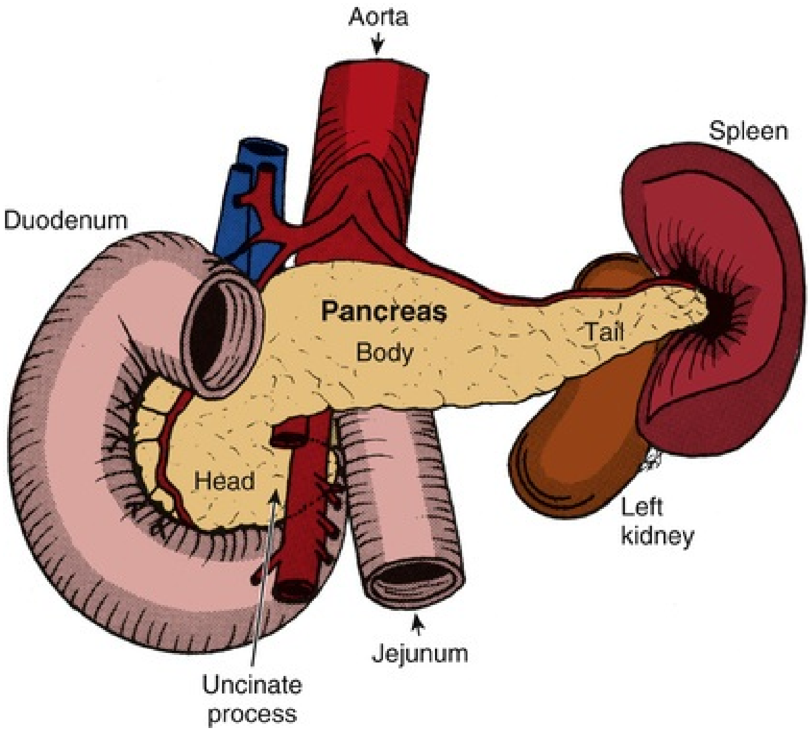
Aorta
Spleen
Duodenum
Pancreas
Body
Tail
Head
Left kidney
Jejunum
Uncinate process

FIG. 374.2 **Anterior view of the pancreas: relationship to neighboring structures. (From Werlin SL: The exocrine pancreas. In Kelly VC, editor: *Practice of pediatrics* , vol 3, Hagerstown, MD, 1980, Harper and Row, Fig. 16.2.)**

By the 13th wk of gestation, exocrine and endocrine cells can be identified. Primitive acini containing immature zymogen granules are found by the 16th wk. Mature zymogen granules containing amylase, trypsinogen, chymotrypsinogen, and lipase are present at the 20th wk. Centroacinar and duct cells, which are responsible for water, electrolyte, and bicarbonate secretion, are also found by the 20th wk. The final 3-dimensional structure of the pancreas consists of a complex series of branching ducts surrounded by grape-like clusters of epithelial cells. Cells containing glucagon are present at the 8th wk. Islets of Langerhans appear between the 12th and 16th wk.

374.1

Pancreatic Anatomic Abnormalities

Steven L. Werlin, Michael Wilschanski

Complete or partial **pancreatic agenesis** is a rare condition. Complete agenesis is associated with severe neonatal diabetes and usually death at an early age (see Chapter 607). Partial or dorsal pancreatic agenesis is often asymptomatic but may be associated with diabetes, congenital heart disease, polysplenia, and recurrent pancreatitis. Pancreatic agenesis is also associated with malabsorption.

An **annular pancreas** results from incomplete rotation of the left (ventral) pancreatic anlage, which may be a result of recessive mutations in the *IHH* or *SHH* genes. Patients usually present in infancy with symptoms of complete or partial bowel obstruction or in the 4th or 5th decade. There is often a history of maternal polyhydramnios. Other congenital anomalies, such as Down syndrome, tracheoesophageal fistula, intestinal atresia, imperforate anus, malrotation and cardiorenal abnormalities, and pancreatitis may be associated with annular pancreas. Some children present with chronic vomiting, pancreatitis, or biliary colic. The treatment of choice is duodenojejunostomy. Division of the pancreatic ring is not attempted because a duodenal diaphragm or duodenal stenosis often accompanies annular pancreas.

Ectopic pancreatic rests in the stomach or small intestine occur in approximately 3% of the population. Most cases (70%) are found in the upper intestinal tract. Recognized on barium contrast studies by their typical umbilicated appearance, they are rarely of clinical importance. On endoscopy, they are irregular, yellow nodules 2-4 mm in diameter. A pancreatic rest may rarely be the lead point of an intussusception, produce hemorrhage, or cause bowel obstruction.

Pancreas divisum , which occurs in 5–15% of the population, is the most common pancreatic developmental anomaly. As the result of failure of the dorsal and ventral pancreatic anlagen to fuse, the tail, body, and part of the head of the pancreas drain through the small accessory duct of Santorini rather than the main duct of Wirsung. Some researchers believe that this anomaly may be associated with recurrent pancreatitis when there is relative obstruction of the outflow of the ventral pancreas. Diagnosis is made by endoscopic retrograde cholangiopancreatography or by magnetic resonance cholangiopancreatography. Pancreatitis in patients with pancreas divisum is associated with mutations in the *CFTR* gene. Sphincterotomy is not recommended unless other anomalies are present or the patient has classic pancreatobiliary-type pain, recurrent pancreatitis, or chronic pancreatitis and no other etiology is found.

Choledochal cysts are dilations of the biliary tract and usually cause biliary tract symptoms, such as jaundice, pain, and fever. On occasion, the presentation may be pancreatitis. The diagnosis is usually made with ultrasonography, CT or biliary scanning, or magnetic resonance cholangiopancreatography. Similarly, a choledochocele—an intraduodenal choledochal cyst—may manifest with pancreatitis. The diagnosis can be difficult and require magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or endoscopic ultrasound.

A number of rare conditions, such as Ivemark (mutation in GDF gene) and Johanson-Blizzard (mutation in UBR1 gene) syndromes, include pancreatic dysgenesis or dysfunction among their features. Many of these syndromes include renal and hepatic dysgenesis along with the pancreatic anomalies.

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374.2

Pancreatic Physiology

Steven L. Werlin, Michael Wilschanski

The acinus is the functional unit of the exocrine pancreas. Acinar cells are arrayed in a semicircle around a lumen. Ducts that drain the acini are lined by centroacinar and ductular cells. This arrangement allows the secretions of the various cell types to mix.

The acinar cell synthesizes, stores, and secretes more than 20 enzymes, which are stored in zymogen granules, some in inactive forms. The relative concentration of the various enzymes in pancreatic juice is affected and perhaps controlled by the diet, probably by regulating the synthesis of specific messenger RNA. The main enzymes involved in digestion include *amylase* , which splits starch into maltose, isomaltose, maltotriose; dextrins; and *trypsin* and *chymotrypsin* , endopeptidases secreted by the pancreas as inactive proenzymes. Trypsinogen is activated in the gut lumen by enterokinase, a brush-border enzyme. Trypsin can then activate trypsinogen, chymotrypsinogen, and procarboxypeptidase into their respective active forms. Pancreatic lipase requires *colipase* , a coenzyme also found in pancreatic fluid, for activity. Lipase liberates fatty acids from the 1 and 3 positions of triglycerides, leaving a monoglyceride.

The stimuli for exocrine pancreatic secretion are neural and hormonal. Acetylcholine mediates the cephalic phase; cholecystokinin (CCK) mediates the intestinal phase. CCK is released from the duodenal mucosa by luminal amino acids and fatty acids. Feedback regulation of pancreatic secretion is mediated by pancreatic proteases in the duodenum. Secretion of CCK is inhibited by the digestion of a trypsin-sensitive, CCK-releasing peptide released in the lumen of the small intestine or by a monitor peptide released in pancreatic fluid.

Centroacinar and duct cells secrete water and bicarbonate. Bicarbonate secretion is under feedback control and is regulated by duodenal intraluminal pH. The stimulus for bicarbonate production is secretin in concert with CCK. Secretin cells are abundant in the duodenum.

Although normal pancreatic function is required for digestion, maldigestion occurs only after considerable reduction in pancreatic function; lipase and colipase secretion must be decreased by 90–98% before fat maldigestion occurs.

Although amylase and lipase are present in the pancreas early in gestation, secretion of both amylase and lipase is low in the infant. Adult levels of these enzymes are not reached in the duodenum until late in the 1st yr of life. Digestion of the starch found in many infant formulas depends in part on the low levels of salivary amylase that reach the duodenum. This explains the diarrhea that may be seen in infants who are fed formulas high in glucose polymers or starch. Neonatal secretion of trypsinogen and chymotrypsinogen is at approximately 70% of the level found in the 1 yr old infant. The low levels of amylase and lipase in duodenal contents of infants may be partially compensated by salivary amylase and lingual lipase. This explains the relative starch and fat intolerance of premature infants.

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CHAPTER 375

Pancreatic Function Tests

Michael Wilschanski, Steven L. Werlin

Pancreatic function can be measured by direct and indirect methods. An indirect test, the measurement of *fecal elastase* , which has become the standard screening test for pancreatic insufficiency, has a sensitivity and specificity >90%. When compared to a 72-hr fecal fat content in both pancreatic insufficient and sufficient patients, an elastase value of 100 µg/g stool has a 99% predictive value in ruling out pancreatic insufficiency based on an abnormal fecal fat finding. Falsely abnormal results can occur in many enteropathies and when the stool is very loose. The activity of other pancreatic enzymes in stool is rarely measured.

Direct Test

Classically, a triple-lumen tube was used to isolate the pancreatic secretions in the duodenum. Measurement of bicarbonate concentration and enzyme activity (*trypsin* , *chymotrypsin* , *lipase* , and *amylase*) is performed on the aspirated secretions. This test is cumbersome and infrequently used. The most commonly used direct test is collection of pancreatic juice at endoscopy after stimulation with secretin and/or cholecystokinin. A 72-hr stool collection for quantitative analysis of fat content is the gold standard for the diagnosis of malabsorption. The collection is usually performed at home, and the parent is asked to keep a careful dietary record, from which fat intake is calculated. A pre-weighed, sealable plastic container is used, which the parent keeps in the freezer. Freezing helps to preserve the specimen and reduce odor. Infants are dressed in disposable diapers with the plastic side facing the skin so that the complete sample can be transferred to the container. Normal fat absorption is >93% of intake. The presence of fat malabsorption does not differentiate between pancreatic dysfunction and enteropathies, such as celiac disease. Qualitative examination of the stool for microscopic fat globules can give false-positive and false-negative results.

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CHAPTER 376

Disorders of the Exocrine Pancreas

Steven L. Werlin, Michael Wilschanski

Disorders Associated With Pancreatic Insufficiency

Other than cystic fibrosis (CF), conditions that cause pancreatic insufficiency are very rare in children. They include Shwachman-Diamond syndrome (SDS), Johanson-Blizzard syndrome, Ivemark syndrome, Pearson syndrome, isolated enzyme deficiencies, enterokinase deficiency (see Chapter 364), chronic pancreatitis, protein-calorie malnutrition (see Chapters 57 and 364), and IMNEPD (infantile onset multisystem neurologic, endocrine, and pancreatic disease).

Cystic Fibrosis (see Chapter 432)

By the end of the 1st yr of life, 85–90% of children with CF have pancreatic insufficiency, which, if untreated, will lead to malnutrition. Treatment of the associated pancreatic insufficiency leads to improvement in absorption, better growth, and more normal stools. Pancreatic function can be monitored in children with CF with serial measurements of fecal elastase. Ten to 15% of children present with a neonatal intestinal obstruction called meconium ileus; in later life a common intestinal complication is distal intestinal obstruction syndrome which is unique to CF. Ten percent of CF patients develop severe liver disease. Ten to 15% of CF patients are pancreatic sufficient and their presentation tends to be later in life, including recurrent pancreatitis, male infertility, and chronic bronchiectasis. CF is part of the newborn screen in every state in the United States and in most countries in the Western world.

Shwachman-Diamond Syndrome (see Chapter 157)

SDS is an autosomal recessive syndrome (1/20,000 births) caused by a mutation of the Shwachman-Bodian-Diamond syndrome *(SBDS)* gene on chromosome 7, which causes ribosomal dysfunction in 90–95% of patients. Signs and symptoms of SDS include pancreatic insufficiency; neutropenia, which may be cyclic; neutrophil chemotaxis defects; metaphyseal dysostosis; failure to thrive; and short stature. Some patients with SDS have liver or kidney involvement, dental disease, or learning difficulty. SDS is a common cause of congenital neutropenia.

Patients typically present in infancy with poor growth and steatorrhea. More varied phenotypes have been described including absence of pancreatic lipomatosis on imaging, normal fecal elastase levels, and normal skeletal survey. These children can be readily differentiated from those with CF by their normal sweat chloride levels, lack of mutations in the CF gene, characteristic metaphyseal lesions, and fatty pancreas characterized by a hypodense appearance on CT and MRI scans (Fig. 376.1).

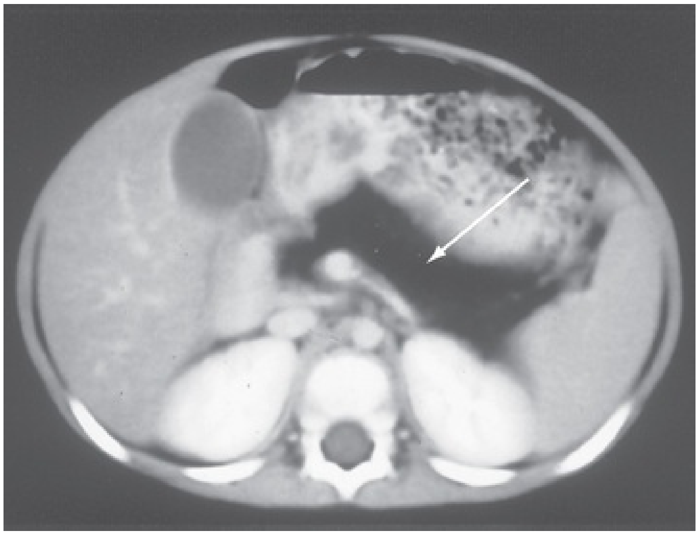

FIG. 376.1 **CT appearance of the pancreas in a patient with Shwachman-Diamond syndrome. Note that the pancreas *(arrow)* retains a typical size and shape, but it is highly fatty and therefore appears as a very low-density structure. (Courtesy Prof. Peter Durie, Hospital for Sick Children, Toronto, Ontario.)**

Despite adequate pancreatic replacement therapy and correction of malabsorption, poor growth commonly continues. Pancreatic insufficiency is often transient, and steatorrhea frequently spontaneously improves with age. Recurrent pyogenic infections (otitis media, pneumonia, osteomyelitis, dermatitis, sepsis) are frequent and are a common cause of death. Thrombocytopenia is found in 70% of patients and anemia in 50%. Development of aplastic anemia or a *myelodysplastic syndrome* can occur, with transformation to *acute myeloid leukemia* in 24%. The pancreatic acini are replaced by fat with little fibrosis. Islet cells and ducts are normal. Bone marrow transplant is the treatment of choice in patients who develop acute myeloid leukemia.

Pearson Syndrome

Pearson (marrow-pancreas) syndrome is caused by a contiguous mitochondrial gene depletion involving several mitochondrial genes affecting oxidative phosphorylation, that manifests in infants with severe **macrocytic anemia** and **variable thrombocytopenia** . The bone marrow demonstrates vacuoles in erythroid and myeloid precursors as well as ringed sideroblasts. In addition to its role in severe bone marrow failure, pancreatic insufficiency contributes to growth failure. Mitochondrial DNA mutations are transmitted through maternal inheritance to both sexes or are sporadic.

Johanson-Blizzard Syndrome

The features of Johanson-Blizzard syndrome include exocrine pancreatic deficiency, aplasia or hypoplasia of the alae nasi, congenital deafness, hypothyroidism, developmental delay, short stature, ectodermal scalp defects, absence of permanent teeth, urogenital malformations, and imperforate anus. This syndrome is caused by a mutation in the *UBR1* gene found on chromosome 15. The UBR1 protein acts as a ubiquitin ligase.

Isolated Enzyme Deficiencies

Isolated deficiencies of trypsinogen, enterokinase, lipase, and colipase have been reported. Although enterokinase is a brush-border enzyme, deficiency causes pancreatic insufficiency because enterokinase is required to activate trypsinogen to trypsin in the duodenum. Deficiencies of trypsinogen or enterokinase manifest with failure to thrive, hypoproteinemia, and edema. Isolated amylase deficiency is typically developmental and resolves by age 2-3 yr.

Other Syndromes Associated With Pancreatic Insufficiency

Pancreatic agenesis, congenital pancreatic hypoplasia, and congenital rubella are rare causes of pancreatic insufficiency. Pancreatic insufficiency has also been reported in duodenal atresia and stenosis and may also be seen in infants with familial or nonfamilial hyperinsulinemic hypoglycemia, who require 95–100% pancreatectomy to control hypoglycemia. Mutations in at least 6 genes have been described. Pancreatic insufficiency, which may be found in children with celiac disease and undernutrition, recovers with nutritional rehabilitation.

IMNEPD is a rare disease due to mutations in the *PTRH2* gene. Neurologic features dominate the phenotype (microcephaly, intellectual disability, cerebellar atrophy, deafness, and neuropathy), but pancreatic insufficiency is seen in most patients.

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CHAPTER 377

Treatment of Pancreatic Insufficiency

Michael Wilschanski, Steven L. Werlin

The most important treatment of pancreatic insufficiency (PI) is pancreatic enzyme replacement therapy (PERT). In modern enzyme capsules the enzymes are enterically coated to protect the enzymes from degradation by gastric acid and from autodigestion in the small intestine. It is common for patients to change from one product to another using a 1 : 1 lipase ratio and then titrating for maximum efficacy (Table 377.1).

Table 377.1

FDA-Approved Pancreatic Enzyme Replacement Products for Exocrine Pancreatic Insufficiency[*]

DRUG	AVAILABLE STRENGTHS	COST ($)[†]
IMMEDIATE-RELEASE–		
Viokace (Allergan)[‡,§,‖]	10,440 or 20,880 units of lipase[¶]	8.80
DELAYED-RELEASE–		
Creon (Abbvie)	3,000, 6,000, 12,000, 24,000, or 36,000 USP units of lipase[¶,**]	8.20
Pancreaze (Janssen)	2,600, 4,200, 10,500, 16,800, or 21,000 units of lipase[¶,**]	8.80
Pertzye (Digestive Care)	4,000, 8,000, 16,000, or 24,000 units of lipase[¶,**]	8.40
Zenpep (Allergan)	3,000, 5,000, 10,000, 15,000, 20,000, 25,000, or 40,000 units of lipase[¶,**]	9.60

[*] Pancrelipase products are not interchangeable. All of these products contain a combination of porcine-derived lipases, proteases, and amylases.

[†] Approximate WAC for one dose (as close as possible to 35,000 USP units of lipase using available formulations) for a 70-kg patient. WAC is wholesaler acquisition cost, or manufacturer's published price to wholesalers; WAC represents published catalogue or list prices and may not represent an actual transactional price.

[‡] Viokace is only approved for use in adults.

[§] Should be used in combination with a proton pump inhibitor to maximize absorption in the duodenum.

[||] FDA-approved only for treatment of adults with EPI due to chronic pancreatitis or pancreatectomy.

[¶] Should not be crushed or chewed.

[**] Capsules can be opened and contents sprinkled on soft acidic food (pH ≤ 4.5) such as applesauce.

From The Medical Letter: Pancreatic enzyme replacement products, *Med Lett* 59(1531):170, 2017.

Source: AnalySource Monthly. September 5, 2017. Reprinted from First Databank, Inc. All rights reserved. ©2017. www.fdbhealth.com/policies/drug-pricing-policy/ .

The North American CF Foundation has published dosing guidelines based on age and fat ingestion (Table 377.2). Because these products contain excess protease compared with lipase, the dosage is estimated from the lipase requirement. The final dosage of PERT for children is often established by trial and error. An adequate dose is one that is followed by resumption of normal growth and the return of stools to normal fat content, which, when desired, can be verified by a 72-hr fecal fat collection and normalization of stool consistency and color. Because there is no elastase in enzyme preparations, fecal elastase cannot be used to monitor appropriateness of PERT dosage. Enzyme replacement should be divided and given at the beginning of and during the meal. Enzymes should not be chewed, crushed, or dissolved in food, which would allow gastric acid to penetrate the enteric coating and destroy the enzymes. Enzymes must also be given with snacks which contain fat. Increasing enzyme supplements beyond the recommended dose does not improve absorption, might retard growth, and can cause fibrosing colonopathy (see below).

Table 377.2

Pancreatic Enzyme Replacement Therapy: North American CF Foundation Consensus Statement

Infants (up to 12 mo)	2,000-4,000 U lipase/120 mL breast milk or formula
12 mo to 4 yr	1,000 U lipase/kg/meal initially, then titrate per response
Children >4 yr and adults	500 U lipase/kg/meal initially, up to maximum of 2,500 U lipase/kg/meal or 10,000 U lipase/kg/day or 4,000 U lipase/g fat ingested per day

PLUS: one half the standard meal dose to be given with snacks.

A major concern has been the ingestion of enzymes by infants. The importance of correct enzyme ingestion in infants and children is obvious but there may be difficulty in feeding the infant microspheres however small they may be. Enterically coated microspheres can be mixed with apple sauce for oral use or crushed for use in tube feeding. Patients treated with this approach do achieve growth and weight gain. Pancreatic enzymes specifically prepared for infants and young children with smaller granules have been developed.

Treatment of exocrine PI by oral enzyme replacement usually corrects protein malabsorption, but steatorrhea is difficult to correct completely. Factors contributing to fat malabsorption include inadequate dosage, incorrect timing of doses in relation to food consumption or gastric emptying, lipase inactivation by gastric acid, and the observation that *chymotrypsin* in the enzyme preparation digests and thus inactivates *lipase* .

When adequate fat absorption is not achieved, gastric acid neutralization with an H_2 -receptor antagonist or, more commonly, a proton pump inhibitor, decreases enzyme inactivation by gastric acid and thus improves delivery of lipase into the intestine. Enteric coating also protects lipase from acid inactivation.

Untoward effects secondary to PERT include allergic reactions and kidney stones. Fibrosing colonopathy, consisting of colonic fibrosis and strictures, can occur 7-12 mo after severe overdose of PERT.

Fat-soluble vitamin supplements are required by PI patients due to the ongoing mild to moderate fat malabsorption that occurs despite PERT.

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CHAPTER 378

Pancreatitis

378.1

Acute Pancreatitis

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Keywords

Acute pancreatitis
acute pancreatitis etiology
acute pancreatitis diagnosis
drug-induced pancreatitis
(serum) amylase
(serum) lipase

Acute pancreatitis (AP), the most common pancreatic disorder in children, is increasing in incidence, and 50 or more cases are usually seen in major pediatric centers per year. In children, blunt abdominal injuries, multisystem disease such as the hemolytic uremic syndrome and inflammatory bowel disease, biliary stones or microlithiasis (sludging), and drug toxicity are the most common etiologies. Although many drugs and toxins can induce AP in susceptible persons, in children, valproic acid, L -asparaginase, 6-mercaptopurine, and azathioprine are the most common causes of drug-induced pancreatitis. Alcohol should be considered in adolescents. Other cases follow organ transplantation or are caused by infections, metabolic disorders, or mutations in susceptibility genes (see Chapter 378.1). Only 10–20% of cases are idiopathic (Table 378.1).

Table 378.1

Etiology of Acute and Recurrent Pancreatitis in Children

DRUGS AND TOXINS
• Acetaminophen overdose • Alcohol • L -Asparaginase • Azathioprine • Cannabis • Carbamazepine • Cimetidine • Corticosteroids • Cytosine arabinoside • Dapsone • Didanosine • Enalapril • Erythromycin • Estrogen • Furosemide • Glucagon-like peptide-1 agents • Interferon α • Isoniazid • Lamivudine • Lisinopril • 6-Mercaptopurine • Methyldopa • Mesalamine • Metronidazole • Octreotide • Organophosphate poisoning • Pentamidine • Procainamide • Retrovirals: DDC (dideoxycytidine), DDI (dideoxyinosine), tenofovir • Rifampin • Sulfonamides: mesalamine, 5-aminosalicytates, sulfasalazine, trimethoprim-sulfamethoxazole • Sulindac • Tetracycline • Thiazides • Valproic acid • Venom (spider, scorpion, Gila monster lizard) • Vincristine • Volatile hydrocarbons
GENETIC
• Cationic trypsinogen gene *(PRSS1)* • Chymotrypsin C gene *(CTRC)* • Cystic fibrosis gene *(CFTR)* • Trypsin inhibitor gene *(SPINK1)*
INFECTIOUS
• Ascariasis

- Coxsackie B virus
- Echovirus
- Enterovirus
- Epstein-Barr virus
- Hepatitides A, B
- Herpes viruses
- Influenzae A, B
- Leptospirosis
- Malaria
- Measles
- Mumps
- Mycoplasma
- Rabies
- Rubella
- Reye syndrome: varicella, influenza B
- Septic shock
- Thyroid fever

OBSTRUCTIVE

- Ampullary disease
- Ascariasis
- Biliary tract malformations
- Choledochal cyst
- Choledochocele
- Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge)
- Duplication cyst
- Endoscopic retrograde cholangiopancreatography (ERCP) complication
- Pancreas divisum
- Pancreatic ductal abnormalities
- Postoperative
- Sphincter of Oddi dysfunction
- Tumor

SYSTEMIC DISEASE

- Autoimmune pancreatitis (IgG_4 -related systemic disease)
- Brain tumor
- Collagen vascular diseases
- Congenital partial lipodystrophy
- Crohn disease
- Diabetes mellitus (ketoacidosis)
- Head trauma
- Henoch-Schönlein purpura
- Hemochromatosis
- Hemolytic uremic syndrome
- Hyperlipidemia: types I, IV, V
- Hyperparathyroidism/hypercalcemia
- Kawasaki disease
- Malnutrition
- Organic acidemia
- Peptic ulcer
- Periarteritis nodosa
- Renal failure
- Scorpion venom
- Systemic lupus erythematosus
- Transplantation: bone marrow, heart, liver, kidney, pancreas
- Vasculitis

TRAUMATIC

- Blunt injury
- Burns
- Child abuse
- Hypothermia
- Surgical trauma
- Total-body cast

After an initial insult, such as ductal disruption or obstruction, there is premature activation of trypsinogen to trypsin within the acinar cell. Trypsin then activates other pancreatic proenzymes, leading to autodigestion, further enzyme activation, and release of active proteases. Lysosomal hydrolases colocalize with pancreatic proenzymes within the acinar cell. Pancreastasis (similar in concept to cholestasis) with continued synthesis of enzymes occurs. Lecithin is activated by phospholipase A_2 into the toxic lysolecithin. Prophospholipase is unstable and can be activated by minute quantities of trypsin. After the insult, cytokines and other proinflammatory mediators are released.

The healthy pancreas is protected from autodigestion by pancreatic proteases that are synthesized as inactive proenzymes; digestive enzymes that are segregated into secretory granules at pH 6.2 by low calcium concentration, which minimizes trypsin activity; the presence of protease inhibitors both in the cytoplasm and zymogen granules; and enzymes that are secreted directly into the ducts.

Histopathologically, interstitial edema appears early. Later, as the episode of pancreatitis progresses, localized and confluent necrosis, blood vessel disruption leading to hemorrhage, and an inflammatory response in the peritoneum can develop.

The diagnosis of pancreatitis in children is made when 2 of 3 of the following are present: abdominal pain; serum amylase and/or lipase activity at least 3 times greater than the upper limit of normal; and imaging findings characteristic of, or compatible with, AP.

Clinical Manifestations

The severity of AP in children has been defined by a consensus committee.

Mild Acute Pancreatitis: AP that is not associated with organ failure, local or systemic complications, and usually resolves within the 1st wk after presentation. This is the most common form of pediatric AP.

The patient with mild AP has moderate to severe abdominal pain, persistent vomiting, and possibly fever. The pain is epigastric or in either upper quadrant, steady, often resulting in the child's assuming an antalgic position with hips and knees flexed, sitting upright, or lying on the side. The child is uncomfortable, irritable, and appears acutely ill. The abdomen may be distended and tender and a mass may be palpable. The pain can increase in intensity for 24-48 hr, during which time vomiting may increase and the patient can require hospitalization for fluid and electrolyte therapy and analgesia. There is no organ failure, and imaging does not demonstrate peri- or pancreatic necrosis. The prognosis for complete recovery in the acute uncomplicated case after 4-7 days is excellent.

Moderately Severe Acute Pancreatitis : AP with either transient organ failure/dysfunction (lasting <48 hr) or development of local or systemic complications, such as exacerbation of previously diagnosed comorbid disease (such as lung or kidney disease). Imaging may reveal sterile (peri-) pancreatic necrosis. The prognosis for these patients is also excellent but recovery may be prolonged.

Severe Acute Pancreatitis*:* AP with development of organ dysfunction that persists longer than 48 hr. Persistent organ failure may be single or multiple. Severe AP is uncommon in children. In this life-threatening condition, the patient is acutely ill with severe nausea, vomiting, and abdominal pain. Shock, high fever, jaundice, ascites, hypocalcemia, and pleural effusions can occur. A bluish discoloration may be seen around the umbilicus (Cullen sign) or in the flanks (Grey Turner sign). The pancreas is necrotic and can be transformed into an inflammatory hemorrhagic mass. The mortality rate, which is approximately 20%, is related to the systemic inflammatory response syndrome with multiple organ dysfunction, shock, renal failure, acute respiratory distress syndrome, disseminated intravascular coagulation, gastrointestinal bleeding, and systemic or intra-abdominal infection. The percentage of necrosis seen on CT and failure of pancreatic tissue to enhance on CT (suggesting necrosis) predicts the severity of the disease.

Diagnosis

AP is usually diagnosed by measurement of serum lipase and amylase activities. Serum lipase is considered the test of choice for AP, as it is more specific than amylase for acute inflammatory pancreatic disease and should be determined when pancreatitis is suspected. The serum lipase rises by 4-8 hr, peaks at 24-48 hr, and remains elevated 8-14 days longer than serum amylase. Serum lipase greater than 7 times the upper limit of normal obtained within 24 hr of presentation may predict a severe course. Serum lipase can be elevated in nonpancreatic diseases. The serum amylase level is typically elevated for up to 4 days. A variety of other conditions can also cause hyperamylasemia without pancreatitis (Table 378.2). Elevation of salivary amylase can mislead the clinician to diagnose pancreatitis in a child with abdominal pain. The laboratory can separate amylase isoenzymes into pancreatic and salivary fractions. Initially serum amylase levels are normal in 10–15% of patients.

Table 378.2

Differential Diagnosis of Hyperamylasemia

PANCREATIC PATHOLOGY
• Acute or chronic pancreatitis • Complications of pancreatitis (pseudocyst, ascites, abscess) • Factitious pancreatitis
SALIVARY GLAND PATHOLOGY
• Parotitis (mumps, *Staphylococcus aureus* , cytomegalovirus, HIV, Epstein-Barr virus) • Sialadenitis (calculus, radiation) • Eating disorders (anorexia nervosa, bulimia)
INTRAABDOMINAL PATHOLOGY
• Biliary tract disease (cholelithiasis) • Peptic ulcer perforation • Peritonitis • Intestinal obstruction • Appendicitis
SYSTEMIC DISEASES
• Metabolic acidosis (diabetes mellitus, shock) • Renal insufficiency, transplantation • Burns • Pregnancy • Drugs (morphine) • Head injury • Cardiopulmonary bypass

Other laboratory abnormalities that may be present in AP include hemoconcentration, coagulopathy, leukocytosis, hyperglycemia, glucosuria, hypocalcemia, elevated γ-glutamyl transpeptidase, and hyperbilirubinemia.

X-ray of the chest and abdomen might demonstrate nonspecific findings such as atelectasis, basilar infiltrates, elevation of the hemidiaphragm, left- (rarely right-) sided pleural effusions, pericardial effusion, and pulmonary edema. Abdominal x-rays might demonstrate a sentinel loop, dilation of the transverse colon (cutoff sign), ileus, pancreatic calcification (if recurrent), blurring of the left psoas margin, a pseudocyst, diffuse abdominal haziness (ascites), and peripancreatic extraluminal gas bubbles.

CT has a major role in the diagnosis and follow-up of children with pancreatitis. Findings can include pancreatic enlargement; a hypoechoic, sonolucent edematous pancreas; pancreatic masses; fluid collections; and abscesses (Fig. 378.1). Normal imaging studies at the time of diagnosis are not uncommon. In adults, CT findings are the basis of a widely accepted prognostic system (Table 378.3). Ultrasonography is more sensitive than CT for the diagnosis of biliary stones. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography are essential in the investigation of recurrent pancreatitis, nonresolving pancreatitis, and disease associated with gallbladder pathology. Endoscopic ultrasonography also helps visualize the pancreaticobiliary system. Complications of AP are noted in Table 378.4 .

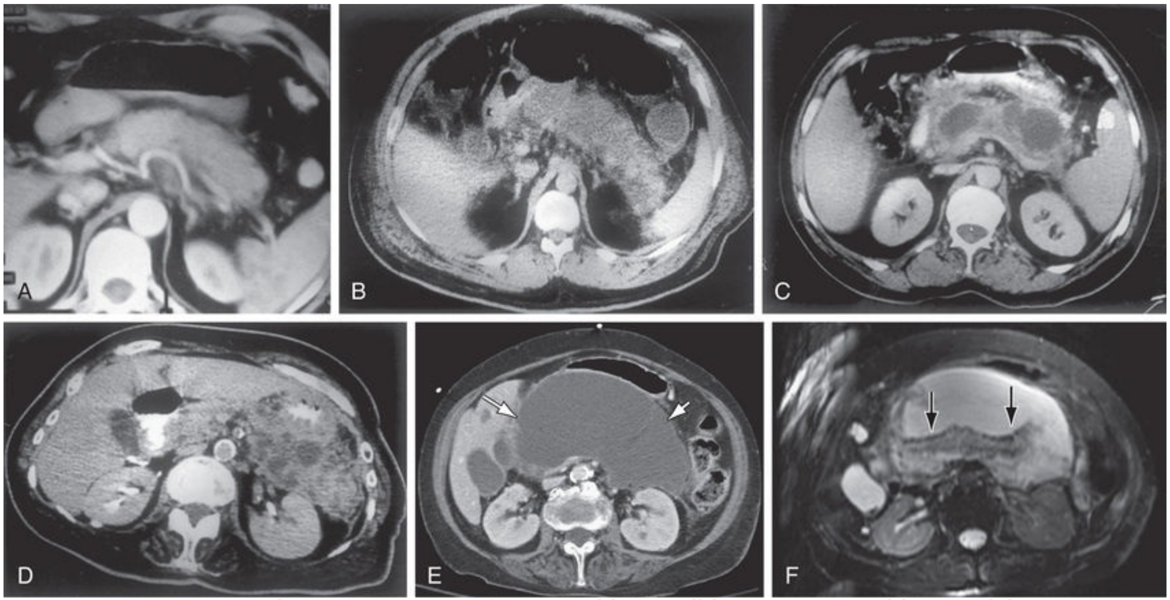

FIG. 378.1 **CT and MRI appearance of pancreatitis. A, Mild acute pancreatitis. Arterial phase spiral CT. Diffuse enlargement of pancreas without fluid accumulation. B, Severe acute pancreatitis. Lack of enhancement of the pancreatic parenchyma due to the necrosis of the entire pancreatic gland. C, Pancreatic pseudocyst. A round fluid collection with thin capsule is seen within the lesser sac. D, Acute severe pancreatitis and peripancreatic abscess formation. Peripancreatic abscess formation is observed within the peripancreatic and the left anterior pararenal space. E, Pancreatic necrosis. A well-defined fluid attenuation collection in the pancreatic bed *(white arrows)* seen on contrast-enhanced CT imaging. F, The same collection is more complex appearing on the corresponding T2-weighted MR image. The internal debris and necrotic tissue are better appreciated because of the superior soft-tissue contrast of MRI *(black arrows)* . (*A-D* , From Elmas N: The role of diagnostic radiology in pancreatitis, *Eur J Radiol* 38[2]:120–132, 2001, Figs. 1, 3b, 4a, and 5. *E* and *F,* From Soakar A, Rabinowitz CB, Sahani DV: Cross-sectional imaging in acute pancreatitis, *Radiol Clin North Am* 45[3]:447–460, 2007, Fig. 14.)**

Table 378.3

Revised Definitions of Morphologic Features of Acute Pancreatitis

INTERSTITIAL EDEMATOUS PANCREATITIS
Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis
• CECT criteria • Pancreatic parenchyma enhancement by intravenous contrast agent • No peripancreatic necrosis
NECROTIZING PANCREATITIS
Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis
• CECT criteria • Lack of pancreatic parenchymal enhancement by intravenous contrast agent • Presence of findings of peripancreatic necrosis
ACUTE PANCREATITIS FLUID COLLECTION
Peripancreatic fluid associated with interstitial edematous pancreatitis with no associated peripancreatic necrosis. Applies only to areas of peripancreatic fluid seen within the first 4 wk after onset of interstitial edematous pancreatitis and without the features of a pseudocyst.
• CECT criteria • Occurs in the setting of interstitial edematous pancreatitis • Homogeneous collection with fluid density • Confined by normal peripancreatic fascial planes • No definable wall encapsulating the collection • Adjacent to pancreas (no intrapancreatic extension)
PANCREATIC PSEUDOCYST
An encapsulated collection of fluid with a well-defined inflammation wall, usually outside the pancreas, with little or no necrosis. Usually occurs more than 4 wk after onset of interstitial edematous pancreatitis.
• CECT criteria • Well circumscribed; usually round or oval • Homogeneous fluid density • No nonliquid component • Well-defined wall that is wholly encapsulated • Maturation usually needs >4 wk after onset of acute pancreatitis; occurs after interstitial edematous pancreatitis
ACUTE NECROTIC COLLECTION
A collection containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis; the necrosis can include the pancreatic parenchyma and/or the peripancreatic tissue.
• CECT criteria • Occurs only in the setting of acute necrotizing pancreatitis • Heterogeneous and nonliquid density of varying degrees in different locations (some seem homogeneous early in their course) • No definable wall encapsulating the collection • Intrapancreatic and/or extrapancreatic
WALLED-OFF NECROSIS
A mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. Usually occurs >4 wk after onset of necrotizing pancreatitis.
• CECT criteria • Heterogeneous with liquid and nonliquid density, with varying locations (some can seem homogeneous)

• Well-defined wall that is wholly encapsulated
• Intrapancreatic and/or extrapancreatic
• Maturation usually needs 4 wk after onset of acute necrotizing pancreatitis

CECT, contrast-enhanced CT.

From PA Banks, TL Bollen, C Dervenis, et al.; the Acute Pancreatitis Classification Working Group Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus *Gut* 62:102-111, 2013.

Table 378.4

Complications of Acute Pancreatitis

LOCAL
Pseudocyst Sterile necrosis Infected necrosis Abscess GI bleeding • Pancreatitis-related • Splenic artery or splenic artery pseudoaneurysm rupture • Splenic vein rupture • Portal vein rupture • Splenic vein thrombosis leading to gastroesophageal variceal bleeding • Pseudocyst or abscess hemorrhage • Postnecrosectomy bleeding Nonpancreatitis-related • Mallory-Weiss tear • Alcoholic gastropathy • Stress-related mucosal gastropathy Splenic complications • Infarction • Rupture • Hematoma • Splenic vein thrombosis Fistulization to or obstruction of the small intestine or colon Hydronephrosis
SYSTEMIC
Respiratory failure Renal failure Shock Hyperglycemia Hypocalcemia Disseminated intravascular coagulation Fat necrosis (subcutaneous nodules) Retinopathy
PSYCHOSIS

From Tenner S, Steinberg WM: Acute pancreatitis. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease,* ed 10, Philadelphia, 2016, Elsevier (Box 58.7, p. 991).

Treatment

The aims of medical management are to relieve pain and restore metabolic homeostasis. Analgesia should be given in adequate doses. Fluid, electrolyte, and mineral balance should be restored and maintained. Nasogastric suction is useful in patients who are vomiting. Early refeeding decreases the complication rate and length of stay. While he or she is vomiting, the patient should be maintained with nothing by mouth. Recovery is usually complete within 4-5 days.

Prophylactic antibiotics are not recommended, but antibiotics are used to treat infected necrosis. Gastric acid secretion is suppressed with proton pump inhibitors. Enteral alimentation by mouth, nasogastric tube, or nasojejunal tube (in severe cases or for those intolerant of oral or nasogastric feedings) within 2-3 days of onset reduces the length of hospitalization, complication rate, and survival in patients with severe AP. In children, surgical therapy of nontraumatic AP is rarely required but may include drainage of necrotic material or abscesses. Endotherapy for common bile duct stones, ductal strictures, and for drainage of fluid collections is the standard of care when indicated.

Prognosis

Children with mild AP do well and recover within 4-5 days. When pancreatitis is associated with trauma or systemic disease, the prognosis is typically related to the associated medical conditions.

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378.2

Acute Recurrent and Chronic Pancreatitis

Steven L. Werlin, Michael Wilschanski

Keywords

Chronic pancreatitis
chronic pancreatitis etiology
chronic pancreatitis genetics

acute recurrent pancreatitis
autoimmune pancreatitis
PRSS1 gene
CTRC gene
CFTR gene
SPINK1 gene
tropical pancreatitis

Acute recurrent pancreatitis (ARP) is defined as ≥2 distinct episodes of AP with intervening return of enzymes to baseline. Chronic pancreatitis (CP) is defined as the presence of typical abdominal pain plus characteristic imaging findings including pancreatic calcifications, inflammation and fibrosis, or exocrine insufficiency plus imaging findings, or endocrine insufficiency plus imaging findings. Most children with CP describe a history of ARP and tend to be older at the time of diagnosis compared with children with ARP, suggesting that ARP and CP are a disease continuum.

ARP and CP in children are often due to genetic mutations or due to congenital anomalies of the pancreatic or biliary ductal system (Tables 378.5 and 378.6). Mutations in the *PRSS1* gene (cationic trypsinogen) located on the long arm of chromosome 7, *SPINK1* gene (pancreatic trypsin inhibitor) located on chromosome 5, in the cystic fibrosis gene *(CFTR)* , and chymotrypsin C *(CTRC)* may all lead to CP (Fig. 378.2).

Table 378.5

Factors Contributing to the Etiology of Chronic Pancreatitis

	No. (%)*
Chronic pancreatitis patients with history of ≥1episode acute pancreatitis	73 (96)
Risk factors for pancreatitis	
Genetic	51 (67)
PRSS1	33 (43)
SPINK1	14 (19)
CFTR	11 (14)
CTRC	2 (3)
Autoimmune	3 (4)
Obstructive	25 (33)
Pancreas divisum	15 (20)
Sphincter of Oddi dysfunction	1 (1)
Gallstones	3 (4)
Pancreatic duct malunion	2 (3)
Pancreatic duct obstruction	1 (1)

Other	5 (7)
Toxic/metabolic	8 (11)
Alcohol (determined by doctor)	1 (1)
Passive smoking (exposure)	3 (4)
Hyperlipidemia	1 (1)
Medication	1 (1)
Metabolic disease	1 (1)
Other	1 (1)
None cited	8 (11)

[*] The total exceeds 100% because some children have more than 1 factor.

From Schwarzenberg SJ, Bellin M, Husain SZ, et al: Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden, *J Pediatr* 166:890–896, 2015 (Table II, p. 892).

Table 378.6

Classification of Chronic Pancreatitis

CHRONIC CALCIFYING PANCREATITIS	CHRONIC OBSTRUCTIVE PANCREATITIS	STEROID-RESPONSIVE PANCREATITIS
Alcohol Smoking Genetic Idiopathic Juvenile-onset Tropical	**Stricture** Blunt trauma Endoscopic stenting Acute pancreatitis Anastomotic stricture **Tumor** Adenocarcinoma IPMN Serious cystadenoma Islet cell tumor	**Autoimmune Pancreatitis** Type 1 Type 2 (IDCP)

IDCP, idiopathic duct-centric pancreatitis; *IPMN,* intraductal papillary mucinous neoplasm.

From Majumder S, Chari ST: Chronic pancreatitis, *Lancet* 387:1957–1966, 2016 (Fig 1, p. 1958).

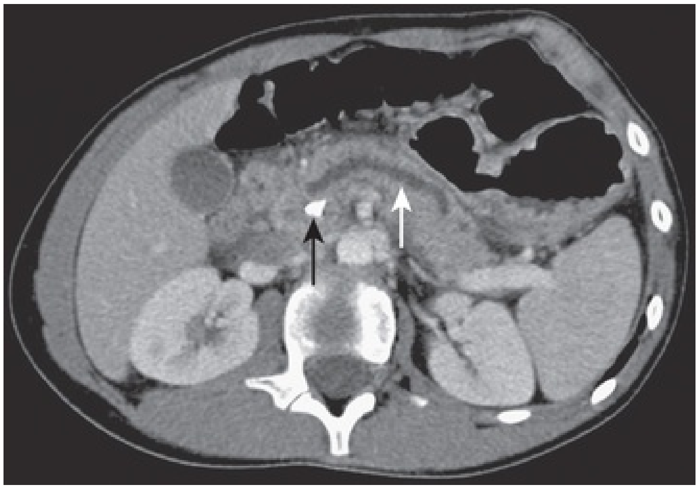

FIG. 378.2 **Chronic pancreatitis. Computed tomogram showing calcification in the head of the pancreas *(black arrow)* and dilated pancreatic duct *(white arrow)* in a 12 yr old patient. (Courtesy Dr. Janet Reid. From Wyllie R, Hyams JS, editors: *Pediatric gastrointestinal and liver disease,* ed 3, Philadelphia, 2006, WB Saunders.)**

Cationic trypsinogen has a trypsin-sensitive cleavage site. Loss of this cleavage site in the abnormal protein permits uncontrolled activation of trypsinogen to trypsin, which leads to autodigestion of the pancreas. Mutations in *PRSS1* act in an autosomal dominant fashion with incomplete penetrance and variable expressivity. Symptoms often begin in the first decade but are usually mild at the onset. Although spontaneous recovery from each attack occurs in 4-7 days, episodes become progressively more severe. Hereditary pancreatitis may be diagnosed by the presence of the disease in successive generations of a family. An evaluation during symptom-free intervals may be unrewarding until calcifications, pseudocysts, or pancreatic exocrine and endocrine insufficiency develop (Fig. 378.3 ; see Fig. 378.2). CP is a risk factor for the development of pancreatic cancer. Multiple mutations of the *PRSS1* gene associated with hereditary pancreatitis have been described.

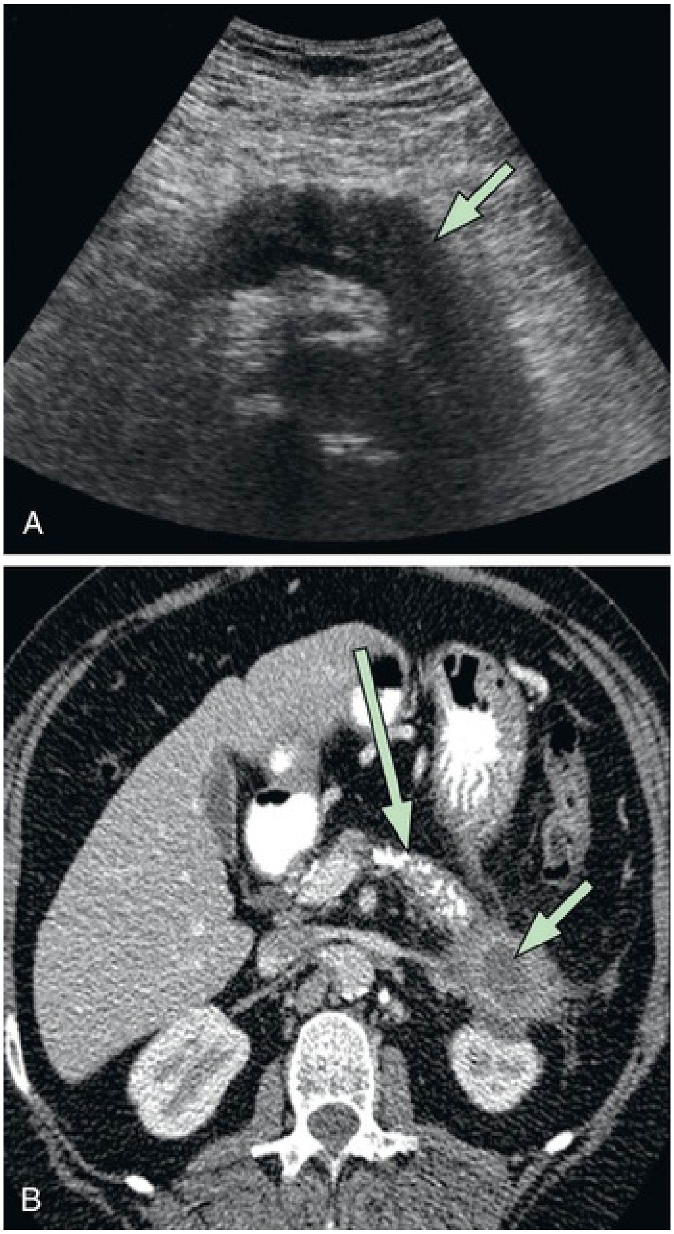

FIG. 378.3 **Examples of ultrasound and multidetector images in patients with chronic pancreatitis. A, Transabdominal ultrasound scan showing a uniformly swollen, hypoechoic pancreas *(arrow)* typical of autoimmune pancreatitis. B, Multidetector CT showing pancreatic calculi in an atrophic pancreas *(long arrow)* and a pseudocyst at the tail of the pancreas *(short arrow)* . (From Braganza JM, Lee SH, McCloy RF, McMahon MJ: Chronic pancreatitis, *Lancet* 377:1184–1197, 2011, Fig. 5, p 1191.)**

Trypsin inhibitor acts as a fail-safe mechanism to prevent uncontrolled autoactivation of trypsin. Mutations in the *SPINK1* gene have been associated with recurrent or CP. In *SPINK1* mutations, this fail-safe mechanism is lost; this gene may be a modifier gene and not the direct etiologic factor.

Mutations of the cystic fibrosis gene *(CFTR)* , associated with pancreatic sufficiency or which do not typically produce pulmonary disease, can cause CP, possibly due to ductal obstruction. Patients with genotypes associated with mild phenotypic effects have a greater risk of developing pancreatitis than those with genotypes associated with moderate to severe phenotypes.

Mutations in the chymotrypsin C gene, which cause a loss of function, may also cause recurrent pancreatitis. Indications for genetic testing include recurrent episodes of AP, CP, a family history of pancreatitis, or unexplained pancreatitis in children.

Other conditions associated with chronic, relapsing pancreatitis are hyperlipidemia (types I, IV, and V), hyperparathyroidism, and ascariasis. Previously, most cases of recurrent pancreatitis in childhood were considered idiopathic; with the discovery of gene families associated with recurrent pancreatitis, this has changed. Congenital anomalies of the ductal systems, such as pancreas divisum, are more common than previously recognized.

Autoimmune pancreatitis (AIP) typically manifests with jaundice, abdominal pain, and weight loss. The pancreas is typically enlarged and is hypodense on CT. The pathogenesis is unknown. **Type 1** is a systemic disease and is associated with high serum IgG4. In addition to pancreatitis in type 1 disease, the patient may have retroperitoneal fibrosis, orbital inflammation, aortitis, sclerosing cholangitis, cutaneous vasculitis, pulmonary fibrosis, and sialoadenitis. These extrapancreatic features may also be present in the absence of pancreatitis (Table 378.7). Tissue biopsy shows fibrosis, plasmacytosis, and positive staining for IgG4; serum IgG4 levels are not always elevated.

Table 378.7

Conditions Classification of Chronic Disorders Now Recognized to Be Part of IgG4-Related Disease

Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
Fibrosing mediastinitis
Hypertrophic pachymeningitis
Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
Inflammatory pseudotumor (affecting the orbits, lungs, kidneys, and other organs)
Küttner tumor (affecting the submandibular glands)
Mikulicz disease (affecting the salivary and lacrimal glands)
Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
Periaortitis and periarteritis
Inflammatory aortic aneurysm
Retroperitoneal fibrosis (Ormond disease)

Riedel thyroiditis
Sclerosing mesenteritis
Conditions once regarded as individual disorders now recognized to be part of IgG4-related disease

From Kamisawa T, Zen Y, Pillai S, Stone JH: IgG4-related disease, *Lancet* 385:1460–1471, 2015 (Panel 1, p. 1461).

Type 2 is limited to diffuse or focal involvement of just the pancreas. IgG4 levels are normal. *Both types respond to steroids* . Children with AIP typically have type 2.

Juvenile tropical pancreatitis is the most common form of CP in developing equatorial countries. The highest prevalence is in the Indian state of Kerala. Tropical pancreatitis occurs during late childhood or early adulthood, manifesting with abdominal pain and irreversible pancreatic insufficiency followed by diabetes mellitus within 10 years. The pancreatic ducts are obstructed with inspissated secretions, which later calcify. This condition is associated with mutations in the *SPINK* gene in 50% of cases.

A thorough diagnostic evaluation of every child with more than one episode of pancreatitis is indicated. Serum lipid, calcium, and phosphorus levels are determined. Stools are evaluated for ascaris, and a sweat test is performed. Plain abdominal films are evaluated for the presence of pancreatic calcifications. Abdominal ultrasound or CT scanning is performed to detect the presence of a pseudocyst. The biliary tract is evaluated for the presence of stones. After genetic counseling, evaluation of *PRSS1*, *SPINK1*, *CFTR* , and *CRTC* genotypes can be measured. Electrophysiologic tests such as nasal potential difference testing may be recommended when the diagnosis of cystic fibrosis (CF) is uncertain.

Magnetic resonance cholangiopancreatography (MRCP) and Endoscopic retrograding cholangiopancreatography (ERCP) are techniques that can be used to define the anatomy of the gland and are mandatory if surgery is considered. MRCP is the test of choice when endotherapy is not being considered and should be performed as part of the evaluation of any child with idiopathic, nonresolving, or recurrent pancreatitis and in patients with a pseudocyst before drainage. In these cases a previously undiagnosed anatomic defect that may be amenable to endoscopic or surgical therapy may be detected. Endoscopic treatments include sphincterotomy, stone extraction, drainage on pseudocysts, and insertion of pancreatic or biliary endoprosthetic stents. These treatments allow the successful nonsurgical management of conditions previously requiring surgical intervention. In patients with intractable pain, total pancreatectomy and islet cell transfusion is performed in specialist centers.

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CHAPTER 379

Pancreatic Fluid Collections

Michael Wilschanski, Steven L. Werlin

Pancreatic pseudocyst formation is an uncommon sequela to acute or chronic pancreatitis.

A pancreatic pseudocyst is a circumscribed collection of fluid rich in pancreatic enzymes, blood, and necrotic tissue, typically located in the lesser sac of the abdomen. Pancreatic pseudocysts are usually complications of pancreatitis, although in children they frequently occur following abdominal trauma. They can enlarge or extend in almost any direction, thus producing a wide variety of symptoms (see Fig. 378.1*C*).

A pancreatic pseudocyst is suggested when an episode of pancreatitis fails to resolve or when a mass develops after an episode of pancreatitis. Clinical features usually include pain, nausea, and vomiting, but many patients are asymptomatic. The most common signs are a palpable mass in 50% of patients and jaundice in 10%. Other findings include ascites and pleural effusions (usually left-sided).

Pancreatic pseudocysts can be detected by transabdominal ultrasonography, CT scanning, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS). Because of its ease, availability, and reliability, ultrasonography is the first choice. Sequential ultrasonography studies have demonstrated that most small pseudocysts (<6 cm) resolve spontaneously. It is recommended that the patient with acute pancreatitis undergo an ultrasonographic evaluation 4 wk after resolution of the acute episode for an evaluation of possible pseudocyst formation.

Treatment of Fluid Collections and

Necrosis

Percutaneous and endoscopic drainage of pseudocysts have replaced open surgical drainage, except for complicated or recurrent pseudocysts. Whereas a pseudocyst must be allowed to mature for 4-6 wk before surgical drainage is attempted, percutaneous or endoscopic drainage can be attempted earlier. In some cases, endoscopic creation of a cyst-gastrostomy is performed. When a surgical treatment is planned an MRCP or ERCP is performed to define anatomic abnormalities and aid the surgeon in planning his approach. EUS is helpful when an endoscopic approach is chosen.

Necrotizing pancreatitis includes both pancreatic gland necrosis and peripancreatic fat necrosis. In the initial phases, the necrotic collection is a mix of semisolid and solid tissue. Over a period of 4 wk or longer, the collection becomes more liquid and becomes encapsulated by a visible wall. At this point, the process is termed walled-off pancreatic necrosis. Sterile necrosis does not require therapy except in the rare case of a collection that obstructs a nearby viscus (e.g., duodenal, bile duct, or gastric obstruction).

The development of *infected* necrosis is the main indication for broad-spectrum antibiotic therapy. The development of fever, leukocytosis, and increasing abdominal pain suggests infection of the necrotic tissue. A CT scan may reveal evidence of air bubbles in the necrotic cavity.

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CHAPTER 380

Pancreatic Tumors

Meghen B. Browning, Steven L. Werlin, Michael Wilschanski

Pancreatic tumors can be of either endocrine or nonendocrine origin. Tumors of endocrine origin include gastrinomas and insulinomas (Table 380.1). These and other functioning tumors occur in the autosomal dominantly inherited multiple endocrine neoplasia type 1 (MEN-1). Hypoglycemia accompanied by higher-than-expected insulin levels or refractory gastric ulcers (Zollinger-Ellison syndrome) indicates the possibility of a pancreatic tumor (see Chapter 372). Most gastrinomas arise outside of the pancreas. The treatment of choice is surgical removal. If the primary tumor cannot be found, or if it has metastasized, cure might not be possible. Treatment with a high dose of a proton pump inhibitor to inhibit gastric acid secretion is then indicated.

Table 380.1

Syndromes Associated With Pancreatic Neuroendocrine Tumors (pNETs)*

SYNDROME	INCIDENCE/10^6 /YEAR	MALIGNANCY (%)	HORMONE
Insulinoma	1-2	<10	Insulin
Gastrinoma (ZES)	0.5-1.5	60–90	Gastrin
VIPoma (Verner-Morrison syndrome, WDHA, pancreatic cholera)	0.05-0.2	>60	VIP
Glucagonoma	0.01-0.1	50–80	Glucagon
Somatostatinoma	Rare	>70	Somatostatin
GRFoma	Unknown	>30	GH-RF
ACTHoma	Uncommon	>95%	ACTH
pNET secreting PTH-rP	Rare	84%	PTH-rP
Pancreatic carcinoid tumor	Rare (<1% of all carcinoids)	77%	Serotonin, tachykinins
pNET secreting renin	Rare	Unknown	Renin
pNET secreting erythropoietin	Rare	Unknown	Erythropoietin

pNET secreting luteinizing hormone	Rare	Unknown	Luteinizing hormone
pNET secreting cholecystokinin (CCKoma)	Rare	Unknown	CCK

[*] These syndromes may also be caused by a GI-NET (carcinoid).

GH-RF , growth hormone–releasing factor; *PP* , pancreatic polypeptide; *PTH-rP* , parathyroid hormone–related protein; *VIP* , vasoactive intestinal polypeptide; *WDHA* , watery diarrhea, hypokalemia, achlorhydria.

From Jensen RT, Norton JA, Oberg K: Neuroendocrine tumors. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, Elsevier, 2016, Philadelphia, Table 33.1.

Insulinomas and persistent hyperinsulinemic hypoglycemia of infancy produce symptomatic hypoglycemia caused by mutations in a variety of genes, most commonly *GUUD1* and *KATP* . Massive subtotal or total pancreatectomy is the treatment of choice when medical treatment fails. These children might then develop pancreatic insufficiency and diabetes as a complication of surgery.

The **watery diarrhea–hypokalemia–acidosis syndrome** is usually produced by the secretion of vasoactive intestinal peptide by a non–α-cell tumor (VIPoma) (see Table 367.7). Vasoactive intestinal peptide levels are often, but not always, increased in the serum. Treatment is surgical removal of the tumor. When this is not possible, symptoms may be controlled by the use of octreotide acetate (cyclic somatostatin, Sandostatin), a synthetic analog of somatostatin. Pancreatic tumors secreting a variety of hormones, including glucagon, somatostatin, and pancreatic polypeptide, have also been described. The treatment is surgical resection when possible.

Pancreatoblastomas, pancreatic adenocarcinomas, cystadenomas, and sarcomas of the pancreas are rarely encountered. Pancreatoblastoma, a malignant embryonal tumor that secretes α-fetoprotein and can contain both endocrine and exocrine elements, is the most common pancreatic neoplasm in young children. Presurgical chemotherapy should be considered for lesions not primarily resectable. Resection can be curative; adjuvant chemotherapy has been used, but its effectiveness is not established.

Sarcomas are very rarely primary pancreatic but may include Ewing sarcoma, rhabdomyosarcoma, or undifferentiated soft tissue sarcomas. They are treated with multimodal therapy including chemotherapy and either resection or radiation.

Carcinoma of the exocrine pancreas is a major problem in adults, accounting for 2% of diagnoses and 5% of deaths from cancer. It is very rare in childhood. No definite causes are known. Several genetic syndromes including mutations in the *PRSS1* and *MEN-1* genes lead to an increased incidence of pancreatic cancer in adult life. The solid pseudopapillary tumor of the pancreas, also called Frantz tumor, is a more indolent pancreatic carcinoma usually found in adolescent/young adult females. Typical presenting symptoms are abdominal pain, mass, or jaundice. The treatment of choice is total surgical removal. Prognosis is very good.

Pancreatic lesions in **von Hippel-Lindau disease** are usually benign and cystic. Cystadenomas, familial adenocarcinomas, and islet cell tumors are less common. Metastases have been reported, but adjuvant therapy after surgical excision cannot yet be recommended. The diagnosis is suggested by CT scan.

Prognosis is good for completely resected endocrine tumors but very poor for sarcomas and carcinomas, excepting rare subtypes. Children who survive partial or complete pancreatectomy may have decreased pancreatic exocrine and endocrine reserve.

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SECTION 6

The Liver and Biliary System

OUTLINE

Chapter 381 Morphogenesis of the Liver and Biliary System

Chapter 382 Manifestations of Liver Disease

Chapter 383 Cholestasis

Chapter 384 Metabolic Diseases of the Liver

Chapter 385 Viral Hepatitis

Chapter 386 Liver Abscess

Chapter 387 Liver Disease Associated With Systemic Disorders

Chapter 388 Mitochondrial Hepatopathies

Chapter 389 Autoimmune Hepatitis

Chapter 390 Drug- and Toxin-Induced Liver Injury

Chapter 391 Acute Hepatic Failure

Chapter 392 Cystic Diseases of the Biliary Tract and Liver

Chapter 393 Diseases of the Gallbladder

Chapter 394 Portal Hypertension and Varices

Chapter 395 Liver Transplantation

CHAPTER 381

Morphogenesis of the Liver and Biliary System

Stacey S. Huppert, William F. Balistreri

During the early embryonic process of gastrulation, the 3 embryonic germ layers (endoderm, mesoderm, and ectoderm) are formed. The liver and biliary system arises from cells of the ventral foregut endoderm; their development can be divided into 3 distinct processes (Fig. 381.1). First, through unknown mechanisms, the ventral foregut endoderm acquires *competence* to receive signals arising from the cardiac mesoderm. These mesodermal signals, in the form of various fibroblast growth factors and bone morphogenetic proteins, lead to *specification* of cells that have the potential to form the liver and activate liver-specific genes. During this period of hepatic fate decision, “pioneer” transcription factors, including *Foxa* and *Gata4* , bind to specific binding sites in compacted chromatin, open the local chromatin structure, and mark genes as competent. However, these will be expressed only if they are correctly induced by additional transcription factors. Newly specified cells then delaminate from the ventral foregut endoderm and migrate in a cranial ventral direction into the septum transversum in the 4th wk of human gestation to initiate liver *morphogenesis.*

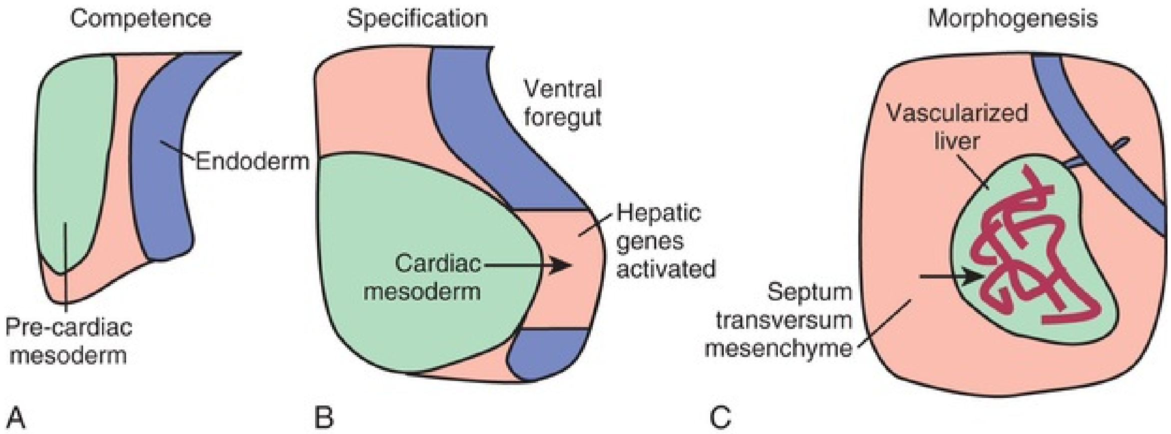
Competence
Specification
Morphogenesis
Endoderm
Pre-cardiac mesoderm
Ventral foregut
Cardiac mesoderm
Hepatic genes activated
Vascularized liver
Septum transversum mesenchyme
A
B
C

FIG. 381.1 Processes involved in early liver development. A, The ventral foregut endoderm acquires *competence* to receive signals arising from the cardiac mesoderm. B, Specific cells of the ventral foregut endoderm undergo *specification* and activation of liver-specific genes under the influence of mesodermal signals. C, Liver *morphogenesis* is initiated as the newly specified cells migrate into the septum transversum under the influence of signaling molecules and extracellular matrix released by septum transversum mesenchymal cells and of primitive endothelial cells. (From Zaret K7S: Liver specification and early morphogenesis, *Mech Dev* 92:83–88, 2000.)

The growth and development of the newly budded liver require interactions with endothelial cells. Certain proteins are important for liver development in animal models (Table 381.1). In addition to these proteins, microRNAs, which consist of small noncoding, single-stranded RNAs, have a functional role in the regulation of gene expression and hepatobiliary development in zebrafish and mouse models.

Table 381.1

Selected Growth Factors, Receptors, Protein Kinases, and Transcription Factors Required for Normal Liver Development in Animal Models

INDUCTION OF HEPATOCYTE FATE THROUGH CARDIAC MESODERM
• Fibroblast growth factors (FGFs) 1, 2, 8 • FGF receptors 1, 4
INDUCTION OF HEPATOCYTE FATE THROUGH SEPTUM TRANSVERSUM
• Bone morphogenetic proteins 2, 4, 7
STIMULATION OF HEPATOBLAST GROWTH AND PROLIFERATION
• Hepatocyte growth factor (HGF) • HGF receptor c-met • “Pioneer” transcription factors Foxa1, Foxa2, and Gata4, Gata6 • Transcription factors Xbp1, Foxm1b, Hlx, Hex, Prox1 • Wnt signaling pathway, β-catenin
SPECIFICATION OF HEPATOCYTE LINEAGE

• HGF • Transforming growth factor-β and its downstream effectors Smad 2, Smad 3 • Hepatocyte nuclear factors (HNFs) 1α, 4α, 6
SPECIFICATION OF CHOLANGIOCYTE LINEAGE
• Jagged 1 (Notch ligand) and Notch receptors 1, 2 • HNF6, HNF1β • Wnt signaling pathway, β-catenin • Vacuolar sorting protein Vps33b

Within the ventral mesentery, proliferation of migrating cells form anastomosing hepatic cords, with the network of primitive liver cells, sinusoids, and septal mesenchyme establishing the basic architectural pattern of liver lobule (Fig. 381.2). The solid *cranial* portion of the hepatic diverticulum (pars hepatis) eventually forms the hepatic parenchyma and the intrahepatic bile ducts. The hepatic lobules are identifiable in the 6th wk of human gestation. The bile canalicular structures, including microvilli and junctional complexes, are specialized loci of the liver cell membrane; these appear very early in gestation, and large canaliculi bounded by several hepatocytes are seen by 6-7 wk.

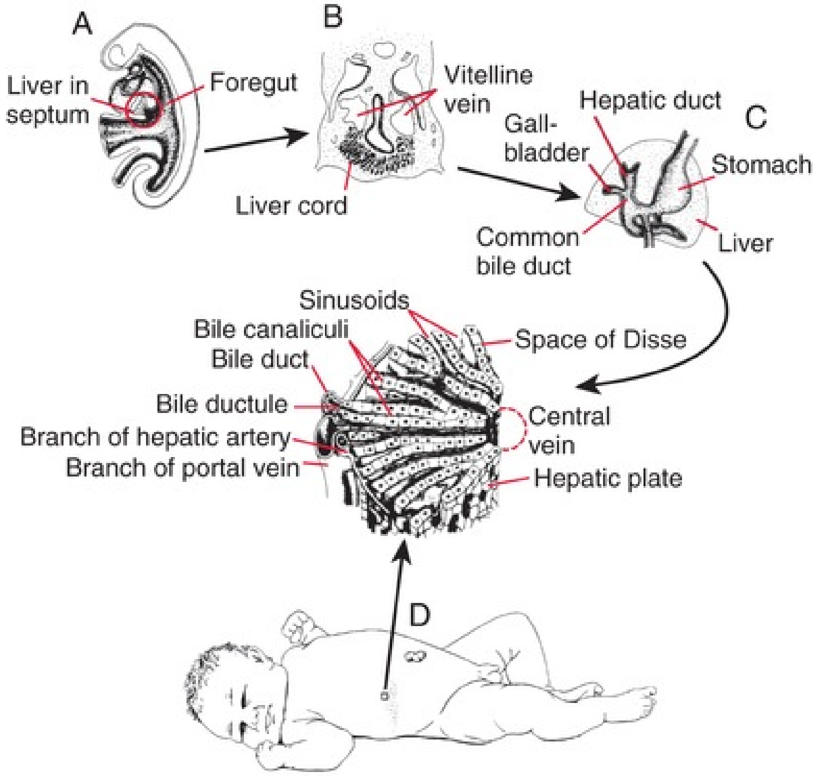
A
Liver in septum
Foregut
B
Vitelline vein
Liver cord
Hepatic duct
C
Gall-bladder
Stomach
Common bile duct
Liver
Sinusoids
Bile canaliculi
Bile duct
Space of Disse
Bile ductule
Branch of hepatic artery
Branch of portal vein
Central vein
Hepatic plate
D

FIG. 381.2 **Hepatic morphogenesis. A, Ventral outgrowth of hepatic diverticulum from foregut endoderm in the 3.5-wk embryo. B, Between the 2 vitelline veins, the enlarging hepatic diverticulum buds off epithelial (liver) cords that become the liver parenchyma, around which the endothelium of capillaries (sinusoids) align (4 wk embryo). C, Hemisection of embryo at 7.5 wk. D, Three-dimensional representation of the hepatic**

lobule as present in the newborn. (From Andres JM, Mathis RK, Walker WA: Liver disease in infants. Part I: developmental hepatology and mechanisms of liver dysfunction, *J Pediatr* 90:686–697, 1977.)

Hepatocytes and bile duct cells (cholangiocytes) originate from hepatoblasts as common precursors. Notch signaling, which is impaired in Alagille syndrome, promotes hepatoblast differentiation into biliary epithelium, whereas hepatocyte growth factor antagonizes differentiation. The development of the intrahepatic bile ducts is determined by the development and branching pattern of the portal vein. Around the 8th wk of gestation, starting at the hilum of the liver, primitive hepatoblasts adjacent to the mesenchyme around the portal vein branches form a cylindrical sleeve, termed the *ductal plate.* From 12 wk of gestation onward, a remodeling of the ductal plate occurs, with some segments of the ductal plate undergoing tubular dilation and excess ductal plate cells gradually disappearing. The ramification of the biliary tree continues throughout human fetal life and at the time of birth the most peripheral branches of the portal veins are still surrounded by ductal plates; these require 4 more wk to develop into definitive portal ducts. Lack of remodeling of the ductal plate results in persistence of primitive ductal plate configurations, an abnormality called *ductal plate malformation* . This histopathologic lesion has been observed in liver biopsies of a variety of liver conditions, including congenital hepatic fibrosis, Caroli disease, and biliary atresia.

The *caudal* part (pars cystica) of the hepatic diverticulum becomes the gallbladder, cystic duct, and common bile duct. The distal portions of the right and left hepatic ducts develop from the extrahepatic ducts, whereas the proximal portions develop from the first intrahepatic ductal plates. The extrahepatic bile ducts and the developing intrahepatic biliary tree maintain luminal continuity and patency from the beginning of organogenesis (see Fig. 381.2*C*).

Fetal hepatic blood flow is derived from the hepatic artery and from the portal and umbilical veins, which form the portal sinus. The portal venous inflow is directed mainly to the right lobe of the liver and umbilical flow primarily to the left. The ductus venosus shunts blood from the portal and umbilical veins to the hepatic vein, bypassing the sinusoidal network. After birth, the ductus venosus becomes obliterated when oral feedings are initiated. The fetal oxygen saturation is lower in portal than in umbilical venous blood; accordingly, the right hepatic lobe has lower oxygenation and greater hematopoietic activity than the left hepatic lobe.

The transport and metabolic activities of the liver are facilitated by the structural arrangement of liver cell cords, which are formed by rows of hepatocytes, separated by sinusoids that converge toward the tributaries of the hepatic vein (the central vein) located in the center of the lobule (see Fig. 381.2*D*). This establishes the pathways and patterns of flow for substances to and from the liver. In addition to arterial input from the systemic circulation, the liver also receives venous input from the gastrointestinal tract via the portal system. The products of the hepatobiliary system are released by 2 different paths: through the hepatic vein and through the biliary system back into the intestine. Plasma proteins and other plasma components are secreted by the liver. Absorbed and circulating nutrients arrive through the portal vein or the hepatic artery and pass through the sinusoids and past the hepatocytes to the systemic circulation at the central vein. Biliary components are transported via the series of enlarging channels from the bile canaliculi through the bile ductule to the common bile duct.

Bile secretion is first noted at the 12th wk of human gestation. The major components of bile vary with stage of development. Near term, cholesterol and phospholipid content is relatively low. Low concentrations of bile acids, the absence of bacterially derived (secondary) bile acids, and the presence of unusual bile acids reflect low rates of bile flow and immature bile acid synthetic pathways.

The liver reaches a peak relative size of approximately 10% of the fetal weight at the 9th wk. Early in development, the liver is a primary site of hematopoiesis. In the 7th wk, hematopoietic cells outnumber functioning hepatocytes in the hepatic anlage. These early hepatocytes are smaller than at maturity (~20 µm vs. 30-35 µm) and contain less glycogen. Near term, the hepatocyte mass expands to dominate the organ, as cell size and glycogen content increase. Hematopoiesis is virtually absent by the 2nd postnatal mo in full-term infants. As the density of hepatocytes increases with gestational age, the relative volume of the sinusoidal network decreases. The liver constitutes 5% of body weight at birth but only 2% in an adult.

Several metabolic processes are immature in a healthy newborn infant, owing in part to the fetal patterns of activity of various enzymatic processes. Many fetal hepatic functions are carried out by the maternal liver, which provides nutrients and serves as a route of elimination of metabolic end products and toxins. Fetal liver metabolism is devoted primarily to the production of proteins required for growth. Toward term, primary functions become production and storage of essential nutrients, excretion of bile, and establishment of processes of elimination. Extrauterine adaptation requires de novo enzyme synthesis. Modulation of these processes depends on substrate and hormonal input via the placenta and on dietary and hormonal input in the postnatal period.

Hepatic Ultrastructure

Hepatocytes exhibit various ultrastructural features that reflect their biologic functions (Fig. 381.3). Hepatocytes, like other epithelial cells, are polarized, meaning that their structure and function are directionally oriented. One result of this polarity is that various regions of the hepatocyte plasma membrane exhibit specialized functions. Bidirectional transport occurs at the *sinusoidal* surface, where materials reaching the liver via the portal system enter and compounds secreted by the liver leave the hepatocyte. *Canalicular* membranes of adjacent hepatocytes form bile canaliculi, which are bounded by tight junctions, preventing transfer of secreted compounds back into the sinusoid. Within hepatocytes, metabolic and synthetic activities are contained within a number of different cell organelles. The oxidation and metabolism of heterogeneous classes of substrates, fatty acid oxidation, key processes in gluconeogenesis, and the storage and release of energy occur in the abundant mitochondria.

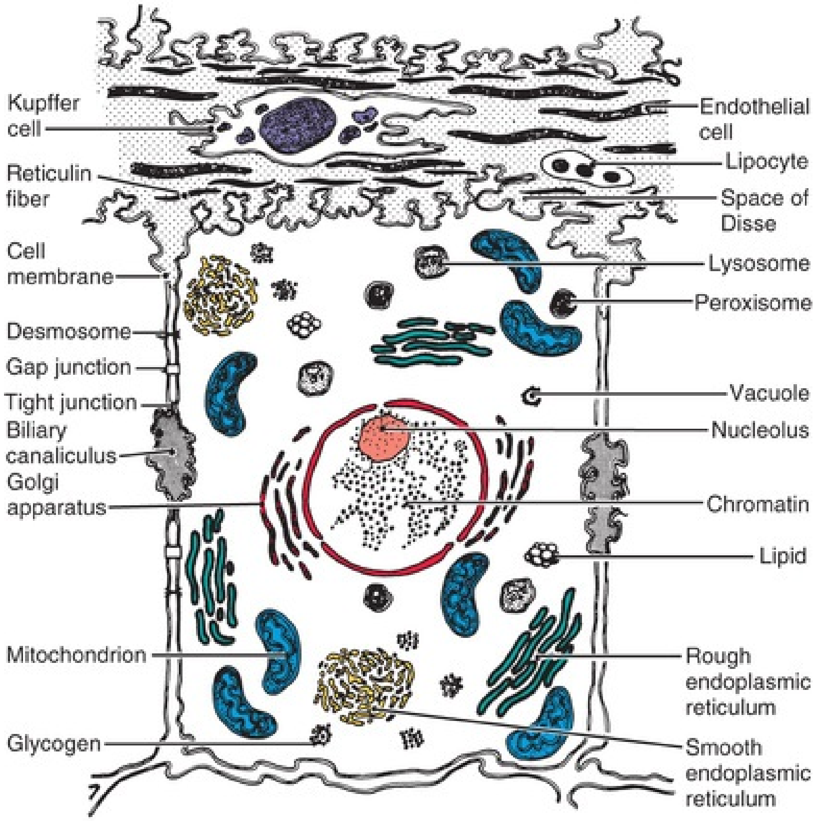
Kupffer cell
Reticulin fiber
Cell membrane
Desmosome
Gap junction
Tight junction
Biliary canaliculus
Golgi apparatus
Mitochondrion
Glycogen
Endothelial cell
Lipocyte
Space of Disse
Lysosome
Peroxisome
Vacuole
Nucleolus
Chromatin
Lipid
Rough endoplasmic reticulum
Smooth endoplasmic reticulum

FIG. 381.3 **Schematic view of the ultrastructure and organelles of hepatocytes. (From Sherlock S: Hepatic cell structure. In Sherlock S, editor: *Diseases of the liver and biliary system,* ed 6. Oxford, 1981, Blackwell Scientific, p. 10, with permission from Blackwell Scientific.)**

The endoplasmic reticulum, a continuous network of rough- and smooth-surfaced tubules and cisternae, is the site of various processes, including protein and triglyceride synthesis and drug metabolism. Low fetal activity of endoplasmic reticulum–bound enzymes accounts for a relative inefficiency of xenobiotic (drug) metabolism. The Golgi apparatus is active in protein packaging and possibly in bile secretion. Hepatocyte peroxisomes are single membrane–limited cytoplasmic organelles that contain enzymes such as oxidases and catalase and those that have a role in lipid and bile acid metabolism. Lysosomes contain numerous hydrolases that have a role in intracellular digestion. The hepatocyte cytoskeleton, composed of actin and other filaments, is distributed throughout the cell and concentrated near the plasma membrane. Microfilaments and microtubules have a role in receptor-mediated endocytosis, in bile secretion, and in maintaining hepatocyte architecture and motility.

Metabolic Functions of the Liver

Carbohydrate Metabolism

The liver regulates serum glucose levels closely via several processes, including storage of excess carbohydrate as glycogen, a polymer of glucose readily hydrolyzed to glucose during fasting. To maintain serum glucose levels, hepatocytes produce free glucose by either glycogenolysis or gluconeogenesis. Immediately after birth, an infant is dependent on hepatic glycogenolysis. Gluconeogenic activity is present at a low level in the fetal liver and increases rapidly after birth. Fetal glycogen synthesis begins at about the 9th wk of gestation, with glycogen stores most rapidly accumulated near term, when the liver contains 2-3 times the amount of glycogen of adult liver. Most of this stored glycogen is used in the immediate postnatal period. Reaccumulation is initiated at about the 2nd wk of postnatal life, and glycogen stores reach adult levels at approximately the 3rd wk in healthy full-term infants. In preterm infants, serum glucose levels fluctuate in part because efficient regulation of the synthesis, storage, and degradation of glycogen develops only near the end of full-term gestation. Dietary carbohydrates such as galactose are converted to glucose, but there is a substantial dependence on gluconeogenesis for glucose in early life, especially if glycogen stores are limited.

Protein Metabolism

During the rapid fetal growth phase, specific decarboxylases that are rate limiting in the biosynthesis of physiologically important polyamines have higher activities than in the mature liver. The rate of synthesis of albumin and secretory proteins in the developing liver parallels the quantitative changes in endoplasmic reticulum. Synthesis of albumin appears at approximately the 7th-8th wk in the human fetus and increases in inverse proportion to that of α-fetoprotein, which is the dominant fetal protein. By the 3rd-4th mo of gestation, the fetal liver is able to produce fibrinogen, transferrin, and low-density lipoproteins. From this period on, fetal plasma contains each of the major protein classes at concentrations considerably below those achieved at maturity.

The *postnatal* patterns of protein synthesis vary with the class of protein. Lipoproteins of each class rise abruptly in the 1st wk after birth to reach levels that vary little until puberty. Albumin concentrations are low in a neonate (~2.5 g/dL), reaching adult levels (~3.5 g/dL) after several mo. Levels of ceruloplasmin and complement factors increase slowly to adult values in the 1st yr. In contrast, transferrin levels at birth are similar to those of an adult, decline for 3-5 mo, and rise thereafter to achieve their final concentrations. Low levels of activity of specific proteins have implications for the nutrition of an infant. A low level of cystathionine γ-lyase (cystathionase) activity impairs the *trans* -sulfuration pathway by which dietary methionine is converted to cysteine. Consequently, the latter must be supplied in the diet. Similar dietary requirements might exist for other sulfur-containing amino acids, such as taurine.

Lipid Metabolism

Fatty acid oxidation provides a major source of energy in early life, complementing glycogenolysis and gluconeogenesis. Newborn infants are relatively intolerant of prolonged fasting, owing in part to a restricted capacity for hepatic ketogenesis. Rapid maturation of the ability of the liver to oxidize fatty acid occurs in the 1st few days of life. Milk provides the major source of calories in early life; this high-fat, low-carbohydrate diet mandates active gluconeogenesis to maintain blood glucose levels. When the glucose supply is limited, ketone body production from endogenous fatty acids can provide energy for hepatic gluconeogenesis and an alternative fuel for brain metabolism. When carbohydrates are in excess, the liver produces triglycerides. Metabolic processes involving lipids and lipoproteins are predominantly hepatic; liver immaturity or disease affects lipid concentrations and lipoproteins.

Biotransformation

Newborn infants have a decreased capacity to metabolize and detoxify certain drugs, owing to underdevelopment of the hepatic microsomal component that is the site of the specific oxidative, reductive, hydrolytic, and conjugation reactions required for these biotransformations. The major components of the monooxygenase system, such as cytochrome P450, cytochrome-*c* reductase, and the reduced form of nicotinamide-adenine dinucleotide phosphate, are present in low concentrations in fetal microsomal preparations. In full-term infants, hepatic uridine diphosphate glucuronosyltransferase and enzymes involved in the oxidation of polycyclic aromatic hydrocarbons are expressed at very low levels.

Age-related differences in pharmacokinetics vary from compound to compound. The half-life of acetaminophen in a newborn is similar to that of an adult, whereas theophylline has a half-life of approximately 100 hr in a premature infant, as compared with 5-6 hr in an adult. These differences in metabolism, as well as factors such as binding to plasma proteins and renal clearance, determine appropriate drug dosage to maximize effectiveness and to avoid toxicity. Dramatic examples of the susceptibility of newborn infants to drug toxicity are the responses to chloramphenicol (the *gray baby* syndrome) or to benzoyl alcohol and its metabolic products, which involve ineffective glucuronide and glycine conjugation, respectively. The low concentrations of antioxidants (vitamin E, superoxide dismutase, glutathione peroxidase) in the fetal and early newborn liver lead to increased susceptibility to deleterious effects of oxygen toxicity and oxidant injury through lipid peroxidation.

Conjugation reactions, which convert drugs or metabolites into water-soluble forms that can be eliminated in bile, are also catalyzed by hepatic microsomal enzymes. Newborn infants have decreased activity of hepatic uridine diphosphate glucuronosyltransferase, which converts unconjugated bilirubin to the readily excreted glucuronide conjugate and is the rate-limiting enzyme in the excretion of bilirubin. There is rapid postnatal development of transferase activity irrespective of gestational age, which suggests that birth-related, rather than age-related, factors are of primary importance in the postnatal development of activity of this enzyme. Microsomal activity can be stimulated by administration of phenobarbital, rifampin, or other inducers of cytochrome P450. Alternatively, drugs such as cimetidine can inhibit microsomal P450 activity.

Hepatic Excretory Function

Hepatic excretory function and bile flow are closely related to hepatic *bile acid* excretion and enterohepatic recirculation. Bile acids, the major products of cholesterol degradation, are incorporated into mixed micelles with cholesterol and phospholipid. These micelles act as an efficient vehicle for solubilization and intestinal absorption of lipophilic compounds, such as dietary fats and fat-soluble vitamins. Secretion of bile acids by the liver cells is the major determinant of bile flow in the mature animal. Accordingly, maturity of bile acid metabolic processes affects overall hepatic excretory function, including biliary excretion of endogenous and exogenous compounds.

In humans, the 2 primary bile acids, cholic acid and chenodeoxycholic acid, are synthesized in the liver. Before excretion, they are conjugated with glycine and taurine. In response to a meal, contraction of the gallbladder delivers bile acids to the intestine to assist in fat digestion and absorption. After mediating fat digestion, the bile acids themselves are reabsorbed from the terminal ileum through specific active transport processes. They return to the liver via portal blood, are taken up by liver cells, and are reexcreted in bile. In an adult, this enterohepatic circulation involves 90–95% of the circulating bile acid pool. Bile acids that escape ileal reabsorption reach the colon, where the bacterial flora, through dihydroxylation and deconjugation, produce the secondary bile acids, deoxycholate and lithocholate. In an adult, the composition of bile reflects the excretion of the primary and also the secondary bile acids, which are reabsorbed from the distal intestinal tract.

Intraluminal concentrations of bile acids are low in newborn infants and increase rapidly after birth. The expansion of the bile acid pool is critical because bile acids are required to stimulate bile flow and absorb lipids, a major component of the diet of a newborn. Nuclear receptors, such as farnesoid X receptor, control intrahepatic bile acid homeostasis through several mechanisms, including regulation of expression of the genes encoding 2 key proteins, cholesterol 7α-hydroxylase (CYP7A1) and bile salt export pump (BSEP). These proteins are critical for bile acid synthesis and canalicular secretion, respectively. Neonatal expression of these nuclear receptors varies depending on the studied animal model and is largely unknown for humans.

Because of inefficient ileal reabsorption of bile acids and the low rate of hepatic clearance of bile acids from portal blood, serum concentrations of bile acids are commonly elevated in healthy newborns, often to levels that would suggest liver disease in older persons. Transient phases of physiologic cholestasis and physiologic steatorrhea can often be observed in low birthweight infants and in full-term infants following perinatal stress, such as hypoxia or infection, but are otherwise uncommon in healthy full-term newborns.

Many of the processes related to immaturity of the newborn in liver morphogenesis and function, as discussed earlier, are implied in the increased susceptibility of infants to liver disease associated with parenteral nutrition. The reduced bile salt pool, hepatic glutathione depletion, and deficient sulfation contribute to production of toxic lithocholic bile acids and cholestasis, whereas deficiencies of essential amino acids, including taurine and cysteine, and excessive lipid infusion can lead to hepatic steatosis in these infants. Beyond the neonatal period, disturbances in bile acid metabolism may be responsible for diverse effects on hepatobiliary and intestinal function (Table 381.2).

Table 381.2

Causes of Impaired Bile Acid Metabolism and Enterohepatic Circulation

DEFECTIVE BILE ACID SYNTHESIS OR TRANSPORT
• Inborn errors of bile acid synthesis (reductase deficiency, isomerase deficiency) • Progressive familial intrahepatic cholestasis (PFIC1, PFIC2, PFIC3) • Intrahepatic cholestasis (neonatal hepatitis) • Acquired defects in bile acid synthesis secondary to severe liver disease
ABNORMALITIES OF BILE ACID DELIVERY TO THE BOWEL
• Celiac disease (sluggish gallbladder contraction) • Extrahepatic bile duct obstruction (e.g., biliary atresia, gallstones)
LOSS OF ENTEROHEPATIC CIRCULATION OF BILE ACIDS
• External bile fistula • Cystic fibrosis • Small bowel bacterial overgrowth syndrome (with bile acid precipitation, increased jejunal absorption, and “short-circuiting”) • Drug-induced entrapment of bile acids in intestinal lumen (e.g., cholestyramine)
BILE ACID MALABSORPTION
• Primary bile acid malabsorption (absent or inefficient ileal active transport) • Secondary bile acid malabsorption • Ileal disease or resection • Cystic fibrosis
DEFECTIVE UPTAKE OR ALTERED INTRACELLULAR METABOLISM
• Parenchymal disease (acute hepatitis, cirrhosis) • Regurgitation from cells • Portosystemic shunting • Cholestasis

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CHAPTER 382

Manifestations of Liver Disease

James E. Squires, William F. Balistreri

Pathologic Manifestations

Congenital and acquired alterations in hepatic structure and function (acute or chronic) can be manifest by varying patterns of reaction of the liver to cell injury. Hepatocyte injury can be caused by viral infection, drugs or toxins, hypoxia, immunologic and structural disorders, or inborn errors of metabolism. The injury results in inflammatory cell infiltration and cell death (necrosis), which may be followed by a healing process of scar formation (fibrosis) and, potentially, nodule formation (regeneration). Cirrhosis is the end result of any progressive fibrotic liver disease.

Cholestasis is an alternative or concomitant response to injury caused by extrahepatic or intrahepatic obstruction to bile flow. Substances that are normally excreted in bile, such as bile acids, conjugated bilirubin, cholesterol, and trace elements, accumulate in serum. Bile pigment accumulation in liver parenchyma can be seen in liver biopsy specimens. In *extrahepatic* obstruction, bile pigment may be visible in the intralobular bile ducts or throughout the parenchyma as bile lakes or infarcts. In *intrahepatic* cholestasis, an injury to hepatocytes or an alteration in hepatic physiology leads to a reduction in the rate of secretion of solute and water. Causes include alterations in enzymatic or canalicular transporter activity, permeability of the bile canalicular apparatus, organelles responsible for bile secretion, or ultrastructure of the cytoskeleton of the hepatocyte. The end result may be clinically indistinguishable from obstructive cholestasis.

Cirrhosis, defined histologically by the presence of bands of fibrous tissue that link central and portal areas and form parenchymal nodules, is an end stage of any acute or chronic liver disease. Cirrhosis can be *macronodular* , with nodules of various sizes (up to 5 cm) separated by broad septa, or *micronodular* , with nodules of uniform size (<1 cm) separated by fine septa; mixed forms occur. The progressive scarring results in altered hepatic blood flow, with further impairment of liver cell function. Increased intrahepatic resistance to portal blood flow leads to portal hypertension.

The liver can be secondarily involved in neoplastic (metastatic) and non-neoplastic (storage diseases, fat infiltration) processes, as well as a number of systemic conditions and infectious processes. The liver can be affected by chronic passive congestion (congestive heart failure) or acute hypoxia, with hepatocellular damage.

Clinical Manifestations

Hepatomegaly

Enlargement of the liver can be caused by several mechanisms (Table 382.1). Normal liver size estimations are based on age-related clinical indices, such as the degree of extension of the liver edge below the costal margin, the span of dullness to percussion, or the length of the vertical axis of the liver, as estimated from imaging techniques. In children, the normal liver edge can be felt up to 2 cm below the right costal margin. In a newborn infant, extension of the liver edge more than 3.5 cm below the costal margin in the right midclavicular line suggests hepatic enlargement. Measurement of liver span is carried out by percussing the upper margin of dullness and by palpating the lower edge in the right midclavicular line. This may be more reliable than an extension of the liver edge alone. The 2 measurements may correlate poorly.

Table 382.1

Mechanisms of Hepatomegaly

INCREASE IN THE NUMBER OR SIZE OF THE CELLS INTRINSIC TO THE LIVER
Storage
Fat: malnutrition, obesity, metabolic liver disease (diseases of fatty acid oxidation and Reye syndrome–like illnesses), lipid infusion (total parenteral nutrition), cystic fibrosis, medication related, pregnancy Specific lipid storage diseases: Gaucher, Niemann-Pick, Wolman disease Glycogen: glycogen storage diseases (multiple enzyme defects); total parenteral nutrition; infant of diabetic mother, Beckwith syndrome, poorly controlled type 1 diabetes mellitus (Mauriac syndrome) Miscellaneous: α_1 -antitrypsin deficiency, Wilson disease, hypervitaminosis A
Inflammation

- Hepatocyte enlargement (hepatitis)
  - Viral: acute and chronic
  - Bacterial: sepsis, abscess, cholangitis
  - Toxic: drugs
  - Autoimmune
- Kupffer cell enlargement
  - Sarcoidosis
  - Systemic lupus erythematosus
  - Hemophagocytic lymphohistiocytosis
  - Macrophage activating syndrome

INFILTRATION OF CELLS

Primary Liver Tumors: Benign

- Hepatocellular
  - Focal nodular hyperplasia
  - Nodular regenerative hyperplasia
  - Hepatocellular adenoma
- Mesodermal
  - Infantile hemangioendothelioma
  - Mesenchymal hamartoma
- Cystic masses
  - Choledochal cyst
  - Hepatic cyst
  - Hematoma
  - Parasitic cyst
  - Pyogenic or amebic abscess

Primary Liver Tumors: Malignant

- Hepatocellular
  - Hepatoblastoma
  - Hepatocellular carcinoma
- Mesodermal
  - Angiosarcoma
  - Undifferentiated embryonal sarcoma
- Secondary or metastatic processes
  - Lymphoma
  - Leukemia
  - Lymphoproliferative disease
  - Langerhans cell histiocytosis
  - Neuroblastoma
  - Wilms tumor

INCREASED SIZE OF VASCULAR SPACE

- Intrahepatic obstruction to hepatic vein outflow
  - Venoocclusive disease
  - Hepatic vein thrombosis (Budd-Chiari syndrome)
  - Hepatic vein web
- Suprahepatic
  - Congestive heart failure
- Pericardial disease/tamponade/constrictive pericarditis
- Post-Fontan procedure
- Hematopoietic: sickle cell anemia, thalassemia

INCREASED SIZE OF BILIARY SPACE

- Congenital hepatic fibrosis
- Caroli disease
- Extrahepatic obstruction

IDIOPATHIC

- Various

- Riedel lobe
- Normal variant
- Downward displacement of diaphragm

The liver span increases linearly with body weight and age in both sexes, ranging from approximately 4.5-5.0 cm at 1 wk of age to approximately 7-8 cm in boys and 6.0-6.5 cm in girls by 12 yr of age. The lower edge of the right lobe of the liver extends downward (Riedel lobe) and can normally be palpated as a broad mass in some people. An enlarged left lobe of the liver is palpable in the epigastrium of some patients with cirrhosis. Downward displacement of the liver by the diaphragm (hyperinflation) or thoracic organs can create an erroneous impression of hepatomegaly.

Examination of the liver should note the consistency, contour, tenderness, and presence of any masses or bruits, as well as assessment of spleen size, along with documentation of the presence of ascites and any stigmata of chronic liver disease.

Ultrasound is useful in assessment of liver size and consistency, as well as gallbladder size. Gallbladder length normally varies from 1.5-5.5 cm (average: 3 cm) in infants to 4-8 cm in adolescents; width ranges from 0.5-2.5 cm for all ages. Gallbladder distention may be seen in infants with sepsis. The gallbladder is often absent in infants with biliary atresia.

Jaundice (Icterus)

Yellow discoloration of the sclera, skin, and mucous membranes is a sign of hyperbilirubinemia (see Chapter 123.3). Clinically apparent jaundice in children and adults occurs when the serum concentration of bilirubin reaches 2-3 mg/dL (34-51 µmol/L); the neonate might not appear jaundiced until the bilirubin level is >5 mg/dL (>85 µmol/L). Jaundice may be the earliest and only sign of hepatic dysfunction. Liver disease must be suspected in the infant who appears only mildly jaundiced but has dark urine or acholic (light-colored) stools. Immediate evaluation to establish the cause is required.

Measurement of the total serum bilirubin concentration allows quantitation of jaundice. Bilirubin occurs in plasma in 4 forms: *unconjugated* bilirubin tightly bound to albumin; *free* or *unbound bilirubin* (the form responsible for kernicterus, because it can cross cell membranes); *conjugated bilirubin* (the only fraction to appear in urine); and *δ fraction* (bilirubin covalently bound to albumin), which appears in serum when hepatic excretion of conjugated bilirubin is impaired in patients with hepatobiliary disease. The δ fraction permits conjugated bilirubin to persist in the circulation and delays resolution of jaundice. Although the terms *direct* and *indirect* bilirubin are used equivalently with *conjugated* and *unconjugated* bilirubin, this is not quantitatively correct, because the direct fraction includes both conjugated bilirubin and δ bilirubin.

Investigation of jaundice in an infant or older child must include determination of the accumulation of both unconjugated and conjugated bilirubin. Unconjugated hyperbilirubinemia might indicate increased production, hemolysis, reduced hepatic removal, or altered metabolism of bilirubin (Table 382.2). Conjugated hyperbilirubinemia reflects decreased excretion by damaged hepatic parenchymal cells or disease of the biliary tract, which may be a result of obstruction, sepsis, toxins, inflammation, and genetic or metabolic disease (Table 382.3).

Table 382.2

Differential Diagnosis of Unconjugated Hyperbilirubinemia

INCREASED PRODUCTION OF UNCONJUGATED BILIRUBIN FROM HEME
Hemolytic Disease (Hereditary or Acquired)
Isoimmune hemolysis (neonatal; acute or delayed transfusion reaction; autoimmune) • Rh incompatibility • ABO incompatibility • Other blood group incompatibilities Congenital spherocytosis Hereditary elliptocytosis Infantile pyknocytosis Erythrocyte enzyme defects Hemoglobinopathy • Sickle cell anemia • Thalassemia • Others Sepsis Microangiopathy • Hemolytic-uremic syndrome • Hemangioma • Mechanical trauma (heart valve) Ineffective erythropoiesis Drugs Infection Enclosed hematoma Polycythemia • Diabetic mother • Fetal transfusion (recipient) • Delayed cord clamping
DECREASED DELIVERY OF UNCONJUGATED BILIRUBIN (IN PLASMA) TO HEPATOCYTE
Right-sided congestive heart failure Portacaval shunt
DECREASED BILIRUBIN UPTAKE ACROSS HEPATOCYTE MEMBRANE

Presumed enzyme transporter deficiency Competitive inhibition • Breast milk jaundice • Lucey-Driscoll syndrome • Drug inhibition (radiocontrast material) Miscellaneous • Hypothyroidism • Hypoxia • Acidosis
DECREASED STORAGE OF UNCONJUGATED BILIRUBIN IN CYTOSOL (DECREASED Y AND Z PROTEINS)
Competitive inhibition Fever
DECREASED BIOTRANSFORMATION (CONJUGATION)
Neonatal jaundice (physiologic) Inhibition (drugs) Hereditary (Crigler-Najjar) • Type I (complete enzyme deficiency) • Type II (partial deficiency) Gilbert disease Hepatocellular dysfunction
ENTEROHEPATIC RECIRCULATION
Breast milk jaundice Intestinal obstruction • Ileal atresia • Hirschsprung disease • Cystic fibrosis • Pyloric stenosis Antibiotic administration

Table 382.3

Differential Diagnosis of Neonatal and Infantile Cholestasis

INFECTIOUS
Generalized bacterial sepsis Viral hepatitis • Hepatitides A, B, C, D, E • Cytomegalovirus • Rubella virus • Herpesviruses: herpes simplex, human herpesvirus 6 and 7 • Varicella virus • Coxsackievirus • Echovirus • Reovirus type 3 • Parvovirus B19 • HIV • Adenovirus Others • Toxoplasmosis • Syphilis • Tuberculosis • Listeriosis

• Urinary tract infection
TOXIC
Sepsis Parenteral nutrition related Drug, dietary supplement, herbal related
METABOLIC
Disorders of amino acid metabolism • Tyrosinemia Disorders of lipid metabolism • Wolman disease • Niemann-Pick disease (type C) • Gaucher disease Cholesterol ester storage disease Disorders of carbohydrate metabolism • Galactosemia • Fructosemia • Glycogenosis IV Disorders of bile acid biosynthesis Other metabolic defects • α_1 -Antitrypsin deficiency • Cystic fibrosis • Hypopituitarism • Hypothyroidism • Zellweger (cerebrohepatorenal) syndrome
• Wilson disease • Gestational alloimmune liver disease (previously *neonatal iron storage disease*) • Indian childhood cirrhosis/infantile copper overload • Congenital disorders of glycosylation • Mitochondrial hepatopathies • Citrin deficiency
GENETIC OR CHROMOSOMAL
Trisomies 17, 18, 21
INTRAHEPATIC CHOLESTASIS SYNDROMES
“Idiopathic” neonatal hepatitis Alagille syndrome Intrahepatic cholestasis (progressive familial intrahepatic cholestasis [PFIC]) • FIC-1 deficiency • Bile salt export pump (BSEP) deficiency • MDR3 deficiency • Tight junction protein 2 deficiency • Farnesoid X receptor (FXR) mutations Familial benign recurrent cholestasis associated with lymphedema (Aagenaes syndrome) ARC (arthrogryposis, renal dysfunction, and cholestasis) syndrome Caroli disease (cystic dilation of intrahepatic ducts)
EXTRAHEPATIC DISEASES
Biliary atresia Sclerosing cholangitis Bile duct stricture/stenosis Choledochal–pancreaticoductal junction anomaly Spontaneous perforation of the bile duct Choledochal cyst Mass (neoplasia, stone) Bile/mucous plug (“inspissated bile”)
MISCELLANEOUS
Shock and hypoperfusion

Associated with enteritis
Associated with intestinal obstruction
Neonatal lupus erythematosus
Myeloproliferative disease (trisomy 21)
Hemophagocytic lymphohistiocytosis (HLH)
COACH syndrome (coloboma, oligophrenia, ataxia, cerebellar vermis hypoplasia, hepatic fibrosis)
Cholangiocyte cilia defects

Pruritus

Intense generalized itching can occur in patients with chronic liver disease often in association with cholestasis (conjugated hyperbilirubinemia). Symptoms can be generalized or localized (commonly to palms and soles), are usually worse at night, are exacerbated with stress and heat, and are relieved by cool temperatures. Pruritus is unrelated to the degree of hyperbilirubinemia; deeply jaundiced patients can be asymptomatic.

The pathogenesis of pruritus remains unknown, however, multiple suspected pruritogens have been reported including bile acids, histamine, serotonin, progesterone metabolites, endogenous opioids, the potent neuronal activator lysophosphatidic acid (LPA), and the LPA-forming enzyme, autotaxin (ATX). Ultimately, a multifactorial process is suspected as evidenced by the symptomatic relief of pruritus after administration of various therapeutic agents including bile acid-binding agents (cholestyramine), choleretic agents (ursodeoxycholic acid), opiate antagonists, antihistamines, serotonin reuptake inhibitors (sertraline), and antibiotics. Plasmapheresis, molecular adsorbent recirculating system therapy, and surgical diversion of bile (partial and total biliary diversion) have been used in attempts to provide relief for medically refractory pruritus.

Spider Angiomas

Vascular spiders *(telangiectasias)* , characterized by central pulsating arterioles from which small, wiry venules radiate, may be seen in patients with chronic liver disease. These are usually most prominent in the superior vena cava distribution area (on the face and chest). Their size varies between 1 and 10 mm and they exhibit central clearing with pressure. They presumably reflect altered estrogen metabolism in the presence of hepatic dysfunction.

Palmar Erythema

Blotchy erythema, most noticeable over the thenar and hypothenar eminences and on the tips of the fingers, is also noted in patients with chronic liver disease. Abnormal serum estradiol levels and regional alterations in peripheral circulation have been identified as possible causes.

Xanthomas

The marked elevation of serum cholesterol levels (to >500 mg/dL) associated with some forms of chronic cholestasis, especially Alagille syndrome, can cause the deposition of lipid in the dermis and subcutaneous tissue. Brown nodules can develop, first over the extensor surfaces of the extremities; rarely, xanthelasma of the eyelids develops.

Portal Hypertension

Portal hypertension occurs when there is increased portal resistance and/or increased portal flow. The portal system drains the splanchnic area (abdominal portion of the gastrointestinal tract, pancreas, and spleen) into the hepatic sinusoids. Normal portal pressure is between 1 and 5 mm Hg. Portal hypertension is defined as a portal pressure greater than or equal to 6 mm Hg. Clinically significant portal hypertension exists when pressure exceeds a threshold of 10-12 mm Hg. Portal hypertension is the main complication of cirrhosis, directly responsible for 2 of the most common and potentially lethal complications: ascites and variceal hemorrhage.

Ascites

Ascites is a consequence of increased hydrostatic and osmotic pressures within the hepatic and mesenteric capillaries resulting in transfer of fluid from the blood vessels to the lymphatics that overcomes the drainage capacity of the lymphatic system. Ascites can also be associated with nephrotic syndrome and other urinary tract abnormalities, metabolic diseases (such as lysosomal storage diseases), congenital or acquired heart disease, and hydrops fetalis. Factors favoring the intraabdominal accumulation of fluid include decreased plasma colloid (albumin) osmotic pressure, increased capillary hydrostatic pressure, increased ascitic colloid osmotic fluid pressure, and decreased ascitic fluid hydrostatic pressure. Abnormal renal sodium retention plays a central role.

Gastrointestinal Bleeding

Chronic liver disease may manifest as gastrointestinal hemorrhage. Bleeding may result from portal hypertensive gastropathy, gastric antral vascular ectasia, or varix rupture. Variceal hemorrhage is classically from an esophageal origin but may be caused by gastric, duodenal, peristomal, or rectal varices. Variceal hemorrhage results from increased pressure within the varix, which leads to changes in the diameter of the varix and increased wall tension. When the variceal wall strength is exceeded, physical rupture of the varix results. Given the high blood flow and pressure in the portosystemic collateral system, coupled with the lack of a natural mechanism to tamponade variceal bleeding, the rate of hemorrhage can be striking.

Encephalopathy

Hepatic encephalopathy can be manifest as any neurologic dysfunction, but it is most likely to present in subtle forms such as deterioration of school performance, sleep disturbances, depression, or emotional outbursts. It can be recurrent and precipitated by intercurrent illness, drugs, bleeding, or electrolyte and acid-base disturbances. The appearance of hepatic encephalopathy depends on the presence of portosystemic shunting, alterations in the blood–brain barrier, and the interactions of toxic metabolites with the central nervous system. Postulated causes include altered ammonia metabolism, synergistic neurotoxins, decreased cerebral oxygen metabolism and blood flow, or false neurotransmitters with plasma amino acid imbalance.

Endocrine Abnormalities

Endocrine abnormalities are more common in older adolescents and adults with hepatic disease than in children. They reflect alterations in hepatic synthetic, storage, and metabolic functions, including those concerned with hormonal metabolism in the liver. Proteins that bind hormones in plasma are synthesized in the liver, and steroid hormones are conjugated in the liver and excreted in the urine; failure of such functions can have clinical consequences. Endocrine abnormalities can also result from malnutrition or specific deficiencies.

Renal Dysfunction

Systemic disease or toxins can affect the liver and kidneys simultaneously, or parenchymal liver disease can produce secondary impairment of renal function. In hepatobiliary disorders, there may be renal alterations in sodium and water economy, impaired renal concentrating ability, and alterations in potassium metabolism. Ascites in patients with cirrhosis may be related to inappropriate retention of sodium by the kidneys and expansion of plasma volume, or it may be related to sodium retention mediated by diminished effective plasma volume.

Hepatorenal syndrome is defined as functional renal failure in patients with end-stage liver disease. The pathophysiology of hepatorenal syndrome is related to splanchnic vasodilation, mesenteric angiogenesis, and decreased effective blood volume with resulting decreased renal perfusion. The hallmark is intense renal vasoconstriction (mediated by hemodynamic, humoral, or neurogenic mechanisms) with coexistent systemic vasodilation. The diagnosis is supported by the findings of oliguria (<1 mL/kg/day), a characteristic pattern of urine electrolyte abnormalities (urine sodium <10 mEq/L, fractional excretion of sodium of <1%, urine: plasma creatinine ratio <10, and normal urinary sediment), absence of hypovolemia, and exclusion of other kidney pathology. The best treatment of hepatorenal syndrome is timely liver transplantation, with complete renal recovery expected.

Pulmonary Involvement

Hepatopulmonary syndrome (HPS) is characterized by the typical triad of hypoxemia, intrapulmonary vascular dilations, and liver disease. There is intrapulmonic right-to-left shunting of blood resulting from enlarged pulmonary vessels that prevents adequate exposure to oxygen-rich alveoli of red blood cells traveling through the center of the vessel. Shunting of vasodilatory mediators from the mesentery away from the liver is thought to contribute. HPS should be suspected and investigated in the child with chronic liver disease with history of shortness of breath or exercise intolerance and clinical examination findings of cyanosis (particularly of the lips and fingers), digital clubbing, and oxygen saturations <96%, particularly in the upright position. Treatment is timely liver transplantation; resolution of pulmonary involvement usually follows.

Portopulmonary hypertension is a condition characterized by an increase in the resistance to pulmonary arterial blood flow in the setting of portal hypertension. It is defined by a pulmonary arterial pressure >25 mm Hg at rest and above 30 mm Hg with exercise, elevated pulmonary vascular resistance with pulmonary arterial occlusion pressure, or a left-ventricular end-diastolic pressure of <15 mm Hg. Although the pathophysiology is unclear, deficiency in endothelial prostacyclin synthase and increased circulating endothelin-1 have been implicated as a cause for the vasculopathy. Autopsy studies have demonstrated the coexistence of portal hypertension, microscopic pulmonary artery thromboembolism, endothelial and smooth muscle proliferation, and platelet aggregates contributing to portopulmonary hypertension development. Symptoms suggesting a diagnosis include exertional dyspnea, fatigue, syncope, palpitations, and chest pain. Pulmonary artery directed therapy is the cornerstone of management, along with consideration of liver transplant.

Recurrent Cholangitis

Ascending infection of the biliary system is often seen in pediatric cholestatic disorders, most commonly because of Gram-negative enteric organisms such as *Escherichia coli*, *Klebsiella*, *Pseudomonas*, and *Enterococcus*. Liver transplantation is the definitive treatment for recurrent cholangitis, especially when medical therapy is not effective.

Miscellaneous Manifestations of Liver Dysfunction

Nonspecific signs of acute and chronic liver disease include anorexia, which often affects patients with anicteric hepatitis and with cirrhosis associated with chronic cholestasis; abdominal pain or distention resulting from ascites, spontaneous peritonitis, or visceromegaly; malnutrition and growth failure; and bleeding, which may be a result of altered synthesis of coagulation factors (biliary obstruction with vitamin K deficiency or excessive hepatic damage) or to portal hypertension with hypersplenism. In the presence of hypersplenism, there can be decreased synthesis of specific clotting factors, production of qualitatively abnormal proteins, or alterations in platelet number and function. Altered drug metabolism can prolong the biologic half-life of commonly administered medications.

382.1

Evaluation of Patients With Possible Liver Dysfunction

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Keywords

liver disease
liver biochemistries
liver function studies
liver biopsy
hepatic imaging

Adequate evaluation of an infant, child, or adolescent with suspected liver disease begins with an appropriate and accurate history, a carefully performed physical examination, and skillful interpretation of signs and symptoms. Further evaluation is aided by judicious selection of diagnostic tests, followed by the use of imaging modalities and/or a liver biopsy (Fig. 382.1). Most of the so-called liver “function” tests *do not* measure any specific hepatic function: a rise in serum aminotransferase levels reflects liver cell *injury* , an increase in immunoglobulin levels reflects an immunologic response to injury, or an elevation in serum bilirubin levels can reflect any of several disturbances of bilirubin metabolism (see Table 382.2). Any single biochemical assay provides limited information, which must be placed in the context of the entire clinical picture. The most cost-efficient approach is to become familiar with the rationale, implications, and limitations of a selected group of tests so that specific questions can be answered. Young infants with cholestatic jaundice should be evaluated promptly to identify patients needing specific medical treatment or surgical intervention.

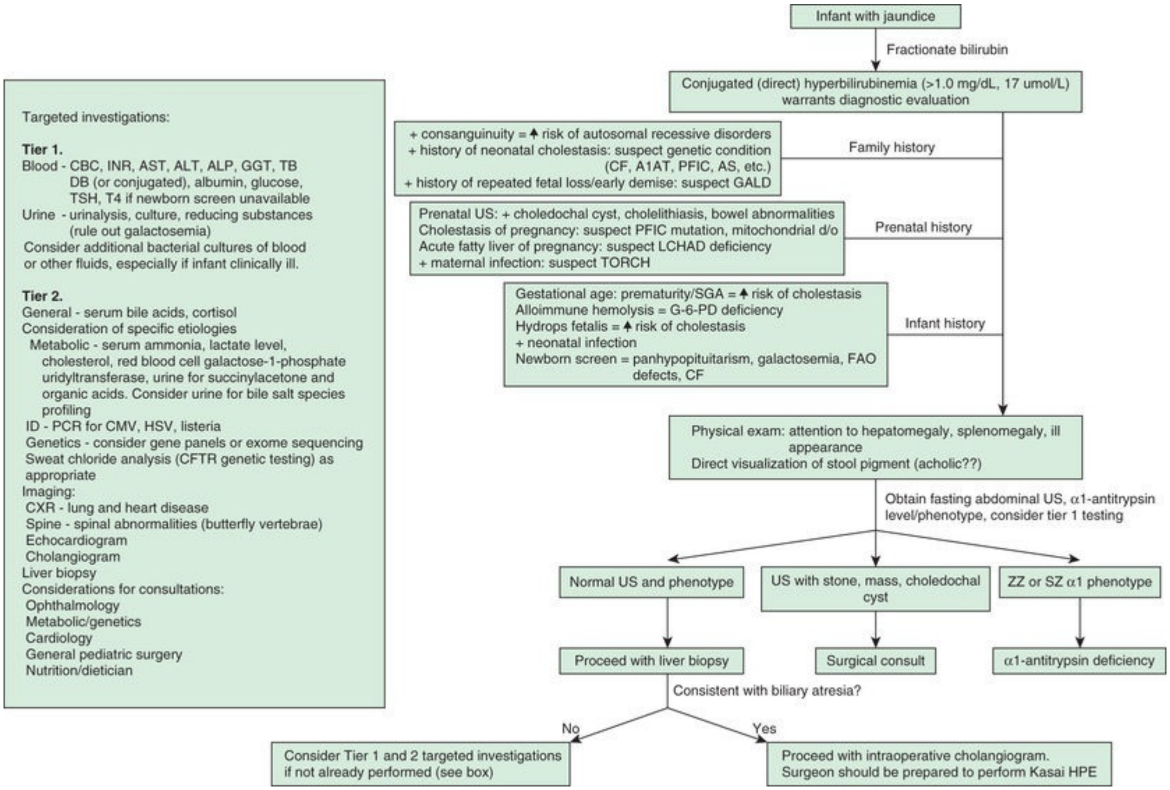
Infant with jaundice
Fractionate bilirubin
Conjugated (direct) hyperbilirubinemia (>1.0 mg/dL, 17 umol/L) warrants diagnostic evaluation
+ consanguinity = ↑ risk of autosomal recessive disorders
+ history of neonatal cholestasis: suspect genetic condition (CF, A1AT, PFIC, AS, etc.)
+ history of repeated fetal loss/early demise: suspect GALD
Family history
Prenatal US: + choledochal cyst, cholelithiasis, bowel abnormalities
Cholestasis of pregnancy: suspect PFIC mutation, mitochondrial d/o
Acute fatty liver of pregnancy: suspect LCHAD deficiency
+ maternal infection: suspect TORCH
Prenatal history
Gestational age: prematurity/SGA = ↑ risk of cholestasis
Alloimmune hemolysis = G-6-PD deficiency
Hydrops fetalis = ↑ risk of cholestasis
+ neonatal infection
Newborn screen = panhypopituitarism, galactosemia, FAO defects, CF
Infant history
Targeted investigations:
Tier 1.
Blood - CBC, INR, AST, ALT, ALP, GGT, TB DB (or conjugated), albumin, glucose, TSH, T4 if newborn screen unavailable
Urine - urinalysis, culture, reducing substances (rule out galactosemia)
Consider additional bacterial cultures of blood or other fluids, especially if infant clinically ill.
Tier 2.
General - serum bile acids, cortisol
Consideration of specific etiologies
Metabolic - serum ammonia, lactate level, cholesterol, red blood cell galactose-1-phosphate uridyltransferase, urine for succinylacetone and organic acids. Consider urine for bile salt species profiling
ID - PCR for CMV, HSV, listeria
Genetics - consider gene panels or exome sequencing
Sweat chloride analysis (CFTR genetic testing) as appropriate
Imaging:
CXR - lung and heart disease
Spine - spinal abnormalities (butterfly vertebrae)
Echocardiogram
Cholangiogram
Liver biopsy
Considerations for consultations:
Ophthalmology
Metabolic/genetics
Cardiology
General pediatric surgery
Nutrition/dietician
Physical exam: attention to hepatomegaly, splenomegaly, ill appearance
Direct visualization of stool pigment (acholic??)
Obtain fasting abdominal US, α1-antitrypsin level/phenotype, consider tier 1 testing
Normal US and phenotype
US with stone, mass, choledochal cyst
ZZ or SZ α1 phenotype
Proceed with liver biopsy
Surgical consult
α1-antitrypsin deficiency
Consistent with biliary atresia?
No
Yes
Consider Tier 1 and 2 targeted investigations if not already performed (see box)
Proceed with intraoperative cholangiogram. Surgeon should be prepared to perform Kasai HPE

FIG. 382.1 Treatment algorithm for a 2-8 wk-old with cholestasis, based on clinical practice guidelines. *A1AT* , alpha one antitrypsin deficiency; *ALP* , alkaline phosphatase; *ALT* , alanine aminotransferase; *AS* , Alagille syndrome; *AST* , aspartate aminotransferase; *CBC* , complete blood count; *CF* , cystic fibrosis; *CFTR* , cystic fibrosis transmembrane receptor; *CMV* , cytomegalovirus; *CXR* , chest x-ray; *DB* , direct bilirubin; *FAO* , fatty acid oxidation; *GALD* , gestational alloimmune liver disease; *GGT* , gamma glutamyl transpeptidase; *HSV* , herpes simplex virus; *INR* , International normalized ratio; *LCHAD* , long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency; *PCR* , polymerase chain reaction; *PFIC* , progressive familial intrahepatic cholestasis; *SGA* , small for gestational age; *TB* , total bilirubin; *TSH* , thyroid stimulating hormone; *US* , ultrasound. (Data from Fawaz R, Baumann U, Ekong U, et al: Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for pediatric gastroenterology, hepatology, and nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, *J Pediatr Gastroenterol Nutr* 64(1):154–168, 2017; and from Feldman AG, Mack CL: Biliary atresia: clinical lessons learned, *J Pediatr Gastroenterol Nutr* 61(2):167–75, 2015.)

For a patient with suspected liver disease, evaluation addresses the following issues in sequence: Is liver disease present? If so, what is its nature? What is its severity? Is specific treatment available? How can we monitor the response to treatment? What is the prognosis?

Biochemical Tests

Laboratory tests commonly used to screen for or to confirm a suspicion of liver disease include measurements of serum aminotransferase (Table 382.4), bilirubin (total and fractionated), alkaline phosphatase (AP) and gamma glutamyl-transpeptidase (GGT) levels, as well as determinations of prothrombin time (PT) or international normalized ratio (INR) and serum albumin level. These tests are complementary, provide an estimation of synthetic and excretory functions, and might suggest the nature of the disturbance (inflammation or cholestasis).

Table 382.4

Causes of Elevated Serum Aminotransferase Levels*

CHRONIC, MILD ELEVATIONS, ALT > AST (<150 U/L OR 5 × NORMAL)
Hepatic Causes
α_1 -Antitrypsin deficiency Autoimmune hepatitis Chronic viral hepatitis (B, C, and D) Hemochromatosis Medications and toxins Steatosis and steatohepatitis Wilson disease
Nonhepatic Causes
Celiac disease Hyperthyroidism
SEVERE, ACUTE ELEVATIONS, ALT > AST (>1,000 U/L OR >20-25 × NORMAL)
Hepatic Causes
Acute bile duct obstruction Acute Budd-Chiari syndrome Acute viral hepatitis Autoimmune hepatitis Drugs and toxins Hepatic artery ligation Ischemic hepatitis Wilson disease
SEVERE, ACUTE ELEVATIONS, AST > ALT (>1,000 U/L OR >20-25 × NORMAL)
Hepatic Cause
Medications or toxins in a patient with underlying alcoholic liver injury
Nonhepatic Cause
Acute rhabdomyolysis
CHRONIC, MILD ELEVATIONS, AST > ALT (<150 U/L, <5 × NORMAL)
Hepatic Causes
Alcohol-related liver injury (AST/ALT > 2 : 1, AST nearly always <300 U/L) Cirrhosis
Nonhepatic Causes

Hypothyroidism Macro-AST Myopathy Strenuous exercise
CHRONIC, MILD ELEVATIONS, ALT > AST (<150 U/L OR 5 × NORMAL)

[*] Virtually any liver disease can cause moderate aminotransferase elevations (5-15 × normal).

The severity of the liver disease may be reflected in clinical signs or biochemical alterations. Clinical signs include encephalopathy, variceal hemorrhage, worsening jaundice, apparent shrinkage of liver mass owing to massive necrosis, or onset of ascites. Biochemical alterations reflective of severity include hypoglycemia, acidosis, hyperammonemia, electrolyte imbalance, continued hyperbilirubinemia, marked hypoalbuminemia, or a prolonged PT or INR that is unresponsive to parenteral administration of vitamin K.

Acute liver cell injury (parenchymal disease) caused by viral hepatitis, drug- or toxin-induced liver disease, shock, hypoxemia, or metabolic disease is best suggested by a marked increase in serum aminotransferase levels. Cholestasis (obstructive disease) involves regurgitation of bile components into serum; the serum levels of total and conjugated bilirubin and serum bile acids are elevated. Elevations in serum AP, 5′ nucleotidase, and GGT levels are also sensitive indicators of obstruction or inflammation of the biliary tract. Fractionation of the total serum bilirubin level into conjugated and unconjugated bilirubin fractions helps to distinguish between elevations caused by processes such as hemolysis and those caused by hepatic dysfunction. A predominant elevation in the conjugated bilirubin level provides a relatively sensitive index of hepatocellular disease or hepatic excretory dysfunction.

Alanine aminotransferase (ALT, serum glutamate pyruvate transaminase) is *liver* specific, whereas aspartate aminotransferase (AST, serum glutamic-oxaloacetic transaminase) is derived from other organs in addition to the liver. The most marked rises of AST and ALT levels can be noted in patients with acute hepatocellular injury; a several thousand–fold elevation can result from acute viral hepatitis, toxic injury (e.g., acetaminophen), hypoxia, or hypoperfusion (see Table 382.4). After blunt abdominal trauma, parallel elevations in aminotransferase levels can provide an early clue to hepatic injury. A differential rise or fall in AST and ALT levels sometimes provides useful information. In acute hepatitis, the rise in ALT may be greater than the rise in AST. In alcohol-induced liver injury, fulminant echovirus infection, and various metabolic diseases, more predominant rises in the AST level are reported. In chronic liver disease or in intrahepatic and extrahepatic biliary obstruction, AST and ALT elevations may be less marked. Elevated serum aminotransferase levels are seen in patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH).

Hepatic synthetic function is reflected in serum albumin and protein levels and in the PT or INR. Examination of serum globulin concentration and of the relative amounts of the globulin fractions may be helpful. Patients with autoimmune hepatitis often have high γ-globulin levels and increased titers of anti–smooth muscle, antinuclear, and anti–liver-kidney-microsome antibodies. Antimitochondrial antibodies may also be found in patients with autoimmune hepatitis. A resurgence in α-fetoprotein levels can suggest hepatoma, hepatoblastoma, or hereditary tyrosinemia. Hypoalbuminemia caused by depressed synthesis can complicate severe liver disease and serve as a prognostic factor. Deficiencies of factor V and of the vitamin K–dependent factors (II, VII, IX, and X) can occur in patients with severe liver disease or fulminant hepatic failure. If the PT or INR is prolonged as a result of intestinal malabsorption of vitamin K (resulting from cholestasis) or decreased nutritional intake of vitamin K, parenteral administration of vitamin K should correct the coagulopathy, leading to normalization within 12-24 hr. *Unresponsiveness to parenteral vitamin K suggests severe hepatic disease* . Persistently low levels of factor VII are evidence of a poor prognosis in patients with fulminant liver disease.

Interpretation of results of biochemical tests of hepatic structure and function must be made in the context of age-related changes. The activity of AP varies considerably with age. Normal growing children have significant elevations of serum AP activity originating from influx into serum of the isoenzyme that originates in bone, particularly in rapidly growing adolescents. An isolated increase in AP does not indicate hepatic or biliary disease if other liver tests are normal. Other enzymes such as 5′ nucleotidase and GGT are increased in cholestatic conditions and may be more specific for hepatobiliary disease. 5′ nucleotidase is not found in bone. GGT exhibits high enzyme activity in early life that declines rapidly with age. Cholesterol concentrations increase throughout life but may be markedly elevated in patients with intra- or extrahepatic cholestasis and decreased in severe acute liver disease such as hepatitis.

Interpretation of serum ammonia values must be carried out with caution because of variability in their physiologic determinants and the inherent difficulty in laboratory measurement.

Liver Biopsy

Liver biopsy combined with clinical data can suggest a cause for hepatocellular injury or cholestatic disease in most cases. Specimens of liver tissue can be used to determine a precise histologic diagnosis in patients with neonatal cholestasis, chronic hepatitis, nonalcoholic fatty liver disease or NASH, metabolic liver disease, intrahepatic cholestasis, congenital hepatic fibrosis, or undefined portal hypertension. The sample may be subjected to enzyme analysis to detect inborn errors of metabolism and to analysis of stored material such as iron, copper, or specific metabolites. Liver biopsies can monitor responses to therapy or detect complications of treatment with potentially hepatotoxic agents, such as aspirin, antiinfectives (minocycline, ketoconazole, isoniazid), antimetabolites, antineoplastics, or anticonvulsant agents.

In infants and children, needle biopsy of the liver is easily accomplished percutaneously. The amount of tissue obtained, even in small infants, is usually sufficient for histologic interpretation and for biochemical analyses, if the latter are deemed necessary. Percutaneous liver biopsy can be performed safely in infants as young as 1 wk of age. Contraindications to the percutaneous approach include prolonged PT or INR; thrombocytopenia; suspicion of a vascular, cystic, or infectious lesion in the path of the needle; and severe ascites. If administration of fresh-frozen plasma or of platelet transfusions fails to correct a prolonged PT, INR, or thrombocytopenia, a tissue specimen can be obtained via alternative techniques. Considerations include either the open laparotomy (wedge) approach by a general surgeon or the transjugular approach under ultrasound and fluoroscopic guidance by an experienced pediatric interventional radiologist in an appropriately equipped fluoroscopy suite. The risk of development of a complication such as hemorrhage, hematoma, creation of an arteriovenous fistula, pneumothorax, or bile peritonitis is small.

Hepatic Imaging Procedures

Various techniques help define the size, shape, and architecture of the liver and the anatomy of the intrahepatic and extrahepatic biliary trees. Although imaging might not provide a precise histologic and biochemical diagnosis, specific questions can be answered, such as whether hepatomegaly is related to accumulation of fat or glycogen or is caused by a tumor or cyst. These studies can direct further evaluation such as percutaneous biopsy and make possible prompt referral of patients with biliary obstruction to a surgeon. Choice of imaging procedure should be part of a carefully formulated diagnostic approach, with avoidance of redundant demonstrations by several techniques.

A *plain x-ray study* can suggest hepatomegaly, but a carefully performed physical examination gives a more reliable assessment of liver size. The liver might appear less dense than normal in patients with fatty infiltration or denser with deposition of heavy metals such as iron. A hepatic or biliary tract mass can displace an air-filled loop of bowel. Calcifications may be evident in the liver (parasitic or neoplastic disease), in the vasculature (portal vein thrombosis), or in the gallbladder or biliary tree (gallstones). Collections of gas may be seen within the liver (abscess), biliary tract, or portal circulation (necrotizing enterocolitis).

Ultrasound provides information about the size, composition, and blood flow to the liver. Increased echogenicity is observed with fatty infiltration; mass lesions as small as 1-2 cm may be shown. Ultrasound has replaced cholangiography in detecting stones in the gallbladder or biliary tree. Even in neonates, ultrasound can accurately assess gallbladder size, detect dilation of the biliary tract, and define a choledochal cyst. In infants with biliary atresia, ultrasound findings might include small or absent gallbladder; nonvisualization of the common duct; and presence of the triangular cord sign, a triangular or tubular-shaped echogenic density in the bifurcation of the portal vein, representing fibrous remnants at the porta hepatis. Hyperechogenic hepatic parenchyma can be seen with metabolic disease (glycogen storage disease) or fatty liver (obesity, malnutrition, parenteral alimentation, corticosteroids). In patients with portal hypertension, Doppler ultrasound can evaluate patency of the portal vein, demonstrate collateral circulation, and assess size of spleen and amount of ascites. Relatively small amounts of *ascitic fluid* can also be detected. The use of Doppler ultrasound has been helpful in determining vascular patency after liver transplantation. In patients with liver lesions, newer intravenous agents consisting of insoluble gas bubbles with a lipoprotein shell have enabled contrast-enhanced ultrasonographic lesion characterization without the associated risks often accompanied by more traditional imaging modalities such as CT scan (radiation, contrast-induced renal injury) and *magnetic resonance imaging* (MRI; sedation).

CT scanning provides information similar to that obtained by ultrasound but is less suitable for use in patients younger than 2 yr of age because of the small size of structures, the paucity of intraabdominal fat for contrast, and the need for heavy sedation or general anesthesia. CT scan may be more accurate than ultrasound in detecting focal lesions such as tumors, cysts, and abscesses. When enhanced by contrast medium, CT scanning can reveal a neoplastic mass density only slightly different from that of a normal liver. When a hepatic tumor is suspected, CT scanning is currently considered the best method to define anatomic extent, solid or cystic nature, and vascularity. CT scanning can also reveal subtle differences in density of liver parenchyma, the average liver attenuation coefficient being reduced with fatty infiltration.

MRI is a useful alternative that limits radiation exposure. Magnetic resonance cholangiography can be of value in differentiating biliary tract lesions. MRI with Eovist (gadoxetate disodium) can assist in the detection and characterization of known or suspected focal liver lesions. In differentiating obstructive from nonobstructive cholestasis, CT scanning or MRI identifies the precise level of obstruction more often than ultrasound. Either CT scanning or ultrasound may be used to guide percutaneously placed fine needles for biopsies, aspiration of specific lesions, or cholangiography.

Elastography is a novel noninvasive method to assess for liver *stiffness* , a measure of the development of hepatic fibrosis in patients with liver disease. Both ultrasound and MR methods have been developed. These noninvasive techniques allow for monitoring fibrosis progression and development of cirrhosis, improved characterization of hepatic tumors, and prognostic stratification of diseases such as nonalcoholic fatty liver disease and NASH.

Radionuclide scanning relies on selective uptake of a radiopharmaceutical agent. Commonly used agents include technetium-99m–labeled sulfur colloid, which undergoes phagocytosis by Kupffer cells; ^{99m} Tc-iminodiacetic acid agents, which are taken up by hepatocytes and excreted into bile in a fashion similar to bilirubin; and gallium-67, which is concentrated in inflammatory and neoplastic cells. The anatomic resolution possible with hepatic scintiscans is generally less than that obtained with CT scanning, MRI, or ultrasound.

The ^{99m} Tc-sulfur colloid scan can detect focal lesions (tumors, cysts, abscesses) >2-3 cm in diameter. This modality can help to evaluate patients with possible cirrhosis and with patchy hepatic uptake and a shift of colloid uptake from liver to bone marrow.

Cholangiography , direct visualization of the intrahepatic and extrahepatic biliary tree after injection of opaque material, may be required in some patients to evaluate the cause, location, or extent of biliary obstruction. Percutaneous transhepatic cholangiography with a fine needle is the technique of choice in infants and young children. The likelihood of opacifying the biliary tract is excellent in patients in whom CT scanning, MRI, or ultrasound demonstrates dilated ducts. Percutaneous transhepatic cholangiography has been used to outline the biliary ductal system.

Endoscopic retrograde cholangiopancreatography is an alternative method of examining the bile ducts in older children. The papilla of Vater is cannulated under direct vision through a fiberoptic endoscope, and contrast material is injected into the biliary and pancreatic ducts to outline the anatomy. The advantage of endoscopic retrograde cholangiopancreatography is that it allows therapeutic interventions of the extrahepatic biliary tree (stone extraction, stent placement).

Selective angiography of the celiac, superior mesenteric, or hepatic artery can be used to visualize the hepatic or portal circulation. Both arterial and venous circulatory systems of the liver can be examined. Angiography is often required to define the blood supply of tumors before surgery and is useful in the study of patients with known or presumed portal hypertension. The patency of the portal system, the extent of collateral circulation, and the caliber of vessels under consideration for a shunting procedure can be evaluated. MRI can provide similar information.

Diagnostic Approach to Infants With Jaundice

Well-appearing infants can have cholestatic jaundice. Biliary atresia and neonatal hepatitis are the most common causes of cholestasis in early infancy. Biliary atresia portends a poor prognosis unless it is identified early. The best outcome for this disorder is with early surgical reconstruction (45-60 days of age). History, physical examination, and the detection of a conjugated hyperbilirubinemia via examination of total and direct bilirubin are the first steps in evaluating the jaundiced infant (see Fig. 382.1). Consultation with a pediatric gastroenterologist should be sought early in the course of the evaluation.

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CHAPTER 383

Cholestasis

383.1

Neonatal Cholestasis

H. Hesham Abdel-Kader Hassan, William F. Balistreri

Neonatal cholestasis is defined biochemically as prolonged elevation of the serum levels of conjugated bilirubin beyond the first 14 days of life. Jaundice that appears after 2 wk of age, continues to progress, or does not resolve by this age should be evaluated and a conjugated bilirubin level determined.

Cholestasis in a newborn can be caused by infectious, genetic, metabolic, or undefined abnormalities giving rise to *mechanical* obstruction of bile flow or to *functional impairment* of hepatic excretory function and bile secretion (see Table 383.1). Mechanical lesions include stricture or obstruction of the common bile duct; biliary atresia is the prototypic obstructive abnormality. Functional impairment of bile secretion can result from congenital defects or damage to liver cells or to the biliary secretory apparatus.

Neonatal cholestasis can be divided into extrahepatic and intrahepatic disease (Fig. 383.1). The clinical features of any form of cholestasis are similar. In an affected neonate, the diagnosis of certain entities, such as galactosemia, cystic fibrosis, sepsis, or hypothyroidism, is relatively simple and a part of most neonatal screening programs. In most cases, the cause of cholestasis is more obscure. Differentiation among biliary atresia and idiopathic neonatal hepatitis is particularly difficult.

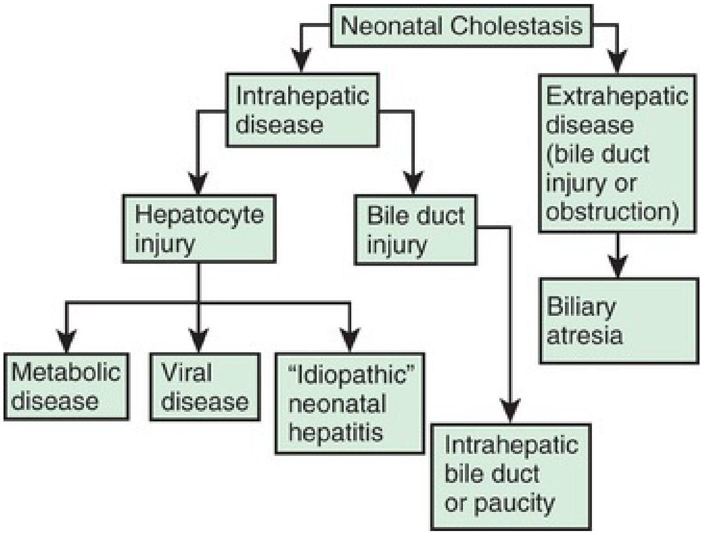
Neonatal Cholestasis
Intrahepatic disease
Extrahepatic disease (bile duct injury or obstruction)
Hepatocyte injury
Bile duct injury
Biliary atresia
Metabolic disease
Viral disease
"Idiopathic" neonatal hepatitis
Intrahepatic bile duct or paucity

FIG. 383.1 **Neonatal cholestasis. Conceptual approach to the group of diseases presenting as cholestasis in the neonate. There are areas of overlap. Patients with biliary atresia might have some degree of intrahepatic injury. Patients with "idiopathic" neonatal hepatitis might, in the future, be determined to have a primary metabolic or viral disease.**

Mechanisms

Metabolic liver disease caused by inborn errors of bile acid synthesis or transport is associated with accumulation of atypical toxic bile acids and failure to produce normal choleretic and trophic bile acids. The clinical and histologic manifestations are nonspecific and are similar to those noted in other forms of neonatal hepatobiliary injury. Autoimmune mechanisms may also be responsible for some of the enigmatic forms of neonatal liver injury.

Some of the histologic manifestations of hepatic injury in early life are not seen in older patients. Giant cell transformation of hepatocytes occurs commonly in infants with cholestasis and can occur in any form of neonatal liver injury. It is more common and more severe in intrahepatic forms of cholestasis. The clinical and histologic findings of patients with neonatal hepatitis and those with biliary atresia are somewhat similar, but there are distinguishing features. The basic process common to both is an undefined initiating insult causing inflammation of the liver cells or of the cells within the biliary tract. If the bile duct epithelium is the predominant site of disease, cholangitis can result and lead to progressive sclerosis and narrowing of the biliary tree, the ultimate state being complete obliteration *(biliary atresia)* . Injury to liver cells can present the clinical and histologic picture of "neonatal hepatitis." This concept does not account for the precise mechanism, but it offers an explanation for well-documented cases of unexpected postnatal evolution of the disease processes; infants initially considered to have neonatal hepatitis, with a patent biliary system shown on cholangiography, can later manifest biliary atresia.

Functional abnormalities in the generation of bile flow can also cause neonatal cholestasis. Bile flow is directly dependent on effective hepatic bile acid excretion by the hepatocytes. During the phase of relatively inefficient bile acid transport and metabolism by the liver cell in early life, minor degrees of hepatic injury can further decrease bile flow and lead to production of atypical and potentially toxic bile acids. Selective impairment of a single step in the series of events involved in hepatic excretion produces the full expression of a cholestatic syndrome. Specific defects in bile acid synthesis are found in infants with various forms of intrahepatic cholestasis (Table 383.1). Severe forms of familial cholestasis are associated with neonatal hemochromatosis, an alloimmune-mediated gestational (maternal antibodies against fetal hepatocytes) disease responsive to maternal intravenous immunoglobulin. Sepsis is known to cause cholestasis, presumably mediated by an endotoxin produced by *Escherichia coli*.

Table 383.1

Proposed Subtypes of Intrahepatic Cholestasis

A. Disorders of membrane transport and secretion
  1. Disorders of canalicular secretion
    a. Bile acid transport: BSEP deficiency
      i. Persistent, progressive (PFIC type 2)
      ii. Recurrent, benign (BRIC type 2)
    b. Phospholipid transport: MDR3 deficiency (PFIC type 3)
    c. Ion transport: cystic fibrosis (CFTR)
    d. Tight junction defect (TJP2 deficiency)
  2. Complex or multiorgan disorders
    a. FIC1 deficiency
      i. Persistent, progressive (PFIC type 1, Byler disease)
      ii. Recurrent, benign (BRIC type 1)
    b. Neonatal sclerosing cholangitis *(CLDN1)*
    c. Arthrogryposis-renal dysfunction-cholestasis syndrome *(VPS33B)*
B. Disorders of bile acid biosynthesis, conjugation and regulation
  1. Δ^4 -3-Oxosteroid-5β- reductase deficiency
  2. 3β- hydroxy-5-C27-steroid dehydrogenase/isomerase deficiency
  3. Oxysterol 7α- hydroxylase deficiency
  4. Bile acid-CoA Ligase deficiency
  5. BAAT deficiency (familial hypercholanemia)
  6. Farnesoid X receptor (FXR) deficiency.
C. Disorders of embryogenesis
  1. Alagille syndrome (Jagged1 defect, syndromic bile duct paucity)

2. Ductal plate malformation (ARPKD, ADPLD, Caroli disease)
D. Unclassified (idiopathic “neonatal hepatitis”): mechanism unknown

Note: FIC1 deficiency, BSEP deficiency, and some of the disorders of bile acid biosynthesis are characterized clinically by low levels of serum GGT despite the presence of cholestasis. In all other disorders listed, the serum GGT level is elevated.

ADPLD, autosomal dominant polycystic liver disease (cysts in liver only); ARPKD, autosomal recessive polycystic kidney disease (cysts in liver and kidney); BAAT, bile acid transporter; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump in; GGT, γ-glutamyl transpeptidase; PFIC, progressive familial intrahepatic cholestasis.

From Balistreri WF, Bezerra JA, Jansen P, et al: Intrahepatic cholestasis: summary of an American Association for the study of liver diseases single-topic conference, *Hepatology* 42(1):222–235, 2005.

Evaluation

Identification of cholestasis warrants a prompt effort to accurately diagnose the cause (Table 383.2). Although cholestasis in the neonate may be the initial manifestation of numerous and potentially serious disorders, the clinical manifestations are usually similar and provide few clues about the etiology. Affected infants have icterus, dark urine, light or acholic stools, and hepatomegaly, all resulting from decreased bile flow as a result of either hepatocyte injury or bile duct obstruction. Hepatic synthetic dysfunction can lead to hypoprothrombinemia and bleeding. Administration of vitamin K should be included in the initial treatment of cholestatic infants to prevent hemorrhage (intracranial).

Table 383.2

Value of Specific Tests in the Evaluation of Patients With Suspected Neonatal Cholestasis

TEST	RATIONALE
Serum bilirubin fractionation (i.e., assessment of the serum level of conjugated bilirubin)	Indicates cholestasis
Assessment of stool color (does the baby have pigmented or acholic stools?)	Indicates bile flow into intestine
Urine and serum bile acid measurement	Confirms cholestasis; low level indicates inborn error of bile acid biosynthesis
Hepatic synthetic function (albumin, coagulation profile)	Indicates severity of hepatic dysfunction
α_1 -Antitrypsin phenotype	Suggests (or excludes) protease inhibitor ZZ phenotype
Thyroxine and thyroid-stimulating hormone	Suggests (or excludes) endocrinopathy
Lysosomal acid lipase enzyme activity	Suggests (or excludes) lysosomal acid lipase deficiency

Sweat chloride and mutation analysis	Suggests (or excludes) cystic fibrosis
Urine and serum amino acids and urine reducing substances	Suggests (or excludes) metabolic liver disease
Ultrasonography	Suggests (or excludes) choledochal cyst; might detect the triangular cord sign, suggesting biliary atresia
Liver biopsy	Distinguishes biliary atresia; suggests alternative diagnosis

In contrast to unconjugated hyperbilirubinemia, which can be physiologic, cholestasis (conjugated bilirubin elevation of any degree) in the neonate is **always pathologic** and prompt differentiation of the cause is imperative. The top priority is to recognize conditions that cause cholestasis and for which specific therapy is available to prevent further damage and avoid long-term complications such as sepsis, an endocrinopathy (hypothyroidism, panhypopituitarism), nutritional hepatotoxicity caused by a specific metabolic illness (galactosemia), or other metabolic diseases (tyrosinemia).

Another potential treatable metabolic disease, lysosomal acid lipase deficiency (LAL-D), is a rare autosomal recessive lysosomal storage disease which results in a mutation in the lysosomal acid lipase *(LIPA)* gene. The mutation creates a decline in the LAL activity, resulting in accumulation of cholesteryl esters and, to a lesser degree, triglycerides in multiple organs, including the liver, spleen, adrenal glands, lymph nodes, intestinal mucosa, vascular endothelium, and skeletal muscle. Clinically, the disease can present in 2 major phenotypes: infantile-onset Wolman disease (WD) and later-onset cholesterol ester storage disease (CESD). LAL-D usually presents in infants with an acute-severe course progressing to liver failure. Sebelipase Alfa (recombinant human LAL enzyme) is approved for the treatment of patients with LAL-D.

Hepatobiliary disease can be the initial manifestation of homozygous α_1-antitrypsin deficiency or of cystic fibrosis. Neonatal liver disease can also be associated with congenital syphilis and specific viral infections, notably echovirus and herpes viruses including cytomegalovirus. These account for a small percentage of cases of neonatal hepatitis syndrome. The hepatitis viruses (A, B, C) rarely cause neonatal cholestasis.

Mitochondrial disorders may present with acute neonatal hepatic failure, or cholestasis; prominent among these disorders are respiratory chain defects and mitochondrial DNA depletion syndromes (Table 383.3).

Table 383.3

Phenotypic Classification of Primary Mitochondrial Hepatopathies

RC (electron transport) defects (OXPHOS)
- Neonatal liver failure
  - Complex I deficiency
  - Complex IV deficiency (*SCO1* mutations)
  - Complex III deficiency (*BCS1L* mutations)
  - Co-enzyme Q deficiency
  - Multiple complex deficiencies (transfer and elongation factor mutations)
  - mtDNA depletion syndrome (*DUGOK* , *MPV17* , *POLG* , *SUCLG1* , *C10orf2/Twinkle* mutations)
- Later-onset liver dysfunction or failure
  - Alpers-Huttenlocher disease (*POLG* mutations)
  - Pearson's marrow pancreas syndrome (mtDNA deletion)
  - Mitochondrial neurogastrointestinal encephalopathy (*TYMP* mutations)
  - NNH (*MPV17* mutations)

Fatty acid oxidation defects
- Long-chain 3 hydroxyacyl-coenzyme A dehydrogenase
- Carnitine palmitoyltransferase I and II deficiencies
- Carnitine-acylcarnitinetranslocase deficiency

Urea cycle enzyme deficiencies
Electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase deficiencies
Phosphoenol pyruvate carboxykinase (mitochondrial) deficiency; nonketotic hyperglycemia
Citrin deficiency; neonatal intrahepatic cholestasis caused by citrin deficiency (*SLC25A13* mutations)

NN, Navajo neurohepatopathy; OXPHOS, oxidative phosphorylation; RC, respiratory chain.

From Lee WS, Sokol RJ: Mitochondrial hepatopathies: advances in genetics, therapeutic approaches, and outcomes, *J Pediatr* 163[4]:942–948, 2013, Table 1, p. 943.

The final and critical step in evaluating neonates with cholestasis is to differentiate extrahepatic biliary atresia from neonatal hepatitis.

Intrahepatic Cholestasis

Neonatal Hepatitis

The term *neonatal hepatitis* implies intrahepatic cholestasis (see Fig. 383.1), which has various forms (see Tables 383.1 and 383.4).

Table 383.4

Molecular Defects Causing Liver Disease

GENE	PROTEIN	FUNCTION, SUBSTRATE	DISORDER
ATP8B1	FIC1	P-type ATPase; aminophospholipid translocase that flips phosphatidylserine and phosphatidylethanolamine from the outer to the inner layer of the canalicular membrane	PFIC 1 (Byler disease), BRIC 1, GFC
ABCB11	BSEP	Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a pump transporting bile acids through the canalicular domain	PFIC 2, BRIC 2
ABCB4	MDR3	Canalicular protein with ATP-binding cassette (ABC family of	PFIC 3, ICP,

		proteins); works as a phospholipid flippase in canalicular membrane	cholelithiasis
AKR1D1	5β-Reductase	Δ^4 -3-Oxosteroid 5β-reductase gene; regulates bile acid synthesis	BAS: neonatal cholestasis with giant cell hepatitis
HSD3B7	C27-3β-HSD	3β-Hydroxy-5-C27-steroid oxido-reductase (C27-3β-HSD) gene; regulates bile acid synthesis	BAS: chronic intrahepatic cholestasis
CYP7BI	CYP7BI	Oxysterol 7α-hydroxylase; regulates the acidic pathway of bile acid synthesis	BAS: neonatal cholestasis with giant cell hepatitis
JAG1	JAG1	Transmembrane, cell-surface proteins that interact with Notch receptors to regulate cell fate during embryogenesis	Alagille syndrome
TJP2	Tight junction protein	Belongs to the family of membrane-associated guanylate kinase homologs that are involved in the organization of epithelial and endothelial intercellular junction; regulates paracellular permeability	Intrahepatic cholestasis
NR1H4	Nuclear hormone receptor	Farnesoid X receptor (FXR), a nuclear hormone receptor that regulates bile acid metabolism	Intrahepatic cholestasis
BAAT	BAAT	Enzyme that transfers the bile acid moiety from the acyl coenzyme A thioester to either glycine or taurine	FHC
EPHX1	Epoxide hydrolase	Microsomal epoxide hydrolase regulates the activation and detoxification of exogenous chemicals	FHC
ABCC2	MRP2	Canalicular protein with ATP-binding cassette (ABC family of proteins); regulates canalicular transport of GSH conjugates and arsenic	Dubin-Johnson syndrome
ATP7B	ATP7B	P-type ATPase; function as copper export pump	Wilson disease
CLDN1	Claudin 1	Tight junction protein	NSC
CIRH1A	Cirhin	Cell signaling?	NAICC
CFTR	CFTR	Chloride channel with ATP-binding cassette (ABC family of proteins); regulates chloride transport	Cystic fibrosis
PKHD1	Fibrocystin	Protein involved in ciliary function and tubulogenesis	ARPKD
PRKCSH	Hepatocystin	Assembles with glucosidase II α subunit in endoplasmic reticulum	ADPLD
VPS33B	Vascular protein sorting 33	Regulates fusion of proteins to cellular membrane	ARC

* Low GGT (PFIC types 1 and 2, BRIC types 1 and 2, ARC).

ADPLD, autosomal dominant polycystic liver disease; ARC, arthrogryposis–renal dysfunction–cholestasis syndrome* ; ARPKD, autosomal recessive polycystic kidney disease; ATP, adenosine triphosphate; BAAT, bile acid transporter; BAS, bile acid synthetic defect; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane conductance regulator; FHC, familial hypercholanemia; GFC, Greenland familial cholestasis; GSH, glutathione; ICP, intrahepatic cholestasis of pregnancy; NAICC, North American Indian childhood cirrhosis; NSC, neonatal sclerosing cholangitis with ichthyosis, leukocyte vacuoles, and alopecia; PFIC, progressive familial intrahepatic cholestasis.*

From Balistreri WF, Bezerra JA, Jansen P, et al: Intrahepatic cholestasis: summary of an American Association for the study of liver diseases single-topic conference, *Hepatology* 42(1):222–235, 2005.

Idiopathic neonatal hepatitis, which can occur in either a sporadic or familial form, is a disease of unknown cause. Patients with the sporadic form presumably have a specific yet undefined metabolic or viral disease. Familial forms, on the other hand, presumably reflect a genetic or metabolic aberration; in the past, patients with α-1 antitrypsin deficiency were included in this category.

Aagenaes syndrome is a form of idiopathic familial intrahepatic cholestasis associated with lymphedema of the lower extremities. The relationship between liver disease and lymphedema is not understood and may be attributable to decreased hepatic lymph flow or hepatic lymphatic hypoplasia. Affected patients usually present with episodic cholestasis with elevation of serum aminotransferase, alkaline phosphatase, and bile acid levels. Between episodes, the patients are usually asymptomatic and biochemical indices improve. Compared to other types of hereditary neonatal cholestasis, patients with Aagenaes syndrome have a relatively good prognosis. The locus for Aagenaes syndrome is mapped to a 6.6 cM interval on chromosome 15q.

Zellweger (cerebrohepatorenal) syndrome is a rare autosomal recessive genetic disorder marked by progressive degeneration of the liver and kidneys. The incidence is estimated to be 1 in 100,000 births; the disease is usually fatal by 6-12 mo of age. Affected infants have severe, generalized hypotonia and markedly impaired neurologic function with psychomotor retardation. Patients have an abnormal head shape and unusual facies, hepatomegaly, renal cortical cysts, stippled calcifications of the patellas and greater trochanter, and ocular abnormalities. Hepatic cells on ultrastructural examination show an absence of peroxisomes. Prenatal diagnosis can be achieved through assays of peroxisomal enzymes activity (dihydroacetone-phosphate acyltransferase), peroxisomal metabolites, or molecular screening techniques. MRI performed in the third trimester can allow analysis of cerebral gyration and myelination, facilitating the prenatal diagnosis of Zellweger syndrome.

Neonatal iron storage disease (neonatal hemochromatosis, gestational alloimmune liver disease) is a rapidly progressive disease characterized by increased iron deposition in the liver, heart, and endocrine organs without increased iron stores in the reticuloendothelial system. Patients have multiorgan failure and shortened survival. Familial cases are reported, and repeated affected neonates in the same family are common. This is an alloimmune disorder with maternal antibodies directed against the fetal liver. Liver injury results in decreased hepatic hepcidin expression and thus dysregulation of placental iron flux. Neonatal hemochromatosis (or fetal loss) seems to be a **gestational alloimmune disease** , and reoccurrence of severe neonatal hemochromatosis in at-risk pregnancies may be reduced by maternal treatment with weekly high-dose intravenous immunoglobulin (1 g/kg) beginning gestational age 18 wk.

Laboratory findings include hypoglycemia, hyperbilirubinemia, hypoalbuminemia, elevated ferritin, and profound hypoprothrombinemia. Serum aminotransferase levels may be high initially but normalize with the progression of the disease. The diagnosis is usually confirmed by buccal mucosal biopsy or MRI demonstrating extrahepatic siderosis. The prognosis is poor; however, liver transplantation can be curative.

Although liver transplantation for infants with neonatal hemochromatosis has a high rate of graft loss and death, outcomes are equivalent to the same age-matched recipients with acute liver failure due to other causes. Immune therapy with exchange transfusion and intravenous immunoglobulin has been reported to improve the outcome and reduce the need for liver transplantation in patients with neonatal hemochromatosis. The differential diagnosis includes familial hemophagocytic lymphohistiocytosis.

Disorders of Transport, Secretion, Conjugation, and Biosynthesis of Bile Acids

Progressive familial intrahepatic cholestasis type 1 (PFIC 1) or FIC 1 disease (formerly known as **Byler disease**) is a severe form of intrahepatic cholestasis. The disease was initially described in the Amish kindred of Jacob Byler. Affected patients present with steatorrhea, pruritus, vitamin D-deficient rickets, gradually developing cirrhosis, and low γ-glutamyl transpeptidase (GGT) levels. **PFIC 1** (FIC-1 deficiency) has been mapped to chromosome 18ql2 and results from defect in the gene for FIC-1 (ATP8Bl; see Tables 383.4 and 383.5). FIC-1 is a P-type adenosine triphosphatase that functions as aminophospholipid flippase, facilitating the transfer of phosphatidyl serine and phosphatidyl ethanolamine from the outer to inner hemileaflet of the cellular membrane. FIC-1 might also play a role in intestinal bile acid absorption, as suggested by the high level of expression in the intestine. Defective FIC-1 might also result in another form of intrahepatic cholestasis: **benign recurrent intrahepatic cholestasis (BRIC) type I** . The disease is characterized by recurrent bouts of cholestasis, jaundice, and severe pruritus. The episodes vary from few episodes per year to 1 episode per decade but can profoundly affect the quality of life. Nonsense, frame shift, and deletional mutations cause PFIC type I; missense and split-type mutations result in BRIC type I. Typically, patients with BRIC type I have normal serum cholesterol and GGT levels.

Table 383.5

Progressive Familial Intrahepatic Cholestasis

	PFIC1	PFIC2	PFIC3
Transmission	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosome	18q21-22	2q24	7q21
Gene	*ATP8B1/F1C1*	*ABCB11/BSEP*	*ABCB4/MDR3*
Protein	FIC1	BSEP	MDR3
Location	Hepatocyte, colon, intestine, pancreas; on apical membranes	Hepatocyte canalicular membrane	Hepatocyte canalicular membrane
Function	ATP-dependent aminophospholipid flippase; unknown effects on intracellular signaling	ATP-dependent bile acid transport	ATP-dependent phosphatidylcholine translocation
Phenotype	Progressive cholestasis, diarrhea, steatorrhea, growth failure, severe pruritus	Rapidly progressive cholestatic giant cell hepatitis, growth failure, pruritus	Later-onset cholestasis, portal hypertension, minimal pruritus, intraductal and gallbladder lithiasis
Histology	Initial bland cholestatic; coarse, granular canalicular bile on EM	Neonatal giant cell hepatitis, amorphous canalicular bile on EM	Proliferation of bile ductules, periportal fibrosis, eventually biliary cirrhosis
Biochemical features	Normal serum γGT; high serum, low biliary bile acid concentrations	Normal serum γGT; high serum, low biliary bile acid concentrations	Elevated serum γGT; low to absent biliary PC; absent serum LPX; normal biliary bile acid concentrations
Treatment	Biliary diversion, ileal exclusion, liver transplantation, but post-OLT diarrhea, steatorrhea, fatty liver	Biliary diversion, liver transplantation	UDCA if residual PC secretion; liver transplantation

ATP, adenosine triphosphate; BCEP, B-cell epitope peptide; BSEP, bile salt export pump; EM, electron microscopy; γGT, γ-glutamyl transpeptidase; LPX, lipoprotein X; OLT, orthotopic liver transplantation; PC, phosphatidylcholine; PFIC, progressive familial intrahepatic cholestasis; UDCA, ursodeoxycholic acid.

From Suchy FJ, Sokol RJ, Balistreri WF, editors: *Liver disease in children* , ed 4, New York, 2014, Cambridge University Press.

PFIC type 2 (BSEP deficiency) is mapped to chromosome 2q24 and is similar to PFIC 1. The disease results from defects in the canalicular adenosine triphosphate -dependent bile acid transporter BSEP (ABCB11). The progressive liver disease results from accumulation of bile acids secondary to reduction in canalicular bile acid secretion. Mutation in ABC11 is also described in another disorder, BRIC type 2, characterized by recurrent bouts of cholestasis.

In contrast to PFIC I and PFIC 2, patients with **PFIC type 3** *(MDR3 disease)* have *high* levels of GGT. The disease results from defects in a canalicular phospholipids flippase, MDR3 *(ABCB4),* which results in deficient translocation of phosphatidylcholine across the canalicular membrane. Mothers who are heterozygous for this gene can develop intrahepatic cholestasis during pregnancy.

Familial hypercholanemia is characterized by an elevated serum bile acid concentration, pruritus, failure to thrive, and coagulopathy. Familial hypercholanemia is a complex genetic trait associated with mutation of bile acid coenzyme A (CoA), amino acid N-acyltransferase (encoded by bile acid transporter *[BAAT]*) as well as mutations in tight junction protein 2 (encoded by *TJP 2,* also known as *ZO-2*). Mutation of BAAT, which is a bile acid-conjugating enzyme, abrogates the enzyme activity. Patients who are homozygous for this mutation have only unconjugated bile acids in their bile. Mutation of both BAAT and TJP 2 can disrupt bile acid transport and circulation. Patients with familial hypercholanemia usually respond to the administration of ursodeoxycholic acid.

Defective bile acid biosynthesis is postulated to be an initiating or perpetuating factor in neonatal cholestatic disorders; the hypothesis is that inborn errors in bile acid biosynthesis lead to absence of normal trophic or choleretic primary bile acids and accumulation of atypical (hepatotoxic) metabolites. Inborn errors of bile acid biosynthesis cause acute and chronic liver disease; early recognition allows institution of targeted bile acid replacement, which reverses the hepatic injury. Several specific defects have been described:

- **Deficiency of Δ^4 -3-oxosteroid-5β reductase** , the fourth step in the pathway of cholesterol degradation to the primary bile acids, manifests with significant cholestasis and liver failure developing shortly after birth, with coagulopathy and metabolic liver injury resembling tyrosinemia. Hepatic histology is characterized by lobular disarray with giant cells, pseudoacinar transformation, and canalicular bile stasis. Mass spectrometry will display increased urinary bile acid excretion and the predominance of oxo-hydroxy and oxo-dihydroxy cholenoic acids. The diagnosis can be established by screening for mutations in *SRD5B1 (AKR1D1)* , the gene encoding Δ4-3-oxosteroid 5β-reductase. Treatment with cholic acid and ursodeoxycholic acid is associated with normalization of biochemical, histologic, and clinical features.

- **Deficiency of 3β-hydroxy- Δ^5 -C^{27} -steroid oxidoreductase (3β-HSD),** the second step in bile acid biosynthesis from cholesterol, causes PFIC. Affected patients usually have jaundice with increased aminotransferase levels and hepatomegaly; GGT levels and serum cholylglycine levels are *normal* . The histology is variable, ranging from giant cell hepatitis to chronic hepatitis. The diagnosis, suggested by mass spectrometry detection of C^{24} bile acids in urine, which retain the 3β-hydroxy-Δ^5 structure, can be confirmed by genetic screening for mutations in *HSD3B7* , the gene encoding 3β-HSD. Primary bile acid therapy, administered orally to down regulate cholesterol 7α-hydroxylase activity, to limit the production of 3β-hydroxy-Δ^5 bile acids, and to facilitate hepatic clearance, has been effective in reversing hepatic injury.

Bile Acid-Coenzyme a Ligase Deficiency

Conjugation with the amino acids glycine and taurine is the final step in bile acid synthesis. Two enzymes catalyze the amidation of bile acids. In the first reaction, a CoA thioester is formed by the rate-limiting bile acid-CoA ligase. The other reaction involves the coupling of glycine or taurine and is catalyzed by a cytosolic bile acid-CoA:amino acid N-acyltransferase. Affected patients present with conjugated hyperbilirubinemia, growth failure, or fat-soluble vitamin deficiency, and are identified with mutation of the bile acid-CoA ligase gene. Administration of conjugates of the primary bile acid, glycocholic acid, may be beneficial and can correct the fat-soluble vitamin malabsorption and improve growth.

Disorders of Embryogenesis

Alagille syndrome (arteriohepatic dysplasia) is the most common syndrome with intrahepatic bile duct paucity. Bile duct *paucity* (often erroneously called *intrahepatic biliary atresia*) designates an absence or marked reduction in the number of interlobular bile ducts in the portal triads, with normal-size branches of portal vein and hepatic arteriole. Biopsy in early life often reveals an inflammatory process involving the bile ducts; subsequent biopsy specimens then show subsidence of the inflammation, with residual reduction in the number and diameter of bile ducts, analogous to the *disappearing bile duct syndrome* noted in adults with immune-mediated disorders. Serial assessment of hepatic histology often suggests progressive destruction of bile ducts.

Clinical manifestations of Alagille syndrome are expressed in various degrees and can be nonspecific; they include unusual facial characteristics (broad forehead; deep-set, widely spaced eyes; long, straight nose; and an underdeveloped mandible). There may also be ocular abnormalities (posterior embryotoxon, microcornea, optic disk drusen, shallow anterior chamber), cardiovascular abnormalities (usually peripheral pulmonic stenosis, sometimes tetralogy of Fallot, pulmonary atresia, ventricular septal defect, atrial septal defect, aortic coarctation), vertebral defects (butterfly vertebrae, fused vertebrae, spina bifida occulta, rib anomalies), and tubulointerstitial nephropathy (Table 383.6 , Fig. 383.2 –383.3). Other findings such as short stature, pancreatic insufficiency, vasculopathy (Moyamoya syndrome, stroke), and defective spermatogenesis can reflect or produce nutritional deficiency. Patients with Alagille syndrome are likely to have pruritus, xanthomas with markedly elevated serum cholesterol levels, and neurologic complications of vitamin E deficiency if untreated. Mutations in human Jagged l gene *(JAG1)*, which encodes a ligand for the notch receptor, are linked to ~90% of patients with Alagille syndrome. Alagille syndrome type 2 is due to mutations in *NOTCH2.* Although cirrhosis and manifestations of end-stage liver disease are uncommon early in life, some patients may later develop these complications. Long-term care includes monitoring cardiac and renal function as well as screening for the development of hepatocellular carcinoma.

Table 383.6

Classic Criteria, Based on 5 Body Systems for a Diagnosis of Alagille Syndrome

SYSTEM/PROBLEM	DESCRIPTION
Liver/cholestasis	Usually presenting as jaundice with conjugated hyperbilirubinemia in the neonatal period, often with pale stools
Dysmorphic facies	Broad forehead, deep-set eyes, sometimes with upslanting palpebral fissures, prominent ears, straight nose with bulbous tip, and pointed chin giving the face a somewhat triangular appearance
Congenital heart disease	Most frequently peripheral pulmonary artery stenosis, but also pulmonary atresia, atrial septal defect, ventricular septal defect, and tetralogy of Fallot
Axial skeleton/vertebral anomalies	“Butterfly” vertebrae may be seen on an antero-posterior radiograph, and occasionally hemivertebrae, fusion of adjacent vertebrae, and spina bifida occulta
Eye/posterior embryotoxon	Anterior chamber defects, most commonly posterior embryotoxon, which is prominence of Schwalbe's ring at the junction of the iris and cornea

From Turnpenny PD, Ellard S: Alagille syndrome: pathogenesis, diagnosis and management, *Eur J Hum Genet* 20(3):251–257, 2012, Table 1, p. 252.

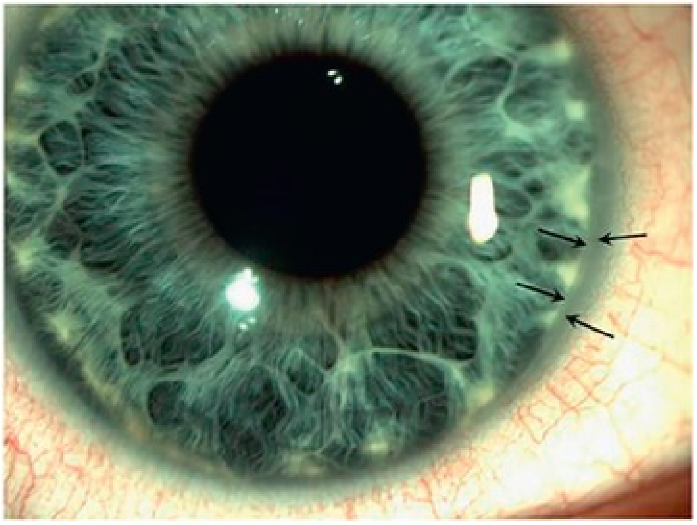

FIG. 383.2 Posterior embryotoxon. (From Turnpenny PD, Ellard S: Alagille syndrome: pathogenesis, diagnosis and management, *Eur J Hum Genet*

20[3]:251–257, 2012, Fig. 1.)

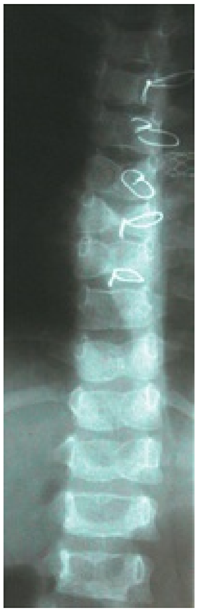

FIG. 383.3 Butterfly vertebrae seen in the thoracic and upper lumbar regions. The child had undergone cardiac surgery, hence the presence of visible wires. (From Turnpenny PD, Ellard S: Alagille syndrome: pathogenesis, diagnosis and management, *Eur J Hum Genet* 20[3]:251–257, 2012, Fig. 2.)

Biliary Atresia

The term *biliary atresia* is imprecise because the anatomy of abnormal bile ducts in affected patients varies markedly. A more appropriate terminology would reflect the pathophysiology, namely noncystic obliterative cholangiopathy. The term *obliterative cholangiopathy* may be divided into 2 major types: cystic and noncystic. The cystic disorders include the different types of **choledochal cysts** while the noncystic forms are different variants of biliary atresia in addition to neonatal sclerosing cholangitis.

Cystic biliary atresia is an uncommon variant of biliary atresia (about 10–20% of cases) and has a relatively favorable prognosis particularly with early surgery. This disorder is often misdiagnosed as a choledochal cyst. However, it can be differentiated by the absence of epithelial lining in biliary atresia as well as the lack of communication with the intrahepatic bile ducts as seen on intraoperative cholangiography.

There are 3 major variants of **noncystic biliary atresia** (Fig. 383.4). The **first type** (correctable biliary atresia), which presents in only 7% of the cases, is characterized by patency of the proximal extrahepatic bile ducts with atresia of the distal bile duct. In the **second type** , which is seen in 15% of the cases, there is atresia of the common hepatic duct at different levels. Patency of the gallbladder, cystic duct, and the common bile duct can be seen in some cases. The patent gall bladder and bile ducts can be used as biliary conduit. In the **third type** (the most *common* variant) there is nonpatency of the entire extrahepatic biliary system and intrahepatic bile ducts at the hilum.

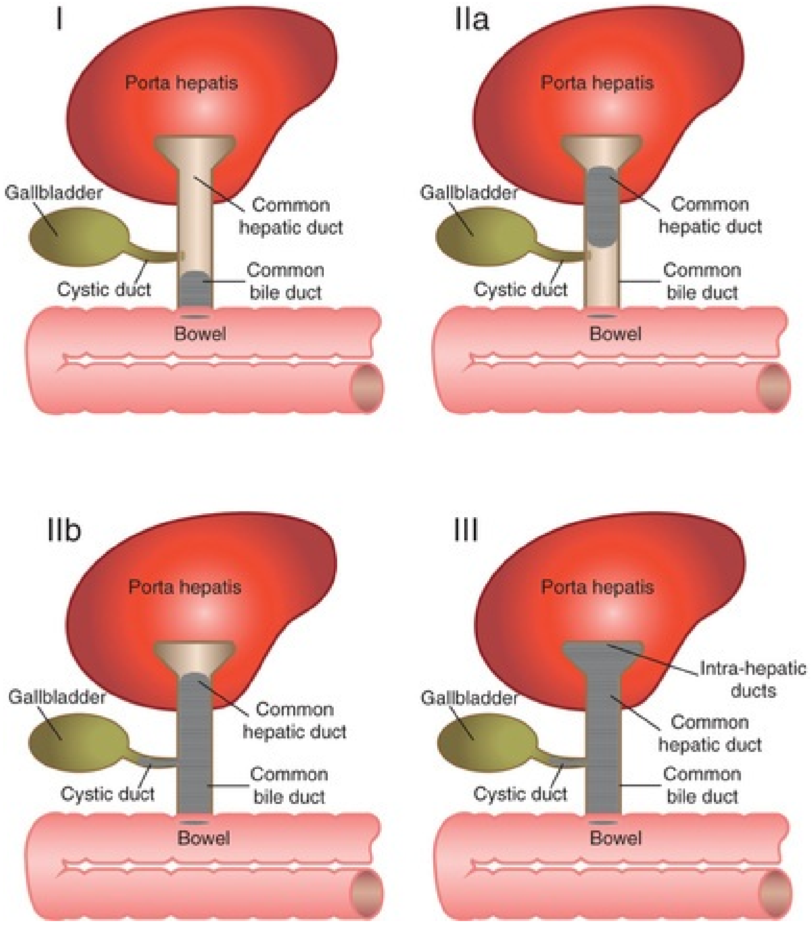
I
Porta hepatis
Gallbladder
Common hepatic duct
Cystic duct
Common bile duct
Bowel
IIa
Porta hepatis
Gallbladder
Common hepatic duct
Cystic duct
Common bile duct
Bowel
IIb
Porta hepatis
Gallbladder
Common hepatic duct
Cystic duct
Common bile duct
Bowel
III
Porta hepatis
Intra-hepatic ducts
Gallbladder
Common hepatic duct
Cystic duct
Common bile duct
Bowel

FIG. 383.4 Biliary atresia classified according to the area of involvement *(gray colored)* . Type I: Atresia of the distal bile duct with patent proximal extrahepatic bile duct. Type IIa: Atresia of the common hepatic duct. Type IIb: Atresia of the common hepatic duct, cystic duct, and common bile duct. Type III: Nonpatency of the entire extrahepatic biliary system and intrahepatic bile ducts at the hilum. (Modified from A-Kader HH, Feerick J, Rodriguez-Davalos M: After two centuries biliary atresia remains the darkest chapter in pediatric hepatology, *Ann Pediatr Child Health* 3[2]:1044,

2015, Fig. 2.)

Biliary atresia can also be classified into 3 categories based on the presence or absence of associated anomalies. The most common type, known as *perinatal* biliary atresia, affecting about 70% of the patients, is not associated with other anomalies or malformations. The patients may not be jaundiced at birth. An evolving process leads to progressive jaundice and acholic stools. Another type, seen in about 15% of the cases, can be associated with heterotaxia malformations including situs inversus, malrotation, polysplenia, interrupted inferior vena cava, and congenital heart disease. This type is also known as **biliary atresia splenic malformation (BASM) syndrome** and usually carries a poor prognosis. Other congenital malformations such as choledochal cysts, kidney anomalies, and cardiac defects can be seen in the third type, which affects the remaining 15% of the cases.

Biliary atresia has been detected in l in 10,000-15,000 live births. Biliary atresia is more common in East Asian countries; patients may be born term or preterm. Screening for biliary atresia in infants after birth is not universal, but stool color cards that help detect acholic stools have been used with some success (Fig. 383.5). In addition, any infant with new onset or persistent jaundice beyond 2 wk of life should be screened with a total and conjugated bilirubin level to detect cholestasis.

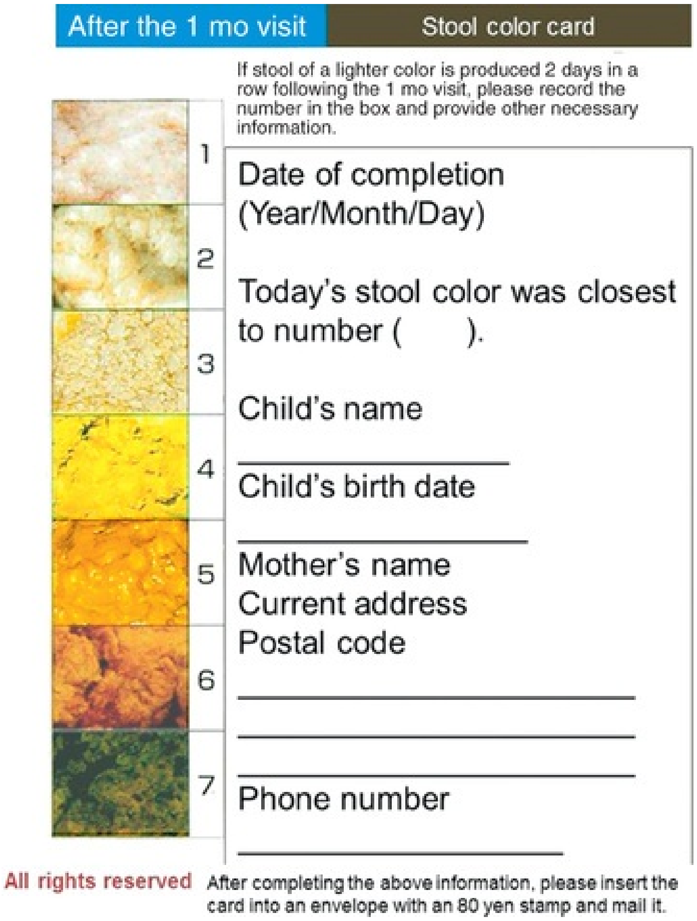

After the 1 mo visit

Stool color card

If stool of a lighter color is produced 2 days in a row following the 1 mo visit, please record the number in the box and provide other necessary information.

Date of completion (Year/Month/Day)

Today's stool color was closest to number (   ).

Child's name ______________

Child's birth date ______________

Mother's name

Current address

Postal code

____

____

____

Phone number

____

All rights reserved

After completing the above information, please insert the card into an envelope with an 80 yen stamp and mail it.

FIG. 383.5 An example of a stool color card used in Tochigi Prefecture from August 1994 to March 2011 consisted of 7 photographic images of stool color taken in both healthy infants and infants with biliary atresia. Images 1-3 denote abnormal stool color, whereas images 4-7 reflect normal stool color. (From Gu YH, Yokoyama K, Mizuta K, et al: Stool color card screening for early detection of biliary atresia and long-term native liver survival: a 19-year cohort study in Japan, *J Pediatr* 166[4]:897–902, 2015, Fig. 2.)

Differentiation of Idiopathic Neonatal Hepatitis From Biliary Atresia

It may be difficult to clearly differentiate infants with biliary atresia who require surgical correction from those with intrahepatic disease (neonatal hepatitis) and patent bile ducts. No single biochemical test or imaging procedure is entirely satisfactory. Diagnostic schemas incorporate clinical, historical, biochemical, and radiologic features.

Idiopathic neonatal hepatitis has a familial incidence of approximately 20%, whereas biliary atresia is unlikely to recur within the same family. A few infants with fetal onset of biliary atresia have an increased incidence of other abnormalities, such as the polysplenia syndrome with abdominal heterotaxia, malrotation, levocardia, and intraabdominal vascular anomalies. Persistently acholic stools suggest biliary obstruction (biliary atresia), but patients with severe idiopathic neonatal hepatitis can have a transient severe impairment of bile excretion. Consistently pigmented stools rule against biliary atresia. Palpation of the liver might find an abnormal size or consistency in patients with biliary atresia; this is less common with idiopathic neonatal hepatitis.

Abdominal ultrasound is a helpful diagnostic tool in evaluating neonatal cholestasis because it identifies choledocholithiasis, perforation of the bile duct, or other structural abnormalities of the biliary tree such as a choledochal cyst. In patients with biliary atresia, ultrasound can detect associated anomalies such as abdominal polysplenia and vascular malformations. The gallbladder either is not visualized or is a microgallbladder in patients with biliary atresia. Children with intrahepatic cholestasis caused by idiopathic neonatal hepatitis, cystic fibrosis, or total parenteral nutrition can have similar ultrasonographic findings. Ultrasonographic triangular cord sign, which represents a cone-shaped fibrotic mass cranial to the bifurcation of the portal vein, may be seen in patients with biliary atresia (Figs. 383.6 and 383.7). The echogenic density, which represents the fibrous remnants at the porta hepatis of biliary atresia cases at surgery, may be a helpful diagnostic tool in evaluating patients with neonatal cholestasis. High-frequency ultrasonography (HUS) imaging produces much improved spatial resolution by sacrificing the depth of penetration and may prove to be superior to conventional ultrasonography in the diagnostic process of biliary atresia.

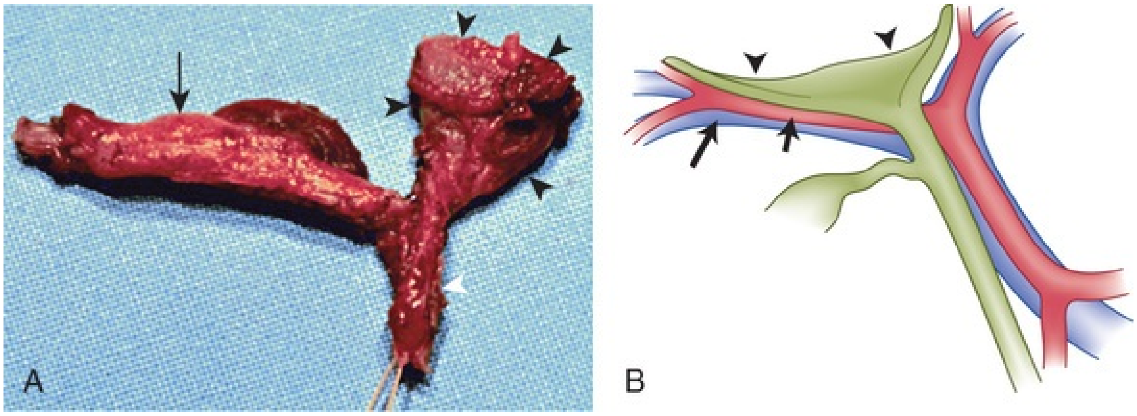

FIG. 383.6 Surgical findings of biliary atresia. A, Photograph of surgical specimen of obliterated extrahepatic bile ducts shows the fibrous ductal remnant *(black arrowheads)* in the porta hepatis, atretic gallbladder *(arrow)* , and fibrous common bile duct *(white arrowhead)* . The fibrous ductal remnant is a triangular cone-shaped mass. B, Schematic represents the anatomic relationship between the fibrous ductal remnant and blood vessels around the porta hepatis. The triangular, cone-shaped, fibrous ductal remnant *(black arrowheads, green*) is positioned anterior and slightly superior to the portal vein *(long arrow, blue)* and the hepatic artery *(short arrow, red)* . (A, From Park WH, Choi SO, Lee HJ, et al: A new diagnostic approach to biliary atresia with emphasis on the ultrasonographic triangular cord sign: comparison of ultrasonography, hepatobiliary scintigraphy, and liver needle biopsy in the evaluation of infantile cholestasis, *J Pediatr Surg* 32[11]:1555–1559, 1997.)

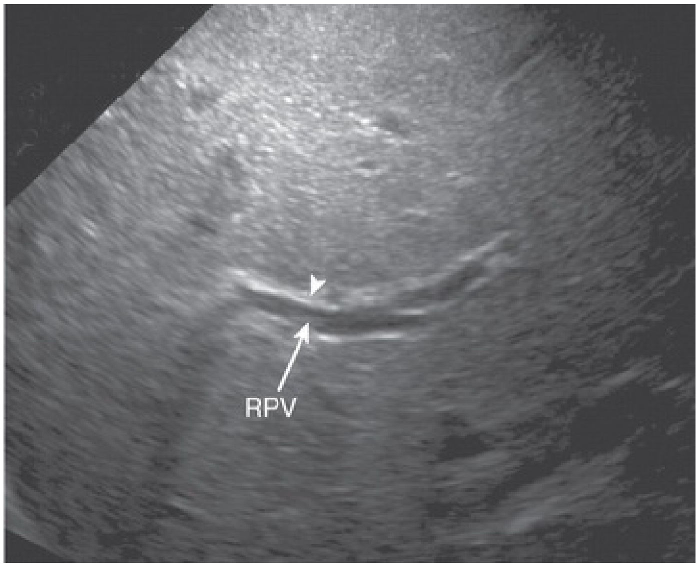

FIG. 383.7 Biliary atresia in an 8 wk old male with elevated conjugated bilirubin. Transverse sonogram shows the triangular cord sign seen as a linear cord of echogenicity *(arrowhead)* along the right portal vein *(RPV)* . (From Lowe LH: Imaging hepatobiliary disease in children, *Semin Roentgenol* 43[1]:39–49, 2008, Fig. 1B.)

Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid derivatives is a sensitive but not specific test for biliary atresia. It fails to identify other structural abnormalities of the biliary tree or vascular anomalies. The lack of the specificity of the test and the inherent delay (5 days of phenobarbital preloading) makes this procedure impractical and of limited value in the evaluation of children with suspected biliary atresia.

The role of endoscopic retrograde cholangiopancreatography (ERCP) in the diagnostic process of biliary atresia remains indeterminate. Similarly, the value of magnetic resonance cholangiopancreatography (MRCP) in the diagnosis of biliary atresia has not been established.

Percutaneous liver biopsy is the most valuable procedure in the evaluation of neonatal hepatobiliary diseases and provides the most reliable discriminatory evidence. Biliary atresia is characterized by bile ductular proliferation, the presence of bile plugs, and portal or perilobular edema and fibrosis, with the basic hepatic lobular architecture intact. In neonatal hepatitis, there is severe, diffuse hepatocellular disease, with distortion of lobular architecture, marked infiltration with inflammatory cells, and focal hepatocellular necrosis; the bile ductules show little alteration. Giant cell transformation is found in infants with either condition and has no diagnostic specificity.

The histologic changes seen in patients with idiopathic neonatal hepatitis can occur in other diseases, including α_1 -antitrypsin deficiency, galactosemia, and various forms of intrahepatic cholestasis. Although paucity of intrahepatic bile ducts may be detected on liver biopsy even in the **first** few weeks of life, later biopsies in such patients reveal a more characteristic pattern.

Management of Patients With Suspected Biliary Atresia

All patients with suspected biliary atresia should undergo exploratory laparotomy and direct cholangiography to determine the presence and site of obstruction. Direct drainage can be accomplished in the patients with a correctable lesion. When no correctable lesion is found, an examination of frozen sections obtained from the transected porta hepatis can detect the presence of biliary epithelium and determine the size and patency of the residual bile ducts. In some cases, the cholangiogram indicates that the biliary tree is patent but of diminished caliber, suggesting that the cholestasis is not due to biliary tract obliteration but to bile duct paucity or markedly diminished flow in the presence of intrahepatic disease. In these cases, transection of or further dissection into the porta hepatis should be avoided.

For patients in whom no correctable lesion is found, the **hepatoportoenterostomy (Kasai) procedure** should be performed. The rationale for this operation is that minute bile duct remnants, representing residual channels, may be present in the fibrous tissue of the porta hepatis; such channels may be in direct continuity with the intrahepatic ductule system. In such cases, transection of the porta hepatis with anastomosis of bowel to the proximal surface of the transection might allow bile drainage. If flow is not rapidly established in the first month of life, progressive obliteration and cirrhosis ensue. If microscopic channels of patency >150 μm in diameter are found, postoperative establishment of bile flow is likely. *The success rate for establishing good bile flow after the Kasai operation is much higher (90%) if performed before 8 wk of life.* Therefore, early referral and prompt evaluation of infants with suspected biliary atresia is important. Educating parents, increased awareness among healthcare providers, and broader implementation of the stool card program are imperative to avoid delayed diagnosis and achieve favorable outcomes.

Some patients with biliary atresia, even of the *noncorrectable* type, derive long-term benefits from interventions such as the Kasai procedure. In most, a degree of hepatic dysfunction persists. Patients with biliary atresia usually have persistent inflammation of the intrahepatic biliary tree, which suggests that biliary atresia reflects a dynamic process involving the entire hepatobiliary system. This might account for the ultimate development of complications such as portal hypertension. The short-term benefit of hepatoportoenterostomy is decompression and drainage sufficient to forestall the onset of cirrhosis and sustain growth until a successful liver transplantation can be done. The use of steroids following the Kasai procedure has not been shown to improve the patient or the native liver survival rates. Similarly, there is no convincing data to support the use of antibiotics or choleretic agents after surgery.

Management of Chronic Cholestasis

With any form of neonatal cholestasis, whether the primary disease is idiopathic neonatal hepatitis, intrahepatic cholestasis, or biliary atresia, affected patients are at increased risk for progression and complications of chronic cholestasis. These reflect various degrees of residual hepatic functional capacity and are due directly or indirectly to diminished bile flow. Any substance normally excreted into bile is retained in the liver, with subsequent accumulation in tissue and in serum. Involved substances include bile acids, bilirubin, cholesterol, and trace elements. Decreased delivery of bile acids to the proximal intestine leads to inadequate digestion and absorption of dietary long-chain triglycerides and fat-soluble vitamins. Impairment of hepatic metabolic function can alter hormonal balance and utilization of nutrients. Progressive liver damage can lead to biliary cirrhosis, portal hypertension, and liver failure.

Treatment of patients with cholestasis is empirical and is guided by careful monitoring (Table 383.7). No therapy is known to be effective in halting the progression of cholestasis or in preventing further hepatocellular damage and cirrhosis. Growth failure is a major concern and is related in part to malabsorption and malnutrition resulting from ineffective digestion and absorption of dietary fat. Use of a medium-chain triglyceride-containing formula can improve caloric balance. With chronic cholestasis and prolonged survival, children with hepatobiliary disease can experience deficiencies of the fat-soluble vitamins (A, D, E, and K). Metabolic bone disease is common. It is essential to monitor the fat-soluble vitamin status in patients.

Table 383.7

Suggested Medical Management of Persistent Cholestasis

CLINICAL IMPAIRMENT	MANAGEMENT
Malnutrition resulting from malabsorption of dietary long-chain triglycerides	Replace with dietary formula or supplements containing medium-chain triglycerides
Fat-soluble vitamin malabsorption	
Vitamin A deficiency (night blindness, thick skin)	Replace with 10,000-15,000 IU/day as Aquasol A
Vitamin E deficiency (neuromuscular degeneration)	Replace with 50-400 IU/day as oral α-tocopherol or TPaGS
Vitamin D deficiency (metabolic bone disease)	Replace with 5,000-8,000 IU/day of D_2 or 3-5 µg/kg/day of 25-hydroxycholecalciferol
Vitamin K deficiency (hypoprothrombinemia)	Replace with 2.5-5.0 mg every other day as water-soluble derivative of menadione
Micronutrient deficiency	Calcium, phosphate, or zinc supplementation
Deficiency of water-soluble vitamins	Supplement with twice the recommended daily allowance
Retention of biliary constituents such as cholesterol (itch or xanthomas)	Administer choleretic bile acids (ursodeoxycholic acid, 15-30 mg/kg/day)
Progressive liver disease; portal hypertension (variceal bleeding, ascites, hypersplenism)	Interim management (control bleeding; salt restriction; spironolactone)
End-stage liver disease (liver failure)	Transplantation

TPGS , D-α-tocopherol polyethylene glycol 1000 succinate.

A **degenerative neuromuscular syndrome** is found in patients with chronic cholestasis, caused by vitamin E deficiency; affected children experience progressive areflexia, cerebellar ataxia, ophthalmoplegia, and decreased vibratory sensation. Specific morphologic lesions were found in the central nervous system, peripheral nerves, and muscles. These lesions are preventable and are not commonly seen today; they were potentially reversible in children younger than 3-4 yr of age. Affected children have low serum vitamin E concentrations, increased hydrogen peroxide hemolysis, and low ratios of serum vitamin E to total serum lipids (<0.6 mg/g for children younger than 12 yr and <0.8 mg/g for older patients). Vitamin E deficiency may be prevented by oral administration of large doses (up to 1,000 IU/day); patients unable to absorb sufficient quantities may require administration of D-α-tocopheryl polyethylene glycol 1,000 succinate orally. Serum levels should be monitored as a guide to efficacy.

Pruritus is a particularly troublesome complication of chronic cholestasis, often with the appearance of xanthomas. Both features seem to be related to the accumulation of cholesterol and bile acids in serum and in tissues. Elimination of these retained compounds is difficult when bile ducts are obstructed, but if there is any degree of bile duct patency, administration of ursodeoxycholic acid can increase bile flow or interrupt the enterohepatic circulation of bile acids and thus decrease the xanthomas and ameliorate the pruritus (see Table 383.7). Ursodeoxycholic acid therapy can also lower serum cholesterol levels. The recommended initial dose is 15 mg/kg/24 hr. Inhibition of the apical sodium dependent bile acid transporter prevents the reabsorption of bile acids in the terminal ileum, is currently under investigation, and may prove to be of therapeutic benefit to relieve pruritus and improve the quality of life.

Partial external biliary diversion (PEBD) is efficacious in managing pruritus refractory to medical therapy and provides a favorable outcome in a select group of patients with chronic cholestasis who have not yet developed cirrhosis. The surgical technique involves resecting a segment of intestine to be used as a biliary conduit. One end of the conduit is attached to the gallbladder and the other end is brought out to the skin, forming a stoma. The main drawback of the procedure is the need to use an ostomy bag. Open button cholecystostomy and laparoscopic PEBD are modified surgical approaches, which have been reported to be efficacious in relieving pruritus. Ileal exclusion has been used successfully but it is less effective compared to PEBD. Unfortunately in some patients who continue to experience excoriating pruritus, liver transplantation is the only remaining consideration.

Progressive fibrosis and cirrhosis lead to the development of portal hypertension and consequently to ascites and variceal hemorrhage. The presence of ascites is a risk factor for the development of spontaneous bacterial peritonitis. *The first step in the management of patients with ascites is to rule out spontaneous bacterial peritonitis and restrict sodium intake to 0.5 g (~1-2 mEq/kg/24 hr)*. There is no need for fluid restriction in patients with adequate renal output. Should this be ineffective, diuretics may be helpful. The diuretic of choice is spironolactone (1-3.3 mg/kg/day orally or divided every 12 hr). If spironolactone alone does not control ascites, the addition of another diuretic such as thiazide or furosemide may be beneficial. Patients with ascites but without peripheral edema are at risk for reduced plasma volume and decreased urine output during diuretic therapy. Tense ascites alters renal blood flow and systemic hemodynamics. Paracentesis and intravenous albumin infusion can improve hemodynamics, renal perfusion, and symptoms. Follow-up includes dietary counseling and monitoring of serum and urinary electrolyte concentrations.

In patients with portal hypertension, variceal hemorrhage and the development of hypersplenism are common. It is important to ascertain the cause of bleeding because episodes of gastrointestinal hemorrhage in patients who have chronic liver disease may be from gastritis or peptic ulcer disease. Because the management of these various complications differs, differentiation, perhaps via endoscopy, is necessary before treatment is initiated. If the patient is volume depleted, blood transfusion should be carefully administered, avoiding over transfusion, which can precipitate further bleeding. Balloon tamponade is not recommended in children because it can be associated with significant complications. Sclerotherapy or endoscopic variceal ligation may be useful palliative measures in the management of bleeding varices and may be superior to surgical alternatives.

For patients with advanced liver disease, hepatic transplantation has a success rate >90%. If the operation is technically feasible, it will prolong life and might correct the metabolic error in diseases such as α_1 -antitrypsin deficiency, tyrosinemia, and Wilson disease. Success depends on adequate intraoperative, preoperative, and postoperative care, and on cautious use of immunosuppressive agents. Scarcity of donors of small livers limits the application of liver transplantation for infants and children. The use of reduced-size transplants and living donors increases the ability to treat small children successfully.

Prognosis

For patients with idiopathic neonatal hepatitis, the variable prognosis might reflect the heterogeneity of the disease. In sporadic cases, 60–70% recover with no evidence of hepatic structural or functional impairment. Approximately 5–10% have persistent fibrosis or inflammation, and a smaller percentage have more severe liver disease, such as cirrhosis. Infants usually die early in the course of the illness, owing to hemorrhage or sepsis. Of infants with idiopathic neonatal hepatitis of the familial variety, only 20–30% recover; 10–15% acquire chronic liver disease with cirrhosis. Liver transplantation may be required.

383.2

Cholestasis in the Older Child

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Cholestasis with onset after the neonatal period is most often caused by acute viral hepatitis or exposure to hepatotoxic drugs. However, many of the conditions causing neonatal cholestasis can also cause chronic cholestasis in older patients. Consequently, older children and adolescents with conjugated hyperbilirubinemia should be evaluated for acute and chronic viral hepatitis, α_1 -antitrypsin deficiency, Wilson disease, liver disease associated with inflammatory bowel disease, sclerosing cholangitis, autoimmune hepatitis, drug-induced liver injury and the syndromes of intrahepatic cholestasis. Other causes include obstruction caused by cholelithiasis, abdominal tumors, enlarged lymph nodes, or hepatic inflammation resulting from drug ingestion. Management of cholestasis in the older child is similar to that proposed for neonatal cholestasis (see Table 383.7).

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CHAPTER 384

Metabolic Diseases of the Liver

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Metabolic liver diseases in children, although individually rare, altogether represent a significant cause of morbidity and mortality. This is because the liver has a central role in synthetic, degradative, and regulatory pathways involving carbohydrate, protein, lipid, trace element, and vitamin metabolism. Therefore, inborn errors of metabolism will result in metabolic abnormalities, specific enzyme deficiencies or defects, and disorders of protein transport that can have primary or secondary effects on the liver (Table 384.1). Liver disease can arise when absence of an enzyme produces a block in a metabolic pathway, when unmetabolized substrate accumulates proximal to a block, when deficiency of an essential substance produced distal to an aberrant chemical reaction develops, or when synthesis of an abnormal metabolite occurs. The spectrum of pathologic changes includes **hepatocyte injury,** with subsequent failure of other metabolic functions, often resulting in cirrhosis and/or liver cancer; abnormal **storage** of lipid, glycogen, or other products manifested as hepatomegaly, often with complications specific to deranged metabolism (hypoglycemia with glycogen storage disease); and absence of structural change despite profound **metabolic effects,** as seen in patients with urea cycle defects. Clinical manifestations of metabolic diseases of the liver mimic infections, intoxications, and hematologic and immunologic diseases (Table 384.2).

Table 384.1

Inborn Errors of Metabolism That Affect the Liver

DISORDERS OF CARBOHYDRATE METABOLISM
• Disorders of galactose metabolism   • Galactosemia (galactose-1-phosphate uridyltransferase deficiency) • Disorders of fructose metabolism

  - Hereditary fructose intolerance (aldolase deficiency)
  - Fructose-1,6 diphosphatase deficiency
- Glycogen storage diseases
  - Type I
  - Von Gierke Ia (glucose-6-phosphatase deficiency)
  - Type Ib (glucose-6-phosphatase transport defect)
  - Type III Cori/Forbes (glycogen debrancher deficiency)
  - Type IV Andersen (glycogen branching enzyme deficiency)
  - Type VI Hers (liver phosphorylase deficiency)
- Congenital disorders of glycosylation (multiple subtypes)

DISORDERS OF AMINO ACID AND PROTEIN METABOLISM

- Disorders of tyrosine metabolism
  - Hereditary tyrosinemia type I (fumarylacetoacetate deficiency)
  - Tyrosinemia, type II (tyrosine aminotransferase deficiency)
- Inherited urea cycle enzyme defects
  - CPS deficiency (carbamoyl phosphate synthetase I deficiency)
  - OTC deficiency (ornithine transcarbamoylase deficiency)
  - Citrullinemia type I (argininosuccinate synthetase deficiency)
  - Argininosuccinic aciduria (argininosuccinate deficiency)
  - Argininemia (arginase deficiency)
  - N-AGS deficiency (*N* -acetylglutamate synthetase deficiency)
- Maple serum urine disease (multiple possible defects[*])

DISORDERS OF LIPID METABOLISM

- Wolman disease (lysosomal acid lipase deficiency)
- Cholesteryl ester storage disease (lysosomal acid lipase deficiency)
- Homozygous familial hypercholesterolemia (low-density lipoprotein receptor deficiency)
- Gaucher disease type I (β-glucocerebrosidase deficiency)
- Niemann-Pick type C (NPC 1 and 2 mutations)

DISORDERS OF BILE ACID METABOLISM

- Defects in bile acid synthesis (several specific enzyme deficiencies)
- Zellweger syndrome—cerebrohepatorenal (multiple mutations in peroxisome biogenesis genes)

DISORDERS OF METAL METABOLISM

- Wilson disease (ATP7B mutations)
- Hepatic copper overload
- Indian childhood cirrhosis
- Neonatal iron storage disease

DISORDERS OF BILIRUBIN METABOLISM

- Crigler-Najjar (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase mutations)
  - Type I
  - Type II
- Gilbert disease (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase polymorphism)
- Dubin-Johnson syndrome (multiple drug-resistant protein 2 mutation)
- Rotor syndrome

MISCELLANEOUS

- α_1 -Antitrypsin deficiency
- Citrullinemia type II (citrin deficiency)
- Cystic fibrosis (cystic fibrosis transmembrane conductance regulator mutations)
- Erythropoietic protoporphyria (ferrochelatase deficiency)
- Polycystic kidney disease
- Mitochondrial hepatopathies (see Table 383.3 and Chapter 388)

[*] Maple syrup urine disease can be caused by mutations in branched-chain α-keto dehydrogenase, keto acid decarboxylase, lipoamide dehydrogenase, or dihydrolipoamide dehydrogenase.

Table 384.2

Clinical Manifestations That Suggest the Possibility of Metabolic Disease

Recurrent vomiting, failure to thrive, short stature
Dysmorphic features
Jaundice, hepatomegaly (±splenomegaly), fulminant hepatic failure, edema/anasarca
Hypoglycemia, organic acidemia, lactic acidemia, hyperammonemia, bleeding (coagulopathy)
Developmental delay/psychomotor retardation, hypotonia, progressive neuromuscular deterioration, seizures, myopathy, neuropathy
Cardiac dysfunction/failure
Unusual odors
Rickets
Cataracts

Many metabolic diseases are detected in expanded newborn metabolic screening programs (see Chapter 102). Clues are provided by family history of a similar illness or by the observation that the onset of symptoms is closely associated with a change in dietary habits; in patients with hereditary fructose intolerance, symptoms follow ingestion of fructose (sucrose). Clinical and laboratory evidence often guides the evaluation. Liver biopsy offers morphologic study and permits enzyme assays, as well as quantitative and qualitative assays of various other constituents (e.g., hepatic copper content in Wilson disease). Genetic/molecular diagnostic approaches are also available. Such studies require cooperation of experienced laboratories and careful attention to collection and handling of specimens. Treatment depends on the specific type of defect and although relatively uncommon, altogether metabolic diseases of the liver account for up to 10% of the indications for liver transplantation in children, a number that may be underestimated given the acute nature of some of these conditions, precluding complete diagnostic investigation prior to transplantation.

384.1

Inherited Deficient Conjugation of Bilirubin (Familial Nonhemolytic Unconjugated Hyperbilirubinemia)

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Bilirubin is the metabolic end product of heme. Before excretion into bile, it is first glucuronidated and made water-soluble by the enzyme bilirubin-uridine diphosphoglucuronate glucuronosyltransferase (UDPGT). UDPGT activity is deficient or altered in 3 genetically and functionally distinct disorders (Crigler-Najjar [CN] syndromes type I and II and Gilbert syndrome), producing congenital nonobstructive, nonhemolytic, **unconjugated** hyperbilirubinemia. UGT1A1 is the primary UDPGT isoform needed for bilirubin glucuronidation. Complete absence of UGT1A1 activity causes CN type I, while CN type II is caused by decreased UGT1A1 activity to ~10% of normal.

Gilbert syndrome, the most common hereditary hyperbilirubinemia syndrome, occurs in 5–10% of the white population. Common polymorphisms resulting in a TA insertion in the promoter region of *UGT1A1* lead to decreased binding of the TATA binding protein and decrease normal gene activity by ~30%. Snapback primer genotyping can distinguish all *UGT1A1* promoter genotypes and can provide a definitive diagnosis. Unlike the CN syndromes, Gilbert syndrome usually occurs after puberty, is not associated with chronic liver disease, and no treatment is required. Disease manifestations include fluctuating mild elevations in total serum bilirubin concentration from 1 to 6 mg/dL with no evidence of liver injury or hemolysis. Because UGT1A1 catalyzes water-soluble glucuronidation and detoxification of multiple substrates other than bilirubin (i.e., drugs, hormones, environmental toxins, and aromatic hydrocarbons), mutations in the *UGT1A1* gene are implicated in cancer risk and predispose to drug toxicity and episodic jaundice specifically in cancer chemotherapy.

Crigler-Najjar Syndrome Type I (Glucuronyl Transferase Deficiency)

CN type I is a rare, autosomal recessive disease caused by homozygous or compound heterozygous mutations in the *UGT1A1* gene which result in a premature stop codon or frameshift mutation and complete absence of UGT1A1 activity. At least 59 mutations have been identified to date. Parents of affected children have partial defects in conjugation, as determined by hepatic specific enzyme assay or by measurement of glucuronide formation but have normal serum unconjugated bilirubin levels.

Clinical Manifestations

Severe unconjugated hyperbilirubinemia develops in homozygous affected infants in the first 3 days of life. Without treatment, serum unconjugated bilirubin concentrations reach 25-35 mg/dL in the 1st mo, which can cause **kernicterus** . Stools are pale yellow. Persistent unconjugated hyperbilirubinemia at levels >20 mg/dL without hemolysis after the 1st wk of life should suggest the syndrome.

Diagnosis

The diagnosis of CN type I is based on the early age of onset and the extreme level of bilirubin elevation in the absence of hemolysis. In affected infants, bile contains no bilirubin glucuronide and bilirubin concentration in bile is <10 mg/dL compared with normal concentrations of 50-100 mg/dL. The diagnosis is established by measuring hepatic glucuronyl transferase activity in a liver specimen obtained by percutaneous liver biopsy; open liver biopsy should be avoided because surgery and anesthesia can precipitate kernicterus. DNA diagnosis is also available and may be preferable. Identification of the heterozygous state in parents also strongly suggests the diagnosis. The differential diagnosis of unconjugated hyperbilirubinemia is discussed in Chapter 123.3 .

Treatment

The serum unconjugated bilirubin concentration should be maintained at <20 mg/dL for the first few weeks of life, and even lower in low birthweight infants. This usually requires repeated exchange transfusions and **phototherapy** in the immediate neonatal period. Oral calcium phosphate supplementation renders phototherapy more effective as it forms complexes with bilirubin in the gut. Phenobarbital therapy, through CYP450 enzyme induction, should be considered to determine responsiveness and differentiation between CN types I and II. In patients with CN type I there is no response to phenobarbital treatment.

The risk of kernicterus persists into adult life, although the serum bilirubin levels required to produce brain injury beyond the neonatal period are considerably higher (usually >35 mg/dL). Therefore, phototherapy is generally continued through the early years of life. In older infants and children, phototherapy is used mainly during sleep so as not to interfere with normal activities. Despite the administration of increasing intensities of light for longer periods, the serum bilirubin response to phototherapy decreases with age. Additional adjuvant therapy using agents that bind photobilirubin products such as cholestyramine or agar can also be used to interfere with the enterohepatic recirculation of bilirubin.

Prompt treatment of intercurrent infections, febrile episodes, and other types of illness might help prevent the later development of kernicterus, which can occur at bilirubin levels of 45-55 mg/dL. All reported patients with CN type I have eventually experienced severe kernicterus by young adulthood.

Orthotopic liver transplantation cures the disease and has been successful in a small number of patients. Isolated hepatocyte transplantation has been reported as bridge therapy to liver transplantation, with most but not all patients eventually requiring orthotopic transplantation. Other therapeutic modalities have included plasmapheresis and limitation of bilirubin production. The latter option, inhibiting bilirubin generation, is possible via inhibition of heme oxygenase using metalloporphyrin therapy.

Crigler-Najjar Syndrome Type II (Partial Glucuronyl Transferase Deficiency)

CN type II is an autosomal recessive disease caused by homozygous missense mutations in UGT1A1 resulting in reduced (partial) enzymatic activity. More than 45 mutations have been identified to date. Type II disease can be distinguished from type I by the marked decline in serum bilirubin level that occurs in type II disease after treatment with phenobarbital secondary to an inducible phenobarbital response element on the UGT1A1 promoter.

Clinical Manifestations

When this disorder appears in the neonatal period, unconjugated hyperbilirubinemia usually occurs in the first 3 days of life; serum bilirubin concentrations can be in a range compatible with physiologic jaundice or can be at pathologic levels. The concentrations characteristically remain elevated into and after the 3rd wk of life, persisting in a range of 1.5-22 mg/dL; concentrations in the lower part of this range can create uncertainty about whether chronic hyperbilirubinemia is present. Development of kernicterus is unusual. Stool color is normal, and the infants are without clinical signs or symptoms of disease. There is no evidence of hemolysis. Liver enzymes, albumin, and PT/INR are typically normal.

Diagnosis

Concentration of bilirubin in bile is nearly normal in patients with CN type II. Jaundiced infants and young children with CN type II syndrome respond readily to 5 mg/kg/day of oral phenobarbital, with a decrease in serum bilirubin concentration to 2-3 mg/dL in 7-10 days.

Treatment

Long-term reduction in serum bilirubin levels can be achieved with continued administration of phenobarbital at 5 mg/kg/day. Therapy must be lifelong. The cosmetic and psychosocial benefit should be weighed against the risks of an effective dose of the drug because there is a small long-term risk of kernicterus even in the absence of hemolytic disease. Orlistat, an irreversible inhibitor of intestinal lipase, increases fecal fat excretion and may decrease plasma unconjugated bilirubin concentrations (~10%) in patients with CN types I and II.

Inherited Conjugated Hyperbilirubinemia

Conjugated hyperbilirubinemia can be caused by rare autosomal recessive conditions characterized by asymptomatic mild jaundice. In these conditions, the transfer of bilirubin and other organic anions from the hepatocyte into bile is defective. Chronic mild conjugated hyperbilirubinemia is usually detected during adolescence or early adulthood but can occur as early as 2 yr of age. The results of other routine liver tests are normal. Jaundice can be exacerbated by infection, pregnancy, oral contraceptives, alcohol consumption, and surgery. There is usually no morbidity and life expectancy is normal.

Dubin-Johnson Syndrome

Dubin-Johnson syndrome is an autosomal recessive inherited defect in hepatocyte secretion of bilirubin glucuronide. The defect in hepatic excretory function is not limited to conjugated bilirubin excretion but also involves several organic anions normally excreted from the liver cell into bile. Disease results from absent function of multiple drug-resistant protein 2 (MRP2, encoded by the gene *ABCC2*), an adenosine triphosphate–dependent canalicular transporter. More than 10 different mutations, including compound heterozygous mutation in the *CMOAT* gene, have been identified and either affect localization of MRP2 with resultant increased degradation or impair MRP2 transporter activity in the canalicular membrane. Bile acid excretion and serum bile acid levels are normal. Total urinary coproporphyrin excretion is normal in quantity but coproporphyrin I excretion increases to approximately 80% with a concomitant decrease in coproporphyrin III excretion. Normally, coproporphyrin III is >75% of the total. Cholangiography fails to visualize the biliary tract and x-ray of the gallbladder is also abnormal. Liver histology demonstrates normal architecture, but hepatocytes contain black pigment similar to melanin. Liver function is normal and prognosis is excellent. The most commonly reported symptoms are abdominal pain and fatigue, jaundice, dark urine, and slight enlargement of the liver. Jaundice fluctuates in intensity and is aggravated by intercurrent disease. Rarely, Dubin-Johnson can present in the neonatal period with severe conjugated hyperbilirubinemia with serum bilirubin >20 mg/dL and hepatosplenomegaly. No treatment is indicated for disease which presents outside of the neonatal period.

Rotor Syndrome

Rotor Syndrome is an autosomal recessive disease resulting from biallelic inactivating mutations in *SLCO1B1* and *SLCO1B3* result in functional deficiencies of both OATP1B1 and OATP1B protein. Importantly, these mutations may confer significant drug toxicity risk. These patients present similarly to Dubin-Johnson syndrome, with asymptomatic mild and fluctuating conjugated hyperbilirubinemia, with total serum bilirubin levels between 2 and 5 mg/dL. Unlike Dubin-Johnson syndrome, total urinary coproporphyrin excretion is elevated with a relative increase in the amount of the coproporphyrin I isomer. If liver biopsy is performed, there is no abnormal pigmentation in contrast to

Dubin-Johnson. The gallbladder is normal by roentgenography. Rotor syndrome is benign and no treatment is indicated.

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384.2

Wilson Disease

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Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder that can be associated with liver disease, degenerative changes in the brain, and Kayser-Fleischer (K-F) rings in the cornea (Fig. 384.1). The incidence is approximately 1/30,000 births worldwide. Specific treatment is available; however this disease is progressive and potentially fatal if untreated. Prompt diagnostic evaluation for Wilson disease in all patients over age 5 yr presenting with any form of liver disease facilitates expeditious initiation of treatment of the disease, appropriate genetic counseling, screening of first-degree relatives, and also allows appropriate treatment of non-Wilsonian liver disease once copper toxicosis is ruled out.

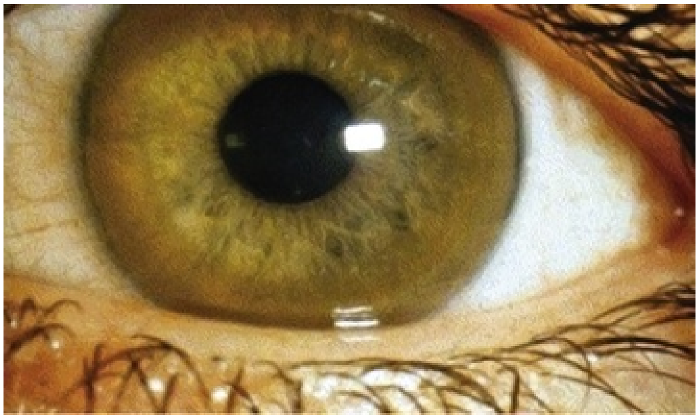

FIG. 384.1 Kayser-Fleischer ring. There is a brown discoloration at the outer margin of the cornea because of the deposition of copper in Descemet's membrane. Here it is clearly seen against the light green iris. Slit-lamp examination is required for secure detection. (From Ala A, Walker AP, Ashkan K, et al: Wilson's disease, *Lancet* 369:397–408, 2007.)

Pathogenesis

The abnormal gene for Wilson disease is found on chromosome 13 (13q14.3), and encodes *ATP7B* , a copper transporting P-type adenosine triphosphatase (ATPase) which is mainly expressed in hepatocytes and is critical for biliary copper excretion and for copper incorporation into ceruloplasmin. Absence or malfunction of ATP7B results in decreased biliary copper excretion and diffuse accumulation of copper in the cytosol of hepatocytes. With time, liver cells become overloaded and copper is redistributed to other tissues, including the brain and kidneys, causing toxicity, primarily as a potent inhibitor of enzymatic processes. Ionic copper inhibits pyruvate oxidase in brain and ATPase in membranes, leading to decreased adenosine triphosphate-phosphocreatine and potassium content of tissue.

More than 500 mutations have been identified, of which >380 have a confirmed role in disease pathogenesis; genetic testing should be able to identify a pathologic variant. Most patients are compound heterozygotes. Mutations that abolish gene function are associated with an onset of disease symptoms as early as 3 yr of age, when Wilson disease might not typically be considered in the differential diagnosis. Milder mutations can be associated with neurologic symptoms or liver disease as late as 80 yr of age. The most commonly occurring disease-causing *ATP7B* mutations result in a protein which binds copper but is unable to effectively traffic to the apical surface of hepatocytes to perform its copper-exporting function. Pharmacologic inhibition of p38 and Jun N-terminal kinase mitogen-activated protein kinase (JNK MAPK) signaling pathways in vitro can rescue this defect and are potential new therapeutic targets.

Clinical Manifestations

Forms of Wilsonian hepatic disease include asymptomatic hepatomegaly (with or without splenomegaly), subacute or chronic hepatitis, and acute hepatic failure (with or without hemolytic anemia). Cryptogenic cirrhosis, portal hypertension, ascites, edema, variceal bleeding, or other effects of hepatic dysfunction (delayed puberty, amenorrhea, coagulation defects) can be manifestations of Wilson disease.

Disease presentations are variable, with a tendency to familial patterns. Liver disease is the most common disease manifestation in children and can precede neurologic symptoms by as long as 10 yr. Females are 3 times more likely than males to present with acute hepatic failure. When Wilson disease presents after age 20, *neurologic symptoms* are the most common manifestation.

Neurologic disorders can develop insidiously or precipitously, with intention tremor, dysarthria, rigid dystonia, Parkinsonism, choreiform movements, lack of motor coordination, deterioration in school performance, psychosis, or behavioral changes. K-F rings are absent in young patients with hepatic Wilson disease up to 50% of the time but are present in 95% of patients with neurologic symptoms. **Psychiatric manifestations** include depression, personality changes, anxiety, obsessive-compulsive behavior, or psychosis.

Coombs-negative **hemolytic anemia** may be an initial manifestation, possibly related to the release of large amounts of copper from damaged hepatocytes; this form of Wilson disease is usually fatal without transplantation. During hemolytic episodes, urinary copper excretion and serum free copper levels are markedly elevated. Manifestations of renal Fanconi syndrome and progressive renal failure with alterations in tubular transport of amino acids, glucose, and uric acid may be present. Unusual manifestations include arthritis, pancreatitis, nephrolithiasis, infertility or recurrent miscarriages, cardiomyopathy, and hypoparathyroidism.

Pathology

All grades of hepatic injury occur in patients with Wilson disease with steatosis, hepatocellular ballooning and degeneration, glycogen granules, minimal inflammation, and enlarged Kupffer cells being most common. The earliest histologic feature of Wilson disease is mild steatosis which may mimic nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. Additionally, the lesion may be indistinguishable from that of autoimmune hepatitis. With progressive parenchymal damage, fibrosis and cirrhosis develop. Ultrastructural changes primarily involve the mitochondria and include increased density of the matrix material, inclusions of lipid and granular material, and increased intracristal space with dilation of the tips of the cristae.

Diagnosis

Wilson disease should be considered in children and teenagers with unexplained acute or chronic liver disease, neurologic symptoms of unknown cause, acute hemolysis, psychiatric illnesses, behavioral changes, Fanconi syndrome, or unexplained bone (osteoporosis, fractures) or muscle disease (myopathy, arthralgia). The clinical suspicion is confirmed by study of indices of copper metabolism.

Most patients with Wilson disease have decreased serum ceruloplasmin levels (<20 mg/dL). The failure of copper to be incorporated into ceruloplasmin leads to a plasma protein with a shorter half-life and, therefore, a reduced steady-state concentration of ceruloplasmin in the circulation. Serum ceruloplasmin levels should be interpreted with caution. Acute inflammatory states and elevated estrogen levels (pregnancy, hormone therapy, or use of oral contraception) can falsely increase ceruloplasmin levels. Additionally, serum ceruloplasmin may be low in autoimmune hepatitis, celiac disease, familial aceruloplasminemia, or in carriers of ATP7B mutations (mild variants of Menkes disease: occipital horn syndrome) who do not show copper overload disease. The serum free copper level may be elevated in early Wilson disease (>1.6 µmol/L), and urinary copper excretion (normally <40 µg/day) is increased to >100 µg/day and often up to 1,000 µg or more per day. Typical urinary copper excretion in patients with untreated Wilson disease is >1.6 µmol/24 hr. in adults and >0.64 µmol/24 hr in children. In equivocal cases, the response of urinary copper output to chelation may be of diagnostic help. Prior to a 24 hr urine collection patients are given 2 500 mg oral doses of D -penicillamine 12 hr apart; affected patients excrete >1,600 µg/24 hr.

Demonstration of K-F rings, which might not be present in younger children, requires a slit-lamp examination by an ophthalmologist. After adequate treatment, K-F rings resolve. Liver biopsy can determine the extent and severity of liver disease and for measuring the hepatic copper content (normally <10 µg/g dry weight) but is only required if clinical signs and noninvasive tests do not allow a final diagnosis or if another liver disorder is suspected. Hepatic copper accumulation is the hallmark of Wilson disease and measurement of hepatic parenchymal copper concentration is the method of choice for diagnosis. Hepatic copper content >250 µg/g dry weight (>4 µmol/g dry weight) is the best biochemical evidence for Wilson disease, but lowering the threshold to 1.2 µmol/g dry weight improves sensitivity without significantly affecting specificity. Intermediate levels of hepatic copper may be present in asymptomatic carriers. In later stages of Wilson disease, hepatic copper content can be unreliable because cirrhosis leads to variable hepatic copper distribution and sampling error.

First-degree relatives of patients with Wilson disease should be screened for presymptomatic disease. This screening should include determination of the serum ceruloplasmin level and 24-hr urinary copper excretion. If these results are abnormal or equivocal, liver biopsy should be carried out to determine morphology and hepatic copper content. Genetic screening by either linkage analysis or direct DNA mutation analysis is possible, especially if the mutation for the proband case is known or the patient is from an area where a specific mutation is prevalent, such as in central and eastern Europe where the *H1069Q* mutation is present in 50–80% of patients.

Treatment

Once the diagnosis of Wilson disease is made, lifelong treatment should be initiated and is focused on limiting copper uptake and promoting copper excretion through dietary and pharmacologic measures. The normal diet contains 2-5 mg of copper per day. For patients with Wilson disease, the dietary intake of copper should be restricted to <1 mg/day. High copper content foods such as liver, shellfish, nuts, and chocolate should be avoided. If the copper content of the drinking water exceeds 0.1 mg/L, it may be necessary to demineralize the water.

The initial treatment in symptomatic patients is the administration of copper-chelating agents, which leads to rapid excretion of excess deposited copper. Chelation therapy is managed with oral administration of D -penicillamine (β,βdimethylcysteine) in a dose of 1 g/day in 2 doses before meals for adults and 20 mg/kg/day for pediatric patients or triethylene tetramine dihydrochloride (Trien, TETA, trientine) at a dose of 0.5-2.0 g/day for adults and 20 mg/kg/day for children. In response to chelation, urinary copper excretion increases, with marked improvement in hepatic and neurologic function and the disappearance of K-F rings.

Approximately 10–50% of patients initially treated with penicillamine for neurologic symptoms have a worsening of their condition. Toxic effects of penicillamine occur in 10–20% and consist of hypersensitivity reactions (i.e., Goodpasture syndrome, systemic lupus erythematosus, and polymyositis), interaction with collagen and elastin, deficiency of other elements such as zinc, and aplastic anemia and nephrosis. Because penicillamine is an antimetabolite of vitamin B_6 , additional amounts of this vitamin are necessary. For these reasons, trientene is the preferred alternative and is considered first-line therapy for some patients. Trientine has few known side effects. Ammonium tetrathiomolybdate is another alternative chelating agent under investigation for patients with neurologic disease; initial results suggest that significantly fewer patients experience neurologic deterioration with this drug compared to penicillamine. The initial dose is 120 mg/day (20 mg between meals 3 times daily and 20 mg with meals 3 times daily). Side effects include anemia, leukopenia, thrombocytopenia, and mild elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Because of its extensive decoppering effect, ammonium tetrathiomolybdate also has antiangiogenic effects.

Zinc has also been used as adjuvant therapy, maintenance therapy, or primary therapy in presymptomatic patients, owing to its unique ability to impair the gastrointestinal absorption of copper. Zinc acetate can be given (adults) at a dose of 25-50 mg of elemental zinc 3 times a day, and 25 mg 3 times a day in children over age 5 yr. Side effects are predominantly limited to gastric irritation but also include reduced leukocyte chemotaxis and elevations in serum lipase and/or amylase. Current guidelines recommend that all symptomatic patients with Wilson disease receive a chelating agent (penicillamine or trientine). Patients should be counseled not to suddenly stop these medications, since sudden discontinuation of therapy can precipitate fulminant Wilson disease. Zinc may have a role as a first-line therapy in patients with neurologic disease, but exclusive monotherapy with zinc in symptomatic liver disease is controversial and not recommended. Antioxidants (vitamin E and curcumin) and pharmacologic chaperones (4-phenylbutyrate and curcumin) may have a role as adjunctive treatment but more research is needed.

Prognosis

Untreated patients with Wilson disease can die of hepatic, neurologic, renal, or hematologic complications. Medical therapy is rarely effective in those presenting with acute liver failure. The prognosis for patients receiving prompt and continuous penicillamine is variable and depends on the time of initiation of and the individual response to chelation. Liver transplantation should be considered for patients with acute liver failure or decompensated cirrhosis due to Wilson disease. Liver transplantation for progressive neurologic disease remains controversial. Liver transplantation is curative, with a 5-yr survival rate of 85–90%. In asymptomatic siblings of affected patients, early institution of chelation or zinc therapy can prevent disease manifestations.

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384.3

Indian Childhood Cirrhosis

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Indian childhood cirrhosis (ICC) is a chronic liver disease of infants and young children unique to the Indian subcontinent, but variants of this syndrome have been described in other populations and have been named accordingly (Tyrolean or North American childhood cirrhosis). ICC-like disease has also been reported in the Middle East, West Africa, and Central America. Affected children present with jaundice, pruritus, lethargy, and hepatosplenomegaly with rapid progression to cirrhosis. Untreated severe ICC has a mortality of 40–50% within 4 wk. Histologically, ICC is characterized by hepatocyte necrosis, Mallory bodies, intralobular fibrosis, inflammation, and excess hepatic copper deposition. Treatment is supportive, especially in the late stages of disease. Copper chelation with D-penicillamine has been beneficial in open-label pre-icteric cases of ICC, however, it is unclear whether these cases were simply less severely affected and would have spontaneously improved without treatment.

The etiology of ICC has remained elusive. It was once believed that excess copper ingestion in the setting of a genetic susceptibility to copper toxicosis was the most likely cause. Epidemiologic data demonstrates that the copper toxicity theory is unlikely. The increased hepatic copper content, usually >700 µg/g dry weight, seen in ICC is only seen in the late stages of disease and is accompanied by even higher levels of zinc, a non-hepatotoxic metal. Furthermore, the copper-contaminated utensils used to feed babies and implicated in excess copper ingestion are found in only 10–15% of all cases. The current hypothesis implicates the postnatal use of local hepatotoxic therapeutic remedies, although the exact causative agent is unknown. North American ICC is due to mutations in the *UTP4* gene.

Over the last few decades, as the awareness of the disease has increased, the incidence of ICC has decreased to the point of being virtually eliminated in some areas of India. However, established and atypical cases are probably being missed because of lack of histologic confirmation and lack of awareness of the protean manifestations and natural history of this disease.

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384.4

Gestational Alloimmune Liver Disease (Neonatal Iron Storage

Disease)

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Neonatal iron storage disease (NISD), also known as **neonatal hemochromatosis,** is a rare form of fulminant liver disease that manifests in the first few days of life. This disease is unrelated to the familial forms of hereditary hemochromatosis that occur in adulthood. NISD has a high rate of recurrence in families, with approximately 80% probability that subsequent infants will be affected. NISD is postulated to be a gestational alloimmune disease and has also been classified as **gestational alloimmune liver disease** . During gestation, the maternal immune system becomes sensitized to an unknown fetal hepatocyte cell surface antigen. Maternal immunoglobulin G to this fetal antigen then crosses the placenta and induces hepatic injury via immune system activation. The defining feature of gestational alloimmune liver disease is complement-mediated hepatocyte injury, the evidence for which comes from detection of the C5b-9 complex by immunohistochemistry on liver tissue of affected infants. Additional evidence of a gestational insult is given by the fact that affected infants may be born prematurely or with intrauterine growth restriction. Several infants with NISD also have renal dysgenesis.

Excess non-transferrin-bound iron in gestational alloimmune liver disease may result from fetal liver injury that causes reduced synthesis of key iron regulatory and transport proteins. The pattern of extrahepatic siderosis appears to be determined by the normal capacity of various tissues to import non–transferrin-bound iron and not export cellular iron. It is thought that fetal liver injury is the primary event leading to the development of the neonatal hemochromatosis phenotype, providing further evidence that this is not a primary iron overload disease.

NISD is a rapidly fatal, progressive illness characterized by hepatomegaly, hypoglycemia, hypoprothrombinemia, hypoalbuminemia, hyperferritinemia, and hyperbilirubinemia. The coagulopathy is refractory to therapy with vitamin K. Liver biopsy demonstrates severe liver injury with acute and chronic inflammation, fibrosis, and cirrhosis; in some cases there are no surviving hepatocytes. The diagnosis is established in the neonate with severe liver injury and evidence of extrahepatic siderosis either by MRI indicating increased iron deposition in organs such as the pancreas or heart, or by increased iron staining in oral submucosal gland biopsy. The differential diagnosis includes other causes of neonatal hepatic failure such as citrin deficiency, herpes simplex virus (HSV) hepatitis, and familial hemophagocytic lymphohistiocytosis.

The prognosis for affected infants is generally poor. Intravenous immunoglobulin (IVIG) combined with double volume exchange transfusion has been shown to remove the injury-causing maternal IgG and improve outcomes in infants with NISD. Liver transplantation should also be an early consideration. Recurrences of NISD in subsequent pregnancies may be modified with IVIG administered to the mother once weekly from the 14th wk of gestation until delivery. The largest experience reports 48 women with previous infants with NISD who successfully delivered 52 babies after IVIG treatment. The majority of infants had biochemical evidence of liver disease with elevated serum α-fetoprotein and ferritin. All infants survived with medical therapy or no therapy.

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384.5

Miscellaneous Metabolic Diseases of the Liver

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α_1 -Antitrypsin Deficiency

α_1 -Antitrypsin deficiency is an autosomal recessive disorder caused by mutation in the *SERPINA1* gene. α_1 -antitrypsin, a protease inhibitor (Pi) synthesized by the liver, protects lung alveolar tissues from destruction by neutrophil elastase (see Chapter 421). α_1 -Antitrypsin is present in more than 20 different codominant alleles, only a few of which are associated with defective Pis. The most common allele of the Pi system is M, and the normal phenotype is PiMM. The Z allele predisposes to clinical deficiency; patients with liver disease are usually PiZZ homozygotes and have serum α_1 -antitrypsin levels <2 mg/mL (~10–20% of normal). The incidence of the PiZZ genotype in the white population is estimated at 1 in 2,000-4,000 live births. A small percentage of patients homozygous for deficiency of the major serum Pi α_1 -antitrypsin develop neonatal cholestasis or later-onset childhood cirrhosis. Compound heterozygotes PiZ-, PiSZ, PiZI are not a cause of liver disease alone but can act as modifier genes, increasing the risk of progression in other liver disease such as nonalcoholic fatty liver disease and hepatitis C. The null phenotype only causes lung disease, and results from either stop codons in the coding exon of the *SERPINA1* gene or complete deletion of *SERPINA1* coding exons leading to the absence of α_1 -antitrypsin protein.

Newly formed α_1 -antitrypsin polypeptide normally enters the endoplasmic reticulum, where it undergoes enzymatic modification and folding before transport to the plasma membrane, where it is excreted as a 55 kDa glycoprotein. In affected patients with PiZZ, the rate at which the α_1 -antitrypsin polypeptide folds is decreased, and this delay allows the formation of polymers that are retained in the endoplasmic reticulum. How the polymers cause liver damage is not completely elucidated, but research indicates that accumulation of abnormally folded protein leads to activation of stress and proinflammatory pathways in the endoplasmic reticulum and hepatocyte programmed cell death. In liver biopsies from patients, polymerized α_1 -antitrypsin peptides can be seen by electron microscopy and histochemically as periodic acid–Schiff-positive diastase-resistant globules primarily in periportal hepatocytes, but also in

Kupffer cells and biliary epithelial cells. The pattern of neonatal liver injury can be highly variable, and liver biopsies might demonstrate hepatocellular necrosis, inflammatory cell infiltration, bile duct proliferation, periportal fibrosis, or cirrhosis.

The course of liver disease is highly variable in patients with α_1 -antitrypsin deficiency. Prospective studies in Sweden have shown that only 10% of patients develop clinically significant liver disease by their fourth decade, indicating that other genetic traits or environmental factors likely influence the development of liver disease. Infants with liver disease are indistinguishable from other infants with “idiopathic” neonatal hepatitis, of whom they constitute approximately 5–10%. Jaundice, acholic stools, and hepatomegaly are present in the 1st wk of life, but the jaundice usually clears by 2-4 mo of age. Complete resolution, persistent liver disease, or the development of cirrhosis can follow. Older children can present with asymptomatic hepatomegaly or manifestations of chronic liver disease or cirrhosis with evidence of portal hypertension. Patients with cirrhosis due to alpha-1 antitrypsin deficiency are at high risk to develop hepatocellular carcinoma. Emphysema is not typically observed in children but an increased risk for developing asthma is reported. Cigarette smoking promotes development of lung disease, so parents should be counseled on smoking cessation and exposure reduction as part of their anticipatory guidance, and older children and adolescents should be advised not to smoke and given cessation counseling if they smoke.

Treatment is supportive, although research is ongoing to develop therapies for α_1 -antitrypsin deficiency-associated liver disease which stimulate intracellular degradation of the abnormally folded Z protein polymers. Liver transplantation is indicated for hepatocellular carcinoma or end-stage liver disease with portal hypertension, with survival rates of ~90%.

Citrin Deficiency

Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) presents in the first few months of life with manifestations that initially may be indistinguishable from other causes of neonatal cholestasis, especially biliary atresia. Patients may have jaundice, hepatomegaly, liver dysfunction with coagulopathy, fatty liver infiltration, and hyperammonemia with or without hypoglycemia. Presymptomatic patients may be identified from the newborn metabolic screen with hypergalactosemia, hypermethionemia, and hyperphenylalanemia, but not all patients are identified by newborn screening.

Mutations in the *SLC25A13* gene cause NICCD with an autosomal recessive pattern of inheritance. *SLC25A13* encodes citrin, a mitochondrial carrier protein (calcium binding aspartate-glutamate carrier) involved in the urea cycle, gluconeogenesis and glycolysis. Mutations are more common in those of East Asian descent. Affected infants have hypergalactosemia, elevated bile acids, vitamin K-dependent coagulopathy, and elevated levels of citrulline and methionine. Treatment is supportive in the form of providing fat-soluble vitamin supplementation and dietary feeding with a low-galactose/lactose formula enriched with medium chain triglycerides. More severely affected patients can develop liver failure requiring liver transplantation in the 1st yr of life.

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CHAPTER 385

Viral Hepatitis

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Viral hepatitis continues to be a major health problem in both developing and developed countries; there has been significant progress in efforts to recognize and to treat infected subjects. This disorder is caused by the 5 pathogenic hepatotropic viruses recognized to date: hepatitides A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV) viruses (Table 385.1). Many other viruses (and diseases) can cause hepatitis, usually as a component of a multisystem disease. These include herpes simplex virus, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, HIV, rubella, adenoviruses, enteroviruses, parvovirus B19, and arboviruses (Table 385.2).

Table 385.1

Features of the Hepatotropic Viruses

VIROLOGY	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Incubation (days)	15-19	60-180	14-160	21-42	21-63
Transmission					
• Parenteral	Rare	Yes	Yes	Yes	No
• Fecal–oral	Yes	No	No	No	Yes
• Sexual	No	Yes	Rare	Yes	No
• Perinatal	No	Yes	Uncommon (5–15%)	Yes	No
Chronic infection	No	Yes	Yes	Yes	No
Fulminant disease	Rare	Yes	Rare	Yes	Yes

HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus.

Table 385.2

Causes and Differential Diagnosis of Hepatitis in Children

INFECTIOUS

Hepatotropic viruses

- Hepatitis A virus (HAV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Hepatitis D virus (HDV)
- Hepatitis E virus (HEV)
- Hepatitis non–A-E viruses

Systemic infection that can include hepatitis

- Adenovirus
- Arbovirus
- Coxsackievirus
- Cytomegalovirus
- Enterovirus
- Epstein-Barr virus
- “Exotic” viruses (e.g., yellow fever)
- Herpes simplex virus
- HIV
- Paramyxovirus
- Rubella
- Varicella zoster

Other

NONVIRAL LIVER INFECTIONS

Abscess
Amebiasis
Bacterial sepsis
Brucellosis
Fitz-Hugh-Curtis syndrome
Histoplasmosis
Leptospirosis
Tuberculosis
Other

AUTOIMMUNE

Autoimmune hepatitis
Sclerosing cholangitis
Other (e.g., systemic lupus erythematosus, juvenile inflammatory arthritis)

METABOLIC

α_1 -Antitrypsin deficiency
Tyrosinemia
Wilson disease
Other

TOXIC

Iatrogenic or drug induced (e.g., acetaminophen)
Environmental (e.g., pesticides)

ANATOMIC

Choledochal cyst
Biliary atresia
Other

HEMODYNAMIC

Shock
Congestive heart failure
Budd-Chiari syndrome
Other

NONALCOHOLIC FATTY LIVER DISEASE

Idiopathic

Reye syndrome
Other

From Wyllie R, Hyams JS, editors: *Pediatric gastrointestinal and liver disease* , ed 3, Philadelphia, 2006, WB Saunders.

The hepatotropic viruses are a heterogeneous group of infectious agents that cause similar acute clinical illness. In most pediatric patients, the acute phase causes no or mild clinical disease. Morbidity is related to rare cases of **acute liver failure (ALF)** in susceptible patients, or to the development of a chronic disease state and attendant complications that several of these viruses (hepatitides B, C, and D) commonly cause.

Issues Common to All Forms of Viral Hepatitis

Differential Diagnosis

Often what brings the patient with hepatitis to medical attention is clinical icterus, with yellow skin and/or mucous membranes. The liver is usually enlarged and tender to palpation and percussion. Splenomegaly and lymphadenopathy may be present. Extrahepatic symptoms (rashes, arthritis) are more commonly seen in HBV and HCV infections. Clinical signs of bleeding, altered sensorium, or hyperreflexia should be carefully sought, because they mark the onset of encephalopathy and ALF.

The differential diagnosis varies with age of presentation. In the newborn period, infection is a common cause of conjugated hyperbilirubinemia; the infectious cause is either a bacterial agent (e.g., *Escherichia coli* , Listeria, syphilis) or a nonhepatotropic virus (e.g., enteroviruses, cytomegalovirus, and herpes simplex virus, which may also cause a nonicteric severe hepatitis). Metabolic diseases (α_1 -antitrypsin deficiency, cystic fibrosis, tyrosinemia), anatomic causes (biliary atresia, choledochal cysts), and inherited forms of intrahepatic cholestasis should always be excluded.

In later childhood, extrahepatic obstruction (gallstones, primary sclerosing cholangitis, pancreatic pathology), inflammatory conditions (autoimmune hepatitis, juvenile inflammatory arthritis, Kawasaki disease), immune dysregulation (hemophagocytic lymphohistiocytosis), infiltrative disorders (malignancies), toxins and medications, metabolic disorders (Wilson disease, cystic fibrosis), and infection (Epstein-Barr virus, varicella, malaria, leptospirosis, syphilis) should be ruled out.

Pathogenesis

The acute response of the liver to hepatotropic viruses involves a direct cytopathic and/or an immune-mediated injury. The entire liver is involved. Necrosis is usually most marked in the centrilobular areas. An acute mixed inflammatory infiltrate predominates in the portal areas but also affects the lobules. The lobular architecture remains intact, although balloon degeneration and necrosis of single or groups of parenchymal cells commonly occur. Fatty change is rare except with HCV infection. Bile duct proliferation, but not bile duct damage, is common. Diffuse Kupffer cell hyperplasia is noticeable in the sinusoids. Neonates often respond to hepatic injury by forming *giant cells* . In fulminant hepatitis, parenchymal collapse occurs on the described background. With recovery, the liver morphology returns to normal within 3 mo of the acute infection. If chronic hepatitis develops, the inflammatory infiltrate settles in the periportal areas and often leads to progressive scarring. Both of these hallmarks of chronic hepatitis are seen in cases of HBV and HCV.

Common Biochemical Profiles in the Acute Infectious Phase

Acute liver injury caused by these viruses manifests in 3 main functional liver biochemical profiles. These serve as an important guide to diagnosis, supportive care, and monitoring in the acute phase of the infection for all viruses. As a reflection of *cytopathic injury* to the hepatocytes, there is a rise in serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The magnitude of enzyme elevation does not correlate with the extent of hepatocellular necrosis and has little prognostic value. There is usually slow improvement over several weeks, but AST and ALT levels *lag* the serum bilirubin level, which tends to normalize first. Rapidly falling aminotransferase levels can predict a poor outcome, particularly if their decline occurs in conjunction with a rising bilirubin level and a prolonged prothrombin time (PT); this combination of findings usually indicates that massive hepatic injury has occurred.

Cholestasis , defined by elevated serum conjugated bilirubin levels, results from abnormal bile flow at the canalicular and cellular level because of hepatocyte damage and inflammatory mediators. Elevation of serum alkaline phosphatase, 5′-nucleotidase, and γ-glutamyl transpeptidase levels, mark cholestasis. Absence of cholestatic markers does not rule out progression to chronicity in HCV or HBV infections.

Altered synthetic function is the most important marker of liver injury. Synthetic dysfunction is reflected by a combination of abnormal protein synthesis (prolonged PT, high international normalized ratio [INR], low serum albumin levels), metabolic disturbances (hypoglycemia, lactic acidosis, hyperammonemia), poor clearance of medications dependent on liver function, and altered sensorium with increased deep tendon reflexes (hepatic encephalopathy). Monitoring of synthetic function should be the main focus in clinical follow-up to define the severity of the disease. In the acute phase, the degree of liver synthetic dysfunction guides treatment and helps to establish intervention criteria. *Abnormal liver synthetic function is a marker of liver failure and is an indication for prompt referral to a transplant center.* Serial assessment is necessary because liver dysfunction does not progress linearly.

Hepatitis A

Hepatitis A is the most prevalent form; this virus is also responsible for most forms of acute and benign hepatitis. Although fulminant hepatic failure due to HAV can occur, it is rare (<1% of cases in the United States) and occurs more often in adults than in children and in hyperendemic communities.

Etiology

HAV is an RNA virus, a member of the picornavirus family. It is heat stable and has limited host range—namely, the human and other primates.

Epidemiology

HAV infection occurs throughout the world but is most prevalent in developing countries. In the United States, 30–40% of the adult population has evidence of previous HAV infection. Hepatitis A is thought to account for approximately 50% of all clinically apparent acute viral hepatitis in the United States. As a result of aggressive implementation of childhood vaccination programs, the prevalence of symptomatic HAV cases worldwide has declined significantly.

However, outbreaks in developing countries and in daycare centers (where the spread of HAV from young, nonicteric, infected children can occur easily) as well as multiple foodborne and waterborne outbreaks have justified the implementation of intensified universal vaccination programs.

HAV is highly contagious. Transmission is almost always by person-to-person contact through the fecal–oral route. Perinatal transmission occurs rarely. No other form of transmission is recognized. HAV infection during pregnancy or at the time of delivery does not appear to result in increased complications of pregnancy or clinical disease in the newborn. In the United States, increased risk of infection is found in contacts with infected persons, childcare centers, and household contacts. Infection is also associated with contact with contaminated food or water and after travel to endemic areas. Common source foodborne and waterborne outbreaks continue to occur, including several caused by contaminated shellfish, frozen berries, and raw vegetables; no known source is found in about half of the cases.

The mean incubation period for HAV is approximately 3 wk. Fecal excretion of the virus starts late in the incubation period, reaches its peak just before the onset of symptoms, and resolves by 2 wk after the onset of jaundice in older subjects. The duration of fecal viral excretion is prolonged in infants. The patient is, therefore, contagious before clinical symptoms are apparent and remains so until viral shedding ceases.

Clinical Manifestations

HAV is responsible for acute hepatitis only. Often, this is an *anicteric* illness, with clinical symptoms indistinguishable from other forms of viral gastroenteritis, particularly in young children.

The illness is more likely to be symptomatic in older adolescents or adults, in patients with underlying liver disorders, and in those who are immunocompromised. It is characteristically an acute febrile illness with an abrupt onset of anorexia, nausea, malaise, vomiting, and jaundice. The typical duration of illness is 7-14 days (Fig. 385.1).

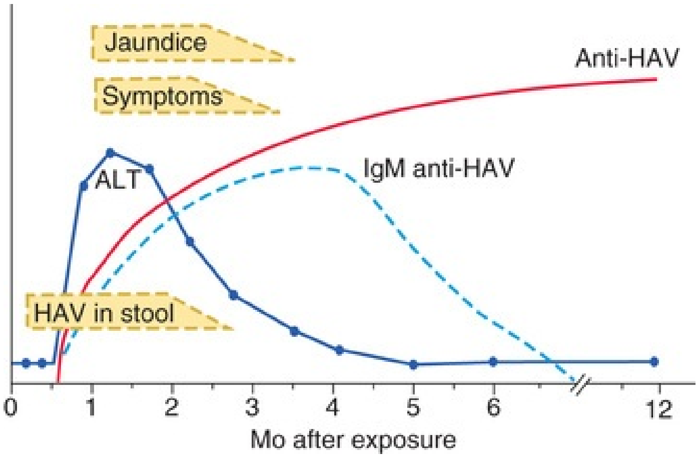

FIG. 385.1 The serologic course of acute hepatitis A. ALT, alanine aminotransferase; HAV, hepatitis A virus; IgM, immunoglobulin class M. (From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, WB Saunders, p 913.)

Other organ systems can be affected during acute HAV infection. Regional lymph nodes and the spleen may be enlarged. The bone marrow may be moderately hypoplastic, and aplastic anemia has been reported. Tissue in the small intestine might show changes in villous structure, and ulceration of the gastrointestinal tract can occur, especially in fatal cases. Acute pancreatitis and myocarditis have been reported, though rarely, and nephritis, arthritis, leukocytoclastic vasculitis, and cryoglobulinemia can result from circulating immune complexes.

Diagnosis

Acute HAV infection is diagnosed by detecting antibodies to HAV, specifically, anti-HAV (immunoglobulin [Ig] M) by radioimmunoassay or, rarely, by identifying viral particles in stool. A viral polymerase chain reaction (PCR) assay is available for research use (Table 385.3). Anti-HAV is detectable when the symptoms are clinically apparent, and it remains positive for 4-6 mo after the acute infection. A neutralizing anti-HAV (IgG) is usually detected within 8 wk of symptom onset and is measured as part of a total anti-HAV in the serum. Anti-HAV (IgG) confers long-term protection. Rises in serum levels of ALT, AST, bilirubin, alkaline phosphatase, 5′-nucleotidase, and γ-glutamyl transpeptidase are almost universally found and do not help to differentiate the cause of hepatitis.

Table 385.3

Diagnostic Blood Tests: Serology and Viral Polymerase Chain Reaction

HAV	HBV	HCV	HDV	HEV
ACUTE/ACTIVE INFECTION				
Anti-HAV IgM (+)	Anti-HBc IgM (+)	Anti-HCV (+)	Anti-HDV IgM (+)	Anti-HEV IgM (+)
Blood PCR positive[*]	HBsAg (+) Anti-HBs (−) HBV DNA (+) (PCR)	HCV RNA (+) (PCR)	Blood PCR positive HBsAg (+) Anti-HBs (−)	Blood PCR positive[*]
PAST INFECTION (RECOVERED)				
Anti-HAV IgG(+)	Anti-HBs (+) Anti-HBc IgG (+)[†]	Anti-HCV (+) Blood PCR (−)	Anti-HDV IgG (+) Blood PCR (−)	Anti-HEV IgG (+) Blood PCR (−)
CHRONIC INFECTION				
N/A	Anti-HBc IgG (+) HBsAg (+) Anti-HBs (−) PCR (+) or (−)	Anti-HCV (+) Blood PCR (+)	Anti-HDV IgG (+) Blood PCR (−) HBsAg (+) Anti-HBs (−)	N/A
VACCINE RESPONSE				
Anti-HAV IgG (+)	Anti-HBs (+) Anti-HBc (−)	N/A	N/A	N/A

[*] Research tool.

[†] Still poses a risk for reactivation.

HAV, hepatitis A virus; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; PCR, polymerase chain reaction.

Complications

Although most patients achieve full recovery, distinct complications can occur. *ALF* from HAV infection is an infrequent complication of HAV. Those at risk for this complication are adolescents and adults, but also immunocompromised patients or those with underlying liver disorders. The height of HAV viremia may be linked to the severity of hepatitis. In the United States, HAV represents <0.5% of pediatric-age ALF; HAV is responsible for up to 3% mortality in the adult population with ALF. In endemic areas of the world, HAV constitutes up to 40% of all cases of pediatric ALF. HAV can also progress to a *prolonged cholestatic syndrome* that waxes and wanes over several months. Pruritus and fat malabsorption are problematic and require symptomatic support with antipruritic medications and fat-soluble vitamin supplementation. This syndrome occurs in the absence of any liver synthetic dysfunction and resolves without sequelae.

Treatment

There is no specific treatment for hepatitis A. Supportive treatment consists of intravenous hydration as needed, and antipruritic agents and fat-soluble vitamins for the prolonged cholestatic form of disease. Serial monitoring for signs of ALF is prudent and, if ALF is diagnosed, a prompt referral to a transplantation center can be lifesaving.

Prevention

Patients infected with HAV are contagious for 2 wk before and approximately 7 days after the onset of jaundice and should be excluded from school, childcare, or work during this period. Careful hand-washing is necessary, particularly after changing diapers and before preparing or serving food. In hospital settings, contact and standard precautions are recommended for 1 wk after onset of symptoms.

Immunoglobulin

Indications for intramuscular administration of Ig include preexposure and postexposure prophylaxis (Table 385.4). Ig is recommended for *preexposure* prophylaxis for susceptible travelers to countries where HAV is endemic, and it provides effective protection for up to 2 mo. *HAV vaccine* given any time before travel is preferred for *preexposure* prophylaxis in healthy persons, but *Ig* ensures an appropriate prophylaxis in children *younger than 12 mo* old, patients allergic to a vaccine component, or those who elect not to receive the vaccine. If travel is planned in <2 wk, older patients, immunocompromised hosts, and those with chronic liver disease or other medical conditions should receive *both* Ig and the HAV vaccine.

Table 385.4

Indications and Updated Dosage Recommendations for GamaSTAN S/D Human Immune Globulin for Preexposure and Postexposure Prophylaxis Against Hepatitis A Infection

INDICATION	UPDATED DOSAGE RECOMMENDATION
Preexposure prophylaxis	

Up to 1 mo of travel	0.1 mL/kg
Up to 2 mo of travel	0.2 mL/kg
2 mo of travel or longer	0.2 mL/kg (repeat every 2 mo)
Postexposure prophylaxis	0.1 mL/kg

From Nelson NP: Updated dosing instruction for immune globulin (human) gamaSTAN S/D for hepatitis A virus prophylaxis, *MMWR* 66(36):959–960, 2017, Table, p. 959.

Ig prophylaxis in *postexposure* situations should be used as soon as possible (it is not effective if administered more than 2 wk after exposure). It is exclusively used for children younger than 12 mo old, immunocompromised hosts, those with chronic liver disease or in whom vaccine is contraindicated. Ig is preferred in patients older than 40 yr of age, with HAV vaccine preferred in healthy persons 12 mo to 40 yr old. An alternative approach is to immunize previously unvaccinated patients who are 12 *mo* old *or older* with the age-appropriate vaccine dosage as soon as possible. Ig is not routinely recommended for sporadic nonhousehold exposure (e.g., protection of hospital personnel or schoolmates). The vaccine has several advantages over Ig, including long-term protection, availability, and ease of administration, with cost similar to, or less than, that of Ig.

Vaccine

The availability of 2 inactivated, highly immunogenic, and safe HAV vaccines has had a major impact on the prevention of HAV infection. Both vaccines are approved for children older than 12 mo. They are administered intramuscularly in a 2-dose schedule, with the second dose given 6-12 mo after the first dose. Seroconversion rates in children exceed 90% after an initial dose and approach 100% after the second dose; protective antibody titer persists for longer than 10 yr in most patients. The immune response in immunocompromised persons, older patients, and those with chronic illnesses may be suboptimal; in those patients, combining the vaccine with Ig for pre- and postexposure prophylaxis is indicated. HAV vaccine may be administered simultaneously with other vaccines. A combination HAV and HBV vaccine is approved in adults older than age 18 yr. For healthy persons at least 12 mo old, vaccine is preferable to Ig for preexposure and postexposure prophylaxis (see Table 385.3).

In the United States and some other countries, universal vaccination is now recommended for all children older than 12 mo. Nevertheless, studies show <50% of U.S. adolescents have received even a single dose of the vaccine, and <30% have received the complete vaccine series. The vaccine is effective in curbing outbreaks of HAV because of rapid seroconversion and the long incubation period of the disease.

Prognosis

The prognosis for the patient with HAV is excellent, with no long-term sequelae. The only feared complication is ALF. Nevertheless, HAV infection remains a major cause of morbidity; it has a high socioeconomic impact during epidemics and in endemic areas.

Hepatitis B

Etiology

HBV, a member of the Hepadnaviridae family, has a circular, partially double-stranded DNA genome composed of approximately 3,200 nucleotides. Four constitutive genes have been identified: the S (surface), C (core), X, and P (polymer) genes. The surface of the virus includes particles, designated as the hepatitis B surface antigen (HBsAg), which consist of 22 nm diameter spherical particles and 22 nm wide tubular particles with a variable length of up to 200 nm. The inner portion of the virion contains the hepatitis B core antigen (HBcAg), the nucleocapsid that encodes the viral DNA, and a nonstructural antigen called the hepatitis B e antigen (HBeAg), a nonparticulate soluble antigen derived from HBcAg by proteolytic self-cleavage. HBeAg serves as a marker of active viral replication and usually correlates with the HBV DNA levels. Replication of HBV occurs predominantly in the liver but also occurs in the lymphocytes, spleen, kidney, and pancreas.

Epidemiology

HBV has been detected worldwide, with an estimated 400 million persons chronically infected. The areas of highest prevalence of HBV infection are sub-Saharan Africa, China, parts of the Middle East, the Amazon basin, and the Pacific Islands. In the United States, the native population in Alaska had the highest prevalence rate before the implementation of their universal vaccination programs. An estimated 1.25 million persons in the United States are chronic HBV carriers, with approximately 300,000 new cases of HBV occurring each year, the highest incidence being among adults 20-39 yr of age. One in 4 chronic

HBV carriers will develop serious sequelae in their lifetime. The number of new cases in children reported each year is thought to be low but is difficult to estimate because many infections in children are asymptomatic. In the United States, since 1982 when the first vaccine for HBV was introduced, the overall incidence of HBV infection has been reduced by more than half. Since the implementation of universal vaccination programs in Taiwan and the United States, substantial progress has been made toward eliminating HBV infection in children in these countries. In fact, in Alaska, where HBV neared epidemic proportions, universal newborn vaccination with mass screening and immunization of susceptible Alaska Natives virtually eliminated symptomatic HBV and secondary hepatocellular carcinoma (HCC).

HBV is present in high concentrations in blood, serum, and serous exudates and in moderate concentrations in saliva, vaginal fluid, and semen. Efficient transmission occurs through blood exposure and sexual contact. Risk factors for HBV infection in children and adolescents include acquisition by intravenous drugs or blood products, contaminated needles used for acupuncture or tattoos, sexual contact, institutional care, and intimate contact with carriers. No risk factors are identified in approximately 40% of cases. HBV is not thought to be transmitted via indirect exposure, such as sharing toys. After infection, the incubation period ranges from 45-160 days, with a mean of approximately 120 days. In children, the most important risk factor for acquisition of HBV remains perinatal exposure to an HBsAg-positive mother. The risk of transmission is greatest if the mother is HBeAg-positive; up to 90% of these infants become chronically infected if untreated. Additional risk factors include high maternal HBV viral load (HBeAg/HBV DNA titers) and delivery of a prior infant who developed HBV despite appropriate prophylaxis. In most perinatal cases, serologic markers of infection and antigenemia appear 1-3 mo after birth, suggesting that transmission occurred at the time of delivery. Virus contained in amniotic fluid or in maternal feces or blood may be the source. Immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and the HBV immunization, given within 12 hr of delivery, is highly effective in preventing infection and protects >95% of neonates born to HBsAg-positive mothers. Of the 22,000 infants born each year to HBsAg-positive mothers in the United States, >98% receive immunoprophylaxis and are thus protected. Infants who fail to receive the complete vaccination series (e.g., homeless children, international adoptees, and children born outside the United States) have the highest incidence of developing chronic HBV. These and all infants born to HBsAg-positive mothers should have follow-up HBsAg and anti-HBs tested to determine appropriate follow-up. The mothers (HBeAg positive) of these infants who develop chronic HBV infection should receive antiviral therapy during the third trimester for subsequent pregnancies.

HBsAg is inconsistently recovered in human milk of infected mothers. Breastfeeding of nonimmunized infants by infected mothers does not seem to confer a greater risk of hepatitis than does formula feeding.

The risk of developing chronic HBV infection, defined as being positive for HBsAg for longer than 6 mo, is inversely related to age of acquisition. In the United States, although <10% of infections occur in children, these infections account for 20–30% of all chronic cases. This risk of chronic infection is 90% in children younger than 1 yr; the risk is 30% for those 1-5 yr of age and 2% for adults. Chronic HBV infection is associated with the development of chronic liver disease and HCC. The carcinoma risk is independent of the presence of cirrhosis and was the most prevalent cancer-related death in young adults in Asia where HBV was endemic.

HBV has 10 genotypes (A-J). A is pandemic, B and C are prevalent in Asia, D is seen in Southern Europe, E in Africa, F in the United States, G in the United States and France, H in Central America, I in southeast Asia, and J in Japan. Genetic variants have become resistant to some antiviral agents.

Pathogenesis

The acute response of the liver to HBV is similar to that of other viruses. Persistence of histologic changes in patients with hepatitis B indicates development of chronic liver disease. HBV, unlike the other hepatotropic viruses, is a predominantly noncytopathogenic virus that causes injury mostly by immune-mediated processes. The severity of hepatocyte injury reflects the degree of the immune response, with the most complete immune response being associated with the greatest likelihood of viral clearance but also the most severe injury to hepatocytes. The first step in the process of acute hepatitis is infection of hepatocytes by HBV, resulting in expression of viral antigens on the cell surface. The most important of these viral antigens may be the nucleocapsid antigens—HBcAg and HBeAg. These antigens, in combination with class I major histocompatibility proteins, make the cell a target for cytotoxic T-cell lysis.

The mechanism for development of chronic hepatitis B is less well understood. To permit hepatocytes to continue to be infected, the core protein or major histocompatibility class I protein might not be recognized, the cytotoxic lymphocytes might not be activated, or some other, yet unknown mechanism might interfere with destruction of hepatocytes. This tolerance phenomenon predominates in the perinatally acquired cases, resulting in a high incidence of persistent HBV infection in children with no or little inflammation in the liver, normal liver enzymes, and markedly elevated HBV viral load. Although end-stage liver disease rarely develops in those patients, the inherent HCC risk is high, possibly related, in part, to uncontrolled viral replication cycles.

ALF has been seen in infants of chronic carrier mothers who have anti-HBe or are infected with a precore-mutant strain. This fact led to the postulate that HBeAg exposure in utero in infants of chronic carriers likely induces tolerance to the virus once infection occurs postnatally. In the absence of this tolerance, the liver is massively attacked by T cells and the patient presents with ALF.

Immune-mediated mechanisms are also involved in the extrahepatic conditions that can be associated with HBV infections. Circulating immune complexes containing HBsAg can result in polyarteritis nodosa, membranous or membranoproliferative glomerulonephritis, polymyalgia rheumatica, leukocytoclastic vasculitis, and Guillain-Barré syndrome.

Clinical Manifestations

Many acute cases of HBV infection in children are asymptomatic, as evidenced by the high carriage rate of serum markers in persons who have no history of acute hepatitis (Table 385.5). The usual acute symptomatic episode is similar to that of HAV and HCV infections but may be more severe and is more likely to include involvement of skin and joints (Fig. 385.2).

Table 385.5

Typical Interpretation of Test Results for Hepatitis B Virus Infection

HBsAg	TOTAL ANTI-HBc	IgM ANTI-HBc	ANTI-HBs	HBV DNA	INTERPRETATION
−	−	−	−	−	Never infected
+	−	−	−	+ or −	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	−	+	Acute infection

−	+	+	+ or −	+ or −	Acute resolving infection
−	+	−	+	−	Recovered from past infection and immune
+	+	−	−	+	Chronic infection
−	+	−	−	+ or −	False-positive (i.e., susceptible); past infection; “low-level” chronic infection; or passive transfer of anti-HBc to infant born to HBsAg-positive mother
−	−	−	+	−	Immune if anti-HBs concentration is ≥10 mIU/mL after vaccine series completion; passive transfer after hepatitis B immune globulin administration

−, negative; +, positive; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; IgM, immunoglobulin class M.

From Schillie S, Vellozzi C, Reingold A, et al: Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices, *MMWR* 67(1):1–29, 2018, Table 1, p. 7.

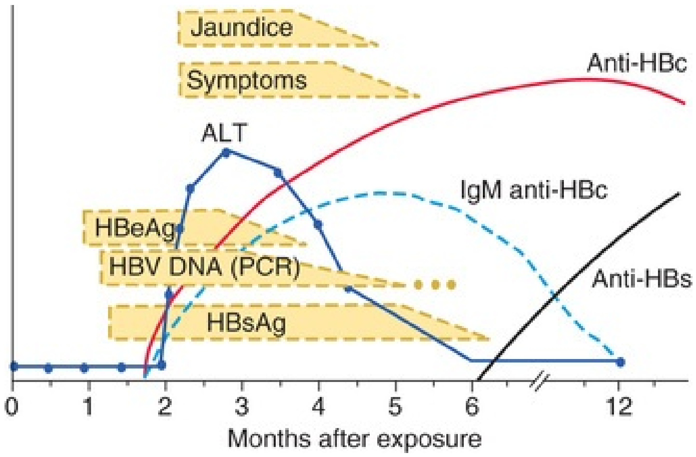

FIG. 385.2 **The serologic course of acute hepatitis B. ALT, alanine aminotransferase; HBc, hepatitis B core; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; IgM, immunoglobulin class M; PCR, polymerase chain reaction. (From Goldman L, Ausiello D: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, WB Saunders, p 914.)**

The first biochemical evidence of HBV infection is elevation of serum ALT levels, which begin to rise just before development of fatigue, anorexia, and malaise, at approximately 6-7 wk after exposure. The illness is preceded, in a few children, by a serum sickness–like prodrome marked by arthralgia or skin lesions, including urticarial, purpuric, macular, or maculopapular rashes. Papular acrodermatitis, the Gianotti-Crosti syndrome, can also occur. Other extrahepatic conditions associated with HBV infections in children include polyarteritis nodosa, glomerulonephritis, and aplastic anemia. Jaundice is present in approximately 25% of acutely infected patients and usually begins approximately 8 wk after exposure and lasts approximately 4 wk.

In the usual course of resolving HBV infection, symptoms persist for 6-8 wk. The percentage of children in whom clinical evidence of hepatitis develops is higher for HBV than for HAV, and the rate of ALF is also greater. Most patients do recover, but the *chronic carrier state* complicates up to 10% of cases acquired in adulthood. The rate of development of chronic infection depends largely on the mode and age of acquisition and occurs in up to 90% of perinatally-infected cases. Cirrhosis and HCC are only seen with chronic infection. Chronic HBV infection has 3 identified phases: immune tolerant, immune active, and inactive. Most children fall in the *immune-tolerant* phase, against which no effective therapy has been developed. Most treatments target the *immune active* phase of the disease, characterized by active inflammation, elevated ALT/AST levels, and progressive fibrosis. Spontaneous HBeAg seroconversion, defined as the development of anti-HBe and loss of HBeAg, occurs in the immune-tolerant phase, albeit at low rates of 4–5% per year. It is more common in childhood-acquired HBV rather than in perinatally transmitted infections. Seroconversion can occur over many years, during which time significant damage to the liver may take place. There are no large studies that accurately assess the lifetime risks and morbidities of children with chronic HBV infection, making decisions regarding the rationale, efficacy, and timing of still less-than-ideal treatments difficult. Reactivation of chronic infection has been reported in immunosuppressed children treated with chemotherapy, biologic immunomodulators such as infliximab, or T-cell depleting agents, leading to an increased risk of ALF or to rapidly progressing fibrotic liver disease (Table 385.6).

Table 385.6

Causes of Hepatitis Flares in Patients With Chronic Hepatitis B

CAUSE OF FLARE	COMMENT
Spontaneous	Factors that precipitate viral replication are unclear
Immunosuppressive therapy	Flares are often observed during withdrawal of the agent; preemptive antiviral therapy is required
Antiviral therapy for HBV	
Interferon	Flares are often observed during the second to third month of therapy in 30% of patients; may herald virologic response
Nucleoside analog	

During treatment	Flares are no more common than with placebo
Drug-resistant HBV	Severe consequences can occur in patients with advanced liver disease
On withdrawal	Flares are caused by the rapid re-emergence of wild-type HBV; severe consequences can occur in patients with advanced liver disease
HIV treatment	Flares can occur as a result of the direct toxicity of HAART or with immune reconstitution; HBV increases the risk of antiretroviral drug hepatotoxicity
Genotypic variation	
Precore and core promoter mutants	Fluctuations in serum alanine aminotransferase levels are common with precore mutants
Superinfection with other hepatitis viruses	May be associated with suppression of HBV replication

HAART, Highly active antiretroviral therapy; HBV, hepatitis B virus.

From Wells JT, Perillo R: Hepatitis B. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , 10/e, Philadelphia, 2016, Elsevier, Table 79.1.

Diagnosis

The serologic profile of HBV infection is more complex than for HAV infection and differs depending on whether the disease is acute or chronic (Fig. 385.3 , see Table 385.5). Several antigens and antibodies are used to confirm the diagnosis of acute HBV infection (see Table 385.3). Routine screening for HBV infection requires assay of multiple serologic markers (HBsAg, anti-HBc, anti-HBs). HBsAg is an early serologic marker of infection and is found in almost all infected persons; its rise closely coincides with the onset of symptoms. Persistence of HBsAg beyond 6 mo defines the chronic infection state. During recovery from acute infection, because HBsAg levels fall before symptoms wane, IgM antibody to HBcAg (anti-HBc IgM) might be the only marker of acute infection. Anti-HBc IgM rises early after the infection and remains positive for many months before being replaced by anti-HBc IgG, which then persists for years. Anti-HBs marks serologic recovery and protection. Only anti-HBs is present in persons immunized with hepatitis B vaccine, whereas both anti-HBs and anti-HBc are detected in persons with resolved infection. HBeAg is present in active acute or chronic infection and is a marker of infectivity. The development of anti-HBe, termed seroconversion, marks improvement and is a goal of therapy in chronically infected patients. HBV DNA can be detected in the serum of acutely infected patients and chronic carriers. High DNA titers are seen in patients with HBeAg, and they typically fall once anti-HBe develops.

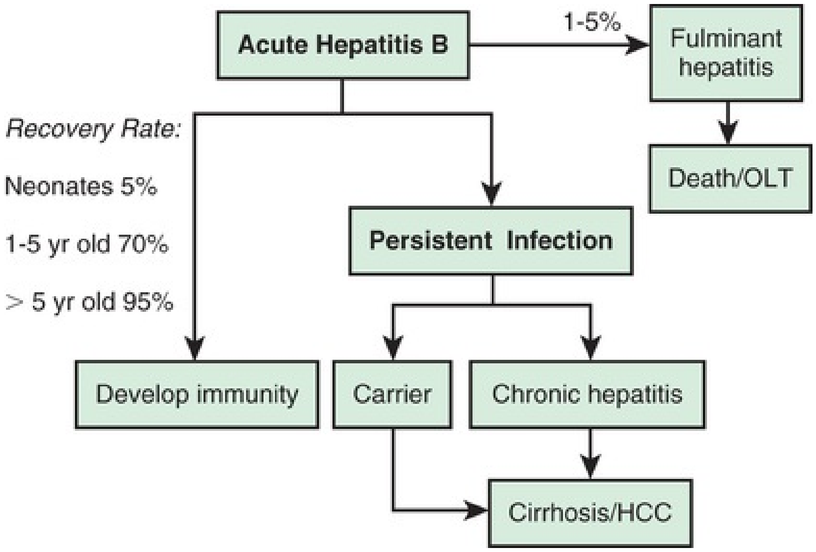
Acute Hepatitis B
1-5%
Fulminant hepatitis
Death/OLT
Recovery Rate:
Neonates 5%
1-5 yr old 70%
> 5 yr old 95%
Persistent Infection
Develop immunity
Carrier
Chronic hepatitis
Cirrhosis/HCC

FIG. 385.3 Natural history of hepatitis B virus infection. HCC, hepatocellular carcinoma; OLT, orthotopic liver transplant.

Complications

ALF with coagulopathy, encephalopathy, and cerebral edema occurs more commonly with HBV than the other hepatotropic viruses. The risk of ALF is further increased when there is coinfection or superinfection with HDV or in an immunosuppressed host. Mortality from ALF is >30%, and liver transplantation is the only effective intervention. Supportive care aimed at sustaining patients and early referral to a liver transplantation center can be lifesaving. As mentioned, HBV infection can also result in chronic hepatitis, which can lead to cirrhosis, end-stage liver disease complications, and HCC. Membranous glomerulonephritis with deposition of complement and HBeAg in glomerular capillaries is a rare complication of HBV infection.

Treatment

Treatment of *acute* HBV infection is largely supportive. Close monitoring for liver failure and extrahepatic morbidities is key. Treatment of *chronic* HBV infection is in evolution; no 1 drug currently achieves consistent, complete eradication of the virus. The natural history of chronic HBV infection in children is complex, and there is a lack of reliable long-term outcome data on which to base treatment recommendations. Treatment of chronic HBV infection in children should be individualized and done under the care of a pediatric hepatologist experienced in treating the disease.

The goal of treatment is to reduce viral replication defined by having undetectable HBV DNA in the serum and development of anti-HBe, termed seroconversion. The development of anti-HBe transforms the disease into an inactive form, thereby decreasing infectivity, active liver injury and inflammation, fibrosis progression, and the risk of HCC. Treatment is only indicated for patients in the immune-active form of the disease, as evidenced by elevated ALT and/or AST, who have fibrosis on liver biopsy, putting the child at higher risk for cirrhosis during childhood.

Treatment Strategies

Interferon-*α2b* (IFN-α2b) has immunomodulatory and antiviral effects (Table 385.7). It has been used in children, with long-term viral response rates similar to the 25% rate reported in adults. Interferon (IFN) use is limited by its subcutaneous administration, treatment duration of 24 wk, and side effects (flu-like symptoms, marrow suppression, depression, retinal changes, autoimmune disorders). IFN is further contraindicated in decompensated cirrhosis. One advantage of IFN, compared to other treatments, is that viral resistance does not develop with its use.

Table 385.7

Positive and Negative Factors to Consider in the Decision to Treat Hepatitis B With Peginterferon or a Nucleoside or Nucleotide Analog

AGENT	POSITIVE FACTORS	NEGATIVE FACTORS
Peginterferon	Finite duration of treatment	Inconvenience of subcutaneous injection
	Durable off-treatment response	Frequent side effects
	More rapid disappearance of HBsAg Immunostimulatory as well as intrinsically antiviral	Clearance of HBsAg in a small minority of patients depending on genotype
		Potential risk of ALT flares in patients with advanced liver fibrosis
	Better tolerability compared with its use in hepatitis C	Relative contraindication in patients older than age 60 or those with comorbid illnesses
Nucleoside or nucleotide analog	Negligible side effects	Slight risk of nephropathy with nucleotide analogs (adefovir, tenofovir)
	Convenience; ready acceptance by patients	Drug expense can be considerable during long-term use
	Potent inhibition of virus replication Reduced drug resistance with the third-generation nucleoside analogs	Long or indefinite treatment needed for both HBeAg-positive and HBeAg-negative patients
		Access issues in developing nations

HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

From Wells JT, Perillo R: Hepatitis B. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , 10/e, Philadelphia, 2016, Elsevier, Table 79.4.

Lamivudine is an oral synthetic nucleoside analog that inhibits the viral enzyme reverse transcriptase. In children older than 2 yr of age, its use for 52 wk resulted in HBeAg clearance in 34% of patients with an ALT >2 times normal; 88% remained in remission at 1 yr. It has a good safety profile. Lamivudine has to be used for ≥ 6 mo after viral clearance, and the emergence of a mutant viral strain (YMDD) poses a barrier to its long-term use. Combination therapy in children using IFN and lamivudine did not seem to improve the rates of response in most series.

Adefovir (a purine analog that inhibits viral replication) is approved for use in children older than 12 yr of age, in whom a prospective 1-yr study showed 23% seroconversion. No viral resistance was noted in that study but has been reported in adults.

Entecavir (a nucleoside analog that inhibits replication) is currently approved for use in children older than 2 yr of age. Prospective data has shown a 21% seroconversion rate in adults with minimal resistance developing. Patients in whom resistance to lamivudine developed have an increased risk of resistance developing to entecavir.

Tenofovir (a nucleotide analog that inhibits viral replication) is also approved for use in children older than 12 yr of age. Prospective data have shown a 21% seroconversion rate with a very low rate of resistance developing. Patients with lamivudine-resistant mutations do not appear to have an increased rate of resistance. Concern exists over long-term use and bone mineral density.

Peginterferon-α_2 has the same mechanism of action as IFN but is given once weekly. This formulation has not been approved in the United States but is recommended for the treatment of chronic HBV in other countries. Patients most likely to respond to currently available drugs have low serum HBV DNA titers, are HBeAg-positive, have active hepatic inflammation (ALT greater than twice the upper limit of normal for at least 6 mo), and recently acquired disease.

Immune tolerant patients—those with normal ALT and AST, who are HBeAg-positive with elevated viral load—are currently not considered for treatment, although the emergence of new treatment paradigms is promising for this large, yet hard-to-treat, subgroup of patients.

Prevention

The most effective prevention strategies have resulted from the screening of pregnant mothers and the use of HBIG and hepatitis B vaccine in infants (Tables 385.8 to 385.11). In HBsAg-positive and HBeAg-positive mothers, a 10% risk of chronic HBV infection exists compared to 1% in HBeAg-negative mothers. This knowledge offers screening strategies that may affect both mother and infant by using antiviral medications during the third trimester. Guidelines suggest that mothers with an HBV DNA viral load >200,000 IU/mL receive an antiviral such as telbivudine, lamivudine, or tenofovir during the third trimester, especially if they had a previous child who developed chronic HBV after receiving HBIG and the hepatitis B vaccine. This practice has proven safe with normal growth and development in infants of treated mothers.

Table 385.8

Strategy to Eliminate Hepatitis B Virus Transmission in the United States[*]

• Screening of all pregnant women for HBsAg
HBV DNA testing for HBsAg-positive pregnant women, with suggestion of maternal antiviral therapy to reduce perinatal transmission when HBV DNA is >200,000 IU/mL
Prophylaxis (HepB vaccine and hepatitis B immunoglobulin) for infants born to HBsAg-positive [†] women
• Universal vaccination of all infants beginning at birth [‡], [§] as a safeguard for infants born to HBV-infected mothers not identified prenatally
• Routine vaccination of previously unvaccinated children aged <19 yr
• Vaccination of adults at risk for HBV infection, including those requesting protection from HBV without acknowledgment of a specific risk factor

[*] Sources: Mast EE, Margolis HS, Fiore AE, et al: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1: immunization of infants, children, and adolescents, *MMWR Recomm Rep* 54(No. RR-16):1–31, 2005; Mast EE, Weinbaum CM, Fiore AE, et al: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults, *MMWR Recomm Rep* 55(No. RR-16):1–33, 2006.

[†] Refer to Table 385.9 for prophylaxis recommendations for infants born to women with unknown HBsAg status.

[‡] Within 24 hr of birth for medically stable infants weighing ≥2,000 g.

[§] Refer to Table 385.9 for birth dose recommendations for infants weighing <2,000 g.

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

From Schillie S, Vellozzi C, Reingold A, et al: Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices, *MMWR* 67[1]:1–29, 2018, Box 2, p. 5.

Table 385.9

Hepatitis B Vaccine Schedules for Infants, by Infant Birthweight and Maternal Hepatitis B Surface Antigen Status

BIRTHWEIGHT	MATERNAL HBsAg STATUS	SINGLE-ANTIGEN VACCINE		SINGLE-ANTIGEN + COMBINATION VACCINE[†]	
		DOSE	AGE	DOSE	AGE
≥2,000 g	Positive	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG[‡]	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1-2 mo	2	2 mo
		3	6 mo [§]	3	4 mo
				4	6 mo [§]
	Unknown[*]	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		2	1-2 mo	2	2 mo
		3	6 mo [§]	3	4 mo
				4	6 mo [§]
	Negative	1	Birth (≤24 hr)	1	Birth (≤24 hr)
		2	1-2 mo	2	2 mo
		3	6-18 mo [§]	3	4 mo
				4	6 mo [§]
<2,000 g	Positive	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1 mo	2	2 mo
		3	2-3 mo	3	4 mo
		4	6 mo [§]	4	6 mo [§]
	Unknown	1	Birth (≤12 hr)	1	Birth (≤12 hr)
		HBIG	Birth (≤12 hr)	HBIG	Birth (≤12 hr)
		2	1 mo	2	2 mo
		3	2-3 mo	3	4 mo
		4	6 mo [§]	4	6 mo [§]
	Negative	1	Hospital discharge or age 1 mo	1	Hospital discharge or age 1 mo
		2	2 mo	2	2 mo
		3	6-18 mo [§]	3	4 mo
				4	6 mo [§]

[*] Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.

[†] Pediarix should not be administered before age 6 wk.

[‡] HBIG should be administered at a separate anatomical site from vaccine.

[§] The final dose in the vaccine series should not be administered before age 24 wk (164 days).

HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen.

From Schillie S, Vellozzi C, Reingold A, et al: Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices, *MMWR* 67(1):1–29, 2018, Table 3, p. 12.

Table 385.10

Recommended Doses of Hepatitis B Vaccine by Group and Vaccine Type

	SINGLE-ANTIGEN VACCINE				**COMBINATION VACCINE**			
	RECOMBIVAX		**ENGERIX**		**PEDIARIX** [*]		**TWINRIX** [†]	
Age Group (yr)	***Dose (µg)***	***Vol (mL)***	***Dose (µg)***	***Vol (mL)***	***Dose (µg)***	***Vol (mL)***	***Dose (µg)***	***Vol (mL)***
Birth-10	5	0.5	10	0.5	10[*]	0.5	N/A	N/A
11-15	10 [‡]	1	N/A	N/A	N/A	N/A	N/A	N/A
11-19	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	10	1	20	1	N/A	N/A	20 [†]	1
HEMODIALYSIS PATIENTS AND OTHER IMMUNE-COMPROMISED PERSONS								
<20	5	0.5	10	0.5	N/A	N/A	N/A	N/A
≥20	40	1	40	2	N/A	N/A	N/A	N/A

[*] Pediarix is approved for use in persons aged 6 wk through 6 yr (prior to the 7th birthday).

[†] Twinrix is approved for use in persons aged ≥18 yr.

[‡] Adult formulation administered on a 2-dose schedule.

N/A, not applicable.

From Schillie S, Vellozzi C, Reingold A, et al: Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices, *MMWR* 67(1):1–29, 2018, Table 2, p. 10.

Table 385.11

Hepatitis B Vaccine Schedules for Children, Adolescents, and Adults

AGE GROUP	**SCHEDULE[*] (INTERVAL REPRESENTS TIME IN MONTHS FROM FIRST DOSE)**
Children (l-10 yr)	0, 1, and 6 mo 0, 1, 2, and 12 mo
Adolescents (11-19 yr)	0, 1, and 6 mo 0, 12, and 24 mo

	0 and 4-6 mo [†] 0, 1, 2, and 12 mo 0, 7 days, 21-30 days, 12 mo [‡]
Adults (≥20 yr)	0, 1, and 6 mo 0, 1, 2, and 12 mo 0, 1, 2, and 6 mo [§] 0, 7 days, 21-30 days, 12 mo [‡]

[*] Refer to package inserts for further information. For all ages, when the HepB vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the 1st dose, the 2nd dose should be administered as soon as possible, and the 2nd and 3rd doses should be separated by an interval of at least 8 wk. If only the 3rd dose has been delayed, it should be administered as soon as possible. The final dose of vaccine must be administered at least 8 wk after the 2nd dose and should follow the 1st dose by at least 16 wk; the minimum interval between the 1st and 2nd doses is 4 wk. Inadequate doses of hepatitis B vaccine or doses received after a shorter-than-recommended dosing interval should be readministered, using the correct dosage or schedule. Vaccine doses administered ≤ 4 days before the minimum interval or age are considered valid. Because of the unique accelerated schedule for Twinrix, the 4-day guideline does not apply to the 1st 3 doses of this vaccine when administered on a 0-day, 7-day, 21-30-day, and 12-mo schedule (new recommendation).

[†] A 2-dose schedule of Recombivax adult formulation (10 µg) is licensed for adolescents aged 11-15 yr. When scheduled to receive the second dose, adolescents aged >15 yr should be switched to a 3-dose series, with doses 2 and 3 consisting of the pediatric formulation administered on an appropriate schedule.

[‡] Twinrix is approved for use in persons aged ≥ 18 yr and is available on an accelerated schedule with doses administered at 0, 7, 21-30 days, and 12 mo.

[§] A 4-dose schedule of Engerix administered in 2 1 mL doses (40 µg) on a 0-, 1-, 2-, and 6-mo schedule is recommended for adult hemodialysis patients.

From Schillie S, Vellozzi C, Reingold A, et al: Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices, *MMWR* 67(1):1–29, 2018, Table 4, p. 13.

Household, sexual, and needle-sharing contacts of patients with chronic HBV infection should be identified and vaccinated if they are susceptible to HBV infection. Patients should be advised about the perinatal and intimate contact risk of transmission of HBV. HBV is not spread by breastfeeding, kissing, hugging, or sharing water or utensils. Children with HBV should not be excluded from school, play, childcare, or work, unless they are prone to biting. A support group might help children to cope better with their disease. Families should not feel obligated to disclose the diagnosis as this information may lead to prejudice or mistreatment of the patient or the patient's family. All patients positive for HBsAg should be reported to the state or local health department, and chronicity is diagnosed if they remain positive past 6 mo HBIG.

HBIG is indicated only for specific *postexposure* circumstances and provides only temporary protection (3-6 mo). It plays a pivotal role in preventing *perinatal* transmission when administered within 12 hr of birth.

Universal Vaccination

Two single-antigen vaccines (Recombivax HB and Engerix-B) are approved for children and are the only preparations approved for infants younger than age 6 mo. Three combination vaccines can be used for subsequent immunization dosing and enable integration of the HBV vaccine into the regular immunization schedule. The safety profile of HBV vaccine is excellent. The most reported side effects are pain at the injection site (up to 29% of cases) and fever (up to 6% of cases). Seropositivity is >95% with all vaccines, achieved after the second dose in most patients. The third dose serves as a booster and may have an effect on maintaining long-term immunity. In immunosuppressed patients and infants whose birthweight is <2,000 g, a fourth dose is recommended (the birth dose does not count as part of the 3-dose series) and these infants should be checked for anti-HBs and HBsAg after completing these shots. In this group of infants, if the anti-HBs level is <10 mIU/mL, they should repeat the 3-dose series. Despite declines in the anti-HBs titer in time, most healthy vaccinated persons remain protected against HBV infection.

Current HBV vaccination recommendations are as noted in Tables 385.9 to 385.11 .

Postvaccination testing for HBsAg and anti-HBs should be done at 9-18 mo. If the result is positive for anti-HBs, the child is immune to HBV. If the result is positive for HBsAg only, the parent should be counseled, and the child evaluated by a pediatric hepatologist. If the result is negative for both HBsAg and anti-HBs, a second complete hepatitis B vaccine series should be administered, followed by testing for anti-HBs to determine if subsequent doses are needed.

Administration of 4 doses of vaccine is permissible when combination vaccines are used after the birth dose; this does not impact vaccine response.

Postexposure Prophylaxis

Recommendations for postexposure prophylaxis for prevention of hepatitis B infection depend on the conditions under which the person is exposed to HBV (see Table 385.11). Vaccination should never be postponed if written records of the exposed person's immunization history are not available, but every effort should still be made to obtain those records.

Special Populations

Patients with cirrhosis may not respond as well to the HBV vaccine and repeating anti-HBs titers should be performed. Adult studies suggest higher dosage or shorter interval between dosages may increase the immunization effectiveness. Patients with inflammatory bowel disease frequently have not been immunized, or did not develop complete immunity to HBV, as demonstrated by inadequate anti-HBs levels. These patients may be at risk for fulminant HBV (reactivation) when immunosuppression is started as part of their treatment regimen, specifically with biologic agents such as infliximab.

Prognosis

In general, the outcome after acute HBV infection is favorable, despite a risk of ALF. The risk of developing chronic infection brings the risks of liver cirrhosis and HCC to the forefront. Perinatal transmission leading to chronicity is responsible for the high incidence of HCC in young adults in endemic areas. Importantly, HBV infection and its complications are effectively controlled and prevented with vaccination and multiple clinical trials are ongoing in an effort to improve and guide treatment regimens.

Hepatitis C

Etiology

HCV is a single-stranded RNA virus, classified as a separate genus within the Flaviviridae family, with marked genetic heterogeneity. It has 6 major genotypes and numerous subtypes and quasi-species, which permit the virus to escape host immune surveillance. Genotype variation might partially explain the differences in clinical course and response to treatment. Genotype 1b is the most common genotype in the United States and is the least responsive to the approved pediatric medications.

Epidemiology

In the United States, HCV infection, the most common cause of chronic liver disease in adults, is responsible for 8,000-10,000 deaths per year. Approximately 4 million people in the United States and 170 million people worldwide are estimated to be infected with HCV. Approximately 85% of infected adults remain chronically infected. In children, seroprevalence of HCV is 0.2% in those younger than age 11 yr and 0.4% in children age 11 yr or older. However, even more children may be infected as only a small percentage of HCV-infected children are identified, and an even smaller number subsequently receive treatment. Appropriate identification, and screening, for infected individuals should be implemented.

Risk factors for HCV transmission in the United States included blood transfusion before 1992 as the most common route of infection, but, with current blood donor screening practices, the risk of HCV transmission is approximately 0.001% per unit transfused. Illegal drug use with exposure to blood or blood products from HCV-infected persons accounts for more than half of adult cases in the United States. Sexual transmission, especially through multiple sexual partners, is the second most common cause of infection. Other risk factors include occupational exposure, but approximately 10% of new infections have no known transmission source. In children, perinatal transmission is the *most* prevalent mode of transmission (see Table 385.1). Perinatal transmission occurs in up to 5% of infants born to viremic mothers. HIV coinfection and high viremia titers (HCV RNA-positive) in the mother can increase the transmission rate to 20%. The incubation period is 7-9 wk (range: 2-24 wk).

Pathogenesis

The pattern of acute hepatic injury is indistinguishable from that of other hepatotropic viruses. In chronic cases, lymphoid aggregates or follicles in portal tracts are found, either alone or as part of a general inflammatory infiltrate of the portal areas. Steatosis is also often seen in these liver specimens. HCV appears to cause injury primarily by cytopathic mechanisms, but immune-mediated injury can also occur. The cytopathic component appears to be mild because the acute illness is typically the least severe of all hepatotropic virus infections.

Clinical Manifestations

Acute HCV infection tends to be mild and insidious in onset (Fig. 385.4 ; see also Table 385.1). ALF rarely occurs. HCV is the most likely of all these viruses to cause chronic infection (Fig. 385.5). Of affected adults, <15% clear the virus; the rest develop chronic hepatitis. In pediatric studies, 6–19% of children achieved spontaneous sustained clearance of the virus during a 6-yr follow-up.

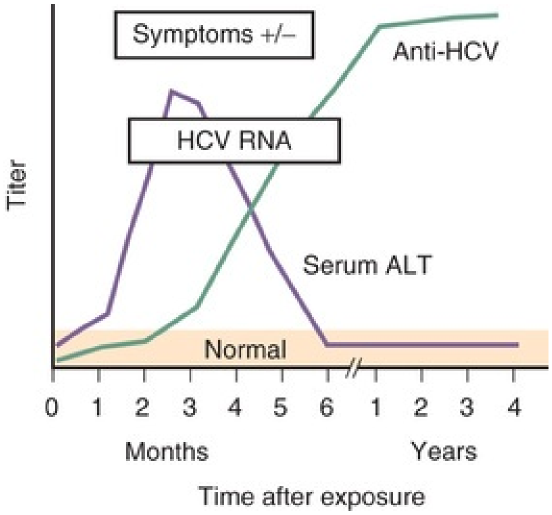

FIG. 385.4 Typical course of acute hepatitis B virus *(HCV)* infection followed by recovery. Symptoms may or may not be present during acute infection. Anti-HCV, antibody to HCV. *ALT,* alanine aminotransferase. (Modified from the Centers for Disease Control and Prevention, www.cdc.gov/hepatitis/Resources/Professionals/Training/Serology/training.htm#one .)

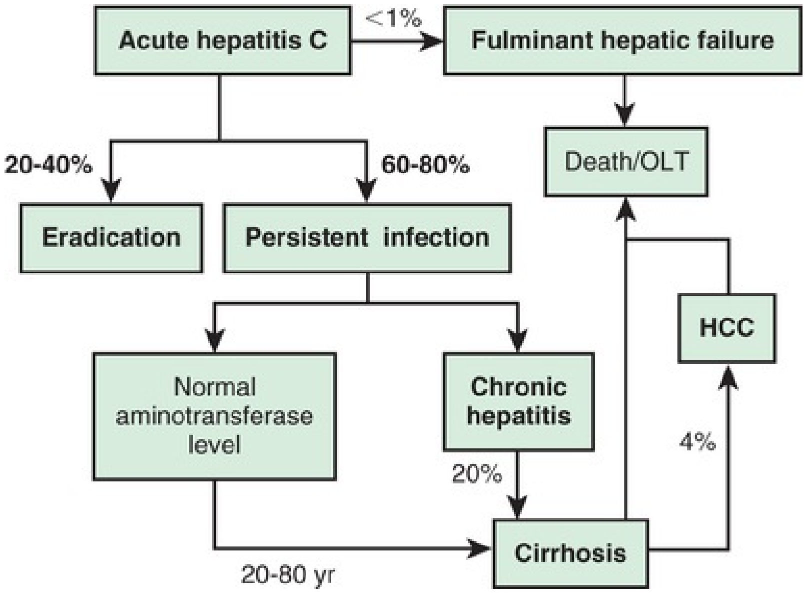
Acute hepatitis C
<1%
Fulminant hepatic failure
Death/OLT
20-40%
60-80%
Eradication
Persistent infection
HCC
Normal aminotransferase level
Chronic hepatitis
4%
20%
Cirrhosis
20-80 yr

FIG. 385.5 Natural history of hepatitis C virus infection. HCC, hepatocellular carcinoma; OLT, orthotopic liver transplant. (From Hochman JA, Balistreri WF: Chronic viral hepatitis: always be current! *Pediatr Rev* 24[12]:399–410, 2003.)

Chronic HCV infection is also clinically silent until a complication develops. Serum aminotransferase levels fluctuate and are sometimes normal, but histologic inflammation is universal. Progression of liver fibrosis is slow over several years, unless comorbid factors are present, which can accelerate fibrosis progression. Approximately 25% of infected patients ultimately progress to cirrhosis, liver failure, and, occasionally, primary HCC within 20-30 yr of the acute infection. Although progression is rare within the pediatric age range, cirrhosis and HCC from HCV have been reported in children. The long-term morbidities constitute the rationale for diagnosis and treatment in children with HCV.

Chronic HCV infection can be associated with small vessel vasculitis and is a common cause of essential mixed cryoglobulinemia. Other extrahepatic manifestations, predominantly seen in adults, include cutaneous vasculitis, porphyria cutanea tarda, lichen planus, peripheral neuropathy, cerebritis, polyarthritis, membranoproliferative glomerulonephritis, and nephrotic syndrome. Antibodies to smooth muscle, antinuclear antibodies, and low thyroid hormone levels may also be present.

Diagnosis

Clinically available assays for detection of HCV infection are based on detection of antibodies to HCV antigens or detection of viral RNA (see Table 385.3); neither can predict the severity of liver disease.

The most widely used serologic test is the third-generation enzyme immunoassay to detect anti-HCV. The predictive value of this assay is greatest in high-risk populations, but the false-positive rate can be as high as 50–60% in low-risk populations. False-negative results also occur because antibodies remain negative for as long as 1-3 mo after clinical onset of illness. Anti-HCV is not a protective antibody and does not confer immunity; it is usually present simultaneously with the virus.

The most commonly used virologic assay for HCV is a PCR assay, which permits detection of small amounts of HCV RNA in serum and tissue samples within days of infection. The *qualitative* PCR detection is especially useful in patients with recent or perinatal infection, hypogammaglobulinemia, or immunosuppression and is highly sensitive. The *quantitative* PCR aids in identifying patients who are likely to respond to therapy and in monitoring response to therapy.

Screening for HCV should include all patients with the following risk factors: history of illegal drug use (even if only once), receiving clotting factors made before 1987 (when inactivation procedures were introduced) or blood products before 1992, hemodialysis, idiopathic liver disease, and children born to HCV-infected women (qualitative PCR in infancy and anti-HCV after 12-18 mo of age). In children, it is also important to consider whether the mother has any of the risk factors noted above that would increase her possibility of developing HCV. Routine screening of all pregnant women is currently not recommended. The Centers for Disease Control now recommends that all individuals born between 1945 and 1965 be screened.

Determining HCV genotype is also important, particularly when therapy is considered, because the response to the current therapeutic agents varies greatly. Genotype 1 traditionally responded poorly to therapy while genotypes 2 and 3 had a more favorable response. Newer agents, however, have led to changes in the treatment duration and anticipated outcome (as discussed later).

Aminotransferase levels typically fluctuate during HCV infection and do not correlate with the degree of liver fibrosis. A liver biopsy was previously the only means to assess the presence and extent of hepatic fibrosis, outside of overt signs of chronic liver disease. Newer noninvasive modalities using ultrasound or magnetic resonance elastography, however, are now used to estimate the degree of fibrosis and decrease the need for biopsy. This technology coupled with newer drug regimens have eliminated the need for liver biopsy in many cases of HCV. A liver biopsy is now primarily indicated to rule out other causes of overt liver disease.

Complications

The risk of ALF caused by HCV is low, but the risk of chronic hepatitis is the highest of all the hepatitis viruses. In adults, risk factors for progression to hepatic fibrosis include older age, obesity, male sex, and even moderate alcohol ingestion (two 1 oz. drinks per day). Progression to cirrhosis or HCC is a major cause of morbidity and the most common indication for liver transplantation in adults in the United States.

Treatment

In adults, *peginterferon* (subcutaneous, weekly) combined with ribavirin (oral, daily) was standard therapy until 2012 for genotype 1. Currently recommended first-line adult therapy for HCV includes taking 1 or 2 oral medications with direct-acting antiviral properties, for 12-24 wk dependent on HCV genotype and other clinical factors. Studies show these treatments are more effective and better tolerated, and these same medications are currently being evaluated in children and adolescents.

Traditionally, patients most likely to respond had mild hepatitis, shorter duration of infection, low viral titers, and either genotype 2 or 3 virus. Patients with genotype 1 virus responded poorly. Response to peginterferon alfa/ribavirin may be predicted by single-nucleotide polymorphisms near the interleukin 28B gene, but with these newer treatment regimens excellent response rates are being reported with shorter duration, IFN-free regimens.

The goal of treatment is to achieve a sustained viral response (SVR), as defined by the absence of viremia at a variable period after stopping the medications; SVR is associated with improved histology and decreased risk of morbidities.

The natural history of HCV infection in children is still being defined. It is believed that children have a higher rate of spontaneous clearance than adults (up to 45% by age 19 yr). A multicenter study followed 359 children infected with HCV over 10 yr. Only 7.5% had cleared the virus, and 1.8% progressed to decompensated cirrhosis. Treatment in adults with *acute* HCV in a pilot study showed an 88% SVR in genotype 1 subjects (treated with IFN and ribavirin for 24 wk). Such data, if confirmed, could raise the question whether children, with shorter duration of infection and fewer comorbid conditions than their adult counterparts, could be ideal candidates for treatment. Given the adverse effects of currently available therapy, this strategy is not recommended outside of clinical trials.

Peginterferon (Schering), IFN-α2b, and ribavirin are approved by the Food and Drug Administration (FDA) for use in children older than 3 yr of age with chronic hepatitis C. Studies of IFN monotherapy in children demonstrated a higher SVR than in adults, with better compliance and fewer side effects. An SVR up to 49% for genotype 1 was achieved in multiple studies. Factors associated with a higher likelihood of response are age younger than 12 yr, genotypes 2 and 3, and, in patients with genotype 1b, an RNA titer of <2 million copies/mL of blood, and viral response (PCR at wk 4 and 12 of treatment). Side effects of medications lead to discontinuation of treatment in a high proportion of patients; these include influenza-like symptoms, anemia, and neutropenia.

Long-term effects of these medicines also need to be evaluated as significant differences were noted in children's weight, height, body mass index, and body composition. Most of these delays improved following cessation of treatment, but height z-scores continued to lag behind.

Treatment may be considered for children infected with genotypes 2 and 3, because they have an 80–90% response rate to therapy with peginterferon and ribavirin. If the child has genotype 1b virus, the treatment choice remains more controversial as newer regimens are quickly becoming available.

Pediatric guidelines recommend treatment to eradicate HCV infection, prevent progression of liver disease and development of HCC, and to remove the stigma associated with HCV. Treatment should be considered for patients with evidence of advanced fibrosis or injury on liver biopsy. One approved treatment consists of 24-48 wk of peginterferon and ribavirin (therapy should be stopped if still detectable on viral PCR at 24 wk of therapy). In addition, sofosbuvir alone or in combination with ledipasvir has FDA approval for children ages 12-17 yr. The combination is indicated for HCV genotypes 1, 4, 5, and 6, while sofosbuvir with ribavirin is indicated for HCV genotypes 2 or 3; both regimens are used in children with mild or no cirrhosis.

Newer Treatments

Varying IFN-free regimens are now available for adults for all HCV genotypes allowing even greater likelihood of achieving viral eradication, with completely oral medication regimens, and without the use of IFN and its attendant side effects. With the rapid development of new medications and regimens, frequent review of up-to-date resources, such as www.hcvguidelines.org , will be vital to provide optimal care (Table 385.12).

Table 385.12

Ongoing Studies With Direct Acting Antiviral Combinations in Children With Chronic Hepatitis C Virus Infection

	GENOTYPE	ESTIMATED ENROLMENT	AGE RANGE (YR)	IDENTIFIER	COMPLETION
Sofosbuvir + ledipasvir, with or without ribavirin	1,4,5,6	222	3–17	NCT02249182	July 2018
Sofosbuvir + ribavirin	2,3	104	3–17	NCT02175758	April 2018
Ombitasvir + paritaprevir +	1,4	74	3–17	NCT02486406	September 2019

ritonavir, with or without dasabuvir, with or without ribavirin					
Sofosbuvir + daclatasvir	4	40	8–17	NCT03080415	June 2018
Sofosbuvir + ledipasvir	1,4	40	12–17	NCT02868242	April 2019
Sofosbuvir + velpatasvir	1–6	200	3–17	NCT03022981	December 2019
Glecaprevir + pibrentasvir	1–6	110	3–17	NCT03067129	May 2022
Gratisovir + ribavirin	1–6	41	10–17	NCT02985281	June 2017

From Indolfi G, Serranti D, Resti M: Direct-acting antivirals for children and adolescents with chronic hepatitis C. *Lancet Child Adolesc* 2:298-304, 2018 (Table 1, p. 299).

Prevention

No vaccine is yet available to prevent HCV, although ongoing research suggests this will be possible in the future. Currently available Ig preparations are not beneficial, likely because preparations produced in the United States do not contain antibodies to HCV because blood and plasma donors are screened for anti-HCV and excluded from the donor pool. Broad neutralizing antibodies to HCV were found to be protective and might pave the road for vaccine development.

Once HCV infection is identified, patients should be screened yearly with a liver ultrasound and serum α-fetoprotein for HCC, as well as for any clinical evidence of liver disease. Vaccinating the affected patient against HAV and HBV will prevent superinfection with these viruses and the increased risk of developing severe liver failure.

Prognosis

Viral titers should be checked yearly to document spontaneous remission. Most patients develop chronic hepatitis. Progressive liver damage is higher in those with additional comorbid factors such as alcohol consumption, viral genotypic variations, obesity, and underlying genetic predispositions. Referral to a pediatric hepatologist is strongly advised to take advantage of up-to-date monitoring regimens and to optimize their enrollment in treatment protocols when available.

Hepatitis D

Etiology

HDV, the smallest known animal virus, is considered defective because it cannot produce infection without concurrent HBV infection. The 36 nm diameter virus is incapable of making its own coat protein; its outer coat is composed of excess HBsAg from HBV. The inner core of the virus is single-stranded circular RNA that expresses the HDV antigen.

Epidemiology

HDV can cause an infection at the same time as the initial HBV infection (coinfection), or HDV can infect a person who is already infected with HBV (superinfection). Transmission usually occurs by intrafamilial or intimate contact in areas of high prevalence, which are primarily developing countries (see Table 385.1). In areas of low prevalence, such as the United States, the parenteral route is far more common. HDV infections are uncommon in children in the United States but must be considered when ALF occurs. The incubation period for HDV superinfection is approximately 2-8 wk; with coinfection, the incubation period is similar to that of HBV infection.

Pathogenesis

Liver pathology in HDV-associated hepatitis has no distinguishing features except that damage is usually severe. In contrast to HBV, HDV causes injury directly by cytopathic mechanisms. The most severe cases of HBV infection appear to result from coinfection of HBV and HDV.

Clinical Manifestations

The symptoms of hepatitis D are similar to, but usually more severe than, those of the other hepatotropic viruses. The clinical outcome for HDV infection depends on the mechanism of infection. In coinfection, *acute* hepatitis, which is much more severe than for HBV alone, is common, but the risk of developing chronic hepatitis is low. In superinfection, acute illness is rare and chronic hepatitis is common. The risk of ALF is highest with superinfection. Hepatitis D should be considered in any child who experiences ALF.

Diagnosis

HDV has not been isolated and no circulating antigen has been identified. The diagnosis is made by detecting IgM antibody to HDV; the antibodies to HDV develop approximately 2-4 wk after coinfection and approximately 10 wk after a superinfection. A test for anti-HDV antibody is commercially available. PCR assays for viral RNA are available as research tools (see Table 385.2).

Treatment

The treatment is based on supportive measures once an infection is identified. There are no specific HDV-targeted treatments to date. The treatment is mostly based on controlling and treating HBV infection, without which HDV cannot induce hepatitis. Small research studies suggest that IFN is the preferred treatment regimen, but ongoing studies still seek the ideal management strategy and the regimen should be personalized for each patient.

Prevention

There is no vaccine for hepatitis D. Because HDV replication cannot occur without hepatitis B coinfection, immunization against HBV also prevents HDV infection. Hepatitis B vaccines and HBIG are used for the same indications as for hepatitis B alone.

Hepatitis E

Etiology

HEV has been cloned using molecular techniques. This RNA virus has a nonenveloped sphere shape with spikes and is similar in structure to the caliciviruses.

Epidemiology

Hepatitis E is the epidemic form of what was formerly called non-A, non-B hepatitis. Transmission is fecal–oral (often waterborne) and is associated with shedding of 27-34 nm particles in the stool (see Table 385.1). The highest prevalence of HEV infection has been reported in the Indian subcontinent, the Middle East, Southeast Asia, and Mexico, especially in areas with poor sanitation. The prevalence, however, appears to be increasing in the United

States and other developed countries and has been postulated to be the most common cause of acute hepatitis and jaundice in the world. The mean incubation period is approximately 40 days (range: 15-60 days).

Pathogenesis

HEV appears to act as a cytopathic virus. The pathologic findings are similar to those of the other hepatitis viruses.

Clinical Manifestations

The clinical illness associated with HEV infection is similar to that of HAV but is often more severe. As with HAV, chronic illness does not occur—the sole exception noted to date is chronic hepatitis E occurring in immunosuppressed patients (e.g., post-transplant). In addition to often causing a more severe episode than HAV, HEV tends to affect older patients, with a peak age between 15 and 34 yr. HEV is a major pathogen in pregnant women, in whom it causes ALF with a high fatality incidence. HEV could also lead to decompensation of preexisting chronic liver disease.

Diagnosis

Recombinant DNA technology has resulted in development of antibodies to HEV particles, and IgM and IgG assays are available to distinguish between acute and resolved infections (see Table 385.3). IgM antibody to viral antigen becomes positive after approximately 1 wk of illness. Viral RNA can be detected in stool and serum by PCR.

Prevention

A recombinant hepatitis E vaccine is highly effective in adults. No evidence suggests that immune-globulin is effective in preventing HEV infections. Ig pooled from patients in endemic areas might prove to be effective.

Approach to Acute or Chronic Hepatitis

Identifying deterioration of the patient with acute hepatitis and the development of ALF is a major contribution of the primary pediatrician (Fig. 385.6). If ALF is identified, the clinician should immediately refer the patient to a transplantation center; this can be lifesaving.

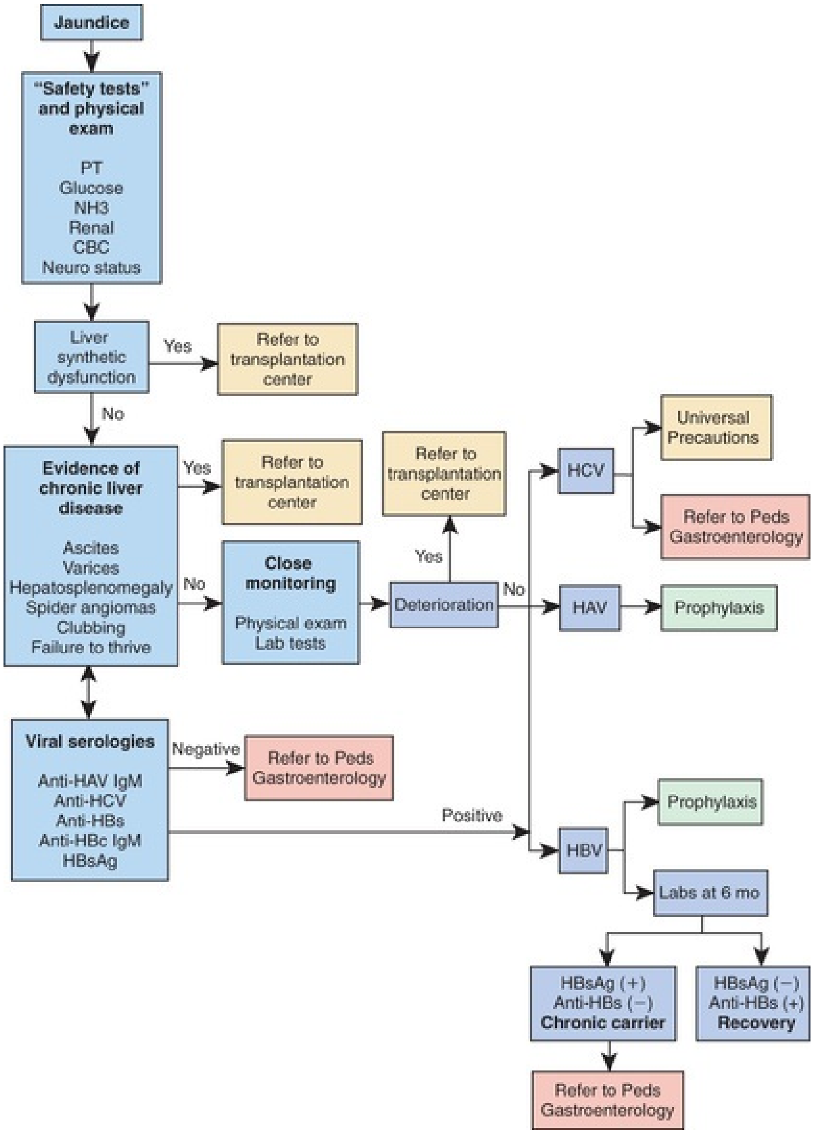
Jaundice
"Safety tests" and physical exam
PT
Glucose
NH3
Renal
CBC
Neuro status
Liver synthetic dysfunction
Yes
Refer to transplantation center
No
Evidence of chronic liver disease
Ascites
Varices
Hepatosplenomegaly
Spider angiomas
Clubbing
Failure to thrive
Yes
Refer to transplantation center
No
Close monitoring
Physical exam
Lab tests
Deterioration
Yes
Refer to transplantation center
No
HCV
Universal Precautions
Refer to Peds Gastroenterology
HAV
Prophylaxis
Viral serologies
Anti-HAV IgM
Anti-HCV
Anti-HBs
Anti-HBc IgM
HBsAg
Negative
Refer to Peds Gastroenterology
Positive
HBV
Prophylaxis
Labs at 6 mo
HBsAg (+)
Anti-HBs (−)
Chronic carrier
HBsAg (−)
Anti-HBs (+)
Recovery
Refer to Peds Gastroenterology

FIG. 385.6 Clinical approach to viral hepatitis. CBC, complete blood count with differential; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M; NH_3 , ammonia; PT, prothrombin time.

Once chronic infection is identified, close follow-up and referral to a pediatric hepatologist is recommended to enroll the patient in appropriate treatment trials. Treatment of chronic HBV and HCV in children should preferably be delivered within, or using data from, pediatric controlled trials as indications, timing, regimen, and outcomes remain to be defined and cannot be extrapolated from adult data. All patients with chronic viral hepatitis should avoid, as much as possible, further insult to the liver; HAV vaccine is recommended. Patients must avoid alcohol consumption and obesity, and they should exercise care when taking new medications, including nonprescription drugs and herbal medications.

International adoption and ease of travel continue to change the epidemiology of hepatitis viruses. In the United States, chronic HBV and HCV have a high prevalence among international adoptee patients; vigilance is required to establish early diagnosis in order to offer appropriate treatment as well as prophylactic measures to limit viral spread.

Chronic hepatitis can be a stigmatizing disease for children and their families. The pediatrician should offer, with proactive advocacy, appropriate support for them as well as needed education for their social circle. Scientific data and information about support groups are available for families on the websites for the American Liver Foundation (www.liverfoundation.org) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (www.naspghan.org), as well as through pediatric gastroenterology centers.

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CHAPTER 386

Liver Abscess

Joshua K. Schaffzin, Robert W. Frenck Jr

Liver abscesses typically have 1 of 2 infectious etiologies: pyogenic, meaning involving bacteria, or parasitic, such as with amebiasis, ascariasis, or toxocariasis. Liver abscesses are typically difficult to detect due to nonspecific presentation, and diagnosis requires a high index of suspicion. Radiographic diagnosis is often contributory, but further confirmation is often indicated to differentiate infectious abscess from hydatid cyst and noninfectious causes, such as malignancy (primary hepatic or metastasis). The differential diagnosis also includes traumatic injury (including procedural, such as a misplaced vascular catheter).

Pyogenic liver abscesses are uncommon in children but have been reported in all ages. Bacteria can invade the liver through 1 of 4 sources: hematogenously through the hepatic artery (e.g., in the presence of bacteremia), through the biliary tract, through the portal vein (portal sepsis), and directly by contiguous infection. In neonates, a portal vein source can include the umbilical vein (e.g., in the presence of omphalitis or injury caused by an umbilical venous catheter). Pyogenic liver abscesses of unknown source are classified as cryptogenic. Children with chronic granulomatous disease (CGD), hyper–immunoglobulin E (hyper-IgE) syndrome, or malignancies are at increased risk of liver abscess. Pyogenic liver abscesses are also uncommon in adults, although the annual incidence is higher in Southeast Asia (estimated 17.6/100,000 population) than in the United States or Europe (estimated 2-5/100,000 population). They tend to occur more frequently in males, older ages, and in patients with diabetes or a history of liver transplantation or malignancy.

Clinical signs and symptoms of pyogenic liver abscess are nonspecific and can include fever, chills, malaise, fatigue, nausea, abdominal pain (with or without right upper quadrant tenderness), and hepatomegaly; jaundice is uncommon. The most common abnormal laboratory findings are elevated inflammatory markers and hypoalbuminemia. Hepatic function testing is often abnormally elevated, and leukocytosis is common. Radiologic confirmation is often obtained by ultrasound or CT (Fig. 386.1). Chest x-rays may show elevation of the right hemidiaphragm with a right pleural effusion. Solitary lesions of the right hepatic lobe are most common, although solitary abscesses can appear in any hepatic lobe or as multiple disseminated lesions (such as with disseminated candidiasis, bartonellosis, or rarely brucellosis).

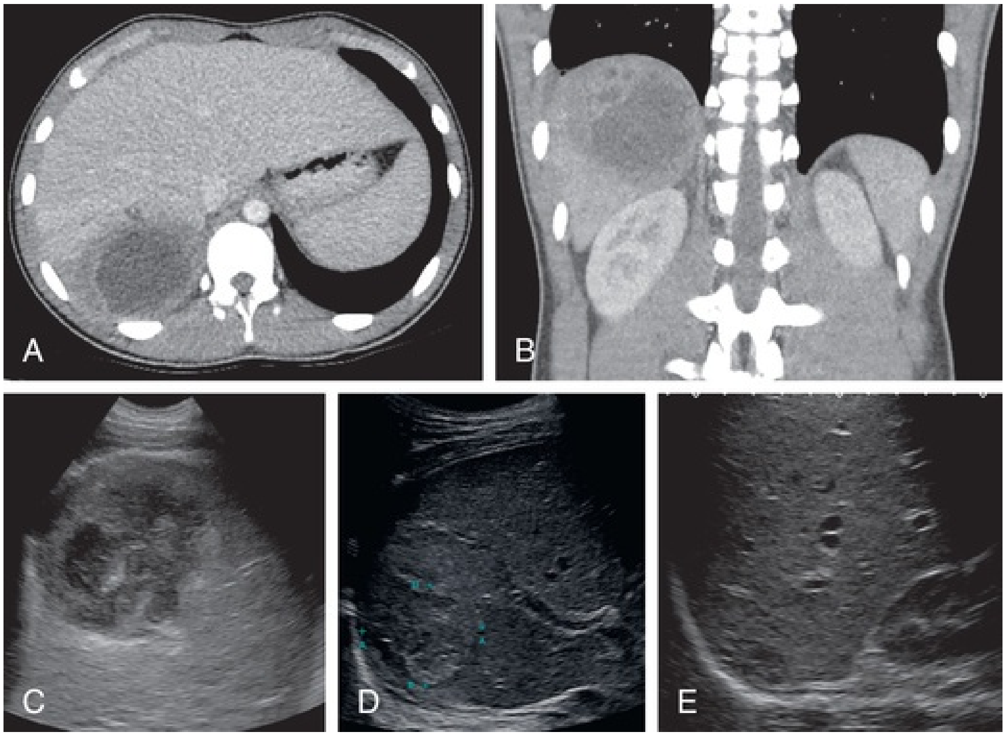

FIG. 386.1 CT (**A** and **B**) and ultrasound **(C)** images of a cryptogenic liver abscess in a 16 yr old male without known risk factors. The lesion was drained percutaneously, and cultures grew multiple anaerobic organisms (*Fusobacterium nucleatum* and *Parvimonas micra*). He was successfully treated with 2 wk of parenteral followed by 4 wk of oral therapy and was followed with serial ultrasounds 5 days **(D)** and 34 days **(E)** after drainage. (Courtesy Dr. Alexander Towbin, Cincinnati Children's Hospital, Cincinnati, Ohio.)

Cultures of pyogenic liver abscesses often yield mixed populations. In children, *Staphylococcus aureus*, *Streptococcus* spp., enteric Gram-negative organisms (*Escherichia coli*, *Klebsiella pneumoniae*, and *Serratia* in CGD patients), and anaerobic organisms are most common. Among adults, *K.*

pneumoniae predominates, followed by *E. coli* , with less common aerobic Gram-positive and anaerobic organisms. Blood cultures are often positive and may be helpful to determine a therapy plan.

Due to the wide range of causative organisms (i.e., aerobic Gram negative, *S. aureus* , and anaerobic organisms) empiric antimicrobial treatment needs to be broad. Potential empiric antimicrobial choices include; piperacillin-tazobactam, ampicillin-sulbactam, or metronidazole with a 3rd-generation cephalosporin. Depending on local prevalence and degree of suspicion, vancomycin may be added to cover methicillin-resistant *S. aureus* . Therapy can be modified based on culture sensitivities. Treatment duration is not standardized, and should be based on fever resolution, clinical and inflammatory marker improvement, and serial ultrasound monitoring. Many sources recommend completing 4-6 wk of therapy, with the first 2 wk administered parentally. Depending on the size and extent of the lesion(s), percutaneous or surgical drainage may be added to obtain samples for cultures and to shorten illness duration. Percutaneous options include single-pass needle or catheter aspiration, or insertion of a continuously draining catheter. In adults, unless there is evidence of rupture or spread, percutaneous drainage should be attempted first for large lesions (≥5-7 cm in diameter). Numerous case series of pyogenic liver abscess in premature infants described complete resolution with antibiotic therapy alone, and some advocate for this as an initial approach in smaller lesions. Resolution can be monitored by trending inflammatory markers and/or serial imaging.

Amebic liver abscess (ALA) is the most common extraintestinal manifestation of *Entamoeba histolytica* infection. Although more common in endemic areas, cases can be diagnosed in the United States among travelers to, and immigrants from, endemic areas. Presentation can be delayed by mo to yr. ALA is more common among adults aged 18-55, and males predominate. Amoebic trophozoites invade colonic mucosa and reach the liver through the portal circulation. Patients may not have an associated colitis. Fever, right upper quadrant pain, anorexia, and weight loss are often present. Laboratory evaluation typically reveals a leukocytosis without eosinophilia and increased alkaline phosphatase. Ultrasonography or CT demonstrates the abscess (Fig. 386.2).

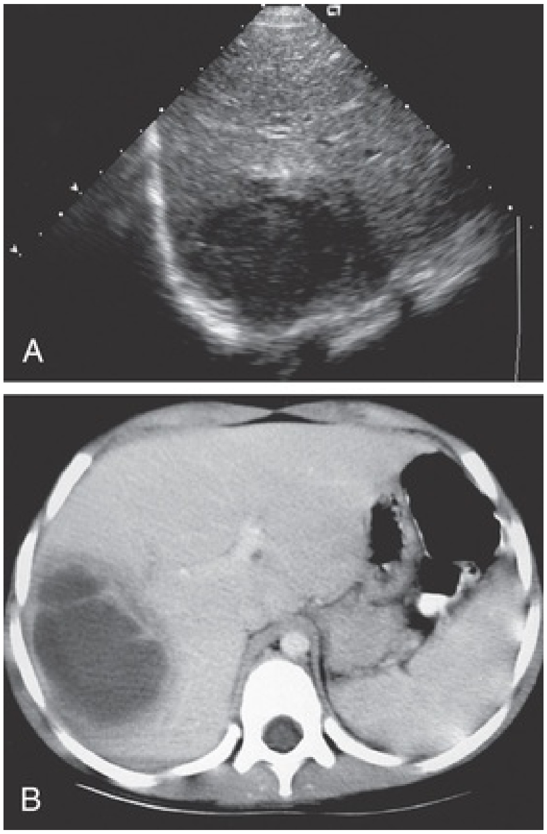

FIG. 386.2 Amebic abscess. **A,** Sonogram demonstrates a hypoechogenic mass in the right lobe of the liver with a more hypoechoic surrounding rim. **B,** CT scan demonstrates a low-attenuation mass in the right lobe of the liver with a prominent halo. (From Kuhn JP, Slovis TL, Haller JO: *Caffrey's pediatric diagnostic imaging* , vol 2, ed 10, Philadelphia, 2004, Mosby, p. 1473.)

Diagnosis of ALA is often confirmed by serum ELISA. Serology is considered reliable in nonendemic areas but can be prone to false negatives early in the infection and cannot distinguish active infection from previous exposure. Testing for *E. histolytica* presence in stool is specific but not very sensitive, and patients with ALA may not have detectable organism in their stool. Most sensitive and specific among stool assays is PCR, followed by stool antigen detection, and least reliable is microscopy, because *E. histolytica* cannot easily be distinguished microscopically from its clinically benign relatives *Entamoeba dispar* and *Entamoeba moshkovskii* .

Prior to effective treatment, ALA-associated mortality was high; it has since decreased significantly. Treatment involves 7-10 days of a nitroimidazole (most commonly metronidazole) to kill trophozoites, followed by 7 days of a luminal agent (such as paromomycin) to kill colonic cysts. Patients with large abscesses

(≥5-7 cm in diameter) may benefit from percutaneous aspiration in addition to medical therapy.

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CHAPTER 387

Liver Disease Associated With Systemic Disorders

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Liver disease is found in a wide variety of systemic illnesses, both as a result of the primary pathologic process and as a secondary complication of the disease or associated therapy.

Inflammatory Bowel Disease

Ulcerative colitis and Crohn disease (Chapter 362) are associated with hepatobiliary disease that includes autoimmune and inflammatory processes related to inflammatory bowel disease (IBD) (sclerosing cholangitis, autoimmune hepatitis [AIH]), drug toxicity (thiopurines, methotrexate, 5-ASA, biologics), malnutrition and disordered physiology (fatty liver, cholelithiasis), bacterial translocation and systemic infections (hepatic abscess, portal vein thrombosis), hypercoagulability (infarction, Budd-Chiari), and long-term complications of these liver diseases, such as ascending cholangitis, cirrhosis, portal hypertension, and biliary carcinoma. Hepatobiliary manifestations may continue to progress even when intestinal symptoms are well-controlled and are unrelated to either the severity or duration of intestinal disease.

Sclerosing cholangitis is the most common hepatobiliary disease associated with IBD, occurring in 2–8% of adult patients with ulcerative colitis and less often in Crohn disease. Conversely, 70–90% of patients with sclerosing cholangitis have ulcerative colitis. In pediatric patients with IBD, the diagnosis typically occurs in the 2nd decade of life, with a median age of 14 yr. Sclerosing cholangitis is characterized by progressive inflammation and fibrosis of segments of the intrahepatic and extrahepatic bile ducts and can progress to complete obliteration. Genetic susceptibility has been demonstrated. Many patients are asymptomatic, and the disease is initially diagnosed by routine liver function testing that reveals elevated serum alkaline phosphatase (AP), 5′-nucleotidase, or γ-glutamyl transpeptidase (GGT) activities. Antinuclear or anti–smooth muscle antibodies might also be present in the serum. Ten to 15% of adult patients present with symptoms including anorexia, weight loss, pruritus, fatigue, right upper quadrant pain, and jaundice; intermittent acute cholangitis accompanied by fever, jaundice, and right upper quadrant pain can also occur. Portal hypertension can develop with progressive disease. These symptoms are less common in children, in whom hepatobiliary disease is often recognized by routine screening of liver function tests. In children with sclerosing cholangitis, approximately 11% present initially with hepatic manifestations, and the associated asymptomatic IBD is discovered only on subsequent endoscopy.

Magnetic resonance cholangiography is an established first line diagnostic test for sclerosing cholangitis. Characteristic findings include beading and irregularity of the intrahepatic and extrahepatic bile ducts. Liver biopsy typically reveals periductal fibrosis and inflammation, fibroobliterative cholangitis, and portal fibrosis, but it is not required for the diagnosis in patients with radiologic evidence of sclerosing cholangitis. However, biopsy is required to evaluate for overlap with autoimmune hepatitis or autoimmune sclerosing cholangitis.

Sclerosing cholangitis is strongly associated with hepatobiliary malignancies (cholangiocarcinoma, hepatocellular carcinoma, gallbladder carcinoma) with a reported incidence varying between 9% and 14%. In 1 large series, patients with IBD and sclerosing cholangitis had a 10-fold increased risk of colorectal carcinoma and a 14-fold increased risk of pancreatic cancer compared with the general population. Tumor serology (CA 19-9) and cross-sectional liver imaging may be a useful screening strategy to identify patients with sclerosing cholangitis at increased risk for cholangiocarcinoma.

There is no definitive medical treatment for sclerosing cholangitis; liver transplantation is the only long-term option for progressive cirrhosis, and autoimmune disease can recur in the allograft in 20–25% of patients. Short-term therapy aims at improving biliary drainage and attempting to slow the obliterative process. Ursodeoxycholic acid, at a dose of 15 mg/kg/24 hr, may improve bile flow and laboratory parameters but has not been shown to improve clinical outcome. Dominant extrahepatic biliary strictures may be dilated or endoscopically stented. Immunosuppressive therapy with corticosteroids and/or azathioprine may improve biochemical parameters but has been disappointing in halting long-term histologic progression. Symptomatic therapy should be initiated for pruritus (rifampin, ursodeoxycholic acid, diphenhydramine), malnutrition (enteral supplementation), and ascending cholangitis (antibiotics) as indicated. Total colectomy has not been beneficial in preventing or managing hepatobiliary complications in patients with ulcerative colitis. However, in patients with end-stage liver disease requiring liver transplantation, those with active IBD are 10-fold more likely to lose their grafts.

IBD-associated AIH can closely resemble IBD-associated sclerosing cholangitis, a condition often referred to as **overlap syndrome** or autoimmune sclerosing cholangitis (ASC). These patients typically exhibit hyperglobulinemia (marked increase in serum immunoglobulin [Ig] G levels). In some children the disease is initially diagnosed as AIH and later is found to be sclerosing cholangitis after cholangiography. In other cases, AIH manifests well after diagnosis of IBD-associated sclerosing cholangitis. Liver biopsy in patients with ASC shows interface hepatitis, in addition to the bile duct injury associated with sclerosing cholangitis. Immunosuppressive medication (corticosteroids and/or azathioprine) is the mainstay of therapy for ASC; long-term response does not appear to be as favorable as in AIH alone. Long-term survival in children with ASC appears to be similar to those with sclerosing cholangitis, with an overall median (50%) survival free of liver transplantation of 12.7 yr.

Fatty liver disease might also be more prevalent in adult patients with IBD, ranging from 25% to 40% in 1 large series and often correlates with severity of IBD. Gallstones are more prevalent in those with Crohn disease (11%) than in those with ulcerative colitis (7.5%) and in normal subjects (5%). However, the true prevalence of these IBD-associated liver diseases in pediatric patients is unknown.

Bacterial Sepsis

Sepsis can mimic liver disease and should be excluded in any critically ill patient who develops cholestasis in the absence of markedly elevated serum aminotransferase or AP levels, even when other signs of infection are not evident. Gram-negative organisms are most often isolated from blood cultures, in particular *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Lipopolysaccharides and other bacterial endotoxins are thought to interfere with bile secretion by directly altering the structure or function of bile canalicular membrane transport proteins. The serum bilirubin level, predominantly the conjugated fraction, is elevated. Serum AP and aminotransferase activities may also be elevated. Liver biopsy shows intrahepatic cholestasis with little or no hepatocyte necrosis. Kupffer cell hyperplasia and an increase in inflammatory cells are also common. Similar findings can occur with urosepsis.

Celiac Disease

Celiac disease (Chapter 364.2) may present with elevated aminotransferase levels and prolonged prothrombin time, as well as hepatic histologic changes, such as mild periportal and lobular inflammation. These abnormalities typically all improve on a gluten-free diet. Gastrointestinal symptoms may not be present. Other autoimmune liver diseases (AIH, primary sclerosing cholangitis) have also been associated with celiac disease, although they may not respond as well to a gluten-free diet.

Cardiac Disease

Hepatic injury can occur as a complication of severe acute or chronic congestive heart failure (Chapter 469), cyanotic congenital heart disease (Chapters 456 and 457), and acute ischemic shock. In all conditions, passive congestion and reduced cardiac output can contribute to liver damage. Elevated central venous pressure is transmitted to the hepatic veins, smaller venules, and, ultimately, the surrounding hepatocytes, resulting in hepatocellular atrophy in the centrilobular zone of the liver. Owing to decreased cardiac output, there is decreased hepatic arterial blood flow, and centrilobular hypoxia results. Hepatic necrosis leads to lactic acidosis, elevated aminotransferase levels, cholestasis, prolonged prothrombin time, cirrhosis, and possibly hypoglycemia due to impaired hepatocellular metabolism. Jaundice, tender hepatomegaly, and, in some cases, ascites and splenomegaly can occur. However, aminotransferases are often minimally elevated with slowly progressive fibrosis because there is minimal inflammation or cell death.

After acute hypovolemic shock, serum aminotransferase levels can rise to extremely high levels but rapidly return to normal when perfusion and cardiac function improve. Hepatic necrosis or acute liver failure can occur in infants with hypoplastic left heart syndrome and coarctation of the aorta. High systemic venous pressures after Fontan procedures can also lead to hepatic dysfunction, marked by prolonged prothrombin time, and cardiac cirrhosis. The aim of therapy in all causes of cardiac-associated liver disease is to improve cardiac output, reduce systemic venous pressures, and monitor for other signs of hypoperfusion. Even mild liver disease can have an impact on mortality after cardiac surgery, with poorer outcomes with progressively worse liver disease. In adults with cirrhosis undergoing cardiac surgery, overall mortality was 17% but varied significantly from 5% with mild disease to 70% with advanced liver disease.

Cholestasis Associated With Chronic Total Parenteral Nutrition

Total parenteral nutrition (TPN) can cause a variety of liver diseases, including hepatic steatosis, gallbladder and bile duct damage, and cholestasis. Cholestasis is the most severe complication and can lead to progressive fibrosis and cirrhosis. It is the major factor limiting effective long-term use of TPN in children and adults. Risk factors for TPN-associated cholestasis include prolonged duration of TPN (particularly soy-based lipids), prematurity, low birthweight, sepsis, necrotizing enterocolitis, and short bowel syndrome.

The pathogenesis of TPN-associated cholestasis is multifactorial. Sepsis; excess caloric intake; high amounts of protein, fat, or carbohydrate; specific amino acid toxicities; nutrient deficiencies; and toxicities related to components such as manganese, aluminum, and copper can all contribute to hepatic injury. The type (soy based), volume, and frequency of lipid administered may be a significant factor. Prolonged enteral fasting compromises mucosal integrity and increases bacterial mucosal translocation. Fasting also decreases release of cholecystokinin, which promotes bile flow. This leads to biliary stasis, cholestasis, and formation of biliary sludge and gallstones, which exacerbates hepatic dysfunction. Sepsis, in particular due to Gram-negative bacteria and associated endotoxins, can also exacerbate liver damage.

Early histologic findings include macrovesicular steatosis, canalicular cholestasis, and periportal inflammation. These changes can regress after cessation of short-term TPN. Prolonged duration of TPN is marked by bile duct proliferation or ductopenia, portal fibrosis, and expansion of portal triads, and it can progress to cirrhosis and end-stage liver disease.

Clinical onset is typically marked by gradual onset of cholestasis, developing after more than 2 wk of TPN. In low birthweight infants, the onset of jaundice can overlap the phase of physiologic (unconjugated) hyperbilirubinemia. Any icteric infant who has received TPN for more than 1 wk should have bilirubin fractionated. With prolonged duration, hepatic enlargement or splenomegaly can develop. Serum bile acid concentrations can increase. Rises in serum aminotransferase levels may be a late finding. An elevation in serum AP activity may be due to rickets, a common complication of TPN in low birthweight infants.

In addition to cholestasis, biliary complications of intravenous nutrition include cholelithiasis and the development of biliary sludge, associated with thick, inspissated gallbladder contents. These may be asymptomatic. Hepatic steatosis or elevated serum aminotransferase levels can also occur in the absence of cholestasis, particularly in older children. This is generally mild and resolves after TPN is discontinued. Serum bilirubin and bile acid levels remain within the normal range. Other causes of liver disease should also be considered, especially if evidence of hepatic dysfunction persists despite weaning from TPN and initiating enteral feeds. If serum AP or aminotransferase levels remain elevated, liver biopsy may be necessary for accurate diagnosis.

Treatment of TPN-associated cholestasis is focused on avoiding progressive liver injury by limiting the duration of the infusion whenever possible. Enteral feeding should be initiated as soon as tolerated and prolonged fasting should be avoided. Even small volumes of nutrients given by intermittent oral feedings or by continuous nasogastric drip promote bile flow, enterohepatic recirculation of bile acids, and intestinal motility, and they enhance mucosal barrier function, reducing the risk of bacterial translocation. Improved TPN solutions that meet the specific needs of neonates can prevent deficiencies and toxicities. The risk of further hepatic injury should always be considered when weighing the option of continuing TPN indefinitely, and all efforts should be made to try to advance enteral feeds whenever possible. There has been concern that the soy-based lipid infusion provided with TPN may be a significant contributing factor to TPN-associated cholestasis as a result of proinflammatory omega-6 fatty acids. Several strategies have been used to minimize exposure to these fatty acids by limiting total lipid and/or introducing alternate sources of lipid including fish oil and olive oil to provide more omega-3 fatty acids. The long-term effects of these strategies on essential fatty acid deficiency or growth are unclear although there is some evidence that TPN-associated cholestasis may improve.

Ursodeoxycholic acid therapy may be beneficial in improving jaundice and hepatosplenomegaly. Other therapies, such as administration of antibiotics to reduce intraluminal bacterial overgrowth or oral administration of taurine or cholecystokinin, remain experimental.

Cystic Fibrosis

Cystic fibrosis (CF) (Chapter 432) is caused by mutations in the *CFTR* gene, which impair chloride transport across the apical membranes of epithelial cells in numerous organs (including cholangiocytes). Many patients with CF have some evidence of hepatobiliary disease; however, less than one-third of these patients develop clinically significant liver disease. Hepatobiliary complications account for approximately 2.5% of overall mortality in patients with CF. The onset of liver disease occurs at a median age of 10 yr, and >90% occurs by 20 yr.

Focal biliary cirrhosis is the pathognomonic liver lesion in CF and is postulated to result, in part, from impaired secretory function of the bile duct epithelium. Blockage of biliary ductules secondary to viscid secretions results in periductal inflammation, bile duct proliferation, and increased fibrosis within focal portal tracts. Gradual progression to multilobular cirrhosis can occur and result in portal hypertension and end-stage liver disease in 1–8% of patients. Liver disease tends to occur mainly in males with pancreatic insufficiency and requires 2 CFTR mutations without residual function. One candidate gene modifier for clinical phenotypes of CF-related liver disease that shows a strong association is SERPINA1. However, additional study of mutational analysis is necessary before we are able to predict which patients with CF will develop liver disease. Clinical risk factors that may be associated with liver disease include older age, pancreatic insufficiency, male gender, and possibly a history of meconium ileus.

Treatment with oral ursodeoxycholic acid (10-15 mg/kg/day) may be beneficial in improving liver function, presumably by improving bile flow; further research is necessary to determine whether a true long-term benefit exists. Because it is difficult to predict which patients will develop liver disease, prophylactic therapy is not possible. Progression of liver disease is generally slow; the major concern is the development of portal hypertension and the associated complications.

Bone Marrow Transplantation

Liver disease is common in patients who have received hematopoietic stem cell transplantation (SCT), whether the cells are harvested from bone marrow or peripheral blood (Chapters 161-165). The pathogenesis is varied and includes infections (viral, bacterial, or fungal); toxicity from parenteral nutrition, chemotherapy, or radiation; venoocclusive disease (VOD); graft versus host disease (GVHD); or hemosiderosis secondary to iron overload from frequent blood transfusions. GVHD, drug toxicity, and sepsis are the most common causes of liver dysfunction after allogeneic SCT.

Diagnosis is often challenging due to the coexistence of multiple risk factors. Clinical course, symptoms and signs, and biochemical liver function and viral serologic tests must be considered in making the correct diagnosis. Percutaneous liver biopsy may be necessary; histology can show extensive bile duct injury in GVHD, viral inclusions in cytomegalovirus disease, or the characteristic endothelial lesion in VOD. It is important to diagnose the cause accurately, because treatment for GVHD differs markedly from that of other conditions (i.e., initiating immunosuppression for GVHD) and can worsen hepatitis secondary to infections.

GVHD of the liver can be acute or chronic but often occurs with the presence of GVHD in other target organs such as the skin and gut (Chapter 163). Hepatic GVHD is caused by immunologic reaction to bile duct epithelium, leading to a nonsuppurative cholangitis. Histologic features of GVHD include loss of intralobular bile ducts, endothelial injury of hepatic and portal venules, and hepatocellular necrosis.

Onset typically occurs at the time of donor engraftment (days 14-21 after SCT). In acute hepatic GVHD, serum aminotransferase levels can rise markedly in the absence of elevated bilirubin, AP, and GGT levels, mimicking viral hepatitis. Acute hepatic GVHD can manifest both early (days 14-21) and late (>day 70) after allogeneic SCT. In chronic hepatic GVHD, serum aminotransferase levels are not as markedly elevated and cholestasis is more prominent, with marked rises in serum conjugated bilirubin, GGT, and AP levels. Other signs and symptoms can include hepatic tenderness, dark urine, acholic stools, itching, and anorexia.

VOD of the liver usually develops in the first 3 wk after SCT. The incidence ranges from 5% to 39% in pediatric patients, with reported mortality rates varying from 0% to 47%. Risk factors include trauma, high-dose conditioning regimens, coagulopathies, sickle cell anemia, leukemia, polycythemia vera, thalassemia major, hepatic abscesses, irradiation, GVHD, iron overload, preexisting liver disease, and younger age. VOD is caused by fibrous obliteration of the terminal hepatic venules and small lobular veins, with resultant damage to the surrounding hepatocytes and sinusoids. It is not associated with thrombus formation, in contrast with Budd-Chiari syndrome, which involves occlusion of the larger hepatic veins or inferior vena cava by a web, mass, or thrombus.

Pathologic changes in patients with VOD are best demonstrated using special (trichrome) stains to highlight the central veins. The lesions may be patchy. Later in the course, hepatic venules may be completely obliterated.

Symptoms typically include jaundice, painful hepatomegaly, rapid weight gain, and ascites, although jaundice can be absent in nearly a third of pediatric patients with VOD. VOD resolves in the majority of patients but can also lead to multisystem organ failure, hepatic encephalopathy, and fulminant hepatic failure. Less-severe forms may be characterized by jaundice and ascites with a slow resolution; in very mild cases, histologic changes may be the sole manifestation. The diagnosis rests on the exclusion of other diseases, such as GVHD, congestive cardiomyopathy, constrictive pericarditis, and Budd-Chiari syndrome.

Treatment for VOD with defibrotide, an agent with antithrombotic and thrombolytic properties, at doses of 20-40 mg/kg/day, has been successful in multicenter trials in both adult and pediatric patients. Complete response rates vary between 36% and 76% and survival >100 days post SCT of 32–79%, with better outcomes in pediatric patients. Little toxicity has been noted; however, pediatric patients are at a higher risk of bleeding with treatment compared with adults. Oral ursodeoxycholic acid can decrease the incidence of severe liver disease in patients undergoing SCT and has been shown to reduce the incidence of VOD and transplant-related mortality in adults. Supportive management includes maintaining intravenous hydration and renal perfusion.

Hemoglobinopathies

Patients with sickle cell anemia (Chapter 489.1) or thalassemia (Chapter 489.10) can have hepatic dysfunction due to acute or chronic viral hepatitis, hemosiderosis from frequent transfusion therapy, hepatic crises related to severe intrahepatic cholestasis, sequestration, or ischemic necrosis. Cholelithiasis and hemosiderosis are both common and treatable. Higher volume of transfusions is associated with both higher hepatic iron content and fibrosis. Chelation therapy for iron overload is usually safe and effective but needs to be properly managed and monitored via imaging and serum ferritin levels.

Hepatic sickle cell crisis or “sickle hepatopathy” occurs in ~10% of patients with sickle cell disease. It manifests with intense RUQ pain and tenderness, fever, leukocytosis, and jaundice. Bilirubin levels may be markedly elevated; serum ALP levels may be only moderately elevated. It can be difficult to distinguish sickle hepatopathy from viral hepatitis, acute cholecystitis, or choledocholithiasis; therefore these conditions should be excluded. In general, hepatic sickle cell crisis is self-limited and symptoms resolve within 1-3 wk. **Sickle cell intrahepatic cholestasis** manifests as hepatomegaly, abdominal pain, hyperbilirubinemia, and coagulopathy and can progress to acute liver failure, leaving transplantation as the only therapeutic option. Transplantation carries a high risk for graft loss due to vascular complications.

On occasion, children with sickle cell disease experience a benign elevation of bilirubin levels >20 mg/dL but unaccompanied by severe pain or fever. There is no change in hematocrit or reticulocyte count nor any association with a hemolytic crisis.

Histiocytic Disorders

Langerhans cell histiocytosis (Chapter 534.1), the most common of the histiocytoses, typically affects the bone and skin. However, it can cause infiltration of high-risk organs such as the liver resulting in periportal inflammation and sclerosing cholangitis. Liver involvement often results in worse outcomes. Hemophagocytic lymphohistiocytosis (HLH) (Chapter 534.2) is a multiorgan, severe, and potentially fatal inflammatory process associated with activation of macrophages that mimics sepsis. The hepatic manifestation of HLH is usually acute liver failure with portal inflammatory infiltrates and hemophagocytosis noted on liver biopsy.

387.1

Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) , a spectrum of liver diseases strongly associated with obesity, is the most common chronic liver disease in children. NAFLD can range from fatty liver alone to a triad of fatty infiltration, inflammation, and fibrosis termed **nonalcoholic steatohepatitis (NASH)** , which resembles alcoholic liver disease but occurs with little or no exposure to ethanol. Unlike adults, NASH in children has 2 distinct histologic types. **Type 1 NASH** resembles adult histologic findings with steatosis and balloon degeneration of hepatocytes and/or periportal fibrosis. **Type 2 NASH** includes steatosis and portal inflammation.

Many patients with NAFLD are asymptomatic. Liver histology, obtained from autopsy data, suggest that 10% of children and 38% of obese children aged 2-19 yr old have NAFLD. The risk is lower in African-American children. Elevated serum aminotransferase levels are not sensitive or specific markers for NAFLD. A normal serum ALT level is present in 21–23% of pediatric patients with NAFLD. Although ultrasonography detects NAFLD, no current imaging modalities distinguish between simple steatosis and NASH. A liver biopsy may be required for a delimiting diagnosis. There are no reliable biomarkers available to serve as an alternative to liver biopsy.

The estimated prevalence of fatty liver disease in adults is thought to be as high as 15–20% for NAFLD overall and 2–4% for NASH. Risk factors in pediatric cohorts include obesity, male gender, white or Hispanic ethnicity, hypertriglyceridemia, and insulin resistance. Hepatic steatosis alone may be benign, but up to a quarter of patients with NASH can develop progressive fibrosis with resultant cirrhosis. The long-term prognosis of NASH that has developed in childhood is unknown.

Children diagnosed with NAFLD should be screened for comorbid conditions, including diabetes, hypertension, dyslipidemia, and obstructive sleep apnea. Obese and overweight children with other risk factors >3 yr of age should be screened for NAFLD by checking aminotransferase levels and liver ultrasound, even though neither is highly sensitive or specific. MRI is in use for clinical trials, but further studies are needed prior to its standard use in patient care.

Lysosomal acid lipase deficiency (LAL-D) , an autosomal recessive disorder due to mutations in *LIPA* may produce a hepatic steatosis like syndrome. In contrast to NAFLD, patients with LAL-D usually demonstrate microvesicular or mixed micro- and macrovesicular steatosis not macrovesicular changes.

Therapeutic trials in children and adolescents with biopsy-proven NAFLD/NASH are rare. Although there is no definitive treatment for NAFLD, gradual weight loss is effective in normalizing serum ALT levels and improving NAFLD. Low glycemic index foods and substituting polyunsaturated fatty acids for saturated fats may help. Vitamin E and vitamin C provide no additional benefit to the efficacy of lifestyle intervention (diet and exercise) in improving steatosis or biochemical abnormalities in pediatric NAFLD. However, vitamin E has been shown to improve balloon degeneration in children with NASH. Metformin has produced mixed results in the treatment of NAFLD. Thiazolidinediones (pioglitazone, rosiglitazone) improve liver histology in adults with NASH but have not been studied in children. In view of the potential role of the gut microbiome in contributing to the pathogenesis of NAFLD, the role of probiotics as an adjunct to lifestyle changes is under investigation. A preliminary study using ω-3 docosahexaenoic acid in children showed improved insulin sensitivity, ALT, triglycerides, BMI, and histology in children with NAFLD. Cysteamine bitartrate (slow release), a potential precursor of glutathione, an antioxidant, may reduce liver enzyme levels, as well as serum leptin and adiponectin levels, and is also a potential candidate for the treatment of NAFLD. GLP-1 is a neuropeptide (incretin) that has an antihyperglycemic effect. A meta-analysis demonstrated decreased ALT and improved imaging findings, as well as histologic features in adults with NAFLD and diabetes treated with GLP-1 agonists. In adults, a fibroblast growth factor 19 (FGF-19)-like agent has shown preliminary positive results. FGF-19 regulates bile acid, carbohydrate and energy metabolism.

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CHAPTER 388

Mitochondrial Hepatopathies

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A wide variety of mitochondrial disorders are associated with liver disease. Hepatocytes contain a high density of mitochondria because the liver, with its biosynthetic and detoxifying functions, is highly dependent on adenosine triphosphate. Defects in mitochondrial function can lead to impaired oxidative phosphorylation, increased generation of reactive oxygen species, impairment of other metabolic pathways, and activation of mechanisms of cellular death.

Mitochondrial disorders can be divided into primary, in which the mitochondrial defect is the primary cause of the disorder, and secondary, in which mitochondrial function is affected by exogenous injury or a genetic mutation that affects nonmitochondrial proteins (see Chapter 105.4). Primary mitochondrial disorders can be caused by mutations affecting mitochondrial DNA (mtDNA) or by nuclear genes that encode mitochondrial proteins or cofactors (see Chapter 383 —Table 383.3 and Table 388.1). Specific patterns may be noted (Table 388.2). Secondary mitochondrial disorders include diseases with an uncertain etiology, such as Reye syndrome; disorders caused by endogenous or exogenous toxins, drugs, or metals; and other conditions in which mitochondrial oxidative injury may be involved in the pathogenesis of liver injury.

Table 388.1

Genotypic Classification of Primary Mitochondrial Hepatopathies and Organ Involvement

GENE	RESPIRATORY CHAIN COMPLEX	HEPATIC HISTOLOGY	OTHER ORGANS INVOLVED	CLINICAL FEATURES
Deletion	Multiple	Steatosis,	Kidney, heart,	Sideroblastic anemia, variable

	(Pearson)	fibrosis	CNS, muscle	thrombocytopenia and neutropenia, persistent diarrhea
MPV17	I, III, IV	Steatosis	CNS, muscle, gastrointestinal tract	Adult-onset multisystemic involvement: myopathy, ophthalmoplegia, severe constipation, parkinsonism
DGUOK	I, III, IV	Steatosis, fibrosis	Kidneys, CNS, muscle	Nystagmus, hypotonia, renal Fanconi syndrome, acidosis
MPV17	I, III, IV	Steatosis, fibrosis	CNS, PNS	Hypotonia
SUCLG1	I, III, IV	Steatosis	Kidneys, CNS, muscle	Myopathy, sensorineural hearing loss, respiratory failure
POLG1	I, III, IV	Steatosis, fibrosis	CNS, muscle	Liver failure preceded by neurologic symptoms, intractable seizures, ataxia, psychomotor regression
C10orf2/Twinkle	I, III, IV	Steatosis	CNS, muscle	Infantile-onset spinocerebellar ataxia, loss of skills
BCS1L	III (GRACILE)		CNS ±, muscle ±, kidneys	Fanconi-type renal tubulopathy
SCO1	IV	Steatosis, fibrosis	Muscle	
TRMU	I, III, IV	Steatosis, fibrosis		Infantile liver failure with subsequent recovery
EFG1	I, III, IV	Steatosis	CNS	Severe, rapidly progressive encephalopathy
EFTu	I, III, IV	Unknown	CNS	Severe lactic acidosis, rapidly fatal encephalopathy

CNS, central nervous system; *GRACILE,* growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death; *PNS,* peripheral nervous system.

From Lee WS, Sokol RJ: Mitochondrial hepatopathies: advances in genetics, therapeutic approaches and outcomes, *J Pediatr* 163:942–948, 2013 (Table 2, p. 944).

Table 388.2

Hepatic Phenotypes of Mitochondrial Cytopathies

- Infantile liver failure
- Neonatal cholestasis
- Pearson syndrome
- Alpers disease
- Chronic liver disease
- Drug-induced mitochondrial toxicity

From Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease* , ed 5, Philadelphia, 2016, Elsevier (Box 71.2, p. 876).

Epidemiology

Mitochondrial respiratory chain disorders of all types affect 1 in 20,000 children younger than 16 yr of age; liver involvement has been reported in 10–20% of patients with respiratory chain defect. Primary mitochondrial disorders, including mtDNA depletion syndromes (MDSs), occur in 1 in 5,000 live births and are a known cause of acute liver failure in children <2 yr of age.

More than 200 pathogenic point mutations, deletions, insertions, and rearrangements that involve mtDNA and nuclear DNA and encodes mitochondrial proteins are identified. Mitochondrial genetics are unique because mitochondria are able to replicate, transcribe, and translate their mitochondrial-derived DNA independently. A typical hepatocyte contains approximately 1,000 copies of mtDNA. Oxidative phosphorylation (the process of adenosine triphosphate production) occurs in the respiratory chain located in the inner mitochondrial membrane and is divided into 5 multienzyme complexes: reduced nicotinamide adenine dinucleotide coenzyme Q reductase (complex I), succinate–coenzyme Q reductase (complex II), reduced coenzyme Q–cytochrome-*c* reductase (complex III), cytochrome-*c* oxidase (complex IV), and adenosine triphosphate synthase (complex V). The respiratory chain peptide components are encoded by both nuclear and mtDNA genes, hence mutations in either genome can result in disorders of oxidative phosphorylation. Thirteen essential polypeptides are synthesized from the small 16.5-kilobase circular double-stranded mtDNA. mtDNA also encodes the 24 transfer RNAs required for intramitochondrial protein synthesis, whereas nuclear genes encode more than 70 respiratory chain subunits and an array of enzymes and cofactors required to maintain mtDNA, including DNA polymerase-γ (POLG), thymidine kinase 2, and deoxyguanosine kinase.

The expression of mitochondrial disorders is complex, and epidemiologic studies are hampered by technical difficulties in collecting and processing the tissue specimens needed to make accurate diagnoses, the variability in clinical presentation, and the fact that most disorders display maternal inheritance with variable penetrance (see Chapter 97). mtDNA mutates 10 times more often than nuclear DNA due to a lack of introns, protective histones, and an effective repair system in mitochondria. Mitochondrial genetics also displays a threshold effect in that the type and severity of mutation required for clinical expression varies among people and organ systems; this is explained by the concept of heteroplasmy, in which cells and tissues harbor both normal and mutant mtDNA in various amounts because of random partitioning during cell division. Mutations, deletions, or duplications in either mitochondrial or nuclear genes can cause disease, and mutations in nuclear genes that control mtDNA replication, transcription, and translation may lead to **MDS** or to a translational disorder.

Clinical Manifestations

Defects in oxidative phosphorylation can affect any tissue to a variable degree, with the most energy-dependent organs being the most vulnerable. One should consider the diagnosis of a mitochondrial disorder in a patient of any age who presents with progressive, multisystem involvement that cannot be explained by a specific diagnosis. Gastrointestinal complaints include vomiting, diarrhea, constipation, failure to thrive, and abdominal pain; certain mitochondrial disorders have characteristic gastrointestinal presentations. Pearson marrow-pancreas syndrome manifests with sideroblastic anemia and exocrine pancreatic insufficiency, whereas mitochondrial neurogastrointestinal encephalomyopathy manifests with chronic intestinal pseudo-obstruction and cachexia. Hepatic presentations range from chronic cholestasis, hepatomegaly, cirrhosis, and steatosis to fulminant hepatic failure and death. Patients with certain mitochondrial diseases may have normal or minimally elevated lactate levels even in the setting of a metabolic crisis. The lactate-to-pyruvate molar ratio (L:P) has been proposed as a screening test for mitochondrial disorders because it reflects the equilibrium between the product and substrate of the reaction catalyzed by lactase dehydrogenase. An L:P ≥ 25 has been considered to be highly suggestive of respiratory chain dysfunction; however, an elevated lactate or an elevated L:P can also represent secondary mitochondrial dysfunction occurring as a result of severe liver disease.

Primary Mitochondrial Hepatopathies

Neonatal Liver Failure

A common presentation of respiratory chain defects is severe liver failure manifested as jaundice, hypoglycemia, coagulopathy, renal dysfunction, and hyperammonemia, with onset within the first few weeks to months of life. **Cytochrome-*c* oxidase** (complex IV) is the most common deficiency in these infants, although complexes I and III and MDSs are also implicated (see Tables 388.1 and 383.3). The key biochemical features include a markedly elevated plasma lactate concentration, an elevated molar ratio of plasma lactate to pyruvate (L:P) (>25), and a raised ratio of β-hydroxybutyrate to acetoacetate

(>4.0). Symptoms are nonspecific and include lethargy and vomiting. Most patients additionally have neurologic involvement that manifests as a weak suck, recurrent apnea, or myoclonic epilepsy. Liver biopsy shows predominantly microvesicular steatosis, cholestasis, bile duct proliferation, glycogen depletion, and iron overload. With standard therapy the prognosis is poor, and most patients die from liver failure or infection in the first few months of life.

Alpers Syndrome (Alpers-Huttenlocher Syndrome or Alpers Hepatopathic Poliodystrophy)

Diagnostic criteria include refractory mixed-type seizures with a focal component; psychomotor regression that is episodic and triggered by intercurrent infections; and hepatopathy with or without acute liver failure. Alpers syndrome manifests from infancy up to 8 yr of age with seizures, hypotonia, feeding difficulties, psychomotor regression, and ataxia. Patients develop hepatomegaly and jaundice and have a slower progression to liver failure than those with cytochrome-*c* oxidase deficiency. Elevated blood or cerebrospinal fluid lactate and pyruvate levels are supportive of the diagnosis, in addition to characteristic electroencephalographic findings (high-amplitude slow activity with polyspikes), asymmetric abnormal visual evoked responses, and low-density areas or atrophy in the occipital or temporal lobes on computed tomography scanning of the brain. In some patients complex I deficiency has been found in liver or muscle mitochondria. The disease is inherited in an autosomal recessive fashion; mutations in the catalytic subunit of the nuclear gene mtDNA *POLG* have been identified in multiple families with Alpers syndrome, leading to the advent of molecular diagnosis for Alpers syndrome. Patients with *POLG* mutations are susceptible to *valproate-induced* liver dysfunction.

Mitochondrial DNA Depletion Syndrome

MDS is characterized by a tissue-specific reduction in mtDNA copy number, leading to deficiencies in complexes I, III, and IV. MDS manifests with phenotypic heterogeneity; multisystem and localized disease forms include myopathic, hepatocerebral, and liver-restricted presentations. Infants with the hepatocerebral form present in the neonatal period. The first symptoms are metabolic; these rapidly progress to hepatic failure with hypoglycemia and vomiting. This stage is followed by neurologic involvement affecting the central and peripheral systems. Laboratory studies are characterized by lactic acidosis, hypoglycemia, and markedly elevated α-fetoprotein in plasma. In some patients, iron overload has been found with elevated transferrin saturation, high ferritin levels, and iron accumulation in hepatocytes and Kupffer cells. Death usually occurs by 1 yr of age. Spontaneous recovery has been reported in a patient with liver-restricted disease. Inheritance is autosomal recessive and mutations in the nuclear deoxyguanosine kinase gene *(DGUOK)* have been identified in many patients with hepatocerebral MDS. Thymidine kinase 2 has been implicated in the myopathic form; no known genetic defect has been identified in liver-restricted MDS. Multiple other nuclear genes including *POLG, MPV17,* Twinkle helicase gene, and *SUCLG1* have been implicated in hepatocerebral MDS. Liver biopsies of patients with MDS show microvesicular steatosis, cholestasis, focal cytoplasmic biliary necrosis, and cytosiderosis in hepatocytes and sinusoidal cells. Ultrastructural changes are characteristic, with oncocytic transformation of mitochondria, which is characterized by mitochondria with sparse cristae, granular matrix, and dense or vesicular inclusions. If the native DNA-encoded complex II is normal and the activities of the other complexes are decreased, one should investigate mtDNA copy numbers for a MDS. Diagnosis is established by the demonstration of a low ratio of mtDNA (<10%) to nuclear DNA in affected tissues and/or genetic testing. Importantly, the sequence of the mitochondrial genome is normal.

Navajo Neurohepatopathy

Navajo neurohepatopathy (NNH) is an autosomal recessive sensorimotor neuropathy with progressive liver disease found only in Navajo Indians of the southwestern United States. The incidence is 1 in 1,600 live births. Diagnostic criteria include sensory neuropathy; motor neuropathy; corneal anesthesia; liver disease; metabolic or infectious complications including failure to thrive, short stature, delayed puberty, or systemic infection; and evidence of central nervous system demyelination on radiographic imaging and peripheral nerves biopsies. An *MPV17* gene mutation is implicated in the pathogenesis of NNH. Interestingly, this is the same gene implicated in MDS (see earlier), demonstrating that NNH may be a specific type of MDS found only in Navajos. NNH is divided into three phenotypic variations based on age of presentation and clinical findings.

First, **classic NNH** appears in infancy with severe progressive neurologic deterioration manifesting clinically as weakness, hypotonia, loss of sensation with accompanying acral mutilation, corneal ulcerations, and poor growth. Liver disease, present in the majority of patients, is secondary and variable; it includes asymptomatic elevations of liver function tests, Reye syndrome–like episodes, and hepatocellular carcinoma or cirrhosis. γ-Glutamyl transpeptidase levels tend to be higher than in other forms of NNH. Liver biopsy might show chronic portal tract inflammation and cirrhosis, but there is shows less cholestasis, hepatocyte ballooning, and giant cell transformation than in other forms of NNH.

Infantile NNH manifests between the ages of 1 and 6 mo with jaundice and failure to thrive and progresses to liver failure and death by 2 yr of age. Patients have hepatomegaly with moderate elevations in aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase. Liver biopsy demonstrates pseudoacinar formation, multinucleate giant cells, portal and lobular inflammation, canalicular cholestasis, and microvesicular steatosis. Progressive neurologic symptoms are not usually noticed at presentation but develop later.

Childhood NNH manifests from age 1-5 yr with the acute onset of fulminant hepatic failure leading to death within months. Most patients also have evidence of neuropathy at presentation. Liver biopsies are similar to those in infantile NNH except for significant hepatocyte ballooning and necrosis, bile duct proliferation, and cirrhosis, which are also seen.

There is no effective treatment for any of the forms of NNH, and neurologic symptoms often preclude liver transplantation. The identical *MPV17* mutation is seen in patients with both the infantile and classic forms of NNH, highlighting the clinical heterogeneity of NNH.

Pearson Syndrome

Pearson marrow-pancreas syndrome has a neonatal-onset with severe macrocytic anemia, variable neutropenia and thrombocytopenia, and ringed sideroblasts in the bone marrow. Diarrhea and fat malabsorption develop in early childhood secondary to extensive pancreatic fibrosis, acinar atrophy, and partial villous atrophy of the small intestine. The liver involvement includes hepatomegaly, steatosis, and cirrhosis. Liver failure and death have been reported before the age of 4 yr. Other features of the syndrome include renal tubular disease, photosensitivity, diabetes mellitus, hydrops fetalis, and the late development of visual impairment, tremor, ataxia, proximal muscle weakness, external ophthalmoplegia, and a pigmentary retinopathy. Methylglutaconic aciduria is a useful diagnostic marker. Large deletions of mtDNA are reported in most patients, resulting in deficiency of complexes I and III. mtDNA deletions can be detected in patients' cultured fibroblasts as well as in peripheral blood lymphocytes.

Villous Atrophy Syndrome

Children with this disease present with severe anorexia, vomiting, chronic diarrhea, and villous atrophy in the 1st yr of life. Hepatic involvement includes mild elevation of aminotransferase levels, hepatomegaly, and steatosis. Lactic acidosis is worsened with high-dextrose intravenous infusions or enteral nutrition. Diarrhea improves by 5 yr of age in association with the normalization of intestinal biopsies. Subsequently patients develop retinitis pigmentosa, cerebellar ataxia, sensorineural deafness, and proximal muscle weakness, with eventual death late in the 1st decade of life. The disease is attributed to a mtDNA rearrangement defect. A complex III deficiency was found in the muscle of affected patients.

GRACILE Syndrome

The acronym GRACILE summarizes the most important clinical features, namely fetal growth restriction (birth weight about −4 SD), aminoaciduria (caused by Fanconi-type tubulopathy), cholestasis (with steatosis and cirrhosis), iron overload, severe lactic acidosis, and early death. The syndrome is associated with mutations of the complex III assembly factor BCS1L. The liver histology shows microvesicular steatosis and cholestasis with abundant iron accumulation in hepatocytes and Kupffer cells. The liver iron content decreases slightly with age, concomitantly with increasing fibrosis and cirrhosis. Abnormal aminotransferase levels and coagulation are noted, but the cause of death seems to be related more to energy depletion than to liver failure. About half of these patients die within the first 2 wk of life.

Mutations in Nuclear Translation and Elongation

Factor Genes

Mutations in nuclear translation factor genes *(TRMU)* of the respiratory chain enzyme complexes have been identified as the etiology of acute liver failure manifesting at ages 1 day to 6 mo. The respiratory chain deficit was similar to that seen in MDS, where the activity of the native DNA-encoded complex II was normal whereas complexes I, III, and IV were decreased. The elongation factor EFG1 (gene *GFM1*) mutation was associated with fetal growth restriction, lactic acidosis, liver dysfunction that progresses into liver failure and death. The mutation in the elongation factor EFTu manifests as severe lactic acidosis and lethal encephalopathy with mild hepatic involvement.

Secondary Mitochondrial Hepatopathies

Secondary mitochondrial hepatopathies are caused by exposure to a hepatotoxic metal, drug, toxin, or endogenous metabolite. In the past, the most common secondary mitochondrial hepatopathy was **Reye syndrome,** the prevalence of which peaked in the 1970s and had a mortality rate of >40%. Although mortality has not changed, the prevalence has decreased from >500 cases in 1980 to approximately 35 cases per year since. The decline in the reported incidence of Reye syndrome may be partially related to more accurate modern diagnosis of infectious, metabolic, or toxic disease, thus reducing the percentage of idiopathic or true cases of Reye syndrome. Reye syndrome is precipitated in a genetically susceptible person by the interaction of a viral infection (influenza, varicella) and salicylate and/or antiemetic use. Clinically it is characterized by a preceding viral illness that appears to be resolving and the acute onset of vomiting and encephalopathy (see Table 388.3). Neurologic symptoms can rapidly progress to seizures, coma, and death. Liver dysfunction is invariably present when vomiting develops, with coagulopathy and elevated serum levels of aspartate aminotransferase, alanine aminotransferase, and ammonia. Importantly, patients remain anicteric and serum bilirubin levels are normal. Liver biopsies show microvesicular steatosis without evidence of liver inflammation or necrosis. Death is usually secondary to increased intracranial pressure and cerebral herniation. Patients who survive have full recovery of liver function but should be carefully screened for fatty-acid oxidation and fatty-acid transport defects (Table 388.4).

Table 388.3

Clinical Staging of Reye Syndrome and Reye-Like Diseases

Symptoms at the time of admission:

I. Usually quiet, **lethargic** and sleepy, vomiting, laboratory evidence of liver dysfunction
II. Deep lethargy, **confusion,** delirium, combativeness, hyperventilation, hyperreflexia
III. Obtunded, **light coma** ± seizures, **decorticate** rigidity, intact pupillary light reaction
IV. Seizures, deepening coma, **decerebrate rigidity,** loss of oculocephalic reflexes, fixed pupils
V. Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, **flaccidity/decerebration** (intermittent); isoelectric electroencephalogram

Table 388.4

Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome

- Metabolic disease
  - Organic aciduria
  - Disorders of oxidative phosphorylation
  - Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)
  - Defects in fatty acid oxidation metabolism
  - Acyl–coenzyme A dehydrogenase deficiencies
  - Systemic carnitine deficiency
  - Hepatic carnitine palmitoyltransferase deficiency
  - 3-OH, 3-methylglutaryl-coenzyme A lyase deficiency
  - Fructosemia
  - Infantile liver failure syndrome 1. Caused by leucyl-tRNA synthetase (LARS) gene mutations
- Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy
- Hemorrhagic shock with encephalopathy
- Drug or toxin ingestion (salicylate, valproate)

Acquired abnormalities of mitochondrial function can be caused by several drugs and toxins, including valproic acid, cyanide, amiodarone, chloramphenicol, iron, the emetic toxin of *Bacillus cereus*, and nucleoside analogs. Valproic acid is a branched fatty acid that can be metabolized into the mitochondrial toxin 4-envalproic acid. Children with underlying respiratory chain defects appear more sensitive to the toxic effects of this drug, and valproic acid is reported to precipitate liver failure in patients with **Alpers syndrome** and **cytochrome-*c* oxidase deficiency.** Nucleoside analogs directly inhibit mitochondrial respiratory chain complexes. The reverse transcriptase inhibitors zidovudine, didanosine, stavudine, and zalcitabine—used to treat HIV-infected patients—inhibit DNA POLG of mitochondria and can block elongation of mtDNA, leading to mtDNA depletion. Other conditions that can lead to mitochondrial oxidative stress include cholestasis, nonalcoholic steatohepatitis,

α_1 -antitrypsin deficiency, and Wilson disease.

Diagnostic Evaluation

Screening tests include common biochemical tests (comprehensive metabolic profile, INR, α-fetoprotein, CPK, phosphorus, complete blood cell count, ammonia, lactate, pyruvate, serum ketone bodies: both quantitative 3-hydroxybutyrate and quantitative acetoacetate, total free fatty acids, serum acylcarnitine profile; serum-free and total carnitines, urine organic acids, and serum amino acids) (Table 388.5). These results will guide subsequent confirmatory testing to establish a molecular diagnosis. Genotyping, including single gene or panel screening for common mitochondrial disease, is used in clinical practice. Whole exome or genome sequencing is also helpful and is replacing single gene or gene panel testing. However, the identification of multiple gene variants of uncertain significance will require detailed clinical and biochemical confirmation for interpretation. Tissue (liver biopsy, skin fibroblast, and muscle biopsy) may be needed to make a specific biochemical diagnosis.

Table 388.5

Tiered Investigations in Suspected Mitochondrial Liver Disease

TIER 1
Pre-/postprandial plasma lactate, glucose, FFA, and 3-OH
Plasma carnitine, acylcarnitines
Plasma amino acids, creatine kinase, thymidine
Urinary organic acids, amino acids, tubular resorption phosphate, albumin/creatinine ratio CSF lactate/protein (if feasible)
Electrocardiography and echocardiography
Electroencephalography and visual-evoked potentials
Common mutations in *POLG, DGUOK, MPV17,* and *TRMU*
TIER 2
Tissue analysis
Liver biopsy : (if feasible). Tissue for light microscopy, electron microscopy, and Oil Red O stain
Frozen tissue for respiratory chain enzyme activity analysis and mtDNA copy number
Muscle biopsy : Tissue for light microscopy, electron microscopy, Oil Red O stain, and histochemistry for respiratory chain complexes
Frozen tissue for respiratory chain enzyme activity analysis and mtDNA copy number

Skin biopsy: set up for fibroblast culture

TIER 3

Cranial MRI/MRS

TIER 4

Extended molecular screening. This will be guided by the clinical phenotype, results of the tissue analysis, and local facilities

Currently suggested genes should include *SUCLG1, BCS1L, SOC1, TFSM, TWINKLE, ACAD9, EARS2, GFM1, RRM2B, TK2* , and *SUCLA2*

From Wyllie R, Hyams JS, Kay M, editors: *Pediatric gastrointestinal and liver disease* , ed 5, Philadelphia, 2016, Elsevier (Box 71-3, p. 876).

Treatment of Mitochondrial Hepatopathies

There is no effective therapy for most patients with mitochondrial hepatopathies; neurologic involvement often precludes orthotopic liver transplantation. Patients with mitochondrial disorders remain at risk for transplant-related worsening of their underlying metabolic disease, especially patients with *POLG* -related disease. Several therapeutic drug combinations—including antioxidants, vitamins, cofactors, and electron acceptors—have been proposed, but no randomized controlled trials have been completed to evaluate them. Treatment strategies are supportive and include the infusion of sodium bicarbonate for acute metabolic acidosis, transfusions for anemia and thrombocytopenia, and exogenous pancreatic enzymes for pancreatic insufficiency. It is important to discontinue or avoid medications that may exacerbate hepatopathy, including sodium valproate, tetracycline, and macrolide antibiotics, azathioprine, chloramphenicol, quinolones, and linezolid. Ringer lactate should be avoided because patients with liver dysfunction may not be able to metabolize lactate. Propofol should be avoided during anesthesia because of potential interference with mitochondrial function. In patients with lactic acidosis, lactate levels should be monitored during procedures. It is important to maintain anabolism using a balanced intake of fat and carbohydrates while avoiding unbalanced intakes (e.g., glucose only at a high intravenous rate) or fasting for >12 hr.

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CHAPTER 389

Autoimmune Hepatitis

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Autoimmune Hepatitis

Chronic Liver Disease

Autoimmune hepatitis is a chronic hepatic inflammatory process manifested by elevated serum aminotransaminase concentrations, liver-associated serum autoantibodies, and/or hypergammaglobulinemia. The serological autoantibody profile defines 2 main types of autoimmune hepatitis: AIH type 1, with positivity for anti-nuclear antibodies (ANA) and/or anti–smooth muscle antibody (SMA) and AIH type 2, with positivity for anti–liver kidney microsomal type 1 antibody (anti-LKM-1). The targets of the inflammatory process can include hepatocytes and to a lesser extent bile duct epithelium. Chronicity is determined either by duration of liver disease (typically >3-6 mo) or by evidence of chronic hepatic decompensation (hypoalbuminemia, thrombocytopenia) or physical stigmata of chronic liver disease (clubbing, spider telangiectasia, splenomegaly, ascites). The severity is variable; the affected child might have only biochemical evidence of liver dysfunction, might have stigmata of chronic liver disease, or can present in hepatic failure.

Chronic hepatitis can also be caused by persistent viral infection (see Chapter 358), drugs (see Chapter 363), metabolic diseases (see Chapter 361), fatty liver disease, or idiopathic disorders, which may have features of autoimmunity (Table 389.1). More than 90% of hepatitis B infections in the 1st yr of life become chronic, compared with 5–10% among older children and adults. Chronic hepatitis develops in >50% of acute hepatitis C virus infections. Transmission can occur during the perinatal period from an infected mother or in adolescents from parenteral drug abuse. Hepatitis A does not lead to chronic liver disease. Hepatitis E can become chronic in immunosuppressed patients.

Drugs commonly used in children that can cause chronic liver injury, which can mimic autoimmune hepatitis, include isoniazid, methyldopa, pemoline, nitrofurantoin, dantrolene, minocycline, pemoline, and the sulfonamides. **Metabolic diseases** can lead to chronic hepatitis, including α_1 -antitrypsin deficiency, inborn errors of bile acid biosynthesis, and Wilson disease. **Nonalcoholic steatohepatitis,** usually associated with obesity and insulin resistance, is another common cause of chronic hepatitis. It can progress to cirrhosis but responds to weight reduction. In many cases the cause of chronic hepatitis is unknown; in some, an autoimmune mechanism is suggested by the finding of serum antinuclear and anti–SMAs and by multisystem involvement (arthropathy, thyroiditis, rashes, Coombs-positive hemolytic anemia).

Table 389.1

Disorders Producing Chronic Hepatitis

- Chronic viral hepatitis
  - Hepatitis B
  - Hepatitis C
  - Hepatitis D
- Autoimmune hepatitis
  - Anti–actin antibody-positive
  - Anti–liver-kidney microsomal antibody-positive
  - Anti–soluble liver antigen antibody-positive
  - Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein)
  - Overlap syndrome with sclerosing cholangitis and autoantibodies
  - Systemic lupus erythematosus
  - Celiac disease
- Drug-induced hepatitis
- Metabolic disorders associated with chronic liver disease
  - Wilson disease
  - Nonalcoholic steatohepatitis
  - α_1 -Antitrypsin deficiency
  - Tyrosinemia
  - Niemann-Pick disease type 2
  - Glycogen storage disease type IV
  - Cystic fibrosis
  - Galactosemia
  - Bile acid biosynthetic abnormalities

Autoimmune hepatitis is a clinical constellation that suggests an immune-mediated process; it is responsive to immunosuppressive therapy (Table 389.2). Autoimmune hepatitis typically refers to a primarily hepatocyte-specific process, whereas autoimmune cholangiopathy and sclerosing cholangitis predominately involve intrahepatic and extrahepatic bile duct injury. Overlap of the process involving both hepatocyte and bile duct–directed injury may be more common in children. De novo hepatitis can be seen in a subset of liver transplant recipients whose initial disease was not autoimmune.

Table 389.2

Classification of Autoimmune Hepatitis

VARIABLE	TYPE 1 AUTOIMMUNE HEPATITIS	TYPE 2 AUTOIMMUNE HEPATITIS
Characteristic autoantibodies	Antinuclear antibody[*]	Antibody against liver-kidney microsome type 1[*]
	Smooth-muscle antibody[*]	
	Antiactin antibody [†]	Antibody against liver cytosol type 1[*]
	Autoantibodies against soluble liver antigen and liver-pancreas antigen [‡]	Antibody against liver-kidney microsomal type 3
	Atypical perinuclear antineutrophil cytoplasmic antibody	
Geographic variation	Worldwide	Worldwide; rare in North America
Age at presentation	Any age	Predominantly childhood and young adulthood
Gender of patients	Female in ~75% of cases	Female in ~95% of cases
Association with other autoimmune diseases	Common	Common [§]
Clinical severity	Broad range, variable	Generally severe
Histopathologic features at presentation	Broad range, mild disease to cirrhosis	Generally advanced
Treatment failure	Infrequent	Frequent
Relapse after drug withdrawal	Variable	Common
Need for long-term maintenance	Variable	~100%

[*] The conventional method of detection is immunofluorescence.

[†] Tests for this antibody are rarely available in commercial laboratories.

[‡] This antibody is detected by enzyme-linked immunosorbent assay.

[§] Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy is seen only in patients with type 2 disease.

Modified from Krawitt EL: Autoimmune hepatitis, *N Engl J Med* 354:54–66, 2006.

Etiology

T Lymphocytes

Autoimmune Regulator Gene

Autoimmune hepatitis arises in a genetically predisposed host after an unknown trigger leads to a T cell–mediated immune response targeting liver autoantigens. A dense portal mononuclear cell infiltrate invades the surrounding parenchyma and comprises T and B lymphocytes, macrophages, and plasma cells. The immunopathogenic mechanisms underlying autoimmune hepatitis are unsettled. Triggering factors can include molecular mimicry, infections, drugs, and the environment (toxins) in a genetically susceptible host. Several human leukocyte antigen class II molecules—particularly DR3, DR4, and DR7 isoforms—confer susceptibility to autoimmune hepatitis. Self-antigenic peptides are processed by populations of antigen-presenting cells and presented to CD4 and CD8 effector T cells. CD4+ T lymphocytes recognizing a self-antigenic liver peptide orchestrate liver injury. Cell-mediated injury by cytokines released by CD8+ cytotoxic T cells and/or antibody-mediated cytotoxicity can be operative. There is also evidence that regulatory T cells from patients with autoimmune hepatitis are impaired in their ability to control the proliferation of CD4 and CD8 effector cells. Cytochrome P450 2D6 is the main autoantigen in type 2 autoimmune hepatitis.

Antibody-coated hepatocytes may be lysed by complement or Fc-bearing natural killer lymphocytes. Heterozygous mutations in the **autoimmune regulator gene *(AIRE),*** which encodes a transcription factor controlling the negative selection of autoreactive thymocytes, can be found in some children with autoimmune hepatitis types 1 and 2. *AIRE* mutations also cause **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy** (also called autoimmune polyendocrinopathy syndrome), in which autoimmune hepatitis occurs in approximately 20% of patients.

Pathology

The histologic features common to untreated cases include inflammatory infiltrates, consisting of lymphocytes and plasma cells that expand portal areas and often penetrate the lobule (interface hepatitis); moderate to severe piecemeal necrosis of hepatocytes extending outward from the limiting plate; variable necrosis, fibrosis, and zones of parenchymal collapse spanning neighboring portal triads or between a portal triad and central vein (bridging necrosis); and variable degrees of bile duct epithelial injury. Distortion of hepatic architecture can be severe; cirrhosis may be present in children at the time of diagnosis. Histologic features in acute liver failure may be obscured by massive necrosis and multilobular collapse. Other histologic features may suggest an alternative diagnosis: characteristic periodic acid–Schiff-positive, diastase-resistant granules are seen in α_1 -antitrypsin deficiency, and macrovesicular and microvesicular steatosis is found in nonalcoholic steatohepatitis and often in Wilson disease. Bile duct injury can suggest an autoimmune cholangiopathy or an overlap syndrome. Ultrastructural analysis might suggest distinct types of storage disorders.

Clinical Manifestations

The clinical features and course of autoimmune hepatitis are extremely variable. Signs and symptoms at the time of presentation comprise a wide spectrum of disease including a substantial number of asymptomatic patients and some who have an acute, even fulminant, onset. In 25–30% of patients with autoimmune hepatitis, particularly children, the illness mimics acute viral hepatitis. In most the onset is insidious. Patients can be asymptomatic or have fatigue, malaise, behavioral changes, anorexia, and amenorrhea, sometimes for many months before jaundice or stigmata of chronic liver disease are recognized. Extrahepatic manifestations can include arthritis, vasculitis, nephritis, thyroiditis, Coombs-positive anemia, and rash. Some patients' initial clinical features reflect cirrhosis (ascites, hypersplenism, bleeding esophageal varices, or hepatic encephalopathy).

There may be mild to moderate jaundice in severe cases. Spider telangiectasias and palmar erythema may be present. The liver may be tender and slightly enlarged but might not be felt in patients with cirrhosis. The spleen is commonly enlarged. Edema and ascites may be present in advanced cases.

Laboratory Findings

The findings are related to the severity of presentation. In many asymptomatic cases, serum aminotransferase ranges between 100 and 300 IU/L, whereas levels in excess of 1,000 IU/L can be seen in young symptomatic patients. Serum bilirubin concentrations may be normal in mild cases but are commonly 2-10 mg/dL in more severe cases. Serum alkaline phosphatase and γ-glutamyl transpeptidase activities are normal to slightly increased but may be more significantly elevated in autoimmune cholangiopathy or in the setting of overlap with sclerosing cholangitis. Serum γ-globulin levels can show marked polyclonal elevations. Hypoalbuminemia is common. The prothrombin time is prolonged, most often as a result of vitamin K deficiency but also as a reflection of impaired hepatocellular function. A normochromic normocytic anemia, leukopenia, and thrombocytopenia are present and become more severe with the development of portal hypertension and hypersplenism.

Most patients with autoimmune hepatitis have hypergammaglobulinemia. Serum immunoglobulin G levels usually exceed 16 g/L. Characteristic patterns of serum **autoantibodies** define distinct subgroups of autoimmune hepatitis (see Table 389.2). The most common pattern (type 1) is associated with the formation of non–organ-specific antibodies, such as **antiactin (smooth muscle)** and ANA. Approximately 50% of these patients are 10-20 yr of age. High titers of a **liver-kidney microsomal** antibody are detected in another form (type 2) that usually affects children 2-14 yr of age. A subgroup of primarily young women might demonstrate autoantibodies against a soluble liver antigen but not against nuclear or microsomal proteins. Antineutrophil cytoplasmic antibodies may be seen more commonly in autoimmune cholangiopathy. Autoantibodies are rare in healthy children, so that titers as low as 1 : 40 may be significant, although nonspecific elevation in autoantibodies can be observed in a variety of liver diseases. Up to 20% of patients with apparent autoimmune hepatitis might not have autoantibodies at presentation but have histological features and clinical course consistent with the disorder. Other, less common autoantibodies include rheumatoid factor, antiparietal cell antibodies, antithyroid antibodies, and anti–liver cytosol type 1 antibody (anti-LC-1). A Coombs-positive hemolytic anemia may be present.

Diagnosis

There is no specific test for autoimmune hepatitis; it is a clinical diagnosis based on certain diagnostic criteria. Diagnostic criteria with scoring systems have been developed for adults and modified slightly for children, although these scoring systems were developed as research rather than diagnostic tools. Important positive features include female gender, primary elevation in transaminases and not alkaline phosphatase (or GGT), elevated γ-globulin levels, the presence of autoantibodies (most commonly antinuclear, smooth muscle, or liver-kidney microsome), and characteristic histologic findings (Fig. 389.1). Important negative features include the absence of viral markers (hepatitides B, C, D) of infection, absence of a history of drug or blood product exposure, and negligible alcohol consumption.

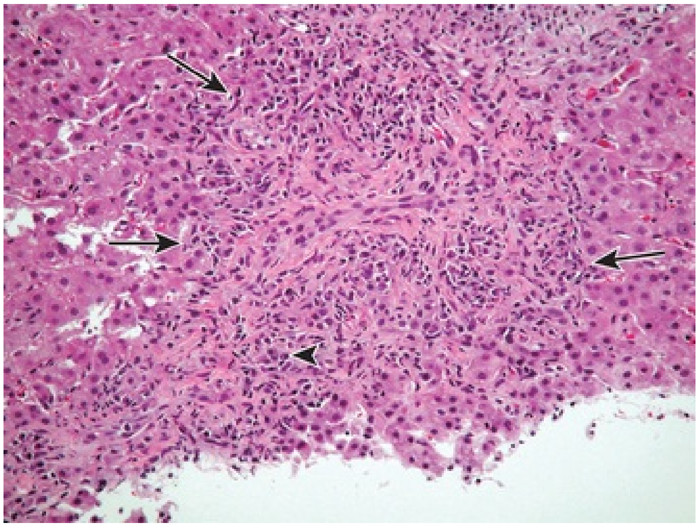

FIG. 389.1 **Autoimmune hepatitis. Liver biopsy showing fibrous expansion of the portal tracts with moderate portal lymphocytic infiltrates rich in plasma cells *(arrowhead).* There is extensive interface hepatitis *(arrows).* Original magnification ×20. (Courtesy Margret Magid, Mount Sinai School of Medicine.)**

Common conditions that might lead to chronic hepatitis should be excluded (see Table 389.1). The differential diagnosis includes α_1 -antitrypsin deficiency (see Chapter 357) and Wilson disease (see Chapter 357.2). The former disorder must be excluded by performing α_1 -antitrypsin phenotyping and the latter by measuring serum ceruloplasmin and 24-hr urinary copper excretion and/or hepatic copper levels. Chronic hepatitis may occur in patients with inflammatory bowel disease, but liver dysfunction in such patients is more commonly caused by pericholangitis or sclerosing cholangitis. Celiac disease (see Chapter 338) is associated with liver disease that is akin to autoimmune hepatitis, and appropriate serologic testing should be performed, including assays for anti–tissue transglutaminase antibodies or antiendomysial antibodies. An ultrasonogram should be done to identify a choledochal cyst or other structural disorders of the biliary system. Magnetic resonance (MR) cholangiography may be very useful for screening for evidence of sclerosing cholangitis. An overlap syndrome with features of primary sclerosing cholangitis and autoimmune hepatitis is being increasingly recognized with wider application of MR cholangiography (Table 389.3). Patients with primary sclerosing cholangitis can have elevated γ-globulin levels and autoantibodies; therefore liver biopsy findings in these children may be especially important. Dilated or obliterated veins on ultrasonography suggest the possibility of the Budd-Chiari syndrome. Diagnosis of autoimmune liver disease in the setting of acute liver failure is difficult and care should be taken in applying standardized approaches. “Seronegative” autoimmune hepatitis has been described, so absence of classic autoimmune markers does not exclude this diagnosis.

Table 389.3

Overlap Syndromes of Autoimmune Hepatitis

	AUTOIMMUNE HEPATITIS WITH OVERLAPPING FEATURES OF:		
	Primary Biliary Cholangitis[*]	**Primary Sclerosing Cholangitis**	**Cholestasis**
Clinical and laboratory features	AMA +	AMA −	AMA −
	Serum AP frequently > 2-fold ULN	Serum AP frequently > 2-fold ULN	Serum AP frequently > 2-fold ULN
		IBD common	No UC
		Abnormal cholangiogram (except in small-duct disease)	Normal cholangiogram
Histology	Destructive cholangitis	Ductopenia	Lymphoplasmacytic portal and acinar infiltrates
	Ductopenia	Cholangiolar proliferation	Lymphocytic destructive cholangitis
	Cholestasis	Swollen fibrotic portal tracts	Swollen hepatocytes
Treatment	Prednisone (10 mg daily) in combination with azathioprine (50 mg daily) if AP ≤ 2 × ULN	Prednisone (10 mg daily) in combination with azathioprine (50 mg daily) and low-dose UDCA (13-15 mg/kg daily)	Prednisone (10 mg daily) in combination with azathioprine (50 mg daily) and/or low-dose UDCA (13-15 mg/kg daily) depending on AP level and histologic features
	Prednisone (10 mg daily) in combination with azathioprine (50 mg daily) and low-dose UDCA (13-15 mg/kg daily) if AP > 2 × ULN and/or florid duct lesions		

[*] Primary biliary cholangitis formerly called primary biliary cirrhosis.

AMA , antimitochondrial antibodies; *AP* , alkaline phosphatase level; *UDCA* , ursodeoxycholic acid; *ULN* , upper limit of normal.

From Czaja AJ: Autoimmune hepatitis. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, Philadelphia, 2016: Elsevier

(Table 90.4).

Treatment

Prednisone, with or without azathioprine or 6-mercaptopurine, improves the clinical, biochemical, and histologic features in most patients with autoimmune hepatitis and prolongs survival in most patients with severe disease. The goal is to suppress or eliminate hepatic inflammation with minimal side effects. Prednisone at an initial dose of 1-2 mg/kg/24 hr is continued until aminotransferase values return to less than twice the upper limit of normal. The dose should then be lowered in 5-mg decrements over 2-4 mo until a maintenance dose of 0.1-0.3 mg/kg/24 hr is achieved. In patients who respond poorly, who experience severe side effects, or who cannot be maintained on low-dose steroids, azathioprine (1.5-2.0 mg/kg/24 hr, up to 100 mg/24 hr) can be added, with frequent monitoring for bone marrow suppression. Measurement of thiopurine methyltransferase activity should be done prior to beginning treatment with the thiopurine drugs azathioprine and 6-mercaptopurine. Patients with low activity (10% prevalence) or absent activity (prevalence 0.3%) are at risk for developing severe drug-induced myelotoxicity from accumulation of the unmetabolized drug. Measurement of the drug metabolites, 6-thioguanine nucleotide and 6-methylmercaptopurine, is useful in determining why a patient is not responding to a standard dose of a thiopurine drug and may help in avoiding myelosuppression and hepatotoxicity. Single-agent therapy with alternate-day corticosteroids should be used with great caution, although addition of azathioprine to alternate-day steroids can be an effective approach that minimizes corticosteroid-related toxicity. In patients with a mild and relatively asymptomatic presentation, some favor a lower starting dose of prednisone (10-20 mg) coupled with the simultaneous early administration of either 6-mercaptopurine (1.0-1.5 mg/kg/24 hr) or azathioprine (1.5-2.0 mg/kg/24 hr). Patients with primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome respond similarly to immunosuppressive therapy. Precise diagnostic criteria for autoimmune disease in the setting of sclerosing cholangitis do not exist. Autoimmune markers and immunoglobulin levels are often elevated in children with sclerosing cholangitis and do not necessarily indicate a diagnosis of coincident autoimmune hepatitis. The choleretic agent, ursodeoxycholic acid, is often used in biliary tract disease, but trials in adults with primary sclerosing cholangitis have not shown efficacy, and patients have experienced toxicity at higher doses. There is a potential role for budesonide combined with azathioprine in treatment of noncirrhotic patients. Budesonide is a corticosteroid with high first-pass clearance by the liver and fewer systemic side effects including suppression of hypothalamic–pituitary axis. Cyclosporine, tacrolimus, mycophenolate mofetil, and sirolimus have been used in the management of cases refractory to standard therapy. Use of these agents should be reserved for practitioners with extensive experience in their administration, because the agents have a more restricted therapeutic to toxic ratio.

Histologic progress does not necessarily need to be assessed by sequential liver biopsies, although biochemical remission does not ensure histologic resolution. Follow-up liver biopsy is an important consideration in patients for whom consideration is given to discontinuing corticosteroid therapy. In patients with disappearance of symptoms and biochemical abnormalities and resolution of the necroinflammatory process on biopsy, an attempt at gradual discontinuation of medication is justified. There is a high rate of relapse after discontinuation of therapy.

Relapse can require reinstitution of induction dosing of immunosuppression to control disease relapse.

Prognosis

The initial response to therapy in autoimmune hepatitis is generally prompt, with a >75% rate of remission. Transaminases and bilirubin fall to near-normal levels, often in the first 1-3 months. When present, abnormalities in serum albumin and prothrombin time respond over a longer period (3-9 mo). In patients meeting the criteria for tapering and then withdrawal of treatment (25–40% of children), 50% are weaned from all medication; in the other 50%, relapse occurs after a variable period. Relapse usually responds to retreatment. Many children will not meet the criteria for an attempt at discontinuation of immunosuppression and should be maintained on the smallest dose of prednisone that minimizes biochemical activity of the disease. A careful balance of the risks of continued immunosuppression and ongoing hepatitis must be continually evaluated. This requires continual screening for complications of medical therapy (monitoring of linear growth velocity, ophthalmologic examination, bone density measurement, blood pressure monitoring). Intermittent flares of hepatitis can occur and can necessitate recycling of prednisone therapy.

Some children have a relatively steroid-resistant form of hepatitis. More extensive evaluations of the etiology of their hepatitis should be undertaken, directed particularly at reassessing for the presence of either sclerosing cholangitis or Wilson disease. Nonadherence to medical therapy is one of the most common causes of “resistance” to medical therapy. Progression to cirrhosis can occur in autoimmune hepatitis despite a good response to drug therapy and prolongation of life. Corticosteroid therapy in fulminant autoimmune disease may be useful, although it should be administered with caution, given the predisposition of these patients to systemic bacterial and fungal infections.

Liver transplantation has been successful in patients with end-stage or fulminant liver disease associated with autoimmune hepatitis (see Chapter 368). Disease recurs after transplantation in approximately 30% of patients and is associated with increased concentrations of serum autoantibodies and interface hepatitis on liver biopsy. Patients generally respond well to an increase in immunosuppression, particularly to the addition of azathioprine.

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CHAPTER 390

Drug- and Toxin-Induced Liver Injury

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The liver is the main site of drug metabolism and is particularly susceptible to structural and functional injury after the ingestion, parenteral administration, or inhalation of chemical agents, drugs, plant derivatives (home remedies), herbal or nutritional supplements, or environmental toxins. The possibility of drug use or toxin exposure at home or in the parents' workplace should be explored for every child with liver dysfunction. The clinical spectrum of illness can vary from asymptomatic biochemical abnormalities of liver function to fulminant failure. Liver injury may be the only clinical feature of an adverse drug reaction or may be accompanied by systemic manifestations and damage to other organs. In hospitalized patients, clinical and laboratory findings may be confused with the underlying illness. After acetaminophen, antimicrobials, supplements, and central nervous system agents are the most commonly implicated drug classes causing liver injury in children.

There is growing concern about environmental hepatotoxins that are insidious in their effects. Many environmental toxins—including the plasticizers, biphenyl A, and the phthalates—are ligands for nuclear receptors that transcriptionally activate the promoters of many genes involved in xenobiotic and lipid metabolism and may contribute to obesity and nonalcoholic fatty liver disease. Some herbal, weight loss, and body building supplements have been associated with hepatic injury or even liver failure (Table 390.1) related to their intrinsic toxicity or because of contamination with fungal toxins, pesticides, or heavy metals.

Table 390.1

Hepatotoxic Herbal Remedies, Dietary Supplements, and Weight Loss Products

REMEDY	POPULAR USES	SOURCE	HEPATOTOXIC COMPONENT	TYPE OF LIVER INJURY
Ayurvedic herbal medicine	Multiple	Multiple	Uncertain (may contain heavy metal contaminants)	Hepatitis
Barakol	Anxiolytic	*Cassia siamea*	Uncertain	Reversible hepatitis or cholestasis
Black cohosh	Menopausal symptoms	*Cimicifuga racemosa*	Uncertain	Hepatitis (causality uncertain)
“Bush tea”	Fever	*Senecio, Heliotropium, Crotalaria* spp.	Pyrrolizidine alkaloids	SOS
Cascara	Laxative	*Cascara sagrada*	Anthracene glycoside	Cholestatic hepatitis
Chaparral leaf (greasewood, creosote bush)	“Liver tonic,” burn salve, weight loss	*Larrea tridenta*	Nordihydroguaiaretic acid	Acute and chronic hepatitis, FHF
Chaso/onshido	Weight loss	—	*N* -nitro-fenfluramine	Acute hepatitis, FHF
Chinese medicines (traditional)				
Jin bu huan	Sleep aid, analgesic	*Lycopodium serratum*	Levo-tetrahydropalmitine	Acute or chronic hepatitis or cholestasis, steatosis
Ma huang	Weight loss	*Ephedra* spp.	Ephedrine	Severe hepatitis, FHF
Shou-wu-pian	Anti-aging, neuroprotection, laxative	*Polygonum multiflorum* Thunb (fleeceflower root)	Anthraquinone	Acute hepatitis or cholestasis
Syo-saiko-to	Multiple	*Scutellaria* root	Diterpenoids	Hepatocellular necrosis, cholestasis, steatosis, granulomas
Comfrey	Herbal tea	*Symphytum* spp.	Pyrrolizidine alkaloid	Acute SOS, cirrhosis
Germander	Weight loss, fever	*Teucrium chamaedry, T. capitatum, T. polium*	Diterpenoids, epoxides	Acute and chronic hepatitis, FHF, autoimmune injury
Greater celandine	Gallstones, IBS	*Chelidonium majus*	Isoquinoline alkaloids	Cholestatic hepatitis, fibrosis
Green tea leaf extract	Multiple	*Camellia sinensis*	Catechins	Hepatitis (causality questioned)
Herbalife	Nutritional supplement, weight loss	—	Various; ephedra	Severe hepatitis, FHF
Hydroxycut	Weight loss	*Camellia sinensis* , among other constituents	Uncertain	Acute hepatitis, FHF
Impila	Multiple	*Callilepsis laureola*	Potassium atractylate	Hepatic necrosis
Kava	Anxiolytic	*Piper methysticum*	Kava lactone, pipermethystine	Acute hepatitis, cholestasis, FHF
Kombucha	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis
Limbrel (Flavocoxid)	Osteoarthritis	Plant bioflavonoids	Baicalin, epicatechin	Acute mixed hepatocellular-cholestatic injury

Lipokinetix	Weight loss	Lichen alkaloid	Usnic acid	Acute hepatitis, jaundice, FHF
Mistletoe	Asthma, infertility	*Viscus album*	Uncertain	Hepatitis (in combination with skullcap)
Oil of cloves	Dental pain	Various foods, oils	Eugenol	Zonal necrosis
Pennyroyal (squawmint oil)	Abortifacient	*Hedeoma pulegoides, Mentha pulegium*	Pulegone, monoterpenes	Severe hepatocellular necrosis
Prostata	Prostatism	Multiple	Uncertain	Chronic cholestasis
Sassafras	Herbal tea	*Sassafras albidum*	Safrole	HCC (in animals)
Senna	Laxative	*Cassia angustifolia*	Sennoside alkaloids; anthrone	Acute hepatitis
Skullcap	Anxiolytic	*Scutellaria*	Diterpenoids	Hepatitis
Valerian	Sedative	*Valeriana officinalis*	Uncertain	Elevated liver enzymes

FHF, fulminant hepatic failure; *HCC,* hepatocellular carcinoma; *SOS,* sinusoidal obstruction syndrome.

From Lewis JH: Liver disease caused by anesthetics, chemicals, toxins, and herbal preparations. In Feldman M, Friedman LS, Brandt LJ, editors: *Sleisenger and Fordtran's gastrointestinal and liver disease* , ed 10, Philadelphia, 2016, Elsevier, (Table 89.6).

Hepatic metabolism of drugs and toxins is mediated by a sequence of enzymatic reactions that in large part transform hydrophobic, less-soluble molecules into more nontoxic, hydrophilic compounds that can be readily excreted in urine or bile (see Chapter 72). Relative liver size, liver blood flow, and extent of protein binding also influence drug metabolism. Phase 1 of the process involves enzymatic activation of the substrate to reactive intermediates containing a carboxyl, phenol, epoxide, or hydroxyl group. Mixed-function monooxygenase, cytochrome-*c* reductase, various hydrolases, and the cytochrome P450 (CYP) system are involved in this process. Nonspecific induction of these enzymatic pathways, which can occur during intercurrent viral infection, with starvation, and with the administration of certain drugs such as anticonvulsants, can alter drug metabolism and increase the potential for hepatotoxicity. A single agent can be metabolized by more than 1 biochemical reaction. The reactive intermediates that are potentially damaging to the cell are enzymatically conjugated in phase 2 reactions with glucuronic acid, sulfate, acetate, glycine, or glutathione. Some drugs may be directly metabolized by these conjugating reactions without first undergoing phase 1 activation. Phase 3 is the energy-dependent excretion of drug metabolites and their conjugates by an array of membrane transporters in the liver and kidney such as the multidrug resistant protein 1.

Pathways for biotransformation are expressed early in the fetus and infant, but many phase 1 and phase 2 enzymes are immature, particularly in the 1st yr of life. CYP3A4 is the primary hepatic CYP expressed postnatally and metabolizes more than 75 commonly used therapeutic drugs and several environmental pollutants and procarcinogens. Hepatic CYP3A4 activity is poorly expressed in the fetus but increases after birth to reach 30% of adult values by 1 mo and 50% of adult values between 6 and 12 mo of age. CYP3A4 can be induced by a number of drugs, including phenytoin, phenobarbital, and rifampin. Enhanced production of toxic metabolites can overwhelm the capacity of phase 2 reactions. Conversely, numerous inhibitors of CYP3A4 from several different drug classes, such as erythromycin and cimetidine, can lead to toxic accumulations of CYP3A4 substrates. By contrast, although CYP2D6 is also developmentally regulated (maturation by 10 yr of age), its activity depends more on genetic polymorphisms than on sensitivity to inducers and inhibitors because more than 70 allelic variants of CYP2D6 significantly influence the metabolism of many drugs. Uridine diphosphate glucuronosyltransferase 1A6, a phase 2 enzyme that glucuronidates acetaminophen, is also absent in the human fetus, increases slightly in the neonate, but does not reach adult levels until sometime after 10 yr of age. Mechanisms for the uptake and excretion of organic ions can also be deficient early in life. Impaired drug metabolism via phase 1 and phase 2 reactions present in the 1st few months of life is followed by a period of enhanced metabolism of many drugs in children through 10 yr of age compared with adults.

Genetic polymorphisms in genes encoding enzymes and transporters mediating phases 1, 2, and 3 reactions can also be associated with impaired drug metabolism and an increased risk of hepatotoxicity. Some cases of idiosyncratic hepatotoxicity can occur as a result of aberrations (polymorphisms) in phase 1 drug metabolism, producing intermediates of unusual hepatotoxic potential combined with developmental, acquired, or relative inefficiency of phase 2 conjugating reactions. Genome-wide association studies have identified HLA associations in certain cases of drug- and toxin-induced liver injury (**DILI**). Children may less susceptible than adults to hepatotoxic reactions; liver injury after the use of the anesthetic halothane is rare in children, and acetaminophen toxicity is less common in infants than in adolescents, whereas most cases of fatal hepatotoxicity associated with sodium valproate use have been reported in children. Excessive or prolonged therapeutic administration of acetaminophen combined with reductions in caloric or protein intake can produce hepatotoxicity in children. In this setting, acetaminophen metabolism may be impaired by reduced synthesis of sulfated and glucuronated metabolites and reduced stores of glutathione. Immaturity of hepatic drug metabolic pathways can prevent degradation of a toxic agent; under other circumstances, the same immaturity might limit the formation of toxic metabolites. Severe sodium valproate hepatotoxicity is often associated with an underlying inherited mitochondrial disorder (Alper syndrome).

Chemical hepatotoxicity can be predictable or idiosyncratic. Predictable hepatotoxicity implies a high incidence of hepatic injury in exposed persons depending on dose. It is understandable that only a few drugs in clinical use fall into this category. These agents might damage the hepatocyte directly through alteration of membrane lipids (peroxidation) or through denaturation of proteins; such agents include carbon tetrachloride and trichloroethylene. Indirect injury can occur through interference with metabolic pathways essential for cell integrity or through distortion of cellular constituents by covalent binding of a reactive metabolite; examples include the liver injury produced by acetaminophen or by antimetabolites such as methotrexate or 6-mercaptopurine.

Idiosyncratic hepatotoxicity is unpredictable and accounts for the majority of adverse reactions. In contrast to previous dogma that idiosyncratic reactions are independent of dose, there is new information that higher doses of drugs metabolized in the liver pose a greater risk for hepatotoxicity. Idiosyncratic drug reactions in certain patients can reflect aberrant pathways for drug metabolism, possibly related to genetic polymorphisms, with production of toxic intermediates (isoniazid and sodium valproate can cause liver damage through this mechanism). Duration of drug use before liver injury varies (weeks to ≥1 yr) and the response to reexposure may be delayed.

An idiosyncratic reaction can also be immunologically mediated as a result of prior sensitization (hypersensitivity); extrahepatic manifestations of hypersensitivity can include fever, rash, arthralgia, and eosinophilia. Duration of exposure before reaction is generally 1-4 wk, with prompt recurrence of injury on reexposure. Studies indicate that arene oxides, generated through oxidative (CYP) metabolism of aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), can initiate the pathogenesis of some hypersensitivity reactions. Arene oxides, formed in vivo, can bind to cellular macromolecules, thus perturbing cell function and possibly initiating immunologic mechanisms of liver injury.

Although the generation of chemically reactive metabolites has received great attention in the pathogenesis of hepatoxicity, increasing evidence now exists for the multifactorial nature of the process, in particular the role played by the host immune system. Activation of liver nonparenchymal Kupffer cells and infiltration by neutrophils perpetuate toxic injury by many drugs by release of reactive oxygen and nitrogen species as well as cytokines. Stellate cells can also be activated, potentially leading to hepatic fibrosis and cirrhosis.

The pathologic spectrum of drug-induced liver disease is extremely wide, is rarely specific, and can mimic other liver diseases (Table 390.2). Predictable hepatotoxins, such as acetaminophen, produce centrilobular necrosis of hepatocytes. Steatosis is an important feature of tetracycline (microvesicular) and ethanol (macrovesicular) toxicities. A cholestatic hepatitis can be observed, with injury caused by erythromycin estolate and chlorpromazine. Cholestasis without inflammation may be a toxic effect of estrogens and anabolic steroids. Use of oral contraceptives and androgens has also been associated with benign and malignant liver tumors. Some idiosyncratic drug reactions can produce mixed patterns of injury, with diffuse cholestasis and cell necrosis. Chronic hepatitis has been associated with the use of methyldopa and nitrofurantoin.

Table 390.2

Patterns of Hepatic Drug Injury

DISEASE	DRUG
Centrilobular necrosis	Acetaminophen
	Carbon tetrachloride
	Cocaine
	Ecstasy
	Iron
	Halothane
Microvesicular steatosis	Valproic acid
	Tetracycline
	Toluene
	Methotrexate
Acute hepatitis	Isoniazid
	Anti–tumor necrosis factor agents
	Valproic acid
General hypersensitivity	Sulfonamides
	Phenytoin
	Minocycline
Fibrosis	Methotrexate
Cholestasis	Chlorpromazine
	Aniline
	Erythromycin
	Paraquat
	Estrogens
	Sertraline
Sinusoidal obstruction syndrome (venoocclusive disease)	Irradiation plus busulfan
	Arsenic

	Cyclophosphamide
Portal and hepatic vein thrombosis	Estrogens
	Androgens
Biliary sludge	Ceftriaxone
Hepatic adenoma or hepatocellular carcinoma	Oral contraceptives
	Anabolic steroids

Clinical manifestations can be mild and nonspecific, such as fever and malaise. Fever, rash, and arthralgia may be prominent in cases of hypersensitivity. In ill hospitalized patients, the signs and symptoms of hepatic drug toxicity may be difficult to separate from the underlying illness. The differential diagnosis should include acute and chronic viral hepatitis, biliary tract disease, septicemia, ischemic and hypoxic liver injury, malignant infiltration, and inherited metabolic liver disease.

The laboratory features of drug- or toxin-related liver disease are extremely variable. Hepatocyte damage can lead to elevations of serum aminotransferase activities and serum bilirubin levels and to impaired synthetic function as evidenced by decreased serum coagulation factors and albumin. Hyperammonemia can occur with liver failure or with selective inhibition of the urea cycle (sodium valproate). Toxicologic screening of blood and urine specimens can aid in the detecting drug or toxin exposure. Percutaneous liver biopsy may be necessary to distinguish drug injury from complications of an underlying disorder or from intercurrent infection. Vanishing bile duct syndrome can be seen in a small portion of patients with idiosyncratic DILI.

Slight elevation of serum aminotransferase activities (generally <2-3 times normal) can occur during therapy with drugs, particularly anticonvulsants, capable of inducing microsomal pathways for drug metabolism. Liver biopsy reveals proliferation of smooth endoplasmic reticulum but no significant liver injury. Liver test abnormalities often resolve with continued drug therapy.

Treatment

Treatment of drug- or toxin-related liver injury is mainly supportive. Contact with the offending agent should be avoided. Corticosteroids might have a role in immune-mediated disease. Treatment with *n* -acetylcysteine, by stimulating glutathione synthesis, is effective in preventing or attenuating hepatotoxicity when administered within 16 hr after an acute overdose of acetaminophen and appears to improve survival in patients with severe liver injury even up to 36 hr after ingestion (see Chapter 63). Intravenous L -carnitine may be of value in treating valproic acid–induced hepatotoxicity. Orthotopic liver transplantation may be required for treatment of drug- or toxin-induced hepatic failure.

Prognosis

The prognosis of DILI depends on its type and severity. Injury is usually completely reversible when the hepatotoxic factor is withdrawn. The mortality of submassive hepatic necrosis with fulminant liver failure can, however, exceeds 50%. Hyperbilirubinemia, coagulopathy, and elevated serum creatinine are associated with an increased risk of death or need for liver transplantation. With continued use of certain drugs, such as methotrexate, effects of hepatoxicity can proceed insidiously to cirrhosis, even with normal or near normal liver tests. Neoplasia can follow long-term androgen therapy. Rechallenge with a drug suspected of having caused previous liver injury is rarely justified and can result in fatal hepatic necrosis.

Prevention

The prevention of drug-induced liver injury remains a challenge. Monitoring of liver biochemical tests may be useful in some cases, but it can prove difficult to sustain for agents used for many years. Such testing may be particularly important in patients with preexisting liver disease. For drugs with hepatotoxic potential, even if episodes are infrequent in children, such as with the use of isoniazid, patients should be advised to immediately stop the medication with onset of nausea, vomiting, abdominal pain, and fatigue until liver damage is excluded. Obvious symptoms of liver disease such as jaundice and dark urine can lag behind severe hepatocellular injury. Monitoring for toxic metabolites and genotyping can be effective in preventing severe toxicity with the use of azathioprine. Advances in pharmacogenomics, such as the use of gene chips to detect variants in some of the CYP enzymes, hold promise of a personalized approach to prevent hepatotoxicity.

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CHAPTER 391

Acute Hepatic Failure

Frederick J. Suchy, Amy G. Feldman

Acute liver failure is a clinical syndrome resulting from massive necrosis of hepatocytes or from severe functional impairment of hepatocytes. The synthetic, excretory, and detoxifying functions of the liver are all severely impaired. In adults, hepatic encephalopathy has been an essential diagnostic feature. However, in pediatrics, this narrow definition may be problematic, as early hepatic encephalopathy can be difficult to detect in infants and children, and some children in acute liver failure may not develop encephalopathy. The accepted definition in children includes biochemical evidence of acute liver injury (usually <8 wk duration); no evidence of chronic liver disease; and hepatic-based coagulopathy defined as a prothrombin time (PT) >15 sec or international normalized ratio (INR) >1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy, or a PT >20 sec or INR >2 regardless of the presence of clinical hepatic encephalopathy.

Liver failure in the perinatal period can be associated with prenatal liver injury and even cirrhosis. Examples include gestational alloimmune liver disease (GALD), tyrosinemia, familial hemophagocytic lymphohistiocytosis (HLH), and some cases of congenital viral (herpes simplex virus [HSV]) infection. Liver disease may be noticed at birth or after several days of apparent well-being. Fulminant Wilson disease and fulminant autoimmune hepatitis also occurs in older children who were previously asymptomatic but, by definition, have preexisting liver disease. Other forms of acute-on-chronic liver failure can occur when a patient with an underlying liver disease such as biliary atresia develops hepatic decompensation after viral or drug-induced hepatic injury. In some cases of liver failure, particularly in the idiopathic form of acute hepatic failure, the onset of encephalopathy occurs later, from 8 to 28 wk after the onset of jaundice.

Etiology

Infection

Acute hepatic failure can be a complication of **viral hepatitis** (A, B, D, and rarely E), Epstein-Barr virus, herpes simplex virus, adenovirus, enterovirus, influenza A, cytomegalovirus, parvovirus B19, human herpesvirus-6, varicella zoster infection, parechovirus, and other respiratory illnesses. An unusually high rate of fulminant hepatic failure occurs in young people who have combined infections with the hepatitis B virus (HBV) and hepatitis D. Mutations in the precore and/or promoter region of HBV DNA are associated with fulminant and severe hepatitis. HBV is also responsible for some cases of fulminant liver failure in the absence of serologic markers of HBV infection but with HBV DNA found in the liver. Hepatitis E virus is an uncommon cause of fulminant hepatic failure in the United States, but can occur in pregnant women, in whom mortality rates rise dramatically to up to 25%. Patients with chronic hepatitis C are at risk if they have superinfection with hepatitis A virus.

Autoimmune Hepatitis

Acute hepatic failure is caused by **autoimmune hepatitis** in approximately 5% of cases. Patients have a positive autoimmune marker (e.g., antinuclear antibody, anti–smooth muscle antibody, liver-kidney microsomal antibody, or soluble liver antigen) and possibly an elevated serum immunoglobulin G level. If a biopsy can be performed, liver histology often demonstrates interface hepatitis and a plasma cell infiltrate.

Metabolic Diseases

Metabolic disorders associated with hepatic failure include Wilson disease, acute fatty liver of pregnancy, galactosemia, hereditary tyrosinemia, hereditary fructose intolerance, defects in β-oxidation of fatty acids, and deficiencies of mitochondrial electron transport, in particular mitochondrial DNA depletion disorders. Patients with Wilson disease who present in acute liver failure often have high bilirubin levels, *low* alkaline phosphatase levels, low uric acid levels, aspartate aminotransferase levels that are higher than alanine aminotransferase levels, and a Coombs-negative hemolytic anemia.

Neoplasm

Acute liver failure can occur with malignancies including leukemia, lymphoma, and **familial HLH** . Acute liver failure is a common feature of HLH caused by several gene defects, infections by mostly viruses of the herpes group, and a variety of other conditions including organ transplantation and malignancies. Impaired function of natural killer cells and cytotoxic T-lymphocyte cells with uncontrolled hemophagocytosis and cytokine overproduction is characteristic for genetic and acquired forms of HLH. Patients with HLH present with a combination of fever, splenomegaly, cytopenias, high triglyceride levels, very high ferritin levels, low natural killer cell activity, high soluble CD25 levels; they may also have hemophagocytosis on bone marrow or liver biopsy (see Chapter 534).

Gestational Alloimmune Liver Disease

GALD is the most common cause of acute liver failure in the neonate. In this alloimmune process, maternal immunoglobulin (Ig) G antibodies bind to fetal liver antigens and activate the terminal complement cascade resulting in hepatocyte injury and death. Infants with GALD present with low/normal aminotransferases that are out of proportion to their degree of liver failure. They may have significant hypoglycemia, jaundice, coagulopathy, and hypoalbuminemia. Alpha fetoprotein levels are typically high as are serum ferritin levels.

Drug-Induced Liver Injury

Various hepatotoxic drugs and chemicals can also cause drug-induced liver injury and acute hepatic failure. Predictable liver injury can occur after exposure to carbon tetrachloride, *Amanita phalloides* mushrooms or after acetaminophen overdose. Acetaminophen is the most common identifiable etiology of acute hepatic failure in children and adolescents in the United States and England. In addition to the acute intentional ingestion of a massive dose, a therapeutic misadventure leading to severe liver injury can also occur in ill children given doses of acetaminophen exceeding weight-based recommendations for many days. Such patients can have reduced stores of glutathione after a prolonged illness and a period of poor nutrition. Idiosyncratic damage can follow the use of drugs such as halothane, isoniazid, ecstasy, or sodium valproate. Herbal and weight loss supplements are additional causes of hepatic failure (see Chapter 390).

Vascular

Ischemia and hypoxia resulting from hepatic vascular occlusion, severe heart failure, cyanotic congenital heart disease, or circulatory shock can produce liver failure.

Idiopathic Acute Liver Failure

Idiopathic acute liver failure accounts for 40–50% of acute hepatic failure cases in children. The disease occurs sporadically and usually without the risk factors for common causes of viral hepatitis. It is likely that the etiology of these cases is heterogeneous, including unidentified or variant viruses, excessive immune activation, and undiagnosed genetic or metabolic disorders. There is increasing recognition of some children presenting with indeterminate acute hepatitis or acute liver failure who have evidence of immune activation including markedly elevated sIL-2R levels but never fulfilling diagnostic criteria for HLH.

Recurrent, acute liver failure has been reported with onset in infancy due to mutations of the neuroblastoma amplified sequence gene *(NBAS)* . Episodes are usually precipitated by fever and characterized by bouts of vomiting and lethargy. Massively elevated aminotransferase levels and coagulopathy are present. Microvesicular steatosis is prominent on liver biopsy. Most patients recovered with restoration of normal liver function after control of fever and maintenance of energy balance with the infusion of intravenous glucose. The function of NBAS protein remains uncertain but it appears to be involved in retrograde transport between the endoplasmic reticulum and Golgi apparatus.

Pathology

Liver biopsy usually reveals patchy or confluent massive necrosis of hepatocytes. Multilobular or bridging necrosis can be associated with collapse of the reticulin framework of the liver. There may be little or no regeneration of hepatocytes. A zonal pattern of necrosis may be observed with certain insults. Centrilobular damage is associated with acetaminophen hepatotoxicity or with circulatory shock. Evidence of severe hepatocyte dysfunction rather than cell necrosis is occasionally the predominant histologic finding (microvesicular fatty infiltrate of hepatocytes is observed in Reye syndrome, β-oxidation defects, and tetracycline toxicity).

Pathogenesis

The mechanisms that lead to acute hepatic failure are poorly understood. It is unknown why only approximately 1–2% of patients with viral hepatitis experience liver failure. Massive destruction of hepatocytes might represent both a direct cytotoxic effect of the virus and an immune response to the viral antigens. Of patients with HBV-induced liver failure, ⅓ – ½ become negative for serum hepatitis B surface antigen within a few days of presentation and often have no detectable HBV antigen or HBV DNA in serum. These findings suggest a hyperimmune response to the virus that underlies the massive liver necrosis. Formation of hepatotoxic metabolites that bind covalently to macromolecular cell constituents is involved in the liver injury produced by drugs such as acetaminophen and isoniazid; acute hepatic failure can follow depletion of intracellular substrates involved in detoxification, particularly glutathione. Whatever the initial cause of hepatocyte injury, various factors can contribute to the pathogenesis of liver failure, including impaired hepatocyte regeneration, altered parenchymal perfusion, endotoxemia, and decreased hepatic reticuloendothelial function.

Clinical Manifestations

Acute hepatic failure can be the presenting feature of liver disease or it can complicate previously known liver disease (acute-on-chronic liver failure). A history of developmental delay and/or neuromuscular dysfunction can indicate an underlying mitochondrial or β-oxidation defect. A child with acute hepatic failure has usually been previously healthy and most often has no risk factors for liver disease such as exposure to toxins or blood products. Progressive jaundice, fetor hepaticus, fever, anorexia, vomiting, and abdominal pain are common. A rapid decrease in liver size without clinical improvement is an ominous sign. A hemorrhagic diathesis and ascites can develop.

Patients should be closely observed for hepatic encephalopathy, which is initially characterized by minor disturbances of consciousness or motor function.

Irritability, poor feeding, and a change in sleep rhythm may be the only findings in infants; asterixis may be demonstrable in older children. Patients are often somnolent, confused, or combative on arousal and can eventually become responsive only to painful stimuli. Patients can rapidly progress to deeper stages of coma in which extensor responses and decerebrate and decorticate posturing appear. Respirations are usually increased early, but respiratory failure can occur in stage IV coma (Table 391.1). The pathogenesis of hepatic encephalopathy is likely related to increased serum levels of ammonia, false neurotransmitters, amines, increased γ-aminobutyric acid receptor activity, or increased circulating levels of endogenous benzodiazepine-like compounds. Decreased hepatic clearance of these substances can produce marked central nervous system dysfunction. The mechanisms responsible for cerebral edema and intracranial hypertension in acute liver failure (ALF) suggest both cytotoxic and vasogenic injury. There is increasing evidence for an inflammatory response (synthesis and release of inflammatory factors from activated microglia and endothelial cells) which acts in synergy with hyperammonemia to cause severe astrocyte swelling/brain edema.

Table 391.1

Stages of Hepatic Encephalopathy

	STAGES			
	I	**II**	**III**	**IV**
Symptoms	Periods of lethargy, euphoria; reversal of day-night sleeping; may be alert	Drowsiness, inappropriate behavior, agitation, wide mood swings, disorientation	Stupor but arousable; confused, incoherent speech	Coma: IVa responds to noxious stimuli; IVb no response
Signs	Trouble drawing figures, performing mental tasks	Asterixis, fetor hepaticus, incontinence	Asterixis, hyperreflexia, extensor reflexes, rigidity	Areflexia, no asterixis, flaccidity
Electroencephalogram	Normal	Generalized slowing, q waves	Markedly abnormal triphasic waves	Markedly abnormal bilateral slowing, d waves, electrocortical silence

Laboratory Findings

Serum direct and indirect bilirubin levels and serum aminotransferase activities may be markedly elevated. Serum aminotransferase activities do not correlate well with the severity of the illness and can decrease as a patient deteriorates. The blood ammonia concentration is usually increased, but hepatic coma can occur in patients with a normal blood ammonia level. PT and the INR are prolonged and often do not improve after parenteral administration of vitamin K. Hypoglycemia can occur, particularly in infants. Hypokalemia, hyponatremia, metabolic acidosis, or respiratory alkalosis can also develop.

Treatment

Specific therapies for identifiable causes of acute liver failure include *N* -acetylcysteine (acetaminophen), acyclovir (herpes simplex virus), penicillin (*Amanita* mushrooms), nucleos(t)ide analogs such as entecavir (hepatitis B virus [HBV]), and prednisone (autoimmune hepatitis). Immunosuppression with corticosteroids should also be considered in children with the indeterminate form of fulminant hepatic failure with immune activation to avoid progression to liver transplantation or death. However, controlled trials have shown a worse outcome in patients treated with corticosteroids in patients without an immune basis for liver injury. Treatment of GALD involves a combination of double-volume exchange transfusion to remove existing reactive antibody followed immediately by administration of high-dose intravenous immunoglobulin (IVIG) (1 g/kg) to block antibody induced complement activation. Management of other types of acute hepatic failure is supportive. No therapy is known to reverse hepatocyte injury or to promote hepatic regeneration.

An infant or child with acute hepatic failure should be cared for in an institution able to perform a liver transplantation if necessary and managed in an intensive care unit with continuous monitoring of vital functions. Endotracheal intubation may be required to prevent aspiration, to reduce cerebral edema by hyperventilation, and to facilitate pulmonary toilet. Mechanical ventilation and supplemental oxygen are often necessary in advanced coma. Sedatives should be avoided unless needed in the intubated patient because these agents can aggravate or precipitate encephalopathy. Opiates may be better tolerated than benzodiazepines. Prophylactic use of proton pump inhibitors should be considered because of the high risk of gastrointestinal bleeding.

Hypovolemia should be avoided and treated with cautious infusions of *isotonic* fluids and blood products. Renal dysfunction can result from dehydration, acute tubular necrosis, or functional renal failure (hepatorenal syndrome). Electrolyte and glucose solutions should be administered intravenously to maintain urine output, to correct or prevent hypoglycemia, and to maintain normal serum potassium concentrations. Hyponatremia is common and should be avoided; it is usually dilutional and not a result of sodium depletion. Parenteral supplementation with calcium, phosphorus, and magnesium may be required. Hypophosphatemia, probably a reflection of liver regeneration, and early phosphorus administration are associated with a better prognosis in acute liver failure, whereas hyperphosphatemia predicts a failure of spontaneous recovery. Coagulopathy should be treated with parenteral administration of vitamin K. Fresh-frozen plasma, cryoprecipitate, platelets, activated factor VII, or prothrombin complex concentrates can be used to treat clinically significant bleeding or can be given if an invasive procedure such as placement of a central line or an intracranial monitor needs to be performed. Plasmapheresis can permit temporary correction of the bleeding diathesis without resulting in volume overload. Continuous hemofiltration is useful for managing fluid overload, acute renal failure, and hyperammonemia.

Patients should be monitored closely for infection, including sepsis, pneumonia, peritonitis, and urinary tract infections. At least 50% of patients experience serious infection. Gram-positive organisms *(Staphylococcus aureus, Staphylococcus epidermidis)* are the most common pathogens, but Gram-negative and fungal infections are also observed.

Gastrointestinal hemorrhage, infection, constipation, sedatives, electrolyte imbalance, and hypovolemia can precipitate encephalopathy and should be identified and corrected. Protein intake should be initially restricted or eliminated, depending on the degree of encephalopathy. If encephalopathy or hyperammonemia develops, lactulose or rifaximin can be administered. *N*-acetylcysteine is not effective in improving the outcome of patients with acute liver failure not associated with acetaminophen.

Cerebral edema is an extremely serious complication of hepatic encephalopathy that responds poorly to measures such as corticosteroid administration and osmotic diuresis. Monitoring intracranial pressure can be useful in preventing severe cerebral edema, in maintaining cerebral perfusion pressure, and in establishing the suitability of a patient for liver transplantation.

Temporary liver support continues to be evaluated as a bridge for the patient with liver failure to liver transplantation or regeneration. Nonbiologic systems, essentially a form of liver dialysis with an albumin-containing dialysate, and biologic liver support devices that involve perfusion of the patient's blood through a cartridge containing liver cell lines or porcine hepatocytes can remove some toxins, improve serum biochemical abnormalities, and, in some cases, improve neurologic function, but there has been little evidence of improved survival, and few children have been treated.

Orthotopic liver transplantation can be lifesaving in patients who reach advanced stages (III, IV) of hepatic coma. Reduced-size allografts and living donor transplantation have been important advances in the treatment of infants with hepatic failure. Partial auxiliary orthotopic or heterotopic liver transplantation is successful in a small number of children, and in some cases it has allowed regeneration of the native liver and eventual withdrawal of immunosuppression. Orthotopic liver transplantation should not be done in patients with liver failure and neuromuscular dysfunction secondary to a mitochondrial disorder because progressive neurologic deterioration is likely to continue after transplantation.

Prognosis

Children with acute hepatic failure fare better than adults. Improved survival can be attributed to careful intensive care and if necessary liver transplantation. In the largest prospective study from the Pediatric Acute Liver Failure Study Group, 709 children were assessed at 21 days: 50.3% of patients survived with supportive care alone, 36.2% survived after liver transplantation, and 13.4% died. A scoring system based on peak values of total serum bilirubin, PT, and plasma ammonia concentration predicted transplant-free survival. Prognosis varies considerably with the cause of liver failure and stage of hepatic encephalopathy. Survival rates with supportive care may be as high as 90% in acetaminophen overdose and with fulminant hepatitis A. By contrast, spontaneous recovery can be expected in only approximately 40% of patients with liver failure caused by the idiopathic (indeterminate) form of acute liver failure or an acute onset of Wilson disease. Prognosis is also poor for spontaneous recovery in patients with mitochondrial deficits, hemophagocytic syndromes, herpes simplex disease, and idiosyncratic drug reactions. In patients who progress to stage IV coma (see Table 391.1), the prognosis is extremely poor. Brain stem herniation is the most common cause of death. Major complications such as sepsis, severe hemorrhage, or renal failure increase the mortality. The prognosis is particularly poor in patients with liver necrosis and multiorgan failure.

Age <1 yr, stage 4 encephalopathy, an INR >4, PT >90 sec, low factor V levels, and the need for dialysis before transplantation are associated with increased mortality. Pretransplantation serum bilirubin concentration or the height of hepatic enzymes is *not* predictive of posttransplantation survival. A plasma ammonia concentration >200 µmol/L is associated with a 5-fold increased risk of death. Children with acute hepatic failure are more likely to die while on the waiting list compared to children with other liver transplant requiring diagnoses. Owing to the severity of their illness, the 6 mo post–liver transplantation survival of approximately 75% for acute liver failure is significantly lower than the 90% achieved in children with chronic liver disease. Patients who recover from fulminant hepatic failure with only supportive care do not usually develop cirrhosis or chronic liver disease. Aplastic anemia occurs in approximately 10% of children with the idiopathic form of fulminant hepatic failure and is often fatal without bone marrow transplantation. Long-term survivors demonstrate average IQ and visual spatial ability but greater than expected impairments in motor skills, attention, executive function, and health-related quality of life.

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CHAPTER 392

Cystic Diseases of the Biliary Tract and Liver

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Cystic lesions of liver may be initially recognized during infancy and childhood. Hepatic fibrosis can also occur as part of an associated developmental defect (Table 392.1). Cystic *renal* disease is usually associated and often determines the clinical presentation and prognosis. Virtually all proteins encoded by genes mutated in combined cystic diseases of the liver and kidney are at least partially localized to primary cilia in renal tubular cells and cholangiocytes.

Table 392.1

Syndromes Associated With Congenital Hepatic Fibrosis

DISORDER	ASSOCIATED FEATURES
Autosomal recessive polycystic kidney disease	Ductal plate malformation, Caroli syndrome
Autosomal dominant polycystic kidney disease	Ductal plate malformation, Caroli syndrome
Autosomal dominant polycystic liver disease	Rarely, congestive heart failure
Jeune syndrome	Asphyxiating thoracic dystrophy, with cystic renal tubular dysplasia, Caroli syndrome
Joubert syndrome	Central nervous system defects, cardiac malformations
COACH syndrome	*C* erebellar vermis hypoplasia, *o* ligophrenia, congenital *a* taxia, ocular *c* oloboma, *h* epatic fibrosis
Meckel-Gruber syndrome	Cystic renal dysplasia, abnormal bile duct development with fibrosis, posterior encephalocele, polydactyly
Carbohydrate-deficient glycoprotein syndrome type 1b	Phosphomannose isomerase 1 deficiency chronic diarrhea, protein-losing enteropathy
Ivemark syndrome type 2	Autosomal-recessive renal-hepatic-pancreatic dysplasia
Nephronophthisis type 3	Tapetoretinal degeneration
Bardet-Biedl syndrome	Retinal degeneration, obesity, limb deformities, hypogonadism
Oral-facial-digital syndrome type 1	Oral clefts, hamartomas or cysts of the tongue, digital anomalies pancreatic cysts

Miscellaneous syndromes	Intestinal lymphangiectasia, enterocolitis, cystic short rib (Beemer-Langer) syndrome, osteochondrodysplasia

After Suchy FJ, Sokol RJ, Balistreri WF, editors: *Liver disease in children,* ed 3, New York, 2014, Cambridge University Press, p. 713.

A solitary, congenital liver cyst (nonparasitic) can occur in childhood and has been identified in some cases on prenatal ultrasound. Abdominal distention and pain may be present, and a poorly defined right-upper-quadrant mass may be palpable. These benign lesions are best left undisturbed unless they compress adjacent structures or a complication occurs, such as hemorrhage into the cyst. Operative management is generally reserved for symptomatic patients and enlarging cysts.

Choledochal Cysts

Choledochal cysts are congenital dilatations of the common bile duct that can cause progressive biliary obstruction and biliary cirrhosis. Cylindrical (fusiform) and spherical (saccular) cysts of the extrahepatic ducts are the most common types (see Table 392.1). Choledochal cysts are classified according to the Todani method (Fig. 392.1). Type 1 choledochal cysts, the most common variant, involve a saccular or fusiform dilation of the common bile duct. Type II cysts are congenital diverticula protruding from the common bile duct. Type III cysts or choledochoceles involve a herniation of the intraduodenal segment of the common bile duct into the duodenum. Type IVa cysts or **Caroli disease** involve multiple intrahepatic and extrahepatic cysts. Type IVb cysts involve only the extrahepatic duct. Solitary liver cysts (type V) are very rare.

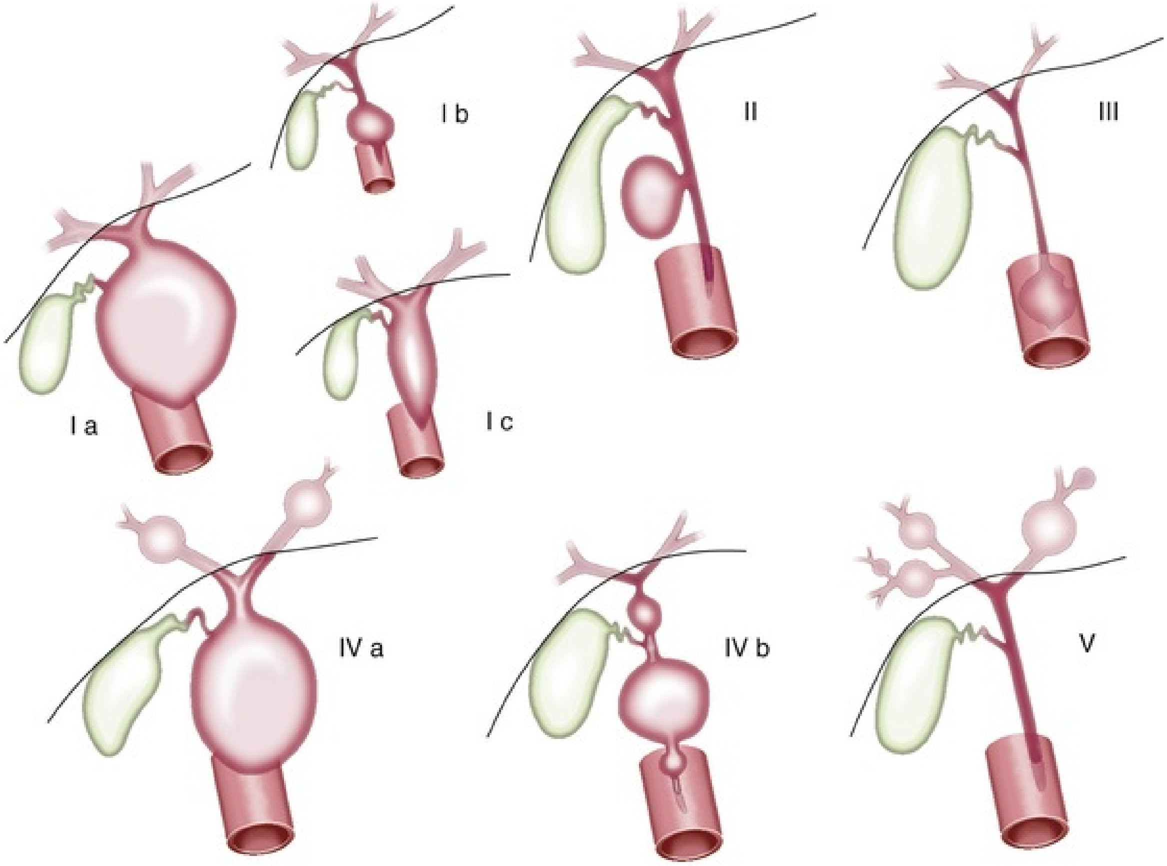

FIG. 392.1 **Classification of choledochal cysts according to Todani and colleagues. Ia, common type; Ib, segmental dilation; Ic, diffuse dilation; II, diverticulum; III, choledochocele; IVa, multiple cysts (intra- and extrahepatic); IVb, multiple cysts (extrahepatic); V, single or multiple dilations of the intrahepatic ducts (Caroli disease). (From Savader SJ, Benenati JF, Venbrux AC, et al. Choledochal cysts: Classification and cholangiographic appearance. AJR Am J Roentgenol 1991;156:327-31.)**

The pathogenesis of choledochal cysts remains uncertain. Some reports suggest that junction of the common bile duct and the pancreatic duct before their entry into the sphincter of Oddi might allow reflux of pancreatic enzymes into the common bile duct, causing inflammation, localized weakness, and dilation of the duct. It has also been proposed that a distal congenital stenotic segment of the biliary tree leads to increased intraluminal pressure and proximal biliary dilation. Other possibilities are that choledochal cysts represent malformations of the common duct or that they occur as part of the spectrum of an infectious disease that includes neonatal hepatitis and biliary atresia.

Approximately 75% of cases appear during childhood. The infant typically presents with cholestatic jaundice; severe liver dysfunction including ascites and coagulopathy can rapidly evolve if biliary obstruction is not relieved. An abdominal mass is rarely palpable. In an older child, the classic triad of abdominal pain, jaundice, and mass occurs in <33% of patients. Features of acute cholangitis (fever, right-upper-quadrant tenderness, jaundice, and leukocytosis) may be present. The diagnosis is made by ultrasonography; choledochal cysts have been identified prenatally using this technique. Magnetic resonance cholangiography is useful in the preoperative assessment of choledochal cyst anatomy.

Choledochal cysts have the potential to develop into cholangiocarcinoma; therefore the treatment of choice is primary excision of the cyst and a Roux-en-Y choledochojejunostomy. The postoperative course can be complicated by recurrent cholangitis or stricture at the anastomotic site. Long-term follow-up is necessary to ensure that no malignancy develops.

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) manifests predominantly in childhood (see Chapter 541.2). Bilateral enlargement of the kidneys is caused by a generalized dilation of the collecting tubules. The disorder is invariably associated with congenital hepatic fibrosis and various degrees of biliary ductal ectasia, discussed in detail later.

The polycystic kidney and hepatic disease 1 *(PKHD1)* gene, mutated in ARPKD, encodes a protein that is called fibrocystin/polyductin, which is localized to cilia on the apical domain of renal collecting cells and cholangiocytes. The primary defect in ARPKD may be ciliary dysfunction related to the abnormality in this protein. Fibrocystin/polyductin appears to have a role in the regulation of cellular adhesion, repulsion, and proliferation and/or the regulation and maintenance of renal collecting tubules and bile ducts, but its exact role in normal and cystic epithelia remains unknown. Kidney and liver disease are independent and variable in severity; they are not explainable by the type of *PKHD1* mutation. Phenotypic variability among affected siblings suggests the importance of modifier genes as well as possibly environmental influences.

In ARPKD, the cysts arise as ectatic expansions of the collecting tubules and bile ducts, which remain in continuity with their structures of origin. ARPKD normally presents in early life, often shortly after birth, and is generally more severe than autosomal dominant polycystic kidney disease (ADPKD). Fetal ultrasound may visualize large echogenic kidneys, also described as bright, with low or absent amniotic fluid (oligohydramnios). However, in many instances the features of ARPKD are not visualized on sonography until the 3rd trimester or after birth.

Patients with ARPKD can die in the perinatal period owing to renal failure or lung dysgenesis. The kidneys in these patients are usually markedly enlarged and dysfunctional. Respiratory failure can result from compression of the chest by grossly enlarged kidneys, from fluid retention, or from concomitant pulmonary hypoplasia. The clinical pathologic findings within a family tend to breed true, although there has been some variability in the severity of the disease and the time for presentation within the same family. In patients surviving infancy because of a milder renal phenotype, liver disease may be a prominent part of the disorder. The liver disease in ARPKD is related to congenital malformation of the liver with varying degrees of periportal fibrosis, bile ductular hyperplasia, ectasia, and dysgenesis. Initial symptoms are liver related in approximately 26% of patients. This can manifest clinically as variable cystic dilation of the intrahepatic biliary tree with congenital hepatic fibrosis. Congenital hepatic fibrosis and Caroli disease likely result from an abnormality in remodeling of the embryonic ductal plate of the liver. **Ductal plate malformation** refers to the persistence of excess embryonic bile duct structures in the portal tracts. ARPKD patients with recurrent cholangitis or complications of portal hypertension may require combined liver-kidney transplant.

Cystic Dilation of the Intrahepatic Bile Ducts (Caroli Disease/Caroli Syndrome)

In Caroli disease there is isolated ectasia or nonobstructing segmental dilatation of the larger intrahepatic ducts. Caroli syndrome is the more common variant, in which malformations of small bile ducts are associated with congenital hepatic fibrosis. Congenital saccular dilation can affect several segments of the intrahepatic bile ducts; the dilated ducts are lined by cuboidal epithelium and are in continuity with the main duct system, which is usually normal. Choledochal cysts have also been associated with Caroli disease. Bile duct dilation leads to stagnation of bile and formation of biliary sludge and intraductal lithiasis. There is a marked predisposition to ascending cholangitis, which may be exacerbated by calculus formation within the abnormal bile ducts.

Affected patients usually experience symptoms of acute cholangitis as children or young adults. Fever, abdominal pain, mild jaundice, and pruritus occur, and a slightly enlarged, tender liver is palpable. Elevated alkaline phosphatase activity, direct-reacting bilirubin levels, and leukocytosis may be observed during episodes of acute infection. In patients with Caroli disease, clinical features may be the result of a combination of recurring bouts of cholangitis, reflecting the intrahepatic ductal abnormalities and portal hypertensive bleeding resulting from hepatic fibrosis. Ultrasonography shows the dilated intrahepatic ducts, but definitive diagnosis and extent of disease must be determined by percutaneous transhepatic, endoscopic, or magnetic resonance cholangiography.

Cholangitis and sepsis should be treated with appropriate antibiotics. Calculi can require surgery. Partial hepatectomy may be curative in rare cases in which cystic disease is confined to a single lobe. The prognosis is otherwise guarded, largely owing to difficulties in controlling cholangitis and biliary lithiasis and to a significant risk for developing cholangiocarcinoma.

Congenital Hepatic Fibrosis

Congenital hepatic fibrosis is usually associated with ARPKD and is characterized pathologically by diffuse periportal and perilobular fibrosis in broad bands that contain distorted bile duct–like structures and that often compress or incorporate central or sublobular veins (see Table 392.1). Irregularly shaped islands of liver parenchyma contain normal-appearing hepatocytes. Caroli disease and choledochal cysts are associated. Most patients have renal disease, mostly autosomal recessive polycystic renal disease and rarely nephronophthisis. Congenital hepatic fibrosis also occurs as part of the COACH syndrome (cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis). Congenital hepatic fibrosis has been described in children with a congenital disorder of glycosylation caused by mutations in the gene encoding phosphomannose isomerase (see Chapter 105.6).

Several different forms of congenital hepatic fibrosis have been defined clinically: portal hypertensive (most common) cholangitic, mixed, and latent. The disorder usually has its onset in childhood, with hepatosplenomegaly or with bleeding secondary to portal hypertension. In a recent study, splenomegaly, as a marker for portal hypertension, developed early in life and was present in 60% of children younger than 5 yr of age.

Cholangitis can occur in these patients, as they have abnormal biliary tracts even without Caroli disease. Hepatocellular function is usually well preserved. Serum aminotransferase activities and bilirubin levels are usually normal in the absence of cholangitis and choledocholithiasis; serum alkaline phosphatase activity may be slightly elevated. The serum albumin level and prothrombin time are normal. Liver biopsy is rarely required for diagnosis, particularly in patients with obvious renal disease.

Treatment of this disorder should focus on control of bleeding from esophageal varices and aggressive antibiotic treatment of cholangitis. Infrequent mild bleeding episodes may be managed by endoscopic sclerotherapy or band ligation of the varices. After more severe hemorrhage, portacaval anastomosis can relieve portal hypertension. The prognosis may be greatly improved by a shunting procedure, but survival in some patients may be limited by renal failure.

Autosomal Dominant Polycystic Kidney Disease

ADPKD (see Chapter 541.3), the most commonly inherited cystic kidney disease, affects 1 in 1,000 live births. It is characterized by progressive renal cyst development and cyst enlargement and an array of extrarenal manifestations. There is a high degree of intrafamilial and interfamilial variability in the clinical expression of the disease.

ADPKD is caused by mutation in 1 of 2 genes, *PKD1* or *PKD2* , which account for 85–90% and 10–15% of cases, respectively. The proteins encoded by these genes, polycystin-1 and polycystin-2, are expressed in renal tubule cells and in cholangiocytes. Polycystin-1 functions as a mechanosensor in cilia, detecting the movement of fluid through tubules and transmitting the signal through polycystin-2, which acts as a calcium channel.

Dilated noncommunicating cysts are most commonly observed. Other hepatic lesions are rarely associated with ADPKD, including the ductal plate malformation, congenital hepatic fibrosis, and biliary microhamartomas (the von Meyenburg complexes). Approximately 50% of patients with renal failure have demonstrable hepatic cysts that are derived from the biliary tract but not in continuity with it. The hepatic cysts increase with age. In one study the prevalence of hepatic cysts was 58% in patients 15-24 yr old. Hepatic cystogenesis appears to be influenced by estrogens. Although the frequency of cysts is similar in males and females, the development of large hepatic cysts is mainly a complication in females. Hepatic cysts are often asymptomatic but can cause pain and are occasionally complicated by hemorrhage, infection, jaundice from bile duct compression, portal hypertension with variceal bleeding, or hepatic venous outflow obstruction from mechanical compression of hepatic veins, resulting in tender hepatomegaly and exudative ascites. Cholangiocarcinoma can occur. Subarachnoid hemorrhage can result from the associated cerebral arterial aneurysms.

Selected patients with severe symptomatic polycystic liver disease and favorable anatomy benefit from liver resection or fenestration. Combined liver-kidney transplantation may be required. There is considerable evidence for a role of cyclic adenosine monophosphate in epithelial proliferation and fluid secretion in experimental renal and hepatic cystic disease. Several clinical trials in adults have shown that somatostatin analogs can blunt hepatic cyst expansion by blocking secretin-induced cyclic adenosine monophosphate generation and fluid secretion by cholangiocytes.

Autosomal Dominant Polycystic Liver Disease

Autosomal dominant polycystic liver disease is a distinct clinical and genetic identity in which multiple cysts develop and are unassociated with cystic kidney disease. Liver cysts arise from but are not in continuity with the biliary tract. Girls are more commonly affected than boys, and the cysts often enlarge during pregnancy. Cysts are rarely identified in children. Cyst complications are related to effects of local compression, infection, hemorrhage, or rupture. The genes associated with autosomal dominant polycystic liver disease are *PRKCSH* and *SEC63* , which encode hepatocystin and Sec63, respectively. Hepatocystin is a protein kinase C substrate adK-H, which is involved in the proper folding and maturation of glycoproteins. It has been localized to the endoplasmic reticulum. *SEC63* encodes the protein SEC63P, which is a component of the protein translocation machinery in the endoplasmic reticulum.

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CHAPTER 393

Diseases of the Gallbladder

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The incidence of gallbladder disease, particularly cholelithiasis and biliary dyskinesia, has been increasing in children, and has been associated with a rise in the number of cholecystectomies.

Anomalies

The gallbladder is congenitally absent in approximately 0.1% of the population. Hypoplasia or absence of the gallbladder can be associated with extrahepatic biliary atresia or cystic fibrosis. Duplication of the gallbladder occurs rarely. Gallbladder ectopia may occur with a transverse, intrahepatic, left-sided, or retroplaced location. Multiseptate gallbladder, characterized by the presence of multiple septa dividing the gallbladder lumen, is another rare congenital anomaly of the gallbladder.

Acute Hydrops

Table 393.1 lists the conditions associated with hydrops of the gallbladder.

Table 393.1

Conditions Associated With Hydrops of the Gallbladder

Cholelithiasis Cholecystitis Kawasaki disease Streptococcal pharyngitis Staphylococcal infection Leptospirosis

Ascariasis
Threadworm
Sickle cell crisis
Typhoid fever
Thalassemia
Total parenteral nutrition
Prolonged fasting
Viral hepatitis
Sepsis
Henoch-Schönlein purpura
Mesenteric adenitis
Necrotizing enterocolitis

Acute noncalculous, noninflammatory distention of the gallbladder can occur in infants and children. It is defined by the absence of calculi, bacterial infection, or congenital anomalies of the biliary system. The disorder may complicate acute infections and Kawasaki disease, but the cause is often not identified. Hydrops of the gallbladder may also develop in patients receiving long-term parenteral nutrition, presumably because of gallbladder stasis during the period of enteral fasting. Hydrops is distinguished from acalculous cholecystitis by the absence of a significant inflammatory process and is a generally benign prognosis.

Affected patients usually have right upper quadrant pain with a palpable mass. Fever, vomiting, and jaundice may be present and are usually associated with a systemic illness such as streptococcal infection. Ultrasonography shows a markedly distended echo-free gallbladder, without dilation of the biliary tree. Acute hydrops is usually treated conservatively with a focus on supportive care and managing the intercurrent illness; cholecystostomy and drainage are rarely needed. Spontaneous resolution and return of normal gallbladder function usually occur over a period of several weeks. If a laparotomy is required, a large edematous gallbladder is found to contain white, yellow, or green bile. Obstruction of the cystic duct by mesenteric adenopathy is occasionally observed. Cholecystectomy is required if the gallbladder is gangrenous. Pathologic examination of the gallbladder wall shows edema and mild inflammation. Cultures of bile are usually sterile.

Cholecystitis and Cholelithiasis

Acute acalculous cholecystitis is uncommon in children and is usually caused by infection. Pathogens include streptococci (groups A and B), Gram-negative organisms—particularly *Salmonella* and *Leptospira interrogans* —and a number of viral infections (hepatitis A, Epstein-Barr [EB] virus, and cytomegalovirus). Parasitic infestation with *Ascaris* or *Giardia lamblia* may be found. Acalculous cholecystitis may be associated with abdominal trauma or burn injury or with a severe systemic illness such as leukemia, end-stage liver disease, and systemic vasculitis.

Clinical features include right upper quadrant or epigastric pain, nausea, vomiting, fever, and jaundice. Right upper quadrant guarding and tenderness are present. Ultrasonography discloses an enlarged, thick-walled gallbladder without calculi. Serum alkaline phosphatase activity and direct-reacting bilirubin levels are elevated. Leukocytosis is usual.

Patients may recover with treatment of systemic and biliary infection. Because the gallbladder can become gangrenous, daily ultrasonography is useful in monitoring gallbladder distention and wall thickness. Cholecystectomy is required in patients who fail to improve with conservative management. Cholecystostomy drainage is an alternative approach in a critically ill patient.

Cholelithiasis is relatively rare in otherwise healthy children, occurring more commonly in patients with various predisposing disorders (Table 393.2). Gallstones are rarely detected by ultrasonography in the fetus, but generally remain asymptomatic and resolve spontaneously during the 1st yr of life. In an ultrasonographic survey of 1570 children (ages 6-19 yr) the overall prevalence of gallstone disease was 0.13% (0.27% in female subjects). Older reports consistently found that >70% of gallstones were the pigment type, 15–20% were cholesterol stones, and the remainder were composed of a mixture of cholesterol, organic matrix, and calcium bilirubinate. Black pigment gallstones, composed mostly of calcium bilirubinate and glycoprotein matrix, are a frequent complication of chronic hemolytic anemias. However, because of obesity, cholesterol gallstones predominate in children, while the number of patients with hemolytic anemia-associated gallstones have remained stable.

Table 393.2

Conditions Associated With Cholelithiasis

Chronic hemolytic disease (sickle cell anemia, spherocytosis, thalassemia, Gilbert disease)
Ileal resection or disease
Cystic fibrosis
Cirrhosis
Cholestasis
Crohn disease
Obesity

Insulin resistance
Prolonged parenteral nutrition
Prematurity with complicated medical or surgical course
Prolonged fasting or rapid weight reduction
Treatment of childhood cancer
Abdominal surgery
Pregnancy
Sepsis
Genetic *(ABCB4, ABCG5/G8)* progressive familial intrahepatic cholestasis
Cephalosporins

Brown pigment stones form mostly in infants as a result of biliary tract infection. Unconjugated bilirubin is the predominant component, formed by the high β-glucuronidase activity of infected bile. Cholesterol gallstones are composed purely of cholesterol or contain >50% cholesterol along with a mucin glycoprotein matrix and calcium bilirubinate. Calcium carbonate stones have also been described in children.

Patients with hemolytic disease (including sickle cell anemia, the thalassemias, and red blood cell enzymopathies) and Wilson disease are at increased risk for black pigment cholelithiasis. In sickle cell disease, pigment gallstones can develop before age 4 yr and have been reported in 17–33% of patients 2-18 yr of age. Genetic variation in the promoter of uridine diphosphate-glucuronosyltransferase 1A1 (the [TA]7/[TA]7 and [TA]7/[TA]8 genotypes) underlies **Gilbert syndrome** , a relatively common, chronic form of unconjugated hyperbilirubinemia, and is a risk factor for pigment gallstone formation in sickle cell disease.

Cirrhosis and chronic cholestasis also increase the risk for pigment gallstones. Sick premature infants may also have gallstones; their treatment is often complicated by such factors as bowel resection, necrotizing enterocolitis, prolonged parenteral nutrition without enteral feeding, cholestasis, frequent blood transfusions, and use of diuretics. Cholelithiasis in premature infants is often asymptomatic and may resolve spontaneously. Brown pigment stones are found in infants with obstructive jaundice and infected intra- and extrahepatic bile ducts. These stones are usually radiolucent, owing to a lower content of calcium phosphate and carbonate and a higher amount of cholesterol than in black pigment stones. MDR3 deficiency caused by *ABCB4* mutations is a cholestatic syndrome related to impaired biliary phospholipid excretion. It is associated with symptomatic and recurring cholelithiasis. Patients may show intrahepatic lithiasis, sludge, or microlithiasis along the biliary tree.

Obesity has assumed an increasingly important role as a risk factor for cholesterol cholelithiasis in children, particularly in adolescent girls. Cholesterol gallstones are also found in children with disturbances of the enterohepatic circulation of bile acids, including patients with ileal disease and bile acid malabsorption, such as those with ileal resection, ileal Crohn disease, and cystic fibrosis. Pigment stones can also occur in these patients.

Cholesterol gallstone formation results from an excess of cholesterol in relation to the cholesterol-carrying capacity of micelles in bile. Supersaturation of bile with cholesterol, leading to crystal and stone formation, could result from decreased bile acid or from an increased cholesterol concentration in bile. Other initiating factors that may be important in stone formation include gallbladder stasis or the presence in bile of abnormal mucoproteins or bile pigments that may serve as a nidus for cholesterol crystallization.

Prolonged use of high-dose ceftriaxone, a 3rd-generation cephalosporin, has been associated with the formation of calcium-ceftriaxone salt precipitates *(biliary pseudolithiasis)* in the gallbladder. Biliary sludge or cholelithiasis can be detected in >40% of children who are treated with ceftriaxone for at least 10 days. In rare cases, children become jaundiced and develop abdominal pain; precipitates usually resolve spontaneously within several months after discontinuation of the drug.

Acute or chronic cholecystitis is often associated with gallstones. The acute form may be precipitated by impaction of a stone in the cystic duct. Proliferation of bacteria within the obstructed gallbladder lumen can contribute to the process and lead to biliary sepsis. Chronic calculous cholecystitis is more common. It can develop insidiously or follow several attacks of acute cholecystitis. The gallbladder epithelium commonly becomes ulcerated and scarred.

More than 50% of patients with gallstones have symptoms, and 18% present with a complication as the first indication of cholelithiasis, such as pancreatitis, choledocholithiasis or acute calculous cholecystitis. The most important clinical feature of cholelithiasis is recurrent abdominal pain, which is often colicky and localized to the right upper quadrant. An older child may have intolerance for fatty foods. Acute cholecystitis is characterized by fever, pain in the right upper quadrant, and often a palpable mass. Jaundice occurs more commonly in children than adults. Pain may radiate to an area just below the right scapula. A plain x-ray of the abdomen may reveal opaque calculi, but radiolucent (cholesterol) stones are not visualized. Accordingly, ultrasonography is the method of choice for gallstone detection. Hepatobiliary scintigraphy is a valuable adjunct in that failure to visualize the gallbladder provides evidence of cholecystitis.

Laboratory evaluation may reveal elevated aminotransferase levels, leukocytosis, and mild hyperbilirubinemia. Marked elevations of the direct bilirubin, alkaline phosphatase, or GGT levels should prompt evaluation for choledocholithiasis.

Patients with cholecystitis and persistent fever or concern for obstruction should be hospitalized and started on antibiotics. Cholecystectomy is curative. Laparoscopic cholecystectomy is routinely performed in symptomatic infants and children with cholelithiasis. Common bile duct stones are unusual in children, occurring in 2–6% of cases with cholelithiasis, often in association with obstructive jaundice and pancreatitis. Operative cholangiography should be done at the time of surgery, however, to detect unsuspected common duct calculi. Endoscopic retrograde cholangiography with extraction of common duct stones is an option before laparoscopic cholecystectomy in older children and adolescents.

Asymptomatic patients with cholelithiasis pose a more difficult management problem. Studies in adults indicate a lag time of more than a decade between initial formation of a gallstone and development of symptoms. Spontaneous resolution of cholelithiasis has been reported in infants and children. However, if surgery is deferred for any patient, parents should be counseled about signs and symptoms consistent with cholecystitis or obstruction of the common bile duct by a gallstone. In patients with chronic hemolysis or ileal disease, cholecystectomy can be carried out at the same time as another surgical procedure. Because laparoscopic surgery can safely be performed in children with sickle cell disease, elective cholecystectomy is being done more frequently at the time of gallstone diagnosis, before symptoms or complications develop. In cases associated with liver disease, severe obesity, or cystic fibrosis, the surgical risk of cholecystectomy may be substantial so that the risks and benefits of the operation need to be carefully considered.

Biliary Dyskinesia

Biliary dyskinesia is a motility disorder of the biliary tract that may cause biliary colic in children, often in association with nausea and fatty food intolerance, but symptoms may overlap with functional abdominal pain. There are no gallstones on imaging. Sphincter of Oddi dysfunction may be a variant that can present with chronic abdominal pain and recurrent pancreatitis. The diagnosis is based on a cholecystokinin–diisopropyl iminodiacetic acid scan or an ultrasound done with a fatty meal demonstrating a gallbladder ejection fraction of <35%. Reproduction of pain on cholecystokinin administration may also be seen, as well as the absence of gallbladder filling on an otherwise normal ultrasound examination. Although laparoscopic cholecystectomy is performed for many patients with this disorder, short-term and long-term symptomatic improvement is highly variable.

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CHAPTER 394

Portal Hypertension and Varices

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Portal hypertension, defined as an elevation of portal pressure >10-12 mm Hg or a hepatic venous pressure gradient >4 mm Hg, is a major cause of morbidity and mortality in children with liver disease. Portal hypertension occurs when there is increased portal resistance or increased blood flow through the portal system. When portal hypertension occurs, children can develop varices, splenomegaly, ascites, and gastrointestinal bleeding.

Etiology

Portal hypertension can result from obstruction to portal blood flow anywhere along the course of the portal venous system (prehepatic, intrahepatic, or posthepatic). Table 394.1 outlines the various disorders associated with portal hypertension.

Table 394.1

Causes of Portal Hypertension

EXTRAHEPATIC PORTAL HYPERTENSION
Portal vein agenesis, atresia, stenosis
Portal vein thrombosis or cavernous transformation
Splenic vein thrombosis
Increased portal flow
Arteriovenous fistula
INTRAHEPATIC PORTAL HYPERTENSION
Hepatocellular disease
Acute and chronic viral hepatitis
Cirrhosis
Congenital hepatic fibrosis
Wilson disease

α_1 -Antitrypsin deficiency
Glycogen storage disease type IV
Hepatotoxicity
Methotrexate
Parenteral nutrition
Biliary tract disease
Extrahepatic biliary atresia
Cystic fibrosis
Choledochal cyst
Sclerosing cholangitis
Intrahepatic bile duct paucity
Idiopathic portal hypertension
Postsinusoidal obstruction
Budd-Chiari syndrome
Venoocclusive disease

Portal vein thrombosis is the most common cause of extrahepatic portal hypertension. The obstruction can occur at any level of the portal vein. In neonates, portal vein thrombosis can occur from umbilical infection (omphalitis) with or without a history of catheterization of the umbilical vein, dehydration, and/or sepsis. Rare developmental anomalies producing extrahepatic portal hypertension include agenesis, atresia, stenosis, or a web of the portal vein. In older children, portal vein thrombosis can occur with intraabdominal infection (appendicitis, peritonitis, pancreatitis), inflammatory bowel disease, primary sclerosing cholangitis, or biliary infection. Portal vein thrombosis is also associated with hypercoagulable states, such as deficiencies of factor V Leiden, protein C, or protein S. The portal vein can be replaced by a fibrous remnant or contain an organized thrombus. At least half of reported cases have no defined cause. Uncommonly, presinusoidal hypertension can be caused by increased flow through the portal system as a result of a congenital or acquired arteriovenous fistula.

The intrahepatic causes of portal hypertension are numerous. The most common cause of portal hypertension in children is **cirrhosis.** The numerous causes of cirrhosis include recognized disorders such as biliary atresia, autoimmune hepatitis, chronic viral hepatitis, and metabolic liver disease such as α_1 -antitrypsin deficiency, Wilson disease, glycogen storage disease type IV, hereditary fructose intolerance, and cystic fibrosis.

Portal infiltration with malignant cells or granulomas can also contribute. An idiopathic form of portal hypertension characterized by splenomegaly, hypersplenism, and portal hypertension without occlusion of portal or splenic veins and with no obvious disease in the liver has been described. In some patients, noncirrhotic portal fibrosis has been observed.

Postsinusoidal causes of portal hypertension are also observed in childhood. **Budd-Chiari syndrome** occurs with obstruction to hepatic veins anywhere between the efferent hepatic veins and the entry of the inferior vena cava into the right atrium. In most cases, no specific cause can be found, but thrombosis can occur from inherited and acquired hypercoagulable states (antithrombin III deficiency, protein C or S deficiency, factor V Leiden or prothrombin mutations, paroxysmal nocturnal hemoglobinemia, pregnancy, oral contraceptives) and can complicate hepatic or metastatic neoplasms, collagen vascular disease, infection, and trauma. Additional causes of the Budd-Chiari syndrome include Behçet syndrome, inflammatory bowel disease, aspergillosis, dacarbazine therapy, autoinflammatory-recurrent fever syndromes, and inferior vena cava webs.

Sinusoidal obstruction syndrome (venoocclusive disease) is the most common cause of hepatic vein obstruction in children. In this disorder, occlusion of the centrilobular venules or sublobular hepatic veins occurs. The disorder most frequently occurs in bone marrow transplant recipients after total body irradiation with or without cytotoxic drug therapy, but can also be seen in patients on azathioprine, mercaptopurine, thioguanine, and those taking herbal remedies that contain pyrrolizidine alkaloids.

Pathophysiology

The primary hemodynamic abnormality in portal hypertension is increased resistance to portal blood flow. This is the case whether the resistance to portal flow has an intrahepatic cause such as cirrhosis or is due to portal vein obstruction. Portosystemic shunting should decompress the portal system and thus significantly lower portal pressures. However, despite the development of significant collaterals deviating portal blood into systemic veins, portal hypertension is maintained by an overall increase in portal venous flow and thus maintenance of portal hypertension. A hyperdynamic circulation is achieved by tachycardia, an increase in cardiac output, decreased systemic vascular resistance, and increased splanchnic dilation. Overall, the increase in portal flow likely contributes to an increase in variceal transmural pressure. The increase in portal blood flow is related to the contribution of hepatic and collateral flow; the actual portal blood flow reaching the liver is reduced. It is also likely that hepatocellular dysfunction and portosystemic shunting lead to the generation of various humoral factors that cause vasodilation and an increase in plasma volume.

Many complications of portal hypertension can be accounted for by the development of a remarkable collateral circulation. Collateral vessels can form prominently in areas in which absorptive epithelium joins stratified epithelium, particularly in the esophagus or anorectal region. The superficial submucosal collaterals, especially those in the esophagus and stomach, and to a lesser extent, those in the duodenum, colon, or rectum, are prone to rupture and bleeding under increased pressure. In portal hypertension, the vascularity of the stomach is also abnormal and demonstrates prominent submucosal arteriovenous communications between the muscularis mucosa and dilated precapillaries and veins. The resulting lesion, a vascular ectasia, has been called *congestive gastropathy* and contributes to a significant risk of bleeding from the stomach.

Clinical Manifestations

Bleeding is the most common presentation of portal hypertension in children. In large series of children with portal hypertension, two thirds presented with hematemesis or melena, most commonly from rupture of an esophageal varix. Less commonly, patients bleed from portal gastropathy, gastric antral ectasia, or stomal, intestinal, or anorectal varices. The risk of a first bleed in children with cirrhosis is 22%, but rises to 38% in children with known varices over a 5-yr period. In children with biliary atresia, 15–25% have bleeding on long-term follow-up. The age of first bleed is dependent on the underlying etiology of portal hypertension. Hemorrhage, particularly in children with portal vein obstruction, can be precipitated by minor febrile, intercurrent illness. The mechanism is often unclear; aspirin or other nonsteroidal antiinflammatory drugs may be a contributing factor by damaging the integrity of a congested gastric mucosa or interfering with platelet function. Coughing during a respiratory illness can also increase intravariceal pressure.

Splenomegaly is the second most common finding in children with portal hypertension and may be initially recognized on routine physical examination. As more than half of patients in many series with portal vein obstruction do not experience bleeding until after 6 yr of age, underlying liver disease should be considered in any child with splenomegaly, especially if there is concurrent cytopenias. Most children with splenomegaly are asymptomatic.

Ascites is the presenting sign of portal hypertension in 7–21% of children. Ascites can develop at any time with cirrhosis or if there is new onset portal vein obstruction. Children with portal hypertension can also suffer from growth impairment, minimal hepatic encephalopathy, and impaired quality of life. Some develop **portal hypertensive biliopathy** , where portal vein obstruction occurs as a result of external compression of the bile ducts by cavernous transformation of the portal vein.

Children with portal hypertension may also develop pulmonary complications, including **hepatopulmonary syndrome** (HPS) and **portopulmonary hypertension** (PP-HTN). HPS is defined as an arterial oxygenation defect induced by intrapulmonary microvascular dilation, resulting from release of a number of endogenous vasoactive molecules, including endothelin-1 and nitric oxide into the venous circulation. HPS develops in ≥10% of patients with portal hypertension. Patients with HPS may present with dyspnea, cyanosis, clubbing, and spider nevi. PP-HTN is defined by a pulmonary arterial pressure greater than 25 mm Hg at rest or a left-ventricular end-diastolic pressure of less than 15 mm Hg. Patients with PP-HTN most commonly present with exertional dyspnea. Histologically, these patients have pulmonary arteriopathy with laminar intimal fibrosis.

Diagnosis

In patients with established chronic liver disease or in those in whom portal vein obstruction is suspected, an experienced ultrasonographer should be able to demonstrate the patency of the portal vein, and Doppler flow ultrasonography can demonstrate the direction of flow within the portal system. The pattern of flow correlates with the severity of cirrhosis and encephalopathy. Reversal of portal vein blood flow (hepatofugal flow) is more likely to be associated with variceal bleeding. Ultrasonography is also effective in detecting the presence of esophageal varices. Another important feature of extrahepatic portal vein obstruction is cavernous transformation of the portal vein, in which an extensive complex of small collateral vessels forms in the paracholedochal and epicholedochal venous system to bypass the obstruction. Other imaging techniques also contribute to further definition of the portal vein anatomy but are required less often; contrast-enhanced CT and magnetic resonance angiography provide information similar to ultrasonography. Selective arteriography of the celiac axis, superior mesenteric artery, and splenic vein may be useful in precise mapping of the extrahepatic vascular anatomy. This is not required to establish a diagnosis but can prove valuable in planning surgical decompression of portal hypertension. The platelet count, spleen length measured by ultrasonography, and serum albumin are the best noninvasive predictors of portal hypertension in children.

In a patient with hypoxia (HPS), intrapulmonary microvascular dilation is demonstrated with contrast-enhanced bubble echocardiography that shows delayed appearance in the left heart of microbubbles from a saline bolus injected into a peripheral vein.

Endoscopy is the most reliable method for detecting esophageal varices and for identifying the source of gastrointestinal bleeding. Although bleeding from esophageal or gastric varices is most common in children with portal hypertension, up to one third of patients, particularly those with cirrhosis, have bleeding from some other source, such as portal hypertensive gastropathy or gastric or duodenal ulcerations. There is a strong correlation between variceal size as assessed endoscopically and the probability of hemorrhage. Red spots apparent over varices at the time of endoscopy are a strong predictor of imminent hemorrhage.

Treatment

The therapy of portal hypertension can be divided into emergency treatment of potentially life-threatening hemorrhage and prophylaxis directed at prevention of initial or subsequent bleeding. It must be emphasized that the use of many therapies is based on experience in adults with portal hypertension; there are few randomized trials of therapies for portal hypertension in the pediatric population.

Treatment of patients with acute variceal hemorrhage must focus on stabilization of the patient. Fluid resuscitation should be administered, initially in the form of crystalloid infusion, followed by the replacement of red blood cells. Care should be taken to avoid overtransfusing children with portal hypertension-induced bleeding, as this can result in overfilling the intravascular space and increasing portal pressure. A reasonable goal hemoglobin level after variceal bleed is between 7 and 9 g/dL. Correction of coagulopathy by administration of vitamin K and/or infusion of platelets or fresh-frozen plasma may be required. A nasogastric tube should be placed to document the presence of blood within the stomach and to monitor for ongoing bleeding. An H_2 -receptor blocker or proton pump inhibitor should be given intravenously to reduce the risk of bleeding from gastric erosions. Intravenous antibiotics should be considered, as there is high risk of infectious complications during variceal bleeding.

Pharmacologic therapy to decrease portal pressure should be initiated in patients with continued bleeding. Vasopressin or one of its analogs is commonly used and is thought to act by increasing splanchnic vascular tone and thus decreasing portal blood flow. Vasopressin is administered initially with a bolus of 0.33 units/kg over 20 min, followed by a continued infusion of the same dose on an hourly basis or a continuous infusion of 0.2 units/1.73 m^2 /min. The drug has a half-life of approximately 30 min. Its use may be limited by the side effects of vasoconstriction, which can impair cardiac function and perfusion to the heart, bowel, and kidneys and can also, as a result, exacerbate fluid retention. More commonly, the somatostatin analog, octreotide, is used, as it decreases splanchnic blood flow with few side effects. Octreotide is initially administered with a bolus of 1 µg/kg followed by a continuous intravenous infusion of 1.0-5.0 µg/kg/hr. A total of 15% of children with a portal hypertensive bleed will have persistent hemorrhage despite initiation of some form of splanchnic vasoconstriction.

After an episode of variceal hemorrhage or in patients in whom bleeding cannot be controlled with pharmacologic therapy, endoscopy with variceal band ligation or variceal sclerotherapy should be performed. Endoscopic band ligation is preferred, as it has been shown in adults to be more effective and has fewer side effects. For smaller children in whom the banding device cannot be used, sclerosants can be injected either intra- or paravariceal until bleeding has stopped. Sclerotherapy treatments may be associated with bleeding, bacteremia, esophageal ulceration, and stricture formation. After band ligation or sclerosis, repeat endoscopy should be performed until varices are obliterated.

In patients who continue to bleed despite pharmacologic and endoscopic methods to control hemorrhage, a Sengstaken-Blakemore tube may be emergently placed to stop hemorrhage by mechanically compressing esophageal and gastric varices. The device is rarely used now, but it may be the only option to control life-threatening hemorrhage until a more definite procedure can be performed. It carries a significant rate of complications and a high rate of bleeding when the device is removed, and it poses a particularly high risk for pulmonary aspiration. The tube is not well tolerated in children without significant sedation and intubation.

Various surgical procedures have been devised to divert portal blood flow and to decrease portal pressure. A portacaval shunt diverts nearly all of the portal blood flow into the subhepatic inferior right vena cava. Although portal pressure is significantly reduced, because of the significant diversion of blood from the liver, patients with parenchymal liver disease have a marked risk for hepatic encephalopathy. Even mild hepatic encephalopathy can impair cognitive function, including school performance. More selective shunting procedures, such as mesocaval or distal splenorenal shunt, can effectively decompress the portal system while allowing a greater amount of portal blood flow to the liver. The small size of the vessels makes these operations technically challenging in infants and small children, and there is a significant risk of failure as a result of shunt thrombosis. A shunt may be good option for a child with relatively well-preserved liver function, as sometimes occurs in patients with biliary atresia, congenital hepatic fibrosis, or cystic fibrosis. For children with an extrahepatic portal vein thrombosis, a Meso-Rex shunt (superior mesenteric vein to left portal vein bypass) may successfully restore physiologic portal blood flow and inflow of hepatotrophic factors. In one large single-center experience, 84% of children with idiopathic extrahepatic portal vein thrombosis were successfully treated with a Meso-Rex shunt. Growth and cognitive function improve after this procedure.

A transjugular intrahepatic portosystemic shunt, in which a stent is placed by an interventional radiologist between the right hepatic vein and the right or left branch of the portal vein, can aid in the management of portal hypertension in children, especially in those needing temporary relief before liver transplantation. The transjugular intrahepatic portosystemic shunt procedure can precipitate hepatic encephalopathy and is prone to thrombosis.

Orthotopic liver transplantation represents a much better therapy for portal hypertension resulting from intrahepatic disease and cirrhosis. A prior portosystemic shunting operation does not preclude a successful liver transplantation but makes the operation technically more difficult.

Long-term treatment with nonspecific β-blockers, such as propranolol, has been used extensively in adults with portal hypertension. These agents might act by lowering cardiac output and inducing splanchnic vasoconstriction. Evidence in adult patients shows that β-blockers can reduce the incidence of variceal hemorrhage and improve long-term survival. A therapeutic effect is thought to result when the pulse rate is reduced by ≥25%. There is limited published experience with the use of this therapy in children.

Prognosis

Portal hypertension secondary to intrahepatic disease has a poor prognosis.

Portal hypertension is usually progressive in these patients and is often associated with deteriorating liver function. Efforts should be directed toward prompt treatment of acute bleeding and prevention of recurrent hemorrhage with available methods. Patients with progressive liver disease and significant esophageal varices ultimately require orthotopic liver transplantation. Liver transplantation is the only effective therapy for HPS and should also be considered for patients with portal hypertension secondary to hepatic vein obstruction or resulting from severe venoocclusive disease.

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CHAPTER 395

Liver Transplantation

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Survival rates for pediatric liver transplantation are now >90% in the United States, in large part to refinements made in the critical care management of children with liver failure and advances in perioperative care and immunosuppression management. Protocols for immune suppression withdrawal enhancing tolerance have introduced the possibility of transplantation without the need for long-term immunosuppression. In the United States, a national allocation system matches donor organs with wait-list candidates (the Organ Procurement and Transplantation Network and the United Network for Organ Sharing [UNOS]); this organization has been given the responsibility of allocating scarce organs to the neediest patients and has undergone continuous revisions with this goal in mind—the most significant in 2002, with the adoption of the Pediatric End-Stage Liver Disease and Medical End-Stage Liver Disease (for adolescents) illness severity scoring system.

Indications

The diseases for which liver transplantation is indicated can be categorized into the following groups:

- *Obstructive biliary tract disease:* biliary atresia, sclerosing cholangitis, traumatic or postsurgical injury
- *Metabolic disorders with liver parenchymal disease:* α_1 -antitrypsin deficiency, tyrosinemia type I, glycogen storage disease type IV, Wilson disease,

gestational alloimmune liver disease (GALD, previously known as neonatal hemochromatosis), cystic fibrosis

◆ *Metabolic disorders without liver parenchymal disease:* Crigler-Najjar type I, familial hypercholesterolemia, primary oxalosis (with kidney), organic acidemia, urea cycle defects

◆ *Acute hepatitis:* fulminant hepatic failure, viral, toxin, or drug-induced

◆ *Chronic hepatitis with cirrhosis:* hepatitis B or C, autoimmune

◆ *Intrahepatic cholestasis:* idiopathic neonatal hepatitis, Alagille syndrome, progressive familial intrahepatic cholestasis, bile acid synthetic disorders

◆ *Primary liver tumors:* benign tumors (hamartomas, hemangioendothelioma), unresectable hepatoblastoma, and hepatocellular carcinoma

◆ *Miscellaneous:* cryptogenic cirrhosis, congenital hepatic fibrosis, Caroli disease, polycystic kidney and liver disease, cirrhosis induced by total parenteral nutrition

◆ *Emerging indications:* graft-versus-host disease (a complication of bone marrow transplantation), hemophilia, and portosystemic shunts

Biliary atresia is the most common indication for liver transplantation in children, accounting for more than half of all pediatric liver transplants performed in the United States, followed by metabolic liver disease and inborn errors of metabolism, autoimmune and familial cholestatic disorders, and acute hepatic necrosis. Biliary atresia may present with 2 clinical patterns: an acquired form for which there may be nonrandom clustering of potential etiologies (80% of cases), and a syndromic/embryonic form that includes other anomalies, such as polysplenia preduodenal portal vein, intestinal malrotation, situs anomalies, and absence of the retrohepatic vena cava. Hepatoportoenterostomy benefits survival if performed within the first 60 days of life; however, some patients with successful drainage later develop cirrhosis with portal hypertension (variceal bleeding and ascites). Children with biliary atresia (or any other obstructive biliary disorder) who do not achieve successful drainage will experience continued decline and end-stage liver disease, usually requiring liver transplantation within the 1st yr of life.

Inborn errors of metabolism result from a single enzyme deficiency that results in alteration of synthesis, breakdown, transport, or function of carbohydrate, fat, or protein. These disorders can be grouped into those diseases that cause liver parenchymal disease and eventual cirrhosis with end-stage liver disease, as well as liver cancer (i.e., α_1 -antitrypsin deficiency, Wilson disease, cystic fibrosis, progressive familial intrahepatic cholestasis), and those inborn errors that manifest principally by their hepatic enzyme deficiency with no hepatocellular injury; complications occur in “satellite” systems such as the brain (hyperammonemic conditions), the kidney (hyperoxaluria type 1), or heart (familial hypercholesterolemia). Some metabolic disorders place patients at risk for decompensation throughout their entire lives, and others manifest principally after adolescence. Liver transplantation is a form of enzyme replacement; the value and risk benefit of doing so in the absence of cirrhosis has prompted the pursuit of gene therapy and hepatocyte transplantation as possible alternatives, but the therapeutic benefit of these modalities of treatment is as yet equivocal.

Although a proportion of children with **acute hepatic necrosis** will survive without transplant, it accounts for approximately 13% of pediatric liver transplantation and requires the most intense concentration of multimodal management/support yet devised. This diagnosis lacks clear etiology in the majority of cases, and posttransplantation survival varies but is worse than the general population, likely due to multifactorial issues related to comorbidities and listing/transplantation graft option availability.

Primary hepatic malignancies in children are rare (<2% of all pediatric malignancies) and account for a fewer than 5% of pediatric transplants. Hepatoblastoma accounts for the majority of cases (75% of primary liver tumors in childhood) and usually presents in an advanced stage; adjuvant chemotherapy and total hepatectomy with transplantation provide cure and long-term survival for the majority of these children. Survival of >85% has been reported by the International Society of Pediatric Oncology and several American centers.

The impact of chronic liver disease and its impact on growth, development, and quality of life of children can be devastating. Liver transplantation is a valid therapy and cure. The allocation of deceased donor livers in the United States follows guidelines based on severity of liver disease as reflected in the Pediatric End-Stage Liver Disease/Model for End-Stage Liver Disease (PELD/MELD) scoring system implemented in 2002, which is calculated from the measurable values of bilirubin, albumin or creatinine (depending upon age), and international normalization ratio. The PELD scoring system was initially modeled from a cohort of 884 children on the pediatric liver transplant wait list, and is intended to predict death, decompensation, or transplantation within 3 mo. Since 2002 the number of liver transplants performed in children in the United States has remained relatively stable, while the number of liver transplants performed in adults has steadily increased by approximately 10% per year. Due to an allocation algorithm that prioritizes local adults over critically ill children nationally, a significant proportion of livers from pediatric deceased donors have been transplanted into adults without ever being offered to a child. This and other issues highlight the importance of advocacy on behalf of children in this growing field.

Contraindications to liver transplantation include uncontrolled infection of extrahepatic origin, extrahepatic malignancies, and severely disabling and uncorrectable disease in other organ systems, principally the brain, heart, and lungs. Although combined liver and heart or lung transplantation has been performed in adults and children, such cases require special consideration and centers dedicated to the complexities of posttransplantation management.

Technical Innovations

There are no limitations on age or weight for liver transplantation; to enhance the availability of liver grafts to children and optimize the timing of transplantation, techniques allowing the use of reduced-size or segmental grafts (a right or left lobe of liver, or the left lateral segment of the left lobe) were developed; this allows a liver from a larger donor to be implanted into a child, overcoming the barrier of size mismatch. In the same era, techniques were developed for the use of segments from living donors (usually the left lateral segment for small pediatric recipients), and then split-liver grafts from deceased donors where the left lateral segment is transplanted into a child and the remaining segments of right lobe and medial segment of left lobe transplanted into an adult, allowing increased utilization of deceased donor grafts without affecting adult wait-list mortality. Reduction of a liver graft is performed ex vivo (i.e., outside of the body); split-liver procurement surgery can be performed either ex vivo or in situ (in the hemodynamically stable brain-dead donor). Donors suitable for aforementioned graft variants should ideally be young (younger than 45 yr of age), healthy, and nonobese; however, variations are guided by the severity of illness and urgency for transplantation of the recipient. Not all centers have the degree of surgical expertise required to perform these more complex surgeries; thus options may be limited for children at centers that only accept size-matched organs.

The implantation of a liver (either whole organ or segment) involves removal of the native liver and encompasses 4 anastomoses: the suprahepatic vena cava, the portal vein, the hepatic artery, and the bile duct. Modifications of the procedure generally involve retaining (or not) of the retrohepatic vena cava, the performance (or not) of a temporary portocaval shunt to decompress the splanchnic venous system during the anhepatic phase, and the use of vascular homografts of donor iliac vein or artery to replace the native inflow (guided by the presence of recipient anomalies or thrombosis of native vessels). The donor bile duct may be connected to a loop of recipient intestine (Roux-en-Y limb) or the native bile duct. UNOS reported outcomes analyzing graft types, and outcomes have shown improved graft survival in children younger than 3 yr of age for live donor grafts when compared with deceased donor whole, split, and reduced grafts. After the 1st yr, however, patient and allograft survivals were similar, independent of graft type.

Immunosuppression

The long-term goal of effective clinical immunosuppression after solid-organ transplantation is to inhibit antigen-induced T-lymphocyte activation and cytokine production, and to interrupt alloimmune–major histocompatibility complex recognition. To prevent weakening the host response to infection, this goal should be achieved while preserving host immunocompetence. A major emphasis is on the prevention of acute and chronic rejection and preserving the ability to reverse refractory acute rejection. These efforts have been successful; the challenge for the future of pediatric liver transplantation is achieving long-term survival and improved quality of life; this inherently involves strategies to minimize the long-term toxicity of immunosuppressive drug therapy, which can include renal failure, cardiovascular complications, and infections. Strategies of drug minimization, steroid free therapy, and complete withdrawal of drugs have been accomplished in select patients and under careful medical supervision.

Immediately peri- or posttransplantation induction immunosuppressive therapy can involve antilymphocyte antibody induction with depleting antibodies (monoclonal or polyclonal), such as antithymocyte globulin antibody, or the use of a chimeric mouse–human antibody that blocks the interleukin-2 receptor of the T cell, thus preventing activation and replication of antigen-selected T cells. Corticosteroids act through the suppression of antibody production and cytokine synthesis (interleukin-2, and interferon-γ), decreasing proliferation of T cells (helper, suppressor, and cytotoxic), B cells, and neutrophils. Maintenance immunosuppression is achieved by using calcineurin phosphatase inhibitor (cyclosporine or tacrolimus); these drugs interfere with the production and release of interleukin-2, a critical factor in the cytotoxic T-cell response. Calcineurin phosphatase inhibitors are most effectively directed toward inhibiting T-cell–mediated acute cellular rejection. Tacrolimus is the mainstay of most immunosuppressive regimens, and its ability to progress or initiate maintenance immunosuppression in the absence of corticosteroids is of particular benefit in the children. Adjuvant immunosuppression, such as azathioprine or mycophenolate mofetil, which inhibits the synthesis of purine nucleosides and subsequently the proliferation of T and B lymphocytes as well as antibody formation, may be added to enhance the antirejection profile, allow for decrease in the calcineurin dosage, or manage chronic rejection. Rapamycin, a macrolide that binds its molecular target of mammalian target of rapamycin receptor, decreases interleukin-2 production, and in turn T- and B-cell activation and proliferation.

Complications

Posttransplantation complications can be related to the pretransplantation condition of the recipient and the donor match and type, immunologic responses to the graft and the need for enhanced immunosuppressive drug therapy, and toxicity effects of these drugs or infections from over-immunosuppression.

Posttransplant complications can occur at varying specific frequencies over a fairly well-defined time course (early, late, remote).

The most anticipated early complications involve those inherent to the transplantation operation: primary nonfunction of the graft, hepatic artery thrombosis, portal/hepatic venous strictures or occlusions, and biliary strictures. Primary nonfunction of the graft is rare in pediatric recipients given the selection criteria of potential donors. Hepatic artery thrombosis is the most frequent and early vascular complication; it occurs in 5–10% of recipients and can have devastating consequences on the graft (acute necrosis and gangrene, biliary leaks/stricture/bilomas) and may require urgent retransplantation. Portal vein or hepatic vein strictures/occlusions are rare and generally occur later posttransplantation. Biliary strictures are the most frequent surgical complication (10–30%) after liver transplantation and should be included in the differential diagnosis of any posttransplantation liver allograft dysfunction. Management of these complications varies and may include interventional radiologic procedures, reoperation, or retransplantation. Advancements in interventional radiology technique have allowed for a less invasive and equally efficacious approach to resolving these complications.

Rejection usually occurs after the first 2 wk after transplantation, with the highest incidence (30–60%) within the first 90 days. Diagnosis of rejection is suspected based on abnormal liver function studies; rarely are there systemic signs such as fever, abdominal pain, new-onset ascites, or hydrothorax. Diagnosing rejection requires biopsy confirmation; treatment algorithms include high doses of corticosteroids and antilymphocyte antibodies. Chronic rejection is less frequent (5–10%) and is characterized by progressive damage and loss of bile ductules with consequent cholestasis; treatment involves long-term enhancement of maintenance immunosuppression with corticosteroids and other agents.

The need to treat rejection can place the patient at a higher risk of drug toxicity or infection. The most common transplantation-related infections are cytomegalovirus and Epstein-Barr virus infections, for which there are well-developed algorithms of prophylaxis and screening. Epstein-Barr virus–induced **posttransplant lymphoproliferative disease** (PTLD) represents a unique complication of over-immunosuppression and infection occurring in approximately 10% of patients. It is managed primarily by withdrawal of immunosuppression and antiviral therapy; some patients require chemotherapy.

Outcomes

The clinical, surgical, and immunosuppressive drug therapy advances since the 1990s have dramatically improved survival of liver transplantation in children. UNOS data reveal a 1 yr patient and graft survival for biliary atresia of 95% and 87%, respectively. Examination of 461 5-yr survivors of pediatric liver transplantation in a North American registry found a 1st graft survival of 88%, with 12% requiring a 2nd graft and 2% requiring a 3rd transplant. The same investigators published a study of 167 10-yr survivors and found that only 30% of the group had an “ideal outcome” of normal liver-associated enzymes, no retransplant, and no evidence of PTLD, chronic rejection, hypertension, or renal disease. Longer-term survival is inherently dependent on adequacy of long term immunosuppression management, adherence to care protocols, and prevention of infection/toxicities/chronic rejection.

Pediatric liver recipients have excellent and sustained survival following childhood transplantation. With improved survival, the new frontier of care needs to battle the issues of growth, patient loss with a functioning graft, cognitive functioning, and quality of life. The goals of the field have been reset to discovery of the induction protocols and long-term strategies that can foster minimization of drug therapy, and even the induction of tolerance and a life free of the burden of immunosuppression.

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SECTION 7

Peritoneum

OUTLINE

Chapter 396 Peritoneal Malformations

Chapter 397 Ascites

Chapter 398 Peritonitis

Chapter 399 Epigastric Hernia

CHAPTER 396

Peritoneal Malformations

Asim Maqbool, Chris A. Liacouras

Congenital peritoneal bands represent anatomically unabsorbed portions of omentum and mesentery, and most commonly occur in the regions of the duodenum, duodenojejunal flexure, ileocecal junction, and ascending colon. Although usually benign, they may be responsible for intestinal obstruction or midgut volvulus and resulting intestinal necrosis. Intraabdominal herniations infrequently occur through ringlike formations produced by anomalous peritoneal bands. Numerous other anomalies can occur in the course of the development of the peritoneum but are rarely of clinical importance. Absence of the omentum or its duplication occurs rarely. Omental cysts arise in obstructed lymphatic channels within the omentum. They may be congenital or can result from trauma and are usually asymptomatic. Abdominal pain or partial small bowel obstruction can result from compression or torsion of the small bowel from traction on the omentum.

Mesenteric cysts are also rare and may co-exist with omental cysts. They may arise from the retroperitoneum, the small bowel mesentery, or even the sigmoid colon. Mesenteric cysts involve the small bowel most frequently but are also reported in association with the colon. Cysts can be single or multiple and are often large. Presentation varies, but most frequently involves abdominal pain and appreciation of an abdominal mass on examination. Gastrointestinal symptoms may also include nausea, emesis, constipation, or loose stools. Mesenteric cysts are mostly benign lesions but may act as lead points for torsion and intussusception. Cysts are usually well defined and identified on imaging via ultrasound or CT scan. Treatment is with simple excision, which can be performed laparoscopically in most cases, with excellent results and generally good prognosis.

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CHAPTER 397

Ascites

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Ascites is the pathologic accumulation of fluid within the peritoneal cavity. Multiple causes of ascites have been described in different age groups (Tables 397.1 to 397.3). In children, hepatic and renal disease are the most common causes, but ascites can also be caused by cardiac disease, trauma, infection, or neoplasia.

Table 397.1

Causes of Fetal Ascites

- Gastrointestinal disorders
  - Meconium peritonitis
  - Intestinal malrotation
  - Small intestinal or colonic atresia
  - Intussusception
  - Volvulus
  - Cystic fibrosis
  - Biliary atresia
  - Portal venous malformations
- Infection
  - Parvovirus
  - Syphilis
  - Cytomegalovirus
  - Toxoplasmosis
  - Acute maternal hepatitis
- Genitourinary disorders
  - Hydronephrosis
  - Polycystic kidney disease
  - Urinary obstruction
  - Ovarian cyst
  - Persistent cloaca
- Chylous ascites
- Cardiac disorders
  - Arrhythmia
  - Heart failure

- Chromosomal abnormalities
  - Trisomy
  - Turner syndrome
- Neoplasm
- Hematologic
  - Hemolytic anemia
  - Neonatal hemochromatosis
- Metabolic disease
  - Niemann-Pick type C
  - Congenital disorders of glycosylation
  - Wolman disease
  - Lysosomal storage disease
- Other
  - Maternal/fetal abuse
  - Idiopathic

From Giefer MJ, Murray KF, Colletti RB: Pathophysiology, diagnosis, and management of pediatric ascites, *J Pediatr Gastroenterol Nutr* 52(5):503–513, 2011 (Table 1).

Table 397.2

Causes of Neonatal Ascites

- Hepatobiliary disorders
  - Cirrhosis
  - Alpha-1-antitrypsin deficiency
  - Congenital hepatic fibrosis
  - Viral hepatitis
  - Budd-Chiari syndrome
  - Biliary atresia
  - Bile duct perforation
  - Portal venous malformation
  - Ruptured mesenchymal hamartoma
- Gastrointestinal disorders
  - Intestinal malrotation
  - Intestinal perforation
  - Acute appendicitis
  - Intestinal atresia
  - Pancreatitis
- Chylous ascites
  - Intestinal lymphangiectasia
  - Lymphatic duct obstruction
  - Lymphatic duct trauma
- Parenteral nutrition extravasation
- Metabolic disease
- Genitourinary disorders
  - Obstructive uropathy
    - Posterior urethral valves
    - Ureterocele
    - Lower ureteral stenosis
    - Ureteral atresia
    - Imperforate hymen
    - Bladder rupture

  - Bladder injury from umbilical artery catheterization
  - Nephrotic syndrome
  - Ruptured corpus luteum cyst
- Cardiac
  - Arrhythmia
  - Heart failure
- Hematologic
  - Neonatal hemochromatosis
- Other
  - Cutis marmorata telangiectatica congenita
  - Intravenous vitamin E
  - Pseudo-ascites
    - Small bowel duplication
  - Abdominal trauma
  - Idiopathic

From Giefer MJ, Murray KF, Colletti RB: Pathophysiology, diagnosis, and management of pediatric ascites, *J Pediatr Gastroenterol Nutr* 52(5):503–513, 2011 (Table 2).

Table 397.3

Causes of Ascites in Infants and Children

- Hepatobiliary disorders Neoplasm
  - Cirrhosis
  - Congenital hepatic fibrosis
  - Acute hepatitis
  - Budd-Chiari syndrome
  - Bile duct perforation
  - Liver transplantation
- Gastrointestinal disorders
  - Acute appendicitis
  - Intestinal atresia
  - Pancreatitis
  - Pyloric duplication
- Serositis
  - Crohn disease
  - Eosinophilic enteropathy
  - Henoch-Schönlein purpura
- Chylous ascites
  - Intestinal lymphangiectasia
  - Lymphatic duct obstruction
  - Lymphatic duct trauma
- Parenteral nutrition extravasation
- Infectious
  - Tuberculosis
  - Abscess
  - Schistosomiasis
- Neoplasm
  - Lymphoma
  - Wilms tumor
  - Clear cell renal sarcoma
  - Glioma
  - Germ cell tumor
  - Ovarian tumor
  - Mesothelioma
  - Neuroblastoma
- Metabolic disease
- Genitourinary disorders
  - Nephrotic syndrome
  - Peritoneal dialysis
- Cardiac
  - Heart failure
- Pseudo-ascites
  - Celiac disease
  - Cystic mesothelioma
  - Omental cyst
  - Ovarian cyst
- Other
  - Systemic lupus erythematosus
  - Ventriculoperitoneal shunt
  - Vitamin A toxicity
  - Chronic granulomatous disease
  - Nonaccidental trauma
  - Protein losing enteropathy
  - Idiopathic

Modified from Giefer MJ, Murray KF, Colletti RB: Pathophysiology, diagnosis, and management of pediatric ascites, *J Pediatr Gastroenterol Nutr* 52(5):503–513, 2011 (Table 3).

The clinical hallmark of ascites is abdominal distention. Early satiety and dyspnea can occur with a moderate amount of ascites. Considerable intraperitoneal fluid can accumulate before ascites is detectable by the classic physical signs: bulging flanks, dullness to percussion, shifting dullness, a fluid wave, and the *puddle sign* (percussion of a supine person's abdomen over the umbilicus becomes dull as the patient is moved to a prone position and ascitic fluid puddles in dependent regions). Umbilical herniation can be associated with tense ascites. Ultrasound examination is useful for detecting small amounts of ascites.

Abdominal paracentesis can provide symptomatic relief and may be diagnostic of the cause of the ascites. Determining the serum-ascites albumin gradient can help determine the cause of ascites. A gradient greater than 1.1 g/dL (high-gradient ascites) is consistent with ascites caused by portal hypertension, whereas a gradient <1.1 g/dL (low-gradient ascites) indicates ascites of non-portal-hypertensive etiology.

The course, prognosis, and treatment of ascites depend entirely on the cause. For most patients, treatment consists of dietary sodium restriction and diuretic therapy with spironolactone, with the addition of furosemide in more severe cases. Supplemental albumin can also aid in ascitic fluid mobilization. Refractory cases may require large volume paracentesis or transjugular intrahepatic portosystemic shunting. Patients with any type of ascites are at increased risk for spontaneous bacterial peritonitis.

397.1

Chylous Ascites

Asim Maqbool, Jessica W. Wen, Chris A. Liacouras

Chylous ascites refers to peritoneal fluid that contains lymphatic drainage with a characteristic milky appearance that is rich in triglycerides. Chylous ascites can result from congenital anomaly, injury, or obstruction of the intraabdominal portion of the thoracic duct. Although uncommon, it can occur at any age. In the pediatric population, the most common cause is lymphatic malformation (lymphangiectasia). Other causes include surgical injury to the lymphatics, trauma, cirrhosis, peritoneal bands, generalized lymphangiomatosis, chronic inflammatory processes of the bowel, and mycobacterial infection. Malignancy is a common cause in the adult population but uncommon in pediatrics. Congenital anomalies of the lymphatic system can be associated with Turner, Noonan, yellow nail, and Klippel-Trenaunay-Weber syndromes. Other etiologies include nephrotic syndrome, familial visceral myopathy, sarcoidosis, intestinal malrotation and volvulus, pancreatitis, constrictive pericarditis, Behcet disease, and after appendectomy.

The most common presentation is painless abdominal distention, and it may be accompanied by poor weight gain and loose stools. Peripheral edema is common. Massive chylous ascites can result in scrotal edema, inguinal and umbilical herniation, and respiratory difficulties.

Diagnosis of chylous ascites depends on the demonstration of milky ascitic fluid obtained via paracentesis after a fat-containing feeding. Ascites fluid analysis reveals high protein content, elevated triglycerides, and lymphocytosis. If the patient has had nothing by mouth, the fluid may appear serous. Hypoalbuminemia, hypogammaglobulinemia, and lymphopenia are common in these patients.

Treatment includes a high-protein, low-fat diet supplemented with medium-chain triglycerides that are absorbed directly into the portal circulation and decrease lymph production. Parenteral alimentation may be necessary if nutrition remains impaired on oral feedings; this may also significantly decrease lymph flow and facilitate sealing at the point of lymph leakage. Octreotide, a somatostatin analog, has been used subcutaneously in chylous ascites. The mechanism is not clearly understood; however, it decreases intestinal blood flow, leading to decreased portal pressure, and it also inhibits lymphatic secretion through somatostatin receptors in the intestinal wall. Paracentesis should be repeated only if abdominal distention causes respiratory distress. Lymphangiography with adjunctive embolization may be very successful in treating chylous ascites with identified site of leakage. Finally, laparotomy may be indicated if conservative management has been unsuccessful for potential surgical ligation of lymphatics.

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CHAPTER 398

Peritonitis

Asim Maqbool, Jessica W. Wen, Chris A. Liacouras

Inflammation of the peritoneal lining of the abdominal cavity can result from infectious, autoimmune, neoplastic, and chemical processes. Infectious peritonitis is usually defined as primary (spontaneous) or secondary. In primary peritonitis, the source of infection originates outside the abdomen and seeds the peritoneal cavity via hematogenous, lymphatic, or transmural spread. Secondary peritonitis arises from the abdominal cavity itself through extension from or rupture of an intraabdominal viscus or an abscess within an organ. Tertiary peritonitis refers to recurrent diffuse or localized disease and is associated with poorer outcomes than secondary peritonitis.

Clinically, patients have abdominal pain, abdominal tenderness, and rigidity on exam. Peritonitis can result from rupture of a hollow viscus, such as the appendix or a Meckel diverticulum; disruption of the peritoneum from trauma or peritoneal dialysis catheter; chemical peritonitis from other bodily fluid, including bile and urine; and infection. Meconium peritonitis is described in Chapter 123.1 . Peritonitis is considered a surgical emergency and requires exploration and lavage of the abdomen, except in spontaneous bacterial peritonitis.

398.1

Acute Primary Peritonitis

Asim Maqbool, Jessica W. Wen, Chris A. Liacouras

Etiology and Epidemiology

Primary peritonitis usually refers to bacterial infection of the peritoneal cavity without a demonstrable intraabdominal source. Most cases occur in children with ascites resulting from cirrhosis and nephrotic syndrome. Infection can result from translocation of gut bacteria as well as immune dysfunction. Rarely, primary peritonitis occurs in previously healthy children. Pneumococci (most common), group A streptococci, enterococci, staphylococci, and Gram-negative enteric bacteria, especially *Escherichia coli* and *Klebsiella pneumoniae* , are most commonly found. *Mycobacterium tuberculosis* , *Neisseria meningitidis* , and *Mycobacterium bovis* are rare causes.

Clinical Manifestations

Onset may be insidious or rapid and is characterized by fever, abdominal pain, and a toxic appearance. Vomiting and diarrhea may be present. Hypotension and tachycardia are common, along with shallow, rapid respirations because of discomfort associated with breathing. Abdominal palpation might demonstrate rebound tenderness and rigidity. Bowel sounds are hypoactive or absent. However, signs and symptoms may be subtle at times, and increased vigilance is needed in cirrhotic patients who have ascites and present with unexplained leukocytosis, azotemia, or metabolic acidosis.

Diagnosis and Treatment

Peripheral leukocytosis with a marked predominance of polymorphonuclear cells is common, although the white blood cell (WBC) count can be affected by preexisting hypersplenism in patients with cirrhosis. Patients with nephrotic syndrome generally have proteinuria, and low serum albumin in these patients is associated with an increased risk of peritonitis. X-ray examination of the abdomen reveals dilation of the large and small intestines, with increased separation of loops secondary to bowel wall thickening. Distinguishing primary peritonitis from appendicitis may be impossible in patients without a history of nephrotic syndrome or cirrhosis; accordingly, the diagnosis of primary peritonitis is made by CT scan, laparoscopy, or laparotomy. In a child with known renal or hepatic disease and ascites, the presence of peritoneal signs should prompt diagnostic paracentesis. Infected fluid usually reveals a WBC count of ≥250 cells/mm^3 , with >50% polymorphonuclear cells.

Primary peritonitis is usually monomicrobial. The presence of mixed bacterial flora on ascitic fluid examination or free air on abdominal roentgenogram in children with presumed peritonitis mandates laparotomy to localize a perforation as a likely intraabdominal source of the infection. Inoculation of ascitic fluid obtained at paracentesis directly into blood culture bottles increases the yield of positive cultures. Parenteral antibiotic therapy with broad spectrum coverage, such as cefotaxime, should be started promptly, with subsequent changes dependent on sensitivity testing (vancomycin for resistant pneumococci). Therapy should be continued for 10-14 days.

Culture-negative neutrocytic ascites is a variant of primary peritonitis with an ascitic fluid WBC count of >500 cells/mm^3 , a negative culture, no intraabdominal source of infection, and no prior treatment with antibiotics. It should be treated in a similar manner as primary peritonitis.

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398.2

Acute Secondary Peritonitis

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Acute secondary peritonitis most often results from entry of enteric bacteria into the peritoneal cavity through a necrotic defect in the wall of the intestines or other viscus as a result of obstruction or infarction or after rupture of an intraabdominal visceral abscess. It most commonly follows perforation of the appendix. Other causes include incarcerated hernias, rupture of a Meckel diverticulum, midgut volvulus, intussusception, hemolytic uremic syndrome, peptic ulceration, inflammatory bowel disease, necrotizing cholecystitis, necrotizing enterocolitis, typhlitis, and traumatic perforation.

Peritonitis in the neonatal period most often occurs as a complication of necrotizing enterocolitis but may be associated with meconium ileus or spontaneous (or indomethacin-induced) rupture of the stomach or intestines. In postpubertal girls, bacteria from the genital tract *(Neisseria gonorrhoeae, Chlamydia trachomatis)* can gain access to the peritoneal cavity via the fallopian tubes, causing secondary peritonitis. The presence of a foreign body, such as a ventriculoperitoneal catheter or peritoneal dialysis catheter, can predispose to peritonitis, with skin microorganisms, such as *Staphylococcus epidermidis, Staphylococcus aureus,* and *Candida albicans* , contaminating the shunt. Secondary peritonitis results from direct toxic effects of bacteria as well as local and systemic release of inflammatory mediators in response to organisms and their products (lipopolysaccharide endotoxin). The development of sepsis depends on various host and disease factors, as well as promptness of antimicrobial and surgical intervention.

Clinical Manifestations

Similar to primary peritonitis, characteristic symptoms include fever, diffuse abdominal pain, nausea, and vomiting. Physical findings of peritoneal inflammation include rebound tenderness, abdominal wall rigidity, a paucity of body motion (lying still), and decreased or absent bowel sounds from paralytic ileus. Massive exudation of fluid into the peritoneal cavity, along with the systemic release of vasodilative substances, can lead to the rapid development of shock. A toxic appearance, irritability, and restlessness are common. Basilar atelectasis as well as intrapulmonary shunting can develop, with progression to acute respiratory distress syndrome.

Laboratory studies reveal a peripheral WBC count >12,000 cells/mm^3 , with a marked predominance of polymorphonuclear forms. X-rays of the abdomen can reveal free air in the peritoneal cavity, evidence of ileus or obstruction, peritoneal fluid, and obliteration of the psoas shadow. Other peritoneal fluid findings suggestive of secondary peritonitis include elevated total protein (>1 g/dL), and low glucose (<50 mg/dL).

Treatment

Aggressive fluid resuscitation and support of cardiovascular function should begin immediately. Stabilization of the patient before surgical intervention is mandatory. Antibiotic therapy must provide coverage for organisms that predominate at the site of presumed origin of the infection. In contrast to primary peritonitis, secondary peritonitis is typically polymicrobial. For perforation of the lower gastrointestinal tract, a regimen of ampicillin, gentamicin, and clindamycin or metronidazole will adequately address infection by *E. coli* , *Klebsiella* , and *Bacteroides* spp. and enterococci. Alternative therapy could include piperacillin/tazobactam or a carbapenem (imipenen-cilastatin, meropenem, ertapenem or doripenem). Surgery to repair a perforated viscus should proceed after the patient is stabilized and antibiotic therapy is initiated. Intraoperative peritoneal fluid cultures will indicate whether a change in the antibiotic regimen is warranted. Empirical treatment for peritoneal dialysis catheter–related peritonitis may include intraperitoneal cefepime or cefazolin plus ceftazidime. Serious infection from peritoneal dialysis catheters can generally be prevented with good catheter hygiene and prompt removal and replacement with signs of progressive infection.

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398.3

Acute Secondary Localized

Peritonitis (Peritoneal Abscess)

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Etiology

Intraabdominal abscesses occur less commonly in children and infants than in adults, but can develop in visceral intraabdominal organs (hepatic, splenic, renal, pancreatic, tubo-ovarian abscesses) or in the interintestinal, periappendiceal, subdiaphragmatic, subhepatic, pelvic, or retroperitoneal spaces. Most commonly, periappendiceal and pelvic abscesses arise from a perforation of the appendix. Transmural inflammation with fistula formation can result in intraabdominal abscess formation in children with inflammatory bowel disease.

Clinical Manifestations

Prolonged fever, anorexia, vomiting, and lassitude suggest the development of an intraabdominal abscess. The peripheral WBC count is elevated, as is the erythrocyte sedimentation rate. With an appendiceal abscess, there is localized tenderness and a palpable mass in the right lower quadrant. A pelvic abscess is suggested by abdominal distention, rectal tenesmus with or without the passage of small-volume mucous stools, and bladder irritability. Rectal examination might reveal a tender mass anteriorly. Subphrenic gas collection, basal atelectasis, elevated hemidiaphragm, and pleural effusion may be present with a subdiaphragmatic abscess. Psoas abscess can develop from extension of infection from a retroperitoneal appendicitis, Crohn disease, or perirenal or intrarenal abscess. Abdominal findings may be minimal, and presentation can include a limp, hip pain, and fever. Ultrasound examination, CT scanning, and MRI may be used to localize intraabdominal abscesses; MRI gives the best resolution of disease involvement.

Treatment

An abscess should be drained, and appropriate antibiotic therapy provided. Drainage can be performed under radiologic control (ultrasonogram or CT guidance) and an indwelling drainage catheter left in place, or surgically depending on location of abscess. Initial broad-spectrum antibiotic coverage such as a combination of ampicillin, gentamicin, and clindamycin or ciprofloxacin and metronidazole should be started and can be modified, depending on the results of sensitivity testing. The treatment of appendiceal rupture complicated by abscess formation may be problematic because intestinal phlegmon formation can make surgical resection more difficult. Intensive antibiotic therapy for 4-6 wk followed by an interval appendectomy is often the treatment course followed.

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CHAPTER 399

Epigastric Hernia

John J. Aiken

Epigastric hernias in children are ventral hernias in the midline of the abdominal wall between the xiphoid process of the sternum and the umbilicus. Epigastric hernias are more likely congenital than acquired. The defect typically contains only preperitoneal fat without a peritoneal sac or abdominal viscera. Because most epigastric hernias are small and asymptomatic, the true incidence is unknown, but the reported incidence in childhood varies from <1% to as high as 5%. The etiology of epigastric hernia is unknown. The 2 main hypotheses are the vascular lacunae hypothesis and the tendinous fiber decussation hypothesis: the former proposes that the protrusion is through small spaces created where the vascular lacunae penetrate the linea alba, and the latter that epigastric hernia occurs exclusively at sites where affected patients do not have triple lines of decussation. In addition, undiagnosed collagen disorders, increased intraabdominal pressure, and in older patients, previous midline incision may play a role in the development of epigastric hernia. Epigastric hernias may be single or multiple and are 2-3 times more common in males than females. Through the small midline defect there is often herniation of preperitoneal fat into the superficial abdominal wall, although as the defect becomes progressively larger, the rare possibility exists of herniation of intraabdominal contents. Epigastric (incisional) hernias can occur in a previous incision site or be associated with ventricular-peritoneal shunts.

Clinical Presentation

Epigastric hernias typically appear in young children as a visible or palpable mass in the midline, between the umbilicus and the xiphoid process of the sternum, noted by the parents or primary care practitioner. The mass is almost always small (<1 cm), asymptomatic, and typically reported as always present, but most apparent at times of irritability or straining. Occasionally the mass is intermittent, and the child relates pain localized to the site. Physical examination demonstrates a firm mass, directly in the midline, anywhere between the umbilicus and the xiphoid process. The mass may be intermittent if the fat reduces with relaxation of the abdominal muscles. Epigastric hernias typically contain only preperitoneal fat, and most are not reducible because of the small size of the fascial defect. Rarely, a fascial defect is noted without a palpable mass. Herniation of intestines or abdominal viscera in an epigastric hernia would be exceptionally rare, if the defect enlarges over time. The mass may be tender to examination, but strangulation of the hernia contents is uncommon. Physical examination is almost always diagnostic, and imaging studies are generally unnecessary. If the diagnosis is unclear, imaging may be useful. Ultrasound typically shows a small mass that is isoechoic to the adjacent subcutaneous fat and possibly connection through a small fascial defect with the preperitoneal fat. MRI imaging might be helpful in diagnosis but is not routinely used.

The natural history of epigastric hernia is for gradual enlargement over time as intermittently more preperitoneal fat is extruded through the defect at times of straining or increased intraabdominal pressure. Left untreated, the defect can enlarge and allow herniation of intraabdominal viscera within a peritoneal sac, mostly seen in adults. Epigastric hernias do not resolve spontaneously, and therefore operative repair is the recommended treatment. The site should be carefully marked preoperatively because the mass and defect can be difficult to localize in a relaxed abdominal wall after induction of anesthesia. A limited transverse incision is made over the mass, and dissection is performed to delineate the edges of the fascial defect. If herniated fat is present, it is dissected free of the subcutaneous tissues and can be reduced or ligated and excised. The defect is closed using absorbable suture. The skin is closed with an absorbable subcuticular suture. Postoperative complications are rare, and the recurrence rate is low.

399.1

Incisional Hernia

Hernia formation in the site of a previous laparotomy is uncommon in childhood. Incisional hernias can also occur at the incision sites for the laparoscopic ports used in minimally invasive surgery. Factors associated with an increased risk of incisional hernia include increased intraabdominal pressure, wound infection, and midline incision. The laparoscopic ports sites pose a technical challenge to visualize the fascia in a small incision. Transverse abdominal incisions are favored because of their increased strength and blood supply, which reduces the likelihood of wound infection and incisional hernia. Although most incisional hernias require repair, operation should be deferred until the child is in optimal medical condition. Some incisional hernias resolve, especially those occurring in infants. Some recommend elastic bandaging to discourage enlargement of the hernia and to promote spontaneous healing. Initial management should be conservative, with repair deferred until around 1 yr of age. Incarceration is very uncommon in incisional hernias but is an indication for prompt repair. Newborns with abdominal wall defects represent the largest group of children with incisional hernias.

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PART XVIII

The Respiratory System

OUTLINE

Section 1 Development and Function

Section 2 Disorders of the Respiratory Tract

SECTION 1

Development and Function

OUTLINE

Chapter 400 Diagnostic Approach to Respiratory Disease
Chapter 401 Chronic or Recurrent Respiratory Symptoms
Chapter 402 Sudden Infant Death Syndrome
Chapter 403 Brief Resolved Unexplained Events and Other Acute Events in Infants

CHAPTER 400

Diagnostic Approach to Respiratory Disease

Julie Ryu, James S. Hagood, Gabriel G. Haddad

History

The history begins with a narrative provided by the parent/caretaker with input from the patient. It should include questions about respiratory symptoms (dyspnea, cough, pain, wheezing, snoring, apnea, cyanosis, exercise intolerance), as well as their chronicity, timing during day or night, and associations with activities including exercise or food intake. The respiratory system interacts with a number of other systems, and questions related to cardiac, gastrointestinal, central nervous, hematologic, and immune systems may be relevant. Questions related to gastrointestinal reflux, congenital abnormalities (airway anomalies, ciliary dyskinesia), or immune status may be important in a patient with repeated pneumonia. The family history is essential and should include inquiries about siblings and other close relatives with similar symptoms, or any chronic disease with respiratory components.

Physical Examination

Respiratory dysfunction usually produces detectable alterations in the pattern of breathing. Values for normal respiratory rates are presented in Table 81.1 and depend on many factors—most importantly, age. Repeated respiratory rate measurements are necessary because respiratory rates, especially in the young, are exquisitely sensitive to extraneous stimuli. Sleeping respiratory rates are more reproducible in infants than those obtained during feeding or activity. These rates vary among infants but average 40-50 breaths/min in the 1st few wk of life and usually <60 breaths/min in the 1st few days of life.

Respiratory control abnormalities can cause the child to breathe at a low rate or periodically. Mechanical abnormalities produce compensatory changes that are generally directed at altering minute ventilation to maintain alveolar ventilation. Decreases in lung compliance require increases in muscular force and breathing rate, leading to variable increases in chest wall retractions and nasal flaring. The respiratory excursions of children with restrictive disease are shallow. An expiratory grunt is common as the child attempts to raise the **functional residual capacity (FRC)** by closing the glottis at the end of expiration. The FRC is the amount of air left in the lungs after tidal expiration. Children with obstructive disease might take slower, deeper breaths. When the obstruction is **extrathoracic** (from the nose to the mid-trachea), inspiration is more prolonged than expiration, and an inspiratory stridor (a predominant inspiratory monophonic noise) can usually be heard (Fig. 400.1). When the obstruction is **intrathoracic** , expiration is more prolonged than inspiration, and the patient often has to make use of accessory expiratory muscles. Intrathoracic obstruction results in air trapping and, therefore, a larger residual volume, as well as a possible increase in FRC (Fig. 400.2).

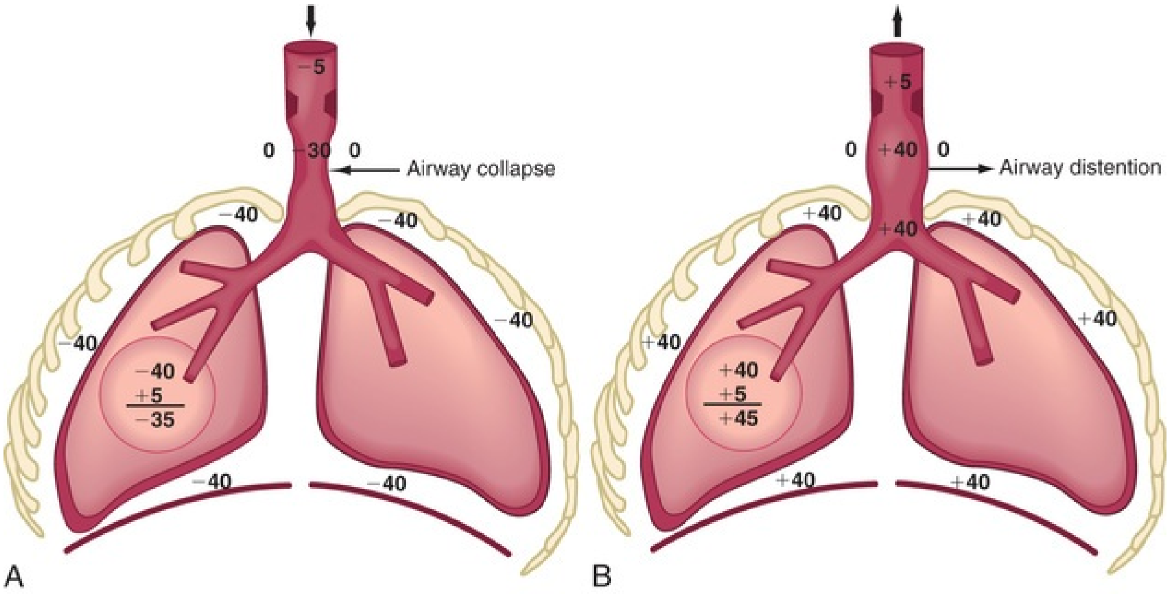

FIG. 400.1 **A,** In extrathoracic airway obstruction, the increased negative pressure during inspiration is transmitted up to the site of obstruction. This results in collapse of the extrathoracic airway below the site of obstruction, making the obstruction worse during inspiration. Note that the pressures are compared with the atmospheric pressure, which is traditionally

represented as 0 cm. Terminal airway pressure is calculated as intrapleural pressure plus lung recoil pressure. Lung recoil pressure is arbitrarily chosen as 5 cm for the sake of simplicity. **B,** During expiration, the positive pressure below the site of obstruction results in distention of extrathoracic airway and amelioration of symptoms.

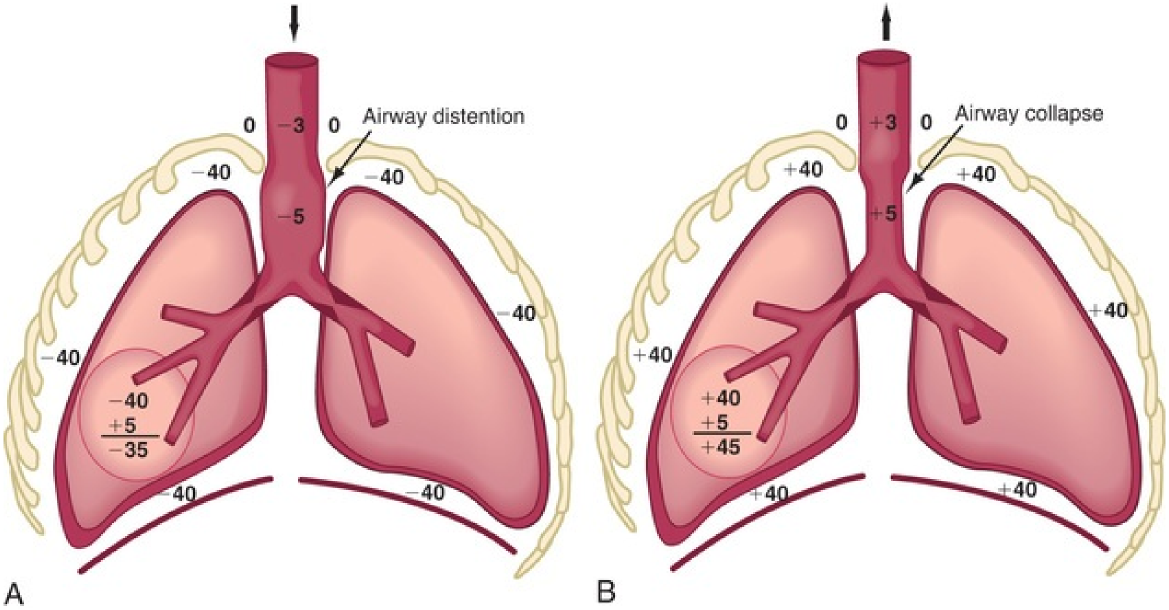

FIG. 400.2 **A** and **B,** In intrapulmonary airway obstruction, even a wider segment of intrathoracic airway is subjected to pressure changes compared with those observed in intrathoracic-extrapulmonary airway obstruction. Such lesions are associated with marked increase in airway obstruction during expiration.

Lung percussion has limited value in small infants because it cannot discriminate between noises originating from tissues that are close to each other. In adolescents and adults, percussion is usually dull in restrictive lung disease, with a pleural effusion, pneumonia, and atelectasis, but it is tympanitic in obstructive disease (asthma, pneumothorax).

Auscultation confirms the presence of inspiratory or expiratory prolongation and provides information about the symmetry and quality of air movement. In addition, it often detects abnormal or adventitious sounds such as **stridor** ; **crackles** or **rales** , high-pitched, interrupted sounds found during inspiration and more rarely during early expiration, which denote opening of previously closed air spaces; or **wheezes** , musical, continuous sounds usually caused by the development of turbulent flow in narrow airways (Table 400.1). **Digital**

clubbing is a sign of chronic hypoxia and chronic lung disease (Fig. 400.3) but may be a result of nonpulmonary etiologies (Table 400.2).

Table 400.1

Respiratory Sounds

BASIC SOUNDS	MECHANISMS	ORIGIN	ACOUSTICS	RELEVANCE
Lung	Turbulent flow, vortices, other	Central (expiration), lobar to segmental airways (inspiration)	Low pass filtered noise (<100 to >1,000 Hz)	Regional ventilation, airway caliber
Tracheal	Turbulent flow, flow impinging on airway walls	Pharynx, larynx, trachea, large airways	Noise with resonances (<100 to >3,000 Hz)	Upper airway configuration
ADVENTITIOUS SOUNDS				
Wheezes	Airway wall flutter, vortex shedding, other	Central and lower airways	Sinusoidal (<100 to >1,000 Hz, duration typically >80 msec)	Airway obstruction, flow limitation
Rhonchi	Rupture of fluid films, airway wall vibration	Larger airways	Series of rapidly dampened sinusoids (typically <300 Hz and duration <100 msec)	Secretions, abnormal airway collapsibility
Crackles	Airway wall stress-relaxation	Central and lower airways	Rapidly dampened wave deflections (duration typically <20 msec)	Airway closure, secretions

Modified from Pasterkamp H, Kraman SS, Wodicka GR: Respiratory sounds. Advances beyond the stethoscope, *Am J Respir Crit Care Med* 156[3]:974–987, 1997.

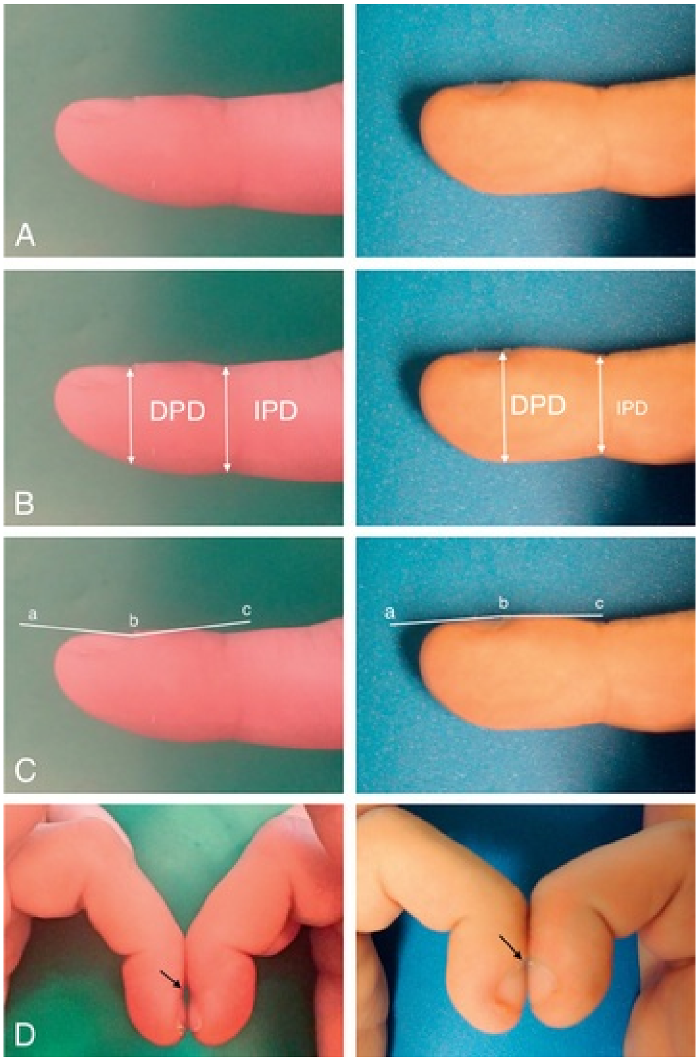

FIG. 400.3 **A,** Normal and clubbed finger viewed in profile. **B,** The normal finger demonstrates a distal phalangeal finger depth *(DPD)* /interphalangeal finger depth *(IPD)* ratio <1. The clubbed finger demonstrates a DPD/IPD ratio >1. **C,** The normal finger on the left demonstrates a normal profile *(abc)* with angle less than 180 degrees. The clubbed finger demonstrates a profile angle >180 degrees. **D,** Schamroth sign is demonstrated in the clubbed finger with the loss of diamond shape window in between finger beds *(arrow)* that is demonstrated in the normal finger. (From Wilmott RW, Bush A, Deterding RR, et al: *Kendig's disorders of the respiratory tract in children* , ed 9, Philadelphia, 2019, Elsevier [Fig. 1.14, p. 20].)

Table 400.2

Nonpulmonary Diseases Associated With Clubbing

CARDIAC

Cyanotic congenital heart disease
Bacterial endocarditis
Chronic heart failure
HEMATOLOGIC
Thalassemia
Congenital methemoglobinemia (rare)
GASTROINTESTINAL
Crohn disease
Ulcerative colitis
Celiac disease
Chronic dysentery, sprue
Polyposis coli
Severe gastrointestinal hemorrhage
Small bowel lymphoma
Liver cirrhosis (including α_1 -antitrypsin deficiency)
Chronic active hepatitis
OTHER
Thyroid deficiency (thyroid acropachy)
Thyrotoxicosis
Chronic pyelonephritis (rare)
Toxic (e.g., arsenic, mercury, beryllium)
Lymphomatoid granulomatosis
Fabry disease
Raynaud disease, scleroderma
Hodgkin disease
Familial
UNILATERAL CLUBBING
Vascular disorders (e.g., subclavian arterial aneurysm, brachial arteriovenous fistula)
Subluxation of shoulder
Median nerve injury
Local trauma

From Pasterkamp H: The history and physical examination. In Wilmott RW, Boat TF, Bush A, et al, editors: *Kendig and Chernick's disorders of the respiratory tract in children,* ed 8, Philadelphia, 2012, Elsevier.

Blood Gas Analysis

The main function of the respiratory system is to remove carbon dioxide from and add oxygen to the systemic venous blood brought to the lung. The composition of the inspired gas, ventilation, perfusion, diffusion, and tissue metabolism has a significant influence on the arterial blood gases.

The total pressure of the atmosphere at sea level is 760 torr. With increasing altitude, the atmospheric pressure decreases. The total atmospheric pressure is equal to the sum of partial pressures exerted by each of its component gases. Alveolar air is 100% humidified, so in alveolar gas calculations, the inspired gas is also presumed to be 100% humidified. At a temperature of 37°C (98.6°F) and

100% humidity, water vapor exerts pressure of 47 torr, regardless of altitude. In a natural setting, the atmosphere consists of 20.93% oxygen. **Partial pressure of oxygen in inspired gas (PiO_2)** at sea level is therefore (760 − 47) × 20.93% = 149 torr. When breathing 40% oxygen at sea level, PiO_2 is (760 − 47) × 40% = 285 torr. At higher altitudes, breathing different concentrations of oxygen, PiO_2 is less than at sea level, depending on the prevalent atmospheric pressures. In Denver (altitude of 5,000 feet and barometric pressure of 632 torr), PiO_2 in room air is (632 − 47) × 20.93% = 122 torr, and in 40% oxygen, it is (632 − 47) × 40% = 234 torr.

Minute volume is a product of V_T and respiratory rate. Part of the V_T occupies the conducting airways (anatomic dead space), which does not contribute to gas exchange in the alveoli. **Alveolar ventilation** is the volume of atmospheric air entering the alveoli and is calculated as (V_T − dead space) × respiratory rate. Alveolar ventilation is inversely proportional to arterial PCO_2 (PaCO_2). When alveolar ventilation is halved, PaCO_2 is doubled. Conversely, doubling of alveolar ventilation decreases PaCO_2 by 50%. **Alveolar PO_2 (PaO_2)** is calculated by the **alveolar air equation** as follows, where R is the respiratory quotient. For practical purposes, PACO_2 is substituted by **arterial PCO_2** (PaCO_2) and R is assumed to be 0.8. According to the alveolar air equation, for a given PiO_2, a rise in PaCO_2 of 10 torr results in a decrease in PAO_2 by 10 ÷ 0.8, or 10 × 1.25, or 12.5 torr. Thus proportionately inverse changes in PAO_2 occur to the extent of 1.25× the changes in PACO_2 (or PaCO_2).

After the alveolar gas composition is determined by the inspired gas conditions and process of ventilation, gas exchange occurs by the process of diffusion and equilibration of alveolar gas with pulmonary capillary blood. Diffusion depends on the alveolar capillary barrier and the amount of available time for equilibration. In health, the equilibration of alveolar gas and pulmonary capillary blood is complete for both oxygen and carbon dioxide. In diseases in which the alveolar capillary barrier is abnormally increased (alveolar interstitial diseases) and/or when the time available for equilibration is decreased (increased blood flow velocity), diffusion is incomplete. Because of its greater solubility in liquid medium, carbon dioxide is 20 times more diffusible than oxygen. Therefore, diseases with diffusion defects are characterized by marked **alveolar-arterial oxygen ($\mathrm{A\text{-}aO}_2$)** gradients and hypoxemia. Significant elevation of CO_2 does not occur as a result of a diffusion defect unless there is coexistent hypoventilation.

Venous blood brought to the lungs is “arterialized” after diffusion is complete. After complete arterialization, the pulmonary capillary blood should have the same PO_2 and PCO_2 as in the alveoli. The arterial blood gas composition is different from that in the alveoli, even in normal conditions, because there is a certain amount of dead space ventilation as well as venous admixture in a normal lung. Dead space ventilation results in a higher PaCO_2 than PACO_2 , whereas venous admixture or right-to-left shunting results in a lower PaO_2 compared with the alveolar gas composition (Fig. 400.4). PaO_2 is a reflection of the amount of oxygen dissolved in blood, which is a relatively minor component of total blood oxygen content. For every 100 torr PO_2 , there is 0.3 mL of dissolved O_2 in 100 mL of blood. The total blood oxygen content is composed of the dissolved oxygen and the oxygen bound to hemoglobin (Hb). Each gram of Hb carries 1.34 mL of O_2 when 100% saturated with oxygen. Thus 15 g of Hb carries 20.1 mL of oxygen. **Arterial oxygen content (CaO_2)** , expressed as mL O_2 /dL blood, can be calculated as ($\mathrm{PaO}_2 \times 0.003$) + ($\mathrm{Hb} \times 1.34 \times \mathrm{SO}_2$), where Hb is grams of Hb per deciliter of blood and SO_2 is percentage of oxyhemoglobin saturation. The relationship of PO_2 and the amount of oxygen carried by the Hb is the basis of the O_2 -Hb dissociation curve (Fig. 400.5). The PO_2 at which Hb is 50% saturated is referred to as P_{50} . At a normal pH, Hb is 94% saturated at PO_2 of 70, and little further gain in saturation is accomplished at a higher PO_2 . At PO_2 <50, there is a steep decline in saturation and therefore the oxygen content.

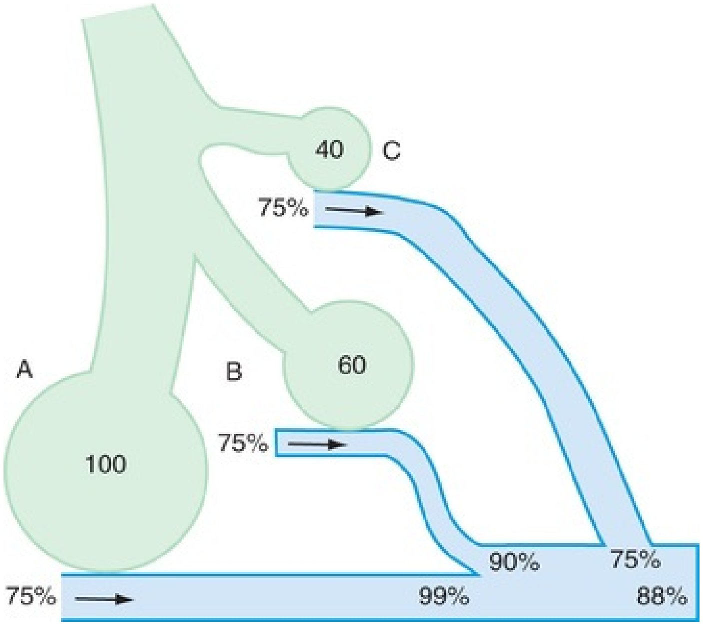

FIG. 400.4 Diagram demonstrating the effects of decreased ventilation–perfusion ratios on arterial oxygenation in the lungs. Three alveolar–capillary units are illustrated. Unit *A* has normal ventilation and an alveolar PO_2 of 100 mm Hg (shown by the number in the middle of the space). The blood that circulates through this unit raises its oxygen saturation from 75% (the saturation of mixed venous blood) to 99%. Unit *B* has a lower ventilation–perfusion ratio and a lower alveolar PO_2 of 60 mm Hg. The blood that circulates through this unit reaches a saturation of only 90%. Finally, unit *C* is not ventilated at all. Its alveolar PO_2 is equivalent to that of the venous blood, which travels through the unit unaltered. The oxygen saturation of the arterial blood reflects the weighted contributions of these 3 units. If it is assumed that each unit has the same blood flow, the arterial blood would have a saturation of only 88%. Ventilation–perfusion mismatch is the most common mechanism of arterial hypoxemia in lung disease. Supplemental oxygen increases the arterial PO_2 by raising the alveolar PO_2 in lung units that, like B, have a ventilation–perfusion ratio >0.

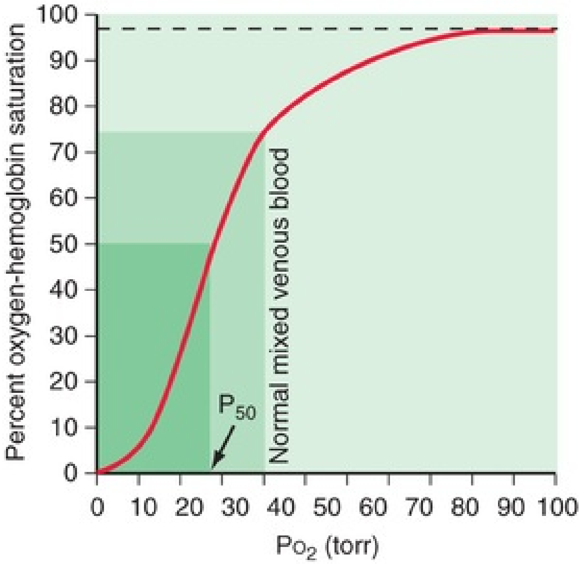

FIG. 400.5 **Oxygen-hemoglobin dissociation curve. P_{50} of adult blood is around 27 torr. Under basal conditions, mixed venous blood has PO_2 of 40 torr and oxygen-hemoglobin saturation of 75%. In arterial blood, these values are 100 torr and 97.5%, respectively. Note that there is a steep decline in oxygen-hemoglobin saturation at PaO_2 <50 torr, but relatively little increase in saturation is gained at PO_2 >70 torr.**

Oxygen delivery to tissues is a product of oxygen content and cardiac output. When Hb is near 100% saturated, blood contains approximately 20 mL oxygen per 100 mL or 200 mL/L. In a healthy adult, cardiac output is approximately 5 L/min, oxygen delivery 1,000 mL/min, and oxygen consumption 250 mL/min. Mixed venous blood returning to the heart has a PO_2 of 40 torr and is 75% saturated with oxygen. Blood oxygen content, cardiac output, and oxygen consumption are important determinants of mixed venous oxygen saturation. Given a steady-state blood oxygen content and oxygen consumption, the mixed venous saturation is an important indicator of cardiac output. A declining mixed venous saturation in such a state indicates decreasing cardiac output.

Clinical observations and interpretation of blood gas values are critical in localizing the site of the lesion and estimating its severity (Table 400.3). In airway obstruction above the carina (subglottic stenosis, vascular ring), blood gases reflect overall alveolar hypoventilation. This is manifested by an elevated $PACO_2$ and a proportionate decrease in PaO_2 as determined by the alveolar air equation. A rise in $PaCO_2$ of 20 torr decreases PaO_2 by 20 × 1.25 or 25 torr. In th absence of significant parenchymal disease and intrapulmonary shunting, such lesions respond very well to supplemental oxygen in reversing hypoxemia. Similar blood gas values, demonstrating alveolar hypoventilation and response to supplemental oxygen, are observed in patients with a depressed respiratory center and ineffective neuromuscular function, resulting in respiratory insufficiency. Such patients can be easily distinguished from those with airway obstruction by their poor respiratory effort.

Table 400.3

Interpretation of Arterial Blood Gas Values

LESION	EFFECT	TYPICAL ABG
Central (above the carina) airway obstruction, or Depressed respiratory center, or Ineffective neuromuscular function	Uniform alveolar hypoventilation	Early increase in P_{CO_2}. Proportionate decrease in P_{O_2} depending on alveolar air equation Response to supplemental oxygen: Excellent
Intrapulmonary airway obstruction	Venous admixture mismatch	Mild: ↓ P_{CO_2}, ↓ P_{O_2}. Moderate: “normal” P_{CO_2}, ↓↓ P_{O_2}. Severe: ↑↑ P_{CO_2}, ↓↓↓ P_{O_2}. Response to supplemental oxygen: good
Alveolar–interstitial pathology	Diffusion defect R → L shunt	Early decrease in P_{O_2} depending on severity Normal or low P_{CO_2}, ↑ P_{CO_2} if fatigue develops Response to supplemental oxygen: fair to poor

ABG, Arterial blood gas.

In intrapulmonary airway obstruction (asthma, bronchiolitis), blood gases reflect ventilation-perfusion imbalance and venous admixture. In these diseases, the obstruction is not uniform throughout the lungs, resulting in areas that are hyperventilated and others that are hypoventilated. Pulmonary capillary blood coming from hyperventilated areas has a higher P_{O_2} and lower P_{CO_2}, whereas that coming from hypoventilated regions has a lower P_{O_2} and higher P_{CO_2}. A lower blood P_{CO_2} can compensate for the higher P_{CO_2} because the Hb-CO_2 dissociation curve is relatively linear. In mild disease, the hyperventilated areas predominate, resulting in hypocarbia. An elevated Pa_{O_2} in hyperventilated areas cannot compensate for the decreased Pa_{O_2} in hypoventilated areas because of the shape of the O_2-Hb dissociation curve. This results in venous admixture, arterial desaturation, and decreased Pa_{O_2} (see Fig. 400.4). With increasing disease severity, more areas become hypoventilated, resulting in normalization of Pa_{CO_2} with a further decrease in Pa_{O_2}. A normal or slightly elevated Pa_{CO_2} in asthma should be viewed with concern as a potential indicator of impending respiratory failure. In severe intrapulmonary airway obstruction, hypoventilated areas predominate, leading to hypercarbia, respiratory acidosis, and hypoxemia. The degree to which supplemental oxygenation raises Pa_{O_2} depends on the severity of the illness and the degree of venous admixture.

In alveolar and interstitial diseases, blood gas values reflect both intrapulmonary right-to-left shunting and a diffusion barrier. Hypoxemia is a hallmark of such conditions occurring early in the disease process. Pa_{CO_2} is either normal or decreased. An increase in Pa_{CO_2} is observed only later in the course, as muscle fatigue and exhaustion result in hypoventilation. Response to supplemental oxygen is relatively poor with shunting and diffusion disorders compared with other lesions.

Most clinical entities present with mixed lesions. A child with a vascular ring might also have an area of atelectasis; the arterial blood gas reflects both processes. The blood gas values reflect the more dominant lesion.

An arterial blood gas analysis is probably the single most useful rapid test of pulmonary function. Although this analysis does not specify the cause of the condition or the specific nature of the disease process, it can give an overall assessment of the functional state of the respiratory system and clues about the pathogenesis of the disease. Because the detection of cyanosis is influenced by skin color, perfusion, and blood Hb concentration, the clinical detection by inspection is an unreliable sign of hypoxemia. Arterial hypertension, tachycardia, and diaphoresis are late, and not exclusive, signs of hypoventilation.

Blood gas exchange is evaluated most accurately by the direct measurement of arterial pressure of oxygen (P_{O_2}), pressure of carbon dioxide (P_{CO_2}), and pH The blood specimen is best collected anaerobically in a heparinized syringe containing only enough heparin solution to displace the air from the syringe. The syringe should be sealed, placed in ice, and analyzed immediately. Although these measurements have no substitute in many conditions, they require arterial puncture and have been replaced to a great extent by noninvasive monitoring, such as capillary samples and/or oxygen saturation.

The age and clinical condition of the patient need to be taken into account when interpreting blood gas tensions. With the exception of neonates, values of arterial P_{O_2} <85 mm Hg are usually abnormal for a child breathing room air at sea level. Calculation of the alveolar–arterial oxygen gradient is useful in the analysis of arterial oxygenation, particularly when the patient is not breathing room air or in the presence of hypercarbia. Values of arterial P_{CO_2} >45 mm Hg usually indicate hypoventilation or a severe ventilation–perfusion mismatch, unless they reflect respiratory compensation for metabolic alkalosis (see Chapter 68).

Transillumination of the Chest

In infants up to at least 6 mo of age, a pneumothorax (see Chapter 122.14) can often be diagnosed by transilluminating the chest wall using a fiberoptic light probe. Free air in the pleural space often results in an unusually large halo of light in the skin surrounding the probe. Comparison with the contralateral chest is often very helpful in interpreting findings. This test is unreliable in older patients and in those with subcutaneous emphysema or atelectasis.

Radiographic Techniques

Chest X-Rays

A posteroanterior and a lateral view (upright and in full inspiration) should be obtained, except in situations in which the child is medically unstable (Fig. 400.6). Portable images although useful in the latter situation, can give a somewhat distorted image. Expiratory images can be misinterpreted, although a comparison of expiratory and inspiratory images may be useful in evaluating a child with a suspected foreign body (localized failure of the lung to empty reflects bronchial obstruction: Chapter 414). Although images taken in a recumbent position are difficult to interpret when there is fluid within the pleural space or a cavity, if pleural fluid is suspected (see Chapter 429), decubitus images are indicated.

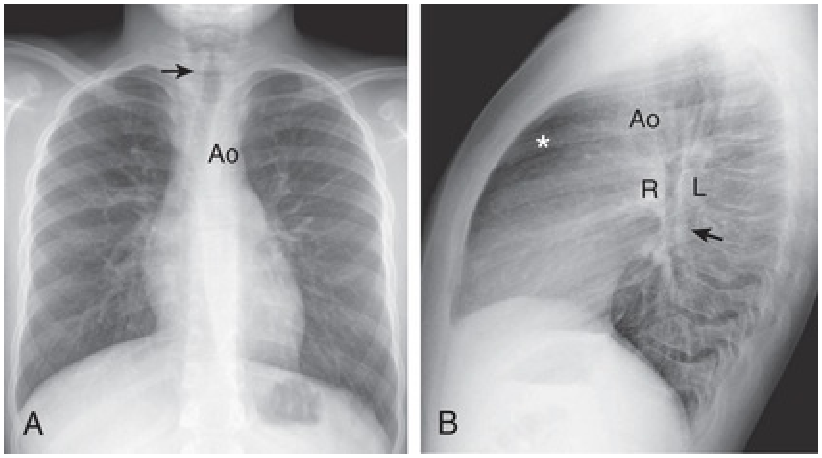

FIG. 400.6 Normal appearance of the trachea and lungs on chest radiography. A, On the frontal view, there is normal shouldering of the subglottic trachea *(arrow)* . The trachea courses inferiorly with a fairly uniform diameter to the level of the carina apart from a mild, smooth indentation at the level of the aortic arch *(Ao)* . The lungs are symmetrically inflated, with normal arborization of the vasculature. The hemidiaphragms are domed, not flattened. The normal heart size is less than 50% the transverse dimension of the chest. B, On the lateral view, the trachea is of uniform diameter to the level of the aortic arch, with the exception of a mild, smooth impression from the aortic arch anteriorly (Ao). The hemidiaphragms are domed. The heart occupies less than 50% of the anteroposterior dimension of the chest and should not fill the retrosternal clear space *(asterisk)* . The bronchus intermedius *(arrow)* courses posterior to the right pulmonary artery *(R)* , and the arch of the left pulmonary artery *(L)* projects posterior to the carina. (From Walters MM, Robertson RL, editors: *Pediatric radiology—The requisites* , ed 4, Philadelphia, 2017, Elsevier [Fig. 2.11].)

Upper Airway Film

A lateral view of the neck can yield invaluable information about upper airway obstruction (see Chapter 412) and particularly about the condition of the retropharyngeal, supraglottic, and subglottic spaces (which should also be viewed in an anteroposterior projection) (Fig. 400.7). Knowing the phase of respiration during which the film was taken is often essential for accurate interpretation. Magnified airway images are often helpful in delineating the upper airways. Patients with suggested obstruction should not be unattended in the radiology department.

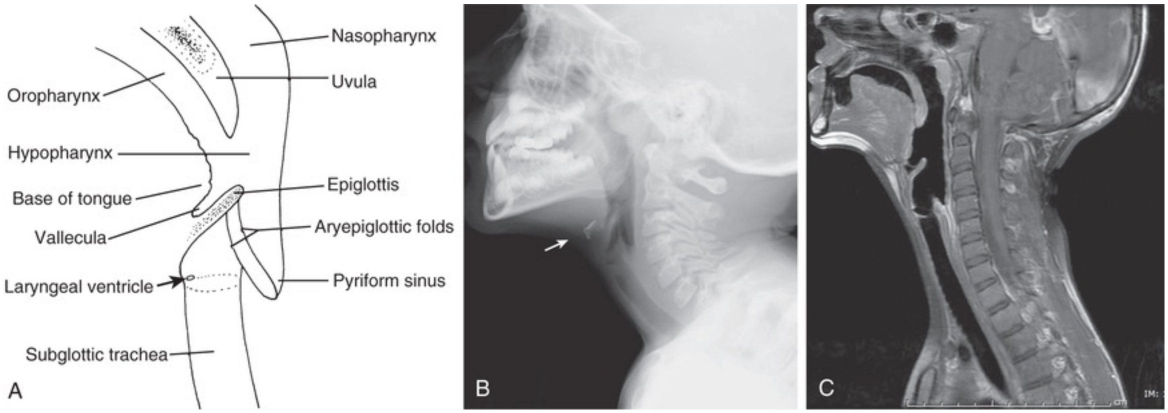

FIG. 400.7 **A,** Diagram depicting the normal anatomy of the upper airway. **B,** Corresponding lateral radiograph of the neck soft tissues. **C,** Sagittal T1-weighted magnetic resonance image. The hyoid bone “points to” the epiglottis on the radiograph *(arrow)* . (From Walters MM, Robertson RL editors: *Pediatric radiology—The requisites* , ed 4, Philadelphia, 2017, Elsevier [Fig. 2.5].)

Sinus and Nasal Images

The general utility of radiologic examination of the sinuses is uncertain because a large number of images have positive findings (low sensitivity and specificity). Imaging studies are not necessary to confirm the diagnosis of sinusitis in children younger than age 6 yr. CT scans are indicated if surgery is required, in cases of complications caused by sinus infection, in immunodeficient patients, and for recurrent infections that are not responsive to medical management.

Chest Computed Tomography and Magnetic Resonance Imaging

Chest CT and MRI can potentially provide images of higher quality and sensitivity than is possible with other imaging modalities. Chest CT identifies early abnormalities in young children with cystic fibrosis before pathologic changes are detectable by either plain chest radiographs or pulmonary function testing. However, several caveats must be noted. Conventional chest CT involves considerably higher radiation doses than plain images (see Chapter 736). The time required to perform chest CT examinations and the complications of respiratory and body motion mandates the use of sedation for this procedure in many infants and young children. However, improvements in imaging hardware and software have drastically reduced required radiation doses as well as imaging time, obviating the need for sedation in many patients. Chest CT is particularly useful in evaluating very small lesions (e.g., early metastases, mediastinal and pleural lesions, solid or cystic parenchymal lesions, pulmonary embolism, and bronchiectasis). The use of intravenous contrast material during CT imaging enhances vascular structures, distinguishing vessels from other soft-tissue densities. MRI does not involve ionizing radiation, but long imaging times are still involved, and sedation will be necessary to limit spontaneous movement. The utility of MRI of the chest is largely limited to the analysis of mediastinal, hilar, and vascular anatomy. Parenchymal structures and lesions are not well evaluated by MRI.

Fluoroscopy

Fluoroscopy is especially useful for evaluating stridor and abnormal movement of the diaphragm or mediastinum. Many procedures, such as needle aspiration or biopsy of a peripheral lesion, are also best accomplished with the aid of fluoroscopy, CT, or ultrasonography. Videotape recording, which does not increase radiation exposure, can allow detailed study during a brief exposure to fluoroscopy, through its replay capabilities.

Barium Swallow

A barium swallow study, performed with fluoroscopy and spot images is indicated in the evaluation of patients with recurrent pneumonia, persistent cough of undetermined cause, stridor, or persistent wheezing. The technique can be modified by using barium of different textures and thicknesses, ranging from thin liquid to solids, to evaluate swallowing mechanics, the presence of vascular rings (see Chapter 413), and tracheoesophageal fistulas (see Chapter 345), especially when aspiration is suspected. A contrast esophagram has been used in evaluating newborns with suggested esophageal atresia, but this procedure entails a high risk of pulmonary aspiration and is not usually recommended. Barium swallows are useful in evaluating suggested gastroesophageal reflux (see Chapter 349), but because of the high incidence of asymptomatic reflux in infants, the applicability of the findings to the clinical problem may be complicated.

Pulmonary Arteriography and Aortograms

Pulmonary arteriography has been used to allow detailed evaluation of the pulmonary vasculature. This imaging technique has also been helpful in assessing pulmonary blood flow and in diagnosing congenital anomalies, such as lobar agenesis, unilateral hyperlucent lung, vascular rings, and arteriovenous malformations. In addition, pulmonary arteriography is sometimes useful in evaluating solid or cystic lesions. Thoracic aortograms demonstrate the aortic arch, its major vessels, and the systemic (bronchial) pulmonary circulation. They are useful in evaluating vascular rings and suspected pulmonary sequestration. Although most hemoptysis is from the bronchial arteries, bronchial arteriography is seldom helpful in diagnosing or treating intrapulmonary bleeding in children. Real-time and Doppler echocardiography, as well as thoracic CT with contrast, are 2 noninvasive methods that often reveal similar information; therefore arteriography is now rarely performed.

Ventilation-Perfusion Relation and Radionuclide Lung Scans

Gravitational force pulls the lung away from the nondependent part of the parietal pleura. Consequently, alveoli and airways in the nondependent parts (the upper lobes in upright position) of the lung are subjected to greater negative intrapleural pressure during tidal respiration and are kept relatively more inflated compared with the dependent alveoli and airways (the lower lobes in upright position). The nondependent alveoli are less compliant because they are already more inflated. Ventilation therefore occurs preferentially in the dependent portions of the lung that are more amenable to expansion during tidal inspiration. Although perfusion is also greater in the dependent portions of the lung because of greater pulmonary arterial hydrostatic pressure from gravity, the increase in perfusion is greater than the increase in ventilation in the dependent portions of the lung. Thus the ratios favor ventilation in the nondependent portions and perfusion in the dependent portions. Because the airways in the dependent portion of the lung are narrower, they close earlier during expiration. The lung volume at which the dependent airways start to close is referred to as the **closing capacity** . In normal children, the FRC is greater than the closing capacity. During tidal respiration, airways remain patent both in the dependent and the nondependent portions of the lung. In newborns, the closing capacity is greater than the FRC, resulting in perfusion of poorly ventilated alveoli during tidal respiration. Therefore, normal neonates have a lower $Pa{O_2}$ compared with older children.

The relationship is adversely affected in a variety of pathophysiologic states. Air movement in areas that are poorly perfused is referred to as **dead space ventilation** . Examples of dead space ventilation include pulmonary thromboembolism and hypovolemia. Perfusion of poorly ventilated alveoli is referred to as **intrapulmonary right-to-left shunting** or **venous admixture** . Examples include pneumonia, asthma, and hyaline membrane disease. In intrapulmonary airway obstruction, the closing capacity is abnormally increased and can exceed the FRC. In such situations, perfusion of poorly ventilated alveoli during tidal respiration results in venous admixture.

The usual scan uses intravenous injection of material (macroaggregated human serum albumin labeled with ^{99m} Tc) that will be trapped in the pulmonary capillary bed. The distribution of radioactivity, proportional to pulmonary capillary blood flow, is useful in evaluating pulmonary embolism, as well as congenital cardiovascular and pulmonary defects. Acute changes in the distribution of pulmonary perfusion can reflect alterations of pulmonary ventilation.

The distribution of pulmonary ventilation can also be determined by scanning after the patient inhales a radioactive gas such as xenon-133. After the intravenous injection of xenon-133 dissolved in saline, pulmonary perfusion and ventilation can be evaluated by continuous recording of the rate of appearance and disappearance of the xenon over the lung. Appearance of xenon early after injection is a measure of perfusion, and the rate of washout during breathing is a measure of ventilation in the pediatric population. The most important indication for this test is the demonstration of defects in the pulmonary arterial distribution that can occur with congenital malformations or pulmonary embolism. **Spiral reconstruction CT** with contrast medium enhancement is very helpful in evaluating pulmonary thrombi and emboli. Abnormalities in regional ventilation are also easily demonstrable in congenital lobar emphysema, cystic fibrosis, and asthma.

Pulmonary Function Testing

Traditionally, lung volumes are measured with a spirogram (Fig. 400.8). **Tidal volume (V_T)** is the amount of air moved in and out of the lungs during each breath; at rest, V_T is normally 6-7 mL/kg body weight. **Inspiratory capacity** is the amount of air inspired by maximum inspiratory effort after tidal expiration. **Expiratory reserve volume** is the amount of air exhaled by maximum expiratory effort after tidal expiration. The volume of gas remaining in the lungs after maximum expiration is **residual volume. Vital capacity (VC)** is defined as the amount of air moved in and out of the lungs through maximum inspiration and expiration. VC, inspiratory capacity, and expiratory reserve volume are decreased in lung pathology but are also effort dependent. **Total lung capacity (TLC)** is the volume of gas occupying the lungs after maximum inhalation.

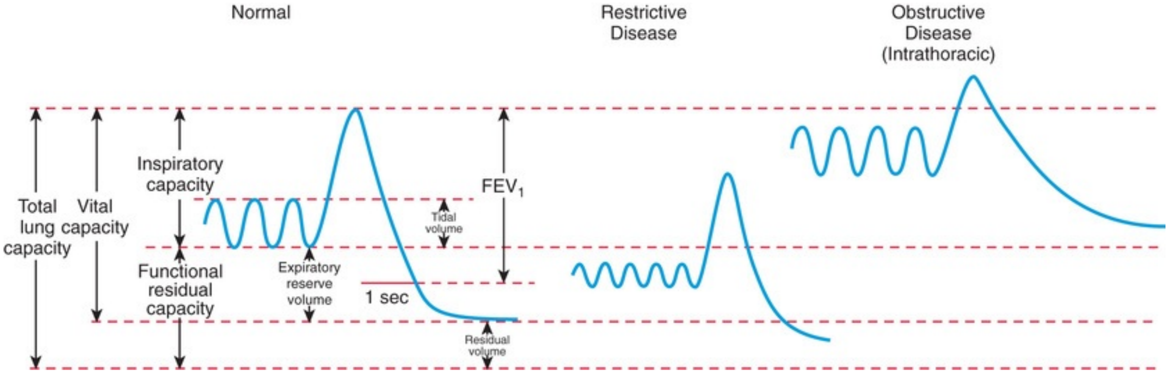

FIG. 400.8 Spirogram showing lung volumes and capacities. Forced expiratory volume 1 *(FEV$_1$)* is the maximum volume exhaled in 1 sec after maximum inspiration. Restrictive diseases are usually associated with decreased lung volumes and capacities. Intrathoracic airway obstruction is associated with air trapping and abnormally high functional residual capacity and residual volume. FEV$_1$ and vital capacity are decreased in both restrictive and obstructive diseases. The ratio of FEV$_1$ to vital capacity is normal in restrictive disease but decreased in obstructive disease.

The **flow volume relationship** offers a valuable means at the bedside or in an office setting to detect abnormal pulmonary mechanics and response to therapy with relatively inexpensive and easy-to-use devices. After maximum inhalation, the patient forcefully exhales through a mouthpiece into the device until residual volume is reached, followed by maximum inhalation (Fig. 400.9). Flow is plotted against volume. **Maximum forced expiratory flow (FEF$_{max}$)** is generated in the early part of exhalation, and it is a commonly used indicator of airway obstruction in asthma and other obstructive lesions. Provided maximum pressure is generated consistently during exhalation, a decrease in flow is a reflection of increased airway resistance (R$_{AW}$). The total volume exhaled during this maneuver is **forced vital capacity (FVC)** . **Volume exhaled in 1 sec** is referred to as **forced expiratory volume 1 (FEV$_1$)** . FEV$_1$ /FVC is expressed as a percentage of FVC. $FEF_{25–75\%}$ is the mean flow between 25% and 75% of FVC, and is considered relatively effort independent. Individual values and shapes of flow-volume curves show characteristic changes in obstructive and restrictive respiratory disorders (Fig. 400.10). In intrapulmonary airway obstruction such as asthma or cystic fibrosis, there is a reduction of FEF_{max} , $FEF_{25–75\%}$, FVC, and FEV_1 /FVC. Also, there is a characteristic concavity in the middle part of the expiratory curve. In restrictive lung disease such as interstitial pneumonia (see Chapter 327.5) and kyphoscoliosis (see Chapter 445.5), FVC is decreased with relative preservation of airflow and FEV_1 /FVC. The flow volume curve assumes a vertically oblong shape compared with normal. Changes in shape of the flow volume loop and individual values depend on the type of disease and the extent of severity. Serial determinations provide valuable information regarding disease evolution and response to therapy.

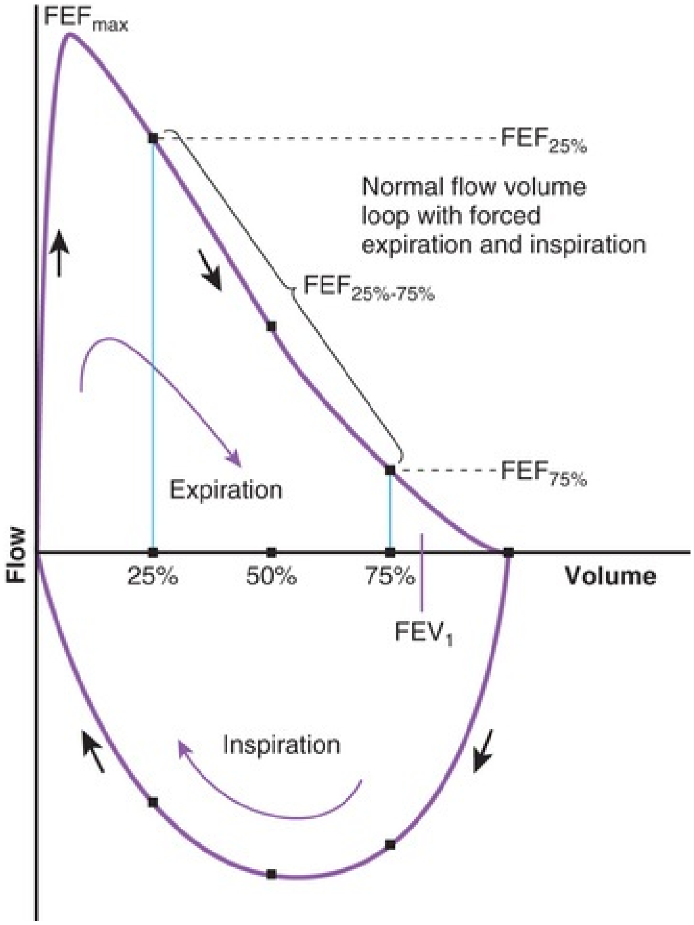

FEFmax
FEF25%
Normal flow volume loop with forced expiration and inspiration
FEF25%-75%
FEF75%
Expiration
Flow
25%
50%
75%
Volume
FEV1
Inspiration

FIG. 400.9 Flow volume loop in a normal person performed after maximal

inspiration followed by forced complete expiration and forced complete inhalation. Maximum forced expiratory flow *(FEF$_{max}$)* represents maximum flow during expiration. This is attained soon after initiation of the expiration. Fall in expiratory flow is gradual until it reaches zero after exhalation is complete. FEF$_{25–75\%}$ represents mean flow from 25% (FEF$_{25\%}$) to 75% (FEF$_{75\%}$) of exhaled forced expiratory volume *(FEV)*, also termed *forced vital capacity* (FVC). FEV$_1$ is amount of volume after 1 sec of forced exhalation. Normally FEV$_1$ is around 80% of FVC.

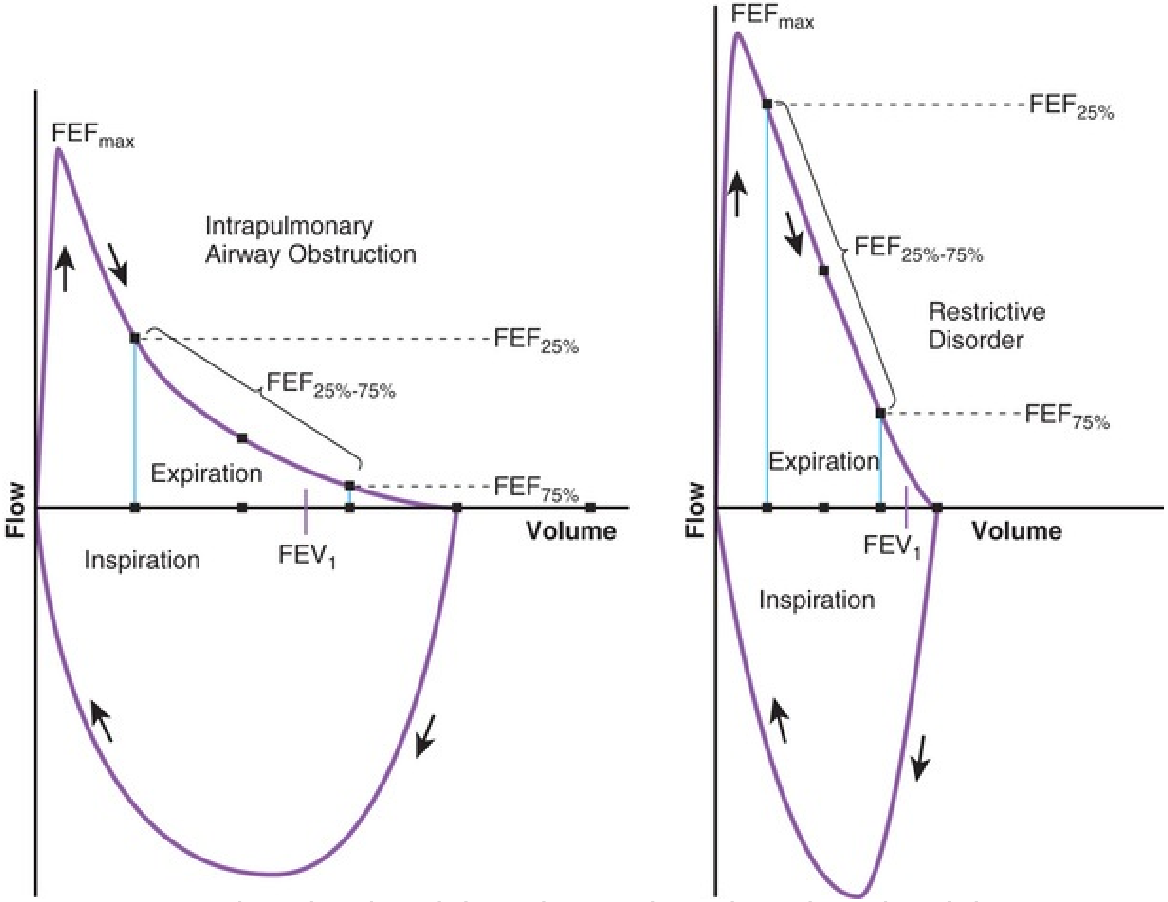

FIG. 400.10 Flow volume loops in intrapulmonary airway obstruction and restrictive disorders. Note that in intrapulmonary airway obstruction, there is a decrease in maximum forced expiratory flow *(FEF$_{max}$)*, FEF$_{25–75\%}$, and forced expiratory volume 1/forced vital capacity (*FEV$_1$*/FVC%). The middle part of expiratory loop appears concave. In restrictive disorder, the flow volume loop assumes a more vertically oblong shape with reduction in FVC but not the FEV$_1$/FVC%. Expiratory and inspiratory flow rates are relatively unaffected.

FRC has important pathophysiologic implications. Chest wall compliance is a major determinant of FRC. Because the chest wall and the lungs recoil in opposite directions at rest, FRC is reached at the point where the outward elastic recoil of the thoracic cage counterbalances the inward lung recoil. This balance is attained at a lower lung volume in a young infant's ribs because they are oriented much more horizontally and the diaphragm is flatter and less domed. Consequently, the infant is unable to duplicate the efficiency of upward and outward movement of obliquely oriented ribs or the downward displacement of a domed diaphragm in an adult to expand the thoracic capacity. This creates an extremely high thoracic compliance compared with older children and adults (Fig. 400.11). The measured FRC in infants is higher than expected because infant respiratory muscles maintain the thoracic cage in an inspiratory position at all times. In addition, young infants experience some amount of air trapping during expiration.

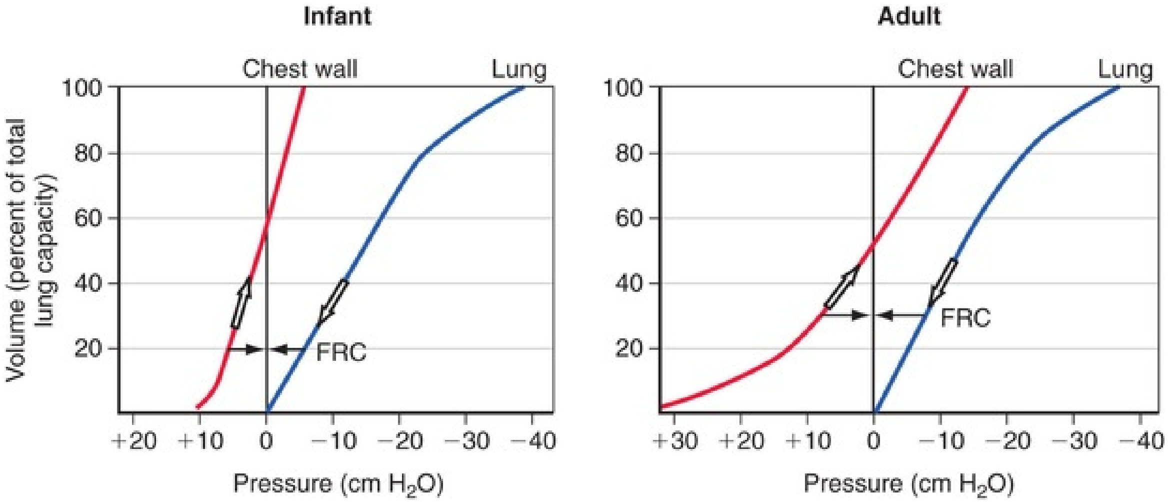

FIG. 400.11 **Schematic of interaction between chest wall and lung recoil in infants compared to adults. The elastic recoil of a relatively more compliant chest wall is balanced by the lung recoil at a lower volume functional residual capacity *(FRC)* in infants compared to adults.**

Alveolar gas composition changes during inspiration and expiration. **Alveolar PO_2 (PAO_2)** increases and **alveolar PCO_2 ($PACO_2$)** decreases during inspiratio as fresh atmospheric gas enters the lungs. During exhalation, PAO_2 decreases an $PACO_2$ increases as pulmonary capillary blood continues to remove oxygen from and add CO_2 into the alveoli (Fig. 400.12). FRC acts as a buffer, minimizing the changes in PAO_2 and $PACO_2$ during inspiration and expiration. FRC represents the environment available for pulmonary capillary blood for gas exchange at all times.

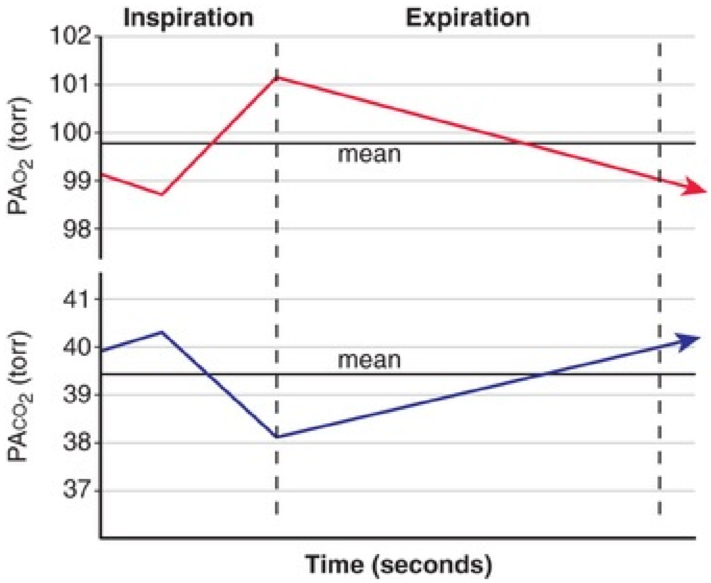

FIG. 400.12 Alveolar PO_2 rises and PCO_2 falls during inspiration as fresh atmospheric gas is brought into the lungs. During expiration, the opposite changes occur as pulmonary capillary blood continues to remove O_2 and add CO_2 from the alveoli without atmospheric enrichment. Note that during the early part of inspiration, alveolar PO_2 continues to fall and PCO_2 continues to rise because of inspiration of the dead space that is occupied by the previously exhaled gas. (Modified from Comroe JH: *Physiology of respiration,* ed 2, Chicago, 1974, Year Book Medical Publishers, p 12.)

A decrease in FRC is often encountered in alveolar interstitial diseases and thoracic deformities. The major pathophysiologic consequence of decreased FRC is **hypoxemia** . Reduced FRC results in a sharp decline in PA_{O_2} during exhalation because a limited volume is available for gas exchange. P_{O_2} of pulmonary capillary blood therefore falls excessively during exhalation, leading to a decline in **arterial** $\mathbf{P_{O_2}}$ **(**$\mathbf{PA_{O_2}}$**)** . Any increase in PA_{O_2} (and therefore Pao during inspiration cannot compensate for the decreased Pa_{O_2} during expiration. The explanation for this lies in the shape of O_2 -Hb dissociation curve, which is sigmoid shaped (see Fig. 400.5). Because most of the oxygen in blood is combined with Hb, it is the percentage of **oxyhemoglobin (**$\mathbf{S_{O_2}}$**)** that gets averaged rather than the P_{O_2} . Although an increase in arterial P_{O_2} cannot increase O_2 -Hb saturation >100%, there is a steep desaturation of Hb below a

P_{O_2} of 50 torr; thus decreased S_{O_2} during exhalation as a result of low FRC lead to overall arterial desaturation and hypoxemia. The adverse pathophysiologic consequences of decreased FRC are ameliorated by applying **positive end-expiratory pressure (PEEP)** and increasing the inspiratory time during mechanical ventilation.

The lung pressure–volume relationship is markedly influenced by FRC (Fig. 400.13). Pulmonary compliance is decreased at abnormally low or high FRC.

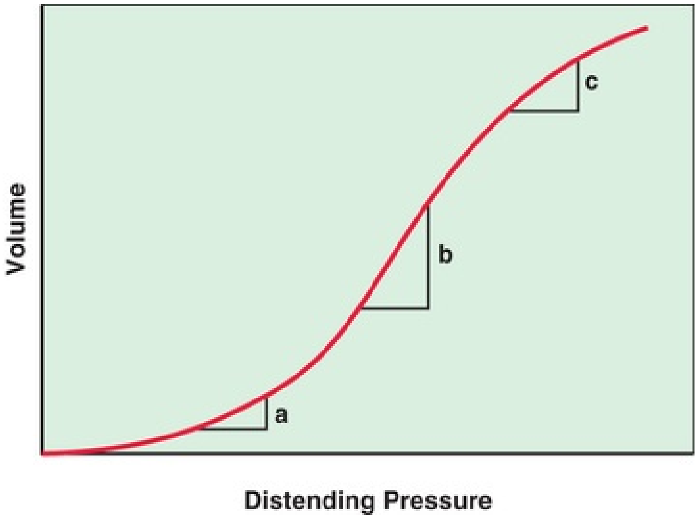

FIG. 400.13 Lung compliance is significantly influenced by the functional residual capacity (FRC). The same change in pressure is associated with less change in volume when FRC is abnormally decreased *(a)* or abnormally increased *(c)* compared to the normal state *(b).*

FRC is abnormally increased in intrathoracic airway obstruction, which results in incomplete exhalation, and abnormally decreased in alveolar-interstitial diseases. At excessively low or high FRC, tidal respiration requires higher inflation pressures compared to normal FRC. Abnormalities of FRC result in increased work of breathing with spontaneous respiration and increased barotrauma in mechanical ventilation.

The measurement of respiratory function in infants and young children can be difficult because of the lack of cooperation. Attempts have been made to overcome this limitation by creating standard tests that do not require the patient's active participation. Respiratory function tests still provide only a partial insight into the mechanisms of respiratory disease at early ages.

Whether restrictive or obstructive, most forms of respiratory disease cause alterations in lung volume and its subdivisions. Restrictive diseases typically decrease **TLC** . TLC includes residual volume, which is not accessible to direct determinations. It must therefore be measured indirectly by gas dilution methods or, preferably, by **plethysmography** . Restrictive disease also decreases **VC** . Obstructive diseases produce gas trapping and thus increase residual volume and FRC, particularly when these measurements are considered with respect to TLC.

Airway obstruction is most commonly evaluated from determinations of gas flow in the course of a forced expiratory maneuver. The **peak expiratory flow** is reduced in advanced obstructive disease. The wide availability of simple devices that perform this measurement at the bedside makes it useful for assessing children who have airway obstruction. Evaluation of peak flows requires a voluntary effort, and peak flows may not be altered when the obstruction is moderate or mild. Other gas flow measurements require that the child inhale to TLC and then exhale as far and as fast as possible for several seconds. Cooperation and good muscle strength are therefore necessary for the measurements to be reproducible. FEV_1 correlates well with the severity of obstructive diseases. The **maximal midexpiratory flow rate** , the average flow during the middle 50% of the forced VC, is a more reliable indicator of mild airway obstruction. Its sensitivity to changes in residual volume and VC, however, limits its use in children with more severe disease. The construction of flow-volume relationships during the forced VC maneuvers overcomes some of these limitations by expressing the expiratory flows as a function of lung volume.

A **spirometer** is used to measure VC and its subdivisions and expiratory (or inspiratory) flow rates (see Fig. 400.8). A simple manometer can measure the maximal inspiratory and expiratory force a subject generates, normally at least 30 cm H_2O. This is useful in evaluating the neuromuscular component of ventilation. Expected normal values for VC, FRC, TLC, and residual volume are obtained from prediction equations based on body height.

Flow rates measured by spirometry usually include the FEV_1 and the **maximal midexpiratory flow rate** . More information results from a maximal expiratory flow-volume curve, in which expiratory flow rate is plotted against expired lung volume (expressed in terms of either VC or TLC). Flow rates at lung volumes less than approximately 75% VC are relatively independent of effort. Expiratory flow rates at low lung volumes (<50% VC) are influenced much more by small airways than flow rates at high lung volumes (FEV_1). The flow rate at 25% VC is a useful index of small airway function. Low flow rates at high lung volumes associated with normal flow at low lung volumes suggest upper airway obstruction.

Airway resistance (R_{AW}) is measured in a plethysmograph, or alternatively, the reciprocal of R_{AW} , **airway conductance** , may be used. Because R_{AW} measurements vary with the lung volume at which they are taken, it is convenient to use **specific airway resistance** , SR_{AW} ($SR_{AW} = R_{AW}$ /lung volume), which is nearly constant in subjects older than age 6 yr (normally <7 sec/cm H_2 O).

The **diffusing capacity for carbon monoxide** is related to oxygen diffusion and is measured by rebreathing from a container having a known initial concentration of carbon monoxide or by using a single-breath technique. Decreases in diffusing capacity for carbon monoxide reflect decreases in effective alveolar capillary surface area or decreases in diffusibility of the gas across the alveolar-capillary membrane. Primary diffusion abnormalities are unusual in children; therefore, this test is most commonly employed in children with rheumatologic or autoimmune diseases and in children exposed to toxic drugs to the lungs (e.g., oncology patients) or chest wall radiation. Regional gas exchange can be conveniently estimated with the perfusion-ventilation xenon scan. Determining arterial blood gas levels also discloses the effectiveness of alveolar gas exchange.

Pulmonary function testing, although rarely resulting in a diagnosis, is helpful in defining the type of process (obstruction, restriction) and the degree of functional impairment, in following the course and treatment of disease, and in estimating the prognosis. It is also useful in preoperative evaluation and in confirmation of functional impairment in patients having subjective complaints but a normal physical examination. In most patients with obstructive disease, a repeat test after administering a bronchodilator is warranted.

Most tests require some cooperation and understanding by the patient. Interpretation is greatly facilitated if the test conditions and the patient's behavior during the test are known. Infants and young children who cannot or will not cooperate with test procedures can be studied in a limited number of ways, which often require sedation. Flow rates and pressures during tidal breathing, with or without transient interruption of the flow, may be useful to assess some aspects of R_{AW} or obstruction and to measure compliance of the lungs and thorax. Expiratory flow rates can be studied in sedated infants with passive compression of the chest and abdomen using a rapidly inflatable jacket. Gas dilution or plethysmographic methods can also be used in sedated infants to measure FRC and R_{AW} .

The measurement of **fractional exhaled nitric oxide** (FENO) is used as a surrogate measure for eosinophilic inflammation of the lower airways. It can be used as a part of a diagnostic evaluation for asthma, a tool for predicting or assessing an individual's response to antiinflammatory therapy, and in monitoring adherence to treatment. There are a number of commercially available devices for measurement of FENO. Some degree of cooperation is required, but FENO has been measured in preschool-aged children. Normal cutoff values vary by age and device. FENO has been used to distinguish asthma (particularly allergic asthma) from other wheezing phenotypes. FENO achieves moderate diagnostic performance for the detection of asthma in children, with sensitivity, specificity, and diagnostic odds ratios of 0.79, 0.81, and 16.52, respectively. Children managed using FENO may have fewer asthma exacerbations. A decrease of FENO by 20% is considered indicative of a positive response to antiinflammatory therapy. Some studies using FENO have contradictory results, and it is likely that FENO may be more useful in some asthma phenotypes than others.

The measurement of **nasal nitric oxide** (nNO) is accomplished by collecting exhaled gas from a nostril during glottic closure, and correlates to nasal mucosal inflammation. There is a great deal of interest in use of nNO to diagnose **primary ciliary dyskinesia** (PCD, see Chapter 404), because of challenges diagnosing PCD with currently available techniques. A cutoff value of less than or equal to 77 nL/min showed excellent sensitivity and specificity using a standardized technique at multiple centers. The sensitivity and specificity of 0.95 and 0.94 is excellent. Equipment for measurement of nNO is not yet FDA-approved in the USA.

Microbiology: Examination of Lung Secretions

The specific diagnosis of infection in the lower respiratory tract depends on the proper handling of an adequate specimen obtained in an appropriate fashion. Nasopharyngeal or throat cultures are often used but might not correlate with cultures obtained by more direct techniques from the lower airways. Sputum specimens are preferred and are often obtained from patients who do not expectorate by deep throat swab immediately after coughing or by saline nebulization. Specimens can also be obtained directly from the tracheobronchial tree by nasotracheal aspiration (usually heavily contaminated), by transtracheal aspiration through the cricothyroid membrane (useful in adults and adolescents but hazardous in children), and in infants and children by a sterile catheter inserted into the trachea either during direct laryngoscopy or through a freshly inserted endotracheal tube. A specimen can also be obtained at bronchoscopy. A percutaneous lung tap or an open biopsy is the only way to obtain a specimen absolutely free of oral flora.

A specimen obtained by direct expectoration is usually assumed to be of tracheobronchial origin, but often, especially in children, it is not from this source. The presence of alveolar macrophages (large mononuclear cells) is the hallmark of tracheobronchial secretions. Nasopharyngeal and tracheobronchial secretions can contain ciliated epithelial cells, which are more commonly found in sputum. Nasopharyngeal and oral secretions often contain large numbers of squamous epithelial cells. Sputum can contain both ciliated and squamous epithelial cells.

During sleep, mucociliary transport continually brings tracheobronchial secretions to the pharynx, where they are swallowed. An early-morning fasting gastric aspirate often contains material from the tracheobronchial tract that is suitable for culture for acid-fast bacilli.

The absence of polymorphonuclear leukocytes in a Wright-stained smear of sputum or **bronchoalveolar lavage** (BAL) fluid containing adequate numbers of macrophages may be significant evidence against a bacterial infectious process in the lower respiratory tract, assuming that the patient has normal neutrophil counts and function. Eosinophils suggest allergic disease. Iron stains can reveal hemosiderin granules within macrophages, suggesting pulmonary hemosiderosis. Specimens should also be examined by Gram stain. Bacteria within or near macrophages and neutrophils can be significant. Viral pneumonia may be accompanied by intranuclear or cytoplasmic inclusion bodies visible on Wright-stained smears, and fungal forms may be identifiable on Gram or silver stains.

With advances in the area of genomics and the speed with which it is possible to identify microbes, microbiologic analysis has been expanded. Specific bacteria in the lungs of children with cystic fibrosis (see Chapter 432) are linked to morbidity and mortality. There is a correlation between patient age and morbidity and mortality (as expected), but that there are important microbes that are correlated either negatively or positively with early or late pathogenic processes. *Haemophilus influenzae* (see Chapter 221) is negatively correlated, and *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* (see Chapter 232.3) have a strong positive correlation with patient age in cystic fibrosis. The microbiota diversity is much broader in those who are healthier individuals or those who are younger patients with cystic fibrosis than the older and sicker population.

In addition, the microbiomes (see Chapter 196) in the respiratory tract of smokers and nonsmokers differ substantially. In all patients, most of the bacteria found in the lungs are also present in the oral cavity, but some bacteria, such as *Haemophilus* and enterobacteria, are much more represented in the lungs than in the mouth. Principal differences in microbiome composition between smokers and nonsmokers are found in the mouth. For example, *Neisseria* levels are much lower in smokers as compared with nonsmokers.

The Microbiome (see Chapter 196)

Exercise Testing

Exercise testing (see Chapter 450.5) is a more-direct approach for detecting diffusion impairment and other forms of respiratory disease. Exercise is a strong provocateur of bronchospasm in susceptible patients, so exercise testing can be useful in the diagnosis of patients with asthma that is only apparent with activity. Measurements of heart and respiratory rate, minute ventilation, oxygen consumption, carbon dioxide production, and arterial blood gases during incremental exercise loads often provide invaluable information about the functional nature of the disease. Often a simple assessment of the patient's exercise tolerance in conjunction with other, more static forms of respiratory function testing can allow a distinction between respiratory and nonrespiratory disease in children.

Sleep Studies

See Chapter 31 .

Airway Visualization and Lung Specimen–Based Diagnostic Tests

Laryngoscopy

The evaluation of stridor, problems with vocalization, and other upper airway abnormalities usually requires direct inspection. Although indirect (mirror) laryngoscopy may be reasonable in older children and adults, it is rarely feasible in infants and small children. Direct laryngoscopy may be performed with either a rigid or a flexible instrument. The safe use of the rigid scope for examining the upper airway requires topical anesthesia and either sedation or general anesthesia, whereas the flexible laryngoscope can often be used in the office setting with or without sedation. Further advantages to the flexible scope include the ability to assess the airway without the distortion that may be introduced by the use of the rigid scope and the ability to assess airway dynamics more accurately. Because there is a relatively high incidence of concomitant lesions in the upper and lower airways, it is often prudent to examine the airways above and below the glottis, even when the primary indication is in the upper airway (stridor).

Bronchoscopy and Bronchoalveolar Lavage

Bronchoscopy is the inspection of the airways. Flexible bronchoscopy is commonly used in pediatrics to visualize the airways. There are several sizes of scopes that enable visualization of the proximal and distal airways. Many fiberoptic bronchoscopes also have a channel that allows for the collection of fluids, or in larger scopes allows for the insertion of tools such as forceps, baskets, or brushes. The smallest scope is a 2.2 mm outer diameter bronchoscope that does not have a channel; therefore only visualization of the airways is possible. The smallest bronchoscope with a channel is a 2.8 mm outer diameter scope, which has a 1.2 mm working channel. This scope is commonly used in pediatrics and is predominately used to visualize the airways and to collect a lavage sample. In larger "adult" scopes (4.9-5.5 mm outer diameter and 2.0 mm working channel), small instruments such as forceps can be inserted. Therapeutic bronchoscopes require an even larger channel (2.8 mm working channel, which requires a larger outer diameter of 6.0-6.3 mm), so they are not used often in the pediatric population. A smaller scope (4.1 mm outer diameter) with a larger working channel (2.0 mm) has become available and may make interventional pediatric bronchoscopy more common in the future.

Visualization of the airway has improved through new advances in optics and insertable tools. **Narrow-band imaging** and **autofluorescence** imaging bronchoscopes are 2 types of bronchoscopes that can aid in the detection of airway lesions. These scopes appear no different than the conventional bronchoscope but utilize different bandwidths of lights to highlight mucosal and submucosal vasculature. These bronchoscopes allow the operator to see airway mucosal lesions that would be difficult or not seen under normal white light. The autofluorescence imaging bronchoscope uses the fluorophores, such as tryptophan, collagen, elastin and porphyrins, within the airway tissue to emit fluorescence when irradiated with a light source. Changes in concentrations of the fluorophores in bronchial mucosa would appear as an irregular lesion when viewed with an autofluorescence imaging bronchoscope. The narrow-band imaging bronchoscope also uses light absorption characteristics of Hb to enhance images of blood vessels. This bronchoscope uses blue wavelengths in the range of 390-445 nm to visualize the mucosal layer capillaries and green wavelengths at 530 and 550 nm to detect deeper submucosal thick blood vessels. Both types of bronchoscopes allow the operator to detect findings that would not be seen under normal white light. These scopes are being used more often in adults where lesions are biopsied to detect premalignant and malignant lesions. These scopes are noninvasive and would be well tolerated in children, but are currently only available in larger “adult” sizes.

The **EBUS** , **endobronchial ultrasound** , is a scope that allows ultrasound images to be captured from the tip of the scope and also contains a working channel to collect a needle biopsy. This technology is particularly useful in the evaluation of mediastinal lymph nodes. This scope may be useful in the diagnosis of other conditions such as sarcoidosis, tuberculosis, and the staging of lung cancers. The EBUS is currently being investigated in older pediatric patients as an alternative to CT-guided transthoracic fine needle aspiration for the evaluation of mediastinal lymph nodes. EBUS has the benefit of no radiation, but has not been extensively studied in pediatrics.

Bronchial thermoplasty (BT) is a technology that can be used to treat patients with severe asthma. This technique uses the working channel of a fiberoptic bronchoscope to deliver targeted thermal energy to the airways to ablate the airway smooth muscle (ASM). The ablation of ASM may reduce the ability to bronchoconstrict. It may also impact the ASM's role in immunomodulation, ultimately altering the pathophysiology of asthma. BT requires a minimum of a 2.0 mm working channel, which limits this technology to bronchoscopes of at least an outer diameter of 4.1 mm. In general, BT is performed over 3 bronchoscopy sessions to ablate different sections of the lung: right lower lobe, left lower lobe, and bilateral upper lobes. The right middle lobe is usually not ablated for the potential risk of stenosis. The treatments are divided into 3 separate procedures to allow for shorter procedure times (30-60 min per session) and decrease the risk of widespread irritation. Patients are also given oral steroids for 3 days prior to the procedure to decrease airway inflammation associated with the ablation procedure. While BT is gaining momentum in the treatment of severe asthma in the adult population, the long-term ramifications of airway smooth muscle ablation in a child are still unknown. In adult studies that investigated BT as a therapeutic tool for asthma, small studies demonstrated an improvement in clinical symptoms, and in a smaller cohort of patients (12 patients), no significant structural abnormalities were seen on chest radiographs 5 yr after the procedure.

The most common diagnostic tool used in conjunction with fiberoptic bronchoscopy is **bronchoalveolar lavage (BAL)** . BAL is a method used to obtain a representative specimen of fluid and secretions from the lower respiratory tract, which is useful for the cytologic and microbiologic diagnosis of lung diseases, especially in those who are unable to expectorate sputum. BAL is performed after the general inspection of the airways and before tissue sampling with a brush or biopsy forceps. It is accomplished by gently wedging the scope into a lobar, segmental, or subsegmental bronchus, and sequentially instilling and withdrawing sterile nonbacteriostatic saline in a volume sufficient to ensure that some of the aspirated fluid contains material that originated from the alveolar space. Nonbronchoscopic BAL can be performed in intubated patients by instilling and withdrawing saline through a catheter passed though the artificial airway and blindly wedged into a distal airway, although nonbronchoscopic BAL is less accurate and therefore has less-reliable results. In either case, the presence of alveolar macrophages documents that an alveolar sample has been obtained. Because the methods used to perform BAL involve passage of the equipment through the upper airway, there is a risk of contamination of the specimen by upper airway secretions. Careful cytologic examination and quantitative microbiologic cultures are important for correct interpretation of the data. BAL can often obviate the need for more-invasive procedures such as open lung biopsy, especially in immunocompromised patients.

Indications for diagnostic bronchoscopy and BAL include recurrent or persistent pneumonia or atelectasis, unexplained or localized and persistent wheeze, the suspected presence of a foreign body, hemoptysis, suspected congenital anomalies, mass lesions, interstitial disease, and pneumonia in the immunocompromised host. Indications for therapeutic bronchoscopy and BAL include bronchial obstruction by mass lesions, foreign bodies or mucus plugs, and general bronchial toilet and bronchopulmonary lavage. The patient undergoing bronchoscopy ventilates around the flexible scope, whereas with the rigid scope, ventilation is accomplished through the scope. Rigid bronchoscopy is preferentially indicated for extracting foreign bodies and removing tissue masses. It is also indicated in patients with massive hemoptysis. In other cases, the flexible scope has multiple advantages: it can be passed through endotracheal or tracheostomy tubes, can be introduced into bronchi that come off the airway at acute angles, and can be safely and effectively inserted with topical anesthesia and conscious sedation.

Regardless of the instrument used, the procedure performed, or the resulting indications, the most common complications are related to sedation. The relatively more common complications related to the bronchoscopy itself include transient hypoxemia, laryngospasm, bronchospasm, and cardiac arrhythmias. Iatrogenic infection, bleeding, pneumothorax, and pneumomediastinum are rare but reported complications of bronchoscopy or BAL. Bronchoscopy in the setting of possible pulmonary abscess or hemoptysis must be undertaken with advance preparations for definitive airway control, mindful of the possibility that pus or blood might flood the airway. Subglottic edema is a more common complication of rigid bronchoscopy than of flexible procedures, in which the scopes are smaller and less likely to traumatize the mucosa. Postbronchoscopy croup is treated with oxygen, mist, vasoconstrictor aerosols, and corticosteroids as necessary.

Thoracoscopy

The pleural cavity can be examined through a thoracoscope, which is similar to a rigid bronchoscope. The thoracoscope is inserted through an intercostal space and the lung is partially deflated, allowing the operator to view the surface of the lung, the pleural surface of the mediastinum and the diaphragm, and the parietal pleura. Multiple thoracoscopic instruments can be inserted, allowing endoscopic biopsy of the lung or pleura, resection of blebs, abrasion of the pleura, and ligation of vascular rings.

Thoracentesis

For diagnostic or therapeutic purposes, fluid can be removed from the pleural space by needle. In general, as much fluid as possible should be withdrawn, and an upright chest roentgenogram should be obtained after the procedure. Complications of thoracentesis include infection, pneumothorax, and bleeding. Thoracentesis on the right may be complicated by puncture or laceration of the capsule of the liver and, on the left, by puncture or laceration of the capsule of the spleen. Specimens obtained should always be cultured, examined microscopically for evidence of bacterial infection, and evaluated for total protein and total differential cell counts. Lactic acid dehydrogenase, glucose, cholesterol, triglyceride (chylous), and amylase determinations may also be useful. If malignancy is suspected, cytologic examination is imperative.

Transudates result from mechanical factors influencing the rate of formation or reabsorption of pleural fluid and generally require no further diagnostic evaluation. Exudates result from inflammation or other disease of the pleural surface and underlying lung, so they require a more complete diagnostic evaluation. In general, transudates have a total protein of <3 g/dL or a ratio of pleural protein to serum protein <0.5, a total leukocyte count of fewer than 2,000/mm^3 with a predominance of mononuclear cells, and low lactate dehydrogenase levels. Exudates have high protein levels and a predominance of polymorphonuclear cells (although malignant or tuberculous effusions can have a higher percentage of mononuclear cells). Complicated exudates often require continuous chest tube drainage and have a pH <7.2. Tuberculous effusions can have low glucose and high cholesterol content.

Lung Tap

Using a technique similar to that used for thoracentesis, a percutaneous lung tap is the most direct method of obtaining bacteriologic specimens from the pulmonary parenchyma and is the only technique other than open lung biopsy not associated with at least some risk of contamination by oral flora. After local anesthesia, a needle attached to a syringe containing nonbacteriostatic sterile saline is inserted using aseptic technique through the inferior aspect of an intercostal space in the area of interest. The needle is rapidly advanced into the lung; the saline is injected and reaspirated, and the needle is withdrawn. These actions are performed as quickly as possible. This procedure usually yields a few drops of fluid from the lung, which should be cultured and examined microscopically.

Major indications for a lung tap are infiltrates of undetermined cause, especially those unresponsive to therapy in immunosuppressed patients who are susceptible to unusual organisms. Complications are the same as for thoracentesis, but the incidence of pneumothorax is higher and somewhat dependent on the nature of the underlying disease process. In patients with poor pulmonary compliance, such as children with *Pneumocystis* pneumonia, the rate can approach 30%, with 5% requiring chest tubes. Bronchopulmonary lavage has replaced lung taps for most purposes.

Lung Biopsy

Lung biopsy may be the only way to establish a diagnosis, especially in protracted, noninfectious disease. In infants and small children, thoracoscopic or open surgical biopsies are the procedures of choice, and in expert hands there is low morbidity. Biopsy through the 3.5 mm diameter pediatric bronchoscopes limits the sample size and diagnostic abilities. In addition to ensuring that an adequate specimen is obtained, the surgeon can inspect the lung surface and choose the site of biopsy. In older children, transbronchial biopsies can be performed using flexible forceps through a bronchoscope, an endotracheal tube, a rigid bronchoscope, or an endotracheal tube, usually with fluoroscopic guidance. This technique is most appropriately used when the disease is diffuse, as in the case of *Pneumocystis* pneumonia, or after rejection of a transplanted lung. The diagnostic limitations related to the small size of the biopsy specimens can be mitigated by the ability to obtain several samples. The risk of pneumothorax related to bronchoscopy is increased when transbronchial biopsies are part of the procedure; however, the ability to obtain biopsy specimens in a procedure performed with topical anesthesia and conscious sedation offers is advantageous.

Sweat Testing

See Chapter 432 .

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CHAPTER 401

Chronic or Recurrent Respiratory Symptoms

Anne G. Griffiths

Respiratory tract symptoms, including cough, wheeze, and stridor, occur frequently or persist for long periods in a substantial number of children; other children have persistent or recurring lung infiltrates with or without symptoms. Determining the cause of these chronic findings can be difficult because symptoms can be caused by a close succession of unrelated acute respiratory tract infections or by a single pathophysiologic process. Specific and easily performed diagnostic tests do not exist for many acute and chronic respiratory conditions. Pressure from the affected child's family for a quick remedy because of concern over symptoms related to breathing may complicate diagnostic and therapeutic efforts.

A systematic approach to the diagnosis and treatment of these children consists of assessing whether the symptoms are the manifestation of a minor problem or a life-threatening process; determining the most likely underlying pathogenic mechanism; selecting the simplest effective therapy for the underlying process, which often is only symptomatic therapy; and carefully evaluating the effect of therapy. Failure of this approach to identify the process responsible or to effect improvement signals the need for more extensive and perhaps invasive diagnostic efforts, including bronchoscopy.

Judging the Seriousness of Chronic Respiratory Complaints

Clinical manifestations suggesting that a respiratory tract illness may be life-threatening or associated with the potential for chronic disability are listed in

Table 401.1 . If none of these findings is detected, the chronic respiratory process is likely to be benign. Active, well-nourished, and appropriately growing infants who present with intermittent noisy breathing but no other physical or laboratory abnormalities require only symptomatic treatment and parental reassurance. Benign-appearing but persistent symptoms are occasionally the harbinger of a serious lower respiratory tract problem. By contrast, occasionally children (e.g., with infection-related asthma) have recurrent life-threatening episodes but few or no symptoms in the intervals. Repeated examinations over an extended period, both when the child appears healthy and when the child is symptomatic, may be helpful in sorting out the severity and chronicity of lung disease.

Table 401.1

Indicators of Serious Chronic Lower Respiratory Tract Disease in Children

Persistent fever
Ongoing limitation of activity
Failure to grow
Failure to gain weight appropriately
Clubbing of the digits
Persistent tachypnea and labored ventilation
Shortness of breath and exercise intolerance
Chronic purulent sputum
Persistent hyperinflation
Substantial and sustained hypoxemia
Refractory infiltrates on chest x-ray
Persistent pulmonary function abnormalities
Hemoptysis
Family history of heritable lung disease
Cyanosis and hypercarbia
Unusual (opportunistic) or recurrent nonpulmonary infections

Recurrent or Persistent Cough

Cough is a reflex response of the lower respiratory tract to stimulation of irritant or cough receptors in the airways' mucosa. The most common cause of recurrent or persistent cough in children is airway reactivity (asthma). Because cough receptors also reside in the pharynx, paranasal sinuses, stomach, and external auditory canal, the source of a persistent cough may need to be sought beyond the lungs. Specific lower respiratory stimuli include excessive secretions, aspirated foreign material, inhaled dust particles or noxious gases, cold or dry air, and an inflammatory response to infectious agents or allergic processes. Table 401.2 lists some of the conditions responsible for chronic cough. Table 401.3 presents characteristics of cough that can aid in distinguishing a cough's origin. Additional useful information can include a history of atopic conditions (asthma, eczema, urticaria, allergic rhinitis), a seasonal or environmental variation in frequency or intensity of cough, and a strong family history of atopic conditions, all suggesting an allergic cause; symptoms of malabsorption or family history indicating cystic fibrosis; symptoms related to feeding, suggesting aspiration or gastroesophageal reflux; a choking episode, suggesting foreign-body aspiration; headache or facial edema associated with sinusitis; and a smoking history in older children and adolescents or the presence of a smoker in the home (Table 401.4).

Table 401.2

Differential Diagnosis of Recurrent and Persistent Cough in Children

RECURRENT COUGH
Reactive airway disease (asthma)
Drainage from upper airways
Aspiration
Frequently recurring respiratory tract infections in immunocompetent or immunodeficient patients
Symptomatic Chiari malformation
Idiopathic pulmonary hemosiderosis
Hypersensitivity (allergic) pneumonitis
PERSISTENT COUGH
Hypersensitivity of cough receptors after infection
Reactive airway disease (asthma)
Chronic sinusitis
Chronic rhinitis (allergic or nonallergic)
Bronchitis or tracheitis caused by infection or smoke exposure
Bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, immunodeficiency
Habit cough
Foreign-body aspiration
Recurrent aspiration owing to pharyngeal incompetence, tracheolaryngoesophageal cleft, or tracheoesophageal fistula
Gastroesophageal reflux, with or without aspiration
Pertussis
Extrinsic compression of the tracheobronchial tract (vascular ring, neoplasm, lymph node, lung cyst)
Tracheomalacia, bronchomalacia
Endobronchial or endotracheal tumors
Endobronchial tuberculosis
Hypersensitivity pneumonitis
Fungal infections
Inhaled irritants, including tobacco smoke

Irritation of external auditory canal
Angiotensin-converting enzyme inhibitors

Table 401.3

Characteristics of Cough and Other Clinical Features and Possible Causes

SYMPTOMS AND SIGNS	POSSIBLE UNDERLYING ETIOLOGY*
Auscultatory findings (wheeze, crepitations/crackles, differential breath sounds)	Asthma, bronchitis, pneumonia, congenital lung disease, foreign body aspiration, airway abnormality
Cough characteristics (e.g., cough with choking, cough quality, cough starting from birth)	Congenital airway or lung abnormalities
Cardiac abnormalities (including murmurs)	Any cardiac illness
Chest pain	Asthma, functional, pleuritis
Chest wall deformity	Any chronic lung disease, neuromuscular disorders
Daily moist or productive cough	Chronic bronchitis, suppurative lung disease
Digital clubbing	Suppurative lung disease, arteriovenous shunt
Dyspnea (exertional or at rest)	Compromised lung function of any chronic lung or cardiac disease
Failure to thrive	Compromised lung function, immunodeficiency, cystic fibrosis
Feeding difficulties (including choking and vomiting)	Compromised lung function, aspiration, anatomic disorders
Hemoptysis	Bronchitis, foreign body aspiration, suctioning trauma, pulmonary hemorrhage
Immune deficiency	Atypical and typical recurrent respiratory or nonrespiratory infections
Medications or drugs	Angiotensin-converting enzyme inhibitors, puffers, illicit drug use
Neurodevelopmental abnormality	Aspiration
Recurrent pneumonia	Immunodeficiency, congenital lung problem, airway abnormality
Symptoms of upper respiratory tract infection	Can coexist or be a trigger for an underlying problem

* This is not an exhaustive list; only the more common respiratory diseases are mentioned.

Modified from Chang AB, Landau LI, Van Asperen PP, et al: Cough in children: definitions and clinical evaluation. Thoracic Society of Australia and New Zealand, *Med J Aust* 184(8):398–403, 2006, Table 2, p. 399.

Table 401.4

Clinical Clues About Cough

CHARACTERISTIC	THINK OF
Staccato, paroxysmal	Pertussis, cystic fibrosis, foreign body, *Chlamydia* spp., *Mycoplasma* spp.
Followed by “whoop”	Pertussis
All day, never during sleep	Habit cough
Barking, brassy	Croup, habit cough, tracheomalacia, tracheitis, epiglottitis

Hoarseness	Laryngeal involvement (croup, recurrent laryngeal nerve involvement), papillomatosis
Abrupt onset	Foreign body, pulmonary embolism
During or following exercise	Reactive airway disease
Accompanies eating, drinking	Aspiration, gastroesophageal reflux, tracheoesophageal fistula
Throat clearing	Postnasal drip, vocal tic
Productive (sputum)	Infection, cystic fibrosis, bronchiectasis
Night cough	Sinusitis, reactive airway disease, gastroesophageal reflux
Seasonal	Allergic rhinitis, reactive airway disease
Immunosuppressed patient	Bacterial pneumonia, *Pneumocystis jiroveci* , *Mycobacterium tuberculosis* , *Mycobacterium avium-intracellulare* , cytomegalovirus, fungi
Dyspnea	Hypoxia, hypercarbia
Animal exposure	*Chlamydia psittaci* (birds), *Yersinia pestis* (rodents), *Francisella tularensis* (rabbits), Q fever (sheep, cattle), hantavirus (rodents), histoplasmosis (pigeons)
Geographic	Histoplasmosis (Mississippi, Missouri, Ohio River Valley), coccidioidomycosis (Southwest), blastomycosis (North and Midwest)
Workdays with clearing on days off	Occupational exposure

From Kliegman RM, Greenbaum LA, Lyle PS: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, WB Saunders, p. 19.

The physical examination can provide much information pertaining to the cause of chronic cough. Posterior pharyngeal drainage combined with a nighttime cough suggests chronic upper airway disease such as sinusitis. An overinflated chest suggests chronic airway obstruction, as in asthma or cystic fibrosis. An expiratory wheeze, with or without diminished intensity of breath sounds, strongly suggests asthma or asthmatic bronchitis, but may also be consistent with a diagnosis of cystic fibrosis, bronchomalacia, vascular ring, aspiration of foreign material, or pulmonary hemosiderosis. Careful auscultation during forced expiration may reveal expiratory wheezes that are otherwise undetectable and that are the only indication of underlying reactive airways. Coarse crackles suggest bronchiectasis, including cystic fibrosis, but can also occur with an acute or subacute exacerbation of asthma. Clubbing of the digits is seen in most patients with bronchiectasis but in only a few other respiratory conditions with chronic cough (see Table 401.2). Tracheal deviation suggests foreign body aspiration, pleural effusion, or a mediastinal mass.

Allowing sufficient examination time to detect a spontaneous cough is important. If a spontaneous cough does not occur, asking the child to take a maximal breath and forcefully exhale repeatedly usually induces a cough reflex. Most children can cough on request by 4-5 yr of age. Children who cough as often as several times a minute with regularity are likely to have a habit (tic) cough (see Chapter 37). If the cough is loose, every effort should be made to obtain sputum; many older children can comply. It is sometimes possible to pick up small bits of sputum with a throat swab quickly inserted into the lower pharynx while the child coughs with the tongue protruding. Clear mucoid sputum is most often associated with an allergic reaction or asthmatic bronchitis. Cloudy (purulent) sputum suggests a respiratory tract infection but can also reflect increased cellularity (eosinophilia) from an asthmatic process. Very purulent sputum is characteristic of bronchiectasis (see Chapter 430). Malodorous expectorations suggest anaerobic infection of the lungs. In cystic fibrosis (see Chapter 432), the sputum, even when purulent, is rarely foul smelling.

Laboratory tests can help in the evaluation of a chronic cough. Only sputum specimens containing alveolar macrophages should be interpreted as reflecting lower respiratory tract processes. Sputum eosinophilia suggests asthma, asthmatic bronchitis, or hypersensitivity reactions of the lung (see Chapter 418), but a polymorphonuclear cell response suggests infection; if sputum is unavailable, the presence of eosinophilia in nasal secretions also suggests atopic disease. If most of the cells in sputum are macrophages, postinfectious hypersensitivity of cough receptors should be suspected. Sputum macrophages can be stained for hemosiderin content, which is diagnostic of pulmonary hemosiderosis (see Chapter 435), or for lipid content, which in large amounts suggests, but is not specific for, repeated aspiration. Rarely, children may expectorate partial casts of the airway, which can be characterized in investigating causes of plastic bronchitis. Children whose coughs persist for more than 6 wk should be tested for cystic fibrosis regardless of their race or ethnicity (see Chapter 432). Sputum culture is helpful in evaluation of cystic fibrosis, but less so for other conditions because throat flora can contaminate the sample.

Hematologic assessment can reveal a microcytic anemia that is the result of pulmonary hemosiderosis (see Chapter 435) or hemoptysis, or eosinophilia that accompanies asthma and other hypersensitivity reactions of the lung. Infiltrates on the chest radiograph suggest cystic fibrosis, bronchiectasis, foreign body, hypersensitivity pneumonitis, tuberculosis, or other infection. When asthma-equivalent cough is suggested, a trial of bronchodilator therapy may be diagnostic. If the cough does not respond to initial therapeutic efforts, more-specific diagnostic procedures may be warranted, including an immunologic or allergic evaluation, chest and paranasal sinus imaging, esophagograms, tests for gastroesophageal reflux (see Chapter 349), and special microbiologic studies including rapid viral testing. Evaluation of ciliary morphology, nasal endoscopy, laryngoscopy, and bronchoscopy may also be indicated.

Tic cough or somatic cough disorder (psychogenic cough or habit cough) must be considered in any child with a cough that has lasted for weeks or months, that has been refractory to treatment, and that disappears with sleep or with distraction. Typically, the cough is abrupt and loud, and has a harsh, honking, or barking quality. A disassociation between the intensity of the cough and the child's affect is typically striking. This cough may be absent if the physician listens outside the examination room, but it will reliably appear immediately on direct attention to the child and the symptom. It typically begins with an upper respiratory infection but then lingers. The child misses many days of school because the cough disrupts the classroom. This disorder accounts for many unnecessary medical procedures and courses of medication. It is treatable with assurance that a pathologic lung condition is absent and that the child should resume full activity, including school. This assurance, together with speech therapy techniques that allow the child to reduce musculoskeletal tension in the neck and chest and that increase the child's awareness of the initial sensations that trigger cough, has been very successful. Self-hypnosis is another successful therapy, often effective with 1 session. The designation “tic cough” or “somatic cough disorder” is preferable to “habit cough” or “psychogenic cough” because it carries no stigma and because most of these children do not have significant emotional problems. When the cough disappears, it does not reemerge as another symptom. Nonetheless, other symptoms such as irritable bowel syndrome may be present in the patient or family.

Frequently Recurring or Persistent Stridor

Stridor, a harsh, medium-pitched, inspiratory sound associated with obstruction of the laryngeal area or the extrathoracic trachea, is often accompanied by a croupy cough and hoarse voice. Stridor is most commonly observed in children with croup (see Chapter 412); foreign bodies and trauma can also cause acute stridor. A few children, however, acquire recurrent stridor or have persistent stridor from the 1st days or weeks of life (Table 401.5). Most congenital anomalies of large airways that produce stridor become symptomatic soon after birth. Increase of stridor when a child is supine suggests **airway malacia** , such as laryngomalacia or tracheomalacia. It is important to note that when evaluating for a specific anatomic cause of abnormal breath sounds, it is not uncommon to identify additional congenital anomalies of the airway. An accompanying history of hoarseness or aphonia suggests involvement of the vocal cords. Associated dysphagia may also suggest a vascular ring. In a child with intermittent stridor (with wheezing) that accompanies physical activity and is not responsive to asthma therapies, **paradoxical vocal cord dysfunction** may be of consideration. Paradoxical vocal cord dysfunction may be highly supported by history and confirmed by laryngoscopy during an exercise challenge test if symptoms are successfully elicited. Speech therapy and behavior modification may be therapeutic.

Table 401.5

Causes of Recurrent or Persistent Stridor in Children

RECURRENT
Allergic (spasmodic) croup Respiratory infections in a child with otherwise asymptomatic anatomic narrowing of the large airways Laryngomalacia
PERSISTENT
Laryngeal obstruction • Laryngomalacia • Papillomas, hemangiomas, other tumors • Cysts and laryngoceles • Laryngeal webs • Bilateral abductor paralysis of the cords • Foreign body Tracheobronchial disease • Tracheomalacia • Subglottic tracheal webs • Endobronchial, endotracheal tumors • Subglottic tracheal stenosis, congenital or acquired Extrinsic masses • Mediastinal masses • Vascular ring • Lobar emphysema • Bronchogenic cysts • Thyroid enlargement • Esophageal foreign body Tracheoesophageal fistula
OTHER
Gastroesophageal reflux Macroglossia, Pierre Robin syndrome Cri-du-chat syndrome Paradoxical vocal cord dysfunction Hypocalcemia Vocal cord paralysis Chiari crisis Severe neonatal episodic laryngospasm caused by *SCN4A* mutation

Physical examination for recurrent or persistent stridor is usually unrewarding, although changes in its severity and intensity due to changes of body position should be assessed. Anteroposterior and lateral radiographs, contrast esophagography, fluoroscopy, computed tomography (CT), and magnetic resonance imaging (MRI) are potentially useful diagnostic tools. In most cases, direct observation by laryngoscopy is necessary for definitive diagnosis. Undistorted views of the larynx are best obtained with fiberoptic laryngoscopy.

Recurrent or Persistent Wheeze

See also Chapter 418 .

Parents often complain that their child wheezes, when, in fact, they are reporting respiratory sounds that are audible without a stethoscope, produce palpable resonance throughout the chest, and occur most prominently in inspiration. Some of these children have stridor, although many have audible sounds when the supraglottic airway is incompletely cleared of feedings or secretions.

True wheezing is a relatively common and particularly troublesome manifestation of obstructive *lower* respiratory tract disease in children. The site of obstruction may be anywhere from the intrathoracic trachea to the small bronchi or large bronchioles, but the sound is generated by turbulence in larger airways that collapse with forced expiration (see Chapter 400). Children younger than 2-3 yr are especially prone to wheezing, because bronchospasm, mucosal edema, and accumulation of excessive secretions have a relatively greater obstructive effect on their smaller airways. In addition, the compliant airways in young children collapse more readily with active expiration. Isolated episodes of acute wheezing, such as can occur with bronchiolitis, are not uncommon, but wheezing that recurs or persists for more than 4 wk suggests other diagnoses (see Table 418.1 in Chapter 418). Most recurrent or persistent wheezing in children is the result of airway reactivity. Nonspecific environmental factors such as cigarette smoke may be important contributors.

Frequently recurring or persistent wheezing starting at or soon after birth suggests a variety of other diagnoses, including congenital structural abnormalities involving the lower respiratory tract or tracheobronchomalacia (see Chapter 413). Wheezing that attends cystic fibrosis is most common in the 1st yr of life. Sudden onset of severe wheezing in a previously healthy child should suggest foreign-body aspiration.

Either wheezing or coughing when associated with tachypnea and hypoxemia may be suggestive of **interstitial lung disease** (see Chapter 427.5). However, many patients with interstitial lung disease demonstrate no symptoms other than rapid breathing on initial physical examination. Although chest roentgenograms may be normal in interstitial lung disease, diffuse abnormalities on chest X-ray may support further evaluation in patients suspected to have interstitial lung disease with characteristic findings described on high-resolution CT scan and lung biopsy.

Repeated examination may be required to verify a history of wheezing in a child with episodic symptoms and should be directed toward assessing air movement, ventilatory adequacy, and evidence of chronic lung disease, such as fixed overinflation of the chest, growth failure, and digital clubbing. Patients should be assessed for oropharyngeal dysphagia in cases of suspected recurrent aspiration. Clubbing suggests chronic lung infection and is rarely prominent in uncomplicated asthma. Tracheal deviation from foreign body aspiration should be sought. It is essential to rule out wheezing secondary to congestive heart failure. Allergic rhinitis, urticaria, eczema, or evidence of ichthyosis vulgaris suggests asthma or asthmatic bronchitis. The nose should be examined for polyps, which can exist with allergic conditions or cystic fibrosis.

Sputum eosinophilia and elevated serum immunoglobulin E levels suggest allergic reactions. A forced expiratory volume in 1 sec increase of 15% in response to bronchodilators confirms reactive airways. Specific microbiologic studies, special imaging studies of the airways and cardiovascular structures, diagnostic studies for cystic fibrosis, and bronchoscopy should be considered if the response is unsatisfactory.

Recurrent and Persistent Lung Infiltrates

Radiographic lung infiltrates resulting from acute pneumonia usually resolve within 1-3 wk, but a substantial number of children, particularly infants, fail to completely clear infiltrates within a 4 wk period. These children may be febrile or afebrile, and may display a wide range of respiratory symptoms and signs. Persistent or recurring infiltrates present a diagnostic challenge (Table 401.6).

Table 401.6

Diseases Associated With Recurrent, Persistent, or Migrating Lung Infiltrates Beyond the Neonatal Period

- Aspiration
  - Pharyngeal incompetence (e.g., cleft palate)
  - Laryngotracheoesophageal cleft
  - Tracheoesophageal fistula
  - Gastroesophageal reflux
  - Lipid aspiration
  - Neurologic dysphagia
  - Developmental dysphagia
- Congenital anomalies
  - Lung cysts (cystic adenomatoid malformation)
  - Pulmonary sequestration
  - Bronchial stenosis or aberrant bronchus
  - Vascular ring
  - Congenital heart disease with large left-to-right shunt
  - Pulmonary lymphangiectasia
- Genetic conditions
  - α_1 -Antitrypsin deficiency
  - Cystic fibrosis
  - Primary ciliary dyskinesia (including Kartagener syndrome)
  - Sickle cell disease (acute chest syndrome)
- Immunodeficiency, phagocytic deficiency
  - Humoral, cellular, combined immunodeficiency states
  - Chronic granulomatous disease and related phagocytic defects
  - Hyper immunoglobulin E syndromes
  - Complement deficiency states
- Immunologic and autoimmune diseases
  - Asthma
  - Allergic bronchopulmonary aspergillosis
  - Hypersensitivity pneumonitis
  - Pulmonary hemosiderosis
  - Collagen-vascular diseases
- Infection, congenital
  - Cytomegalovirus
  - Rubella
  - Syphilis
- Infection, acquired
  - Cytomegalovirus
  - Tuberculosis
  - HIV
  - Other viruses
- *Chlamydia*
- *Mycoplasma, Ureaplasma*
  - Pertussis
  - Fungal organisms
- *Pneumocystis jiroveci*
  - Visceral larva migrans
  - Inadequately treated bacterial infection
- Interstitial pneumonitis and fibrosis
  - Usual interstitial pneumonitis
  - Lymphoid (AIDS)
  - Genetic disorders of surfactant synthesis, secretion

- Desquamative
- Acute (Hamman-Rich)
- Alveolar proteinosis
- Drug-induced, radiation-induced inflammation and fibrosis

Neoplasms and neoplastic-like conditions

- Primary or metastatic pulmonary tumors
- Leukemia
- Histiocytosis
- Eosinophilic pneumonias

Other etiologies

- Bronchiectasis
    - Congenital
    - Postinfectious
- Sarcoidosis

Symptoms associated with chronic lung infiltrates in the 1st several weeks of life (but not related to neonatal respiratory distress syndrome) suggest infection acquired in utero or during descent through the birth canal. Early appearance of chronic infiltrates can also be associated with cystic fibrosis or congenital anomalies that result in aspiration or airway obstruction. A history of recurrent infiltrates such as in **middle lobe syndrome** (see Chapters 430 and 437), wheezing, and cough may reflect asthma, even in the 1st yr of life.

A controversial association has been posed regarding recurrent lung infiltrates in pulmonary hemosiderosis related to cow's milk hypersensitivity or unknown causes appearing in the 1st yr of life. Children with a history of bronchopulmonary dysplasia often have episodes of respiratory distress attended by wheezing and new lung infiltrates. **Recurrent pneumonia** in a child with frequent otitis media, nasopharyngitis, adenitis, or dermatologic manifestations suggests an immunodeficiency state, complement deficiency, or phagocytic defect (see Chapters 148 , 156 , and 160). Primary ciliary dyskinesia is also of consideration in patients with frequent otitis media and suppurative sinopulmonary disease, with or without accompanying heterotaxy, or history of neonatal respiratory distress (see Chapter 433). Pulmonary sequestration may be suspected in patients with recurrent findings on radiograph that occur in the same location, both during illness and when well (see Chapter 423). Traction bronchiectasis may also be suggested on radiography with persistent findings in a given region of the film following a history of respiratory infection. Particular attention must be directed to the possibility that the infiltrates represent lymphocytic interstitial pneumonitis or opportunistic infection associated with HIV infection (see Chapter 302). A history of paroxysmal coughing in an infant suggests pertussis syndrome or cystic fibrosis. Persistent infiltrates, especially with loss of volume, in a toddler may suggest foreign-body aspiration.

Overinflation and infiltrates suggest cystic fibrosis or chronic asthma. A silent chest with infiltrates should arouse suspicion of alveolar proteinosis (see Chapter 434), *Pneumocystis jiroveci* infection (see Chapter 271), genetic disorders of surfactant synthesis and secretion causing interstitial pneumonitis, or tumors. Growth should be carefully assessed to determine whether the lung process has had systemic effects, indicating substantial severity and chronicity as in cystic fibrosis or alveolar proteinosis. Cataracts, retinopathy, or microcephaly suggest in utero infection. Chronic rhinorrhea can be associated with atopic disease, cow's milk intolerance, cystic fibrosis, primary ciliary dyskinesia, or congenital syphilis. The absence of tonsils and cervical lymph nodes suggests an immunodeficiency state.

Diagnostic studies should be performed selectively, based on information obtained from history and physical examination and on a thorough understanding of the conditions listed in Table 401.6 . Cytologic evaluation of sputum, if available, may be helpful. Chest CT often provides more precise anatomic detail concerning the infiltrate or further characterizes a region of anatomic abnormality. Bronchoscopy is indicated for detecting foreign bodies, congenital or acquired anomalies of the tracheobronchial tract, and obstruction by endobronchial or extrinsic masses (see Chapters 413 –417). Bronchoscopy provides access to secretions that can be studied cytologically and microbiologically. Alveolar lavage fluid is diagnostic for alveolar proteinosis and persistent pulmonary hemosiderosis, and can suggest aspiration syndromes. Ciliary biopsy may be obtained from the inferior epithelial surface of nasal turbinates or from the lower airway during bronchoscopy. If all appropriate studies have been completed and the condition remains undiagnosed, lung biopsy might yield a definitive diagnosis, such as in interstitial lung disease or in fungal disease.

Optimal medical or surgical treatment of chronic lung infiltrates often depends on a specific diagnosis, but chronic conditions may be self-limiting (severe and prolonged viral infections in infants); in these cases, symptomatic therapy can maintain adequate lung function until spontaneous improvement occurs. Helpful measures include inhalation and physical therapy for excessive secretions, antibiotics for bacterial infections, supplementary oxygen for hypoxemia, and maintenance of adequate nutrition. Because the lung of a young child has remarkable recuperative potential, normal lung function may ultimately be achieved with treatment despite the severity of pulmonary insult occurring in infancy or early childhood.

401.1

Extrapulmonary Diseases With Pulmonary Manifestations

Susanna A. McColley

Respiratory symptoms commonly originate from extrapulmonary processes. The respiratory system adapts to metabolic demands and is exquisitely responsive to cortical input; therefore, **tachypnea** is common in the presence of metabolic stress such as fever, whereas dyspnea may be related to anxiety. **Cough** most commonly arises from upper or lower respiratory tract disorders, but it can originate from the central nervous system, as with cough tic or psychogenic cough, and it can be a prominent symptom in children with gastroesophageal reflux disease. **Chest pain** does not commonly arise from pulmonary processes in otherwise healthy children but more often has a neuromuscular or inflammatory etiology. **Cyanosis** can be caused by cardiac or hematologic disorders, and **dyspnea** and **exercise intolerance** can have a number of extrapulmonary causes. These disorders may be suspected on the basis of the history and physical examination, or they may be considered in children in whom diagnostic studies have atypical findings or who show poor response to usual therapy. Table 401.7 lists more common causes of such symptoms.

Table 401.7

Respiratory Signs and Symptoms Originating From Outside the Respiratory Tract

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Chest pain	Cardiac disease	Inflammation (pericarditis), ischemia (anomalous coronary artery, vascular disease)	Precordial pain, friction rub on examination; exertional pain, radiation to arm or neck
Chest pain	Gastroesophageal reflux disease	Esophageal inflammation and/or spasm	Heartburn, abdominal pain

Cyanosis	Congenital heart disease	Right-to-left shunt	Neonatal onset, lack of response to oxygen
	Methemoglobinemia	Increased levels of methemoglobin interfere with delivery of oxygen to tissues	Drug or toxin exposure, lack of response to oxygen
Dyspnea	Toxin exposure, drug side effect, or overdose	Variable, but often metabolic acidosis	Drug or toxin exposure confirmed by history or toxicology screen, normal oxygen saturation measured by pulse oximetry
	Anxiety, panic disorder	Increased respiratory drive and increased perception of respiratory efforts	Occurs during stressful situation, other symptoms of anxiety or depression
Exercise intolerance	Anemia	Inadequate oxygen delivery to tissues	Pallor, tachycardia, history of bleeding, history of inadequate diet
Exercise intolerance	Deconditioning	Self-explanatory	History of inactivity, obesity
Hemoptysis	Nasal bleeding	Posterior flow of bleeding causes appearance of pulmonary origin	History and physical findings suggest nasal source; normal chest examination and chest radiography
	Upper gastrointestinal tract bleeding	Hematemesis mimics hemoptysis	History and physical examination suggest gastrointestinal source; normal chest examination and chest radiography
Wheezing, cough, dyspnea	Congenital or acquired cardiac disease	Pulmonary overcirculation (atrioseptal defect, ventriculoseptal defect, patent ductus arteriosus), left ventricular dysfunction	Murmur
			Refractory to bronchodilators
			Radiographic changes (prominent pulmonary vasculature, pulmonary edema)
Wheezing, cough	Gastroesophageal reflux disease	Laryngeal and bronchial response to stomach contents	Emesis, pain, heartburn
		Vagally mediated bronchoconstriction	Refractory to bronchodilators

Evaluation

In the evaluation of a child or adolescent with respiratory symptoms, it is important to obtain a detailed past medical history, family history, and review of systems to evaluate the possibility of extrapulmonary origin. A comprehensive physical examination is also essential in obtaining clues as to extrapulmonary disease.

Disorders of other organ systems, and many systemic diseases, can have significant respiratory system involvement. Although it is most common to encounter these complications in patients with known diagnoses, respiratory system disease is sometimes the sole or most prominent symptom at the time of presentation. Acute aspiration during feeding can be the presentation of neuromuscular disease in an infant who initially appears to have normal muscle tone and development. Complications can be life-threatening, particularly in immunocompromised patients. The onset of respiratory findings may be insidious; for example, pulmonary vascular involvement in patients with systemic vasculitis may appear as an abnormality in diffusing capacity of the lung for carbon monoxide before the onset of symptoms. Table 401.8 lists disorders that commonly have respiratory complications.

Table 401.8

Disorders With Frequent Respiratory Tract Complications

UNDERLYING DISORDER(S)	RESPIRATORY COMPLICATIONS	DIAGNOSTIC TESTS
Autoimmune disorders	Pulmonary vascular disease, restrictive lung disease, pleural effusion (especially systemic lupus erythematosus), upper airway disease (Wegener granulomatosis)	Spirometry, lung volume determination, oximetry, diffusing capacity of the lung for carbon monoxide, chest radiography, upper airway endoscopy, and/or CT
Central nervous system disease (static or progressive)	Aspiration of oral or gastric contents	Chest radiography, videofluoroscopic swallowing study, esophageal pH probe, fiberoptic bronchoscopy
Immunodeficiency	Infection, bronchiectasis	Chest radiography, fiberoptic bronchoscopy, chest CT
Liver disease	Pleural effusion, hepatopulmonary syndrome	Chest radiography, assessment of orthodeoxia
Malignancy and its therapies	Infiltration, metastasis, malignant or infectious effusion, parenchymal infection, graft versus host disease (bone marrow transplant)	Chest radiography, chest CT, fiberoptic bronchoscopy, lung biopsy
Neuromuscular disease	Hypoventilation, atelectasis, pneumonia	Spirometry, lung volume determination, respiratory muscle force measurements
Obesity	Restrictive lung disease, obstructive sleep apnea syndrome, asthma	Spirometry, lung volume determination, nocturnal polysomnography

CT, Computed tomography.

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CHAPTER 402

Sudden Infant Death Syndrome

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Sudden infant death syndrome (SIDS) is defined as the sudden, unexpected death of an infant that is unexplained by a thorough postmortem examination, which includes a complete autopsy, investigation of the scene of death, and review of the medical history. An autopsy is essential to identify possible natural explanations for sudden unexpected death such as congenital anomalies or infection and to diagnose traumatic child abuse (Tables 402.1 to 402.3 ; see Chapter 16). The autopsy typically cannot distinguish between SIDS and intentional suffocation, but the scene investigation and medical history may be of help if inconsistencies are evident. **Sudden unexpected infant death (SUID)** is a term that generally encompasses all SUIDs that occur during sleep, including SIDS (ICD-10 R95), accidental suffocation and strangulation in bed (ICD-10 W75), and ill-defined deaths, also known as undetermined (ICD-10 R99).

Table 402.1

Differential Diagnosis of Sudden Unexpected Infant Death

CAUSE OF DEATH	PRIMARY DIAGNOSTIC CRITERIA	POTENTIAL CONFOUNDING DIAGNOSES	FREQUENCY DISTRIBUTION (%)
EXPLAINED AT AUTOPSY			
Natural			18–20*
Infections	History, autopsy, and cultures	If minimal findings: SIDS	35–46 †
Congenital anomaly	History and autopsy	If minimal findings: SIDS	14–24 †
Unintentional injury	History, scene investigation, autopsy	Traumatic child abuse	15*
Traumatic child abuse	Autopsy and scene investigation	Unintentional injury	13–24*

Other natural causes	History and autopsy	If minimal findings: SIDS, or intentional suffocation	12–17[*]
UNEXPLAINED AT AUTOPSY			
SIDS	History, scene investigation, absence of explainable cause at autopsy	Intentional suffocation	80–82
Intentional suffocation (filicide)	Perpetrator confession, absence of explainable cause at autopsy	SIDS	Unknown, but <5% of all SUID
Accidental suffocation or strangulation in bed (ASSB)	History and scene investigation, ideally including doll re-enactment	Assigned to ICD-10 code (SIDS) for US vital statistics database Unexplained Undetermined	Varies with individual medical examiners and coroners
Genetic mutations	*SCN5A* , *SCN1B-4B* , *SCN4A*, long QT syndromes, plus Table 402.4	May have negative family history secondary to recessive mutations, de novo mutation, or incomplete penetrance	Unknown, perhaps <10%

[*] As a percentage of all sudden unexpected infant deaths explained at autopsy.

[†] As a percentage of all natural causes of sudden unexpected infant deaths explained at autopsy.

ICD-10, International Classification of Diseases, Version 10; *SIDS,* sudden infant death syndrome; *SUID,* sudden unexpected infant death.

Modified from Hunt CE: Sudden infant death syndrome and other causes of infant mortality: diagnosis, mechanisms and risk for recurrence in siblings, *Am J Respir Crit Care Med* 164(3):346–357, 2001.

Table 402.2

Conditions That Can Cause Apparent Life-Threatening Events[*] or Sudden Unexpected Infant Death

CENTRAL NERVOUS SYSTEM
Arteriovenous malformation
Subdural hematoma
Seizures
Congenital central hypoventilation
Neuromuscular disorders (Werdnig-Hoffmann disease)
Chiari crisis
Leigh syndrome
CARDIAC
Subendocardial fibroelastosis
Aortic stenosis
Anomalous coronary artery
Myocarditis

Cardiomyopathy

Arrhythmias (prolonged QT syndrome, Wolff-Parkinson-White syndrome, congenital heart block)

PULMONARY

Pulmonary hypertension

Vocal cord paralysis

Aspiration

Laryngotracheal disease

GASTROINTESTINAL

Diarrhea and/or dehydration

Gastroesophageal reflux

Volvulus

ENDOCRINE–METABOLIC

Congenital adrenal hyperplasia

Malignant hyperpyrexia

Long- or medium-chain acyl coenzyme A deficiency

Hyperammonemias (urea cycle enzyme deficiencies)

Glutaric aciduria

Carnitine deficiency (systemic or secondary)

Glycogen storage disease type I

Maple syrup urine disease

Congenital lactic acidosis

Biotinidase deficiency

INFECTION

Sepsis

Meningitis

Encephalitis

Brain abscess

Pyelonephritis

Bronchiolitis (respiratory syncytial virus)

Infant botulism

Pertussis

TRAUMA

Child abuse

Accidental or intentional suffocation

Physical trauma

Factitious syndrome (formerly Munchausen syndrome) by proxy

POISONING (INTENTIONAL OR UNINTENTIONAL)

Boric acid
Carbon monoxide
Salicylates
Barbiturates
Ipecac
Cocaine
Insulin
Others

[*] Recommended terminology now is “brief resolved unexplained events.”

From Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, Elsevier Saunders, p. 98.

Table 402.3

Differential Diagnosis of Recurrent Sudden Infant Death in a Sibling

IDIOPATHIC
Recurrent sudden infant death syndrome
CENTRAL NERVOUS SYSTEM
Congenital central hypoventilation
Neuromuscular disorders
Leigh syndrome
CARDIAC
Endocardial fibroelastosis
Wolff-Parkinson-White syndrome
Prolonged QT syndrome or other cardiac channelopathy
Congenital heart block
PULMONARY
Pulmonary hypertension
ENDOCRINE–METABOLIC
See Table 402.2
INFECTION
Disorders of immune host defense
CHILD ABUSE
Filicide or infanticide
Factitious syndrome (formerly Munchausen syndrome) by proxy

From Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, Elsevier Saunders, p 101.

Epidemiology

SIDS is the 3rd leading cause of infant mortality in the United States, accounting for approximately 7% of all infant deaths. It is the most common cause of postneonatal infant mortality, accounting for 21% of all deaths between 1 mo and 1 yr of age. The annual rate of SIDS in the United States was stable at 1.3-1.4 per 1,000 live births (approximately 7,000 infants per year) before 1992, when it was recommended that infants sleep nonprone as a way to reduce the risk for SIDS. Since then, particularly after initiation of the national Back to Sleep campaign in 1994, the rate of SIDS progressively declined and then leveled off in 2001 at 0.55 per 1,000 live births (2,234 infants). There has been a slower rate of decline since that time; in 2015 the rate was 0.39 per 1,000 live births (1,568 infants). The decline in the number of SIDS deaths in the United States and other countries has been attributed to increasing use of the supine position for sleep. In 1992, 82% of sampled infants in the United States were placed prone for sleep. Although several other countries have decreased prone sleeping prevalence to ≤2%, in the United States in 2010 (the last year for which these data were collected by the National Infant Sleep Position study), 13.5% of infants were still being placed prone for sleep and 11.9% were being placed in the side position. Among black infants, these rates were even higher: 27.6% prone and 16.1% side in 2010.

There is increasing evidence that infant deaths previously classified as SIDS are now being classified by medical examiners and coroners as due to other causes, notably **accidental suffocation and strangulation in bed** and **ill-defined deaths** . Between 1994 and 2013, there has been a 7-fold increase in the rate of accidental suffocation and strangulation in bed, from 0.03 to 0.21 deaths per 1,000 live births. There has also been an increase in the rate of ill-defined deaths between 1995 and 2013, from 0.21 to 0.28 deaths per 1,000 live births. These sudden and unexpected infant deaths are primarily associated with unsafe sleeping environments, including prone positioning, sharing a sleep surface with others, and soft bedding in the sleep environment. Based on these trends and the commonality of many of the sleep environment risk factors that are associated with both SIDS and other sleep-related SUID, risk reduction measures that will be later described are applicable to all sleep-related SUID.

Pathology

Although there are no autopsy findings pathognomonic for SIDS and no findings are required for the diagnosis, there are some that are commonly seen on postmortem examination. Petechial hemorrhages are found in 68–95% of infants who died of SIDS and are more extensive than in explained causes of infant mortality. Pulmonary edema is often present and may be substantial. The reasons for these findings are unknown. Infants who died of SIDS have higher levels of vascular endothelial growth factor (VEGF) in the cerebrospinal fluid. These increases may be related to VEGF polymorphisms (see “Genetic Risk Factors” later and Table 402.4) or might indicate recent hypoxemic events because VEGF is upregulated by hypoxia.

Table 402.4

Identified Genes for Which the Distribution of Polymorphisms Differs in Sudden Infant Death Syndrome Infants Compared With Control Infants

CARDIAC CHANNELOPATHIES
Potassium ion channel genes *(KCNE2, KCNH2, KCNQ1, KCNJ8)*
Sodium ion channel gene *(SCN5A)* (long QT syndrome 3, Brugada syndrome)
GPD1-L-encoded connexin43 (Brugada syndrome)
SCN3B (Brugada syndrome)
CAV3 (long QT syndrome 9)
SCN4B (long QT syndrome 10)
SNTA-1 (long QT syndrome 11)
RyR2 (catecholaminergic polymorphic ventricular tachycardia)
SEROTONIN (5-HT)
5-HT transporter protein *(5-HTT)*
Intron 2 of *SLC6A4* (variable number tandem repeat [VNTR] polymorphism)
5-HT fifth Ewing variant (FEV) gene
GENES PERTINENT TO DEVELOPMENT OF AUTONOMIC NERVOUS SYSTEM
Paired-like homeobox 2a *(PHOX2A)*
PHOX2B
Rearranged during transfection factor *(RET)*

Endothelin converting enzyme-1 *(ECE1)*
T-cell leukemia homeobox *(TLX3)*
Engrailed-1 *(EN1)*
Tyrosine hydroxylase *(THO1)*
Monamine oxidase A *(MAOA)*
Sodium/proton exchanger 3 *(NHE3)* (medullary respiratory control)

INFECTION AND INFLAMMATION

Complement C4A
Complement C4B
Interleukin-1RN (gene encoding IL-1 receptor antagonist [ra]; proinflammatory)
Interleukin-6 (IL-6; proinflammatory)
Interleukin-8 (IL-8; proinflammatory; associated with prone sleeping position)
Interleukin-10 (IL-10)
Vascular endothelial growth factor (VEGF) (proinflammatory)
Tumor necrosis factor (TNF)- α (proinflammatory)

OTHER

Mitochondrial DNA (mtDNA) polymorphisms (energy production)
Flavin-monooxygenase 3 *(FMO3)* (enzyme metabolizes nicotine; risk factor with smoking mothers)
Aquaporin-4 (T allele and CT/TT genotype associated with maternal smoking and with increased brain/body weight ratio in SIDS infants)
SCN4A (nondystrophic myotonia, laryngospasm)

Modified from Hunt CE, Hauck FR: Sudden infant death syndrome: gene-environment interactions. In Brugada R, Brugada J, Brugada P, editors: *Clinical care in inherited cardiac syndromes* , Guildford, UK, 2009, Springer-Verlag London.

SIDS infants have several identifiable changes in the lungs and other organs. Nearly 65% of these infants have structural evidence of preexisting, chronic, low-grade asphyxia, and other studies have identified biochemical markers of asphyxia. Some studies have shown carotid body abnormalities, consistent with a role for impaired peripheral arterial chemoreceptor function in SIDS. Numerous studies have shown brain abnormalities that could cause or contribute to an impaired autonomic response to an exogenous stressor, including in the hippocampus and brainstem, the latter being the major area responsible for respiratory and autonomic regulation. The affected brainstem nuclei include the retrotrapezoid nucleus and the dorsal motor nucleus of the vagus, primary sites of central chemoreception and respiratory drive. Abnormalities in both the structure and expression of the *PHOX2B* gene, which is involved in neuronal maturation, have also been reported in significantly more SIDS infants than controls.

The ventral medulla has been a particular focus for studies in infants who died of SIDS. It is an integrative area for vital autonomic functions including breathing, arousal, and chemosensory function. Some SIDS infants have hypoplasia of the arcuate nucleus and up to 60% have histopathologic evidence of less-extensive bilateral or unilateral hypoplasia. Consistent with the apparent overlap between putative mechanisms for SIDS and for unexpected late fetal deaths, approximately 30% of sudden intrauterine unexplained deaths also have hypoplasia of the arcuate nucleus. Imaging mass spectroscopy of postmortem medullary tissue has identified abnormal expression of 41 peptides, especially in the raphe, hypoglossal, and pyramidal nuclei that include components for developmental neuronal/glial/axonal growth, cell metabolism, cytoarchitecture, and apoptosis. These findings suggest that SIDS infants have abnormal neurologic development contributing to pathogenesis, with the impairments suggesting delayed neurologic maturation.

Neurotransmitter studies of the arcuate nucleus have also identified several receptor abnormalities relevant to state-dependent autonomic control overall and to ventilatory and arousal responsiveness in particular. These deficits include significant decreases in binding to kainate, muscarinic cholinergic, and serotonin (5-HT) receptors. Studies of the ventral medulla have identified morphologic and biochemical deficits in 5-HT neurons and decreased γ-aminobutyric acid receptor A receptor binding in the medullary serotonergic system. Immunohistochemical analyses reveal an increased number of 5-HT neurons and an increase in the fraction of 5-HT neurons showing an immature morphology, suggesting a failure or delay in the maturation of these neurons. High neuronal levels of interleukin (IL)-1β are present in the arcuate and dorsal vagal nuclei in SIDS infants compared with controls, perhaps contributing to molecular interactions affecting cardiorespiratory and arousal responses.

The neuropathologic data provide compelling evidence for altered 5-HT homeostasis, creating an underlying vulnerability contributing to SIDS. 5-HT is an important neurotransmitter, and the 5-HT neurons in the medulla project extensively to neurons in the brainstem and spinal cord that influence respiratory drive and arousal, cardiovascular control including blood pressure, circadian regulation, and non–rapid eye movement (REM) sleep, thermoregulation, and upper airway reflexes. Decreases in 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor immunoreactivity have been observed in the dorsal nucleus of the vagus, solitary nucleus, and ventrolateral medulla. There are extensive serotoninergic brainstem abnormalities in SIDS infants, including increased 5-HT neuronal count, a lower density of 5-HT$_{1A}$ receptor-binding sites in regions of the medulla involved in homeostatic function, and a lower ratio of 5-HT transporter (5-HTT) binding density to 5-HT neuronal count in the medulla. Male SIDS infants have lower receptor-binding density than do female SIDS infants. Overall, these 5-HT–related studies suggest that the synthesis and availability of 5-HT are decreased within 5-HT pathways, and medullary tissue levels of 5-HT and its primary biosynthetic enzyme (tryptophan hydroxylase) are lower in SIDS infants compared with age-matched controls.

Environmental Risk Factors

Declines of 50% or more in rates of SIDS in the United States and around the world have occurred following national education campaigns directed at reducing risk factors associated with SIDS (Table 402.5). Although many risk factors are nonmodifiable and most of the modifiable factors have not changed appreciably, self-reported maternal smoking prevalence during pregnancy has decreased by 25% in the past decade in the United States.

Table 402.5

Risk Factors Associated With Sudden Infant Death Syndrome

MATERNAL AND ANTENATAL RISK FACTORS
Elevated 2nd trimester serum α-fetoprotein
Smoking
Alcohol use
Drug use (cocaine, heroin)
Nutritional deficiency
Inadequate prenatal care
Low socioeconomic status
Younger age
Lower education
Single marital status

Shorter interpregnancy interval
Intrauterine hypoxia
Fetal growth restriction

INFANT RISK FACTORS

Age (peak 1-4 mo)
Male gender
Race and ethnicity (African American, American Indian, Alaska Native, other minorities)
Growth failure
No breastfeeding
No pacifier (dummy)
Prematurity
Prone and side sleep position
Recent febrile illness (mild infections)
Inadequate immunizations
Smoking exposure (prenatal and postnatal)
Soft sleeping surface, soft bedding
Bed sharing with parent(s) or other children
Thermal stress, overheating
Colder season, no central heating

Nonmodifiable Environmental Risk Factors

Lower socioeconomic status has consistently been associated with higher risk, although SIDS affects infants from all social strata. In the United States, African-American, American Indian, and Alaska Native infants are 2-3 times more likely than white infants to die of SIDS, whereas Asian, Pacific Islander, and Hispanic infants have the lowest incidence. Some of this disparity may be related to the higher concentration of poverty and other adverse environmental factors found within some, but not all, of the communities with higher incidence.

Infants are at greatest risk of SIDS at 1-4 mo of age, with most deaths having occurred by 6 mo. This characteristic age has decreased in some countries as the SIDS incidence has declined, with deaths occurring at earlier ages and with a flattening of the peak age incidence. Similarly, the commonly observed winter seasonal predominance of SIDS has declined or disappeared in some countries as prone prevalence has decreased, supporting prior findings of an interaction between sleep position and factors more common in colder months (overheating as a consequence of elevated interior temperatures or bundling with blankets and heavy clothing, or infection). Male infants are 30–50% more likely to be affected by SIDS than are female infants.

Modifiable Environmental Risk Factors

Pregnancy-Related Factors

An increased SIDS risk is associated with numerous obstetric factors, suggesting that the in utero environment of future SIDS infants is suboptimal. SIDS infants are more commonly of higher birth order, independent of maternal age, and of gestations after shorter interpregnancy intervals. Mothers of SIDS infants generally receive less prenatal care and initiate care later in pregnancy. In addition, low birthweight, preterm birth, and slower intrauterine and postnatal growth rates are risk factors.

Cigarette Smoking

There is a major association between **intrauterine exposure to cigarette smoking** and risk for SIDS. The incidence of SIDS was 2-3 times greater among infants of mothers who smoked in studies conducted before SIDS risk-reduction campaigns and 4 times higher in studies after implementation of risk-reduction campaigns. The risk of death is progressively greater as daily cigarette use increases. The effects of smoking by the infant's father and other household members are more difficult to interpret because they are highly correlated with maternal smoking. There appears to be a small independent effect of paternal smoking, but data on other household members have been inconsistent. The effect of prenatal smoking on SIDS risk is not believed to be caused by lower birthweight, which is often found among infants of smoking mothers.

It is very difficult to assess the independent effect of infant exposure to **environmental tobacco smoke** because parental smoking behaviors during and after pregnancy are also highly correlated. However, a 2-fold increased risk of SIDS is found for infants exposed only to postnatal maternal environmental tobacco smoke. There is a dose-response for the number of household smokers, number of people smoking in the same room as the infant, and the number of cigarettes smoked. These data suggest that keeping the infant free of environmental tobacco smoke can further reduce an infant's risk of SIDS.

Drug and Alcohol Use

Most studies link maternal prenatal drug use, especially opiates, with an increased risk of SIDS, ranging from a 2- to 15-fold increased risk. Studies looking at the association between maternal alcohol use prenatally or postnatally and SIDS have conflicting results. In one study of Northern Plains Indians, periconceptional alcohol use and binge drinking in the 1st trimester were associated with a 6-fold and an 8-fold increased risk of SIDS, respectively. A Danish cohort study found that mothers admitted to the hospital for an alcohol- or a drug-related disorder at any time before or after the birth of their infants had a 3-time higher risk of their infant dying from SIDS, and a Dutch study reported that maternal alcohol consumption in the 24 hr before the infant died carried an 8-fold increased risk of SIDS. Siblings of infants with fetal alcohol syndrome have a 10-fold increased risk of SIDS compared with controls. Although there are conflicting reports of illicit drug use and SIDS overall, prenatal drug use, especially opiates, is associated with an increased risk of SIDS, ranging from 2- to 15-fold. Data on cannabis use and SIDS are extremely limited, with only one study from New Zealand reporting results for postpartum maternal use. This study found that nighttime cannabis use was associated with a 2-fold increased risk of SIDS, whereas daytime use was not associated with increased risk.

Infant Sleep Environment

Sleeping prone has consistently been shown to increase the risk of SIDS. As rates of prone positioning have decreased in the general population, the odds ratios for SIDS in infants still sleeping prone have increased. *The highest risk of SIDS occurs in infants who are usually placed nonprone but placed prone for last sleep (“unaccustomed prone”) or found prone (“secondary prone”).* The “unaccustomed prone” position may be more likely to occur in daycare or other settings outside the home and highlights the need for all infant caretakers to be educated about appropriate sleep positioning.

Side-Sleeping: Significant Risk Factor.

The initial SIDS risk-reduction campaign recommendations considered side-sleeping to be nearly equivalent to the supine position in reducing the risk of SIDS. Subsequent studies documented that side-sleeping infants were twice as likely to die of SIDS as infants sleeping supine. This increased risk may be related to the relative instability of the position. Infants who are placed on their side and roll to prone are at exceptional risk, with one study finding they are almost 9 times more likely to die of SIDS than those placed supine. Although the majority of SIDS occurrences are still associated with infants being found prone, a higher proportion of SIDS is now attributed to being placed on the side for sleeping than for being placed prone. The current recommendations call for supine position for sleeping for all infants except those few with specific medical conditions for which recommending a different position may be justified, in infants with anatomic or functional upper airway compromise.

Many parents and healthcare providers were initially concerned that supine sleeping would be associated with an increase in adverse consequences, such as difficulty sleeping, vomiting, or aspiration. However, evidence suggests that the risk of regurgitation and choking is highest for prone-sleeping infants. Some newborn nursery staff still tend to favor side positioning, which models inappropriate infant care practice to parents. Infants sleeping on their backs do not have more episodes of cyanosis or apnea, and reports of apparent life-threatening events actually decreased in Scandinavia after increased use of the supine position. Among infants in the United States who maintained the same sleep position at 1, 3, and 6 mo of age, no clinical symptoms or reasons for outpatient visits (including fever, cough, wheezing, trouble breathing or sleeping, vomiting, diarrhea, or respiratory illness) were more common in infants sleeping supine or on their sides compared with infants sleeping prone. Three symptoms were actually less common in infants sleeping supine or on their sides: fever at 1 mo, stuffy nose at 6 mo, and trouble sleeping at 6 mo. Outpatient visits for ear infection were less common at 3 and 6 mo for infants sleeping supine and also less common at 3 mo for infants sleeping on their side. These results provide reassurance for parents and healthcare providers and should contribute to universal acceptance of supine as the safest and optimal sleep position for infants.

Soft Sleep Surfaces and Soft or Loose Bedding.

Soft sleep surfaces and soft or loose bedding , including comforters, pillows, bumper pads, stuffed animals, mattress toppers, pillow-top mattresses, sheepskins, polystyrene bean pillows, and old or soft mattresses, are associated with increased risk of SIDS. Infant sleep positioners, including pillows and wedges, which are often marketed to hold infants on their side or at an angle to help with reflux, are also not recommended. Based on available research, **swaddling infants** , or wrapping them in a blanket, is not recommended as a strategy to reduce SIDS. Infants who roll to the prone position while swaddled are at particularly high risk of SIDS. Wearable blankets, which may have a built-in swaddle, are an acceptable alternative.

Overheating.

Overheating, based on indicators such as higher room temperature, a history of fever, sweating, and excessive clothing or bedding, has been associated with increased risk of SIDS. Some studies have identified an interaction between overheating and prone sleeping, with overheating increasing the risk of SIDS only when infants are sleeping prone. Higher external environmental temperatures have not been associated with increased SIDS incidence in the United States.

Bed Sharing.

Several studies have implicated **bed sharing** as a risk factor for SIDS. Bed sharing is particularly hazardous when other children are in the same bed, when the parent is sleeping with an infant on a couch, sofa, or other soft or confining sleeping surface, when the mother is a smoker, and when the bed sharer has used alcohol or arousal-altering drugs or medications. Infants younger than 4 mo of age are at increased risk even when mothers are nonsmokers. A meta-analysis of 19 studies found that low-risk infants (i.e., those who were breastfed and never exposed to cigarette smoke in utero or after birth) still had a 5-fold increased risk of SIDS until the age of 3 mo if bed sharing. Risk is also increased with longer duration of bed sharing during the night, whereas returning the infant to the infant's own crib has not been associated with increased risk. Room sharing without bed sharing is associated with lower SIDS rates and is therefore recommended.

Infant Feeding Care Practices and Exposures

Breastfeeding is Associated With a Lower Risk of Sudden Infant Death Syndrome.

A meta-analysis found that breastfeeding was associated with a 45% reduction in SIDS after adjusting for confounding variables and that this protective effect increased for exclusive breastfeeding compared with partial breastfeeding.

Pacifier (dummy) use is associated with a lower risk of SIDS in the majority of studies. Although it is not known if this is a direct effect of the pacifier itself or from associated infant or parental behaviors, use of the pacifier is protective even if it is dislodged during sleep. Concerns have been expressed about recommending pacifiers as a means of reducing the risk of SIDS for fear of adverse consequences, particularly interference with breastfeeding. However, well-designed clinical trials have found no association between pacifiers and breastfeeding duration.

Upper respiratory tract infections have generally not been found to be an independent risk factor for SIDS, but these and other minor infections may still have a role in the causal pathway of SIDS when other risk factors are present. Risk for SIDS has been found to be increased after illness among prone sleepers, those who were heavily wrapped, and those whose heads were covered during sleep.

No adverse association between immunizations and SIDS has been found. Indeed, SIDS infants are less likely to be immunized than control infants, and, in immunized infants, no temporal relationship between vaccine administration and death has been identified. In a meta-analysis of case-control studies that adjusted for potentially confounding factors, the risk of SIDS for infants immunized with diphtheria, tetanus, and pertussis was half that for nonimmunized infants.

Sudden Infant Death Syndrome Rates Remain Higher Among American Indians, Alaska Natives, and African Americans.

This may be due, in part, to group differences in adopting supine sleeping or other risk-reduction practices. Greater efforts are needed to address this persistent disparity and to ensure that SIDS risk-reduction education reaches all parents and other care providers, including other family members and personnel at daycare centers.

Genetic Risk Factors

As summarized in Table 402.4 , there are numerous genetic differences identified in infants who died of SIDS compared with healthy infants and to infants dying from other causes. Polymorphisms occurring at higher incidence in SIDS infants compared with controls include multiple cardiac ion channelopathy genes that are proarrhythmic, autonomic nervous system development genes, proinflammatory genes related to infection and immunity, and several 5-HT genes.

Multiple studies have established the importance of a pathway to SIDS that involves cardiac sodium or potassium channel dysfunction resulting in **either long QT syndrome (LQTS)** or other proarrhythmic conditions. LQTS is a known cause of sudden unexpected death in children and adults as the result of a prolonged cardiac action potential causing either increased depolarization or decreased repolarization current (Fig. 402.1). The first evidence supporting a causal role for LQTS in SIDS was a large Italian study in which a corrected QT interval >440 msec on an electrocardiogram performed on days 3-4 of life was associated with an odds ratio of 41 for SIDS. Several case reports have subsequently provided proof of concept that cardiac channelopathy polymorphisms are associated with SIDS. LQTS is associated with polymorphisms related mainly to gain-of-function mutations in the **sodium channel gene** *(SCN5A)* that encode critical channel pore-forming α subunits or essential channel-interacting proteins. LQTS also is associated with mainly loss-of-function polymorphisms in potassium channel genes. **Short QT syndrome (SQTS)** is more recently recognized as another cause of life-threatening arrhythmia or sudden death, often during rest or sleep. Gain-of-function mutations in genes including *KCNH2* and *KCNQ1* have been causally linked to SQTS, and some of these deaths have occurred in infants, suggesting that SQTS may also be causally linked to SIDS.

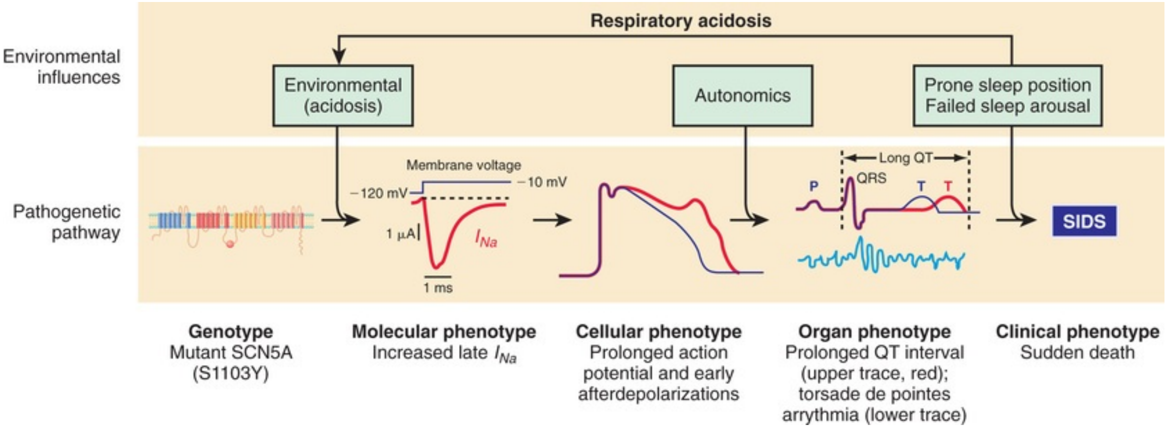
Respiratory acidosis
Environmental influences
Environmental (acidosis)
Autonomics
Prone sleep position
Failed sleep arousal
Pathogenetic pathway
Membrane voltage
−120 mV
−10 mV
1 μA
I_{Na}
1 ms
Long QT
P
QRS
T
T
SIDS
Genotype
Mutant SCN5A (S1103Y)
Molecular phenotype
Increased late I_{Na}
Cellular phenotype
Prolonged action potential and early afterdepolarizations
Organ phenotype
Prolonged QT interval (upper trace, red); torsade de pointes arrythmia (lower trace)
Clinical phenotype
Sudden death

FIG. 402.1 A proarrhythmic pathogenetic pathway for sudden infant death syndrome *(SIDS)* from patient genotype to clinical phenotype, with environmental influences noted. The genetic abnormality—in this instance, a polymorphism in the cardiac Na^+ channel SCN5A—causes a molecular phenotype of increased late Na^+ current (I_{Na}) under the influence of environmental factors such as acidosis. Interacting with other ion currents

that may themselves be altered by genetic and environmental factors, the late Na^+ current causes a cellular phenotype of prolonged action potential duration, as well as early afterdepolarizations. Prolonged action potential in the cells of the ventricular myocardium and further interaction with environmental factors such as autonomic innervation, which, in turn, may be affected by genetic factors, produce a tissue-organ phenotype of a prolonged QT interval on the electrocardiogram (ECG) and torsades de pointes arrhythmia in the whole heart. If this is sustained or degenerates to ventricular fibrillation, the clinical phenotype of SIDS results. Environmental and multiple genetic factors can interact at many different levels to produce the characteristic phenotypes at the molecular, cellular, tissue, organ, and clinical levels. (From Makielski JC: SIDS: genetic and environmental influences may cause arrhythmia in this silent killer, *J Clin Invest* 116(2):297–299, 2006.)

In addition to LQTS and SQTS, the other cardiac ion-related channelopathy polymorphisms are also proarrhythmic, including Brugada syndrome *(BrS1, BrS2)* and catecholaminergic paroxysmal ventricular tachycardia *(CPVT1).* Collectively, these mutations in cardiac ion channels provide a lethal proarrhythmic substrate in some infants (see Fig. 402.1) and may account for 10% or more of SIDS cases.

Impaired central respiratory regulation is an important biologic abnormality in SIDS, and genetic polymorphisms have been identified in SIDS infants that affect both serotonergic and adrenergic neurons. Monoamine oxidase A metabolizes both of these neurotransmitters, and a recent study has observed a high association between SIDS and low expressing alleles in males, perhaps contributing to the higher incidence of SIDS in males. Many genes are involved in the control of 5-HT synthesis, storage, membrane uptake, and metabolism. Polymorphisms in the promoter region of the 5-HTT protein gene occur with greater frequency in SIDS than control infants. The long “L” allele increases effectiveness of the promoter and reduces extracellular 5-HT concentrations at nerve endings, compared with the short “S” allele. White, African-American, and Japanese SIDS infants were more likely than ethnicity-matched controls to have the “L” (long) allele, and there was also a negative association between SIDS and the S/S genotype. The L/L genotype was associated with increased 5-HT transporters on neuroimaging and postmortem binding studies. However, in a large San Diego dataset of SIDS infants, no relationship was found between SIDS and the L allele or the LL genotype.

An association has also been observed between SIDS and a 5-HTT intron 2 polymorphism, which differentially regulates *5-HTT* expression. There were positive associations between SIDS and the intron 2 genotype distributions in

African-American infants who died of SIDS, compared with African-American controls. The human *FEV* gene is specifically expressed in central 5-HT neurons in the brain, with a predicted role in specification and maintenance of the serotoninergic neuronal phenotype. An insertion mutation has been identified in intron 2 of the *FEV* gene, and the distribution of this mutation differs significantly in SIDS compared with control infants.

Molecular genetic studies in SIDS victims have also identified mutations pertinent to early embryologic development of the autonomic nervous system (see Table 402.4). Protein-changing mutations related to the *PHOX2a, RET, ECE1, TLX3,* and *EN1* genes have been identified, particularly in African-American infants who died of SIDS. Eight polymorphisms in the *PHOX2B* gene occurred significantly more frequently in SIDS compared with control infants. One study has reported an association between SIDS and a distinct tyrosine hydroxylase gene *(THO1)* allele, which regulates gene expression and catecholamine production.

Multiple studies have observed altered expression of genes involved in the inflammatory process and immune system regulation. Differences in SIDS infants, compared with controls, have been reported for 2 complement *C4* genes. Some SIDS infants have loss-of-function polymorphisms in the gene promoter region for IL-10, another antiinflammatory cytokine. IL-10 polymorphisms associated with decreased IL-10 levels could contribute to SIDS by delaying initiation of protective antibody production or reducing capacity to inhibit inflammatory cytokine production. However, other studies have not found differences in IL-10 genes in SIDS infants compared with age-matched controls.

An association has been reported between single nucleotide polymorphisms in the proinflammatory gene encoding IL-8 and SIDS infants found prone, compared with SIDS infants found in other sleep positions. IL-1 is another proinflammatory gene, and a higher prevalence of the IL-1 receptor antagonist, which would predispose to higher risk for infection, has been reported in infants who died of SIDS. Significant associations with SIDS are also reported for polymorphisms in VEGF, IL-6, and tumor necrosis factor-α (TNFα). These 3 cytokines are proinflammatory, and these gain-of-function polymorphisms would result in increased inflammatory response to infectious or inflammatory stimuli and hence contribute to an adverse imbalance between proinflammatory and antiinflammatory cytokines. As apparent proof of principle, elevated levels of IL-6 and VEGF have been reported from cerebrospinal fluid in SIDS infants. There were no group differences in the IL6-174G/C polymorphism in a

Norwegian SIDS study, but the aggregate evidence nevertheless suggested an activated immune system in SIDS and implicated genes involved in the immune system. Almost all SIDS infants in one study had positive histories for prone sleeping and fever prior to death and positive HLA-DR expression in laryngeal mucosa, and high HLA-DR expression was associated with high levels of IL-6 in cerebrospinal fluid.

Gene-Environment Interactions

Interactions between genetic and environmental risk factors determine the actual risk for SIDS in individual infants (Fig. 402.2). Equally important, there is a dynamic interaction between genetic or intrinsic vulnerability and the sleep environment (Fig. 402.3). There appears to be an interaction between prone sleep position and impaired ventilatory and arousal responsiveness. Facedown or nearly facedown sleeping does occasionally occur in prone-sleeping infants, but normal healthy infants arouse before such episodes become life-threatening. However, infants with insufficient arousal responsiveness to hypoxia may be at risk for sudden death from resulting episodes of airway obstruction and asphyxia. There may also be links between modifiable risk factors (such as soft bedding, prone sleep position, and thermal stress) and genetic risk factors, such as ventilatory and arousal abnormalities and temperature or metabolic regulation deficits. Cardiorespiratory control deficits could be related to 5-HTT polymorphisms, for example, or to polymorphisms in genes pertinent to autonomic nervous system development. Affected infants could be at increased risk for sleep-related hypoxemia and hence more susceptible to adverse effects associated with unsafe sleep position or bedding. Infants at increased risk for sleep-related hypoxemia could also be at greater risk for fatal arrhythmias in the presence of a cardiac ion channelopathy polymorphism.

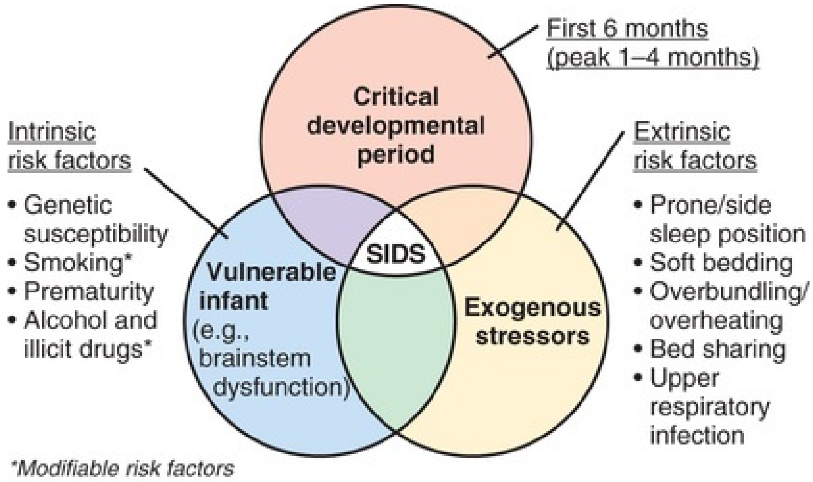
First 6 months
(peak 1–4 months)
Critical developmental period
Intrinsic risk factors
• Genetic susceptibility
• Smoking*
• Prematurity
• Alcohol and illicit drugs*
Extrinsic risk factors
• Prone/side sleep position
• Soft bedding
• Overbundling/overheating
• Bed sharing
• Upper respiratory infection
SIDS
Vulnerable infant (e.g., brainstem dysfunction)
Exogenous stressors
*Modifiable risk factors

FIG. 402.2 Schematic of the triple-risk model for sudden infant death syndrome *(SIDS)* showing the critical interactions between intrinsic risk factors (including genetic risk factors) resulting in a vulnerable infant, a critical developmental period or age, and exogenous stressors or extrinsic risk factors. (Modified from Filiano JJ, Kinney HC: A perspective on the neuropathologic findings in victims of the sudden infant death syndrome: the triple risk model, *Biol Neonate* 65(3–4):194–197, 1994.)

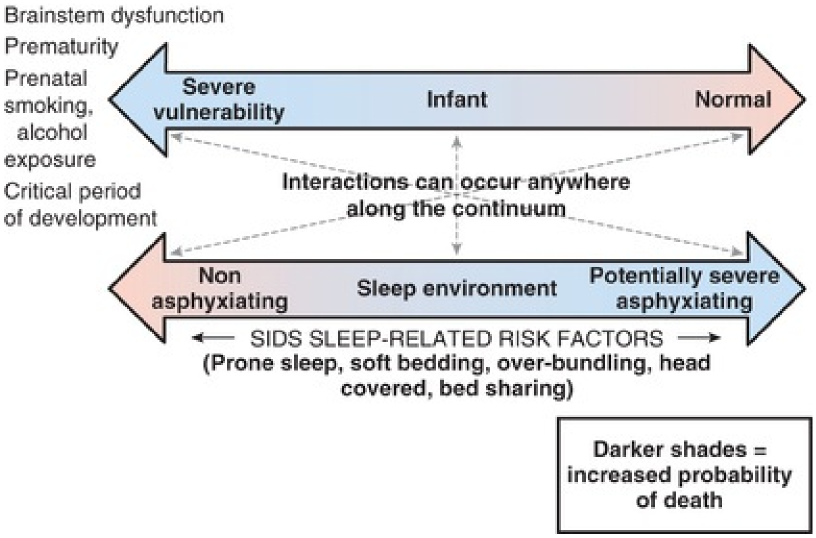
Brainstem dysfunction
Prematurity
Prenatal smoking, alcohol exposure
Critical period of development
Severe vulnerability
Infant
Normal
Interactions can occur anywhere along the continuum
Non asphyxiating
Sleep environment
Potentially severe asphyxiating
SIDS SLEEP-RELATED RISK FACTORS
(Prone sleep, soft bedding, over-bundling, head covered, bed sharing)
Darker shades = increased probability of death

FIG. 402.3 Dynamic interactions between intrinsic vulnerability to sudden infant death syndrome *(SIDS)* and degree of risk of the sleep environment, ranging from nonasphyxiating (completely safe) to potentially severe asphyxiating (very unsafe). Intrinsic vulnerability could be related to genetic risk factors, fetal or early infant exposures, or other factors. (Modified from Hunt CE, Darnall RA, McEntire BL, Hyma BA: Assigning cause for sudden unexpected infant death, *Forensic Sci Med Pathol* 11(2):283–288, 2015.)

In >50% of SIDS victims, recent febrile illnesses, often related to upper respiratory infection, have been documented (see Table 402.5). Benign infections might increase risk for SIDS if interacting with genetically determined proinflammatory or impaired immune responses. Deficient inflammatory responsiveness can also occur as a result of mast cell degranulation, which has been reported in SIDS infants. This is consistent with an anaphylactic reaction to a bacterial toxin, and some family members of SIDS infants also have mast cell hyperreleasability and degranulation, suggesting that increased susceptibility to an anaphylactic reaction is another genetic factor influencing fatal outcomes to otherwise minor infections. Interactions between upper respiratory infections or other minor illnesses and factors such as prone sleeping might also play a role in the pathogenesis of SIDS.

The increased risk of SIDS associated with fetal and postnatal exposure to cigarette smoke may be related at least in part to genetic or epigenetic factors, including those affecting brainstem autonomic control. Infant studies document decreased ventilatory and arousal responsiveness to hypoxia following fetal nicotine exposure, and impaired autoresuscitation after apnea has been associated with postnatal nicotine exposure. Decreased brainstem immunoreactivity to selected protein kinase C and neuronal nitric oxide synthase isoforms occurs in rats exposed to cigarette smoke prenatally, another potential cause of impaired hypoxic responsiveness. Smoking exposure also increases susceptibility to viral and bacterial infections and increases bacterial binding after passive coating of mucosal surfaces with smoke components, implicating interactions between smoking, cardiorespiratory control, and immune status. Flavin-monooxygenase 3 *(FMO3)* is one of the enzymes that metabolizes nicotine, and a polymorphism has recently been identified that occurs more frequently in SIDS infants compared with controls and more frequently in infants whose mothers reported heavy smoking (see Table 402.4). This polymorphism would result in increased nicotine levels and hence is a potential genetic risk factor for SIDS in infants exposed to cigarette smoke.

In infants with a cardiac ion channelopathy, risk for a fatal arrhythmia during sleep may be substantially enhanced by predisposing perturbations that increase electrical instability. These perturbations could include REM sleep with bursts of vagal and sympathetic activation, minor respiratory infections, or any other cause of sleep-related hypoxemia or hypercarbia, especially those resulting in acidosis. The prone sleeping position is associated with increased sympathetic activity.

Infant Groups at Increased Risk for Sudden Infant Death Syndrome

Subsequent Siblings of an Infant who Died of Sudden Infant Death Syndrome

The next-born siblings of first-born infants dying of any noninfectious natural cause are at significantly increased risk for infant death from the same cause, including SIDS. The relative risk is 9.1 for the same cause of recurrent death versus 1.6 for a different cause of death. The relative risk for recurrent SIDS (range: 5.4-5.8) is similar to the relative risk for non-SIDS causes of recurrent death (range: 4.6-12.5). The risk for recurrent infant mortality from the same cause as in the index sibling thus appears to be increased to a similar degree in subsequent siblings for both explained causes and for SIDS. This increased risk for recurrent SIDS in families is consistent with genetic risk factors interacting with environmental risk factors (see Tables 402.4 and 402.5 and Figs. 402.2 and 402.3). However, recurrent SIDS in a family should also alert the clinician to consider other causes of sudden and unexpected death (see Table 402.2).

Prematurity

Despite reductions of more than 50% in SIDS and SUID among infants born preterm since initiation of the Back to Sleep campaign in the United States in 1994, the risk of death remains significantly higher for these infants than for those born full term. The risk increases as gestational age decreases. Compared with infants born at 37-42 wk, the odds ratio for SIDS is greatest for infants born at 24-28 wk gestation (2.57, 95% confidence interval 2.08, 3.17). Even at 33-36 wk gestational age at birth, the risk of SIDS remains significantly increased compared with infants born at term. The peak chronologic age for SIDS is later in infants born preterm; chronologic age at death is inversely proportional to gestational age at birth.

Although infants born preterm are at increased risk for apnea, apnea of prematurity per se *does not* seem to be related to the increased SIDS risk. This increased risk is instead likely related in part to immaturity of brainstem responses; physiologic studies have found impaired cortical arousals, lower baroreflex sensitivity, and impaired autonomic control. Sociodemographic and environmental risk are also important. Infants born preterm have more sociodemographic risk factors overall than infants born at term. In addition, infants born preterm are more likely to be placed prone at home; this may be in part because these infants are often placed prone while mechanically ventilated in the neonatal intensive care unit, and safe sleep practices are often not well-modeled during the remainder of the NICU admission. The association between prone position and SIDS in preterm and low birthweight infants is equal or greater than this association in infants born full term.

Physiologic Studies

Physiologic studies have been performed in healthy infants in early infancy, a few of whom later died of SIDS. Physiologic studies have also been performed on infant groups who were believed to be at increased risk for SIDS, especially those with brief resolved unexplained events (BRUE; formerly known as apparent life-threatening events; Chapter 403) and subsequent siblings of infants who died of SIDS. In the aggregate, these studies have indicated brainstem abnormalities in the neuroregulation of cardiorespiratory control or other autonomic functions and are consistent with the autopsy findings and genetic studies in infants who died of SIDS (see “Pathology ” and “Genetic Risk Factors ”). In addition to physiologic abnormalities in chemoreceptor sensitivity, other observed physiologic abnormalities have been found in respiratory pattern, control of heart and respiratory rate or variability, and asphyxic arousal responsiveness. A deficit in arousal responsiveness may be a necessary prerequisite for SIDS to occur but may be insufficient to cause SIDS in the absence of other genetic or environmental risk factors. **Autoresuscitation (gasping)** is a critical component of the asphyxic arousal response, and a failure of autoresuscitation in SIDS infants may be the final and most devastating physiologic failure. In one study, most normal full-term infants younger than 9 postnatal wk of age aroused in response to mild hypoxia, whereas only 10–15% of infants older than 9 wk of age aroused. These data suggest that ability to arouse to mild to moderate hypoxic stimuli may be at a nadir at the age range of greatest risk for SIDS.

The ability to shorten the QT interval as heart rate increases appears to be impaired in some infants who died of SIDS, suggesting that such infants may be predisposed to ventricular arrhythmia. Although this is consistent with the observations of cardiac ion channel gene polymorphisms in some SIDS infants (see Table 402.4), there are no antemortem QT interval data for these infants that confirm the importance of this finding. Infants who were studied physiologically and then died of SIDS a few weeks later had higher heart rates and lower heart rate variability in all sleep–wake states and diminished heart rate variability during wakefulness. These SIDS infants also had longer QT intervals than control infants during both REM and non-REM sleep, especially in the late hours of the night when most SIDS likely occurs. However, the QT interval exceeded 440 msec in only one of these SIDS infants.

It has been postulated that the decreased heart rate variability and increased heart rate observed in infants who later died of SIDS may in part be related to decreased vagal tone, perhaps from vagal neuropathy or brainstem damage in areas responsible for parasympathetic cardiac control. Power spectrum analysis of heart rate variability is 1 way to assess sympathetic and parasympathetic cardiac control. In a comparison of heart rate power spectra before and after obstructive apneas in clinically asymptomatic infants, infants later dying of SIDS did not have the decreases in low-frequency to high-frequency power ratios observed in infants who survived. Some infants may thus have different autonomic responsiveness to obstructive apnea, perhaps indicating impaired autonomic nervous system control associated with higher vulnerability to external or endogenous stresses, and hence reduced electrical stability of the heart; this may create a vulnerability for SIDS.

Home cardiorespiratory monitors with memory capability have recorded the terminal events in some infants who died of SIDS. However, these recordings did not include pulse oximetry and could not identify obstructed breaths due to reliance on transthoracic impedance for breath detection. In most instances, there was sudden and rapid progression of severe bradycardia that was either unassociated with central apnea or appeared to occur too soon to be explained by the central apnea. These observations are consistent with an abnormality in autonomic control of heart rate variability or with obstructed breaths resulting in bradycardia or hypoxemia and associated with impaired autoresuscitation or arousal.

Clinical Strategies

Home Monitoring

SIDS cannot be *prevented* in individual infants because it is not possible to identify prospective SIDS infants, and no effective intervention has been established even if infants at risk could be prospectively identified. Studies of cardiorespiratory pattern or other autonomic abnormalities do not have sufficient sensitivity and specificity to be clinically useful as screening tests. Home electronic surveillance using existing technology *does not* reduce the risk of SIDS. Although a prolonged QT interval in an infant may be treated if diagnosed, neither the role of routine postnatal electrocardiographic screening, the cost-effectiveness of diagnosis and treatment, nor the safety of treatment in infants has been established (see Chapter 456). Parental electrocardiographic screening is not helpful, in part because spontaneous mutations are common.

Reducing the Risk of Sudden Infant Death Syndrome

Reducing risk behaviors and increasing protective behaviors among infant caregivers to achieve further reductions and eventual elimination of SIDS is a critical goal. Recent plateaus in placing infants supine for sleep in the United States at approximately 75% for all races and only 56% for African Americans are cause for concern and require renewed educational efforts. The American Academy of Pediatrics (AAP) guidelines to reduce the risk of SIDS were updated in 2016 and are aimed at reducing the risk of all sudden and unexpected sleep-related infant deaths. The guidelines are appropriate for most infants, but physicians and other healthcare providers might, on occasion, need to consider alternative approaches. The major components of the AAP guidelines are:

- Full-term and premature infants should be placed for sleep in the supine position. There are no adverse health outcomes from supine sleeping. Side-sleeping is not recommended.
- Infants should be put to sleep on a firm mattress. Waterbeds, sofas, soft mattresses, or other soft surfaces should not be used. In addition, car seats, strollers, swings, and other sitting devices should not be used for sleeping. Sleeping in an upright position

can lead to gastroesophageal reflux or upper airway obstruction from head flexion.

- Breastfeeding is recommended. If possible, mothers should exclusively breastfeed or feed with expressed human milk until the infant is 6 mo of age.
- It is recommended that infants sleep in the same room as their parents but in their own crib or bassinet that conforms to the safety standards of the Consumer Product Safety Commission. Placing the crib or bassinet near the mother's bed facilitates nursing and contact. If parents bring the infant into the adult bed for feeding or comforting, the infant should be returned to a separate sleep surface when the parents are ready for sleep.
- Soft materials and loose bedding in the infant's sleep environment—over, under, or near the infant—should be avoided. These include pillows, comforters, quilts, sheepskins, bumper pads, and stuffed toys. Sleep clothing, such as a wearable blanket, can be used in place of blankets.
- Consider offering a pacifier at bedtime and naptime. The pacifier should be used when placing the infant down for sleep and need not be reinserted once it falls out. For breastfed infants, delay introduction of the pacifier until breastfeeding is well established.
- Mothers should not smoke during pregnancy or after birth, and infants should not be exposed to second-

hand smoke.

- Mothers should avoid alcohol and illicit drug use during pregnancy and after birth.
- Avoid overheating and overbundling. The infant should be lightly clothed for sleep and the thermostat set at a comfortable temperature.
- Pregnant women should obtain regular prenatal care, following guidelines for prenatal visits.
- Infants should be immunized in accordance with recommendations of the AAP and the Centers for Disease Control and Prevention. There is no evidence that immunizations increase the risk of SIDS. Indeed, recent evidence suggests that immunizations may have a protective effect against SIDS.
- Avoid the use of commercial devices that are inconsistent with safe sleep recommendations. Devices advertised to maintain sleep position, “protect” a bed sharing infant, or reduce the risk of rebreathing are not recommended because there is no evidence to support their safety or efficacy.
- Home cardiorespiratory and/or O_2 saturation monitoring may be of value for selected infants who have extreme instability, but there is no evidence that monitoring decreases the incidence of SIDS, and it is therefore not recommended for this purpose.
- Infants should have some time in the prone position (tummy time) while awake and observed. Alternating

the placement of the infant's head, as well as orientation in the crib, can also minimize the risk of head flattening from supine sleeping (positional plagiocephaly).

- Swaddling cannot be recommended as a strategy to reduce SIDS. If infants are placed in a swaddle it should be using a light blanket that is snug around the shoulders but looser around the hips to avoid hip dysplasia. Swaddled infants should always be placed supine, and once infants can roll to the prone position all swaddling should be discontinued.
- Healthcare professionals, staff in newborn nurseries and neonatal intensive care units, and child care providers should adopt the SIDS reduction recommendations beginning at birth to model safe sleep for caregivers.
- Media and manufacturers should follow safe sleep guidelines in their messaging and advertising.
- The national “Safe to Sleep” campaign should be continued with additional emphasis placed on strategies to increase breastfeeding while decreasing bed sharing and tobacco smoke exposure. The campaign should continue to have a special focus on the groups with higher rates of SIDS, including educational strategies tailored to individual racial-ethnic groups. Secondary care providers need to be targeted to receive these educational messages,

including daycare providers, grandparents, foster parents, and baby sitters. Efforts should also be made to introduce sleep recommendations before pregnancy and ideally in secondary school curricula.

- Research and surveillance should be continued on the risk factors, causes, and pathophysiologic mechanisms of SIDS and other sleep-related SUID, with the ultimate goal of preventing these deaths entirely. Federal and private funding agencies need to remain committed to this research.

402.1

Sudden Unexpected Postnatal Collapse

Sarah Vepraskas

Keywords

sudden unexpected postnatal collapse
sudden unexpected infant death
skin-to-skin contact
cardiorespiratory control

Epidemiology

Sudden unexplained postnatal collapse (SUPC) is a rare but potentially fatal event in an otherwise healthy term newborn that includes any condition resulting in temporary or permanent cessation of breathing or cardiorespiratory failure. SUPC results in death in about half of the infants and significant impairment in many survivors.

SUPC, in some definitions, includes both severe apparent life-threatening events (currently referred to as BRUE) and SUID, occurring within the 1st *postnatal week* of life. In general, SUID is a term that encompasses all SUIDs. Some BRUEs may be low risk and require simple interventions such as positional changes, brief stimulation, or procedures to resolve the airway obstruction; these seemingly more benign events are in contrast to SUPC, which can be potentially fatal.

The definition of SUPC used in the AAP report on safe sleep and skin-to-skin care is by the British Association of Perinatal Medicine and includes any term or near-term (defined as >35 wk gestation) infant who meets the following criteria: (1) is well at birth (normal 5-min Apgar and deemed well enough for routine care), (2) collapses unexpectedly in a state of cardiorespiratory extremis such that resuscitation with intermittent positive-pressure ventilation is required, (3) collapses within the 1st 7 days of life, and (4) either dies, goes on to require intensive care, or develops encephalopathy. A majority of reported events occur within 2 hr after birth, often at the time of the 1st breastfeeding attempt. Other potential medical conditions that place infants at higher risk, such as prematurity (<35 wk gestation), perinatal asphyxia, sepsis, or congenital malformations, should be excluded for SUPC to be diagnosed.

The incidence of SUPC is estimated to be 2.6-133 per 100,000 live births. However, the incidence varies widely because there is a lack of consensus on the definition, differing inclusion and exclusion criteria exist, and no standardized reporting system. In addition, a consensus for coding SUPC has not been established, which likely contributes to it being underreported.

The published estimations of SUPC are lower than what occur in the hospital and reflect only the critical events. When a defined time for the SUPC event is described, approximately one third of reported events occur during the 1st 2 hr, another one third between 2 and 24 hr, and another one third between 1 and 7 days after birth.

Pathogenesis

The mechanism for SUPC is not completely known. Many of the events may be related to suffocation or entrapment. It is also hypothesized that the transition from fetal to extrauterine life could make the newborn more vulnerable during the 1st hr of life. During birth there is an initial surge of adenosine and prostaglandins, followed by a postnatal surge of catecholamines. A healthy newborn baby is aroused and awake after birth and starts continuous breathing movements. Shortly after birth, there is a rapid decrease in the inhibitory neuromodulator adenosine as the partial pressure of oxygen in the arterial blood rapidly increases and contributes to the increased activity in the newborn infant compared with the fetus. Following the hormone surges, there is a period of diminished responsiveness to external stimuli and increased vagal tone; it is possible that autonomic instability could make infants vulnerable during this transitioning period.

It is also possible that impaired cardiorespiratory control due to hypoxic ischemic injury occurring days before birth could contribute to fatal cases of SUPC. Mild gliosis in brainstem areas involved in cardiorespiratory control was found at autopsy of 7 infants with SUPC. However, there are insufficient data to support an association between in utero hypoxic events and SUPC.

Risk Factors

Many of reported SUPC cases occur while the infant is in prone position, during skin-to-skin contact (SSC) with their mothers. SSC is traditionally defined as beginning at birth and lasting continually until the end of the first breastfeeding.

Additional risk factors for SUPC include the first breastfeeding attempt, cosleeping, a mother in the episiotomy position, a primiparous mother, and parents left alone with baby during the 1st hr after birth.

SSC and rooming-in have become common practice for healthy newborns and align with Baby-Friendly Hospital Initiative (BFHI), a global program launched by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to encourage and recognize hospitals and birthing centers that promote the optimal level of care for infant feeding and mother/baby bonding. The BFHI recognizes and awards birthing facilities that successfully implement the “Ten Steps to Successful Breastfeeding,” with step 4 being to initiate breastfeeding within 1 hr of birth and step 7 recommending the practice of rooming-in. The AAP clinical report on safe sleep and SSC in the newborn period both reviews the evidence supporting SSC and rooming-in during the newborn period, while addressing the safety concerns and providing suggestions to improve safety after delivery. The literature supporting SSC also emphasizes the importance that mother and baby should not be left unattended during this early period.

Diagnosis and Differential Diagnosis

The diagnosis of SUPC should be made only after other pathologic causes are excluded. One study consisting of 45 cases of unexpected collapse in newborns found that one third of infants had an underlying pathologic or clinical condition, such as sepsis, ductal dependent congenital heart disease, congenital diaphragmatic hernia, intracranial hemorrhage, or a metabolic disorder (1 infant with Zellweger syndrome and another infant with an unidentified metabolic disorder). Additional etiologies to consider include airway obstruction, pneumonia, respiratory distress syndrome, hypoglycemia, vascular thrombosis or embolism, and pulmonary hypertension of the newborn. The differential diagnosis of SUPC is broad, and many conditions overlap with the differential diagnoses for BRUE (Chapter 403), SUID, and SIDS.

For those infants who survive the event, testing to screen for an underlying pathology should be performed and tailored to the specific details of each case. A thorough history and physical exam should be performed prior to initiating the diagnostic workup to assist one in focusing the evaluation. Laboratory tests to consider include electrolytes; metabolic evaluation including glucose, ammonia, and lactate; an infectious evaluation including blood cultures, urinalysis, and urine cultures; and CSF analysis with CSF culture. Chest radiography, neuroimaging, echocardiogram, electrocardiogram, and comprehensive metabolic screening (included as part of the newborn screen in most states) could also be useful diagnostic tools. Postmortem examination in the case of death from presumed SUPC should also be considered because underlying etiology of the event may be discovered during autopsy.

Outcome

Approximately half of SUPC cases are thought to result in death. A review of 17 and 45 SUPC cases in Germany and United Kingdom showed a mortality rate of 42% and 27%, respectively. In the German study, almost two-thirds of the surviving cases had neurologic deficits, and in the United Kingdom study, one third of infants either died or had residual neurologic deficits. Rates of death and neurologic abnormalities reported in the 2 aforementioned studies are comparable with other available case reports.

Treatment

There are data suggesting that hypothermia treatment may improve neurologic outcomes after a SUPC event that results in hypoxic-ischemic encephalopathy (HIE) (see Chapter 120.4). The hypothermia treatment of 4 patients with HIE after SUPC were deemed successful, with follow-up at 24 mo having 3 children being developmentally normal and 1 child having mild cerebral palsy.

Prevention

The known risk factors for SUPC can be used to aid in preventive efforts. Specifically, safety during SSC and rooming-in should be emphasized.

Initiatives developed to standardize the procedure for immediate postnatal SSC have not proven to reduce the risk of SUPC. Frequent assessments of newborns should be performed, including observation of breathing, activity, color, tone, and position, to ensure they are in a position to avoid obstructive breathing or events leading to SUPC. It has also been suggested that continuous monitoring by trained staff members be done during SSC. However, that may be obtrusive to mother-infant bonding. Some have suggested continuous pulse oximetry during this period, but there is no evidence to support this practice and this overmonitoring could lead to unnecessary parental concern. Because many cases of SUPC occur within the 1st few hr of life, the delivery unit should be staffed to permit frequent newborn assessments, while preserving the developing mother-child bond.

Many of the same safety concerns that occur during SSC immediately after birth continue to be a concern during rooming-in, if mother is not given guidance on the safe rooming-in practices. Cosleeping should not be permitted on the postpartum unit. Mothers and families need to be informed of the risks of cosleeping. Staffing ratios should be determined to meet the needs of both mother and infant to allow for frequent assessments, rapid response time to call lights, and time for maternal education.

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CHAPTER 403

Brief Resolved Unexplained Events and Other Acute Events in Infants

Joel S. Tieder

Background

Infants commonly experience acute, self-resolving changes in their breathing, tone, mental status, and skin color. Usually these events are normal manifestations of developmental immaturity. Nonetheless, caregivers may worry that the acute event could have been life-threatening or is a sign of an undiagnosed medical problem and seek medical attention. In most cases, after a comprehensive history and physical examination, a clinician will determine the event to have been a benign or normal process, such as gastroesophageal reflux (GER) or periodic breathing of the newborn. At times, however, the event defies a simple explanation and drives uncertainty about risk from a serious underlying cause or a future event. This situation poses a diagnostic and management challenge for both the family and the clinician.

Historically, these events were feared as precursors to sudden infant death syndrome (SIDS) and were referred to as *near-miss SIDS* , *aborted crib deaths* , or *apparent life-threatening events (ALTEs)* . These terms have been replaced because we now know that these events are not associated with SIDS and are rarely life-threatening. Clinical use of ALTE as a diagnostic term is additionally problematic because it relies on the subjective interpretation of the caregiver and includes a nonspecific constellation of symptoms. It also does not distinguish well-appearing patients from those with symptoms.

Most of these acute events in infants are best described as brief resolved unexplained events (BRUEs). A BRUE is a diagnosis of exclusion and should be used only when the event is transient and remains unexplained after an appropriate medical evaluation.

Definition

A BRUE (pronounced *brew*) is an event that occurs in an infant younger than 1 yr that typically lasts less than 30 sec and is described by the observer as a sudden, brief, and now-resolved episode that involved at least one of the following:

- cyanosis or pallor
- absent, decreased, or irregular breathing
- marked change in tone, either hyper- or hypotonia
- altered level of responsiveness

The diagnosis of BRUE applies only to infants who were asymptomatic prior to the event and during evaluation, and when no explanation for the event is found through appropriate history and physical examination.

Infants who experience a BRUE are categorized as either lower or higher risk for a subsequent event or a serious underlying disorder based on patient factors, characterization of the event, additional historical factors, and the physical examination.

A lower-risk infant is defined as

- age >60 days
- gestational age ≥32 wk and postconceptional age ≥45 wk
- occurrence of only 1 BRUE (no prior BRUE ever and not occurring in a cluster)
- duration of event <1 min
- no cardiopulmonary resuscitation (CPR) by trained medical provider required
- no concerning historical features
- no concerning physical examination finding

Epidemiology

The incidence of BRUEs is unknown. However, studies of ALTE patients provide some insight because BRUEs are a subset of what had been considered ALTEs. Hospitalization for an ALTE was common; 1 out of every 2.5-9.4/1,000 infants was hospitalized for an ALTE. Acute events that do not lead to hospitalization are even more common according to large epidemiologic studies of healthy infants. Of normal infants followed longitudinally with home monitoring, up to 43% had a 20-sec apnea episode over a 3-mo period. Of parents asked when their infant was 1 yr of age, 5% recalled an apneic event.

BRUEs are not precursors to SIDS . The incidence of mortality after a BRUE from an underlying cause is unknown but is also likely to be extremely uncommon. The few reports of mortality in studies of ALTE are limited to patients who would not qualify as a BRUE because of the presence of other symptoms or an explanatory diagnosis.

However, for patients presenting with a BRUE, numerous risks must be considered. First is the risk of an underlying serious diagnosis. Although each is rare, clinicians must consider a wide variety of illnesses, such as cardiac arrhythmias, metabolic disorders, and brain injury (Table 403.1). The risk for an underlying serious diagnosis in patients with a BRUE is much lower than the rate reported in ALTE research, where many of the patients had underlying conditions or ongoing symptoms (e.g., lower respiratory tract infection). In infants meeting lower-risk criteria, the likelihood of an underlying serious cause is extremely low. In higher-risk infants, the likelihood is unknown but probably much lower than suggested by research on ALTEs. Second is the risk of a recurrent event, which is currently unknown. These events can be stressful for caregivers, particularly when the cause is unknown. Third is the risk that the caregivers become unnecessarily concerned about their healthy child. Clinicians should be aware the challenges caregivers face when perceiving a threat of losing their child, there is medical uncertainty, or when their child is hospitalized. Fourth are the risks associated with medical care, such as nosocomial infections and inaccurate testing.

Table 403.1

Symptom-Based Approach to BRUEs: Possible and Other Conditions That Might Be Confused With BRUE

DIAGNOSTIC CATEGORIES	COMMON AND/OR CONCERNING CAUSES TO CONSIDER	SUGGESTIVE HISTORICAL FINDINGS	SUGGESTIVE PHYSICAL EXAMINATION FINDINGS	TESTING TO CONSIDER
Gastrointestinal	GER Intussusception Volvulus Oropharyngeal dysphagia	Coughing, vomiting, choking, gasping temporally related to feeds or regurgitation of gastric contents Feeding difficulties Recent preceding feed Irritability following feeds Milk in mouth/nose Bilious emesis Pulling legs to chest Bloody/mucousy stool Lethargy following event	Gastric contents in the nose and mouth Choking, gagging, or oxygen desaturation temporally related to feeding or regurgitation of gastric contents	Upper GI to assess for anatomic anomalies Clinical swallow evaluation Abdominal ultrasound pH probe
Infectious	Upper and lower respiratory tract infection (RSV, pertussis, pneumonia) Bacteremia Meningitis Urinary tract infection	Preceding URI symptoms Multiple events on the day of presentation Sick exposures Foul-smelling urine	Fever/hypothermia Lethargy Ill appearance Coryza Cough Wheeze Tachypnea	NP swab for RSV, pertussis Chest radiograph CBC and blood culture Cerebrospinal fluid analysis and culture Urinalysis and culture
Neurologic	Seizures Breath holding spells Congenital central hypoventilation syndrome Neuromuscular disorders Congenital malformations of the brain and brainstem Malignancy Intracranial hemorrhage	Multiple events Loss of consciousness Change in tone Abnormal muscular movements Eye deviation Preceding triggers	Papilledema Abnormal muscular movements Hypertonicity or flaccidity Abnormal reflexes Micro- or macrocephaly Dysmorphic features Signs of trauma or poisoning (see “Child maltreatment” below)	EEG Neuroimaging
Respiratory/ENT	Apnea of	Prematurity	Wheezing	Chest radiograph

	prematurity Apnea of infancy Periodic breathing Airway anomaly Aspiration Foreign body Obstructive sleep apnea	Foreign body Aspiration Noisy breathing	Stridor Crackles Rhonchi Tachypnea	Neck radiograph Laryngoscopy Bronchoscopy Esophagoscopy Polysomnography
Child maltreatment	Nonaccidental head trauma Smothering Poisoning Factitious syndrome (formerly Munchausen syndrome) by proxy	Multiple events Unexplained vomiting or irritability Recurrent BRUEs Historical discrepancies Family history of unexplained death, SIDS, or BRUEs Single witness of event Delay in seeking care	Bruising (especially in a nonmobile child) Ear trauma, hemotympanum Acute abdomen Painful extremities Oral bleeding/trauma Frenulum tears Unexplained irritability Retinal hemorrhages Depressed mental status	Skeletal survey Computed tomography/MRI of the head Dilated funduscopic examination if head imaging concerning for trauma Toxicology screen Social work evaluation
Cardiac	Dysrhythmia (prolonged QT syndrome, Wolff-Parkinson-White syndrome) Cardiomyopathy Congenital heart disease Myocarditis	Feeding difficulties Growth difficulties Diaphoresis Prematurity	Abnormal heart rate/rhythm Murmur Decreased femoral pulses	Four-extremity blood pressure Pre- and postductal oxygen saturation measurements ECG Echocardiogram Serum electrolytes, calcium, magnesium
Metabolic/genetic	Hypoglycemia Inborn errors of metabolism Electrolyte abnormalities Genetic syndromes including those with craniofacial malformations	Severe initial event Multiple events Event associated with period of stress or fasting Developmental delay Associated anomalies Growth difficulties Severe/frequent illnesses Family history of BRUE, consanguinity, seizure disorder,	Dysmorphic features Microcephaly Hepatomegaly	Serum electrolytes; glucose, calcium, and magnesium levels Lactate Ammonia Pyruvate Urine organic and serum amino acids Newborn screen

		or SIDS		

BRUE , Brief resolved unexplained event; *ECG* , electrocardiogram; *EEG* , electroencephalogram; *ENT* , ear, nose, and throat; *GER* , gastroesophageal reflux; *GI* , gastrointestinal; *NP* , nasopharyngeal; *RSV* , respiratory syncytial virus; *SIDS* , sudden infant death syndrome; *URI* , upper respiratory infection.

From Kliegman RK, Lye PS, Bordini BJ, et al: *Nelson pediatric symptom-based diagnosis* , Philadelphia, 2018, Elsevier. Table 5.3.

Initial History

An appropriate history and physical examination are key to evaluating an infant who has experienced an acute event (Table 403.2). Attention should be given to characterizing the event and interpreting the subjective experience of the caregiver to provide an objective description. The following questions can guide this process:

Table 403.2

Important Historical Features of a BRUE

PREEVENT	
Condition of child	Awake vs. asleep
Location of child	Prone vs. supine, flat or upright, in crib/car seat, with pillows, blankets
Activity	Feeding, crying, sleeping
EVENT	
Respiratory effort	None, shallow, gasping, increased Duration of respiratory pauses
Color	Pallor, red, cyanotic Peripheral, whole body, circumoral, lighting of room
Tone/movement	Rigid, tonic-clonic, decreased, floppy Focal vs. diffuse Ability to suppress movements
Level of consciousness	Alert, interactive, sleepy, nonresponsive
Duration	Time until normal breathing, normal tone, normal behavior Detailed history of caregiver actions during event to aid in defining time course
Associated symptoms	Vomiting, sputum production, blood in mouth/nose, eye rolling
POSTEVENT	
Condition	Back to baseline, sleepy, postictal, crying If altered after event, duration of time until back to baseline
INTERVENTIONS	
What was performed	Gentle stimulation, blowing in face, mouth-to-mouth, cardiopulmonary resuscitation
Who performed intervention	Medical professional vs. caregiver
Response to intervention	Resolution of event vs. self-resolving

Duration of intervention	How long was intervention performed
MEDICAL HISTORY	
History of present illness	Preceding illnesses, fever, rash, irritability, sick contacts
Past medical history	Prematurity, prenatal exposures, gestational age, birth trauma Noisy breathing since birth Any medical problems, prior medical conditions, prior hospitalizations Developmental delay Medications
Feeding history	Gagging, coughing with feeds, poor weight gain
Family history	Neurologic problems Cardiac arrhythmias Sudden death, childhood deaths, BRUEs Neonatal problems Consanguinity
Social history	Home situation Caregivers Smoke exposure Medications in the home

BRUE , Brief resolved unexplained event.

From Kliegman RK, Lye PS, Bordini BJ, et al: *Nelson pediatric symptom-based diagnosis* , Philadelphia, 2018, Elsevier. Table 5.4.

What was the infant doing before, during, and after the event? An event occurring during or after feeding will likely have a different explanation than one occurring during sleep or after crying. The sequence of events can also be diagnostic. A **breath holding spell** begins with crying, followed by a period of apnea, perioral cyanosis, change of consciousness, and return to baseline.

Did the infant change color? It is often normal for infants to have blueish discoloration (**perioral cyanosis or acrocyanosis**) around the lips or hands because of circulatory immaturity. Turning red or purple is also common when infants cry or become upset. The clinician's goal is to distinguish less concerning color change from **central cyanosis** , which is blue discoloration of the face, trunk, gums, or tongue that can indicate hypoxemia.

Did the infant experience central or obstructive apnea, or just choking or gagging? It is normal for infants to exhibit respiratory pauses of up to 20 sec while awake and asleep. These can reflect **periodic breathing of the newborn** or normal REM sleep. Much more concerning are periods of no air movement that last longer than 20 sec. **Obstructive apnea** results in paradoxical movement of the diaphragm and upper airway. In infants, this is most commonly caused by upper and lower respiratory tract infections (e.g., bronchiolitis) and may precede the recognition of symptoms typically seen in viral respiratory infections. Infants also commonly gag or choke briefly during or shortly after feeds or with GER or vomiting. The resulting reflexive pause in respiration to protect the airway is sometimes referred to as **laryngospasm** . **Central apnea** is always concerning and occurs when the brainstem does not properly control the respiratory muscles. This may be seen in brain trauma from **non-accidental trauma** and in rare disorders such as **congenital central hypoventilation syndrome** .

Was there a concerning change in muscle tone? Seizures in infants are concerning and difficult to diagnose, and they rarely present as typical seizure activity. They can present as staring spells, periods of episodic increased or decreased tone, or **infantile spasms** . It is normal for infants to have rapid jerking movements because of neurological immaturity and infant reflexes (e.g., Moro, startle, and fencing reflex), and sometimes these can appear similar to seizures. One of the most serious and time-sensitive causes of seizures or central apnea is undiagnosed brain trauma from non-accidental trauma, which may result in no other symptoms or physical examination findings upon presentation.

Was there an altered level of responsiveness? Episodic changes in consciousness and mental status can be difficult to assess in infants because of neurological immaturity and variability in sleep-wake cycles. However, abrupt changes where the infant appears to lose consciousness after episodes of apnea or color change can be concerning for hypoxemia, hypoglycemia, or seizures.

Did the event self-resolve, or was an intervention required? Infants with choking from GER, vomit, or feeding difficulties generally improve spontaneously or with help clearing the airway. A serious underlying cause is more likely if CPR was indicated and then provided, though this may be difficult to assess if no medically trained individuals witnessed the event.

Additional History

A careful, detailed history can lead to an explanation; the key elements are summarized in Tables 403.1 and 403.2 . A clinician should inquire about other symptoms (e.g., fever, upper respiratory infection [URI] symptoms, spitting up). A history of breathing problems, prenatal or perinatal concerns, prematurity, and growth and developmental problems is important. Premature infants, particularly those still under 43 wk after correcting for gestational age, are at higher risk for underlying causes, such as apnea of prematurity. A careful feeding history can detect oropharyngeal dysphagia or GER-related problems (i.e., laryngospasm).

A targeted family history can reveal risk for sudden death, cardiac arrhythmias, and metabolic, genetic, and neurologic disease.

A social history, particularly by someone trained to detect non-accidental trauma, can reveal recent trauma, prior child welfare involvement, substance abuse, poisoning or misuse of medications, and environmental exposures (e.g., second-hand smoke and mold). It is important to understand who observed the event, who normally takes care of the infant, and if there are any discrepancies in the explanation of the event.

Consider infectious exposures. Infants exposed to underimmunized family members are at risk for pertussis. Respiratory syncytial virus (RSV) and other respiratory viruses, as well as pertussis, and can present with apnea prior to the onset of URI symptoms.

Physical Examination

A careful physical examination may reveal a causative or underlying diagnosis. Abnormal growth and head circumference may reflect feeding, developmental, and neurological problems. Abnormal vital signs and pulse oximetry can suggest infectious, cardiac, and neurological abnormalities. A careful skin and mouth examination can reveal subtle signs. For example, child abuse should be suspected in infants with bruises, petechiae, or a torn frenulum. Signs of airway abnormalities, such as inspiratory or expiratory stridor or stertor, can lead to diagnosis of respiratory infections, vascular rings, hemangioma, laryngomalacia, tracheomalacia, or facial dysmorphism.

Testing

In the past, it was common for clinicians to routinely test infants presenting with such events using complete blood counts (CBC), appropriate cultures, and GER testing. However, it is known that these tests are unlikely to reveal a cause and even more likely to lead to a false positive result. False positives can, in turn, contribute to missed diagnoses, additional unnecessary testing, patient harm, greater parental concern, and increased costs.

In lower-risk infants, routine laboratory testing and diagnostic imaging (CBC, bacterial cultures, blood gas and glucose, metabolic panels, urinalysis, GER testing, chest radiograph, neuroimaging, electroencephalogram [EEG], sleep study) is not recommended. *The few situations where testing may be considered in the lower-risk population include:*

- *Pertussis* testing in underimmunized or exposed individuals

◆ ECG may reveal a prolonged QtC syndrome, particularly when there is a concerning family history.

◆ Rapid viral testing can help diagnose subclinical viral causes, but these tests can be positive from recent past infections that may not be the cause of the concerning event.

◆ A brief period of continuous pulse oximetry and serial observations to detect hypoxemia and apnea

In higher-risk infants, routine screening tests may not be needed. Testing should be done due to concerns from the history and physical, or to further characterize repeat BRUEs.

◆ Continuous pulse oximetry or cardiorespiratory monitoring under a period of observation may help characterize repeat events.

◆ A swallow evaluation by a trained feeding expert might reveal oropharyngeal dysphagia in premature or young infants.

◆ Head imaging with CT or MRI is indicated when there is suspicion of non-accidental trauma due to bruising in nonambulatory infants, concerning bruising patterns, history of unexplained death in a sibling, or inconsistent history of event.

◆ Neurology consult or EEG or head imaging may lead to a diagnosis of epilepsy if there is a concern for seizure. However, it is reasonable to perform this consultation and testing as an outpatient in well-appearing infants.

◆ Otolaryngology consultation to detect anatomic disorders of the airway (e.g., laryngomalacia, tracheomalacia, and tracheoesophageal fistula)

◆ Pulmonary/sleep medicine consultation to detect disordered breathing (e.g., central apnea and obstructive sleep apnea)

Management

Although the value of hospital admission is debatable, lower-risk infants are much less likely to benefit from admission compared to higher-risk infants. For all BRUEs, it is uncommon for a hospital admission to lead to a diagnosis of a serious underlying disorder. Sometimes, however, a longer period of observation than is practical in a clinic or emergency department can help characterize repeat events, should they recur, and reduce the uncertainty of a recurrent event for parents. Additional benefits of hospitalization include serial assessments of feeding, breathing, sleep, and social patterns. *The decision for hospital admission should incorporate the needs and preferences of the family and patient, and the ability to follow-up closely with a primary care physician* . In weighing the risks and benefits of this decision, it is important to recognize that hospitalization can unnecessarily increase stress for the family and patient through false alarms and iatrogenic complications. CPR education should be considered for all families. Home apnea monitoring should not be done. Close outpatient follow-up with a primary care physician is important to monitor for repeat events and caregiver support.

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SECTION 2

Disorders of the Respiratory Tract

OUTLINE

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Chapter 405 Acquired Disorders of the Nose

Chapter 406 Nasal Polyps

Chapter 407 The Common Cold

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Chapter 409 Acute Pharyngitis

Chapter 410 Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

Chapter 411 Tonsils and Adenoids

Chapter 412 Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis)

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CHAPTER 404

Congenital Disorders of the Nose

Joseph Haddad Jr, Sonam N. Dodhia

Normal Newborn Nose

In contrast to children and adults who preferentially breathe through their nose unless nasal obstruction interferes, most newborn infants are obligate nasal breathers. Significant nasal obstruction presenting at birth, such as choanal atresia, may be a life-threatening situation for the infant unless an alternative to the nasal airway is established. Nasal congestion with obstruction is common in the 1st year of life and can affect the quality of breathing during sleep; it may be associated with a narrow nasal airway, viral or bacterial infection, enlarged adenoids, or maternal estrogenic stimuli similar to rhinitis of pregnancy. The internal nasal airway doubles in size in the 1st 6 mo of life, leading to resolution of symptoms in many infants. Supportive care with a bulb syringe and saline nose drops, topical nasal decongestants, and antibiotics, when indicated, improve symptoms in affected infants.

Physiology

The nose is responsible for the initial warming and humidification of inspired air and olfaction. In the anterior nasal cavity, turbulent airflow and coarse hairs enhance the deposition of large particulate matter; the remaining nasal airways filter out particles as small as 6 µm in diameter. In the turbinate region, the airflow becomes laminar and the airstream is narrowed and directed superiorly, enhancing particle deposition, warming, and humidification. Nasal passages contribute as much as 50% of the total resistance of normal breathing. Nasal flaring, a sign of respiratory distress, reduces the resistance to inspiratory airflow through the nose and can improve ventilation (see Chapter 400).

Although the nasal mucosa is more vascular (especially in the turbinate region) than in the lower airways, the surface epithelium is similar, with ciliated cells, goblet cells, submucosal glands, and a covering blanket of mucus. The nasal secretions contain lysozyme and secretory immunoglobulin A (IgA), both of which have antimicrobial activity, and IgG, IgE, albumin, histamine, bacteria, lactoferrin, and cellular debris, as well as mucous glycoproteins, which provide viscoelastic properties. Aided by the ciliated cells, mucus flows toward the nasopharynx, where the airstream widens, the epithelium becomes squamous, and secretions are wiped away by swallowing. Replacement of the mucous layers occurs about every 10-20 min. Estimates of daily mucus production vary from 0.1 to 0.3 mg/kg/24 hr, with most of the mucus being produced by the submucosal glands.

Congenital Disorders

Congenital *structural nasal malformations* are uncommon compared with acquired abnormalities. The nasal bones can be congenitally absent so that the bridge of the nose fails to develop, resulting in *nasal hypoplasia.* Congenital absence of the nose *(arhinia),* complete or partial duplication, or a single centrally placed nostril can occur in isolation but is usually part of a malformation syndrome. Rarely, *supernumerary teeth* are found in the nose, or teeth grow into it from the maxilla.

Nasal bones can be sufficiently malformed to produce severe narrowing of the nasal passages. Often, such narrowing is associated with a high and narrow hard palate. Children with these defects can have significant obstruction to airflow during infections of the upper airways and are more susceptible to the development of chronic or recurrent hypoventilation (see Chapter 31). Rarely, the alae nasi are sufficiently thin and poorly supported to result in inspiratory obstruction, or there may be congenital nasolacrimal duct obstruction with cystic extension into the nasopharynx, causing respiratory distress.

Choanal Atresia

This is the most common congenital anomaly of the nose and has a frequency of approximately 1 in 7,000 live births. It consists of a unilateral or bilateral bony (90%) or membranous (10%) septum between the nose and the pharynx; most cases are a combination of bony and membranous atresia. The pathogenesis is unknown, but theories include persistence of the buccopharyngeal membranes or failure of the oronasal membrane to rupture. The unilateral defect is more common and the female:male ratio is approximately 2 : 1. Approximately 50–70% of affected infants have other congenital anomalies (CHARGE syndrome [see later], Treacher-Collins, Kallmann syndrome, VATER [vertebral defects, imperforate anus, tracheoesophageal fistula, and renal defects] association, Pfeiffer syndrome), with the anomalies occurring more often in bilateral cases.

The **CHARGE syndrome** (*c* oloboma, *h* eart disease, *a* tresia or stenosis of the choanae, *r* etarded growth and development or central nervous system (CNS) anomalies or both, *g* enital anomalies or hypogonadism or both, and *e* ar [external, middle, inner ear] anomalies or deafness or both) is one of the more common anomalies associated with choanal atresia—approximately 10–20% of patients with choanal atresia have it. The CNS involvement (~90%) includes reduced function of cranial nerves I, V, VII, VIII, IX, and X, as well as vision and hearing deficits. Most (~90%) patients with CHARGE syndrome have autosomal dominant de novo mutations in the *CHD7* gene, which is involved in chromatin organization. Immunologic deficiencies may be noted that overlap with the 22q11.2 deletion syndrome.

Clinical Manifestations

Newborn infants have a variable ability to breathe through their mouths, so nasal obstruction does not produce the same symptoms in every infant. When the obstruction is unilateral, the infant may be asymptomatic for a prolonged period, often until the first respiratory infection, when unilateral nasal discharge or persistent nasal obstruction can suggest the diagnosis. Infants with bilateral choanal atresia who have difficulty with mouth breathing make vigorous attempts to inspire, often suck in their lips, and develop cyanosis. Distressed children then cry (which relieves the cyanosis) and become calmer, with normal skin color, only to repeat the cycle after closing their mouths. Those who are able to breathe through their mouths at once experience difficulty when sucking and swallowing, becoming cyanotic when they attempt to feed.

Diagnosis

Diagnosis is established by the inability to pass a firm catheter through each nostril 3-4 cm into the nasopharynx. The atretic plate may be seen directly with fiberoptic rhinoscopy. The anatomy is best evaluated by using high-resolution CT (Fig. 404.1).

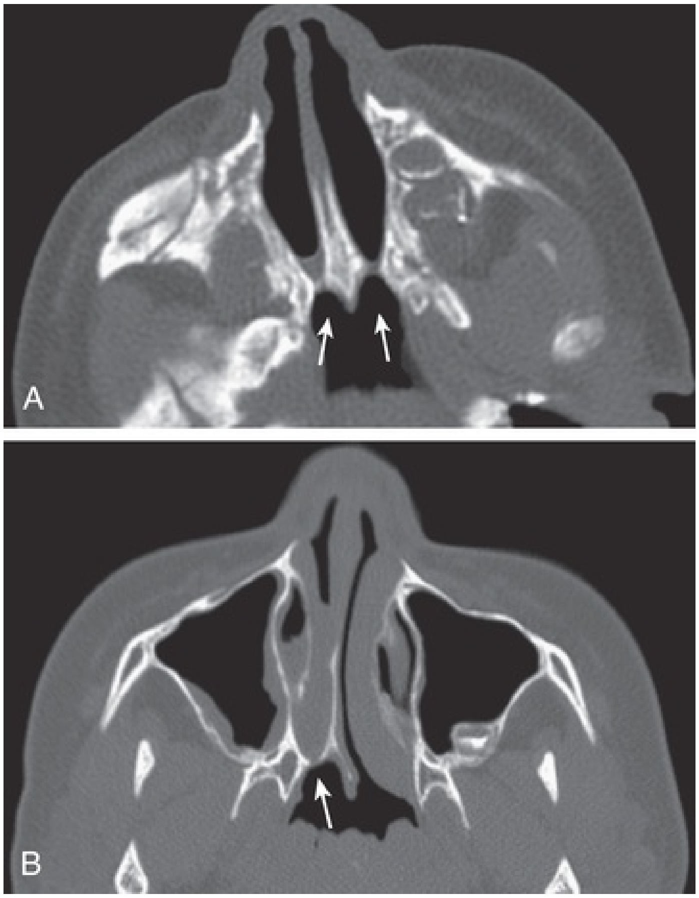

FIG. 404.1 **Choanal atresia. A, Axial CT image in a 1 day old neonate with severe respiratory distress shows bilateral bony choanal atresia with retained fluid in the right nasal cavity, medial bowing of the lateral nasal wall, and a thickened vomer *(arrows)* . B, Axial CT image in a 12 yr old child with chronic nasal obstruction and purulent rhinorrhea shows unilateral *(right)* bony atresia with fluid in the nasal cavity *(arrow)* . (From Coley BD (ed): *Caffey's pediatric diagnostic imaging,* ed 12,vol 1, Philadelphia, 2013, Saunders, Fig. 8.13.)**

Treatment

Initial treatment consists of prompt placement of an oral airway, maintaining the mouth in an open position, or intubation. A standard oral airway (such as that used in anesthesia) can be used, or a feeding nipple can be fashioned with large holes at the tip to facilitate air passage. Once an oral airway is established, the infant can be fed by gavage until breathing and eating without the assisted airway is possible. In bilateral cases, intubation or, less often, tracheotomy may be indicated. If the child is free of other serious medical problems, operative intervention is considered in the neonate; transnasal repair is the treatment of choice, with the introduction of small magnifying endoscopes and smaller surgical instruments and drills. Stents are usually left in place for weeks after the repair to prevent closure or stenosis, although a large meta-analysis demonstrated that there is no benefit to stenting. Another option is a transpalatal repair, and this is done when a transnasal endoscope cannot be placed through the nose due to thick bony atresia or stenosis. Tracheotomy should be considered in cases of bilateral atresia in which the child has other potentially life-threatening problems and in whom early surgical repair of the choanal atresia may not be appropriate or feasible. Operative correction of unilateral obstruction may be deferred for several years. In both unilateral and bilateral cases, restenosis necessitating dilation or reoperation, or both, is common. Mitomycin C has been used to help prevent the development of granulation tissue and stenosis, although its efficacy is questionable.

Congenital Defects of the Nasal Septum

Perforation of the septum is most commonly acquired after birth secondary to infection, such as syphilis or tuberculosis, or trauma; rarely, it is developmental. Continuous positive airway pressure cannulas are a cause of iatrogenic perforation. Trauma from delivery is the most common cause of septal deviation noted at birth. When recognized early, it can be corrected with immediate realignment using blunt probes, cotton applicators, and topical anesthesia. Formal surgical correction, when required, is usually postponed to avoid disturbance of midface growth.

Mild septal deviations are common and usually asymptomatic; abnormal formation of the septum is uncommon unless other malformations are present, such as cleft lip or palate.

Congenital isolated absence of a membranous nasal septum has also been reported.

Pyriform Aperture Stenosis

Infants with this bony abnormality of the anterior nasal aperture present at birth or shortly thereafter with severe nasal obstruction leading to noisy breathing and respiratory distress that worsen with feeding and improve with crying. It can occur in isolation or in association with other malformations including holoprosencephaly, hypopituitarism, and cardiac and urogenital malformations. Diagnosis is made by CT of the nose (Fig. 404.2) with a pyriform aperture width less than ~11 mm. Medical management (nasal decongestants, humidification, nasopharyngeal airway insertion, management of reflux) is typically attempted for about 2 wk; if the child still cannot feed or breathe without difficulty, then surgical repair by means of an anterior, sublabial approach may be needed. A drill is used to enlarge the stenotic anterior bone apertures.

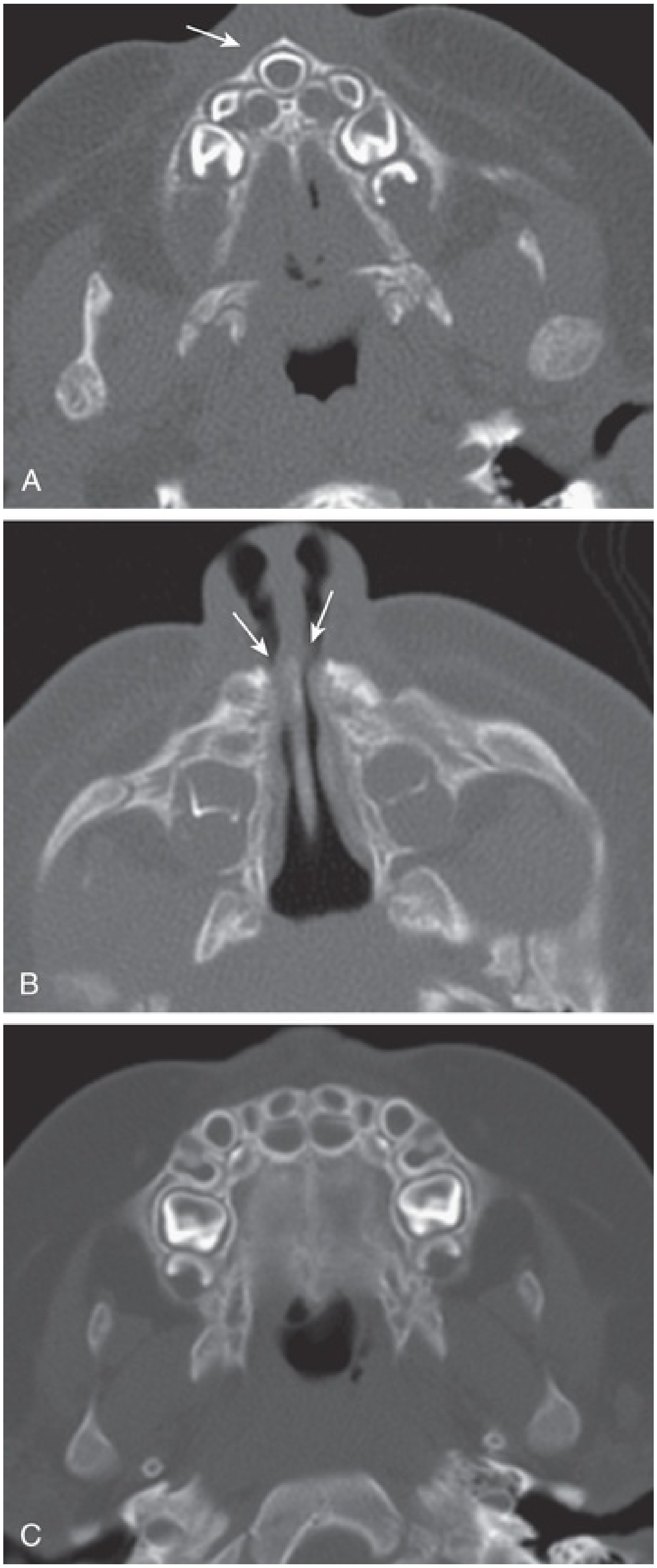
A
B
C

FIG. 404.2 **Congenital nasal pyriform aperture stenosis in a 1½ mo old infant with episodes of respiratory distress during breastfeeding. A, Axial CT image shows a triangular hard palate and solitary central maxillary mega-incisor *(arrow)* . B, An axial CT image shows narrowing of the anterior and inferior nasal passages *(arrows).* C, Normal infant maxilla for comparison. (From Coley BD (ed): *Caffey's pediatric diagnostic imaging,* ed 12, vol 1, Philadelphia, 2013, Saunders, Fig. 8.14.)**

Congenital Midline Nasal Masses

Dermoids, gliomas, and *encephaloceles* (in descending order of frequency) occur intranasally or extranasally and can have intracranial connections or extend intracranially with communication to the subarachnoid space. The theory for the embryologic development of congenital midline nasal masses is faulty retraction of the dural diverticulum. Dermoids and epidermoids are the most common type of congenital midline nasal mass and have been reported to represent up to 61% of lesions. Nasal dermoids are firm, noncompressible, and painless, and often have a dimple or pit on the nasal dorsum (sometimes with hair being present). They can predispose to intracranial infections if an intracranial fistula or sinus is present, although recurrent infection of the dermoid itself is more common; given the risk for serious infection, surgical excision is always indicated for nasal dermoids. Gliomas or heterotopic brain tissue are firm, whereas encephaloceles are soft and enlarge with crying or the Valsalva maneuver. Diagnosis is based on physical examination findings and results from imaging studies. CT provides the best bony detail, but magnetic resonance imaging (MRI) is also helpful because of its superior ability to define intracranial extension (Fig. 404.3). Surgical excision of these masses is generally required, with the extent and surgical approach based on the type and size of the mass.

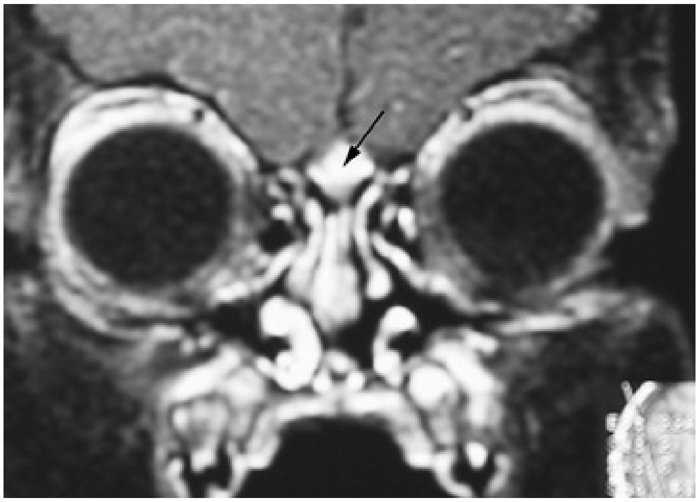

FIG. 404.3 **Coronal CT scan of nasal dermoid with intracranial extension *(arrow)* . (From Manning SC, Bloom DC, Perkins JA, et al: Diagnostic and surgical challenges in the pediatric skull base, *Otolaryngol Clin North Am* 38:773–794, 2005, Fig. 2.)**

Other nasal masses include *hemangiomas, congenital nasolacrimal duct obstruction* (which can occur as an intranasal mass) (Fig. 404.4), nasal polyps, and tumors such as rhabdomyosarcoma (see Chapter 527). Nasal polyps are rarely present at birth, but the other masses often present at birth or in early infancy (see Chapter 406).

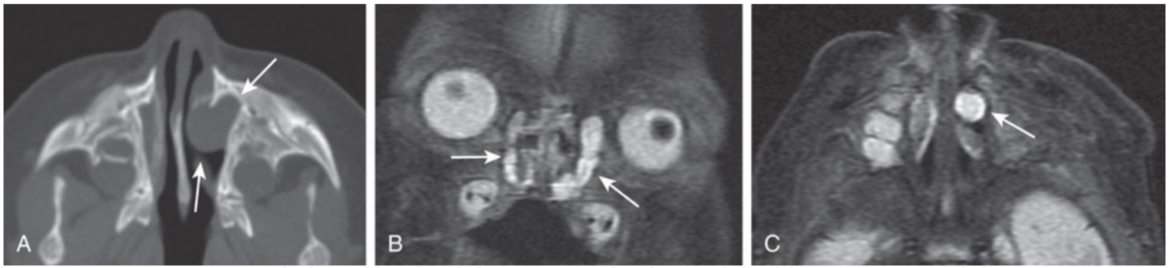

FIG. 404.4 **Congenital nasolacrimal duct mucoceles in a 1 day old neonate. A, Axial CT image shows a left nasal round soft tissue mass with enlargement of the ipsilateral nasolacrimal duct and canal *(arrows)* . B and C, Coronal and axial fast spin echo inversion recovery MR images show bilateral cystic enlargement of the nasolacrimal sacs and ducts *(arrows)* . (From Coley BD (ed): *Caffey's pediatric diagnostic imaging,* ed 12, vol 1, Philadelphia, 2013, Saunders, Fig. 8.15, p. 78.)**

Poor development of the paranasal sinuses and a narrow nasal airway are associated with recurrent or chronic upper airway infection in Down syndrome (see Chapter 98.2).

Diagnosis and Treatment

In children with congenital nasal disorders, supportive care of the airway is given until the diagnosis is established. Diagnosis is made through a combination of flexible scoping and imaging studies, primarily CT scan. In the case of surgically correctable congenital problems such as choanal atresia, surgery is performed after the child is deemed healthy and free of life-threatening problems such as congenital heart disease.

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CHAPTER 405

Acquired Disorders of the Nose

Joseph Haddad Jr, Sonam N. Dodhia

Tumors, septal perforations, and other acquired abnormalities of the nose and paranasal sinuses can manifest with epistaxis. Midface trauma with a nasal or facial fracture may also be accompanied by epistaxis. Trauma to the nose can cause a *septal hematoma;* if treatment is delayed, this can lead to necrosis of septal cartilage and a resultant *saddle nose deformity.* Other abnormalities that can cause a change in the shape of the nose and paranasal bones, with obstruction but few other symptoms, include *fibroosseous lesions* (ossifying fibroma, fibrous dysplasia, cementifying fibroma) and *mucoceles of the paranasal sinuses.* These conditions may be suspected on physical examination and confirmed by CT scan and biopsy. Although these are considered benign lesions, they can all greatly change the anatomy of surrounding bony structures and often require surgical intervention for management.

405.1

Nasal Foreign Bodies

Joseph Haddad Jr, Sonam N. Dodhia

Keywords

foreign body
bromhidrosis
mother's kiss
Katz catheter
disk batteries
magnet

Etiology

Foreign bodies (food, beads, crayons, small toys, erasers, paper wads, buttons, batteries, beans, stones, pieces of sponge, and other small objects) are often placed in the nose by young or developmentally delayed children and constitute ≤1% of pediatric emergency department visits. Nasal foreign bodies can go unrecognized for long periods of time because they initially produce few symptoms and are difficult to visualize. First symptoms include unilateral obstruction, sneezing, relatively mild discomfort, and, rarely, pain. Presenting clinical symptoms include history of insertion of foreign bodies (86%), mucopurulent nasal discharge (24%), foul nasal odor (9%), epistaxis (6%), nasal obstruction (3%), and mouth breathing (2%). Irrigation results in mucosal swelling because some foreign bodies are hygroscopic and increase in size as water is absorbed; signs of local obstruction and discomfort can increase with time. The patient might also present with a generalized body odor known as *bromhidrosis.*

Diagnosis

Unilateral nasal discharge and obstruction should suggest the presence of a foreign body, which can often be seen on examination with a nasal speculum or wide otoscope placed in the nose. Purulent secretions may have to be cleared so that the foreign object can actually be seen; a headlight, suction, and topical decongestants are often needed. The object is usually situated anteriorly, but unskilled attempts at removal can force the object deeper into the nose. A long-standing foreign body can become embedded in granulation tissue or mucosa and appear as a nasal mass. A lateral skull radiograph assists in diagnosis if the foreign body is metallic or radiopaque or if foreign body is suspected but physical exam with sinus endoscopy or anterior rhinoscopy is negative.

Treatment

An initial examination of the nose is made to determine if a foreign body is present and whether it needs to be removed emergently. Planning is then made for office or operating room extrication of the foreign body. Prompt removal minimizes the danger of aspiration and local tissue necrosis, and this can usually be performed with the aid of topical anesthesia, with forceps or nasal suction. Common noninvasive techniques include simple nose blowing and the “mother's kiss” technique. The “mother's kiss” approach has been successful in acute situations where a person occludes the unaffected nostril and then, with a complete seal over the child's mouth, attempts to dislodge the foreign body by blowing into the mouth. A similar approach uses an Ambu bag over the mouth with the unaffected nostril occluded. Other noninvasive options include blowing air into a drinking straw in a child's mouth and applying high flow oxygen (10-15 L/min) to the unaffected nostril. Alternatively, a Katz catheter (made specifically for the removal of foreign bodies from the nose and ear) can be inserted above and distal to the object, inflated, and drawn back with gentle traction. If there is marked swelling, bleeding, or tissue overgrowth, general anesthesia may be needed to remove the object. Infection usually clears promptly after the removal of the object, and generally no further therapy is necessary. Magnets can be used to extract metal foreign bodies, 2% lidocaine can be used to kill live insects before removal, and irrigation should be avoided with vegetable matter or sponges because of the risk of foreign body swelling. Age (>5) and disk-shaped foreign body are predictors for operating room removal of foreign body.

Complications

Serious complications include posterior dislodgement and aspiration, trauma caused by the object itself or removal attempts, infection, and choanal stenosis. Infection is common and gives rise to a purulent, malodorous, or bloody discharge. Local tissue damage from long-standing foreign body, or alkaline injury from a disk battery, can lead to local tissue loss and cartilage destruction. A synechia or scar band can then form, causing nasal obstruction. Loss of septal mucosa and cartilage can cause a septal perforation or saddle nose. Disk batteries are especially dangerous when placed in the nose; they leach base, which causes pain and local tissue destruction in a matter of hours. Magnets also carry a risk of septal perforation and necrosis.

Tetanus is a rare complication of long-standing nasal foreign bodies in nonimmunized children (see Chapter 238). Toxic shock syndrome is also rare and most commonly occurs from nasal surgical packing (see Chapter 208.2); oral antibiotics should be administered when nasal surgical packing is placed.

Prevention

Tempting objects, such as round, shiny beads, should be used only under adult supervision. Disk batteries should be stored away from the reach of small children.

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405.2

Epistaxis

Joseph Haddad Jr, Sonam N. Dodhia

Keywords

Kiesselbach plexus
juvenile nasal angiofibroma
hereditary hemorrhagic telangiectasia
silver nitrate
cautery

Although rare in infancy, nosebleeds are common in children between the ages of 3 and 8, then decline in incidence after puberty. They are also more common during winter months. Diagnosis and treatment depend on the location and cause of the bleeding.

Anatomy

The most common site of bleeding is the Kiesselbach plexus, an area in the anterior septum where vessels from both the internal carotid (anterior and posterior ethmoid arteries) and external carotid (sphenopalatine and terminal branches of the internal maxillary arteries) converge. The thin mucosa in this area, as well as the anterior location, make it prone to exposure to dry air and trauma.

Etiology

Epistaxis can be classified as primary (idiopathic; majority of cases) or secondary based on cause, and this has implications for diagnosis and management. Common causes of secondary nosebleeds from the anterior septum include digital trauma, foreign bodies, dry air, and inflammation, including upper respiratory tract infections, sinusitis, and allergic rhinitis (Table 405.1). There is often a family history of childhood epistaxis. Nasal steroid sprays are commonly used in children, and their chronic use may be associated with nasal mucosal bleeding. Young infants with significant gastroesophageal reflux into the nose rarely present with epistaxis secondary to mucosal inflammation. Susceptibility is increased during respiratory infections and in the winter when dry air irritates the nasal mucosa, resulting in formation of fissures and crusting. Severe bleeding may be encountered with congenital vascular abnormalities, such as *hereditary hemorrhagic telangiectasia* (see Chapter 459.3), varicosities, hemangiomas, and, in children with thrombocytopenia, deficiency of clotting factors, particularly von Willebrand disease (see Chapter 504), hypertension, renal failure, or venous congestion. Recurrent epistaxis despite cauterization is associated with mild coagulation disorders. The family history may be positive for abnormal bleeding (epistaxis or other sites); specific testing for von Willebrand disease is indicated because the prothrombin time or partial thromboplastin time may be normal despite having a bleeding disorder. Nasal polyps or other intranasal growths may be associated with epistaxis. Recurrent, and often severe, unilateral nosebleeds may be the initial presenting symptom in **juvenile nasal angiofibroma,** which occurs in adolescent males.

Table 405.1

Possible Causes of Epistaxis

Epistaxis digitorum (nose picking)
Rhinitis (allergic or viral)
Chronic sinusitis
Foreign bodies
Intranasal neoplasm or polyps
Irritants (e.g., cigarette smoke)
Septal deviation
Septal perforation
Trauma including child abuse
Vascular malformation or telangiectasia (hereditary hemorrhage telangiectasia)
Hemophilia
von Willebrand disease
Platelet dysfunction
Thrombocytopenia
Hypertension
Leukemia

Liver disease (e.g., cirrhosis)
Medications (e.g., aspirin, anticoagulants, nonsteroidal antiinflammatory drugs, topical corticosteroids)
Cocaine abuse

From Kucik CJ, Clenney T: Management of epistaxis, *Am Fam Physician* 71(2):305–311, 2005.

Clinical Manifestations

Epistaxis usually occurs without warning, with blood flowing slowly but freely from 1 nostril or occasionally from both. In children with nasal lesions, bleeding might follow physical exercise. When bleeding occurs at night, the blood may be swallowed and become apparent only when the child vomits or passes blood in the stools. Posterior epistaxis can manifest as anterior nasal bleeding, or, if bleeding is copious, the patient might vomit blood as the initial symptom.

Treatment

Most nosebleeds stop spontaneously in a few minutes. The nares should be compressed and the child kept as quiet as possible, in an upright position with the head tilted forward to avoid blood trickling back into the throat. Cold compresses applied to the nose can also help. If these measures do not stop the bleeding, local application of a solution of oxymetazoline (Afrin) or phenylephrine (Neo-Synephrine) (0.25–1%) may be useful. If bleeding persists, an anterior nasal pack may need to be inserted; if bleeding originates in the posterior nasal cavity, combined anterior and posterior packing is necessary. After bleeding is under control, and if a bleeding site is identified, its obliteration by cautery with silver nitrate may prevent further difficulties. Because the septal cartilage derives its nutrition from the overlying mucoperichondrium, only one side of the septum should be cauterized at a time to reduce the chance of a septal perforation. During the winter, or in a dry environment, a room humidifier, saline drops, and petrolatum (Vaseline) applied to the septum can help to prevent epistaxis. Ointments prevent infection, increase moisture, decrease bleeding, and are commonly used in clinical practice. Antiseptic cream (e.g., mupirocin) has been used for epistaxis because it has been found that many patients with idiopathic epistaxis have nasal bacterial colonization with subsequent inflammation, new vessel formation, and irritation, likely leading to epistaxis. However, studies showing the efficacy of antiseptics in epistaxis are equivocal. Patients with severe epistaxis despite conservative medical measures should be considered for surgical ligation techniques or embolization. In patients with severe or repeated epistaxis, blood transfusions may be necessary. Otolaryngologic evaluation is indicated for these children and for those with bilateral bleeding or with hemorrhage that does not arise from the Kiesselbach plexus. For those with recurrent epistaxis, there may be short-term benefits to using bipolar electrocautery over silver nitrate chemical cautery, although treatments were equivocal after 2 yr. Secondary epistaxis should be managed by identification of the cause, application of appropriate nasal therapy, and correct systemic medical management. Hematologic evaluation (for coagulopathy and anemia), along with nasal endoscopy and diagnostic imaging, may be needed to make a definitive diagnosis in cases of severe recurrent epistaxis. Replacement of deficient clotting factors may be required for patients who have an underlying hematologic disorder (see Chapter 503). Profuse unilateral epistaxis associated with a nasal mass in an adolescent boy near puberty might signal a **juvenile nasopharyngeal angiofibroma.** This unusual tumor has also been reported in a 2 yr old and in 30-40 yr olds, but the incidence peaks in adolescent and preadolescent boys. CT with contrast medium enhancement and magnetic resonance imaging (MRI) are part of the initial evaluation; arteriography, embolization, and extensive surgery may be needed.

Surgical intervention may also be needed for bleeding from the internal maxillary artery or other vessels that can cause bleeding in the posterior nasal cavity.

Prevention

The discouragement of nose picking and attention to proper humidification of the bedroom during dry winter months help to prevent many nosebleeds. Prompt attention to nasal infections and allergies is beneficial to nasal hygiene. Prompt cessation of nasal steroid sprays prevents ongoing bleeding.

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CHAPTER 406

Nasal Polyps

Joseph Haddad Jr, Sonam N. Dodhia

Etiology

Nasal polyps are benign pedunculated tumors formed from edematous, usually chronically inflamed nasal mucosa. They commonly arise from the ethmoidal sinus and occur in the middle meatus. Occasionally they appear within the maxillary antrum and can extend to the nasopharynx (antrochoanal polyp).

It is estimated that between 1% and 4% of the population will develop nasal polyps at some point; the incidence of nasal polyps increases with age. Antrochoanal polyps represent only 4–6% of all nasal polyps in the general population but account for approximately one third of polyps in the pediatric population. Large or multiple polyps can completely obstruct the nasal passage. The polyps originating from the ethmoidal sinus are usually smaller and multiple, as compared with the large and usually single antrochoanal polyp.

Cystic fibrosis (CF; see Chapter 432) is the most common childhood cause of nasal polyposis, and up to 50% of CF patients experience obstructing nasal polyposis, which is rare in non-CF children. Therefore, CF should be suspected in any child younger than 12 yr old with nasal polyps, even in the absence of typical respiratory and digestive symptoms. Nasal polyposis is also associated with chronic sinusitis (see Chapter 408) and allergic rhinitis. Large population studies have noted a significant familial risk in having chronic rhinosinusitis with polyposis. Furthermore, it has been noted in a substantial number of studies that low vitamin D levels are correlated with polypoid chronic rhinosinusitis, likely related to the role vitamin D plays as an immunomodulator in the respiratory epithelium. In the *Samter triad* , nasal polyps are associated with aspirin sensitivity and asthma; this condition is rare in children.

Clinical Manifestations

Obstruction of nasal passages is prominent, with associated hyponasal speech and mouth breathing. Profuse unilateral mucoid or mucopurulent rhinorrhea may also be present. An examination of the nasal passages shows glistening, gray, grape-like masses squeezed between the nasal turbinates and the septum.

Diagnosis and Differential Diagnosis

Examination of the external nose and rhinoscopy should be performed. Ethmoidal polyps can be readily distinguished from the well-vascularized turbinate tissue, which is pink or red; antrochoanal polyps may have a more fleshy appearance (Fig. 406.1). Antrochoanal polyps may prolapse into the nasopharynx; flexible nasopharyngoscopy can assist in making this diagnosis. Prolonged presence of ethmoidal polyps in a child can widen the bridge of the nose and erode adjacent osseous structures. Tumors of the nose cause more local destruction and distortion of the anatomy. CT scan of the midface is key to diagnosis and planning for surgical treatment (Fig. 406.2).

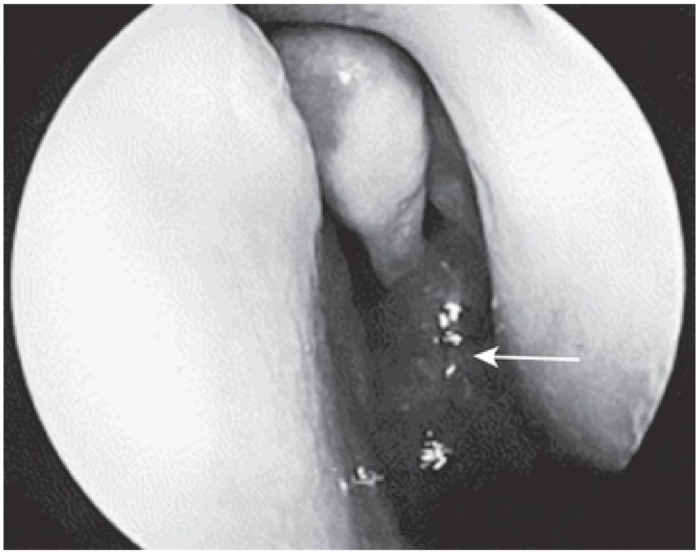

FIG. 406.1 Antrochoanal polyp viewed endoscopically *(arrow).* (From Basak S, Karaman CZ, Akdilli A, et al: Surgical approaches to antrochoanal polyps in children, *Int J Pediatr Otorhinolaryngol* 46:197–205, 1998.)

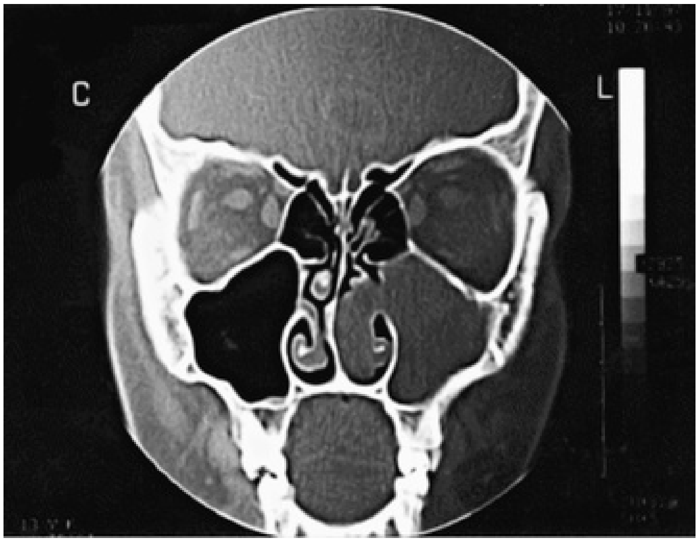

FIG. 406.2 A typical CT image of an isolated antrochoanal polyp on the left side. (From Basak S, Karaman CZ, Akdilli A, et al: Surgical approaches to antrochoanal polyps in children, *Int J Pediatr Otorhinolaryngol* 46:197–205, 1998.)

Treatment

Local or systemic decongestants are not usually effective in shrinking the polyps, although they may provide symptomatic relief from the associated mucosal edema. Intranasal steroid sprays, and sometimes systemic steroids, can provide some shrinkage of nasal polyps with symptomatic relief and have proved useful in children with CF and adults with nasal polyps. Topical nasal steroid therapy, fluticasone, mometasone, and budesonide appears to result in nasal symptom improvement, but were found to have no effect on those with CF. Doxycycline (100 mg daily) has a significant effect on the size of nasal polyps, nasal symptoms, and mucosal and systemic markers of inflammation. Polyps should be removed surgically if complete obstruction, uncontrolled rhinorrhea, or deformity of the nose appears. If the underlying pathogenic mechanism cannot be eliminated (such as CF), the polyps may soon return. Functional endoscopic sinus surgery provides more complete polyp removal and treatment of other associated nasal disease; in some cases, this has reduced the need for frequent surgeries. Nasal steroid sprays should also be started preventively, once postsurgical healing occurs.

Antrochoanal polyps do not respond to medical measures and must be removed surgically, typically via endoscopic sinus surgery, or alternatively with a mini-Caldwell procedure. Since these types of polyps are not associated with any underlying disease process, the recurrence rate is much less than for other types of polyps.

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CHAPTER 407

The Common Cold

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The common cold is an acute viral infection of the upper respiratory tract in which the symptoms of rhinorrhea and nasal obstruction are prominent. Systemic symptoms and signs such as headache, myalgia, and fever are absent or mild. The common cold is frequently referred to as *infectious rhinitis* but may also include self-limited involvement of the sinus mucosa and is more correctly termed *rhinosinusitis*.

Etiology

The most common pathogens associated with the common cold are the more than 200 types of human rhinoviruses (see Chapter 290), but the syndrome can be caused by many different virus families (Table 407.1). Rhinoviruses (HRV) are associated with more than 50% of colds in adults and children. In young children, other viral etiologies of the common cold include respiratory syncytial virus (RSV; see Chapter 287), human metapneumovirus (MPV; see Chapter 288), parainfluenza viruses (PIVs; see Chapter 286), and adenoviruses (see Chapter 289). Common cold symptoms may also be caused by influenza viruses, nonpolio enteroviruses, and human coronaviruses. Many viruses that cause rhinitis are also associated with other symptoms and signs such as cough, wheezing, and fever.

Table 407.1

Pathogens Associated With the Common Cold

ASSOCIATION	PATHOGEN	RELATIVE FREQUENCY*	OTHER COMMON SYMPTOMS AND SIGNS

Agents primarily associated with the common cold	Human rhinoviruses	Frequent	Wheezing/bronchiolitis
	Coronaviruses	Frequent	
Agents primarily associated with other clinical syndromes that also cause common cold symptoms	Respiratory syncytial virus	Occasional	Bronchiolitis in children <2 yr of age
	Human metapneumovirus	Occasional	Pneumonia and bronchiolitis
	Influenza viruses	Uncommon	Influenza, pneumonia, croup
	Parainfluenza viruses	Uncommon	Croup, bronchiolitis
	Adenoviruses	Uncommon	Pharyngoconjunctival fever (palpebral conjunctivitis, watery eye discharge, pharyngeal erythema)
	Enteroviruses Coxsackievirus A Other nonpolio enteroviruses	Uncommon	Herpangina (fever and ulcerated papules on posterior oropharynx) Aseptic meningitis

[*] Relative frequency of colds caused by the agent.

Epidemiology

Colds occur year-round, but the incidence is greatest from the early fall until the late spring, reflecting the seasonal prevalence of the viral pathogens associated with cold symptoms. In the northern hemisphere, the highest incidence of HRV infection occurs in the early fall (August–October) and in the late spring (April–May). The seasonal incidence for PIV usually peaks in the late fall and late spring and is highest between December and April for RSV, influenza viruses, MPV, and coronaviruses. Adenoviruses are detected at a low prevalence throughout the cold season, and enteroviruses may also be detected during summer months or throughout the year.

Young children have an average of 6-8 colds per yr, but 10–15% of children have at least 12 infections per yr. The incidence of illness decreases with increasing age, with 2-3 illnesses per yr by adulthood. The incidence of infection is primarily a function of exposure to the virus. Children in out-of-home daycare centers during the 1st yr of life have 50% more colds than children cared for only at home. The difference in the incidence of illness between these groups of children decreases as the length of time spent in daycare increases, although the incidence of illness remains higher in the daycare group through at least the 1st 3 yr of life. When they begin primary school, children who attended daycare have less frequent colds than those who did not. Mannose-binding lectin deficiency with impaired innate immunity may be associated with an increased incidence of colds in children.

Pathogenesis

Viruses that cause the common cold are spread by three mechanisms: direct hand contact (self-inoculation of one's own nasal mucosa or conjunctivae after touching a contaminated person or object), inhalation of small-particle aerosols that are airborne from coughing, or deposition of large-particle aerosols that are expelled during a sneeze and land on nasal or conjunctival mucosa. Although the different common cold pathogens could be spread by any of these mechanisms, some routes of transmission appear to be more efficient than others for particular viruses. Studies of HRV and RSV indicate that direct contact is an efficient mechanism of transmission of these viruses, although transmission by large-particle aerosols can also occur. By contrast, influenza viruses and coronaviruses appear to be most efficiently spread by small-particle aerosols.

The respiratory viruses have evolved different mechanisms to avoid host defenses. Infections with HRV and adenoviruses result in the development of serotype-specific protective immunity. Repeated infections with these pathogens occur because there are a large number of distinct serotypes of each virus. Influenza viruses change the antigens presented on the surface of the virus due to genetic drift and thus behave as though there were multiple viral serotypes. The interaction of coronaviruses (see Chapter 291) with host immunity is not well defined, but it appears that multiple distinct strains of coronaviruses are capable of inducing at least short-term protective immunity. There are four types of PIV, 2 antigenic subgroups of RSV, and 4 genotypes of MPV. In addition to antigenic diversity, many of these viruses are able to reinfect the upper airway because mucosal immunoglobulin A (IgA) induced by previous infection is short lived, and the brief incubation period of these viruses allows the establishment of infection before immune memory responses. Although reinfection is not completely prevented by the adaptive host response to these viruses, the severity of illness is moderated by preexisting immunity.

Viral infection of the nasal epithelium can be associated with destruction of the epithelial lining, as with influenza viruses and adenoviruses, or there can be no apparent histologic damage, as with HRV, coronaviruses, and RSV. Regardless of the histopathologic findings, infection of the nasal epithelium is associated with an acute inflammatory response characterized by release of a variety of inflammatory cytokines and infiltration of the mucosa by inflammatory cells. This acute inflammatory response appears to be partially or largely responsible for many of the symptoms associated with the common cold. Viral shedding of most respiratory viruses peaks 3-5 days after inoculation, often coinciding with symptom onset; low levels of viral shedding may persist for up to 2 wk in the otherwise recovering healthy host. Inflammation can obstruct the sinus ostia or eustachian tube, predisposing to bacterial sinusitis or otitis media, respectively.

The host immune system is responsible for most cold symptoms, rather than direct damage to the respiratory tract. Infected cells release cytokines, such as interleukin-8, that attract polymorphonuclear cells into the nasal submucosa and epithelium. HRV also increases vascular permeability in the nasal submucosa, releasing albumin and bradykinin, which may contribute to symptoms.

Clinical Manifestations

Symptoms of the common cold vary by age and virus. In infants, fever and nasal discharge may predominate. Fever is uncommon in older children and adults. The onset of common cold symptoms typically occurs 1-3 days after viral infection. The first symptom noted is often sore or scratchy throat, followed closely by nasal obstruction and rhinorrhea. The sore throat usually resolves quickly, and, by the 2nd and 3rd day of illness, nasal symptoms predominate. Cough is associated with two-thirds of colds in children and usually begins after the onset of nasal symptoms. Cough may persist for an additional 1-2 wk after resolution of other symptoms. Influenza viruses, RSV, MPV, and adenoviruses are more likely than HRV or coronaviruses to be associated with fever and other constitutional symptoms. Other symptoms of a cold may include headache, hoarseness, irritability, difficulty sleeping, or decreased appetite. Vomiting and diarrhea are uncommon. The usual cold persists for approximately 1 wk, although 10% last for 2 wk.

The physical findings of the common cold are limited to the upper respiratory tract. Increased nasal secretion is usually obvious; a change in the color or consistency of the secretions is common during the course of the illness and does not indicate sinusitis or bacterial superinfection but may indicate accumulation of polymorphonuclear cells. Examination of the nasal cavity might reveal swollen, erythematous nasal turbinates, although this finding is nonspecific and of limited diagnostic value. Abnormal middle ear pressure is common during the course of a cold. Anterior cervical lymphadenopathy or conjunctival injection may also be noted on exam.

Diagnosis

The most important task of the physician caring for a patient with a cold is to exclude other conditions that are potentially more serious or treatable. The differential diagnosis of the common cold includes noninfectious disorders and other upper respiratory tract infections (Table 407.2).

Table 407.2

Conditions That Can Mimic the Common Cold

CONDITION	DIFFERENTIATING FEATURES
Allergic rhinitis	Prominent itching and sneezing, nasal eosinophils. Hansel stain can aid diagnosis
Vasomotor rhinitis	May be triggered by irritants, weather changes, spicy foods, etc.
Rhinitis medicamentosa	History of nasal decongestant use
Foreign body	Unilateral, foul-smelling secretions
	Bloody nasal secretions
Sinusitis	Presence of fever, headache or facial pain, or periorbital edema or persistence of rhinorrhea or cough for longer than 10-14 days
Streptococcosis	Mucopurulent nasal discharge that excoriates the nares, no cough
Pertussis	Onset of persistent or severe paroxysmal cough
Congenital syphilis	Persistent rhinorrhea with onset in the 1st 3 mo of life

Laboratory Findings

Routine laboratory studies are not helpful for the diagnosis and management of the common cold . A nasal smear for eosinophils (Hansel stain) may be useful if allergic rhinitis is suspected (see Chapter 168). A predominance of polymorphonuclear cells in the nasal secretions is characteristic of uncomplicated colds and *does not* indicate bacterial superinfection. Self-limited radiographic abnormalities of the paranasal sinuses are common during an uncomplicated cold; imaging *is not* indicated for most children with simple rhinitis.

The viral pathogens associated with the common cold can be detected by polymerase chain reaction (PCR), culture, antigen detection, or serologic methods. These studies are generally not indicated in patients with colds, because a specific etiologic diagnosis is useful only when treatment with an antiviral agent is contemplated, such as for influenza viruses. Bacterial cultures, PCR, or antigen detection are useful only when group A streptococcus (see Chapter 210) or *Bordetella pertussis* (see Chapter 224) is suspected. The isolation of other bacterial pathogens from nasopharyngeal specimens is not an indication of bacterial nasal infection and is not a specific predictor of the etiologic agent in sinusitis.

Treatment

The management of the common cold consists primarily of supportive care and anticipatory guidance as recommended by American Academy of Pediatrics and United Kingdom National Institute for Health and Clinical Excellence guidelines.

Antiviral Treatment

Specific antiviral therapy is not available for HRV infections. Ribavirin, which is approved for treatment of severe RSV infections, has no role in the treatment of the common cold. The neuraminidase inhibitors oseltamivir and zanamivir have a modest effect on the duration of symptoms associated with influenza viral infections in children. Oseltamivir also reduces the frequency of influenza-associated otitis media. The difficulty of distinguishing influenza from other common cold pathogens and the necessity that therapy be started early in the illness (within 48 hr of onset of symptoms) to be beneficial are practical limitations to the use of these agents for mild upper respiratory tract infections. *Antibacterial therapy is of no benefit in the treatment of the common cold and should be avoided to minimize possible adverse effects and the development of antibiotic resistance.*

Supportive Care and Symptomatic Treatment

Supportive interventions are frequently recommended by providers. Maintaining adequate oral hydration may help to prevent dehydration and to thin secretions and soothe respiratory mucosa. The common home remedy of ingesting warm fluids may soothe mucosa, increase nasal mucous flow, or loosen respiratory secretions. Topical nasal saline may temporarily remove secretions, and saline nasal irrigation may reduce symptoms. Cool, humidified air has not been well studied but may loosen nasal secretions; however, cool-mist humidifiers and vaporizers must be cleaned after each use. The World Health Organization suggests that neither steam nor cool-mist therapy be used in treatment of a cold.

The use of oral **nonprescription** therapies (often containing antihistamines, antitussives, and decongestants) for cold symptoms in children is controversial. Although some of these medications are effective in adults, no study demonstrates a significant effect in children, and there may be serious side effects. Young children cannot participate in the assessment of symptom severity, so studies of these treatments in children have generally been based on observations by parents or other observers, a method that is likely to be insensitive for detection of treatment effects. Because of the lack of direct evidence for effectiveness and the potential for unwanted side effects, it is recommended that nonprescription cough and cold products *not* be used for infants and children younger than 6 yr of age. A decision whether to use these medications in older children must consider the likelihood of clinical benefit compared with the potential adverse effects of these drugs. The prominent or most bothersome symptoms of colds vary in the course of the illness. If symptomatic treatments are used, it is reasonable to target therapy to specific bothersome symptoms and care should be taken to ensure that caregivers understand the intended effect and can determine the proper dosage of the medications.

Zinc, given as oral lozenges to previously healthy patients, reduces the duration but not the severity of symptoms of a common cold if begun within 24 hr of symptoms. The function of the HRV 3C protease, an essential enzyme for HRV replication, is inhibited by zinc, but there has been no evidence of an antiviral effect of zinc *in vivo* . The effect of zinc on symptoms has been inconsistent, with some studies reporting dramatic treatment effects (in adults), whereas other studies find no benefit. Side effects are common and include decreased taste, bad taste, and nausea.

Fever

Fever is not usually associated with an uncomplicated common cold, and antipyretic treatment is generally not indicated. NSAIDs may decrease discomfort from cold related headache or myalgias.

Nasal Obstruction

Either topical or oral adrenergic agents may be used as nasal decongestants in older children and adults. Effective topical adrenergic agents such as xylometazoline, oxymetazoline, or phenylephrine are available as either intranasal drops or nasal sprays. Reduced-strength formulations of these medications are available for use in younger children, although they are not recommended for use in children younger than 6 yr old. Systemic absorption of the imidazolines (oxymetazoline, xylometazoline) has very rarely been associated with bradycardia, hypotension, and coma. Prolonged use of the topical adrenergic agents should be avoided to prevent the development of **rhinitis medicamentosa,** an apparent rebound effect that causes the sensation of nasal obstruction when the drug is discontinued. The oral adrenergic agents are less effective than the topical preparations and are occasionally associated with systemic effects such as central nervous system stimulation, hypertension, and palpitations. Pseudoephedrine may be more effective than phenylephrine as an oral agent to treat nasal congestion. Aromatic vapors (such as menthol) for external rub may improve perception of nasal patency but do not affect spirometry.

Saline nose drops (wash, irrigation) can improve nasal symptoms and may be used in all age groups.

Rhinorrhea

The 1st-generation antihistamines may reduce rhinorrhea by 25–30%. The effect of the antihistamines on rhinorrhea appears to be related to the anticholinergic rather than the antihistaminic properties of these drugs, and therefore the 2nd-generation or nonsedating antihistamines have no effect on common cold symptoms. The major adverse effects associated with the use of the antihistamines are sedation or paradoxical hyperactivity. Overdose may be associated with respiratory depression or hallucinations. Rhinorrhea may also be treated with ipratropium bromide, a topical anticholinergic agent. This drug produces an effect comparable to the antihistamines but is not associated with sedation. The most common side effects of ipratropium are nasal irritation and bleeding.

Sore Throat

The sore throat associated with colds is generally not severe, but treatment with mild analgesics is occasionally indicated, particularly if there is associated myalgia or headache. The use of acetaminophen during HRV infection is associated with suppression of neutralizing antibody responses, but this observation has no apparent clinical significance. Aspirin *should not* be given to children with respiratory infections, because of the risk of Reye syndrome in children with influenza (see Chapter 388). **Nonsteroidal antiinflammatory drugs** are somewhat effective in relieving discomfort caused by a cold, but there is no clear evidence of an effect on respiratory symptoms.

Cough

Cough suppression is generally not necessary in patients with colds. Cough in some patients appears to be from upper respiratory tract irritation associated with postnasal drip. Cough in these patients is most prominent during the time of greatest nasal symptoms, and treatment with a 1st-generation antihistamine may be helpful. Cough lozenges or hard candy may be temporarily effective and are unlikely to be harmful in children for whom they do not pose risk of aspiration (older than age 6 yr). **Honey** (5-10 mL in children ≥1 yr old) has a modest effect on relieving nocturnal cough and is unlikely to be harmful in children older than 1 yr of age. Honey should be avoided in children younger than 1 yr of age because of the risk for botulism (see Chapter 237).

In some patients, cough may be a result of **virus-induced reactive airways disease** . These patients can have cough that persists for days to weeks after the acute illness and might benefit from bronchodilator or other therapy. Codeine or dextromethorphan hydrobromide has no effect on cough from colds and has potential enhanced toxicity. Expectorants such as guaifenesin are not effective antitussive agents. The combination of camphor, menthol, and eucalyptus oils may relieve nocturnal cough, but studies of their effectiveness are limited.

Ineffective Treatments

Vitamin C, guaifenesin, and inhalation of warm, humidified air are no more effective than placebo for the treatment of cold symptoms.

Echinacea is a popular herbal treatment for the common cold. Although echinacea extracts have biologic effects, echinacea is not effective as a common cold treatment. The lack of standardization of commercial products containing echinacea also presents a formidable obstacle to the rational evaluation or use of this therapy.

There is no evidence that the common cold or persistent acute purulent rhinitis of less than 10 days in duration benefits from antibiotics. In fact, there is evidence that antibiotics cause significant adverse effects when given for acute purulent rhinitis.

Complications

The most common complication of a cold is **acute otitis media (AOM;** see Chapter 658), which may be indicated by new-onset fever and earache after the 1st few days of cold symptoms. AOM is reported in 5–30% of children who have a cold, with the higher incidence occurring in young infants and in children cared for in a group daycare setting. Symptomatic treatment of the common cold symptoms has no effect on the subsequent development of AOM.

Sinusitis is another complication of the common cold (see Chapter 408). Self-limited sinus inflammation is a part of the pathophysiology of the common cold, but 0.5–2% of viral upper respiratory tract infections in adults, and 5–13% in children, are complicated by acute bacterial sinusitis. The differentiation of common cold symptoms from bacterial sinusitis may be difficult. The diagnosis of bacterial sinusitis should be considered if rhinorrhea or daytime cough persists without improvement for at least 10-14 days, if acute symptoms worsen over time, or if acute signs of more severe sinus involvement such as fever, facial pain, or facial swelling develop. There is no evidence that symptomatic treatment of the common cold alters the frequency of development of bacterial sinusitis. Bacterial pneumonia is an uncommon complication of the common cold.

Exacerbation of **asthma** is a potentially serious complication of colds. The majority of asthma exacerbations in children are associated with common cold viruses. There is no evidence that treatment of common cold symptoms prevents this complication; however, studies are underway in patients with underlying asthma to determine effectiveness of preventive or acute treatment at the onset of upper respiratory tract infection symptoms.

Although not a complication, another important consequence of the common cold is the inappropriate use of antibiotics for these illnesses and the associated contribution to the problem of increasing antibiotic resistance of pathogenic respiratory bacteria, as well as adverse effects from antibiotics.

Prevention

Chemoprophylaxis or immunoprophylaxis is generally not available for the common cold. Immunization or chemoprophylaxis against influenza can prevent colds caused by this pathogen, but influenza is responsible for only a small proportion of all colds. Palivizumab is recommended to prevent RSV lower respiratory infection in high-risk infants but does not prevent upper respiratory infections from this virus. Vitamin C, garlic, or echinacea do not prevent the common cold. Vitamin C prophylaxis may shorten the duration of cold symptoms. Vitamin D deficiency is associated with increased risk of viral respiratory tract infection in some studies; nonetheless, vitamin D prophylaxis does not reduce incidence or severity of the common cold in adults; studies in children are lacking. Zinc sulfate taken for a minimum of 5 mo may reduce the rate of cold development. However, because of duration of use and adverse effects of bad taste and nausea, this is not a recommended prevention modality in children.

Hand-to-hand transmission of HRV followed by self-inoculation may be prevented by frequent handwashing and avoiding touching one' s mouth, nose, and eyes. Some studies report the use of alcohol-based hand sanitizers and virucidal hand treatments were associated with decreased transmission. In the experimental setting, virucidal disinfectants or virucidal-impregnated tissues also reduce transmission of cold viruses; under natural conditions none of these interventions prevents common colds.

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CHAPTER 408

Sinusitis

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Sinusitis is a common illness of childhood and adolescence. There are 2 common types of acute sinusitis—viral and bacterial—with significant acute and chronic morbidity as well as the potential for serious complications. Fungal sinusitis is rare in immunocompetent patients but can also occur. The common cold produces a viral, self-limited *rhinosinusitis* (see Chapter 407). Approximately 0.5–2% of viral upper respiratory tract infections in children and adolescents are complicated by acute symptomatic bacterial sinusitis. Some children with underlying predisposing conditions have chronic sinus disease that does not appear to be infectious. The means for appropriate diagnosis and optimal treatment of sinusitis remain controversial.

Typically, the ethmoidal and maxillary sinuses are present at birth, but only the ethmoidal sinuses are pneumatized. The maxillary sinuses are not pneumatized until 4 yr of age. The sphenoidal sinuses are present by 5 yr of age, whereas the frontal sinuses begin development at age 7-8 yr and are not completely developed until adolescence. The ostia draining the sinuses are narrow (1-3 mm) and drain into the ostiomeatal complex in the middle meatus. The paranasal sinuses are normally sterile, maintained by the mucociliary clearance system.

Etiology

The bacterial pathogens causing **acute bacterial sinusitis** in children and adolescents include *Streptococcus pneumoniae* (~30%; see Chapter 209), nontypeable *Haemophilus influenzae* (~30%; see Chapter 221), and *Moraxella catarrhalis* (~10%; see Chapter 223). Approximately 50% of *H. influenzae* and 100% of *M. catarrhalis* are β-lactamase positive. Approximately 25% of *S.*

pneumoniae may be penicillin resistant. *Staphylococcus aureus,* other streptococci, and anaerobes are uncommon causes of *acute* bacterial sinusitis in children. Although *S. aureus* (see Chapter 208.1) is an uncommon pathogen for acute sinusitis in children, the increasing prevalence of methicillin-resistant *S. aureus* is a significant concern. *H. influenzae* , α- and β-hemolytic streptococci, *M. catarrhalis* , *S. pneumoniae* , and coagulase-negative staphylococci are commonly recovered from children with *chronic* sinus disease.

Epidemiology

Acute bacterial sinusitis can occur at any age. Predisposing conditions include viral upper respiratory tract infections (associated with out-of-home daycare or a school-age sibling), allergic rhinitis, and tobacco smoke exposure. Children with immune deficiencies, particularly of antibody production (immunoglobulin (Ig)G, IgG subclasses, IgA; see Chapter 150), cystic fibrosis (see Chapter 432), ciliary dysfunction (see Chapter 433), abnormalities of phagocyte function, gastroesophageal reflux, anatomic defects (cleft palate), nasal polyps, cocaine abuse, and nasal foreign bodies (including nasogastric tubes), can develop chronic or recurrent sinus disease. Immunosuppression for bone marrow transplantation or malignancy with profound neutropenia and lymphopenia predisposes to severe fungal (aspergillus, mucor) sinusitis, often with intracranial extension. Patients with nasotracheal intubation or nasogastric tubes may have obstruction of the sinus ostia and develop sinusitis with the multiple-drug resistant organisms of the intensive care unit.

Acute sinusitis is defined by a duration of <30 days, subacute by a duration of 1-3 mo, and chronic by a duration of longer than 3 mo.

Pathogenesis

Acute bacterial sinusitis typically follows a viral upper respiratory tract infection. Initially, the viral infection produces a viral rhinosinusitis; magnetic resonance imaging (MRI) evaluation of the paranasal sinuses demonstrates abnormalities (mucosal thickening, edema, inflammation) of the paranasal sinuses in 68% of healthy children in the normal course of the common cold. Nose blowing has been demonstrated to generate sufficient force to propel nasal secretions into the sinus cavities. Bacteria from the nasopharynx that enter the sinuses are normally cleared readily, but during viral rhinosinusitis, inflammation and edema can block sinus drainage and impair mucociliary clearance of bacteria. The growth conditions are favorable, and high titers of bacteria are produced.

Clinical Manifestations

Children and adolescents with sinusitis can present with nonspecific complaints, including nasal congestion, purulent nasal discharge (unilateral or bilateral), fever, and cough. Less-common symptoms include bad breath (halitosis), a decreased sense of smell (hyposmia), and periorbital edema (Table 408.1). Complaints of headache and facial pain are rare in children. Additional symptoms include maxillary tooth discomfort and pain or pressure exacerbated by bending forward. Physical examination might reveal erythema and swelling of the nasal mucosa with purulent nasal discharge. Sinus tenderness may be detectable in adolescents and adults. Transillumination reveals an opaque sinus that transmits light poorly.

Table 408.1

Conventional Criteria for the Diagnosis of Sinusitis Based on the Presence of at Least 2 Major or 1 Major and ≥2 Minor Symptoms

MAJOR SYMPTOMS	MINOR SYMPTOMS
• Purulent anterior nasal discharge • Purulent or discolored posterior nasal discharge • Nasal congestion or obstruction • Facial congestion or fullness • Facial pain or pressure • Hyposmia or anosmia • Fever (for acute sinusitis only)	• Headache • Ear pain, pressure, or fullness • Halitosis • Dental pain • Cough • Fever (for subacute or chronic sinusitis) • Fatigue

From Chow AW, Benninger MS, Brook I, et al: IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *CID* 54:e72–e112, 2012, Table 2, p. e78.

Differentiating bacterial sinusitis from a cold may be difficult, but certain patterns suggestive of sinusitis have been identified. These include *persistence* of nasal congestion, rhinorrhea (of any quality), and daytime cough ≥10 days without improvement; *severe symptoms* of temperature ≥39°C (102°F) with purulent nasal discharge for 3 days or longer; and *worsening symptoms* either by recurrence of symptoms after an initial improvement or new symptoms of fever, nasal discharge, and daytime cough (double sickening; Fig. 408.1).

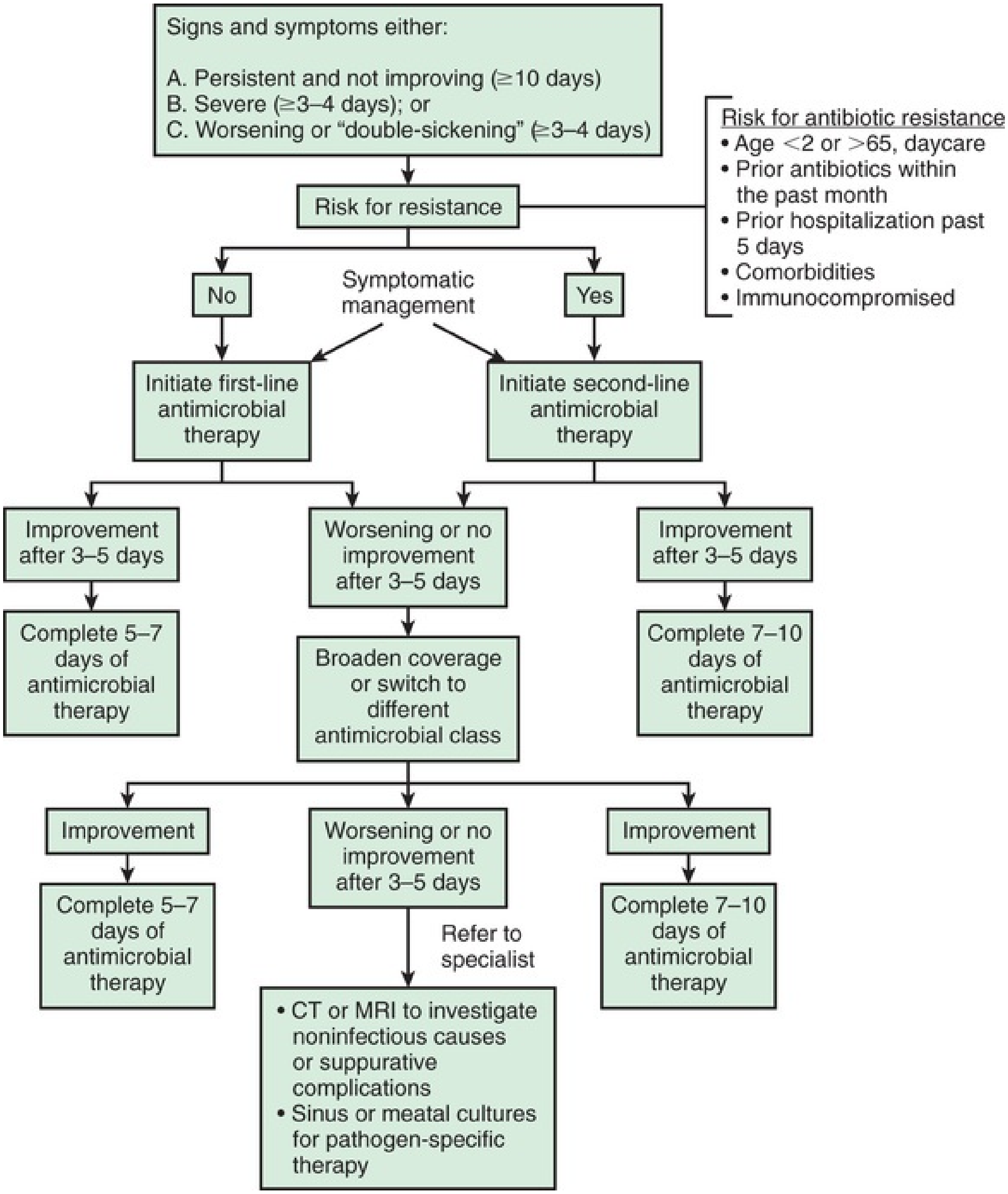
Signs and symptoms either:
A. Persistent and not improving (≥10 days)
B. Severe (≥3–4 days); or
C. Worsening or "double-sickening" (≥3–4 days)
Risk for resistance
Risk for antibiotic resistance
• Age <2 or >65, daycare
• Prior antibiotics within the past month
• Prior hospitalization past 5 days
• Comorbidities
• Immunocompromised
No
Symptomatic management
Yes
Initiate first-line antimicrobial therapy
Initiate second-line antimicrobial therapy
Improvement after 3–5 days
Worsening or no improvement after 3–5 days
Improvement after 3–5 days
Complete 5–7 days of antimicrobial therapy
Broaden coverage or switch to different antimicrobial class
Complete 7–10 days of antimicrobial therapy
Improvement
Worsening or no improvement after 3–5 days
Improvement
Complete 5–7 days of antimicrobial therapy
Refer to specialist
Complete 7–10 days of antimicrobial therapy
• CT or MRI to investigate noninfectious causes or suppurative complications
• Sinus or meatal cultures for pathogen-specific therapy

FIG. 408.1 **Algorithm for the management of acute bacterial rhinosinusitis. (From Chow AW, Benninger MS, Brook I, et al: Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis* 54(8):e72–e112, 2012, Fig. 1.)**

Diagnosis

The clinical diagnosis of *acute* bacterial sinusitis is based on history. Persistent symptoms of upper respiratory tract infection, including nasal discharge and cough, for longer than 10 days without improvement, or severe respiratory symptoms, including temperature of at least 39°C (102°F) and purulent nasal discharge for 3-4 consecutive days, suggest a complicating acute bacterial sinusitis. Bacteria are recovered from maxillary sinus aspirates in 70% of children with such persistent or severe symptoms studied. Children with *chronic* sinusitis have a history of persistent respiratory symptoms, including cough, nasal discharge, or nasal congestion, lasting longer than 90 days.

Sinus aspirate culture is the only accurate method of diagnosis but is not practical for routine use for immunocompetent patients. It may be a necessary procedure for immunosuppressed patients with suspected fungal sinusitis. In adults, *rigid nasal endoscopy* is a less-invasive method for obtaining culture material from the sinus but detects a great excess of positive cultures compared with aspirates. Findings on radiographic studies (sinus plain films, computed tomography [CT] scans), including opacification, mucosal thickening, or presence of an air-fluid level, are not diagnostic and are not recommended in otherwise healthy children. Such findings can confirm the presence of sinus inflammation but cannot be used to differentiate among viral, bacterial, or allergic causes of inflammation.

Given the nonspecific clinical picture, differential diagnostic considerations include viral upper respiratory tract infection, allergic rhinitis, nonallergic rhinitis, and nasal foreign body. Viral upper respiratory tract infections are characterized by clear and usually nonpurulent nasal discharge, cough, and initial fever; symptoms do not usually persist beyond 10-14 days, although a few children (10%) have persistent symptoms even at 14 days. In a recent study using nasal sampling, new viruses were present in 29% of sinusitis episodes in children, suggesting sequential URIs as the cause of persistent symptoms in many cases. Allergic rhinitis can be seasonal; evaluation of nasal secretions should reveal significant eosinophilia.

Treatment

It is unclear whether antimicrobial treatment of clinically diagnosed acute bacterial sinusitis offers any substantial benefit. A randomized, placebo-controlled trial comparing 14-day treatment of children with clinically diagnosed sinusitis with amoxicillin, amoxicillin-clavulanate, or placebo found that antimicrobial therapy did not affect resolution of symptoms, duration of symptoms, or days missed from school. A similar study in adults demonstrated improved symptoms at day 7 but not day 10 of treatment. Major guidelines recommend antimicrobial treatment for acute bacterial sinusitis with severe onset or a worsening course to promote resolution of symptoms and prevent suppurative complications, although 50–60% of children with acute bacterial sinusitis may recover without antimicrobial therapy.

Initial therapy with amoxicillin (45 mg/kg/day divided bid) is adequate for most children with uncomplicated mild to moderate severity acute bacterial sinusitis (Table 408.2). Alternative treatments for the penicillin-allergic patient include cefdinir, cefuroxime axetil, cefpodoxime, or cefixime. In older children, levofloxacin is an alternative antibiotic. *Azithromycin and trimethoprim-sulfamethoxazole are no longer indicated because of a high prevalence of antibiotic resistance.* For children with risk factors (antibiotic treatment in the preceding 1-3 mo, daycare attendance, or age younger than 2 yr) for the presence of resistant bacterial species, and for children who fail to respond to initial therapy with amoxicillin within 72 hr, or with severe sinusitis, treatment with high-dose amoxicillin-clavulanate (80-90 mg/kg/day of amoxicillin) should be initiated. Ceftriaxone (50 mg/kg, IV or IM) may be given to children who are vomiting or who are at risk for poor compliance; it should be followed by a course of oral antibiotics. Failure to respond to these regimens necessitates referral to an otolaryngologist for further evaluation because maxillary sinus aspiration for culture and susceptibility testing may be necessary (Table 408.3). The appropriate duration of therapy for sinusitis has yet to be determined; individualization of therapy is a reasonable approach, with treatment recommended for a minimum of 10 days or 7 days after resolution of symptoms (see Fig. 408.1).

Table 408.2

Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Children

INDICATION	FIRST-LINE (DAILY DOSE)	SECOND-LINE (DAILY DOSE)
Initial empirical therapy	Amoxicillin-clavulanate (45	• Amoxicillin-clavulanate (90 mg/kg/day PO bid)

	mg/kg/day PO bid)	
β-Lactam allergy		
Type I hypersensitivity		• Levofloxacin (10-20 mg/kg/day PO every 12-24 h)
Non-type I hypersensitivity		• Clindamycin* (30-40 mg/kg/day PO tid) plus cefixime (8 mg/kg/day PO bid) or cefpodoxime (10 mg/kg/day PO bid)
Risk for antibiotic resistance or failed initial therapy		• Amoxicillin-clavulanate (90 mg/kg/day PO bid)
		• Clindamycin* (30-40 mg/kg/day PO tid) plus cefixime (8 mg/kg/day PO bid) or cefpodoxime (10 mg/kg/day PO bid)
		• Levofloxacin (10-20 mg/kg/day PO every 12-24 h)
Severe infection requiring hospitalization		• Ampicillin/sulbactam (200-400 mg/kg/day IV every 6 h)
		• Ceftriaxone (50 mg/kg/day IV every 12 h)
		• Cefotaxime (100-200 mg/kg/day IV every 6 h)
		• Levofloxacin (10-20 mg/kg/day IV every 12-24 h)

* Resistance to clindamycin (~31%) is found frequently among *Streptococcus pneumoniae* serotype 19A isolates in different regions of the United States.

bid, 2 times daily; IV, intravenously; PO, orally; qd, daily; tid, 3 times a day.

From Chow AW, Benninger MS, Brook I, et al: IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *CID* 54:e72–e112, 2012, Table 9, p. e94.

Table 408.3

Indications for Referral to a Specialist

- Severe infection (high persistent fever with temperature >39°C [>102°F]; orbital edema; severe headache, visual disturbance, altered mental status, meningeal signs)
- Recalcitrant infection with failure to respond to extended courses of antimicrobial therapy
- Immunocompromised host
- Multiple medical problems that might compromise response to treatment (e.g., hepatic or renal impairment, hypersensitivity to antimicrobial agents, organ transplant)
- Unusual or resistant pathogens
- Fungal sinusitis or granulomatous disease
- Nosocomial infection
- Anatomic defects causing obstruction and requiring surgical intervention
- Multiple recurrent episodes of acute bacterial rhinosinusitis (3-4 episodes per year) suggesting chronic sinusitis
- Chronic rhinosinusitis (with or without polyps or asthma) with recurrent ABRS exacerbations
- Evaluation of immunotherapy for allergic rhinitis

From Chow AW, Benninger MS, Brook I, et al: IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *CID* 54:e72–e112, 2012, Table 14, p. e106.

Frontal sinusitis can rapidly progress to serious intracranial complications and necessitates initiation of parenteral ceftriaxone until substantial clinical improvement is achieved (Figs. 408.2 and 408.3). Treatment is then completed with oral antibiotic therapy.

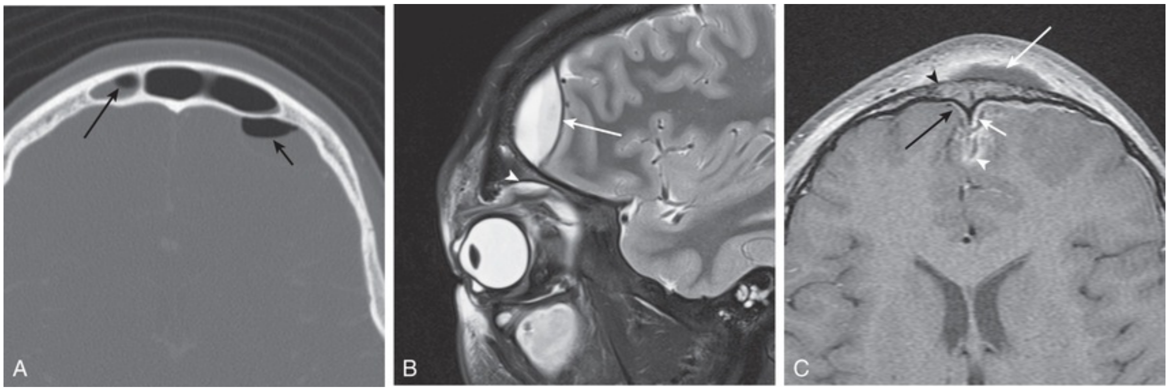

FIG. 408.2 Acute complicated sinusitis. A, Frontal sinusitis and epidural abscess. Axial computed tomography image shows a frontal sinus air–fluid level *(long arrow).* There is also an intracranial air–fluid level associated with an epidural abscess *(short arrow).* B, Frontal sinusitis, epidural abscess, and orbital abscess. Sagittal fat-suppressed (FS) T2-weighted magnetic resonance (MR) image demonstrates a biconvex epidural abscess *(arrow)* containing a sediment level. There is also a small superior extraconal subperiosteal abscess *(arrowhead).* Periorbital STS is present, and there are secretions within the maxillary antrum. C, Pott puffy tumor, frontal osteomyelitis, and subdural empyema. Axial gadolinium-enhanced FS T1-weighted MR image shows frontal scalp swelling ventral to an elliptical low signal intensity, peripherally enhancing, frontal subperiosteal abscess *(long white arrow).* There is enhancement of the subjacent frontal bone, consistent with osteomyelitis *(black arrowhead).* There is also dural enhancement *(black arrow)* and a small left frontal interhemispheric subdural empyema *(short white arrow)* with subtle enhancement of the adjacent frontal leptomeninges and cortex caused by meningitis and cerebritis *(white arrowhead).* (From Walters MM, Robertson RL, editors: *Pediatric radiology, the requisites* , ed 4, Philadelphia, 2017, Elsevier, Fig. 10.40.)

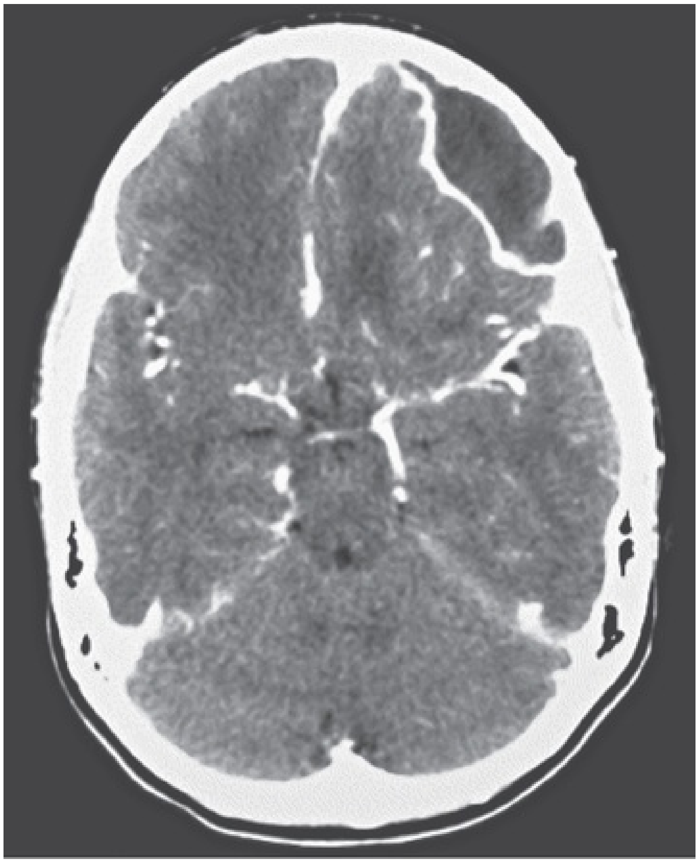

FIG. 408.3 Axial plane contrast-enhanced CT scan of an 11 yr old obtunded girl with a subfrontal lobe abscess secondary to frontal sinusitis. The CT scan demonstrates an eliptiform ring-enhancing fluid-filled cavity adjacent to the frontal lobe with contralateral shift of the midline. (From Parikh SR, Brown SM: Image-guided frontal sinus surgery in children, *Operative Tech Otolaryngol Head Neck Surg* 15:37–41, 2004.)

The use of decongestants, antihistamines, mucolytics, and intranasal corticosteroids has not been adequately studied in children and is not recommended for the treatment of acute uncomplicated bacterial sinusitis. Likewise, saline nasal washes or nasal sprays can help liquefy secretions and act as a mild vasoconstrictor, but the effects have not been systematically evaluated in children.

Complications

Because of the close proximity of the paranasal sinuses to the brain and eyes, serious orbital and/or **intracranial complications** can result from acute bacterial sinusitis and progress rapidly. Orbital complications, including *periorbital* *cellulitis* and more often *orbital cellulitis* (see Chapter 634), are most often secondary to acute bacterial ethmoiditis. Infection can spread directly through the lamina papyracea, the thin bone that forms the lateral wall of the ethmoidal sinus. Periorbital cellulitis produces erythema and swelling of the tissues surrounding the globe, whereas orbital cellulitis involves the intraorbital structures and produces proptosis, chemosis, decreased visual acuity, double vision and impaired extraocular movements, and eye pain (Fig. 408.4). Evaluation should include CT scan of the orbits and sinuses with ophthalmology and otolaryngology consultations. Treatment with intravenous antibiotics should be initiated. Orbital cellulitis may require surgical drainage of the ethmoidal sinuses or orbit.

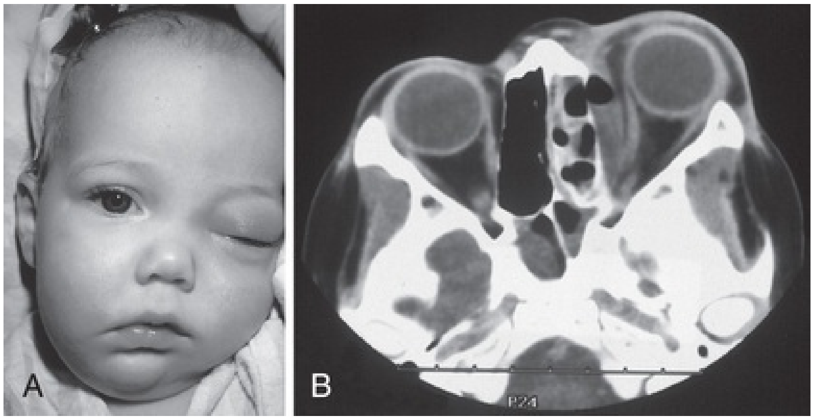

FIG. 408.4 **Orbital complications of acute sinusitis. A, An 11 mo old infant with a swollen left eye and limited ocular movement. B, Axial CT shows opacification of sinuses and an inflammatory mass with an air–fluid level displacing the medial rectus laterally. (From Cooper, ML, Slovis T: The sinuses. In Slovis T, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, Fig. 43-7, p. 573.)**

Intracranial complications can include epidural abscess, meningitis, cavernous sinus thrombosis, subdural empyema, and brain abscess (see Chapter 622). Children with altered mental status, nuchal rigidity, severe headache, focal neurologic findings, or signs of increased intracranial pressure (headache, vomiting) require immediate CT scan of the brain, orbits, and sinuses to evaluate for the presence of intracranial complications of acute bacterial sinusitis. Black children and males are at increased risk, but there is no evidence of increased risk due to socioeconomic status. Treatment with broad-spectrum intravenous antibiotics (usually cefotaxime or ceftriaxone combined with vancomycin) should be initiated immediately, pending culture and susceptibility results. In

50% the abscess is a polymicrobial infection. Abscesses can require surgical drainage. Other complications include osteomyelitis of the frontal bone (**Pott puffy tumor**), which is characterized by edema and swelling of the forehead (see Fig. 408.2), and **mucoceles** , which are chronic inflammatory lesions commonly located in the frontal sinuses that can expand, causing displacement of the eye with resultant diplopia. Surgical drainage is usually required.

Prevention

Prevention is best accomplished by frequent handwashing and avoiding persons with colds. Because acute bacterial sinusitis can complicate influenza infection, prevention of influenza infection by yearly influenza vaccine will prevent some cases of complicating sinusitis. Immunization or chemoprophylaxis against influenza with oseltamivir or zanamivir may be useful for prevention of colds caused by this pathogen and the associated complications; influenza is responsible for only a small proportion of all colds.

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[†] Deceased.

CHAPTER 409

Acute Pharyngitis

Robert R. Tanz

Pharyngitis refers to inflammation of the pharynx, including erythema, edema, exudates, or an enanthem (ulcers, vesicles). Pharyngeal inflammation can be related to environmental exposures, such as tobacco smoke, air pollutants, and allergens; from contact with caustic substances, hot food, and liquids; and from infectious agents. The pharynx and mouth can be involved in various inflammatory conditions such as the periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome, Kawasaki disease, inflammatory bowel disease (IBD), Stevens-Johnson syndrome, and systemic lupus erythematous (SLE). Noninfectious etiologies are typically evident from history and physical exam, but it can be more challenging to distinguish from among the numerous infectious causes of acute pharyngitis.

Acute infections of the upper respiratory tract account for a substantial number of visits to pediatricians and many feature sore throat as a symptom or evidence of pharyngitis on physical examination. The usual clinical task is to distinguish important, potentially serious, and treatable causes of acute pharyngitis from those that are self-limited and require no specific treatment or follow-up. Specifically, identifying patients who have **group A streptococcus** (GAS; *Streptococcus pyogenes* ; see Chapter 210) pharyngitis and treating them with antibiotics forms the core of the management paradigm.

Infectious Etiologies

Viruses

In North America and most industrialized countries, GAS is the most important bacterial cause of acute pharyngitis, but viruses predominate as acute infectious causes of pharyngitis. Viral upper respiratory tract infections are typically spread by contact with oral or respiratory secretions and occur most commonly in fall, winter, and spring—that is, the respiratory season. Important viruses that cause pharyngitis include influenza, parainfluenza, adenoviruses, coronaviruses, enteroviruses, rhinoviruses, respiratory syncytial virus (RSV), cytomegalovirus, Epstein-Barr virus (EBV), herpes simplex virus (HSV), and human metapneumovirus (HMPV) (Table 409.1). Most viral pharyngitis, except mononucleosis, is mild. Common nonspecific symptoms such as rhinorrhea and cough develop gradually before they become prominent. However, specific findings are sometimes helpful in identifying the infectious viral agent (Table 409.2).

Table 409.1

Infectious Agents That Cause Pharyngitis

VIRUSES	BACTERIA
Adenovirus Coronavirus Cytomegalovirus Epstein-Barr virus Enteroviruses Herpes simplex virus (1 and 2) Human immunodeficiency virus Human metapneumovirus Influenza viruses (A and B) Measles virus Parainfluenza viruses Respiratory syncytial virus Rhinoviruses	*Streptococcus pyogenes* (Group A streptococcus)
	Arcanobacterium haemolyticum
	Fusobacterium necrophorum
	Corynebacterium diphtheriae
	Neisseria gonorrhoeae
	Group C streptococci
	Group G streptococci
	Francisella tularensis *Yersinia pestis*
	Chlamydophila pneumoniae
	Chlamydia trachomatis
	Mycoplasma pneumoniae *Mixed anaerobes (Vincent angina)*

Table 409.2

Epidemiologic and Clinical Features Suggestive of Group A Streptococcal and Viral Pharyngitis

FEATURE, BY SUSPECTED ETIOLOGIC AGENT
Group A Streptococcal
• Sudden onset of sore throat • Age 5-15 yr • Fever • Headache • Nausea, vomiting, abdominal pain • Tonsillopharyngeal inflammation

• Patchy tonsillopharyngeal exudates • Palatal petechiae • Anterior cervical adenitis (tender nodes) • Winter and early spring presentation • History of exposure to strep pharyngitis • Scarlatiniform rash
Viral
• Conjunctivitis • Coryza • Cough • Diarrhea • Hoarseness • Discrete ulcerative stomatitis • Viral exanthema

From Shulman ST, Bisno AL, Clegg HW, et al: Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis* 55(10):e86–e102, 2012, Table 4, p. e91.

Gingivostomatitis and ulcerating vesicles throughout the anterior pharynx and on the lips and perioral skin are seen in primary oral HSV infection. High fever and difficulty taking oral fluids are common. This infection can last for 14 days.

Discrete **papulovesicular** lesions or **ulcerations** in the posterior oropharynx, severe throat pain, and fever are characteristic of **herpangina** , caused by various enteroviruses. In **hand-foot-mouth disease** , there are vesicles or ulcers throughout the oropharynx, vesicles on the palms and soles, and sometimes on the trunk and extremities. Coxsackie A16 is the most common agent, but Enterovirus 71 and Coxsackie A6 can also cause this syndrome. Enteroviral infections are most common in the summer.

Various adenoviruses cause pharyngitis. When there is concurrent **conjunctivitis** , the syndrome is called *pharyngoconjunctival fever* . The pharyngitis tends to resolve within 7 days but conjunctivitis may persist for up to 14 days. Pharyngoconjunctival fever can be epidemic or sporadic; outbreaks have been associated with exposure in swimming pools.

Intense, diffuse pharyngeal erythema and Koplik spots, the pathognomonic enanthem, occur in advance of the characteristic rash of measles. Splenomegaly, lymphadenopathy, or hepatomegaly may be the clue to EBV infectious mononucleosis in an adolescent with exudative tonsillitis. Primary infection with HIV can manifest as the **acute retroviral syndrome** , with non-exudative pharyngitis, fever, arthralgia, myalgia, adenopathy, and often a maculopapular rash.

Bacteria Other Than Group A Streptococcus

In addition to GAS, bacteria that cause pharyngitis include group C and group G streptococcus, *Arcanobacterium haemolyticum* , *Francisella tularensis* , *Neisseria gonorrhoeae* , *Mycoplasma pneumoniae* , *Chlamydophila* (formerly *Chlamydia*) *pneumoniae* , *Chlamydia trachomatis* , *Fusobacterium necrophorum* , and *Corynebacterium diphtheriae* . *Haemophilus influenzae* and *Streptococcus pneumoniae* may be cultured from the throats of children with pharyngitis, but their role in causing pharyngitis has not been established.

Group C and Group G streptococcus and *A. haemolyticum* pharyngitis have been diagnosed most commonly in adolescents and adults. They resemble group A β-hemolytic streptococcus (GAS) pharyngitis. A scarlet fever–like rash may be present with *A. haemolyticum* infections.

F. necrophorum has been suggested to be a fairly common cause of pharyngitis in older adolescents and adults (15-30 yr old). Prevalence in studies has varied from 10% to 48% of patients with non-GABHS pharyngitis, but large surveillance studies have not been performed. *F. necrophorum* was detected by PCR in 20.5% of patients with pharyngitis in a study based in a university health clinic and in 9.4% of an asymptomatic convenience sample; some patients had more than 1 bacterial species detected by PCR. Pharyngitis patients with *F. necrophorum* had signs and symptoms similar to GAS pharyngitis: about one third had fever, one third had tonsillar exudates, two thirds had anterior cervical adenopathy, and most did not have cough. This organism is difficult to culture from the throat, and diagnostic testing with PCR is not generally available. *F. necrophorum* pharyngitis is associated with the development of **Lemierre syndrome** (see Chapter 410), internal jugular vein septic thrombophlebitis. Approximately 80% of cases of Lemierre syndrome are caused by this bacterium. Patients present initially with fever, sore throat, exudative pharyngitis, and/or peritonsillar abscess. The symptoms may persist, neck pain and swelling develop, and the patient appears toxic. Septic shock may ensue, along with metastatic complications from septic emboli that can involve the lungs, bones and joints, central nervous system, abdominal organs, and soft tissues. The case fatality rate is 4–9%.

Gonococcal pharyngeal infections are usually asymptomatic but can cause acute ulcerative or exudative pharyngitis with fever and cervical lymphadenitis. Young children with proven gonococcal disease should be evaluated for sexual abuse.

Diphtheria is extremely rare in most developed countries due to extensive immunization with diphtheria toxoid. However, it remains endemic in many areas of the world, including the former Soviet bloc countries, Africa, Asia, the Middle East, and Latin America. It can be considered in patients with recent travel to or from these areas and in unimmunized patients. Key physical findings are bull neck (extreme neck swelling) and a gray pharyngeal pseudomembrane that can cause respiratory obstruction.

Ingestion of water, milk, or undercooked meat contaminated by *F. tularensis* can lead to oropharyngeal tularemia. Severe throat pain, tonsillitis, cervical adenitis, oral ulcerations, and a pseudomembrane (as in diphtheria) may be present. *M. pneumoniae* and *C. pneumonia* e cause pharyngitis, but other upper and lower respiratory infections are more important and more readily recognized. Development of a severe or persistent cough subsequent to pharyngitis may be the clue to infection with 1 of these organisms.

Group A Streptococcus

Streptococcal pharyngitis is relatively uncommon before 2-3 yr of age, is quite common among children 5-15 yr old, and declines in frequency in late adolescence and adulthood. Illness occurs throughout the year but is most prevalent in winter and spring. It is readily spread among siblings and schoolmates. GAS causes 15–30% of pharyngitis in school-age children.

Colonization of the pharynx by GAS can result in either asymptomatic carriage or acute infection. After an incubation period of 2-5 days, pharyngeal infection with GAS classically presents as rapid onset of significant sore throat and fever (see Table 409.2). The pharynx is red, the tonsils are enlarged and often covered with a white, grayish, or yellow exudate that may be blood-tinged. There may be petechiae or doughnut lesions on the soft palate and posterior pharynx, and the uvula may be red and swollen (see Fig. 411.1). The surface of the tongue can resemble a strawberry when the papillae are inflamed and prominent (strawberry tongue). Initially, the tongue is often coated white, and with the swollen papillae it is called a *white strawberry tongue* (see Fig. 210.1*B*). When the white coating is gone after a few days, the tongue is often quite red, and is called a *red strawberry tongue* (see Fig. 210.1*C*). Enlarged and tender anterior cervical lymph nodes are frequently present. Headache, abdominal pain, and vomiting are frequently associated with the infection, but in the absence of clinical pharyngitis, gastrointestinal signs and symptoms should not be attributed to GAS. Ear pain is a frequent complaint, but the tympanic membranes are usually normal. Diarrhea, cough, coryza, ulcerations, croup/laryngitis/hoarseness, and conjunctivitis *are not* associated with GAS pharyngitis and increase the likelihood of a viral etiology (see Table 409.2).

Patients infected with GAS that produce streptococcal pyrogenic exotoxin A, B, or C may demonstrate the fine red, papular (sandpaper) rash of **scarlet fever** (see Fig. 210.1*A* **)** . It begins on the face and then becomes generalized. The cheeks are red, and the area around the mouth is less intensely red (more pale), giving the appearance of circumoral pallor. The rash blanches with pressure, and it may be more intense in skin creases, especially in the antecubital fossae, axillae, and inguinal creases (Pastia lines or sign). Pastia lines are sometimes petechial or slightly hemorrhagic. Capillary fragility can cause petechiae distal to a tourniquet or constriction from clothing, a positive tourniquet test or Rumpel-Leeds phenomenon. Erythema fades in a few days, and when the rash resolves, it typically peels like a mild sunburn. Sometimes there is sheet-like desquamation around the free margins of the finger nails. Streptococcal pyrogenic exotoxin A, encoded by the gene *spe A* , is the exotoxin most commonly associated with scarlet fever.

The M protein is an important GAS virulence factor that facilitates resistance to phagocytosis. The M protein is encoded by the *emm* gene and determines the M type (or *emm* type). Molecular methods have identified more than 200 *emm* genes (*emm* types, M types). The M protein is immunogenic and protects against reinfection with the homologous M type; an individual can experience multiple episodes of GAS pharyngitis in a lifetime because natural immunity is M type–specific and does not prevent infection with a new M type. Numerous GAS M types can circulate in a community simultaneously, and they enter and leave communities unpredictably and for unknown reasons.

Diagnosis

The clinical presentations of streptococcal and viral pharyngitis often overlap. In particular, the pharyngitis of mononucleosis can be difficult to distinguish from GAS pharyngitis. Physicians relying solely on clinical judgment often overestimate the likelihood of a streptococcal etiology. Various clinical scoring systems have been described to assist in identifying patients who are likely to have GAS pharyngitis. Criteria developed for adults by Centor and modified for children by McIsaac give 1 point for each of the following criteria: history of temperature >38°C (100.4°F), absence of cough, tender anterior cervical adenopathy, tonsillar swelling or exudates, and age 3-14 yr. It subtracts a point for age ≥45 yr. At best, a McIsaac score ≥4 is associated with a positive laboratory test for GAS in less than 70% of children with pharyngitis (Table 409.3), so it, too, overestimates the likelihood of GAS. *Consequently, laboratory testing is essential for accurate diagnosis* . Clinical findings and/or scoring systems can best be used to assist the clinician in identifying patients in need of testing. Evaluating patients indiscriminately can lead to overdiagnosis and overtreatment. Streptococcal antibody tests are not useful in assessing patients with acute pharyngitis.

Table 409.3

Positive Predictive Value of McIsaac Score in Children in Clinical Studies*

SCORE	McISAAC, 2004 (*N* = 454) (%)	EDMONSON, 2005 (*N* = 1184) (%)	TANZ, 2009 (*N* = 1848) (%)	FINE, 2012 (*N* = 64,789) (%)
0	—	—	7	17
1	—	0.5	19	23
2	20.5	8.9	20	34
3	27.5	42.4	29	50
≥4	67.8	48.2	49	68
GAS prevalence	34	38	30	37

[*] One point is given for each of the following criteria: history of temperature >38°C (100.4°F); absence of cough; tender anterior cervical adenopathy; tonsillar swelling or exudates; and age 3-14 yr. Note that the Centor score lacks only the age criterion. Positive predictive value refers to the proportion of patients with documented GAS by rapid antigen-detection test and/or throat culture.

Throat culture and rapid antigen-detection tests (RADTs) are the diagnostic tests for GAS most available in routine clinical care. Throat culture plated on blood agar remains the gold standard for diagnosing streptococcal pharyngitis. There are both false-negative cultures as a consequence of sampling errors or prior antibiotic treatment and false-positive cultures as a consequence of misidentification of other bacteria as GAS. Streptococcal RADTs detect the group A carbohydrate of GAS. They are used by the vast majority of office-based pediatricians. All RADTs have very high specificity, generally ≥95%, so when a RADT is positive it is assumed to be accurate and throat culture is unnecessary. Because RADTs are generally much less sensitive than culture, confirming a negative rapid test with a throat culture is recommended. RADTs and throat culture exhibit spectrum bias: they are more sensitive when the pretest probability of GAS is high (signs and symptoms are typical of GAS infection, higher McIsaac scores) and less sensitive when the pretest probability is low. Avoidance of testing when patients have signs and symptoms more suggestive of a viral infection is recommended by expert guidelines.

Many laboratories have replaced throat culture with one of the highly sensitive and specific **GAS molecular tests** . A variety of methods are available to amplify the DNA of a specific GAS gene from a throat swab in less than 1 hr. In studies both sensitivity and specificity are reported to be ≥98% when compared with standard throat culture. Polymerase chain reaction (PCR) usually matches the molecular test when used to adjudicate discrepancies between the culture and molecular test results. Some of these nucleic acid amplification tests are approved by the FDA for use in physician office laboratories and can be used as the initial test for GAS or as a confirmatory test when the RADT is negative. Unlike throat culture and RADTs, molecular tests may not exhibit spectrum bias—that is, although test sensitivity is extremely high, it is independent of the pretest probability that GAS are the cause of illness (using signs and symptoms, McIsaac score), thus increasing the potential to identify a chronic GAS carrier who actually has an intercurrent illness not due to GAS (discussed later). However, the ability of these stand-alone tests to deliver a definitive result in less than 1 hr makes them attractive (there is one test that takes 15 min)—the potential to swab symptomatic children, have them wait or send them home, and electronically prescribe an antibiotic when the test is positive can speed initiation of therapy and subsequent return to school and activities. The role of molecular tests in diagnosis of GAS pharyngitis is currently unclear because of 3 concerns: (1) they are so sensitive they may cause unnecessary treatment of more patients who are carriers than would ordinarily occur with RADT and/or culture; (2) unless rigorous technique is followed, they may be prone to contamination with exogenous GAS DNA from other swabs, a particular concern in physician offices when performed by staff who are not trained laboratory technologists; and (3) they are much more expensive than throat culture.

Testing for bacteria other than GAS is performed infrequently, and should be reserved for patients with persistent symptoms and symptoms suggestive of a specific non-GAS bacterial pharyngitis—for example, when there is concern for gonococcal infection or sexual abuse. Special culture media and a prolonged incubation are required to detect *A. haemolyticum.* A complete blood cell count showing many atypical lymphocytes and a positive mononucleosis slide agglutination test can help confirm a clinical suspicion of EBV infectious mononucleosis. Viral cultures are often unavailable and are generally too expensive and slow to be clinically useful. PCR is more rapid and multiplex PCR (respiratory viral panel) testing for respiratory pathogens can identify a variety of viral and bacterial agents within a few hours. This may be useful in determining the isolation needs of hospitalized patients, assisting in patient prognosis, and epidemiology, but in the absence of specific treatment for most viral infections such testing is usually not necessary or useful. In fact, interpreting such tests can be difficult unless the patient has signs or symptoms characteristic of a specific pathogen.

Treatment

Specific therapy is unavailable for most viral pharyngitis. However, nonspecific, symptomatic therapy can be an important part of the overall treatment plan. An oral antipyretic/analgesic agent (acetaminophen or ibuprofen) can relieve fever and sore throat pain. Anesthetic sprays and lozenges (often containing benzocaine, phenol, or menthol) can provide local relief in children who are developmentally appropriate to use them. Systemic corticosteroids are sometimes used in children who have evidence of upper airway compromise due to mononucleosis. Although corticosteroids are used commonly in adults with pharyngitis, large-scale studies capable of providing safety and efficacy data are lacking in children. *Corticosteroids cannot be recommended for treatment of most pediatric pharyngitis.*

Antibiotic therapy of bacterial pharyngitis depends on the organism identified. On the basis of in vitro susceptibility data, oral penicillin is often suggested for patients with group C streptococcal isolates, and oral erythromycin is recommended for patients with *A. haemolyticum* , but the clinical benefit of such treatment is uncertain.

Most untreated episodes of GAS pharyngitis resolve uneventfully within a few days, but early antibiotic therapy hastens clinical recovery by 12-24 hr and also reduces suppurative complications of GAS pharyngitis such as peritonsillar abscess and cervical adenitis. *The primary benefit and intent of antibiotic treatment is the prevention of acute rheumatic fever (ARF)* ; it is highly effective when started within 9 days of onset of illness. Antibiotic therapy does not prevent acute poststreptococcal glomerulonephritis (APSGN). Antibiotic treatment should not be delayed for children with symptomatic pharyngitis and a positive test for GAS. Presumptive antibiotic treatment can be started when there is a clinical diagnosis of scarlet fever, a symptomatic child has a household contact with documented streptococcal pharyngitis, or there is a history of ARF in the patient or a family member, but a diagnostic test should be performed to confirm the presence of GAS and antibiotics should be discontinued if GAS are not identified.

A variety of antimicrobial agents are effective for GAS pharyngitis (Table 409.4). Group A streptococci are universally susceptible to penicillin and all other β-lactam antibiotics. Penicillin is inexpensive, has a narrow spectrum of activity, and has few adverse effects. Amoxicillin is often preferred for children because of taste, availability as chewable tablets and liquid, and the convenience of once-daily dosing. The duration of oral penicillin and amoxicillin therapy is 10 days. A single intramuscular dose of benzathine penicillin or a benzathine-procaine penicillin G combination is effective and ensures compliance. Follow-up testing for GAS is unnecessary after completion of therapy and is not recommended unless symptoms recur.

Table 409.4

Recommended Treatment for Acute Streptococcal Pharyngitis

MOST PATIENTS				
	WEIGHT <27 kg	**WEIGHT ≥27 kg**	**ROUTE**	**DURATION**
Amoxicillin	50 mg/kg once daily (maximum 1,000 mg)		Oral	10 days
Penicillin V	250 mg bid	500 mg bid	Oral	10 days
Benzathine penicillin G	600,000 units	1.2 million units	IM	Once
Benzathine penicillin G + procaine penicillin G	900,000 units + 300,000 units	900,000 units + 300,000 units	IM	Once
PENICILLIN-ALLERGIC PATIENTS				
	ORAL DOSE	**FREQUENCY**	**DURATION**	
Cephalosporins[*]	Varies with agent chosen		10 days	
Erythromycins Ethylsuccinate Estolate	40 mg/kg/day up to 1,000 mg/day	bid	10 days	
	20-40 mg/kg/day up to 1,000 mg/day	bid	10 days	
Clarithromycin	15 mg/kg/day up to 500 mg/day	bid	10 days	
Azithromycin[†]	12 mg/kg day 1; 6 mg/kg days 2-5	qd	5 days	
Clindamycin	20 mg/kg/day up to 1.8 g/day	tid	10 days	

[*] First-generation cephalosporins are preferred; dosage and frequency vary among agents. Do not use in patients with history of immediate (anaphylactic) hypersensitivity to penicillin or other β-lactam antibiotics.

[†] Maximum dose is 500 mg the 1st day, 250 mg subsequent days.

Patients allergic to the penicillins can be treated with a 10-day course of a narrow-spectrum, 1st-generation cephalosporin (cephalexin or cefadroxil) if the previous reaction to penicillin was not an immediate, type I hypersensitivity reaction. Frequently, penicillin-allergic patients are treated for 10 days with erythromycin, clarithromycin, or clindamycin, or for 5 days with azithromycin.

The increased use of macrolides and related antibiotics for a variety of infections, especially the azalide, azithromycin, is associated with increased rates of resistance to these drugs among GAS in many countries. Approximately 5% of GAS in the United States and more than 10% in Canada are macrolide-resistant (macrolide resistance includes azalide resistance), but there is considerable local variation in both countries. Rates are much higher in many European and Asian countries. Some macrolide-resistant GAS isolates are also resistant to clindamycin. Although not a major hindrance for treatment of pharyngitis, clindamycin resistance may be important in management of invasive GAS infections. The use of macrolides and related antibiotics should be restricted to patients who cannot safely receive a β-lactam drug for GAS pharyngitis. Tetracyclines, fluoroquinolones, or sulfonamides should *not* be used to treat GAS pharyngitis.

Chronic Group a Streptococcus Carriers

Streptococcal carriers are patients who continue to harbor GAS in the pharynx despite appropriate antibiotic therapy or when they are well. They have little or no evidence of an inflammatory response to the organism. The pathogenesis of chronic carriage is not known; it is assuredly not related to penicillin resistance or nonadherence to therapy, and there is little direct evidence to support the concept of co-pathogenicity (presence of β-lactamase-producing organisms in the pharynx). Carriage generally poses little risk to patients and their contacts, but it can confound testing in subsequent episodes of sore throat. A child who is chronically colonized with GAS (streptococcal carrier) can have a positive test for GAS if it is obtained when the child is evaluated for pharyngitis that is actually caused by a viral infection. Patients with repeated test-positive pharyngitis create anxiety among their families and physicians. It is usually unnecessary to attempt to eliminate chronic carriage. Instead, evaluation and treatment of clinical pharyngitis should be undertaken without regard for chronic carriage, using clinical criteria to determine the need for testing, treating test-positive patients in routine fashion, and avoiding antibiotics in patients who have negative tests. This approach often requires considerable effort to reassure the patient and family that chronic carriage is not a significant health risk. Expert opinion suggests that eradication might be attempted in select circumstances: a community outbreak of ARF or APSGN; personal or family history of ARF; an outbreak of GAS pharyngitis in a closed or semiclosed community, nursing home, or healthcare facility; repeated episodes of symptomatic GAS pharyngitis in a family with ping pong spread among family members despite adequate therapy; when tonsillectomy is being considered because of chronic carriage or recurrent streptococcal pharyngitis; and extreme, unmanageable anxiety related to GAS carriage ("streptophobia") among family members. Clindamycin given by mouth for 10 days is effective therapy (20 mg/kg/day divided in 3 doses; adult dose 150-450 mg tid). Amoxicillin-clavulanate (40 mg amoxicillin/kg/day up to 2,000 mg amoxicillin/day divided tid for 10 days), and 4 days of oral rifampin (20 mg/kg/day up to 600 mg divided in 2 doses) plus either intramuscular benzathine penicillin given once or oral penicillin given for 10 days have also been used (rifampin is started on the 1st day of penicillin therapy).

Recurrent Pharyngitis

True recurrent GAS pharyngitis can occur for several reasons: reinfection with the same M type if type-specific antibody has not developed; poor compliance with oral antibiotic therapy; macrolide resistance if a macrolide was used for treatment; and infection with a new M type. Unfortunately, determining the GAS M type in an acute infection is not available to the clinician. Treatment with intramuscular benzathine penicillin eliminates nonadherence to therapy. Apparent recurrences can represent pharyngitis of another cause in the presence of streptococcal carriage. Chronic GAS carriage is particularly likely if the illnesses are mild and otherwise atypical for GAS pharyngitis.

Tonsillectomy may lower the incidence of pharyngitis for 1-2 yr among children with frequent episodes of documented pharyngitis (≥7 episodes in the previous year or ≥5 in each of the preceding 2 yr, or ≥3 in each of the previous 3 yr). However, the frequency of pharyngitis (GAS and non-GAS) generally declines over time. By 2 yr posttonsillectomy, the incidence of pharyngitis in severely affected children is similar among those who have tonsillectomy and those who do not. Few children are so severely affected, and the limited clinical benefit of tonsillectomy for most must be balanced against the risks of anesthesia and surgery. *Undocumented history of recurrent pharyngitis is an inadequate basis for recommending tonsillectomy.*

Recurrent GAS pharyngitis is rarely, if ever, a sign of an immune disorder. However, recurrent pharyngitis can be part of a recurrent fever or autoinflammatory syndrome such as PFAPA syndrome. Prolonged pharyngitis (>1 wk) can occur in infectious mononucleosis and Lemierre syndrome, but it also suggests the possibility of another disorder such as neutropenia, a recurrent fever syndrome, or an autoimmune disease such as SLE or IBD. In such instances, pharyngitis would be 1 of a number of clinical findings that together should suggest the underlying diagnosis.

Complications and Prognosis

Viral respiratory tract infections can predispose to bacterial middle ear infections and bacterial sinusitis. The complications of GAS pharyngitis include local suppurative complications, such as parapharyngeal abscess, and subsequent nonsuppurative illnesses, such as ARF, APSGN, poststreptococcal reactive arthritis, and possibly PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococci) (sometimes referred to as CANS [childhood acute neuropsychiatric symptoms] or PANS [pediatric acute-onset neuropsychiatric syndrome], recognizing that many infections other than GAS may predispose to these syndromes).

Prevention

Vaccines intended to prevent infection with various viruses (e.g., RSV) and GAS are being developed. A recombinant multivalent GAS M-type vaccine uses the terminal portions of various M proteins to take advantage of their immunogenicity. Other GAS vaccines are based on more conserved epitopes in order to avoid the necessity of matching the vaccine with the M types prevalent in a community or target population. None of the investigational GAS vaccines are near licensing for use. A recent comprehensive study of the immune response to childhood GAS pharyngeal acquisition raises questions about how to best design effective vaccines. This is complicated by the variety of clinical scenarios and clinical syndromes associated with GAS and the need to determine the intended clinical benefit(s) of vaccination. Antimicrobial prophylaxis with daily oral penicillin prevents recurrent GAS infections but is recommended only to prevent recurrences of ARF.

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CHAPTER 410

Retropharyngeal Abscess, Lateral Pharyngeal (Parapharyngeal) Abscess, and Peritonsillar Cellulitis/Abscess

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The *retropharyngeal* and the *lateral pharyngeal lymph nodes* that drain the mucosal surfaces of the upper airway and digestive tracts are located in the neck within the *retropharyngeal space* (located between the pharynx and the cervical vertebrae and extending down into the superior mediastinum) and the *lateral pharyngeal space* (bounded by the pharynx medially, the carotid sheath posteriorly, and the muscles of the styloid process laterally). The lymph nodes in these deep neck spaces communicate with each other, allowing bacteria from either cellulitis or node abscess to spread to other nodes. Infection of the nodes usually occurs as a result of extension from a localized infection of the oropharynx. A **retropharyngeal abscess** can also result from penetrating trauma to the oropharynx, dental infection, and vertebral osteomyelitis. Once infected, the nodes may progress through 3 stages: *cellulitis, phlegmon,* and *abscess.* Infection in the retropharyngeal and lateral pharyngeal spaces can result in airway compromise or posterior mediastinitis, making timely diagnosis important. Incidence based on analysis of a 2009 national database is estimated to be 4.6 per 100,000 children in the United States.

Retropharyngeal and Lateral Pharyngeal Abscess

Retropharyngeal abscess occurs most commonly in children younger than 3-4 yr of age; as the retropharyngeal nodes involute after 5 yr of age, infection in older children and adults is much less common. In the United States, abscess formation occurs most commonly in winter and early spring. Males are affected more often than females and approximately two-thirds of patients have a history of recent ear, nose, or throat infection.

Clinical manifestations of retropharyngeal abscess are nonspecific and include fever, irritability, decreased oral intake, and drooling. Neck stiffness, torticollis, and refusal to move the neck may also be present. The verbal child might complain of sore throat and neck pain. Other signs can include muffled voice, stridor, respiratory distress, or even obstructive sleep apnea. Physical examination can reveal bulging of the posterior pharyngeal wall, although this is present in <50% of infants with retropharyngeal abscess. Cervical lymphadenopathy may also be present.

Lateral pharyngeal abscess commonly presents as fever, dysphagia, and a prominent bulge of the lateral pharyngeal wall, sometimes with medial displacement of the tonsil.

The differential diagnosis includes acute epiglottitis and foreign body aspiration. In the young child with limited neck mobility, meningitis must also be considered. Other possibilities include lymphoma, hematoma, and vertebral osteomyelitis.

Incision and drainage and culture of an abscessed node provides the definitive diagnosis, but CT can be useful in identifying the presence of a retropharyngeal, lateral pharyngeal, or parapharyngeal abscess (Figs. 410.1 and 410.2). Deep neck infections can be accurately identified and localized with CT scans, but CT accurately identifies abscess formation in only 63% of patients. Soft-tissue neck films taken during inspiration with the neck extended might show increased width or an air–fluid level in the retropharyngeal space. CT with contrast medium enhancement can reveal central lucency, ring enhancement, or scalloping of the walls of a lymph node. Scalloping of the abscess wall is thought to be a late finding and predicts abscess formation.

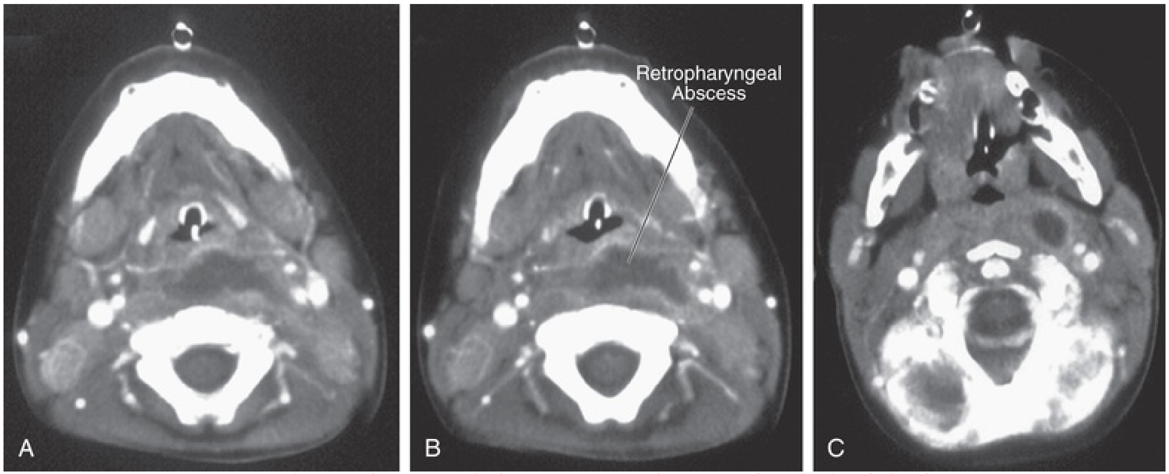

FIG. 410.1 CT of retropharyngeal abscess. A, CT image at level of epiglottis. B, Sequential CT slice exhibiting ring-enhancing lesion. C, Further sequential CT slice demonstrating inferior extent of lesion. (From Philpott CM, Selvadurai D, Banerjee AR: Paediatric retropharyngeal abscess, *J Laryngol Otol* 118:925, 2004.)

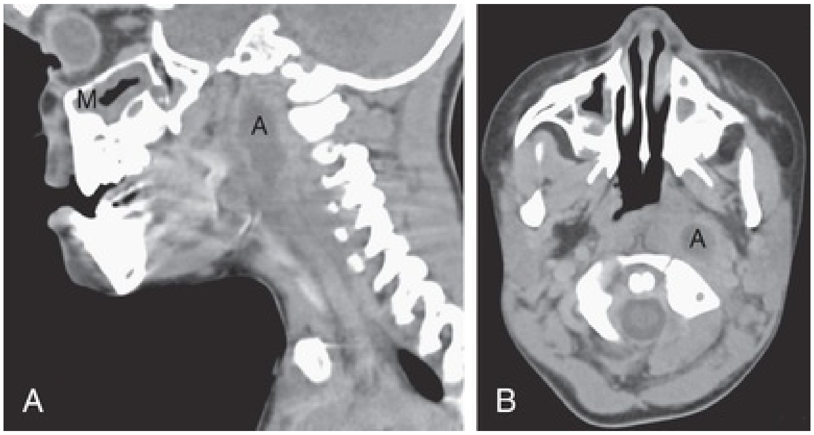

FIG. 410.2 CT of parapharyngeal abscess in a 3 yr old child. A, Sagittal section demonstrating parapharyngeal abscess *(A)* and mucosal swelling *(M)* in the maxillary sinus. B, Coronal section of parapharyngeal abscess *(A).*

Retropharyngeal and lateral pharyngeal infections are most often polymicrobial; the usual pathogens include group A streptococcus (see Chapter 210), oropharyngeal anaerobic bacteria (see Chapter 240), and *Staphylococcus aureus* (see Chapter 208.1). In children younger than age 2 yr, there has been an increase in the incidence of retropharyngeal abscess, particularly with *S. aureus,* including methicillin-resistant strains. Mediastinitis may be identified on CT in some of these patients. Other pathogens can include *Haemophilus influenzae, Klebsiella*, and *Mycobacterium avium-intracellulare.*

Treatment options include intravenous antibiotics with or without surgical drainage. A third-generation cephalosporin combined with ampicillin-sulbactam or clindamycin to provide anaerobic coverage is effective. The increasing prevalence of methicillin-resistant *S. aureus* can influence empiric antibiotic therapy. Studies show that >50% of children with retropharyngeal or lateral pharyngeal abscess as identified by CT can be successfully treated without surgical drainage; the older the child, the more likely it is that antimicrobial treatment alone will be successful. Drainage is necessary in the patient with respiratory distress or failure to improve with intravenous antibiotic treatment. The optimal duration of treatment is unknown; the typical treatment course is intravenous antibiotic therapy for several days until the patient has begun to improve, followed by a course of oral antibiotics.

Complications of retropharyngeal or lateral pharyngeal **abscess** include significant upper airway obstruction, rupture leading to aspiration pneumonia, and extension to the mediastinum. Thrombophlebitis of the internal jugular vein and erosion of the carotid artery sheath can also occur.

An uncommon but characteristic infection of the parapharyngeal space is **Lemierre disease,** in which infection from the oropharynx extends to cause septic thrombophlebitis of the internal jugular vein and embolic abscesses in the lungs (Fig. 410.3). The causative pathogen is *Fusobacterium necrophorum,* an anaerobic bacterial constituent of the oropharyngeal flora. The typical presentation is that of a previously healthy adolescent or young adult with a history of recent pharyngitis who becomes acutely ill with fever, hypoxia, tachypnea, and respiratory distress. Chest radiography demonstrates multiple cavitary nodules, often bilateral and often accompanied by pleural effusion. Blood culture may be positive. Treatment involves prolonged intravenous antibiotic therapy with penicillin or cefoxitin; surgical drainage of extrapulmonary metastatic abscesses may be necessary (see Chapters 409 and 411).

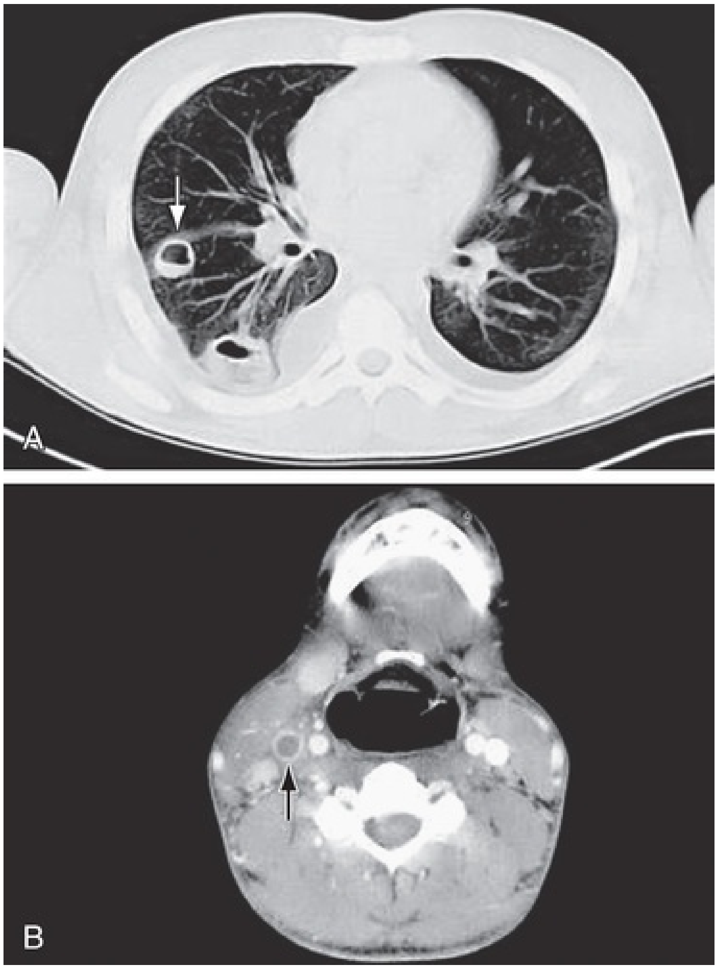

FIG. 410.3 CT of Lemierre disease. A, CT demonstrating nodular appearance of pulmonary infiltrates *(arrow).* B, CT of neck demonstrating thrombosis of right internal jugular vein *(arrow).* (From Plymyer MR, Zoccola DC, Tallarita G: An 18 year old man presenting with sepsis following a recent pharyngeal infection, *Arch Pathol Lab Med* 128:813, 2004. Reprinted with permission from Archives of Pathology & Laboratory Medicine. Copyright 2004. College of American Pathologists.)

Peritonsillar Cellulitis and/or Abscess

Peritonsillar cellulitis and/or abscess, which is relatively common compared to the deep neck infections, is caused by bacterial invasion through the capsule of the tonsil, leading to cellulitis and/or abscess formation in the surrounding tissues. The typical patient with a peritonsillar abscess is an adolescent with a recent history of acute pharyngotonsillitis. Clinical manifestations include sore throat, fever, trismus, muffled or garbled voice, and dysphagia. Physical examination reveals an asymmetric tonsillar bulge with displacement of the uvula. An asymmetric tonsillar bulge is diagnostic, but it may be poorly visualized because of trismus. CT is helpful for revealing the abscess, but recent small studies in adults and children have demonstrated that ultrasound may be used to differentiate peritonsillar abscess from peritonsillar cellulitis and avoids radiation exposure, as well as the need for sedation that CT often necessitates in children. Group A streptococci and mixed oropharyngeal anaerobes are the most common pathogens, with more than four bacterial isolates per abscess typically recovered by needle aspiration.

Treatment includes surgical drainage and antibiotic therapy effective against group A streptococci and anaerobes. Surgical drainage may be accomplished through needle aspiration, incision and drainage, or tonsillectomy. Needle aspiration can involve aspiration of the superior, middle, and inferior aspects of the tonsil to locate the abscess. Intraoral ultrasound can be used to diagnose and guide needle aspiration of a peritonsillar abscess. General anesthesia may be required for the uncooperative patient. Approximately 95% of peritonsillar abscesses resolve after needle aspiration and antibiotic therapy. A small percentage of these patients require a repeat needle aspiration. The 5% with infections that fail to resolve after needle aspiration require incision and drainage. Tonsillectomy should be considered if there is failure to improve within 24 hr of antibiotic therapy and needle aspiration, history of recurrent peritonsillar abscess or recurrent tonsillitis, or complications from peritonsillar abscess. The feared, albeit rare, complication is rupture of the abscess, with resultant aspiration pneumonitis. There is a 10% recurrence risk for peritonsillar abscess.

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† Deceased

CHAPTER 411

Tonsils and Adenoids

Ralph F. Wetmore

Anatomy

The *Waldeyer ring* (the lymphoid tissue surrounding the opening of the oral and nasal cavities into the pharynx) comprises the palatine tonsils, the pharyngeal tonsil or adenoid, lymphoid tissue surrounding the eustachian tube orifice in the lateral walls of the nasopharynx, the lingual tonsil at the base of the tongue, and scattered lymphoid tissue throughout the remainder of the pharynx, particularly behind the posterior pharyngeal pillars and along the posterior pharyngeal wall. The *palatine tonsil* consists of lymphoid tissue located between the palatoglossal fold (anterior tonsillar pillar) and the palatopharyngeal fold (posterior tonsillar pillar) forms. This lymphoid tissue is separated from the surrounding pharyngeal musculature by a thick fibrous capsule. The *adenoid* is a single aggregation of lymphoid tissue that occupies the space between the nasal septum and the posterior pharyngeal wall. A thin fibrous capsule separates it from the underlying structures; the adenoid does not contain the complex crypts that are found in the palatine tonsils but rather more simple crypts. Lymphoid tissue at the base of the tongue forms the *lingual tonsil* that also contains simple tonsillar crypts.

Normal Function

Located at the opening of the pharynx to the external environment, the tonsils and adenoid are well situated to provide primary defense against foreign matter. The immunologic role of the tonsils and adenoids is to induce secretory immunity and to regulate the production of the secretory immunoglobulins. Deep crevices within tonsillar tissue form tonsillar crypts that are lined with squamous epithelium and host a concentration of lymphocytes at their bases. The lymphoid tissue of the Waldeyer ring is most immunologically active between 4 and 10 yr of age, with a decrease after puberty. Adenotonsillar hypertrophy is greatest between ages 3 and 6 yr; in most children tonsils begin to involute after age 8 yr. No major immunologic deficiency has been demonstrated after removal of either or both of the tonsils and adenoid.

Pathology

Acute Infection

Most episodes of acute pharyngotonsillitis are caused by viruses (see Chapter 409). Group A β-hemolytic streptococcus (GABHS) is the most common cause of bacterial infection in the pharynx (see Chapter 210).

Chronic Infection

The tonsils and adenoids can be chronically infected by multiple microbes, which can include a high incidence of β-lactamase–producing organisms. Both aerobic species, such as streptococci and *Haemophilus influenzae,* and anaerobic species, such as *Peptostreptococcus, Prevotella,* and *Fusobacterium,* contribute. The tonsillar crypts can accumulate desquamated epithelial cells, lymphocytes, bacteria, and other debris, causing cryptic tonsillitis. With time, these cryptic plugs can calcify into tonsillar concretions or tonsillolith. Biofilms appear to play a role in chronic inflammation of the tonsils.

Airway Obstruction

Both the tonsils and adenoids are a major cause of upper airway obstruction in children. Airway obstruction in children is typically manifested in sleep-disordered breathing, including obstructive sleep apnea, obstructive sleep hypopnea, and upper airway resistance syndrome (see Chapter 31). Sleep-disordered breathing secondary to adenotonsillar breathing is a cause of growth failure (see Chapter 59).

Tonsillar Neoplasm

Rapid enlargement of one tonsil is highly suggestive of a tonsillar malignancy, typically lymphoma in children.

Clinical Manifestations

Acute Infection

Symptoms of GABHS infection include odynophagia, dry throat, malaise, fever and chills, dysphagia, referred otalgia, headache, muscular aches, and enlarged cervical nodes. Signs include dry tongue, erythematous enlarged tonsils, tonsillar or pharyngeal exudate, palatine petechiae, and enlargement and tenderness of the jugulodigastric lymph nodes (Fig. 411.1 ; see Chapter 210).

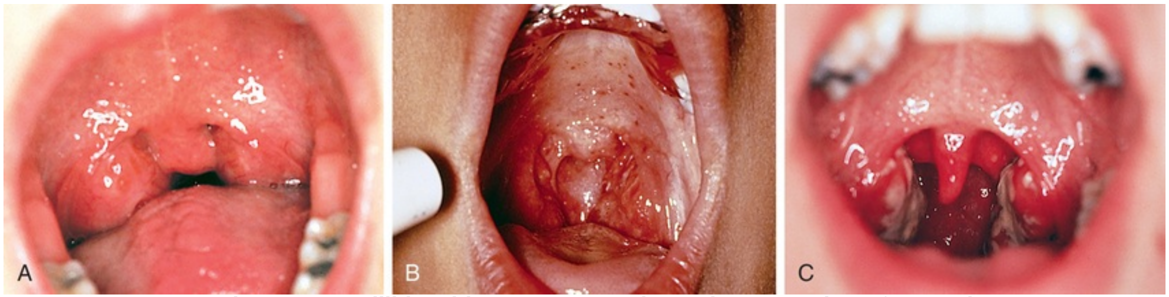

FIG. 411.1 Pharyngotonsillitis. This common syndrome has a number of causative pathogens and a wide spectrum of severity. A, The diffuse tonsillar and pharyngeal erythema seen here is a nonspecific finding that can be produced by a variety of pathogens. B, This intense erythema, seen in association with acute tonsillar enlargement and palatal petechiae, is highly suggestive of group A β-streptococcal infection, though other pathogens can produce these findings. C, This picture of exudative tonsillitis is most commonly seen with either group A streptococcal or Epstein-Barr virus infection. (B, Courtesy Michael Sherlock, MD, Lutherville, MD. From Yellon RF, McBride TP, Davis HW: Otolaryngology. In Zitelli BJ, Davis HW, editors: *Atlas of pediatric physical diagnosis* , ed 4, Philadelphia, 2002, Mosby, p. 852.)

Chronic Infection

Children with chronic or cryptic tonsillitis often present with halitosis, chronic sore throats, foreign-body sensation, or a history of expelling foul-tasting and foul-smelling cheesy lumps. Examination reveals tonsils of a range of sizes, often containing copious debris within the crypts. The offending organism is not usually GABHS.

Airway Obstruction

The diagnosis of airway obstruction (see Chapter 31) can frequently be made by history and physical examination. Daytime symptoms of airway obstruction, secondary to adenotonsillar hypertrophy, include chronic mouth breathing, nasal obstruction, hyponasal speech, hyposmia, decreased appetite, poor school performance, and, rarely, symptoms of right-sided heart failure. Nighttime symptoms consist of loud snoring, choking, gasping, frank apnea, restless sleep, abnormal sleep positions, somnambulism, night terrors, diaphoresis, enuresis, and sleep talking. Large tonsils are typically seen on examination, although the absolute size might not indicate the degree of obstruction. The size of the adenoid tissue can be demonstrated on a lateral neck radiograph or with flexible endoscopy. Other signs that can contribute to airway obstruction include the presence of a craniofacial syndrome or hypotonia.

Tonsillar Neoplasm

The rapid unilateral enlargement of a tonsil, especially if accompanied by systemic signs of night sweats, fever, weight loss, and lymphadenopathy, is highly suggestive of a tonsillar malignancy. The diagnosis of a tonsillar malignancy should also be entertained if the tonsil appears grossly abnormal. Among 54,901 patients undergoing tonsillectomy, 54 malignancies were identified (0.087% prevalence); all but 6 malignancies had been suspected based on suspicious anatomic features preoperatively.

Treatment

Medical Management

The treatment of acute pharyngotonsillitis is discussed in Chapter 409 and antibiotic treatment of GABHS in Chapter 210 . Because copathogens such as staphylococci or anaerobes can produce β-lactamase that can inactivate penicillin, the use of cephalosporins or clindamycin may be more efficacious in the treatment of chronic throat infections. Tonsillolith or debris may be expressed manually with either a cotton-tipped applicator or a water jet. Chronically infected tonsillar crypts can be cauterized using silver nitrate.

Tonsillectomy

Tonsillectomy alone is most commonly performed for recurrent or chronic pharyngotonsillitis. Tonsillectomy has been shown to be effective in reducing the number of infections and the symptoms of chronic tonsillitis such as halitosis, persistent or recurrent sore throats, and recurrent cervical adenitis in severely affected patients. In resistant cases of cryptic tonsillitis, tonsillectomy may be curative. Rarely in children, tonsillectomy is indicated for biopsy of a unilaterally enlarged tonsil to exclude a neoplasm or to treat recurrent hemorrhage from superficial tonsillar blood vessels. Tonsillectomy has not been shown to offer clinical benefit over conservative treatment in children with mild symptoms or in those with severe infections 2 yr after surgery.

There are large variations in surgical rates among children across countries: 144 in 10,000 in Italy; 115 in 10,000 in the Netherlands; 65 in 10,000 in England; and 50 in 10,000 in the United States. Rates are generally higher in boys. With the issuance of practice guidelines, these variations may decrease. The American Academy of Otolaryngology (AAO)–Head and Neck Surgery *Taskforce on Clinical Practice Guidelines: Tonsillectomy in Children* issued evidence-based guidelines in 2019 (Table 411.1). Table 411.2 illustrates the differences and similarities between these guidelines with those of the other major professional groups across the globe. The 2019 guidelines recommend watchful waiting for recurrent throat infections if there has been <7 episodes in the past year, <5 episodes/yr in the past 2 yr, or <3 episodes/yr in the past 3 yr.

Table 411.1

Paradise Criteria for Tonsillectomy

CRITERION	DEFINITION
Minimum frequency of sore throat episodes	At least 7 episodes in the previous year, at least 5 episodes in each of the previous 2 yr, or at least 3 episodes in each of the previous 3 yr
Clinical features	• Sore throat plus at least 1 of the following features qualifies as a counting episode: • Temperature of greater than 38.3°C (100.9°F) • Cervical adenopathy (tender lymph nodes or lymph node size >2 cm) • Tonsillar exudate • Culture positive for group A β-hemolytic streptococcus
Treatment	Antibiotics administered in the conventional dosage for proved or suspected streptococcal episodes
Documentation	Each episode of throat infection and its qualifying features substantiated by contemporaneous notation in a medical record
	If the episodes are not fully documented, subsequent observance by the physician of 2 episodes of throat infection with patterns of frequency and clinical features consistent with the initial history*

* Allows for tonsillectomy in patients who meet all but the documentation criterion. A 12 mo observation period is usually recommended before consideration of tonsillectomy.

Adapted from Baugh RF, Archer SM, Mitchell RB, et al: American Academy of Otolaryngology–Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg* 144(1 Suppl):S8, 2011, Table 5.

Table 411.2

Comparison of American, Italian, and Scottish Guidelines for Tonsillectomy in Children and Adolescents

PARAMETER	AAO-HNS GUIDELINES	ITALIAN GUIDELINES	SCOTTISH GUIDELINES
Audience	Multidisciplinary	Multidisciplinary	Multidisciplinary
Target population	Children and adolescents 1-18 yr of age	Children and adults	Children 4-16 yr of age and adults
Scope	Treatment of children who are candidates for tonsillectomy	Appropriateness and safety of tonsillectomy	Management of sore throat and indications for tonsillectomy
Methods	Based on a priori protocol, systematic literature review, American Academy of Pediatrics scale of evidence quality	Systematic literature review, Italian National Program Guidelines scale of evidence quality	Based on a priori protocol, systematic literature review, Scottish Intercollegiate Guidelines Network scale of evidence quality
Recommendations			
Recurrent infection	Tonsillectomy is an option for children with recurrent throat infection that meets the Paradise criteria (see Table 411.1) for frequency, severity, treatment, and documentation of illness	Tonsillectomy is indicated in patients with at least 1 yr of recurrent tonsillitis (5 or more episodes per year) that is disabling and impairs normal activities, but only after an additional 6 mo of watchful waiting to assess the pattern of symptoms using a clinical diary	Tonsillectomy should be considered for recurrent, disabling sore throat caused by acute tonsillitis when the episodes are well documented, are adequately treated, and meet the Paradise criteria (see Table 411.1) for frequency of illness
Pain control	Recommendation to advocate for pain relief (e.g., provide information, prescribe) and educate caregivers about the importance of managing and reassessing pain	Recommendation for acetaminophen before and after surgery	Recommendation for adequate dose of acetaminophen for pain relief in children
Antibiotic use	Recommendation against perioperative antibiotics	Recommendation for short-term perioperative antibiotics*	NA
Steroid use	Recommendation for a single intraoperative dose of dexamethasone	Recommendation for a single intraoperative dose of dexamethasone	Recommendation for a single intraoperative dose of dexamethasone

Sleep-disordered breathing	Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with sleep-disordered breathing and comorbid conditions	Recommendation for diagnostic testing in children with suspected sleep respiratory disorders	NA
Polysomnography	Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with abnormal polysomnography	Recommendation for polysomnography when pulse oximetry results are not conclusive in agreement with Brouillette criteria	NA
Surgical technique	NA	Recommendation for “cold” technique	NA
Hemorrhage	Recommendation that the surgeon document primary and secondary hemorrhage after tonsillectomy at least annually	NA	NA
Adjunctive therapy	NA	NA	Recommendation against *Echinacea purpurea* for treatment of sore throat
			Recommendation for acupuncture in patients at risk of postoperative nausea and vomiting who cannot take antiemetic drugs

[*] Statement made prior to most recent Cochrane review.

AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; NA, not applicable.

Adapted with permission from Baugh RF, Archer SM, Mitchell RB, et al: American Academy of Otolaryngology–Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg* 144(1 Suppl):S23, 2011, Table 9.

Adenoidectomy

Adenoidectomy alone may be indicated for the treatment of chronic nasal infection (chronic adenoiditis), chronic sinus infections that have failed medical management, and recurrent bouts of acute otitis media, including those in children with tympanostomy tubes who suffer from recurrent otorrhea. Adenoidectomy may be helpful in children with chronic or recurrent otitis media with effusion. Adenoidectomy alone may be curative in the management of patients with nasal obstruction, chronic mouth breathing, and loud snoring suggesting sleep-disordered breathing. Adenoidectomy may also be indicated for children in whom upper airway obstruction is suspected of causing craniofacial or occlusive developmental abnormalities.

Tonsillectomy and Adenoidectomy

The criteria for both tonsillectomy and adenoidectomy for recurrent infection are the same as those for tonsillectomy alone. The other major indication for performing both procedures together is upper airway obstruction secondary to adenotonsillar hypertrophy that results in sleep-disordered breathing, failure to thrive, craniofacial or occlusive developmental abnormalities, speech abnormalities, or, rarely, cor pulmonale. A high proportion of children with failure to thrive in the context of adenotonsillar hypertrophy resulting in sleep disorder experience significant growth acceleration after adenotonsillectomy.

Complications

Poststreptococcal Glomerulonephritis and Acute Rheumatic Fever

The two major complications of untreated GABHS infection are poststreptococcal glomerulonephritis and acute rheumatic fever (see Chapters 537.4 and 210).

Peritonsillar Infection

Peritonsillar infection can occur as either cellulitis or a frank abscess in the region superior and lateral to the tonsillar capsule (see Chapter 409). These infections usually occur in children with a history of recurrent tonsillar infection and are polymicrobial, including both aerobes and anaerobes. Unilateral throat pain, referred otalgia, drooling, and trismus are presenting symptoms. The affected tonsil is displaced down and medial by swelling of the anterior tonsillar pillar and palate. The diagnosis of an abscess can be confirmed by CT or by needle aspiration, the contents of which should be sent for culture.

Retropharyngeal Space Infection

Infections in the retropharyngeal space develop in the lymph nodes that drain the oropharynx, nose, and nasopharynx (see Chapter 410).

Parapharyngeal Space Infection

Tonsillar infection can extend into the parapharyngeal space, causing symptoms of fever, neck pain and stiffness, and signs of swelling of the lateral pharyngeal wall and neck on the affected side. The diagnosis is confirmed by contrast medium-enhanced CT, and treatment includes intravenous antibiotics and external incision and drainage if an abscess is demonstrated on CT (see Chapter 410). Septic thrombophlebitis of the jugular vein, **Lemierre syndrome,** manifests with fever, toxicity, neck pain and stiffness, and respiratory distress as a result of multiple septic pulmonary emboli and is a complication of a parapharyngeal space or odontogenic infection from *Fusobacterium necrophorum.* Concurrent Epstein-Barr virus mononucleosis (see Chapter 281) can be a predisposing event before the sudden onset of fever, chills, and respiratory distress in an adolescent patient. Treatment includes high-dose intravenous antibiotics (ampicillin-sulbactam, clindamycin, penicillin, or ciprofloxacin) and heparinization.

Recurrent or Chronic Pharyngotonsillitis

See Chapter 409 .

Chronic Airway Obstruction

Although rare, children with chronic airway obstruction from enlarged tonsils and adenoids can present with cor pulmonale.

The effects of chronic airway obstruction and mouth breathing on facial growth remain a subject of controversy. Studies of chronic mouth breathing, both in humans and animals, have shown changes in facial development, including prolongation of the total anterior facial height and a tendency toward a retrognathic mandible, the so-called adenoid facies. Adenotonsillectomy can reverse some of these abnormalities. Other studies have disputed these findings.

Tonsillectomy and Adenoidectomy

The risks and potential benefits of surgery must be considered (Table 411.3).

Bleeding can occur in the immediate postoperative period or be delayed (consider von Willebrand disease) after separation of the eschar. The Clinical Guidelines for Tonsillectomy include a recommendation for a single intravenous dose of intraoperative dexamethasone (0.5 mg/kg), which decreases postoperative nausea and vomiting and reduces swelling. There is no evidence that use of dexamethasone in postoperative tonsillectomy patients results in an increased risk of postoperative bleeding. Routine use of antibiotics in the postoperative period is ineffective and thus the AAO Clinical Practice Guidelines advise against its use, although this recommendation is not consistent among the major professional organizations who have issued guidelines (see Table 411.2). Codeine is associated with excessive sedation and fatalities and is not recommended.

Table 411.3

Risks and Potential Benefits of Tonsillectomy or Adenoidectomy or Both

RISKS

• Cost*
• Risk of anesthetic accidents
  • Malignant hyperthermia
  • Cardiac arrhythmia
  • Vocal cord trauma
  • Aspiration with resulting bronchopulmonary obstruction or infection
• Risk of miscellaneous surgical or postoperative complications
  • Hemorrhage
  • Airway obstruction from edema of tongue, palate, or nasopharynx, or retropharyngeal hematoma
  • Central apnea
  • Prolonged muscular paralysis
  • Dehydration
  • Palatopharyngeal insufficiency
  • Otitis media
  • Nasopharyngeal stenosis
  • Refractory torticollis
  • Facial edema
  • Emotional upset
• Unknown risks

POTENTIAL BENEFITS

• Reduction in frequency of ear, nose, throat illness, and thus in
  • Discomfort
  • Inconvenience
  • School absence
  • Parental anxiety
  • Work missed by parents
  • Costs of physician visits and drugs
• Reduction in nasal obstruction with improved

  - Respiratory function
  - Comfort
  - Sleep
  - Craniofacial growth and development
  - Appearance
- Reduction in hearing impairment
- Improved growth and overall well-being
- Reduction in long-term parental anxiety

[*] Cost for tonsillectomy alone and adenoidectomy alone are somewhat lower.

Modified from Bluestone CD, editor: *Pediatric otolaryngology* , ed 4, Philadelphia, 2003, WB Saunders, p. 1213.

Swelling of the tongue and soft palate can lead to acute airway obstruction in the first few hours after surgery. Children with underlying hypotonia or craniofacial anomalies are at greater risk for suffering this complication. Dehydration from odynophagia is not uncommon in the first postoperative week. Rare complications include velopharyngeal insufficiency, nasopharyngeal or oropharyngeal stenosis, and psychologic problems.

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CHAPTER 412

Acute Inflammatory Upper Airway Obstruction (Croup, Epiglottitis, Laryngitis, and Bacterial Tracheitis)

Kristine Knuti Rodrigues, Genie E. Roosevelt

Airway resistance is inversely proportional to the 4th power of the radius (see Chapter 400). Because the lumen of an infant's or child's airway is narrow, minor reductions in cross-sectional area as a result of mucosal edema or other inflammatory processes cause an exponential increase in airway resistance and a significant increase in the work of breathing. The larynx is composed of 4 major cartilages (epiglottic, arytenoid, thyroid, and cricoid cartilages, ordered from superior to inferior) and the soft tissues that surround them. The cricoid cartilage encircles the airway just below the vocal cords and defines the narrowest portion of the upper airway in children younger than 10 yr of age.

Inflammation involving the vocal cords and structures inferior to the cords is called **laryngitis** , **laryngotracheitis** , or **laryngotracheobronchitis** , and inflammation of the structures superior to the cords (i.e., arytenoids, aryepiglottic folds [“false cords”], epiglottis) is called **supraglottitis** . The term **croup** refers to a heterogeneous group of mainly acute and infectious processes that are characterized by a bark-like or brassy cough and may be associated with hoarseness, inspiratory stridor, and respiratory distress. **Stridor** is a harsh, high-pitched respiratory sound that is usually inspiratory but can be biphasic and is produced by turbulent airflow; it is not a diagnosis but a sign of upper airway obstruction (see Chapter 400). Croup typically affects the larynx, trachea, and bronchi. When the involvement of the larynx is sufficient to produce symptoms, these symptoms dominate the clinical picture more so than the tracheal and bronchial signs. A distinction has been made between spasmodic or recurrent croup and laryngotracheobronchitis. Some clinicians believe that spasmodic croup might have an allergic component and improves rapidly without treatment, whereas laryngotracheobronchitis is always associated with a viral infection of the respiratory tract. Others believe that the signs and symptoms are similar enough to consider them within the spectrum of a single disease, in part because studies have documented viral etiologies in both acute and recurrent croup.

412.1

Infectious Upper Airway Obstruction

Kristine Knuti Rodrigues, Genie E. Roosevelt

Etiology and Epidemiology

With the exceptions of diphtheria (see Chapter 214), bacterial tracheitis, and epiglottitis, most acute infections of the upper airway are caused by viruses. The parainfluenza viruses (types 1, 2, and 3; see Chapter 286) account for approximately 75% of cases; other viruses associated with croup include influenza A and B, adenovirus, respiratory syncytial virus, and measles. Influenza A is associated with severe laryngotracheobronchitis. *Mycoplasma pneumoniae* has rarely been isolated from children with croup and causes mild disease (see Chapter 250). Most patients with croup are between the ages of 3 mo and 5 yr, with the peak in the 2nd yr of life. The incidence of croup is higher in boys. It occurs most commonly in the late fall and winter but can occur throughout the year. Approximately 15% of patients have a strong family history of croup. Recurrences are frequent from 3 to 6 yr of age and decrease with growth of the airway. Recurrent croup is defined as 2 or more croup-like episodes. Patients with recurrent croup have a higher incidence of asthma, allergies, and gastroesophageal reflux; less than 9% of patients with recurrent croup demonstrate clinically significant findings on bronchoscopy (e.g., subglottic stenosis, reflux changes, broncho/tracheomalacia).

In the past, *Haemophilus influenzae* type b was the most commonly identified etiology of **acute epiglottitis** . Since the widespread use of the *H. influenzae* type b vaccine, invasive disease caused by *H. influenzae* type b in pediatric patients has been reduced by 99% (see Chapter 221). Therefore, other agents, such as *Streptococcus pyogenes* , *Streptococcus pneumoniae* , nontypeable *H. influenzae* , and *Staphylococcus aureus* , represent a larger portion of pediatric cases of epiglottitis in vaccinated children. In the prevaccine era, the typical patient with epiglottitis caused by *H. influenzae* type b was 2-4 yr of age, although cases were seen in the 1st yr of life and in patients as old as 7 yr of age. Currently, the most common presentation of epiglottitis is an adult with a sore throat, although cases still do occur in underimmunized children; vaccine failures have rarely been reported.

Clinical Manifestations

Croup (Laryngotracheobronchitis)

Viruses typically cause croup, the most common form of acute upper respiratory obstruction. The term laryngotracheobronchitis refers to viral infection of the glottic and subglottic regions. Some clinicians use the term *laryngotracheitis* for the most common and most typical form of croup and reserve the term *laryngotracheobronchitis* for the more severe form that is considered an extension of laryngotracheitis associated with bacterial superinfection that occurs 5-7 days into the clinical course.

Most patients have an upper respiratory tract infection with some combination of rhinorrhea, pharyngitis, mild cough, and low-grade fever for 1-3 days before the signs and symptoms of upper airway obstruction become apparent. The child then develops the characteristic barking cough, hoarseness, and inspiratory stridor. The low-grade fever can persist, although temperatures may occasionally reach 39-40°C (102.2-104°F); some children are afebrile. Symptoms are characteristically worse at night and often recur with decreasing intensity for several days and resolve completely within a week. Agitation and crying greatly aggravate the symptoms and signs. The child may prefer to sit up in bed or be held upright. Other family members might have mild respiratory illnesses with laryngitis. Most young patients with croup progress only as far as stridor and slight dyspnea before they start to recover.

Physical examination can reveal a hoarse voice, coryza, normal to moderately inflamed pharynx, and a slightly increased respiratory rate. Patients vary substantially in their degrees of respiratory distress. Rarely, the upper airway obstruction progresses and is accompanied by an increasing respiratory rate; nasal flaring; suprasternal, infrasternal, and intercostal retractions; and continuous stridor. Croup is a disease of the upper airway, and alveolar gas exchange is usually normal. Hypoxia and low oxygen saturation are seen only when complete airway obstruction is imminent. *The child who is hypoxic, cyanotic, pale, or obtunded needs immediate airway management.* Occasionally, the pattern of severe laryngotracheobronchitis is difficult to differentiate from epiglottitis, despite the usually more acute onset and rapid course of the latter.

Croup is a clinical diagnosis and does not require a radiograph of the neck. Radiographs of the neck can show the typical subglottic narrowing, or steeple sign, of croup on the posteroanterior view (Fig. 412.1). However, the steeple sign may be absent in patients with croup, may be present in patients without croup as a normal variant, and may rarely be present in patients with epiglottitis. The radiographs do not correlate well with disease severity. Radiographs should be considered only after airway stabilization in children who have an atypical presentation or clinical course. Radiographs may be helpful in distinguishing between severe laryngotracheobronchitis and epiglottitis, but airway management should always take priority.

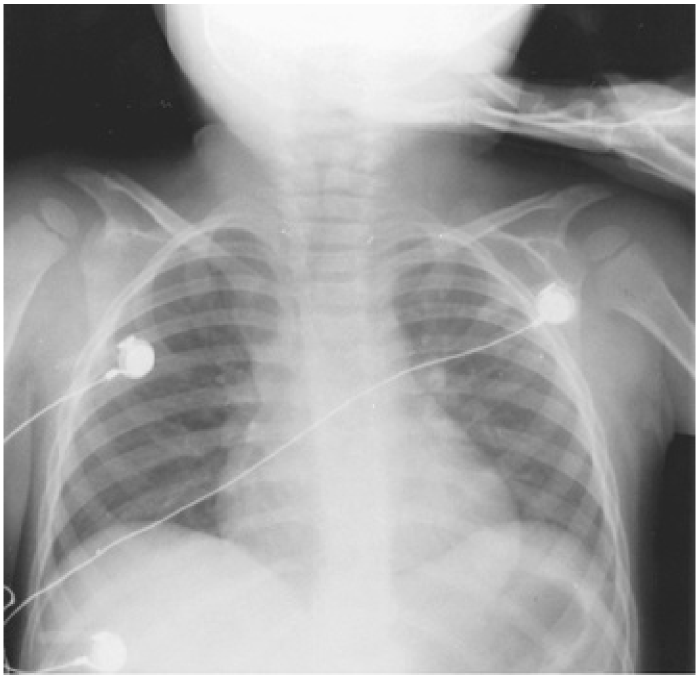

FIG. 412.1 Radiograph of an airway of a patient with croup, showing typical subglottic narrowing (steeple sign).

Acute Epiglottitis (Supraglottitis)

This now rare, but still dramatic and potentially lethal, condition is characterized by an acute rapidly progressive and potentially fulminating course of high fever, sore throat, dyspnea, and rapidly progressing respiratory obstruction. The degree of respiratory distress at presentation is variable. The initial lack of respiratory distress can deceive the unwary clinician; respiratory distress can also be the 1st manifestation. Often, the otherwise healthy child suddenly develops a sore throat and fever. Within a matter of hours, the patient appears toxic, swallowing is difficult, and breathing is labored. Drooling is usually present, and the neck is hyperextended in an attempt to maintain the airway. The child may assume the tripod position, sitting upright and leaning forward with the chin up and mouth open while bracing on the arms. A brief period of air hunger with restlessness may be followed by rapidly increasing cyanosis and coma. Stridor is a late finding and suggests near-complete airway obstruction. Complete obstruction of the airway and death can ensue unless adequate treatment is provided. *The barking cough typical of croup is rare.* Usually no other family members are ill with acute respiratory symptoms.

The diagnosis requires visualization under controlled circumstances of a large, cherry red, swollen epiglottis by laryngoscopy. Occasionally, the other supraglottic structures, especially the aryepiglottic folds, are more involved than the epiglottis itself. In a patient in whom the diagnosis is certain or probable based on clinical grounds, laryngoscopy should be performed expeditiously in a controlled environment such as an operating room or intensive care unit. Anxiety-provoking interventions such as phlebotomy, intravenous line placement, placing the child supine, or direct inspection of the oral cavity should be avoided until the airway is secure. If epiglottitis is thought to be possible but not certain in a patient with acute upper airway obstruction, the patient may undergo lateral radiographs of the upper airway 1st. Classic radiographs of a child who has epiglottitis show the thumb sign (Fig. 412.2). Proper positioning of the patient for the lateral neck radiograph is crucial in order to avoid some of the pitfalls associated with interpretation of the film. Adequate hyperextension of the head and neck is necessary. In addition, the epiglottis can appear to be round if the lateral neck is taken at an oblique angle. If the concern for epiglottitis still exists after the radiographs, direct visualization should be performed. A physician skilled in airway management and use of intubation equipment should accompany patients with suspected epiglottitis at all times. An older cooperative child might voluntarily open the mouth wide enough for a direct view of the inflamed epiglottis.

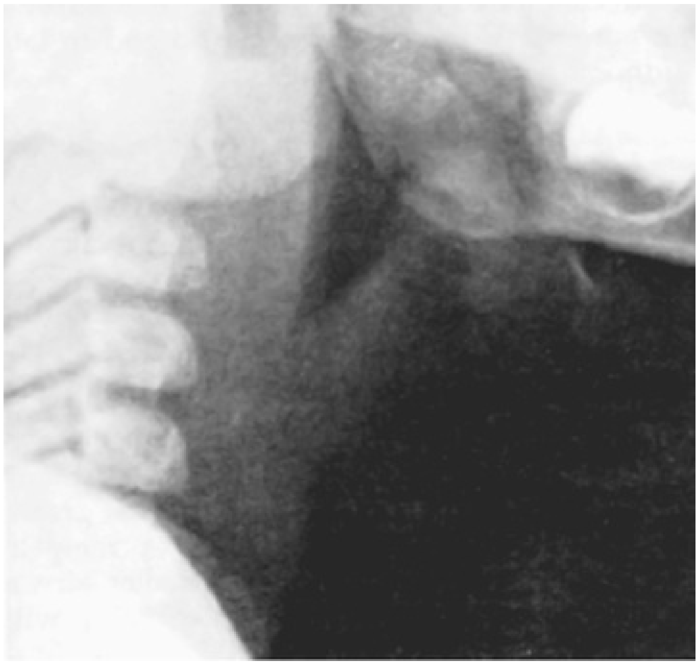

FIG. 412.2 Lateral roentgenogram of the upper airway reveals the swollen epiglottis (thumb sign).

Establishing an airway by endotracheal or nasotracheal intubation or, less often, by tracheostomy is indicated in patients with epiglottitis, regardless of the degree of apparent respiratory distress, because as many as 6% of children with epiglottitis without an artificial airway die, compared with <1% of those with an artificial airway. No clinical features have been recognized that predict mortality. Pulmonary edema can be associated with acute airway obstruction. The duration of intubation depends on the clinical course of the patient and the duration of epiglottic swelling, as determined by frequent examination using direct laryngoscopy or flexible fiberoptic laryngoscopy. In general, children with acute epiglottitis are intubated for 2-3 days, because the response to antibiotics is usually rapid. Most patients have concomitant bacteremia; occasionally, other infections are present, such as pneumonia, cervical adenopathy, or otitis media. Meningitis, arthritis, and other invasive infections with *H. influenzae* type b are rarely found in conjunction with epiglottitis.

Acute Infectious Laryngitis

Laryngitis is a common illness. Viruses cause most cases; diphtheria is an exception but is extremely rare in industrialized countries (see Chapter 214). The onset is usually characterized by an upper respiratory tract infection during which sore throat, cough, and hoarseness appear. The illness is generally mild; respiratory distress is unusual except in the young infant. Hoarseness and loss of voice may be out of proportion to systemic signs and symptoms. The physical examination is usually not remarkable except for evidence of pharyngeal inflammation. Inflammatory edema of the vocal cords and subglottic tissue may be demonstrated laryngoscopically. The principal site of obstruction is usually the subglottic area.

Spasmodic Croup

Spasmodic croup occurs most often in children 1-3 yr of age and is clinically similar to acute laryngotracheobronchitis, except that the history of a viral prodrome and fever in the patient and family are often absent. The cause is viral in some cases, but allergic and other factors may also contribute.

Occurring most commonly in the evening or nighttime, spasmodic croup begins with a sudden onset that may be preceded by mild to moderate coryza and hoarseness. The child awakens with a characteristic barking, metallic cough, noisy inspiration, and respiratory distress, and appears anxious and frightened. The patient is usually afebrile. The severity of the symptoms generally diminishes within several hours, and the following day, the patient often appears well except for slight hoarseness and cough. Similar, but usually less severe, attacks without extreme respiratory distress can occur for another night or 2. Such episodes often recur several times. Spasmodic croup might represent more of an allergic reaction to viral antigens than direct infection, although the pathogenesis is unknown.

Differential Diagnosis

These 4 syndromes must be differentiated from one another and from a variety of other entities that can present as upper airway obstruction. **Bacterial tracheitis** is the most important differential diagnostic consideration and has a high risk of airway obstruction. Diphtheritic croup is extremely rare in North

America, although a major epidemic of diphtheria occurred in countries of the former Soviet Union beginning in 1990 from the lack of routine immunization. Early symptoms of **diphtheria** include malaise, sore throat, anorexia, and low-grade fever. Within 2-3 days, pharyngeal examination reveals the typical gray-white membrane, which can vary in size from covering a small patch on the tonsils to covering most of the soft palate. The membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding. The course is usually insidious, but respiratory obstruction can occur suddenly. **Measles** croup almost always coincides with the full manifestations of systemic disease, and the course may be fulminant (see Chapter 273).

Sudden onset of respiratory obstruction can be caused by aspiration of a **foreign body** (see Chapter 405.1). The child is usually 6 mo to 3 yr of age. Choking and coughing occur suddenly, usually without prodromal signs of infection, although children with a viral infection can also aspirate a foreign body. A **retropharyngeal** or **peritonsillar abscess** can mimic respiratory obstruction (see Chapter 410). CT scans of the upper airway are helpful in evaluating the possibility of a retropharyngeal abscess. A peritonsillar abscess is a clinical diagnosis. Other possible causes of upper airway obstruction include extrinsic compression of the airway (laryngeal web, vascular ring) and intraluminal obstruction from masses (laryngeal papilloma, subglottic hemangioma); these tend to have chronic or recurrent symptoms.

Upper airway obstruction is occasionally associated with **angioedema** of the subglottic areas as part of anaphylaxis and generalized allergic reactions, edema after endotracheal intubation for general anesthesia or respiratory failure, hypocalcemic tetany, infectious mononucleosis, trauma, and tumors or malformations of the larynx. A croupy cough may be an early sign of asthma. Vocal cord dysfunction can also occur. Epiglottitis, with the characteristic manifestations of drooling or dysphagia and stridor, can also result from the accidental ingestion of very hot liquid.

Complications

Complications occur in approximately 15% of patients with viral croup. The most common is extension of the infectious process to involve other regions of the respiratory tract, such as the middle ear, the terminal bronchioles, or the pulmonary parenchyma. Bacterial tracheitis may be a complication of viral croup rather than a distinct disease. If associated with toxin producing *S. aureus* or *S. pyogenes* , toxic shock syndrome can develop. **Bacterial tracheitis** may have a 2-phased illness, with the 2nd phase after a croup-like illness associated with high fever, toxicity, and airway obstruction. Alternatively, the onset of tracheitis occurs without a 2nd phase and appears as a continuation of the initial croup-like illness, but with higher fever and worsening respiratory distress rather than the usual recovery after 2-3 days of viral croup. Pneumonia, cervical lymphadenitis, otitis media, or, rarely, meningitis or septic arthritis can occur in the course of epiglottitis. Pneumomediastinum and pneumothorax are the most common complications of tracheotomy.

Treatment

The mainstay of treatment for children with **croup** is airway management and treatment of hypoxia. Treatment of the respiratory distress should take priority over any testing. Most children with either acute spasmodic croup or infectious croup can be managed safely at home. Despite the observation that cold night air is beneficial, a Cochrane review has found no evidence supporting the use of cool mist in the emergency department for the treatment of croup.

Nebulized racemic epinephrine is the established treatment for moderate or severe croup. The mechanism of action is believed to be constriction of the precapillary arterioles through the β-adrenergic receptors, causing fluid resorption from the interstitial space and a decrease in the laryngeal mucosal edema. Traditionally, racemic epinephrine, a 1 : 1 mixture of the D - and L - isomers of epinephrine, has been administered. A dose of 0.25-0.5 mL of 2.25% racemic epinephrine in 3 mL of normal saline can be used as often as every 20 min. Racemic epinephrine was initially chosen over the more active and more readily available L -epinephrine to minimize anticipated cardiovascular side effects such as tachycardia and hypertension. Current evidence does not favor racemic epinephrine over L-epinephrine (5 mL of 1 : 1,000 solution) in terms of efficacy or safety.

The indications for the administration of nebulized epinephrine include moderate to severe stridor at rest, the possible need for intubation, respiratory distress, and hypoxia. The duration of activity of racemic epinephrine is <2 hr. Consequently, observation is mandated. The symptoms of croup might reappear, but racemic epinephrine does not cause rebound worsening of the obstruction. Patients can be safely discharged home after a 2-3 hr period of observation provided they have no stridor at rest; have normal air entry, normal pulse oximetry, and normal level of consciousness; and have received steroids. Nebulized epinephrine should still be used cautiously in patients with tachycardia, heart conditions such as tetralogy of Fallot, or ventricular outlet obstruction because of possible side effects.

The effectiveness of oral corticosteroids in viral croup is well established. Corticosteroids decrease the edema in the laryngeal mucosa through their antiinflammatory action. Oral steroids are beneficial, even in mild croup, as measured by reduced hospitalization, shorter duration of hospitalization, and reduced need for subsequent interventions such as epinephrine administration. Most studies that demonstrated the efficacy of oral dexamethasone used a single dose of 0.6 mg/kg, a dose as low as 0.15 mg/kg may be just as effective. Intramuscular dexamethasone and nebulized budesonide have an equivalent clinical effect; oral dosing of dexamethasone is as effective as intramuscular administration. A single dose of oral prednisolone is less effective; 1 randomized controlled trial found no difference in the effectiveness of prednisolone 2 mg/kg/day for 3 days versus 1 dose of dexamethasone 0.6 mg/kg. The only adverse effect in the treatment of croup with corticosteroids is the development of *Candida albicans* laryngotracheitis in a patient who received dexamethasone, 1 mg/kg/24 hr, for 8 days. Corticosteroids should not be administered to children with varicella or tuberculosis (unless the patient is receiving appropriate antituberculosis therapy) because they worsen the clinical course.

Antibiotics are not indicated in croup. Nonprescription cough and cold medications should not be used in children younger than 6 yr of age. A helium-oxygen mixture (heliox) may be considered in the treatment of children with severe croup for whom intubation is being considered, although the evidence is inconclusive. Children with croup should be hospitalized for any of the following: progressive stridor, severe stridor at rest, respiratory distress, hypoxia, cyanosis, depressed mental status, poor oral intake, or the need for reliable observation.

Epiglottitis is a medical emergency and warrants immediate treatment with an artificial airway placed under controlled conditions, either in an operating room or intensive care unit. All patients should receive oxygen en route unless the mask causes excessive agitation. Racemic epinephrine and corticosteroids are ineffective. Cultures of blood, epiglottic surface, and, in selected cases, cerebrospinal fluid should be collected after the airway is stabilized. Ceftriaxone, cefepime, or meropenem should be given parenterally, pending culture and susceptibility reports, because 10–40% of *H. influenzae* type b cases are resistant to ampicillin. After insertion of the artificial airway, the patient should improve immediately, and respiratory distress and cyanosis should disappear. Epiglottitis resolves after a few days of antibiotics, and the patient may be extubated; antibiotics should be continued for at least 10 days. Chemoprophylaxis is not routinely recommended for household, childcare, or nursery contacts of patients with invasive *H. influenzae* type b infections, but careful observation is mandatory, with prompt medical evaluation when exposed children develop a febrile illness. **Indications for rifampin prophylaxis** (20 mg/kg orally once a day for 4 days; maximum dose: 600 mg) for all household members include a child within the home who is younger than 4 yr of age and incompletely immunized, younger than 12 mo of age and has not completed the primary vaccination series, or immunocompromised.

Acute laryngeal swelling on an **allergic basis** responds to epinephrine (1 : 1,000 dilution in dosage of 0.01 mL/kg to a maximum of 0.5 mL/dose) administered intramuscularly, or racemic epinephrine (dose of 0.5 mL of 2.25% racemic epinephrine in 3 mL of normal saline) (see Chapter 174). Corticosteroids are often required (1-2 mg/kg/24 hr of prednisone for 3-5 days). After recovery, the patient and parents should be discharged with a preloaded syringe of epinephrine to be used in emergencies. Reactive mucosal swelling, severe stridor, and respiratory distress unresponsive to mist therapy may follow endotracheal intubation for general anesthesia in children. Racemic epinephrine and corticosteroids are helpful.

Endotracheal/Nasotracheal Intubation and Tracheotomy

With the introduction of routine intubation or, less often, tracheotomy for epiglottitis, the mortality rate for epiglottis has decreased to almost zero. These procedures should always be performed in an operating room or intensive care unit if time permits; prior intubation and general anesthesia greatly facilitate performing a tracheotomy without complications. The use of an endotracheal or nasotracheal tube that is 0.5-1.0 mm smaller than estimated by age or height is recommended to facilitate intubation and reduce long-term sequelae. The choice of procedure should be based on the local expertise and experience with the procedure and postoperative care.

Intubation or less often tracheotomy is required for most patients with bacterial tracheitis and all young patients with epiglottitis. It is rarely required for patients with laryngotracheobronchitis, spasmodic croup, or laryngitis. Severe forms of laryngotracheobronchitis that require intubation in a high proportion of patients have been reported during severe measles and influenza A virus epidemics. Assessing the need for these procedures requires experience and judgment because they should not be delayed until cyanosis and extreme restlessness have developed (see Chapter 89). An endotracheal or nasotracheal tube that is 0.5-1.0 mm smaller than estimated by age or height is recommended.

The endotracheal tube or tracheostomy must remain in place until edema and spasm have subsided and the patient is able to handle secretions satisfactorily. It should be removed as soon as possible, usually within a few days. Adequate resolution of epiglottic inflammation that has been accurately confirmed by fiberoptic laryngoscopy, permitting much more rapid extubation, often occurs within 24 hr. Racemic epinephrine and dexamethasone (0.5 mg/kg/dose 6-12 hr prior to extubation then every 6 hr for 6 doses with a maximum dose of 10 mg) may be useful in the treatment of upper airway edema seen postintubation.

Prognosis

In general, the length of hospitalization and the mortality rate for cases of acute infectious upper airway obstruction increase as the infection extends to involve a greater portion of the respiratory tract, except in epiglottitis, in which the localized infection itself can prove to be fatal. Most deaths from croup are caused by a laryngeal obstruction or by the complications of tracheotomy. Rarely, fatal out-of-hospital arrests caused by viral laryngotracheobronchitis have been reported, particularly in infants and in patients whose course has been complicated by bacterial tracheitis. Untreated epiglottitis has a mortality rate of 6% in some series, but if the diagnosis is made and appropriate treatment is initiated before the patient is moribund, the prognosis is excellent. The outcome of acute laryngotracheobronchitis, laryngitis, and spasmodic croup is also excellent.

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412.2

Bacterial Tracheitis

Kristine Knuti Rodrigues, Genie E. Roosevelt

Bacterial tracheitis is an acute bacterial infection of the upper airway that is potentially life-threatening. *S. aureus* (see Chapter 208.1) is the most commonly isolated pathogen, with isolated reports of methicillin-resistant *S. aureus* . *S. pneumoniae* , *S. pyogenes* , *Moraxella catarrhalis* , nontypeable *H. influenzae* ; anaerobic organisms have also been implicated. The mean age is between 5 and 7 yr. There is a slight male predominance. Bacterial tracheitis often follows a viral respiratory infection (especially laryngotracheitis), so it may be considered a bacterial complication of a viral disease, rather than a primary bacterial illness. This life-threatening entity is more common than epiglottitis in vaccinated populations.

Clinical Manifestations

Typically the child has a brassy cough, apparently as part of a viral laryngotracheobronchitis. High fever and toxicity with respiratory distress can occur immediately or after a few days of apparent improvement. The patient can lie flat, does not drool, and does not have the dysphagia associated with epiglottitis. The usual treatment for croup (racemic epinephrine) is ineffective. Intubation or tracheostomy may be necessary, but only 50–60% of patients require intubation for management; younger patients are more likely to need intubation. The major pathologic feature appears to be mucosal swelling at the level of the cricoid cartilage, complicated by copious, thick, purulent secretions, sometimes causing pseudomembranes. Suctioning these secretions, although occasionally affording temporary relief, usually does not sufficiently obviate the need for an artificial airway.

Diagnosis

The diagnosis is based on evidence of bacterial upper airway disease, which includes high fever, purulent airway secretions, and an absence of the classic findings of epiglottitis. X-rays are not needed but can show the classic findings (Fig. 412.3); purulent material is noted below the cords during endotracheal intubation (Fig. 412.4).

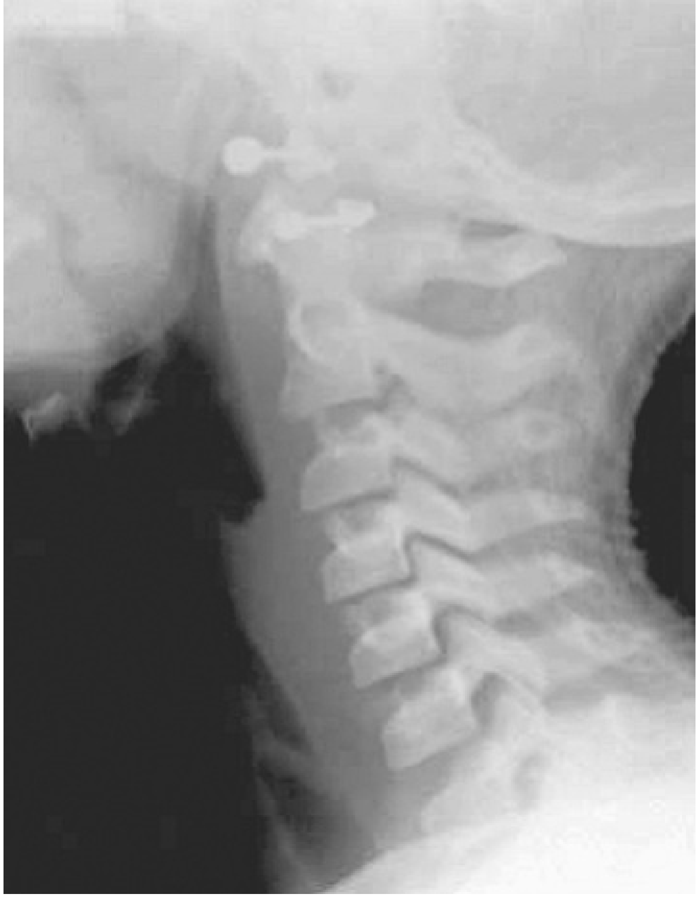

FIG. 412.3 Lateral radiograph of the neck of a patient with bacterial tracheitis, showing pseudomembrane detachment in the trachea. (From Stroud RH, Friedman NR: An update on inflammatory disorders of the pediatric airway: epiglottitis, croup, and tracheitis, *Am J Otolaryngol* 22:268–275, 2001. Photo courtesy of the Department of Radiology, University of Texas Medical Branch at Galveston.)

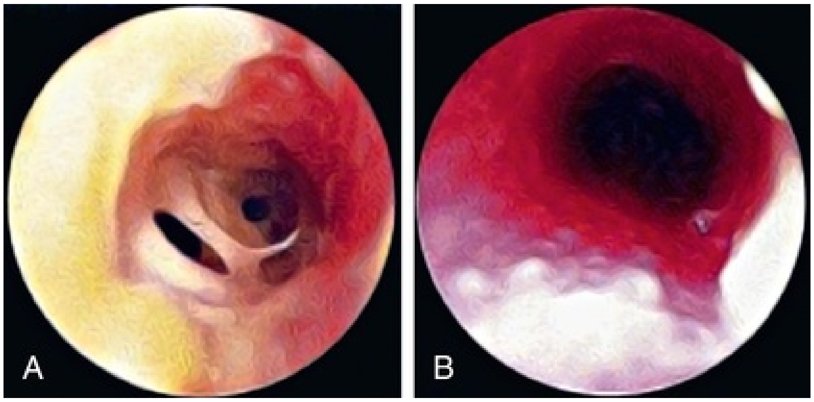

FIG. 412.4 Thick tracheal membranes seen on rigid bronchoscopy. The supraglottis was normal. A, Thick adherent membranous secretions. B, The distal tracheobronchial tree is unremarkable. In contrast to croup, tenacious secretions are seen throughout the trachea, and in contrast to bronchitis, the bronchi are not affected. (From Salamone FN, Bobbitt DB, Myer CM, et al: Bacterial tracheitis reexamined: is there a less severe manifestation? *Otolaryngol Head Neck Surg* 131:871–876, 2004. © 2004 American Academy of Otolaryngology–Head and Neck Surgery Foundation, Inc.)

Treatment

Appropriate antimicrobial therapy, which usually includes antistaphylococcal agents, should be instituted in any patient whose course suggests bacterial tracheitis. Empiric therapy recommendations for bacterial tracheitis include vancomycin or clindamycin and a 3rd-generation cephalosporin (e.g., ceftriaxone or cefepime). When bacterial tracheitis is diagnosed by direct laryngoscopy or is strongly suspected on clinical grounds, an artificial airway should be strongly considered. Supplemental oxygen is usually necessary.

Complications

Chest radiographs often show patchy infiltrates and may show focal densities. Subglottic narrowing and a rough and ragged tracheal air column can often be demonstrated radiographically. If airway management is not optimal, cardiorespiratory arrest can occur. Toxic shock syndrome has been associated with staphylococcal and group A streptococcal tracheitis (see Chapter 208.2).

Prognosis

The prognosis for most patients is excellent. Patients usually become afebrile within 2-3 days of the institution of appropriate antimicrobial therapy, but prolonged hospitalization may be necessary. In recent years, there appears to be a trend toward a less-morbid condition. With a decrease in mucosal edema and purulent secretions, extubation can be accomplished safely, and the patient should be observed carefully while antibiotics and oxygen therapy are continued.

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CHAPTER 413

Congenital Anomalies of the Larynx, Trachea, and Bronchi

Jill N. D'Souza, James W. Schroeder Jr

The larynx functions as a breathing passage, a valve to protect the lungs, and the primary organ of communication; symptoms of laryngeal anomalies are those of airway obstruction, noisy breathing, difficulty feeding, and abnormalities of phonation (see Chapter 400). Obstructive congenital lesions of the upper airway produce turbulent airflow according to the laws of fluid dynamics. This rapid, turbulent airflow across a narrowed segment of respiratory tract produces distinctive sounds that are diagnostically useful. The location of the obstruction produces characteristic changes in the sound of inspiration and/or expiration. Intrathoracic lesions typically cause expiratory wheezing and stridor, often masquerading as asthma. The expiratory wheezing contrasts to the inspiratory stridor caused by the extrathoracic lesions of congenital laryngeal anomalies, specifically laryngomalacia and bilateral vocal cord paralysis. Stertor describes the low-pitched inspiratory snoring sound typically produced by nasal or nasopharyngeal obstruction.

The timing of noisy breathing in relation to the sleep–wake cycle is important. Obstruction of the pharyngeal airway (by enlarged tonsils, adenoids, tongue, or syndromes with midface hypoplasia) typically produces worse obstruction during sleep than during waking. Obstruction that is worse when awake is typically laryngeal, tracheal, or bronchial and is exacerbated by exertion. The location of the obstruction dictates the respiratory phase, tone, and nature of the sound, and these qualities direct the differential diagnosis.

With airway obstruction, the severity of the obstructing lesion, the work of breathing, determines the necessity for diagnostic procedures and surgical intervention. Obstructive symptoms vary from mild to severe stridor with episodes of apnea, cyanosis, suprasternal (tracheal tugging) and subcostal retractions, dyspnea, and tachypnea. Congenital anomalies of the trachea and bronchi can create serious respiratory difficulties from the 1st min of life and may sometimes be diagnosed in the prenatal period. If a severe obstruction is suspected prenatally, an airway birth plan should be developed by a high-risk maternal fetal medicine expert, a neonatologist, and a pediatric airway surgeon. *Congenital high airway obstruction syndrome,* or *CHAOS* , can lead to immediate postnatal distress. Chronic obstruction can cause failure to thrive and chronic hypoxemia and may have long-term effects on growth and development.

413.1

Laryngomalacia

Jill N. D'Souza, James W. Schroeder Jr

Keywords

laryngomalacia
infant
stridor

Clinical Manifestations

Laryngomalacia accounts for 45% to 75% of congenital laryngeal anomalies in children with stridor. Stridor is inspiratory, low-pitched, and exacerbated by any exertion: crying, agitation, or feeding. The stridor is caused, in part, by decreased laryngeal tone leading to supraglottic collapse during inspiration. Symptoms usually appear within the 1st 2 wk and increase in severity for up to 6 mo, although gradual improvement can begin at any time. Gastroesophageal reflux disease, laryngopharyngeal reflux disease, and neurologic disease influence the severity of the disease and thereby the clinical course.

Diagnosis

The diagnosis is made primarily based on symptoms. The diagnosis is confirmed by outpatient flexible laryngoscopy (Fig. 413.1). When the work of breathing is moderate to severe, airway films and chest radiographs are indicated. Laryngomalacia can contribute to feeding difficulties and dysphagia in some children because of decreased laryngeal sensation and poor suck-swallow-breath coordination. When the inspiratory stridor sounds wet or is associated with a cough or when there is a history of repeat upper respiratory illness or pneumonia, dysphagia should be considered. When dysphagia is suspected, a contrast swallow study and/or a fiberoptic endoscopic evaluation of swallowing (FEES) may be considered. Because 15–60% of infants with laryngomalacia have synchronous airway anomalies, complete bronchoscopy is undertaken for patients with moderate to severe obstruction.

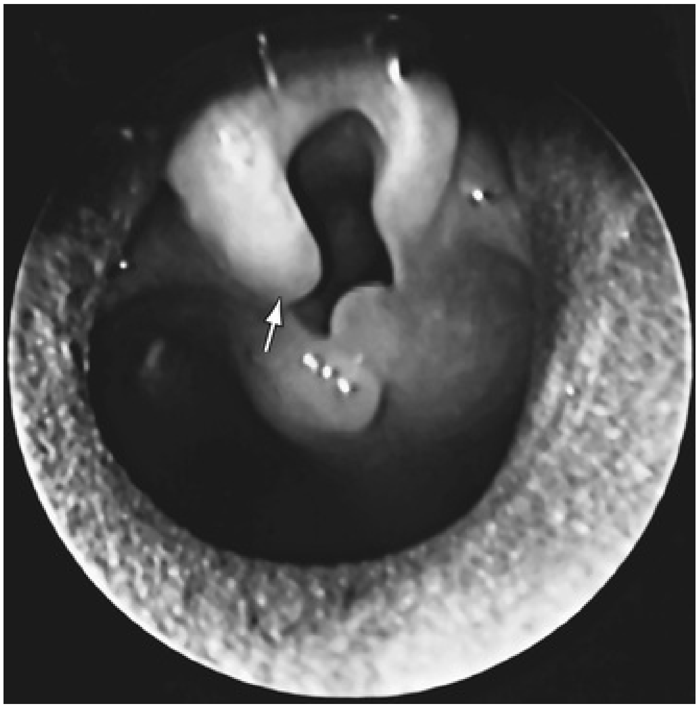

FIG. 413.1 **Endoscopic example of laryngomalacia. On inspiration, the epiglottic folds collapse into the airway. The lateral tips of the epiglottis are also collapsing inward *(arrow).* (From Slovis TL, editor: *Caffey's pediatric diagnostic imaging,* ed 11, Philadelphia, 2008, Mosby.)**

Treatment

Expectant observation is suitable for most infants because most symptoms resolve spontaneously as the child and airway grow. Laryngopharyngeal reflux is managed aggressively with antireflux medications, such as histamine H2 receptor antagonists (H2RAs) or proton pump inhibitors (PPIs). Risk:benefit ratio should be assessed in each patient because these medications, particularly PPIs, have been associated with iron-deficiency anemia, increased incidence of pneumonia, gastroenteritis, and *Clostridium difficile* infections, among others. In 15–20% of patients, symptoms are severe enough to cause progressive respiratory distress, cyanosis, failure to thrive, or cor pulmonale. In these patients, surgical intervention via supraglottoplasty is considered. Supraglottoplasty is 90% successful in relieving upper airway obstruction caused by laryngomalacia. Some comorbidities, such as cardiac disease, neurologic disease, pulmonary disorders, or craniofacial anomalies may be poor prognostic indicators that would suggest earlier intervention.

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413.2

Congenital Subglottic Stenosis

Jill N. D'Souza, James W. Schroeder Jr

Keywords

subglottic stenosis
recurrent bronchiolitis
recurrent croup

Clinical Manifestations

Congenital subglottic stenosis is the second most common cause of stridor. The subglottis is the narrowest part of the upper airway in a child and is located in the space extending from the undersurface of the true vocal folds to the inferior margin of the cricoid cartilage. Subglottic stenosis is a narrowing of the subglottic larynx and manifests in the infant with respiratory distress and biphasic or primarily inspiratory stridor. It may be congenital or acquired. Symptoms often occur with a respiratory tract infection as the edema and thickened secretions of a common cold narrow an already compromised airway leading to recurrent or persistent croup-like symptoms.

Biphasic or primarily inspiratory stridor is the typical presenting symptom for congenital subglottic stenosis. The edema and thickened secretions of the common cold further narrow an already marginal airway that leads to croup-like symptoms. In a child with recurrent bronchiolitis, diagnosis of congenital subglottic stenosis should be considered. The stenosis can be caused by an abnormally shaped cricoid cartilage; by a tracheal ring that becomes trapped underneath the cricoid cartilage; or by soft tissue thickening caused by ductal cysts, submucosal gland hyperplasia, or fibrosis. Acquired subglottic stenosis refers to stenosis caused by extrinsic factors, most commonly resulting from prolonged intubation, and is discussed in further detail in Chapter 415 .

Diagnosis

The diagnosis made by airway radiographs is confirmed by direct laryngoscopy. During diagnostic laryngoscopy the subglottic larynx is visualized directly and sized objectively using endotracheal tubes (Fig. 413.2). The percentage of stenosis is determined by comparing the size of the patients' larynx to a standard of laryngeal dimensions based on age. Stenosis >50% is usually symptomatic and often requires treatment. As with all cases of upper airway obstruction, tracheostomy is avoided when possible. Subglottic stenosis is typically measured using the Myer-Cotton system, with grade I through grade IV subglottic stenosis indicating the severity of narrowing. Dilation and endoscopic laser surgery can be attempted in grade I and II, although they may not be effective because most congenital stenoses are cartilaginous. Anterior cricoid split or laryngotracheal reconstruction with cartilage graft augmentation is typically used in grade III and IV subglottic stenosis. The differential diagnosis includes other anatomic anomalies, as well as a hemangioma or papillomatosis.

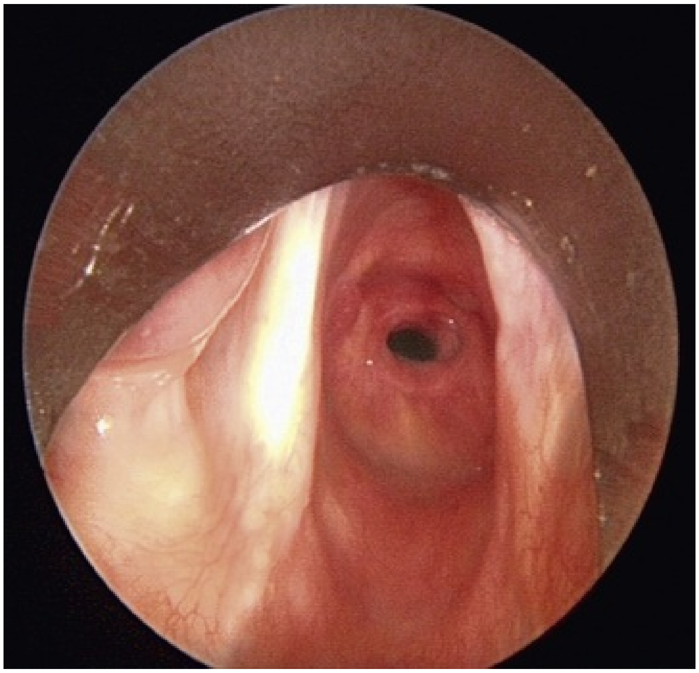

FIG. 413.2 Subglottic stenosis. (Courtesy Rn Cantab, Wikipedia Commons.)

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413.3

Vocal Cord Paralysis

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Keywords

vocal cord paralysis
bilateral
unilateral clinical manifestations

Vocal cord paralysis is the third most common congenital laryngeal anomaly that produces stridor in infants and children. Congenital central nervous system lesions such as Chiari malformation, myelomeningocele, and hydrocephalus or birth trauma may be associated with bilateral paralysis. Bilateral vocal cord paralysis produces airway obstruction manifested by respiratory distress and high-pitched inspiratory stridor, aphonatory or dysphonic sound, or inspiratory weak cry.

Unilateral vocal cord paralysis is most often iatrogenic, as a result of surgical treatment for aerodigestive (tracheoesophageal fistula) and cardiovascular (patent ductus arteriosus repair) anomalies, although they may also be idiopathic. Unilateral paralysis causes aspiration, coughing, and choking; the cry is weak and breathy, but stridor and other symptoms of airway obstruction are less common. Vocal cord paralysis in older children may be due to a Chiari malformation or tumors compressing the vagus or recurrent laryngeal nerve.

Diagnosis

The diagnosis of vocal cord paralysis is made by awake flexible laryngoscopy. The examination will demonstrate an inability or weakness to abduct the involved vocal cord. A thorough investigation for the underlying primary cause is indicated. Because of the association with other congenital lesions, evaluation includes neurology and cardiology consultations, imaging of the course of the recurrent laryngeal nerve, and diagnostic endoscopy of the larynx, trachea, and bronchi.

Treatment

Treatment is based on the severity of the symptoms. Idiopathic vocal cord paralysis in infants usually resolves spontaneously within 6-12 mo. If it is not resolved by 2-3 yr of age, function typically does not recover.

For unilateral vocal cord paralysis, injection laterally to the paralyzed vocal cord moves it medially to reduce aspiration and related complications. Reinnervation procedures using the ansa cervicalis have been successful in regaining some function of unilateral vocal cord.

Bilateral paralysis may require temporary tracheotomy in 50% of patients. Airway augmentation procedures in bilateral vocal cord paralysis typically focus on widening the posterior glottis, such as an endoscopically placed or open posterior glottis cartilage graft, arytenoidectomy, or arytenoid lateralization. These procedures are generally successful in reducing the obstruction; however, they may result in dysphagia and aspiration.

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413.4

Congenital Laryngeal Webs and Atresia

Jill N. D'Souza, James W. Schroeder Jr

Keywords

laryngeal web

glottis web
laryngeal atresia

Congenital laryngeal webs are typically located in the anterior glottis with subglottic extension and associated subglottic stenosis, and they result from incomplete recanalization of the laryngotracheal tube. They may be asymptomatic. Thick webs may be suspected in lateral radiographs of the airway. Chromosomal and cardiovascular anomalies, as well as chromosome 22q11 deletion, are common in patients with congenital laryngeal web. Diagnosis is made by direct laryngoscopy (Fig. 413.3). Treatment might require only incision or dilation. Webs with associated subglottic stenosis are likely to require cartilage augmentation of the cricoid cartilage (laryngotracheal reconstruction). Laryngeal atresia occurs as a complete glottic web due to failure of laryngeal and tracheal recanalization and may be associated with tracheal agenesis and tracheoesophageal fistula. Laryngeal atresia may be detected in the prenatal period, and preparations should be made for establishment of definitive airway at birth. Other times, congenital laryngeal atresia is a cause of respiratory distress in the newborn and is diagnosed only upon initial direct laryngoscopy.

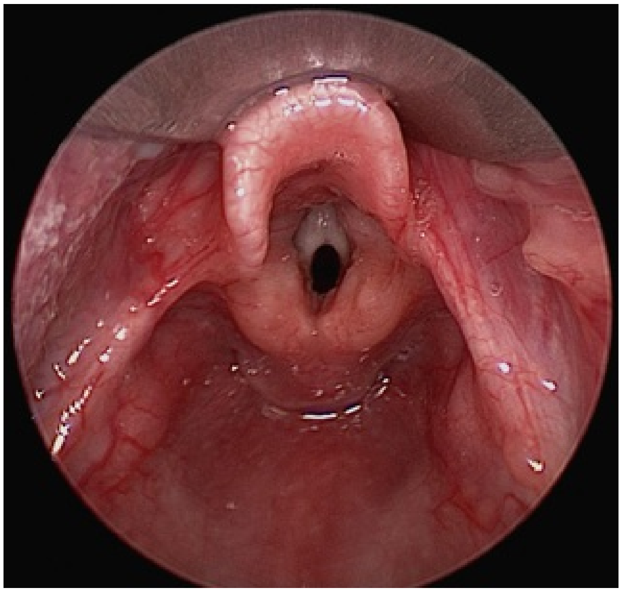

FIG. 413.3 **Anterior glottic web, endoscopic view. (Courtesy Dr. Jeff Rastatter, Division of Pediatric Otolaryngology, Lurie Children's Hospital, Chicago, IL.)**

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413.5

Congenital Subglottic Hemangioma

Jill N. D'Souza, James W. Schroeder Jr

Keywords

subglottic hemangioma
beard distribution
vascular lesions
biphasic stridor

Subglottic hemangioma is a rare cause of early infancy respiratory distress. Symptoms typically present within the 1st 2-6 mo of life. The most common presenting symptom is biphasic stridor, somewhat more prominent during inspiration. This is exacerbated by crying and acute viral illnesses. A barking cough, hoarseness, and symptoms of recurrent or persistent croup are typical.

Only 1% of children who have cutaneous hemangiomas will have a subglottic hemangioma. However, 50% of those with a subglottic hemangioma will have a cutaneous hemangioma. A facial hemangioma is not always present, but when it is evident, it is in the beard distribution, and thus, respiratory distress in a child with a vascular lesion in this area should prompt further investigation. Chest and neck radiographs can show the characteristic asymmetric narrowing of the subglottic larynx. Airway vascular lesions may also be associated with **PHACES syndrome** , characterized by Posterior Fossa Malformations, Hemangioma, Arterial lesions of head and neck, Cardiac anomalies, Eye Anomalies, and Sternal cleft. More than 50% of children with PHACES syndrome have an airway vascular lesion. Treatment options range from conservative monitoring, steroid injection to tracheotomy and airway reconstruction. Propranolol has become a mainstay in initial therapy of subglottic hemangioma; however, it is estimated that up to 50% of patients with subglottic hemangioma may not have a long-term response to propranolol, indicating a need for close airway monitoring in these patients (Fig. 413.4). Treatment is further discussed in Chapter 417.3 .

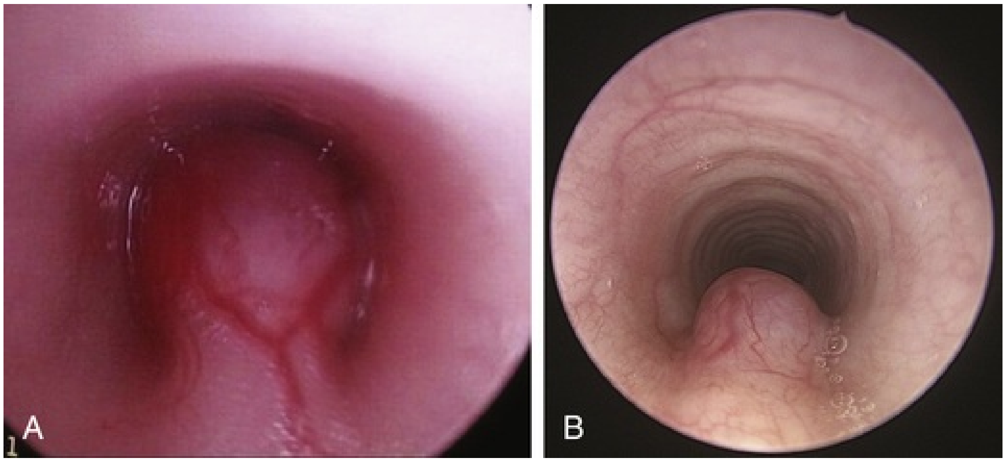

FIG. 413.4 **A** and **B,** Case of tracheal hemangioma prepropranolol and postpropranolol therapy (pictures 2 wk apart). (From Bush A, Abel R, Chitty L, et al: Congenital lung disease. In Wilmott RW, Deterding R, Li A, et al, editors: *Kendig's disorders of the respiratory tract in children* , ed 9, Philadelphia, 2019, Elsevier, Fig. 18.18, p. 308.)

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413.6

Laryngoceles and Saccular Cysts

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Keywords

laryngocele
saccular cyst

A laryngocele is an abnormal air-filled dilation of the laryngeal saccule that arises vertically between the false vocal cord, the base of the epiglottis, and the inner surface of the thyroid cartilage. It communicates with the laryngeal lumen and, when intermittently filled with air, causes hoarseness and dyspnea. A saccular cyst (congenital cyst of the larynx) is distinguished from the laryngocele in that its lumen is isolated from the interior of the larynx and it contains mucus, not air. In infants and children, laryngoceles cause hoarseness and dyspnea that may increase with crying. Saccular cysts may cause respiratory distress and stridor at birth and may require early airway intervention. Intubation can be challenging because the supraglottic and laryngeal anatomy may be distorted. In addition, complete airway obstruction may occur on induction with neuromuscular blockade acting on laryngeal tone. A saccular cyst may be visible on radiography, but the diagnosis is made by laryngoscopy (Fig. 413.5). Needle aspiration of the cyst confirms the diagnosis but rarely provides a cure. Surgical excision is the therapy of choice for management of saccular cysts and laryngoceles. Approaches include endoscopic CO_2 laser excision, endoscopic extended ventriculotomy (marsupialization or unroofing), or, traditionally, external excision.

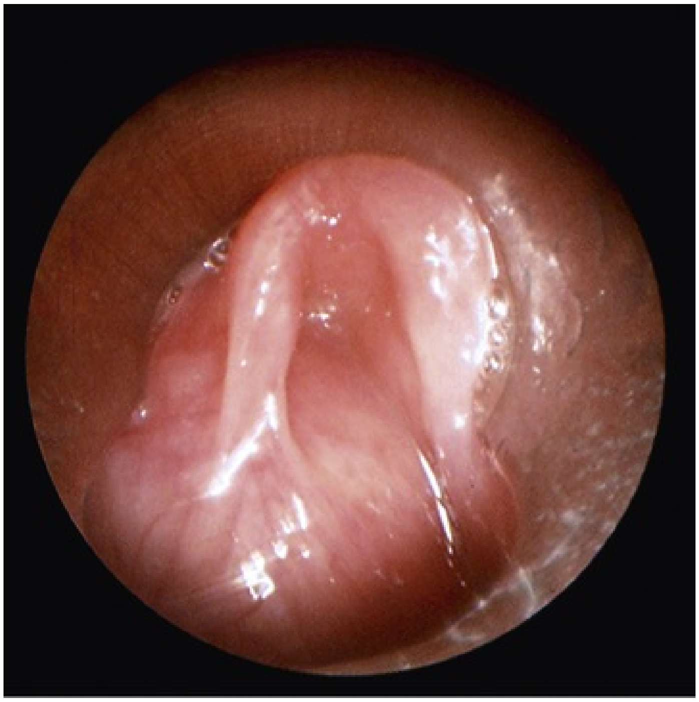

FIG. 413.5 Endoscopic photograph of a saccular cyst. (From Ahmad SM, Soliman AMS: Congenital anomalies of the larynx, *Otolaryngol Clin North Am* 40:177–191, 2007, Fig. 3.)

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413.7

Posterior Laryngeal Cleft and Laryngotracheoesophageal Cleft

Jill N. D'Souza, James W. Schroeder Jr

The posterior laryngeal cleft is characterized by aspiration and is the result of a deficiency in the midline of the posterior larynx. Posterior laryngeal clefts are categorized into 4 types. Type 1 clefts are mild and the interarytenoid notch extends only down to the level of the true vocal cords; 60% of these will cause no symptoms and will not require surgical repair. In severe cases, the cleft (type 4) extends inferiorly into the cervical or thoracic trachea so there is no separation between the trachea and esophagus, creating a laryngotracheoesophageal cleft. Laryngeal clefts can occur in families and are likely to be associated with tracheal agenesis, tracheoesophageal fistula, and multiple congenital anomalies, as with G syndrome, Opitz-Frias syndrome, and Pallister-Hall syndrome.

Initial symptoms are those of aspiration and recurrent respiratory infections. Esophagogram is undertaken to evaluate presence of aspiration or laryngeal penetration of ingested contrast material. A FEES exam may be undertaken by an otolaryngologist with assistance of a speech language and pathology team to observe pattern of liquid spillage during swallow and may identify a cleft. However, the gold standard of diagnosis remains operative laryngoscopy and bronchoscopy with palpation of the posterior larynx. This assists in determining length of the cleft and guides treatment options. A type I cleft extends to, but not beyond, the vocal cords. A type II cleft extends beyond the vocal cords to, but not through, the cricoid cartilage. A type III cleft extends through cricoid into cervical trachea. A type IV cleft extends into thoracic trachea. Treatment is based on the cleft type and the symptoms; in general, a type I cleft may be managed endoscopically, whereas higher grades may require an open procedure. Stabilization of the airway is the first priority. Gastroesophageal reflux must be controlled and a careful assessment for other congenital anomalies is undertaken before repair. Several endoscopic and open cervical and transthoracic surgical repairs have been described.

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413.8

Vascular and Cardiac Anomalies

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Keywords

vascular ring
vascular compression
tracheobronchomalacia

Aberrant cardiopulmonary vascular anatomy may directly impact the trachea and bronchi. The aberrant innominate artery is the most common cause of secondary tracheomalacia (see Chapter 459). It may be asymptomatic and discovered incidentally, or it may cause severe symptoms. Expiratory wheezing and cough occur and, rarely, reflex apnea or "dying spells." Surgical intervention is rarely necessary. Infants are most commonly treated expectantly because the problem is often self-limited.

The term *vascular ring* is used to describe vascular anomalies that result from abnormal development of the aortic arch complex. The double aortic arch is the most common complete vascular ring, encircling both the trachea and esophagus, compressing both. With few exceptions, these patients are symptomatic by 3 mo of age. Respiratory symptoms predominate, but dysphagia may be present. The diagnosis is established by barium esophagogram that shows a posterior indentation of the esophagus by the vascular ring (see Fig. 459.2 in Chapter 459). CT or MRI with angiography provides the surgeon the information needed.

Other vascular anomalies include the pulmonary artery sling, which also requires surgical correction. The most common open (incomplete) vascular ring is the left aortic arch with aberrant right subclavian artery. Although common, it is usually asymptomatic, although dysphagia lusoria may be described. This is characterized as dysphagia caused by an aberrant subclavian coursing behind the esophagus, leading to esophageal compression and difficulty with bolus transit.

Congenital cardiac defects are likely to compress the left main bronchus or lower trachea. Any condition that produces significant pulmonary hypertension increases the size of the pulmonary arteries, which in turn cause compression of the left main bronchus. Surgical correction of the underlying pathology to relieve pulmonary hypertension relieves the airway compression.

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413.9

Tracheal Stenoses, Webs, and Atresia

Jill N. D'Souza, James W. Schroeder Jr

Long segment congenital tracheal stenosis with complete tracheal rings typically occurs within the 1st yr of life, usually after a crisis has been precipitated by an acute respiratory illness. The diagnosis may be suggested by plain radiographs. CT with contrast delineates associated intrathoracic anomalies such as the pulmonary artery sling, which occurs in one third of patients; one-fourth have associated cardiac anomalies. Bronchoscopy is the best method to define the degree and extent of the stenosis and the associated abnormal bronchial branching pattern. Treatment of clinically significant stenosis involves tracheal resection of short segment stenosis, slide tracheoplasty for long segment stenosis or tracheal rings. Congenital soft tissue stenosis and thin webs are rare. Dilation may be all that is required.

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413.10

Foregut Cysts

Jill N. D'Souza, James W. Schroeder Jr

The embryologic foregut gives rise to the pharynx, lower respiratory tract, esophagus, stomach, duodenum, and hepatobiliary tract, and duplication cysts can occur anywhere along this tract. Foregut duplications account for approximately one third of all duplications. The bronchogenic cyst, intramural esophageal cyst (esophageal duplication), and enteric cyst can all produce symptoms of respiratory obstruction and dysphagia. The diagnosis is suspected when chest radiographs or CT scan delineate the mass and, in the case of enteric cyst, the associated vertebral anomaly. The treatment of all foregut cysts is surgical excision.

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413.11

Tracheomalacia and Bronchomalacia

See Chapter 416 .

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CHAPTER 414

Foreign Bodies in the Airway

Allison R. Hammer, James W. Schroeder Jr

Epidemiology and Etiology

Choking is a leading cause of morbidity and mortality among children, especially those younger than 4 yr of age. Most victims of foreign body aspiration are older infants and toddlers (Fig. 414.1); males have been found to be victims up to 1.7 times more likely than females. Studies show that children younger than 4 yr of age account for 61.7–70% of airway foreign body cases. The most common objects on which children choke are food items (59.5–81% of all choking cases). Nuts, seeds, hot dogs, hard candy, gum, bones, and raw fruits and vegetables are the most frequently aspirated food items. From 2001 to 2009, an average of 12,435 children ages 0-14 yr in the United States were treated in emergency departments for choking on food without fatality. Common inorganic objects on which children choke include coins, latex balloons, pins, jewelry, magnets, pen caps, and toys. Globular, compressible, or round objects such as hot dogs, grapes, nuts, balloons, marshmallows, meats, and candies are particularly hazardous due to their ability to completely occlude the airway.

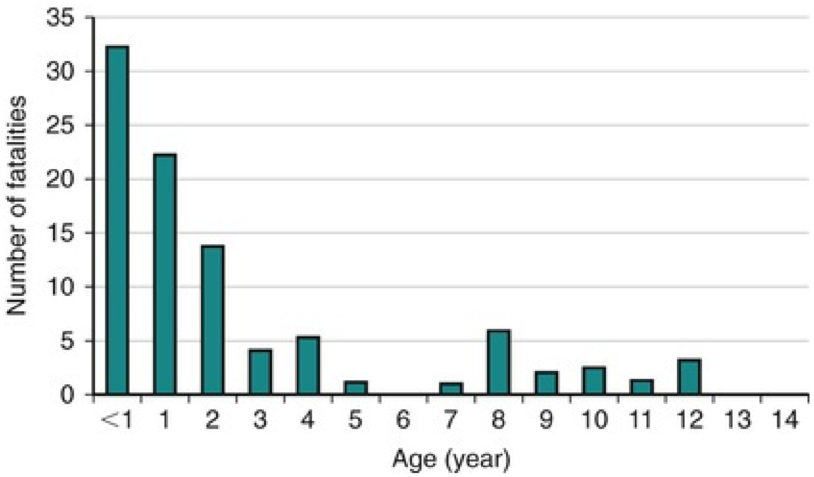

FIG. 414.1 **Number of fatalities versus victim age, all fatality types. (From Milkovich SM, Altkorn R, Chen X, et al: Development of the small parts cylinder: lessons learned, *Laryngoscope* 118[11]:2082–2086, 2008.)**

Young children are more at risk to aspirate a foreign body largely because of their developmental vulnerabilities and their underdeveloped ability to swallow food. Infants and toddlers often use their mouths to explore their surroundings, and children generally are more likely to be distracted, playing, or ambulatory while eating. An infant is able to suck and swallow and is equipped with involuntary reflexes (gag, cough, and glottis closure) that help to protect against aspiration during swallowing. Dentition develops at approximately 6 mo of age with the eruption of the incisors. Molars do not erupt until approximately 1.5 yr of age; mature mastication takes longer to develop. Despite a strong gag reflex, a child's airway is more vulnerable to obstruction than an adult's airway. Young children are more likely to experience significant blockage by small foreign bodies due to their smaller airway diameter. Mucus and secretions may form a seal around the foreign body, making it more difficult to dislodge by forced air. In addition, the force of air generated by an infant or young child's cough is less effective in dislodging an airway obstruction. It is recommended that children younger than 5 yr of age should avoid hard candy and chewing gum and that raw fruits and vegetables be cut into small pieces. Other factors, such as developmental delays or disorders causing neurologic or muscular issues, can also put children at higher risk for foreign body aspiration.

Clinical Manifestations

Foreign bodies of the airway have variable presentations and complications, depending on the characteristics, duration, and location of the foreign body. The clinical manifestations range from an asymptomatic state to severe respiratory distress. The most serious complication of foreign body aspiration is complete obstruction of the airway, which may be recognized in the conscious child as sudden respiratory distress followed by an inability to speak or cough.

There are typically three stages of symptoms that result from aspiration of an object into the airway:

1. **Initial event:** Paroxysms of coughing, choking, gagging, and possibly airway obstruction occur immediately after aspiration of the foreign body. The child is sometimes able to expel the foreign body during this stage.
2. **Asymptomatic interval:** The foreign body becomes lodged, reflexes fatigue, and the immediate irritating symptoms subside. *The lack of symptoms can be particularly misleading to the provider when a child presents in this stage and accounts for a large percentage of delayed diagnoses and overlooked foreign bodies* . A large meta-analysis of more than 30,000 patients showed that diagnosis is delayed more than 25 hr in almost 40% of airway foreign body cases.
3. **Complications:** Obstruction, erosion, or infection develops, which again directs attention to the presence of a foreign body. In this third stage, complications include fever, cough, hemoptysis, pneumonia, and atelectasis. Acute or chronic complications have been reported in almost 15% of cases of foreign bodies of the airway.

Diagnosis

History is the most important factor in determining the need for bronchoscopy. A positive history must never be ignored, but a negative history can be misleading. Because nuts and seeds are the most common bronchial foreign bodies, the physician should specifically question the child's parents about these items, and bronchoscopy should be carried out promptly. A comprehensive physical exam is also essential, including examination of the nose, oral cavity, pharynx, neck, and lungs. Choking or coughing episodes accompanied by new-onset wheezing and asymmetric breath sounds are highly suggestive of foreign body in the airway. In addition to history and physical examination, radiology studies have an important role in diagnosing foreign bodies in the airway. Plain films are typically recommended first, although many foreign bodies are radiolucent (80–96%), and therefore providers often must rely on secondary findings (such as air trapping, asymmetric hyperinflation, obstructive emphysema, atelectasis, mediastinal shift, and consolidation) to indicate suspicion of a foreign body. Expiratory or lateral decubitus films can assist in revealing these suggestive secondary findings. The indication for computed tomography of the chest is currently being explored due to its high sensitivity and specificity, its ability to detect radiolucent objects, and its potential to eliminate the need for an anesthesia and procedure. However, the known risks of radiation must certainly be considered. If there is a high index of suspicion despite negative or inconclusive imaging, bronchoscopy should be performed.

Treatment

The treatment of choice for airway foreign bodies is prompt endoscopic removal with rigid instruments by a specialist (otolaryngologist or pulmonologist). Bronchoscopy is deferred only until providers have obtained preoperative studies and the patient has been prepared by adequate hydration and emptying of the stomach. Airway foreign bodies are usually removed the same day the diagnosis is first considered. As with any treatment modality, providers must give careful consideration to the risks and benefits of the bronchoscopy procedure when diagnosis is unclear. Potential complications of rigid bronchoscopy include bronchospasm, desaturation, bleeding, and airway edema, in addition to the inherent risks of anesthesia.

Beyond the understanding of diagnosis and management of airway foreign bodies, there is a strong need and push for awareness, education, and prevention among caregivers, healthcare providers, and manufacturers of food and toys.

414.1

Laryngeal Foreign Bodies

Allison R. Hammer, James W. Schroeder Jr

Although laryngeal foreign bodies are less common (2–12% of cases) than bronchial or tracheal foreign bodies, they are particularly dangerous due to risk of complete laryngeal obstruction, which can asphyxiate the child unless it is promptly relieved with the Heimlich maneuver (see Chapter 81 and Figs. 81.6 and 81.7). Objects that are partially obstructive of the larynx are usually flat and thin and lodge between the vocal cords in the sagittal plane, causing symptoms of croup, hoarseness, cough, stridor, and dyspnea.

414.2

Tracheal Foreign Bodies

Allison R. Hammer, James W. Schroeder Jr

Tracheal foreign bodies account for 3–12% of airway foreign body cases. Children who have tracheal foreign bodies can present with dysphonia, dysphagia, dry cough, or biphasic stridor. Posteroanterior and lateral soft tissue neck radiographs (airway films) are abnormal in 92% of children, whereas chest radiographs are abnormal in only 58% of these cases.

414.3

Bronchial Foreign Bodies

Allison R. Hammer, James W. Schroeder Jr

Most airway foreign bodies lodge in a bronchus (80–90% of cases). Occasionally, fragments of a foreign body may produce bilateral involvement or shifting infiltrates if they move from lobe to lobe. Some children with bronchial foreign bodies present asymptomatically, whereas others have asymmetric breath sounds, coughing, and wheezing. Posteroanterior and lateral chest radiographs (including the abdomen) are standard in the assessment of infants and children suspected of having aspirated a foreign object. An expiratory posteroanterior chest film is most helpful. During expiration, the bronchial foreign body obstructs the exit of air from the obstructed lung, producing obstructive emphysema and air trapping. The persistent inflation of the obstructed lung causes shift of the mediastinum toward the opposite side (Fig. 414.2). Air trapping is an immediate complication, whereas atelectasis is a late finding. Lateral decubitus chest films or fluoroscopy can provide the same information as expiratory films but are often unnecessary. History and physical examination, not radiographs, determine the indication for bronchoscopy.

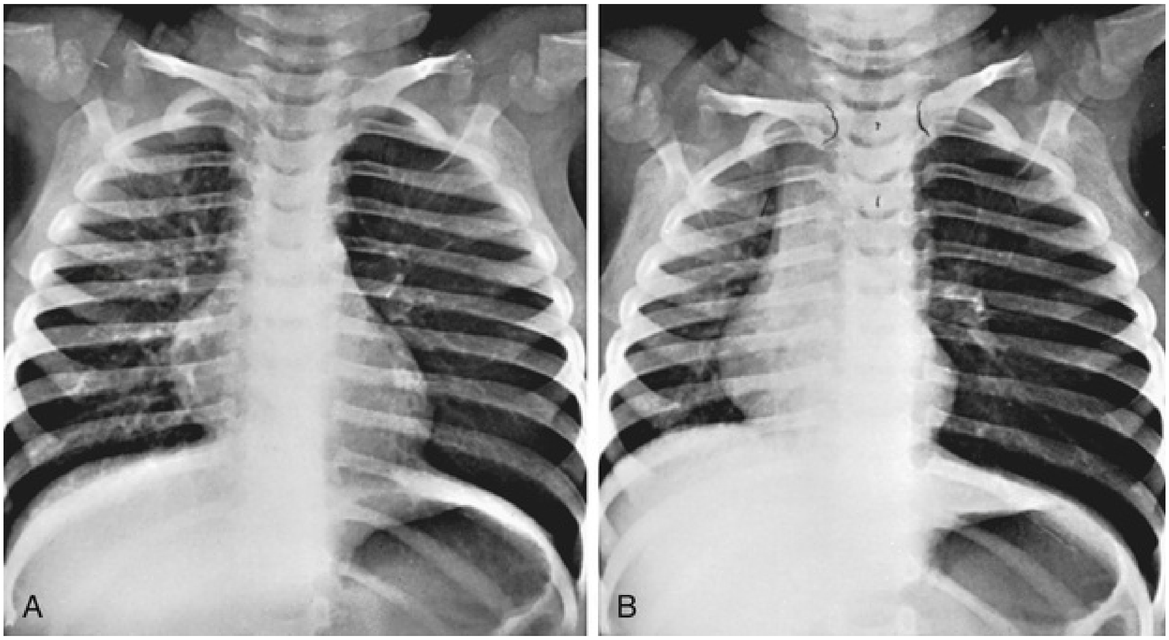

FIG. 414.2 **A,** Normal inspiratory chest radiograph in a toddler with a peanut fragment in the left main bronchus. **B,** Expiratory radiograph of the same child showing the classic obstructive emphysema (air trapping) on the involved *(left)* side. Air leaves the normal right side allowing, the lung to deflate. The medium shifts toward the unobstructed side.

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CHAPTER 415

Laryngotracheal Stenosis and Subglottic Stenosis

Taher Valika, James W. Schroeder Jr

Laryngotracheal stenosis is the second most common cause of stridor in neonates and is the most common cause of airway obstruction requiring tracheostomy in infants. The glottis (vocal cords) and the upper trachea are compromised in most laryngeal stenosis, particularly those that develop following endotracheal intubation. Subglottic stenosis is a narrowing of the subglottic larynx, which is the space extending from the undersurface of the true vocal cords to the inferior margin of the cricoid cartilage. **Subglottic stenosis** is considered congenital when there is no other apparent cause such as a history of laryngeal trauma or intubation. Approximately 90% of cases manifest in the 1st yr of life. Management relies on fine-tuning the airway, while ensuring the patient continues to grow. Knowledge of preventative measures is imperative to all healthcare members.

415.1

Congenital Subglottic Stenosis

Keywords

subglottic stenosis

See Chapter 413.2 .

415.2

Acquired Laryngotracheal Stenosis

Taher Valika, James W. Schroeder Jr

Keywords

subglottic stenosis
laryngotracheal stenosis

Ninety percent of acquired stenoses are a result of endotracheal intubation. The narrowest portion of the pediatric larynx is the subglottic region due to the narrow cricoid cartilage. When the pressure of the endotracheal tube against the cricoid mucosa is greater than the capillary pressure, ischemia occurs, followed by necrosis and ulceration. Secondary infection and perichondritis develop with exposure of cartilage (Fig. 415.1). Granulation tissue forms around the ulcerations. These changes and edema throughout the larynx usually resolve spontaneously after extubation. Chronic edema and fibrous stenosis develop in only a small percentage of cases.

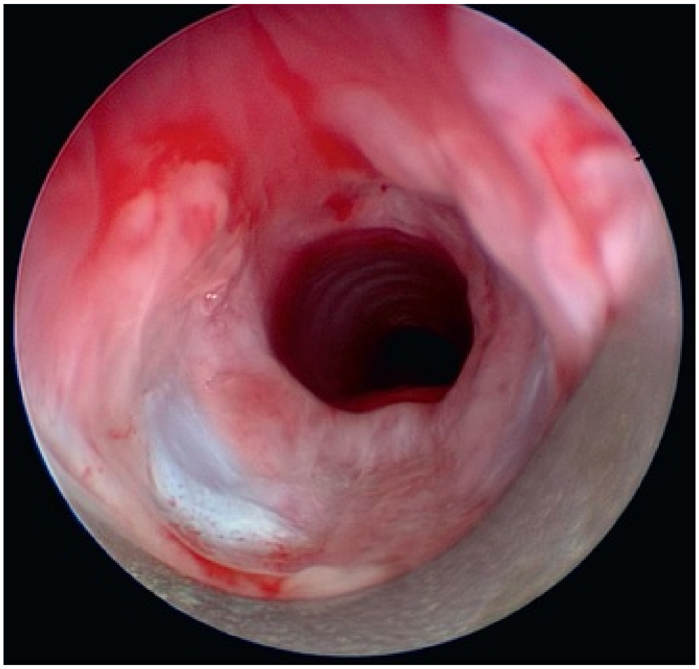

FIG. 415.1 Bronchoscopy in a 2 mo old infant showing mucosal erosion and cartilage exposure in the subglottic region. Child was intubated with an age-appropriate tube but with an excess of air in cuff. (Courtesy Dr. Taher Valika, Division of Pediatric Otolaryngology, Ann & Robert H. Lurie Children's Hospital of Chicago.)

A number of factors predispose to the development of laryngeal stenosis. Laryngopharyngeal reflux of acid and pepsin from the stomach is known to exacerbate endotracheal tube trauma. More damage is caused in areas left unprotected, owing to loss of mucosa. Congenital subglottic stenosis narrows the larynx which makes the patient more likely to develop acquired subglottic stenosis because significant injury is more likely to occur with use of an endotracheal tube of age-appropriate size. Other risk factors for the development of acquired subglottic stenosis include sepsis, malnutrition, chronic inflammatory disorders, and immunosuppression. An oversized endotracheal tube is the most common factor contributing to laryngeal injury. A tube that allows a small air leak at the end of the inspiratory cycle minimizes potential trauma. Other extrinsic factors—traumatic intubation, multiple reintubations, movement of the endotracheal tube, and duration of intubation—can contribute to varying degrees in individual patients.

Clinical Manifestations

Symptoms of acquired and congenital stenosis are similar. Spasmodic croup, the sudden onset of severe croup in the early morning hours, is usually caused by laryngopharyngeal reflux with transient laryngospasm and subsequent laryngeal edema. These frightening episodes resolve rapidly, often before the family and child reach the emergency department. Other presentations can also involve neonates who fail extubation, despite multiple attempts, and children with permanent dyspnea, stridor, or dysphonia.

Diagnosis

The diagnosis can be made by posteroanterior and lateral airway radiographs. The gold standard to confirm the diagnosis is via direct laryngoscopy and bronchoscopy in the operating room. High-resolution CT imaging and ultrasonography are of limited value. This is similar to the workup associated with congenital subglottic stenosis.

Treatment

The severity, location, and type (cartilaginous or soft tissue) of the stenosis determine the treatment. Mild cases can be managed without operative intervention because the airway will improve as the child grows. Moderate soft tissue stenosis is treated by endoscopy using gentle dilations or CO_2 laser. Severe laryngotracheal stenosis is likely to require laryngotracheal reconstructive (expansion) surgery or resection of the narrowed portion of the laryngeal and tracheal airway (cricotracheal resection). Every effort is made to avoid tracheotomy using endoscopic techniques or open surgical procedures.

Fundamental knowledge of the airway can help to reduce the incidence of stenoses. The use of age-appropriate tubes and cuffless tubes, treatment of gastroesophageal reflux, and reducing the duration of mechanical ventilation have led to an overall decrease in laryngotracheal stenoses in the past decade.

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CHAPTER 416

Bronchomalacia and Tracheomalacia

Jonathan D. Finder

Tracheomalacia and bronchomalacia refer to chondromalacia of a central airway, leading to insufficient cartilage to maintain airway patency throughout the respiratory cycle. These are common causes of persistent wheezing in infancy. Tracheomalacia and bronchomalacia can be either primary or secondary (Table 416.1). Primary tracheomalacia and bronchomalacia are often seen in premature infants, although most affected patients are born at term. Secondary tracheomalacia and bronchomalacia refer to the situation in which the central airway is compressed by an adjacent structure (e.g., vascular ring; see Chapter 345) or deficient in cartilage because of tracheoesophageal fistula (see Chapter 345). Bronchomalacia is common following lung transplantation, assumed to be secondary to the loss of bronchial artery supply leading to ischemia of the bronchial cartilage. This form of bronchomalacia may take months to present following transplantation. Laryngomalacia can accompany primary bronchomalacia or tracheomalacia. Involvement of the entire central airway (laryngotracheobronchomalacia) is also seen.

Table 416.1

Classification of Tracheomalacia

PRIMARY TRACHEOMALACIA
Congenital absence of tracheal-supporting cartilages
SECONDARY TRACHEOMALACIA
Esophageal atresia, tracheoesophageal fistula Vascular rings (double aortic arch) Tracheal compression from an aberrant innominate artery Tracheal compression from mediastinal masses Abnormally soft tracheal cartilages associated with connective tissue disorders Prolonged mechanical ventilation, chronic lung disease

From McNamara VM, Crabbe DC: Tracheomalacia, *Paediatr Respir Rev* 5:147–154, 2004.

Clinical Manifestations

Primary tracheomalacia and bronchomalacia are principally disorders of infants, with a male:female ratio of 2 : 1. The dominant finding, low-pitched monophonic wheezing heard predominantly during expiration, is most prominent over the central airways. Parents often describe persistent respiratory congestion even in the absence of a viral respiratory infection. When the lesion involves only one main bronchus (more commonly the left), the wheezing is louder on that side and there may be unilateral palpable fremitus. In cases of tracheomalacia, the wheeze is loudest over the trachea. Hyperinflation and/or subcostal retractions do not occur unless the patient also has concurrent asthma, viral bronchiolitis, or other causes of peripheral airways obstruction. In the absence of asthma, patients with tracheomalacia and bronchomalacia are not helped by administration of a bronchodilator. Acquired tracheomalacia and bronchomalacia are seen in association with vascular compression (vascular rings, slings, and innominate artery compression) or in association with the loss of bronchial artery supply in lung transplantation. Tracheomalacia is the rule following correction of tracheoesophageal fistula. Other causes of acquired tracheomalacia, which may persist after surgical correction include cardiomegaly. The importance of the physical exam cannot be understated; one study found that pediatric pulmonologists made a correct assessment of malacia based on symptoms, history, and lung function prior to bronchoscopy in 74% of cases.

Diagnosis

Definitive diagnoses of tracheomalacia and bronchomalacia are established by flexible or rigid bronchoscopy (Fig. 416.1). The lesion is difficult to detect on plain radiographs. Although fluoroscopy can demonstrate dynamic collapse and avoid the need for invasive diagnostic techniques, it is poorly sensitive. Pulmonary function testing can show a pattern of decreased peak flow and flattening of the flow-volume loop. Other important diagnostic modalities include MRI and CT scanning. MRI with angiography is especially useful when there is a possibility of vascular ring and should be performed when a right aortic arch is seen on plain film radiography.

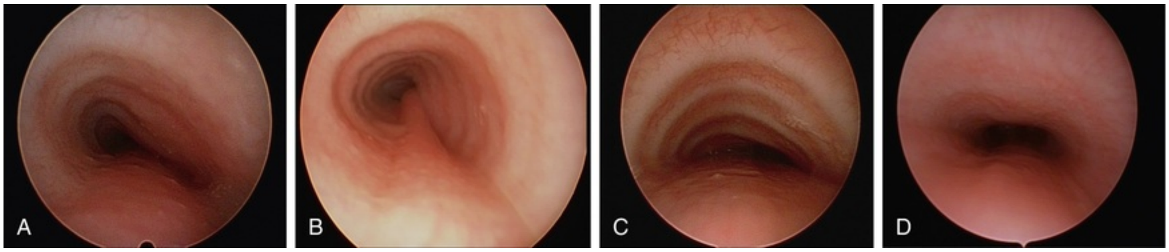

FIG. 416.1 Four examples of tracheomalacia appearances. **A,** Comma-shaped trachea caused by innominate artery compression requiring aortopexy. **B,** Bunched-up trachealis muscle and compressed trachea caused by a double aortic arch. **C,** Flattened trachea and increased trachealis diameter with a tracheoesophageal fistula in the posterior wall. **D,** Ovoid-shaped trachea from external compression by innominate artery. (From Deacon JWF, Widger J, Soma MA: Paediatric tracheomalacia—A review of clinical features and comparison of diagnostic imaging techniques, *Int J Pediatr Otorhinolaryngol* 98:75–81, 2017.)

Treatment

Postural drainage can help with clearance of secretions. β-Adrenergic agents should be avoided in the absence of asthma because they can exacerbate loss of airway patency due to decreased airway tone. Nebulized ipratropium bromide may be useful. Endobronchial stents have been used in severely affected patients but have a high incidence of complications, ranging from airway obstruction due to granulation tissue to erosion into adjacent vascular structures. Continuous positive airway pressure via tracheostomy may be indicated for severe cases. A surgical approach (aortopexy and bronchopexy) is rarely required and only for patients who have life-threatening apnea, cyanosis, and bradycardia (cyanotic spells) from airway obstruction and/or who demonstrated vascular compression. Reports of creation and use of 3-dimensional (3D) printed, bioresorbable external tracheobronchial stents in pediatric patients with life-threatening tracheobronchomalacia have shown great promise.

Prognosis

Primary bronchomalacia and tracheomalacia have excellent prognoses because airflow improves as the child and the airways grow. Patients with primary airway malacia usually take longer to recover from common respiratory infections. Wheezing at rest usually resolves by age 3 yr. Prolonged bacterial bronchitis has been reported as a complication of bronchomalacia. Prognosis in secondary and acquired forms varies with cause. Patients with concurrent asthma need considerable supportive treatment and careful monitoring of respiratory status.

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CHAPTER 417

Neoplasms of the Larynx, Trachea, and Bronchi

Saied Ghadersohi, James W. Schroeder Jr

417.1

Vocal Nodules

Saied Ghadersohi, James W. Schroeder Jr

Keywords

Vocal nodules
Vocal abuse
Voice therapy

Vocal nodules , which are not true neoplasms, are the most common cause of chronic hoarseness in children. Chronic vocal abuse or misuse (i.e., frequent yelling and screaming) produces localized vascular congestion, edema, hyalinization, and epithelial thickening in the bilateral vocal cords. This grossly appears as nodules that disrupt the normal vibration of the cords during phonation. **Vocal abuse** is the main factor, and the voice is worse in the evenings. Differential can include unilateral lesions such as **vocal cord cysts and polyps;** however, these usually have an acute inciting event and are rarer in children.

Treatment is primarily nonsurgical with voice therapy used in children >4 yr of age who can participate in therapy, and clinical monitoring with behavioral therapy in younger children or those with developmental delay. In addition, laryngopharyngeal reflux commonly exacerbates vocal abuse–induced irritation of the cord, Therefore antireflux therapy can also be implemented (see Chapter 349). Surgical excision of vocal cord lesions in children is controversial and is rarely indicated but may be necessary if the child is unable to communicate adequately, becomes aphonic, or requires tension and straining to make any utterance whatsoever.

417.2

Recurrent Respiratory Papillomatosis

Saied Ghadersohi, James W. Schroeder Jr

Keywords

Recurrent Respiratory Papillomas
HPV

Papillomas are the most common respiratory tract neoplasms in children, occurring in 4.3 in 100,000. They are simply warts—benign tumors— caused by the human papillomavirus (HPV), most commonly types 6 and 11 (see Chapter 293). Seventy-five percent of recurrent respiratory papilloma cases occur in children younger than age 5 yr, but the diagnosis may be made at any age. In general, neonatal-onset disease is a negative prognostic factor with higher mortality and need for tracheostomy. Sixty-seven percent of children with RRP are born to mothers who had condylomas during pregnancy or parturition. The mode of HPV transmission is still not clear. Neonates have been reported to have RRP, suggesting intrauterine transmission of HPV. Despite close association with vaginal condylomata, only 1 in 231 to 400 vaginal births go on to develop respiratory papillomatosis. Therefore other risk factors contribute to transmission, and C-section delivery for prevention cannot be recommended. However, preventive measures can include the prospective widespread use of the quadrivalent HPV vaccine to help eliminate maternal and paternal HPV reservoirs and possibly decrease cases of RRP caused by HPV 6 and 11.

Clinical Manifestations

The clinical course involves remissions and exacerbations of recurrent papillomas most commonly on the larynx (usually the vocal cords), causing progressively worsening hoarseness, sleep-disordered breathing, exertional dyspnea, stridor, and, if left untreated, eventually severe airway obstruction (Fig. 417.1). Although it is a benign disease, lesions can spread throughout the aerodigestive tract in 31% of patients, most commonly the oral cavity, trachea, and bronchi. Rarely these lesions can undergo malignant conversion (1.6%); however, some patients may have spontaneous remission. Patients may be initially diagnosed with asthma, croup, vocal nodules, or allergies.

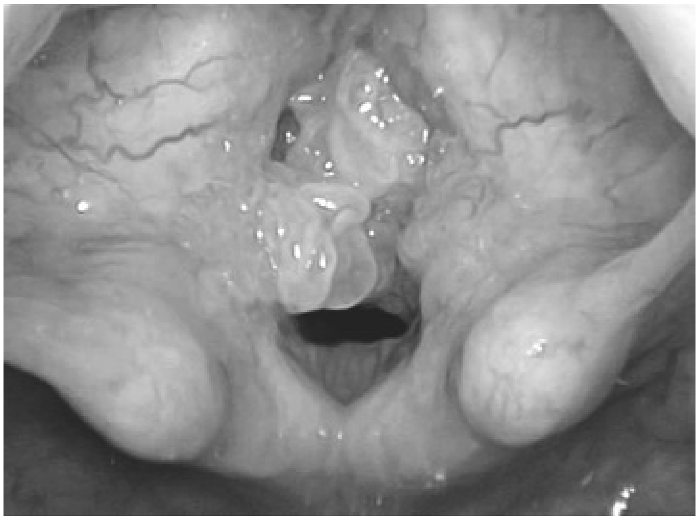

FIG. 417.1 Laryngoscopic view of respiratory papillomas causing near complete obstruction at glottic level. (From Derkay CS, Wiatrak B: Recurrent respiratory papillomatosis: a review, *Laryngoscope* 118:1236–1245, 2008.)

Treatment

The treatment of RRP is endoscopic surgical removal with three goals. First, debulking/complete removal of the lesions, secondly, preservation of normal structures, and finally, prevention of scar formation in the affected areas. Most surgeons in North America prefer the microdebrider, although microsurgery, CO_2 , and KTP laser techniques have been described. Despite these techniques, some form of adjunct therapy may be needed in up to 20% of cases. The most widely accepted indications for adjunct therapy are a need for more than four surgical procedures per year, rapid regrowth of papillomata with airway compromise, or distal multisite spread of disease. Adjunct therapies can be inhaled or administered intralesionally or systemically and include antiviral modalities (interferon, ribavirin, acyclovir, cidofovir), antiangiogenic agents such as bevacizumab (Avastin), photodynamic therapy, dietary supplement (indole-3-carbinol), nonsteroidal antiinflammatory drugs (COX2 inhibitors, Celebrex), retinoids, and mumps vaccination.

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2011;120(10):627–634 [PMID] 22097147.

417.3

Congenital Subglottic Hemangioma

Saied Ghadersohi, James W. Schroeder Jr

Keywords

congenital
infantile
hemangioma
stridor

Clinical Manifestations

Typically, congenital subglottic hemangiomas are symptomatic within the first 2 mo of life, almost all occurring before 6 mo of age. Much like the cutaneous infantile hemangiomas, these lesions have 2 phases: a **proliferative phase** with rapid growth in the first 6 mo of life, then they stabilize by 1 yr, and a slow **involution phase** typically by age 3. Patients present with usually inspiratory but sometimes biphasic stridor. The infant can have a barking cough and temporarily respond to steroids, similar to persistent croup. Fifty percent of congenital subglottic hemangiomas are associated with facial lesions, but the converse is not true. Radiographs classically delineate an asymmetric subglottic narrowing. The diagnosis is made by direct laryngoscopy.

Treatment

The medical treatment of hemangiomas traditionally was with long-term systemic steroids, which often had severe side effects, including growth retardation and adrenal suppression. Prednisone 2-4 mg/kg/day is given orally for 4-6 wk, typically with partial regression of the lesion. The dosage is then tapered. If there is no response, the drug is discontinued. Propranolol was introduced in 2008 and rapidly became the first-line treatment of infantile and subglottic hemangiomas, including in a recent randomized clinical trial comparing it with systemic steroids. The mechanism is thought to be through VEGF or adrenergic vasoconstriction pathways and can involute the lesion in a few days. Typically, treatment is with 1-3 mg/kg/day of propranolol for 4-12 mo, based on clinical monitoring as noted in a 2011 consensus guideline. Prescreening patients with cardiology workup (i.e., electrocardiogram) is advised. Side effects include hypotension, bradycardia, bronchospasm, and hypoglycemia; children treated with propranolol need to be monitored closely.

Surgical management can range from intralesional steroid injection to avoid systemic steroid side effects, CO_2 , or KTP laser endoscopic excision, and ultimately as a last resort tracheostomy can establish a safe airway, allowing time for the lesion to involute per its natural course.

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417.4

Vascular Anomalies

Saied Ghadersohi, James W. Schroeder Jr

Keywords

Vascular malformations
Vascular tumors

Based on the International Society for the Study of Vascular Anomalies classification system, these lesions can be classified into vascular malformations and vascular tumors. The most common vascular tumors are infantile/subglottic hemangiomas and were previously discussed. Vascular malformations are not true neoplastic lesions. They have a normal rate of endothelial turnover and various channel abnormalities. They are subcategorized based on high or low flow and by their predominant type (capillary, venous, arterial, lymphatic, or a combination thereof). Overall, vascular malformations are uncommon, and they rarely occur in the larynx and airway. When they do occur, they are often an extension from elsewhere in the head and neck. It should be noted that these lesions can expand with a viral upper respiratory infection. They can be diagnosed with direct visualization during laryngoscopy or bronchoscopy or seen on CT/MRI imaging. Treatment usually entails a multidisciplinary team approach with early surgical or laser resection or sclerotherapy.

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417.5

Other Laryngeal Neoplasms

James W. Schroeder Jr, Lauren D. Holinger

Keywords

Neurofibromatosis
Rhabdomyosarcoma

Neurofibromatosis (see Chapter 614.1) rarely involves the larynx. When children are affected, limited local resection is undertaken to maintain an airway and optimize the voice. Complete surgical extirpation is virtually impossible without debilitating resection of vital laryngeal structures. Most surgeons select the option of less-aggressive symptomatic surgery because of the poorly circumscribed and infiltrative nature of these fibromas. **Rhabdomyosarcoma** (see Chapter 527) and other malignant tumors of the larynx are rare. Symptoms of hoarseness and progressive airway obstruction prompt initial evaluation by flexible laryngoscopy in the office.

417.6

Tracheal Neoplasms

Saied Ghadersohi, James W. Schroeder Jr, Lauren D. Holinger

Keywords

Inflammatory pseudotumor
hamartomas

Tracheal tumors are extremely rare and include malignant and benign neoplasms; they may initially be misdiagnosed as asthma. The 2 most common benign tumors are inflammatory pseudotumor and hamartoma. The **inflammatory pseudotumor** is probably a reaction to a previous bronchial infection or traumatic insult. Growth is slow, and the tumor may be locally invasive. Hamartomas are tumors of primary tissue elements that are abnormal in proportion and arrangement.

Tracheal neoplasms manifest with stridor, wheezing, cough, or pneumonia and are rarely diagnosed until 75% of the lumen has been obstructed (Fig. 417.2). Chest radiographs or airway films can identify the obstruction. Pulmonary function studies demonstrate an abnormal flow-volume loop. A mild response to bronchodilator therapy may be misleading. Treatment is based upon the histopathology.

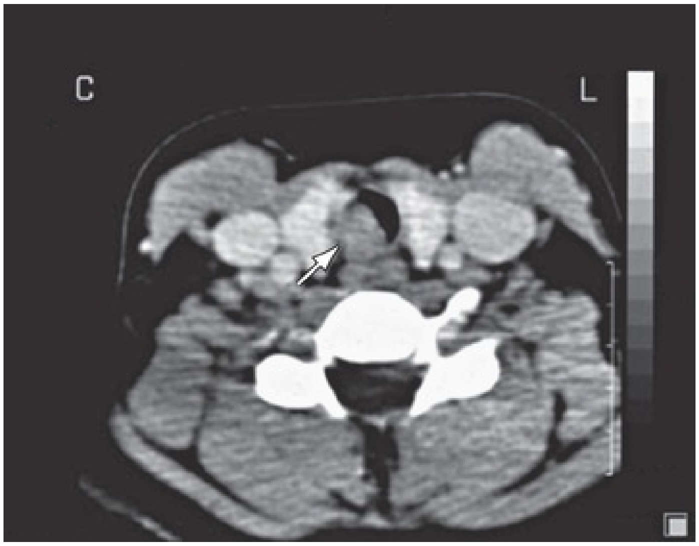

FIG. 417.2 A CT scan of the trachea with a circumscribed intraluminal tracheal mass *(arrow)* in the tracheal wall. (From Venizelos I, Papathomas T, Anagnostou E, et al: Pediatric inflammatory myofibroblastic tumor of the trachea: a case report and review of the literature, *Pediatr Pulmonol* 43:831–835, 2008.)

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417.7

Bronchial Tumors

Saied Ghadersohi, James W. Schroeder Jr

Keywords

Carcinoid tumor
pseudotumor

Bronchial tumors are rare. In 1 series, carcinoid tumors were the most common, followed by mucoepidermoid and pseudotumors. These patients can present with persistent pneumonia despite adequate treatment. The diagnosis is confirmed at bronchoscopy and biopsy; treatment depends on the histopathology.

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CHAPTER 418

Wheezing, Bronchiolitis, and Bronchitis

418.1

Wheezing in Infants: Bronchiolitis

Samantha A. House, Shawn L. Ralston

Keywords

Bronchiolitis
Wheezing
Respiratory Syncytial Virus (RSV)

General Pathophysiology of Wheezing in Infants

Wheezing, the production of a musical continuous sound that originates in narrowed airways, is heard on expiration as a result of airway obstruction. Infants are more likely to wheeze than are older children, as a result of differing lung mechanics. Obstruction of airflow is affected by both airway size and compliance of the infant lung. Resistance to airflow through a tube is inversely related to the radius of the tube to the 4th power. In children younger than 5 yr, small-caliber peripheral airways can contribute up to 50% of the total airway resistance. Marginal additional narrowing, such as that caused by inflammation related to viral infection, is then more likely to result in wheezing.

Infant chest wall compliance is also quite high, thus the inward pressure produced in normal expiration subjects the intrathoracic airways to collapse. Differences in tracheal cartilage and airway smooth muscle tone increase the collapsibility of the infant airways in comparison with older children. These mechanisms combine to make the infant more susceptible to airway obstruction, increased resistance, and subsequent wheezing. The mechanical portion of the infant propensity to wheeze resolves with normal growth and muscular development.

Although wheezing in infants most frequently results from inflammation due to acute viral infections, there are many potential causes of wheezing (Table 418.1).

Table 418.1

Differential Diagnosis of Wheezing in Infancy

INFECTION
Viral
Respiratory syncytial virus Human metapneumovirus Parainfluenza Adenovirus Influenza Rhinovirus Bocavirus Coronavirus Enterovirus
Other
Chlamydia trachomatis Tuberculosis Histoplasmosis Papillomatosis
ASTHMA
ANATOMIC ABNORMALITIES
Central Airway Abnormalities
Malacia of the larynx, trachea, and/or bronchi Laryngeal or tracheal web Tracheoesophageal fistula (specifically H-type fistula) Laryngeal cleft (resulting in aspiration)
Extrinsic Airway Anomalies Resulting in Airway Compression
Vascular ring or sling Mediastinal lymphadenopathy from infection or tumor Mediastinal mass or tumor Esophageal foreign body
Intrinsic Airway Anomalies

Airway hemangioma, other tumor Congenital pulmonary airway malformation (cystic adenomatoid malformation) Bronchial or lung cyst Congenital lobar emphysema Aberrant tracheal bronchus Sequestration Congenital heart disease with left-to-right shunt (increased pulmonary edema) Foreign body
Immunodeficiency States
Immunoglobulin A deficiency B-cell deficiencies AIDS Bronchiectasis
MUCOCILIARY CLEARANCE DISORDERS
Cystic fibrosis Primary ciliary dyskinesia Bronchiectasis
ASPIRATION SYNDROMES
Gastroesophageal reflux disease Pharyngeal/swallow dysfunction
OTHER
Bronchopulmonary dysplasia Eosinophilic granulomatosis with polyangiitis Interstitial lung disease, including bronchiolitis obliterans Heart failure Anaphylaxis Inhalation injury—burns

Acute Bronchiolitis

Acute bronchiolitis is a diagnostic term used to describe the clinical picture produced by several different viral lower respiratory tract infections in infants and very young children. The respiratory findings observed in bronchiolitis include tachypnea, wheezing, crackles, and rhonchi which result from inflammation of the small airways (Fig. 418.1). Despite its commonality, a universal set of diagnostic criteria for bronchiolitis does not exist, with significant disagreement about the upper age limit for appropriate use of the diagnosis. Some clinicians restrict the term to children younger than 1 yr, and others extend it to the age of 2 yr or beyond.

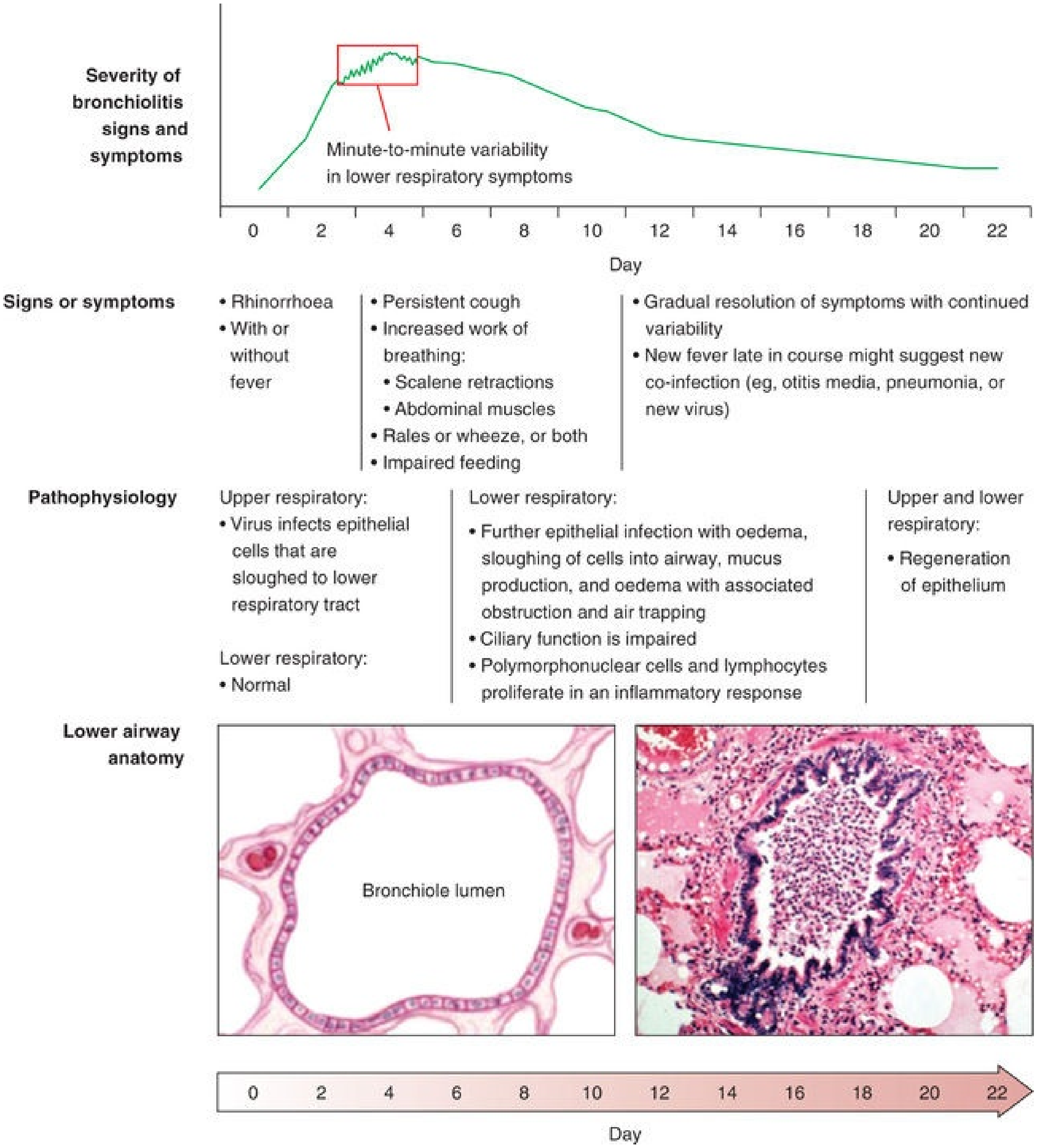
Severity of bronchiolitis signs and symptoms
Minute-to-minute variability in lower respiratory symptoms
0
2
4
6
8
10
12
14
16
18
20
22
Day
Signs or symptoms
Pathophysiology
Lower airway anatomy
Bronchiole lumen
0
2
4
6
8
10
12
14
16
18
20
22
Day

Signs or symptoms

- Rhinorrhoea
- With or without fever

- Persistent cough
- Increased work of breathing:
  - Scalene retractions
  - Abdominal muscles
- Rales or wheeze, or both
- Impaired feeding

- Gradual resolution of symptoms with continued variability
- New fever late in course might suggest new co-infection (eg, otitis media, pneumonia, or new virus)

Pathophysiology

Upper respiratory:

- Virus infects epithelial cells that are sloughed to lower respiratory tract

Lower respiratory:

- Normal

Lower respiratory:

- Further epithelial infection with oedema, sloughing of cells into airway, mucus production, and oedema with associated obstruction and air trapping
- Ciliary function is impaired
- Polymorphonuclear cells and lymphocytes proliferate in an inflammatory response

Upper and lower respiratory:

- Regeneration of epithelium

FIG. 418.1 Typical clinical course and pathophysiology of viral bronchiolitis. (From Florin TA, Plint PC, Zorc JJ: Viral bronchiolitis, *Lancet* 389:211–224, 2017 [Fig. 1, p. 212]).

The pathophysiology of acute bronchiolitis is characterized by bronchiolar obstruction with edema, mucus, and cellular debris (see Fig. 418.1). Resistance in the small air passages is increased during both inspiration and exhalation, but because the radius of an airway is smaller during expiration, the resultant respiratory obstruction leads to expiratory wheezing, air trapping, and lung hyperinflation. If obstruction becomes complete, trapped distal air will be resorbed and the child will develop atelectasis. Hypoxemia is a consequence of ventilation-perfusion mismatch. With severe obstructive disease hypercapnia can develop.

Respiratory syncytial virus (RSV) is responsible for more than 50% of cases of bronchiolitis in most reports. Other agents include human metapneumovirus, rhinovirus, parainfluenza, influenza, bocavirus, and adenovirus. Viral coinfection is reported to impact severity and clinical manifestations, although its significance remains contested. Respiratory viruses can be identified in more than one third of asymptomatic patients younger than the age of 1 yr, calling into question the specificity of current tests for active infection. Although bacterial pneumonia is sometimes confused clinically with bronchiolitis, viral bronchiolitis is rarely followed by bacterial superinfection.

Well over 100,000 young children are hospitalized annually in the United States with the diagnosis of bronchiolitis, making it the most common diagnosis resulting in hospitalization for children younger than 1 yr of age in the United States over the past several decades. The increasing rates of hospitalization for bronchiolitis observed from 1980 to 1996 (thought to reflect increased attendance of infants in daycare centers, changes in criteria for hospital admission linked to pulse oximetry use, and/or improved survival of premature infants and other children at risk for severe disease) have not continued. Hospitalization rates have been stable in subsequent years despite introduction and routine use of RSV immunoprophylaxis in high-risk populations.

Bronchiolitis is more common in males, those exposed to second-hand tobacco smoke, those who have not been breastfed, and those living in crowded conditions. Risk is also higher for infants with mothers who smoked during pregnancy. Older family members, including older siblings, are a common source of infection; they might experience only minor upper respiratory symptoms (colds) given that bronchiolar edema may be less clinically apparent as airway size increases.

Asthma (see Chapter 169) is another important cause of wheezing, and the possibility of this diagnosis complicates the treatment of young children with bronchiolitis, although accurate diagnosis of asthma in the very young can be difficult. In prospective, longitudinal population cohort studies of infants, up to half of the cohort experienced a wheezing illness prior to school age, although when followed into adulthood only about 5–8% of patients prove to have asthma. In the largest U.S. cohort, 3 patterns of infant wheezing were proposed: transient early wheezing, comprising about 20% of the cohort, characterized by lower lung function at birth which improves with growth resulting in resolution of wheezing by age 3; persistent wheezing, comprising about 14% of the cohort, characterized by declining lung function and wheezing before and after age 3; and late-onset wheezing, comprising 15% of the cohort, characterized by relatively stable lung function and wheezing that does not begin until after age 3. The remaining 50% of the population did not suffer a wheezing illness. Following the cohort into adulthood revealed continued declines in the rates of persistent symptoms. Similar patterns are also seen in birth cohort studies in other countries.

Multiple studies attempting to predict which infants suffering from early wheezing illnesses will go on to have asthma in later life have failed to achieve discriminant validity. Interestingly, in both U.S. and U.K. prospective cohorts, wheezing with an onset *after* the first 18-36 mo of life is one of the strongest predictors of eventual asthma in both cohorts. Other proposed risk factors for persistent wheezing include parental history of asthma and allergies, maternal smoking, persistent rhinitis (apart from acute upper respiratory tract infections), allergen sensitization, eczema, and peripheral eosinophilia, although no single factor is strongly discriminative. Despite several randomized trials, there is no evidence that early administration of inhaled corticosteroids to high-risk populations can prevent the development of asthma.

Clinical Manifestations

History and Physical Examination

The initial history of a wheezing infant should describe the recent event including onset, duration, and associated factors (Table 418.2). *Birth history* includes weeks of gestation, neonatal complications including history of intubation or oxygen requirement, maternal complications, and prenatal smoke exposure. Past medical history includes any comorbid conditions. *Family history* of cystic fibrosis, immunodeficiencies, asthma in a first-degree relative, or any other recurrent respiratory conditions in children should be obtained. *Social history* should include any second-hand tobacco or other smoke exposure, daycare exposure, number of siblings, pets, and concerns regarding home environment (e.g., dust mites, construction dust, heating and cooling techniques, mold, cockroaches). The patient's growth chart should be reviewed for signs of failure to thrive.

Table 418.2

Pertinent Medical History in the Wheezing Infant

Did the onset of symptoms begin at birth or thereafter?
Is the infant a noisy breather, and when is it most prominent?
Is the noisy breathing present on inspiration, expiration, or both?
Is there a history of cough apart from wheezing?
Was there an earlier lower respiratory tract infection?
Is there a history of recurrent upper or lower respiratory tract infections?
Have there been any emergency department visits, hospitalizations, or intensive care unit admissions for respiratory distress?
Is there a history of eczema?
Does the infant cough after crying or cough at night?
How is the infant growing and developing?
Is there associated failure to thrive?
Is there a history of electrolyte abnormalities?
Are there signs of intestinal malabsorption including frequent, greasy, or oily stools?
Is there a maternal history of genital herpes simplex virus infection?
What was the gestational age at delivery?
Was the patient intubated as a neonate?
Does the infant bottle-feed in the bed or the crib, especially in a propped position?
Are there any feeding difficulties including choking, gagging, arching, or vomiting with feeds?
Is there any new food exposure?
Is there a toddler in the home or lapse in supervision in which foreign body aspiration could have occurred?
Change in caregivers or chance of nonaccidental trauma?

Acute bronchiolitis is usually preceded by exposure to contacts with a minor respiratory illness within the previous week (see Fig. 418.1). The infant first develops signs of upper respiratory tract infection with sneezing and clear rhinorrhea. This may be accompanied by diminished appetite and fever. Gradually, respiratory distress ensues, with paroxysmal cough, dyspnea, and irritability. The infant is often tachypneic, which can interfere with feeding. Apnea may precede lower respiratory signs early in the disease, particularly with very young infants. Term infants at a postconceptual age of <44 wk and preterm infants at postconceptual age <48 wk are at highest risk for *apneic* events.

On physical examination, evaluation of the patient's vital signs with special attention to the respiratory rate and oxygen saturation is an important initial step. The exam is often dominated by wheezing and crackles. Expiratory time may be prolonged. Work of breathing may be markedly increased, with nasal flaring and retractions. *Complete obstruction to airflow can eliminate the turbulence that causes wheezing; thus the lack of audible wheezing is not reassuring if the infant shows other signs of respiratory distress.* Poorly audible breath sounds suggest severe disease with nearly complete bronchiolar obstruction.

Diagnostic Evaluation

Evaluation of wheezing in infancy and early childhood depends on suspected etiology. The diagnosis of **acute bronchiolitis** is clinical, particularly in a previously healthy infant presenting with a first episode of wheezing following a period of upper respiratory symptoms. Chest radiography is not routinely indicated in children with suspected bronchiolitis. Areas of atelectasis associated with bronchiolitis are often observed on chest radiographs and may be difficult to distinguish from bacterial pneumonia; as a result, obtaining chest radiography in a patient whose clinical course and exam are consistent with bronchiolitis may encourage unnecessary antibiotic use. Laboratory testing is also not routinely indicated; the white blood cell and differential counts are usually normal and are not predictive of bacterial superinfection. Viral testing (polymerase chain reaction, or rapid immunofluorescence) is not routinely recommended in the diagnosis of bronchiolitis but may be helpful if such testing prevents more invasive evaluations. Concurrent serious bacterial infection (sepsis, pneumonia, meningitis) is unlikely, although confirmation of viral bronchiolitis may obviate the need for a sepsis evaluation in the young febrile infant. Otitis media may complicate bronchiolitis.

For young children with wheezing in whom the presentation does not clinically fit with the diagnosis of bronchiolitis, including those without other signs of viral infection, with very severe presentation, or complicated clinical course, further workup should be considered and should be dictated by individual clinical context. Children with recurrent or refractory episodes of wheezing in infancy, particularly if associated with failure to thrive, may require evaluation for chronic disorders such as cystic fibrosis or immunodeficiency.

Treatment

The treatment of children with viral **bronchiolitis** is supportive management. Those who are experiencing respiratory distress (hypoxia, inability to feed, apnea, extreme tachypnea) should be hospitalized. Risk factors for severe disease include younger age, preterm birth, or underlying comorbidity such as cardiovascular, pulmonary, neurologic, or immunologic disease. Hypoxemic children should receive supplemental oxygen. There is a developing consensus surrounding target oxygen saturations; national guidelines in the United States propose a threshold of 90%. Oxygen can be administered via a number of delivery devices, and some children with severe disease may require positive pressure ventilation. High-flow nasal cannula is a noninvasive mode of oxygen delivery capable of providing some positive end expiratory pressure, particularly in young children. Some use high flow as rescue therapy in patients who do not respond to standard care. The utility of high-flow nasal cannula in avoiding intubation in some children and reducing the duration of required supplemental oxygen is being actively explored because current data are mixed.

Some children may also require support with supplemental hydration. Fluid can be administered intravenously or enterally via nasogastric tube, with some preference given to the latter due to an association between better outcomes and continued provision of enteral nutrition. If intravenous fluids are administered, care should be taken to use isotonic fluids due to risk of hyponatremia. Frequent suctioning of nasal and oral secretions often provides relief of distress and improves work of breathing and ability to feed, although this should be limited to the nares or oropharynx because deep tracheal suctioning does not provide additional benefit. Chest physiotherapy has been extensively evaluated and provides *no benefit* to children with bronchiolitis.

Pharmacologic agents have largely proven *ineffective* in the management of bronchiolitis. Cochrane reviews have failed to demonstrate any impact on clinical outcomes with use of albuterol or corticosteroids in bronchiolitis; neither are currently recommended for management. Response to bronchodilators is unlikely and unpredictable in children younger than 1 yr, and there is no validated method of assessing response in the clinical setting. The use of inhaled or oral steroids in very young children with wheezing has not been shown to prevent the progression of childhood wheezing or development of asthma. There is debate over the use of hypertonic saline in children with bronchiolitis, although most studies and meta-analyses fail to demonstrate any benefit. Racemic epinephrine has not been found to improve length of stay or clinical outcomes among inpatients with bronchiolitis, although there is some evidence to suggest that it may reduce risk of hospitalization when used in the outpatient setting. Ribavirin, the only currently available antiviral medication targeting RSV, is also *not* currently recommended, because of minimal impact on disease outcomes, and because it is costly, difficulty to administer, and associated with important toxicities.

Prognosis

Infants with **acute bronchiolitis** are at highest risk for further respiratory compromise in the first 72 hours after onset of cough and dyspnea. The case fatality rate is <1% in developed countries, with death attributable to respiratory arrest and/or failure or severe dehydration and electrolyte disturbances. *A majority of deaths due to bronchiolitis occur in children with complex medical conditions or comorbidities such as bronchopulmonary dysplasia, congenital heart disease, or immunodeficiency.* The median duration of symptoms in ambulatory patients is approximately 14 days; 10% may be symptomatic for 3 wk. Severe lower respiratory tract infection at an early age has been identified as a possible risk factor for the development of asthma, although most children with early childhood wheezing will not go on to suffer from asthma. It is unclear whether viral infections causing bronchiolitis incite an immune response that manifests as asthma later in life or whether those infants have an inherent predilection for asthma that is first manifested as viral bronchiolitis.

Prevention

Meticulous hand hygiene is the best measure to prevent transmission of the viruses responsible for bronchiolitis. For high-risk populations, **palivizumab** , an intramuscular monoclonal antibody to the RSV F protein, may be given as a prophylactic agent. Palivizumab has been demonstrated to reduce risk of hospitalization due to RSV bronchiolitis in certain populations. It has not been shown to decrease mortality and does not protect against bronchiolitis caused by other viruses and is also quite costly. As a result, there is some controversy surrounding which populations should receive palivizumab. U.S. guidelines suggest use for children born at <29-wk completed gestation or those with significant heart disease or chronic lung disease of prematurity, through the 1st or 2nd (for those with persistent chronic lung disease of prematurity) yr of life. Prophylaxis may be considered in infants with neuromuscular disease and immunocompromised states. The development of an effective preventive strategy available at a lower cost would be particularly advantageous in developing nations, where access to care and intervention for severe bronchiolitis are more limited.

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418.2

Bronchitis

Lauren E. Camarda, Denise M. Goodman

Keywords

Bronchitis
Chronic Bronchitis
Chronic Cough

Nonspecific bronchial inflammation is termed bronchitis and occurs in multiple childhood conditions. Acute bronchitis is a syndrome, usually viral in origin, with cough as a prominent feature.

Acute tracheobronchitis is a term used when the trachea is prominently involved. Nasopharyngitis may also be present, and a variety of viral and bacterial agents, such as those causing influenza, pertussis, and diphtheria, may be responsible. Isolation of common bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae* from the sputum might not imply a bacterial cause that requires antibiotic therapy.

Acute Bronchitis

Clinical Manifestations

Acute bronchitis often follows a viral upper respiratory tract infection. It is more common in the winter when respiratory viral syndromes predominate. The tracheobronchial epithelium is invaded by the infectious agent, leading to activation of inflammatory cells and release of cytokines. Constitutional symptoms including fever and malaise follow. The tracheobronchial epithelium can become significantly damaged or hypersensitized, leading to a protracted cough lasting 1-3 wk.

The child first presents with nonspecific upper respiratory infectious symptoms, such as rhinitis. Three to 4 days later, a frequent, dry, hacking cough develops, which may or may not be productive. After several days, the sputum can become purulent, indicating leukocyte migration but not necessarily bacterial infection. Many children swallow their sputum which can produce emesis. Chest pain may be a prominent complaint in older children and is exacerbated by coughing. The mucus gradually thins, usually within 5-10 days, and then the cough gradually abates. The entire episode usually lasts about 2 wk and seldom longer than 3 wk.

Findings on physical examination vary with the age of the patient and stage of the disease. Early findings include no or low-grade fever and upper respiratory signs such as nasopharyngitis, conjunctivitis, and rhinitis. Auscultation of the chest may be unremarkable at this early phase. As the syndrome progresses and cough worsens, breath sounds become coarse, with coarse and fine crackles and scattered high-pitched wheezing. Chest radiographs are normal or can have increased bronchial markings.

The principal objective of the clinician is to exclude pertussis and pneumonia, which is more likely caused by bacterial agents requiring antibiotic therapy. Absence of abnormality of vital signs (tachycardia, tachypnea, fever) and a normal physical examination of the chest reduce the likelihood of pneumonia.

Differential Diagnosis

Persistent or recurrent symptoms should lead the clinician to consider entities other than acute bronchitis. Many entities manifest with cough as a prominent symptom (Table 418.3).

Table 418.3

Disorders With Cough as a Prominent Finding

CATEGORY	DIAGNOSES

Inflammatory	Asthma
Chronic pulmonary processes	Bronchopulmonary dysplasia Postinfectious bronchiectasis Cystic fibrosis Tracheomalacia or bronchomalacia Ciliary abnormalities Other chronic lung diseases
Other chronic disease or congenital disorders	Laryngeal cleft Swallowing disorders Gastroesophageal reflux Airway compression (such as a vascular ring or hemangioma) Congenital heart disease
Infectious or immune disorders	Immunodeficiency Eosinophilic lung disease Tuberculosis Allergy Sinusitis Tonsillitis or adenoiditis *Chlamydia, Ureaplasma* (infants) *Bordetella pertussis* *Mycoplasma pneumoniae*
Acquired	Foreign body aspiration, tracheal or esophageal

Treatment

There is no specific therapy for acute bronchitis. The disease is self-limited, and antibiotics, although often prescribed, do not hasten improvement. Frequent shifts in position can facilitate pulmonary drainage in infants. Older children are sometimes more comfortable with humidity, but this does not shorten the disease course. Cough suppressants can relieve symptoms but can also increase the risk of suppuration and inspissated secretions and therefore should be used judiciously. Antihistamines dry secretions and are not helpful; expectorants are likewise not indicated. Nonprescription cough and cold medicines should not be used in children younger than 4 yr of age, and their use is cautioned in children age 4-11 yr.

Chronic Bronchitis

Chronic bronchitis is well recognized in adults, formally defined as 3 mo or longer of productive cough each year for 2 or more yr. The disease can develop insidiously, with episodes of acute obstruction alternating with quiescent periods. Some predisposing conditions can lead to progression of airflow obstruction or chronic obstructive pulmonary disease, with smoking as the major factor (up to 80% of patients have a smoking history). Other conditions include air pollution, occupational exposures, and repeated infections. In children, cystic fibrosis, bronchopulmonary dysplasia, and bronchiectasis must be ruled out.

The applicability of this definition to children is unclear. The existence of chronic bronchitis as a distinct entity in children is controversial. Like adults, children with chronic inflammatory diseases or those with toxic exposures can develop damaged pulmonary epithelium. Thus chronic or recurring cough in children should lead the clinician to search for underlying pulmonary or systemic disorders (see Table 418.3). One proposed entity that shares characteristics with asthma and other forms of suppurative lung disease is persistent or protracted bacterial bronchitis. Protracted bacterial bronchitis is defined as a chronic (>3 wk) wet cough, characterized by bacterial counts of 10^4 colony-forming units/mL or greater from bronchoalveolar lavage and resolution of cough within 2 wk of treatment with antimicrobial therapy.

Cigarette Smoking and Air Pollution

Exposure to environmental irritants, such as tobacco smoke and air pollution, can incite or aggravate cough. There is a well-established association between tobacco exposure and pulmonary disease, including bronchitis and wheezing. This can occur through cigarette smoking or by exposure to passive smoke. Marijuana smoke and inhalants are other irritants sometimes overlooked when eliciting a history.

A number of pollutants compromise lung development and likely precipitate lung disease, including particulate matter, ozone, acid vapor, and nitrogen dioxide. Proximity to motor vehicle traffic is an important source of these pollutants. Because these substances coexist in the atmosphere, the relative contribution of any one to pulmonary symptoms is difficult to discern.

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CHAPTER 419

Plastic Bronchitis

Brett J. Bordini

Plastic bronchitis is a rare condition characterized by recurrent episodes of airway obstruction secondary to the formation of large proteinaceous branching casts that take on the shape of and obstruct the tracheobronchial tree. It is not a single disease entity, but rather represents a state of altered respiratory epithelial function and is most frequently encountered in the setting of underlying pulmonary or cardiac disease, although plastic bronchitis may also arise in lymphatic disorders, pulmonary infections, and the acute chest syndrome of sickle cell disease (Table 419.1). In comparison with the smaller bronchial and bronchiolar casts seen with mucus plugging, the lesions of plastic bronchitis are more extensive, with casts that can outline large segments of the airway to the level of the terminal bronchioles (Fig. 419.1). These casts may be spontaneously expectorated or may require bronchoscopic removal for relief of potentially fatal airway obstruction. Cast composition varies, although it typically consists of either a fibrin-predominant or mucin-predominant laminated matrix with or without inflammatory cell infiltration. Plastic bronchitis may be classified according to an associated disease, the cast histology, or a combination.

Table 419.1

Conditions Associated With Plastic Bronchitis

PROVEN CONDITIONS
Congenital heart disease with Fontan physiology Pulmonary lymphatic anomalies Influenza A pulmonary infection
POSSIBLE CONDITIONS
Toxic inhalation Sickle cell acute chest syndrome Hypersecretory and near-fatal asthma (eosinophilic casts)

UNLIKELY AND UNPROVEN CONDITIONS
Cystic fibrosis
Chronic obstructive pulmonary disease
Bronchiectasis
Bacterial pneumonia

From Rubin BK: Plastic bronchitis, *Clin Chest Med* 37:405–408, 2016 (Box 1, p. 406).

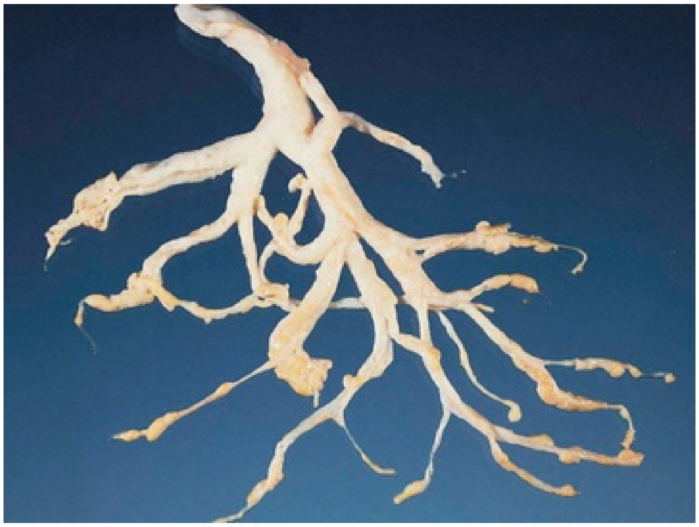

FIG. 419.1 Tracheobronchial casts following bronchoscopic extraction. Casts show branched architecture corresponding to the bronchial tree. (From Corrin B, Nicholson AG: *Pathology of the lungs* , ed 3, London, 2011, Churchill Livingstone. Fig 3.20.)

Epidemiology

Plastic bronchitis is rare, and its true prevalence in the pediatric population is not known but is estimated to be 6.8 cases per 100,000 patients. Prevalence does vary in relation to the underlying associated disease state, with rates as high as 4–14% estimated in patients who have undergone staged palliation of complex congenital heart disease and much lower rates seen complicating asthma and atopic disease. A slight male predominance exists for cast formation in the setting of structural heart disease, whereas cast formation in the setting of asthma and atopic disease demonstrates a female predominance. Children with single-ventricle Fontan physiology are at high risk for developing plastic bronchitis.

Pathogenesis

The mechanism of cast formation is unclear, although it is believed to vary based on the underlying disease association and cast type. One classification system differentiates type 1 inflammatory casts, composed primarily of fibrin with neutrophilic or more often eosinophilic infiltration, and type 2 acellular casts, composed primarily of mucin with little to no cellular infiltration. Type 1 casts tend to be associated with inflammatory and infectious disorders of the lung, whereas type 2 casts tend to be associated with surgically palliated structural heart disease, particularly single ventricle lesions. However, these distinctions are not absolute; patients with structural heart disease can have fibrin-predominant casts, and patients with asthma or atopic disease can have mucin-predominant casts, with both mucin casts and fibrin casts demonstrating various degrees of cellular infiltration.

Cast formation in the setting of structural heart disease may result from alterations in pulmonary blood flow or lymphatic drainage, particularly following staged surgical palliation. Under these circumstances, increased central venous pressure is believed to compromise the integrity of the bronchial mucosa, impeding lymphatic flow and resulting in the development of collateral lymphatic vessels and potentially of lymphoalveolar fistulae that may exude proteinaceous material into the airway lumen.

Clinical Manifestations

Patients with plastic bronchitis may present with cough, dyspnea, wheeze, or pleuritic chest pain. Depending on the degree of airway obstruction, patients may be hypoxemic or in severe respiratory distress. The expectoration of large, branched casts that are often tan in color and rubbery in consistency is pathognomonic for plastic bronchitis. Lung examination may reveal diminished breath sounds or wheezing in the affected area. Rarely, auscultation may reveal a sound similar to a flag flapping in the wind *(bruit de drapeau)* , believed to be related to the free end of a cast striking the bronchial wall during inspiration or expiration. Further examination may provide clues to underlying comorbidities.

Diagnosis

The expectoration or endoscopic discovery of large tracheobronchial casts is pathognomonic for plastic bronchitis. History should be directed at assessing for conditions known to have an associated risk of tracheobronchial cast formation, such as uncorrected or surgically palliated complex congenital heart disease (Fontan physiology); a history of atopic disease or asthma; lymphatic disorders such as Noonan syndrome, Turner syndrome, lymphangiectasia, and yellow nail syndrome; sickle cell disease; and infectious exposures, particularly to tuberculosis or atypical mycobacteria. Other predisposing conditions include cystic fibrosis, allergic bronchopulmonary aspergillosis, bronchiectasis, toxic inhalants, and granulomatous lung diseases.

Physical examination may provide indications of an underlying diagnosis. Digital clubbing of the fingers or toes may suggest long-standing hypoxemia associated with cardiac or pulmonary disease. Cardiac examination may provide information suggesting the presence of unrecognized structural heart disease.

Chest radiography may demonstrate collapse of the involved areas of the lung or areas of bronchiectasis distal to sites of long-standing obstruction.

There should be a high index of suspicion for plastic bronchitis in patients with known comorbidities who present with sudden respiratory decompensation. In the absence of cast expectoration, direct visualization of casts via bronchoscopy is required for diagnosis and is potentially therapeutic in relieving airway obstruction. Cast histology should be defined so as to allow for specific therapies directed at alleviating residual obstruction or preventing recurrence. In particular, the predominant component of the cast's laminated matrix—either fibrin or mucin—should be defined, and signs of inflammation or infiltration, such as the presence of neutrophils, eosinophils, or Charcot-Leyden crystals, should be documented.

Treatment

Treatment is directed at correcting the underlying condition associated with the development of plastic bronchitis, at relieving acute airway obstruction secondary to the presence of casts, and at preventing the development of further casts. Rigid or flexible bronchoscopy is typically required for cast removal, and if the predominant content of the cast is known, therapy with either fibrinolytics such as tissue plasminogen activator or mucolytics such as *N* -acetylcysteine or deoxyribonuclease may be considered as an adjunct to direct removal. Aerosolized heparin or mucolytics have also been used for treatment or prevention of recurrence, with varying success.

In the setting of inflammatory airway disease, additional preventive measures include the appropriate use of bronchodilators as indicated, as well as inhaled or systemic corticosteroids, low-dose azithromycin, and leukotriene inhibitors to minimize airway inflammation.

In patients with surgically palliated complex congenital heart disease, measures aimed at decreasing central venous pressure, such as sildenafil or Fontan conduit fenestration, have had varied success. Lymphangiography may be undertaken to identify aberrant lymphatic vessels contributing to plastic bronchitis in the setting of congenital heart disease or lymphangitic disorders, and MRI-guided selective lymphatic embolization of these channels has led to resolution of plastic bronchitis while preserving central lymphatic flow. Cardiac transplantation typically results in resolution of plastic bronchitis in the setting of repaired complex congenital heart disease.

Complications and Prognosis

Prognosis is related primarily to the underlying condition associated with the development of plastic bronchitis. Patients whose plastic bronchitis is related to surgically palliated complex congenital heart disease are at high risk for plastic bronchitis-related mortality. Mortality can be high if casts obstruct significant portions of the airway, regardless of underlying etiology. Mortality estimates vary from 6% to 50% in the setting of asthma or atopic disease and from 14% to 50% in the setting of complex congenital heart disease, with central airway obstruction leading to death in the majority of patients.

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CHAPTER 420

Emphysema and Overinflation

Steven R. Boas, Glenna B. Winnie

Pulmonary emphysema consists of distention of air spaces with irreversible disruption of the alveolar septa. It can involve part or all of a lung. **Overinflation** is distention with or without alveolar rupture and is often reversible. **Compensatory overinflation** can be acute or chronic and occurs in normally functioning pulmonary tissue when, for any reason, a sizable portion of the lung is removed or becomes partially or completely airless, which can occur with pneumonia, atelectasis, empyema, and pneumothorax. **Obstructive overinflation** results from partial obstruction of a bronchus or bronchiole, when it becomes more difficult for air to leave the alveoli than to enter. Air gradually accumulates distal to the obstruction, the so-called bypass, ball-valve, or check-valve type of obstruction.

Localized Obstructive Overinflation

When a ball-valve type of obstruction partially occludes the main stem bronchus, the entire lung becomes overinflated; individual lobes are affected when the obstruction is in lobar bronchi. Segments or subsegments are affected when their individual bronchi are blocked. When most or all of a lobe is involved, the percussion note is hyperresonant over the area and the breath sounds are decreased in intensity. The distended lung can extend across the mediastinum into the opposite hemithorax. Under fluoroscopic scrutiny during exhalation, the overinflated area does not decrease and the heart and the mediastinum shift to the opposite side because the unobstructed lung empties normally.

Unilateral Hyperlucent Lung

The differential diagnosis for this resultant **unilateral hyperlucent lung** is quite broad and can involve the lung parenchyma, airways, pulmonary vasculature, chest wall (see Chapter 445), and mediastinum. Localized obstructions that can be responsible for overinflation include airway foreign bodies and the inflammatory reaction to them (see Chapter 414), abnormally thick mucus (cystic fibrosis, Chapter 432), endobronchial tuberculosis or tuberculosis of the tracheobronchial lymph nodes (see Chapter 242), and endobronchial or mediastinal tumors.

Patients with unilateral hyperlucent lung can present with clinical manifestations of pneumonia, but in some patients the condition is discovered only when a chest radiograph is obtained for an unrelated reason. A few patients have hemoptysis. Physical findings can include hyperresonance and a small lung with the mediastinum shifted toward the more abnormal lung.

Swyer-James or Macleod Syndrome

The condition is thought to result from an insult to the lower respiratory tract following most commonly adenovirus (see Chapter 289) or respiratory syncytial virus (see Chapter 287), *Mycoplasma pneumoniae* (see Chapter 250), or measles (see Chapter 273). The infection can cause pulmonary vascular hypoplasia with resultant hypoperfusion leading to unilateral hyperlucent lung (underdevelopment). Clinically, children with this condition often have chronic cough, recurrent pneumonia, hemoptysis, and wheezing, although some are asymptomatic. Some patients show a classic mediastinal shift away from the lesion with exhalation. CT scanning or bronchography can often demonstrate bronchiectasis. Thoracoscopic evaluation may be useful. The triad of unilateral hyperlucent lung, diffusely decreased ventilation, and matching decreased perfusion of the affected lung supports the diagnosis. In some patients, previous chest radiographs have been normal or have shown only an acute pneumonia, suggesting that a hyperlucent lung is an acquired lesion. For those with recurrent infection or severe lung destruction, treatment may include immunization with influenza and pneumococcal vaccines, as well as surgical resection. However, without treatment, some individuals may become less symptomatic with time.

Congenital Lobar Emphysema (Congenital Large Hyperlucent Lobe)

Congenital lobar emphysema (CLE) can result in severe respiratory distress in early infancy and can be caused by localized obstruction. Familial occurrence has been reported. In 50% of cases, a cause of CLE can be identified. Congenital deficiency of the bronchial cartilage, external compression by aberrant vessels, bronchial stenosis, redundant bronchial mucosal flaps, and kinking of the bronchus caused by herniation into the mediastinum have been described as leading to bronchial obstruction and subsequent CLE and commonly affect the left upper lobe.

Clinical manifestations usually become apparent in the neonatal period but are delayed for as long as 5-6 yr in 5% of patients. Many cases are diagnosed by antenatal ultrasonography. Infants with prenatally diagnosed cases are not always symptomatic at birth. In some patients, CLE remains undiagnosed until school age or beyond. Clinical signs range from mild tachypnea and wheeze to severe dyspnea with cyanosis. CLE can affect one or more lobes; it affects the upper and middle lobes, and the left upper lobe is the most common site. The affected lobe is essentially nonfunctional because of the overdistention, and atelectasis of the ipsilateral normal lung can ensue. With further distention, the mediastinum is shifted to the contralateral side, with impaired function seen as well (Fig. 420.1). A radiolucent lobe and a mediastinal shift are often revealed by radiographic examination. A CT scan can demonstrate the aberrant anatomy of the lesion, and MRI or MR angiography can demonstrate any vascular lesions, which might be causing extraluminal compression. Nuclear imaging studies are useful to demonstrate perfusion defects in the affected lobe. Fig. 420.2 outlines evaluation of an infant presenting with suspected CLE. The differential diagnosis includes pneumonia with or without an effusion, pneumothorax, and cystic adenomatoid malformation.

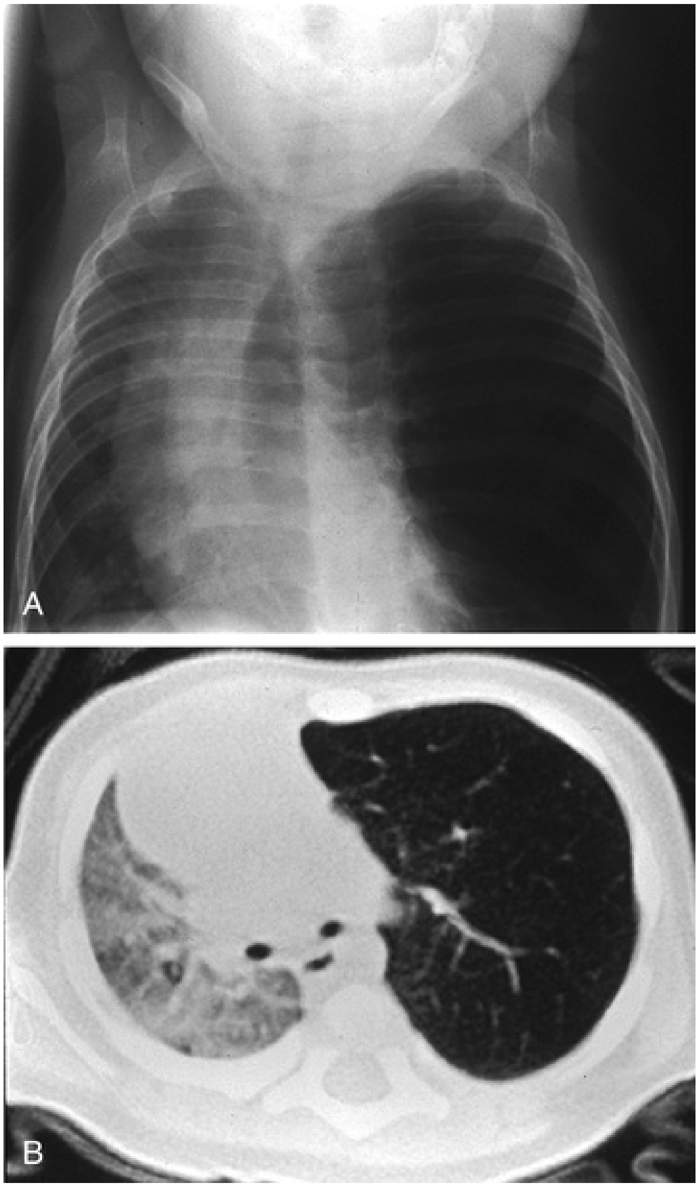

FIG. 420.1 (A) Chest x-ray and (B) computed tomography scan of a congenital large hyperlucent lobe (congenital lobar emphysema). (From Bush A, Abel R, Chitty L, et al: Congenital lung disease. In Wilmott RW, Deterding R, Li A, et al., editors: *Kendig's disorders of the respiratory tract in children* , 9th ed. Elsevier, Philadelphia, 2019. Fig. 18.32.)

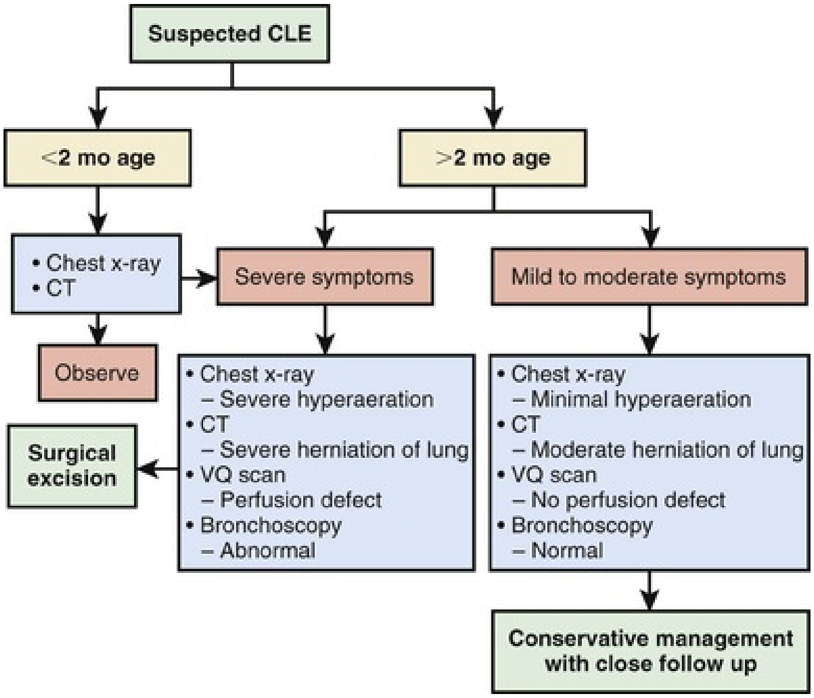
Suspected CLE
<2 mo age
>2 mo age
• Chest x-ray
• CT
Severe symptoms
Mild to moderate symptoms
Observe
• Chest x-ray
– Severe hyperaeration
• CT
– Severe herniation of lung
• VQ scan
– Perfusion defect
• Bronchoscopy
– Abnormal
• Chest x-ray
– Minimal hyperaeration
• CT
– Moderate herniation of lung
• VQ scan
– No perfusion defect
• Bronchoscopy
– Normal
Surgical excision
Conservative management with close follow up

FIG. 420.2 Algorithm for evaluation and treatment of congenital lobar emphysema *(CLE)* . (Adapted from Karnak I, Senocak ME, Ciftci AO, et al: Congenital lobar emphysema: diagnostic and therapeutic considerations, *J Pediatr Surg* 34:1347–1351, 1999, Fig. 4.)

Treatment by immediate surgery and excision of the lobe may be lifesaving when cyanosis and severe respiratory distress are present, but some patients respond to medical treatment. Selective intubation of the unaffected lung may be of value. Some children with apparent CLE have reversible overinflation, without the classic alveolar septal rupture implied in the term *emphysema*. Bronchoscopy can reveal an endobronchial lesion.

Pulmonary Vascular Abnormalities

Unilateral hyperlucency may result from **unilateral pulmonary agenesis** (see Chapter 423) that typically presents in the neonatal period. Volume loss of the affected lung results in a mediastinal shift with hyperinflation of the contralateral lung. An **anomalous origin of the left pulmonary artery** (see Chapter 459), also known as a *pulmonary artery sling* , can impinge the right mainstem bronchus with resultant right-sided hyperinflation or atelectasis producing hyperlucency on either the ipsilateral or contralateral side. **Pulmonary venolobar syndrome** (see Chapter 453), also known as **scimitar syndrome** , can also result in a hyperlucent contralateral lung dependent on the extent of hypoplasia of the right lung.

Generalized Obstructive Overinflation

Acute generalized overinflation of the lung results from widespread involvement of the bronchioles and is usually reversible. It occurs more commonly in infants than in children and may be secondary to a number of clinical conditions including asthma, cystic fibrosis, acute bronchiolitis, interstitial pneumonitis, atypical forms of acute laryngotracheobronchitis, aspiration of zinc stearate powder, chronic passive congestion secondary to a congenital cardiac lesion, and miliary tuberculosis.

Pathology

In chronic overinflation, many of the alveoli are ruptured and communicate with one another, producing distended saccules. Air can also enter the interstitial tissue (i.e., interstitial emphysema), resulting in pneumothorax and pneumomediastinum (see Chapters 439 and 440).

Clinical Manifestations

Generalized obstructive overinflation is characterized by dyspnea, with difficulty in exhaling. The lungs become increasingly overdistended, and the chest remains expanded during exhalation. An increased respiratory rate and decreased respiratory excursion result from the overdistention of the alveoli and their inability to be emptied normally through the narrowed bronchioles. Air hunger is responsible for forced respiratory movements. Overaction of the accessory muscles of respiration results in retractions at the suprasternal notch, the supraclavicular spaces, the lower margin of the thorax, and the intercostal spaces. Unlike the flattened chest during inspiration and exhalation in cases of laryngeal obstruction, minimal reduction in the size of the overdistended chest during exhalation is observed. The percussion note is hyperresonant. On auscultation, the inspiratory phase is usually less prominent than the expiratory phase, which is prolonged and roughened. Fine or medium crackles may be heard. Cyanosis is more common in the severe cases.

Diagnosis

Radiographic and fluoroscopic examinations of the chest assist in establishing the diagnosis. Both leaves of the diaphragm are low and flattened, the ribs are farther apart than usual, and the lung fields are less dense. The movement of the diaphragm during exhalation is decreased, and the excursion of the low, flattened diaphragm in severe cases is barely discernible. The anteroposterior diameter of the chest is increased, and the sternum may be bowed outward.

Bullous Emphysema

Bullous emphysematous blebs or cysts (pneumatoceles) result from overdistention and rupture of alveoli during birth or shortly thereafter, or they may be sequelae of pneumonia and other infections. They have been observed in tuberculosis lesions during specific antibacterial therapy and in end stage cystic fibrosis lung disease. These emphysematous areas presumably result from rupture of distended alveoli, forming a single or multiloculated cavity. The cysts can become large and might contain some fluid; an air-fluid level may be demonstrated on the radiograph (Fig. 420.3). The cysts should be differentiated from pulmonary abscesses. In most cases, treatment is not required as the cysts disappear spontaneously within a few months, although they can persist for a yr or more. Aspiration or surgery is not indicated except in cases of severe respiratory and cardiac compromise.

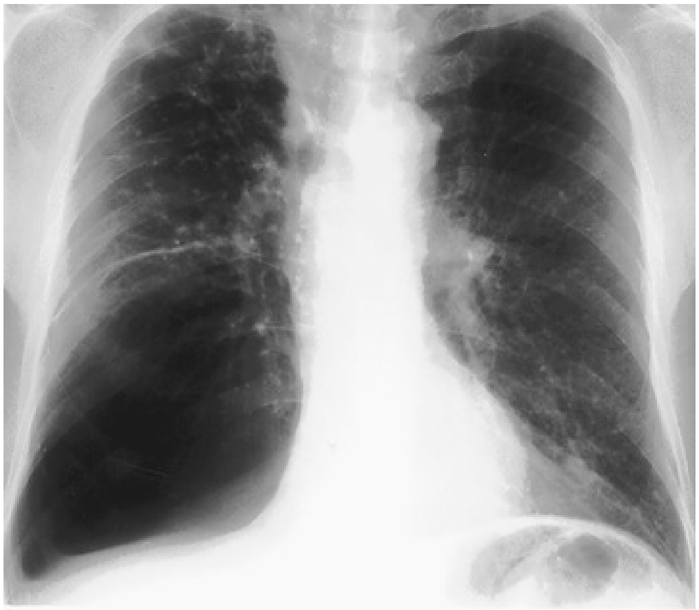

FIG. 420.3 Increased transradiancy in the right lower zone. A large emphysematous bulla occupies the lower half of the right lung, and the apical changes are in keeping with previous tuberculosis. (From Padley SPG, Hansell DM: Imaging techniques. In Albert RK, Spiro SG, Jett JR, editors: *Clinical respiratory medicine* , ed 3, Philadelphia, 2008, Mosby, Fig. 1.48.)

Subcutaneous Emphysema

Subcutaneous emphysema results from any process that allows free air to enter into the subcutaneous tissue (Fig. 420.4). The most common causes include pneumothorax or pneumomediastinum (see Chapters 439 and 440). In addition, it can be a complication of fracture of the orbit, which permits free air to escape from the nasal sinuses. In the neck and thorax, subcutaneous emphysema can follow tracheotomy, deep ulceration in the pharyngeal region, esophageal wounds, or any perforating lesion of the larynx or trachea. It is occasionally a complication of thoracentesis, asthma, or abdominal surgery. Rarely, air is formed in the subcutaneous tissues by gas-producing bacteria.

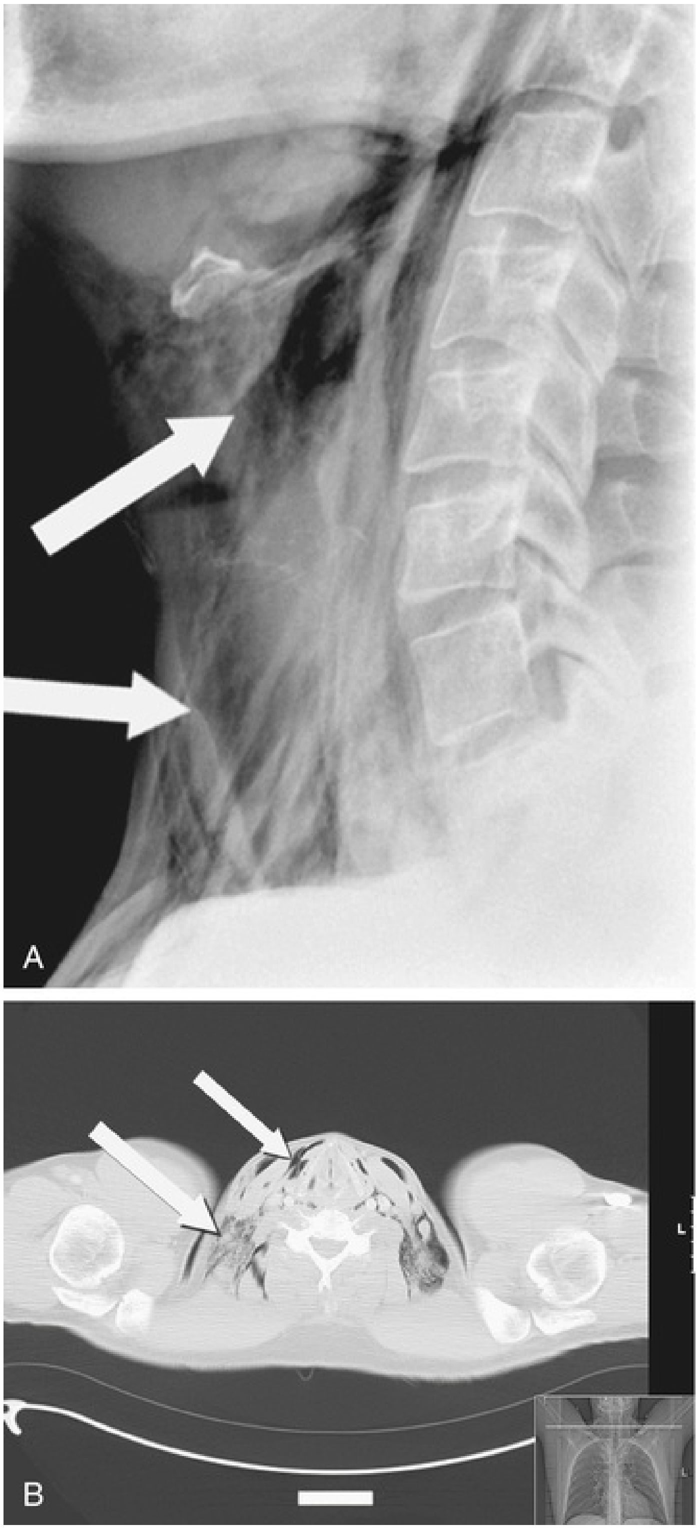

FIG. 420.4 **A,** Lateral X-ray of neck showing subcutaneous emphysema. **B,** Axial section CT neck/thorax showing subcutaneous emphysema and pneumomediastinum. (From Zakaria R, Khwaja H: Subcutaneous emphysema in a case of infective sinusitis: a case report, *J Med Case Rep* 4:235, 2010, Figs, 1 and 2.)

Tenderness over the site of emphysema and a crepitant quality on palpation of the skin are classic manifestations. Subcutaneous emphysema is usually a self-limited process and requires no specific treatment. Minimization of activities that can increase airway pressure (cough, performance of high-pressure pulmonary function testing maneuvers) is recommended. Resolution occurs by resorption of subcutaneous air after elimination of its source. Rarely, dangerous compression of the trachea by air in the surrounding soft tissue requires surgical intervention.

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CHAPTER 421

α_1 -Antitrypsin Deficiency and Emphysema

Glenna B. Winnie, Steven R. Boas

Homozygous deficiency of α_1 -antitrypsin (α_1 -AT) rarely produces lung disease in children, but it is an important cause of early-onset severe panacinar pulmonary emphysema in adults in the 3rd and 4th decades of life and a significant cause of liver disease in children (see Chapter 384.5). It is associated with panniculitis and vasculitis in adults.

Pathogenesis

The type and concentration of α_1 -AT are inherited as a series of codominant alleles on chromosomal segment 14q31-32.3. (See Chapter 384.5 for a discussion of genotypes and liver disease.) The autosomal recessive deficiency affects 1 in 1,600-2,500 people, but it remains underdiagnosed. The highest risk for α_1 -AT deficiency is found in whites, followed by Hispanics and blacks, with the lowest prevalence among Mexican Americans and little to no risk for Asians. Worldwide there are an estimated 116,000,000 carriers and 1,100,000 subjects with severe α_1 -AT deficiency. The normal α_1 -AT PiM protein is secreted by the liver into the circulation at a rate of approximately 34 mg/kg/day; it is also produced by lung epithelial cells and monocytes. Mutant protein is not produced (null) or is misfolded (PiZ and others); it can polymerize in the endoplasmic reticulum or be degraded, with subsequent low serum levels. Early adult-onset emphysema associated with α_1 -AT deficiency occurs most commonly with PiZZ (mutation in *SERPINA1* gene), although Pi (null) (null) and, to less extent, other mutant Pi types such as SZ have been associated with emphysema.

α_1 -AT and other serum antiproteases help to inactivate proteolytic enzymes released from dead bacteria or leukocytes in the lung. Deficiency of these antiproteases leads to an accumulation of proteolytic enzymes in the lung, resulting in destruction of pulmonary tissue with subsequent development of emphysema. Polymerized mutant protein in the lungs may also be proinflammatory, and there is evidence of increased oxidative stress. The concentration of proteases (elastase) in an individual's leukocytes may also be an important factor in determining the severity of clinical pulmonary disease with a given level of α_1 -AT.

Clinical Manifestations

Most patients who have the PiZZ defect have little or no detectable pulmonary disease during childhood. A few have early onset of chronic pulmonary symptoms, including dyspnea, wheezing, and cough, and panacinar emphysema has been documented by lung biopsy; it is probable that these findings occur secondarily to infection which caused inflammation with consequent early disease. Smoking increases the risk of emphysema in patients with mutant Pi types. Although newborn screening to identify children with PiZZ phenotype does not affect parental smoking habits, it does decrease smoking rates among affected adolescents.

Physical examination in *childhood* is usually normal. Affected children very rarely have growth failure, an increased anteroposterior diameter of the chest with a hyperresonant percussion note, crackles if there is active infection, and clubbing. Severe emphysema can depress the diaphragm, making the liver and spleen more easily palpable.

Laboratory Findings

Serum immunoassay measures low levels of α_1 -AT; normal serum levels are ~80-220 mg/dL. Serum electrophoresis reveals the phenotype, and genotype is determined by polymerase chain reaction; whole gene sequencing is possible. In the rare patient with lung disease in adolescence, chest radiograph reveals overinflation with depressed diaphragms. Chest CT can show more hyperexpansion in the lower lung zones, with occasional bronchiectasis; CT densitometry can be a sensitive method to follow changes in lung disease. Lung function testing is usually normal in children, but it can show airflow obstruction and increased lung volumes, particularly in adolescents who smoke.

Treatment

Therapy for α_1 -AT deficiency is intravenous replacement (augmentation) with enzyme derived from pooled human plasma. A level of 80 mg/dL is protective for emphysema. This target level for augmentation therapy is usually achieved with initial doses of 60 mg/kg IV weekly and results in the appearance of the transfused antiprotease in pulmonary lavage fluid. The Food and Drug Administration has approved the use of purified blood-derived human enzyme for ZZ and null-null patients. Replacement therapy is indicated for those with moderately severe obstructive lung disease (forced expiratory volume in 1 sec is 30–65% of predicted) or those with mild lung disease experiencing a rapid decline in lung function. Augmentation therapy is not indicated for persons with the PiMZ type who have pulmonary disease, because their disease is not from enzyme deficiency. Recombinant sources of α_1 -AT are under development, but current products are rapidly cleared from the circulation when given intravenously; they may be useful for inhalation therapy. Inhalation of the plasma-derived product is under evaluation. Lung transplantation has been performed for end-stage disease. Multiple strategies for gene therapy are under development.

Supportive Therapy

Standard supportive therapy for chronic lung disease includes aggressive treatment of pulmonary infection, routine use of pneumococcal and influenza vaccines, bronchodilators, and advice about the serious risks of smoking. Such treatment is also indicated for asymptomatic family members found to have PiZZ or null-null phenotypes but not those with PiMZ type. The clinical significance of the PiSZ type is unclear, but nonspecific treatment is reasonable. All persons with low levels of serum antiprotease should be warned that the development of emphysema is partially mediated by environmental factors and that cigarette smoking is particularly deleterious. Although early identification of affected persons could help to prevent development of obstructive lung disease, population screening programs are being considered but are currently suspended.

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CHAPTER 422

Other Distal Airway Diseases

422.1

Bronchiolitis Obliterans

Steven R. Boas

Keywords

Bronchiolitis obliterans
Bronchiolitis obliterans syndrome
Bronchiolitis obliterans organizing pneumonia
Cryptogenic organizing pneumonia

Epidemiology

Bronchiolitis obliterans (BO) is a histopathologic diagnosis characterized by chronic obstructive lung disease of the bronchioles and smaller airways, resulting from an insult to the lower respiratory tract leading to inflammation and fibrosis of the small airways. In the nontransplant patient, BO most commonly occurs in the pediatric population after respiratory infections, particularly adenovirus (see Chapter 289), but also *Mycoplasma pneumoniae* (see Chapter 250), measles (see Chapter 273), *Legionella pneumophila* (see Chapter 235), influenza (see Chapter 285), and pertussis (see Chapter 224); other causes include inflammatory diseases (juvenile idiopathic arthritis, systemic lupus erythematosus [see Chapter 183], scleroderma [see Chapter 185], Stevens-Johnson syndrome [see Chapter 177]), and inhalation of toxic fumes or particulate exposure (NO_2 , incinerator fly ash, NH_3 , diacetyl flavorings from microwave popcorn, papaverine, fiberglass) (Table 422.1). Postinfection obliterans may be more common in the southern hemisphere and among persons of Asian descent. BO is also commonly seen in post lung or bone marrow transplant recipients.

Table 422.1

Etiology of Bronchiolitis Obliterans

POSTINFECTION
Adenovirus types 3, 7, and 21 Influenza Parainfluenza Measles Respiratory syncytial virus Varicella *Mycoplasma pneumoniae*
POSTTRANSPLANTATION
Chronic rejection of lung or heart/lung transplantation Graft versus host disease associated with bone marrow transplantation
CONNECTIVE TISSUE DISEASE
Juvenile idiopathic arthritis Sjögren syndrome Systemic lupus erythematosus
TOXIC FUME INHALATION
NO_2 NH_3 Diacetyl flavorings (microwave popcorn)
CHRONIC HYPERSENSITIVITY PNEUMONITIS
Avian antigens Mold
ASPIRATION
Stomach contents: gastroesophageal reflux Foreign bodies
DRUGS
Penicillamine Cocaine
STEVENS-JOHNSON SYNDROME
Idiopathic Drug induced Infection related

From Moonnumakal SP, Fan LL: Bronchiolitis obliterans in children, *Curr Opin Pediatr* 20:272–278, 2008.

Bronchiolitis obliterans syndrome (BOS) is a clinical diagnosis related to graft deterioration after transplantation defined as a progressive decline in lung function based on FEV1. The airway obstruction is generally irreversible. BOS is considered once other causes of airway obstruction are excluded. BOS is recognized as a long-term complication of both lung and bone marrow transplantation with more than one third of survivors of lung transplantation developing this disorder. Risk factors for the development of BOS include the presence of CMV pneumonitis, aspergillus colonization, primary graft dysfunction, gastroesophageal reflux, and community-acquired respiratory viruses, as well as prolonged transplantation ischemic time.

Pathogenesis

After the initial insult, inflammation affecting terminal bronchioles, respiratory bronchioles, and alveolar ducts can result in the obliteration of the airway lumen (Fig. 422.1). Epithelial damage resulting in abnormal repair is characteristic of BO. Complete or partial obstruction of the airway lumen can result in air trapping or atelectasis. Parenchymal involvement is not seen. **Bronchiolitis obliterans organizing pneumonia (BOOP)** or what has also been termed **cryptogenic organizing pneumonia** is a histopathologic diagnosis. Although it is similar to many of the histologic features of BO, BOOP is also characterized by extension of the inflammatory process from distal alveolar ducts into alveoli with proliferation of fibroblasts (parenchymal involvement).

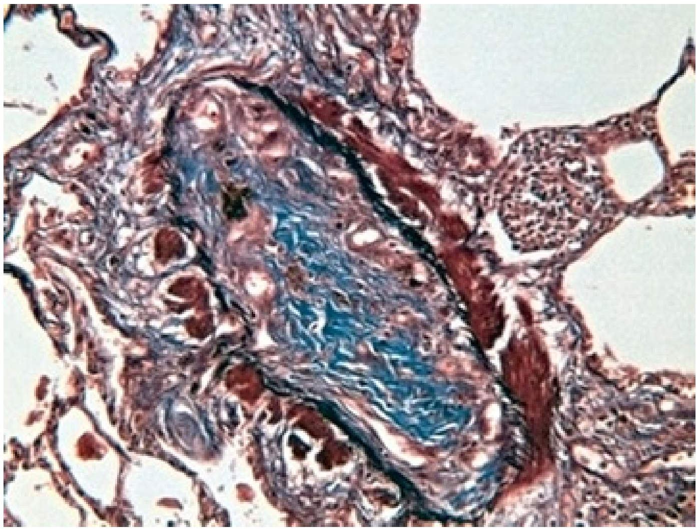

FIG. 422.1 Complete obliteration of airway lumen with fibromyxoid tissue

in lung transplant recipient with bronchiolitis obliterans. (From Kurland G, Michelson P: Bronchiolitis obliterans in children, *Pediatr Pulmonol* 39:193–208, 2005.)

Clinical Manifestations and Diagnosis

Cough, fever, cyanosis, dyspnea, chest pain, and respiratory distress followed by initial improvement may be the initial signs of BO. In this phase, BO is easily confused with pneumonia, bronchitis, or bronchiolitis. Progression of the disease can ensue, with increasing dyspnea, chronic cough, sputum production, and wheezing. Physical examination findings are usually nonspecific and can include wheezing, hypoxemia, and crackles. Chest radiographs may be relatively normal compared with the extent of physical findings but can demonstrate hyperlucency and patchy infiltrates. Occasionally, a Swyer-James syndrome (unilateral hyperlucent lung; see Chapter 420) develops. Pulmonary function tests demonstrate variable findings but typically show signs of airway obstruction with a variable degree of bronchodilator response although more commonly irreversible. Exercise testing shows reduced exercise capacity and impaired oxygen consumption. Ventilation-perfusion scans reveal a typical moth-eaten appearance of multiple matched defects in ventilation and perfusion. High-resolution chest CT often demonstrates patchy areas or a mosaic pattern of hyperlucency, air trapping, and bronchiectasis (Fig. 422.2). Table 422.2 provides an overview of CT findings of BO and related disorders. Physical and radiologic signs can wax and wane over weeks or months. Open lung biopsy or transbronchial biopsy remains the best means of establishing the diagnosis of BO or BOOP.

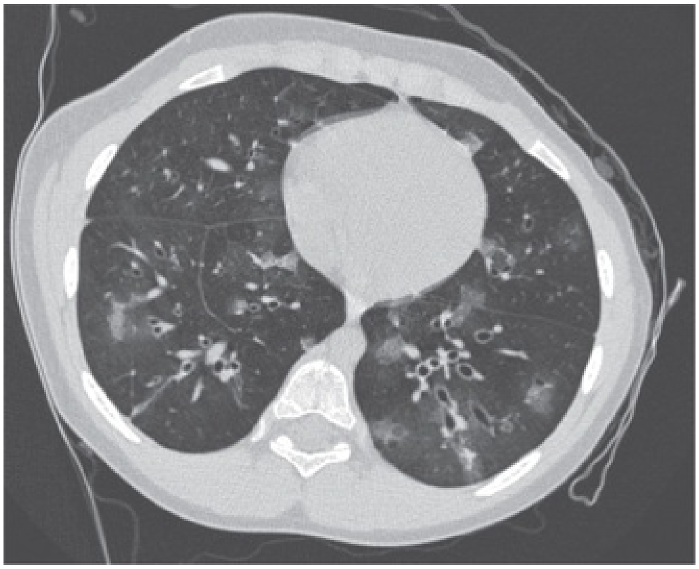

FIG. 422.2 High-resolution CT scan of the chest of a child with bronchiolitis obliterans demonstrating mosaic perfusion and vascular attenuation. Air-trapping is demonstrated by lack of increase in attention or decrease in lung volume in dependent lung. (Image courtesy Alan Brody, MD, Cincinnati Children's Hospital Medical Center, Ohio.)

Table 422.2

High-Resolution CT Patterns in Child With Interstitial Lung Disease

	STUDIES (N)	GROUND-GLASS OPACITY	THICK SEPTA	NODULES	MOSAIC PATTERN	HONEYCOMBING
Bronchiolitis obliterans	4	—	—	—	X	—
Nonspecific interstitial pneumonitis	6	X	—	—	—	X
Desquamative interstitial pneumonitis	4	X	—	—	—	X
Follicular bronchitis or neuroendocrine cell hyperplasia of infancy	4	X	—	—	X	—
Lymphocytic interstitial pneumonitis	4	—	—	X	—	—
Lymphangiomatosis	2	—	X	—	—	—
Lymphangiectasia	2	—	X	—	—	—
Pulmonary alveolar proteinosis	2	X	X	—	—	—

From Long FR: Interstitial lung disease. In Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, Table 74.1; original data from Lynch DA, Hay T, Newell JD Jr, et al: Pediatric diffuse lung disease: diagnosis and classification using high-resolution CT, *AJR Am J*

Roentgenol 173:713–718, 1999, and Copley SJ, Coren M, Nicholson AG, et al: Diagnostic accuracy of thin-section CT and chest radiography of pediatric interstitial lung disease, *AJR Am J Roentgenol* 174:549–554, 2000.

Treatment

No definitive therapy exists for BO. Administration of corticosteroids may be beneficial. Immunomodulatory agents, such as sirolimus, tacrolimus, aerosolized cyclosporine, hydroxychloroquine, and macrolide antibiotics, have been used in post–lung transplantation recipients with BO with variable success. Supportive measures with oxygen, antibiotics for secondary infections, and bronchodilators are adjunct therapies. The role of gastroesophageal reflux and its association with BO has been raised, with treatment suggested whenever the diagnosis is made. Azithromycin may be effective in patients with BOS. For BOOP, use of oral corticosteroids for up to 1 yr has been advocated as first-line therapy for symptomatic and progressive disease. Patients with asymptomatic or nonprogressive BOOP can be observed.

Prognosis

Some patients with BO experience rapid deterioration in their condition and die within weeks of the initial symptoms; most nontransplant patients survive with chronic disability. BO tends to be severe once progression ensues. In contrast to BO, a better prognosis exists for patients with BOOP, with complete recovery seen in many patients, although outcome depends on the underlying systemic disease. BOOP can relapse, especially if treatment duration is <1 yr; BOOP is amenable to repeat courses of oral corticosteroids. Unlike the more common idiopathic BOOP, progressive BOOP characterized by acute respiratory distress syndrome is rare but is aggressive in its clinical course, leading to death.

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422.2

Follicular Bronchitis

Steven R. Boas

Keywords

Follicular bronchitis
Follicular bronchiolitis

Follicular bronchitis is a lymphoproliferative lung disorder characterized by the presence of lymphoid follicles alongside the airways (bronchi or bronchioles) and infiltration of the walls of bronchi and bronchioles. Although the cause is unknown, an infectious etiology (viral, *L. pneumophila;* see Chapter 235) has been proposed. This disorder has been reported following lung transplant and in an HIV-positive child. It can occur in adults and children; in children, onset of symptoms generally occurs by 6 wk of age and peaks between 6 and 18 mo. Cough, moderate respiratory distress, fever, and fine crackles are common clinical findings. Fine crackles generally persist over time, and recurrence of symptoms is common. Chest radiographs may be relatively benign initially (air trapping, peribronchial thickening) but evolve into the typical interstitial pattern. Chest CT can show a fine reticular pattern, as well as bronchiectasis and centrilobular branching, but can also appear normal (see Table 422.2). Definitive diagnosis is made by open lung biopsy (Fig. 422.3). Treatment is limited, although some patients with follicular bronchitis respond to corticosteroid therapy. Prognosis is variable, with some patients having significant progression of pulmonary disease and others developing only mild obstructive airway disease. In children, it is generally associated with immunodeficiency; the differential diagnosis includes the pulmonary complications of HIV infection (see Chapter 302).

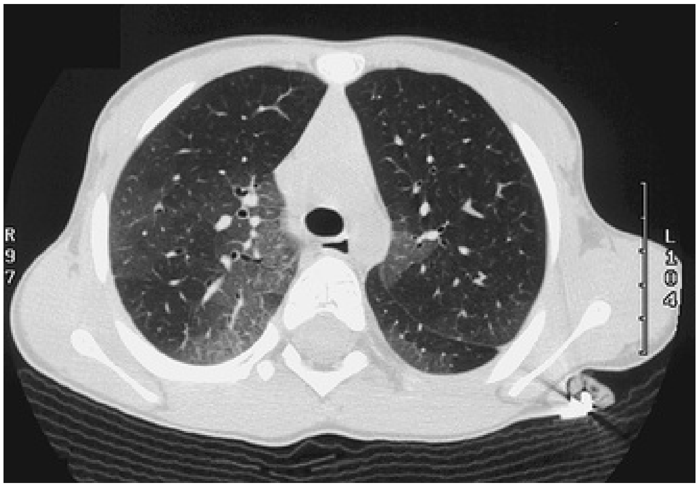

FIG. 422.3 Follicular bronchiolitis in a 3 yr old girl with mosaic attenuation

and cylindrical bronchiectasis. CT findings suggested bronchiolitis obliterans, but a biopsy documented the presence of follicular bronchiolitis. (From Long FR, Druhan SM, Kuhn JP: Diseases of the bronchi and pulmonary aeration. In Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, Fig. 73.71.)

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422.3

Pulmonary Alveolar Microlithiasis

Steven R. Boas

Keyword

Pulmonary alveolar microlithiasis

Pulmonary alveolar microlithiasis (PAM) is a rare disease characterized by the formation of lamellar concretions of calcium phosphate or “microliths” within the alveoli, creating a classic pattern on the radiograph (Fig. 422.4).

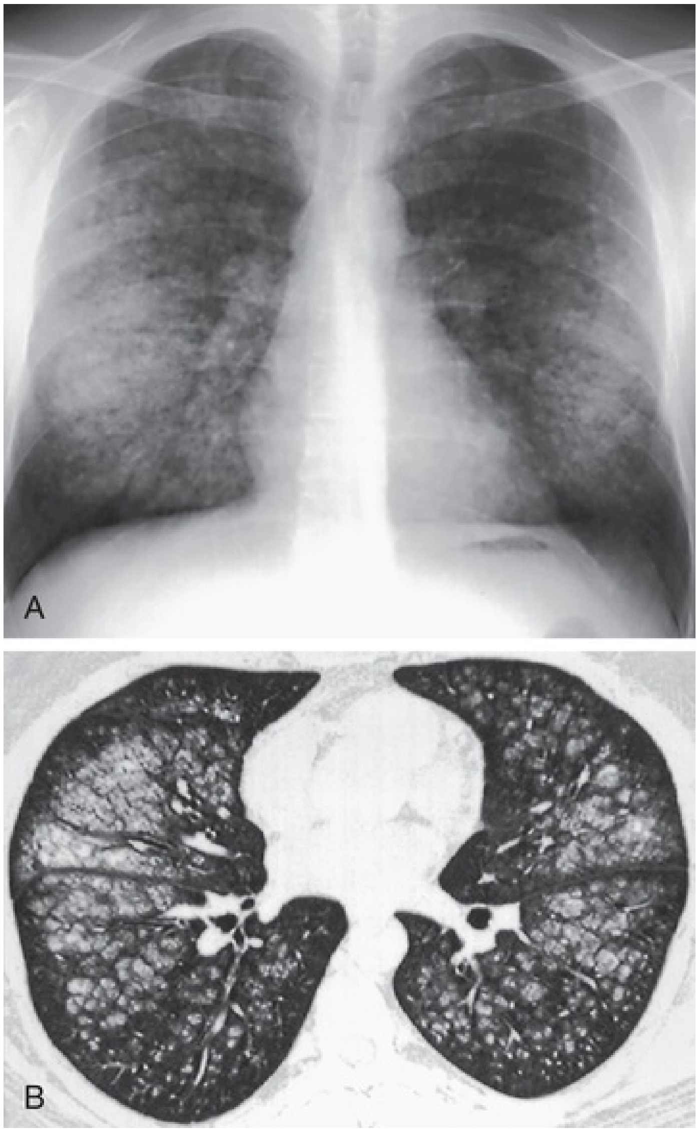

FIG. 422.4 Radiographic features of pulmonary alveolar microlithiasis. **A,** Posteroanterior chest radiograph showing the classic “sandstorm” appearance of pulmonary alveolar microlithiasis, including diffuse, patchy, bilateral sharp micronodular disease. **B,** High-resolution CT scan of the chest showing micronodular densities. (From Brandenburg VM, Schubert H: Images in clinical medicine. Pulmonary alveolar microlithiasis, *N Engl J Med* 348:1555, 2003.)

Epidemiology and Etiology

Although the mean age at time of diagnosis is in the mid-30s, the onset of the disease can occur in childhood and in newborns. PAM is inherited in an autosomal recessive disorder and is caused by a mutation in the type II sodium phosphate cotransporter NPT2b *(SCL34A2)*. There are more than 15 mutations. This gene is expressed in high levels in the lungs, predominantly on the surface of alveolar type II cells. Although the precise role of this protein is unknown, it is speculated that it helps to remove phosphate generated from surfactant metabolism in the alveolar space, as well as functioning as a phosphate regulator in other organs.

In some families, progression of disease is rapid. An equal male and female incidence is noted. Although PAM is found throughout the world, there is a high incidence in Turkey and a lesser incidence in Italy, Japan, and India.

Clinical Manifestations

In early stages of the disease, patients are usually asymptomatic. When symptomatic, patients with PAM usually complain of dyspnea on exertion and nonproductive cough. Physical examination of the lungs can reveal fine inspiratory crackles and diminished breath sounds. Clubbing occurs, although this is usually a more advanced sign. Discordance between the clinical and radiographic manifestations is common. Many children are often asymptomatic on initial presentation and present with symptoms during adulthood. Complications of pneumothorax, pleural adhesions and calcifications, pleural fibrosis, apical bullae, and extrapulmonary sites of microliths have been reported (kidneys, prostate, sympathetic chain, and testes).

Diagnosis

Chest radiography typically reveals bilateral infiltrates with a fine micronodular appearance or sandstorm appearance with greater density in the lower and middle lung fields (see Fig. 422.4). CT of the chest shows diffuse micronodular calcified densities, with thickening of the microliths along the septa and around distal bronchioles, especially in the inferior and posterior regions (see Table 422.2). Diffuse uptake of technetium-99 methylene diphosphonate by nuclear scan has been reported. Open lung and transbronchial lung biopsy reveal 0.1- to 0.3-mm laminated calcific concretions within the alveoli. Although the alveoli are often normal initially, progression to pulmonary fibrosis with advancing disease usually ensues. Sputum expectoration might reveal small microliths, although this finding is not diagnostic for PAM and is not typically seen in children. Detection of calcium deposits in bronchoalveolar lavage (BAL) fluid on bronchoscopy supports the diagnosis. Pulmonary function testing reveals restrictive lung disease with impaired diffusing capacity as the disease progresses, whereas exercise testing demonstrates arterial oxygen desaturation. The diagnosis can usually be established radiographically. However, lung tissue biopsy, BAL, and detection of a mutation in the *SCL34A2* gene can also be used to help confirm the diagnosis. The differential diagnosis includes sarcoidosis, miliary tuberculosis, hemosiderosis, healed disseminated histoplasmosis, pulmonary calcinosis, and metastatic pulmonary calcifications.

Treatment

No specific treatment is effective, although some clinicians have used glucocorticosteroids, etidronate disodium, and bronchopulmonary lavage with limited success. Lung transplantation has been performed for this condition without recurrence in the transplanted lung.

Prognosis

Progressive cardiopulmonary disease can ensue, leading to cor pulmonale, superimposed infections, and subsequent death in mid-adulthood. Because of the familial nature of this disease, counseling and chest radiographs of family members are indicated.

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CHAPTER 423

Congenital Disorders of the Lung

423.1

Pulmonary Agenesis and Aplasia

Joshua A. Blatter, Jonathan D. Finder

Etiology and Pathology

Pulmonary agenesis differs from hypoplasia in that agenesis entails the complete absence of a lung. Agenesis differs from aplasia by the absence of a bronchial stump or carina that is seen in aplasia. Bilateral pulmonary agenesis is incompatible with life, manifesting as severe respiratory distress and failure. Pulmonary agenesis is thought to be an autosomal recessive trait, with an estimated incidence of 1 in 10,000-15,000 births.

Clinical Manifestations and Prognosis

Unilateral agenesis or hypoplasia can have few symptoms and nonspecific findings, resulting in only 33% of the cases being diagnosed while the patient is living. Symptoms tend to be associated with central airway complications of compression, stenosis, and/or tracheobronchomalacia. In patients in whom the right lung is absent, the aorta can compress the trachea and lead to symptoms of central airway compression. Right lung agenesis has a higher morbidity and mortality than left lung agenesis. Pulmonary agenesis is often seen in association with other congenital anomalies such as the **VACTERL sequence** (*v* ertebral anomalies, *a* nal atresia, *c* ongenital heart disease, *t* racheoesophageal fistula, *r* enal anomalies, and *l* imb anomalies), ipsilateral facial and skeletal malformations, and central nervous system and cardiac malformations. Compensatory growth of the remaining lung allows improved gas exchange, but the mediastinal shift can lead to scoliosis and airway compression. Scoliosis can result from unequal thoracic growth.

Diagnosis and Treatment

Chest radiographic findings of unilateral lung or lobar collapse with a shift of mediastinal structures toward the affected side can prompt referral for suspected foreign body aspiration, mucous plug occlusion, or other bronchial mass lesions. The diagnosis requires a high index of suspicion to avoid the unnecessary risks of bronchoscopy, including potential perforation of the rudimentary bronchus. CT of the chest is diagnostic, although the diagnosis may be suggested by chronic changes in the contralateral aspect of the chest wall and lung expansion on chest radiographs. Because pulmonary agenesis can be associated with a wide variety of congenital lesions, whole body MRI can be useful to determine whether other systems (e.g., cardiac, gastrointestinal) are affected. Conservative treatment is usually recommended, although surgery has offered benefit in selected cases.

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423.2

Pulmonary Hypoplasia

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Etiology and Pathology

Pulmonary hypoplasia involves a decrease in both the number of alveoli and the number of airway generations. The hypoplasia may be bilateral in the setting of bilateral lung constraint, as in oligohydramnios or thoracic dystrophy. Pulmonary hypoplasia is usually secondary to other intrauterine disorders that produce an impairment of normal lung development (see Chapter 122). Conditions such as deformities of the thoracic spine and rib cage (thoracic dystrophy), pleural effusions with fetal hydrops, congenital pulmonary airway malformation, and congenital diaphragmatic hernia physically constrain the developing lung. Any condition that produces oligohydramnios (fetal renal insufficiency or prolonged premature rupture of membranes) can also lead to diminished lung growth. In these conditions, airway and arterial branching are inhibited, thereby limiting the capillary surface area. Large unilateral lesions, such as congenital diaphragmatic hernia or pulmonary airway malformation, can displace the mediastinum and thereby produce a contralateral hypoplasia, although usually not as severe as that seen on the ipsilateral side.

Clinical Manifestations

Pulmonary hypoplasia is usually recognized in the newborn period, owing to either the respiratory insufficiency or the presentation of persistent pulmonary hypertension (see Chapter 122.7). Later presentation (tachypnea) with stress or respiratory viral infection can be seen in infants with mild pulmonary hypoplasia.

Diagnosis and Treatment

A variety of imaging techniques, including MRI and ultrasound, with estimation of oligohydramnios, can be helpful to identify hypoplasia but not to predict pulmonary function. Mechanical ventilation and oxygen may be required to support gas exchange. Specific therapy to control associated pulmonary hypertension, such as inhaled nitric oxide, may be useful. In cases of severe hypoplasia, the limited capacity of the lung for gas exchange may be inadequate to sustain life. Extracorporeal membrane oxygenation can provide gas exchange for a critical period of time and permit survival. Rib-expanding devices (vertically expansible prosthetic titanium ribs) can improve the survival of patients with thoracic dystrophies (see Chapter 720).

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423.3

Congenital Cystic Malformation (Congenital Pulmonary Airway Malformation)

Joshua A. Blatter, Jonathan D. Finder

Pathology

Congenital pulmonary airway malformation **(CPAM)** , formerly known as cystic adenomatoid malformation, consists of hamartomatous or dysplastic lung tissue mixed with more normal lung, generally confined to 1 lobe. This congenital pulmonary disorder occurs in approximately 1-4 in 100,000 births. Prenatal ultrasonographic findings are classified as **macrocystic** (single or multiple cysts >5 mm) or **microcystic** (echogenic cysts <5 mm). Five histologic patterns have been described. **Type 0** (acinar dysplasia) is least common (<3%) and consists of microcystic disease throughout the lungs. The prognosis is poorest for this type, and infants die at birth. **Type 1** (60%) is macrocystic and consists of a single or several large (>2 cm in diameter) cysts lined with ciliated pseudostratified epithelium; the lesion is localized involving only a part of 1 lobe. One third of cases have mucus-secreting cells. Presentation is in utero or in the newborn period. Cartilage is rarely seen in the wall of the cyst. This type has a good prognosis for survival. **Type 2** (20%) is microcystic and consists of multiple small cysts with histology similar to that of the type 1 lesion. Type 2 is associated with other serious congenital anomalies (renal, cardiac, diaphragmatic hernia) and carries a poor prognosis. **Type 3** (<10%) is seen mostly in males; the lesion is a mixture of microcysts and solid tissue with bronchiole-like structures lined with cuboidal ciliated epithelium and separated by areas of nonciliated cuboidal epithelium. The prognosis for this type, like type 0, is poor. **Type 4** (10%) is commonly macrocystic and lacks mucus cells. It is associated with malignancy (pleuropulmonary blastoma) and can present either in childhood or in asymptomatic adults.

Etiology

The lesion probably results from an embryologic injury before the 35th day of gestation, with maldevelopment of terminal bronchiolar structures. Histologic examination reveals little normal lung and many glandular elements. Cysts are very common; cartilage is rare. The presence of cartilage might indicate a somewhat later embryologic insult, perhaps extending into the 10th-24th wk. Although growth factor interactions and signaling mechanisms have been implicated in altered lung-branching morphogenesis, the exact roles in the maldevelopment seen here remain obscure.

Diagnosis

Cystic airway malformations can be diagnosed in utero by ultrasonography (Fig. 423.1). Fetal cystic lung abnormalities can include CPAM (40%), pulmonary sequestration (14%) (see Chapter 423.4), or both (26%); the median age at diagnosis is usually 21 wk of gestation. In one series, only 7% had severe signs of fetal distress including hydrops, pleural effusion, polyhydramnios, ascites, or severe facial edema; 96% of the fetuses were born alive, 2 of whom died in the neonatal period. CPAM volume (i.e., CPAM volume ratio [CVR]) can be used to predict risk of hydrops. Lesions causing fetal hydrops have a poor prognosis. Large lesions, by compressing adjacent lung, can produce pulmonary hypoplasia in nonaffected lobes (see Chapter 423.2). Even lesions that appear large in early gestation can regress considerably or decrease in relative size and be associated with good pulmonary function in childhood. CT allows accurate diagnosis and sizing of the lesion and is indicated even in asymptomatic neonates.

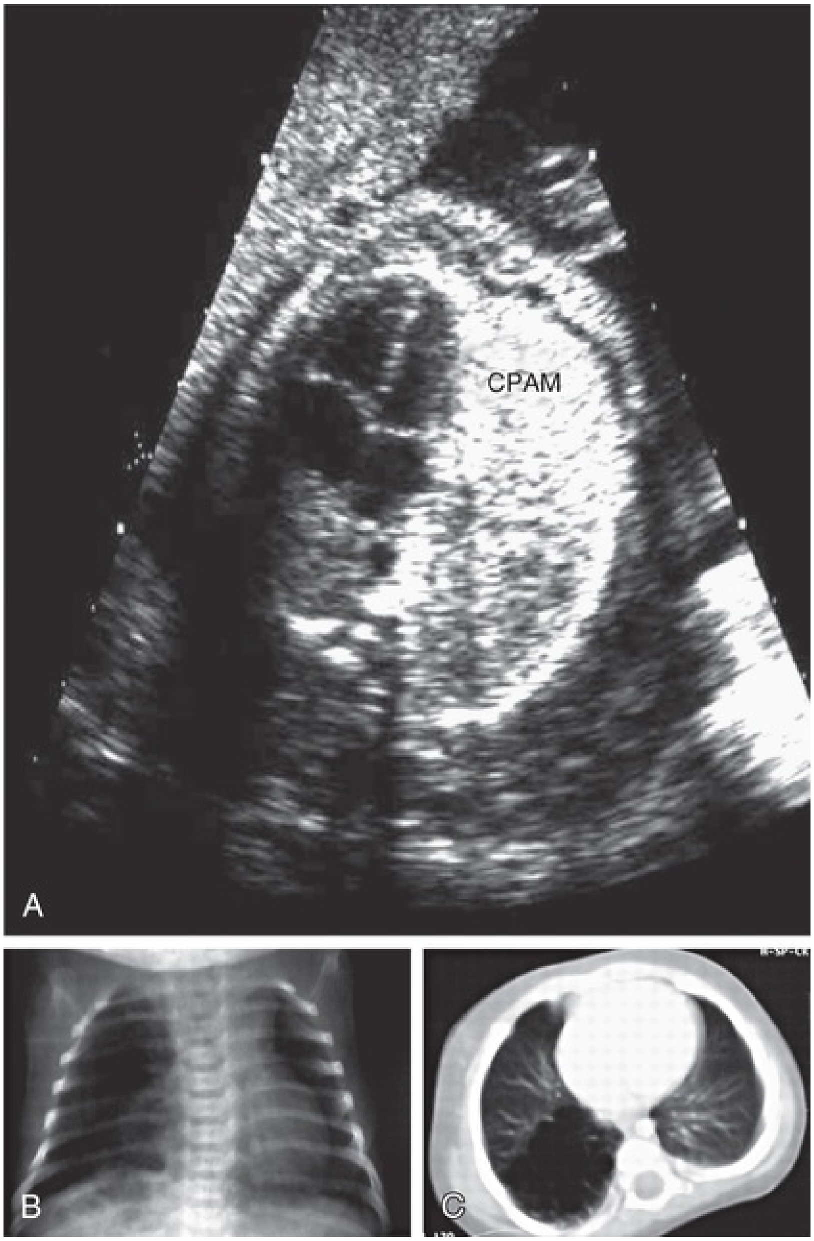

FIG. 423.1 Imaging of congenital pulmonary airway malformation of the lung *(CPAM)* on the same patient with prenatal ultrasound scan **(A),** chest radiograph **(B),** and CT scan **(C).** Note that the lesion is not visible on the chest radiograph. (From Lakhoo K: Management of congenital cystic adenomatous malformations of the lung, *Arch Dis Child Fetal Neonatal Ed* 94:F73–F76, 2009.)

Clinical Manifestations

Patients can present in the newborn period or early infancy with respiratory distress, recurrent respiratory infection, and pneumothorax. The lesion may be confused with a diaphragmatic hernia (see Chapter 122.10). Patients with smaller lesions are usually asymptomatic until mid-childhood, when episodes of recurrent or persistent pulmonary infection or chest pain occur. Breath sounds may be diminished, with mediastinal shift away from the lesion on physical examination. Chest radiographs reveal a cystic mass, sometimes with mediastinal shift (Fig. 423.2). Occasionally, an air-fluid level suggests a lung abscess (see Chapter 431).

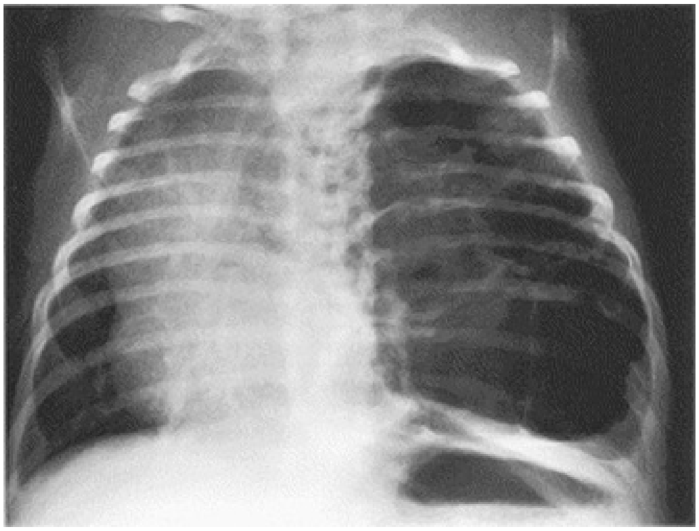

FIG. 423.2 Neonatal chest x-ray showing large multicystic mass in the left hemithorax with mediastinal shift as a result of congenital pulmonary airway malformation. (From Williams HJ, Johnson KJ: Imaging of congenital cystic lung lesions, *Paediatr Respir Rev* 3:120–127, 2002.)

Treatment

Antenatal intervention in severely affected infants is controversial but can include excision of the affected lobe for microcystic lesions, aspiration of macrocystic lesions, and, rarely, open fetal surgery. In the postnatal period, surgery is indicated for symptomatic patients. Although surgery may be delayed for asymptomatic infants because postnatal resolution has been reported, true resolution appears to be very rare in that abnormalities usually remain detectable on CT or MRI. Sarcomatous and carcinomatous degeneration have been described in patients with CPAM, so surgical resection by 1 yr of age is recommended to limit malignant potential. The mortality rate is <10%. Another indication for surgery is to rule out **pleuropulmonary blastoma (PPB)** , a malignancy that can appear radiographically similar to type 1 CPAM. PPB is associated with germline mutations in *DICER1* . In addition to the risk of malignancy, “asymptomatic” patients may have chronic inflammation with subtle systemic manifestations, which parents report resolves after the lesion is resected.

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423.4

Pulmonary Sequestration

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Pulmonary sequestration is a congenital anomaly of lung development that can be intrapulmonary or extrapulmonary, according to the location within the visceral pleura. The majority of sequestrations are intrapulmonary.

Pathophysiology

The lung tissue in a sequestration does not connect to a bronchus and receives its arterial supply from the systemic arteries (commonly off the aorta) and returns its venous blood to the right side of the heart through the inferior vena cava (**extralobar**) or pulmonary veins (**intralobar**). The sequestration functions as a space-occupying lesion within the chest; it does not participate in gas exchange and does not lead to a left-to-right shunt or alveolar dead space. Communication with the airway can occur as the result of rupture of infected material into an adjacent airway. Collateral ventilation within intrapulmonary lesions via pores of Kohn can occur. Pulmonary sequestrations can arise through the same pathoembryologic mechanism as a remnant of a diverticular outgrowth of the esophagus. Some propose that intrapulmonary sequestration is an acquired lesion primarily caused by infection and inflammation; inflammation leads to cystic changes and hypertrophy of a feeding systemic artery. This is consistent with the rarity of this lesion in autopsy series of newborns. Gastric or pancreatic tissue may be found within the sequestration. Cysts also may be present. Other associated congenital anomalies, including CPAM (see Chapter 423.3), diaphragmatic hernia (see Chapter 122.10), and esophageal cysts, are not uncommon. Some believe that intrapulmonary sequestration is often a manifestation of CPAM and have questioned the existence of intrapulmonary sequestration as a separate entity.

Clinical Manifestations and Diagnosis

Physical findings in patients with sequestration include an area of dullness to percussion and decreased breath sounds over the lesion. During infection, crackles may also be present. A continuous or purely systolic murmur may be heard over the back. If findings on routine chest radiographs are consistent with the diagnosis, further delineation is indicated before surgical intervention (Fig. 423.3). CT with contrast can demonstrate both the extent of the lesion and its vascular supply. MR angiography is also useful. Ultrasonography can help to rule out a diaphragmatic hernia and demonstrate the systemic artery. Surgical removal is recommended. Identifying the blood supply before surgery avoids inadvertently severing its systemic artery. Coil embolization (transumbilical in neonates; arterial in older patients) has been successful in treating patients with sequestration.

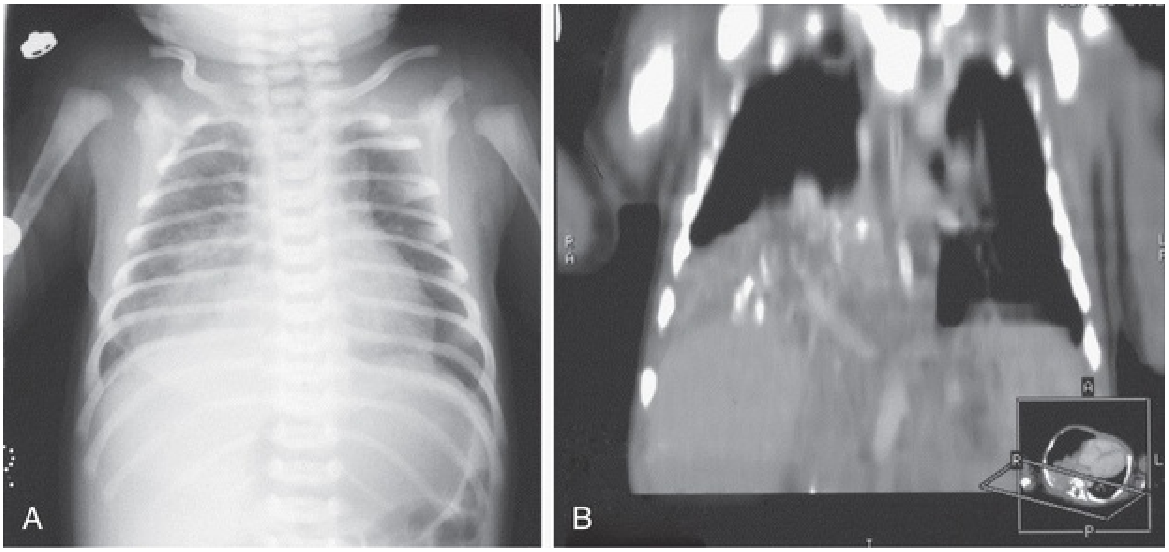

FIG. 423.3 **A,** Plain chest x-ray showing changes in the region of the right lower/middle lobe of the lung. **B,** CT showing parenchymal changes in the right lower lobe of the lung in keeping with a sequestration. (From Corbett HJ, Humphrey GME: Pulmonary sequestration, *Paediatr Respir Rev* 5:59–68, 2004.)

Intrapulmonary sequestration is generally found in a lower lobe and does not have its own pleura. Patients usually present with infection. In older patients, hemoptysis is common. A chest radiograph during a period when there is no active infection reveals a mass lesion; an air-fluid level may be present. During infection, the margins of the lesion may be blurred. There is no difference in the incidence of this lesion in each lung.

Extrapulmonary sequestration is much more common in boys and almost always involves the left lung. This lesion is enveloped by a pleural covering and is associated with diaphragmatic hernia and other abnormalities such as colonic duplication, vertebral abnormalities, and pulmonary hypoplasia. Many of these patients are asymptomatic when the mass is discovered by routine chest radiography. Other patients present with respiratory symptoms or heart failure. Subdiaphragmatic extrapulmonary sequestration can manifest as an abdominal mass on prenatal ultrasonography. The advent of prenatal ultrasonography has also enabled evidence that fetal pulmonary sequestrations can spontaneously regress.

Treatment

Treatment of intrapulmonary sequestration is surgical removal of the lesion, a procedure that usually requires excision of the entire involved lobe. Segmental resection occasionally suffices. Surgical resection of the involved area is often recommended for extrapulmonary sequestration as well, but observation can be considered for asymptomatic patients with small lesions. Coil embolization of the feeding artery has also been successful.

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423.5

Bronchogenic Cysts

Joshua A. Blatter, Jonathan D. Finder

Etiology and Pathology

Bronchogenic cysts arise from abnormal budding of the tracheal diverticulum of the foregut before the 16th wk of gestation and are originally lined with ciliated epithelium. They are more commonly found on the right and near a midline structure (trachea, esophagus, carina), but peripheral lower lobe and perihilar intrapulmonary cysts are not infrequent. Diagnosis may be precipitated by enlargement of the cyst, which causes symptoms by pressure on an adjacent airway. When the diagnosis is delayed until an infection occurs, the ciliated epithelium may be lost, and accurate pathologic diagnosis is then impossible. Cysts are rarely demonstrable at birth. Later, some cysts become symptomatic by becoming infected or by enlarging and compromising the function of an adjacent airway.

Clinical Manifestations and Treatment

Fever, chest pain, and productive cough are the most common presenting symptoms. Dysphagia may be present; some bronchogenic cysts are asymptomatic. A chest radiograph reveals the cyst, which can contain an air-fluid level (Fig. 423.4). CT scan or MRI is obtained in most cases to better demonstrate anatomy and extent of lesion before surgical resection. Treatment of symptomatic cysts is surgical excision after appropriate antibiotic management. Asymptomatic cysts are generally excised in view of the high rate of infection.

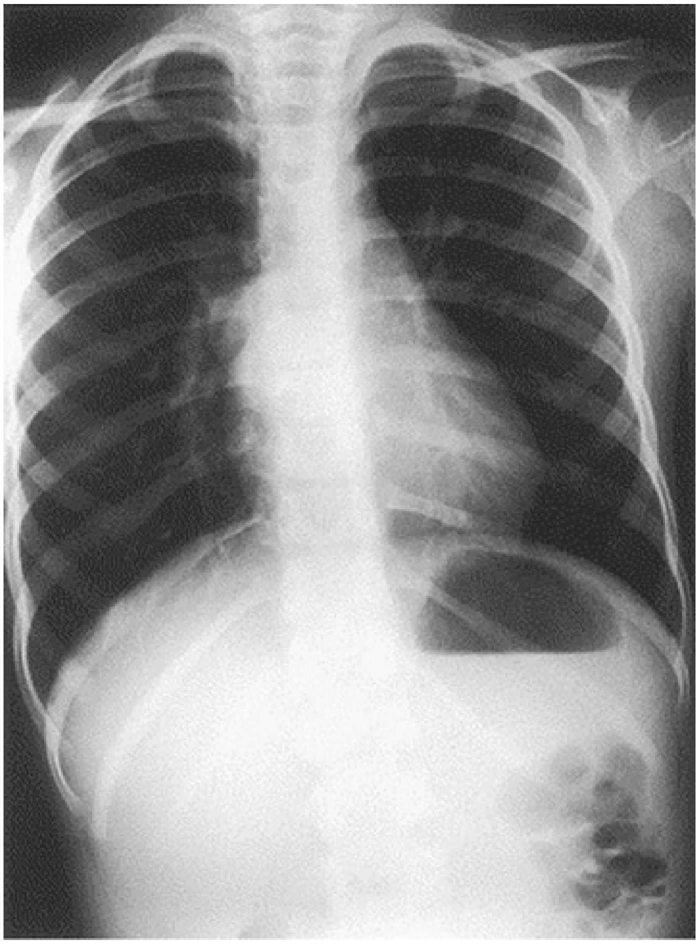

FIG. 423.4 Chest x-ray showing an ovoid, well-defined, soft tissue density causing splaying of the carina due to bronchogenic cyst. (From Williams HJ, Johnson KJ: Imaging of congenital cystic lung lesions, *Paediatr Respir Rev* 3:120–127, 2002.)

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423.6

Congenital Pulmonary Lymphangiectasia

Joshua A. Blatter, Jonathan D. Finder

Etiology and Pathology

Congenital pulmonary lymphangiectasia is characterized by greatly dilated lymphatic ducts throughout the lung. It can occur in three pathologic circumstances: **pulmonary venous obstruction** that produces an elevated transvascular pressure and engorges the pulmonary lymphatics; **generalized lymphangiectasia** , as a generalized disease of several organ systems, including lymphedema, lungs, and the intestines either associated with other syndromes (Noonan, Hennekam, yellow nail, trisomy 21) or nonsyndromic. Gorham-Stout disease (vanishing bone disease) presents with pulmonary and abdominal chylous effusions, destructive bone cysts, and multiple lymphangiomas; and **primary lymphangiectasia** limited to the lung as a manifestation of an abnormality in lymphatic development.

Clinical Manifestations and Treatment

Children with pulmonary venous obstruction or severe pulmonary lymphangiectasia present with dyspnea and cyanosis in the newborn period. Hydrops fetalis may be diagnosed antenatally. Chest radiographs reveal diffuse, dense, reticular densities with prominence of Kerley B lines. Pleural effusions are common; thoracentesis will reveal **chylothorax** in this setting. If the lung is not completely involved, the spared areas appear hyperlucent. Respiration is compromised because of impaired diffusion and decreased pulmonary compliance. The diagnosis can be suggested by CT scan and/or cardiac catheterization; definitive diagnosis requires lymphangiography or lung biopsy (either thoracoscopic or open) (Fig. 423.5).

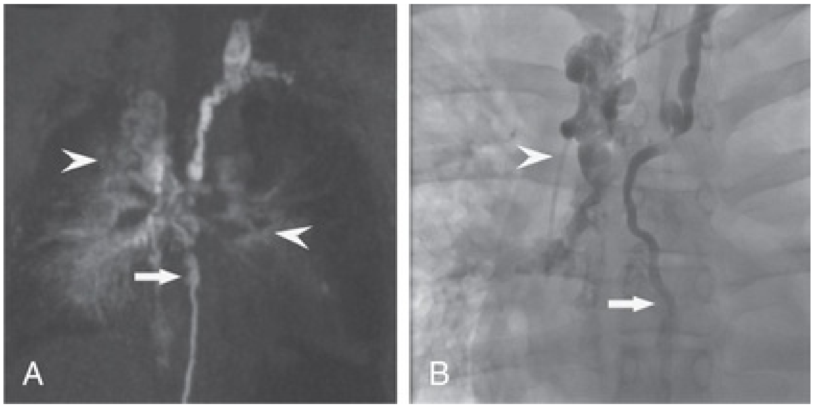

FIG. 423.5 **A,** Dynamic contrast MR lymphangiogram (DCMRL) in a patient with pulmonary lymphangiectasia demonstrating dilated thoracic duct (TD) *(white arrow)* and abnormal pulmonary lymphatic perfusion in the lung hilum *(white arrowheads).* **B,** Corresponding fluoroscopy image of the TD of the same patient, following injection of contrast material through the microcatheter positioned in proximal part of TD, confirms the dilation of the TD *(white arrow)* and retrograde flow of the contrast in the mediastinal lymphatic ducts *(white arrowhead).* (From Itkin M, McCormack FX: Nonmalignant adult thoracic lymphatic disorders, *Clin Chest Med* 37:409–420, 2016. Fig 7.)

Treatment is supportive and includes administration of oxygen, mechanical ventilation, nutritional support (including gastrostomy placement and use of feedings containing medium-chain triglycerides), and careful fluid management with diuretics. Octreotide, the somatostatin analog, can reduce chylous effusion in some patients. Primary pulmonary lymphangiectasia in the neonate can produce severe pulmonary dysfunction that can require long-term mechanical ventilation; long-term survival and resolution of respiratory insufficiency are possible even in severe cases, especially if the chylous effusions can be managed. Occasionally, the pulmonary venous obstruction is secondary to left-sided cardiac lesions; relief of the latter can produce improvement in pulmonary dysfunction. Generalized lymphangiectasia produces milder pulmonary dysfunction, and survival to mid-childhood and beyond is not unusual.

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423.7

Lung Hernia

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Etiology and Pathology

A lung hernia is a protrusion of the lung beyond its normal thoracic boundaries. Approximately 20% are congenital, with the remainder being noted after chest trauma or thoracic surgery or in patients with pulmonary diseases such as cystic fibrosis (see Chapter 432) or asthma (see Chapter 169), which cause frequent cough and generate high intrathoracic pressure. A congenital weakness of the suprapleural membrane (Sibson fascia) or musculature of the neck can play a role in the appearance of a lung hernia. More than half of congenital lung hernias and almost all acquired hernias are cervical. Congenital cervical hernias usually occur anteriorly through a gap between the scalenus anterior and sternocleidomastoid muscles. Cervical herniation is usually prevented by the trapezius muscle (posteriorly, at the thoracic inlet) and by the 3 scalene muscles (laterally).

Clinical Manifestations and Treatment

The presenting sign of a cervical hernia (Sibson hernia) is usually a neck mass noticed while straining or coughing. Some lesions are asymptomatic and detected only when a chest film is taken for another reason. Findings on physical examination are normal except during Valsalva maneuver, when a soft bulge may be noticed in the neck. In most cases, no treatment is necessary, although these hernias can cause problems during attempts to place a central venous catheter through the jugular or subclavian veins. They can resolve spontaneously.

Paravertebral or parasternal hernias are usually associated with rib anomalies. Intercostal hernias usually occur parasternally, where the external intercostal muscle is absent. Posteriorly, despite the seemingly inadequate internal intercostal muscle, the paraspinal muscles usually prevent herniation. Straining, coughing, or playing a musical instrument can have a role in causing intercostal hernias, but in most cases, there is probably a preexisting defect in the thoracic wall.

Surgical treatment for lung hernia is occasionally justified for cosmetic reasons. In patients with severe chronic pulmonary disease and chronic cough and for whom cough suppression is contraindicated, permanent correction might not be achieved.

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423.8

Other Congenital Malformations of the Lung

Joshua A. Blatter, Jonathan D. Finder

Congenital Lobar Emphysema and Pulmonary Cysts

See Chapter 420 .

Pulmonary Arteriovenous Malformation

See Chapters 459 and 471 .

Bronchobiliary Fistula

A bronchobiliary fistula consists of a fistulous connection between the right middle lobe bronchus and the left hepatic ductal system. Although diagnosis can be delayed until adulthood, this rare anomaly typically manifests with life-threatening bronchopulmonary infections in early infancy. Girls are more commonly affected. Definitive diagnosis requires endoscopy or exploratory surgery. Treatment includes surgical excision of the entire intrathoracic portion of the fistula. If the hepatic portion of the fistula does not communicate with the biliary system or duodenum, the involved segment might also have to be resected. Bronchobiliary communications also occur as acquired lesions resulting from hepatic disease complicated by infection.

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CHAPTER 424

Pulmonary Edema

Brandon T. Woods, Robert L. Mazor

Pulmonary edema is an abnormal fluid collection in the interstitium and air spaces of the lung resulting in oxygen desaturation, decreased lung compliance, and respiratory distress. The condition is common in the acutely ill child.

Pathophysiology

Although pulmonary edema is traditionally separated into two categories according to cause (*cardiogenic* and *noncardiogenic*), the end result of both processes is a net fluid accumulation within the interstitial and alveolar spaces. Noncardiogenic pulmonary edema, in its most severe state, is also known as acute respiratory distress syndrome (see Chapters 89 and 400).

The *hydrostatic pressure* and colloid *osmotic (oncotic) pressure* on either side of a pulmonary vascular wall, along with vascular permeability, are the forces and physical factors that determine fluid movement through the vessel wall. Baseline conditions lead to a net filtration of fluid from the intravascular space into the interstitium. This extra interstitial fluid is usually rapidly reabsorbed by pulmonary lymphatics. Conditions that lead to altered vascular permeability, increased pulmonary vascular pressure, and decreased intravascular oncotic pressure increase the net flow of fluid out of the vessel (Table 424.1). Once the capacity of the lymphatics for fluid removal is exceeded, water accumulates in the lung.

Table 424.1

Etiology of Pulmonary Edema

INCREASED PULMONARY CAPILLARY PRESSURE

Cardiogenic, such as left ventricular failure Noncardiogenic, as in pulmonary venoocclusive disease, pulmonary venous fibrosis, mediastinal tumors
INCREASED CAPILLARY PERMEABILITY
Bacterial and viral pneumonia Acute respiratory distress syndrome Inhaled toxic agents Circulating toxins Vasoactive substances such as histamine, leukotrienes, thromboxanes Diffuse capillary leak syndrome, as in sepsis Immunologic reactions, such as transfusion reactions Smoke inhalation Aspiration pneumonia/pneumonitis Drowning and near drowning Radiation pneumonia Uremia
LYMPHATIC INSUFFICIENCY
Congenital and acquired
DECREASED ONCOTIC PRESSURE
Hypoalbuminemia, as in renal and hepatic diseases, protein-losing states, and malnutrition
INCREASED NEGATIVE INTERSTITIAL PRESSURE
Upper airway obstructive lesions, such as croup and epiglottitis Reexpansion pulmonary edema
MIXED OR UNKNOWN CAUSES
Neurogenic pulmonary edema High-altitude pulmonary edema Eclampsia Pancreatitis Pulmonary embolism Heroin (narcotic) pulmonary edema

Modified from Robin E, Carroll C, Zelis R: Pulmonary edema, *N Engl J Med* 288:239, 292, 1973; and Desphande J, Wetzel R, Rogers M: In Rogers M, editor: *Textbook of pediatric intensive care* , ed 3, Baltimore, 1996, Williams & Wilkins, pp. 432–442.

To understand the sequence of lung water accumulation, it is helpful to consider its distribution among four distinct compartments, as follows:

- *Vascular compartment:* This compartment consists of all blood vessels that participate in fluid exchange with the interstitium. The vascular compartment is separated from the interstitium by capillary endothelial cells. Several endogenous inflammatory mediators, as well as exogenous toxins, are implicated in the pathogenesis of pulmonary capillary endothelial damage, leading to the leakiness seen in several systemic processes.

◆ *Interstitial compartment:* The importance of this space lies in its interposition between the alveolar and vascular compartments. As fluid leaves the vascular compartment, it collects in the interstitium before overflowing into the air spaces of the alveolar compartment.

◆ *Alveolar compartment:* This compartment is lined with type 1 and type 2 epithelial cells. These epithelial cells have a role in active fluid transport from the alveolar space, and they act as a barrier to exclude fluid from the alveolar space. The potential fluid volume of the alveolar compartment is many times greater than that of the interstitial space, perhaps providing another reason that alveolar edema clears more slowly than interstitial edema.

◆ *Pulmonary lymphatic compartment:* There is an extensive network of pulmonary lymphatics. Excess fluid present in the alveolar and interstitial compartments is drained via the lymphatic system. When the capacity for drainage of the lymphatics is surpassed, fluid accumulation occurs.

Etiology

The specific clinical findings vary according to the underlying mechanism (see Table 424.1).

Transudation of fluid as a result of increased pulmonary vascular pressure *(capillary hydrostatic pressure)* occurs in several cardiac processes. A significant left-to-right shunting lesion, such as a septal defect, leads to a pressure and volume load on the pulmonary vasculature. The resultant pulmonary edema is one of the hallmarks of congestive heart failure. Left ventricular failure, mitral valve disease, and pulmonary venous obstructive lesions cause increased backpressure in the pulmonary vasculature. This results in an increase in pulmonary capillary pressure.

Increased capillary permeability is usually secondary to endothelial damage. Such damage can occur secondary to direct injury to the alveolar epithelium or indirectly through systemic processes that deliver circulating inflammatory mediators or toxins to the lung. Inflammatory mediators (tumor necrosis factor, leukotrienes, thromboxanes) and vasoactive agents (nitric oxide, histamine) formed during pulmonary and systemic processes potentiate the altered capillary permeability that occurs in many disease processes, with sepsis being a common cause.

Fluid homeostasis in the lung largely depends on drainage via the lymphatics. Experimentally, pulmonary edema occurs with obstruction of the lymphatic system. Increased lymph flow and dilation of lymphatic vessels occur in chronic edematous states.

A decrease in intravascular oncotic pressure leads to pulmonary edema by altering the forces promoting fluid reentry into the vascular space. This occurs in dilutional disorders, such as fluid overload with hypotonic solutions, and in protein-losing states, such as nephrotic syndrome and malnutrition.

The **excessive negative interstitial pressure** seen in upper airway diseases, such as croup and laryngospasm, may promote pulmonary edema. Aside from the physical forces present in these diseases, other mechanisms may also be involved. Theories implicate an increase in CO_2 tension, decreased O_2 tension, and extreme increases in cardiac afterload, leading to transient cardiac insufficiency.

The mechanism causing **neurogenic pulmonary edema** is not clear. A massive sympathetic discharge secondary to a cerebral injury may produce increased pulmonary and systemic vasoconstriction, resulting in a shift of blood to the pulmonary vasculature, an increase in capillary pressure, and edema formation. Inflammatory mechanisms may also play a role by increasing capillary permeability.

The mechanism responsible for **high-altitude pulmonary edema** is unclear, but it may also be related to sympathetic outflow, increased pulmonary vascular pressures, and hypoxia-induced increases in capillary permeability (see Chapter 90).

Active ion transport followed by passive, osmotic water movement is important in clearing the alveolar space of fluid. There are some experimental data that β-agonists and growth factors increase alveolar fluid removal. Interindividual genetic differences in the rates of these transport processes may be important in determining which individuals are susceptible to altitude-related pulmonary edema. Although the existence of these mechanisms suggests that therapeutic interventions may be developed to promote resolution of pulmonary edema, no such therapies currently exist.

Clinical Manifestations

The clinical features depend on the mechanism of edema formation. In general, interstitial edema and alveolar edema prevent the inflation of alveoli, leading to atelectasis and decreased surfactant production. This results in diminished pulmonary compliance and tidal volume. The patient must increase respiratory effort and/or the respiratory rate so as to maintain minute ventilation. The earliest clinical signs of pulmonary edema include increased work of breathing, tachypnea, and dyspnea. As fluid accumulates in the alveolar space, auscultation reveals fine crackles and wheezing, especially in dependent lung fields. In cardiogenic pulmonary edema, a gallop may be present, as well as peripheral edema and jugular venous distention.

Chest radiographs can provide useful ancillary data, although findings of initial radiographs may be normal. Early radiographic signs that represent accumulation of interstitial edema include peribronchial and perivascular cuffing. Diffuse streakiness reflects interlobular edema and distended pulmonary lymphatics. Diffuse, patchy densities, the so-called butterfly pattern, represent bilateral interstitial or alveolar infiltrates and are a late sign. Cardiomegaly is often seen with cardiogenic causes of pulmonary edema. Heart size is usually normal in noncardiogenic pulmonary edema (Table 424.2). Chest tomography demonstrates edema accumulation in the dependent areas of the lung. As a result, changing the patient's position can alter regional differences in lung compliance, functional residual capacity, and alveolar ventilation.

Table 424.2

Radiographic Features That May Help Differentiate Cardiogenic From Noncardiogenic Pulmonary Edema

RADIOGRAPHIC FEATURE	CARDIOGENIC EDEMA	NONCARDIOGENIC EDEMA
Heart size	Normal or greater than normal	Usually normal
Width of the vascular pedicle*	Normal or greater than normal	Usually normal or less than normal
Vascular distribution	Balanced or inverted	Normal or balanced
Distribution of edema	Even or central	Patchy or peripheral
Pleural effusions	Present	Not usually present
Peribronchial cuffing	Present	Not usually present
Septal lines	Present	Not usually present
Air bronchograms	Not usually present	Usually present

* The width of the vascular pedicle in adults is determined by dropping a perpendicular line from the point at which the left subclavian artery exits the aortic arch and measuring across to the point at which the superior vena cava crosses the right mainstem bronchus. A vascular pedicle width >70 mm on a portable digital anteroposterior radiograph of the chest obtained when the patient is supine is optimal for differentiating high from normal-to-low intravascular volume.

From Ware LB, Matthay MA: Acute pulmonary edema, *N Engl J Med* 353:2788–2796, 2005.

Measurement of brain natriuretic peptide, often elevated in heart disease, can help to differentiate cardiac from pulmonary causes of pulmonary edema. A brain natriuretic peptide level >500 pg/mL suggests heart disease; a level <100 pg/mL suggests lung disease.

Treatment

The treatment of a patient with noncardiogenic pulmonary edema is largely supportive, with the primary goal to ensure adequate ventilation and oxygenation. Additional therapy is directed toward the underlying cause. Patients should receive supplemental oxygen to increase alveolar oxygen tension and pulmonary vasodilation. Patients with pulmonary edema of cardiogenic causes should be managed with diuretics, inotropic agents, and systemic vasodilators to reduce left ventricular afterload (see Chapter 442). Diuretics are also valuable in the treatment of pulmonary edema associated with total body fluid overload (sepsis, renal insufficiency). Morphine is often helpful as a vasodilator and a mild sedative.

Positive airway pressure improves gas exchange in patients with pulmonary edema. In tracheally intubated patients, positive end-expiratory pressure can be used to optimize pulmonary mechanics. Noninvasive forms of ventilation, such as mask or nasal prong continuous positive airway pressure, are also effective. The mechanism by which positive airway pressure improves pulmonary edema is not entirely clear but is not associated with decreasing lung water. Rather, continuous positive airway pressure prevents complete closure of alveoli at the low lung volumes present at the end of expiration. It may also recruit already collapsed alveolar units. This leads to increased functional residual capacity and improved pulmonary compliance, improved surfactant function, and decreased pulmonary vascular resistance. The net effect is to decrease the work of breathing, improve oxygenation, and decrease cardiac afterload.

When mechanical ventilation becomes necessary, especially in noncardiogenic pulmonary edema, care must be taken to minimize the risk of development of complications from volutrauma or barotrauma, including pneumothorax, pneumomediastinum, and primary alveolar damage (see Chapter 89.1). Lung protective strategies include setting low tidal volumes, relatively high positive end-expiratory pressure, and allowing for permissive hypercapnia.

High-altitude pulmonary edema should be managed with altitude descent and supplemental oxygen. Portable continuous positive airway pressure or a portable hyperbaric chamber is also helpful. Nifedipine (10 mg initially, and then 20-30 mg by slow release every 12-24 hr) in adults is also helpful. If there is a history of high-altitude pulmonary edema, nifedipine and β-adrenergic agonists (inhaled) may prevent recurrence (see Chapter 90).

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CHAPTER 425

Aspiration Syndromes

John L. Colombo

Aspiration Syndromes

Aspiration of material that is foreign to the lower airway produces a varied clinical spectrum ranging from an asymptomatic condition to acute life-threatening events, such as occur with massive aspiration of gastric contents or hydrocarbon products. Other chapters discuss mechanical obstruction of large- or intermediate-size airways as occurs with foreign bodies (see Chapter 414) and infectious complications of aspiration and recurrent microaspiration (see Chapter 426), such as may occur with gastroesophageal reflux (see Chapter 349.1) or dysphagia (see Chapter 332). Occult aspiration of nasopharyngeal secretions into the lower respiratory tract is a normal event in healthy people, usually without apparent clinical significance.

Gastric Contents

Aspiration of substantial amounts of gastric contents typically occurs in the context of vomiting. It is an infrequent complication of general anesthesia, gastroenteritis, or altered level of consciousness. Among 63,180 pediatric patients undergoing general anesthesia, 24 cases of aspiration occurred, but symptoms developed in only 9. Pathophysiologic consequences can vary, depending primarily on the pH and volume of the aspirate and the amount of particulate material. Increased clinical severity is noted with volumes greater than approximately 0.8 mL/kg and/or $pH < 2.5$. Hypoxemia, hemorrhagic pneumonitis, atelectasis, intravascular fluid shifts, and pulmonary edema all occur rapidly after massive aspiration. These occur earlier, become more severe, and last longer with acid aspiration. Most clinical changes are present within minutes to 1-2 hr after the aspiration event. In the next 24-48 hr, there is a marked increase in lung parenchymal neutrophil infiltrations, mucosal sloughing, and alveolar consolidation that often correlates with increasing infiltrates on chest radiographs. These changes tend to occur significantly later and are more prolonged after aspiration of particulate material. Although infection usually does not have a role in initial lung injury after aspiration of gastric contents, aspiration may impair pulmonary defenses, predisposing the patient to secondary bacterial pneumonia. In the patient who has shown clinical improvement but then demonstrates clinical worsening, especially with fever and leukocytosis, secondary bacterial pneumonia should be suspected.

Treatment

If large-volume or highly toxic substance aspiration occurs in a patient who already has an artificial airway in place, it is important to perform immediate suctioning of the airway. If immediate suctioning cannot be performed, later suctioning or bronchoscopy is usually of limited therapeutic value except when there is suspicion of significant particulate aspiration. Attempts at acid neutralization are not warranted because acid is rapidly neutralized by the respiratory epithelium. Patients in whom large-volume or toxic aspiration is suspected should be observed, should undergo oxygenation measurement by oximetry or blood gas analysis, and should undergo a chest radiograph, even if they are asymptomatic. If the chest radiograph findings and oxygen saturation are normal, and the patient remains asymptomatic, home observation, after a period of observation in the hospital or office, is adequate. No treatment is indicated at that time, but the caregivers should be instructed to bring the child back in for medical attention should respiratory symptoms or fever develop. For patients who present with abnormal findings or in whom such findings develop during observation, oxygen therapy is given to correct hypoxemia. Endotracheal intubation and mechanical ventilation are often necessary for more severe cases. Bronchodilators may be tried, although they are usually of limited benefit. Animal studies indicate that treatment with corticosteroids does not provide benefit, unless given nearly simultaneously with the aspiration event; use of these agents may increase the risk of secondary infection. Prophylactic antibiotics are not indicated, although in the patient with limited reserve, early antibiotic coverage may be appropriate. If used, antibiotics that cover for anaerobic microbes should be considered. If the aspiration event occurs in a hospitalized or chronically ill patient, coverage of *Pseudomonas* , *Staphylococcus aureus,* and enteric Gram-negative organisms should also be considered. Various antibiotic choices have included clindamycin plus ampicillin-sulbactam or a carbapenem or a respiratory fluoroquinolone. If empiric antibiotics are given, they should be discontinued when cultures and course warrant. A mortality rate of ≤ 5% is seen if 3 or fewer lobes are involved. Unless complications develop, such as infection or barotrauma, most patients recover in 2-3 wk. Prolonged lung damage may persist, including scarring, bronchiolitis obliterans, and bronchiectasis.

Prevention

Prevention of aspiration should always be the goal when airway manipulation is necessary for intubation or other invasive procedures. Feeding with enteral tubes passed beyond the pylorus, elevating the head of the bed 30-45 degrees in mechanically ventilated patients, and oral decontamination reduce the incidence of aspiration complications in the intensive care unit. Minimizing use of sedation, monitoring for gastric residuals, and gastric acid suppression may all help prevent aspiration. However, the latter is not without some controversy. Any patient with altered consciousness, especially one who is receiving tube feedings, should be considered at high risk for aspiration. Preoperative restriction of oral fluids to otherwise normal children for 6 hr does not appear to provide benefit compared to restriction for only 2 hr in terms of risk for aspiration.

Hydrocarbon Aspiration

Aspiration and resulting pneumonitis are typically the most dangerous consequences of acute hydrocarbon ingestion (see Chapter 77). Although significant pneumonitis occurs in <2% of all hydrocarbon ingestions, an estimated 20 deaths occur annually from hydrocarbon aspiration in both children and adults. Some of these deaths represent suicides. Hydrocarbons with lower surface tensions (gasoline, turpentine, naphthalene) have more potential for aspiration toxicity than heavier mineral or fuel oils. Ingestion of >30 mL (approximate volume of an adult swallow) of hydrocarbon is associated with an increased risk of severe pneumonitis. Clinical findings including chest retractions, grunting, cough, and fever may occur as soon as 30 min after aspiration or may be delayed for several hours. Lung radiographic changes usually occur within 2-8 hr, peaking in 48-72 hr (Fig. 425.1). Pneumatoceles and pleural effusions may occur. Patients initially presenting with cough, shortness of breath, or hypoxemia are at high risk for pneumonitis. Persistent pulmonary function abnormalities can be present many years after hydrocarbon aspiration. Other organ systems, especially the liver, central nervous system, and heart, may suffer serious injury. Cardiac dysrhythmias may occur and may be exacerbated by hypoxia and acid–base or electrolyte disturbances.

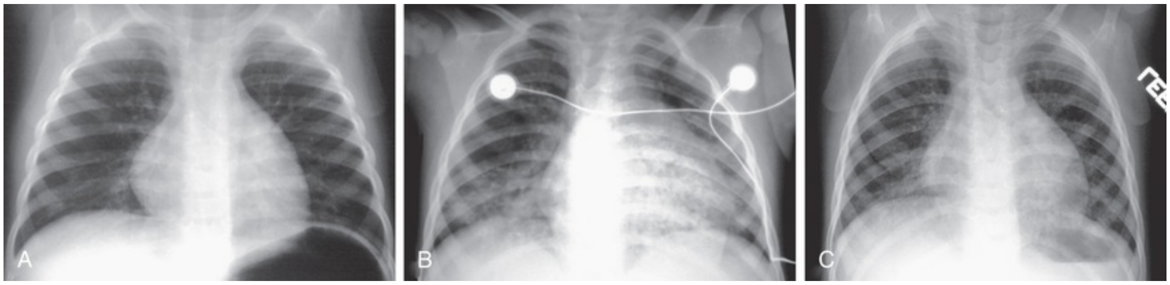

FIG. 425.1 **Chest radiographs of a 17 mo old who ingested furniture polish. A, Three hours after ingestion, the lungs are clear. B, At 24 hr, there are bibasilar coalescing nodular opacities. C, Three days later there is much clearing. (From Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, p. 1287.)**

Treatment

Gastric emptying is contraindicated in nearly all situations because the risk of aspiration is greater than any systemic toxicity. Treatment is generally supportive, consisting of oxygen, fluids, and ventilatory support, and rarely extracorporeal membrane oxygenation, as necessary. Exogenous surfactant administration has been described as helpful in case reports. The child who has no symptoms and normal chest radiograph findings should be observed for 6-8 hr to ensure safe discharge.

Certain hydrocarbons have more inherent systemic toxicity . The mnemonic **CHAMP** refers collectively to the following hydrocarbons: ***c*** amphor, ***h*** alogenated carbons, ***a*** romatic hydrocarbons, and those associated with ***m*** etals and ***p*** esticides. Patients who ingest these compounds in volumes > 30 mL, such as might occur with intentional overdose, *may* benefit from gastric emptying. This is still a high-risk procedure that can result in further aspiration. If a cuffed endotracheal tube can be placed without inducing vomiting, this procedure should be considered, especially in the presence of altered mental status. Treatment of each case should be considered individually, with guidance from a poison control center.

Other substances that are particularly toxic and cause significant lung injury when aspirated or inhaled include baby powder, chlorine, shellac, beryllium, and mercury vapors. Repeated exposure to low concentrations of these agents can lead to chronic lung disease, such as interstitial pneumonitis and granuloma formation. Corticosteroids may help reduce fibrosis development and improve pulmonary function, although the evidence for this benefit is limited.

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CHAPTER 426

Chronic Recurrent Aspiration

John L. Colombo

Etiology

Repeated aspiration of even small quantities of gastric, nasal, or oral contents can lead to recurrent bronchitis or bronchiolitis, recurrent pneumonia, atelectasis, wheezing, cough, apnea, and/or laryngospasm. Pathologic outcomes include granulomatous inflammation, interstitial inflammation, fibrosis, lipoid pneumonia, and bronchiolitis obliterans. Most cases clinically manifest as airway inflammation and are rarely associated with significant morbidity. Table 426.1 lists underlying disorders that are frequently associated with recurrent aspiration. Oropharyngeal incoordination is reportedly the most common underlying problem associated with recurrent pneumonias in hospitalized children. In 2 reports, between 26% and 48% of such children were found to have dysphagia with aspiration as the underlying problem. Lipoid pneumonia may occur after the use of home/folk remedies involving oral or nasal administration of animal or vegetable oils to treat various childhood illnesses. Lipoid pneumonia has been reported as a complication of these practices in the Middle East, Asia, India, Brazil, and Mexico. The initial underlying disease, language barriers, and a belief that these are not medications may delay the diagnosis (see Chapter 11).

Table 426.1

Conditions Predisposing to Aspiration Lung Injury in Children

Anatomical and Mechanical
Tracheoesophageal fistula

Laryngeal cleft Vascular ring Cleft palate Micrognathia Macroglossia Cysts, tumors Achalasia Esophageal foreign body Tracheostomy Endotracheal tube Nasal or oral feeding tube Collagen vascular disease (scleroderma, dermatomyositis) Gastroesophageal reflux disease Obesity
Neuromuscular
Altered consciousness Immaturity of swallowing/Prematurity Dysautonomia Increased intracranial pressure Hydrocephalus Vocal cord paralysis Cerebral palsy Muscular dystrophy Hypotonia Myasthenia gravis Guillain-Barré syndrome Spinal muscular atrophy Ataxia-telangiectasia Cerebral vascular accident
Miscellaneous
Poor oral hygiene Gingivitis Prolonged hospitalization Gastric outlet or intestinal obstruction Poor feeding techniques (bottle propping, overfeeding, inappropriate foods for toddlers) Bronchopulmonary dysplasia Viral infection/bronchiolitis

Gastroesophageal reflux disease (**GERD** ; see Chapter 349) is also a common underlying finding that may predispose to recurrent respiratory disease, but it is less frequently associated with recurrent pneumonia than is dysphagia (see Chapter 349). GERD is associated with microaspiration and bronchiolitis obliterans in lung transplant recipients. Aspiration has also been observed in infants with respiratory symptoms but no other apparent abnormalities. Recurrent microaspiration has been reported in otherwise apparently normal newborns, especially premature infants. Aspiration is also a risk in patients suffering from acute respiratory illness from other causes, such as respiratory syncytial virus infection (see Chapter 287). Modified barium swallow and videofluoroscopy may reveal silent aspiration in these patients. This finding emphasizes the need for a high degree of clinical suspicion for ongoing aspiration in a child with an acute respiratory illness, being fed enterally, who deteriorates unexpectedly.

Diagnosis

Some underlying predisposing factors (see Table 426.1) are frequently clinically apparent but may require specific further evaluation. Initial assessment begins with a detailed history and physical examination. The caregiver should be asked about spitting, vomiting, arching, or epigastric discomfort in an older child; the timing of symptoms in relation to feedings; positional changes; and nocturnal symptoms, such as coughing and wheezing. It is important to remember that coughing or gagging may be minimal or absent in a child with a depressed cough or gag reflex. Observation of a feeding is an essential part of the exam when a diagnosis of recurrent aspiration is being considered. Particular attention should be given to nasopharyngeal reflux, difficulty with sucking or swallowing, and associated coughing and choking. Voice changes (wet voice) and noisy (wet) breathing should be noted. The oral cavity should be inspected for gross abnormalities and stimulated to assess the gag reflex. Drooling or excessive accumulation of secretions in the mouth suggests dysphagia. Lung auscultation may reveal transient crackles or wheezes after feeding, particularly in the dependent lung segments.

The diagnosis of recurrent microaspiration is challenging because of the lack of highly specific and sensitive tests (Table 426.2). A plain chest radiograph is the usual initial study for a child in whom recurrent aspiration is suspected. The classic findings of segmental or lobar infiltrates localized to dependent areas may be found (Fig. 426.1*A*), but there are a wide variety of radiographic findings. These findings include diffuse infiltrates, lobar infiltrates, bronchial wall thickening, hyperinflation, and even no detectable abnormalities. CT scans, though generally not indicated to establish a diagnosis of aspiration, may show infiltrates with decreased attenuation suggestive of lipoid pneumonia (see Fig. 426.1*B*). A carefully performed barium esophagram is useful in looking for anatomic abnormalities such as vascular ring, stricture, hiatal hernia, and tracheoesophageal fistula. It also yields qualitative information about esophageal motility and, when extended, of gastric emptying. However, primarily because of the very short viewing time, the esophagram is quite insensitive and nonspecific for aspiration or GERD. A modified barium swallow study with videofluoroscopy (videofluoroscopic swallowing study) is generally considered the gold standard for evaluating the swallowing mechanism. This study is preferably done with the assistance of a pediatric feeding specialist and a caregiver in the attempt to simulate the usual feeding technique of the child. The child is seated in normal eating position, and various consistencies of barium or barium-impregnated foods are offered. This study is more sensitive for demonstrating aspiration than bedside assessment or a traditional barium swallow study. The sensitivity of the modified barium swallow study is such that it occasionally detects aspiration in patients without apparent respiratory abnormalities.

Table 426.2

Summary of Diagnostic Tests of Aspiration

EVALUATION	BENEFITS	LIMITATIONS
Chest radiograph	Inexpensive and widely available Assesses accumulation of injury over time	Insensitive to early subtle changes of lung injury
High-resolution CT	Sensitive in detecting lung injury, such as bronchiectasis, tree-in-bud opacities, and bronchial thickening Less radiation than conventional CT Assesses accumulation of injury over time	More radiation exposure than plain radiograph Expensive
Video swallow study	Evaluates all phases of swallowing Evaluates multiple consistencies Feeding recommendations made at time of study	Information limited if child consumes only small quantities Difficult to perform in child who has not been feeding by mouth Radiation exposure proportional to study duration Cannot be performed at bedside Limited evaluation of anatomy Evaluates 1 moment in time Expensive
FEES/with sensory testing	Ability to thoroughly evaluate functional anatomy Evaluates multiple consistencies Can assess risk of aspiration in non-orally feeding child; airway protective reflexes can be assessed Feeding recommendations made at time of study Visual feedback for caregivers Can be performed at bedside No radiation exposure	Blind to esophageal phase and actual swallow Invasive and may not represent physiological swallowing conditions Evaluates 1 moment in time Not widely available Expensive
BAL	Evaluates anatomy of entire upper and lower airways Samples the end-organ of damage Sample available for multiple cytological and microbiologic tests Widely available	Uncertainty regarding interpretation of lipid-laden macrophage index Index cumbersome to calculate Requires sedation or anesthesia Invasive Expensive

Esophageal pH monitoring	Current gold standard for diagnosis of acid gastroesophageal reflux Established normative data in children	Blind to majority of reflux (nonacid) events Difficult to establish causal relationship between gastroesophageal reflux and aspiration Somewhat invasive Evaluates short time interval
Esophageal impedance monitoring	Likely gold standard for diagnosis of GERD with supraesophageal manifestations Able to detect acid and nonacid reflux events Detects proximal reflux events Able to evaluate for GERD without stopping medications	Lack of normative data for children Somewhat invasive Expensive and cumbersome to interpret Not widely available Evaluates short time interval
Gastroesophageal scintigraphy	Performed under physiologic conditions Low radiation exposure	Poor sensitivity May not differentiate between aspiration from dysphagia or GERD
Radionuclide salivagram	Child does not have to be challenged with food bolus Low radiation exposure	Unknown sensitivity Unknown relationship to disease outcomes Evaluates 1 moment in time
Dye studies	Can be constructed as screening test or confirmatory test Can evaluate aspiration of secretions or feeds Repeating over time allows for broader evaluation	Uncertainty in interpretation owing to variability of technique Can only be performed in children with tracheostomies
Other biomarkers (pepsin, bile acids) milk protein	Theoretical high specificity and sensitivity	Limited availability and standardization Variable results to date

BAL, bronchoalveolar lavage; FEES, fiberoptic-endoscopic evaluation of swallowing; GERD, gastroesophageal reflux disease.

Modified from Boesch RP, Daines C, Willging JP, et al: Advances in the diagnosis and management of chronic pulmonary aspiration in children, *Eur Respir J* 28:847–861, 2006; and Tutor JD, Gosa MM: Dysphagia and aspiration in children, *Pediatr Pulmonol* 47(4):321–337, 2012.

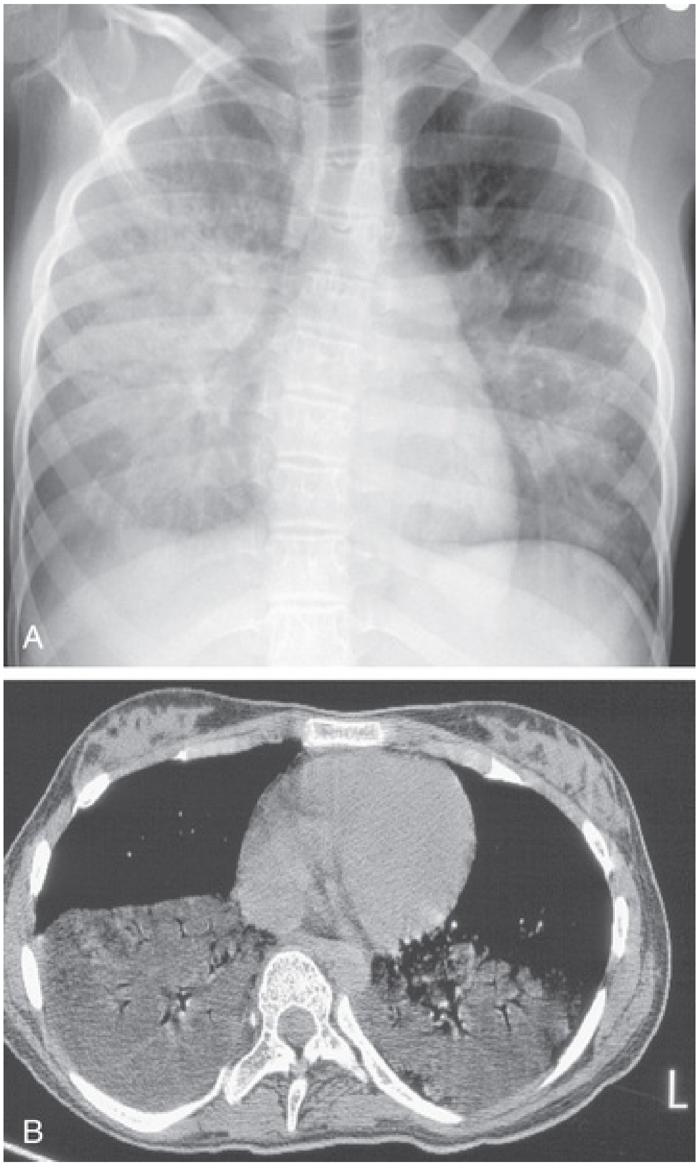

FIG. 426.1 **A,** Chest radiograph of a developmentally delayed 15 yr old with chronic aspiration of oral formula. Note posterior (dependent areas) distribution with sparing of heart borders. **B,** Chest CT scan of same patient. Note lung consolidation in dependent regions is of similar density to subcutaneous fat.

A gastroesophageal milk scintiscan offers theoretical advantages over a barium swallow in being more physiologic and giving a longer window of viewing than the barium esophagram for detecting aspiration and GERD. However, this study has been found to have a low sensitivity and provides relatively little anatomic detail. Another radionuclide scan termed the salivagram may also be useful to assess aspiration of esophageal contents. When this scan is performed by experienced personnel, its sensitivity appears to be comparable to that of the modified barium swallow study. The use of fiberoptic endoscopic evaluation of swallowing has been found useful in adult and some pediatric patients, to observe swallowing directly without radiation exposure. The child's reaction to placement of the endoscope may alter the assessment of function, depending on level of comfort and cooperation.

Tracheobronchial aspirates can be examined for numerous entities to evaluate for aspiration. For patients with artificial airways, the use of an oral dye and visual examination of tracheal secretions is useful. This test should not be done on a chronic basis, such as in tube feedings, because of possible dye toxicity. In using this test acutely, the best method is to place a few drops of dye on the patient's tongue and perform subsequent suctioning of the airway over the next several minutes. Quantitation of lipid-laden alveolar macrophages from bronchial aspirates has been shown to be a sensitive test for aspiration in children, but false-positive tests occur, especially with endobronchial obstruction, use of intravenous lipids, sepsis, and pulmonary bleeding. Bronchial washings may also be examined for various food substances, including lactose, glucose, food fibers, and milk antigens, as well as pepsin. Specificity and sensitivity of these tests have not been well studied.

Treatment

If chronic aspiration is associated with another underlying medical condition, treatment should be directed toward that problem. The level of morbidity from respiratory problems should determine the level of intervention. Often milder dysphagia can be treated with alteration of feeding position, limiting texture of foods to those best tolerated on modified barium esophagram (usually thicker foods), or limiting quantity per feeding. Currently evidence is lacking regarding the advisability of restricting oral intake of water by children whose aspiration is largely of thin fluids. Nasogastric tube feedings can be utilized temporarily during periods of transient vocal cord dysfunction or other dysphagia. Postpyloric feedings may also be helpful, especially if gastroesophageal reflux is present, although this does not eliminate reflux. There are several surgical procedures that may be considered. Tracheostomy, although sometimes predisposing to aspiration, may provide overall benefit from improved bronchial hygiene and the ability to suction aspirated material. Use of a one-way (Passy-Muir) valve on a tracheostomy tube has been shown to improve swallowing. Fundoplication with gastrostomy or jejunostomy feeding tube will reduce the probability of gastroesophageal reflux-induced aspiration, but recurrent pneumonias often persist because of dysphagia and presumed aspiration of upper airway secretions. Medical treatment with anticholinergics, such as glycopyrrolate or scopolamine, may significantly reduce morbidity from salivary aspiration but often has side effects. Aggressive surgical intervention with salivary gland excision, ductal ligation, laryngotracheal separation, or esophagogastric disconnection can be considered in severe, unresponsive cases. Although usually reserved for the most severe cases, surgical therapy may significantly improve quality of life and ease of care for some patients.

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CHAPTER 427

Immune and Inflammatory Lung Disease

427.1

Hypersensitivity Pneumonia

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Keywords

hypersensitivity pneumonia (HP)
extrinsic allergic alveolitis
acute HP
recurrent subacute HP
chronic progressive HP
pet birds
thermophilic organisms

Hypersensitivity pneumonia (HP), aptly called *extrinsic allergic alveolitis* because the inciting agent is almost uniformly inhaled from the environment, is a complex immunologic-mediated syndrome of the pulmonary alveoli and interstitium. There are numerous specific disease names based on the origin of the inhaled offending antigen to describe HP. Prompt recognition of the signs and symptoms allows for complete reversal of the disease without long-term adverse consequences if the source of the exposure is recognized and abated.

Failure to recognize the disease early may lead to chronic irreversible lung changes with persistent symptoms in the patient.

Etiology

The most common sources of offending agents that cause HP include agricultural aerosols, inhaled protein antigens from animals, antigens from microorganisms of bacteria, fungi, or protozoan origin, as well as chemicals of low and high molecular weight (Table 427.1). Many inciting agents are associated with *occupational diseases* in which children do not regularly work. However, the same diseases can occur in children due to exposures to similar antigen sources in nonoccupational environments, or in occupational environments with teenage workers. In addition to HP, the same antigens may lead to allergic asthma or chronic bronchitis as seen with animal proteins, contaminated metal working fluids, and other inhaled antigens.

Table 427.1

Antigen Sources Associated with Specific Causes of Hypersensitivity Pneumonitis

HYPERSENSITIVITY PNEUMONITIS	ANTIGEN SOURCE
Bagassosis (mold on pressed sugar cane)	*Thermoactinomyces sacchari*
	Thermoactinomyces vulgaris
Bat lung (bat droppings)	Bat serum protein
Bible printer's lung	Moldy typesetting water
Bird fancier's lung (parakeets, budgerigars, pigeons)	Droppings, feathers, serum proteins
Byssinosis (“brown lung”) (unclear if a true cause of hypersensitivity pneumonitis; asthma is common)	Cotton mill dust (carding and spinning areas of cotton, flax, and soft-hemp)
Canary fancier's lung	Serum proteins
Cheese washer's lung (moldy cheese)	*Penicillium casei*
	Aspergillus clavatus
Chemical hypersensitivity pneumonitis	Diphenylmethane diisocyanate (MDI)
	Toluene diisocyanate (TDI)
Coffee worker's lung	Coffee-bean dust
Composter's lung	*T. vulgaris*
	Aspergillus species
Contaminated basement (sewage) pneumonitis	*Cephalosporium*
Coptic lung (mummy handler's lung)	Cloth wrappings of mummies
Detergent worker's lung (washing powder lung)	*Bacillus subtilis* enzymes
Dry rot lung	*Merulius lacrymans*
Duck fever	Feathers, serum proteins
Epoxy resin lung	Phthalic anhydride (heated epoxy resin)
Esparto dust (mold in plaster dust)	*Aspergillus fumigatus*

	Thermophilic actinomycetes
Farm worker lung	Thermophilic actinomycetes plus others
Feather duvet (pillow) lung	Goose or duck feathers
Fish meal worker's lung	Fish meal
Furrier's lung (sewing furs; animal fur dust)	Animal pelts
Grain measurer's lung	Cereal grain (*Sporobolomyces*)
	Grain dust (mixture of dust, silica, fungi, insects, and mites)
Hot-tub lung (mists; mold on ceiling and around tub)	*Cladosporium* spp.
	Mycobacterium avium complex
Humidifier fever	*Thermoactinomyces (T. vulgaris, T. sacchari, T. candidus)*
	Klebsiella oxytoca
	Naegleria gruberi
	Acanthamoeba polyphaga
	Acanthamoeba castellani
Laboratory worker's lung (rats, gerbils)	Urine, serum, pelts, proteins
Lifeguard lung	Aerosolized endotoxin from pool-water sprays and fountains
Lycoperdonosis (*Lycoperdon* puffballs)	Puffball spores
Machine operator's lung	*Pseudomonas fluorescens*
	Aerosolized metal working fluid
Malt worker's disease (moldy barley)	*Aspergillus fumigatus, Aspergillus clavatus*
Maple bark disease (moldy maple bark)	*Cryptostroma corticale*
Miller's lung (dust-contaminated grain)	*Sitophilus granarius* (i.e., wheat weevil)
Moldy hay, grain, silage (farmer's lung)	Thermophilic actinomycetes
	Fungi (e.g., *Aspergillus umbrosus*)
Mollusk shell hypersensitivity pneumonitis	Sea-snail shell
Mushroom worker's lung	Mushroom spores
	Thermophilic actinomycetes
Paprika slicer's lung (moldy paprika pods)	*Mucor stolonifer*
Pauli's reagent alveolitis	Sodium diazobenzene sulfate
Pearl oyster shell pneumonitis	Oyster shells
Pituitary snuff taker's disease	Dried, powdered cattle or pig pituitary proteins
Potato riddler's lung (moldy hay around potatoes)	Thermophilic actinomycetes
	T. vulgaris
	Faenia rectivirgula
	Aspergillus spp.
Poultry worker's lung (feather plucker's disease)	Serum proteins (chicken products)
Pyrethrum (pesticide)	Pyrethrum
Sauna taker's lung	*Aureobasidium* spp., other sources
Sequoiosis (moldy wood dust)	*Graphium*
	Pullularia
	Trichoderma spp.
	Aureobasidium pullulans
Suberosis (moldy cork dust)	*Thermoactinomyces viridis*
	Penicillium glabrum
	Aspergillus conidia
Summer-type pneumonitis	*Trichosporon cutaneum*
Tea grower's lung	Tea plants
Thatched-roof lung (huts in New Guinea)	*Saccharomonospora viridis* (dead grasses and leaves)
Tobacco grower's lung	*Aspergillus* spp.

	Scopulariopsis brevicaulis
Turkey handling disease	Serum proteins (turkey products)
Unventilated shower	*Epicoccum nigrum*
Upholstery fabric (nylon filament, cotton/polyester, and latex adhesive)	Aflatoxin-producing fungus, *Fusarium* spp.
Velvet worker's lung	Unknown (? nylon velvet fiber, tannic acid, potato starch)
Vineyard sprayer's lung	Copper sulfate (bordeaux mixture)
Wind instrument lung	Bacteria or mold contamination of instrument
Wine maker's lung (mold on grapes)	*Botrytis cinerea*
Wood dust pneumonitis (oak, cedar, and mahogany dust, pine and spruce pulp)	*Alternaria* spp.
	Bacillus subtilis
Wood pulp worker's disease (oak and maple trees)	*Penicillium* spp.
Wood trimmer's disease (contaminated wood trimmings)	*Rhizopus* spp., *Mucor* spp.

More than 300 antigens have been associated with HP. In children, primary sources of HP have been the result of exposure to pet birds (or feathers in bedding and pillows) such as parakeets, canaries, cockatiels, or cockatoos. Aerosol spread of bird droppings can also occur by clothes dryer vents or by heating vents from a garage where the pet birds were housed. Humidifiers and hot tubs are notorious for contamination with thermophilic organisms (bacteria and mold) as well as *Mycobacterium avium* complex. Buildings with inadequate ventilation and insufficient air turnover present an increased risk of mold exposure from prior flooding or damp condensation. Despite exposures to the same antigen sources, members of the same family may exhibit different presentations of allergic disease. Some family members may have symptoms of asthma or rhinitis, while another may have HP.

Pathogenesis

HP has been traditionally classified as acute, subacute, or chronic. During the acute phase, the offending antigen triggers an inflammatory response promoting the development of immune complexes. These immune complexes activate the complement pathway, ultimately resulting in the accumulation of neutrophils in the airway that release enzymes such as neutrophil elastase, that damage surrounding lung tissue. Activated macrophages in the lung promote recruitment of lymphocytes into the tissues. Pathology shows alveolitis with a mixed cellular infiltration comprised of lymphocytes, macrophage, plasma cells, and neutrophils. Continued exposure to the offending antigen will lead to subacute or chronic HP. This chronic exposure results in the formation of loose, noncaseating granulomas located near the respiratory or terminal bronchioles. It is critical when a biopsy is being performed (transbronchial or surgical) that the pathologist knows that HP is being considered as there are other interstitial lung diseases (ILDs) that produce similar granulomas with subtle location differences depending on their origin.

Clinical Manifestations and Classification

Acute HP is typically caused by heavy exposure to an offending antigen. This is the most common form of exposure but is frequently not recognized. Symptoms are confused with bacterial or viral disease leading to treatment with antibiotics. Four to 8 hr after exposure, patients can present with the abrupt onset of cough, chest tightness, dyspnea, fever, chills, and fatigue (Table 427.2). Rarely, findings of wheezing are present on the initial examination. Rather, tachypnea with fine crackles may be heard by auscultation in the lung bases. However, auscultation may be normal at this stage. After cessation of exposure, symptoms may subside after 24-48 hr.

Table 427.2

Clinical History Clues Leading to a Diagnosis of Hypersensitivity Pneumonitis

Recurrent pneumonia
Pneumonia after repeat exposures (week, season, situation)
Cough, fever, and chest symptoms after making a job change or home change
Cough, fever, wheezing after return to school or only at school
Pet exposure (especially birds that shed dust such as pigeons, canaries, cockatiels, cockatoos)
Bird contaminant exposure (e.g., pigeon infestation)
Farm exposure to birds and hay
History of water damage despite typical cleaning
Use of hot tub, sauna, swimming pool
Other family members or workers with similar recurrent symptoms
Improvement after temporary environment change (e.g., vacation)

When **recurrent subacute HP** is present, the symptoms become progressive with shortness of breath and cough (productive), weight loss, malaise, and loss of appetite. When HP becomes chronic and *progressive* , the patient is hypoxic, and clubbing of the fingers is evident. If the disease progresses to interstitial fibrosis, the symptoms tend to not respond to therapy and mortality risk is increased. Histology is hard to distinguish from **idiopathic pulmonary fibrosis** at this stage.

Distinguishing chronic disease from subacute disease is difficult without clear differentiating criteria, but a diagnosis of HP at any stage results in the clinician recommending very specific interventions for improvement. HP is characterized as (1) acute nonprogressive and intermittent, (2) acute progressive and intermittent, (3) chronic nonprogressive, and (4) chronic progressive (Table 427.3). A diagnosis of HP is certain when the known exposure with immune response to the offending antigen is identified; the medical history and physical finding are abnormal on examination; **bronchoalveolar lavage (BAL)** and lung biopsy are abnormal. Some clinicians have foregone the lung biopsy when a cluster of cases occurs and 1 patient biopsy is already abnormal.

Table 427.3

Criteria Used in the Diagnosis of Hypersensitivity Pneumonitis

1. Identified exposure to offending antigen(s) by:
    - Medical history of exposure to suspected antigen in the patient's living environment
    - Investigations of the environment confirm the presence of an inciting antigen
    - Identification of specific immune responses (immunoglobulin G serum precipitin antibodies against the identified antigen) are suggestive of the potential etiology but are insufficient in isolation to confirm a diagnosis
2. Clinical, radiographic, or physiologic findings compatible with hypersensitivity pneumonitis:
    - Respiratory and often constitutional signs and symptoms
    - Crackles on auscultation of the chest
    - Weight loss
    - Cough
    - Breathlessness
    - Episodic fever
    - Wheezing
    - Fatigue

    NOTE: These findings are especially suggestive of hypersensitivity pneumonitis when they appear or worsen several hours after antigen exposure.

    - A reticular, nodular, or ground-glass opacities on chest radiograph or high-resolution CT
    - Abnormalities in the following pulmonary function tests
    - Spirometry (restrictive, obstructive, or mixed patterns)
    - Lung volumes (low or high)
    - Reduced diffusion capacity by carbon monoxide
    - Altered gas exchange either at rest or with exercise (reduced partial pressure of arterial oxygen by blood gas or pulse oximeter testing)
3. Bronchoalveolar lavage with lymphocytosis:
    - Usually with low CD4:CD8 ratio (i.e., CD8 is higher than normal)
    - Lymphocyte stimulation by offending antigen results in proliferation and cytokine production
4. Abnormal response to inhalation challenge testing to the offending antigen:
    - Reexposure to the environment

    - Inhalation challenge to the suspected antigen (rarely done now because of the risk of exacerbating the disease)
5. Histopathology showing compatible changes with hypersensitivity pneumonitis by 1 of these findings:
    - Poorly formed, noncaseating granulomas (most often found closer to the respiratory epithelium where deposition of the offending antigen occurs)
    - Mononuclear cell infiltrate in the pulmonary interstitium

Laboratory

Most of the abnormal laboratory findings in HP are not specific and represent evidence of activated inflammatory markers or lung injury. Nonspecific elevation of immune globulins or the erythrocyte sedimentation rate and C-reactive protein may also be found. Circulating immune complexes may be detected. Lactate dehydrogenase may be elevated in the presence of lung inflammation and normalizes with response to therapy.

Serum IgG precipitins to the offending agent are frequently positive and have a poor positive predictive value for disease. Among asymptomatic pigeon breeders, precipitating antibodies are nearly universal. False negatives can also be seen due to fluctuating serum antibody levels over time, and lack of standardized commercial antigens and reagents available for laboratory testing. It is critical that laboratories familiar with the performance of these tests be utilized. Those laboratories often recognize the value of processing antigens for precipitation from the *environmental source directly* as the test substrate with patient serum. Skin testing for IgE-mediated disease is not warranted unless there is evidence of mixed lung pathology such as asthma and interstitial lung opacities.

Radiology

Chest radiograph almost always precedes the use of high-resolution computerized tomography (HRCT) of the chest in children because of the need for sedation and concerns regarding risk of irradiation dose from HRCT. The plain radiograph will often demonstrate a ground-glass appearance, interstitial prominence, with a predominant location in the upper and middle lung fields. It is common for a chest radiograph to be considered normal by a radiologist early in the disease progression. Late in the disease, interstitial fibrosis may become prominent in the presence of increasing dyspnea, hypoxemia on room air, and clubbing of the fingers. Mediastinum widening from lymphadenopathy is *not* usually present; when present, the lymph nodes are prominent along the airway near the carina, suggesting that the antigen source is inhaled and being responded to by the immune system.

Classical findings of mid zone and upper zone opacities with ground-glass appearance and nodularity on HRCT in the presence of typical clinical exam HP findings (lung crackles, cough, dyspnea) and lymphocytosis on BAL are almost sufficient to make a diagnosis (Fig. 427.1). These findings must prompt the clinician to identify the exposure in order to secure the diagnosis and eliminate the offending antigen. Without therapy, the progressive inflammatory response leads to air trapping, honeycombing, emphysema, and mild fibrosis in the chronic state. It is in this latter stage that idiopathic pulmonary fibrosis and nonspecific interstitial fibrosis are hard to differentiate. Whether true idiopathic pulmonary fibrosis exists in children where fibroblast foci are found on biopsy with usual interstitial fibrosis has been questioned.

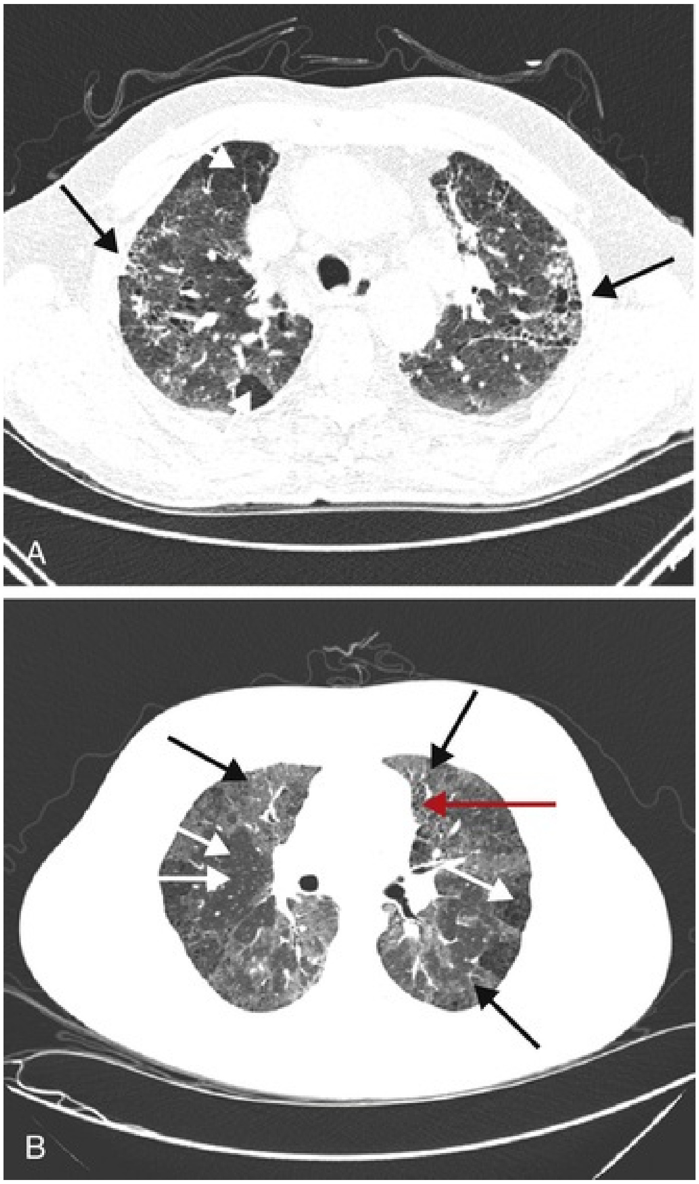

FIG. 427.1 Radiologic findings in subacute (A) and chronic (B) hypersensitivity pneumonitis. **A,** Interstitial fibrosis *(black arrows)* and emphysematous changes *(white arrows)* in chronic HP with superimposed subacute HP. **B,** Ground-glass opacities *(black arrows),* mosaic perfusion *(white arrows),* and fibrosis *(red arrow)* in chronic HP caused by pigeon exposure. (From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE: Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson AF, editor: *Middleton's allergy principles and practice* , Philadelphia, 2014, Elsevier, Fig. 61.5.)

Bronchoalveolar Lavage

BAL is one of the most sensitive tests and very helpful to the clinician in supporting the diagnosis of HP. Lymphocytosis frequently exceeding 50% of the recovered cells is seen on the BAL and should alert the clinician to the possibility of HP. Sarcoid, idiopathic pulmonary fibrosis, cryptogenic organizing pneumonia, berylliosis, granite workers lung disease, amiodarone pneumonia, lymphoma, and Langerhans cell histiocytosis may demonstrate lymphocytosis on BAL. All BAL specimens should have flow cytometry measurements of T-cell markers (CD3, CD4, and CD8 at a minimum). The predominant phenotype of the lymphocytosis is CD3+/CD8+/CD56+/CD57+/CD10−. In the normal circulation, lymphocytes with CD4 markers predominate at a ratio of approximately 2 : 1 compared to CD8 lymphocytes. *In the lung compartment with HP, this ratio becomes approximately equal to or less than 1 (CD4:CD8 ≤ 1) with either an increase in CD8 lymphocytes or a decline in CD4 lymphocytes.* This ratio assists the clinician in making a diagnosis of HP. This is in sharp contrast to other lymphocytic granulomatous diseases, like sarcoidosis, where the CD4:CD8 is ≥ 2, or pulmonary fibrosis associated with connective tissue disease. Cryptogenic organizing pneumonia, a rare disease in children, also may present with BAL where the CD4:CD8 is ≤ 1 and may be confused initially with HP.

Lung Biopsy

Lung biopsy is necessary to confirm a diagnosis of HP in the absence of critical elements like antigen exposure, typical medical history, characteristic physical exam, and CD8+ lymphocytes in the BAL. Open lung biopsy is often the route of choice in young children because of the difficulty in safely obtaining satisfactory amounts of tissue by transbronchial biopsy. Lack of positive serum precipitins to offending antigen and exposure history are common reasons for obtaining lung biopsies. It is crucial to inform the pathologist about the suspicion of HP so that the findings can be interpreted appropriately.

Histological examination shows poorly formed, noncaseating granulomas near the respiratory and terminal bronchioles and multinucleated giant cells. This is in sharp contrast to the well-formed granulomas seen in sarcoidosis. Lymphocytes and plasma cells infiltrate the alveolar walls predominantly in a bronchocentric pattern. Fibrosis in the peribronchial region supports a diagnosis of HP. Foamy cytoplasm accompanying large histiocytes in the alveoli and interstitium may be characteristically found.

Antigen Challenge by Inhalation

Inhalation challenge can support the diagnosis of HP by demonstrating a causal relationship between environmental exposure and symptoms. Inhalation challenge can be performed by 2 methods: (1) reexposure of the patient to the environment where the suspected antigen is present and (2) direct inhalation challenge at the hospital to material collected from the suspected source of the antigen. As the second method has resulted in severe exacerbation of disease in some individuals, its use is discouraged.

Two abnormal response patterns may be seen. Most commonly, where there is HP without asthma, symptoms occur 8-12 hr after direct challenge in the hospital or reexposure at the source of the antigen. The challenges replicate some or all the symptoms observed in the acute syndrome with fever, dyspnea, fatigue, and crackles on lung auscultation. Blood drawn prior to challenge and then repeated during these symptoms often demonstrates an increased neutrophil count compared to baseline. Pulmonary function tests demonstrate a fall in forced vital capacity (FVC) and often a concurrent fall in the forced expiratory volume at 1 sec (FEV_1) with a stable or increasing ratio of FEV_1 :FVC percentage reflecting a restrictive defect. Hypoxemia may accompany this decline in pulmonary function as well as a fall in the diffusion capacity of carbon monoxide (DLCO). To see the complete effect, exercise during this period may show a considerable fall in oxygenation despite normal arterial blood gas oxygen tension and normal pulse oximetry at rest. This finding denotes the onset of worsening restrictive lung disease.

Atopic patients may experience a biphasic response to inhalation challenge. These patients may develop an early reduction in FEV_1 , followed 4 to 6 hr by a second drop in FEV_1 accompanied by decreased FEV_1 and FVC, fever, and leukocytosis.

Treatment

The control of environmental exposure to the offending antigen is a key to curing HP and remains the ideal method of treatment and prevention of recurrence. The clinical and pathologic manifestations of acute and subacute HP are reversible with removal of the offending antigen. Counseling about the risk to children of exposure to birds and feathered bedding, or other environmental antigens, biologic aerosols, or agricultural dusts that are known to induce HP are important. Certainly, the source of the antigen and type of antigen appears to affect the response to treatment and long-term prognosis. Older individuals who contract farmer's lung are likely to recover with minimal permanent residual effect, whereas individuals with bird fancier's lungs from antigens produced by pigeons have a poorer prognosis, especially if fibrosis is detected on lung biopsy. The pediatrician should advise—in the strongest terms—removal of the antigen source from the affected child's environment. This may be an extraordinary challenge given various children's living circumstances and lack of independent control of the environment in which they live.

In addition, pediatricians should be familiar with recommendations about the maintenance of heating, ventilation, and air conditioning systems, as well as of humidifiers and vaporizers. Daily drainage, cleansing of residue, and routine cleaning with hydrogen peroxide or bleach help rid humidifiers and vaporizers of harmful pathogens such as thermophiles that cause HP.

Glucocorticoids at a dose of 0.5 mg/kg/day of prednisolone or equivalent (up to a maximum dose of 60 mg prednisolone daily) will reduce the immune inflammatory response in the lungs. In some cases, high dose pulse intravenous methylprednisolone is required, supplemented by treatment with oral prednisolone or other immunosuppressive therapies including cyclosporine or azathioprine. Comparative trials in adults demonstrate that the use of 4 wk of therapy is as effective as 12 wk of therapy. Removal of antigen alone is sufficient to normalize lung function in most patients, but symptoms and pulmonary functions return to normal faster with the use of glucocorticoids. Because of the rapid reversal of symptoms, successful abatement of the environment is sometimes compromised when the family sees improvement prior to the antigen source removal.

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427.2

Occupational and Environmental Lung Disease

Kevin J. Kelly, Michelle L. Hernandez

Keywords

occupational asthma
reactive airways dysfunction syndrome (RADS)
irritant-induced asthma

reactive upper airway disease syndrome
high molecular weight
low molecular weight

Occupational and environmental lung diseases constitute a larger part of primary care pediatrics, pediatric emergency medicine, and other pediatric subspecialties than most pediatric practitioners expect or realize. Although occupational and environmental lung diseases include **occupational asthma** , **reactive airways dysfunction syndrome (RADS)** , HP, hard metal inhalation lung disease, berylliosis, and air pollution, this chapter focuses on occupational asthma and RADS. Berylliosis has a propensity to form granulomas (see Chapter 427.3). Although some diseases will be seen with regularity, the important role that a part-time workplace, school, daycare, neighbors' housing, multiple family housing, and indoor and outdoor environments may have in the causation of signs and symptoms in the patient is not always considered by the clinician.

The vast array of exposures shown to cause disease of the lungs is daunting, such as the inhalation of baking flour or household cleaning fluids causing asthma, microwave popcorn exposure to diacetyl resulting in bronchiolitis obliterans, and exposure to thermophilic organisms or mold resulting in hypersensitivity pneumonitis. The acute eosinophilic pneumonias associated with new onset of smoking and chemical inhalation of 1,1,1-trichloroethane (Scotchgard) require a high index of suspicion and unique lines of questioning. The same antigen encountered in a work, school, home, or outdoor environment may result in a different disease presentation because of host factors, dose exposure, and genetic susceptibility. One of the most prominent examples is an investigation of workers who inhaled metal working fluid. Despite similar exposures, some developed HP, others developed asthma, and some displayed no symptoms at all. Immunologic evaluation in some exposures has shown similar immune responses in different individuals, but a wide range of disease provocation. When high molecular weight proteins cause asthma, symptoms of rhinoconjunctivitis frequently precede the onset of pulmonary symptoms. The medical history of occupational and environmental lung diseases has used an expanded construct with a simple acronym, **WHACOS** (Table 427.4).

Table 427.4

A Construct (WHACOS) That Has Been Used in Medical Interviewing of Patients,

Coworkers, and Family Members When Environmental or Occupational Lung Disease Is Being Considered

W	***W*** *hat* do you do?
H	***H*** *ow* do you do what you do?
A	Are symptoms ***A*** *cute* or are they *Chronic?*
C	Do any ***C*** *oworkers,* family, classmates, or friends have the same symptoms?
O	Do you have any hobbies, travel, or animal/pet exposures ***O*** *utside* of school or work?
S	Are you ***S*** *atisfied* with work or school?

It is important to remember that in patients with occupational- or environmental-induced disease, the onset of symptoms has a lag time between exposure and symptoms. In **occupational asthma** , there may be an immediate response within 1-2 hr of exposure, demonstrated as a decline in pulmonary function, specifically the FEV_1 . Usually, lung function returns to normal spontaneously unless persistent exposure occurs. Some patients demonstrate no immediate reduction in lung function, but rather experience a delayed response, 4-6 hr after the exposure. Treating physicians can take advantage of this physiology in occupational and environmental asthma by use of spirometry before and after work or school, or peak flow measurements hourly during exposure and after leaving the exposure. Because workers and schoolchildren have prolonged periods of exposure followed by a number of days without exposure, the use of pulmonary function plus bronchial hyperresponsiveness (e.g., methacholine) testing is helpful. Pulmonary function tests prior to starting work on a Monday of a typical work week may be normal. By Friday of a typical work or school week, the baseline pulmonary functions may have fallen, and bronchial responsiveness may have become more sensitive to a lower concentration of histamine, methacholine, or mannitol. By the following Monday, the tests may have returned to normal or near normal with no change other than reduced exposure.

In the case of HP, a lag of 4-8 hr between the time of exposure and the onset of fever, cough, and dyspnea is common. Unfortunately, the return home from hospitalization for culture-negative pneumonia to a source of antigen-causing HP often results in complete reoccurrence of symptoms. Clinicians must have a high index of suspicion for HP with reoccurrence of pulmonary infiltrates shortly after reexposure (see Chapter 427.1).

Classification and Pathogenesis

Occupational and environmental lung diseases include numerous syndromes of human lung disease such as **occupational asthma** , **RADS (reactive upper airway disease syndrome)** , hypersensitivity pneumonitis (see Chapter 427.1), air pollution–induced disease, hard metal inhalation lung disease, berylliosis, occupation-induced lung cancer (e.g., mesothelioma from asbestosis), and chronic obstructive pulmonary disease without smoking. Most of these diseases are not problematic for children, but adolescents may be exposed through part-time work or by single exposures as seen in RADS.

Occupational and Environmental Asthma

The general principles of diagnosis, clinical signs and symptoms, treatment, and causes of asthma are discussed in Chapter 169 . *High molecular weight* causes of occupational and environmental asthma can be characterized as allergens, which are normally proteins and enzymes, inhaled from multiple sources (Table 427.5). These include various animals, shellfish, fish, enzymes (e.g., *Bacillus subtilis* in laundry detergent), and flour or cereals. Occupational and environmental asthma is also caused by a number of low molecular weight agents including reactive chemicals, transition metals, and wood dusts (Table 427.6). These *low molecular weight agents* are sufficient to induce an immune response, but often not by an IgE-mediated mechanism. These low molecular weight chemicals appear to act as haptens that bind directly to human proteins, causing an immune response in the human host.

Table 427.5

High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma

OCCUPATION OR ENVIRONMENT	SOURCE
ANIMAL-DERIVED ANTIGENS	
Agricultural worker	Cow dander
Bakery	Lactalbumin
Butcher	Cow bone dust, pig, goat dander
Cook	Raw beef
Dairy industry	Lactoserum, lactalbumin
Egg producer	Egg protein
Farmer	Deer dander, mink urine
Frog catcher	Frog
Hairdresser	Sericin

Ivory worker	Ivory dust
Laboratory technician	Bovine serum albumin, laboratory animal, monkey dander
Nacre buttons	Nacre dust
Pharmacist	Endocrine glands
Pork producer	Pig gut (vapor from soaking water)
Poultry worker	Chicken
Tanner	Casein (cow's milk)
Various	Bat guano
Veterinarian	Goat dander
Zookeeper	Birds
CRUSTACEANS, SEAFOOD, FISH	
Canning factory	Octopus
Diet product	Shark cartilage
Fish food factory	Gammarus shrimp
Fish processor	Clam, shrimp, crab, prawn, salmon, trout, lobster, turbot, various fishes
Fisherman	Red soft coral, cuttlefish
Jewelry polisher	Cuttlefish bone
Laboratory grinder	Marine sponge
Oyster farm	Hoya (oyster farm prawn or sea-squirt)
Restaurant seafood handler	Scallop and shrimp
Scallop plant processor	King scallop and queen scallop
Technician	Shrimp meal *(Artemia salina)*
ARTHROPODS	
Agronomist	*Bruchus lentis*
Bottling	Ground bug
Chicken breeder	Herring worm *(Anisakis simplex)*
Engineer at electric power plant	Caddis flies *(Phryganeidae)*
Entomologist	Lesser mealworm (*Alphitobius diaperinus* Panzer), moth, butterfly
Farmer	Grain pests (*Eurygaster* and *Pyrale*)
Fish bait handler	Insect larvae *(Galleria mellonella)* , mealworm larvae *(Tenebrio molitor)* , green bottle fly larvae *(Lucila caesar)* , daphnia, fish-feed Echinodorus larva *(Echinodorus plasmosus)* , Chiromids midge *(Chironomus thummi thummi)*
Fish processing	Herring worm *(Anisakis simplex)*
Flight crew	Screw worm fly *(Cochliomyia hominivorax)*
Honey processors	Honeybee
Laboratory worker	Cricket, fruit fly, grasshopper *(Locusta migratoria)* , locust
Mechanic in a rye plant	Confused flour beetle *(Tribolium confusum)*
Museum curator	Beetles (Coleoptera)
Seed house	Mexican bean weevil *(Zabrotes subfasciatus)*
Sericulture	Silkworm, larva of silkworm
Sewage plant worker	Sewer fly *(Psychoda alternata)*
Technician	Arthropods *(Chrysoperla carnea, Leptinotarsa decemlineata, Ostrinia nubilalis,* and *Ephestia kuehniella),* sheep blowfly *(Lucilia cuprina)*
Wool worker	*Dermestidae* spp.
ACARIANS	
Apple grower	Fruit tree red spider mite *(Panonychus ulmi)*
Citrus farmer	Citrus red mite *(Panonychus citri)*

Farmer	Barn mite, two-spotted spider mite *(Tetranychus urticae)* , grain mite
Flour handler	Mites and parasites
Grain-store worker	Grain mite
Horticulturist	*Amblyseius cucumeris*
Poultry worker	Fowl mite
Vine grower	McDaniel spider mite *(Tetranychus mcdanieli)*
MOLDS	
Agriculture	*Plasmopara viticola*
Baker	*Alternaria, Aspergillus* (unspecified)
Beet sugar worker	*Aspergillus* (unspecified)
Coal miner	*Rhizopus nigricans*
Coffee maker	*Chrysonilia sitophila*
Laborer	Sooty molds (*Ascomycetes* , deuteromycetes)
Logging worker	*Chrysonilia sitophila*
Plywood factory worker	*Neurospora*
Sausage processing	*Penicillium nalgiovense*
Sawmill worker	*Trichoderma koningii*
Stucco worker	*Mucor* spp. (contaminating esparto fibers)
Technician	*Dictyostelium discoideum* (mold), *Aspergillus niger*
MUSHROOMS	
Agriculture	*Agaricus bisporus* (white mushroom)
Baker	Baker's yeast *(Saccharomyces cerevisiae), Boletus edulis*
Greenhouse worker	Sweet pea *(Lathyrus odoratus)*
Hotel manager	*Boletus edulis*
Mushroom producer	*Pleurotus cornucopiae*
Mushroom soup processor	Mushroom unspecified
Office worker	*Boletus edulis*
Seller	*Pleurotus ostreatus* (spores of white spongy rot)
ALGAE	
Pharmacist	Chlorella
Thalassotherapist	Algae (species unspecified)
FLOURS	
Animal fodder	Marigold flour *(Tagetes erecta)*
Baker	Wheat, rye, soya, and buckwheat flour; Konjac flour; white pea flour *(Lathyrus sativus)*
Food processing	White Lupin flour *(Lupinus albus)*
POLLENS	
Florist	Cyclamen, rose
Gardener	Canary island date palm *(Phoenix canariensis)* , Bell of Ireland *(Moluccella laevis)* , Bell pepper, chrysanthemum, eggplant *(Solanum melongena)* , *Brassica oleracea* (cauliflower and broccoli)
Laboratory worker	Sunflower (*Helianthus* spp.), thale cress *(Arabidopsis thaliana)*
Olive farmer	White mustard *(Sinapis alba)*
Processing worker	*Helianthus annuus*
PLANTS	
Brewery chemist	Hops
Brush-maker	Tampico fiber in agave leaves
Butcher	Aromatic herb
Chemist	Linseed oilcake, *Voacanga africana* seed dust
Cosmetics	Dusts from seeds of Sacha Inchi *(Plukenetia volubilis)* , chamomile (unspecified)
Decorator	Cacoon seed (Entage gigas)

Floral worker	Decorative flower, safflower *(Carthamus tinctorius)* and yarrow *(Achillea millefolium)* , spathe flower, statice *(Limonium tataricum)* , baby's breath *(Gypsophila paniculata)* , ivy *(Hedera helix)* , flower (various), sea lavender *(Limonium sinuatum)*
Food industry	Aniseed, fenugreek, peach, garlic dust, asparagus, coffee bean, sesame seed, grain dust, carrot *(Daucus carota L.)* , green bean *(Phaseolus multiflorus)* , lima bean *(Phaseolus lunatus)*, onion, potato, swiss chard *(Beta vulgaris L.)* , courgette, carob bean, spinach powder, cauliflower, cabbage, chicory, fennel seed, onion seeds (*Allium cepa* , red onion), rice, saffron *(Crocus sativus)*, spices, grain dust
Gardener	Copperleaf *(Acalypha wilkesiana)*, grass juice, weeping fig *(Ficus benjamina)*, umbrella tree (*Schefflera* spp.), amaryllis (*Hippeastrum* spp.), Madagascar jasmine sap *(Stephanotis floribunda)* , vetch *(Vicia sativa)*
Hairdresser	Henna (unspecified)
Herbal tea processor	Herbal tea, sarsaparilla root, sanyak *(Dioscorea batatas)*, Korean ginseng *(Panax ginseng)*, tea plant dust *(Camellia sinensis)* , chamomile (unspecified)
Herbalist	Licorice roots (*Glycyrrhiza* spp.), wonji *(Polygala tenuifolia)* , herb material
Horticulture	Freesia (Freesia hybrida), paprika *(Capsicum annuum)* , Brazil ginseng *(Pfaffia paniculata)*
Laborer	Citrus food handling (*dl* -limonene, *l* -citronellol, and dichlorophen)
Oil industry	Castor bean, olive oilcake
Pharmaceutical	Rose hip, passion flower *(Passiflora alata)* , cascara sagrada *(Rhamnus purshiana)*
Powder	Lycopodium powder
Sewer	Kapok
Sheller	Almond shell dust
Stucco handler	Esparto (*Stipa tenacissima* and *Lygeum spartum*)
Tobacco manufacturer	Tobacco leaf
PLANT-DERIVED NATURAL PRODUCTS	
Baker	Gluten, soybean lecithin
Candy maker	Pectin
Glove manufacturer	Latex
Health professional	Latex
Rose extraction	Rose oil
BIOLOGIC ENZYMES	
Baker	Fungal amylase, fungal amyloglucosidase and hemicellulase
Cheese producer	Various enzymes in rennet production (proteases, pepsine, chymosins)
Detergent industry	Esterase, *Bacillus subtilis*
Factory worker	*Bacillus subtilis*
Fruit processor	Pectinase and glucanase
Hospital personnel	Empynase (pronase B)
Laboratory worker	Xylanase, phytase from *Aspergillus niger*
Pharmaceutical	Bromelin, flaviastase, lactase, pancreatin, papain, pepsin, serratia peptidase, and lysozyme chloride; egg lysozyme, trypsin
Plastic	Trypsin
VEGETABLE GUMS	
Carpet manufacturing	Guar
Dental hygienist	*Gutta-percha*
Gum importer	Tragacanth
Hairdresser	Karaya
Printer	Acacia

Table 427.6

Low Molecular Weight Chemicals Known to Induce Occupational or Environmental Asthma

CHEMICALS	OCCUPATION OR ENVIRONMENT SOURCE
Diisocyanates	
• Diphenylmethane • Hexamethylene • Naphthalene • Toluene	• Polyurethane • Roofing materials • Insulations • Paint
Anhydrides	Manufacturers or users
• Trimellitic • Phthalic	• Paint • Plastics • Epoxy resins
Dyes	Personal or business use of dyes
• Anthraquinone • Carmine • Henna • Persulfate	• Hair dye • Fur dye • Fabric dye
Glue or resin	Plastic
• Methacrylate • Acrylates • Epoxy	• Manufacturers • Healthcare professionals • Orthopedic specialists
Metals	Metal work
• Chromic acid • Potassium dichromate • Nickel sulfate • Vanadium • Platinum salts	• Plating • Welding
Drugs	Exposure to drugs in environment
• β-Lactams • Opioids • Other	• Pharmaceutical workers • Farmers • Healthcare workers
Chemicals	Exposure in the healthcare field
• Formaldehyde • Glutaraldehyde • Ethylene oxide	• Laboratory work • Healthcare professionals
Wood dust	Workers/hobbyists
• Western red cedar (plicatic acid) • Exotic woods • Maple • Oak	• Sawmill • Carpentry • Woodworking

The pathogenesis of asthma in patients exposed to high molecular weight antigens follows the experience of nonoccupational asthma in patients where atopy, gender, genetics, concentration of antigen, duration of exposure, and other individual factors all contribute to the development of disease. Most individuals require a concentration and duration of exposure sufficient to cause IgE antibody sensitization to the offending allergen with development of bronchial hyperresponsiveness and airway inflammatory disease upon reexposure. If the allergen exposure is sufficient, these proteins can drive the immune response to a T-lymphocyte type 2 phenotype (Th2), even in patients without prior atopic disposition. This occurred in the case of latex allergy, where many nonatopic individuals and patients exposed to allergen in their personal healthcare developed occupational allergy to multiple proteins from natural rubber latex. Atopic individuals are at the highest risk of developing latex allergy. A longitudinal study demonstrated that powdered latex gloves with high allergen content were the reason for the epidemic of latex allergy and occupational asthma. Unfortunately, despite primary removal of the offending sensitizing agent, asthma symptoms and bronchial hyperresponsiveness induced from multiple causes persist in approximately 70% of individuals with occupational asthma.

Reactive Airways Disease Syndrome and Irritant-Induced Asthma

RADS presents with acute respiratory symptoms within minutes or hours following a single inhalation of a *high concentration* of irritant gas, aerosol, or smoke. The clinical manifestations and pathophysiology of RADS have been studied through experimental design or epidemiology studies following exposure to chlorine gas, acetic acid, dimethylaminoethanol, chlorofluorocarbons, epichlorohydrin, and diisocyanates.

Table 427.7 lists the criteria for diagnosis of RADS. Asthma-like symptoms and airway hyperresponsiveness then ensue, which often persist for prolonged periods. Unlike typical asthma, RADS is often not reversible by use of a bronchodilator. This is probably a consequence of the direct injury to the epithelium and subsequent submucosal fibrosis.

Table 427.7

Criteria for the Diagnosis of Reactive Airways Disease Syndrome

• Absence of previous documented respiratory symptom • Onset of symptoms most often occur after a single specific exposure • Exposure is most often to a high concentration of gas, smoke, fume, or vapor with irritant qualities • Symptoms occur within 24 hr of exposure and persist for 3 mo or longer • Symptoms mimic asthma with cough, wheezing, shortness of breath, and/or dyspnea

- Pulmonary function tests may demonstrate airflow obstruction but not always
- Bronchial hyperresponsiveness is documented by methacholine challenge
- Alternative pulmonary diseases are not able to be found

Irritant-induced asthma is a closely related form of asthma resulting from nonimmunologic provocation of bronchial hyperresponsiveness with airflow obstruction. In contrast to RADS, irritant-induced asthma occurs after single or multiple exposures to irritant chemicals in *low concentration* . If the resultant pulmonary symptoms occur after multiple exposures at a plant, it is termed *nonimmunologic-induced asthma* .

Predisposing factors for the development of RADS are not well characterized. Atopy and cigarette smoking may increase the risk of developing RADS when exposure through inhalation of irritant chemicals occurs. In addition to host factors, the type of chemical appears to be important. Higher concentrations of chemicals, the type of chemical (vapor or wet aerosols), and bleaching agents are the most offending agents to cause RADS. Dry particle aerosols are less likely to cause RADS. Analysis of the World Trade Center firefighters indicates that the presence of bronchial hyperresponsiveness prior to a chemical exposure *does not* increase the risk for an individual to develop RADS.

Pathogenesis of RADS follows a typical pattern, driven by the initial injury to the airway epithelium. Initial histology demonstrates rapid denudation of the mucosa accompanied by a submucosal fibrinous, hemorrhagic exudate. Subepithelial edema subsequently occurs with some regeneration of the epithelial layer, proliferation of basal and parabasal cells, and eventually areas of fibrosis. The desquamation, subepithelial fibrosis, thickening of the basement membrane, and regeneration of basal cells are all more prominent in RADS than in occupational asthma. This may explain the limited response to bronchodilator therapy in this syndrome compared to asthma.

The clinical manifestations of RADS and irritant-induced asthma are different from each other mostly in the onset of symptoms. Patients with RADS typically can pinpoint the exact time of onset of symptoms as well as the exact number of hours post exposure. The symptoms are so severe that nearly 80% of subjects in one study presented to an emergency department for care. The lower airway symptoms of cough, dyspnea, chest tightness, and wheezing are prominent features in RADS, with cough being most prevalent. Because of the toxic nature of the inhaled chemical, it is predictable that an upper airway syndrome of throat and nose burning will often accompany the lower airway symptoms. This part of the complex has been referred to as **respiratory upper airway dysfunction syndrome.**

Individuals with **irritant-induced asthma** present with a more insidious onset of symptoms. Because of the recurrent nature of the low concentration of chemical, patients may not be able to identify the underlying trigger initially. Similar to allergic rhinitis, patients may describe nasal congestion, rhinorrhea, sneezing, postnasal drip, ocular irritation, and conjunctival injection. Pulmonary symptoms include those typically seen with asthma exacerbations.

Initial evaluation of the patient with RADS or irritant-induced asthma usually includes the medical history, physical examination, and pulse oximetry. Because of the acute nature of RADS, a chest radiograph is obtained in order to rule out other acute causes of dyspnea including pneumonia or pulmonary edema. In patients with RADS and irritant-induced asthma, the chest radiograph is frequently normal or may show hyperinflation. Ideally, if the patient is not in significant distress, complete pulmonary function testing with spirometry, lung volumes, and diffusion capacity are very helpful in the initial evaluation. The lack of abnormality on initial chest radiograph reassures the clinician that HRCT is not indicated.

Treatment

Treatment of RADS and irritant-induced asthma focuses on prevention of exposure. Because the exposure in RADS is often associated with a single known exposure, this task is readily accomplished. The low, persistent exposures are more challenging to identify and remove.

Implementing treatment guidelines for asthma from all causes is recommended when intervention is required beyond antigen removal. The management of an acute presentation of RADS is essentially the same as the treatment of an acute asthma exacerbation. Short-acting beta-agonist treatment may not be effective in most patients; a trial of inhaled ipratropium may add benefit in the short term. For moderate to severe symptoms and FEV_1 less than 70% of predicted, administration of systemic glucocorticoids (2 mg/kg prednisone equivalent, up to 60 mg daily) can be beneficial based on some clinical case studies and animal studies. Unlike the typical 5-day courses of systemic glucocorticoids for asthma exacerbations, many patients remain symptomatic beyond 5 days due to the extent of the airway epithelial injury. Steroid treatment may be prolonged through 10-15 days after the onset of symptoms, accomplished through a slow taper of corticosteroids. High-dose inhaled corticosteroids (ICS) may be added while the systemic steroids are being tapered. The initial dose of ICS is based on the National Asthma Education and Prevention Program (NAEPP) and the Global Initiative for Asthma (GINA) guidelines. For patients whose initial symptoms are less severe and/or spirometry demonstrates milder airway obstruction (FEV_1 greater than 70% of predicted), high-dose ICS therapy alone can be started without requiring systemic corticosteroid treatment. Once patients' asthma symptoms are improved, ICS doses can be tapered by 25–50% increments over a period of up to 6 mo in some case series based on patient symptoms. However, prolonged ICS treatment beyond 6 mo has also been noted.

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427.3

Granulomatous Lung Disease

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Keywords

GPA
sarcoidosis
cyclophosphamide
rituximab
GLILD
CVID

Granulomatosis With Polyangiitis

Granulomatosis with polyangiitis (GPA) is a disease that involves both the lower and upper respiratory tracts with granulomatous inflammation of small vessels; formerly it was known as *Wegener granulomatosis* (see Chapter 192). The pulmonary disease is frequently associated with glomerulonephritis. The simultaneous presence of pulmonary and renal disease should immediately raise the suspicion that either GPA, microscopic polyangiitis, or anti-glomerular basement membrane (anti-GBM) disease (see Chapter 427.5) may be causing the disease.

Etiology and Epidemiology

The prevalence of GPA disease appears to be increasing by up to 4-fold in the last 2 decades, but without male or female predominance. Improved diagnostic tests, such as antineutrophil antibodies, may explain some of this increased prevalence.

Pathogenesis

Clinically, the development of both upper and lower airway disease with granulomas in GPA implies that exposure to antigen in the airway of endogenous or exogenous source is involved with aberrant cell-mediated immune response. Cytokine expression by peripheral blood CD4+ lymphocytes and cells collected by BAL indicate there is a predominantly T-lymphocyte type 1 response with overexpression of interferon-γ (IFN-γ) and tumor necrosis factor (TNF). In vitro studies demonstrate a skewed T-lymphocyte type 17 response by blood CD4+ T cells in GPA, suggesting there is an immune regulatory defect that leads to excessive production of T-lymphocyte type 1/T-lymphocyte type 17 cytokines (interleukin [IL]-17, TNF, and IFN-γ) presumed to be from the environment or autoantigens. Such an inflammatory response may be sufficient to induce and sustain granuloma formation.

Detection of *autoantibodies reactive against proteins in the cytoplasmic granules of neutrophils and monocytes (antineutrophil cytoplasmic antibodies [ANCAs])* are found in 90% of the patients with GPA. The first major type of ANCA is directed against cytoplasmic proteinase-3 and is frequently named **c-ANCA** . The second major type of ANCA recognizes the enzyme myeloperoxidase. It is found in a small number (<10%) of patients with GPA but is frequent in *microscopic polyangiitis* . Anti-myeloperoxidase antibodies fluoresce in a perinuclear pattern and are often referred to as perinuclear or **p-ANCA** . In contrast, some patients develop the clinical phenotype of GPA in the absence of detectable ANCA.

Clinical Manifestations

Children with GPA present with respiratory complaints accompanied by fever, loss of energy, and vague joint complaints. Some may present with severe nasal disease manifested as ulceration, septal perforation, pain, sinusitis, and/or epistaxis. The septal perforation may lead to deformation of the nasal bridge from erosion of the underlying cartilage but is more common in adults.

Pulmonary disease occurs in the majority of patients as noted above. Symptoms range from cough, hemoptysis (seen in less than 50% of patients), dyspnea, and chest discomfort to asymptomatic infiltrates on chest radiography. Occasionally, patients with GPA will present with hemoptysis or recurrent fleeting infiltrates from *pulmonary hemorrhage* . The pathology is confusing because granulomatous disease may be difficult to demonstrate, and *pulmonary capillaritis* , the other main component seen on histology, can be seen in other disorders including anti-GBM disease, microscopic polyangiitis, idiopathic pulmonary capillaritis, and Henoch-Schönlein purpura. Distinguishing GPA from other pulmonary renal syndromes is easiest when there are classical symptoms of upper airway disease (nasal/sinus), lower airway disease with necrosis, granulomas on biopsy of the lung with vasculitis, and renal disease consistent with glomerulonephritis.

As many as 20% of patients with GPA will present with subglottic or endobronchial stenosis from scarring and inflammatory changes. Although it may be the presenting symptom, it often occurs in conjunction with other disease manifestations. Dyspnea and voice changes are common complaints from the patients.

Skin, ocular (uveitis), and joint symptoms are common in GPA and have been found to accompany the lung and renal disease in most series 50% or more of the time. Biopsy of the skin may show nonspecific leukocytoclastic vasculitis, venulitis, or capillaritis.

Laboratory and Pathology

c-ANCA or anti–proteinase-3 antibodies are found in 90% of patients with GPA. However, they are also found in other types of vasculitis and are not sufficient in themselves to make a diagnosis without a tissue biopsy (see Chapter 192). Because of the necrotizing nature of the vasculitis, lung tissue is required for definitive diagnosis of pulmonary disease. Biopsy of the upper airway may demonstrate evidence of granulomatous disease, but it is uncommon to find evidence of vasculitis therefore lung biopsy is warranted. Usual pathology demonstrates multiple parenchymal nodules that may be located in either the bronchial, vascular, or interstitial tissues (Fig. 427.2). The granulomatous inflammation is often found in areas of necrosis and/or vasculitis.

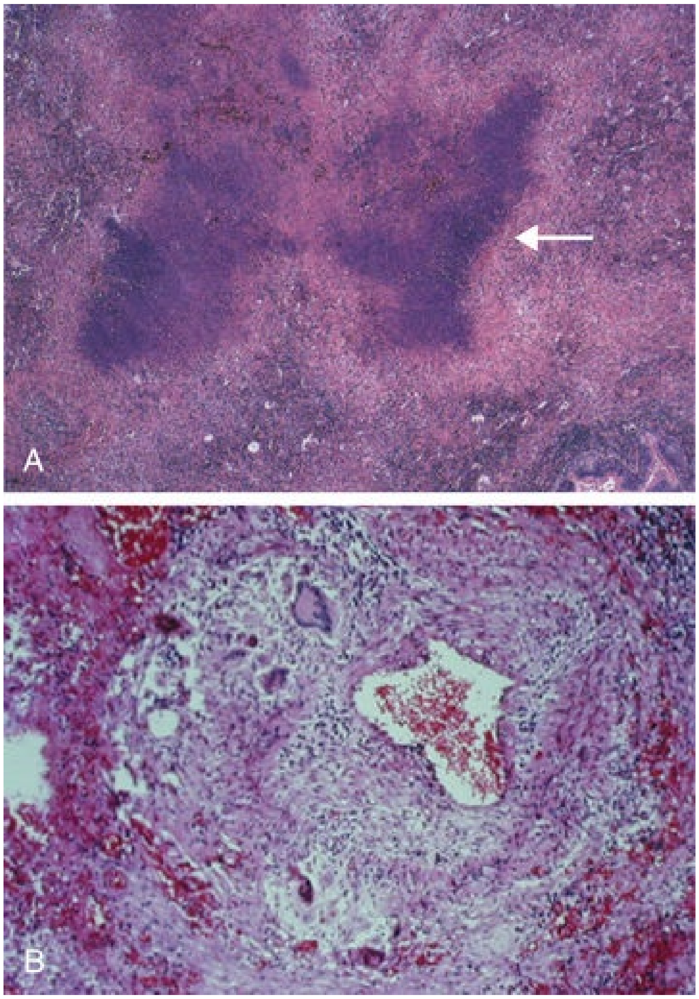

FIG. 427.2 **A,** Low-power view of granulomatous inflammation and geographic necrosis *(arrow)* in a lung biopsy from a patient with GPA. **B,** Granulomatous vasculitis involving a small pulmonary artery in the lung of a patient with GPA. The vessel wall is markedly thickened with an inflammatory infiltrate that includes multinucleated giant cells. (From Sneller MC, Fontana JR, Shelhamer JH: Immunologic nonasthmatic diseases of the lung. In Adkinson AF, editor: *Middleton's allergy principles and practice* , Philadelphia, 2014, Elsevier, Fig. 61.1B and C.)

Renal biopsy rarely demonstrates granulomas or vasculitis. Rather, kidney tissues may show focal, segmental, or necrotizing glomerulonephritis without deposits of immune complexes. When the tissues fail to demonstrate classical findings, a variety of diseases (e.g., tuberculosis, sarcoid, microscopic polyangiitis, malignancy, and other autoimmune disorders) must be considered in the evaluation.

Radiology

Chest radiography in GPA will show multiple infiltrates, nodules, cavitary lesions, or ILD. Fleeting infiltrates may be seen when recurrent hemorrhage is a part of the clinical manifestation. HRCT often demonstrates more extensive lung disease and the cavitation associated with the necrotizing nature of the disease (Fig. 427.3).

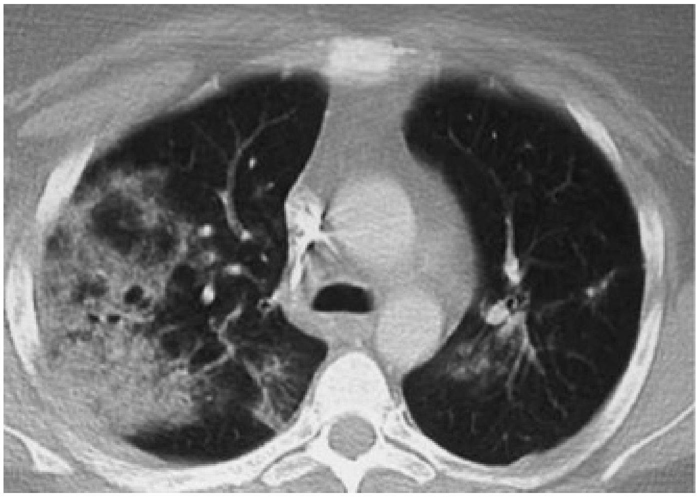

FIG. 427.3 Chest CT scan of a patient with granulomatosis with polyangiitis shows typical nodular lung infiltrate with cavitation. (From Sneller MC, Fontana JR, Shelhamer JH: Immunologic nonasthmatic diseases of the lung. In Adkinson AF, editor: *Middleton's allergy principles and practice* , Philadelphia, 2014, Elsevier, Fig. 61.1A.)

Treatment

Rapidly progressive, debilitating disease may occur when failure to diagnose GPA leads to inadequate treatment. One series of patients showed death occurred in 90% of patients within 2 yr of diagnosis. Glucocorticoid therapy alone resulted in relapses and inadequate control of disease in many subjects.

Therapy is divided into *induction* and *maintenance* phases. Systemic corticosteroids, while ineffective as monotherapy, are a mainstay of therapy in conjunction with other immune suppressive agents. Prednisone can be given orally at a dosage of 1-2 mg/kg/day (max 60 mg). Alternatively, intravenous methylprednisolone may be used at a dosage of 10-30 mg/kg (max 1 gram) given either weekly or for 3 consecutive days monthly. Combination therapy traditionally included cyclophosphamide given either orally at 2 mg/kg/day or intravenous dosing at 15 mg/kg monthly. Rituximab, an anti-CD20 antibody, is as effective as cyclophosphamide in inducing remission of the GPA. Rituximab dosing is either 350 mg/m^2 given weekly for the first 4 wk or 500 mg/ m^2 given on initiation of therapy and 2 wk after initiation. A second dose of 500 mg/m^2 is often given 6 mo after the first dosage of rituximab. Induction therapy should be continued for 3-6 mo.

Continued therapy is required past the initial induction phase to maintain remission, however, due to the toxicity of cyclophosphamide, other immune-suppressive agents are preferred. Both methotrexate and azathioprine have been shown to be equally effective as cyclophosphamide in maintaining remission. Mycophenolate mofetil, in contrast, has higher relapse rates than azathioprine and should be avoided in ANCA-associated vasculitis. Systemic steroid dosages should be progressively weaned at the beginning of the maintenance phase of therapy to a dosage of 5-10 mg/day. Therapy should be continued for an additional 1.5-2 yr. Rituximab, given every 6 mo for 2 yr, is at least as effective in maintaining remission as other regimens.

Adjuvant therapy with plasma exchange may be considered when life-threatening GPA disease presents. This is advocated on the premise that ANCAs are inducing disease and will be removed from the circulation with this intervention; its use has been favorably evaluated in GPA-induced renal disease. Adjuvant plasma exchange has been studied mainly in patients with severe renal vasculitis, but there are also reports of success in severe pulmonary hemorrhage. The results of a meta-analysis of patients with renal vasculitis in 9 trials suggest that adjuvant plasma exchange may be associated with improved renal outcome.

Recurrent disease remains a major problem with relapse rates of up to 50% reported in most studies. ANCA levels have not been shown to correlate with activity of disease or severity. Patients with isolated disease of the sinuses and nose may not warrant such toxic therapy. Therapy with topical corticosteroid and antibiotics for infection appear to be warranted. If unsuccessful, steroid with methotrexate appears to be an effective therapy.

The development of subglottic stenosis requires specific treatment. Use of cyclophosphamide with oral corticosteroid may have an incomplete or no response in the airway. Local injection of a prolonged acting corticosteroid locally appears to be indicated to reduce the inflammation and prevent further scarring. If this complication is found at presentation, simultaneous airway intervention with induction of corticosteroid and cyclophosphamide is warranted and encouraged.

Sarcoidosis

Sarcoidosis is an idiopathic inflammatory disease involving multiple organ systems, with characteristic histology of noncaseating granulomas (see Chapter 190). It has been postulated that sarcoidosis represents an immune response to a yet-to-be-identified agent from the environment that is likely inhaled in a susceptible host. It remains a diagnosis of exclusion from other diseases with granuloma formation on histology, such as immune deficiency of chronic granulomatous disease (CGD), granulomatous lymphocytic ILD associated with common variable immune deficiency (CVID), HP associated with some drugs and inhalation agents, granuloma with polyangiitis, typical and atypical *Mycobacterium* , *Pneumocystis jiroveci* , and malignancy.

Epidemiology and Pathogenesis

African-American females are disproportionately affected by sarcoidosis; however, it can present in any group. Because an asymptomatic sarcoid-like distribution of noncaseating granulomas may be frequently found at autopsy, the contribution of the granulomas to the disease is not always clear. Some countries do mass chest radiograph screening for multiple diseases. In that setting, up to 50% of diagnosed sarcoidosis is asymptomatic. The severity of the disease appears to be worse in African-Americans who tend to have acute illness, whereas white subjects are more likely to be asymptomatic with a more chronic disease. There have been clusters of disease in families and genetic testing suggests that MHC linkage on the short arm of chromosome 6 is most likely to be observed.

Sarcoidosis is rarely found in children younger than the age of 8 yr; those of African descent are most affected. The disease presentation is similar to adults with multisystem disease being the most common. Skin rash, iridocyclitis, and arthritis are seen most often without pulmonary symptoms. In northern Europe, erythema nodosum with the ocular involvement of iridocyclitis is seen most frequently. Despite the lack of symptoms, chest radiography may be abnormal in approximately 90% of children. The pulmonary disease appears to be less progressive compared to adults and patients recover spontaneously without corticosteroids. Rarely, pulmonary disease may progress to fibrosis. Ocular disease is more likely to be progressive and warrant intervention as the inflammatory response may lead to blindness from complications of iritis.

Unrecognized infection or inhalation of an immune response–inducing antigen continues to be at the forefront of consideration as a cause of the disease. Clusters of sarcoidosis in small populations, variable prevalence by geography and race, transfer of disease by organ transplant, and the reproducible granuloma formation only in patients with sarcoidosis in the skin when homogenized lymph node tissue from patients with sarcoid is injected intradermally (Kveim-Siltzbach test) have supported this hypothesis.

Clinical Manifestations

Patients with lung disease are more likely to be asymptomatic as the presentation often may be an abnormal chest radiograph. When symptomatic, patients demonstrate shortness of breath, cough, and dyspnea. Children are more likely to manifest the disease as iridocyclitis, skin rash, and arthritis. African-American children appear to have more frequent lymph node involvement, nonspecific elevations of gamma globulin, erythema nodosum, and hypercalcemia. Physical exam may reveal only an elevated respiratory rate without crackles or rales by auscultation. Pleural involvement has been seen but is uncommon. When present, a lymphocytic predominant exudate may be observed with laboratory evaluation of the pleural fluid. Unusual but reported findings include cases of pneumothorax, hemothorax, and chylothorax. One specific syndrome, **Lofgren syndrome** , with hilar lymphadenopathy, erythema nodosum, and migratory polyarthralgias, is almost exclusively seen in females. This syndrome has a strong association with HLA-DQB1*0201 and polymorphisms in the C-C chemokine receptor 2 (CCR2); these genetic markers are a predictor of a good outcome.

Although almost 90% of patients with sarcoidosis demonstrate parenchymal or mediastinal disease on chest radiography, there are many who have minimal to no symptoms. Approximately 40% of adults with stage 1 disease have endobronchial involvement found at bronchoscopy. The higher the staging level of disease, the more likely patients are to have airway involvement.

Diagnostic Laboratory Testing

The most common but nonspecific findings are hypergammaglobulinemia, hypercalciuria, hypercalcemia, elevated alkaline phosphatase when liver disease is present, and, occasionally, anemia of chronic disease. Serum angiotensin-converting enzyme may be elevated in 75% of patients with untreated sarcoid. False-positive tests occur from other diseases so that it is not considered a diagnostic test but rather a test that strongly supports the diagnosis.

Pulmonary function tests can be performed accurately in most children older than the age of 4 yr. There are no specific diagnostic findings of spirometry, lung volumes, or diffusion capacity in sarcoidosis. Exercise coupled with pulmonary function tests may demonstrate a decline in diffusion capacity when alveolitis is present in hypersensitivity pneumonitis and could add diagnostic help to the clinician when attempting to differentiate sarcoidosis from HP prior to biopsy.

BAL is of great help when differentiating HP from sarcoid. BAL in sarcoid shows a marked predominance of CD4 cells. *A lymphocyte percentage > 16% on BAL, a CD4:CD8 ratio > 4, and noncaseating granulomas on bronchial biopsy in the presence of abnormal angiotensin-converting enzyme levels are nearly completely diagnostic for sarcoid.* In addition, T cells are activated on BAL. BAL in HP shows a significant change in the balance of CD4 to CD8 cells with the 2 cell types being nearly equal compared to the normal mild predominance of CD4 cells in the circulation. A ratio of CD4:CD8 of <1 predicts 100% of patients with BAL lymphocytosis to *not* have sarcoidosis. Neutrophil counts >2% and/or eosinophil counts >1% exclude the diagnosis of sarcoidosis.

The analysis of D-dimers in BAL fluid from subjects with sarcoidosis demonstrates an elevation in 80% of patients compared to no detectable D-dimers in unaffected control.

Histopathology

The characteristic feature of sarcoidosis is the noncaseating granuloma formation in the lung (Fig. 427.4). These granulomas are found in the bronchial walls, alveolar septa, and vascular walls of pulmonary arteries and veins. The formation of noncaseating granulomas is likely preceded by alveolitis involving the interstitium more than the alveolar spaces. There is accumulation of inflammatory cells, including monocytes, macrophages, and lymphocytes that accompany the granulomas. Multinucleated giant cells are frequently found among the epithelioid cells within the granuloma follicle. These may show cytoplasmic inclusions (e.g., asteroid bodies and Schaumann bodies) as well as some birefringent crystalline particles made of calcium oxalate and other calcium salts. These are most often identified in the upper lobes of the lungs which may lead to confusion with diseases such as hypersensitivity pneumonitis, eosinophilic granuloma, collagen vascular disease, pneumoconiosis, berylliosis, and infectious disease such as tuberculosis or histoplasmosis.

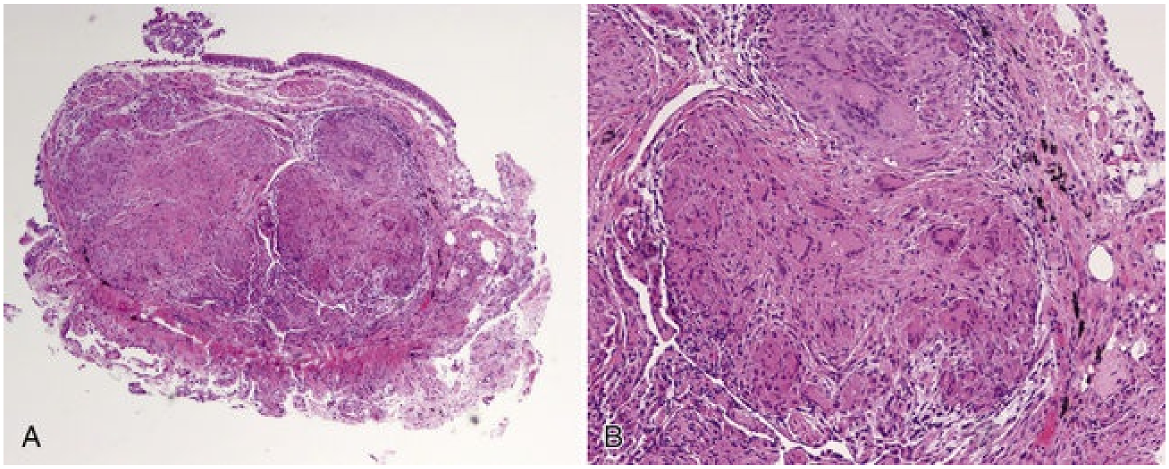

FIG. 427.4 Transbronchial biopsy specimen showing a sarcoid granuloma. **A,** The granulomas are located below the bronchiolar epithelial layer that appears at the top of the frame. **B,** A higher-power view of the same biopsy specimen. The epithelioid granuloma is tightly packed and contains multiple multinucleated giant cells. There is no caseous necrosis. Special stains for acid-fast bacilli and fungi were negative. (From Sneller MC, Fontana JR, Shelhamer JH: Immunologic nonasthmatic diseases of the lung. In Adkinson AF, editor: *Middleton's allergy principles and practice* , Philadelphia, 2014, Elsevier, Fig. 61.6.)

Radiology

Pulmonary imaging in sarcoid has included plain chest radiography, HRCT, positron emission tomography using fluorine-18-fluorodeoxyglucose, and radiotracer using gallium-67. The staging of sarcoid is performed using plain radiography and is outlined as follows:

◆ Stage I—Bilateral hilar lymphadenopathy accompanied by right paratracheal lymphadenopathy

◆ Stage II—Bilateral hilar lymphadenopathy accompanied by reticular opacities are present. If symptomatic, patients have cough and dyspnea.

Occasional fever and fatigue accompany the respiratory symptoms.

- Stage III—Reticular opacities are found predominantly in the upper lobes with regression of hilar lymphadenopathy.
- Stage IV—Reticular opacities start to coalesce and lead to volume loss in the lung fields, traction bronchiectasis from conglomeration of the inflamed tissues. Extensive calcium deposits may be seen at this stage.

HRCT may be helpful in further staging of the disease, as well as in revealing abnormalities not appreciated on chest radiography. Findings in patients with sarcoidosis by HRCT include hilar lymphadenopathy, paratracheal nodules, middle to upper lung parenchymal ground-glass appearance, bronchial wall thickening, bronchiectasis, cystic changes, and fibrosis. The ground-glass appearance suggests that alveolitis, as seen in hypersensitivity pneumonitis, may be present. Biopsy has usually shown granuloma formation as the predominant histologic finding.

Treatment

Because pulmonary sarcoidosis spontaneously resolves without therapy in almost 75% of patients, clear guidelines for treatment focused on minimizing side effects of therapy is required. Glucocorticosteroids (GCSs) have long been the mainstay of therapy in sarcoid and are often used because of extra pulmonary disease. When pulmonary disease is progressive, GCS therapy is aimed at prevention of fibrosis, honeycombing, and irreversible lung disease. Assuring that disseminated infections, heart failure, thromboembolism, or pulmonary hypertension are not present is important. In addition to HRCT of the chest, performance of pulmonary function tests, electrocardiogram, and echocardiogram should be considered prior to starting GCS therapy.

GCS therapy is often not started when stage I or II is present without symptoms. This scrutiny of the benefit of therapy was highlighted when prospective evaluation of GCS therapy for pulmonary disease found that nearly 50% of patients receiving GCSs had active or relapsing disease 2 yr later. In contrast, 90% of patients who did not receive GCSs had spontaneous remission of disease with the other 10% needing intervention 2 yr later. Absolute indications include progressive stage III disease with symptoms of shortness of breath, cough, or other chest symptoms such as pain. Progressive restriction shown on pulmonary function testing is an indication for therapy. Specific pulmonary function changes where lung capacity declines a total of 10% or greater, FVC declines 15% or more, or diffusion capacity degradation is seen of 20% or more are all indications for GCS intervention.

Dosage with oral prednisone at 0.3-0.5 mg/kg is a reasonable starting point depending on the severity of symptoms. Stability is usually achieved within 6-8 wk, after which slow progressive tapering of GCS may occur every 4-8 wk. Many favor the use of alternate-day steroids to reduce the side effects of GCSs, but little data exist to show efficacy.

For patients who do not tolerate GCSs or develop progressive disease, alternative immunosuppressive agents may add benefit to the regimen. Progressive disease also is a reminder for the clinician to reassess the diagnosis of sarcoid and review the chance that beryllium may have been the underlying reason for the progressive disease.

Inhaled GCSs have been evaluated in patients with stage I disease with variable results. Evaluation of therapy with pulmonary function testing and symptoms are the best methods to judge responsiveness to this therapy. Persistent symptoms after 4-8 wk of therapy suggest that systemic GCSs may be indicated.

Berylliosis

Chronic beryllium disease or berylliosis is an example of environmental exposure and unique granulomatous response in the lungs. Beryllium is an alkaline metal that is used in a number of industrial settings.

A diagnosis of berylliosis requires 3 criteria: (1) history of beryllium exposure; (2) positive response to lymphocyte proliferation tests to beryllium in lymphocytes obtained by BAL or blood test; and (3) noncaseating granulomas on lung biopsy. Exposure to beryllium may occur in industries such as automotive, ceramic, aerospace, metal extraction, electronics, computer, jewelry making, and dental alloys. Teenagers working summer jobs in machine work, ceramics, or wire production may be exposed. Sensitization is associated with dose and duration of exposure and has been seen to be as high as 20% in certain industries. Secretaries working in buildings where manufacturing with beryllium is active have developed berylliosis.

Pathogenesis

Genetic susceptibility coupled with immunologic response to beryllium are the 2 key contributors to the development of disease. A T-lymphocyte cell–mediated delayed hypersensitivity response to beryllium appears to be the mechanism involved with granuloma formation in the lung. The lymphocyte proliferation by T cells to beryllium is specific and does not occur in reaction to other metals. Similar to sarcoidosis, CD4+ T cells predominate on bronchoalveolar response. Beryllium appears to be inhaled and then couple with proteins in the lung or can be ingested by antigen-presenting cells. The cytokines elicited and granuloma formation suggests that sensitization is primarily a T-lymphocyte type 1 response with elevated IFN-γ and IL-2 production.

Clinical Manifestations

The clinical manifestations of berylliosis are not specific. Dry cough, fever, fatigue, weight loss, and shortness of breath all may be present. Although symptoms may occur within 3 mo, new disease has been detected up to 3 decades after exposure. Physical examination is somewhat different than the HPs and sarcoid with bibasilar crackles found on auscultation. The other mentioned diseases are more prominent in the upper lobes. Small nodules on exposed skin may also be present.

Laboratory Testing

Suspicion of berylliosis should prompt the clinician to have a blood beryllium lymphocyte proliferation test and complete pulmonary function tests performed. These tests need to be sent to a special center where multiple tests are run with comparison to proper positive and negative controls. When positive, the test has very high specificity for defining the presence of berylliosis at approximately 96%. However, sensitivity of the test hovers at <70%, suggesting that approximately 30% who have the disease may have a negative test.

Similar to other pulmonary granulomatous diseases, increased production of calcitriol is commonly found. The source of this active form of vitamin D is from activated pulmonary macrophages, which may result in hypercalciuria and hypercalcemia.

Radiography

Chest radiographs should be obtained on all patients suspected of having berylliosis. The chest radiograph may be normal, show hilar lymphadenopathy, pulmonary nodules, ground-glass, or alveolar opacities. The parenchymal abnormalities may be diffuse or may be more prominent in the upper lobes. These findings are dependent upon the stage of the disease.

HRCT is the most sensitive test in the identification of chronic berylliosis. Almost 25% of the HRCT exams in patients with biopsy-proven berylliosis are found to be normal. Similar to other granulomatous and HPs of the lungs, HRCT findings include parenchymal nodules of varying size, thick septal lines, ground-glass opacities, cystic cavitation, and lymphadenopathy in the hilum or mediastinum. Pleural abnormalities are less common, but thickening may be observed in proximity to parenchymal nodules.

Treatment

Managing berylliosis involves avoiding further exposure and therapy with glucocorticoids or other immunosuppressive agents. A decision to intervene depends on the severity of symptoms, physiologic impairment based on pulmonary function tests, and extent of radiographic changes. Treatment is usually started when the patient has dyspnea or cough, >10% decline in lung volumes or gas exchange, or abnormal pulmonary function tests at baseline.

Small case series have demonstrated efficacy of steroids judged by improvement of clinical symptoms, radiographic clearing of disease, and improvement in pulmonary functions, including diffusion capacity. Some patients despite improved symptoms have recurrence which may progress to fibrosis and persistent lung disease.

The differentiation between berylliosis and sarcoidosis appears to be important for long-term outcomes. It appears that the longer the delay in prescribing GCSs to patients with berylliosis may lead to a state where the lung disease is unresponsive to therapy. In contrast, use of steroids in sarcoidosis may lead to a higher rate of recurrent disease. What makes the 2 responses different is not known.

Dosing of steroids is similar to sarcoid with a starting dose of 0.5 mg/kg/day of prednisone for a duration of 6-12 wk. Once a response is established, conversion to every-other-day corticosteroid use at the same dose followed by tapering should be attempted until the lowest dose is achieved that controls the disease. Patients may require persistent therapy for the rest of their life. Genetic susceptibility to the disease may predict relapse of disease. Mutations in the HLA-DPB1 gene (homozygous for glutamate substitution at the β69 position) appear to predict specific patients who are susceptible to relapse of symptoms.

When patients fail to respond or experience recurrent relapse, methotrexate in low dose has conferred a favorable response in some patients as has been seen with sarcoidosis. Azathioprine may also be considered since sarcoidosis has responded favorably, however there are no published trials using this immunosuppressive agent. A small number of cases have also shown promise with TNF-α inhibitors both in sarcoid and beryllium-induced disease.

Granulomatous Lung Disease in Primary Immune Deficiency

Primary immune deficiency (PID) often presents with recurrent or persistent pulmonary symptoms of recurrent infections, pneumonia, bronchiectasis, and ILD with or without fibrosis. Immune dysregulation occurs in many of the PIDs with the development of granulomatous lung disease and autoimmune disease. Most effort is focused on the discovery of infectious pathogens in the PID causing pulmonary disturbance, but immune dysregulation may be the primary problem causing symptoms and disease progression. This requires counterintuitive therapies with suppression of the immune system concurrently with immune deficiency therapy. The 2 most prominent PIDs associated with granulomatous lung disease are **chronic granulomatous disease** (see Chapter 156) and **common variable immune deficiency** (see Chapter 150).

The prototype organism causing granuloma formation in the lung is *Mycobacterium tuberculosis* . Nontuberculous mycobacterial infections also can cause granulomas in the presence of specific PID. These have been seen in impaired IL-12/IL-23/ IFN-γ signaling, or the presence of **autoantibodies to**

IFN-γ . Patients with defective regulation of nuclear factor-kappa B (**nuclear factor-kappa B essential modifier defects**) have also been described as well with nontuberculous mycobacteria. The clinician must be certain that this low-virulence organism is not causing disease before therapy for immune dysregulation is considered.

Pathogenesis

CGD is a PID involving multiple defects in the phagocyte nicotinamide adenine dinucleotide phosphate oxidase system, which impairs the respiratory burst capacity to generate reactive species of oxygen (see Chapter 156).

Up to 25% of patients with **CVID** develop lung disease (see Chapter 150). These pulmonary changes include organizing pneumonia, ILD, mucosa-associated lymphoid tissue lymphoma, and noncaseating granulomas in granulomatous and lymphocytic interstitial lung disease (GLILD). Elevated levels of TNF from TNF polymorphisms have been implicated as a possible mechanism. GLILD is becoming recognized more frequently in CVID. It is defined by the presence of granulomatous and a lymphocytic proliferative pattern in the lung. Granulomas may be found in other organs including bone marrow, spleen, gastrointestinal tract, skin, and liver.

The etiology of GLILD is unknown. In a case cohort study, a majority of subjects with pathology diagnostic of GLILD were found to have human herpesvirus 8 infection of the lung. These may represent a subgroup of patients with GLILD which may point to a mechanism underlying the development of pulmonary granulomas.

GLILD is sometimes misdiagnosed as sarcoidosis initially because both involve pulmonary granuloma, often accompanied by hilar and/or mediastinal lymphadenopathy. Sarcoidosis has several features that distinguish it from GLILD, such as normal or elevated serum immunoglobulin levels and frequent spontaneous remissions.

Clinical Manifestations of Granulomatous Lung Disease in Primary Immune Deficiency

Chronic respiratory disease as a result of recurrent infections is common in CGD. This is accompanied by clubbing in some patients and the other organ manifestations in the skin, liver, and genitourinary and gastrointestinal tracts.

Granulomas are especially problematic in the gastrointestinal and genitourinary tracts. The inhalation of fungal spores and hyphae has led to acute pneumonia in CGD with rapid progression to respiratory failure with hypoxemia, dyspnea, and fever. This entity, characterized as *mulch pneumonia*, appears to be best treated with antifungal medications and corticosteroids.

Radiography

Hilar and/or mediastinal lymphadenopathy occur with granulomatous lung involvement. These may manifest as parenchymal nodules and/or ground-glass abnormalities and can be seen commonly in CVID and CGD. Differentiating infectious causes of pulmonary infiltration in PID is often difficult on chest radiography; HRCT is often mandatory in the initial evaluation of the patients with CVID.

Laboratory and Pulmonary Function Testing

Definitive diagnosis is made by lung biopsy. Transbronchial biopsy in children is often insufficient and lung biopsy by video-assisted thoracoscopy or open biopsy is preferred. Unless the patient's underlying immune deficiency is unknown, other laboratory testing except for infectious organisms does not contribute significantly to the diagnosis. When the child is old enough, complete pulmonary functions with spirometry, flow volume loop, lung volumes, and diffusion capacity should be obtained at baseline and then followed serially for response to therapy or progression of disease.

Therapy

The presence of GLILD in CVID can be associated with significant morbidity and possibly death. Without therapy, progressive pulmonary fibrosis and respiratory failure may occur in GLILD. The parenchymal disease may not always be controlled or relieved by glucocorticoid treatment. Other treatments include TNF antagonists, cyclosporine, or a combination therapy with rituximab and azathioprine. Response to therapy is monitored clinically and by interval HRCT of the chest, and pulmonary function testing, including spirometry, lung volumes, and diffusing capacity.

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427.4

Eosinophilic Lung Disease

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Keywords

AEP
ABPA
EGPA
HES

The eosinophilic lung diseases are a group of heterogeneous pulmonary disorders with a predominant diffuse infiltration of eosinophils in the alveolar spaces or interstitial pulmonary spaces. Lung architecture is well preserved throughout the inflammatory response, often with complete reversal of the inflammation without long-term sequelae in the majority of cases. The peripheral white blood count often (but not always) reveals elevated eosinophils. Prompt recognition of the nature of these diseases allows for lifesaving interventions in the idiopathic **acute eosinophilic pneumonia (AEP) syndrome** or resolution of persistent symptoms in the patients with chronic disease.

Etiology

Eosinophilic lung diseases are often classified under 2 subheadings: idiopathic disease and known causation (Tables 427.8 –427.10). They are frequently further subdivided as acute and chronic or infectious and noninfectious. The division of acute or chronic is arbitrary based on the length of symptoms present but is relevant to the clinician in determining the etiology of the symptoms in the differential diagnosis (Table 427.11). Löffler eosinophilic pneumonia, induced by *Ascaris lumbricoides* and other ascarids, produces transient symptoms that self-resolve and is classified as neither acute nor chronic. Löffler syndrome has been more correctly termed **pulmonary infiltrates with eosinophilia syndrome** and is the most common eosinophilic infiltrative disease in children.

Table 427.8

Key Elements in the Medical History and Physical Exam to Raise Clinical Suspicion for Diagnostic Testing to Confirm Eosinophilic Lung Disease

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Medical history and examination

- Drug exposure (especially antibiotics, NSAIDs, antiepileptics, antileukotriene modifiers in EGPA) (see Table 478.10)
- Environmental inhalation exposures to dust or inhaled chemicals
- New onset of smoking cigarettes
- Travel or immigration status from areas endemic with various parasites or coccidioidomycosis
- Asthma (may be severe or poorly controlled with ABPA, CSS, or is relatively new in onset with IAEP)
- ABPA concurrent in 7–10% of patients with cystic fibrosis
- Extrapulmonary symptoms suggestive of vasculitis, neuropathy, heart failure, or neoplasm
- Rash (creeping eruption in visceral larval migrans disease or ulceration in EGPA)

Diagnostic imaging and testing

- Radiography helpful in AEP, CEP, and ABPA
- Radiography not diagnostic in EGPA or drug-induced eosinophilic disease of the lung
- Simple chest radiography findings
- Nonlobar infiltrate
- Classic description as mirror image of pulmonary edema with peripheral infiltrates
- Bilateral pleural effusion in AEP
- Central bronchiectasis in ABPA
- High-resolution computerized tomography of the chest
- Middle and upper lobe nonlobar infiltrates with areas of ground-glass appearance
- Mucous plugging in ABPA
- Central bronchiectasis in ABPA (confused with cystic fibrosis)
- Blood eosinophil count
- Elevated in many eosinophilic lung diseases
- Magnitude of eosinophil blood count does not distinguish different pulmonary diseases
- Usually not elevated in AEP (eosinophilic disease compartmentalized to lungs)
- May occasionally not be elevated in CEP or after use of corticosteroids
- Total serum IgE elevated in ABPA but not always in patients with cystic fibrosis with ABPA
- Serology for helminthic infections or parasites may be diagnostic but are usually not available acutely
- P-ANCA (MPO ANCA) is positive in 40–70% of EGPA (CSS)
- BAL eosinophil percentage
- ≥25% eosinophils diagnostic in AEP
- ≥40% eosinophils diagnostic in CEP or tropical pulmonary eosinophilia
- Eosinophil percentages below these criteria may require lung biopsy
- <25% eosinophils seen in connective tissue disease, sarcoid, drug-induced disease, histiocytosis X of pulmonary Langerhans cells, and interstitial pulmonary fibrosis
- Lung biopsy
- Open lung biopsy or video-assisted thoracoscopic surgery when BAL nondiagnostic
- Transbronchial biopsy is usually insufficient with peripheral infiltrative disease
- Histology with alveolar and interstitial infiltrates of eosinophils, non-necrotizing non-granulomatous vasculitis, multinucleated giant cells without granuloma

- EGPA shows eosinophil rich small to medium vessel, necrotizing, granulomatous vasculitis

ABPA , Allergic bronchopulmonary aspergillosis; *AEP* , acute eosinophilic pneumonia; *BAL* , bronchoalveolar lavage; *CEP* , chronic eosinophilic pneumonia; *CSS* , Churg-Strauss syndrome; *EGPA* , eosinophilic granulomatosis with polyangiitis; *IAEP* , idiopathic acute eosinophilic pneumonia; *MPO ANCA* , myeloperoxidase antineutrophil cytoplasmic antibody; *NSAID* , nonsteroidal antiinflammatory drug; *P-ANCA* , perinuclear antineutrophil cytoplasmic antibody.

Table 427.9

Classification of the Eosinophilic Pneumonias in Clinical Practice

Eosinophilic pneumonias of unknown cause
Solitary idiopathic eosinophilic pneumonias
  Idiopathic chronic eosinophilic pneumonia
  Idiopathic acute eosinophilic pneumonia
Eosinophilic pneumonia in systemic syndromes
  Eosinophilic granulomatosis with polyangiitis
  Idiopathic hypereosinophilic syndromes (lymphocytic or myeloproliferative variant)
Eosinophilic pneumonias of known cause
Allergic bronchopulmonary aspergillosis and related syndromes (including bronchocentric granulomatosis)
Eosinophilic pneumonias of parasitic origin
Eosinophilic pneumonias of other infectious causes
Drug-induced eosinophilic pneumonias
Eosinophilic airways diseases
Eosinophilic asthma
Hypereosinophilic asthma
Idiopathic hypereosinophilic constrictive bronchitis
Other pulmonary syndromes with possible usually mild eosinophilia
Organizing pneumonia, asthma, idiopathic pulmonary fibrosis, Langerhans cell histiocytosis, malignancies, and so forth

From Cottin V: Eosinophilic lung diseases, *Clin Chest Med* 37:535–556, 2016 (Box 1, p. 536).

Table 427.10

Drugs Commonly Causing Eosinophilic Pneumonia

Antiinflammatory drugs and related drugs: acetylsalicylic acid, diclofenac, ibuprofen, naproxen, phenylbutazone, piroxicam, sulindac, and tolfenamic acid

Antibiotics: ethambutol, fenbufen, minocycline, nitrofurantoin, penicillins, pyrimethamine, sulfamides, sulfonamides, and trimethoprim-sulfamethoxazole

Other drugs: captopril, carbamazepine, and GM-CSF

A more extensive list of drugs reported to cause eosinophilic pneumonia may be found at www.pneumotox.com .

From Cottin V, Cordier JF: Eosinophilic lung diseases, *Immunol Allergy Clin*

North Am 32(4):557–586, 2012 (Box 6, p. 575).

Table 427.11

Diagnostic Criteria for Idiopathic Chronic Eosinophilic Pneumonia and for Idiopathic Acute Eosinophilic Pneumonia

IDIOPATHIC CHRONIC EOSINOPHILIC PNEUMONIA

1. Diffuse pulmonary alveolar consolidation with air bronchogram and/or ground-glass opacities at chest imaging, especially with peripheral predominance.
2. Eosinophilia at bronchoalveolar lavage differential cell count ≥ 40% (or peripheral blood eosinophils ≥ 1,000/mm^3).
3. Respiratory symptoms present for at least 2 to 4 wk.
4. Absence of other known causes of eosinophilic lung disease (especially exposure to drug susceptible to induce pulmonary eosinophilia).

IDIOPATHIC ACUTE EOSINOPHILIC PNEUMONIA

1. Acute onset with febrile respiratory manifestations (≤1 mo, and especially ≤ 7 days duration before medical examination).
2. Bilateral diffuse infiltrates on imaging.
3. PaO_2 on room air ≤ 60 mm Hg (8 kPa), or $\text{PaO}_2/\text{FIO}_2$ ≤ 300 mm Hg (40 kPa), or oxygen saturation on room ai < 90%.
4. Lung eosinophilia, with ≥ 25% eosinophils at BAL differential cell count (or eosinophilic pneumonia at lung biopsy when done).
5. Absence of determined cause of acute eosinophilic pneumonia (including infection or exposure to drugs known to induce pulmonary eosinophilia). Recent onset of tobacco smoking or exposure to inhaled dusts may be present.

BAL , Bronchoalveolar lavage.

From Cottin V: Eosinophilic lung diseases, *Clin Chest Med* 37:535–556, 2016 (Box 2, p. 538).

Pathology and Pathogenesis

Eosinophilic lung disease, regardless of the stage of disease or etiology, shows mixed cellular infiltration of the alveoli and interstitial spaces with a predominance of eosinophils when transbronchial biopsy or open lung biopsy is performed. This may be accompanied by a fibrinous exudate with intact lung architecture. Other findings include eosinophilic microabscesses, a nonnecrotizing nongranulomatous vasculitis, and occasional multinucleated giant cells again without granuloma formation. BAL is the diagnostic procedure of choice, especially with the acute types of eosinophilic pneumonia where peripheral eosinophilia is often absent; the differential cell count on the BAL is ≥

25% eosinophils and is often more than 40%. This highly sensitive and specific test has allowed clinicians to forego lung biopsy.

Eosinophils are filled with numerous toxic granules. Evidence of eosinophil degranulation may be found by electron microscopy, biopsy, urine excretion, and BAL fluid. Most commonly, eosinophil-derived neurotoxin, leukotriene E_4 , other granule proteins, such as major basic protein, Charcot Leyden crystals, or proinflammatory cytokines, are identified and support the evidence that eosinophils are not only present but contributing to the disease process.

Clinical Manifestations

Specific eosinophilic lung diseases present with a variable clinical picture; however, there are some common findings across many of the eosinophilic diseases. Dyspnea is the most common and prevalent symptom in patients with acute or chronic eosinophilic pneumonia and is accompanied by cough in the majority of patients (90%). Rhinitis and sinusitis symptoms are of lower prevalence with wide variability in children with eosinophilic pulmonary disease. **Acute eosinophilic pneumonia** often presents with respiratory failure and the requirement for mechanical ventilation at high levels of positive end expiratory pressure and high concentrations of oxygen, whereas chronic eosinophilic pneumonia has a more indolent presentation (see Table 427.11). Although malignancy (e.g., eosinophilic leukemia) and organizing pneumonia may present with need for mechanical ventilation, they are less common. A history of asthma is common in the chronic eosinophilic pneumonias and in allergic bronchopulmonary aspergillosis (**ABPA**); it often precedes the diagnosis of these 2 conditions.

Other symptoms of fever, myalgia, fatigue, weight loss, poor appetite, and night sweats may accompany the acute or chronic eosinophilic pneumonias. When abnormalities of the liver are detected, or if arthralgia, skin changes, pericardial effusion, or peripheral neuropathy accompany the disease presentation, a diagnosis of **eosinophilic granulomatosis with polyangiitis (EGPA)** (formerly known as the Churg-Strauss syndrome) or the **hypereosinophilic syndrome** (HES) should be aggressively investigated.

Chest Imaging

The chest radiograph is one of the most helpful tests for evaluating the child with dyspnea. The characteristic feature of fluffy alveolar infiltrates in the peripheral lung field is classic (Fig. 427.5). The images may be easily recognizable by astute clinicians who have identified the etiology of the disease without eosinophil counts or BAL.

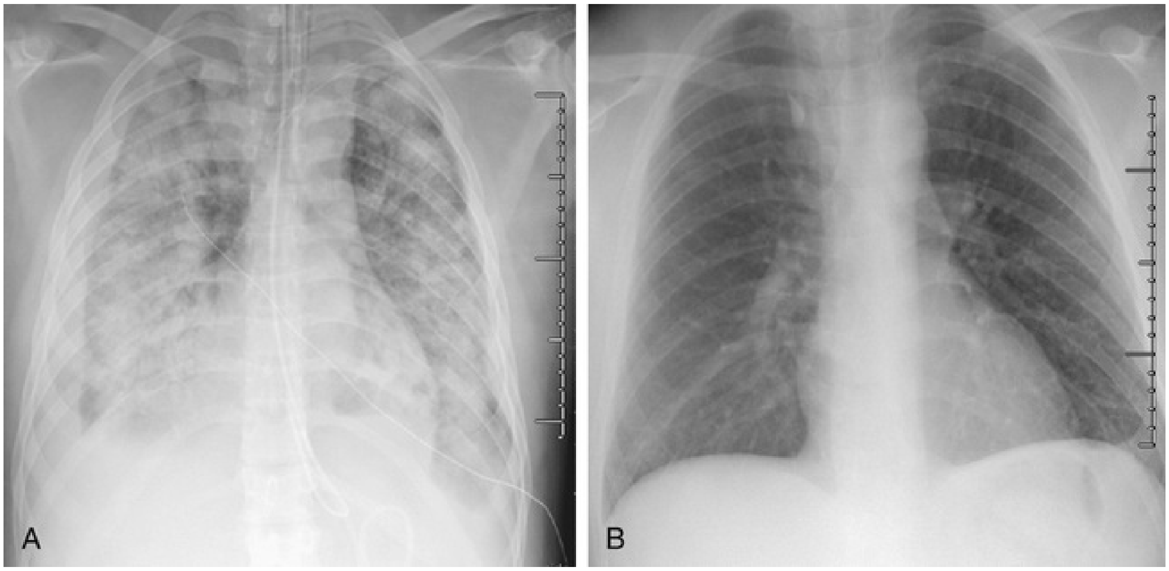

FIG. 427.5 Acute eosinophilic pneumonia demonstrating the mirror image **(A)** pulmonary edema with a right pleural effusion on admission and **(B)** complete clearing upon discharge from the hospital after corticosteroid usage.

HRCT is the best advanced imaging modality for eosinophilic lung disease. Spontaneous migration of lung opacities is commonly seen in the chronic pneumonias. Most often HRCT shows simultaneous evidence of bilateral alveolar infiltrates with both confluent consolidations and ground-glass appearance. The most prominent areas of abnormality are visualized in the upper lobes and subpleural regions. Specific diseases have unique findings, such as *proximal bronchiectasis* in **ABPA** and pleural effusion in acute eosinophilic pneumonia. HRCT is most sensitive in identifying the correct etiology of disease when chest radiographic findings are nonspecific.

Löffler Syndrome

The **transient pulmonary infiltrates with eosinophilia syndrome** that is most often seen in children (formerly known as Löffler syndrome) is characterized by migrating pulmonary infiltrates with peripheral blood eosinophilia caused by the helminthic infections. *A. lumbricoides* or roundworm is the most common parasite causing this disease in the United States. When a fertilized egg is ingested from contaminated food, it becomes a larval worm that can penetrate the duodenum of the small intestine and migrate in the circulation to the liver, heart, and lungs. In the pulmonary venous circulation, the larvae can break through the interstitial space to the alveoli. The juvenile larva may subsequently migrate to the trachea where they are coughed up and swallowed. The cycle may then recur with subsequent absorption of eggs that are produced in the intestinal track. Other nematodes cannot mature in the intestinal tract so their disease is limited to a single passage into the lungs.

Visceral larva migrans from multiple nematodes may cause this disease. The most common cause of these includes the dog roundworm, *Toxocara canis* , while *Toxocara cati, Strongyloides stercoralis, Baylisascaris procyonis,* and *Lagochilascaris minor* can all produce visceral larva migrans. Outside the United States, the common lung fluke, *Paragonimus westermani* , may cause a similar pulmonary disease in older children and adolescents. Western Africa, Central and South America, and the Far East are regions that paragonimiasis may be found, especially in those who eat raw crabs or crawfish. Many other parasites may have a transient pulmonary syndrome, but their diseases are most commonly manifested in other organs.

The pulmonary syndrome is classic with cough, dyspnea, migratory peripheral pulmonary infiltrates, and blood eosinophilia that is self-limited. Young children most often have a history of pica and eating dirt that is contaminated with the eggs. Because the larva can migrate to other organs as well as multiply in the intestinal and biliary tract, symptoms of abdominal pain, vomiting, rarely obstruction, cholecystitis, and pancreatitis may be found. Diagnosis is frequently made by examination of the stool where the eggs may be detected microscopically. Treatment is aimed at the intestinal disease and not the pulmonary disease per se. It is possible that anthelminthic treatment of other organ disease during the pulmonary phase of the disease will increase the inflammatory response in the lung and may require corticosteroid therapy.

Acute Eosinophilic Pneumonia

A unique and dramatic presentation of the eosinophilic pneumonias is **AEP** (see Table 427.11). AEP mimics infectious pneumonia or acute respiratory distress syndrome with its rapid onset and marked hypoxemia. In pediatrics, this disease most frequently occurs in the teenage population. Overall, young adults most commonly contract this idiopathic disease. Essentially all patients present within 7 days of symptom onset with dyspnea, fever, and cough, and more than 50% have chest pain. Myalgia and abdominal pain also frequently accompany this disease. Rarely, patients have presented up to 4-5 wk after onset of symptoms. Physical exam demonstrates tachypnea, tachycardia, and crackles in the lung fields on physical exam. Many patients rapidly deteriorate and require mechanical ventilation.

There is an *absence* of circulating eosinophilia, which contrasts the dramatic number of eosinophils seen in the BAL representing at least 25% of the inflammatory cells (often 40–55%) (Fig. 427.6). This feature helps distinguish it from the chronic pulmonary disease of eosinophilic origin.

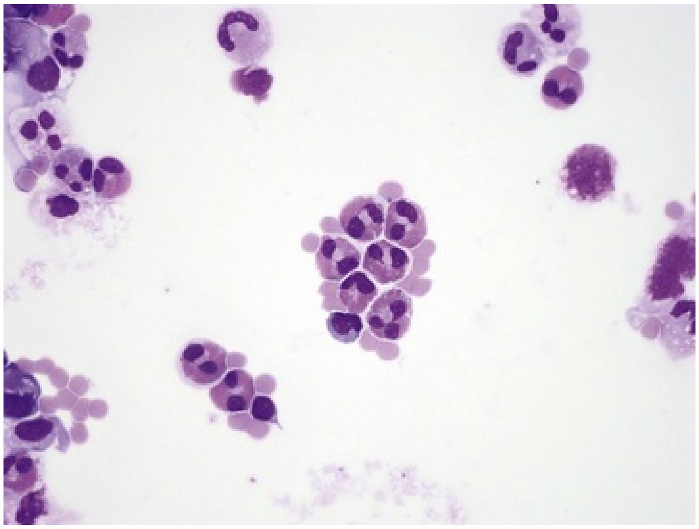

FIG. 427.6 Light microscopy of eosinophils in bronchoalveolar lavage fluid.

Although this disease has been labeled as idiopathic, there have been identifiable exposures (e.g., 1,1,1-trichloroethane or Scotchgard). Numerous reports link the onset of smoking tobacco, change in smoking frequency, reinitiation of smoking in young male adolescents or adults, and even massive secondary smoke exposure as critical associations with onset of AEP. World Trade Center dust is associated with development of AEP. A single smoke challenge study is associated with recurrence. Some medications are also linked to the onset of AEP. The most complete and current resource for medications linked to pulmonary disease is “The Drug-Induced Respiratory Disease Website” (http://www.pneumotox.com). When AEP is identified in a patient, the pediatrician should educate the patient and family about the link to smoking exposure and risk of AEP upon reexposure.

In addition to smoke exposure, AEP has been reported after smoking cocaine; typically, within hours to days after use. Whether this is a unique eosinophilic response to cocaine that represents 1 manifestation of *crack lung* or is a separate disease is unknown. Crack lung refers to diffuse alveolitis with pulmonary hemorrhage from an unknown mechanism that occurs within 48 hr of cocaine smoke inhalation.

Lung function has not been measured frequently in the disease because the patients have proceeded rapidly to the ICU and need for mechanical ventilation. When measured, a restrictive pattern of lung disease and reduced diffusion capacity is the usual finding. Arterial blood gases will also show a significant increase in the alveolar–arterial gradient.

The criteria for diagnosis include the acute onset of disease, bilateral pulmonary infiltrates, reduced oxygen saturation or $Pa_{O_2} \leq 60$ mm Hg, BAL of ≥ 25%, and absence of a determined cause of eosinophilia (see Table 427.11). The recent onset of tobacco exposure, dust, or chemical inhalation are supporting factors in confirming a diagnosis.

Treatment has uniformly been the use of a corticosteroid (e.g., methylprednisolone 1-2 mg/kg/day) either intravenously or orally for 2-4 wk. A minimum or maximum treatment time has not been determined. Rare fatalities have been reported. Complete recovery has been seen in days with resolution of pleural effusions within the 4 wk treatment time. Most important, relapse and persistent symptoms are rare, which sharply contrasts the idiopathic chronic eosinophilic pneumonias. Follow-up testing of pulmonary function is usually normal which supports the contention that lung parenchyma heals without evidence of compromise or fibrosis.

Chronic Eosinophilic Pneumonia

Chronic eosinophilic pneumonia is another idiopathic pulmonary condition without a known exposure to toxin, dust, or chemical inhalation. Eosinophils infiltrate the lung parenchyma resulting in dyspnea, cough, fever, and weight loss. It is primarily a problem for adults, with a female predominance (2 : 1

female:male ratio) usually in patients who are nonsmokers. Chest examination reveals tachypnea, crackles, and occasional wheezing as preceding asthma is a common finding. The classic finding on chest x-ray of the *radiographic negative of pulmonary edema* is found in these patients: central clear lung fields but fluffy, patchy peripheral infiltrates of the lung parenchyma.

When compared to AEP, the onset of disease is indolent and subtle, but the accompanying fever and weight loss may lead the clinician to a concern for an underlying malignancy prior to chest radiograph and laboratory investigation. *Peripheral* blood eosinophilia is commonly as high as 5,000/mm^3 or greater, accompanied by BAL eosinophilia >40% on the differential count (see Table 427.11). The peripheral eosinophilia sharply contrasts the lack of eosinophils seen in the blood in AEP. HRCT scan contrasts the AEP with pleural effusion as a rare finding, as well as rare cavitation.

In contrast to AEP, pulmonary function testing shows a mixed obstructive and restrictive pattern when asthma occurs concurrently with pneumonia.

Inflammatory markers associated with migration and activation of eosinophils are predictably found in BAL and the urine. These include the T-lymphocyte type 2 cytokines of IL-4, IL-5, IL-6, IL-10, IL-13, and IL-18. However, T-lymphocyte type 1 cytokines of IL-2 and IL-12 are also present with many of the potent eosinophilic chemoattractants such as CCL5 (RANTES [regulated upon activation, normal T cell expressed and secreted]) and CCL11 (eotaxin-1). Toxic granule proteins of major basic protein, eosinophil-derived neurotoxin, and eosinophil cationic protein are frequently present. Unfortunately, these important molecules help confirm the eosinophilic nature of the disease, but their presence adds no additional sensitivity or specificity over the presence of eosinophils on BAL.

Treatment is similar to most eosinophilic lung syndromes where corticosteroids (oral) are the mainstay of treatment. The minimum dose of steroid needed to induce remission is not known, but most clinicians recommend prednisone (or equivalent) at 0.5 mg/kg/day for 2 wk. The dose is reduced to half (0.025 mg/kg/day) for an additional 2 wk if symptoms have abated. The remaining dose of steroid may need to be weaned over 6 mo. Symptoms and pulmonary infiltrates rapidly disappear after initiation of this treatment but frequently recur with tapering of the steroid. Asthma concurrently in patients with chronic eosinophilic pneumonia identifies a phenotype of the disease that appears to have lower relapse risk yet up to 50% of all identified patients with chronic eosinophilic pneumonia relapse during or after corticosteroid taper.

Many believe that this disease is a precursor to the development of EGPA (formerly Churg-Strauss syndrome). The utility of ICS in chronic eosinophilic pneumonia is unknown but is warranted for the persistent asthma phenotype of disease. A subset of patients develops permanent lower airway obstruction without reversibility, which requires patients with this disease to have close follow-up and monitoring of pulmonary function tests routinely.

Eosinophilic Granulomatosis With Polyangiitis (the Churg-Strauss Syndrome)

The EGPA syndrome is a systemic disease involving multiple organs but most prominently the lung. Patients present with difficult to control asthma, allergic rhinitis, and peripheral eosinophilia (>10% or >1,500 cells/µL) in the blood. Evidence of vasculitis on clinical grounds must be present in at least 2 organs. The polyangiitis appears later in the disease process with asthma being the precursor symptom in more than 90% of the cases reported. EGPA affects multiple organs including the skin, heart, gastrointestinal tract, kidneys, and central nervous system (Table 427.12). Rhinitis is present in 75% of the patients but is not specific. Symptom complexes of fever, weight loss, fatigue, arthralgia, and myalgia may be seen in approximately two-thirds of patients. Cardiac and renal involvement is insidious in onset and should be screened for. It is the multiple organ involvement that results in the morbidity and mortality of this disease. The typical progression of the disease is in 3 phases: rhinitis and asthma first, tissue eosinophilia second, and, finally, systemic vasculitis.

Table 427.12

Eosinophilic Granulomatosis With Polyangiitis

	VASCULITIC PHENOTYPE	EOSINOPHILIC TISSULAR DISEASE PHENOTYPE
Respective frequency	~40%	~60%
ANCA	Present (mostly perinuclear-ANCA with anti-MPO specificity)	Absent
Predominant manifestations	Glomerular renal disease Peripheral neuropathy Purpura	Cardiac involvement (eosinophilic myocarditis) Eosinophilic pneumonia

	Biopsy-proven vasculitis	Fever

ANCA, Antineutrophil cytoplasmic antibody; *MPO* , myeloperoxidase.

Data from Sablé-Fourtassou R, Cohen P, Mahr A, et al: Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome, *Ann Intern Med* 2005;143:632–638; and Sinico RA, Di Toma L, Maggiore U, et al: Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome, *Arthritis Rheum* 2005;52:2926–2935.

From Cottin V, Cordier JF: Eosinophilic lung diseases, *Immunol Allergy Clin North Am* 32(4):557–586, 2012 (Table 2, p. 569).

The pathogenesis of EGPA is still unknown but several factors are suspected to contribute to the development of the disease. The possible link between leukotriene-receptor antagonists (zafirlukast, montelukast, or pranlukast) is controversial but still considered possible. It is suspected that use of this class of adjunctive medications in severe asthma allows for the reduction in use of corticosteroid leading to the full-blown (unmasking) manifestation of EGPA. Isolated use of leukotriene-receptor antagonists may induce disease, lead to remission with cessation of leukotriene-receptor antagonists, and cause recurrence of EGPA upon reintroduction of this class of medications. Many refrain from use of leukotriene-receptor antagonists when the EGPA syndrome has been diagnosed.

Clinical and laboratory findings pinpoint the diagnosis with high specificity (99.7%) and sensitivity (85%) when 4 of 6 criteria are met (asthma, eosinophilia >10%, mononeuropathy or polyneuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormalities, and biopsy findings of extravascular eosinophil infiltrates). In contrast to GPA, the rhinitis is not destructive and nasal septal perforation does not occur in EGPA.

Radiography of the chest by plain radiography or HRCT demonstrates the migratory, peripheral predominant opacities with ground-glass appearance to full consolidation. Bronchiectasis and bronchial wall thickening are reported. Pleural effusion should raise suspicion for the presence of heart failure from **cardiomyopathy** .

Laboratory findings include striking eosinophilia with values generally between 5,000 and 20,000/mm^3 at the time of diagnosis. These counts often parallel vasculitis activity. The BAL shows striking eosinophilia with differential counts of >60%. Other organ system levels reflect activity of eosinophils and are not specific for the EGPA diagnosis.

ANCAs may be present in the EGPA syndrome. The perinuclear-ANCA targeting myeloperoxidase is specifically found in EGPA in approximately 40%

of the patients; the absence of myeloperoxidase-ANCA does not exclude the diagnosis. Those patients with eosinophilic pneumonia, fever, and cardiac involvement are less likely to have myeloperoxidase-ANCA detected. Those with peripheral neuropathy, renal glomerular disease, and skin purpura usually have detectable myeloperoxidase-ANCAs (see Table 427.12).

Pulmonary function tests while on bronchodilators and ICS for asthma show an obstructive pattern. The pulmonary obstruction is responsive to oral corticosteroid use but often has mild persistence of obstruction.

Treatment of EGPA with systemic oral corticosteroid remains the mainstay of therapy at a starting dose of 1 mg/kg/day for 4 wk. This therapy is often required for up to 12 mo or longer with a steady taper in dosage over that time. EGPA resistant to corticosteroid has responded to cyclophosphamide, IFN-α, cyclosporine, intravenous immunoglobulin, and plasmapheresis. The use of anti–IL-5 (mepolizumab) has been encouraging and may be used as a steroid-sparing agent in the future.

Allergic Bronchopulmonary Aspergillosis

ABPA is a complex mixed immunologic hypersensitivity reaction in the lungs and bronchi in response to exposure and colonization of *Aspergillus* species (usually *Aspergillus fumigatus* ; see Chapter 264). This disease almost exclusively occurs in patients with preexisting asthma and up to 15% of patients with cystic fibrosis (see Chapter 432). The quantity of *Aspergillus* exposure does not correlate with the severity of disease.

The clinical pattern of disease (Table 427.13) is remarkably similar with a clinical presentation of difficult-to-treat asthma, periods of acute obstructive lung disease with bronchial mucous plugs, elevated total IgE antibody, elevated specific IgE and IgG anti-*Aspergillus* antibodies, skin prick test reactions to *Aspergillus* species, precipitating antibody to *Aspergillus* species, as well as proximal bronchiectasis. Other clinical manifestations include dyspnea, cough, shortness of breath, and peripheral eosinophilia, as well as pulmonary eosinophilia with infiltration of the parenchyma. The use of systemic corticosteroid may lower the total IgE antibody levels such that a diagnosis may be in question when the first tests are performed at that time.

Table 427.13

Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis–central bronchiectasis
• Medical history of asthma[*] • Immediate skin prick test reaction to *Aspergillus* antigens[*] • Precipitating (IgG) serum antibodies to *Aspergillus fumigatus* [*] • Total IgE concentration > 417 IU/mL (>1,000 ng/mL)[*] • Central bronchiectasis on chest CT[*] • Peripheral blood eosinophilia $>500/\text{mm}^3$ • Lung infiltrates on chest x-ray or chest HRCT • Elevated specific serum IgE and IgG to *A. fumigatus*
Allergic bronchopulmonary aspergillosis seropositive [†]
• Medical history of asthma [†] • Immediate skin prick test reaction to *A. fumigatus* antigens [†] • Precipitating (IgG) serum antibodies to *A. fumigatus* [†] • Total IgE concentration > 417 IU/mL (>1,000 ng/mL) [†]

[*] The criteria required for diagnosis of ABPA with central bronchiectasis.

[†] The first 4 criteria are required for a diagnosis of seropositive ABPA.

ABPA , Allergic bronchopulmonary aspergillosis; *CSD* , corticosteroid dependent; *HRCT* , high-resolution computerized tomography.

ABPA should be considered in patients with cystic fibrosis when clinical deterioration occurs without evidence of an identifiable cause. Symptoms heralding such deterioration include increasing cough, wheezing, loss of exercise tolerance, worsening exercise-induced asthma, reduction of pulmonary function, or increased sputum production without another discernible reason. Clinical findings of elevated total IgE antibody, anti-*Aspergillus* IgE, precipitating antibodies to *A. fumigatus* , and/or new abnormalities on chest radiography that fail to clear with antibiotics should alert the clinician to the possibility of ABPA.

When evaluating a child with asthma symptoms, the clinician must distinguish asthma from ABPA. If the diagnosis is suspected, skin prick test for evidence of IgE-specific antibody directed against *A. fumigatus* is essential. Intradermal skin testing when the skin prick test is negative, although not routinely performed because of poor specificity, may be performed. The absence of a positive skin prick test and intradermal test to *A. fumigatus* virtually excludes the diagnosis of ABPA. The prevalence of ABPA in patients with an existing diagnosis of asthma and an abnormal immediate skin prick test response to *A. fumigatus* has been evaluated. Between 2% and 32% of patients with asthma with concurrent skin prick test–positive reactions to *Aspergillus* have evidence of ABPA.

It is uncommon for the patient with cystic fibrosis to develop ABPA before the age of 6 yr. When the total IgE antibody in patients with cystic fibrosis exceeds 500 IU/mL (1,200 ng/mL), a strong clinical suspicion of ABPA is necessary.

ABPA pathology has characteristic findings of mucoid bronchi impaction, eosinophilic pneumonia, and bronchocentric granulomas in addition to the typical histologic features of asthma. Septated hyphae are often found in the mucus-filled bronchial tree. However, the fungi do not invade the mucosa in this unique disease. *Aspergillus* may be cultured from sputum in more than 60% of ABPA patients. Interestingly, hyphae may not always be seen on microscopy.

Staging of the disease (Table 427.14) represents distinct phases of the disease but do not necessarily progress in sequence from stage 1 to stage 5. Staging of ABPA is important for treatment considerations. In many hypersensitivity diseases where IgE antibody contributes to the pathogenesis (e.g., asthma), total IgE is often used for screening for an atopic state but is not a test that helps the clinician with serial measures. In sharp contrast, the measurement of IgE during acute exacerbations, remission, and recurrent ABPA disease is helpful in identifying the activity of disease and may herald the recurrence. During stage 1 disease, the level of IgE antibody is often very high. During stage 2 remission, a fall in the levels may be as much as 35% or more. Recurrence of activity may result in a marked rise of total IgE with a doubling of the baseline level seen during remission. During the use of glucocorticoid therapy, monthly or bimonthly levels of IgE are followed serially to assist the clinician in tapering therapy. Because exacerbations of ABPA are asymptomatic to the patient in approximately 25% of the recurrences, serial IgE accompanied by chest radiography are helpful to the clinician to guide therapy.

Table 427.14

Staging of Allergic Bronchopulmonary Aspergillosis

Staging of allergic bronchopulmonary aspergillosis			
Stage 1	Acute	Upper and middle lobe infiltration	High IgE
Stage 2	Remission	No infiltrate off steroids >6 mo	Normal to high IgE
Stage 3	Exacerbation	Upper and middle lobe infiltration	High IgE
Stage 4	CSD asthma	Minimal infiltrate	Normal to high IgE
Stage 5	End stage	Fibrosis and/or bullae	Normal

CSD , Corticosteroid dependent.

Radiography

Plain chest X-ray shows evidence of infiltrates especially in the upper lobes and the classic findings of bronchiectasis (Fig. 427.7). The use of HRCT demonstrates central bronchiectasis in the central regions of the lung (Fig. 427.8). HRCT may add value, for the patient with a positive skin prick test and normal chest radiograph, to detecting characteristic abnormalities of ABPA.

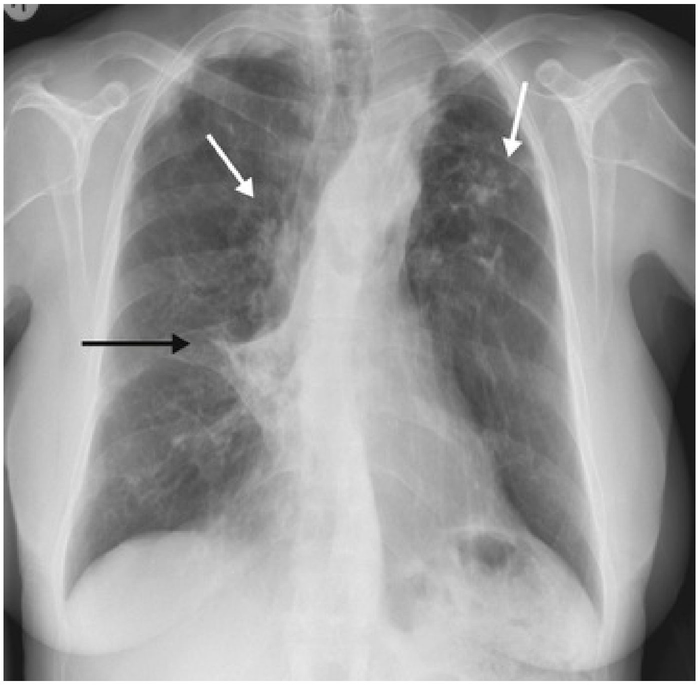

FIG. 427.7 Transitory opacities *(white arrows)* and lobar collapse *(black arrow)* in patient with allergic bronchopulmonary aspergillosis. (From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE: Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson AF, editor: *Middleton's allergy principles and practice* , Philadelphia, 2014, Elsevier, Fig. 61.2.)

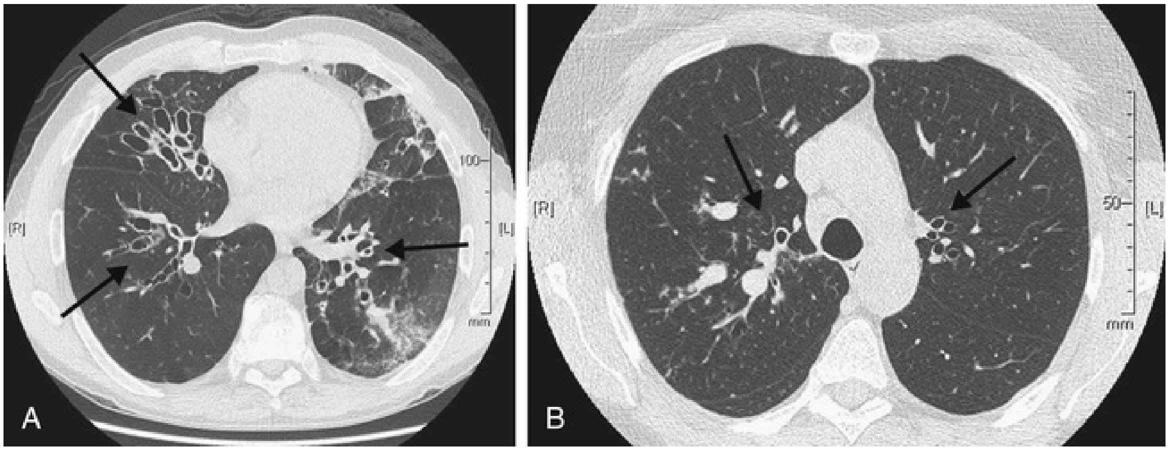

FIG. 427.8 **A,** Central bronchiectasis in patient with ABPA *(arrows).* **B,** Central bronchiectasis in the upper lobes *(arrows).* (From Douglass JA, Sandrini A, Holgate ST, O'Hehir RE: Allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis. In Adkinson AF, editor: *Middleton's allergy principles and practice* , Philadelphia, 2014, Elsevier, Fig. 61.3.)

Treatment

The mainstay of therapy for ABPA has been systemic glucocorticoids with adjunct therapy, antifungal medications, and anti-IgE therapy with omalizumab. Exacerbations in stages 1 and 3 are treated for 14 days with 0.5-1 mg/kg of glucocorticoid followed by every-other-day usage and tapering over 3 mo or as long as 6 mo. Stage 2 remission phase and stage 5 where fibrosis has occurred do not require glucocorticoid therapy. Stage 4 denotes a state where glucocorticoid weaning has not been successful and continued long-term therapy is required.

Antifungal therapy with a 16-wk course of itraconazole improves the response rate during exacerbations allowing the reduction of glucocorticoid dosage by 50% and resulting in a reduction of total serum IgE of 25% or more. The proposed mechanisms of action have been to either reduce the antigen load driving the immune response or possibly raising the corticosteroid serum levels by slowing the metabolism of the steroid. This latter mechanism would be true for prednisone, which is methylated in the liver, but not for methylprednisolone, which does not require methylation.

The adult dosage recommendation for itraconazole is 200 mg 3 times per day for 3 days followed by 200 mg twice daily for the remainder of the 16 wk. Children should receive 5 mg/kg/day in a single dose. If the proper calculated dose exceeds 200 mg, then the total dose should be divided equally and given twice daily. Serum levels of itraconazole are necessary to ensure proper absorption of the drug is occurring from the capsule form. The liquid form is more readily absorbed and has achieved substantially higher levels. The use of proton pump inhibitors and histamine 2 antagonists may reduce absorption by blocking acid production. Voriconazole has been used as a substitute antifungal medication. Proper dosing has been established for invasive *Aspergillus* disease, but not for ABPA. Typical dosage regimen in children of 7 mg/kg/day may cause hepatotoxicity so liver function must be monitored.

Omalizumab, an anti-IgE humanized monoclonal antibody, has been used in case series of patients with cystic fibrosis and ABPA as well as a small cohort of adults without cystic fibrosis but with ABPA. Both case series demonstrated significant reductions in asthma exacerbations, ABPA exacerbations, and glucocorticoid usage. The dose prescribed has been 300-375 mg every 2 wk by subcutaneous injection.

Hypereosinophilic Syndrome

See Chapter 155 .

The HES is a descriptive name of a group of disorders that are characterized by the persistent overproduction of eosinophils accompanied by eosinophil infiltration in multiple organs with end-organ damage from mediator release. The term HES should only be used when there is eosinophilia with end-organ damage from the eosinophils and not from another cause. The discovery of underlying genetic, biochemical, or neoplastic reasons for HES has led to the classification of primary, secondary, and idiopathic HES (Table 427.15). Specific syndromes such as EGPA have eosinophilia but the contribution of eosinophils to the organ damage is incompletely understood.

Table 427.15

Hypereosinophilic Syndrome Variants

Myeloproliferative	Nonclonal Clonal–F1P1L1/PDGFRA-positive chronic eosinophilic leukemia
Lymphocytic	Nonclonal T cells Clonal T-cell expansion with T-cell activation
Overlap	Organ restricted
Familial	Family history of eosinophilia without known cause

Associated	Eosinophilia in chronic disease like inflammatory bowel disease or EGPA (Churg-Strauss syndrome)
Undefined	Asymptomatic Cyclic angioedema with eosinophilia (Gleich syndrome) Symptomatic without myeloproliferation or lymphocytic form

EGPA , Eosinophilic granulomatosis with polyangiitis; *PDGFRA* , platelet-derived growth factor receptor-α.

Some variants of HES have genetic mutations in tyrosine kinase receptor platelet-derived growth factor receptor-α (*PDGFRA*); males are almost exclusively affected. Otherwise, HES appears to be distributed equally among females and males.

Hypereosinophilia is defined as an absolute eosinophil number in the blood that exceeds 1.5 × 10^9 eosinophils on 2 separate occasions separated by at least 1 mo. Tissues are abnormal when more than 20% of nucleated cells in the bone marrow are of eosinophil origin, a pathologist determines the presence of eosinophilia, or the presence of extensive eosinophilic granule proteins are determined on biopsy to be deposited in large quantities. These disorders can be subclassified into primary (neoplastic), secondary (reactive), and idiopathic (Fig. 427.9).

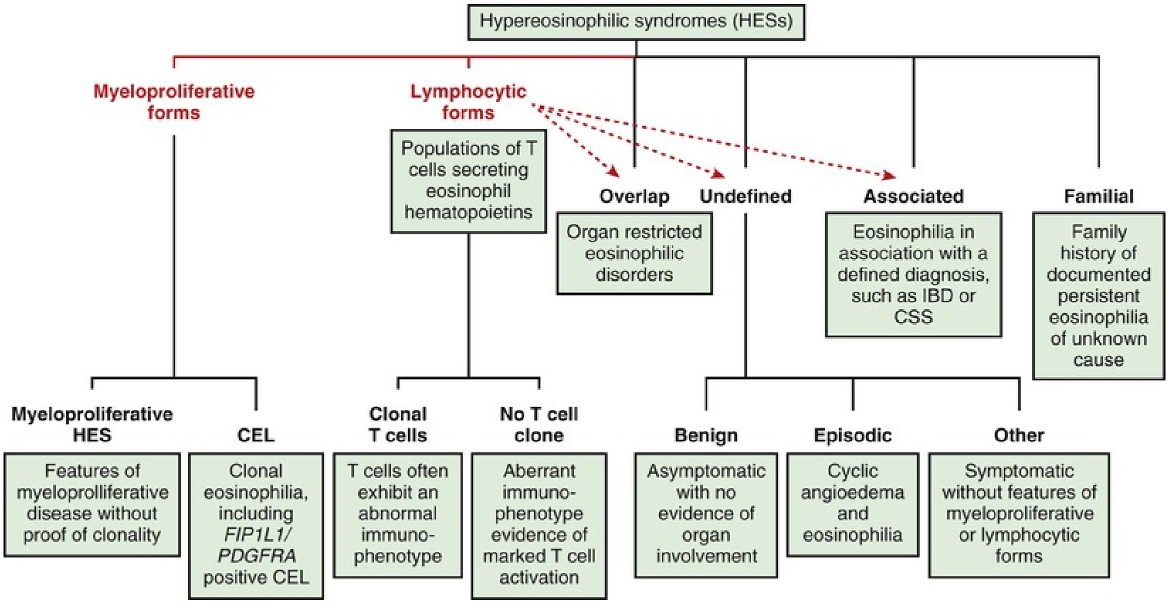
Hypereosinophilic syndromes (HESs)
Myeloproliferative forms
Lymphocytic forms
Populations of T cells secreting eosinophil hematopoietins
Overlap
Undefined
Associated
Familial
Organ restricted eosinophilic disorders
Eosinophilia in association with a defined diagnosis, such as IBD or CSS
Family history of documented persistent eosinophilia of unknown cause
Myeloproliferative HES
CEL
Clonal T cells
No T cell clone
Benign
Episodic
Other
Features of myeloprolliferative disease without proof of clonality
Clonal eosinophilia, including FIP1L1/ PDGFRA positive CEL
T cells often exhibit an abnormal immuno- phenotype
Aberrant immuno- phenotype evidence of marked T cell activation
Asymptomatic with no evidence of organ involvement
Cyclic angioedema and eosinophilia
Symptomatic without features of myeloproliferative or lymphocytic forms

FIG. 427.9 A revised classification of hypereosinophilic syndrome *(HES)* . Changes from the previous classification are indicated in red. *Dashed arrows* identify HES forms in some patients that have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin-producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES.

CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. (From Simon H, Rothenberg ME, Bochner BS, et al: Refining the definition of hypereosinophilic syndrome, *J Allergy Clin Immunol* 126:45–49, 2010, Fig. 1.)

Clinical manifestations of the HES include organ involvement of the heart (5%), gastrointestinal (14%), skin (37%), and pulmonary (25–63%). The HES is complicated by thrombosis and/or neurologic disease in many patients, although the exact prevalence of this problem is incompletely categorized. Peripheral neuropathy, encephalopathy, transverse sinus thrombosis, or cerebral emboli are the most common neurologic complications. The exact mechanism of the manifestations is unclear especially in major artery thrombosis such as the femoral artery.

The most frequent pulmonary symptoms include cough and dyspnea. Many patients have obstructive lung disease with clinical wheezing. Evidence of pulmonary fibrosis and pulmonary emboli are seen with regularity. Because biopsy shows eosinophilic infiltrates similar to other pulmonary eosinophilic diseases of the lung, it is the constellation of other organ involvement or thromboembolic phenomena and other organs that must lead the clinician to a high index of suspicion for the HES.

Laboratory evaluation should include evaluation of liver enzymes, kidney function tests, creatine kinase, and troponin. The extent of cardiac involvement should be evaluated by electrocardiogram and echocardiogram. Some unique biomarkers may be tested when evaluating the myeloproliferative and T-lymphocyte HES diagnoses. Vitamin B_{12} and serum tryptase may be elevated, especially the latter, when the myeloproliferative disease is accompanied by mastocytosis. These 2 biomarkers are most frequently elevated when the mutation is present or fusion in the FIP1L1/PDGFRA sites.

Because of the extensive pulmonary disease that is seen in the HES, pulmonary function tests should be performed at diagnosis when possible to include spirometry and lung volumes. Dead space ventilation may be significantly elevated in the patients with pulmonary emboli. Pulse oximetry may be very helpful in the evaluation as well.

Chest radiography and CT are very helpful in the evaluation. Spiral chest CT should also be performed when pulmonary emboli are being considered. In 1 series of patients, nearly half of the patients with HES had evidence of pulmonary abnormalities including ground-glass appearing infiltrates, pulmonary emboli, mediastinal lymphadenopathy, and/or pleural effusion.

Treatment of HES depends on the type of variant (myeloproliferative, lymphocytic forms, undefined, associated with systemic diseases such as EGPA, or familial). Rarely, some patients present with marked eosinophilia, where the total count exceeds 100,000 cells/μL, and vascular insufficiency symptoms. Prednisone at 15 mg/kg is indicated to acutely reduce the eosinophil count after diagnostic tests are performed and when safe. If the patient is unstable, the glucocorticoid should be administered to prevent progression of symptoms. Other acute therapies aimed at reduction of eosinophil counts include vincristine, imatinib mesylate, or even leukophoresis.

When eosinophil counts are not as dramatically elevated, therapy begins with glucocorticoids at 1 mg/kg for patients who do not have the FIP1L1/PDGFRA mutation. Patients with this mutation are resistant to glucocorticoids and initial treatment should begin with imatinib, a tyrosine kinase inhibitor. Because this genetic test is often not readily available, surrogate markers for the presence of this mutation are vitamin B_{12} levels > 2,000 pg/mL or serum tryptase >11.5 ng/mL. It denotes the presence of resistant disease that should initially be treated with imatinib. The goal of therapy is to reduce and maintain eosinophil counts below 1.5×10^9 at the lowest dose of prednisone possible to reduce or avoid corticosteroid side effects. If corticosteroid doses cannot be lowered below 10 mg/day, then imatinib can be added as combination therapy in order to spare the dose of steroid. Caution must be used in the presence of cardiac disease as introduction of imatinib has precipitated left ventricular failure.

Additional or alternative adjunct therapies that have shown promise include hydroxyurea, interferon α, anti–IL-5 monoclonal antibody therapy, and a monoclonal antibody directed against CD52. Failure of the above modalities may signal a need for hematopoietic stem cell transplantation. This therapy has been successful in some patients.

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427.5

Interstitial Lung Disease

Kevin J. Kelly, Timothy J. Vece

Keywords

ILD
anti-GBM disease
DSM
NEHI

ILD in children is caused by a large group of rare, heterogeneous, familial, or sporadic diseases that involve the pulmonary parenchyma and cause significant impairment of gas exchange (Tables 427.16 and 427.17). While there are some shared diseases, ILD in children is often different than ILD in adults, especially notable for the absence of idiopathic pulmonary fibrosis in children. Despite wide variations in cause, these disorders are classified together because of the similar clinical, physiologic, radiographic, and pathologic processes involving disruption of alveolar interstitium and airways. Prevalence estimates vary widely with a range of 0.13-16.2 cases/100,000 children, likely due to the lack of standardization of diseases included in the definition of ILD in children. The pathophysiology is believed to be more complex than that of adult disease because pulmonary injury occurs during the process of lung growth and differentiation. In ILD, the initial injury causes damage to the alveolar epithelium and capillary endothelium. Abnormal healing of injured tissue may be more prominent than inflammation in the initial steps of the development of chronic ILD. Genetic causes of ILD are becoming increasingly important, especially disorders of surfactant metabolism (DSM) and immune dysregulatory disorders.

Table 427.16

The Pediatric Interstitial Lung Diseases in Children Under 2 Yr of Age

AGE-RELATED INTERSTITIAL LUNG DISEASES IN INFANCY AND EARLY CHILDHOOD	
Diffuse developmental disorders	
	Acinar dysplasia
	Congenital alveolar dysplasia
	Alveolar capillary dysplasia with misalignment of pulmonary veins (some due to *FOXF1* mutation)
Growth abnormalities reflecting deficient alveolarization	
	Pulmonary hypoplasia
	Chronic neonatal lung disease
	Chromosomal disorders
	Congenital heart disease
Neuroendocrine cell hyperplasia of infancy	
	Pulmonary interstitial glycogenosis (infantile cellular interstitial pneumonia)
	Surfactant dysfunction disorders (pulmonary alveolar proteinosis)
	Surfactant protein–B mutation
	Surfactant protein–C mutation
	ABCA3 mutation
	Granulocyte-macrophage colony-stimulating factor receptor (*CSF2RA*) mutation
	NKX2.1 (transcription factor for SP-B, SPC, ABCA3)
INTERSTITIAL LUNG DISEASE DISORDERS WITH KNOWN ASSOCIATIONS	
Infectious/postinfectious processes	
	Adenovirus viruses
	Influenza viruses
	Chlamydia pneumoniae
	Mycoplasma pneumoniae
Environmental agents	
	Hypersensitivity pneumonitis
	Toxic inhalation
Aspiration syndromes	
PULMONARY DISEASES ASSOCIATED WITH PRIMARY AND SECONDARY IMMUNE	

DEFICIENCY
Opportunistic infections
Granulomatous lymphocytic interstitial lung disease associated with common variable immunodeficiency syndrome
Lymphoid intestinal pneumonia (HIV infection)
Therapeutic interventions: chemotherapy, radiation, transplantation, and rejection
IDIOPATHIC INTERSTITIAL LUNG DISEASES
Usual interstitial pneumonitis
Desquamative interstitial pneumonitis
Lymphocytic interstitial pneumonitis and related disorders
Nonspecific interstitial pneumonitis (cellular/fibrotic)
Eosinophilic pneumonia
Bronchiolitis obliterans syndrome
Pulmonary hemosiderosis and acute idiopathic pulmonary hemorrhage of infancy
Pulmonary alveolar proteinosis
Pulmonary vascular disorders
Pulmonary lymphatic disorders
Pulmonary microlithiasis
Persistent tachypnea of infancy
Brain-thyroid-lung syndrome
SYSTEMIC DISORDERS WITH PULMONARY MANIFESTATIONS
Anti-GBM disease
Gaucher disease and other storage diseases
Malignant infiltrates
Hemophagocytic lymphohistiocytosis
Langerhans cell histiocytosis
Sarcoidosis
Systemic sclerosis
Polymyositis/dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Lymphangioleiomyomatosis
Pulmonary hemangiomatosis
Neurocutaneous syndromes
Hermansky-Pudlak syndrome

Modified from Deutsch GH, Young LR, Deterding RR, et al: diffuse lung disease in young children: application of a novel classification scheme, *Am J Respir Crit Care Med* 176:1120–1128, 2007.

Table 427.17

The Pediatric Interstitial Lung Diseases in Children Over 2 Yr of Age

DISORDERS OF THE IMMUNOCOMPETENT HOST
Disorders of Infancy
• Growth abnormalities • NEHI • Disorders of surfactant metabolism
Systemic Disease

• Immune mediated disorders
  • Connective tissue disease related lung disease
  • Pulmonary hemorrhage syndromes
• Storage diseases
• Sarcoidosis

DISORDERS OF THE IMMUNOCOMPROMISED HOST
• Opportunistic infections • Related to treatment • Chemotherapy • Radiation • Drug hypersensitivity • Related to transplantation • Rejection • GVHD • PTLD • Lymphoid Infiltrates

GVHD , Graft-versus-host disease; *NEHI* , neuroendocrine cell hyperplasia of infancy; *PTLD* , post-transplant lymphoproliferative disease.

Modified from Fan LL, Dishop MK, Galambos C, et al: Diffuse lung disease in biopsied children 2 to 18 years of age. Application of the chILD Classification Scheme, *Ann Am Thorac Soc* 2015;12(10):1498–1505.

Classification and Pathology

Through the work of both the children's ILD research network in the United States and the children's ILD-European Union group in Europe, consensus on a classification scheme has been reached. The classification is broken down by age with 2 yr of age serving as a cut-off, and by histologic pattern. The classification scheme was first applied to biopsies from children under 2 and was extended to children over 2 yr of age (see Tables 427.16 and 427.17). Growth disorders such as alveolar simplification, unique diseases of infants such as neuroendocrine cell hyperplasia of infancy (**NEHI**), and **DSM** were common in children under 2. In contrast, disorders of the immunocompromised host such as ILD related to immune deficiency, and disorders of systemic diseases such as the collagen vascular disorders, were much more common in older children.

Neuroendocrine Cell Hyperplasia of Infancy

See Chapter 427.6 .

Disorders of Surfactant Metabolism

One of the more important groups of disorders in pediatric ILD is the **DSM** (Table 427.18). These disorders likely account for previously unknown cases of neonatal respiratory distress in full-term infants. Surfactant protein B deficiency, caused by mutations in the surfactant protein B gene, is a cause of severe neonatal respiratory distress. Chest CT often has a pattern of diffuse ground-glass opacities with septal thickening. Histopathology reveals alveolar proteinosis with interstitial widening, and electron microscopy shows disorganized lamellar bodies. Most children die within the first 2 mo of life without a lung transplant. Surfactant protein C deficiency can cause disease in older infants, children, or adults. Chest CT can show diffuse ground-glass opacities with septal thickening early in the disease or significant fibrosis and honeycombing in more advanced disease. Histopathologic findings vary with age, with alveolar proteinosis and interstitial widening seen in young children, and fibrosis seen in older children and adults. Electron microscopy reveals normal lamellar bodies. ABCA3 mutations cause variable lung disease in children with some having severe disease similar to surfactant protein B deficiency, while other children have less severe disease similar to surfactant protein C. Chest CT most often shows diffuse ground-glass opacities with septal thickening early in the disease (Fig. 427.10). Histopathology depends on the age of the child similar to surfactant protein C, however, electron microscopy shows characteristic changes in the lamellar bodies with an eccentric electron dense body without the characteristic concentric circles—the so-called fried egg appearance. **DSM** due to mutations in the gene NKX2.1 has also been described. NKX2.1 encodes for thyroid transcription factor 1 (TTF-1), which is a major regulator or surfactant protein transcription. Mutations in NKX2.1 cause variable disease in the lungs, brain, and thyroid (see Table 427.18). Lung disease is variable and can present similar to surfactant protein B deficiency, or as recurrent pulmonary infections. Finally, mutations in the alpha and beta subunits of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor cause failure of response to GM-CSF by the pulmonary alveolar macrophages. This leads to an inability to recycle surfactant with subsequent accumulation of proteinaceous material and pulmonary alveolar proteinosis.

Table 427.18

Clinical Features, Age, and Onset of Surfactant Protein Dysfunction Syndromes (SPDS)

SPDS	**CLINICAL FEATURES**	**AGE AND ONSET**
SFTPB	Neonatal ▸ Respiratory distress	Neonate, acute
ABCA3	Neonatal ▸ Respiratory distress Infancy ▸ Cough ▸ Tachypnoea, hypoxemia ▸ Failure to thrive Childhood ▸ Wheeze, crackles ▸ Exercise intolerance ▸ Dyspnea ▸ Retractions, crackles, digital clubbing ▸ Low body weight	Neonate, acute Infancy and childhood, subacute Late childhood and adulthood, chronic
SFTPC	Neonatal ▸ Respiratory distress Childhood ▸ Cough ▸ Tachypnoea, hypoxemia	Neonate, acute (infrequent) Infancy and childhood, subacute Late childhood and adulthood, chronic
NKX2.1	Respiratory ▸ Neonatal respiratory distress ▸ Recurrent infections ▸ Chronic interstitial lung disease Neurological ▸ Chorea ▸ Ataxia ▸ Developmental delay ▸ Hypotonia Hypothyroidism	Any age Acute or chronic

ABCA3 , ATP binding cassette number A3.

From Gupta A, Zheng SL: Genetic disorders of surfactant protein dysfunction: when to consider and how to investigate, *Arch Dis Child* 102:84–90, 2017 (Table 2, p. 86).

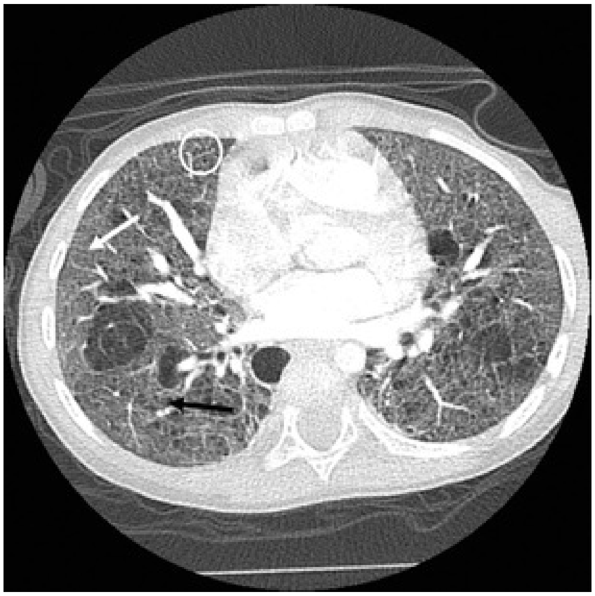

FIG. 427.10 Chest CT from a 2 yr old with a disorder of surfactant metabolism from mutations in ABCA3. Note the ground-glass opacities *(white arrow)* and septal thickening *(white circle)* and early cyst formation *(black arrow)* . (Courtesy R. Paul Guillerman, MD.)

Interstitial Lung Disease Due to Systemic Disease

ILD due to systemic disease is more common in older children with diffuse lung disease. The most common lung disease seen on biopsy is nonspecific interstitial pneumonia, however, other patterns are seen depending on the underlying disorder, such as lymphocytic interstitial pneumonia in Sjögren syndrome or cryptogenic organizing pneumonia in dermatomyositis. CT scans depend on the underlying ILD with nonspecific interstitial pneumonia having areas of ground-glass opacities and septal thickening in the early cellular phase of the disease (Fig. 427.11), progressing to diffuse fibrosis with traction bronchiectasis and peripheral cysts in the later fibrotic stage of the disease. The exact mechanism for disease is unknown but likely is due to auto-antibodies to respiratory tissue.

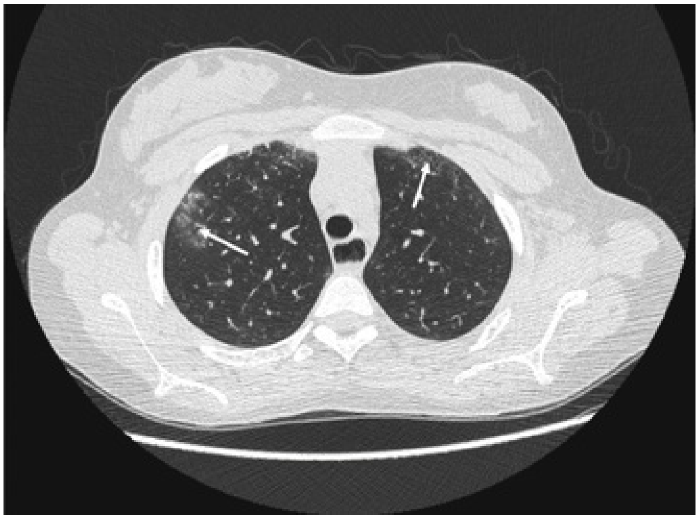

FIG. 427.11 Chest CT from a 11 yr old patient with systemic sclerosis and cellular nonspecific interstitial pneumonia. Note the areas of ground-glass opacities in the periphery *(white arrow)* . (Courtesy R. Paul Guillerman, MD.)

Pulmonary vasculitis, either due to GPA, microscopic polyangiitis, idiopathic pulmonary capillaritis, or anti-glomerular basement membrane syndrome (formerly Goodpasture disease) is another common manifestation of systemic diseases. Disease is likely due to auto-antibody stimulation of lymphocytes with resultant inflammation of pulmonary endothelium causing interstitial changes and pulmonary hemorrhage. Histopathology reveals diffuse alveolar hemorrhage, interstitial widening, and with the exception of anti-glomerular basement membrane disease, neutrophilic inflammation of the pulmonary vasculature.

Genetic causes of immune dysregulation may also be responsible for ILD in children. Mutations in both *STAT3b* and *LRBA* have been shown to cause lymphocytic interstitial pneumonia and lymphoproliferative disease. Mutations in *COPA* , a protein involved in ER to Golgi transport, cause familial pulmonary hemorrhage and/or ILD.

Persistent pulmonary symptoms can occur after **respiratory infections** caused by adenoviruses, influenza viruses, *Chlamydia pneumoniae* , and *Mycoplasma pneumoniae* . The resultant pulmonary disease is called **bronchiolitis obliterans** and is characterized by obstructive lung disease and obliteration or constriction of the bronchioles on lung biopsy. There is a characteristic appearance on HRCT with mosaicism, vascular attenuation, and central bronchiectasis, which if present, can obviate the need for lung biopsy (Fig. 427.12). **Aspiration** is a frequent cause of chronic lung disease in childhood and can mimic ILD.

Children with developmental delay or neuromuscular weakness are at an increased risk for aspiration of food, saliva, or foreign matter, secondary to swallowing dysfunction and/or gastroesophageal reflux (GER). An undiagnosed tracheoesophageal fistula can also result in pulmonary complications related to aspiration of gastric contents and interstitial pneumonia.

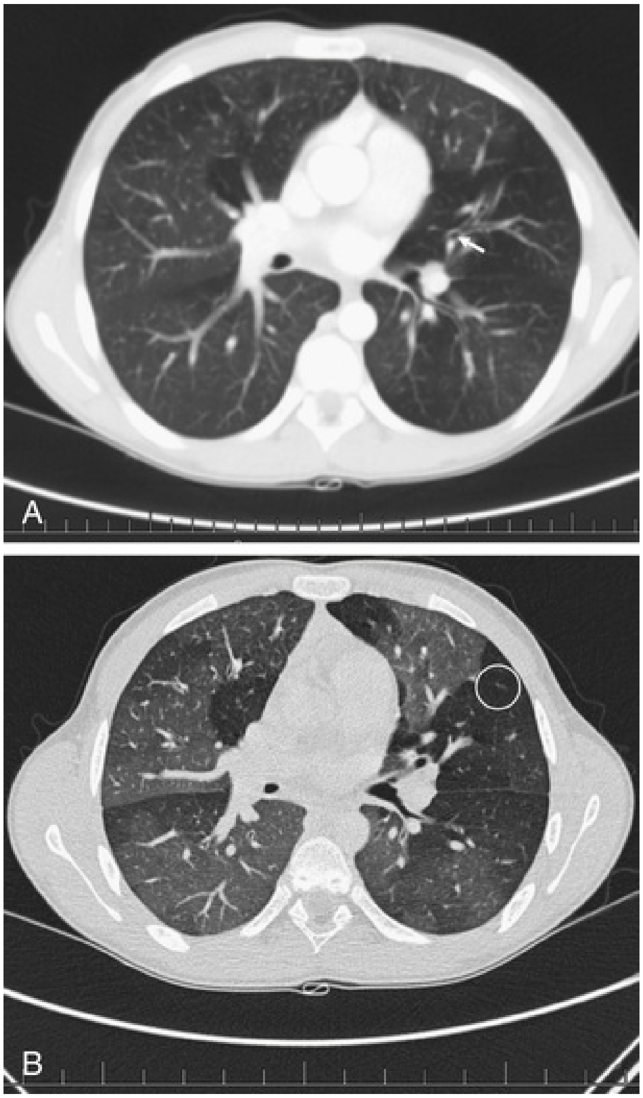

FIG. 427.12 Chest CT from an 11 yr old patient with bronchiolitis obliterans after Stevens-Johnson syndrome. **A,** Volumetric scan at full inspiration shows central bronchiectasis *(arrow)* and mosaic attenuation. **B,** High-resolution image taken in exhalation better highlights the mosaic attenuation, as well as vascular attenuation *(circle)* .

Children experiencing an exaggerated immunologic response to organic dust, molds, or bird antigens may demonstrate hypersensitivity pneumonitis. Children with malignancies may have ILD related to the primary malignancy, an opportunistic infection, or chemotherapy or radiation treatment.

Clinical Manifestations

A detailed history is needed to assess the severity of symptoms and the possibility of an underlying systemic disease in a patient with suspected ILD as well as any family history of lung disease. Identification of precipitating factors, such as exposure to molds or birds and a severe lower respiratory infection, is important in establishing the diagnosis and instituting avoidance measures. Most patients develop hypoxia and hypercarbia, usually a late and ominous complication. Symptoms are usually insidious and occur in a continuous, not episodic, pattern. Tachypnea, crackles on auscultation, and retractions are noted on physical examination in children with ILD, but chest physical examination findings can be normal. Wheezing and fever are uncommon findings in pediatric ILD. Cyanosis accompanied by a prominent P2 heart sound is indicative of severe disease with the development of secondary pulmonary hypertension. Anemia or hemoptysis suggests a pulmonary vascular disease or pulmonary hemosiderosis. Rashes or joint complaints are consistent with an underlying connective tissue disease.

Diagnosis

Radiography

Chest radiographic abnormalities can be classified as interstitial, reticular, nodular, reticulonodular, or honeycombed. The chest radiographic appearance may also be normal despite significant clinical impairment and may correlate poorly with the extent of disease. HRCT of the chest better defines the extent and distribution of disease and can provide specific information for selection of a biopsy site. Volume-controlled full-inspiratory and end-expiratory protocols used during HRCT can provide more information. These protocols may show air trapping, ground-glass patterns, mosaic patterns of attenuation, hyperinflation, bronchiectasis, cysts, and/or nodular opacities. Serial HRCT scans have been beneficial in monitoring disease progression and severity.

Pulmonary Function Tests

Pulmonary function tests are important in defining the degree of pulmonary dysfunction and in following the response to treatment. In ILD, pulmonary function abnormalities demonstrate a restrictive ventilatory deficit with decreased lung volumes and reduced lung compliance. The functional residual capacity is often reduced but is usually less affected than vital capacity and total lung capacity (TLC). The residual volume (RV) is usually maintained; therefore, ratios of functional residual capacity:TLC and RV:TLC are increased. Diffusion capacity of the lung is often reduced. Exercise testing may detect pulmonary dysfunction, even in the early stage of ILD with a decline in oxygen saturation.

Bronchoalveolar Lavage

BAL may provide helpful information regarding secondary infection, bleeding, and aspiration and allows cytology and molecular analyses. Evaluation of cell counts, differential, and lymphocyte markers may be helpful in determining the presence of hypersensitivity pneumonitis or sarcoid. Although BAL does not usually determine the exact diagnosis, it can be diagnostic for disorders such as pulmonary alveolar proteinosis.

Lung Biopsy

Lung biopsy for histopathology by conventional thoracotomy or video-assisted thoracoscopy *is usually the final step and is often necessary for a diagnosis* , except in **NEHI** and bronchiolitis obliterans. Biopsy yields a diagnosis in greater than 80% of patients. Due to the small size of biopsies obtained and low diagnostic yield, transbronchial biopsies are not recommended for the evaluation of ILD in children. Genetic testing for surfactant dysfunction mutational analysis is available. Evaluation for possible systemic disease may also be necessary.

Treatment

Supportive care of patients with ILD is essential and includes supplemental oxygen for hypoxia and adequate nutrition for growth failure. Antimicrobial treatment may be necessary for secondary infections. Some children may receive symptomatic relief from the use of bronchodilators. Antiinflammatory treatment with corticosteroids remains the initial treatment of choice. Controlled trials in children are lacking, however, and the clinical responses reported in case studies are variable. The usual dose of prednisone is 1-2 mg/kg/24 hr or 10-30 mg/kg of IV methylprednisolone given either weekly or for 3 consecutive days per month. Treatment length varies but is often initially given for 3-6 mo with tapering of dosage dictated by clinical response. Alternative, but not adequately evaluated, agents include hydroxychloroquine, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and intravenous immunoglobulin. Investigational approaches involve specific agents directed against the action of cytokines, growth factors, or oxidants. Lung transplantation for progressive or end-stage ILD is used and outcomes are similar to other end-stage lung diseases in children such as cystic fibrosis. Appropriate treatment for underlying systemic disease is indicated. Preventive measures include avoidance of all inhalation irritants, such as tobacco smoke and, when appropriate, molds and bird antigens. Supervised pulmonary rehabilitation programs may be helpful.

Genetic Counseling

A high incidence of ILD in some families suggests a genetic predisposition to either development of the disease or severity of the disorder. Genetic counseling may be beneficial if a positive familial history is obtained.

Prognosis

The overall mortality of ILD is variable and depends on specific diagnosis. Some children recover spontaneously without treatment, but other children steadily progress to death. Pulmonary hypertension, failure to thrive, and severe fibrosis are considered poor prognostic indicators.

Anti-Glomerular Basement Membrane Disease (Anti-GBM Disease)

Anti-glomerular basement membrane disease, (**anti-GBM disease**) formerly known as Goodpasture disease, is the prototypical immunologic mediated ILD (see Chapter 538.4). Because of the concurrent presentation of renal and pulmonary disease, the differential diagnosis focuses on distinguishing anti-

GBM disease from GPA, microscopic polyangiitis, Henoch-Schönlein purpura, and idiopathic pulmonary hemorrhage syndromes.

Pathophysiology

Immunology Factors

The development of anti-GBM antibodies directly correlates with the development of pulmonary and renal disease. Removal of such antibodies by plasmapheresis results in improvement of the disease process in some patients but not in all. The anti-GBM antibodies are IgG_1 and IgG_4 complement-binding subclasses of IgG which activate complement. Complement fragments signal the recruitment of neutrophils and macrophage in both the lung and kidney basement membranes resulting in damage and capillaritis.

Genetic Factors

Genetics appears to contribute strongly to the development of this disease with the presence of major histocompatibility complex class II alleles DR15, DR4, DRB1*1501, DRB1*04, and DRB1*03 predisposing to disease.

Environmental Factors

Exposure to smoke appears to be a strong factor in the development anti-GBM disease. Whether smoking alters the ultrastructure of the basement membrane or exogenous particles or noxious substances in smoke alter the type IV collagen is unknown. Smokers are more likely to develop pulmonary hemorrhage than non-smokers who have anti-GBM disease. Other injuries to the alveoli from infection, hydrocarbon inhalation, or cocaine inhalation have been reported as associated events prior to development of anti-GBM disease.

Clinical Manifestations

The majority of patients present with many days or weeks of cough, dyspnea, fatigue, and sometimes hemoptysis. Young children tend to swallow small amounts of blood from hemoptysis and may present with vomiting blood. Occasionally, the hemoptysis is large and resultant anemia is a consequence of large quantities of blood loss. Renal compromise is found with abnormal renal function tests. Younger patients tend to present with both the pulmonary and renal syndrome concurrently. Adults are less likely to develop pulmonary disease.

Laboratory

Serologic detection of anti-GBM antibodies is positive in more than 90% of patients with anti-GBM disease. A complete blood count will show anemia that is normocytic and normochromic as seen in chronic inflammatory disease. Urinalysis may reveal hematuria and proteinuria, while blood tests demonstrate renal compromise with elevated blood urea nitrogen and creatinine.

Studies for pANCA (antimyeloperoxidase ANCA) should also be performed and are positive in approximately 25–30% of patients concurrently with anti-GBM antibodies. Clinical disease may be more difficult to treat, and the presence of these antibodies may herald a more severe form of disease.

Chest Radiography

Chest radiography in anti-GBM disease will often show widely scattered patches of pulmonary infiltrates. If these infiltrates are in the periphery of the lung, they may be difficult to distinguish from the eosinophilic lung diseases. Interstitial patterns of thickening may be found as well. HRCT is usually not performed in this disease as the constellation of pulmonary hemorrhage, renal compromise, and positive serologic tests with anti-GBM antibodies detected often preclude the need for this test.

Pulmonary Function Testing

Pulmonary spirometry often reveals a restrictive defect with reduction in FVC and FEV_1 . DLCO is a valuable test when pulmonary hemorrhage is a strong consideration. The intent of this test is to measure the ability of the lung to transfer inhaled gas to the red blood cell in the pulmonary capillary bed. This takes advantage of the hemoglobin's high affinity to bind carbon monoxide. It was once thought that reduction of DLCO was a measure of reduced surface area of the alveoli. Current data suggests that it directly correlates with the volume of blood in the pulmonary capillary bed. In pulmonary hemorrhage syndromes, blood in the alveoli plus the blood in the capillary bed increase the DLCO significantly and should alert the clinician to the possibility of pulmonary hemorrhage.

Bronchoscopy and Bronchoalveolar Lavage

Pulmonary abnormalities can often be best assessed by a bronchoscopy with BAL. The visual presence of blood on inspection as well as BAL will be obvious. Infections must be ruled out in many cases, and this technique adds significant value. BAL cell count will show hemosiderin-laden macrophages that have engulfed and broken down the red blood cells, leaving iron in these cells.

Lung Biopsy

Lung biopsy in patients with active disease reveals capillaritis from neutrophils, hemosiderin-laden macrophages, type II pneumocyte hyperplasia, and interstitial thickening at the level of the alveolus. Staining for IgG and complement is found by immunofluorescence along the basement membrane in a linear pattern. This antibody deposition pattern led to the investigation of endogenous antigens in the basement membrane.

Treatment

More than half of patients with anti-GBM disease who forego treatment die within 2 yr from either respiratory failure, renal failure, or both. After a diagnosis is made, therapy with corticosteroids (e.g., prednisone, 1 mg/kg/day) coupled with oral cyclophosphamide (2.5 mg/kg/day) is begun. The addition of daily plasmapheresis for 2 wk may accelerate improvement. Cyclophosphamide may be discontinued after 2-3 mo. Steroids are often weaned over a 6-9 mo period. Survival is affected by the need for ongoing dialysis. Patients who do not require persistent dialysis have a survival rate at 1 yr of 80% or more.

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427.6

Neuroendocrine Cell Hyperplasia of Infancy

W. Adam Gower

Keywords

Neuroendocrine cell hyperplasia of infancy
NEHI
neuroendocrine cell (NEC)
neuroendocrine bodies (NEB)
diffuse lung disease (DLD)

interstitial lung disease (ILD)

Background/Summary

Neuroendocrine cell hyperplasia of Infancy (NEHI) (previously called persistent tachypnea of infancy) is an idiopathic form of diffuse lung disease that typically presents within the 1st yr of life with persistent tachypnea, retractions, hypoxemia, crackles, failure to thrive, and characteristic findings on chest imaging studies and lung histopathology. Pulmonary function studies typically demonstrate an obstructive picture with air trapping. There are no effective specific therapies for NEHI, and the usual approach is supportive care. The natural course is typically one of gradual improvement of symptoms, although exacerbations may occur throughout childhood. The long-term consequences of this disorder are not entirely known.

Epidemiology

The prevalence of NEHI is not known, but it is generally regarded to be a rare lung disease. Children with NEHI have accounted for around 10% of children who had lung biopsies in previous multicenter case series. There does not appear to be a clear racial or gender predisposition, and no other maternal or patient-level risk factors have been identified. Cases of NEHI have been reported in the literature from North and South America, Europe, Asia, and Australia.

Pathophysiology

The primary clue to the pathophysiology of NEHI is increased numbers of airway neuroendocrine cells (NEC) in the airways of affected children. These cells are normally found in the airways, where they exist as innervated clusters known as NEB and secrete factors such as bombesin and serotonin (5-HT). They are thought to be involved in local oxygen sensing and may transmit neuroendocrine signals to other cells. Increases in NECs are seen in other respiratory disorders of childhood, usually with other additional findings. It is unclear whether their presence in increased numbers in NEHI causes the clinical picture, or is the result of abnormal pulmonary physiology secondary to some other primary factor. Increased numbers of NECs seem to be associated with increased small airways obstruction.

Although most cases appear to be sporadic, familial NEHI has been described, suggesting a possible inherited mechanism and/or shared environmental influences. The association of NEHI with heterozygosity for a variant in the gene *Nkx2.1* , which encodes the protein TTF-1, has been described in one kindred. Variants in this gene are also known to cause a wide spectrum of disorders, including more severe forms of diffuse lung disease (see Chapter 427.5).

Clinical Presentation

The symptoms of NEHI characteristically appear during infancy, although the diagnosis may be delayed until after the 1st yr of life. The typical presentation includes persistent tachypnea, hypoxemia, retractions, and poor weight gain in an otherwise healthy infant. The exam usually reveals crackles or clear lung sounds, while cough and wheezing are uncommon. Typically, affected infants do not have a history of premature delivery. Echocardiograms usually show absence of structural heart disease or pulmonary hypertension.

Diagnosis

The diagnosis of NEHI requires that other more common causes of the presenting symptoms are ruled out. Although children with NEHI may have GER and/or swallowing dysfunction, this is not thought to be sufficient to cause all of the findings, and may be secondary to tachypnea and increased work of breathing. Plain chest films may show hyperinflation. When biopsy material from the lung is stained with bombesin, increased numbers of positive-staining cells are noted in the airways. In general, biopsies from children with NEHI are remarkably void of fibrosis, inflammation, or signs of airway or parenchymal injury (Fig. 427.13).

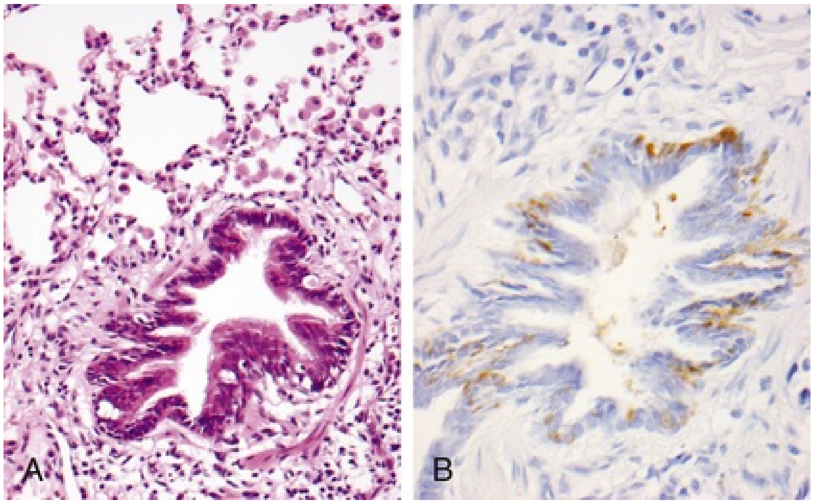

FIG. 427.13 Neuroendocrine cell hyperplasia of infancy. **(A)** A small airway showing only minimal chronic inflammation on routine staining but **(B)** staining for bombesin shows increased numbers of neuroendocrine cells within the surface epithelium. (From Corrin B, Nicholson AG: *Pathology of the lungs* , ed 3, Churchill Livingstone, 2011. Fig. 2.19.)

Although the pattern of NEC hyperplasia seen in histopathology has classically been the gold standard for diagnosis of NEHI, high-resolution chest computed tomography (CT) has a high specificity, such that biopsy may be avoided in most cases. The classic pattern seen on chest CT is ground-glass opacities in the lingula, right middle lobe, and perihilar regions, with air trapping on expiratory images. The lungs otherwise appear normal (Fig. 427.14). Some designate a diagnosis made clinically without biopsy as **NEHI syndrome** and reserve the term NEHI for a diagnosis made by biopsy. If a patient with clinically diagnosed NEHI syndrome has a more severe clinical course than expected, biopsy may be helpful to rule out other pathology.

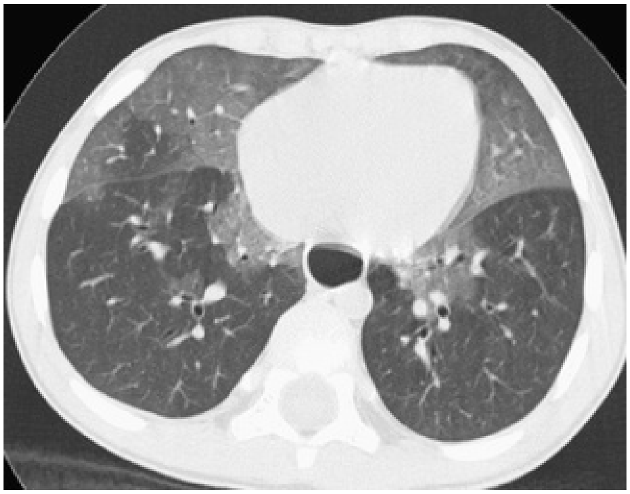

FIG. 427.14 2 yr old boy with neuroendocrine cell hyperplasia of infancy. CT shows well-defined areas of ground-glass opacity seen centrally and in the right middle lobe and lingula. (From Brody AS: Imaging considerations: interstitial lung disease in children, *Radiol Clin North Amer* 43:391–403, 2005. Fig. 4.)

The diagnosis of NEHI may be supported by an obstructive pattern that does not reverse with bronchodilators, on either infant pulmonary function testing (iPFT) or standard spirometry. Static lung volumes may show air trapping with increased RV relative to the TLC. BAL findings are notable for lack of inflammatory markers, as compared to other pulmonary diseases of infancy.

Genetic testing may be useful to rule out DSM and other causes of infant diffuse lung disease. Targeted testing for variants in *Nkx2.1* can be considered, but as this association has been found in only one kindred thus far, the predictive value of such testing is limited.

Natural Course and Treatment

As the symptoms of NEHI typically improve and eventually largely resolve over the first few years of life, the standard approach to treatment of NEHI is supportive. The time frame for clinical improvement in NEHI is variable, and symptoms with rest may improve while those on exertion or with sleep persist. Until this occurs, affected children may require supplemental oxygen to maintain normal saturations, sometimes only with sleep or illnesses, but often at all times. The degree of obstruction on iPFTs may be somewhat predictive of degree of desaturation and obstruction in the future.

Because they may expend more energy to breathe, children with NEHI may have difficulty gaining weight, and often require supplemental nutrition. This is often delivered by gastrostomy tube. Management of GER when present may be helpful. When the disease improves, the need for supplemental oxygen and/or nutritional support typically decreases. *Inhaled or systemic corticosteroids are generally not thought to be helpful in treating the primary manifestations of NEHI*. Children with NEHI, whose symptoms have shown improvement, may experience exacerbations later in childhood. These episodes are associated with increased air trapping.

Although the symptoms of NEHI typically resolve during childhood, limited data suggest that some symptoms may persist into the adult years. This may manifest as exercise intolerance, or an asthma-like picture. Obstruction with air trapping may be seen on PFT and persistent abnormalities may be identified on chest imaging. No cases of respiratory failure, need for lung transplantation, or death associated with NEHI have been reported. **Diffuse idiopathic neuroendocrine epithelial cell hyperplasia** may be a related disorder but is seen predominantly in adult females who have diffuse pulmonary nodules and fixed obstruction or obstructive/restrictive lung disease on pulmonary function testing.

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427.7

Fibrotic Lung Disease

Deborah R. Liptzin, Jason P. Weinman, Robin R. Deterding

Keywords

Fibrosis
pulmonary function
oxygen
nonspecific interstitial pneumonia

Pulmonary fibrosis is scarring in the lung parenchyma (as opposed to bronchiectasis which is scarring of the airways). Idiopathic pulmonary fibrosis is a common form of fibrotic lung disease in adults. This presents with usual interstitial pneumonia (a pathologic finding with patchy interstitial fibrosis, fibroblastic foci, and honeycomb change) (see Chapter 427.5). Additional adult fibrotic lung diseases include sarcoidosis, silicosis, coal workers pneumoconiosis and hypersensitivity pneumonitis (e.g., farmer's lung). In children, fibrotic lung disease is rare, and *idiopathic* pulmonary fibrosis has not been described. The differential diagnosis of *fibrotic* lung disease includes surfactant dysfunction mutations (Chapter 423), radiation-induced fibrosis, bronchiolitis obliterans (Chapter 422.1), nonspecific interstitial pneumonia (connective tissue disorders) (Chapter 427), hypersensitivity pneumonitis (Chapter 427.1), and aspiration (Chapter 425) (Tables 427.19 –427.21).

Table 427.19

Diseases Associated With Pulmonary Fibrosis

- Idiopathic pulmonary fibrosis / nonspecific interstitial pneumonia
- Familial pulmonary fibrosis / familial interstitial pneumonia
- Hypersensitivity pneumonitis (many agents)
- Cryptogenic organizing pneumonia
- Adverse reaction to therapy (drugs, radiation)
- Pleuroparenchymal fibroelastosis
- Hermansky–Pudlak syndrome
- Sarcoidosis
- Eosinophilic pneumonia (primary or parasitic)
- Langerhans cell histiocytosis
- Dyskeratosis congenita
- Tuberous sclerosis
- Neurofibromatosis
- Erdheim–Chester disease
- Gaucher disease
- Niemann–Pick disease
- Familial hypocalciuric hypercalcemia

- Lysinuric protein intolerance
- IgG4 mediated immune disorder
- Myelodysplastic syndrome
- Progressive systemic sclerosis
- Other connective tissue diseases (SLE, dermatomyositis)
- Granulomatosis with polyangiitis
- Eosinophilic granulomatosis with polyangiitis

Table 427.20

Pediatric Fibrotic Lung Diseases

DISEASES	CT FINDINGS	PATHOLOGY FINDINGS	ADDITIONAL EVALUATION	TREATMENT
Surfactant dysfunction	**Early:** Diffuse ground glass, septal thickening (crazy paving) **Chronic:** See NSIP	Variable: fibrosis, honeycomb cysts at end stage, NSIP, CPI, few globules of pulmonary alveolar proteinosis, foamy macrophages and cholesterol clefts (endogenous lipoid pneumonia)	Genetic testing	Hydroxychloroquine, azithromycin, high-dose intravenous steroids. Genetic counseling
Aspiration	**Acute:** Consolidation and centrilobular (tree in bud) nodules with a dependent distribution. **Chronic:** possible UIP with honeycombing	Airway-centered lesions/bronchiolitis, food particles with or without granulomas, foamy macrophages (endogenous lipoid pneumonia), organizing pneumonia	Video fluoroscopic swallow evaluation	Stop aspiration through thickening feeds, gastric feeds, cleft repair
Radiation fibrosis	Architectural distortion, volume loss, traction bronchiectasis. Often with geometric distribution related to radiation field	Pleural, septal, and paraseptal fibrosis; reactive atypia of alveolar epithelium and endothelium		
Bronchopulmonary dysplasia	Hyperlucent regions, architectural distortion (linear and subpleural triangular opacities)	Alveolar simplification and enlargement. Patchy hyperinflation. Interstitial fibrosis, with or without interlobular septal fibrosis.		Supportive care. Consider inhaled corticosteroids
Nonspecific interstitial pneumonia (NSIP)	Basilar predominant findings of ground-glass opacities (often with subpleural sparing), reticulation, architectural distortion, and traction bronchiectasis	Interstitial lymphocytic inflammation and fibrosis with homogenous distribution		
Hypersensitivity pneumonitis (chronic)	Patchy and often parahilar reticulation, ground glass,	Airway-centered small non-caseating granulomas, multinucleated giant cells,	Lymphocytosis in bronchoalveolar	Remove trigger, intravenous steroids

	centrilobular nodules. Honeycombing (rare)	lymphocytic bronchiolitis and peribronchiolitis, airway fibrosis, organizing pneumonia	lavage, precipitins to specific antigen	
Autoimmune connective tissue disorders (collagen vascular disease)	See NSIP. Honeycombing (rare)	NSIP. Lymphoid hyperplasia. Fibrosis and cystic change. Pleuritis and pleural fibrosis (variable). Chronic vasculopathy (variable). Airway fibrosis (variable).	Serologic studies	Disease-specific immune modulation
Drug reactions	Peripheral predominant consolidation or ground glass. Reverse halo sign. See NSIP. Honeycombing (rare)	Variable: organizing pneumonia, NSIP, UIP, DAD, pulmonary hemorrhage, eosinophilic pneumonia		Drug avoidance
Infection	**Acute:** Consolidation and centrilobular (tree in bud) nodules. Appearance and distribution varies with type of infection. **Chronic:** May progress to IPF/UIP with honeycombing	**Acute:** Neutrophilic alveolitis (bacterial) or lymphocytic bronchiolitis (viral). **Chronic:** Variable airway fibrosis (constrictive/obliterative bronchiolitis) and interstitial fibrosis.		Antimicrobials
Immunodeficiency	Bronchiectasis, consolidation, centrilobular nodules	Follicular bronchiolitis or diffuse lymphoid hyperplasia. NSIP. LIP. GLILD	Immunologic and genetic testing	Treat underlying immunodeficiency
Usual interstitial pneumonia (UIP)	Honeycombing, reticulation, traction bronchiectasis, ground glass (less prominent than NSIP)	Fibroblast foci. Interstitial, septal, and pleural fibrosis with heterogenous distribution. Minimal to absent inflammation.	Genetic testing	

Table 427.21

Genes Associated With Familial* or Idiopathic Pulmonary Fibrosis

GENE	GENE FUNCTION
IL1RN	Inhibitor of pro-inflammatory effect of IL-1alpha and IL-1beta
IL8	Pro-inflammatory cytokine
FAM13A	Signal transduction
TLR3	Pathogen recognition and activation of innate immunity
TERT	Enzyme in telomerase complex maintaining telomere length
HLA-DRB1	Major histocompatibility complex—immune system
DSP	Tightly links adjacent cells
OBFC1	Stimulates the activity of DNA polymerase-alpha-primase
MUC5B	Influence on rheological properties of airway mucus, mucociliary transport, and airway defense

MUC2	Mucin production
TOLLIP	Regulator of innate immune responses mediated by toll-like receptor and the transforming growth factor β signaling pathway
ATP11A	Phospholipid translocation
MDGA2	Cell–cell interaction
MAPT	Promotes microtubule assembly and stability
SPPL2C	Protein cleavage
DPP9	Cell–cell adhesion
TGFB1	Set of peptides that controls proliferation, differentiation, and other functions in many cell types
SFTPC[†]	Component of surfactant fluid
SFTPA2[†]	To modulate innate and adaptive immunity
ABCA3[†]	Transport of lipids across plasma membrane
TERC[†]	Template in telomerase complex
DKC1[†]	Stabilization of the template in telomerase complex
TINF2[†]	Telomere maintenance
RTELI[†]	DNA helicase
PARN[†]	mRNA stability

[*] Also called familial interstitial pneumonia.

[†] Rarer variant.

Adapted from Kaur A, Mathai SK, Schwartz DA: Genetics in idiopathic pulmonary fibrosis pathogenesis, prognosis, and treatment. *Frontiers Med* 4:154, 2017. Tables 1 and 2.

Clinical Presentation

Patients with pulmonary fibrosis will typically present with nonspecific respiratory symptoms such as cough, crackles, wheezes, prolonged expiratory phase, exercise intolerance, and hypoxemia, especially at nighttime. Symptom onset can be insidious or rapid.

Evaluation

Pulmonary function tests typically show restriction and reduced diffusion capacity. Air trapping can also be seen. Patients may desaturate with exercise challenges or 6-min walks.

There are a variety of findings on computed tomography scan that suggest pulmonary fibrosis. These include reticular opacities, architectural distortion, traction bronchiectasis, and honeycomb cysts. A common late finding in several etiologies of fibrotic lung disease in children is nonspecific interstitial pneumonia: subpleural sparing, ground-glass opacities, reticular change, and bronchiectasis. Typical CT findings in pediatric patients with nonspecific interstitial pneumonia include basilar predominant ground-glass opacities, reticulation, mild cystic change, and bronchiectasis (Fig. 427.15).

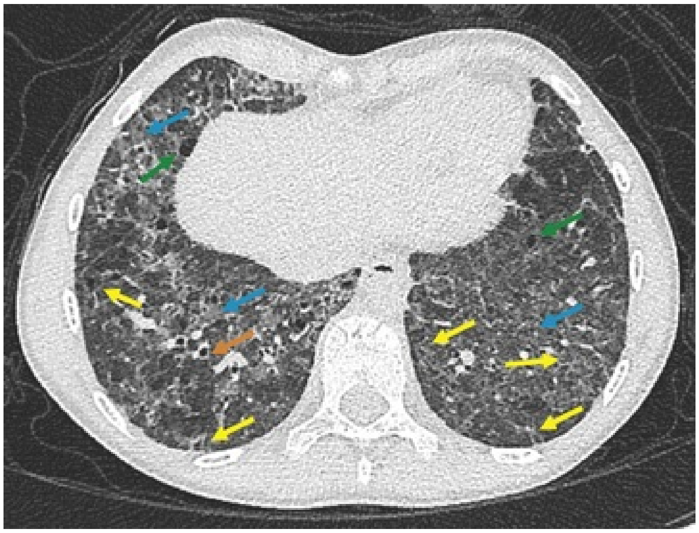

FIG. 427.15 Chest CT demonstrates typical CT findings in a pediatric patient with nonspecific interstitial pneumonia including basilar-predominant ground-glass opacities (blue arrows), reticulation (yellow arrows), mild cystic change (green arrows) and bronchiectasis (orange arrow).

In certain disease processes such as surfactant dysfunction mutations (positive genetic testing) or bronchiolitis obliterans (decline in lung function and typical computed tomography scan), biopsy is not necessary for diagnosis. In the absence of a definitive diagnosis, a thoracoscopic wedge biopsy is necessary for diagnosis and to guide treatment. Transthoracic biopsies in pediatrics are of limited utility because the small instruments typically obtain inadequate tissue specimens; transthoracic biopsies in pediatrics are limited to monitoring post-lung transplantation and for diagnosis of sarcoidosis. Pathologic findings in pulmonary fibrosis are variable, depending on duration and etiology of disease (see Table 427.20), but typically include a component of interstitial inflammation, interstitial expansion by dense collagen, and lobular remodeling (parenchymal architectural distortion and honeycomb cysts). Interlobular septal fibrosis, pleural fibrosis, and chronic pulmonary arteriopathy are common associated findings. Rare dense globules of pulmonary alveolar proteinosis material may indicate a genetic disorder of surfactant metabolism. Reactive lymphoid follicles suggest an immunologic process, such as autoimmune disease or immunodeficiency. Organizing pneumonia (polypoid aggregates of fibroblasts, *Masson bodies*) is a common feature in hypersensitivity pneumonitis and autoimmune diseases. The usual interstitial pneumonia pattern is signaled by fibroblast foci arising within a background of dense interstitial fibrosis and is a rare pattern of disease in children. Connective tissue stains, such as Masson trichrome, Elastic Verhoff von Giesen, and Movat pentachrome, aid in determining the severity and distribution of collagen deposition.

Treatment

Treatment varies based on disease process (see Tables 427.19 –427.21). Due to the nature of rare disease, treatment regimens are largely based on expert opinion as controlled clinical trials are challenging to perform. Antifibrotic agents approved in adults with idiopathic pulmonary fibrosis (pirfenidone and nintedanib) are not approved for use in children.

Patients with fibrotic lung disease should be closely followed by pediatric pulmonary specialists for disease and comorbidity monitoring. Monitoring may include evaluation of pulmonary function (spirometry, lung volumes, and diffusion capacity), functional evaluation of exercise (6-min walk), and screening for comorbidities such as pulmonary hypertension, aspiration, and sleep disordered breathing. Treatment is disease specific but should also include nutritional support secondary to increased metabolic demands. Respiratory support varies depending on each patient's needs, from no support to oxygen via nasal cannula while asleep only, oxygen via nasal cannula all the time, or with ventilation (noninvasive or invasive). Comorbidities should be treated appropriately. Genetic counseling and recurrence risk should be provided with genetic forms of fibrotic lung disease. Patients should be counseled about preventing further lung damage from air pollution, smoking (cigarette, electronic cigarettes, hookah, water pipe, marijuana, etc.), and secondhand smoke exposure.

Outcomes

Outcomes vary depending on the underlying disease process.

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CHAPTER 428

Community-Acquired Pneumonia

Matthew S. Kelly, Thomas J. Sandora

Epidemiology

Pneumonia, defined as inflammation of the lung parenchyma, is the leading infectious cause of death globally among children younger than 5 yr, accounting for an estimated 920,000 deaths each year (Fig. 428.1). Pneumonia mortality is closely linked to poverty. More than 99% of pneumonia deaths are in low- and middle-income countries, with the highest pneumonia mortality rate occurring in poorly developed countries in Africa and South Asia (Table 428.1).

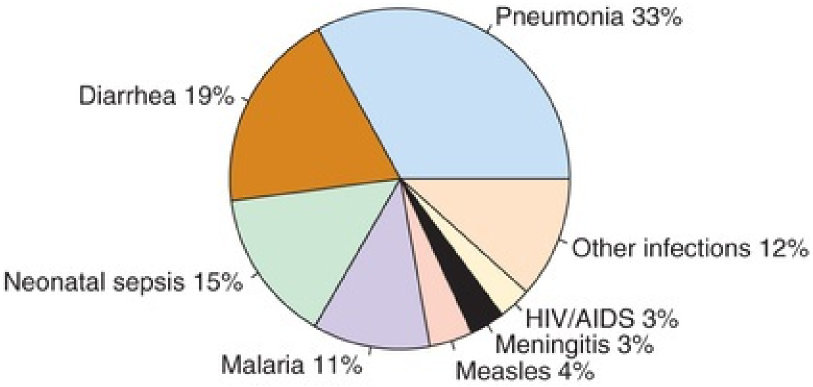

FIG. 428.1 Pneumonia is the leading infectious killer of children worldwide, as shown by this illustration of global distribution of cause-specific infectious mortality among children younger than age 5 yr in 2015. Pneumonia causes one-third of all under-5 deaths from infection. (From World Health Organization and Maternal and Child Epidemiology Estimation Group estimates, 2015.)

Table 428.1

Pneumonia Cases and Mortality Rate in Children Younger Than Age 5 Yr by UNICEF Region, 2015

UNICEF REGIONS	PNEUMONIA CASES IN CHILDREN YOUNGER THAN 5 YR OF AGE	PNEUMONIA MORTALITY RATE (UNDER-5 DEATHS PER 1,000 LIVE BIRTHS)
West and Central Africa	298,000	16.2
Sub-Saharan Africa	490,000	13.7
Eastern and Southern Africa	177,000	10.9
South Asia	282,000	7.9
Middle East and North Africa	46,000	4.1
East Asia and the Pacific	81,000	2.7
Latin America and the Caribbean	23,000	2.1
Least Developed Countries	363,000	12.0
World	920,000	6.6

From United Nations Children's Fund: One is too many—ending child deaths from pneumonia and diarrhoea. https://data.unicef.org/resources/one-many-ending-child-deaths-pneumonia-diarrhoea/ . Accessed January 21, 2017.

In the United States, mortality from pneumonia in children declined by 97% between 1939 and 1996. This decline likely resulted from the development of antibiotics and vaccines and the expansion of medical insurance coverage for children. Effective vaccines against measles (see Chapter 273) and pertussis (see Chapter 224) contributed to the decline in pneumonia-related mortality during the 20th century. *Haemophilus influenzae* type b (see Chapter 221) was also an important cause of bacterial pneumonia in young children but became uncommon following licensure of a conjugate vaccine in 1987. The introduction of pneumococcal conjugate vaccines (PCVs) (see Chapter 209) has been an important contributor to the further reductions in pneumonia-related mortality achieved over the past 15 yr.

Etiology

Although most cases of pneumonia are caused by microorganisms, noninfectious causes include aspiration (of food or gastric acid, foreign bodies, hydrocarbons, and lipoid substances), hypersensitivity reactions, and drug- or radiation-induced pneumonitis (see Chapter 427). The cause of pneumonia in an individual patient is often difficult to determine because direct sampling of lung tissue is invasive and rarely performed. Bacterial cultures of sputum or upper respiratory tract samples from children typically do not accurately reflect the cause of lower respiratory tract infection. *Streptococcus pneumoniae* (pneumococcus) is the most common bacterial pathogen in children 3 wk to 4 yr of age, whereas *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are the most frequent bacterial pathogens in children age 5 yr and older. In addition to pneumococcus, other bacterial causes of pneumonia in previously healthy children in the United States include group A streptococcus (*Streptococcus pyogenes* ; see Chapter 210) and *Staphylococcus aureus* (see Chapter 208.1) (Tables 428.2 , 428.3 , and 428.4). *S. aureus* pneumonia often complicates an illness caused by influenza viruses.

Table 428.2

Causes of Infectious Pneumonia

BACTERIAL	
COMMON	
Streptococcus pneumoniae	Consolidation, empyema
Group B streptococci	Neonates
Group A streptococci	Empyema
Staphylococcus aureus	Pneumatoceles, empyema; infants; nosocomial pneumonia
Mycoplasma pneumoniae *	Adolescents; summer–fall epidemics
Chlamydophila pneumoniae *	Adolescents
Chlamydia trachomatis	Infants
Mixed anaerobes	Aspiration pneumonia
Gram-negative enterics	Nosocomial pneumonia
UNCOMMON	
Haemophilus influenzae type b	Unimmunized
Moraxella catarrhalis	
Neisseria meningitidis	
Francisella tularensis	Animal, tick, fly contact; bioterrorism
Nocardia species	Immunocompromised patients
Chlamydophila psittaci *	Bird contact (especially parakeets)
Yersinia pestis (plague)	Rat contact; bioterrorism
Legionella species*	Exposure to contaminated water; nosocomial
Coxiella burnetii * (Q fever)	Animal (goat, sheep, cattle) exposure
VIRAL	
COMMON	
Respiratory syncytial virus	Bronchiolitis
Parainfluenza types 1-4	Croup
Influenza A, B	High fever; winter months
Adenovirus	Can be severe; often occurs between January and April

Human metapneumovirus	Similar to respiratory syncytial virus
UNCOMMON	
Rhinovirus	Rhinorrhea
Enterovirus	Neonates
Herpes simplex	Neonates, immunocompromised persons
Cytomegalovirus	Infants; immunocompromised persons (particularly HIV-infected infants)
Measles	Rash, coryza, conjunctivitis
Varicella	Unimmunized; immunocompromised persons
Hantavirus	Southwestern United States, rodents
Coronaviruses [severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS)]	Asia, Arabian Peninsula
FUNGAL	
Histoplasma capsulatum	Ohio/Mississippi River valley; bird, bat contact
Blastomyces dermatitidis	Ohio/Mississippi River valley
Coccidioides immitis	Southwestern United States, Great Lakes states
Cryptococcus neoformans and *C. gattii*	Bird contact; immunocompromised; Northwestern United States *(C. gattii)*
Aspergillus species	Immunocompromised persons; nodular lung infection
Mucormycosis	Immunocompromised persons
Pneumocystis jiroveci	Immunocompromised persons (particularly HIV-infected infants); steroids
RICKETTSIAL	
Rickettsia rickettsiae	Tick bite
MYCOBACTERIAL	
Mycobacterium tuberculosis	Travel to endemic region; exposure to high-risk persons
Mycobacterium avium complex	Immunocompromised (particularly HIV-infected) persons
Other non-tuberculous mycobacteria	Immunocompromised persons; cystic fibrosis
PARASITIC	
Various parasites (e.g., *Ascaris* , *Strongyloides* species)	Eosinophilic pneumonia

[*] Atypical pneumonia syndrome; may have extrapulmonary manifestations, low-grade fever, patchy diffuse infiltrates, and poor response to β-lactam antibiotics.

Adapted from Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis & therapy* , ed 2, Philadelphia, 2004, Elsevier, p. 29.

Table 428.3

Pneumonia Etiologies Grouped by Age of the Patient

AGE GROUP	FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)
Neonates (<3 wk)	Group B streptococcus, *Escherichia coli*, other Gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type b,[*] nontypeable)
3 wk-3 mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, human metapneumovirus, adenovirus), *S. pneumoniae, H. influenzae* (type b,[*] nontypeable); if patient is afebrile, consider *Chlamydia trachomatis*

4 mo-4 yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, human metapneumovirus, adenovirus), *S. pneumoniae, H. influenzae* (type b,* nontypeable), *Mycoplasma pneumoniae*, group A streptococcus
≥5 yr	*M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b,* nontypeable), influenza viruses, adenovirus, other respiratory viruses, *Legionella pneumophila*

* *H. influenzae* type b is uncommon with routine immunization.

Adapted from Kliegman RM, Marcdante KJ, Jenson HJ, et al: *Nelson essentials of pediatrics* , ed 5, Philadelphia, 2006, Elsevier, p. 507.

Table 428.4

Pneumonia: Etiology Suggested by Exposure History

EXPOSURE HISTORY	**INFECTIOUS AGENT**
Exposure to concurrent illness in school dormitory or household setting	*Neisseria meningitidis, Mycoplasma pneumoniae*
ENVIRONMENTAL EXPOSURES	
Exposure to contaminated aerosols (e.g., air coolers, hospital water supply)	Legionnaires' disease
Exposure to goat hair, raw wool, animal hides	Anthrax
Ingestion of unpasteurized milk	Brucellosis
Exposure to bat droppings (caving) or dust from soil enriched with bird droppings	Histoplasmosis
Exposure to water contaminated with animal urine	Leptospirosis
Exposure to rodent droppings, urine, saliva	Hantavirus
Potential bioterrorism exposure	Anthrax, plague, tularemia
ZOONOTIC EXPOSURES	
Employment as abattoir work or veterinarian	Brucellosis
Exposure to cattle, goats, pigs	Anthrax, brucellosis
Exposure to ground squirrels, chipmunks, rabbits, prairie dogs, rats in Africa or southwestern United States	Plague
Hunting or exposure to rabbits, foxes, squirrels	Tularemia
Bites from flies or ticks	Tularemia
Exposure to birds (parrots, budgerigars, cockatoos, pigeons, turkeys)	Psittacosis
Exposure to infected dogs and cats	*Pasteurella multocida*, Q fever *(Coxiella burnetii)*
Exposure to infected goats, cattle, sheep, domestic animals, and their secretions (milk, amniotic fluid, placenta, feces)	Q fever *(C. burnetii)*
TRAVEL EXPOSURES	
Residence in or travel to San Joaquin Valley, southern California, southwestern Texas, southern Arizona, New Mexico	Coccidioidomycosis
Residence in or travel to Mississippi or Ohio river valleys, Great Lakes States, Caribbean, Central America, or Africa	Histoplasmosis, blastomycosis
Residence in or travel to southern China	SARS, avian influenza
Residence in or travel to Arabian peninsula	MERS-CoV
Residence in or travel to Southeast Asia	Paragonimiasis, melioidosis
Residence in or travel to West Indies, Australia, or Guam	Melioidosis

MERS-CoV, Middle East respiratory syndrome coronavirus; SARS, severe acute respiratory syndrome.

From Ellison RT III, Donowitz GR: Acute pneumonia, In Bennett JE, Dolin R, Blaser MJ, editors:

Mandell, Douglas, and Bennett's principles and practice of infectious diseases , ed 8, vol 1, Philadelphia, 2015, Elsevier, Table 69.3, p. 828.

S. pneumoniae, H. influenzae, and *S. aureus* are the major causes of hospitalization and death from bacterial pneumonia among children in developing countries, although in children with HIV infection, *Mycobacterium tuberculosis* (see Chapter 242), non-tuberculous mycobacteria (see Chapter 244), *Salmonella* (see Chapter 225), *Escherichia coli* (see Chapter 227), *Pneumocystis jiroveci* (see Chapter 271), and cytomegalovirus (see Chapter 282) must be considered. The incidence of pneumonia caused by *H. influenzae* or *S. pneumoniae* has been significantly reduced in areas where routine immunization has been implemented.

Viral pathogens are the most common causes of lower respiratory tract infections in infants and children older than 1 mo but younger than 5 yr of age. Viruses can be detected in 40–80% of children with pneumonia using molecular diagnostic methods (e.g., polymerase chain reaction [PCR]). Of the respiratory viruses, respiratory syncytial virus (RSV; see Chapter 287) and rhinoviruses (see Chapter 290) are the most commonly identified pathogens, especially in children younger than 2 yr of age. However, the role of rhinoviruses in severe lower respiratory tract infection remains unclear as these viruses are frequently detected with co-infecting pathogens and among asymptomatic children. Other common viruses causing pneumonia include influenza viruses (see Chapter 285), human metapneumovirus (see Chapter 288), parainfluenza viruses (see Chapter 286), adenoviruses (see Chapter 289), and enteroviruses (see Chapter 277). Infection with more than one respiratory virus occurs in up to 20% of cases. The age of the patient can suggest the likely pathogens (see Table 428.3).

Lower respiratory tract viral infections are much more common in the fall and winter in both the northern and southern hemispheres in relation to the seasonal epidemics of respiratory viruses that occur each year. The typical pattern of these epidemics usually begins in the fall, when parainfluenza virus infections appear and most often manifest as croup. Later in winter, RSV, human metapneumovirus, and influenza viruses cause widespread infection, including upper respiratory tract infections, bronchiolitis, and pneumonia. RSV is particularly severe among infants and young children, whereas influenza viruses cause disease and excess hospitalization for acute respiratory illness in all age groups. Knowledge of the prevailing viruses circulating in the community may lead to a presumptive initial diagnosis.

Immunization status is relevant because children fully immunized against *H.*

influenzae type b and *S. pneumoniae* are less likely to have pneumonia caused by these pathogens. Children who are immunocompromised or who have certain medical comorbidities may be at risk for specific pathogens, such as *Pseudomonas* spp. in patients with cystic fibrosis (see Chapter 432).

Pathogenesis

The lower respiratory tract possesses a number of defense mechanisms against infection, including mucociliary clearance, macrophages and secretory immunoglobulin A, and clearing of the airways by coughing. Previously, it was believed that the lower respiratory tract was—in the absence of infection—kept sterile by these mechanisms, supported primarily by culture-based studies. However, recent use of culture-independent techniques, including high-throughput sequencing methods, suggests that the lower respiratory tract contains diverse microbial communities. These data have challenged the traditional model of pneumonia pathogenesis that maintained that pneumonia was the result of invasion of the sterile lower respiratory tract by a single pathogen. More recent conceptual models postulate that pneumonia results from disruption of a complex lower respiratory ecosystem that is the site of dynamic interactions between potential pneumonia pathogens, resident microbial communities, and host immune defenses.

Viral pneumonia usually results from spread of infection along the airways, accompanied by direct injury of the respiratory epithelium, which results in airway obstruction from swelling, abnormal secretions, and cellular debris. The small caliber of airways in young infants makes such patients particularly susceptible to severe infection. Atelectasis, interstitial edema, and hypoxemia from ventilation–perfusion mismatch often accompany airway obstruction. Viral infection of the respiratory tract can also predispose to secondary bacterial infection by disturbing normal host defense mechanisms, altering secretions, and through disruptions in the respiratory microbiota.

Bacterial pneumonia most often occurs when respiratory tract organisms colonize the trachea and subsequently gain access to the lungs, but pneumonia may also result from direct seeding of lung tissue after bacteremia. When bacterial infection is established in the lung parenchyma, the pathologic process varies according to the invading organism. *M. pneumoniae* (see Chapter 250) attaches to the respiratory epithelium, inhibits ciliary action, and leads to cellular destruction and an inflammatory response in the submucosa. As the infection progresses, sloughed cellular debris, inflammatory cells, and mucus cause airway obstruction, with spread of infection occurring along the bronchial tree, as is seen in viral pneumonia. *S. pneumoniae* produces local edema that aids in the proliferation of organisms and their spread into adjacent portions of lung, often resulting in the characteristic focal lobar involvement. Group A streptococcus lower respiratory tract infection typically results in more diffuse lung involvement with interstitial pneumonia. The pathology includes necrosis of tracheobronchial mucosa; formation of large amounts of exudate, edema, and local hemorrhage, with extension into the interalveolar septa; and involvement of lymphatic vessels with frequent pleural involvement. *S. aureus* pneumonia manifests as confluent bronchopneumonia, which is often unilateral and characterized by the presence of extensive areas of hemorrhagic necrosis and irregular areas of cavitation of the lung parenchyma, resulting in pneumatoceles, empyema, and, at times, bronchopulmonary fistulas.

Recurrent pneumonia is defined *as 2 or more* episodes in a single year *or 3 or more* episodes ever, with radiographic clearing between occurrences. An underlying disorder should be considered if a child experiences recurrent pneumonia (Table 428.5).

Table 428.5

Differential Diagnosis of Recurrent Pneumonia

HEREDITARY DISORDERS
Cystic fibrosis Sickle cell disease
DISORDERS OF IMMUNITY
HIV/AIDS Bruton agammaglobulinemia Selective immunoglobulin G subclass deficiencies Common variable immunodeficiency syndrome Severe combined immunodeficiency syndrome Chronic granulomatous disease Hyperimmunoglobulin E syndromes Leukocyte adhesion defect
DISORDERS OF CILIA
Primary ciliary dyskinesia Kartagener syndrome
ANATOMIC DISORDERS
Pulmonary sequestration Lobar emphysema Congenital cystic adenomatoid malformation Gastroesophageal reflux Foreign body

Tracheoesophageal fistula (H type)
Bronchiectasis
Aspiration (oropharyngeal incoordination)
Aberrant bronchus

Adapted from Kliegman RM, Marcdante KJ, Jenson HJ, et al: *Nelson essentials of pediatrics* , ed 5, Philadelphia, 2006, Elsevier, p. 507.

Clinical Manifestations

Pneumonia is frequently preceded by several days of symptoms of an upper respiratory tract infection, typically rhinitis and cough. In viral pneumonia, fever is usually present but temperatures are generally lower than in bacterial pneumonia. Tachypnea is the most consistent clinical manifestation of pneumonia. Increased work of breathing accompanied by intercostal, subcostal, and suprasternal retractions, nasal flaring, and use of accessory muscles is common. Severe infection may be accompanied by cyanosis and lethargy, especially in infants. Auscultation of the chest may reveal crackles and wheezing, but it is often difficult to localize the source of these adventitious sounds in very young children with hyperresonant chests. It is often not possible to distinguish viral pneumonia (especially adenovirus) clinically from disease caused by *Mycoplasma* and other bacterial pathogens.

Bacterial pneumonia in adults and older children typically begins suddenly with high fever, cough, and chest pain. Other symptoms that may be seen include drowsiness with intermittent periods of restlessness; rapid respirations; anxiety; and, occasionally, delirium. In many children, splinting on the affected side to minimize pleuritic pain and improve ventilation is noted; such children may lie on one side with the knees drawn up to the chest.

Physical findings depend on the stage of pneumonia. Early in the course of illness, diminished breath sounds, scattered crackles, and rhonchi are commonly heard over the affected lung field. With the development of increasing consolidation or complications of pneumonia such as pleural effusion or empyema, dullness on percussion is noted and breath sounds may be diminished. A lag in respiratory excursion often occurs on the affected side. Abdominal distention may be prominent because of gastric dilation from swallowed air or ileus. Abdominal pain is common in lower-lobe pneumonia. The liver may seem enlarged because of downward displacement of the diaphragm secondary to hyperinflation of the lungs or superimposed congestive heart failure.

Symptoms described in adults with pneumococcal pneumonia may be noted in older children but are rarely observed in infants and young children, in whom the clinical pattern is considerably more variable. In infants, there may be a prodrome of upper respiratory tract infection and poor feeding, leading to the abrupt onset of fever, restlessness, apprehension, and respiratory distress. These infants typically appear ill, with respiratory distress manifested as grunting; nasal flaring; retractions of the supraclavicular, intercostal, and subcostal areas; tachypnea; tachycardia; air hunger; and often cyanosis. Auscultation may be misleading, particularly in young infants, with meager findings disproportionate to the degree of tachypnea. Some infants with bacterial pneumonia may have associated gastrointestinal disturbances characterized by vomiting, anorexia, diarrhea, and abdominal distention secondary to a paralytic ileus. Rapid progression of symptoms is characteristic in the most severe cases of bacterial pneumonia.

Diagnosis

In 2011, the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA) published clinical practice guidelines for community-acquired pneumonia in children older than 3 mo of age. These evidence-based guidelines provide recommendations for diagnostic testing and treatment of previously healthy children with pneumonia in both outpatient and inpatient settings.

An infiltrate on chest radiograph (posteroanterior and lateral views) supports the diagnosis of pneumonia; images may also identify a complication such as a pleural effusion or empyema. Viral pneumonia is usually characterized by hyperinflation with bilateral interstitial infiltrates and peribronchial cuffing (Fig. 428.2). Confluent lobar consolidation is typically seen with pneumococcal pneumonia (Fig. 428.3). The radiographic appearance alone does not accurately identify pneumonia etiology, and other clinical features of the illness must be considered. Repeat chest radiographs are not required for proof of cure for patients with uncomplicated pneumonia. Moreover, current PIDS–IDSA guidelines do not recommend that a chest radiograph be performed for children with suspected pneumonia (cough, fever, localized crackles, or decreased breath sounds) who are well enough to be managed as outpatients because imaging in this context only rarely changes management.

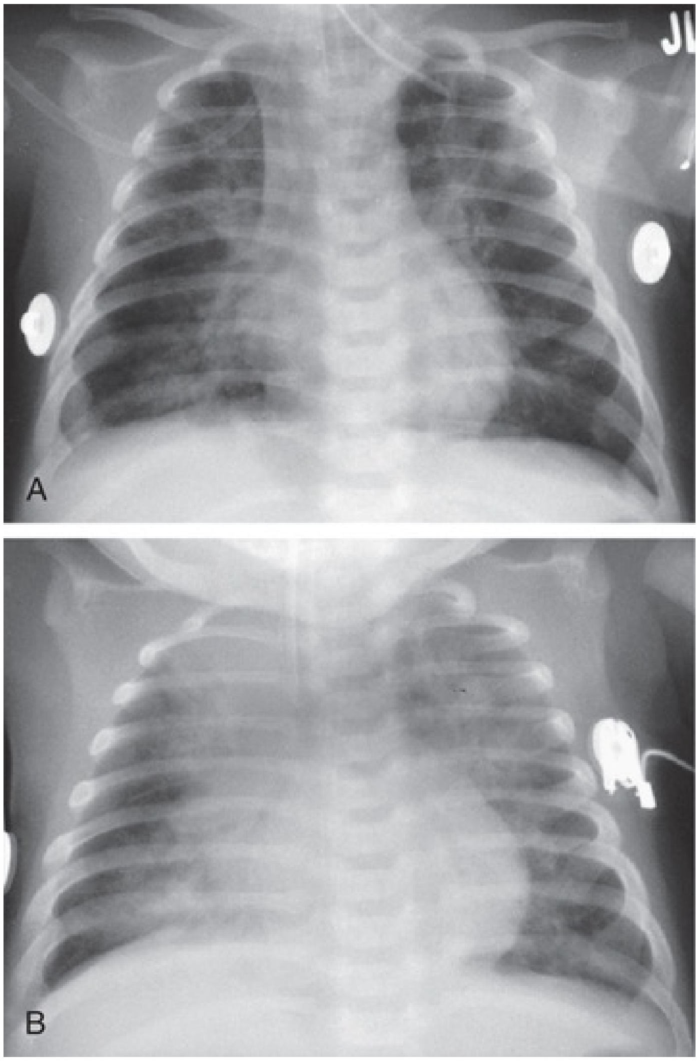

FIG. 428.2 **A,** Radiographic findings characteristic of respiratory syncytial virus pneumonia in a 6 mo old infant with rapid respirations and fever. Anteroposterior radiograph of the chest shows hyperexpansion of the lungs with bilateral fine air space disease and streaks of density, indicating the presence of both pneumonia and atelectasis. An endotracheal tube is in place. **B,** One day later, the anteroposterior radiograph of the chest shows increased bilateral pneumonia.

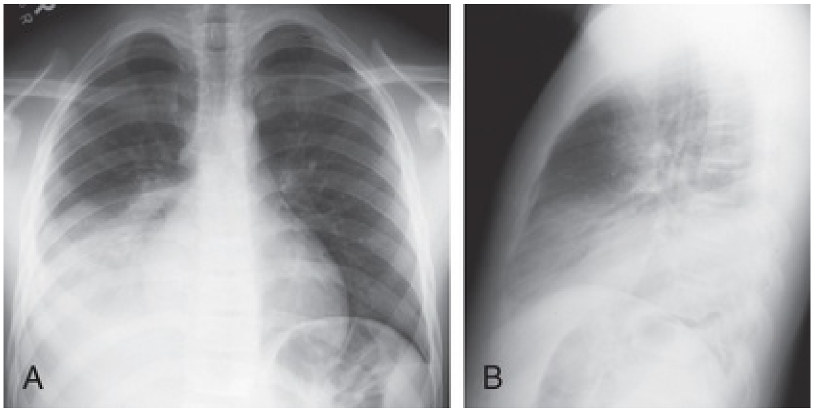

FIG. 428.3 Radiographic findings characteristic of pneumococcal pneumonia in a 14 yr old boy with cough and fever. Posteroanterior (A) and lateral (B) chest radiographs reveal consolidation in the right lower lobe, strongly suggesting bacterial pneumonia.

Point-of-care use of portable or handheld ultrasonography is highly sensitive and specific in diagnosing pneumonia in children by determining lung consolidations and air bronchograms or effusions (Fig. 428.4). However, the reliability of this imaging modality for pneumonia diagnosis is highly user-dependent, which has limited its widespread use.

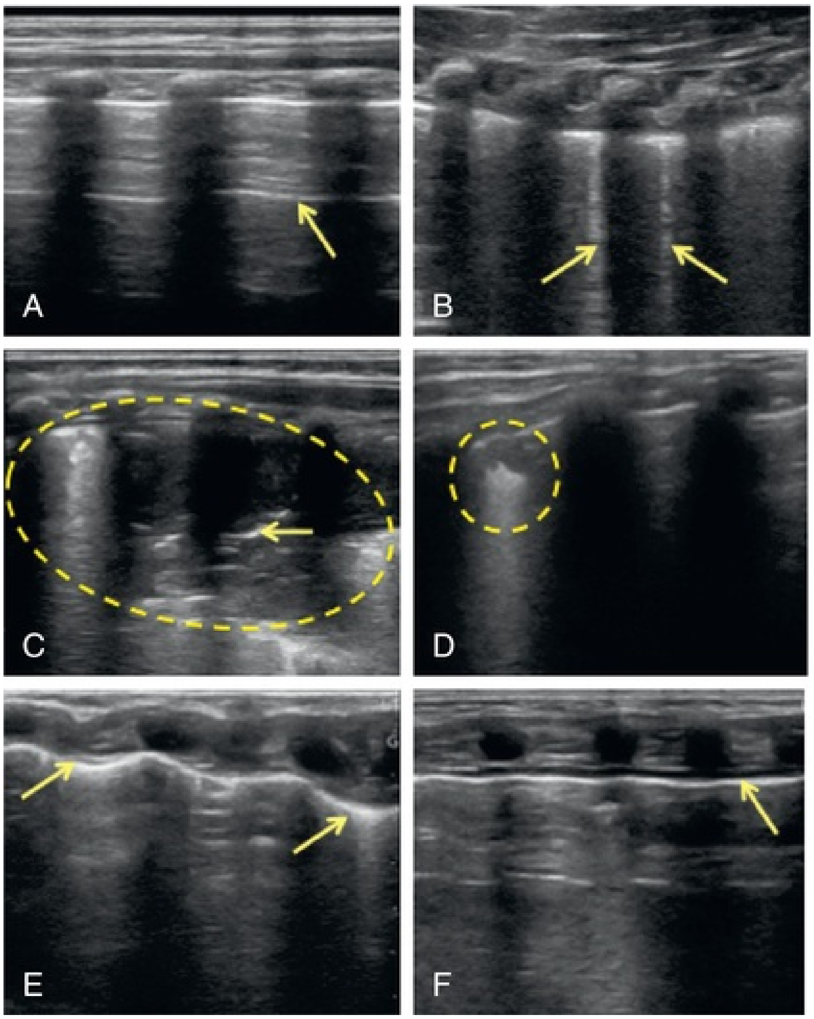

FIG. 428.4 Lung ultrasound patterns. A, Negative lung ultrasound pattern with A-line *(arrow)* and no other findings. Positive lung ultrasound patterns with (B) B-lines *(arrows)* ; (C) large consolidation (>1 cm) with tissue-like echo-texture *(circle)* and ultrasonographic bronchograms *(arrow)* ; (D) small consolidation (<1 cm; *circle*); (E) pleural line abnormality with thickening and irregularity (arrows); and (F) pleural effusion *(arrow)* . (From Varshney T, Mok E, Shapiro AJ, et al: Point-of-care lung ultrasound in young children with respiratory tract infections and wheeze, *Emerg Med J* 33(9):603–610, 2016, Fig. 1, p. 604.)

The peripheral white blood cell (WBC) count can be useful in differentiating viral from bacterial pneumonia. In viral pneumonia, the WBC count can be normal or elevated but is usually not higher than 20,000/mm^3 , with a lymphocyte predominance. Bacterial pneumonia is often associated with an elevated WBC count, in the range of 15,000-40,000/mm^3 , and a predominance of polymorphonuclear leukocytes. A large pleural effusion, lobar consolidation, and a high fever at the onset of the illness are also suggestive of a bacterial etiology. Atypical pneumonia caused by *C. pneumoniae* or *M. pneumoniae* is difficult to distinguish from pneumococcal pneumonia on the basis of radiographic and laboratory findings; although pneumococcal pneumonia is associated with a higher WBC count, erythrocyte sedimentation rate, procalcitonin, and C-reactive protein level, there is considerable overlap.

The definitive diagnosis of a viral infection rests on the detection of the viral genome or antigen in respiratory tract secretions. Reliable PCR assays are widely available for the rapid detection of many respiratory viruses, including RSV, parainfluenza, influenza, human metapneumovirus, adenovirus, enterovirus, and rhinovirus. Serologic techniques can also be used to diagnose a recent respiratory viral infection but generally require testing of acute and convalescent serum samples for a rise in antibodies to a specific virus. This diagnostic technique is laborious, slow, and not generally clinically useful because the infection usually has resolved by the time it is confirmed serologically. Serologic testing may be valuable as an epidemiologic tool to define the incidence and prevalence of the various respiratory viral pathogens.

The definitive diagnosis of a typical bacterial infection requires isolation of an organism from the blood, pleural fluid, or lung. Culture of sputum is of little value in the diagnosis of pneumonia in young children, while percutaneous lung aspiration is invasive and not routinely performed. Blood culture is positive in only 10% of children with pneumococcal pneumonia and is not recommended for nontoxic-appearing children treated as outpatients. Blood cultures are recommended for children who fail to improve or have clinical deterioration, have complicated pneumonia (Table 428.6), or require hospitalization. Urinary antigen tests should not be used to diagnose pneumonia caused by *S. pneumoniae* in children because of a high rate of false positives resulting from nasopharyngeal carriage. Pertussis infection can be diagnosed by PCR or culture of a nasopharyngeal specimen; although culture is considered the gold standard for pertussis diagnosis, it is less sensitive than the available PCR assays. Acute infection caused by *M. pneumoniae* can be diagnosed on the basis of a PCR test result from a respiratory specimen or seroconversion in an immunoglobulin G assay. Cold agglutinins at titers > 1 : 64 are also found in the blood of roughly half of patients with *M. pneumoniae* infections; however, cold agglutinins are nonspecific because other pathogens such as influenza viruses may also cause increases. Serologic evidence, such as antistreptolysin O and anti-DNase B titers, may also be useful in the diagnosis of group A streptococcal pneumonia.

Table 428.6

Factors Suggesting Need for Hospitalization of Children

With Pneumonia

Age <6 mo
Immunocompromised state
Toxic appearance
Moderate to severe respiratory distress
Hypoxemia (oxygen saturation <90% breathing room air, sea level)
Complicated pneumonia*
Sickle cell anemia with acute chest syndrome
Vomiting or inability to tolerate oral fluids or medications
Severe dehydration
No response to appropriate oral antibiotic therapy
Social factors (e.g., inability of caregivers to administer medications at home or follow-up appropriately)

* Pleural effusion, empyema, abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory distress syndrome, extrapulmonary infection (meningitis, arthritis, pericarditis, osteomyelitis, endocarditis), hemolytic uremic syndrome, or sepsis.

Adapted from Baltimore RS: Pneumonia. In Jenson HB, Baltimore RS, editors: *Pediatric infectious diseases: principles and practice,* Philadelphia, 2002, WB Saunders, p. 801.

There is a great deal of interest in developing a non-invasive diagnostic test that can accurately differentiate children with bacterial versus viral causes of pneumonia. Various biomarkers, including C-reactive protein, procalcitonin, lipocalin-2, and tumor necrosis factor-related apoptosis-inducing ligand, have been evaluated for their ability to differentiate these pneumonia etiologies. For many of these biomarkers, values differ in children with bacterial compared with viral causes of pneumonia, but the reliability of these tests is not sufficiently high to justify routine use. Studies of these biomarkers have also been hampered by the lack of a gold standard for determining pneumonia etiology and the relatively frequent occurrence of viral–bacterial co-infections. Patient peripheral cell gene expression patterns determined by microarray reverse transcription PCR is an emerging technology that may help differentiate bacterial from viral causes of pneumonia, although further study is needed.

Treatment

Treatment of suspected bacterial pneumonia is based on the presumptive cause and the age and clinical appearance of the child. For mildly ill children who do not require hospitalization, amoxicillin is recommended. With the emergence of penicillin-resistant pneumococci, high doses of amoxicillin (90 mg/kg/day orally divided twice daily) should be prescribed unless local data indicate a low prevalence of resistance (Table 428.7). Therapeutic alternatives include cefuroxime and amoxicillin/clavulanate. For school-aged children and adolescents or when infection with *M. pneumoniae* or *C. pneumoniae* is suspected, a macrolide antibiotic is an appropriate choice for outpatient management. Azithromycin is generally preferred, while clarithromycin or doxycycline (for children 8 yr or older) are alternatives. For adolescents, a respiratory fluoroquinolone (levofloxacin, moxifloxacin) may also be considered as an alternative if there are contraindications to other agents.

Table 428.7

Selection of Antimicrobial Therapy for Specific Pathogens

PATHOGEN	PARENTERAL THERAPY	ORAL THERAPY (STEP-DOWN THERAPY OR MILD INFECTION)
Streptococcus pneumoniae with MICs for penicillin ≤ 2.0 µg/mL	Preferred: ampicillin (150-200 mg/kg/day every 6 hr) or penicillin (200,000-250,000 U/kg/day every 4-6 hr); Alternatives: ceftriaxone (50-100 mg/kg/day every 12-24 hr) (preferred for parenteral outpatient therapy); may also be effective: clindamycin (40 mg/kg/day every 6-8 hr) or vancomycin (40-60 mg/kg/day every 6-8 hr)	Preferred: amoxicillin (90 mg/kg/day in 2 doses or 45 mg/kg/day in 3 doses); Alternatives: second- or third-generation cephalosporin (cefpodoxime, cefixime, cefprozil); oral levofloxacin, if susceptible (16-20 mg/kg/day in 2 doses for children 6 mo to 5 yr old and 8-10 mg/kg/day once daily for children 5-16 yr old; maximum daily dose, 750 mg) or oral linezolid (30 mg/kg/day in 3 doses for children <12 yr old and 20 mg/kg/day in 2 doses for children ≥12 yr old)
S. pneumoniae resistant to penicillin, with MICs ≥ 4.0 µg/mL	Preferred: ceftriaxone (100 mg/kg/day every 12-24 hr); Alternatives: ampicillin (300-400 mg/kg/day every 6 hr), levofloxacin (16-20 mg/kg/day every 12 hr for children 6 mo to 5 yr old and 8-10 mg/kg/day once daily for children 5-16 yr old; maximum daily dose, 750 mg), or linezolid (30 mg/kg/day every 8 hr for children <12 yr old and 20 mg/kg/day every 12 hr for children ≥12 yr old); may also be effective: clindamycin (40 mg/kg/day every 6-8 hr) or vancomycin (40-60 mg/kg/day every 6-8 hr)	Preferred: oral levofloxacin (16-20 mg/kg/day in 2 doses for children 6 mo to 5 yr and 8-10 mg/kg/day once daily for children 5-16 yr, maximum daily dose, 750 mg), if susceptible, or oral linezolid (30 mg/kg/day in 3 doses for children <12 yr and 20 mg/kg/day in 2 doses for children ≥12 yr); Alternative: oral clindamycin (30-40 mg/kg/day in 3 doses)
Group A streptococcus	Preferred: intravenous penicillin (100,000–250,000 U/kg/day every 4-6 hr) or ampicillin (200 mg/kg/day every 6 hr); Alternatives: ceftriaxone (50-100 mg/kg/day every 12-24 hr); may also be effective: clindamycin, if susceptible (40 mg/kg/day every 6-8 hr) or vancomycin (40-60 mg/kg/day every 6-8 hr)	Preferred: amoxicillin (50-75 mg/kg/day in 2 doses), or penicillin V (50-75 mg/kg/day in 3 or 4 doses); Alternative: oral clindamycin (40 mg/kg/day in 3 doses)
Staphylococcus aureus ,	Preferred: cefazolin (150 mg/kg/day every 8 hr) or semisynthetic penicillin, e.g., oxacillin	Preferred: oral cephalexin (75-100 mg/kg/day in 3 or 4 doses);

methicillin susceptible (combination therapy not well studied)	(150-200 mg/kg/day every 6-8 hr); Alternatives: clindamycin (40 mg/kg/day every 6-8 hr) or vancomycin (40-60 mg/kg/day every 6-8 hr)	Alternative: oral clindamycin (30-40 mg/kg/day in 3 or 4 doses)
S. aureus , methicillin resistant, susceptible to clindamycin (combination therapy not well-studied)	Preferred: vancomycin (40-60 mg/kg/day every 6-8 hr or dosing to achieve an AUC/MIC ratio of >400) or clindamycin (40 mg/kg/day every 6-8 hr); Alternatives: linezolid (30 mg/kg/day every 8 hr for children <12 yr old and 20 mg/kg/day every 12 hr for children ≥ 12 yr old)	Preferred: oral clindamycin (30-40 mg/kg/day in 3 or 4 doses); Alternatives: oral linezolid (30 mg/kg/day in 3 doses for children <12 yr and 20 mg/kg/day in 2 doses for children ≥12 yr)
S. aureus, methicillin resistant, resistant to clindamycin (combination therapy not well studied)	Preferred: vancomycin (40-60 mg/kg/day every 6-8 hr or dosing to achieve an AUC/MIC ratio of >400); Alternatives: linezolid (30 mg/kg/day every 8 hr for children <12 yr old and 20 mg/kg/day every 12 hr for children ≥12 yr old)	Preferred: oral linezolid (30 mg/kg/day in 3 doses for children <12 yr and 20 mg/kg/day in 2 doses for children ≥12 yr old); Alternatives: none; entire treatment course with parenteral therapy may be required
Haemophilus influenza, typeable (A-F) or nontypeable	Preferred: intravenous ampicillin (150-200 mg/kg/day every 6 hr) if β-lactamase negative, ceftriaxone (50-100 mg/kg/day every 12-24 hr) if β-lactamase producing Alternatives: intravenous ciprofloxacin (30 mg/kg/day every 12 hr) or intravenous levofloxacin (16-20 mg/kg/day every 12 hr for children 6 mo to 5 yr old and 8-10 mg/kg/day once daily for children 5-16 yr old; maximum daily dose, 750 mg)	Preferred: amoxicillin (75-100 mg/kg/day in 3 doses) if β-lactamase negative, or amoxicillin clavulanate (amoxicillin component, 45 mg/kg/day in 3 doses or 90 mg/kg/day in 2 doses) if β-lactamase producing; Alternatives: cefdinir, cefixime, cefpodoxime, or ceftibuten
Mycoplasma pneumoniae	Preferred: intravenous azithromycin (10 mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible); Alternatives: intravenous erythromycin lactobionate (20 mg/kg/day every 6 hr) or levofloxacin (16-20 mg/kg/day every 12 hr; maximum daily dose, 750 mg)	Preferred: azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2-5); Alternatives: clarithromycin (15 mg/kg/day in 2 doses) or oral erythromycin (40 mg/kg/day in 4 doses); for children >7 yr old, doxycycline (2-4 mg/kg/day in 2 doses; for adolescents with skeletal maturity, levofloxacin (500 mg once daily) or moxifloxacin (400 mg once daily)
Chlamydia trachomatis or *Chlamydophila pneumoniae*	Preferred: intravenous azithromycin (10 mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible); Alternatives: intravenous erythromycin lactobionate (20 mg/kg/day every 6 hr) or levofloxacin (16-20 mg/kg/day in 2 doses for children 6 mo to 5 yr old and 8-10 mg/kg/day once daily for children 5-16 yr old; maximum daily dose, 750 mg)	Preferred: azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily days 2-5); Alternatives: clarithromycin (15 mg/kg/day in 2 doses) or oral erythromycin (40 mg/kg/day in 4 doses); for children >7 yr old, doxycycline (2-4 mg/kg/day in 2 doses); for adolescents with skeletal maturity, levofloxacin (500 mg once daily) or moxifloxacin (400 mg once daily)

Doses for oral therapy should not exceed adult doses.

[a] Clindamycin resistance appears to be increasing in certain geographic areas among *S. pneumoniae* And *S. aureus* infections.

[b] For β-lactam–allergic children.

AUC, area under the time vs. serum concentration curve; MIC, minimum inhibitory concentration.

From Bradley JS, Byington CL, Shah SS, et al: The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America, *Clin Infect Dis* 53(7):617–630, 2011, Table 5, pp. 623–624.

The empiric treatment of suspected bacterial pneumonia in a hospitalized child requires an approach based on local epidemiology, the immunization status of the child, and the clinical manifestations at the time of presentation. In areas without substantial high-level penicillin resistance among *S. pneumoniae* , children who are fully immunized against *H. influenzae* type b and *S. pneumoniae* and are not severely ill should receive ampicillin or penicillin G. For children who do not meet these criteria, ceftriaxone or cefotaxime may be used. If clinical features suggest staphylococcal pneumonia (pneumatoceles, empyema), initial antimicrobial therapy should also include vancomycin or clindamycin. Moreover, if infection with *M. pneumoniae* or *C. pneumoniae* is suspected, a macrolide antibiotic should be included in the treatment regimen.

If viral pneumonia is suspected, it is reasonable to withhold antibiotic therapy, especially for preschool-aged patients who are mildly ill, have clinical evidence suggesting viral infection, and are in no respiratory distress. However, up to 30% of patients with known viral infection, particularly influenza viruses, may have coexisting bacterial pathogens. Therefore, if the decision is made to withhold antibiotic therapy on the basis of presumptive diagnosis of a viral infection, deterioration in clinical status should signal the possibility of superimposed bacterial infection, and antibiotic therapy should be initiated.

Table 428.7 notes the indications for admission to a hospital. Hospitalized children should receive supportive care and may require intravenous fluids; respiratory support, including supplemental oxygen, continuous positive airway pressure (CPAP), or mechanical ventilation; or vasoactive medications for hypotension or sepsis physiology.

The optimal duration of antibiotic treatment for pneumonia has not been well-established in controlled studies. However, antibiotics should generally be continued until the patient has been afebrile for 72 hr, and the total duration should not be less than 10 days (or 5 days if azithromycin is used). Shorter courses (5-7 days) may also be effective, particularly for children managed on an outpatient basis, but further study is needed. Available data do not support prolonged courses of treatment for uncomplicated pneumonia. Preliminary studies suggest that a reduction of previously elevated serum procalcitonin levels to an absolute level (0.1-0.25 μg/L) may help determine when to stop treatment.

Despite substantial gains over the past 15 yr, in developing countries less than two-thirds of children with symptoms of pneumonia are taken to an appropriate caregiver, and fewer than half receive antibiotics. The World Health Organization and other international groups have developed systems to train mothers and local healthcare providers in the recognition and appropriate antibiotic treatment of pneumonia. In addition to antibiotics, oral zinc (10 mg/day for < 12 mo, 20 mg/day for ≥ 12 mo given for 7 days) may reduce mortality among children in developing countries with clinically defined severe pneumonia. Bubble CPAP improves mortality from pneumonia with hypoxemia compared with standard oxygen therapy in settings without access to ventilator-derived CPAP or mechanical ventilation.

Prognosis

Typically, patients with uncomplicated community-acquired bacterial pneumonia show response to therapy, with improvement in clinical symptoms (fever, cough, tachypnea, chest pain), within 48-72 hr of initiation of antibiotics. Radiographic evidence of improvement lags substantially behind clinical improvement. A number of possibilities must be considered when a patient does not improve with appropriate antibiotic therapy: (1) complications, such as pleural effusion or empyema (see Table 428.6); (2) bacterial resistance; (3) nonbacterial etiologies such as viruses or fungi and aspiration of foreign bodies or food; (4) bronchial obstruction from endobronchial lesions, foreign body, or mucous plugs; (5) preexisting diseases such as immunodeficiencies, ciliary dyskinesia, cystic fibrosis, pulmonary sequestration, or congenital pulmonary airway malformation; and (6) other noninfectious causes (including bronchiolitis obliterans, hypersensitivity pneumonitis, eosinophilic pneumonia, and granulomatosis with polyangiitis, formerly called Wegener granulomatosis). A chest radiograph is the first step in determining the reason for a lack of response to initial treatment. Bronchoalveolar lavage may be indicated in children with respiratory failure; high-resolution CT scans may better identify complications or an anatomic reason for a poor response to therapy.

Mortality from community-acquired pneumonia in developed countries is rare, and most children with pneumonia do not experience long-term pulmonary sequelae. Some data suggest that up to 45% of children have symptoms of asthma 5 yr after hospitalization for pneumonia; this finding may reflect either undiagnosed asthma at the time of presentation or a propensity for development of asthma after pneumonia.

Complications

Complications of pneumonia (see Table 428.6) are usually the result of direct spread of bacterial infection within the thoracic cavity (pleural effusion, empyema, and pericarditis) or bacteremia and hematologic spread (Fig. 428.5). Meningitis, endocarditis, suppurative arthritis, and osteomyelitis are rare complications of hematologic spread of pneumococcal or *H. influenzae* type b infection.

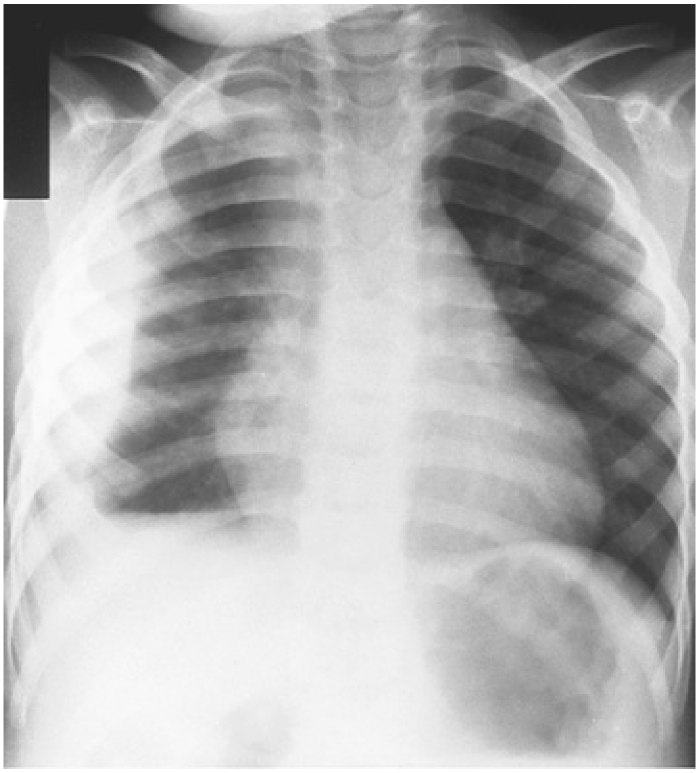

FIG. 428.5 Pneumococcal empyema on the chest radiography of a 3 yr old child who has had upper respiratory symptoms and fever for 3 days. A pleural fluid collection can be seen on the right side. The patient had a positive pleural tap and blood culture result for pneumococci. The child recovered completely within 3 wk. (From Kuhn JP, Slovis TL, Haller JO,

editors: *Caffrey's pediatric diagnostic imaging,* ed 10, Philadelphia, 2004, Mosby, p. 1002.)

S. aureus, *S. pneumoniae*, and *S. pyogenes* are the most common causes of parapneumonic effusions and empyema. Nonetheless many effusions that complicate bacterial pneumonia are sterile. Analysis of pleural fluid parameters, including pH, glucose, protein, and lactate dehydrogenase, can differentiate transudative from exudative effusions (Table 428.8). However, current PIDS–IDSA guidelines do not recommend that these tests be performed because this distinction rarely changes management. Pleural fluid should be sent for Gram stain, and bacterial culture as this may identify the bacterial cause of pneumonia. Molecular methods, including bacterial species-specific PCR assays or sequencing of the bacterial 16S ribosomal RNA gene, detect bacterial DNA and can often determine the bacterial etiology of the effusion if the culture is negative, particularly if the pleural fluid sample was obtained after initiation of antibiotics. A pleural fluid WBC count with differential may be helpful if there is suspicion for pulmonary tuberculosis or a noninfectious etiology for the pleural effusion, such as malignancy.

Table 428.8

Features Differentiating Exudative From Transudative Pleural Effusion

FEATURE	TRANSUDATE	EXUDATE
Appearance	Serous	Cloudy
Leukocyte count	$<10,000/mm^3$	$>50,000/mm^3$
pH	>7.2	<7.2
Protein	<3.0 g/dL	>3.0 g/dL
Ratio of pleural fluid protein to serum	<0.5	>0.5
LDH	<200 IU/L	>200 IU/L
Ratio of pleural fluid LDH to serum	<0.6	>0.6
Glucose	≥60 mg/dL	<60 mg/dL

LDH, lactate dehydrogenase.

From Septimus EJ: Pleural effusion and empyema, In Bennett JE, Dolin R, Blaser MJ, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* , ed 8, vol 1, Philadelphia, 2015, Elsevier, Table 70-1, p. 851.

Small (<1 cm on lateral decubitus radiograph), free-flowing parapneumonic effusions often do not require drainage but respond to appropriate antibiotic therapy. Larger effusions should typically be drained, particularly if the effusion is purulent (empyema) or associated with respiratory distress. Chest ultrasound, or alternatively CT, may be helpful in determining whether loculations are present. The mainstays of therapy include antibiotic therapy and drainage by tube thoracostomy with the instillation of fibrinolytic agents (urokinase, streptokinase, tissue plasminogen activator). Video-assisted thoracoscopy is a less often employed alternative that enables debridement or lysis of adhesions and drainage of loculated areas of pus. Early diagnosis and intervention, particularly with fibrinolysis or less often video-assisted thoracoscopy, may obviate the need for thoracotomy and open debridement.

Prevention

The introduction of PCVs resulted in a substantial reduction in the incidence of pneumonia hospitalizations among children. The annual rate of all-cause pneumonia hospitalization among children younger than 2 yr of age in the United States was 12.5 per 1,000 children during the period from 1997 to 1999. In 2000, 7-valent pneumococcal conjugate vaccine (PCV7) was licensed and recommended. In 2006, the pneumonia hospitalization rate in this age group was 8.1 per 1,000 children, a 35% decrease from the pre-vaccine rate. In 2010, 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States. Early data indicate that introduction of this vaccine resulted in a 16–27% further reduction in pneumonia hospitalizations among children relative to the post-PCV7 era.

Influenza vaccine may also prevent pneumonia hospitalizations among children and should be administered to all children >6 mo of age. For infants <6 mo of age, household contacts and other primary caregivers should be immunized. Maintaining high rates of vaccination for *H. influenzae* type b, pertussis, and measles remains important for the prevention of pneumonia from these causes. Several RSV vaccines are currently under development; introduction of an effective vaccine against RSV would be anticipated to substantially reduce pneumonia incidence among children, particularly young infants.

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CHAPTER 429

Pleurisy, Pleural Effusions, and Empyema

Glenna B. Winnie, Aarthi P. Vemana, Suraiya K. Haider, Steven V. Lossef

Pleurisy is the inflammation of the pleura; it may be accompanied by an effusion. The most common cause of pleural effusion in children is bacterial pneumonia (see Chapter 428); heart failure (see Chapter 469), rheumatologic causes, and metastatic intrathoracic malignancy are also common causes. A variety of other diseases account for the remaining cases, including tuberculosis (see Chapter 242), lupus erythematosus (see Chapter 183), aspiration pneumonitis (see Chapter 425), uremia, pancreatitis, subdiaphragmatic abscess, and rheumatoid arthritis.

Inflammatory processes in the pleura are usually divided into 3 types: dry pleurisy, serofibrinous or serosanguineous, and purulent pleurisy or empyema.

429.1

Dry Pleurisy

Glenna B. Winnie, Aarthi P. Vemana, Suraiya K. Haider, Steven V. Lossef

Etiology

Dry pleurisy, formerly called plastic pleurisy, may be associated with acute bacterial or viral pulmonary infections or may develop during the course of an acute upper respiratory tract illness. The condition is also associated with tuberculosis and autoimmune diseases such as systemic lupus erythematosus.

Pathology and Pathogenesis

The process is usually limited to the visceral pleura, with small amounts of yellow serous fluid and adhesions between the pleural surfaces. In tuberculosis, pleurisy can be caused by a severe delayed-type hypersensitivity reaction to *Mycobacterium tuberculosis* ; the adhesions develop rapidly, and the pleura are often thickened. Occasionally, fibrin deposition and adhesions are severe enough to produce a fibrothorax that markedly inhibits the excursions of the lung.

Clinical Manifestations

The primary disease often overshadows signs and symptoms of pleurisy. Pain, the principal symptom, is exaggerated by deep breathing, coughing, and straining. Occasionally, pleural pain is described as a dull ache, which is less likely to vary with breathing. The pain is often localized over the chest wall and is referred to the shoulder or the back. Pain with breathing is responsible for grunting and guarding of respirations, and the child often lies on the affected side in an attempt to decrease respiratory excursions. Early in the illness, a leathery, rough, inspiratory and expiratory friction rub may be audible, but it usually disappears rapidly. If the layer of exudate is thick, increased dullness to percussion and decreased breath sounds may be heard. Pleurisy may be asymptomatic. Chronic pleurisy is occasionally encountered with conditions such as atelectasis, pulmonary abscess, connective tissue diseases, and tuberculosis.

Laboratory Findings

Dry pleurisy may be detected on radiographs as a diffuse haziness at the pleural surface or a dense, sharply demarcated shadow (Figs. 429.1 and 429.2). The latter finding may be indistinguishable from small amounts of pleural exudate. Chest radiographic findings may be normal, but ultrasonography or CT findings will be positive.

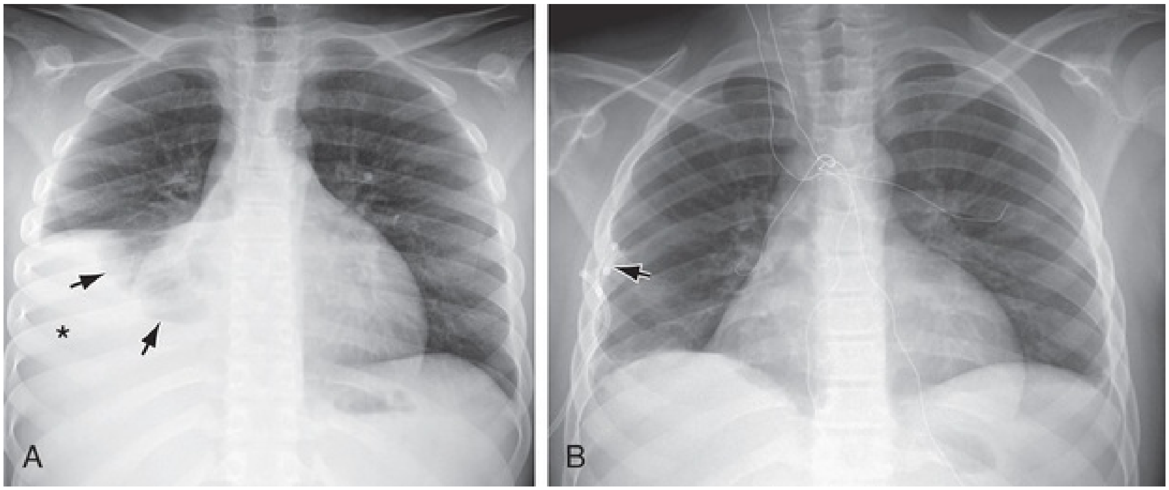

FIG. 429.1 **A,** Right pleural effusion *(asterisk)* caused by lupus erythematosus in a 12 yr old child. Note compressed middle and lower lobes of the right lung *(arrows)* . **B,** The effusion was evacuated and the right lung was completely reexpanded after insertion of the pigtail chest tube *(arrow)* .

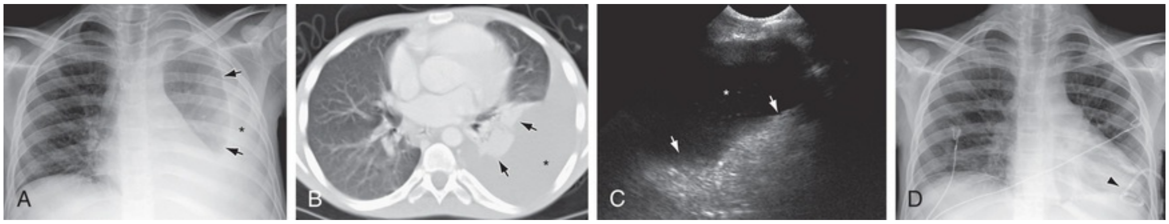

FIG. 429.2 Left pleural effusion in a teenager with AIDS and *Mycobacterium avium-intracellulare* infection. The pleural effusion *(asterisk)* is clearly seen on the chest radiograph **(A),** CT scan **(B),** and ultrasonogram **(C)** of the left chest. *Arrows* point to the compressed and atelectatic left lung. **D,** A pigtail chest tube *(arrowhead)* was inserted, resulting in reexpansion of the left lung.

Differential Diagnosis

Pleurisy must be distinguished from other diseases, such as epidemic pleurodynia, trauma to the rib cage (rib fracture), lesions of the dorsal root ganglia, tumors of the spinal cord, herpes zoster, gallbladder disease, and trichinosis. Even if evidence of pleural fluid is not found on physical or radiographic examination, a CT- or ultrasound-guided pleural tap in suspected cases often results in the recovery of a small amount of exudate, which when cultured may reveal the underlying bacterial cause in patients with an acute pneumonia. Patients with pleurisy and pneumonia should always be screened for tuberculosis.

Treatment

Therapy should be aimed at the underlying disease. When pneumonia is present, neither immobilization of the chest with adhesive plaster nor therapy with drugs capable of suppressing the cough reflex is indicated. If pneumonia is not present or is under good therapeutic control, strapping of the chest to restrict expansion may afford relief from pain. Analgesia with nonsteroidal antiinflammatory agents may be helpful.

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429.2

Serofibrinous or Serosanguineous Pleurisy With Pleural Effusion

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Keywords

effusion

fibrinolytic therapy
pleurisy
transudate
exudate
Light's criteria
video-assisted thoracoscopic surgery
VATS

Etiology

Serofibrinous pleurisy is defined by a fibrinous exudate on the pleural surface and an exudative effusion of serous fluid into the pleural cavity. In general, it is associated with infections of the lung or with inflammatory conditions of the abdomen or mediastinum; occasionally, it is found with connective tissue diseases such as lupus erythematosus, periarteritis, and rheumatoid arthritis, and it may be seen with primary or metastatic neoplasms of the lung, pleura, or mediastinum. Tumors are commonly associated with a hemorrhagic pleurisy.

Pathogenesis

Pleural fluid originates from the capillaries of the parietal pleura and is absorbed from the pleural space via pleural stomas and the lymphatics of the parietal pleura. The rate of fluid formation is dictated by the Starling law, by which fluid movement is determined by the balance of hydrostatic and osmotic pressures in the pleural space and pulmonary capillary bed, and the permeability of the pleural membrane. Normally, approximately 10 mL of fluid is present in the pleural space, but if formation exceeds clearance, fluid accumulates. Pleural inflammation increases the permeability of the plural surface, with increased proteinaceous fluid formation; there may also be some obstruction to lymphatic absorption.

Clinical Manifestations

Because serofibrinous pleurisy is often preceded by the dry type, early signs and symptoms may be those of dry pleurisy. As fluid accumulates, pleuritic pain may disappear. The patient may become asymptomatic if the effusion remains small, or there may be only signs and symptoms of the underlying disease. Large fluid collections can produce cough, dyspnea, retractions, tachypnea, orthopnea, or cyanosis.

Physical findings depend on the amount of effusion. Dullness to flatness may be found on percussion. Breath sounds are decreased or absent, and there is a diminution in tactile fremitus, a shift of the mediastinum away from the affected side, and, occasionally, fullness of the intercostal spaces. If the fluid is not loculated, these signs may shift with changes in position. If extensive pneumonia is present, crackles and rhonchi may also be audible. Friction rubs are usually detected only during the early or late plastic stage. In infants, physical signs are less definite, and bronchial breathing may be heard instead of decreased breath sounds.

Laboratory Findings

Radiographic examination shows a generally homogeneous density obliterating the normal markings of the underlying lung. Small effusions may cause obliteration of only the costophrenic or cardiophrenic angles or a widening of the interlobar septa. Examinations should be performed with the patient both supine and upright, to demonstrate a shift of the effusion with a change in position; the decubitus position may be helpful. Ultrasonographic examinations are useful and may guide thoracentesis if the effusion is loculated. Examination of the fluid is essential to differentiate **exudates** from **transudates** and to determine the type of exudate (see Table 428.8). Depending on the clinical scenario, pleural fluid is sent for culture for bacterial, fungal, and mycobacterial cultures; antigen testing; Gram staining; and chemical evaluation of content, including protein, lactic dehydrogenase and glucose, amylase, specific gravity, total cell count and differential, cytologic examination, and pH. Complete blood count and serum chemistry analysis should be obtained; hypoalbuminemia is often present. **Exudates** usually have at least 1 of the following features: protein level >3.0 g/dL, with pleural fluid:serum protein ratio >0.5; pleural fluid lactic dehydrogenase values >200 IU/L; or fluid:serum lactic dehydrogenase ratio >0.6. Although systemic acidosis reduces the usefulness of pleural fluid pH measurements, pH < 7.20 suggests an exudate (see Chapter 400). Glucose is usually <60 mg/dL in malignancy, rheumatoid disease, and tuberculosis; the finding of many small lymphocytes and a pH < 7.20 suggest tuberculosis. The fluid of serofibrinous pleurisy is clear or slightly cloudy and contains relatively few leukocytes and, occasionally, some erythrocytes. Gram staining may occasionally show bacteria; however, acid-fast staining rarely demonstrates tubercle bacilli.

Diagnosis and Differential Diagnosis

Thoracentesis should be performed when pleural fluid is present or is suggested, unless the effusion is small, and the patient has a classic-appearing lobar pneumococcal pneumonia. Thoracentesis can differentiate serofibrinous pleurisy, empyema, hydrothorax, hemothorax, and chylothorax. Exudates are usually associated with an infectious process. In hydrothorax, the fluid has a specific gravity <1.015, and evaluation reveals only a few mesothelial cells rather than leukocytes. Chylothorax and hemothorax usually have fluid with a distinctive appearance, but differentiating serofibrinous from purulent pleurisy is impossible without microscopic examination of the fluid. Cytologic examination may reveal malignant cells. Serofibrinous fluid may rapidly become purulent.

Complications

Unless the fluid becomes purulent, it usually disappears relatively rapidly, particularly with appropriate treatment of bacterial pneumonia. It persists somewhat longer if a result of tuberculosis or a connective tissue disease and may recur or remain for a long time if caused by a neoplasm. As the effusion is absorbed, adhesions often develop between the 2 layers of the pleura, but usually little or no functional impairment results. Pleural thickening may develop and is occasionally mistaken for small quantities of fluid or for persistent pulmonary infiltrates. Pleural thickening may persist for months, but the process usually disappears, leaving no residua.

Treatment

Therapy should address the underlying disease. If the effusion is less than 10 mm in size on a chest x-ray, then there is no need for drainage. With a large effusion, draining the fluid makes the patient more comfortable. When a diagnostic thoracentesis is performed, as much fluid as possible should be removed for therapeutic purposes. Rapid removal of ≥1 L of pleural fluid may be associated with the development of reexpansion pulmonary edema (see Chapter 396). If the underlying disease is adequately treated, further drainage is usually unnecessary, but if sufficient fluid reaccumulates to cause respiratory embarrassment, chest tube drainage should be performed. In older children with suspected parapneumonic effusion, tube thoracostomy is considered necessary if the pleural fluid pH is <7.20 or the pleural fluid glucose level is <50 mg/dL. If the fluid is thick, loculated, or clearly purulent, tube drainage with fibrinolytic therapy or less often video-assisted thoracoscopic surgery (VATS) is indicated. Patients with pleural effusions may need analgesia, particularly after thoracentesis or insertion of a chest tube. Those with acute pneumonia may need supplemental oxygen in addition to specific antibiotic treatment. Studies in adults suggest that dexamethasone may be beneficial in addition to antibiotics and drainage in patients with parapneumonic effusions.

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429.3

Empyema

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Keywords

Empyema
fibrinolytic

VATS

Etiology

Empyema is an accumulation of pus in the pleural space. It is most often associated with pneumonia (see Chapter 428) caused by *Streptococcus pneumoniae* (see Chapter 209), although *Staphylococcus aureus* (see Chapter 208.1) is most common in developing nations and Asia, as well as in posttraumatic empyema. The relative incidence of *Haemophilus influenzae* (see Chapter 221) empyema has decreased since the introduction of the *H. influenzae* type b vaccination. Group A streptococcus, Gram-negative organisms, tuberculosis, fungi, viruses, and malignancy are less common causes. The disease can also be produced by rupture of a lung abscess into the pleural space, by contamination introduced from trauma or thoracic surgery, or, rarely, by mediastinitis or the extension of intraabdominal abscesses.

Epidemiology

Empyema is most frequently encountered in infants and preschool children. Although rates of bacterial pneumonia have decreased, the incidence of parapneumonic effusions has increased. This may be related to a shift towards more virulent organisms after the introduction of the heptavalent pneumococcal vaccine with a trend towards serotypes not covered by the vaccine. It occurs in 5–10% of children with bacterial pneumonia and in up to 86% of children with necrotizing pneumonia.

Pathology

Empyema has 3 stages: exudative, fibrinopurulent, and organizational. During the exudative stage, fibrinous exudate forms on the pleural surfaces. In the fibrinopurulent stage, fibrinous septa form, causing loculation of the fluid and thickening of the parietal pleura. If the pus is not drained, it may dissect through the pleura into lung parenchyma, producing bronchopleural fistulas and pyopneumothorax, or into the abdominal cavity. Rarely, the pus dissects through the chest wall (i.e., empyema necessitatis). During the organizational stage, there is fibroblast proliferation; pockets of loculated pus may develop into thick-walled abscess cavities or the lung may collapse and become surrounded by a thick, inelastic envelope (peel).

Clinical Manifestations

The initial signs and symptoms are primarily those of bacterial pneumonia. Children treated with antibiotic agents may have an interval of a few days between the clinical pneumonia phase and the evidence of empyema. Most patients are febrile, develop increased work of breathing or respiratory distress, and often appear more ill. Physical findings are identical to those described for serofibrinous pleurisy, and the 2 conditions are differentiated only by thoracentesis, which should always be performed when empyema is suspected.

Laboratory Findings

Radiographically, all pleural effusions appear similar, but the absence of a shift of the fluid with a change of position indicates a loculated empyema (Figs. 429.3 to 429.5). Although on an ultrasound a lenticular shape may indicate the presence of loculated fluid, septa are better visualized by CT. The maximal amount of fluid obtainable should be withdrawn by thoracentesis and studied as described in Chapter 429.2 . The effusion is an empyema if bacteria are present on Gram staining, the pH is <7.20, and there are >100,000 neutrophils/µL (see Chapter 428). Cultures of the fluid must always be performed to help identify the causal organism. Using standard culture methods, the organism can be identified in up to 60% of cases. The yield improves significantly with concomitant use of nucleic acid amplification techniques. Blood cultures may be positive and have a higher yield than cultures of the pleural fluid. Leukocytosis and an elevated sedimentation rate may be found.

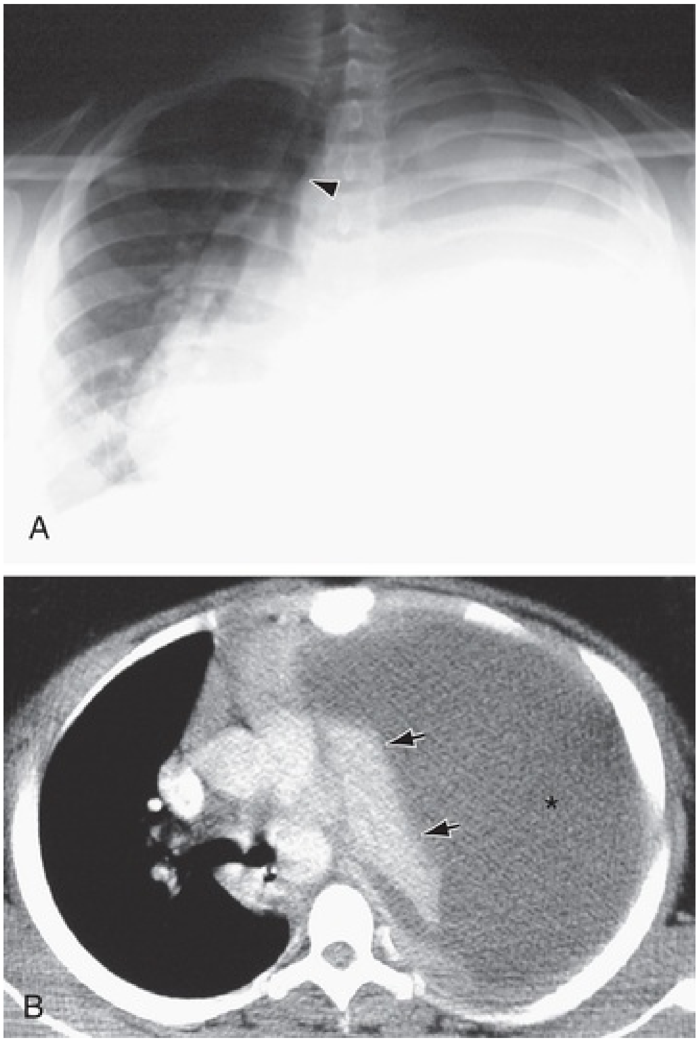

FIG. 429.3 Empyema and pneumonia in a teenager. **A,** Chest radiograph shows opacification of the left thorax. Note shift of mediastinum and trachea *(arrowhead)* to right. **B,** Thoracic CT scan shows massive left pleural effusion *(asterisk)* . Note the compression and atelectasis of the left lung *(arrows)* and shift of the mediastinum to the right.

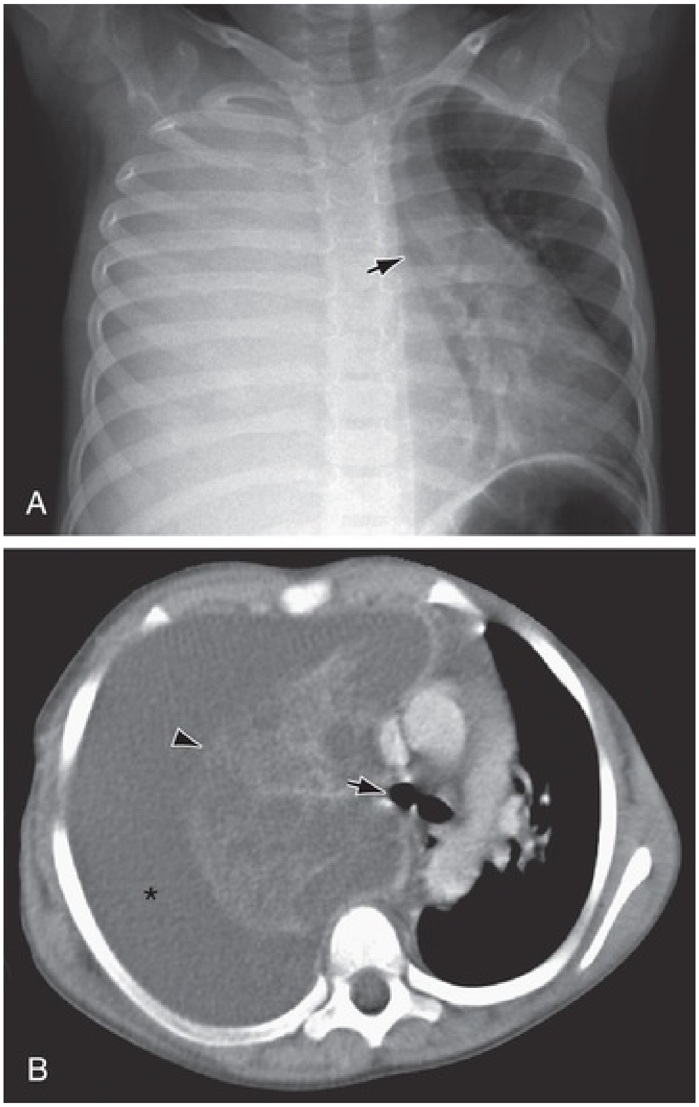

FIG. 429.4 Pneumonia and parapneumonic effusion in a 4 yr old child. **A,** Chest radiograph shows complete opacification of the right thorax as a result of a large pleural effusion. Note the shift of the mediastinum and trachea *(arrow)* to the left. **B,** Thoracic CT scan shows a large right pleural effusion *(asterisk)* surrounding and compressing the consolidated right lung *(arrowhead)* . Note the shift of the mediastinum and tracheal carina *(arrow)* to the left.

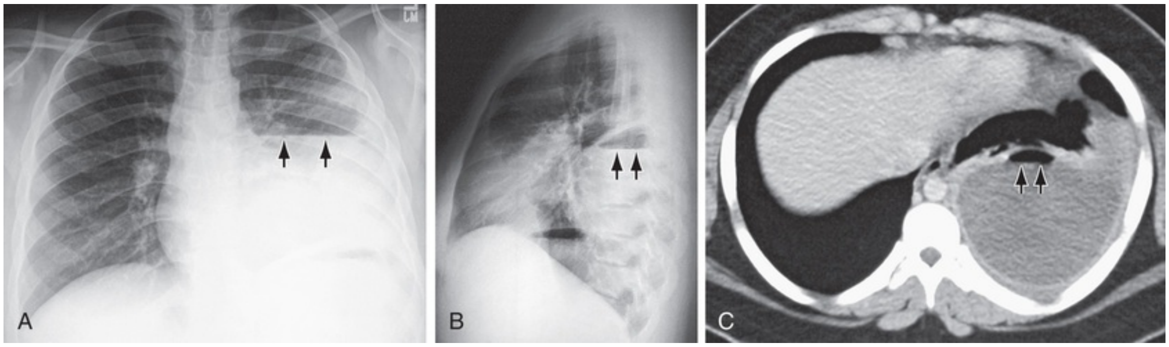

FIG. 429.5 Loculated hydropneumothorax. Frontal **(A)** and lateral **(B)** chest radiographs show loculated hydropneumothorax that complicated pneumonia in a 14 yr old child. *Arrows* point to the horizontal air-fluid level at the interface between the intrapleural effusion and air. **C,** Thoracic CT scan helps to localize the loculated hydropneumothorax, with its air-fluid level *(arrows)* .

Complications

With staphylococcal infections, bronchopleural fistulas and pyopneumothorax commonly develop. Other local complications include purulent pericarditis, pulmonary abscesses, peritonitis from extension through the diaphragm, and osteomyelitis of the ribs. Septic complications such as meningitis, arthritis, and osteomyelitis may also occur. Septicemia is often encountered in *H. influenzae* and pneumococcal infections. The effusion may organize into a thick "peel," which may restrict lung expansion and may be associated with persistent fever and temporary scoliosis.

Treatment

The aim of empyema treatment is to sterilize pleural fluid and restore normal lung function. Treatment includes systemic antibiotics and thoracentesis and chest tube drainage initially with a fibrinolytic agent; if no improvement occurs, VATS is indicated. Open decortication is indicated if fibrinolysis and VATS are ineffective (see Chapter 439). If empyema is diagnosed early, antibiotic treatment plus thoracentesis achieves a complete cure. The selection of antibiotic should be based on the in vitro sensitivities of the responsible organism. See Chapters 208 , 209 , and 221 for treatment of infections by *Staphylococcus, S. pneumoniae* , and *H. influenzae* , respectively. Clinical response in empyema is slow, and systemic antibiotics may be needed for up to 4 wk. Instillation of antibiotics into the pleural cavity does not improve results.

When pus is obtained by thoracentesis or pleural fluid septation is detected on radiographic studies, closed-chest tube drainage with fibrolytics is the initial procedure, followed by VATS if there is no improvement. Multiple aspirations of the pleural cavity should not be attempted. Closed-chest tube drainage is controlled by an underwater seal or continuous suction; sometimes more than 1 tube is required to drain loculated areas. Closed drainage is usually continued for 5-7 days. Chest tubes that are no longer draining are removed.

Instillation of fibrinolytic agents into the pleural cavity via the chest tube often promotes drainage, decreases the length of time a chest tube is in place, decreases fever, lessens need for surgical intervention, and shortens hospitalization. The optimal fibrinolytic drug and dosages have not been determined. Streptokinase 15,000 units/kg in 50 mL of 0.9% saline, urokinase 40,000 units in 40 mL saline, and alteplase (tPA) 4 mg in 40 mL of saline have been used in the pediatric population. The combination of fibrinolytic therapy with DNAse is superior to the use of fibrinolytics alone to promote chest tube drainage. There is a risk of anaphylaxis with streptokinase, and all 3 drugs can be associated with hemorrhage and other complications.

Extensive fibrinous changes may take place over the surface of the lungs owing to empyema, but they eventually resolve. In the child who remains febrile and dyspneic for more than 72 hr after initiation of therapy with intravenous antibiotics and thoracostomy tube drainage, surgical decortication via VATS or, less often, open thoracotomy may speed recovery. If pneumatoceles form, no attempt should be made to treat them surgically or by aspiration, unless they reach sufficient size to cause respiratory compromise or become secondarily infected. Pneumatoceles usually resolve spontaneously with time. The long-term clinical prognosis for adequately treated empyema is excellent, and follow-up pulmonary function studies suggest that residual restrictive disease is uncommon, with or without surgical intervention.

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CHAPTER 430

Bronchiectasis

Oren J. Lakser

Bronchiectasis is characterized by irreversible abnormal dilation and anatomic distortion of the bronchial tree and represents the common end stage of many nonspecific and unrelated antecedent events. Its incidence has been decreasing overall in industrialized countries, but it persists as a problem in lower- and middle-income countries and among some ethnic groups in industrialized nations (particularly in aboriginal children). Females are afflicted more frequently than males.

Pathophysiology and Pathogenesis

In industrialized nations, cystic fibrosis (see Chapter 432) is the most common cause of clinically significant bronchiectasis. Other conditions associated with bronchiectasis include primary ciliary dyskinesia (see Chapter 433), foreign body aspiration (see Chapter 405), aspiration of gastric contents, immune deficiency syndromes (especially humoral immunity), and infection, especially pertussis, measles, and tuberculosis (Table 430.1). Bronchiectasis can also be congenital, as in **Williams-Campbell syndrome** , in which there is an absence of annular bronchial cartilage, and **Marnier-Kuhn syndrome** (congenital tracheobronchomegaly), in which there is a connective tissue disorder. Other disease entities associated with bronchiectasis are **yellow nail syndrome** (pleural effusion, lymphedema, discolored nails) and **right middle lobe syndrome** . The right middle lobe syndrome is mostly associated with other generalized causes of bronchiectasis including asthma, cystic fibrosis, primary ciliary dyskinesia, severe pneumonia, aspiration pneumonia, foreign bodies, and immune deficient states. Early phases of the right middle lobe syndrome manifest as persistent or recurrent right middle lobe infiltrates (pneumonia). The right middle lobe syndrome may be classified as intrinsic or extrinsic obstructive (tumors, granulomas, lymphadenopathy) and nonobstructive (aspiration, asthma, cystic fibrosis).

Table 430.1

Conditions That Predispose to Bronchiectasis in Children

PROXIMAL AIRWAY NARROWING
Airway wall compression (i.e., vascular ring, adenopathy impinging on airways)
Airway intraluminal obstruction (e.g., inhaled foreign body, granulation tissue)
Airway stenosis and malacia
AIRWAY INJURY
Bronchiolitis obliterans (e.g., postviral, after lung transplantation)
Recurrent pneumonitis or pneumonia (e.g., pneumococcal pneumonia, aspiration pneumonia)
ALTERED PULMONARY HOST DEFENSES
Cystic fibrosis
Ciliary dyskinesia
Impaired cough (e.g., neuromuscular weakness conditions)
ALTERED IMMUNE STATES
Primary abnormalities (e.g., hypogammaglobulinemia, common variable immune deficiency)
Secondary abnormalities (e.g., HIV infection, immunosuppressive agents)
OTHER
Allergic bronchopulmonary aspergillosis
Plastic bronchitis
Right middle lobe syndrome

From Redding GJ: Bronchiectasis in children, *Pediatr Clin North Am* 56:157–171, 2009, Box 1, p. 158.

Three basic mechanisms are involved in the pathogenesis of bronchiectasis. **Obstruction** can occur because of tumor, foreign body, impacted mucus because of poor mucociliary clearance, external compression, bronchial webs, and atresia. **Infections** caused by *Bordetella pertussis* , measles, rubella, togavirus, respiratory syncytial virus, adenovirus, and *Mycobacterium tuberculosis* induce chronic inflammation, progressive bronchial wall damage, and dilation. More recently, nontypeable *Haemophilus influenzae* seems to be a common cause of infection in adults and children with bronchiectasis. *Streptococcus pneumoniae* and *Moraxella catarrhalis* are more common in children with bronchiectasis than in adult patients. **Chronic inflammation** similarly contributes to the mechanism by which obstruction leads to bronchiectasis. Both inadequate and exaggerated/dysregulated immune responses may play a role in the development of bronchiectasis. Activation of Toll-like receptors results in the activation of nuclear factor κB and the release of proinflammatory cytokines interleukin (IL)-1β, IL-8, and tumor necrosis factor-α. IL-8 is a chemoattractant for neutrophils, which are the main inflammatory cell involved in the pathogenesis of bronchiectasis. Once activated, neutrophils produce neutrophil elastase and matrix metalloproteinases, MMP-8 and MMP-9. IL-6, IL-8, and tumor necrosis factor-α are elevated in the airways of patients with bronchiectasis. Eosinophils are also elevated in airways of indigenous children with bronchiectasis which promote neutrophil recruitment, goblet cell hyperplasia, and airway destruction. There is an increase in proinflammatory cytotoxic T lymphocytes in peripheral blood of children with bronchiectasis. The mechanism by which bronchiectasis occurs in congenital forms is likely related to abnormal cartilage formation. The common thread in the pathogenesis of bronchiectasis consists of difficulty clearing secretions and recurrent infections with a “vicious cycle” of infection and inflammation resulting in airway injury and remodeling (Fig. 430.1). In early stages, bronchiectasis consists primarily of bronchiolar wall thickening and destruction of elastin resulting in bronchial dilatation. In later stages, the bronchial walls develop cartilage destruction with associated pulmonary artery/arteriole vascular remodeling, resulting in pulmonary hypertension.

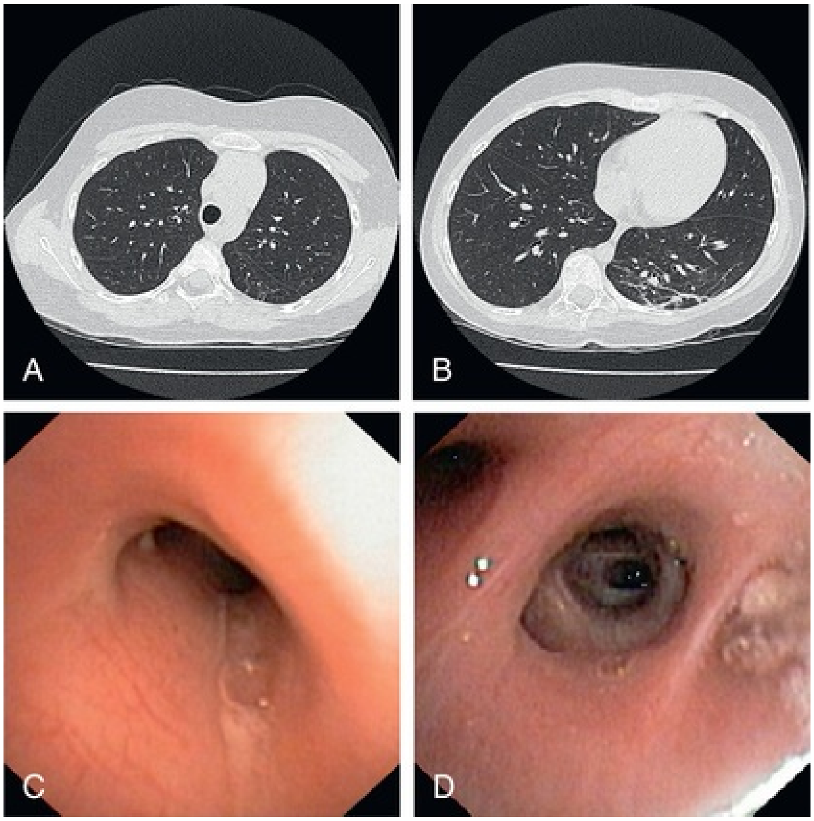

FIG. 430.1 Chest high-resolution computed tomography scan (**A** and **B**) and bronchoscopy (**C** and **D**) in a child with bronchiectasis. (**C** and **D**) Bronchoscopy findings. Images from a chest high-resolution computed tomography (cHRCT) scan (**A** and **B**) in a 10 yr old girl who presented with a chronic wet cough. The child was treated with a 2-wk course of IV antibiotics (after failing oral antibiotic treatment). The scan was reported as having no evidence of bronchiectasis by pediatric radiologists. At bronchoscopy thick mucopus was seen in the trachea (**C**) and the right lower lobe (**D**). The case highlights the need to consider the diagnosis of bronchiectasis on the basis of history, examination findings and using the pediatric cutoff (bronchoarterial ratio >0.8) 104 for defining bronchiectasis on the cHRCT scan. (From Goyal V, Grimwood K, Marchant J, et al: Pediatric bronchiectasis: no longer an orphan disease, *Pediatr Pulmonol* 51:450–469, 2016.)

Bronchiectasis can manifest in any combination of 3 pathologic forms, best defined by high-resolution CT (HRCT) scan (Fig. 430.2). In **cylindrical** bronchiectasis, the bronchial outlines are regular, but there is diffuse dilation of the bronchial unit. The bronchial lumen ends abruptly because of mucous plugging. In **varicose** bronchiectasis, the degree of dilation is greater, and local constrictions cause an irregularity of outline resembling that of varicose veins. There may also be small sacculations. In **saccular** (cystic) bronchiectasis, bronchial dilation progresses and results in ballooning of bronchi that end in fluid- or mucus-filled sacs. This is the most severe form of bronchiectasis. Bronchiectasis lies within a disease spectrum of chronic pediatric suppurative lung disease. The following definitions have been proposed: **prebronchiectasis** (chronic or recurrent endobronchial infection with nonspecific HRCT changes; may be reversible); **HRCT bronchiectasis** (clinical symptoms with HRCT evidence of bronchial dilation; may persist, progress, or improve and resolve); **established bronchiectasis** (like the previous but with no resolution within 2 yr). Early diagnosis and aggressive therapy are important to prevent the development of established bronchiectasis.

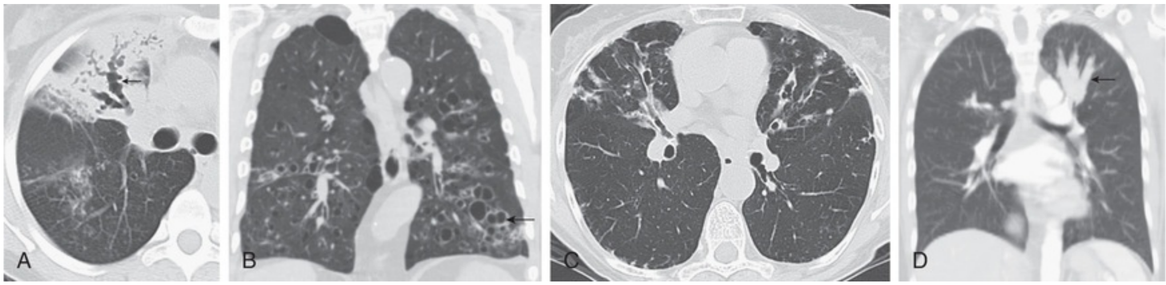

FIG. 430.2 Bronchiectasis. **A,** Axial CT image demonstrates a beaded appearance of dilated bronchi *(arrow)* in the right upper lobe, consistent with varicoid bronchiectasis. **B,** Coronal reformation CT image shows multiple foci of cystic bronchiectasis, with a few air-fluid levels *(arrow)* . Also note paraseptal emphysema, most marked at the right apex. **C,** Bronchiectatic form of chronic atypical mycobacterial infection. Axial CT scan shows extensive bronchiectasis, bronchial wall thickening, and centrilobular nodules, most severe in the middle lobe and lingula. **D,** Allergic bronchopulmonary aspergillosis. Coronal reformation CT image demonstrates impacted bronchi in the left upper lobe *(arrow)* producing a “gloved finger” appearance. (From Boiselle PM: Airway. In Haaga JR, Boll DT: CT and MRI of the whole body, ed 6, Philadelphia, 2017, Elsevier, Figs 40-30, 32-34.)

Clinical Manifestations

The most common complaints in patients with bronchiectasis are cough and production of copious purulent sputum. Younger children may swallow the sputum. Hemoptysis is seen with some frequency. Fever can occur with infectious exacerbations. Anorexia and poor weight gain may occur as time passes. Physical examination typically reveals crackles localized to the affected area but wheezing as well as digital clubbing may also occur. In severe cases, dyspnea and hypoxemia can occur. Pulmonary function studies may demonstrate an obstructive, restrictive, or mixed pattern. Typically, impaired diffusion capacity is a late finding.

Diagnosis

Conditions that can be associated with bronchiectasis should be ruled out by appropriate investigations (e.g., sweat test, immunologic workup). Chest radiographs of patients with bronchiectasis tend to be nonspecific. Typical findings can include increase in size and loss of definition of bronchovascular markings, crowding of bronchi, and loss of lung volume. In more severe forms, cystic spaces, occasionally with air-fluid levels and honeycombing, may occur. Compensatory overinflation of unaffected lung may be seen. Thin-section HRCT scanning is the gold standard because it has excellent sensitivity and specificity. CT provides further information on disease location, presence of mediastinal lesions, and the extent of segmental involvement. The addition of radiolabeled aerosol inhalation to CT scanning can provide even more information. The CT findings in patients with bronchiectasis typically include cylindrical (“tram lines,” “signet ring appearance”), varicose (bronchi with “beaded contour”), cystic (cysts in “strings and clusters”), or mixed forms (see Fig. 430.2). The lower lobes are most commonly affected.

Treatment

The initial therapy for patients with bronchiectasis is medical and aims at decreasing airway obstruction and controlling infection. Airway clearance techniques (e.g., gravity-assisted drainage, active cycle of breathing, positive expiratory pressure [PEP], acapella, high-frequency chest wall oscillation), antibiotics, and bronchodilators are essential. Two to 4 wk of parenteral antibiotics is often necessary to manage acute exacerbations adequately. Exacerbations can be defined as the presence of 1 major criteria (wet cough enduring longer than 72 hr, increased cough frequency over 72 hr) *plus* 1 laboratory criteria (C-reactive protein >3 mg/L, serum IL-6 >2 ng/L, serum amyloid A >5 mg/L, elevated neutrophil percentage), 2 major criteria, or 1 major criteria *plus* 2 minor criteria (change in sputum color, breathlessness, chest pain, crackles/crepitations, wheeze). Antibiotic choice is dictated by the identification and sensitivity of organisms found on deep throat, sputum (induced or spontaneous), or bronchoalveolar lavage fluid cultures. The most common organisms found in children with bronchiectasis include *S. pneumoniae* , *H. influenzae* non–type b, *M. catarrhalis* , and *Mycoplasma pneumoniae* . Amoxicillin/clavulanic acid (22.5 mg/kg/dose twice daily) has been particularly successful at treating most pulmonary exacerbations. Viruses (most commonly human rhinovirus) are often found in children with bronchiectasis suffering from an exacerbation. Long-term prophylactic macrolide antibiotics or nebulized antibiotics (e.g., tobramycin, colistin, aztreonam) may be beneficial (reduced exacerbations and hospitalizations, improved lung function) but may also increase antibiotic resistance. Airway hydration (inhaled hypertonic saline or mannitol) also improves quality of life in adults with bronchiectasis. Any underlying disorder (immunodeficiency, aspiration) that may be contributing must be addressed. When localized bronchiectasis becomes more severe or resistant to medical management, segmental or lobar resection may be warranted. Lung transplantation can also be performed in patients with bronchiectasis. A review of randomized trials among children and adult patients with bronchiectasis did not find strong evidence to support the routine use of inhaled corticosteroids, although some studies demonstrate improved quality of life and reduced exacerbations in patients with bronchiectasis treated with inhaled corticosteroids. Although preventative strategies, including immunization against typical respiratory pathogens (influenza, pneumococci), are generally recommended, no studies have been conducted to date to address the efficacy of these recommendations.

Prognosis

Children with bronchiectasis often suffer from recurrent pulmonary illnesses, resulting in missed school days, stunted growth, osteopenia, and osteoporosis. The prognosis for patients with bronchiectasis has improved considerably in the past few decades. Earlier recognition or prevention of predisposing conditions, specialist multidisciplinary management, more powerful and broad-spectrum antibiotics, and improved surgical outcomes are likely reasons.

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CHAPTER 431

Pulmonary Abscess

Oren J. Lakser

Lung infection that destroys the lung parenchyma, resulting in cavitations and central necrosis, can result in localized areas composed of thick-walled purulent material, called lung abscesses. Primary lung abscesses occur in previously healthy patients with no underlying medical disorders and are usually solitary. Secondary lung abscesses occur in patients with underlying or predisposing conditions and may be multiple. Lung abscesses are much less common in children (estimated at 0.7 per 100,000 admissions per year) than in adults.

Pathology and Pathogenesis

A number of conditions predispose children to the development of pulmonary abscesses, including aspiration, pneumonia, cystic fibrosis (see Chapter 432), gastroesophageal reflux (see Chapter 349), tracheoesophageal fistula (see Chapter 345), immunodeficiencies, postoperative complications of tonsillectomy and adenoidectomy, seizures, a variety of neurologic diseases, and other conditions associated with impaired mucociliary defense. In children, aspiration of infected materials or a foreign body is the predominant source of the organisms causing abscesses. Initially, pneumonitis impairs drainage of fluid or the aspirated material. Inflammatory vascular obstruction occurs, leading to tissue necrosis, liquefaction, and abscess formation. Abscess can also occur as a result of pneumonia and hematogenous seeding from another site.

If the aspiration event occurred while the child was recumbent, the right and left upper lobes and apical segment of the right lower lobes are the dependent areas most likely to be affected. In a child who was upright, the posterior segments of the upper lobes were dependent and therefore are most likely to be affected. Primary abscesses are found most often on the right side, whereas secondary lung abscesses, particularly in immunocompromised patients, have a predilection for the left side.

Both anaerobic and aerobic organisms can cause lung abscesses. Common anaerobic bacteria that can cause a pulmonary abscess include *Bacteroides* spp., *Fusobacterium* spp., and *Peptostreptococcus* spp. Abscesses can be caused by aerobic organisms such as *Streptococcus* spp., *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and very rarely *Mycoplasma pneumoniae* . Aerobic and anaerobic cultures should be part of the workup for all patients with lung abscess. Occasionally, concomitant viral-bacterial infection can be detected. Fungi can also cause lung abscesses, particularly in immunocompromised patients.

Clinical Manifestations

The most common symptoms of pulmonary abscess in the pediatric population are fever, cough, and emesis. Other common symptoms include tachypnea, dyspnea, chest pain, sputum production, weight loss, and hemoptysis. Physical examination typically reveals tachypnea, dyspnea, retractions with accessory muscle use, decreased breath sounds, and dullness to percussion in the affected area. Crackles and occasionally a prolonged expiratory phase may be heard on lung examination.

Diagnosis

Diagnosis is most commonly made on the basis of chest radiography. Classically, the chest radiograph shows a parenchymal inflammation with a cavity containing an air-fluid level (Fig. 431.1). A chest CT scan can provide better anatomic definition of an abscess, including location and size (Fig. 431.2).

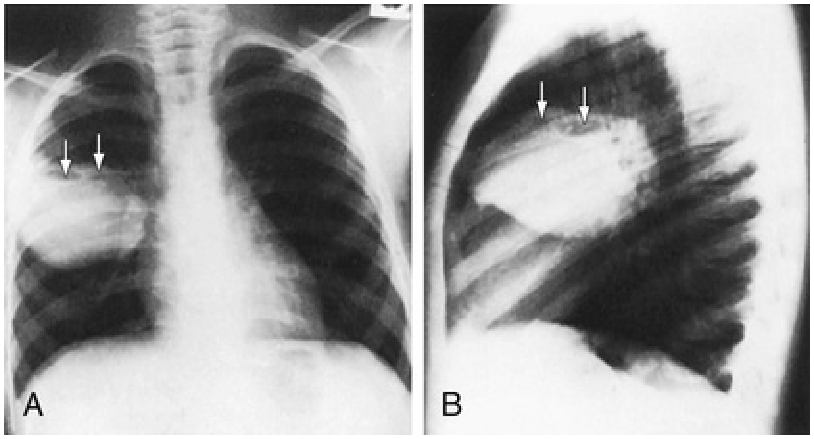

FIG. 431.1 **A** and **B,** Multiloculated lung abscess *(arrows)* . (From Brook I: Lung abscess and pulmonary infections due to anaerobic bacteria. In Chernick V, Boat TF, Wilmott RW, et al, editors: *Kendig's disorders of the respiratory tract in children* , ed 7, Philadelphia, 2006, WB Saunders, p. 482.)

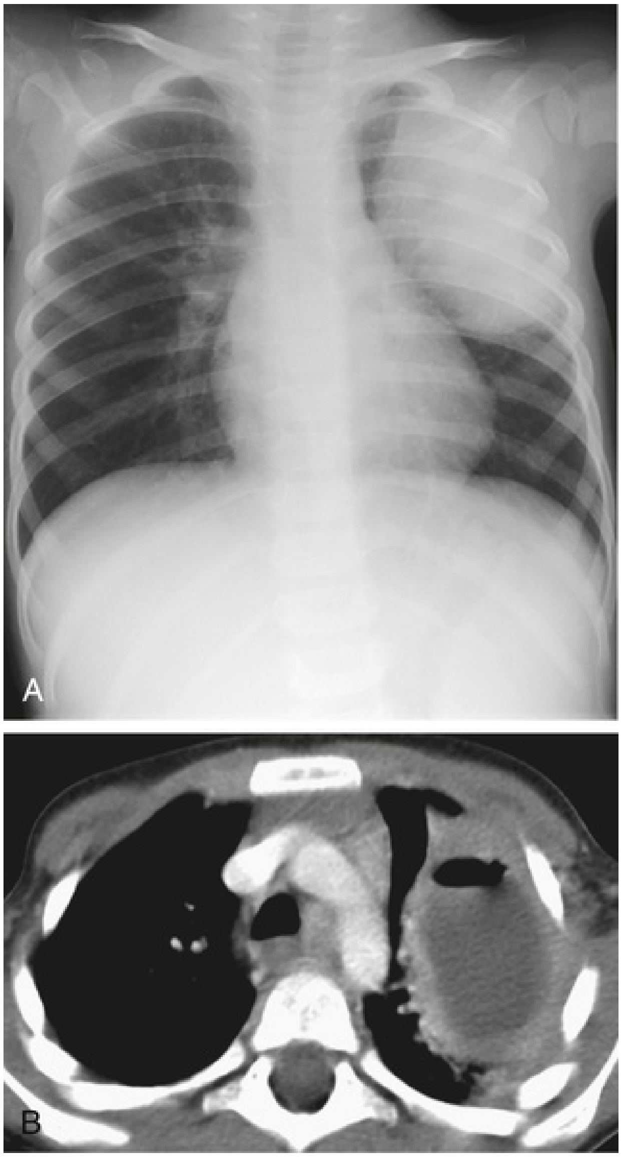

FIG. 431.2 Pulmonary abscess in a 2 yr old boy with persistent cough. **A,** Chest radiograph shows large oval mass in the left upper lobe. **B,** CT scan demonstrates an abscess with a thick enhancing wall that contains both air and fluid. (From Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, Fig. 78-3, p. 1297.)

An abscess is usually a thick-walled lesion with a low-density center progressing to an air-fluid level. Abscesses should be distinguished from pneumatoceles, which often complicate severe bacterial pneumonias and are characterized by thin- and smooth-walled, localized air collections with or without air-fluid level (Fig. 431.3). Pneumatoceles often resolve spontaneously with the treatment of the specific cause of the pneumonia.

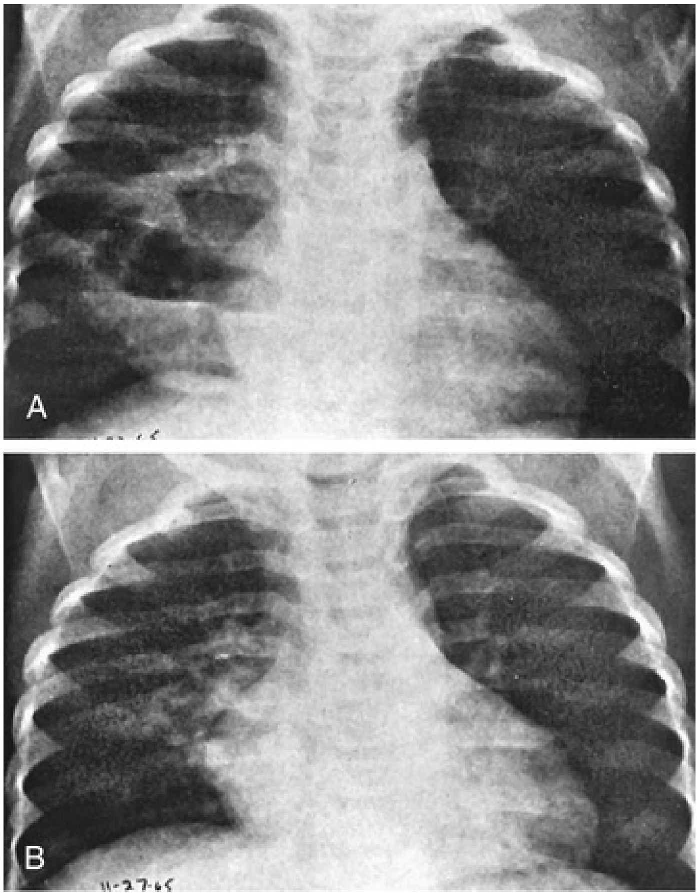

FIG. 431.3 Appearance over a period of 5 days of a large multiloculated pneumonocele in a segment of alveolar consolidation. **A,** There is a large cavity with 2 air-fluid levels in a segment of alveolar pneumonia in the right upper lobe. **B,** Five days later, the cavity and most of the pneumonic consolidation have disappeared. (From Silverman FN, Kuhn JP: *Essentials of Caffey's pediatric x-ray diagnosis,* Chicago, 1990, Year Book, p. 303.)

The determination of the etiologic bacteria in a lung abscess can be very helpful in guiding antibiotic choice. Although Gram stain of sputum can provide an early clue as to the class of bacteria involved, sputum cultures typically yield mixed bacteria and therefore are not always reliable. Attempts to avoid contamination from oral flora include direct lung puncture, percutaneous (aided by CT guidance) or transtracheal aspiration, and bronchoalveolar lavage specimens obtained bronchoscopically. Bronchoscopic aspiration should be avoided because it can be complicated by massive intrabronchial aspiration, and great care should therefore be taken during the procedure. To avoid invasive procedures in previously normal hosts, empiric therapy can be initiated in the absence of culturable material.

Treatment

Conservative management is recommended for pulmonary abscess. Most experts advocate a 2- to 3-wk course of parenteral antibiotics for uncomplicated cases, followed by a course of oral antibiotics to complete a total of 4-6 wk. Antibiotic choice should be guided by results of Gram stain and culture but initially should include agents with aerobic and anaerobic coverage. Treatment regimens should include a penicillinase-resistant agent active against *S. aureus* and anaerobic coverage, typically with clindamycin or ticarcillin/clavulanic acid. If gram-negative bacteria are suspected or isolated, an aminoglycoside should be added. Early CT-guided percutaneous aspiration or drainage has been advocated because it can hasten the recovery and shorten the course of parenteral antibiotic therapy needed.

For severely ill patients, patients with larger abscess, or those whose status fails to improve after 7-10 days of appropriate antimicrobial therapy, surgical intervention should be considered. Minimally invasive percutaneous aspiration techniques, often with CT guidance, are the initial and, often, only intervention required. Thoracoscopic drainage has also been successfully used with minimal complications. In rare complicated cases, thoracotomy with surgical drainage or lobectomy and/or decortication may be necessary. Abscess drainage is reportedly required in ~20% of cases of pulmonary abscess in children.

Prognosis

Overall, prognosis for children with primary pulmonary abscesses is excellent. The presence of aerobic organisms may be a negative prognostic indicator, particularly in those with secondary lung abscesses. Most children become asymptomatic within 7-10 days, although the fever can persist for as long as 3 wk. Radiologic abnormalities usually resolve in 1-3 mo but can persist for years.

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CHAPTER 432

Cystic Fibrosis

Marie E. Egan, Michael S. Schechter, Judith A. Voynow

Cystic fibrosis (CF) is an inherited multisystem disorder of children and adults; it is the most common life-limiting recessive genetic trait among whites. Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, the primary defect, leads to a wide and variable array of presenting manifestations and complications.

CF is responsible for most cases of exocrine pancreatic insufficiency in early life and is the major cause of severe chronic lung disease in children. It is also responsible for many cases of hyponatremic salt depletion, nasal polyposis, pansinusitis, rectal prolapse, pancreatitis, cholelithiasis, and nonautoimmune insulin-dependent hyperglycemia. Because CF may manifest as failure to thrive and hepatic dysfunction, including cirrhosis, this disorder enters into the differential diagnosis of many pediatric conditions (Table 432.1).

Table 432.1

Complications of Cystic Fibrosis

RESPIRATORY
Bronchiectasis, bronchitis, bronchiolitis, pneumonia
Atelectasis
Hemoptysis
Pneumothorax
Nasal polyps
Sinusitis
Reactive airway disease
Mucoid impaction of the bronchi
Allergic bronchopulmonary aspergillosis
Cor pulmonale
Respiratory failure
GASTROINTESTINAL
Meconium ileus, meconium plug (neonate)
Meconium peritonitis (neonate)

Distal intestinal obstruction syndrome (non-neonatal obstruction)
Rectal prolapse
Intussusception
Volvulus
Fibrosing colonopathy (strictures)
Appendicitis
Intestinal atresia
Pancreatitis
Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism)
Neonatal obstructive jaundice
Hepatic steatosis
Gastroesophageal reflux
Cholelithiasis
Inguinal hernia
Growth failure (malabsorption)
Vitamin deficiency states (vitamins A, K, E, D)
Insulin deficiency, symptomatic hyperglycemia, diabetes
Malignancy (rare)
OTHER
Infertility
Delayed puberty
Edema-hypoproteinemia
Dehydration–heat exhaustion
Hypertrophic osteoarthropathy-arthritis
Clubbing
Amyloidosis
Diabetes mellitus
Aquagenic palmoplantar keratoderma (skin wrinkling)

Adapted from Silverman FN, Kuhn JP: *Essentials of Caffey's pediatric x-ray diagnosis,* Chicago, 1990, Year Book, p. 649.

Genetics

CF occurs most frequently in white populations of northern Europe, North America, and Australia/New Zealand. The prevalence in these populations varies but approximates 1 in 3,500 live births (1 in 9,200 individuals of Hispanic descent and 1 in 15,000 African Americans). Although less frequent in African, Hispanic, Middle Eastern, South Asian, and eastern Asian populations, the disorder does exist in these populations as well (Fig. 432.1).

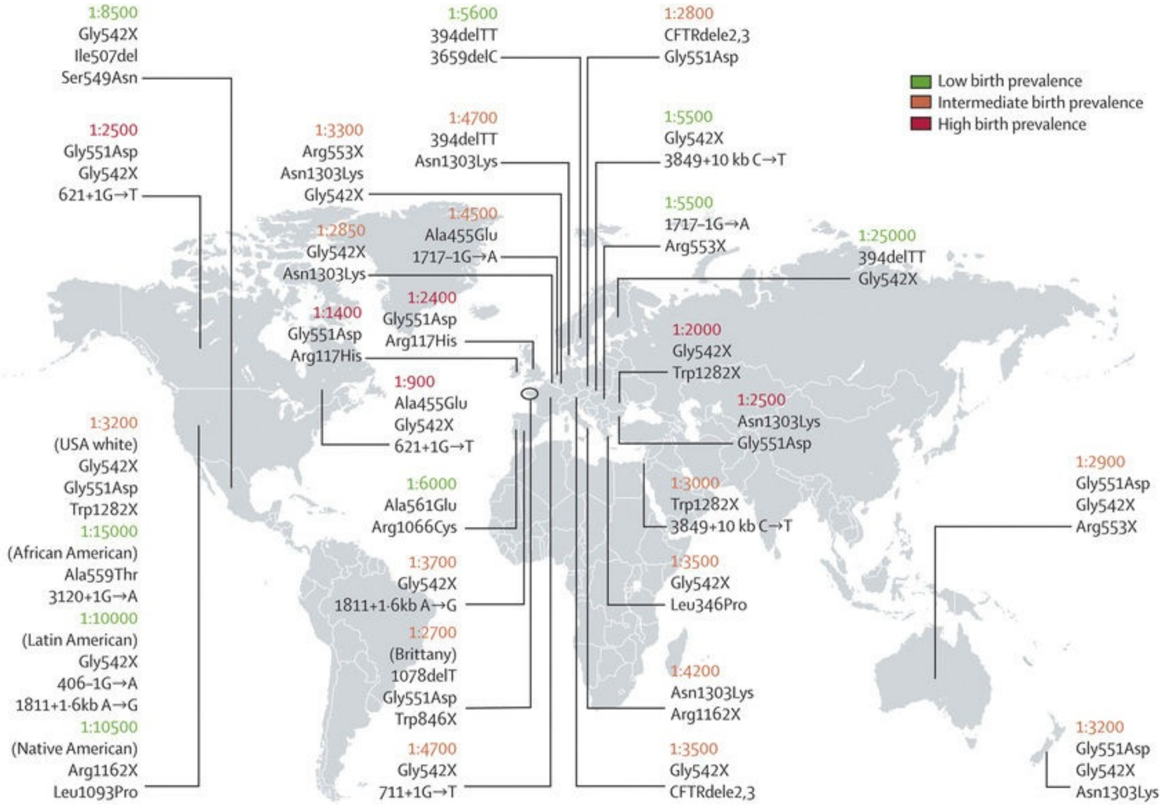
1:8500
Gly542X
Ile507del
Ser549Asn
1:5600
394delTT
3659delC
1:2800
CFTRdele2,3
Gly551Asp
🟩 Low birth prevalence
🟧 Intermediate birth prevalence
🟥 High birth prevalence
1:2500
Gly551Asp
Gly542X
621+1G→T
1:3300
Arg553X
Asn1303Lys
Gly542X
1:4700
394delTT
Asn1303Lys
1:5500
Gly542X
3849+10 kb C→T
1:4500
Ala455Glu
1717-1G→A
1:2850
Gly542X
Asn1303Lys
1:5500
1717-1G→A
Arg553X
1:25000
394delTT
Gly542X
1:2400
Gly551Asp
Arg117His
1:1400
Gly551Asp
Arg117His
1:2000
Gly542X
Trp1282X
1:900
Ala455Glu
Gly542X
621+1G→T
1:2500
Asn1303Lys
Gly551Asp
1:3200
(USA white)
Gly542X
Gly551Asp
Trp1282X
1:15000
(African American)
Ala559Thr
3120+1G→A
1:10000
(Latin American)
Gly542X
406-1G→A
1811+1·6kb A→G
1:10500
(Native American)
Arg1162X
Leu1093Pro
1:6000
Ala561Glu
Arg1066Cys
1:3000
Trp1282X
3849+10 kb C→T
1:2900
Gly551Asp
Gly542X
Arg553X
1:3700
Gly542X
1811+1·6kb A→G
1:3500
Gly542X
Leu346Pro
1:2700
(Brittany)
1078delT
Gly551Asp
Trp846X
1:4200
Asn1303Lys
Arg1162X
1:4700
Gly542X
711+1G→T
1:3500
Gly542X
CFTRdele2,3
1:3200
Gly551Asp
Gly542X
Asn1303Lys

FIG. 432.1 Approximate cystic fibrosis birth prevalence and common mutations for selected countries. Birth prevalence is reported as number of live births per case of cystic fibrosis. Common/important mutations in each region are listed below the prevalence figures. The birth prevalence can vary greatly among ethnic groups in a country. (From O'Sullivan BP, Freedman SD: Cystic fibrosis, *Lancet* 373:1891–1902, 2009.)

CF is inherited as an autosomal recessive trait. The CF gene codes for the CFTR protein, which is 1,480 amino acids. CFTR is expressed largely in epithelial cells of airways, the gastrointestinal tract (including the pancreas and biliary system), the sweat glands, and the genitourinary system. CFTR is a member of the adenosine triphosphate–binding cassette superfamily of proteins. It functions as a chloride channel and has other regulatory functions that are perturbed variably by the different mutations. More than 1,900 *CFTR* polymorphisms have been described, many of which are not clearly of clinical significance. Those that are associated with clinical manifestations may be grouped into 6 main classes based upon how they impact upon protein structure and function (Table 432.2 ; Fig. 432.2). Mutation class I-III are generally considered to be *severe* mutations in that they lead to a complete or nearly complete absence of CFTR function, whereas class IV-VI mutations are associated with some residual functional protein. The most prevalent mutation of

CFTR is the deletion of a single phenylalanine residue at amino acid 508 (F508del). This mutation is responsible for the high incidence of CF in northern European populations and is considerably less frequent in other populations, such as those of southern Europe and Israel. Nearly 50% of individuals with CF in the United States Cystic Fibrosis Foundation (CFF) Patient Registry are homozygous for F508del, and approximately 87% carry at least 1 F508del gene. Remaining patients have an extensive array of mutations, none of which has a prevalence of more than several percentage points, except in certain populations; for example, the W1282X mutation occurs in 60% of Ashkenazi Jews with CF. Through the use of probes for 40 of the most common mutations, the genotype of 80–90% of Americans with CF can be ascertained. Genotyping using a discreet panel of mutation probes is quick and less costly than more comprehensive sequencing and is the approach typically used in state newborn screening programs. In remaining patients, sequencing the entire *CFTR* gene and looking for deletions and duplications are necessary to establish the genotype. As sequencing technologies evolve and costs decrease, sequencing the entire *CFTR* gene may become mainstream for all patients.

Table 432.2

One Proposed Classification of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Mutations

CLASS	EFFECT ON CFTR	FUNCTIONAL CFTR PRESENT?	SAMPLE MUTATIONS
I	Lack of protein production	No	Stop codons (designation in X; e.g., Trp1282X, Gly542X); splicing defects with no protein production (e.g., 711+1G→T, 1717-1G→A)
II	Defect in protein trafficking with ubiquitination and degradation in endoplasmic reticulum/Golgi body	No/substantially reduced	Phe508del, Asn1303Lys, Gly85Gly, leu1065Pro, Asp507, Ser549Arg
III	Defective regulation; CFTR not activated by adenosine triphosphate or cyclic adenosine monophosphate	No (nonfunction CFTR present in apical membrane)	Gly551Asp, Ser492Phe, Val520Phe, Arg553Gly, Arg560Thr, Arg560Ser
IV	Reduced chloride transport through CFTR at the apical membrane	Yes	Ala455Glu, Arg117Cys, Asp1152His, Leu227Arg, Arg334Trp, Arg117His*
V	Splicing defect with reduced production of CFTR	Yes	3849+10kbC→T, 1811+16kbA→G, IVS8-5T, 2789+5G→A

* Function of Arg117His depends on the length of the polythymidine track on the same chromosome in intron 8 (IVS8): 5T, 7T, or 9T. There is more normal CFTR function with a longer polythymidine track.

From O'Sullivan BP, Freedman SD: Cystic fibrosis, *Lancet* 373:1891–1902, 2009.

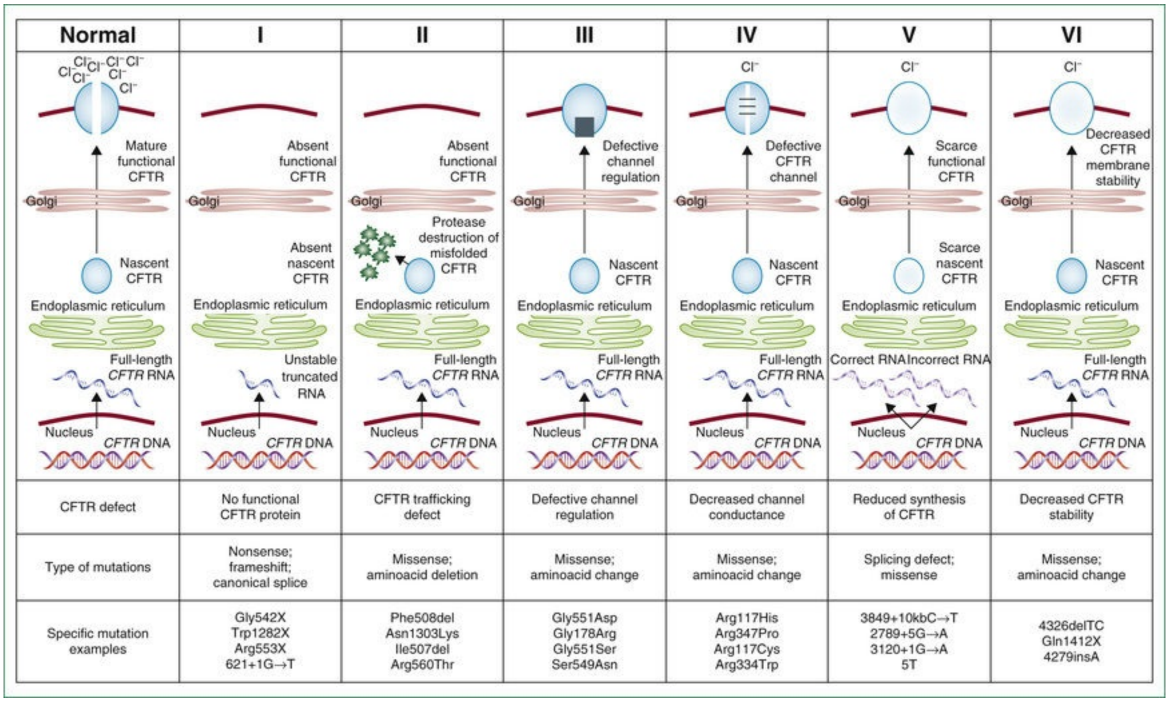
Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻ Cl⁻
Mature functional CFTR
Golgi
Nascent CFTR
Endoplasmic reticulum
Full-length CFTR RNA
Nucleus
CFTR DNA
Absent functional CFTR
Absent nascent CFTR
Unstable truncated RNA
Protease destruction of misfolded CFTR
Defective channel regulation
Defective CFTR channel
Scarce functional CFTR
Scarce nascent CFTR
Correct RNA
Incorrect RNA
Decreased CFTR membrane stability

Normal	I	II	III	IV	V	VI
CFTR defect	No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Type of mutations	Nonsense; frameshift; canonical splice	Missense; aminoacid deletion	Missense; aminoacid change	Missense; aminoacid change	Splicing defect; missense	Missense; aminoacid change
Specific mutation examples	Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

FIG. 432.2 Classes of cystic fibrosis transmembrane conductance regulator *(CFTR)* mutations. Mutations in the *CFTR* gene can be divided into 6 classes. Class I mutations result in no protein production. Class II mutations (including the most prevalent, Phe508del) cause retention of a misfolded protein at the endoplasmic reticulum and subsequent degradation in the proteasome. Class III mutations affect channel regulation, impairing channel opening (e.g., Gly551Asp). Class IV mutants show reduced conduction—that is, decreased flow of ions (e.g., Arg117His). Class V mutations cause substantial reduction in mRNA or protein, or both, Class VI mutations cause substantial plasma membrane instability and include Phe508del when rescued by most correctors (rPhe508del). (From Boyle MP, De Boeck K: A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect, *Lancet Respir Med* 1:158–63, 2013.)

The relationship between CFTR genotype and clinical phenotype is highly complex. CFTR mutation class is strongly associated with pancreatic dysfunction and will usually predict this manifestation in any given patient. Respiratory complications and lung function decline are also correlated with mutation class severity but with greater variation due to the influence of non-CFTR modifier gene polymorphisms and environmental influences on the manifestations of lung disease in any one individual. Studies have identified specific non-CFTR modifier genes of importance; genome-wide association studies identified a polymorphism on chromosome 11 in the intergenic region between EHF (an epithelial transcription factor) and APIP (an inhibitor of apoptosis) that is associated with lung disease severity and may influence the expression of *EHF* and *APIP*, as well as other genes in the region, including *PDHX* , *CD44* , and *ELF5* . A region on chromosome 20 may also be found to relate to lung disease severity. This region encompasses several genes *(MC3R, CASS4, AURKA)* that may play a role in lung host defense involving neutrophil function, apoptosis, and phagocytosis. Genome-wide association studies analysis also identified genetic regions that predispose to risk for liver disease, CF-related diabetes, and meconium ileus.

The high-frequency of *CFTR* mutations has been ascribed to resistance to the morbidity and mortality associated with infectious dysenteries through the ages. Cultured CF intestinal epithelial cells homozygous for the F508del mutation are unresponsive to the secretory effects of cholera toxin. CFTR heterozygous mice experience less mortality when treated with cholera toxin than their unaffected wild-type littermates.

Pathogenesis

A number of long-standing observations of CF are of fundamental pathophysiologic importance; they include failure to clear mucous secretions, a paucity of water in mucous secretions, an elevated salt content of sweat and other serous secretions, and chronic infection limited to the respiratory tract. In addition, there is a greater negative potential difference across the respiratory epithelia of patients with CF than across the respiratory epithelia of control subjects. Aberrant electrical properties are also demonstrated for CF sweat gland duct and rectal epithelia. The membranes of CF epithelial cells are unable to secrete chloride or bicarbonate in response to cyclic adenosine monophosphate–mediated signals, and at least in the respiratory epithelial cells, excessive amounts of sodium are absorbed through these membranes. These defects can be traced to a dysfunction of CFTR. CFTR function is highly regulated and energy dependent; it requires both cyclic adenosine monophosphate–stimulated protein kinase A phosphorylation of the regulatory domain and ATP binding and hydrolysis at the nucleotide binding domains. CFTR also interacts with other ion channels, signal transduction proteins, and the cytoskeleton (Fig. 432.3 and see Fig. 432.2).

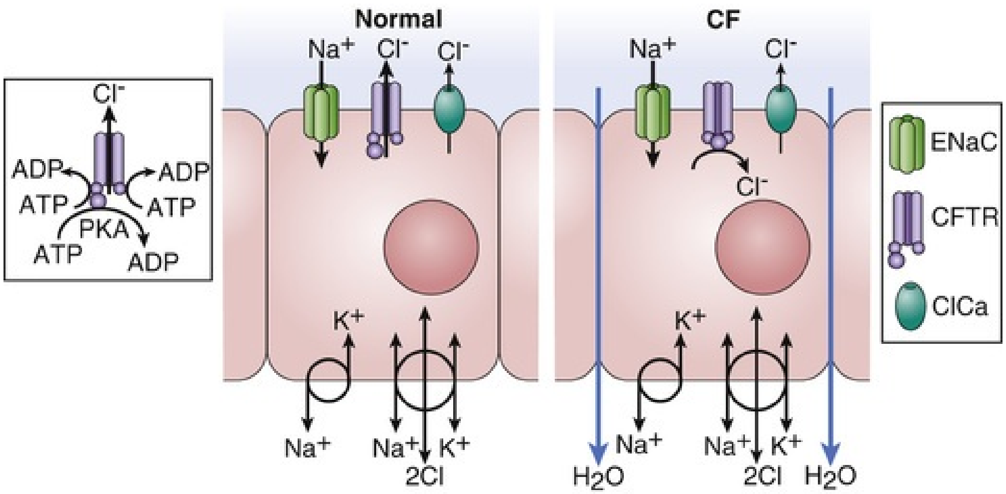

FIG. 432.3 Schematic diagram depicting cystic fibrosis *(CF)* epithelial channel defects, characterized by impaired chloride secretion, massive sodium absorption, and movement of water through the epithelium, leading to a dehydrated airway surface. *ADP,* Adenosine diphosphate; *ATP,* adenosine triphosphate; *CFTR,* cystic fibrosis transmembrane conductance regulator; *ClCa,* alternative chloride channel; *ENaC,* epithelium sodium channel; *PKA,* protein kinase A. (From Michelson P, Faro A, Ferkol T: Pulmonary disease in cystic fibrosis. In *Kendig's Disorders of the Respiratory Tract in Children* , ed 9, Philadelphia, 2019, Elsevier, [Fig. 51.1, p. 778].)

Many hypotheses have been postulated to explain how CFTR dysfunction results in the clinical phenotype (Fig. 432.4). It is likely that no one hypothesis explains the full spectrum of disease. One model is that airway hydration homeostasis requires both CFTR and $P2Y_2$ -regulated calcium-activated chloride secretion. When extracellular ATP is depleted such as after viral infections, calcium-activated chloride secretion is not activated and the failure of mutant CFTR chloride secretion results in dehydrated airway secretions, increased concentration of mucin solids, and more viscoelastic mucus that is not cleared by normal mucociliary transport. Another mechanism that is supported by both primary human airway studies and investigations in the CF pig is that mutant CFTR causes failure of HCO_3^- secretion and a more acidic airway surface liquid, which increases mucous viscoelasticity resulting in poor mucociliary clearance. Mucous secretions are tethered to submucosal gland ducts and are retained and obstruct airways, starting with those of the smallest caliber, the bronchioles. Airflow obstruction at the level of small airways is the earliest observable physiologic abnormality of the respiratory system. CFTR dysfunction in airway smooth muscle has been implicated in tracheal and airway abnormalities in humans and in animal models of the disease (pig and mice). These data suggest that CFTR expression in this nonepithelial tissue contributes to airway constriction.

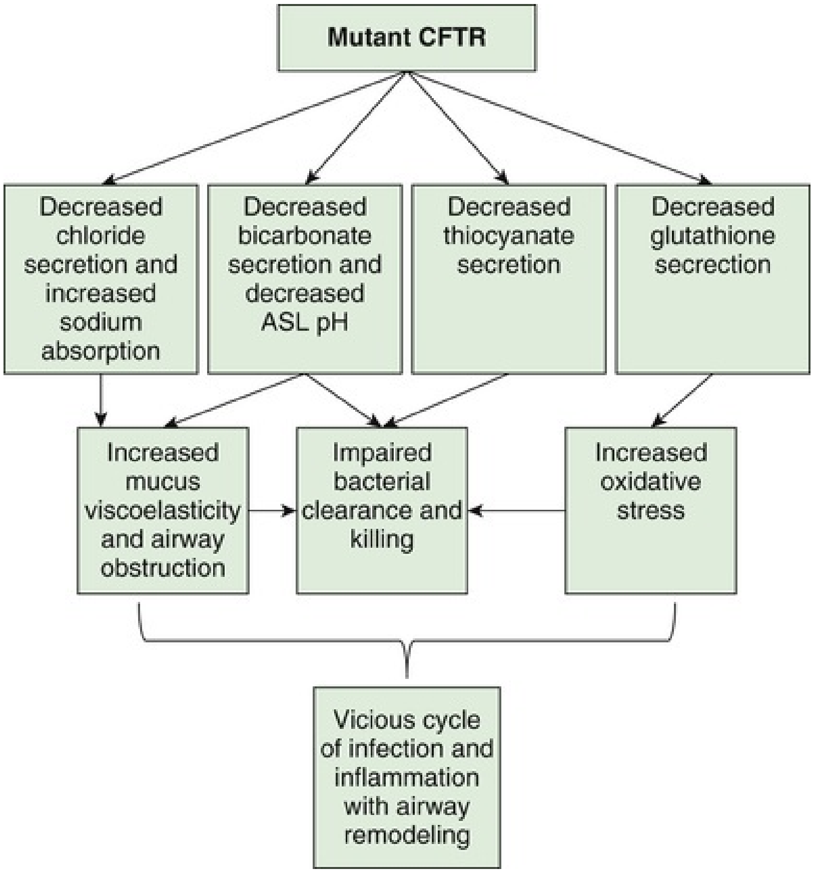
Mutant CFTR
Decreased chloride secretion and increased sodium absorption
Decreased bicarbonate secretion and decreased ASL pH
Decreased thiocyanate secretion
Decreased glutathione secrection
Increased mucus viscoelasticity and airway obstruction
Impaired bacterial clearance and killing
Increased oxidative stress
Vicious cycle of infection and inflammation with airway remodeling

FIG. 432.4 Schema of mutant cystic fibrosis transmembrane conductance regulator *(CFTR)* mechanisms of chronic airway disease. CFTR conducts several anions including chloride, bicarbonate, thiocyanate, and glutathione. The loss of CFTR function impacts critical airway epithelial functions: (1) It increases the risk for dehydration of airway surface liquid *(ASL)* with loss of chloride efflux and associated increased sodium channel activity. (2) The loss of secreted bicarbonate and/or acidic pH of the ASL increases mucous viscoelasticity resulting in failure of mucociliary transport. (3) Acidic pH in the ASL impairs normal innate immune clearance of bacteria. (4) Loss of thiocyanate impairs lactoperoxidase bacterial killing. (5) Loss of glutathione secretion depletes the antioxidant capacity of the airway resulting in increased inflammation, increased mucous secretion, and increased mucous viscoelasticity. These factors lead to a vicious cycle of infection and inflammation that is progressive.

It is plausible that similar pathophysiologic events take place in the pancreatic and biliary ducts (and in the vas deferens), leading to desiccation of proteinaceous secretions and obstruction. Because the function of sweat gland duct cells is to absorb rather than secrete chloride, salt is not retrieved from the isotonic primary sweat as it is transported to the skin surface; chloride and sodium levels are consequently elevated.

Chronic infection in CF is limited to the airways. One explanation for infection is a sequence of events starting with failure to clear inhaled bacteria promptly and then proceeding to persistent infection and an inflammatory response in airway walls. Another explanation for early infection is the failure of innate immune proteins to kill bacteria in an abnormally acidic airway milieu. In addition, it has been proposed that abnormal CFTR creates a proinflammatory state or amplifies the inflammatory response to initial infections (viral or bacterial). Some investigators have identified primary differences in CF-affected immune cells (including macrophage, neutrophils, lymphocytes, and dendritic cells) and have suggested that these alterations contribute to this proinflammatory state as well as a dysregulated immune response. It appears that inflammatory events occur first in small airways, perhaps because it is more difficult to clear altered secretions and microorganisms from these regions. The agents of airway injury include neutrophil products, such as oxidative radicals and proteases, and immune reaction products. These inflammatory products further aggravate airway obstruction by increasing mucin secretion and altering mucin structure to promote both intramolecular and intermolecular interactions. Excessive inflammatory cell polymers in CF sputum, including DNA, filamentous actin, and glycosaminoglycans, further contribute to abnormal mucous viscoelastic properties and airway obstruction. Chronic bronchiolitis and bronchitis are the initial lung manifestations (see Chapter 418), but after months to years, structural changes in airway walls produce bronchiolectasis and **bronchiectasis** . With advanced lung disease, infection may extend to peribronchial lung parenchyma.

A central feature of lung disease in patients with CF is the high prevalence of airway infection with ***Staphylococcus aureus*** (see Chapter 208.1), ***Pseudomonas aeruginosa*** (see Chapter 232.1), and ***Burkholderia cepacia* complex** (see Chapter 232.2), organisms that rarely infect the lungs of other individuals. It has been postulated that the CF airway epithelial cells or surface liquids may provide a favorable environment for harboring these organisms. CF airway epithelium may be compromised in its innate defenses against these organisms, through either acquired or genetic alterations. Antimicrobial activity is diminished in CF secretions; this diminution may be related to hyperacidic surface liquids or other effects on innate immunity. Another puzzle is the propensity for *P. aeruginosa* to undergo mucoid transformation in the CF airways. The complex polysaccharide produced by these organisms generates a biofilm that provides a hypoxic environment and thereby protects *Pseudomonas* against antimicrobial agents.

Altered lipid homeostasis has been implicated as a predisposing factor for respiratory tract infection and inflammation. Concentrations of lipoxins—molecules that suppress neutrophilic inflammation—are suppressed in CF airways. There is an imbalance of lipids with increased arachidonic acid and decreased docosahexaenoic acid, which promotes inflammation. There is also an imbalance of ceramide in the CF airway that is proinflammatory. Supporting the idea that altered lipid uptake affects infection and inflammation is the observation that the 10–15% of individuals with CF who retain substantial exocrine pancreatic function have delayed acquisition of *P. aeruginosa* and slower deterioration of lung function. However, it appears that nutritional factors are contributory only because preservation of pancreatic function does not preclude development of typical lung disease.

The variation in progression of lung disease seen in patients with CF is largely influenced by social and physical environment factors, whose impact matches that of CFTR genotype. Exposure to environmental tobacco smoke and outdoor air pollutants, and early acquisition of respiratory virus infections, as well as pathogenic organisms like *P. aeruginosa* and methicillin-resistant *S. aureus*, have been implicated as causes of worsening disease. Sex/gender disparities also seem to exist, with females having a poorer prognosis. Although studies have suggested that estrogen may influence disease exacerbations, the gap seems to be narrowing in the past decade.

Although most CF care is delivered at specialty centers and is broadly influenced by current clinical guidelines, there is enough variability in treatment approaches to cause large variation in respiratory and nutritional outcomes across the care networks in both North America and Europe. Social determinants of health are associated with significant disparities in outcome; socioeconomic status has been shown to be a strong predictor of mortality, as well as both nutritional status and lung function on both sides of the Atlantic. The specific mechanism of effect is unclear, but evidence suggests a role for socioeconomic status–related differences in health behaviors and disease self-management practices, stress and mental health issues, and environmental tobacco smoke exposure. Differential access to specialty care and medications is not a major factor in North American children (lack of insurance in some adults is a problem); however, differences in disease outcomes across European countries of varying wealth are quite clear.

Pathology

The earliest pathologic lesion in the lung is that of **bronchiolitis** (mucous plugging and an inflammatory response in the walls of the small airways); with time, mucous accumulation and inflammation extend to the larger airways (**bronchitis**) (see Chapter 418.2). Goblet cell hyperplasia and submucosal gland hypertrophy become prominent pathologic findings, which is most likely a response to chronic airway infection. Organisms appear to be confined to the endobronchial space; invasive bacterial infection is not characteristic. With long-standing disease, evidence of airway destruction such as **bronchiolar obliteration, bronchiolectasis,** and **bronchiectasis** (see Chapter 430) becomes prominent. Imaging modalities demonstrate both increased airway wall thickness and luminal cross-sectional area relatively early in lung disease evaluation. Bronchiectatic cysts and emphysematous bullae or subpleural blebs are frequent with advanced lung disease, the upper lobes being most commonly involved. These enlarged air spaces may rupture and cause pneumothorax. Interstitial disease is not a prominent feature, although areas of fibrosis appear eventually. Bronchial arteries are enlarged and tortuous, contributing to a propensity for hemoptysis in bronchiectatic airways. Small pulmonary arteries eventually display medial hypertrophy, which would be expected in secondary pulmonary hypertension.

The **paranasal sinuses** are uniformly filled with secretions containing inflammatory products, and the epithelial lining displays hyperplastic and hypertrophied secretory elements (see Chapter 408). Polypoid lesions within the sinuses and erosion of bone have been reported. The nasal mucosa may form large or multiple **polyps** , usually from a base surrounding the ostia of the maxillary and ethmoidal sinuses.

The **pancreas** is usually small, occasionally cystic, and often difficult to find at postmortem examination. The extent of involvement varies at birth. In infants, the acini and ducts are often distended and filled with eosinophilic material. In 85–90% of patients, the lesion progresses to complete or almost complete disruption of acini and replacement with fibrous tissue and fat. Infrequently, foci of calcification may be seen on radiographs of the abdomen. The islets of Langerhans contain normal-appearing β cells, although they may begin to show architectural disruption by fibrous tissue in the 2nd decade of life.

The **intestinal tract** shows only minimal changes. Esophageal and duodenal glands are often distended with mucous secretions. Concretions may form in the appendiceal lumen or cecum. Crypts of the appendix and rectum may be dilated and filled with secretions.

Focal biliary cirrhosis secondary to blockage of intrahepatic bile ducts is uncommon in early life, although it is responsible for occasional cases of prolonged neonatal jaundice. This lesion becomes much more prevalent and extensive with age and is found in 70% of patients at postmortem examination. This process can proceed to symptomatic multilobular biliary cirrhosis that has a distinctive pattern of large irregular parenchymal nodules and interspersed bands of fibrous tissue. Approximately 30–70% of patients have fatty infiltration of the liver, in some cases despite apparently adequate nutrition. At autopsy, hepatic congestion secondary to cor pulmonale is frequently observed. The gallbladder may be hypoplastic and filled with mucoid material and often contains stones. The epithelial lining often displays extensive mucous metaplasia. Atresia of the cystic duct and stenosis of the distal common bile duct have been observed.

Glands of the **uterine cervix** are distended with mucus, copious amounts of which collect in the cervical canal. In >95% of males, the body and tail of the epididymis, the vas deferens, and the seminal vesicles are obliterated or atretic, resulting in male infertility.

Clinical Manifestations

Since the universal adoption of CF newborn screening in the United States and overseas, as well as the evolution of aggressive and proactive treatment approaches, the clinical face of CF is very different from what it was in earlier decades. Diagnosis is typically accomplished before 1 mo of age, prior to any obvious clinical symptoms or signs, and treatment is targeted on immediately correcting nutritional deficiencies and delaying the respiratory complications of the disease. The interaction of mutational heterogeneity and environmental factors leads to highly variable involvement of the lungs, pancreas, and other organs. A summary of the time course of potential development of clinical manifestations is shown in Fig. 432.5 .

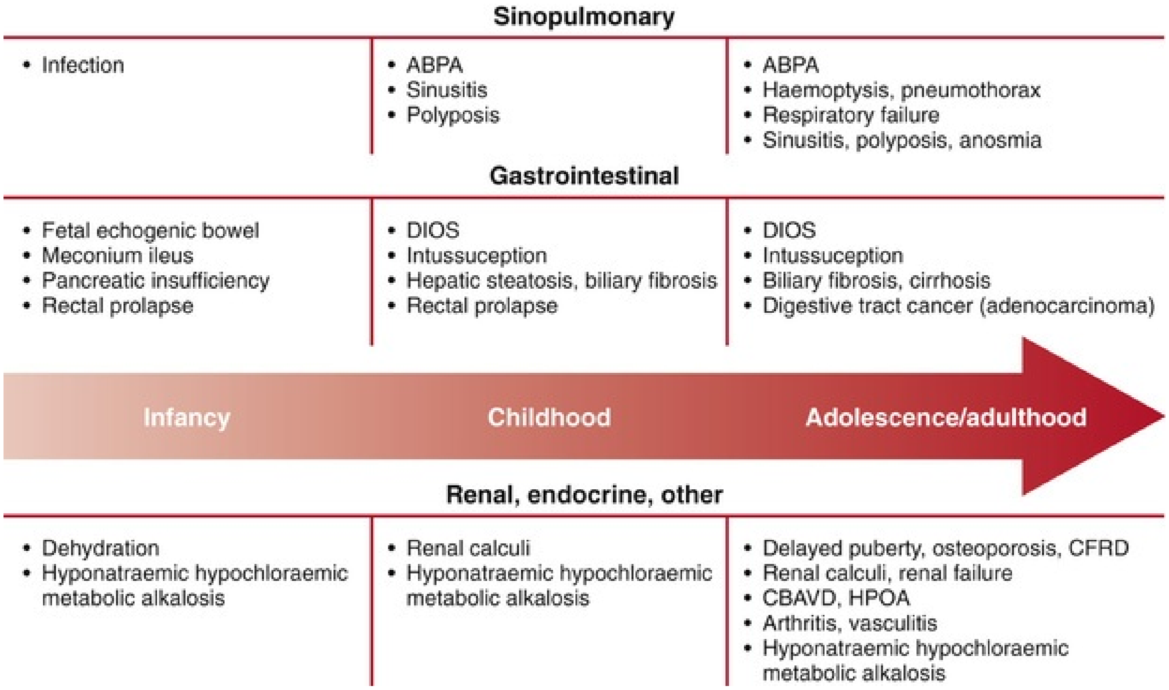
Sinopulmonary
• Infection
• ABPA
• Sinusitis
• Polyposis
• ABPA
• Haemoptysis, pneumothorax
• Respiratory failure
• Sinusitis, polyposis, anosmia
Gastrointestinal
• Fetal echogenic bowel
• Meconium ileus
• Pancreatic insufficiency
• Rectal prolapse
• DIOS
• Intussusception
• Hepatic steatosis, biliary fibrosis
• Rectal prolapse
• DIOS
• Intussusception
• Biliary fibrosis, cirrhosis
• Digestive tract cancer (adenocarcinoma)
Infancy
Childhood
Adolescence/adulthood
Renal, endocrine, other
• Dehydration
• Hyponatraemic hypochloraemic metabolic alkalosis
• Renal calculi
• Hyponatraemic hypochloraemic metabolic alkalosis
• Delayed puberty, osteoporosis, CFRD
• Renal calculi, renal failure
• CBAVD, HPOA
• Arthritis, vasculitis
• Hyponatraemic hypochloraemic metabolic alkalosis

FIG. 432.5 Approximate age of onset of clinical manifestations of cystic fibrosis. *ABPA,* Allergic bronchopulmonary aspergillosis; *CBAVD,* congenital bilateral absence of the vas deferens; *CFRD,* cystic fibrosis–related diabetes mellitus; *DIOS,* distal intestinal obstruction syndrome; *HPOA,* hypertrophic pulmonary osteoarthritis. (From O'Sullivan BP, Freedman SD: Cystic fibrosis, *Lancet* 373:1891–1902, 2009.)

Respiratory Tract

Infants diagnosed by CF newborn screening are generally asymptomatic from a respiratory standpoint. Nonetheless, the majority are infected with *S. aureus* , *Haemophilus influenza* , or even *P. aeruginosa* within the 1st mo of life, and chest CT scans show characteristic heterogeneous air trapping in ⅔ of infants by their first birthday, and bronchiectasis is found in more than 10% of 1 yr olds and ∼60% of 5 yr olds. The earliest symptom is usually cough that may begin with a viral respiratory tract infection but then persists unless treated with antibiotics. With treatment, the generally realized goal is for patients to remain asymptomatic throughout childhood, except for the periodic development of cough, chest congestion, sputum production, and/or wheezing that define a *pulmonary exacerbation* .

The rate of progression of lung disease is the chief determinant of morbidity and mortality. As lung disease slowly progresses, chronic cough, sputum production, exercise intolerance, shortness of breath, and failure to thrive are noted. Cor pulmonale, respiratory failure, and death eventually supervene unless lung transplantation is accomplished; this has become increasingly uncommon in childhood. Infection with certain strains of *B. cepacia* and other multidrug-resistant organisms may be associated with particularly rapid pulmonary deterioration and death.

Eventual physical findings include increased anteroposterior diameter of the chest, generalized hyperresonance, scattered or localized coarse crackles, and digital clubbing. Expiratory wheezes may be heard, a manifestation of airway inflammation and edema that may or may not be associated with bronchodilator responsiveness. Cyanosis is a late sign. Common pulmonary complications include atelectasis, hemoptysis, pneumothorax, and cor pulmonale; these usually appear in late adolescence or beyond.

Even though the paranasal sinuses are virtually always opacified radiographically, acute sinusitis is infrequent. Nasal obstruction and rhinorrhea are common, caused by inflamed, swollen mucous membranes or, in some cases, nasal polyposis. Nasal polyps are most troublesome between 5 and 20 yr of age.

Intestinal Tract

In 15–20% of newborn infants with CF, the ileum is completely obstructed by meconium (**meconium ileus**). The frequency is greater among siblings born subsequent to a child with meconium ileus and is particularly striking in monozygotic twins, reflecting a genetic contribution from one or more unknown modifying genes. Abdominal distention, emesis, and failure to pass meconium appear in the first 24-48 hr of life (see Chapters 123.1 and 356.2) and often requires surgical intervention. Abdominal radiographs (Fig. 432.6) show dilated loops of bowel with air-fluid levels and, frequently, a collection of granular, “ground-glass” material in the lower central abdomen. Rarely, **meconium peritonitis** results from intrauterine rupture of the bowel wall and can be detected radiographically as the presence of peritoneal or scrotal calcifications.

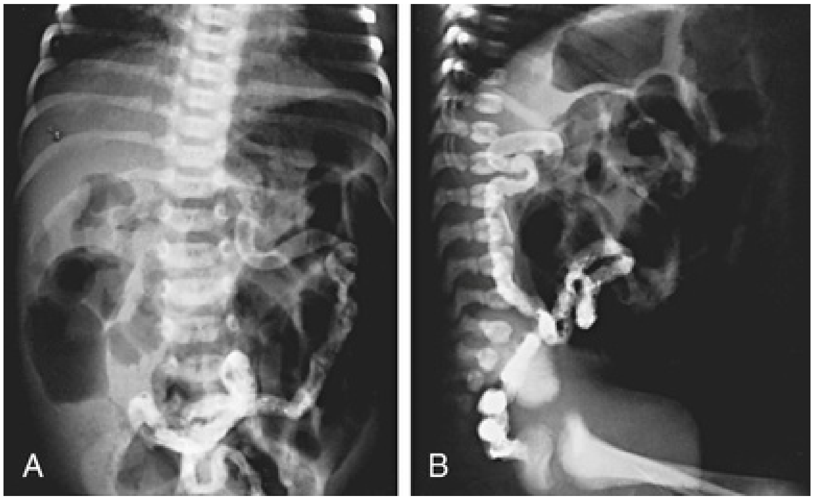

FIG. 432.6 **A** and **B,** Contrast enema study in a newborn infant with abdominal distention and failure to pass meconium. Notice the small diameter of the sigmoid and ascending colon and dilated, air-filled loops of small intestine. Several air-fluid levels in the small bowel are visible on the upright lateral view.

Ileal obstruction with fecal material (**distal intestinal obstruction syndrome [DIOS]**) occurs in older children, causing cramping abdominal pain, abdominal distention, and obstruction that can be treated with medical approaches to bowel evacuation.

More than 85% of children with CF have *exocrine* pancreatic insufficiency, causing protein and fat malabsorption. Symptoms, if untreated, include frequent, bulky, greasy stools and failure to gain weight even when food intake appears to be large. Weight gain can be challenging, but attainment of normal growth and development is an expectation of treatment. A protuberant abdomen, decreased muscle mass, poor growth, and delayed maturation are classic and rarely seen physical signs. Excessive flatus may be a problem. Supplementation with fat-soluble vitamin preparations has made deficiencies of vitamin A, E, and K unusual, but vitamin D deficiency continues to be prevalent and, although rickets is rare, osteoporosis is common, especially in older patients and those with more severe lung disease. Class IV-VI mutations are associated with pancreatic sufficiency, but patients with these mutations are prone to pancreatitis when they reach adolescence.

Historically a relatively common event, **rectal prolapse** occurs much less frequently as the result of earlier diagnosis and initiation of pancreatic enzyme replacement therapy.

Biliary Tract

Infants may occasionally present with **neonatal jaundice** suggestive of biliary obstruction. Evidence for liver dysfunction is most often detected in the first 15 yr of life and can be found in up to 30% of individuals. **Biliary cirrhosis** becomes symptomatic in only 5–7% of patients. Manifestations can include icterus, ascites, hematemesis from esophageal varices, and evidence of hypersplenism. Biliary colic secondary to cholelithiasis may occur in the 2nd decade or later. Liver disease occurs independent of genotype but is associated with meconium ileus and pancreatic insufficiency.

Cystic Fibrosis–Related Diabetes and Pancreatitis

Endocrine pancreatic insufficiency tends to develop in the 2nd decade and beyond and is more common in patients with a family history of type II diabetes mellitus. It most commonly begins with postprandial hyperglycemia and may or may not be accompanied by weight loss or flattening weight gain. Fasting hyperglycemia and elevated hemoglobin A_{1c} are later manifestations. Ketoacidosis usually does not occur, but eye, kidney, and other vascular complications have been noted in patients living ≥10 yr after the onset of hyperglycemia. Recurrent, acute pancreatitis occurs occasionally in individuals who have residual exocrine pancreatic function and may be the sole manifestation of homozygotic *CFTR* mutations.

Genitourinary Tract

Virtually all males are **azoospermic** because of failure of development of wolffian duct structures, but sexual function is generally unimpaired. The female fertility rate is diminished, especially in women who have poor nutrition or advanced lung disease. Pregnancy is generally tolerated well by women with good pulmonary function but may accelerate pulmonary progression in those with advanced lung problems and may lead to glucose intolerance. Urinary incontinence associated with cough occurs in 18–47% of female children and adolescents.

Sweat Glands

Excessive loss of salt in the sweat predisposes young children to salt depletion episodes, especially during episodes of gastroenteritis and during warm weather. These children may present with **hypochloremic alkalosis.** Hyponatremia is a risk particularly in warm climates. Frequently, parents notice salt *frosting* of the skin or a salty taste when they kiss the child. A few genotypes are associated with normal sweat chloride values.

Diagnosis and Assessment

The diagnosis of CF has been based on a positive quantitative sweat test ($Cl^- \geq$ 60 mEq/L) in conjunction with one or more of the following features: identification of 2 CFTR mutations, typical chronic obstructive pulmonary disease, documented exocrine pancreatic insufficiency, and a positive family history. With newborn screening, diagnosis is often made prior to obvious clinical manifestations such as failure to thrive and chronic cough. Diagnostic criteria have been recommended to include additional testing procedures (Table 432.3).

Table 432.3

Diagnostic Criteria for Cystic Fibrosis (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)
or
A history of CF in a sibling
or
A positive newborn screening test
plus
Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:
Two elevated sweat chloride concentrations obtained on separate days
or
Identification of two CF mutations
or
An abnormal nasal potential difference measurement

Sweat Testing

The sweat test, which involves using pilocarpine iontophoresis to collect sweat and performing chemical analysis of its chloride content, is the standard approach to diagnosis of CF. The procedure requires care and accuracy. An electric current is used to carry pilocarpine into the skin of the forearm and locally stimulate the sweat glands. If an adequate amount of sweat is collected, the specimens are analyzed for chloride concentration. Infants with a positive newborn screen for CF should have the sweat chloride testing performed after 36-wk corrected gestational age and at a weight greater than 2 kg and at age greater than 10 days to increase the likelihood of sufficient sweat collection for an accurate study. Positive results should be confirmed; for a negative result, the test should be repeated if suspicion of the diagnosis remains.

More than 60 mmol/L of chloride in sweat is diagnostic of CF when one or more other criteria are present. In individuals with a positive newborn screen, a sweat chloride level less than 30 mmol/L indicates that CF is unlikely. Borderline (or intermediate) values of 30-59 mmol/L have been reported in patients of all ages who have CF with atypical involvement and require further testing. Table 432.4 lists the conditions associated with false-negative and false-positive sweat test results.

Table 432.4

Conditions Associated With False-Positive and False-Negative Sweat Test Results

WITH FALSE-POSITIVE RESULTS
Eczema (atopic dermatitis)
Ectodermal dysplasia
Malnutrition/failure to thrive/deprivation
Anorexia nervosa
Congenital adrenal hyperplasia
Adrenal insufficiency
Glucose-6-phosphatase deficiency
Mauriac syndrome
Fucosidosis
Familial hypoparathyroidism
Hypothyroidism
Nephrogenic diabetes insipidus
Pseudohypoaldosteronism
Klinefelter syndrome
Familial cholestasis syndrome
Autonomic dysfunction
Prostaglandin E infusions
Munchausen syndrome by proxy
WITH FALSE-NEGATIVE RESULTS

Dilution
Malnutrition
Edema
Insufficient sweat quantity
Hyponatremia
Cystic fibrosis transmembrane conductance regulator mutations with preserved sweat duct function

DNA Testing

Several commercial laboratories test for 30-96 of the most common *CFTR* mutations. This testing identifies ≥90% of individuals who carry 2 CF mutations. Some children with typical CF manifestations are found to have 1 or no detectable mutations by this methodology. Some laboratories perform comprehensive mutation analysis screening for all the >1,900 identified mutations.

Other Diagnostic Tests

The finding of increased potential differences across nasal epithelium (nasal potential difference) that is the increased voltage response to topical amiloride application, followed by the absence of a voltage response to a β-adrenergic agonist, has been used to confirm the diagnosis of CF in patients with equivocal or frankly normal sweat chloride values. This testing is primarily used in research applications and has never undergone extensive validation as a clinical tool.

Pancreatic Function

The diagnosis of pancreatic malabsorption can be made by the quantification of *elastase-1 activity* in a fresh stool sample by an enzyme-linked immunosorbent assay specific for human elastase. The quantification of fat malabsorption with a 72-hr stool collection is rarely necessary in the clinical setting. CF-related diabetes affects approximately 20% of adolescents and 40–50% of adults, and clinical guidelines recommend yearly oral glucose tolerance testing (OGTT) after age 10. OGTT may sometimes be clinically indicated at an earlier age. Spot testing of blood and urine glucose levels and glycosylated hemoglobin levels are not sufficiently sensitive.

Radiology

Hyperinflation of lungs occurs early and is often accompanied by nonspecific peribronchial thickening (Fig. 432.7). Bronchial thickening and plugging and ring shadows suggesting bronchiectasis usually appear first in the upper lobes. Nodular densities, patchy atelectasis, and confluent infiltrate follow. Hilar lymph nodes may be prominent. With advanced disease, impressive hyperinflation with markedly depressed diaphragms, anterior bowing of the sternum, and a narrow cardiac shadow are noted. Cyst formation, extensive bronchiectasis, dilated pulmonary artery segments, and segmental or lobar atelectasis is often apparent with advanced disease. Most CF centers obtain chest radiographs (posteroanterior [PA] and lateral) at least annually. Standardized scoring of radiologic changes has been used to follow progression of lung disease. CT of the chest can detect heterogeneous hyperinflation and localized thickening of bronchial airway walls, mucous plugging, focal hyperinflation, and early bronchiectasis (Fig. 432.8). CT abnormalities are commonly seen at a young age, even in asymptomatic children with normal lung function.

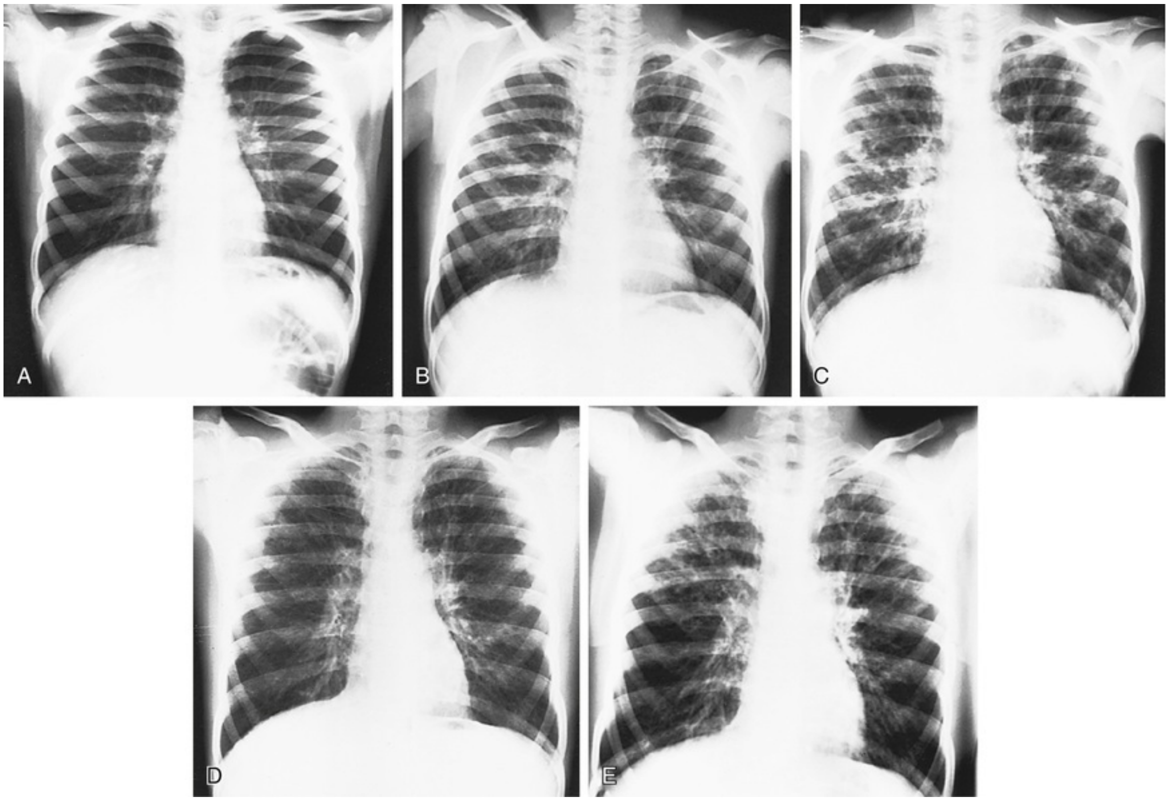

FIG. 432.7 Serial radiographs in a boy show the changing appearance of

cystic fibrosis over 6 yr. **A,** At 9 yr, frontal radiograph shows minimal peribronchial thickening and hyperaerated lungs indistinguishable from asthma. **B,** Nineteen mo later, the radiographic picture has worsened considerably. Extensive peribronchial thickening is now noted. Mucoid impaction of the bronchus is seen in the left upper lobe and hilar shadows have become abnormally prominent. **C,** Ten mo later, further deterioration is obvious. Widespread typical changes of cystic fibrosis (CF) are noted throughout both lungs. **D,** Follow-up studies show considerable improvement, which suggested that some of the changes evident on **C** were from superimposed infection. **E,** One yr later, note the progressive changes of CF—most severe in the upper lobes bilaterally. (From Long FR, Druhan SM, Kuhn JP. Diseases of the bronchi and pulmonary aeration. In Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, Fig. 73-54.)

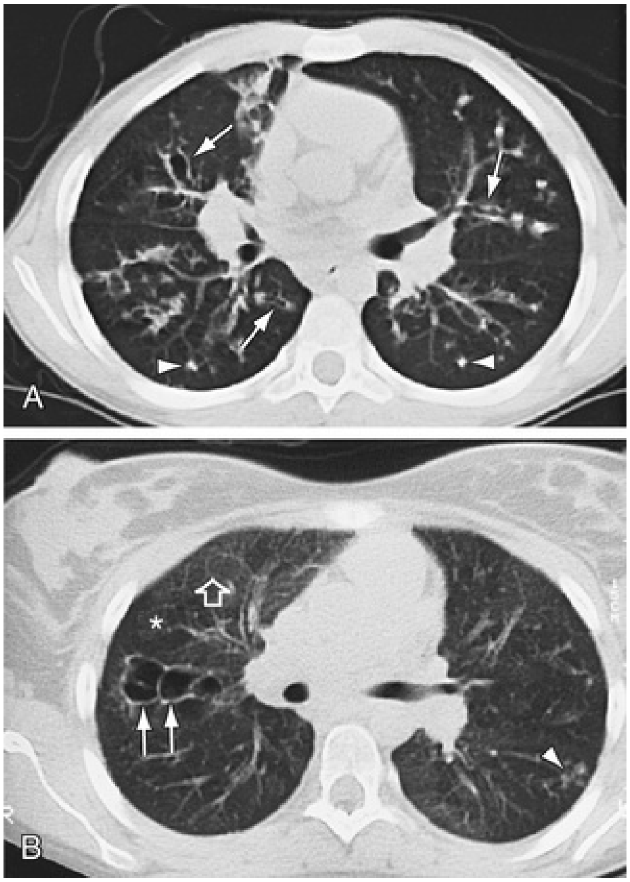

FIG. 432.8 CT scans of the chest in cystic fibrosis. **A,** A 12 yr old boy with moderate lung disease. Airway and parenchymal changes are present throughout both lungs. Multiple areas of bronchiectasis *(arrows)* and mucous plugging *(arrowheads)* can be seen. **B,** A 19 yr old girl has mostly normal lung with 1 area of saccular bronchiectasis in the right upper lobe *(arrows)* and a focal area of peripheral mucous plugging in the right lower

lobe *(arrowhead).* Lung density is heterogeneous with areas of normal lung *(open arrow)* and areas of low attenuation reflecting segmental and subsegmental air trapping *(asterisk).*

Radiographs of paranasal sinuses reveal panopacification and, often, failure of frontal sinus development. CT provides better resolution of sinus changes if this information is required clinically. Fetal ultrasonography may show pancreatic changes indicative of CF and suggest ileal obstruction with meconium early in the second trimester, but this finding is not predictive of meconium ileus at birth.

Pulmonary Function

Infant pulmonary function testing is done routinely for clinical evaluation at a few CF centers but, given its complexity and the need for sedation, for the most part it is reserved for research protocols. Lung clearance index (LCI) measured by multiple breath washout can be done in infants and young children and is a sensitive measure of ventilation inhomogeneity caused by small airways disease. Currently it is primarily used for research, but given its ease and applicability it may be adopted as a standard monitoring tool in the future as CF care centers become more accustomed to its use.

Standard pulmonary function studies are usually obtained starting at about 4 yr of age and are routinely done by age 6. **Forced expiratory volume in 1 sec** (FEV_1) is the measurement that has been shown to correlate most closely with mortality and shows a gradual decline averaging 2–3% per year throughout childhood. Although a small number of children may already show evidence of airway obstruction by age 6, trends over the past several decades, as reported by the CFF patient registry, show a steady improvement in average FEV1 of the CF population, and as of 2015 ∼75% had normal or near-normal lung function at age 18 yr. Residual volume and functional residual capacity are increased early in the course of lung disease and are the cause of decreasing forced vital capacity (FVC) measurement. Restrictive changes, characterized by declining total lung capacity and vital capacity, correlate with extensive lung injury and fibrosis and are a late finding. Testing at each clinic visit is recommended to evaluate the course of the pulmonary involvement and allow for early intervention when clinically significant decrements are documented—this is probably the most sensitive indicator of a pulmonary exacerbation that should be treated with systemic antibiotics.

Microbiologic Studies

H. influenza and *S. aureus* are the most common organisms recovered in young children (Fig. 432.9). *Pseudomonas* may be acquired early and is eventually an organism of key significance. *P. aeruginosa* appears to have a special propensity for the CF airway and over time characteristically develops a biofilm associated with a mucoid appearance in the microbiology lab and which correlates with more rapid progression of lung disease. Once *P. aeruginosa* develops a mucoid phenotype, it is extremely difficult to eradicate from the airway. A wide range of other organisms are frequently recovered, particularly in advanced lung disease; they include a variety of Gram-negative rods including the *Burkholderia cepacia* complex, which may be associated with a fulminant downhill course (the cepacia syndrome); *Stenotrophomonas maltophilia* , and *Achromobacter xylosoxidans;* assorted fungi, especially *Aspergillus fumigatus* , which is most important due to the relatively common development of **allergic bronchopulmonary aspergillosis** ; and nontuberculous mycobacterial species, especially *Mycobacterium avium* complex and *Mycobacterium abscessus* . Airway cultures are obtained regularly, most typically using oropharyngeal swabs in young children, and then sputum (which may be induced) in older children capable of expectoration. Oropharyngeal swabs typically give a good indication of the lower airway flora, but fiberoptic bronchoscopy may be used to gather lower respiratory tract secretions of infants and young children who do not expectorate if there is a concern for false-negative cultures, especially regarding the presence of *P. aeruginosa* .

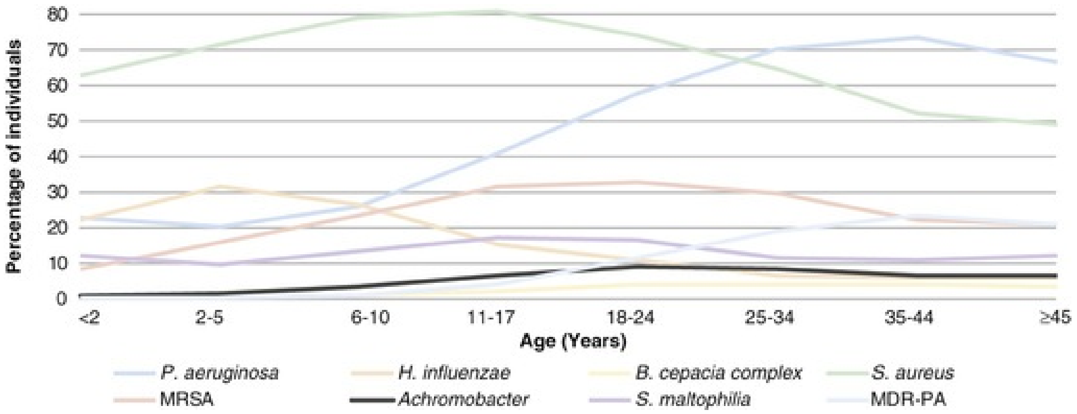

FIG. 432.9 Prevalence of respiratory microorganisms by age cohort. In young patients, early colonization with *Haemophilus influenza* and *Staphylococcus aureus* take place. Over time, *Pseudomonas aeruginosa* is

detected in respiratory cultures and may become chronic. *P. aeruginosa* may change over time to become mucoidy, and *P. aeruginosa* is at risk for becoming multidrug resistant *(MDR)* . Other organisms may infect the CF airway including methicillin-resistant *S. aureus (MRSA)* , *Achromobacter* , *Burkholderia cepacia* complex, and *Stenotrophomonas maltophilia* . (From the Cystic Fibrosis Foundation Patient Registry 2015. Annual Data Report. ©2016 Cystic Fibrosis Foundation, Bethesda, Maryland.)

The CF airway microbiome consists of a large number of additional organisms, especially anaerobes that are identified through antigen detection but not culture methods. The significance of this finding and its therapeutic implications remain somewhat unclear, but it has long been appreciated that response to antibiotic treatment of pulmonary exacerbations is not always predictable based upon culture and sensitivity of airway cultures.

Newborn Screening

Newborn screening for CF is mandated in all 50 states and is the most common way that CF is diagnosed. A variety of newborn screening algorithms are in place to identify infants with CF. Most algorithms use a combination of immunoreactive trypsinogen (IRT) results and limited DNA testing on blood spots; because not all mutations can be found using this approach, babies with an elevated IRT and a single detected mutation are considered a positive screen, and all positive screens are followed by a confirmatory sweat analysis. Depending upon race and ethnicity, about 10–15% of infants with a positive screen based on the finding of only 1 CF mutation will be found to have CF. This screening test is ≈95% sensitive and should result in a median age at diagnosis of less than 1 mo. Newborn diagnoses can prevent early nutritional deficiencies and improve long-term growth and may improve cognitive function. Importantly, good nutritional status (50 percentile weight for length or 50 percentile body mass index) is associated with better lung function at 6 yr of age.

An occasional patient may be missed by newborn screening, and those caring for adolescents and adults need to be aware that most of those older patients were not screened at birth and may present at later ages, into late adulthood. Prior to the advent of newborn screening, infants and children commonly presented with malabsorption and failure to thrive, in addition to respiratory symptoms. Most older patients whose diagnosis was missed early in life will have unusual class IV, V, or VI mutations and therefore *normal* pancreatic function. They will more typically present with chronic productive cough due to either bronchitis or chronic sinusitis and may have nasal polyps or allergic bronchopulmonary aspergillosis or unexplained bronchiectasis. The most common nonrespiratory manifestations will be congenital bilateral absence of the vas deferens (CBAVD) (in males) or recurrent pancreatitis. It is important to recognize that sweat testing at an adept lab (typically limited to CF Foundation accredited care centers) is the most accurate way to diagnose CF in this group. CFTR mutation testing with standard panels is never as sensitive as sweat testing and will frequently miss the unusual mutations that are seen more commonly in people who present late in this manner.

There is a subset of infants with a positive newborn screen for CF who have a nondiagnostic sweat chloride (30-59 mmol/L) and/or 1 or 2 CFTR mutations that is not clearly disease causing. These infants have **CFTR -related metabolic syndrome (CRMS)** (also called CFTR-related disease) and should be followed in a CF center closely through the 1st yr and then annually to evaluate them for the development of CF symptoms. Indeed, in some (∼10%) patients, the sweat test becomes clearly abnormal over time and they can be diagnosed as having CF. Because CRMS is a condition defined by asymptomatic detection in the context of newborn screening and CF newborn screening has been commonly performed only in the past decade or so, it is not clear whether some children in this group will eventually develop manifestations of CFTR-related disorder, such as CBAVD, chronic sinusitis, recurrent pancreatitis, or even bronchiectasis. An approach to the evaluation of patients with CRMS is seen in Fig. 432.10 .

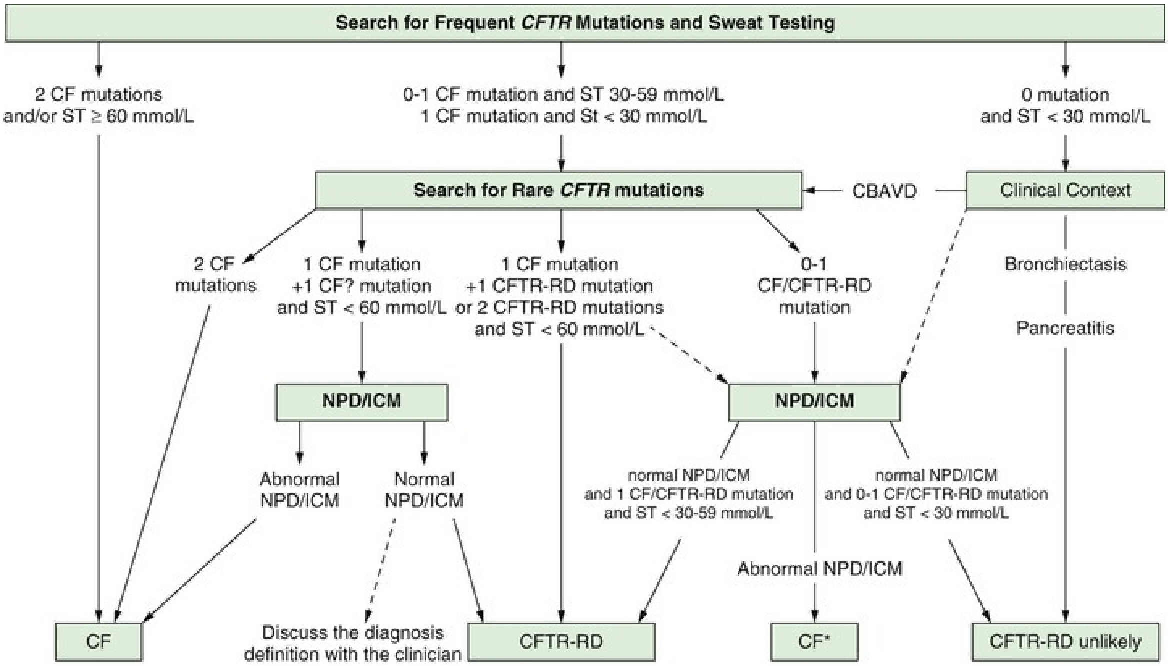
Search for Frequent CFTR Mutations and Sweat Testing
2 CF mutations and/or ST ≥ 60 mmol/L
0-1 CF mutation and ST 30-59 mmol/L
1 CF mutation and St < 30 mmol/L
0 mutation and ST < 30 mmol/L
Search for Rare CFTR mutations
CBAVD
Clinical Context
2 CF mutations
1 CF mutation +1 CF? mutation and ST < 60 mmol/L
1 CF mutation +1 CFTR-RD mutation or 2 CFTR-RD mutations and ST < 60 mmol/L
0-1 CF/CFTR-RD mutation
Bronchiectasis
Pancreatitis
NPD/ICM
NPD/ICM
Abnormal NPD/ICM
Normal NPD/ICM
normal NPD/ICM and 1 CF/CFTR-RD mutation and ST < 30-59 mmol/L
normal NPD/ICM and 0-1 CF/CFTR-RD mutation and ST < 30 mmol/L
Abnormal NPD/ICM
CF
Discuss the diagnosis definition with the clinician
CFTR-RD
CF*
CFTR-RD unlikely

FIG. 432.10 2015 European Cystic Fibrosis Society recommended process for diagnosis of CFTR-RD. Global diagnostic algorithm for CF and CFTR-RD. A global flow-chart of genetic and functional diagnostic testing in CF and CFTR-RD is presented. *CBAVD,* congenital bilateral absence of the vas deferens; *CF,* cystic fibrosis; *CF? mutation* , mutation of unproven or uncertain clinical significance; *CF** , diagnosis of CF or consider this diagnosis; *CFTR,* cystic fibrosis transmembrane conductance regulator; *CFTR-RD* , CFTR-related disorders; *ICM* , intestinal current measurement; *NPD* , nasal potential difference; *ST* , sweat test (repeated; false positive should be excluded/sought in a specialized center). (From Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, et al. Recommendations for the classification of diseases as CFTR-related disorders, *J Cyst Fibros* 10(Suppl 2):S86–102, 2011. Fig 1.)

Treatment

General Approach to Care

Initial efforts after diagnosis should be intensive and should include baseline assessment, initiation of treatment to prevent pulmonary involvement in young infants or reverse it in those diagnosed later, nutritional maintenance or remediation, and education of the patient and parents. Follow-up evaluations are scheduled every 1-3 mo, depending on the age at diagnosis, because many aspects of the condition require careful monitoring. An interval history and physical examination should be obtained at each visit. A sputum sample or, if that is not available, a lower pharyngeal swab taken during or after a forced cough is obtained for culture and antibiotic susceptibility studies. Because irreversible loss of pulmonary function from low-grade infection can occur gradually and without acute symptoms, emphasis is placed on a thorough pulmonary history and physical exam and routine pulmonary function testing. Table 432.5 lists symptoms and signs that suggest the need for more intensive antibiotic and physical therapy (PT). Protection against exposure to methicillin-resistant *S. aureus*, *P. aeruginosa*, *B. cepacia*, and other resistant Gram-negative organisms is essential, including contact isolation procedures and careful attention to cleaning of inhalation therapy equipment. A nurse, physical therapist, respiratory therapist, social worker, and dietitian, as members of the multidisciplinary care team, should evaluate children regularly and contribute to the development of a comprehensive daily care plan. Considerable education and programs to empower families and older children to take responsibility for care are likely to result in the best adherence to daily care programs. Screening patients and caregivers for anxiety and depression annually is expected to identify issues that can interfere with adherence to daily care. Standardization of practice, on the part of both caregivers and families, as well as close monitoring and early intervention for new or increasing symptoms appears to result in the best long-term outcomes.

Table 432.5

Symptoms and Signs Associated With Exacerbation of Pulmonary Infection in Patients With Cystic Fibrosis

SYMPTOMS
Increased frequency and duration of cough
Increased sputum production
Change in appearance of sputum
Increased shortness of breath
Decreased exercise tolerance
Decreased appetite
Feeling of increased congestion in the chest
SIGNS
Increased respiratory rate
Use of accessory muscles for breathing
Intercostal retractions
Change in results of auscultatory examination of chest
Decline in measures of pulmonary function consistent with the presence of obstructive airway disease
Fever and leukocytosis
Weight loss
New infiltrate on chest radiograph

From Ramsey B: Management of pulmonary disease in patients with cystic fibrosis, *N Engl J Med* 335:179, 1996.

Because secretions of CF patients are not adequately hydrated, attention in early childhood to oral hydration, especially during warm weather or with acute gastroenteritis, may minimize complications associated with impaired mucous clearance. Intravenous therapy for dehydration should be initiated early.

The goal of therapy is to maintain a stable condition for prolonged periods. This can be accomplished for most patients by interval evaluation and adjustments of the home treatment program. Some children have episodic acute or low-grade chronic lung infection that progresses. For these patients, intensive inhalation and airway clearance and intravenous antibiotics are indicated. Improvement is most reliably accomplished in a hospital setting; selected patients have demonstrated successful outcomes while completing these treatments at home. Intravenous antibiotics may be required infrequently or as often as every 2-3 mo. The goal of treatment is to return patients to their previous pulmonary and functional status.

The basic daily care program varies according to the age of the child, the degree of pulmonary involvement, other system involvement, and the time available for therapy. The major components of this care are pulmonary and nutritional therapies. Because therapy is medication intensive, iatrogenic problems frequently arise. Monitoring for complications is also an important part of management

Pulmonary Therapy

The object of pulmonary therapy is to clear secretions from airways and to control infection. When a child is not doing well, every potentially useful aspect of therapy should be reconsidered.

Inhalation Therapy

Human recombinant DNase (2.5 mg) enzymatically dissolves extracellular DNA released by neutrophils, a major contributor to the characteristically sticky and viscous CF airway secretions. It is usually given as a single daily aerosol dose, improves pulmonary function, decreases the number of pulmonary exacerbations, and promotes a sense of well-being. Benefit for those with mild, moderate, and severe lung disease has been documented. Improvement is sustained for 12 mo or longer with continuous therapy.

Nebulized hypertonic saline, acting as a hyperosmolar agent, is believed to draw water into the airway and rehydrate mucus and the periciliary fluid layer, resulting in improved mucociliary clearance. Seven percent hypertonic saline nebulized 2-4 times daily increases mucous clearance and reduces pulmonary exacerbation, with only a slight short-term improvement in pulmonary function.

Airway Clearance Therapy

Airway clearance treatment begins in infancy with chest percussion (with or without postural drainage) and derives its rationale from the idea that cough clears mucus from large airways, but chest vibrations are required to shear secretions for the airway wall and move secretions from small airways, where expiratory flow rates are low. **Chest PT** can be particularly useful for patients with CF because they accumulate secretions in small airways first, even before the onset of symptoms. Cessation of chest PT in children with mild to moderate airflow limitation results in deterioration of lung function within 3 wk, and prompt improvement of function occurs when therapy is resumed, but it is less clear which available modality is best. Airway clearance therapy is recommended 2-4 times a day, depending on the severity of lung dysfunction, and usually increased during acute exacerbations. Cough, huffing, or forced expirations are encouraged intermittently throughout the session. Vest-type mechanical percussors *(high-frequency chest wall oscillation)* are commonly used past infancy due to their convenience, as are a variety of oscillatory positive expiratory pressure devices (such as Acapella and Aerobika) and other controlled breathing techniques (e.g., *autogenic drainage*). Routine aerobic exercise appears to slow the rate of decline of pulmonary function, and benefit has also been documented with weight training. No one airway clearance technique can be shown to be superior to any other, so all modes should be considered in the development of an airway clearance prescription. Adherence to daily therapy is important but rarely achieved; therefore airway clearance technique plans are individualized for each patient.

Antibiotic Therapy

Antibiotics are the mainstay of therapy designed to control progression of lung infection. The goal is to reduce the intensity of endobronchial infection and to delay progressive lung damage. The usual guidelines for acute chest infections, such as fever, tachypnea, or chest pain, are often absent. Consequently, all aspects of the patient's history and examination, including anorexia, weight loss, and diminished activity, must be used to guide the frequency and duration of therapy. Antibiotic treatment varies from intermittent short courses of 1 antibiotic to nearly continuous treatment with 1 or more antibiotics. Dosages for some antibiotics are often 2-3 times the amount recommended for minor infections because patients with CF have proportionately more lean body mass and higher clearance rates for many antibiotics than other individuals. In addition, it is difficult to achieve effective drug levels of many antimicrobials in respiratory tract secretions.

Oral Antibiotic Therapy

Indications for oral antibiotic therapy in a patient with CF include the presence of respiratory tract symptoms, physical signs, or changes in pulmonary function testing or chest x-ray. Treatment is guided by identification of pathogenic organisms in respiratory tract cultures and in vitro sensitivity testing. Common organisms, including *S. aureus (MRSA or MSSA)*, nontypeable *H. influenzae, P. aeruginosa; B. cepacia* and other Gram-negative rods, are encountered with increasing frequency. The usual course of therapy is 2 wk, and maximal doses are recommended. Table 432.6 lists useful oral antibiotics. The quinolones are the only broadly effective oral antibiotics for *Pseudomonas* infection, but resistance against these agents may emerge. Macrolides may reduce the virulence properties of *P. aeruginosa,* such as biofilm production, and contribute antiinflammatory effects. Long-term therapy with azithromycin 3 times a week improves lung function in patients with chronic *P. aeruginosa* infection.

Table 432.6

Antimicrobial Agents for Cystic Fibrosis Lung Infection

ROUTE	ORGANISMS	AGENTS	DOSAGE (mg/kg/24 hr)	NO. DOSES/24 hr
Oral	*Staphylococcus aureus*	Dicloxacillin	25-50	4
		Linezolid	20	2
		Cephalexin	50	4
		Clindamycin	10-30	3-4
		Amoxicillin-clavulanate	25-45	2-3
	Haemophilus influenzae	Amoxicillin	50-100	2-3
	Pseudomonas aeruginosa	Ciprofloxacin	20-30	2-3
	Burkholderia cepacia	Trimethoprim-	8-10*	2-4

		sulfamethoxazole		
	Empirical	Azithromycin	10, day 1; 5, days 2-5	1
		Erythromycin	30-50	3-4
Intravenous	*S. aureus*	Nafcillin	100-200	4-6
		Vancomycin	40	3-4
	P. aeruginosa	Tobramycin	8-12	1-3
		Amikacin	15-30	2-3
		Ticarcillin	400	4
		Piperacillin	300-400	4
		Ticarcillin-clavulanate	400 [†]	4
		Piperacillin-tazobactam	240-400 [‡]	3
		Meropenem	60-120	3
		Imipenem-cilastatin	45-100	3-4
		Ceftazidime	150	3
		Aztreonam	150-200	4
	B. cepacia	Chloramphenicol	50-100	4
		Meropenem	60-120	3
Aerosol		Tobramycin (inhaled)	300 [§]	2
		Aztreonam (inhaled)	75	3

[*] Quantity of trimethoprim.

[†] Quantity of ticarcillin.

[‡] Quantity of piperacillin.

[§] In mg per dose.

Aerosolized Antibiotic Therapy

Aerosolized antibiotics are often used as part of daily therapy when the airways are infected with *P. aeruginosa* . Aerosolized tobramycin inhalation solution or powder, or aztreonam inhalation solution used as a suppressive therapy (on 1 mo, off 1 mo), may reduce symptoms, improve pulmonary function, and decrease the occurrence of pulmonary exacerbations. Although these therapies are sometimes used in acute pulmonary exacerbations, the evidence to support this application is limited.

Another important indication for aerosolized antibiotic therapy is to eradicate *P. aeruginosa* in the airways after initial detection. Early infection may be cleared for mo to several yr in this way, although eventual reinfection is common. Other antibiotics have been used via inhalation, including liposomal amikacin and levofloxacin for *P. aeruginosa* , and there was no inferiority of efficacy compared with inhaled tobramycin.

Intravenous Antibiotic Therapy

For the patient who has not responded to oral antibiotics and intensive home measures with return of signs, symptoms, and FEV_1 to baseline, intravenous antibiotic therapy is indicated. This therapy is usually initiated in the hospital but is sometimes completed on an ambulatory basis if the likelihood of complete adherence to the therapeutic regimen is good. The ideal duration of treatment is unknown; although many patients show improvement within 7 days, many CF physicians believe that it is usually advisable to extend the period of treatment to at least 14 days. Permanent intravenous access can be provided for long-term or frequent courses of therapy in the hospital or at home. Thrombophilia screening should be considered before the use of totally implantable intravenous devices or for recurring problems with venous catheters.

Table 432.6 lists commonly used intravenous antibiotics. In general, treatment of *Pseudomonas* infection is thought to require 2-drug therapy. A 3rd agent may be given for optimal coverage of *S. aureus* or other organisms. Aminoglycosides are usually effective when given every 24 hr to minimize toxicity and optimize convenience. Some CF physicians use peak and trough levels to guide dosing, but most clinical pharmacists recommend measuring levels at other times, commonly 2 and 12 hr, to use pharmacokinetic calculations to guide dosing. Changes in therapy should be guided by lack of improvement more than by culture results; sensitivities do not always predict response to therapy, and this may be due to the presence of other organisms that are not detected by culture methods. If patients do not show improvement, complications such as right heart failure, asthma, or infection with viruses, *A. fumigatus* (especially ABPA) (see Chapter 237), nontuberculous mycobacteria (see Chapters 217 and 399), or other unusual organisms should be considered. *B. cepacia* complex and acinetobacter are Gram-negative rods that may be particularly refractory to antimicrobial therapy. Infection control in both the outpatient and inpatient medical setting is critically important to prevent nosocomial spread of resistant bacterial organisms between patients.

Bronchodilator Therapy

Reversible airway obstruction occurs in many children with CF, sometimes in conjunction with frank asthma or allergic bronchopulmonary aspergillosis. Reversible obstruction is conventionally defined as improvement of ≥12% in FEV1 or FVC after inhalation of a bronchodilator. In many patients with CF, these may improve by only 5–10% (physiologic response), but subjects may report subjective benefit.

Antiinflammatory Agents

Corticosteroids are useful for the treatment of allergic bronchopulmonary aspergillosis and severe asthma occasionally encountered in children with CF. Prolonged systemic corticosteroid treatment of CF lung disease reduces the decline in lung function modestly but causes predictably prohibitive side effects. Inhaled corticosteroids have theoretical appeal, but there are contradictory and weak data regarding efficacy unless the patient has clinically diagnosable asthma. Ibuprofen, given chronically in high doses adjusted to achieve a peak serum concentration of 50-100 µg/mL, is associated with a slowing of disease progression, particularly in younger patients with mild lung disease. However, there are concerns regarding side effects of nonsteroidal antiinflammatory drugs, so this therapy has not gained broad acceptance. Macrolide antibiotics have an antiinflammatory effect, and 3 days/wk azithromycin has been shown to reduce the likelihood of development of pulmonary exacerbations, especially in patients with chronic *Pseudomonas* airway infection, so this is a commonly used therapy.

Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapies

A major breakthrough in CF therapy is ivacaftor, a small molecule potentiator of the CFTR mutation, G551D (present in ∼5% of patients). Ivacaftor activates the CFTR-G551D mutant protein, a class III CFTR mutation that results in protein localized to the plasma membrane but loss of chloride channel function (Fig. 432.11). Ivacaftor therapy resulted in improvement in FEV_1 by an average of 10.6%, decreased the frequency of pulmonary exacerbations by 55%, decreased sweat chloride by an average of 48 mEq/L, and increased weight gain by an average of 2.7 kg. Ivacaftor is approved for patients older than 2 yr of age with class III and class IV mutations.

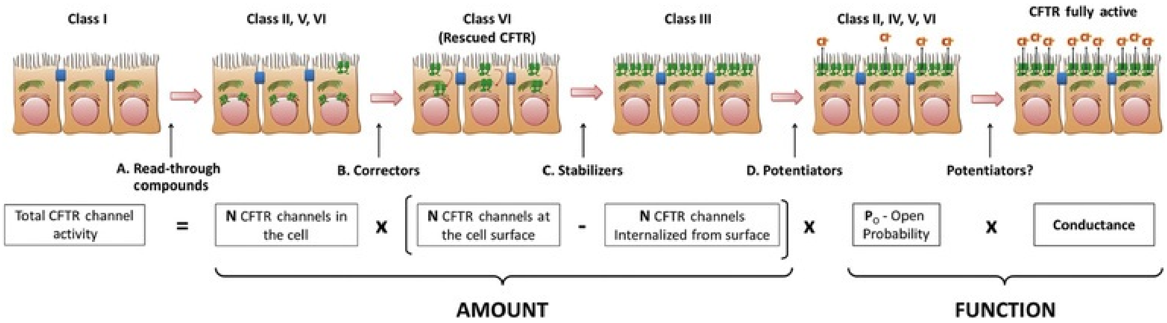
Class I
Class II, V, VI
Class VI
(Rescued CFTR)
Class III
Class II, IV, V, VI
CFTR fully active
Cl⁻
A. Read-through compounds
B. Correctors
C. Stabilizers
D. Potentiators
Potentiators?
Total CFTR channel activity
=
N CFTR channels in the cell
x
N CFTR channels at the cell surface
-
N CFTR channels Internalized from surface
x
P₀ - Open Probability
x
Conductance
AMOUNT
FUNCTION

FIG. 432.11 Cystic fibrosis transmembrane conductance regulator *(CFTR)* pharmacologic modulators have different modes of action. **A,** Read-through compounds which include aminoglycoside antibiotics (e.g., gentamicin, tobramycin) act by suppressing premature termination codons (PTCs), thus permitting translation to continue to the normal termination of the transcript and thus increasing the total amount of complete CFTR being produced in the cell. **B,** Correctors (e.g., VX-809 also known as lumacaftor; VX-661) potentially promote folding of mutant CFTR protein, allowing it to escape ER degradation and reach the cell surface, thus increasing the number of channels present at the plasma membrane. **C,** Stabilizers include compounds (e.g., hepatocyte growth factor) that enhance CFTR retention/anchoring at the cell surface, thus also contributing to increase the number of channels present at the cell surface. **D,** Potentiators (e.g., VX-770 also known as ivacaftor) activate CFTR, that is, increase the open probability *(P_o)* of the channel by regulating its gating and possibly also the conductance. (From Bell SC, De Boeck K, Amaral MD: New pharmacological approaches for cystic fibrosis: promises, progress, pitfalls, *Pharmacol Therapeu* 145:19–34, 2015 [Fig. 4, p. 26].)

The combination of ivacaftor with lumacaftor, a corrector that stabilizes misfolded F508del and enables trafficking of the mutant molecule to the apical cell membrane where it is potentiated by ivacaftor, is available for patients older than 6 yr of age who are homozygous for the F508del mutation (see Fig. 432.11). This medication is associated with smaller increments in pulmonary and nutritional outcomes but is an important proof-of-concept treatment.

Tezacaftor and ivacaftor is another combination indicated for patients ≥ 12 yr with 1 or 2 Phe508del alleles. This combination improves predicted FEV_1 and overall well-being (Table 432.7). VX-445 combined with tezacaftor-ivacaftor adds another CFTR correction agent; the triple combination improves predicted FEV_1 and reduces sweat chloride levels.

Table 432.7

Cystic Fibrosis Transmembrane Regulator Modulators for Cystic Fibrosis

DRUG	FDA-APPROVED INDICATION	FORMULATIONS	USUAL DOSAGE
Ivacaftor	≥ 12 mo with a responsive mutation [1]	150 mg tabs; 50, 75 mg granule packets [2]	≥ 6 years: 150 mg q12 hr [3]
Lumacaftor/ivacaftor	≥ 2 yr, F508del-homozygous	100/125, 200/125 mg tabs; 100/125, 150/188 mg granule packets [2]	6-11 yr: 200/250 mg q12 hr ≥ 12 yr: 400/250 mg q12 hr [4]
Tezacaftor/ivacaftor	≥ 12 yr, F508del-homozygous or F508del-heterozygous with another responsive mutation [1]	100/150 mg tabs co-packaged with ivacaftor 150 mg tabs	≥ 12 yr: 100/150 mg tab qAM, then 150 mg ivacaftor qPM

[1] Responsive mutations are those in which chloride transport is expected to increase to at least 10% of untreated normal over baseline with drug therapy, based on clinical or in vitro data.

[2] The granules should be mixed with 5 mL of room-temperature or cold soft food or liquid and consumed within 1 hr.

[3] In patients 12 mo to 6 yr old, the recommended dosage is 50 mg every 12 hr for those weighing <14 kg, and 75 mg every 12 hr for those weighing ≥ 14 kg.

[4] In patients 2-5 yr old, the recommended dosage is 100/125 mg every 12 hr for those weighing <14 kg, and 150/188 mg every 12 hr for those weighing ≥ 14 kg.

Modified from The Medical Letter on Drugs and Therapeutics: Tezacaftor/Ivacaftor (Symdeko) for cystic fibrosis; *Med Lett* 60(1558):174–176, 2018 (Table 3, p. 175).

Other Therapies

Attempts to clear recalcitrant atelectasis and airway plugging with bronchopulmonary lavage and direct installation of various medications are sometimes used in exceptional cases; there is no evidence for sustained benefit from repeated procedures. Expectorants such as iodides and guaifenesin do not effectively assist with the removal of secretions from the respiratory tract. Inspiratory muscle training can enhance maximum oxygen consumption during exercise, as well as FEV_1 .

Treatment of Pulmonary Complications

Atelectasis

Lobar atelectasis occurs relatively infrequently; it may be asymptomatic and noted only at the time of a routine chest radiograph. Aggressive intravenous therapy with antibiotics and increased chest PT directed at the affected lobe may be effective. If there is no improvement in 5-7 days, bronchoscopic examination of the airways may be indicated. If the atelectasis does not resolve, continued intensive home therapy is indicated because atelectasis may resolve during a period of wk or mo.

Hemoptysis

Endobronchial bleeding usually reflects airway wall erosion into hypertrophied bronchial vessels secondary to infection. Although more common in patients with advanced disease, it is sometimes seen in adolescents with relatively mild lung disease. Blood streaking of sputum is particularly common. Small-volume hemoptysis (<20 mL) is usually viewed as a need for intensified antimicrobial therapy and chest PT. **Massive hemoptysis,** defined as total blood loss of ≥250 mL in a 24-hr period, is rare in the 1st decade and occurs in <1% of adolescents, but it requires close monitoring and the capability to replace blood losses rapidly. Bronchoscopy rarely reveals the site of bleeding. Bronchial artery embolization can be useful to control persistent, significant hemoptysis.

Pneumothorax

Pneumothorax (see Chapter 439) is encountered uncommonly in children and teenagers with CF, although it may lead to significant compromise in lung function and occasionally may be life threatening. The episode may be asymptomatic but is often attended by chest and shoulder pain, shortness of breath, or hemoptysis. A small air collection that does not grow can be observed closely. Chest tube placement with or without pleurodesis is often the initial therapy. Intravenous antibiotics are also begun on admission. Video-assisted thoracoscopic surgery (VATS) with plication of blebs, apical pleural stripping, and basal pleural abrasion should be considered if the air leak persists. Surgical intervention is usually well tolerated even in cases of advanced lung disease. The thoracotomy tube is removed as soon as possible. Previous pneumothorax with or without pleurodesis is not a contraindication to subsequent lung transplantation.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis occurs in 5–10% of patients with CF and may manifest as wheezing, increased cough, shortness of breath, and marked hyperinflation, or most commonly, a decrease in FEV_1 that does not respond to antibiotic therapy (see Chapters 237 and 399). In some patients, a chest radiograph shows new, focal infiltrates. A very elevated total serum immunoglobulin E (IgE) level (>1,000) is usually the initial indication of the diagnosis. The presence of rust-colored sputum, the recovery of *Aspergillus* organisms from the sputum, a positive skin test for *A. fumigatus* , the demonstration of specific IgE and IgG antibodies against *A. fumigatus,* or the presence of eosinophils in a fresh sputum sample supports the diagnosis. Treatment is directed at controlling the inflammatory reaction with oral corticosteroids. Oral antifungals are usually reserved for patients who relapse after initial steroid treatment. For refractory cases, omalizumab, humanized monoclonal anti-IgE, has been effective.

Nontuberculous Mycobacteria Infection

See Chapter 244 .

Injured airways with poor clearance may be colonized by *Mycobacterium avium*- complex but also *Mycobacterium abscessus* , *Mycobacterium chelonae* , and *Mycobacterium kansasii.* Distinguishing endobronchial colonization (frequent) from invasive infection (infrequent) is challenging. Persistent fevers and new infiltrates or cystic lesions coupled with the finding of acid-fast organisms on sputum smear suggest infection. Infection with these organisms, or at least its recognition, had become increasing common. Treatment is prolonged and requires multiple antimicrobial agents. Symptoms may improve, but the nontuberculous mycobacteria are not usually cleared from the lungs.

Bone and Joint Complications

Hypertrophic osteoarthropathy causes elevation of the periosteum over the distal portions of long bones and bone pain, overlying edema, and joint effusions. Acetaminophen or ibuprofen may provide relief. Control of lung infection usually reduces symptoms. Intermittent arthropathy unrelated to other rheumatologic disorders occurs occasionally, has no recognized pathogenesis, and usually responds to nonsteroidal antiinflammatory agents. Back pain or rib fractures from vigorous coughing may require pain management to permit adequate airway clearance. These and other fractures may stem from diminished bone mineralization, the result of reduced vitamin D absorption, corticosteroid therapy, diminished weight-bearing exercises, and perhaps other factors. There may be a bone phenotype in CF that is unrelated to therapies or nutritional status and may be due to CFTR dysfunction.

Sleep-Disordered Breathing

Particularly with advanced pulmonary disease and during chest exacerbations, individuals with CF may experience more sleep arousals, less time in rapid eye movement sleep, nocturnal hypoxemia, hypercapnia, and associated neurobehavioral impairment. Nocturnal hypoxemia may hasten the onset of pulmonary hypertension and right-sided heart failure. Efficacy of specific interventions for this complication of CF has not been systematically assessed. Prompt treatment of airway symptoms and nocturnal oxygen supplementation or bilevel positive airway pressure support should be considered in selected cases, especially in patients with advanced lung disease.

Acute Respiratory Failure

Acute respiratory failure (see Chapter 89) rarely occurs in patients with mild to moderate lung disease and is usually the result of a severe viral or other infectious illness. Because patients with this complication can regain their previous status, intensive therapy is indicated. In addition to aerosol, postural drainage, and intravenous antibiotic treatment, oxygen is required to raise the arterial $Pa\text{O}_2$. An increasing $P\text{CO}_2$ may require ventilatory assistance. Endotracheal or bronchoscopic suction may be necessary to clear airway inspissated secretions and can be repeated daily. Right-sided heart failure should be treated vigorously. High-dose steroids have been anecdotally reported to be of benefit in this setting. Recovery is often slow. Intensive intravenous antibiotic therapy and postural drainage should be continued for 1-2 wk after the patient has regained baseline status.

Chronic Respiratory Failure

Patients with CF acquire chronic respiratory failure after prolonged deterioration of lung function. Although this complication can occur at any age, it is seen most frequently in adult patients. Because a long-standing $Pa\text{O}_2 < 50$ mm Hg promotes the development of right-sided heart failure, patients usually benefit from low-flow oxygen to raise arterial $P\text{O}_2$ to ≥55 mm Hg. Increasing hypercapnia may prevent the use of optimal fraction of inspired oxygen. Most patients improve somewhat with intensive antibiotic and pulmonary therapy measures and can be discharged from the hospital. Low-flow oxygen therapy is needed at home, especially with sleep. Noninvasive ventilatory support can improve gas exchange and has been documented to enhance quality of life. Ventilatory support may be particularly useful for patients awaiting lung transplantation. These patients usually display pulmonary hypertension and cor pulmonale, and this complication should be treated. Caution should be exercised to avoid ventilation-suppressing metabolic alkalosis that results from CF-related chloride depletion and, in many cases, from diuretic-induced bicarbonate retention. Chronic pain (headache, chest pain, abdominal pain, and limb pain) is frequent at the end of life and responds to judicious use of analgesics, including opioids. Dyspnea has been ameliorated with nebulized fentanyl.

Lung transplantation is an option for end-stage lung disease that is increasingly offered (see Chapter 470). Criteria for referral continue to be a subject of investigation and ideally include estimates of longevity with and without transplant based on lung function and exercise tolerance data. Survival and quality of life after lung transplantation is better in patients with CF than other chronic lung diseases, probably due to the relatively younger age of recipients with CF, but the current estimated 5-yr survival is about 50%, somewhat reduced compared with that of other solid organ transplants. Because of bronchiolitis obliterans (see Chapter 422.1) and other complications, transplanted lungs cannot be expected to function for the lifetime of a recipient, and repeat transplantation is increasingly common. The demand for donor lungs exceeds the supply, and waiting lists and duration of waits continue to be a problem.

Pulmonary Hypertension and Cor Pulmonale

Individuals with long-standing, advanced pulmonary disease, especially those with severe hypoxemia ($Pa_{O_2} < 50$ mm Hg), often acquire pulmonary hypertension and chronic right-sided heart failure. Evidence for concomitant left ventricular dysfunction is often found. The arterial P_{O_2} should be maintained at >50 mm Hg, if possible, and hypercarbia corrected with noninvasive ventilation or intubation if necessary. Intensive pulmonary therapy, including intravenous antibiotics, is most important. Adjunctive therapy with salt restriction, diuretics, and pulmonary vasodilators may be indicated. The prognosis for heart failure is poor, but a number of patients survive for ≥5 yr after the appearance of heart failure. Heart-lung transplantation may be an option (see preceding section).

Nutritional Therapy

Up to 90% of patients with CF have loss of exocrine pancreatic function leading to inadequate digestion and absorption of fats and proteins. They require dietary adjustment and augmentation, pancreatic enzyme replacement, and supplementary vitamins. In general, children with CF need to exceed the usual required daily caloric intake to grow. Daily supplements of the fat-soluble vitamins are required.

Diet

Historically, at the time of diagnosis, many infants presented with nutritional deficits; this situation has changed because of newborn screening, but even at 2-4 wk it is not uncommon to see that weight gain has begun to fall off the standard curve.

Most children with CF have a higher-than-normal caloric need because of malabsorption despite the use of pancreatic enzyme supplementation. Encouragement to eat high-calorie foods is important and often begins with more concentrated, high-calorie formulas in the 1st yr. Even so, most mothers can breastfeed successfully. It is vitally important to promote adequate weight gain in the early years, both because of a clear relationship to later lung function and also because early deficiencies make later catch up growth more difficult. Not infrequently, parent–child interactions at feeding time are maladaptive, and behavioral interventions can improve caloric intake. The liberal use of appetite stimulants, especially cyproheptadine, in early childhood, makes the struggle a bit easier. Poorly controlled lung disease increases metabolism and decreases appetite and needs to be considered when efforts to improve weight gain are unsuccessful.

Maintenance of good weight gain and body mass index in the 1st yr of life leads to better long-term preservation of lung function, but there is a strong correlation between body mass index and FEV_1 that persists through all ages in people with CF. Better nutrition also leads to improved quality of life and psychologic well-being and provides better reserves when weight loss occurs in association with intermittent acute pulmonary exacerbations.

Malabsorption is an important contributor to nutritional deficiencies, and it is important to ensure that pancreatic enzyme dosing is adequate and consistently being taken correctly with all meals and feedings. Appetite stimulants when cyproheptadine is not successful may include megestrol, oxandrolone, dronabinol, antidepressants such as mirtazaoine, and even growth hormone. CF-related diabetes needs to be ruled out.

When all these therapies fail, weight stabilization or gain can be achieved with nocturnal feeding via nasogastric tube or gastrostomy tube. These are most commonly resorted to in infants and adolescents, the 2 age groups that have the most difficulty with weight gain due to high normal demands.

Pancreatic Enzyme Replacement

Pancreatic exocrine replacement therapy given with ingested food reduces but does not fully correct stool fat and nitrogen losses. Current products are enteric-coated, pH-sensitive enzyme microspheres that come in capsules and given to children before they can swallow by opening the capsule and mixing the beads in small amounts of acidic foods such as applesauce. Strengths ranging from 3 to 40,000 IU of lipase/capsule are available. Administration of excessive doses has been linked to fibrosing colonopathy and **colonic strictures,** so recommendations are for enzyme dosing to stay below 2,500 lipase units/kg/meal in most circumstances. Snacks should also be covered. Some individuals require proton pump inhibitor therapy to correct acid pH in the duodenum which is due to lack of exocrine pancreatic secretions; neutralization of duodenal pH permits activation of enteric-coated pancreatic exocrine replacement therapy granules.

Vitamin and Mineral Supplements

Because pancreatic insufficiency results in malabsorption of fat-soluble vitamins (A, D, E, K), vitamin supplementation is recommended. Several vitamin preparations containing all 4 vitamins for patients with CF are available. They should be taken daily. Despite this supplementation, vitamin D deficiency is common and should be treated with doses of cholecalciferol (vitamin D3) rather than ergocalciferol (vitamin D2) in the range of 1,000 units/kg/wk. Salt supplementation is also needed during infancy and is started at the time of diagnosis.

Treatment of Intestinal Complications

Meconium Ileus

When meconium ileus (see Chapter 102) is suspected, diatrizoate (Gastrografin) enemas with reflux of contrast material into the ileum not only confirm the diagnosis but may also result in the passage of meconium and clearing of the obstruction. Children in whom this procedure fails require operative intervention. Children who have had meconium ileus are at greater risk for nutritional deficiency and more likely to develop problems with DIOS when older. Infants with meconium ileus should be assumed to have CF unless proven otherwise.

Distal Intestinal Obstruction Syndrome and Other Causes of Abdominal Symptoms

Despite appropriate pancreatic enzyme replacement, a number of patients accumulate fecal material in the terminal portion of the ileum and in the cecum, which may result in partial or complete obstruction. For intermittent symptoms, pancreatic enzyme replacement should be continued or even increased, and stool hydrators such as polyethylene glycol (MiraLAX) should be given. If this fails or symptoms are more severe, large-volume bowel lavage with a balanced salt solution containing polyethylene glycol may be taken by mouth or by nasogastric tube. When there is complete obstruction, a diatrizoate enema, accompanied by large amounts of intravenous fluids, can be therapeutic.

Rectal Prolapse

See Chapter 371.5 .

Although uncommon, rectal prolapse occurs most often in infants with CF and less frequently in older children with the disease. It was much more frequently seen in the past among undiagnosed young children with steatorrhea, malnutrition, and repetitive cough. The prolapsed rectum can usually be replaced manually by continuous gentle pressure with the patient in the knee-chest position. Sedation may be helpful. To prevent an immediate recurrence, the buttocks can be temporally taped closed. Adequate pancreatic enzymes, stool softener, and control of pulmonary infection result in improvement.

Occasionally, a patient may continue to have rectal prolapse and may require sclerotherapy or surgery.

Hepatobiliary Disease

Liver function abnormalities associated with biliary cirrhosis can be improved by treatment with ursodeoxycholic acid. The ability of bile acids to prevent progression of cirrhosis has not been clearly documented. Portal hypertension with esophageal varices, hypersplenism, or ascites occurs in ≤8% of children with CF (see Chapter 394).

Obstructive jaundice in newborns with CF needs no specific therapy once the etiology has been established. End-stage liver disease is an indication for liver transplantation in children with CF (see Chapter 395).

Pancreatitis

Recurrent pancreatitis is seen primarily in patients with pancreatic sufficiency, and it can lead to the development of pancreatic insufficiency. Patients can be treated with pancreatic enzyme therapy and a low-fat diet (in well-nourished patients) to rest the pancreas. Further treatment of this disorder is discussed in Chapter 378 .

Cystic Fibrosis-Related Hyperglycemia and Diabetes

Onset of hyperglycemia occurs most frequently *after* the 1st decade. Approximately 20% of young adults are treated for hyperglycemia, although the incidence of CF-related diabetes may be up to 50% in CF adults. Ketoacidosis is rarely encountered. The pathogenesis includes both impaired insulin secretion and insulin resistance. Routine screening consisting of an annual 2-hr oral glucose tolerance test is recommended in children older than 10 yr of age, although some cases may begin earlier. Glucose intolerance with blood sugars that remain less than 200 is usually not treated unless nutrition is compromised or lung function seems affected. When treatment is indicated, insulin treatment should be instituted. The development of significant hyperglycemia favors acquisition of *P. aeruginosa* and *B. cepacia* in the airways and may adversely affect pulmonary function, especially in women. Thus careful control of blood glucose level is an important goal. Long-term vascular complications of diabetes can occur, providing an additional rationale for good control of blood glucose levels.

Other Complications

Nasal Polyps

Nasal polyps (see Chapter 406) occur in 15–20% of patients with CF and are most prevalent in the 2nd decade of life. Local corticosteroids and nasal decongestants occasionally provide some relief. When the polyps completely obstruct the nasal airway, rhinorrhea becomes constant or widening of the nasal bridge is noticed, surgical removal of the polyps is indicated; polyps may recur promptly or after a symptom-free interval of months to years. Polyps inexplicably stop developing in many adults.

Rhinosinusitis

Opacification of paranasal sinuses is universal in CF and is not an indication for intervention. Acute or chronic sinus-related symptoms are treated initially with antimicrobials, with or without maxillary sinus aspiration for culture. Functional endoscopic sinus surgery has anecdotally provided benefit.

Salt Depletion

Salt losses from sweat in patients with CF can be high, especially in warm arid climates. Children should have free access to salt, especially when thirsty in hot weather. Salt supplements are often prescribed to newborns and to children who live in hot weather climates. Hypochloremic alkalosis should be suspected in any patient who feels unwell in hot weather or who has had symptoms of gastroenteritis, and prompt fluid and electrolyte therapy should be instituted as needed.

Surgery

Patients with good or excellent pulmonary status can tolerate general anesthesia without any intensive pulmonary measures before the procedure but should be adherent to their usual prescribed airway clearance therapy. Those with moderate or severe pulmonary infection usually do better with a 1- to 2-wk course of intensive antibiotic treatment and increased airway clearance before surgery. If this approach is impossible, prompt intravenous antibiotic therapy is indicated once it is recognized that major surgery is required. General anesthesia may provide an opportunity to perform bronchoscopy to evaluate the airway and obtain good cultures, and this should be considered in any child with CF who will undergo surgery for any indication.

After major surgery, cough should be encouraged, and airway clearance treatments should be reinstituted as soon as possible, usually within 24 hr.

Prognosis

CF remains a life-limiting disorder, although survival has dramatically improved (Fig. 432.12). With exceptions, most children remain relatively healthy into adolescence or adulthood. The slow progression of lung disease eventually does reach disabling proportions. Life table data indicate a median cumulative survival of more than 40 yr, and the expectation is younger children with the disease have a life expectancy far in excess of this estimate. Outcomes are variable and related to CFTR mutation class, modifier genes, biologic and chemical exposures, disease management, and socioeconomic status.

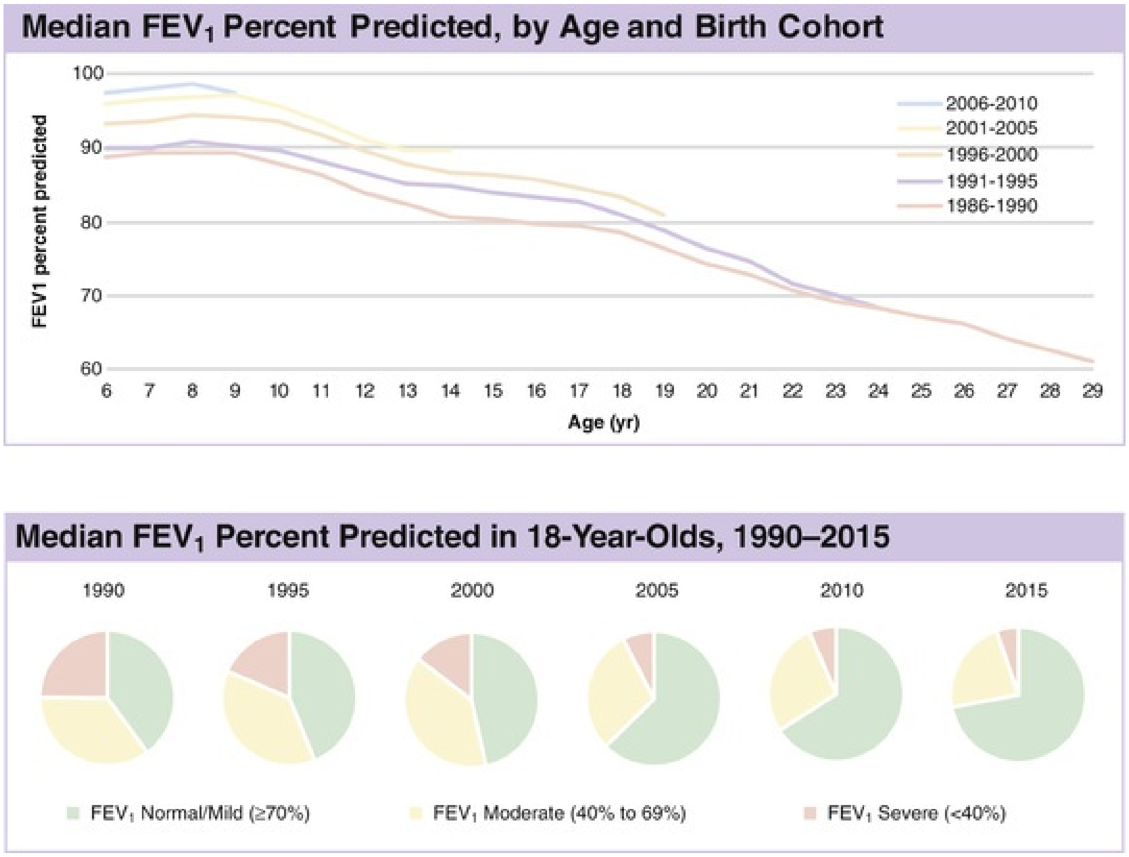

FIG. 432.12 Forced expiratory volume in 1 sec (FEV_1) percent predicted is steadily improving and currently is greater than 90% predicted into early adolescence. The proportion of people with CF age 18 yr who are in the normal/mild category (FEV1 ≥ 70% predicted) has increased from 39.9% in 1990 to 72.1% in 2015, whereas the proportion in the severe category (FEV1 < 40% predicted) has decreased from 24.9% to 5.3%. (From the Cystic Fibrosis Foundation Patient Registry 2015. Annual Data Report. ©2016 Cystic Fibrosis Foundation, Bethesda, Maryland.)

Children with CF should not be restricted in their activities. A high percentage eventually attend and graduate from college. Most adults with CF find satisfactory employment, and an increasing number marry. Transitioning care from pediatric to adult care centers by 21 yr of age is an important objective and requires a thoughtful, supportive approach involving both the pediatric and internal medicine specialists.

With increasing life span for patients with CF, a new set of psychosocial considerations has emerged, including dependence-independence issues, self-care, peer relationships, sexuality, reproduction, substance abuse, educational and vocational planning, medical care costs and other financial burdens, and anxiety concerning health and prognosis. Anxiety and depression are prevalent, as in any other chronic disease, and impact quality of life and disease self-management; screening for both is now part of comprehensive care. Many of these issues are best addressed in an anticipatory fashion, before the onset of psychosocial dysfunction. With appropriate medical and psychosocial support, children and adolescents with CF generally cope well. Achievement of an independent and productive adulthood is a realistic goal for many.

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CHAPTER 433

Primary Ciliary Dyskinesia (Immotile Cilia Syndrome, Kartagener Syndrome)

Thomas W. Ferkol Jr

Primary ciliary dyskinesia (PCD) is an inherited disorder characterized by impaired ciliary function leading to diverse clinical manifestations, including chronic sinopulmonary disease, persistent middle ear effusions, laterality defects, and infertility. The estimated frequency of PCD is 1 in 12,000 to 1 in 20,000 live births, but its prevalence in children with repeated respiratory infections has been estimated to be as high as 5%.

Normal Ciliary Ultrastructure and Function

Three types of cilia exist in humans: motile cilia, primary (sensory) cilia, and nodal cilia. The respiratory epithelium in the nasopharynx, middle ear, paranasal sinuses, and larger airways are lined by a ciliated, pseudostratified columnar epithelium that is essential for mucociliary clearance. A mature ciliated epithelial cell has approximately 200 uniform **motile cilia** , hair-like organelles that move fluids, mucus, and inhaled particulates vectorially from conducting airways (Fig. 433.1). Motor cilia are anatomically and functionally oriented in the same direction, moving with intracellular and intercellular synchrony. Anchored by a basal body to the apical cytoplasm and extending from the apical cell surface into the airway lumen, each cilium is a complex, specialized structure, composed of hundreds of proteins. It contains a cylinder of microtubule doublets organized around a central pair of microtubules (Fig. 433.2), leading to the characteristic

“9+2” arrangement seen on cross-sectional views on transmission electron microscopy. A membrane continuous with the plasma membrane covers the central fibrillar structure, or axoneme. The ciliary axoneme is highly conserved across species, and the structural elements of simple algal flagella and the mammalian cilium are similar. Attached to the A microtubules as distinct inner and outer dynein arms, multiple adenosine triphosphatases, called dyneins, serve as motors of the cilium and promote microtubule sliding, which is converted into bending. Each dynein arm is a multimer with heavy, intermediate, and light chains, with each dynein protein encoded by a different gene. The inner dynein arm influences the bend shape of the cilium, whereas the outer dynein arm controls beat force and frequency. The inner dynein arm and radial spokes are also parts of the dynein regulatory complex, a key regulator of motor activity. Nexin links connecting adjacent outer microtubular doublets limit the degree of sliding between microtubules. All these structures lead to synchronized ciliary beating, resulting in a ciliary stroke and coordinated beating at a frequency constant throughout the airway, 8-20 beats/sec, but can be negatively affected by several factors, such as anesthetics and dehydration. Alternatively, beat frequency may be accelerated by exposure to irritants or bioactive molecules, including β-adrenergic agents, acetylcholine, and serotonin. Cilia beat frequency can be increased through the activity of nitric oxide synthases that are localized in the apical cytoplasm. The coordinated wavelike pattern of ciliary motion has important functions in fluid and cell movement, and any disturbance in the precise, orchestrated movement of the cilia can lead to disease.

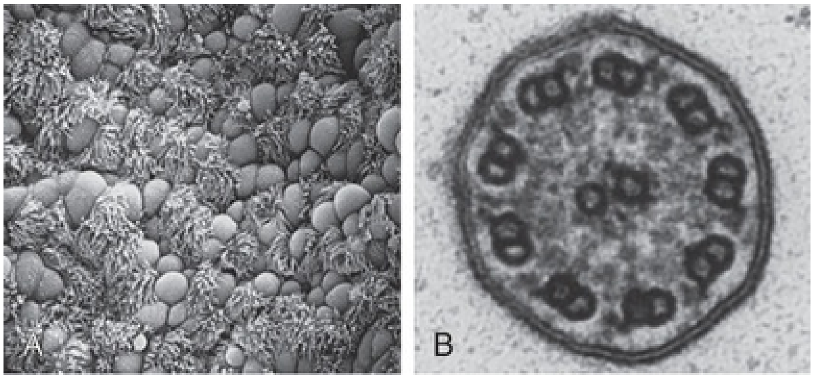

FIG. 433.1 Electron photomicrographs showing **(A)** an airway epithelium grown in primary culture, showing ciliated and nonciliated cells and **(B)** a normal motor cilium.

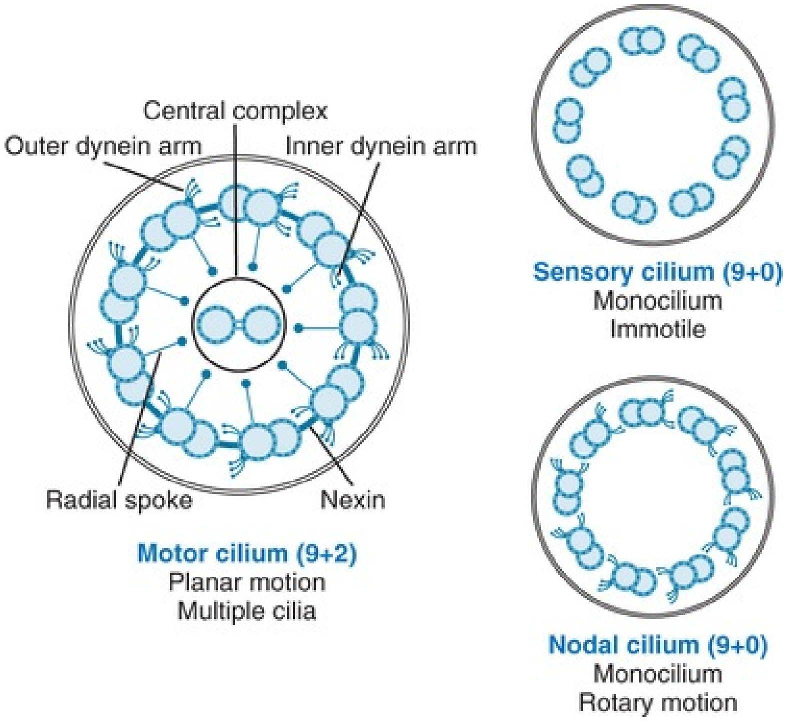
Central complex
Outer dynein arm
Inner dynein arm
Radial spoke
Nexin
Motor cilium (9+2)
Planar motion
Multiple cilia
Sensory cilium (9+0)
Monocilium
Immotile
Nodal cilium (9+0)
Monocilium
Rotary motion

FIG. 433.2 Schemata showing the 3 general classes of normal cilia (motile "9+2," motile "9+0," and nonmotile "9+0"), which demonstrate the complex structure and arrangement of the ciliary axoneme.

Primary (sensory) cilia are solitary organelles present during interphase on most cell types. These cilia lack a central microtubule doublet and dynein arms, thus creating a "9+0" arrangement and leaving them immotile (see Fig. 433.2). These structures were once considered nonfunctional vestigial remnants, but primary cilia are important signaling organelles that sense the extracellular environment. They are mechanoreceptors, chemosensors, and osmosensors and, in specialized cases, detect changes in light, temperature, and gravity. Defects (ciliopathies) are linked to wide-ranging pediatric conditions, such as various polycystic kidney diseases, nephronophthisis, Bardet-Biedl syndrome, Meckel-Gruber syndrome, Joubert syndrome, Alström syndrome, Ellis-van Creveld syndrome, and Jeune thoracic dystrophy.

The third type of cilia exists only during a brief period of embryonic development. **Nodal cilia** have a "9+0" microtubule arrangement similar to that of primary cilia, but they exhibit a whirling, rotational movement (see Fig. 433.2), resulting in leftward flow of extracellular fluid that establishes body sidedness. Nodal cilia defects result in body orientation abnormalities, such as **situs inversus totalis** , **situs ambiguus** , and **heterotaxy** associated with congenital heart disease, asplenia, and polysplenia (see Chapter 458.11).

Genetics of Primary Ciliary Dyskinesia

PCD typically has autosomal recessive patterns of inheritance, although X-linked inheritance has been reported. PCD is a genetically heterogeneous disorder involving multiple genes; mutations in any protein that is involved in ciliary assembly, structure, or function could theoretically cause disease. Early linkage studies showed substantial locus heterogeneity, which made correlations between ciliary defects and the underlying mutations difficult. Mutations in 40 different genes have been linked to PCD (Fig. 433.3), including those that encode proteins integral to the outer dynein arm: *DNAH5*, *DNAH1*, *DNAI1*, *DNAL1*, *DNAI2*, *TXNDC3*, *CCDC114*, *CCDC151*, *ARMC4* , and *TTC25* ; dynein regulatory complex and nexin components: *CCDC39*, *CCDC40* , and *GAS8* ; and radial spoke and central apparatus proteins: *RSPH1, RSPH3, RSPH4A, RSPH9*, *HYDIN* , and *DNAJB13* . Mutations in genes coding several cytoplasmic proteins, not part of the cilia axoneme, have also been identified and appear to have roles in cilia assembly or protein transport, including: *HEATR2*, *DNAAF1*, *DNAAF2*, *DNAAF3*, *CCDC103*, *LRRC6*, *DYX1C1*, *SPAG1*, *ZMYND10* , and an open reading frame sequence, *C21orf59.* Not all patients with PCD have an identifiable genetic mutation.

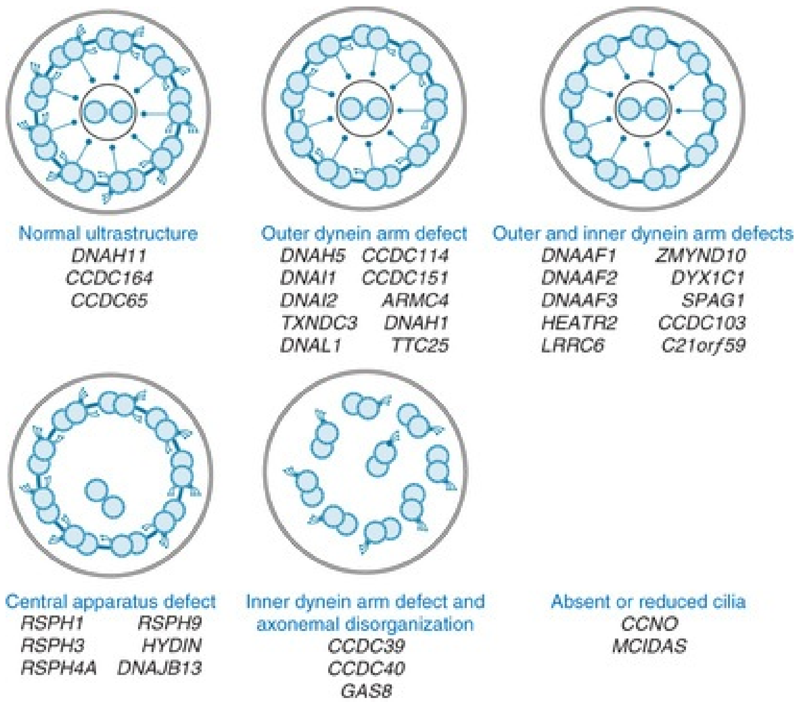
Normal ultrastructure
DNAH11
CCDC164
CCDC65
Outer dynein arm defect
DNAH5 CCDC114
DNAI1 CCDC151
DNAI2 ARMC4
TXNDC3 DNAH1
DNAL1 TTC25
Outer and inner dynein arm defects
DNAAF1 ZMYND10
DNAAF2 DYX1C1
DNAAF3 SPAG1
HEATR2 CCDC103
LRRC6 C21orf59
Central apparatus defect
RSPH1 RSPH9
RSPH3 HYDIN
RSPH4A DNAJB13
Inner dynein arm defect and axonemal disorganization
CCDC39
CCDC40
GAS8
Absent or reduced cilia
CCNO
MCIDAS

FIG. 433.3 Classification of genes mutated in primary ciliary dyskinesia based on ultrastructural findings.

The genetic bases of ciliopathies have yielded greater understanding of genotype-phenotype relationships in PCD. Mutations in nexin-dynein regulatory complex proteins create inconsistent ultrastructural abnormalities characterized by absent inner dynein arms in all axonemes, but misplaced radial spokes and microtubular disorganization in only some cilia. A cross-sectional study showed that children who had microtubular disorganization, primarily due to biallelic mutations in *CCDC39* or *CCDC40* , had more severe lung disease. In contrast, patients with mutations in *RSPH1* appear to have milder respiratory phenotypes.

Clinical Manifestations of Primary Ciliary Dyskinesia

See Table 433.1 .

Table 433.1

Clinical Manifestations of Primary Ciliary Dyskinesia

RESPIRATORY
• Unexplained respiratory distress in term neonate
• Daily productive (wet) cough since early infancy
• Daily, nonseasonal rhinosinusitis since early infancy
• Chronic otitis media and persistent middle ear effusions
• Digital clubbing (rare in children)
• Atypical asthma unresponsive to therapy
• Recurrent pneumonias
• Bronchiectasis
LEFT-RIGHT LATERALITY DEFECTS
• Situs inversus totalis
• Heterotaxy with or without complex congenital heart disease
MISCELLANEOUS
• Male infertility, immotile sperm
• Female subfertility, ectopic pregnancy
• Hydrocephalus (rare)

PCD has several characteristic clinical features. Neonatal respiratory distress (NRD) is a common feature, and most affected term newborns develop increased work of breathing, tachypnea, and upper and middle lobe atelectasis on chest radiographs. The association of respiratory distress in *term neonates* with PCD has been underappreciated. Often diagnosed with transient tachypnea of the newborn or pneumonia, PCD infants frequently require supplemental oxygen flow for days to weeks. When NRD occurs in infants with situs anomalies, PCD is highly likely.

Chronic, year-round productive (wet) cough that begins in infancy is an almost universal feature of PCD. Bacterial cultures of sputum or lavage fluid frequently yield nontypeable *Haemophilus influenzae* (see Chapter 221), *Staphylococcus aureus* (see Chapter 208.1), *Streptococcus pneumoniae* (see Chapter 209), and *Pseudomonas aeruginosa* (see Chapter 232.1). Persistent airway infection and inflammation lead to **bronchiectasis** , even in preschool children. Clubbing is a sign of long-standing pulmonary disease.

Persistent nasal congestion and rhinitis is common, typically presenting in early infancy with little to no seasonal variation. Most patients describe chronic mucopurulent nasal drainage. Inadequate innate mucous clearance leads to chronic sinusitis (see Chapter 408) and nasal polyposis. Middle ear disease occurs in nearly all children with PCD, with varying degrees of **chronic otitis media** leading to conductive hearing loss and requiring myringotomy tube placement, which is often complicated by intractable otorrhea. Middle ear findings may be most helpful in distinguishing PCD from cystic fibrosis or other causes of chronic lung disease.

Left-right laterality defects (e.g., *situs inversus totalis*) are found in half of all children with PCD. Without functional nodal cilia in the embryonic period, thoracoabdominal orientation is random. Approximately 25% of patients who have *situs inversus totalis* have PCD; therefore *situs inversus totalis* alone does not establish the diagnosis. Other laterality defects, such as heterotaxy, are also associated with PCD and may coexist with congenital cardiac defects, asplenia, or polysplenia.

Most men with PCD have dysmotile spermatozoa because flagellar and ciliary ultrastructure is similar. Male infertility is typical but not always found in this disease. Subfertility has also been reported in affected women and may be due to ciliary dysfunction in the fallopian tubes.

A few case reports have associated **neonatal hydrocephalus** with PCD. The ependyma of the brain ventricles are lined by ciliated epithelium and are important for cerebrospinal fluid flow through the ventricles and aqueduct of Sylvius. The finding of enlarged brain ventricles on sonograms, when linked with *situs inversus totalis,* has been proposed as a prenatal diagnostic marker for PCD. X-linked retinitis pigmentosa has been associated with recurrent respiratory infections in families with *RPGR* gene mutations. Intraflagellar transport proteins are essential for photoreceptor assembly and, when mutated, lead to apoptosis of the retinal pigment epithelium (see Chapter 648).

Diagnosis of Primary Ciliary Dyskinesia

The diagnosis of PCD should be suspected in children with chronic or recurring upper and lower respiratory tract symptoms that begin in early infancy and is currently based on the presence of characteristic clinical phenotype and ultrastructural defects of cilia, though this approach will miss affected individuals (Table 433.2). The diagnosis is often delayed, even in children who have classic clinical features, such as *situs inversus totalis* . A high index of suspicion is necessary. The diagnosis should be entertained in infants and children with unexplained NRD in term newborns, daily year-round productive (wet) cough that begins in infancy, persistent rhinosinusitis, and left-right laterality defects.

Table 433.2

New Consensus-Based Primary Ciliary Dyskinesia (PCD) Diagnostic Criteria by Age

NEWBORNS (0–1 MO OF AGE)
Situs inversus totalis and unexplained neonatal respiratory distress (NRD) at term birth, plus at least one of the following:
• Diagnostic ciliary ultrastructure on electron micrographs or 2 mutations in PCD-associated gene
CHILDREN (1 MO TO 5 YR)
2 or more major PCD clinical criteria (NRD,* daily wet cough, persistent nasal congestion, laterality defect), plus at least one of the following (nasal nitric oxide not included in this age group because it is not yet sufficiently tested):
• Diagnostic ciliary ultrastructure on electron micrographs
• 2 mutations in 1 PCD-associated gene
• Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions
CHILDREN (5–18 YR OF AGE) AND ADULTS
2 or more PCD clinical criteria (NRD,* daily productive cough or bronchiectasis, persistent nasal congestion, laterality defect), plus at least one of the following:
• Nasal nitric oxide during plateau <77 nL/min on 2 occasions, >2 mo apart (with CF excluded)
• Diagnostic ciliary ultrastructure on electron micrographs
• Two mutations in 1 PCD-associated gene
• Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions

* In term neonates.

Imaging studies show extensive involvement of the paranasal sinuses. Chest radiographs frequently demonstrate bilateral lung overinflation, peribronchial infiltrates, and lobar atelectasis. Computed x-ray tomography of the chest often reveals bronchiectasis, often involving the anatomic right middle lobe or lingula, even in young children. *Situs inversus totalis* in a child who has chronic respiratory tract symptoms is highly suggestive of PCD, but this configuration occurs in only half of patients with PCD. Pulmonary function tests may be normal early but demonstrate obstructive airway disease as the disease progresses. Typical findings include decreased expiratory flow rates and increased residual volume. Bronchodilator responsiveness is variable. Longitudinal analyses of children with PCD show wide variation in intrathoracic airway obstruction.

Transmission electron microscopy is the current gold standard to assess structural defects within the cilium. These ultrastructural defects are found in cilia throughout the upper and lower airways and oviduct, as well as in sperm flagella. Curettage from the nasal epithelium or endobronchial brushing can provide an adequate specimen for review. Identification of a discrete, consistent defect in any aspect of the ciliary structure with concurrent phenotypic features is sufficient to make the diagnosis. There are several characteristic ciliary abnormalities: outer dynein arm defects, combined inner and outer dynein arm defects, central apparatus defects, and inner dynein arm defects with microtubular disorganization. Inner dynein arm defects alone are uncommon. Ultrastructural examination of cilia as a diagnostic test for PCD has limitations. First, the absence of axonemal defects does not exclude PCD; nearly 30% of all affected individuals have normal ciliary ultrastructure. Other patients with symptoms consistent with PCD have been found to have ciliary aplasia or few motor cilia on the epithelial surface (Table 433.3).

Table 433.3

Electron Microscopic Findings in Primary Ciliary Dyskinesia

DYNEIN ARM DEFECTS
• Total or partial absence of outer dynein arms
• Total or partial absence of inner and outer dynein arms
• Total or partial absence of inner dynein arms alone (rare)
RADIAL SPOKE DEFECTS
• Total absence of radial spokes
• Absence of radial spoke heads
MICROTUBULAR TRANSPOSITION DEFECTS

• Inner dynein arm defect with microtubular derangement (in some axonemes)
• Absent central pair of tubules with outer doublet transposition
OTHER
• Central microtubular agenesis
• Ciliary aplasia or reduced cilia numbers
• Normal ultrastructure

Careful interpretation of the ultrastructural findings is necessary because nonspecific changes may be seen in relation to exposure to environmental pollutants or infection. Ciliary defects can be acquired. Acute airway infection or inflammation can result in structural changes (e.g., compound cilia or blebs). Ciliary disorientation has been proposed as a form of PCD, but this phenomenon is the result of airway injury. Frequently, the diagnosis of PCD can be delayed or missed because of inadequate tissue collection or sample processing, or misinterpretation of ciliary defects. Some investigators have advocated culturing of airway epithelial cells and allowing the secondary changes to resolve.

Qualitative tests to assess ciliary function have been used to screen for PCD. Ciliary beat frequency measurements that use conventional microscopic techniques have been used as a screen, but this method alone will miss cases of PCD. Cilia inspection using standard light microscopy is insufficient to support or exclude the diagnosis. High-resolution, high-speed, digital imaging of ciliary motion in multiple planes permits comprehensive analysis of cilia beating, which has shown that certain beat patterns are associated with specific ultrastructural defects. This approach is available only at a limited number of clinical centers, primarily in Europe, and requires sophisticated software and expertise. Immunofluorescent staining for ciliary proteins is a newer approach that holds promise and may address some limitations of transmission electron microscopy. This approach is currently a research tool and not widely available.

Another promising approach has exploited the observation that nasal nitric oxide concentrations are reduced in subjects with PCD. Because nasal nitric oxide measurements are relatively easy to perform and noninvasive, this method is a promising screen and potentially a diagnostic test for PCD, provided that cystic fibrosis has been excluded (see Chapter 432). Few studies in children <5 yr have been reported, and the accuracy of nasal nitric oxide measurements in infants has not been established.

PCD is highly heterogenic owing to the large number of proteins involved in cilia assembly and function. Recent advances in gene sequencing techniques have led to the identification of a growing number of PCD-associated genes. Biallelic, disease-causing mutations have been found in more than 70% of known cases.

There are limitations in traditional diagnostic approaches. For instance, *DNAH11* mutations have been shown to cause typical clinical phenotypes without ultrastructural defects or reduced ciliary beat frequency. Children with mutations in cyclin O (CCNO) and multiciliate differentiation and DNA synthesis–associated cell cycle protein (MCIDAS) have symptoms consistent with PCD with only rare cilia on the epithelial surface. Thus genetic testing has become an important diagnostic tool for PCD.

Treatment

No therapies have been shown to correct ciliary dysfunction in PCD. Many of the treatments applied to PCD patients are similar to those used in other chronic suppurative lung diseases characterized by impaired airway clearance and bronchiectasis, such as cystic fibrosis, but none has been adequately studied to demonstrate efficacy in PCD.

Strategies to enhance mucociliary clearance are central to PCD therapy, and routine airway clearance techniques using postural drainage, percussion vests, positive expiratory pressure devices, or other techniques should be instituted daily. Because ciliary function is impaired, cough becomes a critical mechanism for mucous clearance and should not be suppressed. Exercise can enhance airway clearance in patients with PCD and should be encouraged. Inhaled mucolytic agents are often used in cystic fibrosis care, but only a few case reports have shown improvement in lung function in patients with PCD after treatment.

When children with PCD develop increasing respiratory symptoms consistent with infection, antimicrobial therapy should be instituted based on respiratory culture results and bacterial sensitivities. Early eradication strategies to clear bacteria from the PCD lung have not been studied. Maintenance therapy with inhaled or oral antibiotics can be used cautiously in patients with PCD who have bronchiectasis or frequent exacerbations, though current literature lacks evidence supporting long-term antimicrobial therapy. Immunizations against pertussis, influenza, and pneumococci are cornerstones of care. Additional preventive measures include avoidance of cigarette smoke and other airway irritants.

Although β-adrenergic agonists increase ciliary beat frequency in normal epithelial cells, data are lacking that show these agents improve function of dyskinetic cilia. Moreover, they do not necessarily provide bronchodilation in patients with PCD and obstructive airway disease.

Surgical resection of bronchiectatic lung has been performed on patients with PCD, typically in cases of localized disease with severe hemoptysis or intractable infections. It is unclear whether surgical interventions provide reduction in symptoms or survival benefit.

Progression to end-stage lung disease and respiratory failure has been reported in patients with PCD. Adult patients have undergone successful heart-lung, double lung, or living donor lobar lung transplantation. *Situs inversus totalis* complicates the procedure, owing to anatomic considerations. Otherwise, survival is similar to that for other transplant recipients.

Treatment of chronic otitis media and middle ear effusions in patients with PCD is controversial. Myringotomy tubes are frequently placed in affected children, but they are not without complications because they may lead to chronic mucoid otorrhea, tympanosclerosis, and permanent membrane perforation. Myringotomy tubes have not measurably improved hearing acuity. While hearing tends to improve with time, patients should be routinely screened and hearing aids used when necessary.

Chronic rhinitis and sinusitis are frequent clinical manifestations of PCD. No treatments have been shown to be effective, although patients are often treated with nasal washes, paranasal sinus lavage, and systemic antibiotics when they are symptomatic. As with any overuse of antimicrobial agents, the development of resistant organisms is a concern. When nasal symptoms are severe or refractory to medical management, endoscopic sinus surgery can be used to promote drainage or local delivery of medications, but the benefit may be short lived.

Prognosis

Although signs and symptoms related to upper respiratory involvement predominate early in PCD, clinical manifestations of lower respiratory tract disease tend to increase with age and become the leading cause of morbidity and mortality in PCD patients. It is believed that progression and extent of lung disease can be slowed with early diagnosis and therapy. Thus routine surveillance studies recommended for the care of children with PCD include (1) regular spirometry to monitor pulmonary function, (2) chest imaging, and (3) sputum or oropharyngeal cultures to assess respiratory flora.

Patients with PCD typically have slower decline in pulmonary function than those with cystic fibrosis. Its prognosis and long-term survival are better. Many patients have a normal or near-normal life span, while others can experience progressive bronchiectasis and respiratory deterioration at a younger age.

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CHAPTER 434

Diffuse Lung Diseases in Childhood

See also Chapter 427 .

434.1

Inherited Disorders of Surfactant Metabolism

Jennifer A. Wambach, Lawrence M. Nogee, F. Sessions Cole III, Aaron Hamvas

Pulmonary surfactant is a mixture of phospholipids and proteins synthesized, packaged, and secreted by alveolar type II pneumocytes (AEC2s) that line the distal air spaces. This mixture forms a monolayer at the air–liquid interface that lowers surface tension at end-expiration of the respiratory cycle, preventing atelectasis and ventilation–perfusion mismatch. Four surfactant-associated proteins have been characterized: surfactant proteins A and D (SP-A, SP-D) participate in host defense in the lung, whereas surfactant proteins B and C (SP-B, SP-C) contribute to the surface tension–lowering activity of pulmonary surfactant. The adenosine triphosphate–binding cassette protein member A3, ABCA3, is a transporter located on the limiting membrane of lamellar bodies, the storage organelle for surfactant within alveolar type II cells, and has an essential role in surfactant phospholipid metabolism. The proper expression of the surfactant proteins and ABCA3 is dependent on a number of transcription factors, particularly thyroid transcription factor 1 (TTF-1). Two genes for SP-A *(SFTPA1, SFTPA2)* and 1 gene for SP-D *(SFTPD)* are located on human chromosome 10, whereas single genes encode SP-B *(SFTPB),* SP-C *(SFTPC),* TTF-1 *(NKX2-1),* and ABCA3 *(ABCA3),* which are located on human chromosomes 2, 8, 14, and 16, respectively. Inherited disorders of SP-B, SP-C, ABCA3, and TTF-1 have been recognized in humans and are collectively termed **surfactant dysfunction disorders** (Table 434.1).

Table 434.1

Comparison of Surfactant Dysfunction Disorders

	SP-B DEFICIENCY	SP-C DISEASE	ABCA3 DEFICIENCY	TTF-1 DISORDERS
Gene name	*SFTPB*	*SFTPC*	*ABCA3*	*NKX2-1*
Age of onset	Birth	Birth–adulthood	Birth–childhood; rarely adult	Birth–childhood
Inheritance	Recessive	Dominant/sporadic	Recessive	Sporadic/dominant
Mechanism	Loss of function	Gain of toxic function or dominant negative	Loss of function	Loss of function Gain of function
Natural history	Lethal	Variable	Generally lethal, may be chronic	Variable
DIAGNOSIS				
Biochemical (tracheal aspirate)	Absence of SP-B and presence of incompletely processed proSP-C	None	None	None
Genetic (DNA)	Sequence SFTPB	Sequence SFTPC	Sequence ABCA3	Sequence NKX2-1; deletion analysis
Ultrastructural (lung biopsy–electron microscopy)	Disorganized lamellar bodies	Not specific; may have dense aggregates	Small dense lamellar bodies with eccentrically placed dense cores	Variable
Treatment	Lung transplantation or compassionate care	Supportive care, lung transplantation if progressing	Lung transplantation or compassionate care for infants with biallelic null mutations; lung transplantation for other mutations if progressing	Supportive care; treat coexisting conditions (hypothyroidism)

SP , Surfactant protein.

Pathology

Histopathologically, these disorders share a unique constellation of features, including AEC2 hyperplasia, alveolar macrophage accumulation, interstitial thickening and inflammation, and alveolar proteinosis. A number of different descriptive terms have historically been applied to these disorders, including ones borrowed from adult forms of interstitial lung disease (**desquamative interstitial pneumonia** , nonspecific interstitial pneumonia) as well as a disorder unique to infancy (**chronic pneumonitis of infancy**). These diagnoses in infants and children are strongly indicative of surfactant dysfunction disorders but do not distinguish which gene is responsible. As the prognosis and inheritance patterns differ depending upon the gene involved, genetic testing should be offered when one of these conditions is reported in the lung biopsy or autopsy of a child.

Deficiency of Surfactant Protein B (Surfactant Metabolism Dysfunction, Pulmonary, 1; Smdp1; Omim #265120)

Clinical Manifestations

Infants with an inherited deficiency of SP-B present in the *immediate* neonatal period with respiratory failure. This autosomal recessive disorder is clinically and radiographically similar to the respiratory distress syndrome (RDS) of premature infants (see Chapter 122.3) but typically affects full-term infants. The initial degree of respiratory distress is variable, but the disease is progressive and is refractory to mechanical ventilation, surfactant replacement therapy, and glucocorticoid administration. SP-B deficiency is observed in diverse racial and ethnic groups. Almost all affected patients have died without lung transplantation, but prolonged survival is possible in cases of partial deficiency of SP-B. Humans heterozygous for loss-of-function mutations in *SFTPB* are clinically normal as adults but may be at increased risk for obstructive lung disease if they also have a history of smoking.

Genetics

Multiple loss-of-function mutations in *SFTPB* have been identified. The most common is a net 2 base-pair insertion in codon 133 (originally termed “121ins2”, currently termed c.397delCinsGAA, p.Pro133Glu*fs* *95) that results in a frameshift, an unstable SP-B transcript, and absence of SP-B protein production. This mutation has accounted for 60–70% of the alleles found to date in infants identified with SP-B deficiency and is present in approximately 0.07% of European-descent individuals in large-scale sequencing projects. Most other mutations have been family-specific. A large deletion encompassing 2 exons of the SP-B gene has also been reported.

Diagnosis

A rapid, definitive diagnosis can be established with sequence analysis of *SFTPB,* which is available through clinical laboratories (http://www.genetests.org). While sequencing of *SFTPB* alone is available, as the phenotype of SP-B deficiency overlaps that of other surfactant dysfunction disorders, multi-gene panels using next generation sequencing (NGS) methods are supplanting sequencing of single genes. For families in which *SFTPB* mutations were previously identified, antenatal diagnosis can be established by preimplantation genetic diagnosis or molecular assays of DNA from chorionic villous biopsy or amniocytes, which permits advanced planning of a therapeutic regimen. Other laboratory tests remain investigational, including analysis of tracheal aspirate (effluent) for the presence or absence of SP-B protein and for incompletely processed precursor proSP-C peptides that have been identified in SP-B–deficient human infants. Immunostaining of lung biopsy tissue for the surfactant proteins can also support the diagnosis, although immunohistochemical assays for SP-B and SP-C are also generally available only on a research basis. Staining for SP-B is usually absent, but robust extracellular staining for proSP-C because of incompletely processed proSP-C peptides is observed and is diagnostic for SP-B deficiency. Such studies require a lung biopsy in a critically ill child but may be performed on lung blocks acquired at the time of autopsy, allowing for retrospective diagnosis. With electron microscopy, a lack of tubular myelin, disorganized lamellar bodies, and an accumulation of abnormal-appearing multivesicular bodies suggest abnormal lipid packaging and secretion.

Surfactant Protein C Gene Abnormalities (Surfactant Metabolism Dysfunction, Pulmonary, 2; Smdp2; Omim #610913)

SP-C is a very low molecular weight, extremely hydrophobic protein that, along with SP-B, enhances the surface tension–lowering properties of surfactant phospholipids. It is derived from proteolytic processing of a larger precursor protein (proSP-C).

Clinical Manifestations

The clinical presentation of patients with *SFTPC* mutations is quite variable. Some patients present at birth with symptoms, signs, and radiographic findings typical of RDS. Others present later in life, *ranging from early infancy until well into adulthood* , with gradual onset of respiratory insufficiency, hypoxemia, failure to thrive, and chest radiograph demonstration of interstitial lung disease, or, in the 5th or 6th decade of life, as **pulmonary fibrosis** . The age and severity of disease vary even within families with the same mutation. The natural history is also quite variable, with some patients improving either spontaneously or as the result of therapy or prolonged mechanical ventilation, some with persistent respiratory insufficiency, and some progressing to the point of requiring lung transplantation. This variability in severity and course of the disease does not appear to correlate with the specific mutation and also hinders accurate assessment of prognosis.

Genetics

Multiple mutations in *SFTPC* have been identified in association with acute and chronic lung disease in patients ranging in age from newborn to adult. A mutation on only *one SFTPC* allele is sufficient to cause disease. Approximately half of these mutations arise spontaneously, resulting in sporadic disease, but the remainder are inherited as a *dominant trait* . A threonine substitution for isoleucine in codon 73 (termed p.I73T or p.Ile73Thr) has accounted for 25–35% of the cases identified to date but is rare (not identified in gnomAD ~123,000 individuals). *SFTPC* mutations have been identified in diverse racial and ethnic groups. Mutations in *SFTPC* are thought to result in production of misfolded proSP-C that accumulates within the alveolar type II cell and causes cellular injury, or alters the normal intracellular routing of proSP-C.

Diagnosis

Sequencing of *SFTPC*, the only definitive diagnostic test, is available in clinical laboratories. The relatively small size of the gene facilitates such analyses, which are quite sensitive, but because most *SFTPC* mutations are missense mutations, distinguishing true disease-causing mutations from rare yet benign sequence variants may be difficult. Immunostaining of lung tissue may demonstrate proSP-C aggregates but is available only on a research basis.

Disease Caused by Mutations in ABCA3 (Surfactant Metabolism Dysfunction, Pulmonary, 3; Smdp3; Omim #610921)

Clinical Manifestations

Lung disease caused by mutations in *ABCA3* generally presents as either a severe, lethal form that manifests in the *immediate newborn period* clinically similar to SP-B deficiency, or a chronic form that appears most typically in the 1st yr of life with **interstitial lung disease** similar to SP-C–associated disease. Infants who are homozygous or compound heterozygous for null mutations, that is, the mutation is predicted to result in absence of protein expression (i.e., nonsense or frameshift mutations), typically present with lethal neonatal respiratory failure, whereas infants with other types of mutations have more variable age of onset and outcomes. Heterozygosity for an *ABCA3* mutation may contribute to the risk for RDS in late preterm and term infants, who, in contrast to ABCA3-deficient infants with mutations on both alleles, may eventually completely recover from their initial lung disease.

Genetics

Recessive mutations in *ABCA3* were first described among infants who presented with lethal RDS in the newborn period, but now have been identified in older infants and children with interstitial lung disease. There is considerable allelic heterogeneity: more than 400 mutations scattered throughout the gene have been identified, most of which are family-specific. The presence of null mutations on both alleles that are predicted to preclude any ABCA3 production has been associated with early-onset disease and a uniformly fatal prognosis. A missense mutation that results in a valine substitution for glutamine in codon 292 (p.E292V or p.Glu292Val) in association with a 2nd *ABCA3* mutation has been found in children with severe neonatal respiratory failure and in older children with interstitial lung disease and is present in approximately 0.7% of European-descent individuals. *ABCA3* mutations have been identified in diverse racial and ethnic groups. The precise frequency of disease is unknown, but large-scale sequencing projects indicate that the overall carrier rate for *ABCA3* mutations may be as high as 1 in 50 to 1 in 70 individuals. ABCA3 deficiency may thus contribute to a substantial proportion of *unexplained fatal lung disease* in term infants and of *interstitial lung disease* in older children.

Diagnosis

Sequence analysis of *ABCA3* is available in clinical laboratories and is the most definitive approach for diagnosis. Considerable variation in *ABCA3* necessitates careful interpretation regarding the functionality of an individual variant and its contribution to the clinical presentation. Additionally, *sequence analysis is not 100% sensitive* as functionally significant mutations may exist in untranslated regions that are not generally analyzed. In these situations, lung biopsy with electron microscopy to examine lamellar body morphology may be a useful adjunct to the diagnostic approach. Small lamellar bodies that contain electron-dense inclusions may be observed in association with *ABCA3* mutations. These findings support the hypothesis that ABCA3 function is necessary for lamellar body biogenesis. There are no biochemical markers to establish the diagnosis.

Disease Caused by Mutations in *NKX2-1* (Thyroid Transcription Factor 1, Choreoathetosis, Hypothyroidism, and Neonatal Respiratory Distress, Omim #600635)

Clinical Manifestations

A large deletion of the region of chromosome 14 (14q13.3) encompassing the *NKX2-1* locus was first recognized in an infant with hypothyroidism and neonatal RDS. Since then, multiple large deletions involving the *NKX2-1* locus and contiguous genes as well as missense, frameshift, nonsense, and small insertion or deletion mutations scattered throughout the gene have been reported in individuals with hypothyroidism, lung disease, and neurologic symptoms, including benign familial chorea. Manifestation of dysfunction in all 3 organ systems has been referred to as **brain-thyroid-lung syndrome** , but disease may manifest in only 1 or 2 organ systems. The lung disease can range from severe and eventually *lethal neonatal respiratory distress* to *chronic lung disease in childhood and adulthood* . Recurrent pulmonary infections have been reported, likely caused by reduced expression of the pulmonary collectins, SP-A and SP-D, but could also result from decreased expression of other proteins. No clear genotype–phenotype correlations have emerged, but children harboring complete gene deletions have tended to have more severe and earlier-onset disease. This observation could also be related to the deletion of other adjacent genes. While limited data are available, the pulmonary phenotype may depend upon the expression of which *NKX2-1* target genes are most affected. Children with decreased SP-B or ABCA3 expression may present with acute neonatal respiratory failure whereas those with decreased SP-C or pulmonary collectin expression are more likely to have chronic lung disease.

Genetics

The gene is small, spanning < 3,000 bases, with only 3 exons. TTF-1 is expressed not only in the lung but also in the thyroid gland, as well as in the central nervous system. In the lung it is important for the expression of a wide variety of proteins, including the surfactant proteins, ABCA3, club cell secretory protein, and many others. Two transcripts that differ depending upon whether the transcriptional start site is in the 1st or 2nd exon have been recognized, although the shorter transcript is the predominant transcript in the lung. Most mutations are thought to result in a loss of function, with the mechanism of disease thus being haploinsufficiency, but discordant effects on different target genes have been reported. Loss of function mutations in *NKX2-1* are rare in large sequencing projects, but the prevalence of disease is unknown. Mutations in diverse ethnic groups have been recognized. Most reported mutations and deletions have occurred *de novo* resulting in sporadic disease, but familial disease transmitted in a dominant manner has been recognized.

Diagnosis

Sequence analysis of the *NKX2-1* gene is available through clinical laboratories and is the preferred method for diagnosis. As deletions comprise a significant fraction of reported mutant alleles, specific methods to look for such deletions should also be performed, such as a comparative genomic hybridization assay, a multiplex ligation-dependent probe amplification assay, or utilizing NGS methodology. A mutation on 1 allele is sufficient to cause disease. While isolated pulmonary disease has been recognized, the majority of reported affected individuals have manifestations in 2 or more other organ systems. Thus the presence of **hypothyroidism** or neurologic abnormality in a proband or a family history of chorea should prompt consideration of the diagnosis. The most specific neurologic finding is **chorea** , but hypotonia, developmental delay, ataxia, and dysarthria have been reported. In very young, non-ambulatory infants the neurologic symptoms may not be evident, or muscle weakness or hypotonia may be attributed to the severity of lung disease or a result of the hypothyroidism. Affected individuals may not be overtly hypothyroid but have compensated hypothyroidism with borderline low T4 (thyroxine) and high thyroid-stimulating hormone levels. The lung pathology associated with *NKX2-1* mutations may be typical of that of other surfactant dysfunction disorders, but because *NKX2-1* is important for lung development, growth abnormalities and arrested pulmonary development also may be seen. Immunostaining studies of surfactant protein expression have yielded variable results, with decreased expression of one or more surfactant-related proteins observed in some patients. No characteristic electron microscopy findings have been identified.

Treatment of Surfactant Dysfunction Disorders

Virtually all patients with SP-B deficiency die within the 1st yr of life. Conventional neonatal intensive care interventions can maintain extrapulmonary organ function for a limited time (weeks to months). Replacement therapy with commercially available surfactants is ineffective. Lung transplantation has been successful, but the pretransplantation, transplantation, and posttransplantation medical and surgical care is highly specialized and available only at pediatric pulmonary transplantation centers; prompt recognition is critical if patients are to be considered for lung transplantation. Palliative care consultation is helpful.

No specific treatment is available for patients with lung disease caused by mutations in *SFTPC* or *ABCA3* . Therapeutic approaches used for interstitial lung diseases, such as the use of corticosteroids, quinolones, and macrolide antibiotics have been reported but not systematically evaluated (Fig. 434.1). Infants with severe and progressive respiratory failure attributable to ABCA3 deficiency may be candidates for lung transplantation. The variable natural history of patients with *SFTPC* mutations and older children with ABCA3 deficiency makes predictions of prognosis difficult. Lung transplantation is reserved for patients with progressive and refractory respiratory failure who would otherwise qualify for transplantation irrespective of their diagnosis.

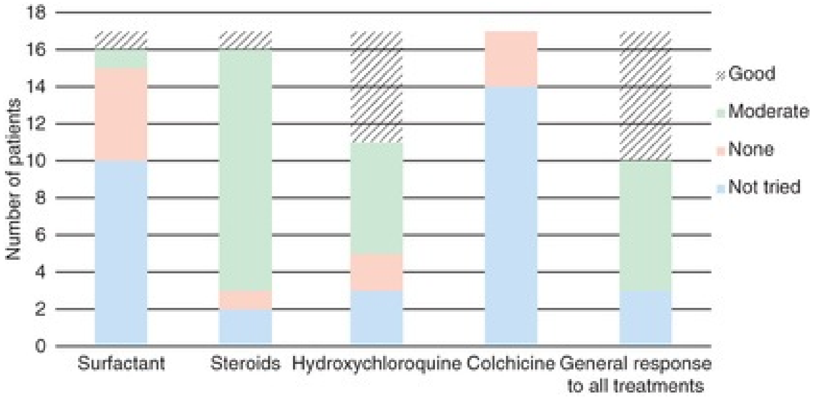

FIG. 434.1 Response to therapies for 17 patients with SFTPC mutations. (Data from Kröner C, Reu S, Teusch V, et al: Genotype alone does not predict the clinical course of SFTPC deficiency in paediatric patients, *Eur Respir J* 46:197–206, 2015.)

Treatment for patients with *NKX2-1* mutations is largely supportive. Hypothyroidism if present should be treated with thyroid replacement. Corticosteroids and other agents used for other types of surfactant dysfunction have not been formally evaluated. Some individuals have progressive lung disease and have undergone lung transplantation. The variable progression of disease and presence of extrapulmonary disease may make evaluation and selection of subjects for transplantation particularly difficult.

Parents of children with surfactant dysfunction disorders should be offered genetic counseling to inform recurrence risk for future pregnancies, to present antenatal diagnostic options and offer delivery at a center with neonatal intensive care, and to facilitate discussions regarding whether testing should be offered to other family members who may not be symptomatic.

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434.2

Pulmonary Alveolar Proteinosis

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Pulmonary alveolar proteinosis (PAP) is a rare syndrome characterized by the intra-alveolar and terminal airway accumulation of surfactant leading to progressive hypoxemic respiratory failure. PAP can result from abnormalities in surfactant production or surfactant clearance. Histopathologic examination shows distal air spaces are filled with a granular, eosinophilic material that stains positively with periodic acid–Schiff reagent and is diastase resistant. This material contains large amounts of surfactant proteins and lipids and the primary mechanism for its accumulation is impaired catabolism by alveolar macrophages. PAP is classified as either *primary* due to disruption of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling or *secondary* due to several different diseases that reduce alveolar macrophage number or function (Table 434.2). A fulminant, usually lethal form of PAP manifesting shortly after birth has been termed **congenital alveolar proteinosis** , but because this condition is caused by disrupted surfactant metabolism or surfactant dysfunction within alveolar type II cells, the disease is included under “Inherited Disorders of Surfactant Metabolism,” above (see Chapter 434.1).

Table 434.2

Comparison of Pulmonary Alveolar Proteinosis Syndromes

	AUTOIMMUNE	**GM-CSF RECEPTOR DEFICIENCY**	**LYSINURIC PROTEIN INTOLERANCE**	***MARS* DEFICIENCY**	**GATA DEFI**
Gene(s)		*CSFR2A, CSFR2B*	*SLC7A7*	*MARS*	*GATA2*
Age of onset	Adult > child	Childhood to adult	Childhood	Childhood to adult	Childhood
Inheritance	N.A.	Recessive	Recessive	Recessive	Sporadic/
Mechanism	Neutralizing antibodies to GM-CSF	Loss of function	Loss of function	Loss of function	Loss of fu haploinsuf
Other manifestations			Emesis; failure to thrive	Liver disease; hypothyroidism	Immune d myelodysp
DIAGNOSIS					
Biochemical	Detection of serum GM-CSF autoantibody	Elevated serum GM-CSF levels	Increased cationic amino acids in urine, especially lysine	None	None
Genetic (*DNA*)	N.A.	Sequence *CSFR2A, CSFR2B*	Sequence *SLC7A7*	Sequence *MARS*	Sequence
Treatment	Whole lung lavage; inhaled GM-CSF	Whole lung lavage; bone marrow transplantation	Whole lung lavage, dietary protein restriction, administration of citrulline and nitrogen scavenging drugs	Whole lung lavage	Whole lun bone marr transplanta

GM-CSF , Granulocyte-macrophage colony-stimulating factor.

Etiology and Pathophysiology

Primary Alveolar Proteinosis

Disordered signaling of GM-CSF leading to impaired alveolar macrophage maturation is the major underlying cause of primary PAP in children and adults. Most cases of primary PAP in older children and adults are mediated by neutralizing autoantibodies directed against GM-CSF, which can be detected in serum and bronchoalveolar lavage (BAL) fluid. These autoantibodies block binding of GM-CSF to its receptor, thereby inhibiting alveolar macrophage maturation and function and surfactant clearance. Mutations in the genes encoding both the α and β subunits of the GM-CSF receptor *(CSF2RA, CSFR2B)* in children with primary alveolar proteinosis account for a genetic basis for some cases of primary PAP in childhood.

Secondary Alveolar Proteinosis

Alveolar proteinosis has also been reported in children, including young infants, with lysinuric protein intolerance, a rare autosomal recessive disorder caused by mutations in the cationic amino acid transporter SLC7A7 (see Chapter 103.14). These children generally present with vomiting, hyperammonemia, and failure to thrive, although their pulmonary disease may prove fatal. Defective macrophage function has been demonstrated in lysinuric protein intolerance and a case of *recurrence* of the disease after lung transplantation also supports a primary role for alveolar macrophage dysfunction in the pathogenesis of PAP associated with lysinuric protein intolerance. PAP is also a prominent feature in patients with biallelic mutations in the gene encoding methionyl tRNA synthetase *(MARS)* , who have a multi-organ phenotype that also includes liver disease as a prominent feature, and is prevalent among individuals on Reunion Island. The mechanism for PAP in patients with *MARS* mutations is unknown. Heterozygous mutations in the gene encoding the transcription factor GATA2 have also been associated with a phenotype that includes PAP, as well as immune deficiencies, myelodysplasia, and lymphatic abnormalities. The mechanism for PAP in patients with such mutations is likely related to GATA2's role in alveolar macrophage development. PAP may also be associated with some subtypes of Niemann-Pick disease (see Chapter 104.4).

Secondary alveolar proteinosis also may occur in association with *infection* , particularly in immunocompromised individuals. However, because the same pathologic process occurs in severely immunodeficient mice raised in a pathogen-free environment, it is not clear whether this phenotype results from a secondary infection or the underlying immunodeficiency. Environmental exposures to dust, silica, and chemicals and chemotherapeutic agents, hematologic disorders (esp. myelodysplastic syndrome), and non-hematologic malignancies have also been associated with the development of secondary alveolar proteinosis.

Clinical Manifestations

Infants and children with PAP present with dyspnea, fatigue, cough, weight loss, chest pain, or hemoptysis. In the later stages, cyanosis and digital clubbing may be seen. Pulmonary function changes include decreased diffusing capacity of carbon monoxide, lung volumes with a restrictive abnormality, and arterial blood gas values indicating marked hypoxemia and/or chronic respiratory acidosis. Alveolar proteinosis in infants and children is rare and males are affected 3 times as often as females.

Diagnosis

Histopathologic examination of lung biopsy specimens currently remains the gold standard for diagnosis of PAP in children, although this is likely to change as molecular tests become available. Immunohistochemical staining reveals abundant quantities of alveolar and intracellular surfactant proteins A, B, and D. Latex agglutination tests for the presence of anti–GM-CSF antibodies in BAL fluid or blood are highly sensitive and specific for the autoimmune forms of alveolar proteinosis. Elevations of GM-CSF in peripheral blood suggest a GM-CSF receptor defect, and molecular analysis of these genes should be pursued. The examination of sputum or BAL fluid for surfactant components has been used diagnostically in adults, but these methods have not been validated in children. Examination of peripheral blood and/or bone marrow for clonogenic stimulation of monocyte-macrophage precursors, GM-CSF receptor and ligand expression, and GM-CSF binding and signaling studies are available through research protocols.

Treatment

The natural history of primary PAP is highly variable, making prognostic and therapeutic decisions difficult. Total lung lavage has been associated with prolonged remissions of PAP in adults and remains a therapeutic option for patients with childhood PAP (Fig. 434.2). Younger infants with PAP may be more likely to have genetic mechanisms underlying their disease, and the role of repeated BAL in children has not been well studied, nor is it likely to be effective. It may provide a temporizing measure in some circumstances and may benefit patients with autoimmune or secondary PAP. Subcutaneous or inhaled administration of recombinant GM-CSF may improve pulmonary function in some adults with later-onset PAP. The role of exogenous GM-CSF treatment in children has not been well studied, although successful treatment has been reported in an adolescent with autoimmune-mediated PAP. Because children with GM-CSF receptor defects generally have high serum levels of GM-CSF, exogenous GM-CSF seems unlikely to be effective in most such cases. Depending upon the nature of the mutation(s) responsible for the deficiency, some responsiveness of the receptor may be retained such that a response to exogenous GM-CSF is possible. As the primary defect for PAP resides in the alveolar macrophage, which is a bone marrow–derived cell, lung transplantation would not be expected to correct primary PAP.

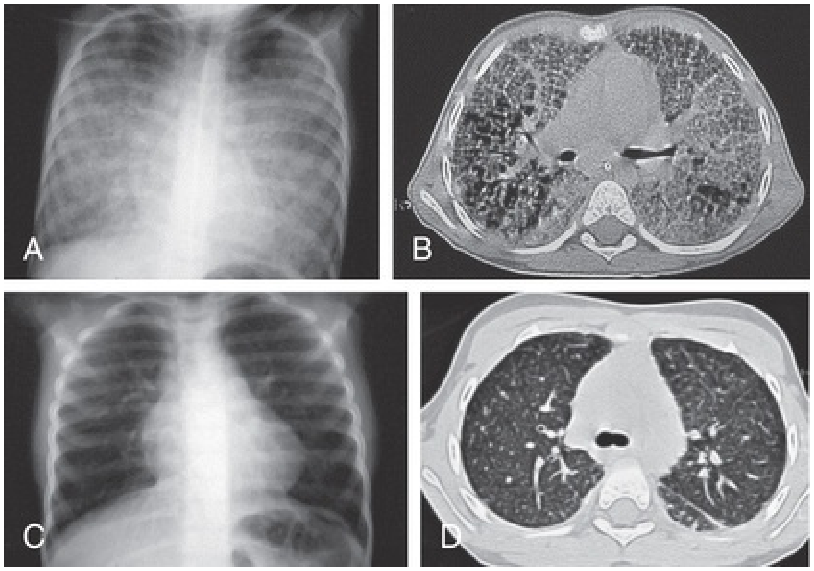

FIG. 434.2 **A** and **B,** Severe pulmonary alveolar proteinosis in a 5 yr old boy before therapeutic lung lavage. **A,** Chest radiograph shows diffuse alveolointerstitial infiltrates. **B,** CT scan demonstrates major air-space opacities and crazy-paving pattern. **C** and **D,** Same patient after 12 therapeutic lung lavages. **C,** Chest radiograph demonstrates improvement of alveolointerstitial infiltrates. **D,** CT scan shows regression of the air-space opacities with a residual micronodular pattern. (From De Blic J: Pulmonary alveolar proteinosis in children, *Paediatr Respir Rev* 5:316–322, 2004.)

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CHAPTER 435

Pulmonary Hemosiderosis

Mary A. Nevin

Pulmonary hemorrhage may be characterized as focal or diffuse based on the location(s) of bleeding. A detailed review of pulmonary hemorrhage is in Chapter 436.2 . The diagnosis of pulmonary hemosiderosis refers to the subset of patients with **diffuse alveolar hemorrhage (DAH)** . Bleeding in DAH occurs as a result of injury to the microvasculature of the lung and may be slow and insidious due to the low-pressure pulmonary circulation. Pulmonary hemosiderosis has classically been characterized by the triad of iron-deficiency anemia, hemoptysis, and radiographic evidence of alveolar infiltration. However, many of those affected, particularly young patients, are likely to present atypically and a high index of suspicion for this condition must be maintained. Pulmonary hemosiderosis can exist in isolation, but more commonly occurs in association with an underlying condition. A precise etiology for hemorrhage may not always be found. A diagnosis of **idiopathic pulmonary hemosiderosis (IPH)** is made when DAH occurs in isolation and an exhaustive evaluation for an underlying pathologic etiology is found to be unrevealing or nondiagnostic.

Etiology

The varied etiologies of pulmonary hemosiderosis are classified on the basis of the presence or absence of pulmonary **capillaritis** , a pathologic process that is characterized by inflammation and cellular disruption of the alveolar interstitium and capillary bed. Although the finding of pulmonary capillaritis is nonspecific with regard to underlying diagnosis, its presence appears to be an important negative prognostic factor in DAH and may indicate an underlying systemic vasculitic process or collagen vascular disease.

Disorders associated with pulmonary capillaritis may include systemic lupus erythematosus (SLE; see Chapter 183), drug-induced capillaritis, granulomatosis with polyangiitis (previously Wegener granulomatosis), Goodpasture syndrome, and Henoch-Schönlein purpura (see Chapter 192). The finding of DAH in patients with granulomatosis with polyangiitis and microscopic polyangiitis (MPA; see Chapter 192) is frequently associated with pathologic evidence of pulmonary capillaritis. In patients with Goodpasture syndrome or SLE, DAH has been reported both with and without the associated finding of capillaritis. A number of systemic autoimmune and inflammatory disorders may predispose a host to DAH with pulmonary capillaritis. Similarly, a variety of drugs have been associated with the finding of pulmonary capillaritis but mechanisms of cellular derangement are as yet unidentified.

These disorders are distinguished from those without pulmonary capillaritis. Those disorders in which the pathologic finding of capillary network disruption is absent are further divided into cardiac (pulmonary hypertension, mitral stenosis) and noncardiac (immunodeficiency, Heiner syndrome, coagulopathies, IPH) etiologies. Table 435.1 provides a summary and classification of the diagnoses that may manifest as recurrent or chronic pulmonary bleeding.

Table 435.1

Diffuse Alveolar Hemorrhage Syndromes

CLASSIFICATION	**SYNDROME**
DISORDERS WITH PULMONARY CAPILLARITIS	
	Idiopathic (isolated) pulmonary capillaritis (ANCA positive or negative) Granulomatosis with polyangiitis (Wegener granulomatosis) Microscopic polyangiitis Systemic lupus erythematosus (SLE) Scleroderma Polymyositis Goodpasture syndrome Antiphospholipid antibody syndrome Henoch-Schönlein purpura Immunoglobulin A nephropathy Behçet syndrome Cryoglobulinemia Drug-induced capillaritis (phenytoin, retinoic acid, propylthiouracil) Idiopathic pulmonary-renal syndrome Acute lung transplant rejection Eosinophilic granulomatosis angiitis (Churg-Strauss syndrome) Idiopathic pulmonary fibrosis
Disorders without pulmonary capillaritis	
Noncardiovascular causes	Idiopathic pulmonary hemosiderosis Heiner syndrome Acute idiopathic pulmonary hemorrhage of infancy

	Bone marrow transplantation Immunodeficiency Coagulation disorders Hemolytic uremic syndromes Celiac disease (Lane-Hamilton syndrome) SLE Non-accidental trauma Radiation therapy Infection (HIV, cryptococcosis, Legionnaires disease) Drugs—toxins
Cardiovascular causes	Mitral stenosis Pulmonary venoocclusive disease Arteriovenous malformations Pulmonary lymphangioleiomyomatosis Pulmonary hypertension Pulmonary capillary hemangiomatosis Chronic heart failure Vascular thrombosis with infarction Endocarditis

Modified from Susarla SC, Fan LL: Diffuse alveolar hemorrhage syndromes in children, *Curr Opin Pediatr* 19:314–320, 2007.

Epidemiology

Disorders that present as DAH are highly variable in their severity, as well as in their associated symptomatology and identifiable abnormalities in laboratory testing; the diagnosis may be significantly delayed, making frequency estimates unreliable. Similarly, the prevalence of IPH is largely unknown. Of the children and young adults diagnosed with IPH in the past, it has been postulated that the etiology of the hemorrhage might have been discovered if they had been studied with the newer and more advanced diagnostics available today; specific serologic testing has vastly improved our ability to appreciate immune mediated disease. Estimates of prevalence obtained from Swedish and Japanese retrospective case analyses vary from 0.24 to 1.23 cases per million. Children and adolescents account for 30% of cases. The ratio of affected males:females is 1 : 1 in the childhood diagnosis group, and men are only slightly more affected in the group diagnosed as young adults.

Pathology

In pulmonary capillaritis, key histologic features include (1) fibrin thrombi, which occlude capillaries, (2) fibrin clots adherent to interalveolar septae, (3) fibrinoid necrosis of capillary walls, and (4) interstitial erythrocytes and hemosiderin. Illustrative but nonspecific pathologic findings, such as vascular smooth muscle hypertrophy (pulmonary hypertension), edema (mitral stenosis), or thrombosis (vascular thrombosis with infarction), may be found in those disorders that cause DAH without pulmonary capillaritis. The finding of blood in the airways or alveoli is representative of a recent hemorrhage. With repeated episodes of pulmonary hemorrhage, lung tissue appears brown secondary to this presence of hemosiderin. *Hemosiderin-laden macrophages (HLMs)* are seen with recovering, recurrent, or chronic pulmonary hemorrhage and are identifiable both in bronchoalveolar lavage fluid and in pathologic specimens of lung tissue. It takes 48-72 hr for the alveolar macrophages to convert iron from erythrocytes into hemosiderin. In a murine model, HLMs appear 3 days after a single episode of pulmonary hemorrhage and peak at 7-10 days. HLMs may be detectable for weeks to months after a hemorrhagic event. Other nonspecific pathologic findings include thickening of alveolar septa, goblet cell hyperplasia, and hypertrophy of type II pneumocytes. Fibrosis may be seen with chronic disease.

Pathophysiology

Diffuse Alveolar Hemorrhage Associated With Pulmonary Capillaritis

Granulomatosis with polyangiitis is a recognized etiology for DAH in children. This disease is classically characterized by necrotizing granuloma formation (with or without cavitation) of the upper and lower respiratory tract and by a necrotizing glomerulonephritis and small vessel vasculitis. In children, presentations attributable to the upper airway, including subglottic stenosis, may suggest the diagnosis. The presence of antineutrophil cytoplasmic antibodies (ANCAs) may be helpful in diagnosis and management, but the clinician must be aware that other ANCA-positive vasculitides, such as MPA and Churg-Strauss syndrome, may share this nonspecific laboratory finding. In small-vessel vasculitides, ANCAs cause an inflammatory reaction that results in injury to the microvasculature. Antiproteinase-3 antibodies (cANCA) are classically associated with granulomatosis with polyangiitis whereas antimyeloperoxidase antibodies (pANCA) are typically found in patients with MPA.

Patients with **MPA** (previously the microscopic variant of polyarteritis nodosa) demonstrate a systemic necrotizing vasculitis with a predilection for small vessels (venules, arterioles, capillaries) but without necrotizing granuloma formation. This diagnosis is precluded by the finding of immune complex deposition in order to differentiate MPA from other diseases (Henoch-Schönlein purpura, cryoglobulinemic vasculitis) that are associated with immune complex–mediated small-vessel vasculitis.

Goodpasture syndrome is an immune complex–mediated disease in which anti–glomerular basement membrane (GBM) antibody binds to the basement membrane of both the alveolus and the glomerulus. GBM antibodies attach to type IV collagen contained in the vascular endothelium. At the alveolar level, immunoglobulin (Ig) G, IgM, and complement are deposited at alveolar septa. Electron microscopy shows disruption of basement membranes and vascular integrity, which allows blood to escape into alveolar spaces.

Although alveolar hemorrhage is not commonly encountered in association with SLE, its occurrence is often severe and potentially life-threatening; mortality rates exceed 50%. Pathologic vasculitic features may be absent. Some immunofluorescent studies have revealed IgG and C3 deposits at the alveolar septa. However, a clear link between immune complex formation and alveolar hemorrhage has not been established.

In **Henoch-Schönlein purpura,** pulmonary hemorrhage is a rare but recognized complication. Pathologic findings have included transmural neutrophilic infiltration of small vessels, alveolar septal inflammation, and intra-alveolar hemorrhage. Vasculitis is the proposed mechanism for hemorrhage.

Pulmonary renal syndromes are defined as those where pulmonary and renal disease manifestations are predominant. These include the aforementioned granulomatosis with polyangiitis, Goodpasture syndrome, SLE, and MPA. As Henoch-Schönlein purpura may also have renal involvement, it has been suggested for inclusion as a pulmonary renal syndrome.

Diffuse Alveolar Hemorrhage Not Associated With Pulmonary Capillaritis

A premature infant's neonatal course can be complicated by pulmonary hemorrhage. The alveolar and vascular networks are immature and particularly prone to inflammation and damage by ventilator mechanics, barotrauma, oxidative stress, and infection. Pulmonary hemorrhage may be unrecognized if the volume of blood is insufficient to reach the proximal airways. The chest radiographic findings in pulmonary hemorrhage may be appreciated instead as a worsening picture of respiratory distress syndrome, edema, or infection.

Pulmonary hemosiderosis in association with **cow's milk hypersensitivity** was first reported by Heiner in 1962. This condition is characterized by variable symptoms of milk intolerance. Symptoms can include grossly bloody or occult heme-positive stools, vomiting, failure to thrive, symptoms of gastroesophageal reflux, and/or upper airway congestion. Pathologic findings have included elevations of IgE and peripheral eosinophilia, as well as alveolar deposits of IgG, IgA, and C3. Association with pulmonary hemorrhage has remained controversial, but multiple case series have provided support for the anecdotal association. In one series, infants presenting with recurrent respiratory symptoms and iron-deficiency anemia; all infants improved with elimination of cow's milk from their diets and a subset thereafter had a recurrence of pulmonary disease with a cow's milk challenge. However, many patients with milk precipitins did not have symptoms of hemosiderosis and patients with hemosiderosis did not always have milk precipitins; the relationship may be an association rather than causal in nature.

A number of case reports and case series have suggested an association between **celiac disease** (see Chapter 364.2) and DAH. In these reports, a resolution of intestinal and pulmonary symptoms along with resolution of radiographic disease has been seen after the adoption of a gluten-free diet. Consideration of testing for celiac disease in those patients with pulmonary hemorrhage and suggestive gastrointestinal symptomatology may be warranted.

A number of additional associated conditions and exposures exist as causes for DAH. These are typically noninflammatory in nature and may be diversely attributable to cardiac, vascular, lymphatic, or hematologic etiologies. **Graft-versus-host disease** has been implicated in transplant recipients and DAH may rarely be attributable to nonaccidental trauma. These etiologies for DAH occur relatively infrequently in the pediatric population, and suggested mechanisms for hemorrhage are variable.

The diagnosis of IPH is a diagnosis of exclusion and is only made when there is evidence of chronic or recurrent DAH and when exhaustive evaluations for primary or secondary etiologies have negative results. Renal and systemic involvement should be absent and a biopsy specimen should not reveal any evidence of granulomatous disease, vasculitis, infection, infarction, immune complex deposition, or malignancy. Some patients initially diagnosed with IPH will later be found to have Goodpasture syndrome, SLE, or MPA; therefore some cases of IPH may represent unrecognized immune-mediated disorders.

Clinical Manifestations

The clinical presentation of pulmonary hemosiderosis is highly variable. In most symptomatic cases, DAH is heralded by symptoms of hemoptysis and dyspnea with associated hypoxemia and the finding of alveolar infiltration on chest radiograph. The diagnosis may be problematic as young children often lack the ability to effectively expectorate and may not present with hemoptysis. As the presence of blood in the lung is a trigger for airway irritation and inflammation, the patient may present after an episode of hemorrhage with wheezing, cough, dyspnea, and alterations in gas exchange, reflecting bronchospasm, edema, mucus plugging, and inflammation; this presentation may result in an incorrect diagnosis of asthma or bronchiolitis. A lack of pulmonary symptoms does not preclude the diagnosis of DAH and children may present only with chronic fatigue or pallor. In particular, young infants and children with DAH may come to attention with entirely nonspecific and nonpulmonary symptomatology such as failure to thrive or jaundice.

Primary or reported symptoms may reflect an underlying and associated disease process or comorbid condition. Presentations can vary widely from a relative lack of symptoms to shock or sudden death. Bleeding may occasionally be recognized from the presence of alveolar infiltrates on a chest radiograph alone. It should be noted, however, that the absence of an infiltrate does not rule out an ongoing hemorrhagic process.

On physical examination, the patient may be pale with tachycardia and tachypnea. During an acute exacerbation, children are frequently febrile. Examination of the chest may reveal retractions and differential or decreased aeration, with crackles or wheezes. The patient may present in shock with respiratory failure from massive hemoptysis.

Laboratory Findings and Diagnosis

Pulmonary hemorrhage is classically associated with a microcytic, hypochromic anemia. Reductions of serum iron levels, decreased or normal total iron-binding capacity, and normal to increased ferritin levels may be found with chronic disease. An elevated erythrocyte sedimentation rate is a nonspecific finding. The reticulocyte count is frequently elevated. Patients with pulmonary capillaritis have lower hematocrits and higher erythrocyte sedimentation rates. The anemia of IPH can mimic a hemolytic anemia. Elevations of plasma bilirubin are caused by absorption and breakdown of hemoglobin in the alveoli. Any or all of these hematologic manifestations may be absent in the presence of recent hemorrhage.

White blood cell count and differential should be evaluated for evidence of infection and eosinophilia. A peripheral smear and direct Coombs test may suggest a vasculitic process. A stool specimen positive for occult blood may suggest associated gastrointestinal disease but can also reflect swallowed blood. Renal and liver functions should be reviewed. A urinalysis should be obtained to assess for evidence of a pulmonary–renal syndrome. A coagulation profile, quantitative immunoglobulins (including IgE), and complement studies are recommended. Testing for von Willebrand disease is also indicated.

Testing for ANCA (cANCA, pANCA), antinuclear antibody, double-stranded DNA, rheumatoid factor, antiphospholipid antibody, and GBM antibody evaluates for a number of immune-mediated and vasculitic processes that may be associated with pulmonary capillaritis.

Sputum or pulmonary secretions should be analyzed for significant evidence of blood or HLMs and may provide supportive evidence in a patient who is able to adequately expectorate secretions from the lower airway. Gastric secretions may also reveal HLMs. Flexible bronchoscopy provides visualization of any areas of active bleeding. With bronchoalveolar lavage, pulmonary secretions may be sent for pathologic review and culture analysis. The ability to perform flexible bronchoscopy will be limited if there are large amounts of blood or clots in the airway. Active bleeding may be exacerbated by airway occlusion with a bronchoscope and by installation of fluid. A patient with respiratory failure can be ventilated more effectively through a rigid bronchoscope.

Chest x-rays may reveal evidence of acute or chronic disease. Hyperaeration is frequently seen, especially during an acute hemorrhage. Infiltrates are typically symmetric and may spare the apices of the lung. Atelectasis may also be appreciated. With chronic disease, fibrosis, lymphadenopathy, and nodularity may be seen. CT findings may demonstrate a subclinical and contributory disease process. The presence of a cardiac murmur, cardiomegaly on X-ray, or a clinical suspicion for left-sided heart lesion suggests the need for a complete cardiac evaluation, including electrocardiogram and echocardiogram.

Pulmonary function testing will likely reveal primarily obstructive disease in the acute period. With more chronic disease, fibrosis and restrictive disease tend to predominate. Oxygen saturation levels may be decreased. Lung volumes may reveal air trapping acutely and decreases in total lung capacity chronically. The diffusing capacity of carbon monoxide may be low or normal in the chronic phase but is likely to be elevated in the setting of an acute hemorrhage, because carbon monoxide binds to the hemoglobin in extravasated red blood cells.

Lung biopsy is warranted when DAH occurs without discernible etiology, extrapulmonary disease, or circulating GBM antibodies. When surgically obtained, pulmonary tissue should be evaluated for evidence of vasculitis, immune complex deposition, and granulomatous disease.

Many have supported a diagnosis of IPH without lung biopsy if the patient has a typical presentation with diffuse infiltration on radiography, anemia, HLMs in bronchoalveolar lavage, sputum or gastric aspirate, absence of systemic disease, and negative serology for immune-mediated disease. However, a number of patients meeting these criteria have been proven to have pulmonary capillaritis on review of pathologic lung tissue specimens. Therefore, a lung biopsy is recommended in any child presenting with DAH of uncertain etiology.

Treatment

Supportive therapy, including volume resuscitation, ventilatory support, supplemental oxygen, and transfusion of blood products, may be warranted in the patient presenting acutely with pulmonary hemorrhage. Surgical or medical therapy should be directed at any treatable underlying condition. In IPH, systemic corticosteroids are frequently utilized as first-line treatment and are expected to be of particular benefit in the setting of immune-mediated disease. Steroids modulate neutrophil influx and the inflammation associated with hemorrhage; consequently, they may decrease progression toward fibrotic disease.

Medication dosing may vary with regard to primary diagnosis, age, comorbidities, and other factors. Clinical-pharmacologic correlation is advocated. Treatment may be provided in the form of methylprednisolone 2-4 mg/kg/day divided every 6 hr or in the form of prednisone 0.5-1 mg/kg daily and decreased to every other day after resolution of acute symptoms. Successful treatment is also associated with the use of pulse steroid therapy; methylprednisolone may be given at a dose of 10-30 mg/kg (maximum 1 g) infused over 1 hr for 3 consecutive days and repeated weekly or monthly. Early treatment with corticosteroids appears to decrease episodes of hemorrhage.

Steroid therapy is associated with improved survival and may be tapered as tolerated with disease remission or chronically maintained.

A variety of steroid-sparing and alternative immunosuppressive agents, including cyclophosphamide, cytoxan, azathioprine, hydroxychloroquine, methotrexate, rituximab, 6-mercaptopurine, and intravenous Ig, have all been successfully used anecdotally as adjunctive therapy in patients with severe, chronic, unremitting, or recurrent hemorrhage. Maintenance therapy with 6-mercaptopurine may produce favorable results in achieving long-term remission.

Plasmapheresis is a recognized therapy for anti-GBM antibody disease. Intravenous Ig has been used in immune complex–mediated disease.

In the most critically ill children, additional life-sustaining interventions may be required; extracorporeal membrane oxygenation (ECMO) combined with immunosuppression was reported to be successful in allowing recovery from a severe hemorrhage with hypoxemic respiratory failure in the setting of p-ANCA positive MPA. In neonatal and infantile pulmonary hemorrhage, clinical improvement in blood gas and ventilatory requirements have been described with intrapulmonary administration of exogenous surfactant.

The potential adverse effects of these pharmacologic and therapeutic interventions should be recognized and treated patients must be closely monitored for drug-related complications. Cushing syndrome is a well-recognized complication of chronic steroid therapy. Thrombocytopenia in association with low-dose cyclophosphamide has also been reported. Chronically immunosuppressed patients are at risk for opportunistic infection; *Legionella* pneumonia infection has been described in a survivor of IPH.

In chronic disease, progression to debilitating pulmonary fibrosis has been described. Lung transplantation has been performed in patients with IPH refractory to immunosuppressive therapy. In one reported case study, IPH recurred in the transplanted lung.

Many patients (~50%) are diagnosed with IPH 2 mo after presentation. Additionally ~15% are diagnosed after a period of 6 mo.

Prognosis

The outcome of patients suffering from DAH is largely dependent on the underlying disease process. Some conditions respond well to immunosuppressive therapies and remissions of disease are well documented. Other syndromes, especially those associated with pulmonary capillaritis, carry a poorer prognosis. In IPH, mortality is usually attributable to massive hemorrhage or, alternatively, to progressive fibrosis, respiratory insufficiency, and right-sided heart failure.

Long-term prognosis in patients with IPH varies among studies. Initial case study reviews suggested an average survival after symptom onset of only 2.5 yr. In this early review, a minority of patients were treated with steroids. Newer reviews have demonstrated vastly improved 5 yr (86%) and 8 yr (93%) survival in association with the use of immunosuppressive therapies. To date, specific immunosuppressive treatment regimens have not been studied in a prospective manner.

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CHAPTER 436

Pulmonary Embolism, Infarction, and Hemorrhage

436.1

Pulmonary Embolus and Infarction

Mary A. Nevin

Keywords

pulmonary hemorrhage
pulmonary embolism
deep venous thrombosis
air embolism
thrombophilia
partial thromboplastin time
hemosiderin
bronchoalveolar lavage
acute idiopathic pulmonary hemorrhage of infancy (AIPHI)

Venous thromboembolic disease (VTE) has become an increasingly recognized critical problem in children and adolescents with chronic disease, as well as in patients without identifiable risk factors (Table 436.1). Improvements in survival with chronic illness have likely contributed to the larger number of children presenting with these thromboembolic events; they are a significant source of morbidity and mortality and may only be recognized on postmortem examination. A high level of clinical suspicion and appropriate identification of at-risk individuals is therefore recommended.

Table 436.1

Risk Factors for Pulmonary Embolism

ENVIRONMENTAL
Long-haul air travel (>4 hr)
Obesity
Cigarette smoking
Hypertension
Immobility
WOMEN'S HEALTH
Oral contraceptives, including progesterone-only and, especially, third-generation pills
Pregnancy or puerperium
Hormone replacement therapy
Septic abortion
MEDICAL ILLNESS
Personal or family history of prior pulmonary embolism or deep venous thrombosis
Cancer
Heart failure
Chronic obstructive pulmonary disease
Diabetes mellitus
Inflammatory bowel disease
Antipsychotic drug use
Long-term indwelling central venous catheter
Permanent pacemaker
Internal cardiac defibrillator
Stroke with limb paresis
Spinal cord injury
Nursing home confinement or current or repeated hospital admission
SURGICAL
Trauma
Orthopedic surgery
General surgery
Neurosurgery, especially craniotomy for brain tumor
Vascular anomalies
May-Turner syndrome
THROMBOPHILIA
Factor V Leiden mutation
Prothrombin gene (20210G A) mutation
Hyperhomocysteinemia (including mutation in methylenetetrahydrofolate reductase)
Antiphospholipid antibody syndrome
Deficiency of antithrombin III, protein C, or protein S
High concentrations of factor VIII or XI
Increased lipoprotein (a)
NONTHROMBOTIC
Air
Foreign particles (e.g., hair, talc, as a consequence of intravenous drug misuse)
Amniotic fluid

Bone fragments, bone marrow
Fat
Tumors (Wilms tumor)

Modified from Goldhaber SZ: Pulmonary embolism, *Lancet* 363:1295–1305, 2004.

Etiology

A number of risk factors may be identified in children and adolescents; the presence of immobility, malignancy, pregnancy, infection, indwelling central venous catheters, and a number of inherited and acquired thrombophilic conditions have all been identified as placing an individual at risk. In children, a significantly greater percentage of VTEs are risk associated as compared with their adult counterparts. Children with **deep venous thrombosis (DVT)** and **pulmonary embolism (PE)** are much more likely to have one or more identifiable conditions or circumstances placing them at risk. In contrast to adults, idiopathic thrombosis is a rare occurrence in the pediatric population. In a retrospective cohort of patients with VTE in U.S. children's hospitals from 2001 to 2007, the majority (63%) of affected children were found to have one or more chronic medical comorbidities. In a large Canadian registry, 96% of pediatric patients were found to have one risk factor and 90% had two or more risk factors. In contrast, approximately 60% of adults with this disorder have an identifiable risk factor (see Table 436.1). The most common identified risk factors in children include infection, congenital heart disease, and the presence of an indwelling central venous catheter.

Embolic disease in children is varied in its origin. An embolus can contain thrombus, air, amniotic fluid, septic material, or metastatic neoplastic tissue. Thromboemboli are the type most commonly encountered. A commonly encountered risk factor for DVT and PE in the pediatric population is the presence of a central venous catheter. More than 50% of DVTs in children and more than 80% in newborns are found in patients with indwelling central venous lines. The presence of a catheter in a vessel lumen, as well as instilled medications, can induce endothelial damage and favor thrombus formation.

Children with malignancies are also at considerable risk. Although PE has been described in children with leukemia, the risk of PE is more significant in children with solid rather than hematologic malignancies. A child with malignancy may have numerous risk factors related to the primary disease process and the therapeutic interventions. Infection from chronic immunosuppression may interact with hypercoagulability of malignancy and chemotherapeutic effects on the endothelium. In a retrospective cohort of patients with VTE from 2001 to 2007, pediatric malignancy was the medical condition most strongly associated with recurrent VTE.

In the neonatal period, thromboembolic disease and PE may be related to indwelling catheters used for parenteral nutrition and medication delivery. Pulmonary thromboemboli in neonates generally occurs as a complication of underlying disease; the most common associated diagnosis is congenital heart disease, but sepsis and birth asphyxia are also notable associated conditions. Other risk factors include a relative immaturity of newborn infants' coagulation; plasma concentrations of vitamin K-dependent coagulation factors (II, VII, IX, X); factors XII, XI, and prekallikrein and high molecular weight kininogen are only approximately half of adult levels (see Chapter 502). PE in neonates may occasionally reflect maternal risk factors, such as diabetes and toxemia of pregnancy. Infants with congenitally acquired homozygous deficiencies of antithrombin, protein C, and protein S are also more likely to present with thromboembolic disease in the neonatal period (see Chapter 505).

Pulmonary air embolism is a defined entity in the newborn or young infant and is attributed to the conventional ventilation of critically ill (and generally premature) infants with severe pulmonary disease. In the majority of instances, the pulmonary air embolism is preceded by an air-leak syndrome. Infants may become symptomatic and critically compromised by as little as 0.4 mL/kg of intravascular air; these physiologic derangements are thought to be secondary to the effects of nitrogen.

Prothrombotic disease can also manifest in older infants and children. Disease can be congenital or acquired. **Inherited thrombophilic** conditions include deficiencies of antithrombin, protein C, and protein S, as well as mutations of factor V Leiden (G1691A) (see Chapter 505) and prothrombin (factor II 20210A mutation) (see Chapter 505), and elevated values of lipoprotein A. In addition, multiple acquired thrombophilic conditions exist; these include the presence of lupus anticoagulant (may be present without the diagnosis of systemic lupus erythematosus), anticardiolipin antibody, and anti–β_2 -glycoprotein 1 antibody. Finally, conditions such as hyperhomocysteinemia (see Chapter 104) may have both inheritable and dietary determinants. All have all been linked to thromboembolic disease. DVT/PE may be the initial presentation.

Children with sickle cell disease are also at high risk for pulmonary embolus and infarction. Acquired prothrombotic disease is seen in conditions such as nephrotic syndrome (see Chapter 545) and antiphospholipid antibody syndrome. From one-quarter to one-half of children with systemic lupus erythematosus (see Chapter 183) have thromboembolic disease. There is a significant association with VTE onset in children for each inherited thrombophilic trait evaluated, thereby illuminating the importance of screening for thrombophilic conditions for those at risk for VTE. Septic emboli are rare in children but may be caused by osteomyelitis, jugular vein or umbilical thrombophlebitis, cellulitis, urinary tract infection, and right-sided endocarditis.

Other risk factors include infection, cardiac disease, recent surgery, and trauma. Surgical risk is thought to be more significant when immobility will be a prominent feature of the recovery. Use of oral contraceptives confers additional risk, although the level of risk in patients taking these medications appears to be decreasing, perhaps because of the lower amounts of estrogen in current formulations. In a previously healthy adolescent patient, the risk factors are often unknown or are similar to adults (see Tables 436.1 and 436.2).

Table 436.2

Clinical Decision Rules for Deep Vein Thrombosis and Pulmonary Embolism

WELLS' SCORE FOR DEEP VEIN THROMBOSIS [*]		
Active cancer	+1	NA
Paralysis, paresis, or recent plaster cast on lower extremities	+1	NA
Recent immobilization >3 days or major surgery within the past 4 wk	+1	NA
Localized tenderness of deep venous system	+1	NA
Swelling of entire leg	+1	NA
Calf swelling >3 cm compared to asymptomatic side	+1	NA
Unilateral pitting edema	+1	NA
Collateral superficial veins	+1	NA
Previously documented deep vein thrombosis	+1	NA
Alternative diagnosis at least as likely as deep vein thrombosis	−2	NA
WELLS' SCORE FOR PULMONARY EMBOLISM [†, ‡]		
Alternative diagnosis less likely than pulmonary embolism	+3	+1
Clinical signs and symptoms of deep vein thrombosis	+3	+1
Heart rate >100 beats/min	+1·5	+1
Previous deep vein thrombosis or pulmonary embolism	+1·5	+1
Immobilization or surgery within the past 4 wk	+1·5	+1
Active cancer	+1	+1
Hemoptysis	+1	+1
REVISED GENEVA SCORE FOR PULMONARY EMBOLISM [§, ‖]		
Heart rate ≥95 beats/min	+5	+2
Heart rate 75–94 beats/min	+3	+1
Pain on lower-limb deep venous palpation and unilateral edema	+4	+1

Unilateral lower-limb pain	+3	+1
Previous deep vein thrombosis or pulmonary embolism	+3	+1
Active cancer	+2	+1
Hemoptysis	+2	+1
Surgery or fracture within the past 4 wk	+2	+1
Age >65 yr	+1	+1

[*] Classification for original Wells' score for deep vein thrombosis: deep vein thrombosis unlikely if score ≤2; deep vein thrombosis likely if score >2.

[†] Classification for original Wells' score for pulmonary embolism: pulmonary embolism unlikely if score ≤4; pulmonary embolism likely if score >4.

[‡] Classification for simplified Wells' score for pulmonary embolism: pulmonary embolism unlikely if score ≤1; pulmonary embolism likely if score >1.

[§] Classification for original revised Geneva score for pulmonary embolism: non-high probability of pulmonary embolism if score ≤10; high probability of pulmonary embolism if score >10.

[||] Classification for simplified revised Geneva score for pulmonary embolism: non-high probability of pulmonary embolism if score ≤4; high probability of pulmonary embolism if score >4.

From Di Nisio M, van Es N, Büller HR: Deep vein thrombosis and pulmonary embolism, *Lancet* 388:3060–3069, 2016 (Table 1, p. 3062).

Epidemiology

A retrospective cohort study was performed with patients younger than 18 yr of age, discharged from 35 to 40 children's hospitals across the United States from 2001 to 2007. During this time, a dramatic increase was noted in the incidence of VTE; the annual rate of VTE increased by 70% from 34 to 58 cases per 10,000 hospital admissions. Although this increased incidence was noted in all age groups, a bimodal distribution of patient ages was found, consistent with prior studies; infants younger than 1 yr of age and adolescents made up the majority of admissions with VTE, but neonates continue to be at greatest risk. The peak incidence for VTE in childhood appears to occur in the 1st mo of life. It is in this neonatal period that thromboembolic events are more problematic, likely as a result of an imbalance between procoagulant factors and fibrinolysis. The yearly incidence of venous events was estimated at 5.3/10,000 hospital admissions in children and 24/10,000 in the neonatal intensive care.

Pediatric autopsy reviews have estimated the incidence of thromboembolic disease in children as between 1% and 4%, although not all were clinically significant. Thromboembolic pulmonary disease is often unrecognized, and antemortem studies may underestimate the true incidence. Pediatric deaths from isolated pulmonary emboli are rare. Most thromboemboli are related to central venous catheters. The source of the emboli may be lower or upper extremity veins as well as the pelvis and right heart. In adults, the most common location for DVT is the lower leg. However, one of the largest pediatric VTE/PE registries found two-thirds of DVTs occurring in the upper extremity.

Pathophysiology

Favorable conditions for thrombus formation include injury to the vessel endothelium, hemostasis, and hypercoagulability. In the case of PE, a thrombus is dislodged from a vein, travels through the right atrium, and lodges within the pulmonary arteries. In children, emboli that obstruct <50% of the pulmonary circulation are generally clinically silent unless there is significant coexistent cardiopulmonary disease. In severe disease, right ventricular afterload is increased with resultant right ventricular dilation and increases in right ventricular and pulmonary arterial pressures. In severe cases, a reduction of cardiac output and hypotension may result from concomitant decreases in left ventricular filling. In rare instances of death from massive pulmonary embolus, marked increases in pulmonary vascular resistance and heart failure are usually present.

Arterial hypoxemia results from unequal ventilation and perfusion; the occlusion of the involved vessel prevents perfusion of distal alveolar units, thereby creating an increase in dead space and hypoxia with an elevated alveolar–arterial oxygen tension difference (see Chapter 400). Most patients are hypocarbic secondary to hyperventilation, which often persists even when oxygenation is optimized. Abnormalities of oxygenation and ventilation are likely to be less significant in the pediatric population, possibly owing to less underlying cardiopulmonary disease and greater reserve. The vascular supply to lung tissue is abundant, and pulmonary infarction is unusual with pulmonary embolus but may result from distal arterial occlusion and alveolar hemorrhage.

Clinical Manifestations

Presentation is variable, and many pulmonary emboli are silent. Rarely, a massive PE may manifest as cardiopulmonary failure. Children are more likely to have underlying disease processes or risk factors but might still present asymptomatically with small emboli. Common symptoms and signs of PE caused by larger emboli include hypoxia (cyanosis), dyspnea, tachycardia, cough, pleuritic chest pain, and hemoptysis. Pleuritic chest pain is the most common presenting symptom in adolescents (84%), whereas unexplained and persistent tachypnea may suggest PE in all pediatric patients. Localized crackles may occasionally be appreciated on examination. A high level of clinical suspicion is required because a variety of diagnoses may cause similar symptoms; nonspecific complaints may frequently be attributed to an underlying disease process or an unrelated/incorrect diagnosis. Confirmatory testing should follow a clinical suspicion for PE. In older adolescents and adults, clinical prediction rules have been published and are based on risk factors, clinical signs, and symptoms (see Table 436.2). No such clinical prediction rules have been validated in the pediatric population.

Laboratory Findings and Diagnosis

The electrocardiogram, arterial blood gas, and chest radiograph may be used to rule out contributing or comorbid disease but are not sensitive or specific in the diagnosis of PE. Electrocardiographs may reveal ST-segment changes or evidence of pulmonary hypertension with right ventricular failure (cor pulmonale); such changes are nonspecific and nondiagnostic. Radiographic images of the chest are often normal in a child with PE and any abnormalities are likely to be nonspecific. Patients with septic emboli may have multiple areas of nodularity and cavitation, which are typically located peripherally in both lung fields. Many patients with PE have hypoxemia. The alveolar–arterial oxygen tension difference gradient is more sensitive in detecting gas exchange derangements.

A review of results of a complete blood count, urinalysis, and coagulation profile is warranted. Prothrombotic diseases should be highly suspected on the basis of past medical or family history; additional laboratory evaluations include fibrinogen assays, protein C, protein S, and antithrombin III studies, and analysis for factor V Leiden mutation, as well as evaluation for lupus anticoagulant and anticardiolipin antibodies.

Echocardiograms may be warranted to assess ventricular size and function. An echocardiogram is required if there is any suspicion of intracardiac thrombi or endocarditis.

Noninvasive venous ultrasound testing with Doppler flow can be used to confirm DVT in the lower extremities; ultrasonography may not detect thrombi in the upper extremities or pelvis (Fig. 436.1*A*). In patients with significant venous thrombosis, D dimers are usually elevated. It is a sensitive but nonspecific test for venous thrombosis. The D dimer may not be clinically relevant in the children with PE as this group is more likely to have an underlying comorbid condition that is also associated with an increased level of D dimers. When a high level of suspicion exists, confirmatory testing with venography should be pursued. DVT can be recurrent and multifocal and may lead to repeated episodes of PE.

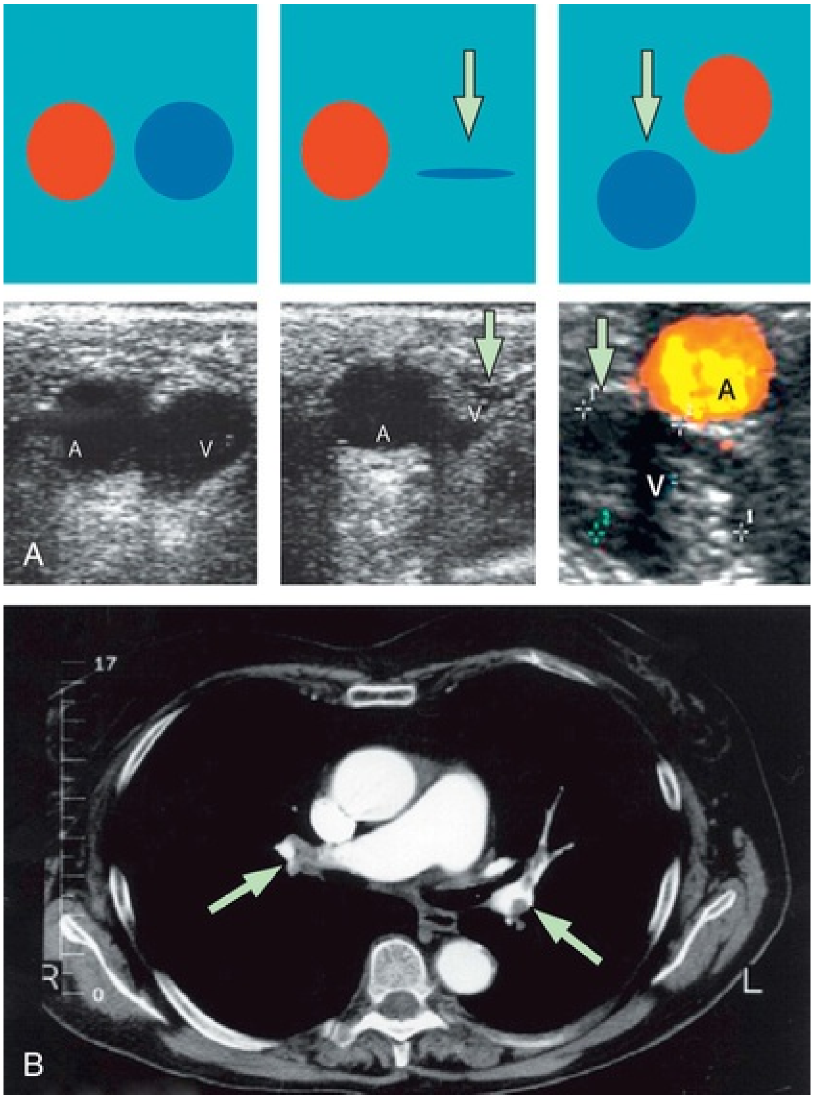

FIG. 436.1 **A,** Compression ultrasound. Upper series, from left to right, representation of vein and artery without and with *(arrow)* gentle

compression with the echocardiographic probe; lower series, corresponding echocardiographic findings. The third image from the left shows a thrombus in the vein (vein not compressible by the probe). **B,** CT angiography. CT angiography showing several emboli *(arrows)* in the main right pulmonary artery and in left lobar and segmental arteries. *A* , Artery; *V* , vein. (From Goldhaber SZ, Bounameaux H: Pulmonary embolism and deep vein thrombosis, *Lancet* 379:1835–1844, 2012, Fig. 2, p. 1838.)

Although much more commonly encountered in the adult population, thrombus migration to the pulmonary circulation in children and adolescents may be prevented through surgical placement of an inferior vena cava (IVC) filter. This may be considered when DVT is detected and risk of pulmonary thrombus is high or when there is a medical contraindication to or intolerance for anticoagulant therapy. IVC filter may also be considered prophylactically in the setting of trauma.

Although a ventilation–perfusion ($\dot{V} - \dot{Q}$) radionuclide scan is a noninvasive and potentially sensitive method of pulmonary embolus detection, the interpretation of $\dot{V} - \dot{Q}$ scans can be problematic. *Helical or spiral CT with an intravenous contrast agent is valuable and the diagnostic test of choice to detect a PE* (see Fig. 436.1*B*). CT studies detect emboli in lobar and segmental vessels with acceptable sensitivities. Poorer sensitivities may be encountered in the evaluation of the subsegmental pulmonary vasculature. Pulmonary angiography is the gold standard for diagnosis of PE, but with availability of multidetector spiral CT angiography, it is not necessary except in unusual cases.

MRI may be emerging as a diagnostic option for patients with VTE. The accuracy of this method is similar to that of multidetector CT. It may be preferable in patients with allergic reactions to contrast material and in pediatric patients in whom the risk of early exposure to ionizing radiation has been established.

Treatment

Initial treatment should always be directed toward stabilization of the patient. Careful approaches to ventilation, fluid resuscitation, and inotropic support are always indicated, because improvement in one area of decompensation can often exacerbate coexisting pathology.

After the patient with a PE has been stabilized, the next therapeutic step is anticoagulation. Evaluations for prothrombotic disease must precede anticoagulation. Acute-phase anticoagulation therapy may be provided with unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Heparins act by enhancing the activity of antithrombin. LMWH is generally preferred in children; this drug can be administered subcutaneously and the need for serum monitoring is decreased. The risk of heparin-induced thrombocytopenia is also decreased with LMWH as compared to UFH. Alternatively, UFH is preferred with patients who have an elevated risk of bleeding as UFH has a shorter half-life than LMWH. UFH is also used preferentially in patients with compromised renal function. In monitoring of drug levels, laboratories must be aware of the drug chosen in order to use the appropriate assay. For UFH, the therapeutic range is 0.3-0.7 anti-Xa activity units/mL. In LMWH, the therapeutic range is 0.5-1.0 units/mL. When the anti-Xa assay is not available, the activated partial thromboplastin time may be used with a goal of 60-85 sec or approximately 1.5-2 times the upper limit of age appropriate normal values. The recommended duration of heparinization during acute treatment is 5-10 days; this length of therapy has been extrapolated from adult data. Long-term therapy with heparin should be avoided whenever possible. Side effects include the aforementioned heparin-induced thrombocytopenia as well as bleeding and osteoporosis.

Extension of anticoagulation therapy occurs in the subacute phase and may utilize LMWH or warfarin. Warfarin is generally initiated after establishing effective anticoagulation with heparin because severe congenital deficiencies of protein C may be associated with warfarin skin necrosis. When the international normalized ratio (INR) is measured between 1.0 and 1.3, the starting dose for warfarin in children is recommended as 0.2-0.3 mg/kg administered orally once daily. Titration of dosing may be needed to achieve a therapeutic INR of 2 to 3. Dosing requirements may vary and clinical pharmacologic correlation is required. The INR is generally monitored 5 days after initiating therapy or a similar period after dose changes and weekly thereafter until stable. The INR should be obtained with any evidence of abnormal bleeding and should be discontinued at least 5 days prior to invasive procedures. The utilization of an anticoagulation team and/or established treatment algorithms is recommended in order to optimize patient safety. With a first occurrence of VTE, anticoagulation is recommended for 3-6 mo in the setting of an identifiable, reversible, and resolved risk factor (e.g., postoperative state). Longer treatment is indicated in patients with idiopathic VTE (6-12 mo) and in those with chronic clinical risk factors (12 mo-lifelong). In the setting of a congenital thrombophilic condition, the duration of therapy is often indefinite. Inhibitors of factor Xa (rivaroxaban, etc.) may become an alternate therapy for both acute PE and long-term treatment (Table 436.3).

Table 436.3

Anticoagulant Therapies for Deep Vein Thrombosis and Pulmonary Embolism

	ROUTE OF ADMINISTRATION	RENAL CLEARANCE (%)	HALF-LIFE	INITIAL TREATMENT DOSING	MAINTENANCE TREATMENT DOSING	E T D
Unfractionated heparin (UFH)	Intravenous	~30	~1.5 hr	Maintain aPTT 1.5-times upper limit of normal		
Low molecular weight heparin (LMWH)	Subcutaneous	~80	3-4 hr	Weight-based dosing	Weight-based dosing[*]	
Fondaparinux	Subcutaneous	100	17-21 hr	Weight-based dosing	Weight-based dosing	
Vitamin K antagonists	Oral	Negligible	Acenocoumarol 8-11 hr; warfarin 36 hr; phenprocoumon 160 hr	Target at INR at 2.0-3.0 and give parallel heparin treatment for at least 5 days	Maintain INR at 2.0-3.0	M a
Dabigatran	Oral	~80[†]	14-17 hr	Requires at least 5 days heparin lead-in	150 mg twice a day	1 d
Rivaroxaban	Oral	~33[‡]	7-11 hr	15 mg twice a day for 3 wk	20 mg once a day	2 d
Apixaban	Oral	~25[‡]	8-12 hr	10 mg twice a day for 1 wk	5 mg twice a day	2 d
Edoxaban	Oral	~35[‡]	6-11 hr	Requires at least 5 days heparin lead-in	60 mg once a day[§]	6 d
Aspirin	Oral	~10	15 min			8 o

[*] Treatment with low molecular weight heparin is recommended for patients with active cancer and pregnant women.

[†] Dabigatran is contraindicated in patients with a creatinine clearance below 30 mL/min.

[‡] Apixaban, edoxaban, and rivaroxaban are contraindicated in patients with a creatinine clearance below 15 mL/min.

[§] The recommended edoxaban dose is 30 mg once a day for patients with a creatinine clearance of 30–50 mL/min, a bodyweight less than or equal to 60 kg, or for those on certain strong P-glycoprotein inhibitors.

Medication dosing may vary with regard to primary diagnosis, age, comorbidities, and other factors. Clinical-pharmacologic correlation is advocated.

aPTT , activated partial thromboplastin time; *INR* , international normalized ratio.

From Di Nisio M, van Es N, Büller HR: Deep vein thrombosis and pulmonary embolism, *Lancet* 388:3060–3069, 2016 (Table 2, p. 3065).

Thrombolytic agents such as recombinant tissue plasminogen activator, may be utilized in combination with anticoagulants in the early stages of treatment; their use is most likely to be considered in children with hemodynamically significant PE (echocardiogram evidence of right ventricular dysfunction) or other severe potential clinical sequelae of VTE. Combined therapy may reduce the incidences of progressive thromboembolism, pulmonary embolus, and postthrombotic syndrome. Mortality rate appears to be unaffected by additional therapies; nonetheless, the additional theoretic risk of hemorrhage limits the use of combination therapy in all but the most compromised patients. The use of thrombolytic agents in patients with active bleeding, recent cerebrovascular accidents, or trauma is contraindicated.

Surgical embolectomy is invasive and is associated with significant mortality. Its application should be limited to those with large emboli that result in persistent hemodynamic compromise refractory to standard therapy.

Prognosis

Mortality in pediatric patients with PE is likely to be attributable to an underlying disease process rather than to the embolus itself. Short-term complications include major hemorrhage (either due to the thrombosis or secondary to anticoagulation). Conditions associated with a poorer prognosis include malignancy, infection, and cardiac disease. The mortality rate in children from PE is 2.2%. Recurrent thromboembolic disease may complicate recovery. The practitioner must conduct an extensive evaluation for underlying pathology so as to prevent progressive disease. Postthrombotic syndrome is another recognized complication of pediatric thrombotic disease. Venous valvular damage can be initiated by the presence of DVT, leading to persistent venous hypertension with ambulation and valvular reflux. Symptoms include edema, pain, increases in pigmentation, and ulcerations. Affected pediatric patients may suffer lifelong disability.

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436.2

Pulmonary Hemorrhage and Hemoptysis

Mary A. Nevin

Pulmonary hemorrhage is relatively uncommon but a potentially fatal occurrence in children. The patient with suspected hemoptysis may present acutely or subacutely and to a variety of different practitioners with distinct areas of specialty. Diffuse, slow bleeding in the lower airways may become severe and manifest as anemia, fatigue, or respiratory compromise without the patient ever experiencing episodes of hemoptysis. Hemoptysis must also be separated from episodes of hematemesis or epistaxis, each of which may have indistinguishable presentations in the young patient.

Etiology

Table 436.4 and Table 435.1 (in Chapter 435) present conditions that can manifest as pulmonary hemorrhage or hemoptysis in children. The chronic (opposed to an acute) presence of a foreign body can lead to inflammation and/or infection, thereby inducing hemorrhage. Bleeding is more likely to occur in association with a chronically retained foreign body of vegetable origin.

Table 436.4

Etiology of Pulmonary Hemorrhage (Hemoptysis)

FOCAL HEMORRHAGE
Bronchitis and bronchiectasis (especially cystic fibrosis–related)
Infection (acute or chronic), pneumonia, abscess
Tuberculosis
Trauma
Pulmonary arteriovenous malformation (with or without hereditary hemorrhagic telangiectasia)
Foreign body (chronic)

Neoplasm including hemangioma
Pulmonary embolus with or without infarction
Bronchogenic cysts
DIFFUSE HEMORRHAGE
Idiopathic of infancy
Congenital heart disease (including pulmonary hypertension, venoocclusive disease, congestive heart failure)
Prematurity
Cow's milk hyperreactivity (Heiner syndrome)
Goodpasture syndrome
Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis)
Henoch-Schönlein purpura and vasculitic disorders
Granulomatous disease (granulomatosis with polyangiitis)
Celiac disease
Coagulopathy (congenital or acquired)
Malignancy
Immunodeficiency
Exogenous toxins, especially inhaled
Hyperammonemia
Pulmonary hypertension
Pulmonary alveolar proteinosis
Idiopathic pulmonary hemosiderosis
Tuberous sclerosis
Lymphangiomyomatosis or lymphangioleiomyomatosis
Physical injury or abuse
Catamenial

See also Table 435.1 .

Hemorrhage most commonly reflects chronic inflammation and infection such as that seen with bronchiectasis due to cystic fibrosis or with cavitary disease in association with infectious tuberculosis. Hemoptysis may occasionally reflect an acute and intense infectious condition such as bronchitis or bronchopneumonia.

Other relatively common etiologies are congenital heart disease and trauma. Pulmonary hypertension secondary to cardiac disease is a prominent etiology for hemoptysis in those patients without cystic fibrosis. Traumatic irritation or damage in the airway may be accidental in nature. Traumatic injury to the airway and pulmonary contusion may result from motor vehicle crashes or other direct force injuries. Bleeding can also be related to instrumentation or iatrogenic irritation of the airway as is commonly seen in a child with a tracheostomy or a child with repeated suction trauma to the upper airway. Children who have been victims of nonaccidental trauma or deliberate suffocation can also be found to have blood in the mouth or airway (see Chapter 16). Factitious hemoptysis may rarely be encountered in the setting of Factitious Disorder by Proxy (formerly Munchausen's by proxy; see Chapter 16.2).

Rare causes for hemoptysis include tumors and vascular anomalies such as arteriovenous malformations (Fig. 436.2). Congenital vascular malformations in the lung may also be associated with **hereditary hemorrhagic telangiectasia** . Tumors must be cautiously investigated when encountered with a flexible fiberoptic bronchoscope as bleeding may be massive and difficult to control.

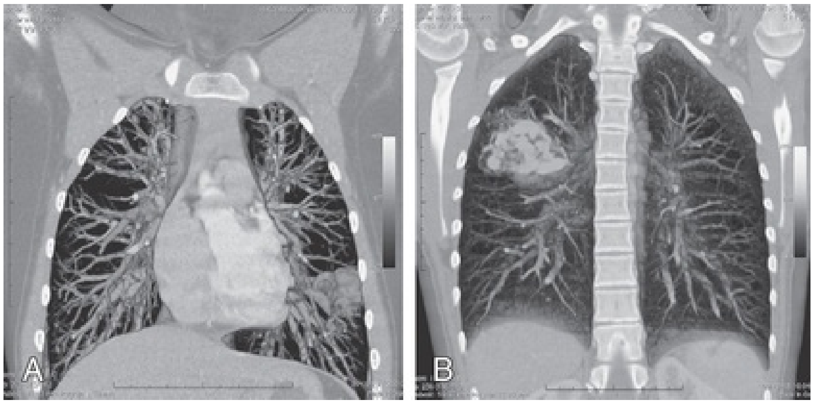

FIG. 436.2 **A,** Volume-rendering reconstruction of the contrast-enhanced spiral CT showing a large arteriovenous fistula in the left upper lobe (lingula). **B,** Volume-rendering reconstruction of the contrast-enhanced spiral CT showing an arteriovenous fistula in the right upper lobe. (From Grzela K, Krenke K, Kulus M: Pulmonary arteriovenous malformations: clinical and radiological presentation, *J Pediatr* 158:856, 2011, Figs. 1 and 2, p. 856.)

Syndromes associated with vasculitic, autoimmune, and idiopathic disorders can be associated with diffuse alveolar hemorrhage (see Chapter 435).

Acute idiopathic pulmonary hemorrhage of infancy is a distinct entity and is described as an episode of pulmonary hemorrhage in a previously healthy infant born at greater than 32 wk of gestation and whose age is less than 1 yr with the following: (1) abrupt or sudden onset of overt bleeding or frank evidence of blood in the airway, (2) severe presentation leading to acute respiratory distress or failure and requiring intensive care and invasive ventilatory support, and (3) diffuse bilateral infiltration on chest radiographs or computed tomography. Prior suggestions of an association between acute idiopathic pulmonary hemorrhage of infancy and toxic mold exposure have not been supported on subsequent review.

Epidemiology

The frequency with which pulmonary hemorrhage occurs in the pediatric population is difficult to define. This difficulty is largely related to the variability in disease presentation. Chronic bronchiectasis as seen in cystic fibrosis (see Chapter 432) or ciliary dyskinesia (see Chapter 433) can cause hemoptysis, but usually occurs in children older than 10 yr of age. The incidence of pulmonary hemorrhage may be significantly underestimated because many children and young adults swallow rather than expectorate mucus, a behavior that may prevent recognition of hemoptysis, the primary presenting symptom of the disorder.

Pathophysiology

Pulmonary hemorrhage can be localized or diffuse. Focal hemorrhage from an isolated bronchial lesion is often secondary to infection or chronic inflammation. Erosion through a chronically inflamed airway into the adjacent bronchial artery is a mechanism for potentially massive hemorrhage. Bleeding from such a lesion is more likely to be bright red, brisk, and secondary to enlarged bronchial arteries and systemic arterial pressures. The severity of more diffuse hemorrhage can be difficult to ascertain. The rate of blood loss may be insufficient to reach the proximal airways. Therefore, the patient may present without hemoptysis. The diagnosis of pulmonary hemorrhage is generally achieved by finding evidence of blood or hemosiderin in the lung. Within 48-72 hr of an episode of bleeding, alveolar macrophages convert the iron from erythrocytes into hemosiderin. It may take weeks to clear these hemosiderin-laden macrophages completely from the alveolar spaces. This fact may allow differentiation between acute and chronic hemorrhage. Hemorrhage is often followed by the influx of neutrophils and other proinflammatory mediators. With repeated or chronic hemorrhage, pulmonary fibrosis can become a prominent pathologic finding.

Clinical Manifestations

The severity of presentation in patients with hemoptysis and pulmonary hemorrhage is highly variable. Older children and young adults with a focal hemorrhage may complain of warmth or a “bubbling” sensation in the chest wall. This can occasionally aid the clinician in locating the area involved. Rapid and large-volume blood loss manifests as symptoms of cyanosis, respiratory distress, and shock. Chronic, subclinical blood loss may manifest as anemia, fatigue, dyspnea, or altered activity tolerance. Less commonly, patients present with persistent infiltrates on chest radiograph or symptoms of chronic illness such as failure to thrive. Pulmonary arteriovenous malformations may present with hemoptysis, hemothorax, a round localized mass on x-ray or CT, clubbing, cyanosis, or embolic phenomenon (central nervous system).

Laboratory Findings and Diagnosis

A patient with suspected hemorrhage should have a laboratory evaluation with complete blood count and coagulation studies. The complete blood count result may demonstrate a microcytic, hypochromic anemia but may be normal early in an acute bleeding episode. If iron stores are sufficient, a reticulocytosis may be present. Other laboratory findings are highly dependent on the underlying diagnosis. A urinalysis may show evidence of nephritis in patients with a comorbid pulmonary renal syndrome. The classic and definitive finding in pulmonary hemorrhage is that of **hemosiderin-laden macrophages** in pulmonary secretions. Hemosiderin-laden macrophages may be detected by sputum analysis with Prussian blue staining when a patient is able to successfully expectorate sputum from the lower airways. In younger children, or in weak or neurodevelopmentally compromised patients unable to expectorate sputum, induced sputum may provide an acceptable specimen; alternatively, a flexible bronchoscopy with **bronchoalveolar lavage** may be required for specimen retrieval.

Chest radiographs may demonstrate fluffy bilateral densities, as seen in acute idiopathic pulmonary hemorrhage of infancy (Fig. 436.3) or the patchy consolidation seen in idiopathic pulmonary hemosiderosis (Fig. 436.4). Alveolar infiltrates seen on chest radiograph may be regarded as a representation of recent bleeding, but their absence does not rule out the occurrence of pulmonary hemorrhage. Infiltrates, when present, are often symmetric and diffuse and may be preferentially located in the perihilar regions and lower lobes. The costophrenic angles and lung apices are frequently spared. CT may be indicated to assess for underlying disease processes.

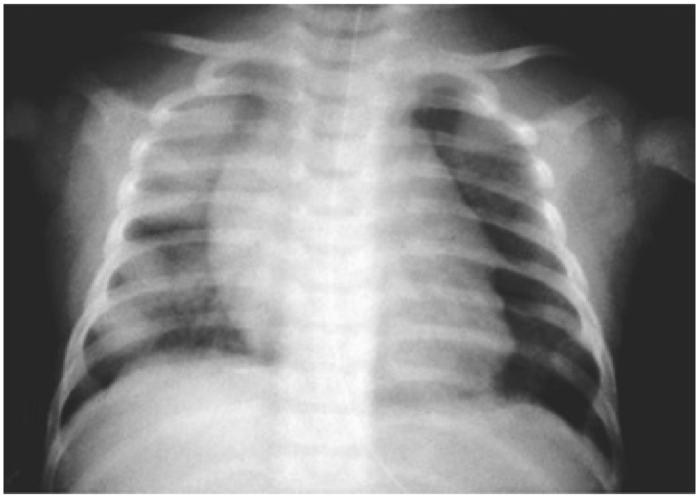

FIG. 436.3 Radiographic appearance of acute idiopathic pulmonary hemorrhage in infancy. (From Brown CM, Redd SC, Damon SA, Centers for Disease Control and Prevention [CDC]: Acute idiopathic pulmonary hemorrhage among infants: recommendations from the Working Group for Investigation and Surveillance, *MMWR Recomm Rep* 53:1–12, 2004.)

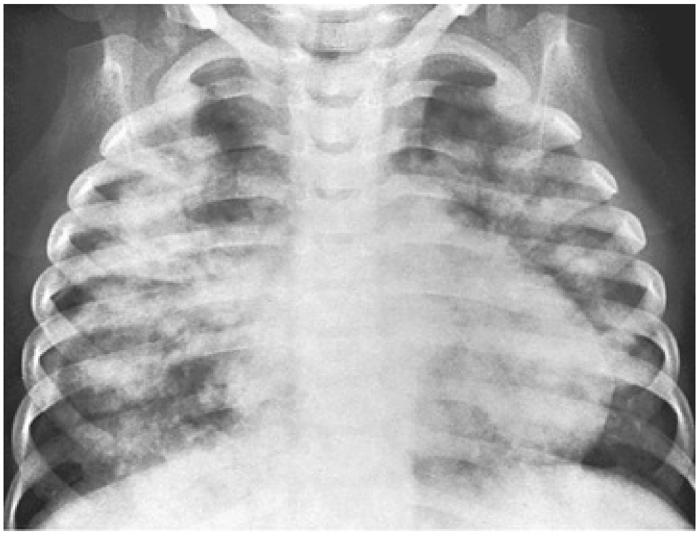

FIG. 436.4 Diffuse pulmonary hemorrhage that was thought to be the result of idiopathic pulmonary hemosiderosis in a 3 yr old boy. Frontal radiograph reveals bilateral airspace consolidation that is patchy. Tracheal washing contained large numbers of macrophages filled with hemosiderin. Ten days later, most of the consolidative changes in the lungs had cleared. The patient's anemia was successfully treated with blood transfusion. (From Slovis T, editor: *Caffey's pediatric diagnostic imaging,* ed 11, Philadelphia, 2008, Mosby/Elsevier; courtesy of Bertram Girdany, MD, Pittsburgh, PA.)

Lung biopsy is rarely necessary unless bleeding is chronic or an etiology cannot be determined with other methods. Pulmonary function testing, including a determination of gas exchange, is important to assess the severity of the ventilatory defect. In older children, spirometry may demonstrate evidence of predominantly obstructive disease in the acute period. Restrictive disease secondary to fibrosis is typically seen with more chronic disease. Diffusion capacity of carbon monoxide measurements are typically elevated in the setting of pulmonary hemorrhage because of the strong affinity of the intra-alveolar hemoglobin for carbon monoxide.

Treatment

In the setting of massive blood loss, volume resuscitation and transfusion of blood products are necessary. Maintenance of adequate ventilation and circulatory function is crucial. Rigid bronchoscopy may be utilized for localization of bleeding and for removal of debris, but active bleeding may be exacerbated by airway manipulation. Flexible bronchoscopy and bronchoalveolar lavage may be required for diagnosis. Ideally, treatment is directed at the specific pathologic process responsible for the hemorrhage. When bronchiectasis is a known entity and a damaged artery can be localized, bronchial artery embolization is often the therapy of choice. If embolization fails, total or partial lobectomy may be required. Embolization is the initial treatment of choice for an arteriovenous malformation. In circumstances of diffuse hemorrhage, corticosteroids and other immunosuppressive agents have been shown to be of benefit. Transcatheter vaso-occlusive embolotherapy with detachable stainless-steel coils or other occlusive devices is the treatment of choice for pulmonary arteriovenous malformation (pulmonary AVM). Prognosis depends largely on the underlying disease process and the chronicity of bleeding.

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CHAPTER 437

Atelectasis

Ranna A. Rozenfeld

Atelectasis is the incomplete expansion or complete collapse of air-bearing tissue, resulting from obstruction of air intake into the alveolar sacs. Segmental, lobar, or whole lung collapse is associated with the absorption of air contained in the alveoli, which are no longer ventilated.

Pathophysiology

The causes of atelectasis can be divided into 5 groups (Table 437.1). Respiratory syncytial virus (see Chapter 287) and other viral infections, including influenza viruses in young children can cause multiple areas of atelectasis. Mucous plugs are a common predisposing factor to atelectasis. Massive collapse of one or both lungs is most often a postoperative complication but occasionally results from other causes, such as trauma, asthma, pneumonia, tension pneumothorax (see Chapter 439), aspiration of foreign material (see Chapters 414 and 425), paralysis, or after extubation. Massive atelectasis is usually produced by a combination of factors, including immobilization or decreased use of the diaphragm and the respiratory muscles, obstruction of the bronchial tree, and abolition of the cough reflex.

Table 437.1

Anatomic Causes of Atelectasis

CAUSE	CLINICAL EXAMPLES
External compression on the pulmonary parenchyma	Pleural effusion, pneumothorax, intrathoracic tumors, diaphragmatic hernia
Endobronchial obstruction completely obstructing the	Enlarged lymph node, tumor, cardiac enlargement, foreign body, mucoid plug, broncholithiasis

ingress of air	
Intraluminal obstruction of a bronchus	Foreign body, asthma, granulomatous tissue, tumor, secretions including mucous plugs, bronchiectasis, pulmonary abscess, chronic bronchitis, acute laryngotracheobronchitis, plastic bronchitis
Intrabronchiolar obstruction	Bronchiolitis, interstitial pneumonitis, asthma
Respiratory compromise or paralysis	Neuromuscular abnormalities, osseous deformities, overly restrictive casts and surgical dressings, defective movement of the diaphragm, or restriction of respiratory effort

Clinical Manifestations

Symptoms vary with the cause and extent of the atelectasis. A small area is likely to be asymptomatic. When a large area of previously normal lung becomes atelectatic, especially when it does so suddenly, dyspnea accompanied by rapid shallow respirations, tachycardia, cough, and often cyanosis occurs. If the obstruction is removed, the symptoms disappear rapidly. Although it was once believed that atelectasis alone can cause fever, studies have shown no association between atelectasis and fever. Physical findings include limitation of chest excursion, decreased breath sound intensity, and coarse crackles. Breath sounds are decreased or absent over extensive atelectatic areas.

Massive pulmonary atelectasis usually presents with dyspnea, cyanosis, and tachycardia. An affected child is extremely anxious and, if old enough, complains of chest pain. The chest appears flat on the affected side, where decreased respiratory excursion, dullness to percussion, and feeble or absent breath sounds are also noted. Postoperative atelectasis usually manifests within 24 hr of operation but may not occur for several days.

Acute lobar collapse is a frequent occurrence in patients receiving intensive care. If undetected, it can lead to impaired gas exchange, secondary infection, and subsequent pulmonary fibrosis. Initially, hypoxemia may result from ventilation-perfusion mismatch. In contrast to atelectasis in adult patients, in whom the lower lobes and, in particular, the left lower lobe are most often involved, 90% of cases in children involve the upper lobes and 63% involve the right upper lobe. There is also a high incidence of upper lobe atelectasis and, especially, right upper lobe collapse in patients with atelectasis being treated in neonatal intensive care units. This high incidence may be a result of movement of the endotracheal tube into the right mainstem bronchus, where it obstructs or causes inflammation of the bronchus to the right upper lobe.

Diagnosis

The diagnosis of atelectasis can usually be established by chest radiograph. Typical findings include volume loss and displacement of fissures. Atypical presentations include atelectasis manifesting as a mass-like opacity and atelectasis in an unusual location. Lobar atelectasis may be associated with pneumothorax.

In asthmatic children, chest radiography demonstrates an abnormality rate of 44%, compared with a thorax high-resolution CT scan abnormality rate of 75%. Children with asthma and atelectasis have an increased incidence of right middle lobe syndrome, acute asthma exacerbations, pneumonia, and upper airway infections.

In foreign-body aspiration, atelectasis is one of the most common radiographic findings. The site of atelectasis usually indicates the site of the foreign body (see Chapter 405.1). Atelectasis is more common when diagnosis of foreign-body aspiration is delayed for greater than 2 wk. Bronchoscopic examination reveals a collapsed main bronchus when the obstruction is at the tracheobronchial junction and may also disclose the nature of the obstruction.

Massive pulmonary atelectasis is generally diagnosed on chest radiograph. Typical findings include elevation of the diaphragm, narrowing of the intercostal spaces, and displacement of the mediastinal structures and heart toward the affected side (Fig. 437.1).

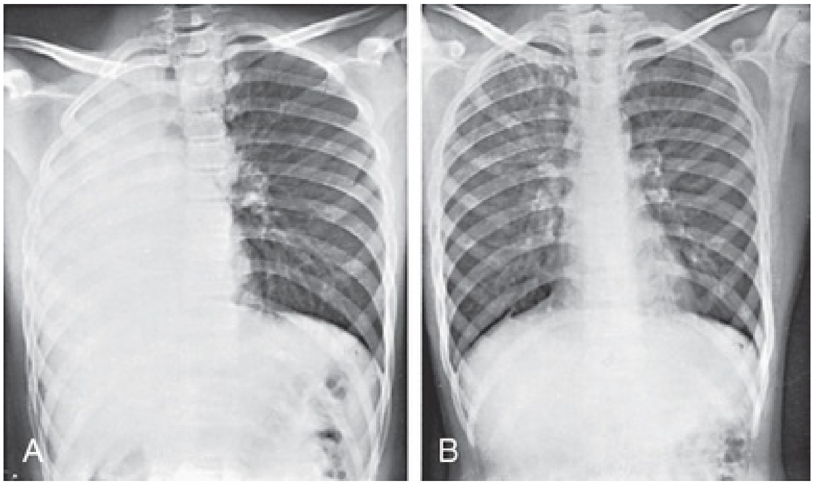

FIG. 437.1 **A,** Massive atelectasis of the right lung. The patient has asthma. The heart and other mediastinal structures shift to the right during the atelectatic phase. **B,** Comparison study after reaeration subsequent to

bronchoscopic removal of a mucous plug from the right mainstem bronchus.

Treatment

Treatment depends on the cause of the collapse (Table 437.2). If effusion or pneumothorax is responsible, the external compression must first be removed. Often vigorous efforts at cough, deep breathing, and percussion will facilitate expansion. Aspiration with sterile tracheal catheters may facilitate removal of mucous plugs. Continuous positive airway pressure may improve atelectasis.

Table 437.2

Treatment for Atelectasis

CAUSE OF ATELECTASIS	TREATMENT
Pleural effusion or pneumothorax	Relieve compression
Mucus plug	Tracheal or bronchoscopic aspiration Continuous positive airway pressure
Foreign body	Bronchoscopic examination
Asthma	Bronchodilator and corticosteroid treatment Recombinant human deoxyribonuclease (off label use) Hypertonic saline with or without bronchodilator
Neuromuscular diseases	Intermittent positive pressure breathing Mechanical insufflator–exsufflator Noninvasive bi-level positive pressure ventilation
Cystic fibrosis	Airway clearance therapies Hypertonic saline with or without bronchodilator

Bronchoscopic examination is immediately indicated if atelectasis is the result of a foreign body or any other bronchial obstruction that can be relieved. For bilateral atelectasis, bronchoscopic aspiration should also be performed immediately. It is also indicated when an isolated area of atelectasis persists for several weeks. If no anatomic basis for atelectasis is found and no material can be obtained by suctioning, the introduction of a small amount of saline followed by suctioning allows recovery of bronchial secretions for culture and, possibly, for cytologic examination. Frequent changes in the child's position, deep breathing, and chest physiotherapy may be beneficial. Intrapulmonary percussive ventilation is a chest physiotherapy technique that is safe and effective. Oxygen therapy is indicated when there is dyspnea or desaturation. Intermittent positive-pressure breathing and incentive spirometry are recommended when atelectasis does not improve after chest physiotherapy.

In some conditions, such as asthma, bronchodilator and corticosteroid treatment may accelerate atelectasis clearance. Recombinant human deoxyribonuclease, which is approved only for the treatment of cystic fibrosis, has been used off-label for patients without cystic fibrosis who have persistent atelectasis. This product reduces the viscosity of purulent bronchial debris. In patients with acute severe asthma, diffuse airway plugging with thick viscous secretions frequently occurs, with the resulting atelectasis often refractory to conventional therapy. Recombinant human deoxyribonuclease is used in both nebulized form for nonintubated patients with acute asthma as well as intratracheally for atelectasis in intubated asthmatics, with resolution of atelectasis unresponsive to conventional asthma therapies. Recombinant human deoxyribonuclease is also used in ventilated infants and children with atelectasis not caused by asthma.

Hypertonic saline solution increases mucociliary clearance in patients with asthma, bronchiectasis, and cystic fibrosis and infants with acute bronchiolitis. It is delivered via nebulization either via face mask or endotracheal tube. It can be delivered alone or in combination with a bronchodilator. This therapy is being used in the outpatient and inpatient setting, as well as in both the neonatal intensive care unit and the pediatric intensive care unit, to help facilitate airway clearance, though studies of its use in bronchiolitis have had mixed results (see Chapter 418.1).

Lobar atelectasis in cystic fibrosis is discussed in Chapter 432 .

Atelectasis can occur in patients with neuromuscular diseases. These patients tend to have ineffective cough and difficulty expelling respiratory tract secretions, which lead to pneumonia and atelectasis. Several devices and treatments are available to assist these patients, including intermittent positive-pressure breathing, a mechanical insufflator–exsufflator, and noninvasive bi-level positive-pressure ventilation via nasal mask or full-face mask. Patients with neuromuscular disease who have undergone surgery are at substantial risk for postoperative atelectasis and subsequent pneumonia. Migrating atelectasis in the newborn infant, a rare and unique presentation, may be secondary to neuromuscular disease.

There is an association between the development of lobar collapse and the requirement for mechanical ventilation. Although lobar collapse is rarely a cause of long-term morbidity, its occurrence may necessitate the prolongation of mechanical ventilation or re-intubation. In ventilated patients, positive-end expiratory pressure or continuous positive airway pressure is generally indicated.

Airway clearance therapies used for adults are often recommended and/or used in pediatric populations. However, given the differences in respiratory physiology and anatomy between children and adults, practices applicable to one may or may not apply to the other. Atelectasis caused by cystic fibrosis is the only pediatric entity that clearly benefits from airway clearance therapy, although atelectasis caused by neuromuscular disease, cerebral palsy, or mechanical ventilation probably benefits from such therapy. Thus far no specific airway clearance therapy has been demonstrated to be superior.

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CHAPTER 438

Pulmonary Tumors

Susanna A. McColley

Etiology

Primary tumors of the lung are rare in children and adolescents. An accurate estimate of frequency is currently not possible because the literature is composed of case reports and case series. A high incidence of "inflammatory pseudotumors" further clouds the statistics. Bronchial adenomas (including bronchial carcinoid, adenoid cystic carcinoma, and mucoepidermoid carcinomas) are the most common primary tumors; bronchial carcinoid tumors represent ~80%. Carcinoids are low-grade malignancies; carcinoid syndrome is rare in children. Metastatic lesions are the most common forms of pulmonary malignancy in children; primary processes include Wilms tumor, osteogenic sarcoma, and hepatoblastoma (see Part XXI: Cancer and Benign Tumors). Adenocarcinoma and undifferentiated histology are the most common pathologic findings in primary lung cancer; pulmonary blastoma is rarer and frequently occurs in the setting of cystic lung disease. Mediastinal involvement with lymphoma is more common than primary pulmonary malignancies.

Clinical Manifestations and Evaluation

Pulmonary tumors may manifest as fever, hemoptysis, wheezing, cough, pleural effusion, chest pain, dyspnea, or recurrent or persistent pneumonia or atelectasis. Localized wheezing, and wheezing unresponsive to bronchodilators, can occur with bronchial tumors. Tumors may be suspected from plain chest radiographs; CT scanning of the chest is necessary for precise anatomic definition (Fig. 438.1). Depending on the tumor size and location, pulmonary function tests may be normal or show an obstructive, restrictive, or mixed pattern; as with the physical exam, there is no responsiveness to bronchodilators. Bronchial tumors are occasionally diagnosed during fiberoptic bronchoscopy performed for persistent or recurrent pulmonary infiltrates or for hemoptysis.

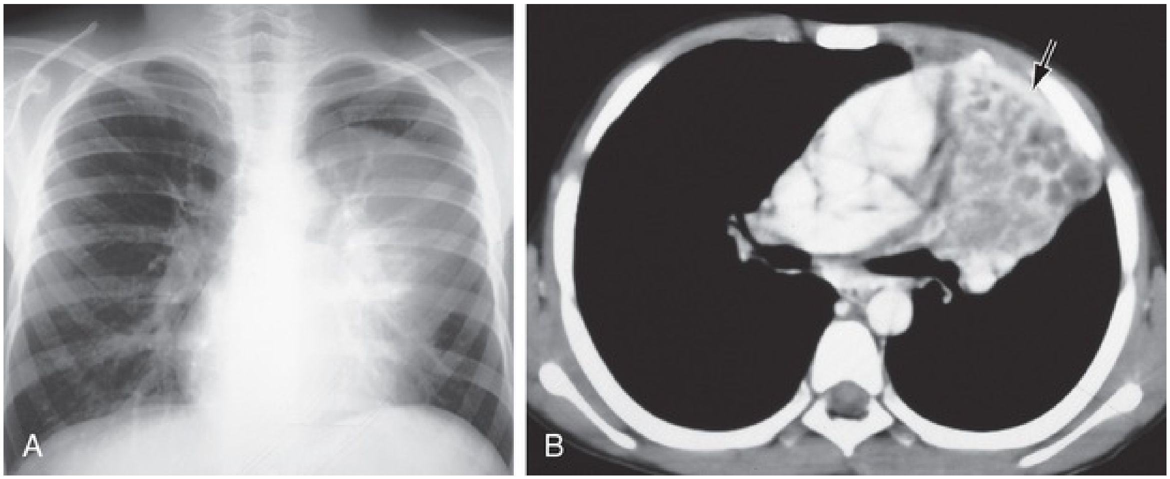

FIG. 438.1 Endobronchial mucoepidermoid carcinoma in a 10 yr old boy who presented with cough and fever. **A,** The chest radiograph shows a left upper lobe mass, a hyperinflated left lower lobe, and a prominent left hilum. **B,** The CT scan shows complete obstruction of the left upper lobe bronchus by a low-attenuation mass *(arrow)* that extends into the left mainstem bronchus. (From Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, Fig. 78-20.)

Patients with symptoms or with radiographic or other laboratory findings suggesting pulmonary malignancy should be evaluated carefully for a tumor at another site before surgical excision is carried out. Isolated primary lesions and isolated metastatic lesions discovered long after the primary tumor has been removed are best treated by excision. The prognosis varies and depends on the type of tumor involved; outcomes for inflammatory pseudotumors and primary pulmonary carcinoid tumors treated with resection are good.

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CHAPTER 439

Pneumothorax

Glenna B. Winnie, Suraiya K. Haider, Aarthi P. Vemana, Steven V. Lossef

Pneumothorax is the accumulation of extrapulmonary air within the chest, most commonly from leakage of air from within the lung. Air leaks can be primary or secondary and can be spontaneous, traumatic, iatrogenic, or catamenial (Table 439.1). Pneumothorax in the neonatal period is also discussed in Chapter 122.1 .

Table 439.1

Causes of Pneumothorax in Children

SPONTANEOUS
Primary Idiopathic (no underlying lung disease)
Spontaneous rupture of subpleural blebs
Secondary (underlying lung disease)
Congenital lung disease
• Congenital cystic adenomatoid malformation
• Bronchogenic cysts
• Pulmonary hypoplasia
• Birt-Hogg-Dube syndrome
Conditions associated with increased intrathoracic pressure
• Asthma
• Bronchiolitis
• Cystic fibrosis
• Airway foreign body
• Smoking (cigarettes, marijuana, crack cocaine)
Infection
• Tuberculosis
• *Pneumocystis carinii (jirovecii)*
• Echinococcosis
• Pneumatocele
• Lung abscess
• Bronchopleural fistula
Lung disease
• Langerhans cell histiocytosis
• Tuberous sclerosis
• Marfan syndrome
• Ehlers-Danlos syndrome

• Pulmonary fibrosis • Sarcoidosis • Rheumatoid arthritis, scleroderma, ankylosing spondylitis • Metastatic neoplasm—usually osteosarcoma (rare) • Pulmonary blastoma
TRAUMATIC
Non-iatrogenic • Penetrating trauma • Blunt trauma **Iatrogenic** • Thoracotomy • Thoracoscopy, thoracentesis • Tracheostomy • Tube or needle puncture • Mechanical ventilation • High-flow therapy (moved from non-iatrogenic)

Adapted from Noppen M. Spontaneous pneumothorax:epidemiology, pathophysiology and cause. *Eur Respir Rev* 19:117, 217–219, 2010 (Table 1, 2, p 218).

Etiology and Epidemiology

A **primary spontaneous pneumothorax** occurs without trauma or underlying lung disease. Spontaneous pneumothorax with or without exertion occurs occasionally in teenagers and young adults, most frequently in males who are tall, thin, and thought to have subpleural blebs. Smoking and asthma are also risk factors for developing pneumothorax. Familial cases of spontaneous pneumothorax occur and have been associated with mutations in the folliculin gene *(FCLN)* . Over 150 unique *FCLN* mutations have been associated in the Birt-Hogg-Dube syndrome (skin fibrofolliculomas, multiple basal lung cysts, renal malignancies) or in patients with familial or recurrent spontaneous pneumothoraces. Individuals with other inherited disorders such as α_1 -antitrypsin (see Chapter 421) and homocystinuria are also predisposed to pneumothorax. Patients with collagen synthesis defects such as Ehlers-Danlos disease (see Chapter 678) and Marfan syndrome (see Chapter 722) are at increased risk for the development of pneumothorax.

A pneumothorax arising as a complication of an underlying lung disorder but without trauma is a **secondary spontaneous pneumothorax.** Pneumothorax can occur in pneumonia, usually with empyema; it can also be secondary to pulmonary abscess, gangrene, infarct, rupture of a cyst or an emphysematous bleb (in asthma), or foreign bodies in the lung. In infants with staphylococcal pneumonia, the incidence of pneumothorax is relatively high. It can be found in children hospitalized with asthma exacerbations, and usually resolves without treatment. Pneumothorax is a serious complication in cystic fibrosis (see Chapter 432). Pneumothorax also occurs in patients with lymphoma or other malignancies, and in graft-versus-host disease with bronchiolitis obliterans.

External chest or abdominal blunt or penetrating trauma can tear a bronchus or abdominal viscus, with leakage of air into the pleural space. Ecstasy (methylenedioxymethamphetamine), crack cocaine, and marijuana abuse are associated with pneumothorax.

Iatrogenic pneumothorax can complicate transthoracic needle aspiration, tracheotomy, subclavian line placement, thoracentesis, or transbronchial biopsy. It may occur during mechanical or noninvasive ventilation, high-flow nasal cannula therapy, acupuncture, and other diagnostic or therapeutic procedures.

Catamenial pneumothorax, an unusual condition that is related to menses, is associated with diaphragmatic defects and pleural blebs.

Pneumothorax can be associated with a serous effusion (hydropneumothorax), a purulent effusion (pyopneumothorax), or blood (hemopneumothorax). Bilateral pneumothorax is rare after the neonatal period but has been reported after lung transplantation and with *Mycoplasma pneumoniae* infection and tuberculosis.

Pathogenesis

The tendency of the lung to collapse, or elastic recoil, is balanced in the normal resting state by the inherent tendency of the chest wall to expand outward, creating negative pressure in the intrapleural space. When air enters the pleural space, the lung collapses. Hypoxemia occurs because of alveolar hypoventilation, ventilation–perfusion mismatch, and intrapulmonary shunt. In simple pneumothorax, intrapleural pressure is atmospheric, and the lung collapses up to 30%. In **tension pneumothorax** , continuing leak causes increasing positive pressure in the pleural space, with further compression of the lung, shift of mediastinal structures toward the contralateral side, and decreases in venous return and cardiac output causing hemodynamic instability.

Clinical Manifestations

The onset of pneumothorax is usually abrupt, and the severity of symptoms depends on the extent of the lung collapse and on the amount of preexisting lung disease. Pneumothorax may cause dyspnea, chest pain, and cyanosis. When it occurs in infancy, symptoms and physical signs may be difficult to recognize. Moderate pneumothorax may cause little displacement of the intrathoracic organs and few or no symptoms. The severity of pain usually does not directly reflect the extent of the collapse.

Usually, there is respiratory distress, with retractions, markedly decreased breath sounds, and a tympanitic percussion note over the involved hemithorax. The larynx, trachea, and heart may be shifted toward the unaffected side. When fluid is present, there is usually a sharply limited area of tympany above a level of flatness to percussion. The presence of bronchial breath sounds or, when fluid is present in the pleural cavity, of gurgling sounds synchronous with respirations suggests an open fistula connecting with air-containing tissues.

Diagnosis and Differential Diagnosis

The diagnosis of pneumothorax is usually established by radiographic examination (Figs. 439.1 to 439.6). The amount of air outside the lung varies with time. A radiograph that is taken early shows less lung collapse than one taken later if the leak continues. Expiratory views accentuate the contrast between lung markings and the clear area of the pneumothorax (see Fig. 439.1). Variations exist in the measurement techniques defining the size of a pneumothorax. A large pneumothorax is measured by The American College of Chest Physicians as ≥3 cm from the lung apex to the thoracic cupola, and by the British Thoracic Society as ≥2 cm from the lung margin to the chest wall at the level of the hilum.

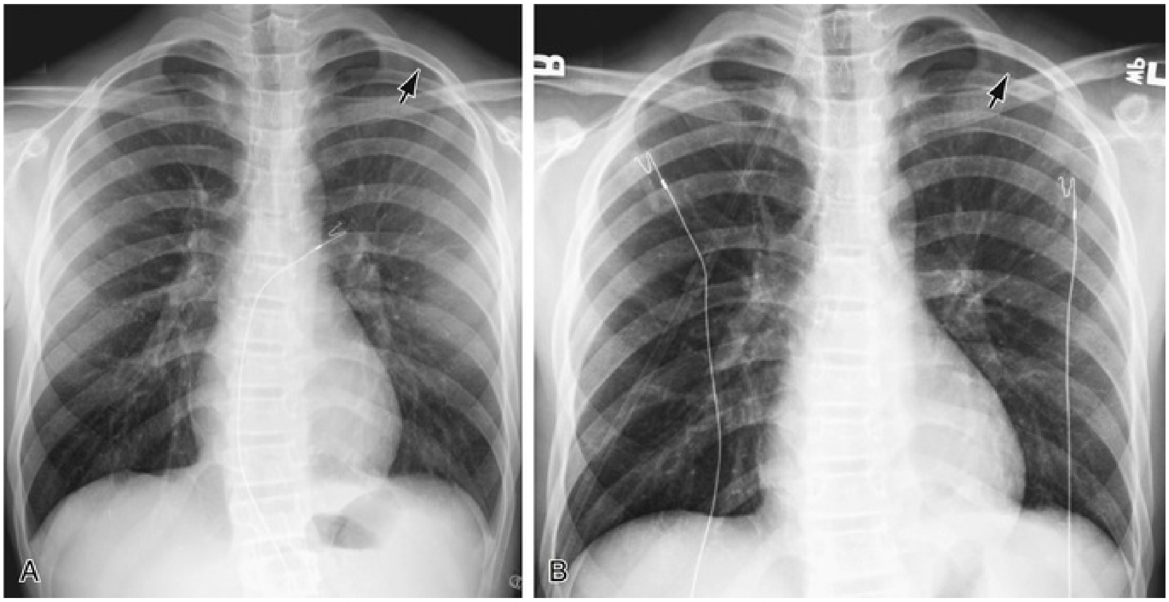

FIG. 439.1 Utility of an expiratory film in detection of a small pneumothorax. **A,** Teenage boy with stab wound and subtle radiolucency in the left apical region *(arrow)* on inspiratory chest radiograph. The margin of the visceral pleura is very faintly visible. **B,** On an expiratory film, the pneumothorax *(arrow)* is more obvious as the right lung has deflated and become more opaque, providing better contrast with the air in the pleural space.

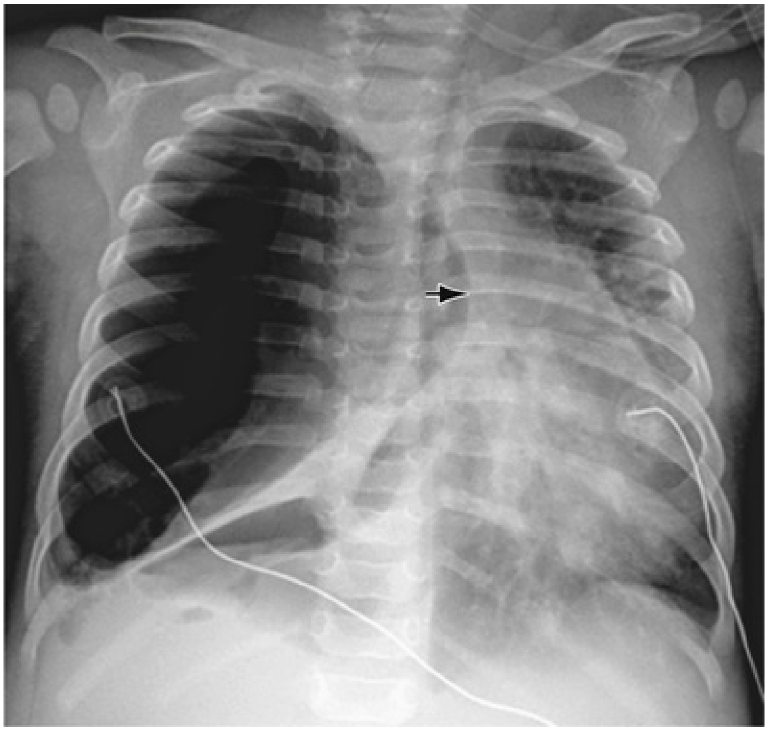

FIG. 439.2 Right pneumothorax, with lung collapse of a compliant lung. Shift of the mediastinum to the left *(arrow)* indicates that this is a tension pneumothorax.

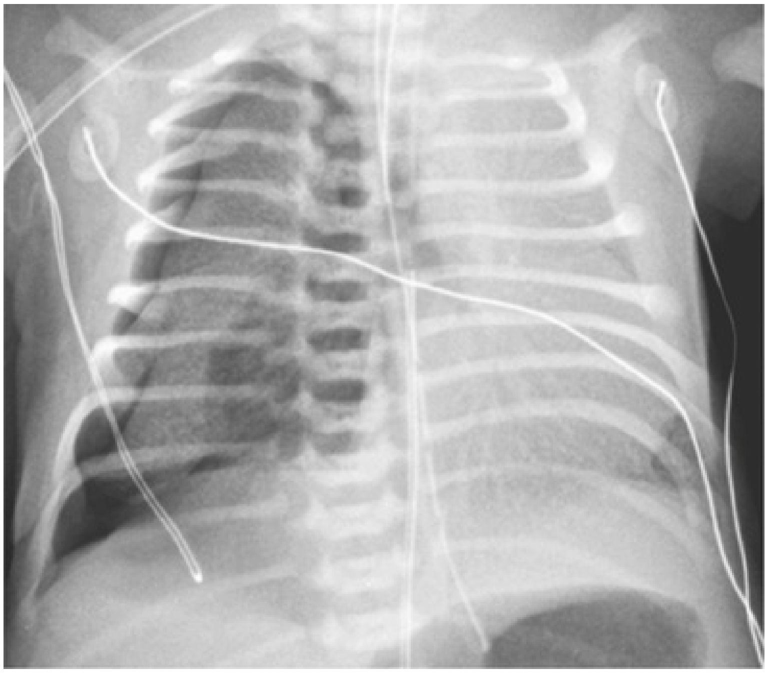

FIG. 439.3 Right pneumothorax, with only limited collapse of a poorly

compliant lung.

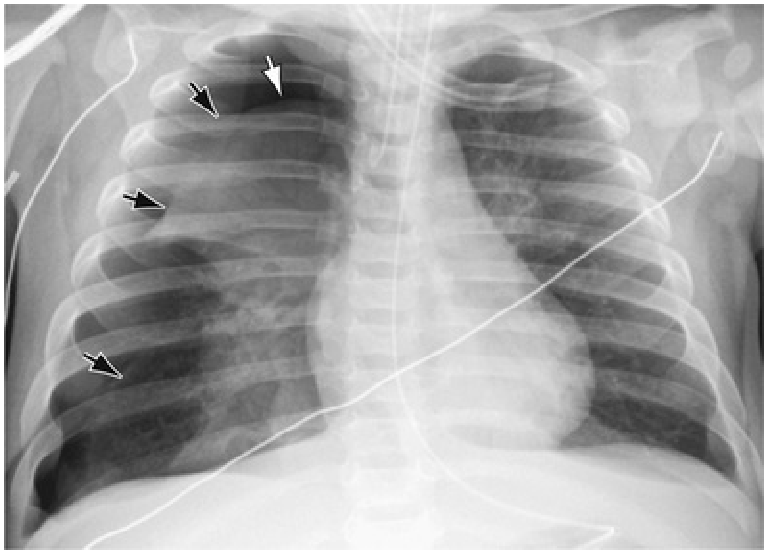

FIG. 439.4 Pneumothorax, with collapse of right lung *(arrows)* caused by barotrauma in a 7 mo old child who was intubated for respiratory failure.

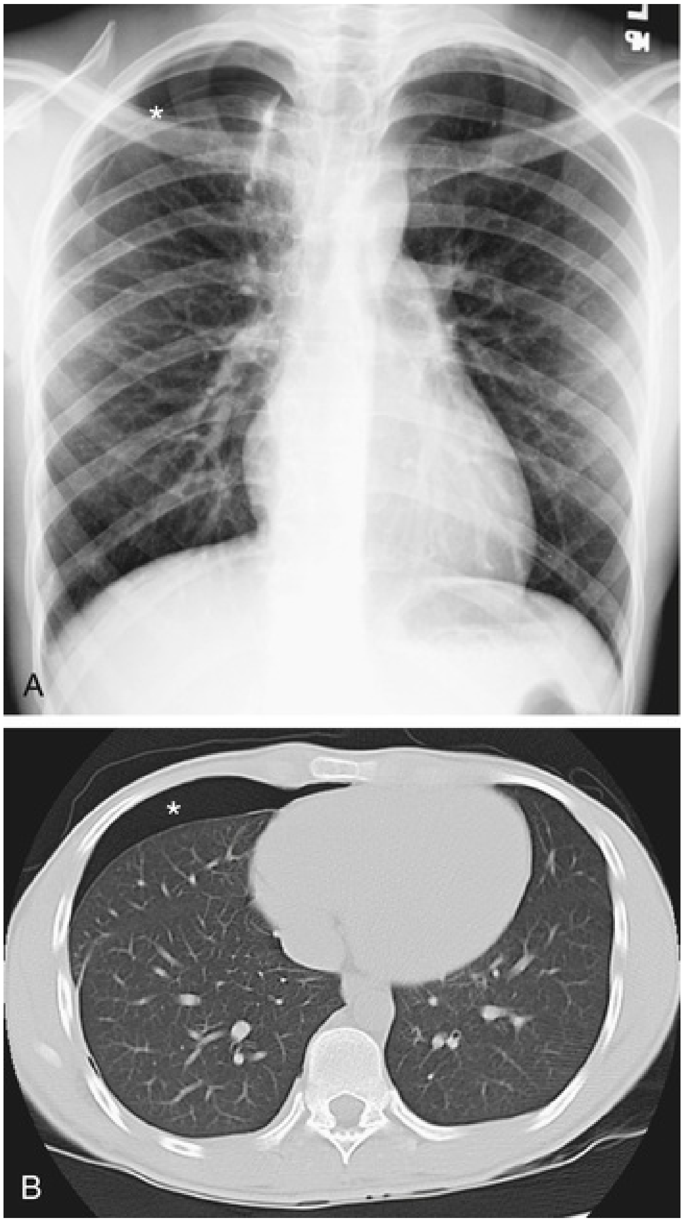

FIG. 439.5 Teenager in whom a spontaneous right pneumothorax developed because of a bleb. He had a persistent air leak despite recent surgical resection of the causative apical bleb. Chest radiograph **(A)** and CT scan **(B)** clearly show the persistent pneumothorax *(asterisk).*

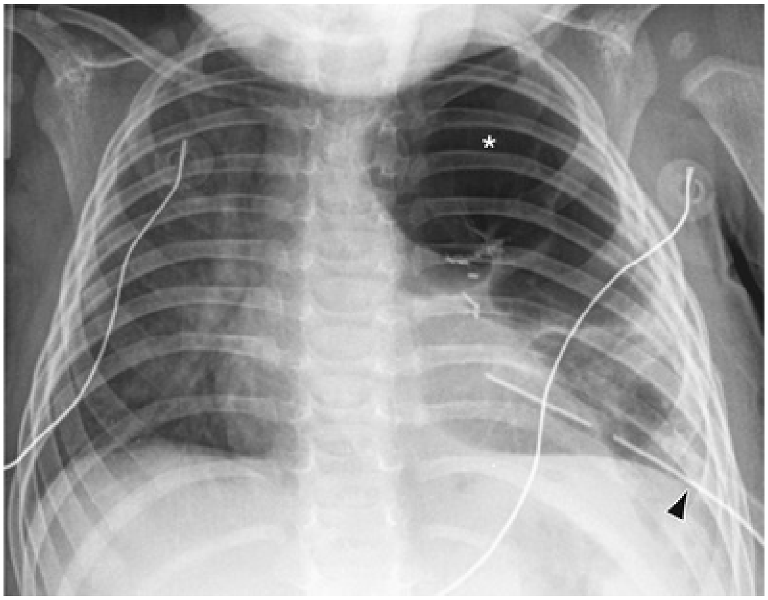

FIG. 439.6 Bronchopleural fistula following surgical resection of the left upper lobe as a result of congenital lobar emphysema. Chest radiograph shows localized pneumothorax *(asterisk)* that persisted despite prior insertion of a large-bore chest tube *(arrowhead)* .

It may be difficult to determine whether a pneumothorax is under tension. Tension pneumothorax is present when there is a shift of mediastinal structures away from the side of the air leak. A shift may be absent in situations in which the other hemithorax resists the shift, such as in the case of bilateral pneumothorax. On occasion, the diagnosis of tension pneumothorax is made only on the basis of evidence of circulatory compromise or on hearing a "hiss" of rapid exit of air under tension with the insertion of the thoracostomy tube. When the lungs are both stiff, such as in cystic fibrosis or respiratory distress syndrome, the unaffected lung may not collapse easily, and shift may not occur (see Fig. 439.3).

Pneumothorax must be differentiated from localized or generalized emphysema, an extensive emphysematous bleb, large pulmonary cavities or other cystic formations, diaphragmatic hernia, compensatory overexpansion with contralateral atelectasis, and gaseous distention of the stomach. In most cases, chest radiography or CT differentiates among these possibilities. In addition, CT may identify underlying pathology such as blebs (Fig. 439.7). Further evaluation to determine if a diaphragmatic hernia is present should include a barium swallow with a small amount of barium to demonstrate that it is not free air but is a portion of the gastrointestinal tract that is in the thoracic cavity (Chapter 122.10). Ultrasound can also be used to establish the diagnosis.

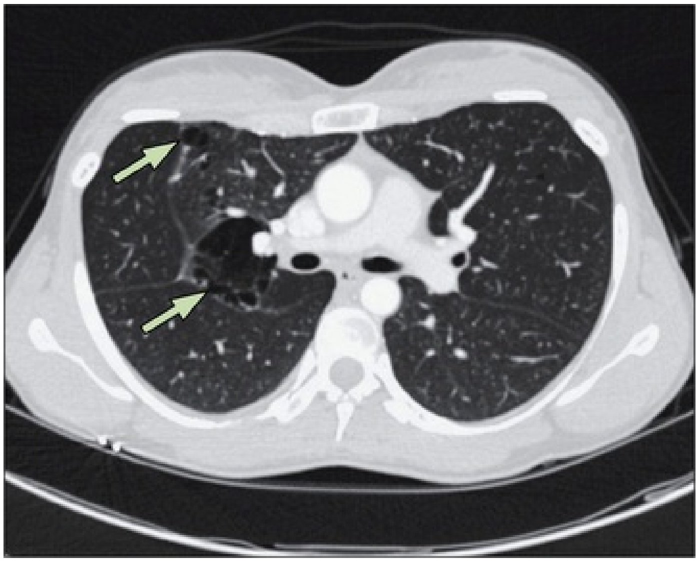

FIG. 439.7 High-resolution CT thorax showing multiple basal cysts. (From Hopkins TG, Maher ER, Reid E, Marciniak S: Recurrent pneumothorax, *Lancet* 377:1624, 2011, Fig. 1, p. 1624.)

Treatment

Therapy varies with the extent of the collapse and the nature and severity of the underlying disease. A small or even moderate-sized pneumothorax in an otherwise normal child may resolve without specific treatment, usually within 1 wk. A small pneumothorax complicating asthma may also resolve spontaneously. Administering 100% oxygen may hasten resolution, but patients with chronic hypoxemia should be monitored closely during administration of supplemental oxygen. Pleural pain deserves analgesic treatment. Needle aspiration into the second intercostal space in the midclavicular line may be required on an emergency basis for tension pneumothorax and is as effective as tube thoracostomy in the emergency room management of primary spontaneous pneumothorax. If the pneumothorax is recurrent, secondary, or under tension, or there is more than a small collapse, chest tube drainage may be necessary. Pneumothorax-complicating cystic fibrosis frequently recurs, and definitive treatment may be justified with the first episode. Similarly, if pneumothorax complicating malignancy does not improve rapidly with observation, chemical pleurodesis or surgical thoracotomy is often necessary. In cases with severe air leak or bronchopleural fistula, occlusion with an endobronchial balloon has been successful.

Closed thoracotomy (simple insertion of a chest tube) and drainage of the trapped air through a catheter, the external opening of which is kept in a dependent position under water, is adequate to reexpand the lung in most patients; pigtail catheters are frequently used. In the case of recurrent pneumothorax, a sclerosing procedure may be indicated to induce the formation of strong adhesions between the lung and chest wall with the introduction of talc, doxycycline, or iodopovidone into the pleural space (chemical pleurodesis). Open thoracotomy through a limited incision, with plication of blebs, closure of fistula, stripping of the pleura (usually in the apical lung, where the surgeon has direct vision), and basilar pleural abrasion is also an effective treatment for recurrent pneumothorax. Stripping and abrading the pleura leaves raw, inflamed surfaces that heal with sealing adhesions. Postoperative pain is comparable to that with chemical pleurodesis, but the chest tube can usually be removed in 24-48 hr, compared with the usual 72 hr minimum for closed thoracotomy and pleurodesis. Video-assisted thoracoscopic surgery (VATS) is a preferred therapy for blebectomy, pleural stripping, pleural brushing, and instillation of sclerosing agents, with less morbidity than occurs with traditional open thoracotomy. There is risk of recurrence after VATS in the pediatric population, although this is often not related to surgical failure, but rather associated with the formation of new bullae.

Pleural adhesions help prevent recurrent pneumothorax, but they also make subsequent thoracic surgery difficult. When lung transplantation may be a future consideration (e.g., in cystic fibrosis), steps should be taken to avoid, if at all possible, chemical or mechanical pleurodesis. It should also be kept in mind that the longer a chest tube is in place, the greater the chance of pulmonary deterioration, particularly in a patient with cystic fibrosis, in whom strong coughing, deep breathing, and postural drainage are important. These are all difficult to accomplish with a chest tube in place.

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CHAPTER 440

Pneumomediastinum

Glenna B. Winnie, Aarthi P. Vemana, Suraiya K. Haider

Air or gas in the mediastinum is called **pneumomediastinum.**

Etiology

Pneumomediastinum is typically caused by alveolar rupture which can be due to either a spontaneous or traumatic cause. A spontaneous pneumomediastinum can either be primary without an underlying etiology or can occur secondary to an underlying cause. Primary pneumomediastinum can be due to increases in intrathoracic pressure as is seen with a Valsalva maneuver, vomiting, Boerhaave syndrome (esophageal perforation), weightlifting, and choking events. Common causes of secondary pneumomediastinum in children younger than age 7 years are lower respiratory tract infections and asthma exacerbations. Simultaneous pneumothorax is unusual in these patients. Other causes of secondary pneumomediastinum are anorexia nervosa, normal menses, and diabetes mellitus with ketoacidosis. Traumatic causes of pneumomediastinum include both iatrogenic (dental extractions, adenotonsillectomy, high flow nasal cannula therapy, esophageal perforation, and inhalation of helium gas), and non-iatrogenic (inhaled foreign body, penetrating chest trauma, and illicit drug use).

Pathogenesis

According to the **Macklin effect** , after an intrapulmonary alveolar rupture, air dissects along the pressure gradient through the perivascular sheaths and other soft tissue planes toward the hilum and enters the mediastinum.

Clinical Manifestations

Dyspnea and transient stabbing chest pain that may radiate to the neck are the principal features of pneumomediastinum. Other symptoms may be present and may include globus pharyngeus, abdominal pain, cough, chest tightness, facial swelling, choking, tachypnea, fever, stridor, and sore throat. Pneumomediastinum is difficult to detect by physical examination alone. Subcutaneous emphysema is present in the majority of patients. When present, **Hamman sign** (a mediastinal "crunch") is nearly pathognomonic for pneumomediastinum. Cardiac dullness to percussion may be decreased, but the chests of many patients with pneumomediastinum are chronically overinflated and it is unlikely that the clinician can be sure of this finding.

Laboratory Findings

Chest radiography reveals mediastinal air, with a more distinct cardiac border than normal (Figs. 440.1 and 440.2). A "spinnaker sail sign" or "angel wing sign" occurs when air deviates the thymus upward and outward, which is seen more often in pediatric patients. On the lateral projection, the posterior mediastinal structures are clearly defined, there may be a lucent ring ("ring sign") around the right pulmonary artery, and retrosternal air can usually be seen. Vertical streaks of air in the mediastinum and subcutaneous air are often observed (see Fig. 440.1). If a pneumomediastinum is clinically suspected, but is not visualized on a chest x-ray, a chest CT can be performed to provide further radiologic evidence.

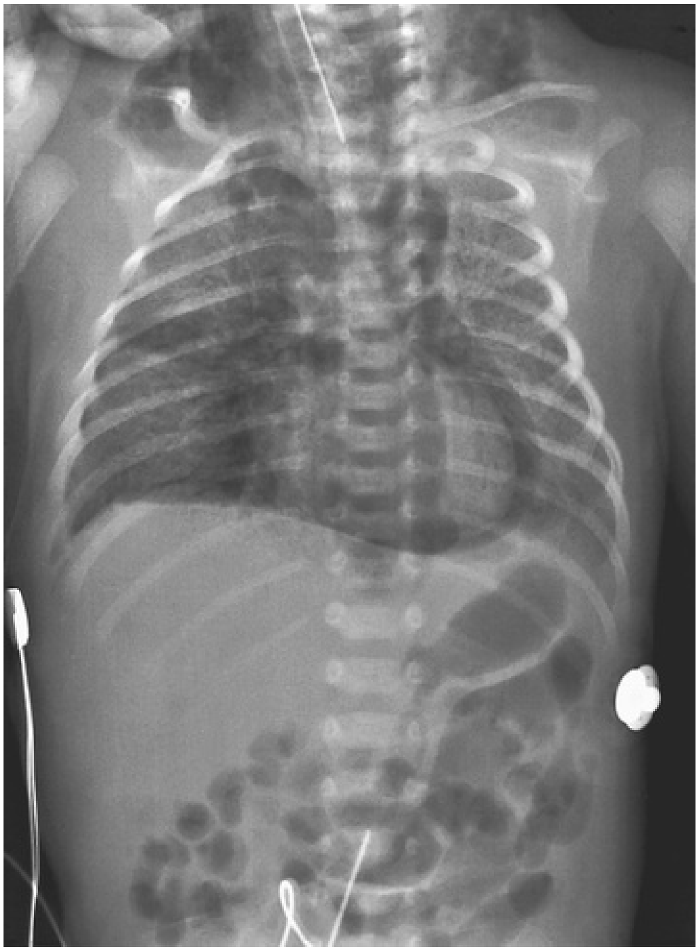

FIG. 440.1 Large pneumomediastinum surrounding the heart and dissecting into the neck. (From Clark DA: *Atlas of neonatology* , ed 7, Philadelphia, 2000, WB Saunders.)

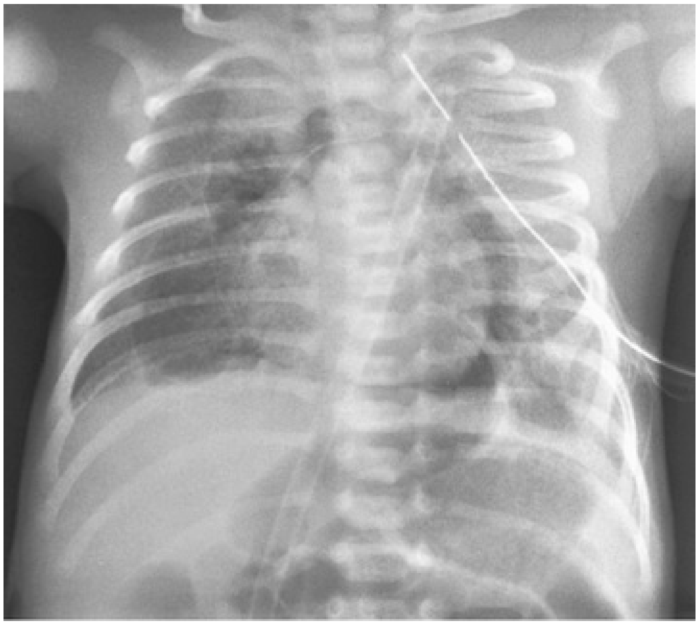

FIG. 440.2 Sail sign—thymic elevation. (From Clark DA: *Atlas of neonatology* , ed 7, Philadelphia, 2000, WB Saunders, p. 94.)

Treatment

Treatment is directed primarily at the underlying obstructive pulmonary disease or other precipitating condition. Children who have had pneumomediastinum should be screened for asthma. Analgesics are occasionally needed for chest pain. Children can be observed in the emergency room and discharged if stable. They should be cautioned to avoid heavy lifting and the Valsalva maneuver. Hospital admission with supplemental oxygen administration is more common for patients with secondary pneumomediastinum. Rarely, subcutaneous emphysema can cause sufficient tracheal compression to justify tracheotomy; the tracheotomy also decompresses the mediastinum.

Complications

Pneumomediastinum is rarely a major problem in older children because the mediastinum can be depressurized by escape of air into the neck or abdomen. In the newborn, however, the rate at which air can leave the mediastinum is limited, and pneumomediastinum can lead to dangerous cardiovascular compromise or pneumothorax (see Chapters 122.14 and 439).

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CHAPTER 441

Hydrothorax

Glenna B. Winnie, Aarthi P. Vemana, Suraiya K. Haider

Hydrothorax is a transudative pleural effusion; typically, it is caused by abnormal pressure gradients in the lung.

Etiology

Hydrothorax is most often associated with cardiac, renal, or hepatic disease. It can also be a manifestation of severe nutritional edema and hypoalbuminemia. Rarely, it results from superior vena cava obstruction by neoplasms, enlarged lymph nodes, pulmonary embolism, or adhesions. It may occur from a ventriculoperitoneal shunt, central venous catheter, or peritoneal dialysis.

Clinical Manifestations

Hydrothorax is usually bilateral, but in cardiac or hepatic disease it can be limited to the right side or greater on the right than on the left side. The physical signs are the same as those described for serofibrinous pleurisy (see Chapter 429.2), but in hydrothorax there is more rapid shifting of the level of dullness with changes of position. Depending on the etiology, it can be associated with an accumulation of fluid in other parts of the body.

Laboratory Findings

The fluid is **transudative** , noninflammatory, has few cells, and has a lower specific gravity (<1.015) than that of a serofibrinous exudate (see Chapters 428 and 429). The ratio of pleural fluid to serum total protein is <0.5, the ratio of pleural fluid to serum lactic dehydrogenase is <0.6, and the pleural fluid lactic dehydrogenase value is less than 66% of the upper limit of the normal serum lactic dehydrogenase range. In a patient with a VP shunt, B-transferrin assays and radionuclide tracer shunt series may be helpful for diagnosis. Peritoneal scintigraphy may be considered to evaluate for a peritoneal-pleural leak. In hepatic hydrothorax, the pleural fluid resembles spontaneous bacterial peritonitis, with positive bacterial cultures and polymorphonuclear leukocyte counts >250 cell/mm^3 .

Treatment

Therapy is directed at the underlying disorder. If a transudative fluid is clinically suspected, aspiration may not be needed unless pressure symptoms are noted or there are atypical symptoms such as fever, pleuritic pain, or asymmetric effusions.

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CHAPTER 442

Hemothorax

Glenna B. Winnie, Suraiya K. Haider, Aarthi P. Vemana, Steven V. Lossef

Hemothorax, an accumulation of blood in the pleural cavity, is rare in children.

Etiology

Bleeding into the chest cavity most commonly occurs after chest trauma, either blunt or penetrating. It can be the result of iatrogenic trauma, including surgical procedures and venous line insertion. Hemothorax can also result from erosion of a blood vessel in association with inflammatory processes such as tuberculosis and empyema. It may complicate a variety of congenital anomalies including sequestration, patent ductus arteriosus, and pulmonary arteriovenous malformation (see Fig. 436.2 in Chapter 436). It is also an occasional manifestation of intrathoracic neoplasms, costal exostoses, blood dyscrasias, bleeding diatheses, or thrombolytic therapy. Rupture of an aneurysm is unlikely during childhood. Hemothorax may occur spontaneously in neonates and older children but is very rare. A pleural hemorrhage associated with a pneumothorax is a *hemopneumothorax;* it is usually the result of a ruptured bulla with lung volume loss causing a torn pleural adhesion.

Clinical Manifestations

In addition to the symptoms and signs of pleural effusion (see Chapter 429.2), hemothorax is associated with hemodynamic compromise related to the amount and rapidity of bleeding, with ventilatory collapse. Spontaneous hemothorax presents with sudden onset of chest or back pain or dyspnea and can progress rapidly to hemorrhagic shock.

Diagnosis

The diagnosis of a hemothorax is initially suspected from radiographs or CT scans but can be made definitively with thoracentesis (Fig. 442.1). In every case, an effort must be made to determine and treat the cause.

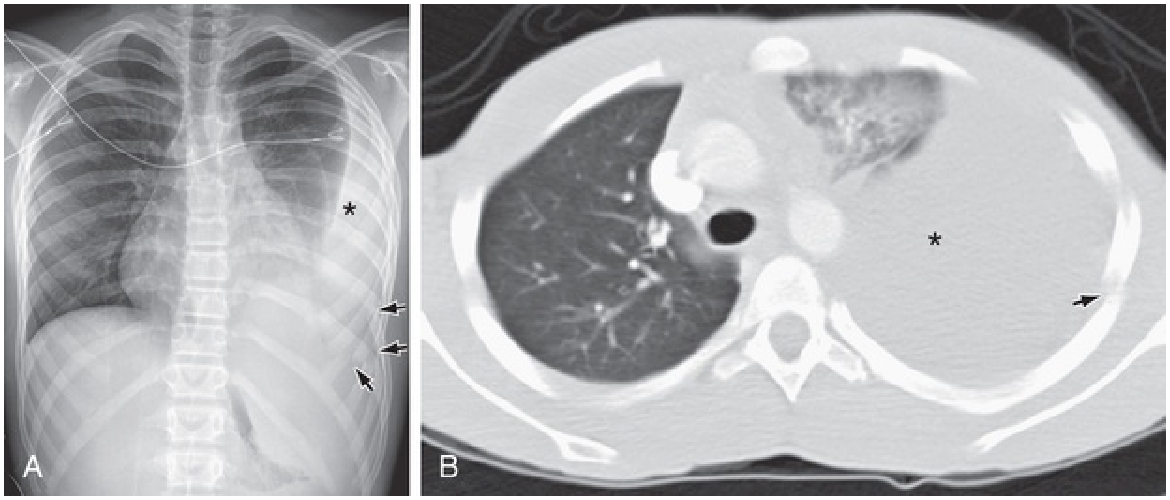

FIG. 442.1 Hemothorax *(asterisk)* and associated rib fractures *(arrows)* in a teenager involved in a motor vehicle accident. **A,** Chest radiograph. **B,** CT scan.

Treatment

Therapy includes supplemental oxygen, fluid resuscitation (including possible blood transfusion), and tube thoracostomy. Video-assisted thorascopic surgery (VATS) can be considered in most patients with stable vital signs to visualize the source of bleeding, remove blood clots, resect bullae or blebs, and to perform pleurodesis. An open thoracotomy may be indicated if there is uncontrolled bleeding or in a hemodynamically compromised patient. Inadequate removal of blood in extensive hemothorax leading to a retained hemothorax can increase the risk for development of pneumonia, empyema, or substantial restrictive disease secondary to organization of fibrin. Fibrinolytic therapy or a decortication may then be necessary. Embolization is the treatment of choice for an arteriovenous malformation.

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CHAPTER 443

Chylothorax

Glenna B. Winnie, Suraiya K. Haider, Aarthi P. Vemana, Steven V. Lossef

Chylothorax is a pleural collection of fluid formed by the escape of chyle from the thoracic duct or lymphatics into the thoracic cavity.

Etiology

Chylothorax in children occurs most frequently because of thoracic duct injury as a complication of cardiothoracic surgery (post Fontan surgery) (Fig. 443.1). Other cases are associated with chest injury (Fig. 443.2), extracorporeal membrane oxygenation, or with primary or metastatic intrathoracic malignancy, particularly lymphoma. In newborns, rapidly increased venous pressure during delivery may lead to thoracic duct rupture. Chylothorax has also been associated with Down syndrome, Noonan syndrome, and Turner syndrome. Less common causes include lymphangiomatosis (Fig. 443.3); restrictive pulmonary diseases; thrombosis of the duct, superior vena cava, or subclavian vein; tuberculosis or histoplasmosis; and congenital anomalies of the lymphatic system (Fig. 443.4). Refractory chylothorax in the fetus has been associated with a missense mutation in integrin α_9 β1 gene. Chylothorax can occur in trauma and child abuse (see Chapter 16). It is important to establish the etiology because treatment varies with the cause. In some patients no specific cause is identified.

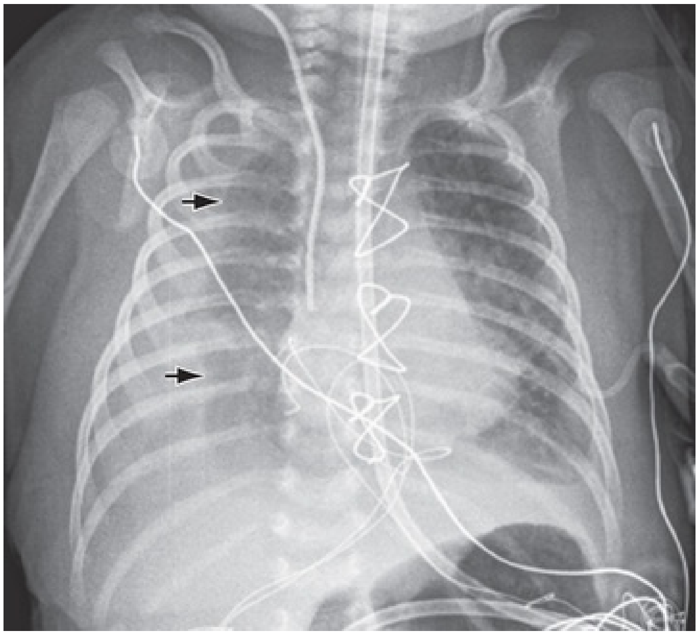

FIG. 443.1 Chylothorax *(arrows)* following cardiac surgery in a 2 wk old infant.

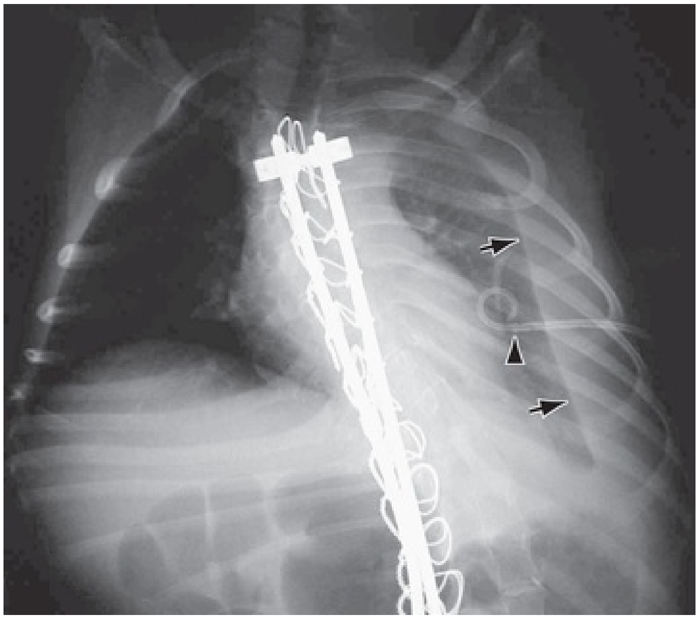

FIG. 443.2 Left chylothorax *(arrows)* following spinal fusion with Harrington rods. It is postulated that the thoracic duct was injured during spine surgery. The pigtail chest tube *(arrowhead)* needed to be retracted to better drain the effusion.

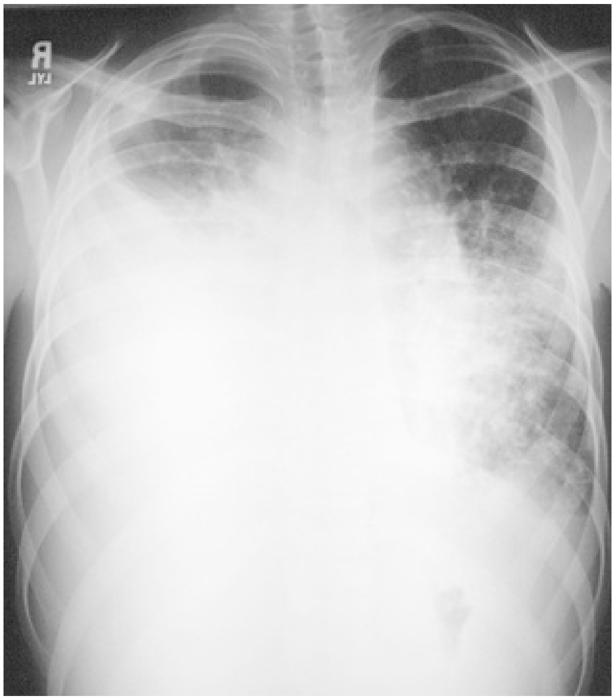

FIG. 443.3 Large right chylous effusion opacifying much of the right thorax in a teenager with pulmonary lymphangiomatosis and hemangiomatosis. Note the associated interstitial lung disease.

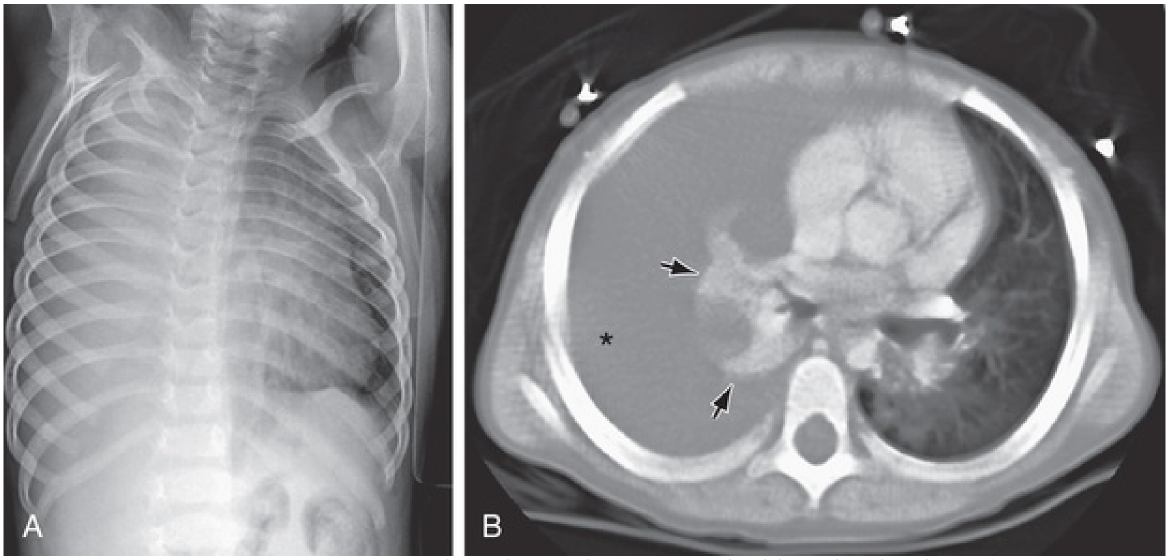

FIG. 443.4 Spontaneous chylothorax in a 4 yr old with a duplication of chromosome 6. **A,** Chest radiograph shows opacification of the right thorax. **B,** CT scan shows the chylous pleural effusion *(asterisk)* compressing the atelectatic right lung *(arrows).*

Clinical Manifestations

The signs and symptoms of chylothorax are the same as those from pleural effusion of similar size including cough, chest discomfort, and dyspnea. **Chyle** is not irritating, so pleuritic pain is uncommon. Onset is often gradual. However, after trauma to the thoracic duct chyle may accumulate in the posterior mediastinum for days and then rupture into the pleural space with sudden onset of dyspnea, hypotension, and hypoxemia. Approximately 50% of newborns with chylothorax present with respiratory distress in the 1st day of life. Chylothorax is rarely bilateral and usually occurs on the right side.

Laboratory Findings

Chest radiographs can help to delineate the location of an effusion; CT scans show normal pleural thickness and may demonstrate a mediastinal mass such as a lymphoma as the etiology of the chylothorax. Thoracentesis demonstrates a chylous effusion, a milky fluid containing triglycerides, protein, lymphocytes, and other constituents of chyle; fluid may be yellow or bloody. In newborn infants or those who are not ingesting food, the fluid may be clear. A pseudochylous milky fluid may be present in chronic serous effusion, in which fatty material arises from degenerative changes in the fluid and not from lymph. In chylothorax, the fluid triglyceride level is >110 mg/dL, the pleural fluid:serum triglyceride ratio is >1.0, and pleural fluid:serum cholesterol ratio is <1.0; lipoprotein analysis reveals chylomicrons. Fluid immunoglobulin levels are elevated. The cells are primarily (~90%) T lymphocytes and often exceed 1,000 cells per mm^3 . After diagnosing chylothorax, a lymphangiogram can localize the site of the leak, and lymphoscintigraphy may demonstrate abnormalities of the lymphatic trunks and peripheral lymphatics.

Treatment

Spontaneous recovery occurs in >50% of cases of neonatal chylothorax. Therapy includes enteral feedings with a low-fat or medium-chain triglyceride, high-protein diet, and total parenteral nutrition. Thoracentesis is repeated as needed to relieve pressure symptoms; tube thoracostomy is often performed. Somatostatin and octreotide have been used to manage chylothorax. Various octreotide dosages have been described in the literature including 1-4 μg/kg/hr intravenously and 10 μg/kg/day subcutaneously; however, the optimal dose is not known and further study is needed. Other therapeutic approaches include percutaneous thoracic duct embolization, pressure control ventilation with positive end-expiratory pressure, and inhalation of nitric oxide. If medical management is unsuccessful, surgical options should be considered and can include a pleuroperitoneal shunt, thoracic duct ligation, and pleurodesis with the use of a sclerosing agent such as fibrin glue, talc, or iodopovidone. Treatment is similar for traumatic chylothorax. Chemical pleurodesis or irradiation is used in malignant chylothorax. OK432 (picibanil) has been used to treat fetal and newborn chylothorax. Etilefrine, a sympathomimetic agent with both α- and β-adrenergic activity, has been successfully used in a few patients. Constriction of the thoracic duct by this drug may reduce pleural chyle accumulation. Percutaneous thoracic duct embolization or treatment of other lymphatic vessels is a highly successful interventional radiology strategy. Surgery should be considered earlier in neonates with massive chylothorax and chyle output of > 50 mL/kg/day despite maximum medical therapy for 3 days.

Complications

If repeated thoracenteses are required due to the rapid reaccumulation of chyle, malnutrition may occur with significant loss of calories, protein, and electrolytes. Immunodeficiencies, including hypogammaglobulinemia and abnormal cell-mediated immune responses, have been associated with repeated and chronic thoracenteses for chylothorax. The loss of T lymphocytes is associated with increased risk of infection in neonates; otherwise, infection is uncommon, but patients should not receive live virus vaccines. Lack of resolution of chylothorax can lead to malnutrition, infection, and death.

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CHAPTER 444

Bronchopulmonary Dysplasia

Sharon A. McGrath-Morrow, J. Michael Collaco

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease of infancy and childhood that occurs primarily in preterm infants born at less than 32 wk gestation. BPD is characterized by alveolar hypoplasia, often with concomitant small airway dysfunction and impaired pulmonary vascular growth. Contributing factors to the development of BPD may include early gestational age, low birth weight, lung barotrauma, exposure to hyperoxia, lung inflammation, and pre- and postnatal infections, as well as potential modifier genes and epigenetic factors. The currently accepted definition includes an oxygen requirement for 28 days postnatally, and the disorder is graded as mild, moderate, or severe on the basis of supplemental oxygen and ventilation requirements at specific timepoints (Table 444.1). For initial inpatient presentation and management, see Chapter 122 .

Table 444.1

Definitions of Bronchopulmonary Dysplasia

FEATURES OF ALL BPD	ADDITIONAL FEATURES OF MILD BPD	ADDITIONAL FEATURES OF MODERATE BPD	ADDITIONAL FEATURES OF SEVERE BPD
<32 wk gestational age at birth Oxygen requirement for at least 28 days	Breathing room air at 36 wk PMA or at discharge, whichever comes first	<30% supplemental oxygen at 36 wk PMA or at discharge, whichever comes first	>30% supplemental oxygen and/or positive pressure ventilation at 36 wk PMA or at discharge, whichever comes first
>32 wk	Breathing room air at 56	<30% supplemental oxygen	>30% supplemental oxygen and/or

gestational age at birth Oxygen requirement for at least 28 days	days of life or at discharge, whichever comes first	at 56 days of life or at discharge, whichever comes first	positive pressure ventilation at 56 days of life or at discharge, whichever comes first

BPD , bronchopulmonary dysplasia; *PMA* , postmenstrual age.

Clinical Manifestations

Physical findings of the pulmonary exam vary with the severity of disease and with respiratory illnesses. Although some patients may appear to be comfortably breathing when well, they can experience significant deterioration when ill or with periods of stress due to decreased pulmonary reserve secondary to alveolar hypoplasia and small airway disease. Children with BPD may exhibit tachypnea, head bobbing, and retractions when ill or at baseline depending on the severity of disease. Although breath sounds may be clear, many patients have baseline wheeze or coarse crackles. A persistent fixed wheeze or stridor suggests subglottic stenosis (see Chapter 415) or large airway malacia. Fine crackles may be present in patients prone to fluid overload. Chest radiographs may demonstrate air trapping, focal atelectasis, interstitial changes, and/or peribronchial thickening.

The most severely affected patients may require respiratory support to achieve adequate gas exchange. Supplemental oxygen may be required to maintain acceptable oxygen saturations and often is needed to minimize the work of breathing. Chronic respiratory insufficiency may be evidenced as elevation of serum bicarbonate, elevated carbon dioxide on blood gas analysis, hypoxemia, or polycythemia; the most severe cases may require tracheostomy and ventilation to achieve long-term respiratory stability. Patients must be monitored for the development of pulmonary hypertension, especially if they require supplemental oxygen and have chronic respiratory insufficiency.

Aspiration from dysphagia and/or gastroesophageal reflux (GERD) (see Chapter 349) can compromise pulmonary status. The risk of aspiration may increase during periods of illness due to worsening tachypnea and air trapping. Other comorbidities resulting from premature birth that complicate the management of BPD include fixed and functional upper airway obstruction, CNS injuries leading to abnormal control of breathing, abnormal airway tone, increased aspiration risk, gastrointestinal dysmotility, systemic hypertension, and poor growth. Of note, infants with significant lung disease can exhibit growth failure from the elevated energy expenditure essential to maintain the increased metabolic demands of respiration and/or ongoing hypoxia.

A *pulmonary exacerbation* in a child with BPD is typically triggered during viral respiratory infections. Other frequent risk factors for pulmonary exacerbations may include weather changes, exposure to cigarette smoke, attending daycare, and aspiration. During an exacerbation, the infant may exhibit increased work of breathing, crackles, and wheezing, with tachypnea and retractions becoming more prominent. Underlying pulmonary hypertension may worsen with pulmonary exacerbations as well.

Treatment

Treatment is directed toward decreasing the work of breathing and normalizing gas exchange, to allow for optimal growth and neurodevelopment. After initial hospital discharge, infants and children with BPD are at high risk for rehospitalization. Up to 50% of infants with BPD are readmitted for acute respiratory illnesses within the first 2 yr of life. These children also may require multiple daily medications, supplemental oxygen, and/or chronic ventilation.

Adherence to prescribed daily medication regimens may decrease the risk of acute care use and chronic respiratory symptoms; however, there are no standard guidelines for management of BPD with regard to post-NICU care. Although commonly used, there are limited data regarding the efficacy of diuretics in the outpatient setting.

With regard to respiratory support, targeted oxygen saturations should be ≥92% outside of the NICU to ensure adequate growth and neurocognitive development. Pulse-oximetry and polysomnography may be helpful for titration purposes. Prior to initial hospital discharge, infants and children who require chronic ventilatory support have been shown to benefit from standardized protocols to determine medical readiness, assess familial proficiency in respiratory cares, and establish adequate support in an outpatient setting. After discharge, these patients will require close follow-up from pulmonologists and otolaryngologists to manage ventilator titration and weaning, and tracheostomy cares and decannulation, respectively. As infants and children with tracheostomies are at high risk for adverse events, including death, an awake and alert trained caregiver is recommended at all times.

Pulmonary function testing in children with a history of BPD has consistently demonstrated obstructive small airway disease. Small airway disease in this population may be partially responsive to bronchodilators, but may also have a fixed obstructive component. Inhaled corticosteroids and β-agonists may be effective in treating symptoms, such as wheezing or chronic cough. Leukotriene-modifying agents may be a useful adjunct therapy.

Adequate caloric intake is important to ensure catch-up lung growth. Some children may require fortified breast milk or formula to achieve adequate growth. Patients at risk for aspiration and those with inadequate oral intake may require tube feeding to meet nutritional goals. Placement of a gastrostomy tube should be considered prior to discharge to home to avoid inadvertent dislodgement. Aspiration secondary to dysphagia and/or gastroesophageal reflux should be considered in patients with recurrent respiratory symptoms or pneumonia without obvious infectious etiologies. Due to their tenuous respiratory status, some infants and children with BPD may not be able to tolerate even minimal amounts of aspiration from gastroesophageal reflux. There are limited data regarding risks and benefits of anti-reflux medications in infants with BPD, such has histamine-2 blockers, proton pump inhibitors, and motility agents. Medications that reduce gastric acidity may increase the risk of pneumonia in some children. Consideration for either Nissen fundoplication or gastrojejunostomy tubes may be required in cases of failure of anti-reflux medical therapy.

Up to 15–25% of infants with severe BPD will be diagnosed with **pulmonary hypertension** , which may be secondary to decreased pulmonary vascular growth and/or a reactive vascular bed. Other risk factors for developing pulmonary hypertension may include extreme prematurity and decreased intrauterine growth; recurrent aspiration, hypoxia, and hypercarbia may worsen severity. Pulmonary hypertension is associated with increased morbidity and mortality compared to infants without pulmonary hypertension. Although definitive diagnosis of pulmonary hypertension requires cardiac catheterization, in practice transthoracic echocardiography provides a low-risk screening tool. Screening should also attempt to identify potential structural causes of pulmonary hypertension such as pulmonary vein stenosis. Serum biomarkers, such as brain natriuretic protein, may be useful in tracking response to therapy. Abrupt worsening of pulmonary hypertension *(pulmonary hypertensive crises)* can occur in the context of illnesses and with anesthesia. Crises can occur even in stable children with a history of pulmonary hypertension who become acutely ill. Although pulmonary hypertension that is associated with BPD can improve with adequate lung growth, therapies such as sildenafil and other anti-pulmonary hypertensive agents have been used in management.

Prevention of respiratory viral illness is vitally important; frequent handwashing by caregivers (especially before they handle the baby) and avoidance of contact with children and adults with current respiratory symptoms are essential. Respiratory syncytial virus (see Chapter 260) immunoprophylaxis should be considered on the basis of the severity of lung disease, as well as the patient's gestational age and current age. Another environmental factor that can worsen respiratory symptoms is exposure to secondhand tobacco smoke (see Chapter 737.1).

Prognosis

The prognosis for infants with BPD is generally good, although the presence of BPD may result in a longer initial hospitalization compared to preterm infants without BPD. Most infants are weaned off of oxygen during the 1st yr of life, and those requiring home mechanical ventilation are often weaned from this support during toddlerhood. Many children exhibit an asthma-like phenotype during early childhood, characterized by episodes of wheezing or coughing triggered by upper respiratory tract infections, exertion, allergens, etc. For some of these children symptoms improve by school age; others may continue to have asthma-like exacerbations with viral illnesses and exercise throughout childhood, which may persist into adulthood. Even asymptomatic patients with a history of BPD can continue to demonstrate small airway flow limitations by spirometry.

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CHAPTER 445

Skeletal Diseases Influencing Pulmonary Function

Steven R. Boas

Pulmonary function is influenced by the structure of the chest wall (see Chapter 400). Chest wall abnormalities can lead to restrictive or obstructive pulmonary disease, impaired respiratory muscle strength, and decreased ventilatory performance in response to physical stress. The congenital chest wall deformities include *pectus excavatum*, *pectus carinatum*, *sternal clefts*, *Poland syndrome* , and skeletal and *cartilage dysplasias* . Vertebral anomalies such as kyphoscoliosis can alter pulmonary function in children and adolescents.

445.1

Pectus Excavatum (Funnel Chest)

Steven R. Boas

Keywords

pectus excavatum
Nuss procedure
Ravitch procedure

Etiology

Pectus excavatum—midline narrowing of the thoracic cavity—is usually an isolated skeletal abnormality. The cause is unknown. Pectus excavatum can occur in isolation or it may be associated with a connective tissue disorder (Marfan [see Chapter 722] or Ehlers-Danlos syndrome [see Chapter 678]). It may be acquired secondarily to chronic lung disease, neuromuscular disease, or trauma.

Epidemiology

Pectus excavatum occurs in 1 in 400 births with a 9 : 1 male preponderance and accounts for >90% of congenital chest wall anomalies. There is a positive family history in one-third of cases.

Clinical Manifestations

The deformity is present at or shortly after birth in one-third of cases but is usually not associated with any symptoms at that time. In time, fatigue, chest pain, palpitations, recurrent respiratory infections, wheezing, stridor, and cough may be present. Decreased exercise tolerance is one of the most common symptoms. Because of the cosmetic nature of this deformity, children may experience significant psychologic stress. Physical examination may reveal sternal depression, protracted shoulders, kyphoscoliosis, dorsal lordosis, inferior rib flares, rib cage rigidity, forward head tilt, scapular winging, and loss of vertebral contours (Fig. 445.1). Patients exhibit paroxysmal sternal motion and a shift of point of maximal impulse to the left. Innocent systolic murmurs may be heard.

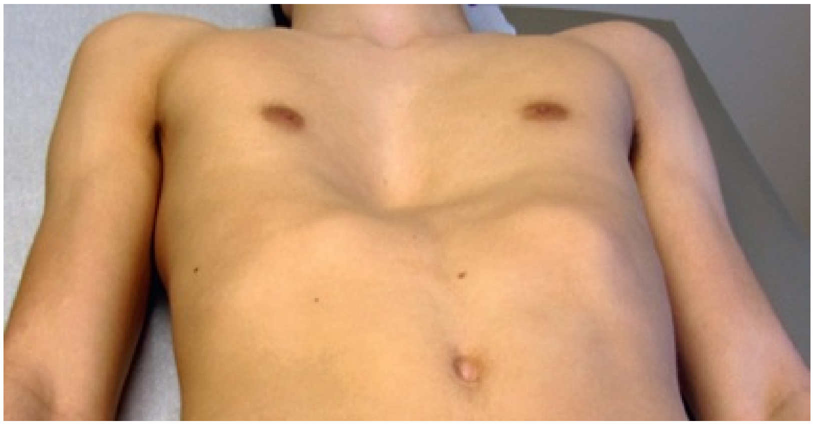

FIG. 445.1 Pectus excavatum in a 15 yr old male. Note the presence of protracted shoulders, inferior rib flares, and sternal depression.

Laboratory Findings

Lateral chest radiograms demonstrate the sternal depression. The Haller index on chest CT (maximal internal transverse diameter of the chest divided by the minimal anteroposterior diameter at the same level) in comparison with age- and gender-appropriate normative values have been used historically to help determine the extent of the anatomic abnormality. However, the correlation of the Haller index with the physiologic compromise or associated systems appears suboptimal. Use of 3D chest optical imaging or “surface scan” is gaining popularity in the evaluation. An electrocardiogram may show a right-axis deviation or Wolff-Parkinson-White syndrome (see Chapter 463); an echocardiogram may demonstrate mitral valve prolapse (see Chapter 455.3) and ventricular compression. Results of static pulmonary function tests may be normal but commonly show an obstructive defect in the lower airways and, less commonly, a restrictive defect as the result of abnormal chest wall mechanics. Exercise testing may demonstrate either normal tolerance or limitations from underlying cardiopulmonary dysfunction that are associated with the severity of the defect. Pulmonary limitations such as ventilatory limitations and associated flow volume loop abnormalities are commonly seen in younger children and adolescents, whereas additional cardiac limitations secondary to stroke volume impairments are more commonly seen in older adolescents and young adults.

Treatment

Treatment is based on the severity of the deformity and the extent of physiologic compromise as defined by physical examination and physiologic assessment of cardiopulmonary function (lung function and exercise tolerance assessment). Therapeutic options include careful observation, use of physical therapy to address musculoskeletal compromise, corrective surgery, cosmetic surgery, and noninvasive thorascopic techniques. For patients with significant physiologic compromise, surgical correction may improve the cosmetic deformity and may help minimize progression or even improve the cardiopulmonary compromise. The 2 main surgical interventions are the Ravitch and Nuss procedures. Superiority of one approach has not been established. The extent of the anatomic defect including the degree of asymmetry may help determine the appropriate surgical approach. While surgical repair may result in improved exercise tolerance for some individuals, usually observed at submaximal exercise intensities, many patients do not show improvement in either respiratory or cardiac function. Normalization of lung perfusion scans and maximal voluntary ventilation have also been observed after surgery. Utilization of a magnetic brace with gradual remodeling (Magnetic Mini Mover procedure) of the pectus deformity is under clinical investigation. The use of surgically placed silicone implants for cosmetic appearance has also been utilized with high patient satisfaction. For selected patients, the use of a more noninvasive approach (i.e., cup suction) has been gaining popularity. Regardless of the treatment approach, addressing the secondary musculoskeletal findings is commonly employed before and after any intervention.

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445.2

Pectus Carinatum and Sternal Clefts

Steven R. Boas

Keywords

pectus carinatum
sternal clefts

Pectus Carinatum

Etiology and Epidemiology

Pectus carinatum is a sternal deformity accounting for 5–15% of congenital chest wall anomalies. Anterior displacements of the mid and lower sternum and adjacent costal cartilages are the most common types. They are most commonly associated with protrusion of the upper sternum; depression of the lower sternum occurs in only 15% of patients. Asymmetry of the sternum is common, and localized depression of the lower anterolateral chest is also often observed. Males are affected 4 times more often than females. There is a high familial occurrence and a common association of mild to moderate scoliosis. Mitral valve disease and coarctation of the aorta are associated with this anomaly. Three types of anatomic deformity occur (upper, lower, and lateral pectus carinatum), with corresponding physiologic changes and treatment algorithms.

Clinical Manifestations

In early childhood, symptoms appear minimal. School-age children and adolescents commonly complain of dyspnea with mild exertion, decreased endurance with exercise, and exercise-induced wheezing. The incidence of increased respiratory infections and use of asthma medication is higher than in nonaffected individuals. On physical examination, a marked increase in the anteroposterior chest diameter is seen, with resultant reduction in chest excursion and expansion (Fig. 445.2). Spirometry has demonstrated both restrictive and obstructive patterns, although the majority of individuals have normal values. Increases in residual volume are often present and result in tachypnea and diaphragmatic respirations. Exercise testing shows variable results. Chest radiographs show an increased anteroposterior diameter of the chest wall, emphysematous-appearing lungs, and a narrow cardiac shadow. The pectus severity score (width of chest divided by distance between sternum and spine; analogous to the Haller index) is reduced.

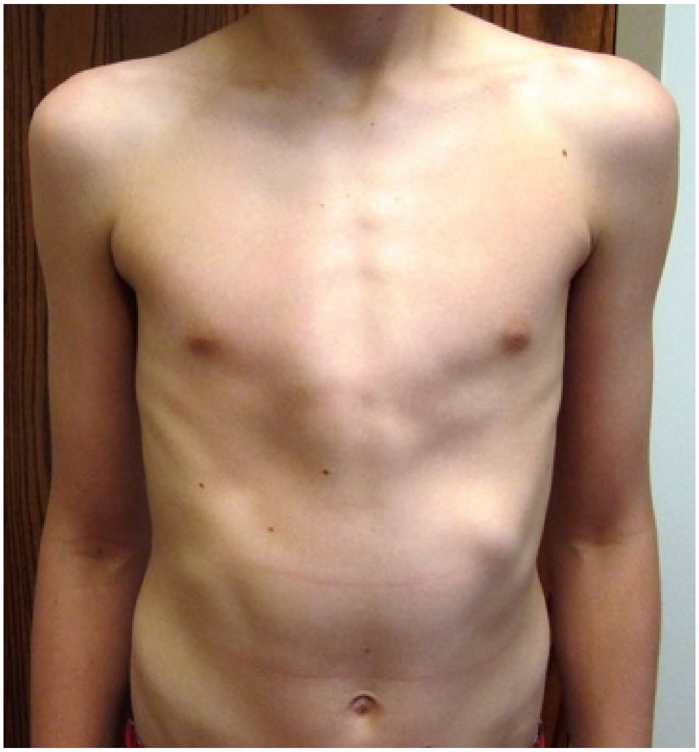

FIG. 445.2 Pectus carinatum in a 13 yr old male. Note the central sternal prominence.

Treatment

For symptomatic patients with pectus carinatum, minimally invasive surgical correction procedures may result in improvement of the clinical symptoms.

Many surgeons prefer to use bracing techniques as a first-line treatment. Although surgery is performed for some individuals who are symptomatic, it is often performed for cosmetic and psychological reasons.

Sternal Clefts

Sternal clefts are rare congenital malformations that result from the failure of the fusion of the sternum during the 8th wk of gestation. No familial predisposition has been described. Sternal clefts occur in less than 1% of all chest wall deformities. Sternal clefts are classified as partial or complete. Partial sternal clefts are more common and may involve the superior sternum in association with other lesions, such as vascular dysplasias and supraumbilical raphe, or the inferior sternal clefts, which are often associated with other midline defects (pentalogy of Cantrell). Complete sternal clefts with complete failure of sternal fusion are rare. These disorders may also occur in isolation. The paradoxic movement of thoracic organs with respiration may alter pulmonary mechanics. Rarely, respiratory infections and even significant compromise result. Surgery is required early in life, before fixation and immobility occur.

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445.3

Asphyxiating Thoracic Dystrophy (Thoracic-Pelvic-Phalangeal Dystrophy)

Steven R. Boas

Keywords

asphyxiating thoracic dystrophy
Jeune syndrome

Etiology

A multisystem autosomal recessive disorder, asphyxiating thoracic dystrophy results in a constricted and narrow rib cage. Also known as *Jeune syndrome* , the disorder is associated with characteristic skeletal abnormalities as well as variable involvement of other systems, including renal, hepatic, neurologic, pancreatic, and retinal abnormalities (see Chapter 720).

Clinical Manifestations

Most patients with this disorder die shortly after birth from respiratory failure, although less-aggressive forms have been reported in older children. For those who survive the neonatal period, progressive respiratory failure often ensues, owing to impaired lung growth, recurrent pneumonia, and atelectasis originating from the rigid chest wall.

Diagnosis

Physical examination reveals a narrowed thorax that, at birth, is much smaller than the head circumference. The ribs are horizontal, and the child has short extremities. Chest radiographs demonstrate a bell-shaped chest cage with short, horizontal, flaring ribs and high clavicles.

Treatment

No specific treatment exists, although thoracoplasty to enlarge the chest wall and long-term mechanical ventilation has been tried. Rib-expanding (vertical expandable prosthetic titanium rib/[VEPTR]) procedures have resulted in improved survival (Fig. 445.3).

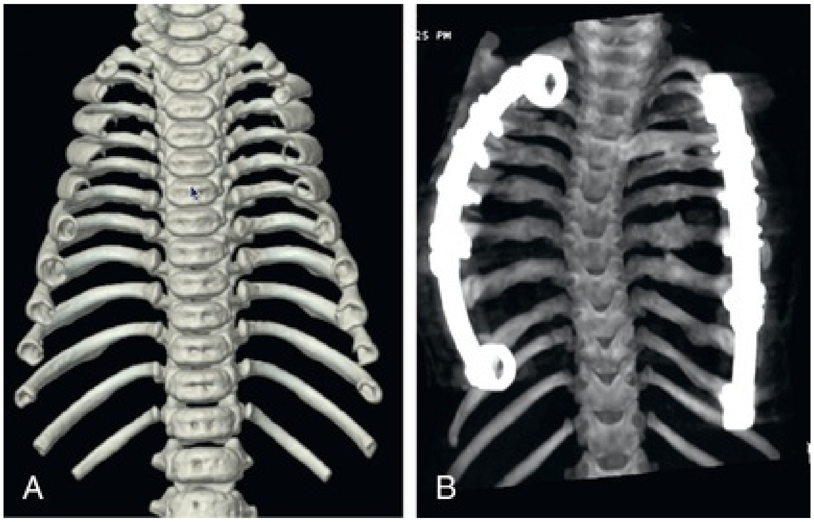

FIG. 445.3 **A,** Seven month old with Jeune syndrome preoperatively. **B,** 18 mo post-VEPTR insertion. (From Mayer OH: Chest wall hypoplasia—

principles and treatment. *Pediatr Respir Rev* 16:30–34, 2015, Fig. 3, p. 34.)

Prognosis

For some children with asphyxiating thoracic dystrophy, improvement in the bony abnormalities occurs with age. However, children younger than age 1 yr often succumb to respiratory infection and failure. Progressive renal disease often occurs with older children. Use of vaccines for influenza and other respiratory pathogens is warranted, as is aggressive use of antibiotics for respiratory infections.

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445.4

Achondroplasia

Steven R. Boas

Keyword

achondroplasia

Etiology

Achondroplasia is the most common condition characterized by disproportionate short stature (see Chapter 716). This condition is inherited as an autosomal dominant disorder that results in disordered growth. Much has been learned about this disorder, including its genetic origins (95% of cases caused by mutations in the gene coding for fibroblast growth factor receptor type 3) and how to minimize its serious complications.

Clinical Manifestations

Restrictive pulmonary disease, affecting <5% of children with achondroplasia who are younger than 3 yr, is more likely at high elevation. Recurrent infections, cor pulmonale, and dyspnea are commonly associated. There is an increased risk of obstructive sleep apnea or hypopneas. Hypoxemia during sleep is a common feature. Onset of restrictive lung disease can begin at a very young age. On examination, the breathing pattern is rapid and shallow, with associated abdominal breathing. The anteroposterior diameter of the thorax is reduced. Special growth curves for chest circumference of patients with achondroplasia from birth to 7 yr are available. Three distinct phenotypes exist: phenotypic group 1 patients possess relative adenotonsillar hypertrophy, group 2 patients have muscular upper airway obstruction and progressive hydrocephalus, and group 3 patients have upper airway obstruction without hydrocephalus. Kyphoscoliosis may develop during infancy.

Diagnosis

Pulmonary function tests reveal a reduced vital capacity that is more pronounced in males. The lungs are small but functionally normal. Sleep studies are recommended due to the high prevalence of sleep-disordered breathing. Chest radiographs demonstrate the decreased anteroposterior diameter along with anterior cupping of the ribs. The degree of foramen magnum involvement correlates with the extent of respiratory dysfunction.

Treatment

Treatment of sleep apnea, if present, is supportive (see Chapter 31). Physiotherapy and bracing may minimize the complications of both kyphosis and severe lordosis. Aggressive treatment of respiratory infections and scoliosis is warranted.

Prognosis

The life span is normal for most children with this condition, except for the phenotypic groups with hydrocephalus or with severe cervical or lumbar spinal compression.

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445.5

Kyphoscoliosis: Adolescent Idiopathic Scoliosis and Congenital Scoliosis

Steven R. Boas

Keywords

scoliosis
idiopathic scoliosis
congenital scoliosis

Etiology

Adolescent idiopathic scoliosis (AIS) is characterized by lateral bending of the spine (see Chapter 699). It commonly affects children during their teen years, as well as during periods of rapid growth. The cause is unknown. Congenital scoliosis is uncommon, affecting females more than males, and is apparent in the 1st yr of life (see Chapter 699.2).

Clinical Manifestations

The pulmonary manifestations of scoliosis may include chest wall restriction, leading to a reduction in total lung capacity, abnormal gas exchange, airway obstruction, and hypoinflation with associated atelectasis. The angle of scoliosis deformity has been correlated with the degree of lung impairment only for patients with thoracic curves. Vital capacity, forced expiratory volume in 1 sec (FEV_1), work capacity, oxygen consumption, diffusion capacity, chest wall compliance, and partial pressure of arterial oxygen decrease as the severity of thoracic curve increases. These findings can be seen in even mild to moderate AIS (Cobb angle <30 degrees) but generally do not occur in other, nonthoracic curves. Respiratory compromise is often more severe in children younger than 5 yr of age with large scoliotic curves. Reduction in peripheral muscle function is associated with AIS through either intrinsic mechanisms or deconditioning. Severe impairment can lead to cor pulmonale or respiratory failure and can occur before age 20 yr. Children with severe scoliosis (Cobb's angle >70 degrees), especially males, may have abnormalities of breathing during sleep, and the resultant periods of hypoxemia may contribute to the eventual development of pulmonary hypertension.

Diagnosis

Physical examination and an upright, posteroanterior radiograph with subsequent measurement of the angle of curvature (Cobb technique) remain the gold standard for assessment of scoliosis. Curves >10 degrees define the presence of scoliosis. Lung volume, respiratory muscle strength, and exercise capacity determination are essential in assessing the degree of respiratory compromise associated with scoliosis.

Treatment

Depending on the extent of the curve and the degree of skeletal maturation, treatment options include reassurance, observation, bracing, and surgery (spinal fusion). Influenza vaccine should be administered, given the extent of pulmonary compromise that may coexist. Because vital capacity is a strong predictor for the development of respiratory failure in untreated AIS, surgical goals are to diminish the scoliotic curve, maintain the correction, and prevent deterioration in pulmonary function. Abnormalities of vital capacity and total lung capacity, exercise intolerance, and the rate of change of these variables over time should be taken into consideration for the timing of surgical correction. Preoperative assessment of lung function (i.e., lung volumes, oxygen consumption, muscle strength, ventilation/perfusion) may assist in predicting postsurgical pulmonary difficulties. Many patients undergoing surgical correction may be managed postoperatively without mechanical ventilation. Even patients with mild scoliosis may have pulmonary compromise immediately after spinal fusion, secondary to pain and a body cast that may restrict breathing and interfere with coughing. Children with a preoperative $FEV_1 < 40\%$ predicted are at risk for requiring prolonged postoperative mechanical ventilation. Rib-expanding procedures have been successful in severe cases of congenital scoliosis. Choice of surgical approach may also impact lung function postoperatively.

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445.6

Congenital Rib Anomalies

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Keyword

congenital rib anomalies

Clinical Manifestations

Isolated defects of the highest and lowest ribs have minimal clinical pulmonary consequences. Missing midthoracic ribs are associated with the absence of the pectoralis muscle (Poland syndrome), and lung function can become compromised. Associated kyphoscoliosis and hemivertebrae may accompany this defect. If the rib defect is small, no significant sequelae ensue. When the 2nd to 5th ribs are absent anteriorly, lung herniation and significant abnormal respiration ensue. The lung is soft and nontender and may be easily reducible on examination. Complicating sequelae include severe lung restriction (secondary to scoliosis), cor pulmonale, and congestive heart failure. Symptoms are often minimal but can cause dyspnea. Respiratory distress is rare in infancy.

Diagnosis

Chest radiographs demonstrate the deformation and absence of ribs with secondary scoliosis. Most rib abnormalities are discovered as incidental findings on a chest film.

Treatment

If symptoms are severe enough to cause clinical compromise or significant lung herniation, then homologous rib grafting can be performed. Rib-expanding procedures are also of great value. A modified Nuss procedure has been used to correct associated chest wall anomalies with rib abnormalities. Adolescent girls with congenital rib anomalies may require cosmetic breast surgery.

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CHAPTER 446

Chronic Respiratory Insufficiency

446.1

Chronic Respiratory Failure and Long-Term Mechanical Ventilation

Denise M. Goodman, Steven O. Lestrud

Epidemiology

There are continual improvements in invasive (ventilation through a tracheostomy) and noninvasive (mask ventilation) devices and management to care for those conditions predisposing to the need for chronic ventilation, such as acute respiratory failure, prematurity, and neuromuscular disease. Although difficult to determine the prevalence of chronic ventilation, estimates range from approximately 4 to 6/100,000 children. With a US Census estimate of 73,604,909 children under 18 in 2015 [https://www.census.gov/quickfacts/table/PST045216/00 . Accessed January 17, 2017] this would mean that 3,000-4,000 children are currently receiving home ventilation. This number may be much higher, as studies rarely focus on children alone (a Canadian study found a prevalence of 12.9/100,000 general population) and studies may report invasive, noninvasive, or total ventilation. There may be approximately 3 times more children receiving mask ventilation than invasive mechanical ventilation. One study using the Kids' Inpatient Database reported that there were 7,812 discharges in 2006 of children on either invasive or noninvasive long-term ventilation. The conditions leading to the need for home ventilation are diverse. Most literature focuses on single-center experience, but broad themes emerge. About two-thirds of children have a primary neurologic indication, including neuromuscular weakness or abnormal ventilatory control, and about one-third have chronic lung disease (Table 446.1).

Table 446.1

Indications for Long-Term Mechanical Ventilation

PULMONARY/ALVEOLAR
BRONCHOPULMONARY DYSPLASIA (BPD)
PARDS (Severe acquired lung disease, such as after pediatric acute respiratory distress syndrome)
Pulmonary fibrosis syndromes
AIRWAY
Severe tracheomalacia
Severe bronchomalacia
Obstructive sleep apnea
Storage diseases
CHEST (SEE CHAPTER 445)
Kyphoscoliosis
Skeletal dysplasias
Obesity
NEUROMUSCULAR
Spinal muscular atrophy
Spinal cord injury
Diaphragmatic dysfunction
Mitochondrial diseases
CNS
Congenital central hypoventilation syndrome (CCHS)
Rapid-onset obesity with hypothalamic dysregulation, hypoventilation, and autonomic dysfunction (ROHHAD)
Severe ischemic brain injury
Myelomeningocele with Arnold-Chiari type II malformation
Acquired hypoventilation syndromes

Patients with primarily pulmonary indications have a greater likelihood of ultimately being weaned from the need for ventilation than do those with neuromuscular or central nervous system disease. Mortality for patients requiring chronic ventilation is reported to be approximately 12–34% depending on underlying disease. The lower mortality range is for children with neonatal lung disease, with the higher value for children with congenital heart disease. An overall mortality rate of 20% is common. Approximately 12–40% of children are eventually weaned from ventilation and decannulated, again reflecting the underlying cause for which ventilation is required. This can usually be accomplished within the first 5 yr of life. Nonetheless, the care of these children can be challenging. One study reported that up to 40% of chronically ventilated children are readmitted within the 1st yr of discharge, usually within the first 3 mo. Children requiring long-term mechanical ventilation (LMV) benefit from comprehensive care coordination incorporating generalists, specialists, home nursing, therapies, and a durable medical equipment (DME) resource.

Modalities for Respiratory Support

The goals of home mechanical ventilation are to maintain appropriate oxygenation and ventilation, minimizing metabolic demands of chronic respiratory failure to ensure adequate somatic growth and optimal developmental gains (see Chapter 446.4).

Invasive Positive Pressure Ventilation

The term *invasive* designates ventilation through a tracheostomy. Some devices are suitable for both noninvasive positive pressure ventilation (NPPV) and invasive ventilation, while other devices are suitable for only one approach. The ideal home ventilator is lightweight, portable, and quiet. All home ventilators differ from hospital-based ventilators in that air movement is affected either by a piston or turbine that is electrically controlled. This contrasts with hospital ventilators which are often gas-driven. A home ventilator should be able to provide continuous flow and have a wide range of settings (particularly for pressure, volume, pressure support, and rate) that allows ventilatory support from infancy to adulthood. Battery power for the ventilator, both internal and external, should be sufficient to permit unrestricted portability in the home and community. The equipment must also be impervious to electromagnetic interference and must be relatively easy to understand and troubleshoot. A variety of ventilators that are approved for home use are available, and familiarity with these devices is necessary to choose the best option for the individual child.

While families and care teams may at first resist placement, a tracheostomy has several advantages. It provides a secure and stable airway, a standardized interface for attaching the ventilator circuit to the patient, and the ability to easily remove airway secretions and deliver inhaled medications. Pediatric tracheostomy tubes typically have a single lumen and may have an inflatable cuff. Tracheostomy tubes with/without cuff inflation should be sized to control the air leak around the tube and promote adequate gas exchange, yet allow enough space around the tube to facilitate vocalization and prevent tracheal irritation and erosion from the tube. The child's caregivers need to learn stoma care, elective and emergent tracheostomy changes, proper securing of the tube, suctioning of secretions, and recognition of emergencies such as tube obstruction or decannulation.

Optimal Ventilator Support

Factors such as underlying neuromuscular disease; medications such as sedatives, analgesics, steroids, and muscle relaxants; and prolonged immobility, as well as utilization of mechanical ventilation, may decondition the respiratory muscles, and more so the diaphragm, resulting in muscle weakness. Consequently, it is important to avoid 24 hr/day patient synchrony with ventilation and titrate the amount of ventilator support to prevent fatigue, yet facilitate spontaneous breathing. While assessing ventilator needs frequent evaluation of gas exchange is needed, but can usually be done noninvasively. Ventilator settings should be stable for a period of time, dictated by severity of pulmonary disease, before discharge home.

Other Management Considerations

Airway Clearance

One of the most important considerations is maintenance of airway patency. Adequate removal of secretions may minimize intercurrent pulmonary infections. In turn, infections may cause a transient increase in secretions requiring an escalation of clearance strategies. If the child has an adequate cough, periodic suctioning may be all that is needed. Some children, however, need additional help mobilizing and clearing secretions. This becomes particularly important in children with neuromuscular disease, for whom regularly scheduled clearance therapies are an imperative. There are 2 main types of devices that are used. **Vest therapy** (high frequency chest wall oscillation) uses an inflatable vest that encircles the chest. Air inflates and deflates the vest with phasic pulses against the chest wall, loosening secretions. This device still requires a preserved and strong enough cough to expel secretions. The **cough assist** device provides more active airway clearance, delivering a forceful positive pressure adjunct during inspiration and active negative pressure during expiration. Thus, the cough is more effective due to the rapid pressure changes. The cough assist can be used with an artificial airway or mask. Controls will set the inspiratory and expiratory pressures and periods.

Inhalation Medications

Clearance of secretions may be promoted with delivery of hypertonic (3% saline) nebulizations. These are often timed to cough assist sessions to maximize the clearance benefits of both. Children requiring ventilation also commonly need bronchodilators.

Mucolytics and Anticholinergics

Some patients may need additional interventions due to excess secretions. Anticholinergic drugs, principally glycopyrrolate, are often effective, but must be dosed carefully to avoid thickening secretions excessively, which can lead to inspissated secretions and life-threatening plugging of the airway. Oral secretions are sometimes amenable to localized injection of botulinum toxin, or select surgical ligation of salivary ducts. It is also wise to ensure that the patient is adequately hydrated as dehydration may produce thick tenacious secretions. At times a mucolytic may be used. Hypertonic saline is the most common mucolytic, but a number of other agents have been tried, such as dornase alfa and N-acetylcysteine.

Monitoring

A patient who is ventilated in the home must be electronically and/or physically monitored at all times. Infants and young children, children who are cognitively impaired, and children who are completely tracheostomy dependent for airway patency because of suprastomal obstruction must be under direct observation of the caregivers at all times. Caregivers should also closely monitor children whose pulmonary status is fragile or fluctuant. Continuous monitoring of O_2 saturation and heart rate is recommended during sleep, and either continuous or intermittent monitoring during the daytime, depending on patient stability. Patients with congenital central hypoventilation syndrome (CCHS) or pulmonary hypertension are particularly vulnerable to episodes of hypoxemia and/or hypercarbia, and those with pulmonary hypertension are particularly susceptible to rapid drops in O_2 saturation.

Supplemental Oxygen

Supplemental oxygen may be delivered from a tank or concentrator. Whether on room air or oxygen at baseline, even mild intercurrent infections may lead to an increase in oxygen requirement. In these situations, the child should be evaluated in person rather than over the phone to ensure that a more serious illness is not developing.

Nutrition

Ventilated patients may have nutritional needs that are equal to, greater, or lesser than those of comparably aged well children. Growth should be tracked at each well-child and subspecialty visit. Excessive growth is as harmful as inadequate growth, and excess calories may lead to increased carbon dioxide (CO_2) production. Anthropometry or measured energy expenditure may be needed to assure a more precise prescription of nutritional support. Many children with tracheostomies have oral aversion and/or dyscoordination of swallowing, with resultant risk for aspiration. In these children a gastrostomy tube may ensure adequate nutrition in the interim while ongoing speech therapy promotes oral feeding.

Physical, Occupational, Speech Therapy

The technology needed to support physical well-being should not overshadow the inherent developmental needs common to all children—to play, grow, develop, and interact. Ongoing physical therapy, occupational therapy, and speech therapy can help a child reach full potential, and many achieve complete catch-up development. Early intervention programs and access to play groups are important factors to attaining cognitive and social milestones. When normal development is not attainable, therapies can improve mobilization and muscle strength. Core trunk and abdominal strength is particularly important for pulmonary rehabilitation and essential for successful weaning off ventilation. Other important skills include oromotor skills for feeding and communication. Evaluation of swallow is a key component of therapy for children with chronic respiratory failure. Sign language is frequently used for communication because of delayed speech or hearing loss. Audiology specialists should be involved in the assessment of hearing because there is a higher incidence of hearing loss in patients undergoing long-term ventilation.

Preparing for Discharge

A number of components need to come together for a safe and effective discharge, including medical stability, family education, financial support (insurance or a state waiver program), availability of a DME company, and, when appropriate, home private-duty nursing. A poor outcome may occur with any of the many medical or process factors, or family factors including not only education but also home readiness and psychosocial supports. A standardized discharge process can ensure that all details are addressed, minimizing length of stay and improving safety. An awake and attentive trained caregiver should be in the home of a child with invasive ventilation at all times; this expectation may differ for those receiving NPPV depending on clinical circumstance. For those receiving invasive ventilation, the caregiver may be a nurse, but nursing resources are often scarce, so many programs require 2 trained family caregivers. The training given to the family includes tracheostomy stoma care, suctioning, equipment expertise, administration of medications, and facility with other devices, such as gastrostomy tubes. In addition, the family is instructed in emergency preparedness, including what to do for acute changes in clinical status, desaturation, or airway obstruction or decannulation. Cardiopulmonary resuscitation training is essential. Parents also need to be able to travel portably with the child and equipment. A standardized emergency bag containing critical tracheostomy and ventilator supplies should accompany the child at all times. Other preparations center around home readiness, including accessibility (number of stairs if any, members of the household, assuring no smoking in the home) and notification of utility companies such as the electric or heating company to ensure the home is serviced quickly in the event of power interruption. The family must also have a functioning telephone to ensure adequate accessibility and communication between the family and care team. For those going home with invasive mechanical ventilation, both a primary and back-up ventilator may be needed, as well as batteries, a self-inflating bag and mask, suctioning equipment, supplemental oxygen, and appropriate monitoring including a pulse oximeter. Family training often culminates in an autonomous 24 hr stay *in the hospital* during which time 1 caregiver must continuously remain awake, and all cares including ventilator checks, suctioning, tracheostomy tube changes, medications, and the like are provided by the family.

Care by the General Pediatrician

See Chapters 446.4 and 734.1 .

Infections

Tracheitis (see Chapter 412.2), bronchitis (see Chapter 418.2), and pneumonia (see Chapters 426 and 428) are common in patients with chronic respiratory failure. Infections may be caused by community-acquired viruses (adenovirus, influenza, respiratory syncytial virus, parainfluenza, rhinovirus) or community- or hospital-acquired bacteria. Common pathogens are Gram-negative, highly antimicrobial-resistant pathogens that may cause further deterioration in pulmonary function. Bacterial infection is most likely in the presence of fever, deteriorating lung function (hypoxia, hypercarbia, tachypnea, and retractions), leukocytosis, and mucopurulent sputum. The presence of leukocytes and organisms on Gram stain of tracheal aspirate, as well as the visualization of new infiltrates on radiographs, may be consistent with bacterial infection.

Infection must be distinguished from tracheal *colonization* of bacteria, which is asymptomatic and associated with normal amounts of clear tracheal secretions. Colonization may also be distinguished from infection in that colonization usually has few, if any, white blood cells on Gram stain of tracheal secretions. If infection is suspected, it must be treated with antibiotics, based on the culture and sensitivities of organisms recovered from the tracheal aspirate. At times inhaled antibiotic such as tobramycin might avert progression of infection. Antibiotics should be used judiciously to prevent further colonization with drug-resistant organisms. However, some patients who have recurrent infections may benefit from prophylaxis with inhaled antibiotics. Clinical decisions will be based on the child's appearance, any increased need for ventilation or supplemental oxygen, and consultation with the subspecialist. A final caveat is that, if a respiratory viral panel is desired, this must be obtained from nasal secretions similar to a well child; tracheal aspirate does not provide an appropriate specimen.

Care by the Subspecialty Team

See Chapter 734.1 .

Weaning Off the Ventilator

A substantial number of children are eventually weaned from mechanical ventilation. Typically the ventilator settings are reduced minimizing ventilator parameters to achieve physiologic respiratory rates and 6-8 mL/kg tidal volumes. Subsequent maneuvers will evaluate the patient free breathing, initially with simple observed transition times of 5-10 min, extending time off as clinically indicated. This can be done in the outpatient setting during visits with the pulmonologist or other subspecialist responsible for ventilator management. Additional factors that reflect tolerance of increased work of breathing, including weight gain, energy levels, general behavior, and sleep patterns, are also monitored carefully. When the child has completely weaned off ventilator support while awake and is only on the ventilator approximately 6 hr nightly during sleep, a polysomnogram study performed off the ventilator may be considered prior to complete liberation from the mechanical ventilation device. Successful liberation from mechanical ventilation, if it occurs, often takes place between the ages of 2 and 5 yr. One thought is that with ambulation and development of core strength, respiratory reserve improves, facilitating weaning. Even so, residual lung disease is common. Children with a history of bronchopulmonary dysplasia (BPD) and previous ventilator dependence often have significant airway obstruction on pulmonary function testing.

Psychosocial Considerations

Caring for a child on long-term ventilatory support in the home is a complex, physically demanding, emotionally taxing, and expensive process for the family. It changes the family routines, priorities, and overall lifestyle, and may adversely affect relationships both within the family and with extended family and friends. Practical considerations include loss of spontaneity in family outings, sleep disturbance, extra expenses, having strangers in the house providing care, and adhering to medical regimens and follow-up visits. Intangible stresses are also prominent, including disruption in the usual parent-child caregiving roles, and stresses between parent partners and with other children. The loss of normality, sense of isolation, and concerns regarding what is best for the child are additional sources of distress. For children with a life-limiting condition, there is the additional need to periodically revisit the child's current medical state, sense of well-being, and trajectory of illness, as critical decisions will eventually arise regarding end-of-life care. The general pediatrician can often be a familiar and comfortable safe place to explore these issues, as parents may be conflicted in wanting to be a good parent while feeling guilty about their own needs and vulnerabilities.

Adult Transition

There are a growing number of children surviving into adulthood who require chronic ventilation. There is little empiric data regarding this transition, including identifying patients for whom transition is appropriate, implementing a standardized transition process, partnering with adult pulmonologists, or replicating in an adult environment the care coordination provided by the pediatric care team. The pulmonary team ideally initiates ongoing discussions regarding self-care responsibilities and transitioning of medical care to adult providers with the adolescent and his/her parents when the patient reaches the early teens. Discussion about self-care should take into consideration realistic expectations about the adolescent's physical and cognitive capabilities. The actual transition of care occurs for most young adults at age 18-21 yr, and includes referral to an internist as well as an adult pulmonologist. Transition of medical care also includes transition from pediatric to adult support services for funding sources and nursing care. Ideally, an outpatient visit that includes current and future adult medical providers together is completed to facilitate communication and formally transition care.

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446.2

Congenital Central Hypoventilation Syndrome

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Keywords

congenital central hypoventilation syndrome
Hirschsprung disease
neuroblastoma neural crest tumors
ganglioneuroblastoma
ganglioneuroma
diaphragm pacing
autonomic dysregulation
control of breathing

CCHS is a clinically complex *neurocristopathy* that includes a variable severity of respiratory and autonomic dysregulation, as well as Hirschsprung disease and neural crest tumors in a subset of patients. In the classic CCHS presentation, symptoms of alveolar hypoventilation manifest in the newborn period and during sleep only—with diminished tidal volume and a typically monotonous respiratory rate leading to cyanosis and hypercarbia. In more severe cases of CCHS, the hypoventilation manifests during wakefulness and sleep. In the later-onset cases of CCHS (LO-CCHS), symptoms appear after 1 mo of age and older (often into childhood and adulthood). Hypoventilation is typically during sleep only and usually milder in later-onset cases than in patients who present in the neonatal period. CCHS and LO-CCHS are further characterized by partial to complete peripheral and central chemoreceptor failure to properly respond to hypercarbia and hypoxemia during wakefulness and sleep, coupled with physiologic and/or anatomic autonomic nervous system (ANS) dysregulation (ANSD). Physiologic dysregulation may include all organ systems affected by the ANS, specifically the respiratory, cardiac, sudomotor, vasomotor, ophthalmologic, neurologic, and enteric systems (Table 446.2). The anatomic or structural ANSD includes Hirschsprung disease and tumors of neural crest origin (neuroblastoma, ganglioneuroma, or ganglioneuroblastoma).

Table 446.2

Congenital Central Hypoventilation Syndrome-Related Symptoms

THE SYMPTOMS EMERGE FROM DIFFERENT ORGAN SYSTEMS AND COULD BE OVERLOOKED BY THE CLINICIANS	
Respiratory symptoms	Nocturnal hypoventilation and possible daytime hypoventilation Ability to hold breath for a long period of time and absence of air hunger afterwards
Cardiovascular symptoms	Arrhythmias Reduced heart rate variability Vasovagal syncope Syncope Cold extremities Postural hypotension
Neurologic symptoms	Developmental delay Seizures (primarily during infancy) Motor and speech delay Learning disabilities Altered perception of pain
Gastrointestinal symptoms	Hirschsprung disease-related symptoms: dysphagia, constipation, and gastroesophageal reflux
Ophthalmologic symptoms	Nonreactive/sluggish pupils Altered lacrimation and near response Anisocoria, miosis, and ptosis Strabismus
Temperature instability	Altered perspiring Absence of fever with infections
Malignancies	Tumors of neural crest origin
Psychological	Decreased anxiety

From Lijubić K, Fister I Jr, Fister I: Congenital central hypoventilation syndrome: a comprehensive review and future challenges, *J Respir Med* 856149:1–8, 2014 (Table 1, p. 3).

Genetics

The paired-like homeobox 2B *(PHOX2B)* gene is the disease-defining gene for CCHS. *PHOX2B* encodes a highly conserved homeodomain transcription factor, is essential to the embryologic development of the ANS from the neural crest, and is expressed in key regions and systems that explain much of the CCHS phenotype. Individuals with CCHS are **heterozygous** for either a *polyalanine repeat expansion mutation (PARM)* in exon 3 of the *PHOX2B* gene (normal number of alanines is 20 with normal genotype 20/20), such that individuals with CCHS have 24-33 alanines on the affected allele (genotype range is 20/24-20/33), or a *non-polyalanine repeat expansion mutation (NPARM)* resulting from a missense, nonsense, frameshift, stop codon, or splice site mutation.

Approximately 90–92% of the cases of CCHS have PARMs and the remaining 8–10% of cases have NPARMs.

LO-CCHS cases have consistently had short PARMs (primarily 20/25 genotype but 20/24 genotype also presents as LO-CCHS), or occasionally very mild NPARMs. The specific type of *PHOX2B* mutation is clinically significant because it can help with anticipatory guidance in patient management. Less than 1% of CCHS cases will have a deletion of a majority of exon 3 or the entire *PHOX2B* gene, although the specific phenotype related to these large deletion mutations is not entirely clear. Step-wise clinical *PHOX2B* testing for probands with the CCHS phenotype is advised—step 1: *PHOX2B* Screening Test (fragment analysis), then if negative, step 2: sequel *PHOX2B* Sequencing Test, then if negative, step 3: *PHOX2B* Multiplex Ligation-dependent Probe Amplification (MLPA) Test to minimize expenses and expedite confirmation of the diagnosis.

The majority of CCHS cases occur because of a de novo *PHOX2B* mutation, but up to 35% of children with CCHS inherit the mutation in an autosomal dominant manner from a seemingly asymptomatic parent who is mosaic for the *PHOX2B* mutation. An individual with CCHS has a 50% chance of transmitting the mutation, and resulting disease phenotype, to each offspring. Mosaic parents have up to a 50% chance of transmitting the *PHOX2B* mutation to each successive offspring, with risk related to the percent of mosaicism. Genetic counseling is essential for family planning and for delivery room preparation in anticipation of a CCHS birth. *PHOX2B* testing is also advised for both parents of a child with CCHS to anticipate risk of recurrence in subsequent pregnancies (if mosaic) and to determine if a parent has yet undiagnosed LO-CCHS. Fragment analysis *PHOX2B* testing (also known as the Screening Test) will best identify low-level somatic mosaicism. Prenatal testing for *PHOX2B* mutation is clinically available (www.genetests.org) for families with a known *PHOX2B* mutation.

Ventilator Dependence and Control of Breathing

Patients with CCHS have deficient CO_2 sensitivity during wakefulness and sleep such that they do not respond with a normal increase in ventilation in either state nor do they arouse in response to hypercarbia and/or hypoxemia during sleep. During wakefulness, a subset of patients may respond sufficiently to avoid significant hypercarbia, but most individuals with CCHS have hypoventilation that is severe enough that hypercarbia is apparent in the resting *awake* state.

Children with CCHS also have altered sensitivity to hypoxia while awake and asleep. A key feature of CCHS is the lack of respiratory distress or sense of asphyxia with physiologic compromise (hypercarbia and/or hypoxemia). This lack of responsiveness to hypercarbia and/or hypoxemia, which can result in respiratory failure, does not consistently improve with advancing age. A subset of older children with CCHS may show an increase in ventilation (specifically increase in respiratory rate rather than increase in tidal volume) when they are exercised at various work rates. This response is possibly secondary to neural reflexes from rhythmic limb movements, although an increase in minute ventilation is often insufficient to avoid physiologic compromise. Report of oral contraceptives improving awake CO_2 chemosensitivity in 2 adult women suggests need for further exploration.

The greater the number of extra alanines, the more likely the need for continuous ventilatory support, at least among the most common *PHOX2B* PARM genotypes (20/25, 20/26, 20/27). Thus, patients with the 20/25 genotype seldom require awake ventilatory support, although they do require artificial ventilation during sleep. Patients with the 20/26 genotype have variable awake support needs, but all require artificial ventilation during sleep. Patients with the 20/27 genotype and those with NPARMs are likely to need continuous ventilatory support. Although *PHOX2B* genotype seems to anticipate severity of hypoventilation, it does not correlate with exogenous ventilatory challenge responses. Infants and young children as a group have improved ventilatory response slopes while awake, but this advantage seems to vanish by school age.

Hirschsprung Disease (Chapter 358)

Overall, 20% of children with CCHS also have Hirschsprung disease (HSCR), and any infant or child with CCHS or LO-CCHS who presents with constipation should undergo rectal biopsy to screen for absence of ganglion cells. The frequency of Hirschsprung disease seems to increase with the longer polyalanine repeat tracts (genotypes 20/27-20/33) and in those with NPARMs. Thus far, only 1 infant with the 20/25 genotype has ever been reported to have Hirschsprung disease. Even in cases without frank HSCR disease, individuals with CCHS may display symptoms of gastrointestinal abnormalities such as severe constipation and abnormal esophageal motility, suggesting ganglion cell dysfunction.

Tumors of Neural Crest Origin (Chapter 525)

Tumors of neural crest origin are more frequent in patients with NPARMs (50%) than in those with PARMs (1%). These extracranial tumors are more often neuroblastomas in individuals with NPARMs, but ganglioneuromas and ganglioneuroblastomas in a small subset of patients with longer PARMs (20/29, 20/30, and 20/33 genotype only). Thus far, only 1 infant with a PARM (20/33 genotype) has been reported to have a neuroblastoma.

Cardiac Asystole

Transient, abrupt, and prolonged sinus pauses have been identified in patients with CCHS, necessitating implantation of cardiac pacemakers when the pauses are ≥3 sec. Among patients with the most common *PHOX2B* genotypes, 19% of those with the 20/26 genotype and 83% of those with the 20/27 genotype have cardiac pauses of 3 sec or longer. Children with the 20/25 genotype have not been noted to have prolonged asystole, although 2 adults diagnosed with LO-CCHS have demonstrated prolonged asystoles of 4-8 sec duration. Risk for sinus pauses among children with NPARMs is unknown at present.

Heart rate variability is characteristically decreased in CCHS due to a decrease in cardiac baroreflex sensitivity and blunted sympathetic response. A recent report demonstrated a genotype-phenotype relationship for heart rate variability during exogenous ventilatory response testing, prompting assessment of risk for sinus pauses. Introduction of 72-hr Holter recordings every 12 mo at a minimum has allowed for early identification of these sinus pauses, permitting timely cardiac pacemaker implantation.

Autonomic Nervous System Dysregulation

A higher number of polyalanine repeats on the affected allele among patients with a PARM is associated with an increased number of physiologic symptoms of ANSD. In addition, there is a spectrum of physiologic ANSD symptoms, including decreased heart rate variability, esophageal/gastric/colonic dysmotility, decreased pupillary response to light, reduced basal body temperature, altered distribution and amount of diaphoresis, altered vasomotor tone, and altered pain and anxiety perception.

Neuropathology

Brain imaging studies and functional MRI (fMRI) responses have identified structural deficiencies in CCHS cases which may contribute to the observed respiratory and autonomic phenotypes. These findings may be primarily due to *PHOX2B* mutation-induced failure of neurogenesis in the human embryo, but a significant contribution from postnatal hypoxic, hypercarbic, or perfusion damage cannot be excluded. The neuroanatomic defects in CCHS are likely the result of focal *PHOX2B* (mis)expression coupled with sequelae of recurrent hypoxemia/hypercarbia in the subset of suboptimally managed patients. On the basis of rodent studies and fMRI studies in humans, the following regions pertinent to respiratory control in the pons and medulla of the brainstem show *PHOX2B* expression: locus coeruleus, dorsal respiratory group, nucleus ambiguus, parafacial respiratory group, among other areas. Physiologic evidence suggests that the respiratory failure in these children is mostly based on defects in central mechanisms, but peripheral mechanisms (mainly carotid bodies) may also be important.

Clinical Manifestations

Patients with CCHS usually present with symptoms in the first few hours after birth. Most children are the products of uneventful pregnancies and are term infants with appropriate weight for gestational age. Variable Apgar scores have been reported. The affected infants do not show signs of respiratory distress, but their shallow respirations and respiratory pauses (apnea) usually evolve to respiratory failure with apparent cyanosis in the 1st days of life. In neonates with CCHS, $PaCO_2$ accumulates during sleep to very high levels, sometimes >90 mm Hg, and may decline to normal levels after the infants awaken. This problem becomes most apparent when multiple attempts at extubation fail in an intubated neonate, who appears well with ventilatory support but develops respiratory failure after removal of the support. However, more severely affected infants hypoventilate awake and asleep; thus, the previously described difference in $PaCO_2$ between states may not be apparent. Often, the respiratory rate is higher in rapid eye movement (REM) sleep than in non-REM sleep in individuals with CCHS, and in general, respiratory rates are higher in infants and children with CCHS than peers with intact control of breathing.

LO-CCHS should be suspected in infants, children, and adults who have unexplained centrally mediated hypoventilation and/or seizures or cyanosis, especially subsequent to the use of anesthetic agents and/or sedation, acute respiratory illness or recurrent severe respiratory illness with difficulty weaning from ventilator support (and failed extubations), and potentially obstructive sleep apnea (OSA) unresponsive to traditional intervention. These individuals may have other evidence of chronic hypoventilation, including pulmonary hypertension, polycythemia, elevated bicarbonate concentration, difficulty concentrating, and mild unexplained neurocognitive impairment. A heightened level of suspicion has led to increasing numbers of older children and adults diagnosed with LO-CCHS receiving proper treatment. This later presentation reflects the variable penetrance of a subset of *PHOX2B* mutations and potential role of an environmental cofactor.

In addition to treatment for the alveolar hypoventilation, children with CCHS require comprehensive physiologic evaluation during sleep and wakefulness, including activities of daily living such as eating, as their hypoxemia and hypercarbia from insufficient artificial ventilation may go unnoticed. It is necessary to provide coordinated care to optimally manage associated, multisystem abnormalities such as Hirschsprung disease, tumors of neural crest origin, and symptoms of physiologic ANSD including cardiac asystole, among other findings (details provided in American Thoracic Society 2010 Statement on CCHS).

Differential Diagnosis

Testing should be performed to rule out primary neuromuscular, lung, and cardiac disease as well as an identifiable brainstem lesion that could account for the full constellation of symptoms characteristic of CCHS. The availability of clinical *PHOX2B* genetic testing allows for early and definitive diagnosis of CCHS (Table 446.3). Because individual features of CCHS mimics many treatable and/or genetic diseases, the following disorders should also be considered: altered airway or intrathoracic anatomy (diagnosis made with bronchoscopy and chest CT), diaphragm dysfunction (diagnosis made with diaphragm fluoroscopy), a structural hindbrain or brainstem abnormality (diagnosis made with MRI of the brain and brainstem), Möbius syndrome (diagnosis made with MRI of the brain and brainstem and neurologic examination), and specific metabolic diseases, such as Leigh syndrome, pyruvate dehydrogenase deficiency, and discrete carnitine deficiency. However, profound hypercarbia without respiratory distress during sleep will quickly lead the clinician to consider the diagnosis of CCHS or LO-CCHS.

Table 446.3

Differential Diagnoses of Congenital Central Hypoventilation Syndrome

METABOLIC
Mitochondrial defects, e.g., Leigh disease
Pyruvate dehydrogenase deficiency
Hypothyroidism
NEUROLOGIC
Structural central nervous system abnormalities, e.g., Arnold Chiari malformation, Moebius syndrome
Vascular injury, e.g., central nervous system (CNS) hemorrhage, infarct
Trauma
Tumor
PULMONARY
Primary lung disease
Respiratory muscle weakness, e.g., diaphragm paralysis, congenital myopathy
GENETIC
Prader Willi syndrome
Familial dysautonomia
SEDATIVE DRUGS
OTHER
Rapid-onset obesity, hypothalamic dysregulation hypoventilation, autonomic dysregulation (ROHHAD)

Modified from Healy F, Marcus CL: Congenital central hypoventilation syndrome in children, *Pediatr Respir Rev* 12:253–263, 2011 (Table 1, p. 258).

Management

Supported Ventilation—Diaphragm Pacing

Depending on the severity of the hypoventilation, the individual with CCHS can have various options for artificial ventilation: positive pressure ventilation (noninvasive via mask or via tracheostomy) or negative pressure ventilation (pneumosuit, chest cuirass, or diaphragm pacing). Chronic mechanical ventilation is addressed in Chapters 446.1 and 446.4 . Diaphragm pacing offers another mode of supported ventilation, involving bilateral surgical implantation of electrodes beneath the phrenic nerves, with connecting wires to subcutaneously implanted receivers. The external transmitter, which is much smaller and lighter in weight than a ventilator, sends a signal to flat donut-shaped antennae that are placed on the skin over the subcutaneously implanted receivers. A signal travels from the external transmitter to the phrenic nerve to stimulate contraction of the diaphragm. A tracheostomy is typically required, because the pacers induce a negative pressure on inspiration as a result of the contraction of the diaphragm being unopposed by pharyngeal dilatation, resulting in airway obstruction with paced breaths. Individuals with CCHS who are ventilator-dependent for 24 hr a day are ideal candidates for diaphragm pacing to provide increased ambulatory freedom (without the ventilator tether) while they are awake; however, they still require mechanical ventilator support while they are asleep. This balance between awake pacing and asleep mechanical ventilation allows for a rest from phrenic nerve stimulation at night. In addition, a growing number of children and adults who require artificial ventilatory support only during sleep are now using diaphragm pacing. This is likely because of the introduction of thoracoscopic diaphragm pacer implantation and shortened postoperative recovery time. However, in the absence of a tracheostomy, diaphragm pacing during sleep may cause airway obstruction at varied levels of the airway depending on the specific patient. The potential for these obstructions needs to be carefully considered before diaphragm pacer implantation, and definitely before tracheal decannulation.

Monitoring in the Home

Home monitoring for individuals with CCHS and LO-CCHS is distinctly different from and more conservative than that for other children requiring long-term ventilation, because CCHS individuals lack innate ventilatory and arousal responses to hypoxemia and hypercarbia. In the event of physiologic compromise, other children will show clinical signs of respiratory distress. By contrast, for children and adults with CCHS and LO-CCHS, the only means of determining adequate ventilation and oxygenation is with objective measures from a pulse oximeter, end-tidal CO_2 monitor, and close supervision of these values by a highly trained registered nurse (RN) in the home and at school. While awake, patients with CCHS themselves are unable to sense or adequately respond to a respiratory challenge that may occur with ensuing respiratory illness, increased exertion, or even the simple activity of eating. At a minimum, it is essential that individuals with CCHS have continuous monitoring with pulse oximetry and end-tidal CO_2 with RN supervision during all sleep time, but ideally 24 hr/day. These recommendations apply to all CCHS and LO-CCHS patients regardless of the nature of their artificial ventilatory support, but especially those with diaphragm pacers as they have no intrinsic alarms in the diaphragm pacer device.

Noninvasive Equipment

Supplemental oxygen with positive pressure support can be administered by nasal cannulae. The nasal cannula system has the ability to deliver heated, supersaturated, high-flow gases. There are a number of mechanical devices available for the delivery of bi-level ventilation via an actual ventilator, but this is suitable only for children with milder hypoventilation during sleep only. Long-term use of mask ventilation in small children may result in mid-face dysplasia or pressure wounds.

Positive Pressure Ventilators

Ideally, a ventilator intended for home use is lightweight and small, quiet so it does not interfere with activities of daily living or sleep, is able to entrain room air, preferably has continuous flow, and has a wide range of settings (particularly for pressure support, pressure, volume, and rate) that allows ventilatory support from infancy to adulthood. Battery power for the ventilator, both internal and external, should be sufficient to permit unrestricted portability in the home and community. The equipment must also be impervious to electromagnetic interference and must be relatively easy to understand and troubleshoot. A variety of ventilators that are approved for home use are available, and familiarity with these devices is necessary to choose the best option for the individual child. Children who are chronically ventilated via positive pressure ventilation will require surgical placement of a tracheostomy tube. The tracheostomy tube provides stable access to the airway, a standardized interface for attaching the ventilator circuit to the patient, and the ability to easily remove airway secretions or deliver inhaled medications. Pediatric tracheostomy tubes typically have a single lumen and may have an inflatable cuff. Tracheostomy tubes with/without cuff inflation should be sized to control the air leak around the tube and promote adequate gas exchange, yet allow enough space around the tube to facilitate vocalization and prevent tracheal irritation and erosion from the tube.

When a tracheostomy tube is surgically placed, a slit opening is made in the trachea between the cartilaginous rings. Stay sutures are attached to the margins of the incision to facilitate emergent tube replacement prior to healing of the stoma tract. The tracheostomy tube is often electively changed by ENT about 1 wk after initial placement, and the child is subsequently cleared for tracheostomy tube changes by the nursing staff. The child's caregivers, usually parents or family members and home nursing staff, are instructed in all aspects of tracheostomy care: stoma care, elective and emergent tracheostomy change, proper securing of the tracheostomy tube, suctioning of secretions, and recognition of tube obstruction or decannulation. The child's caregivers have to demonstrate competency with all the tasks, and with cardiopulmonary resuscitation, prior to home discharge.

Optimizing Neurocognitive Performance

Impaired oxygen delivery to the brain, whether acute or chronic, can have detrimental effects on neurocognitive development. The ATS statement recommends positive pressure ventilation via tracheostomy in the first several years of life to ensure optimal oxygenation and ventilation. The method of choice in later years will depend on a variety of factors including severity of disease, patient age, level of patient and family cooperation, and availability and quality of home health care, among other factors. The level of oxygen stability obtained with each varies. Thus, the method of respiratory assistance, especially in infancy and early childhood, is likely to play a factor in neurocognitive outcome.

Past literature has indicated deficiencies of mental abilities in school-age children with CCHS. Even in preschool years, children with CCHS demonstrate reduced neurocognitive performance. In these cases, *PHOX2B* genotype is clearly associated with both mental and motor outcomes. This association is also found with CCHS-related features such as severe cyanotic breath holding spells, sinus pauses, seizures, and severity of hypoventilation. It is unclear if this association is intrinsic to the specific mutation, the phenotypes associated with the mutation, or most likely both. Despite observed delays, 29% of preschool subjects had mid-average mental development scores, and 13% performed above that level. These findings suggest the potential for excellent neurocognitive outcome. This potential appears greatest in individuals with a 20/25 genotype (Bayley mental scores over the population mean of 100). However, a 2015 report identified remarkably low IQs in a cohort of 19 Japanese children with the 20/25 genotype, with 42% of these cases reported as having displayed cognitive impairment. Many of these 20/25 genotype Japanese patients were diagnosed after the 1st mo of life and some were managed with minimal support including home oxygen only, despite clear recommendations against such support. These contrasting results indicating disparity within the same genotype emphasizes need for early recognition and conservative management to insure optimized neurocognitive outcome. Recognizing this, neurodevelopmental monitoring would be most beneficial beginning in early infancy.

Efforts are underway to evaluate and characterize the CCHS phenotype longitudinally through the International CCHS Registry (https://clinicaltrials.gov/show/NCT03088020) (Northwestern University). Delineating markers of disease progression and understanding the clinical manifestations of CCHS with advancing age will provide more accurate guidelines to healthcare providers, allowing physicians, families, and patients to better anticipate healthcare needs of affected individuals.

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446.3

Other Conditions Affecting Respiration

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Myelomeningocele With Arnold-Chiari Type II Malformation

Arnold-Chiari type II malformation (see Chapter 609) is associated with myelomeningocele, hydrocephalus, and herniation of the cerebellar tonsils, caudal brainstem, and the 4th ventricle through the foramen magnum. Sleep-disordered breathing, including OSA and hypoventilation, has been reported. Direct pressure on the respiratory centers or brainstem nuclei or increased intracranial pressure because of the hydrocephalus may be responsible. Vocal cord paralysis, apnea, hypoventilation, and bradyarrhythmias have also been reported. Patients with Arnold-Chiari type II malformation have blunted responses to hypercapnia, and, to a lesser degree, hypoxia.

Management

An acute change in the ventilatory state of a patient with this malformation requires immediate evaluation. Consideration must be given to posterior fossa decompression and/or treatment of the hydrocephalus. If this treatment is unsuccessful in resolving central hypoventilation or apnea, tracheostomy and LMV should be considered.

Rapid-Onset Obesity, Hypothalamic Dysfunction, and Autonomic Dysregulation

See Chapter 60.1 .

Obesity Hypoventilation Syndrome

As its name implies, obesity hypoventilation syndrome is a syndrome of central hypoventilation during wakefulness in obese patients with sleep-disordered breathing. Although it was initially described mainly in adult obese patients, obese children have also demonstrated the syndrome. Sleep-disordered breathing is a combination of OSA, hypopnea, and/or sleep hypoventilation syndrome. Patients are hypercapnic with cognitive impairment, morning headache, and hypersomnolence during the day. Chronic hypoxemia may lead to pulmonary hypertension and cor pulmonale.

Obesity is associated with reduced respiratory system compliance, increased airway resistance, reduced functional residual capacity, and increased work of breathing. Affected patients are unable to increase their respiratory drive in response to hypercapnia. Leptin may have a role in this syndrome. The sleep-disordered breathing leads to compensatory metabolic alkalosis. Because of the long half-life of bicarbonate, its elevation causes compensatory respiratory acidosis during wakefulness with elevated $PaCO_2$.

Management

The use of **CPAP** during sleep may be sufficient for many patients. Patients with hypoxemia may require **BiPAP** and supplemental oxygen. Tracheostomy may be considered for patients who do not tolerate mask ventilation.

Acquired Alveolar Hypoventilation

Traumatic, ischemic, and inflammatory injuries to the brainstem, brainstem infarction, brain tumors, bulbar polio, and viral paraneoplastic encephalitis may also result in central hypoventilation.

Obstructive Sleep Apnea

Epidemiology

Habitual snoring during sleep is extremely common during childhood. As many as 27% of children who snore are affected by **OSA** . The current obesity epidemic has affected the epidemiology of this condition. Peak prevalence is at 2-8 yr of age. The ratio between habitual snoring and OSA is 4:1 to 6:1.

Pathophysiology

OSA occurs when the luminal cross-sectional area of the upper airway is significantly reduced during inspiration. With increased airway resistance and reduced activation of pharyngeal dilators, negative pressure leads to upper airway collapse. The site of upper airway closure in children with OSA is at the level of tonsils and adenoids. The size of tonsils and adenoids increases throughout childhood up to 12 yr of age. Environmental irritants such as cigarette smoke or allergic rhinitis may accelerate the process. Reports suggest that early viral infections may affect adenotonsillar proliferation.

Clinical Presentation

Snoring during sleep, behavioral disturbances, learning difficulties, excessive daytime sleepiness, metabolic issues, and cardiovascular morbidity may alert the parent or physician to the presence of OSA. Diagnosis is made with the help of airway radiograms and a polysomnogram.

Treatment

When adenotonsillar hypertrophy is suspected, a consultation with an ear, nose, and throat specialist for adenoidectomy and/or tonsillectomy may be indicated. For patients who are not candidates for surgical intervention or persist with OSA despite adenoidectomy and/or tonsillectomy, CPAP or BiPAP during sleep may alleviate the obstruction (see Chapter 31).

Spinal Cord Injury

Epidemiology

There are an estimated 11,000 new spinal cord injuries **(SCIs)** annually in the United States, with more than 50% resulting in quadriplegia. SCI is relatively rare in pediatric patients, with an incidence of 1–13% of all SCI patients. The incidence in infancy and early childhood is similar for boys and girls. The preponderance of SCI in adolescents is in males. Motor vehicle accidents, falls, sports injuries, and assaults are the main causes. SCI usually leads to lifelong disability.

Pathophysiology

Children with SCI have a disproportionately higher involvement of the upper cervical spine, high frequency of SCI without radiographic abnormality, delayed onset of neurologic deficits, and higher proportion of complete injury. Thus, there is a high likelihood in pediatric SCI of quadriplegia with intercostal muscle and/or diaphragmatic paralysis leading to respiratory failure.

Management

Immobilization and stabilization of the spine must be accomplished simultaneously with initial patient resuscitation. Children with high SCI typically require lifelong ventilation, so the decision to place a tracheostomy for chronic ventilatory support is usually made early in their course of treatment. Depending on the child's age and general condition, diaphragmatic pacing may be considered. Often patients with diaphragmatic pacing need tracheostomy placement if there is dyscoordination between pacing and glottal opening. Muscle spasms occur frequently in the SCI patient and are treated with muscle relaxants. Occasionally the muscle spasms involve the chest and present a serious impediment to ventilation. Continuous intrathecal infusion of muscle relaxant via an implanted subcutaneous pump may be indicated (see Chapter 83).

Metabolic Disease

Mucopolysaccharidoses

See Chapter 107 .

Mucopolysaccharidoses are a group of progressive hereditary disorders that lack the lysosomal enzymes that degrade glycosaminoglycans. Incompletely catabolized mucopolysaccharides accumulate in connective tissue throughout the body. The inheritance is autosomal recessive except for Hunt syndrome, which is X-linked. The diagnosis is suggested by the presence of glycosaminuria and is confirmed by a lysosomal enzyme assay. I-cell disease mucolipidosis type II is an inherited lysosomal disorder with accumulation of mucolipids. Phenotypically, it is similar to mucopolysaccharidoses, but the age of onset is earlier and there is no mucopolysacchariduria. Mucopolysaccharide deposits are frequently found in the head and neck and cause airway obstruction. Typically, the affected child has a coarse face and large tongue. Significant deposits are found in the adenoids, tonsils, and cartilage. Airway radiograms and a polysomnogram may help define the severity of the upper airway obstruction.

Treatment options have included enzyme replacement therapy and stem cell transplantation with limited success. Adenoidectomy and/or tonsillectomy may be indicated but surgery alone seldom solves the problem of airway obstruction. Noninvasive CPAP or BiPAP, or tracheostomy with ventilatory support may be helpful.

Dysplasias

Campomelic dysplasia (see Chapter 718) and thanatophoric dysplasia (see Chapter 716) affect rib cage size, shape, and compliance, leading to respiratory failure. Most patients with these disorders do not survive beyond early infancy. Tracheostomy and ventilation may prolong life.

Glycogenosis Type II

See Chapter 105.1 .

Glycogenosis type II is an autosomal recessive disorder. Clinical manifestations include cardiomyopathy and generalized muscle weakness. Cardiac issues may include heart failure and arrhythmias. Muscle weakness leads to respiratory insufficiency and sleep-disordered breathing. Treatment includes emerging therapies such as enzyme replacement therapy, chaperone molecules, and gene therapy. Supportive therapy may consist of either noninvasive ventilation, or tracheostomy and mechanical ventilation. Cardiac medications, protein-rich nutrition, and judicious physical therapy are additional measures that can be utilized.

Severe Tracheomalacia and/or Bronchomalacia (Airway Malacia)

Conditions associated with airway malacia include tracheoesophageal fistula, innominate artery compression, and pulmonary artery sling after surgical repair (see Chapter 416). Patients with tracheobronchomalacia present with cough, lower airway obstruction, and wheezing. Diagnosis is made via bronchoscopy, preferably with the patient breathing spontaneously in order to evaluate dynamic airway function. Positive end-expiratory pressure titration during the bronchoscopy helps identify the ideal airway pressure required to maintain airway patency and prevent tracheobronchial collapse.

Neuropathy of Severe Illness

Children recuperating from severe illness in the intensive care unit often have neuromuscular weakness from suboptimal nutrition. This neuromuscular weakness can be devastating when coupled with the catabolic effects of severe illness and the residual effects of sedatives, analgesics, and muscle relaxants, particularly if corticosteroids were administered. Children with neuromuscular compromise have limited ability to increase ventilation and usually do so by increasing respiratory rate. Because of weakness, costal and sternal retractions may not be observed. Children with severe neuromyopathy may respond to increased respiratory load by becoming apneic. A look of panic, a change in vital signs such as significant tachycardia or bradycardia, and cyanosis may be the only signs of impending respiratory failure.

Mitochondrial Diseases

See Chapter 106 .

Mitochondria are primarily responsible for the production of adenosine triphosphate. Mitochondrial diseases are a heterogeneous group of diseases in which adenosine triphosphate production is disrupted. Mitochondrial diseases are increasingly recognized and diagnosed in the pediatric population. Organs with high-energy requirements such as the neurons, and skeletal and cardiac muscles are particularly vulnerable. Although myopathy is the most frequently recognized presentation of mitochondrial disease, it is often part of a multisystem disease process. Neurologic complications include progressive proximal myopathy, kyphoscoliosis, dyskinesia, dystonia and spasticity, stroke, epilepsy, and visual and hearing impairment. Nonneurologic manifestations include cardiomyopathy, gastrointestinal dysmotility, gastroesophageal reflux, delayed gastric emptying, and pseudoobstruction.

Respiratory complications of mitochondrial disease are multi-factorial. Muscle weakness, kyphoscoliosis, muscle spasms, and movement disorders may result in a restrictive pattern, and respiratory compromise. Additionally, dyscoordinated swallow and reflux may result in aspiration. In some mitochondrial diseases such as Leigh syndrome (see Chapter 106), central hypoventilation is an integral part of the disease. Supportive care for these patients may include noninvasive or invasive ventilation, tracheostomy placement, diuretics, appropriate nutrition, and dietary supplements.

446.4

Long-Term Mechanical Ventilation

Robert J. Graham

Keywords

chronic respiratory failure
home ventilation
decision-making
tracheostomy
noninvasive ventilation
weaning
chronic disease
complex care

See also Chapter 734.1 .

Goals and Decision-Making

The decision to implement LMV has many challenges stemming from a diversity of underlying pathophysiology, uncertain disease trajectories, the development of new condition-specific therapies, personal experiences, and values held by providers, patients, parents, and the broader community, variability in resources, and lack of standards. While optimizing gas exchange (i.e., oxygenation and CO_2 removal) remains a primary objective, it represents a tool for the comprehensive care of children with complex needs (see Chapters 446.1 and 734.1).

LMV has a role within the spectrum of palliative care. It is used proactively to attenuate cumulative morbidities (respiratory and cardiac) associated with progressive neuromuscular conditions, such as Duchenne muscular dystrophy. LMV is also used reactively when acute illness (e.g., acute respiratory distress syndrome) does not resolve. In infants with premature lung disease or complex airway anomalies, LMV may be implemented as a temporary measure, as these conditions may resolve with maturity or surgical interventions. LMV can also represent a bridge to lung transplant for those with intrinsic pulmonary or pulmonary vascular disease. LMV has become a destination therapy to optimize symptom management and prolong life in complex conditions. Etiology of the respiratory insufficiency includes, but is not limited to, congenital anomalies (e.g., complex cardiac conditions, central nervous system disorders, interruptions in aerodigestive morphogenesis, and skeletal dysplasias), acquired central neurological injuries from perinatal, infectious, traumatic, and hypoxic-ischemic events, metabolic disorders, or progressive neuromuscular conditions. Progress in other areas of medicine, such as gene-targeted therapy in spinal muscular atrophy and myotubular myopathy, may alter the LMV decision-making landscape as families foresee the prospect of improvement.

Noninvasive and Transtracheal Supports

The essential modalities for LMV include negative pressure, noninvasive positive pressure ventilation (NIPPV with either continuous or biphasic support provided through an occlusive mask interface), or transtracheal positive pressure. Considerations for a given patient should include, but are not limited to, anatomic factors, physiologic goals, long-term care goals, comfort, tolerability/compliance, and safety (mobility/portability, monitoring, device availability and back-up, training capacity).

Negative pressure devices, such as the cuirass ventilator, do not require any interface with the face or trachea and are more *natural* from a mechanical perspective. *NIPPV* can address dynamic upper airway obstruction as well as augment respiratory mechanics and gas-exchange. This modality may, however, have limitations if upper airway obstruction is severe or fixed or the need for oxygen supplementation is high. Masks, prongs, and pillows of varying sizes are available for nasal, oral, combination, and full interface, including those for infants. Mouthpiece interface has also been demonstrated to be effective and feasible. The choice of continuous positive airway pressure (CPAP) versus biphasic positive airway pressure (BiPAP) is dependent upon the underlying pathophysiology. Conceptually, CPAP can overcome a dynamic upper airway obstruction and allow for spontaneous ventilation, while BiPAP is more versatile in compensating for upper airway obstruction and supporting lung recruitment and gas-exchange. In practice, CPAP is limited to management of mild OSA.

While NIPPV can be maintained 24 hr/day, efficacy of ventilation, difficult airway considerations (i.e., Can the child be intubated?), developmental needs, implications for midface hypoplasia, and secretion clearance are among factors that impact the decision to pursue tracheostomy placement and invasive LMV.

Transtracheal LMV provides the most secure and effective respiratory support. Fixed and dynamic upper airway obstruction are bypassed with tracheostomy tube placement. Secretions are more readily cleared from the lower airway. Positive pressure and oxygen delivery via a tracheostomy tube more consistently address primary impairments in gas exchange (within limits) as well as mechanical disadvantages from neuromuscular insufficiency and restrictive disease. When possible, placement of a tracheostomy tube in a child should be coordinated at an institution with pediatric expertise, because the short-term morbidities and, potentially, mortality are not insignificant.

Individuals using NIPPV are at risk for pressure ulcerations on the face as well as on the scalp. Proper fit of the interface must be assured since a tighter fit is not necessarily commensurate with better support. Alternating masks on a regular basis may alleviate pressure on a given site. Additional non-adhesive dressings can also be used to facilitate mask seal and minimize skin breakdown. For those with a tracheostomy tube in place, care of tracheostomy ties and regular assessment of the stoma is required. Moisture-wicking dressings can attenuate risk of maceration, but their use should be balanced against the value of exposure to air for drying. Stomal assessment should include evaluation for granulation, fissures, and traction created by additional torque from ventilator tubing, which should be maintained midline and without weight displacement on the tracheostomy tube itself. Any areas of integument interruption are potential niduses for infection and of great concern for immunocompromised hosts.

Augmented Secretion Clearance

(See Chapter 446.1).

Aerodigestive and Communication Considerations

Assessment of swallowing and speaking capacity should be part of an assessment for LMV and may help guide the modality. In general, implementation of noninvasive or transtracheal supports will not further impair either of these functions. Rather, the underlying condition is the primary determinant. This consideration is most notable in patients with neurologic injury or neuromuscular conditions. Decision-making around placement of a transabdominal gastric or gastrojejunal enteral feeding tube, if not already in place, should coincide with decisions around LMV. Nasogastric tubes, it should be appreciated, may impair NIPPV mask seal as well as cause laryngeal irritation in the long-term.

Use of NIPPV must be approached cautiously in those with impaired swallowing as positive pressure will increase the risk of macro- and microaspiration. Individuals using NIPPV can eat and drink while on support with risk versus benefit determination and quality of life. Aerophagia on NIPPV is also problematic, regardless of bulbar function and swallowing capacity; abdominal distention is uncomfortable, contributes to satiety as well as vomiting risk, and further impairs respiratory mechanics with decreased functional residual capacity and increased inspiratory workload. If a gastrostomy is present, active evacuation of swallowed air and use of passive *venting* tubes can be helpful.

Children with swallowing capacity can continue to eat and drink by mouth with a tracheostomy tube in place on LMV. The presence of a cuffed tracheostomy tube does not prevent aspiration if swallowing is impaired. Speaking may be facilitated by LMV, as settings can be increased or a speaking valve utilized to increased airflow across the vocal cords. Regardless, multidisciplinary care with a speech language pathologist, feeding specialist, and augmented communication services can be helpful for many children and their families utilizing LMV. Conditioned aversions to oral stimulation can be challenging for infants but developmental gains should not be impeded by LMV.

Gas-Exchange Goals and Ventilator Strategies

Pressure- or volume-regulated modes, spontaneous or controlled settings, and mixed modes are all feasible for NIPPV and transtracheal supports with new devices. The appropriate support should coincide with oxygenation and ventilation goals on a case-by-case basis. Consideration, however, should be given to the site of care and contingencies for presentation to acute cure during intercurrent illness or emergency. Providers should assess limitations in oxygen supplementation outside of the hospital; measured or estimated delivered fractional inspired oxygen (F_{IO_2}) will inform families and providers of capacity when adding oxygen in liters/minute flow to the ventilator circuit; dilution can have a dramatic effect and achieving $F_{IO_2} > 0.60$ may be difficult when oxygen is added to a home ventilator circuit. Safety allowances should also account for the duration of portable oxygen provision, which is based upon liter flow and tank/reservoir volume.

Monitoring of CO_2 in the homecare setting is not usual, although portable end-tidal CO_2 devices are available. Conditions such as congenital central hypoventilation syndrome warrant vigilance, and parameters for implementation, or titration, of mechanical ventilation should be discussed with families. Recognition that significant and indolent hypercapnia can precede hypoxia is necessary, and long-term effects on cerebral and pulmonary vasculature should be considered. In the absence of direct CO_2 monitoring, periodic measurement of serum bicarbonate may be helpful to assess for renal compensation for altered CO_2 clearance; interpretation, however, may be altered in the presence of diuretic therapy, metabolic disease, or ketogenic diets.

Cardiopulmonary Interactions

Closely linked to the gas-exchange goals are considerations for cardiopulmonary interactions. While there are subtle implications for systemic venous return of any form of positive pressure ventilation, LMV can be used to decrease transmural myocardial load as well as optimize right ventricular afterload through lung recruitment and pulmonary vascular reactivity. The prolonged survival of young males with Duchenne muscular dystrophy is in part due to consistent respiratory support to optimize lung health as well as attenuate myocardial dysfunction. Primary or secondary pulmonary hypertension, whether overt or indolent, requires consideration of oxygenation and ventilation goals. Echocardiograms are not required for all patients with LMV, but this modality may be helpful to guide management in cohorts with congenital heart lesions, cardiomyopathies, severe obstructive pulmonary disease, significant central dysregulation, and on a case-by-case basis.

When considering gas-change goals and cardiopulmonary interactions, providers must also consider daytime and nocturnal differences. Neuromuscular-derived hypoventilation is more prominent at night as is upper airway obstructive disease; the latter is more important for those using noninvasive LMV. Daytime support provision must account for increased oxygen consumption and demand based upon variable activity as well as stressors, including environmental temperature. Providers and families must factor in mobility, behavioral tolerance, and quality of life.

Chest Wall/Thoracic Configuration

Positive pressure through LMV in early childhood for children with neuromuscular conditions and/or restrictive lung disease is also used to improve thoracic compliance and configuration. Lung inflation can be used to attenuate the impact of thoracic asphyxiation as well as progressive parasol chest deformation in diaphragm-dependent conditions, such spinal muscular atrophy. This use has implications for atelectasis and secretion inspissation, associated pulmonary vasoconstriction, and cumulative restrictive or asymmetric pulmonary mechanics.

Nutrition and Weight Gain

See Chapter 446.1 .

Developmental Considerations

Decisions regarding the LMV modality, noninvasive or transtracheal, requires consideration of development as well. Beyond safety factors, tolerance of interventions, availability of appropriate sized interfaces, and portability, there remains substantial subjectivity with respect to perspective on the implication for social interactions (i.e., devices covering the face versus a device in the neck). While there are no published series, long-term or near-continuous NIV also has implications for midface hypoplasia and potentially compounds upper airway obstructive symptoms, as is evident by images of *BiPAP faces* . Swallowing and speech capacity primarily reflect the child's underlying condition rather than the LMV.

Projected Interventions and Needs

Trajectory and management of the underlying disease as well as symptom management are primary drivers in determining the need and duration of LMV. Stakeholders should also consider future interventions, specifically surgical procedures. LMV, noninvasive or transtracheal, can be utilized to optimize perioperative standing and facilitate recovery and provision of opiate-based analgesia that could alter respiratory drive. The maintenance of a tracheostomy tube in anticipation of sequential surgeries (e.g., spinal instrumentation, craniofacial and airway reconstruction, or serial cardiac interventions) may be required for practical reasons, but also minimizes the need for repeated intubation.

Monitoring

Conceptually, monitoring is used to detect early physiologic changes and determine adequacy of LMV to minimize cumulative morbidities and risk of mortality. Recommendations for monitoring children and young adults on LMV vary based upon underlying vulnerability, care setting, and activity (e.g., home, long-term care facility, school, or in transport via car), and adjuvant supports (e.g., home nursing or personal care assistant). Pulse oximetry can be used intermittently or on a continuous basis with oxygen and heart rate parameters determined on a case-by-case basis. Internal ventilator alarm settings, for both NIV and transtracheal ventilators, are utilized to monitor high- and low-pressure parameters and minute ventilation. Stakeholders must acknowledge, however, that internal alarms may be insufficient in the setting of a large mask or peri-tracheal leak or in the event of a device malfunction. There are also pragmatic considerations of signal-to-noise when determining monitoring parameters; recurrent false alarms will desensitize providers and may disturb a child's sleep; conversely, wide alarm parameters circumvent early warning systems with significant consequences.

Transitioning From Acute Care to Rehabilitation or Community Setting

Disposition of children and young adults with LMV will vary based upon their relative stability, local support services, and goals of care. A proactive, comprehensive care model is required to assure safe and effective provision. The impact of care needs on the child and family are inextricably linked.

Routine Health Maintenance

Airway Evaluation

There is no standard for regular airway assessment for children with LMV, specifically those with transtracheal support, but annual evaluation should represent the minimum. Office-based transtracheal tube endoscopy can facilitate assessment of tube upsizing for linear growth, presence of granulation tissue, airway inflammation, and general mucosal integrity. Formal diagnostic laryngoscopy and bronchoscopy under general anesthesia is required to assess for suprastomal and laryngeal level pathology as well as the rare, acquired trachea-esophageal fistulae. Of note, independent of routine evaluation, recurrent or unexpected tracheal bleeding may warrant evaluation for a trachea-vascular fistula via CT angiogram and bronchoscopy.

Bacterial Colonization

Chronic respiratory failure lends itself to airway bacterial colonization due to alterations in secretion clearance, aerodigestive interactions, the presence of artificial airways with the development of biofilms, and other factors. Hydrophilic and Gram-negative bacteria (e.g., *Pseudomonas*, *Serratia*, and *Stenotrophomonas*) are not uncommon. There is no standard of care for determining pathogenicity versus colonization. Use of systemic or inhaled antibacterial agents to decrease colonization load, frequency of tracheostomy tube exchanges to reduce biofilm accumulation, utility of viral screening, and threshold for treatment of an acute lower airway process or tracheitis is provider and case dependent. Providers should appreciate that recurrent empiric antibacterial treatment may select for resistant bacterial strains and has implications for enteric bacterial colonization.

Dental Care

Routine daily and office-based dental care should follow standard recommendations for all children. Extrapolation from the acute care setting and general population would suggest that oropharyngeal care and minimization of bacterial overgrowth would impact the risk of superimposed respiratory illness in LMV and long-term cardiovascular outcomes, respectively. Special consideration with respect to aspiration risk, developmental tolerance, and prophylaxis and procedural sedation for intervention may require engagement of specialty providers.

Immunizations

There are no immunizations specifically indicated for individuals receiving LMV. Routine provision is recommended, including seasonal vaccinations for viral pathogens.

Radiography, Laboratory Evaluation, Polysomnography, and Pulmonary Function Testing

There are no recommendations for routine chest radiography, standard or cross-sectional, in the context of LMV. The cumulative radiation exposure would need to be considered. Gas exchange adequacy can often be assessed noninvasively. Venous, capillary, or arterial puncture for determining resting and long-term oxygenation and ventilation status may be of limited utility and validity, as intercurrent illness, technique with tourniquet, and associated agitation will alter results. Condition-specific (e.g., muscular dystrophy, polysomnography, spirometry, or pulmonary function) testing recommendations have been established. Regular assessment may also be helpful when gauging disease trajectory, LMV titration, safety parameters, and weaning potential.

Long-Term Mechanical Ventilation Weaning and Tracheal Decannulation

Reassessment of the role of LMV should be part of routine and family-centered care. Determination should include, but is not limited to, the factors described above with open discussion of goals of care, developmental appropriateness, physiologic and anatomic consideration, growth implications, and contingencies.

As there are no definitive conditioning regimens or LMV weaning strategies, providers can determine the value of time off versus decreased level of supports as well as pragmatic considerations for the child and family. Continuity of care, however, holds implicit value. Monitoring provision may need to be increased during weaning. If tracheal decannulation is required, a formal diagnostic laryngoscopy and bronchoscopy should be considered to rule out granulation (supra and infrastomal) as well as dynamic airway collapse that may prohibit immediate tracheostomy tube removal. If positive pressure or oxygen supplementation will still be required after decannulation, determination of the child's tolerance of NIV or other interventions (e.g., cough assist) should be determined in advance. Desensitization may be required.

Ultimately, LMV has an increasing role in the support of children and young adults with chronic respiratory failure. Transition from pediatric to adult services should be anticipated as this population ages. Additional research is required to inform all stakeholders regarding daily management decisions as well as healthcare resource utilization and long-term patient-centered outcomes.

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PART XIX

The Cardiovascular System

OUTLINE

Section 1 Developmental Biology of the Cardiovascular System

Section 2 Evaluation of the Cardiovascular System and the Child with A Heart Murmur

Section 3 Congenital Heart Disease

Section 4 Cardiac Arrhythmias

Section 5 Acquired Heart Disease

Section 6 Diseases of the Myocardium and Pericardium

Section 7 Cardiac Therapeutics

Section 8 Diseases of the Peripheral Vascular System

SECTION 1

Developmental Biology of the Cardiovascular System

OUTLINE

Chapter 447 Cardiac Development
Chapter 448 The Fetal to Neonatal Circulatory Transition

CHAPTER 447

Cardiac Development

Daniel Bernstein

Knowledge of the cellular and molecular mechanisms of cardiac development is necessary for understanding congenital heart defects and will be even more important in developing strategies for prevention, whether cell or molecular therapies or fetal cardiac interventional procedures. Cardiac defects have traditionally been grouped by common morphologic patterns: for example, abnormalities of the outflow tracts (**conotruncal lesions** such as tetralogy of Fallot and truncus arteriosus) and **abnormalities of atrioventricular septation** (primum atrial septal defect, complete atrioventricular canal defect). These morphologic categories may be revised or eventually supplanted by new categories as our understanding of the genetic basis of congenital heart disease progresses.

447.1

Early Cardiac Morphogenesis

Daniel Bernstein

In the early presomite embryo, the first identifiable cardiac progenitor cell clusters are arranged in the anterior lateral plate mesoderm on both sides of the embryo's central axis; these clusters form paired cardiac tubes by 18 days of gestation. The *cardiac progenitor zone* is shaped by a balanced gradient of positive and negative signals arising from the tissues surrounding the cardiac mesodermal cells, with signals from the surrounding ventral/lateral tissues promoting cardiogenesis through signaling molecules such as **BMP** (bone morphogenetic protein) and **FGF8** (fibroblast growth factor 8), and signals from dorsal/medial structures such as members of the Wnt/β-catenin pathway inhibiting cardiogenesis. Cardiogenic signals activate the expression of cardiac-specific transcription factors (e.g., Tbx, GATA, Nkx2.5) to activate cardiac gene expression. The paired tubes fuse in the midline on the ventral surface of the embryo to form the primitive *heart tube* by 22 days. This straight heart tube is composed of an outer myocardial layer, an inner endocardium, and a middle layer of extracellular matrix (ECM) known as the *cardiac jelly* . There are 2 distinct cell lineages: the **first heart field** (regulated mainly by Nkx2.5) provides precursor cells for the left ventricle; the **second heart field** (regulated mainly by Isl1) provides precursors for the atria and right ventricle. Premyocardial cells, including epicardial cells and cells derived from the neural crest, continue their migration into the region of the heart tube. Regulation of this early phase of cardiac morphogenesis is controlled in part by the interaction of specific signaling molecules or ligands, usually expressed by one cell type, with specific receptors, usually expressed by another cell type. Positional information is conveyed to the developing cardiac mesoderm by factors such as *retinoids* (isoforms of vitamin A), which bind to specific nuclear receptors and regulate gene transcription. Migration of epithelial cells into the developing heart tube is directed by ECM proteins (e.g., fibronectin) that interact with cell surface receptors (the *integrins*). The clinical importance of these signaling pathways is revealed by the spectrum of **cardiac teratogenic effects** caused by the retinoid-like drug isotretinoin.

As early as 20-22 days, before cardiac looping, the embryonic heart begins to contract and exhibit phases of the cardiac cycle that are surprisingly similar to those in the mature heart. Morphologists initially identified segments of the heart tube that were believed to correspond to structures in the mature heart (Fig. 447.1): the *sinus venosus* and atrium (right and left atria), the primitive ventricle (left ventricle), the *bulbus cordis* (right ventricle), and the *truncus arteriosus* (aorta and pulmonary artery). However, this model is oversimplified. Only the **trabecular** (most heavily muscularized) portions of the left ventricular myocardium are present in the early cardiac tube; the cells that will become the inlet portion of the left ventricle migrate into the cardiac tube at a later stage (after looping is initiated). Even later to appear are the primordial cells that give rise to the great arteries (truncus arteriosus), including cells derived from the neural crest, which are not present until after cardiac looping is complete. Chamber-specific transcription factors participate in the differentiation of atria from ventricles and in the right and left ventricles. The basic helix-loop-helix (**bHLH**) transcription factor dHAND is expressed in the developing right ventricle; disruption of this gene or of other transcriptional factors such as myocyte enhancer factors 2C (MEF2C) in mice leads to hypoplasia of the right ventricle. Other genetic markers of second heart field (early right ventricle) cells include Irx4, Tbx20, Isl1, TnT, MLC2v, and Tbx1. The transcription factor eHAND is expressed in the developing left ventricle and conotruncus and is also critical to their development. Other genetic markers of first heart field (early left ventricle) cells include Tbx5, Ncx2.5, TnT, MLC2V, and HCN4.

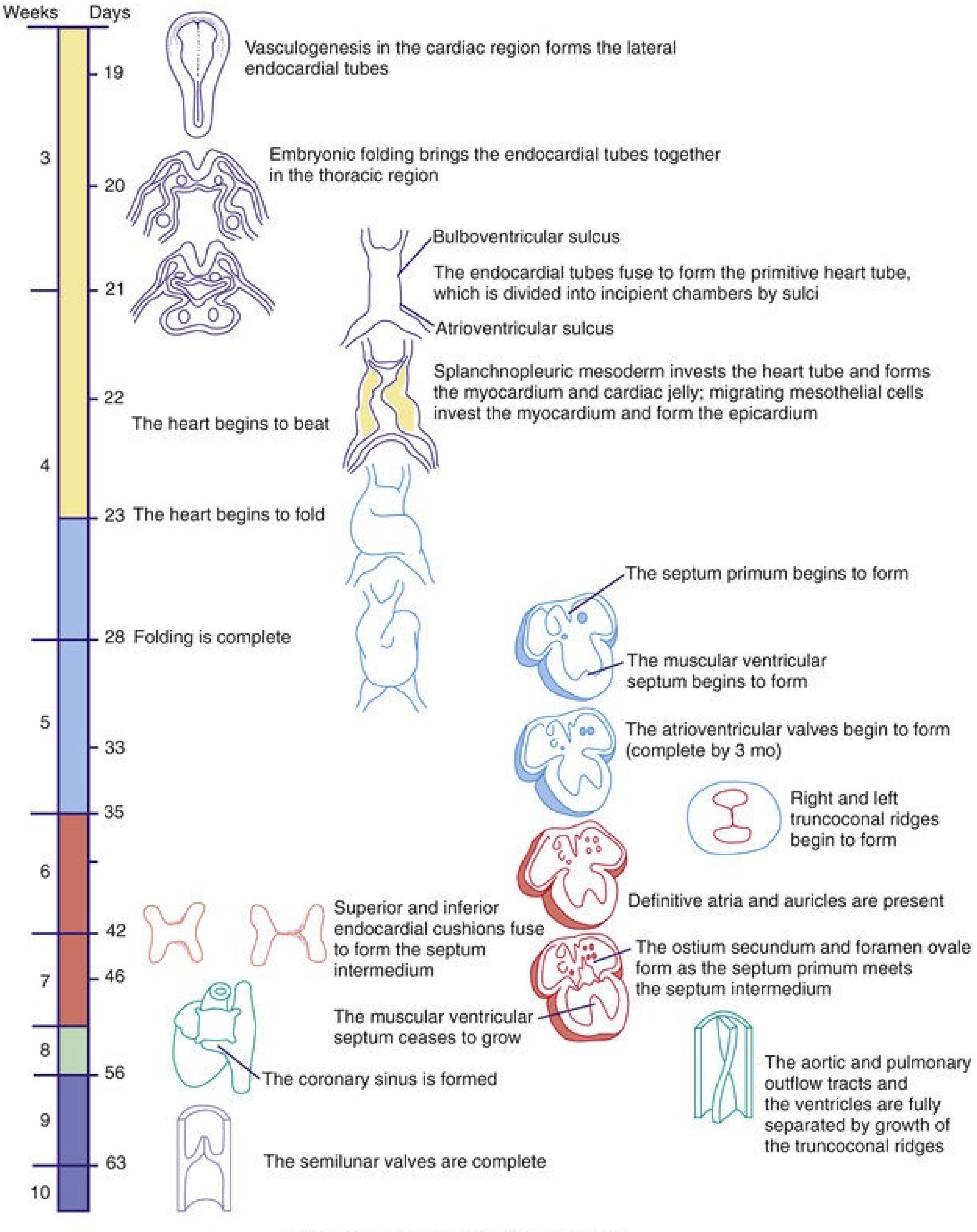
Weeks
Days
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42
46
56
63
Vasculogenesis in the cardiac region forms the lateral endocardial tubes
Embryonic folding brings the endocardial tubes together in the thoracic region
Bulboventricular sulcus
The endocardial tubes fuse to form the primitive heart tube, which is divided into incipient chambers by sulci
Atrioventricular sulcus
Splanchnopleuric mesoderm invests the heart tube and forms the myocardium and cardiac jelly; migrating mesothelial cells invest the myocardium and form the epicardium
The heart begins to beat
The heart begins to fold
The septum primum begins to form
Folding is complete
The muscular ventricular septum begins to form
The atrioventricular valves begin to form (complete by 3 mo)
Right and left truncoconal ridges begin to form
Definitive atria and auricles are present
Superior and inferior endocardial cushions fuse to form the septum intermedium
The ostium secundum and foramen ovale form as the septum primum meets the septum intermedium
The muscular ventricular septum ceases to grow
The coronary sinus is formed
The aortic and pulmonary outflow tracts and the ventricles are fully separated by growth of the truncoconal ridges
The semilunar valves are complete
TIMELINE. FORMATION OF THE HEART.

FIG. 447.1 **Timeline of cardiac morphogenesis. (From Larsen WJ: *Essentials of human embryology,* New York, 1998, Churchill Livingstone.)**

Recent research has focused on how regulation of developmentally coordinated groups of genes is achieved. One mechanism is through the expression of small, noncoding RNAs known as **micro** RNAs, each of which regulates the expression of multiple target genes. Another is through modifications in **chromatin** , the DNA scaffolding that acts as a controller of gene expression. Chromatin remodeling mediated by factors such as Brg1, Chd7, histone demethylases, and methyltransferases is associated with cardiac developmental defects.

447.2

Cardiac Looping

Daniel Bernstein

At approximately 22-24 days, the heart tube begins to bend ventrally and toward the right (see Fig. 447.1). The heart is the first organ to escape from the bilateral symmetry of the early embryo. An asymmetric signaling program that also affects the position of the lungs, liver, spleen, and gastrointestinal tract determines the direction of cardiac looping. During gastrulation, before organ formation begins, asymmetric expression of sonic hedgehog (SHH) and nodal (a member of the TGF-β family) are directed in the lateral mesoderm. These directionality signals set up a concentration gradient between the right and left sides of the embryo in the expression of critical signaling molecules. This asymmetric signaling is then amplified and propagated through the transcription factor Pitx2, which is expressed on the left side of the early heart tube, lefty1 and LR dynein. Interestingly, mice in which the LR dynein gene has been inactivated display random left-right (L-R) orientation of the heart and abdominal viscera, with 50% of their hearts looping to the right and 50% looping to the left. Other potential mechanisms of cardiac looping include differential growth rates for myocytes on the convex vs the concave surface of the curve, differential rates of programmed cell death (apoptosis), and mechanical forces generated within myocardial cells at the inner and outer edges of the bending heart tube through their actin cytoskeleton.

Looping brings the future left ventricle leftward and in continuity with the sinus venosus (future left and right atria), whereas the future right ventricle is shifted rightward and in continuity with the truncus arteriosus (future aorta and pulmonary artery). This pattern of development explains the relatively common occurrence of the cardiac anomalies **double-outlet right ventricle** and **double-inlet left ventricle** and the extreme rarity of double-outlet left ventricle and double-inlet right ventricle (see Chapter 457.5). When cardiac looping is abnormal (**situs inversus** , **heterotaxia**), the incidence of serious cardiac malformations is high, and there are usually associated abnormalities in the L-R patterning of the lungs and abdominal viscera, including absence of the spleen (**asplenia**) or multiple small spleens (**polysplenia**).

447.3

Cardiac Septation

Daniel Bernstein

When looping is complete, the external appearance of the heart is similar to that of a mature heart; internally, the structure resembles a single tube, although it now has several bulges resulting in the appearance of primitive chambers. The common atrium (comprising both right and left atria) is connected to the primitive ventricle (future left ventricle) via the atrioventricular canal. The primitive ventricle is connected to the *bulbus cordis* (future right ventricle) via the *bulboventricular foramen* . The distal portion of the bulbus cordis is connected to the *truncus arteriosus* via an outlet segment (the *conus*).

The heart tube now consists of several layers of myocardium and a single layer of endocardium separated by cardiac jelly (acellular ECM secreted by myocardium). Septation of the heart begins at approximately day 26 with the ingrowth of large tissue masses, the *endocardial cushions* , at both the atrioventricular and conotruncal junctions (see Fig. 447.1). These cushions consist of protrusions of ECM (cardiac jelly), which, in addition to their role in development, also serve a physiologic function as primitive heart valves. Endocardial cells dedifferentiate and migrate into the cardiac jelly in the region of the endocardial cushions, eventually becoming mesenchymal cells (endothelial-mesenchymal transformation) that will form part of the atrioventricular valves. The endocardium, secondary heart field, and neural crest all contribute to the formation of the valve leaflets. Besides direct contribution to valve tissue, these progenitor cells also interact with each other and with other cells in the heart to orchestrate cardiac valve development.

Complete septation of the atrioventricular canal occurs with fusion of the endocardial cushions. Most of the atrioventricular valve tissue is derived from the ventricular myocardium in a process involving undermining of the ventricular walls. Because this process occurs asymmetrically, the tricuspid valve annulus sits closer to the apex of the heart than the mitral valve annulus. Physical separation of these 2 valves produces the atrioventricular septum, the absence of which is the primary common defect in patients with **atrioventricular canal defects** (see Chapter 453.5). If the process of undermining is incomplete, the right atrioventricular valve may not separate normally from the ventricular myocardium, a possible cause of **Ebstein anomaly** (see Chapter 457.7).

Septation of the atria begins at around 30 days with growth of the septum primum downward toward the endocardial cushions (see Fig. 447.1). The orifice that remains is the ostium primum. The endocardial cushions then fuse and, together with the completed septum primum, divide the atrioventricular canal into right and left segments. A second opening appears in the posterior portion of the septum primum, the ostium secundum, and it allows a portion of the fetal venous return to the right atrium to pass across to the left atrium. Finally, the septum secundum grows downward, just to the right of the septum primum. Together with a flap of the septum primum, the ostium secundum forms the *foramen ovale* , through which fetal blood passes from the inferior vena cava to the left atrium (see Chapter 448).

Septation of the ventricles begins at about embryonic day 25 with protrusions of endocardium in both the inlet (primitive ventricle) and outlet (bulbus cordis) segments of the heart. The inlet protrusions fuse into the bulboventricular septum and extend posteriorly toward the inferior endocardial cushion, where they give rise to the inlet and trabecular portions of the interventricular septum. **Ventricular septal defects** can occur in any portion of the developing interventricular septum (see Chapter 453.6). The outlet or conotruncal septum develops from ridges of cardiac jelly, similar to the atrioventricular cushions. These ridges fuse to form a spiral septum that brings the future pulmonary artery into communication with the anterior and rightward right ventricle and the future aorta into communication with the posterior and leftward left ventricle. Differences in cell growth of the outlet septum lead to lengthening of the segment of smooth muscle beneath the pulmonary valve (conus), a process that separates the tricuspid and pulmonary valves. In contrast, disappearance of the segment beneath the aortic valve leads to fibrous continuity of the mitral and aortic valves. Within the lumen of distal outflow tract, local tissue swellings (*truncal cushions*) arise and are later populated by mesenchymal cells originating from the neural crest, participating in the formation of the semilunar (pulmonary and aortic) valves. Defects in these processes are responsible for **conotruncal** and **aortic arch defects** (truncus arteriosus, tetralogy of Fallot, pulmonary atresia, double-outlet right ventricle, interrupted aortic arch), a group of cardiac anomalies often associated with deletions of the DiGeorge critical region of **chromosome 22q11** (see Chapters 450 and 451). The transcription factor Tbx1 has been implicated as a candidate gene, which may be responsible for DiGeorge syndrome. Several genes have been implicated in valve formation, including *PTPN11* , which encodes the tyrosine phosphatase Shp-2, and when present in a mutated form, is one of the genes responsible for **Noonan syndrome** , associated with pulmonary valve stenosis, and **NOTCH1** , a regulator of cell differentiation associated with aortic valve disease.

447.4

Aortic Arch Development

Daniel Bernstein

The aortic arch, head and neck vessels, proximal pulmonary arteries, and ductus arteriosus develop from the aortic sac, arterial arches, and dorsal aortae. When the straight heart tube develops, the distal outflow portion bifurcates into the right and left 1st aortic arches, which join the paired dorsal aortae (Fig. 447.2). The dorsal aortae will fuse to form the descending aorta. The proximal aorta from the aortic valve to the left carotid artery arises from the aortic sac. The 1st and 2nd arches largely regress by about 22 days, with the 1st aortic arch giving rise to the maxillary artery and the 2nd to the stapedial and hyoid arteries. The 3rd arches participate in the formation of the innominate artery and the common and internal carotid arteries. The right 4th arch gives rise to the innominate and right subclavian arteries, and the left 4th arch participates in formation of the segment of the aortic arch between the left carotid artery and the ductus arteriosus. The 5th arch does not persist as a major structure in the mature circulation. The 6th arches join the more distal pulmonary arteries, with the right 6th arch giving rise to a portion of the proximal right pulmonary artery and the left 6th arch to the ductus arteriosus. The aortic arch between the ductus arteriosus and left subclavian artery is derived from the left-sided dorsal aorta, whereas the aortic arch distal to the left subclavian artery is derived from the fused right and left dorsal aortae. Abnormalities in development of the paired aortic arches are responsible for **right aortic arch** , **double aortic arch** , and **vascular rings** (see Chapter 459.1).

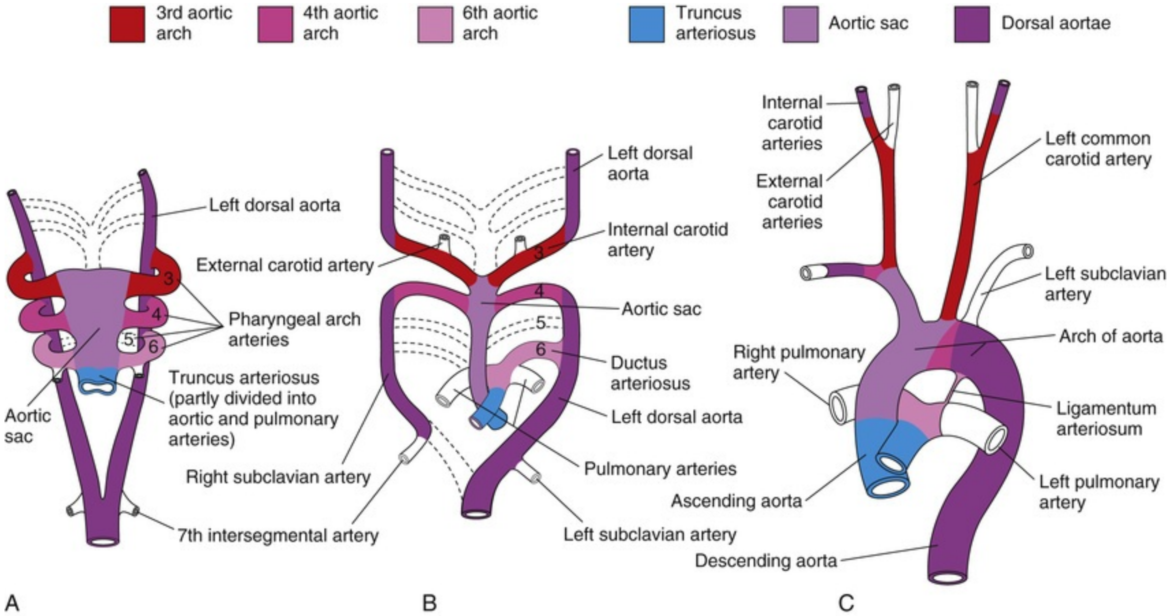
3rd aortic arch
4th aortic arch
6th aortic arch
Truncus arteriosus
Aortic sac
Dorsal aortae
Left dorsal aorta
External carotid artery
3
4
5
6
Pharyngeal arch arteries
Truncus arteriosus (partly divided into aortic and pulmonary arteries)
Aortic sac
Right subclavian artery
7th intersegmental artery
Left dorsal aorta
Internal carotid artery
3
4
5
6
Aortic sac
Ductus arteriosus
Left dorsal aorta
Pulmonary arteries
Left subclavian artery
Internal carotid arteries
External carotid arteries
Left common carotid artery
Left subclavian artery
Arch of aorta
Right pulmonary artery
Ligamentum arteriosum
Left pulmonary artery
Ascending aorta
Descending aorta
A
B
C

FIG. 447.2 Schematic drawings illustrating the changes that result during transformation of the truncus arteriosus, aortic sac, aortic arches, and dorsal aortae into the adult arterial pattern. The vessels that are *not* shaded or colored are not derived from these structures. **A,** Aortic arches at 6 wk; by this stage the 1st 2 pairs of aortic arches have largely disappeared. **B,** Aortic arches at 7 wk; the parts of the dorsal aortae and aortic arches that normally disappear are indicated by *broken lines* . **C,** Arterial vessels of 6 mo old infant. (From Moore KL, Persaud TVN, Torchia M: *The developing human,* Philadelphia, 2007, Elsevier.)

447.5

Cardiac Differentiation

Daniel Bernstein

The process by which the totipotential cells of the early embryo become committed to specific cell lineages is termed *differentiation* . Precardiac mesodermal cells differentiate into mature cardiac muscle cells with an appropriate complement of cardiac-specific contractile elements, regulatory proteins, receptors, and ion channels. Expression of the contractile protein myosin occurs at an early stage of cardiac development, even before fusion of the bilateral heart primordia. Differentiation in these early mesodermal cells is regulated by signals from the anterior endoderm, a process known as *induction* . Several putative early signaling molecules include fibroblast growth factor, activin, and insulin. Signaling molecules interact with receptors on the cell surface; these receptors activate second messengers, which in turn activate specific nuclear transcription factors (GATA-4, MEF2, Nkx, bHLH, and retinoic acid receptor family) that induce the expression of specific gene products to regulate cardiac differentiation. Some of the primary disorders of cardiac muscle, the **cardiomyopathies,** may be related to defects in some of these signaling molecules (see Chapter 466).

Developmental processes are chamber specific. Early in development, ventricular myocytes express both ventricular and atrial isoforms of several proteins, such as atrial natriuretic peptide (ANP) and myosin light chain (MLC). Mature ventricular myocytes do not express ANP and express only a ventricular-specific MLC 2v isoform, whereas mature atrial myocytes express ANP and an atrial-specific MLC 2a isoform. Heart failure (see Chapter 469), volume overload (Chapters 453 and 455), and pressure overload hypertrophy (Chapter 454) are associated with a recapitulation of fetal cell phenotypes in which mature myocytes reexpress fetal proteins. Because different isoforms have different contractile behavior (fast vs slow activation, high vs low adenosine triphosphatase activity), expression of different isoforms may have important functional consequences.

447.6

Developmental Changes in Cardiac Function

Daniel Bernstein

During development, the composition of the myocardium undergoes profound changes that result in an increase in the number and size of myocytes. During prenatal life, this process involves myocyte division (**hyperplasia**), whereas after the 1st few postnatal weeks, subsequent cardiac growth occurs mostly by an increase in myocyte size (**hypertrophy**). The myocytes themselves change shape from round to cylindrical, the proportion of myofibrils (which contain the contractile apparatus) increases, and the myofibrils become more regular in their orientation.

The *plasma membrane* (known as the *sarcolemma* in myocytes) is the location of the ion channels and transmembrane receptors that regulate the exchange of chemical information from the cell surface to the cell interior. Ion fluxes through these channels control the processes of depolarization and repolarization. Developmental changes have been described for the sodium-potassium pump, the sodium-hydrogen exchanger, and voltage-dependent calcium channels. As the myocyte matures, extensions of the sarcolemma develop toward the interior of the cell (the t-tubule system), which dramatically increases its surface area and enhances rapid activation of the myocyte. Regulation of the membrane's α- and β-adrenergic receptors with development enhances the ability of the sympathetic nervous system to control cardiac function as the heart matures.

The *sarcoplasmic reticulum* (SR), a series of tubules surrounding the myofibrils, controls the intracellular calcium concentration. A series of pumps regulate calcium release to the myofibrils for initiation of contraction (ryanodine-sensitive calcium channel) and calcium uptake for initiation of relaxation (adenosine triphosphate–dependent SR calcium pump). This SR calcium transport system is less well developed in immature hearts, which thus increasingly depend on transport of calcium from outside the cell for contraction. In a mature heart the majority of the calcium to activate contraction comes from the SR. This developmental phenomenon may explain the sensitivity of the infant heart to sarcolemmal calcium channel blockers such as verapamil, which can result in a marked depression in contractility (see Chapter 462).

The major contractile proteins (myosin, actin, tropomyosin, and troponin) are organized into the functional unit of cardiac contraction, the *sarcomere* . Each has several isoforms that are expressed differentially by location (atrium vs ventricle) and by developmental stage (embryo, fetus, newborn, adult).

Changes in myocardial structure and myocyte biochemistry result in easily quantifiable differences in cardiac function with development. Fetal cardiac function is less responsive to changes in both preload (filling volume) and afterload (systemic resistance). The most effective means of increasing ventricular function in a fetus is through increasing the heart rate. After birth and with further maturation, preload and afterload play an increasing role in regulating cardiac function. The rate of cardiac relaxation is also developmentally regulated. The decreased ability of the immature SR calcium pump to remove calcium from the contractile apparatus is manifested as a decreased ability of the fetal heart to enhance relaxation in response to sympathetic stimulation.

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CHAPTER 448

The Fetal to Neonatal Circulatory Transition

448.1

The Fetal Circulation

Daniel Bernstein

Keywords

ductus venosus
foramen ovale
ductus arteriosus
total fetal cardiac output
hypoplastic left heart syndrome
patent ductus arteriosus

The human fetal circulation and its adjustments after birth are similar to those of other large mammals, although rates of maturation differ. In the fetal circulation, the right and left ventricles exist in a parallel circuit, as opposed to the series circuit of a newborn or adult (Fig. 448.1*A*). In the fetus, the placenta provides for gas and metabolite exchange. Because the lungs do not provide gas exchange, the pulmonary vessels are vasoconstricted, diverting blood away from the pulmonary circulation. Three cardiovascular structures unique to the fetus are important for maintaining this parallel circulation: the *ductus venosus,* *foramen ovale,* and *ductus arteriosus.*

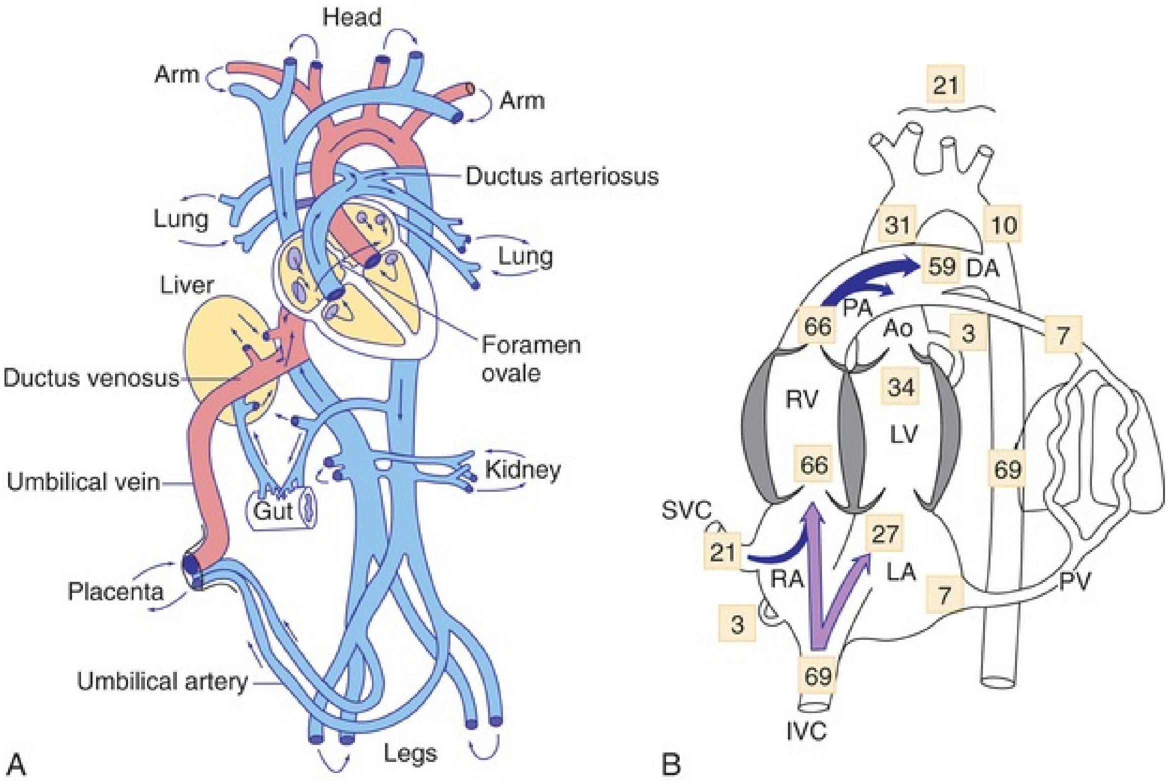
Head
Arm
Arm
Ductus arteriosus
Lung
Lung
Liver
Foramen ovale
Ductus venosus
Umbilical vein
Kidney
Gut
Placenta
Umbilical artery
Legs
A
21
31
10
59 DA
PA
66
Ao
3
7
RV
34
LV
66
69
SVC
21
27
LA
RA
7
PV
3
69
IVC
B

FIG. 448.1 **A,** The human circulation before birth (partly after Dawes). *Red* indicates more highly oxygenated blood, and *arrows* indicate the direction of flow. More highly oxygenated blood from the placenta passes through the foramen ovale from the right to the left atrium, thus bypassing the lungs. **B,** Percentages of combined ventricular output that return to the fetal heart, that are ejected by each ventricle, and that flow through the main vascular channels. Figures are those obtained from studies of late-gestation fetal lambs. Ao, Aorta; DA, ductus arteriosus; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava. (From Rudolph AM: *Congenital diseases of the heart,* Chicago, 1974, Year Book.)

The placenta is not as efficient an oxygen-exchange organ as the lungs, so that umbilical venous partial pressure of oxygen (P_{O_2}), the highest O_2 level providec to the fetus, is only 30-35 mm Hg. Approximately 50% of the umbilical venous blood enters the hepatic circulation, whereas the rest bypasses the liver and joins the inferior vena cava (IVC) via the ductus venosus, where it partially mixes with poorly oxygenated IVC blood derived from the lower part of the fetal body. This combined lower body plus umbilical venous blood flow (P_{O_2} of 26-28 mm

Hg) enters the right atrium and is preferentially directed by a flap of tissue at the right atrium–IVC junction, the eustachian valve, across the foramen ovale to the left atrium (see Fig. 448.1*B*). This is the major source of left ventricular (LV) blood flow, because pulmonary venous return is minimal. LV blood is then ejected into the ascending aorta, where it supplies predominantly the fetal upper body and brain.

Fetal superior vena cava (SVC) blood, which is considerably less oxygenated (P_{O_2} of 12-14 mm Hg) than IVC blood, enters the right atrium and preferentially flows across the tricuspid valve, rather than the foramen ovale, into the right ventricle. From the right ventricle, the blood is ejected into the pulmonary artery. Because the pulmonary arterial circulation is vasoconstricted, only approximately 5% of right ventricular (RV) outflow enters the lungs. The major portion of this blood bypasses the lungs and flows right-to-left through the ductus arteriosus into the descending aorta to perfuse the lower part of the fetal body, including providing flow to the placenta via the 2 umbilical arteries. Thus the upper part of the fetal body (including the coronary and cerebral arteries and those to the upper extremities) is perfused exclusively from the left ventricle with blood that has a slightly higher P_{O_2} than the blood perfusing the lower part of the fetal body, which is derived mostly from the right ventricle. Only a small volume of blood from the ascending aorta (10% of fetal cardiac output) flows all the way around the aortic arch (aortic isthmus) to the descending aorta.

The **total fetal cardiac output** —the combined output of both the left and right ventricles—is approximately 450 mL/kg/min. Approximately 65% of descending aortic blood flow returns to the placenta; the remaining 35% perfuses the fetal organs and tissues. In the sheep fetus, where most of these circulatory pathways were studied, RV output is approximately twice LV output. In the human fetus, which has a larger percentage of blood flow going to the brain, RV output is probably closer to 1.3 times LV flow. Thus, during fetal life the right ventricle is not only pumping against systemic blood pressure, but also performing a slightly greater volume of work than the left ventricle. Thus the RV wall is as thick as the LV wall during fetal and immediate neonatal life, explaining the unique features of the neonatal electrocardiogram (showing what would be called *right ventricular hypertrophy* in an adult).

Blood flow is believed to be an important determinant of growth of fetal cardiac chambers, valves, and blood vessels. Thus, in the presence of a narrowing (stenosis) of an upstream structure such as the mitral valve, flow downstream into the left ventricle is limited and LV growth may be compromised, which may be a cause of **hypoplastic left heart syndrome** (HLHS; see Chapter 458.10). Similarly, stenosis of a downstream structure such as the aortic valve can disrupt flow into the left ventricle and also potentially lead to HLHS. Fetal cardiac interventional treatments, currently experimental, are aimed at opening stenotic aortic valves in mid-gestation fetuses and allowing more normal LV growth. However, the outcome of these procedures does not enhance LV growth in all patients, suggesting that in many cases of HLHS there is a separate defect in the LV cardiomyocytes themselves (i.e., cell-autonomous defect).

448.2

The Transitional Circulation

Daniel Bernstein

At birth, mechanical expansion of the lungs and an increase in arterial P_{O_2} result in a rapid decrease in pulmonary vascular resistance (PVR). Concomitantly, removal of the low-resistance placental circulation leads to an increase in systemic vascular resistance (SVR). The output from the right ventricle now flows entirely into the pulmonary circulation, and because PVR becomes lower than SVR, the shunt through the ductus arteriosus reverses and becomes left to right. Over several days the high arterial P_{O_2} constricts and eventually closes the ductus arteriosus, which eventually becomes the ligamentum arteriosum. The increased volume of pulmonary blood flow returning to the left atrium from the lungs increases left atrial volume and pressure sufficiently to close the flap of the foramen ovale functionally, although the foramen may remain patent, on probing, for several years.

Removal of the placenta from the circulation also results in closure of the ductus venosus. The left ventricle is now coupled to the high-resistance systemic circulation, and its wall thickness and mass begin to increase. In contrast, the right ventricle is now coupled to the low-resistance pulmonary circulation, and its wall thickness and mass decrease. The left ventricle, which in the fetus pumped blood only to the upper part of the body and brain, must now deliver the entire systemic cardiac output (approximately 350 mL/kg/min), an almost 200% increase in output. This marked increase in LV performance is achieved through a combination of hormonal and metabolic signals, including an increase in the level of circulating catecholamines and in the density of myocardial β-adrenergic receptors, through which catecholamines have their effect.

When superimposed on these dramatic physiologic changes, congenital structural cardiac defects often impede this smooth transition and greatly increase the burden on the newborn myocardium. In addition, because the ductus arteriosus and foramen ovale do not close completely at birth, they may remain patent in certain congenital cardiac lesions. Patency of these fetal pathways may either provide a lifesaving pathway for blood to bypass a congenital defect (patent ductus in **pulmonary atresia** or **coarctation of aorta** , foramen ovale in **transposition of great vessels**) or present an additional stress to the circulation (**patent ductus arteriosus** in premature infant, pathway for **right-to-left shunting** in infant with pulmonary hypertension). Therapeutic agents may either maintain these fetal pathways (e.g., *prostaglandin* E_1) or hasten their closure (e.g., *indomethacin*). This pharmacology explains why indomethacin and similar drugs are contraindicated during the third trimester.

448.3

The Neonatal Circulation

Daniel Bernstein

At birth, the fetal circulation must immediately adapt to extrauterine life as gas exchange is transferred from the placenta to the lungs (see Chapter 122.1). Some of these changes are virtually instantaneous with the first breath, whereas others develop over hours or weeks. With the onset of breathing and lung ventilation, pulmonary vascular resistance is greatly decreased as a consequence of both active (i.e., P_{O_2} related) and passive (i.e., mechanical related) pulmonary vasodilation. In a normal neonate, closure of the ductus arteriosus and the fall in PVR decreases pulmonary arterial and RV pressures. The largest decline in PVR from the high fetal levels to the lower “adult” levels in the human infant at sea level usually occurs within 2-3 days, but may be prolonged for ≥7 days after birth. Over the next several weeks of life, PVR decreases even further, secondary to a remodeling of the pulmonary vasculature, including thinning of the vascular smooth muscle and recruitment of new vessels. This decrease in PVR significantly influences the timing of the clinical appearance of many congenital heart lesions dependent on the relative levels of SVR and PVR. The left-to-right shunt through a large ventricular septal defect (VSD) may be minimal in the 1st week after birth, when PVR is still high. As PVR decreases in the next 1 or 2 wk, the volume of the left-to-right shunt through the VSD increases and eventually leads to symptoms of heart failure within the 1st or 2nd mo of postnatal life.

Significant differences between the neonatal circulation and that of older infants: (1) right-to-left or left-to-right shunting may persist across the patent foramen ovale; (2) in the presence of cardiopulmonary disease, continued patency of the ductus arteriosus may allow left-to-right, right-to-left, or bidirectional shunting; (3) the neonatal pulmonary vasculature constricts more vigorously in response to hypoxemia, hypercapnia, and acidosis; (4) the wall thickness and muscle mass of the neonatal left and right ventricles are almost equal; and (5) newborn infants at rest have relatively high oxygen consumption, which is associated with relatively high cardiac output. The newborn cardiac output (350 mL/kg/min) falls in the 1st 2 mo of life to approximately 150 mL/kg/min and then more gradually to the normal adult cardiac output of 75 mL/kg/min. Although fetal hemoglobin is beneficial to delivery of oxygen in the low-P_{O_2} fetal circulation, the high percentage of fetal hemoglobin present in the newborn may actually interfere with delivery of oxygen to tissues in the high–systemic P_{O_2} neonatal circulation (see Chapter 122.1).

The foramen ovale is usually functionally closed by the 3rd mo of life, although it is possible to pass a probe through the overlapping flaps in a large percentage of children and in 15–25% of adults. Functional closure of the ductus arteriosus is usually complete by 10-15 hr of postnatal age in a normal neonate, although the ductus may remain patent much longer in the presence of congenital heart disease, especially when associated with cyanosis. In premature newborn infants, an evanescent systolic murmur with late accentuation or a continuous murmur may be audible, and in the context of respiratory distress syndrome, the presence of a patent ductus arteriosus should be suspected (see Chapter 122.5).

The normal ductus arteriosus differs morphologically from the adjoining aorta and pulmonary artery in that the ductus has a significant amount of circularly arranged smooth muscle in its medial layer. During fetal life, patency of the ductus arteriosus appears to be maintained by the combined relaxant effects of low oxygen tension and endogenously produced prostaglandins, specifically prostaglandin E_2 . In a full-term neonate, oxygen is the most important factor controlling ductal closure. When the PO_2 of the blood passing through the ductus reaches about 50 mm Hg, the ductal wall begins to constrict. The effects of oxygen on ductal smooth muscle may be direct or mediated by its effects on prostaglandin synthesis. Gestational age also appears to play an important role; the ductus of a premature infant is less responsive to oxygen, even though its musculature is developed.

448.4

Persistent Pulmonary Hypertension of the Neonate (Persistence of Fetal Circulatory Pathways)

See Chapter 122.9 .

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SECTION 2

Evaluation of the Cardiovascular System and the Child with A Heart Murmur

OUTLINE

Chapter 449 History and Physical Examination in Cardiac Evaluation

Chapter 450 Laboratory Cardiac Evaluation

CHAPTER 449

History and Physical Examination in Cardiac Evaluation

Daniel Bernstein

The importance of the history and physical examination cannot be overemphasized in the evaluation of infants and children with suspected cardiovascular disorders. One of the most common reasons for cardiac evaluation in young children is the heart murmur; **innocent or functional murmurs** may be heard in up to 30% of patients at some time during childhood. Functional murmurs are usually accentuated by fever and first noticed during a visit for an intercurrent illness. Thus the general pediatrician must be able to distinguish those murmurs that are functional from those that are potentially pathologic and refer patients with pathologic-sounding murmurs or murmurs of uncertain nature for evaluation by a pediatric cardiologist.

Although several attempts have been made to develop computerized systems for distinguishing innocent from pathologic murmurs, the accuracy of these systems is still wanting, and there is no substitute for a careful examination by the clinician. Patients may require further laboratory evaluation and eventual treatment, or the family may be reassured that no significant problem exists. Although the ready availability of echocardiography may entice the clinician to skip these preliminary steps, an initial evaluation by a skilled cardiologist is preferred for several reasons: (1) a cardiac examination allows the cardiologist to guide the echocardiographic evaluation toward confirming or eliminating specific diagnoses, thereby increasing its accuracy; (2) because most childhood murmurs are innocent, evaluation by a pediatric cardiologist can eliminate unnecessary and expensive laboratory tests; and (3) the cardiologist's knowledge and experience are important in reassuring the patient's family and preventing unnecessary restrictions on healthy physical activity. An experienced pediatric cardiologist can differentiate an innocent murmur from serious congenital heart disease by history and physical examination alone with high sensitivity and specificity.

History

The evaluation begins with a comprehensive cardiac history, as diagnosis of a functional murmur can only be made in the absence of any concerning symptoms, signs, or family history. A comprehensive cardiac history starts with details of the perinatal period, including the presence of cyanosis, respiratory distress, or prematurity. **Maternal complications** such as gestational diabetes, teratogenic medications, systemic lupus erythematosus, or substance abuse can be associated with cardiac problems. If cardiac symptoms began during infancy, the timing of the initial symptoms should be noted to provide important clues about the specific cardiac condition.

Many of the symptoms of **heart failure** in infants and children are age specific. In infants, feeding difficulties are common. Inquiry should be made about the frequency of feeding and either the volume of each feeding or the time spent on each breast. An infant with heart failure often takes less volume per feeding and becomes dyspneic or diaphoretic while sucking. After falling asleep exhausted, the baby, inadequately fed, will awaken for the next feeding after a brief time. This cycle continues around the clock and must be carefully differentiated from colic or other feeding disorders. Additional symptoms and signs include those of respiratory distress: rapid breathing, nasal flaring, cyanosis, and chest retractions. In older children, heart failure may be manifested as exercise intolerance, difficulty keeping up with peers during sports or the need for a nap after coming home from school, poor growth, or chronic abdominal complaints. Eliciting a history of fatigue in an older child requires questions about age-specific activities, including stair climbing, walking, bicycle riding, physical education class, and competitive sports; information should be obtained regarding more severe manifestations such as orthopnea and nocturnal dyspnea.

Parents often overlook their baby's **cyanosis** at rest; it may be mistaken for a normal individual variation in color. Cyanosis during crying or exercise, however, is more often noted as abnormal by observant parents. Many infants and toddlers turn “blue around the lips” when crying vigorously or during breath-holding spells; this condition must be carefully differentiated from **cyanotic heart disease** by inquiring about inciting factors, the length of episodes, and whether the tongue and mucous membranes also appear cyanotic.

Newborns often have cyanosis of their extremities (**acrocyanosis**) when undressed and cold; this response to cold must be carefully differentiated from true cyanosis, where the mucous membranes are also blue.

Chest pain is an unusual manifestation of cardiac disease in pediatric patients, although it is a frequent cause for referral to a pediatric cardiologist, especially in adolescents. Nonetheless, a careful history, physical examination, and, if indicated, laboratory or imaging tests will assist in identifying the cause of chest pain (Table 449.1). For patients with some forms of repaired congenital heart disease (CHD) or those with a history of Kawasaki disease (see Chapter 471.1), chest pain should be evaluated carefully for a coronary etiology.

Table 449.1

Differential Diagnosis of Chest Pain in Pediatric Patients

Musculoskeletal (Common)

Trauma (accidental, abuse)
Exercise, overuse injury (strain, bursitis)
Costochondritis (Tietze syndrome)
Herpes zoster (cutaneous or without rash)
Pleurodynia
Fibrositis
Slipping rib
Rib fracture
Precordial catch
Sickle cell anemia vasoocclusive crisis
Osteomyelitis (rare)
Primary or metastatic tumor (rare)
Fibromyalgia
Nerve entrapment

Pulmonary (Common)

Pneumonia
Pleurisy

Asthma
Chronic cough
Pneumothorax
Infarction (sickle cell anemia)
Foreign body
Embolism (rare)
Pulmonary hypertension (rare)
Tumor (rare)
Bronchiectasis

Gastrointestinal (Less Common)

Esophagitis (gastroesophageal reflux, infectious, pill)
Esophageal foreign body
Esophageal spasm
Cholecystitis
Subdiaphragmatic abscess
Perihepatitis (Fitz-Hugh-Curtis syndrome)
Peptic ulcer disease
Pancreatitis
Splenic rupture

Cardiac (Less Common)

Pericarditis
Postpericardiotomy syndrome
Endocarditis
Myocarditis
Cardiomyopathy
Mitral valve prolapse
Aortic or subaortic stenosis
Arrhythmias (supraventricular, ventricular, tachycardias)
Marfan syndrome (dissecting aortic aneurysm)
Kawasaki disease
Cocaine, sympathomimetic ingestion
Ischemia (familial hypercholesterolemia, anomalous coronary artery)

Takotsubo cardiomyopathy (primary or secondary)

Idiopathic (Common)

Anxiety, hyperventilation
Panic disorder

Other (Less Common)

Spinal cord or nerve root compression
Breast-related pathologic condition (mastalgia)
Castleman disease (lymph node neoplasm)

Cardiac disease may be a manifestation of a known congenital malformation syndrome with typical physical findings (Table 449.2) or a manifestation of a generalized disorder affecting the heart and other organ systems (Table 449.3). **Extracardiac malformations** may be noted in 20–45% of infants with CHD. Between 5% and 10% of patients have a known chromosomal abnormality; the importance of genetic evaluation will increase as our knowledge of specific gene defects linked to CHD increases (Fig. 449.1).

Table 449.2

Congenital Malformation Syndromes Associated With Congenital Heart Disease

SYNDROME	FEATURES
CHROMOSOMAL DISORDERS	
Trisomy 21 (Down syndrome)	Endocardial cushion defect, VSD, ASD
Trisomy 21p (cat-eye syndrome)	Miscellaneous, total anomalous pulmonary venous return
Trisomy 18	VSD, ASD, PDA, TOF, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 13	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 9	Miscellaneous, VSD
XXXXY	PDA, ASD
Penta X	PDA, VSD
Triploidy	VSD, ASD, PDA
XO (Turner syndrome)	Bicuspid aortic valve, coarctation of aorta
Fragile X	Mitral valve prolapse, aortic root dilatation
Duplication 3q2	Miscellaneous

Deletion 4p	VSD, PDA, aortic stenosis
Deletion 9p	Miscellaneous
Deletion 5p (cri du chat syndrome)	VSD, PDA, ASD, TOF
Deletion 10q	VSD, TOF, conotruncal lesions*
Deletion 13q	VSD
Deletion 18q	VSD
Deletion 1p36	ASD, VSD, PDA, TOF, cardiomyopathy
Deletion/duplication 1q21.1	ASD, VSD, PS
Deletion 17q11 (William syndrome)	Supravalvar AS, branch PS
Deletion 11q 24-25 (Jacobsen syndrome)	VSD, left sided lesions
SYNDROME COMPLEXES	
CHARGE association (*c* oloboma, *h* eart, *a* tresia choanae, *r* etardation, *g* enital, and *e* ar anomalies)	VSD, ASD, PDA, TOF, endocardial cushion defect
DiGeorge sequence, CATCH 22 (*c* ardiac defects, *a* bnormal facies, *t* hymic aplasia, *c* left palate, *h* ypocalcemia, and deletion 22q11)	Aortic arch anomalies, conotruncal anomalies
Alagille syndrome (arteriohepatic dysplasia)	Peripheral pulmonic stenosis, PS, TOF
VATER association (*v* ertebral, *a* nal, *t* racheo*e* sophageal, *r* adial, and *r* enal anomalies)	VSD, TOF, ASD, PDA
FAVS (*f* acio*a* uriculo*v* ertebral *s* pectrum)	TOF, VSD
CHILD (*c* ongenital *h* emidysplasia with *i* chthyosiform erythroderma, *l* imb *d* efects)	Miscellaneous
Mulibrey nanism (muscle, liver, brain, eye)	Pericardial thickening, constrictive pericarditis
Asplenia syndrome	Complex cyanotic heart lesions with decreased pulmonary blood flow, transposition of great arteries, anomalous pulmonary venous return, dextrocardia, single ventricle, single atrioventricular valve
Polysplenia syndrome	Acyanotic lesions with increased pulmonary blood flow, azygos continuation of inferior vena cava, partial anomalous pulmonary venous return, dextrocardia, single ventricle, common atrioventricular valve
PHACE syndrome (*p* osterior brain fossa anomalies, facial *h* emangiomas, *a* rterial anomalies, *c* ardiac anomalies and aortic coarctation, *e* ye anomalies)	VSD, PDA, coarctation of aorta, arterial aneurysms
TERATOGENIC AGENTS	
Congenital rubella	PDA, peripheral pulmonic stenosis
Fetal hydantoin syndrome	VSD, ASD, coarctation of aorta, PDA
Fetal alcohol syndrome	ASD, VSD
Fetal valproate effects	Coarctation of aorta, hypoplastic left side of heart, aortic stenosis, pulmonary atresia, VSD
Maternal phenylketonuria	VSD, ASD, PDA, coarctation of aorta
Retinoic acid embryopathy	Conotruncal anomalies
OTHERS	
Apert syndrome	VSD
Autosomal dominant polycystic kidney disease	Mitral valve prolapse
Carpenter syndrome	PDA
Conradi syndrome	VSD, PDA
Crouzon disease	PDA, coarctation of aorta
Cutis laxa	Pulmonary hypertension, pulmonic stenosis
De Lange syndrome	VSD
Ellis–van Creveld syndrome	Single atrium, VSD

Holt-Oram syndrome	ASD, VSD, 1st-degree heart block
Infant of diabetic mother	Hypertrophic cardiomyopathy, VSD, conotruncal anomalies
Kartagener syndrome	Dextrocardia
Meckel-Gruber syndrome	ASD, VSD
Noonan syndrome	Pulmonic stenosis, ASD, cardiomyopathy
Pallister-Hall syndrome	Endocardial cushion defect
Primary ciliary dyskinesia	Heterotaxia disorders
Rubinstein-Taybi syndrome	VSD
Scimitar syndrome	Hypoplasia of right lung, anomalous pulmonary venous return to inferior vena cava
Smith-Lemli-Opitz syndrome	VSD, PDA
TAR syndrome (thrombocytopenia and absent radius)	ASD, TOF
Treacher Collins syndrome	VSD, ASD, PDA

[*] Conotruncal includes TOF, pulmonary atresia, truncus arteriosus, and transposition of great arteries.

ASD, Atrial septal defect; AV, aortic valve; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 449.3

Cardiac Manifestations of Systemic Diseases

SYSTEMIC DISEASE	CARDIAC COMPLICATIONS
INFLAMMATORY DISORDERS	
Sepsis	Hypotension, myocardial dysfunction, pericardial effusion, pulmonary hypertension
Juvenile idiopathic arthritis	Pericarditis, rarely myocarditis
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, coronary arteritis, coronary atherosclerosis (with steroids), congenital heart block
Scleroderma	Pulmonary hypertension, myocardial fibrosis, cardiomyopathy
Dermatomyositis	Cardiomyopathy, arrhythmias, heart block
Kawasaki disease	Coronary artery aneurysm and thrombosis, myocardial infarction, myocarditis, valvular insufficiency
Sarcoidosis	Granuloma, fibrosis, amyloidosis, biventricular hypertrophy, arrhythmias
Lyme disease	Arrhythmias, myocarditis
Löffler hypereosinophilic syndrome	Endomyocardial disease
INBORN ERRORS OF METABOLISM	
Refsum disease	Arrhythmia, sudden death
Hunter or Hurler syndrome	Valvular insufficiency, heart failure, hypertension
Fabry disease	Mitral insufficiency, coronary artery disease with myocardial infarction
Glycogen storage disease IIa (Pompe disease)	Short P-R interval, cardiomegaly, heart failure, arrhythmias
Carnitine deficiency	Heart failure, cardiomyopathy
Gaucher disease	Pericarditis
Homocystinuria	Coronary thrombosis
Alkaptonuria	Atherosclerosis, valvular disease
Morquio-Ullrich syndrome	Aortic incompetence
Scheie syndrome	Aortic incompetence

CONNECTIVE TISSUE DISORDERS	
Arterial calcification of infancy	Calcinosis of coronary arteries, aorta, heart failure, hypertension
Marfan syndrome	Aortic and mitral insufficiency, dissecting aortic aneurysm, mitral valve prolapse
Congenital contractural arachnodactyly	Mitral insufficiency or prolapse
Ehlers-Danlos syndrome	Mitral valve prolapse, dilatated aortic root
Osteogenesis imperfecta	Aortic incompetence
Pseudoxanthoma elasticum	Peripheral arterial disease
NEUROMUSCULAR DISORDERS	
Friedreich ataxia	Cardiomyopathy
Duchenne dystrophy	Cardiomyopathy, heart failure
Tuberous sclerosis	Cardiac rhabdomyoma
Familial deafness	Occasionally arrhythmia, sudden death
Neurofibromatosis	Pulmonic stenosis, pheochromocytoma, coarctation of aorta
Riley-Day syndrome	Episodic hypertension, postural hypotension
Von Hippel–Lindau disease	Hemangiomas, pheochromocytomas
ENDOCRINE-METABOLIC DISORDERS	
Graves' disease	Tachycardia, arrhythmias, heart failure
Hypothyroidism	Bradycardia, pericardial effusion, cardiomyopathy, low-voltage electrocardiogram
Pheochromocytoma	Hypertension, myocardial ischemia, myocardial fibrosis, cardiomyopathy
Carcinoid	Right-sided endocardial fibrosis
HEMATOLOGIC DISORDERS	
Sickle cell anemia	High-output heart failure, cardiomyopathy, pulmonary hypertension
Thalassemia major	High-output heart failure, hemochromatosis
Hemochromatosis (1st or 2nd degree)	Cardiomyopathy
OTHERS	
Appetite suppressants (fenfluramine and dexfenfluramine)	Cardiac valvulopathy, pulmonary hypertension
Cockayne syndrome	Atherosclerosis
Familial dwarfism and nevi	Cardiomyopathy
Jervell and Lange-Nielsen syndrome	Prolonged Q-T interval, sudden death
Kearns-Sayre syndrome	Heart block
LEOPARD syndrome (lentiginosis)	Pulmonic stenosis, prolonged Q-T interval
Progeria	Accelerated atherosclerosis
Osler-Weber-Rendu disease	Arteriovenous fistula (lung, liver, mucous membrane)
Romano-Ward syndrome	Prolonged Q-T interval, sudden death
Weill-Marchesani syndrome	Patent ductus arteriosus
Werner syndrome	Vascular sclerosis, cardiomyopathy

LEOPARD, Multiple *l* entigines, *e* lectrocardiographic conduction abnormalities, *o* cular hypertelorism, *p* ulmonary stenosis, *a* bnormal genitals, *r* etardation of growth, sensorineural *d* eafness.

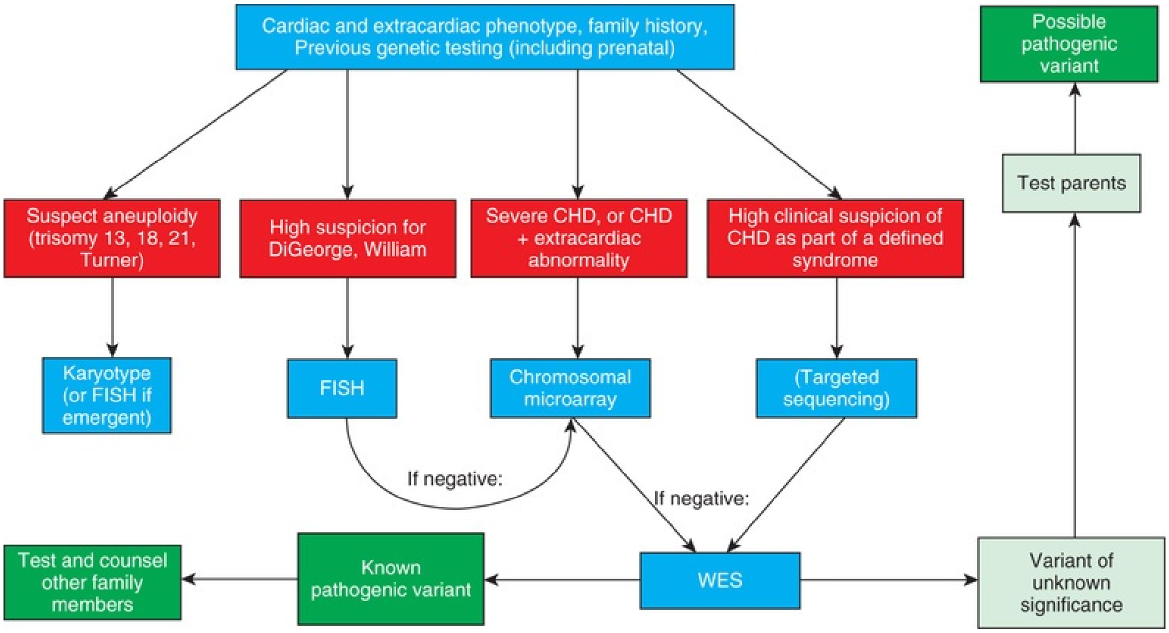
Cardiac and extracardiac phenotype, family history, Previous genetic testing (including prenatal)
Possible pathogenic variant
Test parents
Suspect aneuploidy (trisomy 13, 18, 21, Turner)
High suspicion for DiGeorge, William
Severe CHD, or CHD + extracardiac abnormality
High clinical suspicion of CHD as part of a defined syndrome
Karyotype (or FISH if emergent)
FISH
Chromosomal microarray
(Targeted sequencing)
If negative:
If negative:
Test and counsel other family members
Known pathogenic variant
WES
Variant of unknown significance

FIG. 449.1 Genetics screening algorithm for congenital heart disease (CHD) patients. FISH, Fluorescence in situ hybridization; WES, whole exome sequencing. (From Simmons MA, Brueckner M: The genetics of congenital heart disease… understanding and improving long-term outcomes in congenital heart disease: a review for the general cardiologist and primary care physician, Curr Opin Pediatr 29:520–528, 2017, Fig 2, p 526.)

A careful family history may also reveal early (at age <50 yr) coronary artery disease or stroke (suggestive of familial hypercholesterolemia or thrombophilia), sudden death (suggestive of cardiomyopathy or familial arrhythmic disorder), generalized muscle disease (suggestive of one of the muscular dystrophies, dermatomyositis, or familial or metabolic cardiomyopathy), or first-degree relatives with congenital heart disease.

General Physical Examination

In the evaluation of a child with a heart murmur, a general physical examination is always performed, with specific attention directed toward the presence of cyanosis, abnormalities in growth, chest wall abnormalities, and any evidence of respiratory distress. Although the murmur may be the most prominent part of the overall examination, any murmur must be placed in context of other physical findings. Associated findings such as quality of the pulses, presence of a **ventricular heave** or **thrill** , or **splitting of the second heart sound** provide important clues to a specific cardiac diagnosis.

Accurate measurement of height and weight and plotting on a standard growth chart are important because both cardiac failure and chronic cyanosis can result in **failure to thrive** . Growth failure is manifested predominantly by poor weight gain; if length or head circumference is also affected, additional congenital malformations or metabolic disorders should be suspected.

Mild cyanosis may be too subtle for early detection, and clubbing of the fingers and toes is not usually manifested until late in the 1st year of life, even in the presence of severe arterial oxygen desaturation. Cyanosis is best observed over the nail beds, lips, tongue, and mucous membranes. **Differential cyanosis** , manifested as blue lower extremities and pink upper extremities (usually the right arm), is seen with right-to-left shunting across a ductus arteriosus in the presence of coarctation or an interrupted aortic arch. Circumoral cyanosis or blueness around the forehead may be the result of prominent venous plexuses in these areas, rather than decreased arterial oxygen saturation. The extremities of infants often turn blue when the infant is unwrapped and cold (acrocyanosis), and this condition can be distinguished from central cyanosis by examination of the tongue and mucous membranes.

Heart failure in infants and children usually results in some degree of hepatomegaly and occasionally splenomegaly. The sites of **peripheral** edema are age dependent. In infants, edema is usually seen around the eyes and over the flanks, especially on initially waking. Older children and teenagers manifest both periorbital edema and pedal edema. An initial complaint in these older patients may be that their clothes no longer fit.

The **heart rate** of newborn infants is rapid and subject to wide fluctuations (Table 449.4). The average rate ranges from 120-140 beats/min and may increase to 170+ beats/min during crying and activity or drop to 70-90 beats/min during sleep. As the child grows older, the average pulse rate decreases and may be as low as 40 beats/min at rest in athletic adolescents. Persistent **tachycardia** (>200 beats/min in neonates, 150 beats/min in infants, or 120 beats/min in older children), bradycardia, or an irregular heartbeat other than sinus arrhythmia requires investigation to exclude pathologic arrhythmias (see Chapter 462). **Sinus arrhythmia** can usually be distinguished by the rhythmic nature of the heart rate variations, occurring in concert with the respiratory cycle, and with a P wave before every QRS complex.

Table 449.4

Pulse Rates at Rest

AGE	LOWER LIMITS OF NORMAL (beats/min)		AVERAGE (beats/min)		UPPER LIMITS OF NORMAL (beats/min)	
Newborn	70		125		190	
1–11 mo	80		120		160	
2 yr	80		110		130	
4 yr	80		100		120	
6 yr	75		100		115	
8 yr	70		90		110	
10 yr	70		90		110	
	GIRLS	**BOYS**	**GIRLS**	**BOYS**	**GIRLS**	**BOYS**
12 yr	70	65	90	85	110	105
14 yr	65	60	85	80	105	100
16 yr	60	55	80	75	100	95
18 yr	55	50	75	70	95	90

Careful evaluation of the character of the **pulses** is an important early step in the physical diagnosis of CHD. A wide pulse pressure with bounding pulses may suggest an aortic runoff lesion such as patent ductus arteriosus (PDA), aortic insufficiency, an arteriovenous communication, or increased cardiac output secondary to anemia, anxiety, or conditions associated with increased catecholamine or thyroid hormone secretion. The presence of diminished pulses in all extremities is associated with pericardial tamponade, left ventricular outflow obstruction, or cardiomyopathy. The radial and femoral pulses should always be palpated simultaneously. Normally, the femoral pulse should be appreciated immediately before the radial pulse. In infants with coarctation of the aorta, the femoral pulses may be decreased. However, in older children with coarctation of the aorta, blood flow to the descending aorta may channel through collateral vessels and results in the femoral pulse being palpable but delayed until after the radial pulse **(radial-femoral delay).**

Blood pressure (BP) should be measured in the legs as well as in the arms to be certain that coarctation of the aorta is not overlooked. Palpation of the femoral or dorsalis pedis pulse, or both, is not reliable alone to exclude coarctation. In older children, a mercury sphygmomanometer with a cuff that covers approximately two thirds of the upper part of the arm or leg may be used for BP measurement. A cuff that is too small results in falsely high readings, whereas a cuff that is too large records slightly decreased BP. Pediatric clinical facilities should be equipped with 3, 5, 7, 12, and 18 cm cuffs to accommodate the large spectrum of pediatric patient sizes. The first **Korotkoff sounds** indicate systolic pressure. As cuff pressure is slowly decreased, the sounds usually become muffled before they disappear. Diastolic pressure may be recorded when the sounds become muffled (preferred) or when they disappear altogether; the former is usually slightly higher and the latter slightly lower than true diastolic pressure. For lower-extremity BP determination, the stethoscope is placed over the popliteal artery. Typically, the BP recorded in the legs with the cuff technique is approximately 10 mm Hg higher than that in the arms.

In infants, BP can be determined by auscultation, palpation, or an oscillometric (Dinamap) device that, when properly used, provides accurate measurements in infants as well as older children.

Blood pressure varies with the age of the child and is closely related to height and weight. Significant increases occur during adolescence, and many temporary variations take place before the more stable levels of adult life are attained. Exercise, excitement, coughing, crying, and struggling may raise the systolic BP of infants and children as much as 40-50 mm Hg greater than their usual levels. Variability in BP in children of approximately the same age and body build should be expected, and serial measurements should always be obtained when evaluating a patient with hypertension (Figs. 449.2 and 449.3).

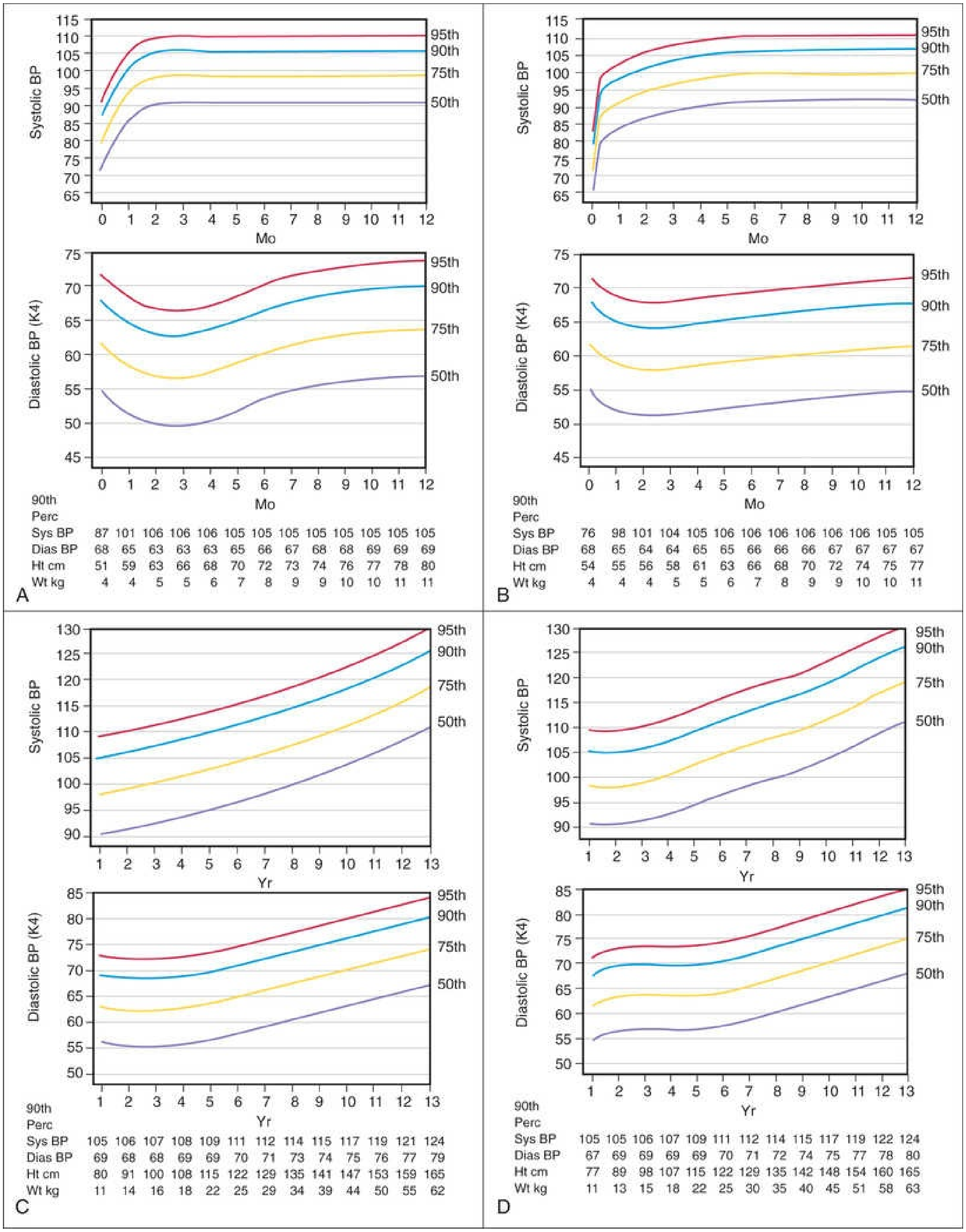

90th Perc													
Sys BP	87	101	106	106	106	105	105	105	105	105	105	105	105
Dias BP	68	65	63	63	63	65	66	67	68	68	69	69	69
Ht cm	51	59	63	66	68	70	72	73	74	76	77	78	80
Wt kg	4	4	5	5	6	7	8	9	9	10	10	11	11

90th Perc													
Sys BP	76	98	101	104	105	106	106	106	106	106	106	105	105
Dias BP	68	65	64	64	65	65	66	66	66	67	67	67	67
Ht cm	54	55	56	58	61	63	66	68	70	72	74	75	77
Wt kg	4	4	4	5	5	6	7	8	9	9	10	10	11

90th Perc													
Sys BP	105	106	107	108	109	111	112	114	115	117	119	121	124
Dias BP	69	68	68	69	69	70	71	73	74	75	76	77	79
Ht cm	80	91	100	108	115	122	129	135	141	147	153	159	165
Wt kg	11	14	16	18	22	25	29	34	39	44	50	55	62

90th Perc													
Sys BP	105	105	106	107	109	111	112	114	115	117	119	122	124
Dias BP	67	69	69	69	69	70	71	72	74	75	77	78	80
Ht cm	77	89	98	107	115	122	129	135	142	148	154	160	165
Wt kg	11	13	15	18	22	25	30	35	40	45	51	58	63

FIG. 449.2 **Age-specific percentiles of blood pressure (BP) measurements: birth to 13 yr. A, Boys from birth to 12 mo of age. B, Girls from birth to 12 mo of age. C, Boys 1-13 yr of age. D, Girls 1-13 yr of age. Korotkoff phase IV (K4) used for diastolic BP. Dias, Diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. (From Report of the Second Task Force on Blood Pressure Control in Children—1987. National Heart, Lung, and Blood Institute, Bethesda, MD, Pediatrics 79:1–25, 1987. Copyright 1987 by the**

American Academy of Pediatrics.)

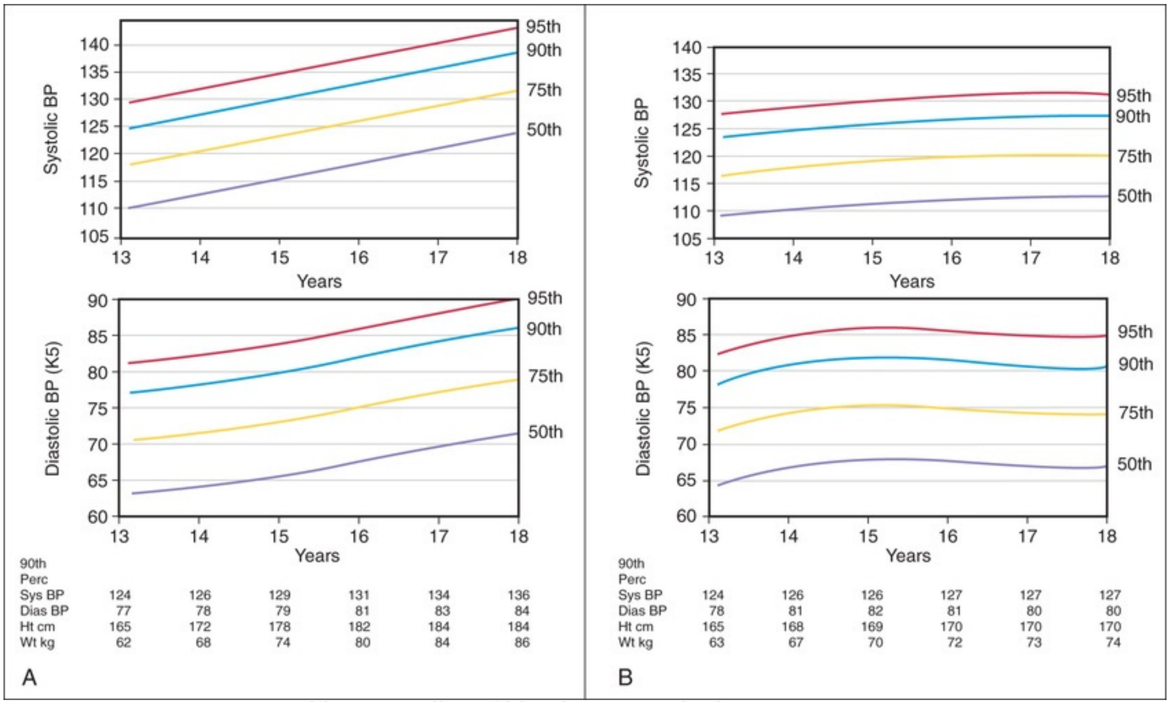

A

90th Perc						
Sys BP	124	126	129	131	134	136
Dias BP	77	78	79	81	83	84
Ht cm	165	172	178	182	184	184
Wt kg	62	68	74	80	84	86

B

90th Perc						
Sys BP	124	126	126	127	127	127
Dias BP	78	81	82	81	80	80
Ht cm	165	168	169	170	170	170
Wt kg	63	67	70	72	73	74

FIG. 449.3 **Age-specific percentiles of blood pressure (BP) measurements: age 13-18 yr. A, Boys 13-18 yr of age. B, Girls 13-18 yr of age. Korotkoff phase V (K5) used for diastolic BP. Dias, Diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. (From Report of the Second Task Force on Blood Pressure Control in Children—1987, National Heart, Lung, and Blood Institute, Bethesda, MD, Pediatrics 79:1–25, 1987. Copyright 1987 by the American Academy of Pediatrics.)**

Although of little use in infants, in cooperative older children, inspection of the **jugular venous pulse** wave provides information about central venous and right atrial pressure. The neck veins should be inspected with the patient sitting at a 90-degree angle. The external jugular vein should not be visible above the clavicles unless central venous pressure is elevated. Increased venous pressure transmitted to the internal jugular vein may appear as venous pulsations without visible distention; such pulsation is not seen in normal children reclining at an angle of 45 degrees. Because the great veins are in direct communication with the right atrium, changes in pressure and the volume of this chamber are also transmitted to the veins. The one exception occurs in superior vena cava obstruction, in which venous pulsatility is lost.

Cardiac Examination

The heart should be examined in a systematic manner, starting with inspection and palpation. Any abnormalities on inspection and/or palpation strongly suggest a pathologic rather than a functional etiology of any heart murmur. A **precordial bulge** to the left of the sternum with increased precordial activity suggests cardiac enlargement; such bulges can often best be appreciated by having the child lay supine with the examiner looking up from the child's feet. A **substernal thrust** indicates the presence of right ventricular enlargement, whereas an **apical heave** is noted with left ventricular enlargement. A **hyperdynamic precordium** suggests a volume load such as that found with a large left-to-right shunt, although it may be normal in a thin patient. An overly silent precordium with a barely detectable apical impulse suggests pericardial effusion or severe cardiomyopathy, but may be normal in an obese patient.

The relationship of the **apical impulse** to the midclavicular line is also helpful in the estimation of cardiac size: the apical impulse moves laterally and inferiorly with enlargement of the left ventricle. Right-sided apical impulses signify dextrocardia, tension pneumothorax, or left-sided thoracic space-occupying lesions (e.g., diaphragmatic hernia).

Thrills are the palpable equivalent of murmurs and correlate with the area of maximal auscultatory intensity of the murmur. It is important to palpate the suprasternal notch and neck for aortic bruits, which may indicate the presence of aortic stenosis or, when faint, pulmonary stenosis. Right lower sternal border and apical systolic thrills are characteristic of ventricular septal defect (VSD) and mitral insufficiency, respectively. Diastolic thrills are occasionally palpable in the presence of atrioventricular valve stenosis. The timing and localization of thrills should be carefully noted.

Auscultation is an art that improves with practice. The diaphragm of the stethoscope is placed firmly on the chest for high-pitched sounds; a lightly placed bell is optimal for low-pitched sounds. The physician should initially concentrate on the characteristics of the individual heart sounds and their variation with respirations and later concentrate on murmurs. In some congenital heart diseases, such as atrial septal defect (ASD), the murmur is very nonspecific and sounds identical to many functional murmurs, and it is the abnormality of the second heart sound that points to a pathologic condition. The patient should be supine, lying quietly, and breathing normally. The **first heart sound** (S_1) is best heard at the apex, whereas the **second heart sound** (S_2) should be evaluated at the upper left and right sternal borders. S_1 is caused by closure of the atrioventricular valves (mitral and tricuspid). S_2 is caused by closure of the semilunar valves (aortic and pulmonary) (Fig. 449.4). During inspiration, the decrease in intrathoracic pressure results in increased filling of the right side of the heart, which leads to an increased right ventricular ejection time and thus delayed closure of the pulmonary valve; consequently, **splitting of the second heart sound** increases during inspiration and decreases during expiration.

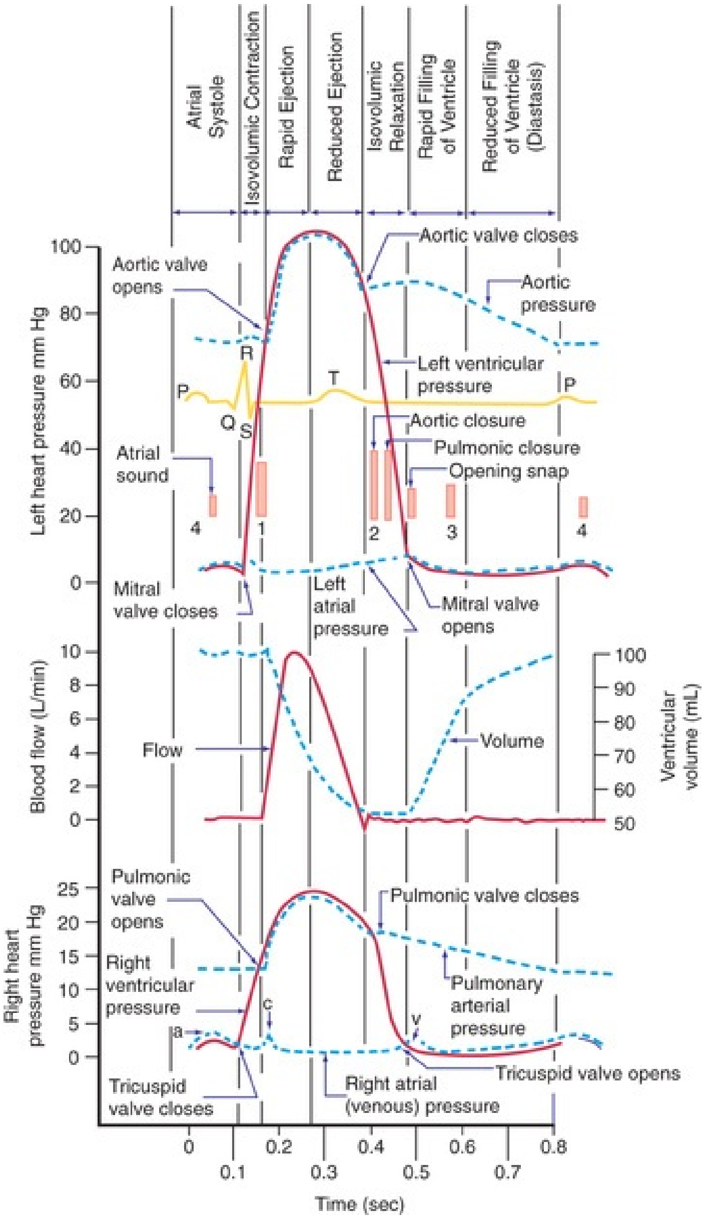

FIG. 449.4 **Idealized diagram of the temporal events of a cardiac cycle.**

Often, S_2 seems to be single during expiration. The presence of a normally split S_2 is strong evidence against the diagnosis of ASD, defects associated with pulmonary arterial hypertension, severe pulmonary valve stenosis, aortic and pulmonary atresia, and truncus arteriosus. Wide S_2 splitting is noted in ASD, pulmonary stenosis, Ebstein anomaly, total anomalous pulmonary venous return, and right bundle branch block. An accentuated pulmonic component of S_2 with narrow splitting is a sign of pulmonary hypertension. A single S_2 occurs in pulmonary or aortic atresia or severe stenosis, truncus arteriosus, and, often, transposition of the great arteries.

A **third heart sound** (S_3) is best heard with the bell at the apex in mid-diastole. A **fourth heart sound** (S_4) occurring in conjunction with atrial contraction may be heard just before the S_1 in late diastole. S_3 may be normal in an adolescent with a relatively slow heart rate, but in a patient with the clinical signs of heart failure and tachycardia, S_3 may be heard as a gallop rhythm and may merge with an S_4 , a finding known as a **summation gallop** . A gallop rhythm is attributed to poor compliance of the ventricle, and exaggeration of the normal S_3 is associated with ventricular filling.

Ejection clicks , which are heard in early systole, are usually caused by a mildly to moderately stenotic aortic or pulmonary valve or to a dilated ascending aorta or pulmonary artery. They are heard so close to S_1 that they may be mistaken for a split S_1 . **Aortic** ejection clicks are best heard at the left middle to right upper sternal border and are constant in intensity. They occur in conditions where the aortic valve is stenotic or the aorta is dilated (e.g., tetralogy of Fallot, truncus arteriosus). **Pulmonary** ejection clicks, which are associated with mild to moderate pulmonary stenosis, are best heard at the left middle to upper sternal border and vary with respirations, often disappearing with inspiration. Split first heart sounds are usually heard best at the lower left sternal border. A midsystolic click heard at the apex, often preceding a late systolic murmur, suggests mitral valve prolapse.

Murmurs should be described according to their intensity, pitch, timing (systolic or diastolic), variation in intensity, time to peak intensity, area of maximal intensity, and radiation to other areas. Auscultation for murmurs should be carried out across the upper precordium, down the left or right sternal border, and out to the apex and left axilla. Auscultation should also always be performed in the right axilla and over both sides of the back. Systolic murmurs are classified as ejection, pansystolic, or late systolic according to the timing of the murmur in relation to S_1 and S_2 . The intensity of systolic murmurs is graded from I to VI: **I** , barely audible; **II** , medium intensity; **III** , loud but no thrill; **IV** , loud with a thrill; **V** , very loud but still requiring positioning of the stethoscope at least partly on the chest; and **VI** , so loud that the murmur can be heard with the stethoscope off the chest. In patients who have undergone prior heart surgery, a murmur of grade IV or greater may be heard in the absence of a thrill.

Systolic ejection murmurs start a short time after a well-heard S_1 , increase in intensity, peak, and then decrease in intensity; they usually end before S_2 . In patients with severe pulmonary stenosis, however, the murmur may extend beyond the first component of S_2 , thus obscuring it. **Pansystolic or holosystolic murmurs** begin almost simultaneously with S_1 and continue throughout systole, on occasion becoming gradually decrescendo. It is helpful to remember that after closure of the atrioventricular valves (S_1), a brief period occurs during which ventricular pressure increases but the semilunar valves remain closed (isovolumic contraction; see Fig. 449.3). Thus, pansystolic murmurs (heard during both isovolumic contraction and the ejection phases of systole) cannot be caused by flow across the semilunar valves because these valves are closed during isovolumic contraction. Pansystolic murmurs must therefore be related to blood exiting the contracting ventricle via either an abnormal opening (VSD) or atrioventricular (mitral or tricuspid) valve insufficiency. Systolic ejection murmurs usually imply increased flow or stenosis across one of the ventricular outflow tracts (aortic or pulmonic). In infants with rapid heart rates, it is often difficult to distinguish between ejection and pansystolic murmurs. If a clear and distinct S_1 can be appreciated, the murmur is most likely ejection in nature.

A **continuous murmur** is a systolic murmur that continues or “spills” into diastole and indicates continuous flow, such as in the presence of a PDA or other aortopulmonary communication. This murmur should be differentiated from a **to-and-fro murmur** , where the systolic component of the murmur ends at or before S_2 , and the diastolic murmur begins after semilunar valve closure (aortic or pulmonary stenosis combined with insufficiency). A **late systolic murmur** begins well beyond S_1 and continues until the end of systole. Such murmurs may be heard after a midsystolic click in patients with mitral valve prolapse and insufficiency.

Several types of **diastolic murmurs** (graded I-IV) can be identified. A

decrescendo diastolic murmur is a blowing murmur along the left sternal border that begins with S_2 and diminishes toward mid-diastole. When high-pitched, this murmur is associated with aortic valve insufficiency or pulmonary insufficiency related to pulmonary hypertension. When low-pitched, this murmur is associated with pulmonary valve insufficiency in the absence of pulmonary hypertension. A low-pitched decrescendo diastolic murmur is typically noted after surgical repair of the pulmonary outflow tract in defects such as tetralogy of Fallot or in patients with absent pulmonary valves. A **rumbling mid-diastolic murmur** at the left middle and lower sternal border may be caused by increased blood flow across the tricuspid valve, such as occurs with ASD or, less often, because of actual stenosis of this valve. When this murmur is heard at the apex, it is caused by increased flow across the mitral valve, such as occurs with large left-to-right shunts at the ventricular level (VSDs), at the great vessel level (PDA, aortopulmonary shunts), or with increased flow because of mitral insufficiency. When an apical diastolic rumbling murmur is longer and is accentuated at the end of diastole (presystolic), it usually indicates anatomic mitral valve stenosis.

The absence of a precordial murmur does not rule out significant congenital or acquired heart disease. Congenital heart defects, some of which are ductal dependent, may not demonstrate a murmur if the ductus arteriosus closes. These lesions include pulmonary or tricuspid valve atresia and transposition of the great arteries. Murmurs may seem insignificant in patients with severe aortic stenosis, ASDs, anomalous pulmonary venous return, atrioventricular septal defects, coarctation of the aorta, or anomalous insertion of a coronary artery. Careful attention to other components of the physical examination (growth failure, cyanosis, peripheral pulses, precordial impulse, heart sounds) increases the index of suspicion of congenital heart defects in these patients. In contrast, loud murmurs may be present in the absence of structural heart disease, for example, in patients with a large noncardiac arteriovenous malformation, myocarditis, severe anemia, or hypertension.

Many murmurs are not associated with significant hemodynamic abnormalities. These murmurs are referred to as *functional, normal, insignificant,* or **innocent** (the preferred term). During routine random auscultation, >30% of children may have an innocent murmur at some time in their lives; this percentage increases when auscultation is done under nonbasal circumstances (high cardiac output because of fever, infection, anxiety). The most common **innocent murmur** is a medium-pitched, vibratory or “musical,” relatively short *systolic ejection murmur*, which is heard best along the left lower and midsternal border and has no significant radiation to the apex, base, or back. It is heard most frequently in children between 3 and 7 yr of age. The intensity of the murmur often changes with respiration and position and may be attenuated in the sitting or prone position. Innocent *pulmonic* murmurs are also common in children and adolescents and originate from normal turbulence during ejection into the pulmonary artery. These are higher-pitched, blowing, brief, early systolic murmurs of grades I-II in intensity and are best detected in the 2nd left parasternal space with the patient in the supine position. Features suggestive of heart disease include murmurs that are pansystolic, grade III or higher, harsh, located at the left upper sternal border, and associated with an early or midsystolic click or an abnormal S_2 .

A **venous hum** is another example of a common innocent murmur heard during childhood. Such hums are produced by turbulence of blood in the jugular venous system; they have no pathologic significance and may be heard in the neck or anterior portion of the upper part of the chest. A venous hum consists of a soft humming sound heard in both systole and diastole; it can be exaggerated or made to disappear by varying the position of the head, or it can be decreased by lightly compressing the jugular venous system in the neck. These simple maneuvers are sufficient to differentiate a venous hum from the murmurs produced by organic cardiovascular disease, particularly a PDA.

The lack of significance of an innocent murmur should be discussed with the child's parents. It is important to offer complete reassurance because lingering doubts about the importance of a cardiac murmur may have profound effects on child-rearing practices, most often in the form of overprotectiveness. An underlying fear that a cardiac abnormality is present may negatively affect a child's self-image and subtly influence personality development. The physician should explain that an innocent murmur is simply a “noise” and does not indicate the presence of a significant cardiac defect. When asked, “Will it go away?” the best response is to state that because the murmur has no clinical significance, it does not matter whether it “goes away.” Parents should be warned that the intensity of the murmur might increase during febrile illnesses, a time when, typically, another physician examines the child. With growth, however, innocent murmurs are less well heard and often disappear completely. At times, additional studies may be indicated to rule out a congenital heart defect. However, “routine” electrocardiographic, chest radiographic, and echocardiographic examinations should be avoided in well children with an innocent murmur.

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CHAPTER 450

Laboratory Cardiac Evaluation

450.1

Radiologic Cardiac Assessment

Daniel Bernstein

Keywords

cardiothoracic ratio
ventricular hypertrophy
bundle branch block
polycythemia
echocardiography
TTE
TEE
exercise ECG
E/A ratio
fractional shortening
cardiac balloon angioplasty
catheterization
transcatheter valve implantation

Despite the widespread easy access to advanced imaging techniques, such as echocardiography, computed tomography (CT) scan, and magnetic resonance imaging (MRI), the chest x-ray film (radiograph, roentgenogram) remains a highly valuable diagnostic tool and is often the first imaging study performed in a child suspected of having a cardiac defect. It can provide information about cardiac size and shape, pulmonary blood flow (vascularity), pulmonary edema, and associated lung and thoracic anomalies that may be associated with congenital syndromes (e.g., skeletal dysplasias, extra or deficient number of ribs, abnormal vertebrae, previous cardiac surgery). Combined with a careful physical examination, the chest radiograph can help the clinician to establish a diagnosis of **congenital heart disease** (CHD), as opposed to pulmonary disease, and to narrow the differential diagnosis to specific categories of CHD (e.g., left-to-right shunt lesions vs obstructive lesions).

The most frequently used measurement of cardiac size is the maximal width of the cardiac shadow in a posteroanterior (PA) chest film taken mid-inspiration. A vertical line is drawn down the middle of the sternal shadow, and perpendicular lines are drawn from the sternal line to the extreme right and left borders of the heart; the sum of the lengths of these lines is the **maximal cardiac width** . The **maximal chest width** is obtained by drawing a horizontal line between the right and left inner borders of the rib cage at the level of the top of the right diaphragm. When the maximal cardiac width is more than half the maximal chest width (cardiothoracic ratio >50%), the heart is usually enlarged. Cardiac size should be evaluated only when the film is taken during inspiration with the patient in an upright position. A diagnosis of “cardiac enlargement” on expiratory or prone films is a common cause of unnecessary referrals and laboratory studies.

The **cardiothoracic ratio** is a less useful index of cardiac enlargement in infants than in older children because the horizontal position of the heart may increase the ratio to >50% in the absence of true enlargement. Furthermore, the thymus may overlap not only the base of the heart but also virtually the entire mediastinum, thus obscuring the true cardiac silhouette.

A *lateral* chest radiograph may be helpful in infants as well as in older children with pectus excavatum or other conditions that result in a narrow anteroposterior (AP) chest dimension. The heart may appear small in the lateral view and suggest that the apparent enlargement in the PA projection was caused by either the thymic image (anterior mediastinum only) or flattening of the cardiac chambers as a result of a structural chest abnormality.

In the PA view the left border of the cardiac shadow consists of 3 convex shadows produced, from above downward, by the aortic knob, the main and left pulmonary arteries, and the left ventricle (Fig. 450.1). In cases of moderate to marked left atrial enlargement, the atrium may project between the pulmonary artery and the left ventricle. The right ventricular outflow tract (RVOT) does not contribute to the shadows formed by the left border of the heart. The aortic knob is not as easily seen in infants and children as in adults. The side of the aortic arch (left or right) can often be inferred as being opposite the side of the midline from which the air-filled trachea is visualized. This observation is important because a right-sided aortic arch is often present in cyanotic CHD, particularly in tetralogy of Fallot. Three structures contribute to the right border of the cardiac silhouette. In the view from above, they are the superior vena cava, the ascending aorta, and the right atrium.

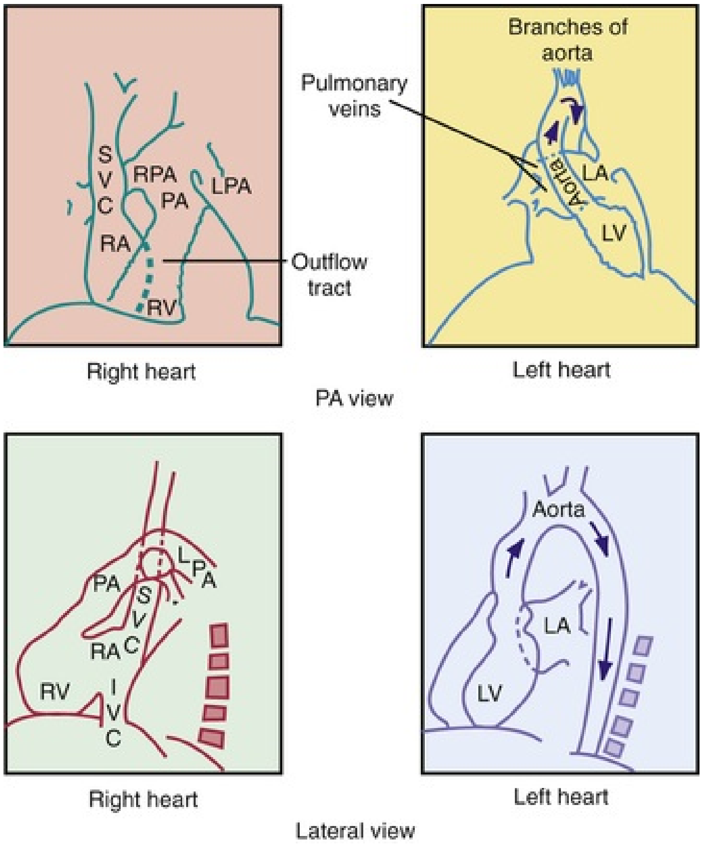
S
V
C
RPA
PA
LPA
RA
RV
Outflow tract
Pulmonary veins
Branches of aorta
Aorta
LA
LV
Right heart
Left heart
PA view
PA
LPA
SVC
RA
RV
IVC
Aorta
LA
LV
Right heart
Left heart
Lateral view

FIG. 450.1 **Idealized diagrams showing normal position of the cardiac chambers and great blood vessels. IVC, Inferior vena cava; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava. (Adapted and redrawn from Dotter CT, Steinberg I: Angiocardiographic interpretation, *Radiology* 153:513, 1949.)**

Enlargement of cardiac chambers or major arteries and veins results in prominence of the areas in which these structures are normally outlined on the chest radiograph. In contrast, the electrocardiogram is a more sensitive and accurate index of **ventricular hypertrophy** , which is a thickening of the ventricular wall and may or may not be associated with dilation of the affected cardiac chamber**.**

The chest radiograph is also an important tool for assessing the degree of pulmonary vascularity. **Pulmonary overcirculation** is usually associated with left-to-right shunt lesions, whereas **pulmonary undercirculation** is associated with obstruction of the RVOT. The esophagus is closely related to the great vessels, and a barium esophagogram can help delineate these structures in the initial evaluation of suspected vascular rings, although this has largely been supplanted by CT.

Echocardiographic examination best defines the morphologic features of intracardiac chambers, cardiac valves, and intracardiac shunts. CT is used as an adjunct to echo to evaluate extracardiac vascular morphology. MRI is used most often to provide a more quantitative assessment of ventricular volumes, cardiac function, and shunt and regurgitant fractions than is possible with echo.

450.2

Electrocardiography

Daniel Bernstein

Developmental Changes

The marked changes that occur in cardiac physiology and chamber dominance during the perinatal transition (see Chapter 448) are reflected in the evolution of the electrocardiogram (ECG) during the neonatal period. Because vascular resistance in the pulmonary and systemic circulations is nearly equal in a term fetus, the intrauterine work of the heart results in an equal mass of both the right and left ventricles. After birth, systemic vascular resistance (SVR) rises when the placental circulation is eliminated, and pulmonary vascular resistance (PVR) falls when the lungs expand. These changes are reflected in the ECG as the right ventricular (RV) wall begins to thin.

The ECG demonstrates these anatomic and hemodynamic features principally by changes in QRS and T-wave morphologic features. Typically, pediatric ECGs include several additional leads rarely used in adults, such as V_3 R and V_4 R, which are mirror images of leads V_3 and V_4 and are important in the evaluation of **right ventricular hypertrophy** (RVH). On occasion, lead V_1 is inappropriately positioned too far leftward to reflect RV forces accurately. This problem is present particularly in premature infants, in whom the electrocardiographic electrode gel may produce contact among all the precordial leads. An additional lead used in children is V_7 , located more laterally than V_6 and useful for assessing left-sided forces.

During the 1st postnatal days of life, right axis deviation, large R waves, and upright T waves in the right precordial leads (V_3 R or V_4 R and V_1) are the norm (Fig. 450.2). As PVR decreases in the 1st few days after birth, the right precordial T waves become negative. In the great majority of cases, this change occurs within the 1st 48 hr of postnatal life. Upright T waves that persist in leads V_3 R, V_4 R, or V_1 beyond 1 wk of life are an abnormal finding indicating RVH or RV strain, even in the absence of QRS voltage criteria. The T wave in V_1 should never be positive before 6 yr of age and may remain negative into adolescence or early adulthood. This finding represents one of the most important yet subtle differences between pediatric and adult ECGs and is a common source of error when adult cardiologists interpret pediatric ECGs.

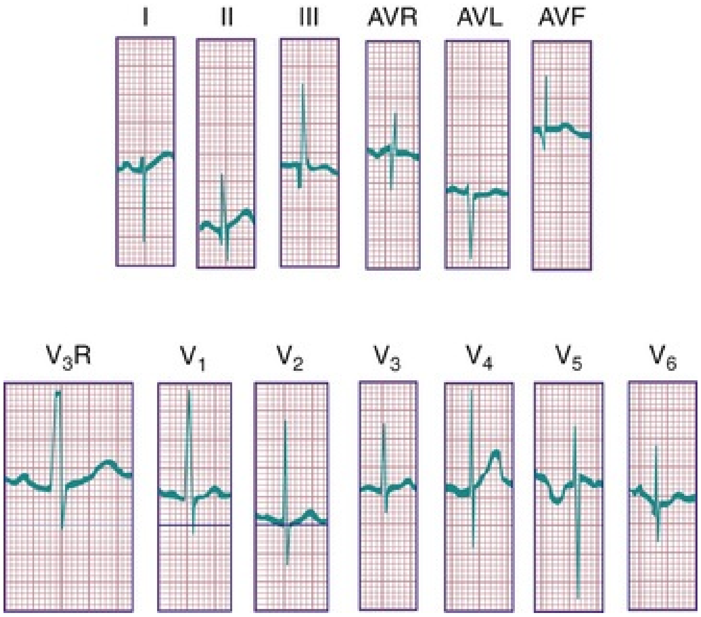

FIG. 450.2 Electrocardiogram in a normal neonate <24 hr of age. Note the dominant R wave and upright T waves in leads V_3 R and V_1 (V_3 R paper speed = 50 mm/sec).

In a newborn the mean **QRS frontal-plane axis** normally lies in the range of +110 to +180 degrees, reflecting the co-dominance of the fetal right and left ventricles. The right-sided chest leads reveal a larger positive (**R**) than negative (**S**) wave and may do so for months because the right ventricle remains relatively thick throughout infancy. Left-sided leads (V_5 and V_6) also reflect right-sided dominance in the early neonatal period, when the R:S ratio in these leads may be <1. A dominant R wave in V_5 and V_6 , reflecting left ventricular (LV) forces, quickly becomes evident within the 1st few days of life (Fig. 450.3). As the child matures, the QRS axis gradually shifts leftward, and the RV forces slowly regress. Leads V_1 , V_3 R, and V_4 R display a prominent R wave until 6 mo to 8 yr of age. Most children have an R:S ratio >1 in lead V_4 R until age 4 yr. The T waves are inverted in leads V_4 R, V_1 , V_2 , and V_3 during infancy and may remain so into the middle of the 2nd decade of life and beyond. The processes of RV thinning and LV growth are best reflected in the QRS-T pattern over the right precordial leads. The diagnosis of RVH or left ventricular hypertrophy (LVH) in a pediatric patient can be made only with an understanding of the normal developmental physiology of these chambers at various ages until adulthood is reached. As the left ventricle becomes dominant, the ECG evolves to the characteristic pattern of older children (Fig. 450.4) and adults (Fig. 450.5).

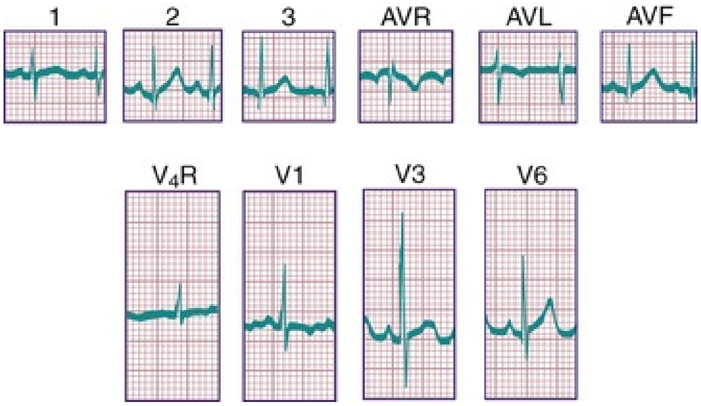
1
2
3
AVR
AVL
AVF
V4R
V1
V3
V6

FIG. 450.3 Electrocardiogram of a normal infant. Note the tall R and small S waves in V_4 R and V_1 and the inverted T wave in these leads. A dominant R wave is also present in V_6 .

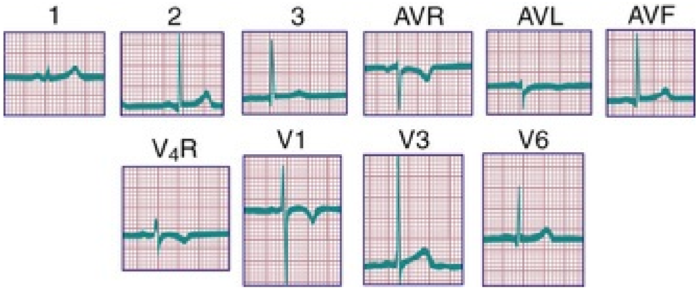
1
2
3
AVR
AVL
AVF
V4R
V1
V3
V6

FIG. 450.4 Electrocardiogram of a normal child. Note the relatively tall R waves and inversion of the T waves in V_4 R and V_1 .

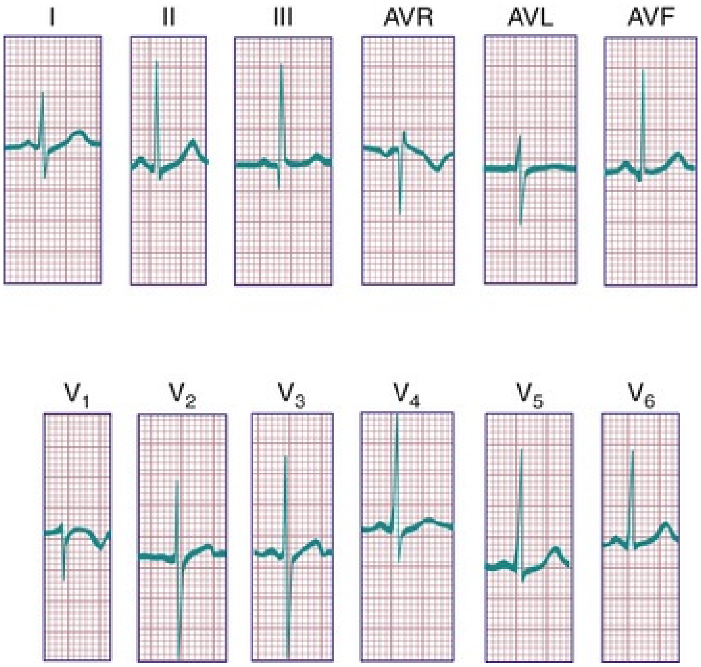

FIG. 450.5 **Normal adult electrocardiogram. Note the dominant S wave in lead V_1 . This pattern in an infant would indicate the presence of left ventricular hypertrophy.**

Ventricular hypertrophy may result in increased voltage in the R and S waves in the chest leads. The height of these deflections is governed by the proximity of the specific electrode to the surface of the heart; by the sequence of electrical activation through the ventricles, which can result in variable degrees of cancellation of forces; and by hypertrophy of the myocardium. Because the chest wall in infants and children, as well as in adolescents, may be relatively thin, the diagnosis of ventricular hypertrophy should not be based solely on voltage changes unless those voltages are greatly increased.

The diagnosis of **pathologic** RVH is difficult in the 1st wk of postnatal life because physiologic RVH is a normal finding. Serial tracings are often necessary to determine whether marked right axis deviation and potentially abnormal right precordial forces or T waves, or both, will persist beyond the neonatal period (Fig. 450.6). In contrast, an adult ECG pattern (see Fig. 450.5) seen in a neonate suggests LVH. The exception is a premature infant, who may display a more “mature” ECG than a full-term infant (Fig. 450.7), as a result of lower PVR secondary to underdevelopment of the medial muscular layer of the pulmonary arterioles. Some premature infants display a pattern of generalized low voltage across the precordium.

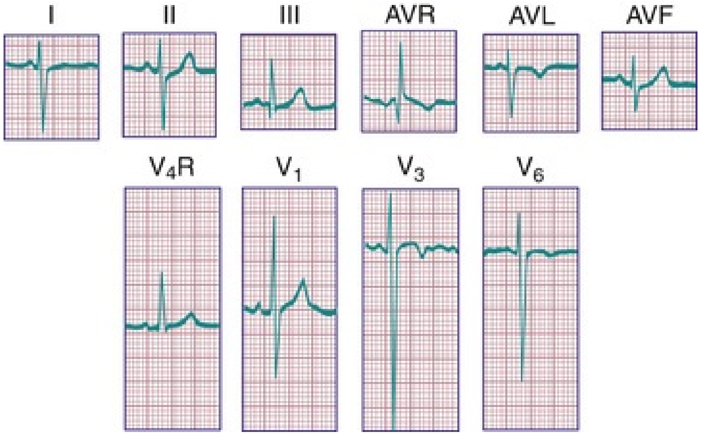

FIG. 450.6 Electrocardiogram of an infant with right ventricular hypertrophy (tetralogy of Fallot). Note the tall R waves in the right precordium and deep S waves in V_6 . The positive T waves in V_4 R and V_1 are also characteristic of right ventricular hypertrophy.

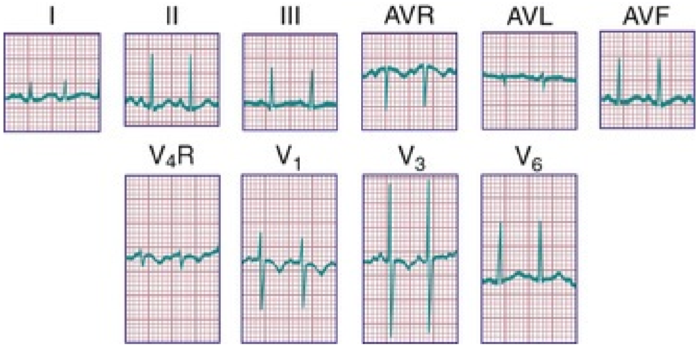

FIG. 450.7 Electrocardiogram of a premature infant. Weight 2 kg and age 5 wk at the time of the tracing. The cardiovascular system was clinically normal. Left ventricular dominance is manifested by R-wave progression across the chest, similar to tracings obtained from older children. Compare with the tracing from a normal full-term infant (see Fig. 450.3).

The ECG should always be evaluated systematically to avoid overlooking a minor but important abnormality. One approach is to begin with an assessment of rate and rhythm, followed by a calculation of the mean frontal-plane QRS axis, measurements of segment intervals, assessment of voltages, and lastly assessment of ST and T-wave abnormalities.

Rate and Rhythm

A brief rhythm strip should be examined to assess whether a P wave always precedes each QRS complex. The P-wave axis should then be estimated as an indication of whether the rhythm is originating from the **sinus node** . If the atria are situated normally in the chest, the P wave should be upright in leads I and aVF and inverted in lead aVR. With atrial inversion (**situs inversus**), the P wave may be inverted in lead I. Inverted P waves in leads II and aVF are seen in low atrial, nodal, or junctional rhythms. The absence of P waves indicates a rhythm originating more distally in the conduction system. In this case, the morphologic features of the QRS complexes are important in differentiating a **junctional** (usually a narrow QRS complex) from a **ventricular** (usually a wide QRS complex) rhythm.

P Waves

Tall (>2.5 mm), narrow, and spiked P waves are indicative of **right atrial enlargement** and are seen in congenital pulmonary stenosis, Ebstein anomaly of the tricuspid valve, tricuspid atresia, and sometimes cor pulmonale. These abnormal waves are most obvious in leads II, V_3 R, and V_1 (Fig. 450.8*A*). Similar waves are sometimes seen in thyrotoxicosis. **Broad P waves,** commonly **bifid** and sometimes **biphasic** , are indicative of **left atrial enlargement** (Fig. 450.8*B*). They are seen in some patients with large left-to-right shunts (ventricular septal defect [VSD], patent ductus arteriosus) and with severe mitral stenosis or mitral regurgitation. Left atrial enlargement, however, is one of the most common false-positive readings generated by computerized ECG machines. Flat P waves may be encountered in patients with hyperkalemia.

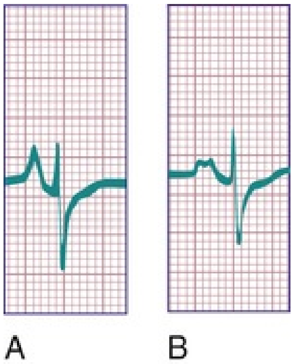

FIG. 450.8 Atrial enlargement. A, Peaked narrow P waves characteristic of right atrial enlargement. B, Wide, bifid M-shaped P waves typical of left atrial enlargement.

QRS Complex

Right Ventricular Hypertrophy

For the most accurate assessment of ventricular hypertrophy, pediatric ECGs should include the right precordial lead V_3 R or V_4 R, or both. The diagnosis of RVH depends on demonstration of the following changes (see Fig. 450.6): (1) a qR pattern in the RV surface leads; (2) a positive T wave in leads V_3 R-V_4 R and V_1 -V_3 between ages 6 days and 6 yr; (3) a monophasic R wave in V_3 R, V_4 R, or V_1 ; (4) an rsR′ pattern in the right precordial leads with the 2nd R wave taller than the 1st; (5) age-corrected increased voltage of the R wave in leads V_3 R-V_4 R or the S wave in leads V_6 -V_7 , or both; (6) marked right axis deviation (>120 degrees in patients beyond the newborn period); and (7) complete reversal of the normal adult precordial RS pattern. At least 2 of these changes should be present to support a diagnosis of RVH.

Abnormal ventricular loading can be characterized as either systolic (as a result of RVOT obstruction, as in pulmonic stenosis) or diastolic (as a result of increased volume load, as in atrial septal defect [ASD]). These 2 types of abnormal loads result in distinct electrocardiographic patterns. The **systolic overload pattern** is characterized by tall, pure R waves in the right precordial leads. In older children the T waves in these leads are initially upright and later become inverted. In infants and children <6 yr the T waves in V_3 R-V_4 R and V_1 are abnormally upright. The **diastolic overload pattern** (typically seen in patients with ASD) is characterized by an rsR′ pattern (Fig. 450.9) and a slightly increased QRS duration (which is known as a *minor right ventricular conduction delay* rather than a true bundle branch block). Patients with mild to moderate pulmonary stenosis may also exhibit an rsR′ pattern in the right precordial leads.

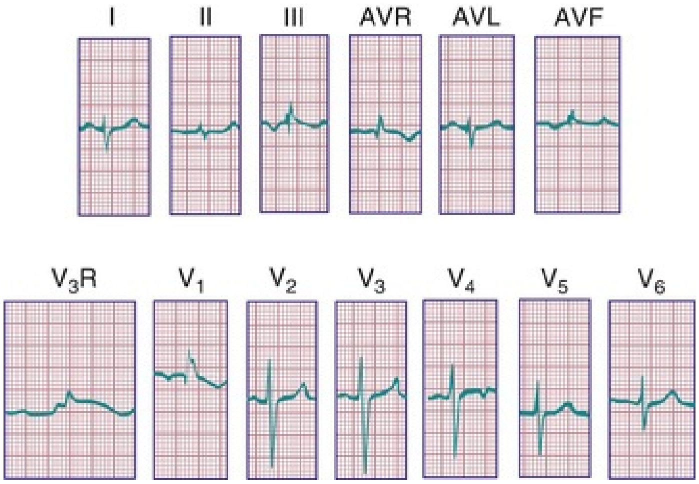

FIG. 450.9 Electrocardiogram showing right ventricular conduction delay characterized by an rsR′ pattern in V_1 and a deep S wave in V_6 (V_3 R paper speed = 50 mm/sec).

Left Ventricular Hypertrophy

The following features indicate the presence of LVH (Fig. 450.10): (1) depression of the ST segments and inversion of the T waves in the left precordial leads (V_5 , V_6 , and V_7), known as a **left ventricular strain** pattern—these findings suggest the presence of a more severe lesion; (2) a deep Q wave in the left precordial leads; and (3) increased voltage of the S wave in V_3 R and V_1 or the R wave in V_6 -V_7 , or both. It is important to emphasize that evaluation of LVH should *not* be based on voltage criteria alone, especially in adolescents and young adults, and within these groups, especially in males. The concepts of systolic and diastolic overload, although not always consistent, are also useful in evaluating LV enlargement. Severe systolic overload of the left ventricle is suggested by straightening of the ST segments and inverted T waves over the left precordial leads; diastolic overload may result in tall R waves, a large Q wave, and normal T waves over the left precordium. Finally, an infant with an ECG that would be considered “normal” for an older child may in fact have LVH.

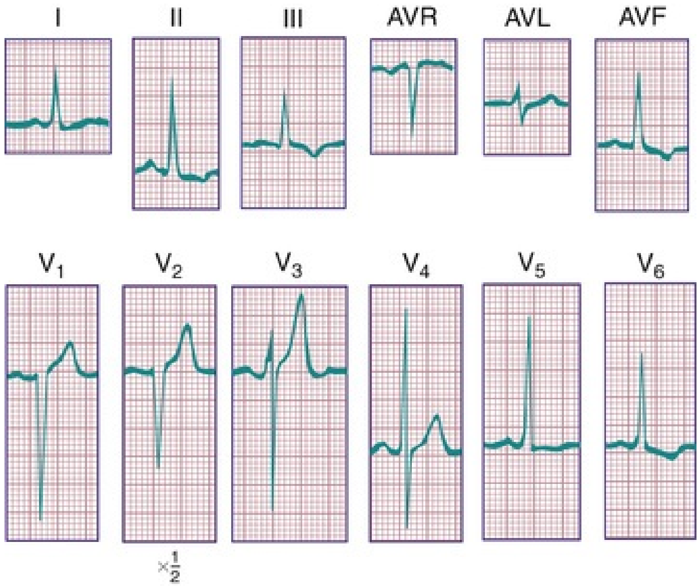

FIG. 450.10 **Electrocardiogram showing left ventricular hypertrophy in a 12 yr old child with aortic stenosis. Note the deep S wave in V_1 -V_3 and tall R in V_5 . In addition, T-wave inversion is present in leads II, III, aVF, and V_6 .**

Bundle Branch Block

A complete **right bundle-branch block** (prolonged QRS complex which is usually upright with an rSR′ in lead V1; wide S wave in lead V_6) may be congenital or may be acquired after surgery for CHD, especially when a partial right ventriculotomy has been performed, as in repair of the tetralogy of Fallot. **Left bundle branch block** (LBBB; prolonged QRS complex, which is usually upright with an rSR′ in lead V_6 ; wide S wave in lead V_1) is less common in children; this pattern is often seen in adults with cardiomyopathy, but much less in children with cardiomyopathy. LBBB may be seen after surgery on the aortic or mitral valve caused by surgical injury to one of the left-sided conduction bundles. Alternatively, a bundle branch block pattern may be indicative of a bypass tract associated with one of the preexcitation syndromes (see Chapter 462).

P-R and Q-T Intervals

The duration of the P-R interval shortens with increasing heart rate; thus assessment of this interval should be based on age- and rate-corrected nomograms. A long P-R interval is diagnostic of a **first degree heart block** , the cause of which may be congenital, postoperative (after open heart surgery), inflammatory (myocarditis, pericarditis, Lyme disease, rheumatic fever), or pharmacologic (digitalis).

The duration of the Q-T interval varies with the cardiac rate; a corrected Q-T interval (Q-Tc) can be calculated by dividing the measured Q-T interval by the square root of the preceding R-R interval. A normal Q-Tc should be <0.45. It is often lengthened with hypokalemia and hypocalcemia; in the former, a U wave may be noted at the end of the T wave (Fig. 450.11). A number of medications can also lengthen the Q-T interval. A congenitally prolonged Q-T interval may also be seen in children with one of the long QT syndromes (Fig. 450.12). These patients are at high risk for ventricular arrhythmias, including a form of ventricular tachycardia known as **torsades de pointes,** and sudden death (see Chapter 462.5).

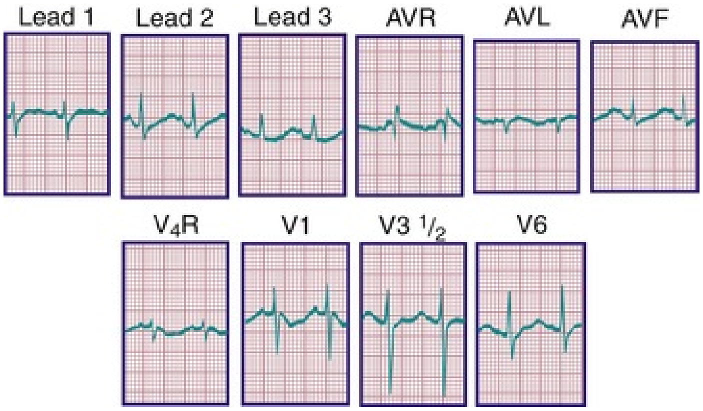

FIG. 450.11 **Electrocardiogram in hypokalemia. Serum potassium, 2.7 mEq/L; serum calcium, 4.8 mEq/L at the time of the tracing. Note the prolongation of electrical systole, as evidenced by a widened TU wave, as well as depression of the ST segment in V_4 R, V_1 , and V_6 .**

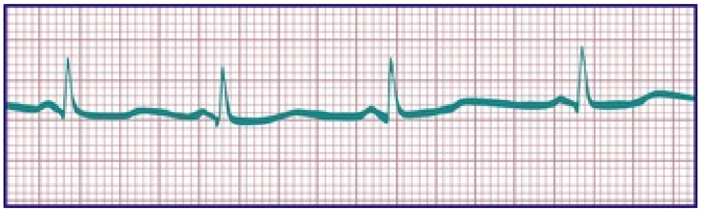

FIG. 450.12 Prolonged Q-T interval in a patient with long QT syndrome.

ST Segment and T-Wave Abnormalities

Coronary ischemia, leading to typical ST and T-wave abnormalities seen in adults, is rare in children. A slight elevation of the ST segment (J-point elevation) is often seen in normal teenagers and is attributed to early repolarization of the heart. In pericarditis, irritation of the epicardium may cause elevation of the ST segment, followed by abnormal T-wave inversion as healing progresses. Administration of digitalis is sometimes associated with sagging of the ST segment and abnormal inversion of the T wave.

Depression of the ST segment may also occur in any condition that produces myocardial damage or ischemia, including severe anemia, carbon monoxide poisoning, aberrant origin of the left coronary artery from the pulmonary artery, glycogen storage disease of the heart, myocardial tumors, and mucopolysaccharidoses. An aberrant origin of the left coronary artery from the pulmonary artery may lead to changes indistinguishable from those of acute myocardial infarction in adults. ECG findings of ischemia may be seen in patients with Kawasaki disease who have developed coronary artery aneurysms (see Chapters 191 and 471.1). Similar changes may occur in patients with other rare abnormalities of the coronary arteries and in those with cardiomyopathy, even in the presence of normal coronary arteries. These patterns are often misread in young infants because of the unfamiliarity of pediatricians with this “infarct” pattern, and thus a high index of suspicion must be maintained in infants with dilated cardiomyopathy or with symptoms compatible with coronary ischemia (e.g., inconsolable crying).

T-wave inversion may occur in myocarditis and pericarditis, or it may be a sign of either RVH or LVH and ventricular strain. Hypothyroidism may produce flat or inverted T waves in association with generalized low voltage. In hyperkalemia, the T waves are usually of high voltage and are tent shaped (Fig. 450.13), although tall T waves can be an early sign in myocardial infarction.

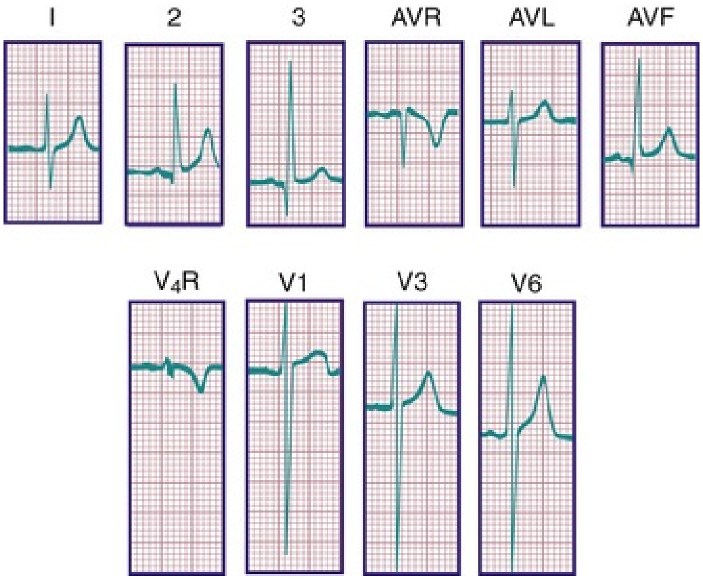

FIG. 450.13 **Electrocardiogram in hyperkalemia. Serum potassium, 6.5 mEq/L; serum calcium, 5.1 mEq/L. Note the tall, tent-shaped T waves, especially in leads I, II, and V_6 .**

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450.3

Hematologic Data

Daniel Bernstein

In acyanotic infants with large left-to-right shunts, the onset of heart failure often coincides with the nadir of the normal physiologic anemia of infancy. Increasing the hematocrit in these patients to >40% may decrease shunt volume and result in an improvement in symptoms; however, this form of treatment is generally reserved for infants who are not otherwise surgical candidates (extremely premature infants or those with exceedingly complex CHD for whom only palliative surgery is possible). In these select infants, regular evaluation of the hematocrit and booster transfusions when appropriate may be helpful in improving growth.

Polycythemia is frequently noted in chronically cyanotic patients with right-to-left shunts. Patients with severe polycythemia are in a delicate balance between the risks of intravascular thrombosis and a bleeding diathesis. The most frequent abnormalities include accelerated fibrinolysis, thrombocytopenia, abnormal clot retraction, hypofibrinogenemia, prolonged prothrombin time, and prolonged partial thromboplastin time. The preparation of cyanotic, polycythemic patients for elective noncardiac surgery, such as dental extraction, includes evaluation and treatment of abnormal coagulation.

Because of the high viscosity of polycythemic blood (hematocrit >65%), patients with cyanotic CHD are at risk for the development of vascular thromboses, especially of cerebral veins. Dehydration increases the risk of thrombosis, and thus adequate fluid intake must be maintained during hot weather or intercurrent gastrointestinal illnesses. Diuretics should be used with caution in these patients and may need to be decreased if fluid intake is a concern. Polycythemic infants with concomitant **iron deficiency** are at even greater risk for cerebrovascular accidents, probably because of the decreased deformability of microcytic red blood cells. Iron therapy may reduce this risk somewhat, but surgical treatment of the cardiac anomaly is the best therapy.

Severely cyanotic patients should have periodic determinations of hemoglobin and hematocrit. Increasing polycythemia, often associated with headache, fatigue, dyspnea, or a combination of these conditions, is one indication for palliative or corrective surgical intervention. In cyanotic patients with inoperable conditions, partial exchange transfusion may be required to treat symptomatic (most often headache or chest pain) individuals whose hematocrit has risen to the 65–70% level. This procedure is not without risk, especially in patients with an extreme elevation in PVR. Because these patients do not tolerate wide fluctuations in circulating blood volume, blood should be replaced with fresh-frozen plasma or albumin.

450.4

Echocardiography

Daniel Bernstein

Transthoracic echocardiography (TTE) has replaced invasive studies such as cardiac catheterization for the *diagnosis* of most forms of CHD. The echocardiographic examination can be used to evaluate cardiac structures in congenital heart lesions using two-dimensional (2D) and three-dimensional (3D) imaging, estimate intracardiac pressures and gradients across stenotic valves and vessels using echo-Doppler and color flow Doppler, quantitate cardiac contractile function (both systolic and diastolic), determine the direction of flow across a defect, examine the integrity of the coronary arteries, and detect the presence of vegetations from endocarditis, as well as the presence of pericardial fluid, cardiac tumors, and chamber thrombi.

Echocardiography may also be used to assist in the performance of interventional procedures, including pericardiocentesis, balloon atrial septostomy (see Chapter 458.2), ASD or VSD closure, transcatheter valve implantation, and endocardial biopsy. **Transesophageal echocardiography** (TEE) is used routinely to monitor ventricular function in patients during surgical procedures and can provide an immediate assessment of the results of surgical repair of congenital heart lesions. A complete TTE examination usually entails a combination of M-mode and 2D and 3D imaging, as well as pulsed, continuous, and color Doppler flow studies. Doppler tissue imaging provides a more quantitative assessment of ventricular systolic and diastolic function.

M-Mode Echocardiography

M-mode echocardiography displays a one-dimensional slice of cardiac structure varying over time (Fig. 450.14). It is used mostly for the measurement of cardiac dimensions (wall thickness and chamber size) and cardiac function (fractional shortening, wall thickening). M-mode echocardiography is also useful for assessing the motion of intracardiac structures (opening and closing of valves, movement of free walls and septa) and the anatomy of valves (Fig. 450.15). The most frequently used index of cardiac function in children is **percent fractional shortening** (%FS), which contrasts to adults, where ejection fraction is the most common functional measurement. %FS is calculated as (LVED − LVES)/LVED, where LVED is left ventricular dimension at end-diastole and LVES is left ventricular dimension at end-systole. Normal fractional shortening is approximately 28–42%. Other M-mode indices of cardiac function include the mean velocity of fiber shortening (mean V_{CF}), systolic time intervals (LVPEP = LV preejection period, LVET = LV ejection time), and isovolemic contraction time. M-mode measurements are highly susceptible to errors because of differences in wall motion between different segments of the heart (more frequently seen in adults with ischemic heart disease, but which can be seen in children with congenital and acquired heart disease, especially after surgical repair).

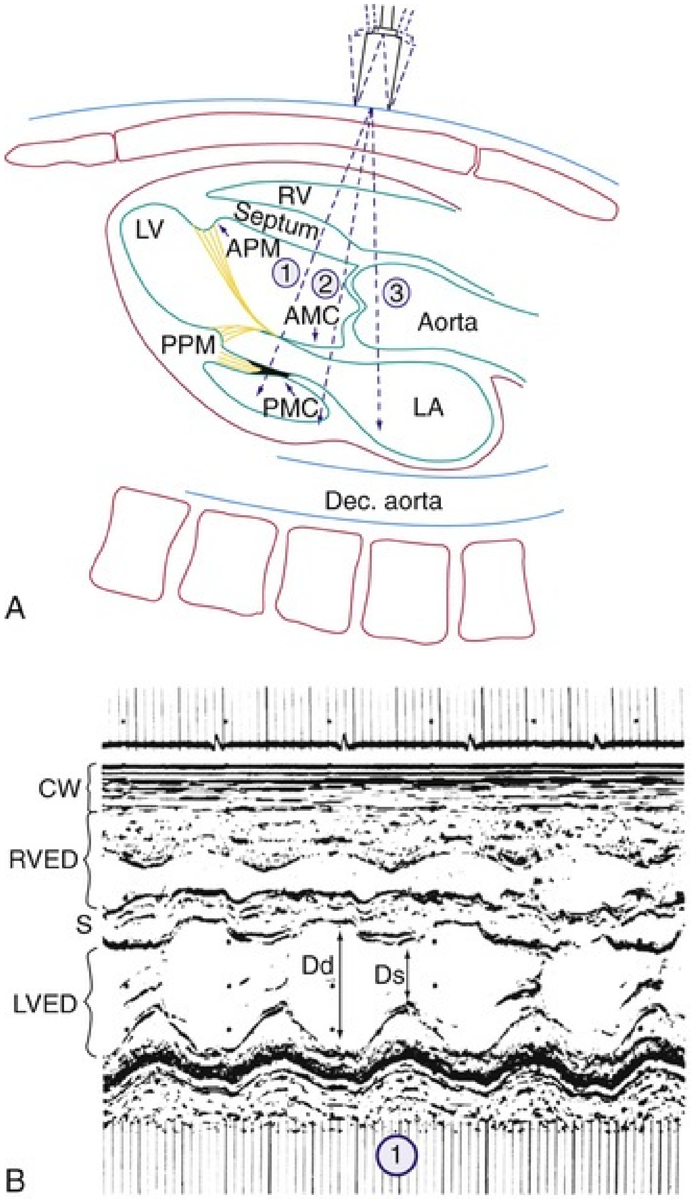

FIG. 450.14 M-mode echocardiogram. A, Diagram of a sagittal section of a heart showing the structures traversed by the echo beam as it is moved superiorly to positions (1), (2), and (3). AMC, Anterior mitral cusp; APM, anterior papillary muscle; Dec. aorta, descending aorta; LA, left atrium; LV, left ventricle; PMC, posterior mitral cusp; PPM, posterior papillary muscle; RV, right ventricle. B, Echocardiogram from transducer position (1); this view is the best one for measuring cardiac dimensions and fractional shortening. Fractional shortening is calculated as (LVED − LVES)/LVED. CW, Chest wall; Ds, LV dimension in systole; LVED, LV dimension at end-diastole (Dd); RVED, RV dimension at end-diastole.

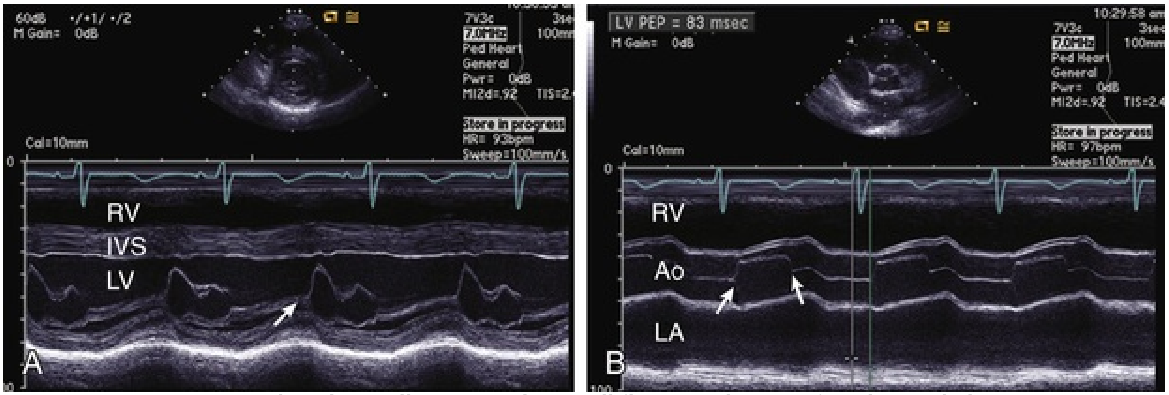

FIG. 450.15 M-mode echocardiograms. The small figure at the top of each panel shows the 2D parasternal short axis echo image from which the M-modes are derived. The cursor can be seen midway through the image, indicating the one-dimensional line through which the M-mode is being sampled. A, M-mode echocardiogram of a normal mitral valve. *Arrow* shows the opening of the anterior leaflet in early diastole (see ECG tracing above for reference). B, M-mode echocardiogram of a normal aortic valve. The opening and closing of the aortic leaflets in systole are outlined by the 2 *arrows* . Ao, Aorta; IVS, interventricular septum; LV, left ventricle; RV, right ventricle.

Two-Dimensional Echocardiography

Two-dimensional echocardiography provides a real-time image of cardiac structures. With 2D echocardiography, the contracting heart is imaged in real time using several standard views, including parasternal long axis (Fig. 450.16), parasternal short axis (Fig. 450.17), apical 4 chamber (Fig. 450.18), subcostal (Fig. 450.19), and suprasternal (Fig. 450.20), each of which emphasizes specific structures. Two-dimensional echocardiography has replaced cardiac angiography for the preoperative diagnosis and follow-up of the vast majority of congenital heart lesions. However, when information from the cardiac examination or other studies is not consistent with the echocardiogram (e.g., size of left-to-right shunt), cardiac catheterization remains an important tool to confirm the anatomic diagnosis and evaluate the degree of physiologic derangement. MRI is also a valuable adjunct to provide a better quantification of ventricular size and function.

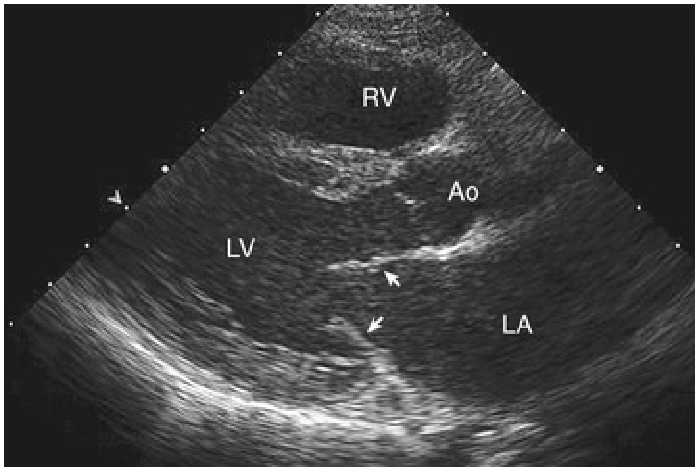

FIG. 450.16 Normal parasternal long axis echocardiographic window. The transducer is angulated slightly posteriorly, imaging the left-sided cardiac structures. If the transducer were to be angulated more anteriorly, the right ventricular structures would be imaged. The mitral valve leaflets can be seen in partially open position in early diastole *(arrows).* The closed aortic valve leaflets can be seen just below the label Ao (aorta). LA, Left atrium; LV, left ventricle; RV, right ventricle.

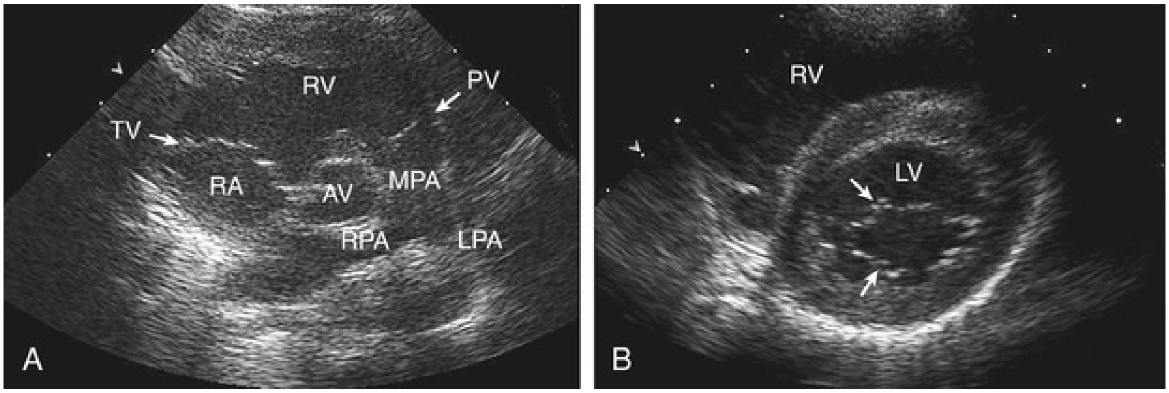

FIG. 450.17 Normal parasternal short axis echocardiographic windows. A, With the transducer angled superiorly and rightward, the aortic valve (AV) is imaged, surrounded by both inflow and outflow portions of the right ventricle (RV). LPA, Left pulmonary artery; MPA, main pulmonary artery; PV, pulmonary valve; RA, right atrium; RPA, right pulmonary artery; TV, tricuspid valve. B, With the transducer angled inferiorly and leftward, the left ventricular chamber is imaged along with cross-sectional view of the mitral valve *(arrows).* LV, Left ventricle; RV, right ventricle.

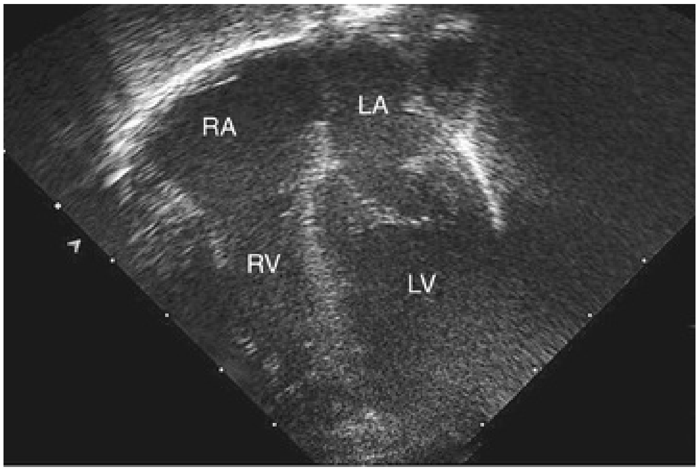

FIG. 450.18 Normal apical 4-chamber echocardiographic window showing all 4 cardiac chambers and both atrioventricular valves opened in diastole. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

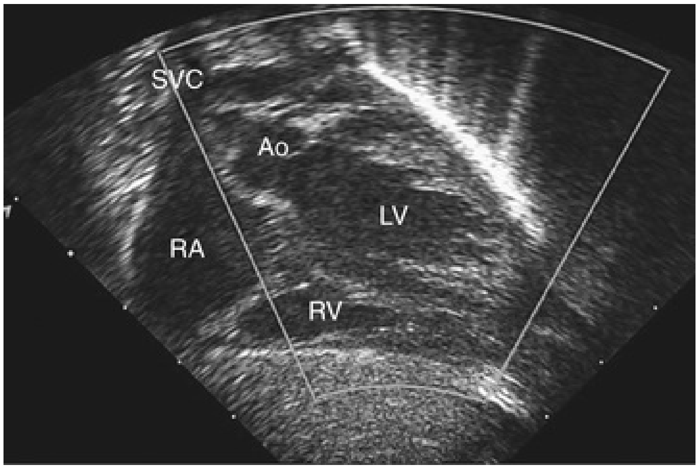

FIG. 450.19 Normal subcostal echocardiographic window showing the left ventricular outflow tract. The right-sided structures are not fully imaged in this view. Ao, Ascending aorta; LV, left ventricle; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

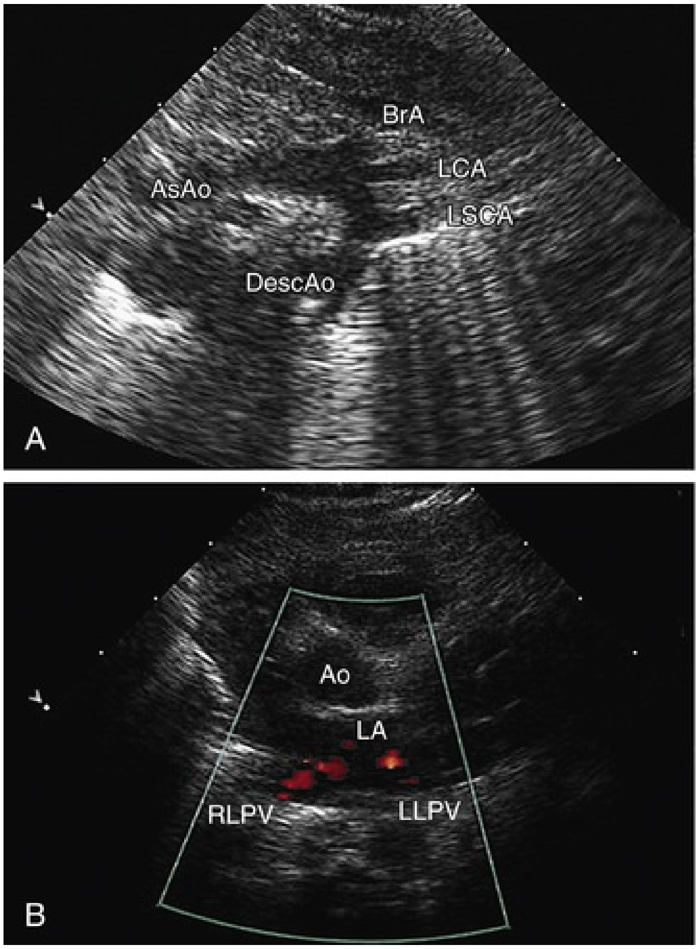

FIG. 450.20 **A,** Normal suprasternal echocardiographic window showing the aortic arch and its major branches. AsAo, Ascending aorta; BrA, brachiocephalic artery; DescAo, descending aorta; LCA, left carotid artery; LSCA, left subclavian artery. **B,** Normal high parasternal window showing color Doppler imaging of normal pulmonary venous return to the left atrium (LA) of both right (RLPV) and left (LLPV) lower pulmonary veins.

Doppler Echocardiography

Doppler echocardiography displays blood flow in cardiac chambers and vascular channels based on the change in frequency imparted to a sound wave by the movement of erythrocytes. In pulsed Doppler and continuous wave Doppler, the speed and direction of blood flow in the line of the echo beam change the transducer's reference frequency. This frequency change can be translated into volumetric flow (L/min) data for estimating systemic or pulmonary blood flow and into pressure (mm Hg) data for estimating gradients across the semilunar or atrioventricular valves or across septal defects or vascular communications such as shunts. Color Doppler permits highly accurate assessment of the presence and direction of intracardiac shunts and allows identification of small or multiple left-to-right or right-to-left shunts (Fig. 450.21). The severity of valvular insufficiency can be evaluated qualitatively with both pulsed and color Doppler (Fig. 450.22). Alterations in venous Doppler flow patterns can be used to detect abnormalities of systemic and pulmonary veins, and alterations of atrioventricular valve Doppler flow patterns can be used to assess ventricular diastolic functional abnormalities, particularly the **E/A ratio** , the ratio of peak velocity flow in diastole (i.e., the ratio of the early-diastole E wave to the peak velocity flow in late diastole caused by atrial [A] contraction wave).

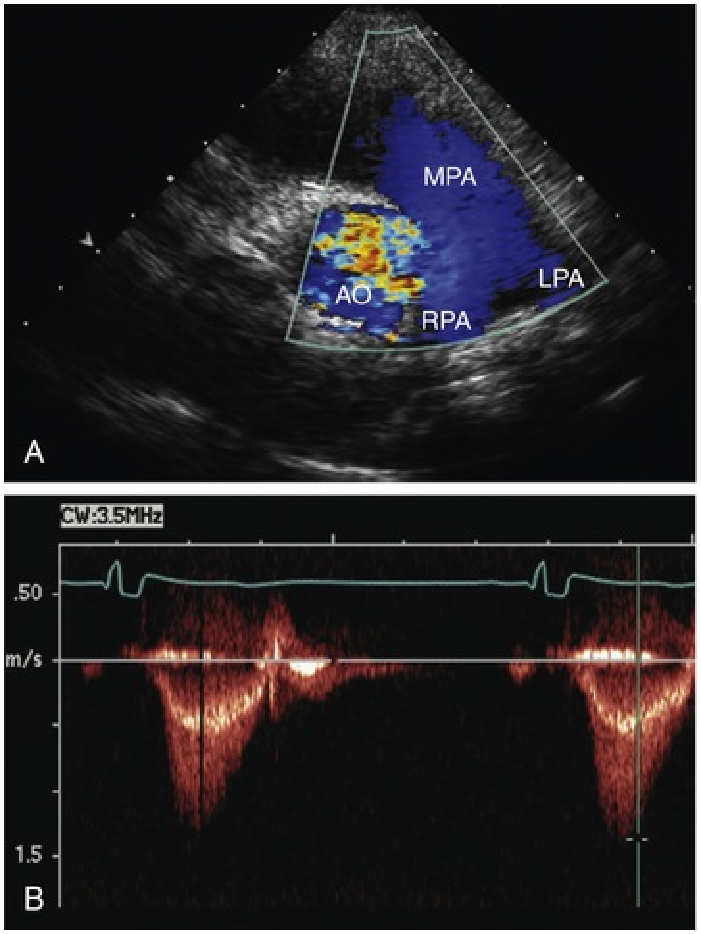

FIG. 450.21 Color and pulsed Doppler evaluation of pulmonary arterial flow. A, Color Doppler evaluation of a parasternal short axis view showing normal flow through the pulmonary valve to the main and branch pulmonary arteries. The color of the Doppler flow is *blue,* indicating that the flow is moving away from the transducer (which is located at the top of the figure, at the apex of the *triangular* ultrasound window). Note that the color assigned to the Doppler signal does not indicate the oxygen saturation of

the blood. AO, Aorta; LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery. B, Pulsed wave Doppler flow pattern through the pulmonary valve showing a low velocity of flow (<1.5 m/sec), indicating the absence of a pressure gradient across the valve. The envelope of the flow signal is below the line, indicating that the flow is moving away from the transducer.

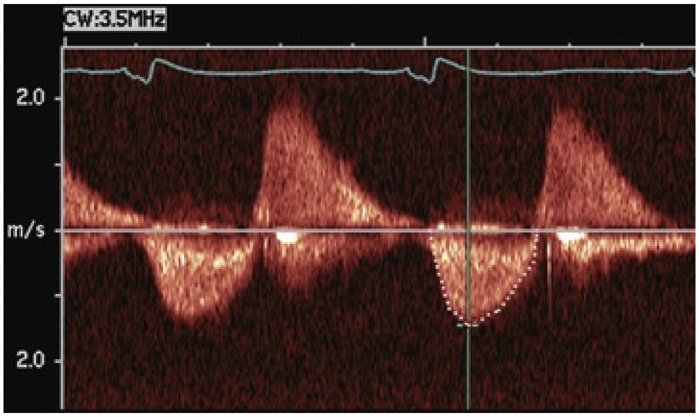

FIG. 450.22 **Doppler evaluation of a patient who had previously undergone repair of tetralogy of Fallot and who has mild pulmonary stenosis and moderate pulmonary regurgitation. The tracing shows the to-and-fro flow across the pulmonary valve with the signal below the line representing forward flow in systole (see ECG tracing for reference) and the signal above the line representing regurgitation during diastole.**

M-mode, 2D, and Doppler echocardiographic methods of assessing LV systolic and diastolic function (e.g., end-systolic wall stress, dobutamine stress echocardiography, Doppler tissue imaging) have proved useful in the serial assessment of patients at risk for the development of both systolic and diastolic ventricular dysfunction and ventricular dyssynchrony (where the coordination of left and right ventricular contraction is abnormal). Such patients include those with cardiomyopathies, those receiving anthracycline drugs for cancer chemotherapy, those at risk for iron overload, and those being monitored for rejection or coronary artery disease after heart transplantation.

Three-Dimensional Echocardiography

Real-time 3D echocardiographic reconstruction is most valuable for the detailed assessment of cardiac morphology (Fig. 450.23). Details of valve structure, the size and location of septal defects, abnormalities of the ventricular myocardium, and details of the great vessels, which may not be as readily apparent using 2D imaging, can often be appreciated on 3D echocardiography. Reconstruction of the view that the surgeon will encounter in the operating room makes this technique a valuable adjunct for preoperative imaging.

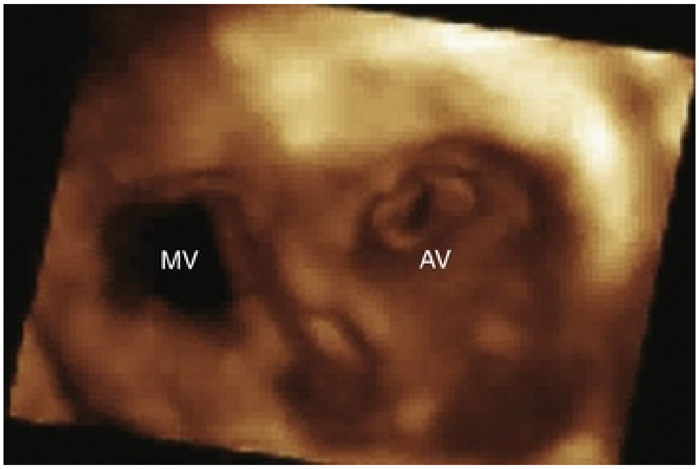

FIG. 450.23 **Three-dimensional echocardiogram showing a short axis view of the left ventricle. AV, Aortic valve; MV, mitral valve. (Courtesy of Dr. Norman Silverman, Stanford University, Stanford, CA.)**

Transesophageal Echocardiography

TEE is an extremely sensitive imaging technique that produces a clearer view of smaller lesions such as vegetations in endocarditis, especially in larger patients. It is useful in visualizing posteriorly located structures such as the atria, aortic root, and atrioventricular valves. TEE is extremely useful as an intraoperative technique for monitoring cardiac function during both cardiac and noncardiac surgery and for screening for residual cardiac defects after the patient is initially weaned from cardiopulmonary bypass but before being disconnected from the bypass circuit. This technique has been especially helpful in evaluating the degree of residual regurgitation or stenosis after valve repairs and in searching for small muscular VSDs that may have been missed during the closure of larger defects. It is always preferable to make the diagnosis of **excessive valve regurgitation** while the patient is still in the operating room, so that the repair can be revised or the valve replaced, rather than after surgery, when the patient is already in the postoperative care unit. However, hemodynamic measurements made while the chest is open and the patient is still under anesthesia may be different from those made under more normal conditions, as when the patient is ready to be discharged from the hospital.

Fetal Echocardiography

Fetal echocardiography can be used to evaluate cardiac structures or disturbances in cardiac rhythm (Fig. 450.24). Obstetricians are attuned to detect gross abnormalities in cardiac structure on routine obstetric ultrasonography (4-chamber view) or may refer the patient because of unexplained hydrops fetalis, a family history of CHD, or a maternal condition associated with fetal cardiac pathology, such as gestational diabetes. Fetal echocardiography can diagnose most significant congenital heart lesions as early as 17-19 wk of gestation; accuracy at this early stage is limited, however, and families should understand that these studies cannot totally eliminate the possibility of CHD. Serial fetal echocardiograms have also demonstrated the importance of flow disturbance in the pathogenesis of CHD; such studies can show the intrauterine progression of a moderate lesion, such as aortic stenosis, into a more severe lesion, such as **hypoplastic left heart syndrome** (HLHS). M-mode echocardiography can diagnose rhythm disturbances in the fetus and can determine the success of antiarrhythmic therapy administered to the mother. A screening fetal echocardiogram is recommended for women with a previous child or first-degree relative with CHD, for those who are at higher risk of having a child with cardiac disease (e.g., insulin-dependent diabetic patients, women exposed to teratogenic drugs during early pregnancy), and in any fetus in whom a chromosomal abnormality is suspected or confirmed.

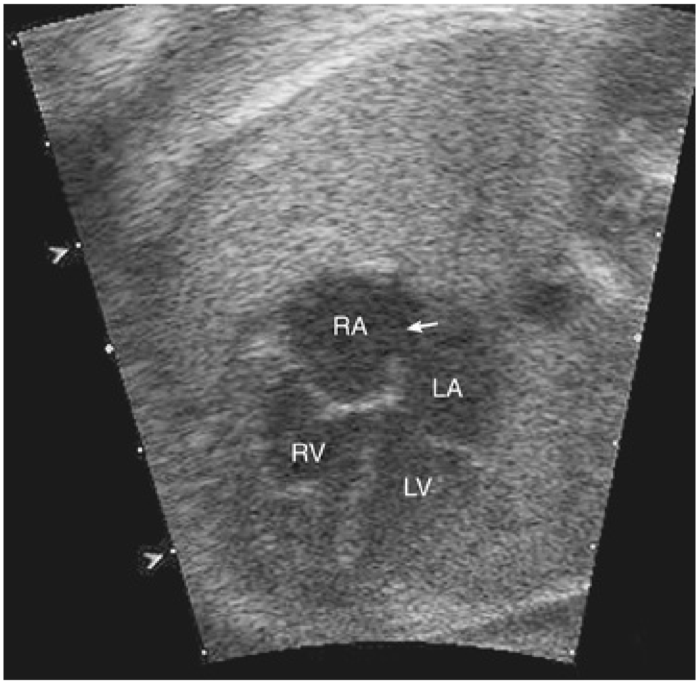

FIG. 450.24 **Normal 4-chamber view echocardiogram on a fetus at 20 wk of gestation. The foramen ovale *(arrow)* can be seen between the right and left atria. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.**

Early detection provides the opportunity to counsel and educate the parents about the severity of the cardiac lesion and potential therapeutic or palliative care options. Referral to a high-risk perinatal service is then performed, for further ultrasound screening for associated anomalies of other organs and potential amniocentesis or sequencing of cell-free DNA in maternal blood for karyotyping. For fetuses with ductal dependent lesions, delivery can be planned at a tertiary care center, avoiding the requirement for postnatal transport of an unstable infant. For fetuses with complex CHD at high risk for complications immediately at birth (e.g., HLHS with intact atrial septum), delivery can be arranged with an operating room and surgeon standing by. In utero treatment of CHD is still an experimental procedure, with the most common procedure being aortic balloon valvuloplasty for HLHS. Current results are mixed.

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450.5

Exercise Testing

Daniel Bernstein

The normal cardiorespiratory system adapts to the extensive demands of exercise with a several-fold increase in oxygen consumption and cardiac output. Because of the large reserve capacity for exercise, significant abnormalities in cardiovascular performance may be present without symptoms at rest or during ordinary activities. When patients are evaluated in a resting state, significant abnormalities in cardiac function may not be appreciated, or if detected, their implications for quality of life may not be recognized. Permission for children with cardiovascular disease to participate in various forms of physical activity is frequently based on totally subjective criteria. As the importance of aerobic exercise is increasingly recognized, even for children with complex congenital heart lesions, exercise testing can provide a quantitative evaluation of the child's ability to participate safely in both competitive and noncompetitive sports. Exercise testing can also play an important role in evaluating symptoms and quantitating the severity of cardiac abnormalities.

In older children, exercise studies are generally performed on a graded treadmill apparatus with timed intervals of increasing grade and speed. In younger children, exercise studies are often performed on a bicycle ergometer. Many laboratories have the capacity to measure both cardiac and pulmonary function noninvasively during exercise. This allows measurement of both resting and maximal oxygen consumption (VO_{2max}) and the point at which anaerobic threshold is reached, which are important indicators of cardiovascular fitness.

As a child grows, the capacity for muscle work is enhanced with increased body size and skeletal muscle mass. All indices of cardiopulmonary function do not increase in a uniform manner. A major response to exercise is an increase in cardiac output, principally achieved through an increase in heart rate, but stroke volume (SV), systemic venous return, and pulse pressure are also increased. Systemic vascular resistance is greatly decreased as the blood vessels in working muscle dilate in response to increasing metabolic demands. As the child becomes older and larger, the response of the heart rate to exercise remains prominent, but cardiac output increases because of growing cardiac volume capacity and thus SV. Responses to dynamic exercise are not dependent solely on age. For any given body surface area, boys have a larger SV than size-matched girls. This increase is also mediated by posture. Augmentation of SV with upright, dynamic exercise is facilitated by the pumping action of working muscles, which overcomes the static effect of gravity and increases systemic venous return.

Dynamic exercise testing defines not only endurance and exercise capacity but also the effect of such exercise on myocardial blood flow and cardiac rhythm. Significant ST segment depression reflects abnormalities in myocardial perfusion, such as the subendocardial ischemia that typically occurs during exercise in children with hypertrophied left ventricles. The **exercise ECG** is considered abnormal if the ST segment depression is >2 mm and extends for at least 0.06 sec after the J point (onset of the ST segment) in conjunction with a horizontal-, upward-, or downward-sloping ST segment. A decrease in blood pressure before maximal exercise is reached is a risk indicator in patients with hypertrophic cardiomyopathy. Provocation of rhythm disturbances during an exercise study is an important method of evaluating select patients with known or suspected rhythm disorders. The effect of pharmacologic management can also be tested in this manner.

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450.6

Cardiac Imaging Studies

Daniel Bernstein

Magnetic resonance imaging (MRI) and **magnetic resonance angiography (MRA)** are extremely helpful in the diagnosis and management of patients with CHD. These techniques produce tomographic images of the heart in any projection (Fig. 450.25), with excellent contrast resolution of fat, myocardium, and lung, as well as moving blood from blood vessel walls. MRI is useful in evaluating areas that are less well visualized by echocardiography, such as distal branch pulmonary artery anatomy and anomalies in systemic and pulmonary venous return.

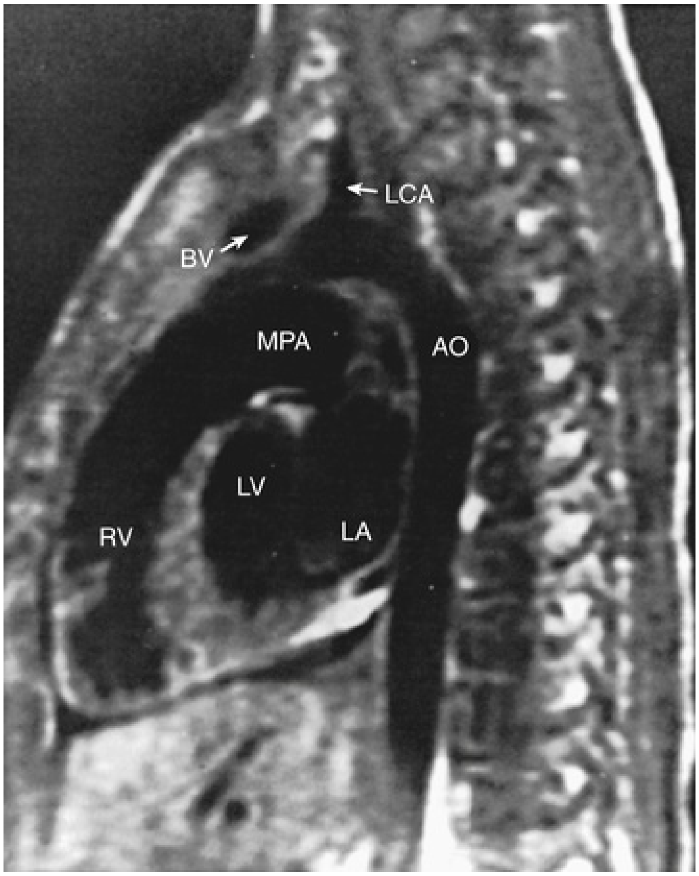

FIG. 450.25 Normal sagittal MRI. AO, Aorta; BV, brachiocephalic vein; LA, left atrium; LCA, left coronary artery; LV, left ventricle; MPA, main pulmonary artery; RV, right ventricle. (From Bisset GS III: Cardiac and great vessel anatomy. In El-Khoury GY, Bergman RA, Montgomery WJ, editors: *Sectional anatomy by MRI/CT,* New York, 1990, Churchill Livingstone.)

MRA allows the acquisition of images in several tomographic planes. Within each plane, images are obtained at different phases of the cardiac cycle. Thus, when displayed in a dynamic “cine” format, changes in wall thickening, chamber volume, and valve function can be displayed and analyzed. Blood flow velocity and blood flow volume can be calculated. MRA is an excellent technique for following patients serially after repair of complex CHD, such as tetralogy of Fallot. In these patients, MRA can be used to assess RV volume and mass as well as quantify the amount of regurgitation through either the pulmonary or tricuspid valve. Other MRI techniques, such as myocardial delayed enhancement and tissue T1 weighting, can be used to quantify areas of myocardial scar in patients with cardiomyopathy or in patients after CHD repair, especially tetralogy of Fallot. **Magnetic resonance spectroscopy** , predominantly a research tool at present, provides a means of demonstrating relative concentrations of high-energy metabolites (adenosine triphosphate, adenosine diphosphate, inorganic phosphate, and phosphocreatine) within regions of the working myocardium.

Computer processing of MRA images allows the noninvasive visualization of the cardiovascular system from inside of the heart or vessels, a technique known as *fly-through imaging*. These images allow the cardiologist to image the interiors of various cardiovascular structures (Fig. 450.26). These techniques are especially helpful in imaging complex peripheral arterial stenoses, especially after balloon angioplasty.

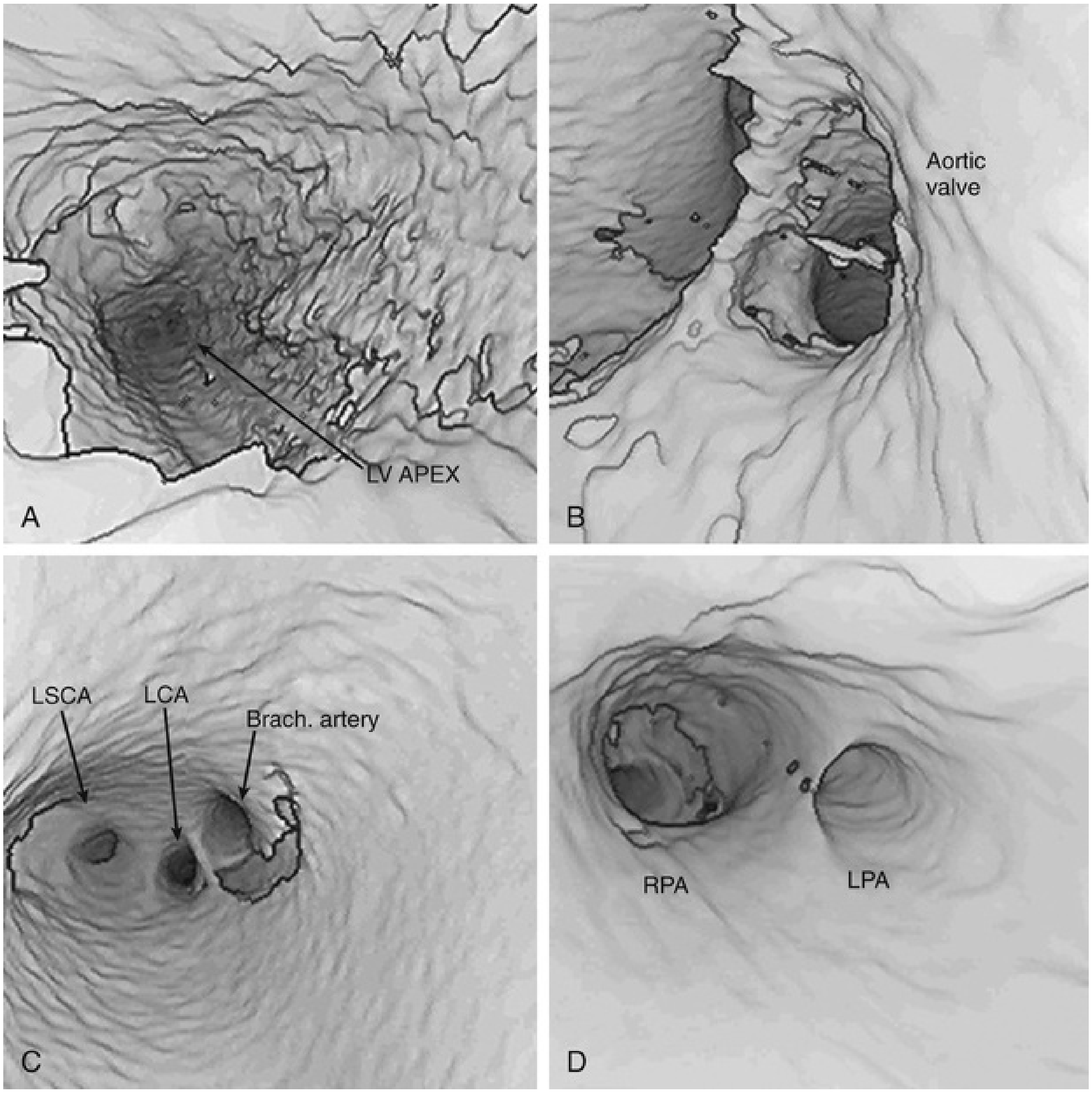

FIG. 450.26 **Fly-through imaging in a patient with an aortopulmonary window. This series of still frames shows the progression from the left ventricular (LV) chamber (A),**

through the aortic valve (B), out to the ascending aorta (C), and then through the defect to the branch pulmonary arteries (D). Brach., Brachiocephalic; LCA, left carotid artery; LPA, left pulmonary artery; LSCA, left subclavian artery; RPA, right pulmonary artery.

CT scanning can now be used to perform rapid, respiration-gated cardiac imaging in children with resolutions down to 0.5 mm. Three-dimensional reconstruction of CT images is especially useful in evaluating branch pulmonary arteries, anomalies in systemic and pulmonary venous return, and great vessel anomalies such as coarctation of the aorta (Fig. 450.27).

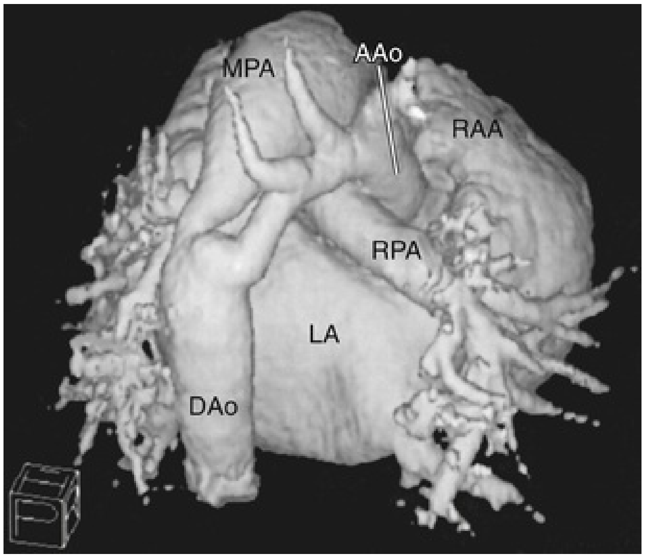

FIG. 450.27 **Three-dimensional reconstruction of CT images from a neonate with severe coarctation of the aorta. The patent ductus arteriosus can be seen toward the left leading from the main pulmonary artery to the descending aorta. The tortuous and narrow coarctated segment is just to the right of the ductus. The transverse aorta is hypoplastic as well. AAo, Ascending aorta; DAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RAA, right atrial appendage; RPA, right pulmonary artery. (Courtesy of Dr. Paul Pitlick, Stanford University, Stanford, CA.)**

Radionuclide angiography may be used to detect and quantify shunts and to analyze the distribution of blood flow to each lung. This technique is particularly useful in quantifying the volume of blood flow distribution between the 2 lungs in patients with abnormalities of the pulmonary vascular tree or after a shunt operation (Blalock-Taussig or Glenn), or to quantify the success of balloon angioplasty and intravascular stenting procedures. Gated blood pool scanning can be used to calculate hemodynamic measurements, quantify valvular regurgitation, and detect regional wall motion abnormalities. Thallium imaging can be performed to evaluate cardiac muscle perfusion. These methods can be used at the bedside of seriously ill children and can be performed serially, with minimal discomfort and low radiation exposure.

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450.7

Diagnostic and Interventional Cardiac Catheterization

Daniel Bernstein

The catheterization laboratory, once the site for initial diagnosis of congenital heart disease, has become the center of high-technology interventional procedures, allowing for the nonsurgical repair or palliation of heart defects that once required open heart surgery. Some centers have developed hybrid catheterization laboratories, combining standard fluoroscopic imaging with an operating suite, allowing combined approaches to treat complex congenital heart lesions.

Diagnostic Cardiac Catheterization

Diagnostic catheterization is still performed (1) to assist in the initial diagnosis of some complex congenital heart lesions (e.g., tetralogy of Fallot with pulmonary atresia and major aortopulmonary collateral arteries, pulmonary atresia with intact ventricular septum and coronary sinusoids, HLHS with mitral stenosis); (2) in cases in which other imaging studies are equivocal; (3) in patients for whom hemodynamic assessment is critical (to determine the size of a left-to-right shunt in borderline cases, or to determine the presence or absence of pulmonary vascular disease in an older patient with a left-to-right shunt); (4) between stages of repair of complex CHD (e.g., hypoplastic left or right heart syndromes); (5) for long-term surveillance of patients with complex CHD (e.g., after Fontan palliation for single ventricles); (6) for myocardial biopsy in the diagnosis of cardiomyopathy or in screening for cardiac rejection after cardiac transplantation; and (7) for electrophysiologic study in the evaluation of cardiac arrhythmias (see Chapter 462).

Cardiac catheterization should be performed with the patient in as close to a basal state as possible. Conscious sedation or low-level anesthesia is routine. If a deeper level of general anesthesia is required, careful choice of an anesthetic agent is warranted to avoid depression of cardiovascular function and subsequent distortion of the calculations of cardiac output, PVR and SVR, and shunt ratios.

Cardiac catheterization in critically ill infants with CHD should be performed in a center where a pediatric cardiovascular surgical team is available in the event that an operation is required immediately afterward. The complication rate of cardiac catheterization and angiography is greatest in critically ill infants; they must be studied in a thermally neutral environment and treated quickly for hypothermia, hypoglycemia, acidosis, or excessive blood loss.

Catheterization may be limited to the right-sided cardiac structures, the left-sided structures, or both the right and left sides of the heart. The catheter is passed into the heart under fluoroscopic guidance through a percutaneous entry point in a femoral or jugular vein. In infants and in a number of older children, the left side of the heart can be accessed by passing the catheter across a patent foramen ovale to the left atrium and left ventricle. If the foramen is closed, the left side of the heart can be catheterized by passing the catheter retrograde via a percutaneous entry site in the femoral artery, or if necessary, via a transatrial septal puncture. The catheter can be manipulated through abnormal intracardiac defects (ASD, VSD). Blood samples are obtained for measuring oxygen saturation in each cardiac chamber or blood vessel, allowing the calculation of shunt volumes. Pressures are measured for calculating gradients, septal defects, or valves and valve areas. Radiopaque contrast is injected to delineate cardiac and vascular structures. A catheter with a thermosensor tip can be used to measure cardiac output by thermodilution. Specialized catheters can be used to measure more sophisticated indices of cardiac function; those with pressure-transducer tips can measure the first derivative of LV pressure (dP/dt). Conductance catheters can be used to generate pressure-volume loops, from which indices of both contractility (end-systolic elastance) and relaxation can be derived, although these are almost exclusively used in research studies. Complete hemodynamics can be calculated, including cardiac output, intracardiac left-to-right and right-to-left shunts, and SVR and PVR. Fig. 450.28 depicts normal circulatory dynamics.

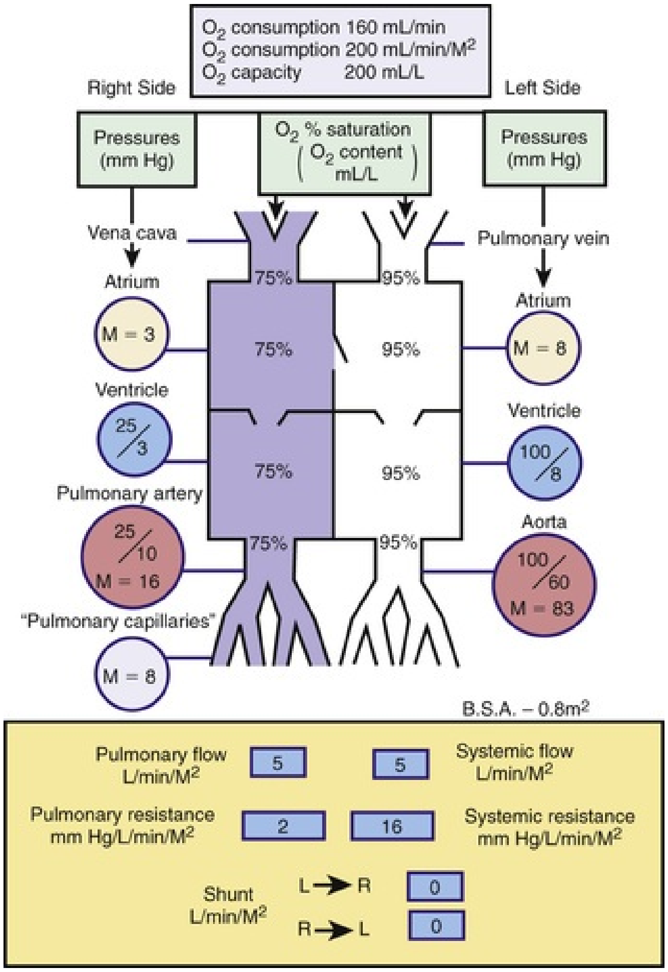
O2 consumption 160 mL/min
O2 consumption 200 mL/min/M2
O2 capacity 200 mL/L
Right Side
Left Side
Pressures (mm Hg)
O2 % saturation (O2 content mL/L)
Pressures (mm Hg)
Vena cava
Pulmonary vein
Atrium
M = 3
Atrium
M = 8
75%
95%
75%
95%
Ventricle
25/3
Ventricle
100/8
75%
95%
Pulmonary artery
25/10 M = 16
Aorta
100/60 M = 83
75%
95%
"Pulmonary capillaries"
M = 8
B.S.A. – 0.8m2
Pulmonary flow L/min/M2
5
5
Systemic flow L/min/M2
Pulmonary resistance mm Hg/L/min/M2
2
16
Systemic resistance mm Hg/L/min/M2
Shunt L/min/M2
L → R
0
R → L
0

FIG. 450.28 Diagram of normal circulatory dynamics with pressure readings, oxygen content, and percent saturation; B.S.A., body surface area. (Modified from Nadas AS, Fyler DC: *Pediatric cardiology,* ed 3, Philadelphia, 1972, Saunders.)

Thermodilution Measurement of Cardiac Output

The thermodilution method for measuring cardiac output is performed with a flow-directed, thermistor-tipped, pulmonary artery (Swan-Ganz) catheter. A known change in the heat content of the blood is induced at one point in the circulation (usually the right atrium or inferior vena cava) by injecting room-temperature saline, and the resultant change in temperature is detected at a point downstream (usually the pulmonary artery). This method is used to measure cardiac output in the catheterization laboratory in patients without shunts.

Monitoring cardiac output by the thermodilution method can occasionally be useful in managing critically ill infants and children in an intensive care setting after cardiac surgery or in the presence of shock. In this case, a triple-lumen catheter is used for both cardiac output determination and measurement of pulmonary artery and pulmonary capillary wedge pressure.

Angiocardiography

The major blood vessels and individual cardiac chambers may be visualized by selective angiocardiography, the injection of contrast material into specific chambers or great vessels. This method allows identification of structural abnormalities without interference from the superimposed shadows of normal chambers. **Fluoroscopy** is used to visualize the catheter as it passes through the various heart chambers. After the cardiac catheter is properly placed in the chamber to be studied, a small amount of contrast medium is injected with a power injector, and cineangiograms are exposed at rates ranging from 15-60 frames/sec. Modern catheterization labs utilize digital imaging technology, allowing for a significant reduction in radiation exposure. **Biplane cineangiocardiography** allows detailed evaluation of specific cardiac chambers and blood vessels in 2 planes simultaneously with the injection of a single bolus of contrast material. This technique is standard in pediatric cardiac catheterization laboratories and allows one to minimize the volume of contrast material used, which is safer for the patient. Various angled views (e.g., left anterior oblique, cranial angulation) are used to display specific anatomic features optimally in individual lesions.

Rapid injection of contrast medium under pressure into the circulation is not without risk, and each injection should be carefully planned. Contrast agents consist of hypertonic solutions, with some containing organic iodides, which can cause complications, including nausea, a generalized burning sensation, central nervous system symptoms, renal insufficiency, and allergic reactions. For patients with known renal insufficiency who require angiography, there are protocols to protect the kidneys involving prehydration and drugs such as *N*-acetylcysteine. Intramyocardial injection is generally avoided by careful placement of the catheter before injection. Hypertonicity of the contrast medium may result in transient myocardial depression and a drop in blood pressure, followed soon afterward by tachycardia, an increase in cardiac output, and a shift of interstitial fluid into the circulation. This shift can transiently increase the symptoms of heart failure in critically ill patients.

Interventional Cardiac Catheterization

Catheter treatment is the standard of practice for most cases of isolated pulmonary or aortic valve stenosis as well as for recoarctation of the aorta. A special catheter with a sausage-shaped balloon at the distal end is passed through the obstructed valve. Rapid filling of the balloon with a mixture of contrast material and saline solution results in tearing of the stenotic valve tissue, usually at the site of inappropriately fused raphe. Valvular pulmonary stenosis can be treated successfully by **balloon angioplasty** ; in most patients, angioplasty has replaced surgical repair as the initial procedure of choice. The clinical results of this procedure are similar to those obtained by open heart surgery, but without the need for sternotomy or prolonged hospitalization. **Balloon valvuloplasty** for aortic stenosis has also yielded excellent results, although, as with surgery, aortic stenosis often recurs as the child grows, and multiple procedures may thus be required. One complication of both valvuloplasty and surgery is the creation of **valvular insufficiency** . This complication has more serious implications when it occurs on the aortic vs the pulmonary side of the circulation because regurgitation is less well tolerated at systemic arterial pressures.

Balloon angioplasty is the procedure of choice for patients with restenosis of **coarctation of the aorta** after earlier surgery. It remains controversial whether angioplasty is the best procedure for native (unoperated) coarctation of the aorta because of reports of late aneurysm formation, and many centers still refer primary coarctation in infants and young children for surgical repair. However, in older patients with previously undiagnosed coarctation, especially those with decreased LV function, primary angioplasty with stent placement may be considered. Other applications of the balloon angioplasty technique include amelioration of mitral stenosis, dilation of surgical conduits (e.g., RV-PA conduits), relief of branch pulmonary artery (PA) narrowing, dilation of systemic or pulmonary venous obstructions, and the long-used balloon atrial septostomy (**Rashkind procedure**) for transposition of the great arteries (see Chapter 458.2).

Interventional catheterization techniques are being adapted for use in the **fetus** with lesions such as aortic stenosis to prevent their progression to more complex lesions such as HLHS. In these procedures, after administration of appropriate anesthesia, a needle is passed through the maternal abdominal wall, the uterine wall, and the fetal chest wall and directly into the fetal left ventricle (see Fig. 458.13). A coronary angioplasty balloon catheter is passed through the needle and across the stenotic aortic valve, which is then dilated. With the restoration of normal LV blood flow, it is hoped that normal LV growth potential is restored. Midterm results with this technique in a growing number of patients continue to show mixed results, with good ventricular growth leading to a 2-ventricle circulation in approximately 25% of highly preselected patients.

In patients with branch pulmonary artery stenoses, the previously mixed results with balloon angioplasty alone have been enhanced with the use of **intravascular stents** delivered over a balloon catheter and expanded within the vessel lumen (Fig. 450.29). Once placed, the stents can often be dilated to successively greater sizes as the patient grows, although their use in younger infants and children is limited by the extent they can be further expanded. Research into biodissolvable stents may solve this problem in the future. As mentioned, stents are also being used in adolescents and young adults with coarctation of the aorta.

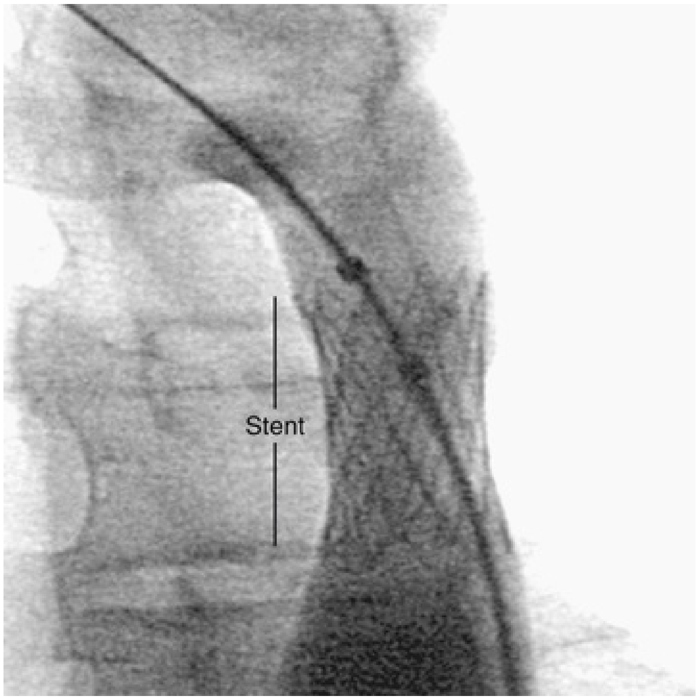

FIG. 450.29 Descending aortic angiogram showing intravascular stent placed in the descending aorta for treatment of recurrent coarctation of the aorta.

Closure of a small patent ductus arteriosus (PDA) is routinely achieved with catheter-delivered **coils** (see Fig. 453.11), whereas a larger PDA can be closed with a variety of sandwich-type devices. Closure of anomalous vascular connections (coronary fistulas, venovenous collaterals in cyanotic heart lesions) can also be achieved using coils. Secundum ASDs are now routinely closed with a double-disk occluder device (see Fig. 453.3). Versions of these devices are currently in clinical trials for closure of surgically difficult-to-reach muscular VSDs and for the more common perimembranous VSD. Catheter-delivered devices may also be used as an adjunct to complex surgical repairs (e.g., dilation or stenting of branch pulmonary artery or pulmonary vein stenosis). High-risk patients undergoing the Fontan operation (see Fig. 457.9) often have a small fenestration created between the right and left sides of the circulation to serve as a "pop-off valve" for high right-sided pressure in the early surgical period. Patients with these "fenestrated Fontans" are usually candidates for subsequent closure of the fenestration with a catheter-delivered device.

One of the greatest advances in interventional catheterization over the past decade has been **transcatheter valve implantation** . Typically, a porcine valve is sewn into an expandable stent (commercially available), which is then collapsed around a balloon catheter. The device is positioned across a stenotic or insufficient pulmonary or aortic valve and the balloon inflated, expanding both the stent and the tissue value. The balloon catheter is then removed, leaving the new valve in place, well anchored by the stent to the walls of the main pulmonary artery or aorta. At this time, the most common application in children is replacement of the **pulmonary valve** (Melody Valve) in patients who have had prior surgery for tetralogy of Fallot (usually because of residual pulmonary insufficiency) (Fig. 450.30). In older adults, the most common application is replacement of a stenotic aortic valve, particularly in a patient who is too fragile to undergo open heart surgery. Stent valves have even been placed in the tricuspid position in children with tricuspid insufficiency, although the numbers are currently too small for evaluation as to efficacy and complication rate.

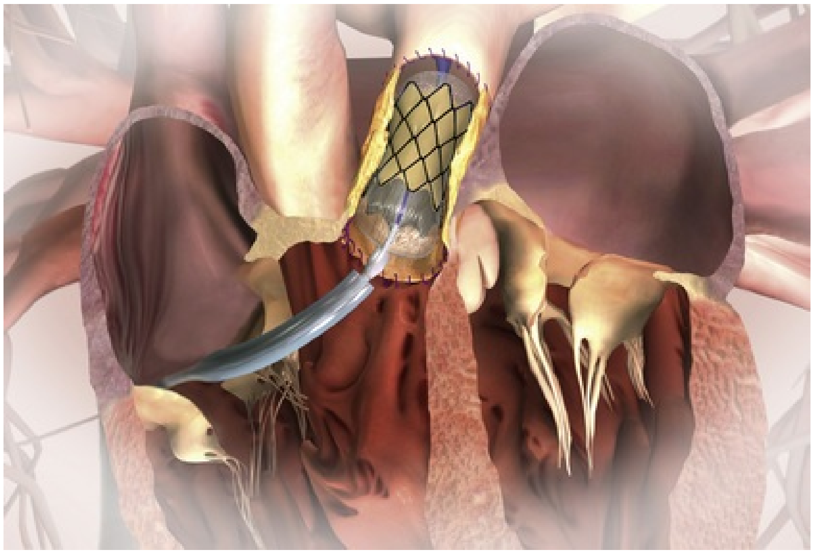

FIG. 450.30 Illustration of implantation of a Melody stent-valve delivered to the pulmonary position by a catheter inserted into the right femoral vein. (© Medtronic 2017, used with permission.)

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SECTION 3

Congenital Heart Disease

OUTLINE

Chapter 451 Epidemiology and Genetic Basis of Congenital Heart Disease
Chapter 452 Evaluation and Screening of the Infant or Child With Congenital Heart Disease
Chapter 453 Acyanotic Congenital Heart Disease Left-to-Right Shunt Lesions
Chapter 454 Acyanotic Congenital Heart Disease Obstructive Lesions
Chapter 455 Acyanotic Congenital Heart Disease Regurgitant Lesions
Chapter 456 Cyanotic Congenital Heart Disease Evaluation of the Critically Ill Neonate With Cyanosis and Respiratory Distress
Chapter 457 Cyanotic Congenital Heart Disease Lesions Associated With Decreased Pulmonary Blood Flow
Chapter 458 Cyanotic Congenital Heart Disease Lesions Associated With Increased Pulmonary Blood Flow
Chapter 459 Other Congenital Heart and Vascular Malformations
Chapter 460 Pulmonary Hypertension
Chapter 461 General Principles of Treatment of Congenital Heart Disease

CHAPTER 451

Epidemiology and Genetic Basis of Congenital Heart Disease

Daniel Bernstein

Prevalence

Congenital heart disease (CHD) occurs in approximately 0.8% of live births. The incidence is higher in stillborns (3–4%), spontaneous abortuses (10–25%), and premature infants (approximately 2% excluding patent ductus arteriosus [PDA]). This overall incidence does not include mitral valve prolapse, PDA of preterm infants, and bicuspid aortic valves (present in 1–2% of adults). Congenital cardiac defects have a wide spectrum of severity in infants: approximately 2-3 in 1,000 newborn infants will be symptomatic with heart disease in the 1st yr of life. The diagnosis is established by 1 wk of age in 40–50% of patients with CHD and by 1 mo of age in 50–60%. With advances in both corrective and palliative surgery, the number of children with CHD surviving to adulthood has increased dramatically. Despite these advances, CHD remains the leading cause of death in children with congenital malformations. Table 451.1 summarizes the relative frequency of the most common congenital cardiac lesions.

Table 451.1

Relative Frequency of Major Congenital Heart Lesions*

LESION	% OF ALL LESIONS
Ventricular septal defect	35-30
Atrial septal defect (secundum)	6-8
Patent ductus arteriosus	6-8
Coarctation of aorta	5-7
Tetralogy of Fallot	5-7
Pulmonary valve stenosis	5-7
Aortic valve stenosis	4-7

D -Transposition of great arteries	3-5
Hypoplastic left ventricle	1-3
Hypoplastic right ventricle	1-3
Truncus arteriosus	1-2
Total anomalous pulmonary venous return	1-2
Tricuspid atresia	1-2
Single ventricle	1-2
Double-outlet right ventricle	1-2
Others	5-10

[*] Excluding patent ductus arteriosus in preterm neonates, bicuspid aortic valve, physiologic peripheral pulmonic stenosis, and mitral valve prolapse.

Most congenital defects are well tolerated in the fetus because of the parallel nature of the fetal circulation. Even the most severe cardiac defects, such as **hypoplastic left heart syndrome (HLHS)** , can usually be well compensated for by the fetal circulation. In HLHS the entire fetal cardiac output would be ejected by the right ventricle via the ductus arteriosus into both the descending and ascending aortae (the latter filling in a retrograde fashion), so that fetal organ blood flow would be minimally perturbed. Because the placenta provides for gas exchange and the normal fetal circulation has mixing between more highly and more poorly oxygenated blood, fetal organ oxygen delivery is also not dramatically affected. It is only after birth when the fetal pathways (ductus arteriosus and foramen ovale) begin to close that the full hemodynamic impact of an anatomic abnormality becomes apparent. One notable exception is the case of severe regurgitant lesions, most frequently of the tricuspid valve. In these lesions, such as **Ebstein anomaly** of the tricuspid valve or severe right ventricular outflow obstruction (see Chapter 457.7), the parallel fetal circulation cannot compensate for the volume load imposed on the right side of the heart. In utero heart failure, often with fetal pleural and pericardial effusions, and generalized ascites (nonimmune hydrops fetalis) may occur.

Although the most significant transitions in circulation occur in the immediate perinatal period, the circulation continues to undergo changes after birth, and these later changes may also have a hemodynamic impact on cardiac lesions and their apparent incidence. As pulmonary vascular resistance (PVR) falls in the 1st several wk of life, left-to-right shunting through intracardiac defects increases and symptoms become more apparent. Thus, in patients with a **ventricular septal defect (VSD)** , heart failure is often first noticed between 1 and 3 mo of age (see Chapter 453.6). The severity of various defects can also change dramatically with growth; some VSDs may become smaller and even close as the child ages. Alternatively, stenosis of the aortic or pulmonary valve, which may be only moderate in the newborn period, may become worse if valve orifice growth does not keep pace with patient growth (see Chapter 454.5). The physician should always be alert for associated congenital malformations, which can adversely affect the patient's prognosis (see Table 449.2).

Etiology

The cause of most congenital heart defects is still unknown. Many cases of CHD are multifactorial and result from a combination of **genetic** predisposition and an as-yet-to-be-determined **environmental** stimulus. A small percentage of congenital heart lesions are related to known chromosomal abnormalities, in particular, trisomies 21, 13, and 18 and Turner syndrome; heart disease is found in >90% of patients with trisomy 18, 50% of patients with trisomy 21, and 40% of those with Turner syndrome. Other genetic factors may have a role in CHD; for example, certain types of VSDs (supracristal) are more common in Asian children. The risk of CHD increases if a first-degree relative (parent or sibling) is affected.

A growing list of congenital heart lesions has been associated with specific chromosomal abnormalities, and several have even been linked to specific gene defects. **Fluorescence in situ hybridization (FISH)** analysis allows clinicians rapid screening of suspected cases once a specific chromosomal abnormality has been identified, although clinical laboratory tests for specific gene defects are still uncommon. Chromosome microarray tools, including **array comparative genome hybridization** and **single nucleotide polymorphism (SNP) arrays** have identified previously unknown copy number variations (microdeletions or microduplications) or single nucleotide variants in many patients with CHD and suspicion of a congenital anomaly syndrome. These variants are submicroscopic and thus not visible on routine chromosome analysis. Comparative genome hybridization has in many cases replaced routine karyotyping in the clinical workup of newborns with CHD.

A well-characterized genetic cause of CHD is the deletion of a large region (1.5-3 Mb) of chromosome 22q11.2, known as the **DiGeorge critical region** . At least 30 genes have been mapped to the deleted region; *Tbx1*, a transcription factor involved in early outflow tract development, is one gene that has been implicated as a possible cause of DiGeorge syndrome. The estimated prevalence of 22q11.2 deletions is 1 in 4,000 live births. Cardiac lesions associated with 22q11.2 deletions are most often seen in association with either the DiGeorge syndrome or the **Shprintzen (velocardiofacial) syndrome.** The acronym **CATCH 22** has been used to summarize the major components of these syndromes: cardiac defects, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia. The specific cardiac anomalies are **conotruncal** defects (tetralogy of Fallot, truncus arteriosus, double-outlet right ventricle, subarterial VSD) and **branchial arch** defects (coarctation of the aorta, interrupted aortic arch, right aortic arch). Congenital airway anomalies such as tracheomalacia and bronchomalacia are sometimes present. Although the risk of recurrence is extremely low in the absence of a parental 22q11.2 deletion, it is 50% if 1 parent carries the deletion. More than 90% of patients with the clinical features of DiGeorge syndrome have a deletion at 22q11.2. A 2nd genetic locus on the short arm of chromosome 10 (10p13p14) has also been identified, the deletion of which shares some, but not all, phenotypic characteristics with the 22q11.2 deletion; patients with del(10p) have an increased incidence of sensorineural hearing loss.

Other structural heart lesions associated with specific chromosomal abnormalities include **familial secundum atrial septal defect** (ASD) associated with **heart block** (the transcription factor Nkx2.5 on chromosome 5q35), familial ASD without heart block (the transcription factor GATA4), **Alagille syndrome** (Jagged1 on chromosome 20p12), and **Williams syndrome** (elastin on chromosome 7q11). Of interest, patients with VSDs and atrioventricular septal defects have been found to have multiple Nkx2.5 mutations in cells isolated from diseased heart tissues, but not from normal heart tissues or from circulating lymphocytes, indicating a potential role for *somatic* mutations leading to mosaicism in the pathogenesis of congenital heart defects. Tables 451.2 and 451.3 are a compilation of known genetic causes of CHD.

Table 451.2

Genetics of Congenital Heart Disease: Defects Associated With Syndromes

CARDIOVASCULAR DISEASE	CHROMOSOMAL LOCATION	GENE(S) IMPLICATED*	COMMON CARDIAC DEFECTS
DiGeorge syndrome, velocardiofacial syndrome	22q11.2, 11p13p14	*TBX1*	TOF, IAA, TA, VSD
Familial ASD with heart block	5q35	*NKX2.5*	ASD, heart block
Familial ASD without	8p22-23	*GATA4*	ASD

heart block			
Alagille syndrome (bile duct hypoplasia, right-sided cardiac lesions)	20p12, 1p12	*JAGGED1*, *NOTCH2*	Peripheral pulmonary hypoplasia, PS, TOF
Holt-Oram syndrome (limb defects, ASD)	12q24	*TBX5*	ASD, VSD, PDA
Trisomy 21 (Down syndrome)	21q22	Not known	AVSD
Isolated familial AV septal defect (without trisomy 21)	1p31-p21, 3p25	*CRELD1*	AVSD
Familial TAPVR	4p13-q12	Not known	TAPVR
Noonan syndrome (PS, ASD, hypertrophic cardiomyopathy)	12q24, 12p1.21, 2p212, 3p25.2, 7q34, 15q22.31, 11p15.5, 1p13.2, 10q25.2, 11q23.3,17q11.2	*PTPN11*, *KRAS*, *SOS1*, *SOS2*, *RAF1*, *BRAF*, *MEK1*, *HRAS*, *NRAS*, *SHOC2*, *CBL*, *NF1*	PS, ASD, VSD, PDA, cardiomyopathy
Ellis–van Creveld syndrome (polydactyly, ASD)	4p16	*EVC*, *EVC2*	ASD, common atrium
Char syndrome (craniofacial, limb defects, PDA)	6p12-21.1	*TFAP2B*	PDA
Williams-Beuren syndrome (supravalvular AS, branch PS, hypercalcemia)	7q11.23	*ELN* (Elastin)	Supravalvular AS, peripheral PS
Marfan syndrome (connective tissue weakness, aortic root dilation)	15q21	Fibrillin	Aortic aneurysm, mitral valve disease
Familial laterality abnormalities	Xq24-2q7, 1q42, 9p13-21	*ZIC3*, *DNAI1*	Situs inversus, complex congenital heart disease
Turner syndrome	X	Not known	Coarctation of the aorta, aortic stenosis
Trisomy 13 (Patau syndrome)	13	Not known	ASD, VSD, PDA, valve abnormalities
Trisomy 18 (Edwards syndrome)	18	Not known	ASD, VSD, PDA, valve abnormalities
Cri du chat syndrome	5p15.2	*CTNND2*	ASD, VSD, PDA, TOF
Cat-eye syndrome	22q11	Not known	TAPVR, TOF
Jacobsen	11q23	*JAM3*	HLHS
Costello	11p15.5	*HRAS*	PS, hypertrophic cardiomyopathy, arrhythmias
CHARGE	8p12, 7q21.11	*CHD7*, *SEMA3E*	ASD, VSD, TOF
Kabuki syndrome	12q13.12	*MLL2*	ASD, VSD, TOF, coarctation, TGA

Carney syndrome	2p16	*PRKAR1A*	Atrial and ventricular myxomas

[*] In many cases, mutation of a single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; AVSD, atrioventricular septal defect; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Table 451.3

Genetics of Isolated Congenital Heart Disease (Nonsyndromic)

GENE IMPLICATED[*]	**PROTEIN ENCODED**	**CARDIAC DEFECTS**
GENES ENCODING TRANSCRIPTION FACTORS		
ANKRD1	Ankyrin repeat domain	TAPVR
CITED2	cAMP responsive element-binding protein	ASD, VSD
FOG2/ZFPM2	Friend of GATA	TOF
GATA6	GATA6 transcription factor	ASD, VSD, TOF, PS, AVSD, PDA
HAND2	Helix-loop-helix transcription factor	TOF
IRX4	Iroquois homeobox 4	VSD
MED13L	Mediator complex subunit 13-like	TGA
NKX2-5/NKX2.5	Homeobox containing transcription factor	ASD, VSD, TOF, HLHS, CoA, TGA, IAA
TBX20	T-Box 20 transcription factor	ASD, VSD, mitral stenosis
ZIC3	Zinc finger transcription factor	TGA, PS, TAPVR, HLHS, ASD, VSD
GENES ENCODING RECEPTORS AND SIGNALING MOLECULES		
ACVR1/ALK2	BMP receptor	AVSD
ACVR2B	Activin receptor	PS, DORV, TGA
ALDH1A2	Retinaldehyde dehydrogenase	TOF
CFC1/CRYPTIC	Cryptic protein	TOF, TGA, AVSD, ASD, VSD, IAA, DORV
CRELD1	Epidermal growth factor–related proteins	ASD; AVSD
FOXH1	Forkhead activin signal transducer	TOF, TGA
GDF1	Growth differentiation factor-1	TOF, TGA, DORV, heterotaxy
GJA1	Connexin 43	ASD, HLHS, TAPVR
LEFTY2	Left-right determination factor	TGA, AVSD, IAA, CoA

NODAL	Nodal homolog (TGF-β superfamily)	TGA, PA, TOF, DORV, TAPVR, AVSD
NOTCH1	NOTCH1 (Ligand of JAG1)	Bicuspid aortic valve, AS, CoA, HLHS
PDGFRA	Platelet-derived growth factor receptor α	TAPVR
SMAD6	MAD-related protein	Bicuspid aortic valve, CoA, AS
TAB2	TGF-β–activated kinase	Outflow tract defects
TDGF1	Teratocarcinoma-derived growth factor 1	TOF, VSD
VEGF	Vascular endothelial growth factor	CoA, outflow tract defects
GENES ENCODING STRUCTURAL PROTEINS		
ACTC	α Cardiac actin	ASD
MYH11	Myosin heavy chain 11	PDA, aortic aneurysm
MYH6	α-Myosin heavy chain	ASD, TA, AS, TGA
MYH7	β-Myosin heavy chain	Ebstein anomaly, ASD

[*] In many cases, mutation of a single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

AS, Aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; cAMP, cyclic adenosine monophosphate; CoA, coarctation of the aorta; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PA, pulmonary artery; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TGF, transforming growth factor; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Partially adapted from Fahed AC, Gelb BD, Seidman JG, Seidman CE: Genetics of congenital heart disease: the glass half empty. *Circ Res* 112:707–720, 2013.

The most progress in identifying the genetic origin of cardiovascular disease has been made in the genetic **cardiomyopathies** , and in particular, **hypertrophic cardiomyopathy.** Mutations in about a dozen genes have been implicated, most of which encode protein components of the cardiac sarcomere, either components of the thick filaments (myosin) or associated regulatory subunits, although mutations in mitochondrial genes are increasingly recognized and play a larger role in those presenting with hypertrophic cardiomyopathy as young infants than in older children and adults. Mutations of the cardiac **β-myosin heavy-chain gene *MYH7*** (chromosome 14q1) and the **myosin-binding protein C** gene (chromosome 11q11) are the most common (see Table 451.4), with less common mutations including the cardiac troponin T and I genes, α-tropomyosin, regulatory and essential myosin light chains, titin, and the α-myosin heavy chain. Several hundred mutations have been identified in these genes, and some patients (up to 15% in one study) may carry mutations in more than one gene. Routine clinical laboratory tests are now available for most of these mutations, however, not all mutations causing hypertrophic cardiomyopathy have been identified, so a negative test does not eliminate a genetic cause.

Table 451.4

Genetics of Cardiomyopathies

CARDIOMYOPATHY	CHROMOSOMAL LOCATION	GENE
Hypertrophic cardiomyopathy	14q1	β-Myosin heavy chain
	15q2	α-Tropomyosin
	1q31	Troponin T
	19p13.2-19q13.2	Troponin I
	11p13-q13	Myosin-binding protein C
	12q23	Cardiac slow myosin regulatory light chain
	13p21	Ventricular slow myosin essential light chain
	2q31	Titin
	3p25	Caveolin-3
	Mitochondrial DNA	tRNA-glycine
	Mitochondrial DNA	tRNA-isoleucine
Hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome	7q36.1	AMP-activated protein kinase
Other Genetic Diseases Causing Cardiac Hypertrophy		
Familial amyloid disease	18q12.1	Transthyretin (TTR)
Noonan syndrome	12q24.1, 2p22.1, 3p25, 12p12.1	Protein tyrosine phosphatase 11 (PTPN11), son of sevenless homolog 1 (SOS1), RAF1 protooncogene, GTPase KRAS
Fabry disease	Xq22	α-Galactoside A (GLA)
Danon disease	Xq24	Lysosomal-associated membrane protein 2 (LAMP2)
Hereditary hemochromatosis	6p21.3	Hereditary hemochromatosis protein (HFE)
Pompe disease	17q25	Acid α-glucosidase (GAA)
Dilated cardiomyopathy		
X-linked	Xp21	Dystrophin
	Xp28	Tafazzin
Autosomal recessive	19p13.2-19q13.2	Troponin I

Autosomal dominant : Genes encoding multiple proteins have been identified, including cardiac actin; desmin; δ-sarcoglycan; β-myosin heavy chain; cardiac troponin C and T; α-tropomyosin; titin; metavinculin; myosin-binding protein C; muscle LIM protein; α-actinin-2; phospholamban; Cypher/LIM binding domain 3; α-myosin heavy chain; SUR2A (regulatory subunit of K_{ATP} channel); and lamin A/C.

Isolated noncompaction of the left ventricle : Autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns have been reported. Genes that have been implicated include those for α-dystrobrevin, Cypher/ZASP, lamin A/C, Tafazzin, MIB1, and LIM domain-binding protein 3 (LDB3).

Partially adapted from Dunn KE, Caleshu C, Cirino AL, et al: A clinical approach to inherited hypertrophy: the use of family history in diagnosis, risk assessment, and management, *Circ*

Cardiovasc Genet 6:118–131, 2013.

Progress has also been made in identifying the genetic basis of **dilated cardiomyopathy,** which is familial in 20–50% of cases. Autosomal dominant inheritance is most often encountered, and similar to hypertrophic cardiomyopathy, multiple genes have been identified (see Table 451.2). X-linked inheritance accounts for 5–10% of cases of familial dilated cardiomyopathy. Mutations in the *dystrophin* gene (chromosome Xp21) are the most common in this group, causing **Duchene or Becker muscular dystrophy** . Mutations in the gene encoding *tafazzin* are associated with **Barth syndrome** and some cases of isolated noncompaction of the left ventricle (LVNC). Autosomal recessive inheritance is associated with a mutation in cardiac troponin I. Mitochondrial myopathies may be caused by mutations of enzymes of the electron transport chain encoded by nuclear DNA (in which inheritance will follow mendelian genetic patterns) or enzymes of fatty acid oxidation encoded by mitochondrial DNA (which is inherited solely from the mother). Table 451.4 is a compilation of the most common genetic causes of cardiomyopathy.

The genetic basis of **heritable arrhythmias** , most notably the **long QT syndromes** , has been linked to mutations of genes coding for subunits of cardiac potassium and sodium channels (see Table 451.2). Other heritable arrhythmias include **arrhythmogenic right ventricular dysplasia** , familial atrial fibrillation, familial complete heart block, and **Brugada syndrome** . Table 451.5 is a compilation of the most common genetic causes of arrhythmias.

Table 451.5

Genetics of Arrhythmias

ARRHYTHMIA	CHROMOSOMAL LOCATION	GENE(S) IMPLICATED
Complete heart block	19q13	Not known
Long QT syndrome		
LQT1 (autosomal dominant)	11p15.5	*KVLQT1* (K^+ channel)
LQT2 (autosomal dominant)	7q35	*HERG* (K^+ channel)
LQT3 (autosomal dominant)	3p21	*SCN5A* (Na^+ channel)
LQT4 (autosomal dominant)	4q25-27	Not known
LQT5 (autosomal dominant)	21q22-q22	*KCNE1* (K^+ channel)
LQT6	21q22.1	*KCNE2* (K^+ channel)
Jervell and Lange-Nielsen syndrome (autosomal recessive, congenital deafness)	11p15.5	*KVLQT1* (K^+ channel)

LQT8-13	Unknown	Private mutations (rare)
Arrhythmogenic right ventricular dysplasia (ARVD): 11 genes are now associated with ARVD (*ARVD1* through *ARVD11*) usually with autosomal dominant inheritance, but with variable penetrance. These genes include *TGF* β_3 (transforming growth factor β), *RYR2* (ryanodine receptor), *LAMR1* (laminin receptor-1), *PTPLA* (protein tyrosine phosphatase), *DSP* (desmoplakin), *PKP2* (plakophilin-2), *DSG2* (desmoglein), and *DSC2* (desmocollin).		
Familial atrial fibrillation (autosomal dominant)	10q22-q24, 6q14-16	Not known
	11p15.5	*KVLQT1* (K^+ channel)
	11p15.5	*KCNQ1* (K^+ channel)
	21q22	*KCNE2* (K^+ channel)
	17q23.1-q24.2	*KCNJ2* (K^+ channel)
	7q35-q36	*KCNH2* (K^+ channel)
Brugada syndrome (right bundle branch block, ST segment elevation, unexpected sudden death)	3p21-p24	*SCN5A* (Na^+ channel)
	3p22-p24	*GPD-1L* (glycerol-3-phosphate dehydrogenase)
Catecholaminergic polymorphic ventricular tachycardia	—	*RYR2* (autosomal dominant)
	—	*CASQ2* (autosomal recessive)

Of all cases of congenital heart disease, 2–4% are associated with known environmental or adverse maternal conditions and teratogenic influences, including maternal diabetes mellitus, maternal phenylketonuria, or systemic lupus erythematosus; congenital rubella syndrome; and maternal ingestion of drugs (lithium, ethanol, warfarin, thalidomide, antimetabolites, vitamin A derivatives, anticonvulsant agents) (see Table 449.2). Associated noncardiac malformations noted in identifiable syndromes may be seen in as many as 25% of patients with CHD.

Gender differences in the occurrence of specific cardiac lesions have been identified. Transposition of the great arteries and left-sided obstructive lesions are slightly more common in boys (65%), whereas ASD, VSD, PDA, and pulmonic stenosis are more common in girls. No racial differences in the occurrence of congenital heart lesions as a whole have been noted; for specific lesions such as transposition of the great arteries, a higher occurrence is seen in white infants.

Next-Generation Genome Sequencing and Congenital Heart Disease

The US National Institutes of Health (NIH) launched the **Pediatric Cardiac Genomics Consortium (PCGC)** in 2009 with the aim of performing genome sequencing on 10,000 children with CHD and both parents (known as a *trio*), to identify de novo gene variants associated with congenital heart defects. In one study, in >300 trios, de novo mutations in several hundred genes were found to contribute to 10% of cases of severe CHD. Another major PCGC study found that the incidence of de novo gene variants was 10-fold higher (20% vs 2%) in patients with CHD and neurodevelopmental defects than in those with CHD alone, linking CHD with neurodevelopmental disorders at the genetic level.

The identification of a *candidate* de novo mutation is far from proof of its role in causing CHD, which must be verified in animal models or by identifying multiple additional patients with a similar genotype-phenotype connection. The relationship between a specific gene variant and CHD is further complicated by the tremendous genotype-phenotype variability; a single mutation may lead to a wide variety of heart defects or sometimes to none at all.

Genetic Counseling

Parents who have a child with CHD require counseling regarding the probability of a cardiac malformation occurring in subsequent children (see Chapter 94.1). Except for syndromes caused by mutation of a single gene, most CHD is still relegated to a multifactorial inheritance pattern, which should result in a low risk of recurrence. As more genetic etiologies are identified, these risks will need constant updating. The incidence of CHD in the normal population is 0.8%, increasing to 2–6% for a 2nd pregnancy after the birth of a child with CHD or if a parent is affected. This recurrence risk is highly dependent on the type of lesion in the 1st child. When 2 first-degree relatives have CHD, the risk for a subsequent child may reach 20–30%. When a 2nd child is found to have CHD, it will tend to be of a similar class as the lesion in their first-degree relative (conotruncal lesions, left- or right-sided obstructive lesions, atrioventricular septation defects). The degree of severity may vary, as may the presence of associated defects. Careful echocardiographic screening of first-degree relatives will often uncover mild forms of CHD that were clinically silent. The incidence of bicuspid aortic valve is more than double (5% vs 2% in the general population) in the relatives of children with left ventricular outflow obstructions (aortic stenosis, coarctation of the aorta, HLHS). Consultation with a knowledgeable genetic counselor is the most reliable way of providing the family with up-to-date information regarding the risk of recurrence.

Fetal echocardiography improves the rate of detection of congenital heart lesions in high-risk patients (see Chapter 450.4). This type of ultrasound is much more comprehensive than the screening ultrasound performed by an obstetrician and is usually performed and interpreted by a pediatric cardiologist specializing in fetal echocardiography. The resolution and accuracy of fetal echocardiography are excellent, but not perfect; families should be counseled that a normal fetal echocardiogram does not guarantee the absence of CHD. Congenital heart lesions may evolve in the course of the pregnancy; moderate aortic stenosis with a normal-sized left ventricle at 18 wk of gestation may evolve into aortic atresia with a hypoplastic left ventricle by 34 wk because of decreased flow through the atria, ventricle, and aorta in the latter half of gestation. This progression has prompted initial clinical trials of interventional treatment, such as fetal aortic balloon valvuloplasty, for the prevention of HLHS (see Chapter 450.7).

The major factor in determining whether a **woman with congenital heart disease,** either unoperated or operated, will be able to carry a fetus to term is the mother's cardiovascular status. In the presence of a mild congenital heart defect or after successful repair of a more complex lesion, normal childbearing is likely. In a woman with palliated CHD or with poor cardiac function, however, the increased hemodynamic burden imposed by pregnancy may result in a significantly increased risk to both the mother and fetus and these pregnancies should be managed by an experienced high risk obstetrician/perinatologist in conjunction with a cardiologist with expertise in adult CHD (see Chapter 461.1).

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CHAPTER 452

Evaluation and Screening of the Infant or Child With Congenital Heart Disease

Daniel Bernstein

The initial evaluation for suspected congenital heart disease (CHD) involves a systematic approach with 3 major components. First, congenital cardiac defects can be divided into 2 major groups based on the presence or absence of **cyanosis** , which can be determined by physical examination aided by pulse oximetry. Second, these 2 groups can usually be further subdivided based on whether the chest radiograph shows evidence of increased, normal, or decreased pulmonary vascular markings. Third, the electrocardiogram (ECG) can be used to determine whether right, left, or biventricular **hypertrophy** exists. The character of the heart sounds and the presence and character of any murmurs further narrow the differential diagnosis. The final diagnosis is then confirmed by echocardiography, cardiac CT or MRI and/or cardiac catheterization.

Multiple studies demonstrate the benefit of routine **pulse oximetry screening** for all newborns to detect unsuspected critical cyanotic CHD; lesions include hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, truncus arteriosus, neonatal coarctation of the aorta, and aortic arch hypoplasia/atresia. Many of these lesions are ductal dependent, and if the ductus arteriosus closes, severe cardiac decompensation will ensue. In addition, pulse oximetry may also detect respiratory disorders and primary pulmonary hypertension. Such screening has been endorsed by the American Academy of Pediatrics, American Heart Association, American College of Cardiology, and the March of Dimes, and recommended, although not mandated, in the United States by the Department of Health and Human Services. Screening is performed between 24 and 48 hr of life and before discharge in asymptomatic newborns. A pulse oximetry saturation of 90–94% in the right hand or either foot requires *urgent* echocardiography. A pulse oximetry saturation <95% in either location or a saturation difference >3% between the right hand and either foot is considered a positive test and should be repeated in an hour; if positive again, it should be repeated in another hour. If it remains positive, **echocardiography** is indicated. In addition, a careful reexamination of the pulses and blood pressure in the upper and lower extremity as well as cardiac auscultation are indicated in children with an initial positive screen.

Acyanotic Congenital Heart Lesions

Acyanotic congenital heart lesions can be classified according to the predominant physiologic load that they place on the heart. Although many congenital heart lesions induce >1 physiologic disturbance, it is helpful to focus on the primary load abnormality for purposes of classification. The most common lesions are those that produce a **volume load** , and the most common of these are the left-to-right shunt lesions. Atrioventricular (AV) valve regurgitation and dilated cardiomyopathies are other causes of increased volume load. The 2nd major class of lesions causes an increase in **pressure load** , most often secondary to ventricular outflow obstruction (pulmonic or aortic valve stenosis) or narrowing of a great vessel (branch pulmonary artery stenosis or coarctation of the aorta). The chest radiograph and ECG are useful tools for differentiating between these major classes of volume- and pressure-overload lesions.

Lesions Resulting in Increased Volume Load

The most common lesions resulting in increased volume load are those that cause **left-to-right shunting** (see Chapter 453): atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defects (previously known as AV canal or endocardial cushion defects), and patent ductus arteriosus. The pathophysiologic common denominator in this group is the presence of a **communication** between the systemic and pulmonary sides of the circulation, which results in **shunting** of fully oxygenated blood back into the lungs for a 2nd passage. This shunt can be quantitated by calculating the ratio of pulmonary-to-systemic blood flow (Qp:Qs). Thus a 3 : 1 shunt implies 3 times the normal pulmonary blood flow, which is a moderately large shunt likely to cause symptoms of heart failure.

The direction and magnitude of the shunt across such a communication depend on the size of the defect, the relative pulmonary and systemic pressure and vascular resistance, and the compliances of the 2 chambers connected by the defect. These factors are dynamic and may change dramatically with age; intracardiac defects may grow smaller with time; pulmonary vascular resistance (PVR), which is high in the immediate newborn period, decreases to normal adult levels by several weeks of life; and chronic exposure of the pulmonary circulation to high pressure and blood flow results in a gradual increase in PVR (**Eisenmenger physiology** ; see Chapter 460.2). Thus, a lesion such as a large VSD may be associated with little shunting and few symptoms during the initial 1-2 wk of life. When PVR declines over the next 2-4 wk, the volume of the left-to-right shunt increases, and symptoms begin to appear.

The increased volume of blood in the lungs decreases pulmonary compliance and increases the work of breathing. Fluid leaks into the interstitial space and alveoli and causes pulmonary edema. The infant develops the symptoms we refer to as **heart failure** , such as tachypnea, tachycardia, sweating, chest retractions, nasal flaring, and wheezing. For children with large left-to-right shunts, however, the term *heart failure* is a misnomer; total left ventricular output is not decreased but is actually several times greater than normal, although much of this output is ineffective because it returns back to the lungs. To maintain this high level of left ventricular output, heart rate and stroke volume are increased, in part mediated by the Frank-Starling relation as the increased ventricular volume stretches the cardiac sarcomeres, and in part mediated by an increase in sympathetic nervous system activity. The increase in catecholamine release, combined with the increased work of breathing, results in an elevation in total body oxygen consumption (due to increased β-receptor stimulation), often beyond the oxygen transport ability of the circulation. Sympathetic activation leads to peripheral vasoconstriction (due to increased α-receptor stimulation) and to the additional symptoms of sweating and irritability, and the imbalance between oxygen supply and demand leads to failure to thrive. Remodeling of the heart occurs, with predominantly chamber dilation caused by the increased volume load and a lesser degree of hypertrophy. If left untreated, the PVR eventually begins to rise, and by several years of age, the shunt volume will decrease and symptoms will improve. If still uncorrected, the shunt will eventually reverse to right-to-left as the PVR rises (see Chapter 460.2).

Additional lesions that impose a volume load on the heart include the

regurgitant lesions (see Chapter 455) and the **dilated cardiomyopathies** (see Chapter 466.1). Regurgitation through the AV valves is most frequently encountered in patients with partial or complete AV septal defects (AV canal or endocardial cushion defects). In these lesions, the combination of a left-to-right shunt with AV valve regurgitation increases the volume load on the heart and often leads to more severe symptoms. Isolated regurgitation through the tricuspid valve is seen in **Ebstein anomaly** (see Chapter 457.7). Regurgitation involving one of the semilunar (aortic or pulmonary) valves also results in a volume load but is often also associated with some degree of stenosis, leading to a combined pressure and volume load. Aortic regurgitation may be encountered in patients with a VSD directly under the aortic valve (supracristal VSD), leading to 2 sources of volume load on the left ventricle.

In contrast to left-to-right shunts, in which intrinsic cardiac muscle function is generally either normal or increased, heart muscle function can be decreased in the cardiomyopathies. **Cardiomyopathies** may affect systolic contractility or diastolic relaxation, or both. Decreased cardiac function results in increased atrial and ventricular filling pressure, and pulmonary edema occurs secondary to increased capillary pressure. Poor cardiac output leads to decreased end-organ blood flow, sympathetic activation, and the symptoms of poor perfusion and decreased urine output. The major causes of cardiomyopathy in infants and children include viral myocarditis, metabolic disorders, and gene mutations in sarcomeric and other cardiac structural and functional genes (see Chapter 466).

Lesions Resulting in Increased Pressure Load

The pathophysiologic common denominator of lesions resulting in increased pressure load is an **obstruction to normal blood flow** . The most frequent are **obstructions to ventricular outflow** : valvular pulmonic stenosis, valvular aortic stenosis, and coarctation of the aorta (see Chapter 454). Less common are **obstructions to ventricular inflow** : tricuspid or mitral stenosis, cor triatriatum, and obstruction of the pulmonary veins. Ventricular outflow obstruction can occur at the valve, below the valve (double-chambered right ventricle, subaortic membrane), or above it (branch pulmonary stenosis or supravalvular aortic stenosis). Unless the obstruction is severe, cardiac output will be maintained and the clinical symptoms of heart failure will be either subtle or absent. The heart compensates for the increased afterload by increasing wall thickness (hypertrophy), but in later stages the affected chamber develops fibrosis and will begin to dilate and can progress to ventricular failure.

The clinical picture is different when obstruction to outflow is severe, which is usually encountered in the immediate newborn period. The infant may become critically ill within several hours of birth. Severe pulmonic stenosis in the newborn period (called **critical pulmonic stenosis**) results in signs of right-sided heart failure (hepatomegaly, peripheral edema) as well as cyanosis from right-to-left shunting across the foramen ovale. Severe aortic stenosis in the newborn period (**critical aortic stenosis**) is characterized by signs of left-sided heart failure (pulmonary edema, poor perfusion) and often combined with right-sided failure (hepatomegaly, peripheral edema), and it may progress rapidly to total circulatory collapse. In older children, severe pulmonic stenosis leads to symptoms of right-sided heart failure, but usually not to cyanosis unless a pathway persists for right-to-left shunting (e.g., patency of foramen ovale).

Coarctation of the aorta in older children and adolescents is usually manifested as upper body hypertension and diminished pulses in the lower extremities. In the immediate newborn period, presentation of coarctation can range from decreased pulses in the lower extremities to total circulatory collapse, depending on the severity of the narrowing. However, the clinical presentation of coarctation may be delayed because of the normally patent ductus arteriosus in the 1st few days of life. In these patients, even as the ductus begins to close, the open aortic end serves as a conduit for blood flow to partially bypass the obstruction; in more severe coarctations, blood leaving the right ventricle traverses the ductus to directly supply the descending aorta (as it did in the fetus). These infants then become symptomatic, often dramatically, when the ductus finally closes, usually within the 1st few wk of life.

Cyanotic Congenital Heart Lesions

The cyanotic group of congenital heart lesions can also be further divided according to pathophysiology: where pulmonary blood flow is *decreased,* usually from an **obstruction to right ventricular outflow** (tetralogy of Fallot, tetralogy with pulmonary atresia, or pulmonary atresia with an intact septum), or an **obstruction to right ventricular inflow** (tricuspid atresia), or total anomalous pulmonary venous return (TAPVR) with obstruction; or where pulmonary blood flow is *increased* and where oxygenated and deoxygenated blood are *mixing* (transposition of the great arteries, single ventricle, truncus arteriosus, TAPVR without obstruction). The chest radiograph is a valuable tool for initial differentiation between these 2 categories.

Cyanotic Lesions With Decreased Pulmonary Blood Flow

For cyanosis to occur, these lesions must include both an obstruction to pulmonary blood flow (at the tricuspid valve or pulmonary valve level) *and* a pathway by which systemic venous blood can shunt from right to left and enter the systemic circulation (via a patent foramen ovale, ASD, or VSD). Common lesions in this group include tricuspid atresia, tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, pulmonary atresia with intact septum, and various forms of single ventricle with pulmonary stenosis or atresia (see Chapter 457). In these lesions, the degree of cyanosis depends on the degree of obstruction to pulmonary blood flow. If the obstruction is mild, cyanosis may be absent at rest. These patients may have hypercyanotic ("tet") spells during conditions of stress. In contrast, if the obstruction is severe, pulmonary blood flow may be totally dependent on patency of the ductus arteriosus. When the ductus closes in the 1st few days of life, the neonate experiences profound hypoxemia.

Cyanotic Lesions With Increased Pulmonary Blood Flow

This group of lesions is not associated with obstruction to pulmonary blood flow. Cyanosis is caused by either abnormal ventricular-arterial connections or total mixing of systemic venous (deoxygenated) and pulmonary venous (oxygenated) blood within the heart (see Chapter 458). **Transposition of the great arteries** (or **vessels**) is the most common of the former group of lesions. In this condition the aorta arises from the right ventricle, and the pulmonary artery arises from the left ventricle. Systemic venous blood returning to the right atrium is pumped directly back to the body, and oxygenated blood returning from the lungs to the left atrium is pumped back into the lungs. The **persistence of fetal pathways** (foramen ovale and ductus arteriosus) allows for some degree of mixing in the immediate newborn period, keeping the systemic saturation from falling precipitously when the ductus begins to close; these infants can become extremely cyanotic.

Total mixing lesions include cardiac defects with a common atrium or ventricle, TAPVR, and truncus arteriosus (see Chapter 458). In this group, deoxygenated systemic venous blood and oxygenated pulmonary venous blood mix completely in the heart and, as a result, the oxygen saturation is equal in the pulmonary artery and aorta. If pulmonary blood flow is not obstructed, these infants have a combination of cyanosis and pulmonary overcirculation leading to heart failure. In contrast, if pulmonary stenosis is present, these infants may have cyanosis alone, similar to patients with tetralogy of Fallot.

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CHAPTER 453

Acyanotic Congenital Heart Disease

Left-to-Right Shunt Lesions

453.1

Atrial Septal Defect

Daniel Bernstein

Atrial septal defects (**ASDs**) can occur in any portion of the atrial septum —**secundum** , **primum** , or **sinus venosus** —depending on which embryonic septal structure has failed to develop normally (Fig. 453.1) (see Chapter 447). Less often, the atrial septum may be almost absent, with the creation of a functional single atrium. Isolated secundum ASDs account for approximately 7% of congenital heart defects. The majority of cases of ASD are sporadic; autosomal dominant inheritance does occur as part of the **Holt-Oram syndrome** (hypoplastic or absent thumbs, radii, triphalangism, phocomelia, first-degree heart block, ASD) or in families with both secundum ASD and heart block (see Table 451.2).

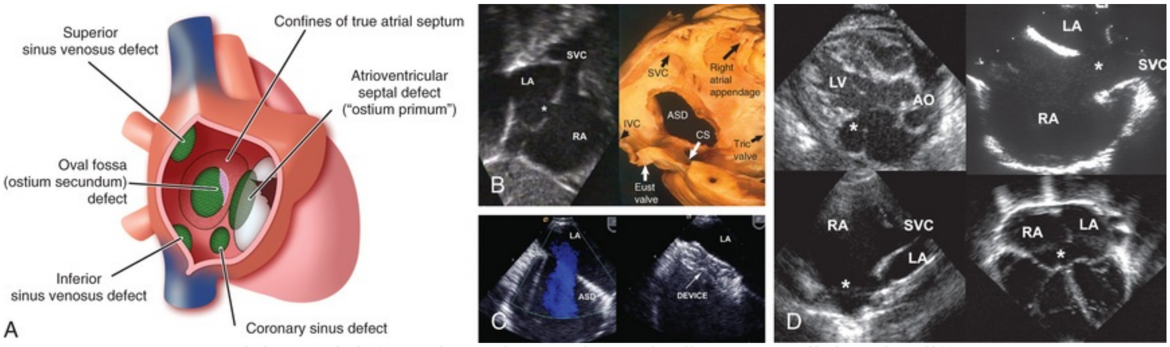
Superior sinus venosus defect
Confines of true atrial septum
Atrioventricular septal defect ("ostium primum")
Oval fossa (ostium secundum) defect
Inferior sinus venosus defect
Coronary sinus defect
A
SVC
LA
RA
B
SVC
Right atrial appendage
ASD
IVC
CS
Tric valve
Eust valve
LA
ASD
LA
DEVICE
C
LV
AO
LA
SVC
RA
RA
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LA
RA
LA
D

FIG. 453.1 Atrial septal defects (ASDs). A, Schematic diagram outlining the different types of interatrial shunting that can be encountered. Note that only the central defect is suitable for device closure. B, *Left panel,* Subcostal right anterior oblique view of a secundum ASD *(asterisk)* that is suitable for device closure. *Right panel,* Specimen as seen in a similar view, outlining the landmarks of the defect. C, *Left image,* Transesophageal echocardiogram with color flow before device closure. *Right image,* Taken following release of an Amplatzer device. D, Montage of echocardiographic interatrial communications that are not secundum ASDs *(asterisks)* and therefore not suitable for device closure. *Top left image,* Coronary sinus defect caused by unroofing; *top right image,* superior sinus venosus defect; *bottom left image,* inferior sinus venosus defect; *bottom right image,* ASD in the setting of an atrioventricular septal defect. AO, Aorta; CS, coronary sinus; Eus, eustachian; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; SVC, superior vena cava; Tric, tricuspid. (From Webb GD, Smallhorn JF, Therrien J, Redington AN: Congenital heart disease in the adult and pediatric patient. In *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2018, Elsevier, Fig 75.17, p 1536.)

An isolated valve-incompetent **patent foramen ovale (PFO)** is a common echocardiographic finding during infancy. It is usually of no hemodynamic significance and is not considered an ASD; a PFO may play an important role if other structural heart defects are present. If another cardiac anomaly is causing increased right atrial pressure (pulmonary stenosis or atresia, tricuspid valve abnormalities, right ventricular dysfunction), venous blood may shunt across the PFO into the left atrium with resultant cyanosis. Because of the anatomic structure of the PFO, left-to-right shunting is unusual outside the immediate newborn period. In the presence of a large volume load or a hypertensive left atrium (e.g., secondary to mitral stenosis), the foramen ovale may be sufficiently dilated to result in a significant atrial left-to-right shunt. A valve-competent but probe-patent (able to be pushed opened with a catheter) PFO may be present in 15–30% of adults. An isolated PFO does not require surgical treatment, although it may be a risk for paradoxical (right to left) systemic embolization. Device closure of these defects is one treatment option considered in adults with a history of thromboembolic stroke.

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453.2

Ostium Secundum Defect

Daniel Bernstein

An ostium secundum defect in the region of the fossa ovalis is the most common form of ASD and is associated with structurally normal atrioventricular (AV) valves (see Fig. 453.1). **Mitral valve prolapse** has been described in association with this defect but is rarely an important clinical consideration. Secundum ASDs may be single or multiple (fenestrated atrial septum), and openings ≥2 cm in diameter are common in symptomatic older children. Large defects may extend inferiorly toward the inferior vena cava (IVC) and ostium of the coronary sinus, superiorly toward the superior vena cava (SVC), or posteriorly. Females outnumber males 3 : 1 in incidence. **Partial anomalous pulmonary venous return** (PAPVR), usually of the right upper pulmonary vein, may be an associated lesion.

Pathophysiology

The degree of left-to-right shunting depends on the size of the defect, the relative compliance of the right and left ventricles, and the relative vascular resistance in the pulmonary and systemic circulations. In large defects, a considerable shunt of oxygenated blood flows from the left to the right atrium (Fig. 453.2). This blood is added to the usual venous return to the right atrium and is pumped by the right ventricle to the lungs. With large defects, the ratio of pulmonary-to-systemic blood flow (Qp:Qs) is usually between 2 : 1 and 4 : 1. The paucity of symptoms in infants with ASDs is related to the structure of the right ventricle in early life, when its muscular wall is thick and less compliant, thus limiting the left-to-right shunt. As the infant becomes older and pulmonary vascular resistance (PVR) drops, the right ventricular (RV) wall becomes thinner, and the left-to-right shunt across the ASD increases. The increased blood flow through the right side of the heart results in enlargement of the right atrium and ventricle and dilation of the pulmonary artery. The left atrium may also be enlarged as the increased pulmonary blood flow returns to the left atrium, but the left ventricle and aorta are normal in size. Despite the large pulmonary blood flow, pulmonary arterial pressure is usually initially normal because of the absence of a high-pressure communication between the pulmonary and systemic circulations. PVR remains low throughout childhood, although it may begin to increase in adulthood and may eventually result in reversal of the shunt and clinical cyanosis.

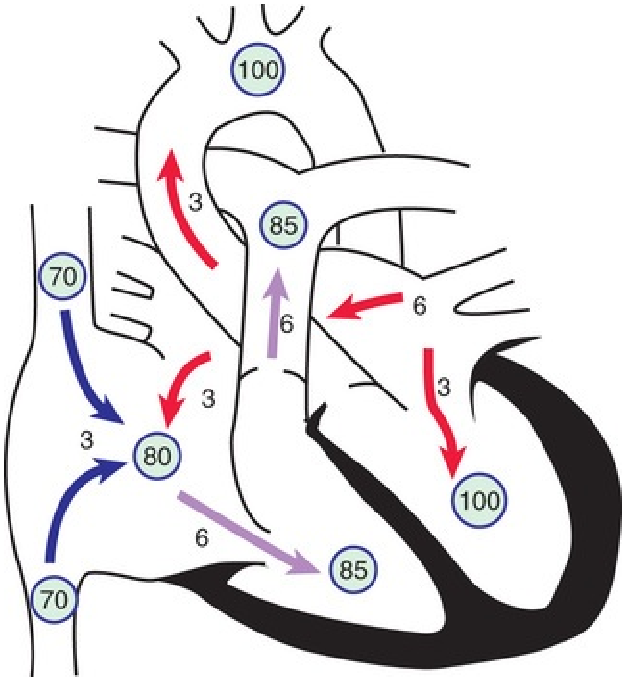

FIG. 453.2 **Physiology of atrial septal defect (ASD). *Circled numbers* represent oxygen saturation (SO_2) values. The *numbers next to the arrows* represent volumes of blood flow (in $L/min/m^2$). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2 : 1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 $L/min/m^2$ and mixes with an additional 3 L of fully saturated blood shunting left to right across the ASD; the result is an increase in SO_2 in the right atrium. Six liters of blood flows through the tricuspid valve and causes a mid-diastolic flow rumble. SO_2 may be slightly higher in the right ventricle because of incomplete mixing at the atrial level. The full 6 L flows across the right ventricular outflow tract and causes a systolic ejection flow murmur. Six liters returns to the left atrium, with 3 L shunting left to right across the defect and 3 L crossing the mitral valve to be ejected by the left ventricle into the ascending aorta (normal cardiac output).**

Clinical Manifestations

A child with an ostium secundum ASD is most often asymptomatic; the lesion is often discovered inadvertently during physical examination. Even an extremely large secundum ASD rarely produces clinically evident heart failure in childhood. On closer evaluation, however, younger children may show subtle failure to thrive, and older children may have varying degrees of exercise intolerance. Often, the degree of limitation may go unnoticed by the family until after repair, when the child's growth or activity level greatly increases (e.g., “I never knew she could run so fast”).

The physical findings of an ASD are usually characteristic but fairly subtle and require careful examination of the heart, with special attention to the heart sounds. Examination of the chest may reveal a mild left precordial bulge. An RV systolic lift may be palpable at the left sternal border. Sometimes a pulmonic ejection click can be heard. In most patients with an ASD, the characteristic finding is that the second heart sound (S_2) is **widely split and fixed** in its splitting during all phases of respiration. Normally, the duration of RV ejection varies with respiration, with inspiration increasing RV volume and delaying closure of the pulmonary valve, widening the S_2 split. With an ASD, RV diastolic volume is constantly increased, and ejection time is prolonged throughout all phases of respiration. A systolic ejection murmur is heard; it is usually no greater than a grade 3/6, medium pitched, without harsh qualities, seldom accompanied by a thrill, and best heard at the left middle and upper sternal border. It is produced by the increased flow across the RV outflow tract into the pulmonary artery. Flow across the ASD between the 2 low-pressure atria does not cause an audible murmur. A short, rumbling mid-diastolic murmur produced by the increased volume of blood flow across the tricuspid valve is often audible at the lower left sternal border. This finding, which may be subtle and is heard best with the bell of the stethoscope, usually indicates a Qp:Qs ratio of at least 2 : 1.

Diagnosis

The chest radiograph shows varying degrees of enlargement of the right ventricle and atrium, depending on the size of the shunt. The pulmonary artery is enlarged, and pulmonary vascularity is increased. These signs vary and may not be conspicuous in mild cases. Cardiac enlargement is often best appreciated on the lateral view because the right ventricle protrudes anteriorly as its volume increases. The **electrocardiogram** (ECG) shows RV volume overload: the QRS axis may be normal or exhibit right axis deviation, and a minor RV conduction delay (rsR′ pattern in the right precordial leads) may be present. **Right ventricular hypertrophy** would be unusual in the absence of pulmonary hypertension or other lesions (e.g., valvar pulmonic stenosis).

The **echocardiogram** shows findings characteristic of RV volume overload, including an increased RV end-diastolic dimension and flattening and abnormal motion of the ventricular septum (see Fig. 453.1). A normal septum moves posteriorly during systole and anteriorly during diastole (synchronous with the left ventricular contractions). With RV overload and normal PVR, septal motion is either flattened or reversed—that is, anterior movement in systole. The location and size of the ASD are readily appreciated by two-dimensional (2D) scanning, with a characteristic brightening of the echo image seen at the edge of the defect caused by the increased reflectivity of ultrasound at the tissue-blood interface (T-artifact). The shunt is confirmed by pulsed and color flow Doppler. The normal entry of all pulmonary veins into the left atrium should be confirmed.

Patients with the classic features of a hemodynamically significant ASD on physical examination and chest radiography, in whom echocardiographic identification of an isolated secundum ASD is made, need not undergo diagnostic **catheterization** before repair, with the exception of an older patient, in whom PVR may be a concern. If pulmonary vascular disease is suspected, cardiac catheterization confirms the presence of the defect and allows measurement of the shunt ratio and pulmonary pressure and resistance.

If catheterization is performed, usually at the time of device closure (see Treatment), the oxygen content of blood from the right atrium will be much higher than that from the SVC. This feature is not specifically diagnostic because it may occur with PAPVR to the right atrium, with a **ventricular septal defect** (VSD) in the presence of tricuspid insufficiency, with AV septal defects associated with left ventricular–to–right atrial shunts, and with aorta–to–right atrial communications (ruptured sinus of Valsalva aneurysm). Pressure in the right side of the heart is usually normal, but small to moderate pressure gradients (<25 mm Hg) may be measured across the RV outflow tract because of functional stenosis related to excessive blood flow. If the pressure gradient across the pulmonary valve is greater, pathologic pulmonary stenosis is likely present. In children and adolescents, PVR is almost always normal. The shunt is variable and depends on the size of the defect, but it may be of considerable volume (as high as 20 L/min/m^2). **Cineangiography** , performed with the catheter through the defect and in the right upper pulmonary vein, demonstrates the defect and confirms the location of the right upper pulmonary venous drainage (normal or aberrant into SVC). **Pulmonary angiography** demonstrates the defect on the *levophase* (return of contrast to left side of heart after passing through lungs).

Complications

Secundum ASDs are usually isolated, although they may be associated with PAPVR, pulmonary valvular stenosis, VSD, pulmonary artery branch stenosis, and persistent left SVC, as well as mitral valve prolapse and insufficiency. Secundum ASDs are associated with the autosomal dominant Holt-Oram syndrome. The gene responsible for this syndrome, situated in the region 12q21-q22 of chromosome 12, is *TBX5,* a member of the T-box transcriptional family. A familial form of secundum ASD associated with AV conduction delay has been linked to mutations in another transcription factor, Nkx2.5. Patients with familial ASD without heart block may carry a mutation in the transcription factor GATA4, located on chromosome 8p22-23 (see Table 451.2).

Treatment

Transcatheter device or surgical closure is advised for all symptomatic patients, as well as for asymptomatic patients with Qp:Qs ratio of at least 2 : 1 and those with RV enlargement. The timing for elective closure is usually after the 1st yr of life and before entry into school. Closure carried out at open heart surgery is associated with a mortality rate of <1%. Repair is preferred during early childhood because surgical mortality and morbidity are significantly greater in adulthood; the long-term risk of arrhythmia caused by chronic atrial dilation is also greater after ASD repair in adults. For most patients, *the procedure of choice is percutaneous catheter device closure using an atrial septal occlusion device,* implanted transvenously in the cardiac catheterization laboratory (Fig. 453.3). The results are excellent, and patients are usually discharged from the hospital the following day. With the latest generation of devices, the incidence of serious complications (e.g., device erosion) is 0.1% and can be decreased by identifying high-risk patients, such as those with a deficient rim of septum in the area where the device would be anchored. Echocardiography can usually determine whether a patient is a good candidate for device closure. In patients with small secundum ASDs and minimal left-to-right shunts without RV enlargement, the consensus is that closure is not required. Infants with small to moderate-sized ASDs can be watched closely, since these defects will often grow smaller in the 1st yr of life. It is unclear at present whether the persistence of a small ASD into adulthood increases the risk for stroke enough to warrant prophylactic closure of all these defects.

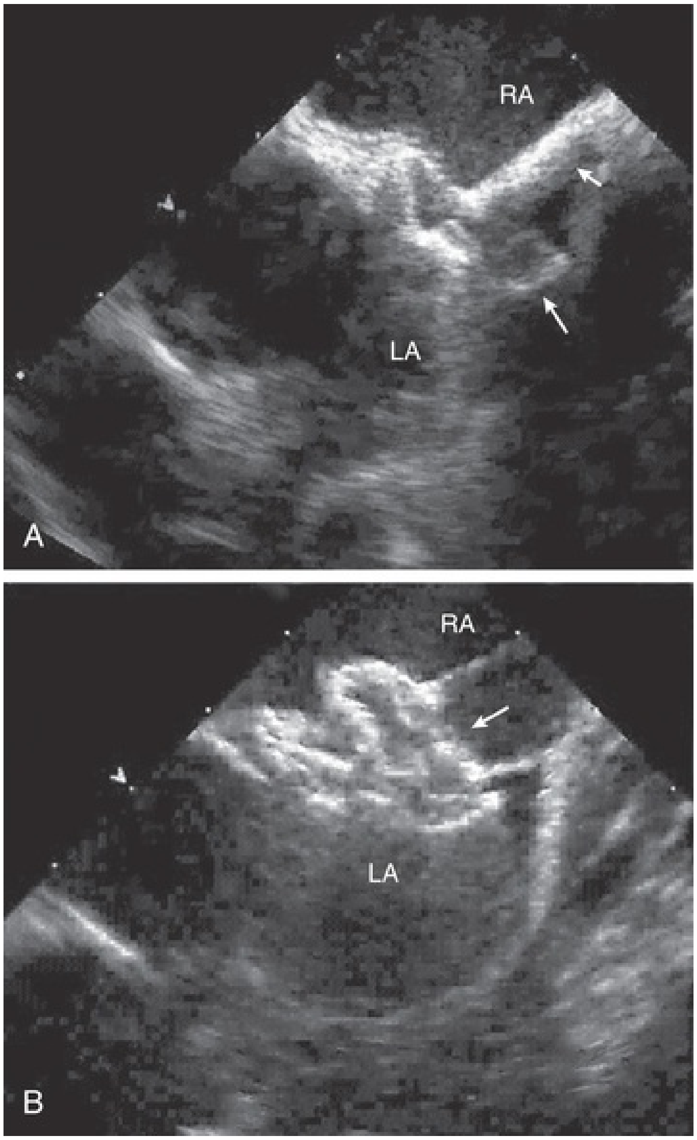

FIG. 453.3 Intravascular ultrasound imaging of transcatheter occlusion of an atrial septal defect (ASD). A, Catheter *(small arrow)* has been advanced across the ASD, and the left-sided disk of the device *(large arrow)* has been extruded from the sheath into the left atrium (LA). B, The right atrial disk *(arrow)* has now been extruded into the right atrium (RA). The 2 halves of the device are then locked together and the catheter detached from the occluder device and removed.

Prognosis

Small to moderate-sized ASDs detected in term infants may grow smaller or close spontaneously. Secundum ASDs are well tolerated during childhood, and significant symptoms do not usually appear until the 3rd decade or later. Pulmonary hypertension, atrial dysrhythmias, tricuspid or mitral insufficiency, and heart failure are late manifestations; these symptoms may initially appear during the increased volume load of pregnancy. Infective endocarditis is extremely rare, and antibiotic prophylaxis for isolated secundum ASDs is not recommended.

The results after surgical or device closure in children with moderate-size to large shunts are excellent. Symptoms, if present, disappear rapidly, and growth is frequently enhanced. Heart size decreases to normal, and the ECG shows decreased RV volume load. Late right-sided heart failure and arrhythmias are less common in patients who have had early repair, becoming more common in patients who undergo surgery after 20 yr of age. Although early and midterm results with device closure are excellent, the long-term effects are not yet known. Reports of resolution of migraine headaches in patients after device closure of ASD or PFO are intriguing, suggesting a possible thromboembolic etiology. However, there are also paradoxical reports of patients whose migraines began or worsened after placement of one of these devices.

453.3

Sinus Venosus Atrial Septal Defect

Daniel Bernstein

A sinus venosus ASD is situated in the upper part of the atrial septum in close relation to the entry of the superior vena cava (see Fig. 453.1). Often, one or more pulmonary veins (usually from the right lung) drain anomalously into the SVC. The SVC sometimes straddles the defect; in this case, some systemic venous blood enters the left atrium, but only rarely does it cause clinically evident cyanosis. The hemodynamic disturbance, clinical picture, ECG, and radiograph are similar to those seen in secundum ASD. The **diagnosis** can usually be made by echocardiography. If questions remain after echo regarding pulmonary venous drainage, cardiac CT or MRI is usually diagnostic. Cardiac catheterization is rarely required, except in adult patients in whom PVR assessment may be important. **Anatomic correction** generally requires the insertion of a patch to close the defect while incorporating the entry of any anomalous pulmonary veins into the left atrium. If the anomalous vein drains high in the SVC, the vein can be left intact and the ASD closed to incorporate the SVC mouth into the left atrium. The SVC proximal to the venous entrance is then detached and anastomosed directly to the right atrium. This procedure avoids direct suturing of the pulmonary vein, with less chance of future stenosis. Surgical results are generally excellent. Rarely, sinus venosus defects involve the IVC.

453.4

Partial Anomalous Pulmonary Venous Return

Daniel Bernstein

One or several pulmonary veins may return anomalously to the SVC or IVC, right atrium, or coronary sinus and produce a left-to-right shunt of oxygenated blood. Partial anomalous pulmonary venous return (PAPVR) usually involves some or all of the veins from only 1 lung, typically the right. When an associated ASD is present, it is generally of the sinus venosus type but can be secundum (see Chapters 453.2 and 453.3). When an ASD is detected by echocardiography, one must always search for associated PAPVR. The history, physical signs, and electrocardiographic and radiologic findings are indistinguishable from those of an isolated ostium secundum ASD. Occasionally, an anomalous vein draining into the IVC is visible on chest radiography as a crescentic shadow of vascular density along the right border of the cardiac silhouette (**scimitar syndrome**); in these patients an ASD is not usually present, but **pulmonary sequestration** or **lung hypoplasia** and anomalous arterial supply to that lobe are common findings. **Total anomalous pulmonary venous return** (TAPVR) is a cyanotic lesion and is discussed in Chapter 458.7 . Echocardiography generally confirms the diagnosis. MRI and CT are also useful if there is a question regarding pulmonary venous drainage or in cases of scimitar syndrome. If cardiac catheterization is performed, the presence of anomalous pulmonary veins is demonstrated by selective pulmonary arteriography, and anomalous pulmonary arterial supply to the right lung is demonstrated by descending aortography.

The prognosis for PAPVR is excellent, similar to that for ostium secundum ASDs. When a large left-to-right shunt is present, surgical repair is performed. The associated ASD should be closed in such a way that pulmonary venous return is directed to the left atrium. A single anomalous pulmonary vein without an atrial communication may be difficult to redirect to the left atrium; if the shunt is small and the right ventricle is not enlarged, it may be left unoperated.

453.5

Atrioventricular Septal Defects (Ostium Primum and Atrioventricular Canal or Endocardial Cushion Defects)

Daniel Bernstein

The abnormalities encompassed by atrioventricular (AV) septal defects are grouped together because they represent a spectrum of a basic embryologic abnormality, a **deficiency of the AV septum** . The tricuspid valve sits slightly lower (more toward the cardiac apex) than does the mitral valve, and thus a small portion of septum separates the left ventricle from the right atrium. This is the AV septum that is deficient in all forms of AV septal defect. When the AV septum is absent and there is also an **ostium primum** defect, the main communication is situated in the lower portion of the atrial septum and overlies the mitral and tricuspid valves. In most cases a **cleft in the anterior leaflet of the mitral valve** is also noted. The tricuspid valve is usually functionally normal, although some anatomic abnormality of the septal leaflet is present. The ventricular septum is intact.

An AV septal defect, formerly known as an *AV canal defect* or *endocardial cushion defect*, consists of a defect of the AV septum and contiguous atrial and ventricular septal defects with a common AV valve. The severity of the AV valve abnormality varies considerably. In the **complete** form of AV septal defect, a single AV valve is common to both ventricles and consists of an anterior and a posterior bridging leaflet related to the ventricular septum, with a lateral leaflet in each ventricle. The anterior bridging leaflet can be divided into right- and left-sided components or may be single and free floating over the ventricular septum. Complete AV septal defect is common in children with **Down syndrome** .

Transitional varieties of these defects also occur and include ostium primum defects with clefts in the anterior mitral and septal tricuspid valve leaflets and small VSDs, and less commonly, ostium primum defects with normal AV valves. In some patients the atrial septum is intact, but a VSD is seen in the inlet septum, similar to that found in the complete form of AV septal defect. Sometimes, AV septal defects are associated with varying degrees of hypoplasia of one of the ventricles, known as either **left-dominant** or **right-dominant AV septal defect** . If the affected ventricular chamber is too small to establish a 2-ventricle circulation, surgical palliation, aiming for an eventual Fontan procedure, is performed (see Chapters 457.4 and 458.10).

Pathophysiology

The basic abnormality in patients with ostium primum defects is the combination of a left-to-right shunt across the atrial defect and mitral (or occasionally tricuspid) insufficiency. The shunt is usually moderate to large, the degree of mitral insufficiency is generally mild to moderate, and pulmonary artery pressure (PAP) is typically normal or only mildly increased. The physiology of this lesion is therefore similar to that of an ostium secundum ASD.

In complete AV septal defects, left-to-right shunting occurs at both the atrial and the ventricular level (Fig. 453.4). Additional shunting may occur directly from the left ventricle to the right atrium (known as a *Gerbode shunt*) because of absence of the AV septum. Pulmonary hypertension and an early tendency to increase PVR are common. AV valvular insufficiency, which may be moderate to severe, further increases the volume load on one or both ventricles. If the defect is large enough, some right-to-left shunting may also occur at the atrial and ventricular levels and lead to mild arterial desaturation. With time, progressive pulmonary vascular disease increases the right-to-left shunt so that clinical cyanosis develops (**Eisenmenger physiology** ; see Chapter 460.2). The risk for development of pulmonary vascular disease is greater in patients with Down syndrome, and therefore surgical correction is usually considered early in these patients, within the 1st 3-6 mo of life.

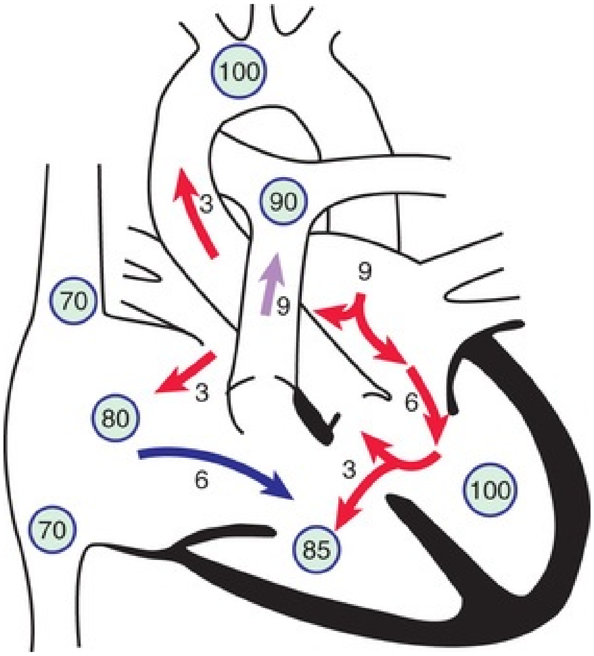

FIG. 453.4 **Physiology of atrioventricular (AV) septal defect. *Circled numbers* represent oxygen saturation (SO $_2$) values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 3 : 1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and mixes with 3 L of fully saturated blood shunting left to right across the atrial septal defect; the result is an increase in SO $_2$ in the right atrium. Six liters of blood flows through the right side of the**

common AV valve, joined by an additional 3 L of saturated blood shunting left to right at the ventricular level, further increasing SO_2 in the right ventricle. The full 9 L flows across the right ventricular outflow tract into the lungs. Nine liters returns to the left atrium, with 3 L shunting left to right across the defect and 6 L crossing the left side of the common AV valve and causing a mid-diastolic flow rumble. Three liters of this volume shunts left to right across the ventricular septal defect, and 3 L is ejected into the ascending aorta (normal cardiac output).

Clinical Manifestations

Many children with ostium primum defects are asymptomatic, and the anomaly is discovered during a general physical examination. In patients with moderate shunts and mild mitral insufficiency, the physical signs are similar to those of the secundum ASD, but with an additional apical holosystolic murmur caused by mitral insufficiency.

A history of exercise intolerance, easy fatigability, and recurrent pneumonia may be obtained, especially in infants with large left-to-right shunts and severe mitral insufficiency. In these patients, cardiac enlargement is moderate or marked, and the precordium is hyperdynamic. Auscultatory signs produced by the left-to-right shunt include a normal or accentuated first heart sound (S_1); wide, fixed splitting of S_2; a pulmonary systolic ejection murmur sometimes preceded by a click; and a low-pitched, mid-diastolic rumbling murmur at the lower left sternal edge or apex, or both, as a result of increased flow through the AV valves. **Mitral insufficiency** may be manifested by a harsh (occasionally very high-pitched) **apical holosystolic murmur** that radiates to the left axilla.

With complete AV septal defects, heart failure and intercurrent pulmonary infection usually appear in infancy. The liver is enlarged, and the infant often develops feeding intolerance and failure to thrive. Cardiac enlargement is moderate to marked, and a systolic thrill is frequently palpable at the lower left sternal border. A precordial bulge and lift may be present as well. S_1 is normal or accentuated. S_2 is widely split if the pulmonary flow is massive. A low-pitched, mid-diastolic rumbling murmur is audible at the lower left sternal border, indicative of increased blood flow across the right side of the common AV valve, and a pulmonary systolic ejection murmur is produced by the large pulmonary flow. The harsh apical holosystolic murmur of mitral insufficiency may also be present.

Diagnosis

Chest radiographs of children with complete AV septal defects often show moderate to severe cardiac enlargement caused by the prominence of both ventricles and atria. The pulmonary artery is large, and pulmonary vascularity is increased.

The ECG in patients with a complete AV septal defect is *distinctive* and usually diagnostic. The principal abnormalities are (1) superior orientation of the mean frontal QRS axis with axis deviation to the right upper quadrant (QRS negative in both lead I and lead aVF), (2) counterclockwise inscription of the superiorly oriented QRS vector loop (manifest by a Q wave in leads I and aVL), (3) signs of biventricular hypertrophy or isolated RV hypertrophy, (4) RV conduction delay (rSR′ pattern in leads V_3 R and V_1), (5) normal or tall P waves, and (6) occasional prolongation of the P-R interval (Fig. 453.5).

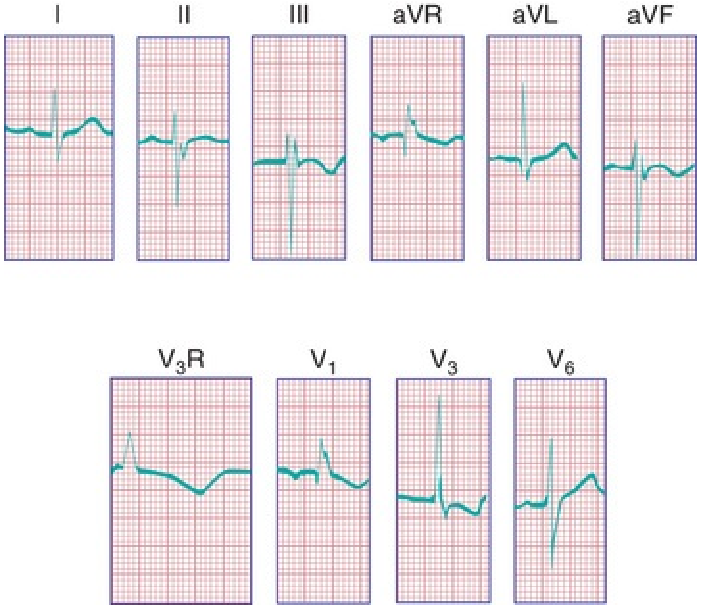

FIG. 453.5 **Electrocardiogram from child with atrioventricular septal defect. Note the QRS axis of −60 degrees and the right ventricular conduction delay with an RSR′ pattern in V_1 and V_3 R (V_3 R paper speed = 50 mm/sec).**

The echocardiogram is diagnostic and shows signs of RV enlargement (Fig. 453.6). There is encroachment of the mitral valve into the left ventricular outflow tract; the abnormally low position of the AV valves results in a “gooseneck” deformity of the LVOT. In normal hearts the tricuspid valve inserts slightly more toward the apex than does the mitral valve. In AV septal defects, both valves insert at the same level because of absence of the AV septum. In complete AV septal defects the ventricular septum is also deficient, and the common AV valve is readily appreciated. Pulsed and color flow Doppler echocardiography will demonstrate left-to-right shunting at the atrial, ventricular, or left ventricular–right atrial levels and can be used to semiquantitate the degree of AV valve insufficiency. Echocardiography is useful for determining the insertion points of the chordae of the common AV valve and for evaluating the presence of associated lesions such as patent ductus arteriosus (PDA) or coarctation of the aorta.

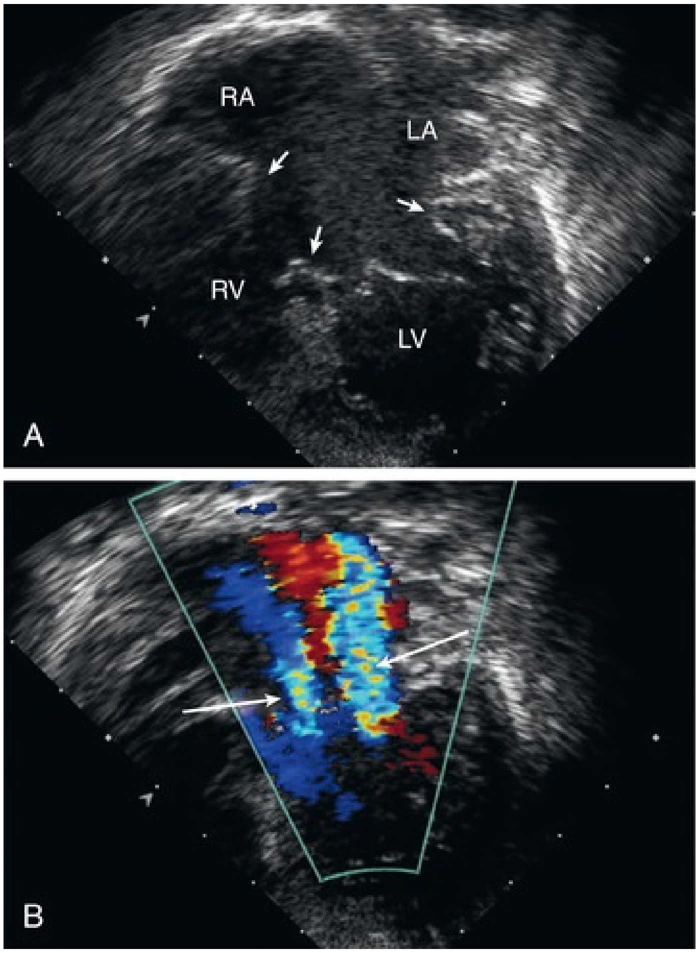

FIG. 453.6 **Echocardiograms of atrioventricular (AV) septal defect. A, Subcostal 4-chamber view demonstrating the common AV valve *(arrows)* spanning the atrial and ventricular septal defects. B, Doppler imaging shows 2 jets of regurgitation through the left side of the common AV valve *(arrows).* LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.**

Cardiac catheterization and angiocardiography is rarely required to confirm the diagnosis unless pulmonary vascular disease is suspected, as when diagnosis has been delayed beyond early infancy, especially in patients with Down syndrome in whom the development of pulmonary vascular disease may be more rapid. Catheterization demonstrates the magnitude of the left-to-right shunt, the degree of PVR elevation, and the severity of insufficiency of the common AV valve. By oximetry, the shunt is usually demonstrable at both the atrial and the ventricular level. Arterial oxygen saturation is normal or only mildly reduced unless pulmonary vascular disease is present. Children with ostium primum defects generally have normal or only moderately elevated PAP. Conversely, complete AV septal defects are associated with RV and pulmonary hypertension and, in older patients, increased PVR (see Chapter 460.2).

Selective left **ventriculography** will demonstrate deformity of the common AV valve and distortion of the LVOT caused by the abnormally apical position of this valve (gooseneck deformity). The abnormal anterior leaflet of the mitral valve is serrated, and insufficiency is noted. Direct shunting of blood from the left ventricle to the right atrium may also be demonstrated.

Treatment

Ostium primum defects are approached surgically from an incision in the right atrium. The cleft in the mitral valve is located through the atrial defect and is repaired by direct suture. The defect in the atrial septum is usually closed by insertion of a patch prosthesis. The surgical mortality rate for ostium primum defects is very low.

Surgical treatment of complete AV septal defects is more complex, although highly successful. The postoperative course may be prolonged in infants with severe cardiac failure and in those with pulmonary hypertension. Because of the risk of **pulmonary vascular disease** developing as early as 6-12 mo of age, surgical intervention must be performed during infancy. Full correction of these defects can be readily accomplished in infancy. Palliation with *pulmonary arterial banding* , once more common, is reserved for the small subset of patients who have other associated lesions that make early corrective surgery too risky, and may not be as effective in patients with a large amount of AV valve regurgitation. The atrial and ventricular defects are patched, using either 1 or 2 separate patches, and the AV valves are reconstructed. Uncommon complications include surgically induced heart block requiring placement of a permanent pacemaker and excessive LVOT narrowing requiring surgical revision. More often there may be residual tricuspid or mitral regurgitation, which requires long-term surveillance because it may require replacement with a prosthetic valve later in life.

Prognosis

The prognosis for unrepaired complete AV septal defects depends on the magnitude of the left-to-right shunt, degree of PVR elevation, and severity of AV valve insufficiency. Death from cardiac failure during infancy was common before the advent of early corrective surgery. Patients who survived without surgery usually developed pulmonary vascular obstructive disease. Most patients with ostium primum defects and minimal AV valve involvement are asymptomatic or have only minor, nonprogressive symptoms until they reach the 3rd or 4th decade of life, similar to the course of patients with secundum ASDs. Late postoperative **complications** include atrial arrhythmias and heart block, progressive narrowing of the LVOT requiring surgical revision, and eventual worsening of AV valve regurgitation (usually on the left side) requiring replacement with a prosthetic valve.

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453.6

Ventricular Septal Defect

Daniel Bernstein

Ventricular septal defect is the most common cardiac malformation and accounts for 25% of congenital heart disease. Defects may occur in any portion of the ventricular septum, but the most common are of the **membranous** type (Fig. 453.7). These defects are in a posteroinferior position, anterior to the septal leaflet of the tricuspid valve. VSDs between the crista supraventricularis and the papillary muscle of the conus may be associated with pulmonary stenosis and other manifestations of tetralogy of Fallot (see Chapter 457.1). VSDs superior to the crista supraventricularis (**supracristal**) are less common; these are found just beneath the pulmonary valve and may impinge on an aortic sinus and cause aortic insufficiency (see Chapter 453.7). Supracristal VSDs are more common in patients of Asian descent. VSDs in the midportion or apical region of the ventricular septum are muscular in type and may be single or multiple (“Swiss cheese” septum).

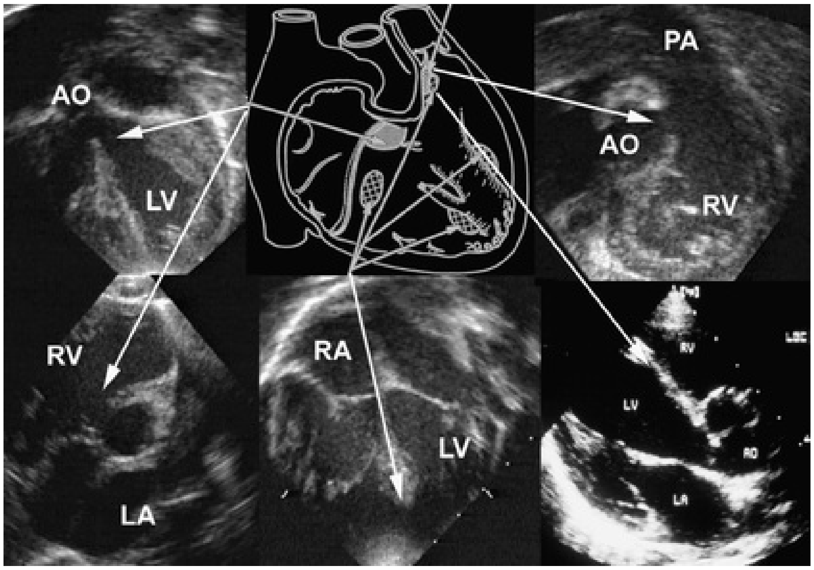

FIG. 453.7 **Montage of the different types of ventricular septal defects (VSDs). The central diagram outlines the location of the various types of defects as seen from the right ventricle. Two left images show a perimembranous VSD as seen in the 5-chamber and short axis views. Note the defect is roofed by the aorta and is next to the tricuspid valve. Bottom middle echocardiogram shows a muscular apical defect. Upper right image is a right anterior oblique view in a doubly committed VSD. Lower right image is a short axis view showing an outlet VSD with prolapse of the right coronary cusp. AO, Aorta; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle. (From Webb GD, Smallhorn JF, Therrien J, Redington AN: Congenital heart disease in the adult and pediatric patient. In *Braunwald's heart disease, a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2018, Elsevier, Fig 75.21, p 1514.)**

Pathophysiology

The physical size of the VSD is a major (but not the only) determinant of the size of the left-to-right shunt. When the defect is large, the level of pulmonary vascular resistance (PVR) in relation to systemic vascular resistance (SVR) is the major determinant of the shunt's magnitude. When a small communication is present (usually <5 mm), the VSD is deemed to be pressure **restrictive** , meaning that right ventricular (RV) pressure is normal or only slightly elevated. The higher pressure in the left ventricle drives the shunt left to right, and the size of the defect limits the magnitude of the shunt. In larger, **nonrestrictive** VSDs (usually >10 mm), RV and left ventricular (LV) pressures are equalized. In these defects the direction of shunting and the shunt magnitude are determined by the PVR/SVR ratio (Fig. 453.8).

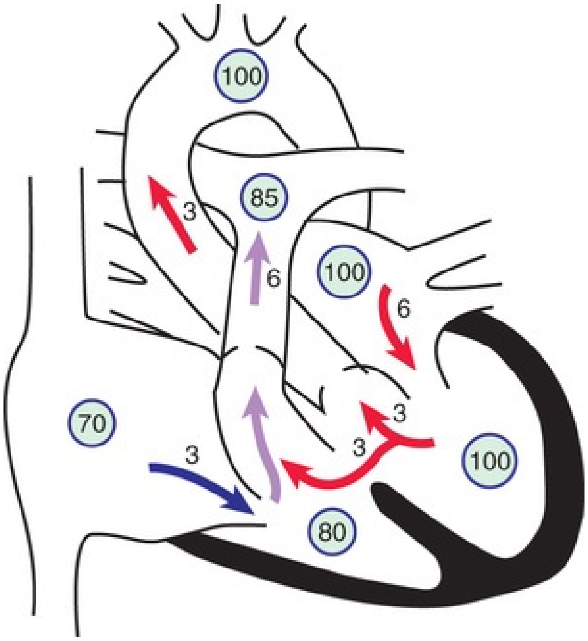

FIG. 453.8 **Physiology of a large ventricular septal defect. *Circled numbers* represent oxygen saturation (SO $_2$) values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2 : 1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and flows across the tricuspid valve. An additional 3 L of blood shunts left to right across the VSD, resulting in increased SO $_2$ in the right ventricle. Six liters of blood is ejected into the lungs. Pulmonary arterial saturation may be further increased because of incomplete mixing at right ventricular level. Six liters returns to the left atrium, crosses the mitral valve, and causes a mid-diastolic flow rumble. Three liters of this volume shunts left to right across the VSD, and 3 L is ejected into the ascending aorta (normal cardiac output).**

After birth in patients with a large VSD, PVR may remain elevated, delaying the normal postnatal decrease, and thus the size of the left-to-right shunt may initially be limited. Because of normal involution of the media of small pulmonary arterioles, PVR begins to fall in the 1st few wk after birth, and the size of the left-to-right shunt then increases. Eventually, a large left-to-right shunt develops, and clinical symptoms become apparent. In most cases during early infancy, PVR is only slightly elevated, and the major contribution to pulmonary hypertension is the large communication allowing exposure of the pulmonary circulation to systemic pressure and the large pulmonary blood flow. With continued exposure of the pulmonary vascular bed to high systolic pressure and high flow, pulmonary vascular obstructive disease eventually develops. When the PVR/SVR ratio approaches 1 : 1, the shunt becomes bidirectional, signs of heart failure abate, and the patient begins to show signs of cyanosis (**Eisenmenger physiology** ; see Chapter 460.2), intermittent at first, but then more constant. In rare infants with a large VSD, more often in those with Down syndrome, PVR never decreases, and symptoms may remain minimal until Eisenmenger physiology becomes evident.

The magnitude of intracardiac shunts is usually described by the Qp:Qs ratio. If the left-to-right shunt is small (Qp:Qs < 1.5 : 1), the cardiac chambers are not appreciably enlarged, and the pulmonary vascular bed is probably normal. If the shunt is large (Qp:Qs > 2 : 1), left atrial and LV volume overload occurs, and RV and pulmonary arterial hypertension may be present if the defect is large. The main pulmonary artery, left atrium, and left ventricle are enlarged.

Clinical Manifestations

The clinical findings of patients with a VSD vary according to the size of the defect and pulmonary blood flow and pressure. Small VSDs with trivial left-to-right shunts and normal pulmonary artery pressure (PAP) are the most common. These patients are asymptomatic, and the cardiac lesion is usually found during routine physical examination. Characteristically, a loud, harsh, or blowing holosystolic murmur is present and heard best over the lower left sternal border, and it is frequently accompanied by a thrill. In a few cases the murmur ends before the second heart sound (S_2), presumably because of closure of the defect during late systole. A short, loud, harsh systolic murmur localized to the apex in a neonate is often a sign of a tiny VSD in the apical muscular septum. In premature infants the murmur may be heard early because PVR decreases more rapidly.

Large VSDs with excessive pulmonary blood flow and pulmonary hypertension are responsible for signs of congestive heart failure: dyspnea, feeding difficulties, poor growth, profuse perspiration, and recurrent pulmonary infections in early infancy. Cyanosis is usually absent, but duskiness is sometimes noted during infections or crying. Prominence of the left precordium is common, as are a palpable parasternal lift, a laterally displaced apical impulse and apical thrust, and a systolic thrill. The holosystolic murmur of a large VSD is generally less harsh than that of a small VSD and more blowing in nature because of the absence of a significant pressure gradient across the defect. It is even less likely to be prominent in the newborn period. The pulmonic component of S_2 may be increased as a result of pulmonary hypertension. The presence of a mid-diastolic, low-pitched rumble at the apex is caused by increased blood flow across the mitral valve and usually indicates a Qp:Qs ratio $\geq 2 : 1$. This murmur is best appreciated with the bell of the stethoscope.

Diagnosis

In patients with small VSDs, the chest radiograph is usually normal, although minimal cardiomegaly and a borderline increase in pulmonary vasculature may be observed. The ECG is generally normal but may suggest LV hypertrophy. The presence of RV hypertrophy on ECG is a warning that the defect is not small and that the patient has pulmonary hypertension or an associated lesion such as pulmonic stenosis. In large VSDs the chest radiograph shows gross cardiomegaly with prominence of both ventricles, the left atrium, and the pulmonary artery (Fig. 453.9). Pulmonary vascular markings are increased, and frank pulmonary edema, including pleural effusions, may be present. The ECG shows biventricular hypertrophy; the P waves may be notched (indicative of LA enlargement).

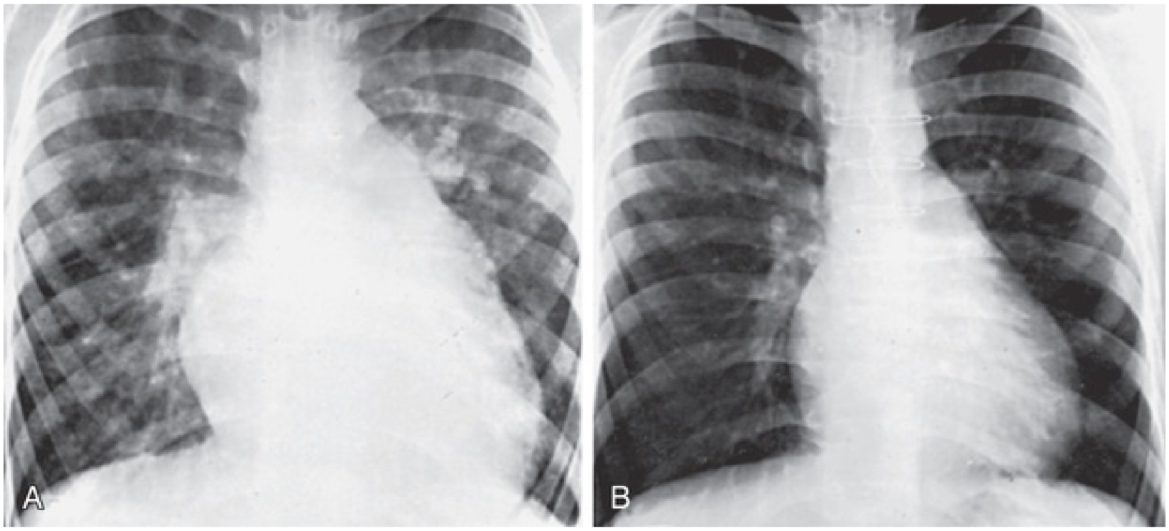

FIG. 453.9 **A,** Preoperative radiograph in a patient with a ventricular septal defect with a large left-to-right shunt and pulmonary hypertension. Significant cardiomegaly, prominence of the pulmonary arterial trunk, and pulmonary overcirculation are evident. **B,** Three years after surgical closure of the defect, heart size is greatly decreased, and the pulmonary vasculature is normal.

The 2D echocardiogram shows the position and size of the VSD (see Fig. 453.7). In small defects, especially those of the muscular septum, the defect itself may be difficult to image and is visualized only by color Doppler examination. In defects of the **membranous septum** , a thin membrane (called a **ventricular septal aneurysm** but consisting of abnormal tricuspid valve tissue) can partially cover the defect and limit the volume of the left-to-right shunt. Echocardiography is also useful for estimating shunt size by examining the degree of volume overload of the left atrium and left ventricle; in the absence of associated lesions, the extent of their increased dimensions is a good reflection of the size of the left-to-right shunt. Pulsed Doppler examination shows whether the VSD is pressure restrictive by calculating the pressure gradient across the defect. Such calculation allows an estimation of RV pressure and helps determine whether the patient is at risk for the development of early pulmonary vascular disease. The echocardiogram can also be useful to determine the presence of aortic valve insufficiency or aortic leaflet prolapse in the case of supracristal VSDs.

The hemodynamics of a VSD can also be demonstrated by cardiac catheterization, although catheterization currently is performed only when laboratory data do not fit well with the clinical findings or when pulmonary vascular disease is suspected. Oximetry demonstrates increased oxygen content in the right ventricle; because some defects eject blood almost directly into the pulmonary artery (streaming), the full magnitude of the oxygen saturation increase is occasionally apparent only when pulmonary arterial blood is sampled. Small, restrictive VSDs are associated with normal right-sided heart pressures and PVR. Large, nonrestrictive VSDs are associated with equal or near-equal pulmonary and systemic systolic pressure and variable elevations in PVR. Pulmonary blood flow may be 2-4 times systemic blood flow. In patients with such "hyperdynamic pulmonary hypertension," PAP is at systemic level, but PVR is only minimally elevated because of the high pulmonary blood flow (resistance is equal to pressure divided by flow). However, if left untreated until Eisenmenger syndrome is present, systolic and diastolic PAP will be elevated, but the degree of left-to-right shunting minimal. In these cases, desaturation of blood in the left ventricle is usually encountered. The size, location, and number of ventricular defects can be demonstrated by left ventriculography. Contrast medium passes across the defect(s) to opacify the right ventricle and pulmonary artery. Administration of 100% oxygen with and without nitric oxide can be used to determine whether PVR, if elevated, is still reactive and therefore more likely to decrease after surgical repair.

Treatment

The natural course of a VSD depends to a large degree on the size of the defect. A significant number (30–50%) of small defects close spontaneously, most frequently during the 1st 2 yr of life. Small *muscular* VSDs are more likely to close (up to 80%) than *membranous* VSDs (up to 35%). Most defects that close do so before age 4 yr, although spontaneous closure has been reported in adults. VSDs that close often have ventricular septal aneurysm (accessory tricuspid valve) tissue that limits the magnitude of the shunt. Most children with small restrictive defects remain asymptomatic, without evidence of an increase in heart size, PAP, or PVR; a long-term risk is infective endocarditis. Some long-term studies of adults with unoperated small VSDs show an increased incidence of arrhythmia, subaortic stenosis, and exercise intolerance. Guidelines from the **Council on Cardiovascular Disease in the Young** of the American Heart Association (AHA) state that an isolated, small, hemodynamically insignificant VSD is not an indication for surgery. However, the declining risk of open heart surgery has led some to suggest that all VSDs be closed electively by mid-childhood.

It is less common for moderate or large VSDs to close spontaneously, although even defects large enough to result in heart failure may become smaller, and up to 8% may close completely. More frequently, infants with large defects have repeated episodes of respiratory infection and heart failure despite optimal medical management. Heart failure may be manifested in many of these infants primarily as failure to thrive. Pulmonary hypertension occurs as a result of high pulmonary blood flow. These patients are at risk for pulmonary vascular disease if the defect is not repaired during early infancy.

Patients with VSD are also at risk for the development of **aortic valve regurgitation** , the greatest risk occurring in patients with a supracristal VSD (see Chapter 453.7), where the position of the defect undermines support for the aortic valve right coronary or noncoronary leaflet. A small number of patients with VSD develop **acquired infundibular pulmonary stenosis,** which then protects the pulmonary circulation from the short-term effects of pulmonary overcirculation and the long-term effects of pulmonary vascular disease. In these patients the clinical picture changes from that of a VSD with a large left-to-right shunt to a VSD with pulmonary stenosis. The shunt may diminish in size, become balanced, or even become a net right-to-left shunt. These patients must be carefully distinguished from those in whom an Eisenmenger physiology develops (see Chapter 460.2).

In patients with small VSDs, parents should be reassured of the relatively benign nature of the lesion, and the child should be encouraged to live a normal life, with no restrictions on physical activity. Surgical repair is not recommended. As protection against infective endocarditis, the integrity of primary and permanent teeth should be carefully maintained; with the latest revision of the AHA guidelines, antibiotic prophylaxis is no longer recommended for dental visits or surgical procedures (see Chapter 464). These patients can be monitored by a combination of clinical examination and noninvasive laboratory tests until the VSD has closed spontaneously. Echocardiography is used to estimate PAP, screen for the development of LVOT pathology (subaortic membrane or aortic regurgitation), and to confirm spontaneous closure.

In infants with a large VSD, management has 2 goals: control the symptoms of heart failure (see Chapter 469) and prevent the development of pulmonary vascular disease. If early treatment is successful, sometimes the shunt may diminish in size with spontaneous improvement, especially during the 1st yr of life. The clinician must be alert not to confuse clinical improvement caused by a decrease in defect size with clinical changes caused by the development of Eisenmenger physiology. Because surgical closure can be carried out at low risk in most infants, medical management should not be pursued in symptomatic infants after an initial unsuccessful trial. Because pulmonary vascular disease can usually be prevented when surgery is performed within the 1st yr of life, even infants with well-controlled heart failure should not have surgery delayed inordinately unless there is evidence that the defect is becoming pressure restrictive.

Indications for surgical closure of a VSD include patients at any age with large defects in whom clinical symptoms and failure to thrive cannot be controlled medically; infants between 6 and 12 mo of age with moderate to large defects associated with pulmonary hypertension, even if the symptoms are controlled by medication; and patients older than 24 mo with a Qp:Qs ratio greater than 2 : 1. Patients with a supracristal VSD of any size are usually referred for surgery because of their higher risk for developing aortic valve regurgitation (see Chapter 453.7). Severe pulmonary vascular disease nonresponsive to pulmonary vasodilators is a contraindication to closure of a VSD.

Transcatheter occlusion closure has been used successfully in treating larger muscular VSDs, which may be difficult to access by surgery. Perimembranous VSD catheter closure has a high risk of postprocedural heart block and is currently not routinely performed. Hybrid methods employing a sternotomy with device placement through the anterior wall of the right ventricle under transesophageal echocardiographic and fluoroscopic visualization has been performed in difficult-to-approach muscular defects.

Prognosis

The results of primary surgical repair are excellent, and complications leading to long-term problems (residual ventricular shunts requiring reoperation or heart block requiring a pacemaker) are rare. Palliation with pulmonary artery banding with repair in later childhood, once the standard of care, is now reserved for extremely complicated cases or very premature infants. Surgical risks are somewhat higher for defects in the muscular septum, particularly apical defects and multiple (Swiss cheese–type) VSDs. These patients may require pulmonary arterial banding if symptomatic, with subsequent debanding and repair of multiple VSDs at an older age.

After surgical obliteration of the left-to-right shunt, the hyperdynamic heart becomes quiet, cardiac size decreases toward normal (see Fig. 453.9), thrills and murmurs are abolished, and pulmonary artery hypertension regresses. The patient's clinical status greatly improves. Most infants begin to thrive, often quite rapidly after hospital discharge, and cardiac medications are no longer required. Catch-up growth occurs in most patients within the next year. In some patients, after successful surgery, systolic ejection murmurs of low intensity persist for months. The long-term prognosis after surgery is excellent. Patients with a small VSD and those who have undergone surgical closure without residua are considered to be at standard risk for health and life insurance.

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453.7

Supracristal Ventricular Septal Defect With Aortic Insufficiency

Daniel Bernstein

A supracristal VSD can be complicated by **prolapse of the aortic valve** into the defect and aortic insufficiency, which may eventually develop in 50–90% of these patients. Although supracristal VSD accounts for approximately 5% of all patients with VSD, the incidence is higher in Asian children and in males. The VSD, which may be small or moderate in size, is located anterior to and directly below the pulmonary valve in the outlet septum, superior to the muscular ridge known as the *crista supraventricularis,* which separates the trabecular body of the right ventricle from the smooth outflow portion. The right or, less often, the noncoronary aortic cusp prolapses into the defect and may partially or even completely occlude it. Such occlusion may limit the amount of left-to-right shunting and give the false impression that the defect is not large. Aortic insufficiency is most often not recognized until after 5 yr of age, or even later. Although most common with supracristal VSDs, aortic insufficiency is occasionally associated with VSDs located in the membranous septum.

Early heart failure secondary to a large left-to-right shunt rarely occurs, but without surgery, moderate-to-severe aortic insufficiency and left ventricular failure may eventually ensue. The murmur of a supracristal VSD is usually heard at the mid- to upper left sternal border, as opposed to the lower left sternal border, and it is sometimes confused with that of pulmonic stenosis. A decrescendo diastolic murmur will be appreciated at the upper right or mid-left sternal borders if there is aortic insufficiency. More advanced degrees of aortic insufficiency will be associated with a wide pulse pressure and a hyperdynamic precordium. These clinical findings must be distinguished from PDA or other defects associated with aortic runoff.

The clinical manifestations vary widely, from trivial aortic regurgitation and small left-to-right shunts in asymptomatic children to florid aortic insufficiency and massive cardiomegaly in symptomatic adolescents. Closure of all supracristal ventricular VSDs is usually recommended to prevent the development of aortic regurgitation, even in an asymptomatic child. Patients who already have significant aortic insufficiency require surgical intervention to prevent irreversible left ventricular dysfunction. Surgical options depend on the degree of damage to the valve and for mild insufficiency may include simple closure of the defect to bolster the valve apparatus without touching the valve itself, valvuloplasty for more significant degrees of involvement, and replacement with a prosthesis or homograft or aortopulmonary translocation for severe involvement.

453.8

Patent Ductus Arteriosus

Daniel Bernstein

During fetal life, most of the pulmonary arterial blood is shunted right-to-left through the ductus arteriosus into the aorta (see Chapter 448). Functional closure of the ductus normally occurs soon after birth, usually within the 1st wk of life, but if the ductus remains patent when PVR falls, aortic blood then is shunted left to right into the pulmonary artery. The aortic end of the ductus is just distal to the origin of the left subclavian artery, and the ductus enters the pulmonary artery at its bifurcation. Female patients with patent ductus arteriosus (PDA) outnumber males 2 : 1. PDA is also associated with maternal rubella infection during early pregnancy, an uncommon occurrence in the vaccination era. PDA is a common problem in premature infants because the smooth muscle in the wall of the preterm ductus is less responsive to high P_{O_2} and therefore less likely to constrict after birth. In these infants the shunt through a PDA can cause severe hemodynamic derangements and several major sequelae (see Chapter 122.3).

When a term infant is found to have a PDA, the wall of the ductus is deficient in both the mucoid endothelial layer and the muscular media, whereas in the premature infant the PDA usually has a normal structure. Thus a PDA persisting beyond the 1st few wk of life in a term infant rarely closes spontaneously or with pharmacologic intervention, whereas if early pharmacologic or surgical intervention is not required in a premature infant, spontaneous closure occurs in most instances. A PDA is seen in 10% of patients with other congenital heart lesions and often plays a critical role in providing a source of pulmonary blood flow when the right ventricular outflow tract is stenotic or atretic (see Chapter 457) or in providing systemic blood flow in the presence of aortic coarctation or interruption (see Chapters 454.6 to 454.8).

Pathophysiology

Because of the higher aortic pressure postnatally, blood shunts left to right through the ductus, from the aorta to the pulmonary artery. The extent of the shunt depends on the size of the ductus and on the PVR/SVR ratio. If the PDA is small, pressures within the pulmonary artery, the right ventricle, and the right atrium are normal. If the PDA is large, PAP may be elevated to systemic levels during both systole and diastole. Thus, patients with a large PDA are at high risk for the development of pulmonary vascular disease if left unoperated.

Clinical Manifestations

A small PDA is usually asymptomatic and is usually diagnosed by the presence of a heart murmur. A large PDA will result in heart failure similar to that encountered in infants with a large VSD. Retardation of physical growth may be a major manifestation in infants with large shunts. A small PDA is associated with normal peripheral pulses, and a large PDA results in bounding peripheral arterial pulses and a *wide pulse pressure* , caused by runoff of blood into the pulmonary artery during diastole. Although normal in size when the ductus is small, the heart is moderately or grossly enlarged in cases with a large communication; in these patients the apical impulse is prominent and, with cardiac enlargement, is heaving. A **thrill** , maximal in the 2nd left interspace, is often present and may radiate toward the left clavicle, down the left sternal border, or toward the apex. It is usually systolic but may also be palpated throughout the cardiac cycle. The classic continuous murmur is described as “machinery-like” in quality. It begins soon after onset of S_1 , reaches maximal intensity at the end of systole, and wanes in late diastole. It may be localized to the 2nd left intercostal space or radiate down the left sternal border or to the left clavicle. When PVR is increased, the diastolic component of the murmur may be less prominent or absent. In patients with a large left-to-right shunt, a low-pitched mitral mid-diastolic murmur may be audible at the apex as a result of the increased volume of blood flow across the mitral valve.

Diagnosis

If the left-to-right shunt is small, the ECG is normal; if the ductus is large, LV or biventricular hypertrophy is present. The diagnosis of an isolated, uncomplicated PDA is untenable when RV hypertrophy is present on the ECG.

Radiographic studies in patients with a large PDA show a prominent pulmonary artery with increased pulmonary vascular markings. Cardiac size depends on the degree of left-to-right shunting; it may be normal or moderately to greatly enlarged. The chambers involved are the left atrium and left ventricle. The aortic knob may be normal or prominent.

On echocardiogram the cardiac chambers will be normal in size if the ductus is small. With large shunts, left atrial and LV dimensions are increased. The ductus can easily be visualized directly and its size estimated. Color and pulsed Doppler examinations demonstrate systolic or diastolic (or both) retrograde turbulent flow in the pulmonary artery, and aortic retrograde flow in diastole in the presence of a large shunt (Fig. 453.10).

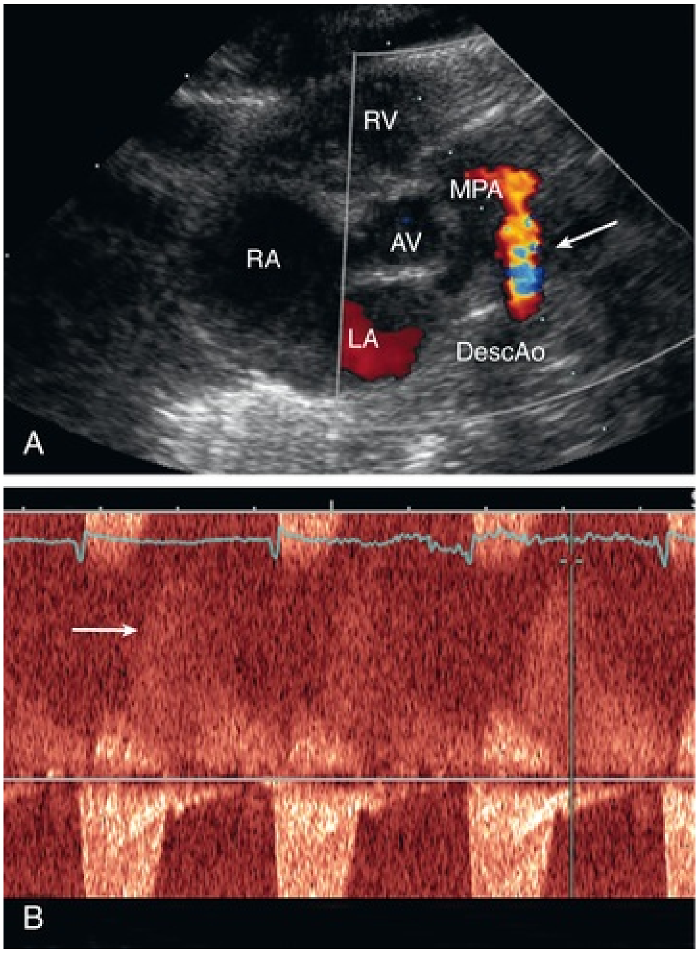

FIG. 453.10 Echocardiogram in a newborn with a small to moderate-size patent ductus arteriosus. A, Color Doppler evaluation in a parasternal short axis view shows flow *(arrow)* from the aorta into the main pulmonary artery. B, Doppler evaluation demonstrates retrograde diastolic flow into the pulmonary artery. AV, Aortic valve; DescAo, descending aorta; LA, left atrium; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle.

The clinical signs and echocardiographic findings are sufficiently distinctive to allow an accurate diagnosis by noninvasive methods in most patients. In rare patients with atypical findings, cardiac catheterization may be indicated for confirmation of diagnosis. Cardiac catheterization will demonstrate either normal or increased pressure in the right ventricle and pulmonary artery, depending on the size of the ductus. The presence of oxygenated blood shunting into the pulmonary artery confirms the left-to-right shunt. The catheter may pass from the pulmonary artery through the ductus into the descending aorta. Injection of contrast medium into the ascending aorta shows opacification of the pulmonary artery from the aorta and identifies the ductus.

Other conditions can produce systolic and diastolic murmurs in the pulmonic area in an acyanotic patient (see Chapter 449). An **aorticopulmonary window defect** may rarely be clinically indistinguishable from a patent ductus, although in most cases the murmur is only systolic and is loudest at the right rather than the left upper sternal border (see Chapter 453.9). A sinus of Valsalva aneurysm that has ruptured into the right side of the heart or pulmonary artery, a coronary arteriovenous fistula, and an aberrant left coronary artery with massive collaterals from the right coronary display dynamics similar to that of a PDA with a continuous murmur and a wide pulse pressure. Truncus arteriosus with torrential pulmonary flow also can present with an aortic runoff physiology. A peripheral arteriovenous fistula also results in a wide pulse pressure, but the distinctive precordial murmur of a PDA is not present. VSD with aortic insufficiency, repaired tetralogy of Fallot, and combined aortic and mitral insufficiency (usually from rheumatic fever) may be confused with a PDA, but the murmurs should be differentiated by their to-and-fro rather than continuous nature. In a to-and-fro murmur there is a quiet segment between the systolic and diastolic components, whereas in a continuous murmur there is flow disturbance throughout the cardiac cycle (even if the murmur is louder during systole than diastole). The combination of a large VSD and a PDA results in findings more like those of an isolated VSD. Echocardiography should be able to eliminate these other diagnostic possibilities.

Prognosis and Complications

Spontaneous closure of the ductus after infancy is extremely rare. Patients with a small PDA may live a normal span with few or no cardiac symptoms, but late manifestations may occur. In patients with a large PDA, cardiac failure most often occurs in early infancy but may occur later in life, even with a moderate-sized communication.

Infective endarteritis may be seen at any age. Pulmonary or systemic emboli may occur. Rare complications include aneurysmal dilation of the pulmonary artery or the ductus, calcification of the ductus, noninfective thrombosis of the ductus with embolization, and paradoxical emboli. Pulmonary hypertension (Eisenmenger syndrome) usually develops in patients with a large PDA who do not undergo ductal closure (see Chapter 460.2).

Treatment

Irrespective of age, patients with a PDA require either catheter or surgical closure. In patients with a small PDA, the rationale for closure is prevention of bacterial endarteritis or other late complications. In patients with a moderate to large PDA, closure is accomplished to treat heart failure or prevent the development of pulmonary vascular disease, or both. Once the diagnosis of a moderate to large PDA is made, treatment should not be unduly postponed after adequate medical therapy for cardiac failure has been instituted.

Transcatheter PDA closure is routinely performed in the cardiac catheterization laboratory (Fig. 453.11). Small PDAs are generally closed with intravascular coils. Moderate to large PDAs may be closed with an umbrella-like device or with a catheter-introduced sac into which several coils are released. Surgical closure of a PDA can be accomplished by a standard left thoracotomy or using thoracoscopic minimally invasive techniques. The case fatality rate with interventional or surgical treatment is considerably less than 1%; thus closure of the ductus is indicated even in asymptomatic patients. Pulmonary hypertension is not a contraindication to surgery at any age if it can be demonstrated at cardiac catheterization that the shunt flow is still predominantly left to right and that severe pulmonary vascular disease is not present. After closure, symptoms of cardiac failure rapidly disappear. Infants who had failed to thrive usually have immediate improvement in physical development. The pulse and blood pressure return to normal, and the machinery-like murmur disappears. A functional systolic murmur over the pulmonary area may persist; it may represent turbulence in a persistently dilated pulmonary artery. The radiographic signs of cardiac enlargement and pulmonary overcirculation disappear over several months, and the ECG becomes normal.

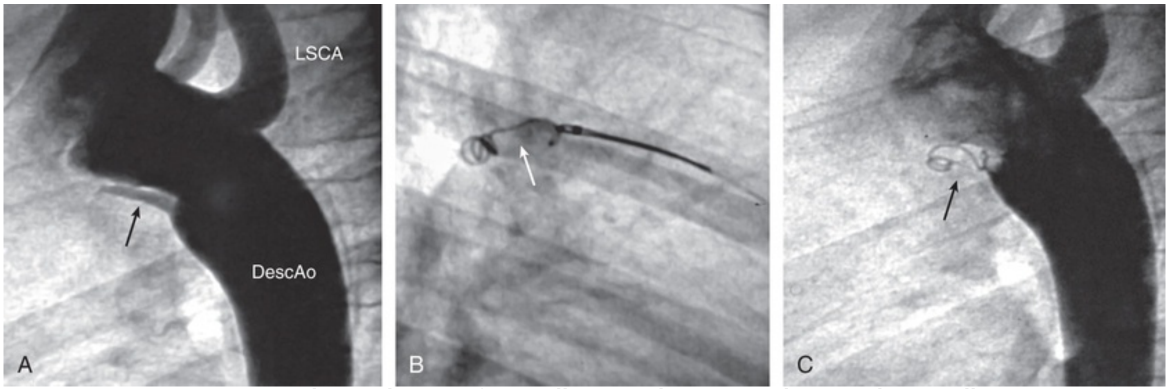

FIG. 453.11 Transcatheter closure of a small patent ductus arteriosus using a coil. A, Angiogram of transverse and descending aorta shows small PDA *(arrow).* B, Coil *(arrow)* has been extruded from sheath and is being positioned in ductal lumen. C, Angiogram demonstrating total occlusion of PDA by coil *(arrow).* DescAo, Descending aorta; LSCA, left subclavian artery.

Patent Ductus Arteriosus in Low-Birthweight Infants

See Chapter 122.5 .

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453.9

Aortopulmonary Window Defect

Daniel Bernstein

An aortopulmonary window defect consists of a communication between the ascending aorta and the main pulmonary artery. The presence of pulmonary and aortic valves and an intact ventricular septum distinguishes this anomaly from **truncus arteriosus** (see Chapter 458.8). Symptoms of heart failure appear during early infancy; occasionally, minimal cyanosis is present. The defect is usually large, and the cardiac murmur is usually systolic with an apical mid-diastolic rumble as a result of the increased blood flow across the mitral valve. In the rare instance when the communication is smaller and pulmonary hypertension is absent, the findings on examination can mimic those of a PDA (wide pulse pressure and a continuous murmur at the upper sternal borders). The ECG shows either LV or biventricular hypertrophy. Radiographic studies demonstrate cardiac enlargement and prominence of the pulmonary artery and intrapulmonary vasculature. The echocardiogram shows enlarged left-sided heart chambers; the window defect can best be delineated with color flow Doppler. CT or MR angiography can also be used to visualize the defect (see Chapter 450 , Fig. 450.26).

Cardiac catheterization, usually performed in older children to evaluate pulmonary vascular resistance, reveals a left-to-right shunt at the level of the pulmonary artery, as well as hyperkinetic pulmonary hypertension, because the defect is almost always large. Selective aortography with injection of contrast medium into the ascending aorta demonstrates the lesion, and manipulation of the catheter from the main pulmonary artery directly to the ascending aorta is also diagnostic.

An aortopulmonary window defect is surgically corrected during infancy. If surgery is not carried out in infancy, survivors carry the risk of progressive pulmonary vascular obstructive disease, similar to that of other patients who have large intracardiac or great vessel communications.

453.10

Coronary Artery Fistula

Daniel Bernstein

A congenital fistula may exist between a coronary artery and an atrium, ventricle (especially the right), or pulmonary artery. Sometimes, multiple fistulas exist. Regardless of the recipient chamber, the clinical signs are similar to those of PDA, although the machinery-like murmur may be more diffuse. If the flow is substantial, the involved coronary artery may be dilated or aneurysmal. The anatomic abnormality is usually demonstrable by color flow Doppler echocardiography and, during catheterization, by contrast injection into the ascending aorta. Small fistulas may be hemodynamically insignificant and may even close spontaneously. If the shunt is large, treatment consists of either transcatheter coil embolization or, for lesions not amenable to catheter intervention, surgical closure of the fistula.

453.11

Ruptured Sinus of Valsalva Aneurysm

Daniel Bernstein

When one of the sinuses of Valsalva of the aorta is weakened by congenital or acquired disease, an aneurysm may form and eventually rupture, usually into the right atrium or ventricle. This condition is extremely rare in childhood. The onset is usually sudden. The diagnosis should be suspected in a patient in whom symptoms of acute heart failure develop in association with a new, loud, to-and-fro murmur. Color Doppler echocardiography and cardiac catheterization demonstrate the left-to-right shunt at the atrial or ventricular level. Urgent surgical repair is generally required. This condition is often associated with infective endocarditis of the aortic valve.

CHAPTER 454

Acyanotic Congenital Heart Disease

Obstructive Lesions

454.1

Pulmonary Valve Stenosis With Intact Ventricular Septum

Daniel Bernstein

Of the various forms of right ventricular (RV) outflow obstruction with an intact ventricular septum, the most common is isolated **valvular pulmonary stenosis** , which accounts for 7–10% of all congenital heart defects. The valve cusps are deformed to various degrees and, as a result, the valve opens incompletely during systole. The valve may be bicuspid or tricuspid and the leaflets partially fused together with an eccentric outlet. This fusion may be so severe that only a pinhole central opening remains. If the valve is not severely thickened, it produces a domelike obstruction to RV outflow during systole. Isolated infundibular or subvalvular stenosis, supravalvular pulmonary stenosis, and branch pulmonary artery stenosis are also encountered. In cases where pulmonary valve stenosis is associated with a **ventricular septal defect** (VSD), but without anterior deviation of the infundibular septum and overriding aorta, this condition is better classified as pulmonary stenosis with VSD rather than as **tetralogy of Fallot** (see Chapter 457.1). Pulmonary stenosis and an **atrial septal defect** (ASD) are also occasionally seen as associated defects.

The clinical and laboratory findings reflect the dominant lesion, but it is important to rule out any associated anomalies. Pulmonary stenosis as a result of valve dysplasia is the most common cardiac abnormality in **Noonan syndrome** (see Chapter 98) and is associated, in approximately 50% of cases, with a mutation in the gene *PTPN11,* encoding the protein tyrosine phosphatase SHP-2 on chromosome 12. The mechanism for pulmonic stenosis is unknown, although maldevelopment of the distal portion of the bulbus cordis and the sequelae of fetal endocarditis have been suggested as etiologies. Pulmonary stenosis can also be a component of **LEOPARD syndrome** (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness syndrome), often associated with hypertrophic cardiomyopathy. Mutations in the genes *PTPN11* , *RAF1,* and *BRAF* have been implicated in LEOPARD syndrome. Pulmonary stenosis, either of the valve or the branch pulmonary arteries, is a common finding in patients with arteriohepatic dysplasia, also known as **Alagille syndrome** (see Chapter 383). In this syndrome and in some patients with isolated pulmonic stenosis, a mutation is present in the *JAGGED1* gene. In addition to valvular pulmonary stenosis, these patients can have stenosis of their branch pulmonary arteries as well.

Pathophysiology

The obstruction to outflow from the right ventricle to the pulmonary artery results in increased RV systolic pressure and wall stress, which leads to hypertrophy of the right ventricle (Fig. 454.1). The severity of these abnormalities depends on the size of the restricted valve opening. In severe cases, RV pressure may be higher than systemic arterial systolic pressure, whereas with milder obstruction, RV pressure is only mildly or moderately elevated. Pulmonary artery pressure (PAP, distal to the obstruction) is normal or decreased. Arterial oxygen saturation will be normal even in cases of severe stenosis, unless an intracardiac communication such as a VSD or ASD is allowing blood to shunt from right to left. When severe pulmonic stenosis occurs in a neonate, decreased RV compliance often leads to cyanosis as a result of right-to-left shunting through a **patent foramen ovale** (PFO), a condition termed **critical pulmonic stenosis** .

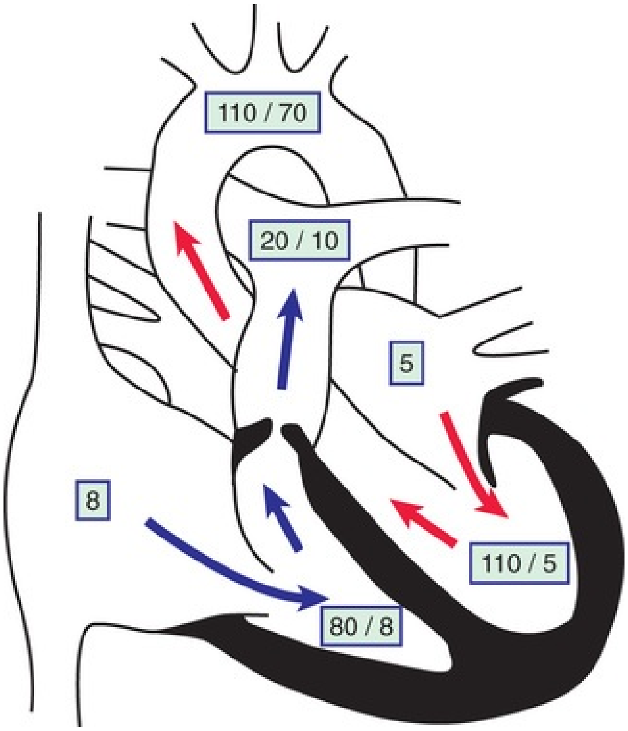

FIG. 454.1 Physiology of valvular pulmonary stenosis. *Boxed numbers* represent pressure in mm Hg. Because of the absence of right-to-left or left-to-right shunting, blood flow through all cardiac chambers is normal at 3 L/min/m^2 . The pulmonary-to-systemic blood flow ratio (Qp:Qs) is 1 : 1. Right atrial pressure is increased slightly as a result of decreased right ventricular compliance. The right ventricle is hypertrophied, and systolic and diastolic pressure is increased. The pressure gradient across the thickened pulmonary valve is 60 mm Hg. The main pulmonary artery pressure is slightly low, and poststenotic dilation is present. Left-sided heart pressure is normal. Unless right-to-left shunting is occurring through a foramen ovale, the patient's systemic oxygen saturation will be normal.

Clinical Manifestations and Laboratory Findings

Patients with mild or moderate stenosis usually have no symptoms. Growth and development are most often normal. If the stenosis is severe, signs of RV failure such as hepatomegaly, peripheral edema, and exercise intolerance may be present. In a neonate or young infant with critical pulmonic stenosis, signs of RV failure may be more prominent, and cyanosis is often present because of right-to-left shunting at the foramen ovale.

With **mild pulmonary stenosis** , venous pressure and pulse are normal. The heart is not enlarged, the apical impulse is normal, and the RV impulse is not palpable. A sharp pulmonic ejection click immediately after the first heart sound

(S_1) is heard at the left upper sternal border during expiration. The second heart sound (S_2) is split, with a pulmonary component of normal intensity that may be slightly delayed. A relatively short, low- or medium-pitched systolic ejection murmur is maximally audible over the pulmonic area and radiates minimally to the lung fields bilaterally. The electrocardiogram (ECG) is normal, or characteristics of mild **right ventricular hypertrophy** (RVH) are present: inversion of the T waves in the right precordial leads may be seen. Note that the T wave in lead V_1 should normally be inverted until at least 6-8 yr of age. Therefore, a positive T wave in V_1 in a young child is a sign of RVH even in the absence of voltage criteria. The only abnormality demonstrable radiographically is usually poststenotic dilation of the pulmonary artery. Two-dimensional (2D) echocardiography shows RVH and a slightly thickened pulmonic valve, which domes in systole. Doppler studies demonstrate a right ventricle–to–pulmonary artery (RV-PA) pressure gradient of ≤30 mm Hg.

In **moderate pulmonic stenosis** , venous pressure may be slightly elevated; in older children, a prominent *a* wave may be noted in the jugular pulse. An RV lift may be palpable at the lower left sternal border. S_2 is split, with a delayed and soft pulmonic component. As valve motion becomes more limited with more severe degrees of stenosis, both the pulmonic ejection click and the pulmonic S_2 may become inaudible. With increasing degrees of stenosis, the peak of the systolic ejection murmur is prolonged later into systole, and its quality becomes louder and harsher (higher frequency). The murmur radiates more prominently to both lung fields.

The ECG reveals RVH, sometimes with a prominent spiked P wave. Radiographically, the heart can vary from normal size to mildly enlarged with uptilting of the apex because of the prominence of the right ventricle; pulmonary vascularity may be normal or slightly decreased. The echocardiogram shows a thickened pulmonic valve with restricted systolic motion. Doppler examination demonstrates an RV-PA pressure gradient of 30-60 mm Hg. Mild tricuspid regurgitation may be present and allows Doppler confirmation of RV systolic pressure.

In **severe pulmonary stenosis** , mild to moderate cyanosis may be noted in patients with an interatrial communication (ASD or PFO). In the absence of any intracardiac shunt, cyanosis is absent. If present, hepatic enlargement and peripheral edema are an indication of RV failure. Elevation of venous pressure is common and is caused by a large presystolic jugular *a* wave. The heart is moderately or greatly enlarged, and a conspicuous parasternal RV lift is present and frequently extends to the left midclavicular line. The pulmonic component of S_2 is usually inaudible. A loud, long, and harsh systolic ejection murmur, usually accompanied by a thrill, is maximally audible in the pulmonic area and may radiate over the entire precordium, to both lung fields, into the neck, and to the back. The peak of the murmur occurs later in systole as valve opening becomes more restricted. The murmur frequently encompasses the aortic component of S_2 but is not preceded by an ejection click.

The ECG shows gross RVH, frequently accompanied by a tall, spiked P wave. Radiographic studies confirm the presence of cardiac enlargement with prominence of the right ventricle and right atrium. Prominence of the main pulmonary artery (MPA) segment may be seen from poststenotic dilation (Fig. 454.2). Intrapulmonary vascularity is decreased. The 2D echocardiogram shows severe deformity of the pulmonary valve and RVH (Fig. 454.3). In the late stages of the disease, systolic dysfunction of the right ventricle may be seen, and in these cases the ventricle may become dilated, with prominent tricuspid regurgitation. Doppler studies demonstrate a high gradient (>60 mm Hg) across the pulmonary valve. The classic findings of severe pulmonary stenosis in older children are rarely seen because of early intervention. Signs of critical pulmonic stenosis, with all the features of severe pulmonic stenosis plus cyanosis, are usually encountered in the neonatal period.

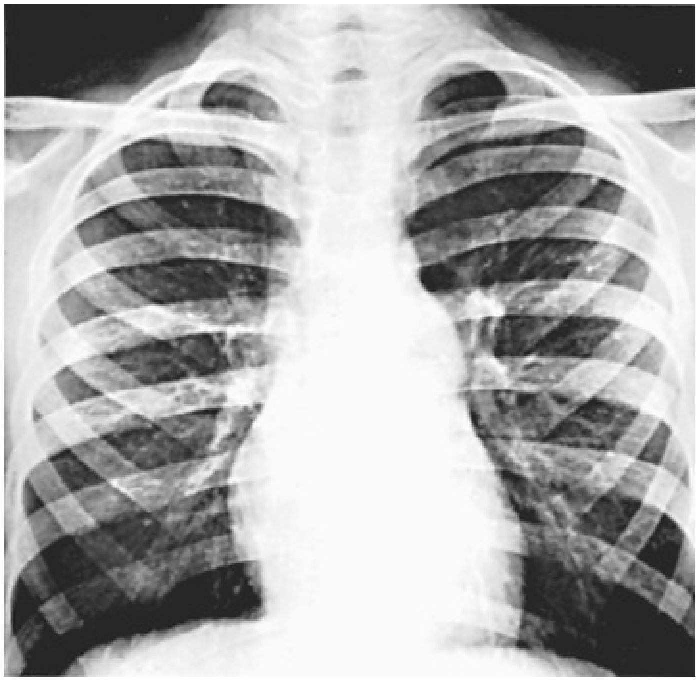

FIG. 454.2 Radiograph of patient with valvular pulmonary stenosis and normal aortic root. The heart size is within normal limits, but poststenotic dilation of the pulmonary artery is present.

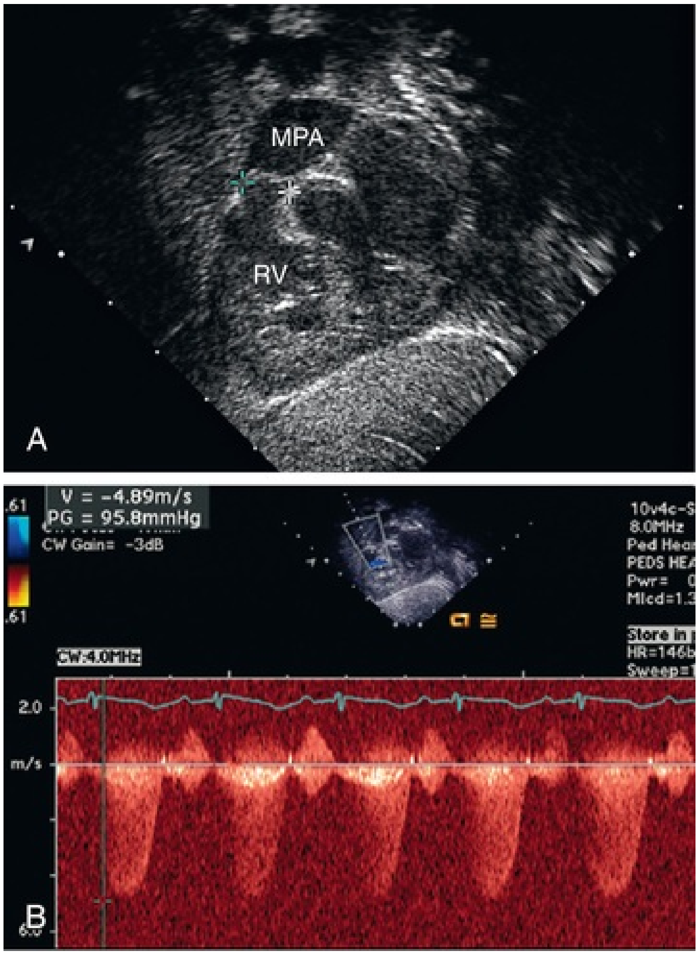

FIG. 454.3 **Echocardiogram demonstrating valvar pulmonic stenosis. A, Subcostal view showing thickened pulmonary valve leaflets (between crosshatches). B, Doppler study indicating a 95 mm Hg peak pressure gradient across the stenotic valve. MPA, Main pulmonary artery; RV, right ventricle.**

Cardiac catheterization is not generally required for diagnostic purposes but is undertaken as part of a **balloon valvuloplasty** procedure. Catheterization demonstrates an abrupt pressure gradient across the pulmonary valve. PAP is either normal or low. The severity of the stenosis is graded based on the ratio of RV systolic pressure to systemic systolic pressure or the RV-PA pressure gradient: 10-30 mm Hg in mild cases, 30-60 mm Hg in moderate cases, and >60 mm Hg or with RV pressure greater than systemic pressure in severe cases. If cardiac output is low or a significant right-to-left shunt exists across the atrial septum, the pressure gradient may underestimate the degree of valve stenosis. Selective right ventriculography demonstrates the thickened, poorly mobile valve. In mild to moderate stenosis, doming of the valve in systole is readily seen. Flow of contrast medium through the stenotic valve in ventricular systole produces a narrow jet of dye that fills the dilated MPA. Subvalvular hypertrophy may be present and may intensify the obstruction.

Treatment

Patients with moderate or severe isolated pulmonary stenosis require relief of the obstruction. Balloon valvuloplasty is the initial treatment of choice for the majority of patients (Fig. 454.4). Patients with severely thickened pulmonic valves, especially common in those with Noonan syndrome, may require surgical intervention. In a neonate with critical pulmonic stenosis, urgent treatment by either balloon valvuloplasty or surgical valvotomy is warranted.

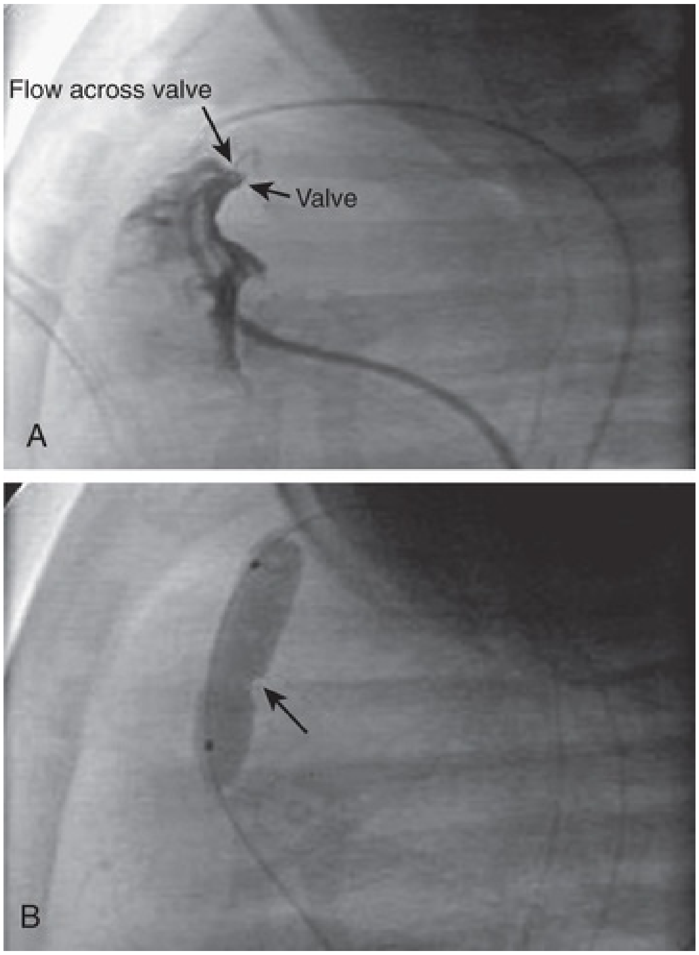

FIG. 454.4 Valvar pulmonary stenosis and balloon valvuloplasty. A, Right ventricular angiogram showing severely stenotic pulmonary valve with narrow jet of blood flowing across. B, Inflation of the balloon catheter showing the indentation *(arrow)* made on the balloon from the stenotic valve. (Photos courtesy of Dr. Jeffrey Feinstein, Stanford University, Stanford, CA.)

Excellent results are obtained in most patients. The gradient across the pulmonary valve is greatly reduced or abolished. In the early period after balloon valvuloplasty, a small to moderate residual gradient may remain because of muscular infundibular narrowing; it usually resolves with time. A short, early decrescendo diastolic murmur may be heard at the midsternal to upper left sternal border as a result of pulmonary valvular insufficiency. The degree of insufficiency is usually not clinically significant, although it can occasionally worsen over time. No difference in patient status after valvuloplasty or surgery is noted at late follow-up; recurrence is unusual after successful treatment except in those patients with extremely dysplastic valves. In the small minority of patients where the degree of pulmonary regurgitation is more severe, RV dilation may ensue, and these patients require careful follow-up and may require surgical intervention or placement of a transcatheter stent-valve.

Prognosis and Complications

Heart failure occurs only in severe cases and most often during the 1st mo of life. The development of cyanosis from a right-to-left shunt across a foramen ovale is almost exclusively seen in the neonatal period when the stenosis is severe. Infective endocarditis is a risk but is not common in childhood.

Children with mild stenosis can lead a normal life, but their progress should be evaluated at regular intervals. Patients who have small gradients rarely show progression and do not need intervention, but a significant gradient is more likely to develop in children with moderate stenosis as they grow older. Worsening of obstruction may also be caused by the development of secondary subvalvular muscular and fibrous tissue hypertrophy. In untreated severe stenosis, the course may abruptly worsen with the development of RV dysfunction and cardiac failure. Infants with critical pulmonic stenosis require urgent catheter balloon valvuloplasty or surgical valvotomy. Development of RV failure many years after pulmonary balloon valvuloplasty is uncommon. Nonetheless, patients should be followed serially for worsening pulmonary insufficiency and RV dilation.

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454.2

Infundibular Pulmonary Stenosis and Double-Chamber Right Ventricle

Daniel Bernstein

Infundibular pulmonary stenosis is caused by muscular or fibrous obstruction in the outflow tract of the right ventricle. The site of obstruction may be close to the pulmonary valve or well below it; an infundibular chamber may be present between the right ventricular cavity and the pulmonary valve. In many cases, a VSD may have been present initially and later closed spontaneously. When the pulmonary valve is also stenotic, the combined defect is primarily classified as valvular stenosis with secondary infundibular hypertrophy. The hemodynamics and clinical manifestations of patients with isolated infundibular pulmonary stenosis are similar, for the most part, to those described for isolated valvular pulmonary stenosis (see Chapter 454.1).

A common variation in RV outflow obstruction below the pulmonary valve is that of a **double-chambered right ventricle** . In this condition, a muscular band is present in the mid-RV region; the band divides the chamber into 2 parts and creates obstruction between the inlet and outlet portions. An associated VSD that may close spontaneously is often noted. Obstruction is not usually seen early in life but may progress rapidly in a similar manner to the progressive infundibular obstruction observed with tetralogy of Fallot (see Chapter 457.1).

The diagnosis of isolated RV infundibular stenosis or double-chambered right ventricle is usually made by echocardiography. The ventricular septum must be evaluated carefully to determine whether an associated VSD is present. The prognosis for untreated cases of severe RV outflow obstruction is similar to that for valvular pulmonary stenosis. When the obstruction is moderate to severe, surgery is indicated. After surgery, the pressure gradient is abolished or greatly reduced, and the long-term outlook is excellent.

454.3

Pulmonary Stenosis in Combination With an Intracardiac Shunt

Daniel Bernstein

Valvular or infundibular pulmonary stenosis, or both, may be associated with either an ASD or a VSD. In these patients the clinical features depend on the degree of pulmonary stenosis, which determines whether the net shunt is from left to right or from right to left.

The presence of a large left-to-right shunt at the atrial or ventricular level is evidence that the pulmonary stenosis is mild. These patients have symptoms similar to those of patients with an isolated ASD or VSD. With increasing age, worsening of the obstruction may limit the shunt and result in a gradual improvement in symptoms. Eventually, particularly in patients with pulmonary stenosis and VSD, a further increase in obstruction may lead to right-to-left shunting and cyanosis. When a patient with a VSD has evidence of decreasing heart failure and increased RV forces on the ECG, one must differentiate between the development of increasing pulmonary stenosis vs the onset of pulmonary vascular disease (**Eisenmenger syndrome** ; see Chapter 460.2).

These anomalies are readily repaired surgically. Defects in the atrial or ventricular septum are closed, and the pulmonary stenosis is relieved by resection of infundibular muscle or pulmonary valvotomy, or both, as indicated. Patients with a predominant right-to-left shunt have symptoms similar to those of patients with tetralogy of Fallot (see Chapter 457.1).

454.4

Peripheral Pulmonary Stenosis

Daniel Bernstein

Single or multiple constrictions may occur anywhere along the major branches of the pulmonary arteries and may range from mild to severe and from localized to extensive. Frequently, these defects are associated with other types of congenital heart disease, including valvular pulmonic stenosis, tetralogy of Fallot, patent ductus arteriosus (PDA), VSD, ASD, and supravalvular aortic stenosis. A familial tendency has been recognized in some patients with peripheral pulmonic stenosis. A high incidence is found in infants with congenital rubella syndrome. The combination of supravalvular aortic stenosis with pulmonary arterial branch stenosis, idiopathic hypercalcemia of infancy, elfin facies, and mental retardation is known as **Williams syndrome** , a condition associated with deletion of the elastin gene in region 7q11.23 on chromosome 7. Peripheral pulmonary stenosis is also associated with the **Alagille syndrome,** which may be associated with a mutation in the *JAGGED1* gene.

A mild constriction has little effect on the pulmonary circulation. With multiple severe constrictions, pressure is increased in the right ventricle and in the pulmonary artery proximal to the site of obstruction. When the anomaly is isolated, the diagnosis is suspected by the presence of murmurs in widespread locations over the chest, either anteriorly or posteriorly. These murmurs are usually systolic ejection in quality but may be continuous. Most often, the physical signs are dominated by the associated anomaly, such as tetralogy of Fallot (see Chapter 457.1).

In the immediate newborn period, a mild and transient form of peripheral pulmonic stenosis may be present. Physical findings are generally limited to a soft systolic ejection murmur, which can be heard over either or both lung fields. It is the absence of other physical findings of valvular pulmonic stenosis (RV lift, soft pulmonic S_2 , systolic ejection click, murmur loudest at upper left sternal border) that supports this diagnosis. This murmur usually disappears by age 1-2 mo.

If the stenosis is severe, the ECG shows evidence of RV and right atrial hypertrophy, and the chest radiograph shows cardiomegaly and prominence of the MPA. The pulmonary vasculature is usually normal; in some cases, however, small intrapulmonary vascular shadows are seen that represent areas of poststenotic dilation. Echocardiography is limited in its ability to visualize the distal branch pulmonary arteries. Doppler examination demonstrates the acceleration of blood flow through the stenoses and, if tricuspid regurgitation is present, allows an estimation of RV systolic pressure. MRI and CT are extremely helpful in delineating distal obstructions. If moderate to severe disease is suspected, the diagnosis is usually confirmed by cardiac catheterization.

Severe obstruction of the MPA and its primary branches can be relieved during corrective surgery for associated lesions such as the tetralogy of Fallot or valvular pulmonary stenosis. If peripheral pulmonic stenosis is isolated, it may be treated by catheter balloon dilation, sometimes with placement of an intravascular stent (see Fig. 450.29).

454.5

Aortic Stenosis

Daniel Bernstein

Pathophysiology

Congenital aortic stenosis accounts for approximately 5% of cardiac malformations recognized in childhood; a bicuspid aortic valve, one of the most common congenital heart lesions overall, is identified in up to 1.5% of adults and may be asymptomatic in childhood. Aortic stenosis is more frequent in males (3 : 1). There are families with multiple individuals affected with bicuspid aortic valve, and several genes have been implicated, including *NOTCH1* on chromosome 9q34.3.

In the most common form, **valvular aortic stenosis** , the leaflets are thickened and the commissures are fused to varying degrees. Left ventricular (LV) systolic pressure is increased as a result of the obstruction to outflow. The LV wall hypertrophies in compensation; as its compliance decreases, end-diastolic pressure increases as well.

Subvalvular (subaortic) stenosis with a discrete fibromuscular shelf below the aortic valve is also an important form of left ventricular outflow tract (LVOT) obstruction. This lesion is frequently associated with other forms of congenital heart disease such as mitral stenosis and coarctation of the aorta (**Shone syndrome**) and may progress rapidly in severity. It is less often diagnosed during early infancy and may develop despite previous documentation of no LVOT obstruction. Subvalvular aortic stenosis may become apparent after successful surgery for other congenital heart defects (coarctation of the aorta, PDA, VSD), may develop in association with mild lesions that have not been surgically repaired, or may occur as an isolated abnormality. Subvalvular aortic stenosis may also be caused by a markedly hypertrophied ventricular septum in association with hypertrophic cardiomyopathy (see Chapter 466.2).

Supravalvular aortic stenosis , the least-common type, may be sporadic, familial, or associated with **Williams syndrome** , which includes developmental delay (IQ range: 41-80), elfin facies (full face, broad forehead, flattened bridge of the nose, long upper lip, and rounded cheeks) (Fig. 454.5), as well as idiopathic hypercalcemia of infancy. Additional features include loquacious personality, hypersensitivity to sound, spasticity, hypoplastic nails, dental anomalies (partial anodontia, microdontia enamel hypoplasia), joint hypermobility, nephrocalcinosis, hypothyroidism, and poor weight gain. Narrowing of the coronary artery ostia can occur in patients with supravalvar aortic stenosis and should be carefully evaluated. Stenosis of other arteries, particularly the branch pulmonary arteries, may also be present. Williams syndrome has been shown to be caused by a deletion involving the elastin gene on chromosome 7q11.23.

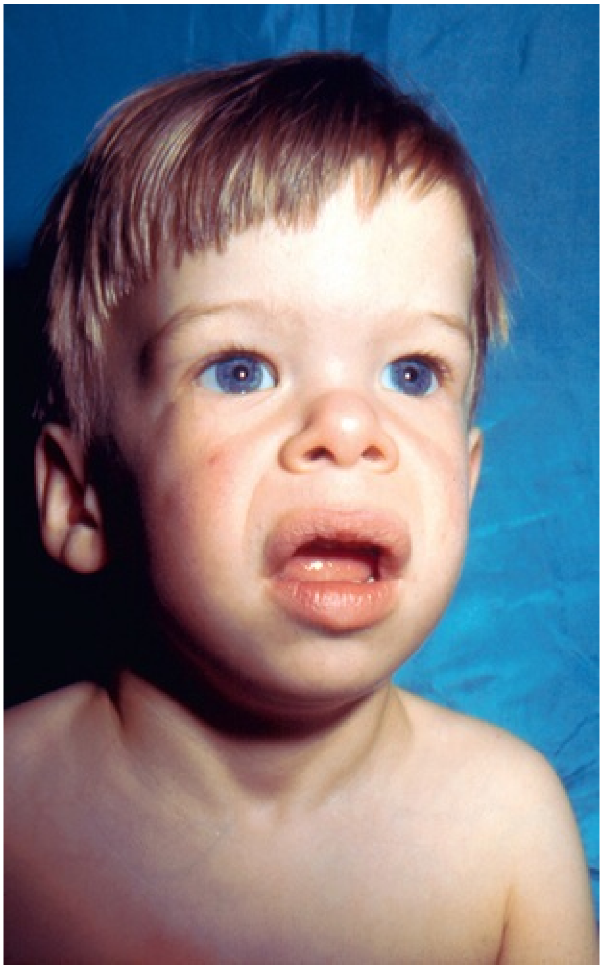

FIG. 454.5 Williams syndrome. (From Jones KL, Smith DW: The Williams elfin facies syndrome: a new perspective, *J Pediatr* 86:718, 1975.)

Clinical Manifestations

Symptoms in patients with aortic stenosis depend on the severity of the obstruction. Severe aortic stenosis that occurs in early infancy is termed **critical aortic stenosis** and is associated with LV failure and signs of low cardiac output. Heart failure, cardiomegaly, and pulmonary edema are severe, the pulses are weak in all extremities, and the skin may be pale or grayish. Urine output may be diminished. If cardiac output is significantly decreased, the intensity of the murmur at the right upper sternal border may be minimal. Most children with less severe forms of aortic stenosis remain asymptomatic and display normal growth and development. The murmur is usually discovered during routine physical examination. Rarely, fatigue, angina, dizziness, or syncope may develop in an older child with previously undiagnosed severe obstruction to LV outflow. Sudden death has been reported with aortic stenosis but usually occurs in patients with severe LVOT obstruction in whom surgical relief has been delayed.

The physical findings are dependent on the degree of obstruction to LV outflow. In mild stenosis, the pulses, heart size, and apical impulse are all normal. With increasing degrees of severity, the pulses become diminished in intensity and the heart may be enlarged, with an LV apical thrust. Mild to moderate valvular aortic stenosis is usually associated with an early systolic ejection click, best heard at the apex and left sternal edge. Unlike the click in pulmonic stenosis, its intensity does not vary with respiration. Clicks are unusual in more-severe aortic stenosis or in discrete subaortic stenosis. If the stenosis is severe, S_1 may be diminished because of decreased compliance of the thickened left ventricle. Normal splitting of S_2 is present in mild to moderate obstruction. In patients with severe obstruction, the intensity of aortic valve closure is diminished, and rarely in children, S_2 may be split paradoxically (becoming wider in expiration). A fourth heart sound (S_4) may be audible when the obstruction is severe as a result of decreased LV compliance.

The intensity, pitch, and duration of the systolic ejection murmur are other indications of severity. The louder, harsher (higher pitch), and longer the murmur, the greater is the degree of obstruction. The typical murmur is audible maximally at the right upper sternal border and radiates to the neck and the left midsternal border. It is usually accompanied by a thrill in the suprasternal notch. In patients with subvalvular aortic stenosis, the murmur may be maximal along the left sternal border or even at the apex. A soft, decrescendo diastolic murmur indicative of aortic insufficiency is often present when the obstruction is subvalvular or in patients with a bicuspid aortic valve. Occasionally, an apical short mid-diastolic rumbling murmur is audible; this murmur should raise suspicion of associated mitral valve stenosis.

Laboratory Findings and Diagnosis

The diagnosis can usually be made on the basis of the physical examination, and the severity of obstruction confirmed by laboratory tests. If the pressure gradient across the aortic valve is mild, the ECG is likely to be normal. The ECG may occasionally be normal even with more severe obstruction, but evidence of left ventricular hypertrophy (LVH) and LV strain (inverted T waves in left precordial leads) is generally present if severe stenosis is long-standing. The chest radiograph frequently shows a prominent ascending aorta, but the aortic knob is normal. Heart size is typically normal. Valvular calcification has been noted only in older children and adults. Echocardiography identifies both the site and the severity of the obstruction. Two-dimensional imaging shows LVH and the thickened and domed aortic valve (Fig. 454.6). The echo will also demonstrate the number of valve leaflets and their morphology, and the presence of a subaortic membrane or supravalvar stenosis. Associated anomalies of the mitral valve or aortic arch or a VSD or PDA are present in up to 20% of cases. In the absence of LV failure, the shortening fraction of the left ventricle may be increased because the ventricle is hypercontractile. In infants with critical aortic stenosis, the LV shortening fraction is usually decreased and may be quite poor. The endocardium may appear bright, indicative of the development of endocardial fibrous scarring, known as **endocardial fibroelastosis** . Doppler studies show the specific site of obstruction and determine the peak and mean systolic LVOT gradients. When severe aortic obstruction is associated with LV dysfunction, the Doppler-derived valve gradient may greatly underestimate the severity of the obstruction because of the low cardiac output across the valve.

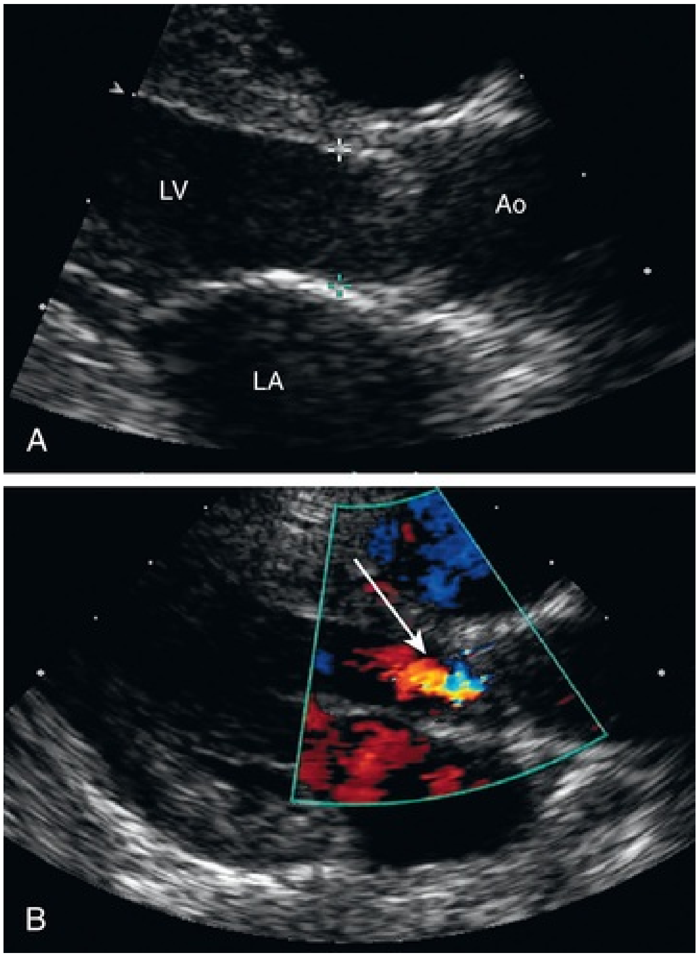

FIG. 454.6 Echocardiogram showing valvar aortic stenosis with regurgitation. A, In this parasternal long axis view, the stenotic aortic valve can be seen doming in systole. The *crosshatch* marks delineate the aortic annulus. B, Doppler study shows the presence of aortic regurgitation *(arrow).* Ao, Aorta; LA, left atrium; LV, left ventricle.

Left-sided heart catheterization, usually performed in conjunction with aortic balloon valvuloplasty, demonstrates the magnitude of the pressure gradient from the left ventricle to the aorta. The aortic pressure curve is abnormal if the obstruction is severe. In patients with severe obstruction and decreased LV compliance, left atrial pressure is increased and pulmonary hypertension may be present. When a critically ill infant with LVOT obstruction undergoes cardiac catheterization, LV function is often greatly decreased. As with the echocardiogram, the gradient measured across the stenotic aortic valve may underestimate the degree of obstruction because of low cardiac output. Actual measurement of cardiac output by thermodilution and calculation of the aortic valve area may be helpful.

Treatment

Balloon valvuloplasty is indicated for children with moderate to severe valvular aortic stenosis to prevent progressive LV dysfunction and the risk of syncope and sudden death. Valvuloplasty should be advised when the peak-to-peak systolic gradient between the left ventricle and aorta exceeds 60-70 mm Hg at rest, assuming normal cardiac output, or for lesser gradients when symptoms or electrocardiographic changes are present. For more rapidly progressive subaortic obstructive lesions, a gradient of 40-50 mm Hg or the presence of aortic insufficiency is considered an indication for surgery. Balloon valvuloplasty is the procedure of choice even in the neonatal period. Surgical treatment is usually reserved for extremely dysplastic aortic valves that are not amenable to balloon therapy or in patients who also have subvalvar or valvar (also known as *supravalvar*) stenosis.

Discrete subaortic stenosis can be resected without damage to the aortic valve, the anterior leaflet of the mitral valve, or the conduction system. This type of obstruction is not usually amenable to catheter treatment. Relief of supravalvular stenosis is also achieved surgically, and the results are excellent if the area of obstruction is discrete and not associated with a hypoplastic aorta. In association with supravalvular aortic stenosis, one or both coronary arteries may be stenotic at their origins because of a thick supraaortic fibrous ridge. For patients who have aortic stenosis in association with severe tunnel-like subaortic obstruction, the LVOT can be enlarged by “borrowing” space anteriorly from the RVOT (the **Konno procedure**).

Regardless of whether surgical or catheter treatment has been carried out, aortic insufficiency or calcification with restenosis is likely to occur years or even decades later and eventually require reoperation and often aortic valve replacement. When recurrence develops, it may not be associated with early symptoms. Signs of recurrent stenosis include electrocardiographic signs of LVH, an increase in the Doppler echocardiographic gradient, deterioration in echocardiographic indices of LV function, and recurrence of signs or symptoms during graded treadmill exercise. Evidence of significant aortic regurgitation includes symptoms of heart failure, cardiac enlargement on radiograph, and LV dilation on echocardiogram. The choice of reparative procedure depends on the relative degree of stenosis and regurgitation.

When **aortic valve replacement** is necessary, the choice of procedure often depends on the age of the patient. Homograft valves tend to calcify more rapidly in younger children, but they do not require chronic anticoagulation. Mechanical prosthetic valves are much longer lasting but require anticoagulation, which can be difficult to manage in young children. In adolescent females who are nearing childbearing age, consideration of the teratogenic effects of warfarin may warrant the use of a homograft valve. None of these options is perfect for a younger child who requires valve replacement because neither homograft nor mechanical valves grow with the patient. An alternative operation is **aortopulmonary translocation (Ross procedure)** ; it involves removing the patient's own pulmonary valve and using it to replace the abnormal aortic valve. A homograft is then placed in the pulmonary position. The potential advantage of this procedure is the possibility for growth of the translocated living “neoaortic” valve and the increased longevity of the homograft valve when placed in the lower-pressure pulmonary circulation. The long-term success of this operation, especially in young children, is still being investigated. **Transcatheter stent valves** , which are tissue valves sewn into the inside of an expandable metal stent, are currently in clinical trials in adults, mainly in those who are too ill to be candidates for standard surgical replacement. These can be implanted in the cardiac catheterization laboratory using a percutaneous approach. Tissue-engineered replacement valves grown in the laboratory from the patient's own arterial endothelial cells are another prospect for long-term palliation and are currently under development in animal models.

Prognosis

Neonates with critical aortic stenosis may have severe heart failure and deteriorate rapidly to a low-output shock state. Emergency surgery or balloon valvuloplasty is lifesaving, but the mortality risk is not trivial. Neonates who die of critical aortic stenosis frequently have significant LV endocardial fibroelastosis. Those who survive may develop signs of LV diastolic muscle dysfunction (restrictive cardiomyopathy) and require cardiac transplantation (see Chapter 470).

In older infants and children with mild to moderate aortic stenosis, the prognosis is reasonably good, although disease progression over 5-10 yr is common. Patients with aortic valve gradients <40-50 mm Hg are considered to have *mild* disease; those with gradients of 40-70 mm Hg have *moderate* disease. These patients usually respond well to treatment (either surgery or valvuloplasty), although reoperations on the aortic valve are often required later in childhood or in adult life, and many patients eventually require valve replacement. In unoperated patients with severe obstruction, sudden death is a significant risk and often occurs during or immediately after exercise. Aortic stenosis is one of the causes of sudden cardiac death in the pediatric age-group.

Patients with moderate to severe degrees of aortic stenosis should not participate in active competitive sports. In those with milder disease, sports participation is less severely restricted. The status of each patient should be reviewed at least annually and intervention advised if progression of signs or symptoms occurs. Prophylaxis against infective endocarditis is no longer recommended unless a prosthetic valve has been inserted.

Older children and adults with isolated bicuspid aortic valve are at increased risk for developing dilation of their ascending aorta, even in the absence of significant stenosis. This risk increases with age, and the rate of increase is greatest in those with the largest aortic roots. In children, this dilation is usually mild and remains stable over many years of observation, but in older patients the aorta can dilate substantially and progressively. Whether these patients have some undiagnosed form of connective tissue disorder remains to be determined (this form of dilation is similar to that seen in Marfan syndrome). Patients with Turner syndrome and bicuspid aortic valve do have an increased risk of aortic dilation. Although dissection and rupture are described complications of severe aortic root dilation in adults, there are not yet sufficient data to determine these risks in children. Only isolated cases have been reported.

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454.6

Coarctation of the Aorta

Daniel Bernstein

Constrictions of the aorta of varying degrees may occur at any point from the transverse arch to the iliac bifurcation, but 98% occur just below the origin of the left subclavian artery at the origin of the ductus arteriosus (**juxtaductal coarctation**). The anomaly occurs twice as often in males as in females. Coarctation of the aorta may be a feature of **Turner syndrome** (see Chapters 98 and 604.1) and is associated with a bicuspid aortic valve in >70% of patients. Mitral valve abnormalities (a supravalvular mitral ring or parachute mitral valve) and subaortic stenosis are potential associated lesions. When this group of left-sided obstructive lesions occurs together, they are referred to as the **Shone complex** .

Pathophysiology

Coarctation of the aorta can occur as a discrete juxtaductal obstruction or as tubular hypoplasia of the transverse aorta starting at one of the head or neck vessels and extending to the ductal area (previously referred to as *preductal* or *infantile-type coarctation;* Fig. 454.7). Often, both components are present. It is postulated that coarctation may be initiated in fetal life by the presence of a cardiac abnormality that results in decreased blood flow anterograde through the aortic valve (e.g., bicuspid aortic valve, VSD). Alternatively, coarctation may be caused by abnormal extension of contractile ductal tissue into the aortic wall.

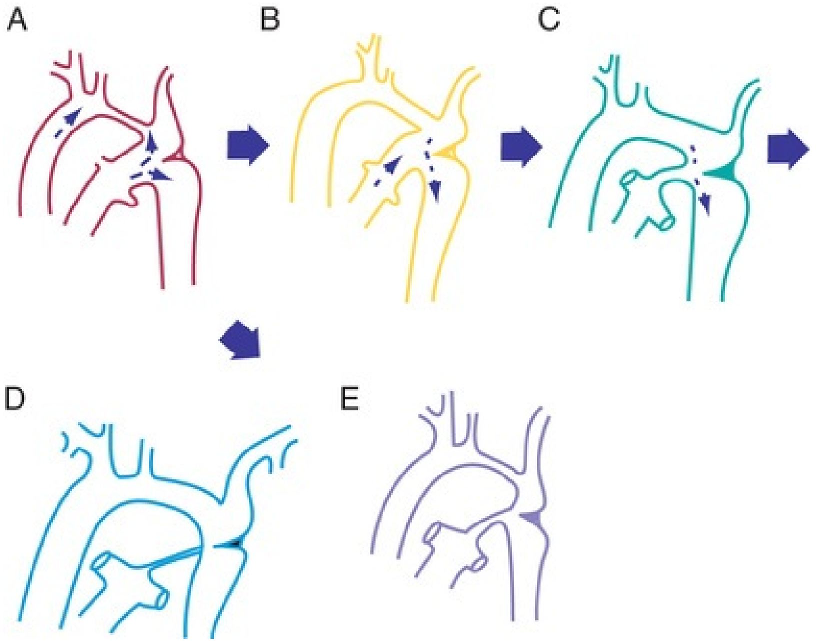

FIG. 454.7 Metamorphosis of coarctation. A, Fetal prototype with no flow obstruction. B, Late gestation. The aortic ventricle increases its output and dilates the hypoplastic segment. Antegrade aortic flow bypasses the shelf via the ductal orifice. C, Neonate. Ductal constriction initiates the obstruction by removing the bypass and increasing antegrade arch flow. D, Mature juxtaductal stenosis. The bypass is completely obliterated, and intimal hypoplasia on the edge of the shelf is aggravating the stenosis. Collaterals develop. E, Persistence of the infantile-type fetal prototype. An intracardiac left-sided heart obstruction precludes an increase in antegrade aortic flow before or after birth. Both isthmus hypoplasia and a contraductal shelf are present. Lower-body flow often depends on patency of the ductus. (From Gersony WM: Coarctation of the aorta. In Adams FH, Emmanouilides GC, Riemenshneider T, editors: *Moss heart disease in infants, children, and adolescents,* ed 4, Baltimore, 1989, Williams & Wilkins.)

In patients with discrete juxtaductal coarctation, ascending aortic blood flows through the narrowed segment to reach the descending aorta, although LV hypertension and hypertrophy result. In the 1st few days of life, the PDA may serve to widen the juxtaductal area of the aorta and provide temporary relief from the obstruction. Net left-to-right ductal shunting occurs in these acyanotic infants. With more-severe juxtaductal coarctation or in the presence of transverse arch hypoplasia, RV blood is ejected through the ductus to supply the descending aorta. Perfusion of the lower part of the body is then dependent on RV output (see Fig. 454.7). In this situation the femoral pulses are palpable, and differential blood pressures may not be helpful in making the diagnosis. The ductal right-to-left shunting is manifested as differential cyanosis, with the upper extremities being pink and the lower extremities blue.

Such infants may have severe pulmonary hypertension and high pulmonary vascular resistance. Signs of heart failure are prominent. Occasionally, severely hypoplastic segments of the aortic isthmus may become completely atretic and result in an interrupted aortic arch, with the left subclavian artery arising either proximal or distal to the interruption. Coarctation associated with arch hypoplasia was once referred to as *infantile* type because its severity usually led to recognition of the condition in early infancy. *Adult* type referred to isolated juxtaductal coarctation, which, if mild, was not usually recognized until later childhood. These terms have been replaced with the more accurate anatomic terms describing the location and severity of the defect.

Blood pressure (BP) is elevated in the vessels that arise proximal to the coarctation; BP as well as pulse pressure is lower below the constriction. The hypertension is not caused by the mechanical obstruction alone, but also involves neurohumoral mechanisms. Unless surgically corrected in infancy, coarctation of the aorta usually results in the development of an extensive collateral circulation, chiefly from branches of the subclavian, superior intercostal, and internal mammary arteries, to create channels for arterial blood to bypass the area of coarctation. The vessels contributing to the collateral circulation may become greatly enlarged and tortuous by early adulthood.

Clinical Manifestations

Coarctation of the aorta recognized after infancy is not usually associated with significant symptoms. Some children or adolescents complain about weakness or pain/claudication (or both) in the legs after exercise, but in many cases, even patients with severe coarctation are asymptomatic. Older children are frequently brought to the cardiologist's attention when they are found to be hypertensive on routine physical examination.

The classic sign of coarctation of the aorta is a disparity in pulsation and BP in the arms and legs. The femoral, popliteal, posterior tibial, and dorsalis pedis pulses are weak (or absent in up to 40% of patients), in contrast to the bounding pulses of the arms and carotid vessels. The radial and femoral pulses should always be palpated simultaneously for the presence of a **radial-femoral delay** . Normally, the femoral pulse occurs slightly before the radial pulse. A radial-femoral delay occurs when blood flow to the descending aorta is dependent on collaterals, in which case the femoral pulse is felt after the radial pulse. In normal persons (except neonates), systolic BP in the legs obtained by the cuff method is 10-20 mm Hg higher than that in the arms. In coarctation of the aorta, BP in the legs is lower than that in the arms; frequently, it is difficult to obtain. This differential in BPs is common in patients with coarctation who are older than 1 yr, approximately 90% of whom have systolic hypertension in an upper extremity >95th percentile for age. It is important to determine the BP in each arm; a BP higher in the right than the left arm suggests involvement of the left subclavian artery in the area of coarctation. Occasionally, the right subclavian may arise anomalously from below the area of coarctation and result in a left arm BP that is higher than the right. With exercise, a more prominent rise in systemic BP occurs, and the upper-to-lower extremity pressure gradient will increase.

The precordial impulse and heart sounds are usually normal; the presence of a systolic ejection click or thrill in the suprasternal notch suggests a bicuspid aortic valve (present in 70% of cases). A short systolic murmur is often heard along the left sternal border at the 3rd and 4th intercostal spaces. The murmur is well transmitted to the left infrascapular area and occasionally to the neck. Often, the typical murmur of mild aortic stenosis can be heard in the 3rd right intercostal space. Occasionally, more significant degrees of obstruction are noted across the aortic valve. The presence of a low-pitched mid-diastolic murmur at the apex suggests mitral valve stenosis. In older patients with well-developed collateral blood flow, systolic or continuous murmurs may be heard over the left and right sides of the chest laterally and posteriorly. In these patients, a palpable thrill can occasionally be appreciated in the intercostal spaces on the back.

Neonates or infants with more severe coarctation, usually including some degree of transverse arch hypoplasia, initially have signs of lower-body hypoperfusion, acidosis, and severe heart failure. These signs may be delayed days or weeks until after closure of the ductus arteriosus. If detected before ductal closure, patients may exhibit differential cyanosis, best demonstrated by simultaneous oximetry of the upper and lower extremities. On physical examination the heart is large, and a systolic murmur is heard along the left sternal border with a loud S_2 .

Diagnosis

Findings on x-ray examination depend on the age of the patient and on the effects of hypertension and the collateral circulation. Cardiac enlargement and pulmonary congestion are noted in infants with severe coarctation. During childhood, the findings are not striking until after the 1st decade, when the heart tends to be mildly or moderately enlarged because of LV prominence. The enlarged left subclavian artery typically produces a prominent shadow in the left superior mediastinum. **Notching of the inferior border of the ribs** from pressure erosion by enlarged collateral vessels is common by late childhood. In most patients the descending aorta has an area of poststenotic dilation.

The ECG is usually normal in young children but reveals evidence of LV hypertrophy in older patients. Neonates and young infants display right or biventricular hypertrophy. The segment of coarctation can generally be visualized by 2D echocardiography (Fig. 454.8); associated anomalies of the mitral and aortic valve can also be demonstrated. The descending aorta is hypopulsatile. Color Doppler is useful for demonstrating the specific site of the obstruction. Pulsed and continuous wave Doppler studies determine the pressure gradient directly at the area of coarctation; in the presence of a PDA, however, the severity of the narrowing may be underestimated. CT and MRI are valuable noninvasive tools for evaluation of coarctation when the echocardiogram is equivocal. Cardiac catheterization with selective left ventriculography and aortography is useful in occasional patients with additional anomalies and as a means of visualizing collateral blood flow. In cases that are well defined by echocardiography, CT, or MRI, diagnostic catheterization is not usually required before surgery.

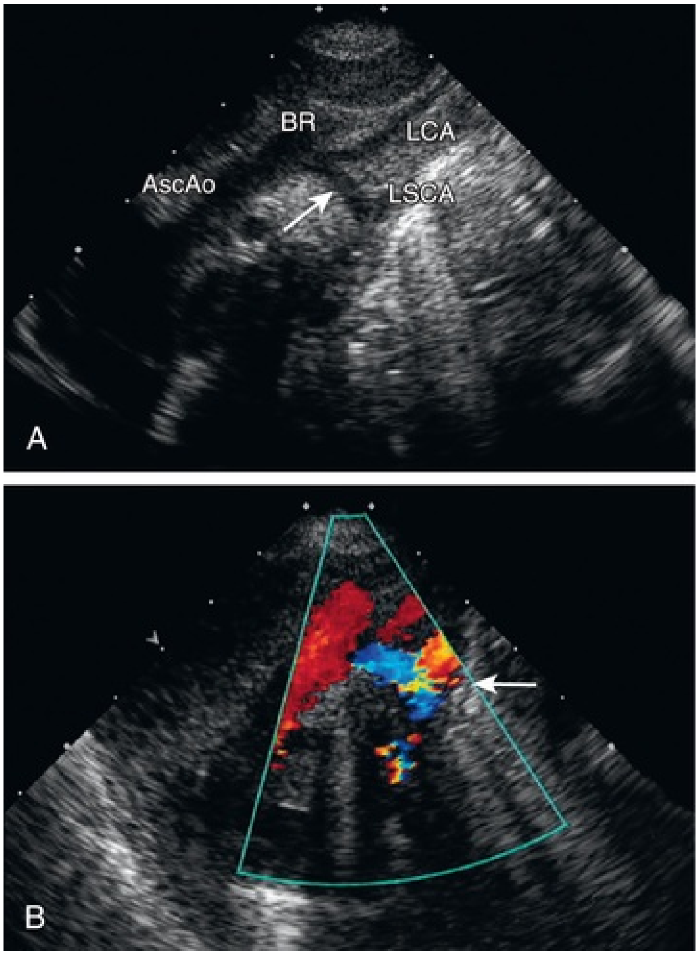

FIG. 454.8 Echocardiogram demonstrating coarctation of the aorta with hypoplastic transverse arch. A, Suprasternal notch 2D echocardiogram showing marked narrowing beginning just distal to the brachiocephalic artery. B, Color Doppler demonstrates turbulent flow in the juxtaductal area *(arrow).* AscAo, Ascending aorta; BR, brachiocephalic artery; LCA, left carotid artery; LSCA, left subclavian artery.

Treatment

In **neonates** with severe coarctation of the aorta, closure of the ductus often results in hypoperfusion, acidosis, and rapid deterioration. These patients should be given an infusion of **prostaglandin E_1** to reopen the ductus and reestablish adequate lower-extremity blood flow. Once a diagnosis has been confirmed and the patient stabilized, surgical repair should be performed. **Older infants** with heart failure but good perfusion should be managed with anticongestive measures to improve their clinical status before surgical intervention. There is usually no reason to delay surgical repair waiting for patient growth; successful repairs have been performed in small premature infants.

Older children with significant coarctation of the aorta should be treated relatively soon after diagnosis. Delay is unwarranted, especially after the 2nd decade of life, when the operation may be less successful because of decreased LV function and degenerative changes in the aortic wall. Nevertheless, if cardiac reserve is sufficient, satisfactory repair is possible well into mid-adult life.

The procedure of choice for isolated juxtaductal coarctation of the aorta is controversial. Surgery remains the treatment of choice at most centers, and several surgical techniques are used. The area of coarctation can be excised and a primary reanastomosis performed. Most often, the transverse aorta is splayed open and an “extended end-to-end” anastomosis performed to increase the effective cross-sectional area of the repair. The subclavian flap procedure, which involves division of the left subclavian artery and its incorporation into the wall of the repaired coarctation, has fallen out of favor because of a higher degree of residual stenosis. Some centers favor a patch aortoplasty, in which the area of coarctation is enlarged with a roof of prosthetic material. The use of **primary angioplasty** for native coarctation remains controversial because of concern over subsequent recoarctation, aortic dissection, and aneurysm development. The use of **primary stent placement** is under evaluation and is most useful in conditions where surgical intervention may be associated with increased risk in patients with severe LV dysfunction. In adolescents and adults, primary stenting after angioplasty has been successful for native coarctation and restenosis (Fig. 454.9). In older children, a 2nd, larger stent may be needed later to accommodate aortic growth.

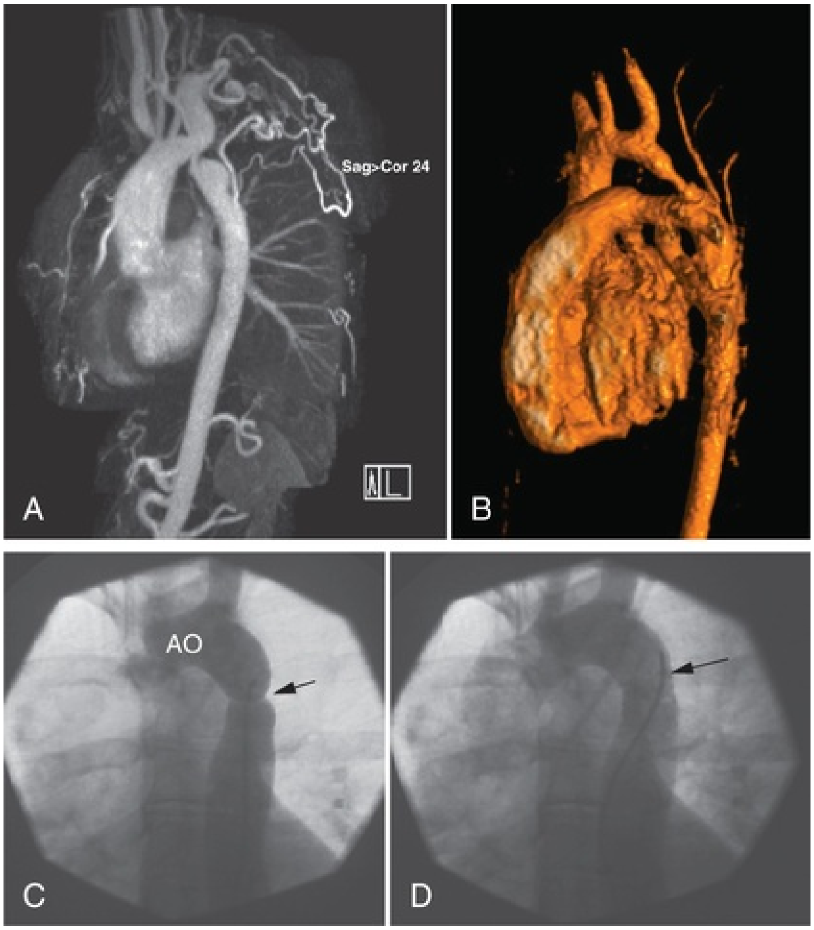

FIG. 454.9 Coarctation of the aorta. A, CT angiogram of coarcation. B, 3D reconstruction. Angiograms of the coarctation before (C) and after (D) stenting *(arrows).* AO, Aorta. (Adapted from Webb GD, Smallhorn JF, Therrien J, Redington AN: Congenital heart disease in the adult and pediatric patient. In *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2018, Elsevier, Fig 75.41, p 1561.)

After surgery, a striking increase in the amplitude of pulsations in the lower extremities is noted. In the immediate postoperative course, “rebound” hypertension can occur and requires medical management. This exaggerated acute hypertension gradually subsides, and in most patients, antihypertensive medications can be discontinued. Residual murmurs are common and may result from associated cardiac anomalies, a residual flow disturbance across the repaired area, or collateral blood flow. Rare operative problems include spinal cord injury from aortic cross-clamping (if the collaterals are poorly developed), chylothorax, diaphragm injury, and laryngeal nerve injury. If a left subclavian flap approach is used, the radial pulse and BP in the left arm are diminished or absent.

Postcoarctectomy Syndrome

Postoperative **mesenteric arteritis** may be associated with acute hypertension and abdominal pain in the immediate postoperative period. The pain varies in severity and may occur in conjunction with anorexia, nausea, vomiting, leukocytosis, intestinal hemorrhage, bowel necrosis, and small bowel obstruction. Relief is usually obtained with antihypertensive drugs (e.g., nitroprusside, esmolol, captopril) and intestinal decompression; surgical exploration is rarely required for bowel obstruction or infarction.

Prognosis

Although restenosis in older patients after coarctectomy is rare, a significant number of infants operated on before 1 yr of age require revision later in childhood. All patients should be monitored carefully for the development of recoarctation and an aortic anastomotic aneurysm. Should recoarctation occur, **balloon angioplasty** is the procedure of choice. In these patients, scar tissue from previous surgery may make reoperation more difficult yet makes balloon angioplasty safer because of the lower incidence of aneurysm formation. Relief of obstruction with this technique is usually excellent. **Intravascular stents** are typically used, especially in adolescents and young adults, with generally excellent results.

Repair of coarctation in the 2nd decade of life or beyond may be associated with a higher incidence of premature cardiovascular disease, even in the absence of residual cardiac abnormalities. Early onset of adult chronic hypertension may occur, even in patients with adequately resected coarctation.

Abnormalities of the aortic valve are present in most patients. Bicuspid aortic valves are common but do not generally produce clinical signs unless the stenosis is significant. The association of a PDA and coarctation of the aorta is also common. VSDs and ASDs may be suspected by signs of a left-to-right shunt; they are exacerbated by the increased resistance to flow through the left side of the heart. Mitral valve abnormalities are also occasionally seen, as is subvalvular aortic stenosis.

Severe neurologic damage or even death may rarely occur from associated cerebrovascular disease. Subarachnoid or intracerebral hemorrhage may result from rupture of congenital aneurysms in the circle of Willis, rupture of other vessels with defective elastic and medial tissue, or rupture of normal vessels;

these accidents are secondary to hypertension. Children with **PHACE syndrome** (posterior brain fossa anomalies, facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, eye anomalies syndrome) may have strokes (see Table 449.2). Abnormalities of the subclavian arteries may include involvement of the left subclavian artery in the area of coarctation, stenosis of the orifice of the left subclavian artery, and anomalous origin of the right subclavian artery.

Untreated, the great majority of older patients with coarctation of the aorta would succumb between ages 20 and 40 yr; some live well into middle life without serious disability. The common serious complications are related to systemic hypertension, which may result in premature coronary artery disease, heart failure, hypertensive encephalopathy, or intracranial hemorrhage. Heart failure may be worsened by associated anomalies. Infective endocarditis or endarteritis is a significant complication in adults. Aneurysms of the descending aorta or the enlarged collateral vessels may develop.

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454.7

Coarctation With Ventricular Septal Defect

Daniel Bernstein

Coarctation in the presence of a VSD results in both increased preload and afterload on the left ventricle, and patients with this combination of defects will be recognized either at birth or in the 1st mo of life and often have intractable cardiac failure. The magnitude of the left-to-right shunt through a VSD depends on the ratio of pulmonary to systemic vascular resistance. In the presence of coarctation, resistance to systemic outflow is enhanced by the obstruction, and the volume of the shunt is greatly increased. The clinical picture is that of a seriously ill infant with tachypnea, failure to thrive, and typical findings of heart failure. Often, the BP difference between the upper and lower extremities is not very marked because cardiac output may be low. Medical management should be used to stabilize the patient initially, but should not be used to delay corrective surgery inordinately.

In most cases, coarctation is the major anomaly causing the severe symptoms, and resection of the coarcted segment results in striking improvement. Many centers routinely repair both the VSD and coarctation at the same operation through a midline sternotomy using cardiopulmonary bypass. Some centers repair the coarctation through a left lateral thoracotomy and, at the same time, place a pulmonary artery band to decrease the ventricular-level shunt. This may be performed when a complicated VSD is present (multiple VSDs, apical muscular VSD), to avoid open heart surgery during infancy for these complex ventricular septal abnormalities.

454.8

Coarctation With Other Cardiac Anomalies and Interrupted Aortic Arch

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Daniel Bernstein

Coarctation often occurs in infancy in association with other major cardiovascular anomalies, including hypoplastic left heart, severe mitral or aortic valve disease, transposition of the great arteries, and variations of double-outlet or single ventricle. The clinical manifestations depend on the effects of the associated malformations, as well as on the coarctation itself.

Coarctation of the aorta associated with severe **mitral** and **aortic valve disease** may have to be treated within the context of the hypoplastic left heart syndrome (see Chapter 458.10), even if the LV chamber is not severely hypoplastic. Such patients usually have a long segment of narrow, transverse aortic arch in addition to an isolated coarctation at the site of the ductus arteriosus. Coarctation of the aorta with **transposition of the great arteries** or **single ventricle** may be repaired alone or in combination with other corrective or palliative measures.

Complete interruption of the aortic arch is the most severe form of coarctation and is usually associated with other intracardiac pathology. Interruption may occur at any level, although it is most often seen between the left subclavian artery and the insertion of the ductus arteriosus (**type A**), followed in frequency by those between the left subclavian and left carotid arteries (**type B**), or between the left carotid and brachiocephalic arteries (**type C**). In newborns with an interrupted aortic arch, the ductus arteriosus provides the sole source of blood flow to the descending aorta, and differential oxygen saturations between the right arm (normal saturation) and the legs (decreased saturation) is noted. When the ductus begins to close, severe congestive heart failure, lower-extremity hypoperfusion, anuria, and shock usually develop. Patients with an interrupted aortic arch can be supported with prostaglandin E_1 to keep the ductus patent before surgical repair. As one of the conotruncal malformations, an interrupted aortic arch, especially type B, can be associated with **DiGeorge syndrome** (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization demonstrates deletion of a segment of chromosome 22q11, known as the **DiGeorge critical region** .

454.9

Congenital Mitral Stenosis

Daniel Bernstein

Congenital mitral stenosis is a rare anomaly that can be isolated or associated with other defects, the most common being subvalvar and valvar aortic stenosis and coarctation of the aorta (**Shone complex**). The mitral valve may be funnel shaped, with thickened leaflets and chordae tendineae that are shortened and deformed. Other mitral valve anomalies associated with stenosis include **parachute** mitral valve, caused by a single papillary muscle, and **double-orifice** mitral valve.

If the stenosis is moderate to severe, symptoms usually appear within the 1st 2 yr of life. These infants have failure to thrive and various degrees of dyspnea and pallor. In some patients, wheezing may be a dominant symptom, and a misdiagnosis of bronchiolitis or reactive airway disease may have been made. Heart enlargement because of dilation and hypertrophy of the right ventricle and left atrium is common. Most patients have rumbling apical diastolic murmurs, but the auscultatory findings may be relatively obscure. S_2 is loud and split. An opening snap of the mitral valve may be present. The ECG reveals RVH and may show bifid or spiked P waves indicative of left atrial enlargement. Radiographs usually show left atrial and RV enlargement and pulmonary congestion in a perihilar or venous pattern. The echocardiogram is characteristic and shows thickened mitral valve leaflets, a significant reduction of the mitral valve orifice, abnormal papillary muscle structure (or a single papillary muscle), and an enlarged left atrium with a normal or small left ventricle. A double orifice may also be visualized. Doppler studies demonstrate a mean pressure gradient across the mitral orifice. Associated anomalies such as aortic stenosis and coarctation can be evaluated. Cardiac catheterization is usually performed to confirm the transmitral pressure gradient before surgery. An increase in RV, pulmonary artery, and pulmonary capillary wedge pressure can be noted. Angiocardiography shows delayed emptying of the left atrium and the small mitral orifice.

The results of surgical treatment depend on the anatomy of the valve, but if the mitral orifice is significantly hypoplastic, reduction of the gradient may be difficult. In some patients, a mitral valve prosthesis is required, and if the valve orifice is too small, the prosthesis may be placed in the supramitral position. However, whatever prosthesis is used, it must be replaced serially as the child grows. These patients must be managed by anticoagulation with warfarin, and complications of excessive and insufficient anticoagulation are fairly common in infancy. Transcatheter balloon valvuloplasty has been used as a palliative procedure with disappointing results, except in the situation of rheumatic mitral stenosis. Recent experience using the Melody stent-valve in selected patients in the mitral position are encouraging.

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454.10

Pulmonary Venous Hypertension

Daniel Bernstein

A variety of lesions may give rise to chronic pulmonary venous hypertension, which when extreme may result in pulmonary arterial hypertension and right-sided heart failure. These lesions include congenital **mitral stenosis** , **mitral insufficiency** , **total anomalous pulmonary venous return with obstruction** , **left atrial myxomas** , **cor triatriatum** , individual **pulmonary vein stenosis** , and **supravalvular mitral rings** . Early symptoms can be confused with chronic pulmonary disease such as asthma because of a lack of specific cardiac findings on physical examination. Subtle signs of pulmonary hypertension may be present. The ECG shows RVH with spiked P waves. Radiographic studies reveal cardiac enlargement and prominence of the pulmonary veins in the hilar region, the right ventricle and atrium, and the main pulmonary artery; the left atrium is normal in size or only slightly enlarged.

The echocardiogram may demonstrate left atrial myxoma, cor triatriatum, stenosis of 1 or more pulmonary veins, or a mitral valve abnormality, especially supravalvar mitral ring. Cardiac catheterization excludes the presence of a shunt and demonstrates pulmonary hypertension with elevated pulmonary arterial wedge pressure. Left atrial pressure is normal if the lesion is at the level of the pulmonary veins, but it is elevated if the lesion is at the level of the mitral valve. Selective pulmonary arteriography usually delineates the anatomic lesion. Cor triatriatum, left atrial myxoma, and supravalvular mitral rings can all be successfully managed surgically.

The differential diagnosis includes **pulmonary venoocclusive disease** , an idiopathic process that produces obstructive lesions in 1 or more pulmonary veins. The cause is uncertain, and disease that begins in 1 vein can spread to others. Although it is usually encountered in patients after repair of obstructed total anomalous pulmonary venous return (see Chapter 458.7), it can occur in the absence of congenital heart disease. The patient initially presents with left-sided heart failure on the basis of congested lungs with apparent pulmonary edema. Dyspnea, fatigue, and pleural effusions are common. Left atrial pressure is normal, but pulmonary arterial wedge pressure is usually elevated. A normal wedge pressure may be encountered if collaterals have formed or the wedge recording is performed in an uninvolved segment. Angiographically, the pulmonary veins return normally to the left atrium, but one or more pulmonary veins are narrowed, either focally or diffusely.

Studies using lung biopsy have demonstrated pulmonary venous and, occasionally, arterial involvement. Pulmonary veins and venules demonstrate fibrous narrowing or occlusion, and pulmonary artery thrombi may be present. Attempts at surgical repair, balloon dilation, and transcatheter stenting have not significantly improved the generally poor prognosis of these patients. Clinical trials of antiproliferative chemotherapy are currently in progress. Combined heart-lung transplantation is often the only alternative therapeutic option (see Chapter 470.2).

CHAPTER 455

Acyanotic Congenital Heart Disease

Regurgitant Lesions

455.1

Pulmonary Valvular Insufficiency and Congenital Absence of the Pulmonary Valve

Daniel Bernstein

Keywords

- pulmonary valvular insufficiency
- congenital absence of pulmonary valve
- mitral valve prolapse
- mitral insufficiency
- atrioventricular septal defect
- tricuspid regurgitation
- Ebstein anomaly

Pulmonary valvular insufficiency most often accompanies other cardiovascular diseases or may be secondary to severe **pulmonary hypertension** .

Incompetence of the valve is an expected result after surgery for right ventricular outflow tract (RVOT) obstruction, including pulmonary valvotomy in patients with **valvular pulmonic stenosis** or valvotomy with infundibular resection in patients with **tetralogy of Fallot** . Isolated congenital insufficiency of the pulmonary valve is rare. These patients are usually asymptomatic because the insufficiency is generally mild.

The prominent physical sign is a decrescendo diastolic murmur at the upper and mid-left sternal border, which has a lower pitch than the murmur of aortic insufficiency because of the lower pressure involved. Radiographs of the chest show prominence of the main pulmonary artery and, if the insufficiency is severe, right ventricular (RV) enlargement. The electrocardiogram (ECG) is normal or shows an rSR′ pattern in the right precordial leads (V_1 , V_2) and minimal RV hypertrophy. Pulsed and color Doppler studies demonstrate retrograde flow from the pulmonary artery to the right ventricle during diastole. Cardiac magnetic resonance angiography (MRA) is the best method for quantifying both RV volume and the regurgitant fraction, as well as RV systolic function (ejection fraction). Isolated pulmonary valvular insufficiency is generally well tolerated and does not require surgical treatment. When pulmonary insufficiency is severe, especially if significant tricuspid insufficiency has begun to develop, replacement with a homograft valve or transcatheter stent valve may become necessary to preserve RV function.

Congenital absence of the pulmonary valve is usually associated with a ventricular septal defect (VSD), often in the context of tetralogy of Fallot (see Chapter 457.1). In many of these neonates, the pulmonary arteries become widely dilated and compress the bronchi, with subsequent recurrent episodes of wheezing, pulmonary collapse, and pneumonitis. The presence and degree of cyanosis are variable. Florid pulmonary valvular incompetence may not be well tolerated, and death may occur from a combination of bronchial compression, hypoxemia, and heart failure. Correction involves plication of the massively dilated pulmonary arteries, closure of the VSD, and placement of a homograft across the RVOT.

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455.2

Congenital Mitral Insufficiency

Daniel Bernstein

Congenital mitral insufficiency is rare as an isolated lesion and is more often associated with other anomalies. It is most frequently encountered in combination with an **atrioventricular septal defect** , either an ostium primum defect or a complete atrioventricular septal defect (see Chapter 453.5). Mitral insufficiency is also seen in patients with dilated cardiomyopathy (see Chapter 466.1) as their left ventricular (LV) function deteriorates, secondary to dilation of the valve ring. Mitral insufficiency may also be encountered in conjunction with coarctation of the aorta, VSD, corrected transposition of the great vessels, anomalous origin of the left coronary artery from the pulmonary artery, or Marfan syndrome. In the absence of other congenital heart disease, endocarditis or rheumatic fever should be suspected in a patient with isolated severe mitral insufficiency (Table 455.1).

Table 455.1

Causes and Mechanisms of Mitral Regurgitation

	ORGANIC			**FUNCTIONAL**
	Type I*	**Type II †**	**Type IIIa ‡**	**Type I* /TYPE IIIb ‡**
Nonischemic	Endocarditis (perforation); degenerative (annular calcification); congenital (cleft leaflet)	Degenerative (billowing/flail leaflets); endocarditis (ruptured chordae); traumatic (ruptured chord/PM); rheumatic (acute RF)	Rheumatic (chronic RF); iatrogenic (radiation/drug); inflammatory (lupus/anticardiolipin), eosinophilic (endocardial disease, endomyocardial fibrosis)	Cardiomyopathy; myocarditis; left-ventricular dysfunction (any cause)
Ischemic	—	Ruptured PM	—	Functional ischemic

[*] Mechanism involves normal leaflet movement.

[†] Mechanism involves excessive valve movement.

[‡] Restricted valve movement, IIIa in diastole, IIIb in systole.

PM, Papillary muscle; RF, rheumatic fever.

Adapted from Sarano ME, Akins CW, Vahanian A: Mitral regurgitation, *Lancet* 373:1382–1394, 2009, Table 1.

In isolated mitral insufficiency, the mitral valve annulus is usually dilated, the chordae tendineae are short and may insert anomalously, and the valve leaflets are deformed. When mitral insufficiency is severe enough to cause clinical symptoms, the left atrium enlarges as a result of the regurgitant flow, and the left ventricle becomes hypertrophied and dilated. Pulmonary venous pressure is increased, and the increased pressure ultimately results in pulmonary hypertension and RV hypertrophy and dilation. Mild lesions produce no symptoms; the only abnormal sign is the apical holosystolic murmur of mitral regurgitation. Severe regurgitation results in symptoms that can appear at any age, including poor physical development, frequent respiratory infections, fatigue on exertion, and episodes of pulmonary edema or congestive heart failure. Often, a diagnosis of reactive airways disease will have been made because of the similarity in pulmonary symptoms, including wheezing, which may be a dominant finding in infants and young children.

The typical murmur of mitral insufficiency is a moderately high-pitched, apical blowing holosystolic murmur. If the insufficiency is moderate to severe, it is usually associated with a low-pitched, apical mid-diastolic rumbling murmur indicative of increased diastolic flow across the mitral valve. The pulmonic component of the second heart sound will be accentuated in the presence of pulmonary hypertension. The ECG usually shows bifid P waves consistent with left atrial enlargement, signs of LV hypertrophy, and sometimes signs of RV hypertrophy. Radiographic examination shows enlargement of the left atrium, which at times is massive. The left ventricle is prominent, and pulmonary vascularity is normal or prominent. The echocardiogram demonstrates the enlarged left atrium and ventricle. Color Doppler demonstrates the extent of the insufficiency, and pulsed Doppler of the pulmonary veins detects retrograde flow when mitral insufficiency is severe. Cardiac catheterization shows elevated left atrial pressure. Pulmonary artery hypertension of varying severity may be present. Selective left ventriculography reveals the severity of mitral regurgitation.

Mitral valvuloplasty can result in striking improvement in symptoms and heart size, but in some patients, installation of a prosthetic mechanical mitral valve may be necessary. Before surgery, associated anomalies must be identified. Clinical studies using stent-valves in the mitral position show early encouraging results in selected patients.

455.3

Mitral Valve Prolapse

Daniel Bernstein

Mitral valve prolapse results from an abnormal mitral valve mechanism that causes billowing of 1 or both mitral leaflets, especially the posterior cusp, into the left atrium toward the end of systole. The abnormality is predominantly congenital but may not be recognized until adolescence or adulthood. Mitral valve prolapse is usually sporadic, is more common in girls, and may be inherited as an autosomal dominant trait with variable expression. It is common in patients with Marfan syndrome, straight back syndrome, pectus excavatum, scoliosis, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. The dominant abnormal signs are auscultatory, although occasional patients may have chest pain or palpitations. The apical murmur is late systolic and may be preceded by a click, but these signs may vary in the same patient, and at times, only the click is audible. In the standing or sitting position the click may occur earlier in systole, and the murmur may be more prominent in late systole. Arrhythmias may occur and are primarily unifocal or multifocal premature ventricular contractions.

The ECG is usually normal but may show biphasic T waves, especially in leads II, III, aVF, and V_6 ; the T-wave abnormalities may vary at different times in the same patient. The chest radiograph is normal. The echocardiogram shows a characteristic posterior movement of the posterior mitral leaflet during mid- or late systole or demonstrates pansystolic prolapse of both the anterior and posterior mitral leaflets. These echocardiographic findings must be interpreted cautiously because the appearance of minimal mitral prolapse may be a normal variant. Prolapse is more precisely defined by single or bileaflet prolapse of >2 mm beyond the long axis annular plane with or without leaflet thickening. Prolapse with valve thickening >5 mm is “classic”; a lesser degree is “nonclassic.” Two-dimensional real-time echocardiography shows that both the free edge and the body of the mitral leaflets move posteriorly in systole toward the left atrium. Doppler can assess the presence and severity of mitral regurgitation.

This lesion is not progressive in childhood, and specific therapy is not indicated. Antibiotic prophylaxis is no longer recommended during surgery and dental procedures (see Chapter 464).

Adults (men more often than women) with mitral valve prolapse are at increased risk for cardiovascular complications (sudden death, arrhythmia, cerebrovascular accident, progressive valve dilation, heart failure, and endocarditis) in the presence of thickened (>5 mm) and redundant mitral valve leaflets. Risk factors for morbidity also include poor LV function, moderate to severe mitral regurgitation, and left atrial enlargement.

Often, confusion exists concerning the diagnosis of mitral valve prolapse. The high frequency of mild prolapse on the echocardiogram in the absence of clinical findings suggests that, in these cases, true mitral valve prolapse syndrome is not present. These patients and their parents should be reassured of this fact, and no special recommendations should be made regarding management or frequent laboratory studies.

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455.4

Tricuspid Regurgitation

Daniel Bernstein

Isolated tricuspid regurgitation is most often associated with **Ebstein anomaly of the tricuspid valve** . Ebstein anomaly may occur either without cyanosis or with varying degrees of cyanosis, depending on the severity of the tricuspid regurgitation and the presence of an atrial-level communication (patent foramen ovale or atrial septal defect). Older children tend to have the acyanotic form, whereas if detected in the newborn period, Ebstein anomaly is usually associated with severe cyanosis (see Chapter 457.7).

Tricuspid regurgitation often accompanies RV dysfunction. When the right ventricle becomes dilated because of volume overload or intrinsic myocardial disease, or both, the tricuspid annulus also enlarges, with resultant valve insufficiency. This form of regurgitation may improve if the cause of the RV dilation is corrected, or it may require surgical plication of the valve annulus. Tricuspid regurgitation is also encountered in newborns with perinatal asphyxia. The cause may be related to an increased susceptibility of the papillary muscles to ischemic damage and subsequent transient papillary muscle dysfunction. Lastly, tricuspid regurgitation is seen in up to 30% of children after heart transplantation, which can be a risk factor for graft dysfunction, but is also seen as a result of valve injury caused by endomyocardial biopsy.

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CHAPTER 456

Cyanotic Congenital Heart Disease

Evaluation of the Critically Ill Neonate With Cyanosis and Respiratory Distress

Daniel Bernstein

See also Chapter 122 .

A severely ill neonate with cardiorespiratory distress and cyanosis is a diagnostic challenge. The clinician must perform a rapid evaluation to determine whether congenital heart disease is a cause so that potentially lifesaving measures can be instituted. The differential diagnosis of neonatal cyanosis is presented in Table 119.2 (Chapter 119).

Cardiac Disease Leading to Cyanosis

Congenital heart disease (CHD) produces cyanosis when obstruction to right ventricular inflow or outflow causes intracardiac right-to-left shunting or when complex anatomic defects cause an admixture of pulmonary (deoxygenated) and systemic (oxygenated) venous return in the heart. Cyanosis from pulmonary edema may also develop in patients with heart failure caused by left-to-right shunts, although the degree is usually less severe. Cyanosis may be caused by persistence of fetal pathways, such as right-to-left shunting across the foramen ovale and ductus arteriosus in the presence of pulmonary outflow tract obstruction or **persistent pulmonary hypertension of the newborn (PPHN)** (see Chapter 122.9).

Differential Diagnosis

The **hyperoxia test** is one method of distinguishing cyanotic CHD from pulmonary disease. Neonates with cyanotic CHD usually are unable to significantly raise their arterial blood partial pressure of oxygen (Pa_{O_2}) during administration of 100% oxygen. This test is usually performed using a hood rather than nasal cannula or face mask, to best guarantee delivery of almost 100% oxygen to the patient. False-positive tests can occur if this is not done correctly. If the Pa_{O_2} rises above 150 mm Hg during 100% oxygen administration, an intracardiac right-to-left shunt can usually be excluded. This is not 100% confirmative, however, because some patients with cyanotic CHD may be able to increase their Pa_{O_2} to >150 mm Hg because of favorable intracardiac streaming patterns. In patients with pulmonary disease, Pa_{O_2} generally increases significantly with 100% oxygen as ventilation-perfusion inequalities are overcome. In infants with cyanosis from a central nervous system disorder, the Pa_{O_2} usually normalizes completely during artificial ventilation. Hypoxia in many heart lesions is profound and constant, whereas in respiratory disorders and in PPHN, Pa_{O_2} often varies with time or changes in ventilator management. Hyperventilation may improve the hypoxia in neonates with PPHN and only occasionally in those with cyanotic CHD.

Although a significant heart murmur usually suggests a cardiac basis for the cyanosis, several of the more severe cardiac defects (e.g., transposition of the great vessels) may not initially be associated with a murmur. The chest radiograph may be helpful in the differentiation of pulmonary and cardiac disease; in the latter, it indicates whether pulmonary blood flow is increased, normal, or decreased (Fig. 456.1).

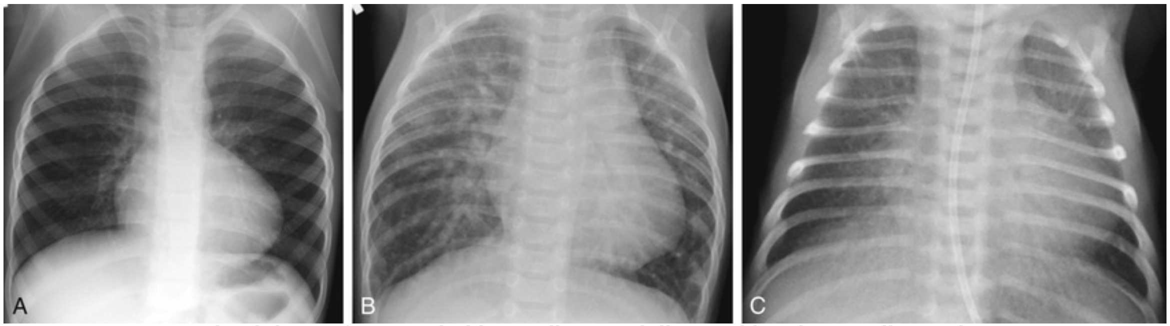

FIG. 456.1 **Physiology of congenital heart disease delineated by chest radiography. A,**

Mild cardiomegaly with an upturned cardiac apex, a concave main pulmonary artery segment, and symmetric, severely diminished pulmonary blood flow in a 4 yr old child with tetralogy of Fallot/pulmonary atresia. B, Moderate cardiomegaly and symmetric, increased pulmonary blood flow in a 3 mo old infant with a large atrial septal defect and ventricular septal defect. C, Moderate cardiomegaly with interstitial edema in an 8 day old newborn with critical aortic stenosis. (From Frost JL, Krishnamurthy R, Sena L: Cardiac imaging. In Walters MM, Robertson RL, editors: *Pediatric radiology—the requisites,* ed 4, Philadelphia, 2017, Elsevier, Fig 3.9, p 68.)

Two-dimensional echocardiography with Doppler is the definitive noninvasive test to determine the presence of CHD. Cardiac catheterization is less often used for diagnostic purposes and is usually performed to examine structures that are sometime less well visualized by echocardiography, such as distal branch pulmonary arteries or aortopulmonary collateral arteries in patients with tetralogy of Fallot with pulmonary atresia (see Chapter 457.2), or coronary arteries and right ventricular sinusoids in patients with pulmonary atresia and intact ventricular septum (see Chapter 457.3). If echocardiography is not immediately available to confirm a diagnosis of cyanotic CHD, the clinician caring for a newborn with possible cyanotic CHD should not hesitate to start a prostaglandin infusion (for a possible ductal-dependent lesion). Because of the risk of hypoventilation associated with prostaglandins, a practitioner skilled in neonatal endotracheal intubation must be available.

CHAPTER 457

Cyanotic Congenital Heart Disease

Lesions Associated With Decreased Pulmonary Blood Flow

457.1

Tetralogy of Fallot

Daniel Bernstein

Tetralogy of Fallot is one of the **conotruncal** family of heart lesions in which the primary defect is an anterior deviation of the *infundibular septum* (the muscular septum that separates the aortic and pulmonary outflows). The consequences of this deviation are the 4 components: (1) obstruction to right ventricular (RV) outflow (pulmonary stenosis), (2) a malalignment type of ventricular septal defect (VSD), (3) dextroposition of the aorta so that it overrides the ventricular septum, and (4) right ventricular hypertrophy (Fig. 457.1). Obstruction to pulmonary artery blood flow is usually at both the right ventricular infundibulum (subpulmonic area) and the pulmonary valve. The main pulmonary artery (MPA) may also be small, and various degrees of branch pulmonary artery stenosis may be present. Complete obstruction of RV outflow (tetralogy with pulmonary atresia) is classified as an *extreme* form of tetralogy of Fallot (see Chapter 457.2). The degree of pulmonary outflow obstruction and whether the ductus arteriosus is open or closed determine the degree of the patient's cyanosis and the age at first presentation.

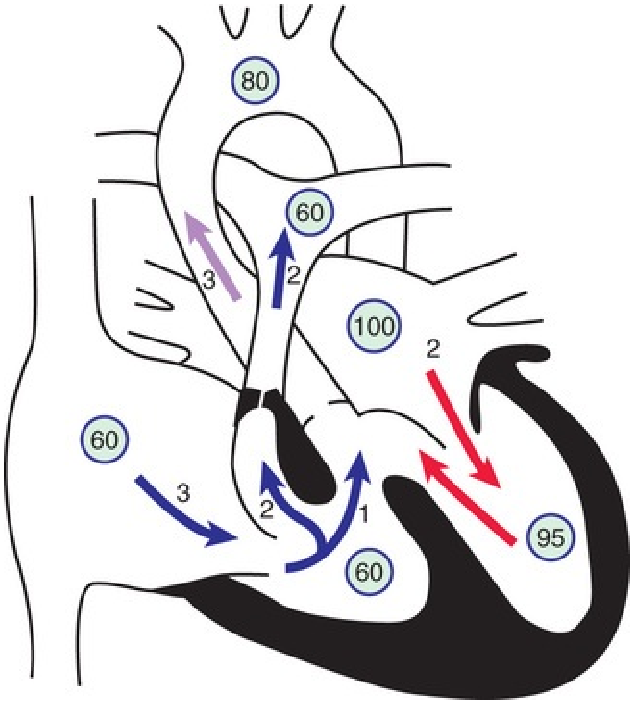

FIG. 457.1 Physiology of tetralogy of Fallot. *Circled numbers* represent oxygen saturation values. The *numbers next to the arrows* represent volumes of blood flow (in L/min/m^2). Atrial (mixed venous) oxygen saturation is decreased because of the systemic hypoxemia. A volume of 3 L/min/m^2 of desaturated blood enters the right atrium and traverses the tricuspid valve. Two liters flows through the right ventricular outflow tract into the lungs, whereas 1 L shunts right to left through the ventricular septal defect (VSD) into the ascending aorta. Thus, pulmonary blood flow is two-thirds normal (Qp:Qs [pulmonary-to-systemic blood flow ratio] of 0.7 : 1). Blood returning to the left atrium is fully saturated. Only 2 L of blood flows across the mitral valve. Oxygen saturation in the left ventricle may be slightly decreased because of right-to-left shunting across the VSD. Two liters of saturated left ventricular blood mixing with 1 L of desaturated right ventricular blood is ejected into the ascending aorta. Aortic saturation is decreased, and cardiac output is normal.

Pathophysiology

The pulmonary valve annulus may range from being nearly normal in size to being severely hypoplastic. The valve itself is often bicuspid or unicuspid and, occasionally, is the only site of stenosis. More often, the subpulmonic or infundibular muscle, known as the *crista supraventricularis,* is hypertrophic, which contributes to the subvalvar stenosis and results in an infundibular chamber of variable size and contour. When the right ventricular outflow tract (RVOT) is completely obstructed (**pulmonary atresia**), the anatomy of the branch pulmonary arteries is extremely variable. An MPA segment may be in continuity with right ventricular outflow, separated by a fibrous but imperforate pulmonary valve; the MPA may be moderately or severely hypoplastic but still supply part or all of the pulmonary bed; or the entire main pulmonary artery segment may be absent. Occasionally, the branch pulmonary arteries may be discontinuous. Pulmonary blood flow may be supplied by a **patent ductus arteriosus** (PDA) or by multiple **major aortopulmonary collateral arteries** (MAPCAs) arising from the ascending and/or descending aorta and supplying various lung segments.

The VSD is usually nonrestrictive and large, is located just below the aortic valve, and is related to the posterior and right aortic cusps. Rarely, the VSD may be in the inlet portion of the ventricular septum (atrioventricular septal defect). The normal fibrous continuity of the mitral and aortic valves is usually maintained, and if not (because of the presence of a subaortic muscular conus), the classification is usually that of **double-outlet right ventricle** (DORV) instead of tetralogy of Fallot (see Chapter 457.5). The aortic arch is right sided in 20% of cases, and the aortic root is usually large and overrides the VSD to varying degrees. When the aorta overrides the VSD by >50% (in which case they may also be a subaortic conus) this defect may be classified as a form of DORV; however, the circulatory dynamics and the method of repair are the same as for tetralogy of Fallot.

Systemic venous return to the right atrium and right ventricle is normal. When the right ventricle contracts in the presence of marked pulmonary stenosis, blood is shunted across the VSD into the aorta. Persistent arterial desaturation and cyanosis result, with the degree of abnormality dependent on the severity of the pulmonary obstruction. Pulmonary blood flow, when severely restricted by the obstruction to RV outflow, may be supplemented by a PDA. Peak systolic and diastolic pressures in each ventricle are similar and at systemic level. A large pressure gradient occurs across the obstructed RVOT, and pulmonary artery pressure is either normal or lower than normal. The degree of RV outflow obstruction determines the timing of the onset of symptoms, the severity of cyanosis, and the degree of **right ventricular hypertrophy** (RVH). When obstruction to RV outflow is mild to moderate and a balanced shunt is present across the VSD, the patient may not be visibly cyanotic (**acyanotic** or “pink” tetralogy of Fallot). When obstruction is severe, cyanosis will be present from birth and worsen when the ductus arteriosus begins to close.

Clinical Manifestations

Infants with mild degrees of RV outflow obstruction may initially even have symptoms of heart failure caused by a ventricular-level left-to-right shunt. In these patients, cyanosis is not present at birth; but with increasing hypertrophy of the RV infundibulum as the patient grows, cyanosis occurs later in the 1st few mo of life. In contrast, in infants with severe degrees of RV outflow obstruction, neonatal cyanosis is noted immediately. In these infants, pulmonary blood flow may be partially or almost totally dependent on flow through the ductus arteriosus. When the ductus begins to close in the 1st few hr or days of life, severe cyanosis and circulatory collapse may occur. All degrees of variation exist between these 2 clinical extremes. Older children with long-standing cyanosis who have not undergone surgery may have dusky blue skin, gray sclerae with engorged blood vessels, and marked clubbing of the fingers and toes. Chapter 461 describes the extracardiac manifestations of long-standing cyanotic congenital heart disease.

In older children with unrepaired tetralogy, dyspnea occurs on exertion. They may play actively for a short time and then sit or lie down. Older children may be able to walk a block or so before stopping to rest. Characteristically, children assume a **squatting** position for the relief of dyspnea caused by physical effort; the child is usually able to resume physical activity after a few minutes of squatting. These findings occur most often in patients with significant cyanosis at rest.

Paroxysmal hypercyanotic attacks (hypoxic, “blue,” or “tet” spells) are a problem during the 1st year of life. The infant becomes hyperpneic and restless, cyanosis increases, gasping respirations ensue, and syncope may follow. The spells occur most frequently in the morning on initially awakening or after episodes of vigorous crying. Temporary disappearance or a decrease in intensity of the systolic murmur is usual as flow across the RVOT diminishes during the spell. Tet spells may last from a few minutes to a few hours. Short episodes are followed by generalized weakness and sleep. Severe spells may progress to unconsciousness and occasionally to convulsions or hemiparesis. The onset is usually spontaneous and unpredictable. Spells are associated with reduction of an already compromised pulmonary blood flow, which, when prolonged, results in severe systemic hypoxia and metabolic acidosis. Infants who are only mildly cyanotic at rest may be more prone to the development of hypoxic spells because they have not acquired the homeostatic mechanisms to tolerate rapid lowering of arterial oxyhemoglobin saturation ($Sa\textsc{o}_2$), such as polycythemia.

Depending on the frequency and severity of hypercyanotic attacks, 1 or more of the following procedures should be instituted in sequence: (1) placement of the infant on the abdomen in the knee-chest position while making certain that the infant's clothing is not constrictive, (2) administration of oxygen (although increasing inspired oxygen will not reverse cyanosis caused by intracardiac shunting), and (3) injection of morphine subcutaneously in a dose not in excess of 0.2 mg/kg. Calming and holding the infant in a knee-chest position may abort progression of an early spell. Premature attempts to obtain blood samples may cause further agitation and may be counterproductive.

Because metabolic acidosis develops when arterial oxygen tension ($\text{Pa}O_2$) is <40 mm Hg, rapid correction (within several minutes) with intravenous (IV) administration of sodium bicarbonate is necessary if the spell is unusually severe and the child shows a lack of response to the foregoing therapy. Recovery from the spell is usually rapid once the pH has returned to normal. Repeated blood pH measurements may be necessary because rapid recurrence of acidosis may ensue. For spells that are resistant to this therapy, intubation and anesthetic sedation are often sufficient to break the spell. Drugs that increase systemic vascular resistance, such as IV phenylephrine, can improve RV outflow, decrease the right-to-left shunt, and improve the symptoms. β-Adrenergic blockade by the IV administration of propranolol (0.1 mg/kg given slowly to a maximum of 0.2 mg/kg) has also been used.

Growth and development may be delayed in patients with severe untreated tetralogy of Fallot, particularly when their $\text{Sa}O_2$ is chronically <70%. Puberty may also be delayed in patients who have not undergone surgery.

The pulse is usually normal, as are venous and arterial pressures. In older infants and children, the left anterior hemithorax may bulge anteriorly because of long-standing RVH. A substernal RV impulse can usually be detected. A systolic thrill may be felt along the left sternal border in the 3rd and 4th parasternal spaces. The systolic murmur is usually loud and harsh; it may be transmitted widely, especially to the lungs, but is most intense at the left sternal border. The murmur is generally ejection in quality at the upper sternal border, but it may sound more holosystolic toward the lower sternal border. It may be preceded by a click. The murmur is caused by turbulence through the RVOT. It tends to become louder, longer, and harsher as the severity of pulmonary stenosis increases from mild to moderate; however, it can actually become less prominent with severe obstruction, especially during a hypercyanotic spell, because of shunting of blood away from the RV outflow through the aortic valve. Either the second heart sound (S_2) is single, or the pulmonic component is soft because of the decreased excursion of the stenotic valve. Infrequently, a continuous murmur may be audible, especially if prominent collaterals are present.

Diagnosis

The typical radiologic configuration as seen in the anteroposterior (AP) view consists of a narrow base, concavity of the left heart border in the area usually occupied by the pulmonary artery, and normal overall heart size. The hypertrophied right ventricle causes the rounded apical shadow to be uptilted so that it is situated higher above the diaphragm than normal and pointing horizontally to the left chest wall. The cardiac silhouette has been likened to that of a *boot* (“coeur en sabot”) (Fig. 457.2). The hilar areas and lung fields are relatively clear because of diminished pulmonary blood flow or the small size of the pulmonary arteries, or both. The aorta is usually large, and in approximately 20% of patients it arches to the right, which results in an indentation of the leftward-positioned air-filled tracheobronchial shadow in the AP view.

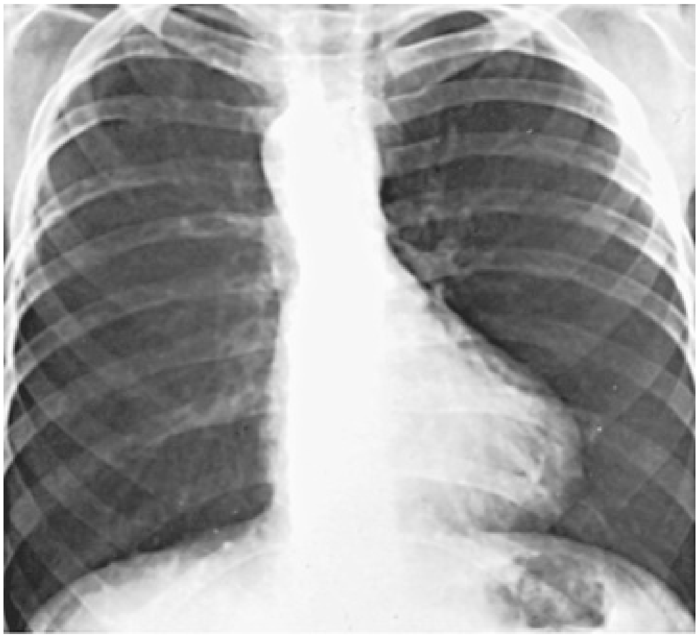

FIG. 457.2 **Chest radiograph of 8 yr old boy with tetralogy of Fallot. Note the normal heart size, some elevation of the cardiac apex, concavity in the region of the main pulmonary artery, right-sided aortic arch, and diminished pulmonary vascularity.**

The electrocardiogram (ECG) demonstrates right axis deviation and evidence of RVH. A dominant R wave appears in the right precordial chest leads (V_1 , V_2) or an RSR′ pattern. In some cases the only sign of RVH may initially be a positive T wave in leads V_3 R and V_1 . The P wave may be tall and peaked, suggesting right atrial enlargement (see Chapter 450 , Fig. 450.6).

Two-dimensional (2D) echocardiography with Doppler establishes the diagnosis (Fig. 457.3) and provides information about the extent of aortic override of the septum, the location and degree of the RVOT obstruction, the size of the pulmonary valve annulus and main and proximal branch pulmonary arteries, and the side of the aortic arch. The echocardiogram is also useful in determining whether a PDA is supplying a portion of the pulmonary blood flow. In a patient with tetralogy of Fallot without pulmonary atresia, echocardiography usually obviates the need for catheterization before surgical repair. However, in patients with pulmonary atresia, catheterization is necessary to image the source of blood supply to and size of each lung vascular segment.

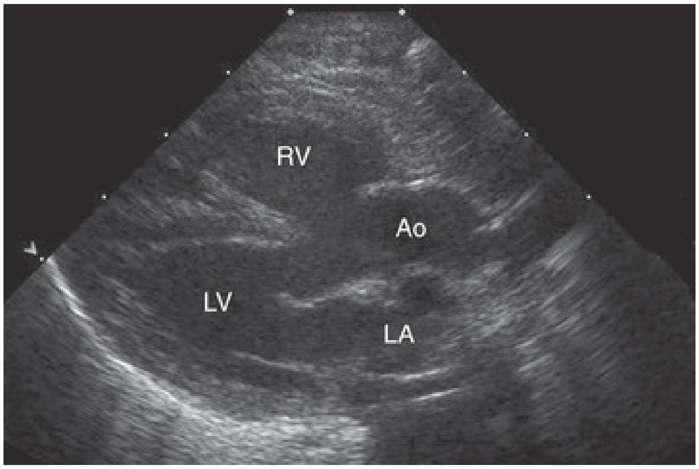

FIG. 457.3 **Echocardiogram in patient with tetralogy of Fallot. This parasternal long axis 2D view demonstrates anterior displacement of the outflow ventricular septum that resulted in stenosis of the subpulmonic right ventricular outflow tract, overriding of the aorta, and an associated ventricular septal defect. Ao, Overriding aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.**

Cardiac catheterization demonstrates a systolic pressure in the right ventricle equal to the systemic pressure, since the right ventricle is connected directly to the overriding aorta. If the pulmonary artery is entered, the pressure is greatly decreased, although crossing the RVOT, especially in severe cases, may precipitate a tet spell. Pulmonary artery pressure is usually lower than normal, in the range of 5-10 mm Hg. The Sa_{O_2} level depends on the magnitude of the right-to-left shunt; in “pink tets,” the systemic So_2 may be normal, whereas in a moderately cyanotic patient at rest, it is usually 75–85%.

Selective right ventriculography will demonstrate all the anatomic features. Contrast medium outlines the heavily trabeculated right ventricle. The infundibular stenosis varies in length, width, contour, and distensibility (Fig. 457.4). The pulmonary valve is usually thickened, and the annulus may be small. In patients with tetralogy and pulmonary atresia, echocardiography alone is not adequate to assess the anatomy of the true pulmonary arteries and collateral MAPCAs. Cardiac CT is extremely helpful, and cardiac catheterization with injection into each arterial collateral is indicated. Complete and accurate information regarding the size and peripheral distribution of the main pulmonary arteries and any collateral vessels (MAPCAs) is important when evaluating these children as surgical candidates.

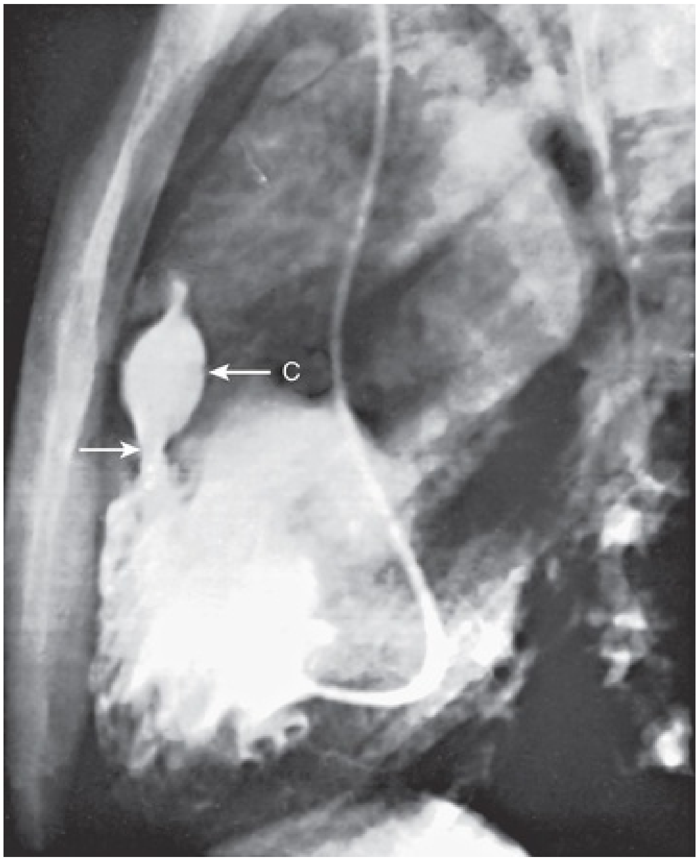

FIG. 457.4 **Lateral view of selective right ventriculogram in patient with tetralogy of Fallot. The *left arrow* points to an infundibular stenosis that is below the infundibular chamber (C). The narrowed pulmonary valve orifice is seen at the distal end of the infundibular chamber.**

Aortography or coronary arteriography outlines the course of the coronary arteries. In 5–10% of patients with the tetralogy of Fallot, coronary artery abnormalities may be present, most often an aberrant coronary artery crossing over the RVOT; this artery must not be cut during surgical repair. Verification of normal coronary arteries is important when considering surgery in young infants who may need a patch across the pulmonary valve annulus. Echocardiography can usually delineate the coronary artery anatomy; angiography is reserved for cases in which questions remain.

Complications

Before the advent of corrective surgery, patients with tetralogy of Fallot were susceptible to several serious complications. For this reason, most children undergo complete repair (or in some cases palliation) in the 1st few mo of life; consequently, these complications are now rare. **Cerebral thromboses,** usually occurring in the cerebral veins or dural sinuses and occasionally in the cerebral arteries, are sequelae of extreme polycythemia and dehydration. Thromboses occur most often in patients younger than 2 yr. These patients may have iron-deficiency anemia, frequently with hemoglobin and hematocrit levels in the normal range (but too low for cyanotic heart disease). Therapy consists of adequate hydration and supportive measures. Phlebotomy and volume replacement with albumin or saline are indicated in extremely polycythemic patients who are symptomatic.

Brain abscess is less common than cerebrovascular events and extremely rare today. Patients with a brain abscess are usually older than 2 yr. The onset of the illness is often insidious and consists of low-grade fever or a gradual change in behavior, or both. Some patients have an acute onset of symptoms that may develop after a recent history of headache, nausea, and vomiting. Seizures may occur; localized neurologic signs depend on the site and size of the abscess and the presence of increased intracranial pressure. CT or MRI confirms the diagnosis. Antibiotic therapy may help keep the infection localized, but surgical drainage of the abscess is usually necessary (see Chapter 622).

Bacterial endocarditis may occur in the right ventricular infundibulum or on the pulmonic, aortic, or rarely tricuspid valve. Endocarditis may complicate palliative shunts or, in patients with corrective surgery, any residual pulmonic stenosis or VSD. Heart failure is not a usual feature in patients with tetralogy of

Fallot, with the exception of some young infants with “pink” or acyanotic tetralogy of Fallot. As the degree of pulmonary obstruction worsens with age, the symptoms of heart failure resolve, and eventually the patient experiences cyanosis, usually by 4-6 mo of age. These patients are at increased risk for hypercyanotic spells at this time.

Associated Anomalies

A PDA may be present, and defects in the atrial septum are occasionally seen. A right aortic arch occurs in approximately 20% of patients, and other anomalies of the pulmonary arteries and aortic arch may also be seen. Persistence of a left superior vena cava draining into the coronary sinus is common but not a concern. Multiple VSDs are occasionally present and must be diagnosed before corrective surgery. Coronary artery anomalies are present in 5–10% and can complicate surgical repair. Tetralogy of Fallot may also occur with an atrioventricular septal defect, often associated with Down syndrome.

Congenital absence of the pulmonary valve produces a distinct syndrome that is usually marked by signs of upper airway obstruction (see Chapter 455.1). Cyanosis may be absent, mild, or moderate; the heart is large and hyperdynamic; and a loud to-and-fro murmur is present. Marked aneurysmal dilation of the main and branch pulmonary arteries results in compression of the bronchi and then produces stridulous or wheezing respirations and recurrent pneumonia. If the airway obstruction is severe, reconstruction of the trachea at the time of corrective cardiac surgery may be required to alleviate the symptoms.

Absence of a branch pulmonary artery , most often the left, should be suspected if the radiographic appearance of the pulmonary vasculature differs on the 2 sides; absence of a pulmonary artery is often associated with hypoplasia of the affected lung. It is important to recognize the absence of a pulmonary artery because occlusion of the remaining pulmonary artery during surgery seriously compromises the already reduced pulmonary blood flow.

As one of the conotruncal malformations, tetralogy of Fallot can be associated with **DiGeorge syndrome** or **velocardiofacial syndrome** , also known by the acronym **CATCH 22** (cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, hypocalcemia). Cytogenetic analysis using fluorescence in situ hybridization (FISH) demonstrates deletions of a large segment of **chromosome 22q11.2** known as the **DiGeorge critical region** . Deletion or mutation of the gene encoding the transcription factor *Tbx1* has been implicated as a possible cause of DiGeorge syndrome, although several other genes have been identified as possible candidates or as modifier genes.

Treatment

Treatment of tetralogy of Fallot depends on the severity of the RVOT obstruction. Infants with severe tetralogy require urgent medical treatment and surgical intervention in the neonatal period. Therapy is aimed at providing an immediate increase in pulmonary blood flow to prevent the sequelae of severe hypoxia. The infant should be transported to a medical center adequately equipped to evaluate and treat neonates with congenital heart disease (CHD) under optimal conditions. Prolonged, severe hypoxia may lead to shock, respiratory failure, and intractable acidosis and will significantly reduce the chance of survival, even when surgically amenable lesions are present. It is critical that normal body temperature be maintained during the transfer because cold increases oxygen consumption, which places additional stress on a cyanotic infant, whose oxygen delivery is already limited. Blood glucose levels should be monitored because hypoglycemia is more likely to develop in infants with cyanotic heart disease.

Neonates with marked RVOT obstruction may deteriorate rapidly because, as the ductus arteriosus begins to close, pulmonary blood flow is further compromised. The IV administration of **prostaglandin E_1** (PGE_1 ; 0.01-0.20 µg/kg/min), a potent and specific relaxant of ductal smooth muscle, causes dilation of the ductus arteriosus and usually provides adequate pulmonary blood flow until a surgical procedure can be performed. This agent should be administered intravenously as soon as cyanotic CHD is clinically suspected and continued through the preoperative period and during cardiac catheterization. Because prostaglandin can cause apnea, an individual skilled in neonatal intubation should be readily available.

Infants with less severe RVOT obstruction who are stable and awaiting surgical intervention require careful observation. Acyanotic patients can progress fairly quickly to having cyanotic episodes. Prevention or prompt treatment of dehydration is important to avoid hemoconcentration and possible thrombotic episodes. In the past, oral propranolol (0.5-1 mg/kg every 6 hr) was used to decrease the frequency and severity of hypercyanotic spells, but with the excellent surgical results available, surgical treatment is indicated, usually before spells begin.

Infants with symptoms and severe cyanosis in the 1st mo of life usually have marked obstruction of the RVOT. Two options are available in these infants. The 1st option is **corrective open heart surgery** performed in early infancy and even in the newborn period in critically ill infants. This approach currently has widespread acceptance with excellent short- and long-term results and has supplanted palliative shunts (see later) for most cases. Early total repair carries the theoretical advantage that early physiologic correction allows for improved growth of the branch pulmonary arteries. In infants with less severe cyanosis who can be maintained with good growth and absence of hypercyanotic spells, primary repair is performed electively at 4-6 mo of age.

Corrective surgical therapy consists of relief of the RVOT obstruction by resecting obstructive muscle bundles and by patch closure of the VSD. If the pulmonary valve is stenotic, as it usually is, a valvotomy is performed. If the pulmonary valve annulus is too small or the valve is extremely thickened, a valvectomy may be performed, the pulmonary valve annulus split open, and a transannular patch placed across the pulmonary valve ring. The surgical risk of total correction in major centers is <5%. A right ventriculotomy was once the standard approach; a transatrial-transpulmonary approach is routinely performed to reduce the long-term risks of a large right ventriculotomy. In the past, surgeons placed large transannular patches with the goal of eliminating any possibility of residual pulmonary stenosis, even if these resulted in wide-open pulmonary insufficiency. Currently, surgeons have resorted to using smaller patches and are more accepting of small RVOT gradients if the degree of valve insufficiency can be minimized. Which of these 2 approaches will result in the best long-term outcomes is still an open question.

The 2nd option, more common in previous years, is a palliative systemic-to-pulmonary artery shunt (**Blalock-Taussig shunt**) performed to augment pulmonary artery blood flow. The rationale for this surgery, previously the only option for these patients, is to augment pulmonary blood flow to decrease the amount of hypoxia and improve linear growth, as well as augment growth of the branch pulmonary arteries. The modified Blalock-Taussig shunt is currently the most common aortopulmonary shunt procedure and consists of a Gore-Tex conduit anastomosed side to side from the subclavian artery to the homolateral branch of the pulmonary artery (Fig. 457.5). Sometimes the shunt is brought directly from the ascending aorta to the MPA; in this case it is called a *central shunt.* Postoperative complications after a Blalock-Taussig shunt include chylothorax, diaphragmatic paralysis, and Horner syndrome. Postoperative pulmonary overcirculation leading to symptoms of cardiac failure may be caused by too large a shunt; Chapter 469 describes its treatment. Vascular problems other than a diminished radial pulse and occasional long-term arm length discrepancy are rarely seen in the upper extremity supplied by the subclavian artery used for the anastomosis.

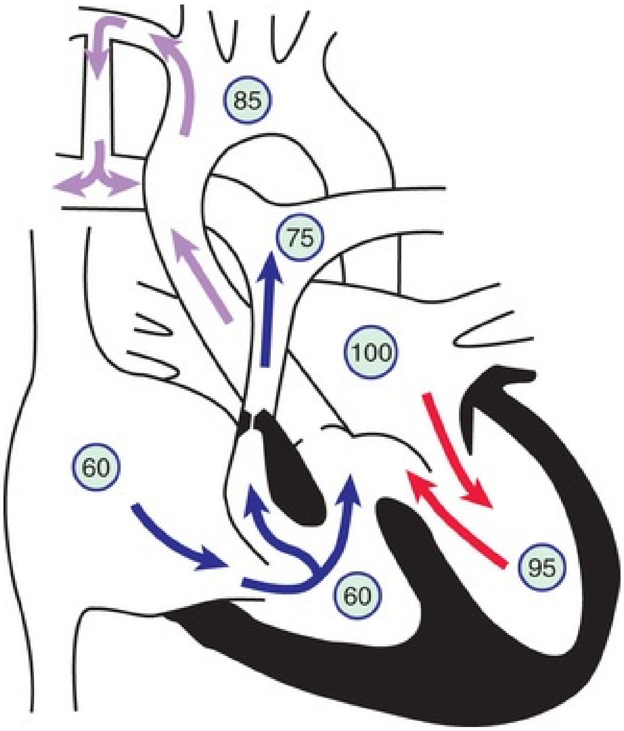

FIG. 457.5 **Physiology of Blalock-Taussig shunt in patient with tetralogy of Fallot. *Circled numbers* represent oxygen saturation values. The intracardiac shunting pattern is as described for Fig. 457.1 . Blood shunting left to right across the shunt from the right subclavian artery to the right pulmonary artery increases total pulmonary blood flow and results in a higher oxygen saturation than would exist without the shunt.**

After a successful shunt procedure, cyanosis diminishes. The development of a continuous murmur over the lung fields after the operation indicates a functioning anastomosis. A good continuous shunt murmur may not be heard until several days after surgery. The duration of symptomatic relief is variable. As the child grows, more pulmonary blood flow is needed, and the shunt eventually becomes inadequate. When increasing cyanosis develops rapidly, thrombosis of the shunt should be suspected, often requiring emergent surgery.

Blalock-Taussig shunts are usually reserved for patients with comorbidities, such as other major congenital anomalies or prematurity, that would make full repair a higher-risk option. However, many surgeons still recommend full repair in these situations, being preferable to the combined risks of a staged procedure, and successful repairs have been done even in small premature infants.

Prognosis

After successful total correction, patients are generally asymptomatic and are able to lead unrestricted lives. Uncommon immediate postoperative problems include RV failure, transient heart block, residual VSD with left-to-right shunting, and myocardial infarction from interruption of an aberrant coronary artery. The long-term effects of isolated, surgically induced pulmonary valvular insufficiency or of insufficiency and mild stenosis (as is more typical with modern-era smaller transannular patches) are still being defined as more patients with repaired tetralogy of Fallot reach adulthood, but pulmonary insufficiency is generally well tolerated through childhood and early adolescence. Many patients after tetralogy repair and all those with transannular patch repairs have a to-and-fro murmur at the left sternal border, usually indicative of mild outflow obstruction and mild to moderate pulmonary insufficiency. Patients with more marked or long-standing pulmonary valve insufficiency may also have moderate to more severe degrees of RV enlargement and may develop tricuspid regurgitation as the tricuspid valve annulus dilates. These patients will develop a holosystolic murmur at the lower left sternal border. Patients with a moderate to severe residual gradient (stenosis) across the RVOT usually require reoperation, but milder degrees of residual obstruction usually do not require reintervention.

Follow-up of patients 5-20 yr after surgery indicates that the marked improvement in symptoms is generally maintained. Asymptomatic patients nonetheless have lower-than-normal exercise capacity, maximal heart rate, and cardiac output. These abnormal findings are more common in patients who underwent placement of a transannular outflow tract patch and may be less frequent when surgery is performed at an early age. As these children move into adolescence and adulthood, some (more often those with transannular patches) will develop RV dilation as a result of severe pulmonary regurgitation. Careful surveillance for excessive RV dilation and early signs of RV dysfunction is critical. After reaching adulthood, lifelong follow-up by a specialist in adult CHD is important. Serial echocardiography and the more quantitative magnetic resonance angiography (MRA) are valuable tools for assessing the degree of RV dilation, the presence of early stages of RV dysfunction, and for quantifying the regurgitant fraction. Valve replacement is indicated for those patients with increasing RV dilation and tricuspid regurgitation. For patients requiring valve replacement, new nonsurgical options are now available. Stent-valves, which can be delivered in the cardiac catheterization laboratory, have been used successfully in many patients with repaired tetralogy of Fallot. The initial versions of these devices were designed to be used predominantly in patients who have previously had a homograft or other artificial conduit placed between the RV and pulmonary arteries; however, newer stent-valves designed to be inserted into the native RVOT are in clinical trials.

Conduction disturbances can occur after surgery. The atrioventricular node and the bundle of His and its divisions are close to the VSD and may be injured during surgery; however, permanent complete heart block after tetralogy repair is rare. When present, it should be treated by placement of a permanently implanted pacemaker. Even transient complete heart block in the immediate postoperative period is rare; it may be associated with an increased incidence of late-onset complete heart block and sudden death. In contrast, right bundle branch block is quite common on the postoperative ECG. The duration of the QRS interval has been shown to predict both the presence of residual hemodynamic derangement and the long-term risk of arrhythmia and sudden death. Biventricular pacing (in which a pacemaker is used to resynchronize the activation of the right and left ventricles) has been shown to improve hemodynamics in patients with RV dysfunction and long ventricular conduction delays on ECG.

Many children have **premature ventricular beats** after repair of the tetralogy of Fallot. These beats, if isolated and infrequent, may be benign but are of particular concern in patients with residual hemodynamic abnormalities. Approximately 10% of patients with repaired tetralogy are at risk of life-threatening ventricular arrhythmias, and 30% are at risk of atrial arrhythmias as they reach adulthood. Long-duration electrocardiographic monitoring studies, such as Holter (24-48 hr) or ZioPatch (1-2 wk), should be performed on a regular basis to ensure that occult episodes of ventricular tachycardia are not occurring. Exercise studies may be useful in provoking cardiac arrhythmias that are not apparent at rest. In the presence of complex ventricular arrhythmias or severe residual hemodynamic abnormalities, prophylactic antiarrhythmic therapy or an implantable defibrillator is warranted. Surgical or transcatheter intervention is indicated if significant residual RVOT obstruction or severe pulmonary insufficiency is present, because arrhythmia risk may improve after hemodynamics are restored to a more normal level.

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457.2

Tetralogy of Fallot With Pulmonary Atresia

Daniel Bernstein

Pathophysiology

Tetralogy of a Fallot with pulmonary atresia is the most extreme form of the tetralogy of Fallot. The pulmonary valve is atretic (absent), and the pulmonary trunk may be hypoplastic or atretic as well. The entire RV output is ejected into the aorta. Pulmonary blood flow is then dependent on MAPCAs or rarely a PDA. The ultimate prognosis depends on the degree of development of the true branch pulmonary arteries, which needs to be assessed by a combination of CT and cardiac catheterization. If the pulmonary arteries are severely hypoplastic and fail to grow after surgical intervention, heart-lung transplantation may be the only therapy (see Chapter 470.2). Tetralogy of Fallot with pulmonary atresia is also associated with the 22q11.2 deletion and DiGeorge syndrome. The association of severe **tracheomalacia** or **bronchomalacia** with these severe forms of tetralogy/pulmonary atresia may complicate postoperative recovery.

Clinical Manifestations

Patients with tetralogy of Fallot/pulmonary atresia have findings similar to those in patients with severe tetralogy of Fallot. Cyanosis usually appears within the 1st few hours or days after birth; however, the prominent systolic murmur associated with tetralogy is usually absent. The first heart sound (S_1) may be followed by an ejection click caused by the enlarged aortic root, S_2 is single and loud, and continuous murmurs of collateral flow may be heard over the entire precordium, both anteriorly and posteriorly. Most patients are moderately cyanotic and are initially stabilized with a PGE_1 infusion pending cardiac catheterization or CT scan to further delineate the anatomy. Patients with several large MAPCAs may be less cyanotic and, once the diagnosis is confirmed, can be taken off prostaglandin while awaiting palliative surgical intervention. Some patients may even develop symptoms of heart failure caused by increased pulmonary blood flow via these collateral vessels.

Diagnosis

The chest radiograph demonstrates a varying heart size, depending on the amount of pulmonary blood flow, a concavity at the position of the pulmonary arterial segment, and often the reticular pattern of bronchial collateral flow. The ECG shows RVH. The echocardiogram identifies aortic override, a thick RV wall, and atresia of the pulmonary valve. Pulsed and color Doppler echocardiographic studies show an absence of forward flow across the pulmonary valve, with pulmonary blood flow being supplied by MAPCAs, which can usually be seen using color Doppler arising from the descending aorta. At cardiac catheterization, right ventriculography reveals a large aorta, opacified immediately by passage of contrast medium through the VSD, but with no dye entering the lungs through the RVOT. It is important in planning surgical repair to delineate carefully the often diminutive native pulmonary arteries, if present, to determine whether they are continuous or discontinuous and whether they arborize to all lung segments. The location and arborization of all MAPCAs and the presence of any localized stenosis, which become more common as the patient grows older, are determined by selective contrast injection into each vessel from its origin in the aorta. CT angiography has been shown to be highly valuable to assist in mapping the extent of MAPCA arborization.

Treatment

The surgical procedure of choice depends on whether the MPA segment is present and, if so, on the size and branching pattern of the branch pulmonary arteries. If these arteries are well developed, a 1-stage surgical repair with a homograft conduit between the right ventricle and pulmonary arteries and closure of the VSD is feasible. If the pulmonary arteries are hypoplastic, extensive reconstruction may be required. This usually involves several staged surgical procedures. If the native pulmonary artery is present but small, a connection made between the aorta and the hypoplastic native pulmonary artery (**aortopulmonary window**) is performed in the newborn period to induce growth of the native pulmonary arteries. At 3-4 mo of age, the multiple MAPCAs are gathered together (**unifocalization procedure**) and eventually incorporated into the final repair along with the native pulmonary arteries. This may be accomplished through successive lateral thoracotomies, or through a single midline sternotomy if the anatomy is more favorable.

To be a candidate for full repair, the pulmonary arteries must be of adequate size to accept the full volume of RV output. Complete repair includes closure of the VSD and placement of a homograft conduit from the right ventricle to the pulmonary artery. At the time of reparative surgery, previous shunts are taken down. Because of patient growth as well as homograft narrowing caused by proliferation of intimal tissue and calcification, replacement of the homograft conduit replacement is usually required in later life, and multiple replacements may be needed. Many of these patients are candidates for placement of a transcatheter stent-valve in the pulmonary position. Patients with obstruction of the very distal branches of the pulmonary arteries may undergo repeat surgical procedures or transcatheter balloon dilation and stenting of the multibranch pulmonary arterial stenosis. Careful follow-up is warranted for these patients to ensure maximal chance of growth of all pulmonary artery segments.

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457.3

Pulmonary Atresia With Intact Ventricular Septum

Daniel Bernstein

Pathophysiology

In pulmonary atresia with an intact ventricular septum, the pulmonary valve leaflets are completely fused to form a membrane and the RVOT is atretic. Because no VSD is present, no egress of blood from the right ventricle can occur. Any blood that enters the right ventricle will regurgitate back across the tricuspid valve into the right atrium. Right atrial pressure increases, and blood shunts via the foramen ovale into the left atrium, where it mixes with pulmonary venous blood and enters the left ventricle (Fig. 457.6). The combined left and right ventricular output is pumped solely by the left ventricle into the aorta. In a newborn with pulmonary atresia, the only source of pulmonary blood flow occurs via a PDA. The right ventricle and tricuspid valve are usually hypoplastic, although the degree of hypoplasia varies considerably. Patients who have a small RV cavity also tend to be those with the smallest tricuspid valve annulus, which limits RV inflow. Patients with pulmonary atresia and intact ventricular septum may have **coronary sinusoidal channels** within the RV wall that communicate directly with the coronary arterial circulation. The high RV pressure results in desaturated blood flowing retrograde through these channels into the coronary arteries. Sometimes there are also stenoses of the coronary arteries proximal to where the sinusoids enter, so that distal coronary artery flow is dependent on flow from the right ventricle (known as *right ventricle–dependent coronary circulation*). The prognosis in patients with these sinusoids and proximal stenosis of the coronary arteries is more guarded than in those patients without sinusoids or with sinusoids but no coronary stenoses. Rarely, the proximal coronary artery may be totally absent.

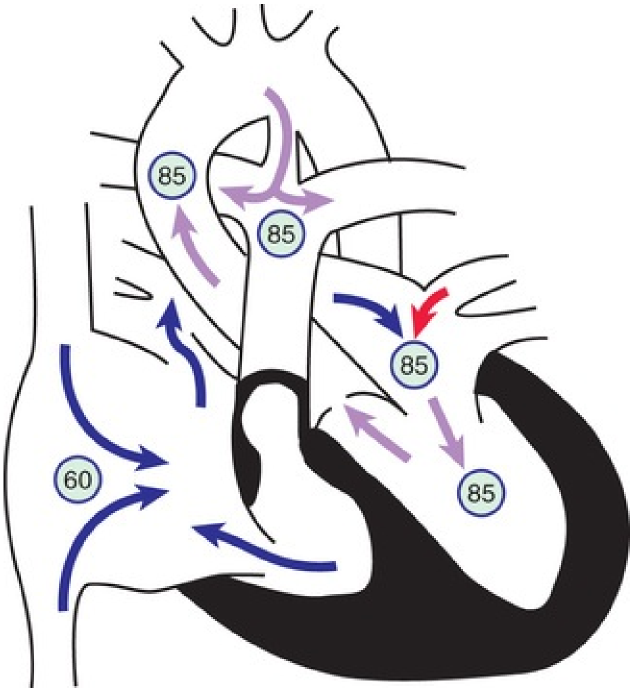

FIG. 457.6 Physiology of pulmonary atresia with intact ventricular septum. ***Circled numbers*** represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. A small amount of the blood

entering the right atrium may cross the tricuspid valve, which is often stenotic as well. The right ventricular cavity is hypertrophied and may be hypoplastic. No outlet from the right ventricle exists because of the atretic pulmonary valve; thus any blood entering the right ventricle returns to the right atrium via tricuspid regurgitation. Most of the desaturated blood shunts right to left via the foramen ovale into the left atrium, where it mixes with fully saturated blood returning from the lungs. The only source of pulmonary blood flow is via the patent ductus arteriosus. Aortic and pulmonary arterial oxygen saturation will be identical (definition of a total mixing lesion).

Clinical Manifestations

As the ductus arteriosus closes in the 1st hr and days of life, infants with pulmonary atresia and an intact ventricular septum become markedly cyanotic because their only source of pulmonary blood flow is removed. Untreated, most patients die within the 1st wk of life. Physical examination reveals severe cyanosis and respiratory distress. S_2 , representing only aortic closure, is single and loud. Often, no murmurs are audible; sometimes a systolic or continuous murmur can be heard secondary to ductal blood flow. A harsh holosystolic murmur may be heard at the lower left sternal border if there is significant tricuspid regurgitation.

Diagnosis

The ECG shows a frontal QRS axis between 0 and +90 degrees, the amount of leftward shift reflecting the degree of RV hypoplasia. Tall, spiked P waves indicate right atrial enlargement. QRS voltages are consistent with left ventricular dominance or hypertrophy; RV forces are decreased in proportion to the decreased size of the RV cavity. Most patients with small right ventricles have decreased RV forces, but occasionally, patients with larger, thickened RV cavities may have evidence of RVH. The chest radiograph shows decreased pulmonary vascularity, the degree depending on the size of the branch pulmonary arteries and the patency of the ductus. Unlike in patients with pulmonary atresia and tetralogy of Fallot, the presence of MAPCAs is rare.

The 2D echocardiogram is useful in estimating RV dimensions and the size of the tricuspid valve annulus, which have been shown to be of prognostic value. Echocardiography can often suggest the presence of sinusoidal channels but cannot be used to evaluate coronary stenoses. Thus, cardiac catheterization is necessary for complete evaluation. Pressure measurements reveal right atrial and

RV hypertension. Ventriculography demonstrates the size of the RV cavity, the atretic RVOT, the degree of tricuspid regurgitation, and the presence or absence of intramyocardial sinusoids filling the coronary vessels. Aortography shows filling of the pulmonary arteries by the PDA and is helpful in determining the size and branching patterns of the pulmonary arterial bed. An aortogram or, if necessary, selective coronary angiography is performed to evaluate for the presence of proximal coronary artery stenosis (RV-dependent coronary circulation).

Treatment

Infusion of PGE_1 (0.01-0.20 µg/kg/min) is usually effective in keeping the ductus arteriosus open before intervention, thus reducing hypoxemia and acidemia before surgery. The choice of surgical procedure depends on whether there is an RV-dependent coronary circulation and on the size of the RV cavity. In patients with only mild to moderate RV hypoplasia without sinusoids, or in patients with sinusoids but no evidence of coronary stenoses, a surgical pulmonary valvotomy is carried out to relieve outflow obstruction. Often, the RVOT is widened with a patch. To preserve adequate pulmonary blood flow, an aortopulmonary shunt may also be performed during the same procedure. An alternative approach uses interventional catheterization, in which the imperforate pulmonary valve is first punctured either with a wire or a radiofrequency ablation catheter, followed by a balloon valvuloplasty. If this course is taken, it may take days to weeks before the RV muscle regresses enough for the patient to be weaned from prostaglandin, and many of these patients will still require surgical intervention.

The aim of surgery or interventional catheterization is to encourage growth of the RV chamber by allowing some forward flow through the pulmonary valve while using the shunt to ensure adequate pulmonary blood flow. Later, if the tricuspid valve annulus and RV chamber grow to adequate size, the shunt is taken down and any remaining atrial level shunt can be closed. If the RV chamber remains too small for use as a pulmonary ventricle, the patient is treated as having a single-ventricle circulation, with a **Glenn procedure** followed by a modified **Fontan procedure** (see Chapter 457.4), allowing blood to bypass the hypoplastic right ventricle by flowing to the pulmonary arteries directly from the venae cavae. When coronary artery stenoses are present and retrograde coronary perfusion occurs from the right ventricle through myocardial sinusoids, the prognosis is more guarded because of a higher risk of arrhythmias, coronary ischemia, and sudden death. It is important for these patients not to try to open the RVOT, because dropping the RV pressure will reduce coronary perfusion, leading to ischemia. These patients are usually treated with an aortopulmonary shunt, followed by the Glenn and Fontan procedure. Although at higher risk than those without coronary stenoses, recent reports show good success with this approach. A small number of these infants, especially those with total atresia of a proximal coronary artery, are referred instead for heart transplantation.

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457.4

Tricuspid Atresia

Daniel Bernstein

Pathophysiology

In tricuspid atresia, no outlet from the right atrium to the right ventricle is present; the entire systemic venous return leaves the right atrium and enters the left side of the heart through the foramen ovale or, most often, an atrial septal defect (ASD) (Fig. 457.7). The physiology of the circulation and the clinical presentation will depend on the presence of other congenital heart defects, most notably on whether the great vessels are normally related or are transposed (aorta arising from the right ventricle, pulmonary artery from the left ventricle). In patients with normally related great vessels, left ventricular (LV) blood supplies the systemic circulation through the aorta. Blood also usually flows into the right ventricle through a VSD (if the ventricular septum is intact, the right ventricle will be completely hypoplastic and pulmonary atresia will be present [see Chapter 457.3]). *Pulmonary blood flow (and thus the degree of cyanosis) depends on the size of the VSD and the presence and severity of any associated pulmonic stenosis* . Pulmonary blood flow may be augmented by or totally dependent on a PDA. The inflow portion of the right ventricle is always missing, but the outflow portion is of variable size. The clinical presentation of patients with tricuspid atresia and *normally* related great vessels will depend on the degree of pulmonary obstruction. Patients with at least moderate degrees of pulmonary stenosis are recognized in the early days or weeks of life by decreased pulmonary blood flow and cyanosis. Alternatively, in those with a large VSD and minimal or no RVOT obstruction, pulmonary blood flow may be high; these patients have only mild cyanosis and present with signs of pulmonary overcirculation and heart failure.

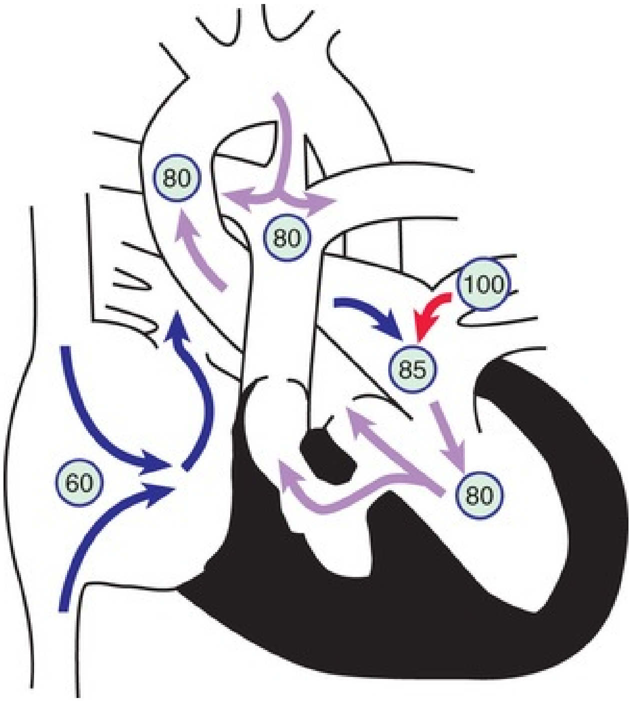

FIG. 457.7 **Physiology of tricuspid atresia with normally related great vessels. *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. The tricuspid valve is nonpatent, and the right ventricle may manifest varying degrees of hypoplasia. The only outlet from the right atrium involves shunting right to left across an atrial septal defect or patent foramen ovale to the left atrium. There, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected either through the aorta or via a ventricular septal defect (VSD) into the right ventricle. In this example, some pulmonary blood flow is derived from the right ventricle, the rest from a patent ductus arteriosus (PDA). In patients with tricuspid atresia, the PDA may close or the VSD may grow smaller and result in a marked decrease in systemic oxygen saturation.**

In patients with tricuspid atresia and **transposition of the great arteries (TGA)** , LV blood flows directly into the pulmonary artery, whereas systemic blood must traverse the VSD and right ventricle to reach the aorta. In these patients, pulmonary blood flow is usually massively increased and heart failure develops early. If the VSD is restrictive, aortic blood flow may be compromised. **Coarctation of the aorta** is often noted in this setting.

Clinical Manifestations

Some degree of cyanosis is usually evident at birth, with the extent depending on the degree of limitation to pulmonary blood flow. An increased LV impulse may be noted, in contrast to most other causes of cyanotic heart disease, in which an increased RV impulse is usually present. Most patients have holosystolic murmurs audible along the left sternal border; S_2 is usually single. Pulses in the lower extremities may be weak or absent in the presence of transposition with coarctation of the aorta. Patients with tricuspid atresia are at risk for spontaneous narrowing or even closure of the VSD, which can occasionally occur rapidly and lead to a marked increase in cyanosis.

Diagnosis

Radiologic studies show either pulmonary undercirculation (usually in patients with normally related great vessels) or overcirculation (usually in patients with transposed great vessels). Left axis deviation and LV hypertrophy are generally noted on the ECG (except in patients with TGA), and these unique features distinguish tricuspid atresia from most other cyanotic heart lesions. Thus the combination of cyanosis and left axis deviation on the ECG is highly suggestive of tricuspid atresia. In the right precordial leads, the normally prominent R wave is replaced by an rS complex. The left precordial leads show a qR complex, followed by a normal, flat, biphasic, or inverted T wave. RV_6 is normal or tall, and SV_1 is generally deep. The P waves are usually biphasic, with the initial component tall and spiked in lead II. 2D echocardiography reveals the presence of a fibromuscular membrane in place of a tricuspid valve, a variably small right ventricle, VSD, and the large left ventricle (Fig. 457.8). The relationship of the great vessels (normal or transposed) can be determined. The degree of obstruction at the level of the VSD or at the RVOT can be determined by Doppler examination. Blood flow through a patent ductus can be evaluated by color flow and pulsed Doppler.

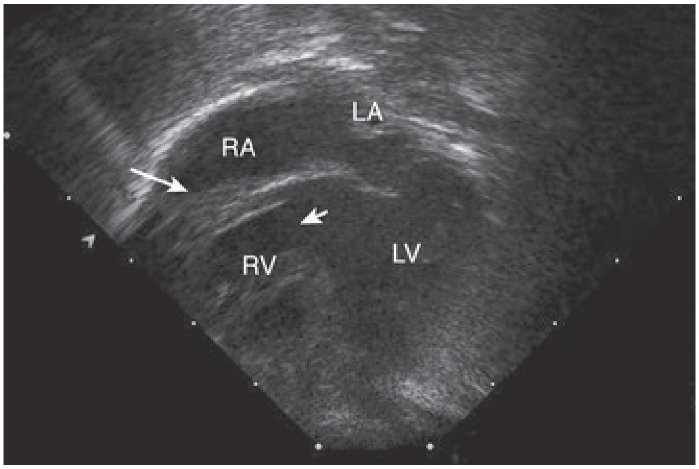

FIG. 457.8 **Echocardiogram demonstrating tricuspid atresia. The floor of the right atrium consists of a fibromuscular membrane *(longer arrow)* instead of the normal tricuspid valve apparatus. The large secundum atrial septal defect can be seen between the right and left atria. The *short arrow* shows the ventricular septal defect. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.**

Cardiac catheterization, indicated usually only if questions remain after echocardiography, shows normal or slightly elevated right atrial pressure with a prominent *a* wave. If the right ventricle is entered through the VSD, the pressure may be lower than on the left if the VSD is restrictive in size. Right atrial angiography shows immediate opacification of the left atrium from the right atrium, followed by left ventricular filling and visualization of the aorta. Absence of direct flow to the right ventricle results in an angiographic filling defect between the right atrium and the left ventricle.

Treatment

Management of patients with tricuspid atresia depends on the adequacy of pulmonary blood flow. Severely cyanotic neonates should be maintained on an IV infusion of PGE_1 (0.01-0.20 µg/kg/min) until a surgical aortopulmonary shunt procedure can be performed to increase pulmonary blood flow. The Blalock-Taussig procedure (see Chapter 457.1) or a variation is the preferred anastomosis. Rare patients with restrictive atrial-level communications also benefit from a Rashkind balloon atrial septostomy (see Chapter 458.2) or surgical septectomy.

Infants with increased pulmonary blood flow because of an unobstructed pulmonary outflow tract (more often patients with aortopulmonary transposition) may require pulmonary arterial banding to decrease the symptoms of heart failure and protect the pulmonary bed from the development of pulmonary vascular disease. Infants with just adequate pulmonary blood flow who are well balanced between cyanosis and pulmonary overcirculation can be watched closely for the development of increasing cyanosis, which may occur as the VSD begins to shrink or the pulmonary outflow becomes narrower and is an indication for surgery.

The next stage of palliation for patients with tricuspid atresia involves the creation of an anastomosis between the superior vena cava and the pulmonary arteries (**bidirectional Glenn shunt** ; Fig. 457.9*A*). This procedure is performed at usually between 2 and 6 mo of age. The benefit of the Glenn shunt is that it reduces the volume load on the left ventricle and may lessen the chance of LV dysfunction developing later in life.

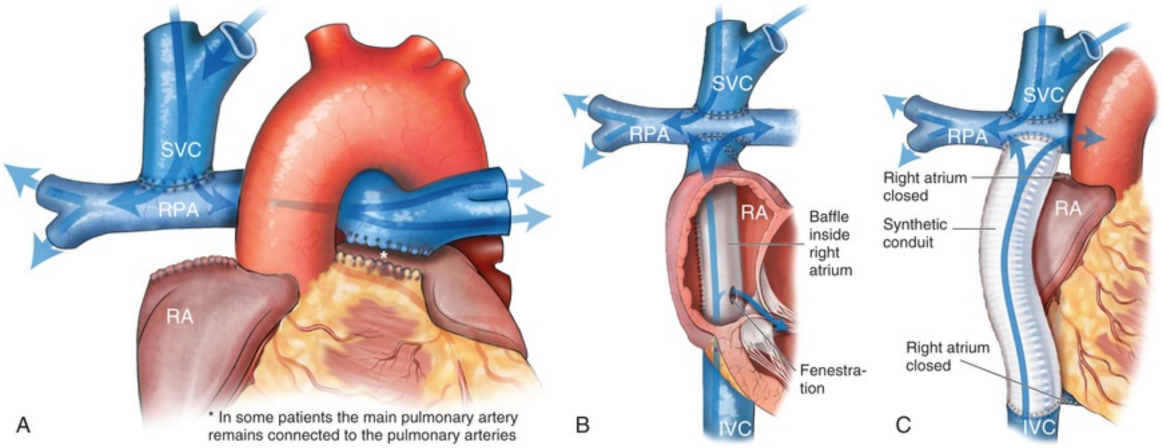

* In some patients the main pulmonary artery remains connected to the pulmonary arteries

FIG. 457.9 Staged surgical approach to palliation of the patient with a single ventricle circulation. **A,** Bidirectional Glenn shunt. The superior vena cava (SVC) is divided and detached from the right atrium (RA) and anastomosed end-to-side to the pulmonary artery, which has also been divided and detached from the right ventricle. **B,** Lateral tunnel Fontan. Inferior vena caval flow is directed upward through a synthetic or pericardial baffle sutured to the RA wall. The lower portion of the SVC (previously divided during the Glenn shunt) is now sutured directly to the right pulmonary artery. Thus blood flows from the upper body via the SVC directly into the lungs via the previous Glenn shunt, and from the lower body via the baffle, through the RA but not emptying into the RA, directly into the lungs. The only remaining blood flow entering into the RA is from the coronary sinus, which represents the small amount of venous return coming directly from the left ventricle. The RA is thus excluded from the Fontan circuit. **C,** Extracardiac Fontan. The inferior vena cava (IVC) is detached from the RA and an extracardiac synthetic conduit or homograft is used to direct that flow, outside the heart, to the inferior aspect of the right pulmonary artery (RPA). Both Fontan approaches achieve the same

endpoint in isolating the venous circulation (blue blood) from the arterial circulation (red blood). The external conduit Fontan procedure is more common today due to concerns about atrial arrhythmias and/or blood clots related to the baffle in the RA. Many surgeons orient the connection from the IVC more centrally on the pulmonary arteries than shown in C to avoid a ”collision” of flow from the upper and lower bodies, which in flow dynamic modeling studies has been shown to reduce the efficiency of the Fontan circulation, especially during exercise. (Adapted from Burchill LJ, Wald RM, Mertens L. Single ventricles: echocardiographic assessment after the Fontan operation. In Otto CM (ed): The practice of clinical echocardiography, ed 5, Philadelphia, 2017, Elsevier, Figs 49-6, 8, and 9.)

The **modified Fontan operation** is the preferred approach to later surgical management. It is usually performed between 2 and 3 yr of age, after the patient is ambulatory. Initially, this procedure was performed by anastomosing the right atrium or atrial appendage directly to the pulmonary artery. The procedure used most often now is a modification of the Fontan procedure, known as a **cavopulmonary isolation procedure** , which involves anastomosing the inferior vena cava directly to the pulmonary arteries by a homograft or Gore-Tex tube running outside the heart (external-conduit Fontan). An older version of this procedure uses an internal baffle that runs along the lateral wall of the right atrium (lateral-tunnel Fontan; Fig. 457.9*B*). The advantage of these later approaches is that blood flows by a more direct route into the pulmonary arteries, thereby decreasing the risk of right atrial dilation and greatly reducing the incidence of postoperative pleural effusions, which were common with the earlier method. In a completed Fontan repair, desaturated blood flows from both venae cavae directly into the pulmonary arteries. Oxygenated blood returns to the left atrium, enters the left ventricle, and is ejected into the systemic circulation. The volume load is completely removed from the left ventricle, and the right-to-left shunt is abolished. Because of the reliance on passive filling of the pulmonary circulation, the Fontan procedure is contraindicated in patients with elevated pulmonary vascular resistance, in those with pulmonary artery hypoplasia, and in patients with LV dysfunction. The patient also must not have significant mitral insufficiency. Patients who are not in normal sinus rhythm are at increased risk, and if a pacemaker is required in these patients, dual-chamber pacing is the preferred approach.

Postoperative problems after the Fontan procedure include marked elevation of systemic venous pressure, fluid retention, and pleural or pericardial effusions. In the past, pleural effusions were a problem in 30–40% of patients using the standard Fontan procedure, but the cavopulmonary isolation procedure now in use reduces this risk to approximately 5%, although prolonged chest tube drainage in the immediate postoperative period can occur but eventually resolves. Some centers use a fenestration at the time of the Fontan, consisting of a small communication between the inferior vena cava and the pulmonary artery conduit and the left atrium. This serves as a “pop-off” during early postoperative recovery and may hasten hospital discharge. The fenestration will result in some amount of right-to-left shunting and is therefore usually closed with a catheter closure device after the immediate postoperative period.

Late complications of the Fontan procedure include stenosis of the superior or inferior vena cava anastomosis, vena cava or pulmonary artery thromboembolism, protein-losing enteropathy, plastic bronchitis, immune deficiency, supraventricular arrhythmias (atrial flutter, paroxysmal atrial tachycardia), and hepatic cirrhosis (and possibly hepatic carcinoma) as a result of persistently elevated central venous pressures. Oral **budesonide** or **sildenafil** has been used with varying success to treat protein-losing enteropathy associated with the Fontan procedure. Thoracic duct ligation or embolization has been used to treat plastic bronchitis. LV dysfunction may be a late occurrence, usually not until adolescence or young adulthood. Heart transplantation is a successful treatment option for pediatric patients with “failed” Fontan circuits but is a somewhat riskier procedure in adults. Patients with combined heart failure and liver dysfunction have been treated with combined heart-liver transplantation with good result.

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457.5

Double-Outlet Right Ventricle

Daniel Bernstein

Double-outlet right ventricle (**DORV**) is characterized when both the aorta and pulmonary artery arise from the right ventricle. The outlet from the left ventricle is through a VSD into the right ventricle. Normally, the aortic and mitral valves are in fibrous continuity; in DORV the aortic and mitral valves are separated by a smooth muscular **conus,** similar to that seen under the normal pulmonary valve. In DORV the great arteries may be *normally related,* with the aorta closer to the VSD, or *malposed,* with the pulmonary artery closer to the VSD. The great artery closest to the VSD may override the defect by a variable amount but is at least 50% committed to the right ventricle. When the VSD is subaortic, the defect may be viewed as part of a continuum with the **tetralogy of Fallot** , and the physiology as well as the history, physical examination, ECG, and radiography depend on the degree of pulmonary stenosis, similar to the situation in tetralogy of Fallot (see Chapter 457.1). If the VSD is subpulmonic, there may be subvalvar, valvar, or supravalvar aortic stenosis, and coarctation is a possibility as well. This is known as the **Taussig-Bing malformation** . The clinical presentation of these patients will depend on the degree of aortic obstruction, but because the pulmonary artery is usually wide open, the presentation will usually include some degree of pulmonary overcirculation and heart failure. If the aortic obstruction is severe or there is a coarctation, poor pulses, hypoperfusion, and cardiovascular collapse are possible presenting signs.

The 2D echocardiogram demonstrates both great vessels arising from the right ventricle and mitral-aortic valve discontinuity. The relationships between the aorta and pulmonary artery to the VSD can be delineated, and the presence of either pulmonary obstruction or aortic obstruction can be evaluated. Cardiac catheterization is not necessarily required if the echocardiogram is straightforward. Angiography will show that the aortic and pulmonary valves lie in the same horizontal plane, and that both arise predominantly or exclusively from the right ventricle.

Surgical correction depends on the relationship of the great vessels to the VSD. If the VSD is *subaortic*, the repair may be similar to that used for tetralogy of Fallot, or consist of creating an intraventricular tunnel so that the left ventricle ejects blood through the VSD, into the tunnel, and into the aorta. The pulmonary obstruction is relieved either with an outflow patch or with a right ventricle–to–pulmonary artery homograft conduit (**Rastelli operation**). If the VSD is *subpulmonic*, the great vessels can be switched (see Chapter 457.6) and the Rastelli operation performed. However, if there is substantial aortic obstruction, or if one of the ventricles is hypoplastic, a Norwood-style single-ventricle repair may be necessary (see Chapter 458.10). In small infants, palliation with an aortopulmonary shunt provides symptomatic improvement and allows for adequate growth before corrective surgery is performed.

457.6

Transposition of the Great Arteries With Ventricular Septal Defect and Pulmonary Stenosis

Daniel Bernstein

The combination of TGA with VSD and pulmonary stenosis may mimic tetralogy of Fallot in its clinical features (see Chapter 457.1). However, because of the transposed great vessels, the site of obstruction is in the left as opposed to the right ventricle. The obstruction can be either valvular or subvalvular; the latter type may be *dynamic*, related to the interventricular septum or atrioventricular valve tissue, or *acquired*, as in patients with transposition and VSD after pulmonary arterial banding.

The age at which clinical manifestations initially appear varies from soon after birth to later infancy, depending on the degree of pulmonic stenosis. Clinical findings include cyanosis, decreased exercise tolerance, and poor physical development, similar to those described for tetralogy of Fallot; the heart is usually more enlarged. The pulmonary vasculature as seen on radiograph depends on the degree of pulmonary obstruction. The ECG usually shows right axis deviation, right and left ventricular hypertrophy, and sometimes tall, spiked P waves. Echocardiography confirms the diagnosis and is useful in sequential evaluation of the degree and progression of the LV outflow tract obstruction. Cardiac catheterization, if necessary, shows that pulmonary arterial pressure is low and that oxygen saturation in the pulmonary artery exceeds that in the aorta. Selective right and left ventriculography demonstrates the origin of the aorta from the right ventricle, the origin of the pulmonary artery from the left ventricle, the VSD, and the site and severity of the pulmonary stenosis.

An infusion of PGE_1 (0.01-0.20 µg/kg/min) should be started in neonates who present with cyanosis. When necessary, **balloon atrial septostomy** is performed to improve atrial-level mixing and to decompress the left atrium (see Chapter 458.2). Cyanotic infants may be palliated with an aortopulmonary shunt (see Chapter 457.1), followed by a Rastelli operation when older, as the preferred corrective procedure. The Rastelli procedure achieves physiologic and anatomic correction by (1) closure of the VSD using an interventricular tunnel so that LV blood flow is directed to the aorta and (2) connection of the right ventricle to the distal pulmonary artery by an extracardiac homograft conduit (Fig. 457.10). These conduits will eventually become stenotic or functionally restrictive with patient growth and require replacement. Patients with milder degrees of pulmonary stenosis amenable to simple valvotomy may be able to undergo complete correction with an **arterial switch procedure** (see Chapter 458.2) and closure of the VSD. Surgical correction by the **Mustard operation** (see Chapter 458.2) with simultaneous closure of the VSD and relief of LV outflow obstruction may be an alternative when the position of the VSD is not suitable for a Rastelli operation; however, this procedure leaves the right ventricle as the systemic pumping chamber and has fallen out of favor.

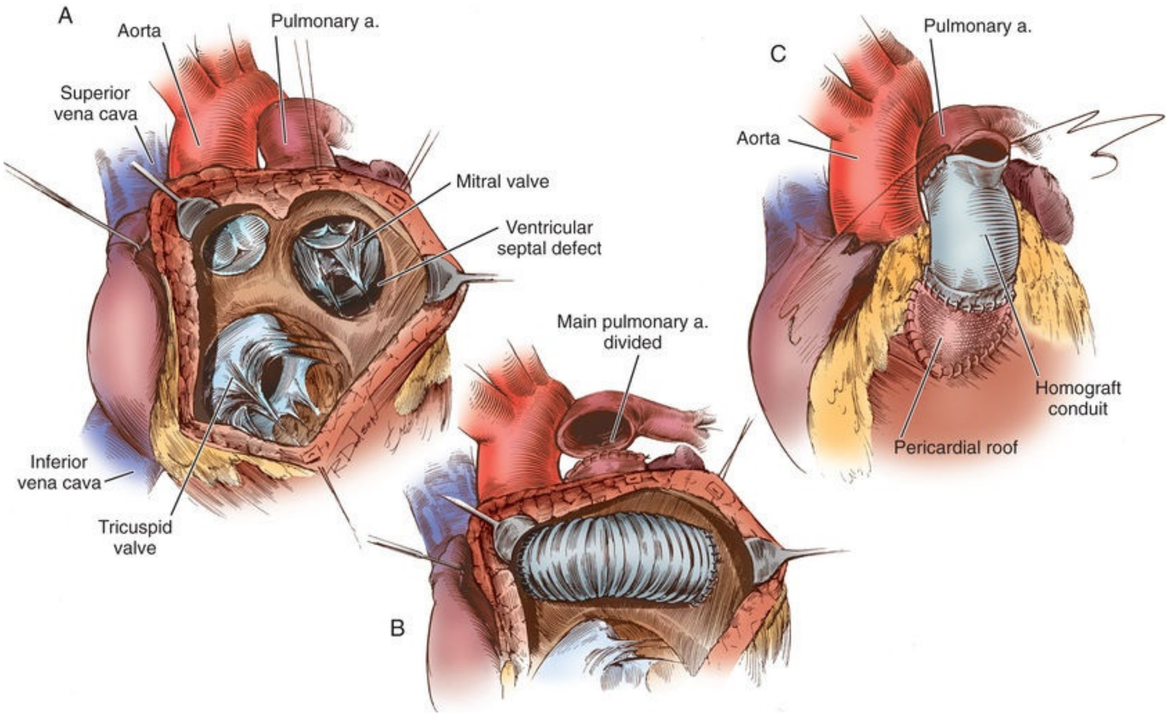
A
Aorta
Pulmonary a.
Superior vena cava
Mitral valve
Ventricular septal defect
Inferior vena cava
Tricuspid valve
Main pulmonary a. divided
B
C
Pulmonary a.
Aorta
Homograft conduit
Pericardial roof

FIG. 457.10 **A,** Taussig-Bing type of double-outlet right ventricle with subpulmonary stenosis necessitating repair by the Rastelli technique. **B,** The main pulmonary artery is divided and oversewn proximally. The pulmonary valve lies within the baffle pathway. **C,** Completion of the Rastelli repair with a right ventricle-pulmonary artery allograft conduit. (From Castañeda AR, Jonas RA, Mayer JE Jr, et al: Single-ventricle tricuspid atresia. In *Cardiac surgery of the neonate and infant,* Philadelphia, 1994, Saunders.)

457.7

Ebstein Anomaly of the Tricuspid Valve

Daniel Bernstein

Pathophysiology

Ebstein anomaly consists of downward displacement of an abnormal tricuspid valve into the right ventricle. The defect arises from failure of the normal process by which the tricuspid valve is separated from the RV myocardium (see Chapter 447). The anterior cusp of the valve retains some attachment to the valve ring, but the other leaflets are adherent to the wall of the right ventricle. The right ventricle is thus divided into 2 parts by the abnormal tricuspid valve: the first, a thin-walled “atrialized” portion, is continuous with the cavity of the right atrium; the second, often smaller portion consists of normal ventricular myocardium. The right atrium is enlarged as a result of tricuspid valve regurgitation, although the degree is extremely variable. In more severe forms of Ebstein anomaly, the effective output from the right side of the heart is decreased because of a combination of the poorly functioning small right ventricle, tricuspid valve regurgitation, and RVOT obstruction produced by the large, sail-like, anterior tricuspid valve leaflet. In newborns, RV function may be so compromised that it is unable to generate enough force to open the pulmonary valve in systole, thus producing “functional” pulmonary atresia. Some infants have true anatomic pulmonary atresia. The increased volume of right atrial blood shunts through the foramen ovale (or through an associated ASD) to the left atrium and produces cyanosis (Fig. 457.11).

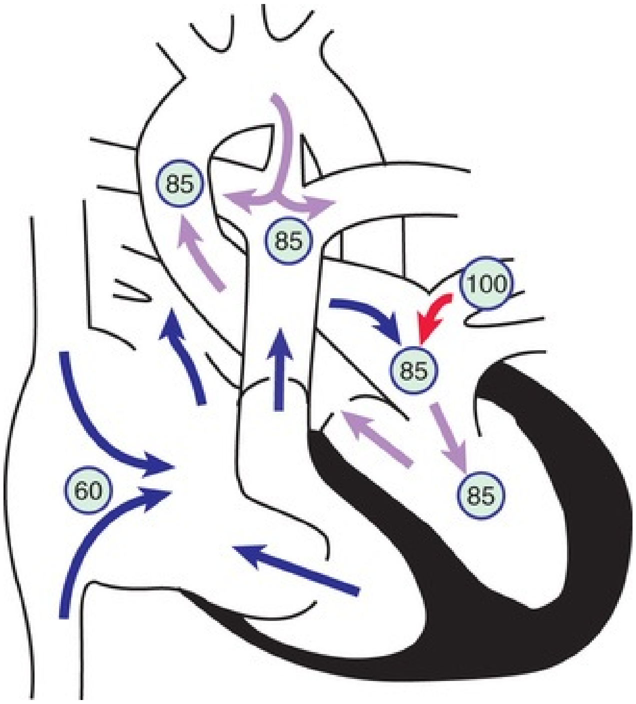

FIG. 457.11 Physiology of Ebstein anomaly of the tricuspid valve. *Circled numbers* represent oxygen saturation values. Inferior displacement of the tricuspid valve leaflets into the right ventricle has resulted in a thin-walled, low-pressure "atrialized" segment of right ventricle. The tricuspid valve is grossly insufficient. Right atrial blood flow is shunted right to left across an atrial septal defect or patent foramen ovale into the left atrium. Some blood may cross the right ventricular outflow tract and enter the pulmonary artery; however, in severe cases, the right ventricle may generate insufficient force to open the pulmonary valve, and "functional pulmonary atresia" results. In the left atrium, desaturated blood mixes with saturated pulmonary venous return. Blood enters the left ventricle and is ejected via the aorta. In this example, some pulmonary blood flow is derived from the right ventricle, the rest from a patent ductus arteriosus (PDA). Severe cyanosis will develop in neonates with a severe Ebstein anomaly when the PDA closes.

Clinical Manifestations

The severity of symptoms and the degree of cyanosis are highly variable and depend on the extent of displacement of the tricuspid valve and the severity of RVOT obstruction. In many patients, symptoms are mild and may be delayed until the teenage years or young adult life; the patient may initially have fatigue or palpitations as a result of cardiac dysrhythmias. The atrial right-to-left shunt is responsible for cyanosis and polycythemia. Jugular venous pulsations, an index of central venous pressure, may be normal or increased in those with tricuspid insufficiency. On palpation, the precordium is quiet. A holosystolic murmur caused by tricuspid regurgitation is audible over most of the anterior left side of the chest. A gallop rhythm is common and often associated with multiple clicks at the lower left sternal border. A scratchy diastolic murmur may also be heard at the left sternal border. This murmur may mimic a pericardial friction rub.

Newborns with severe forms of Ebstein anomaly have marked cyanosis, massive cardiomegaly, and long holosystolic murmurs. Death may result from cardiac failure, hypoxemia, and pulmonary hypoplasia, the result of severe long-standing intrauterine right atrial enlargement. Spontaneous improvement may occur in some neonates as pulmonary vascular resistance falls and improves the ability of the right ventricle to provide pulmonary blood flow. The majority are dependent on a PDA, and thus on a prostaglandin infusion, for pulmonary blood flow. Fetuses diagnosed with Ebstein anomaly on fetal ultrasound can present a particular challenge. Severe leakage of the tricuspid valve is one of the few congenital heart lesions that cannot be bypassed by the parallel fetal circulation, and thus cardiac enlargement and fetal heart failure may supervene. As the heart enlarges, particularly the right atrium, compression of the lungs can result, and pulmonary hypoplasia can develop.

Diagnosis

The ECG usually shows a right bundle branch block without increased right precordial voltage, normal or tall and broad P waves, and a normal or prolonged P-R interval. **Wolff-Parkinson-White syndrome** may be present, and these patients may have episodes of supraventricular tachycardia (see Chapter 462). On radiographic examination, heart size varies from slightly enlarged to massive, box-shaped cardiomegaly caused by enlargement of the right atrium. *In newborns with severe Ebstein anomaly, the heart may totally obscure the pulmonary fields.* Echocardiography is diagnostic and shows the degree of displacement of the tricuspid valve leaflets, a dilated right atrium, and any RVOT obstruction (Fig. 457.12). Pulsed and color Doppler examination demonstrates the degree of tricuspid regurgitation. In severe cases the pulmonary valve may appear immobile, and pulmonary blood flow may come solely from the ductus arteriosus. It may be difficult to distinguish true from functional pulmonary valve atresia. Cardiac catheterization, which is not usually necessary, confirms the presence of a large right atrium, an abnormal tricuspid valve, and any right-to-left shunt at the atrial level. The risk of arrhythmia is significant during catheterization and angiographic studies.

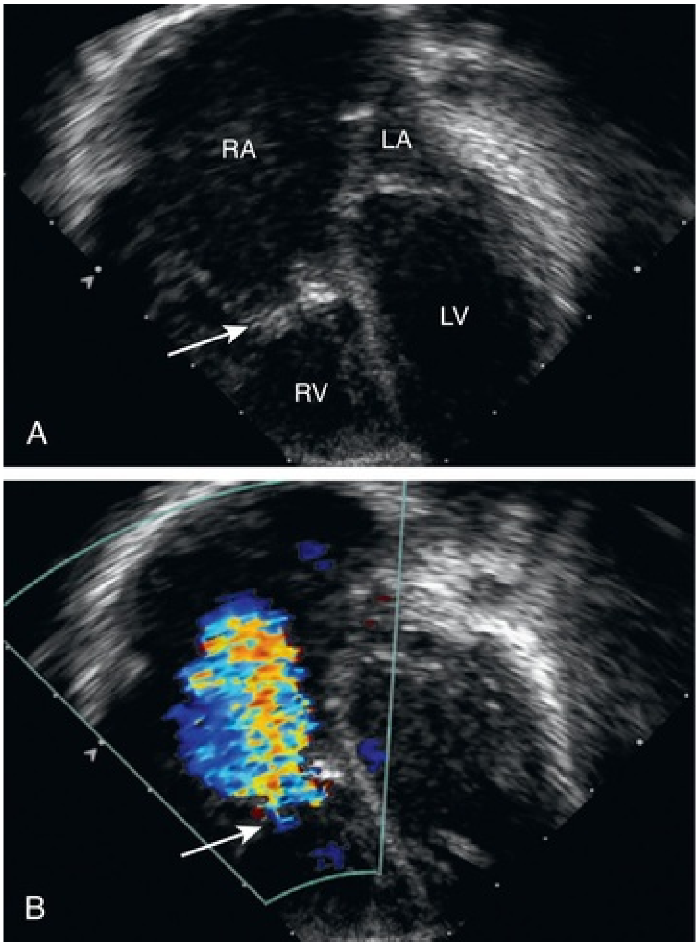

FIG. 457.12 Echocardiographic demonstration of Ebstein anomaly of the tricuspid valve. A, Subcostal, 4-chamber, 2D view showing severe displacement of the tricuspid valve leaflets *(large arrow)* inferiorly into the right ventricle. The location of the tricuspid valve annulus is outlined by the arrows. The portion of the right ventricle between the valve annulus and the valve leaflets is the "atrialized" component. B, Color Doppler examination showing severe regurgitation of the dysplastic tricuspid valve. Note that the regurgitant turbulent flow *(arrow)* begins halfway into the right ventricular chamber, at the location of the displaced valve leaflets. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Prognosis and Complications

The prognosis in Ebstein anomaly is extremely variable and depends on the severity of the defect. The prognosis is more guarded for neonates or infants with intractable symptoms and cyanosis. Patients with milder degrees of Ebstein anomaly usually survive well into adult life. An associated form of left ventricular cardiomyopathy, **isolated left ventricular noncompaction (LVNC)** , is seen in up to 18% of patients with Ebstein anomaly, and the severity of the LV dysfunction directly impacts the prognosis.

Treatment

Neonates with severe hypoxia who are prostaglandin dependent have been treated with an aortopulmonary shunt alone, by repair of the tricuspid valve, or by surgical patch closure of the tricuspid valve, atrial septectomy, and placement of an aortopulmonary shunt (with eventual single-ventricle repair using the Fontan procedure [see Chapter 457.4]). Many infants with Ebstein anomaly who have undergone valve repair will still have enough regurgitation that a Glenn shunt is performed to reduce the volume load on the right ventricle (see Chapter 457.4). In older children with mild or moderate disease, control of supraventricular dysrhythmias is of primary importance; surgical treatment may not be necessary until adolescence or young adulthood. Patients with severe tricuspid regurgitation undergo repair or replacement of the abnormal tricuspid valve along with closure of the ASD. In some older patients, a bidirectional Glenn shunt is also performed, with the superior vena cava anastomosed to the pulmonary arteries. This procedure reduces the volume of blood that the dysfunctional right side of the heart has to pump, thus creating a "one-and-one-half ventricle repair."

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CHAPTER 458

Cyanotic Congenital Heart Disease

Lesions Associated With Increased Pulmonary Blood Flow

458.1

d-Transposition of the Great Arteries

Daniel Bernstein

Transposition of the great arteries, or vessels, a common cyanotic congenital anomaly, accounts for approximately 5% of all congenital heart disease. In this anomaly, the systemic veins return normally to the right atrium and the pulmonary veins return to the left atrium. The connections between the atria and ventricles are also normal (**atrioventricular concordance**). The aorta arises from the right ventricle and the pulmonary artery from the left ventricle (Fig. 458.1). In normally related great vessels, the aorta is posterior and to the right of the pulmonary artery. In d-transposition of the great arteries (**d-TGA**), the aorta is anterior and to the right of the pulmonary artery (the *d* indicates a dextropositioned aorta, *transposition* indicates that it arises from the anterior right ventricle). Desaturated blood returning from the body to the right side of the heart goes inappropriately out the aorta and back to the body again, whereas oxygenated pulmonary venous blood returning to the left side of the heart is returned directly to the lungs. Thus the systemic and pulmonary circulations exist as 2 parallel circuits. Survival in the immediate newborn period is provided by the foramen ovale and the ductus arteriosus, which permit some mixture of oxygenated and deoxygenated blood. Approximately 50% of patients with d-TGA also have a ventricular septal defect (VSD), which usually provides for better mixing. The clinical findings and hemodynamics vary in relation to the presence or absence of associated defects (e.g., VSD or pulmonary stenosis). D-TGA is more common in infants of diabetic mothers and in males (3 : 1). Especially when accompanied by other cardiac defects such as pulmonic stenosis or right aortic arch, d-TGA can be associated with deletion of chromosome 22q11.2 (**DiGeorge syndrome** ; see Chapter 451). Before the modern era of corrective or palliative surgery, mortality was >90% in the 1st yr of life.

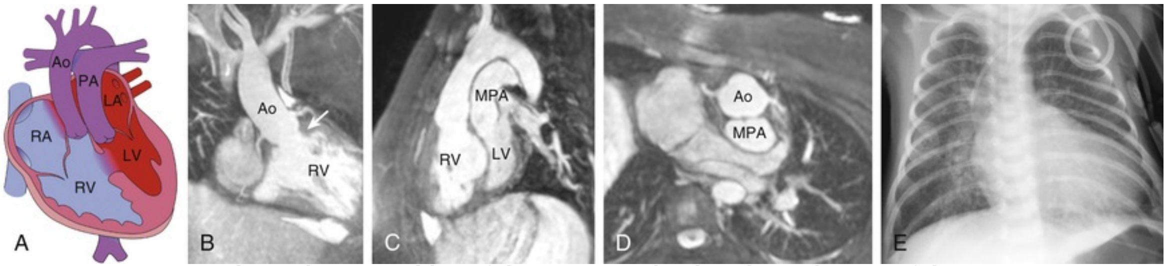

FIG. 458.1 D-looped transposition of the great arteries (TGA). A, Diagram of d-TGA, with the main pulmonary artery (MPA) arising from the left ventricle (LV) and the aorta (Ao) arising from the right ventricle (RV). The degree of cyanosis is variable and depends on the presence of intracardiac shunts such as an atrial septal defect or a ventricular septal defect (VSD) to get oxygenated blood into the systemic circulation. LA, Left atrium; PA, pulmonary artery; RA, right atrium. B and C, Oblique reformatted images from a 3D steady-state free-precession sequence show (B) the Ao arising from the anterior RV with a subaortic conus *(arrow),* and (C) the MPA arising from the posterior LV. D, The Ao and MPA have a parallel “back-to-front” arrangement. E, This parallel back-to-front arrangement contributes to the narrow mediastinum and “egg on a string” appearance seen on chest radiography. This patient has a large VSD with increased pulmonary blood flow. (From Frost JL, Krishnamurthy R, Sena L: Cardiac imaging. In Waters MM, Robertson RL editors: *Pediatric radiology—the requisites,* ed 4, Philadelphia, 2017, Elsevier, Fig 3-20, p 75.)

458.2

d-Transposition of the Great Arteries With Intact Ventricular Septum

d-TGA with an intact ventricular septum is also referred to as **simple TGA** or **isolated TGA** . Before birth, oxygenation of the fetus is only slightly abnormal, but after birth, once the ductus arteriosus begins to close, the minimal mixing of systemic and pulmonary blood by the patent foramen ovale is usually insufficient, and severe hypoxemia ensues, generally within the 1st few days of life.

Clinical Manifestations

Cyanosis and tachypnea are most often recognized within the first hours or days of life. Untreated, most of these infants would not survive the neonatal period. Hypoxemia is usually moderate to severe, depending on the degree of atrial level shunting and whether the ductus is partially open or totally closed. This condition is a medical emergency, and only early diagnosis and appropriate intervention can avert the development of prolonged severe hypoxemia and acidosis, which lead to death. Physical findings, other than cyanosis, may be remarkably nonspecific. The precordial impulse may be normal, or a parasternal heave may be present. The second heart sound (S_2) is usually single and loud, although it may be split. Murmurs may be absent, or a soft systolic ejection murmur may be noted at the mid-left sternal border.

Diagnosis

The electrocardiogram (ECG) is usually normal, showing the expected neonatal right-sided dominant pattern. Chest radiographs may show mild cardiomegaly, a narrow mediastinum (the classic “egg-shaped heart”), and normal to increased pulmonary blood flow. In the early newborn period, the chest radiograph is generally normal. As pulmonary vascular resistance (PVR) drops during the first several weeks of postnatal life, evidence of increased pulmonary blood flow becomes apparent. Arterial blood partial pressure of oxygen ($Pa{O}_2$) is low and does not rise appreciably after the patient breathes 100% oxygen (hyperoxia test), although this test may not be totally reliable. Echocardiography is diagnostic and confirms the transposed ventricular-arterial connections (Fig. 458.2). The size of the interatrial communication and the ductus arteriosus can be visualized and the degree of mixing assessed by pulsed and color Doppler examination. The presence of any associated lesion, such as left ventricular outflow tract obstruction or a VSD, can also be assessed. The origins of the coronary arteries can be imaged, although echocardiography is generally not as accurate as catheterization for this purpose. Cardiac catheterization may be performed in patients for whom noninvasive imaging is diagnostically inconclusive, where an unusual coronary artery anomaly is suspected, or in patients who require emergency balloon atrial septostomy (**Rashkind procedure**). Catheterization will show right ventricular pressure to be systemic because this ventricle is supporting the systemic circulation. The blood in the left ventricle and pulmonary artery has a higher oxygen saturation than that in the aorta. Depending on the age at catheterization, left ventricular and pulmonary artery pressure can vary from systemic level to <50% of systemic-level pressure. Right ventriculography demonstrates the anterior and rightward aorta originating from the right ventricle, as well as the intact ventricular septum. Left ventriculography shows that the pulmonary artery arises exclusively from the left ventricle.

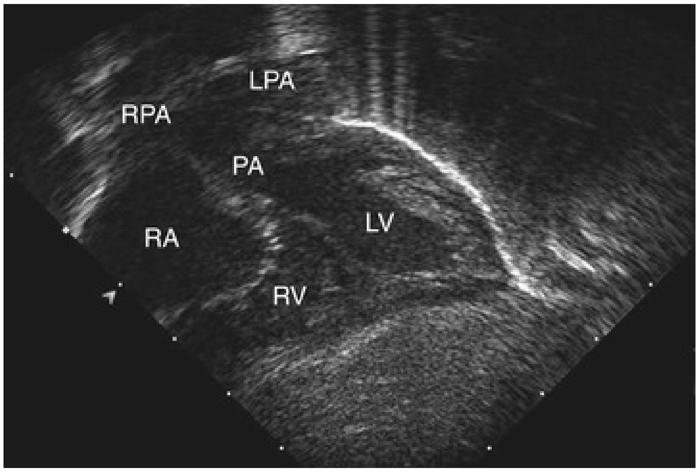

FIG. 458.2 Subcostal 4-chamber 2D echocardiographic demonstration of d-transposition of the great arteries. The pulmonary artery (PA) can be seen arising directly from the left ventricle (LV). The immediate bifurcation of this great vessel into the branch pulmonary arteries differentiates it from the aorta, which branches more distally from the heart. LPA, Left pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle.

Anomalous coronary arteries are noted in 10–15% of patients and defined by an aortic root injection or by selective coronary arteriography.

Treatment

When transposition is suspected, an infusion of prostaglandin E_1 (PGE_1 ; 0.01-0.20 µg/kg/min) should be initiated immediately to maintain patency of the ductus arteriosus and improve oxygenation. Because of the risk of apnea associated with prostaglandin infusion, an individual skilled in neonatal endotracheal intubation should be available. Hypothermia intensifies the metabolic acidosis resulting from hypoxemia, and thus the patient should be kept warm. Prompt correction of acidosis and hypoglycemia is essential.

Infants who remain severely hypoxic or acidotic despite prostaglandin infusion should undergo **Rashkind balloon atrial septostomy** (Fig. 458.3). A Rashkind atrial septostomy is also usually performed in all patients in whom any significant delay in surgery is necessary. If surgery is planned during the 1st 2 wk of life, and the patient is stable, catheterization and atrial septostomy may be avoided.

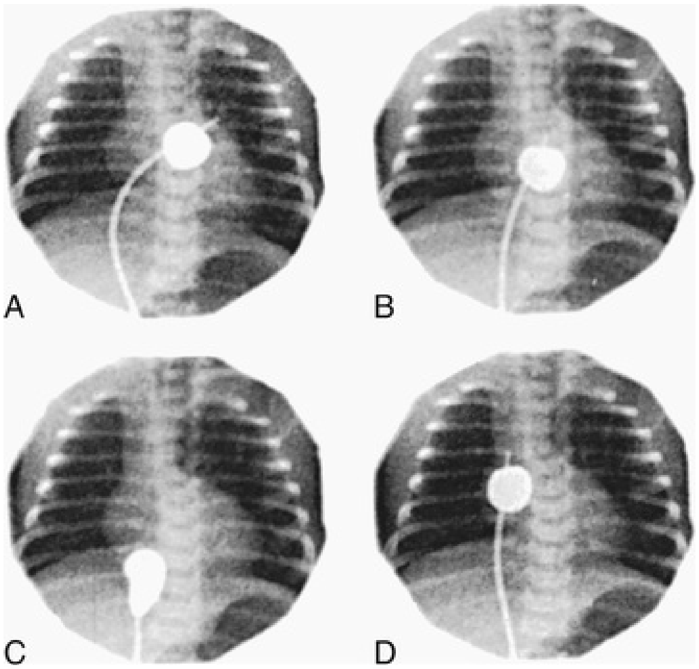

FIG. 458.3 Rashkind balloon atrial septostomy. Four frames from a continuous cineangiogram show the creation of an atrial septal defect in a hypoxemic newborn infant with transposition of the great arteries and an intact ventricular septum. A, Balloon inflated in the left atrium. B, The catheter is jerked suddenly so that the balloon ruptures the foramen ovale. C, Balloon in the inferior vena cava. D, Catheter advanced to the right atrium to deflate the balloon. The time from A to C is <1 sec.

A successful Rashkind atrial septostomy should result in a rise in PaO_2 to 35-50 mm Hg and elimination of any pressure gradient across the atrial septum. Some patients with TGA and VSD (see Chapter 458.3) may require balloon atrial septostomy because of poor mixing, even though the VSD is large. Others may benefit from decompression of the left atrium to alleviate the symptoms of increased pulmonary blood flow and left-sided heart failure.

The **arterial switch (Jatene) procedure** is the surgical treatment of choice for neonates with d-TGA and an intact ventricular septum and is usually performed within the first 2 weeks of life. The reason for this time frame is that as PVR declines after birth, pressure in the left ventricle (connected to the pulmonary vascular bed) also declines. This pressure drop results in a decrease in left ventricular (LV) mass over the first few weeks of life. If the arterial switch operation is attempted after LV pressure (and mass) has declined too far, the left ventricle will be unable to generate adequate pressure to pump blood to the high-pressure systemic circulation. The arterial switch operation involves dividing the aorta and pulmonary artery just above the sinuses and reanastomosing them in their correct anatomic positions. The coronary arteries are removed from the old aortic root along with a button of aortic wall and reimplanted in the old pulmonary root (the **neoaorta**). By using a button of great vessel tissue, the surgeon avoids having to suture directly onto the coronary artery (Fig. 458.4); this is the major innovation that has allowed the arterial switch to replace previous atrial switch operations for d-TGA. Rarely, a 2-stage arterial switch procedure, with initial placement of a pulmonary artery band, may be used in patients presenting late who already have had a reduction in LV muscle mass and pressure.

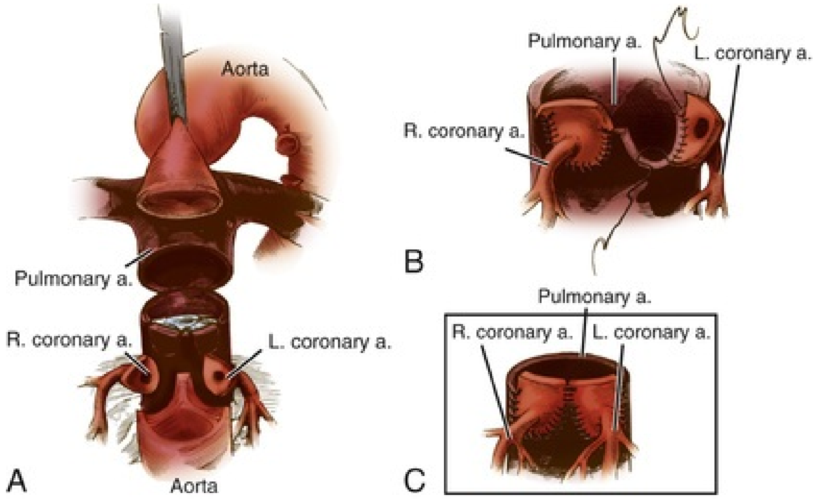

FIG. 458.4 Method for translocating the coronary arteries in the arterial switch (Jatene) procedure. A, The aorta (anterior) and the pulmonary artery (posterior) have been transected to allow visualization of the left and right coronary arteries. The coronaries have been excised from their respective sinuses, including a large flap (button) of arterial wall. Equivalent segments of the wall of the pulmonary artery (which will become the neoaorta) are also removed. B, The aortocoronary buttons are sutured into the proximal portion of the neoaorta. With this technique all sutures are placed in the button of aortic wall rather than directly on the coronary arteries. C, Completed anastomosis of the left and right coronary arteries to the neoaorta. (Adapted from Castañeda AR, Jonas RA, Mayer JE Jr, et al: *Cardiac surgery of the neonate and infant,* Philadelphia, 1994, Saunders.)

The arterial switch procedure has a survival rate of >95% for uncomplicated d-TGA. It restores the normal physiologic relationships of systemic and pulmonary arterial blood flow and eliminates the long-term complications of the previously used atrial switch procedure.

Previous operations for d-TGA consisted of some form of **atrial switch procedure** (**Mustard** or **Senning** operation). These procedures produced excellent early survival (85–90%) but had significant long-term morbidities. Atrial switch procedures reverse blood flow at the atrial level by the creation of an interatrial baffle that directs systemic venous blood returning from the venae cavae to the left atrium, where it will enter the left ventricle and then, via the pulmonary artery, the lungs. The same baffle also permits oxygenated pulmonary venous blood to cross over to the right atrium, right ventricle, and aorta. Atrial switch procedures involve significant atrial surgery and have been associated with the late development of atrial conduction disturbances, sick sinus syndrome with bradyarrhythmia and tachyarrhythmia, atrial flutter, sudden death, superior or inferior vena cava syndrome, edema, ascites, and protein-losing enteropathy. The atrial switch procedure also leaves the right ventricle as the systemic pumping chamber, and these “systemic” right ventricles often begin to fail in young adulthood. Atrial switch operations are currently reserved for patients whose anatomy is such that they are not candidates for the arterial switch procedure.

458.3

Transposition of the Great Arteries With Ventricular Septal Defect

Daniel Bernstein

If the VSD associated with d-TGA is small, the clinical manifestations, laboratory findings, and treatment are similar to those described previously for transposition with an intact ventricular septum. A harsh systolic murmur is audible at the lower left sternal border, resulting from flow through the defect. Many of these small defects eventually close spontaneously and may not be addressed at the time of surgery.

When the VSD is large and not restrictive to ventricular ejection, significant mixing of oxygenated and deoxygenated blood usually occurs and clinical manifestations of cardiac failure are seen. The degree of cyanosis may be subtle and sometimes may not be recognized until an oxygen saturation measurement is performed. The murmur is holosystolic and generally indistinguishable from that produced by a large VSD in patients with normally related great arteries. The heart is usually significantly enlarged.

Cardiomegaly, a narrow mediastinal waist, and increased pulmonary vascularity are demonstrated on the chest radiograph. The ECG shows prominent P waves and isolated right ventricular hypertrophy or biventricular hypertrophy. Occasionally, dominance of the left ventricle is present. Usually, the QRS axis is to the right, but it can be normal or even to the left. The diagnosis is confirmed by echocardiography, and the extent of pulmonary blood flow can also be assessed by the degree of enlargement of the left atrium and ventricle. In equivocal cases, the diagnosis can be confirmed by cardiac catheterization. Right and left ventriculography indicate the presence of arterial transposition and demonstrate the site and size of the VSD. Systolic pressure is equal in the 2 ventricles, the aorta, and pulmonary artery. Left atrial pressure may be much higher than right atrial pressure, a finding indicative of a restrictive communication at the atrial level. At the time of cardiac catheterization, Rashkind balloon atrial septostomy may be performed to decompress the left atrium, even when adequate mixing is occurring at the ventricular level.

Surgical treatment is advised soon after diagnosis, because heart failure and failure to thrive are difficult to manage and pulmonary vascular disease can develop unusually rapidly in these patients. Preoperative management with diuretics lessens the symptoms of heart failure and stabilizes the patient before surgery.

Patients with d-TGA and a VSD without pulmonic stenosis can be treated with an arterial switch procedure combined with VSD closure. In these patients, the arterial switch operation can be safely performed after the 1st 2 wk of life because the VSD results in equal pressure in both ventricles and prevents regression of LV muscle mass. At major centers, however, there is no reason to delay repair, because results are excellent whether the surgery is performed in the neonatal period or later.

458.4

L-Transposition of the Great Arteries (Corrected Transposition)

Daniel Bernstein

In l-transposition (l-TGA), the atrioventricular relationships are discordant: the right atrium is connected to a left ventricle and the left atrium to a right ventricle (also known as **ventricular inversion**). The great arteries are also transposed, with the aorta arising from the right ventricle and the pulmonary artery from the left. In contrast to d-TGA, the aorta arises to the left of the pulmonary artery (thus the designation *l* for levo-transposition). The aorta may be anterior to the pulmonary artery, although often they are nearly side by side.

The physiology of l-TGA is quite different from that of d-TGA. Desaturated systemic venous blood returns via the vena cavae to a normal right atrium, from which it passes through a bicuspid atrioventricular (mitral) valve into a right-sided ventricle that has the architecture and smooth wall morphologic features of the normal left ventricle (Fig. 458.5). Because transposition is also present, however, the desaturated blood ejected from this left ventricle enters the transposed pulmonary artery and flows into the lungs, as it would in the normal circulation. Oxygenated pulmonary venous blood returns to a normal left atrium, passes through a tricuspid atrioventricular valve into a left-sided ventricle, which has the trabeculated morphologic features of a normal right ventricle, and is then ejected into the transposed aorta. The double inversion of the atrioventricular and ventriculoarterial relationships result in desaturated right atrial blood appropriately flowing to the lungs and oxygenated pulmonary venous blood appropriately flowing to the aorta. The circulation is thus physiologically “corrected.” Without other defects, the hemodynamics would be almost normal. In most patients, associated anomalies coexist: VSD, Ebstein-like abnormalities of the left-sided atrioventricular (tricuspid) valve, pulmonary valvular or subvalvular stenosis (or both), and atrioventricular conduction disturbances (complete heart block, accessory pathways such as Wolff-Parkinson-White syndrome).

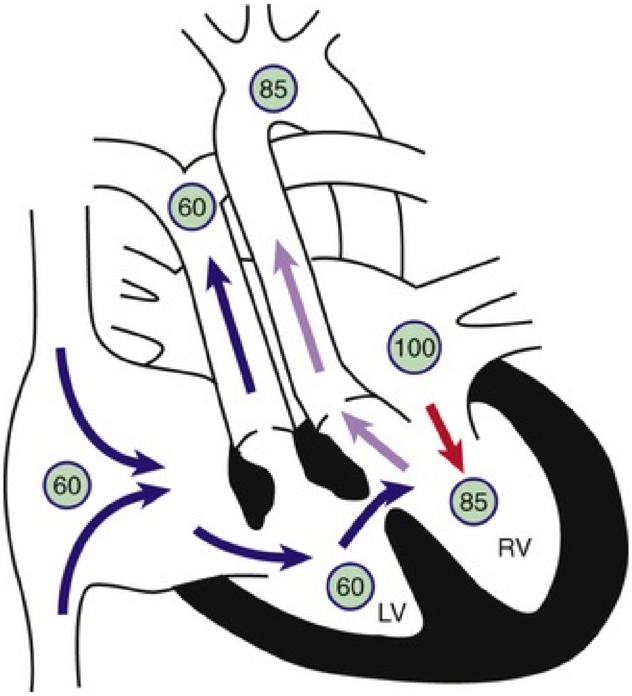

FIG. 458.5 Physiology of l-transposition or corrected transposition of the great arteries (l-TGA) with a ventricular septal defect and pulmonic stenosis (VSD + PS). *Circled numbers* represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Blood from the right atrium flows through the mitral valve into the "inverted" left ventricle (LV). The left ventricle is, however, attached to the transposed pulmonary artery. Therefore, despite the anomalies, desaturated blood still winds up in the pulmonary circulation. Saturated blood returns to the left atrium, traverses the tricuspid valve into the "inverted" right ventricle (RV), and is pumped into the transposed aorta. This circulation would be totally "corrected" were it not for the frequent association of other congenital anomalies, in this case, VSD + PS. Because of the stenotic pulmonary valve, some left ventricular blood flow crosses the VSD and into the right ventricle and the ascending aorta, and systemic desaturation results.

Clinical Manifestations

Symptoms and signs are widely variable and are determined by the associated lesions. If pulmonary outflow is unobstructed, the clinical signs are similar to those of an isolated VSD. If l-TGA is associated with pulmonary stenosis and a VSD, the clinical signs are more similar to those of tetralogy of Fallot.

Diagnosis

The chest radiograph may suggest the abnormal position of the great arteries; the ascending aorta occupies the upper left border of the cardiac silhouette and has a straight profile. The ECG, in addition to any atrioventricular conduction disturbances, may show abnormal P waves; absent Q waves in V_6 ; abnormal Q waves in leads III, aVR, aVF, and V_1 ; and upright T waves across the precordium. The echocardiogram is diagnostic. The characteristic echocardiographic features of the right ventricle (moderator band, coarser trabeculations, tricuspid valve that sits more inferiorly compared to the bicuspid mitral valve, and a smooth muscular conus or infundibulum separating the atrioventricular valve from the semilunar valve) allow the echocardiographer to determine the presence of **atrioventricular discordance** (right atrium connected to left ventricle; left atrium to right ventricle).

Surgical treatment of the associated anomalies, most often the VSD, is complicated by the position of the bundle of His, which can be injured at surgery and result in heart block. Identification of the usual course of the bundle in corrected transposition (running superior to the defect) has been accomplished by mapping of the conduction system so that the surgeon can avoid the bundle of His during repair. Even without surgical injury, patients with l-TGA are at risk for heart block as they grow older.

Because simple surgical correction leaves the right ventricle as the systemic pumping chamber, and thus vulnerable to late ventricular failure, surgeons have become more aggressive about trying operations that utilize the left ventricle as the systemic pumping chamber. This is accomplished by performing an atrial switch operation, to reroute the systemic and pulmonary venous returns, in combination with an arterial switch operation to reroute the ventricular outflows (**double switch procedure**). The long-term benefit of this approach in preserving systemic ventricular function is still under investigation.

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458.5

Double-Outlet Right Ventricle Without Pulmonary Stenosis

Daniel Bernstein

In double-outlet right ventricle without pulmonary stenosis, both the aorta and the pulmonary artery arise from the right ventricle (see Chapter 457.5). The only outlet from the left ventricle is through a VSD. In the absence of obstruction to pulmonary blood flow, clinical manifestations are similar to those of an uncomplicated VSD with a large left-to-right shunt, although mild systemic desaturation may result from mixing of oxygenated and deoxygenated blood in the right ventricle. The ECG usually shows biventricular hypertrophy. Echocardiography is diagnostic and shows the right ventricular origin of both great arteries, their anteroposterior relationship, as well as the relationship of the VSD to each of the great arteries. Surgical correction is dependent on these relationships. If the VSD is subaortic, it is accomplished by creation of an intracardiac tunnel. Blood is then ejected from the left ventricle via the VSD into the aorta. If the VSD is subpulmonic, an arterial switch may be performed in combination with an intracardiac tunnel. If pulmonary blood flow is excessive enough to cause congestive heart failure, pulmonary arterial banding may be required in infancy, followed by surgical correction when the child is bigger.

When associated pulmonary stenosis is present, cyanosis is more marked, pulmonary blood flow is decreased, and clinical presentation may be similar to that of tetralogy of Fallot.

458.6

Double-Outlet Right Ventricle With Malposition of the Great Arteries (Taussig-Bing Anomaly)

Daniel Bernstein

In double-outlet right ventricle with malposed great arteries, the VSD is usually directly subpulmonic and the aorta distant from the left ventricle. Sometimes both the pulmonary and the aortic valve may be located close to the VSD (**doubly committed** VSD) and sometimes neither is (**doubly uncommitted** VSD). The term *malposition* is used instead of *transposition* because both great arteries arise from the right ventricle. Aortic obstructive lesions are common, including valvular and subvalvular aortic stenosis, coarctation of the aorta, and interruption of the aortic arch. Because pulmonary blood flow is unobstructed, patients experience cardiac failure early in infancy and are at risk for the development of pulmonary vascular disease and cyanosis. If aortic obstructive lesions are a component, patients can present with poor systemic output and cardiovascular collapse, particularly after the ductus begins to close. Cardiomegaly is usual, and a parasternal systolic ejection murmur is audible, sometimes preceded by an ejection click and loud closure of the pulmonary valve. The ECG shows right axis deviation and right, left, or biventricular hypertrophy. The chest radiograph shows cardiomegaly and prominence of the pulmonary vasculature. The anatomic features of the anomaly and associated abnormalities are usually demonstrated by echocardiography, augmented if necessary by either cardiac catheterization, MRI, or CT. Palliation may be achieved by pulmonary arterial banding in infancy and surgical correction at a later age, which may be accomplished by an arterial switch procedure (see Chapter 458.2) combined with an intracardiac baffle, or some modification of the Rastelli procedure (see Chapter 457.5).

458.7

Total Anomalous Pulmonary Venous Return

Daniel Bernstein

Pathophysiology

Abnormal development of the pulmonary veins may result in either partial or complete anomalous drainage into the systemic venous circulation. Partial anomalous pulmonary venous return is usually an acyanotic lesion (see Chapter 453.4). Total anomalous pulmonary venous return (TAPVR) is associated with total mixing of systemic venous and pulmonary venous blood flow within the heart and thus produces cyanosis.

In TAPVR, there is no direct pulmonary venous connection into the left atrium (Fig. 458.6). The pulmonary veins may drain **above** the diaphragm into the right atrium directly, into the coronary sinus, or into the superior vena cava by a "vertical vein," or they may drain **below** the diaphragm and join into a "descending vein" that enters into the inferior vena cava or one of its major tributaries, often through the ductus venosus. This latter form of anomalous venous drainage is most often associated with *obstruction* to venous flow, usually as the ductus venosus closes soon after birth, although **supracardiac** anomalous veins may also become obstructed. Occasionally, the drainage may be **mixed** , with some veins draining above and others below the diaphragm.

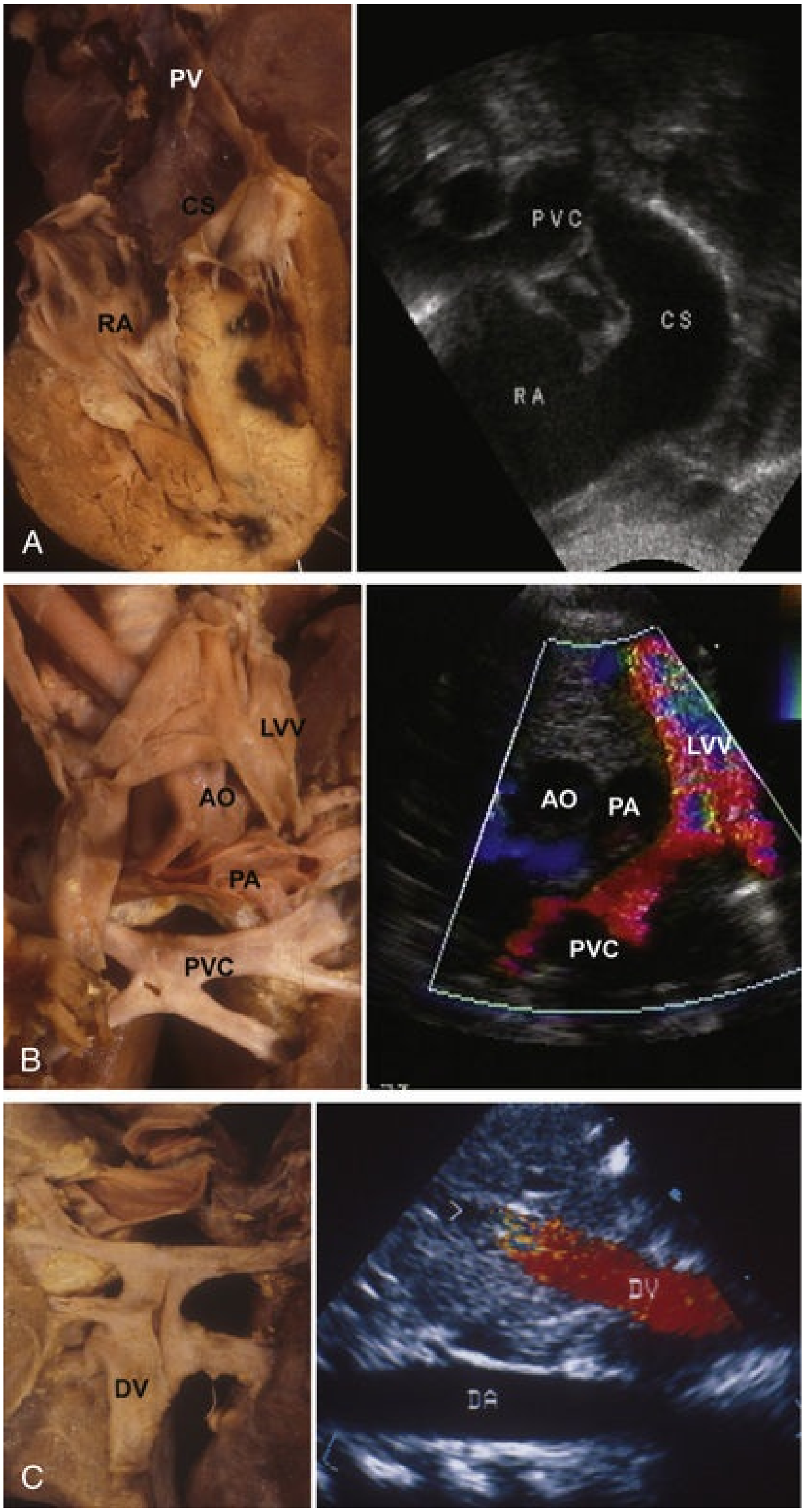
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FIG. 458.6 **A,** Subcostal view demonstrating total anomalous pulmonary drainage to the coronary sinus. Note the dilated coronary sinus in both images. The echocardiogram also demonstrates an associated confluence that connects to the coronary sinus. **B,** Suprasternal view demonstrating total anomalous pulmonary venous drainage to a left vertical vein. Note the

direction of flow in the vertical vein that differentiates it from a left superior vena cava. **C,** Total anomalous pulmonary venous drainage below the diaphragm. The specimen shows the pulmonary veins as they enter the confluence, whereas the echocardiogram demonstrates the descending veins as they enter the liver. Note that the direction of flow is away from the heart. AO, Aorta; CS, coronary sinus; DA, descending aorta; DV, descending vein; LVV, left vertical vein; PA, pulmonary artery; PV, pulmonary vein; PVC, pulmonary venous confluence; RA, right atrium. (From Webb GD, Smallhorn, JF, Therrien J, Redington, AN: Congenital heart disease in the adult and pediatric patient. In *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2018, Elsevier, Fig 75-32, p 1553).

All forms of TAPVR involve mixing of oxygenated and deoxygenated blood before or at the level of the right atrium (**total mixing lesion**). This mixed right atrial blood either passes into the right ventricle and pulmonary artery or passes through an atrial septal defect (ASD) or patent foramen ovale into the left atrium, which will be the only source of systemic blood flow. The right atrium and ventricle and the pulmonary artery are generally enlarged, whereas the left atrium and ventricle may be normal or small. The clinical manifestations of TAPVR depend on the presence or absence of *obstruction* of the venous channels (Table 458.1). If pulmonary venous return is obstructed, severe pulmonary congestion and pulmonary hypertension develop; rapid deterioration occurs without surgical intervention. *Obstructed TAPVR is a pediatric cardiac surgical emergency because prostaglandin therapy is usually not effective.*

Table 458.1

Total Anomalous Pulmonary Venous Return

SITE OF CONNECTION (% OF CASES)	% WITH SIGNIFICANT OBSTRUCTION
Supracardiac (50)	
Left superior vena cava (40)	40
Right superior vena cava (10)	75
Cardiac (25)	
Coronary sinus (20)	10
Right atrium (5)	5
Infracardiac (20)	95-100
Mixed (5)	

Clinical Manifestations

Two major clinical patterns of TAPVR are seen, depending on the presence or absence of obstruction. Those neonates with severe obstruction to pulmonary venous return, most prevalent in the **infracardiac** group (see Table 458.1), present with severe cyanosis and respiratory distress. Murmurs may not be present. These infants are severely ill and fail to respond to mechanical ventilation. Rapid diagnosis and surgical correction are necessary for survival. In contrast, those with mild or no obstruction to pulmonary venous return are usually characterized by the development of heart failure as the pulmonary vascular resistance falls, with mild to moderate degrees of desaturation. Systolic murmurs may be audible along the left sternal border, and a gallop rhythm may be present. Some infants may have mild obstruction in the neonatal period and develop worsening obstruction as time passes.

Diagnosis

The ECG demonstrates right ventricular hypertrophy (usually qR pattern in V_3 R and V_1 , and P waves are frequently tall and spiked). In neonates with marked pulmonary venous obstruction, the chest radiograph demonstrates a very dramatic perihilar pattern of pulmonary edema and a small heart. This appearance can sometimes be confused with primary pulmonary disease, and the differential diagnosis includes persistent pulmonary hypertension of the newborn, respiratory distress syndrome, pneumonia (bacterial, meconium aspiration), pulmonary lymphangiectasia, and other heart defects (hypoplastic left heart syndrome). In older children, if the anomalous pulmonary veins enter the innominate vein and persistent left superior vena cava (Fig. 458.7), a large supracardiac shadow can be seen, which together with the normal cardiac shadow forms a “snowman” appearance. In most cases without obstruction, the heart is enlarged, the pulmonary artery and right ventricle are prominent, and pulmonary vascularity is increased.

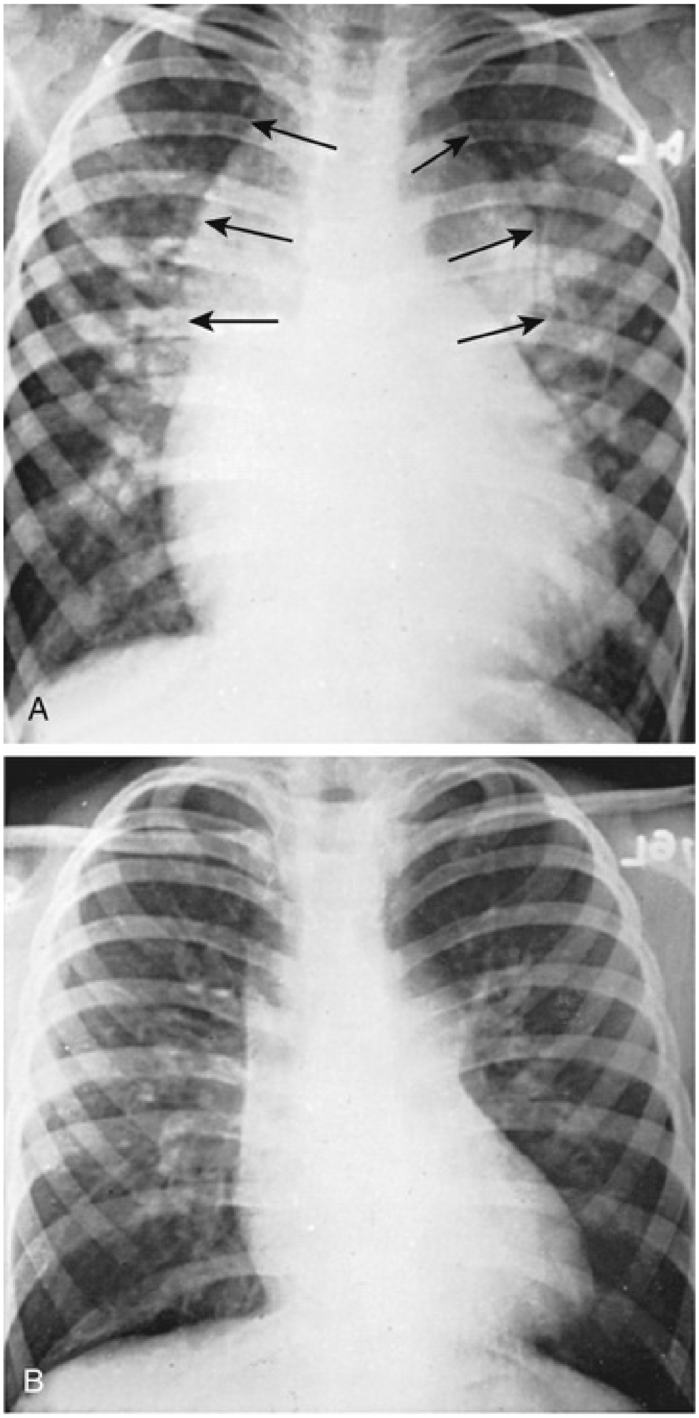

FIG. 458.7 **Chest radiographs of total anomalous pulmonary venous return to the left superior vena cava. A, Preoperative image. *Arrows* point to the supracardiac shadow, which produces the "snowman" or figure-8 configuration. Cardiomegaly and increased pulmonary vascularity are evident. B, Postoperative image showing a decrease in the size of the heart and the supracardiac shadow.**

The echocardiogram demonstrates a large right ventricle and usually identifies the pattern of abnormal pulmonary venous connections (see Fig. 458.6). The demonstration of any vein with Doppler flow away from the heart is pathognomonic of TAPVR, because normal venous flow is usually toward the heart. Shunting occurs from right to left at the atrial level. The size of the left atrium and left ventricle can be measured, and the presence of any associated cardiac defects determined.

Echocardiography should be adequate to demonstrate TAPVR in most cases; however, if there is question about the drainage of 1 or more pulmonary veins, cardiac catheterization, MRI, or CT is performed. Catheterization shows that the oxygen saturation of blood in both atria, both ventricles, and the aorta is similar, indicative of a total mixing lesion. An increase in systemic venous saturation occurs at the site of entry of the abnormal pulmonary venous channel, either above or below the diaphragm. In older patients, pulmonary arterial and right ventricular pressure may be only moderately elevated, but in infants with pulmonary venous obstruction, pulmonary hypertension is usual. Selective pulmonary arteriography shows the anatomy of the pulmonary veins and their point of entry into the systemic venous circulation.

Treatment

Surgical correction of TAPVR is indicated during infancy, with emergent repair performed for those patients with venous obstruction. If surgery cannot be performed urgently, extracorporeal membrane oxygenation may be required to maintain oxygenation. Surgically, the pulmonary venous confluence is anastomosed directly to the left atrium, the ASD is closed, and any connection to the systemic venous circuit is interrupted. Early results are generally good, even for critically ill neonates. The postoperative period may be complicated by pulmonary vascular hypertensive crises. In some patients, especially those in whom the diagnosis was delayed or the obstruction was severe, recurrent stenosis and development of pulmonary venoocclusive disease may occur. Attempts have been made to treat recurrent stenosis with surgery, balloon angioplasty, stents, and antiproliferative chemotherapy. To date, the long-term prognosis in these patients is very guarded. In those with aggressive venoocclusive disease, **heart-lung transplantation** may be the only option (see Chapter 470.2).

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458.8

Truncus Arteriosus

Daniel Bernstein

Pathophysiology

In truncus arteriosus, a single arterial trunk (truncus arteriosus) arises from the heart and supplies the systemic, pulmonary, and coronary circulations. A VSD is always present, with the truncus overriding the defect and receiving blood from both the right and left ventricles (Fig. 458.8). The number of truncal valve cusps varies from 2 to as many as 6, and the valve may be stenotic, regurgitant, or both. The pulmonary arteries can arise together from the posterior left side of the persistent truncus arteriosus and then divide into left and right pulmonary arteries (**type I**). In types II and III truncus arteriosus, no main pulmonary artery is present, and the right and left pulmonary arteries arise from separate orifices on the posterior (**type II**) or lateral (**type III**) aspects of the truncus arteriosus. *Type IV truncus* is a term no longer used because, in this case, there is no identifiable connection between the heart and pulmonary arteries, and pulmonary blood flow is derived from major aortopulmonary collateral arteries arising from the transverse or descending aorta; this is essentially a form of pulmonary atresia (see Chapter 457.2).

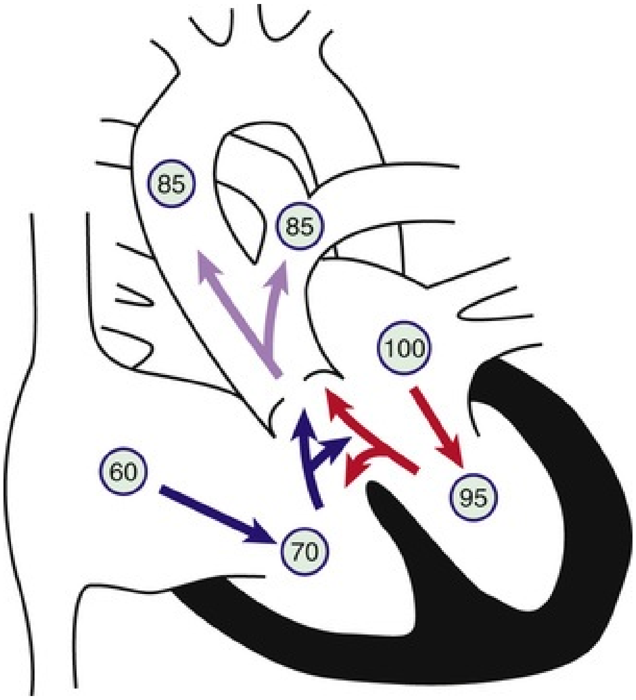

FIG. 458.8 **Physiology of truncus arteriosus.** ***Circled numbers*** **represent oxygen saturation values. Right atrial (mixed venous) oxygen saturation is decreased secondary to systemic hypoxemia. Desaturated blood enters the right atrium, flows through the tricuspid valve into the right ventricle, and is ejected into the truncus.**

Saturated blood returning from the left atrium enters the left ventricle and is also ejected into the truncus. The common aortopulmonary trunk gives rise to the ascending aorta and to the main or branch pulmonary arteries. Oxygen saturation in the aorta and pulmonary arteries is usually the same (definition of a total mixing lesion). As pulmonary vascular resistance decreases in the 1st few wk of life, pulmonary blood flow increases dramatically and mild cyanosis and congestive heart failure result.

Both ventricles are at systemic pressure, and both eject blood into the truncus. When pulmonary vascular resistance (PVR) is relatively high immediately after birth, pulmonary blood flow may be normal; as PVR drops in the 1st mo of life, blood flow to the lungs is greatly increased and heart failure ensues. Truncus arteriosus is a total mixing lesion with complete admixture of pulmonary and systemic venous return. Because of the large volume of pulmonary blood flow, clinical cyanosis is usually mild. If the lesion is left untreated, PVR eventually increases, pulmonary blood flow decreases, and cyanosis becomes more prominent (**Eisenmenger physiology** ; see Chapter 460.2).

Clinical Manifestations

The clinical signs of truncus arteriosus vary with age and depend on the level of PVR. In the immediate newborn period, signs of heart failure are usually absent; a murmur and minimal cyanosis may be the only initial findings. Over the next 1-2 mo of life, pulmonary blood flow begins to become torrential, and the clinical picture is dominated by heart failure, with still mild cyanosis. Runoff of blood from the truncus to the pulmonary circulation may result in a wide pulse pressure and bounding pulses. These findings will be further exaggerated if truncal valve insufficiency is present. The heart is usually enlarged, and the precordium is hyperdynamic. S_2 is loud and single. A systolic ejection murmur, sometimes accompanied by a thrill, is generally audible along the left sternal border. The murmur is frequently preceded by an early systolic ejection click caused by the abnormal truncal valve. In the presence of truncal valve insufficiency, a high-pitched early diastolic decrescendo murmur is heard at the mid-left sternal border. An apical mid-diastolic rumbling murmur caused by increased flow through the mitral valve is often audible with the bell of the stethoscope, especially as heart failure develops. Truncus arteriosus is a conotruncal malformation and may be associated with **DiGeorge syndrome** , linked to a deletion of a large region of **chromosome 22q11** (see Chapter 451).

Diagnosis

The ECG shows right, left, or combined ventricular hypertrophy. The chest radiograph also shows considerable variation. Cardiac enlargement will develop over the 1st several wk of life and is a result of the prominence of both ventricles. The truncus may produce a prominent shadow that follows the normal course of the ascending aorta and aortic knob; the aortic arch is right sided in 50% of patients. Sometimes a high bulge left of the aortic knob is produced by the main or left pulmonary artery. Pulmonary vascularity is increased after the 1st few wk of life. Echocardiography is diagnostic and demonstrates the large truncal artery overriding the VSD and the pattern of origin of the branch pulmonary arteries (Fig. 458.9). Associated anomalies such as an interrupted aortic arch may be noted. Pulsed and color Doppler studies are used to evaluate truncal valve regurgitation. If required, cardiac catheterization shows a left-to-right shunt at the ventricular level, with right-to-left shunting into the truncus. Systolic pressure in both ventricles and the truncus is similar. Angiography reveals the large truncus arteriosus and more defines the origin of the pulmonary arteries.

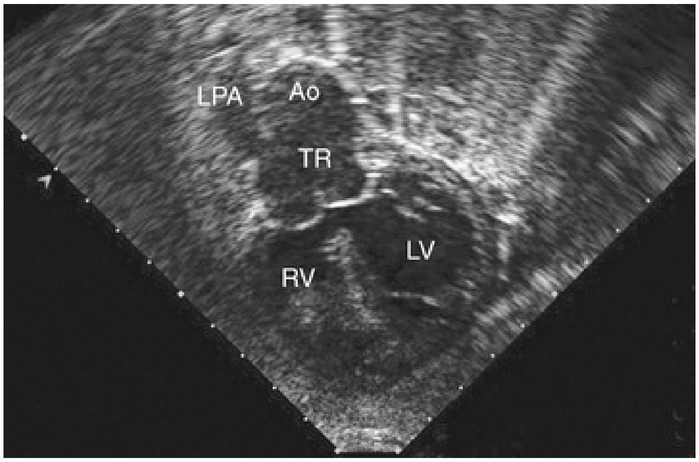

FIG. 458.9 Subcostal 2D echocardiographic demonstration of truncus arteriosus. The large truncal valve can be seen overriding the ventricular septal defect. In this case, only the left pulmonary artery (LPA) arises from the truncus (TR). The pulmonary arteries are discontinuous, and the right pulmonary artery arises from the descending aorta via the ductus arteriosus (not shown). Ao, Aorta; LV, left ventricle; RV, right ventricle.

Prognosis and Complications

Surgical results have been excellent, and many patients with repaired truncus are entering mid-adulthood with several centers reporting 30 and 40 yr old survivors. The need to replace the right ventricular–to–pulmonary artery conduit as the child grows means that these patients will need to undergo multiple operations by the time they reach adulthood. The development of transcatheter stent-valves may reduce this in the future (see Chapter 450). When truncus arteriosus is associated with DiGeorge syndrome, the associated endocrine, immunologic, craniofacial, and airway abnormalities may complicate recovery.

Treatment

In the first few weeks of life, many of these infants can be managed with anticongestive medications; as PVR falls, heart failure symptoms worsen and surgery is indicated, usually within the 1st few mo. Delay of surgery much beyond this time period may increase the likelihood of pulmonary vascular disease; many centers now perform routine neonatal repair at the time of diagnosis. At surgery, the VSD is closed, the pulmonary arteries are separated from the truncus, and continuity is established between the right ventricle and the pulmonary arteries with a homograft conduit. Immediate surgical results are excellent, but these conduits will develop either regurgitation or stenosis over time and must be replaced, often several times, as the child grows. If regurgitation is the primary problem, patients can now be treated with a transcatheter stent-valve.

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458.9

Single Ventricle (Double-Inlet Ventricle, Univentricular Heart)

Daniel Bernstein

Pathophysiology

With a single ventricle, both atria empty through a common atrioventricular valve or through 2 separate valves into a single ventricular chamber, with total mixing of systemic and pulmonary venous return. This chamber may have left, right, or indeterminate ventricular anatomic characteristics. The aorta and pulmonary artery both arise from this single chamber, although one of the great vessels may originate from a rudimentary outflow chamber. The aorta may be posterior, anterior (malposition), or side-by-side with the pulmonary artery and either to the right or to the left. Pulmonary stenosis or atresia is common.

Clinical Manifestations

The clinical picture is variable and depends on the associated intracardiac anomalies. If pulmonary outflow is obstructed, the findings are usually similar to those of tetralogy of Fallot: marked cyanosis without heart failure. If pulmonary outflow is unobstructed, the findings are similar to those of transposition with VSD: minimal cyanosis with increasing heart failure.

In patients with **pulmonary stenosis** , cyanosis is present in early infancy. Cardiomegaly is mild or moderate, a left parasternal lift is palpable, and a systolic thrill is common. The systolic ejection murmur is usually loud; an ejection click may be audible, and S_2 is single and loud. In patients with **unobstructed pulmonary flow** , as PVR drops, torrential pulmonary blood flow develops, and these patients present with tachypnea, dyspnea, failure to thrive, and recurrent pulmonary infections. Cyanosis is only mild or moderate. Cardiomegaly is generally marked, and a left parasternal lift is palpable. A systolic ejection murmur is present but is not usually loud or harsh, and S_2 is loud and closely split. A third heart sound (S_3) is common and may be followed by a short mid-diastolic rumbling murmur caused by increased flow through the atrioventricular valves. The eventual development of pulmonary vascular disease reduces pulmonary blood flow so that the cyanosis increases, and signs of cardiac failure appear to improve (Eisenmenger physiology; see Chapter 460.2).

Diagnosis

ECG findings are nonspecific. P waves are normal, spiked, or bifid. The precordial lead pattern suggests right ventricular hypertrophy, combined ventricular hypertrophy, or sometimes left ventricular dominance. The initial QRS forces are usually to the left and anterior. Radiographic examination confirms the degree of cardiomegaly. If present, a rudimentary outflow chamber may produce a bulge on the upper left border of the cardiac silhouette in the posteroanterior projection. In the absence of pulmonary stenosis, pulmonary vasculature is increased, whereas in the presence of pulmonary stenosis, pulmonary vasculature is diminished. Echocardiography will confirm the absence or near-absence of the ventricular septum and can usually determine whether the single ventricle has right, left, or mixed morphologic features. The presence of a rudimentary outflow chamber under one of the great vessels can be identified, and pulsed Doppler can be used to determine whether flow through this communication (known as a *bulboventricular foramen*) is obstructed.

If cardiac catheterization is performed, the pressure in the single ventricular chamber is at systemic level; however, a gradient may be demonstrated across the entrance to a rudimentary outflow chamber. Pressure measurements and angiography demonstrate whether pulmonary stenosis is present.

Prognosis and Complications

Unoperated, some patients succumb during infancy from heart failure. Others may survive to adolescence and early adult life but finally succumb to the effects of chronic hypoxemia or, in the absence of pulmonary stenosis, to the effects of pulmonary vascular disease. Patients with moderate pulmonary stenosis have the best prognosis because pulmonary blood flow, though restricted, is still adequate. Surgical palliation, eventually leading to Fontan-type circulatory physiology (see Chapter 457.4), has very good short- and intermediate-term results.

Treatment

If pulmonary stenosis is severe, a **Blalock-Taussig aortopulmonary shunt** is performed to provide a reliable source of pulmonary blood flow (see Chapter 457.1). If pulmonary blood flow is unrestricted, pulmonary arterial banding is used to control heart failure and prevent progressive pulmonary vascular disease. The **bidirectional Glenn shunt** is usually performed at 2-6 mo of age, followed by a **modified Fontan operation** (cavopulmonary isolation procedure; see Chapter 457.4) at 2-3 yr. If subaortic stenosis is present because of a restrictive connection to a rudimentary outflow chamber (*restrictive* bulboventricular foramen), surgical relief can be provided by anastomosing the proximal pulmonary artery to the side of the ascending aorta (**Damus-Stansel-Kaye operation**).

458.10

Hypoplastic Left Heart Syndrome

Daniel Bernstein

Pathophysiology

The term *hypoplastic left heart* is used to describe a related group of anomalies that include various degrees of underdevelopment of the left side of the heart: stenosis or atresia of the aortic and mitral valves, and hypoplasia of the left ventricular cavity and ascending aorta. Two broad categories include aortic atresia with hypoplastic but perforate mitral valve or with mitral atresia. The left ventricle may be only moderately hypoplastic, very small and nonfunctional, or totally atretic; in the immediate neonatal period the right ventricle maintains both the pulmonary circulation and the systemic circulation via the ductus arteriosus (Fig. 458.10). Pulmonary venous blood passes through an ASD (may also be restrictive) or dilated foramen ovale from the left to the right side of the heart, where it mixes with systemic venous blood (total mixing lesion). When the ventricular septum is intact, which is usually the case, all the right ventricular blood is ejected into the main pulmonary artery; the descending aorta is supplied via the ductus arteriosus, and flow from the ductus also fills the ascending aorta and coronary arteries in a retrograde fashion. The major hemodynamic abnormalities are inadequate maintenance of the systemic circulation and, depending on the size of the atrial-level communication, either pulmonary venous hypertension (restrictive foramen ovale) or pulmonary overcirculation (moderate or large ASD).

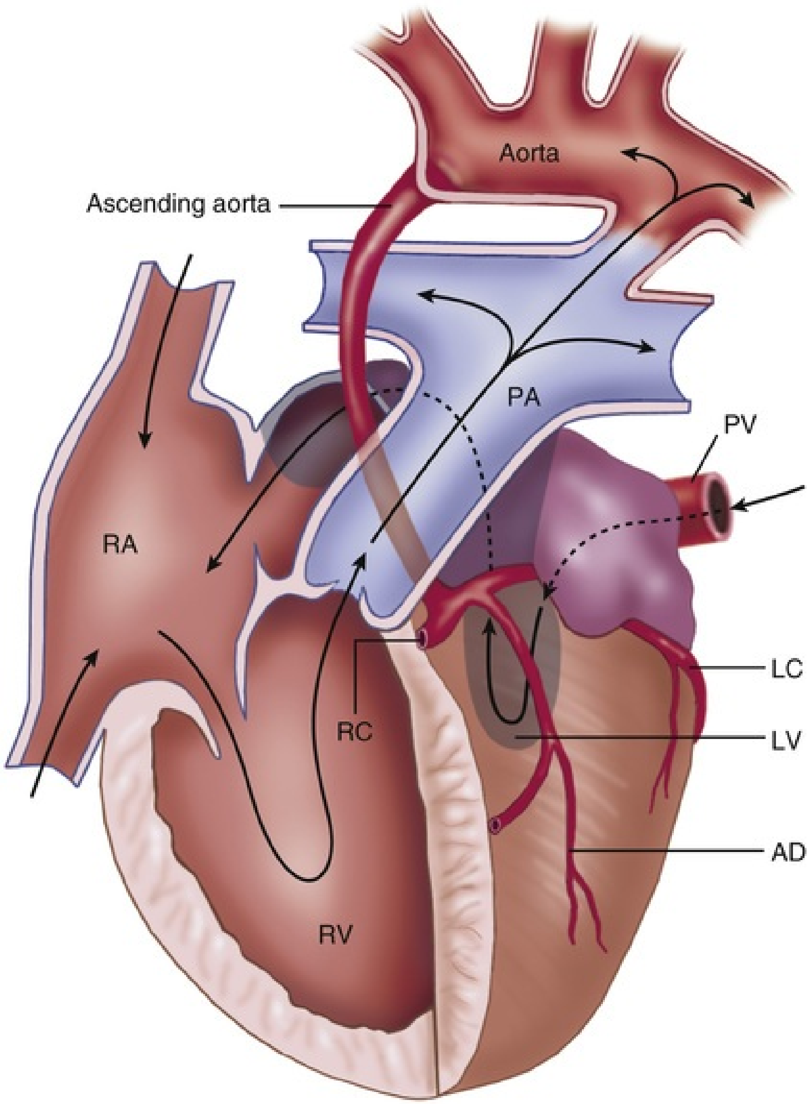

FIG. 458.10 Hypoplastic left heart with aortic hypoplasia, aortic valve atresia, and a hypoplastic mitral valve and left ventricle. AD, Anterior descending; LC, left circumflex; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RC, right coronary artery; RV, right ventricle. (From Webb GD, Smallhorn, JF, Therrien J, Redington, AN: Congenital heart disease in the adult and pediatric patient. In *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2018, Elsevier, Fig 75-28, p 1548. Adapted from historical illustrations in Neufeld HN, Adams P Jr, Edwards JE, et al: Diagnosis of aortic atresia by retrograde aortography, *Circulation* 25:278, 1962; and Edwards JE, Dry TJ, Parker RL, et al: *An atlas of congenital anomalies of the heart and great vessels.* Springfield, IL, 1954, Charles C Thomas.)

Clinical Manifestations

Although cyanosis may not always be obvious in the 1st 48 hr of life, a grayish blue skin color is soon apparent and denotes a mix of cyanosis and poor perfusion. The condition is diagnosed in most infants in the 1st few hr or days of life. Once the ductus arteriosus begins to close, signs of poor systemic perfusion and shock predominate. All the peripheral pulses may be weak or absent. A palpable right ventricular parasternal lift may be present along with a nondescript systolic murmur.

This lesion may be isolated or associated in 5–15% of patients with known genetic syndromes, such as Turner syndrome, trisomy 13, 18, or 21, Jacobsen syndrome (11q deletion), Holt-Oram syndrome, and Rubinstein-Taybi syndrome. In these circumstances, noncardiac manifestations of the syndrome may be evident and influence the clinical outcomes. Occasionally it is familial and inherited as an autosomal recessive trait.

Diagnosis

On chest radiograph, the heart is variable in size in the 1st days of life, but cardiomegaly develops rapidly and is associated with increased pulmonary vascularity. The initial ECG may show only the normal neonatal pattern of right ventricular dominance, but later, P waves become prominent and right ventricular hypertrophy is usual with reduced left ventricular forces. The echocardiogram is diagnostic and demonstrates absence or hypoplasia of the mitral valve and aortic root, a variably small left atrium and left ventricle, and a large right atrium and right ventricle (Fig. 458.11). The size of the atrial communication, by which pulmonary venous blood leaves the left atrium, is assessed directly and by pulsed and color flow Doppler studies. The small ascending aorta and transverse aortic arch are identified, and a discrete coarctation of the aorta in the juxtaductal area may be present, although in the presence of a large ductus, it may be difficult to identify. Doppler echocardiography demonstrates whether the mitral and aortic valves are severely stenotic or totally atretic. The presence of left ventricular coronary sinusoids can be identified. The diagnosis of hypoplastic left heart syndrome (HLHS) can usually be made without need for cardiac catheterization. If catheterization is necessary, the hypoplastic ascending aorta is demonstrated by angiography.

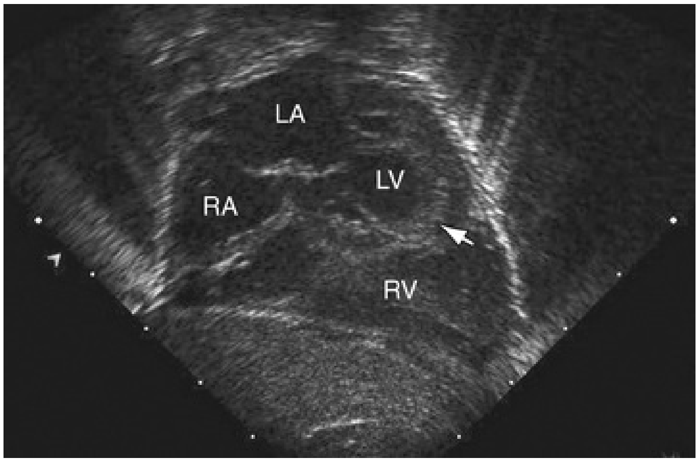

FIG. 458.11 **Subcostal 2D echocardiographic diagnosis of hypoplastic left heart syndrome. The small left ventricular chamber can be seen, the apex of which *(arrowhead)* does not form the apex of the heart. The atrial septum can be seen bowing from the left to the right, indicating that the communication between the 2 atria is pressure restrictive. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.**

Prognosis and Complications

Untreated patients most often succumb during the 1st few mo of life, usually during the 1st or 2nd wk. Occasionally, unoperated patients may live for months or, rarely, years. Up to 30% of infants with HLHS have evidence of either a major or a minor central nervous system abnormality. Other dysmorphic features may be found in up to 40% of patients. Thus, careful preoperative evaluation (genetic, neurologic, ophthalmologic) should be performed in patients being considered for surgical therapy.

Intermediate-term follow-up after completion of all 3 stages of the Norwood procedure demonstrates generally good exercise capacity, and complications equivalent to other patients who have had the Fontan palliation (see Chapter 457.4). Some studies show that patients with HLHS have a higher risk of neurodevelopmental problems than those with other complex congenital heart lesions. Whether the poor neurodevelopmental outcome is due to genetically associated central nervous system malformation, prenatal central nervous system injury, alterations of cerebral hemodynamics during bypass surgery, or poor postoperative perfusion is unknown. In addition, poor outcome is associated with prematurity, chromosome syndromes, and poverty.

Treatment

Surgical therapy for HLHS is associated with improving survival rates, reported as high as 90–95% for the 1st-stage palliation in experienced centers. The 1st-stage repair is designed to construct a reliable source of systemic blood flow arising from the single right ventricle using a combination of aortic and pulmonary arterial tissue, and to limit pulmonary blood flow to avoid heart failure and prevent the development of pulmonary vascular disease. The surgical procedure typically used is the **Norwood procedure** (Fig. 458.12) or the **Sano procedure.** Primary heart transplantation, previously advocated by a few centers, is much less common because of the substantially improved survival rates with standard surgery and the limited supply of donor organs in this age-group.

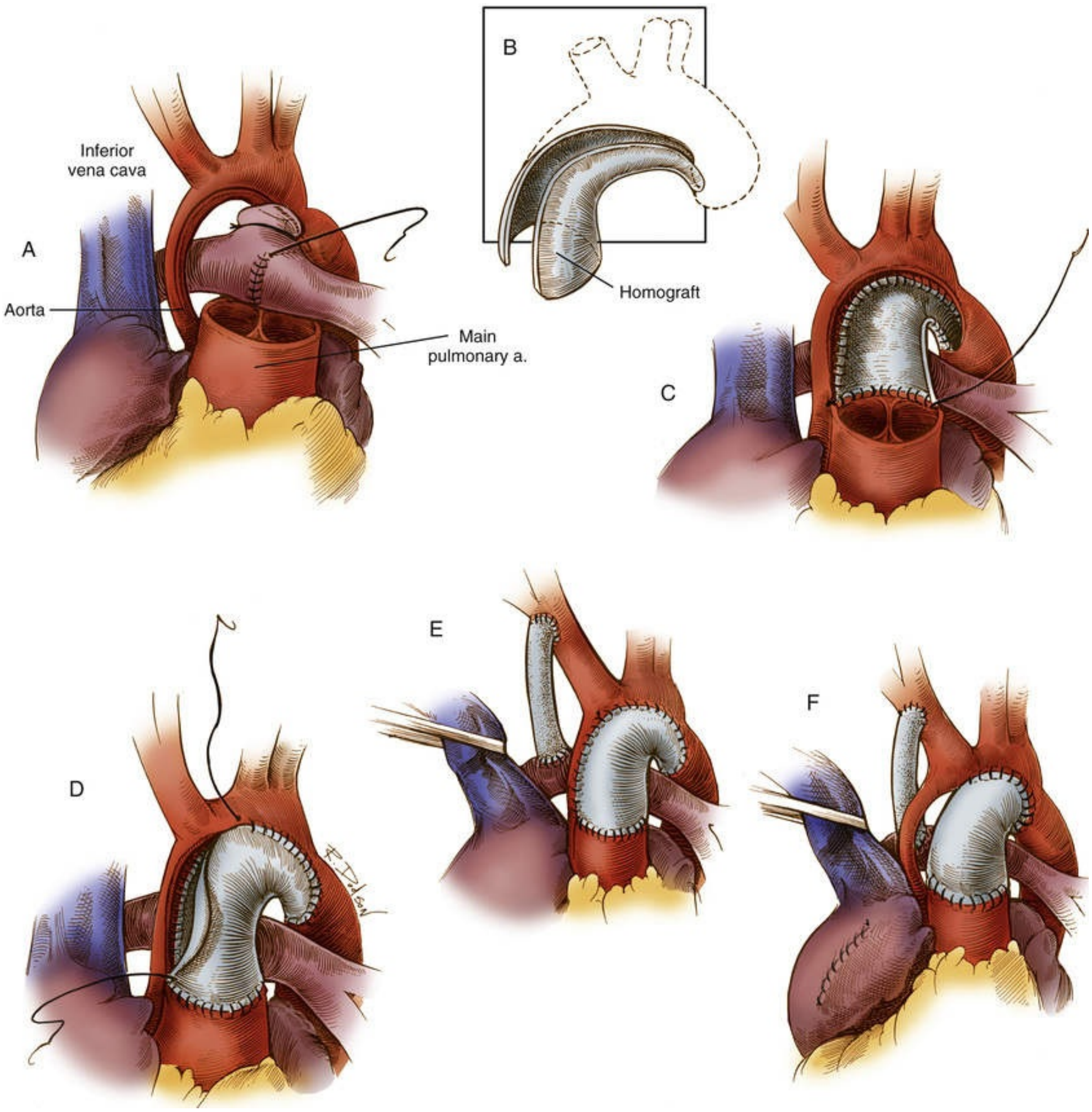

FIG. 458.12 **Norwood procedure, 1 of the 2 current techniques for 1st-stage palliation of hypoplastic left heart syndrome. A, Incisions used for the procedure incorporate a cuff of arterial wall allograft. The distal divided main pulmonary artery may be closed by direct suture or with a patch. B, Dimensions of the cuff of the arterial wall allograft. C, The arterial wall allograft is used to supplement the anastomosis between the proximal divided main pulmonary artery and the ascending aorta, aortic arch, and proximal descending aorta. D and E, The procedure is completed by an atrial septectomy and a 3.5 mm modified right Blalock shunt. F, When the ascending aorta is particularly small, an alternative procedure involves placement of a complete tube of arterial allograft. The tiny ascending aorta may be left in situ, as indicated, or implanted into the side of the neoaorta. (From Castañeda AR, Jonas RA, Mayer JE Jr, et al: Single-ventricle tricuspid atresia. In *Cardiac surgery of the neonate and infant,* Philadelphia, 1994, Saunders.)**

If a Norwood or Sano procedure is to be performed, preoperative medical management includes correction of acidosis and hypoglycemia, maintenance of ductus arteriosus patency with PGE_1 (0.01-0.20 µg/kg/min) to support systemic blood flow, and prevention of hypothermia. Preoperative management should avoid excessive pulmonary blood flow; either through management of ventilator settings, increasing the concentration of inspired CO_2 or decreasing the concentration of inspired O_2 . Balloon dilation of the atrial septum (if restrictive) may be indicated.

The Norwood or Sano procedure is usually performed in 3 stages. **Stage I** (see Fig. 458.12) includes an atrial septectomy and transection and ligation of the distal main pulmonary artery; the proximal pulmonary artery is then connected to the transversely opened hypoplastic aortic arch to form a “neoaorta,” extending through the coarcted segment of the juxtaductal aortic arch. A synthetic aortopulmonary (Blalock-Taussig) shunt connects the aorta to the main pulmonary artery to provide controlled pulmonary blood flow. In the Sano modification, a right ventricle–to–pulmonary artery conduit is used instead of an aortopulmonary shunt to provide pulmonary blood flow, temporarily creating a double-outlet right ventricle. The operative risk for these 1st-stage procedures has improved dramatically in the past 2 decades, and the best reported results demonstrate a 90–95% survival rate.

Stage II consists of a Glenn shunt anastomosis to connect the superior vena cava to the pulmonary arteries (see Chapter 458.4), at 2-6 mo of age. **Stage III** , usually performed at 2-3 yr, consists of a modified Fontan procedure (cavopulmonary isolation) to connect the inferior vena cava to the pulmonary arteries via either an intraatrial or external baffle. After stage III, all systemic venous return enters the pulmonary circulation directly. Pulmonary venous flow enters the left atrium and is directed across the atrial septum to the tricuspid valve and subsequently to the right (now the systemic) ventricle. Blood leaves the right ventricle via the neoaorta, which supplies the systemic circulation. The old aortic root now attached to the neoaorta provides coronary blood flow. The risks associated with stages II and III are even less than those of stage I; interstage mortality (usually between stages I and II) has been dramatically reduced with the use of home monitoring programs. The short- and long-term benefits of using the Norwood vs the Sano procedure remain to be demonstrated.

An alternative therapeutic approach is to perform a **hybrid procedure** for the 1st stage. This involves performing a Rashkind balloon atrial septostomy, catheter placement of a stent in the ductus arteriosus, and surgical placement of bilateral pulmonary artery bands. After the hybrid procedure, patients can be weaned off prostaglandin and discharged from the hospital. After the hybrid procedure, patients need to undergo a more extensive 2nd-stage procedure involving construction of a neoaorta and removal of the pulmonary artery bands.

Another alternative therapy is **cardiac transplantation** , either in the immediate neonatal period, thereby obviating stage I of the Norwood procedure, or after a successful stage I Norwood procedure is performed as a bridge to transplantation. After transplantation, patients usually have normal cardiac function and no symptoms of heart failure; however, these patients have the chronic risk of organ rejection and lifelong immunosuppressive therapy (see Chapter 470.1). The combination of donor shortage and improved results with standard surgical and hybrid procedures has caused most centers to stop recommending transplantation except when associated lesions make the Norwood operation an exceptionally high-risk procedure, or for patients who develop poor ventricular function at some time after the standard surgical approach.

There are some subgroups of patients with HLHS that may be at increased surgical risk, particularly those with mitral stenosis plus aortic atresia. These data need confirmation in larger studies, and alternative approaches remain to be developed. Several centers have initiated clinical trials of stem cell therapies in an effort to preserve right ventricular function in patients after the 1st stage Norwood palliation, however, no results are available at this time.

Prevention

Serial fetal echocardiographic studies demonstrate that in some fetuses, HLHS may be a progressive in utero lesion, beginning with simple valvar aortic stenosis in midgestation. The decreased flow through the stenotic aortic valve reduces flow through the left ventricle during development, resulting in gradual ventricular chamber hypoplasia. The potential for preventing this hypoplasia has been demonstrated by performing in utero aortic balloon valvuloplasty in midgestation fetuses (Fig. 458.13). Early results are encouraging, although even if the aortic valve is successfully opened, adequate ventricular growth occurs in only about 30% of patients. At present, this procedure is regarded as experimental.

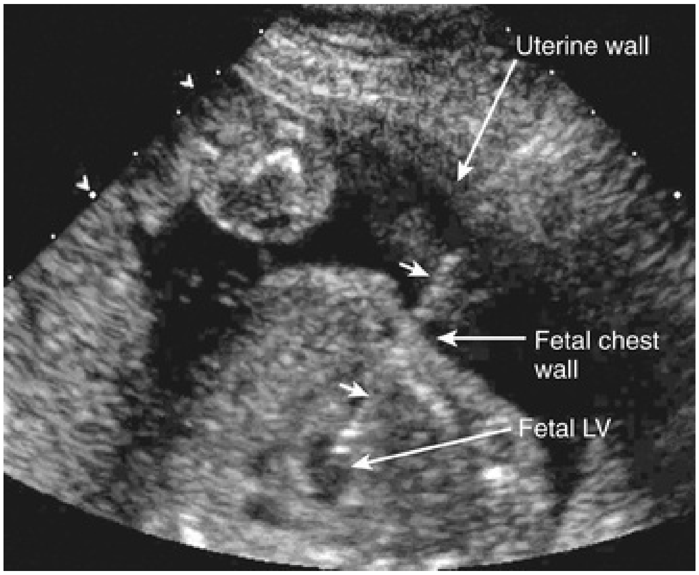

FIG. 458.13 **Fetal treatment of critical aortic stenosis to prevent development of hypoplastic left heart syndrome. Fetal ultrasound showing insertion of a needle *(arrowheads)* via the maternal abdominal wall, through the uterus and the fetal chest wall, and into the fetal left ventricle (LV). A balloon catheter is next inserted via the needle into the left ventricular chamber and across the stenotic aortic valve. The balloon is inflated to dilate the valve, the catheter and needle are removed. (Courtesy of Dr. Stanton Perry, Stanford University, Stanford, CA.)**

Because of the high mortality of HLHS with an intact or restrictive atrial septum, in utero attempts to improve atrial mixing with either fetal atrial septoplasty or atrial stent placement are undergoing clinical investigation.

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458.11

Abnormal Positions of the Heart and the Heterotaxy Syndromes (Asplenia, Polysplenia)

Daniel Bernstein

Classification and diagnosis of abnormal cardiac position are best performed through a *segmental* approach, with the position of the viscera and atria defined first, and then the ventricles, followed by the great vessels (Fig. 458.14). Determination of **visceroatrial situs** can be made by radiographic demonstration of the position of the abdominal organs and the tracheal bifurcation for recognition of the right and left bronchi and by echocardiography. The atrial situs is usually similar to the situs of the viscera and lungs. In **situs solitus** the viscera are in their normal positions (stomach and spleen on the left, liver on the right), the 3-lobed right lung is on the right, and the 2-lobed left lung on the left; the right atrium is on the right, and the left atrium is on the left. When the abdominal organs and lung lobation are reversed, an arrangement known as **situs inversus** occurs: the left atrium is on the right and the right atrium on the left. If the visceroatrial situs cannot be readily determined, a condition known as **situs indeterminus** or **heterotaxia** exists. The 2 major variations are **asplenia syndrome** (right isomerism or bilateral right-sidedness), which is associated with a centrally located liver, absent spleen, and 2 morphologic right lungs (Fig. 458.15); and **polysplenia syndrome** (left isomerism or bilateral left-sidedness), which is associated with multiple small spleens, absence of the intrahepatic portion of the inferior vena cava, and 2 morphologic left lungs (Fig. 458.16). The heterotaxia syndromes are usually associated with severe congenital heart lesions: ASD, VSD, atrioventricular septal defect, hypoplasia of 1 of the ventricles, pulmonary stenosis or atresia, and anomalous systemic venous or pulmonary venous return (Table 458.2).

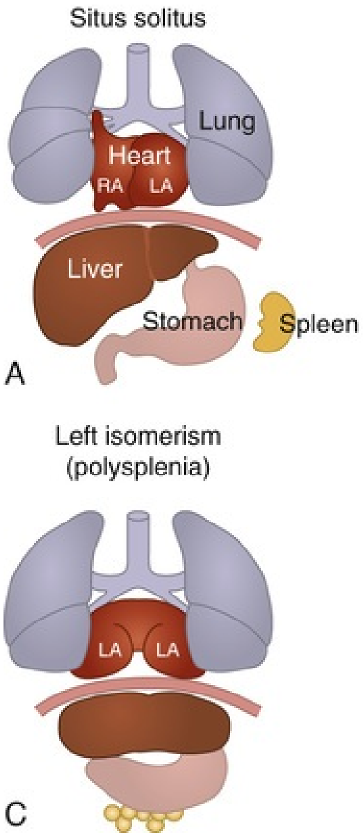

FIG. 458.14 **Variations in thoracoabdominal situs in congenital heart disease. A, *Situs solitus:* on the right side there is a 3-lobed lung, a right atrium (with superior and inferior vena cava entering), and the liver; on the left side there is a 2-lobed lung, a left atrium (with pulmonary veins entering), the stomach and the spleen. B, *Situs inversus totalis:* all the structures are mirror image reversed: on the right side there is a 2-lobed lung, a left atrium, the stomach, and the spleen; on the left side there is a 3-lobed lung, a right atrium, and the liver. C, *Left isomerism (polysplenia):* there are 2 left sides: on the right side there is a 2-lobed lung and a structure that resembles the left atrium; on the left side there is also a 2-lobed lung and a structure that resembles the left atrium; there is usually a midline liver and stomach, and multiple small spleens. D, *Right isomerism (asplenia):* there are 2 right sides: on the right side there is a 3-lobed lung and a structure that resembles the right atrium; on the left side there is also a 3-lobed lung and a structure that resembles the right atrium; there is usually a midline liver and stomach, and absent spleen. (Adapted from Fliegauf M, Benzing T, Omran H: When cilia go bad: cilia defects and ciliopathies, *Nat Rev Mol Cell Biol* 8:880-893, 2007, Fig 2.)**

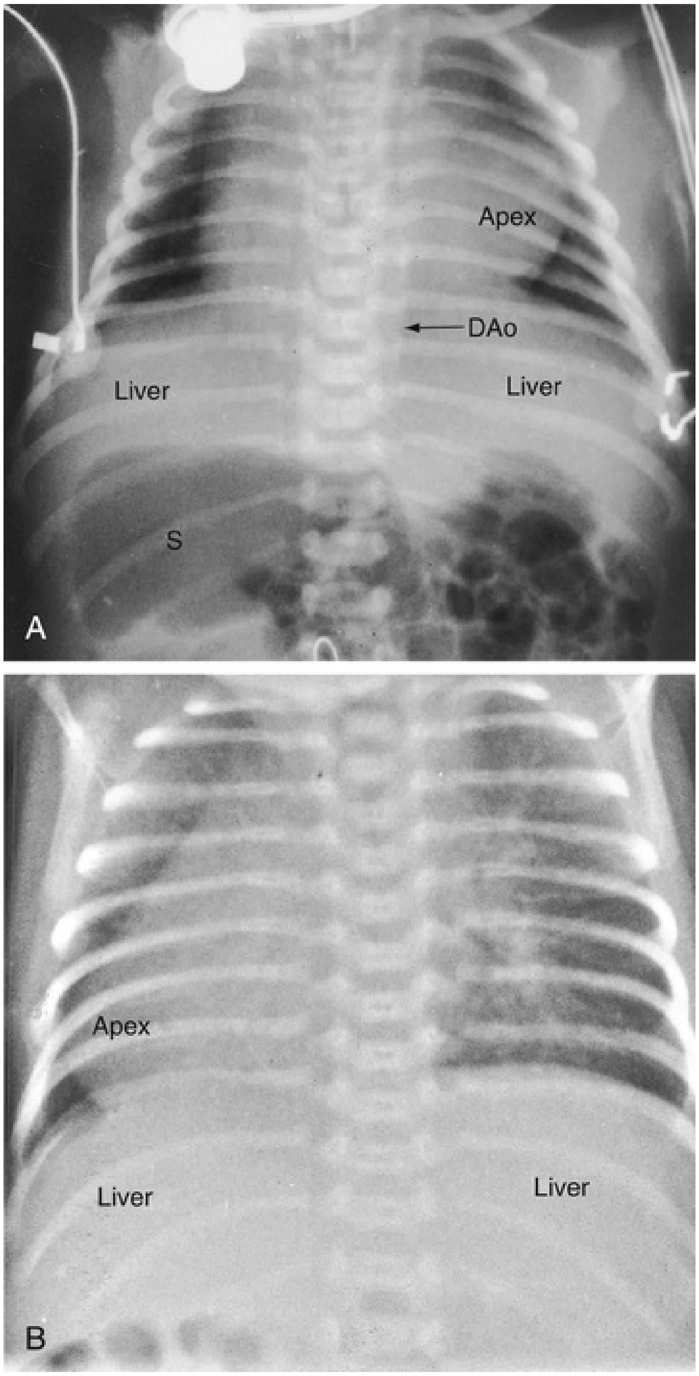

FIG. 458.15 **Radiographs from asplenic male neonate with right isomerism. A, The liver is transverse, the stomach (S) is on the right, and the heart is midline, but the base to apex axis points to the left. DAo, Descending aorta. B, The liver is transverse, the base to apex axis points to the right, and heart is to the right of midline. The ground-glass appearance of the lungs was caused by total anomalous pulmonary venous connection with obstruction. (From Perloff JK, Marelli AJ: *Perloff's clinical recognition of congenital heart disease,* ed 6, Philadelphia, 2012, Elsevier Saunders, Fig 3-31, p 32.)**

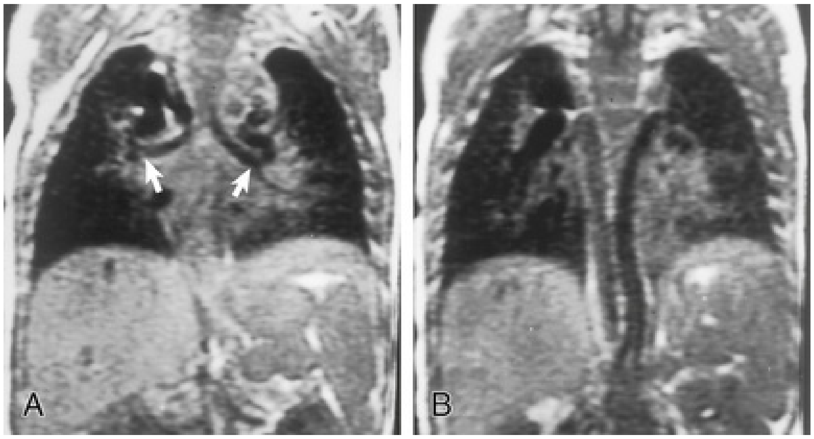

FIG. 458.16 **A,** Coronal T1-weighted MR image of a patient with heterotaxy syndrome (polysplenia) demonstrates a bilateral hyparterial bronchial branching pattern *(arrows)* and left upper quadrant spleens. **B,** More posterior coronal T1-weighted MR image shows left azygos-hemiazygos continuation to the left superior vena cava and right thoracic aorta. (From Applegate KE, Goske MJ, Pierce G, Murphy D: Situs revisited: imaging of the heterotaxy syndrome, *Radiographics* 19:837–852, 1999, Fig 4.)

Table 458.2

Comparison of Cardiosplenic Heterotaxy Syndromes

FEATURE	ASPLENIA (RIGHT ISOMERISM)	POLYSPLENIA (LEFT ISOMERISM)
Spleen	Absent	Multiple
Sidedness (isomerism)	Bilateral right	Bilateral left
Lungs	Bilateral trilobar with eparterial bronchi	Bilateral bilobar with hyparterial bronchi
Sex	Male (65%)	Female ≥ male
Right-sided stomach	Yes	Less common
Symmetric liver	Yes	Yes
Partial intestinal rotation or malrotation	Yes	Yes
Risk for midgut volvulus	Yes	Yes
Dextrocardia (%)	30-40	30-40
Pulmonary blood flow	Decreased (usually)	Increased (usually)
Severe cyanosis	Yes	No
Transposition of great arteries (%)	60-75	15
Total anomalous pulmonary venous return (%)	70-80	Rare
Common atrioventricular valve (%)	80-90	20-40
Single ventricle (%)	40-50	10-15
Absent inferior vena cava	No	Characteristic

with azygos continuation		
Bilateral superior venae cavae	Yes	Yes
Other common defects	PA, PS, right-sided aortic arch	Partial anomalous pulmonary venous return, ventricular septal defect, double-outlet right ventricle
Risk of pneumococcal sepsis	Yes	Yes
Howell-Jolly and Heinz bodies, pitted erythrocytes	Yes	No
Risk of nosocomial infection	Yes	Yes
Absent gallbladder; biliary atresia	No	Yes

PA, Pulmonary atresia; PS, pulmonary stenosis.

Human heterotaxia syndromes may be related to disorders in cilia and in utero left-right axis development. Genes involved in the Nodal signaling pathway, including *NODAL* (known asymmetric gene), as well as those influenced by Nodal such as the transforming growth factor (TGF)-β superfamily (*LEFTYA, LEFTYB*) and Pitx2, may be implicated in the development of heterotaxia syndromes (Fig. 458.17). Diagnostic gene panels are available to identify a possible genetic basis.

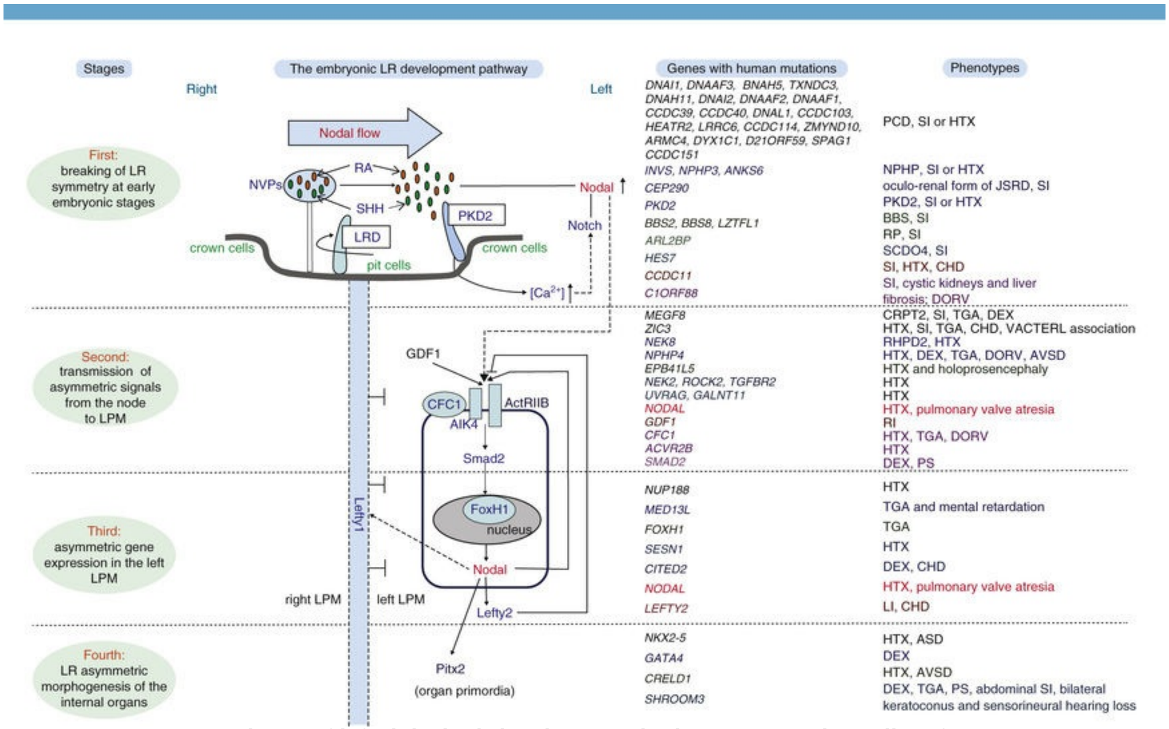
Stages
The embryonic LR development pathway
Genes with human mutations
Phenotypes
Right
Left
Nodal flow
First:
breaking of LR symmetry at early embryonic stages
NVPs
RA
SHH
LRD
PKD2
crown cells
pit cells
crown cells
Nodal
Notch
[Ca2+]
Second:
transmission of asymmetric signals from the node to LPM
GDF1
CFC1
AIK4
ActRIIB
Smad2
Third:
asymmetric gene expression in the left LPM
Lefty1
FoxH1
nucleus
Nodal
right LPM
left LPM
Lefty2
Fourth:
LR asymmetric morphogenesis of the internal organs
Pitx2
(organ primordia)
DNAI1, DNAAF3, BNAH5, TXNDC3, DNAH11, DNAI2, DNAAF2, DNAAF1, CCDC39, CCDC40, DNAL1, CCDC103, HEATR2, LRRC6, CCDC114, ZMYND10, ARMC4, DYX1C1, D21ORF59, SPAG1 CCDC151
PCD, SI or HTX
INVS, NPHP3, ANKS6
NPHP, SI or HTX
CEP290
oculo-renal form of JSRD, SI
PKD2
PKD2, SI or HTX
BBS2, BBS8, LZTFL1
BBS, SI
ARL2BP
RP, SI
HES7
SCDO4, SI
CCDC11
SI, HTX, CHD
C1ORF88
SI, cystic kidneys and liver fibrosis; DORV
MEGF8
CRPT2, SI, TGA, DEX
ZIC3
HTX, SI, TGA, CHD, VACTERL association
NEK8
RHPD2, HTX
NPHP4
HTX, DEX, TGA, DORV, AVSD
EPB41L5
HTX and holoprosencephaly
NEK2, ROCK2, TGFBR2
HTX
UVRAG, GALNT11
HTX
NODAL
HTX, pulmonary valve atresia
GDF1
RI
CFC1
HTX, TGA, DORV
ACVR2B
HTX
SMAD2
DEX, PS
NUP188
HTX
MED13L
TGA and mental retardation
FOXH1
TGA
SESN1
HTX
CITED2
DEX, CHD
NODAL
HTX, pulmonary valve atresia
LEFTY2
LI, CHD
NKX2-5
HTX, ASD
GATA4
DEX
CRELD1
HTX, AVSD
SHROOM3
DEX, TGA, PS, abdominal SI, bilateral keratoconus and sensorineural hearing loss

FIG. 458.17 **Pathway of left-right (LR) development in the mouse embryo, list of genes associated with human LR asymmetry disorders, and corresponding phenotypes in humans. LRD-containing monocilia generate leftward nodal flow, and polycystin 2–containing cilia sense nodal flow and initiate an asymmetric calcium signal, which induces Nodal expression around the node. Nodal signaling is involved in asymmetric morphogenesis by inducing expression of the Nodal-responsive genes (*NODAL,***

***LEFTY2,* and *PITX2*) in the left lateral plate mesoderm (LPM), and expression of *LEFTY1* at the midline. Mutations of genes associated with ciliopathies and Nodal signal transduction pathway have been identified in human LR asymmetry disorders. *Full arrows* indicate a direct positive effect on gene expression; *dotted arrows* indicate an indirect effect; and *lines* indicate inhibition. ASD, Atrial septal defect; AVSD, atrioventricular septal defects; BBS, Bardet-Biedl syndrome; CHD, congenital heart disease; CRPT2, Carpenter syndrome 2; DEX, dextrocardia; DORV, double-outlet right ventricle; HTX, heterotaxy; JSRD, Joubert syndrome-related disorders; LI, left isomerism; NPHP, nephronophthisis; NVPs, nodal vesicular parcels; PCD, primary ciliary dyskinesia; PKD2, polycystic kidney disease 2; PS, pulmonary stenosis; RA, retinoic acid; RHPD2, renal-hepatic-pancreatic dysplasia 2; RI, right isomerism; RP, retinitis pigmentosa; SCDO4, spondylocostal dysostosis 4; SHH, sonic hedgehog; SI, situs inversus; TGA, transposition of the great arteries. (From Deng H, Xia H, Deng S: Genetic basis of human left-right asymmetry disorders, *Expert Rev Mol Med* 16:e19, 2014, Fig 1.)**

The next segment is localization of the **ventricles** , which depends on the direction of development of the embryonic cardiac loop. Initial protrusion of the loop to the right (**d-loop**) carries the future right ventricle anteriorly and to the right, whereas the left ventricle remains posterior and on the left. With situs solitus, a d-loop yields normal atrioventricular connections (right atrium connecting to right ventricle, left atrium to left ventricle). Protrusion of the loop to the left (**l-loop**) carries the future right ventricle to the left and the left ventricle to the right. In this case, in the presence of situs solitus, the right atrium connects with the left ventricle and the left atrium with the right ventricle (**ventricular inversion**).

The final segment is that of the **great vessels** . With each type of cardiac loop, the ventricular-arterial relationships may be regarded as either normal (right ventricle to pulmonary artery, left ventricle to aorta) or transposed (right ventricle to aorta, left ventricle to pulmonary artery). A further classification can be based on the position of the aorta (normally to the right and posterior) relative to the pulmonary artery. In transposition the aorta is usually anterior and either to the right of the pulmonary artery (**d-transposition**) or to the left (**l-transposition**).

These segmental relationships can usually be determined by echocardiographic studies demonstrating both atrioventricular and ventriculoarterial relationships. The clinical manifestations of these syndromes of abnormal cardiac position are determined primarily by their associated cardiovascular anomalies.

Dextrocardia occurs when the heart is in the right side of the chest. **Levocardia** (the normal situation) is present when the heart is in the left side of the chest. Dextrocardia without associated situs inversus and levocardia in the presence of situs inversus are most often complicated by other severe cardiac malformations. Surveys of older children and adults indicate that dextrocardia with situs inversus and normally related great arteries (“mirror-image” dextrocardia) is often associated with a functionally normal heart, although congenital heart disease of a less severe nature is common.

Anatomic or functional abnormalities of the lungs, diaphragm, and thoracic cage may result in displacement of the heart to the right (**dextroposition**). In this case, however, the cardiac apex is pointed normally to the left. This anatomic position is less often associated with congenital heart lesions, although hypoplasia of a lung may be accompanied by anomalous pulmonary venous return from that lung (**scimitar syndrome** ; see Chapter 453.4).

The ECG is difficult to interpret in the presence of lesions with discordant atrial, ventricular, and great vessel anatomy. Diagnosis usually requires detailed echocardiographic and sometimes MRI, CT, or cardiac catheterization studies. The **prognosis** and **treatment** of patients with one of the cardiac positional anomalies are determined by the underlying defects and are covered in their respective chapters. Asplenia increases the risk of serious infections, such as bacterial sepsis, and thus requires daily antibiotic prophylaxis. Patients with polysplenia frequently have poor splenic function and also require prophylaxis against pneumococcal sepsis. Patients with heterotaxia are also at increased risk of intestinal malrotation and volvulus and of ciliary dyskinesia and associated pulmonary complications.

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CHAPTER 459

Other Congenital Heart and Vascular Malformations

459.1

Anomalies of the Aortic Arch

Daniel Bernstein

Right Aortic Arch

In this abnormality, the aorta curves to the right and, if it descends on the right side of the vertebral column, is usually associated with other cardiac malformations. It is found in 20% of cases of tetralogy of Fallot and is also common in truncus arteriosus. A right aortic arch without other cardiac anomalies is not associated with symptoms. It can often be visualized on the chest radiograph. The trachea is deviated slightly to the left of the midline rather than to the right, as in the presence of a normal left arch. On a **barium esophagogram** the esophagus is indented on its right border at the level of the aortic arch.

Vascular Rings

Congenital abnormalities of the aortic arch and its major branches result in the formation of vascular rings around the trachea and esophagus with varying degrees of compression (Table 459.1). The origin of these lesions can best be appreciated by reviewing the embryology of the aortic arch (see Chapter 447 , Fig. 447.1). The most common anomalies include (1) double aortic arch (Fig. 459.1*A*), (2) right aortic arch with a left ligamentum arteriosum, (3) anomalous innominate artery arising farther to the left on the arch than usual, (4) anomalous left carotid artery arising farther to the right than usual and passing anterior to the trachea, and (5) anomalous left pulmonary artery (**vascular sling**). In the latter anomaly, the abnormal vessel arises from an elongated main pulmonary artery or from the right pulmonary artery. It courses between and compresses the trachea and the esophagus. Associated congenital heart disease may be present in 5–50% of patients, depending on the vascular anomaly.

Table 459.1

Vascular Rings

LESION	SYMPTOMS	PLAIN FILM	BARIUM SWALLOW	BRONCHOSCOP
DOUBLE ARCH				
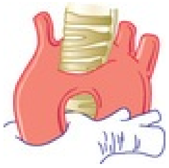	Stridor Respiratory distress Swallowing dysfunction Reflex apnea	AP—wider base of heart Lat.—narrowed trachea displaced forward at C3-C4	Bilateral indentation of esophagus	Bilateral tracheal compression—both pulsatile
RIGHT ARCH AND LIGAMENTUM/DUCTUS				
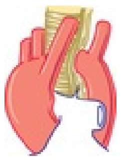	Respiratory distress Swallowing dysfunction	AP—tracheal deviation to left (right arch)	Bilateral indentation of esophagus R > L	Bilateral tracheal compression—r. pulsatile
ANOMALOUS INNOMINATE				
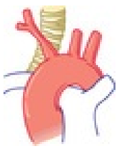	Cough Stridor Reflex apnea	AP—normal Lat.—anterior tracheal compression	Normal	Pulsatile anterior tracheal compressic
ABERRANT RIGHT SUBCLAVIAN				
	Occasional swallowing	Normal	AP—oblique	Usually normal

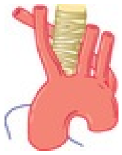	dysfunction		defect upward to right Lat.—small defect on right posterior wall	
PULMONARY SLING				
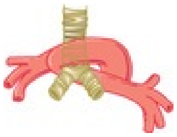	Expiratory stridor Respiratory distress	AP—low l. hilum, r. emphysema/atelectasis Lat.—anterior bowing of right bronchus and trachea	±Anterior indentation above carina between esophagus and trachea	Tracheal displacement to left Compression of right main bronchus

AP, Anteroposterior; L and l., left; Lat., lateral; MRI, magnetic resonance imaging; R and r., right.

From Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, Elsevier, p 88.

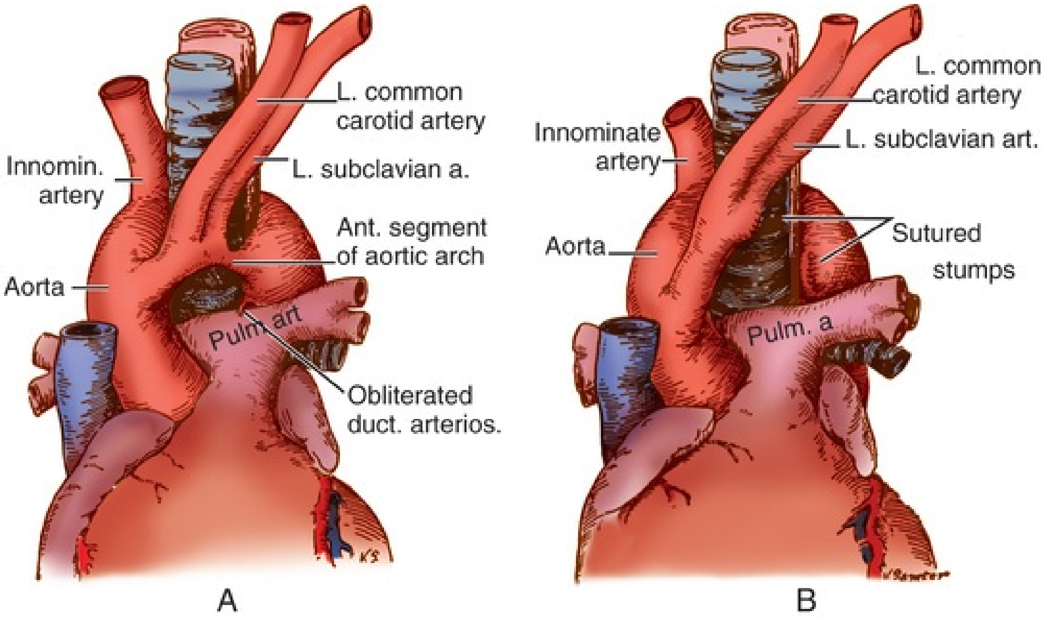
L. common carotid artery
Innomin. artery
L. subclavian a.
Ant. segment of aortic arch
Aorta
Pulm art
Obliterated duct. arterios.
KS
A
L. common carotid artery
Innominate artery
L. subclavian art.
Sutured stumps
Aorta
Pulm. a
B

FIG. 459.1 Double aortic arch. A, Small anterior segment of the double aortic arch (most common type). B, Operative procedure for release of the vascular ring. L., Left; a. and art., artery; ant., anterior; innom., innominate; duct. arterios., ductus arteriosus; pulm., pulmonary.

Clinical Manifestations

If the vascular ring produces compression of the trachea and esophagus, symptoms are frequently present during infancy. Chronic wheezing is exacerbated by crying, feeding, and flexion of the neck. Extension of the neck tends to relieve the noisy respiration. Vomiting may also be a component. Affected infants may have a brassy cough, pneumonia, or rarely, sudden death from aspiration.

Diagnosis

Standard radiographic examination is not usually helpful. In the past, performing a barium esophagogram was the standard method of diagnosis (Fig. 459.2), now replaced by echocardiography in combination with either MRI or CT. Cardiac catheterization is reserved for cases with associated anomalies or in rare cases where these other modalities are not diagnostic. Bronchoscopy may be helpful in more severe cases to determine the extent of airway narrowing.

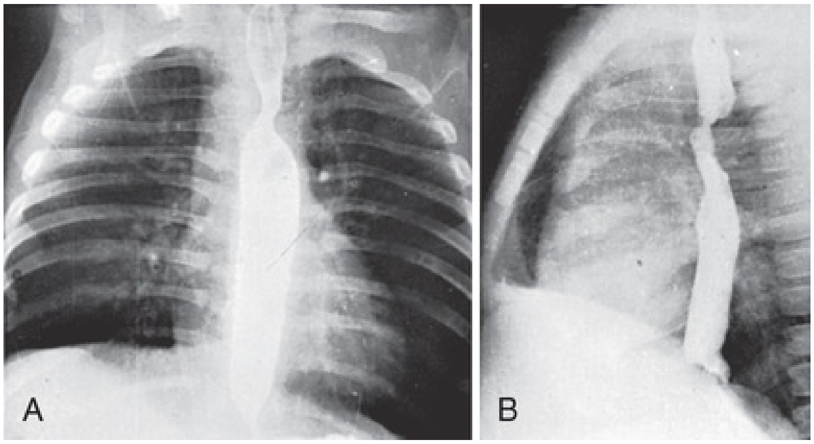

FIG. 459.2 **Double aortic arch in an infant age 5 mo. A, Anteroposterior view. The barium-filled esophagus is constricted on both sides. B, Lateral view. The esophagus is displaced forward. The anterior arch was the smaller and was divided at surgery.**

Treatment

Surgery is advised for symptomatic patients who have evidence of tracheal compression. The anterior vessel is usually divided in patients with a double aortic arch (see Fig. 459.1*B*). Compression produced by a right aortic arch and left ligamentum arteriosum is relieved by division of the latter. Anomalous innominate or carotid arteries cannot be divided; attaching the adventitia of these vessels to the sternum usually relieves the tracheal compression. An anomalous left pulmonary artery is corrected by division at its origin and reanastomosis to the main pulmonary artery after it has been brought in front of the trachea. Severe tracheomalacia, if present, may require reconstruction of the trachea as well.

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459.2

Anomalous Origin of the Coronary Arteries

Daniel Bernstein

Table 459.2 provides a classification system for coronary artery anomalies. Although many of these are isolated, congenital anomalies of the coronary arteries may also be seen in patients with congenital heart disease (tetralogy of

Fallot, transposition of the great arteries, congenitally corrected transposition of the great arteries, single ventricle, tricuspid atresia, truncus arteriosus, quadricuspid or bicuspid aortic valves, double-outlet ventricle). In addition, acquired lesions of the coronary arteries caused by existing congenital heart disease may develop as a consequence of hypertension or alterations in blood flow; congenital heart lesions include coarctation of the aorta, supravalvular aortic stenosis, aortic regurgitation, pulmonary atresia with intact ventricular septum, hypoplastic left heart syndrome, and coronary ectasia secondary to cyanotic heart disease.

Table 459.2

Congenital Anomalies of Coronary Arteries Unassociated With Congenital Heart Disease

Anomalous Aortic Origin

- Eccentric ostium within an aortic sinus
- Ectopic ostium above an aortic sinus
- Conus artery from the right aortic sinus
- Circumflex coronary artery from the right aortic sinus or from the right coronary artery
- Origin of left anterior descending and circumflex coronary arteries from separate ostia in the left aortic sinus (absence of left main coronary artery)
- Atresia of the left main coronary artery
- Origin of the left anterior descending coronary artery from the right aortic sinus or from the right coronary artery
- Origin of the right coronary artery from the left aortic sinus, from posterior aortic sinus, or from left coronary artery
- Origin of a single coronary artery from the right or left aortic sinus
- Anomalous origin from a noncardiac systemic artery

Anomalous Aortic Origin With Anomalous Proximal Course

- Acute proximal angulation
- Ectopic right coronary artery passing between aorta and pulmonary trunk

        - Ectopic left main coronary artery
        - Between aorta and pulmonary trunk
        - Anterior to the pulmonary trunk
        - Posterior to the aorta
- Within the ventricular septum (intramyocardial)
- Ectopic left anterior descending coronary artery that is anterior, posterior, or between the aorta and pulmonary trunk

Anomalous Origin of a Coronary Artery From the Pulmonary Trunk

- Left main coronary artery
- Left anterior descending coronary artery
- Right coronary artery
- Both right and left coronary arteries
- Circumflex coronary artery
- Accessory coronary artery

From Perloff JK, Marelli J: *Perloff's clinical recognition of congenital heart disease,* ed 6, Philadelphia, 2012, Elsevier Saunders (Table 32-3, p 532).

Anomalous Origin of Left Coronary Artery From Pulmonary Artery

In anomalous origin of the left coronary artery from the pulmonary artery (**ALCAPA**), the blood supply to the left ventricular (LV) myocardium is severely compromised. Soon after birth, as pulmonary artery pressure falls, perfusion pressure to the left coronary artery (LCA) becomes inadequate; myocardial ischemia, infarction, and fibrosis result. In some cases, interarterial collateral anastomoses develop between the right coronary artery (RCA) and LCA. Blood flow in the LCA is then reversed, and it empties into the pulmonary artery, a condition known as the “myocardial steal” syndrome. The left ventricle becomes dilated, and its performance is decreased. Mitral insufficiency is a frequent complication secondary to a dilated valve ring or infarction of a papillary muscle. Localized aneurysms may also develop in the LV free wall. Occasional patients have adequate myocardial blood flow during childhood and, later in life, a continuous murmur and a small left-to-right shunt via the dilated coronary system (aorta to RCA to LCA to pulmonary artery).

Clinical Manifestations

Evidence of heart failure becomes apparent within the 1st few mo of life and may be exacerbated by respiratory infection. Recurrent attacks of discomfort, restlessness, irritability, sweating, dyspnea, and pallor occur and probably represent an infantile version of **angina pectoris** . Cardiac enlargement ranges from moderate to massive. A gallop rhythm is common. Murmurs may be of the nonspecific ejection type or may be holosystolic because of mitral insufficiency. Older patients with abundant intercoronary anastomoses may have continuous murmurs and minimal LV dysfunction. During adolescence, they may experience angina during exercise. Rare patients with an anomalous RCA may also have such clinical findings.

Diagnosis

Radiographic examination confirms cardiomegaly. The electrocardiogram (ECG) resembles the pattern described in lateral wall myocardial infarction in adults. A QR pattern followed by inverted T waves is seen in leads I and aVL. The LV surface leads (V_5 and V_6) may also show deep Q waves and exhibit elevated ST segments and inverted T waves (Fig. 459.3). Two-dimensional (2D) echocardiography with color Doppler usually confirms the diagnosis; however, in rare cases, echocardiography may not be reliable in diagnosing this condition. On 2D imaging alone, the LCA may appear as though it is arising from the aorta. Color Doppler ultrasound has improved the accuracy of diagnosis of this lesion, demonstrating the presence of retrograde flow in the LCA. CT or MRI can confirm the origin of the coronary arteries. Cardiac catheterization is diagnostic; aortography shows immediate opacification of the RCA only. This vessel is large and tortuous. After filling of the intercoronary anastomoses, the LCA is opacified, and contrast can be seen to enter the pulmonary artery. Pulmonary arteriography may also opacify the origin of the anomalous LCA. Selective left ventriculography usually demonstrates a dilated left ventricle that empties poorly and mitral regurgitation.

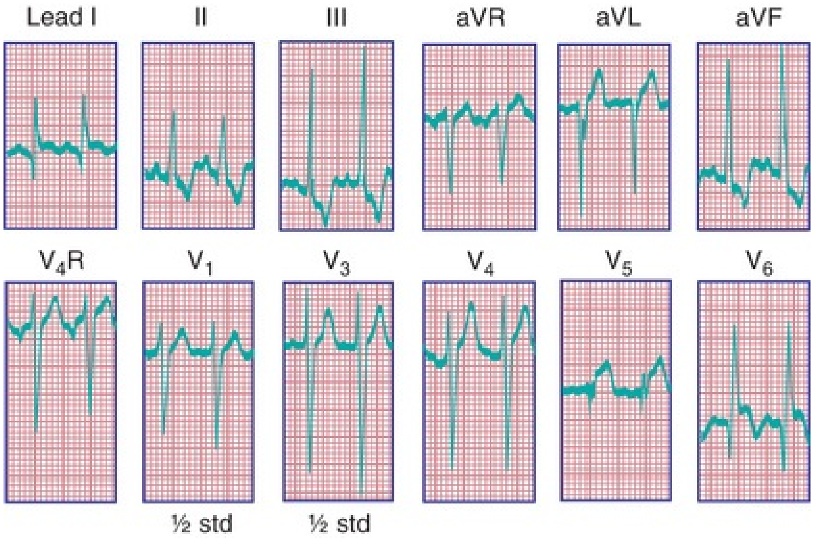

FIG. 459.3 Electrocardiogram of a 3 mo old child with anomalous origin of the left coronary artery from the pulmonary artery. Lateral myocardial infarction is present as evidenced by abnormally large and wide Q waves in leads I, V_5 , and V_6 ; an elevated ST segment in V_5 and V_6 ; and inversion of TV_6 .

Treatment and Prognosis

Untreated, death often occurs from heart failure within the 1st 6 mo of life. Those who survive generally have abundant intercoronary collateral anastomoses. Medical management includes standard therapy for heart failure (diuretics, angiotensin-converting enzyme inhibitors) and for controlling ischemia (nitrates, β-blocking agents).

Surgical treatment consists of detaching the anomalous coronary artery from the pulmonary artery and anastomosing it to the aorta to establish normal myocardial perfusion. In patients who have already sustained a significant myocardial infarction, cardiac transplantation may be the only option (see Chapter 470.1).

Anomalous Origin of Right Coronary Artery From Pulmonary Artery

Anomalous origin of the RCA from the pulmonary artery is rarely manifested in infancy or early childhood. The LCA is enlarged, whereas the RCA is thin walled and mildly enlarged. In early infancy, perfusion of the RCA is from the pulmonary artery, whereas later, perfusion is from collaterals of the left coronary vessels. Angina and sudden death can occur in adolescence or adulthood. When recognized, this anomaly should be repaired by reanastomosis of the RCA to the aorta.

Ectopic Origin of a Coronary Artery From the Aorta With Aberrant Proximal Course

In ectopic origin of the coronary artery from the aorta with an aberrant proximal course, the aberrant artery may be a left, right, or major branch coronary artery. The site of origin may be the wrong sinus of Valsalva (anomalous origin of a coronary artery from the opposite sinus, **ACAOS**) or a proximal coronary artery. The ostium may be hypoplastic, slit-like, or of normal caliber. The aberrant vessel may pass anteriorly, posteriorly, or between the aorta and right ventricular outflow tract (RVOT); it may tunnel in the conal or interventricular septal tissue. Obstruction resulting from hypoplasia of the ostia, tunneling between the aorta and RVOT or interventricular septum, and acute angulation produces myocardial infarction. Unobstructed vessels produce no symptoms (Table 459.3). Patients with this rare abnormality are often initially seen with severe myocardial infarction, ventricular arrhythmias, angina pectoris, or syncope; sudden death may occur, especially in young athletes.

Table 459.3

Classification of Coronary Anomalies Based on Ischemia

ISCHEMIA	CLASSIFICATION
Absence of ischemia	Most anomalies (split RCA, ectopic RCA from right cusp; ectopic RCA from left cusp)
Episodic ischemia	Anomalous origin of a coronary artery from the opposite sinus (ACAOS); coronary artery fistulas; myocardial bridge
Typical ischemia	Anomalous left coronary artery from the pulmonary artery (ALCAPA); coronary ostial atresia or severe stenosis

RCA, Right coronary artery.

From Mehran R, Dangas GD: Coronary angiography and intravascular imaging. In *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2018, Elsevier (Fig 20.8, p 385).

Diagnostic modalities include ECG, stress testing, 2D echocardiography, CT or MRI, radionuclide perfusion scan, and cardiac catheterization with selective coronary angiography.

Treatment is indicated for obstructed vessels and consists of aortoplasty with reanastomosis of the aberrant vessel or, occasionally, coronary artery bypass grafting. The management of asymptomatic patients with these forms of ectopic coronary origin remains controversial. Previously, the risk of **sudden cardiac death** attributed to certain coronary anomalies was thought to be quite high, since the risk assessment was based on autopsy series. The risk attributed to certain anomalous coronary arteries is much lower than once believed (Table 459.3). The risk appears to be highest with anomalous LCA from the right sinus of Valsalva with interarterial course, notably when the young patient is participating in vigorous physical exertion, such as with competitive sports. A multicenter registry, the **Anomalous Aortic Origin of the Coronary Artery (AAOCA) Registry** of the Congenital Heart Surgeons Society, is developing data to understand the risk for sudden cardiac death in this population.

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459.3

Pulmonary Arteriovenous Fistula

Daniel Bernstein

Fistulous vascular communications in the lungs may be large and localized or multiple, scattered, and small. The most common form of this unusual condition is the **Osler-Weber-Rendu syndrome** (hereditary hemorrhagic telangiectasia type I), which is also associated with angiomas of the nasal and buccal mucous membranes, gastrointestinal (GI) tract, or liver. Mutations in the endoglin gene, a cell surface component of the transforming growth factor (TGF)-β receptor complex, causes this syndrome. The usual communication is between the pulmonary artery and pulmonary vein; direct communication between the pulmonary artery and left atrium is extremely rare. Desaturated blood in the pulmonary artery is shunted through the fistula into the pulmonary vein, thus bypassing the lungs, and then enters the left side of the heart, resulting in systemic arterial desaturation and sometimes clinically detectable cyanosis. The shunt across the fistula is at low pressure and resistance, so pulmonary artery pressure is normal; cardiomegaly and heart failure are not present.

The clinical manifestations depend on the magnitude of the shunt. Large fistulas are associated with dyspnea, cyanosis, clubbing, a continuous murmur, and polycythemia. Hemoptysis is rare, but when it occurs, it may be massive. Features of the Osler-Weber-Rendu syndrome are seen in approximately 50% of patients (or other family members) and include recurrent epistaxis and GI tract bleeding. Transitory dizziness, diplopia, aphasia, motor weakness, or convulsions may result from cerebral thrombosis, abscess, or paradoxical emboli. Soft systolic or continuous murmurs may be audible over the site of the fistula. The ECG is normal. Chest radiographs may show opacities produced by large fistulas; multiple small fistulas may be visualized by fluoroscopy (as abnormal pulsations), MRI, or CT. Selective pulmonary arteriography demonstrates the site, extent, and distribution of the fistulas.

Treatment consisting of excision of solitary or localized lesions by lobectomy or wedge resection results in complete disappearance of symptoms. In most patients, fistulas are so widespread that surgery is not possible. Any direct communication between the pulmonary artery and the left atrium can be obliterated.

Patients who have undergone a **Glenn cavopulmonary anastomosis** for cyanotic congenital heart disease (see Chapter 457.4) are also at risk for the development of pulmonary **arteriovenous malformations** (AVMs). In these patients the AVMs are usually multiple, and the risk increases over time after the Glenn procedure. Pulmonary AVMs rarely occur after the heart disease is fully palliated by completion of the **Fontan operation** . This finding suggests that the pulmonary circulation requires an as yet undetermined hepatic factor to suppress the development of AVMs. The hallmark of the development of pulmonary AVMs is a decrease in the patient's oxygen saturation. The diagnosis can often be made with contrast echocardiography; cardiac catheterization is the definitive test. Completion of the Fontan circuit, so that inferior vena cava blood flow (containing hepatic venous drainage) is routed through the lungs, usually results in improvement or resolution of the malformations.

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459.4

Ectopia Cordis

Daniel Bernstein

In the most common thoracic form of ectopia cordis, the sternum is split and the heart protrudes outside the chest. In other forms, the heart protrudes through the diaphragm into the abdominal cavity or may be situated in the neck. Associated intracardiac anomalies are common. **Pentalogy of Cantrell** consists of ectopia cordis, midline supraumbilical abdominal defect, deficiency of the anterior diaphragm, defect of the lower sternum, and an intracardiac defect (ventricular septal defect, tetralogy of Fallot, or diverticulum of left ventricle). Death may occur early in life, usually from infection, cardiac failure, or hypoxemia. Surgical therapy for neonates without overwhelmingly severe cardiac anomalies consists of covering the heart with skin without compromising venous return or ventricular ejection. Repair or palliation of associated defects is also necessary.

459.5

Diverticulum of the Left Ventricle

Daniel Bernstein

Left ventricular diverticulum is a rare anomaly in which the diverticulum protrudes into the epigastrium. The lesion may be isolated or associated with complex cardiovascular anomalies. A pulsating mass is usually visible and palpable in the epigastrium. Systolic or systolic-diastolic murmurs produced by blood flow into and out of the diverticulum may be audible over the lower part of the sternum and the mass. The ECG shows a pattern of complete or incomplete left bundle branch block. The chest radiograph may or may not show the mass. Associated abnormalities include defects of the sternum, abdominal wall, diaphragm, and pericardium (see earlier). Surgical treatment of the diverticulum and associated cardiac defects can be performed in selected cases. Occasionally, a diverticulum may be small and not associated with clinical signs or symptoms. These small diverticula are diagnosed at echocardiographic examination for other indications.

CHAPTER 460

Pulmonary Hypertension

460.1

Primary Pulmonary Hypertension

Daniel Bernstein, Jeffrey A. Feinstein

Pathophysiology

Pulmonary hypertension (**PH** , elevated pressure in the pulmonary arteries) is characterized by pulmonary vascular obstructive disease and right-sided heart failure. The etiologies are varied, but all lead to similar symptoms (Tables 460.1 and 460.2). PH occurs at any age, although in pediatric patients the mean age at diagnosis is 7-10 yr. In patients with idiopathic or familial disease, females outnumber males 1.7 : 1; in other patients, both genders are represented equally. Mutations in the gene for bone morphogenetic protein receptor-2 (*BMPR2* , a member of the transforming growth factor [TGF]-β receptor family) on chromosome 2q33 have been identified in 70% of patients with **familial primary pulmonary hypertension** (known as *PPH1*) and in 10–20% with idiopathic sporadic PH. Other potential disease causing genes include *PPH2* , *ALK1*, *ENG*, *SMAD9*, *CAV1*, and *KCNK3* , which cause a channelopathy in familial and sporadic cases of primary PH. Viral infection, such as with the vasculotropic human herpesvirus 8, has been suggested as a trigger factor in some patients.

Table 460.1

Updated Classification of Pulmonary Hypertension (PH)*

1. Pulmonary arterial hypertension (PAH)
    - 1.1 Idiopathic PAH
    - 1.2 Heritable PAH
        - 1.2.1 *BMPR2*
        - 1.2.2 *ALK1*, *ENG*, ***SMAD9*** , ***CAV1*** , ***KCNK3***
        - 1.2.3 Unknown
    - 1.3 Drug and toxin induced
    - 1.4 Associated with:
        - 1.4.1 Connective tissue disease
        - 1.4.2 HIV infection
        - 1.4.3 Portal hypertension
        - 1.4.4 Congenital heart disease
        - 1.4.5 Schistosomiasis

1′. Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis

1″. **Persistent pulmonary hypertension of the newborn (PPHN)**

2. Pulmonary hypertension due to left heart disease
    - 2.1 Left ventricular systolic dysfunction
    - 2.2 Left ventricular diastolic dysfunction
    - 2.3 Valvular disease
    - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
    - 3.1 Chronic obstructive pulmonary disease
    - 3.2 Interstitial lung disease
    - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
    - 3.4 Sleep-disordered breathing
    - 3.5 Alveolar hypoventilation disorders
    - 3.6 Chronic exposure to high altitude
    - 3.7 Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms
    5.1 Hematologic disorders: **chronic hemolytic anemia** , myeloproliferative disorders, splenectomy
    5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
    5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
    5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, **segmental PH**

BMPR2, Bone morphogenetic protein receptor type II; CAV1, caveolin 1; ENG, endoglin; KCNK3, potassium channel K3.

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[*] Modified as compared with the Dana Point classification.

From Simonneau G, Gatzoulis MA, Adatia I: Updated clinical classification of pulmonary hypertension, *J Am Coll Cardiol* 62:D34–D41, 2013.

Table 460.2

Developmental Lung Diseases Associated With Pulmonary Hypertension

Congenital diaphragmatic hernia
Bronchopulmonary dysplasia
Alveolar capillary dysplasia (ACD)
ACD with misalignment of veins
Lung hypoplasia (“primary” or “secondary”)
Surfactant protein abnormalities
    Surfactant protein B (SPB) deficiency
    SPC deficiency
    ATP-binding cassette A3 mutation
    Thyroid transcription factor 1/Nkx2.1 homeobox mutation
Pulmonary interstitial glycogenosis
Pulmonary alveolar proteinosis
Pulmonary lymphangiectasia

From Ivy DD, Abman SH, Barst RJ, et al: Pediatric pulmonary hypertension, *J Am Coll Cardiol* 62(25): D118–D126, 2013 (Table 2, p D119).

PH is associated with precapillary obstruction of the pulmonary vascular bed as a result of hyperplasia of the muscular and elastic tissues and a thickened intima of the small pulmonary arteries and arterioles (Fig. 460.1). Secondary atherosclerotic changes may be found in the larger pulmonary arteries as well. In children, **pulmonary venoocclusive disease** may account for some cases of primary PH. Before a diagnosis of primary PH can be made, other causes of elevated pulmonary artery pressure must be eliminated; these include chronic pulmonary parenchymal disease, persistent obstruction of the upper airway, congenital cardiac malformations, recurrent pulmonary emboli, alveolar capillary dysplasia, liver disease, autoimmune disease, and moyamoya disease (Table 460.2). PH associated with congenital heart disease is currently the most common in pediatric patients (40–55%), followed by chronic respiratory disorders (20–35%) and idiopathic or familial disease (10–15%). PH associated with chronic lung disease (bronchopulmonary dysplasia) in premature infants is growing to encompass a larger portion of new cases.

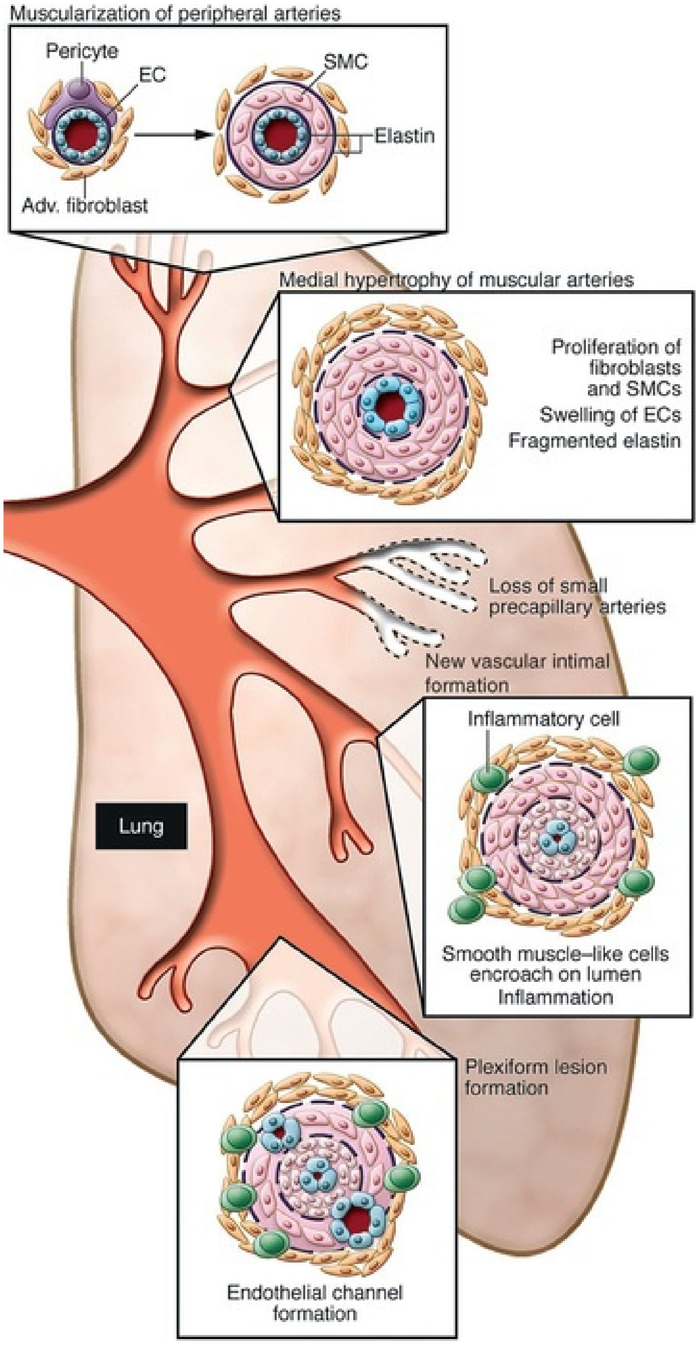
Muscularization of peripheral arteries
Pericyte
EC
SMC
Elastin
Adv. fibroblast
Medial hypertrophy of muscular arteries
Proliferation of fibroblasts and SMCs
Swelling of ECs
Fragmented elastin
Loss of small precapillary arteries
New vascular intimal formation
Inflammatory cell
Lung
Smooth muscle–like cells encroach on lumen
Inflammation
Plexiform lesion formation
Endothelial channel formation

FIG. 460.1 Vascular abnormalities associated with pulmonary arterial hypertension: abnormal muscularization of distal and medial precapillary arteries, loss of precapillary arteries, thickening of large pulmonary arterioles, and new vascular intimal formation that is occlusive in vessels <500-100 µM and in plexiform lesions therein. Adv.; EC, endothelial cell; SMC, smooth muscle cell. (From Rabinovitch M: Molecular pathogenesis of pulmonary arterial hypertension. *J Clin Invest* 122:4306–4313, 2012, Fig 1.)

PH places an afterload burden on the right ventricle, which results in **right**

ventricular hypertrophy (RVH). Dilation of the pulmonary artery is present, and pulmonary valve insufficiency may occur. In the later stages of the disease, the right ventricle dilates, tricuspid insufficiency develops, and cardiac output is decreased. Arrhythmias, syncope, and sudden death are known complications.

Clinical Manifestations

The predominant symptoms include exercise intolerance (dyspnea) and fatigability; occasionally, precordial chest pain, dizziness, or headaches are noted. Syncope may be noted in approximately 30% of pediatric patients. Patients often undergo an incorrect workup and are treated for asthma or seizures before a proper diagnosis is made. Peripheral cyanosis may be present, especially during exercise or in patients with a patent foramen ovale through which blood can shunt from right to left. In the late stages of disease, patients may have cold extremities and a gray appearance associated with low cardiac output. Arterial oxygen-hemoglobin saturation is usually normal unless there is an associated intracardiac shunt. If right-sided heart failure has supervened, jugular venous pressure is elevated, and hepatomegaly and edema are present. Jugular venous *a* waves are present, and in those with functional tricuspid insufficiency, a conspicuous jugular *cv* wave and systolic hepatic pulsations are manifested. The heart is moderately enlarged, and a right ventricular heave can be noted. The first heart sound is often followed by an ejection click emanating from the dilated pulmonary artery. The second heart sound (S_2) is narrowly split, loud, and sometimes booming in quality; it is frequently palpable at the upper left sternal border. A presystolic gallop rhythm may be audible at the lower left sternal border. The systolic murmur is soft and short and is sometimes followed by a blowing decrescendo diastolic murmur caused by pulmonary insufficiency. In later stages, a holosystolic murmur of tricuspid insufficiency is appreciated at the lower left sternal border.

Diagnosis

Chest radiographs reveal a prominent pulmonary artery and right ventricle (Fig. 460.2). The pulmonary vascularity in the hilar areas may be prominent, in contrast to the peripheral lung fields in which pulmonary markings are decreased. The electrocardiogram (ECG) shows RVH, often with spiked P waves. Echocardiography is used to screen for any congenital cardiac malformations. Doppler evaluation of the tricuspid valve, if insufficiency is present, will allow estimation of the right ventricular (and thus pulmonary arterial) systolic pressure.

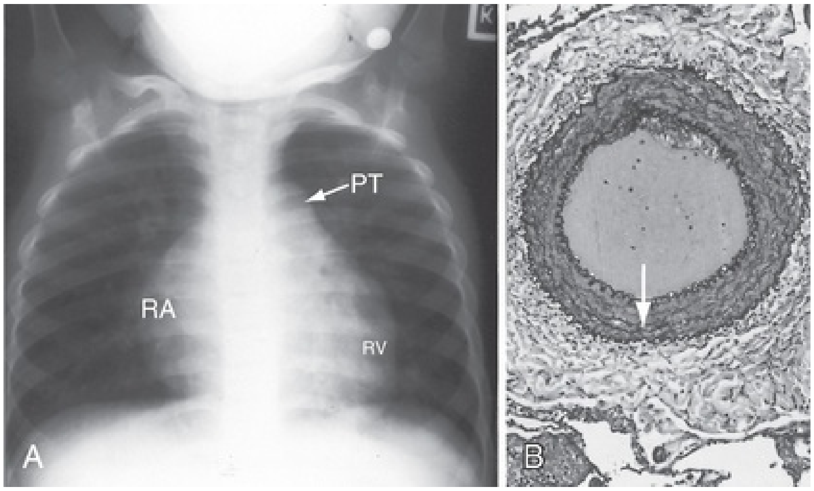

FIG. 460.2 **A,** Radiograph from a 3 yr old girl with primary pulmonary hypertension. Pulmonary vascularity is reduced. The pulmonary trunk (PT), right atrium (RA), and right ventricle (RV) are considerably enlarged. **B,** Histology of an intrapulmonary artery at necropsy shows medial hypertrophy *(arrow).* (From Perloff JK, Marelli AJ: *Perloff's clinical recognition of congenital heart disease,* ed 6, Philadelphia, 2012, Elsevier Saunders, Fig 14-17, p 207.)

At cardiac catheterization, the presence of left-sided obstructive lesions (pulmonary venous stenosis, mitral stenosis, restrictive cardiomyopathy) that result in pulmonary venous hypertension can be evaluated (see Chapters 454.9 , 458.7 , and 466.3). The presence of pulmonary arterial hypertension (PAH) with a normal pulmonary capillary wedge pressure is diagnostic of PAH. If the wedge pressure is elevated and left ventricular end-diastolic pressure (LVEDP) is normal, obstruction at the level of the pulmonary veins, left atrium, or mitral valve should be suspected. If LVEDP is also elevated, the diagnosis of restrictive cardiomyopathy should be entertained. The risks associated with cardiac catheterization are increased in severely ill patients with primary PH.

Prognosis and Treatment

Most forms of PH are progressive, and no cure is currently available. Fig. 460.3 provides a general treatment approach to PH. Some success has been reported with oral calcium channel blockers (**CCBs**) such as nifedipine in children who demonstrate pulmonary vasoreactivity when these agents are administered during catheterization. Continuous intravenous infusion of the arachidonic acid metabolite **prostacyclin** (epoprostenol) provides relief as long as the infusion is continued. Despite the success of prostacyclin in reducing symptoms and improving quality of life, it slows but does not stop the progression of the disease. **Treprostinil** , a prostacyclin analog with a longer half-life, has also been shown to be effective. Nebulized forms of prostacyclin, oral pulmonary vasodilators such as endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors have been used with success in adults and in a small number of clinical studies in children (Table 460.3).

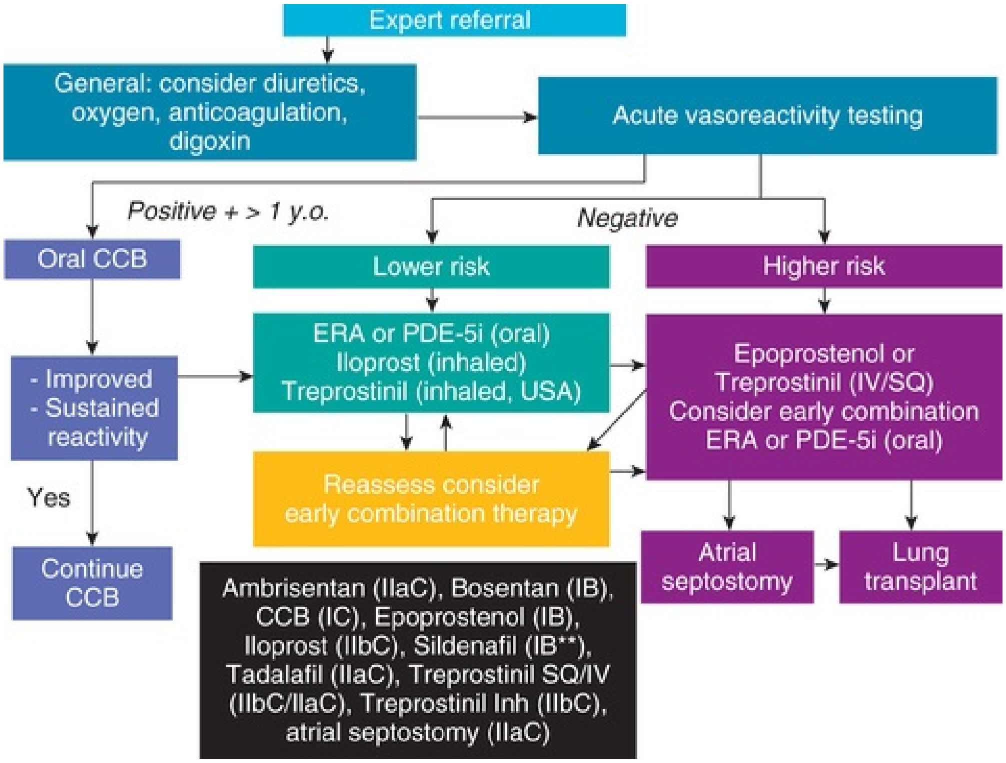
Expert referral
General: consider diuretics, oxygen, anticoagulation, digoxin
Acute vasoreactivity testing
Positive + > 1 y.o.
Negative
Oral CCB
Lower risk
Higher risk
ERA or PDE-5i (oral)
Iloprost (inhaled)
Treprostinil (inhaled, USA)
Epoprostenol or
Treprostinil (IV/SQ)
Consider early combination
ERA or PDE-5i (oral)
- Improved
- Sustained
reactivity
Yes
Reassess consider
early combination therapy
Continue CCB
Atrial septostomy
Lung transplant
Ambrisentan (IIaC), Bosentan (IB), CCB (IC), Epoprostenol (IB), Iloprost (IIbC), Sildenafil (IB**), Tadalafil (IIaC), Treprostinil SQ/IV (IIbC/IIaC), Treprostinil Inh (IIbC), atrial septostomy (IIaC)

FIG. 460.3 **World Symposium on Pulmonary Hypertension 2013 Consensus Pediatric IPAH/HPAH Treatment Algorithm.* *Use of all agents is considered off-label in children aside from sildenafil in Europe. **Dosing recommendations per European approved dosing for children. See text for discussion of use of sildenafil in children in the United States. CCB, Calcium channel blocker; ERA, endothelin receptor antagonist; HPAH, hereditary pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; PDE-5i, phosphodiesterase-5 inhibitor; SQ, subcutaneous; y.o., year old. (From Ivy DD, Abman SH, Barst RJ et al: Pediatric pulmonary hypertension, *J Am Coll Cardiol* 62(25): D118–D126, 2013, Fig 3, p D122.)**

Table 460.3

Summary of Drugs Used to Treat Pulmonary Hypertension*

DRUG AND MECHANISM OF ACTION	DOSES USED IN PEDIATRIC STUDIES	COMMON SIDE EFFECTS
Epoprostenol (prostacyclin [PGI_2], a potent vasodilator; also inhibits platelet aggregation)	1 ng/kg/min initially. Increase based on clinical course and tolerance to 5-50 ng/kg/min. Some patients may require even higher doses. Must be given by continuous infusion that is not interrupted.	Flushing, headache, nausea, diarrhea, hypotension, chest pain, jaw pain
Iloprost (synthetic analog of PGI_2)	2.5-5.0 µg 6-9 times daily (not more frequently than every 2 hr) via inhalation	Flushing, headache, diarrhea, hypotension, jaw pain, exacerbation of pulmonary symptoms (cough, wheezing)
Treprostinil (synthetic analog of PGI_2)	1 ng/kg/min initially. Target dose ranges from 20-80 ng/kg/min. Given either IV or SC via continuous infusion. Longer half-life than epoprostenol.	Flushing, headache, diarrhea, hypotension, jaw pain. Pain at infusion site when given SC.
Ambrisentan (selective endothelin EtA receptor antagonist)	Target dose ranges from 1.25-10 mg. Use ½ dose for 1st mo.	Flushing, headache, hypotension, fluid retention/edema, nasopharyngitis, sinusitis, anemia, fluid retention, exacerbation of heart failure, anemia, palpitations
Bosentan (nonselective endothelin receptor EtA and EtB antagonist)	2 mg/kg/dose bid. Use ½ dose for 1st mo and check for LFT abnormalities before up-titrating.	Flushing, headache, nasopharyngitis, fluid retention, exacerbation of heart failure, anemia, elevated LFTs, palpitations
Macitentan (nonselective endothelin receptor EtA and EtB antagonist)	—	Flushing, headache, fluid retention, exacerbation of heart failure, anemia, nasopharyngitis, bronchitis, influenza, urinary tract infections
Sildenafil (inhibitor of cGMP-specific phosphodiesterase 5)	1 mg/kg/dose given 3-4 times daily. Initial dosing should be ½ final target dose to evaluate for hypotension	Flushing, headache, diarrhea, myalgia, hypotension, priapism, visual disturbance (blue coloration), tinnitus
Tadalafil, a phosphodiesterase type 5 inhibitor	1 mg/kg/dose given daily. Initial dosing should be ½ final target dose to evaluate for hypotension.	Flushing, headache, diarrhea, myalgia, hypotension, priapism, visual disturbance (blue coloration), tinnitus
Calcium channel blockers (amlodipine, diltiazem, nifedipine)	Previously widely used. Now indicated only for patients who show a strong response to nitric oxide during cardiac catheterization.	Flushing, headache, edema, arrhythmia, headache, hypotension, rash, nausea, constipation, elevated LFTs

* These medications should only be administered under the direction of a specialist in pulmonary hypertension.

cGMP, Cyclic guanosine monophosphate; IV, Intravenously; LFT, liver function test; SC, subcutaneously.

Anticoagulation may be of value in patients with previous pulmonary thromboemboli; some of these patients may respond to balloon angioplasty of narrowed pulmonary artery segments. Riociguat, a soluble guanylate cyclase stimulator, with vasorelaxation, antiproliferation, and antifibrotic properties, has proved effective in adults with chronic thromboembolic or idiopathic pulmonary hypertension. Despite many advances, definitive therapy is still heart-lung or lung **transplantation** (see Chapter 470.2). In patients with severe PH and low cardiac output, the terminal event is often sudden and related to a lethal arrhythmia. Patients with PH diagnosed in infancy, especially those in premature infants with chronic lung disease, or with pulmonary vein stenosis often have rapid progression and high mortality.

460.2

Pulmonary Vascular Disease (Eisenmenger Syndrome)

Daniel Bernstein, Jeffrey A. Feinstein

Pathophysiology

The term *Eisenmenger syndrome* refers to patients with an intracardiac defect or aortopulmonary connection through which blood is shunted partially or totally from right to left as a result of the development of pulmonary vascular disease. This physiologic abnormality can occur with ventricular or atrioventricular septal defects, patent ductus arteriosus, aortopulmonary window, or any other communication between the aorta and pulmonary artery, as well as in many forms of complex congenital heart disease with unrestricted pulmonary blood flow. Pulmonary vascular disease with an isolated atrial septal defect can occur, but this is less common and does not occur until late in adulthood.

In Eisenmenger syndrome, pulmonary vascular resistance (PVR) after birth either remains high or, after having decreased during early infancy, rises thereafter because of increased shear stress on pulmonary arterioles. Factors playing a role in the rapidity of development of pulmonary vascular disease include increased pulmonary artery pressure, increased pulmonary blood flow, and the presence of hypoxia or hypercapnia. Early in the course of disease, PH is the result of markedly increased pulmonary blood flow (*hyperkinetic* PH). This form of PH decreases with the administration of pulmonary vasodilators such as nitric oxide, or oxygen, or both. With the development of Eisenmenger syndrome, pulmonary hypertension is the result of pulmonary vascular disease (obstructive pathologic changes in the pulmonary vessels). This form of PH is usually only minimally responsive to pulmonary vasodilators or oxygen or unresponsive.

Pathology and Pathophysiology

The pathologic changes of Eisenmenger syndrome occur in the small pulmonary arterioles and muscular arteries (<300 µm) and are graded on the basis of histologic characteristics (Heath-Edwards classification):

- **Grade I** changes involve medial hypertrophy alone.
- **Grade II** consists of medial hypertrophy and intimal hyperplasia.
- **Grade III** involves near-obliteration of the vessel lumen.
- **Grade IV** includes arterial dilation.
- **Grades V and VI** include plexiform lesions, angiomatoid formation, and fibrinoid necrosis.

Grades IV-VI indicate irreversible pulmonary vascular obstructive disease. Eisenmenger physiology is usually defined by an absolute elevation in pulmonary arterial resistance to >12 Wood units (resistance units indexed to body surface area) or by a ratio of pulmonary-to-systemic vascular resistance of

≥1.0.

Pulmonary vascular disease occurs more rapidly in patients with trisomy 21 who have left-to-right shunts. It also complicates the natural history of patients with elevated pulmonary venous pressure secondary to mitral stenosis or left ventricular dysfunction, especially in those with restrictive cardiomyopathy (see Chapter 466.3). Pulmonary vascular disease can also occur in any patient with transmission of systemic pressure to the pulmonary circulation via a shunt at the interventricular or great vessel level, as well as in patients chronically exposed to low partial pressure of oxygen (because of high altitude). Patients with cyanotic congenital heart lesions associated with unrestricted pulmonary blood flow are at particularly high risk.

Clinical Manifestations

Symptoms do not usually develop until the 2nd or 3rd decade of life, although a more fulminant course may occur. Intracardiac or extracardiac communications that would normally shunt from left to right are converted to right-to-left shunting as PVR exceeds systemic vascular resistance. Cyanosis becomes apparent, and dyspnea, fatigue, and a tendency toward dysrhythmias begin to occur. In the late stages of the disease, heart failure, chest pain, headaches, syncope, and hemoptysis may be seen. Physical examination reveals a right ventricular heave and a narrowly split S_2 with a loud pulmonic component. Palpable pulmonary artery pulsation may be present at the left upper sternal border. A holosystolic murmur of tricuspid regurgitation may be audible along the left sternal border. An early decrescendo diastolic murmur of pulmonary insufficiency may also be heard along the left sternal border. The degree of cyanosis depends on the stage of the disease.

Diagnosis

On chest radiograph, the heart varies in size from normal to greatly enlarged; the latter usually occurs late in the course of the disease. The main pulmonary artery is generally prominent, similar to other causes of PAH (see Fig. 460.2*A*). The pulmonary vessels are enlarged in the hilar areas and taper rapidly in caliber in the peripheral branches. The right ventricle and atrium are prominent. The ECG shows marked RVH. The P wave may be tall and spiked. Cyanotic patients have various degrees of polycythemia that depend on the severity and duration of hypoxemia.

The echocardiogram shows a thick-walled right ventricle and demonstrates the underlying congenital heart lesion. 2D echocardiography assists in eliminating from consideration lesions such as obstructed pulmonary veins, supramitral membrane, mitral stenosis, and restrictive cardiomyopathy. Doppler studies demonstrate the direction of the intracardiac shunt and the presence of a typical hypertension waveform in the main pulmonary artery. Tricuspid and pulmonary regurgitation can be used in the Doppler examination to estimate pulmonary artery systolic and diastolic pressures.

Cardiac catheterization usually shows a bidirectional shunt at the site of the defect. Systolic pressure is generally equal in the systemic and pulmonary circulations. Pulmonary capillary wedge pressure is normal unless a left-sided heart obstructive lesion or left ventricular failure is the cause of the PAH. Arterial oxygen-hemoglobin saturation is decreased depending on the magnitude of the right-to-left shunt. The response to vasodilator therapy (oxygen, prostacyclin, nitric oxide) may identify patients with less severe disease. Selective pulmonary artery injections may be necessary if pulmonary venous obstruction is suspected because of high wedge pressure and low LVEDP.

Treatment

The best management for patients who are at risk for the development of late pulmonary vascular disease is prevention by early surgical elimination of large intracardiac or great vessel communications during infancy. Some patients may be missed because they have not shown early clinical manifestations. Rarely, PVR never decreases at birth in these infants, and therefore they never acquire enough left-to-right shunting to become clinically apparent. Such delayed recognition is a particular risk in patients with congenital heart disease who live at high altitude. It is also a risk in infants with trisomy 21, who have a propensity for earlier development of pulmonary vascular disease. Because of the high incidence of congenital heart disease associated with trisomy 21, routine echocardiography is recommended at the time of initial diagnosis, even in the absence of other clinical findings.

Medical treatment of Eisenmenger syndrome is primarily symptomatic. Many patients benefit substantially from either oral (CCB, endothelin antagonist, phosphodiesterase inhibitors) or chronic intravenous (prostacyclin) therapy.

Combined heart-lung or bilateral lung transplantation is the only surgical option for many of these patients (see Chapter 470.2).

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CHAPTER 461

General Principles of Treatment of Congenital Heart Disease

Daniel Bernstein

Most patients who have mild congenital heart disease (CHD) do not require treatment. The parents and child should be made aware that a normal life is expected, and that no restriction of the child's activities is necessary. Overprotective parents may use the presence of a mild congenital heart lesion or even a functional heart murmur as a means to exert excessive control over their child's activities. Although fears may not be expressed overtly, the child may become anxious regarding early death or debilitation, especially when an adult member of the family acquires unrelated symptomatic heart disease. The family may have an unexpressed fear of sudden death, and the rarity of this manifestation should be emphasized in discussions directed at improving their understanding of the child's congenital heart defect. The difference between CHD and degenerative coronary disease in adults should be emphasized. General health maintenance, including a well-balanced “heart-healthy” diet, aerobic exercise, and avoidance of smoking, should be encouraged.

Even patients with moderate to severe heart disease need not be restricted from all physical activity, although many will tend to limit their own activities. Physical education should be modified appropriately to the child's capacity to participate; the extent of such modification can be guided by formal exercise testing in an appropriately equipped pediatric exercise laboratory. Although competitive sports for some patients may need to be discouraged, decisions are made on an individual basis. The influence of coach and peer pressure should be taken into account when recommending competitive vs noncompetitive athletics. Many cardiologists will also prohibit certain high-impact activities (“collision sports”) such as tackle football or contact martial arts in patients with prior open heart surgery.

Routine immunizations should be given, with the inclusion of influenza vaccine during the appropriate season. Prophylaxis against the respiratory syncytial virus (RSV) is recommended during RSV season in young infants with unrepaired CHD and significant hemodynamic abnormalities. Careful consideration of the timing of administration of live-virus vaccination is required in patients who are potential candidates for heart or heart-lung transplantation, and these patients cannot receive live-virus vaccines after they have received their transplant.

Bacterial infections should be treated vigorously, but the presence of CHD is not a reason to use antibiotics indiscriminately. **Prophylaxis against bacterial endocarditis** should be carried out during dental procedures for appropriate patients. The American Heart Association (AHA) over time has significantly revised these recommendations, with most patients no longer requiring routine prophylaxis (see Chapter 464). Even for patients who do require endocarditis prophylaxis, it is generally recommended only for dental or oral surgical procedures and no longer recommended for gastrointestinal or genitourinary procedures.

Cyanotic patients need to be monitored for noncardiac manifestations of oxygen deficiency (Table 461.1). With modern surgical procedures, it is rare today for a patient to remain significantly cyanotic beyond the 1st few years of life, although mild degrees of cyanosis may be seen in patients with a single ventricle (e.g. hypoplastic left heart) who have a fenestration in their Fontan conduits allowing right-to-left shunting. These patients should also be carefully observed for excessive **polycythemia** . Cyanotic patients should avoid situations where dehydration may occur, which leads to increased viscosity and increases the risk of stroke. Diuretics may need to be decreased or temporarily discontinued during episodes of acute gastroenteritis. High altitudes and sudden changes in the thermal environment should also be avoided. Treatment of iron-deficiency anemia is important in cyanotic patients, who may have a low mean corpuscular hemoglobin concentration despite polycythemia. These patients will show improved exercise tolerance and general well-being with restoration of normal hemoglobin levels, and their risk of stroke may be reduced if the red blood cells are not microcytic. Phlebotomy with partial exchange transfusion is carried out only in symptomatic patients with severe polycythemia (usually those with hematocrit >65%).

Table 461.1

Extracardiac Complications of Cyanotic Congenital Heart Disease and Eisenmenger Physiology

PROBLEM	ETIOLOGY	THERAPY
Polycythemia	Persistent hypoxia	Phlebotomy if symptomatic
Relative anemia	Nutritional deficiency	Iron replacement
CNS abscess	Right-to-left shunting	Antibiotics, drainage
CNS thromboembolic stroke	Right-to-left shunting or polycythemia	Anticoagulation, phlebotomy
Low-grade DIC, thrombocytopenia	Polycythemia	None for DIC unless bleeding, then phlebotomy
Hemoptysis	Pulmonary infarct, thrombosis, or rupture of pulmonary artery plexiform lesion	Embolization
Plastic bronchitis	Fontan procedure	Bronchoscopy, vascular coiling, lymphatic ablation
Gum disease	Polycythemia, gingivitis, bleeding	Dental hygiene
Gout	Polycythemia, diuretic agent	Allopurinol
Arthritis, clubbing	Hypoxic osteoarthropathy	None
Pregnancy complications: miscarriage, fetal growth retardation, prematurity increase, maternal illness	Poor placental perfusion, poor ability to increase cardiac output	Pregnancy prevention counseling, high-risk obstetric management
Infections	Associated asplenia, DiGeorge syndrome, endocarditis	Antibiotics
	Fatal RSV pneumonia with pulmonary hypertension	Ribavirin; RSV immunoglobulin (prevention)
Failure to thrive	Increased oxygen consumption, decreased nutrient intake	Treat heart failure; correct defect early; increase caloric intake
Protein-losing enteropathy	s/p Fontan; high right-sided pressures	Oral budesonide or sildenafil
Chylothorax	Injury to thoracic duct	Medium-chain triglyceride diet Octreotide Surgical ligation of thoracic duct
Neurodevelopmental disabilities	Chronic hypoxia, cardiac surgery, genetic	Early school-based evaluation and intervention
Psychosocial adjustment	Limited activity, cyanotic appearance, chronic disease, multiple hospitalizations	Counseling

CNS, Central nervous system; DIC, disseminated intravascular coagulation; RSV, respiratory syncytial virus; s/p, status post (after).

Patients with moderate to severe forms of CHD or a history of rhythm disturbance should be carefully monitored during anesthesia for even routine surgical or dental procedures. Consultation with an anesthesiologist experienced in the care of children with CHD is recommended even if the surgical procedure is not cardiac related.

Women with unrepaired severe CHD should be counseled on the risks associated with childbearing and on the use of contraceptives and other methods to prevent pregnancy, such as tubal ligation. Women with mild to moderate CHD and many who have had corrective surgery can have normal pregnancies, although those with residual hemodynamic derangements or with systemic right ventricles should be followed by a high-risk perinatologist and a cardiologist with expertise in caring for adults with CHD. Pregnancy may be highly dangerous to both mother and fetus for patients with palliated complex CHD, chronic cyanosis, or pulmonary arterial hypertension; for patients with a Fontan circulation, the miscarriage rate has been reported as ranging from 27–50%, and the rate of prematurity at 69%. Risks to the mother include heart failure, thromboembolism, and arrhythmia. Several risk stratification schemes have been developed for pregnant women with CHD, including the Cardiac Disease in Pregnancy (**CARPREG**) score, the **ZAHARA** (Zwangerschap bij Aangeboren HARtAfwijkingen) score, and the World Health Organization (WHO) classification. Based on the WHO system, patients for whom pregnancy is associated with a significantly increased risk of mortality of morbidity include those with a systemic right ventricle (e.g., corrected transposition), Fontan circulation, bicuspid aortic valve with enlarged aortic root of 45-50 mm, **Marfan syndrome** with enlarged aortic root of 40-45 mm, and those with a mechanical valve replacement. Patients for whom pregnancy is considered contraindicated include those with pulmonary arterial hypertension, severe aortic or mitral stenosis or unrepaired coarctation of the aorta, bicuspid aortic valve with aortic root >50 mm, Marfan syndrome with dilated aortic root >45 mm, and patients with systemic ventricular dysfunction with ejection fraction <30% or with New York Heart Association Class III-IV.

Postoperative Management

After successful open heart surgery, the severity of the congenital heart defect, the age and condition (nutritional status) of the patient before surgery, the events in the operating room (OR), and the quality of the postoperative care influence the patient's course. **Intraoperative** factors that influence survival and that should be noted when a patient returns from the OR include the duration of **cardiopulmonary bypass** (CPB), duration of **aortic cross-clamping** (time the heart is not being perfused), and duration of **profound hypothermia** (used in some newborns; time the entire body is not being perfused). New surgical techniques to provide ongoing perfusion to the upper body and brain even during surgery on the aortic arch (e.g., in hypoplastic left heart syndrome) have eliminated the use of profound hypothermia in many centers.

Immediate postoperative care should be provided in an intensive care unit (ICU) staffed by a team of physicians, nurses, and technicians experienced with the unique problems encountered after open heart surgery in childhood. In most major centers, this occurs in a dedicated pediatric cardiovascular ICU. Preparation for postoperative monitoring begins in the OR, where the anesthesiologist or surgeon places an arterial catheter to allow direct arterial pressure measurements and arterial sampling for blood gas determination. A central venous catheter is also placed for measuring central venous pressure and for infusions of cardioactive medications. In more complex cases, right or left atrial or pulmonary artery catheters may be inserted directly into these cardiac structures and used for pressure monitoring purposes. Temporary pacing wires are placed on the atrium or ventricle, or both, in case temporary postoperative heart block occurs. Transcutaneous oximetry provides for continuous monitoring of arterial oxygen saturation. Near-infrared spectroscopy has been used to monitor cerebral and other end-organ perfusion in the perioperative period.

Functional failure of 1 organ system may cause profound physiologic and biochemical changes in another. Respiratory insufficiency, for example, leads to hypoxia, hypercapnia, and acidosis, which in turn compromise cardiac, vascular, and renal function. The latter problems cannot be managed successfully until adequate ventilation is reestablished. Thus, it is essential that the primary source of each postoperative problem be identified and treated.

Respiratory failure is a serious postoperative complication encountered after open heart surgery. CPB performed in the presence of pulmonary congestion results in decreased lung compliance, copious tracheal and bronchial secretions, atelectasis, and increased breathing effort. Because fatigue and subsequently hypoventilation and acidosis may rapidly ensue, mechanical positive pressure endotracheal ventilation is usually continued after open heart surgery for a minimum of several hours in relatively stable patients and for up to 2-3 days or longer in severely ill patients, especially infants. More recently, protocols for early extubation have been successfully used in older children with uncomplicated intraoperative courses. Patients with certain congenital heart lesions, particularly those with **DiGeorge syndrome** , may also have airway abnormalities (micrognathia, tracheomalacia, bronchomalacia) that can make both ventilation and extubation more difficult.

The electrocardiogram (ECG) should be monitored continuously during the postoperative period. A change in heart rate, even without arrhythmia, may be the first indication of a serious complication such as hemorrhage, hypothermia, hypoventilation, or heart failure. **Cardiac rhythm disorders** must be diagnosed quickly because a prolonged untreated arrhythmia may add a severe hemodynamic burden to the heart in the critical early postoperative period (see Chapter 462). Injury to the heart's conduction system during surgery can result in postoperative complete heart block. This complication is usually temporary and is treated with surgically placed pacing wires that can later be removed. Occasionally, complete heart block is permanent. If heart block persists beyond 10-14 days postoperatively, insertion of a permanent pacemaker is required. Tachyarrhythmias are a common problem in postoperative patients. Junctional ectopic tachycardia can be a particularly troublesome rhythm to manage, although it usually responds to antiarrhythmic medications such as intravenous amiodarone.

Heart failure with poor cardiac output after cardiac surgery may be secondary to respiratory failure, serious arrhythmias, myocardial injury, blood loss, hypovolemia, a significant residual hemodynamic abnormality, or any combination of these factors. Treatment specific to the cause should be instituted. Catecholamines, phosphodiesterase inhibitors, nitroprusside and other afterload-reducing agents, and diuretics are the cardioactive agents most often used in patients with myocardial dysfunction in the early postoperative period (see Chapter 469). Postoperative pulmonary hypertension can be managed with hyperventilation and inhaled nitric oxide (NO). In the rare patients who are unresponsive to standard pharmacologic treatment, various ventricular assist devices are available, depending on the patient's size. If pulmonary function is adequate, a **left ventricular assist device** (LVAD) may be used. If pulmonary function is inadequate, **extracorporeal membrane oxygenation** (ECMO) may be used. These extraordinary measures are helpful in maintaining the circulation until cardiac function improves, usually within 2-5 days. They have also been used as a bridge to transplantation in patients with severe nonremitting postoperative cardiac failure.

Acidosis secondary to low cardiac output, renal failure, or hypovolemia must be prevented, or if present, promptly corrected. Serial monitoring of arterial blood gases (ABGs) and lactate concentrations is performed. A low arterial pH may be a sign of decreased perfusion, and acidosis can worsen cardiac function and may be the forerunner of arrhythmias or cardiac arrest.

Renal function may be compromised by congestive heart failure and further impaired by prolonged CPB. Blood and fluid replacement, cardiac inotropic agents, and vasodilators will usually reestablish normal urine flow in patients with hypovolemia or cardiac failure. Renal failure secondary to tubular injury contributes to postoperative fluid overload and may require temporary peritoneal or hemodialysis or hemofiltration.

Neurologic abnormalities can develop after CPB, especially in the neonatal period. Seizures may occur when the patient awakens from sedation and can usually be controlled with anticonvulsant medications. In the absence of other neurologic signs, self-limited isolated seizures in the immediate postoperative period usually carry a good long-term prognosis. Thromboembolism and stroke are rarer but serious complications of open heart surgery. In the long term, both subtle and more substantial learning disabilities may develop. Patients who have undergone surgery entailing CPB, especially in the newborn period, should be watched carefully during their early school years for signs of mild to moderate learning disabilities or attention deficit disorders, which are often amenable to early remedial intervention. The risk is higher in patients who have undergone repair using hypothermic total circulatory arrest than in those where systemic blood flow is maintained using CPB.

The **postpericardiotomy syndrome** may occur toward the end of the 1st postoperative wk or may sometimes be delayed until weeks or months after surgery. This febrile illness is characterized by fever, decreased appetite, listlessness, nausea, and vomiting. Chest pain is not always present, so a high index of suspicion should be maintained in any recently postoperative patient. Echocardiography is diagnostic. In most instances the postpericardiotomy syndrome is self-limited; however, when pericardial fluid accumulates rapidly, the potential danger of cardiac tamponade should be recognized (see Chapter 467). Rarely, arrhythmias may also occur. Symptomatic patients usually respond to salicylates or indomethacin and bed rest. Occasionally, corticosteroid therapy or pericardiocentesis is required. Late recurrences are rare and can lead to chronic pericarditis.

Hemolysis of mechanical origin is seen, although rarely, after repair of certain cardiac defects, for example, atrioventricular septal defects (AVSDs), or after the insertion of a mechanical prosthetic valve. It is caused by unusual turbulence of blood at increased pressure. Reoperation may be necessary in rare patients with severe and progressive hemolysis who require frequent blood transfusions, but in most cases the problem slowly regresses.

Infection is another potentially serious postoperative problem. Patients usually receive a broad-spectrum antibiotic for the initial postoperative period. Potential sites of infection include the lungs (generally related to postoperative atelectasis), the subcutaneous tissues at the incision site, the sternum, and the urinary tract (especially after an indwelling catheter has been in place). Sepsis with infective endocarditis is an infrequent complication and can be difficult to manage, especially if prosthetic material was placed at surgery (see Chapter 464). Patients who undergo CPB during a viral infection, even if mild, can develop severe complications; therefore many anesthesiologists will postpone elective surgery if a child presents with a viral infection, either upper respiratory or gastrointestinal.

Interstage Management

One group of infants at particularly high risk for both morbidity and mortality are those who have completed their 1st-stage **Norwood** or **Sano** palliation for hypoplastic left heart syndrome (HLHS) and are awaiting the next stage (**Glenn shunt**) of their 3-stage palliation. Mortality in this group of infants had been reported as high as 10–15%, motivating the National Pediatric Cardiology Quality Improvement Collaborative (**NPC-QIC**) to develop an **interstage home monitoring program** that was successful in reducing mortality by 44%.

Long-Term Management

With advances in open heart surgery and in postoperative management, the survival rate for CHD surgery has improved dramatically over the past 2 decades. There are now more adults with CHD alive in the United States (>1 million) than children. As more of these patients survive to adulthood, there has been a dramatic shift in mortality associated with CHD from infancy to adulthood (Fig. 461.1). Patients who have undergone surgery for CHD can be divided into 3 major categories: lesions for which total repair has been achieved; lesions for which both anatomic and physiologic correction have been achieved; and lesions for which only palliation, although potentially long term, has been achieved. There is some disagreement among cardiologists as to exactly which categories a particular congenital heart lesion might fall, and to some degree every case should be considered individually. Many argue that only for isolated patent ductus arteriosus (PDA) is total repair really achieved, with no requirement for long-term follow-up. Patients who are able to undergo anatomic and physiologic correction include many of the left-to-right shunt lesions (atrial and ventricular septal defects) and milder forms of obstructive lesions (e.g., valvar pulmonic stenosis, some forms of valvar aortic stenosis, coarctation of aorta), and some forms of cyanotic heart disease (e.g., uncomplicated tetralogy of Fallot, simple transposition of great arteries). These patients usually have achieved total or near-total physiologic correction of their lesion; however, they are still at some risk of long-term sequelae, including late heart failure or arrhythmia, or recurrence of a significant physiologic abnormality (e.g., recoarctation of aorta, worsening mitral regurgitation in patients with AVSDs, long-standing pulmonary regurgitation in patients with tetralogy of Fallot repaired with transannular patch). These patients require regular follow-up with a pediatric cardiologist (and when old enough, with an **adult congenital heart disease specialist** ; see Chapter 461.1); however, their long-term prognosis is generally very good, although some will require repeat surgeries or catheter-based interventions. Patients with more complex lesions, such as those with single-ventricle physiology, are at much higher risk of long-term sequelae and require even closer follow-up. These patients, particularly those who have undergone the Fontan procedure, are at risk long-term for arrhythmia, thrombosis, protein losing enteropathy, plastic bronchitis, end-organ (especially hepatic) dysfunction, and heart failure. Some may eventually require heart or heart-liver transplantation.

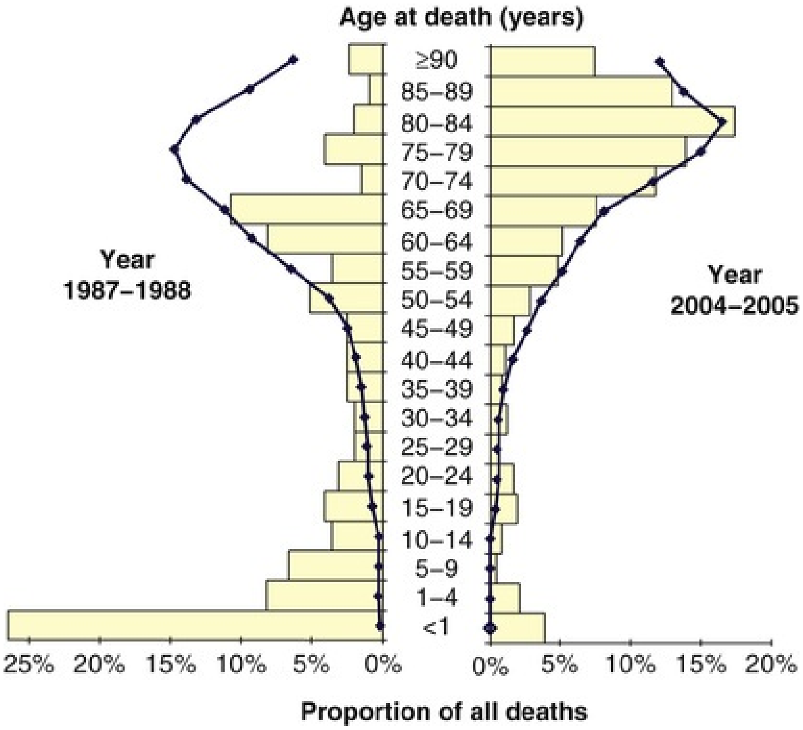

FIG. 461.1 Histogram shows change in distribution of age at death in patients with congenital heart disease over 2 eras: 1987–1988 vs 2004–2005. *Bold black curves with diamonds* represent the age at death in the general Quebec population during the same periods. (From Khairy P, Ionescu-Ittu R, Mackie AS, et al: Changing mortality in congenital heart disease, J Am Coll Cardiol 56(14):1149-57, 2010, Fig 1.)

Physical limitations are variable, ranging from minimal to none in patients with physiologic correction, to mild to moderate in patients with palliative procedures. The extent to which a patient should be allowed to participate in athletics, both recreational and competitive, can best be determined by the cardiologist, often with the assistance of the data that can be derived from cardiopulmonary exercise testing (see Chapter 450.5).

Long-term morbidities affecting neurologic function and behavior are influenced by many factors, including the effects of any genetic alterations on the developing central nervous system (CNS). There may be a greater role for prenatal CNS abnormalities (anatomic, genetic, or secondary lesions due to alterations in fetal cerebral blood flow or oxygenation) than previously suspected; these include microcephaly, cerebral atrophy, and altered cerebral biochemistry. Chronic hypoxemia and failure to thrive also may influence the developing brain, and there is evidence that the type of intervention required (CPB, hypothermic total circulatory arrest, catheter-based therapy) plays a substantial role. Data from the **Pediatric Cardiac Genomics Consortium** has shown that there is also a **genetic** component to these learning disabilities. Performing exome sequencing on patients and their parents (trios), de novo gene variants were found in 2% of patients with CHD, but in 20% of patients with CHD and neurodevelopmental delay. The identity of these gene variants and their mechanism of action is under study. In general, in the absence of a significant genetic syndrome or major perioperative complication, most children function at a fairly high level after repair of congenital heart defects and are able to attend regular school. Group mean scores on standard cognitive tests are no different from the general population; however, some areas appear to be more at risk than others, including certain aspects of motor function, speech, visual-motor tracking, and phonologic awareness. Awareness of these potential issues is critical to obtaining prompt remedial assistance if a child is found to be struggling in school.

461.1

Congenital Heart Disease in Adults

Salil Ginde, Michael G. Earing

Keywords

adult congenital heart disease
congestive heart failure
cardiac arrhythmias
pregnancy cardiovascular complications
atrial switch
arterial switch
Rastelli operation

Approximately 90% of children with congenital heart disease survive to adulthood. More adults than children are living with CHD in the United States, with a 5% increase every year. In the last decade, 35% of hospitalizations for CHD were patients older than 18 yr (mean age: 55 yr).

Long-Term Medical Considerations

Approximately 25% of adults with CHD have a mild form that has allowed them to survive into adulthood without surgical or interventional cardiac catheterization. The most common lesions in this category include mild aortic valve stenosis (usually in setting of bicuspid aortic valve), small restrictive ventricular septal defects (VSDs), mild pulmonary valve stenosis, and mitral valve prolapse (Table 461.2). These patients need less frequent follow-up to assess for progression of disease and to identify associated complications. Many adults with CHD living in the United States are patients who have had previous intervention (Table 461.3). Although most children who undergo surgical intervention will survive to adulthood, with few exceptions, *total correction is not the rule.* The few exceptions include PDA, VSDs, and atrial septal defects (ASDs); this is true only if they are closed early, before the development of irreversible pulmonary vascular changes, and if no residual lesions exist.

Table 461.2

Congenital Heart Defects Associated With Survival Into Adulthood Without Surgery or Interventional Cardiac Catheterization

Mild pulmonary valve stenosis
Bicuspid aortic valve
Small to moderate-size atrial septal defect
Small ventricular septal defect
Small patent ductus arteriosus
Mitral valve prolapse
Partial atrioventricular canal (ostium primum atrial septal defect and cleft mitral valve)
Marfan syndrome
Ebstein anomaly
Congenitally corrected transposition (atrioventricular and ventriculoarterial discordance)

Table 461.3

Most Common Congenital Heart Defects in Patients Surviving to Adulthood After Surgery or Interventional Catheterization

Aortic valve disease following balloon valvuloplasty or surgical valvotomy
Pulmonary valve stenosis following balloon valvuloplasty or surgical valvotomy
Tetralogy of Fallot
Ventricular septal defect
Complete atrioventricular canal defect
Transposition of the great arteries
Coarctation of the aorta
Complex single ventricles after the modified Fontan procedure

It has become apparent that even the simplest congenital heart lesions can be associated with long-term complications, including both cardiac and noncardiac problems (Tables 461.4 and 461.5 and Fig. 461.2). *Cardiac* complications include arrhythmias and conduction defects, ventricular dysfunction, residual shunts, valvular lesions (regurgitation and stenosis), hypertension, and aneurysms. *Noncardiac* sequelae (**comorbidities**) include pulmonary, renal, and hepatic dysfunction that is caused either directly or indirectly by the underlying CHD. Abnormal pulmonary function most often presents as restrictive lung physiology and likely results from prior sternotomy or thoracotomy, scoliosis, diaphragmatic dysfunction, or parenchymal lung disease. Reduced pulmonary function contributes to reduced exercise tolerance and is a risk factor for mortality in adults with CHD. Renal dysfunction may result from chronic cyanosis, multiple surgeries requiring CPB, or from other comorbid conditions, such as hypertension and diabetes mellitus. Hepatic injury from chronic liver congestion in patients with elevated central venous pressures, particularly patients palliated with the Fontan procedure, can result in hepatic fibrosis, cirrhosis, hepatic dysfunction, and rarely hepatocellular carcinoma. Adults with CHD are at risk for developmental abnormalities such as intellectual impairment, somatic abnormalities such as facial dysmorphism (cleft palate/lip), CNS abnormalities such as seizure disorders from previous thromboembolic events or cerebrovascular accidents, and impairments of hearing or vision loss. Psychosocial problems involving employment, life and health insurance, participation in sports, sexual activity, and contraception are common. As a result of these long-term complications, the majority of adults with CHD need lifelong follow-up. When adults with CHD are hospitalized, it is usually for heart failure or an arrhythmia; others may require catheterization or another cardiac surgical procedure.

Table 461.4

Risks in Adults Who Have Congenital Heart Disease

Rhythm Disorders

Supraventricular tachycardia
Right bundle branch block
Heart block
Ventricular tachycardia
Sudden death

Coarctation of Aorta

Essential hypertension
Recoarctation
Aneurysm formation

Residual Lesions (Shunts)

Ventral septal defect
Atrial septal defect
Patent ductus arteriosus

Acquired Lesions

Subacute bacterial endocarditis
Subvalvular stenosis

Supravalvular stenosis
Valvular insufficiency
Valvular restenosis
Eisenmenger complex

Pregnancy Risk (See Table 461.5)

Table 461.5

Lesion-Specific Risks of Maternal and Neonatal Complications of Pregnancy

RISK	LESION/COMPLICATION
No additional risk	Small septal defects Surgically closed ASD, VSD, PDA Mild to moderate aortic regurgitation Mild to moderate pulmonary stenosis
Slightly increased risk	Postoperative repair of tetralogy of Fallot Transposition of the great arteries, s/p arterial switch procedure
Moderate risk	Transposition of the great arteries, s/p atrial switch procedure Congenitally corrected transposition of the great arteries Single ventricle physiology, s/p Fontan procedure
Severe risk	Cyanotic congenital heart disease, unoperated or palliated Marfan syndrome Prosthetic valves Obstructive lesions including coarctation
Pregnancy contraindicated	Severe pulmonary hypertension Severe obstructive lesions Marfan syndrome, aortic root >40 mm

ASD, Atrial septal defect; PDA, patent ductus arteriosus; s/p, status post (after); VSD, ventricular septal defect.

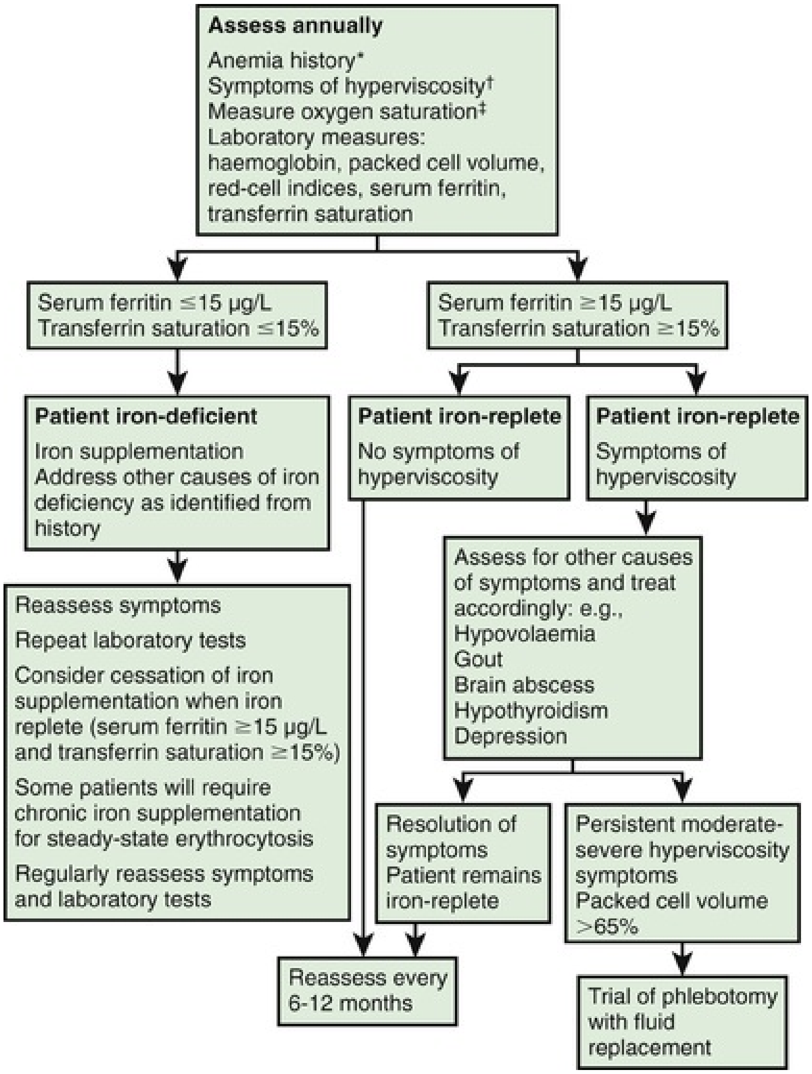
Assess annually
Anemia history*
Symptoms of hyperviscosity†
Measure oxygen saturation‡
Laboratory measures: haemoglobin, packed cell volume, red-cell indices, serum ferritin, transferrin saturation
Serum ferritin ≤15 µg/L
Transferrin saturation ≤15%
Serum ferritin ≥15 µg/L
Transferrin saturation ≥15%
Patient iron-deficient
Iron supplementation
Address other causes of iron deficiency as identified from history
Patient iron-replete
No symptoms of hyperviscosity
Patient iron-replete
Symptoms of hyperviscosity
Reassess symptoms
Repeat laboratory tests
Consider cessation of iron supplementation when iron replete (serum ferritin ≥15 µg/L and transferrin saturation ≥15%)
Some patients will require chronic iron supplementation for steady-state erythrocytosis
Regularly reassess symptoms and laboratory tests
Assess for other causes of symptoms and treat accordingly: e.g.,
Hypovolaemia
Gout
Brain abscess
Hypothyroidism
Depression
Resolution of symptoms
Patient remains iron-replete
Persistent moderate-severe hyperviscosity symptoms
Packed cell volume >65%
Reassess every 6-12 months
Trial of phlebotomy with fluid replacement

FIG. 461.2 Crucial issues to address at transition to adulthood in patients with cyanotic congenital heart disease. (From Spence MS, Balaratnam MS, Gatzoulis MA: Clinical update: cyanotic adult congenital heart disease, *Lancet* 370:1531, 2007.)

Specific Lesions

Left-to-Right Shunts

If the initial lesion has a shunt that is large and nonrestrictive (allowing transmission of near-systemic pressure to the pulmonary arteries), irreversible pulmonary vascular changes can occur, resulting in pulmonary hypertension at systemic levels with reversed or bidirectional shunting at the level of the defect (Eisenmenger syndrome; see Chapter 460.2).

Atrial Septal Defects

See Chapter 453.1 .

Although, most individuals with an ASD are diagnosed during childhood after a murmur is noted, a minority of patients present with symptoms for the first time as adults. Most patients are asymptomatic during the 1st and 2nd decades of life. In the 3rd decade, an increasing number of patients then develop exercise intolerance, palpitations from atrial arrhythmias, and cardiac enlargement. If untreated, survival into adulthood is the rule; life expectancy is reduced, however, and there is significant long-term morbidity. After age 40 the mortality rate increases by 6% per year, and >20% of patients will have developed atrial fibrillation (AF). By age 60 the number of patients with AF increases to >60%.

Late Outcome Following Closure of Atrial Septal Defect

Most patients who have undergone early ASD closure will have excellent long-term survival with low morbidity if repair is undertaken before age 25 yr. Older age at repair is associated with decreased late survival with an associated increased risk for the development of atrial arrhythmias, thromboembolic event, and pulmonary hypertension. Long-term late complications and survival after transcatheter device closure remain unknown; early and intermediate results are excellent, with a high rate of ASD closure and few major complications.

Ventricular Septal Defects

See Chapter 453.6 .

Although isolated VSDs are among the most common forms of CHD, the diagnosis of a VSD in an adult is rare. The primary reason is that most patients with a hemodynamically significant VSD will have undergone repair in childhood or will have died earlier in life. As result, the spectrum of isolated VSD in adults is limited to (1) those with small restrictive defects, (2) those with Eisenmenger syndrome, and (3) those who had their defects closed in childhood.

For patients with **small restrictive VSD** , long-term survival is excellent, with estimated 25-yr survival of 96%. In addition, the long-term morbidity for patients with a restrictive VSD also appears to be low. Their clinical course is not completely benign. Reported long-term complications include endocarditis, progressive aortic regurgitation secondary to prolapse of aortic valve into the defect (highest risk is with supracristal type, but also can occur in setting of perimembranous defect), and the development of both right and left outflow tract obstruction from a double-chamber right ventricle or a subaortic membrane. For patients who develop **Eisenmenger syndrome** , survival into the 3rd decade is common. With increasing age, the long-term complications of right-sided heart failure, paradoxical emboli, and polycythemia, usually result in progressive decline in survival, with death at an average age of 37 yr.

Adults with **previous VSD closure** , without pulmonary hypertension or residual defects, live a normal life expectancy. Because patients with small VSDs are asymptomatic, these patients should be managed conservatively. Given the long-term risks, they do need intermittent follow-up for life to monitor for the development of late complications. The exception to this rule is patients with small supracristal or perimembranous VSD with associated prolapse of the aortic cusp into the defect resulting in progressive aortic regurgitation. These patients should be considered for surgical repair at diagnosis to prevent progressive aortic valve damage.

Complete Atrioventricular Canal

See Chapter 453.5 .

The natural history for patients with complete AVSD is characterized by the early development of pulmonary vascular disease, leading to irreversible damage often by age 1 yr (especially in children with Down syndrome). Thus, patients who present in adulthood can be categorized into 2 groups: those with Eisenmenger syndrome and those who had their defects closed in childhood.

Overall, for those patients who underwent early repair before the development of pulmonary vascular disease, the long-term prognosis is good. The most common long-term complication is **left atrioventricular valve regurgitation** , with approximately 5–10% of patients requiring surgical revision for left atrioventricular valve repair or replacement during follow-up. The 2nd most common long-term complication for this patient group is **subaortic stenosis** , occurring in up to 5% of patients after repair. Other long-term complications include residual atrial- or ventricular-level shunts, complete heart block, atrial and ventricular arrhythmias, and endocarditis.

For patients who have developed Eisenmenger syndrome, all are symptomatic with exertional dyspnea, fatigue, palpitations, edema, and syncope. Survival is similar to other forms of Eisenmenger syndrome, with a mean age at death of 37 yr. Strong predictors for death include syncope, age at presentation of symptoms, poor functional class, low oxygen saturation (<85%), elevated serum creatinine and uric acid concentrations, and Down syndrome.

Patients who underwent previous repair and develop significant left atrioventricular valve regurgitation causing symptoms, atrial arrhythmias, or deterioration in ventricular function should undergo elective valve repair or replacement. Those previously repaired patients who develop significant subaortic stenosis (defined as a peak cardiac catheterization or echo gradient of >50 mm Hg) should undergo surgical repair.

Patent Ductus Arteriosus

See Chapter 453.8 .

A PDA is usually an isolated lesion in the adult patient. The size of the defect is the primary determinant of clinical course in the adult patient. These clinical courses can be grouped into 5 main categories: silent PDAs; small, hemodynamically insignificant PDAs; moderate-size PDAs; large PDAs; and previously repaired PDAs.

A **silent** PDA is a tiny defect that cannot be heard by auscultation and is only detected by other means such as echocardiography. Life expectancy is always normal in this population and the risk for endocarditis is extremely low.

Patients with a **small** PDA have an audible long-ejection or continuous murmur heard best at the left upper sternal border that radiates to the back. In addition, they have normal peripheral pulses. Because there is negligible left to right shunting these patients have normal left aorta and left ventricle (LV) size and normal pulmonary artery pressure by echocardiography and chest x-ray film. These patients like those with silent PDAs are asymptomatic and live a normal life expectancy. They have a higher risk for endocarditis.

Patients with **moderate-size** PDAs may present during adulthood. These patients often will have wide, bounding peripheral pulses and an audible continuous murmur. These patients all have significant volume overload and develop some degree of left aorta and LV enlargement and some degree of pulmonary hypertension. These patients are symptomatic with dyspnea, palpitations, and heart failure.

Patients with **large** PDAs typically present with signs of severe pulmonary hypertension and Eisenmenger syndrome. By adulthood, the continuous murmur is typically absent and there is differential cyanosis (lower extremity saturations lower than the right arm saturation). These patients have a similar prognosis as other patients with Eisenmenger syndrome.

Patients who underwent **repair** of a PDA prior to the development of pulmonary hypertension have a normal life expectancy without restrictions.

All patients with *clinical evidence* of a PDA are at increased risk for endocarditis. As result, all PDAs except for small silent PDAs and those patients with severe irreversible pulmonary hypertension should be considered for closure. Catheter device closure is the preferred method in most centers today. Surgical closure is reserved for patients with PDA too large for device closure or when the anatomy is distorted, as in the setting of a large ductal aneurysm.

Cyanotic Heart Disease

See Chapters 456 , 457 , and 458 .

Unlike the acyanotic forms of CHD, the majority of patients with cyanotic CHD will have had at least 1 and often several previous interventions prior to adulthood. The most frequent defects seen in the outpatient adult CHD setting are tetralogy of Fallot, complete transposition of the great arteries (TGA, also known as d-transposition), pulmonary valve stenosis, and various forms of functional single ventricles. Other defects include total anomalous pulmonary venous return, truncus arteriosus, and double-outlet right ventricle.

Tetralogy of Fallot

See Chapter 457.1 .

In the developed world, the unoperated adult patient with tetralogy of Fallot has become a rarity because the majority of patients will have undergone palliation or, more often, repair in childhood. Survival in the unoperated patient to the 7th decade has been described but is rare. In general, only 11% of unoperated patients are alive by age 20 and only 3% by age 40.

Late survival after repair of tetralogy of Fallot is excellent. Repair is typically performed at 3-12 mo of age and consists of patch closure of the VSD and relief of the pulmonary outflow tract obstruction by patch augmentation of the right ventricular outflow tract, pulmonary valve annulus, or both. Survival rates at age 32 and 35 yr have been reported to be 86% and 85%, respectively, compared to 95% in age- and sex-matched controls. Most patients live an unrestricted life. Many patients do develop late symptoms that include exertional dyspnea, palpitations, syncope, and sudden cardiac death. Late complications include endocarditis, aortic regurgitation with or without aortic root dilation (typically caused by damage to the aortic valve during VSD closure or secondary to an intrinsic aortic root abnormality), left ventricular dysfunction (secondary to inadequate myocardial protection during previous repair or chronic LV volume overload caused by long-standing palliative arterial shunts), residual pulmonary valve obstruction, residual pulmonary valve regurgitation, RV dysfunction (as a result of pulmonary regurgitation or pulmonary stenosis), atrial arrhythmias (typically atrial flutter), ventricular arrhythmias, and heart block.

Reintervention is necessary in approximately 10% of patients after reparative surgery at 20-year follow-up. With longer follow-up, the incidence of reintervention continues to increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary valve regurgitation.

Transposition of the Great Arteries

See Chapter 458.1 .

The natural history of patients with unrepaired TGA is so poor that very few patients survive past childhood without intervention. The first definitive operations for TGA were described by Senning in 1959 and Mustard in 1964 (**atrial switch** procedures). With these procedures the systemic and pulmonary venous returns are rerouted in the atrium by constructing baffles. The systemic venous return from the superior and inferior venae cavae is directed through the mitral valve and into the left ventricle (connected to the pulmonary artery). The pulmonary venous return is then directed through the tricuspid valve into the right ventricle (connected to the aorta). These procedures result in physiologic correction and can be performed with low mortality, but leave the left as the pulmonary ventricle and the right as the systemic ventricle. Long-term follow-up studies after the atrial switch procedure show a small but ongoing attrition rate with numerous other intermediate- and long-term complications. Two specific problems are most concerning: loss of sinus rhythm with development of atrial arrhythmias, occurring in 50% of TGA patients by age 25, and development of systemic ventricular dysfunction, occurring in 50% by age 35. Other long-term complications include endocarditis, baffle leaks, baffle obstruction, tricuspid valve regurgitation, and sinus node dysfunction requiring pacemaker placement.

As result of these long-term complications, the **arterial switch** operation has become the procedure of choice to treat TGA patients since 1985. The great arteries are transected and reanastomosed to the correct ventricle (left ventricle to aorta, right ventricle to pulmonary artery) with coronary artery transfer. Operative survival after the arterial switch procedure in the current surgical era is very good, with a surgical mortality rate of 2–5%. Long-term data on survival and complications are not available, but intermediate results are promising. Reported intermediate complications include endocarditis, pulmonary outflow tract obstruction (at the supravalvular level or at the takeoff of the peripheral pulmonary arteries), aortic valve regurgitation, and coronary artery compromise (ranging from minor stenosis to complete occlusion).

The **Rastelli operation** represents a 3rd type of repair for TGA, typically when there is associated VSD and pulmonary outflow tract obstruction. This operation, originally described in 1969, involves the creation of an intracardiac baffle that closes the VSD in a way that directs flow from the left ventricle to the aorta. The pulmonary valve is oversewn and a valved conduit placed between the right ventricle and pulmonary artery. Operative mortality is low, but patients require multiple reoperations for replacement of the pulmonary conduit during long-term follow-up. Other complications include complete heart block and LV outflow tract obstruction.

Because of the high incidence of observed and potential medical problems, all patients who have had atrial, arterial, or Rastelli repair of TGA should have lifelong follow-up by a cardiologist at a center specializing in adult CHD.

Pulmonary Valve Stenosis

See Chapter 454.1 .

Most patients with pulmonary valve stenosis are asymptomatic and present with a cardiac murmur. Survival into adult life and the need for intervention however is directly correlated to the degree of obstruction. Patients with **trivial** stenosis (defined as a peak gradient <25 mm Hg) followed for 25 yr remain asymptomatic and have no significant progression of obstruction over time. For those patients with **moderate** pulmonary valve stenosis (defined as a peak gradient of 25-49 mm Hg), there is an approximately 20% chance of requiring intervention by age 25. For those patients with severe stenosis (defined as a peak gradient >50 mm Hg), the majority ultimately require an intervention, either surgery or balloon valvuloplasty by age 25.

After surgical valvotomy for isolated pulmonary stenosis, long-term survival is excellent. With longer follow-up the incidence of late complications and the need for reintervention do increase. The most common indication for reintervention is pulmonary valve replacement for severe pulmonary regurgitation. Other long-term complications include recurrent atrial arrhythmias, endocarditis, and residual RV outflow tract obstruction.

Patients with **moderate to severe** pulmonary stenosis (defined as a peak gradient >50 mm Hg) should be considered for intervention even in the absence of symptoms. Since 1985, percutaneous balloon valvuloplasty has been the accepted treatment for patients of all ages. Before 1985, surgical valvotomy had been the gold standard. Surgical valvotomy is reserved for patients who are unlikely to have successful results from balloon valvuloplasty, such as those with an extremely dysplastic or calcified valve.

Left-Sided Obstructive Lesions

Coarctation of the Aorta

See Chapter 454.6 .

The clinical presentation of coarctation of the aorta depends on the severity of obstruction and the associated anomalies. Unrepaired coarctation typically presents with symptoms before adulthood. These symptoms include headaches related to hypertension, leg fatigue or cramps, exercise intolerance, and systemic hypertension (may be asymptomatic). Those untreated patients surviving to adulthood thus typically have only mild coarctation of the aorta. In the era before surgery, without treatment the mean age of death was 32 yr. Causes of death included LV failure, intracranial hemorrhage, endocarditis, aortic rupture/dissection, and premature coronary artery disease (CAD).

After surgical repair, long-term survival is good but is directly correlated with the age at repair, with those repaired after age 14 yr having a lower 20 yr survival than those who were repaired earlier, 91% vs 79%. With longer follow-up the incidence of long-term complications continues to rise. The most common long-term complication is persistent or new systemic hypertension at rest or during exercise. Other long-term complications include aneurysms of the ascending or descending aorta, recoarctation at the site of previous repair, CAD, aortic stenosis or regurgitation (in the setting of an associated bicuspid aortic valve), rupture of an intracranial aneurysm, and endocarditis.

Patients with significant native or residual coarctation of the aorta (symptomatic patients with a peak gradient across the coarctation >20 mm Hg) should be considered for intervention, either surgery or catheter intervention with balloon angioplasty with or without stent placement. Surgical repair in the adult patient is technically difficult and is associated with high morbidity. Catheter-based intervention is the preferred method in most experienced adult CHD centers.

Aortic Valve Stenosis

See Chapter 454.5 .

The natural history of aortic valve stenosis in adults is quite variable but is characterized by progressive stenosis over time. By age 45 yr, approximately 50% of bicuspid aortic valves will have some degree of stenosis.

Most patients with aortic valve stenosis are asymptomatic and are diagnosed after a murmur is detected. The severity of obstruction at diagnosis correlates with the pattern of progression. Symptoms are rare until patients have severe aortic valve stenosis (mean gradient by echocardiography >40 mm Hg). Symptoms include chest pain, exertional dyspnea, near-syncope, and syncope. When any of these symptoms is present, the risk of sudden cardiac death is very high, so surgical intervention is mandated. For patients requiring surgical valvotomy to relieve the stenosis prior to adulthood, the majority of patients do well. However, at 25 yr follow-up, up to 40% of patients will have required a 2nd operation for residual stenosis or regurgitation.

Patients with symptoms and severe aortic valve stenosis should be considered for intervention. Treatment involves manipulating the valve to reduce stenosis. This can be accomplished by balloon dilation of the valve, open surgical valvotomy, or valve replacement. In absence of significant aortic regurgitation, most centers favor balloon dilation or surgical valvotomy for children and young adults who have pliable valves with fusion of commissures. In older adults, aortic valve replacement is the treatment of choice.

Endocarditis Prophylaxis

See Chapter 464 .

The AHA found that very few cases of endocarditis are prevented with antibiotic prophylaxis. Only patients with cardiac conditions associated with the highest risk for adverse outcomes should continue antibiotic prophylaxis before surgery: previous endocarditis; unrepaired cyanotic CHD, including palliative shunts and conduits; completely repaired congenital heart defects with prosthetic material or device, surgically placed or by catheter intervention, during the 1st 6 mo after the procedure; and repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization). Except for the conditions just listed, antibiotic prophylaxis is no longer recommended for other forms of CHD.

Pregnancy and Congenital Heart Disease

CHD is the most common form of heart disease encountered during pregnancy in developed countries. Heart disease does not preclude a successful pregnancy but increases the risk to both the mother and the baby. During pregnancy, substantial hemodynamic changes occur. The hemodynamic changes in pregnancy result in a steady increase in cardiac output during pregnancy until the 32nd wk of gestation, at which time the cardiac output reaches a plateau at 30–50% above the prepregnancy level. At delivery, with uterine contractions an additional 300-500 mL of blood enters the circulation. This, in conjunction with increased blood pressure and heart rate during labor, increases the cardiac output at delivery to 80% the prepregnancy level.

Despite these hemodynamic changes, the outcome of pregnancy is favorable in most women with CHD provided that functional class and systemic ventricular function are good (see Table 461.5). Pulmonary artery hypertension presents a serious risk during pregnancy, particularly when the pulmonary pressure exceeds 70% of systemic pressure, regardless of functional class. Other contraindications to pregnancy include severe obstructive left-sided lesions (coarctation of the aorta, aortic valve stenosis, mitral valve stenosis, hypertrophic cardiomyopathy), Marfan syndrome with coexisting dilated ascending aorta (defined as >4 cm), persistent cyanosis, and systemic ventricular dysfunction (ejection fraction of ≤40%). The need for full anticoagulation during pregnancy, although not a contraindication, poses an increased risk to both mother and fetus. The relative risks and benefits of the different anticoagulant approaches need to be discussed fully with the mother.

Pregnancy counseling should begin early in adolescence and should be part of the routine cardiac follow-up visit. Counseling should include a discussion about the risk of CHD in the offspring. In the general population the incidence of CHD is 1%. In the offspring of a mother with CHD the risk increases to 5–6%. Often the cardiac lesion in the offspring is not the same as that in the mother, except in the case of a syndrome with autosomal dominant inheritance (Marfan syndrome, hypertrophic cardiomyopathy). Risk stratification should include the specific CHD lesion but also needs to consider the maternal functional class. Although the specific CHD lesion is important, multiple studies demonstrate that the maternal functional class before pregnancy is highly predictive of both maternal and fetal outcomes, with those in the best functional class having the best outcomes.

Contraception

A critical part of caring for adults with CHD is to provide (or make available) advice on contraception. Unfortunately, data are limited on the safety of various contraceptive techniques in adult CHD patients. The estrogen-containing oral contraceptives (OCs) can be used in many adult CHD patients but is not recommended in adult CHD patients at risk for thromboembolism, such as those with cyanosis, prior Fontan procedure, AF, or pulmonary artery hypertension. In addition, OCs may upset anticoagulation control. Although slightly less effective than OCs containing combined estrogen/progesterone, medroxyprogesterone, the progesterone-only pills, and levonorgestrel are good options for most adult CHD patients. Medroxyprogesterone and levonorgestrel, however, can cause fluid retention and thus need to be used with caution in patients with heart failure. These medications are also associated with depression and often breakthrough bleeding. Tubal ligation, although the most secure method of contraception, can be a high-risk procedure in patients with complex CHD or those with pulmonary hypertension. Hysteroscopic sterilization (Essure) may be reasonable for high-risk patients. In the past, intrauterine devices (IUDs) were seldom used in cardiac patients because of the associated risk of bacteremia, pelvic inflammatory disease, and endocarditis. IUDs such as the Mirena appear to be safe and effective and are rapidly becoming one of the most common form of contraception in the adult CHD population.

Adolescent Transition

It is well recognized that as part of the process of obtaining independence, adolescents or young adults must develop a forward-looking, independent approach to their medical care. For children with heart disease, the transition process must begin during early adolescence and should be encouraged by both the primary care provider and the pediatric cardiologist, who must identify an appropriate adult CHD program to which transition and transfer will be made at an appropriate time (Table 461.6).

Table 461.6

Adolescent Transition Issues Requiring Coordination of Patient Care Between Cardiologist and Primary Care Physician

Antibiotic prophylaxis for endocarditis
Medications and drug interactions
Anticoagulation with prosthetic valves
Exercise and sports participation
Educational and vocational planning
Contraception and pregnancy
Drug, alcohol, and tobacco use
Noncardiac surgical planning
Anesthetic issues
New symptoms or acute illnesses
Comorbid conditions
Travel

A successful transition program includes the following elements:

◆ Development of a written transition plan that should begin by age 14 yr

◆ Because adolescents and young adults are frequently unaware of the details of their cardiac diagnosis and history, a complete, concise, portable medical record, including all pertinent aspects of cardiac care, should be shared with adolescents and their family and prepared for transmittal to the eventual adult care destination.

◆ The primary care provider and cardiologist must address unique adolescent medical issues as they impact the cardiovascular system. In addition to medical problems, education, vocational planning, psychosocial issues, and access to medical care should be discussed with adolescents and their family.

Young adults tend to avoid medical care because of lack of education, denial, or difficulty with access to the medical care system. Thus a critical goal of the adolescent transition process is to identify an appropriate site for ongoing medical care and ensure maintenance of the medical record and continuity of care for the young adult. The site of care for a young adult with CHD may be a pediatric program or facility or a specialized center or program for the adult with CHD. The critical issues are the continuity of care, the preparation of the patient, and the patient's participation in the process.

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SECTION 4

Cardiac Arrhythmias

OUTLINE

Chapter 462 Disturbances of Rate and Rhythm of the Heart
Chapter 463 Sudden Death

CHAPTER 462

Disturbances of Rate and Rhythm of the Heart

Aarti S. Dalal, George F. Van Hare

The term *arrhythmia* refers to a disturbance in heart rate or rhythm. Such disturbances can lead to heart rates that are abnormally fast, slow, or irregular. They may be transient or incessant, congenital or acquired, or caused by a toxin or by drugs. They may be associated with particular forms of congenital heart disease (CHD), may be a complication of surgical repair of CHD, may be a result of certain genetic causes, or may be caused by fetal inflammation, as in maternal connective tissue disease. Arrhythmias, either slow or fast, may lead to acutely decreased cardiac output, degeneration into a more dangerous arrhythmia such as ventricular fibrillation, or if incessant may lead to cardiomyopathy. Arrhythmias may lead to syncope or to sudden death. When a patient has an arrhythmia, it is important to determine whether the particular rhythm is likely to lead to severe symptoms or to deteriorate into a life-threatening condition. Rhythm abnormalities such as single premature atrial and ventricular beats are common, and in children without heart disease, these usually pose no risk to the patient.

A number of pharmacologic agents are available for treating arrhythmias; many have not been studied extensively in children. Insufficient data are available regarding pharmacokinetics, pharmacodynamics, and efficacy in the pediatric population, and therefore the selection of an appropriate agent is necessarily empirical. Fortunately, most rhythm disturbances in children can be reliably controlled with a single agent (Table 462.1). Transcatheter ablation is acceptable therapy not only for life-threatening or drug-resistant arrhythmias, but also for the cure of arrhythmias. For patients with bradycardia, implantable pacemakers are small enough for use in all ages, and even in premature infants. Implantable cardioverter-defibrillators are available for use in high-risk patients with malignant ventricular arrhythmias and an increased risk of sudden death.

Table 462.1

Antiarrhythmic Drugs Commonly Used in Pediatric Patients, by Class

DRUG	INDICATIONS	DOSING	SIDE EFFECTS	DRUG INTERACTIONS	DRUG LEVEL
CLASS IA: INHIBITS Na$^+$ FAST CHANNEL, PROLONGS REPOLARIZATION					
Quinidine	SVT, atrial fibrillation, atrial flutter, VT. In atrial flutter, an AV node–blocking drug (digoxin, verapamil, propranolol) must be given first to prevent 1 : 1 conduction	Oral: 30-60 mg/kg/24 hr divided q6h (sulfate) or q8h (gluconate) In adults, 10 mg/kg/day divided q6h Max dose: 2.4 g/24 hr	Nausea, vomiting, diarrhea, fever, cinchonism, QRS and QT prolongation, AV nodal block, asystole syncope, thrombocytopenia, hemolytic anemia, SLE, blurred vision, convulsions, allergic reactions, exacerbation of periodic paralysis	Enhances digoxin, may increase PTT when given with warfarin	2-6 µg/mL
Procainamide	SVT, atrial fibrillation, atrial flutter, VT	Oral: 15-50 mg/kg/24 hr divided q4h Max dose: 4 g/24 hr IV: 10-15 mg/kg over 30-45 min load followed by 20-80 µg/kg/min Max dose: 2 g/24 hr	PR, QRS, QT interval prolongation, anorexia, nausea, vomiting, rash, fever, agranulocytosis, thrombocytopenia, Coombs-positive hemolytic anemia, SLE, hypotension, exacerbation of periodic paralysis, proarrhythmia	Toxicity increased by amiodarone and cimetidine	4-8 µg/mL With NAPA <40 µg/mL
Disopyramide	SVT, atrial fibrillation, atrial flutter	Oral: <2 yr: 20-30 mg/kg/24 hr divided q6h or q12h (long-acting form); 2-10 yr: 9-24 mg/kg/24 hr divide q6h or q12h (long-acting form); 11 yr: 5-13 mg/kg/24 hr divided q6h or q12h (long-acting) Max dose: 1.2 g/24 hr	Anticholinergic effects, urinary retention, blurred vision, dry mouth, QT and QRS prolongation, hepatic toxicity, negative inotropic effects, agranulocytosis, psychosis, hypoglycemia, proarrhythmia		2-5 µg/ml

CLASS IB: INHIBITS Na^+ FAST CHANNEL, SHORTENS REPOLARIZATION					
Lidocaine	VT, VF	IV: 1 mg/kg repeat q 5 min 2 times followed by 20-50 µg/kg/min (max dose: 3 mg/kg)	CNS effects, confusion, convulsions, high-grade AV block, asystole, coma, paresthesias, respiratory failure	Propranolol, cimetidine, increases toxicity	1-5 µg/mL
Mexiletine	VT	Oral: 6-15 mg/kg/24 hr divided q8h	GI upset, skin rash, neurologic	Cimetidine	0.8-2 µg/mL
Phenytoin	Digitalis intoxication	Oral: 3-6 mg/kg/24 hr divided q12h Max dose: 600 mg IV: 10-15 mg/kg over 1 hr load	Rash, gingival hyperplasia, ataxia, lethargy, vertigo, tremor, macrocytic anemia, bradycardia with rapid push	Amiodarone, oral anticoagulants, cimetidine, nifedipine, disopyramide, increase toxicity	10-20 µg/mL
CLASS IC: INHIBITS Na^+ CHANNEL					
Flecainide	SVT, atrial tachycardia, VT	Oral: 6.7-9.5 mg/kg/24 hr divided q8h In older children, 50-200 mg/m^2 /day divided q12h	Blurred vision, nausea, decrease in contractility, proarrhythmia	Amiodarone increases toxicity	0.2-1 µg/mL
Propafenone	SVT, atrial tachycardia, atrial fibrillation, VT	Oral: 150-300 mg/m^2 /24 hr divided q6h	Hypotension, decreased contractility, hepatic toxicity, paresthesia, headache, proarrhythmia	Increases digoxin levels	0.2-1 µg/mL
CLASS II: β-BLOCKERS					
Propranolol	SVT, long QT	Oral: 1-4 mg/kg/24 hr divided q6h Max dose 60 mg/24 hr IV: 0.1-0.15 mg/kg over 5 min Max IV dose: 10 mg	Bradycardia, loss of concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF	Co-administration with disopyramide, flecainide, or verapamil may decrease ventricular function.	
Atenolol	SVT	Oral: 0.5-1 mg/kg/24 hr once daily or divided q12h	Bradycardia, loss of concentration, school performance problems	Co-administration with disopyramide, flecainide, or verapamil may decrease ventricular function.	
Nadolol	SVT, long QT	Oral: 1-2 mg/kg/24	Bradycardia, loss of	Co-administration	

		hr given once daily	concentration, school performance problems bronchospasm, hypoglycemia, hypotension, heart block, CHF	with disopyramide, flecainide, or verapamil may decrease ventricular function.	
CLASS III: PROLONGS REPOLARIZATION					
Amiodarone	SVT, JET, VT	Oral: 10 mg/kg/24 hr in 1-2 divided doses for 4-14 days; reduce to 5 mg/kg/24 hr for several weeks; if no recurrence, reduce to 2.5 mg/kg/24 hr IV: 2.5-5 mg/kg over 30-60 min, may repeat 3 times, then 2-10 mg/kg/24 hr continuous infusion	Hypothyroidism or hyperthyroidism, elevated triglycerides, hepatic toxicity, pulmonary fibrosis	Digoxin (increases levels), flecainide, procainamide, quinidine, warfarin, phenytoin	0.5-2.5 mg/L
CLASS IV AND MISCELLANEOUS MEDICATIONS					
Digoxin	SVT (not WPW), atrial flutter, atrial fibrillation	Oral/load instructions: Premature: 20 µg/kg Newborn: 30 µg/kg >6 mo: 40 µg/kg	PAC, PVC, bradycardia, AV block, nausea, vomiting, anorexia, prolongs PR interval	Quinidine Amiodarone, verapamil, increase digoxin levels	1-2 mg/mL
		Give ½ total dose followed by ¼ q8-12h × 2 doses			
		Maintenance: 10 µg/kg/24 hr divide q12h Max dose: 0.5 mg			
		IV: ¾ PO dose Max dose: 0.5 mg			
Verapamil	SVT (not WPW)	Oral: 2-7 mg/kg/24 hr divided q8h Max dose: 480 mg IV: 0.1-0.2 mg/kg q 20 min × 2 doses Max dose: 5-10	Bradycardia, asystole, high degree AV block, PR prolongation, hypotension, CHF	Use with β-blocker or disopyramide exacerbates CHF, increases digoxin level and toxicity	

		mg			
Adenosine	SVT	IV: 50-300 µg/kg by need rapid IV push Begin with 50 µg/kg and increase by 50-100 µg/kg/dose Max dose: 18 mg	Chest pain, flushing, dyspnea, bronchospasm, atrial fibrillation, bradycardia, asystole		

AV, Atrioventricular; CHF, congestive heart failure; CNS, central nervous systems; GI, gastrointestinal; IV, intravenous; JET, junctional ectopic tachycardia; NAPA, *N* -acetyl procainamide; PAC, premature atrial contraction; PTT, partial thromboplastin time; PVC, premature ventricular contraction; SLE, systemic lupus erythematosus–like illness; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

462.1

Principles of Antiarrhythmic Therapy

Aarti S. Dalal, George F. Van Hare

When considering drug therapy in the pediatric population, it is important to recognize that there may be marked differences in pharmacokinetics by age and comparison with adults. Infants may have slower absorption, slow gastric emptying, and differing sizes of drug tissue compartments affecting the volume of distribution. Hepatic metabolism and renal excretion may vary within the pediatric age-group as well as in comparison to adults. Special consideration must also be given to the frequency and diet of an infant when choosing specific antiarrhythmics. When considering antiarrhythmic therapy, it is important to recognize that the likely arrhythmia mechanism may be different for the pediatric than the adult population.

Many antiarrhythmic agents are available for rhythm control. The majority are not approved by the U.S. Food and Drug Administration (FDA) for use in children; their use is therefore considered “off-label.” Pediatric cardiologists have experience with these drugs, with well-recognized standards for dosing.

With the availability of potentially curative ablation procedures, medical therapy has become less important. Clinicians and patients accept fewer drug side effects. Intolerable side effects, as well as the potential for a proarrhythmia induced by an antiarrhythmic drug, can seriously limit medical therapy and will lead the physician and family toward a potentially curative ablation procedure.

Antiarrhythmic drugs are frequently categorized using the **Vaughan-Williams classification** . This system comprises 4 classes: **class I** includes agents that primarily block the sodium channel, **class II** drugs are the β-blockers, **class III** includes agents that prolong repolarization by blocking potassium channels, and **class IV** drugs are the calcium channel blockers. Class I is further divided by the strength of the sodium channel blockade (see Table 462.1).

462.2

Sinus Arrhythmias and Extrasystoles

Aarti S. Dalal, George F. Van Hare

Phasic sinus arrhythmia represents a normal physiologic variation in impulse discharges from the sinus node related to respirations. The heart rate slows during expiration and accelerates during inspiration. Occasionally, if the sinus rate becomes slow enough, an **escape beat** arises from the atrioventricular (AV) junction region (Fig. 462.1). Normal phasic sinus arrhythmia is caused by the activity of the parasympathetic nervous system and can be quite prominent in healthy children. It may mimic frequent premature contractions, but the relationship to the phases of respiration can be appreciated with careful auscultation. Drugs that increase vagal tone, such as digoxin, may exaggerate sinus arrhythmia; it is usually abolished by exercise. Other irregularities in sinus rhythm, especially bradycardia associated with periodic apnea, are common in premature infants.

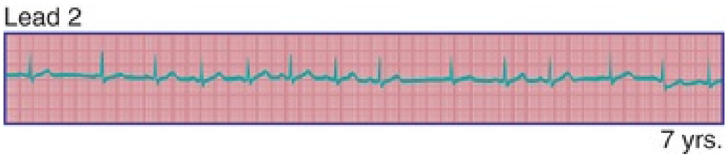

FIG. 462.1 Phasic sinus arrhythmia with a junctional escape beat. Note the variation in P-P interval with no significant change in P-wave morphology or PR interval. When the sinus rate is slow enough, the atrioventricular junction takes over and produces escape beats. This rhythm is normal.

Sinus bradycardia is a result of slow discharge of impulses from the sinus node, the heart's "natural pacemaker." A sinus rate <90 beats/min in neonates and <60 beats/min in older children is considered sinus bradycardia. It is typically seen in well-trained athletes; in healthy individuals it generally has no significance. Sinus bradycardia may occur in systemic disease (hypothyroidism, anorexia nervosa), and it resolves when the disorder is under control. It may also be seen in association with conditions in which there is high vagal tone, such as gastrointestinal obstruction or intracranial processes. Low-birthweight infants display great variation in sinus rate. Sinus bradycardia is common in these infants, in conjunction with apnea, and may be associated with junctional escape beats; premature atrial contractions are also frequent. These rhythm changes, especially bradycardia, appear more often during sleep and are not associated with symptoms. Usually, no therapy is necessary.

Wandering atrial pacemaker is defined as an intermittent shift in the pacemaker of the heart from the sinus node to another part of the atrium (Fig. 462.2). It is not uncommon in childhood and usually represents a normal variant. It may also be seen in association with sinus bradycardia in which the shift in atrial focus is an escape phenomenon.

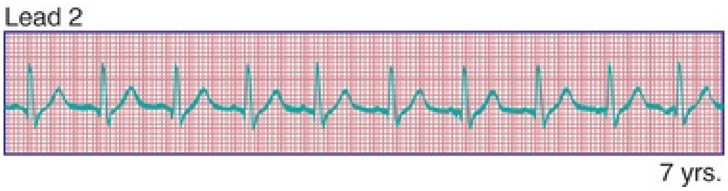

FIG. 462.2 Wandering atrial pacemaker. Note the change in P-wave configuration in the 7th, 9th, and 10th beats. The 7th P wave may represent a fusion between the sinus P and the ectopic atrial pacemaker seen in the 10th beat.

Extrasystoles are produced by the premature discharge of an ectopic focus that may be situated in the atrium, the AV junction, or the ventricle. Usually, isolated extrasystoles are of no clinical or prognostic significance. Under certain circumstances, however, premature beats may be caused by organic heart disease (inflammation, ischemia, fibrosis) or drug toxicity.

Premature atrial contractions or **complexes (PACs)** are common in childhood, usually in the absence of cardiac disease. Depending on the degree of prematurity of the beat (coupling interval) and the preceding R-R interval (cycle length), PACs may result in a normal, a prolonged (aberrancy), or an absent (blocked PAC) QRS complex. The last occurs when the premature impulse cannot conduct to the ventricle due to refractoriness of the AV node or distal conducting system (Fig. 462.3). Atrial extrasystoles must be distinguished from premature ventricular contractions. Careful scrutiny of the electrocardiogram (ECG) for a premature P wave preceding the QRS will show either a premature P wave superimposed on and deforming the preceding T wave or a P wave that is premature and has a different contour from that of the other sinus P waves. PACs usually reset the sinus node pacemaker, leading to an incomplete compensatory pause, but this feature is not regarded as a reliable means of differentiating atrial from ventricular premature complexes in children.

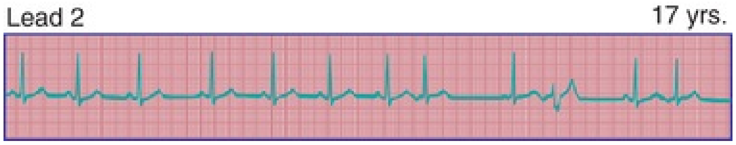

FIG. 462.3 Premature atrial contraction (PAC). QRS complexes—the 8th, 10th, and final—in this strip are preceded by a P wave that is inverted, indicative of an ectopic origin of atrial depolarization. Note that the 8th and final QRS complexes resemble those of sinus origin, whereas the 10th is aberrantly conducted. This shift in origin is a function of the preceding cycle length, which influences the refractory period of the bundle branches. The fact that the pause after the PAC is longer than 2 P-P intervals implies that the premature atrial depolarization has invaded and discharged the sinus node and then reset it so that it fires later.

Premature ventricular contractions or **complexes (PVCs)** may arise in any region of the ventricles. PVCs are characterized by premature, widened, bizarre QRS complexes that are not preceded by a premature P wave (Fig. 462.4). When all premature beats have identical contours, they are classified as *uniform,* suggesting origin from a common site. When PVCs vary in contour, they are designated as *multiform,* suggesting origin from more than 1 ventricular site. Ventricular extrasystoles are often, but not always, followed by a full compensatory pause. The presence of **fusion beats** , that is, complexes with morphologic features that are intermediate between those of normal sinus beats and those of PVCs, proves the ventricular origin of the premature beat. Extrasystoles produce a smaller stroke and pulse volume than normal and, if quite premature, may not be audible with a stethoscope or palpable at the radial pulse. When frequent, extrasystoles may assume a definite rhythm, for example, alternating with normal beats (**bigeminy**) or occurring after 2 normal beats (**trigeminy**). Most patients are unaware of single PVCs, although some may be aware of a “skipped beat” over the precordium. This sensation is caused by the increased stroke volume of the normal beat after a compensatory pause. Anxiety, a febrile illness, or ingestion of various drugs or stimulants may exacerbate PVCs.

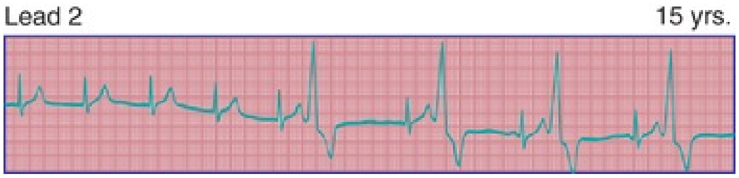

FIG. 462.4 Premature ventricular contractions in a bigeminal rhythm, in a patient who is hyperventilating. Note that the premature beat is wide and has a completely different morphology from that of the sinus beat. The premature beat is not preceded by a discernible premature P wave or any appreciable deformation of the preceding T wave.

It is important to distinguish PVCs that are benign from those that are likely to lead to more severe arrhythmias. The former usually disappear during the tachycardia of exercise. If they persist or become more frequent during exercise, the arrhythmia may have greater significance. The following criteria are indications for further investigation of PVCs that could require **suppressive therapy** : (1) ≥2 PVCs in a row; (2) multiform PVCs; (3) increased ventricular ectopic activity with exercise; (4) R-on-T phenomenon (premature ventricular depolarization occurs on the T wave of the preceding beat); (5) extreme frequency of beats (e.g., >20% of total beats on Holter monitoring); and (6) most importantly, the presence of underlying heart disease, a history of heart surgery, or both. The best therapy for benign PVCs is reassurance that the arrhythmia is not life threatening, although very symptomatic individuals may benefit from suppressive therapy.

Malignant PVCs are usually secondary to another medical problem (electrolyte imbalance, hypoxia, drug toxicity, cardiac injury). Successful treatment includes correction of the underlying abnormality. An intravenous lidocaine bolus and drip is the first line of therapy, with more effective drugs such as amiodarone reserved for refractory cases or for patients with underlying ventricular dysfunction or hemodynamic compromise.

462.3

Supraventricular Tachycardia

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Supraventricular tachycardia (**SVT**) is a general term that includes essentially all forms of paroxysmal or incessant tachycardia except ventricular tachycardia. The category of SVT can be divided into 3 major subcategories: reentrant tachycardias using an accessory pathway, reentrant tachycardias without an accessory pathway, and ectopic or automatic tachycardias. **Atrioventricular reciprocating tachycardia (AVRT)** involves an accessory pathway and is the most common mechanism of SVT in infants. **Atrioventricular node reentry tachycardia (AVNRT)** is rare in infancy, but there is an increasing incidence of AVNRT in childhood and into adolescence. Atrial flutter is rarely seen in children with normal hearts (see later), whereas intraatrial reentry tachycardia (also known as atrial flutter) is common in patients following cardiac surgery. Atrial and junctional ectopic tachycardias are more often associated with abnormal hearts (cardiomyopathy) and the immediate postoperative period after surgery for CHD.

Clinical Manifestations

Reentrant SVT is characterized by an abrupt onset and termination; it may occur when the patient is at rest or exercising, and in infants it may be precipitated by an acute infection. Attacks may last only a few seconds or may persist for hours. The heart rate usually exceeds 180 beats/min and may occasionally be as rapid as 300 beats/min. The only complaint may be awareness of the rapid heart rate.

Many children tolerate these episodes extremely well, and it is unlikely that short paroxysms are a danger to life. If heart rate is exceptionally rapid or the attack is prolonged, precordial discomfort and heart failure may occur. In children, SVT may be exacerbated by exposure to caffeine, nonprescription decongestants, or bronchodilators.

In young infants the diagnosis may be more obscure because of their inability to communicate their symptoms. The heart rate at this age is normally higher than in older children and increases greatly with crying. Occasionally, infants with SVT initially present with heart failure because the tachycardia may go unrecognized for a long time. The heart rate during episodes is frequently in the range of 240-300 beats/min. If the attack lasts 6-24 hr or more, heart failure may be recognized, and the infant will have an ashen color and will be restless and irritable, with tachypnea, poor pulses, and hepatomegaly. When tachycardia occurs in the fetus, it can cause **hydrops fetalis** , the in utero manifestation of heart failure.

In neonates, SVT is usually manifested as a narrow QRS complex (<0.08 sec). The P wave is visible on a standard ECG in only 50–60% of neonates with SVT, but it is detectable with a transesophageal lead in most patients. *Differentiation from sinus tachycardia* may be difficult but is important because sinus tachycardia requires treatment of the underlying problem (e.g., sepsis, hypovolemia) rather than antiarrhythmic medication. If the rate is >230 beats/min with an abnormal P-wave axis (a normal P wave is positive in leads I and aVF), sinus tachycardia is *not* likely. The heart rate in SVT also tends to be *relatively unvarying* , whereas in sinus tachycardia the heart rate *varies* with changes in vagal and sympathetic tone. AVRT uses a bypass tract that may be able to conduct bidirectionally (**Wolff-Parkinson-White** [**WPW**] **syndrome**) or may be retrograde only (**concealed accessory pathway**). Patients with WPW syndrome have a small but real risk of sudden death. If the accessory pathway rapidly conducts in antegrade fashion, the patient is at risk for atrial fibrillation begetting ventricular fibrillation. Risk stratification, including 24 hr Holter monitoring and exercise study, may help differentiate patients at higher risk for sudden death from WPW. However, it is important to note that intermittent preexcitation may not decrease a patient's risk profile. Syncope is an ominous symptom in WPW, and any patient with syncope and WPW syndrome should have an **electrophysiology study** (EPS) and likely catheter ablation.

The typical electrocardiographic features of the WPW syndrome are seen when the patient is not having tachycardia. These features include a short P-R interval and slow upstroke of the QRS (delta wave) (Fig. 462.5). Although most often presenting in patients with a normal heart, WPW syndrome may also be associated with **Ebstein anomaly** of the tricuspid valve or hypertrophic cardiomyopathy. The critical anatomic structure is an accessory pathway consisting of a muscular bridge connecting atrium to ventricle on either the right or the left side of the AV ring (Fig. 462.6). During sinus rhythm, the impulse is carried over both the AV node and the accessory pathway; it produces some degree of fusion of the 2 depolarization fronts that results in an abnormal QRS. During AVRT, an impulse is carried in *antegrade* fashion through the AV node (**orthodromic tachycardia**), which results in a normal QRS complex, and in *retrograde* fashion through the accessory pathway to the atrium, thereby perpetuating the tachycardia. In these cases, only after cessation of the tachycardia is the typical ECG features of WPW syndrome recognized (see Fig. 462.5). When rapid antegrade conduction occurs through the accessory pathway during tachycardia, and the retrograde reentry pathway to the atrium is by the AV node (**antidromic tachycardia**), the QRS complexes are wide, and the potential for more serious arrhythmias (ventricular fibrillation) is greater, especially if atrial fibrillation occurs.

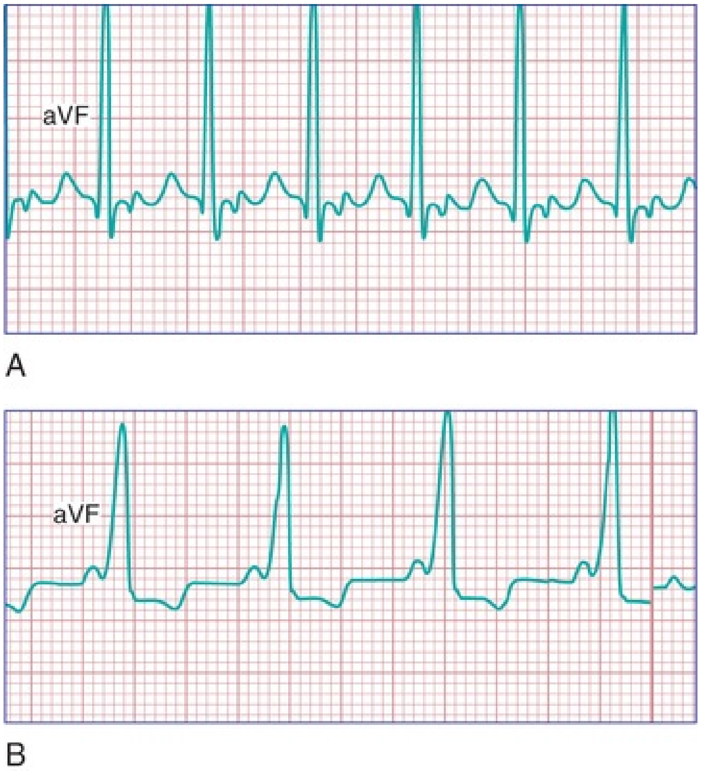

FIG. 462.5 **A,** Supraventricular tachycardia in a child with Wolff-Parkinson-White (WPW) syndrome. Note the normal QRS complexes during the tachycardia, as well as clear retrograde P waves seen on the upstroke of the T waves. **B,** Later, the typical features of WPW syndrome are apparent (short P-R interval, delta wave, wide QRS).

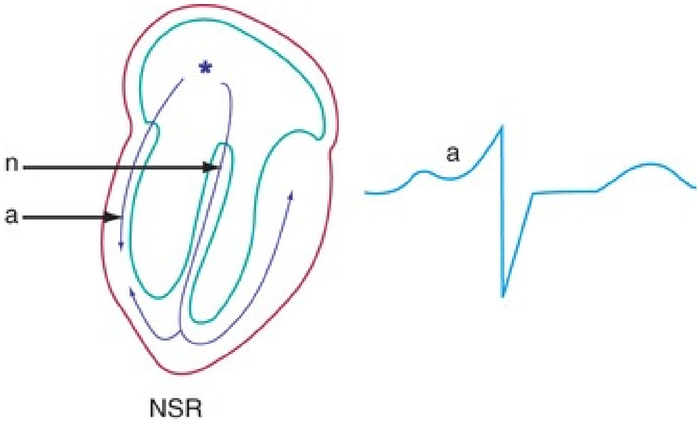

FIG. 462.6 Schematic representation of the heart with a right-sided accessory pathway (WPW syndrome). The *asterisk* indicates initiation of the sinus beat. The *arrows* indicate the direction and spread of excitation. The electrocardiographic complex shown represents a fusion beat that combines activation over the normal *(n)* and accessory *(a)* pathways. The latter inscribes the delta wave. NSR, Normal sinus rhythm.

AVNRT involves the use of 2 functional pathways within the AV node, the *slow* and *fast* AV node pathways. This arrhythmia is more often seen in adolescence. It is one of the few forms of SVT that is occasionally associated with syncope. This arrhythmia is often seen in association with exercise.

Treatment

Vagal stimulation by placing of the face in ice water (in older children) or by placing an ice bag over the face (in infants) may abort the attack. To terminate the attack, older children may be taught **vagal maneuvers** such as the Valsalva maneuver, straining, breath holding, or standing on their head. Ocular pressure must never be performed, and carotid sinus massage is rarely effective. When these measures fail, several pharmacologic alternatives are available (see Table 462.1). In stable patients, **adenosine** by rapid intravenous push is the treatment of choice (0.1 mg/kg, maximum dose 6 mg) because of its rapid onset of action and minimal effects on cardiac contractility. The dose may need to be increased (0.2 mg/kg, maximum 12 mg) if no effect on the tachycardia is seen. Because of the potential for adenosine to initiate atrial fibrillation, it should never be administered without a means for direct current (**DC**) **cardioversion** near at hand. Calcium channel blockers such as **verapamil** have also been used in the initial treatment of SVT in older children. Verapamil may reduce cardiac output and produce hypotension and cardiac arrest in infants younger than 1 yr and therefore is contraindicated in this age-group. In urgent situations when symptoms of severe heart failure have already occurred, *synchronized* DC cardioversion (0.5-2 J/kg) is recommended as the initial management (see Chapter 81).

Once the patient has been converted to sinus rhythm, a longer-acting agent is selected for maintenance therapy. In patients without an antegrade accessory pathway (non-WPW), the β-adrenergic blockers are the mainstay of drug therapy. **Digoxin** is also popular and may be effective in infants, but less so in older children. In children with WPW, digoxin or calcium channel blockers may *increase* the rate of antegrade conduction of impulses through the bypass tract, with the possibility of ventricular fibrillation, and are therefore contraindicated. These patients are usually managed with β-blockers. In patients with resistant tachycardias, flecainide, propafenone, sotalol, and amiodarone have all been used. Most antiarrhythmic agents have the potential of causing new dangerous arrhythmias (**proarrhythmia**) and decreasing heart function. Flecainide and propafenone should be limited to use in patients with otherwise normal hearts.

If cardiac failure occurs because of prolonged tachycardia in an infant with a normal heart, cardiac function usually returns to normal after sinus rhythm is reinstituted, although it may take days to weeks. Infants with SVT diagnosed within the 1st 3-4 mo of life have a lower incidence of recurrence than those initially diagnosed at a later age. These patients have up to an 80% chance of resolution by the 1st yr of life, although approximately 30% will have recurrences later in childhood; if medical therapy is required, it can be tapered within 1 yr and the patient watched for signs of recurrence. Parents should be taught to measure the heart rate in their infants, so that prolonged unapparent episodes of SVT may be detected before heart failure occurs.

The use of **24 hr electrocardiographic (Holter) monitoring** assists in following the course of therapy and detecting brief runs of asymptomatic tachycardia, particularly in younger children and infants. Some centers use **transesophageal pacing** to evaluate the effects of therapy in infants. More detailed electrophysiology studies performed in the cardiac catheterization laboratory are often indicated in patients with refractory SVTs who are candidates for **catheter ablation** . During an EPS, multiple electrode catheters are placed transvenously in different locations in the heart. Pacing is performed to evaluate the conduction characteristics of the accessory pathway and to initiate the tachyarrhythmia, and mapping is performed to locate the accessory pathway. **Catheter ablation** of an accessory pathway is frequently used in children and teenagers, as well as in patients who require multiple agents or find drug side effects intolerable or for whom arrhythmia control is poor. Ablation may be performed either by **radiofrequency ablation** , which creates tissue heating, or **cryoablation** , in which tissue is frozen (Fig. 462.7). The overall initial success rate for catheter ablation ranges from 90–98%, depending on the location of the accessory pathway. Surgical ablation of bypass tracts is rarely done and proposed only in carefully selected patients.

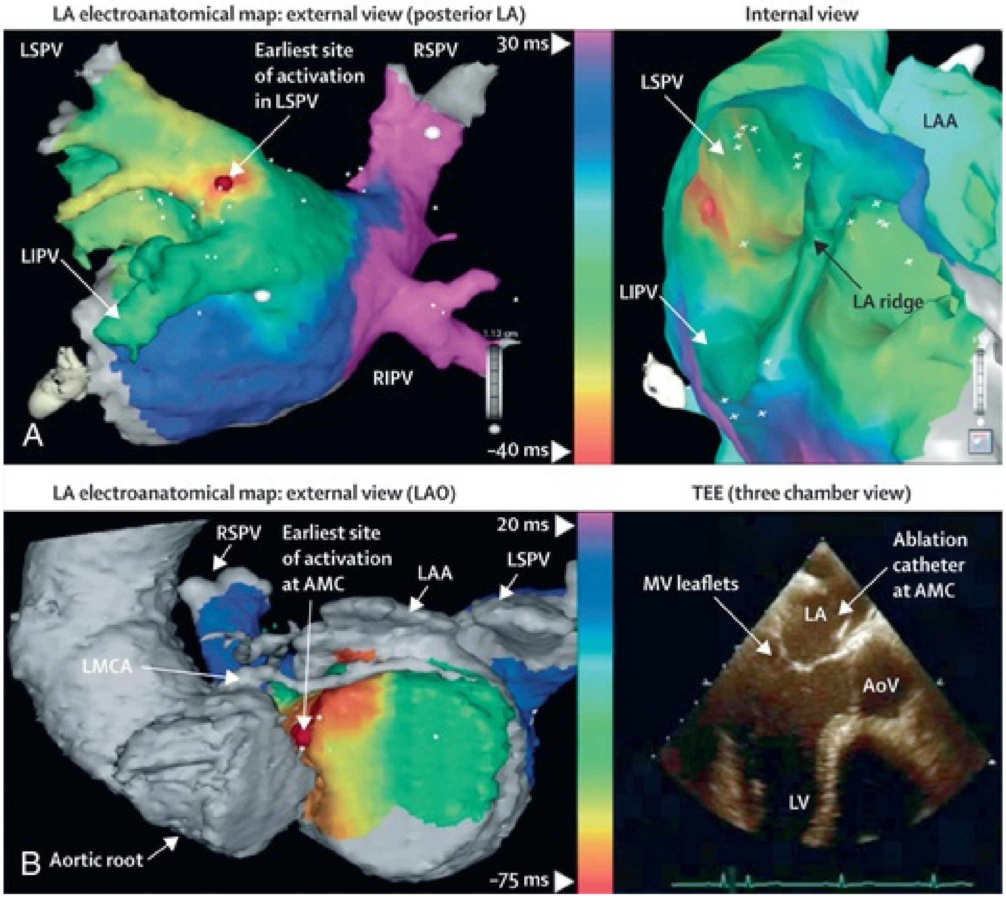
LA electroanatomical map: external view (posterior LA)
Internal view
LSPV
Earliest site of activation in LSPV
RSPV
30 ms
LIPV
RIPV
A
-40 ms
LSPV
LAA
LIPV
LA ridge
LA electroanatomical map: external view (LAO)
TEE (three chamber view)
RSPV
Earliest site of activation at AMC
LAA
LSPV
20 ms
LMCA
B
Aortic root
-75 ms
MV leaflets
Ablation catheter at AMC
LA
AoV
LV

FIG. 462.7 **Three-dimensional electroanatomical mapping of focal atrial tachycardias. Focal site of early activation *(red)* is shown, with radial propagation away from that central site. The activation map was superimposed onto the patient's cardiac CT scan, taken the day before the procedure and imported into the mapping system. A, Earliest site of activation, mapped to the posterior aspect of the LSPV ostium. Posterior external view *(left side)* and endoluminal or internal view looking from within the left atrium into the mouth of the LSPV *(right side)* are shown. B, Earliest site mapped to the aortomitral continuity. The anatomic relation between the mitral annulus and the aortic root can be clearly appreciated *(left side).* The location of the ablation catheter at the site of earliest atrial activation during atrial tachycardia is shown on the TEE image *(right side).* AMC, Aortomitral continuity; AoV, aortic valve; LA, left atrium; LAA, left atrial appendage; LAO, left anterior oblique; LIPV, left inferior pulmonary vein; LMCA, left main coronary artery; LSPV, left superior pulmonary vein; LV, left ventricle; MV, mitral valve; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; TEE, transesophageal echocardiogram. (From Lee G, Sanders P, Kalman JM: Catheter ablation of atrial arrhythmias: state of the art. *Lancet* 380:1509–1518, 2012, Fig 3.)**

The management of SVT caused by AVNRT is almost identical to that for AVRT. Children with AVNRT are not at increased risk of sudden death because they do not have a manifest accessory pathway. In practice, their episodes are more likely to be brought on by exercise or other forms of stress, and the heart rates can be quite fast, leading to chest pain, dizziness, and occasionally syncope. If chronic antiarrhythmic medication is desired, β-blockers are the drugs of choice; acutely, AVNRT responds to adenosine. Less is known about the natural history, but patients with AVNRT are seen quite frequently in adulthood, so spontaneous resolution seems unlikely. Patients are quite amenable to catheter ablation, either using radiofrequency energy or cryoablation, with high success rates and low complication rates.

Atrial ectopic tachycardia is an uncommon tachycardia in childhood. It is characterized by a variable rate (seldom >200 beats/min), identifiable P waves with an abnormal axis, and either a sustained or incessant nonsustained tachycardia. This form of atrial tachycardia has a single automatic focus. Identification of this mechanism is aided by monitoring the ECG while initiating vagal or pharmacologic therapy. Reentry tachycardias “break” suddenly, whereas automatic tachycardias gradually slow down and then gradually speed up again. Atrial ectopic tachycardias are usually more difficult to control pharmacologically than the more common reentrant tachycardias. If pharmacologic therapy with a single agent is unsuccessful, catheter ablation is suggested and has a success rate >90%.

Chaotic or multifocal atrial tachycardia is defined as atrial tachycardia with ≥3 ectopic P waves, frequent blocked P waves, and varying P-R intervals of conducted beats. This arrhythmia occurs most often in infants younger than 1 yr, usually without cardiac disease, although some evidence suggests an association with viral myocarditis or pulmonary disease. The goal of drug treatment is slowing of the ventricular rate, because conversion to sinus may not be possible, and multiple agents are often required. When this arrhythmia occurs in infancy, it usually terminates spontaneously by 3 yr of age.

Accelerated junctional ectopic tachycardia (JET) is an automatic (non-reentry) arrhythmia in which the junctional rate exceeds that of the sinus node and AV dissociation results. This arrhythmia is most often recognized in the early postoperative period after cardiac surgery and may be extremely difficult to control. Reduction of the infusion rate of catecholamines and control of fever and pain are important adjuncts to management. Congenital JET may be seen in the absence of surgery. It is incessant and can lead to dilated cardiomyopathy. Intravenous amiodarone is effective in the treatment of postoperative JET. Patients who require chronic therapy may respond to amiodarone or sotalol. Congenital JET can be cured by catheter ablation, but long-term AV block requiring a pacemaker is a prominent complication.

Atrial flutter , also known as *intraatrial reentrant tachycardia*, is an atrial tachycardia characterized by atrial activity at a rate of 250-300 beats/min in children and adolescents, and 400-600 beats/min in neonates. The mechanism of common atrial flutter consists of a reentrant rhythm originating in the right atrium circling the tricuspid valve annulus. Because the AV node cannot transmit such rapid impulses, some degree of **AV block** is virtually always present, and the ventricles respond to every 2nd to 4th atrial beat (Fig. 462.8). Occasionally, the response is variable, and the rhythm appears irregular.

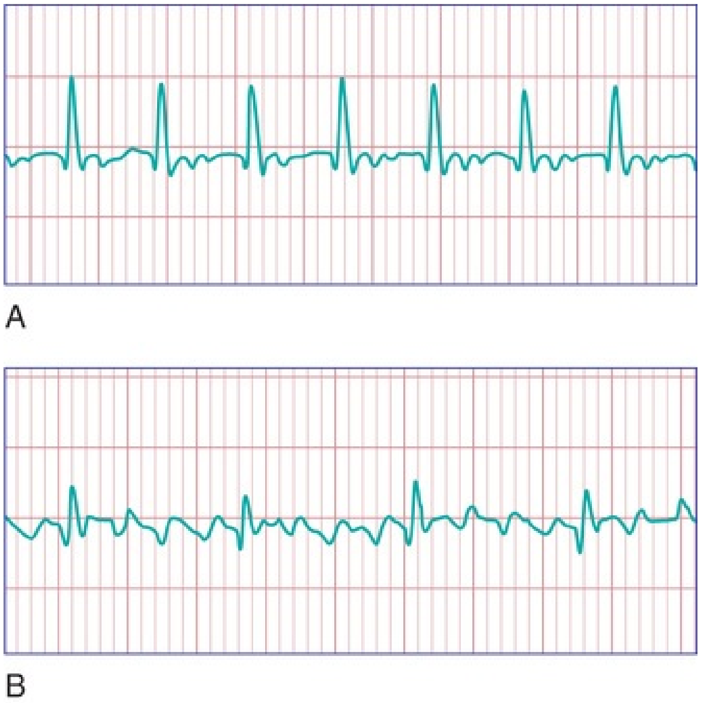

FIG. 462.8 Neonatal atrial flutter. Note that the flutter waves are not obvious in the 1st tracing (A), but once a dose of adenosine is given, flutter waves at a rate of about 450 beats/min emerge (B).

In older children, atrial flutter usually occurs in the setting of CHD; neonates with atrial flutter frequently have normal hearts. Atrial flutter may occur during acute infectious illnesses but is most often seen in patients with large stretched atria, such as those associated with long-standing mitral or tricuspid insufficiency, tricuspid atresia, Ebstein anomaly, or rheumatic mitral stenosis. Atrial flutter can also occur after palliative or corrective intraatrial surgery. Uncontrolled atrial flutter may precipitate heart failure. Vagal maneuvers or adenosine may produce a temporary slowing of the heart rate as a result of increased AV block, allowing a diagnosis to be made. The diagnosis is confirmed by ECG, which demonstrates the rapid and regular atrial saw-toothed flutter waves. Atrial flutter usually converts immediately to sinus rhythm by synchronized DC cardioversion, which is most often the treatment of choice. Patients with chronic atrial flutter in the setting of CHD may be at increased risk for **thromboembolism** and stroke and should thus undergo anticoagulation before elective cardioversion. β-Blockers or calcium channel blockers may be used to slow the ventricular response in atrial flutter by prolonging the AV node refractory period. Other agents may be used to maintain sinus rhythm, including class I agents such as procainamide or propafenone or class III agents such as amiodarone and sotalol. Catheter ablation has been used in patients with normal hearts and those with CHD with moderate success. After cardioversion, neonates with normal hearts may be followed off antiarrhythmic therapy or may be treated with digoxin, propranolol, or sotalol for 6-12 mo, after which the medication can usually be discontinued, since neonatal atrial flutter generally does not recur.

Atrial fibrillation is uncommon in children and is rare in infants. The atrial excitation is chaotic and more rapid (400-700 beats/min) and produces an *irregularly* irregular ventricular response and pulse (Fig. 462.9). This rhythm disorder is often associated with atrial enlargement or disease. Atrial fibrillation may be seen in older children with rheumatic mitral valve stenosis. It is also seen rarely as a complication of atrial surgery, in patients with left atrial enlargement secondary to left AV valve insufficiency, and in patients with WPW syndrome. Thyrotoxicosis, pulmonary embolism, pericarditis, or cardiomyopathy may be suspected in a previously normal older child or adolescent with atrial fibrillation. Very rarely, atrial fibrillation may be familial. The best initial treatment is **rate control** , most effectively with calcium channel blockers, to limit the ventricular rate during atrial fibrillation. Digoxin is not given if WPW syndrome is present. Normal sinus rhythm may be restored with intravenous procainamide, ibutilide, or amiodarone; DC cardioversion is the first choice in hemodynamically unstable patients. Patients with chronic atrial fibrillation are at risk for thromboembolism and stroke and should undergo anticoagulation with warfarin. Patients being treated by elective cardioversion should also undergo anticoagulation.

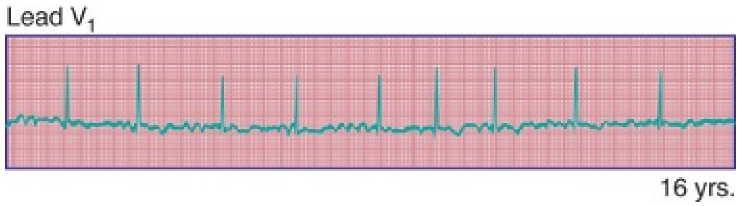

FIG. 462.9 **Atrial fibrillation, characterized by the absence of clear P waves and an irregularly irregular ventricular response. One can appreciate the irregular, rapid undulations (F waves). Fibrillatory waves may not be visible in all leads and should be carefully sought in every tracing with irregular R-R intervals. Note that no 2 R-R intervals are the same.**

462.4

Ventricular Tachyarrhythmias

Aarti S. Dalal, George F. Van Hare

Ventricular tachycardia (VT) is less common than SVT in pediatric patients. VT is defined as at least 3 PVCs at >120 beats/min (Fig. 462.10). It may be paroxysmal or incessant. VT may be associated with myocarditis, anomalous origin of a coronary artery, arrhythmogenic cardiomyopathy, mitral valve prolapse, primary cardiac tumors, and dilated or hypertrophic cardiomyopathy. It is seen with prolonged QT interval of either congenital or acquired (proarrhythmic drugs) causation, WPW syndrome, and drug use (cocaine, amphetamines). It may develop years after intraventricular surgery (especially tetralogy of Fallot and related defects) or occur without obvious organic heart disease. VT must be distinguished from SVT with aberrancy or rapid conduction over an accessory pathway (Table 462.2). The presence of clear capture and fusion beats confirms the diagnosis of VT. Although some children tolerate rapid ventricular rates for many hours, this arrhythmia should be promptly treated because hypotension and degeneration into ventricular fibrillation may result. For patients who are hemodynamically stable, intravenous amiodarone, lidocaine, or procainamide is the initial drug of choice. If treatment is to be successful, it is critical to search for and correct any underlying abnormalities, such as electrolyte imbalance, hypoxia, or drug toxicity. **Amiodarone** is the treatment of choice during cardiac arrest (see Chapter 81). Hemodynamically unstable patients with VT should be immediately treated with DC cardioversion. Overdrive ventricular pacing, through temporary pacing wires or a permanent pacemaker, may also be effective, although it may cause the arrhythmia to deteriorate into ventricular fibrillation. In the neonatal period, VT may be associated with an anomalous left coronary artery (see Chapter 459.2) or a myocardial tumor.

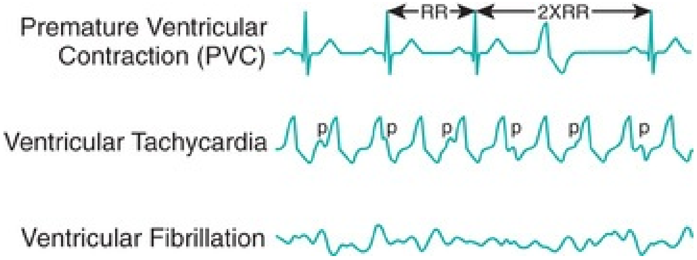

FIG. 462.10 Ventricular arrhythmias. (From Park MY: *Pediatric cardiology for practitioners,* ed 5, Philadelphia, 2008, Mosby Elsevier, Fig. 24-6, p 429.)

Table 462.2

Diagnosis of Tachyarrhythmias: Electrocardiographic Findings

	HEART RATE (BEATS/MIN)	P WAVE	QRS DURATION	REGULARITY
Sinus tachycardia	<230	Always present, normal axis	Normal	Rate varies with respiration
Atrial tachycardia	180-320	Present Abnormal P wave morphology and axis	Normal or prolonged (with aberration)	Usually regular but ventricular response may be variable because of Wenckebach conduction
Atrial fibrillation	120-180	Fibrillatory waves	Normal or prolonged (with aberration)	Irregularly irregular (no 2 R-R intervals alike)
Atrial flutter	Atrial: 250-400 Ventricular response variable: 100-320	Saw-tooth flutter waves	Normal or prolonged (with aberration)	Regular ventricular response (e.g., 2 : 1, 3 : 1, 3 : 2, and so on)
Junctional tachycardia	120-280	Atrioventricular dissociation with no fusion, and normal QRS capture beats	Normal or prolonged (with aberration)	Regular (except with capture beats)
Ventricular tachycardia	120-300	Atrioventricular dissociation with capture beats and fusion beats	Prolonged for age	Regular (except with capture beats)

Unless a clearly reversible cause is identified, EPS is usually indicated for patients in whom VT has developed, and depending on the findings, catheter ablation and/or ICD implantation may be indicated.

A related arrhythmia, **ventricular accelerated rhythm** , is occasionally seen in infants. It is defined the same way as VT, but the rate is only slightly faster than the coexisting sinus rate (within 10%). It is generally benign and resolves spontaneously.

Ventricular fibrillation (VF) is a chaotic rhythm that results in death unless an effective ventricular beat is rapidly reestablished (see Fig. 462.10). Usually, cardiopulmonary resuscitation and DC defibrillation are necessary. If defibrillation is ineffective or VF recurs, amiodarone or lidocaine may be given intravenously, and defibrillation repeated (see Chapter 81). After recovery from VF, a search should be made for the underlying cause. EPS is indicated for patients who have survived VF unless a clearly reversible cause is identified. If WPW syndrome is noted, catheter ablation should be performed. For patients in whom no correctable abnormality can be found, an ICD is almost always indicated because of the high risk of sudden death.

462.5

Long QT Syndromes

Aarti S. Dalal, George F. Van Hare

Long QT syndromes are genetic abnormalities of ventricular repolarization, with an estimated incidence of about 1 per 10,000 births (Table 462.3 ; also outlines other genetic arrhythmia syndromes). They present as a long QT interval on the surface ECG and are associated with malignant ventricular arrhythmias (**torsades de pointes** and VF). They are a cause of syncope and sudden death and may be the cause of some cases of sudden infant death syndrome, drowning, and intrauterine fetal demise (Fig. 462.11). In perhaps 80% of cases, there is an identifiable genetic mutation. The old distinction between dominant and recessive forms of the disease (Romano-Ward syndrome vs Jervell-Lange-

Nielsen syndrome) is no longer made, because the latter recessive condition is known to result from the homozygous state. **Jervell-Lange-Nielsen syndrome** is associated with congenital sensorineural deafness. Asymptomatic but at-risk patients carrying the gene mutation may not all have a prolonged QT duration. QT interval prolongation may become apparent with exercise or during catecholamine infusions.

Table 462.3

Updated Summary of Heritable Arrhythmia Syndrome Susceptibility Genes

GENE	LOCUS	PROTEIN
LONG QT SYNDROME (LQTS)		
Major LQTS Genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, K_v 7.1)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, K_v 11.1)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit (Na_v 1.5)
Minor LQTS Genes (Listed Alphabetically)		
AKAP9	7q21-q22	Yotiao
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v 1.2)
CALM1	14q32.11	Calmodulin 1
CALM2	2p21	Calmodulin 2
CALM3	19q13.2-q13.3	Calmodulin 3
CAV3	3p25	Caveolin-3
KCNE1	21q22.1	Potassium channel beta subunit (MinK)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNJ5	11q24.3	Kir3.4 subunit of I_{KACH} channel
SCN4B	11q23.3	Sodium channel $beta_4$ subunit
SNTA1	20q11.2	Syntrophin-$alpha_1$
TRIADIN KNOCKOUT (TKO) SYNDROME		
TRDN	6q22.31	Cardiac triadin
ANDERSEN-TAWIL SYNDROME (ATS)		
KCNJ2 (ATS1)	17q23	I_{K1} potassium channel (Kir2.1)
TIMOTHY SYNDROME (TS)		
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v 1.2)
Cardiac-Only TS (COTS)		
CACNA1C	12p13.3	Voltage-gated L-type calcium channel (Ca_v 1.2)
SHORT QT SYNDROME (SQTS)		
KCNH2 (SQT1)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, K_v 11.1)
KCNQ1 (SQT2)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, K_v 7.1)
KCNJ2 (SQT3)	17q23	I_{K1} potassium channel (Kir2.1)
CACNA1C (SQT4)	12p13.3	Voltage-gated L-type calcium channel (Ca_v 1.2)
CACNB2 (SQT5)	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
CACN2D1 (SQT6)	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)		

RYR2 (CPVT1)	1q42.1-q43	Ryanodine receptor 2
CASQ2 (CPVT2)	1p13.3	Calsequestrin 2
KCNJ2 (CPVT3)	17q23	I_{K1} potassium channel (Kir2.1)
CALM1	14q32.11	Calmodulin 1
CALM3	19q13.2-q13.3	Calmodulin 3
TRDN	6q22.31	Cardiac triadin
BRUGADA SYNDROME (BrS)		
SCN5A (BrS1)	3p21-p24	Cardiac sodium channel alpha subunit (Na_v 1.5)
Minor Brs Genes (Listed Alphabetically)		
ABCC9	12p12.1	ATP-binding cassette, subfamily C member 9
CACNA1C	2p13.3	Voltage-gated L-type calcium channel (Ca_v 1.2)
CACNA2D1	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CACNB2	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
FGF12	3q28	Fibroblast growth factor 12
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1–like
KCND3	1p13.2	Voltage-gated potassium channel (I_{to}) subunit K_v 4.3
KCNE3	11q13.4	Potassium channel $beta_3$ subunit (MiRP2)
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
HEY2	6q	Hes-related family BHLH transcription factor with YRPW motif 2
PKP2	12p11	Plakophilin-2
RANGRF	17p13.1	RAN guanine nucleotide release factor 1
SCN1B	19q13	Sodium channel $beta_1$
SCN2B	11q23	Sodium channel $beta_2$
SCN3B	11q24.1	Sodium channel $beta_3$
SCN10A	3p22.2	Sodium voltage-gated channel $alpha_{10}$ subunit (Na_v 1.8)
SLMAP	3p14.3	Sarcolemma-associated protein
EARLY REPOLARIZATION SYNDROME (ERS)		
ABCC9	12p12.1	ATP-binding cassette, subfamily C member 9
CACNA1C	2p13.3	Voltage-gated L-type calcium channel (Ca_v 1.2)
CACNA2D1	7q21-q22	Voltage-gated L-type calcium channel 2 $delta_1$ subunit
CACNB2	10p12	Voltage-gated L-type calcium channel $beta_2$ subunit
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit (Na_v 1.5)
SCN10A	3p22.2	Sodium voltage-gated channel $alpha_{10}$ subunit (Na_v 1.8)
IDIOPATHIC VENTRICULAR FIBRILLATION (IVF)		
ANK2	4q25-q27	Ankyrin B
CALM1	14q32.11	Calmodulin 1
DPP6	7q36	Dipeptidyl-peptidase-6
KCNJ8	12p12.1	Inward rectifier K^+ channel Kir6.1
RYR2	1q42.1-q43	Ryanodine receptor 2
SCN3B	11q23	Sodium channel $beta_3$ subunit
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit (Na_v 1.5)
PROGRESSIVE CARDIAC CONDUCTION DISEASE/DEFECT (PCCD)		
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit (Na_v 1.5)
TRPM4	19q13.33	Transient receptor potential cation channel, subfamily M, member 4
SICK SINUS SYNDROME (SSS)		
ANK2	4q25-q27	Ankyrin B
HCN4	15q24-q25	Hyperpolarization-activated cyclic nucleotide–gated channel 4
MYH6	14q11.2	Myosin, heavy chain 6, cardiac muscle, alpha
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit (Na_v 1.5)

“ANKYRIN-B SYNDROME”		
ANK2	4q25-q27	Ankyrin B
FAMILIAL ATRIAL FIBRILLATION (FAF)		
ANK2	4q25-q27	Ankyrin B
GATA4	8p23.1-p22	GATA-binding protein 4
GATA5	20q13.33	GATA-binding protein 5
GJA5	1q21	Connexin 40
KCNA5	12p13	I_{Kur} potassium channel (K_v 1.5)
KCNE2	21q22.1	Potassium channel beta subunit (MiRP1)
KCNH2	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, K_v 11.1)
KCNJ2	17q23	I_{K1} potassium channel (Kir2.1)
KCNQ1	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, K_v 7.1)
NPPA	1p36	Atrial natriuretic peptide precursor A
NUP155	5p13	Nucleoporin 155 kD
SCN5A	3p21-p24	Cardiac sodium channel alpha subunit (Na_v 1.5)

From Tester DJ, Ackerman MJ: Genetics of cardiac arrhythmias. In *Braunwald's heart disease,* ed 11, Philadelphia, 2018, Elsevier (Table 33.1, p 605.)

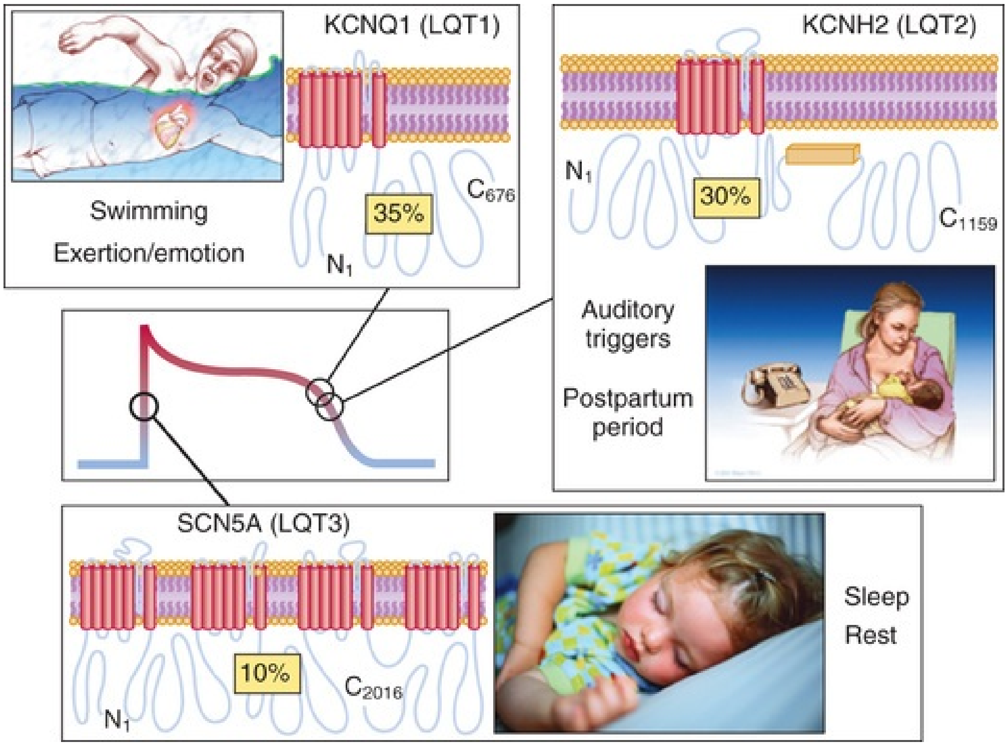

FIG. 462.11 Genotype-phenotype correlations in long QT syndrome (LQTS). About 75% of clinically strong LQTS is caused by mutations in 3 genes (35% *KCNQ1* , 30% *KCNH2* , and 10% *SCN5A*) encoding for ion channels that are critically responsible for the orchestration of the cardiac action potential. Observed genotype-phenotype correlations include swimming/exertion/emotion and LQT1, auditory triggers/postpartum period and LQT2, and sleep/rest and LQT3. (From Tester DJ, Ackerman MJ: Genetics of cardiac arrhythmias. In *Braunwald's heart disease,* ed 11, Philadelphia, 2018, Elsevier, Fig 33-3, p 607.)

Genetic studies have identified mutations in cardiac potassium and sodium channels (Table 462.3). Additional forms (up to 13 variants) of long QT syndrome (LQTS) have been described, but these are much more uncommon. Genotype may predict clinical manifestations; for example, LQTS type 1 (**LQT1**) events are usually induced by stress or exertion, whereas events in **LQT3** often occur at rest, especially during sleep (Fig. 462.11). **LQT2** events have an intermediate pattern, often occurring in the postpartum period or with auditory triggers. LQT3 has the highest probability for sudden death, followed by LQT2 and then LQT1. Drugs may prolong the QT interval directly but more often do so when drugs such as erythromycin or ketoconazole inhibit their metabolism (Table 462.4).

Table 462.4

Acquired Causes of QT Prolongation*

Drugs

Antibiotics—erythromycin, clarithromycin, azithromycin, telithromycin, trimethoprim/sulfamethoxazole, fluoroquinolones †
Antifungal agents † —fluconazole, itraconazole, ketoconazole
Antiprotozoal agents—pentamidine isethionate
Antihistamines—astemizole, terfenadine (Seldane; Seldane has been removed from the market for this reason)
Antidepressants—tricyclics such as imipramine (Tofranil), amitriptyline (Elavil), desipramine (Norpramin), and doxepin (Sinequan)
Antipsychotics—haloperidol, risperidone, phenothiazines such as thioridazine (Mellaril) and chlorpromazine (Thorazine), selective serotonin uptake inhibitors
Antiarrhythmic agents
Class 1A (sodium channel blockers)—quinidine, procainamide, disopyramide
Class III (prolong depolarization)—amiodarone (rare), bretylium, dofetilide, *N* -acetyl-procainamide, sotalol
Lipid-lowering agents—probucol
Antianginals—bepridil
Diuretics (through K^+ loss)—furosemide (Lasix), ethacrynic acid

(bumetanide [Bumex])
Opiates—methadone, oxycodone
Oral hypoglycemic agents—glibenclamide, glyburide
Organophosphate insecticides
Motility agents—cisapride, domperidone
Vasodilators—prenylamine
Other drugs—ondansetron, HIV protease inhibitors, Chinese herbs

Electrolyte Disturbances

Hypokalemia—diuretics, hyperventilation
Hypocalcemia
Hypomagnesemia

Underlying Medical Conditions

Bradycardia—complete atrioventricular block, severe bradycardia, sick sinus syndrome
Myocardial dysfunction—anthracycline cardiotoxicity, congestive heart failure, myocarditis, cardiac tumors
Endocrinopathy—hyperparathyroidism, hypothyroidism, pheochromocytoma
Neurologic—encephalitis, head trauma, stroke, subarachnoid hemorrhage
Nutritional—alcoholism, anorexia nervosa, starvation

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[*] A more exhaustive updated list of medications that can prolong the QTc interval is available at the University of Arizona Center for Education and Research of Therapeutics website (www.crediblemeds.org).

[†] Combinations of quinolones plus azoles increase the risk of prolonged QT intervals.

From Park MY: *Pediatric cardiology for practitioners*, ed 5, Philadelphia, 2008, Mosby Elsevier, Box 24-1, p 433.

The **clinical manifestation** of LQTS in children is most often a syncopal episode brought on by exercise, fright, or a sudden startle; some events occur during sleep (LQT3). Patients can initially be seen with seizures, presyncope, or palpitations; approximately 10% are initially in cardiac arrest. The diagnosis is based on electrocardiographic and clinical criteria. Not all patients with long QT intervals have LQTS, and patients with normal QT intervals on a resting ECG may have LQTS. A heart rate–corrected QT interval of >0.47 sec is highly indicative, whereas a QT interval of >0.44 sec is suggestive. Other features include notched T waves in 3 leads, T-wave alternans, a low heart rate for age, a history of syncope (especially with stress), and a familial history of either LQTS or unexplained sudden death. Exercise testing and 24 hr Holter monitoring are adjuncts to the diagnosis. Genotyping is available and can identify the mutation is approximately 80% of patients known to have LQTS by clinical criteria. Genotyping is not useful in ruling out the diagnosis in individuals with suspected disease, but when positive is very useful in identifying asymptomatic affected relatives of the index case.

Short QT syndromes manifest with atrial or ventricular fibrillation and are associated with syncope and sudden death (see Table 462.3). They are often caused by a gain-of-function mutation in cardiac potassium channels.

Treatment of LQTS includes the use of β-blocking agents at doses that blunt the heart rate response to exercise. Propranolol and nadolol may be more effective than atenolol and metoprolol. Some patients require a **pacemaker** because of drug-induced bradycardia. An **implantable cardiac-defibrillator** (ICD) is indicated in patients with continued syncope despite treatment with β-blockers, and those who have experienced cardiac arrest. Genotype-phenotype correlative studies suggest that β-blockers are not effective in patients with LQT3, and an ICD is usually indicated. Recent studies have shown that the use of **mexiletine** is helpful in patients with LQT3.

462.6

Sinus Node Dysfunction

Aarti S. Dalal, George F. Van Hare

Sinus arrest and sinoatrial block may cause a sudden pause in the heartbeat. **Sinus arrest** is presumably caused by failure of impulse formation within the sinus node. **Sinoatrial block** results from a block between the sinus pacemaker complex and the surrounding atrium. These arrhythmias are rare in childhood except in patients who have had extensive atrial surgery.

Sick sinus syndrome is the result of abnormalities in the sinus node or atrial conduction pathways, or both. This syndrome may occur in the absence of CHD and has been reported in siblings, but it is most commonly seen after surgical correction of congenital heart defects, especially the **Fontan procedure** and the **atrial switch** (Mustard or Senning) operation for transposition of the great arteries. Clinical manifestations depend on the heart rate. Most patients remain asymptomatic without treatment, but dizziness and syncope can occur during periods of marked sinus slowing with failure of junctional escape. Pacemaker therapy is indicated in patients who experience symptoms such as exercise intolerance or syncope.

Patients with sinus node dysfunction may also have episodes of SVT (**“tachy-brady” syndrome**) with symptoms of palpitations, exercise intolerance, or dizziness (Fig. 462.12). Treatment must be individualized. Drug therapy to control tachyarrhythmias (propranolol, sotalol, amiodarone) may suppress sinus and AV node function to such a degree that further symptomatic bradycardia may be produced. Therefore, insertion of a pacemaker in conjunction with drug therapy is usually necessary for such patients, even in the absence of symptoms ascribable to low heart rate.

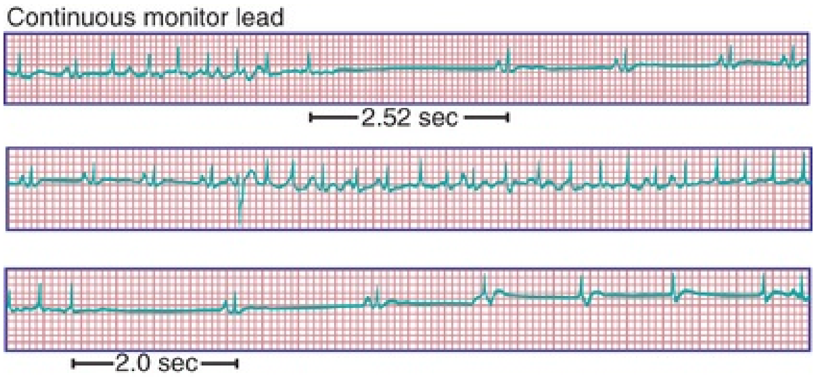

FIG. 462.12 **The “tachy-brady” syndrome with sinus node dysfunction. Note the bursts of supraventricular tachycardia, probably multifocal atrial in origin, followed by long periods of sinus arrest and by sinus bradycardia. Often, symptoms are caused by the long sinus pauses following termination of tachycardia, rather than by the tachycardia itself.**

462.7

Atrioventricular Block

Aarti S. Dalal, George F. Van Hare

Atrioventricular block may be divided into 3 forms (Fig. 462.13). In **first-degree AV block** , the PR interval is prolonged, but all the atrial impulses are conducted to the ventricle. In **second-degree AV block** , not every atrial impulse is conducted to the ventricle. In the variant of second-degree block known as the **Wenckebach type** (also called **Mobitz type I**), the PR interval increases progressively until a P wave is not conducted. In the cycle following the dropped beat, the PR interval normalizes. In **Mobitz type II** there is no progressive conduction delay or subsequent shortening of the PR interval after a blocked beat. This conduction defect is less common but has more potential to cause syncope and may be progressive. A related condition is **high-grade second-degree AV block** , in which 2 or more P waves in a row fail to conduct. This is even more dangerous. In **third-degree AV block (complete heart block)** , no impulses from the atria reach the ventricles. An independent escape rhythm is usually present but may not be reliable, leading to symptoms such as syncope.

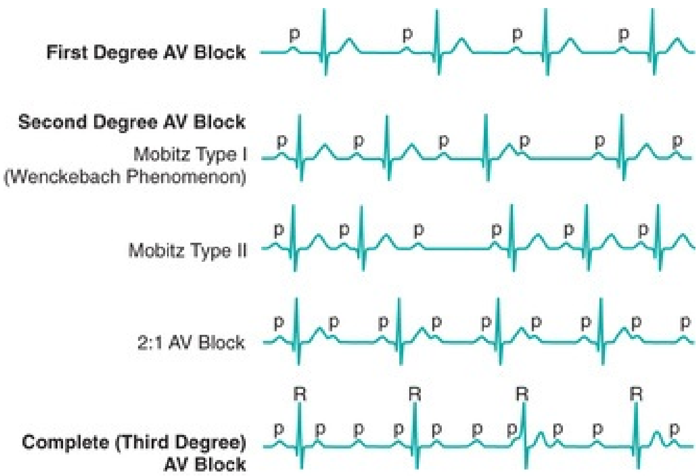

FIG. 462.13 Atrioventricular (AV) block. (From Park MY: *Pediatric cardiology for practitioners,* ed 5, Philadelphia, 2008, Mosby Elsevier, Fig 25-1, p 446.)

Congenital complete AV block in children is presumed to be caused by autoimmune injury of the fetal conduction system by maternally derived immunoglobulin G antibodies (anti-SSA/Ro, anti-SSB/La) in a mother with overt or, more often, asymptomatic systemic lupus erythematosus (SLE) or Sjögren syndrome. Autoimmune disease accounts for 60–70% of all cases of congenital complete AV block and 80% of cases in which the heart is structurally normal (Fig. 462.14). A mutation of the homeobox gene *NKX2-5* is described in which congenital AV block is seen most often in association with atrial septal defects. Complete AV block is also seen in patients with complex CHD and abnormal embryonic development of the conduction system. It has been associated with myocardial tumors and myocarditis. Complete AV block is a known complication of myocardial abscess secondary to endocarditis. It is also seen in genetic abnormalities, including LQTS and Kearns-Sayre syndrome. Postoperative AV block can be a complication of CHD repair; in particular repairs involving ventricular septal defect closure.

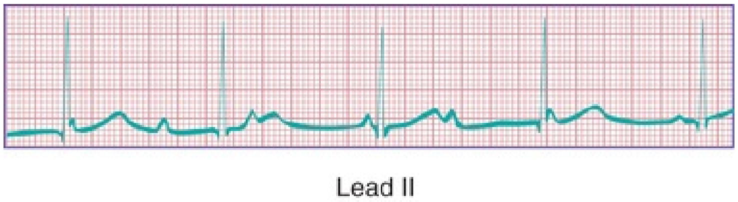

FIG. 462.14 Congenital complete atrioventricular (AV) block. The ventricular rate is regular at 53 beats/min. The atrial rate is somewhat variable, 65-95 beats/min, and completely dissociated from the ventricle. The QRS morphology is normal, which is common in congenital complete AV block.

The incidence of congenital complete AV block is 1 per 20,000-25,000 live births; a high fetal loss rate may cause an underestimation of its true incidence. In some infants of mothers with SLE, complete AV block is not present at birth but develops within the 1st 3-6 mo after birth. The arrhythmia is often diagnosed in the fetus (secondary to the dissociation between atrial and ventricular contractions seen on fetal echocardiography) and may produce hydrops fetalis. Maternal treatment with corticosteroids to halt progression or reverse AV block is controversial. Infants with associated CHD and heart failure have a high mortality rate.

In older children with otherwise normal hearts, complete AV block is often asymptomatic, although syncope and sudden death may occur. Infants and toddlers may have night terrors, tiredness with frequent naps, and irritability. The peripheral pulse is prominent because of the compensatory large ventricular stroke volume and peripheral vasodilation; systolic blood pressure is elevated. Jugular venous pulsations occur irregularly and may be large when the atrium contracts against a closed tricuspid valve (cannon wave). Exercise and atropine may produce an acceleration of 10-20 beats/min or more. Systolic murmurs are frequently audible along the left sternal border, and apical mid-diastolic murmurs are not unusual. The first heart sound is variable because of variable ventricular filing with AV dissociation. AV block results in enlargement of the heart based on increased diastolic ventricular filling.

The **diagnosis** is confirmed by electrocardiography; the P waves and QRS complexes have no constant relationship (see Fig. 462.14). The QRS duration may be prolonged, or it may be normal if the heartbeat is initiated high in the AV node or bundle of His.

The **prognosis** for congenital complete AV block is usually favorable; patients who have been observed to age 30-40 have lived normal, active lives. Some patients have episodes of exercise intolerance, dizziness, and syncope (Stokes-Adams attacks); syncope requires the implantation of a permanent cardiac pacemaker. Pacemaker implantation should be considered for patients who develop symptoms such as progressive cardiac dilation, prolonged pauses, or daytime average heart rates of ≤50 beats/min. In addition, prophylactic pacemaker implantation in adolescents is reasonable considering the low risk of the implant procedure and the difficulty in predicting who will develop sudden severe symptoms.

Cardiac pacing is recommended in neonates with low ventricular rates (≤55 beats/min), evidence of heart failure, wide complex rhythms, or CHD (with ventricular rates <70 beats/min). Isoproterenol, atropine, or epinephrine may be tried to increase the heart rate temporarily until pacemaker placement can be arranged. Transthoracic epicardial pacemaker implants have traditionally been used in infants; transvenous placement of pacemaker leads is available for young children. Postsurgical complete AV block can occur after any open heart procedure requiring suturing near the AV valves or crest of the ventricular septum. Postoperative heart block is initially managed with temporary pacing wires. The likelihood of a return to sinus rhythm after 10-14 days is low; a permanent pacemaker is recommended after that time.

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CHAPTER 463

Sudden Death

Aarti S. Dalal, George F. Van Hare

Sudden death other than sudden infant death syndrome is rare in children younger than 18 yr (see Chapter 402). Sudden death can be divided into having either a traumatic or a nontraumatic origin. *Traumatic* causes of sudden death are the most common in children; these include motor vehicle crashes, violent deaths, recreational deaths, and occupational deaths. *Nontraumatic* sudden deaths are often the result of specific **cardiac** causes. The incidence of sudden death varies from 0.8-6.2 per 100,000 per year in children and adolescents, in contrast to the higher incidence of **sudden cardiac death (SCD)** in adults of 1 per 1,000. Approximately 65% of sudden deaths are a result of heart-related problems in patients with either normal or congenitally (corrected, palliated, or unoperated) abnormal hearts. Competitive high school **sports** (basketball, football) are high-risk environmental factors. Common identifiable causes of death in competitive athletes includes hypertrophic cardiomyopathy, with or without obstruction to left ventricular outflow, other cardiomyopathies, and anomalous coronary arteries; most are sudden *unexplained* deaths (Fig. 463.1). Table 463.1 lists other potential causes. These can be classified as *structural* abnormalities, including aortic stenosis and coronary artery abnormalities; myocardial disease, such as myocarditis; conduction system disease, including long QT syndrome; and miscellaneous causes, including seizures, pulmonary hypertension, and commotio cordis. Symptoms may be absent before the event but, if present, include syncope, chest pain, dyspnea, and palpitations. Patients may have a family history of heart disease (dilated or hypertrophic cardiomyopathy, long QT interval, arrhythmogenic right ventricular dysplasia, Brugada or Marfan syndromes) or sudden unexplained death. Death often follows exertion or exercise.

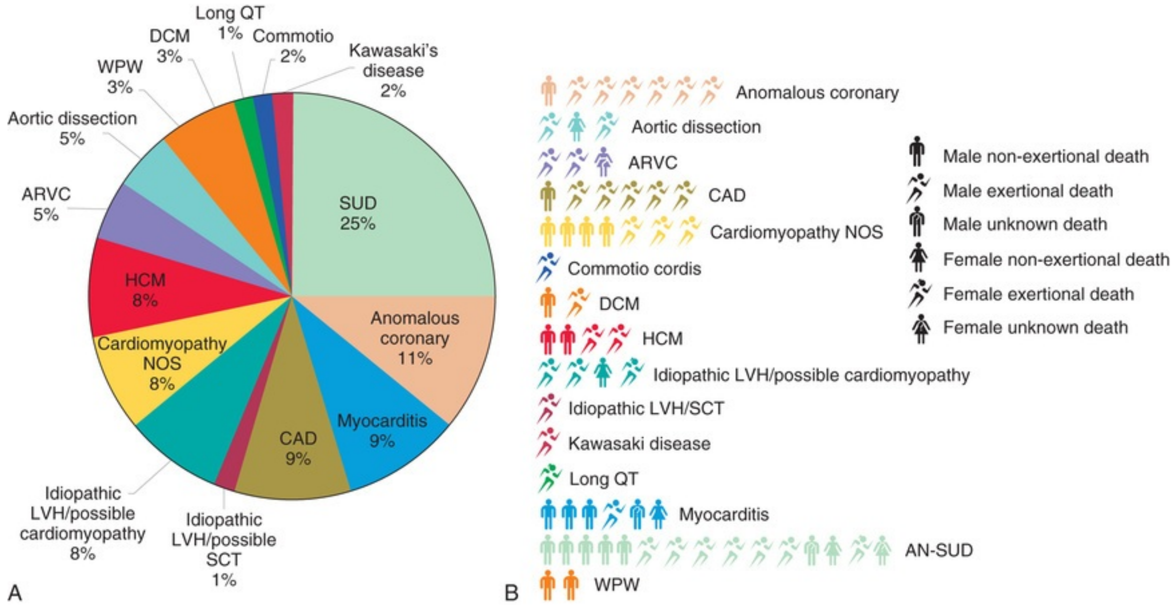

FIG. 463.1 **A,** Causes of sudden cardiac death in adolescent and young adult athletes. **B,** Cause and activity at time of death. One person figure equals 1 death; female figures follow male figures, unless no male deaths were present. AN-SUD, Autopsy-negative sudden unexplained death; ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; NOS, not otherwise specified; SCT, sickle cell trait; SUD, sudden unexplained death; WPW, Wolff-Parkinson-White syndrome. (From Harmon KG, Asif I, Maleszewski JJ, et al: Incidence, cause, and comparative frequency of sudden cardiac death in National Collegiate Athletic Association athletes, *Circulation* 132:10-19, 2015, Fig 2, p 16.)

Table 463.1

Potential Causes of Sudden Death in Infants, Children, and Adolescents

Sids and Sids "MIMICS"

SIDS
Long QT syndromes*
Inborn errors of metabolism
Child abuse
Myocarditis
Ductal-dependent CHD

Corrected or Unoperated Chd

Aortic stenosis
Tetralogy of Fallot
Transposition of great vessels (postoperative atrial switch)
Mitral valve prolapse
Hypoplastic left heart syndrome
Eisenmenger syndrome

Coronary Arterial Disease

Anomalous origin*
Anomalous tract (tunneled)
Kawasaki disease
Periarteritis
Arterial dissection
Marfan syndrome (rupture of aorta)
Myocardial infarction

Myocardial Disease

Myocarditis
Hypertrophic cardiomyopathy*
Dilated cardiomyopathy
Arrhythmogenic (right ventricular) cardiomyopathy
Lyme carditis
Takotsubo syndrome

Conduction System Abnormality/Arrhythmia

Long QT syndromes*
Brugada syndrome
Proarrhythmic drugs
Wolff-Parkinson-White syndrome
Complete AV block

Commotio cordis
Idiopathic ventricular fibrillation
Arrhythmogenic (right ventricular) cardiomyopathy
Catecholaminergic polymorphic ventricular tachycardia
Heart tumor

Miscellaneous

Seizures
Pulmonary hypertension
Pulmonary embolism
Heat stroke
Cocaine and other stimulant drugs or medications
Anorexia nervosa
Electrolyte disturbances

CHD, Congenital heart disease; SIDS, sudden infant death syndrome.

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* Common.

Mechanism of Sudden Death

There are 3 recognized mechanisms of sudden death: *arrhythmic*, *nonarrhythmic cardiac* (circulatory and vascular causes), and *noncardiac*. **Ventricular fibrillation (VF)** , while the most common final cause of sudden death in adults, is only the final cause in 10–20% of children with SCD. More often, **bradycardia** leads either to VF or asystole (see Chapter 462).

Congenital Heart Disease

Valvar aortic stenosis is the congenital defect most often associated with sudden death in children. Historically, approximately 5% of children with this disease die, although this has become quite rare in the modern era. A history of syncope, chest pain, and evidence of severe obstruction and left ventricular hypertrophy are risk factors (see Chapter 454.5).

Coronary artery anomalies are also frequently associated with sudden death in children and adolescents. The most common abnormality associated with sudden death is the origin of the left main coronary artery from the right sinus of Valsalva. The coronary artery therefore courses between the aorta and pulmonary artery and may also be intramural in course. Exercise results in a rise in pulmonary and aortic pressure, and this is thought to compress the left main coronary artery and results in ischemia due to compression or kinking. Anomalous origin of the right coronary artery from the left sinus of Valsalva is much more common, but only rarely is a cause of sudden death.

Cardiomyopathy

All 3 major types of cardiomyopathy (hypertrophic, dilated, and restrictive) are associated with sudden death in the pediatric population; sudden death may be the initial manifestation of the cardiomyopathy (see Chapter 466).

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in the athletic adolescent. The annual risk of sudden death in young patients with HCM is 2% per year. Risk factors for sudden death include a family history of sudden death, symptoms, ventricular arrhythmias, and presentation at an early age. Many patients with HCM have obstruction to the left ventricular outflow tract (LVOT). The mechanism of sudden death is arrhythmic and may be secondary to development of dynamic obstruction with exercise and resultant loss of cardiac output, or may be related to cardiac ischemia. Thus, patients without LVOT obstruction are also at risk of sudden death. The **dilated cardiomyopathies** are also associated with SCD in children, although the risk is clearly lower than in adults.

Arrhythmogenic cardiomyopathy (also referred to as **arrhythmogenic right ventricular cardiomyopathy**) is a specific form of cardiomyopathy associated with exercise-induced ventricular arrhythmias and sudden death. It mainly affects the right ventricle, but the left can be involved as well. The diagnosis can be difficult; MRI, electrophysiology study, or endomyocardial biopsy is used with limited reliability. Pathology includes transmural fatty replacement of right ventricular myocardium, with patchy areas of fibrosis.

Myocarditis has often been found on pathology of patients with sudden death of unknown etiology. Symptoms before sudden death may be absent or may include overt heart failure or subtle findings such as a high heart rate. Pediatric patients may have complete heart block or ventricular arrhythmias with this disease.

Cardiac Arrhythmia

A primary conduction system abnormality may result in sudden death. Causes include Wolff-Parkinson-White (WPW) syndrome, long QT syndrome, and Brugada syndrome. Besides causing supraventricular tachycardia, **WPW syndrome** can result in atrial fibrillation with rapid conduction across the accessory pathway, leading to VF and sudden death (Fig. 463.2). This is unusual in pediatric patients but has an increasing incidence in adolescence. In adults, there is an incidence of sudden death in asymptomatic patients of 1 per 1,000 patient-years, but this rate may well be higher in children, who have not yet survived to adulthood. As digoxin and verapamil can augment conduction down accessory pathways, these drugs are contraindicated in WPW syndrome.

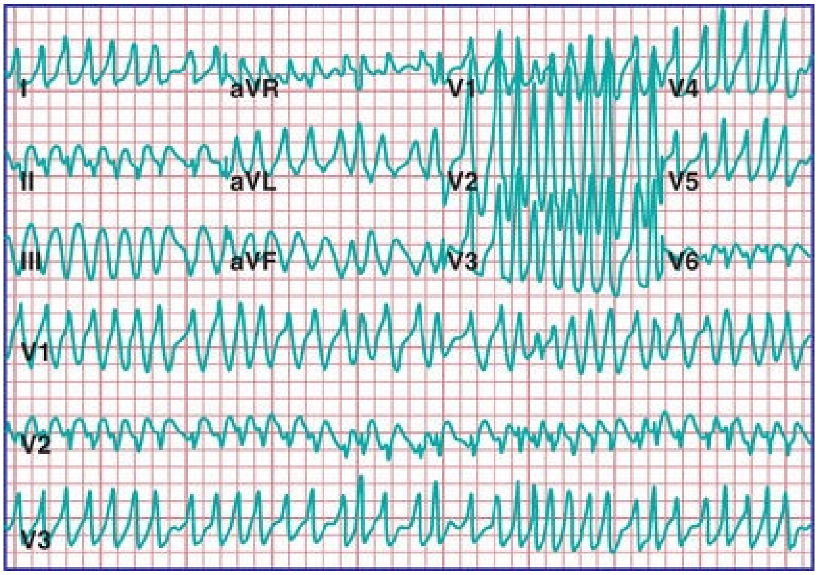

FIG. 463.2 **Atrial fibrillation in a patient with Wolff-Parkinson-White syndrome and rapid conduction to the ventricle. Note the wide QRS complexes, a result of full preexcitation, and the irregularly irregular ventricular response, caused by the atrial fibrillation.**

Long QT syndrome (LQTS; see Chapter 462), a group of channelopathies that affect ventricular repolarization, is also associated with sudden death (Fig. 463.3). The mechanism of sudden death is polymorphic ventricular tachycardia (**torsades de pointes**) (Fig. 463.4). An initial presentation of SCD is found in 9% of patients. Thus, treatment of asymptomatic patients with a long QT interval on electrocardiogram (ECG) and positive family history is advised.

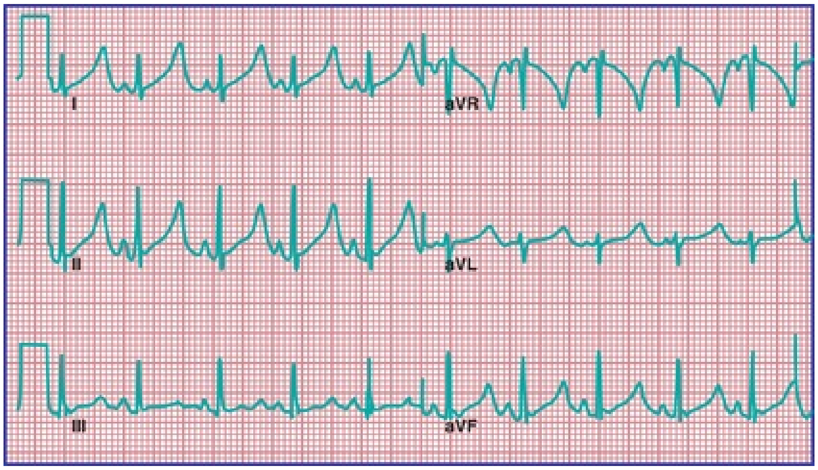

FIG. 463.3 Long QT syndrome in a neonate. QTc is markedly prolonged. T waves are also peaked and abnormal in appearance.

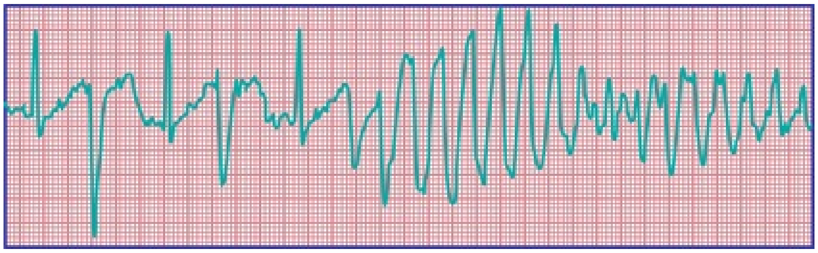

FIG. 463.4 Episode of torsades de pointes in a patient with long QT syndrome.

Acquired long QT interval may be seen in patients with marked electrolyte abnormalities, central nervous system injury, or starvation (including bulimia and anorexia nervosa). Medications can also result in prolongation of the QT interval (see Table 462.4). These patients are also at risk of malignant ventricular arrhythmias, and correction of the underlying problem may be necessary to reduce the risk of sudden death.

Brugada syndrome , an autosomal dominant disorder caused by a mutation in the *SCN5A* gene in approximately 30% of patients, is associated with SCD, often occurring with fever, drugs, nighttime electrolyte disorders, or after a large meal (Fig. 463.5). Typical ECG findings include *coved* ST segment elevations in leads V_1 -V_3 ; death results from either VF or ventricular tachycardia.

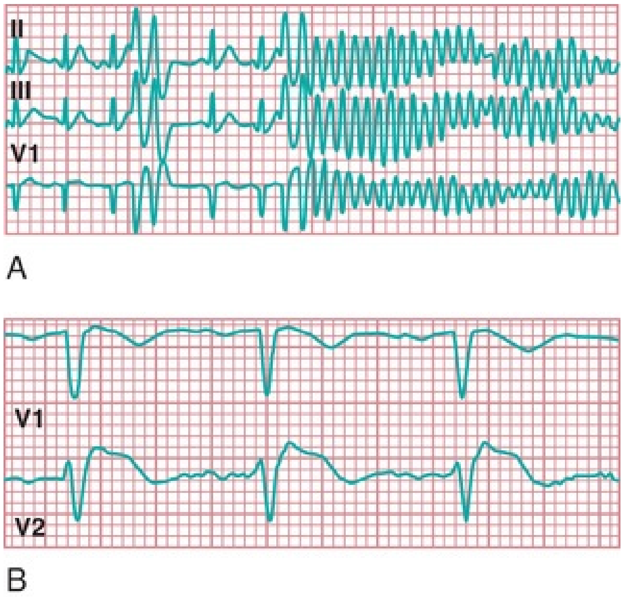

FIG. 463.5 **Brugada syndrome. A, Frequent ventricular ectopy and sustained polymorphic ventricular tachycardia. B, Persistent coved-type ST segment elevation in lead V_1 and V_2 characteristic of Brugada type I. (From Talib S, van de Poll SE: Brugada syndrome diagnosed after Ramadan, *Lancet* 382:100, 2013.)**

Miscellaneous Causes

Commotio cordis is an almost universally fatal condition that follows blunt nonpenetrating trauma to the chest (e.g., from a baseball or hockey puck). Occasionally, innocent-appearing chest blows incurred at home or at a playground may be fatal. Patients experience immediate VF in the absence of identifiable cardiac trauma (contusion, hematoma, lacerated coronary artery). This risk is highest in children before adolescence. Historically, death results from VF that is unresponsive to resuscitative efforts in 85–90% of children. Immediate direct current (DC) defibrillation may be effective, if available, particularly if employed immediately; however, it is reported to be successful in only approximately 25% of cases.

Evaluation and Therapy for Resuscitated Patients

It is important to focus therapy on potentially reversible causes of sudden death. These include correction of major hemodynamic defects, pacing therapy for a patient with bradycardia, or supportive therapy for myocarditis. Unfortunately, reversible causes are not always found in young cardiac arrest survivors. Adding to this dilemma is the limited ability to predict antiarrhythmic drug response or risk of recurrence. Thus, the **implantable-cardioverter defibrillator** (ICD) is the therapy of choice for survivors of arrhythmic sudden death.

Medication for Attention-Deficit/Hyperactivity Disorder

Concern has been raised that stimulant medications prescribed for children with attention-deficit/hyperactivity disorder might increase the risk of sudden death (see Chapter 49). The concern arises from a limited number of reports to the U.S. Food and Drug Administration (FDA) of sudden death of unknown etiology in individuals taking stimulant medications, mostly adults. In a few cases, left ventricular hypertrophy caused by hypertension, coarctation of the aorta, or HCM has been identified at postmortem examination. No prospective studies support the notion that these medications increase the risk, with little or no evidence that ECG screening will reliably identify a subgroup at risk. Some suggest ECG screening of children before starting these medications, but there is no consensus that such an approach is effective. The 2008 American Academy of Pediatrics (AAP) recommendations do not support ECG screening before the initiation of stimulant medication in the absence of a positive cardiac history.

Prevention of Sudden Death

The probability of survival to hospital discharge for a young patient who experiences an out-of-hospital cardiac arrest is <20%. The presence of immediate **automatic external defibrillators** (AEDs), when combined with standard cardiopulmonary resuscitation (CPR) at the site of exercise (gym, track, basketball, or football arena), may improve survival substantially. Thus, identifying patients at risk is extremely important.

Many of the more common causes of sudden death in children and adolescents can be identified from the patient's history (prodromal symptoms), the family history, and physical examination. AAP has a downloadable “Preparticipation Physical Evaluation” form that is useful for this purpose (http://www.aap.org). Of paramount importance is the careful evaluation of any child who experiences **syncope** in association with **exercise** , since this may be the last opportunity to diagnose a life-threatening condition in such a patient.

Patient avoidance of high-risk behavior (cocaine use, anorexia nervosa) and knowledge of drug side effects or drug interactions and contraindications is critical. Chest-protecting equipment has not been shown to prevent commotio cordis. Prompt bystander CPR and rapid defibrillation by an AED has the best chance of leading to survival. Family survivors of victims of sudden death should be evaluated for genetic causes (e.g., LQTS, HCM).

The use of a preparticipation ECG for the detection of those athletes at risk for sudden death has long been controversial. Because many athletes either have no preevent symptoms or are unwilling to admit to symptoms for concern of not being able to play, some have proposed that the ECG may identify a small but at-risk group with HCM or the prolonged QT, Brugada, or WPW syndromes. These ECGs would fail to identify patients with phenotype-negative LQTS or catecholaminergic polymorphic ventricular tachycardia., as well as coronary artery anomalies. In addition, many false positives may be identified, requiring further evaluation to exclude worrisome diagnoses. ECG testing is mandatory in several European countries but not in the United States, although many athletic groups with varsity-level or professional membership (e.g., collegiate or professional sports organizations) are requiring such testing is part of the medical evaluation. If the ECG is positive, **echocardiography** is performed. Cost-effectiveness studies suggest that the cost for implementation of a national program in the United States would be prohibitive because of the low incidence of sudden death in the pediatric population, the high rate of false-positive ECGs, and the difficulty in definitively excluding cardiac disease in patients with borderline ECG findings. Although studies of regional or national screening programs have suggested some benefit (e.g., the Veneto region of Italy), others have failed to demonstrate any effect of screening on the background incidence of sudden death in young individuals.

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SECTION 5

Acquired Heart Disease

OUTLINE

Chapter 464 Infective Endocarditis
Chapter 465 Rheumatic Heart Disease

CHAPTER 464

Infective Endocarditis

Thomas S. Murray, Robert S. Baltimore

Infective endocarditis includes acute and subacute *bacterial* endocarditis, as well as *nonbacterial* endocarditis, caused by viruses, fungi, and other microbiologic agents. It is a significant cause of morbidity and mortality in children and adolescents despite advances in the management and prophylaxis of the disease with antimicrobial agents. The inability to eradicate infective endocarditis by prevention or early treatment stems from several factors. The disease represents a complex interplay between a pathogen and host factors such as endothelial disruption and immune function that is still not completely understood; the nature of the infecting organism has changed over time; and diagnosis may be difficult during early stages and thus is often delayed until a more serious infection has developed. Also, special risk groups have emerged, including intravenous drug users; survivors of cardiac surgery, especially those with mechanical prosthesis; patients taking immunosuppressant medications; and patients who require chronic intravascular catheters. Some patients have endocarditis on a native valve previously thought to be healthy but found to have mild structural abnormalities on surgical inspection.

Etiology

Viridans-type streptococci (α-hemolytic streptococci groups such as *Streptococcus mitis, S. anginosus, S. mutans, S. salivarius,* and *S. bovis*) and *Staphylococcus aureus* remain the leading causative agents for endocarditis in pediatric patients. Other organisms cause endocarditis less frequently, and in approximately 6% of cases, blood cultures are negative for any organisms (Table 464.1). No relationship exists between the infecting organism and the type of congenital defect, duration of illness, or age of the child. Staphylococcal endocarditis is more common in patients with no underlying heart disease. Viridans group streptococcal infection is more common after dental procedures; group D enterococci are seen more often after lower bowel or genitourinary manipulation.

Table 464.1

Bacterial Agents in Pediatric Infective Endocarditis

Common: Native Valve or Other Cardiac Lesions

Viridans group streptococci (*Streptococcus mutans, S. sanguinis, S. mitis*)
Staphylococcus aureus
Group D streptococcus (enterococcus) (*Streptococcus bovis, S. faecalis*)

Uncommon: Native Valve or Other Cardiac Lesions

Streptococcus pneumoniae
Haemophilus influenzae
Coagulase-negative staphylococci
Abiotrophia defectiva (nutritionally variant streptococcus)
Coxiella burnetii (Q fever)*
Neisseria gonorrhoeae
Brucella *
Chlamydia psittaci *
Chlamydia trachomatis *
Chlamydia pneumoniae *
Legionella *
Bartonella *
Tropheryma whipplei * (Whipple disease)
HACEK group [†]
Streptobacillus moniliformis *
Pasteurella multocida *
Campylobacter fetus
Culture negative (6% of cases)

Prosthetic Valve

Staphylococcus epidermidis
Staphylococcus aureus
Viridans group streptococcus
Pseudomonas aeruginosa
Serratia marcescens
Diphtheroids
Legionella spp.*
HACEK group †
Fungi ‡

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* These fastidious bacteria plus some fungi may produce culture-negative endocarditis. Detection may require special media, incubation for >7 days, polymerase chain reaction on blood or valve for 16SrRNA (bacteria) or 18SrRNA (fungi), or serologic tests.

† The HACEK group includes *Haemophilus* spp. *(H. paraphrophilus, H. parainfluenzae, H. aphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella* spp.

‡ *Candida* spp., *Aspergillus* spp., *Pseudallescheria boydii, Histoplasma capsulatum.*

Pseudomonas aeruginosa or *Serratia marcescens* is seen more frequently in intravenous drug users; and fungal organisms are encountered after open heart surgery. Coagulase-negative staphylococci are common in the presence of an indwelling central venous catheter.

Epidemiology

Infective endocarditis is often a complication of congenital or rheumatic heart disease but can also occur in children without any abnormal valves or cardiac malformations. In developed countries, **congenital heart disease** (CHD) is the overwhelming predisposing factor. Endocarditis is rare in infancy; in this age-group it usually follows open heart surgery or is associated with a central venous line.

Patients with congenital heart lesions where there is turbulent blood flow because of a hole or stenotic orifice, especially if there is a high-pressure gradient across the defect, are most susceptible to endocarditis. This turbulent flow traumatizes the vascular endothelium, creating a substrate for deposition of fibrin and platelets, leading to the formation of a **nonbacterial thrombotic embolus (NBTE)** that is thought to be the initiating lesion for infective endocarditis. Biofilm forms on the surface of implanted mechanical devices such as valves, catheters, or pacemaker wires, which also serve as the adhesive substrate for infection. The development of transient bacteremia then colonizes this NBTE or biofilm, leading to proliferation of bacteria within the lesion. Bacterial surface proteins, such as the FimA antigen in viridans streptococci, act as adhesion factors to the NBTE or biofilm, after which bacteria can rapidly proliferate within the vegetation. Given the heavy colonization of mucosal surfaces (the oropharynx, or gastrointestinal, vaginal, or urinary tracts) by potentially pathogenic bacteria, these surfaces are thought to be the origin of this transient bacteremia. There is controversy over the extent to which daily activities (e.g., brushing or flossing the teeth) vs invasive procedures (e.g., dental cleaning or surgery) contribute to this bacteremia. Transient bacteremia is reported to occur in 20–68% of patients after tooth brushing and flossing, and even in 7–51% of patients after chewing food. The magnitude of this bacteremia is also similar to that resulting from dental procedures. Maintenance of good oral hygiene may be a more important factor in decreasing the frequency and magnitude of bacteremia.

Children at **highest risk** of adverse outcome after infective endocarditis include those with prosthetic cardiac valves or other prosthetic material used for cardiac valve repair, unrepaired cyanotic CHD (including those palliated with shunts and conduits), completely repaired defects with prosthetic material or device during the 1st 6 mo after repair, repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or device, valve stenosis or insufficiency occurring after heart transplantation, permanent valve disease from **rheumatic fever** (mitral stenosis, aortic regurgitation), and previous infective endocarditis. Patients with high-velocity blood flow lesions such as ventricular septal defects and aortic stenosis are also at high risk. In older patients, congenital bicuspid aortic valves and mitral valve prolapse with regurgitation pose additional risks for endocarditis. Surgical correction of CHD may reduce but does not eliminate the risk of endocarditis, except for the repair of a simple atrial septal defect or patent ductus arteriosus without prosthetic material.

In approximately 30% of patients with infective endocarditis, a predisposing factor is presumably recognized. Although a preceding dental procedure may be identified in 10–20% of patients, the time of the procedure may range from 1-6 mo before the onset of symptoms; thus the continued controversy over the absolute risk of infective endocarditis after dental procedures. Primary bacteremia with *S. aureus* is thought to be another risk for endocarditis. The occurrence of endocarditis directly after most routine heart surgery is relatively low, but it can be an antecedent event, especially if prosthetic material is used. In the small group of patients with culture-negative endocarditis, epidemiologic or exposure factors may contribute to the diagnosis (Table 464.2).

Table 464.2

Epidemiologic Clues in Etiologic Diagnosis of Culture-Negative Endocarditis

EPIDEMIOLOGIC FEATURE	COMMON MICROORGANISM
Injection drug use (IDU)	*Staphylococcus aureus* , including community-acquired oxacillin-resistant strains Coagulase-negative staphylococci β-Hemolytic streptococci Fungi Aerobic gram-negative bacilli, including *Pseudomonas aeruginosa* Polymicrobial
Indwelling cardiovascular medical devices	*S. aureus* Coagulase-negative staphylococci Fungi Aerobic gram-negative bacilli *Corynebacterium* spp.
Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion	*Enterococcus* spp. Group B streptococci (*S. agalactiae*) *Listeria monocytogenes* Aerobic gram-negative bacilli *Neisseria gonorrhoeae*
Chronic skin disorders, including recurrent infections	*S. aureus* β-Hemolytic streptococci *S. aureus* β-Hemolytic streptococci
Poor dental health, dental procedures	Viridans group streptococci Nutritionally variant streptococci *Abiotrophia defectiva* *Granulicatella* spp. *Gemella* spp. HACEK organisms
Alcoholism, cirrhosis	*Bartonella* spp. *Aeromonas* spp. *Listeria* spp.

	Streptococcus pneumoniae β-Hemolytic streptococci
Burns	*S. aureus* Aerobic gram-negative bacilli, including *P. aeruginosa* Fungi
Diabetes mellitus	*S. aureus* β-Hemolytic streptococci *S. pneumoniae*
Early (≤1 yr) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* Aerobic gram-negative bacilli Fungi *Corynebacterium* spp. *Legionella* spp.
Late (>1 yr) prosthetic valve placement	Coagulase-negative staphylococci *S. aureus* Viridans group streptococci *Enterococcus* spp. Fungi *Corynebacterium* spp.
Dog or cat exposure	*Bartonella* spp. *Pasteurella* spp. *Capnocytophaga* spp.
Contact with contaminated milk or infected farm animals	*Brucella* spp. *Coxiella burnetii* *Erysipelothrix* spp.
Homeless, body lice	*Bartonella* spp.
HIV/AIDS	*Salmonella* spp. *S. pneumoniae* *S. aureus*
Pneumonia, meningitis	*S. pneumoniae*
Solid-organ transplantation	*S. aureus* *Aspergillus fumigatus* *Enterococcus* spp. *Candida* spp.
Gastrointestinal lesions	*Streptococcus gallolyticus (bovis*) *Enterococcus* spp. *Clostridium septicum*

HACEK, *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* spp; HIV/AIDS, human immunodeficiency virus infection and acquired immunodeficiency syndrome.

From Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. *Circulation* 132:1435-1486, 2015.

Clinical Manifestations

Table 464.3 outlines the manifestations of infective endocarditis. Early manifestations are usually mild, especially when viridans group streptococci are the infecting organisms. Prolonged fever without other manifestations (except occasionally weight loss) that persists for as long as several months may be the only symptom. Alternatively, with pathogenic organisms such as *S. aureus* , the onset may be acute and severe, with high intermittent fever and prostration. Usually the onset and course vary between these 2 extremes. The symptoms are often nonspecific and consist of low-grade fever with afternoon elevations, fatigue, myalgia, arthralgia, headache, and at times chills, nausea, and vomiting. **New or changing heart murmurs** are common, particularly with associated heart failure. Splenomegaly and petechiae are seen in <50% of patients. Serious neurologic complications such as embolic strokes, cerebral abscesses, mycotic aneurysms, and hemorrhage are most often associated with staphylococcal disease and may be late manifestations. Meningismus, increased intracranial pressure, altered sensorium, and focal neurologic signs are manifestations of these complications. Meningitis may be seen together with pneumococcal endocarditis. Myocardial abscesses may occur with staphylococcal disease and may damage the cardiac conducting system, causing heart block, or may rupture into the pericardium and produce purulent pericarditis. Pulmonary (with right-sided endocarditis) and systemic emboli (with left-sided lesions) are infrequent, except with fungal disease.

Table 464.3

Manifestations of Infective Endocarditis

History

Prior congenital or rheumatic heart disease
Preceding dental, urinary tract, or intestinal procedure
Intravenous drug use
Central venous catheter
Prosthetic heart valve

Symptoms

Fever
Chills
Chest and abdominal pain
Arthralgia, myalgia

Dyspnea
Malaise, weakness
Night sweats
Weight loss
CNS manifestations (stroke, seizures, headache)

Signs

Elevated temperature
Tachycardia
Embolic phenomena (Roth spots, petechiae, splinter nail bed hemorrhages, Osler nodes, CNS or ocular lesions)
Janeway lesions
New or changing murmur
Splenomegaly
Arthritis
Heart failure
Arrhythmias
Metastatic infection (arthritis, meningitis, mycotic arterial aneurysm, pericarditis, abscesses, septic pulmonary emboli)
Clubbing

Laboratory Studies

Positive blood culture
Elevated erythrocyte sedimentation rate; may be low with heart or renal failure
Elevated C-reactive protein
Anemia
Leukocytosis
Immune complexes
Hypergammaglobulinemia
Hypocomplementemia
Cryoglobulinemia
Rheumatoid factor
Hematuria

Renal failure: azotemia, high creatinine (glomerulonephritis)
Chest radiograph: bilateral infiltrates, nodules, pleural effusions
Echocardiographic evidence of valve vegetations, prosthetic valve dysfunction or leak, myocardial abscess, or new-onset valve insufficiency

CNS, Central nervous system.

Many of the classic **skin findings** develop late in the disease; they are seldom seen in appropriately treated patients. Such manifestations include **Osler nodes** (tender, pea-size intradermal nodules in the pads of the fingers and toes), **Janeway lesions** (painless, small, erythematous or hemorrhagic lesions on the palms and soles), and **splinter hemorrhages** (linear lesions beneath the nails). These lesions may represent vasculitis produced by circulating antigen-antibody complexes. Retinal lesions are seen in 10–20%.

In the newborn infant the major risk factor for infective endocarditis is the presence of a **central intravenous line** . Thus, prematurity is a risk as is other severe congenital abnormalities. CHD is less likely to be the underlying condition than it is for older children. The clinical conditions are variable and may be indistinguishable from sepsis or congestive heart failure. Identification of infective endocarditis is most often based on a high index of suspicion during evaluation of an infection in a child with an underlying risk factor.

Diagnosis

The critical information for appropriate treatment of infective endocarditis is obtained from **blood cultures** . All other laboratory data are secondary in importance (see Table 464.3). Blood specimens for culture should be obtained as promptly as possible, even if the child feels well and has no other physical findings. While increased blood volume can increase the sensitivity of the blood culture, smaller volumes are reasonable in neonates and small children. When small volumes of blood are present, a single aerobic blood culture bottle should be inoculated. Ideally, for patients weighing 2-12.7 kg, the volume of the 1st blood culture is 4 mL (repeat culture is 2 mL); for patients 12.8-36.3 kg it is 10 mL for initial and repeat, and for patients >36.3 kg, 20-30 mL for both. Three to 5 separate blood collections should be obtained after careful preparation of the phlebotomy site. Contamination presents a special problem because bacteria found on the skin may cause infective endocarditis. The timing of collections is not important because bacteremia can be expected to be relatively constant. In 90% of cases of endocarditis, the causative agent is recovered from the 1st 2 blood cultures. Bacteremia is low grade in 80% (<100 colony-forming units/mL of blood). The laboratory should be notified that endocarditis is suspected so that, if necessary, the blood can be cultured on enriched media for longer than usual (>5 days) to detect nutritionally deficient and fastidious bacteria or fungi.

Although bacteremia may occur in the absence of endocarditis, bacteremia secondary to *Streptococcus mutans* , *S. bovis I* , *S. mitis* , *S. sanguinis,* and *Staphylococcus aureus* (in the absence of focal musculoskeletal infection) is highly concerning for endocarditis. Antimicrobial pretreatment of the patient reduces the yield of blood cultures by 50–60%. Other specimens that may be cultured include scrapings from cutaneous lesions, urine, synovial fluid, abscesses, and in the presence of manifestations of meningitis, cerebrospinal fluid. Serologic diagnosis or polymerase chain reaction of resected valve tissues is necessary in patients with unusual or fastidious microorganisms, when there is suspicion of culture-negative endocarditis or if the patient has received prior antibiotics (Table 464.4 and Fig. 464.1). Suspicion should be high when evaluating infection in a child with an underlying contributing factor. The combination of transthoracic and transesophageal echocardiography enhances the ability to diagnose endocarditis. Two-dimensional echocardiography can identify the size, shape, location, and mobility of the lesion; when combined with Doppler studies, the presence of valve dysfunction (regurgitation, obstruction) can be determined and its effect on left ventricular performance quantified (Fig. 464.2). Echocardiography may also be helpful in predicting embolic complications, given that lesions >1 cm and fungating masses are at greatest risk for embolization. The absence of vegetations does not exclude endocarditis, and vegetations are often not visualized in the early phases of the disease or in patients with complex congenital heart lesions. Electrocardiography should be part of the evaluation and can demonstrate new rhythm disorders such as **ventricular ectopy** and conduction disorders such as **complete heart block** . The presence of either of these findings, particularly heart block, may signal a serious or even life-threatening complication of endocarditis.

Table 464.4

Diagnostic Approach to Uncommon Pathogens Causing Endocarditis

PATHOGEN	DIAGNOSTIC PROCEDURE
Brucella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Coxiella burnetii	Serology (IgG phase I >1 in 800); tissue culture, immunohistology, and PCR of surgical material
Bartonella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Chlamydia spp.	Serology; culture, immunohistology, and PCR of surgical material
Mycoplasma spp.	Serology; culture, immunohistology, and PCR of surgical material
Legionella spp.	Blood cultures; serology; culture, immunohistology, and PCR of surgical material
Tropheryma whipplei	Histology and PCR of surgical material

IgG, Immunoglobulin G; PCR, polymerase chain reaction.

From Moreillon P, Que YA: Infective endocarditis, *Lancet* 363:139–148, 2004.

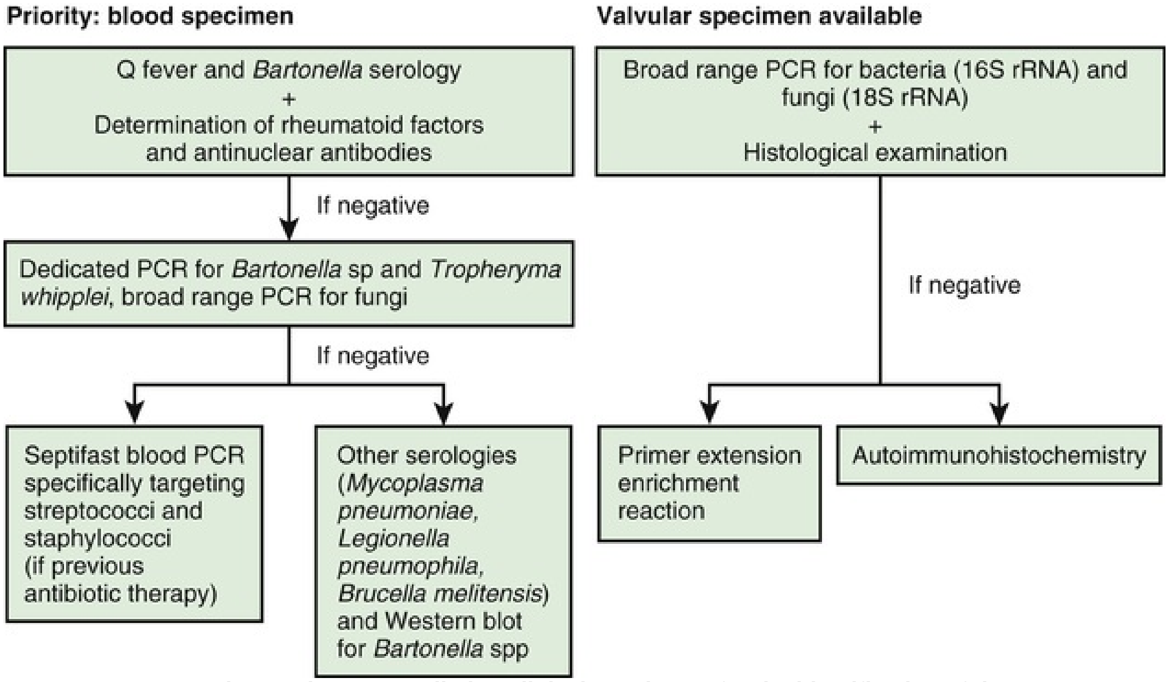
Priority: blood specimen
Valvular specimen available
Q fever and *Bartonella* serology + Determination of rheumatoid factors and antinuclear antibodies
If negative
Dedicated PCR for *Bartonella* sp and *Tropheryma whipplei*, broad range PCR for fungi
If negative
Septifast blood PCR specifically targeting streptococci and staphylococci (if previous antibiotic therapy)
Other serologies (*Mycoplasma pneumoniae, Legionella pneumophila, Brucella melitensis*) and Western blot for *Bartonella* spp
Broad range PCR for bacteria (16S rRNA) and fungi (18S rRNA) + Histological examination
If negative
Primer extension enrichment reaction
Autoimmunohistochemistry

FIG. 464.1 **Diagnostic tests applied to clinical specimens for the identification of the causative agents of blood culture–negative endocarditis. Septifast, LightCycler SeptiFast (Roche). Serum should be considered a priority specimen, with Q fever and *Bartonella* serologic analysis routinely done. We also suggest that detection of antinuclear antibodies and rheumatoid factor should be routinely done for diagnosis of noninfective endocarditis. (From Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives, *Lancet* 379:965–975, 2012, Fig 2, p 969.)**

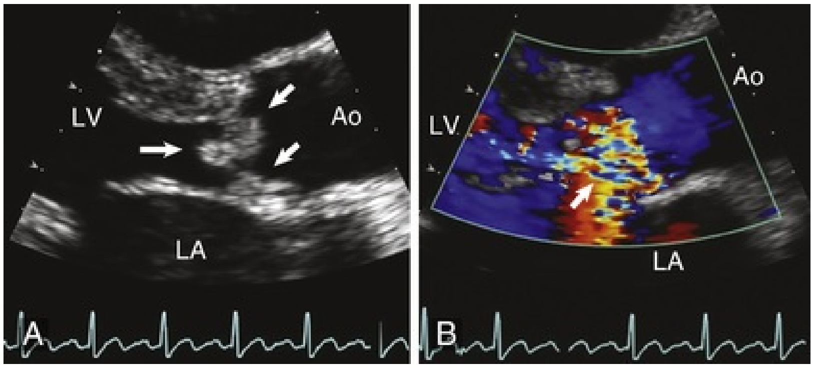

FIG. 464.2 Infective endocarditis of the native aortic valve. A, Transthoracic echocardiography shows vegetations *(small arrows)* attached to the left ventricular aspects of the valve cusps and prolapsing into the left ventricular outflow tract *(large arrow)* during diastole. B, Severe aortic regurgitation *(arrow)* is shown by color Doppler. Ao, Ascending aorta; LA, left atrium; LV, left ventricle. (From Baddour LM, Freeman WK, Suri RM, Wilson WR: Cardiovascular infections. In *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2018, Elsevier, Fig 73-1, p 1490.)

The **Duke criteria** help in the diagnosis of endocarditis (Table 464.5). Two major criteria, 1 major and 3 minor, or 5 minor criteria suggest definite endocarditis. Additional minor criteria to those listed include newly diagnosed clubbing, splenomegaly, splinter hemorrhages, or petechiae; high erythrocyte sedimentation rate or C-reactive protein level; presence of central nonfeeding or peripheral lines; and microscopic hematuria.

Table 464.5

Definition of Infective Endocarditis (IE): Modified Duke Criteria

Definite Infective Endocarditis

Pathologic Criteria

- Microorganisms demonstrated by results of cultures or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; *or*
- Pathologic lesions; vegetation, or intracardiac abscess confirmed by results of histologic examination showing active endocarditis

Clinical Criteria

- 2 major criteria, *or*
- 1 major criterion and 3 minor criteria, *or*
- 5 minor criteria

Possible Infective Endocarditis

- 1 major criterion and 1 minor criterion, *or*
- 3 minor criteria

Rejected Diagnosis of Infective Endocarditis

- Firm alternate diagnosis explaining evidence of suspected IE, *or*
- Resolution of IE syndrome with antibiotic therapy for ≤4 days, *or*
- No evidence of IE at surgery or autopsy, on antibiotic therapy for ≤4 days, *or*
- Does not meet criteria for possible IE

Definition of Terms Used in Modified Duke Criteria

Major Criteria

- Blood culture findings positive for IE

  Typical microorganisms consistent with IE from 2 separate blood cultures:

  - Viridans streptococci, *Streptococcus gallolyticus* (formerly known as *S. bovis*), *Staphylococcus aureus*, HACEK group, *or*
  - Community-acquired enterococci, in the absence of a primary focus, *or*

  Microorganisms consistent with IE from persistently positive blood culture findings, defined as:

  - ≥2 positive culture findings of blood samples drawn >12 hr apart, *or*
  - 3 or most of ≥4 separate culture findings of blood (with first and last sample drawn ≥1 hr apart)

    - Single positive blood culture for *Coxiella burnetii* or anti–phase I lgG titer ≥1 : 800
- Evidence of endocardial involvement
  Echocardiographic findings positive for IE (TEE recommended in patients with prosthetic valves, rated at least *possible* IE by clinical criteria or *complicated* IE [paravalvular abscess]; TTE as 1st test in other patients), defined as follows:
    - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, *or*
    - Abscess, *or*
    - New partial dehiscence of prosthetic valve

  New valvular regurgitation; worsening or changing of preexisting murmur not sufficient

Minor Criteria

- Predisposition, predisposing heart condition, or intravenous drug use
- Fever—temperature >38°C
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Microbiologic evidence: positive blood culture finding but does not meet a major criterion as noted above (excludes single positive culture findings for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

TEE, Transesophageal echocardiography; TTE, transthoracic echocardiography.

Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis, *Clin Infect Dis* 30:633,

2000.

Prognosis and Complications

Despite the use of antibiotic agents, mortality remains high, in the range of 20–25%. Serious morbidity occurs in 50–60% of children with documented infective endocarditis; the most common is heart failure caused by vegetations involving the aortic or mitral valve. Myocardial abscesses and toxic myocarditis may also lead to heart failure without characteristic changes in auscultatory findings and, occasionally, to life-threatening arrhythmias. Systemic emboli, often with central nervous system manifestations, are a major threat. Pulmonary emboli may occur in children with ventricular septal defect (VSD) or tetralogy of Fallot, although massive life-threatening pulmonary embolization is rare. Other complications include mycotic aneurysms, rupture of a sinus of Valsalva, obstruction of a valve secondary to large vegetations, acquired VSD, and heart block as a result of involvement (abscess) of the conduction system. Additional complications include meningitis, osteomyelitis, arthritis, renal abscess, purulent pericarditis, and immune complex–mediated glomerulonephritis.

Treatment

Antibiotic therapy should be instituted immediately once a definitive diagnosis of infectious endocarditis is made. When virulent organisms are responsible, small delays may result in progressive endocardial damage and are associated with a greater likelihood of severe complications. The choice of antibiotics, method of administration, and length of treatment should be coordinated with consultants from both cardiology and infectious diseases (Tables 464.6 and 464.7). Empirical therapy after appropriate blood cultures are drawn but before the identifiable agent is recovered may be initiated with vancomycin plus gentamicin in patients without a prosthetic valve and when there is a high risk of *S. aureus*, enterococcus, or viridans streptococci (the 3 most common organisms). High serum bactericidal levels must be maintained long enough to eradicate organisms that are growing in relatively inaccessible avascular vegetations. Between 5 and 20 times the minimal in vitro inhibiting concentration must be produced at the site of infection to destroy bacteria growing at the core of these lesions. Several weeks are required for a vegetation to organize completely; therapy must be continued through this period so that recrudescence can be avoided. A total of 4-6 wk of treatment is usually recommended. Depending on the clinical and laboratory responses, antibiotic therapy may require modification, and some patients require more prolonged treatment. With highly sensitive viridans group streptococcal infections, shortened regimens that include oral penicillin for some portion have been recommended for certain adults, but effectiveness studies in children are lacking. In *nonstaphylococcal* disease, bacteremia usually resolves in 24-48 hr, whereas fever resolves in 5-6 days with appropriate antibiotic therapy. Resolution with *staphylococcal* disease takes longer.

Table 464.6

Therapy of Native Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *Streptococcus bovis*

REGIMEN	DOSAGE[*] AND ROUTE	DURATION	COMMENTS
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in 4 or 6 equally divided doses	4 wk	Preferred in patients with impairment of 8th cranial nerve function or renal function
Or			
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose	4 wk	
	Pediatric dose[†] : penicillin 200,000 U/kg/24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg/24 hr IV/IM in 1 dose		
Aqueous crystalline penicillin G sodium	12-18 million U/24 hr IV either continuously or in 6 equally divided doses	2 wk	2 wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired 8th cranial nerve function, or *Abiotrophia*, *Granulicatella*, or *Gemella* spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3-4 µg/mL and trough serum concentration of <1 µg/mL when 3 divided doses are used; nomogram used for single daily dosing
or			
Ceftriaxone sodium	2 g/24 hr IV/IM in 1 dose	2 wk	
plus			
Gentamicin sulfate[‡]	3 mg/kg/24 hr IV/IM in 1 dose, or 3 equally divided doses **Pediatric dose** :	2 wk	

	penicillin 200,000 U/kg/24 hr IV in 4-6 equally divided doses; ceftriaxone 100 mg/kg/24 hr IV/IM in 1 dose; gentamicin 3 mg/kg/24 hr IV/IM in 1 dose or 3 equally divided doses[§]		
Vancomycin hydrochloride[¶]	30 mg/kg/24 hr IV in 2 equally divided doses, not to exceed 2 g/24 hr unless concentrations in serum are inappropriately low **Pediatric dose** : 40 mg/kg/24 hr IV in 2-3 equally divided doses	4 wk	Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dosage should be adjusted to obtain peak (1 hr after infusion completed) serum concentration of 30-45 μg/mL and a trough concentration range of 10-15 μg/mL

[*] Dosages recommended are for patients with normal renal function.

[†] Pediatric dose should not exceed that of a normal adult.

[‡] Other potentially nephrotoxic drugs (e.g., nonsteroidal antiinflammatory drugs) should be used with caution in patients receiving gentamicin therapy.

[§] Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of infective endocarditis exist.

[¶] Vancomycin dosages should be infused during course of at least 1 hr to reduce risk of histamine-release “red man” syndrome.

Minimum inhibitory concentration ≤0.12 μg/mL.

IV, Intravenously; IM, intramuscularly.

From Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications, *Circulation* 111:e394–e433, 2005; correction: *Circulation* 112:2373, 2005.

Table 464.7

Therapy for Endocarditis Caused by Staphylococci in the Absence of Prosthetic Materials

REGIMEN	DOSAGE[*] AND ROUTE	DURATION	COMMENTS
OXACILLIN-SUSCEPTIBLE STRAINS			
Nafcillin or oxacillin[†]	12 g/24 hr IV in 4-6 equally divided doses	6 wk	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk
With			
Optional addition of gentamicin	3 mg/kg/24 hr IV/IM in 2 or 3 equally divided doses	3-5 days	

sulfate [‡]	**Pediatric dose** [§] : nafcillin or oxacillin 200 mg/kg/24 hr IV in 4-6 equally divided doses; gentamicin 3 mg/kg/24 hr IV/IM in 3 equally divided doses		Clinical benefit of aminoglycosides has not been established.
For penicillin-allergic (nonanaphylactoid-type) patients:			Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin	6 g/24 hr IV in 3 equally divided doses	6 wk	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases. [§]
With			
Optional addition of gentamicin sulfate	3 mg/kg/24 hr IV/IM in 2 or 3 equally divided doses	3-5 days	Clinical benefit of aminoglycosides has not been established.
	Pediatric dose : cefazolin 100 mg/kg/24 hr IV in 3 equally divided doses; gentamicin 3 mg/kg/24 hr IV/IM in 3 equally divided doses		
OXACILLIN-RESISTANT STRAINS			
Vancomycin [¶]	30 mg/kg/24 hr IV in 2 equally divided doses **Pediatric dose** : 40 mg/kg/24 hr IV in 2 or 3 equally divided doses	6 wk	Adjust vancomycin dosage to achieve 1 hr serum concentration of 30-45 µg/mL and trough concentration of 10-15 µg/mL.

[*] Dosages recommended are for patients with normal renal function.

[†] Penicillin G 24 million U/24 hr IV in 4-6 equally divided doses may be used in place of nafcillin or oxacillin if strain is penicillin susceptible (minimum inhibitory concentration ≤0.1 µg/mL) and does not produce β-lactamase.

[‡] Gentamicin should be administered in close temporal proximity to vancomycin, nafcillin, or oxacillin dosing.

[§] Pediatric dose should not exceed that of a normal adult.

[¶] For specific dosing adjustment and issues concerning vancomycin, see Table 464.6 footnotes.

IE, Infective endocarditis; IV, intravenously; IM, intramuscularly.

From Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications, *Circulation* 111:e394–e433, 2005; corrections *Circulation* 112:2373, 2005.

If the infection occurs on a valve and induces or increases symptoms and signs of heart failure, appropriate therapy should be instituted, including diuretics, afterload reducing agents, and in some cases, digitalis. Surgical intervention for infective endocarditis is indicated for severe aortic, mitral, or prosthetic valve involvement with intractable heart failure (Table 464.8). Severe heart failure may be associated with acute valve regurgitation, obstruction, or fistula formation. Rarely, a mycotic aneurysm, rupture of an aortic sinus, intraseptal abscess causing complete heart block, or dehiscence of an intracardiac patch requires emergency surgery. Other surgical indications include failure to sterilize the blood despite adequate antibiotic levels in 7-10 days in the absence of extracardiac infection, myocardial abscess, recurrent emboli, and increasing size of vegetations while receiving therapy. Vegetations (aortic, mitral, prosthetic valve) >10-15 mm are at high risk of embolism. Although antibiotic therapy should be administered for as long as possible before surgical intervention, active infection is not a contraindication if the patient is critically ill as a result of severe hemodynamic deterioration from infective endocarditis. Removal of vegetations and, in some instances, valve replacement may be lifesaving, and sustained antibiotic administration will most often prevent reinfection. Replacement of infected prosthetic valves carries a higher risk.

Table 464.8

Echocardiographic Features that Suggest Potential Need for Surgical Intervention

Vegetation

Persistent vegetation after systemic embolization
Anterior mitral valve leaflet vegetation, particularly if it is highly mobile with size >10 mm*
One or more embolic events during the 1st 2 wk of antimicrobial therapy*
Increase in vegetation size despite appropriate antimicrobial therapy* †

Valvular Dysfunction

Acute aortic or mitral insufficiency with signs of ventricular failure †
Heart failure unresponsive to medical therapy †
Valve perforation or rupture †

Perivalvular Extension

Valvular dehiscence, rupture, or fistula †

New heart block † ‡

Large abscess or extension of abscess despite appropriate antimicrobial therapy †

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[*] Surgery may be required because of risk of embolization.

[†] Surgery may be required because of heart failure or failure of medical therapy.

[‡] Echocardiography should *not* be the primary modality used to detect or monitor heart block.

From Baddour LM, Freeman WK, Suri RM, Wilson WR: Cardiovascular infections. In *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 11, Philadelphia, 2018, Elsevier (Table 73-5, p 1492).

Fungal endocarditis is difficult to manage and has a poorer prognosis. It has been encountered after cardiac surgery, in severely debilitated or immunosuppressed patients, and in patients on a prolonged course of antibiotics. The drugs of choice are amphotericin B (liposomal or standard preparation) and 5-fluorocytosine. Surgery to excise infected tissue is occasionally attempted, but often with limited success. Recombinant tissue plasminogen activation may help lyse intracardiac vegetations and avoid surgery in some high-risk patients.

Prevention

The American Heart Association (AHA) recommendations for antimicrobial prophylaxis before dental and other surgical procedures underwent a major revision in 2007. A substantial reduction in the number of patients who require prophylactic treatment and the procedures requiring coverage was recommended. The primary reasons for these revised recommendations were that (1) infective endocarditis is much more likely to result from exposure to the more frequent random bacteremias associated with daily activities than from a dental or surgical procedure; (2) routine prophylaxis may prevent “an exceedingly small” number of cases; and (3) the risk of antibiotic- related adverse events exceeds the benefits of prophylactic therapy. Improving general dental hygiene was thought to be a more important factor in reducing the risk of infective endocarditis resulting from routine daily bacteremias. The current recommendations limit the use of prophylaxis to those patients with cardiac conditions associated with the greatest risk of an adverse outcome from infective endocarditis (Table 464.9). Patients with permanently damaged valves from rheumatic heart disease should also be considered for prophylaxis. Prophylaxis for these patients is recommended for “all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.” Furthermore, “placement of removable prosthodontic or endodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa” are not indications for prophylaxis. Given that many invasive respiratory tract procedures do cause bacteremia, prophylaxis for many of these procedures is considered reasonable. In contrast to prior recommendations, prophylaxis for gastrointestinal or genitourinary procedures is no longer recommended in the majority of cases. Prophylaxis for patients undergoing cardiac surgery with placement of prosthetic material is still recommended. Given the highly individual nature of these recommendations and the continued concern among some cardiologists over their adoption, direct consultation with the child's cardiologist is still the best method for determining a specific patient's ongoing need for prophylaxis (Table 464.10).

Table 464.9

Cardiac Conditions Associated with Highest Risk of Adverse Outcome from Infective Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable (2007 AHA Statement)

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis

Congenital Heart Disease (CHD)*

Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired CHD with prosthetic material or device, whether

placed by surgery or catheter intervention, during the 1st 6 mo after the procedure [†]

Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch, or prosthetic device (which inhibit endothelialization)

Cardiac transplantation recipients who develop cardiac valvulopathy

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[*] Except for the conditions listed here, antibiotic prophylaxis is no longer recommended by the AHA for any other form of CHD.

[†] Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.

From Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis: guidelines from the American Heart Association, *Circulation* 116:1736–1754, 2007.

Table 464.10

Prophylactic Antibiotic Regimens for a Dental Procedure (2007 AHA Statement)

SITUATION	AGENT	ADULTS	CHILDREN
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin *or* Cefazolin or ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[*][†] *or* Clindamycin *or* Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone [†] *or* Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

[*] Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

[†] Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

IM, Intramuscularly; IV, intravenously.

From Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis: guidelines from the American Heart Association, *Circulation* 116:1736–1754, 2007.

Continuing education regarding both oral hygiene and in appropriate cases the need for prophylaxis is important, especially in teenagers and young adults. Vigorous treatment of sepsis and local infections and careful asepsis during heart surgery and catheterization reduce the incidence of infective endocarditis.

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Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. guidelines from the American heart association. *Circulation* . 2007;116:1736–1754.

CHAPTER 465

Rheumatic Heart Disease

Michael R. Carr, Stanford T. Shulman

Rheumatic involvement of the cardiac valves is the most important sequela of **acute rheumatic fever (ARF)** and also the 2nd most common major manifestation after arthritis (see Chapter 210.1). The valvular lesions begin as small verrucae composed of fibrin and blood cells along the borders of 1 or more of the heart valves. The *mitral valve* is affected most often, followed in frequency by the aortic valve. Isolated aortic valve disease is rare and generally seen with concomitant mitral valve involvement. Right-sided heart manifestations are quite rare and are virtually only associated with left-sided valve disease. As the inflammation subsides, the verrucae tend to disappear and leave scar tissue. With repeated attacks of rheumatic fever, new verrucae form near the previous ones, and the mural endocardium and chordae tendineae become involved. A single episode of **acute rheumatic carditis** often results in complete healing of the valvular lesions, while *repeated* episodes, especially involving previously affected valves, result in chronic rheumatic heart disease (**RHD**), which is the rationale for secondary prophylaxis.

The diagnosis of ARF requires the fulfillment of the **Jones criteria** (see Chapter 210.1), with carditis being a major criterion. Previously, the diagnosis of RHD was based on cardiac auscultatory findings of mitral or aortic valve involvement, which was insensitive for early valve injury. This was based on endocarditis or valvulitis being seen more frequently in ARF compared with pericarditis or myocarditis, both of which lack more readily apparent physical examination findings. Screening large, high-risk populations with echocardiography demonstrated a substantially greater number of patients with RHD than those detected by auscultation alone. Because access to echocardiography is often available, the current version of the Jones Criteria focused on the concept of **subclinical carditis (SCC)** detected by echocardiography. SCC is defined as echocardiographic evidence of mitral or aortic valvulitis in the absence of auscultatory findings and not consistent with physiologic mitral or aortic insufficiency (Table 465.1). Echocardiography with Doppler should be performed for all cases of confirmed or suspected ARF. Additional recommendations are that echocardiography should be performed in moderate- to high-risk patient populations if ARF is considered likely, and that echocardiography can be used to exclude cardiac findings consistent with ARF in patients with cardiac murmurs thought to be suggestive of rheumatic carditis. Additionally, serial echocardiography should be considered in patients with diagnosed or suspected ARF even if there is no evidence of valvulitis by echocardiography at diagnosis. The echocardiographic finding of SCC now fulfills the major criterion for carditis.

Table 465.1

Echocardiographic Findings in Rheumatic Valvulitis

PATHOLOGIC MITRAL REGURGITATION*	PATHOLOGIC AORTIC REGURGITATION*
1. Seen in at least 2 views	1. Seen in at least 2 views
2. Jet length ≥2 cm in at least 1 view	2. Jet length ≥1 cm in at least 1 view
3. Peak velocity >3 meters/sec	3. Peak velocity >3 meters/sec
4. Pan-systolic jet in at least 1 envelope	4. Pan-diastolic jet in at least 1 envelope

[*] All 4 criteria need to be met.

Adapted from Gewitz MH, Baltimore RS, Tani LY, etal: On behalf of the American Heart Association Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association, Circulation 131:1806–1818, 2015.

Patterns of Valvular Disease

Mitral Insufficiency

Pathophysiology

Mitral insufficiency is the result of structural changes that may include some loss of valvular substance and/or changes to the subvalvular apparatus, including elongation of the chordae, both of which can lead to valve dysfunction. During ARF with severe cardiac involvement, heart failure is caused by a combination of mitral insufficiency coupled with a **pancarditis** , involving the pericardium and myocardium in addition to the endocardium/valve. Because of the increased volume load from the mitral insufficiency and the inflammatory process, the left ventricle dilates. The left atrium also enlarges to accommodate the regurgitant volume. Increased left atrial pressure results in pulmonary congestion and symptoms of left-sided heart failure. Spontaneous improvement often occurs with time, even in patients in whom mitral insufficiency is severe at the onset. The resultant chronic lesion is most often mild or moderate in severity, and the patient is often asymptomatic. More than half of patients with acute mitral insufficiency no longer have an audible mitral insufficiency murmur 1 yr later, although they still may demonstrate insufficiency on echocardiography. In patients with severe chronic mitral insufficiency, pulmonary artery pressure (PAP) becomes elevated, the right ventricle and atrium become enlarged, and right-sided heart failure subsequently develops.

Clinical Manifestations

The physical signs of mitral insufficiency depend on its severity. With mild disease, signs of heart failure are not present, the precordium is quiet, and auscultation reveals a high-pitched **holosystolic murmur** at the apex that radiates to the axilla. With severe mitral insufficiency, signs of acute or chronic heart failure may be noted. The heart is enlarged, with a heaving apical left ventricular (LV) impulse and often an apical systolic **thrill** . The second heart sound (S_2) may be accentuated if pulmonary hypertension is present. A third heart sound or **gallop** is generally prominent. A holosystolic murmur is heard at the apex with radiation to the axilla. A short mid-diastolic rumbling murmur is caused by increased blood flow across the mitral valve as a result of the significant insufficiency. Therefore, auscultation of a diastolic murmur, often referred to as **relative mitral stenosis** (**Carey-Coombs murmur**), does not necessarily mean that true mitral stenosis is present. The latter lesion takes many years to develop and is characterized by a diastolic murmur of greater length, usually with presystolic accentuation.

The electrocardiogram and chest radiographs are normal if the mitral insufficiency is mild. With more severe insufficiency, the ECG shows prominent, longer duration and often bifid P waves, signs of LV hypertrophy, and associated right ventricular (RV) hypertrophy if pulmonary hypertension is present. On chest radiograph, prominence of the left atrium and ventricle can be seen, the former of which is better seen on lateral projections. Congestion of the perihilar vessels, a sign of pulmonary venous hypertension, may also be evident.

Calcification of the mitral valve is rare in children. Echocardiography in the acute phase may demonstrate enlargement of the left atrium and ventricle. LV systolic function can be impaired if there is also a component of myocardial inflammation. Mitral annular dilation, chordal elongation, and at times, evidence of chordal rupture resulting in a flail leaflet may be noted. The leaflet tips demonstrate a nodular appearance and prolapse of the anterior mitral valve leaflet tip (much more often than the posterior leaflet) is seen. Doppler evaluation demonstrates the severity of the mitral regurgitation. Chronic mitral insufficiency from RHD is characterized on echocardiography by leaflet and chordal thickening, chordal fusion, and restricted leaflet motion. These changes often lead to stenosis, but poor coaptation of the abnormal leaflets can also lead to variable degrees of regurgitation. Cardiac catheterization and left ventriculography are considered only if diagnostic questions are not completely resolved by noninvasive assessment, or in rare cases with a concern for significantly elevated PAP.

Complications

Severe mitral insufficiency may result in cardiac failure that may be precipitated by progression of the rheumatic process, recurrent episodes of ARF, the onset of **atrial fibrillation (AF)** or other arrhythmias, or infective endocarditis. The effects of chronic mitral insufficiency may become manifest after many years and include LV and RV failure and atrial and ventricular arrhythmias.

Treatment

In patients with mild mitral insufficiency, **prophylaxis** against recurrences of rheumatic fever is all that is required, in addition to the typical treatment for ARF (see Chapter 210.1). For more significant insufficiency, corticosteroids are added in the acute phase. Treatment of complicating heart failure (see Chapter 469), arrhythmias (Chapter 462), and infective endocarditis (Chapter 464) is described elsewhere. Afterload-reducing agents—angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may reduce the regurgitant volume, attenuate pathologic compensatory mechanisms, and preserve left ventricular function, but these have not been proven to alter the natural history of the disease process. Diuretics may also provide some symptomatic and clinical benefit in select cases. In rare cases, phosphodiesterase inhibitors such as milrinone may be used in the acute stage, because of their inotropic, lusitropic, and systemic vascular dilating effects. Surgical treatment is indicated for patients who, despite adequate medical therapy, have persistent heart failure, dyspnea with moderate activity, and progressive cardiomegaly, often with pulmonary hypertension. Although **annuloplasty** provides good results in some children and adolescents, **valve replacement** may be required, which can be more complicated in younger children. In patients with a prosthetic mitral valve replacement, prophylaxis against bacterial endocarditis is warranted for dental procedures, as the routine antibiotics taken by these patients for rheumatic fever prophylaxis are insufficient to prevent endocarditis. Additionally, current recommendations suggest selecting a different class of antibiotic for such procedures, rather than increasing the dose of the antibiotic taken for rheumatic fever prophylaxis. Lastly, it is important to remember that all attempts should be made at maximizing medical management of severe mitral insufficiency during the acute phase of the disease process, before considering surgical intervention, since surgery carries a poorer prognosis and an increased risk for reoperation when performed during the acute phase.

Mitral Stenosis

Pathophysiology

Mitral stenosis of rheumatic origin results from fibrosis of the mitral ring, commissural adhesions, and contracture of the valve leaflets, chordae, and papillary muscles over time. This is a chronic process and often takes ≥10 yr for the lesion to become fully established, although the process may occasionally be accelerated. In the developed world, rheumatic mitral stenosis is seldom encountered before adolescence and is not usually recognized until adult life. Significant mitral stenosis results in increased left atrial pressure and subsequent enlargement and hypertrophy of the left atrium, pulmonary venous hypertension, increased pulmonary vascular resistance, and eventually overt pulmonary hypertension (see Chapter 460). RV hypertrophy and right atrial dilation ensue and are followed by RV dilation, tricuspid regurgitation, and clinical signs of right-sided heart failure.

Clinical Manifestations

Generally, the correlation between symptoms and the severity of obstruction is good. Patients with mild stenosis are asymptomatic. More severe degrees of obstruction are associated with exercise intolerance and dyspnea. Critical lesions can result in orthopnea, paroxysmal nocturnal dyspnea, and overt pulmonary edema, as well as atrial arrhythmias. When pulmonary hypertension has developed, RV dilation may result in functional tricuspid insufficiency, hepatomegaly, ascites, and edema. Hemoptysis caused by rupture of bronchial or pleurohilar veins and, occasionally, pulmonary infarction may occur.

Jugular venous pressure is increased in severe disease with heart failure, tricuspid valve disease/regurgitation, or severe pulmonary hypertension. In mild disease, heart size is normal; however, moderate cardiomegaly is typical with severe mitral stenosis. Cardiac enlargement can be massive when AF and heart failure supervene. A parasternal RV lift is palpable when PAP is high. The principal auscultatory findings are a loud first heart sound, an opening snap of the mitral valve, and a long, low-pitched, rumbling mitral diastolic murmur with presystolic accentuation at the apex. The mitral diastolic murmur may be virtually absent in patients who are in significant heart failure from the elevated LV filling pressures. A holosystolic murmur secondary to tricuspid insufficiency may be audible at the left lower sternal border. In the presence of pulmonary hypertension, the pulmonic component of S_2 is accentuated. An early diastolic murmur may be caused by associated rheumatic aortic insufficiency or pulmonary valvular insufficiency secondary to pulmonary hypertension.

ECGs and chest radiographs are normal if the stenosis is mild; as the severity increases, prominent and notched P waves and varying degrees of RV hypertrophy become evident. AF or other atrial arrhythmias are common late manifestations. Moderate to severe lesions are associated with radiographic signs of left atrial enlargement and prominence of the pulmonary artery and right-sided heart chambers; calcifications may be noted in the region of the mitral valve. Severe stenosis is associated with a redistribution of pulmonary blood flow so that the apices of the lung have greater perfusion (the reverse of normal). Lastly, horizontal lines in the lower lung periphery, called **Kerley B lines** , may be evident. Echocardiography demonstrates thickening of the mitral valve and chordal apparatus, as well as restricted motion of the valve. The typical “elbow” or “dog leg” appearance of the anterior leaflet of the mitral valve can aid in the distinction of a rheumatic valve from the various forms of congenital mitral stenosis. Left atrial dilation is common; color Doppler flow across the mitral valve shows a narrow jet with flow acceleration, and variable degrees of tricuspid insufficiency can be seen from left atrial hypertension. Doppler can estimate the **transmitral pressure gradient** but can underestimate the gradient if there is LV dysfunction. Cardiac catheterization quantitates the diastolic gradient across the mitral valve well, allows for the calculation of cross-sectional valve area in older children, and assesses the degree of PAP elevation.

Treatment

Intervention is indicated in patients with clinical signs and hemodynamic evidence of severe obstruction, but before the onset of severe manifestations. Pharmacologic therapy (diuretics and β-blockers) can be considered but is generally used only for symptom control and much less often in children. Surgical valvotomy or balloon catheter mitral valvuloplasty generally yields good results; valve replacement is avoided unless absolutely necessary. Balloon valvuloplasty is indicated for symptomatic, stenotic, pliable, noncalcified valves of patients without significant atrial arrhythmias or thrombi.

Aortic Insufficiency

In acute rheumatic aortic insufficiency, poor coaptation of the leaflets or leaflet prolapse is seen. Chronic rheumatic aortic insufficiency leads to sclerosis of the valve and results in distortion and retraction of the cusps. In both settings, regurgitation of blood leads to LV volume overload with dilation and hypertrophy of the left ventricle, as it attempts to compensate for the excessive volume load. Combined mitral and aortic insufficiency in the acute phase of ARF is much more common than aortic involvement alone.

Clinical Manifestations

Symptoms are unusual except in severe aortic insufficiency, or in the presence of significant concomitant mitral valve involvement or myocardial dysfunction. The large stroke volume and forceful LV contractions may result in palpitations. Sweating and heat intolerance are related to excessive vasodilation. Dyspnea on exertion can progress to orthopnea and pulmonary edema; angina may be precipitated by heavy exercise. Nocturnal attacks with sweating, tachycardia, chest pain, and hypertension may occur.

The pulse pressure is wide with bounding peripheral pulses (**water-hammer** or **Corrigan pulse**). Systolic blood pressure is elevated, and diastolic pressure is lowered. In severe aortic insufficiency, the heart is enlarged, with an LV apical heave. A diastolic thrill may be present. The typical murmur begins immediately with S_2 and continues until late in diastole. The murmur is heard over the upper left and mid-left sternal border with radiation to the apex and upper right sternal border. Characteristically, it has a high-pitched blowing quality and is easily audible in full expiration with the diaphragm of the stethoscope placed firmly on the chest and the patient leaning forward. An aortic systolic ejection murmur is frequently heard because of the increased stroke volume. An apical presystolic murmur (**Austin Flint murmur**) resembling that of mitral stenosis is sometimes heard and is caused by the large regurgitant aortic flow in diastole preventing the mitral valve from opening fully.

Chest radiographs demonstrate enlargement of the left ventricle and aorta. The ECG may be normal, but in advanced cases it reveals signs of LV hypertrophy with a strain pattern and prominent P waves. Echocardiography shows a dilated left ventricle and diastolic mitral valve flutter or oscillations caused by aortic regurgitant flow hitting the valve leaflets. The aortic valve may demonstrate irregular or focal thickening, decreased systolic excursion, a coaptation defect, and leaflet prolapse. Doppler evaluation demonstrates the degree of aortic insufficiency. Magnetic resonance angiography (MRA) can be useful in quantitating regurgitant volume, as well as assessing LV size and systolic function. Cardiac catheterization is generally only necessary when echocardiographic or axial imaging data are equivocal.

Prognosis and Treatment

Mild and moderate degrees of aortic insufficiency are well tolerated. Unlike mitral insufficiency, aortic insufficiency does not generally regress. Patients with combined lesions during the episode of ARF may have only aortic involvement 1-2 yr later. Treatment consists of ACE inhibitors or ARBs and prophylaxis against ARF recurrence. Surgical intervention, which is typically aortic valve replacement, but occasionally can involve aortic valve repair, should be done well in advance of the onset of heart failure, pulmonary edema, and angina or when signs of decreasing myocardial performance become evident, as manifested by increasing LV dimensions and decreasing systolic function on echocardiography. Surgery is considered when early symptoms are present, ST-T wave changes are seen on the ECG, or evidence of decreasing LV ejection fraction is noted.

Tricuspid Valve Disease

Primary tricuspid valve involvement is rare during both the acute and chronic stages of rheumatic fever. Tricuspid insufficiency is more common secondary to RV dilation, resulting from significant left-sided cardiac lesions. The clinical signs of tricuspid insufficiency include prominent pulsations of the jugular veins, systolic pulsations of the liver, and a blowing holosystolic murmur at the lower left sternal border that increases in intensity during inspiration. Concomitant signs of mitral or aortic valve disease, with or without AF, are common. In these cases, signs of tricuspid insufficiency often decrease or even disappear when heart failure produced by the left-sided valvular lesions is successfully treated. Tricuspid valvuloplasty may be required in very rare cases.

Pulmonary Valve Disease

Pulmonary insufficiency secondary to ARF is rare and usually occurs on a functional basis secondary to pulmonary hypertension and is a late finding with severe mitral stenosis. The murmur (**Graham Steell murmur**) is similar to that of aortic insufficiency, but peripheral arterial signs (bounding pulses) are absent. The correct diagnosis is confirmed by two-dimensional echocardiography and Doppler studies.

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SECTION 6

Diseases of the Myocardium and Pericardium

OUTLINE

Chapter 466 Diseases of the Myocardium
Chapter 467 Diseases of the Pericardium
Chapter 468 Tumors of the Heart

CHAPTER 466

Diseases of the Myocardium

John J. Parent, Stephanie M. Ware

The extremely heterogeneous heart muscle diseases associated with structural remodeling and abnormalities of cardiac function (**cardiomyopathy**) are important causes of morbidity and mortality in the pediatric population. Several classification schemes have been formulated in an effort to provide logical, useful, and scientifically based etiologies for the cardiomyopathies. Insight into the molecular genetic basis of cardiomyopathies has increased exponentially, and etiologic classification schemes continue to evolve (Table 466.1).

Table 466.1

Classification of the Cardiomyopathies by Phenome and Genome

TYPE	PHENOTYPE				GENOME
	Morphology	**Physiology**	**Pathology**	**Systemic Conditions, Clinical Features, Risk Factors**	**Nonsyndromic, Usually Single Gene**
Dilated (DCM)	Dilation of LV and RV with minimal or no wall thickening	Reduced contractility is the primary defect; variable degree of diastolic dysfunction	Myocyte hypertrophy; scattered fibrosis	Hypertension, alcohol, thyrotoxicosis, myxedema, persistent tachycardia, toxins (e.g., chemotherapy, especially anthracyclines), radiation	Diverse gene ontology with >30 genes implicated
Restrictive (RCM)	Usually normal chamber sizes; minimal wall thickening	Contractility normal or near-normal with a marked increase in	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others	Endomyocardial fibrosis, amyloid, sarcoid, scleroderma, Churg-Strauss syndrome, cystinosis, lymphoma,	If not associated with systemic genetic disease, genetic cause usually from sarcomeric gene mutations

		end-diastolic filling pressure		pseudoxanthoma elasticum, hypereosinophilic syndrome, carcinoid	
Hypertrophic (HCM)	Usually normal or reduced internal chamber dimension; wall thickening pronounced, especially septal hypertrophy	Systolic function increased or normal	Myocyte hypertrophy, classically with disarray	Severe hypertension can confound clinical, morphologic diagnosis	Mutations of genes encoding sarcomeric proteins
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	Scattered fibrofatty infiltration, classically of RV but also of LV; dilation of RV or LV, or both, is common but not universal	Ventricular arrhythmias (VT, VF) early or late, reduced contractility with progressive disease; can mimic DCM	Islands of fatty replacement; fibrosis	Palmoplantar keratoderma, wooly hair in Naxos syndrome	Mutations of genes encoding proteins of desmosome
Left ventricular noncompaction (LVNC)	Ratio of noncompacted to compacted myocardium increased with normal LV or RV or any other phenotype	Normal to reduced systolic function	Myocardium normal and ranging to findings consistent with other coexisting cardiomyopathies	Phenotype observed in setting of other types of cardiomyopathy	Various cardiomyopathy genes associated, but uncertain whether genetic cause or developmental defect during organogenesis
Infiltrative	Usually thickened walls; occasional dilation	Restrictive physiology; systolic function usually mildly reduced	Specific to type, diagnosis: amyloid, iron, glycogen storage disease, others		See RCM, above
Inflammatory	Normal or dilated without hypertrophy	Reduced systolic function	Inflammatory infiltrates	Hypereosinophilic syndrome, acute myocarditis	
Ischemic	Normal or dilated without hypertrophy	Reduced systolic function	Areas of infarcted myocardium	Hypercholesterolemia, hypertension, diabetes, cigarette smoking, family history	Familial hypercholesterolemia; other heritable lipid disorders
Infectious	Normal or dilated without	Reduced systolic function	Specific to infection	Viral (especially acute myocarditis); protozoal (e.g.,	Genetic predisposition to infection and/or

	hypertrophy			Chagas disease); bacterial, direct infection (e.g., Lyme disease) or from acute cellular toxicity as result of systemic toxins (e.g., *Streptococcus* , gram-negative, others)	variable response to infective agent

LV, Left ventricle; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like symptoms; MERRF, myoclonic epilepsy associated with ragged-red fibers; RV, right ventricle; VF, ventricular fibrillation; VT, ventricular tachycardia.

From Falk RH, Hershberger RE: The dilated, restrictive, and infiltrative cardiomyopathies. In Zipes DP, Libby P, Bonow RO, editors: *Braunwald's heart disease,* ed 11, Philadelphia, 2019, Saunders (Table 77.1).

Table 466.2 classifies the cardiomyopathies based on their anatomic (ventricular morphology) and functional pathophysiology. **Dilated cardiomyopathy** , the most common form of cardiomyopathy, is characterized predominantly by left ventricular (LV) dilation and decreased LV systolic function (Fig. 466.1). **Hypertrophic cardiomyopathy** demonstrates increased ventricular myocardial wall thickness, normal or increased systolic function, and often, diastolic (relaxation) abnormalities (Table 466.3 and Figs. 466.2 and 466.3). **Restrictive cardiomyopathy** is characterized by near-normal ventricular chamber size and wall thickness with preserved systolic function, but dramatically impaired diastolic function leading to elevated filling pressures and atrial enlargement (Fig. 466.4). **Arrhythmogenic right ventricular cardiomyopathy** is characterized by fibrofatty infiltration and replacement of the normal right ventricular (RV) myocardium and occasionally the left ventricle, leading to RV (and LV) systolic and diastolic dysfunction and arrhythmias. **Left ventricular noncompaction** is characterized by a trabeculated LV apex and lateral wall, with a heterogeneous group of associated phenotypes (most often a dilated phenotype with LV dilation and dysfunction). Cardiomyopathies may be primary or associated with other organ involvement (Tables 466.4 to 466.6).

Table 466.2

Etiology of Pediatric Myocardial Disease

CARDIOMYOPATHY	
Dilated Cardiomyopathy (DCM)	
Neuromuscular	Muscular dystrophies (e.g., Duchenne, Becker, limb-girdle, Emery-Dreifuss, congenital

diseases	muscular dystrophy), myotonic dystrophy, myofibrillar myopathy
Inborn errors of metabolism	Fatty acid oxidation disorders (trifunctional protein, VLCAD), carnitine abnormalities (carnitine transport, CPTI, CPTII), mitochondrial disorders (including Kearns-Sayre syndrome), organic acidemias (propionic acidemia), Danon disease (DCM more common in females).
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic DCM
Genetic syndromes	Alström syndrome, Barth syndrome (phospholipid disorders)
Ischemic	Most common in adults
Chronic tachyarrhythmias	Atrial tachycardias (intractable reentrant supraventricular tachycardia [AVRT, AVNRT], multifocal atrial tachycardia, permanent junctional reciprocating tachycardia), ventricular tachycardia
Hypertrophic Cardiomyopathy (HCM)	
Inborn errors of metabolism	Mitochondrial disorders (including Friedreich ataxia, mutations in nuclear or mitochondrial genome), storage disorders (glycogen storage disorders, especially Pompe; mucopolysaccharidoses; Fabry disease; sphingolipidoses; hemochromatosis; Danon disease)
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic HCM
Genetic syndromes	Noonan, Costello, cardiofaciocutaneous, and Beckwith-Wiedemann syndromes
Infant of a diabetic mother	Transient hypertrophy
Restrictive Cardiomyopathy (RCM)	
Neuromuscular disease	Myofibrillar myopathies
Metabolic	Storage disorders
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic RCM
Secondary	Rare in children; radiation therapy of thorax, amyloidosis, sarcoidosis, hemochromatosis, β-thalassemia
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	
Genetic mutations in cardiomyocyte structural apparatus	Familial or sporadic ARVC
Left Ventricular Noncompaction	
Genetic mutations in cardiomyocyte structural apparatus	LVNC phenotype associated with HCM or DCM
Other	X-linked (Barth syndrome), autosomal recessive, mitochondrial inheritance, 1p36 deletion syndrome, and other chromosome abnormalities or genomic disorders; associated with congenital heart defects

SECONDARY OR ACQUIRED MYOCARDIAL DISEASE	
Myocarditis (see also Table 466.8)	**Viral:** parvovirus B19, adenovirus, coxsackievirus A and B, echovirus, rubella, varicella, influenza, mumps, Epstein-Barr virus, cytomegalovirus, measles, poliomyelitis, smallpox vaccine, hepatitis C virus, human herpesvirus 6, HIV, opportunistic infections **Rickettsial:** psittacosis, *Coxiella* , Rocky Mountain spotted fever, typhus **Bacterial:** diphtheria, mycoplasma, meningococcus, leptospirosis, Lyme disease, typhoid fever, tuberculosis, streptococcus, listeriosis **Parasitic:** Chagas disease, toxoplasmosis, *Loa loa, Toxocara canis,* schistosomiasis, cysticercosis, echinococcus, trichinosis **Fungal:** histoplasmosis, coccidioidomycosis, actinomycosis
Systemic inflammatory disease	SLE, infant of mother with SLE, scleroderma, Churg-Strauss vasculitis, rheumatoid arthritis, rheumatic fever, sarcoidosis, dermatomyositis, periarteritis nodosa, hypereosinophilic syndrome (Löffler syndrome), acute eosinophilic necrotizing myocarditis, giant cell myocarditis, Kawasaki disease
Nutritional deficiency	Beriberi (thiamine deficiency), kwashiorkor, Keshan disease (selenium deficiency)
Drugs, toxins	Doxorubicin (Adriamycin), cyclophosphamide, chloroquine, ipecac (emetine), sulfonamides, mesalazine, chloramphenicol, alcohol, hypersensitivity reaction, envenomations, irradiation, herbal remedy (blue cohosh)
Coronary artery disease	Kawasaki disease, medial necrosis, anomalous left coronary artery from pulmonary artery, other congenital coronary anomalies (anomalous right coronary artery, coronary ostial stenosis), familial hypercholesterolemia
Hematology-oncology	Anemia, sickle cell disease, leukemia
Endocrine-neuroendocrine	Hyperthyroidism, carcinoid tumor, pheochromocytoma, adrenal crisis
Stress (takotsubo) cardiomyopathy	Endocrine (see above) Neurologic (stroke, bleed) Induction of anesthesia Fright Medications/drugs (sympathomimetic agents, venlafaxine)

CPTI/CPTII, Carnitine palmitoyltransferase 1/2; LVNC, left ventricular noncompaction; SLE, systemic lupus erythematosus; VLCAD, very-long-chain acyl-coenzyme A dehydrogenase.

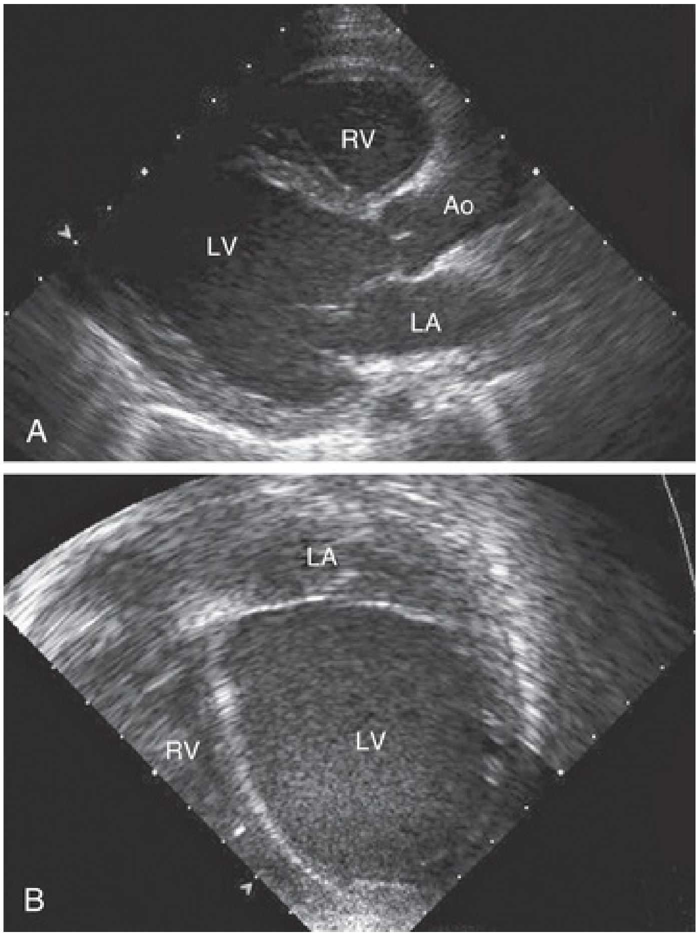

FIG. 466.1 Echocardiogram of a patient with dilated cardiomyopathy. A, Parasternal long axis view showing the enlarged left ventricle. B, Apical 4-chamber view showing the large left ventricle compressing the right ventricle. Ao, Ascending aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

Table 466.3

Cardiomyopathies

	DCM	HCM	RCM	LVN
Prevalence	50/100,000	1/500	Unknown	Unkn
Causes	Sarcomeric/cytoskeletal/desmosomal gene mutation, neuromuscular disease, inborn error of metabolism, mitochondrial disease, genetic syndrome, infection	Sarcomeric/cytoskeletal/desmosomal gene mutation, genetic syndrome, inborn error of metabolism/mitochondrial disease	Sarcomeric gene mutation, neuromuscular disease, genetic syndrome	Sarc cytos desm gene neur disea error metal mito disea genet

				synd
Inheritance	30–50% AD, AR, X-L, Mt	50% AD, Mt	AD, % unknown	AD, % un
Sudden death	Yes	Yes	Yes	Yes
Arrhythmias	Atrial, ventricular, and conduction disturbances	Atrial and ventricular	Atrial fibrillation	Atria ventr and cond distu
Ventricular function	Systolic and diastolic dysfunction	Diastolic dysfunction Dynamic systolic outflow obstruction	Diastolic dysfunction Normal systolic function	Systo diasto dysfu

ACE, Angiotensin-converting enzyme; AD, autosomal dominant inheritance; AR, autosomal recessive inheritance; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LVNC, left ventricular noncompaction; Mt, mitochondrial inheritance; RCM, restrictive cardiomyopathy; X-L, X-linked inheritance.

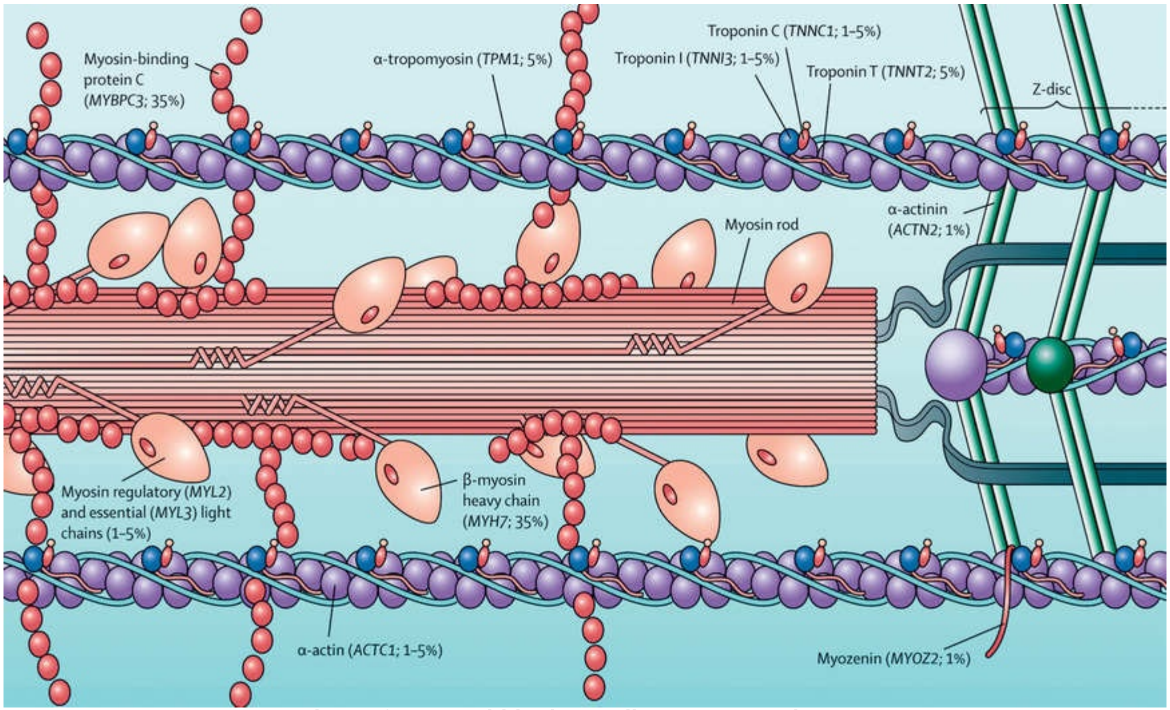
Myosin-binding protein C (MYBPC3; 35%)
α-tropomyosin (TPM1; 5%)
Troponin C (TNNC1; 1–5%)
Troponin I (TNNI3; 1–5%)
Troponin T (TNNT2; 5%)
Z-disc
α-actinin (ACTN2; 1%)
Myosin rod
Myosin regulatory (MYL2) and essential (MYL3) light chains (1–5%)
β-myosin heavy chain (MYH7; 35%)
α-actin (ACTC1; 1–5%)
Myozenin (MYOZ2; 1%)

FIG. 466.2 **Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy. Prevalence of every gene (derived from data of unrelated hypertrophic cardiomyopathy probands with positive genotyping) is shown in parentheses. (From Maron BJ, Maron MS: Hypertrophic cardiomyopathy, *Lancet***

381:242–252, 2013, Fig 1, p 243.)

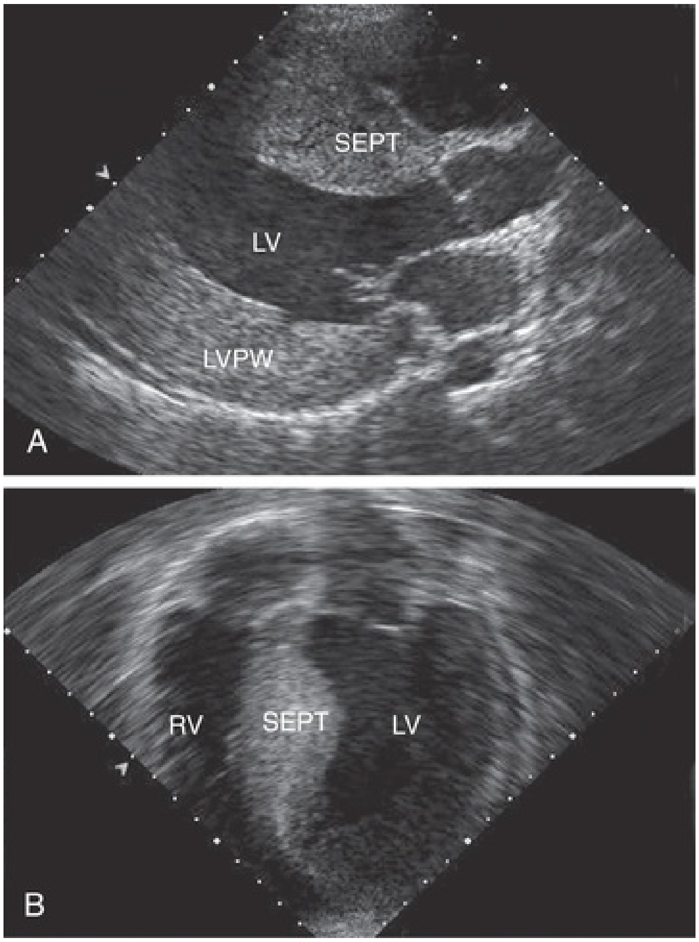

FIG. 466.3 Echocardiograms demonstrating hypertrophic cardiomyopathy. **A,** Parasternal long axis view of a patient with severe concentric left ventricular hypertrophy. **B,** Four-chamber view of a patient with asymmetric septal hypertrophy. LV, Left ventricle; LVPW, left ventricular posterior wall; RV, right ventricle; SEPT, septum.

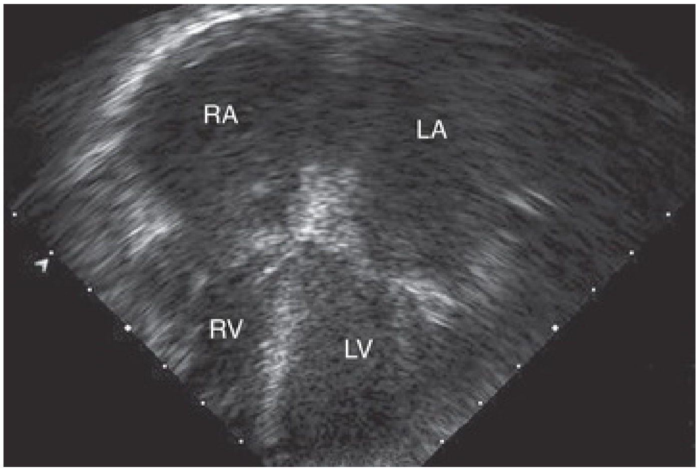

FIG. 466.4 Echocardiogram of a patient with restrictive cardiomyopathy. Apical 4-chamber view shows the greatly enlarged right and left atria, compared to the normal-size left and right ventricular chambers. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Table 466.4

Nuclear DNA Abnormalities Associated With Cardiomyopathy and Arrhythmias or Conduction Defects*

CONDITION	GENETIC DEFECT	HEART FINDINGS	OTHER CLINICAL FEATURES
ISOLATED COMPLEX DEFICIENCIES			
Complex I deficiency	Multiple complex I subunit genes, *ACAD9, FOXRED 1*	HCM, DCM, LVNC, WPW	Leigh syndrome, FILA. MELAS, leukoencephalopathy, seizures, hypotonia, pigmentary retinopathy, optic atrophy, hearing loss, liver dysfunction
Complex II deficiency	*SDHA, SDHD*	HCM, DCM, LVNC, AF, heart block	Leukoencephalopathy, cerebellar atrophy, seizures, spasticity, myopathy, liver dysfunction, kidney dysfunction
Complex III deficiency	*BCS1L*	HCM	Developmental delay, psychosis, hearing loss
Complex IV deficiency	*SCO2, SURF1, C2orf64, Cl2orf62, COX6B1*	HCM, DCM	Leigh syndrome, encephalopathy, ataxia, liver dysfunction, kidney dysfunction
MITOCHONDRIAL TRANSLATION DEFECTS			
GTP-binding protein-3 deficiency	*GTPBP3*	HCM, DCM, heart block, WPW	Leigh syndrome, encephalopathy
Mitochondrial translational activator protein deficiency	*MTOI*	HCM, heart block	Encephalopathy, hypotonia
Alanyl-tRNA synthetase deficiency	*AARS2*	HCM	Leukoencephalopathy, myopathy

Tyrosyl-tRNA synthetase deficiency	*YARS2*	HCM	MLASA syndrome
tRNA methyltransferase-*5* deficiency	*TRMTS*	HCM	Developmental delay, hypotonia, peripheral neuropathy, renal tubulopathy
RNA processing defect	*ELAC2*	HCM, PSVE	Microcephaly, growth deficiency, hearing loss
Mitochondrial ribosomal subunit deficiencies	*MRPS22, MRPl3, MRPL44*	HCM, WPW	Leukoencephalopathy, seizures, liver dysfunction, renal tubulopathy
mtDNA DEPLETION SYNDROMES			
MNGIE	*TYMP*	Mild or asymptomatic HCM	Leukoencephalopathy, severe gastrointestinal dysmotility, ophthalmoplegia, hearing loss, peripheral neuropathy
F-box protein deficiency	*FBXL4*	Cardiomyopathy, unspecified	Encephalopathy, brain atrophy
Coenzyme Q_{10} biosynthesis defects	*COQ2, COQ4, COQ9*	HCM	Leigh syndrome, encephalomyopathy, retinitis pigmentosa, hearing loss, liver dysfunction, renal tubulopathy
3-METHYLGLUTACONIC ACIDURIAS			
Barth syndrome	*TAZ*	HCM, DCM, LVNC, EFE, VT, LQTS	Myopathy, short stature, neutropenia
Dilated cardiomyopathy and ataxia syndrome	*DNAJC19*	DCM, LVNC	Ataxia, optic ataxia, short stature, testicular abnormalities, liver disease
Complex V deficiency	*TMEM70*	HCM	Cataracts, leukodystrophy, ataxia, myopathy, short stature
Sengers syndrome	*AGK*	HCM	Cataracts, myopathy, exercise intolerance, short stature

[*] Examples of conditions that are associated with heart disease and feature abnormal nDNA are shown, along with the causative molecular defects and clinical findings. The genetic defects noted above are provided as major contributors to the various mitochondrial conditions but are not a comprehensive compilation.

AF, Atrial fibrillation; DCM, dilated cardiomyopathy; EFE, endocardial fibroelastosis; FILA, fatal infantile lactic acidosis; GTP, guanosine triphosphate; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MLASA, myopathy, lactic acidosis, sideroblastic anemia; MNGIE, mitochondrial neurogastrointestinal encephalopathy; PSVE, paroxysmal supraventricular extrasystoles; LVNC, left ventricular noncompaction; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

From Enns GM: Pediatric mitochondrial diseases and the heart, *Curr Opin Pediatr* 29:541–551, 2017 (Table 2, p 543).

Table 466.5

Mitochondrial DNA Abnormalities Associated With

Cardiomyopathy and Arrhythmias or Conduction Defects*

CONDITION	GENETIC DEFECT	HEART FINDINGS	OTHER CLINICAL FEATURES
Kearns-Sayre syndrome	mtDNA deletion	HCM, DCM, heart block, PMVT	Progressive external ophthalmoplegia, pigmentary retinopathy, cerebellar ataxia, hearing loss, increased CSF protein, diabetes mellitus, renal tubulopathy
MELAS	tRNA$^{\text{Lou}}$ point mutation	HCM, DCM, LVNC, RCM, heart block, WPW	Encephalopathy, seizures, stroke-like episodes, headaches, hearing loss, myopathy
MERRF	tRNA$^{\text{Lys}}$ point mutation	HCM, DCM, HiCM, WPW	Myoclonus, seizures, ataxia, optic atrophy, hearing loss, short stature
Complex I deficiency	Multiple complex I subunit genes	HCM, DCM	Leigh syndrome, leukoencephalopathy, seizures, optic atrophy
Complex III deficiency	*MTCYB*	HCM, DCM, HiCM	Exercise intolerance, myopathy, seizures, optic atrophy, short stature
Complex IV deficiency	*MT-CO1, MT-CO2, MT-CO3*	HCM, DCM, HiCM	Encephalopathy, seizures, pigmentary retinopathy, hearing loss, myopathy, liver dysfunction
Complex V deficiency	*MT-ATP6, MT-ATP8*	HCM	Ataxia, peripheral neuropathy

* Relatively common conditions that are associated with heart disease and feature abnormal mtDNA are shown, along with the most common molecular defects and clinical findings. Although the most common molecular defects are indicated in the table, in most cases multiple genetic abnormalities can cause similar clinical presentations.

CSF, Cerebrospinal fluid; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HiCM, histiocytoid cardiomyopathy; LVNC, left ventricular noncompaction; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; PMVT, polymorphic ventricular tachycardia; RCM, restrictive cardiomyopathy; WPW, Wolff-Parkinson-White syndrome.

From Enns GM: Pediatric mitochondrial diseases and the heart, *Curr Opin Pediatr* 29:541–551, 2017 (Table 3, p 546).

Table 466.6

Gene Mutations and Cardiac Manifestations of Neuromuscular Disorders

DISORDER	GENE MUTATION	CARDIOMYOPATHY	ECG	ARRHYTHMIA
Duchenne muscular dystrophy (DMD)	Dystrophin	Dilated	Short PR interval, prolonged QT interval, increased QT:PT ratio, right ventricular	Increased baseline HR, decreased rate variability, premature

			hypertrophy, deep Q waves II, III, aVF, V_5 , V_6	ventricular beats (58% of patients by 24 yr of age)
DMD—female carrier	Dystrophin	Dilated	None	Uncommon
Becker muscular dystrophy	Dystrophin	Dilated	Conduction system disease	Similar to DMD
Emery-Dreifuss autosomal dominant or proximal dominant limb-girdle muscular dystrophy IB	Lamin A/C	Dilated	Conduction abnormalities: prolonged PR interval, sinus bradycardia	Atrial fibrillation or flutter and atrial standstill; ventricular dysrhythmias
Limb-girdle muscular dystrophy	α, β, γ, δ sarcoglycans	Dilated	Incomplete right bundle branch block, tall R waves in V_I and $V_{2,}$ left anterior hemiblock	Uncommon
Congenital muscular dystrophy	Laminin α_2	Dilated	None	None
Limb-girdle muscular dystrophy 21	Fukutin	Dilated	AV node and bundle branch block; age at onset: late teens and early 20s	Atrial arrhythmias and/or ventricular arrhythmias
Emery-Dreifuss X-linked	Emerin	Rare	Conduction abnormalities: prolonged PR interval, sinus bradycardia	Atrial fibrillation or flutter and atrial standstill
Friedreich ataxia	Frataxin gene	Hypertrophic	T-wave inversion, left axis deviation, repolarization abnormalities	Ventricular arrhythmias
Myotonic dystrophy type 1, infantile	Myotonic dystrophy protein kinase gene	Hypertrophic	Conduction disease, prolonged PR interval, widening of QRS complex	Atrial fibrillation and flutter, complete heart block
Myotonic dystrophy type 1	Myotonic dystrophy protein kinase gene	LVNC	Conduction disease, prolonged PR interval, widening of QRS complex	Atrial fibrillation and flutter, complete heart block

AV, Atrioventricular; HR, heart rate; LVNC, left ventricular noncompaction.

From Hsu DT: Cardiac manifestations of neuromuscular disorders in children, *Pediatr Respir Rev* 11:35–38, 2010 (Table 1, p 37).

466.1

Dilated Cardiomyopathy

John J. Parent, Stephanie M. Ware

Keywords

cardiac transplantation
heart failure
systolic dysfunction
inotrope
pacemaker

Etiology and Epidemiology

Dilated cardiomyopathy (**DCM**), the most common form of cardiomyopathy in children, is the cause of significant morbidity and mortality as well as a common indication for cardiac transplantation. The etiologies are diverse. Unlike adult patients with DCM, ischemic etiologies are rare in children, although these include anomalous origin of the left coronary artery from the pulmonary artery, premature coronary atherosclerosis (homozygous familial hypercholesterolemia, rare genetic syndromic disease such as progeria), and coronary inflammatory diseases, such as Kawasaki disease. It is estimated that up to 50% of cases are **genetic** (usually autosomal dominant; some are autosomal recessive or X-linked), including some with metabolic causes (see Tables 466.1 and 466.2). Although the most common etiology of DCM remains **idiopathic** , it is likely that undiagnosed familial/genetic conditions and myocarditis predominate. The annual incidence of DCM in children younger than 18 yr is 0.57 cases per 100,000 per year. Incidence is higher in males, blacks, and infants <1 yr old.

Pathogenesis

The pathogenesis of the ventricular dilation and altered contractility seen in DCM varies depending on the underlying etiology; systolic dysfunction and myocyte injury are common. Genetic abnormalities of several components of the cardiac muscle, including sarcomere proteins, the cytoskeleton, and the proteins that bridge the contractile apparatus to the cytoskeleton, have been identified in autosomal dominant and X-linked inherited disorders. DCM can occur following viral myocarditis. Although the primary pathogenesis varies from direct myocardial injury to viral-induced inflammatory injury, the resulting myocardial damage, ventricular enlargement, and poor function likely occur by a final common pathway similar to that in genetic disorders.

In 20–50% of cases, the DCM is familial with autosomal dominant inheritance most common (see Table 466.3). **Duchenne and Becker muscular dystrophies** are X-linked cardiomyopathies that account for 5–10% of DCM cases (see Chapter 627.1). These dystrophinopathies result in an abnormal sarcomere-cytoskeleton connection, causing impaired myocardial force generation, myocyte damage/scarring, chamber enlargement, and altered function (see Table 466.6). Female carriers of dystrophinopathies may also manifest DCM.

Mitochondrial myopathies , as with the muscular dystrophies, may present clinically with a predominance of extracardiac findings and are inherited in a recessive or mitochondrial pattern (see Tables 466.4 and 466.5). Disorders of **fatty acid oxidation** present with systemic derangements of metabolism (hypoketotic hypoglycemia, acidosis, and hepatic dysfunction), some with peripheral myopathy and neuropathy, and others with sudden death or life-threatening cardiac arrhythmias.

Anthracycline cardiotoxicity (doxorubicin [Adriamycin]) on rare occasion causes acute inflammatory myocardial injury, but more classically results in DCM and occurs in up to 30% of patients given a cumulative dose of doxorubicin exceeding 550 mg/m^2 . The risk of toxicity appears to be exacerbated by concomitant radiation therapy. Identifying methods to reduce toxicity and developing precision medicine approaches to identify and treat individuals at high risk are active areas of research.

Clinical Manifestations

Although more prevalent in patients <1 yr of age, all age-groups may be affected. Clinical manifestations of DCM are typically those of heart failure but can also include palpitations, syncope, and sudden death. Irritability or lethargy can be accompanied by additional nonspecific complaints of failure to thrive, nausea, vomiting, or abdominal pain. Respiratory symptoms (tachypnea, wheezing, cough, or dyspnea on exertion) are often present. Infrequently, patients may present acutely with pallor, altered mentation, hypotension, and shock. Patients can be tachycardic with narrow pulse pressure and may have hepatic enlargement and rales or wheezing. The precordial cardiac impulse is increased, and the heart may be enlarged to palpation or percussion. Auscultation may reveal a gallop rhythm in addition to tachycardia and occasionally murmurs of mitral or, less often, tricuspid insufficiency may be present. The presence of hypoglycemia, acidosis, hypotonia, or signs of liver dysfunction suggests an inborn error of metabolism. Neurologic or skeletal muscle deficits are associated with mitochondrial disorders or muscular dystrophies (see Tables 466.4 to 466.6).

Laboratory Findings

Electrocardiographic screening reveals atrial or ventricular hypertrophy, nonspecific T-wave abnormalities, and occasionally, atrial or ventricular arrhythmias. The chest radiograph may demonstrate cardiomegaly and pulmonary vascular prominence or pleural effusions. The echocardiogram is often diagnostic, demonstrating the characteristic findings of LV enlargement, decreased ventricular contractility, and occasionally a globular (remodeled) LV contour (see Fig. 466.1). RV enlargement and depressed function are occasionally noted. Echo Doppler studies can reveal evidence of pulmonary hypertension, mitral regurgitation, or other structural cardiac or coronary abnormalities. Cardiac MRI is useful for patients with suboptimal imaging echocardiographic windows or in patients with concern of acute myocarditis where, in contrast to echocardiography, recognition of inflammation of the myocardium is possible.

Additional testing may include complete blood count, renal and liver function tests, creatine phosphokinase (CPK), cardiac troponin I, lactate, brain natriuretic peptide (BNP), plasma amino acids, urine organic acids, and an acylcarnitine profile. Additional genetic and enzymatic testing may be useful (see Table 466.3). Cardiac catheterization and endomyocardial biopsy are not routine but may be useful in patients with acute DCM. Biopsy samples can be examined histologically for the presence of mononuclear cell infiltrates, myocardial damage, storage abnormalities, and for evidence of infection. It is considered standard of care to screen first-degree family members utilizing echocardiography and electrocardiogram (ECG) in idiopathic and familial cases of DCM.

Prognosis and Management

The 1 and 5 yr freedom from death or transplantation in patients diagnosed with DCM is 60–70% and 50–60%, respectively. Independent risk factors at DCM diagnosis for subsequent death or transplantation include older age, heart failure, lower LV fractional shortening *z* score, and underlying etiology. DCM is the most common cause for cardiac transplantation in pediatric and adult studies.

The therapeutic approach to patients with DCM includes a careful assessment to uncover possible treatable etiologies, screening of family members, and rigorous pharmacologic therapy. **Medications** aimed at reverse remodeling (improving ventricular size and function) include angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) plus β-adrenergic blockade with carvedilol or metoprolol. Each of these medications have proved independently and in combination to improve survival and symptoms and reduce hospital admissions in adults with DCM. Additionally, furosemide may be used to reduce symptoms of pulmonary or systemic venous congestion. Digoxin therapy can also be considered in some patients. Implantable cardiac defibrillators may be considered for certain select patients with a high risk of sudden cardiac arrest. **Pacemakers** , including dual-chamber and biventricular pacing therapy, can improve patients with certain underlying electrical derangements. In patients presenting with extreme degrees of heart failure or circulatory collapse, intensive care measures are often required, including intravenous inotropes and diuretics, mechanic ventilatory support, and on occasion, mechanical circulatory support, which may include ventricular assist device (VAD), total artificial heart, extracorporeal membrane oxygenation (ECMO), and ultimately cardiac transplantation. In patients with DCM and atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be instituted.

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466.2

Hypertrophic Cardiomyopathy

John J. Parent, Stephanie M. Ware

Keywords

asymmetric septal hypertrophy
sarcomere
Pompe disease
Noonan syndrome
diastolic dysfunction
syncope
fibrosis

Etiology and Epidemiology

Hypertrophic cardiomyopathy (**HCM**) is a heterogeneous, relatively common, and potentially life-threatening form of cardiomyopathy. The causes of HCM include inborn errors of metabolism, neuromuscular disorders, syndromic conditions, and genetic abnormalities of the structural components of the cardiomyocyte (see Tables 466.1 and 466.2). Both the age of onset and the associated features are helpful in identifying the underlying etiology.

HCM is a genetic disorder and frequently occurs because of mutations in sarcomere or cytoskeletal components of the cardiomyocyte (see Fig. 466.2).

Mutations of the genes encoding cardiac β-myosin heavy-chain *(MYH7)* and myosin-binding protein C *(MYBPC3)* are the most common (see Table 466.3). Mutations are inherited in an autosomal dominant pattern with a high penetrance but variable expressivity. Some patients have mutations in >1 sarcomere or cytoskeletal gene, and some speculate this may lead to earlier disease presentation, but this has not been proved. Additional genetic causes for HCM include nonsarcomeric protein mutations, such as the γ_2 -regulatory subunit of adenosine monophosphate–activated protein kinase *(PRKAG2)* and the lysosome-associated membrane protein 2α-galactosidase (**Danon disease** , a form of glycogen storage disease). Syndromic conditions, such as **Noonan syndrome** , may present with HCM at birth, and recognition of extracardiac manifestations is important in making the diagnosis.

Glycogen storage disorders such as **Pompe disease** often present in infancy with a heart murmur, abnormal ECG, systemic signs and symptoms, and occasionally heart failure. The characteristic ECG in Pompe disease demonstrates prominent P waves, a short P-R interval, and massive QRS voltages. The echocardiogram confirms severe, often concentric, LV hypertrophy.

Pathogenesis

HCM is characterized by the presence of increased LV wall thickness in the absence of structural heart disease or hypertension. Often the interventricular septum is disproportionately involved, leading to the previous designation of *idiopathic hypertrophic subaortic stenosis* or the current term of **asymmetric septal hypertrophy** . In the presence of a resting or provocable outflow tract gradient, the term **hypertrophic obstructive cardiomyopathy** is used. Although the left ventricle is predominantly affected, the right ventricle may be involved, particularly in infancy. The mitral valve can demonstrate systolic anterior motion and mitral insufficiency. Left ventricular outflow tract (LVOT) obstruction occurs in 25% of patients, is dynamic in nature, and may in part be secondary to the abnormal position of the mitral valve as well as the obstructing subaortic hypertrophic cardiac muscle. The cardiac myofibrils and myofilaments demonstrate disarray and myocardial fibrosis.

Typically, systolic function is preserved or even hyperdynamic, although systolic dysfunction may occur late and is a predictor for death or need for cardiac transplant. LVOT obstruction with or without mitral insufficiency may be provoked by physiologic manipulations such as the Valsalva maneuver, positional changes, and physical activity. Frequently, the hypertrophic and fibrotic cardiac muscle demonstrates relaxation abnormalities (diminished compliance), and LV filling may be impaired (diastolic dysfunction).

Clinical Manifestations

Many patients are asymptomatic, and 50% of cases present with a heart murmur or during screening when another family member has been diagnosed with HCM. Symptoms of HCM may include palpitations, chest pain, easy fatigability, dyspnea, dizziness, and syncope. Sudden death is a well-recognized but uncommon manifestation that occurs during physical exertion. Characteristic physical examination findings include an overactive precordial impulse with a lift or heave, a systolic ejection murmur in the aortic region *not* associated with an ejection click, and an apical blowing murmur of mitral insufficiency.

Diagnosis

The ECG typically demonstrates LV hypertrophy with ST segment and T-wave abnormalities (particularly T-wave inversion in the left precordial leads). Intraventricular conduction delays and signs of ventricular preexcitation (**Wolff-Parkinson-White syndrome**) may be present and should raise the possibility of Danon disease or Pompe disease. Chest radiography demonstrates normal or mildly increased heart size with a prominence of the left ventricle. Echocardiography is diagnostic in identifying, localizing, and quantifying the degree of myocardial hypertrophy (see Fig. 466.3). Doppler interrogation defines, localizes, and quantifies the degree of LVOT obstruction and also demonstrates and quantifies the degree of mitral insufficiency and diastolic dysfunction.

Cardiac catheterization is rarely used in diagnosis of HCM but may be helpful if there is concern for a **myocardial bridge** (when a coronary artery runs through vs on top of the myocardium) that may be causing intermittent coronary insufficiency during dynamic obstruction. Myocardial bridges can be seen on coronary angiography. Additionally, cardiac catheterization my occasionally be used to better define hemodynamics in patients.

Additional diagnostic studies include metabolic testing, genetic testing for specific syndromes, or genetic testing for mutations in genes known to cause isolated HCM (see Table 466.3). Clinical genetic testing panels continue to expand. Genetic diagnosis is also useful to identify at-risk family members who require ongoing surveillance.

Prognosis and Management

Children <1 yr of age or with inborn errors of metabolism or malformation syndromes or those with a mixed HCM/DCM have a significantly poorer prognosis. The risk of sudden death in older patients is greater in those with a personal or family history of cardiac arrest, ventricular tachycardia, exercise hypotension, syncope, or excessive (>3 cm) ventricular wall thickness. Although intrafamilial variability in symptoms occurs, a family history of sudden death is a highly significant predictor of risk. Restriction from competitive sports and strenuous physical activity is highly recommended, and additional recreational exercise activities should be tailored to each individual based on their overall clinical status. β-Adrenergic blocking agents (propranolol, atenolol, metoprolol) or calcium channel blockers (verapamil) may be useful in diminishing LVOT obstruction, modifying LV hypertrophy, and improving ventricular filling. They also confer an antiarrhythmic benefit and may reduce symptoms. In patients with atrial or ventricular arrhythmias, specific antiarrhythmic therapy should be used. Patients with documented, previously aborted sudden cardiac arrest, strong family histories of sudden death, ventricular wall end-diastolic dimensions of ≥3 cm, unexplained syncope, nonsustained ventricular tachycardia, or blunted or hypotensive blood pressure response to exercise should be treated with an **implantable cardioverter-defibrillator** (ICD). Early identification of HCM, family screening/surveillance, appropriate activity restriction, and utilization of ICDs have greatly reduced mortality of HCM to approximately 0.5% per year in the modern era.

Innovative interventional procedures have been used to reduce the degree of LVOT obstruction anatomically or physiologically. Dual-chamber pacing, alcohol septal ablation, surgical septal myomectomy, and mitral valve replacement have all met with some success but are typically reserved for patients with significant symptoms despite medical therapy (Fig. 466.5).

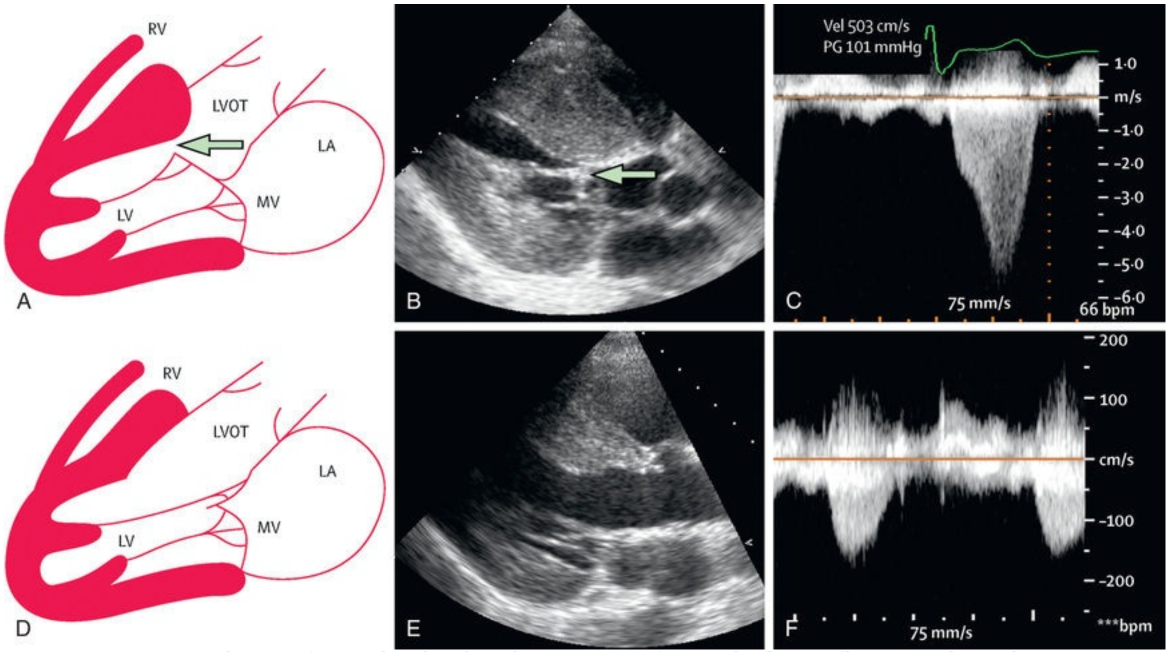

FIG. 466.5 Scheme of septal reduction therapy. A, Left ventricular outflow tract (LVOT) obstruction *(arrow)* created by hypertrophied basal septum and systolic anterior motion. B, Transthoracic echocardiography with systolic anterior motion *(arrow).* C, Continuous wave Doppler imaging of dynamic LVOT obstruction. D, Schematic finding after septal reduction. E, Transthoracic echocardiography after septal reduction procedure. F, Absence of LVOT obstruction in continuous wave Doppler imaging after septal reduction therapy. LA, Left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. (From Veselka J, Anavekar NS, Charron P: Hypertrophic obstructive cardiomyopathy, *Lancet* 389:1253–1264, 2017, Fig 5, p 1259.)

First-degree relatives of patients identified as having HCM should be screened with ECG and echocardiogram. Genetic testing is available clinically and is of high utility. It is important first to test the affected individual in the family rather than “at-risk” individuals, because 20–50% of cases of HCM will not demonstrate mutations in currently available panels of genes. If a causative mutation is identified, at-risk members of the family can be effectively tested. In families with HCM without demonstrable gene mutations, repeat noninvasive cardiac screening with ECG and echo should be undertaken in at-risk individuals yearly until young adulthood (age 21 yr) and then every 3-5 yr if no prior evidence of HCM is present. Gene-positive but phenotype-negative pediatric patients may remain asymptomatic during childhood but require careful and frequent follow-up.

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466.3

Restrictive Cardiomyopathy

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Keywords

diastolic heart failure
pulmonary hypertension
cardiac transplantation
arrhythmia

Etiology and Epidemiology

Restrictive cardiomyopathy (**RCM**) accounts for <5% of cardiomyopathy cases. Incidence increases with age and is more common in females. In equatorial Africa, RCM accounts for a large number of deaths. Infiltrative myocardial causes and storage disorders frequently result in associated LV hypertrophy and may represent HCM with restrictive physiology. Noninfiltrative causes include mutations in genes encoding sarcomeric or cytoskeletal proteins. Although there has been significant success in discovering new gene mutations causing RCM, the majority of cases are considered **idiopathic** .

Pathogenesis

RCM is characterized by normal ventricular chamber dimensions, normal myocardial wall thickness, and preserved systolic function. Dramatic atrial dilation can result from the abnormal ventricular myocardial compliance and high ventricular diastolic pressure. Autosomal dominant inheritance has been demonstrated for families with mutations in sarcomeric and cytoskeletal genes.

Clinical Manifestations

Abnormal ventricular filling, sometimes referred to as *diastolic heart failure,* is manifest in the systemic venous circulation with edema, hepatomegaly, or ascites. Elevation of left-sided filling pressures result in cough, dyspnea, or pulmonary edema. With activity, patients may experience chest pain, shortness of breath, syncope/near-syncope, or even sudden death. Pulmonary hypertension and pulmonary vascular disease develop and may progress rapidly. Heart murmurs are typically absent, but a gallop rhythm may be prominent. In the presence of pulmonary hypertension, an overactive RV impulse and pronounced pulmonary component of the second heart sound (S_2) are present in RCM.

Diagnosis

The characteristic electrocardiographic finding of prominent P waves is usually associated with normal QRS voltages and nonspecific ST and T-wave changes. RV hypertrophy occurs in patients with pulmonary hypertension. The chest radiograph may be normal or may demonstrate a prominent atrial shadow and pulmonary vascular redistribution. The echocardiogram is often diagnostic, demonstrating normal-sized ventricles with preserved systolic function and dramatic enlargement of the atria (see Fig. 466.4). Flow and tissue Doppler interrogation reveal abnormal filling parameters. It is critical to differentiate RCM from **constrictive pericarditis** , which can be treated surgically (see Chapter 467.2). MRI may be necessary to demonstrate the thickened or calcified pericardium often present in constrictive pericardial disease.

Prognosis and Management

Pharmacologic modalities are of limited use, and the prognosis of patients with RCM is generally poor, with often progressive clinical deterioration. Sudden death is a significant risk, with a 2 yr survival of 50%. When signs of heart failure exist, judicious use of diuretics can result in clinical improvement. As a result of the dramatic atrial enlargement and ventricular scarring, these patients are predisposed to the development of atrial tachyarrhythmias, complete heart block, and thromboemboli. Antiarrhythmic agents may be necessary, and anticoagulation with platelet inhibitors or warfarin (Coumadin) is indicated.

Cardiac transplantation is the treatment of choice in many centers for patients with RCM, and the results are excellent in patients without pulmonary hypertension, pulmonary vascular disease, or severe congestive heart failure. Some patients may need bridging to transplant with a VAD if they have elevate pulmonary pressures or significant heart failure.

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466.4

Left Ventricular Noncompaction,

Arrhythmogenic Right Ventricular Cardiomyopathy, Endocardial Fibroelastosis, and Takotsubo Cardiomyopathy

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John J. Parent, Stephanie M. Ware

Keywords

trabeculation
Barth syndrome
mitochondria
fibrofatty replacement
mumps

Left ventricular noncompaction (LVNC) is characterized by a distinctive trabeculated or spongy-appearing left ventricle commonly associated with LV dysfunction and/or dilation and at times hypertrophy, diastolic dysfunction, and arrhythmias (Fig. 466.6). LVNC may be isolated or associated with structural congenital cardiac defects. Patients may present with signs of heart failure, arrhythmias, syncope, sudden death, or as an asymptomatic finding during screening of family members. Whether LVNC represents a an actual cardiomyopathy or is a phenotypic trait associated with cardiomyopathy or congenital heart defects is controversial.

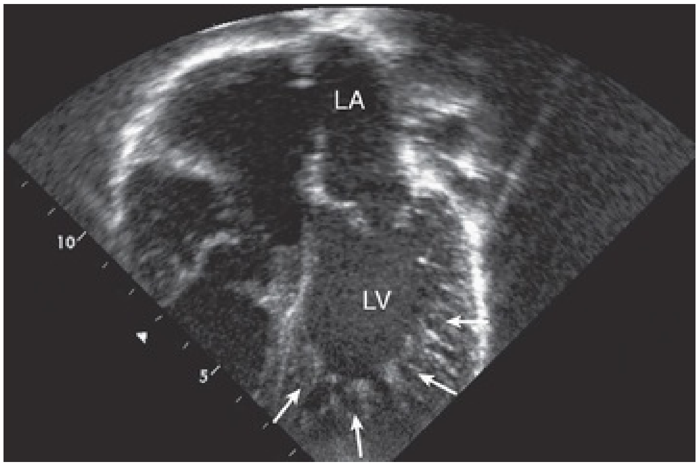

FIG. 466.6 **Echocardiogram of a patient with left ventricular noncompaction cardiomyopathy. Apical view showing abnormal trabeculations of left ventricle at the apex *(arrows).* For comparison, see the smooth-walled LV in Fig. 466.2 . LA, Left atrium; LV, left ventricle.**

Imaging studies using ultrasound or MRI can demonstrate the characteristic pattern of deeply trabeculated LV myocardium, most characteristically within the apex. ECG findings are nonspecific and include chamber hypertrophy, ST and T-wave changes, or arrhythmias. In some patients, preexcitation is notable, and giant QRS voltages occur in approximately 30% of younger children. Metabolic screening should be considered, especially in young children. Elevated serum lactate and urine 3-methylglutaconic acid may be seen in **Barth syndrome** , an X-linked disorder of phospholipid metabolism caused by a mutation in the tafazzin (*TAZ*) gene. Clinical testing for *TAZ* mutations is available and should be considered, especially in males. Patients with mitochondrial disorders frequently demonstrate signs of LVNC. These children are at risk for atrial or ventricular arrhythmias and thromboembolic complications. Treatment includes anticoagulation, antiarrhythmic therapy if needed, and treatment of heart failure if present. In patients refractory to medical therapy, cardiac transplantation has been used successfully.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is relatively uncommon in North America compared to the high prevalence in Europe, especially Italy. Autosomal dominant inheritance is common. In addition, recessive forms associated with severe ARVC and skin manifestations are known. Comprehensive genetic screening has been reported to identify a cause in up to 50% of cases. ARVC is typically characterized by a dilated right ventricle with fibrofatty infiltration of the RV wall; increasingly, LV involvement is being recognized. Global and regional RV and LV dysfunction and ventricular tachyarrhythmias are the major clinical findings. Syncope or aborted sudden death can occur and should be treated with antiarrhythmic medications and placement of an ICD. In patients with ventricular dysfunction, heart failure management as indicated for patients with DCM may be of use.

Endocardial fibroelastosis (EFE) , once an important cause of heart failure in children, is uncommon. The decline in primary EFE is likely related to the abolition of mumps virus infections by immunization practices. Rare familial cases exist, but the causative genes are unknown. Secondary EFE can occur with severe left-sided obstructive lesions such as aortic stenosis or atresia, hypoplastic left heart syndrome, or coarctation of the aorta. EFE is characterized by an opaque, white, fibroelastic thickening on the endocardial surface of the ventricle, which leads to systolic and/or diastolic dysfunction. Surgical removal of the endocardial fibrosis has been successfully done to improve cardiac function. Standard heart failure management, including transplantation, has been used in the management of EFE.

Takotsubo cardiomyopathy is a reversible stress-induced syndrome associated with transient systolic and diastolic dysfunction and regional ventricular wall motion abnormalities characterized by ventricular apical ballooning. Physical or emotional stress and associated etiologies (see Table 466.2) precipitate transient episodes of chest pain or heart failure. Treatment includes that for heart failure (β-blockers, ACE inhibitors, diuretics) and addressing the precipitating event (thyrotoxicosis, pheochromocytoma, drug ingestion).

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466.5

Myocarditis

John J. Parent, Stephanie M. Ware

Keywords

inflammation
coxsackievirus
myocyte necrosis
inotrope

Acute or chronic inflammation of the myocardium is characterized by inflammatory cell infiltrates, myocyte necrosis, or myocyte degeneration and may be caused by infectious, connective tissue, granulomatous, toxic, or idiopathic processes. There may be associated systemic manifestations of the disease, and occasionally the endocardium or pericardium is involved, but coronary pathology is uniformly absent. Patients may be asymptomatic, have nonspecific prodromal symptoms, or present with overt congestive heart failure, compromising arrhythmias, or sudden death. It is thought that **viral** infections are the most common etiology, although myocardial toxins, drug exposures, hypersensitivity reactions, and immune disorders may also lead to myocarditis (Table 466.7).

Table 466.7

Etiology of Myocarditis

Infectious Causes

Viral: adenoviruses, echoviruses, enteroviruses (e.g., coxsackieviruses), herpesviruses (human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), hepatitis C virus, human immunodeficiency virus, influenza A virus, parvovirus B19

Bacterial: *Chlamydia, Corynebacterium diphtheriae* , *Legionella, Mycobacterium tuberculosis* , *Mycoplasma, Staphylococcus,* streptococcus A, *Streptococcus pneumoniae* , Whipple disease

Fungal: *Actinomyces, Aspergillus, Candida, Cryptococcus*

Helminthic: *Echinococcus granulosus* , *Trichinella spiralis*

Protozoal: *Toxoplasma gondii* , *Trypanosoma cruzi*

Rickettsial: *Coxiella burnetii* , *Rickettsia typhi*

Spirochetal: *Borrelia burgdorferi* , *Leptospira, Treponema pallidum*

Autoimmune Diseases

Celiac disease, Churg-Strauss syndrome, Crohn disease, dermatomyositis, giant cell myocarditis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematosus, lymphofollicular myocarditis, rheumatoid arthritis, sarcoidosis, scleroderma, ulcerative colitis

Hypersensitivity Reactions

Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamides, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants

Toxic Reactions to Drugs

Amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab

Toxic

Ethanol, snakebite, scorpion bite, electric shock, spider bite

Other Causes

Arsenic, copper, iron, radiotherapy, thyrotoxicosis, immune modulation

Adapted from Canter CE, Simpson KE: Diagnosis and treatment of myocarditis in children in the current era, *Circulation* 129:115–128, 2014 (Table 1, p 116).

Etiology and Epidemiology

Viral Infections

Coxsackievirus and other enteroviruses, adenovirus, parvovirus B19, Epstein-Barr virus, parechovirus, influenza virus, and cytomegalovirus are the most common causative agents in children. In Asia, hepatitis C virus appears to be significant as well. The true incidence of viral myocarditis is unknown because mild cases probably go undetected. The disease is typically sporadic but may be epidemic. Manifestations are, to some degree, age dependent: in neonates and young infants, viral myocarditis can be fulminant; in children it often occurs as an acute, myopericarditis with heart failure; and in older children and adolescents it may present with signs and symptoms of acute or chronic heart failure or chest pain.

Bacterial Infections

Bacterial myocarditis has become much less common with the advent of advanced public health measures, which have minimized infectious causes such as diphtheria. **Diphtheritic myocarditis** is unique because bacterial toxin may produce circulatory collapse and toxic myocarditis characterized by atrioventricular block, bundle branch block, or ventricular ectopy (see Chapter 214). Any overwhelming systemic bacterial infection can manifest with circulatory collapse and shock with evidence of myocardial dysfunction, characterized by tachycardia, gallop rhythm, and low cardiac output. Additional nonviral infectious causes of myocarditis include rickettsiae, protozoa, parasitic infections, and fungal disease.

Pathophysiology

Myocarditis is characterized by myocardial inflammation, injury or necrosis, and ultimately fibrosis. Cardiac enlargement and diminished systolic function are a direct result of the myocardial damage. Typical signs of congestive heart failure occur and may progress rapidly to shock, atrial or ventricular arrhythmias, and sudden death. Viral myocarditis may also become a chronic process, with persistence of viral nucleic acid in the myocardium, and the perpetuation of chronic inflammation secondary to altered host immune response, including activated T lymphocytes (cytotoxic and natural killer cells) and antibody-dependent cell-mediated damage. Additionally, persistent viral infection may alter the expression of major histocompatibility complex (MHC) antigens with resultant exposure of neoantigens to the immune system. Some viral proteins share antigenic epitopes with host cells, resulting in autoimmune damage to the antigenically related myocyte. Cytokines such as tumor necrosis factor-α and interleukin-1 are inhibitors of myocyte response to adrenergic stimuli and result in diminished cardiac function. The final result of viral-associated inflammation can be DCM.

Clinical Manifestations

Manifestations of myocarditis range from asymptomatic or nonspecific generalized illness to acute cardiogenic shock and sudden death. Infants and young children more often have a fulminant presentation with fever, respiratory distress, tachycardia, hypotension, gallop rhythm, and cardiac murmur. Associated findings may include a rash or evidence of end organ involvement such as hepatitis or aseptic meningitis.

Patients with acute or chronic myocarditis may present with chest discomfort, fever, palpitations, easy fatigability, or syncope/near-syncope. Cardiac findings include overactive precordial impulse, gallop rhythm, and apical systolic murmur of mitral insufficiency. In patients with associated pericardial disease, a rub may be noted. Hepatic enlargement, peripheral edema, and pulmonary findings such as wheezes or rales may be present in patients with decompensated heart failure.

Diagnosis

Electrocardiographic changes are nonspecific and may include sinus tachycardia, atrial or ventricular arrhythmias, heart block, diminished QRS voltages, and nonspecific ST and T-wave changes, often suggestive of acute ischemia. Chest radiographs in severe, symptomatic cases reveal cardiomegaly, pulmonary vascular prominence, overt pulmonary edema, or pleural effusions. Echocardiography often shows diminished ventricular systolic function, cardiac chamber enlargement, mitral insufficiency, and occasionally, evidence of pericardial infusion.

Cardiac MRI is a standard imaging modality for the diagnosis of myocarditis; information on the presence and extent of edema, gadolinium-enhanced hyperemic capillary leak, myocyte necrosis, LV dysfunction, and evidence of an associated pericardial effusion assist in the cardiac MRI diagnosis of myocarditis (Table 466.8 and Fig. 466.7).

Table 466.8

MRI Findings Suggestive of Myocarditis

- T2-weighted edema (global or regional)
- Regional hyperemia/capillary leak by early gadolinium enhancement ratio (EGEr)
- Myocardial fibrosis or necrosis on late gadolinium enhancement (LGE)
- Features often present in a midmyocardial, subepicardial, and nonvascular distribution
- Repeat MRI if no *early* MRI evidence present but clinical manifestation suggests myocarditis

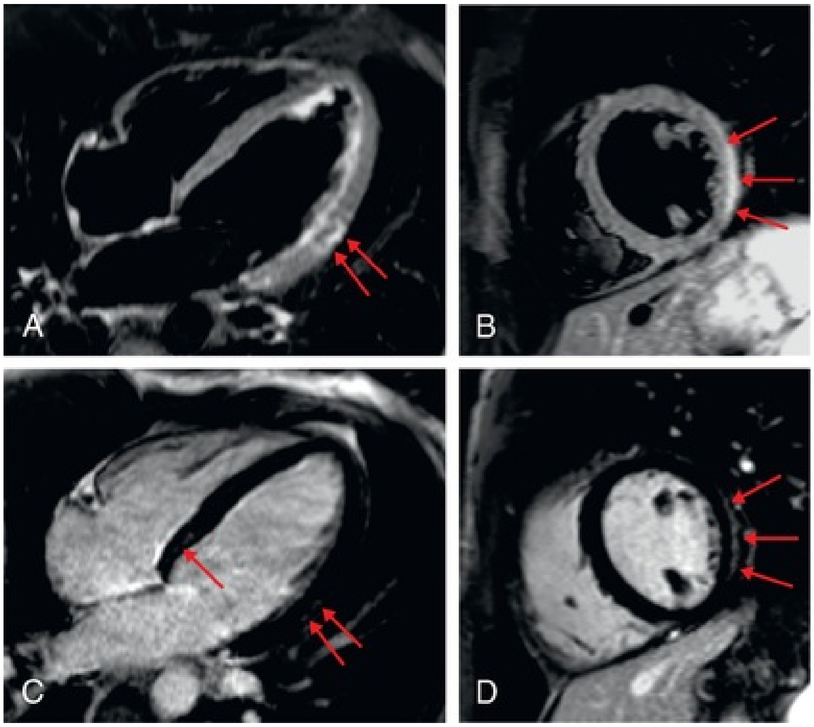

FIG. 466.7 **MRI findings in patients with myocarditis. Cardiac MR images of a young patient presenting with acute chest pain syndrome caused by acute myocarditis. A, Long axis, and B, short axis, T2-weighted images demonstrating focal myocardial edema in subepicardium of left midventricular lateral wall *(red arrows)* . Corresponding C, long axis, and D, short axis, T1-weighted images demonstrate presence of typical late gadolinium enhancement in subepicardium of left midventricular lateral wall and basal septum *(red arrows)* . (From Kindermann I, Barth C, Mahfoud F, et al: Update on myocarditis, *J Am Coll Cardiol* 59(9):779–792, 2012, Fig 3, p 783.)**

Endomyocardial biopsy may be useful in identifying inflammatory cell infiltrates or myocyte damage and performing molecular viral analysis using polymerase chain reaction techniques. Catheterization and biopsy, although not without risk (perforation and arrhythmias), should be performed by experienced personnel in patients suspected to have myocarditis, or if unusual forms of cardiomyopathy are strongly suspected, such as storage diseases or mitochondrial defects. Nonspecific tests include erythrocyte sedimentation rate, CPK isoenzymes, cardiac troponin I, and BNP levels.

Differential Diagnosis

The predominant diseases mimicking acute myocarditis include carnitine deficiency, other metabolic disorders of energy generation, hereditary mitochondrial defects, idiopathic DCM, pericarditis, EFE, and anomalies of the coronary arteries (see Table 466.2).

Treatment

Primary therapy for acute myocarditis is supportive, including β-blockers and ACE inhibitors (see Chapter 469). Acutely, the use of inotropic agents, preferably milrinone, should be considered but used with caution because of their proarrhythmic potential. Diuretics are often required as well. If in extremis, mechanical ventilatory support and mechanical circulatory support with VAD implantation or ECMO may be needed to stabilize the patient's hemodynamic status and serve as a bridge to recovery or cardiac transplantation. Diuretics, β-blockers, ACE inhibitors, and ARBs are of use in patients with compensated congestive heart failure in the outpatient setting, but may be contraindicated in those presenting with fulminant heart failure and cardiovascular collapse. In patients manifesting with significant atrial or ventricular arrhythmias, specific antiarrhythmic agents (e.g., amiodarone) should be administered and ICD placement considered.

Immunomodulation of patients with myocarditis is controversial. Intravenous immune globulin (IVIG) may have a role in the treatment of acute or fulminant myocarditis, and corticosteroids have been reported to improve cardiac function, but the data are not convincing in children. Relapse has been noted in patients receiving immunosuppression who were weaned from therapy. There are no studies to recommend specific antiviral therapies for myocarditis. Fulminant myocarditis has also been treated with ECMO or a VAD.

Prognosis

The prognosis of symptomatic acute myocarditis in newborns is poor, and a 75% mortality has been reported. The prognosis is better for children and adolescents, although patients who have persistent evidence of DCM often progress to need for cardiac transplantation. Recovery of ventricular function, however, has been reported in 10–50% of patients.

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CHAPTER 467

Diseases of the Pericardium

John J. Parent, Stephanie M. Ware

The heart is enveloped in a bilayer membrane, the *pericardium,* which normally contains a small amount of serous fluid. The pericardium is not vital to normal function of the heart, and primary diseases of the pericardium are uncommon. However, the pericardium may be affected by a variety of conditions, often as a manifestation of a systemic illness, and can result in serious, even life-threatening, cardiac compromise (Table 467.1).

Table 467.1

Etiology of Pericardial Disease

Congenital

Absence (partial, complete)
Cysts
Mulibrey nanism (*TRIM 37* gene mutation)
Camptodactyly-arthropathy–coxa vara–pericarditis syndrome (*PRG4* gene mutation)
Myhre syndrome (*SMAD4* gene mutation)

Infectious

Viral: coxsackievirus B, Epstein-Barr virus, influenza, adenovirus, parvovirus, HIV, mumps
Bacterial: *Haemophilus influenzae* , streptococcus, pneumococcus, staphylococcus, meningococcus, mycoplasma, tularemia, *Listeria,* leptospirosis, tuberculosis, Q fever, salmonella

Immune complex mediated: meningococcus, *H. influenzae*
Fungal: actinomycosis, histoplasmosis
Parasitic: toxoplasmosis, echinococcosis

Noninfectious

Idiopathic
Systemic inflammatory diseases: acute rheumatic fever, juvenile idiopathic arthritis, systemic lupus erythematosus, mixed connective tissue disorders, systemic sclerosis, Kawasaki disease, Churg-Strauss syndrome, Behçet syndrome, sarcoidosis, familial Mediterranean fever and other recurrent fever syndromes, pancreatitis, granulomatosis with polyangiitis
Metabolic: uremia, hypothyroidism, Gaucher disease, very-long-chain acyl-CoA dehydrogenase deficiency
Traumatic: surgical, catheter, blunt
Lymphomas, leukemia, radiation therapy
Primary pericardial tumors

467.1

Acute Pericarditis

John J. Parent, Stephanie M. Ware

Keywords

pericardial effusion
cardiac tamponade
purulent pericarditis
tuberculous pericarditis

postpericardiotomy syndrome

Pathogenesis

Inflammation of the pericardium may have only minor pathophysiologic consequences in the absence of significant fluid accumulation in the pericardial space. When the amount of fluid in the nondistensible pericardial space becomes excessive, pressure within the pericardium increases and is transmitted to the heart, resulting in impaired filling by compressing the chambers (atria or ventricles). Although small to moderate amounts of **pericardial effusion** can be well tolerated and clinically silent, once the noncompliant pericardium has been distended maximally, any further fluid accumulation causes abrupt impairment of cardiac filling and is termed **cardiac tamponade** . When untreated, tamponade can lead to shock and death. Pericardial effusions may be serous/transudative, exudative/purulent, fibrinous, or hemorrhagic.

Clinical Manifestations

The most common symptom of acute pericarditis is **chest pain** , typically described as sharp/stabbing, positional, radiating, worse with inspiration, and relieved by sitting upright or prone. Cough, fever, dyspnea, abdominal pain, and vomiting are nonspecific symptoms associated with pericarditis. Additionally, signs and symptoms of organ system involvement may occur in the presence of generalized systemic disease.

Muffled or distant heart sounds, tachycardia, narrow pulse pressure, jugular venous distention, and a pericardial friction rub provide clues to the diagnosis of acute pericarditis. Cardiac tamponade is recognized by the excessive fall of systolic blood pressure (>10 mm Hg) with inspiration. This pulsus paradoxus can be assessed by careful auscultatory blood pressure determination (automated blood pressure cuffs are inadequate), arterial pressure line waveform, or pulse oximeter tracing inspection. Conditions other than cardiac tamponade that may result in pulsus paradoxus include severe dyspnea, obesity, and positive pressure ventilator support.

Diagnosis

The electrocardiogram is often abnormal in acute pericarditis, although the findings are nonspecific. Low-voltage QRS amplitude may be seen as a result of pericardial fluid accumulation. Tachycardia and abnormalities of the ST segments (diffuse ST segment elevation), PR segments, and T waves (inversion or flattening) may be present as well.

Although the chest x-ray findings in a patient with pericarditis without effusion are usually normal in the presence of a significant effusion, cardiac enlargement will be seen and cardiac contour may be unusual (Erlenmeyer flask or water bottle appearance) (Fig. 467.1). Echocardiography is the most sensitive technique for identifying the size and location of a pericardial effusion. Compression and collapse of the right atrium and/or right ventricle are present with cardiac tamponade (Fig. 467.2). Abnormal diastolic filling parameters have also been described in cases of tamponade.

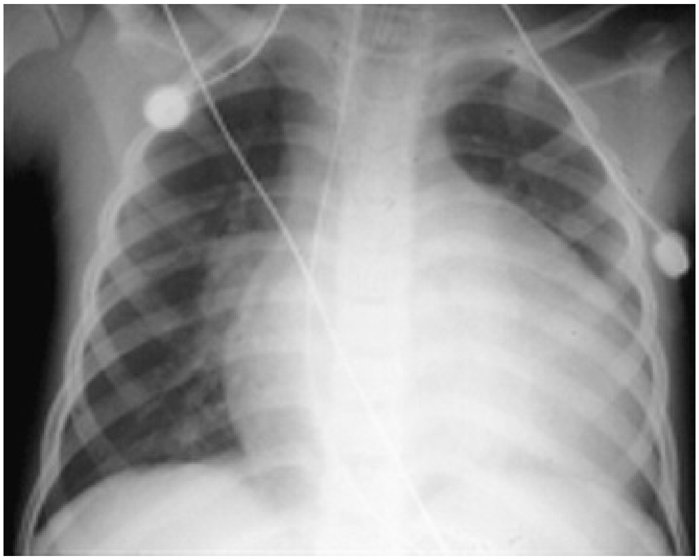

FIG. 467.1 “Water bottle” silhouette. This chest radiograph shows marked cardiomegaly, also known as a water bottle silhouette, which is seen in the presence of large pericardial effusions. Also note the associated pulmonary edema from associated high left atrial and left ventricular filling pressures. (Courtesy of Dr. Steven M. Selbst, Wilmington, DE; from Durani Y, Giordani K, Goudie BW: Myocarditis and pericarditis in children, *Pediatr Clin North Am* 57:1281–1303, 2010, Fig 7.)

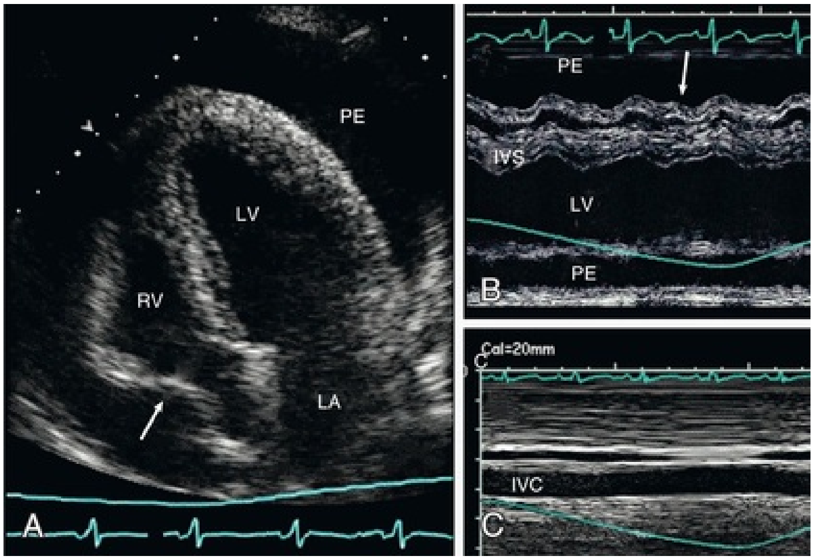

FIG. 467.2 Echocardiographic images of large pericardial effusion with features of tamponade. A, Apical 4-chamber view of LV, LA, and RV that shows large PE with diastolic right atrial collapse *(arrow)*. B, M-mode image with cursor placed through RV, IVS, and LV in parasternal long axis. The view shows circumferential PE with diastolic collapse of RV free wall *(arrow)* during expiration. C, M-mode image from subcostal window in same patient that shows IVC plethora without inspiratory collapse. IVC, Inferior vena cava; IVS, interventricular septum; LA, left atrium; LV, left ventricle; PE, pericardial effusion; RV, right ventricle. (From Troughton RW, Asher CR, Klein AL: Pericarditis, *Lancet* 363:717–727, 2004.)

Differential Diagnosis

Chest pain similar to that present in pericarditis can occur with lung diseases, especially pleuritis, and with gastroesophageal reflux or costochondritis, with the latter being reproducible on palpation. Pain related to myocardial ischemia is usually more severe and prolonged and occurs with exercise, allowing distinction from pericarditis-induced pain. The presence of a pericardial effusion by echocardiography is virtually diagnostic of pericarditis.

Infectious Pericarditis

A number of viral agents are known to cause pericarditis, and the clinical course of the majority of these infections is mild and spontaneously resolving. The term *acute benign pericarditis* is synonymous for viral pericarditis. Agents identified as causing pericarditis include the enteroviruses, influenza, adenovirus, respiratory syncytial virus, and parvovirus. Because the course of this illness is usually benign, symptomatic treatment with nonsteroidal antiinflammatory drugs

(NSAIDs) is often sufficient. Persistent or early recurrence episodes may need courses of corticosteroids. Patients with large effusions and tamponade may require **pericardiocentesis** . Presumed viral but often idiopathic pericarditis may have an autoimmune component. Up to 30% of patients may have recurrences of pericarditis. Treatment and prevention of recurrences with **colchicine** improve symptoms and avoid recurrences in most of these patients. Patients with idiopathic recurrent pericarditis may also respond to treatment with **anakinra** . If the condition becomes chronic or relapsing, surgical pericardiectomy or creation of a pericardial window may be necessary.

Echocardiography is useful in differentiating pericarditis from *myocarditis,* which will show evidence of diminished myocardial contractility or valvular dysfunction (see Chapter 466.5). Pericarditis and myocarditis may occur together in some cases of viral infection.

Purulent pericarditis , often caused by bacterial infections, has become much less common with the advent of new immunizations for *Haemophilus influenzae* and pneumococcal disease. Historically, purulent pericarditis was seen in association with severe pneumonias, epiglottitis, meningitis, or osteomyelitis. Patients with purulent pericarditis are acutely ill. Unless the infection is recognized and treated expeditiously, the course can be fulminant, leading to tamponade and death. **Tuberculous pericarditis** is rare in developed countries but can be a relatively common complication of HIV infection in regions where tuberculosis is endemic and access to antiretroviral therapy is limited. **Immune complex–mediated pericarditis** is a rare complication that may result in a nonpurulent (sterile) effusion following systemic bacterial infections such as meningococcus or *Haemophilus.*

Noninfectious Pericarditis

Systemic inflammatory diseases such as autoimmune, rheumatologic, and connective tissue disorders may involve the pericardium and result in serous pericardial effusions. Pericardial inflammation may be a component of the type II hypersensitivity reaction seen in patients with acute rheumatic fever. It is often associated with rheumatic valvulitis and responds quickly to antiinflammatory agents, including corticosteroids. Tamponade is very uncommon (see Chapters 210.1 and 465).

Juvenile idiopathic arthritis, usually systemic-onset disease, can manifest with pericarditis. Differentiating rheumatoid pericardial inflammation from that seen with systemic lupus erythematosus is difficult and requires careful rheumatologic evaluation. Aspirin and corticosteroids can result in rapid resolution of a pericardial effusion but may be needed on a chronic basis to prevent relapse. Many of the autoinflammatory recurrent fever syndromes present with pericarditis, usually with other manifestations of those disorders (see Chapter 188).

Patients with chronic renal failure or hypothyroidism may have pericardial effusions. Clinical suspicion warrants careful screening with physical examination and, if indicated, imaging studies during the course of their illness.

Especially common in referral centers with hematology/oncology units is the presence of pericardial effusion related to neoplastic disease. Conditions resulting in effusion include Hodgkin disease, lymphomas, and leukemia. Radiation therapy directed to the mediastinum of patients with malignancy can result in pericarditis and later constrictive pericardial disease.

The **postpericardiotomy syndrome** occurs in patients having undergone cardiac surgery and is characterized by fever, lethargy, anorexia, irritability, and chest/abdominal discomfort beginning 1-4 wk postoperatively. There can be associated pleural effusions and serologic evidence of elevated antiheart antibodies. Postpericardiotomy syndrome is effectively treated with aspirin, NSAIDs, and in severe cases, corticosteroids. Pericardial drainage is necessary in those patients with cardiac tamponade.

In many patients the etiology of pericarditis is not known. Approximately 30% of these patients have multiple occurrences and are treated with colchicine to reduce the risk of recurrent pericarditis. Other treatments have included NSAIDs and corticosteroids. Refractory idiopathic recurrent pericarditis may require pericardiectomy; anakinra has demonstrated promise to treat steroid-dependent patients.

467.2

Constrictive Pericarditis

John J. Parent, Stephanie M. Ware

Keywords

fibrosis
pericardial calcification
malignancy

Rarely, chronic pericardial inflammation can result in fibrosis, calcification, and thickening of the pericardium. Pericardial scarring may lead to impaired cardiac distensibility and filling and is termed *constrictive pericarditis*. Constrictive pericarditis can result from recurrent or chronic pericarditis, cardiac surgery, or radiation to the mediastinum as a treatment for malignancies, most often Hodgkin disease or lymphoma.

Clinical manifestations of systemic venous hypertension predominate in cases of restrictive pericarditis. Jugular venous distention, peripheral edema, hepatomegaly, and ascites may precede signs of more significant cardiac compromise, such as tachycardia, hypotension, and pulsus paradoxus. A pericardial knock, rub, and distant heart sounds might be present on auscultation. Abnormalities of liver function tests, hypoalbuminemia, hypoproteinemia, and lymphopenia may be present. On occasion, chest radiographs demonstrate calcifications of the pericardium.

Constrictive pericarditis may be difficult to distinguish clinically from **restrictive cardiomyopathy** because both conditions result in impaired myocardial filling (see Chapter 466.3). Echocardiography may be helpful in distinguishing constrictive pericardial disease from restrictive cardiomyopathy, but MRI and CT are more sensitive in detecting abnormalities of the pericardium. In rare cases, exploratory thoracotomy with direct examination of the pericardium may be required to confirm the diagnosis.

Although acute pericardial constriction is reported to respond to antiinflammatory agents, the more typical chronic constrictive pericarditis will respond only to pericardiectomy with extensive resection of the pericardium.

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CHAPTER 468

Tumors of the Heart

John J. Parent, Stephanie M. Ware

Although cardiac tumors occur rarely in pediatric patients, they may result in serious hemodynamic or electrophysiologic abnormalities depending on tumor type and location.

The vast majority of tumors originating from the heart are benign. **Rhabdomyomas** are the most common pediatric cardiac tumors and are associated with tuberous sclerosis in 70–95% of cases (see Chapter 614.2). Rhabdomyomas may occur at any age, from fetal life through late adolescence. They are often multiple, can occur in any cardiac chamber, and originate within the myocardium, often extending into the atrial or ventricular cavities (Fig. 468.1). Depending on their location and size, rhabdomyomas can result in inflow or outflow obstruction, leading to cyanosis or cardiac failure; many are asymptomatic. Atrial and ventricular arrhythmias have been reported with rhabdomyomas, and on occasion, ventricular preexcitation (Wolff-Parkinson-White syndrome) is present on electrocardiogram (ECG).

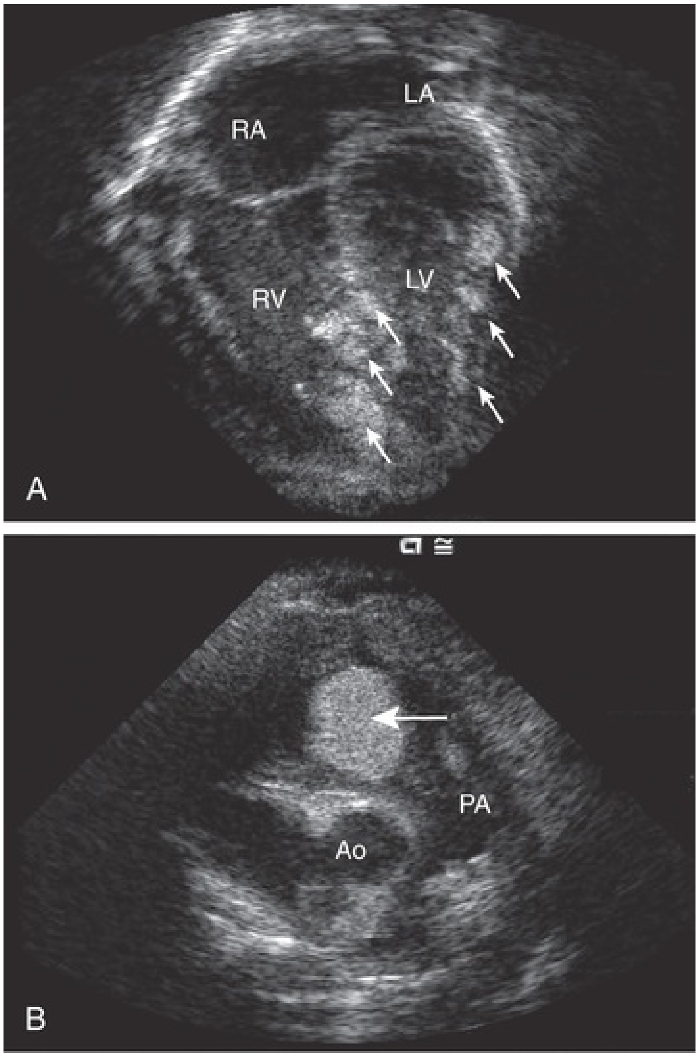

FIG. 468.1 **Echocardiograms demonstrating rhabdomyomas. A, Apical 4-chamber view showing multiple rhabdomyomas *(arrows)* within the septum and left ventricular myocardium. B, Short axis view showing a large rhabdomyoma *(arrow)* extending into the right ventricular outflow tract. Ao, Ascending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.**

Fibromas are the 2nd most common pediatric cardiac tumor and, in contrast to rhabdomyomas, are usually solitary and intramyocardial. The size and location of fibromas can lead to heart failure, cyanosis, or rhythm disturbances. Loss of the tumor suppressor *PTCH1* is associated with the development of cardiac fibromas in sporadic cases. There is an increased incidence in patients with **Gorlin syndrome** (3%).

Myxomas , the most common cardiac tumor seen in adults, occur infrequently in the pediatric population. Myxomas are predominantly intraatrial, appear pedunculated, and are rather mobile. They may cause obstruction to inflow or outflow and may present with a murmur, heart failure, or syncope. On occasion, atrial myxomas are associated with systemic symptoms of fever, malaise, and arthralgia. **Carney complex** is a familial autosomal dominant multiple neoplasia (often endocrine: pituitary adenoma, thyroid, testis, ovarian) and lentiginosis syndrome in which cardiac myxomas can occur at a young age in any or all cardiac chambers. Pathogenic variants in the *PRKAR1A* gene are causative in some families.

Other benign tumors include hemangiomas, Purkinje cell tumors, papillomas, lipomas, and mesotheliomas. Depending on their location, these benign tumors can result in valvular function abnormalities, myocardial dysfunction, or heart block and other arrhythmias.

Malignant pediatric cardiac tumors are much less common than benign tumors (75% vs 25%), and the vast majority of such malignancies are sarcomas, including angiosarcomas, rhabdosarcomas, or fibrosarcomas. Lymphomas and pheochromocytomas are reported but rare. Tumors originating from noncardiac sources that invade, extend, or metastasize to the heart are more frequently seen than primary malignant cardiac tumors. In pediatric patients, **Wilms tumor** and lymphoma/leukemia are the most common causes of such secondary tumors.

Although the manifestations of cardiac tumors in pediatric patients are protean, when a tumor is suspected, noninvasive imaging with echocardiography and/or MRI may be diagnostic and can determine tumor type, location, extent, and hemodynamic impact. ECG and Holter studies are valuable adjuncts when rhythm abnormalities are suspected. Cardiac catheterization is rarely indicated but may be used to confirm tumor location, assess intracardiac hemodynamics, and perform biopsy for histologic assessment. Such risks as blood loss, perforation, arrhythmia, and vessel injury should be considered when discussing catheterization and biopsy.

Because the natural history of rhabdomyomas is one of spontaneous diminution or complete resolution, **treatment** of the majority of cardiac tumors in pediatric patients is usually unnecessary. *Everolimus*, an inhibitor of the mammalian target of rapamycin (mTOR), may enhance resolution in symptomatic patients with cardiac rhabdomyomas. Careful clinical follow-up and imaging are important. Antiarrhythmic medications may be prescribed to control rhythm disorders. Surgical removal of a cardiac tumor may be indicated to relieve obstruction, improve myocardial or valve function, or control arrhythmias. Heart transplantation has been performed in cases of unresectable tumors with significant hemodynamic compromise. Wilms tumors extending from the inferior vena cava into the atrium may require cardiopulmonary bypass support during the course of primary resection of the renal tumor. Radiation or chemotherapy can improve cardiac function in rare cases of lymphoma or leukemia compressing the heart with hemodynamic compromise.

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SECTION 7

Cardiac Therapeutics

OUTLINE

Chapter 469 Heart Failure
Chapter 470 Pediatric Heart and Heart-Lung Transplantation

CHAPTER 469

Heart Failure

Joseph W. Rossano

The International Society for Heart and Lung Transplantation (ISHLT) defines heart failure as follows:

> *A clinical and pathological syndrome that results from ventricular dysfunction, volume, or pressure overload, alone or in combination. It leads to characteristic signs and symptoms, such as poor growth, feeding difficulties, respiratory distress, exercise intolerance, and fatigue, and is associated with circulatory, neurohormonal, and molecular abnormalities. Heart failure has numerous etiologies that are a consequence of cardiac and noncardiac disorders, either congenital or acquired.*

Pathophysiology

The heart can be viewed as a pump with an output proportional to its filling volume and inversely proportional to the resistance against which it pumps. As ventricular end-diastolic volume increases, a healthy heart increases cardiac output until a maximum is reached and cardiac output can no longer be augmented (the **Frank-Starling principle** ; Fig. 469.1). The increased stroke volume obtained in this manner is a result of stretching of myocardial fibers, but it also results in increased wall tension, which elevates myocardial oxygen consumption. Hearts working under various types of stress function along different Frank-Starling curves. Cardiac muscle with compromised intrinsic contractility requires a greater degree of dilation to produce increased stroke volume and does not achieve the same maximal cardiac output as normal myocardium does. If a cardiac chamber is already dilated because of a lesion causing increased preload (e.g., a left-to-right shunt or valvular insufficiency), there is little room for further dilation as a means of augmenting cardiac output. The presence of lesions that result in increased afterload to the ventricle (e.g., aortic or pulmonic stenosis, coarctation of the aorta) decreases cardiac performance, thereby resulting in a depressed Frank-Starling relationship.

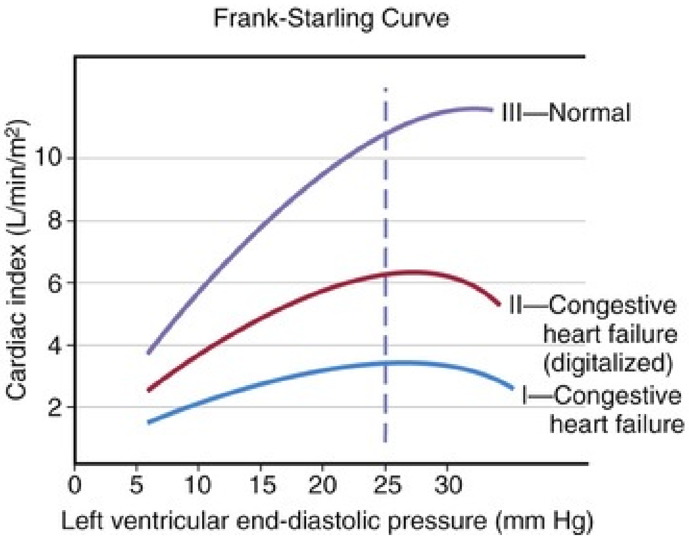

FIG. 469.1 **The Frank-Starling relationship. As left ventricular end-diastolic (LVED) pressure increases, the cardiac index increases, even in the presence of congestive heart failure, until a critical level of LVED pressure is reached. Adding an inotropic agent (digoxin) shifts the curve from I to II. (From Gersony WM, Steep CN. In Dickerman JD, Lucey JF, editors: *Smith's The critically ill child: diagnosis and medical management,* ed 3, Philadelphia, 1984, Saunders.)**

Systemic oxygen transport is calculated as the product of cardiac output and systemic oxygen content. **Cardiac output** can be calculated as the product of heart rate and stroke volume. The primary determinants of stroke volume are the *afterload* (pressure work), *preload* (volume work), and *contractility* (intrinsic myocardial function). Abnormalities in heart rate can also compromise cardiac output; for example, tachyarrhythmias shorten the diastolic time interval for ventricular filling. Alterations in the oxygen-carrying capacity of blood (e.g., anemia or hypoxemia) also lead to a decrease in systemic oxygen transport and, if compensatory mechanisms are inadequate, can result in decreased delivery of substrate to tissues.

In some cases of heart failure, cardiac output is normal or increased, yet because of decreased systemic oxygen content (e.g., secondary to anemia) or increased oxygen demands (e.g., secondary to hyperventilation, hyperthyroidism, or hypermetabolism), an inadequate amount of oxygen is delivered to meet the body's needs. This condition, **high-output failure** , results in the development of signs and symptoms of heart failure when there is no basic abnormality in myocardial function and cardiac output is greater than normal. It is also seen with large systemic arteriovenous fistulas (e.g., vein of Galen malformation). These conditions reduce peripheral vascular resistance and cardiac afterload and increase myocardial contractility. Heart failure results when the demand for cardiac output exceeds the ability of the heart to respond. Chronic severe high-output failure may eventually result in a decrease in myocardial performance as the metabolic requirements of the myocardium are not met.

There are multiple systemic compensatory mechanisms used by the body to adapt to chronic heart failure. Some are mediated at the molecular/cellular level, such as upregulation or downregulation of various metabolic pathway components leading to changes in efficiency of oxygen and other substrate utilizations. Others are mediated by neurohormones such as the renin-angiotensin system and the sympathoadrenal axis. One of the principal mechanisms for increasing cardiac output is an increase in sympathetic tone secondary to increased secretion of circulating epinephrine by the adrenals and increased release of norepinephrine at the neuromuscular junction. The *initial* beneficial effects of sympathetic stimulation include an increase in heart rate and myocardial contractility, mediated by these hormones’ action on cardiac β-adrenergic receptors, increasing cardiac output. These hormones also cause vasoconstriction, mediated by their action on peripheral arterial α-adrenergic receptors. Some vascular beds may constrict more readily than others, so that blood flow is redistributed from the cutaneous, visceral, and renal beds to the heart and brain. Whereas these acute effects are beneficial, *chronically* increased sympathetic stimulation can have deleterious effects, including hypermetabolism, increased afterload, arrhythmogenesis, and increased myocardial oxygen requirements. Peripheral vasoconstriction can result in decreased renal, hepatic, and gastrointestinal tract function. Chronic exposure to circulating catecholamines leads to a decrease in the number of cardiac β-adrenergic receptors (downregulation) and also causes direct myocardial cell damage. Therapeutic agents for heart failure are directed at restoring balance to these neuroendocrine systems.

Clinical Manifestations

The clinical manifestations of heart failure depend in part on the degree of the child's cardiac reserve. A critically ill infant or child who has exhausted the compensatory mechanisms to the point that cardiac output is no longer sufficient to meet the basal metabolic needs of the body may present in **cardiogenic shock** . Other patients may be comfortable when quiet but are incapable of increasing cardiac output in response to even mild activity without experiencing significant symptoms. Conversely, it may take rather vigorous exercise to compromise cardiac function in children who have less severe heart disease.

A thorough **history** is extremely important in making the diagnosis of heart failure and in evaluating the possible causes. Parents who observe their child on a daily basis may not recognize subtle changes that have occurred over the course of days or weeks. Gradually worsening perfusion or increasing respiratory effort may not be recognized as an abnormal finding. Edema, which is general absent in infants and young children, may be passed off as normal weight gain, and exercise intolerance as lack of interest in an activity. The history of a young infant should also focus on **feeding** . An infant with heart failure often takes less volume per feeding, becomes dyspneic while sucking, and may perspire profusely. Eliciting a history of fatigue in an older child requires detailed questions about activity level and its course over several months.

In children, the signs and symptoms of heart failure may be similar to those in adults and include fatigue, effort intolerance, anorexia, dyspnea, edema, and cough. Many children, however, may have primarily abdominal symptoms (abdominal pain, nausea, anorexia) and a surprising lack of respiratory complaints. Attention to the cardiovascular system may come only after an abdominal radiograph unexpectedly catches the lower end of an enlarged heart. The elevation in systemic venous pressure may be gauged by clinical assessment of jugular venous pressure and liver enlargement. Orthopnea and basilar rales are variably present; edema is usually discernible in dependent portions of the body, or anasarca may be present. Cardiomegaly is invariably noted. A **gallop rhythm** is common; when ventricular dilation is advanced, the **holosystolic murmur** of mitral or tricuspid valve regurgitation may be heard.

In infants, heart failure may be difficult to distinguish from other causes of respiratory distress. Prominent manifestations of heart failure include tachypnea, feeding difficulties, poor weight gain, excessive perspiration, irritability, weak cry, and noisy, labored respirations with intercostal and subcostal retractions, as well as flaring of the alae nasi. The signs of cardiac-induced pulmonary congestion may be indistinguishable from those of bronchiolitis; wheezing is often a more prominent finding in young infants with heart failure than rales. Pneumonitis with or without atelectasis is common as result of bronchial compression by the enlarged heart. Hepatomegaly usually occurs, and cardiomegaly is invariably present. Despite pronounced tachycardia, a gallop rhythm can frequently be recognized. The other auscultatory signs are those produced by the underlying cardiac lesion. Clinical assessment of jugular venous pressure in infants may be difficult because of the shortness of the neck and the difficulty of observing a relaxed state; palpation of an enlarged liver is a more reliable sign. The etiologies of heart failure are age dependent (Table 469.1).

Table 469.1

Etiology of Heart Failure

Fetal

Severe anemia (hemolysis, fetal-maternal transfusion, parvovirus B19–induced anemia, hypoplastic anemia)
Supraventricular tachycardia
Ventricular tachycardia
Complete heart block
Severe Ebstein anomaly or other severe right-sided lesions
Myocarditis

Premature Neonate

Fluid overload
Patent ductus arteriosus
Ventricular septal defect
Cor pulmonale (bronchopulmonary dysplasia)
Hypertension
Myocarditis
Genetic/metabolic cardiomyopathy

Full-Term Neonate

Asphyxial cardiomyopathy
Arteriovenous malformation (vein of Galen, hepatic)
Left-sided obstructive lesions (coarctation of aorta, hypoplastic left heart syndrome)
Large mixing cardiac defects (single ventricle, truncus arteriosus)
Myocarditis
Genetic/metabolic cardiomyopathy

Infant-Toddler

Left-to-right cardiac shunts (ventricular septal defect)
Hemangioma (arteriovenous malformation)
Anomalous left coronary artery
Genetic/metabolic cardiomyopathy
Acute hypertension (hemolytic-uremic syndrome)
Supraventricular tachycardia
Kawasaki disease
Myocarditis

Child-Adolescent

Congenital heart disease (various forms including single-ventricle heart disease)
Rheumatic fever
Acute hypertension (glomerulonephritis)
Myocarditis
Thyrotoxicosis
Hemochromatosis-hemosiderosis
Cancer therapy (radiation, doxorubicin)
Sickle cell anemia
Endocarditis
Cor pulmonale (cystic fibrosis)
Genetic/metabolic cardiomyopathy (hypertrophic, dilated)

Diagnosis

X-ray films of the chest show cardiac enlargement. Pulmonary vascularity is variable and depends on the cause of the heart failure. Infants and children with large left-to-right shunts have exaggeration of the pulmonary arterial vessels to the periphery of the lung fields, whereas patients with cardiomyopathy may have a relatively normal pulmonary vascular bed early in the course of disease. Fluffy perihilar pulmonary markings suggestive of venous congestion and acute pulmonary edema are seen only with more severe degrees of heart failure. Cardiac enlargement is often noted as an unexpected finding on a chest radiography performed to evaluate for a possible pulmonary infection, bronchiolitis, or asthma.

Chamber hypertrophy noted by electrocardiography may be helpful in assessing the cause of heart failure but does not establish the diagnosis. In cardiomyopathies, left or right ventricular ischemic changes may correlate with other noninvasive parameters of ventricular function. Low-voltage QRS morphologic characteristics with ST-T–wave abnormalities may also suggest myocardial inflammatory disease but can be seen with pericarditis as well. The **electrocardiogram** (ECG) is the best tool for evaluating rhythm disorders as a potential cause of heart failure, especially tachyarrhythmias.

Echocardiography is the standard technique for assessing ventricular function. Ventricular function as be quantitated simply and reliably with commonly used parameters such as fractional shortening (a single-dimensional variable) and an ejection fraction. The *fractional shortening* is determined as the difference between end-systolic and end-diastolic diameter divided by end-diastolic diameter. Normal fractional shortening is between approximately 28% and 42%. The *ejection fraction* uses 2-dimensional data to calculate a 3-dimensional volume; the normal range is 55–65%. In children with right ventricular enlargement or other cardiac pathology resulting in flattening of the interventricular septum, ejection fraction is used because fractional shortening measured in the standard echocardiographic short axis view will not be accurate. Doppler studies can also be used to estimate cardiac output. Doppler assessment of transmitral flow can also be used as a noninvasive assessment of diastolic function. Magnetic resonance angiography (MRA) is also very useful in quantifying left and right ventricular function, volume, and mass as well as coronary artery anatomy. If valvular regurgitation is present, MRA can quantify the regurgitant fraction.

Arterial oxygen levels may be decreased when ventilation-perfusion inequalities occur secondary to pulmonary edema. When heart failure is severe, respiratory acidosis or metabolic acidosis, or both, may be present. Infants with heart failure often display hyponatremia as a result of renal water retention. Chronic diuretic treatment can decrease serum sodium levels further. Serum **B-type (brain) natriuretic peptide (BNP)** (or N-terminal pro-BNP), a cardiac neurohormone released in response to increased ventricular wall tension, is elevated in patients with heart failure. In children, BNP may be elevated in patients with heart failure as a result of systolic dysfunction (e.g., cardiomyopathy), as well as in children with volume overload (e.g., left-to-right shunts such as ventricular septal defect). Table 469.2 lists other causes of an elevated BNP.

Table 469.2

Caused of Elevated Concentrations of Natriuretic Peptides

Cardiac

- Heart failure (HFpEF, HFrEF)
- Acute coronary symptoms
- Pulmonary embolism
- Myocarditis
- Left ventricular hypertrophy
- Hypertrophic or restrictive cardiomyopathy
- Valvular heart disease
- Congenital heart disease
- Atrial and ventricular tachyarrhythmias
- Heart contusion
- Cardioversion ICD shock
- Surgical procedures involving the heart
- Pulmonary hypertension

Noncardiac

- Ischemic stroke
- Subarachnoid hemorrhage
- Renal dysfunction

Liver dysfunction (mainly liver cirrhosis with ascites)
Paraneoplastic syndrome
Chronic obstructive pulmonary disease
Severe infections (including pneumonia and sepsis)
Severe burns
Anemia
Severe metabolic and hormone abnormalities (e.g., thyrotoxicosis, diabetic ketosis)

HFpEF, Heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator.

Adapted from Ponikowski P, Voors AA, Anker SD, et al: 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure, Eur Heart J 37(27):2129–2200, 2016 (Table 12-3, p 2175).

Treatment

The underlying cause of cardiac failure must be removed or alleviated if possible. If the cause is a congenital cardiac anomaly amenable to surgery, medical treatment of the heart failure is indicated to prepare the patient for surgery. With the current excellent outcomes of primary surgical repair of congenital heart defects, even in the neonatal period, few children require aggressive heart failure management to grow big enough for surgery. In contrast, if the cause of heart failure is cardiomyopathy, medical management provides temporary relief from symptoms and may allow the patient to recover if the insult is reversible (e.g., myocarditis). If the lesion is not reversible, heart failure management usually allows the child to return to normal activities for some period and to delay, sometimes for months or years, the need for heart transplantation.

General Measures

Strict bed rest is rarely necessary except in extreme cases, but it is important that the child be allowed to rest during the day as needed and sleep adequately at night. Some older patients feel better sleeping in a semi-upright position, using several pillows (**orthopnea**). As patients respond to treatment, restrictions on activities can often be modified within the context of the specific diagnosis and the patient's ability. Formal **cardiopulmonary exercise** testing can be used to assess the patient's ability to perform exercise in a controlled environment and is useful for recommending rational exercise restrictions. For patients with pulmonary edema, positive pressure ventilation (PPV) may be required along with other drug therapies. For those in low-output heart failure, PPV can significantly reduce total body oxygen consumption by eliminating the work of breathing and help to reverse metabolic acidosis. β-Adrenergic agonists such as dopamine, dobutamine, and epinephrine may be needed in combination with phosphodiesterase inhibitors such as milrinone for patients with markedly advanced heart failure and cardiogenic shock. If the blood pressure will permit, afterload-reducing agents such as nitroprusside, angiotensin-converting enzyme inhibitors (**ACEIs**), or angiotensin receptor blockers (**ARBs**) may be beneficial. These agents are initiated in an intensive care setting with proper invasive monitoring of central venous and arterial blood pressure.

Diet

Infants with heart failure usually fail to thrive because of a combination of increased metabolic demands and decreased caloric intake. Increasing daily calories is an important aspect of their management. Increasing the number of calories per ounce of infant formula (or supplementing breastfeeding) may be beneficial. Many infants do not tolerate an increase beyond 24 calories/oz because of diarrhea or because these formulas provide too large a solute load for compromised kidneys.

Severely ill infants and children may lack sufficient strength for effective sucking because of extreme fatigue, rapid respirations, and generalized weakness. In these circumstances, nasogastric feedings may be helpful. In many patients with cardiac enlargement, **gastroesophageal reflux** is a major problem. The use of continuous drip nasogastric feedings at night, administered by pump, may improve caloric intake while decreasing problems with reflux. Occasionally, especially in infants with heart failure caused by complex congenital heart disease, medical or surgical intervention to correct reflux is necessary (Nissen fundoplication). Continued **malnutrition** may be an important factor in the decision to undertake earlier surgical intervention in patients who have an operable congenital heart lesion or to proceed with mechanical circulatory support and/or listing for transplantation in patients with cardiomyopathy.

The use of low-sodium formulas in the routine management of infants with heart failure is not recommended because these preparations are often poorly tolerated and may exacerbate diuretic-induced hyponatremia. Human breast milk is the ideal low-sodium nutritional source. The use of more potent diuretic agents allows more palatable standard formulas to be used for nutrition while controlling salt and water balance by chronic diuretic administration. Most older children can be managed with “no added salt” diets and abstinence from foods containing large amounts of sodium. A strict, extremely-low-sodium diet is rarely required or followed.

Diuretics

Diuretics interfere with reabsorption of water and sodium by the kidneys, which results in a reduction in circulating blood volume and thereby reduces pulmonary fluid overload and ventricular filling pressure. Diuretics are usually the first mode of therapy initiated in patients with congestive heart failure.

Furosemide is the most commonly used diuretic in pediatric patients with heart failure. It inhibits the reabsorption of sodium and chloride in the distal tubules and the loop of Henle. Patients requiring acute diuresis should be given intravenous (IV) or intramuscular (IM) furosemide at an initial dose of 1-2 mg/kg, which usually results in rapid diuresis and prompt improvement in clinical status, particularly if symptoms of pulmonary congestion are present. Chronic furosemide therapy is then prescribed at a dose of 1-4 mg/kg/24 hr given between 1 and 4 times a day. Careful monitoring of electrolytes is necessary with long-term furosemide therapy because of the potential for significant loss of potassium. Potassium chloride supplementation is usually required unless the potassium-sparing diuretics are given concomitantly. Chronic administration of furosemide may cause contraction of the extracellular fluid compartment and result in “contraction alkalosis” (see Chapter 68.7). Diuretic-induced hyponatremia may become difficult to manage in patients with severe heart failure.

Spironolactone is an inhibitor of aldosterone and enhances potassium retention, often eliminating the need for oral potassium supplementation, which is frequently poorly tolerated. This drug is usually given orally in 2 divided doses of 2 mg/kg/24 hr. Combinations of spironolactone and chlorothiazide are sometimes used for convenience. Adults with heart failure have improved survival when an aldosterone inhibitor is included in the diuretic regimen, likely through multiple effects, including a favorable effect on cardiac fibrosis. Eplerenone is an alternative to spironolactone and does not have the side effect of gynecomastia.

Chlorothiazide is also used for diuresis in children with heart failure. It is less immediate in action and less potent than furosemide, and it affects the reabsorption of electrolytes in the renal tubules only. The usual dose is 10-40 mg/kg/24 hr in 2 divided doses. Potassium supplementation is often required if chlorothiazide is used alone.

Afterload Reducers, Including Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

The ACEIs and ARBs reduce ventricular afterload by decreasing peripheral vascular resistance and thereby improving myocardial performance. Some of these agents also decrease systemic venous tone, which significantly reduces preload. Afterload reducers may be useful in children with heart failure secondary to cardiomyopathy and in patients with severe mitral or aortic insufficiency. They may also be effective in patients with heart failure caused by left-to-right shunts. ACEIs and ARBs may have additional beneficial effects on cardiac remodeling independent of their influence on afterload by directly influencing cardiac intracellular signaling pathways. In adult patients with dilated cardiomyopathy, the addition of an ACEI to standard medical therapy reduces both morbidity and mortality. Afterload-reducing agents are most often used in conjunction with other anticongestive drugs such as diuretics and, in some patients, digoxin.

Intravenously administered agents such as **nitroprusside** should be administered only in an intensive care setting and for as short a time as possible. Nitroprusside's short IV half-life makes it ideal for titrating the dose in critically ill patients. Peripheral arterial vasodilation and afterload reduction are the major effects, but venodilation causing a decrease in venous return to the heart may also be beneficial. Blood pressure must be continuously monitored because sudden hypotension can occur. Consequently, nitroprusside is contraindicated in patients with preexisting hypotension. Because the drug is metabolized, small amounts of circulating cyanide are produced and detoxified in the liver to thiocyanate, which is excreted in urine. When high doses of nitroprusside are administered for several days, toxic symptoms related to *thiocyanate poisoning* may occur (fatigue, nausea, disorientation, acidosis, and muscular spasm). If nitroprusside use is prolonged, blood thiocyanate levels should be monitored. Phosphodiesterase inhibitors (see later) are also excellent, although somewhat less potent afterload reducers but without the toxicity of nitroprusside.

The orally active ACEIs **captopril** and **enalapril** produce arterial dilation by blocking the production of angiotensin II, thereby resulting in significant afterload reduction. Venodilation and consequent preload reduction also have been reported. In addition, these agents interfere with aldosterone production and therefore also help control salt and water retention. ACEIs have additional beneficial effects on cardiac structure and function that may be independent of their effect on afterload. Adverse reactions to ACEIs include hypotension and its sequelae (weakness, dizziness, syncope) and hyperkalemia. A maculopapular pruritic rash is encountered in a small number of patients, but the drug may be continued because the rash often disappears spontaneously with time. Neutropenia, renal toxicity, and chronic cough also occur.

While ACEIs/ARBs along with β-adrenergic blocking agents have been shown in multiple prospective, randomized, controlled trials in adults to improve symptoms and mortality in adult heart failure patients, it is unclear if these medications improve the natural history of heart failure in children. Nonetheless, these medications are commonly used for the treatment of heart failure and are recommended by consensus guidelines from the ISHLT and Canadian Cardiovascular Society.

Digitalis Glycosides

Digoxin, once the mainstay of heart failure management in both children and adults, is currently used less frequently, as a result of the introduction of other therapies and the recognition of its potential toxicities. Some cardiologists will use digitalis as an adjunct to ACEIs and diuretics in patients with symptomatic heart failure, whereas others have stopped using it altogether. Despite multiple clinical studies, predominantly in adults, the controversy over digitalis remains. Some data suggest a beneficial effect of digoxin on reducing death among infants with single-ventricle heart disease.

Digoxin is the digitalis glycoside used most often in pediatric patients. It has a half-life of 36 hr and it is absorbed well by the gastrointestinal tract (60–85%), even in infants. An initial effect is seen as early as 30 min after administration, and the peak effect for oral digoxin occurs at 2-6 hr. When the drug is administered intravenously, the initial effect is seen in 15-30 min, and the peak effect occurs at 1-4 hr. The kidney eliminates digoxin, so dosing must be adjusted according to the patient's renal function. The half-life of digoxin may be up to 6 days in patients with anuria because slower hepatic excretion pathways are used in these patients.

Rapid digitalization of infants and children may be carried out intravenously. This should be done with caution in patients with severe heart failure. The dose depends on the patient's age (Table 469.3). The recommended digitalization schedule is to give half the total digitalizing dose immediately and the succeeding 2 one-quarter doses at 12-hr intervals later. The ECG must be closely monitored, and rhythm strips obtained before each of the 3 digitalizing doses. Digoxin should be discontinued if a new rhythm disturbance is noted. Prolongation of the P-R interval is not necessarily an indication to withhold digitalis, but a delay in administering the next dose or a reduction in the dosage should be considered, depending on the patient's clinical status. Minor ST segment or T-wave changes are frequently noted with digitalis administration and should not affect the digitalization regimen. Baseline serum electrolyte levels should be measured before and after digitalization. **Hypokalemia** and **hypercalcemia** exacerbate digitalis toxicity. Because hypokalemia is relatively common in patients receiving diuretics, potassium levels should be monitored closely in those receiving a potassium-wasting diuretic in combination with digitalis. In patients with active myocarditis, some cardiologists recommend avoiding digitalis altogether and if used, maintenance digitalis should be started at half the normal dose without digitalization because of the increased risk of arrhythmia in these patients.

Table 469.3

Dosage of Drugs Commonly Used for the Treatment of Congestive Heart Failure

DRUG	DOSAGE*
DIGOXIN	
Digitalization ($\frac{1}{2}$ initially, followed by $\frac{1}{4}$ q12h × 2)	Premature: 20 μg/kg Full-term neonate (up to 1 mo): 20-30 μg/kg
	Infant or child: 25-40 μg/kg
	Adolescent or adult: 0.5-1 mg in divided doses
	Note: These doses are PO; IV dose is 75% of PO dose
Maintenance	5-10 μg/kg/day, divided q12h

digoxin [†]	*Note:* These doses are PO; IV dose is 75% of PO dose
DIURETICS	
Furosemide (Lasix)	IV: 0.5-2 mg/kg/dose
	PO: 1-4 mg/kg/day, divided qd-qid
Bumetanide (Bumex)	IV: 0.01-0.1 mg/kg/dose
	PO: 0.01-0.1 mg/kg/day q24-48h
Chlorothiazide (Diuril)	PO: 20-40 mg/kg/day, divided bid or tid
Spironolactone (Aldactone)	PO: 1-3 mg/kg/day, divided bid or tid
ADRENERGIC AGONISTS (ALL IV)	
Dobutamine	2-20 µg/kg/min
Dopamine	2-20 µg/kg/min
Epinephrine	0.01-1.0 µg/kg/min
PHOSPHODIESTERASE INHIBITORS (ALL IV)	
Milrinone	0.25-1.0 µg/kg/min
AFTERLOAD-REDUCING AGENTS	
Captopril (Capoten), all PO	Prematures: start at 0.01 mg/kg/dose; 0.1-0.4 mg/kg/day, divided q6-24h
	Infants: start at 0.15-0.3 mg/kg/dose; 1.5-6 mg/kg/day, divided q6-12h
	Children: start at 0.3-0.5 mg/kg/dose; 2.5-6 mg/kg/day, divided q6-12h
Enalapril (Vasotec), all PO	0.08-0.5 mg/kg/day, divided q12-24h
Hydralazine (Apresoline)	IV: 0.1-0.5 mg/kg/dose (maximum: 20 mg)
	PO: 0.75-5 mg/kg/day, divided q6-12h
Nitroglycerin	IV: 0.25-0.5 µg/kg/min start; increase to 20 µg/kg/min maximum
Nitroprusside (Nipride)	IV: 0.5-8 µg/kg/min
β-ADRENERGIC BLOCKERS	
Carvedilol (Coreg)	PO: initial dose: 0.1 mg/kg/day (maximum: 6.25 mg) divided bid (may use tid in infants), increase gradually (usually 2 wk intervals) to maximum of 0.5-1 mg/kg/day over 8-12 wk as tolerated; adult maximum dose: 50-100 mg/day
Metoprolol (Lopressor, Toprol-XL)	PO, non–extended-release form: 0.2 mg/kg/day divided bid, increase gradually (usually 2 wk intervals) to maximum dose of 1-2 mg/kg/day
	PO, extended-release form (Toprol-XL): given once daily; adult initial dose: 25 mg/day, maximum: 200 mg/day

[*] Pediatric doses based on weight should not exceed adult doses. Because recommendations may change, these doses should always be double-checked. Doses may also need to be modified in any patient with renal or hepatic dysfunction.

[†] Maintenance digitalis therapy is started approximately 12 hr after full digitalization. The daily dosage, one quarter of the total digitalizing dose, is divided in 2 and given at 12 hr intervals. The oral maintenance dose is usually 20–25% higher than when digoxin is used parenterally. The normal daily dose of digoxin for older children (>5 yr of age) calculated by body weight should not exceed the usual adult dose of 0.125-0.5 mg/24 hr.

IV, Intravenous; PO, oral; bid, twice daily, tid, 3 times daily; qid, 4 times daily; qd, every day.

Patients who are not critically ill may be given digitalis initially by the oral route, and in most instances, digitalization is completed within 24 hr. When slow digitalization is desirable, for example, in the immediate postoperative period, initiation of a maintenance digoxin schedule without a previous loading dose achieves full digitalization in 7-10 days.

Measurement of serum digoxin levels is useful (1) when an unknown amount of digoxin has been administered or ingested accidentally, (2) when renal function is impaired or if drug interactions are possible, (3) when questions regarding compliance are raised, and (4) when a toxic response is suspected. In suspected toxicity, elevated serum digoxin levels are not in themselves diagnostic of toxicity but must be interpreted as an adjunct to other clinical and electrocardiographic findings (rhythm and conduction disturbances). Hypokalemia, hypomagnesemia, hypercalcemia, cardiac inflammation secondary to myocarditis, and prematurity may all potentiate digitalis toxicity. A cardiac arrhythmia that develops in a child who is taking digitalis may also be related to the primary cardiac disease rather than the drug, however, any arrhythmia occurring after the institution of digitalis therapy must be considered to be drug related until proven otherwise. Many drugs interact with digoxin and may increase levels or risk of toxicity, so care should be taken when a patient receiving digoxin is being considered for any additional pharmacologic therapy.

Alpha- and β-Adrenergic Agonists

The α- and β-adrenergic receptor agonists are usually administered in an intensive care setting, where the dose can be carefully titrated to hemodynamic response. Continuous determinations of arterial blood pressure and heart rate are performed; measuring serial mixed venous oxygen saturations or cardiac output directly with a pulmonary thermodilution (Swan-Ganz) catheter may be helpful in assessing drug efficacy, although this technique is used much less in children than adults. Although extremely efficacious in the acute intensive care setting, long-term administration of adrenergic agonists has been shown to increase morbidity and mortality in adults with heart failure and is usually avoided unless the patient is totally dependent on these agents.

Dopamine is a predominantly β-adrenergic receptor agonist, but it has α-adrenergic effects at higher doses. Dopamine has less chronotropic and arrhythmogenic effect than the pure β-agonist isoproterenol. At a dose of 2-10 µg/kg/min, dopamine results in increased contractility with little peripheral vasoconstrictive effect. If the dose is increased beyond 15 µg/kg/min, however, its peripheral α-adrenergic effects may result in vasoconstriction.

Fenoldopam is a dopamine DA1 receptor agonist and is used at a low dose (0.03 µg/kg/min) to increase renal blood flow and urine output. It can cause hypotension, so blood pressure should be carefully monitored.

Dobutamine , a derivative of dopamine, is also useful in treating low cardiac output. It has direct inotropic effects and causes a moderate reduction in peripheral vascular resistance. Dobutamine can be used alone or as an adjunct to dopamine therapy to avoid the vasoconstrictive effects of higher-dose dopamine. Dobutamine is also less likely to cause cardiac rhythm disturbances than isoproterenol.

Isoproterenol is a pure β-adrenergic agonist that has a marked chronotropic effect; it is most effective in patients with slow heart rate. It is often used in the immediate post–heart transplant period.

Epinephrine is a mixed α- and β-adrenergic receptor agonist that is usually reserved for patients with cardiogenic shock and low arterial blood pressure. Although epinephrine can raise blood pressure effectively, it also increases systemic vascular resistance, and therefore increases the afterload against which the heart has to work and is associated with an increased risk of arrhythmia. Additionally, epinephrine is proarrhythmic and can result in direct cardiac toxicity, including myocardial necrosis and apoptosis.

Phosphodiesterase Inhibitors

Milrinone is useful in treating patients with low cardiac output who are refractory to standard therapy. It has been shown to be highly effective in managing the low-output state present in children after open heart surgery. It works by inhibition of phosphodiesterase, which prevents the degradation of intracellular cyclic adenosine monophosphate. Milrinone has both positive inotropic effects on the heart and peripheral vasodilatory effects and has generally been used as an adjunct to dopamine or dobutamine therapy in the intensive care unit. It is given by IV infusion at 0.25-1 µg/kg/min, sometimes with an initial loading dose of 50 µg/kg. A major side effect is **hypotension** secondary to peripheral vasodilation, especially when a loading dose is used. The hypotension can generally be managed by the administration of IV fluids to restore adequate intravascular volume. Long-term milrinone is often used to support patients while listed for heart transplantation, and in select patients can be used in the outpatient setting.

Chronic Treatment With β-Blockers

Studies in adults with dilated cardiomyopathy show that β-adrenergic blocking agents, introduced gradually as part of a comprehensive heart failure treatment program, improve exercise tolerance, decrease hospitalizations, and reduce overall mortality. The agents most often used are **carvedilol** , with both α- and β-adrenergic receptor–blocking as well as free radical–scavenging effects, and **metoprolol** , a β_1 -adrenergic receptor selective antagonist. β-Blockers are used for the chronic treatment of patients with heart failure and should not be administered when patients are still in the acute phase of heart failure (i.e., receiving IV adrenergic agonist infusions). Although very efficacious in adults, clinical studies in children have shown mixed results, potentially from the significant heterogeneity of the populations being studied and differences in the types of β-blocking agents.

New Therapies

Several newer medications have shown promise in the treatment of adult heart failure patients are now also being studied in pediatric patients. **Serelaxin** , recombinant human relaxin-2, resulted in fewer deaths when used for the treatment of acute heart failure in hospitalized patients. For chronic heart failure, **ivabradine** has been studied in patients with elevated heart rates. Ivabradine is a selective inhibitor of the I_f current in the sinus node and lowers heart rates without decreasing myocardial contractility. The use of ivabradine was associated with improved outcomes in heart failure patients, including decreased hospital admissions and cardiovascular death. A large, prospective randomized trial showed that the combination of an ARB and a **neprilysin inhibitor** can lead to several beneficial effects, including vasodilation, decreased aldosterone levels, and improved natriuresis, and patients randomized to the medication had a lower risk of death and hospitalization. Further studies are needed to determine what role, if any, these medications will have in the treatment of pediatric heart failure.

Electrophysiologic Approaches to Heart Failure Management

Significant improvements in symptomatology and functional capacity have been achieved in select adult patients with cardiomyopathy using **biventricular**

resynchronization pacing . This technique improves cardiac output by restoring normal synchrony between right and left ventricular contraction, which is often lost in patients with dilated cardiomyopathy (these patients usually manifest a left bundle branch block on ECG). There is growing experience with resynchronization pacing in children, but it remains uncertain which population of patients with heart failure benefit from this therapy.

Arrhythmias are a leading cause of sudden death in patients with severe cardiomyopathy (both dilated and hypertrophic). Although antiarrhythmic medications can sometimes reduce this risk, for patients at particularly high risk (e.g., those with a condition known to be associated with a high risk of ventricular arrhythmia or those who have already experienced a "missed sudden death" episode), use of an **implantable cardioverter-defibrillator** can be lifesaving (see Chapter 463).

469.1

Cardiogenic Shock

Joseph W. Rossano

Cardiogenic shock may be caused by (1) severe cardiac dysfunction before or after cardiac surgery, (2) septicemia, (3) severe burns, (4) anaphylaxis, (5) cardiomyopathy, (6) myocarditis, (7) myocardial infarction or stunning, and (8) acute central nervous system (CNS) disorders. It is characterized by low cardiac output and results in inadequate tissue perfusion (see Chapter 88).

Treatment is aimed at reinstitution of adequate cardiac output to prevent the untoward effects of prolonged ischemia on vital organs, as well as management of the underlying cause. Under normal physiologic conditions, cardiac output is increased as a result of sympathetic stimulation, which increases both contractility and heart rate. If contractility is depressed, cardiac output may be improved by increasing heart rate, increasing ventricular filling pressure (preload) through the Frank-Starling mechanism, or by decreasing systemic vascular resistance (afterload). Optimal filling pressure is variable and depends on a number of extracardiac factors, including ventilatory support and intraabdominal pressure. The increased pressure necessary to fill a relatively noncompliant ventricle should also be considered, particularly after open heart surgery, or in patients with restrictive or hypertrophic cardiomyopathies. If carefully administered incremental fluid does not result in improved cardiac output, abnormal myocardial contractility or an abnormally high afterload, or both, must be implicated as the cause of the low cardiac output. Although an increase in heart rate *may* improve cardiac output, an excessive increase in heart rate may reduce cardiac output because of decreased time for diastolic filling. Additionally, high heart rates will increase myocardial oxygen demand, which may be counterproductive in a state of limited tissue oxygen supply.

Myocardial contractility usually improves when treatment of the basic cause of shock is instituted, hypoxia is eliminated, and acidosis is corrected. β-Adrenergic agonists such as dopamine, epinephrine, and dobutamine improve cardiac contractility, increase heart rate, and ultimately increase cardiac output. However, some of these agents also have α-adrenergic effects, which cause peripheral vasoconstriction and increase afterload, so careful consideration of the balance of these effects in an individual patient is important. The use of cardiac glycosides to treat acute low cardiac output states should be avoided.

Patients in cardiogenic shock may have a marked increase in systemic vascular resistance (SVR) resulting in high afterload and poor peripheral perfusion. If the increased SVR is persistent and the administration of positive inotropic agents alone does not improve tissue perfusion, the use of afterload-reducing agents may be appropriate, such as nitroprusside or milrinone in combination with a β-adrenergic agonist. Milrinone, a phosphodiesterase inhibitor (see earlier), is also a positive inotropic agent, and combined with a β-adrenergic agonist, it works synergistically to increase levels of myocardial cyclic adenosine monophosphate.

Sequential evaluation and management of cardiovascular shock are mandatory (see Chapter 88). Table 469.4 outlines the general treatment principles for acute cardiac circulatory failure under most circumstances. In addition to cardiac-specific medications, other treatments aimed at improving oxygen capacity (e.g., blood transfusion for patients with anemia) and decreasing oxygen demand (e.g., intubation, mechanical ventilation, sedation) can be beneficial. Treatment of infants and children with low cardiac output after cardiac surgery also depends on the nature of the operative procedure, any intraoperative complications, and the physiology of the circulation after repair or palliation (see Chapter 461). If cardiogenic shock does not respond rapidly to medical therapy, consideration of mechanical support is warranted.

Table 469.4

Treatment of Cardiogenic Shock*

	DETERMINANTS OF STROKE VOLUME		
	Preload	**Contractility**	**Afterload**
Parameters measured	CVP, PCWP, LAP, cardiac chamber size on echocardiography	CO, BP, fractional shortening or ejection fraction on echocardiography, MV O_2 saturation	BP, peripheral perfusion, SVR
Treatment to improve cardiac output	Volume expansion (crystalloid, colloid, blood)	β-Adrenergic agonists, phosphodiesterase inhibitors	Afterload-reducing agents: milrinone, nitroprusside, ACEIs

* The goal is to improve peripheral perfusion by increasing cardiac output, where: cardiac output = heart rate × stroke volume.

ACEIs, Angiotensin-converting enzyme inhibitors; BP, blood pressure; CO, cardiac output (measured with a thermodilation catheter); CVP, central venous pressure; LAP, left atrial pressure (measured with an indwelling LA line); MV O_2 saturation, mixed venous oxygen saturation (measured with a central venous catheter); PCWP, pulmonary capillary wedge pressure (measured with a thermodilation catheter); SVR, systemic vascular resistance (calculated from CO and mean BP).

Mechanical Circulatory Support

Extracorporeal membrane oxygenation (ECMO) , which can provide total cardiopulmonary support, is the most common *short-term* modality to support circulatory failure in children. In experienced centers, children can be placed on ECMO rapidly, and therefore the modality can be used in multiple settings, including low cardiac output syndrome (low-output heart failure) after cardiac surgery, rapidly deteriorating hemodynamics in several scenarios (e.g., myocarditis), and as resuscitation from refractory cardiac arrest. The modality is ideal for short-term support when the underlying disease requiring EMCO is expected to resolve within days to weeks. For multiple reasons, including the relatively high complication rate and decreased mobility of many patients on ECMO, it is not an ideal support modality for long-term myocardial support.

Given of limitations of ECMO, there is a need to develop long-term support options for children with refractory heart failure. With advancements in the current era, almost 50% of children with dilated cardiomyopathy will be supported on a **ventricular assist device** (VAD) prior to heart transplantation.

For infants and small children, the most commonly used VAD is the Berlin Heart EXCOR. This device can be used for left, right, or biventricular support. It is classified as a *paracorporeal pneumatic pulsatile device,* and the pump sits outside the body. Among adults, these older types of devices have been replaced by newer-generation devices classified as *intracorporeal continuous flow devices.* These are completely internalized except for a drive line that connects to the power source (Fig. 469.2). These VADs have fewer complications and can provide long-term durable support outside the hospital. These devices are often used in older children and adolescents, with many of these patients discharged home on VAD support.

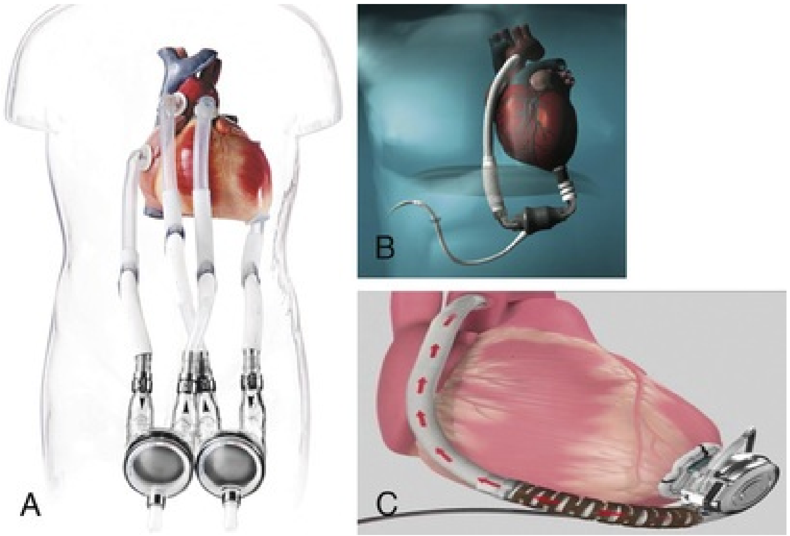

FIG. 469.2 **Commonly used ventricular assist devices in children. A, Paracorporeal pneumatic pulsatile Berlin Heart EXCOR. B and C, Continuous flow devices: B, axial flow HeartMate II; C, centrifugal flow HeartWare HVAD. (*A,* Courtesy Berlin Heart, LLC; *B,* reproduced with permission of St. Jude Medical, ©2017 [All rights reserved. HeartMate II and St. Jude Medical are trademarks of St. Jude Medical, LLC or its related companies]; *C,* courtesy Medtronic, Inc.)**

Other types of devices, including **temporary VAD** for short-term support and the **total artificial heart** for long-term support, have also been used in children, but less frequently. In children, most of these devices are used with the intention of subsequently performing a heart transplantation, although the devices can be removed if myocardial function recovers. This is in contrast to adult patients, many of whom are placed on these devices with no plan for heart transplantation, the so-called destination therapy. Successfully managing patients on VAD support requires a dedicated multidisciplinary team.

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CHAPTER 470

Pediatric Heart and Heart-Lung Transplantation

470.1

Pediatric Heart Transplantation

Joseph W. Rossano

Pediatric heart transplantation is considered the standard therapy that offers long-term survival for end-stage heart disease in children. In adults, ventricular assist devices (VADs) are usually employed as a long-term therapy for patients not eligible for heart transplantation, but in children the vast majority of VADs are used as a *bridge* to transplantation as opposed to an alternative to transplantation. As of January 2017, almost 9000 heart transplants had been performed on children in the United States since 1988, with about 400 transplants annually; a quarter of these in children <1 yr of age. Survival rates have improved significantly over time, with most of the improvement occurring in the early period after transplant. This period continues to the associated with the greatest risk of death, and many patients who survive the 1st yr after transplant are alive 20 yr later (Fig. 470.1). Indeed, a growing number of patients receiving a heart transplant in childhood are approaching their 15, 20, and 30 yr posttransplant anniversaries.

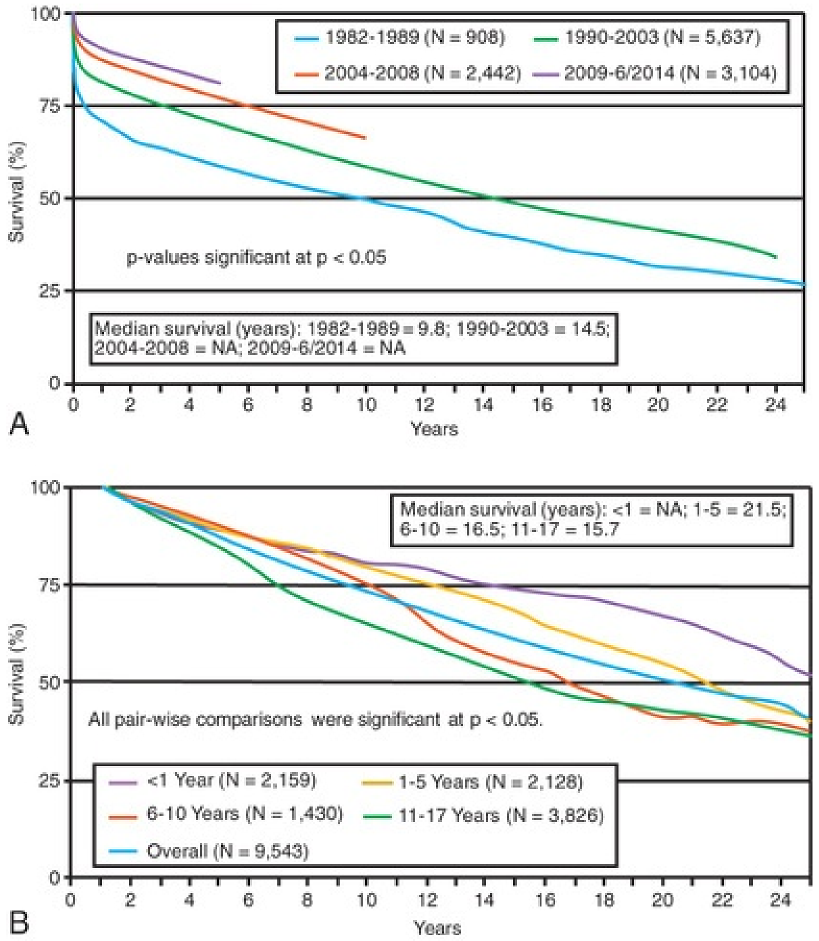

FIG. 470.1 **A,** Survival after pediatric heart transplantation comparing current and past eras. **B,** Long-term survival among patients that lived to one-year post-transplant. NA, Not applicable. (From Rossano JW, Dipchand AI, Edwards LB, et al: The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report—2016. Focus theme: primary diagnostic indications for transplant, J Heart Lung Transplant 35(10):1185–1195, 2016, Figs 6 and 7.)

Indications

Heart transplantation is performed (1) in infants and children with end-stage cardiomyopathy who have become refractory to medical therapy, (2) in patients with previously repaired or palliated congenital heart disease (CHD) who have developed ventricular dysfunction or other nonoperable late-term complications, and (3) less frequently in patients with complex CHD—pulmonary atresia with intact septum and coronary arterial stenoses, some forms of hypoplastic left heart syndrome (HLHS)—for whom standard surgical procedures are extremely high risk. Additionally, **retransplantation** accounts for approximately 5% of transplants annually. **Cardiomyopathies** account for >50% of heart transplants in pediatric patients older than 1 yr, with the percentage of patients with previously repaired complex CHD at approximately 30%. In infants younger than 1 yr, CHD previously represented >80% of transplants; this has decreased to 60% as standard surgical results for complex CHD (e.g., HLHS) have improved.

Recipient and Donor Selection

Potential heart transplant recipients must be free of serious noncardiac medical problems such as neurologic disease, active systemic infection, severe hepatic or renal disease, and severe malnutrition. Many children with ventricular dysfunction are at risk for the development of **pulmonary vascular disease** , which if severe enough would also preclude heart transplantation. Therefore, pulmonary vascular resistance (PVR) is measured at cardiac catheterization in heart transplant candidates, both at rest and, if elevated, in response to vasodilators. Patients with fixed elevated PVR are at higher risk for heart transplantation and may be considered candidates for heart-lung transplantation (see Chapter 470.2). However, with advances in postoperative management of pulmonary hypertension (e.g., inhaled nitric oxide), many patients with moderate elevation in PVR can undergo heart transplant alone. A comprehensive social services evaluation is an important component of the recipient evaluation. Because of the complex posttransplantation medical regimen, the family must have a history of compliance. Detailed informed consent must be obtained, indicating that the family (and if old enough, the patient) understand the lifelong commitment to immunosuppressive medication and careful monitoring.

Donor shortage is a serious problem for both adults and children. At the national registry of transplant recipients in the United States, the **United Network for Organ Sharing (UNOS)** , allografts are matched by ABO blood group and body weight. ABO matching may not be required for young infants; the exact age under which ABO tolerance develops has not yet been determined. Patients, especially with a history of CHD, who have undergone prior operations may have antibodies against human leukocyte antigens (HLAs). Patients with elevated anti-HLA antibodies are at risk for a positive crossmatch and early graft dysfunction. These antibodies can also contribute to late graft dysfunction through antibody-mediated rejection and development of cardiac allograft vasculopathy. For patients with these elevated antibodies, there are strategies to avoid a positive crossmatch through a prospective crossmatch or a virtual crossmatch, although this may prolong the waiting list time. Contraindications to organ donation include prolonged cardiac arrest with persistent moderate to severe cardiac dysfunction, ongoing systemic illness or infection, and preexisting severe cardiac disease. Physicians caring for a patient who may be a potential donor should always contact the organ donor coordinator at their institution, who can best judge the appropriateness of organ donation and has experience in interacting with potential donor families. A history of resuscitation alone or reparable CHD is not an automatic exclusion for donation.

The decision of when to place a patient on the transplant waiting list is based on many factors, including poor ventricular function, markedly decreased exercise tolerance as determined by cardiopulmonary exercise testing (see Chapter 450.5), poor response to medical heart failure therapy, multiple hospitalizations for heart failure, arrhythmia, progressive deterioration in renal or hepatic function, early stages of pulmonary vascular disease, and poor nutritional status. In patients awaiting transplantation, those with poor left ventricular function are often started on a regimen of anticoagulation to reduce the risk of mural thrombosis and thromboembolism. Patients with progressive heart failure resulting in decreases in end-organ (renal or hepatic) function unresponsive to standard pharmacologic treatment may be candidates for a VAD. The use of these devices has increased dramatically over the last decade, and currently almost half of patients with dilated cardiomyopathy are on VAD support before transplant. VADs can improve hemodynamics and end-organ function, and some patients can even be discharged home on VAD support (see Chapter 469).

Perioperative Management

In the **classic operation** , both donor and recipient hearts were excised so that the posterior portions of the atria containing the venae cavae and pulmonary veins are left intact. The aorta and pulmonary artery are divided above the level of the semilunar valves. The anterior portion of the donor's atria was then connected to the remaining posterior portion of the recipient's atria, thereby avoiding the need for delicate suturing of the venae cavae or pulmonary veins. The donor and recipient great vessels were connected via end-to-end anastomoses. This has been supplanted in many centers by the *bicaval* anastomosis, with the donor right atrium (and sinus node) left intact and the suture lines at the superior and inferior vena cavae; the left atrial connection is still performed as in the classic procedure.

Heterotopic heart transplantation has been used occasionally for patients with left ventricular cardiomyopathy and elevated PVR. In this operation the donor and recipient hearts are connected in parallel so that the recipient right ventricle (which has hypertrophied over time because of elevated pulmonary pressures) pumps mostly to the lungs, and the donor left ventricle pumps mostly to the body. This operation may be preferable to heart-lung transplant for appropriate candidates (patients with pulmonary hypertension but without parenchymal lung disease, without evidence of right ventricular failure, and without serious CHD). However, this procedure is very uncommon in the current era.

In the immediate postoperative period, **immunosuppression** is achieved with either a triple-drug or a double-drug regimen, with more centers adopting a minimal corticosteroid or steroid-free regimen. The most common combinations are a *calcineurin inhibitor* (cyclosporine or tacrolimus) plus an *antiproliferative agent* (mycophenolate mofetil or azathioprine), plus or minus *prednisone* . In many centers, induction therapy (usually an antilymphocyte preparation) is added in the 1st week; common agents include antithymocyte globulin (ATG) and the humanized anti–interleukin-2 receptor antibodies (basiliximab). In children who do not experience significant graft rejection, corticosteroids can be gradually eliminated in the early transplant period. Some centers do not use steroids as part of maintenance immunosuppression, but do use them as bolus treatment for acute rejection episodes.

Many pediatric heart transplant recipients can be extubated from endotracheal intubation and mechanical ventilation support within the 1st 48 hr after transplantation and are out of bed in several days. In patients with preexisting high-risk factors, postoperative recovery may be considerably prolonged. For those with preoperative pulmonary hypertension, the use of nitric oxide in the postoperative period can allow the donor right ventricle to hypertrophy in response to elevated pulmonary artery pressures. Occasionally, these patients will require right ventricular assist device support or extracorporeal membrane oxygenation (ECMO).

Diagnosis and Management of Acute

Graft Rejection

Posttransplantation management consists of adjusting medications to maintain a balance between the risk of rejection and the side effects of over-immunosuppression. **Acute graft rejection** is a leading cause of death in pediatric heart transplant recipients. The incidence of acute rejection is greatest in the 1st 3 mo after transplantation and decreases considerably thereafter. Many pediatric patients experience at least 1 episode of acute rejection in the 1st 2 yr after transplantation, although modern immunosuppressive regimens have decreased the frequency of serious rejection episodes. Because the symptoms of rejection can mimic many routine pediatric illnesses (e.g., pneumonia, gastroenteritis), the transplant center should be notified whenever a heart transplant recipient is seen in the pediatrician's office or emergency department for acute illnesses.

Clinical manifestations of acute rejection may include fatigue, fluid retention, fever, diaphoresis, abdominal symptoms, and a gallop rhythm. The electrocardiogram (ECG) may show reduced voltage, atrial or ventricular arrhythmias, or heart block but is usually nondiagnostic. X-ray examination may show an enlarged heart, effusions, or pulmonary edema but typically only in the more advanced stages of rejection. Natriuretic peptide levels are usually increased during episodes of acute rejection. Most rejection episodes occur without any detectable clinical symptoms. On echocardiography, indices of systolic left ventricular function may be decreased; however, these usually do not deteriorate until rejection is at least moderately severe. Techniques to evaluate wall thickening and left ventricular diastolic function have not fulfilled their promise as predictors of early rejection. Most transplant centers do not rely on echocardiography alone for rejection surveillance.

Myocardial biopsy is the most reliable method of monitoring patients for rejection. Biopsy specimens are taken from the right ventricular side of the interventricular septum and can be harvested relatively safely, even in small infants. In infants, surveillance biopsies are usually performed less often and may be as infrequent as once or twice per year. Children may have clinically unsuspected rejection episodes even 5-10 yr after transplantation; most pediatric transplant centers continue routine surveillance biopsies, although at less frequent intervals.

Criteria for grading cardiac rejection are based on a system developed by the **International Society for Heart and Lung Transplantation (ISHLT)** that takes into account the degree of cellular infiltration and whether myocyte necrosis is present. ISHLT rejection grade 1R is usually mild enough that it is often not treated with bolus steroids, and many of these episodes resolve spontaneously. For patients with ISHLT grade 2R rejection, treatment is instituted with either intravenous (IV) methylprednisolone or a “bump and taper” of oral prednisone. Asymptomatic patients further out from transplant with normal echocardiograms are may treated as outpatients. Patients with grade 3R, or anyone with hemodynamic instability, are admitted to the hospital for IV corticosteroid and potentially more aggressive antirejection therapy. For rejection episodes resistant to steroid therapy, additional therapeutic regimens include antilymphocyte preparation (antithymocyte globulin), methotrexate, or total lymphoid irradiation. Patients with repeated episodes of rejection may also benefit from the switch from cyclosporine to tacrolimus (or vice versa) or the addition of a proliferation single inhibitor (e.g., sirolimus). Refractory rejection is not considered a good indication for retransplantation because of the relatively poor outcomes compared with other indications for retransplantation.

Gene expression profiling of peripheral blood mononuclear cells has been validated in adults as a highly sensitive, moderately selective method of rejection surveillance. These results have not been confirmed in children. Other promising current techniques include the profiling of donor cell–free DNA released in the serum of patients during episodes of graft injury. Progress has also been made in genetic profiling as a means to determine which patients are most at risk for rejection. Children who have single nucleotide polymorphisms (SNPs) leading to greater activity of inflammatory cytokines or decreased activity of regulatory cytokines are at increased risk of rejection.

Some rejection episodes are not associated with a cellular infiltrate on biopsy. These cases of antibody-mediated rejection are mediated by circulating donor-specific antibodies (DSAs) and can be detected by immunostaining of the biopsy specimen for the complement component C4d, for macrophages expressing CD68, and for evidence of histologic damage. Antibody-mediated rejection is less responsive to standard therapies for acute cellular rejection (e.g., bolus corticosteroids) and has been treated with plasmapheresis, intravenous immune globulin (IVIG), the anti-CD20 monoclonal antibody rituximab, and the proteasome inhibitor bortezomib, all with mixed results. The long-term outcome of patients with persistent DSAs is poor, with many having early graft failure.

Complications of Immunosuppression

Infection

Infection is also a leading cause of death in pediatric transplant patients (Fig. 470.2). The incidence of infection is greatest in the 1st 3 mo after transplantation, when immunosuppressive doses are highest. **Viral** infections are most common and account for as many as 25% of infectious episodes. **Cytomegalovirus (CMV)** infection was once a leading cause of morbidity and mortality and may occur as a primary infection in patients without previous exposure to the virus or as a reactivation. Severe CMV infection can be disseminated or associated with pneumonitis or gastroenteritis and may provoke an episode of acute graft rejection or graft coronary disease. Most centers use IV ganciclovir or CMV immune globulin (CytoGam), or both, as prophylaxis in any patient receiving a heart from a donor who is positive for CMV or in any recipient who has serologic evidence of previous CMV disease. Oral preparations of ganciclovir with improved absorption profiles are available for chronic therapy and have largely replaced IV preparations for prophylaxis. These regimens have significantly reduced the burden of CMV disease in heart transplant patients. Polymerase chain reaction (PCR) enhances the ability to diagnose CMV infection and monitor the efficacy of therapy serially.

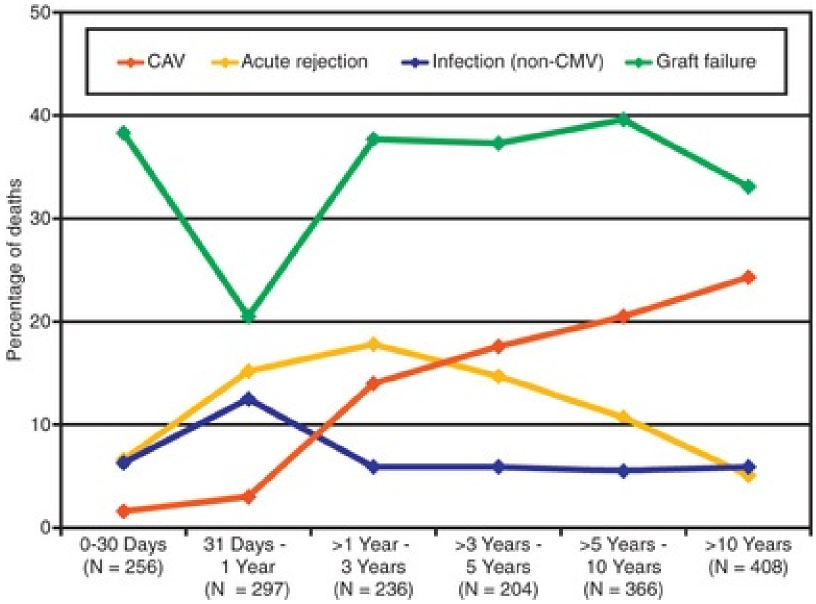

FIG. 470.2 Major causes of death after pediatric heart transplantation by

time since transplant. CAV, Cardiac allograft vasculopathy; CMV, cytomegalovirus. (From Rossano JW, Dipchand AI, Edwards LB, et al: The Registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report—2016. Focus theme: primary diagnostic indications for transplant, J Heart Lung Transplant 35(10):1185–1195, 2016, Fig 10.)

Most normal childhood viral illnesses are well tolerated and do not usually require special treatment. Otitis media and routine upper respiratory tract infections can be treated in the outpatient setting, although fever or symptoms that last beyond the usual course require further investigation. **Gastroenteritis** , especially with vomiting, can result in greatly reduced absorption of immunosuppressive medications and provoke a rejection episode. In this setting, drug levels should be closely monitored and use of IV medications considered. Gastroenteritis can also be a sign of rejection, so a high index of suspicion must always be maintained. Varicella is another childhood illness of concern for immunosuppressed patients. If a heart transplant recipient acquires clinical varicella infection, treatment with IV acyclovir usually attenuates the illness.

Bacterial infections occur next in frequency after viral, with the lung the most common site of infection, followed by blood, urinary tract, and less often the sternotomy site. Other sources of posttransplantation infection include fungi and protozoa. Many centers use nystatin mouthwash to decrease fungal colonization and trimethoprim-sulfamethoxazole during a patient's corticosteroid prophylaxis to prevent *Pneumocystis jiroveci* infection.

Growth Retardation

Patients requiring chronic corticosteroid therapy usually have decreased linear growth. Thus, many pediatric transplant programs aim for steroid-free immunosuppression within the 1st yr after transplant. In patients who experience rejection when steroids are withdrawn, alternate-day corticosteroid regimens may result in improved linear growth. **Total lymphoid irradiation** has also shown promise as a steroid-sparing protocol. Despite these concerns, the majority of long-term survivors of pediatric heart transplantation have normal growth.

Hypertension

Hypertension is common in patients treated with calcineurin inhibitors, caused by a combination of plasma volume expansion and defective renal sodium excretion. Corticosteroids usually potentiate calcineurin-induced hypertension.

Renal Function

Chronic administration of cyclosporine or tacrolimus can lead to a tubulointerstitial nephropathy in adults, but severe renal dysfunction is less common in children. Most pediatric patients gradually have an increase in serum creatinine in the 1st yr after transplantation; if renal dysfunction occurs, it usually responds to a decrease in calcineurin inhibitor (CNI) dosage. The addition of sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, instead of mycophenolate mofetil (MMF) allows a reduction in CNI dose in patients with renal dysfunction, although it is unclear whether this strategy leads to long-term improved renal function. Infection with BK virus, a growing problem in renal transplant patients, has been described as a source of renal dysfunction in heart transplant patients. Fortunately, pediatric heart transplant patients infrequently require renal transplantation.

Neurologic Complications

Neurologic side effects of cyclosporine and tacrolimus include tremor, myalgias, paresthesias, and rarely, seizures. These complications can be treated with reduced doses of medication and occasionally with oral magnesium supplementation. Intracranial infections pose a significant risk, especially because some of the more frequent signs (nuchal rigidity) may be absent in immunosuppressed patients. Potential organisms include *Aspergillus, Cryptococcus neoformans,* and *Listeria monocytogenes.* A rare form of encephalopathy known as **posterior reversible encephalopathy syndrome** (PRES) can occur in patients taking CNIs (cyclosporine or tacrolimus). PRES presents with hypertension, headaches and seizures, requires MRI for diagnosis, and is usually managed by changing CNI or in rare cases eliminating CNIs totally in favor of other immunosuppressive agents (e.g., sirolimus, MMF).

Tumors

One of the serious complications limiting long-term survival in pediatric heart transplant patients is the risk of neoplastic disease. The most common is

posttransplant lymphoproliferative disease (PTLD), a condition associated with Epstein-Barr virus (EBV) infection. Patients who are EBV seronegative at transplant (usually infants and young children) are at increased risk of developing PTLD if they subsequently seroconvert, acquiring the virus either from the donor organ or from primary infection. Unlike true cancer, many cases of PTLD respond to a reduction in immunosuppression. A monoclonal antibody directed against the CD20 antigen on activated lymphocytes (rituximab) has been effective against some forms of PTLD. However, PTLD can behave more aggressively, and many patients eventually require chemotherapy. An increased risk of skin cancer requires that children use appropriate precautions when exposed to sunlight.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is a disease of the coronary arteries that occurs in approximately 20% of children 5 yr after transplant. The cause is still unclear, although it is thought to be a form of immunologically mediated vessel injury. Multiple factors, including rejection episodes, infections, hypercholesterolemia, and hyperglycemia, are thought to increase the risk of CAV. Unlike native coronary atherosclerosis, CAV is a diffuse process with a high degree of distal vessel involvement. Because the transplanted heart has been denervated, patients may not experience symptoms such as angina pectoris during ischemic episodes, and the initial manifestation may be cardiovascular collapse or sudden death. Most centers perform coronary angiography annually to screen for coronary abnormalities; some also perform coronary intravascular ultrasound in larger children and adolescents. Standard coronary artery bypass procedures are usually not helpful because of the diffuse nature of the process, although transcatheter stenting can sometimes be effective for isolated lesions. For patients with severe CAV, repeat heart transplantation has been the only effective treatment. Thus, prevention has been the focus of most current research. The cell-cycle inhibitors sirolimus and everolimus have been shown to decrease coronary arterial intimal thickening in adult transplant patients. Other drugs that have been associated with a lower the risk of CAV include the calcium channel blockers (e.g., diltiazem) and the cholesterol-lowering HMG-CoA (3-hydroxy-3-methyl-coenzyme A) reductase inhibitors (e.g., pravastatin, atorvastatin).

Other Complications

Corticosteroids usually result in cushingoid facies, steroid acne, and striae. Cyclosporine can cause a subtle change in facial features, such as hypertrichosis and gingival hyperplasia. These cosmetic features can be particularly disturbing to adolescents and may be the motivation for noncompliance, one of the leading risks for late morbidity and mortality. Most of these cosmetic complications are dose related and improve as immunosuppressive medications are weaned. Tacrolimus does not have the cosmetic side effects of cyclosporine. Osteoporosis and aseptic necrosis are additional reasons for reducing the steroid dosage as soon as possible. Diabetes and pancreatitis are rare but serious complications.

Rehabilitation

Despite the potential risks of immunosuppression, the prospect for rehabilitation in pediatric heart transplant recipients is excellent; most have no functional limitations in their daily lives. They can attend daycare or school and participate in competitive sports and other age-appropriate activities. Standardized measurements of ventricular function are close to normal. Because the transplanted heart is denervated, the increase in heart rate and cardiac output during exercise is slower in transplant recipients, and maximal heart rate and cardiac output responses are mildly attenuated. These subtle abnormalities are rarely noticeable by the patient.

Growth of the transplanted heart is excellent, although a mild degree of ventricular hypertrophy is usually seen, even years after transplantation. The sites of atrial and great vessel anastomoses usually grow without the development of obstruction. In neonates who undergo transplantation for HLHS, however, juxtaductal aortic coarctation may recur.

A serious problem with noncompliance may occur once patients reach adolescence, and life-threatening rejection may result. Early intervention by social workers, counselors, and psychologists may be able to reduce this risk.

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470.2

Heart-Lung and Lung Transplantation

Joseph W. Rossano, Samuel B. Goldfarb

More than 700 heart-lung and 2,200 lung (single or double) pediatric transplants have been performed and reported to ISHLT, with >100 procedures performed annually. The majority of these are lung transplantation, with only 11 heart-lung transplants reported in 2014. Primary indications for lung transplantation include cystic fibrosis, pulmonary hypertension, interstitial lung disease, surfactant deficiencies, and retransplant. Indications for heart-lung transplant include complex CHD along with either pulmonary parenchymal or vascular disease. Patients with normal hearts are candidates for lung transplantation even in the setting of right ventricular dysfunction. This had led to the marked decline in heart-lung transplant procedures in the current era. In some patients with CHD, double-lung transplantation can be performed in combination with repair of intracardiac defects. Patients with cystic fibrosis are *not* candidates for single-lung grafts because of the risk of infection from the diseased contralateral lung. Patients are selected according to many of the same criteria as for heart transplant recipients (see Chapter 470.1).

Posttransplant immunosuppression is usually achieved with a triple-drug regimen, combining a CNI (cyclosporine or tacrolimus) with an antiproliferative agent (MMF or azathioprine) and prednisone. Most patients receive induction therapy with an antithymocyte or anti–T-cell preparation. Unlike patients with isolated heart transplants, patients with lung or heart-lung transplants cannot be weaned totally off steroids. Prophylaxis against *P. jiroveci* infection is achieved with trimethoprim-sulfamethoxazole or aerosolized pentamidine. Ganciclovir and CMV immune globulin prophylaxis are used as in heart transplant recipients (see Chapter 470.1). Antifungal medications are used in the perioperative and posttransplant periods in patients who have pretransplant colonization.

Pulmonary rejection is common in lung or heart-lung transplant recipients, whereas heart rejection is encountered much less often than in patients with isolated heart transplants. Acute rejection occurs in approximately 25% of patients in the 1st yr after transplant. Symptoms of lung rejection may include fever and fatigue, although many episodes are minimally symptomatic. Signs of rejection could include changes in lung function testing and radiographic findings. Surveillance for rejection is performed by monitoring pulmonary function (forced vital capacity; forced expiratory volume in 1 sec [FEV_1]; forced expiratory flow, midexpiratory phase [$FEF_{25\text{-}75\%}$]), systemic arterial oxygen tension, chest radiographs, chest CT, transbronchial biopsy, and open lung biopsy. In heart-lung transplant recipients, hearts are assessed for rejection similar to the approach described in Chapter 470.1 .

Actuarial survival rates after lung or heart-lung transplantation in children are currently 75–80% at 1 yr and 50% at 5 yr after transplant; improved patient selection and postoperative management are continually improving these survival statistics from prior eras. Some groups, such as patients with CHD in the absence of Eisenmenger syndrome, have particular poor outcomes with transplant. Graft failure and infection are the leading cause of early death, whereas a form of chronic rejection known as **bronchiolitis obliterans** accounts for almost 50% of late mortality. Other causes of early morbidity and mortality include technical complications, multiorgan failure, primary graft dysfunction, and cardiovascular causes. Additional late complications include the development of late graft failure, malignancies, infection, and other side effects of chronic immunosuppression.

Postoperative indices of cardiopulmonary function and exercise capacity show significant improvement. Problems of donor availability are even more severe with lung transplantation than with isolated heart transplantation. However, significant advances in ex vivo lung perfusion has great potential to expand the number of organs available for transplantation.

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SECTION 8

Diseases of the Peripheral Vascular System

OUTLINE

Chapter 471 Diseases of the Blood Vessels (Aneurysms and Fistulas)

Chapter 472 Systemic Hypertension

CHAPTER 471

Diseases of the Blood Vessels (Aneurysms and Fistulas)

471.1

Kawasaki Disease

Daniel Bernstein

Keywords

aneurysm
arteriovenous fistula
hemangioma
vein of Galen malformation
embolization
generalized arterial calcification of infancy
pseudoxanthoma elasticum
arterial calcification of CD73 deficiency
arterial tortuosity syndrome

See also Chapter 191 .

Aneurysms of the coronary and occasionally the systemic arteries may complicate Kawasaki disease and are the leading cause of morbidity in this disease (Figs. 471.1 and 471.2). Other than in Kawasaki disease, aneurysms are not common in children and occur most frequently in the aorta in association with coarctation of the aorta, patent ductus arteriosus, Ehlers-Danlos syndrome type IV (arterial ecchymotic form), hyper-IgE syndrome, Marfan syndrome, and the 4 forms of Loeys-Dietz syndrome in intracranial vessels (see Chapter 619). Aneurysms may also occur secondary to an infected embolus; infection contiguous to a blood vessel; trauma; congenital abnormalities of vessel structure, especially the medial wall; and arteritis, including polyarteritis nodosa, Behçet syndrome, and Takayasu arteritis (see Chapter 192.2).

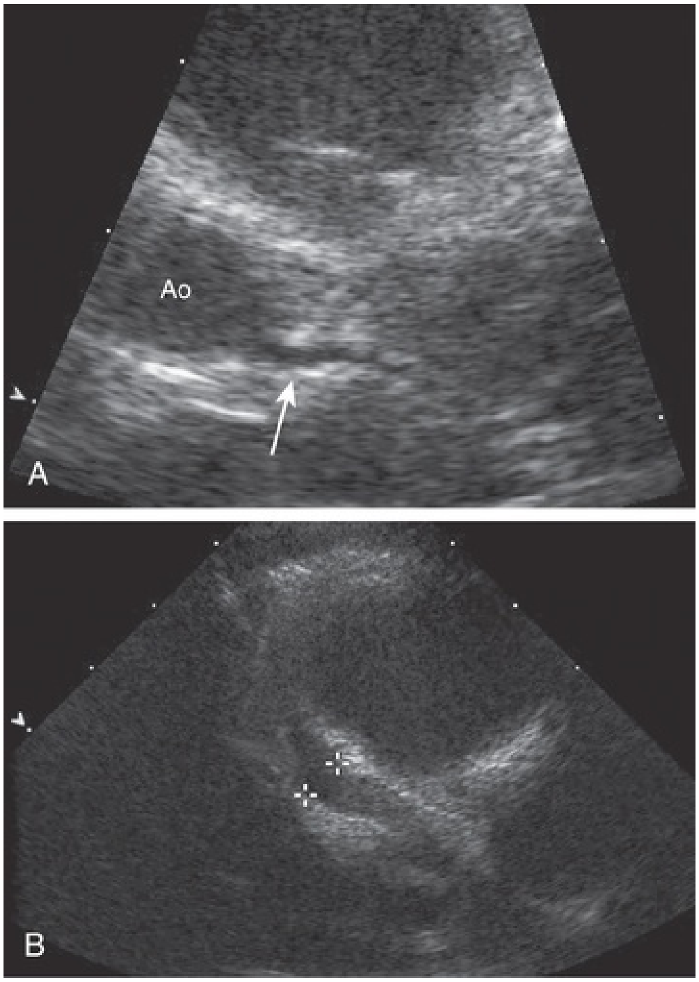

FIG. 471.1 Two-dimensional echocardiograms comparing a normal left main coronary artery (*arrow* in **A**) with a giant coronary artery aneurysm (outlined by *cross marks* in **B**) in a patient with Kawasaki disease. Ao, Aorta.

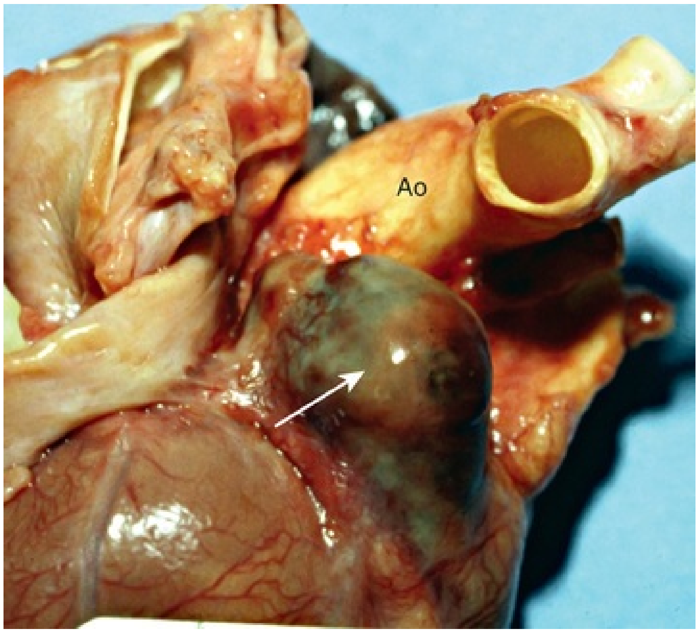

FIG. 471.2 Pathologic specimen showing giant aneurysm of left main coronary artery *(arrow).* Ao, Ascending aorta.

471.2

Arteriovenous Fistulas

Daniel Bernstein

Arteriovenous fistulas may be limited and small or may be extensive, producing systemic complications (see Chapters 532 and 669). The most common sites in infants and children are within the cranium, in the liver, in the lung, in the extremities, and in vessels in or near the thoracic wall. These fistulas, although usually **congenital** , may follow trauma or may be a manifestation of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). Femoral arteriovenous fistulas are a rare complication of percutaneous femoral catheterization.

Clinical Manifestations

Clinical symptoms occur only in association with large arteriovenous communications when arterial blood flows into a low-pressure venous system without the resistance of the capillary bed; local venous pressure is increased, and arterial flow distal to the fistula is decreased. Systemic arterial resistance falls because of the runoff of blood through the fistula. Compensatory mechanisms include tachycardia and increased stroke volume so that cardiac output rises. Total blood volume is also increased. In large fistulas, left ventricular dilation, a widened pulse pressure, and high-output heart failure occur. CT, MRI, or injection of contrast material into an artery proximal to the fistula confirms the diagnosis.

Large intracranial arteriovenous fistulas most often occur in newborn infants in association with a **vein of Galen malformation** . The large intracranial left-to-right shunt results in heart failure secondary to the demand for high cardiac output. Patients with smaller communications may not have cardiovascular manifestations but may later be disposed to hydrocephalus (see Chapter 609.11) or seizure disorders. The diagnosis can often be made by auscultation of a continuous murmur over the cranium. Older children with more diffuse intracranial arteriovenous malformations may be recognized on the basis of intracranial calcification and high cardiac output without cardiac failure.

Hepatic arteriovenous fistulas may be generalized or localized in the liver and may be hemangioendotheliomas or cavernous hemangiomas. The fistula may be located between the hepatic artery and the ductus venosus or portal vein. Congenital hemorrhagic telangiectasia may also be present. Large arteriovenous fistulas are associated with increased cardiac output and heart failure. Hepatomegaly is usual, and systolic or continuous murmurs may be audible over the liver.

Peripheral arteriovenous fistulas generally involve the extremities and are associated with disfigurement, swelling of the extremity, and visible hemangiomas. Some are located in areas that result in upper airway obstruction. Because only a small minority results in large arterial runoff, cardiac failure is uncommon.

Treatment

Medical management of heart failure is initially helpful in neonates with these conditions; with time, the size of the shunt may diminish and symptoms spontaneously regress. Hemangiomas of the liver often eventually disappear completely. Large liver hemangiomas have been treated with corticosteroids, β-blockers, ε-aminocaproic acid, interferon, local compression, embolization, or local irradiation; the beneficial effects of these management options are not firmly established because individual patients display marked variation in clinical course without treatment. **Catheter embolization** is becoming the treatment of choice for many patients with a symptomatic arteriovenous fistula. Embolic agents that have been used include detachable balloons, steel (Gianturco) coils, and liquid tissue adhesives (cyanoacrylate). Often, multiple procedures are necessary before flow is significantly reduced. **Gamma knife radiosurgery** has been used successfully in patients with cerebral arteriovenous malformations. Surgical removal of a large fistula may be attempted in patients with severe cardiac failure and lack of improvement with medical treatment. Surgical treatment may be contraindicated or unsuccessful when the lesion is extensive and diffuse or is located in a position where adjoining tissue may be injured during the surgery or related procedures. β-Adrenergic blockers such as propranolol have dramatically changed the treatment for cutaneous hemangiomas, with excellent results.

471.3

Generalized Arterial Calcification of Infancy/Idiopathic Infantile Arterial Calcification

Robert M. Kliegman

Generalized arterial calcification of infancy (GACI) is a rare and often lethal autosomal recessive disorder characterized by calcification of muscular arteries with fibrotic myointimal proliferation and subsequent vascular stenosis leading to tissue ischemia, poor function, or infarction. Diffuse arterial calcification may begin in utero, leading to hydrops fetalis; in the neonate, diffuse arterial calcification leads to respiratory distress and heart failure or myocardial infarction (coronary, pulmonary arteries), hypertension (renal arteries), and poor femoral pulses (aorta, femoral arteries).

Mutations in the ectonucleotide pyrophosphatase 1 gene (*ENPP1*) are noted in 75% of patients. Serum calcium, phosphate, and alkaline phosphatase levels are normal; the vascular calcification may be seen on plain x-ray films (Fig. 471.3), ultrasonography (Fig. 471.4), or CT scans (Fig. 471.5), which may reveal calcifications not visible on plain films.

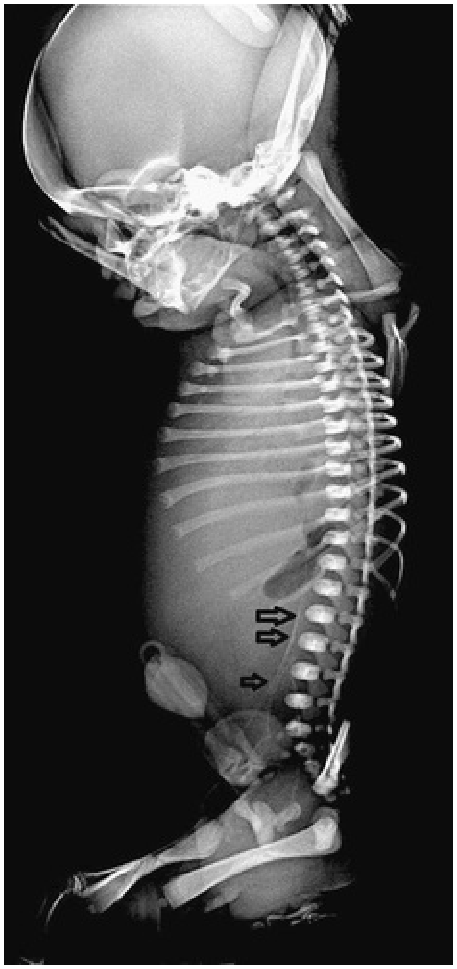

FIG. 471.3 Lateral radiograph of the neonate showing calcification of descending aorta and its bifurcation *(arrows)* . (From Karthikeyan G: Generalized arterial calcification of infancy, *J Pediatr* 162:1074, 2013, Fig 3.)

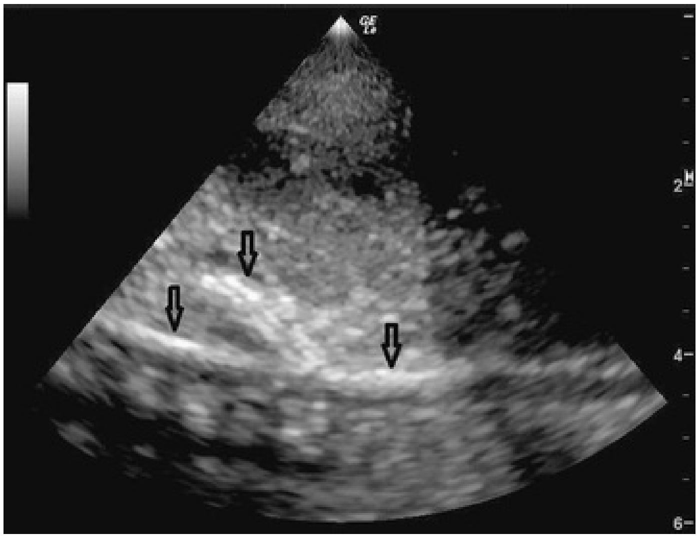

FIG. 471.4 Ultrasonography of abdominal aorta showing calcification of descending aorta and its branches *(arrows).* (From Karthikeyan G: Generalized arterial calcification of infancy, *J Pediatr* 162:1074, 2013, Fig. 1, p. 1074.)

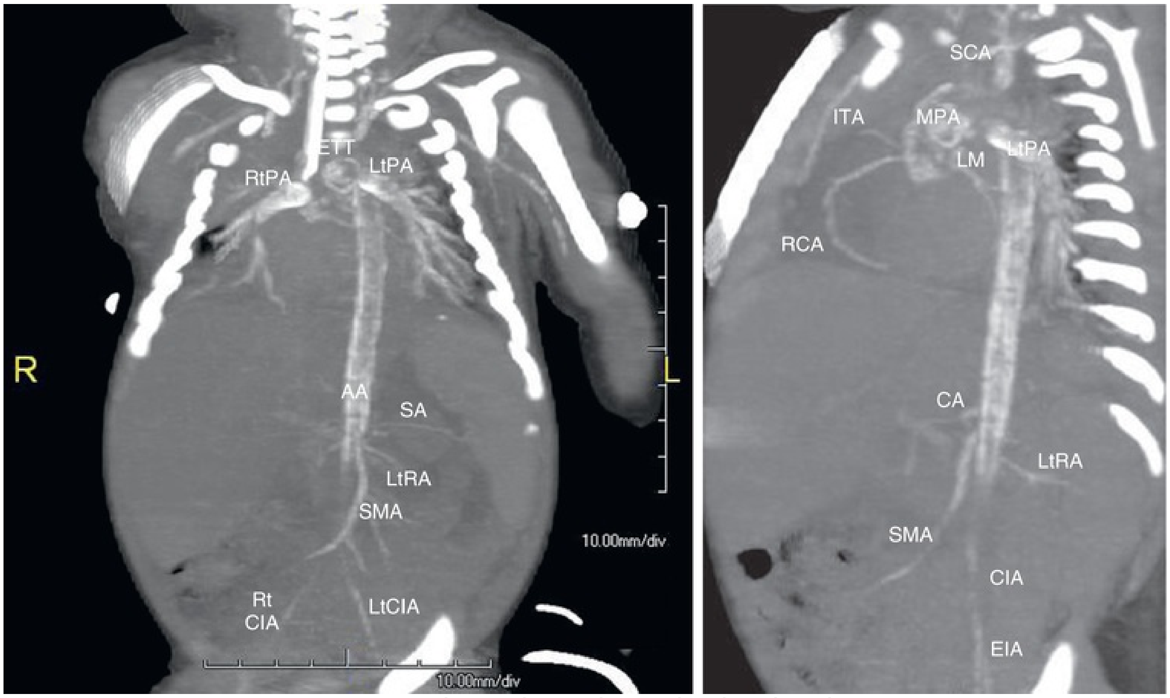
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FIG. 471.5 Coronal maximum intensity projection (MIP) CT scans demonstrate an endotracheal tube (ETT) and extensive vascular

calcifications. PA, Pulmonary artery; SA, splenic artery; RA, renal artery; CIA, common iliac artery; BA, brachial artery; CA, celiac axis; SMA, superior mesenteric artery; SCA, subclavian artery. (From Bolster F, Ali Z, Southall P, Fowler D: Generalized arterial calcification of infancy—findings at post-mortem computed tomography and autopsy, *Forensic Sci Int* 254:e7–e12, 2015, Fig 3.)

A subset of patients with GACI have monoallelic or biallelic mutations in the adenosine triphosphate–binding cassette subfamily C number 6 gene (*ABCC6*), which is the gene responsible for **pseudoxanthoma elasticum** (PXE). PXE, an autosomal recessive disorder, is classically associated with a later onset of ectopic mineralization of elastic fibers in the skin, eyes, joints, and arteries. In addition, some surviving infants with *ENPP1* mutation develop PXE symptoms involving skin and retina (angioid streaking).

Infants with GACI have been treated with bisphosphonates with variable success. In addition, some survivors with the *ENPP1* mutation have developed hypophosphatemic-hyperphosphaturic rickets.

In the absence of stroke or encephalomalacia, most survivors are developmentally normal. In some survivors the vascular calcification resolves and is replaced by fibrosis. The differential diagnosis includes Singleton-Merten syndrome (aortic calcification, dental anomalies, osteopenia), hypervitaminosis D, hyperparathyroidism, congenital syphilis (aortitis), twin-twin transfusion syndrome (recipient), and idiopathic iliac artery calcification of infancy.

Arterial Calcifications Caused by Deficiency of CD73

This rare autosomal recessive disorder, caused by mutations in the 5-exonucleotidase CD73 (*NT5E*), results in joint and arterial (lower-extremity) calcification in adults. Patients present with intermittent claudication and joint pain. Onset is probably before adulthood, since patients may be undiagnosed with nonspecific findings during adolescence.

471.4

Arterial Tortuosity

Robert M. Kliegman

Arterial tortuosity may be seen in many different diseases and genes (Table 471.1). These disorders are usually recognized by their phenotype, and all may present during childhood. Tortuosity is best defined by magnetic resonance angiography (Fig. 471.6). When present, it often increases the risk for early cardiovascular morbidity for patients with Marfan or Loeys-Dietz syndromes.

Table 471.1

Genetic Disorders Associated With Aortic Disease and Arterial Tortuosity

GENE	DISORDER
TGFBR1	Loeys-Dietz syndrome, FTAAD
TGFBR2	Loeys-Dietz syndrome, FTAAD
FBN1	Marfan syndrome
SMAD3	Osteoarthritis-aneurysm syndrome, FTAAD
SLC2A10	Arterial tortuosity syndrome
TGFB2	FTAAD
PRKG1	FTAAD
FBLN4 /EFEMP2	Cutis laxa
ATP7A	Occipital horn syndrome, Menkes syndrome
Monosomy X/mosaic monosomy X	Turner syndrome
FTAAD	Familial aortic aneurysm and dissection

FTAAD, Familial thoracic aortic aneurysm and dissection.

Adapted from Morris SA: Arterial tortuosity in genetic arteriopathies, *Curr Opin Cardiol* 30:587–593, 2015 (Table 1, p 590).

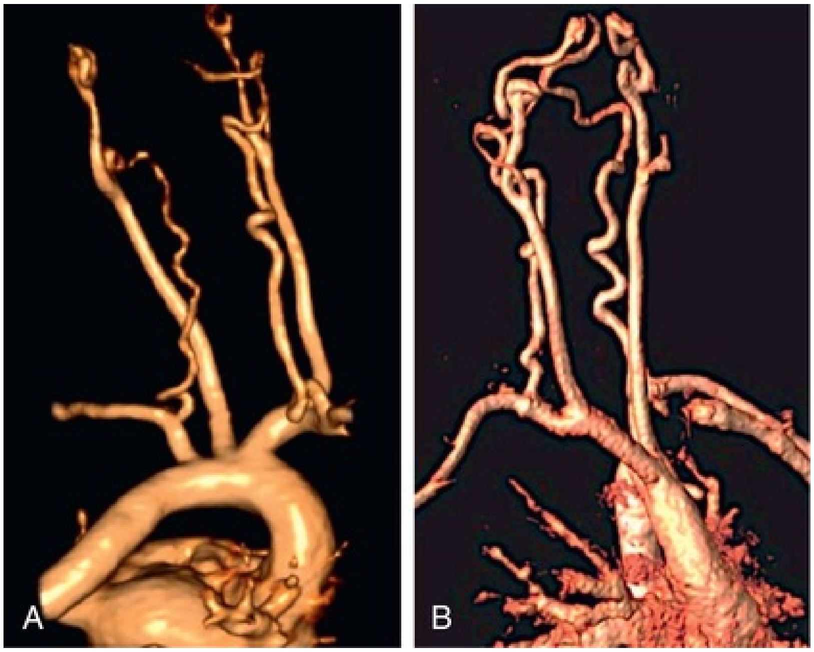

FIG. 471.6 Examples of vertebral artery tortuosity in **A,** Marfan syndrome with *FBN1* mutation, and **B,** Loeys-Dietz syndrome with a *TGFBR2* mutation. (From Morris SA: Arterial tortuosity in genetic arteriopathies, *Curr Opin Cardiol* 30:587–593, 2015, Fig 1.)

Arterial tortuosity syndrome is another genetic arteriopathy, caused by mutations in the *SCL2A10* gene. It has many features of other connective tissue diseases, including hyperextensible and soft velvety skin, high-arched palate, micrognathia, abdominal hernias, and joint hypermobility. The prognosis for patients with the arterial tortuosity syndrome is quite variable, but the presence of vascular stenosis is associated with a poorer prognosis.

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CHAPTER 472

Systemic Hypertension

Ian R. Macumber, Joseph T. Flynn

Primary (essential) hypertension occurs frequently in adults and, if untreated, is a major risk factor for myocardial infarction, cerebrovascular accident (stroke), and renal failure. In adults with hypertension, a 5 mm Hg increase in diastolic blood pressure (BP) increases the risk of coronary artery disease by 20% and the risk of stroke by 35%. Furthermore, along with diabetes, hypertension is 1 of the 2 leading causes of end-stage renal disease in adults. The prevalence of adult hypertension increases with age, ranging from 15% in young adults to 60% in individuals older than 65 yr.

Hypertensive children, although frequently asymptomatic, already may manifest evidence of target organ damage. Up to 40% of hypertensive children have left ventricular hypertrophy, and hypertensive children have increased carotid intima-to-media thickness, a marker of early atherosclerosis. Primary hypertension occurring during childhood often continues into adulthood. Children with BP >90th percentile exhibit a 2.4-fold greater risk of having hypertension as adults. Similarly, almost half of hypertensive adults had a BP >90th percentile as children. Adolescent hypertension is also an independent predictor of both end-stage renal disease and left ventricular dysfunction in middle-aged men.

Prevalence of Hypertension in Children

In infants and young children, systemic hypertension is uncommon, with a prevalence of <1% but, when present often indicates an underlying disease process (**secondary hypertension**). *Severe and symptomatic hypertension in children is usually caused by secondary hypertension.* In contrast, the prevalence of primary hypertension, mostly in older school-age children and adolescents, has increased in prevalence in parallel with the obesity epidemic. Estimates are variable, but recent data from the U.S. National Health and Nutrition Examination Survey (NHANES) show that approximately 9% of American youth have **prehypertension** and 3-4% have **hypertension** . The influence of obesity on elevated BP is evident in children as young as 2-5 yr old. Approximately 20% of American youth are obese, and up to 10% of obese youth have hypertension.

Definition of Hypertension

Normal BP in adults is 120/80 mm Hg (or lower). **Elevated** blood pressure is considered systolic BP of 120-129 *and* diastolic BP <80 mm Hg. **Stage 1** hypertension is systolic 130-139 *or* diastolic 80-89 mm Hg; **Stage 2** is systolic ≥140 *or* diastolic ≥90 mm Hg. This definition is based on *potential* since it relates degree of BP elevation with significant likelihood of subsequent cardiovascular events. Because hypertension-associated cardiovascular events (e.g., MI, stroke) occur rarely in childhood, the definition of hypertension in children is statistical and based on the *distribution of BP in healthy children,* not outcomes. The clinical practice guideline on childhood hypertension, issued by the American Academy of Pediatrics (AAP) in 2017, maintains the same statistical approach to defining and categorizing childhood BP as in previous guidelines from the **National High Blood Pressure Education Program (NHBPEP)** :

- **Normal BP:** BP <90th percentile for age, sex, and height; or <120/<80 (systolic/diastolic) mm Hg for adolescents ≥13 yr old
- **Elevated BP:** BP reading ≥90th percentile and <95th percentile for age, sex, and height; or 120-129/<80 mm Hg for adolescents ≥13 yr old
- **Hypertension:** BP >95th percentile for age, sex, and height; or ≥130/80 mm Hg for adolescents ≥13 yr old. Hypertensive-level BP is further staged as follows:

Stage 1 hypertension: BP >95th percentile for age, sex, and height up to the 95th percentile + 11 mm Hg; or 130-139/80-89 mm Hg for adolescents ≥13 yr of age

Stage 2 hypertension: BP ≥95th percentile + 12 mm Hg for age, sex, and height; or >140/90 mm Hg for adolescents ≥13 yr of age

The BP cutpoints for adolescents ≥13 yr old and the use of the term *elevated BP* in the AAP guideline were chosen to correspond to revised BP cutpoints and terminology found in the American Heart Association/American College of Cardiology (AHA/ACC) guideline for adult hypertension. The 2016 European Society of Hypertension (ESH) pediatric BP guideline also suggested that an absolute BP cutoff be used for adolescents age 16 and older, rather than using BP percentiles. For these older adolescents, the ESH guidelines define *high-normal* BP as 130-139/85-89 mm Hg, and *hypertension* as ≥140/90 mm Hg.

The 2017 AAP guideline* also contains new tables of normative BP values for children and adolescents based on a reanalysis of the NHBPEP database, removing all overweight and obese children. This revision results in BP values that are 2-3 mm Hg lower than the corresponding BP values in the 2004 NHBPEP Fourth Report, illustrating the impact of the childhood obesity epidemic on BP in young persons. The 2017 AAP guideline also contains a *simplified table* of BP values that may require further evaluation, which should be useful for screening (Table 472.1).

Table 472.1

Simplified Table of Screening Blood Pressure Values (mm Hg) Requiring Further Evaluation

AGE (yr)	BOYS		GIRLS	
	Systolic	Diastolic	Systolic	Diastolic
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62

5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

From Flynn JT, Kaelber DC, Baker-Smith CM, et al: Clinical practice guideline for screening and management of high blood pressure in children and adolescents, *Pediatrics* 140(3):e20171904, 2017 (Table 6, p 15).

Blood Pressure Measurement in Children

The 2017 AAP guideline recommends that children 3 yr or older should have their BP measured during annual preventive visits, unless the child has risk factors such as obesity, chronic kidney disease (CKD), or diabetes, in whom it should be checked at every healthcare encounter. In contrast, the 2016 ESH pediatric guideline recommends checking BP at every healthcare encounter for all children >3 yr old. Selected children <3 yr old should also have their BP measured, including those with a history of prematurity, congenital heart disease, renal disease, solid-organ transplant, cancer, treatment with drugs known to raise BP, other illnesses associated with hypertension (e.g., neurofibromatosis, tuberous sclerosis), or evidence of increased intracranial pressure. The preferred method is by auscultation using a sphygmomanometer (BP) cuff appropriate for the size of the child's arm.

Elevated readings should be confirmed on repeat visits before determining that a child is hypertensive. The BP should be measured with the child in the seated position after a period of quiet for at least 5 min, and it is recommended that the BP is checked 3 times, averaging the results. Careful attention to **cuff size** is necessary to avoid overdiagnosis, because a cuff that is too short or narrow artificially increases BP readings. An appropriate-sized cuff has an inflatable bladder whose length covers 80–100% of the upper arm circumference (measured midway between the acromion process and olecranon) and whose width is at least 40% of the arm circumference. A wide variety of cuff sizes should be available in any medical office where children are routinely seen.

Systolic blood pressure (SBP) is indicated by appearance of the *first* Korotkoff sound. Diastolic blood pressure (DBP) has been defined by consensus as the *fifth*

Korotkoff sound, unless the Korotkoff sounds can be heard down to 0 mm Hg, in which case the *fourth* Korotkoff sound should be reported as the DBP. Palpation is useful for rapid assessment of SBP, although the palpated BP is generally about 10 mm Hg lower than that obtained by auscultation. Oscillometric techniques are used frequently in infants and young children, but they are susceptible to artifacts and are best for measuring mean arterial pressure (MAP). In addition, different devices use different proprietary algorithms to back-calculate SBP and DBP from the MAP, making comparison between devices difficult.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (**ABPM**) is frequently used as a tool to assess pediatric hypertension. The patient wears a device that records BP every 20-30 min, throughout a 24 hr period, during usual daily activities, including sleep. This monitoring allows calculation of the mean daytime BP, sleep BP, and mean BP over 24 hr. The physician can also determine the proportion of BP measurements that are in the hypertensive range (BP load) and whether there is an appropriate decrease in BP during sleep (nocturnal dip), generally considered *normal* if there is a decrease in nocturnal BP of >10% from awake values. The cuff should be placed on the patient's nondominant arm. It is recommended that the patient keep a journal of sleep and awake times, medication timing, and other events that may be relevant to BP readings. Clinicians should only perform ABPM if they have had specific training in performing interpreting the results.

ABPM readings are more strongly correlated with target-organ damage in children than casual/office BP readings; the 2017 AAP guideline strongly recommends that ABPM be performed on all patients with elevated office readings in order to confirm the diagnosis of hypertension. In addition, ABPM is necessary to diagnose **white coat hypertension** (elevated office BP but normal ambulatory BP) as well as **masked hypertension** (normal office BP but elevated ambulatory BP). ABPM is also a useful tool for evaluating effectiveness of antihypertensive therapy. ABPM is also recommended to assess BP patterns in high-risk patient populations, such as children with CKD, solid-organ transplant, diabetes mellitus, and severe obesity.

ABPM is an extremely useful tool for evaluating and managing hypertension in appropriate patient populations, but it does have limitations. Not every patient will tolerate APBM, including younger children (although there are reports of successful ABPM in toddlers 18 mo old) and some children with developmental delay. Nonetheless, it is feasible to perform ABPM in children ≥6-7 yr. The most accepted normative data come from the German Working Group on Pediatric Hypertension. However, there are concerns with this dataset: (1) it includes only central European Caucasian children and thus might not be generalizable to other ethnicities; (2) there were relatively few shorter children included, which may limit its application to patients with chronic diseases such as CKD; and (3) there was very little variability in DBP values, which is not consistent with data from other BP measurement techniques showing that DBP varies with both age and height.

Etiology and Pathophysiology

Blood pressure is the product of cardiac output (CO) and peripheral vascular resistance (PVR). An increase in either CO or PVR results in an increase in BP; if either of these factors increases while the other decreases, BP may not increase. When hypertension is the result of another disease process, it is referred to as *secondary hypertension.* When no identifiable cause can be found, it is referred to as *primary hypertension.*

Secondary hypertension is most common in infants and younger children. It is most often caused by renal abnormalities; additional etiologies include cardiovascular disease and endocrinopathies. Younger age, severely elevated BP, and symptomatic hypertension make a secondary cause of hypertension more likely. Many childhood diseases can be responsible for *chronic hypertension* (Table 472.2) or *acute/intermittent hypertension* (Table 472.3). The most likely cause varies with age. Hypertension in the premature infant is sometimes associated with umbilical artery catheterization, renal artery thrombosis, or bronchopulmonary dysplasia. Hypertension during early childhood may be caused by renal disease, coarctation of the aorta, endocrine disorders, or medications.

Table 472.2

Conditions Associated With Chronic Hypertension in Children

Renal

Recurrent pyelonephritis/renal scarring
Chronic glomerulonephritis
Prematurity
Congenital dysplastic kidney
Polycystic kidney disease
Vesicoureteral reflux nephropathy
Segmental hypoplasia (Ask-Upmark kidney)
Obstructive kidney disease
Renal tumors
Renal trauma
Systemic lupus erythematosus (other connective tissue diseases)

Vascular

Coarctation of thoracic or abdominal aorta
Renal artery lesions (stenosis, fibromuscular dysplasia, thrombosis, aneurysm)
Umbilical artery catheterization with thrombus formation
Neurofibromatosis (intrinsic or extrinsic narrowing for vascular lumen)
Renal vein thrombosis
Vasculitis (ANCA associated, polyarteritis nodosa, Takayasu arteritis)
Arteriovenous shunt
Williams-Beuren syndrome
Moyamoya disease

Endocrine

Hyperthyroidism
Congenital adrenal hyperplasia (11β-hydroxylase and 17-hydroxylase defect)
Cushing syndrome
Primary hyperaldosteronism
Apparent mineralocorticoid excess
Glucocorticoid remedial aldosteronism (familial aldosteronism type 1)
Glucocorticoid resistance (Chrousos syndrome)
Pseudohypoaldosteronism type 2 (Gordon syndrome)

- Pheochromocytoma
- Other neural crest tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)
- Liddle syndrome
- Geller syndrome

Central Nervous System

- Intracranial mass
- Hemorrhage
- Residual following brain injury
- Quadriplegia (dysautonomia)
- Sleep disordered breathing

ANCA, Antineutrophil cytoplasmic antibody.

Table 472.3

Conditions Associated With Transient or Intermittent Hypertension in Children

Renal

- Acute postinfectious glomerulonephritis
- Henoch-Schönlein purpura with nephritis
- Hemolytic-uremic syndrome
- Acute kidney injury
- After renal transplantation (immediately and during episodes of rejection)
- Hypervolemia
- Pyelonephritis
- Renal trauma
- Leukemic infiltration of the kidney

Drugs and Poisons

- Cocaine
- Oral contraceptives

Sympathomimetic agents
Amphetamines
Phencyclidine
Corticosteroids and adrenocorticotropic hormone
Cyclosporine, sirolimus, or tacrolimus treatment after transplantation
Licorice (glycyrrhizic acid)
Lead, mercury, cadmium, thallium
Antihypertensive withdrawal (clonidine, methyldopa, propranolol)
Vitamin D intoxication

Central and Autonomic Nervous System

Increased intracranial pressure
Guillain-Barré syndrome
Burns
Familial dysautonomia
Stevens-Johnson syndrome
Posterior fossa lesions
Porphyria
Poliomyelitis
Encephalitis
Spinal cord injury (autonomic storm)

Miscellaneous

Preeclampsia
Pain, anxiety
Hypercalcemia
After coarctation repair
White blood cell transfusion
Extracorporeal membrane oxygenation

Renal disease (e.g., chronic glomerulonephritis, reflux or obstructive nephropathy, hemolytic-uremic syndrome, polycystic kidney disease, congenital anomalies of the kidney and urinary tract) and **renovascular hypertension** account for approximately 90% of children with secondary hypertension. Renal parenchymal disease and renal artery stenosis lead to water and sodium retention thought to be, in part, secondary to increased renin secretion. **Coarctation of the aorta** must always be considered. Several **endocrinopathies** are associated with hypertension, usually those involving the thyroid, parathyroid, and adrenal glands. Systolic hypertension and tachycardia are common in hyperthyroidism; DBP is not usually elevated. **Hypercalcemia** , whether secondary to hyperparathyroidism or other causes, often results in mild elevation in BP because of an increase in vascular tone. **Adrenocortical disorders** (e.g., aldosterone-secreting tumors, sodium-retaining congenital adrenal hyperplasia, Cushing syndrome) may produce hypertension in patients with increased mineralocorticoid secretion. It is important to consider conditions associated with real or apparent **mineralocorticoid excess** and thus a *suppressed* renin level (with or without hypokalemia) form of secondary hypertension (Table 472.4). **Pheochromocytomas** are catecholamine-secreting tumors that give rise to hypertension because of the cardiac and peripheral vascular effects of epinephrine and norepinephrine. Children with pheochromocytoma usually have sustained rather than intermittent or exercise-induced hypertension. Pheochromocytoma develops in approximately 5% of patients with neurofibromatosis and can also be seen in certain genetic disorders such as von Hippel–Lindau disease. Rarely, secondary hypertension can be caused by **pseudohyperaldosteronism** , which leads to elevated BP in the face of a suppressed renin level. Such disorders include Liddle syndrome, apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism. Altered sympathetic tone can be responsible for acute or intermittent elevation of BP in children with Guillain-Barré syndrome, poliomyelitis, burns, and Stevens-Johnson syndrome. Intracranial lesions also affect sympathetic outflow from the central nervous system.

Table 472.4

Clinical Findings in Patients With Mineralocorticoid Excess

CONDITION	CLINICAL PRESENTATION
CAH: 11β-hydroxylase deficiency	Early growth spurt initially, then short adult stature, advanced bone age, premature adrenarche, acne, precocious puberty in males, amenorrhea/hirsutism/virilism in females (autosomal recessive)
CAH: 17α-hydroxylase deficiency	Pseudohermaphroditism (male), sexual infantilism (female) (autosomal recessive)
Apparent mineralocorticoid excess	Growth retardation/short stature, nephrocalcinosis (autosomal recessive)

Liddle syndrome	Severe hypertension, hypokalemia, and metabolic alkalosis, muscle weakness (autosomal dominant)
Geller syndrome (exacerbated by pregnancy)	Early onset of hypertension (before age 20 yr), exacerbated in pregnancy
Glucocorticoid remediable aldosteronism (GRA) (familial aldosteronism type 1)	Early onset of hypertension, presence of family history of mortality or morbidity from early hemorrhagic stroke (autosomal dominant)
Pseudohypoaldosteronism type 2 (Gordon syndrome)	Short stature, hyperkalemic and hyperchloremic metabolic acidosis, borderline blood pressure (autosomal dominant)
Glucocorticoid resistance (children) (Chrousos syndrome)	Ambiguous genitalia, precocious puberty; women may have androgen excess: acne, excessive hair, oligo/anovulation, infertility (familial or sporadic)

CAH, Congenital adrenal hyperplasia.

From Melcescu E, Phillips J, Moll G, et al: 11 Beta-hydroxylase deficiency and other syndromes of mineralocorticoid excess as a rare cause of endocrine hypertension, Horm Metab Res 44:867–878, 2012 (Table 1, p 869).

A number of **drugs of abuse** , **therapeutic agents** , and **toxins** may cause hypertension. Cocaine may provoke a rapid increase in BP and can result in seizures or intracranial hemorrhage. Phencyclidine causes transient hypertension that may become persistent in chronic abusers. Tobacco use may also increase BP. Sympathomimetic agents used as nasal decongestants, appetite suppressants, and stimulants for attention-deficit disorder produce peripheral vasoconstriction and varying degrees of cardiac stimulation. Individuals vary in their susceptibility to these effects. Oral contraceptives should be suspected as a contributor to elevated BP in adolescent girls, although the incidence is lower with the use of low-estrogen preparations. Immunosuppressant agents such as cyclosporine and tacrolimus cause hypertension in organ transplant recipients, and the effect is exacerbated by the co-administration of corticosteroids. BP may be elevated in patients with poisoning by a heavy metal (lead, cadmium, mercury).

In older school-age children and adolescents, **primary hypertension** becomes increasingly common. These patients often are overweight, have a strong family history of hypertension, and have BP values at, or only slightly above, the 95th percentile for age. Isolated systolic hypertension is also more consistent with primary hypertension, whereas diastolic hypertension may suggest a secondary cause. The cause of primary hypertension is likely to be multifactorial; obesity, genetic alterations in calcium and sodium transport, vascular smooth muscle reactivity, the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system overactivity, and insulin resistance have been implicated in this disorder. Elevated **uric acid** levels may play a role in the pathophysiology of primary hypertension, and proof-of-concept studies have confirmed that lowering of uric acid levels results in lower BP in overweight youth with hypertension or prehypertension. Some children and adolescents demonstrate *salt-sensitive hypertension* , a factor that is ameliorated with weight loss and sodium restriction.

Normotensive children of hypertensive parents may show abnormal physiologic responses that are similar to those of their parents. When subjected to stress or competitive tasks, the offspring of hypertensive adults, as a group, respond with greater increases in heart rate and BP than do children of normotensive parents. Similarly, some children of hypertensive parents may excrete higher levels of urinary catecholamine metabolites or may respond to sodium loading with greater weight gain and increases in BP than do those without a family history of hypertension. The abnormal responses in children with affected parents tend to be greater in the black population than among white individuals.

Clinical Manifestations

Children and adolescents with primary hypertension are usually asymptomatic; the BP elevation is usually mild and is detected during a routine examination or evaluation before athletic participation. These children may also be obese. Children with secondary hypertension can have BP elevations ranging from mild to severe. Unless the BP has been sustained or is rising rapidly, hypertension does not usually produce symptoms. Therefore, clinical manifestations may instead reflect the underlying disease process, such as growth failure in children with CKD. Children and adolescents with **acute severe hypertension** , in contrast, present with BP elevation well above stage 2 hypertension and severe symptoms that may represent acute target-organ injury.

Subclinical hypertensive **target-organ injury** is a common clinical manifestation in children with primary hypertension. Using echocardiography with pediatric normative data, left ventricular hypertrophy is detected in up to 40% of hypertensive children. Other markers of target-organ damage that have been demonstrated in hypertensive children include hypertensive retinopathy, increased carotid intima-to-media thickness, and increased vascular stiffness. Children with prehypertension also have evidence of target-organ damage, often at a magnitude intermediate between that of normotensive and hypertensive children.

Diagnosis

The 1st step in diagnosing hypertension is recognition of elevated BP. BP readings taken in the office should be compared to normative BP tables (see 2017 AAP guidelines), indexed by height and sex, to ensure that the patient is normotensive. Multiple studies have shown substantial underrecognition of hypertension in children and adolescents, with the medical record showing only 8–26% of pediatric patients with documented elevated BP. This may be related to the complexity of the normative tables, although other factors such as provider experience and the presence or absence of obesity have also been shown to affect recognition of elevated BP readings. In addition to use of the simplified screening table found in the 2017 AAP guideline (see Table 472.1), this issue could also be overcome by building alerts into the electronic medical record. Elevated office BP readings should be confirmed using ABPM to identify children with white coat hypertension, who may not require further evaluation.

Once the diagnosis of sustained hypertension is made, the evaluation should be directed toward uncovering potential underlying causes of the hypertension, evaluating for comorbidities, and screening for evidence of target-organ damage. The extent of the evaluation for underlying causes of hypertension depends on the type of hypertension that is suspected. An extensive evaluation may be necessary when secondary hypertension is a strong consideration, such as in younger children with severe and symptomatic hypertension (Fig. 472.1). Alternatively, overweight adolescents with a family history of hypertension who have mild elevations of BP may only need limited testing.

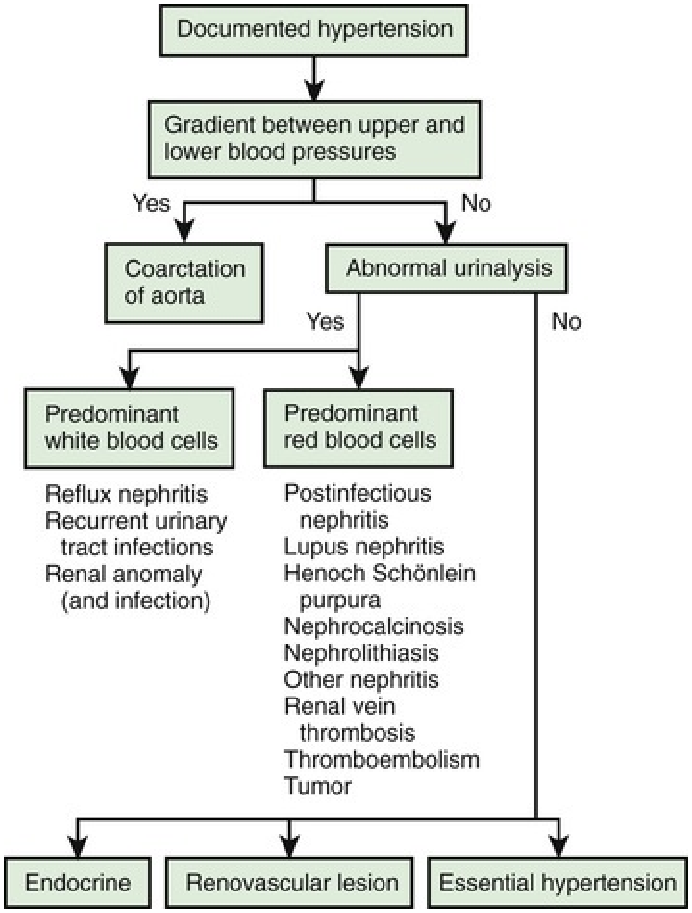
Documented hypertension
Gradient between upper and lower blood pressures
Yes
No
Coarctation of aorta
Abnormal urinalysis
Yes
No
Predominant white blood cells
Predominant red blood cells
Reflux nephritis
Recurrent urinary tract infections
Renal anomaly (and infection)
Postinfectious nephritis
Lupus nephritis
Henoch Schönlein purpura
Nephrocalcinosis
Nephrolithiasis
Other nephritis
Renal vein thrombosis
Thromboembolism
Tumor
Endocrine
Renovascular lesion
Essential hypertension

FIG. 472.1 **Initial diagnostic algorithm in the evaluation of hypertension. (From Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, Elsevier, p 222.)**

In all patients, a careful **history** and **physical examination** are warranted. Birth history should be documented to screen for prematurity and other perinatal events that may affect later BP. A family history for metabolic disease, renal disease, early cardiovascular events, and other forms of secondary hypertension should be obtained. Growth parameters should be determined to detect evidence of chronic disease. BP should be obtained in all 4 extremities to detect coarctation (thoracic or abdominal) of the aorta. Table 472.5 identifies other features of the physical examination that may provide evidence of an underlying cause of hypertension. Unless the history and physical examination suggest another cause, children with confirmed hypertension should have an evaluation to detect renal disease, including urinalysis, electrolytes, blood urea nitrogen, creatinine, and complete blood count. Standard renal ultrasound should be considered in patients with a higher suspicion of secondary hypertension to assess for discrepancies in renal size, structural abnormalities, and other potential causes of hypertension. Table 472.6 provides a more complete list of studies to consider in the clinical evaluation of a child with confirmed hypertension. Measuring serum potassium is essential because hypokalemia may be present in renovascular hypertension and many monogenic forms of hypertension (including Liddle syndrome, glucocorticoid remedial aldosteronism, and apparent mineralocorticoid excess), whereas hyperkalemia may be seen in Gordon syndrome.

Table 472.5

Findings to Look for on Physical Examination in Patients With Hypertension

PHYSICAL FINDINGS	POTENTIAL RELEVANCE
GENERAL	
Pale mucous membranes, edema, growth retardation	Chronic renal disease
Elfin facies, poor growth, retardation	Williams syndrome
Webbing of neck, low hairline, widespread nipples, wide carrying angle	Turner syndrome
Moon face, buffalo hump, hirsutism, truncal obesity, striae, acne	Cushing syndrome
HABITUS	
Thinness	Pheochromocytoma, renal disease, hyperthyroidism
Virilization	Congenital adrenal hyperplasia
Rickets	Chronic renal disease
SKIN	
Café au lait spots, neurofibromas	Neurofibromatosis, pheochromocytoma
Tubers, “ash-leaf” spots	Tuberous sclerosis
Rashes	Systemic lupus erythematosus, vasculitis (Henoch-Schönlein purpura), impetigo with acute nephritis
Pallor, evanescent flushing, sweating	Pheochromocytoma
Needle tracks	Illicit drug use
Bruises, striae	Cushing syndrome
Acanthosis nigricans	Type 2 diabetes, insulin resistance
EYES	
Extraocular muscle palsy	Nonspecific, chronic, severe
Fundal changes	Nonspecific, chronic, severe
Proptosis	Hyperthyroidism
HEAD AND NECK	
Goiter	Thyroid disease
Adenotonsillar hypertrophy	Sleep-disordered breathing
Webbed neck	Turner syndrome
CARDIOVASCULAR SIGNS	
Absent of diminished femoral pulses, low leg pressure relative to arm pressure	Aortic coarctation
Heart size, rate, rhythm; murmurs; respiratory difficulty, hepatomegaly	Aortic coarctation, congestive heart failure

Bruits over great vessels	Arteritis or arteriopathy
Rub	Pericardial effusion secondary to chronic renal disease
PULMONARY SIGNS	
Pulmonary edema	Congestive heart failure, acute nephritis
Picture of bronchopulmonary dysplasia	Bronchopulmonary dysplasia–associated hypertension
ABDOMEN	
Epigastric bruit	Primary renovascular disease or in association with Williams syndrome, neurofibromatosis, fibromuscular dysplasia, or arteritis
Abdominal masses	Wilms tumor, neuroblastoma, pheochromocytoma, polycystic kidneys, hydronephrosis, dysplastic kidneys
Jaundice	Alagille arteriohepatic dysplasia
NEUROLOGIC SIGNS	
Neurologic deficits	Chronic or severe acute hypertension with stroke
Muscle weakness	Hyperaldosteronism, Liddle syndrome (hypokalemic low renin hypertension)
GENITALIA	
Ambiguous, virilized	Congenital adrenal hyperplasia (11β- or 17α-hydroxylase deficiencies)
SKELETAL	
Short metacarpal (4th, 5th) bones, short stature	Autosomal dominant hypertension with brachydactyly (Bilginturan disease)

Table 472.6

Clinical Evaluation of Confirmed Hypertension

STUDY OR PROCEDURE	PURPOSE	TARGET POPULATION
EVALUATION FOR IDENTIFIABLE CAUSES		
History, including sleep history, family history, risk factors, diet, and habits such as smoking and drinking alcohol; physical examination	History and physical examination help focus subsequent evaluation	All children with persistent BP ≥90th percentile
Blood urea nitrogen, creatinine, electrolytes, urinalysis, and urine culture	R/O renal disease and chronic pyelonephritis, mineralocorticoid excess states	All children with persistent BP ≥95th percentile
Complete blood count	R/O anemia, consistent with chronic renal disease	All children with signs of chronic kidney disease
Renal ultrasound	R/O renal scar, congenital anomaly, or disparate renal size	All children with signs or symptoms concerning for secondary cause of hypertension
EVALUATION FOR COMORBIDITY		
Fasting lipid panel, fasting glucose	Identify hyperlipidemia, identify metabolic abnormalities	Overweight patients with BP at 90th-94th percentile; all patients with BP ≥95th percentile; family history of hypertension or cardiovascular disease; child with chronic renal disease
Drug screen	Identify substances that might cause hypertension	History suggestive of possible contribution by substances or drugs
Polysomnography	Identify sleep-	History of loud, frequent snoring, or daytime

	disordered breathing	somnolence
EVALUATION FOR TARGET-ORGAN DAMAGE		
Echocardiogram	Identify left ventricular hypertrophy and other indications of cardiac involvement	Patients with comorbid risk factors* and BP 90th-94th percentile; all patients with BP ≥95th percentile
Retinal exam	Identify retinal vascular changes	Patients with comorbid risk factors and BP 90th-94th percentile; all patients with BP ≥95th percentile
ADDITIONAL EVALUATION AS INDICATED		
Ambulatory blood pressure monitoring	Identify white coat hypertension, abnormal diurnal BP pattern, BP load	All children with persistent BP ≥95th percentile
Renovascular imaging Magnetic resonance or CT angiography	Identify renovascular disease	Young children with stage 1 hypertension and any child or adolescent with stage 2 hypertension.
Arteriography: digital subtraction or classic		
Plasma and urine catecholamines	Identify catecholamine-mediated hypertension	Patients with signs and symptoms concerning for pheochromocytoma

* Comorbid risk factors also include diabetes mellitus and kidney disease.

R/O, Rule out.

From National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, *Pediatrics* 114(2 Suppl 4th Report):562, 2004.

Renovascular hypertension is often associated with other diseases but may be isolated (Table 472.7). Magnetic resonance (MR) or computed tomography (CT) angiography can reveal renal artery stenosis, but formal intraarterial angiography may be needed to detect intrarenal vascular stenoses (Fig. 472.2) and in infants and young children, in whom noninvasive imaging techniques often are not helpful because of small vessel size. Doppler renal ultrasonography is of similar limited utility in children because of poor patient cooperation, imaging difficulties related to obesity, and operator inexperience. Doppler renal ultrasonography has a sensitivity of approximately 60–65% in patients with renovascular disease; specificity is 95%. CT angiography has a sensitivity and specificity of 88% and 81%, respectively, compared to 80% and 63% for MR angiography. *Doppler ultrasonography is not recommended when screening for renovascular hypertension in the 2017 AAP guideline except in selected patients.*

Table 472.7

Causes of Renovascular Hypertension in

Children

- Fibromuscular dysplasia
- Syndromic causes
    - Neurofibromatosis type 1
    - Tuberous sclerosis
    - Williams syndrome
    - Marfan syndrome
    - Other syndromes
- Vasculitis
    - Takayasu arteritis (disease)
    - Polyarteritis nodosa
    - Kawasaki disease
    - Other systemic vasculitides
- Extrinsic compression
    - Neuroblastoma
    - Wilms tumor
    - Other tumors
- Other causes
    - Radiation
    - Umbilical artery catheterization
    - Trauma
    - Congenital rubella syndrome
    - Transplant renal artery stenosis

From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, *Lancet* 371:1453–1463, 2008 (Panel 1, p 1454).

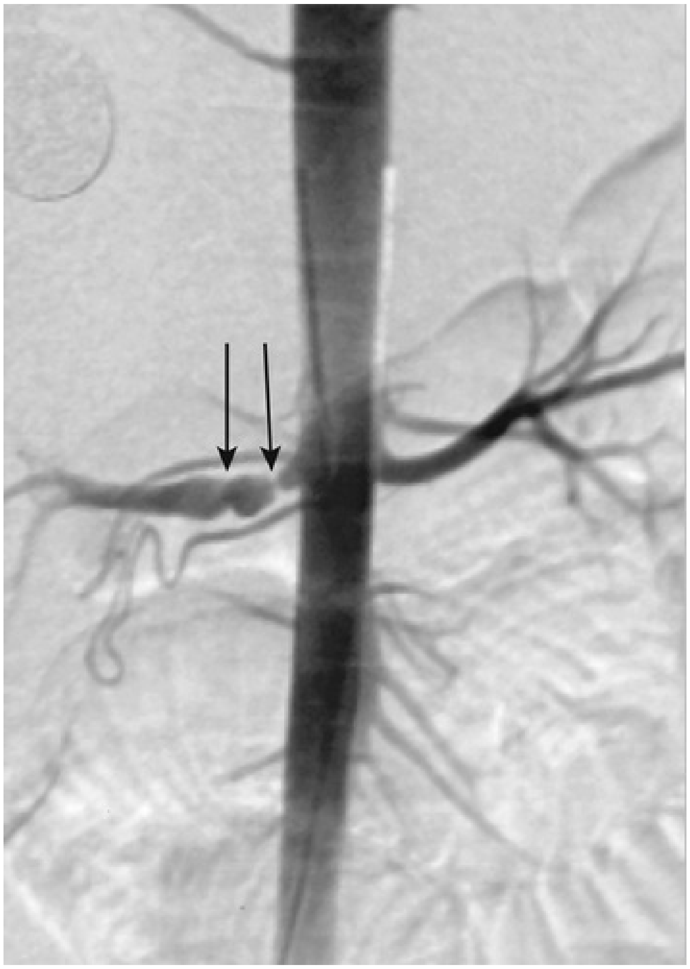

FIG. 472.2 **Renal angiogram in 7 yr old boy with hypertension. Right renal artery is visible with a string-of-beads appearance characteristic of fibromuscular dysplasia *(arrows).* The aorta and left renal artery appear normal. (From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, *Lancet* 371:1453–1463, 2008, Fig 1, p 1454.)**

The presence of primary hypertension often clusters with other risk factors. All hypertensive children should be screened for comorbidities that may increase cardiovascular risk, including dyslipidemia and glucose intolerance. A nonfasting lipid panel is usually sufficient to screen for dyslipidemia but should be followed up by a fasting panel if abnormal. Similarly, a random fasting glucose level may be obtained initially but will need to be followed up with a fasting level if abnormal. In addition, a sleep history should be obtained in children with confirmed hypertension to screen for **sleep-disordered breathing** , an entity that is associated with high BP, particularly in overweight children. Patients with symptoms of sleep-disordered breathing should be referred to a sleep specialist for evaluation.

Left ventricular hypertrophy (LVH) is the most common manifestation of target-organ damage in hypertensive children. Left ventricular (LV) mass measurements should be indexed to height to account for the effect of body size and body surface area (BSA). LVH is defined as LV mass >51 g/m$^{2.7}$ or LV mass >115 g/BSA for boys and >95 g/BSA for girls. According to the 2017 AAP guideline, echocardiography should be obtained when treatment with antihypertensive medications is being considered.

Prevention

Prevention of high BP may be viewed as part of the prevention of cardiovascular disease and stroke, the leading cause of death in adults in the United States. Other risk factors for cardiovascular disease include obesity, elevated serum cholesterol levels, high dietary sodium intake, and a sedentary lifestyle, as well as alcohol and tobacco use. The increase in arterial wall rigidity and blood viscosity that is associated with exposure to the components of **tobacco** may exacerbate hypertension. Public health, population-based approaches to prevention of primary hypertension in both adults and children include a reduction in obesity, reduced sodium intake, avoidance of tobacco intake, and an increase in physical activity through school- and community-based programs. The **DASH** (Dietary Approaches to Stop Hypertension) diet has been suggested as a nutritional approach to prevent or even treat hypertension (www.dashdiet.org). The diet focuses on lowering sodium intake and increasing potassium-, calcium-, and magnesium-containing foods, such as 6-8 servings of whole grains, 4-5 servings of fruits, and 4-5 servings of vegetables per day and low-fat dairy foods. For adults, the standard DASH diet contains 2300 mg of sodium (also recommended by the American Heart Association) and the low-sodium DASH diet recommends up to 1500 mg of sodium per day.

Treatment

The mainstay of therapy for children with asymptomatic mild hypertension without evidence of target-organ damage is therapeutic **lifestyle modification** with dietary changes and regular exercise. **Weight loss** is the primary therapy in obesity-related hypertension. It is recommended that all hypertensive children have a diet increased in fresh fruits, fresh vegetables, fiber, and nonfat dairy and reduced in sodium. The DASH diet is beneficial in lowering BP in adolescents as well as in adults. In addition, regular aerobic physical activity for at least 30-60 min on most days along with a reduction of sedentary activities to <2 hr/day is recommended.

Indications for **pharmacologic therapy** include symptomatic hypertension, stage 2 hypertension without a modifiable risk factor, hypertension in patients with comorbidities such as diabetes (types 1 and 2) or CKD, and persistent hypertension despite nonpharmacologic measures. When indicated, antihypertensive medication should be initiated as a single agent at low dose (Fig. 472.3). The dose can then be increased until the goal BP is achieved. Once the highest recommended dose is reached, or if the child develops side effects, a 2nd drug from a different class can be added. There are few data directly comparing the efficacy of different classes of antihypertensives in the pediatric population. However, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), thiazide diuretics, and calcium channel blockers are generally considered acceptable initial agents for use in children. The choice of antihypertensive agent for a patient should be tailored to the etiology of that patient's hypertension whenever possible. Table 472.8 gives recommended dosing information for antihypertensive agents in children and adolescents.

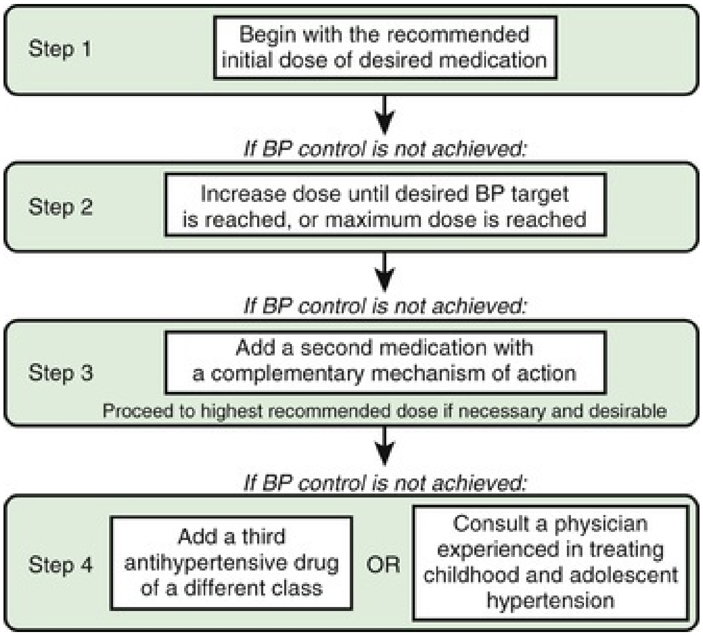
Step 1
Begin with the recommended initial dose of desired medication
If BP control is not achieved:
Step 2
Increase dose until desired BP target is reached, or maximum dose is reached
If BP control is not achieved:
Step 3
Add a second medication with a complementary mechanism of action
Proceed to highest recommended dose if necessary and desirable
If BP control is not achieved:
Step 4
Add a third antihypertensive drug of a different class
OR
Consult a physician experienced in treating childhood and adolescent hypertension

FIG. 472.3 **Stepped-care approach to antihypertensive therapy in children and adolescents. BP, Blood pressure. (From Flynn JT, Daniels SR: Pharmacologic treatment of hypertension in children and adolescents, *J Pediatr* 149:746–754, 2006, Fig 2, p**

751.)

Table 472.8

Recommended Doses for Selected Antihypertensive Agents for Use in Hypertensive Children and Adolescents

CLASS	DRUG	STARTING DOSE	INTERVAL	MAXIMUM DOSE*
Aldosterone receptor antagonist	Eplerenone	25 mg/day	qd-bid	100 mg/day
	Spironolactone †	1 mg/kg/day	qd-bid	3.3 mg/kg/day up to 100 mg/day
Angiotensin-converting enzyme inhibitors	Benazepril †	0.2 mg/kg/day up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Captopril †	0.5 mg/kg/dose (0.05 mg/kg/dose in infants)	tid	6 mg/kg/day up to 450 mg/day
	Enalapril †	0.08 mg/kg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Fosinopril	0.1 mg/kg/day up to 10 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Lisinopril †	0.07 mg/kg/day up to 5 mg/day	qd	0.6 mg/kg/day up to 40 mg/day
	Quinapril	5-10 mg/day	qd	80 mg/day
	Ramipril	1.6 mg/m^2 /day	qd	6 mg/m^2 /day up to 10 mg/day
Angiotensin receptor blockers	Candesartan	1-6 yr: 0.2 mg/kg/day 6-17 yr: <50 kg 4-8 mg qd >50 kg 8-16 mg qd	qd	1-6 yr: 0.4 mg/kg up to 4 mg/day 6-17 yr: <50 kg: 16 mg qd >50 kg: 32 mg qd
	Losartan †	0.75 mg/kg/day up to 50 mg/day	qd	1.4 mg/kg/day up to 100 mg/day
	Olmesartan	20 to <35 kg 10 mg qd; ≥35 kg 20 mg qd	qd	20 to <35 kg: 20 mg qd ≥35 kg: 40 mg qd
	Valsartan †	6-17 yr: 1.3 mg/kg/day up to 40 mg/day	qd	6-17 yr: 2.7 mg/kg/day up to 160 mg/day
α- and β-Adrenergic antagonists	Labetalol †	2-3 mg/kg/day	bid	10-12 mg/kg/day up to 1.2 g/day
	Carvedilol	0.1 mg/kg/dose up to 6.25 mg bid	bid	0.5 mg/kg/dose up to 25 mg bid
β-adrenergic antagonists	Atenolol †	0.5-1 mg/kg/day	qd-bid	2 mg/kg/day up to 100 mg/day
	Bisoprolol/HCTZ	2.5/6.25 mg/day	qd	10/6.25 mg/day
	Metoprolol	1-2 mg/kg/day	bid	6 mg/kg/day up to 200 mg/day
	Propranolol	1 mg/kg/day	bid-tid	8 mg/kg/day up to 640 mg/day

Calcium channel blockers	Amlodipine[†]	1-5 yr: 0.1 mg/kg/day ≥6 yr: 2.5 mg/day	qd	1-5 yr: 0.6 mg/kg/day up to 5 mg/day ≥6 yr: 10 mg/day
	Felodipine	2.5 mg/day	qd	10 mg/day
	Isradipine[†]	0.05-0.15 mg/kg/dose	tid-qid	0.6 mg/kg/day up to 10 mg/day
	Extended-release nifedipine	0.2-0.5 mg/kg/day	qd-bid	3 mg/kg/day up to 120 mg/day
Central α-agonist	Clonidine[†]	5-10 µg/kg/day	bid-tid	25 µg/kg/day up to 0.9 mg/day
Diuretics	Amiloride	5-10 mg/day	qd	20 mg/day
	Chlorthalidone	0.3 mg/kg/day	qd	2 mg/kg/day up to 50 mg/day
	Chlorothiazide	10 mg/kg/day	bid	20 mg/kg/day up to 375 mg/day
	Furosemide	0.5-2.0 mg/kg/dose	qd-bid	6 mg/kg/day
	HCTZ	0.5-1 mg/kg/day	qd	3 mg/kg/day up to 37.5 mg/day
Vasodilators	Hydralazine	0.25 mg/kg/dose	tid-qid	7.5 mg/kg/day up to 200 mg/day
	Minoxidil	0.1-0.2 mg/kg/day	bid-tid	1 mg/kg/day up to 50 mg/day

[*] The maximum recommended adult dose should never be exceeded.

[†] Information on preparation of a stable extemporaneous suspension is available for these agents.

bid, Twice daily; HCTZ, hydrochlorothiazide; qd, once daily; qid, 4 times daily; tid, 3 times daily.

Adapted from Flynn JT: Management of hypertension in the young: role of antihypertensive medications, *J Cardiovasc Pharmacol* 58(2)111−120, 2011.

There have been changes in the recommended BP goals for treatment of hypertension in children and adolescents. Data from the SPRINT (SBP intervention) trial group suggests that stricter goals (SBP goal of 120 vs 140 mm Hg) improve cardiovascular outcomes in adults. In children with CKD, the ESCAPE (Effects of Strict BP Control and Angiotensin-Converting Enzyme Inhibition on the Progress of Chronic Renal Failure in Pediatric Patients) trial group showed slower progression of CKD if the 24 hr MAPs were kept below the 50th percentile on ABPM compared to the 50th-95th percentile. It is now recommended that treatment achieve BP <90th percentile for age, or <130/80 mm Hg, whichever is lower. A lower goal based on ABPM (24 hr MAP <50th percentile) is recommended for children and adolescents with CKD. ACEIs or ARBs should be used for children with diabetes and microalbuminuria or proteinuric renal disease.

Acute severe hypertension , sometimes referred to as *accelerated hypertension* or *hypertensive crisis*, is defined as severe hypertension (often with BP values well in excess of stage 2 hypertension) accompanied by symptoms such as headache, dizziness, or nausea/vomiting, and in more severe cases, retinopathy, encephalopathy, cardiac failure, renal injury, and seizures. These situations have also been described as *hypertensive urgency* and *hypertensive emergency* , respectively. This nomenclature can lead to confusion because there is often no absolute distinction between the 2 situations, and treatment will often depend on clinical judgment. *Hypertensive encephalopathy* (generalized or posterior reversible encephalopathy syndrome) is suggested by the presence of headache, vomiting, temperature elevation, visual disturbances, ataxia, depressed level of consciousness, imaging abnormalities, and seizures (Fig. 472.4); it is one of the more common presentations of acute severe hypertension in children and adolescents. Acute severe hypertension may also manifest with decreased vision (cortical blindness) and papilledema, congestive heart failure, or accelerated deterioration of renal function.

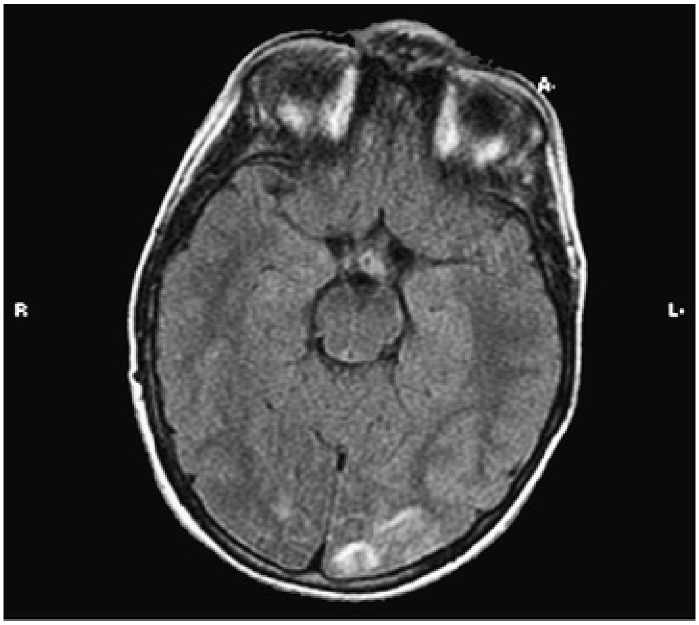

FIG. 472.4 **Magnetic resonance image of brain of a 6 yr old boy with end-stage renal disease and hypertensive encephalopathy (i.e., posterior reversible leukoencephalopathy syndrome). Bilateral occipital high signal intensity is more pronounced on the left side. (From Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, editors, *Bradley's neurology in clinical practice,* ed 6, vol 2, Philadelphia, 2012, Elsevier Saunders, Fig 49B.4, p 924.)**

For patients with acute severe hypertension and life-threatening symptoms, intensive care unit (ICU) admission and intravenous (IV) drug infusion is indicated so that decreases in BP can be carefully monitored and titrated (Table

472.9). Arterial lines should be used for continuous BP monitoring. Drug choices include labetalol, nicardipine, and sodium nitroprusside. Because too rapid a reduction in BP may interfere with adequate organ perfusion, a stepwise reduction in pressure should be planned. In general, BP should be reduced by no more than 25% of the planned reduction over the 1st 8 hr, with a gradual normalization of BPs over next 24-48 hr. For patients with less severe symptoms, such as headache or nausea/vomiting, oral medications such as clonidine or isradipine can be used if the patient can tolerate oral medications. Short-acting IV medications such as hydralazine or labetalol are acceptable if the patient cannot take oral drugs.

Table 472.9

Antihypertensive Drugs for Management of Severe Hypertension in Children Age 1-17 yr

DRUG	CLASS	DOSE	ROUTE	COMMENTS
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LIFE-THREATENING SYMPTOMS				
Esmolol	β-Adrenergic blocker	100-500 μg/kg/min	IV infusion	Very short acting—constant infusion preferred; may cause profound bradycardia
Hydralazine	Direct vasodilator	0.2-0.4 mg/kg/dose	IV, IM	Should be given every 4 hr when given IV bolus
Labetalol	α- and β-Adrenergic blocker	Bolus: 0.20-1.0 mg/kg/dose, up to 40 mg/dose Infusion: 0.25-3.0 mg/kg/hr	IV bolus or infusion	Asthma and overt heart failure are relative contraindications.
Nicardipine	Calcium channel blocker	Bolus: 30 μg/kg up to 2 mg/dose Infusion: 0.5-4 μg/kg/min	IV bolus or infusion	May cause reflex tachycardia
Sodium nitroprusside	Direct vasodilator	0.5-10 μg/kg/min	IV infusion	Monitor cyanide levels with prolonged (>72 hr) use or in renal failure; or co-administer with sodium thiosulfate.
USEFUL FOR SEVERELY HYPERTENSIVE PATIENTS WITH LESS SIGNIFICANT SYMPTOMS				
Clonidine	Central α-agonist	0.05-0.1 mg/dose, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness.
Fenoldopam	Dopamine receptor agonist	0.2-0.8 μg/kg/min	IV infusion	Produced modest reductions in blood pressure in a pediatric clinical trial in patients up to age 12 yr
Hydralazine	Direct vasodilator	0.25 mg/kg/dose, up to 25 mg/dose	PO	Extemporaneous suspension stable for only 1 wk
Isradipine	Calcium channel blocker	0.05-0.15 mg/kg/dose, up to 5 mg/dose	PO	Stable suspension can be compounded.

Minoxidil	Direct vasodilator	0.1-0.2 mg/kg/dose, up to 10 mg/dose	PO	Most potent oral vasodilator; long acting

ACE, Angiotensin-converting enzyme; IM, intramuscular; IV, intravenous; PO, oral.

Adapted from Flynn JT, Tullus K: Correction to severe hypertension in children and adolescents: pathophysiology and treatment, *Pediatr Nephrol* 27(3):503–504, 2012.

Treatment of secondary hypertension must also focus on the underlying disease, such as chronic renal disease, hyperthyroidism, pheochromocytoma, coarctation of the aorta, or renovascular hypertension. The treatment of renovascular stenosis includes antihypertensive medications, angioplasty, or surgery (Fig. 472.5). If bilateral renovascular hypertension or renovascular disease in a solitary kidney is suspected, drugs acting on the RAAS are usually contraindicated because they may reduce glomerular filtration rate and lead to acute kidney injury.

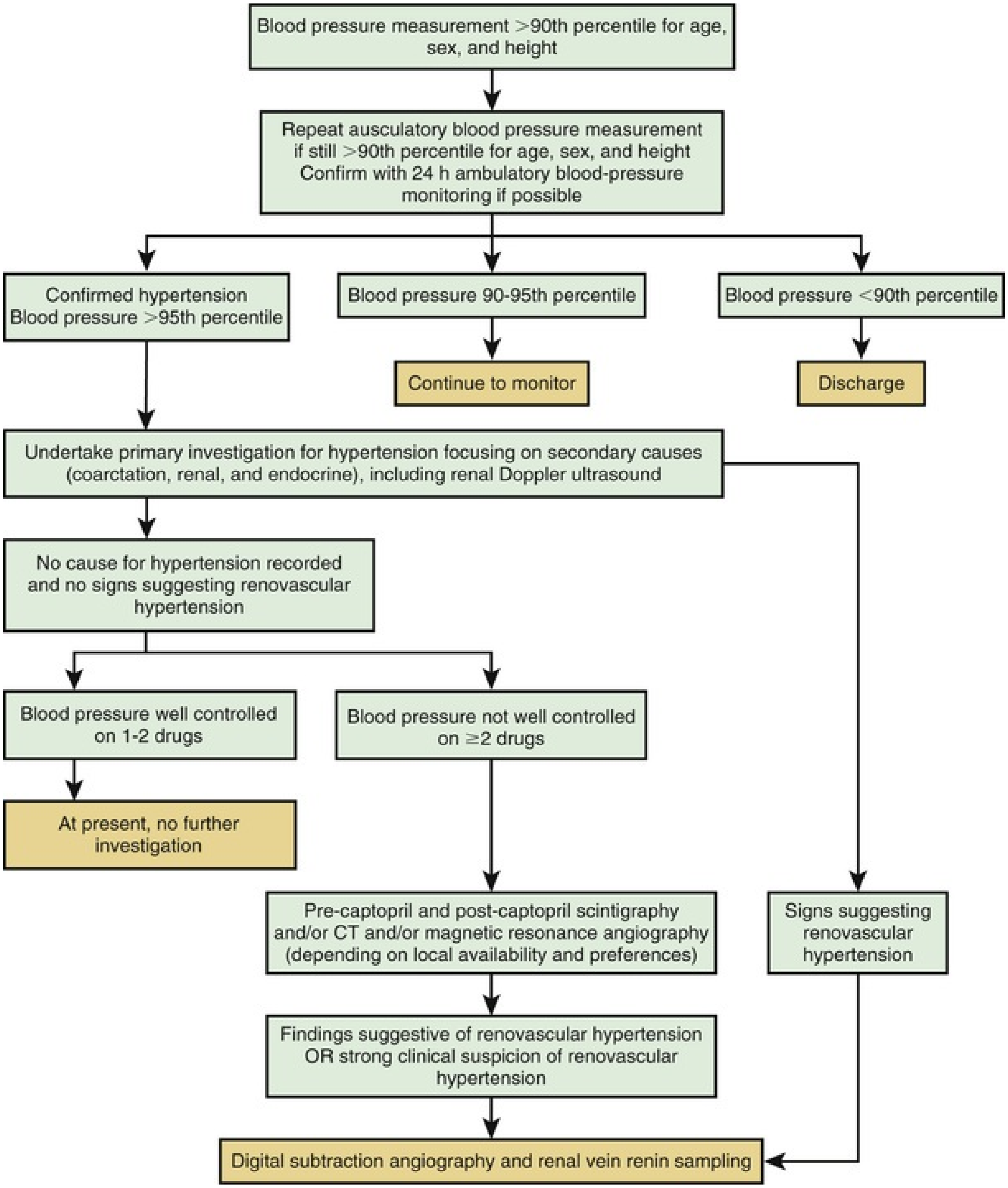
Blood pressure measurement >90th percentile for age, sex, and height
Repeat ausculatory blood pressure measurement if still >90th percentile for age, sex, and height Confirm with 24 h ambulatory blood-pressure monitoring if possible
Confirmed hypertension Blood pressure >95th percentile
Blood pressure 90-95th percentile
Blood pressure <90th percentile
Continue to monitor
Discharge
Undertake primary investigation for hypertension focusing on secondary causes (coarctation, renal, and endocrine), including renal Doppler ultrasound
No cause for hypertension recorded and no signs suggesting renovascular hypertension
Blood pressure well controlled on 1-2 drugs
Blood pressure not well controlled on ≥2 drugs
At present, no further investigation
Pre-captopril and post-captopril scintigraphy and/or CT and/or magnetic resonance angiography (depending on local availability and preferences)
Signs suggesting renovascular hypertension
Findings suggestive of renovascular hypertension OR strong clinical suspicion of renovascular hypertension
Digital subtraction angiography and renal vein renin sampling

FIG. 472.5 **Diagnostic pathway for renovascular hypertension. (From Tullus K, Brennan E, Hamilton G, et al: Renovascular hypertension in children, *Lancet* 371:1453–1463, 2008, Fig 6, p 1458.)**

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PART XX

Diseases of the Blood

OUTLINE

Section 1 The Hematopoietic System
Section 2 Anemias of Inadequate Production
Section 3 Hemolytic Anemias
Section 4 Polycythemia (Erythrocytosis)
Section 5 The Pancytopenias
Section 6 Blood Component Transfusions
Section 7 Hemorrhagic and Thrombotic Diseases
Section 8 The Spleen
Section 9 The Lymphatic System

SECTION 1

The Hematopoietic System

OUTLINE

Chapter 473 Development of the Hematopoietic System
Chapter 474 The Anemias

CHAPTER 473

Development of the Hematopoietic System

Stella T. Chou

Hematopoiesis in the Human Embryo and Fetus

Hematopoiesis is the process by which the cellular elements of blood are formed. In the developing human embryo and fetus, hematopoiesis has 3 developmental waves and is conceptually divided into 3 anatomic stages: mesoblastic, hepatic, and myeloid. *Mesoblastic* hematopoiesis occurs in extraembryonic structures, principally in the yolk sac, and begins between the 10th and 14th days of gestation. By 6-8 wk of gestation, the liver replaces the yolk sac as the primary site of blood cell production, and during this time the placenta also contributes as a hematopoietic site. By 10-12 wk, extraembryonic hematopoiesis has ceased. *Hepatic* hematopoiesis occurs through the remainder of gestation and then diminishes during the second trimester while bone marrow (*myeloid*) hematopoiesis increases. The liver is the predominant erythropoietic organ through 20-24 wk of gestation.

Each hematopoietic organ houses distinct populations of cells. The yolk sac predominantly produces erythrocytes, megakaryocytes, and macrophages. The fetal liver is primarily an erythropoietic organ, while the bone marrow produces erythrocytes, megakaryocytes, and leukocytes. The types of leukocytes present in the fetal liver and marrow differ with gestation. Macrophages precede neutrophils in the marrow, and the ratio of macrophages to neutrophils decreases as gestation progresses. Regardless of gestational age or anatomic location, production of all hematopoietic tissues begins with multipotent cells capable of both self-renewal and clonal maturation into all blood cell lineages. Progenitor cells differentiate under the influence of transcription factors and hematopoietic growth factors (Table 473.1).

Table 473.1

Characteristics of Hematopoietic Growth Factors

GROWTH FACTOR	MOLECULAR MASS (kDa)	CHROMOSOMAL LOCATION	PRINCIPAL TARGET CELL
ERYTHROPOIETIN	30-39	7q11-12	CFU-E, fetal BFU-E, endothelial cells, neurons, astrocytes, oligodendrocytes
COLONY-STIMULATING FACTORS			
G-CSF	18-22	17q11.2-21	CFU-G, CFU-MIX, mature neutrophils
GM-CSF	18-30	5q23-31	CFU-MIX, CFU-GM, BFU-E, monocytes, mature neutrophils
M-CSF	45-70 (Dimer of 2 subunits)	5q33.1	CFU-M, macrophages
SCF	36	12q21.32	CFU-MIX, BFU-E, CFU-GM, mast cells
TGF-β	25 Homodimeric protein	19q13.2	BL-CFC
CSF-1	192 Amino acid protein	1p13.3	Monocytes, macrophages, dendritic cells, Langerhans cells
INTERLEUKINS			
IL-1	17	Alpha 2q13 Beta 2q13-21	Hepatocytes, macrophages, lymphocytes
IL-2	15-20	4q26-27	T cells, cytotoxic lymphocytes
IL-3	14-30	5q23-31	CFU-MIX, CFU-Meg, CFU-GM, BFU-E, macrophage
IL-4	16-20	5q23-31	T cells, B cells, dendritic cells
IL-5	46 (Dimer of 2 subunits)	5q23-31	CFU-Eo, B cells
IL-6	19-26	7p21-24	CFU-MIX, CFU-GM, BFU-E, monocytes, B cells, T cells, cytotoxic lymphocytes
IL-7	35	8q12-13	B cells
IL-8	8-10	4q13.3	Neutrophils, endothelial cells, T cells
IL-9	16	5q31-32	BFU-E, CFU-MIX
IL-10	18.7	1q32.1	Macrophages, lymphocytes
IL-11	23	19q13	CFU-Meg, B cells, keratinocytes
IL-12	70-75 (Dimer of 2 subunits)	p35/p40	3 (p35) and 11 (p40) T cells, NK cells, macrophages
IL-13	9	5q23-31	Pre-B lymphocytes, macrophages
IL-14	53	5q31	B cells
IL-15	14-15	4q25-35	B cells, T cells
IL-16	12-14	15q23-26	T cells
IL-17	20-30	2q31	Marrow stromal cells
IL-18	24	9p13	$CD4^+$ T cells, NK cells
IL-21		4q26-q27	T cells
IL-23	Dimer of subunits	p19/IL-12p40	$CD4^+$ T cells
IL-25		14q11.2	T cells, monocytes, marrow stromal cells
IL-31	4-Helix bundle	12q24.31	T cells, hematopoietic progenitors

IL-34	222 Amino acid protein	16q22.1	Monocytes, macrophages
THROMBOPOIETIN	35-38	3q27–28	Megakaryocyte progenitors, megakaryocytes

BFU-E, Burst-forming units–erythroid; BL-CFU, blast colony-forming cell; CFU-E, colony-forming units–erythroid; CFU-Eo, colony-forming units–eosinophil; CFU-G, colony-forming units–granulocyte; CFU-GM, colony-forming units–granulocyte-macrophage; CFU-M, colony-forming units–macrophage; CFU-Meg, colony-forming units–megakaryocyte; CFU-MIX, colony-forming units–mixed; CSF-1, colony-stimulating factor-1; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; M-CSF, macrophage colony-stimulating factor; NK, natural killer; SCF, stem cell factor; TGF-β, transforming growth factor-beta.

The classical model of hematopoietic differentiation involves differentiation into increasingly lineage-specific progenitors, although there may also be alternate pathways that are used separately or in combination with classical pathways (Fig. 473.1). In the classical pathway, *long-term repopulating hematopoietic stem cells* (LTR-HSCs) are characterized by their ability to self-renew and differentiate into cells that are multipotent. *Multipotent progenitors* (MPPs) have reduced self-renewal capacity and differentiate into *common lymphoid progenitors* (CLPs) or *common myeloid progenitors* (CMPs). The CMP differentiates into all the blood lineages except for lymphoid. The commitment of hematopoietic cells to increasingly lineage-restricted cells requires cytokine stimulation and regulation by transcription factors.

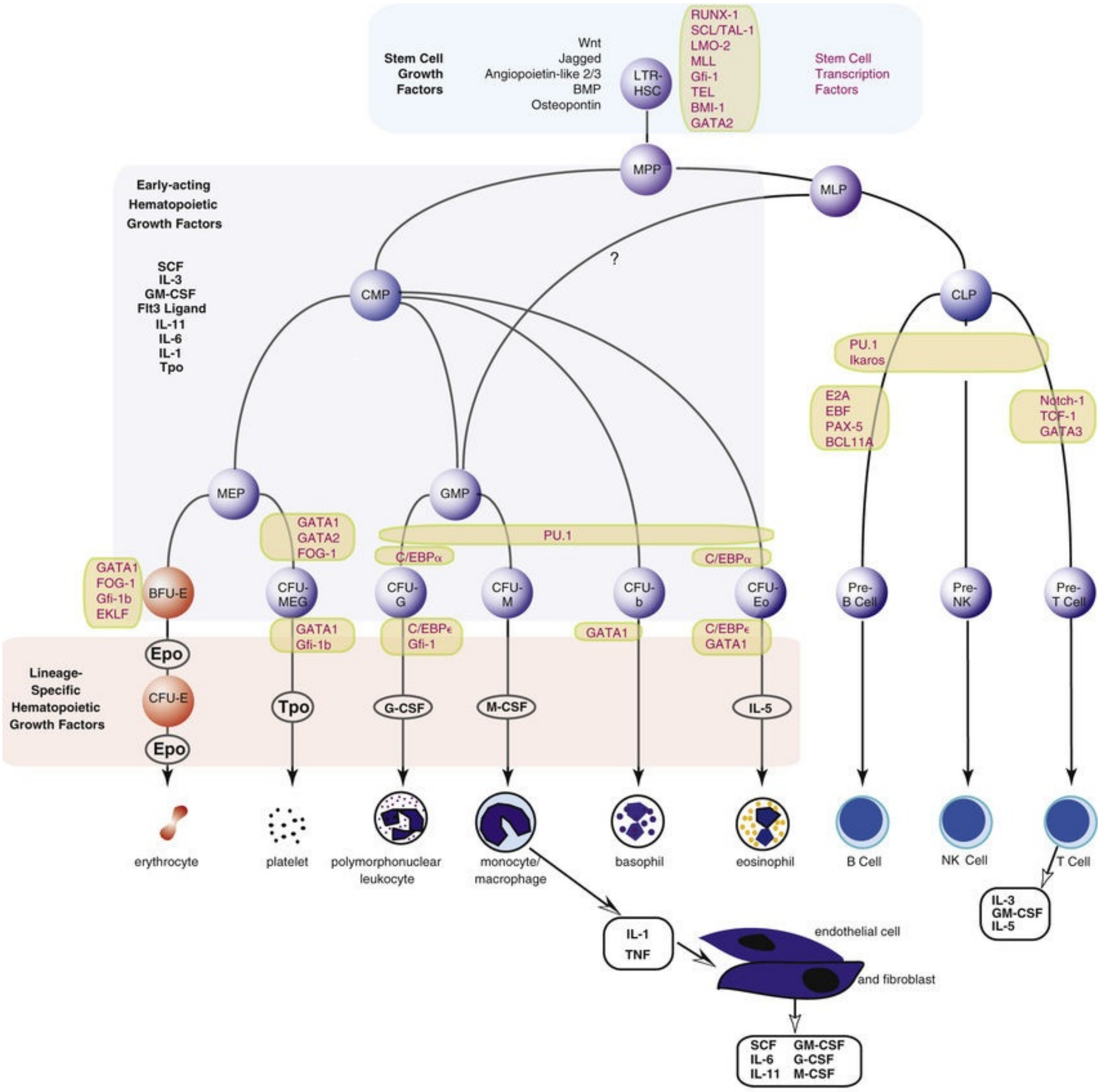
Stem Cell Growth Factors
Wnt
Jagged
Angiopoietin-like 2/3
BMP
Osteopontin
LTR-HSC
RUNX-1
SCL/TAL-1
LMO-2
MLL
Gfi-1
TEL
BMI-1
GATA2
Stem Cell Transcription Factors
MPP
MLP
Early-acting Hematopoietic Growth Factors
SCF
IL-3
GM-CSF
Flt3 Ligand
IL-11
IL-6
IL-1
Tpo
?
CMP
CLP
PU.1
Ikaros
E2A
EBF
PAX-5
BCL11A
Notch-1
TCF-1
GATA3
MEP
GMP
GATA1
GATA2
FOG-1
PU.1
C/EBPα
C/EBPα
GATA1
FOG-1
Gfi-1b
EKLF
BFU-E
CFU-MEG
CFU-G
CFU-M
CFU-b
CFU-Eo
Pre-B Cell
Pre-NK
Pre-T Cell
GATA1
Gfi-1b
C/EBPε
Gfi-1
GATA1
C/EBPε
GATA1
Epo
Lineage-Specific Hematopoietic Growth Factors
CFU-E
Epo
Tpo
G-CSF
M-CSF
IL-5
erythrocyte
platelet
polymorphonuclear leukocyte
monocyte/ macrophage
basophil
eosinophil
B Cell
NK Cell
T Cell
IL-3
GM-CSF
IL-5
IL-1
TNF
endothelial cell
and fibroblast
SCF
IL-6
IL-11
GM-CSF
G-CSF
M-CSF

FIG. 473.1 Major cytokine sources and actions to promote hematopoiesis. Cells of the bone marrow microenvironment, such as macrophages, endothelial cells, and reticular fibroblasts, produce macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF) after stimulation. These cytokines and others listed in the text have overlapping interactions during hematopoietic differentiation, as indicated; for all lineages, optimal development requires a combination of early- and late-acting factors. BFU, Burst-forming unit; CFU, colony-forming unit; Epo, erythropoietin; MSC, myeloid stem cells; PSC, pluripotent stem cells; SCF, stem cell factor; TNF, tumor necrosis factor; Tpo, thrombopoietin. (From Sieff CA, Daley GO, Zon LI: The anatomy and physiology of hematopoiesis. In Orkin SH, Nathan DG, Ginsburg D, et al, editors: *Nathan and Oski's hematology of infancy and childhood* , ed 8, Philadelphia, 2015, Elsevier.)

Erythrocytes in the fetus are larger than in adults, and at 22-23 wk gestation the mean corpuscular volume can be as high as 135 femtoliters (fL) (Fig. 473.2 , *upper panel*). Similarly, the mean corpuscular hemoglobin is very high at 22-23 wk and falls relatively linearly with advancing gestation (Fig. 473.2 , *lower panel*). In contrast, the mean corpuscular hemoglobin concentration is constant throughout gestation at 34 ±1 g/dL. While the size and quantity of hemoglobin in erythrocytes diminish during gestation, the hematocrit and blood hemoglobin concentration gradually increase (Fig. 473.3 , *upper* and *lower panels* , respectively).

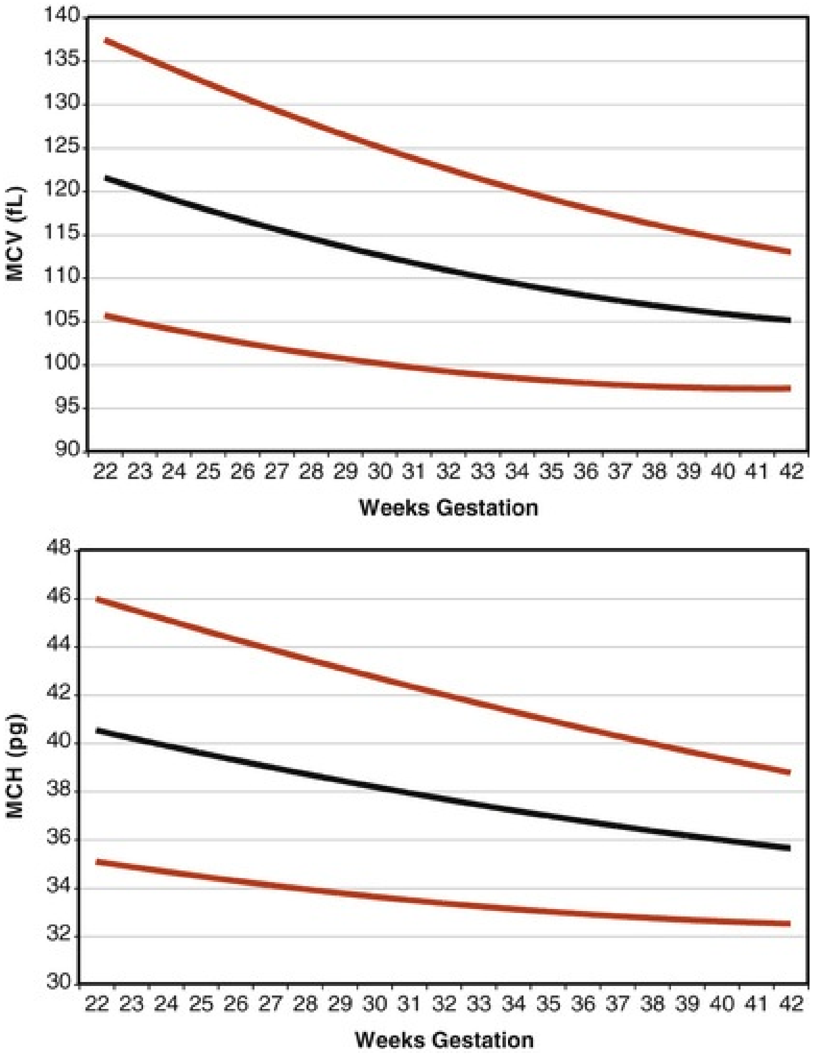

FIG. 473.2 **Erythrocyte mean corpuscular volume (MCV, *top*) and mean corpuscular hemoglobin (MCH, *bottom*) from 22 wk gestation through term. The *lines* represent the 5th percentile, the mean, and the 95th percentile reference range. (From Christensen RD, Jopling J, Henry E, et al: The erythrocyte indices of neonates, defined using data from over 12,000 patients in a multihospital healthcare system, *J Perinatol* 28:24–28, 2008.)**

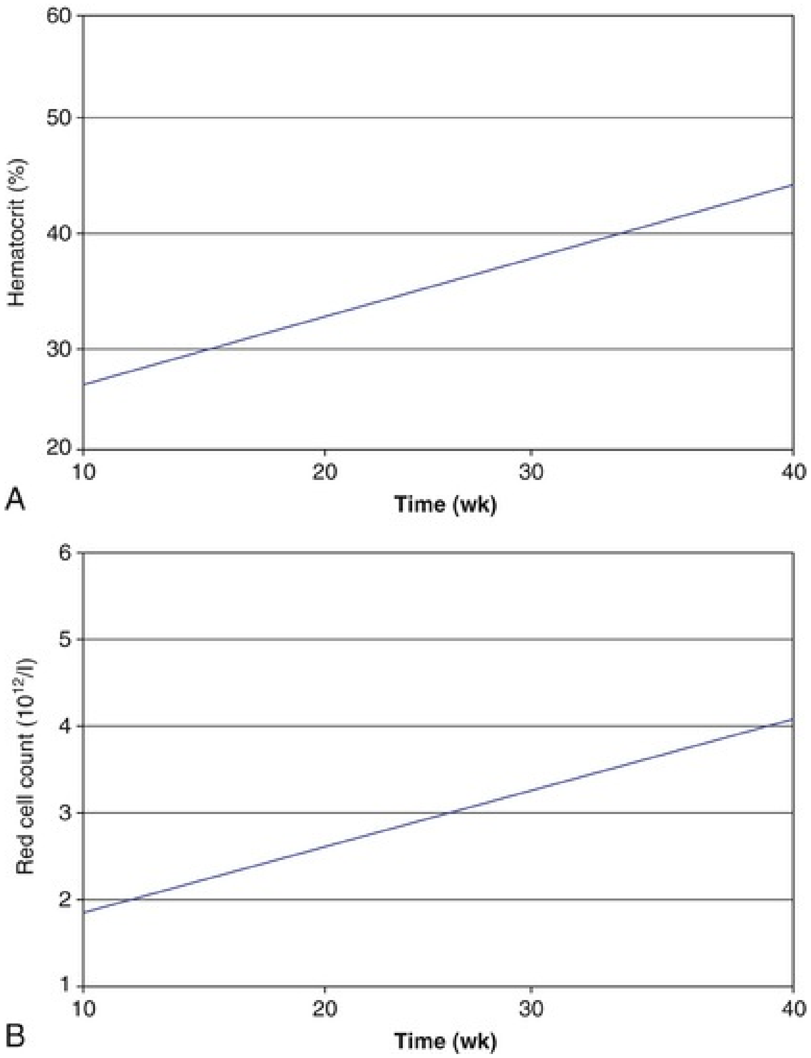

FIG. 473.3 Reference ranges of fetal hematocrit **(A)** and fetal red blood cell count **(B)** by cordocentesis throughout gestations.

Concentrations of **platelets** in the blood increase gradually between 22 and 40 wk gestation (Fig. 473.4), but the platelet size, assessed by mean platelet volume, remains constant at 8 ±1 fL. No differences are observed between males and females in fetal and neonatal reference ranges for erythrocyte indices, hematocrit, hemoglobin, platelet counts, or mean platelet volume measurements.

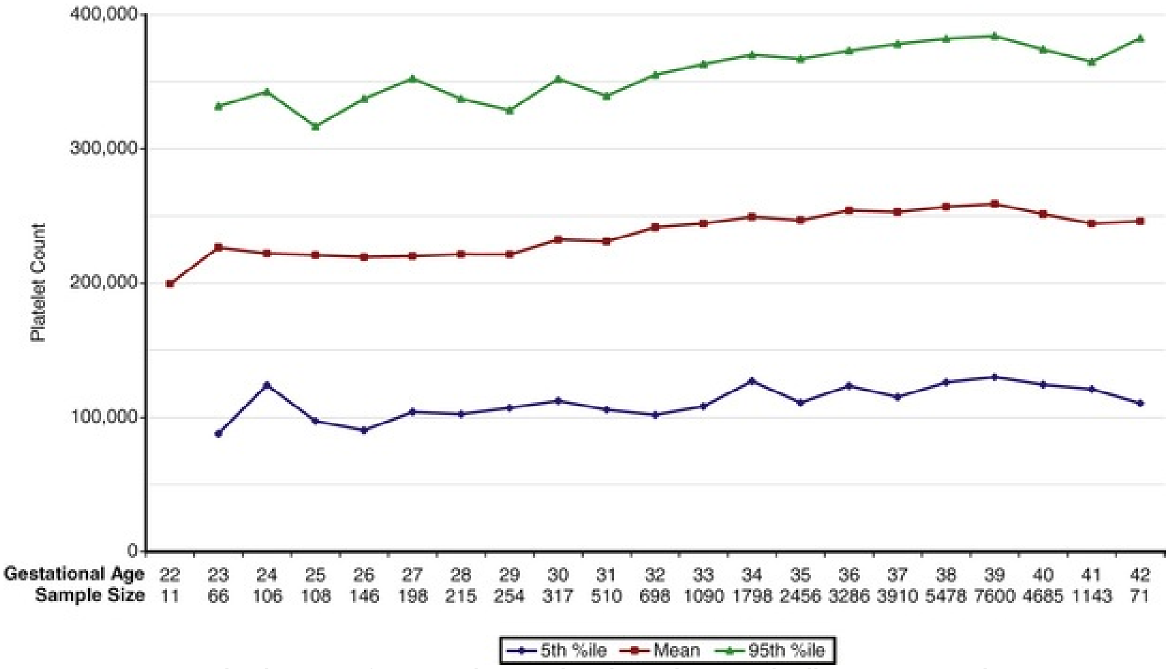

FIG. 473.4 Platelet count from 22 wk gestation through term. The *lines* represent the 5th percentile, the mean, and the 95th percentile reference range. (From Wiedmeier SE, Henry E, Sola-Visner MC, et al: Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system, *J Perinatol* 29:130–136, 2009.)

Fetal Granulocytopoiesis

Neutrophils are first observed in the human fetus about 5 wk after conception as small clusters of cells around the aorta. The fetal bone marrow space begins to develop around the 8th wk, and from 8-10 wk the marrow space enlarges, but no neutrophils appear there until 10.5 wk. From 14 wk through term, the most common granulocytic cell type in the fetal bone marrow space is the neutrophil. Neutrophils and macrophages originate from a common progenitor cell, but macrophages appear before neutrophils in the fetus, first in the yolk sac, liver, lung, and brain, all before the bone marrow cavity is formed.

Granulocyte colony-stimulating factor (G-CSF) and macrophage colony-stimulating factor (M-CSF) are expressed in developing fetal bone as early as 6 wk after conception, and both are expressed in the fetal liver as early as 8 wk. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and stem cell factor (SCF) also are distributed widely in human fetal tissues. However, no changes in expression of any of these factors, or of their specific receptors, appear to be the signal for fetal production of neutrophils or macrophages, because those signals have not yet been identified.

Fetal blood contains few neutrophils until the third trimester. At 20 wk gestation the blood neutrophil count is 0-500/mm^3 . Although mature neutrophils are scarce, progenitor cells with the capacity to generate neutrophil clones are abundant in fetal blood. When cultured in vitro in the presence of recombinant G-CSF, they mature into large colonies of neutrophils. The physiologic role of G-CSF includes upregulating neutrophil production, and this appears to be the case for the fetus and neonate as well as for adults. Thus the low number of circulating neutrophils in the mid-trimester human fetus may be caused in part by low production of G-CSF. Monocytes isolated from the blood of adults produce G-CSF when stimulated with a variety of inflammatory mediators, such as bacterial lipopolysaccharide (LPS) or interleukin (IL)-1. In contrast, monocytes isolated from the blood or organs of fetuses up to 24 wk gestation generate only small quantities of G-CSF protein and messenger RNA (mRNA) after LPS or IL-1 stimulation. Despite this, G-CSF receptors on the surface of neutrophils of newborn infants are equal in number and affinity to those on adult neutrophils.

In the fetus, actions of the granulocytopoietic factors (G-CSF, M-CSF, GM-CSF, and SCF) are not limited to hematopoiesis. Receptors for each of these are located in areas of the fetal central nervous system and gastrointestinal tract, where their patterns of expression change with development.

Fetal Thrombopoiesis

Several biologic differences exist between fetal/neonatal and adult megakaryopoiesis and thrombopoiesis. There is a developmentally unique pattern of fetal/neonatal megakaryopoiesis characterized by rapid proliferation, followed by full cytoplasmic maturation without polyploidization. Fetal and neonatal megakaryocytes are significantly smaller, exhibit lower ploidy, and produce fewer platelets. However, fetal and neonatal megakaryocytes have a higher proliferative potential than adult progenitors. These differences allow fetuses and neonates to populate their rapidly expanding bone marrow space and blood volume while maintaining normal platelet counts.

Megakaryocyte progenitors are categorized as *burst-forming unit–megakaryocytes* (BFU-MK), which are primitive megakaryocyte progenitors, and *colony-forming unit–megakaryocytes* (CFU-MK), which are more differentiated. BFU-MK produce large multifocal colonies containing ≥50 megakaryocytes, whereas CFU-MK generate smaller (3-50 cells/colony) unifocal colonies. **Megakaryocytes** are identified by their morphologic characteristics as they undergo endoreduplication, which results in large cells with polyploid nuclei. Megakaryocytes, unlike megakaryocyte progenitors, do not have the capacity to generate colonies. Rather, they undergo maturation, progressing from small mononuclear cells to large polyploid cells. The modal megakaryocyte *ploidy* (the number of sets of complete chromosomes) in normal adult marrow is 16N. In the fetus and neonate, ploidy is lower, primarily 2N and 4N, and megakaryocyte size is smaller. Large megakaryocytes generate more platelets than do small megakaryocytes; it is assumed that megakaryocytes of neonates produce fewer platelets than do their adult counterparts.

The exact mechanisms by which megakaryocytes release platelets into the circulation remain incompletely understood. In situ examination of this process suggests that mature megakaryocytes migrate to a perivascular site and extend a process through the endothelium, giving rise to proplatelets, which then release platelets. An alternate mechanism is that platelets are released from megakaryocytes in the lungs as a result of shear forces.

Thrombopoietin (TPO) is the dominant regulator of megakaryocyte development and platelet production (see Table 473.1). TPO is predominantly produced in the liver from early fetal to adult life but is also expressed by cells in the kidney, and to a lesser extent, by smooth muscle and marrow cells. TPO concentrations are higher in healthy neonates of any gestational age than in healthy adults. TPO is a primary stimulator of megakaryocyte and platelet production, but SCF, IL-3, IL-11, IL-6, and erythropoietin also stimulate megakaryopoiesis and thrombopoiesis in vitro and in vivo. Importantly, TPO also promotes expansion of hematopoietic stem cells (HSCs) and progenitor cells, and the TPO receptor is expressed on HSCs and erythroid progenitors in addition to megakaryocyte progenitors, megakaryocytes, and mature platelets.

Fetal Erythropoiesis

Similar to hematopoietic production of other cell lineages, fetal erythropoiesis is regulated by growth factors produced by the fetus, not by the mother. **Erythropoietin (EPO)** does not cross the human placenta. Stimulating maternal EPO production does not enhance fetal erythropoiesis, and suppressing maternal erythropoiesis by hypertransfusion does not suppress fetal erythropoiesis.

EPO plays a central regulatory role on the proliferation and maturation of erythroid progenitors. Erythroid-committed progenitors consist of *burst-forming unit–erythroid* (BFU-E) and *colony-forming unit–erythroid* (CFU-E) cells. In colony-forming assays, human BFU-E are more proliferative, forming colonies of multiple clusters of erythroblasts, vs CFU-E, which form 1 or 2 clusters with each containing 8-100 hemoglobinized erythroblasts. EPO is essential for erythrocyte production from CFU-E cells by inducing survival and proliferation of erythroblasts. EPO binds to specific receptors on the surface of committed erythroid precursors, and its expression is regulated by an oxygen-sensing mechanism through the hypoxia-inducible factor (HIF) family of proteins. HIF-1α and HIF-2α are regulated by oxygen tension, whereas HIF-1β is constitutively expressed. Together, HIF proteins maintain oxygen homeostasis and regulate erythropoiesis by inducing EPO under hypoxic conditions.

EPO is produced by monocytes and macrophages in the fetal liver during the first and second trimesters. After birth, the anatomic site of EPO production shifts to the kidney. The specific stimulus for this shift is unknown but may involve the increase in arterial oxygen tension that occurs at birth. Epigenetic modification of gene expression may also play a role, since it appears that renal and hepatic EPO genes are methylated to different degrees. Although EPO mRNA and protein can be found in the human fetal kidney, it is not known whether this production is biologically relevant. It appears that renal production of EPO is not essential for normal fetal erythropoiesis, as evidenced by the normal serum EPO concentration and normal hematocrit of anephric fetuses.

Hemoglobins in the Fetus and Neonate

Hemoglobin is a tetramer of 4 *globin* chains with an iron-containing porphyrin ring called *heme* bound to each chain. A dynamic interaction between heme and globin gives hemoglobin its unique properties in the reversible transport of oxygen. The hemoglobin molecule consists of 2 alpha (α)-like and 2 beta (β)-like polypeptide chains, with each chain having a heme group attached. The α-globin and β-globin gene clusters are located on chromosome 16 and 11, respectively (Fig. 473.5). There are 2 β-globin genes and 4 α-globin genes. Within erythrocytes of an early embryo, fetus, child, and adult, 6 different hemoglobins may normally be detected (Fig. 473.6): the **embryonic** hemoglobins (Gower-1, Gower-2, and Portland), **fetal** hemoglobin (HbF), and the **adult** hemoglobins (HbA and HbA_2). The electrophoretic mobilities of hemoglobins vary with their chemical structures.

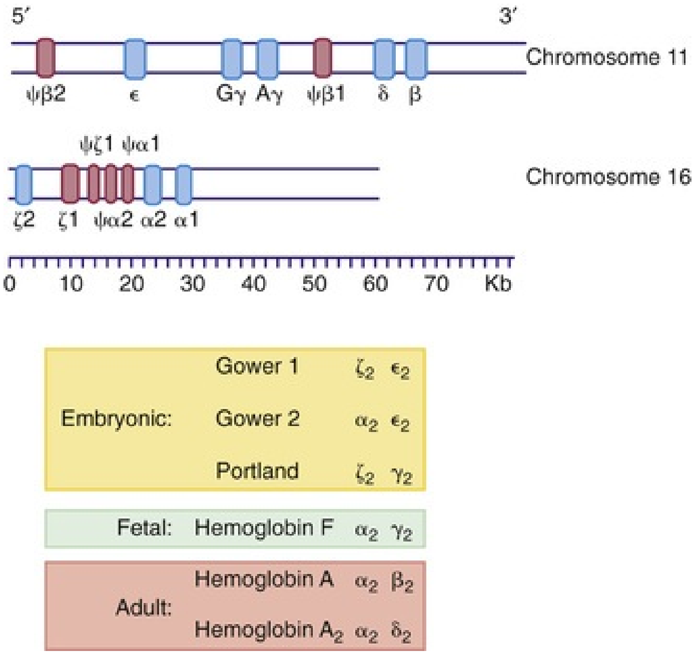
5′
3′
Chromosome 11
ψβ2
ϵ
Gγ
Aγ
ψβ1
δ
β
ψζ1
ψα1
Chromosome 16
ζ2
ζ1
ψα2
α2
α1
0
10
20
30
40
50
60
70
Kb
Embryonic:
Gower 1 ζ_2 ϵ_2
Gower 2 α_2 ϵ_2
Portland ζ_2 γ_2
Fetal:
Hemoglobin F α_2 γ_2
Adult:
Hemoglobin A α_2 β_2
Hemoglobin A_2 α_2 δ_2

FIG. 473.5 Organization of the globin genes. The *bottom line* reflects the scale in kilobases. The *upper segment* represents the β-like globin genes on chromosome 11, and the *lower segment* the α-like genes on chromosome 16. Regions of the gene that code for primary globin proteins are shown as *blue segments* , and regions that code for pseudogenes (“ψ,” nonexpressed remnants) are shown as *pink segments* . The composition of embryonic, fetal, and adult hemoglobins is listed. α, Alpha; β, beta; γ, gamma; δ, delta; ε, epsilon; ζ, zeta.

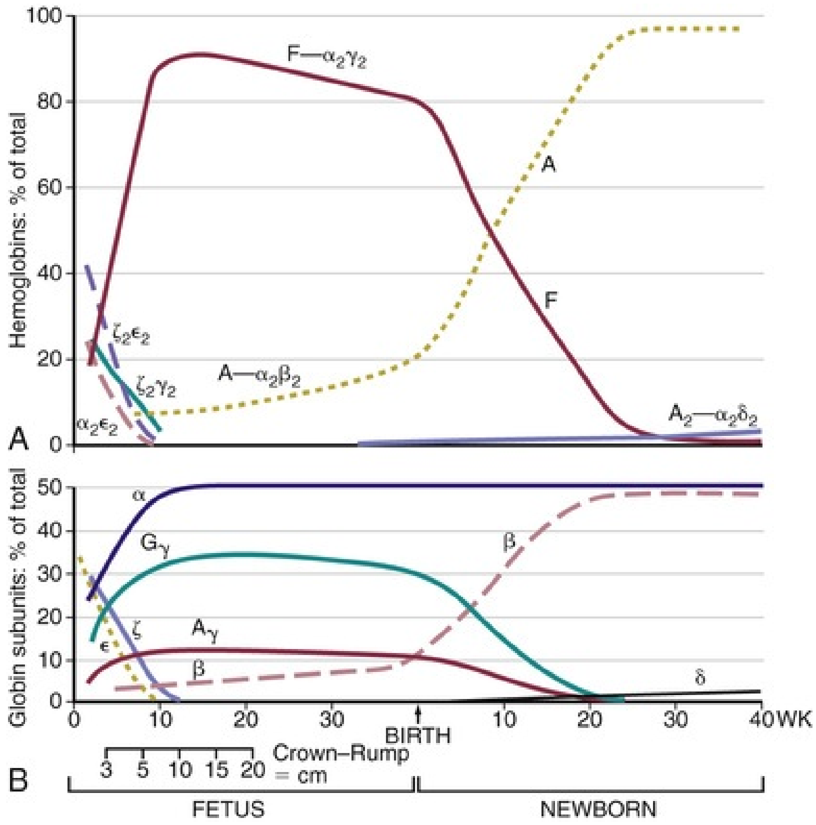

FIG. 473.6 Changes in hemoglobin tetramers (**A**) and in globin subunits (**B**) during human development from embryo to early infancy. (From Polin RA, Fox WW: *Fetal and neonatal physiology* , ed 2, Philadelphia, 1998, Saunders, p 1769.)

Expression and quantitative relationships among the hemoglobins are determined by complex developmental processes. Globin chain expression is developmental stage specific and occurs through 2 hemoglobin switches, mediated primarily through changes of the β-globin genes expressed. There are 5 functional β-like globin chain genes: embryonic (*HBE1*), 2 fetal (*HBG1*, *HBG2*), and 2 adult (*HBD*, *HBB*); and 3 α-like globin chain genes: embryonic (*HBZ*) and 2 adult (*HBA1*, *HBA2*). Primitive erythroid cells primarily express embryonic globins. The 1st β-globin switch occurs at approximately 6 wk gestation to fetal globin (*HBG*), which coincides with the onset of definitive hematopoiesis. The major hemoglobin in the fetus (HbF) consists of 2 α and 2 gamma (γ) globin chains ($\alpha_2 \gamma_2$). The 2nd globin switch is responsible for the expression of the major hemoglobin of a normal adult (HbA), consisting of 2 α and 2 β polypeptide chains ($\alpha_2 \beta_2$) and is first expressed at mid-gestation. A key regulator of the fetal-to-adult hemoglobin switch is the transcription factor **BCL11A** , which binds to the β-globin gene and acts to silence γ-globin expression and thus HbF.

Embryonic Hemoglobins

The blood of early human embryos contains 2 slowly migrating hemoglobins, *Gower-1* and *Gower-2*, and *Hb Portland,* which has HbF-like mobility. The zeta (ζ) chains of Hb Portland and Gower-1 are structurally quite similar to α chains. Both Gower hemoglobins contain the epsilon (ε) β-like globin polypeptide chain. Hb Gower-1 has the structure $\zeta_2 \varepsilon_2$, whereas Gower-2 has $\alpha_2 \varepsilon_2$. Hb Portland has the structure $\zeta_2 \gamma_2$. In embryos up to 6 wk gestation, the Gower hemoglobins predominate but are no longer detectable by 3 mo of gestation.

Fetal Hemoglobin

By 6-8 wk gestation, HbF ($\alpha_2 \gamma_2$) is the predominant hemoglobin; at 24 wk gestation it constitutes 90% of the total hemoglobin. HbF declines modestly in the third trimester, such that the HbF comprises 70–80% of the total hemoglobin. HbF production decreases rapidly postnatally (Fig. 473.7), and by 6-12 mo of age reaches adult levels of <2%. Understanding the molecular basis of the fetal-to-adult hemoglobin switch is of interest because of the therapeutic benefits to patients with β-thalassemia and sickle cell disease, whose clinical severity is improved with modest elevation of HbF. The exact mechanisms by which BCL11A acts to repress HbF are not fully elucidated, but erythroid-specific enhancers of BCL11A have been identified and are potential targets for therapeutic HbF induction.

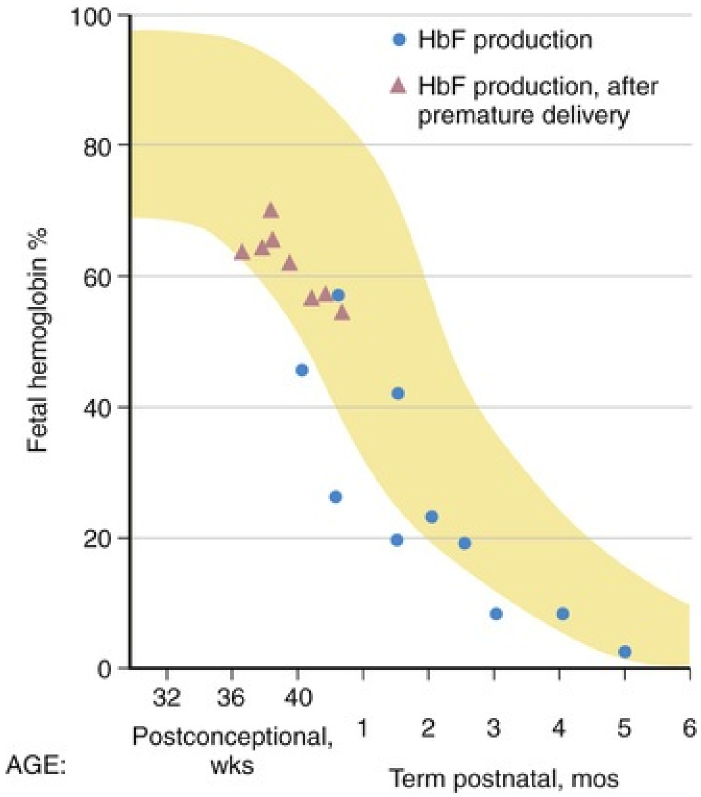

FIG. 473.7 Pre- and postnatal changes in the percentage of total hemoglobin represented by fetal hemoglobin (HbF) (*yellow*). The *triangles* represent postnatal production by reticulocytes in premature infants, and the *circles* represent cord blood and postnatal reticulocyte production in term infants. (From Brown MS: Fetal and neonatal erythropoiesis. In Stockman JA, Pochedly C, editors: *Developmental and neonatal hematology* , New York, 1988, Raven Press.)

Adult Hemoglobins

HbA constitutes 5–10% of total hemoglobin at 24 wk gestation and steadily increases, so that at term, HbA averages 30% of total hemoglobin. By 6-12 mo of age, individuals reach adult levels of HbA. The minor adult hemoglobin component, HbA_2 , contains delta (δ) chains and has the structure $\alpha_2 \delta_2$. At birth, <1.0% of HbA_2 is detected, but by 12 mo of age the normal level is 2.0–3.4%. Throughout life, the normal ratio of HbA to HbA_2 is about 30 : 1.

Alterations of the Hemoglobins by Disease

HbF levels may be elevated with hemoglobinopathies, hereditary persistence of fetal hemoglobin, or bone marrow failure syndromes or may be associated with stress erythropoiesis. Since the HbF level is elevated during the 1st yr of life, knowledge of its normal pattern of decline is important (see Figs. 473.6 and 473.7). Two disorders resulting from mutations in the β-globin gene (HBB), β-thalassemia and sickle cell disease, become symptomatic postnatally as fetal γ-globin expression decreases and adult β-globin increases. In both these disorders, elevated HbF levels persist in childhood and later. In patients with the most severe type, β^0 thalassemia, except for a small amount of HbA_2 , HbF is the only hemoglobin produced. At the other end of the spectrum, in individuals with β-thalassemia trait, the postnatal decrease of HbF is delayed and mildly elevated levels of HbF (>2%) may persist throughout life. Individuals with sickle cell disease, who also have a mutation in the *HBB* gene, typically demonstrate elevated levels of HbF, ranging from approximately 5% to up to 30%. In contrast, elevated HbF is not characteristic of α-thalassemia syndromes, but tetramers of γ chains (γ_4 or Hb Barts) may be found in the neonatal period. Since α-globin chains are expressed in fetal and adult hemoglobin, 4 α gene mutations leading to functional deletions is not compatible with life. Fetuses die in utero or shortly after birth from the severe anemia and hydrops fetalis. Inheritance of only 1 normal gene of the 4 (α −/−) results in **hemoglobin H disease** , which is usually associated with a moderate anemia. Inheritance of 2 or 3 normal α genes results in α-**thalassemia** trait or carrier status, respectively.

Hereditary persistence of fetal hemoglobin (HPFH) is a benign genetic condition caused by heterozygous deletions or nucleotide substitutions in regions of the β-globin locus that regulate transcription of *HBG1* and *HBG2* , causing persistent pancellular HbF expression levels of approximately 30% of total hemoglobins. Individuals with HPFH do not exhibit anemia.

Preterm infants treated with human recombinant EPO increase HbF production during active erythropoiesis. Moderate elevations of HbF may also occur in many diseases accompanied by hematologic stress, such as hemolytic anemias, leukemia, and bone marrow failure syndromes such as Diamond Blackfan anemia.

The normal adult level of HbA_2 (2.0–3.4%) is seldom altered. Levels of HbA_2 >3.4% are found in most persons with the β-thalassemia trait and in those with megaloblastic anemias secondary to vitamin B_{12} and folic acid deficiency. Decreased HbA_2 levels are found in those with iron-deficiency anemia (see Chapter 482) and α-thalassemia (see Chapter 489.10).

Red Cell Life Span in the Fetus and Neonate

In general, the highest hematocrit during a person's lifetime occurs at birth, and the lowest hematocrit occurs at the physiologic nadir that occurs 8-10 wk postnatally. A shortened life span of fetal and neonatal red blood cells (RBCs) has been suggested as an important component. The average erythrocyte life span in normal adults is approximately 120 days. The life span of fetal/neonatal erythrocytes was once estimated to be considerably less, with an average of 60-90 days suggested by chromium (^{51} Cr)-labeled erythrocyte studies. However, newer studies indicate that the life span of fetal/neonatal RBCs is similar to that of adults. **Neocytolysis** is the active removal of young erythrocytes that were generated in relatively hypoxic conditions, following normoxic or hyperoxic conditions. This process has also been suggested as an explanation for the physiologic nadir of neonates.

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CHAPTER 474

The Anemias

Courtney D. Thornburg

Anemia is defined as a reduction of the **hemoglobin** concentration or red blood cell (RBC) volume below the range of values occurring in healthy persons. "Normal" hemoglobin and hematocrit (packed red cell volume) vary substantially with age and sex (Table 474.1). There are also racial differences, with significantly lower hemoglobin levels in African American children than in white non-Hispanic children of comparable age (Table 474.2). Anemia is a significant global health problem affecting children and reproductive-age women (Figs. 474.1 and 474.2).

Table 474.1

Normal Mean and Lower Limits of Normal for Hemoglobin, Hematocrit, and Mean Corpuscular Volume

AGE (yr)	HEMOGLOBIN (g/dL)		HEMATOCRIT (%)		MEAN CORPUSCULAR VOLUME (μM^3)	
	Mean	Lower Limit	Mean	Lower Limit	Mean	Lower Limit
0.5-1.9	12.5	11.0	37	33	77	70
2-4	12.5	11.0	38	34	79	73
5-7	13.0	11.5	39	35	81	75
8-11	13.5	12.0	40	36	83	76
12-14 female	13.5	12.0	41	36	85	78
12-14 male	14.0	12.5	43	37	84	77
15-17 female	14.0	12.0	41	36	87	79
15-17 male	15.0	13.0	46	38	86	78
18-49 female	14.0	12.0	42	37	90	80
18-49 male	16.0	14.0	47	40	90	80

From Brugnara C, Oski FJ, Nathan DG: *Nathan and Oski's hematology of infancy and childhood* , ed 7, Philadelphia, 2009, Saunders, p 456.

Table 474.2

NHANES-III Hemoglobin Values for Non-Hispanic Whites and African Americans Ages 2-18 Yr[*]

AGE (yr)	WHITE NON-HISPANIC		AFRICAN AMERICAN	
	Mean	**−2 SD**	**Mean**	**−2 SD**
2-5	12.21	10.8	11.95	10.37
6-10	12.87	11.31	12.40	10.74
11-15 male	13.76	11.76	13.06	10.88
11-15 female	13.32	11.5	12.61	10.85
16-18 male	15.00	13.24	14.18	12.42
16-18 female	13.39	11.61	12.37	10.37

[*] Sample size is 5,142 (white, 2,264; African-American, 2,878).

NHANES-III, Third National Health and Nutrition Examination Survey; SD, standard deviation.

Adapted from Robbins EB, Blum S: Hematologic reference values for African American children and adolescents, *Am J Hematol* 82:611–614, 2007.

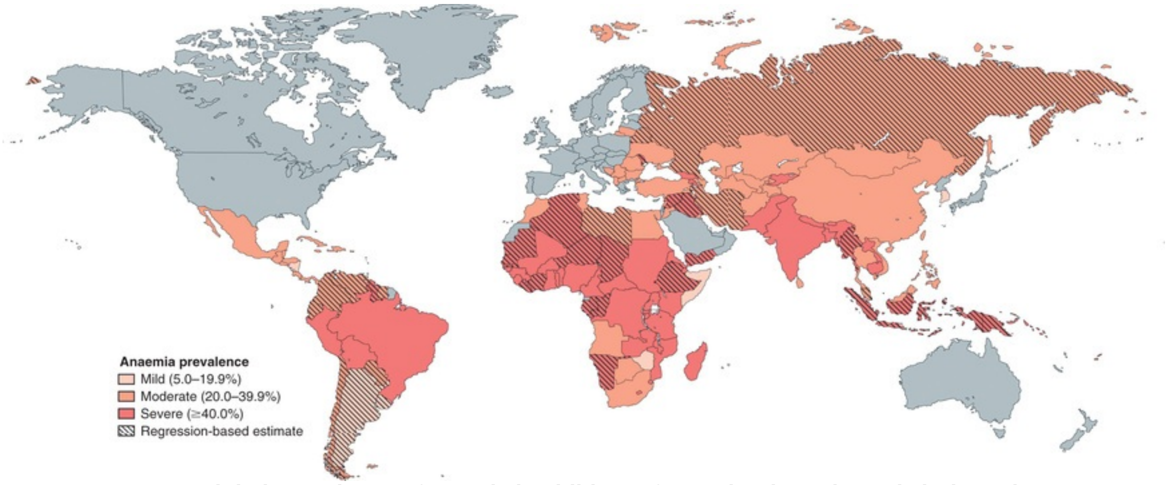

FIG. 474.1 Global prevalence of anemia in children of preschool age (0-5 yr). (Adapted from Worldwide prevalence of anaemia 1993–2005. In *WHO global database on anaemia,* Geneva, 2008, World Health Organization.)

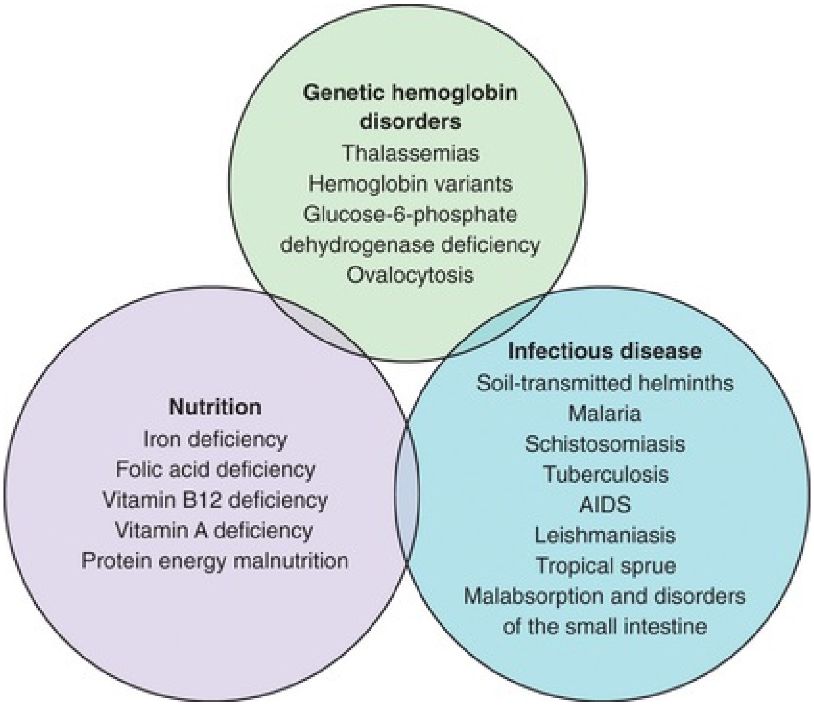
Genetic hemoglobin disorders
Thalassemias
Hemoglobin variants
Glucose-6-phosphate dehydrogenase deficiency
Ovalocytosis
Nutrition
Iron deficiency
Folic acid deficiency
Vitamin B12 deficiency
Vitamin A deficiency
Protein energy malnutrition
Infectious disease
Soil-transmitted helminths
Malaria
Schistosomiasis
Tuberculosis
AIDS
Leishmaniasis
Tropical sprue
Malabsorption and disorders of the small intestine

FIG. 474.2 **Causes of anemia in countries with low- or middle-income populations. (From Balarajan Y, Ramakrishnan U, Özaltin E, et al: Anaemia in low-income and middle-income countries, *Lancet* 378:2123–2134, 2011, Fig 3.)**

Physiologic adjustments to anemia include increased cardiac output, augmented oxygen extraction (increased arteriovenous oxygen difference), and a shunting of blood flow toward vital organs and tissues. In addition, the concentration of 2,3-diphosphoglycerate increases within the RBC. The resultant "shift to the right" of the oxygen dissociation curve reduces the affinity of hemoglobin for oxygen and results in more complete transfer of oxygen to the tissues. The same shift in the oxygen dissociation curve can also occur at high altitude. Higher levels of erythropoietin (EPO) and consequent increased RBC production by the bone marrow further assist the body to adapt.

History and Physical Examination

As with any medical condition, a detailed history and thorough physical exam are essential when evaluating an anemic child. Important historical facts should include age, sex, race and ethnicity, diet, medications, chronic diseases, infections, travel, and exposures. A family history of anemia and associated difficulties (e.g., splenomegaly, jaundice, early-age onset of gallstones) is also important. Often, few physical symptoms or signs result solely from a low hemoglobin, particularly when the anemia develops slowly. Clinical findings generally do not become apparent until the hemoglobin level falls to <7-8 g/dL. Clinical features can include pallor, sleepiness, irritability, and decreased exercise tolerance. Pallor can involve the tongue, nail beds, conjunctiva, palms, or palmar creases. A flow murmur is often present. Ultimately, weakness, tachypnea, shortness of breath on exertion, tachycardia, cardiac dilation, and high-output heart failure will result from increasingly severe anemia, regardless of its cause. Unusual physical findings linked to particular underlying disease etiologies are discussed in detail in sections describing the associated disorders and in Table 474.3 .

Table 474.3

Physical Findings in the Evaluation of Anemia

SYSTEM	OBSERVATION	SIGNIFICANCE
Skin	Hyperpigmentation	Fanconi anemia, congenital dyskeratosis
	Café au lait spots	Fanconi anemia
	Vitiligo	Vitamin B_{12} deficiency
	Partial oculocutaneous albinism	Chédiak-Higashi syndrome
	Jaundice	Hemolysis, hepatitis
	Petechiae, purpura	Bone marrow infiltration, autoimmune hemolysis with autoimmune thrombocytopenia, hemolytic-uremic syndrome
	Erythematous rash	Parvovirus, Epstein-Barr virus
	Butterfly rash	Systemic lupus erythematosus
Head	Frontal bossing	Thalassemia major, severe iron deficiency, chronic subdural hematoma
	Microcephaly	Fanconi anemia Diamond-Blackfan syndrome
Eyes	Microphthalmia	Fanconi anemia
	Retinopathy	Hemoglobin SS, SC disease
	Optic atrophy, blindness	Osteopetrosis
	Blocked lacrimal gland	Dyskeratosis congenital
	Kayser-Fleischer ring	Wilson disease
	Blue sclera	Iron deficiency
Ears	Deafness	Osteopetrosis
Mouth	Glossitis	Vitamin B_{12} deficiency, iron deficiency
	Angular stomatitis	Iron deficiency
	Cleft lip, palate	Diamond-Blackfan syndrome
	Pigmentation	Peutz-Jeghers syndrome (intestinal blood loss)
	Telangiectasia	Osler-Weber-Rendu syndrome (blood loss)
	Leukoplakia	Dyskeratosis congenital
Chest	Shield chest or widespread nipples	Diamond-Blackfan syndrome
	Murmur	Endocarditis; prosthetic valve hemolysis
Abdomen	Hepatomegaly	Hemolysis, infiltrative tumor, chronic disease, hemangioma, cholecystitis
	Splenomegaly	Hemolysis, sickle cell disease (early), thalassemia, malaria, lymphoma,

		Epstein-Barr virus, portal hypertension, hemophagocytic syndromes
	Nephromegaly	Fanconi anemia
	Absent kidney	Fanconi anemia
Extremities	Absent thumbs	Fanconi anemia
	Thenar eminence hypoplasia: triphalangeal thumb	Diamond-Blackfan syndrome
	Spoon nails	Iron deficiency
	Beau line (nails)	Heavy metal intoxication, severe illness
	Mees line (nails)	Heavy metals, severe illness, sickle cell anemia
	Dystrophic nails	Dyskeratosis congenital
	Edema	Milk-induced protein-losing enteropathy with iron deficiency, renal failure
Rectal	Hemorrhoids	Portal hypertension
	Heme-positive stool	Intestinal hemorrhage
Nerves	Irritable, apathy	Iron deficiency
	Peripheral neuropathy	Deficiency of vitamins B_1 and B_{12} , lead poisoning
	Dementia	Deficiency of vitamins B_{12} and E
	Ataxia, posterior column signs	Deficiency of vitamins B_{12} and E
	Stroke	Sickle cell anemia, paroxysmal nocturnal hemoglobinuria

Adapted from Scott JP: Hematology. In Behrman RE, Kliegman RM, editors. *Nelson essentials of pediatrics,* ed 2, Philadelphia, 1994, Saunders, p 520.

Laboratory Studies

Initial laboratory testing should include hemoglobin, hematocrit, and RBC indices as well as a white blood cell (WBC) count and differential, platelet count, reticulocyte count, and examination of the peripheral blood smear. The need for additional laboratory studies is dictated by the history, physical exam, and results of this initial testing.

Differential Diagnosis

Anemia is not a specific entity but rather can result from any of a number of underlying pathologic processes. To narrow the diagnostic possibilities, anemias may be classified on the basis of their morphology and physiology (Fig. 474.3).

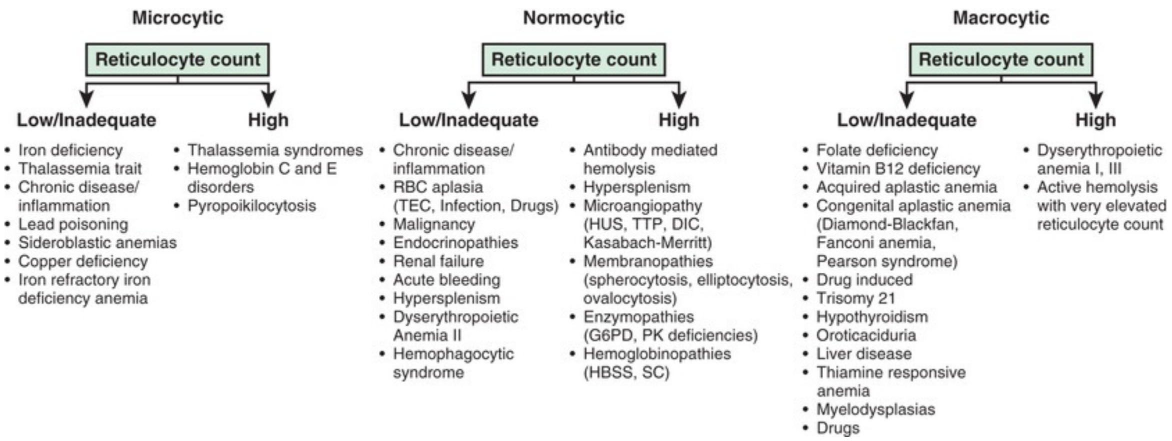
Microcytic
Reticulocyte count
Low/Inadequate
• Iron deficiency
• Thalassemia trait
• Chronic disease/ inflammation
• Lead poisoning
• Sideroblastic anemias
• Copper deficiency
• Iron refractory iron deficiency anemia
High
• Thalassemia syndromes
• Hemoglobin C and E disorders
• Pyropoikilocytosis
Normocytic
Reticulocyte count
Low/Inadequate
• Chronic disease/ inflammation
• RBC aplasia (TEC, Infection, Drugs)
• Malignancy
• Endocrinopathies
• Renal failure
• Acute bleeding
• Hypersplenism
• Dyserythropoietic Anemia II
• Hemophagocytic syndrome
High
• Antibody mediated hemolysis
• Hypersplenism
• Microangiopathy (HUS, TTP, DIC, Kasabach-Merritt)
• Membranopathies (spherocytosis, elliptocytosis, ovalocytosis)
• Enzymopathies (G6PD, PK deficiencies)
• Hemoglobinopathies (HBSS, SC)
Macrocytic
Reticulocyte count
Low/Inadequate
• Folate deficiency
• Vitamin B12 deficiency
• Acquired aplastic anemia
• Congenital aplastic anemia (Diamond-Blackfan, Fanconi anemia, Pearson syndrome)
• Drug induced
• Trisomy 21
• Hypothyroidism
• Oroticaciduria
• Liver disease
• Thiamine responsive anemia
• Myelodysplasias
• Drugs
High
• Dyserythropoietic anemia I, III
• Active hemolysis with very elevated reticulocyte count

FIG. 474.3 **Use of the mean corpuscular volume (MCV) and reticulocyte count in the diagnosis of anemia. (Adapted from Brunetti M, Cohen J: *The Harriet Lane handbook* , ed 17, Philadelphia, 2005, Elsevier Mosby, p 338.)**

Anemias may be morphologically categorized on the basis of red cell size (mean corpuscular volume [MCV]) and microscopic appearance. Anemias can be classified as *microcytic, normocytic,* or *macrocytic* based on whether the MCV is low, normal, or high, respectively. RBC size also changes with age, and normal developmental changes in MCV should be recognized before a designation is made (see Table 474.1). Examination of a peripheral blood smear often reveals changes in RBC appearance that will help to narrow further the diagnostic categories (Fig. 474.4 and Table 474.4). Details regarding morphologic changes associated with particular disorders are described in subsequent sections.

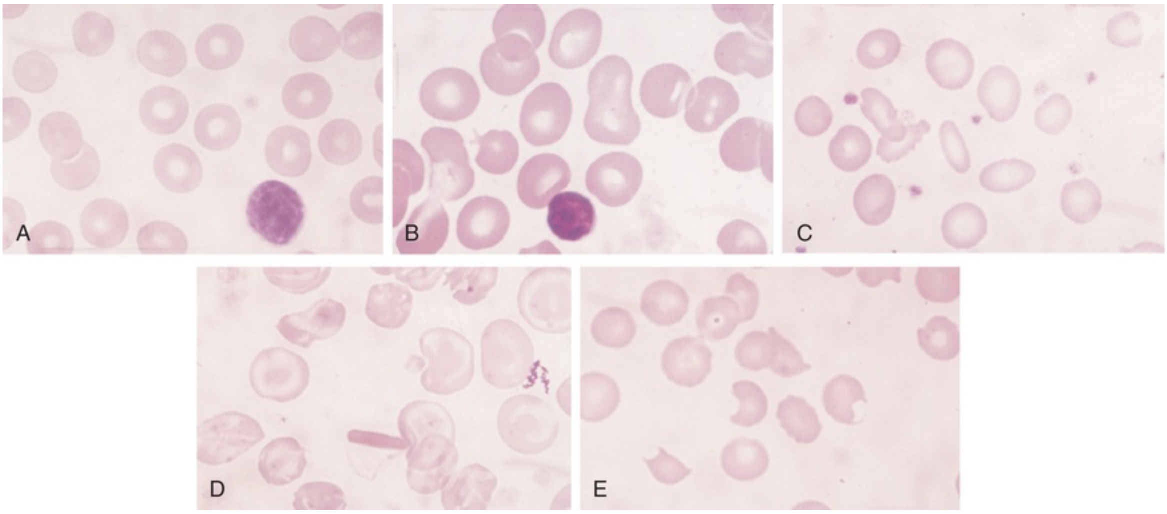

FIG. 474.4 **Morphologic abnormalities of the red blood cell. A, Normal. B, Macrocytes (folic acid or vitamin B_{12} deficiency). C, Hypochromic microcytes (iron deficiency). D,**

Target cells (HbCC disease). E, Schizocytes (hemolytic-uremic syndrome). (Courtesy of Dr. E. Schwartz.)

Table 474.4

Peripheral Blood Morphologic Findings in Various Anemias

Microcytes

- Iron deficiency
- Thalassemias
- Lead toxicity
- Anemia of chronic disease

Macrocytes

- Newborns
- Vitamin B_{12} or folate deficiency
- Diamond-Blackfan anemia
- Fanconi anemia
- Aplastic anemia
- Liver disease
- Down syndrome
- Hypothyroidism

Spherocytes

- Hereditary spherocytosis
- Immune hemolytic anemia (newborn or acquired)
- Hypersplenism

Sickled Cells

- Sickle cell anemias
  - SS disease

SC disease
Sβ^+ thalassemia
Sβ^0 thalassemia

Elliptocytes

Hereditary elliptocytosis
Iron deficiency
Megaloblastic anemia

Target Cells

Hemoglobinopathies (especially hemoglobin C, SC, and thalassemia)
Liver disease
Xerocytosis

Basophil Stippling

Thalassemia
Lead intoxication
Myelodysplasia

RBC Fragments, Helmet Cells, Burr Cells

Disseminated intravascular coagulation
Hemolytic-uremic syndrome
Thrombotic thrombocytopenic purpura
Kasabach-Merritt syndrome
Waring blender syndrome
Uremia
Liver disease

Hypersegmented Neutrophils

Vitamin B_{12} or folate deficiency

Blasts

Leukemia (ALL or AML)
Severe infection (rarely)
Leukopenia, thrombocytopenia
Fanconi anemia
Aplastic anemia
Leukemia
Hemophagocytic histiocytosis

Howell-Jolly Bodies

Asplenia, hyposplenia
Severe iron deficiency

ALL, Acute lymphocytic leukemia; AML, acute myeloid leukemia.

From Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis*, Philadelphia, 2018, Elsevier (Table 37-7, p 666).

Anemias may also be further divided on the basis of underlying physiology. The 2 major categories are **decreased production** and **increased destruction** (or **loss**). The 2 groups are not always mutually exclusive. Decreased RBC production may be a consequence of ineffective erythropoiesis or a complete or relative failure of erythropoiesis. Increased destruction or loss may be secondary to hemolysis, sequestration, or bleeding. The peripheral blood reticulocyte percentage or absolute number helps to distinguish between the 2 physiologic categories. The normal reticulocyte percentage of total RBCs during most of childhood is approximately 1%, with an absolute reticulocyte count of 25,000-75,000/mm^3 . In the presence of anemia, EPO production and the absolute number of reticulocytes should rise. Low or normal numbers of reticulocytes generally represent an inadequate response to anemia that is associated with relative bone marrow failure or ineffective erythropoiesis. Increased numbers of reticulocytes represent a normal bone marrow response to ongoing RBC destruction (hemolysis), sequestration, or loss (bleeding).

Fig. 474.3 presents a useful approach to assessing the common causes of anemia in the pediatric age-group. Children with **microcytic anemia** and low or normal reticulocyte counts most often have defects in erythroid maturation or ineffective erythropoiesis. **Iron deficiency** is the most common cause (see Chapter 482). **Thalassemia trait** constitutes the primary differential diagnosis when iron deficiency is suspected (see Chapter 489). Distinctions between these entities are presented in Table 482.2 (see Chapter 482). Chronic disease or inflammation (more often normocytic), lead poisoning, and sideroblastic anemias should also be considered and are discussed in other chapters. Microcytosis and elevated reticulocyte counts are associated with thalassemia syndromes and hemoglobins C and E (see Chapter 489). Notably, thalassemias and hemoglobinopathies are most often seen in patients of Mediterranean, Middle Eastern, African, or Asian descent.

Normocytic anemia and low reticulocyte count characterize a large number of anemias. The **anemia of chronic disease/inflammation** is usually normocytic (see Chapter 482). The anemia associated with renal failure, primarily a result of reduced EPO production, will invariably be associated with clinical and laboratory evidence of significant kidney disease. Decreased or absent RBC production secondary to transient erythroblastopenia of childhood, infection, drugs, or endocrinopathy usually results in a normocytic anemia, as does bone marrow infiltration by malignancy. In the case of invading leukemia or malignancy, abnormal leukocytes or tumor cells in association with thrombocytopenia or reduced or elevated WBC counts may be seen. Acute bleeding, hypersplenism, and congenital dyserythropoietic anemia type II are also normocytic (see Chapter 479).

In children with normocytic anemia and an appropriate (high) reticulocyte response, the anemia is usually caused by bleeding, hypersplenism, or ongoing hemolysis. In hemolytic conditions, reticulocytosis, indirect hyperbilirubinemia, and increased serum lactate dehydrogenase are indicators of accelerated erythrocyte destruction. Many causes of hemolysis result from conditions that are extrinsic (usually acquired) or intrinsic (usually congenital) to the erythrocyte. Abnormal RBC morphology (e.g., spherocytes, sickle forms, microangiopathy) identified on the peripheral smear is often helpful in ascertaining the cause.

The anemia seen in children with macrocytic blood cells is sometimes megaloblastic, resulting from impaired DNA synthesis and nuclear development (see Chapter 481). The peripheral blood smear in **megaloblastic anemias** contains large macroovalocytes, and the neutrophils often show nuclear hypersegmentation. The major causes of megaloblastic anemia include folate deficiency, vitamin B_{12} deficiency, and rare inborn errors of metabolism. Other **macrocytic anemias** with low or normal reticulocyte counts include acquired and congenital (Diamond-Blackfan and Fanconi syndromes) aplastic anemias and hypothyroidism. Patients with trisomy 21 have macrocytic cells, although an accompanying anemia is generally not present. High MCV and reticulocytosis is seen in congenital dyserythropoietic anemias I and III and in situations where hemolysis results in such a large outpouring of young red cells that the mean MCV is abnormally high.

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SECTION 2

Anemias of Inadequate Production

OUTLINE

Chapter 475 Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)
Chapter 476 Pearson Syndrome
Chapter 477 Acquired Pure Red Blood Cell Anemia
Chapter 478 Anemia of Chronic Disease and Renal Disease
Chapter 479 Congenital Dyserythropoietic Anemias
Chapter 480 Physiologic Anemia of Infancy
Chapter 481 Megaloblastic Anemias
Chapter 482 Iron-Deficiency Anemia
Chapter 483 Other Microcytic Anemias

CHAPTER 475

Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)

Courtney D. Thornburg

Diamond-Blackfan anemia (DBA) is a rare, congenital **bone marrow failure syndrome** that usually becomes symptomatic in early infancy. More than 90% of cases are recognized in the 1st yr of life. The disorder is characterized by anemia, usually normochromic and macrocytic; reticulocytopenia; and insufficient or absent red blood cell (RBC) precursors in an otherwise normally cellular bone marrow. Up to 50% of affected individuals have additional, extrahematopoietic anomalies.

Etiology

DBA-associated mutations were initially identified in 1997 in *RPS19*, a gene that encodes a component protein of the small 40S ribosomal subunit. Such *RPS19* mutations, all dominantly inherited, were found to be present in approximately 25% of patients. Additional ribosomal protein (RP) genes, each encoding a different small (40S) or large (60S) ribosomal subunit protein, have been identified. Mutations in RP genes were ultimately identified in up to 70% of cases, most with autosomal dominant inheritance. Novel mutations continue to be identified and reported. Since the majority of causative mutations are in RP genes, the disorder is often referred to as a **ribosomopathy** .

GATA1 , a non-RP gene, has also been implicated in DBA. The *GATA1* mutations are inherited as X-linked recessive and usually have no extrahematopoietic manifestations. It remains unclear whether 2 pathways, 1 related to ribosomal dysfunction and 1 to impaired *GATA1* production, independently cause the same phenotype, or alternatively, that DBA results from problems in a single pathway involving functional links between ribosomes and *GATA1* (Fig. 475.1).

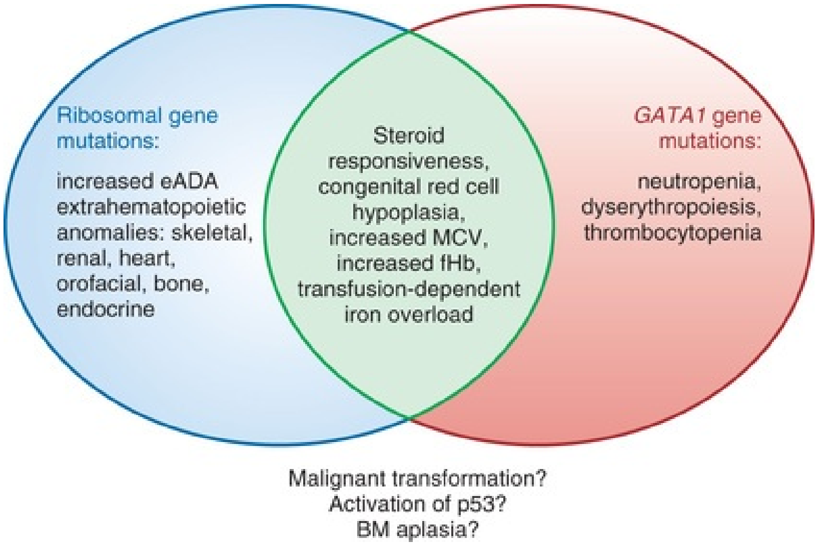
Ribosomal gene mutations:
increased eADA
extrahematopoietic anomalies: skeletal, renal, heart, orofacial, bone, endocrine
Steroid responsiveness, congenital red cell hypoplasia, increased MCV, increased fHb, transfusion-dependent iron overload
GATA1 gene mutations:
neutropenia, dyserythropoiesis, thrombocytopenia
Malignant transformation?
Activation of p53?
BM aplasia?

FIG. 475.1 Common and distinct phenotypes in congenital red cell aplasia caused by mutations in RP genes and in *GATA1* . BM, Bone marrow; eADA, erythrocyte adenosine deaminase activity; fHb, fetal hemoglobin; *MCV,* mean corpuscular volume. (Adapted from Weiss MJ, Mason PJ, Bessler M: What's in a name? J Clin Invest 122:2346–2349, 2012.)

Epidemiology

DBA affects about 7 individuals per 1 million live births. It is primarily an autosomal dominant disease, although other inheritance patterns may yet be demonstrated. Notably, there is substantial phenotypic diversity in DBA, even in families whose members share the same mutation, suggesting that additional genetic modifiers affect phenotypic expression of the disease. International consensus recommendations suggest that a diagnosis of “nonclassical” DBA be applied to family members harboring an established mutation or those without a known mutation but with an associated anomaly or laboratory abnormality.

Clinical Manifestations

Profound anemia usually becomes evident by 2-6 mo of age, occasionally somewhat later. Approximately 25% of patients are anemic at birth, and hydrops fetalis occurs rarely; 92% are diagnosed within the 1st yr of life. Approximately 40–50% of patients have congenital anomalies, and >1 anomaly is found in 25% of DBA patients (Table 475.1). Craniofacial abnormalities are the most common (50% of patients) and include snub nose and high-arched palate. Skeletal anomalies, mostly upper limb and hand, affect 30%. Thumb abnormalities, including flattening of the thenar eminence and triphalangeal thumb, may be bilateral or unilateral. The radial pulse may be absent. Genitourinary (38%), cardiac (30%), ophthalmologic, and musculoskeletal anomalies have also been identified. Short stature is common, but it is often unclear whether this characteristic results from the disease itself, related therapies, or both.

Table 475.1

Range of Congenital Anomalies Observed in Diamond-Blackfan Anemia

TYPE/LOCATION	ANOMALIES
Craniofacial	Hypertelorism Broad, flat nasal bridge Cleft palate High-arched palate Microcephaly Micrognathia Microtia Low-set ears Low hairline Ptosis
Ophthalmologic	Congenital glaucoma Strabismus Epicanthal folds Congenital cataract
Neck	Short neck Webbed neck Sprengel deformity Klippel-Feil deformity
Thumbs	Triphalangeal Duplex or bifid Hypoplastic Flat thenar eminence Absent radial artery
Urogenital	Absent kidney Horseshoe kidney Hypospadias
Cardiac	Ventricular septal defect Atrial septal defect Coarctation of the aorta Complex cardiac anomalies
Other	Low birthweight

	Short stature Syndactyly Learning difficulties

Multiple anomalies, most often including craniofacial, are present in up to 25% of affected individuals. At least 1 anomaly is present in 40–50%.

From Vlachos A, Ball S, Dahl N, et al: Diagnosing and treating Diamond-Blackfan anaemia: results of an international clinical consensus conference, *Br J Haematol* 142(6): 859–876, 2008 (Table IV).

Laboratory Findings

The RBCs are usually macrocytic for age, but no hypersegmented neutrophils or other characteristics of megaloblastic anemia are appreciated on the peripheral blood smear. RBC enzyme patterns are similar to those of a “fetal” RBC population, with increased expression of “i” antigen and elevated fetal hemoglobin (HbF). **Erythrocyte adenosine deaminase** (eADA) activity is increased in most patients with DBA, a finding that helps distinguish congenital RBC aplasia from acquired **transient erythroblastopenia of childhood** (TEC) (see Chapter 477). Because elevated eADA activity is not a fetal RBC feature, measurement of this enzyme may be particularly helpful when diagnosing DBA in very young infants. Thrombocytosis, or rarely thrombocytopenia, and occasionally neutropenia, may also be present. Reticulocyte percentages are characteristically very low despite severe anemia. Bone marrow erythrocyte precursors are greatly reduced in most patients; other marrow elements are usually normal. Serum iron levels are elevated. Unlike Fanconi anemia, there is no increase in chromosomal breaks when lymphocytes are exposed to alkylating agents. Table 475.2 outlines suggested diagnostic criteria.

Table 475.2

Diagnostic Criteria for Patients With Diamond-Blackfan Anemia

DIAGNOSTIC CRITERIA	**SUPPORTING CRITERIA**	
	Major Criteria	**Minor Criteria**
Age younger than 1 yr	Pathogenic mutations	Elevated red cell adenosine deaminase
Macrocytic anemia	Positive family history	Congenital anomalies of Diamond-Blackfan anemia
Reticulocytopenia		Elevated fetal hemoglobin

Paucity of bone marrow erythroid precursors		No evidence for other inherited bone marrow failure syndromes

From Vlachos A, Ball S, Dahl N, et al: Diagnosing and treating Diamond-Blackfan anaemia: results of an international clinical consensus conference, *Br J Haematol* 142(6):859–876, 2008.

Differential Diagnosis

DBA must be differentiated from other anemias associated with low reticulocyte counts. The syndrome of TEC is often the primary alternative diagnosis. Table 477.1 shows a useful comparison of findings in these 2 disorders (see Chapter 477). TEC often is differentiated from DBA by its relatively late onset, although it occasionally develops in infants <6 mo of age. Macrocytosis, congenital anomalies, fetal RBC characteristics, and elevated eADA are generally associated with DBA and not with TEC.

Other inherited macrocytic bone marrow failure syndromes, particularly **Fanconi anemia** and **Shwachman-Diamond syndrome** (see Chapter 495), should also be considered, as should myelodysplastic syndrome. **Aase syndrome** includes congenital RBC aplasia with triphalangeal thumb, congenital heart disease, and cleft palate. **Hemolytic disease of the newborn** can also mimic features of DBA because it can have a protracted course and can be coupled with greatly reduced erythropoiesis. The anemia in this disorder usually resolves spontaneously at 5-8 wk. of age. Several types of chronic hemolytic disease may be complicated by an **aplastic crisis** , characterized by reticulocytopenia and decreased numbers of RBC precursors. This event usually occurs after the 1st several mo of life and is often caused by **parvovirus B19 infection** (see Chapter 477). Infection with parvovirus B19 in utero also may be associated with pure RBC aplasia in infancy, and even with hydrops fetalis at birth (see Chapter 278). When diagnosing DBA in young infants, it is important to rule out parvovirus B19 infection using the polymerase chain reaction. Other infections, including HIV, as well as drugs, immune processes, and Pearson syndrome (see Chapter 476), should also be ruled out.

Treatment

Corticosteroids are a mainstay of therapy, and approximately 80% of patients initially respond. Because corticosteroids impair linear growth as well as physical and neurocognitive development, many hematologists maintain infants on chronic transfusion therapy and delay the start of steroids until after age 1 yr. Prednisone or prednisolone in doses totaling 2 mg/kg/day is used as an initial trial. An increase in RBC precursors is usually seen in the bone marrow 1-3 wk. after therapy is begun and is followed by peripheral reticulocytosis. The hemoglobin can reach normal levels in 4-6 wk., although the rate of response is quite variable. Once it is established that the hemoglobin concentration is increasing, the dose of corticosteroid may be reduced gradually by tapering and then by eliminating all except a single, lowest effective daily dose. This dose may then be doubled, used on alternate days, and tapered still further while maintaining the hemoglobin level at ≥9 g/dL. The target maintenance dose should not exceed 0.5 mg/kg/day or 1 mg/kg every other day. In some patients, very small amounts of prednisone, as low as 2.5 mg twice a week., may be sufficient to sustain adequate erythropoiesis. Scheduled surveillance examinations and testing for corticosteroid side effects should be pursued in all patients, regardless of dose. Appropriate *Pneumocystis* prophylaxis should be used after the 1st mo of high-dose steroids and continued until the patient is on low-dose alternate-day therapy. Many children with DBA stop taking corticosteroids, usually because of unacceptable side effects or the evolution of corticosteroid refractoriness.

Chronic **red cell transfusions** are required in approximately 35% of patients, including patients who are never steroid responsive (30%), are steroid refractory (15%), or cannot be weaned to acceptable low dose (50%). Transfusions are given at intervals of 3-5 wk. to maintain a hemoglobin level >8 g/dL. Some younger children may require hemoglobin >9 g/dL to sustain normal growth and activities. Appropriate screening and ultimately the initiation of chelation therapy are required for transfusion-related iron overload. In one case report, a patient with DBA treated with L -leucine became transfusion independent and remained in remission at >5 mo. Further preclinical and clinical investigations are underway.

Spontaneous remission of anemia with independence from steroid or red cell transfusion therapy has been reported. The likelihood of remission is 25% by age 25 yr., with the majority of patients experiencing remission during the 1st decade. Mild macrocytic anemia and increased erythrocyte ADA levels persist in these circumstances.

Hematopoietic stem cell transplantation (HSCT) can be curative. The best reported outcomes occur using human leukocyte antigen (HLA)–matched sibling donors in patients ≤9 yr of age. HLA-matched sibling HSCT is recommended in affected, transfusion-dependent children at a young age. One recommendation is for HSCT between ages 3 and 9 yr, and some advocate HSCT at a younger age to avoid iron overload and allosensitization from chronic red cell transfusions. It is important that sibling donors be carefully screened, including genotype if known, to ensure that the donor does not carry the patient's DBA gene. Improvements in alternative donor HSCT suggest that this modality may also provide an important option for select patients.

Prognosis

DBA has been identified as a *cancer predisposition syndrome* because of the higher risk of myelodysplastic syndrome, acute myeloid leukemia, colon carcinoma, osteogenic sarcoma, and female genital cancers. Patients are at risk for iron overload related endocrine abnormalities (diabetes, hypogonadism), especially if transfused. Patients who have undergone HSCT are at risk of associated late effects (see Chapters 163-165). The overall actuarial survival of all patients with DBA is approximately 75% at age 40 yr, with approximately 87% for those maintained on corticosteroids and approximately 57% for transfusion-dependent patients. Of reported deaths, 67% were treatment related and 22% were DBA related (malignancy and severe aplastic anemia).

Treatment outcome and survival data are collected through the Diamond-Blackfan Anemia Registry (https://www.dbar.org).

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CHAPTER 476

Pearson Syndrome

Courtney D. Thornburg

Pearson marrow-pancreas syndrome (PS) is a rare mitochondrial disorder that presents with a hypoplastic anemia that may be initially confused with Diamond-Blackfan syndrome (anemia) or transient erythroblastopenia of childhood (see Chapter 477). The marrow failure usually appears in the neonatal period and is characterized by a **macrocytic anemia** and, occasionally, neutropenia and thrombocytopenia. There are vacuolated erythroblasts and myeloblasts in the bone marrow (Fig. 476.1). PS is considered a unique variant of **congenital sideroblastic anemia** because the marrow also contains ringed sideroblasts. The hemoglobin F level is elevated. There is multiorgan involvement manifested by failure to thrive and symptoms of exocrine pancreas dysfunction, liver and renal tubular defects, malabsorption, and myopathy. Endocrine dysfunction (type 1 diabetes, adrenal insufficiency, hypoparathyroid, hypothyroid) has also been reported. In rare cases, when the disease is not fatal in early childhood, PS may evolve to include symptoms consistent with **Kearns-Sayre syndrome** , a very rare, early-onset, mitochondrial disorder resulting in lactic acidosis and progressive external ophthalmoplegia (impaired eye movement and ptosis), pigmentary retinitis, deafness, cerebellar ataxia, and heart block

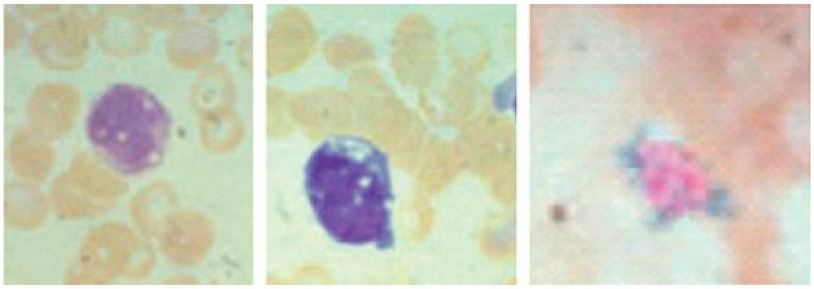

FIG. 476.1 **Bone marrow morphology in Pearson syndrome. *Left,* Vacuoles in myeloid**

precursor. *Middle,* Vacuoles in erythroid precursor. *Right,* Ringed sideroblast. (From Shimamura A, Alter BP: Pathophysiology and management of inherited bone marrow failure syndromes, *Blood Rev* 24:101–122, 2010, Fig 14.)

Pearson syndrome is caused by a maternally inherited **mitochondrial DNA (mtDNA) deletion** of variable size and location that is similar to the mtDNA deletion found in Kearns-Sayre syndrome. There is heterogeneity in different tissues and between patients, accounting for the variable clinical picture. The proportion of deleted mtDNA in the bone marrow correlates with the severity of the hematologic picture, and a change in the percentage of tissue mtDNA types over time may be associated with spontaneous improvement of red blood cell hypoproliferation. PS may be misdiagnosed as Diamond-Blackfan anemia (DBA) based on the overlapping features, including severe anemia starting at a young age. Evaluation for mtDNA deletion will differentiate PS from DBA (see Chapter 475).

Therapy for the hematologic manifestations of the disease is primarily supportive and includes red cell transfusions to correct anemia and granulocyte colony-stimulating factor to reverse episodes of severe neutropenia. Significant morbidity is associated with episodes of lactic acidosis and the development of pancytopenia. In 2 patients requiring hematopoietic stem cell transplantation for pancytopenia, both the hematologic and the mitochondrial abnormalities were corrected.

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CHAPTER 477

Acquired Pure Red Blood Cell Anemia

Courtney D. Thornburg

Transient Erythroblastopenia of Childhood

Transient erythroblastopenia of childhood (**TEC**) is the most common *acquired red cell aplasia* occurring in children. It is more prevalent than congenital hypoplastic anemia (Diamond-Blackfan anemia, DBA). This syndrome of severe, transient hypoplastic anemia occurs mainly in previously healthy children between 6 mo and 3 yr of age; most of the children are >12 mo at onset. Only 10% of affected patients are >3 yr of age. The annual incidence is estimated to be 4.3 cases per 100,000 children, although it is likely higher, because many cases may go undiagnosed and because TEC usually resolves spontaneously. The suppression of erythropoiesis has been linked to IgG, IgM, and cell-mediated mechanisms. Familial cases have been reported, suggesting a hereditary component. TEC often follows a viral illness, although no specific virus has been consistently implicated.

The temporary suppression of erythropoiesis results in **reticulocytopenia** and moderate to severe normocytic anemia. Some degree of neutropenia occurs in up to 20% of cases. Platelet numbers are normal or elevated. Similar to the situation observed in iron-deficiency anemia and other red blood cell (RBC) hypoplasias, thrombocytosis is presumably caused by increased erythropoietin (EPO), which has some homology with thrombopoietin (TPO). Mean corpuscular volume (MCV) is characteristically normal for age, and fetal hemoglobin (HbF) levels are normal before the recovery phase. RBC adenosine deaminase levels are normal in TEC, thus contrasting with the elevation noted in most cases of congenital hypoplastic anemia (Table 477.1). Differentiation from DBA is sometimes difficult, but differences in age at onset and in age-related MCV, HbF, and adenosine deaminase are usually helpful. The peak occurrence of TEC coincides with that of iron-deficiency anemia in infants receiving milk as their main caloric source; differences in MCV should help to distinguish between TEC and DBA.

Table 477.1

Comparison of Diamond-Blackfan Anemia and Transient Erythroblastopenia of Childhood

FEATURE	DBA	TEC
Male : female	1 : 1	1 : 3
AGE AT DIAGNOSIS, MALE (mo)		
Mean	10	26
Median	2	23
Range	0-408	1-120
AGE AT DIAGNOSIS, FEMALE (mo)		
Mean	14	26
Median	3	23
Range	0-768	1-192
Boys >1 yr	9%	82%
Girls >1 yr	12%	80%
Etiology	Genetic	Acquired, possibly familial
Antecedent history	None	Viral illness
Physical examination abnormal (congenital anomalies present)	25%	0%
LABORATORY		
Hemoglobin (g/dL)	1.2-14.8	2.2-12.5
WBCs <5,000/µL	15%	20%
Platelets >400,000/µL	20%	45%
Adenosine deaminase	Increased	Normal
MCV increased at diagnosis	80%	5%
MCV increased during recovery	100%	90%
MCV increased in remission	100%	0%
HbF increased at diagnosis	100%	20%
HbF increased during recovery	100%	100%
HbF increased in remission	85%	0%
i Antigen increased	100%	20%
i Antigen increased during recovery	100%	60%
i Antigen increased in remission	90%	0%

DBA, Diamond-Blackfan anemia; HbF, fetal hemoglobin; MCV, mean cell volume; TEC, transient erythroblastopenia of childhood; WBC, white blood cell.

From Nathan DG, Orkin SH, Ginsburg D, et al, editors: *Nathan and Oski's hematology of infancy and childhood* , ed 6, vol 1, Philadelphia, 2003, Saunders, p. 329. Adapted from Alter BP: The bone marrow failure syndromes. In Nathan DG, Oski FA, editors: *Hematology of infancy and childhood* , ed 3, Philadelphia, 1987, Saunders, p 159; and Link MP, Alter BP: Fetal erythropoiesis during recovery from transient erythroblastopenia of childhood (TEC), *Pediatr Res* 15:1036–1039, 1981.

Virtually all children recover within 1-2 mo. RBC transfusions may be necessary for severe anemia in the absence of signs of early recovery. The anemia develops slowly, and significant symptoms usually develop only with severe anemia. *Corticosteroid therapy is of no value in this disorder.* Any child with presumed TEC who requires >1 transfusion should be reevaluated for another possible diagnosis. In rare instances, a prolonged case of apparent TEC may be caused by parvovirus-induced RBC aplasia, occurring in children with *hemolytic anemia* or *congenital* or *acquired immunodeficiencies* .

Red Cell Aplasia Associated With Parvovirus B19 Infection

Parvovirus B19 is a common infectious agent that causes **erythema infectiosum** (fifth disease) (see Chapter 278). It is also the best-documented viral cause of RBC aplasia in patients with **chronic hemolysis** , patients who are immunocompromised, and fetuses in utero. This small, nonenveloped single-stranded virus is particularly infective and cytotoxic to marrow erythroid progenitor cells, interacting specifically by binding to the red cell P antigen. In addition to decreased or absent erythroid precursors, characteristic nuclear inclusions in erythroblasts and giant pronormoblasts may be seen under light microscopy in bone marrow specimens. The virus does not cause significant anemia in immunocompetent individuals with normal RBC life span.

Because parvovirus infection is usually transient, with recovery occurring in <2 wk, anemia is either not present or not appreciated in otherwise normal children whose peripheral RBC life span is 100-120 days. The RBC life span is much shorter in patients with **hemolysis** secondary to conditions such as hereditary spherocytosis, immune hemolytic anemia, or sickle cell disease. In these children, a brief cessation of erythropoiesis can cause severe anemia, a condition known as an **aplastic crisis** . When a definitive diagnosis is required, the workup should include serum parvovirus IgM and IgG titers and, if needed, viral detection using polymerase chain reaction (PCR) techniques. Recovery from moderate to severe anemia is usually spontaneous, heralded by the appearance of nucleated RBCs and subsequent reticulocytosis in the peripheral blood. A RBC transfusion may be necessary if the anemia is associated with significant symptoms. Parvovirus-induced aplastic crisis usually occurs only once in children with chronic hemolysis. In families with >1 child affected with a hemolytic disorder, parents should be warned that a similar aplastic episode can occur in the other children if they have not been previously infected. During the episode of aplastic crisis, the child is potentially contagious and should be isolated from at-risk patients.

Persistent parvovirus infection may occur in children with **congenital immunodeficiency** diseases, lymphoproliferative disorders, those being treated with immunosuppressive agents, and those with HIV/AIDS, because these children may be unable to mount an adequate antibody response. The resultant pure RBC aplasia may be severe, and affected children may be thought to have TEC. This type of RBC aplasia differs from TEC in that there is no spontaneous recovery, and >1 transfusion is often needed. The diagnosis of parvovirus infection is made by PCR of peripheral blood or bone marrow DNA because the usual serologic responses, reflected by parvovirus serum IgM or IgG titers, are impaired in immunodeficient children. In chronically infected patients the disease may be treated with high doses of intravenous immune globulin, which contains neutralizing antibody to parvovirus and is effective in the short term.

Parvovirus infection and destruction of erythroid precursors can also occur in utero. Such events are associated with increased fetal wastage in the first and second trimesters. Infants may be born with **hydrops fetalis** and anemia (see Chapter 124). The presence of persistent congenital parvovirus infection is detected by PCR of peripheral blood and/or bone marrow DNA, because immunologic tolerance to the virus can prevent the usual development of specific antibodies.

Other Red Cell Aplasias in Children

Acquired red cell aplasia in adults is usually mediated by a chronic antibody and often associated with disorders such as chronic lymphocytic leukemia, lymphoma, thymoma, lymphoproliferative disorders, and systemic lupus erythematosus. This chronic antibody-mediated type of RBC aplasia, often responsive to immunosuppressive therapy, is quite rare in childhood. Cases of acquired pure RBC aplasia attributable to T-cell suppression have also been described.

Infections other than parvovirus, such as cytomegalovirus and Epstein-Barr virus, may cause pure RBC aplasia. Certain drugs, such as chloramphenicol, also can inhibit erythropoiesis in a dose-dependent manner. Reticulocytopenia, erythroid hypoplasia, and vacuolated pronormoblasts in the bone marrow are reversible effects of this drug. These effects are distinct from the idiosyncratic and rare development of severe aplastic anemia in chloramphenicol recipients. Acquired antibody-mediated pure RBC aplasia has also been found to be a rare complication in chronic kidney disease patients treated with erythropoiesis-stimulating agents. In addition to discontinuing erythropoiesis-stimulating agents therapy and addressing anemia with red cell transfusions, further treatment may include immunosuppression and renal transplantation.

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CHAPTER 478

Anemia of Chronic Disease and Renal Disease

478.1

Anemia of Chronic Disease

Courtney D. Thornburg

The anemia of chronic disease (**ACD**), also referred to as **anemia of inflammation** , is found in conditions where there is ongoing immune activation. It occurs in a wide a range of disorders, including infections, malignancies, chronic renal disease, autoimmunity, and graft-versus-host disease. A similar anemia is associated with chronic kidney disease. ACD is typically a mild to moderate normocytic, normochromic, hypoproliferative anemia associated with a decreased serum iron and low transferrin saturation.

Etiology

Decreased red cell life span, impaired erythropoiesis, and an increased uptake of iron in the reticuloendothelial system are important mechanisms contributing to the anemia. The modest reduction in erythrocyte longevity is perhaps the least understood part of the pathophysiology of ACD. Elevated levels of cytokines such as interleukin-1 may increase the macrophage's ability to ingest and destroy erythrocytes. Defective erythropoiesis, both proliferation and differentiation of precursors, has been attributed to immune cell/cytokine–driven inhibition of erythropoietin production and suppression of the bone marrow.

ACD-associated alterations in iron recycling are characterized by an accumulation of iron in reticuloendothelial macrophages despite low levels of serum iron. The diversion of iron from the circulation into the reticuloendothelial system results in *functional* iron deficiency, which results in the impaired heme synthesis and iron-restricted erythropoiesis that contribute to anemia. These alterations in iron metabolism have been attributed to inflammation-associated excess synthesis of **hepcidin** , a key regulatory protein that controls intestinal iron absorption and tissue distribution. Hepcidin, although mainly synthesized by hepatocytes, is also expressed in other cells, including monocytes and macrophages. It functions by binding to and initiating the degradation of the iron exporter, **ferroportin** (Fig. 478.1).

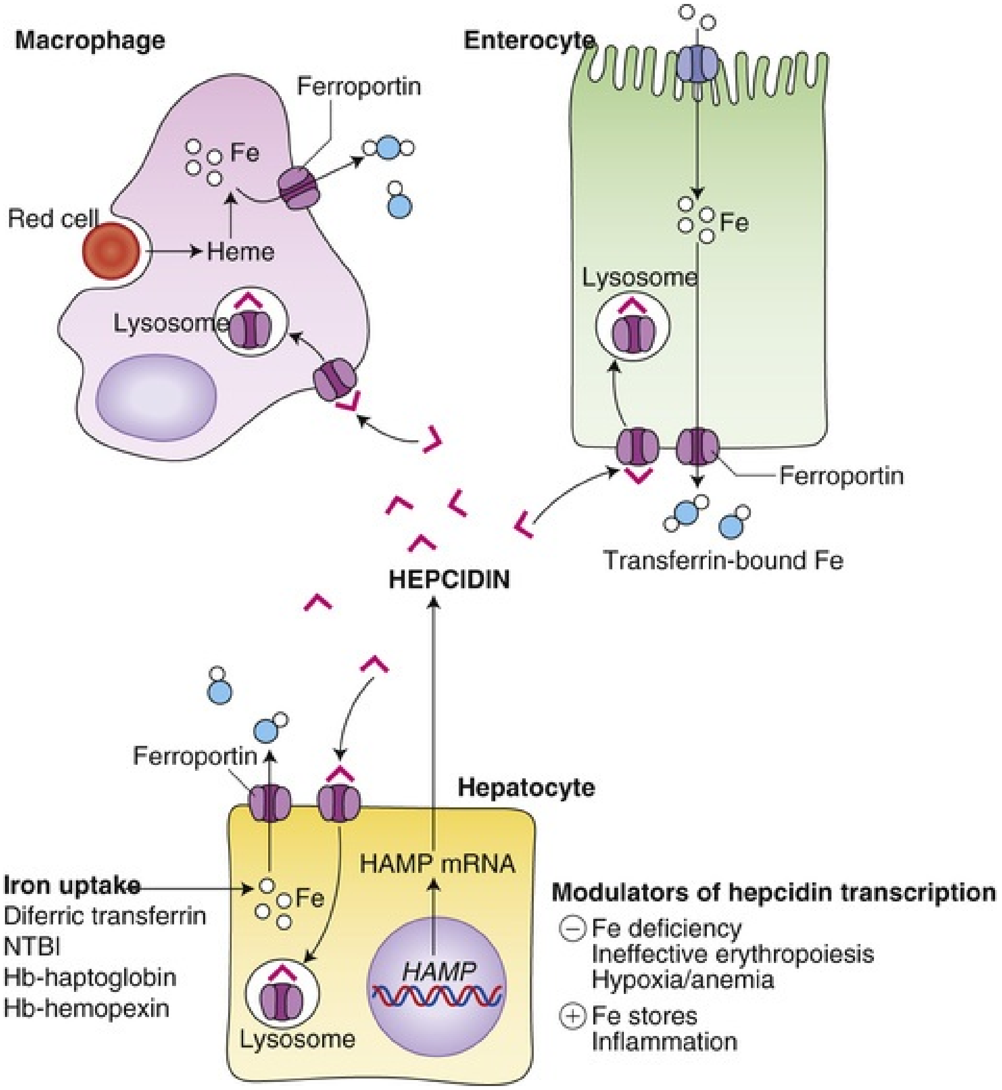
Macrophage
Enterocyte
Ferroportin
Fe
Red cell
Heme
Lysosome
Fe
Lysosome
Ferroportin
Transferrin-bound Fe
HEPCIDIN
Ferroportin
Hepatocyte
HAMP mRNA
Iron uptake
Diferric transferrin
NTBI
Hb-haptoglobin
Hb-hemopexin
Fe
Lysosome
HAMP
Modulators of hepcidin transcription
⊖ Fe deficiency
Ineffective erythropoiesis
Hypoxia/anemia
⊕ Fe stores
Inflammation

FIG. 478.1 **Central role of hepcidin in iron metabolism. Hepcidin, produced by hepatocytes, downregulates iron export to circulating transferrin from iron "donor" cells (hepatocytes, macrophages, and duodenal enterocytes) by promoting the internalization and lysosomal degradation of ferroportin. Hepatocytes take up iron in a number of forms, whereas enterocytes obtain their iron predominantly from the gut lumen, and macrophages are specialized to deal with the high throughput of iron from senescent red cells. (From Pippard M: Iron deficiency anemia, anemia of chronic disorders and iron overload. In Porwit A, McCullough J, Erber WN, editors: *Blood and bone marrow pathology,* ed 2, London, 2011, Elsevier, Fig 11-5.)**

Clinical Manifestations

Although the important symptoms and signs associated with ACD are those of the underlying disease, the mild to moderate anemia can affect the patient's quality of life.

Laboratory Findings

Hemoglobin concentrations are generally 6-9 g/dL. The anemia is usually normochromic and normocytic, although some patients have modest hypochromia and microcytosis, particularly if there is concomitant iron deficiency. Absolute reticulocyte counts are normal or low, and leukocytosis is common. The serum iron level is low, without the increase in serum transferrin (the iron transport protein) that occurs in iron deficiency. This pattern of low serum iron and low-to-normal serum transferrin is a regular but valuable diagnostic feature. *The serum ferritin level may be elevated secondary to inflammation* . **Soluble transferring receptor** (sTfR) is a diagnostic test used to distinguish ACD from iron-deficiency anemia (IDA); sTfR levels are high in IDA and normal in ACD. The bone marrow has normal cellularity; the red blood cell precursors are decreased or adequate, marrow hemosiderin may be increased, and granulocytic hyperplasia may be present.

Treatment

The best approach to ACD is the treatment, when possible, of the underlying disorder. If the associated systemic disease can be controlled, the anemia will improve or resolve. Transfusions raise the hemoglobin concentration temporarily but are rarely indicated. **Erythropoietic stimulating agents** (ESAs), such as recombinant human erythropoietin (EPO) or related extended–half-life formulations, increase the hemoglobin level and improve activity and the sense of well-being. When using ESAs, *treatment with iron* is usually necessary to produce optimal effect. Response to these agents is highly variable, and poorly responsive patients may require high doses to reach target hemoglobin levels. In adults, such high doses are associated with a higher incidence of adverse events, such as stroke, cardiovascular events, cancer progression, and death, leading the U.S. Food and Drug Administration (FDA) to require a “black box” warning on labels.

ACD does not respond to iron alone unless there is concomitant deficiency. Unfortunately, it is a common clinical challenge to identify iron deficiency in patients with an inflammatory disease (see Chapters 474 and 482). In this circumstance, a trial of iron therapy might be helpful, although there may be no response because persistent inflammation impairs iron absorption and utilization; intravenous iron may further increase hepcidin production. Therapeutic agents that target the hepcidin-ferroportin axis are under investigation.

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478.2

Anemia of Renal Disease

Courtney D. Thornburg

Anemia is common in children with **chronic kidney disease** (CKD). The anemia is usually normocytic, and the absolute reticulocyte count is normal or low. Although most patients with end-stage renal disease (ESRD) are anemic, earlier stages of CKD are associated with a lower prevalence. In adults, lower glomerular filtration rate (GFR) has been correlated with lower hemoglobin concentration, and hemoglobin has been reported to decline below a GFR threshold of 40-60 mL/min/1.73 m^2 . In children with CKD, hemoglobin levels decline as the GFR decreases below 43 mL/min/1.73 m^2 .

Decreased hemoglobin values are linked to increased incidence of left ventricular hypertrophy, impaired physical activity, and a reduced quality of life in pediatric patients with CKD. In those with ESRD who are on dialysis, anemia is also associated with increased risk of hospitalization and mortality.

Etiology

Although the anemia of CKD shares many features with anemia of chronic disease, its predominant cause is decreased **erythropoietin** (EPO) production by diseased kidneys. Other important causes include absolute and/or functional iron deficiency as a result of chronic blood loss (from blood sampling, surgeries, and dialysis) and disturbances in the iron metabolic pathway. Higher hepcidin levels have also been implicated in the anemia of CKD. Hepcidin is filtered by the glomerulus and excreted by the kidney; serum concentrations are increased in patients with decreased GFR. Inflammation may also be a contributing factor in pediatric dialysis patients who have elevated levels of proinflammatory cytokines. Hyperparathyroidism and deficiencies of vitamin B_{12} , folate, and carnitine may also have a role in anemia of CKD.

Laboratory Findings

Anemia in children with CKD is defined by age: hemoglobin <11.0 g/dL (0.5-5 yr), <11.5 g/dL (5-12 yr), <12 g/dL (12-15 yr), <13.0 g/dL (males >15 yr), and <12.0 g/dL (females >15 yr). The anemia of CKD is hypoproliferative and usually normocytic and normochromic, unless there is concomitant iron deficiency or vitamin deficiency. The EPO level and absolute reticulocyte count are usually low. White cell and platelet counts are generally normal. Ferritin will be low if there is accompanying iron deficiency and high if there is associated inflammation.

Treatment

Oral iron therapy is recommended for all pediatric CKD patients with anemia. Consideration of IV iron therapy may be given for those receiving maintenance hemodialysis and those who to do not respond to oral iron. Modern intravenous iron preparations (iron-gluconate, iron-sucrose, iron-carboxymaltose, iron-isomaltoside, ferumoxytol) have iron as a core within a carbohydrate stabilizer shell, thus preventing the uncontrolled release of free iron and thus reducing serious side effects.

Erythrocyte-stimulating agents (ESAs) are the mainstay of therapy and, particularly for children with ESRD, have greatly reduced the need for frequent transfusions, decreasing the incidence of associated iron overload and alloimmunization. It is suggested to start ESAs in all children with CKD when hemoglobin concentration is 9-10 g/dL, with a goal of 11-12 g/dL (some recommend 11-13 g/dL) for children on maintenance ESA therapy. Dosing varies with age and dialysis modality. **Darbepoetin** , a synthetic form of EPO, appears to be equally effective as recombinant human EPO and has the benefit of less frequent dosing because of a longer half-life. Iron therapy should be prescribed when using ESAs because treatment demands additional iron for erythropoiesis. Infants and children require higher doses of ESAs.

In the rare case in which antibody-mediated (to EPO) pure red cell aplasia develops, ESA therapy should be stopped, and immunomodulatory therapy may be indicated to suppress the antibody response**.**

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CHAPTER 479

Congenital Dyserythropoietic Anemias

Courtney D. Thornburg

The congenital dyserythropoietic anemias (**CDAs**) are a heterogeneous class of inherited disorders resulting from abnormalities of late erythropoiesis. These rare conditions are characterized by variable degrees of anemia, ineffective erythropoiesis, and secondary hemochromatosis (iron overload). They may be misdiagnosed as other congenital anemias, such as hereditary spherocytosis or thalassemia. **Dyserythropoiesis** is the major cause of anemia but a shortened half-life of circulating red blood cells (RBCs) may also contribute. The CDAs have historically been classified into 3 major types (I, II, and II) based on distinctive bone marrow morphology, clinical features, and genetic variants, although additional subgroups and variants (*GATA1* and *KLF1)* have also been identified.

Congenital Dyserythropoietic Anemia Type I

Pathogenesis

Type I CDA (**CDA I**) is an autosomal recessive disorder. The causative gene (*CDAN1*) was mapped to chromosome 15 between q15.1 and q15.3. The gene encodes codanin-1, which is a ubiquitously expressed protein that may expedite histone assembly into chromatin and regulate the cell cycle. Although the majority of patients with bone marrow characteristics indicative of CDA1 have mutations within *CDAN1,* such mutations have not been detected in approximately 11% of families. Two distinctive mutations in the gene

C15ORF41 , predicted to encode an endonuclease, have been identified in 3 different CDA I pedigrees.

Clinical Manifestations

There are more than 300 reported cases. Although CDA I may be diagnosed at any age, most cases are recognized during childhood or adolescence. CDA I is rarely diagnosed in utero. In addition to anemia-related symptoms, other findings often include splenomegaly, jaundice, and hepatomegaly. In more severe cases, evidence of extramedullary hematopoiesis in frontal or parietal bones of the skull and in paravertebral tumors may be present. Cholelithiasis and iron overload develop over time. Type I CDA has been associated with **dysmorphic features** in 4–14% of patients, primarily involving the digits (syndactyly, absence of nails, supernumerary toes). Retinal angioid streaks and macular abnormalities also have been reported.

Laboratory Findings

Hemoglobin concentrations generally range between 7 and 11 g/dL. The anemia is usually macrocytic (mean corpuscular volume: 100-120 fL), but normocytic indices may be seen during childhood. **Anisopoikilocytosis** is appreciated on the peripheral blood smear. In some cases, normoblasts and basophilic stippling of RBCs may be seen. The reticulocyte count is inadequate for the degree of anemia. Laboratory evidence of iron overload may be present. The bone marrow aspirate shows erythroid hyperplasia, megaloblastosis, and basophilic stippling. Binucleated and, more rarely, multinucleated polychromatophilic erythroblasts are also appreciated. Incompletely divided cells with thin chromatin bridges between nuclei of pairs of erythrocytes are highly specific for type I CDA. **Electron microscopy** is the gold standard for diagnosis, revealing erythroblasts with a characteristic “Swiss cheese” heterochromatin pattern.

Treatment

Treatment of this disorder is primarily supportive. Approximately 50% of neonates with CDA I will need at least 1 red cell transfusion, and some may remain transfusion dependent over subsequent years. Adolescents and adults may only require episodic transfusions during aplastic crises, infection, or pregnancy. If anemia is further exacerbated by co-inherited disorders, such as thalassemia or RBC enzymopathy, the patient may become transfusion dependent. Treatment with interferon-α can reduce transfusion requirements. Patients do not respond to erythropoietin. Splenectomy is generally not recommended. Cholecystectomy is often required for management of pigmented gallstones. Allogeneic bone marrow transplantation from a human leukocyte antigen (HLA)-identical sibling has been successful in a few severe cases.

The most important long-term complication is **hemosiderosis** , caused by increased intestinal absorption of iron and ineffective erythropoiesis and transfusion therapy. Regular phlebotomies result in normal ferritin concentrations, but if this approach is untenable, oral chelation therapy should be employed when repeated ferritin levels exceed 1,000 µg/L or liver iron is elevated as determined by hepatic R_2 * magnetic resonance.

Congenital Dyserythropoietic Anemia Type II

Pathogenesis

CDA type II (**CDA II**) is also an autosomal recessive disorder. Genome-wide linkage analysis identified a region of chromosome 20p11.2 as the location of the candidate *CDAN2* gene that was later identified to be the *SEC23B* gene. This gene is known to encode the cytoplasmic coat protein (COP) II component SEC23B that is involved in endoplasmic reticulum vesicle trafficking. *SEC23B* gene mutations have been associated with the majority of CDA II cases.

Clinical Manifestations

There are more than 450 reported cases, making CDA II the most common form of CDA. Reported cases are mostly from Europe and the Middle East. In contrast to CDA I, this diagnosis is usually made later in life, often because symptoms may be milder. Also, CDA II may be initially misdiagnosed as **hereditary spherocytosis** . Characteristic findings can include anemia, jaundice, splenomegaly, or hepatomegaly. Posterior mediastinal or paravertebral masses of extramedullary hematopoietic tissue may be noted, and signs of iron overload may also be present.

Laboratory Findings

The anemia is normocytic and is generally mild with inappropriately low reticulocytosis. Hemoglobin levels are lower in children than adults and range between 8 and 11 g/dL. Anisopoikilocytosis is noted, and occasional basophilic stippling, as well as a few, sometimes binucleate, mature erythroblasts, may be found on the peripheral smear. The bone marrow aspirate is normoblastic but hypercellular, with erythroid hyperplasia. In contrast to CDA I, there are many binucleate late polychromatic erythroblasts (10–35%) as well as a few that are multinucleate. Pseudo-Gaucher cells may be present. Electron micrographs show vesicles that are laden with endoplasmic reticulum proteins running beneath the plasma membrane. The pathognomonic finding in CDA II is that the patient's RBCs lyse in acidified serum because of an IgM antibody that recognizes an antigen present on CDA II cells but absent on normal cells. CDA II is also known by the acronym **HEMPAS** (*h* ereditary *e* rythroblastic *m* ultinuclearity with a *p* ositive *a* cidified *s* erum test) because it features both erythroblast multinuclearity and circulating RBCs that are sensitive to lysis by acidified normal serum. As this test is technically difficult, the diagnosis is usually made by analyzing RBC membrane proteins with sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE). In CDA II there is a thinner band size and faster migration of erythrocyte anion transporter (EA1), or band 3, and band 4.5 proteins.

Treatment

Approximately 10% of patients will require red cell transfusions in infancy and childhood but rarely during adulthood. In contrast to CDA I, splenectomy may provide hematologic improvement. Splenectomy does not prevent further iron overloading, even in those patients whose hemoglobin is normalized, presumably because of persistent ineffective erythropoiesis in the bone marrow. As with CDA I, secondary hemochromatosis is the most prominent long-term complication and should be approached as previously outlined. Allogeneic bone marrow transplantation has been successful in several patients with CDA II. Most patients can lead a normal life and have a normal life expectancy if complications and consequences are managed appropriately.

Congenital Dyserythropoietic Anemia Type III

CDA type III (**CDA III**) is an extremely rare, poorly defined entity characterized by a mild to moderate macrocytic anemia. It is inherited in an autosomal dominant fashion, although there have been cases that might represent de novo mutations or other inheritance patterns. The gene for CDA III is *KIF23* , which encodes a ubiquitous protein, mitotic kinesin-lie protein 1, which regulates daughter cell separation during mitosis. In contrast to other CDA types, iron overload is not clinically significant (probably because hemolysis is predominantly intravascular), and spleen size is generally normal. Patients can present with angioid streaks with macular degeneration. The blood smear shows macrocytes, anisopoikilocytosis, and occasional basophilic stippling. The bone marrow is notable for giant erythroid precursors that are often multinucleated, containing up to 12 nuclei per cell. Such multinucleated erythroblasts can also be seen in myelodysplasia and erythroleukemia. Transfusions are usually not required.

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CHAPTER 480

Physiologic Anemia of Infancy

Courtney D. Thornburg

At birth, normal full-term infants have higher hemoglobin (Hb) levels and larger red blood cells (RBCs) than do older children and adults. However, within the 1st wk of life, a progressive decline in Hb level begins and then persists for 6-8 wk. The resulting anemia is known as the **physiologic anemia of infancy** .

With the onset of respiration at birth, considerably more oxygen becomes available for binding to Hb, and as a result the Hb-oxygen saturation increases from 50% to 95% or more. There is also a gradual, normal developmental switch from fetal to adult Hb synthesis after birth that results in the replacement of high-oxygen-affinity **fetal Hb** with lower-affinity adult Hb, capable of delivering more oxygen to tissues. The increase in blood oxygen content and delivery results in the downregulation of **erythropoietin** (EPO) production, leading to suppression of erythropoiesis. Because there is no erythropoiesis, aged RBCs that are removed from the circulation are not replaced, and the Hb level decreases. The Hb concentration continues to decline until tissue oxygen needs become greater than oxygen delivery. Normally, this point is reached between 8 and 12 wk of age, when the Hb concentration is about 11 g/dL. In healthy term infants, the nadir rarely falls below 10 g/dL. At this juncture, EPO production increases and erythropoiesis resumes. The supply of stored reticuloendothelial iron, derived from previously degraded RBCs, remains sufficient for this renewed Hb synthesis, even in the absence of dietary iron intake, until approximately 20 wk. of age. In all, this “anemia” should be viewed as a physiologic adaptation to extrauterine life, reflecting the excess oxygen delivery relative to tissue oxygen requirements. There is no hematologic problem, and no therapy is required unless physiologic anemia of infancy is exacerbated by other ongoing processes.

A late **hyporegenerative anemia** , with absence of reticulocytes, can occur in infants with mild **hemolytic disease of the newborn** . The persistence of maternally derived anti-RBC antibodies in the infant's circulation can lead to an ongoing low-grade hemolytic anemia that can exaggerate the physiologic anemia. Lower-than-expected Hb at the “physiologic” nadir has also been seen in infants after intrauterine or neonatal RBC transfusions. When infants are transfused with adult blood containing HbA, the associated shift of the oxygen dissociation curve facilitates oxygen delivery to the tissues. Accordingly, the definition of anemia and the need for transfusion should be based not only on the infant's Hb level, but also on oxygen requirements and the ability of circulating RBCs to release oxygen to the tissues. The degree of anemia at birth is correlated with maternal hemoglobin.

Premature infants also develop a physiologic anemia, known as **physiologic anemia of prematurity** . The Hb decline is both more extreme and more rapid. Hb levels of 7-9 g/dL usually are reached by 3-6 wk of age, and levels may be even lower in very small premature infants (see Chapter 124). The same physiologic factors at play in term infants are operative in preterm infants but are exaggerated. In premature infants the physiologic Hb decline may be intensified by blood loss from repeated phlebotomies obtained to monitor ill neonates. Demands on erythropoiesis are further heightened by the premature infant's presumed shortened RBC life span (40-60 days) and the accelerated expansion of RBC mass that accompanies the premature baby's rapid rate of growth. Nonetheless, plasma EPO levels are lower than would be expected for the degree of anemia, resulting in a suboptimal erythropoietic response. The reason for diminished EPO levels is not fully understood. During fetal life, EPO synthesis is handled primarily by the liver, and the liver's oxygen sensor is relatively insensitive to hypoxia compared to that of the kidney. The developmental switch from liver to kidney EPO production is not accelerated by early birth, and thus the preterm infant must rely on the liver as the primary site for synthesis, leading to diminished responsiveness to anemia. An additional mechanism thought to contribute to diminished EPO levels may be accelerated EPO metabolism. Because the pronounced decline in Hb that occurs in many very-low-birthweight infants may be associated with abnormal clinical signs, this “anemia of prematurity” is not considered benign and usually requires transfusions when symptomatic.

Some dietary factors, such as folic acid deficiency, can aggravate physiologic anemia. Unless there has been significant blood loss, iron stores should be sufficient to maintain erythropoiesis during the 1st 1-2 mo of life. Vitamin E deficiency does not play a role in anemia of prematurity. Breast milk and infant formulas provide adequate vitamin E.

Treatment

In the full-term infant, physiologic anemia requires no therapy beyond ensuring that the infant's diet contains essential nutrients for normal hematopoiesis. In premature infants, an optimal Hb has not been established and is usually dictated by the infant's overall clinical condition. Transfusions may be needed to maintain the Hb at what is considered safe for that child. Premature infants who are feeding well and growing normally rarely need transfusion unless iatrogenic blood loss has been significant. Although factors such as poor weight gain, respiratory difficulties, and abnormal heart rate have prompted transfusion, the beneficial effect has not been documented. Laboratory tests such as blood lactate, EPO, and mixed venous oxygen saturation have poor predictive value. Liberal and restrictive transfusion strategies have been compared in this population. A restrictive strategy does not increase infant morbidity or mortality. In addition, long-term neurodevelopmental outcomes have been found to be poorer in liberally transfused neonates. Late exposure to packed RBCs may be related to the development of necrotizing enterocolitis, and early transfusions may be associated with the risk of intraventricular hemorrhage.

When transfusions are necessary, an RBC volume of 10-15 mL/kg is recommended. It is good practice to split units derived from a single donor so that sequential transfusions can be given as required and donor exposure minimized. In early preterm infants (weighing <1,250 g), the half-life of *transfused* RBCs is about 30 days. Delayed cord clamping or umbilical cord milking at birth results in fewer transfusions and a reduction in both intraventricular hemorrhage and necrotizing enterocolitis in preterm infants. Given the impact of phlebotomy losses during monitoring in the neonatal intensive care unit, attention to reducing unnecessary blood draws also has been advocated.

Because premature infants are known to have low plasma EPO levels, recombinant human EPO may be an alternative to transfusion for the prevention or treatment of symptomatic anemia of prematurity. Iron supplementation should be given with EPO to optimize effect.

The current approach to anemia of prematurity is to limit phlebotomies and donor exposure; EPO use is variable but not universally recommended.

Iron therapy is indicated for all neonates with anemia of prematurity starting at 1 mo of age and continuing until about 1 yr. Starting dose is 1-2 mg/kg/day of elemental iron.

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CHAPTER 481

Megaloblastic Anemias

Courtney D. Thornburg

Megaloblastic anemia describes a group of disorders that are caused by **impaired DNA synthesis** . Red blood cells (RBCs) are larger than normal at every developmental stage, and there is **maturational asynchrony** between the nucleus and cytoplasm of erythrocytes. The delayed nuclear development becomes increasingly evident as cell divisions proceed. Myeloid and platelet precursors are also affected, and giant metamyelocytes and neutrophil bands are often present in the bone marrow. *There is often an associated thrombocytopenia and leukopenia* . The peripheral blood smear is notable for large, often oval RBCs with increased mean corpuscular volume. Neutrophils are characteristically hypersegmented, with many having >5 lobes. Most cases of childhood megaloblastic anemia result from a deficiency of folic acid or vitamin B_{12} (cobalamin), vitamins essential for DNA synthesis (Table 481.1). Rarely, these anemias may be caused by inborn errors of metabolism. Megaloblastic anemias resulting from malnutrition are relatively uncommon in the United States but are important worldwide (see Chapters 57 , 59 , and 474).

Table 481.1

Causes of Red Blood Cell Macrocytosis

CAUSATIVE CONDITIONS	ACCOMPANYING HEMATOLOGIC FEATURES
MEGALOBLASTIC ANEMIA	
Cobalamin (vitamin B_{12}) deficiency Folate deficiency Antifolate drugs (e.g., methotrexate) Cytotoxic drugs (e.g., hydroxyurea, 5-FU) Immunosuppressive drugs (e.g., azathioprine) Thiamine-responsive anemia Hereditary orotic aciduria	Megaloblastic changes, including hypersegmented neutrophils Macrocytosis can become severe. Mild reticulocytopenia Pancytopenia (when the megaloblastic process is severe)

DISORDERS OF ERYTHROID PRODUCTION	
Aplastic anemia, PRCA, Blackfan-Diamond anemia Some sideroblastic anemias CDA, non-CDA dyserythropoiesis, Fanconi anemia Myelodysplasia, myeloproliferative diseases	Nonmegaloblastic Some disorders feature dyserythropoiesis and sometimes hyposegmented neutrophils. Macrocytosis can often be severe (e.g., aplastic processes). Reticulocytopenia (often severe)
RETICULOCYTOSIS	
Chronic hemolytic anemia	Nonmegaloblastic; no hypersegmented neutrophils
DRUGS AND TOXINS	
Alcohol abuse Some antiviral drugs (e.g., nucleoside RT inhibitors) Some anticonvulsant drugs	Mechanism of macrocytosis is often unknown. No hypersegmented neutrophils
NONHEMATOLOGIC DISEASES	
Chronic liver diseases Hypothyroidism Copper deficiency	Nonmegaloblastic; no hypersegmented neutrophils Macrocytes are rarely oval.
ARTIFACTS	
RBC clumping by cold agglutinins; some warm RBC antibodies Severe hyperglycemia Hyponatremia	Nonmegaloblastic; no hypersegmented neutrophils Disparity between high MCV and normal morphologic examination

CDA, Congenital dyserythropoietic anemia; MCV, mean corpuscular volume; PRCA, pure red cell aplasia; RBC, red blood cell; RT, reverse transcriptase; 5-FU, 5-fluorouracil.

From *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, vol 1, Philadelphia, 2015, Elsevier (Table 10-3).

481.1

Folic Acid Deficiency

Courtney D. Thornburg

Folic acid, or *pteroylglutamic acid,* consists of pteroic acid conjugated to glutamic acid. Biologically active *folates* are derived from folic acid and serve as 1-carbon donors and acceptors in many biosynthetic pathways. To form functional compounds, folates must be reduced to tetrahydrofolates in a process catalyzed by the enzyme dihydrofolate reductase. As such, they are essential for

DNA replication and cellular proliferation. Like other mammals, humans cannot synthesize folate and depend on dietary sources, including green vegetables, fruits, and animal organs (e.g., liver, kidney). Folates are heat labile and water soluble; consequently, boiling or heating folate sources leads to decreased amounts of vitamin. Naturally occurring folates are in a polyglutamated form that is less efficiently absorbed than the monoglutamate species (i.e., folic acid). Dietary folate polyglutamates are hydrolyzed to simple folates that are absorbed primarily in the proximal small intestine by a specific carrier-mediated system. Folates travel in the bloodstream and are taken up in cells primarily in the form of unconjugated methyltetrahydrofolate, which is subsequently reconjugated (polyglutamated) in the cell. There is an active enterohepatic circulation. Although rare, megaloblastic anemia as a consequence of folate deficiency has its peak incidence at 4-7 mo of age, somewhat earlier than iron-deficiency anemia, although both conditions may be present concomitantly in infants with poor nutrition.

Etiology

Folic acid deficiency can result from inadequate folate intake, decreased folate absorption, or acquired and congenital disorders of folate metabolism or transport (Table 481.2).

Table 481.2

Causes of Folate Deficiency* in Adults and Children

Inadequate Nutrition

Poor diet [†]
Poor food preparation methods
Exclusive feeding with goat's milk

Defects in Absorption

Gastric achlorhydria [§]
Diseases of the upper small intestine

    - Tropical sprue
    - Celiac disease
    - Dermatitis herpetiformis
    - Inflammatory bowel disease
- Oral pancreatic replacement therapy [§]
- Hereditary folate malabsorption

Increased Requirements or Losses

- Pregnancy
- Lactation [§]
- Prematurity [§, ‖]
- Chronic hemolytic anemia [§]
- Dialysis
- Hyperthyroidism [§]
- Lesch-Nyhan syndrome

Disorders of Transport

- Cerebral folate deficiency (genetic or acquired) [¶]

Disorders of Cellular Metabolism

- Drugs inhibiting folate metabolism
    - Antifolates (e.g., methotrexate)
    - Pyrimethamine [§] ; trimethoprim [§]
    - Sulfasalazine [§]
    - Valproic acid [§, #]
- Inherited defects
    - Methylenetetrahydrofolate reductase (MTHFR) deficiency
    - Methionine synthase deficiency (cbIE and cbIG diseases)
    - Dihydrofolate reductase deficiency
    - Methylenetetrahydrofolate dehydrogenase, cyclohydrolase, and formyltetrahydrofolate synthetase 1 (MTHFD1) deficiency
    - Others

Multifactorial or Uncertain Mechanisms

Alcohol abuse [‡]
Anticonvulsants [§]
Oral contraceptives (?) [§]

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[*] Folate deficiency often has multifactorial causes. Many may be mild and incapable alone of producing deficiency or overt clinical expression, unless additional causes augment the deficiency or limit the compensation.

[†] Relative dietary insufficiency (i.e., intake that is adequate under usual circumstances) is a particularly important cofactor that can convert borderline folate deficiency to clinically overt deficiency when other conditions coexist, such as increased requirements for folate or mild malabsorption.

[§] Megaloblastic anemia rarely results unless other limitations of folate status coexist.

[‖] Neonatal stores are low in premature infants.

[¶] Cerebral folate deficiency can occur on a genetic basis or an autoimmune basis; megaloblastic anemia does not occur because folate deficiency appears not to exist outside the central nervous system.

[#] Disrupts mitochondrial folate metabolism in utero.

[‡] Poor intake is often associated with alcoholism in adults.

From *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, vol 1, Philadelphia, 2015, Elsevier (Table 10-2).

Inadequate Folate Intake

In the United States, anemia caused by insufficient folate intake usually occurs in the context of increased vitamin requirements associated with pregnancy, periods of accelerated growth, and chronic hemolysis (see Chapter 62.6). Folate requirements greatly increase during pregnancy, in part to meet fetal needs, and deficiencies are common in mothers, particularly those who are poor or malnourished. *Folate supplementation is recommended from the start of pregnancy to prevent neural tube defects and to meet the needs of the developing fetus.* Fortunately, folate-deficient mothers generally do not give birth to infants with clinical folate deficiency because there is selective transfer of folate to the fetus via placental folate receptors. Rapid growth after birth increases demands for folic acid, and infants who are premature or ill and those with certain hemolytic disorders will have particularly high folate requirements. Human breast milk, infant formulas, and pasteurized cow's milk provide adequate amounts of folic acid. *Goat's milk is folate deficient, and supplementation must be given when it is the child's main food.* Unless supplemented, powdered milk may also be a poor source of folic acid.

Malnutrition is the most common cause of folate deficiency in older children, and those with hemoglobinopathies, infections, or malabsorption are at increased risk. Because body stores of folate are limited, deficiency can develop quickly in malnourished individuals. On a folate-free diet, megaloblastic anemia will occur after 2-3 mo.

Decreased Folate Absorption

Malabsorption caused by chronic diarrheal states or diffuse inflammatory disease can lead to folate deficiency. In both situations, some of the decreased folate absorption may be caused by impaired folate conjugase activity. Chronic diarrhea also interferes with the enterohepatic circulation of folate, thereby enhancing folate losses because of rapid intestinal passage. Megaloblastic anemia caused by folic acid deficiency can occur in celiac disease or chronic infectious enteritis and in association with enteroenteric fistulas. Previous intestinal surgery is another potential cause of decreased folate absorption.

Certain anticonvulsant drugs (e.g., phenytoin, primidone, phenobarbital) can impair folic acid absorption, and many patients treated with these drugs have low serum levels. Frank megaloblastic anemia is rare and readily responds to folic acid therapy, even when administration of the offending drug is continued. Alcohol overuse also is associated with folate malabsorption.

Congenital Abnormalities in Folate Transport and Metabolism

Inborn errors of folate transport or metabolism are rare but can be life threatening. Those associated with megaloblastic anemia include hereditary folate malabsorption and certain extremely uncommon enzyme deficiencies.

Hereditary folate malabsorption (HFM) is an autosomal recessive disorder that is linked to several loss-of-function mutations in the *SLC46A1* gene encoding the protein-coupled folate transporter. HFM is associated with an inability to absorb folic acid, 5-tetrahydrofolate, 5-methyltetrahydrofolate, or 5-formyltetrahydrofolate (folinic acid). It can become apparent at 2-6 mo of age with megaloblastic anemia and other deficits, including infections and diarrhea. Neurologic abnormalities attributable to folate deficiency in the central nervous system (CNS) include seizures, developmental delay, and intellectual disability. Folate transport is impaired both in the intestine and at the brain's choroid plexus. Serum and cerebrospinal fluid (CSF) folate levels are very low, with a loss of the normal 3:1 ratio of CSF to serum folate.

Treatment, specifically in the context of HFM, usually involves parenteral folate, although oral administration has been useful in some cases. Reduced folates are more effective than folic acid. Folate sufficiency should be maintained in both blood and CSF to avoid important complications. The megaloblastic anemia in HFM can be reversed with relatively low levels of serum folate, but adequate CSF levels may be quite difficult to achieve, and very large folate doses may be needed.

Functional methionine synthase deficiency may result from mutations affecting the function of methionine synthase reductase or methionine synthase. These disorders are autosomal recessive and are characterized not only by megaloblastic anemia, but also by cerebral atrophy, nystagmus, blindness, and altered muscle tone. Both respond to hydroxocobalamin plus betaine with variable clinical success. **Dihydrofolate reductase (DHFR) deficiency** is extremely rare and is associated with homozygous mutations in the *DHFR* gene. Clinical symptoms include megaloblastic anemia and neurologic manifestations. Although **methylenetetrahydrofolate reductase (MTHFR) deficiency** is the most common inborn error of folate metabolism, and severe cases can produce a number of neurologic and vascular complications, there is *no* associated megaloblastic anemia.

Drug-Induced Abnormalities in Folate Metabolism

A number of drugs have anti–folic acid activity as their primary pharmacologic effect and regularly produce megaloblastic anemia. *Methotrexate* binds to dihydrofolate reductase and prevents formation of tetrahydrofolate, the active form of folate. *Pyrimethamine*, used in the therapy of toxoplasmosis, and *trimethoprim*, used for treatment of various infections, can induce folic acid deficiency and occasionally megaloblastic anemia. Therapy with **folinic acid** (5-formyltetrahydrofolate) is usually beneficial.

Clinical Manifestations

In addition to the clinical features associated with anemia, folate-deficient infants and children may manifest irritability, chronic diarrhea, and poor weight gain. Hemorrhages from thrombocytopenia may occur in advanced cases. Congenital folate malabsorption and other rare etiologies of folate deficiency may be further associated with hypogammaglobulinemia, severe infections, failure to thrive, neurologic abnormalities, and cognitive delays.

Laboratory Findings

The anemia is macrocytic (mean corpuscular volume >100 fL). Variations in RBC shape and size are common (see Chapter 474 , Fig. 474.4*B*). The reticulocyte count is low, and nucleated RBCs with megaloblastic morphology are often seen in the peripheral blood. Neutropenia and thrombocytopenia may be present, particularly in patients with long-standing and severe deficiencies. The neutrophils are large, some with *hypersegmented nuclei* . The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation are also seen.

Normal serum folic acid levels are 5-20 ng/mL; with deficiency, levels are <3 ng/mL. *Levels of RBC folate are a better indicator of chronic deficiency.* The normal RBC folate level is 150-600 ng/mL of packed cells. Levels of iron and vitamin B_{12} in serum usually are normal or elevated. Serum activity of lactate dehydrogenase, a marker of ineffective erythropoiesis, is markedly elevated.

Treatment

When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. If the specific diagnosis is in doubt, smaller doses of folate (0.1 mg/day) may be used for 1 wk as a diagnostic test, because a hematologic response can be expected within 72 hr. Doses of folate >0.1 mg can correct the anemia of vitamin B_{12} deficiency but might aggravate any associated neurologic abnormalities. In most medical settings in developed countries, this therapeutic trial to distinguish the different causes of megaloblastic anemia is rarely necessary because vitamin B_{12} and folate blood levels are usually readily available. Folic acid therapy (0.5-1.0 mg/day) should be continued for 3-4 wk until a definite hematologic response has occurred. Maintenance therapy with a multivitamin (containing 0.2 mg of folate) is adequate. Very high doses of folate may be required in the setting of HFM. Transfusions are indicated only when the anemia is severe or the child is very ill.

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481.2

Vitamin B_{12} (Cobalamin) Deficiency

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Keywords

cobalamin
hereditary intrinsic factor deficiency
homocysteinemia
homocystinuria
Imerslund-Grasbeck syndrome
megaloblastic anemia
methylmalonic acid
pernicious anemia
vitamin B_{12} deficiency

Vitamin B_{12} , a generic term encompassing all biologically active **cobalamins** , is a water-soluble vitamin with a central, functional cobalt atom and a planar corrin ring. Methylcobalamin and adenosylcobalamin are the metabolically active derivatives, serving as cofactors in 2 essential metabolic reactions, methylation of homocysteine to methionine (via methionine synthase) and conversion of methyl-malonyl-coenzyme A (CoA) to succinyl CoA (via L -methyl-malonyl-CoA mutase). The products and by-products of these enzymatic reactions are critical to DNA, RNA, and protein synthesis.

Cobalamin (Cbl) is synthesized *exclusively* by microorganisms, and humans must rely on dietary sources (animal products, including meat, eggs, fish, and milk) for their needs (see Chapter 62.7). Unlike folate, older children and adults have sufficient vitamin B_{12} stores to last 3-5 yr. In young infants born to mothers with low vitamin B_{12} stores, clinical signs of Cbl deficiency can become apparent in the 1st 6-18 mo of life.

Metabolism

Under normal circumstances, cobalamin is released from food protein in the stomach through peptic digestion. Cbl then binds to *haptocorrin* (HC), a salivary glycoprotein. This complex moves into the duodenum, where HC is digested by pancreatic proteases and Cbl is liberated. Cbl then binds to *intrinsic factor* (IF), another glycoprotein that is produced by gastric parietal cells. The Cbl-IF complex subsequently enters mucosal cells of the distal ileum by receptor-mediated endocytosis. The IF-Cbl receptors are composed of a complex of 2 proteins, cubilin (CUBN) and amnionless (AMN), collectively known as *cubam*. After internalization into enterocytes, IF is degraded in the lysosome, and Cbl is released. The transporter ABCC1 (also known as MRP1) exports Cbl bound to the transport protein *transcobalamin* (TC), out of the cell. In the bloodstream, Cbl is associated with either TC (approximately 20%) or HC. TC mediates the transport of B_{12} across cells after complexing with the TC receptor, which is internalized in the lysosome. Lysosomal degradation of TC releases Cbl, which remains in the cell, where it is further processed. Two distinct membrane proteins transport Cbl across the lysosomal membrane into the cytoplasm. Cobalamins are processed in the cytoplasm to a common intermediate that can be allocated to the methylcobalamin and adenosylcobalamin synthesis pathways to meet cellular needs. It is postulated that the MMACHC protein, a product of the Cbl C locus, accepts the cobalamins exiting the lysosome. A definitive role for HC is yet to be established, but it may play a role in B_{12} storage.

Etiology

Vitamin B_{12} deficiency can result from inadequate dietary intake of Cbl, lack of IF, impaired intestinal absorption of IF-Cbl, or absence of vitamin B_{12} transport protein (see Table 481.1).

Inadequate Vitamin B_{12} Intake

Vitamin B_{12} deficiency in infants is most often nutritional, resulting from low Cbl levels in the breast milk of B_{12} -deficient mothers. Associated **megaloblastic anemia** often appears during the 1st yr of life. Maternal deficiency may be caused by **pernicious anemia** or gastrointestinal disorders such as *Helicobacter pylori* infection, celiac disease, Crohn disease, or pancreatic insufficiency. Previous gastric bypass surgery, treatment with proton pump inhibitors, or inadequate intake from a strict unsupplemented vegetarian diet has also been implicated. Fortunately, as a result of active placental Cbl transport in utero, most children of B_{12} -deficient mothers maintain Cbl levels sufficient to support adequate prenatal development. Such infants are born with low B_{12} stores, the depletion of which is associated with a gradual onset of clinical manifestations. *Vitamin B_{12} replacement often results in rapid improvement, but the longer the deficient period, the greater the likelihood of permanent disabilities.* Neonatal screening programs may detect maternal-neonatal nutritional B_{12} deficiency because of an increase in propionyl carnitine, but there is higher sensitivity using a measurement of methylmalonic acid. In high-income countries, dietary deficiency during childhood or adolescence is infrequent but can result from strict vegetarian or vegan diet. Daily requirements range from 0.4-2.4 µg.

Impaired Vitamin B_{12} Absorption

Gastric surgery or medications that impair gastric acid secretion may result in IF deficiency, leading to decreased vitamin B_{12} absorption. Pancreatic insufficiency can also lead to Cbl deficiency because of impaired cleavage and IF complex formation. Patients with neonatal necrotizing enterocolitis, inflammatory bowel disease, celiac disease, or surgical removal of the terminal ileum may also have impaired absorption of vitamin B_{12} . An overgrowth of intestinal bacteria within diverticula or duplications of the small intestine can cause vitamin B_{12} deficiency by consumption of (or competition for) the vitamin or by splitting of its complex with IF. In these cases, *hematologic response can follow appropriate antibiotic therapy.* In endemic areas, when the fish tapeworm *Diphyllobothrium latum* infests the upper small intestine, similar mechanisms may be operative. When megaloblastic anemia occurs in such situations, the serum vitamin B_{12} level is low, and the gastric fluid contains IF.

Hereditary intrinsic factor deficiency (HIFD) is a rare autosomal recessive disorder caused by a variety of mutations in the IF gene that produce a lack of gastric IF or a functionally abnormal IF. HIFD differs from typical adult pernicious anemia in that gastric acid is secreted normally and the stomach is histologically normal. It is not associated with antibodies or endocrine abnormalities. Unlike Imerslund-Grasbeck syndrome, described next, HIFD is only occasionally associated with proteinuria. Symptoms become prominent at an early age (6-24 mo), consistent with exhaustion of vitamin B_{12} stores acquired in utero. As the anemia becomes severe, weakness, irritability, anorexia, and listlessness occur. The tongue is smooth, red, and painful. Neurologic manifestations include ataxia, paresthesias, hyporeflexia, Babinski responses, and clonus. Oral vitamin B_{12} is usually *ineffective* , and lifelong intramuscular (IM) or intranasal Cbl should be used to bypass the absorption defect. The natural form, hydroxocobalamin (OHCbl), is believed to be more effective than the synthetic form, cyanocobalamin (CNCbl).

Imerslund-Grasbeck syndrome is a rare, recessively inherited pediatric disorder resulting in selective vitamin B_{12} malabsorption in the ileum and consequent vitamin B_{12} deficiency. It usually becomes clinically apparent within the 1st 6 yr of life. In addition to megaloblastic anemia, the patient may also have neurologic defects (e.g., hypotonia, developmental delay, brain atrophy, movement disorders, dementia) and/or proteinuria. Patients carry mutations in either CUBN or AMN, proteins that form the cubam receptor for the ileal IF-Cbl complex. Because CUBN is also a key receptor for protein reabsorption in the kidney, impaired expression at this site results in associated proteinuria. The disease can be fatal if it remains untreated. Early diagnosis and treatment with IM or intranasal Cbl will reverse the hematologic and neurologic abnormalities. Proteinuria does not respond to therapy.

Classic pernicious anemia (autoimmune gastritis) usually occurs in older adults but can rarely affect children. This disorder (**juvenile pernicious anemia**) usually presents during adolescence. In such cases the disease is associated with various detectable antibodies, including those against IF and the hydrogen-potassium adenosine triphosphatase proton pump in gastric parietal cells. These children can have additional immunologic abnormalities, cutaneous candidiasis, hypoparathyroidism, and other endocrine deficiencies; atrophy of the gastric mucosa and achlorhydria may occur. IM or intranasal vitamin B_{12} should be administered regularly.

Absence of Vitamin B_{12} Transport Protein Transcobalamin

Transcobalamin deficiency is a rare cause of megaloblastic anemia. A congenital deficiency is inherited as an autosomal recessive condition resulting in a failure to absorb and transport vitamin B_{12} . Most patients lack TC but some have functionally defective forms. This disorder usually manifests in the first weeks of life. Characteristically, there is failure to thrive, diarrhea, vomiting, glossitis, neurologic abnormalities, and megaloblastic anemia. The diagnosis can be difficult given that total serum vitamin B_{12} levels are often normal because approximately 80% of serum Cbl is bound to HC. The diagnosis is suggested by the presence of severe megaloblastic anemia in the face of normal folate levels and no evidence of another inborn error of metabolism. Plasma homocysteine and methylmalonic acid levels are elevated. A definitive diagnosis is made by measuring plasma TC. The serum vitamin B_{12} levels must be kept high to force enough Cbl into cells and allow normal function using high-dose oral supplementation or IM or intranasal treatment. Symptoms and laboratory studies should be monitored and doses adjusted as needed.

Inborn Errors of Cobalamin Metabolism

The conversion of Cbl to methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl) involves a number of steps, abnormalities of which have been tied to several distinct alphabetically labeled disorders. In CblE and CblG, defective N5-methyltetrahydrofolate-homocysteine methyltransferase fails to produce MeCbl. Patients present in infancy with megaloblastic anemia, vomiting, and developmental delay and are found to have **homocystinuria** and **hyperhomocysteinemia** . They do not have methylmalonic aciduria or methylmalonic acidemia. They show good response to CNCbl. AdoCbl and MeCbl are both affected by CblC (the most common of the Cbl inborn errors), CblD, and CblF. Patients can present in early infancy through adolescence. Newborns have lethargy, failure to thrive, and neurologic problems. Older patients may present with neurologic difficulties, dementia, and psychological problems. Megaloblastic anemia occurs in about *half* the cases. Patients have elevations of homocysteine and methylmalonic acid in both urine and blood. Affected individuals respond partially to OHCbl or CNCbl. CblA, CblB, and CblH are associated with methylmalonic aciduria and a variety of serious symptoms, but megaloblastic anemia is absent.

Clinical Manifestations

Children with Cbl deficiency often present with nonspecific manifestations such as weakness, lethargy, feeding difficulties, failure to thrive, and irritability. Other common findings include pallor, glossitis, vomiting, diarrhea, and icterus. Neurologic symptoms can include paresthesia, sensory deficits, hypotonia, seizures, developmental delay, developmental regression, neuropsychiatric changes, and brain/spine MRI changes. Neurologic problems from vitamin B_{12} deficiency may occur in the *absence* of any hematologic abnormalities.

Laboratory Findings

The hematologic manifestations of folate and Cbl deficiency are identical. The anemia resulting from Cbl deficiency is macrocytic, with prominent macro-ovalocytosis of the RBCs (see Chapter 474 , Fig. 474.2). The neutrophils may be large and hypersegmented. In advanced cases, neutropenia and thrombocytopenia can occur, simulating aplastic anemia or leukemia. Serum vitamin B_{12} levels are low, and the serum concentrations of methylmalonic acid and homocysteine are usually elevated. Concentrations of serum iron and serum folic acid are normal or elevated. Serum lactate dehydrogenase activity is markedly increased, a reflection of ineffective erythropoiesis. Moderate elevations of serum bilirubin levels (2-3 mg/dL) also may be found. Excessive excretion of methylmalonic acid in the urine (normal: 0-3.5 mg/24 hr) is a reliable and sensitive index of vitamin B_{12} deficiency.

Diagnosis

A comprehensive medical history is essential to the clinical recognition of possible Cbl deficiency. Information regarding clinical symptoms, dietary history, diseases, surgeries, or medications is likely to provide important clues. The physical examination may reveal relevant findings such as irritability, pallor, or specific neurologic symptoms. Screening laboratory findings offer important information, but more focused testing will be required to confirm a diagnosis of vitamin B_{12} deficiency and its cause. Cbl deficiency is usually identified by measuring total or TC bound vitamin B_{12} in the blood. Although an extremely low level is generally diagnostic, this may not be the case because false negatives and false positives are reportedly common using currently available assays. As a result, it is wise not to discount vitamin B_{12} deficiency, particularly in the face of clinical symptoms, macrocytic anemia, an abnormal blood smear, and a normal folate level. In untreated patients, methylmalonic acid and total homocysteine levels are often helpful because they are greatly elevated in the majority of those with clinical signs of B_{12} deficiency. Again, excessive urinary methylmalonic acid excretion is also a sensitive test of B_{12} deficiency. Although modest increases occur with renal failure, elevated methylmalonic acid is otherwise quite specific for B_{12} deficiency. Notably, however, serum homocysteine is also elevated in folate deficiency, homocystinuria, and renal failure.

If vitamin B_{12} deficiency has been confirmed and there is no evidence of inadequate dietary intake or, in the case of an infant, inadequate maternal B_{12} , malabsorption should be investigated. In the past the Schilling test, a measure of Cbl absorption, was the gold standard, but it is no longer available, with no comparable replacement. Anti-IF antibodies and anti–parietal cell antibodies are useful for the diagnosis of pernicious anemia. Measurement of IF and testing from more specialized laboratories may be required for less common disorders.

Treatment

Treatment regimens in children have not been well studied. The cause of vitamin B_{12} deficiency should ultimately dictate treatment dosage and route of administration as well as the duration of therapy. Cyanocobalamin is available as a nasal spray as an alternative to parenteral injection. Dose adjustments should be made in response to clinical status and laboratory values. The physiologic requirement for vitamin B_{12} is about 1-3 µg/day. Hematologic responses have been observed with small doses, indicating that a minidose may be administered as a therapeutic test when the diagnosis of vitamin B_{12} deficiency is in doubt or in circumstances where the anemia is severe and higher initial doses might result in severe metabolic disturbances.

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481.3

Other Rare Megaloblastic Anemias

Courtney D. Thornburg

Keywords

orotic aciduria
ringed sideroblasts
thiamine-responsive megaloblastic anemia

Orotic aciduria is a rare autosomal recessive disorder that usually appears in the 1st yr of life and is characterized by growth failure, developmental delay, megaloblastic anemia, and increased urinary excretion of orotic acid (see Chapter 108). Rarely, orotic aciduria occurs without megaloblastic anemia. This defect is the most common metabolic error in the de novo synthesis of pyrimidines and therefore affects nucleic acid synthesis. The usual form of hereditary orotic aciduria is caused by a deficiency (in all body tissues) of orotic phosphoribosyl transferase and orotidine-5-phosphate decarboxylase, 2 sequential enzymatic steps in pyrimidine nucleotide synthesis. The diagnosis is suggested by the presence of severe megaloblastic anemia with normal serum B_{12} and folate levels and no evidence of TC deficiency. A presumptive diagnosis is made by finding increased urinary orotic acid. However, confirmation of the diagnosis requires assay of the transferase and decarboxylase enzymes in the patient's erythrocytes. Failure to thrive and intellectual disability often accompany this condition. The anemia is refractory to vitamin B_{12} or folic acid, but responds promptly to administration of uridine.

Thiamine-responsive megaloblastic anemia (Rogers syndrome) is a very rare autosomal recessive disorder characterized by megaloblastic anemia, sensorineural deafness, and diabetes mellitus. Congenital heart defects, arrhythmias, visual problems, short stature, trilineage myelodysplasia, and strokes are also described. Thiamine-responsive megaloblastic anemia usually presents in infancy but may occasionally develop in childhood and adolescence and occurs in several ethnically distinct populations. The bone marrow is characterized not only by megaloblastic changes but also by **ringed sideroblasts** . The defect is caused by mutations in the *SCL19A2* gene on chromosome 1, which encodes a high-affinity plasma membrane thiamine transporter. Continuous thiamine supplementation usually reverses the anemia and diabetes, but not existing hearing defects.

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CHAPTER 482

Iron-Deficiency Anemia

Jennifer A. Rothman

Iron deficiency is the most widespread and common nutritional disorder in the world. It is estimated that 30–50% of the global population has iron-deficiency anemia, and most of these individuals live in developing countries. In the United States, 8–14% of children ages 12-36 mo are *iron deficient* , and 30% of this group progresses to iron-deficiency *anemia* .

A full-term newborn infant contains about 0.5 g of iron, compared to 5 g of iron in adults. This change in quantity of iron from birth to adulthood means that an average of 0.8 mg of iron must be absorbed each day during the 1st 15 yr of life. A small additional amount is necessary to balance normal losses of iron by shedding of cells. It is therefore necessary to absorb approximately 1 mg daily to maintain positive iron balance in childhood. Because <10% of dietary iron is usually absorbed, a dietary intake of 8-10 mg of iron daily is necessary to maintain iron levels. During infancy, when growth is most rapid, the 1 mg/L of iron in cow's and breast milk makes it difficult to maintain body iron. Breastfed infants have an advantage, because they absorb iron 2-3 times more efficiently than infants fed cow's milk; nonetheless, breastfed infants are at risk of developing iron deficiency without regular intake of iron-fortified foods by 6 mo of age.

Etiology

Most iron in neonates is in circulating hemoglobin. As the relatively high hemoglobin concentration of the newborn infant falls during the first 2-3 mo of life, considerable iron is recycled. These iron stores are usually sufficient for blood formation in the 1st 6-9 mo of life in term infants. Stores are depleted sooner in premature infants, low-birthweight infants, or infants with perinatal blood loss, because their iron stores are smaller. Delayed (1-3 min) clamping of the umbilical cord can improve iron status and reduce the risk of iron deficiency, whereas early clamping (<30 sec) puts the infant at risk for iron deficiency. Dietary sources of iron are especially important in these infants. In term infants, anemia caused solely by inadequate dietary iron usually occurs at 9-24 mo of age and is relatively uncommon thereafter. The usual dietary pattern observed in infants and toddlers with nutritional iron-deficiency anemia in developed countries is excessive consumption of cow's milk (low iron content, blood loss from milk protein colitis) in a child who is often overweight or bottle feeding beyond 12 mo of age. Worldwide, **undernutrition** is usually responsible for iron deficiency.

Blood loss must be considered as a possible cause in every case of iron-deficiency anemia. Sources of blood loss, particularly in older children and adolescents, include menstrual losses, recurrent nosebleeds, or intravascular hemolysis with hemoglobinuria, as seen in diseases such as malaria. Chronic iron-deficiency anemia from occult bleeding may be caused by a lesion of the gastrointestinal (GI) tract, such as peptic ulcer, Meckel diverticulum, polyp, hemangioma, or inflammatory bowel disease. Infants can have chronic intestinal blood loss induced by exposure to whole cow's milk protein. Involved infants characteristically develop anemia that is more severe and occurs earlier than would be expected simply from an inadequate intake of iron. The ongoing loss of blood in the stools can be prevented either by breastfeeding or by delaying the introduction of whole cow's milk in the 1st yr of life and then limiting the quantity to <24 oz/24 hr. Unrecognized blood loss also can be associated with chronic diarrhea and rarely, with pulmonary hemosiderosis. In developing countries, infections with hookworm, *Trichuris trichiura*, and *Plasmodium* often contribute to iron deficiency. Since iron is absorbed in the proximal duodenum with the assistance of gastric acid, gastric bypass procedures or *Helicobacter pylori* infection may interfere with iron absorption. Similarly, inflammation of the bowel from celiac disease and giardiasis may also interfere with iron absorption.

Approximately 2% of adolescent girls have iron-deficiency anemia, largely as a result of their adolescent growth spurt and menstrual blood loss. The highest risk of iron-deficiency anemia (>30%) is among teenagers who are or have been pregnant.

Clinical Manifestations

Most children with iron-deficiency anemia are asymptomatic and are identified by routine laboratory screening at 9-12 mo of age. Normal hemoglobin values vary according to age, gender, race, and method of testing, such as capillary vs venous blood. Pallor is the most recognized clinical sign of iron-deficiency anemia but is not usually visible until the hemoglobin falls to 7-8 g/dL. It is most readily noted as pallor of the palms, palmar creases, nail beds, or conjunctivae. Parents often fail to note the pallor because of the typical slow decline of hemoglobin over time. Often a visiting friend or relative is the first to notice. Older individuals may report cold intolerance, fatigue, exercise-induced dyspnea, or decreased mental acuity. In mild to moderate iron-deficiency anemia (i.e., hemoglobin levels of 6-10 g/dL), compensatory mechanisms, including increased levels of 2,3-diphosphoglycerate and a shift of the oxygen dissociation curve, may be so effective that few symptoms of anemia aside from mild irritability are noted. When the hemoglobin level falls to <5 g/dL, irritability, anorexia, and lethargy develop, and systolic flow murmurs are often heard. If the hemoglobin continues to fall, tachycardia and high output cardiac failure can occur.

Iron deficiency has nonhematologic systemic effects. Both iron deficiency and iron-deficiency anemia are associated with impaired neurocognitive function in infancy. Iron-deficiency anemia s also associated with later, possibly irreversible, cognitive defects. Although there is support for iron deficiency with or without anemia causing these defects, it has not been established unequivocally. Some studies suggest an increased risk of seizures, strokes, breath-holding spells in children, and exacerbations of restless legs syndrome in adults. Given the frequency of iron deficiency and iron-deficiency anemia and the potential for adverse neurodevelopmental outcomes, minimizing the incidence of iron deficiency is an important goal.

Other nonhematologic consequences of iron deficiency include **pica** , the desire to ingest nonnutritive substances, and **pagophagia** , the desire to ingest ice. The pica can result in the ingestion of lead-containing substances and result in concomitant **plumbism** (see Chapter 739).

Laboratory Findings

In progressive iron deficiency, a sequence of biochemical and hematologic events occurs (Table 482.1). First, tissue iron stores are depleted. This depletion is reflected by reduced serum *ferritin*, an iron-storage protein, which provides an estimate of body iron stores in the absence of inflammatory disease. Next, serum iron levels decrease, the iron-binding capacity of the serum (serum *transferrin*) increases, and the transferrin saturation falls below normal. As iron stores decrease, iron becomes unavailable to complex with protoporphyrin to form heme. Free erythrocyte protoporphyrins accumulate, and hemoglobin synthesis is impaired. At this point, iron deficiency progresses to iron-deficiency anemia. With less available hemoglobin in each cell, the red blood cells (RBCs) become smaller and varied in size. The variation in RBC size is measured by an increasing red cell distribution width (RDW). These changes are associated with a decrease in mean corpuscular volume (MCV) and mean corpuscular hemoglobin. Developmental changes in MCV require the use of age-related standards for recognizing microcytosis (see Table 474.1). The RBC count also decreases. The reticulocyte percentage may be normal or moderately elevated, but absolute reticulocyte counts indicate an insufficient response to the degree of anemia. The blood smear reveals hypochromic, microcytic RBCs with substantial variation in cell size. Elliptocytic or cigar-shaped RBCs are often seen (Fig. 482.1). Detection of increased soluble transferrin receptor and decreased reticulocyte hemoglobin concentration provides very useful and early indicators of iron deficiency, but availability of these tests is more limited. **Bone marrow iron staining** is the most accurate method of diagnosing iron-deficiency anemia but is invasive and expensive and usually unnecessary.

Table 482.1

Indicators of Iron-Deficiency Anemia

INDICATOR	SELECTED CUTOFF VALUES TO DEFINE IRON DEFICIENCY	COMMENTS
Hemoglobin (g/dL)	<11.0 for non-Hispanic whites age 0.5-4 yr	When used alone, has low specificity and sensitivity. Use appropriate age-specific normal values found in Table 474.1 . Normal values for African Americans are found in Table 474.2 .
Mean corpuscular volume (MCV) (μm^3)	<70 for age 6-24 mo	A reliable, but late indicator of iron deficiency (ID) Low values can also be a result of thalassemia and other causes of microcytosis. False-negative results can be seen in liver disease. Normal values listed in Table 474.1 .
Serum ferritin (SF) (µg/L)	Age ≤5 yr: <12 Children >5 yr: <15	Probably the most useful laboratory measure of iron stores, and helps identify ID; low SF value is diagnostic of iron-deficiency anemia (IDA) in a patient with anemia.

	All age-groups in presence of infection: <30-100	SF is an acute-phase reactant that increases in many acute or chronic inflammatory conditions independent of iron status. Combining SF with a measurement of C-reactive protein (CRP) may help to identify these false-negative SF results.
Reticulocyte hemoglobin content (CHr) (pg)	Infants and young children: <27.5 Adults: ≤28.0	A sensitive indicator that falls within days of onset of iron-deficient erythropoiesis and is unaffected by inflammation. It is an excellent tool to recognize ID as well as IDA. False-normal values can occur when MCV is increased and in thalassemia. Not yet widely available on hematology analyzers.
Serum transferrin receptor (sTfR)	Cutoff varies with assay and with patient's age and ethnic origin.	This soluble receptor is upregulated in ID and is found in increased amounts in serum. It also increased during enhanced erythropoiesis. sTfR is not substantially affected by the acute-phase response. Levels can be increased in hemolytic anemia or other conditions that increase red cell mass.
Transferrin saturation	<16%	Inexpensive, but use is limited by diurnal variation in serum iron and by many clinical disorders that affect transferrin concentrations, including inflammatory conditions, aging, and nutrition.
Erythrocyte zinc protoporphyrin (ZPP) (μmol/mol heme)	Age ≤5 yr: >70 Children >5 yr: >80 Children >5 yr on washed red cells: >40	Can be measured directly on a drop of blood with a portable hematofluorometer. Useful screening test in field surveys, particularly in children, in whom uncomplicated ID is the primary cause of anemia. Lead poisoning can increase values, particularly in urban and industrial settings.
Hepcidin	To be defined; usually ≤10 ng/mL	Extremely elevated in anemia of inflammation and suppressed in IDA, but has limited commercial availability

Adapted from Zimmermann MB, Hurrell RF: Nutritional iron deficiency, *Lancet* 370:511–520, 2007.

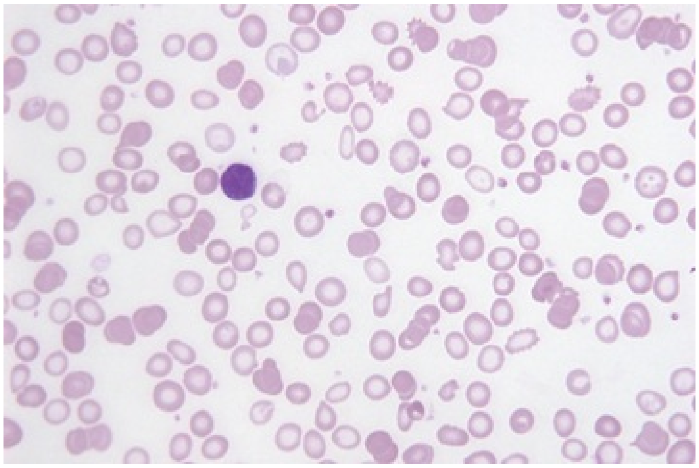

FIG. 482.1 **Peripheral blood smear in iron deficiency. Note the small, pale (microcytic, hypochromic) red blood cells with variable sizes and shapes (anisopoikilocytosis). Occasional target cells with central hemoglobin pooling, as well as several somewhat elongated hypochromic microcytes (pencil cells), are present. (From Fleming MD: Disorders of iron and copper metabolism, the sideroblastic anemias, and lead toxicity. In Orkin SH, Nathan DG, Ginsburg D, et al, editors: Nathan and Oski's hematology and oncology of infancy and childhood, ed 8, Philadelphia, 2015, Elsevier, Fig 11-7.)**

White blood cell (WBC) count is normal, but *thrombocytosis* is often present. Thrombocytopenia is occasionally seen with iron deficiency, potentially confusing the diagnosis with bone marrow failure disorders. Stool for occult blood should be checked to exclude blood loss as the cause of iron deficiency.

A presumptive diagnosis of iron-deficiency anemia is most often made by a complete blood count (CBC) demonstrating a microcytic anemia with a high RDW, reduced RBC count, normal WBC count, and normal or elevated platelet count. Other laboratory studies, such as reduced serum ferritin, reduced serum iron, and increased total iron-binding capacity, are not usually necessary unless severe anemia requires a more rapid diagnosis, other complicating clinical factors are present, or the anemia does not respond to iron therapy. An increase in hemoglobin ≥1 g/dL after 1 mo of iron therapy is usually the most practical means to establish the diagnosis.

A diagnosis of iron deficiency in the absence of anemia is more challenging. Serum ferritin is a useful measure whose value is increased by also measuring C-reactive protein to help identify false-negative results because of concomitant inflammation. Tests to detect increased soluble transferrin receptor and decreased reticulocyte hemoglobin concentration may find increasing use if they become more available.

Differential Diagnosis

The most common alternative causes of microcytic anemia are α- or β-thalassemia and other hemoglobinopathies, including hemoglobins E and C (see Chapter 489). The anemia of inflammation is usually normocytic but can be microcytic in a minority of cases (see Chapter 478.1). Lead poisoning can cause microcytic anemia, but more often the microcytic anemia is caused by iron deficiency resulting in pica and secondary lead intoxication (see Chapter 739). Table 482.2 compares the use of laboratory studies in the diagnosis of the most common microcytic anemias. Table 482.3 lists other etiologies of microcytic anemia (see Chapter 483). Although the platelet count can be abnormal, WBC and neutrophil counts should be normal.

Table 482.2

Laboratory Studies Differentiating the Most Common Microcytic Anemias

STUDY	IRON-DEFICIENCY ANEMIA	α- OR β-THALASSEMIA	ANEMIA OF CHRONIC DISEASE
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal-decreased
RDW	Increased	Normal or minimally increased	Normal-increased
RBC	Decreased	Normal-increased	Normal-decreased
Serum ferritin	Decreased	Normal	Increased
Total Fe binding capacity	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
FEP	Increased	Normal	Increased
Soluable transferrin receptor	Increased	Normal	Normal
Reticulocyte hemoglobin concentration	Decreased	Normal	Normal-decreased

FEP, Free erythrocyte protoporphyrin; MCV, mean corpuscular volume; RBC, red blood cell count; RDW, red cell distribution width.

Adapated from Zimmermann MB, Hurrell RF: Nutritional iron deficiency, *Lancet* 370:511–520, 2007.

Table 482.3

Differential Diagnosis of Microcytic Anemia That Fails to Respond to Oral Iron

- Poor compliance (true intolerance of Fe is uncommon)
- Incorrect dose or medication
- Malabsorption of administered iron (celiac disease, giardiasis, other)
- Medications
  - Antacids
  - Proton pump inhibitors
  - Histamine$_2$ blocking agents
  - Bran
  - Tannins
  - Phytates
- Ongoing blood loss, including gastrointestinal, menstrual, and respiratory
- Concurrent infection or inflammatory disorder inhibiting the response to iron
- Concurrent vitamin B$_{12}$ or folate deficiency
- Lead or aluminum toxicity
- Diagnosis other than iron deficiency
  - Thalassemias

Hemoglobins C and E disorders
Anemia of chronic disease
Lead poisoning
Sickle thalassemias, hemoglobin SC disease
Iron-refractory iron-deficiency anemia (IRIDA; see Chapter 482.1)
Rare microcytic anemias (see Chapter 483)

When anemia is identified solely by hemoglobin or hematocrit, 60% of children in developed countries with anemia have an explanation other than iron deficiency. Caution should be used in treating these children with iron without the benefit of a CBC with differential to ensure that a more serious diagnosis is not missed.

Prevention

Iron deficiency is best prevented to avoid both its systemic manifestations and the anemia. Breastfeeding should be encouraged, with the addition of supplemental iron at 4 mo of age. Infants who are not breastfed should only receive iron-fortified formula (12 mg iron/L) for the 1st yr, and thereafter cow's milk should be limited to <20-24 oz daily. This approach encourages the ingestion of foods richer in iron and prevents blood loss as a result of cow's milk–induced enteropathy.

Routine screening for all children using hemoglobin or hematocrit is done at age 9-12 mo or earlier, if at 4 mo the child is assessed to be at high risk for iron deficiency, as recommended by the American Academy of Pediatrics (AAP). The U.S. Preventive Service Task Force does not recommend for or against routine screening. Routine hemoglobin screening at 12 mo will not detect iron deficiency without anemia. Children with identified risk factors for iron deficiency should be screened with a CBC.

Treatment

The regular response of iron-deficiency anemia to adequate amounts of iron is a critical diagnostic and therapeutic feature (Table 482.4). Oral administration of simple ferrous salts (most often ferrous sulfate) provides inexpensive and effective therapy. There is no evidence that the addition of any trace metal, vitamin, or other hematinic substance significantly increases the response to simple ferrous salts. Calcium and fiber may decrease the absorption of iron, but this can be overcome with co-administration of vitamin C. Tea is a significant inhibitor of iron absorption. Aside from the unpleasant taste of iron, intolerance to oral iron is uncommon in young children. In contrast, older children and adolescents sometimes have GI complaints that may improve with lower doses of iron.

Table 482.4

Responses to Iron Therapy in Iron-Deficiency Anemia

TIME AFTER IRON ADMINISTRATION	RESPONSE
12-24 hr	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite; increased serum iron
36-48 hr	Initial bone marrow response; erythroid hyperplasia
48-72 hr	Reticulocytosis, peaking at 5-7 days
4-30 days	Increase in hemoglobin level; increase in mean corpuscular volume; increase in ferritin
1-3 mo	Repletion of stores

The therapeutic dose should be calculated in terms of elemental iron. **A daily total dose of 3-6 mg/kg of elemental iron in 1 or 2 doses is adequate** , with the higher dose used in more severe cases. The maximum dose is 150-200 mg of elemental iron daily. Ferrous sulfate is 20% elemental iron by weight and is ideally given between meals with vitamin C–containing juice, although this timing is usually not critical with a therapeutic dose. Parenteral iron preparations are considered when malabsorption is present or when compliance is poor, because oral therapy is otherwise as effective, much less expensive and less toxic. When necessary, intravenous low-molecular-weight iron dextran, parenteral iron sucrose, ferric carboxymaltose, and ferric gluconate complex are available, although only LMW iron dextran is U.S. Food and Drug Administration (FDA) approved for use in children for iron deficiency.

Iron therapy may increase the virulence of malaria and certain gram-negative bacteria, particularly in developing countries. Iron overdose is associated with *Yersinia* infection.

In addition to iron therapy, dietary counseling is usually necessary. Excessive intake of milk, particularly cow's milk, should be limited. Dietary iron should also be increased. Iron from heme sources is 10 times more bioavailable than iron from nonheme sources. Iron deficiency in adolescent girls secondary to menorrhagia is treated with iron and menstrual control with hormone therapy (see Chapter 142.2).

If the anemia is mild, the only additional study is to repeat the blood count approximately 1 mo after initiating therapy. At this point, the hemoglobin has usually risen by at least 1-2 g/dL and has often normalized. If the anemia is more severe, earlier confirmation of the diagnosis can be made by the appearance of a reticulocytosis, usually within 48-96 hr of instituting treatment. The hemoglobin will then begin to increase 0.1-0.4 g/dL/day depending on the severity of the anemia. Iron medication should be continued for 2-3 mo after blood values normalize to reestablish iron stores. Good follow-up is essential to ensure a response to therapy. When the anemia responds poorly or not at all to iron therapy, the multiple considerations include diagnoses other than iron deficiency (see Table 482.3). If there are concerns regarding adherence or absorption, an oral iron absorption test may be performed.

Because a rapid hematologic response can be confidently predicted in typical iron deficiency, blood transfusion is rarely necessary. It should only be used when heart failure is imminent, or if the anemia is severe with evidence of substantial ongoing blood loss. Unless there is active bleeding, transfusions must be given slowly to avoid precipitating or exacerbating congestive heart failure.

482.1

Iron-Refractory Iron-Deficiency Anemia

Karin E. Finberg

Keywords

hepcidin

hypoferremia
IRIDA
iron
iron-refractory iron-deficiency anemia
matriptase-2
TMPRSS6

Iron-refractory iron-deficiency anemia (**IRIDA**) is a rare, autosomal recessive disorder of systemic iron balance characterized by defects in both the absorption and the utilization of iron. Patients with IRIDA exhibit iron-deficiency anemia that is refractory to oral iron therapy and only partially responsive to parenteral iron administration.

Etiology

IRIDA is caused by loss-of-function mutations in the gene *TMPRSS6* (transmembrane serine protease 6). At least 45 different *TMPRSS6* mutations have been associated with the IRIDA phenotype, with most mutations appearing unique to individual kindreds. The underlying genetic defect in IRIDA results in dysregulated production of *hepcidin*, a small peptide released by hepatocytes that serves as the central hormonal regulator of systemic iron balance. Hepcidin regulates the entry of iron into the circulation by limiting the export of iron from intestinal enterocytes as well as from reticuloendothelial macrophages (which recycle iron from phagocytosed senescent RBCs). Because hepcidin production is regulated in response to body iron stores, the liver normally responds to systemic iron deficiency by decreasing hepcidin production, providing a means to raise circulating iron levels and thus increase iron availability for erythropoiesis. However, in patients with IRIDA, circulating hepcidin levels are inappropriately elevated. This hepcidin elevation explains the underlying pathophysiology of IRIDA, including (1) the development of systemic iron deficiency in response to impaired intestinal absorption, (2) the inefficacy of oral iron formulations in treating the anemia, and (3) the impaired utilization of parenteral iron formulations, which require macrophage processing before the iron can be made available for erythropoiesis. The *TMPRSS6* gene product, a membrane-spanning serine protease termed *matriptase-2*, suppresses hepcidin production by dampening signaling through a key transduction pathway that promotes hepcidin transcription by hepatocytes in response to bone morphogenetic protein ligands.

Clinical Manifestations

Patients with IRIDA demonstrate a hypochromic, microcytic anemia associated with severe **hypoferremia** that usually presents in early childhood. Treatment with a course of oral iron that is of appropriate dose and duration (see Chapter 482) generally fails to produce a hematologic response. When a response is observed, it is not sustained after discontinuation of oral iron therapy, and the hypoferremia persists. In patients with IRIDA, anemia has not been detected at birth, and the clinical phenotype has been reported to develop only after the neonatal period. Typically, the anemia is identified during laboratory screening performed as part of a routine pediatric evaluation. Despite their chronic iron deficiency, affected individuals have been reported to exhibit normal growth and neurocognitive development on long-term follow up. The presence of an affected sibling may suggest an inherited basis for the anemia. However, many cases appear sporadic because of the recessive mode of transmission and small pedigree sizes. The anemia and microcytosis tend to improve with age, which may reflect the greater iron demands for growth during childhood. In some cases, however, the anemia may not be recognized until adulthood, suggesting that IRIDA may be underdiagnosed.

Laboratory Findings

Children with IRIDA typically present with a moderate to severe microcytic anemia (hemoglobin, 6-9 g/dL). RBC indices are notable for a very low erythrocyte MCV (typically 45-65 fL). Peripheral blood smear morphology is similar to that observed in severe acquired iron-deficiency anemia, revealing hypochromic, microcytic RBCs with marked variation in size and shape. Hypoferremia is severe, with transferrin saturation typically <5%. Serum ferritin levels may be low or within the normal range but are generally inappropriately high relative to the degree of iron deficiency. Results from an *oral iron challenge*, a minimally invasive procedure that assesses the ability of serum iron levels to rise after oral administration of ferrous sulfate, may aid in distinguishing a defect in intestinal iron absorption from other causes of chronic iron deficiency. Although not specific for IRIDA, the failure to achieve an appropriate increase in serum iron level is indicative of an intestinal iron absorption defect. Sequencing of the *TMPRSS6* gene may be performed to establish the genetic diagnosis. The finding of an inappropriately elevated serum or plasma hepcidin level is supportive of, but not specific for, the diagnosis of IRIDA. However, although multiple analytical methods have been developed to measure hepcidin levels in the research setting, at present none has been FDA approved for clinical use.

Differential Diagnosis

IRIDA must be differentiated from acquired forms of iron deficiency (see Chapter 482) and from other genetic causes of microcytic anemia such as the thalassemias. Gastrointestinal blood loss, dietary insufficiency, and acquired intestinal disorders associated with malabsorption (e.g., celiac disease, inflammatory bowel disease, *Helicobacter pylori* infection) should be excluded. Other rare, recessive microcytic anemias that result from defective iron utilization by erythroblasts can be differentiated from IRIDA by their distinct clinical and laboratory features. For example, patients with mutations in *SLC11A2* , which encodes a divalent metal transporter that performs key functions in erythroblasts, enterocytes, and macrophages, display elevated serum iron levels and develop systemic iron overload, whereas patients with **hereditary atransferrinemia** (caused by mutation in the transferrin gene) exhibit low or undetectable serum transferrin levels that are accompanied by the deposition of non–transferrin-bound iron in parenchymal tissues. Because hepcidin production is induced by inflammatory stimuli, hepcidin elevation is also a feature of the **anemia of chronic disease** (ACD). However, in contrast to patients with IRIDA, in whom the hepcidin dysregulation is congenital, patients with ACD generally retain normal to high iron stores because of the acquired nature of their hepcidin elevation (see Chapter 478.1). Rare medical causes that may mimic IRIDA include Castleman disease, lymphangiomas, autoimmune gastritis, *H. pylori* infection, and mutations in *KCNQ1* .

Treatment

Because of the underlying pathophysiology of IRIDA, *parenteral iron* *supplementation* is required to correct the anemia. Although parenteral iron therapy raises body iron stores, the hematologic response is usually slow and not completely corrective. This likely results from insufficient export of the processed iron from macrophages into the circulation, an expected consequence of hepcidin elevation. Serum ferritin levels increase with parenteral iron therapy in a dose-dependent manner and may raise concerns for iron overload, which would be expected to exhibit a reticuloendothelial rather than a parenchymal pattern of iron loading. Given the limited number of IRIDA cases reported to date, the optimal formulation and dosing of parenteral iron have not yet been established. Although oral iron supplementation does not appear to have a significant role in treatment of IRIDA, the addition of ascorbic acid to a ferrous sulfate oral supplement has been associated with hematologic responses in isolated cases. Treatment with recombinant erythropoietin has not been found to produce significant clinical benefit in patients with IRIDA.

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CHAPTER 483

Other Microcytic Anemias

Jennifer A. Rothman

A number of rare microcytic anemias need to be considered when children with microcytic anemia fail to respond to oral iron. These anemias include thalassemia or thalassemia trait (see Chapter 489), infantile poikilocytosis and hereditary pyropoikilocytosis (Chapter 486), and anemia of chronic disease (Chapter 478.1). Additionally, rare nutritional disorders and disorders of iron metabolism can cause microcytosis.

Infantile Poikilocytosis and Hereditary Pyropoikilocytosis

Infants with common **hereditary elliptocytosis** (see Chapter 486) may initially present with hemolytic anemia characterized by marked poikilocytosis with budding and fragmentation of the red blood cells (RBCs). These small RBC fragments reduce the overall mean corpuscular volume (MCV), resulting in microcytosis. By 2 yr of age, the findings become typical of hereditary elliptocytosis. **Hereditary pyropoikilocytosis** is a much less common variant of hereditary elliptocytosis, in which the hemolytic anemia and RBC changes are more severe.

Copper Deficiency

Copper deficiency is a rare cause of microcytic anemia and neurologic dysfunction. Copper is absorbed in the stomach and proximal duodenum. Deficiency is associated with malabsorption; severe malnutrition, often with feeding of milk alone; gastric surgery or feedings that bypass the stomach and duodenum; or parenteral nutrition with inadvertent omission of supplemental copper. Zinc and copper are competitively absorbed from the gastrointestinal (GI) tract, so zinc excess may inadvertently lead to copper deficiency. Diagnosis is made by measuring a serum copper level and possibly a zinc level. Treatment includes either oral or parenteral supplementation, depending on the underlying cause.

Defects of Iron Metabolism

Rare microcytic anemias may be associated with defects in iron trafficking and regulation. Most are inherited and usually identified in childhood, including defects of iron absorption, transport, utilization, and recycling. A *defect of iron absorption* is **iron-refractory iron-deficiency anemia** (see Chapter 482.1). *Defects of iron recycling* include aceruloplasminemia and atransferrinemia. **Aceruloplasminemia** is an autosomal recessive disorder in the *CP* gene that encodes ceruloplasmin. Iron cannot be appropriately transported from macrophages to plasma to be available for RBC production but accumulates instead in the brain and visceral organs. The diagnosis is made by a combination of absence of serum ceruloplasmin, low serum copper and iron, elevated ferritin, and increased liver iron concentration. Hypotransferrinemia or **atransferrinemia** is also an autosomal recessive disorder caused by mutations in the transferrin (*TF*) gene. Diagnosis is made by low or absent serum transferrin and liver iron overload. Genetic testing can confirm the diagnosis for both disorders. Treatment includes iron chelation therapy, limiting iron supplementation and dietary iron, and possibly fresh-frozen plasma to replace ceruloplasmin and/or transferrin. Purified transferrin (apotransferrin) infusions are available.

Defects of mitochondrial iron utilization are a diverse group of acquired and inherited defects known as **sideroblastic anemias** (Table 483.1). Several genes associated with these disorders have been described. Impaired heme synthesis leads to retention of iron within the mitochondria of marrow RBCs. The perinuclear distribution of mitochondria results in a pattern of iron staining surrounding the nucleus. These are *ringed sideroblasts* (Fig. 483.1), which are distinct from the more diffuse cytoplasmic distribution of iron in normal RBC precursors. The anemia is characterized by hypochromic, microcytic RBCs mixed with normal RBCs, so the complete blood count indicates a very high RBC distribution width. The serum iron concentration usually is elevated, and the transferrin saturation of iron is increased.

Table 483.1

Clinical and Genetic Features of Congenital Sideroblastic Anemias

	XLSA	***SLC25A38***	**XLSA/A**	***GLRX5*** **[*]**	**PMPS**	**MLASA/PUS1**	**MLASA**	**SIF**
Inheritance	X-linked	Autosomal recessive	X-linked	Autosomal recessive	Maternal [†]	Autosomal recessive	Autosomal recessive	Aut rece
Chromosome	p11.21	3p22.1	q13	14q32.2	mtDNA	14q24.33	12p11.21	?
Gene	*ALAS2*	*SLC25A38*	*ABCB7*	*GLRX5*	Variable	*PUS1*	*YARS2*	*TR*
Gender distribution	M > F	M = F	M	M	M ≈ F	M = F	M = F	M =
Carrier phenotype	+	−	+	?	NA	−	−	−
Mean cell volume	↓↓ [‡]	↓↓	↓/NMA	↓↓	↑	Normal/↑	Normal/↑	↓
Iron overload	+ /++	++	−	++	−/+	−/+	−/+	+
Vitamin response	Pyridoxine	−	−	−	−	−	−	−
Transfusion	−/+	++	−	+	+	+ /−	+ /−	+ /−
Associated phenotypes	−	−	Cerebellar hypoplasia, ataxia	−	Exocrine pancreas insufficiency, cytopenias, lactic acidosis, myopathy	Myopathy, lactic acidosis, craniofacial abnormalities, intellectual disability	Myopathy, lactic acidosis	Im feve deve dela

[*] A *GLRX5* mutation has been described in only 1 patient.

[†] Essentially, all cases of PMPS are sporadic, but rare maternally inherited cases are reported.

[‡] Mean cell volume is typically normal or increased in female carriers.

+ , Present; −, absent; ↑, increased; ↓, decreased; NA, not applicable; mtDNA, mitochondrial DNA.

XLSA, X-linked sideroblastic anemia; XLSA/A, X-linked sideroblastic anemia and spinocerebellar ataxia; PMPS, Pearson marrow pancreas syndrome; MLASA, Mitochondrial myopathy lactic acidosis and sideroblastic anemia; SIFD, Sideroblastic anemia, immunodeficiency (B cell), periodic fevers, and developmental delay; TRMA, thiamine responsive megaloblastic anemia.

Adapted from Fleming MD: Congenital sideroblastic anemias: iron and heme lost in mitochondrial translation, *Hematology Am Soc Hematol Educ Program* 2011, pp 525–553.

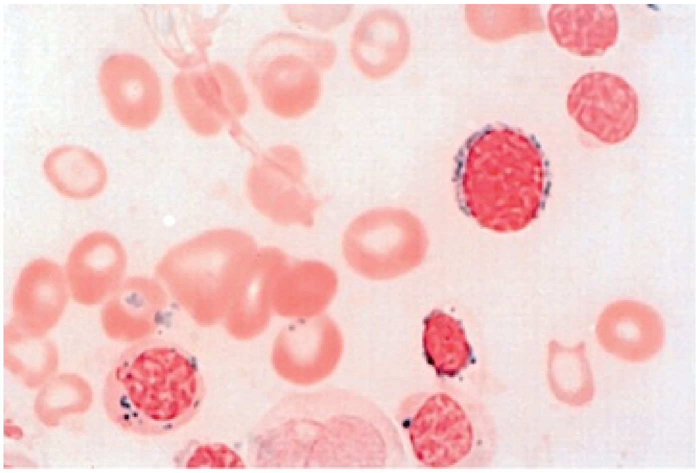

FIG. 483.1 Ring sideroblast in myelodysplastic syndrome (refractory anemia with ring sideroblasts)—iron stain. (From Ryan DH, Cohen HJ: Bone marrow examination. In Hoffman R, Benz EJ Jr, Shattil SJ, et al, editors: *Hematology* , ed 4, Philadelphia, 2005, Churchill Livingstone.)

Congenital sideroblastic anemia is usually an X-linked disorder and is most often a result of mutations in erythrocytic isozyme 5-aminolevulinic acid synthetase, the rate-limiting enzyme reaction in heme synthesis. An important cofactor for 5-ALA synthetase is *pyridoxal phosphate,* with several mutations occurring near its binding site. Severe anemia is recognized in infancy or early childhood, whereas milder cases might not become apparent until early adulthood or later. Clinical findings include pallor, icterus, and moderate splenomegaly and/or hepatomegaly. The severity of the anemia varies such that some patients require no therapy and others need regular RBC transfusions. A subset of patients with hereditary sideroblastic anemia manifest a hematologic response to pyridoxine doses of 50-200 mg/day. Iron overload, as manifested by elevated serum ferritin, elevated serum iron, and increased transferrin saturation, is a major complication of this disorder. Clinical evidence of iron overload (e.g., diabetes mellitus, liver dysfunction) may be found in some patients who have little or no anemia, which may require iron chelation therapy. Stem cell transplantation has been used to treat affected children who are dependent on RBC transfusions.

A unique variant of congenital sideroblastic anemia is **Pearson syndrome** (see Chapter 476), but the anemia is usually *macrocytic* and not microcytic. Another rare variant of sideroblastic anemia is caused by mutations in *TRNT1* and manifests with developmental delay, periodic fevers, and B-cell immunodeficiency in addition to sideroblastic anemia.

Acquired sideroblastic anemias can be triggered by copper deficiency or drugs and toxins that disturb mitochondrial iron metabolism, including lead, chloramphenicol, penicillamine, ethanol, and isoniazid. The acquired neoplastic sideroblastic syndromes (myelodysplasias) seen in adults are very rare in children.

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SECTION 3

Hemolytic Anemias

OUTLINE

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Chapter 491 Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias
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CHAPTER 484

Definitions and Classification of Hemolytic Anemias

Matthew D. Merguerian, Patrick G. Gallagher

Hemolysis is defined as the premature destruction of red blood cells (RBCs). Anemia results when the rate of destruction exceeds the capacity of the marrow to produce additional RBCs. Normal RBC survival time is 110-120 days (half-life: 55-60 days), and thus approximately 0.85% of the most senescent RBCs are removed and replaced each day. During hemolysis, RBC survival is shortened, the RBC count falls, erythropoietin is increased, and marrow erythropoietic activity is stimulated. This sequence leads to compensatory erythroid hyperplasia with increased RBC production, reflected by an increase in the reticulocyte count. The marrow can increase its output 2-3–fold acutely, with a maximum of 6-8–fold in chronic hemolysis. The reticulocyte percentage can be corrected to measure the magnitude of marrow production in response to hemolysis as follows:

$$\text{Reticulocyte index} = \text{Reticulocyte\%} \times \frac{\text{Observed hematocrit}}{\text{Normal hematocrit}} \times \frac{1}{\mu}$$

where μ is a maturation factor of 1-3 related to the severity of the anemia (Fig. 484.1). The normal reticulocyte index is 1.0; therefore the index measures the fold increase in erythropoiesis (e.g., 2-fold, 3-fold). Because the reticulocyte index is essentially a measure of RBC production per day, the maturation factor, μ, provides this correction.

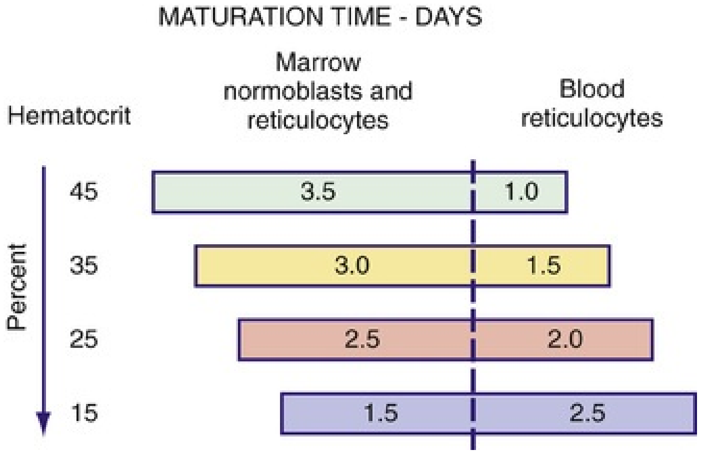

FIG. 484.1 Number of days for maturation of reticulocytes to mature erythrocytes in the marrow and blood. The duration of maturation as blood reticulocytes is taken as μ, which is used in the correction equation in this chapter. (Modified from Hillman RS, Finch CA: *Red cell manual* , Philadelphia, 1983, FA Davis.)

When hemolysis is chronic, compensatory erythroid hyperplasia may lead to significant expansion of the medullary spaces at the expense of cortical bone. This effect is particularly prominent in children with severe chronic hemolytic anemia, such as thalassemia. These changes may be evident on physical examination or radiography of the skull and long bones. In severe cases, there is increased propensity for long-bone fracture. Hemolysis also leads to increased degradation of hemoglobin. This process can result in indirect hyperbilirubinemia, increased biliary excretion of heme pigment derivatives, and formation of bilirubinate gallstones.

During hemolysis, heme-binding proteins in the plasma are altered (Fig. 484.2). Hemoglobin binds to haptoglobin and hemopexin, both of which are cleared more rapidly as heme-bound complexes. Oxidized heme binds to albumin to form methemalbumin, which is increased in the plasma during hemolysis. When the capacity of these heme-binding molecules is exceeded, free hemoglobin appears in the plasma. Free hemoglobin in the plasma is considered prima facie evidence of intravascular hemolysis. Free hemoglobin dissociates into dimers and is filtered by the kidneys. When the tubular reabsorptive capacity of the kidneys for hemoglobin is exceeded, free hemoglobin appears in the urine. Even in the absence of hemoglobinuria, iron loss can result from reabsorbed hemoglobin and the shedding of renal epithelial cells in which the iron from hemoglobin is stored as hemosiderin. This iron loss can lead to iron deficiency during chronic intravascular hemolysis. The ongoing presence of circulating free hemoglobin and hemin have been linked to vascular disease, including pulmonary hypertension, thrombosis, inflammation, and impaired renal function.

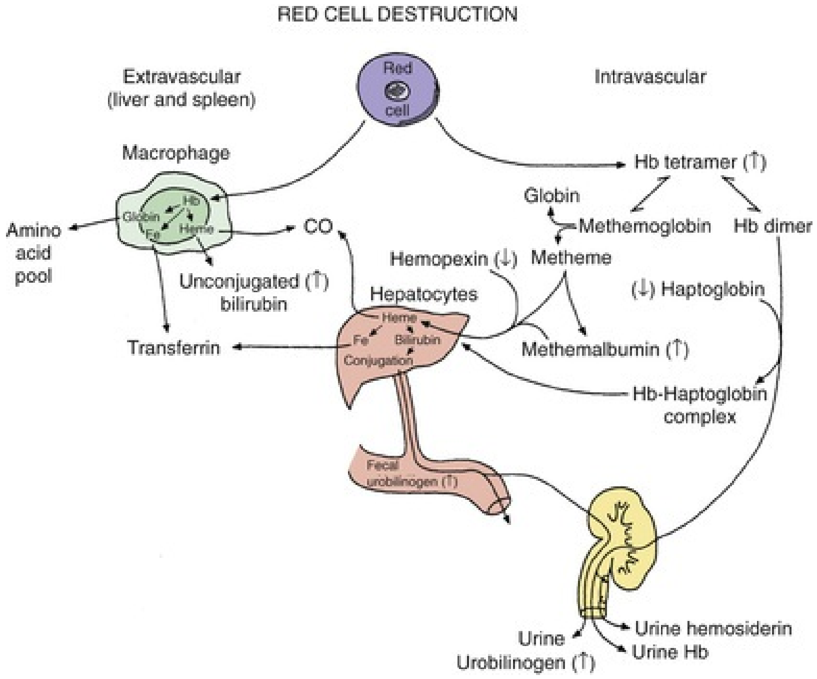
RED CELL DESTRUCTION
Extravascular
(liver and spleen)
Red
cell
Intravascular
Macrophage
Hb
Globin
Fe
Heme
Amino
acid
pool
CO
Unconjugated (↑)
bilirubin
Transferrin
Hb tetramer (↑)
Globin
Methemoglobin
Hb dimer
Hemopexin (↓)
Metheme
(↓) Haptoglobin
Hepatocytes
Heme
Fe
Bilirubin
Conjugation
Methemalbumin (↑)
Hb-Haptoglobin
complex
Fecal
urobilinogen (↑)
Urine
Urobilinogen (↑)
Urine hemosiderin
Urine Hb

FIG. 484.2 **Red cell destruction and catabolism of hemoglobin (Hb). Based on the description by Hillman and Finch. CO, Carbon monoxide; Fe, iron. (From Hillman RS, Finch CA: *Red cell manual* , Philadelphia, 1983, FA Davis.)**

Hemolytic anemia may be classified in several different ways. It can be classified by whether there is a cellular abnormality of the erythrocyte (**intrinsic** or intracorpuscular) or an extracellular abnormality of the erythrocyte (**extrinsic** or extracorpuscular) resulting from antibodies, mechanical factors, or plasma factors. Hemolytic anemia can be also classified as **inherited** or **acquired** , whether there is immune-mediated (**immune**) or nonimmune-mediated (**nonimmune**) hemolysis, whether hemolysis is **acute** or **chronic** , or whether hemolysis occurs in the vasculature (**intravascular**) or in the reticuloendothelial system (**extravascular**) (Tables 484.1 and 484.2). Most intrinsic defects are inherited, such as hereditary disorders of the erythrocyte membrane, metabolic defects of the erythrocyte, and hemoglobin disorders (though paroxysmal nocturnal hemoglobinuria is acquired). Most extrinsic defects are acquired, with examples including immune-mediated mechanisms such as warm and cold agglutinin hemolysis and nonimmune causes such as systemic diseases, drug- or toxin-mediated effects, and mechanical destruction of erythrocytes (although abetalipoproteinemia with acanthocytosis is inherited).

Table 484.1

Classification of Nonimmune Hemolytic Anemias

DISORDERS/CAUSES	LABORATORY FINDINGS	DIAGNOSTIC TEST
CONGENITAL DISORDERS		
Membrane Disorders		
Hereditary spherocytosis	Spherocytes	EMA binding, osmotic fragility
Hereditary elliptocytosis	Elliptocytes	Blood smear
Hereditary pyropoikilocytosis	Microcytes, fragments	
Hemoglobin Disorders		
Sickle cell disease	Sickle cells, targets	Hemoglobin electrophoresis
Unstable hemoglobins	Bite cells	Supravital stain, heat or alcohol stability test
Enzyme Disorders		
G6PD deficiency	Bite cells, blister cells	Supravital stain, G6PD level
Others	Variable	Individual enzyme levels
ACQUIRED DISORDERS		
Microangiopathic Hemolytic Anemias		
TTP, HUS, DIC, cancer, heart valves	Schistocytes, red blood cell fragments	Targeted to diagnosis
Infections		
Malaria, babesiosis, *Clostridium perfringens*	Parasite (malaria, babesiosis)	Giemsa stain (babesiosis)
Toxins and Physical Agents		
Arsenic, lead, copper	Basophilic stippling (lead)	Element levels
Insert, spider, snake venoms	Schistocytes, fragments	Targeted to diagnosis
Systemic Diseases		
Liver disease	Acanthocytes, target cells	Liver function tests
Burns	Spherocytes, blister cells, fragments	Targeted to diagnosis
Paroxysmal nocturnal hemoglobinuria	Variable	Flow cytometry

DIC, Disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

From Cornett PA: Hemolytic anemia. In *Conn's current therapy,* Philadelphia, 2017, Elsevier (Table 1, p 374).

Table 484.2

Etiology of Hemolytic Anemias

Intrinsic Hemolysis

Hemoglobinopathies

α-Thalassemias
β-Thalassemias
Sickle cell disease

- Unstable hemoglobins

RBC Membrane Defects

- Hereditary spherocytosis
- Hereditary elliptocytosis, pyropoikilocytosis, and related disorders
- Hereditary stomatocytosis syndromes
  - Xerocytosis
  - Hydrocytosis
  - Rh null syndrome
  - GLUT1 deficiency
  - Tangier disease
  - Abetalipoproteinemia
  - Phytosterolemia

Enzymopathies

- HMP shunt abnormality
  - Glucose-6-phosphate dehydrogenase
- Embden-Meyerhof defect (glycolysis)
  - Pyruvate kinase
  - Hexokinase
  - Glucose phosphate isomerase
  - Phosphofructokinase
  - Triosephosphate kinase
  - Phosphoglycerate kinase
- Aldolase deficiency
- Glutathione metabolism defect
- 5′-Nucleotidase deficiency

Extrinsic Hemolysis

Immune Mediated

Primary

- Warm-reactive autoimmune hemolytic anemia
- Alloimmune hemolytic anemia

- Acute hemolytic transfusion reaction
- Delayed hemolytic transfusion reaction
- Drug-induced hemolytic anemias (some types)

Secondary

- Autoimmune or inflammatory disorders
- Evans syndrome
- Primary immunodeficiency
  - Wiskott-Aldrich syndrome
  - Common variable immune deficiency
- Acquired immunodeficiency
  - HIV infection
- Malignancy (lymphoproliferative disorders: lymphomas)
- Infection
- Posttransplant

Cold Agglutinins

Primary

Secondary

- Infection (e.g., *Mycoplasma* , EBV syphilis)
- Malignancy
  - Lymphoid
  - Nonlymphoid
- Mixed, cold and warm
  - SLE and other rheumatology disorders
- Paroxysmal cold hemoglobinuria
  - Immune
  - Postinfectious

Other

- Recluse spider venom
- Toxins: arsenic, lead, copper
- Clostridial sepsis
- Snake venom

Erythrocyte Fragmentation

Primary Thrombotic Microangiopathy (TMA)

- Inherited
  - ADAMTS13 deficiency/TTP (mutations in *ADAMTS13*)
  - Complement mediated (mutations in *CFH*, *CFI*, *CFB*, *C3*, *CD46*)
  - Metabolism mediated (*MMACHC* mutations)
  - Coagulation mediated (*DGKE*, *PLG*, *THBD* mutations)
- Acquired
  - TTP (autoantibody)
  - Shiga toxin–mediated TMA (SH-TTP)
  - Pneumococcal-induced HUS
  - Drug mediated (immune mediated)
  - Drug mediated (toxic dose related)
  - Complement mediated (antibody)
- Vitamin B_{12} deficiency

Systemic Disorders

- DIC—many causes
- HELLP (hemolysis, microangiopathic blood smear, elevated liver enzymes, low platelet count)
- Malignancy
- Malignant hypertension
- Scleroderma renal crisis
- Antiphospholipid syndrome
- Infection
  - Complicated malaria
  - Clostridia or *Haemophilus influenzae* type b
  - Babesiosis

Isolated Intravascular Sites of Hemolysis

- Kasabach-Merritt syndrome
- Renal artery stenosis
- Large-vessel thrombi

    - Severe aortic coarctation
    - TIPS
    - Vasculitis
    - Dysfunctional cardiac valves or cardiac assist devices

Other Mechanical Causes

- Heat denaturation (blood warmer, thermal burns)
- Osmotic stress
    - Drowning
- Mechanical trauma
    - March hemoglobinuria
    - Marathon runners
- Direct trauma
    - “Cell saver” devices
    - Thrombectomy
    - Cardiac bypass
    - Extracorporeal membrane oxygenation
    - Dialysis

Hypersplenism

Drug Induced

DIC, Disseminated intravascular coagulation; EBV, Epstein-Bar virus; HMP, hexose monophosphate shunt; HUS, hemolytic-uremic syndrome; SLE, systemic lupus erythematosus; TIPS, transjugular intravascular portal shunt; TTP, thrombotic thrombocytopenia purpura.

Initial evaluation of a patient with suspected hemolytic anemia includes a detailed history of the current illness with attention to coexisting diagnoses, past medical history, family history, detailed list of medications, or recent exposures (Table 484.3). A complete blood count with erythrocyte indices, peripheral blood smear examination, reticulocyte count, and a direct antiglobulin test should be obtained (Table 484.4). Increased indirect bilirubin, increased serum lactate dehydrogenase, or serum decreased haptoglobin, indicating the presence of hemolysis, may also be obtained. *Haptoglobin* levels are favored by some because of the rapid decline in intravascular hemolysis, but are not specific.

Haptoglobin levels may be decreased in cases of brisk extravascular hemolysis, may be significantly influenced by genetic variation, and may be an acute-phase reactant (resulting in normal concentrations in patients with concomitant infection or inflammation in the presence of hemolysis). These initial investigations will provide evidence that there is hemolysis and may provide clues to further diagnostic evaluations.

Table 484.3

Clinical and Laboratory Features Suggestive of Hemolytic Anemia

Pallor
Icterus
Splenomegaly
Gallstones
History of neonatal icterus
Positive family history of anemia, splenectomy, cholecystectomy
↑ Reticulocyte count
↑ RDW (caused by ↑ reticulocyte count)
Abnormal RBC morphology
↑ Indirect bilirubin (normal direct bilirubin)
↓ Serum haptoglobin level
↑ Urinary urobilinogen level
Hemoglobinuria (+ dipstick test result for blood; no RBCs in urine)
↑ LDH level

LDH, Lactate dehydrogenase; RBC, red blood cell; RDW, red cell distribution width.

From Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis*, Philadelphia, 2018, Elsevier (Table 37-12, p 674).

Table 484.4

Hemolytic Anemia: Diagnostic Clues Based on Red Blood Cell (RBC) Shape

Sickle cells: sickle cell disease
Target cells: hemoglobinopathies (HbC, HbS, thalassemia), liver disease
Schistocytes/burr cells/helmet cells/RBC fragments: microangiopathic hemolytic anemia (DIC, HUS, TTP)
Spherocytes: hereditary spherocytosis, autoimmune hemolytic anemia
Cigar-shaped cells: hereditary elliptocytosis
“Bite” cells: G6PD deficiency
Poikilocytosis, microcytosis, fragmented erythrocytes, elliptocytes: hereditary pyropoikilocytosis

DIC, Disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenia purpura.

From Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis*, Philadelphia, 2018, Elsevier (Table 37-13, p 674).

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CHAPTER 485

Hereditary Spherocytosis

Matthew D. Merguerian, Patrick G. Gallagher

Hereditary spherocytosis (HS) is a common cause of inherited hemolytic anemia, with a prevalence of approximately 1 in 2,000-5,000 persons. Described in patients of all ethnic groups, it is the most common inherited abnormality of the erythrocyte associated with inherited hemolytic anemia in persons of Northern European origin. HS is marked by wide variability in the associated clinical, laboratory, and genetic manifestations. Symptomatology ranges from asymptomatic patients with well-compensated anemia to severely affected patients with hemolytic anemia requiring regular blood transfusions.

Etiology

The pathophysiology underlying HS is twofold: an intrinsic defect of the erythrocyte membrane and an intact spleen that selectively retains, damages, and removes mutant HS erythrocytes. Qualitative or quantitative defects of key membrane proteins lead to a multistep process of accelerated HS erythrocyte destruction. Abnormalities of **ankyrin** or **spectrin** are the most common molecular defects (Table 485.1). Defects in these membrane proteins result in uncoupling of the "vertical" interactions of the lipid bilayer with the underlying membrane skeleton, with subsequent release of membrane microvesicles. The loss of membrane surface area without a proportional loss of cell volume causes decreased erythrocyte deformability. This impairs cell passage from the splenic cords to the splenic sinuses, leading to the trapping and premature destruction of HS erythrocytes by the spleen (Figs. 485.1 and 485.2). Splenectomy greatly improves erythrocyte life span and may be indicated in some patients with HS.

Table 485.1

Common Gene Mutations in Hereditary Spherocytosis

PROTEIN	GENE	COMMON MUTATIONS	PREVALENCE	INHERITANCE	DISEASE SEVERITY
Ankyrin-1	*ANK1*	Frameshift Nonsense Splicing Missense Insertion/deletion Promoter region	50–67% 5–10% in Japan	Mostly dominant, rare recessive	Mild to moderate
Band 3	*AE1 (SLC4A1)*	Missense Nonsense	15–20%	Dominant	Mild to moderate
β-Spectrin	*SPTB*	Nonsense Missense Insertion/deletion	15–20%	Dominant	Mild to moderate
α-Spectrin	*SPTA1*	Splicing Nonsense Missense	<5%	Recessive	Severe
Protein 4.2	*EPB42*	Missense Nonsense Splicing Deletion	<5% 45–50% in Japan	Recessive	Mild to moderate

Adapted from Bolton-Maggs PHB, Langer JC, Iolascon A, et al: Guidelines for the diagnosis and management of hereditary spherocytosis—2011 update, *Br J Haematol* 156:37–49, 2011.

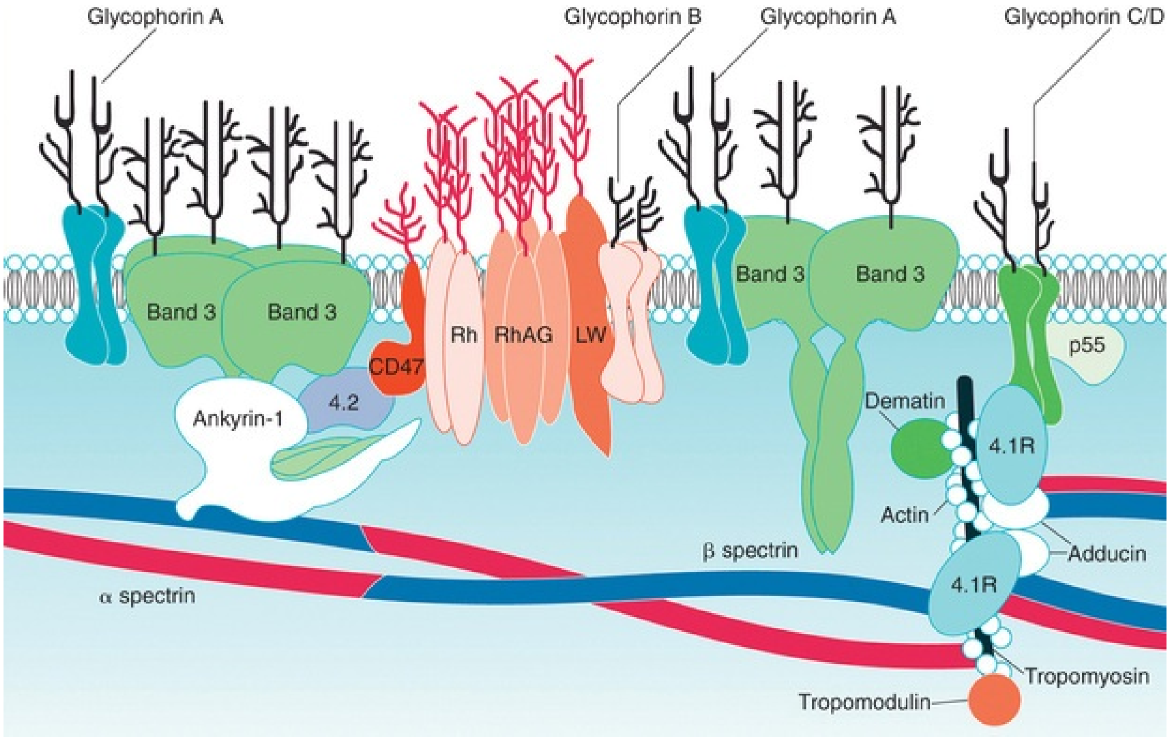
Glycophorin A
Glycophorin B
Glycophorin A
Glycophorin C/D
Band 3
Band 3
Rh
RhAG
LW
CD47
Band 3
Band 3
p55
Ankyrin-1
4.2
Dematin
4.1R
Actin
Adducin
β spectrin
4.1R
α spectrin
Tropomyosin
Tropomodulin

FIG. 485.1 Simplified cross section of the red blood cell (RBC, erythrocyte) membrane.

The lipid bilayer forms the equator of the cross section, with its polar heads *(small circles)* turned outward. 4.1R, Protein 4.1R; 4.2, protein 4.2; LW, Landsteiner-Wiener glycoprotein; Rh, Rhesus polypeptide; RhAG, Rh-associated glycoprotein. (From Perrotta S, Gallagher PG, Mohandas N: Hereditary spherocytosis, *Lancet* 372:1411–1426, 2008.)

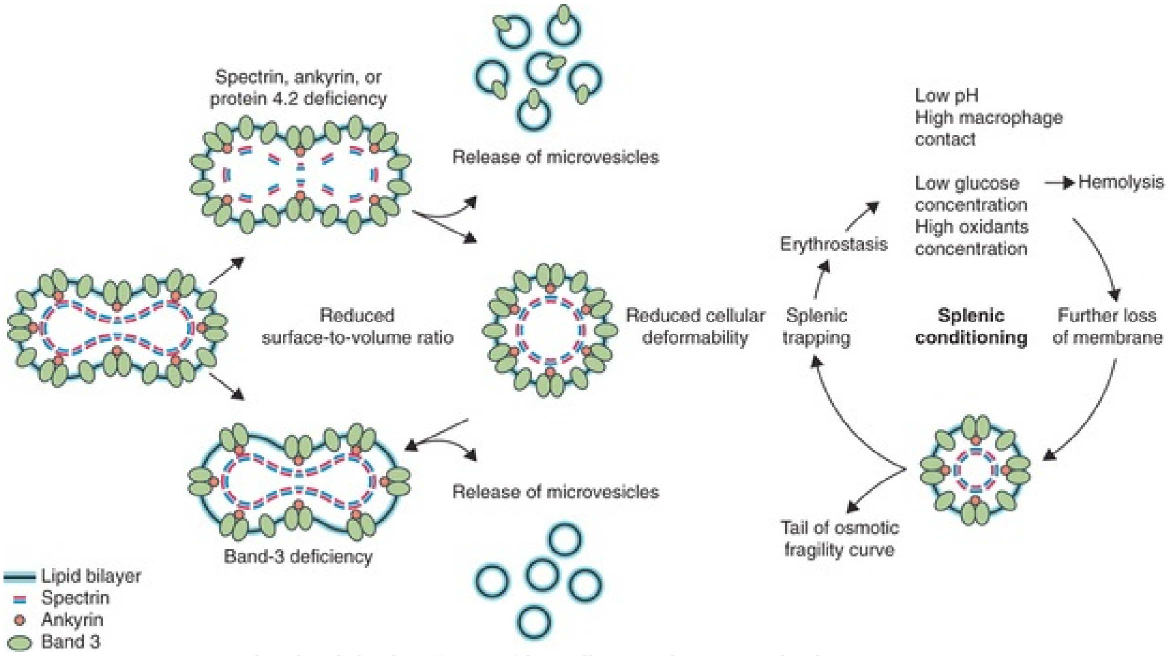
Spectrin, ankyrin, or protein 4.2 deficiency
Release of microvesicles
Reduced surface-to-volume ratio
Reduced cellular deformability
Release of microvesicles
Band-3 deficiency
Lipid bilayer
Spectrin
Ankyrin
Band 3
Low pH
High macrophage contact
Low glucose concentration
High oxidants concentration
Hemolysis
Erythrostasis
Splenic trapping
Splenic conditioning
Further loss of membrane
Tail of osmotic fragility curve

FIG. 485.2 **Pathophysiologic effects of hereditary spherocytosis. (From Perrotta S, Gallagher PG, Mohandas N: Hereditary spherocytosis, *Lancet* 372:1411–1426, 2008.)**

Clinical Manifestations

Hereditary spherocytosis is usually transmitted (approximately 75%) as an autosomal dominant trait. However, as many as 25% of patients have no previous family history, representing recessive inheritance or de novo mutations.

In the neonatal period, HS is a significant cause of hemolysis and can manifest as anemia and/or hyperbilirubinemia severe enough to require phototherapy, transfusion, or exchange transfusions. Hemolysis may be *more prominent* in the newborn because hemoglobin F binds 2,3-diphosphoglycerate poorly, and the increased level of free 2,3-DPG destabilizes interactions among spectrin, actin, and protein 4.1 in the red blood cell (RBC) membrane (see Fig. 485.1). The need for transfusions in infancy is not indicative of more severe disease later in life because infants are typically slow to mount an adequate reticulocyte response for the 1st few mo after birth.

Disease severity varies and can be used to clinically classify HS (Table 485.2). Mild cases (20–30% of all HS) are asymptomatic into adulthood and have well-compensated mild anemia, where reticulocyte production and erythrocyte destruction are essentially balanced. Cases of moderate or “typical” HS (60–70%) have partially compensated hemolytic anemia with reticulocytosis, frequently with symptoms of fatigue, pallor, and intermittent jaundice. **Splenomegaly** is common after infancy and is present in almost all HS patients by young adulthood. Patients with severe HS (3–5%) have life-threatening anemia and are transfusion dependent.

Table 485.2

Clinical and Laboratory Classification of Hereditary Spherocytosis

	NORMAL	MILD SPHEROCYTOSIS	MODERATE SPHEROCYTOSIS	MODERATELY SEVERE SPHEROCYTOSIS	SEVERE SPHEROCYTOS
Inheritance	—	Autosomal dominant	Autosomal dominant, de novo mutation	Autosomal dominant, de novo mutation	Autosomal recess
Proportion of hereditary spherocytosis cases	—	≈20–30%	≈60–70%	≈10%	<5%
Hemoglobin (Hb, g/dL)[†]	11.5-16[‡]	10.5-15	8-12	6-8	<6
Reticulocytes (%)[†]	0.5-1.5	1.5-6	≥6	≥10	≥10
Bilirubin (mg/dL)[†, ‖]	0-1	0.5-2	≥2	≥2	≥3
Peripheral smear[*]	Normal	Mild spherocytosis	Spherocytosis	Spherocytosis	Spherocytosis ± poikilocytosis
Osmotic fragility (fresh)	Normal	Normal or slightly increased	Increased	Increased	Greatly increased
Osmotic fragility (incubated)	Normal	Usually increased	Increased	Increased	Greatly increased
MCHC (g/dL)[§]	32-36	34-37	34-38	35-39	
RDW (%)[§]	11-14	12-19	16-23	20-30	
Hb/MCHC[*]	0.38-0.41	0.35-0.40	0.29-0.33	0.18-0.28	
Hb/RDW[§]	0.95-1.05	0.7-1.0	0.48-0.74	0.16-0.35	
Serum	18-25	30-65	80-125	100-150	

transferrin receptor (nmol/L) [§]					
Erythropoietin (mlU/mL) [§]	7-16	9-30	25-90	30-300	
Membrane protein patterns (SDS-PAGE) [¶]	—	“Normal” [#] Slight ↓ spectrin Slight ↓ spectrin and ankyrin Slight ↓ band 3 and 4.2 Absent protein 4.2 and ↓ CD47	↓ Spectrin ↓ Spectrin and ankyrin ↓ Band 3 and protein 4.2 Absent protein 4.2 and ↓ CD47	↓ Spectrin ↓ Spectrin and ankyrin ↓ Band 3 and protein 4.2	↓↓ Spectrin ↓↓ Spectrin ar ankyrin ↓↓ Band 3 anc protein 4.2[**]
Transfusions	—	No	Sometimes required in infancy or with aplastic crisis	Occasionally with crises	Regular[*]
Splenectomy	—	Rarely, partial splenectomy [††]	Sometimes; consider partial splenectomy	Usually (6-9 yr)	Yes (>3 yr)

[*] Patients with severe disease are transfusion dependent by definition. Values are in untransfused patients or at nadir before transfusion.

[†] Data modified from Eber SW, Armbrust R, Schröter W: Variable clinical severity of hereditary spherocytosis: relation to erythrocytic spectrin concentration, osmotic fragility and autohemolysis, *J Pediatr* 177:409–416, 1990.

[‡] Varies with age.

[§] Ranges shown encompass the majority of individuals in each category.

[||] Multiply by 17.1 to convert to µmol/L.

[¶] Indicates common patterns observed on SDS gels. Decreased spectrin alone is seen in α-spectrin or β-spectrin defects. Decreased spectrin and ankyrin arc observed with ankyrin defects. Decreased band 3 and protein 4.2 occur with band 3 defects. Absent protein 4.2 and decreased CD47 occur with protein 4.2 defects.

[#] Patients with mild spherocytosis who appear normal probably have small deficits (10–15%) that cannot be distinguished from normal findings on SDS gels.

[**] Rare patients with severe spherocytosis who are homozygous or compound heterozygous for band 3 defects.

[††] Consider in adolescents and adults who require a cholecystectomy or have disfiguring chronic jaundice.

From Rocha S, Costa E, Rocha-Pereira P, et al: Complementary markers for the clinical severity classification of hereditary spherocytosis in unsplenectomized patients, *Blood Cells Mol Dis* 46:166–170, 2011.

MCHC, Mean corpuscular hemoglobin concentration; RDW, red cell distribution width (measure of variation in shape); SDS-PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis; ↓, decreased.

From *Nathan & Oski's hematology and oncology of infancy and childhood,* ed 8, Philadelphia, 2015, Elsevier (Table 16.3, p 518).

Bilirubin **gallstone** formation is a function of age; gallstones can form as early as 4-5 yr and are present in most adult HS patients.

HS patients are susceptible to aplastic crises primarily as a result of **parvovirus B19** infection, **hypoplastic crises** associated with other infections, and **megaloblastic crises** caused by folate deficiency (Fig. 485.3). During these crises, high RBC turnover in the setting of erythroid marrow failure can result in profound anemia (hematocrit <10%), high-output heart failure, cardiovascular collapse, and death. Leukocyte and platelet counts may also fall.

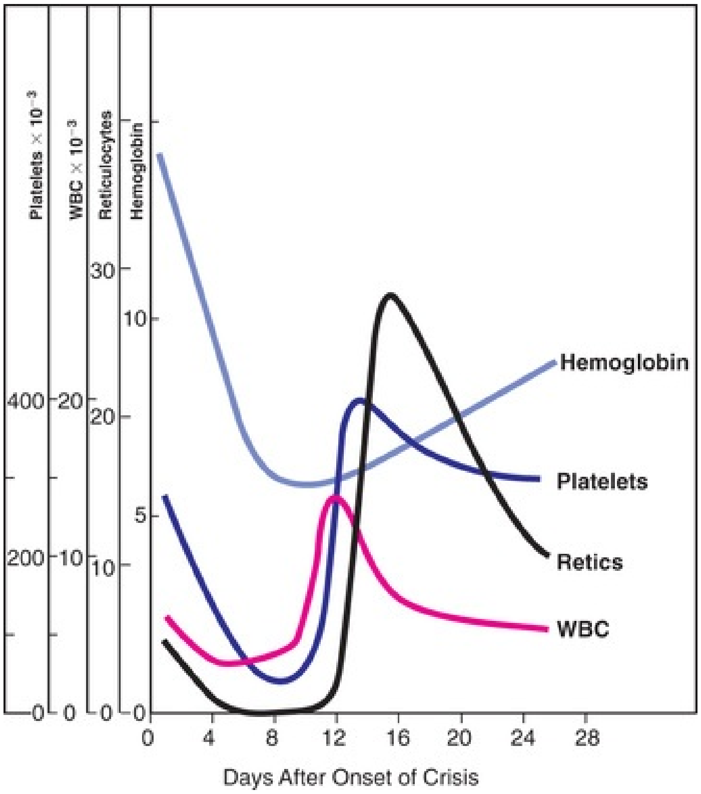

FIG. 485.3 Parvovirus-induced aplastic crisis. Progression of the changes in blood count is shown for a patient with hereditary spherocytosis and infection with parvovirus. Note that the fall in baseline reticulocytosis is associated with a rapid fall in hemoglobin. White blood cells (WBC) and platelets are also affected; Retics, reticulocytes. (Adapted from Nathan DG, Orkin SH, Ginsburg D, et al, editors: *Hematology of infancy and childhood,* ed 6, Philadelphia, 2003, Saunders.)

Rare complications associated with HS include splenic sequestration crisis, gout, cardiomyopathy, priapism, leg ulcers, and neurologic or muscular abnormalities, including spinocerebellar degeneration.

Diagnosis

Typically, there is evidence of hemolytic anemia with reticulocytosis and indirect hyperbilirubinemia. The mean corpuscular volume (MCV) of HS erythrocytes is low normal or even slightly decreased, and the mean corpuscular hemoglobin concentration (MCHC) is usually increased (>35 g/dL). An MCHC >35.4 g/dL combined with a red cell distribution width (RDW) $<14\%$ has been suggested as a screening test for HS. Erythroid cells on peripheral blood smear vary in size and include spherocytes and polychromatophilic reticulocytes. *Spherocytes* are smaller in diameter, are hyperchromic because of elevated hemoglobin concentration from cellular dehydration, and lack central pallor (Fig. 485.4). Numbers of spherocytes are variable, with increased numbers likely reflecting the severity of disease. Other markers of hemolysis include decreased haptoglobin and elevated lactic dehydrogenase.

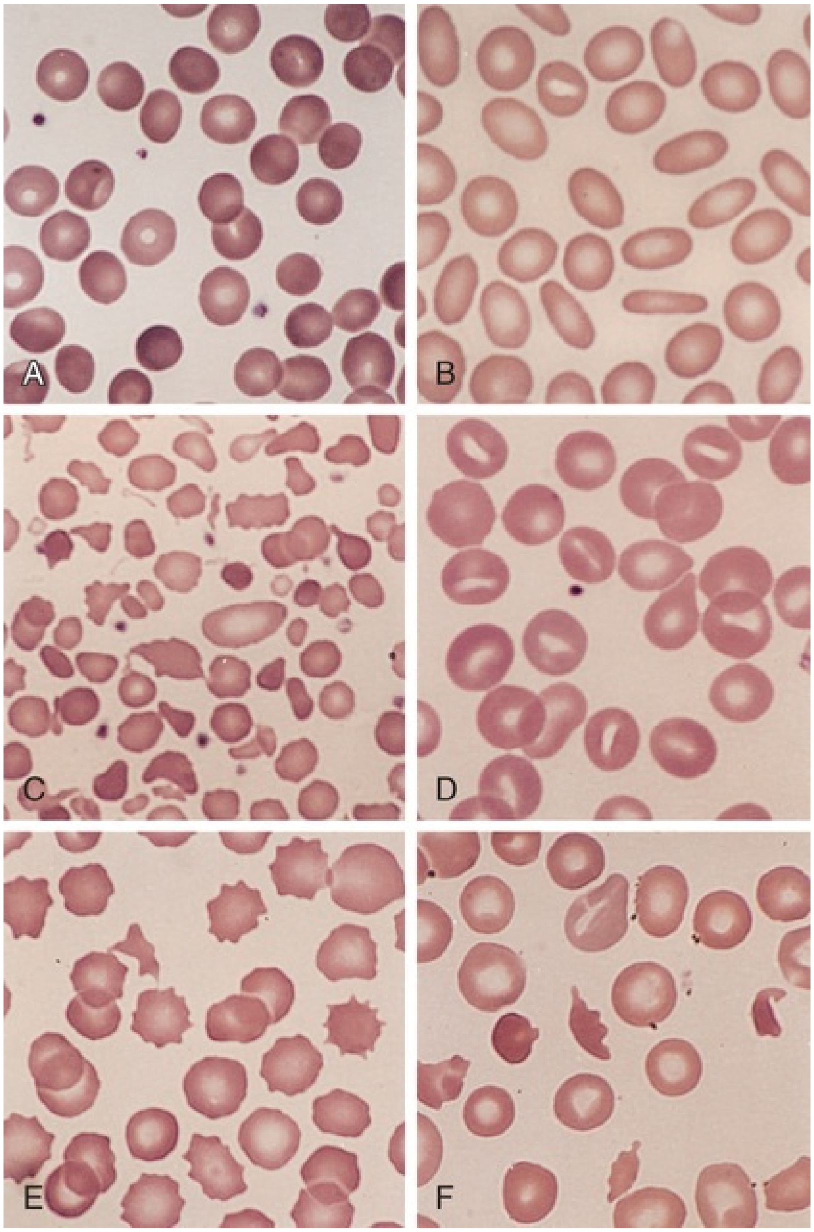

FIG. 485.4 **Morphology of abnormal red cells. A, Hereditary spherocytosis. B, Hereditary elliptocytosis. C, Hereditary pyropoikilocytosis. D, Hereditary stomatocytosis. E, Acanthocytosis. F, Fragmentation hemolysis.**

The diagnosis of HS can be established from a positive family history and the presence of typical clinical and laboratory features of the disease: splenomegaly, spherocytes on the blood smear, reticulocytosis, and an elevated MCHC. If these are present, no additional testing is necessary to confirm the diagnosis clinically. If the diagnosis is less certain, additional testing can be performed. Binding of fluorescence labeled eosin-5-maleimide (EMA) to band 3 and other membrane proteins is decreased in HS erythrocytes. This flow cytometry–based test is easy to perform and has good diagnostic sensitivity and specificity. In the classic incubated *osmotic fragility test,* HS erythrocytes are incubated in progressive dilutions of sodium chloride causing the cells to swell and lyse, with spherocytes lysing at a lower dilution because of their lower surface area:volume ratio. This test detects the presence of spherocytes in the blood, but it is not specific to HS and may be abnormal in other anemias with prominent spherocytosis. Osmotic fragility testing has poor sensitivity and may miss cases of mild HS where the numbers of spherocytes are few. Other assays, such as the cryohemolysis test, the acidified glycerol lysis test, and osmotic gradient ektacytometry, have been used for diagnosis of HS, but these tests are not available in many laboratories. Genetic diagnosis is available, and the cost continues to decrease. The precise role of molecular testing in HS is evolving. Some experts suggest molecular testing before splenectomy to verify the diagnosis of HS.

Diagnosis in the neonatal period requires a high index of suspicion because the disease presents differently than in older children, particularly in de novo and recessively inherited cases where family history is not available for guidance. Jaundice is frequently observed, and kernicterus can occur. Hemolytic anemia may be severe enough to require blood transfusion. In fact, HS is the leading cause of Coombs-negative hemolytic anemia requiring transfusion in the 1st months of life. Splenomegaly is uncommon in neonates.

HS may be masked by various comorbidities, such as iron, folate, and vitamin B_{12} deficiencies, as well as, cholestatic liver disease, hemoglobin SC disease, and β-thalassemia.

Differential Diagnosis

The differential diagnosis for spherocytosis on peripheral blood smear includes isoimmune and autoimmune hemolysis. Isoimmune **hemolytic disease of the newborn** , particularly when a result of ABO incompatibility, closely mimics the appearance of HS. The detection of antibody on an infant's RBCs using a direct antiglobulin (Coombs) test should establish the diagnosis of immune hemolysis. Autoimmune hemolytic anemias also are characterized by spherocytosis, but there will typically be evidence of previously normal values for hemoglobin, hematocrit, and reticulocyte count. Rare causes of spherocytosis include thermal injury, hemolytic transfusion reaction, clostridial sepsis, severe hypophosphatemia, Wilson disease, congenital dyserythropoietic anemia type II (see Chapter 479), hereditary stomatocytosis, and snake, bee, or wasp envenomation, all of which may manifest as transient spherocytic hemolytic anemia.

Treatment

General Supportive Care

Infants born to a parent with known HS should be monitored carefully because hyperbilirubinemia may peak several days after birth. Parents should be advised of the risk of neonatal anemia, jaundice, and the potential need for transfusion, phototherapy, and exchange transfusion to treat anemia or hyperbilirubinemia. A subset of infants will be transfusion dependent until development of adequate erythropoiesis to compensate for the ongoing hemolysis, usually between 6 and 12 mo of age. Transfusion dependence after this time is rare and is most likely caused by recessive HS.

Once the baseline level of disease severity is reached, an annual visit to the hematologist usually is sufficient follow-up. Growth should be monitored, and exercise tolerance and spleen size should be documented. Vaccinations should be up to date. Screening for gallbladder disease should begin at about 4 yr of age, repeated every 3-5 yr, or as indicated clinically. Documentation of parvovirus B19 susceptibility or immunity should be obtained in new patients. Similarly, HIV and hepatitis serology should be documented in patients who have received transfusions. Folic acid supplementation is recommended in patients with moderate and severe HS because of the demands of brisk erythropoiesis. Parents should receive anticipatory guidance regarding the risk of aplastic crisis secondary to parvovirus infection and hypoplastic crises with other infections. Parents and patients should be informed of an increased risk for gallstone development.

Guidelines for Splenectomy

Because spherocytes are destroyed almost exclusively in the spleen, splenectomy is curative in most patients because hemolysis, anemia, hyperbilirubinemia, and the incidence of gallstones are significantly lessened, if not completely eradicated, after splenectomy. Thus, splenectomy became routine in the care of HS patients. However, splenectomy is associated with short-term risks related to the procedure as well as long term risks, particularly increased lifelong risk for sepsis, often caused by encapsulated bacteria. This risk is not eliminated with the requisite preoperative and postoperative vaccination against pneumococcus, meningococcus, and *Haemophilus influenzae* type b. In addition, the emergence of penicillin-resistant pneumococci is an increasing concern, as is the increased risk for cardiovascular diseases, including thrombosis, pulmonary hypertension, and atherosclerosis, which have tempered the practice of routine splenectomy in HS.

When considering splenectomy, the patient and the parents, together with their healthcare providers, should review and consider the risks and benefits. Individual-specific factors may confer additional risk after splenectomy, such as time and distance from medical care for patients with febrile illness and residence in or travel to areas where parasitic diseases such as malaria or babesiosis occur.

Most experts recommend splenectomy for patients with severe HS and believe it should be strongly considered for patients with moderate HS and frequent hypoplastic or aplastic crises, poor growth, or cardiomegaly. It is generally not recommended for patients with mild HS. When splenectomy is indicated, it should be performed after age 6 yr, if possible, to avoid the heightened risk of postsplenectomy sepsis in younger children. The laparoscopic approach has less surgical morbidity and is the technique of choice. Partial or subtotal splenectomy (removal of 85–95% of spleen volume) decreases the hemolytic rate while preserving some splenic phagocytic function, although the decrease in hemolysis is less than that achievable with total splenectomy. Partial splenectomy is most attractive in children with severe HS requiring frequent transfusion early in childhood.

In children undergoing splenectomy, a concomitant cholecystectomy should be performed if there are gallstones. It is controversial whether to perform a concomitant splenectomy in less severely ill patients who are undergoing cholecystectomy for gallstone disease. Postsplenectomy thrombocytosis is frequently observed, but requires no treatment and usually resolves spontaneously. The patient, household contacts, and other frequent contacts should remain current with their vaccinations. Prophylactic antibiotics are typically prescribed at least until the patient is 5 yr old or at least 2 yr after splenectomy. Folate supplementation should be continued if the hemoglobin level and reticulocyte count do not normalize.

Splenectomy failure may occur in patients with accessory spleen, accidental autotransplantation of splenic tissue into peritoneum at surgery, inaccurate diagnosis, or another co-inherited hemolytic anemia. Clues include return of hemolysis and disappearance of Howell-Jolly bodies on peripheral blood smear. The diagnosis can be made by radionucleotide studies.

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CHAPTER 486

Hereditary Elliptocytosis, Hereditary Pyropoikilocytosis, and Related Disorders

Matthew D. Merguerian, Patrick G. Gallagher

Hereditary elliptocytosis, hereditary pyropoikilocytosis, and related disorders are characterized by the finding of *elliptocytes* on peripheral blood smear (Table 486.1). Whereas **hereditary spherocytosis** is viewed as a disorder of the vertical interactions coupling the erythrocyte membrane skeleton to the lipid bilayer, the hereditary elliptocytosis syndromes interfere with the horizontal interactions that link *spectrin* molecules to each other and to membrane skeleton junctional complexes, leaving the cell vulnerable to shear stress (see Chapter 485 , Fig. 485.1).

Table 486.1

Clinical Subtypes of Hereditary Elliptocytosis

CLINICAL MANIFESTATIONS	LABORATORY MANIFESTATION
TYPICAL HETEROZYGOUS HE	
Asymptomatic Dominant inheritance: 1 parent with HE No splenomegaly Variants: Some neonates have moderately severe hemolytic anemia and HPP-like smear; converts to typical HE by “1 yr”. Some patients with typical HE have mild to moderate chronic hemolysis and some poikilocytosis, caused by co-inheritance of the low-expression variant α-spectrin$^{\text{LELY}}$, coexistence of chronic disease producing splenomegaly, or unknown factors.	Blood smear: elliptocytes, rod forms, few or no poikilocytes No anemia, little or no hemolysis (reticulocytes, 1–3%) Normal osmotic fragility Usually a defect in α-spectrin or β-spectrin leading to decreased spectrin self-association, or a defect in protein 4.1 leading to partial deficiency or dysfunction
HOMOZYGOUS HE OR HPP	
Moderate to severe hemolytic anemia Splenomegaly	Blood smear: bizarre poikilocytes, fragments, ± spherocytes, ± elliptocytes

Intermittent jaundice Aplastic crises Recessive inheritance: typically 1 parent with HE and 1 with α-spectrin mutation, or both parents with HE Good improvement after splenectomy	Reticulocytosis Decreased MCV because of red cell fragmentation Increased osmotic fragility, positive EMA test α-Spectrin defects: Decreased red cell and spectrin heat stability Marked defect in spectrin self-association In the more severe variants, partial spectrin deficiency (indicated by more spherocytes on the blood smear)
SPHEROCYTIC HE	
Mild to moderate hemolytic anemia Splenomegaly Intermittent jaundice Aplastic crises Dominant inheritance pattern Excellent response to splenectomy	Blood smear: rounded elliptocytes, ± spherocytes; may see variable morphology within a kindred Reticulocytosis Increased osmotic fragility Variable molecular defects: C-terminal truncation of β-spectrin Protein 4.2 deficiency (some patients); variable morphology: spherocytes, ovalocytes, stomatocytes, or spiculated cells, sometimes resembling spherocytic HE Glycophorin C deficiency (rare)
SOUTHEAST ASIAN OVALOCYTOSIS	
Anemia and jaundice in neonatal period; then asymptomatic Dominant inheritance Lowland aboriginal tribes, especially in Melanesia, Malaysia, and the Philippines Very rigid red cells that resist invasion by malarial parasites in vitro and protect against cerebral malaria in vivo	Blood smear: rounded elliptocytes, some with a transverse bar that divides the central clear space (theta cells) No hemolysis or anemia after neonatal period Normal osmotic fragility, positive EMA test Mutant band 3 that lacks anion exchange function and tends to aggregate, leading to a rigid membrane

EMA, Eosin-5′-maleimide; HE, hereditary elliptocytosis; HPP, hereditary pyropoikilocytosis; MCV, mean cell volume.

Adapted from Walensky ID, Narla M, Lux SF: Disorders of the red cell membrane. In Handin RI, Lux SF, Stossel TP, editors: *Blood: principles and practice of hematology,* Philadelphia, 2003, Lippincott.

Hereditary elliptocytosis (HE) is the prototypical member of this group of disorders and is characterized by elliptical deformation of the cell over time, resulting from abnormal shear stress. HE is much more common than hereditary spherocytosis, but it is much less likely to cause significant clinical symptomatology. The severity of HE varies greatly, with the overwhelming majority of patients experiencing little or no symptomatology beyond the finding of elliptocytes on peripheral blood smear. About 10% of patients have hemolytic HE with ongoing hemolysis and anemia. HE is often worse during infancy, with hemolytic anemia and hyperbilirubinemia that evolves to a well-compensated state with anemia that is absent, sporadic, or chronic. HE occurs worldwide and in all ethnic groups but is more common in patients with ancestry linked to areas of endemic malaria.

Hereditary pyropoikilocytosis (HPP) is a subtype of HE characterized by severe hemolytic anemia with findings on peripheral blood smear reminiscent of a thermal burn (*pyro* , fire). HE and HPP are seen co-segregating in the same families because they involve overlapping mutations in *spectrin.* HPP occurs predominantly in patients of African descent.

Southeast Asian ovalocytosis (SAO) is a disorder characterized by the presence of ovalocytes (less elongated and plumper than elliptocytes) on peripheral smear, some with 1 or 2 transverse ridges. SAO is found in individuals form New Guinea, Malaysia, Indonesia, and the Philippines. Unlike HE and HPP, SAO is caused by a defect in a transmembrane protein, *band 3*, affecting vertical skeletal interactions, leading to increased red blood cell (RBC) rigidity. These changes may lead to protection from malaria, particularly cerebral malaria.

Etiology

Various molecular defects have been described in HE syndromes. HE is inherited as an autosomal dominant disorder with occasional de novo cases. Most often, there are point mutations in α- or β-spectrin that interfere with the formation of spectrin heterodimers into *tetramers,* the primary structural unit of the membrane skeleton (see Fig. 485.1). Erythrocytes carrying many of these spectrin mutations are resistant to malaria *in vitro* , hypothesized to explain the increased prevalence of HE in malaria-endemic areas. Less frequently, elliptocytosis results from mutations in *protein 4.1* or *glycophorin C,* proteins of the junctional complex that link spectrin tetramers to the actin cytoskeleton. These defects in horizontal membrane skeleton protein interactions leave the cell susceptible to shearing forces, leading to the characteristic elliptical deformation of the cell and potentially membrane fragmentation.

In HPP, 2 abnormal spectrin alleles are inherited. Frequently, an HPP patient inherits an abnormal spectrin allele carrying a self-association site missense mutation from one parent, who has mild or asymptomatic HE, and a production-defective allele that leads to quantitative deficiency of spectrin from the other parent, who is otherwise clinically well.

SAO is an autosomal dominant disorder associated with an in-frame 9–amino acid deletion in band 3.

Clinical Manifestations

Most HE patients do not have clinically significant hemolysis (see Fig. 485.4*B*). Elliptocytosis may be an incidental finding on a blood film examination for an unrelated indication. The diagnosis of HE is established by the findings on the peripheral blood smear, the autosomal dominant inheritance pattern, and the absence of other causes of elliptocytosis. The differential diagnosis for other causes of elliptocytosis includes iron, folic acid, or vitamin B_{12} deficiency; thalassemia; myelodysplastic syndromes; and pyruvate kinase deficiency.

Interestingly, elliptocytes are not always present on the peripheral blood smear in the 1st few mo of life. Even in hemolytic HE, which may lead to neonatal jaundice and anemia, the peripheral blood smear typically shows bizarre *poikilocytes* and *pyknocytes* with rare to no elliptocytes. Hemolysis and anemia are aggravated in the newborn period because of the increased presence of hemoglobin F, which binds poorly to 2,3-diphosphoglycerate. The increased free 2,3-DPG tends to destabilize the spectrin–actin–protein 4.1 complex, leading to membrane instability (see Fig. 485.1). The usual features of a chronic hemolytic process caused by hemolytic HE manifests as anemia, jaundice, and splenomegaly. Cholelithiasis may occur in later childhood, and aplastic crises have been reported.

HPP is characterized by extreme microcytosis (mean corpuscular volume, 50-65 fL/cell), extraordinary variation in cell size and shape, and microspherocytosis with occasional elliptocytosis (see Fig. 485.4*C*). Hemolysis is chronic and significant.

SAO is associated with neonatal hyperbilirubinemia but is associated with little to no hemolysis later in life.

Laboratory Findings

Examination of the peripheral blood smear is essential to establish the diagnosis of HE (see Fig. 485.4*B*). HE elliptocytes are normochromic and normocytic with varying degrees of elongation. Because some HE patients may present with relatively low numbers of elliptocytes, there is no cutoff percentage that is useful diagnostically. In hemolytic HE, other abnormal RBC shapes may be present, depending on the severity of hemolysis, including spherocytes, pyknocytes, and other poikilocytes. In HPP, microspherocytes, RBC fragments, and occasional elliptocytes are seen. SAO is suggested when *ovalocytes,* which are less elongated than elliptocytes, are observed.

Reticulocyte levels and other markers of hemolysis, such as total bilirubin, lactate dehydrogenase, and haptoglobin, are helpful in establishing the severity of hemolysis, if present. In hemolytic HE and HPP, additional testing may include the eosin-5-maleimide (EMA) binding test, which detects binding to band 3 by flow cytometry, or incubated osmotic fragility testing. In cases of chronic hemolysis, splenomegaly and cholelithiasis can be assessed with abdominal ultrasound.

Treatment

If the presentation is that of typical HE—an isolated peripheral blood smear abnormality without clinically evident hemolysis—no treatment is necessary. For chronic HE and HPP, RBC transfusions are occasionally required. Splenectomy decreases the hemolysis and should be considered using criteria similar to those for hereditary spherocytosis (see Chapter 485). If hemolysis continues after splenectomy, patients should receive folic acid to prevent secondary folic acid deficiency. SAO does not require treatment beyond the newborn period.

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CHAPTER 487

Hereditary Stomatocytosis

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The hereditary stomatocytosis syndromes are a group of heterogeneous, dominantly inherited disorders in which alterations in red cell cation permeability lead to alterations in intracellular water content (Table 487.1). A net increase in sodium (Na^+) and potassium (K^+) ions allows water to enter the erythrocyte, creating *stomatocytes* or *hydrocytes*, whereas a net loss of Na^+ and K^+ leads to water loss, creating dehydrated red blood cells (RBCs), or *xerocytes*.

Table 487.1

Features of Hereditary Stomatocytosis-Xerocytosis Syndromes

FEATURE (NORMAL VALUE)	OTHER HEREDITARY STOMATOCYTOSIS SYNDROMES			SOUTHEAST ASLAN OVALOCYTOSIS	HEREDITARY XEROCYTOS (DEHYDRATE STOMATOCY	
	Overhydrated Hereditary Stomatocytosis	Mild Hereditary Stomatocytosis	Hereditary Cryohydrocytosis		Typical	P H
Hemolysis	Severe	Mild to moderate	Mild to moderate	Mild (neonatal only)	Moderate	M
Anemia	Moderate to severe	Mild to moderate	Mild to moderate to completely compensated	Mild (neonatal only)	Mild to moderate to completely compensated	N
Blood smear	Stomatocytes; ± spherocytes	Stomatocytes; ± spherocytes	Stomatocytes, sometimes with curved or offset stoma; ± spherocytes; ± target cells	Rounded elliptocytes, some with a double central clearing and a theta (θ) shape; ± stomatocytes	Target cells; sometimes small numbers of echinocytes or stomatocytes	T fe st
MCV	Increased	Normal to	Normal to		High normal	N

		increased	increased		to increased	ir
MCHC	Decreased	Normal to decreased	Normal to increased		Normal to increased	N ir
Unincubated osmotic fragility	Very increased	Variable	Variable	Unknown	Decreased to very decreased	S d
RBC Na^+ (5-12 mEq/L)*	60-150	30-60	15-100	Normal	5-30	1
RBC K* (90-105 mEq/L)*	20-55	40-85	30-100	Normal	60-90	7
RBC $Na^+ + K^+$ (95-110 mEq/L)*	110-170	115-145	70-130	Normal	70-100	8
RBC passive membrane leak* †	20-40	≈3-10	1-6	2-4	2-4	1
Cold hemolysis	No	Unknown	Yes	Yes	No	N
Pseudohyperkalemia	Sometimes	Unknown	Yes	Unknown	Sometimes	Y
Perinatal ascites	No	Unknown	No	Wo	Sometimes	N
Stomatin markedly decreased	Yes	No	No (type 1) Yes (type 2)	No	No	N
Effect of splenectomy on hemolysis	Some benefit	Some benefit	Minimal or no effect	No significant hemolysis	No effect	N h
Thromboembolism risk after splenectomy	Yes	Unknown	?Yes	Unknown	Yes	U
Genetics	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	A d
Defective gene(s)	*KHAG*	Band 3 *(SLC4A1)*	Type 1: Band 3 *(SLC4A1)* Type 2: Glut 1 *(SLC2A1)*	Band 3 *(SLC4A1)* in-frame deletion	*PIEZO1*	*P* *A*

[*] Based on a relatively small number of measurements reported in the literature.

[†] Times normal. Defined as the ouabain- and bumetanide-resistant $^{86}Rb^+$ influx at 37°C, and expressed as the ratio of patient residual leak to normal residual leak (normal: 0.06-0.10 mmol/L RBC/hr).

MCHC, Mean corpuscular hemoglobin concentration; MCV, mean cell volume; RBC, red blood cell.

From *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, Philadelphia, 2015, Elsevier (Table 16.12, p 561).

Hereditary Xerocytosis

Hereditary xerocytosis (HX), the most common type of the hereditary stomatocytosis syndromes, is a dominant disorder of erythrocyte dehydration. The underlying defect is typically a point mutation in PIEZO1, a mechanosensory transduction protein, associated with delayed channel inactivation. In a few patients, mutations in the Gardos channel, important in erythrocyte dehydration in sickle cell disease, have been observed. Typically, there is a net loss of intracellular K^+ that is not accompanied by a compensatory increase in Na^+ . Subsequently, the gradual loss of intracellular water leads to erythrocyte dehydration. HX may be associated with a syndrome of **hydrops fetalis** with perinatal anemia and ascites. These findings are transient and remain unexplained.

Affected patients exhibit a mild compensated macrocytic hemolytic anemia with variable degrees of splenomegaly and intermittent jaundice. The MCHC and MCV are elevated, erythrocyte osmotic fragility is decreased, and K^+ concentration and total monovalent cation content are decreased. There are small numbers of stomatocytes, target cells, and contracted RBCs with hemoglobin puddled to the side on peripheral blood smear.

Treatment is supportive, similar to other disorders with congenital hemolytic anemia. Because of the apparent predisposition to major thromboses postsplenectomy, *splenectomy is not recommended in hereditary xerocytosis and related disorders.* Another unusual manifestation of HX is the propensity for iron overload, independent of transfusion history. Thus iron indices should be monitored on regular intervals.

Hereditary Hydrocytosis

Hereditary hydrocytosis is a very rare, dominant disorder associated with large, swollen stomatocytic erythrocytes. The principal defect is an increase in Na^+ and K^+ permeability leading to greatly increased intracellular Na^+ and water content. The molecular defect is unknown in most cases. In a subset of cases, missense mutations in the Rh-associated glycoprotein (RhAG) have been identified.

Hereditary hydrocytosis is the most clinically severe disorder of altered erythrocyte volume regulation. It is characterized by moderate to severe hemolysis, macrocytosis (110-150 fL) with a low MCHC (24–30%), elevated erythrocyte Na^+ concentration, reduced K^+ concentration, increased total Na^+ and K^+ content, and increased erythrocyte osmotic fragility. There are large numbers (10–30%) of stomatocytes on peripheral blood smear. Patients typically develop jaundice, splenomegaly, and cholelithiasis.

Treatment is supportive. RBC transfusions are occasionally required. Patients should be followed for evidence of hematologic decompensation during acute illness. Interval ultrasonography to detect cholelithiasis should be obtained. When there is significant hemolysis, *folate* should be prescribed daily. Similar to HX, significant postsplenectomy major thromboses have been observed, and thus *splenectomy is not recommended in hereditary hydrocytosis.*

Intermediate Syndromes and Other Variants

Hereditary xerocytosis and hereditary hydrocytosis are at the extremes of disorders with alterations in erythrocyte permeability. Patients with intermediate defects have been described with varying degrees of hemolysis and anemia.

Cryohydrocytosis

One of the intermediate syndromes is cryohydrocytosis, in which affected patients typically have mild anemia associated with stomatocytes, spherocytes, and spherostomatocytes on peripheral blood smear. Cryohydrocytosis erythrocytes are deficient in band 3 and demonstrate a significant cation leak on cooling to low temperature. This disorder is caused by missense mutations in band 3 that likely convert band 3 from an anion exchanger to a nonselective cation leak channel.

Rh Deficiency Syndrome

Also known as **$\mathbf{Rh}_{\mathbf{null}}$ syndrome** , Rh deficiency syndrome is associated mild to moderate hemolytic anemia associated with greatly decreased (Rh_{mod}) or absent (Rh_{null}) Rh antigens on the erythrocyte membrane. Rh_{null} erythrocytes, which lack all Rh antigens, lack Landsteiner-Wiener (LW) and Fy5 antigens, and have reduced expression of Ss, U, and Duclos antigens, are dehydrated with decreased cell cation and water content. Findings on blood smear include reticulocytes, stomatocytes, and spherocytes. In response to immunization during pregnancy or after blood transfusion, Rh_{null} patients produce antibodies varying in specificity from reacting with “e” or C to reacting with all erythrocytes tested, an antibody called “anti–total Rh.”

Familial Deficiency of High-Density Lipoproteins

Also called **Tangier disease** , familial deficiency of high-density lipoproteins (HDLs) is a rare recessive disorder that results from mutations in the cholesterol and phospholipid transport protein ABCA1, leading to perturbations of cellular cholesterol transport, and resulting in the accumulation of cholesterol esters in many tissues. Hematologic manifestations include a mild to moderate stomatocytic hemolytic anemia and thrombocytopenia. Affected patients can also have large orange tonsils, hepatosplenomegaly, lymphadenopathy, cloudy corneas, peripheral neuropathy, and premature atherosclerosis.

Sitosterolemia

Also known as **phytosterolemia,** sitosterolemia is a recessive disorder in which the absorption of sterols, both cholesterol and its plant-derived relatives (e.g., sitosterol), is unlimited and unselective. Clinical manifestations include early-onset xanthomatosis, short stature, and premature coronary artery disease. Hematologic abnormalities include macrothrombocytopenia and stomatocytic hemolytic anemia. The plasma cholesterol may or may not be abnormal, but mass spectrometry always shows a massive increase in plant sterol levels in the plasma as well in the membranes of platelets and erythrocytes. Mutations in ABCG5 or ABCG8, transporters that actively pump plant sterols out of intestinal cells back into the intestine and out of liver cells into bile ducts, leads to gastrointestinal hyperabsorption and decreased biliary elimination of plant sterols as well as altered cholesterol metabolism. **Treatment** involves dietary restriction of cholesterol and plant sterols and prescription of *ezetimibe*, a sterol absorption inhibitor, and cholestyramine and other related bile acid–sequestering agents.

Other Disorders Associated With Stomatocytosis

Acquired stomatocytosis may be seen with liver disease, alcoholism, malignancy, cardiovascular disease, and after vinca alkaloid administration. Stomatocytes can be seen as a blood smear processing artifact.

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CHAPTER 488

Paroxysmal Nocturnal Hemoglobinuria and Acanthocytosis

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Paroxysmal Nocturnal Hemoglobinuria

Etiology

Paroxysmal nocturnal hemoglobinuria (**PNH**) is an *acquired* disorder of the cell membranes of multipotent bone marrow stem cells. The underlying *somatic* mutation propagates into a clonal population of stem cells so that all blood cells derived from these mutant clonal progenitors, especially red blood cells (RBCs), are susceptible to complement-mediated destruction (Fig. 488.1). The mutation causes cell membranes to be deficient (either partially or completely) in proteins that impede complement-mediated lysis via the constitutively active alternative pathway (Table 488.1). These complement-regulating proteins include decay-accelerating factor (DFA, CD55), the membrane inhibitor of reactive lysis (CD59), and the C8-binding protein. The underlying defect involves the glycolipid anchor that maintains these protective proteins on the cell surface. Various mutations in the *PIGA* gene, which encodes the glycosylphosphatidylinositol anchor protein (GPI-AP), have been identified in patients with PNH.

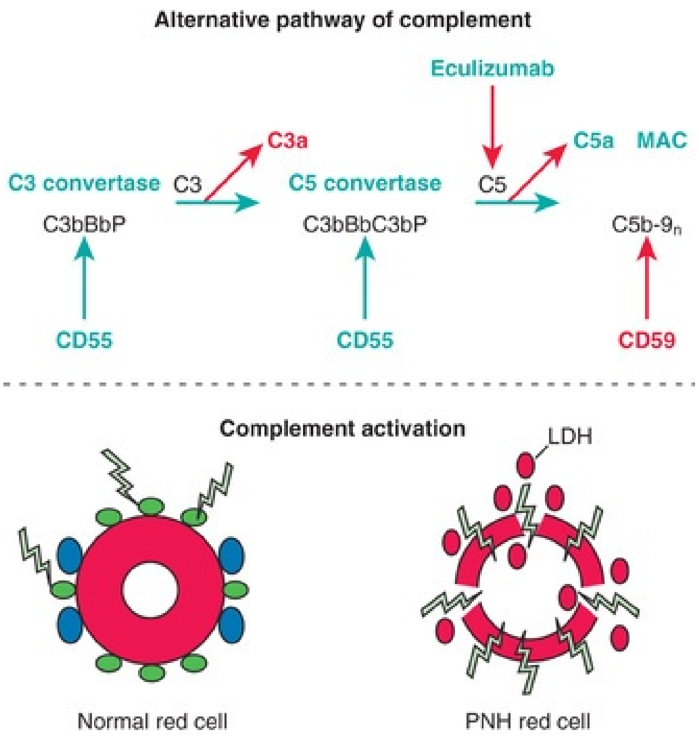
Alternative pathway of complement
Eculizumab
C3a
C5a
MAC
C3 convertase
C3
C5 convertase
C5
C3bBbP
C3bBbC3bP
C5b-9n
CD55
CD55
CD59
Complement activation
LDH
Normal red cell
PNH red cell

FIG. 488.1 Complement-mediated lysis in paroxysmal nocturnal hemoglobinuria (PNH). *Red ovals* are hemoglobin. *Blue ovals* are decay accelerating factor (CD55). *Green ovals* are membrane inhibitor of reactive lysis (CD59). Bb, Activated factor B; C3b, activated C3; C5b, activated C5; GPI, glycosylphosphatidylinositol; LDH, lactate dehydrogenase; MAC, membrane attack complex (consisting of C5b, C6, C7, C8, and several molecules of C9 [9n]). (From Parker C: Eculizumab for paroxysmal nocturnal haemoglobinuria, *Lancet* 373:759–767, 2009.)

Table 488.1

Glycosylphosphytidylinositol–Anchored Proteins Deficient in Paroxysmal Nocturnal Hemoglobinuria (PNH)*

Complement Regulatory Proteins †

CD55 (decay-accelerating factor)
CD59 (membrane inhibitor of reactive lysis)

Proteins With Immunologic Significance

CD58 (lymphocyte function antigen-3)
CDl6b (Fc receptor gamma lllb)

CD14 (endotoxin-binding protein)

Receptors

CD87 (urokinase plasminogen activator receptor)
Folate receptor
Cellular prion protein *(on resting platelets)*

Enzymes

Leukocyte alkaline phosphatase
Acetylcholinesterase
5′-Ectonucleotidase

Miscellaneous Proteins

CD24
CD48
CD52 (Campath-1)
CD66c
CD66b (formerly CD67}
CD90 (Thy-1)
CD108 (JMH-bearing protein)
p50-80, GP109, GP157, GP175, GP500

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[*] Partial list.

[†] Deficiency of complement regulatory proteins underlies the hemolytic anemia of PNH.

From *Nathan and Oski's hematology and oncology of infancy and childhood*, ed 8, Philadelphia, 2015, Elsevier (Box 14-1).

Clinical Manifestations

PNH is a rare disorder in children. Approximately 60% of pediatric patients have marrow failure, and the remainder have either intermittent or chronic anemia, often with prominent intravascular hemolysis (Table 488.2). Nocturnal and morning hemoglobinuria is the classic finding in adults, but only a minority of PNH patients have this manifestation. Most patients experience chronic hemolysis, often with thrombocytopenia and leukopenia. Hemoglobinuria is rarely seen in children compared to adults with PNH. **Thrombosis** and **thromboembolic phenomena** are serious complications that may be related to altered glycoproteins on the platelet surface and resultant platelet activation and production of procoagulant microparticles. Abdominal venous thrombosis presents as recurrent episodes of abdominal pain, Budd-Chiari syndrome (hepatic veins), or splenomegaly (splenic vein). Furthermore, released free hemoglobin results in depletion of nitric oxide, fostering vasoconstriction, thrombosis, and pain **.** Back and head pain may also be prominent. Hypoplastic or aplastic pancytopenia can precede or follow the diagnosis of PNH; rarely, PNH may progress to acute myelogenous leukemia. At the time of presentation, >90% of patients with PNH have some cell line abnormality (including approximately 35% with anemia alone, 15% with anemia and thrombocytopenia, 7% with anemia and neutropenia, and 30% with pancytopenia), >10% have abdominal pain, and >5% have thrombosis. The mortality in PNH is related primarily to the development of aplastic anemia or thrombotic complications. The predicted survival rate for children before the development of eculizumab was 80% at 5 yr, 60% at 10 yr, and 28% at 20 yr.

Table 488.2

Classification of Paroxysmal Nocturnal Hemoglobinuria

CATEGORY	RATE OF INTRAVASCULAR HEMOLYSIS*	BONE MARROW	FLOW CYTOMETRY	BENEFIT FROM ECULIZUMAB
Classic clinical PNH	Florid (markedly abnormal LDH, often with episodic macroscopic hemoglobinuria)	Cellular marrow caused by erythroid hyperplasia and normal or near-normal morphology †	Large population (>50%) of GPI-AP– PMNs §	Yes
Clinical PNH in the setting of another bone marrow failure syndrome ‡	Mild (often with minimal abnormalities of biochemical markers of hemolysis)	Evidence of a concomitant bone marrow failure syndrome ‡	Although variable, the percentage of GPI-AP– PMNs is usually relatively small (<50%)	Typically no, but some patients have relatively large clones and clinically significant hemolysis and may benefit from treatment.

Subclinical PNH	No clinical or biochemical evidence of intravascular hemolysis	Evidence of a concomitant bone marrow failure syndrome [‡]	Small (<1%) population of GPI-AP– PMNs detected by high-resolution flow cytometry	No

[*] Based on macroscopic hemoglobinuria, serum LDH concentration and reticulocyte count.

[†] Karyotypic abnormalities are uncommon.

[‡] Aplastic anemia or low-risk myelodysplastic syndrome.

[§] Analysis of PMNs is more informative than analysis of red blood cells because of selective destruction GPI-AP– RBCs.

GPI-AP–, Glycosylphosphatidylinositol–anchored protein–deficient; LDH, lactate dehydrogenase; PMNs, polymorphonuclear leukocytes.

From Parker CJ, Ware RE: Paroxysmal nocturnal hemoglobinuria. In Orkin SH, Nathan DG, Ginsburg D, et al, editors: Nathan and Oski's hematology and oncology of infancy and childhood, ed 8, Philadelphia, 2015, Elsevier, Table 14-1.

Laboratory Findings

Hemoglobin levels can range from normal to greatly decreased. Common findings reflect chronic intravascular hemolysis and include hemosiderinuria, an elevated reticulocyte percentage, a low serum haptoglobin, and increased serum lactate dehydrogenase (LDH). Initially, the anemia is normocytic, but if iron deficiency develops, it becomes microcytic. On the blood smear, poikilocytosis and anisocytosis may be present. Greatly reduced levels of RBC acetylcholinesterase activity and DAF also are found. Flow cytometry is the diagnostic test of choice for PNH. With the use of anti-CD59 for RBCs and anti-CD55 and anti-CD59 for granulocytes, flow cytometry is more sensitive than the classic RBC lysis (Ham or sucrose) tests in detecting these reduced glycolipid-bound membrane proteins. Fluorescence-labeled aerolysin testing can heighten the sensitivity of detection by binding selectively to GPI anchors.

Treatment

The emergence of **eculizumab therapy** has resulted in sustained survival in the patient majority. Eculizumab is a monoclonal antibody against complement component C5 that interrupts formation of the membrane attack complex, blocking downstream complement destruction of RBCs and activation of platelets. It decreases the rate of hemolysis, stabilizes hemoglobin levels, reduces the number of transfusions, reduces the risk of thrombosis, and improves quality of life. Eculizumab is an approved and effective treatment for PNH in adults. A phase I/II trial demonstrated safety and efficacy in patients 11-17 yr of age. Because of the cost and duration of treatment (lifelong) often required, particularly in children, it may be most useful in preventing thrombosis, anemia, and other symptoms while stem cell transplant is considered (Fig. 488.2). Survival in adults with PNH treated with eculizumab may not be different from sex- and age-matched control patients from the general population. However, the medication does not improve the hematopoietic clonal expansion or prevent marrow failure. Before beginning eculizumab, it is recommended to immunize patients with the meningococcal vaccines (MenACYW and MenB) if the patient has not already received these vaccines, because a serious risk of complement inhibition is increased susceptibility to meningococcal infections. Vaccination provides incomplete protection against meningococcal disease to patients receiving eculizumab, and thus antibiotic prophylaxis with penicillin should be also considered. Headache is a common adverse effect after the first few doses of eculizumab, but disappears subsequently. A poor response to eculizumab may be caused by polymorphisms in the C5 gene that produce resistance to eculizumab blockades. Patients receiving eculizumab therapy require regular monitoring, including complete blood counts with reticulocytes, LDH, total bilirubin, and repeat flow cytometry every 6-12 mo.

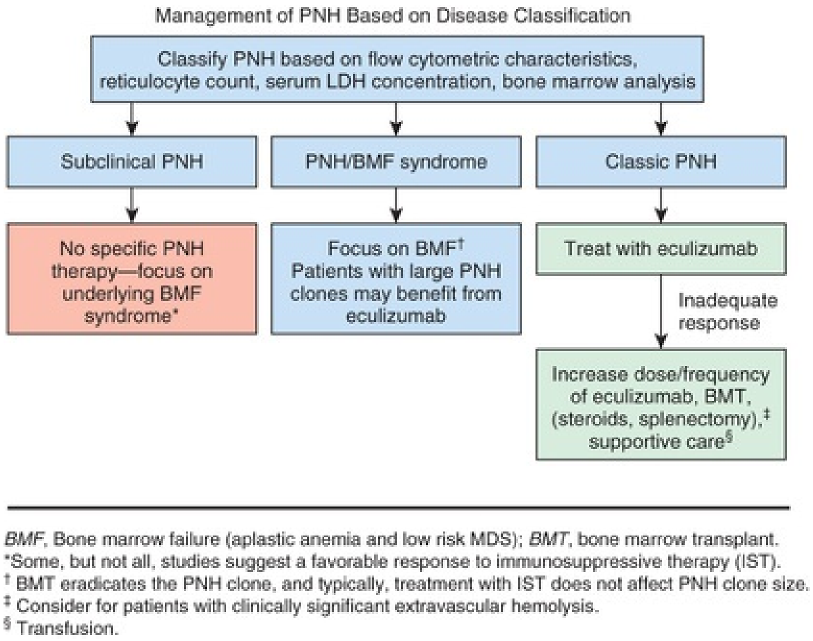
Management of PNH Based on Disease Classification
Classify PNH based on flow cytometric characteristics, reticulocyte count, serum LDH concentration, bone marrow analysis
Subclinical PNH
PNH/BMF syndrome
Classic PNH
No specific PNH therapy—focus on underlying BMF syndrome*
Focus on BMF† Patients with large PNH clones may benefit from eculizumab
Treat with eculizumab
Inadequate response
Increase dose/frequency of eculizumab, BMT, (steroids, splenectomy),‡ supportive care§

BMF, Bone marrow failure (aplastic anemia and low risk MDS); *BMT*, bone marrow transplant.
*Some, but not all, studies suggest a favorable response to immunosuppressive therapy (IST).
† BMT eradicates the PNH clone, and typically, treatment with IST does not affect PNH clone size.
‡ Consider for patients with clinically significant extravascular hemolysis.
§ Transfusion.

FIG. 488.2 Management of paroxysmal nocturnal hemoglobinuria (PNH). A management scheme based on classification of PNH into 3 categories: subclinical, PNH in the setting of another bone marrow failure syndrome (PNH/BMF), and classic PNH (see Table 488.2 for characteristics of each category). ***LDH,*** **Lactate dehydrogenase. (From *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, Philadelphia, 2015, Elsevier, Fig 14-9.)**

Hematopoietic stem cell transplantation (HSCT) is a key therapeutic consideration if a suitable donor exists, particularly in children. Severe aplastic anemia is a strong indication for transplant in PNH (Fig. 488.2). HSCT is the only potentially curative therapy available for PNH. Nonmyeloablative transplantation (with reduced-intensity conditioning regimens) are often used to reduce transplant-related mortality and morbidity; since eradication of only the PNH clones is sought, total myeloablation is not necessary.

Glucocorticoids such as prednisone can be used for acute hemolytic episodes; the dosage should be tapered as soon as the hemolysis abates. Prolonged **anticoagulation** (heparin or low-molecular-weight heparin) therapy may be of benefit when thromboses occur. Because of chronic urinary loss of iron as hemosiderin, **iron therapy** may be necessary. **Androgens** (e.g., fluoxymesterone), antithymocyte globulin, cyclosporine, and growth factors (e.g., erythropoietin, granulocyte colony-stimulating factor) have been used to treat marrow failure.

Acanthocytosis

Acanthocytosis is characterized by RBCs with irregular circumferential pointed projections (**acanthocytes** , also known as *spur cells*) (see Fig. 485.4*E*). This morphologic finding results from alterations in the membrane ratio of cholesterol to phospholipid, with the morphology attributed to an excess of lipid in the outer layer relative to the inner layer of the membrane bilayer. In liver disease, acanthocytes develop because of an increased abundance of free cholesterol, as patients develop splenic congestion, hemolytic anemia, and jaundice. **Abetalipoproteinemia** is an inherited autosomal recessive disease in which acanthocytosis is associated with fat malabsorption, progressive ataxia, and retinitis pigmentosa. The fat malabsorption may become apparent in the 1st yr of life. The ataxia develops at school age. The anemia is usually mild. **Hypobetalipoproteinemia** is a recessive familial disease that has a similar clinical spectrum, but with milder findings.

There are 4 genetically diverse *neuroacanthocytosis syndromes* (Table 488.3). **Chorea-acanthocytosis** is an adult-onset disease without anemia, variable numbers of acanthocytes on peripheral blood smear, with multiple neurologic findings such as limb chorea, tics, and hypotonia. The rare X-linked **McLeod syndrome** (marked by absence of the Kell antigen) presents with mild hemolytic anemia, late-onset myopathy, peripheral neuropathy, chorea, and splenomegaly. There are usually >3% acanthocytes on peripheral smear and caudate atrophy noted on MRI. McLeod syndrome is the only neuroacanthocytosis syndrome likely to present in childhood. Acanthocytes also are seen in **pantothenate kinase–associated neurodegeneration** (with dystonia, rigidity, chorea, dysarthria, spasticity, retinopathy) and **Huntington disease–like 2** .

Table 488.3

Neuroacanthocytosis Syndromes

DISEASE	INHERITANCE	GENE
Chorea-acanthocytosis	Autosomal recessive	*VPS13A*
McLeod syndrome	X-linked recessive	*XK*
Huntington disease–like 2	Autosomal dominant	*JPH3*
Pantothenate kinase–associated neurodegeneration	Autosomal recessive	*PANK2*

In contrast to acanthocytes, **echinocytes** or *burr cells* have a more regular distribution of projections or serrations along the surface of the RBCs and will tend to a more spheroidal cell contour as they age. They are seen often as artifacts (e.g., caused by elevated pH, contact with glass, or blood storage) and infrequently in end-stage renal disease, liver disease, uremia, pyruvate kinase deficiency, long-distance runners, and patients with hypomagnesemia and hypophosphatemia.

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CHAPTER 489

Hemoglobinopathies

Kim Smith-Whitley, Janet L. Kwiatkowski

Hemoglobin Disorders

Hemoglobin is a tetramer consisting of 2 pairs of globin chains. Abnormalities in these proteins are referred to as *hemoglobinopathies.*

More than 800 variant hemoglobins have been described. The most common and useful clinical classification of hemoglobinopathies is based on nomenclature associated with alteration of the involved *globin chain.* Two hemoglobin (Hb) gene clusters are involved in Hb production and are located at the end of the short arms of chromosomes 16 and 11. Their control is complex, including an upstream locus control region on each respective chromosome and an X-linked control site. On chromosome 16, there are 3 genes within the alpha (α) gene cluster: zeta (ζ), alpha 1 (α_1), and alpha 2 (α_2). On chromosome 11, there are 5 genes within the beta (β) gene cluster: epsilon (ε), gamma 1 (γ_1), gamma 2 (γ_2), delta (δ), and beta (β).

The order of gene expression within each cluster roughly follows the order of expression during the embryonic period, fetal period, and eventually childhood. After 8 wk of fetal life, the embryonic hemoglobins, Gower-1 ($\zeta_2 \varepsilon_2$), Gower-2 ($\alpha_2 \varepsilon_2$), and Portland ($\zeta_2 \gamma_2$), are formed. At 9 wk of fetal life, the major hemoglobin is HbF ($\alpha_2 \gamma_2$). HbA ($\alpha_2 \beta_2$) first appears at approximately 1 mo of fetal life, but does not become the dominant hemoglobin until after birth, when HbF levels start to decline. HbA_2 ($\alpha_2 \delta_2$) is a minor hemoglobin that appears shortly before birth and remains at a low level after birth. The final hemoglobin distribution pattern that occurs in childhood is not achieved until at least 6 mo of age and sometimes later. The normal hemoglobin pattern is ≥95% HbA, ≤3.5 HbA_2 , and <2.5% HbF.

489.1

Sickle Cell Disease

Kim Smith-Whitley

Children with sickle cell disease should be followed by experts in the management of this disease, most often by pediatric hematologists. Medical care provided by a pediatric hematologist is also associated with a decreased frequency of emergency department (ED) visits and length of hospitalization when compared to patients who were not seen by a hematologist within the last year.

Pathophysiology

Hemoglobin S (HbS) is the result of a single base-pair change, thymine for adenine, at the 6th codon of the β-globin gene. This change encodes valine instead of glutamine in the 6th residue in the β-globin molecule. Sickle cell anemia (HbSS), homozygous HbSS, occurs when both β-globin alleles have the sickle cell mutation (βs). Sickle cell disease refers not only to patients with sickle cell anemia, but also to compound heterozygotes where one β-globin allele includes the sickle cell mutation and the 2nd β-globin allele includes a gene mutation other than the sickle cell mutation, such as HbC, β-thalassemia, HbD, and HbO^{Arab} . In sickle cell anemia, HbS is typically as high as 90% of the total hemoglobin, whereas in sickle cell disease, HbS is >50% of all hemoglobin.

In red blood cells (RBCs), the hemoglobin molecule has a highly specified conformation allowing for the transport of oxygen in the body. In the absence of globin-chain mutations, hemoglobin molecules do not interact with one another. However, the presence of HbS results in a conformational change in the Hb tetramer, and in the deoxygenated state, HbS molecules interact with each other, forming rigid polymers that give the RBC its characteristic “sickled” shape. The lung is the only organ capable of reversing the polymers, and any disease of the lung can be expected to compromise the degree of reversibility.

Intravascular sickling primarily occurs in the postcapillary venules and is a function of both mechanical obstruction by sickled erythrocytes, platelets, and leukocytes and increased adhesion between these elements and the vascular endothelium. Sickle cell disease is also an inflammatory disease based on nonspecific markers of inflammation, including, but not limited to, elevated baseline white blood cell (WBC) count and cytokines. Intraerythrocytic changes lead to a shortened RBC life span and hemolysis. Hemolysis leads to multiple changes, including altered nitric oxide metabolism and oxidant stress that contribute to endothelial dysfunction.

Diagnosis and Epidemiology

Every state in the United States has instituted a mandatory newborn screening program for sickle cell disease. Such programs identify newborns with the disease and provide prompt diagnosis and referral to providers with expertise in sickle cell disease for anticipatory guidance and the initiation of penicillin before 4 mo of age.

The most commonly used procedures for newborn diagnosis include **thin-layer/isoelectric focusing** (IEF) and **high-performance liquid chromatography** (HPLC). Some laboratories perform genetic testing on specimens demonstrating abnormal hemoglobins. A confirmatory step is recommended, with all patients who have initial abnormal screens being retested during the first clinical visit. In addition, a complete blood cell count (CBC) and Hb phenotype determination is recommended for both parents to confirm the diagnosis and to provide an opportunity for genetic counseling. Infants who may have **HbS-hereditary persistence fetal hemoglobin** (HbSHPFH) but do not have full parental studies should have molecular testing for β-globin genotype before 12 mo of age. Table 489.1 correlates the initial hemoglobin phenotype at birth with the type of hemoglobinopathy.

Table 489.1

Various Newborn Sickle Cell Disease Screening Results With Baseline Hemoglobin

NEWBORN SCREENING RESULTS: SICKLE CELL DISEASE*	POSSIBLE HEMOGLOBIN PHENOTYPE †	BASELINE HEMOGLOBIN RANGE AFTER AGE 5 YR	EXPERTISE IN HEMATOLOGY CARE REQUIRED

FS	SCD-SS	6-11 g/dL	Yes
	SCD-S β^0 thal	6-10 g/dL	Yes
	SCD-S β^+ thal	9-12 g/dL	Yes
	SCD-S $\delta\beta^-$ thal	10-12 g/dL	Yes
	S HPFH	12-14 g/dL	Yes
FSC	SCD-SC	10-15 g/dL	Yes
FSA [‡]	SCD-S β^+ thal	9-12 g/dL	Yes
FS other	SCD-S β^0 thal	6-10 g/dL	Yes
	SCD-SD, SO^{Arab} , SC^{Harlem} , S^{Lepore}	Variable	Yes
AFS [‡] [§]	SCD-SS	6-10 g/dL	Yes
	SCD-S β^+ thal	6-9 g/dL	Yes
	SCD-S β^0 thal	7-13 g/dL variable	Yes

[*] Hemoglobins are reported in order of quantity.

[†] Requires confirmatory hemoglobin analysis after at least 6 mo of age and, if possible, β-globin gene testing or hemoglobin analysis from both parents for accurate diagnosis of hemoglobin phenotype.

[‡] Sickle cell trait is another possible diagnosis

[§] Impossible to determine the diagnosis because the infant most likely received a blood transfusion before testing.

A, Normal hemoglobin; C, hemoglobin C; F, fetal hemoglobin; HPFH, hereditary persistence of fetal hemoglobin; O^{Arab} , hemoglobin O^{Arab} ; S, sickle hemoglobin; SC, sickle-hemoglobin C; SCD, sickle cell disease; SS, homozygous sickle cell disease; thal, thalassemia.

In newborn screening programs, the hemoglobin with the greatest quantity is reported first, followed by other hemoglobins in order of decreasing quantity. Some states perform IEF initially on newborn blood samples, then use DNA probes to confirm abnormal hemoglobins found on IEF. In newborns with a hemoglobin analysis result of **HbFS** , the pattern supports HbSS, HbSHPFH, or HbSβ^0 -thalassemia. In a newborn with a hemoglobin analysis of **HbFSA** , the pattern is supportive of the diagnosis of HbSβ^+ -thalassemia. The diagnosis of HbSβ^+ -thalassemia is confirmed if at least 50% of the hemoglobin is HbS, HbA is present, and the amount of HbA_2 is elevated (typically >3.5%), although HbA_2 is not elevated in the newborn period. In newborns with a hemoglobin analysis of **HbFSC** , the pattern supports a diagnosis of HbSC. In newborns with a hemoglobin analysis of **HbFAS** , the pattern supports a diagnosis of HbAS (sickle cell trait); however, in this circumstance, care must be taken to confirm that the newborn has not received a red cell transfusion before testing.

A newborn with a hemoglobin analysis of **AFS** either has been transfused with RBCs before collection of the newborn screen to account for the greater amount of HbA than HbF, or there has been an error. The patient may have either sickle cell disease or sickle cell trait and should be started on penicillin prophylaxis until the final diagnosis can be determined.

Given the implications of a diagnosis of sickle cell disease vs sickle cell trait in a newborn, the importance of repeating the Hb identification analysis in the patient and obtaining a Hb identification analysis and CBC to evaluate the peripheral blood smear and RBC parameters in the parents for genetic counseling cannot be overemphasized. Unintended mistakes do occur in state newborn screening programs. Newborns who have the initial phenotype of HbFS but whose final true phenotype is HbSβ^+ -thalassemia have been described as one of the more common errors identified in newborn screening hemoglobinopathy programs. Determining an accurate phenotype is important for appropriate genetic counseling for the parents. In addition, distinguishing HbSS from HbSHPFH in the newborn period usually requires parental or genetic testing. In infants who maintain HbF percentages above 25% after 12 mo of age without evidence of hemolysis should have testing for β-globin gene deletions consistent with HPFH. These children have a much milder clinical course and do not require penicillin prophylaxis or hydroxyurea therapy.

If the parents are tested for sickle cell trait or hemoglobinopathy trait full disclosure to the parents must be provided, and in some circumstances the issue of paternity may be disclosed. For this reason and because of healthcare privacy, common practice is to always seek permission for the genetic testing and to report the hemoglobinopathy trait results back to each parent separately.

In the United States, sickle cell disease is the most common genetic disorder identified through the state-mandated newborn screening program, occurring in 1 : 2,647. In regard to race in the United States, sickle cell disease occurs in African Americans at a rate of 1 : 396 births and in Hispanics at a rate of 1 : 36,000 births. In the United States, an estimated 100,000 people are affected by sickle cell disease, with an ethnic distribution of 90% African American and 10% Hispanic. The U.S. sickle cell disease population represents a fraction of the worldwide burden of the disease, with global estimates of 312,000 neonates born annually with HbSS disease.

Clinical Manifestations and Treatment of Sickle Cell Anemia (HbSS)

For a comprehensive discussion of the clinical management of children and adolescents with sickle cell disease, refer to National Heart, Lung and Blood Institute (NHLBI) 2014 Expert Panel Report on the Evidence-based Management of Sickle Cell Disease (https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report.pdf).

Fever and Bacteremia

Fever in a child with sickle cell anemia is a medical emergency, requiring prompt medical evaluation and delivery of antibiotics because of the increased risk of bacterial infection and subsequent high mortality rate. As early as 6 mo of age, infants with sickle cell anemia develop abnormal immune function because of splenic dysfunction. By 5 yr of age, most children with sickle cell anemia have complete functional asplenia. Regardless of age, all patients with sickle cell anemia are at increased risk of infection and death from bacterial infection, particularly encapsulated organisms such as *Streptococcus pneumoniae* , *Haemophilus influenzae* type b, and *Neisseria meningitidis* .

The rate of bacteremia in children with sickle cell disease presenting with fever is <1%. Several clinical strategies have been developed to manage children with sickle cell disease who present with fever. These strategies range from hospital admission for intravenous (IV) antimicrobial therapy to administering a third-generation cephalosporin in an ED or outpatient setting to patients without established risk factors for occult bacteremia (Table 489.2). Given the observation that the average time for a positive blood culture is <20 hr in children with sickle cell anemia, admission for 24 hr is probably the most prudent strategy for children and families who live out of town or who are identified as high risk for poor follow-up.

Table 489.2

Clinical Factors Associated With Increased Risk of Acute Complications* in Febrile Children With Sickle Cell Disease

Seriously ill appearance
Hypotension: systolic blood pressure <70 mm Hg at 1 yr of age or <70 mm

Hg + 2 × age (yr) for older children
Poor perfusion: capillary refill time >4 sec
Temperature >40.0°C (104°F)
Corrected white blood cell count >30,000/mm^3 or <5000/mm^3
Platelet count <100,000/mm^3
History of pneumococcal sepsis
Severe pain
Dehydration: poor skin turgor, dry mucous membranes, history of poor fluid intake, or decreased output of urine
Presence of acute chest syndrome (new infiltrate on chest radiograph)
Hemoglobin level <5.0 g/dL

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[*] Including serious infection requiring hospital admission.

Adapted from Williams JA, Flynn PM, Harris S et al: A randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease, *N Engl J Med* 329:472–476, 1993.

Outpatient management of fever without a source should be considered in children with the lowest risk of bacteremia and after appropriate cultures are obtained and IV ceftriaxone or another cephalosporin is given. Observation after antibiotic administration is important, because children who have sickle cell anemia treated with ceftriaxone can develop severe, rapid, and life-threatening immune hemolysis. In the event that *Salmonella* spp. or *Staphylococcus aureus* bacteremia occurs, strong consideration should be given to an evaluation for osteomyelitis with a bone scan, given the increased risk of osteomyelitis in children with sickle cell anemia compared to the general population. Screening laboratory and radiologic studies are strongly recommended to identify those at risk for transient red cell aplasia, acute splenic sequestration, and acute chest syndrome (**ACS**), because many children with these diagnoses present to acute care settings with isolated fever. Screening children and caregivers for psychosocial factors that could impede their return to the hospital in the case of a positive blood culture is essential.

Aplastic Crisis

Human parvovirus B19 infection poses a unique threat for patients with sickle cell disease because this infection results in temporary **red cell aplasia** , limiting the production of reticulocytes and causing profound anemia (see Fig. 485.3 in Chapter 485). Any child with sickle cell disease, fever, and *reticulocytopenia* should be presumed to have parvovirus B19 infection until proven otherwise. Reticulocytosis and increased nucleated RBCs may be seen in the recovery phase. Testing for the presence of human parvovirus B19 with PCR testing is superior to using IgM and IgG titers. The acute exacerbation of anemia is treated conservatively using red cell transfusion when the patient becomes hemodynamically symptomatic or has a concurrent illness, such as ACS or acute splenic sequestration. In addition, acute infection with parvovirus B19 is associated with pain, splenic sequestration, ACS, glomerulonephritis, arthropathy, and stroke. Many patients with parvovirus-associated aplastic crisis are contagious, and infection precautions should be taken to avoid nosocomial spread of the infection and to avoid exposure of pregnant caregivers.

Splenic Sequestration

Acute splenic sequestration is a life-threatening complication occurring primarily in infants and young children with sickle cell anemia. The incidence of splenic sequestration has declined from an estimated 30% to 12.6% with early identification by newborn screening and improved parental education. Sequestration can occur as early as 5 wk of age but most often occurs in children between ages 6 mo and 2 yr. Patients with the SC and $S\beta^+$ -thalassemia types of sickle cell disease can have acute splenic sequestration events throughout adolescence and adulthood.

Splenic sequestration is associated with rapid spleen enlargement causing left-sided abdominal pain and Hb decline of at least 2 g/dL from the patient's baseline. Sequestration may lead to signs of hypovolemia as a result of the trapping of blood in the spleen and profound anemia, with total Hb falling below 3 g/dL. A decrease in WBC and platelet count may also be present. Sequestration may be triggered by fever, bacteremia, or viral infections.

Treatment includes early intervention and maintenance of hemodynamic stability using isotonic fluid or blood transfusions. Careful blood transfusions with RBCs are recommended to treat both the sequestration and the resultant anemia. Blood transfusion aborts the RBC trapping in the spleen and allows release of the patient's blood cells that have become sequestered, often raising

Hb above baseline values. A reasonable approach is to provide only 5 mL/kg of RBCs and/or a posttransfusion Hb target of 8 g/dL, keeping in mind that the goal of transfusion is to prevent hypovolemia. Blood transfusion that results in Hb levels >10 g/dL may put the patient at risk for **hyperviscosity syndrome** because blood may be released from the spleen after transfusion.

Repeated episodes of splenic sequestration are common, occurring in two thirds of patients. Most recurrent episodes develop within 6 mo of the previous episode. Prophylactic splenectomy performed after an acute episode has resolved is the only effective strategy for preventing future life-threatening episodes. Although blood transfusion therapy has been used with the goal of preventing subsequent episodes, evidence strongly suggests that this strategy does not reduce the risk of recurrent splenic sequestration compared to no transfusion therapy. However, a short course of regular red cell transfusions can be used until splenectomy is arranged. Children should be appropriately immunized with meningococcal and pneumococcal vaccines before surgery. Penicillin prophylaxis should be prescribed after splenectomy.

Hepatic and Gallbladder Involvement

See Chapters 387 and 393 .

Sickle Cell Pain

Dactylitis , referred to as **hand-foot syndrome** , is often the first manifestation of pain in infants and young children with sickle cell anemia, occurring in 50% of children by their 2nd yr of life (Fig. 489.1). Dactylitis often manifests with symmetric or unilateral swelling of the hands and/or feet. Unilateral dactylitis can be confused with osteomyelitis, and careful evaluation to distinguish the two is important because treatment differs significantly. Dactylitis requires palliation with pain medications, such as hydrocodone or oxycodone, whereas osteomyelitis requires at least 4-6 wk of IV antibiotics. Given the association between genotype and metabolism of codeine, a subgroup of children may not get pain relief from codeine. Therefore, feedback from the parents is needed to determine if therapy was successful in relieving pain.

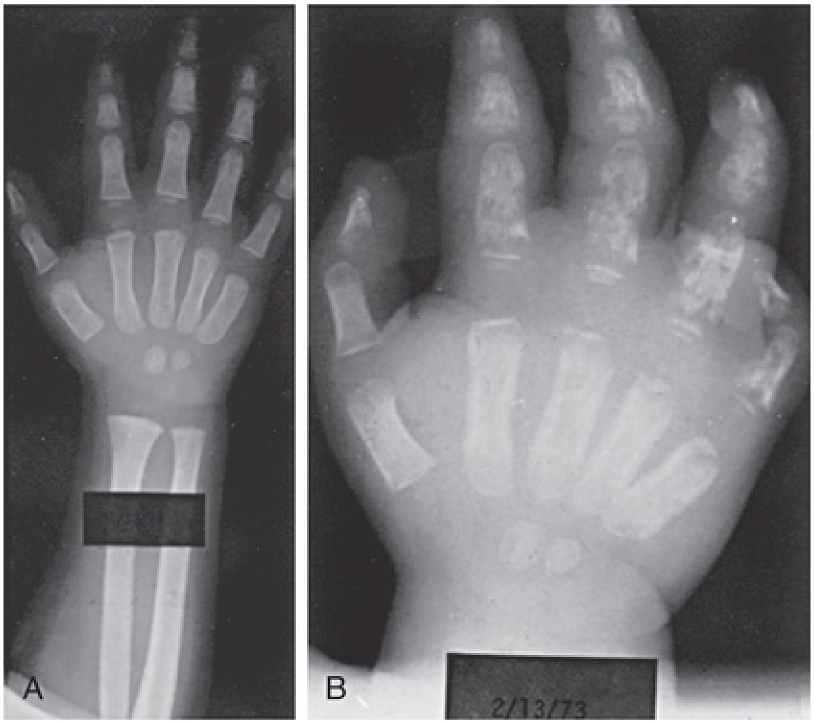

FIG. 489.1 **X-ray films of an infant with sickle cell anemia and acute dactylitis. A, The bones appear normal at the onset of the episode. B, Destructive changes and periosteal reaction are evident 2 wk later.**

The cardinal clinical feature of sickle cell disease is **acute vasoocclusive pain** . Acute sickle cell pain is characterized as unremitting discomfort that can occur in any part of the body but most often occurs in the chest, abdomen, or extremities. These painful episodes are often abrupt and cause disruption of daily life activities and significant stress for children and their caregivers. A patient with sickle cell anemia has approximately 1 painful episode per year that requires medical attention.

The exact etiology of pain is unknown, but the pathogenesis may be initiated when blood flow is disrupted in the microvasculature by sickled red blood cells and other cellular elements, resulting in tissue ischemia. Acute sickle cell pain may be precipitated by physical stress, infection, dehydration, hypoxia, local or systemic acidosis, exposure to cold, and swimming for prolonged periods. However, most pain episodes occur without an identifiable trigger. Successful treatment of these episodes requires education of both caregivers and patients regarding the recognition of symptoms and the optimal management strategy. Given the absence of any reliable objective laboratory or clinical parameter associated with pain, trust between the patient and the treating physician is paramount to successful clinical management. Specific therapy for pain varies greatly but generally includes the use of acetaminophen or a nonsteroidal antiinflammatory drug (NSAID) early in the course of pain, followed by escalation to a combination analgesic regimen using a single-agent short-acting oral opioid, long-acting oral opioid, and continued nonopioid agent.

Some patients require treatment in an acute care setting for administration of IV morphine or derivatives of morphine. The primary goal of treatment in these settings is timely administration of analgesics to provide relief of pain. The incremental increase and decrease in the use of the medication to relieve pain roughly parallels the 8 phases associated with a chronology of pain and comfort in children (Table 489.3). When pain requires continued parenteral analgesic administration, hospitalization is required. The average hospital length of stay for children admitted in pain is 4.4 days. The NHLBI clinical guidelines for treating acute and chronic pain in children and adults with sickle cell disease are comprehensive and represent a starting point for treating pain.

Table 489.3

Phases of a Painful Episode in Patients With Sickle Cell Disease

PHASE	DESCRIPTION AND COMFORT MEASURES
Data From Children	
I	***Baseline***
	No pain and no comfort measures
II	***Prepain phase***
	No evidence of pain
	Child begins to display some prodromal signs and symptoms of VOE (yellow eyes, fatigue)
	No comfort measures used
	Caregivers encouraged child to increase fluids to prevent the pain event from occurring
III	***Pain starting point***
	Child complained of mild “ache-ish” pain in one specific area, which gradually or rapidly increased or “waxed”
	Mild analgesics (ibuprofen and acetaminophen) given
	Child maintained normal activities and continued to attend school
	Caregivers hoped to prevent an increase in pain intensity
IV	***Pain acceleration***
	Pain continued to escalate; intensity increased from mild to moderate; pain appeared in more areas of the body; child was kept home from school; decreased level of activity; differences in behaviors, appearance, and mood
	Stronger oral analgesics may be combined with rest, rubbing, heat, distraction, and psychological comfort
V	***Peak pain experience***
	Pain continued to escalate
	Some children were incapacitated and unable to obtain pain relief
	Pain described as “stabbing,” “drilling,” “pounding,” “banging,” “excruciating,” “unbearable,” or

	“throbbing”
	Caregivers sometimes decide to seek help from ED for stronger analgesics and protection from complications such as fever or respiratory distress
	Caregivers may be exhausted from caring for the child for several days with little or no rest
	All methods of comfort were used around the clock to reduce the pain and avoid going to the hospital
	Pain increased despite all efforts
	Decision is made to take the child to ED
VI	***Pain decrease starting point***
	Pain begins to resolve after the use of IV fluids and analgesics
	Analgesics sedate the child and allow the child to sleep for longer periods
	Pain described as “slowly decreasing”
	Pain is still sharp and throbbing
VII	***Steady pain decline***
	Pain decreased slowly or rapidly
	Child takes more interest in surroundings, roommates, and visitors
	Child is less irritable
	Level of activity increased—child may be taken to tub room for warm bath, may watch television, may play games with other children or hospital volunteers
	Mobility was improved
	Pain levels reported as “just a little”
	More animation in behaviors evident
VIII	***Pain resolution***
	Pain was at a tolerable level
	Child may be discharged from the hospital on mild oral analgesics; child is at or close to baseline conditions, with behavior, appearance, and mood more normal
	Caregiver and child attempt to regain, recapture, and catch up with life as it was before the pain event
Data From Adults	
I	***Evolving/infarctive phase***
	3 days
	↓ RBC deformability
	↓ Hemoglobin
	↑ % of dense RBCs
	↑ RDW, ↑ HDW
	S/S: fear, anorexia, anxiety, ↑ pain
II	***Postinfarctive/inflammatory phase***
	4-5 days
	↓ Hemoglobin
	↑ White blood cells (leukocytosis)
	↑ Acute-phase reactants C-reactive protein
	↑ Reticulocytes, ↑ LDH, ↑ CPK
	↑ % dense RBCs
	↑ RDW, ↑ HDW
	S/S: fever, severe steady pain, swelling, tenderness, joint stiffness, joint effusions
III	***Resolving/healing/recovery/postcrisis phase***
	↑ RBC deformability
	Hemoglobin returns to precrisis level
	Retics return to precrisis levels
	↓ % of dense RBCs
	↓ RDW, ↓ HDW
	↓ ISC
	Precursors to relapse that happens in phase III: ↑ platelets, ↑ acute-phase reactants (fibrinogen, α_1 -acid glycoprotein, osmomucoid), ↑ viscosity, ↑ ESR
	↑ Retics expressing the ↑ α_4 β_1 -integrin complex ICAM-1

CPK, Creatinine phosphokinase; ED, emergency department; ESR, erythrocyte sedimentation rate; HDW, hemoglobin distribution width; ICAM, intracellular adhesion molecule; ISC, irreversibly sickled cells; LDH, lactate dehydrogenase; RBC, red blood cell; RDW, red cell distribution width; S/S, signs and symptoms; VOE, vasoocclusive episode.

Adapted from Jacob E: The pain experience of patients with sickle cell anemia, *Pain Manage Nurs* 2(3):74–83, 2001; with data from Ballas SK, Smith ED: Red blood cell changes during the evolution of the sickle cell painful crisis, *Blood* 79:2154–2163, 1992; and Beyer JE, Simmons L, Woods GM, Woods PM: A chronology of pain and comfort in children with sickle cell disease, *Arch Pediatr Adolesc Med* 153:913–920, 1999.

The only measure for degree of pain is the patient. Healthcare providers working with children in pain should use a consistent, validated pain scale (e.g., Wong-Baker FACES Scale) for assessing pain. Although pain scales have proved useful for some children, others require prenegotiated activities to determine when opioid therapy should be initiated and decreased. For example, sleeping through the night might be an indication for decreasing pain medication by 20% the following morning. The majority of painful episodes in patients with sickle cell disease are managed at home with comfort measures, such as heating blanket, relaxation techniques, massage, and oral pain medication.

Several myths have been propagated regarding the treatment of pain in sickle cell disease. The concept that painful episodes in children should be managed without opioids is without foundation and results in unwarranted suffering on the part of the patient. Blood transfusion therapy during an existing painful episode does not decrease the intensity or duration of the painful episode, because tissue necrosis occurs well before the ability to administer the transfusion. IV hydration does not relieve or prevent pain and is appropriate when the patient is dehydrated or unable to drink as a result of the severe pain. *Opioid dependency in children with sickle cell disease is rare and should never be used as a reason to withhold pain medication.* However, patients with multiple painful episodes requiring hospitalization within 1 yr or with pain episodes that require hospitalization for >7 days should be evaluated for comorbidities and environmental stressors that are contributing to the frequency or duration of pain. Children with chronic pain should be evaluated for other reasons associated with vasoocclusive pain episodes, including, but not limited to, presence of avascular necrosis, leg ulcers, and vertebral body compression fractures. A careful history is warranted to distinguish chronic pain that often is not relieved by opioids vs recurrent acute prolonged vasoocclusive pain episodes.

Skeletal pain (bone or bone marrow infarction) with or without fever must be differentiated from **osteomyelitis** . Both *Salmonella* spp. and *S. aureus* cause osteomyelitis in children with sickle cell disease, often involving the diaphysis of long bones (in contrast to children without sickle cell anemia, in whom osteomyelitis is in the metaphyseal region of the bone). Differentiating **osteonecrosis** from a vasoocclusive crisis and osteomyelitis is often difficult. Clinical signs and symptoms can be consistent with both osteonecrosis and vasoocclusive crises, as low-grade fever pain, swelling of the affected area, high WBC counts, and elevated C-reactive protein levels can be present in both. Blood cultures, when positive, are helpful. MRI may be useful for locating an area to obtain fluid for culture. MR findings suggestive of osteomyelitis include localized medullary fluid, sequestrum, and cortical defects. Ultimately, aspiration with or with or without biopsy and culture will be needed to differentiate the 2 processes (see Chapter 704).

Avascular Necrosis

Avascular necrosis (**AVN**) occurs at a higher rate among children with sickle cell disease than in the general population and is a source of both acute and chronic pain. Most often the femoral head is affected. Unfortunately, AVN of the hip may cause limp and leg-length discrepancy. Other sites affected include the humeral head and mandible. Risk factors for AVN include HbSS disease with α-thalassemia trait, frequent vasoocclusive episodes, and elevated hematocrit (for patients with sickle cell anemia). Optimal treatment of AVN has not been determined, and individual management requires consultation with the disease-specific specialist, orthopedic surgeon, physical therapist, hematologist, and primary care physician. Initial management should include referral to a pediatric orthopedist and a physical therapist to address strategies to increase strength and decrease weight-bearing daily activities that may exacerbate the pain associated with AVN. Opioids are often used but usually can be tapered after the acute pain has subsided. Regular blood transfusion therapy has not been demonstrated as an effective therapy to abate the acute and chronic pain associated with AVN.

Priapism

Priapism, defined as an unwanted painful erection of the penis, affects males of all genotypes but most frequently affects males with sickle cell anemia. The mean age of first episode is 15 yr, although priapism has been reported in children as young as 3 yr. The actuarial probability of a patient experiencing priapism is approximately 90% by 20 yr of age.

Priapism occurs in 2 patterns: *prolonged* , lasting >4 hr, or *stuttering* , with brief episodes that resolve spontaneously but may occur in clusters and herald a prolonged event. Both types occur from early childhood to adulthood. Most episodes occur between 3 and 9 AM . Priapism in sickle cell disease represents a low-flow state caused by venous stasis from RBC sickling in the corpora cavernosa. Recurrent prolonged episodes of priapism are associated with erectile dysfunction (impotence).

The optimal treatment for acute priapism is unknown. Supportive therapy, such as a hot shower, short aerobic exercise, or pain medication, is often used by patients at home. A prolonged episode lasting >4 hr should be treated by aspiration of blood from the corpora cavernosa, followed by irrigation with dilute epinephrine to produce immediate and sustained *detumescence*. Urology consultation is required to initiate this procedure, with appropriate input from a hematologist. Simple blood transfusion with exchange transfusion has been proposed for the acute treatment of priapism, but limited evidence supports this strategy as the initial management. If no benefit is obtained from surgical management, transfusion therapy should be considered. However, detumescence may not occur for up to 24 hr (much longer than with urologic aspiration) after transfusion, and transfusion for priapism has been associated with acute neurologic events. Consultation with a hematologist and urologist will help identify therapies to prevent recurrences.

Neurologic Complications

Neurologic complications associated with sickle cell disease are varied and complex, ranging from **acute** ischemic stroke with focal neurologic deficit to clinically **silent** abnormalities found on radiologic imaging. Before the development of transcranial Doppler ultrasonography to screen for stroke risk among children with sickle cell anemia, approximately 11% experienced an overt stroke and 20% a silent stroke before age 18 yr. A functional definition of *overt stroke* is the presence of a focal neurologic deficit lasting for >24 hr and/or abnormal neuroimaging of the brain indicating a cerebral infarct on T2-weighted MRI corresponding to the focal neurologic deficit (Figs. 489.2 and 489.3). A *silent cerebral infarct* lacks focal neurologic findings lasting >24 hr and is diagnosed by abnormal imaging on T2-weighted MRI. Children with other types of sickle cell disease, such as HbSC or HbSβ^+ -thalassemia, develop overt or silent cerebral infarcts as well, but at a lower frequency than children with HbSS and HbSβ^0 -thalassemia. Other neurologic complications include transient ischemic attacks, headaches that may or may not correlate to degree of anemia, seizures, cerebral venous thrombosis, and **posterior reversible encephalopathy syndrome (PRES)** . Chiari I malformations can occur in older children with sickle cell disease. **Fat embolism syndrome** is a rapidly progressive, potentially fatal complication involving pain, respiratory distress, changes in mental status, and multiorgan system failure. When this syndrome is identified early, exchange transfusion therapy has improved patient survival in small case series.

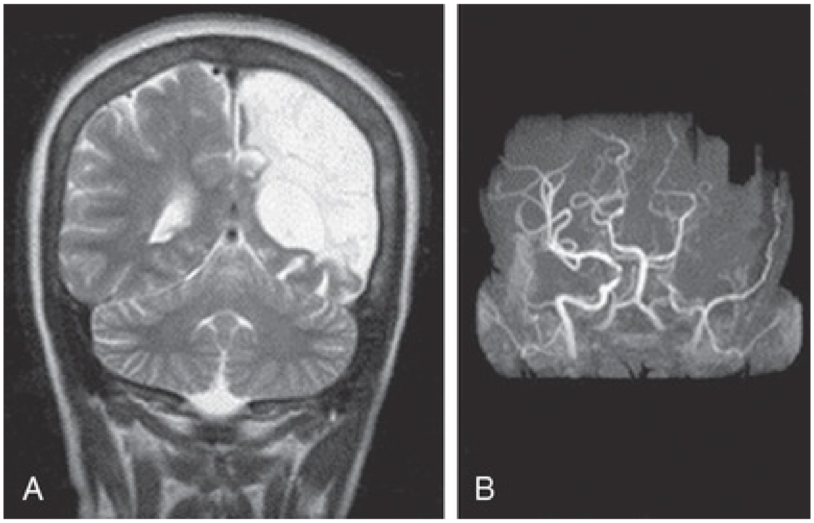

FIG. 489.2 MRI and magnetic resonance angiography of the brain. A, T2-weighted MRI shows remote infarction of the territories of the left anterior cerebral artery and middle cerebral artery. B, MRA shows occlusion of the left internal carotid artery siphon distal to the takeoff of the ophthalmic artery.

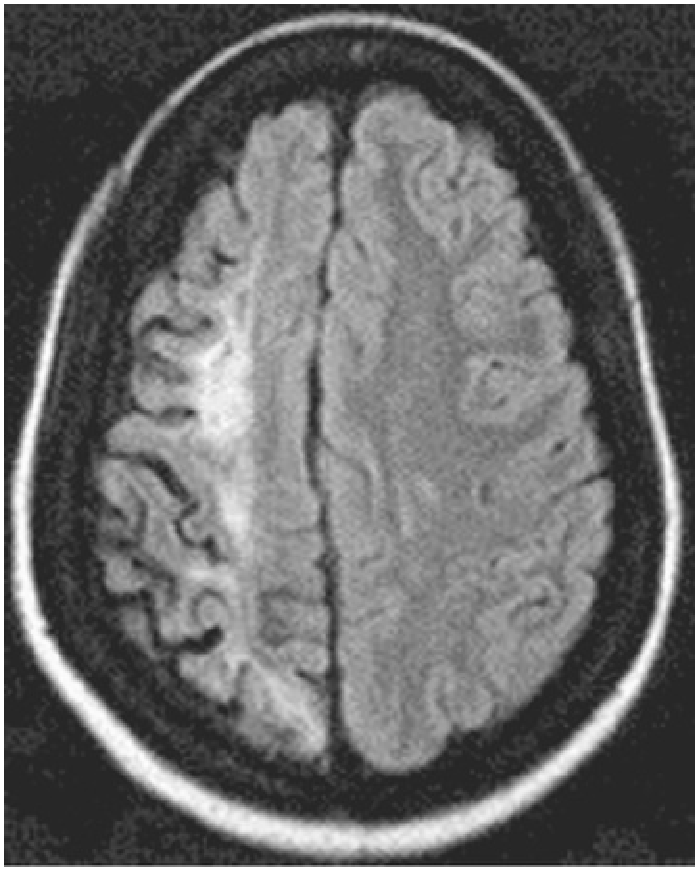

FIG. 489.3 Fast fluid-attenuated inversion recovery sequence MRI of the brain showing a right hemisphere border-zone cerebral infarction in a child with sickle cell anemia. (From Switzer JA, Hess DC, Nichols F, et al: Pathophysiology and treatment of stroke in sickle-cell disease: present and future, *Lancet Neurol* 5:501–512, 2006.)

For patients presenting with acute focal neurologic deficit, a prompt pediatric neurologic evaluation and consultation with a pediatric hematologist is recommended. In addition, oxygen administration to keep oxygen saturation (SO_2) >96% and simple blood transfusion within 1 hr of presentation, with a goal of increasing Hb to a maximum of 10 g/dL, is warranted. A timely simple blood transfusion is important because this is the most efficient strategy to dramatically increase oxygen content of the blood, if SO_2 is >96%. However, greatly exceeding this posttransfusion Hb limits oxygen delivery to the brain as a result of hyperviscosity by increasing the Hb significantly over the patient's baseline values. Subsequently, prompt treatment with an exchange transfusion should be considered, either manually or with automated erythrocytapheresis, to reduce the HbS percentage to at least <50% and ideally <30%. Exchange transfusion at the time of acute stroke is associated with a decreased risk of 2nd stroke compared to simple transfusion alone. CT of the head to exclude cerebral hemorrhage should be performed as soon as possible, and if available, MRI of the brain with diffusion-weighted imaging to distinguish between ischemic infarcts and PRES. MR venography is useful to evaluate the possibility of **cerebral venous thrombosis** , a rare but potential cause of focal neurologic deficit in children with sickle cell disease. MR angiography may identify evidence of cerebral vasculopathy; these images are not critical in the initial time management of a child with sickle cell disease presenting with a focal neurologic deficit.

The clinical presentation of PRES or central venous thrombosis can mimic a stroke but would require a different treatment course. For both PRES and cerebral venous thrombosis, the optimal management has not been defined in patients with sickle cell disease, resulting in the need for consultation with both a pediatric neurologist and a pediatric hematologist. The primary approach for **prevention** of recurrent overt stroke is blood transfusion therapy aimed at keeping the maximum HbS concentration <30%. Despite regular blood transfusion therapy, approximately 20% of patients will have a 2nd stroke and 30% of this group will have a 3rd stroke.

Transcranial Doppler Ultrasonography

Primary prevention of overt stroke can be accomplished using screening transcranial Doppler ultrasonography (TCD) assessment of the blood velocity in the terminal portion of the internal carotid and the proximal portion of the middle cerebral artery. Children with sickle cell anemia with an elevated *time-averaged mean maximum* (TAMM) blood flow velocity >200 cm/sec are at increased risk for a cerebrovascular event. A TAMM measurement of <200 but ≥180 cm/sec represents a conditional threshold. A repeat measurement is suggested within a few months because of the high rate of conversion to a TCD velocity >200 cm/sec in this group of patients. However a single value ≥220 cm/sec is concerning and does not require repeating before recommending an intervention.

Two distinct methods of measuring TCD velocity are a nonimaging technique and an imaging technique. The *nonimaging* technique was the method used in the stroke prevention trial sponsored by the National Institutes of Health, whereas most pediatric radiologists in practice use the *imaging* technique. When compared to each other, the imaging technique produces values that are 10–15% below those of the nonimaging technique. The imaging technique uses the *time-*

averaged mean of the maximum velocity (TAMX), and this measure is believed to be equivalent to the nonimaging calculation of TAMM. A downward adjustment for the transfusion threshold is appropriate for centers using the imaging method to assess TCD velocity. The magnitude of the transfusion threshold in the imaging technique has not been settled, but a transfusion threshold of a TAMX of 185 cm/sec and a conditional threshold of TAMX of 165 cm/sec seem reasonable. Alternatively, some experts recommend using the same thresholds regardless of technique.

Children with TCD values above defined thresholds should begin chronic blood transfusion therapy to maintain HbS levels <30% to decrease the risk of 1st stroke. This strategy results in an 85% reduction in the rate of overt strokes. Once transfusion therapy is initiated, a subset of patients at low risk for the development of increased TCD values, such as those without MRI-confirmed cerebral vasculopathy, may be able to transition from chronic transfusions to long-term hydroxyurea therapy. Acute stroke risk is decreased when hydroxyurea use and chronic transfusions overlap until a robust therapeutic response to hydroxyurea is achieved.

Pulmonary Complications

Lung disease in children with sickle cell disease is the 2nd most common reason for hospital admission and is associated with significant mortality. **Acute chest syndrome** refers to a life-threatening pulmonary complication of sickle cell disease defined as a new radiodensity on chest radiography plus any 2 of the following: fever, respiratory distress, hypoxia, cough, and chest pain (Fig. 489.4). Even in the absence of respiratory symptoms, very young children with fever should receive a chest radiograph to identify evolving ACS, because clinical examination alone is insufficient to identify patients with a new radiographic density. Early detection of ACS may alter clinical management. The radiographic findings in ACS are variable but may include single-lobe involvement, predominantly left lower lobe; multiple lobes, most often both lower lobes; and pleural effusions, either unilateral or bilateral. ACS may progress rapidly from a simple infiltrate to extensive infiltrates and a pleural effusion. Therefore, continued pulse oximetry and frequent clinical exams are required, and repeat chest x-ray films may be indicated for progressive hypoxia, dyspnea, tachypnea, and other signs of respiratory distress.

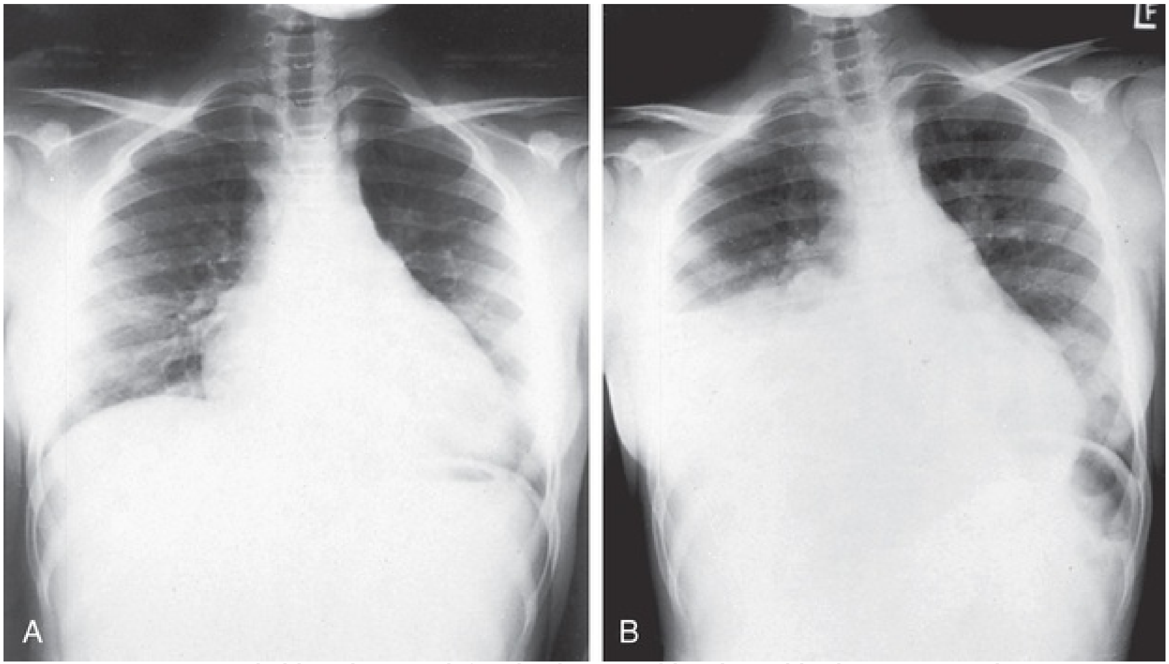

FIG. 489.4 Probable pulmonary infarction in 15 yr old patient with HbSS. A, Frontal radiograph shows consolidation and a small pleural effusion posteriorly in the right lower lobe. B, Radiograph obtained <24 hr later shows massive right middle and lower lobe consolidation and effusion. No organisms could be cultured. The diagnosis of "probably pulmonary infarction" was established clinically. (Courtesy of Dr. Thomas L. Stovis, Children's Hospital of Michigan, Detroit, MI. From Kuhn JP, Stovis TL, Haller JO: *Caffey's pediatric diagnostic imaging,* vol 1, ed 10, Philadelphia, 2004, Mosby, p 1087.)

Most patients with ACS do not have a single identifiable cause. Infection is the most well-known etiology, yet only 30% of ACS episodes will have positive sputum or bronchoalveolar culture, and the most common bacterial pathogens are *S. pneumoniae* , *Mycoplasma pneumoniae*, and *Chlamydia* spp. The most frequent event preceding ACS is a painful episode requiring systemic opioid treatment. **Fat emboli** have also been implicated as a cause of ACS, arising from infarcted bone marrow, and can be life threatening if large amounts are released to the lungs. Fat emboli can be difficult to diagnose but should be considered in any patient with sickle cell disease presenting with rapid onset of respiratory distress and altered mental status changes. Petechial rash may also occur, but may be difficult to detect if not carefully sought.

Given that the causes of ACS are varied, recommended management is also multimodal (Table 489.4). The type of opioid, with morphine being more likely to cause ACS than nalbuphine hydrochloride, is associated with an increase in the risk of ACS in part because of sedation and hypoventilation. However, under no circumstance should opioid administration be limited to prevent ACS; rather, other measures must be taken to prevent ACS from developing. In patients with chest pain, regular use of an **incentive spirometer** at 10-12 breaths every 2 hr can significantly reduce the frequency of subsequent ACS episodes. Because of the clinical overlap between pneumonia and ACS, all episodes should be treated promptly with antimicrobial therapy, including at least a macrolide and possibly a third-generation cephalosporin. A previous diagnosis of asthma or wheezing with ACS should prompt treatment following standard of care for an asthma exacerbation with bronchodilators. The diagnosis of ACS does not negate the recommended management of a patient with asthma exacerbation. Oxygen should be administered for patients who demonstrate hypoxia. Blood transfusion therapy using either simple or exchange (manual or automated) transfusion is the only method to abort a rapidly progressing ACS episode. The decision when to give blood and whether the transfusion should be a simple or exchange transfusion is less clearly defined. Usually, blood transfusions are given when at least 1 of the following clinical features are present: decreasing SO_2, increasing work of breathing, rapidly changing respiratory effort either with or without a worsening chest radiograph, a dropping Hb of 2 g/dL below the patient's baseline, or previous history of severe ACS requiring admission to the intensive care unit.

Table 489.4

Overall Strategies for the Management of Acute Chest Syndrome

Prevention

Incentive spirometry and periodic ambulation in patients admitted for sickle cell pain, surgery, or febrile episodes
Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)
Cautious use of intravenous fluids
Intense education and optimum care of patients who have sickle cell anemia and asthma

Diagnostic Testing and Laboratory Monitoring

Blood cultures, if febrile

Nasopharyngeal samples for viral culture (respiratory syncytial virus, influenza), depending on clinical setting
Complete blood counts every day and appropriate chemistries
Continuous pulse oximetry
Chest radiographs, for persistent or progressive illness

Treatment

Blood transfusion (simple or exchange), depending on clinical features; consider maintaining an active type and crossmatch
Supplemental O_2 for drop in pulse oximetry by 4% over baseline, or values <90%
Empirical antibiotics (third-generation cephalosporin and macrolide)
Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)
Bronchodilators and corticosteroids for patients with asthma
Optimum pain control and fluid management

Pulmonary hypertension has been identified as a major risk factor for death in adults with sickle cell anemia. The natural history of pulmonary hypertension in children with sickle cell anemia is unknown. Optimal strategies for screening at risk patients have not been identified (echocardiogram results are not supported by right-sided heart catheterization results demonstrating elevated pulmonary artery pressures), and the best diagnostic methodology carries significant risk of harm. Attempts to identify targeted therapeutic interventions to alter the natural history of pulmonary hypertension in adults have been unsuccessful.

Renal Disease and Enuresis

Renal disease among patients with sickle cell disease is a major comorbid condition that can lead to premature death. Seven sickle cell disease nephropathies have been identified: gross hematuria, papillary necrosis, nephrotic syndrome, renal infarction, hyposthenuria, pyelonephritis, and renal medullary carcinoma. The presentation of these entities is varied but may include hematuria, proteinuria, renal insufficiency, concentrating defects, or hypertension.

The common presence of **nocturnal enuresis** occurring in children with sickle cell disease is not well defined but is troublesome for affected children and their parents. The overall prevalence of enuresis was 33% in the Cooperative Study of Sickle Cell Disease, with the highest prevalence (42%) among children 6-8 yr old. Furthermore, enuresis may still occur in approximately 9% of older adolescents. Patients with sickle cell disease and nocturnal enuresis should have a systematic evaluation for recurrent urinary tract infections, kidney function, and possibly obstructive sleep apnea syndrome. Unfortunately, most children with nocturnal enuresis do not have an etiology, and targeted therapeutic interventions have been of limited success. However, referrals to pediatric urologists should be considered.

Cognitive and Psychological Complications

Good health maintenance must include routine psychological and social assessment. Ongoing evaluation of the family unit and identification of the resources available to cope with a chronic illness are critical for optimal management. Children and adolescents with sickle cell disease have decreased quality of life, as measured on standardized assessments, compared to their siblings and children with other chronic diseases. Furthermore, children with sickle cell disease are at great risk for academic failure and have a 20% high school graduation rate, possibly because, among other reasons, approximately one third of children with sickle cell anemia have had a cerebral infarct, either silent or an overt stroke. Children with cerebral infarcts require ongoing cognitive and school performance assessment so that education resources can be focused to optimize educational attainment. Participation in relevant support groups and group activities, such as camps for children with sickle cell disease, may be of direct benefit by improving self-esteem and establishing peer relationships.

Other Complications

In addition to the previous organ dysfunctions, patients with sickle cell disease can have other significant complications. These complications include, but are not limited to, sickle cell retinopathy, delayed onset of puberty, and leg ulcers. Optimal treatment for each of these entities has not been determined, and individual management requires consultation with the hematologist and primary care physician.

Therapeutic Considerations

Hydroxyurea

Hydroxyurea, a myelosuppressive agent, is a well-established drug proven effective in reducing the frequency of acute pain episodes. In adults with sickle cell anemia, hydroxyurea decreases the rate of hospitalization for painful episodes by 50% and the rate of ACS and blood transfusion by almost 50%. In addition, adults taking hydroxyurea have shorter hospital stay and require less analgesic medication during hospitalization. In children with sickle cell anemia, a safety feasibility trial demonstrated that hydroxyurea was safe and well tolerated in children >5 yr of age. No clinical adverse events were identified in this study; the primary toxicities were limited to myelosuppression that reversed on cessation of the drug. In addition, infants treated with hydroxyurea experienced fewer episodes of pain, dactylitis, and ACS; were hospitalized less frequently; and less often required a blood transfusion. Despite taking a myelosuppressive agent, the infants treated with hydroxyurea did not experience increased rates of bacteremia or serious infection. *Current recommendations are that all children with sickle cell anemia should be offered hydroxyurea beginning at 9 mo of age.*

Hydroxyurea may be indicated for other sickle cell–related complications, especially in patients who are unable to tolerate other treatments. For patients who either will not or cannot continue blood transfusion therapy to prevent recurrent stroke, hydroxyurea therapy may be a reasonable alternative. The trial assessing the efficacy of hydroxyurea as an alternative to transfusions to prevent a 2nd stroke was terminated early after the data safety and monitoring found an increased stroke rate in the hydroxyurea arm compared to the transfusion arm (0 vs 7 [10%]). Hydroxyurea alone is inferior to transfusion therapy for secondary stroke prevention in patients who do not have contraindications to ongoing transfusions.

The long-term toxicity associated with initiating hydroxyurea in very young children has not yet been established. However, all evidence to date suggests that the benefits far outweigh the risks. For these reasons, very young children starting hydroxyurea require well-informed parents and medical care by pediatric hematologists, or at least co-management by a physician with expertise in immunosuppressive medications. The typical starting dose of hydroxyurea is 15-20 mg/kg once daily, with an incremental dosage increase every 8 wk of 5 mg/kg, and if no toxicities occur, up to a maximum of 35 mg/kg per dose. The infant hydroxyurea study found young children could safely be started at 20 mg/kg/day without increased toxicity. Achievement of the therapeutic effect of hydroxyurea can require several months, and for this reason, initiating hydroxyurea to address short-term symptom relief is not optimal. We prefer to introduce the concept to parents within the 1st yr of life, preferably by 9 mo; provide literature that describes both the pros and cons of starting hydroxyurea in children with severe symptoms of sickle cell disease; and educate parents on starting hydroxyurea in asymptomatic children as a preventive therapy for repetitive pain and ACS events. Other effects of hydroxyurea that may vary include an increase in the total Hb level and a decrease in the TCD velocity.

The FDA has approved oral L-glutamine, used as an add on to hydroxyurea, for patients ≥5 yr. L-glutamine has been shown to reduce hospitalizations and sickle cell crisis.

Hematopoietic Stem Cell Transplantation

The only cure for sickle cell anemia is transplantation with human leukocyte antigen (HLA)–matched hematopoietic stem cells from a sibling or unrelated donor. Clinical trials are underway to determine whether gene therapy or gene editing therapy is a safe, effective, long-term cure for those with sickle cell anemia. The most common indications for transplant are recurrent ACS, stroke, and abnormal TCD. Sibling-matched stem cell transplantation has a lower risk for graft-versus-host disease than unrelated donors. Surveys suggest that younger children may have lower morbidity and mortality. However, few children have suitable sibling donors. Stem cell transplantation using an unrelated but well-matched donor remains a focus of clinical research. The decision to consider unrelated transplantation should involve appropriate consultation and counseling from physicians with expertise in sickle cell transplantation.

Stem cell transplantation for children with sickle cell disease who have a genetically matched sibling and few complications is not routinely performed. The use of hydroxyurea has dramatically decreased the disease burden for the patient and family, with far fewer hospitalizations for pain or ACS episodes and less use of blood transfusions. Furthermore, the field of stem cell transplantation is progressing so rapidly that nonsibling donor, including haploidentical, transplantation and gene therapy studies are underway. Transplant-related complications caused by conditioning regimens may be decreased by using low-intensity, nonmyeloablative HLA-matched sibling, allogenic stem cell transplantation.

Red Blood Cell Transfusions

RBC transfusions are used frequently both in the treatment of acute complications and to prevent acute or recurrent complications. Typically, short-term transfusions are used to prevent progression of acute complications such as ACS, aplastic crisis, splenic sequestration, and acute stroke, as well as to prevent surgery-related ACS. RBC transfusions are not recommended for uncomplicated acute pain events. Select RBC volumes judiciously to avoid high posttransfusion Hb levels and hyperviscosity. Long-term or chronic transfusion therapy is used to prevent 1st stroke in patients with abnormal TCD or MRI findings (silent stroke), recurrent stroke, or recurrent ACS. Patients with sickle cell disease are at increased risk of developing *alloantibodies* to less common RBC surface antigens after receiving even a single transfusion. In addition to standard cross matching for major blood group antigens (A, B, O, RhD), more *extended matching* should be performed to identify donor units that are C-, E-, and Kell-antigen matched. Some centers have begun to perform full RBC antigen phenotyping or genotyping for patients receiving chronic blood transfusions, in order to have the red cell units least likely to result in alloimmunization available for these patients.

Three methods of **blood transfusion therapy** are used in the management of acute and chronic complications associated with sickle cell disease: automated erythrocytapheresis, manual exchange transfusion (phlebotomy of a set amount of patient's blood followed by rapid administration of donated packed RBCs), and simple transfusion. The decision on which method to use depends on the patient's pretransfusion Hb level, the clinical indication, RBC alloimmunization, and transfusional iron overload. *Automated erythrocytapheresis* is the preferred method for patients requiring chronic blood transfusion therapy because there is a minimum net iron balance after the procedure, followed by manual exchange transfusion. However, this method requires technical expertise, special machines, and good patient venous access. *Manual exchange* is more accessible. However, both methods may expose the patient to more red cell units and possible alloimmunization. *Simple transfusion* therapy may lower donor exposure but may result in higher net iron burden when compared to erythrocytapheresis or exchange transfusion.

Preparation for surgery for children with sickle cell disease requires a coordinated effort from the hematologist, surgeon, anesthesiologist, and primary care provider. Historically, ACS was associated with general anesthesia in patients with sickle cell disease. Blood transfusion prior to surgery for children with sickle cell disease is recommended to raise Hb level preoperatively to no more than 10 g/dL, to avoid ACS development. Because of better general perioperative care and the use of long-term therapies such as hydroxyurea and chronic transfusions, the decision to transfuse before general anesthesia should be made in conjunction with the medical team who provides sickle cell disease–related care for the patient. When preparing a child with sickle cell disease for surgery with a simple blood transfusion, caution must be used not to elevate Hb level beyond 10 g/dL because of the risk of hyperviscosity syndrome. For children with milder forms of sickle cell disease, such as HbSC or HbSβ-thalassemia, a decision must be made on a case-by-case basis as to whether an exchange transfusion is warranted, because a simple transfusion may raise the hemoglobin to an unacceptable level.

Iron Overload

The primary toxic effect of blood transfusion therapy relates to excessive iron stores or iron overload, which can result in organ damage and premature death. Excessive iron stores develop after 100 mL/kg of red cell transfusion, or about 10 transfusions. The assessment of iron overload in children receiving regular blood transfusions is difficult. The most common and least invasive method of estimating total body iron involves serum **ferritin** levels. Ferritin measurements have significant limitations in their ability to estimate iron stores for several reasons, including, but not limited to, elevation during acute inflammation and poor correlation with excessive iron in specific organs after 2 yr of regular blood transfusion therapy. MRI of the liver has proved to the most effective approach for assessment of iron stores. The imaging strategy is more accurate than serum ferritin in measuring heart and liver iron content. MRI T2* and MRI R2 and R2* sequences are used to estimate iron levels in the heart and liver. The standard for iron assessment previously was liver biopsy, which is an invasive procedure exposing children to the risk of general anesthesia, bleeding, and pain. Liver biopsy alone does not accurately estimate total body iron because iron deposition in the liver is not homogeneous and varies among the affected organs; that is, the amount of iron found in the liver is not equivalent to cardiac tissues. The major advantage of a liver biopsy is that histologic assessment of the parenchyma can be ascertained along with appropriate staging of suspected pathology, particularly cirrhosis.

The primary **treatment** of transfusion-related iron overload requires iron chelation using medical therapy. In the United States, 3 chelating agents are approved for use in transfusional iron overload. *Deferoxamine* is administered subcutaneously 5 of 7 nights/wk for 10 hr a night. Deferasirox is taken by mouth daily, and deferiprone is available in tablets taken orally twice a day. The Food and Drug Administration (FDA) approved *deferasirox*, the newest oral chelator, in 2005 for use in patients age ≥2 yr. A pill formulation of deferasirox is available that does not require mixing before oral administration. *Deferiprone* is an older oral chelator that has been widely used outside the United States for many years and was approved by the FDA in 2011, but requires weekly CBC monitoring because of neutropenia risk throughout therapy. Transfusion-related excessive iron stores in children with sickle cell disease should be managed by a physician with expertise in chelation therapy because of the risk of significant toxicity from available chelation therapies.

Other Sickle Cell Syndromes

The most common sickle cell syndromes besides HbSS are HbSC, HbSβ^0 -thalassemia, and HbSβ$^+$ -thalassemia. The other syndromes—HbSD, HbSO^{Arab} , HbSHPFH, HbSE, and other variants—are much less common. Patients with HbSβ^0 -thalassemia have a clinical phenotype similar to those with HbSS. In the red cells of patients with HbSC, crystals of HbC interact with membrane ion transport, dehydrating RBCs and inducing sickling. Children who have HbSC disease can experience the same symptoms and complications as those with severe HbSS disease, but less frequently. Children with HbSC have increased incidence of retinopathy, chronic hypersplenism, and acute splenic sequestration over the life span. The natural history of the other sickle cell syndromes is variable and difficult to predict because of the lack of systematic evaluation.

There is no validated model that can predict the clinical course of an individual with sickle cell disease. A patient with HbSC can have a more severe clinical course than a patient with HbSS. Management of end-organ dysfunction in children with sickle cell syndromes requires the same general principles as managing patients with sickle cell anemia; however, each situation should be managed on a case-by-case basis and requires consultation with a pediatric hematologist.

Anticipatory Guidance

Children with sickle cell disease should receive general health maintenance as recommended for all children, with special attention to disease-specific guidance and infection prevention education. In addition to counseling regarding adherence to penicillin and a vaccination schedule, patients, parents and caregivers should be instructed to seek immediate medical attention for all febrile illness. In addition, early detection of acute splenic sequestration has been shown to decrease mortality. Therefore, parents and caregivers should be educated early and repeatedly about the importance of daily penicillin administration and correct palpation of the spleen.

Prophylactic Penicillin

Children with sickle cell anemia should receive prophylactic oral penicillin VK until at least 5 yr of age (125 mg twice daily up to age 3 yr, then 250 mg twice daily thereafter). No established guidelines exist for penicillin prophylaxis beyond 5 yr of age; some clinicians continue penicillin prophylaxis, and others recommend discontinuation. Continuation of penicillin prophylaxis should be continued beyond 5 yr in children with a history of pneumococcal infection because of the increased risk of a recurrent infection. An alternative for children who are allergic to penicillin is erythromycin ethylsuccinate.

Immunizations

In addition to penicillin prophylaxis, routine childhood immunizations, as well as the annual administration of influenza vaccine, are highly recommended. Children with sickle cell disease develop functional asplenia and also require immunizations to protect against encapsulated organisms, including additional pneumococcal and meningococcal vaccinations. The U.S. Centers for Disease Control and Prevention (CDC) provides vaccination guidelines at https://www.cdc.gov/vaccines/hcp/acip-recs/index.html .

Spleen Palpation

Splenomegaly is a common complication of sickle cell disease, and splenic sequestration can be life threatening. Parents and primary caregivers should be taught how to palpate the spleen to determine if the spleen is enlarging starting at the 1st visit, with reinforcement at subsequent visits. Parents should also demonstrate spleen palpation to the provider.

Transcranial Doppler Ultrasound

Primary stroke prevention using TCD has resulted in a decrease in the prevalence of overt stroke among children with sickle cell anemia. Children with HbSS or HbSβ^0 -thalassemia should be screened annually with TCD starting at age 2 yr. TCD is best performed when the child is quietly awake and in his or her usual state of health. TCD measurements may be falsely elevated or decreased in the settings of acute anemia, sedation, pain, fever, or immediately after blood transfusions. Screening should occur annually from age 2-16 yr. Abnormal values should be repeated within 2-4 wk to identify patients at greatest risk of overt stroke. Conditional values should be repeated within 3 mo, and normal values should be repeated annually. Routine neuroimaging with MRI in asymptomatic patients requires consultation with a pediatric hematologist or neurologist with expertise in sickle cell disease.

Hydroxyurea

Recommendations provided in the 2014 NHLBI Expert Panel Report include offering hydroxyurea therapy to all children with sickle cell anemia starting at 9 mo of age regardless of clinical symptoms. Monitoring children receiving hydroxyurea is labor intensive. Hydroxyurea is a chemotherapeutic agent, and patients receiving this agent require the same level of nursing and physician oversight as any child with cancer receiving chemotherapy. The parents must be educated about the consequences of therapy, and when ill, children should be promptly evaluated. Starting doses should be approximately 20 mg/kg/day. CBC with differential and reticulocyte count should be checked within 4 wk after initiation of therapy or any dose change to monitor for hematologic toxicity, then every 8-12 wk. Dose escalation should be based on clinical and laboratory parameters. If necessary, dose increases should be in 5 mg/kg/day increments to a maximum of 35 mg/kg/day.

While receiving hydroxyurea, steady-state absolute neutrophil count should be approximately 2,000/µL or higher and platelet count should be 80,000/µL or higher. Younger children may tolerate lower absolute neutrophil counts while receiving hydroxyurea. Holding hydroxyurea and adjusting to lower doses may be required for neutropenia and thrombocytopenia. Hydroxyurea is a pregnancy class D medication, and adolescents should be counseled regarding methods to prevent pregnancy while taking this medication. Close monitoring of the patient requires a commitment by the parents and the patient as well as diligence by a physician to identify toxicity early. Information is scarce regarding the impact of hydroxyurea on fertility, although hydroxyurea has been shown to further reduce sperm count in males with sickle cell disease in several case reports, suggesting that this effect may be reversible once hydroxyurea is discontinued.

Red Cell Transfusion Therapy

At the initiation of blood transfusion therapy, children with sickle cell disease should have testing to identify the presence of alloantibodies and RBC phenotyping or genotyping, which is performed to identify the best matched blood. Red cell units selected should be extended antigen-matched for C, E, and K, when feasible. Goals of transfusion for acute events should be established before initiating therapy, including target posttransfusion Hb level and HbS percentage, or both. For children receiving chronic transfusion therapy, pretransfusion HbS goals should be defined; the most common goal is <30%. Posttransfusion Hb values should be targeted to avoid hyperviscosity. Children, parents, and caregivers should be educated about the symptoms of delayed hemolytic transfusion reactions. Any child with sickle cell disease with a recent history of red cell transfusion who presents with pain, dark urine, increased scleral icterus, or symptoms of worsening anemia should be screened for a delayed hemolytic transfusion reaction after consultation with the blood bank. Children meeting criteria for chronic transfusion therapy should receive annual evaluation for transfusion-transmitted infections, including hepatitis B, hepatitis C, and HIV. After receiving 100 mL/kg RBC transfusions, regular assessments of iron overload should begin, usually including measurements of serum ferritin and assessments for hepatic and cardiac iron every 1-2 yr. For children requiring chelation therapy, an audiogram should be performed annually and monitoring of liver function and pituitary function performed regularly because of iron deposition.

Pulmonary and Asthma Screening

Pulmonary complications of sickle cell disease are common and life threatening. Asthma is common in children with sickle cell disease, and thus evaluation for asthma symptoms and asthma risk factors should be performed routinely, particularly given the high morbidity and mortality. All children should receive annual screening for signs and symptoms of lower airway disease, such as nighttime cough and exercise-induced cough. In children with symptoms consistent with lower airway disease, consultation with an asthma specialist should be considered. Pulse oximetry readings should be performed during well visits to identify children with abnormally low daytime oxygen saturation. For children with snoring, daytime somnolence, and symptoms associated with obstructive sleep apnea syndrome (OSAS), sleep studies should be performed as necessary.

Retinopathy

Effective therapy is available for retinopathy associated with sickle cell disease. Although all patients are at risk for development of retinopathy, those with SC are at very high risk. Patients should receive annual screening by an ophthalmologist to identify vascular changes that would benefit from laser therapy. Although changes may occur earlier, children with sickle cell disease should begin annual screening no later than age 10 yr.

Renal Disease

Sickle cell–associated renal disease starts in infancy and may not become clinically evident until adulthood. Chronic kidney disease is common in adults with sickle cell disease, with high morbidity and mortality. Screening protocols for early signs of sickle nephropathy in children have not been adopted due to lack of data. However, when creatinine elevation, microalbuminuria, or macroalbuminuria is detected, a nephrologist should be consulted to determine next steps for further evaluation and possible treatment. The age to begin screening for proteinuria has not been defined, but some experts recommend screening annually after at least 10 yr, if not sooner. If proteinuria is detected, urine studies should be repeated with an early-morning urine collection; if the protein remains elevated, the patient should be referred to a pediatric nephrologist. Males with sickle cell disease should also receive counseling regarding the diagnosis and treatment of priapism. Because of the high frequency of enuresis beyond early childhood, approximately 9% between 18 and 20 yr of age, parents and caregivers should be educated about the prolonged nature of enuresis in this disease. OSAS is associated with an increased prevalence of enuresis in sickle cell disease. Unfortunately, no evidence-based therapies have been developed to treat enuresis in children and young adults with sickle cell disease. In children with enuresis who have symptoms and clinical features of OSAS, referral to specialists for evaluation is recommended.

Echocardiography

Echocardiography is a screening tool to identify individuals with sickle cell disease who have pulmonary artery hypertension. No evidence currently shows that children with sickle cell disease and elevated tricuspid jet velocity >2.5 cm/sec have an increased rate of mortality. Studies in adults with sickle cell disease have found that echocardiography is insensitive at identifying individuals truly at risk for pulmonary hypertension, although an elevated tricuspid velocity measurement may still be a risk factor for premature death in adults with sickle cell disease. The current recommendation is to refer those with severe cardiopulmonary symptoms from associated pulmonary artery hypertension to a pediatric cardiologist for a more formal evaluation.

Additional Screening

Patients with sickle cell disease are at increased risk for behavioral health issues, including anxiety and depression. Screening should be performed at routine and acute visits. Avascular necrosis of the hips and shoulders is increased in patients with sickle cell disease and may be identified early on routine physical exam. Plain radiographs may not detect early disease; thus, when AVN is suspected and plain films are normal, MRI should be obtained. When AVN is confirmed, patients should be referred promptly to orthopedics and physical therapy.

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489.2

Sickle Cell Trait (Hemoglobin AS)

Kim Smith-Whitley

The prevalence of sickle cell trait varies throughout the world; in the United States the incidence is 7–10% of African Americans. Because all state newborn screening programs include sickle cell disease, for most children, sickle cell trait is first identified on their newborn screen. Communication of sickle cell trait status from infancy to young adulthood for the affected individual, family, and healthcare providers is often inconsistent, and many young adults are unaware of their sickle cell trait status.

The production of HbS is influenced by the number of α-thalassemia genes present and the amount of HbS. By definition, among individuals with sickle cell trait, the HbS level is <50%. The life span of people with sickle cell trait is normal, and serious complications are extremely rare. The CBC is within the normal range (Fig. 489.5*B*). Hemoglobin analysis is diagnostic, revealing a predominance of HbA, typically >50%, and HbS <50%. Rare complications of sickle cell trait may exist, but published data do not support this concern, largely because of poorly designed clinical studies. Sickle cell trait is reported to be associated with exertional rhabdomyolysis in military recruits, and possibly with sudden death during rigorous exercise. However, whether these reports establish sickle cell trait as a risk factor that is nonmodifiable by other genetic factors remains unclear. Other complications reported with sickle cell trait include splenic infarction at high altitude, hematuria, hyposthenuria, deep vein thrombosis, and susceptibility to progressive eye injury after hyphema (Table 489.5). Renal medullary carcinoma has been reported almost exclusively in individuals with sickle cell trait and occurs predominantly in young people.

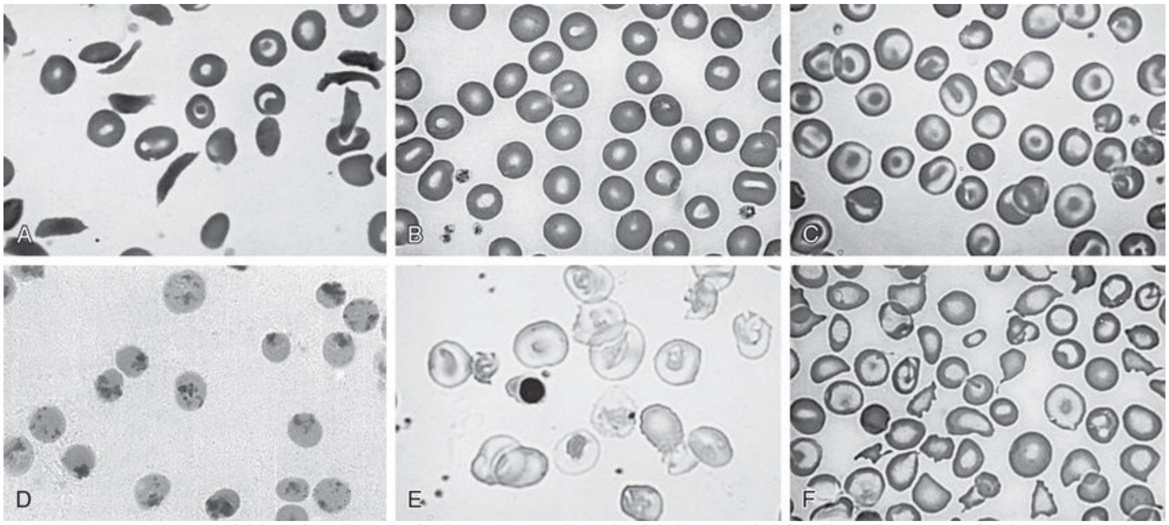

FIG. 489.5 Red blood cell morphology associated with hemoglobin disorders. A, Sickle cell anemia (HbSS): target cells and fixed (irreversibly sickled) cells. B, Sickle cell trait (HbAS): normal red blood cell (RBC) morphology. C, Hemoglobin CC: target cells and occasional spherocytes. D, Congenital Heinz body anemia (unstable hemoglobin): RBCs stained with supravital stain (brilliant cresyl blue) reveal intracellular inclusions. E, Homozygous β^0 -thalassemia: severe hypochromia with deformed RBCs and normoblasts. F, Hemoglobin H disease (α-thalassemia): anisopoikilocytosis with target cells. (Courtesy of Dr. John Bolles, The ASH Collection, University of Washington, Seattle.)

Table 489.5

Complications Reported With Sickle Cell Trait

Definite Associations

Renal medullary cancer
Hematuria
Renal papillary necrosis
Hyposthenuria
Splenic infarction
Exertional rhabdomyolysis
Protection against severe falciparum malaria
Microalbuminuria (adults)

From Tsaras G, Owusu-Ansah A, Boateng O, et al: Complications associated with sickle cell trait: a brief narrative review, *Am J Med* 122:507–512, 2009.

Children with sickle cell trait do not require limitations on physical activities. **Sudden death** in persons with sickle cell trait while exercising under extreme conditions is most likely associated with a 2nd genetic factor and/or environmental factors and not the presence of sickle cell trait itself. However, if **exertional rhabdomyolysis** is identified, evaluation by metabolism and cardiology should be considered. No causal pathway has been implicated for the presence of sickle cell trait and sudden death. All patients with sickle cell trait who participate in rigorous athletic activities should receive maximum hydration and appropriate rest during exertion, as would be the precautionary steps for all athletes, particularly when participating in hot, humid conditions. The presence of sickle cell trait should never be a reason to exclude a person from athletic participation, but rather should serve as an indication that prudent surveillance is necessary to ensure appropriate hydration and prevention of exhaustion from heat or other strenuous exercise. If athletes are to be screened for sickle cell trait, the appropriate procedure is testing using a hemoglobin electrophoresis followed by genetic counseling, along with the knowledge that genetic information may provide opportunities to challenge paternity. Such situations are typically handled by a pediatrician or hematologist accustomed to providing both a balanced approach to genetic counseling and addressing the challenges about paternity.

Bibliography

Nelson DA, Deuster PA, Carter IIIR, et al. Sickle cell trait, rhabdomyolysis, and mortality among US army soldiers. *N Engl J Med* . 2016;375(5):425–442.

489.3

Other Hemoglobinopathies

Kim Smith-Whitley

Hemoglobin C

The mutation for HbC is at the same site as in HbS, with substitution of lysine instead of valine for glutamine. In the United States, hemoglobin C trait (**HbAC**) occurs in 1 : 40 and homozygous hemoglobin C disease (**HbCC**) occurs in 1 : 5,000 African Americans. HbAC is asymptomatic. HbCC can result in mild anemia, splenomegaly, and cholelithiasis; rare cases of spontaneous splenic rupture have been reported. Splenic dysfunction does not occur. This condition is usually diagnosed through newborn screening programs. HbC crystallizes, disrupting the red cell membrane, and HbC crystals may be visible on peripheral smear (see Fig. 489.5*C*).

Hemoglobin E

HbE is an abnormal hemoglobin resulting from a qualitative mutation in the β-globin gene and is the 2nd most common globin mutation worldwide. Patients may have asymptomatic hemoglobin E trait (**HbAE**) or benign homozygous hemoglobin E disease (**HbEE**). Compound heterozygous hemoglobin E/β-thalassemia produces clinical phenotypes ranging from moderate to severe anemia, depending on the β-thalassemia mutation. In California, HbE/β-thalassemia is found almost exclusively in persons of Southeast Asian descent, with a prevalence of 1 : 2,600 births.

Hemoglobin D

At least 16 variants of HbD exist. HbD-Punjab (Los Angeles) is a rare hemoglobin that is seen in 1-3% of Western Indians and in some Europeans with Asian-Indian ancestry and produces symptoms of sickle cell disease when present in combination with HbS. Heterozygous HbD or hemoglobin D trait (**HbAD**) is clinically silent. Homozygous hemoglobin D disease (**HbDD**) produces a mild to moderate anemia with splenomegaly.

489.4

Unstable Hemoglobin Disorders

Kim Smith-Whitley

At least 200 rare unstable hemoglobins have been identified; the most common is **Hb Köln** . Most patients seem to have de novo mutations rather than inherited hemoglobin disorders. The best-studied unstable hemoglobins are the ones leading to hemoglobin denaturation from mutations affecting heme binding. The denatured hemoglobin can be visualized during severe hemolysis or after splenectomy as **Heinz bodies** . Unlike the Heinz bodies seen after toxic exposure, in unstable hemoglobins, Heinz bodies are present in reticulocytes and older RBCs (see Fig. 489.5*D*). Heterozygotes are asymptomatic.

Children with homozygous gene mutations can present in early childhood with anemia and splenomegaly or with unexplained hemolytic anemia. Hemolysis is increased with febrile illness and with the ingestion of oxidant medications (similar to glucose-6-phosphate dehydrogenase [G6PD] deficiency [see Chapter 490.3]) with some unstable hemoglobins. If the spleen is functional, the blood smear can appear almost normal or have only hypochromasia and basophilic stippling. A diagnosis may be made by demonstrating Heinz bodies, Hb instability, or an abnormal Hb analysis (although some unstable hemoglobins have normal mobility and are not detected on Hb analysis).

Treatment is supportive. Transfusion may be required during hemolytic episodes in severe cases. Oxidative drugs should be avoided, and folate supplementation may be helpful if dietary deficiency is a concern. Splenectomy may be considered in patients requiring recurrent transfusion or demonstrating poor growth, but the complications of splenectomy, including bacterial sepsis, risk of thrombosis, and risk of developing pulmonary hypertension, should be considered before surgery.

489.5

Abnormal Hemoglobins With Increased Oxygen Affinity

Kim Smith-Whitley

More than 110 high-affinity hemoglobins have been characterized. These mutations affect the state of Hb configuration during oxygenation and deoxygenation. Hemoglobin changes structure when in the oxygenated vs the deoxygenated state. The deoxygenated state is termed the **T (tense) state** and is stabilized by 2,3-diphosphoglycerate. When fully oxygenated, hemoglobin assumes the **R (relaxed) state** . The exact molecular interactions between these 2 states are unknown. High-affinity hemoglobins contain mutations that either stabilize the R form or destabilize the T form. The interactions between the R and T forms are complex, and the mechanisms of the mutations are not known. In most cases, the high-affinity hemoglobins can be identified by Hb analysis; approximately 20% must be characterized under controlled conditions where measurements are obtained with the P_{50} lowered to 9-21 mm Hg (normal: 23-29 mm Hg). The decreased P_{50} in these hemoglobins leads to an erythrocytosis with Hb levels of 17-20 g/dL. Levels of erythropoietin and 2,3-DPG are normal. Patients are usually asymptomatic and do not need phlebotomy. If phlebotomy is performed, oxygen delivery could be problematic because of the reduced number of Hb molecules to carry oxygen.

489.6

Abnormal Hemoglobins Causing Cyanosis

Kim Smith-Whitley

Abnormal hemoglobins causing cyanosis, also called **structural methemoglobinemias** , are rare. They are referred to as **M hemoglobins** and represent a group of hemoglobin variants that result from point mutations in one of the globin chains, α, β, or γ, located in the heme pocket; 13 known variants exist. These unstable hemoglobins lead to hemolytic anemia, most pronounced when the β-globin gene is affected. Clinically, these children are cyanotic from birth, without other signs or symptoms of disease, if the mutation is in the **α-globin** gene (HbM Boston, HbM Iwate, Hb Auckland). Infants with **β-globin** mutations become cyanotic later in infancy after the fetal hemoglobin switch (HbM Saskatoon, HbM Chile, HbM Milwaukee 1 and 2). The **γ-chain** mutations (HbF-M Fort Ripley, HbF-M Osaka, HbF Cincinnati, HbF Circleville, HbF Toms River, HbF Viseu) are all transient, presenting with cyanosis at birth, which resolves during the neonatal period after HbF production discontinues.

The abnormal M hemoglobins exhibit autosomal dominant inheritance and are diagnosed by Hb analysis. HbM variants may not be isolated reliably using Hb analysis (HPLC or IEF); consequently, diagnostic confirmation may require DNA sequencing or mass spectrometry. There is no specific treatment, and affected patients do not respond to treatments used for *enzyme-deficient* methemoglobinemia. Beyond cyanosis, individuals are otherwise asymptomatic and do not require additional monitoring. Children with the β-globin form should avoid oxidant drugs. Individuals with all forms have a normal life expectancy and pregnancy course.

Low-affinity hemoglobins have less cyanosis than the M hemoglobins. The amino acid substitutions destabilize the oxyhemoglobin and lead to decreased oxygen saturation. The best characterized are Hb Kansas, Hb Beth Israel, and Hb Denver. Hb analysis (IEF and HPLC techniques) may be normal in affected individuals. When clinically suspected, oxygen affinity studies reveal a right-shifted dissociation curve, and heat testing demonstrates unstable hemoglobin. Children present with mild cyanosis only.

489.7

Hereditary Methemoglobinemia

Kim Smith-Whitley

Hereditary methemoglobinemia is a clinical syndrome caused by an increase in the serum concentration of methemoglobin either as a result of congenital changes in hemoglobin synthesis or of metabolism leading to imbalances in reduction and oxidation of hemoglobin. The iron molecule in hemoglobin is normally in the ferrous state (Fe^{2+}), which is essential for oxygen transport. Under physiologic conditions there is a slow, constant loss of electrons to released oxygen, and the ferric (Fe^{3+}) form combines with water, producing **methemoglobin (MetHb)** . The newly formed MetHb has a reduced ability to bind oxygen.

Two pathways for MetHb reduction exist. The physiologic and predominant pathway is a reduced form of nicotinamide adenine dinucleotide (NADH)–dependent reaction catalyzed by cytochrome b5 reductase. This mechanism is >100-fold more efficient than the production of MetHb. The alternate pathway utilizes NAD phosphate generated by G6PD in the hexose monophosphate shunt and requires an extrinsic electron acceptor to be activated (i.e., methylene blue, ascorbic acid, riboflavin). In normal individuals, oxidation of hemoglobin to MetHb occurs at a slow rate, 0.5–3%, which is countered by MetHb reduction to maintain a steady state of 1% MetHb.

MetHb may be increased in the RBC because of exposure to toxic substances or to absence of reductive pathways, such as NADH-cytochrome b5 reductase deficiency. **Toxic methemoglobinemia** is much more common than hereditary methemoglobinemia (Table 489.6). Infants are exceptionally vulnerable to hemoglobin oxidation because their erythrocytes have half the amount of cytochrome b5 reductase seen in adults, fetal hemoglobin is more susceptible to oxidation than hemoglobin A, and the more alkaline infant gastrointestinal tract promotes the growth of nitrite-producing gram-negative bacteria. When MetHb levels are >1.5 g/24 hr, cyanosis is visible (15% MetHb); a level of 70% MetHb is lethal. The MetHb level is usually reported as a percentage of normal hemoglobin, and the toxic level is lower at a lower Hb level. Methemoglobinemia has been described in infants who ingested foods and water high in **nitrates** , who were exposed to aniline teething gels or other chemicals, and in some infants with severe gastroenteritis and acidosis. Methemoglobin can color the blood brown (Fig. 489.6). A patient with significant methemoglobinemia is cyanotic and does not respond to 100% oxygen. Arterial oxygen tension will be normal or elevated despite cyanosis, but blood oxygen saturation determined by multiwavelength co-oximetry will be low. Oxygen saturation calculated from arterial blood gas or pulse oximetry is misleading and inaccurate. Although pulse oximetry is usually lower than normal, it does not reflect the true degree of desaturation.

Table 489.6

Known Etiologies of Acquired Methemoglobinemia

Medications

Benzocaine
Chloroquine
Dapsone
EMLA (eutectic mixture of local anesthetics) topical anesthetic (lidocaine 2.5% and prilocaine 2.5%)
Flutamide
Lidocaine
Metoclopramide
Nitrates
Nitric oxide
Nitroglycerin
Nitroprusside
Nitrous oxide
Phenazopyridine
Prilocaine
Primaquine
Riluzole
Silver nitrate
Sodium nitrate
Sulfonamides

Medical Conditions

Pediatric gastrointestinal infection, sepsis
Recreational drug overdose with amyl nitrate (“poppers”)
Sickle cell disease–related painful episode

Miscellaneous

Aniline dyes
Fume inhalation (automobile exhaust, burning of wood and plastics)
Herbicides
Industrial chemicals: nitrobenzene, nitroethane (found in nail polish, resins, rubber adhesives)
Pesticides
Gasoline octane booster

From Ash-Bernal R, Wise R, Wright SM: Acquired methemoglobinemia, *Medicine (Baltimore)* 83:265–273, 2004.

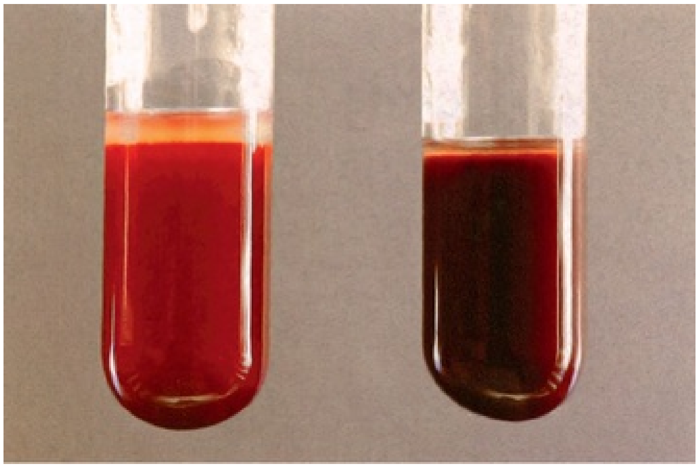

FIG. 489.6 Normal arterial blood vs methemoglobinemia. Arterial whole blood with 1% methemoglobin *(left)* vs arterial whole blood with 72% methemoglobin *(right).* Note the characteristic chocolate-brown color of the sample with an elevated methemoglobin level. Both samples were briefly exposed to 100% oxygen and shaken. This quick analysis is a good bedside test for methemoglobinemia. The sample on the *left* turned bright red, whereas the sample on the *right* remained chocolate-brown. *Methods:* Whole blood samples were drawn at the same time from the same person. The measured hemoglobin concentration was 11.7 g/dL. Calculated concentration of methemoglobin: 11.7 g/dL × 0.01 = 0.117 g/dL *(left)* and 11.7 g/dL × 0.72 = 8.42 g/dL *(right)* . An elevated methemoglobin level was made in vitro by adding 0.1 mL of a 0.144 molar solution of sodium nitrate *(right),* and 0.1 mL of normal saline was added as a control *(left).* Cooximetry measurements were taken on both samples shortly after the blood was drawn and 20 min after the addition of sodium nitrate solution. Both blood

samples were exposed to 100% oxygen before the 2nd measurement. ***(Protocol based on personal communication with Dr. Ali Mansouri, December 2002.)***

489.8

Hereditary Methemoglobinemia With Deficiency of NADH Cytochrome b5 Reductase

Kim Smith-Whitley

The first reported inherited disorder causing methemoglobinemia resulted from an enzymatic deficiency of NADH cytochrome b5 reductase, which was classified into 2 distinct phenotypes. **In type I** , the most common form, the deficiency of NADH cytochrome b5 activity is found only in erythrocytes, with other cell types unaffected. In **type II** the enzyme deficiency is present in all tissues and results in more significant symptoms beginning in infancy with encephalopathy, intellectual impairment, spasticity, microcephaly, and growth retardation, with death most often by 2 yr of age. Both types exhibit an autosomal recessive inheritance pattern.

Cyanosis varies in intensity with season and diet. The time of cyanosis onset also varies, appearing in some patients at birth and others as late as adolescence. Although as much as 50% of the total circulating hemoglobin may be in the form of nonfunctional MetHb, little or no cardiorespiratory distress occurs in these patients, except on exertion.

Daily oral treatment with *ascorbic acid* (200-500 mg/day in divided doses) gradually reduces the MetHb to approximately 10% of the total pigment and alleviates the cyanosis as long as therapy is continued. Chronic high doses of ascorbic acid have been associated with hyperoxaluria and renal stone formation. Ascorbic acid should not be used to treat *toxic* methemoglobinemia. When immediately available, poison control should be contacted to verify the most up-to-date therapeutic strategies. As with ascorbic acid, *riboflavin* uses the alternate pathway of MetHb reduction and is most effective when given in high doses (400 mg once daily). *Methylene blue* , administered intravenously (1-2 mg/kg initially), is used to treat toxic methemoglobinemia. An oral dose can be administered (100-300 mg/day) as maintenance therapy.

Methylene blue should not be used in patients with G6PD deficiency. This treatment is ineffective and can cause severe oxidative hemolysis. If methylene blue is given to a patient with G6PD deficiency, symptoms will not improve, and marked hemolysis has been reported within 24 hr of administration. Because G6PD deficiency status is rarely known at the time of treatment, a careful history should be elicited. When the history is negative for symptoms of G6PD deficiency, treatment with methylene blue should be initiated judiciously, and the patient should be closely monitored for improvement.

489.9

Syndromes of Hereditary Persistence of Fetal Hemoglobin

Kim Smith-Whitley

Hereditary persistence of fetal hemoglobin (**HPFH**) syndromes are a form of thalassemia; mutations are associated with a decrease in the production of either or both β- and δ-globins. There is an imbalance in the α:non-α synthetic ratio characteristic of thalassemia. More than 20 variants of HPFH have been described. They are deletional, $\delta\beta^0$ (Black, Ghanaian, Italian), nondeletional (Tunisian, Japanese, Australian), linked to the β-globin–gene cluster (British, Italian-Chinese, Black), or unlinked to the β-globin–gene cluster (Atlanta, Czech, Seattle). The $\delta\beta^0$ forms have deletions of the entire δ- and β-globin gene sequences, and the most common form in the United States is the Black (**HPFH 1**) variant. As a result of the δ and β gene deletions, there is production only of γ-globin and formation of HbF. In the homozygous form, no manifestations of thalassemia are present. There is only HbF with very mild anemia and slight microcytosis. When inherited with other variant hemoglobins, HbF is elevated into the 20–30% range; when inherited with HbS, sickle cell disease is ameliorated, with fewer complications.

489.10

Thalassemia Syndromes

Janet L. Kwiatkowski

Thalassemia refers to a group of genetic disorders of globin-chain production in which there is an imbalance between the α-globin and β-globin chain production. **β-Thalassemia** syndromes result from a decrease in β-globin chains, which results in a relative excess of α-globin chains. **β^0 -thalassemia** refers to the absence of production of the β-globin. When patients are homozygous for the β^0 -thalassemia gene, they cannot make any normal β-globin chains (HbA). **β^+ -thalassemia** indicates a mutation that makes decreased amounts of normal β-globin (HbA). β^0 -thalassemia syndromes are generally more severe than β^+ -thalassemia syndromes, but there is significant variability between the genotype and phenotype. β-thalassemia *major* , or transfusion-dependent thalassemia, refers to severe β-thalassemia that requires early transfusion therapy. β-thalassemia *intermedia* (or non–transfusion dependent) is a clinical diagnosis of a patient with a less severe clinical phenotype that usually does not require regular transfusion therapy in childhood. Many of these patients have at least 1 β^+ -thalassemia mutation. β-thalassemia syndromes usually require a β-thalassemia mutation in both β-globin genes. Carriers with a single β-globin mutation are generally asymptomatic, except for microcytosis and mild anemia.

In **α-thalassemia** , there is an absence or reduction in α-globin production usually due to deletions of α-globin genes. Normal individuals have 4 α-globin genes; the more genes affected, the more severe the disease. **α^0 -thalassemia** indicates no α-chains produced from that chromosome (− −/). **α^+ -thalassemia** produces a decreased amount of α-globin chain from that chromosome (-alpha/).

The primary pathology in the thalassemia syndromes stems from the *quantity* of globin produced, whereas the primary pathology in sickle cell disease is related to the *quality* of β-globin produced.

Epidemiology

There are >200 different mutations resulting in absent or decreased globin production. Although most are rare, the 20 most common abnormal alleles constitute 80% of the known thalassemias worldwide; 3% of the world's population carries alleles for β-thalassemia, and in Southeast Asia 5–10% of the population carry alleles for α-thalassemia. In a particular region, there are fewer common alleles. In the United States, an estimated 2,000 persons have β-thalassemia major.

Pathophysiology

Two related features contribute to the sequelae of **β-thalassemia syndromes** : inadequate β-globin gene production leading to decreased levels of normal hemoglobin (HbA) and unbalanced α- and β-globin chain production leading to ineffective erythropoiesis. In β-thalassemia α-globin chains are in excess to non–α-globin chains, and α-globin tetramers (α_4) are formed and appear as RBC inclusions. The free α-globin chains and inclusions are very unstable, precipitate in RBC precursors, damage the RBC membrane, and shorten RBC survival, leading to anemia and increased erythroid production (Table 489.7). This results in a marked increase in erythropoiesis, with early erythroid precursor death in the bone marrow. Clinically, this is characterized by a lack of maturation of erythrocytes and an inappropriately low reticulocyte count. This ineffective erythropoiesis and the compensatory massive marrow expansion with erythroid hyperactivity characterize β-thalassemia. Due to the low or absent production of β-globin, the α-chains combine with γ-chains, resulting in HbF ($\alpha_2 \gamma_2$) being the dominant hemoglobin. In addition to the natural survival effect, the γ-globin chains may be produced in increased amounts, regulated by genetic polymorphisms. The δ-chain synthesis is not usually affected in β-thalassemia or β-thalassemia trait, and therefore patients have a relative or absolute increase in HbA_2 production ($\alpha_2 \delta_2$).

Table 489.7

The Thalassemias

THALASSEMIA	GLOBIN GENOTYPE	RED BLOOD CELL FEATURES	CLINICAL FEATURES	HEMOGLOBIN ANALYSIS
α-Thalassemia				
1 Gene deletion	−,α/α,α	Normal	Normal	Newborn: Bart: 1–2%
2 Gene deletion (α-thalassemia trait)	−,α/−,α −, −/α,α	Microcytosis, mild hypochromasia	Normal, mild anemia	Newborn: Bart: 5–10%
3 Gene deletion hemoglobin H	−,−/−,α	Microcytosis, hypochromic	Mild anemia, transfusions not required	Newborn: Bart: 20–30%
2 Gene deletion + Constant Spring	$-,-/\alpha,\alpha^{\text{Constant Spring}}$	Microcytosis, hypochromic	Moderate to severe anemia, transfusion, splenectomy.	2–3% Constant Spring, 10–15% HbH
4 Gene deletion	−,−/−,−	Anisocytosis, poikilocytosis	Hydrops fetalis	Newborn: 89–90% Bart with Gower-1, Gower-2, and Portland
Nondeletional	$\alpha,\alpha/\alpha,\alpha^{\text{variant}}$	Microcytosis, mild anemia	Normal	1–2% variant hemoglobin
β-Thalassemia				
β^0 or β^+ heterozygote: trait	β^0 /A,β^+ /A	Variable microcytosis, mild anemia	Normal	Elevated A_2 , variable elevation of F
β^0 or β^+ - Thalassemia severe	β^0 /β^0 , β^+ /β^0 , β^+ β^+ E/β^0	Microcytosis, nucleated RBC	Transfusion dependent	F 98% and A_2 2%, E 30–40% (E/β^0); variably low Hb A with β^+
β^0 or β^+ thalassemia intermedia		Hyopchromic, microcytosis	Mild to moderate anemia, intermittent transfusions	A_2 2–5%, F 10–30%, Hb A variably low levels
Dominant (rare)	B^0 /A	Microcytosis, abnormal RBCs	Moderately severe anemia, splenomegaly	Elevated F and A_2
δ-Thalassemia	A/A	Normal	Normal	A_2 absent
$(\delta\beta)^0$ - Thalassemia	$(\delta\beta)^0$ /A	Hypochromic	Mild anemia	F 5–20%
$(\delta\beta)^+$ - Thalassemia Lepore	β^{Lepore} /A	Microcytosis	Mild anemia	Lepore 8–20%
Homozygous Hb Lepore	β^{Lepore} / β^{Lepore}	Microcytic, hypochromic	Thalassemia intermedia	F 80%, Lepore 20%
γδβ-Thalassemia	$(\gamma^A\ \delta\beta)^{0/}$ A	Microcytosis, microcytic, hypochromic	Moderate anemia, splenomegaly, homozygote: thalassemia intermedia	Decreased F and A_2 compared with δβ-thalassemia
γ-Thalassemia	$(\gamma^A\ \gamma^G)^0$ /A	Microcytosis	Insignificant unless homozygote	Decreased F

In the **α-thalassemia syndromes** , there is a reduction in α-globin production. Normally, there are 4 α-globin genes (2 from each parent) that control α-globin production. α-thalassemia syndromes vary from complete absence (hydrops fetalis) to only slightly reduced (α-thalassemia silent carrier) α-globin production. In the α-thalassemia syndromes, an excess of β- and γ-globin chains are produced. These excess chains form **Bart hemoglobin (γ_4)** in fetal life and **HbH** (β_4) after birth. These abnormal tetramers are nonfunctional hemoglobins with very high oxygen affinity. They do not transport oxygen and result in extravascular hemolysis. A fetus with the most severe form of α-thalassemia (**hydrops fetalis**) develops in utero anemia and the pregnancy usually results in fetal loss because HbF production requires sufficient amounts of α-globin. In contrast, infants with β-thalassemia major become symptomatic only after birth when HbA predominates and insufficient β-globin production manifests in clinical symptoms.

Homozygous β-Thalassemia (Thalassemia Major, Cooley Anemia)

Clinical Manifestations

If not treated, children with homozygous β^0 -thalassemia usually become symptomatic from progressive anemia, with profound weakness and cardiac decompensation during the 2nd 6 mo of life. Depending on the mutation and degree of HbF production, regular transfusions are necessary beginning in the 2nd mo to 2nd yr of life, but rarely later. The decision to transfuse is multifactorial but is not determined solely by the degree of anemia. The presence of signs of ineffective erythropoiesis, such as growth failure, bone deformities secondary to marrow expansion, and hepatosplenomegaly, are important variables in determining transfusion initiation.

The classic presentation of children with severe disease includes *thalassemic facies* (maxilla hyperplasia, flat nasal bridge, frontal bossing), pathologic bone fractures, marked hepatosplenomegaly, and cachexia and is primarily seen in countries without access to chronic transfusion therapy. Occasionally, patients with moderate anemia develop these features because of severe compensatory, ineffective erythropoiesis.

In nontransfused patients with severe ineffective erythropoiesis, marked **splenomegaly** can develop with hypersplenism and abdominal symptoms. The features of ineffective erythropoiesis include expanded medullary spaces (with massive expansion of the marrow of the face and skull), extramedullary hematopoiesis, and higher metabolic needs (Fig. 489.7). The chronic anemia and increased erythroid drive produce an increase in iron absorption from the gastrointestinal tract and secondary hemosiderosis-induced organ injury.

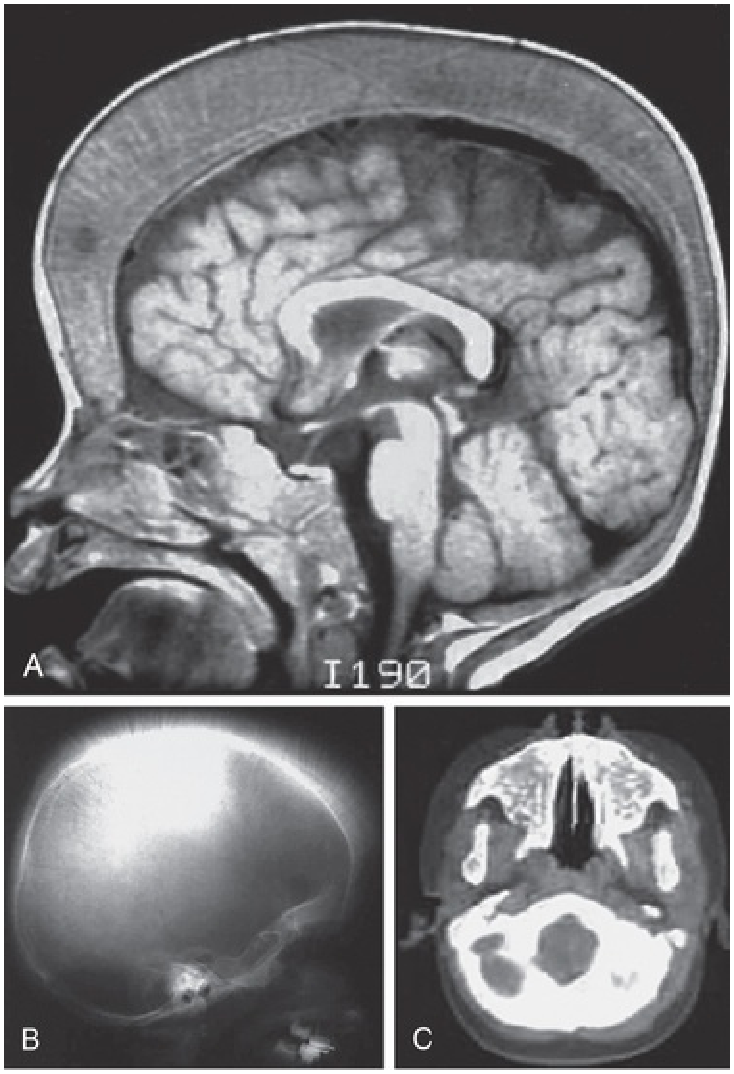

FIG. 489.7 Ineffective erythropoiesis in 3 yr old patient who has β-thalassemia major and has not received a transfusion. A, Massive widening of the diploic spaces of the skull as seen on MRI. B, Radiographic appearance of the trabeculae as seen on plain radiograph. C, Obliteration of the maxillary sinuses with hematopoietic tissue as seen on CT scan.

Chronic transfusion therapy dramatically improves the quality of life and reduces the complications of severe thalassemia. Transfusion-induced **hemosiderosis** becomes the major clinical complication of transfusion-dependent thalassemia. Each mL of packed red cells contains approximately 1 mg of iron. Physiologically, there is no mechanism to eliminate excess body iron. Iron is initially deposited in the liver and is followed by deposition in the endocrine organs and the heart. This leads to a high rate of hypothyroidism, hypogonadotrophic gonadism, growth hormone deficiency, hypoparathyroidism, and diabetes mellitus. Iron deposition in the heart causes heart failure and arrhythmias, and heart disease is the leading cause of death in inadequately chelated patients. Eventually, most patients not receiving adequate iron chelation therapy die from cardiac failure or cardiac arrhythmias secondary to hemosiderosis. Hemosiderosis-induced morbidity can be prevented by adequate iron chelation therapy.

Laboratory Findings

In the United States, some children with β-thalassemia major will be identified on newborn screening as a result of the detection of only HbF on hemoglobin electrophoresis. However, infants with β^+ mutations might be missed on newborn screen if small amounts of hemoglobin A are present. A hemoglobin FE pattern can be consistent with hemoglobin E β^0 -thalassemia, or the more benign hemoglobin EE disease, and needs to be followed up. The lack of standardized neonatal diagnosis of thalassemia disorders requires close follow-up of newborns with unclear thalassemia mutations and babies from high-risk ethnic groups.

Infants with serious β-thalassemia disorders have a progressive anemia after the newborn period. Microcytosis, hypochromia, and targeting characterize the RBCs. Nucleated RBCs, marked anisopoikilocytosis, and a relative reticulocytopenia are typically seen (see Fig. 489.5*E*). The Hb level falls progressively often to <6 g/dL unless transfusions are given. The reticulocyte count is commonly <8% and is inappropriately low compared to the degree of anemia caused by ineffective erythropoiesis. The unconjugated serum bilirubin level is usually elevated, but other chemistries may be initially normal. Even if the child does not receive transfusions, iron eventually accumulates with elevated serum ferritin and transferrin saturation. Evidence of bone marrow hyperplasia can be seen on radiographs (see Fig. 489.7).

Early definitive diagnosis is recommended. Newborn screening techniques such as hemoglobin electrophoresis is not definitive. DNA diagnosis of the β-thalassemia mutations, along with testing for common genetic modifiers of the clinical phenotype, is recommended. Co-inheritance of 1 or more α-thalassemia deletions is common, and it decreases the severity of the β-thalassemia disease as it improves the α:β chain imbalance. Some patients' mutations cannot be diagnosed by standard electrophoresis or common DNA probes. Referral of the samples to a tertiary laboratory is indicated, along with parental and family testing. Following the definitive diagnosis, families should undergo detailed counseling.

Management and Treatment of Thalassemia

Transfusion Therapy

β-thalassemia major is a clinical diagnosis that requires the integration of laboratory findings and clinical features. Of patients with homozygous β^0 -thalassemia (the most severe mutations), 15–20% may have a clinical course that is phenotypically consistent with thalassemia intermedia. In contrast, 25% of patients with homozygous β^+ -thalassemia, typically a more benign genotype, may have transfusion-dependent thalassemia. Transient clinical events, such as a sudden fall in hemoglobin secondary to an episode of parvovirus requiring transfusion, do not necessarily indicate a transfusion-dependent patient. The long-term observation of the clinical characteristics, such as growth, bony changes, and hemoglobin, are necessary to determine chronic transfusion therapy.

Guidelines for Transfusion Therapy.

Patients who require transfusion therapy should have an extended red cell phenotype and/or genotype. Patients should receive RBCs depleted of leukocytes and matched for D, C, c, E, e, and Kell antigens at a minimum. Cytomegalovirus-safe units are indicated in stem cell transplantation candidates. Transfusions should generally be given at intervals of 3-4 wk, with the goal being to maintain a pretransfusion Hb level of 9.5-10.5 g/dL. Ongoing monitoring for transfusion-associated transmitted infections (hepatitis A, B, and C, HIV), alloimmunization, annual blood transfusion requirements, and transfusion reactions is essential.

Iron Overload Monitoring

Excessive iron stores from transfusion cause many of the complications of β-thalassemia major. Accurate assessment of excessive iron stores is essential to optimal therapy. Serial serum ferritin levels provide a useful screening technique in assessing iron balance trends, but results may not accurately predict quantitative iron stores. Undertreatment or overtreatment of presumed excessive iron stores can occur in managing a patient based on serum ferritin alone. Quantitative measurement of liver iron and cardiac iron by magnetic resonance imaging are standard noninvasive methods to measure tissue iron overload; estimation of pancreatic and gonadal iron is being studied. This technology, along with access to multiple chelators, enable targeted chelation therapy for patients with organ-specific hemosiderosis before the onset of overt organ failure. Integration of these imaging technologies with chelation therapy may prevent heart failure, diabetes, and other organ dysfunction.

Quantitative liver iron by approved R2 or R2* MRI is the best indicator of total body iron stores and should be obtained in patients after chronic transfusion therapy has been initiated. The liver iron results will help guide the chelation regimen. Quantitative cardiac iron, determined by T2* MRI cardiac software, is usually obtained starting at 10 yr old, but should be obtained earlier in the setting of severe iron overload or if the transfusion and chelation history is not known. There may be a discrepancy between the liver iron and the heart iron because of different rates of tissue loading and unloading and the differential effects of iron chelators on organ-specific iron removal.

Chelation Therapy

Iron-chelation therapy should start as soon as the patient becomes significantly iron-overloaded. In general, this occurs after 1 yr of transfusion therapy and correlates with the serum ferritin >1,000 ng/mL and/or a liver iron concentration of >5,000 µg/g dry weight. Iron chelation is not currently labeled for use in children <2 yr.

There are 3 available iron chelators (deferoxamine, deferasirox, and deferiprone); each varies in its route of administration, pharmacokinetics, adverse events, and efficacy. Combination chelation therapy may be required for high iron burden. The overall goal is to prevent hemosiderosis-induced tissue injury and avoid chelation toxicity. This requires close monitoring of the patients. In general, chelation toxicity increases as iron stores decrease.

Deferoxamine (Desferal) is the most studied iron chelator; it has an excellent safety and efficacy profile. It requires subcutaneous or IV administration because of its poor oral bioavailability and short half-life of <30 min, necessitating administration as a continuous infusion over at least 8 hr daily, 5-7 days/wk. Deferoxamine is initially started at 25 mg/kg and can be increased to 60 mg/kg in heavily iron-overloaded patients. The major problem with deferoxamine is poor adherence because of the difficult, time-consuming route of administration. Adverse side effects include local skin reactions, ototoxicity, retinal changes, and bone dysplasia with truncal shortening.

The *oral* iron chelator **deferasirox** (Exjade, JadeNu) is commercially available in the United States. Of patients treated with deferoxamine, 70% have switched to deferasirox because it is orally available. Deferasirox has a half-life of >16 hr and requires once-daily administration. Two forms of the drug are available, a dispersible tablet that is dissolved in water or juice and a film-coated tablet. A granule form that is sprinkled on soft food and ingested recently was FDA approved. Dosing is different for the different deferasirox formulations. For the dispersible tablet form (Exjade), the initial dose typically is 20 mg/kg/day and can be escalated to as high as 40 mg/kg/day based on the iron burden. The dosing for the film-coated tablet and granule (JadeNu) forms is 30% lower than the dispersible tablet, with a starting dose of 14 mg/kg/day, which can be escalated to a maximum of 28 mg/kg/day. The most common side effects are gastrointestinal (GI) symptoms, which may be lessened with the film-coated tablet form because it does not contain lactose and sodium laureate, which are found in the dispersible tablet and are thought to be responsible for some of the GI symptoms. The most serious side effect of deferasirox is potential kidney damage. Up to 30% of patients have transient increases in creatinine that may require temporary modifications of dosing. This toxicity may occur more commonly in the setting of dehydration. Long-term studies in thousands of patients have not demonstrated progressive renal dysfunction, but isolated cases of renal failure in patients have occurred. In addition, hepatic transaminitis may occur, with an increase to >5 times the upper limit of normal in approximately 8% of patients. All patients require monthly chemistry panels and ongoing monitoring for proteinuria.

Deferiprone (Ferriprox), an oral iron chelator, is approved in the United States for use as a second-line agent. Deferiprone has a half-life of approximately 3 hr and requires dosing 3 times daily. The starting dose is 75 mg/kg/day and can be escalated to 99 mg/kg/day based on the degree of iron overload. Deferiprone, a small molecule, effectively enters cardiac tissue and may be more effective than other chelators in reducing cardiac hemosiderosis. The most serious side effect of deferiprone is transient agranulocytosis, which occurs in 1% of patients and usually in the 1st yr of treatment. It has been associated with rare deaths where patients were not adequately monitored. The use of deferiprone requires frequent blood count monitoring, typically weekly for at least the 1st yr of therapy. Most importantly, the drug should be held and the neutrophil count checked with all febrile illnesses.

As thalassemia patients live longer, the iron chelation goals have changed. Aggressive treatment with combination chelation therapy is often used in heavily iron-overloaded patients to prevent or reverse organ dysfunction. Deferoxamine, in combination with deferiprone, is routinely used in patients with increased cardiac iron. Combination therapy of deferoxamine and deferasirox or deferasirox and deferiprone may also be efficacious in patients with severe iron overload.

Hydroxyurea

Hydroxyurea, a DNA antimetabolite, increases HbF production. It has been most successfully used in sickle cell disease and in some patients with β-thalassemia intermedia. Studies in β-thalassemia major are limited. In many parts of the world, hydroxyurea therapy is used in β-thalassemia intermedia patients. Even though increases in HbF levels are observed, they do not predictively correlate with increase in total Hb in these patients. In general, there appears to be a mean increase in Hb of 1 g/dL (range: 0.1-2.5 g/dL). Hydroxyurea therapy in thalassemia intermedia is associated with a reduced risk of leg ulcers, pulmonary hypertension, and extramedullary hematopoiesis. The initial starting dose for thalassemia intermedia is 10 mg/kg and may be escalated to 20 mg/kg/day. Patients with β-thalassemia are at increased risk of developing cytopenias with hydroxyurea use, which may prevent dose escalation. Close monitoring of the CBC with differential is required.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation has cured >3,000 patients who had β-thalassemia major. In low-risk HLA-matched sibling patients, there is at least a 90% survival and an 80% event-free survival. In general, myeloablative conditioning regimens have been used to prevent graft rejection and thalassemia recurrence. Most success has been in children <14 yr old without excessive iron stores and hepatomegaly who undergo sibling HLA-matched allogeneic transplantation. All children who have an HLA-matched sibling should be offered the option of bone marrow transplantation. Alternative transplantation regimens for patients without appropriate donors are experimental and have variable success. Gene therapy approaches are under study, and early results with lentiviral vectors have been promising, particularly for patients with β^+ - or HbE β-thalassemia genotypes.

Splenectomy

Splenectomy may be required in thalassemia patients who develop hypersplenism. These patients have a falling steady-state Hb level and/or a rising transfusion requirement. However, splenectomy is less frequently used as a therapeutic option; serious adverse effects of splenectomy are increasingly recognized beyond infection risk. In thalassemia intermedia, splenectomized patients have a marked increased risk of venous thrombosis, pulmonary hypertension, leg ulcers, and silent cerebral infarction compared to nonsplenectomized patients. All patients should be fully immunized against encapsulated bacteria and receive appropriate instructions regarding fever management. Prophylactic penicillin should be administered after splenectomy to prevent sepsis, and families need to be educated on the risk of fever and sepsis.

Preventive Monitoring of Thalassemia Patients

Cardiac Disease

Cardiac disease is the major cause of death in thalassemia. Serial echocardiograms should be monitored to evaluate cardiac function and pulmonary artery pressure. Pulmonary hypertension frequently occurs in non-transfusion dependent thalassemia patients and may be an indication for transfusion therapy. After approximately 8 yr of chronic transfusion therapy, cardiac hemosiderosis may occur; consequently, cardiac T2* MRI imaging studies are recommended. Patients with cardiac hemosiderosis and decreasing cardiac ejection fraction require intensive combination chelation therapy. Periodic electrocardiogram studies also are obtained after age 10 yr because of the risk of arrhythmia from cardiac iron overload.

Endocrine Disease

Endocrine function progressively declines with age secondary to hemosiderosis and nutritional deficiencies. Iron deposition in the pituitary and endocrine organs can result in multiple endocrinopathies, including hypothyroidism, growth hormone deficiency, delayed puberty, hypoparathyroidism, diabetes mellitus, osteoporosis, and adrenal insufficiency. Monitoring for endocrine dysfunction starts early, about 5 yr of age, or after at least 3 yr of chronic transfusions. All children require monitoring of their height, weight, pubertal assessment, and sitting height semiannually. Bone density scans should be obtained starting in the 2nd decade of life given the high rate of osteopenia. Nutritional assessments are required. Most patients need vitamin D, vitamin C, and zinc replacement. Fertility is a growing concern among patients and should be assessed routinely.

Psychosocial Support

Thalassemia imposes major disruption in the family unit and significant obstacles to normal development. Culturally sensitive anticipatory counseling is necessary, and the early use of child life services decreases psychological trauma of therapy. Early social service consultation to address financial and social issues is mandatory.

Other β-Thalassemia Syndromes

Non–Transfusion-Dependent Thalassemia: β-Thalassemia Intermedia

The β-thalassemia syndromes are characterized by decreased production of β-globin chains of HbA. There are 200-300 β-thalassemia mutations that have been characterized. These mutations can affect any step in the transcription of β-globin genes. As discussed, β^0 -thalassemia is absent production of normal β-chains, and Hb A production of with β^+ mutations is decreased. Some β-thalassemia mutations have structural mutations such as HbE. Others, such as δβ-thalassemia or HPFH, are variants of β-thalassemia that have decreased production of β-globin gene with increased compensatory production of HbF. Because phenotypic correlation with genotype is variable, β-thalassemia patients are largely classified by their clinical spectrum. Transfusion-dependent thalassemia, or thalassemia major, is the most severe group. Non–transfusion-dependent thalassemia (thalassemia intermedia) include a spectrum of patients who initially are not chronically transfused in infancy but may be sporadically transfused throughout their lifetime. The major determining characteristic of these patients is less α-β–globin chain imbalance than observed in thalassemia major. Sometimes, genetic modifiers alter the primary mutation severity and improve the globin-chain imbalance. Co-inheritance of α-thalassemia trait or polymorphisms of globin promoters such as BCL11 may lessen disease severity and result in a non-transfusion dependent thalassemia. HbE β-thalassemia is a common cause of both transfusion-dependent and non–transfusion-dependent thalassemia. These secondary genetic modifiers play a role in altering the severity of this disorder. Occasionally, patients with a single β-thalassemia mutation or autosomal dominant β-thalassemia trait have clinical features of thalassemia intermedia, or non–transfusion-dependent thalassemia. Genetic studies of these patients often uncover co-inheritance of genetic modifiers that worsens the condition, such as α-gene triplication or an unstable β-globin mutation.

Thalassemia intermedia patients have significant ineffective erythropoiesis that leads to microcytic anemia with hemoglobin of approximately 7 g/dL (range: 6-10 g/dL). These patients have some of the complications characterized in untransfused thalassemia major patients, but the severity varies depending on the degree of ineffective erythropoiesis. They can develop medullary hyperplasia, hepatosplenomegaly, hematopoietic pseudotumors, pulmonary hypertension, leg ulcers, thrombotic events, and growth failure. Many patients develop hemosiderosis secondary to increased GI absorption of iron requiring chelation. Extramedullary hematopoiesis can occur in the vertebral canal, compressing the spinal cord and causing neurologic symptoms; the latter is a medical emergency requiring immediate local radiation therapy to halt erythropoiesis. Transfusions are indicated in thalassemia intermedia patients with significant clinical morbidity.

Thalassemia trait is often misdiagnosed as iron deficiency in children, because the 2 diagnoses produce similar hematologic abnormalities on CBC. However, *iron deficiency is much more prevalent.* A short course of iron and reevaluation is all that is required to identify children who will need further evaluation. Children who have β-thalassemia trait have a persistently normal red cell distribution width and low mean corpuscular volume (MCV), whereas patients with iron deficiency develop an elevated red cell distribution width (RDW) with treatment. On Hb analysis, patients with β-thalassemia trait have elevated levels of HbA_2 and variably increased Hb F. There are “silent” forms of β-thalassemia trait, and if the family history is suggestive, further studies may be indicated.

α-Thalassemia Syndromes

The same evolutionary pressures that produced β-thalassemia and sickle cell disease produced α-thalassemia. Infants are identified in the newborn period by the increased production of Bart hemoglobin (γ_4) during fetal life and its presence at birth. The α-thalassemia syndromes occur most frequently in Southeast Asia. Deletion mutations are most common in α-thalassemia. In addition to deletional mutations, there are nondeletional α-globin gene mutations, the most common being Constant Spring (α^{CS} α); these mutations cause a more severe anemia and clinical course than the deletional mutations. Normally, there are 4 α-globin genes. The different phenotypes in α-thalassemia largely result from whether 1 (α^{+} -thalassemia) or both (α^{0} -thalassemia) α-globin genes are deleted in each of the 2 loci.

The deletion of 1 α-globin gene (silent trait) is not identifiable hematologically. Specifically, no alterations are noted in the MCV and mean corpuscular hemoglobin (MCH). Persons with this deletion are usually diagnosed after the birth of a child with a 2-gene deletion or HbH (β_4), but some newborn screening programs report even low concentrations of Hb Bart. During the newborn period, <3% Hb Bart is observed. The deletion of 1 α-globin gene is common in African Americans.

The deletion of 2 α-globin genes results in α-thalassemia trait. The α-globin alleles can be lost in a *trans* (−α/−α) or *cis* ($\alpha,\alpha/^{-SEA}$) configuration. The *trans* or *cis* mutations can combine with other mutations or deletions and lead to HbH or α-thalassemia major. In persons from Africa or of African descent, the most common α-globin deletions are in the *trans* configuration, whereas in persons from or descended from Asia or the Mediterranean region, *cis* deletions are most common.

α-Thalassemia trait (2 missing α-globin genes) manifest as a microcytic anemia that can be mistaken for iron-deficiency anemia (see Fig. 489.5*F*). The Hb analysis is normal, except during the newborn period, when Hb Bart is typically <8% but >3%. Children with a deletion of 2 α-globin genes are commonly mistaken to have iron deficiency, given the presence of both low MCV and MCH. The simplest approach to distinguish between iron deficiency and α-thalassemia trait is with a good dietary history. Children with iron-deficiency anemia often have a diet that is low in iron and drink significant amount of cow's milk. Alternatively, a brief course of iron supplementation along with monitoring of erythrocyte parameters might confirm the diagnosis of iron deficiency. If both parents of a child diagnosed with α-thalassemia trait are carriers in the *cis* conformation, they are at risk for a future hydrops fetalis pregnancy. Thus, family screening and genetic counseling are indicated.

The deletion of 3 α-globin genes leads to the diagnosis of HbH disease. A more severe form of HbH disease may be caused by a nondeletional α-globin mutation in combination with 2 gene deletions. HbH Constant Spring ($-\alpha/\alpha,\alpha^{CS}$) is the most common type of nondeletional HbH disease.

In California, where a large population of persons of Asian descent resides, approximately 1 : 10,000 of all newborns have HbH disease. The simplest manner of diagnosing HbH disease is during the newborn period, when excess in γ-tetramers are present and Hb Bart is commonly >25%. Obtaining supporting evidence from the parents is helpful. Later in childhood, there is an excess of β-globin chain tetramers that results in HbH. A definitive diagnosis of HbH disease requires DNA analysis. Brilliant cresyl blue can stain HbH, but it is rarely used for diagnosis. Patients with HbH disease have a marked microcytosis, anemia, mild splenomegaly, and, occasionally, scleral icterus or cholelithiasis. Chronic transfusion is not usually required for therapy because the Hb range is 7-11 g/dL, with MCV 51-73 fL, but intermittent transfusions for worsening anemia may be needed. Individuals with non-deletional Hb H disease are more likely to require transfusions than individuals with deletional Hb H disease.

The deletion of all 4 α-globin gene alleles causes profound anemia during fetal life, resulting in **hydrops fetalis** ; the ζ-globin gene must be present for fetal survival. There are no normal hemoglobins present at birth (primarily Hb Bart, with Hb Gower-1, Gower-2, and Portland). Intrauterine transfusions may rescue the fetus, but congenital abnormalities and neurodevelopmental delay often result. Infants with severe α-thalassemia will have lifelong transfusion dependence, and hematopoietic stem cell transplantation is the only cure.

Treatment of HbH disease requires ongoing monitoring of growth and organ dysfunction. Dietary supplement with folate and multivitamins without iron is indicated. Older patients may develop decreased bone density with calcium and vitamin D deficiency. Vitamin D supplementation is indicated if the level is low, and adequate dietary calcium intake should be encouraged to promote bone health. Iron supplementation should be avoided as patients are at risk of developing iron overload. Intermittent transfusion requirements during intercurrent infection may occur, particularly in nondeletional HbH. Splenectomy is occasionally indicated, and because of the high risk of postsplenectomy thrombosis, aspirin or other anticoagulant therapy following splenectomy should be considered. Hemosiderosis, secondary to GI iron absorption or transfusion exposure, may develop in older patients and require chelation therapy. Because HbH is an unstable hemoglobin sensitive to oxidative injury, oxidative medications should be avoided. At-risk couples for hydrops fetalis should be identified and offered molecular diagnosis on fetal tissue obtained early in pregnancy. Later in pregnancy, intrauterine transfusion can improve fetal survival, but chronic transfusion therapy or bone marrow transplantation for survivors will be required.

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CHAPTER 490

Enzymatic Defects

490.1

Pyruvate Kinase Deficiency

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Keywords

adenosine triphosphate
ATP
congenital hemolytic anemia
hemolysis
polychromatophilia
PK deficiency
pyruvate kinase
reticulocytosis

Congenital hemolytic anemia occurs in persons homozygous or compound heterozygous for autosomal recessive genes that cause either a marked reduction in red blood cell (RBC) pyruvate kinase (PK) or production of an abnormal enzyme with decreased activity resulting in impaired conversion of phosphoenolpyruvate to pyruvate. Generation of adenosine triphosphate (ATP) within RBCs at this step is impaired, and low levels of ATP, pyruvate, and the oxidized form of nicotinamide adenine dinucleotide (NAD^+) are found (Fig.

490.1). The concentration of 2,3-diphosphoglycerate is increased; this isomer is beneficial in facilitating oxygen release from hemoglobin but detrimental in inhibiting hexokinase and enzymes of the hexose monophosphate shunt. In addition, an unexplained decrease occurs in the sum of the adenine (ATP, adenosine diphosphate, and adenosine monophosphate) and pyridine (NAD^+ and reduced form of NAD) nucleotides, further impairing glycolysis. As a consequence of decreased ATP, RBCs cannot maintain their potassium and water content; the cells become rigid, and their life span is considerably reduced.

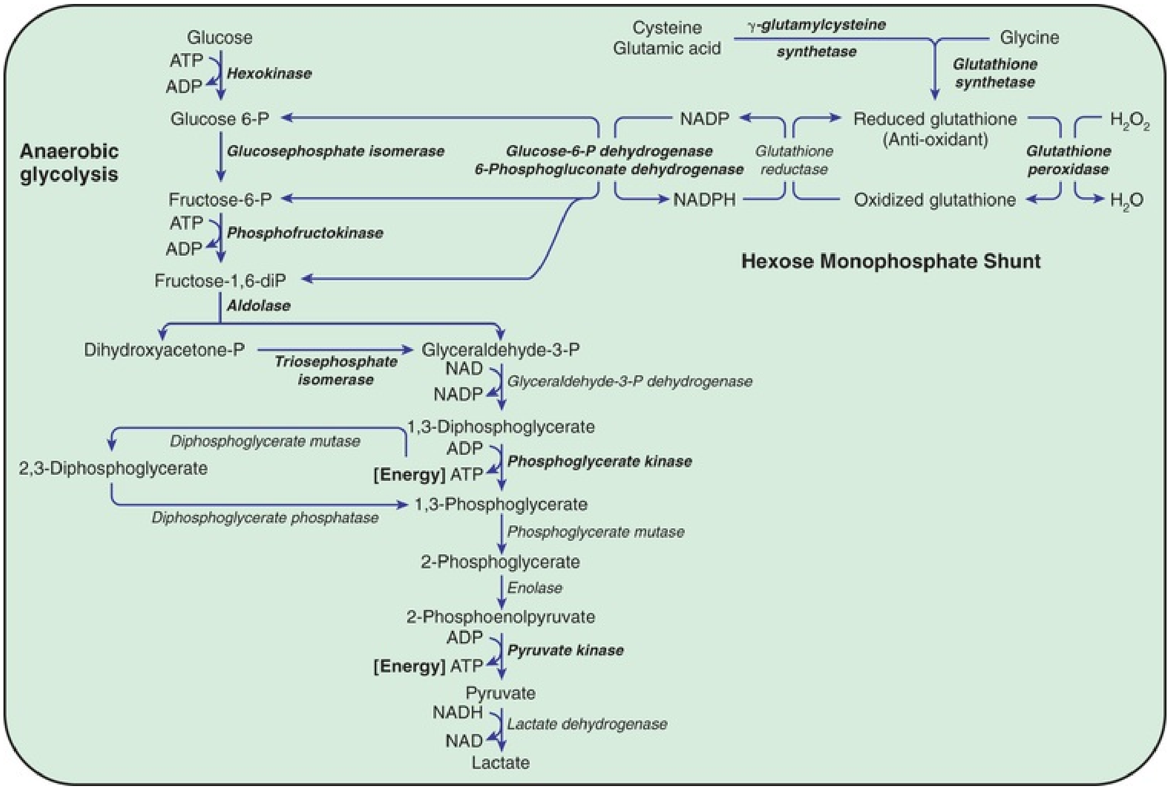
Glucose
ATP
ADP
Hexokinase
Glucose 6-P
Anaerobic glycolysis
Glucosephosphate isomerase
Fructose-6-P
ATP
ADP
Phosphofructokinase
Fructose-1,6-diP
Aldolase
Dihydroxyacetone-P
Triosephosphate isomerase
Glyceraldehyde-3-P
NAD
NADP
Glyceraldehyde-3-P dehydrogenase
1,3-Diphosphoglycerate
Diphosphoglycerate mutase
2,3-Diphosphoglycerate
ADP
[Energy] ATP
Phosphoglycerate kinase
Diphosphoglycerate phosphatase
1,3-Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
Enolase
2-Phosphoenolpyruvate
ADP
[Energy] ATP
Pyruvate kinase
Pyruvate
NADH
NAD
Lactate dehydrogenase
Lactate
Cysteine
Glutamic acid
γ-glutamylcysteine synthetase
Glycine
Glutathione synthetase
NADP
Reduced glutathione (Anti-oxidant)
H_2O_2
Glucose-6-P dehydrogenase
6-Phosphogluconate dehydrogenase
Glutathione reductase
Glutathione peroxidase
NADPH
Oxidized glutathione
H_2O
Hexose Monophosphate Shunt

FIG. 490.1 Red blood cell metabolism: glycolysis and hexose monophosphate pathway. The enzyme deficiencies clearly associated with hemolysis are shown in bold . ATP, Adenosine triphosphate; ADP, adenosine diphosphate; NADP, nicotinamide adenine dinucleotide phosphate; NADPH, reduced form of NADP.

Etiology

There are 2 mammalian PK genes, but only the *PKLR* gene is expressed in RBCs. The human *PKLR* gene is located on chromosome 1q21. More than 180 mutations are reported in this structural gene, which codes for a 574–amino acid protein that forms a functional tetramer. These mutations include missense, splice site, and insertion-deletion alterations, and there is some correlation of the type, location, and amino acid substitution with disease severity. Most affected patients are compound heterozygotes for 2 different PK gene defects. The many possible combinations likely account for the variability in clinical severity. The mutations 1456 C to T and 1529 G to A are the most common mutations in the white population.

Clinical Manifestations and Laboratory Findings

The clinical manifestations of PK deficiency vary from severe neonatal hemolytic anemia to mild, well-compensated hemolysis first noted in adulthood (Table 490.1). Severe jaundice and anemia may occur in the neonatal period, and kernicterus has been reported. The hemolysis in older children and adults varies in severity, with hemoglobin (Hb) values ranging from 8-12 g/dL associated with some pallor, jaundice, and splenomegaly. Reticulocyte counts are often extremely elevated, reflecting the severe ongoing hemolysis. Patients with these findings usually do not require transfusion. A severe form of the disease has a relatively high incidence among the Amish of the Midwestern United States. PK deficiency may possibly provide protection against falciparum malaria.

Table 490.1

Hexokinase Variants Associated With Hemolytic Anemia

CLINICAL FEATURES			**PROPERTIES OF RBC HEXOKINASE**			
Inheritance	**Anemia**	**Other**	**Activity**	**Kinetic Abnormalities**	**Stability**	**Mobility**
—	+	Congenital malformations	13-24*	0	—	—
Recessive	++		15-20*	+	Normal	Abnormal
Recessive	++		16*	0	—	Abnormal
Recessive	+++	Hydrops fetalis	17			
Recessive	+		20*	0	Normal	Normal
Recessive	++	Low platelet and fibroblast HK activity	20*	0	Low	Normal
Recessive	++	Low platelet HK activity	25*	+	Normal	Abnormal
Recessive	+		25*	0	Low	Normal
Dominant	+	Spherocytes, ovalocytes	30*	0	Low	Normal

Recessive	+	Developmental and cognitive delays	45[†]	+	Normal	Normal
Recessive	+		50[*]	0	Normal	Normal
—	+	Congenital malformations	33[*]	+	—	—
Recessive	+		40-53[*]	+	Low	Normal
—	+		50[*]	+	—	—
			53			
Dominant	+		45-91[†]	+	Normal	Abnormal
Dominant	++	WBC HK activity low	75[*]	+	Normal	Abnormal
Recessive	±		77[†]			

[*] Maximal enzyme activity (V_{max}) compared with reticulocytosis controls.

[†] Maximal enzyme activity (V_{max}) compared with normal red cells.

HK, Hexokinase; RBC, red blood cell; WBC, white blood cell.

From *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, vol 1, Philadelphia, 2015, Elsevier (Table 17-2, p 583).

Polychromatophilia and mild macrocytosis reflect the elevated reticulocyte count. Spherocytes are uncommon, but a few spiculated pyknocytes may be found. Diagnosis relies on demonstration of a marked reduction of RBC PK activity or an increase in the Michaelis-Menten dissociation constant (K_m) for its substrate, phosphoenolpyruvate (high K_m variant). Other RBC enzyme activity is normal or elevated, reflecting the reticulocytosis. No abnormalities of hemoglobin are noted. The white blood cells (WBCs) have normal PK activity and must be rigorously excluded from the RBC hemolysates used to measure PK activity. Heterozygous carriers usually have moderately reduced levels of PK activity.

Treatment

Phototherapy and exchange transfusions may be indicated for hyperbilirubinemia in newborns. Transfusions of packed RBCs are necessary for severe anemia or for aplastic crises. If the anemia is consistently severe and frequent transfusions are required, iron chelation may be necessary. Splenectomy should be considered after the child is 5-6 yr of age to decrease the need for transfusions and minimize iron overload. Although not curative, splenectomy may be followed by higher Hb levels and by strikingly high (30–60%) reticulocyte counts. Death resulting from overwhelming pneumococcal sepsis has followed splenectomy; thus immunization with vaccines for encapsulated organisms should be given before splenectomy and prophylactic penicillin administered after the procedure. Splenectomy has also been associated with thrombosis and pulmonary hypertension. Gallstones should be considered in any patient with congenital hemolytic anemia and recurrent abdominal pain. There is currently no curative therapy; a pharmacologic PK activator is being studied in early-phase clinical trials. The natural history of the disease is limited and is currently being studied through an international registry.

490.2

Other Glycolytic Enzyme Deficiencies

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Keywords

aldolase
glucose phosphate isomerase
glycogen storage disease
Heinz bodies
hexokinase
phosphofructokinase deficiency
phosphoglycerate kinase
triose phosphate isomerase deficiency

Chronic nonspherocytic hemolytic anemias of varying severity have been associated with deficiencies of other enzymes in the glycolytic pathway, including hexokinase, glucose phosphate isomerase, and aldolase, which are inherited as autosomal recessive disorders. **Phosphofructokinase deficiency,** which occurs primarily in Ashkenazi Jews in the United States, results in hemolysis associated with a myopathy classified as **glycogen storage disease type VII** (see Chapter 105.1). Clinically, hemolytic anemia is complicated by muscle weakness, exercise intolerance, cramps, and possibly myoglobinuria.

Enzyme assays for phosphofructokinase yield low values for RBCs and muscle.

Triose phosphate isomerase deficiency is an autosomal recessive disorder affecting many systems. Affected patients have hemolytic anemia, cardiac abnormalities, and lower motor neuron and pyramidal tract impairment, with or without evidence of cerebral impairment. They usually die in early childhood. The gene for triose phosphate isomerase has been cloned and sequenced and is located on chromosome 12.

Phosphoglycerate kinase (PGK) is the first ATP-generating step in glycolysis. At least 23 kindreds with PGK deficiency have been described. PGK is the only glycolytic enzyme inherited on the X chromosome. Affected males may have progressive extrapyramidal disease, myopathy, seizures, and variable mental retardation in conjunction with hemolytic anemia. Nine Japanese patients had neural or myopathic symptoms with hemolysis; 6 had hemolysis alone; 7 had neural or myopathic symptoms alone; and 1 had no symptoms. The gene for PGK is particularly large, spanning 23 kb, and various genetic abnormalities, including nucleotide substitutions, gene deletions, missense, and splicing mutations, result in PGK deficiency.

Deficiencies of Enzymes of Hexose Monophosphate Pathway

The most important function of the hexose monophosphate pathway is to maintain glutathione in its reduced state (GSH) as protection against the oxidation of RBCs (see Fig. 490.1). Approximately 10% of the glucose taken up by RBCs passes through this pathway to provide the reduced form of NAD phosphate (NADPH) necessary for the conversion of oxidized glutathione to GSH. Maintenance of GSH is essential for the physiologic inactivation of oxidant compounds, such as hydrogen peroxide, that are generated within RBCs. If glutathione, or any compound or enzyme necessary for maintaining it in the reduced state, is decreased, the SH groups of the RBC membrane are oxidized, and the hemoglobin becomes denatured and may precipitate into RBC inclusions called **Heinz bodies** . Once Heinz bodies have formed, an acute hemolytic process results from damage to the RBC membrane by the precipitated hemoglobin, the oxidant agent, and the action of the spleen. The damaged RBCs then are rapidly removed from the circulation.

490.3

Glucose-6-Phosphate Dehydrogenase Deficiency and Related Deficiencies

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Keywords

anisopoikilocytosis
bite cells
favism
G6PD deficiency
nonspherocytic hemolytic anemia
oxidant threats
polychromasia
X-linked deficiency

Glucose-6-phosphate dehydrogenase (**G6PD**) deficiency, the most frequent disease involving enzymes of the hexose monophosphate pathway, is responsible for 2 clinical syndromes, episodic *acute* hemolytic anemia and *chronic* nonspherocytic hemolytic anemia. The most common manifestations are neonatal jaundice and episodic acute hemolytic anemia, which is induced by infections, certain drugs, and rarely, fava beans. This X-linked deficiency affects >400 million people worldwide, representing an overall 4.9% global prevalence. The global distribution of this disorder parallels that of malaria, representing an example of "balanced polymorphism," in which there is an evolutionary advantage of resistance to falciparum malaria in heterozygous females that outweighs the small negative effect of affected hemizygous males.

The deficiency is caused by inheritance of any of a large number of abnormal alleles of the gene responsible for the synthesis of the G6PD protein. About 140 mutations have been described in the gene responsible for the synthesis of the

G6PD protein. Many of these mutations are single-base changes leading to amino acid substitutions and destabilization of the G6PD enzyme. A web-accessible database catalogs G6PD mutations (http://www.bioinf.org.uk/g6pd). Fig. 490.2 shows some of the mutations that cause episodic vs chronic hemolysis. Milder disease is associated with mutations near the *amino* terminus of the G6PD molecule, and chronic nonspherocytic hemolytic anemia is associated with mutations clustered near the *carboxyl* terminus. The normal enzyme found in most populations is designated G6PD B+. A normal variant, designated G6PD A+, is common in Americans of African descent.

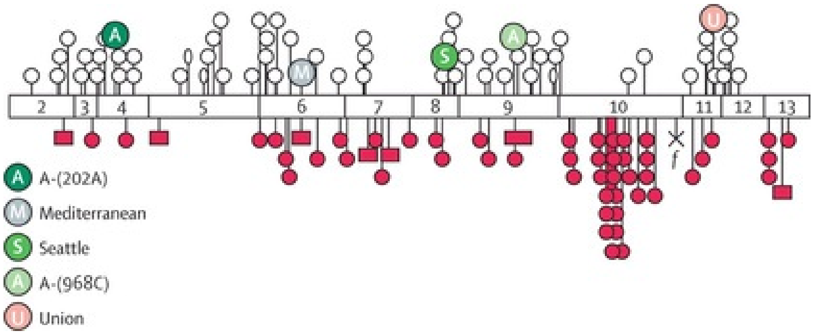

FIG. 490.2 Most common mutations along coding sequence of G6PD gene. Exons are shown as *open numbered boxes* . *Open circles* are mutations causing classes II and III variants. *Filled circles* represent sporadic mutations giving rise to severe variants (class I). *Open ellipses* are mutations causing class IV variants. X is a nonsense mutation; *f,* a splice site mutation; *filled squares,* small deletions. 202A and 968C are the 2 sites of base substitution in G6PD-A. (From Cappellini MD, Fiorelli G: Glucose-6-phosphate dehydrogenase deficiency, *Lancet* 371:64–74, 2008.)

Episodic or Induced Acute Hemolytic Anemia

Etiology

G6PD catalyzes the conversion of glucose 6-phosphate to 6-phosphogluconic acid. This reaction produces NADPH, which maintains GSH (glutathione in its reduced, functional state; see Fig. 490.1). GSH provides protection against **oxidant threats** from certain drugs and infections that would otherwise cause precipitation of hemoglobin (Heinz bodies) or damage the RBC membrane.

Synthesis of RBC G6PD is determined by a gene on the X chromosome.

Thus, heterozygous females have intermediate enzymatic activity and have 2 populations of RBCs: one is normal, and the other is deficient in G6PD activity. Because they have fewer susceptible cells, most heterozygous females do not have clinically evident hemolysis after exposure to oxidant drugs. Rarely, the majority of RBCs is G6PD deficient in heterozygous females because the inactivation of the normal X chromosome is random and sometimes exaggerated (Lyon-Beutler hypothesis).

Disease involving this enzyme therefore occurs more frequently in males than in females. Approximately 13% of male Americans of African descent have a mutant enzyme (**G6PD A−)** that results in a deficiency of RBC G6PD activity (5–15% of normal). Italians, Greeks, and other Mediterranean, Middle Eastern, African, and Asian ethnic groups also have a high incidence, ranging from 5–40%, of a variant designated **G6PD B−** (**G6PD Mediterranean**). In these variants, the G6PD activity of homozygous females or hemizygous males is <5% of normal. Therefore, the defect in Americans of African descent is *less severe* than that in Americans of European descent. A 3rd mutant enzyme with greatly reduced activity (**G6PD Canton**) occurs in approximately 5% of the Chinese population.

Clinical Manifestations

Most individuals with G6PD deficiency are asymptomatic, with no clinical manifestations of illness unless triggered by infection, drugs, or ingestion of fava beans. Typically, hemolysis ensues in about 24-48 hr after a patient has ingested a substance with **oxidant properties** . In severe cases, hemoglobinuria and jaundice result, and the Hb concentration may fall precipitously. Drugs that elicit hemolysis in these individuals include aspirin, sulfonamides, rasburicase, and antimalarials, such as primaquine (Table 490.2). The degree of hemolysis varies with the inciting agent, amount ingested, and severity of the enzyme deficiency. In some individuals, ingestion of fava beans also produces an acute, severe hemolytic syndrome, known as **favism** . Fava beans contain divicine, isouramil, and convicine, which ultimately lead to production of hydrogen peroxide and other reactive oxygen products. Favism is thought to be more frequently associated with the G6PD B− variant.

Table 490.2

Agents Precipitating Hemolysis in Glucose-6-

Phosphate Dehydrogenase Deficiency

Medications

Antibacterials

Sulfonamides
Ciprofloxacin
Moxifloxacin
Norfloxacin
Ofloxacin
Dapsone
Trimethoprim-sulfamethoxazole
Nalidixic acid
Chloramphenicol
Nitrofurantoin

Antimalarials

Primaquine
Pamaquine
Chloroquine
Quinacrine

Anthelminthics

β-Naphthol
Stibophen
Niridazole

Others

Acetanilide
Vitamin K analogs
Methylene blue
Toluidine blue

Probenecid
Dimercaprol
Acetylsalicylic acid
Phenazopyridine
Rasburicase

Chemicals

Phenylhydrazine
Benzene
Naphthalene (mothballs)
2,4,6-Trinitrotoluene

Illness

Diabetic acidosis
Hepatitis
Sepsis

From Asselin BL, Segel GB: In Rakel R, editor: *Conn's current therapy* , Philadelphia, 1994, Saunders, p 341.

In the G6PD A− variant, the stability of the folded protein dimer is impaired, and this defect is accentuated as the RBCs age. Thus, hemolysis decreases as older RBCs are destroyed, even if administration of the drug is continued. This recovery results from the age-labile enzyme, which is abundant and more stable in younger RBCs (Fig. 490.3). The associated reticulocytosis produces a compensated hemolytic process in which the blood hemoglobin may be only slightly decreased, despite continued exposure to the offending agent.

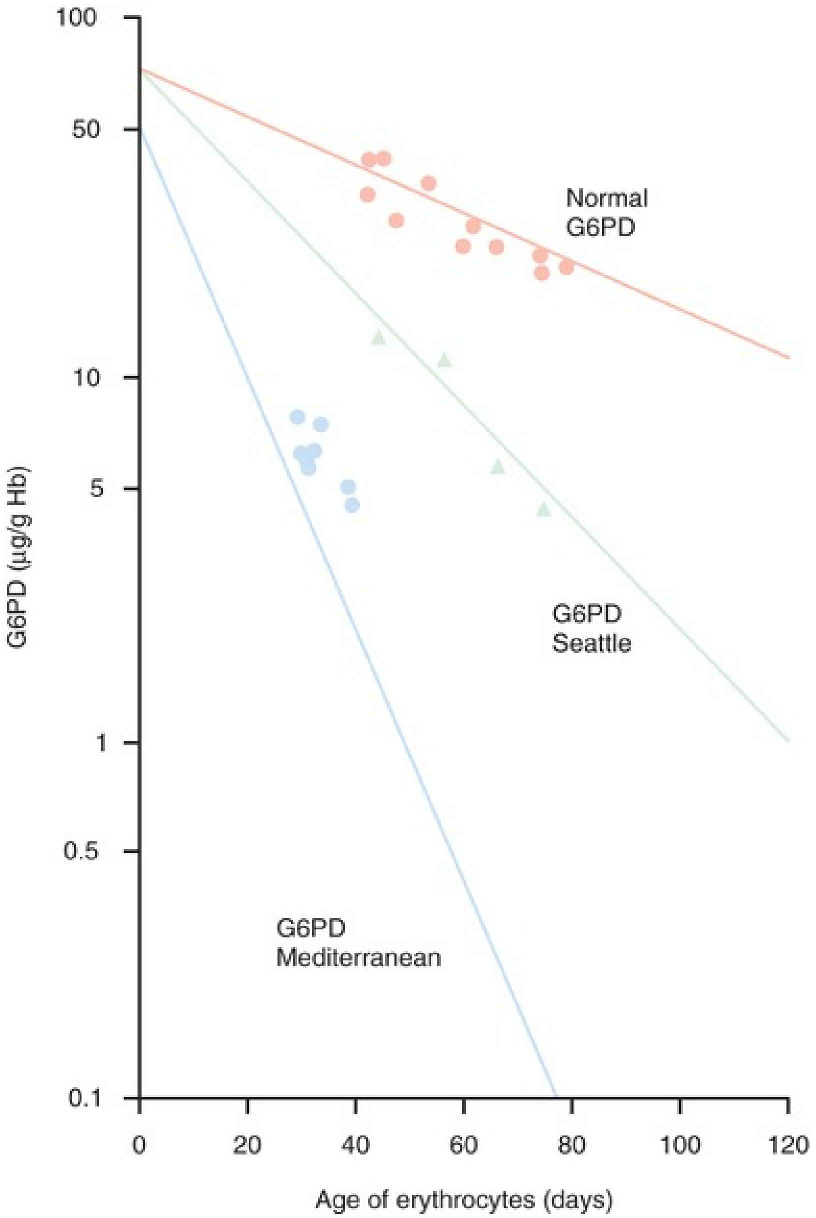

FIG. 490.3 Main mechanism of G6PD deficiency in RBCs is in vivo instability of mutant enzyme. For many G6PD variants, such as the 2 studied here, this is essentially acceleration of a process that takes place normally with the aging of RBCs in the circulation. Hb, Hemoglobin. (Adapted from Morelli A, Benatti U, Gaetani GF, et al.: Biochemical mechanisms of glucose-6-phosphate dehydrogenase deficiency, *Proc Natl Acad Sci USA* 75:1979–1983, 1978.)

G6PD deficiency can produce hemolysis in the neonatal period. In G6PD A–, spontaneous hemolysis and hyperbilirubinemia have been observed in preterm infants. In newborns with the G6PD B− and G6PD Canton varieties, hyperbilirubinemia and even kernicterus may occur. Neonates with co-inheritance of G6PD deficiency and a mutation of the promoter of uridine-diphosphate-glucuronyl transferase (UGT1A1), seen in **Gilbert syndrome** , have more severe neonatal jaundice. When a pregnant woman ingests oxidant drugs, they may be transmitted to her G6PD-deficient fetus, and hemolytic anemia and jaundice may be apparent at birth.

Laboratory Findings

The onset of acute hemolysis usually results in a precipitous fall in hemoglobin and hematocrit. If the episode is severe, the Hb-binding proteins, such as haptoglobin, are saturated, and free hemoglobin may appear in the plasma and subsequently in the urine. Unstained or supravital preparations of RBCs reveal precipitated hemoglobin, or Heinz bodies. The RBC inclusions are not visible on the Wright-stained blood film. Cells that contain these inclusions are seen only within the first 3-4 days of illness because they are rapidly cleared from the blood. Also, the blood film may contain red cells with what appears to be a bite taken from their periphery ("bite cells") and **polychromasia** (evidence of bluish, larger RBCs), representing reticulocytosis (Fig. 490.4).

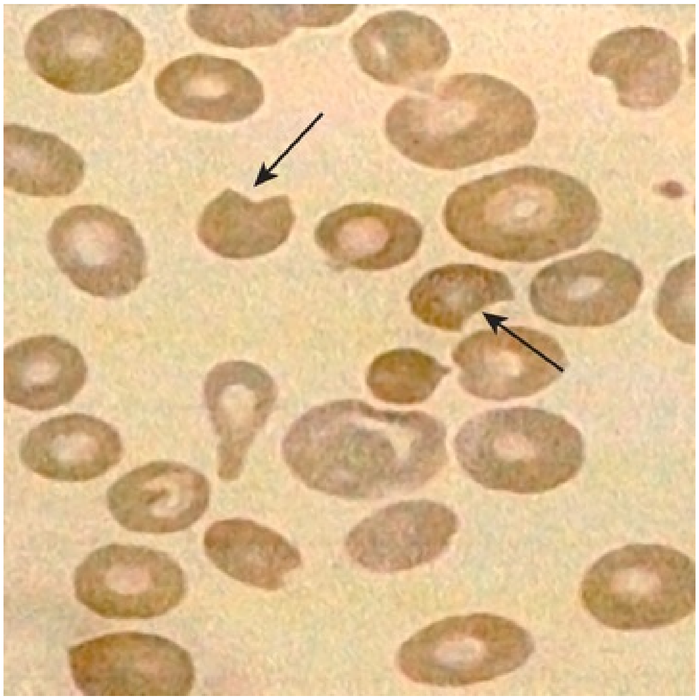

FIG. 490.4 Morphologic erythrocyte changes (anisopoikilocytosis, bite cells) during acute hemolysis in a G6PD-deficient patient. *Arrows* show bite

cells. *Anisopoikilocytosis* is abnormality in the shape or size of erythrocytes. (From Cappellini MD, Fiorelli G: Glucose-6-phosphate dehydrogenase deficiency, *Lancet* 371:64–74, 2008.)

Diagnosis

The diagnosis depends on direct or indirect demonstration of reduced G6PD activity in RBCs. By direct measurement, enzyme activity in affected persons is ≤10% of normal, and the reduction of enzyme activity is more extreme in Americans of European descent and in Asians than in Americans of African descent. Satisfactory screening tests are based on decoloration of methylene blue, reduction of methemoglobin, or fluorescence of NADPH. Immediately after a hemolytic episode, reticulocytes and young RBCs predominate. These young cells have significantly higher enzyme activity than do older cells in the A − variety (African). Testing may therefore have to be deferred for a few weeks before a diagnostically low level of enzyme can be shown. The diagnosis can be suspected when G6PD activity is within the low-normal range in the presence of a high reticulocyte count. G6PD variants also can be detected by electrophoretic and molecular analysis. G6PD deficiency should be considered in any neonatal patients with hyperbilirubinemia and borderline-low G6PD activity.

Prevention and Treatment

Prevention of hemolysis constitutes the most important therapeutic measure. When possible, males belonging to ethnic groups with a significant incidence of G6PD deficiency (e.g., Greeks, southern Italians, Sephardic Jews, Filipinos, southern Chinese, Americans of African descent, Thais) should be tested for the defect before known oxidant drugs are given. The usual doses of aspirin and trimethoprim-sulfamethoxazole do not cause clinically relevant hemolysis in the A− variety. Aspirin administered in doses used for acute rheumatic fever (60-100 mg/kg/24 hr) may produce a severe hemolytic episode. Infants with severe neonatal jaundice who belong to these ethnic groups also require testing for G6PD deficiency because of their heightened risk for this defect. If severe hemolysis has occurred, supportive therapy may require blood transfusions, although recovery is the rule when the oxidant agent is discontinued.

Chronic Hemolytic Anemias Associated With Deficiency of G6PD or Related Factors

Chronic **nonspherocytic hemolytic anemia** has been associated with profound deficiency of G6PD caused by enzyme variants, particularly those defective in quantity, activity, or stability. The gene defects leading to chronic hemolysis are located primarily in the region of the NADP-binding site near the carboxyl terminus of the protein (see Fig. 490.2). These include the Loma Linda, Tomah, Iowa, Beverly Hills, Nashville, Riverside, Santiago de Cuba, and Andalus variants. Persons with G6PD B− enzyme deficiency occasionally have chronic hemolysis, and the hemolytic process may worsen after ingestion of oxidant drugs. Splenectomy is of little value in these types of chronic hemolysis.

Other enzyme defects may impair the regeneration of GSH as an oxidant “sump” (see Fig. 490.1). Mild, chronic nonspherocytic anemia has been reported in association with decreased RBC GSH, resulting from γ-glutamylcysteine or GSH synthetase deficiencies. Deficiency of 6-phosphogluconate dehydrogenase has been associated primarily with drug-induced hemolysis, and hemolysis with hyperbilirubinemia has been related to a deficiency of GSH peroxidase in newborn infants.

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CHAPTER 491

Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias

Amanda M. Brandow

Immune Hemolytic Anemias

A number of extrinsic agents and disorders may lead to premature destruction of red blood cells (RBCs). Among the most clearly defined are antibodies associated with immune hemolytic anemias. The hallmark of this group of diseases is the positive result of the direct antiglobulin (Coombs) test, which detects a coating of immunoglobulin or components of complement on the RBC surface. The most important immune hemolytic disorder in pediatric practice is **hemolytic disease of the newborn** (erythroblastosis fetalis), caused by transplacental transfer of maternal antibody active against the RBCs of the fetus, that is, **isoimmune** hemolytic anemia (see Chapter 124.2).

Various other immune hemolytic anemias are **autoimmune** (Table 491.1) and may be idiopathic or related to various infections (Epstein-Barr virus, rarely HIV, cytomegalovirus, and mycoplasma), immunologic diseases (systemic lupus erythematosus [SLE], rheumatoid arthritis), immunodeficiency diseases (agammaglobulinemia, autoimmune lymphoproliferative disorder, dysgammaglobulinemia), neoplasms (lymphoma, leukemia, Hodgkin disease), or drugs (methyldopa, L -dopa). Other drugs (penicillins, cephalosporins) cause hemolysis by means of “drug-dependent antibodies”—antibodies directed toward the drug and in some cases toward an RBC membrane antigen as well.

Table 491.1

Diseases Characterized by Immune-Mediated

Red Blood Cell Destruction

Autoimmune Hemolytic Anemia Caused by Warm-Reactive Autoantibodies

- Primary (idiopathic)
- Secondary
  - Lymphoproliferative disorders
  - Connective tissue disorders (especially systemic lupus erythematosus)
  - Nonlymphoid neoplasms (e.g., ovarian tumors)
  - Chronic inflammatory diseases (e.g., ulcerative colitis)
  - Immunodeficiency disorders

Autoimmune Hemolytic Anemia Caused by Cold-Reactive Autoantibodies (Cryopathic Hemolytic Syndromes)

- Primary (idiopathic) cold agglutinin disease
- Secondary cold agglutinin disease
  - Lymphoproliferative disorders
  - Infections (*Mycoplasma pneumoniae* , Epstein-Barr virus)
  - Paroxysmal cold hemoglobinuria
- Primary (idiopathic)
  - Viral syndromes (most common)
  - Congenital or tertiary syphilis

Drug-Induced Immune Hemolytic Anemia (See Table 491.2)

- Hapten/drug adsorption (e.g., penicillin)
- Ternary (immune) complex (e.g., quinine, quinidine)
- True autoantibody induction (e.g., methyldopa)

Adapted from Packman CH: Autoimmune hemolytic anemias. In Rakel R, editor: *Conn's current therapy,* Philadelphia, 1995, Saunders, p 305.

Autoimmune Hemolytic Anemias Associated With “Warm” Antibodies

Etiology

In the autoimmune hemolytic anemias, autoantibodies are directed against RBC membrane antigens, but the pathogenesis of antibody induction is uncertain. The autoantibody may be produced as an inappropriate immune response to an RBC antigen or to another antigenic epitope similar to an RBC antigen, known as *molecular mimicry.* Alternatively, an infectious agent may alter the RBC membrane so that it becomes “foreign” or antigenic to the host. The antibodies usually react to *epitopes* (antigens) that are “public” or common to all human RBCs, such as Rh proteins.

In most instances of **warm antibody hemolysis** , no underlying cause can be found; this is the *primary* or idiopathic type (see Table 491.1). If the autoimmune hemolysis is associated with an underlying disease, such as a lymphoproliferative disorder, SLE, Evans syndrome, or immunodeficiency, it is *secondary.* In as many as 20% of cases of immune hemolysis, drugs may be implicated (Table 491.2).

Table 491.2

Selected Drugs That Cause Immune-Mediated Hemolysis

MECHANISM	DRUG ADSORPTION (HAPTEN)	TERNARY (IMMUNE) COMPLEX	AUTOANTIBODY INDUCTION
Direct antiglobulin test	Positive (anti-IgG)	Positive (anti-C3)	Positive (anti-IgG)
Site of hemolysis	Extravascular	Intravascular	Extravascular
Medications	Penicillins Cephalosporins 6-Mercaptopurine Tetracycline Oxaliplatin Hydrocortisone	Cephalosporins Quinidine Amphotericin B Hydrocortisone Rifampin (Rifadin) Metformin Quinine Probenecid Chlorpromazine Oxaliplatin	α-Methyldopa Cephalosporins Oxaliplatin L -Dopa Procainamide Ibuprofen Diclofenac (Voltaren) Interferon alfa

Adapted from Packman CH: Hemolytic anemia resulting from immune injury. In Kaushansky K, Lichtman MA, Beutler E, et al, editors: *Williams hematology,* ed 8, New York, 2010, McGraw-Hill.

Drugs (penicillin or sometimes cephalosporins) that cause hemolysis through the “hapten” mechanism (immune but not autoimmune) bind tightly to the RBC membrane. Antibodies to the drug, either newly or previously formed, bind to the drug molecules on RBCs, mediating their destruction in the spleen. In other cases, certain drugs, such as quinine and quinidine, do not bind to RBCs, but rather form part of a “ternary complex,” consisting of the drug, an RBC membrane antigen, and an antibody that recognizes both (see Table 491.2). Methyldopa and sometimes cephalosporins may, by unknown mechanisms, incite true autoantibodies to RBC membrane antigens, so that the presence of the drug is not required to cause hemolysis. Cephalosporins are the most common cause of drug-induced immune hemolytic anemia.

Clinical Manifestations

Autoimmune hemolytic anemias may occur in either of 2 general clinical patterns. The first, an *acute transient* type lasting 3-6 mo and occurring predominantly in children age 2-12 yr., accounts for 70–80% of patients. It is frequently preceded by an infection, usually respiratory. Onset may be acute, with pallor, jaundice, fever, and hemoglobinuria, or more gradual, with primarily fatigue and pallor. The spleen is usually enlarged and is the primary site of destruction of IgG-coated RBCs. Underlying systemic disorders are unusual. A consistent response to glucocorticoid therapy, a low mortality rate, and full recovery are characteristic of the acute form. The other clinical pattern involves a *prolonged chronic* course, which is more frequent in infants and in children >12 yr old. Hemolysis may continue for many months or years. Abnormalities involving other blood elements are common, and the response to glucocorticoids is variable and inconsistent.

Laboratory Findings

In many cases, anemia is profound with hemoglobin levels <6 g/dL. Considerable spherocytosis, polychromasia (reflecting the reticulocyte response) are present. More than 50% of the circulating RBCs may be reticulocytes, and nucleated RBCs usually are present. In some cases, a *low reticulocyte count* may be found, particularly early in the episode. Leukocytosis is common. The platelet count is usually normal, but concomitant immune thrombocytopenic purpura sometimes occurs (**Evans syndrome**). Patients with Evans syndrome often have or eventually develop a chronic disease, including SLE, an immunodeficiency syndrome, or the autoimmune lymphoproliferative syndrome.

Results of the **direct antiglobulin test (Coombs test)** are strongly positive, and free antibody can sometimes be demonstrated in the serum **(indirect Coombs test**). These antibodies are active at 35-40°C (95-104°F) (“warm” antibodies) and most often belong to the immunoglobulin G (IgG) class. They do not require complement for activity. Antibodies from the serum and those eluted from the RBCs react with the RBCs of many persons in addition to those of the patient. They often have been regarded as *nonspecific panagglutinins*, but careful studies have revealed specificity for RBC antigens of the Rh system in 70% of patients (50% of adult patients). Complement, particularly fragments of C3b, may be detected on the RBCs in conjunction with IgG. The Coombs test result is *rarely* negative because of the sensitivity of the Coombs reaction. A minimum of 260-400 molecules of IgG per cell is necessary on the RBC membrane to produce a positive reaction. Special tests are required to detect the antibody in cases of “Coombs-negative” autoimmune hemolytic anemia. In warm antibody hemolytic anemia, the direct Coombs test may detect IgG alone, both IgG and complement fragments, or solely complement fragments if the level of RBC-bound IgG is below the detection limit of the anti-IgG Coombs reagent.

Treatment

Transfusions may provide only transient benefit but may be lifesaving in cases of severe anemia until the effects of other treatments are observed. All tested units for transfusion are serologically incompatible. It is important to identify the patient's ABO blood group to avoid a hemolytic transfusion reaction mediated by anti-A or anti-B. The blood bank should also test for the presence of an underlying alloantibody, which could cause rapid hemolysis of transfused red cells. Patients who have been neither previously transfused nor pregnant are unlikely to harbor an alloantibody. Early consultation between the clinician and the blood bank physician is essential. Failure to transfuse a profoundly anemic infant or child may lead to serious morbidity and even death.

Patients with mild disease and compensated hemolysis may not require treatment. *If the hemolysis is severe and results in significant anemia or symptoms, treatment with glucocorticoids is initiated.* Glucocorticoids decrease the rate of hemolysis by blocking macrophage function by downregulating Fcγ receptor expression, decreasing the production of the autoantibody, and perhaps enhancing the elution of antibody from the RBCs. *Prednisone* or its equivalent is administered at a dose of 2 mg/kg/24 hr. In some patients with severe hemolysis, doses of prednisone of up to 6 mg/kg/24 hr may be required to reduce the rate of hemolysis. Treatment should be continued until the rate of hemolysis decreases, with the dose then gradually reduced. If relapse occurs, resumption of the full dosage may be necessary. The disease tends to remit spontaneously within a few weeks or months. The Coombs test result may remain positive even after the hemoglobin (Hb) level returns to normal. It is usually safe to discontinue prednisone once the direct Coombs test result becomes negative. When hemolytic anemia remains severe despite glucocorticoid therapy, or if very large doses are necessary to maintain a reasonable Hb level, intravenous (IV) immunoglobulin may be tried. *Rituximab,* a monoclonal antibody that targets B lymphocytes, the source of antibody production, *is useful in chronic cases refractory to conventional therapy.* Plasmapheresis has been used in refractory cases but generally is not helpful. Splenectomy may be beneficial but is complicated by a heightened risk of infection with encapsulated organisms, particularly in patients <6 yr old. Prophylaxis is indicated with appropriate vaccines (pneumococcal, meningococcal, and *Haemophilus influenzae* type b) before splenectomy and with oral penicillin after splenectomy. Thrombosis and pulmonary hypertension are also increasingly recognized problems after splenectomy.

Course and Prognosis

Acute idiopathic autoimmune hemolytic disease in childhood varies in severity but is self-limited; death from untreatable anemia is rare. Approximately 30% of patients have chronic hemolysis, often associated with an underlying disease, such as SLE, immunodeficiency or lymphoma. The presence of antiphospholipid antibodies in adult patients with immune hemolysis predisposes to thrombosis. Mortality in chronic cases depends on the primary disorder.

Autoimmune Hemolytic Anemias Associated With “Cold” Antibodies

“Cold” antibodies agglutinate RBCs at temperatures <37°C (98.6°F). They are primarily of the IgM class and require complement for hemolytic activity. The highest temperature at which RBC agglutination occurs is called the *thermal amplitude.* A higher thermal amplitude antibody—that is, one that can bind to RBCs at temperatures achievable in the body—results in hemolysis with exposure to a cold environment. High antibody titers are associated with high thermal amplitude.

Cold Agglutinin Disease

Cold antibodies usually have specificity for the oligosaccharide antigens of the I/i system. They may occur in primary or idiopathic cold agglutinin disease, secondary to infections such as those from *Mycoplasma pneumoniae* and Epstein-Barr virus, or secondary to lymphoproliferative disorders. After *M. pneumoniae* infection, the anti-I levels may increase considerably, and occasionally, enormous increases may occur to titers ≥1/30,000. The antibody has specificity for the I antigen and thus reacts poorly with human cord RBCs, which possess the i antigen but exhibit low levels of I. Patients with infectious mononucleosis occasionally have cold agglutinin disease, and the antibodies in these patients often have anti-i specificity. This antibody causes less hemolysis in adults than in children because adults have fewer i molecules on their RBCs. Spontaneous RBC agglutination is observed in the cold and in vitro, and RBC aggregates are seen on the blood film (**rouleaux formation**). Mean corpuscular volume (MCV) may be spuriously elevated because of RBC agglutination and reticulocytosis. The severity of the hemolysis is related to the thermal amplitude of the antibody, which itself partly depends on the IgM antibody titer.

When very high titers of cold antibodies are present and active near body temperature, severe intravascular hemolysis with **hemoglobinemia** and **hemoglobinuria** may occur and may be heightened on a patient's exposure to cold (external temperature or ingested foods). Each IgM molecule has the potential to activate a C1 molecule, so that large amounts of complement are found on the RBCs in cold agglutinin disease. These sensitized RBCs may undergo intravascular complement-mediated lysis or may be destroyed in the liver and spleen. Only complement, not IgM, is detected on RBCs because the IgM is removed during the washing steps of the direct antiglobulin (Coombs) test.

Cold agglutinin disease is less common in children than in adults and more frequently results in an acute, self-limited episode of hemolysis. RBC transfusion is indicated based on symptoms and severity of anemia.

Glucocorticoids are much less effective in cold agglutinin disease than in hemolytic disease with warm antibodies. Patients should avoid exposure to cold and should be treated for any underlying disease. In the uncommon patient with severe hemolytic disease, immunosuppression and plasmapheresis can be used. Successful treatment of cold agglutinin disease has been reported with rituximab, which effectively depletes B lymphocytes. Splenectomy is not useful in cold agglutinin disease.

Paroxysmal Cold Hemoglobinuria

Paroxysmal cold hemoglobinuria is mediated by the **Donath-Landsteiner (D-L) hemolysin** , which is an IgG cold-reactive autoantibody with anti-P specificity. In vitro, the D-L antibody binds to RBCs in the cold, and the RBCs are lysed by complement as the temperature is increased to 37°C. A similar sequence is thought to occur in vivo as RBCs move from the cooler extremities to warmer parts of the circulation. Most reported cases are self-limited; many patients experience only one paroxysm of hemolysis. Congenital or acquired syphilis was once the most common underlying cause of paroxysmal cold hemoglobinuria, but currently, most cases are associated with nonspecific viral infections. Treatment includes transfusion for severe anemia and avoidance of cold ambient temperatures.

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CHAPTER 492

Hemolytic Anemias Secondary to Other Extracellular Factors

Amanda M. Brandow

Fragmentation Hemolysis

See Table 484.2 in Chapter 484 .

Red blood cell (RBC) destruction may occur in hemolytic anemias because of **mechanical injury** as the cells traverse a damaged vascular bed. Damage may be microvascular when RBCs are sheared by fibrin in the capillaries during intravascular coagulation or when renovascular disease accompanies the **hemolytic-uremic syndrome (HUS)** (see Chapter 538.5) or **thrombotic thrombocytopenic purpura (TTP)** (see Chapter 511.5). Larger vessels may be involved in **Kasabach-Merritt syndrome** (giant hemangioma and thrombocytopenia; see Chapter 532) or when a replacement heart valve is poorly epithelialized. The blood film shows many *schistocytes,* or fragmented cells, as well as **polychromatophilia** , reflecting the reticulocytosis (see Fig. 485.4*F* in Chapter 485). Secondary iron deficiency may complicate the intravascular hemolysis because of urinary hemoglobin and hemosiderin iron loss (see Fig. 484.2 in Chapter 484). **Treatment should be directed toward the underlying condition** , and the prognosis depends on the effectiveness of this treatment. The benefit of transfusion may be transient because the transfused cells are destroyed as quickly as those produced by the patient.

It is critical to determine the precise etiology of the fragmentation hemolysis because the treatment depends on the underlying problem (Table 492.1). **Acquired TTP** results from an antibody to an enzyme (**ADAMTS13**) that regulates the size of von Willebrand multimers. The lack of this enzyme results in a marked increase in multimer size and a resultant **thrombotic microangiopathy** . **Congenital TTP** can result in the inability to produce adequate amounts of the enzyme ADAMTS13 and results in the same pathophysiology. The treatment for acquired TTP involves plasmapheresis to remove the antibody and replace the ADAMTS13. The treatment for congenital TTP involves scheduled plasma infusions to replace the ADAMTS13. In contrast, HUS results from *Shiga* toxin produced by *Escherichia coli* 0157 and may not be helped by plasmapheresis. **Atypical HUS** involves activation of the alternative complement pathway and can be treated with *eculizumab* (anti-C5), an inhibitor of the complement pathway. Plasmapheresis may reduce the RBC fragmentation and improve the platelet count but has little effect on the tissue (kidney) vasculopathy and thus is not usually recommended. **Pneumococcal-induced HUS** results from neuraminidase produced by the bacteria, which damages the membranes of the RBCs and the kidney, exposing the **T-antigen** . Plasma contains natural antibody to the T-antigen, producing hemolysis, renal damage, and a thrombotic microangiopathy. Thus, patients with T-antigen activation from suspected pneumococcal-induced HUS should not be given plasma infusions, because this will significantly exacerbate the RBC hemolysis and can lead to life-threatening anemia.

Table 492.1

Thrombotic Microangiopathies

DISEASE*	PATHOPHYSIOLOGY	LAB FINDINGS	MANAGEMENT
Thrombotic thrombocytopenic purpura (TTP)	*Acquired:* Ab to ADAMTS13 *Congenital:* Inadequate ADAMTS13 production	Ab to ADAMTS13 ADAMTS13 <10%	*Acquired:* Plasmapheresis with plasma *Congenital:* Scheduled plasma infusions
Hemolytic-uremic syndrome (HUS)	*E. coli* 0157, *Shiga* toxin	*E. coli* 0157, *Shiga* toxin	Supportive ? Value of plasmapheresis
Atypical HUS	Complement-mediated alternative pathway	ADAMTS13 >10% Decreased factors H and I (inhibitors of complement) †	Eculizumab (Ab to C5) Plasmapheresis not indicated
Pneumococcal-induced HUS	Neuraminidase-induced RBC, platelet, and kidney damage Exposure of T-antigen on RBC and kidney	Pneumococcal infection ADAMTS13 >10%	Plasmapheresis with albumin for neuraminidase and endogenous T Ab removal Avoid plasma infusions, which will exacerbate RBC hemolysis
Disseminated intravascular coagulation	Sepsis, shock, endotoxin	Decreased fibrinogen, increased fibrin split products, decreased clotting factors and platelets	Treat underlying condition; replace factors and platelets if bleeding

(DIC)			

[*] All show fragmentation hemolytic anemia, thrombocytopenia, and potential renal and other organ damage. An elevated lactate dehydrogenase and reduced haptoglobin usually are present secondary to hemolysis.

[†] May be related to inherited defect in factor H or I.

Ab, Antibody; RBC, red blood cell.

Thermal Injury

Extensive burns may directly damage the RBCs and cause hemolysis that results in the formation of *spherocytes*. Blood loss and marrow suppression may contribute to anemia and require blood transfusion. Erythropoietin (**EPO**) has been used as treatment for diminished RBC production.

Renal Disease

The anemia of uremia is multifactorial in origin. Erythropoietin production may be decreased, and the marrow suppressed by toxic metabolites. Furthermore, the RBC life span often is shortened because of retention of metabolites and organic acidemia. The use of EPO in chronic renal disease can decrease the need for blood transfusion.

Liver Disease

A change in the ratio of cholesterol to phospholipids in the plasma may result in changes in the composition of the RBC membrane and shortening of the RBC life span. Some patients with liver disease have many target RBCs on the blood film, whereas others have a preponderance of *spiculated cells*. These morphologic changes reflect the alterations in the plasma lipid composition.

Toxins and Venoms

Bacterial sepsis caused by *Haemophilus influenzae*, staphylococci, or streptococci may be complicated by accompanying hemolysis. Particularly severe hemolytic anemia has been observed in clostridial infections and results from a hemolytic clostridial toxin. Large numbers of spherocytes may be seen on the blood film. **Spherocytic hemolysis** also may be noted after bites by various snakes, including cobras, vipers, and rattlesnakes, which have phospholipases in their venom. Large numbers of bites by insects, such as bees, wasps, and yellow jackets, also may cause spherocytic hemolysis by a similar mechanism (see Chapter 746).

Wilson Disease

See Chapter 384.2 .

An acute and self-limited episode of hemolytic anemia may precede by years the onset of hepatic or neurologic symptoms in Wilson disease. This event appears to result from the toxic effects of free copper on the RBC membrane. The blood film often (but not always) shows large numbers of spherocytes, and the Coombs test result is negative. Because early diagnosis of Wilson disease permits prophylactic treatment with penicillamine and prevention of hepatic and neurologic disease, correct assessment of this rare type of hemolysis is important.

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SECTION 4

Polycythemia (Erythrocytosis)

OUTLINE

Chapter 493 Polycythemia
Chapter 494 Nonclonal Polycythemia

CHAPTER 493

Polycythemia

Amanda M. Brandow, Bruce M. Camitta

Polycythemia exists when the red blood cell (RBC) count, hemoglobin level, and total RBC volume all exceed the upper limits of normal. In postpubertal individuals, an RBC mass >25% above the mean normal value (based on body surface area) or a hemoglobin level >18.5 g/dL (in males) or >16.5 g/dL (in females) indicate **absolute erythrocytosis** . A decrease in plasma volume, such as occurs in acute dehydration and burns, may result in a high hemoglobin value. These situations are more accurately designated as **hemoconcentration** or **relative polycythemia** because the RBC mass is not increased and normalization of the plasma volume restores hemoglobin to normal levels. Once the diagnosis of true polycythemia is made, sequential studies should be done to determine the underlying etiology (Fig. 493.1).

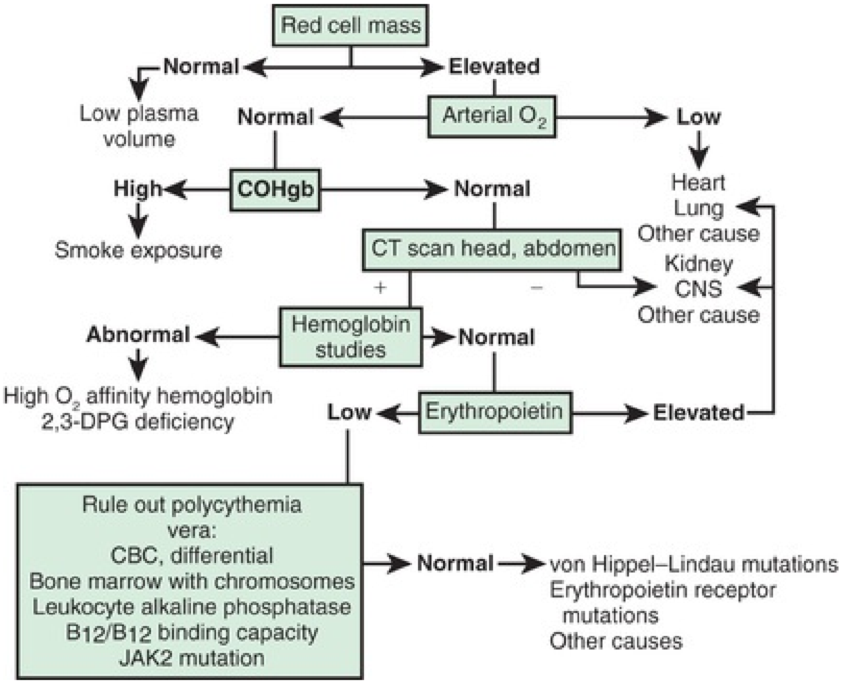
Red cell mass
Normal
Elevated
Low plasma volume
Normal
Arterial O_2
Low
Heart
Lung
Other cause
High
COHgb
Normal
Smoke exposure
CT scan head, abdomen
+
−
Kidney
CNS
Other cause
Abnormal
Hemoglobin studies
Normal
High O_2 affinity hemoglobin
2,3-DPG deficiency
Low
Erythropoietin
Elevated
Rule out polycythemia vera:
CBC, differential
Bone marrow with chromosomes
Leukocyte alkaline phosphatase
B12/B12 binding capacity
JAK2 mutation
Normal
von Hippel–Lindau mutations
Erythropoietin receptor mutations
Other causes

FIG. 493.1 **Sequential studies to evaluate polycythemia. CBC, Complete blood count; CNS, central nervous system; COHgb, carboxyhemoglobin; 2,3-DPG, 2,3-diphosphoglycerate.**

Clonal (Primary) Polycythemia (Polycythemia Vera)

Pathogenesis

Polycythemia vera is an acquired clonal myeloproliferative disorder. Although primarily manifesting as erythrocytosis, thrombocytosis and leukocytosis can also be seen. When isolated severe thrombocytosis exists in the absence of erythrocytosis, the myeloproliferative disorder is called **essential thrombocythemia** . Polycythemia vera is rare in children. A gain-of-function mutation of *JAK2,* a cytoplasmic tyrosine kinase, is found in >90% of adult patients with polycythemia vera, but in <30% of children with this condition. The erythropoietin receptor is normal, and serum erythropoietin levels are normal or low. Patients without *JAK* mutations may have mutations in the calreticulin or thrombopoietin receptor genes. In vitro cultures do not require added erythropoietin to stimulate growth of erythroid precursors. Risk factors for development of polycythemia vera include a family history of polycythemia vera and presence of an autoimmune disorder.

Clinical Manifestations

Patients with polycythemia vera usually have **hepatosplenomegaly** . Erythrocytosis may cause hypertension, headache, shortness of breath, or neurologic symptoms and increases the risk of thrombosis. Granulocytosis may cause diarrhea or pruritus from histamine release. Thrombocytosis (with or without platelet dysfunction) may cause thrombosis or hemorrhage. Table 493.1 lists the diagnostic criteria for polycythemia vera.

Table 493.1

World Health Organization (WHO) Diagnostic Criteria for Polycythemia Vera

Major Criteria
1. Hb >18.5 g/dL (men) or Hb >16.5 g/dL (women)
or
Hb or Hct >99th percentile of reference range for age, sex, or altitude of residence
or
Hb >17 g/dL (men) or Hb >15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency
or
Elevated red cell mass >25% above mean normal predicted value
2. Presence of *JAK2* or similar mutation
Minor Criteria
1. Bone marrow trilineage myeloproliferation
2. Subnormal serum erythropoietin level
3. Endogenous erythroid colony growth
Diagnosis
Both major criteria and 1 minor criterion
or
First major criteria and 2 minor criteria

Hb, Hemoglobin; Hct, hematocrit.

From Tefferi A, Vardiman JW: Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms, *Leukemia* 22:14–22, 2008.

Treatment

Phlebotomy is the initial treatment of choice to alleviate symptoms of hyperviscosity and decrease the risk of thrombosis. Iron supplementation should be given to prevent viscosity problems from iron-deficient microcytosis or thrombocytosis. In patients with marked thrombocytosis, antiplatelet agents (e.g., aspirin) may reduce the risks of thrombosis and bleeding. If these treatments are unsuccessful or the patient has progressive hepatosplenomegaly, antiproliferative treatments (hydroxyurea, anagrelide, interferon-α) may be helpful. The use of JAK2 inhibitors is an active area of investigation in the treatment of pediatric polycythemia vera. Transformation of the disease into myelofibrosis or acute leukemia is rare in children. Prolonged survival is not unusual.

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CHAPTER 494

Nonclonal Polycythemia

Amanda M. Brandow, Bruce M. Camitta

Pathogenesis

Nonclonal polycythemia is diagnosed when polycythemia is caused by a physiologic process that is not derived from a single cell (Table 494.1). Nonclonal polycythemia can be congenital or acquired (secondary).

Table 494.1

Differential Diagnosis of Polycythemia

CLONAL (PRIMARY)
Polycythemia vera
NONCLONAL
Congenital
High–oxygen affinity hemoglobinopathy (e.g., hemoglobin Chesapeake, Malmo, San Diego) Erythropoietin receptor mutations (primary familial and congenital polycythemia [PFCP]) Methemoglobin reductase deficiency Hemoglobin M disease 2,3-Diphosphoglycerate deficiency
Acquired
Hormonal Adrenal disease: virilizing hyperplasia, Cushing syndrome Anabolic steroid therapy Malignant tumors: adrenal, cerebellar, hepatic, other Renal disease: cysts, hydronephrosis, renal artery stenosis Hypoxia Altitude Cardiac disease Lung disease Central hypoventilation Chronic carbon monoxide exposure Neonatal: delayed cord clamping (placental-fetal transfusion) Normal intrauterine environment Placental insufficiency (preeclampsia, maternal chronic hypertension, placental abruption) Twin-twin or maternal-fetal hemorrhage

Perinatal asphyxia Infants of diabetic mothers Intrauterine growth restriction Trisomy 13, 18, or 21 Adrenal hyperplasia Maternal-congenital hyperthyroidism
Spurious
Plasma volume decrease

Congenital Polycythemia

Lifelong or familial polycythemia should trigger a search for a congenital problem. These inherited conditions may be transmitted as dominant or recessive disorders. Autosomal dominant causes include hemoglobins that have increased oxygen affinity (P_{50} [partial pressure of oxygen in the blood at which the hemoglobin is 50% saturated] <20 mm Hg), erythropoietin receptor mutations resulting in an enhanced effect of erythropoietin or mutations in the von Hippel–Lindau gene that result in altered intracellular oxygen sensing. Another rare cause is autosomal recessive 2,3-diphosphoglyceric acid deficiency, which leads to a left shift of the oxygen dissociation curve, increased oxygen affinity, and consequent polycythemia.

Subtle decreases in oxygen delivery to tissues may cause polycythemia. Congenital **methemoglobinemia** resulting from an autosomal recessive deficiency of cytochrome b5 reductase may cause cyanosis and polycythemia (see Chapter 489.7). Most affected individuals are asymptomatic. Neurologic abnormalities may be present in patients whose enzyme deficits are not limited to hematopoietic cells. Hemoglobin M disease (autosomal dominant) causes methemoglobinemia and can lead to polycythemia. Cyanosis may occur in the presence of as little as 1.5 g/dL of methemoglobin but is uncommon in other hemoglobin variants unless hyperviscosity results in localized hypoxemia.

Acquired Polycythemia

Polycythemia may be present in clinical situations associated with chronic arterial oxygen desaturation. Cardiovascular defects involving right-to-left shunts and pulmonary diseases interfering with proper oxygenation are the most common causes of **hypoxic polycythemia** . Clinical findings usually include cyanosis, hyperemia of the sclerae and mucous membranes, and clubbing of the fingers. As the hematocrit rises to >65%, clinical manifestations of

hyperviscosity , such as headache and hypertension, may require phlebotomy. Living at high altitudes also causes hypoxic polycythemia; the hemoglobin level increases approximately 4% for each rise of 1,000 m (~3,300 ft) in altitude. Partial obstruction of a renal artery rarely results in polycythemia. Polycythemia has also been associated with benign and malignant tumors that secrete erythropoietin. Exogenous or endogenous excess of anabolic steroids also may cause polycythemia. A common spurious cause is a decrease in plasma volume, as occurs in moderate to severe dehydration.

Diagnosis

See Chapter 493 ; Fig. 493.1 outlines sequential studies to evaluate polycythemia.

Treatment

For mild disease, observation is sufficient. When the hematocrit is >65–70% (hemoglobin >23 g/dL), blood viscosity greatly increases. Periodic phlebotomy may prevent or decrease symptoms such as headache, dizziness, or exertional dyspnea. Apheresed blood should be replaced with plasma or saline to prevent hypovolemia in patients accustomed to a chronically elevated total blood volume. Increased demand for red blood cell production may cause iron deficiency. Iron-deficient microcytic red cells are more rigid, further increasing the risk of intracranial and other thromboses in patients with polycythemia. Periodic assessment of iron status should be performed, and iron deficiency should be treated.

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SECTION 5

The Pancytopenias

OUTLINE

Chapter 495 Inherited Bone Marrow Failure Syndromes With Pancytopenia

Chapter 496 The Acquired Pancytopenias

CHAPTER 495

Inherited Bone Marrow Failure Syndromes With Pancytopenia

Yigal Dror, Michaela Cada

Pancytopenia refers to a reduction below normal values of all 3 peripheral blood lineages: leukocytes, platelets, and erythrocytes. Identifying the etiology of pancytopenia usually requires microscopic examination of the peripheral blood smear, as well as bone marrow biopsy and aspirate specimens to assess overall cellularity and morphology. The 3 general categories of pancytopenia are related to bone marrow pathologies and can frequently be differentiated based on bone marrow findings.

Pancytopenia with hypocellular bone marrow on biopsy is seen with *inherited bone marrow failure syndromes* (IBMFSs) with pancytopenia, *acquired* aplastic anemia of varied etiologies, and the *hypoplastic* variant of *myelodysplastic syndrome* (MDS). **Pancytopenia with cellular bone marrow** is seen with primary bone marrow disease (e.g., acute leukemia, myelodysplasia) and secondary to autoimmune disorders (e.g., autoimmune lymphoproliferative syndrome, systemic lupus erythematosus), vitamin B_{12} or folate deficiency, storage diseases (e.g., Gaucher, Niemann-Pick), overwhelming infection, sarcoidosis, and hypersplenism. **Pancytopenia with bone marrow infiltration** can be seen in metastatic solid tumors, myelofibrosis, hemophagocytic lymphohistiocytosis, and osteopetrosis. It is important to note that exceptions exist with regard to this classification. For example, IBMFSs can manifest as normocellular or hypercellular bone marrow at early stages of presentation or in cases where MDS develops.

Inherited pancytopenias with hypocellular bone marrow are IBMFSs that feature decreased bone marrow production of the 3 major hematopoietic lineages occurring on an inherited basis and resulting in anemia, neutropenia, and thrombocytopenia. It is noteworthy that patients may have single-lineage or bilineage cytopenia at presentation and gradually develop pancytopenia over time. All disorders for which a genetic basis has been deciphered have thus far been shown to be monogenic. Transmission of mutant genes is mendelian and in an autosomal dominant, autosomal recessive, or X-linked manner (Table 495.1). Modifying genes and acquired factors may also be operative. Inherited pancytopenias account for approximately 30% of cases of pediatric bone marrow failure. Fanconi anemia is considered the most common of the inherited pancytopenias.

Table 495.1

Inherited Bone Marrow Failure Syndromes

SYNDROME	INHERITANCE PATTERN	PERIPHERAL BLOOD MANIFESTATIONS	ASSOCIATED MALIGNANT DISEASES	GENE
Fanconi anemia (FA, MIM # 227650)	AR	Pancytopenia	MDS/AML SCC Other tumors	*FANCA*
	XLR			*FANCB*
	AR			*FANCC*
	AR			*FANCD1/BRCA2*
	AR		AML Wilms tumor Medulloblastoma	*FANCD2*
	AR		MDS/AML SCC Other tumors	*FANCE*
	AR			*FANCF*
	AR			*FANCG/XRCC*
	AR			*FANCI*
	AR			*FANCJ/BACH1/BRIP1*
	AR			*FANCL*
	AR			*FANCM*
	AR		Wilms tumor Medulloblastoma	*FANCN/PALB2*
	AR		?	*FANCO/RAD51C*
	AR		?	*FANCP/* SLX4
Dyskeratosis congenita (DC)	XLR (MIM # 305000)	Pancytopenia	MDS/AML SCC Other tumors	*DKC1*
	AD (MIM # 127550)			*TERC*
	AD (MIM # 613989)			*TERT*
	AD (MIM # 613990)		Unknown	*TINF2*
	AR (MIM # 224230)		Unknown	*NOP10/NOLA3*

	AR (MIM # 613987)		Unknown	*NHP2/NOLA2*
	AR (MIM # 613988)		Unknown	*WDR79/TCAB1/WRAP53*
	AR (MIM # 612199)		Unknown	*CTC1*
	AR (MIM # 615190)		Unknown	*RTEL1*
Shwachman-Diamond syndrome (SDS, MIM # 260400)	AR	Neutropenia with progression to pancytopenia	MDS/AML	*SBDS*
Cartilage-hair hypoplasia (CHH, MIM # 250250)	AR	Neutropenia Lymphopenia Anemia	Lymphoma Basal cell carcinoma	*RMRP*
Pearson marrow-pancreas syndrome (PS, MIM # 557000)	Mitochondrial	Neutropenia with progression to pancytopenia	None	mtDNA deletion
Diamond-Blackfan anemia (DBA, MIM # 105650)	AR	Anemia with rare progression to pancytopenia	MDS/AML* Osteosarcoma	*RPS19*
				RPS24
				RPS17
				RPS10
				RPS26
				RPS7
				RPS29
				RPL35a
				RPL5
				PRL11
				RPL26
				RPL15
	XLR	Anemia and neutropenia		*GATA1*
Hyper-IgM immunodeficiency syndrome (XHIM, MIM # 308230)	XLR	Neutropenia Pancytopenia	None reported	*CD40LG (HIGM1)*
Congenital amegakaryocytic thrombocytopenia (CAMT, MIM #60448)	AR	Thrombocytopenia with progression to pancytopenia	AML	*c-MPL*
Amegakaryocytic thrombocytopenia with radioulnar	AD	Thrombocytopenia with progression to pancytopenia	AML	*HOXA11*

synostosis (ARTUS, MIM # 605432)				
RARE FORMS OF INHERITED BONE MARROW FAILURE SYNDROMES				
Nijmegen breakage syndrome (NBS, MIM # 251260)	AR	Pancytopenia	AML Lymphoma	*NSB1*
DNA ligase IV syndrome (LIG4, MIM # 606593)	AR	Pancytopenia	Leukemia	*LIG4*
Seckel syndrome (SCKL1, MIM # 210600)	AR	Pancytopenia (not genetically subtyped)	Leukemia Lymphoma Oropharyngeal cancer (not genetically subtyped)	*ATR* *SKC1*
				PCNT *SCKL4*
	AR			*CENPJ SCKL4*
	AR			*CEP152* *SCKL5*
	AR			*CtIP/RBBP8* *SCKL2*
	AR			*ATRIP*
Dubowitz syndrome (MIM %223370)	AR	Pancytopenia	Leukemia Lymphoma Neuroblastoma Cancer	Unknown
Schimke syndrome (SIOD, MIM # 242900)	AR	Pancytopenia	Lymphoma	*SMARCAL1*
Duncan/Purtilo syndrome (XPL, MIM # 308240)	XLR	Pancytopenia	EBV lymphoma	*SH2D1A/SAP*

[*] No specific ribosomal gene mutation has been associated with AML/MDS.

AML , Acute myeloid leukemia; *AR,* autosomal recessive; *AD,* autosomal dominant; *ATR,* ataxia-telangiectasia and Rad3 related; EBV, Epstein-Barr virus; *GCSF,* granulocyte colony-stimulating factor; *MDS,* myelodysplastic syndrome, myelodysplasia; MIM #, *Mendelian Inheritance in Man* with responsible gene identified; MIM %, *Mendelian Inheritance in Man* with responsible gene not identified; SCC, squamous cell carcinoma; *XLR,* X-linked recessive.

Adapted from *Nathan and Oski's hematology and oncology of infancy and childhood,* ed 8, vol 1, Philadelphia, 2015, Elsevier (Table 7.1, p 183).

Fanconi Anemia

Etiology and Epidemiology

Fanconi anemia (FA) is a rare multisystem hereditary disorder resulting in the development of bone marrow failure in those affected and a predisposition to malignancy, including myelodysplasia (MDS), acute myeloid leukemia (AML), and epithelial cancers. Individuals with FA often have congenital malformations and high sensitivity to alkylating agents and radiation. The estimated frequency of FA is 1 in 200,000 in most populations but is higher in Ashkenazi Jews (1 : 30,000) and Afrikaners (1 : 22,000). Carrier frequency is approximately 1 : 200-300 in most populations. Currently, mutations in 21 genes, designated *FANC* genes, have been reported to cause FA or FA-like disease. All these mutations except for one are inherited in an autosomal recessive manner. One uncommon form is X-linked recessive. FA occurs in all racial and ethnic groups. At presentation, patients may have typical physical anomalies and abnormal hematologic findings (majority of patients), normal physical features but abnormal hematologic findings (about one third of patients), or physical anomalies and normal hematologic findings (unknown percentage of patients). There can be sibling discordance in clinical and hematologic manifestations, even in affected monozygotic twins.

Pathology

All FA genes code for proteins that play roles in various cellular pathways and most prominently in DNA cross linking and repair. Patients with FA have faulty DNA repair and increased chromosomal fragility caused by DNA interstrand cross-linking agents such as diepoxybutane (DEB) and mitomycin C (MMC). Cell fusion of FA cells with normal cells or with cells from some unrelated patients with FA produces a corrective effect on chromosomal fragility, a process called *complementation.* This process was often used in the past to screen for a patient's mutated gene, before next-generation gene panels that include the known FA genes became widely available. The classic FA phenotype that clearly defined the FA-associated genes (*FANCA, FANCB, FANCC, FANCD1/BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ/BACH1/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCP/SLX4, FANCQ/ERCC4, UBE2T, REV7*) includes the triad of **bone marrow failure** , **congenital anomalies** , and **elevated chromosome fragility** . These genes can be mutated in patients who have one or all of the components of the triad. Genes that were found to be associated with 1 or 2 but not all 3 of the components are **FA-like genes** (*FANCO/RAD51C, RAD51*, *FANCS/BRCA1*, *FANCR/EXCC2*). *FANCA* accounts for approximately 64% of FA cases, *FANCC* for 14%, and *FANG* for 9%. *FANCB* , *FANCD1* /*BRCA2* , *FANCD2* , *FANCE,* and *FANCF* are collectively mutated in almost 13% of FA patients. The remaining genes are mutated in rare cases.

The proteins encoded by wild-type *FANC* genes are involved in the DNA damage recognition and repair biochemical pathway. Therefore, mutant proteins lead to genomic instability and chromosome fragility. FANC proteins are involved in other cellular activities, such as reactive oxygen species detoxification, energetic metabolism, and cytokine signaling. Thus, FANC mutations likely affect several cellular and biochemical roles of the respective proteins, which eventually leads to the FA phenotype. The observed disease complexity and heterogeneity is likely caused by the involvement of multiple cellular and biochemical pathways both in unrelated individuals and in family members with the same genetic mutation.

Clinical Manifestations

The most common congenital anomalies in FA are skeletal and include absence of radii and/or thumbs that are hypoplastic, supernumerary, bifid, or absent. Anomalies of the feet, congenital hip dislocation, and leg abnormalities can also be seen (Fig. 495.1 and Table 495.2). Skin hyperpigmentation of the trunk, neck, and intertriginous areas, café-au-lait spots, and vitiligo, alone or in combination, occur with similar frequency. Short stature is common and in some patients is aggravated by subnormal growth hormone (GH) secretion or hypothyroidism. Male patients with FA may have an underdeveloped penis, undescended, atrophic, or absent testes, and hypospadias or phimosis, and all are infertile. Females can have malformations of the vagina, uterus, and ovary, and all have reduced fertility. Many patients have characteristic facial dysmorphisms, including microcephaly, small eyes, epicanthal folds, and abnormal shape, size, or positioning of the ears (Fig. 495.1*B*). Kidneys may be ectopic, pelvic, horseshoe shaped, hypoplastic, dysplastic, or absent. Cardiovascular and gastrointestinal (GI) malformations also occur. Approximately 10% of patients with FA are cognitively delayed. Neonates with FA usually have intrauterine growth restriction and low birthweight and may show malformations consistent with VACTERL/VACTERL-H association (vertebral anomalies, anal atresia, cardiac malformations, tracheoesophageal fistula with esophageal atresia, renal and limb structural abnormalities with hydrocephalus).

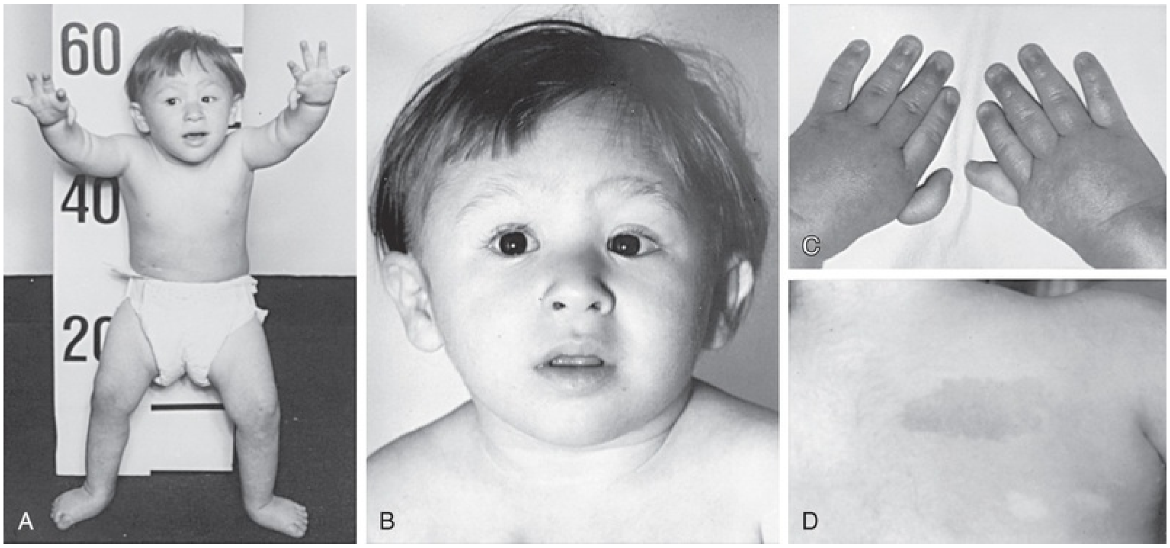

FIG. 495.1 A 3 yr old boy with Fanconi anemia who exhibits several classic phenotypic features. A, Front view. B, Face. C, Hands. D, Back right shoulder. The features to be noted include short stature, dislocated hips, microcephaly, a broad nasal base, epicanthal folds, micrognathia, thumbs attached by a thread, and café-au-lait spots with hypopigmented areas beneath. (From Nathan DC, Orkin SH, Ginsburg D, et al, editors: *Nathan and Oski's hematology of infancy and childhood,* ed 6, vol I, Philadelphia, 2003, Saunders, p 285.)

Table 495.2

Specific Types of Anomalies in Fanconi Anemia*

SKIN (40%)

Generalized hyperpigmentation on the trunk, neck, and intertriginous areas; café-au-lait spots; hypopigmented areas

BODY (40%)

Short stature, delicate features, small size, underweight

UPPER LIMBS (35%)

Thumbs (35%): absent or hypoplastic; supernumerary, bifid, or duplicated; rudimentary; short, low set, attached by a thread; triphalangeal, tubular, stiff, hyperextensible

Radii (7%): absent or hypoplastic (only with abnormal thumbs); absent or weak pulse

Hands (5%): clinodactyly; hypoplastic thenar eminence; 6 fingers; absent 1st

EYES (20%)

Small eyes, strabismus, epicanthal folds, short or almond-shaped palpebral fissures, hypertelorism, ptosis, slanting, cataracts, astigmatism, blindness, epiphora, nystagmus, proptosis, small iris

EARS (10%)

Deafness (usually conductive); abnormal shape; atresia; dysplasia; low set, large, or small; infections; abnormal middle ear; absent eardrum; dimples; rotated; canal stenosis

KIDNEY (20%)

Ectopic or pelvic; abnormal, horseshoe, hypoplastic, or dysplastic; absent; hydronephrosis or hydroureter; infections; duplicated; rotated; reflux; hyperplasia; no function; abnormal artery

GASTROINTESTINAL SYSTEM (5%)

High-arched palate, atresia (esophagus, duodenum, jejunum), imperforate anus, tracheoesophageal fistula, Meckel diverticulum, umbilical hernia, hypoplastic uvula, abnormal biliary ducts, megacolon, abdominal diastasis, Budd-Chiari syndrome

UROGENITAL

metacarpal; enlarged, abnormal fingers; short fingers; transverse crease Ulnae (1%): dysplastic or absent **LOWER LIMBS (5%)** Feet: toe syndactyly, abnormal toes, flat feet, short toes, clubfeet, 6 toes, supernumerary toe Legs: congenital hip dislocation, Perthes disease, coxa vara, abnormal femur, thigh osteoma, abnormal legs **GONADS** Males (25%): hypogenitalia, undescended testes, hypospadias, abnormal genitalia, absent testis, atrophic testes, azoospermia, phimosis, abnormal urethra, micropenis, delayed development Females (2%): hypogenitalia; bicornuate uterus; abnormal genitalia; aplasia of uterus and vagina; atresia of uterus, vagina, and ovary **OTHER SKELETAL ANOMALIES** Head (20%) and face (2%): microcephaly, hydrocephalus, micrognathia, peculiar face, birdlike face, flat head, frontal bossing, scaphocephaly, sloped forehead, choanal atresia, dental abnormalities Neck (1%): Sprengel deformity; short, low hairline; webbed Spine (2%): spina bifida (thoracic, lumbar, cervical, occult sacral), scoliosis, abnormal ribs, sacral agenesis, sacrococcygeal sinus, Klippel-Feil syndrome, vertebral anomalies, extra vertebrae	Males (25%): micropenis, penile-scrotal fusion, undescended or atrophic or absent testes, hypospadias, chordae, phimosis, azoospermia Females (2%): bicornuate uterus, aplasia or hypoplasia of vagina and uterus, atresia of vagina, hypoplastic uterus, hypoplastic or absent ovary, hypoplastic fused labia **CARDIOPULMONARY SYSTEM (6%)** Patent ductus arteriosus, ventricular septal defect, abnormal heart, peripheral pulmonic stenosis, aortic stenosis, coarctation, absent lung lobes, vascular malformation, aortic atheromas, atrial septal defect, tetralogy of Fallot, pseudotruncus, hypoplastic aorta, abnormal pulmonary drainage, double aortic arch, cardiac myopathy **CENTRAL NERVOUS SYSTEM (3%)** Hyperreflexia, Bell palsy, CNS arterial malformation, moyamoya syndrome, Arnold-Chiari malformation, stenosis of internal carotid artery, small pituitary gland, absent corpus callosum Slow development (10%)

[*] Abnormalities are listed in the approximate order of frequency within each category.

Adapted from Shimamura A, Alter BP: Pathophysiology and management of inherited bone marrow failure syndromes, *Blood Rev* 24:101–122, 2010.

Bone marrow failure usually appears within the 1st decade of life. Thrombocytopenia, red blood cell (RBC) macrocytosis, and increased hemoglobin F, as a result of bone marrow stress, often appear first. At these stages, bone marrow aspirate and biopsy often show a hypoplastic specimen. Subsequently, patients develop neutropenia and then anemia. Severe aplasia develops in most cases, usually over a few years.

Complications

In addition to the low blood counts and physical anomalies, patients with FA have a high risk of developing cancer. The most frequent solid tumors are *squamous cell carcinomas* (SCCs) of the head and neck (600-fold higher risk than the general population) and carcinoma of the upper esophagus (2000-fold higher risk), the vulva (3000-fold higher risk), and/or anus, cervix, and lower esophagus. Onset of solid-tumor malignancy is much sooner than that seen in the general population, with median age of onset of SCC in the FA population occurring at 33 yr, vs 60-70 yr in the general population. Human papillomavirus (HPV) is suspected in the pathogenesis of SCC. Benign and malignant liver tumors can occur (adenomas, hepatomas) and are usually associated with androgen therapy for aplastic anemia. Androgens are also implicated in the etiology of peliosis hepatis (blood-filled hepatic sinusoids), which is reversible when androgen therapy is discontinued. Clonal bone marrow cytogenetic abnormalities are common in FA and on follow-up can either be stable, intermittently detected, or progressive. The cumulative incidence of clonal and malignant myeloid transformation by age 18 yr, which includes clonal cytogenetic marrow abnormalities, MDS, and AML, is approximately 75%. A 2003 study indicated that by age 40 yr, the cumulative incidence of leukemia is 33%.

Diagnosis

FA should be considered in all children and young adults with unexplained cytopenias. Abnormal hematologic findings and characteristic physical anomalies suggest the diagnosis, which can be confirmed with lymphocyte chromosomal breakage study done with and without the addition of cross-linking agents such as DEB and MMC. Increased chromosome fragility is indicated by spontaneously occurring chromatid breaks, rearrangements, gaps, endoreduplications, and chromatid exchanges in blood lymphocytes cultured with phytohemagglutinin, as well as in cultured skin fibroblasts, underscoring the constitutional nature of FA. With addition of DEB or MMC, fragility is strikingly enhanced in lymphocyte cultures of patients with FA compared with those of controls. Abnormal chromosome breakage analysis and genetic testing for prenatal diagnosis can be performed on amniotic fluid cells or on tissue from a chorionic villus biopsy. No other inherited pancytopenia is associated with a prominent in vitro hypersensitivity to DEB or MMC by the chromosomal breakage study. From 10–15% of patients with suspected FA have *somatic* *mosaicism* and may not show the characteristically high degree of chromosomal fragility in their lymphocytes, reflecting the presence of mixed populations of somatic cells, some with 2 abnormal alleles and some with only 1. The latter population of lymphocytes derives from a portion of hematopoietic stem cells (HSCs) that underwent spontaneous somatic gene correction on one allele. Testing of skin fibroblasts should be performed if the suspicion of FA is high despite negative testing on peripheral blood lymphocytes.

Because of the large number of *FANC* genes, genetic diagnosis has traditionally been started with complementation testing, determining whether cellular hypersensitivity to cross-linking agents is reduced or eliminated after generating a hybrid of the patient cells with known genetic complementation cells or after transducing patient cells with a known *FANC* wild-type gene. The mutant allele is diluted when the wild-type *FANC* gene of the same complementation group is introduced by these methods, resulting in the correction of the abnormal chromosome fragility initially observed in the patient. Next-generation sequencing (NGS) has largely replaced the need for 2-step genetic testing (complementation group testing followed by targeted gene testing) and is most often used. NGS is an efficient and accurate method for diagnosing FA but can occasionally be limited by difficulties in interpreting previously unreported variants. When no definite causative variants are found, high-resolution copy number variation analysis techniques can be employed, followed by a genome-wide search for novel associated genes.

Extensive screening for potential medical problems is necessary after the diagnosis of FA is established. Imaging using radiation should be minimized as much as possible because of the carcinogenic risk inherent to this genetic instability disease; MRI should replace CT whenever possible. In addition to detailed review of the past medical history and thorough physical examination, the screen should include ultrasonographic examination of the abdomen and echocardiography to rule out internal congenital anomalies. Other imaging may be done as deemed necessary and based on the initial screen. Subspecialty consultations for anomalies and disabilities that have been identified can be arranged during this interval. If growth velocity is below expectations, endocrine evaluation is needed to assess for GH deficiency. Blood work should include evaluation of renal, liver, thyroid, metabolic, and immune systems.

Treatment

Whenever possible, a hematologist, preferably one who specializes in IBMFSs, with a multidisciplinary team should manage patients with FA. At diagnosis, a detailed assessment of the patient's blood counts, bone marrow function, growth, development, and other organ function should be carried out. Special research modalities are necessary to evaluate the cost-benefit of surveillance tools in rare disorders such as FA. However, the following tests are widely applied and are recommended.

If hematologic abnormalities are mild to moderate and stable and there is no transfusion requirement, patients can be observed closely with peripheral blood counts every 3 mo and bone marrow aspiration surveillance every year for clonal cytogenetic abnormalities, MDS, and AML. Bone marrow biopsy might also be intermittently done during bone marrow testing to evaluate changes in percentage of cellularity and fibrosis. More frequent monitoring can be applied when deemed necessary, as when a decline in blood counts occurs. Glucose levels should be performed annually or biannually, depending on the degree of hyperglycemia found on initial testing. Screening for hypothyroidism should be performed yearly. Patients should be assessed for solid tumors at least annually, with a careful physical examination that includes comprehensive inspection of the skin, oral cavity, and other organs for unusual masses. After a certain age (e.g., 10 yr) or after hematopoietic stem cell transplantation (HSCT), fluoroscopic examination of the orolaryngeal cavity and occult fecal blood testing are also recommended. Beginning at menarche, female patients should be screened annually for gynecologic cancer. Administration of HPV quadrivalent vaccine to decrease the risk of SCC is advised.

Chromosome fragility (and/or targeted genetic testing) should be offered to siblings and parents of affected patients for identification of other affected individuals. Human leukocyte antigen (HLA) typing of patient, biological parents, and full siblings for future HSCT should also occur early.

HSCT is the only curative therapy for the hematologic abnormalities observed in FA patients. Outcomes have improved significantly over the last 2 decades because of modified reduced-intensity regimens, which have decreased the toxicities experienced by FA patients, who have high sensitivity to DNA-damaging agents such as alkylating drugs and irradiation. Those who undergo transplant using an HLA-identical sibling donor without irradiation in the preparative regimen have an overall 3-5 yr survival rate of >80%. The overall survival of FA patients transplanted with a fully matched *unrelated* donor is 65–70%. Those transplanted before they receive multiple transfusions or develop clonal and malignant myeloid transformation (MDS or AML) do better. Survival rates are higher for patients who undergo transplant at <10 yr of age. Improvement in high-resolution HLA typing has led to better unrelated-donor selection and improved outcomes. Molecular technology has led to preimplantation genetic diagnosis on parent-derived blastomeres, allowing for the unaffected ones to be implanted and resulting in the creation of an HLA-matched sibling donor without FA.

Androgens produce a response in approximately 70% of patients, heralded by reticulocytosis and a rise in hemoglobin within 1-2 mo. White blood cell (WBC) counts may increase next, followed by platelet counts. After the initial response is seen, counts may continue to improve over many months until a maximum response is achieved. If a low dose is initially employed, the androgen dose can be increased every 3-4 wk as long as no major side effects are seen and until the desired response is achieved. If a high dose is initially employed, androgen dosage can be slowly reduced to the minimum dose that maintains the required blood counts. Oral oxymetholone and danazol are the 2 most commonly used androgenic drugs. Patients typically stop responding to androgens after several months or years, as their bone marrow failure progresses or as they develop MDS or AML. Thus, androgen therapy is not curative but is used rather as a bridge while waiting for a suitable donor for HSCT or while weighing the risks and benefits of transplant. Side effects of androgens include masculinization, increased linear growth, increased mood swings or aggressiveness, elevated hepatic enzymes, cholestasis, peliosis hepatis, and liver tumors. Screening for these should be performed regularly.

The potential for recombinant growth factor (cytokine) therapy for FA has not been defined. Granulocyte colony-stimulating factor (G-CSF) can usually induce an increase in the absolute neutrophil count; however, there may be a heightened risk of expansion of bone marrow cells with clonal cytogenetic abnormalities such as monosomy 7. In one study, combination therapy consisting of G-CSF given subcutaneously daily or every 2 days along with erythropoietin given subcutaneously or intravenously 3 times per week resulted in improved neutrophil counts in most patients and a sustained rise in hemoglobin and platelet levels in approximately one third of patients. Most patients lost the response due to progression of bone marrow disease.

Prognosis

Improvements in supportive care, careful surveillance of known complications, prompt intervention, and improved transplant techniques have resulted in patients with FA surviving into their 30s. Unfortunately, there is an increased risk of solid tumors after HSCT. For example, head and neck cancer risk is increased 4.4-fold and is accelerated by approximately 15 yr compared to nontransplanted patients. The cumulative incidence of malignancy 20 yr after transplant is 35–40%.Some of the increased risk might be attributed to the use of DNA-damaging agents or the occurrence of graft-versus-host disease (GVHD).

Shwachman-Diamond Syndrome

Etiology and Epidemiology

Shwachman-Diamond syndrome (SDS) is inherited in an autosomal recessive manner and occurs in all racial and ethnic groups. As with FA, SDS is a multisystem disorder. However, the nonhematologic manifestations of SDS are substantially different and usually include exocrine pancreatic insufficiency and skeletal abnormalities such as metaphyseal dysplasia (Table 495.3). SDS is a **ribosomopathy** , and the underlying defect is in ribosome assembly. There is no increased chromosomal breakage after DEB testing of SDS lymphocytes.

Table 495.3

Major Clinical Features of Shwachman-Diamond Syndrome

CLINICAL FEATURE	TOTAL/AVERAGE
Number of patients	225
Hematologic *	
Neutropenia	90%
Severe (≤500/μL)	46%
Anemia	46%
Thrombocytopenia	42%
Pancytopenia	21%
Gastrointestinal	
Exocrine pancreatic insufficiency*	98%
Liver (elevated transaminases)	61%
Skeletal abnormalities	70%
Metaphyseal dysostosis	53%
Rib cage abnormalities	35%
Short stature (<3rd percentile)	66%

* Hematologic abnormalities and exocrine pancreatic insufficiency are defining features of SDS, thus the near-100% incidence of these findings.

Data from Ginzberg H, Shin J, Ellis L, et al: Shwachman syndrome: phenotypic manifestations of sibling sets and isolated cases in a large patient cohort are similar, *J Pediatr* 135:81–88 1999; Cipolli M, D'Orazio C, Delmarco A, et al: Shwachman's syndrome: pathomorphosis and long-term outcome, *J Pediatr Gastroenterol Nutr* 29:265–272, 1999; and Kuijpers TW, Alders M, Tool AT, et al: Hematologic abnormalities in Shwachman-Diamond syndrome: lack of genotype-phenotype relationship, *Blood* 106:356–361 2005.

Pathology

Three genes have been linked to SDS. *SBDS* is the 1st gene that was described to be mutated in SDS in 2003. *SBDS* maps to chromosome 7q11 and accounts for 80–90% of SDS cases. *SBDS* plays a role in the late stage of the pre-60S ribosome subunit maturation, binding to the *EFL1* GTPase and facilitating the release of eIF6 to enable 80S monosome formation. *DNAJC21* is the 2nd reported SDS gene. The function of the human *DNAJC21* , and its homolog in *Saccharomyces cerevisiae*, Jjj1, is required for the release and recycling of the Arx1/Alb1 heterodimer from the pre-60S biogenesis factors. The 3rd SDS gene discovered is *EFL1* . The underlying genetic defects of SDS indicate that the last step in ribosome biogenesis is associated with pancytopenia (most often neutropenia) and a hypoplastic bone marrow. Defects in ribosomal proteins that are involved in earlier stages of ribosome subunit maturation and are structural components of the ribosome are associated with predominantly anemia and pure red cell aplasia.

Pancreatic insufficiency is caused by failure of pancreatic acinar development in SDS, and fatty replacement of pancreatic tissue is prominent. **Bone marrow failure** is characterized by dysfunctional HSCs, accelerated apoptosis of bone marrow progenitors, and a defective bone marrow microenvironment that does not support and maintain normal hematopoiesis.

Clinical Manifestations

Most patients with SDS have symptoms of fat malabsorption from birth that are caused by pancreatic insufficiency, but steatorrhea is not always obvious. Approximately 50% of patients appear to exhibit an improvement in pancreatic enzyme secretion as they age. The clinical picture can be dominated by complications from anemia, neutropenia, or thrombocytopenia. Bacterial and fungal infections secondary to neutropenia, neutrophil dysfunction, and immunodeficiency can occur. Short stature is a consistent feature of SDS. Most patients show normal growth velocity, yet remain consistently below the 3rd percentile for height and weight. The occasional SDS adult achieves the 25th percentile for height. Although skeletal abnormalities are variable, classic findings are metaphyseal dysplasia, osteopenia, delayed appearance of secondary ossification centers, short or flared ribs, and thoracic dystrophy. Some patients have hepatomegaly and elevations of liver enzymes. Most patients have dental abnormalities and poor oral health. Many have neurocognitive problems and poor social skills.

Laboratory Findings

Pancreatic insufficiency in SDS is associated with reduced age-adjusted serum trypsinogen and pancreatic isoamylase levels. Since serum pancreatic isoamylase is physiologically low in the 1st 3 yr of life, and reduced serum trypsinogen is typically seen in young infants and improves with age, testing both enzymes is helpful. Fecal elastase is often reduced in SDS patients. Fat-soluble vitamin (A, D, E, and K) absorption is impaired, and thus measurement of vitamin A, D, and E levels as well as prothrombin time is helpful to assess consequences of fat malabsorption. Ultrasound or CT scan can visualize fatty replacement of pancreatic tissue. Fat malabsorption can be proven by assay on a 72 hr stool collection. Pancreatic function tests show greatly impaired enzyme secretion, but with preservation of ductal function. The latter test is rarely performed and has largely been replaced with serum and fecal enzyme assays and pancreatic imaging.

Neutropenia is observed in about 70% of patients with SDS at presentation and is seen in almost 100% of patients on follow-up. It is chronic but can be persistent or intermittent and mild, moderate, or severe. It has been identified in some neonates during an episode of sepsis. Neutrophils may have a defect in mobility, migration, and chemotaxis because of alterations in neutrophil cytoskeletal or microtubular function. Anemia, thrombocytopenia, and pancytopenia are seen in 40–66%, 40–60%, and 21–44% of cases, respectively. Pancytopenia can be severe as a result of full-blown aplastic anemia. Bone marrow biopsy specimens and aspirates show varying degrees of bone marrow hypoplasia and fat infiltration. However, at a young age or when patients develop MDS or leukemia, the bone marrow can be normocellular or even hypercellular. Patients may also have B-cell defects with 1 or more of the following: low immunoglobulin G or IgG subclasses, low percentage of circulating B lymphocytes, decreased in vitro B-cell proliferation, and lack of specific antibody production. Patients may have a low percentage of circulating T cells, subsets, or natural killer cells and decreased in vitro T-cell proliferation.

Diagnosis

The clinical diagnosis of SDS relies on having evidence of bone marrow dysfunction and exocrine pancreatic insufficiency. However, up to 20% of patients lack clear evidence of exocrine pancreatic defects at diagnosis. Therefore, it is recommended that all patients with hypoplastic/aplastic bone marrow of unknown etiology be considered for SDS genetic testing. Mutational analysis for *SBDS* , *DNAJC21* , and *EFL1* are definitive in all or almost all cases of SDS. **Pearson syndrome** , consisting of refractory sideroblastic anemia, cytoplasmic vacuolization of bone marrow precursors, metabolic acidosis, exocrine pancreatic insufficiency, and a diagnostic mitochondrial DNA mutation, is similar to SDS, but the clinical course, morphologic features of the bone marrow, and gene mutation are different. Also, severe anemia requiring transfusion, rather than neutropenia, is present in Pearson syndrome from birth to 1 yr of age. SDS shares some manifestations with **Fanconi anemia** , such as bone marrow dysfunction and growth failure, but patients with SDS are readily distinguished because of pancreatic insufficiency with fat malabsorption, fatty changes within the pancreatic body visualized by imaging, characteristic skeletal abnormalities not seen in FA, and a normal chromosomal breakage study with DEB and MMC. Distinguishing SDS from **dyskeratosis congenita** may not be possible based solely on clinical findings and pancreatic enzyme levels, and telomere length measurement may facilitate a correct diagnosis.

In difficult cases of IBMFSs that cannot be easily classified, comprehensive genetic testing using an NGS panel of all known IBMFS genes or unbiased testing using whole exome/genome sequencing are likely to assist in establishing a diagnosis.

Complications

Patients with SDS are predisposed to MDS and leukemic transformation. Approximately 25% of patients develop clonal marrow cytogenetic abnormalities, MDS, or leukemia by age 18 yr. About one third of patients have been reported to develop leukemia by age 30 yr. Isochromosome 7q[i(7q)] is particularly common, suggesting that it is a fairly specific clonal marker of SDS and might be related to the presence of mutant *SBDS* on 7q11. Other clonal chromosome abnormalities include monosomy 7, i(7q) combined with monosomy 7, deletions or translocations involving part of 7q, and deletions of 20q [Del(20q)]. The i(7q) and del(20q) are associated with relatively low risk and very slow progression to MDS or leukemic transformation; however, their prognostic significance and that of other bone marrow clonal changes require further prospective monitoring.

Treatment

Fat malabsorption responds to oral pancreatic enzyme replacement and supplemental fat-soluble vitamins, administered according to guidelines similar to those for cystic fibrosis. A long-term plan should be initiated to monitor changes in peripheral blood counts that require corrective action and to look for early evidence of malignant myeloid transformation. The latter requires periodic bone marrow aspirations for smears and cytogenetic testing and bone marrow biopsy. One recommendation is to perform bone marrow testing every 1-3 yr and complete blood counts every 3 mo.

Daily *subcutaneous G-CSF* for profound neutropenia is effective in inducing a sustained increase in neutrophils. Some patients require transfusion support for management of severe anemia or thrombocytopenia. Experience with erythropoietin is limited. In some patients who received androgens plus steroids, blood counts have improved.

The only curative option for severe bone marrow failure and advanced MDS or leukemia in SDS is allogeneic HSCT, although experience has been limited. Traditional myeloablative HSCT results in treatment-related mortality in 35–50% of patients. Reduced-intensity conditioning regimens that incorporate *fludarabine* appear to be safer and are effective for SDS HSCT. Results of treatment for advanced MDS and AML are generally limited, and outcome is typically poor.

Prognosis

The accurate life expectancy of SDS patients is unknown; analysis of published cases revealed a median survival of 35 yr. Since the number of undiagnosed patients with mild or asymptomatic disease is not known, the overall prognosis may be better than previously thought. Approximately 50% of patients experience spontaneous conversion from pancreatic insufficiency to pancreatic sufficiency as a result of improvement in pancreatic enzyme secretion. Although all patients have some degree of hematologic cytopenia at diagnosis, the changes in most patients are mild to moderate and do not require therapeutic intervention. Severe neutropenia responds well to G-CSF, but there is concern that G-CSF may promote the growth of evolving MDS or leukemia clones because of the agent's powerful growth stimulus on bone marrow cells. HSCT for severe bone marrow failure has produced a 50–70% survival rate, but safer protocols are being introduced. Malignant bone marrow transformation remains ominous.

Dyskeratosis Congenita

Etiology and Epidemiology

Dyskeratosis congenita (DC) is an inherited multisystem telomere disorder. A diagnostic triad of mucocutaneous features was proposed when the disorder was first described and included **dysplastic nails** , lacy **reticular pigmentation** of the upper chest and/or neck, and **oral leukoplakia** (Fig. 495.2). *However, the triad is not present in all individuals.* If it occurs, skin and nail findings usually become apparent in the 1st 10 yr of life, whereas oral leukoplakia may be noticed later. Manifestations tend to progress as patients age. Varying degrees of bone marrow failure are seen in approximately 90% of patients. Severe aplastic anemia occurs in approximately 50% of cases, with the age of onset varying according to the genetic group. In some genetic groups the disease usually starts in the 1st decade of life (e.g., *DKC1* , *TINF2, PARN*), whereas in others it typically starts after the 1st decade (e.g., *TERT, TERC*). In addition to progressive bone marrow failure, patients with DC are also at high risk of pulmonary and hepatic fibrosis, other congenital anomalies, and a predisposition to solid tumors and MDS or AML. DC is rare, with an incidence in childhood of approximately 4 cases per 1 million population per year.

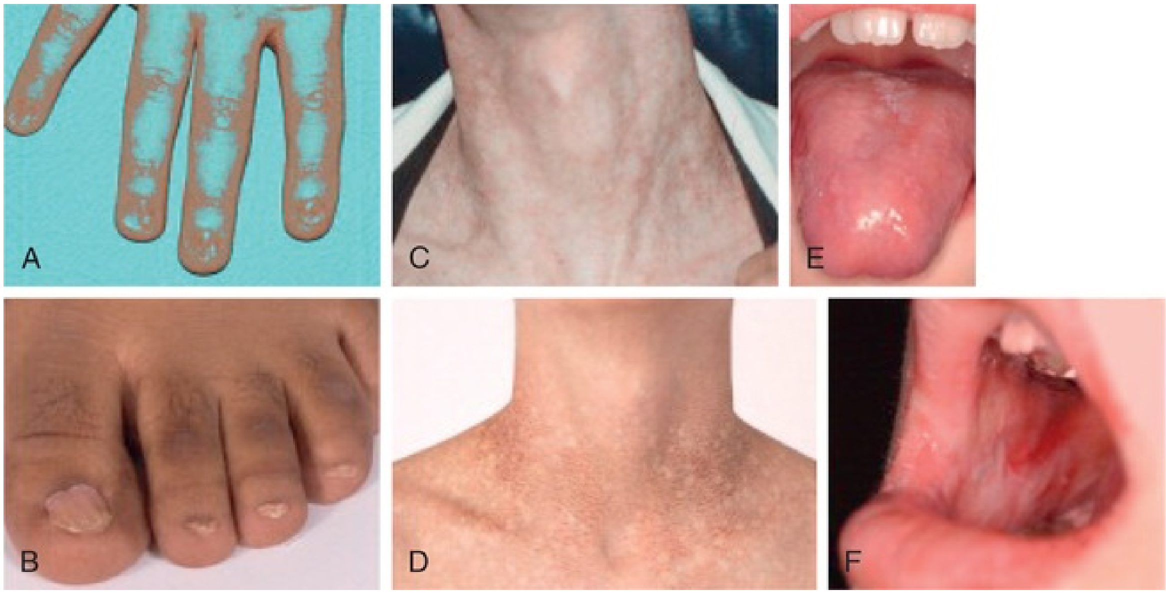

FIG. 495.2 Features of the diagnostic triad in dyskeratosis congenita. A and B, Dystrophic nails on hands and feet. C and D, Lacy reticular pigmentation on neck and upper thorax. E and F, Oral leukoplakia on tongue and buccal mucosa. (*A-C* and *E* , From Shimamura A, Alter BP: Pathophysiology and management of inherited bone marrow failure syndromes, *Blood Rev* 24:101–122, 2010, Fig 8; *D* and *F* , from Savage SA, Alter BP: Dyskeratosis congenital, *Hematol Oncol Clin North Am* 23:215–231, 2009).

Pathology

DC is genetically heterogeneous, and patients have mutations in genes that encode components of the telomerase complex (*TERT* , *DKC1* , *TERC* , *NOP* 10, and *NHP* 2), the T-loop disassembly protein (*RTEL1*), the telomere-capping complex (*CTC1*, *STN1*), the telomere-shelterin complex (*TINF2*, *ACD*), the telomerase-trafficking protein (*TCAB1/WRAP53*), the deadenylase poly(A)-specific ribonuclease (*PARN*), as well as a recently identified gene with an as-yet unclear role (*NAF1*). All components are critical for telomere maintenance. The **X-linked recessive** form of DC maps to Xq28, and many mutations have been identified in the *DKC1* gene, which codes for the nuclear protein dyskerin. The **autosomal dominant** form of disease is caused by mutations in *TINF2, TERC, TERT, RTEL1, ACD* , and *NAF1*. **Autosomal recessive** DC is linked to mutations in *NOP10, NHP2, PARN, TCAB1/WRAP53, CTC1,* and *STN1,* as well as *TERT, RTEL,* and *ACD* . Because of impaired telomere maintenance in all 3 inherited forms of DC, extremely short telomeres (<1st percentile for age) are demonstrated in the peripheral blood cells of all patients. Finding extremely short telomeres in lymphocytes performed by automated multicolor flow fluorescence in situ hybridization (FISH) has 97% sensitivity and 91% specificity for DC. Approximately 70% of individuals who meet clinical diagnostic criteria of DC have a pathogenic variant in 1 of the known DC-related genes. Mutations in *DKC1* are most common (20–25% of individuals), followed by *TINF2* (12–20% of individuals), *TERC* (5–10% of individuals), *RTEL1* , *TERT*, and *CTC1* . The remainder of the genetic mutations have been described in ≤6 families. Bone marrow failure is likely caused by progressive attrition and depletion of HSCs because of premature senescence, apoptosis, or chromosome instability, which manifests as pancytopenia.

Clinical Manifestations

The clinical criteria for classic DC were first described in 2006 and include the presence of at least 2 of the 4 major features—abnormal skin pigmentation, nail dystrophy, leukoplakia, and bone marrow failure—and 2 or more of the other somatic features known to occur in DC. However, making a diagnosis continues to be challenging, since individuals develop clinical features of DC at variable rates and ages, even within the same family. In approximately 30% of individuals with DC, pathogenic mutations in the known DC-related genes cannot be identified. The spectrum ranges from individuals who develop bone marrow failure first, then years later develop other classic findings such as nail abnormalities, to others who have severe nail problems and abnormalities of skin pigmentation at presentation but normal bone marrow function. In classic disease, skin pigmentation and nail changes typically appear first, usually in the 1st decade of life. Bone marrow failure usually develops within the 1st 2 decades, with 80% of patients developing bone marrow failure by age 30 yr and almost 90% of patients having bone marrow failure at some point in their life.

Lacy reticulated **skin pigmentation** affecting the face, neck, chest, and arms is a common finding (89%). The degree of pigmentation increases with age and can involve the entire skin surface. There may also be a telangiectatic erythematous component. Nail dystrophy of both hands and feet is the next most common finding (88%). It usually starts with longitudinal ridging, splitting, or pterygium formation and may progress to complete nail loss. **Leukoplakia** usually involves the oral mucosa (78%), especially the tongue, but may also be seen in the conjunctiva and the anal, urethral, or genital mucosa. Excessive tearing (**epiphora**) secondary to nasolacrimal duct obstruction is common and is observed in about 30% of individuals. Approximately 25% of individuals have learning difficulties and/or developmental delay. Hyperhidrosis of the palms and soles, hair loss and graying, dental caries or loss, esophageal stricture, pulmonary disease with reduced diffusion capacity and/or a restrictive defect due to pulmonary fibrosis and abnormalities in pulmonary vasculature, and short stature are each seen in approximately 15–20% of individuals.

Ocular abnormalities include conjunctivitis, blepharitis, loss of eyelashes, strabismus, cataracts, and optic atrophy. **Skeletal** abnormalities include osteoporosis, avascular necrosis of the hips or shoulders, abnormal bone trabeculation, scoliosis, and mandibular hypoplasia. **Genitourinary** abnormalities include hypoplastic testes, hypospadias, phimosis, urethral stenosis, and horseshoe kidney. **Gastrointestinal** findings, such as vascular lesions causing bleeding, hepatomegaly, peptic ulceration, and fibrosis, are seen in 10% of cases.

Laboratory Findings

The initial hematologic change in DC is usually thrombocytopenia, anemia, or both, followed by pancytopenia and aplastic anemia. The red cells are often macrocytic, and the fetal hemoglobin is elevated. Initial bone marrow specimens may be normocellular or hypercellular, but with time, a symmetric depletion of all hematopoietic lineages ensues. Some patients have immunologic abnormalities, including reduced or elevated immunoglobulin values, decreased B- and/or T-lymphocyte counts, and reduction or absence of lymphocyte proliferative responses to phytohemagglutinin. This is particularly common and severe in the *DKC1* -associated disease. Unlike patients with Fanconi anemia, patients with DC do not have increased chromosomal breakage in phytohemagglutinin-stimulated lymphocytes spontaneously or after exposure to cross-linking agents. However, primary skin fibroblasts in culture have abnormal morphologic features and doubling rate and show numerous unbalanced chromosome rearrangements, such as dicentrics, tricentrics, and translocations, in the absence of DEB or MMC. These findings provide evidence of a defect that predisposes patient cells to chromosomal rearrangements and possibly to DNA damage.

Diagnosis

The following abnormalities are seen in patients with DC but not in those with

Fanconi anemia: nail dystrophy, leukoplakia, tooth abnormalities, hyperhidrosis of the palms and soles, and hair loss. There are several relatively more severe forms of DC. **Hoyeraal-Hreidarsson syndrome** is a multisystem disorder that presents in early childhood, which requires the features of DC along with **cerebellar hypoplasia** to establish the diagnosis. Patients have the classic diagnostic DC triad, in addition to developmental delay, intrauterine growth restriction (IUGR), and bone marrow failure. Hoyeraal-Hreidarsson syndrome is genetically heterogeneous and caused by X-linked recessive mutations in *DKC1* . Some patients may also have severe immunodeficiency. **Revesz syndrome** has many of the features of DC and presents in early childhood. Bilateral exudative retinopathy is required to establish a diagnosis. Patients may also have intracranial calcifications, IUGR, developmental delay, and bone marrow failure. *TINF2* is mutated in Revesz syndrome, making it mostly an autosomal dominant condition, but a few patients have been described without an identified mutation. Individuals with these severe forms of DC have even shorter telomere lengths than those with classic DC. **Coats plus syndrome** is caused by compound heterozygous mutations in the *CTC1* gene and has overlapping features with DC, including sparse and graying hair, dystrophic nails, and anemia. Telomeres are very short. Coats plus syndrome is characterized by retinal telangiectasia and exudates, intracranial calcification, leukodystrophy, brain cysts, osteopenia, GI bleeding, and portal hypertension caused by the development of vasculature ectasias in the stomach, small intestine, and liver.

Complications

Cancer develops in approximately 10–15% of patients with DC, usually in the 3rd and 4th decades of life. Patients with DC are predisposed to MDS and AML, as well as to solid tumors. Forty percent of the cancers in such patients are squamous cell carcinomas of the head and neck (tongue, mouth, pharynx). SCCs of the skin and GI tract (esophagus, stomach, colon) as well as anorectal adenocarcinoma are common. The risk of MDS increases with age and is 2362-fold higher than that in the general population. The actuarial risk of clonal and malignant myeloid disease is 25% by age 18 yr. Other life-threatening complications include pulmonary fibrosis, liver fibrosis, and severe GI bleeding.

Treatment

Androgens can induce improvement of bone marrow function in approximately 70% of patients, and in some this treatment can result in normal trilineage blood counts for a number of years. Patients with DC become refractory to androgens as aplastic anemia progresses. They also tend to be more sensitive to the side effects of androgens than FA patients, making it important to start with lower doses and monitor for side effects frequently. When the response is maximal, the androgen dose can be slowly and gradually reduced to the minimum dose required to maintain desired and safe blood cell counts, but cannot be stopped. There is little published information on the use of immunosuppressive therapy for DC patients, but there are anecdotal reports of several patients who were misdiagnosed with acquired aplastic anemia and were treated with immunosuppressive therapy without response. Although reports are scanty, cytokine therapy with granulocyte-macrophage colony stimulating factor (GM-CSF) or with G-CSF alone or combined with erythropoietin appears to offer potential benefit, at least in the short term. Use of cytokines needs to be balanced with a potential growth-promoting effect of these medications on as-yet undetected MDS or AML cells.

Allogeneic HSCT is the only curative option for severe bone marrow failure, MDS, and AML. Long-term survival, even with sibling HLA-matched HSC donors, is poor and about 50%. Morbidity and mortality result from transplant-related complications such as graft failure, GVHD, sepsis, or venoocclusive disease or from emergence of DC-related complications such as pulmonary fibrosis and GI bleeding related to vascular anomalies. The mortality rate associated with HSCT is higher than that observed with other IBMFSs and is likely caused by the high level of pulmonary vascular complications seen in patients with DC that are related to the underlying telomere maintenance defect. Although the mutated genes for most cases of DC are known, prospects for gene therapy are not imminent.

Prognosis

Considerable heterogeneity exists in DC, and some data about genotype-phenotype correlations are available. Patients with certain genetic groups (e.g., *TERC, TERT*) may develop severe aplastic anemia or fibrosis of the liver and lungs, but these complications may appear later on in life and may not be accompanied by multisystem involvement. Patients with other genetic groups (e.g., *DKC1* , *TINF2, PARN, ACD, RTEL1*) appear to have more physical anomalies and a higher incidence and earlier onset of aplastic anemia and cancer. The mean age of death for patients with DC who are diagnosed in childhood is approximately 30 yr. The main causes of death are bone marrow failure, complications of HSCT, cancer, fatal pulmonary problems, and GI bleeding.

Congenital Amegakaryocytic Thrombocytopenia

Etiology and Epidemiology

Congenital amegakaryocytic thrombocytopenia (**CAMT**) is less common than FA, SDS, and DC. It is transmitted in an autosomal recessive manner. CAMT typically manifests in infancy as isolated thrombocytopenia caused by reduction or absence of bone marrow megakaryocytes with initial preservation of granulopoietic and erythroid lineages. Pancytopenia due to aplastic anemia often ensues in the 1st few yr of life. Development of MDS and AML was reported in patients with CAMT and persistent aplastic anemia.

The defect in CAMT is directly related to mutations in *MPL,* the gene for the receptor of thrombopoietin. *Thrombopoietin* is a growth factor that promotes HSC survival and stimulates megakaryocyte proliferation and maturation. Heterozygotes of the mutant gene have normal hematology, whereas affected individuals have mutations in both alleles. Genotype-phenotype correlations predict disease course and prognosis. **Nonsense mutations** cause a complete loss of function of the thrombopoietin receptor, resulting in persistently low platelet counts in early infancy due to absence of megakaryocytes, and a fast progression to pancytopenia and aplastic anemia (**CAMT type I**). Impaired stem cell survival with *MPL* nonsense mutations explains the evolution of CAMT into aplastic anemia, because thrombopoietin also has an antiapoptotic and cell survival effect on HSCs. **Missense mutations** of *MPL* are associated with a milder disease course, a later presentation, a partial and transient increase in platelets during the 1st yr of life after presentation, and a delayed onset, if any, of pancytopenia, indicating residual receptor function (**CAMT type II**). Biologically active plasma thrombopoietin is consistently elevated in all patients with CAMT.

Clinical Manifestations

Patients with CAMT have a petechial rash, bruising, or bleeding. Onset of symptoms may depend on the severity of mutations and ranges from birth to the 1st year of life. Most patients with CAMT have normal physical and imaging features. About 10–20% of published phenotypic CAMT cases involved physical anomalies. The most common anomalies are neurologic and cardiac. Findings related to cerebellar and cerebral atrophy are frequent, and developmental delay is a prominent feature. Congenital heart disease includes atrial and ventricular septal defects, patent ductus arteriosus, tetralogy of Fallot, and coarctation of the aorta. Some of these occur in combinations. Other anomalies include abnormal hips or feet, kidney malformations, eye anomalies, and cleft or high-arched palate. Some patients have microcephaly and abnormal facies.

Laboratory Findings

Thrombocytopenia is the major laboratory finding in CAMT, with normal hemoglobin levels and WBC counts initially. Peripheral blood platelets are reduced or totally absent. As in other IBMFSs, RBCs may be macrocytic. Hemoglobin F may be elevated, and there may be increased expression of i antigen. Initial bone marrow aspirates and biopsy specimens show normal cellularity with marked reduction or absence of megakaryocytes. In patients in whom aplastic anemia develops, bone marrow cellularity is decreased, with fatty replacement; erythropoietic and granulopoietic lineages are also symmetrically reduced.

Diagnosis

If thrombocytopenia persists beyond the neonatal period or is associated with adequate platelet transfusion response and no obvious precipitating cause such as infections or immunologic reactions, a bone marrow aspirate and biopsy are indicated. Deficient megakaryocytes in such cases suggest the diagnosis, and mutational analysis will confirm it. If CAMT occurs at birth or shortly after, it must be distinguished from other causes of inherited and acquired neonatal thrombocytopenia. Thrombocytopenia with absent radii (**TAR syndrome**) is distinguished from CAMT because radii are absent in TAR. The distinction from DC may be evident by a lack of mucocutaneous, neurologic, and immunologic findings that are characteristic of the early-onset forms of DC. Telomere lengths below the 1st percentile matched for age to healthy controls is characteristic of

DC and not CAMT. Finally, CAMT blood lymphocytes do not show increased chromosomal breakage when exposed to DEB, distinguishing the disease from Fanconi anemia.

Complications

In some patients, clonal marrow cytogenetic abnormalities such as monosomy 7 and trisomy 8 appear. CAMT can evolve into MDS and acute leukemia, but the true risk cannot be defined because of the rarity of the disease and the paucity of published data.

Therapy and Prognosis

The mortality rate from thrombocytopenic bleeding, complications of aplastic anemia, or leukemic transformation in patients with *MPL* **nonsense** mutations is close to 100% if bone marrow function is not improved. Patients with **missense** mutations have a milder course but may still have serious complications. HSCT is the only curative option. The majority of patients with CAMT who undergo HSCT are cured, especially if the procedure is performed with HLA-matched sibling donors. Before transplantation, platelet transfusion should be used discretely. Platelet count should not always be the sole indication for treatment, but symptoms such as clinical bleeding are an appropriate trigger. Single-donor, leuko-reduced platelets are preferred to minimize sensitization. In a patient who is a candidate for HSCT, all blood products should be irradiated and free of cytomegalovirus. Corticosteroids are not effective treatment for the thrombocytopenia. No data support the use of androgens for temporary improvement of aplastic anemia. The role of thrombomimetic agents such as eltrombopag or romiplostim might be suitable for some patients (CAMT type II) and need to be studied further. However, the promotion of fibrosis by these agents and the risk of MDS and leukemia in CAMT render HSCT the preferred treatment for patients with severe cytopenia.

Other Inherited Aplastic Anemias

A substantial number of genes that are associated with bone marrow failure with pancytopenia have been identified with the emergence of whole genome screening methods (see Table 495.1). The specific gene-associated disorders may vary by phenotype but frequently include physical malformations, familial distribution, early age of disease onset, pancytopenia, and a risk of MDS and AML. Significant overlap exists between inherited pancytopenia syndromes, and familial MDS and AML syndromes.

Reticular Dysgenesis

Reticular dysgenesis is a variant of severe combined immunodeficiency with congenital agranulocytosis. Anemia and thrombocytopenia may also be present. Reticular dysgenesis is caused by homozygous or compound heterozygous mutations in the mitochondrial adenylate kinase-2 gene (*AK2)* on chromosome 1p35. Additional genes and other inheritance modes are possible and indeed may be discovered in the future. Cellular and humoral immunity are absent in reticular dysgenesis, and severe lymphopenia and neutropenia are also seen. The degree of anemia and thrombocytopenia varies, and severe aplastic anemia sometimes develops. Bone marrow specimens are hypocellular, with greatly reduced myeloid and lymphoid elements. The only curative therapy is HSCT.

Cartilage-Hair Hypoplasia

Cartilage-hair hypoplasia (**CHH**) is an autosomal recessive syndrome seen mostly in Finnish or Amish populations. It is characterized by metaphyseal dysostosis, short-limbed dwarfism, and fine, sparse hair. Additional skeletal findings are scoliosis, lordosis, chest deformity, and varus of the lower limbs. GI abnormalities also occur. CHH is caused by mutations in the *RMRP* gene. Macrocytic anemia is seen in most patients and is sometimes severe and persistent. Neutropenia, lymphopenia, and a predisposition to lymphoma and other cancers are also features. HSCT is curative.

Other Inherited Syndromes With Occasional Significant Bone Marrow Failure

Down Syndrome

Down syndrome (trisomy 21) has a unique association with aberrant hematologic findings. Patients have a propensity for acute lymphoblastic and myeloblastic leukemias, especially acute megakaryoblastic leukemia. Rare patients with Down syndrome and pancytopenia caused by aplastic anemia have been reported.

Dubowitz Syndrome

Dubowitz syndrome is an autosomal recessive disorder characterized by a peculiar facies, infantile eczema, small stature, and mild microcephaly. The face is small, with a shallow supraorbital ridge, a nasal bridge at the same level as the forehead, short palpebral fissures, variable ptosis, and micrognathia. There is a predilection to cancer in these patients. Approximately 10% of patients have hematopoietic disorders, including moderate pancytopenia, hypoplastic anemia, bone marrow hypoplasia, and full-blown aplastic anemia. Dubowitz syndrome is associated with mutations in *NSUN2* (an RNA methyltransferase) and *LIG4* (a nuclear DNA ligase).

Seckel Syndrome

Seckel (**SCKL**) syndrome, sometimes called “bird-headed dwarfism,” is an autosomal recessive developmental disorder characterized by marked growth failure and mental deficiency, microcephaly, a hypoplastic face with a prominent nose, and low-set and/or malformed ears. Approximately 25% of patients have aplastic anemia or malignancies. There is broad genetic heterogeneity comprising at least 8 classifiable types: SCKL1, *ATR* mutation; SCKL2, *RBBP8* mutation; SCKL3, maps to 14q21-q22; SCKL4, *CENPJ* mutation; SCKL5, *CEP152* mutation; SCKL6, *CEP63* mutation; SCKL7, *NIN* mutation; and SCKL8, *ATRIP* mutation.

Schimke Immunoosseous Dysplasia

Schimke immunoosseous dysplasia is an autosomal recessive disorder caused by mutations in the chromatin remodeling protein *SMARCAL1* . Patients have spondyloepiphyseal dysplasia with exaggerated lumbar lordosis and a protruding abdomen. There are pigmentary skin changes and abnormally discolored and configured teeth. Renal dysfunction can be problematic, with proteinuria and nephrotic syndrome. Approximately 50% of patients have hypothyroidism; 50%

have cerebral ischemia; 10% have bone marrow failure with neutropenia, thrombocytopenia, and anemia; and about 5% are predisposed to non-Hodgkin lymphoma. Lymphopenia and altered cellular immunity are present in almost all patients. In 2 published case reports, 2 patients underwent successful bone marrow transplantation.

Noonan Syndrome

Noonan syndrome is a developmental disorder characterized by the “Noonan facies” (hypertelorism, ptosis, short neck, low-set ears), short stature, congenital heart disease, and multiple skeletal and hematologic abnormalities. It is primarily an autosomal dominant disorder composed of multiple genetic types (see Table 495.1). Heterozygous mutations in *PTPN11* cause about 50% of Noonan cases. Other cases are caused by mutations in other RAS pathway–associated genes such as *KRAS, SOS1* , and *NRAS* . Autosomal recessive forms have also been identified due to mutations of *SHOC2* or *CBL*. In addition to an association with juvenile myelomonocytic leukemia, Noonan syndrome patients can develop amegakaryocytic thrombocytopenia as well as pancytopenia with a hypocellular marrow.

Unclassified Inherited Bone Marrow Failure Syndromes

Unclassified IBMFSs are heterogeneous disorders that may be either atypical presentations of identifiable diseases or new syndromes. Unbiased approaches such as comprehensive panels of all known IBMFS genes regardless of the specific hematologic (e.g., isolated neutropenia or pancytopenia) or nonhematologic manifestations or whole exome/genome sequencing have proved this to be true. These disorders do not fit into classic genetic bone marrow failure diseases because all features of disease may not be evident at presentation. All are characterized by various cytopenias caused by underproductive bone marrow with or without physical manifestations. Compared with classic disorders (presentation at approximately 1 mo of age), infants with unclassified disorders present later (9 mo) and manifest single or multilineage cytopenia, aplastic anemia, myelodysplasia, or malignancy with variable expression of malformations. Table 495.4 lists criteria for the diagnosis, which include evidence of chronic bone marrow failure, in addition to factors that indicate a high likelihood of inherited disease (e.g., family history, congenital anomalies, young age at presentation).

Table 495.4

Canadian Inherited Marrow Failure Registry Criteria for Unclassified Inherited Bone Marrow Failure Syndromes

FULFILLS CRITERIA 1 AND 2:

1. Does not fulfill criteria for any categorized inherited bone marrow failure syndrome[*]
2. Fulfills both of the following:

FULFILLS AT LEAST 2 OF THE FOLLOWING:

a. Chronic cytopenia(s) detected on at least 2 occasions over at least 3 mo [†]
b. Reduced marrow progenitors or reduced clonogenic potential of hematopoietic progenitor cells or evidence of ineffective hematopoiesis [‡]
c. High fetal hemoglobin for age [‡]
d. Red blood cell macrocytosis (not caused by hemolysis or a nutritional deficiency)

FULFILLS AT LEAST 1 OF THE FOLLOWING:

a. Family history of bone marrow failure
b. Presentation at age <1 yr
c. Anomalies involving multiple systems to suggest an inherited syndrome

[*] The Canadian Inherited Marrow Failure Registry diagnostic guidelines for selected syndromes were adapted from the literature and are available at www.sickkids.ca/cimfr .

[†] Cytopenia was defined as follows: neutropenia, neutrophil count of <1.5 × 10^9 /L; thrombocytopenia, platelet count of <150 × 10^9 /L; anemia, hemoglobin concentration of >2 standard deviations below mean, adjusted for age.

[‡] Hemoglobinopathies with ineffective erythropoiesis and high hemoglobin F should be excluded by clinical or laboratory testing.

Modified from Teo JT, Klaassen R, Fernandez CV, et al: Clinical and genetic analysis of unclassifiable inherited bone marrow failure syndromes, *Pediatrics* 22:e139–e148, 2008.

When patients present later and without physical malformations, an acquired etiology cannot be ruled out. Detailed genetic testing for known IBMFS genes or testing by whole exome/genome sequencing may identify an inherited etiology. In addition, some syndromes have been shown to demonstrate typical physical features during follow-up.

Determining the actual genetic cause helps group patients according to disease and guides counseling and proper medical care. Implementing a treatment plan is urgent in many cases. In such patients the management should be according to the type of complications that the patient has at presentation and the lessons that can be learned from published experience on unclassified cases in the literature.

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CHAPTER 496

The Acquired Pancytopenias

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Etiology and Epidemiology

Drugs, chemicals, toxins, infectious agents, radiation, and immune disorders can result in pancytopenia by direct destruction of hematopoietic progenitors, disruption of the marrow microenvironment, or immune-mediated suppression of marrow elements (Tables 496.1 and 496.2). A careful history of exposure to known risk factors should be obtained for every child presenting with pancytopenia. Even in the absence of the classic associated physical findings, the possibility of a *genetic predisposition to bone marrow failure* should always be considered (see Chapter 495). Many cases of acquired marrow failure in childhood are *idiopathic* , in that no causative agent is identified. Many are probably immune-mediated through activated T lymphocytes and cytokine destruction of marrow stem and progenitor cells. Patients with an initial diagnosis of acquired aplastic anemia may have developed somatic mutations in genes associated with *myelodysplastic syndromes* and *acute myeloid leukemia* (AML). Clonal hematopoiesis resulting from these acquired somatic mutations may over time lead to the development of myelodysplasia (MDS) or AML. The overall incidence of **acquired aplastic anemia** is relatively low, with an approximate incidence in both children and adults in the United States and Europe of 2-6 cases per 1 million population per year. The incidence is higher in Asia, with as many as 14 cases per 1 million per year in Japan.

Table 496.1

Etiology of Acquired Aplastic Anemia

Radiation, drugs, and chemicals

- Predictable: chemotherapy, benzene
- Idiosyncratic: chloramphenicol, antiepileptics, gold, 3,4-methylenedioxymethamphetamine, NSAIDs, antibiotics
- See also Table 496.2 .

Viruses
- Cytomegalovirus
- Epstein-Barr
- Hepatitis B
- Hepatitis C
- Hepatitis non-A, non-B, non-C (seronegative hepatitis)
- HIV

Immune diseases
- Eosinophilic fasciitis
- Hypoimmunoglobulinemia
- Thymoma

Pregnancy

Paroxysmal nocturnal hemoglobinuria

Marrow replacement
- Leukemia
- Myelodysplasia
- Myelofibrosis

Autoimmune

Nutritional
- Vitamin B_{12}
- Folate
- Copper

Other
- Cryptic dyskeratosis congenita (no physical stigmata)
- Telomerase reverse transcriptase haploinsufficiency

Table 496.2

Drugs and Toxins Associated With Aplastic Anemia

DOSE DEPENDENT

Antineoplastic Agents

Antimetabolites: fluorouracil, mercaptopurine, 6-thioguanine, methotrexate, cytosine arabinoside, gemcitabine, fludarabine, cladribine, pentostatin, hydroxyurea

Alkylating and cross-linking agents: busulfan, cyclophosphamide, chlorambucil,nitrogen mustard, melphalan, cisplatin, carboplatin, ifosfamide, nitrosoureas (BCNU and CCNU), mitomycin C

Cytotoxic antibiotics: daunorubicin, doxorubicin, mitoxantrone

Plant alkaloids: vinblastine, paclitaxel

Topoisomerase inhibitors: etoposide

Antimicrobial Agents

Chloramphenicol, dapsone, fluorocytosine

Antiinflammatory and Antirheumatic Agent

Colchicine

Insecticides

Chlordane, chlorophenothane (DDT), lindane, parathion

Other Chemicals

Benzene

Benzene-containing chemicals: kerosene, chlorophenols, carbon tetrachloride

DOSE INDEPENDENT *

Idiosyncratic, likely immune mediated

Antimicrobial Agents

Chloramphenicol, dapsone, sulfonamides, tetracycline, methicillin, amphotericin,quinacrine, chloroquine, pyrimethamine

Anticonvulsants

Hydantoins, carbamazepine, phenacemide, primidone, ethosuximide

Antiinflammatory Agents

Phenylbutazone, indomethacin, ibuprofen, oxyphenbutazone, sulindac, naproxen

Antiarrhythmic Drugs

Quinidine, tocainide, procainamide

Metals

Gold, arsenic, mercury, bismuth

Antihistamines

Cimetidine, ranitidine, chlorpheniramine, pyrilamine, tripelennamine

Diuretics

Acetazolamide, furosemide, chlorothiazide, methazolamide

Hypoglycemic Agents

Chlorpropamide, tolbutamide

Antithyroid Drugs

Propylthiouracil, potassium perchlorate, methylthiouracil, methimazole, carbimazole

Antihypertensive Agents

Methyldopa, enalapril, captopril

Sedatives

Chlordiazepoxide, chlorpromazine, meprobamate, prochlorperazine

[*] Most agents listed in this group should be considered to be possibly associated with aplastic anemia.

From *Goldman-Cecil medicine,* ed 25, vol 1, Philadelphia, 2016, Elsevier (Table 165.2, p 1115).

Severe bone marrow suppression can develop after exposure to many different drugs and chemicals, including certain chemotherapeutic agents, insecticides, antibiotics, anticonvulsants, nonsteroidal antiinflammatory drugs (NSAIDs), and recreational drugs. Some of the most notable agents are benzene, chloramphenicol, gold, and, 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy).

A number of viruses can either directly or indirectly result in bone marrow failure. *Parvovirus B19* is classically associated with isolated red blood cell (RBC) aplasia, but in patients with sickle cell disease or immunodeficiency, it can result in transient pancytopenia (see Chapter 278). Prolonged pancytopenia can occur after infection with many of the hepatitis viruses, herpesviruses, Epstein-Barr virus (see Chapter 281), cytomegalovirus (see Chapter 282), and HIV (see Chapter 302).

Patients with evidence of bone marrow failure should also be evaluated for inherited forms of marrow failure, **paroxysmal nocturnal hemoglobinuria** (PNH; see Chapter 488), and collagen vascular diseases. Pancytopenia without peripheral blasts may be caused by bone marrow replacement by leukemic blasts or neuroblastoma cells.

Pathology and Pathogenesis

The hallmark of aplastic anemia is peripheral pancytopenia, coupled with hypoplastic or aplastic bone marrow. The severity of the clinical course is related to the degree of myelosuppression. **Severe aplastic anemia** is defined as a condition in which ≥2 cell components have become seriously compromised (absolute neutrophil count <500/mm^3 , platelet count <20,000/mm^3 , reticulocyte count <1% after correction for hematocrit) in a patient whose bone marrow biopsy material has <30% cellularity. Approximately 65% of patients who first present with **moderate aplastic anemia** (absolute neutrophil count 500-1,500/mm^3 , platelet count 20,000-100,000/mm^3 , reticulocyte count <1%) eventually progress to meet the criteria for severe disease, if they are simply observed. Bone marrow failure may be a consequence of a direct cytotoxic effect on hematopoietic stem cells (HSCs) from a drug or chemical or may result from either cell-mediated or antibody-dependent cytotoxicity. There is strong evidence that many cases of idiopathic aplastic anemia are caused by an immune-mediated process, with increased circulating activated T lymphocytes producing cytokines (interferon-γ) that suppress hematopoiesis. Abnormal telomere length and telomerase activity in granulocytic precursors and increased expression of cell surface Flt3 ligand (a member of the class III receptor tyrosine kinase family) in the lymphocytes of patients with aplastic anemia suggest that early apoptosis of hematopoietic progenitors may play a role in the pathogenesis of this disease.

Cytogenetic abnormalities associated with aplastic anemia include uniparental disomy 6p, monosomy 7/del (7q), and trisomy 8, 6, or 15. Genes associated with aplastic anemia include telomere complex genes *(TERT, TERC)* and *BCOR/BCORL, PIGA, DNMT3A*, and *ASXL1* .

Clinical Manifestations, Laboratory Findings, and Differential Diagnosis

Pancytopenia results in increased risks of cardiac failure, infection, bleeding, and fatigue. Acquired pancytopenia is typically characterized by anemia, leukopenia, and thrombocytopenia in the setting of elevated serum cytokine values. Other treatable disorders, such as cancer, collagen vascular disorders, PNH, and infections, that may respond to specific therapies (IV immune globulin for parvovirus), should be considered in the differential diagnosis. Careful examination of the peripheral blood smear for RBC, leukocyte, and platelet morphologic features is important. A reticulocyte count should be performed to assess erythropoietic activity. In children the possibility of congenital pancytopenia must always be considered, and chromosomal breakage analysis should be performed to evaluate for **Fanconi anemia** (see Chapter 495). The presence of fetal hemoglobin suggests congenital pancytopenia but is not diagnostic. To assess for possible PNH, flow cytometric analysis of erythrocytes for CD55 and CD59 is the most sensitive test. Bone marrow examination should include both aspiration and biopsy, and the marrow should be carefully evaluated for morphologic features, cellularity, and cytogenetic abnormalities.

Treatment

The treatment of children with acquired pancytopenia requires comprehensive supportive care coupled with an attempt to treat the underlying marrow failure. For patients with a human leukocyte antigen–matched family member donor, allogeneic hematopoietic stem cell transplantation (HSCT) offers a 90% chance of long-term survival. The typical preparative regimen today consists of cyclophosphamide, fludarabine, and horse antithymocyte globulin (ATG). Preliminary data also suggest that children with severe aplastic anemia can be successfully transplanted using *alemtuzumab* (humanized monoclonal antibody against CD52 on lymphocytes)–based conditioning. The risks associated with bone marrow transplantation include the immediate complications of transplantation, graft failure, and graft-versus-host disease. Late adverse effects associated with transplantation may include secondary cancers, cataracts, short stature, hypothyroidism, and gonadal dysfunction (see Chapters 163 and 164). Only approximately 20% of patients have an HLA-matched family member donor, so matched-related HSCT is not an option for the majority of patients.

For patients without a sibling donor, the major form of therapy is immunosuppression with horse ATG and cyclosporine, with a response rate of 70–80%. The median time to response is 6 mo. As many as 30% of patient responders experience relapse after discontinuation of immunosuppression, and some patients must continue cyclosporine for several years to maintain a hematologic response. Among those who relapse after immunosuppression, approximately 50% show response to a second course of ATG and cyclosporine. There is an increased risk (<10%) of clonal bone marrow disease (e.g., AML, MDS, PNH) after immunosuppression with karyotypic abnormalities most frequently involving chromosomes 6, 7, and 8. To accelerate neutrophil recovery, a hematopoietic colony-stimulating factor (e.g., granulocyte CSF, granulocyte-macrophage CSF) is sometimes added to ATG and cyclosporine for treatment of patients with very severe neutropenia (absolute neutrophil count $<200/mm^3$), but there is no clear evidence that this treatment influences response rate or survival. Higher baseline reticulocyte count correlates with a higher probability of response to immunosuppression and survival. There is an inverse correlation between telomere length and the probability of relapse after immunosuppression.

For patients who show no response to immunosuppression or who experience relapse after immunosuppression, matched-unrelated HSCT and T-cell–depleted haploidentical family member–donor HSCT are treatment options, with a response rate approaching 90%. Cord blood transplants have been performed in this refractory group of patients, but there is a significant incidence of non-engraftment. High-dose cyclophosphamide has been used successfully in the treatment of patients with newly diagnosed aplastic anemia and in patients without adequate response to immunosuppression. This therapy leads to prolonged severe pancytopenia, increasing the risk of life-threatening infection, especially fungal. Other therapies that have been used in the past with inconsistent results include androgens, corticosteroids, and plasmapheresis. Ongoing studies using *eltrombopag* (an oral thrombopoietin mimetic agent) or alemtuzumab have shown promise in patients with refractory disease. The use of eltrombopag resulted in a hematologic response with improvements in platelet and neutrophil counts and hemoglobin levels in some patients. In patients who responded, bone marrow biopsies demonstrated trilineage normalization of hematopoiesis; some who were dependent on platelet or erythrocyte transfusions no longer needed transfusions. Alemtuzumab as monotherapy in relapsed disease showed improved response rates and 3-yr survival compared to additional courses of ATG and cyclosporine.

Complications

The major complications of severe pancytopenia are predominantly related to the risk of life-threatening bleeding from prolonged thrombocytopenia or to infection secondary to protracted neutropenia. Patients with protracted neutropenia as a result of bone marrow failure are at risk not only for serious bacterial infections but also for invasive mycoses. Patients who have been transfused with RBCs regularly over a long period are at increased risk of developing alloantibodies to RBC antigens and may require iron chelation therapy for transfusional iron overload. The general principles of *supportive care* that have evolved from the use of chemotherapy-related myelosuppression to treat patients with cancer should be fully extended to the care of patients with acquired pancytopenia.

Prognosis

Spontaneous recovery from pancytopenia rarely occurs. If left untreated, severe pancytopenia has an overall mortality rate of approximately 50% within 6 mo of diagnosis and of >75% overall, with infection and hemorrhage being the major causes of morbidity and mortality. The majority of children with acquired severe aplastic anemia show response to allogeneic marrow transplantation or immunosuppression, leaving them with normal or near-normal blood cell counts.

Pancytopenia Caused by Marrow Replacement

Processes that either infiltrate or replace the bone marrow can manifest as acquired pancytopenia. Infiltration can be caused by malignancy (classically, neuroblastoma or leukemia) or result from myelofibrosis, MDS, or osteoporosis. Although uncommon, evidence of hypoplastic anemia can precede the onset of acute leukemia, generally by a few months. This relationship is important to appreciate in evaluating and monitoring children who present with what appears to be acquired aplastic anemia. Morphologic examination of the peripheral blood and bone marrow and marrow cytogenetic studies are critically important in making the diagnoses of leukemia, myelofibrosis, and MDS.

Myelodysplasia is very rare in children, but when it occurs, its clinical course is more aggressive than the same category of MDS in adults. Pediatric MDS can be subdivided into **refractory cytopenia of childhood** (peripheral blasts <2% and marrow blasts <5%), **refractory anemia with excess blasts** (peripheral blasts 2–19% and/or marrow blasts 5–19%), and **refractory anemia with excess blasts in transformation** (peripheral and/or marrow blasts 20–29%). Disease in children with >30% blasts is usually defined as *acute myelocytic leukemia* .

Myelodysplastic syndromes are a heterogeneous group of bone marrow failure disorders that have in common ineffective hematopoiesis that leads to pancytopenia over time. In one group, there are somatic mutations (in >25 genes) leading to MDS. In another group, usually in younger patients (<55 yr), there is autoimmune suppression of hematopoiesis by clonal expansion of T lymphocytes, particularly in those patients who look similar to patients with idiopathic aplastic anemia. In all patients, other causes of MDS (medications and vitamin B_{12} , folate, or copper deficiencies) must be ruled out.

A number of inherited conditions are associated with an increased risk for development of MDS, including Down syndrome, severe congenital neutropenia, Noonan syndrome, Fanconi anemia, trisomy 8 mosaicism, neurofibromatosis, Shwachman-Diamond syndrome, and some familial MDS syndromes caused by mutations in *ANKRD26, CEBPA, DDX41, ETV6, GATA2, RUNX1*, *SRP72* genes. Significant clonal abnormalities are found within the marrow of approximately 50% of patients with MDS, with monosomy 7 being most common but prognostically neutral. Those with a structurally complex karyotype have a very poor outcome (see Chapter 495).

The transition time from pediatric MDS to acute leukemia is relatively short, 14-26 mo, so aggressive treatment such as HSCT must be considered shortly after diagnosis. With allogeneic HSCT, the survival rate is approximately 60%. One exception to such an aggressive therapeutic approach is MDS and acute myelocytic leukemia in children with Down syndrome, because these diseases in this specific population are very responsive to conventional chemotherapy, with long-term survival rates >80%.

The decision on how to treat a child with MDS who lacks a suitable HSC donor should be made with the specific clonal abnormality found within the child's marrow taken into consideration. Lenalidomide produces the best responses among patients who have the chromosomal abnormality 5q−. Immunosuppressive therapy with ATG and cyclosporine is most effective in patients with trisomy 8, especially in the presence of a PNH clone. Imatinib mesylate targets mutations in the tyrosine kinase receptor family of genes found in patients with t(5;12) and del(4q12). The DNA hypomethylating agents azacitidine and decitabine have also been used in treating MDS without a known molecular target and have some effect.

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SECTION 6

Blood Component Transfusions

OUTLINE

Chapter 497 Red Blood Cell Transfusions and Erythropoietin Therapy

Chapter 498 Platelet Transfusions

Chapter 499 Neutrophil (Granulocyte) Transfusions

Chapter 500 Plasma Transfusions

Chapter 501 Risks of Blood Transfusions

CHAPTER 497

Red Blood Cell Transfusions and Erythropoietin Therapy

Cassandra D. Josephson, Ronald G. Strauss

Red blood cells (RBCs) are transfused to increase the oxygen-carrying capacity of the blood, with the goal to increase or maintain satisfactory tissue oxygenation. This goal may not be achieved simply by increasing the hemoglobin (Hb) concentration or hematocrit (Hct) by an RBC transfusion because tissue oxygenation depends on several additional factors, including oxygen off-loading from RBCs, microvascular blood flow, and diffusion of oxygen into tissue cells. Although some attempts have been made to accurately relate posttransfusion Hb or Hct values to changes in posttransfusion tissue oxygenation (e.g., improvements in the ratio of cerebral vs mesenteric oxygenation patterns assessed by serial near-infrared spectroscopy measurements), decisions to transfuse RBCs per physiologic indications, rather than degree of anemia, remain investigational. This information can be applied to approaches for transfusion in both preterm infants/neonates and children/adolescents. However, neonates, especially extremely-low-birthweight infants (≤1000 g), are not “small” children (i.e., RBC physiology and pathophysiology of anemia of prematurity are unique); thus RBC transfusions for neonates and children are considered separately.

RBC Transfusion in Children and Adolescents

Guidelines for RBC transfusions in children and adolescents are based on maintaining a specified Hb or Hct level considered to be optimal (per the best evidence available) for the clinical condition present at the time of transfusion.

The guidelines are similar to those for adults (Table 497.1). Transfusions may be given more stringently to children, because normal Hb levels are lower in healthy children than in adults and, as is often the case, most children do not have the underlying multiorgan, cardiorespiratory, and vascular diseases that develop with aging in adults to suggest a need for RBC transfusions. As a result, children may compensate better for RBC loss than elderly adults, thus requiring less RBC transfusion support. In general, there is increasing enthusiasm for applying patient blood management strategies, encompassing conservative transfusion practices (i.e., accepting lower pretransfusion Hct values to “trigger” a RBC transfusion) to all patient ages with evidence-based support.

Table 497.1

Guidelines for Pediatric Red Blood Cell Transfusions[*] [†]

CHILDREN AND ADOLESCENTS

1. Maintain stable status with acute loss of >25% of circulating blood volume.
2. Maintain hemoglobin >7.0 g/dL[†] in the perioperative period.
3. Maintain hemoglobin >12.0 g/dL with *severe* cardiopulmonary disease.
4. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation.
5. Maintain hemoglobin >7.0 g/dL and *symptomatic* chronic anemia.
6. Maintain hemoglobin >7.0 g/dL and *marrow failure.*

INFANTS ≤4 MO OLD

1. Maintain hemoglobin >12.0 g/dL and *severe* pulmonary disease.
2. Maintain hemoglobin >12.0 g/dL during extracorporeal membrane oxygenation.
3. Maintain hemoglobin >10.0 g/dL and *moderate* pulmonary disease.
4. Maintain hemoglobin >12.0 g/dL and *severe* cardiac disease.
5. Maintain hemoglobin >10.0 g/dL preoperatively and during *major* surgery.
6. Maintain hemoglobin >7.0 g/dL postoperatively.
7. Maintain hemoglobin >7.0 g/dL and *symptomatic* anemia.

[*] Words in *italics* must be defined for local transfusion guidelines.

[†] Pretransfusion blood hemoglobin (Hb) level (convert to hematocrit values if preferred by multiplying Hb values by 3) “triggering” an RBC transfusion. Hb values to maintain vary among published reports, and the guideline values to maintain should be determined locally to fit the practices judged to be optimal by local physicians.

In the **perioperative period** it is unnecessary for most children to maintain Hb of ≥8 g/dL, a level frequently desired for adults. Instead, Hb of ≥7 g/dL is an acceptable level, although the optimal value for individual patients is based on clinical and laboratory circumstances, as influenced by the following factors. The desired preoperative Hb level should consider the estimated blood loss for the surgical procedure planned and the rate of bleeding. There should be a compelling reason to prescribe any postoperative RBC transfusion, such as continued bleeding with hemodynamic instability, because most children (without continued bleeding) can restore their RBC mass with iron therapy (in a relatively short time).

The most important measures in the treatment of **acute hemorrhage** are to control the hemorrhage and, if blood loss is modest, to restore the circulating blood volume and tissue perfusion with crystalloid or, less often, colloid solutions. If the estimated blood loss is >25% of the circulating blood volume (>15 mL/kg of an estimated 60 mL/kg total estimated blood volume) *and* the patient's condition is unstable despite initial intravenous (IV) fluids, RBC transfusions should be given without undo hesitation, along with plasma transfusions at a 1 : 1 ratio of RBC/plasma volumes. Some experts recommend transfusing platelets early if bleeding is sustained or “massive” (i.e., approximating 1 blood volume or 60 mL/kg, which may occur very quickly in infants and small pediatric patients). Details of combined RBC and plasma transfusions, the volume ratio transfused, and considerations for adding platelet transfusions to treat bleeding patients are controversial. Accordingly, each hospital should develop and follow a “massive transfusion” protocol to ensure consistent practices.

In critically ill children with severe cardiac or pulmonary disease requiring assisted ventilation, it is common practice to maintain the Hb level close to the normal range, although the efficacy of this practice has not been well documented. A similar approach is used for children with acute cardiac, pulmonary, or cardiopulmonary disorders managed with extracorporeal membrane oxygenation (ECMO).

The pretransfusion Hb level or Hct that should “trigger” a RBC transfusion remains controversial (i.e., restrictive or a low pretransfusion level vs liberal or a high pretransfusion level) despite a substantial amount of published information, including randomized clinical trials. The current trend in critical care settings is to transfuse RBCs conservatively, following restrictive guidelines, and to permit modest anemia because there appears to be no disadvantage to conservative/restrictive transfusion practices, and some patients with Hb levels maintained close to the normal range by RBC transfusions (i.e., liberal guidelines) have poorer outcomes. Studies in critically ill adults demonstrated better outcomes when Hb level was maintained at 7-9 g/dL vs 10-12 g/dL. Anemic adults with *significant cardiac disease* did better with Hb level maintained at 13 g/dL rather than 10 g/dL. A similar study in children admitted to intensive care units found no inferiority when RBC transfusions were given by restrictive guidelines (*transfusion threshold of 7 g/dL*). It must be remembered that the children studied were in stable clinical status and needed few transfusions. Therefore, results of the trial cannot be automatically generalized to all patients admitted to ICUs, since unstable critically ill children (who were not included in the study) may need more liberal RBC transfusion approaches.

With **chronic anemia** the decision to transfuse RBCs should not be based solely on blood Hb levels, because children compensate well and may be asymptomatic despite low Hb levels. Patients with iron-deficiency anemia are often treated successfully with oral iron alone, even at Hb levels <5 g/dL. Factors other than Hb concentration to be considered in the decision to transfuse RBCs include (1) the patient's symptoms, signs, and compensatory capacities; (2) the presence of underlying cardiorespiratory, vascular, and central nervous system disease; (3) the cause and anticipated course of the anemia; and (4) alternative therapies, such as recombinant human **erythropoietin** (EPO) therapy, which is known to reduce the need for RBC transfusions and to improve the overall condition of children with chronic renal insufficiency (see Chapter 550.2). In anemias that are likely to be permanent, it is also important to balance the detrimental effects of the degree of long-standing anemia on growth and development against the potential toxicity associated with repeated transfusions (i.e., iron overload and risks of transfusion-transmitted diseases) given to maintain the Hb concentration at a specified level. RBC transfusions for disorders such as sickle cell anemia and thalassemia are discussed in Chapters 489.1 and 489.10 .

RBC Transfusion in Preterm Infants and Neonates

For neonates, almost all aspects of RBC transfusions remain controversial—the accepted indications for RBC transfusions, restrictive vs liberal pretransfusion Hb/Hct levels, optimal RBC product to be transfused, and fresh vs stored RBC units—and clinical practices vary greatly. Generally, RBCs are given to maintain an Hb value believed to be the most desirable for each neonate's clinical status. Restrictive guidelines (i.e., lower pretransfusion Hb/Hct levels) have been compared to more liberal transfusion practices, but both short-term and long-term results and outcomes have been inconsistent and controversial, particularly as to neurodevelopmental status, with poorer outcomes seen in both the restrictive and liberal study arms. Accordingly, conventional guidelines are recommended to avoid problems caused by undertransfusion or overtransfusion, until more definitive data are published (see Table 497.1).

This clinical approach is imprecise, but more physiologic guidelines and indications, such as measurement of RBC mass, calculations of oxygen delivery and tissue extraction, imaging of microcirculatory flow, and comparative measures of tissue perfusion (e.g., ratio of cerebral/mesenteric oxygenation patterns), are too cumbersome for day-to-day clinical practice.

During the 1st few wk of life, all neonates experience a decline in circulating RBC mass caused by physiologic factors and, in sick premature infants, by phlebotomy blood losses. In healthy term infants, the nadir Hb value rarely falls to <11 g/dL at age 10-12 wk. This benign drop in Hb does not require transfusions. In contrast, the decline occurs earlier and is more pronounced in premature infants, in whom the mean Hb concentration falls to approximately 7 g/dL in infants weighing <1 kg at birth, resulting in the **anemia of prematurity** , for which there often is need for RBC transfusions, particularly when the anemia is worsened by blood draws for laboratory testing.

A key reason that the nadir Hb values of premature infants are lower than those of term infants is the premature infant's relatively diminished plasma EPO level in response to anemia (see Chapters 124.1 and 474). Another factor is the rapid disappearance of EPO from infant plasma (i.e., accelerated metabolism). Low plasma EPO levels provide a rationale for the possible use of recombinant EPO in the treatment of anemia of prematurity; treatment with EPO and iron effectively stimulate neonatal erythropoiesis. Despite its erythropoietic effect, the efficacy of EPO therapy to substantially diminish the need for RBC transfusions has not been convincingly demonstrated, particularly for sick, extremely premature neonates, and recombinant EPO has not been widely accepted as a treatment for anemia of prematurity (see Chapter 124.1).

Because of the controversies over recombinant EPO therapy, many low-birthweight preterm infants need RBC transfusions (see Table 497.1). Although the practice to maintain a very high Hb level >13 g/dL, or Hct >40%) was once widely recommended, currently more restrictive guidelines have been suggested. However, a recent prospective, observational, multisite, birth cohort study of very-low-birthweight infants (≤1500 g) found a 6-fold increased risk of necrotizing enterocolitis (NEC) per week when an infant's hemoglobin was ≤8 g/dL. Importantly, RBC transfusion in a given week did not significantly increase the rate of NEC in this population. Consistent with the rationale for oxygen delivery in neonates with severe respiratory disease, it also seems appropriate to keep the Hb value relatively high in neonates with *severe cardiac disease* leading to either cyanosis or congestive heart failure, but convincing and consistent data are lacking.

The optimal Hb level for neonates facing major surgery has not been established. However, it seems reasonable to begin surgery in neonates with the Hb level no lower than 10 g/dL (hematocrit >30%) and to maintain that value during major surgery, because even modest blood loss will have a relatively large effect on the small blood volume of the neonate. Neonates with underlying pulmonary problems have limited ability to compensate for anemia due to the inability to increase ventilation and the inferior off-loading of oxygen because of the diminished interaction between fetal hemoglobin and 2,3-diphosphoglycerate. Postoperatively, a lower pretransfusion Hb value should be followed to “trigger” a transfusion.

Stable neonates do not require RBC transfusion, regardless of their blood Hb levels, unless they exhibit clinical symptoms attributable to anemia. Proponents of RBC transfusions for symptomatic anemia in preterm neonates believe that the low RBC mass contributes to tachypnea, dyspnea, tachycardia, apnea and bradycardia, feeding difficulties, and lethargy, which can be alleviated by transfusion of RBCs. However, anemia is only one of several possible causes of these problems, and RBC transfusions should only be given when clinical benefit seems likely.

RBC Product and Dose

The RBC product of choice to transfuse neonates, infants, children, and adolescents is prestorage leukocyte-reduced RBCs suspended in an anticoagulant/preservative storage solution at Hct of approximately 60–70% for storage up to 35-42 days. For those infants with birthweight <1500 g, irradiation is recommended to prevent transfusion-associated graft-versus-host disease. Additionally, both leukoreduction and cytomegalovirus-seronegative RBC units have been recommended by some (estimated risk of *transfusion-transmission cytomegalovirus* [TT-CMV] infection: 0–0.3% per unit) as first-line therapy to prevent TT-CMV. However, given the low risks of TT-CMV with improvements in modern leukoreduction techniques, others have recommended use of leukoreduced blood without need for CMV antibody testing as an acceptably safe and low-risk alternative. RBC transfusion should not be delayed if CMV-negative blood is unavailable, and CMV-untested leukoreduced blood should be used, since the risk of TT-CMV is relatively low, with possibly more harm to the patient if transfusion is withheld or delayed. The usual dose is 10-15 mL/kg, but transfusion volumes vary greatly depending on clinical circumstances (continued vs arrested bleeding, hemolysis). For neonates, some prefer a centrifuged RBC concentrate (Hct 70–90%). Unless transfusions are being given to treat rapid bleeding, RBCs are infused slowly (over 2-4 hr) at a dose of approximately 10-15 mL/kg. In this small-volume setting, because of the small quantity of extracellular fluid transfused and the slow rate of infusion, the type of RBC anticoagulant/preservative solution does not pose any risk for premature infants when the dose does not exceed 20 mL/kg. However, the additive solutions (e.g., AS-1, AS-3, AS-5) have not been studied by comparative randomized clinical trials in the setting of >20 mL/kg dosing or massive transfusion settings such as cardiopulmonary bypass, ECMO, or massive transfusion for trauma. Although a few anecdotal reports suggest RBCs in additive solutions are safe for large-volume transfusions while awaiting more definitive information, some hospitals that manage these complex neonates and children maintain separate inventories of different RBC products earmarked either for neonates and infants (e.g., citrate-phosphate-dextrose or citrate-phosphate-dextrose-adenine) or for older children (e.g., additive solutions).

Storage Age of RBC Units

The historical practice of transfusing fresh RBCs (<7 days of storage) for the small-volume (15 mL/kg) transfusions commonly given was supplanted several years ago in most centers by reserving a single unit of RBCs for an infant, from which multiple aliquots were obtained for transfusions as needed throughout the 42 days of storage. Concerns about high concentrations of extracellular potassium, loss of 2,3-diphosphoglycerate, altered RBC shape and deformability, and nitric oxide quenching were found not to pose clinically significant problems. Preterm neonates allocated to “fresh RBC” (<7 days’ storage) transfusions vs “stored RBC” (up to 42 days’ storage) transfusions have no advantage for fresh RBC transfusions in altering the composite clinical outcome of mortality, plus NEC, retinopathy of prematurity, bronchopulmonary dysplasia, and intraventricular hemorrhage, or of the individual disorders.

For children weighing >30 kg who are to undergo elective surgery for whom

RBC transfusions are likely to be needed, autologous RBC transfusions offer an alternative to donor allogeneic RBCs. **Preoperative autologous** blood collections from the patient occur up to 6 wk before the surgery and require careful considerations for the volume to be drawn, vascular access, and use of EPO and iron to help restore the donated RBCs. **Acute normovolemic hemodilution** occurs in the preoperative period, in which blood is withdrawn from the patient and replaced with saline, a task often difficult in centers without experience in the process. **Salvaged autologous blood** is collected from blood loss during the operation but is impractical unless the volume of blood salvaged is fairly large to permit washing and transfusion of a significant number of RBCs. Because of all these difficulties, plus the relative safety of the usual allogeneic blood supply, autologous RBC transfusions are not typically used in the pediatric setting.

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CHAPTER 498

Platelet Transfusions

Cassandra D. Josephson, Ronald G. Strauss

Children and Adolescents

Guidelines for platelet (**PLT**) support of children and adolescents with quantitative and qualitative PLT disorders are similar to those for adults, in whom the risk of life-threatening bleeding occurring after injury or spontaneously can be related to the severity of thrombocytopenia, although somewhat imprecisely (Table 498.1).

Table 498.1

Guidelines for Pediatric Platelet (PLT) Transfusion*

CHILDREN AND ADOLESCENTS
1. Maintain PLT count >50 × 10^9 /L with bleeding. 2. Maintain PLT count >50 × 10^9 /L with *major invasive* procedure; >25 × 10^9 /L with minor. 3. Maintain PLT count >20 × 10^9 /L and *marrow failure* WITH hemorrhagic risk factors. 4. Maintain PLT count >10 × 10^9 /L and *marrow failure* WITHOUT hemorrhagic risk factors. 5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding or invasive procedure.
INFANTS ≤4 MO OLD
1. Maintain PLT count >100 × 10^9 /L with bleeding or during extracorporeal membrane oxygenation. 2. Maintain PLT count >50 × 10^9 /L and an invasive procedure. 3. Maintain PLT count >20 × 10^9 /L and *clinically stable.* 4. Maintain PLT count >50 × 10^9 /L and *clinically unstable and/or bleeding or not when on indomethacin, nitric oxide, antibiotics, etc., affecting PLT function.* 5. Maintain PLT count at any level with PLT dysfunction PLUS bleeding invasive procedure.

* Words in *italics* must be defined for local transfusion guidelines.

For children and adolescents with overt bleeding, therapeutic PLT transfusions should be given when the blood PLT count falls below 50 × 10^9 /L and repeated as needed to maintain the PLT count >50 × 10^9 /L during bleeding and for 48 hr after bleeding ceases to allow the clot to “stabilize.” Similarly, for a major invasive procedure (e.g., surgical), the PLT count should be maintained >50 × 10^9 /L until any bleeding that occurs ceases and the patient is stable. For minor invasive procedures (e.g., lumbar puncture, intravascular catheter placement), practices vary. It is reasonable to maintain the PLT count >25 × 10^9 /L, although these procedures often are performed in children with cancer or recent transplants, and it is important to be mindful of possible clotting abnormalities and anemia that may affect hemostasis beyond the effects of thrombocytopenia. Historical studies of patients with **thrombocytopenia** resulting from bone marrow failure suggest that the risk of spontaneous bleeding increases when blood PLT levels fall to <20 × 10^9 /L, particularly when hemorrhagic risk factors (infection, organ failure, clotting abnormalities, minor skin/mucosal bleeding, mucosal lesions, severe graft-versus-host disease [GVHD], anemia) are present. In this high-risk setting, prophylactic PLT transfusions are given to maintain a PLT count >20 × 10^9 /L. This threshold has been challenged by several studies of adult patients, who in many instances were carefully selected to be in relatively good clinical condition *without* hemorrhagic risk factors. Consequently, a lower PLT transfusion trigger of 10 × 10^9 /L is recommended for stable (i.e., low-risk) patients.

In practice, severe thrombocytopenia that is prolonged beyond 1 wk usually becomes complicated by the development of risk factors, including fever, antimicrobial therapy, GVHD, active bleeding, need for an invasive procedure, disseminated intravascular coagulation, and liver or kidney dysfunction with clotting abnormalities. In these situations, prophylactic PLT transfusions are given to maintain relatively high PLT counts (e.g., at least >30 × 10^9 /L). Despite the desire by some physicians to elevate the blood PLT count to 80 × 10^9 /L or 100 × 10^9 /L, there are no definitive data to justify a true benefit of PLT transfusions given at a PLT count >50 × 10^9 /L, unless bleeding is ongoing despite a PLT count between 50 and 100 × 10^9 /L *and* thrombocytopenia seems to be the only cause for the bleeding.

Qualitative PLT disorders may be *inherited* or *acquired*, as in advanced hepatic or renal insufficiency or when blood flows through an extracorporeal circuit, such as during extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass. In patients with inherited disorders, PLT transfusions are justified only if the risk of significant bleeding is quite high or if bleeding is overt, because inherited PLT dysfunction often is lifelong and repeated transfusions may lead to alloimmunization and refractoriness (i.e., poor response to PLT transfusions). Accordingly, prophylactic PLT transfusions are rarely justified unless an invasive procedure is planned, and therapeutic PLT transfusions must be given judiciously.

When managing patients with PLT dysfunction, it is important to remember that an abnormal test result with a modern PLT function device or, historically, a bleeding time more than twice the upper limit of normal provides diagnostic evidence of PLT dysfunction. However, an abnormal bleeding time or any other abnormal laboratory test is poorly predictive of hemorrhagic risk or the need to transfuse PLTs. Alternative therapies, particularly desmopressin acetate, should be considered to avoid PLT transfusions. Antiplatelet medications (nonsteroidal antiinflammatory drugs) should also be avoided.

Infants and Neonates

In neonates, thrombopoiesis and the risks of bleeding are substantially different from that in older children; the approach to thrombocytopenia and PLT transfusions likewise differs (see Table 498.1). **Thrombopoietin** (TPO) levels are higher in healthy neonates than in older individuals. Relative to adult PLT progenitors, *megakaryocyte* progenitors of neonates are more sensitive to TPO, have higher proliferative potential, and give rise to larger megakaryocyte colonies. Fetal/neonatal megakaryocytes are smaller in size and have lower ploidy than do their adult counterparts; this information is important, because small megakaryocytes of low ploidy produce fewer PLTs than do larger megakaryocytes of higher ploidy. Presumably, this allows the expanding marrow of the growing fetus and neonate to be supplied with sufficient numbers of megakaryocytes, yet not allowing blood PLT counts to become excessively high during proliferation, because of the lower numbers of PLTs produced by each megakaryocyte.

An important contrasting point is that older children and adults respond to situations of increased demand for PLTs by first increasing megakaryocyte size and ploidy, which is followed in 3-5 days by increased megakaryocyte number. In thrombocytopenic neonates, megakaryocyte numbers but not size increase. Moreover, although cytoplasmic maturation is achieved per TPO stimulation, increases in ploidy are relatively diminished and actually appear to be inhibited by TPO, resulting in large numbers of small megakaryocytes that are cytoplasmically mature, but with low ploidy and, consequently, lower PLT production.

PLT counts ≥150 × 10^9 /L are present after 17 wk gestational age, and it is accepted that neonates have PLT counts in the same range as older children and adults (150,000-450,000/µL). However, other data suggest a lower limit of 120,000/µL for extremely small preterm infants. Approximately 1% of term infants demonstrate PLT counts <150 × 10^9 /L, but bleeding in such infants is rare. In contrast, 18–35% of preterm neonates treated in intensive care units exhibit PLT counts <150 × 10^9 /L at some time during admission, with approximately 4% overall receiving PLT transfusions. Notably, when only extremely-low-birthweight preterm infants (<1 kg) were considered in one report, 70% had PLT counts <150 × 10^9 /L, and 5–9% of infants received platelet transfusions.

Debate continues in the United States as to the appropriate prophylactic platelet transfusion threshold for neonates, with a wide range in practice patterns. Multiple pathogenetic mechanisms underlie thrombocytopenia in these sick neonates, including predominantly accelerated PLT destruction plus diminished PLT production, as evidenced by decreased numbers of megakaryocyte progenitors and relatively low upregulation of TPO levels during thrombocytopenia, when compared with thrombocytopenic children and adults.

PLT counts <100 × 10^9 /L pose significant clinical risks for premature neonates. Bleeding time may be prolonged at PLT counts <100 × 10^9 /L in infants with birthweight <1500 g, and PLT dysfunction is suggested by bleeding times (a test no longer performed) that are disproportionately long for the degree of thrombocytopenia. The risk of hemorrhage may be increased in thrombocytopenic infants. However, in a randomized trial, transfusing PLTs prophylactically whenever the PLT count fell to <150 × 10^9 /L (i.e., at lower limit of normal range) to maintain the average PLT count at >200 × 10^9 /L, compared to not transfusing PLTs until the PLT count fell to <50 × 10^9 /L to maintain the average PLT count at approximately 100 × 10^9 /L, *did not result* in a lower incidence of intracranial hemorrhage (28% vs 26%, respectively). A U.S. multicenter observational study of very-low-birthweight infants in 6 neonatal intensive care units found wide variation in PLT thresholds for transfusion, ranging from 10,000 to 139,000/µL in the 1st wk of life and <10,000/µL to >50,000/µL after the 1st wk. The most common thresholds were 80,000-89,000/µL in the 1st 7 days of life and 40,000-49,000/µL after the 1st 7 days. Furthermore, after controlling for severity of thrombocytopenia, the authors found PLT transfusions were not associated with a lower risk of intraventricular hemorrhage. Thus, there is no documented benefit for prophylactic PLT transfusions to maintain PLT counts within the normal range or to correct moderate thrombocytopenia (PLT count >50 × 10^9 /L). As an exception, infants with inherited PLT dysfunction disorders *and* bleeding, as well as infants at high risk of bleeding because of acquired PLT dysfunction, such as during ECMO, typically receive transfusions to keep their PLT counts >100 × 10^9 /L.

A recent randomized clinical trial reported a significantly higher rate of new major hemorrhage or death within 28 days of randomization in very low birthweight neonates given prophylactic PLT transfusions at a pretransfusion PLT count of 50,000/µl (26%) vs. a pretransfusion PLT count of 25,000/µl (19%). Results are too preliminary to permit changes in practice but support other published findings indicating no need to maintain normal PLT counts and add to the belief that a PLT count of 50,000/µl is too high to serve as the pretransfusion PLT count for transfusions in stable low birthweight neonates.

Table 498.1 lists pediatric PLT transfusion guidelines that are acceptable to many neonatologists. One particularly contentious issue is how to manage critically ill neonates receiving agents known to adversely affect PLT function (e.g., indomethacin, nitric oxide, antibiotics). Some reports suggest increased risk of bleeding for these neonates, but the efficacy of PLT transfusions has not been convincingly proved, particularly when given prophylactically. For optimal PLT transfusion practices, each hospital should modify their guidelines to comply with local practices, with audits and reviews done to avoid violations of the recommended practices.

Platelet Products and Dosing

In the United States, 2 types/sources of PLT units are available, although any 1 blood bank or hospital may stock only 1 of these types. Whole blood–derived PLT units (**PLT concentrates**) and PLT units collected by apheresis (**pheresis PLTs**) differ in their PLT content and plasma volume. Although a PLT concentrate contains approximately 5.5-10 × 10^{10} PLTs in approximately 50 mL, and 1 pheresis PLT unit contains at least 3 × 10^{11} PLTs in 300-600 mL, the PLT content may vary considerably among different blood suppliers. Accordingly, it is prudent for hospital blood banks to confirm the composition of the PLT units they issue for transfusion, at the very least by contacting their blood supplier. It is often easier to use PLT concentrates for infants and small children, because pheresis PLTs usually need to be prepared as *aliquots* to provide the correct dose (10-15 mL/kg). However, many blood centers exclusively provide only 1 type of PLT component. Platelet products generally have a 5-day expiration time, although 7-day storage has been approved for apheresis platelet units within certain stipulations to reduce the risk of bacterial contamination and are stored at room temperature with constant agitation.

The posttransfusion goal of most PLT transfusions is to raise the PLT count well above 50×10^9 /L, hopefully to $\geq 100 \times 10^9$ /L. These increases can be achieved consistently in children weighing up to 30 kg by infusion of 5-10 mL/kg of standard (unmodified) PLT concentrates, obtained either from PLT concentrates or pheresis PLTs. For larger children, the appropriate dose is 4-8 pooled PLT concentrates or 1 apheresis unit. Because PLT concentration/quantity varies in different PLT products made available for transfusion, each hospital should monitor posttransfusion PLT counts to determine the dose that works best locally. PLT concentrates may be transfused as rapidly as the patient's overall condition permits, certainly within 2 hr, but not longer than 4 hr. Neonates/infants requiring repeated PLT transfusions should receive leukocyte-reduced blood products to diminish HLA alloimmunization and PLT refractoriness and to reduce the risk of transfusion-transmission cytomegalovirus infection (TT-CMV). For those infants weighing <1500 g at birth, **irradiation** is recommended to prevent transfusion-associated GVHD. Additionally, some recommend both leukoreduction and CMV-seronegative RBC units (estimated risk of TT-CMV infection: 0–0.3% per unit) as first-line therapy to prevent TT-CMV. However, given the low risks of TT-CMV with improvements in modern leukoreduction techniques, others have recommended use of leukoreduced blood from CMV-untested donors as an acceptably safe and low-risk alternative. PLT transfusion should not be delayed if CMV-negative units are unavailable; CMV-untested leukoreduced units should be used, since the risk of TT-CMV is relatively low, and more harm may come to the patient if transfusion is withheld or delayed.

Routinely reducing the volume of PLT concentrates for infants and small children by additional centrifugation steps is both unnecessary and unwise. Transfusion of 10-15 mL/kg of an unmodified PLT concentrate is adequate because it adds approximately 10×10^9 PLTs to 70 mL of blood (estimated intravascular blood volume of 1 kg neonate), a dose/volume calculated to increase the PLT count by 100×10^9 /L. This calculated increment is consistent with actual posttransfusion increment reported in patients. Moreover, 10-15 mL/kg is not an excessive transfusion volume, provided that the intake of other IV fluids, medications, and nutrients is monitored and adjusted.

It is important to select PLT units for transfusion with the donor ABO group identical to that of the neonate/infant and to avoid repeated transfusion of group O PLTs to group A or B recipients, because passive transfusion anti-A or anti-B in group O plasma can occasionally lead to intravascular hemolysis.

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CHAPTER 499

Neutrophil (Granulocyte) Transfusions

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Table 499.1 lists guidelines for granulocyte transfusion (**GTX**). GTX has been used sparingly in older infants and children. The current ability to collect markedly higher numbers of neutrophils from donors stimulated with combined recombinant granulocyte colony-stimulating factor (G-CSF) plus dexamethasone has led to renewed interest for patients with neutropenic infections, particularly when severe neutropenia is prolonged (e.g., in the setting of placental/cord blood hematopoietic progenitor cell transplantation). As a result, higher neutrophil yields are collected with this approach, making the addition of GTX to antibiotics a therapeutic consideration. This is especially true at institutions where neutropenic patients continue to die of progressive bacterial and fungal infections or to suffer substantial morbidity despite optimal antiinfection measures, including antibiotics and recombinant myeloid growth factors.

Table 499.1

Guidelines for Pediatric Granulocyte Transfusions*

CHILDREN AND ADOLESCENTS
1. Severe neutropenia (blood neutrophil count <0.5 × 10^9 /L) and infection (bacterial, yeast, or fungal) *unresponsive or progressive* despite appropriate antimicrobial therapy. 2. Qualitative neutrophil defect, neutropenia not required, and infection (bacterial or fungal) *unresponsive or progressive* to appropriate antimicrobial therapy.
INFANTS ≤4 MO OLD †
Blood neutrophil count <3.0 × 10^9 /L in 1st wk of life or <1.0 × 10^9 /L thereafter and *fulminant* bacterial infection.

* Words in *italics* must be defined for local transfusion guidelines.

† No longer commonly used.

Granulocyte Transfusions for Children

The use of GTX added to antibiotics for children with **severe neutropenia** (neutrophil count $<0.5 \times 10^9$ /L) because of bone marrow failure is similar to that for adults. Unfortunately, 2 randomized clinical trials comparing antibiotics plus GTX from donors stimulated with G-CSF plus dexamethasone vs antibiotics without GTX to treat neutropenic infections in children have not provided definitive guidelines. However, in practice, neutropenic patients with bacterial infections usually show response to antibiotics alone, provided bone marrow function recovers within the 1st 7-10 days of infection onset, so that severe neutropenia is relatively brief. Children with newly diagnosed acute lymphoblastic leukemia show rapid response to induction chemotherapy and are rarely candidates for GTX. In contrast, infected children with more sustained bone marrow failure and consequent severe neutropenia (e.g., acute myeloblastic leukemia, malignant neoplasms resistant to treatment, severe aplastic anemia, placental/cord blood hematopoietic progenitor cell transplant recipients) may benefit when GTX is added to antibiotics.

Currently, the efficacy of GTX obtained from G-CSF plus dexamethasone–stimulated donors for bacterial sepsis unresponsive to antibiotics in patients with severe neutropenia (neutrophil count $<0.5 \times 10^9$ /L) *is not well supported* by trials in children. Furthermore, GTX efficacy for yeast and fungal infections remains unproven, despite transfusing GTX with relatively large numbers of neutrophils.

Children with **qualitative neutrophil defects** (**neutrophil dysfunction**) usually have adequate or even increased numbers of blood neutrophils but develop serious infections, because their neutrophils kill pathogenic microorganisms inefficiently. Neutrophil dysfunction syndromes are rare; accordingly, no definitive studies have established GTX efficacy. However, several patients with progressive life-threatening infections have shown striking improvement with the addition of GTX, often given for long periods, to antimicrobial therapy. These disorders are chronic and thus associated with an increased risk of alloimmunization to leukocyte antigens, specifically to Kell system antigens on the red blood cells in some patients with chronic granulomatous disease, and GTX is recommended only when serious infections are clearly unresponsive to antimicrobial drugs.

Granulocyte Transfusion for Neonates

Neonates are unusually susceptible to severe bacterial infections, and a number of defects of neonatal defenses contribute to this susceptibility, including actual or “relative” neutropenia. Neonates with fulminant sepsis who exhibit **relative neutropenia** (blood neutrophil count <3.0 × 10^9 /L during the 1st wk of life and <1.0 × 10^9 /L thereafter) and a severely diminished neutrophil marrow storage pool (with <10% of nucleated marrow cells being postmitotic neutrophils) are at risk of dying if treated only with antibiotics. Despite this risk, GTX has not provided the solution. GTX is rarely used in neonates, because the results of clinical trials are mixed and not uniformly convincing, and it is difficult to obtain neutrophil apheresis concentrates in a timely fashion.

Current data are insufficient to conclude that recombinant myeloid growth factors have a role in treating septic neonates, despite that both G-CSF and granulocyte-macrophage CSF have been demonstrated to enhance myelopoiesis and raise neutrophil counts in infants. In contrast to the uncertain role of G-CSF and GM-CSF to treat infections in many clinical settings, it is important to remember that G-CSF is efficacious for the long-term treatment of several types of severe congenital neutropenia.

Granulocyte Product

If the decision to provide a GTX has been made, an adequate dose of neutrophils/granulocytes collected by leukapheresis must be transfused as shortly after collection as possible. To facilitate this goal, experienced donors with recently performed negative testing for HIV and hepatitis (usually within the past 30 days) are selected. Granulocyte donors should be documented to be CMV antibody negative (seronegative). These donors should also be ABO/Rh crossmatch compatible with the recipient, because there is a large volume of red blood cells in the granulocyte product.

Granulocyte Product Dosing

Neonates and **infants** weighing <10 kg should receive 1-2 × 10^9 /kg neutrophils per each GTX. **Larger infants** and **small children** should receive a minimal total dose of 1 × 10^{10} neutrophils per each GTX. The preferred dose for

adolescents is 5-8 × 10^{10} neutrophils per each GTX, a dose requiring donors to be stimulated with G-CSF plus dexamethasone. GTX should be given daily until either the infection resolves or the blood neutrophil count is sustained above 1.5 × 10^{9} /L for a few days. Because neutrophils transfused through the GTX often passively increase the blood neutrophil count, it may be necessary to skip 1-2 days of GTXs to accurately assess whether endogenous myelopoiesis and neutrophil production have recovered.

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CHAPTER 500

Plasma Transfusions

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Guidelines for plasma transfusion in pediatric patients are similar to those for adults, but with the understanding that plasma levels of coagulant and anticoagulant proteins can be developmentally low in preterm infants (Table 500.1). Therefore, transfusions of plasma and plasma-derived commercial concentrates should be determined by actual bleeding or a significant risk of bleeding, not simply by prolonged clotting time results. Plasma is transfused to replace clinically significant congenital or acquired deficiencies of plasma proteins for which more highly purified protein concentrates, treated to reduce infectious disease risks, or recombinant products are not available. Plasma and plasma derivatives are required to provide clotting proteins when bleeding is actually occurring or in settings when prevention of bleeding is deemed critical.

Table 500.1

Guidelines for Children and Infants for Plasma Transfusions*

1. *Severe* clotting factor deficiency AND bleeding.
2. *Severe* clotting factor deficiency AND an invasive procedure.
3. *Emergency reversal* of warfarin effects.
4. Dilutional coagulopathy and bleeding (e.g., massive transfusion).
5. Anticoagulant protein (antithrombin III, proteins C and S) replacement.
6. Plasma exchange replacement fluid for thrombotic thrombocytopenic purpura or for disorders with overt bleeding or in which there is risk of bleeding because of clotting protein abnormalities (e.g., liver failure).

* Words in *italics* must be defined for local transfusion guidelines.

Plasma Products and Patient Testing

Two interchangeable plasma products are available for transfusion, plasma frozen within 8 hours of collection (**fresh-frozen plasma** , FFP) and plasma frozen within 24 hr of collection **(F24)** . Although levels of factors V and VIII are modestly reduced in F24 (generally, not more than 25% lower), they are equally efficacious for all indications for which plasma is transfused in infants and children (see Table 500.1). Recommendations for the volume of plasma to be transfused vary with the specific protein being replaced and the severity of the deficiency, but a starting dose of 15 mL/kg is usually sufficient to elevate plasma levels satisfactorily.

Transfusion of plasma is efficacious for the treatment of deficiencies of clotting factors II, V, X, and XI. Deficiencies of factor XIII and fibrinogen are treated either with cryoprecipitate or specific commercial concentrates; although for patients being given large doses of plasma (e.g., in massive transfusion settings or to treat bleeding in liver failure), additional sources of fibrinogen may not be necessary, because plasma contains large amounts of fibrinogen. It is always useful to include a measurement of plasma fibrinogen (a separate test) when performing clotting assays, including prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT).

Plasma Transfusion in Children

Transfusion of plasma is not recommended for the treatment of patients with severe hemophilia A or B, von Willebrand disease, or factor VII deficiency, because safer plasma-derived and recombinant factor products for VII, VIII, IX, and von Willebrand factor are available. Moreover, mild to moderate hemophilia A and certain types of **von Willebrand disease** can be treated with intranasal or intravenous desmopressin (see Chapter 504). An important use of plasma is for rapid reversal of the effects of warfarin in patients who are actively bleeding or who require emergency surgery (in whom functional deficiencies of vitamin K–dependent factors II, VII, IX, and X cannot be rapidly reversed by vitamin K administration). Plasma-derived and virally inactivated prothrombin “complex” concentrates can also be used for this purpose.

Results of screening coagulation tests (PT/INR, aPTT, thrombin time, and plasma fibrinogen level) should not be assumed to reflect the integrity of the coagulation system or be regarded as indications for plasma transfusions. This is particularly true for neonates. To justify plasma transfusions, coagulation test results must be related to the patient's clinical condition in regard to bleeding and the risk of bleeding. Transfusion of plasma in patients with chronic liver disease and prolonged clotting times is not recommended unless bleeding is present or an invasive procedure is planned, because prophylactic correction of the clotting factor deficiencies is brief and of questionable benefit.

Plasma also contains several anticoagulant proteins (antithrombin III, protein C, and protein S) whose deficiencies have been associated with thrombosis. In select situations, plasma as replacement therapy along with anticoagulant treatment may be appropriate in patients with these disorders; when available, purified concentrates are preferred. Other indications for plasma include replacement fluid during plasma exchange in patients with **thrombotic thrombocytopenic purpura** (i.e., thrombotic microangiopathies) or other disorders for which plasma is likely to be beneficial. This includes plasma exchange in a patient with overt bleeding caused by the underlying disorder (e.g., Goodpasture syndrome, vasculitis), or disorders with significant severe coagulopathy that would substantially worsen with replacement by albumin solutions only. Plasma is not indicated for correction of hypovolemia or as immunoglobulin replacement therapy, because safer alternatives exist (albumin or crystalloid solutions and IV immunoglobulin, respectively).

Plasma Transfusion in Neonates

In neonates, clotting times are “physiologically” prolonged because of developmental deficiency of clotting proteins; plasma should be transfused only after reference to normal values adjusted for the birthweight and age of the infant (*not* to normal ranges for older children and adults). The indications for plasma in neonates include (1) reconstitution of red blood cell (RBC) concentrates to simulate whole blood for use in massive transfusions (exchange transfusion, cardiac bypass surgery, and extracorporeal membrane oxygenation), (2) hemorrhage secondary to vitamin K deficiency, (3) disseminated intravascular coagulation *with* bleeding, and (4) bleeding in congenital coagulation factor deficiency when more specific treatment is either unavailable or inappropriate. The use of prophylactic plasma transfusion to prevent intraventricular hemorrhage in premature infants is not recommended. Plasma should not be used as a suspending agent to adjust the hematocrit values of RBC concentrates before small-volume RBC transfusions to neonates, because it offers no apparent medical benefit over the use of sterile solutions such as crystalloid and albumin. Similarly, the use of plasma in partial exchange transfusion for the treatment of neonatal hyperviscosity syndrome is unnecessary, because safer crystalloid or colloid solutions are available.

In the treatment of bleeding infants, *cryoprecipitate* is often considered because of its small infusion volume. However, cryoprecipitate contains significant quantities of only fibrinogen, von Willebrand factor, and factors VIII and XIII. Thus, it is not effective for treating the usual clinical situation in bleeding infants with multiple clotting factor deficiencies. However, cryoprecipitate is an excellent source of fibrinogen (much more concentrated than frozen plasma), and with a dose of 1-2 units/kg, the patient's fibrinogen level can be quickly raised by 60-100 mg/dL.

In preliminary studies, infusions of very small volumes of recombinant activated factor VII have been lifesaving in patients with hemorrhage caused by several mechanisms. Because the efficacy and toxicity of factor VIIa have not been fully defined in these “off-label” uses (not approved by the U.S. Food and Drug Administration), it must be considered “experimental” therapy at this time.

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CHAPTER 501

Risks of Blood Transfusions

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The greatest risk of a blood transfusion is mistakenly receiving a transfusion intended for another patient. *Misidentification* is usually a result of mistakes made in labeling the patient's blood sample sent to the blood bank or not accurately matching the unit with the patient at the bedside when the blood is transfused. This risk is particularly high for infants, especially if ABO type-specific or type-compatible blood is transfused, because (1) identification bands may not be attached directly to their bodies, (2) difficulties in drawing blood samples for pretransfusion compatibility testing may lead to deviations from usual policies, and (3) infants cannot speak to identify themselves. Thus, particular care must be taken to ensure accurate patient and blood sample identification.

Infectious Risks of Transfusion

Although the infectious disease risks of allogeneic blood transfusions are extremely low, transfusions must be given judiciously because “emerging infections,” such as Ebola or Zika virus, when they first arise, pose a potential threat until they are studied definitively and, accordingly, are of constant concern, and testing is not done for every microorganism possibly transmitted by blood transfusions (Table 501.1 and Fig. 501.1). Taking nucleic acid amplification testing (NAT) and all other donor-screening activities (antibody and epidemiology screening) into account, a current estimate of the risk of transfusion-associated **HIV** infection is approximately 1 per every 2 million donor exposures. Similarly, with NAT, the risk of hepatitis C virus (**HCV**) infection is 1 per every 1.5-2 million donor exposures (Table 501.1). NAT identifies circulating microbial nucleic acids that appear in the window before antibodies develop, and NAT is used routinely to detect HIV, HCV, and West Nile virus, hepatitis B virus, *Trypanosoma cruzi*, *Babesia microti*, and Zika virus.

Table 501.1

Estimated Risks in Transfusion per Unit Transfused in the United States

ADVERSE EFFECT	ESTIMATED RISK
Febrile nonhemolytic reaction	1 in 300
Urticaria or other cutaneous reaction	1 : 50-100
Red blood cell alloimmunization	1 : 100
Mistranfusion	1 : 14,000-19,000
Hemolytic reaction, acute and delayed	1 : 2,500-6,000
Fatal hemolysis	1 : 1 million
Transfusion-related acute lung injury (TRALI)	1 : 5,000-50,000
HIV-1 and HIV-2	1 : 2-3 million
Hepatitis B	1 : 100,000-200,000
Hepatitis C	1 : 1-2 million
Human T-cell lymphotrophic virus (HTLV) I and II	1 : 641,000
Bacterial contamination (usually platelets)	1 : 5 million
Malaria	1 : 4 million
Anaphylaxis	1 : 20,000-50,000
Graft-versus-host disease	Uncommon
Immunomodulation	Unknown
Posttransfusion purpura	Unknown
Hepatitis A	Unknown
Parvovirus	Unknown
Dengue fever	Unknown
Babesiosis	Unknown
West Nile virus	Unknown
Trypanosoma cruzi	Unknown
Leishmania spp.	Unknown
Variant Creutzfeldt-Jakob prion disease	Unknown
Zika virus	Unknown

Adapted from Klein HG, Spahn DR, Carson JL: Red blood cell transfusion in clinical practice, *Lancet* 370:415–426, 2007.

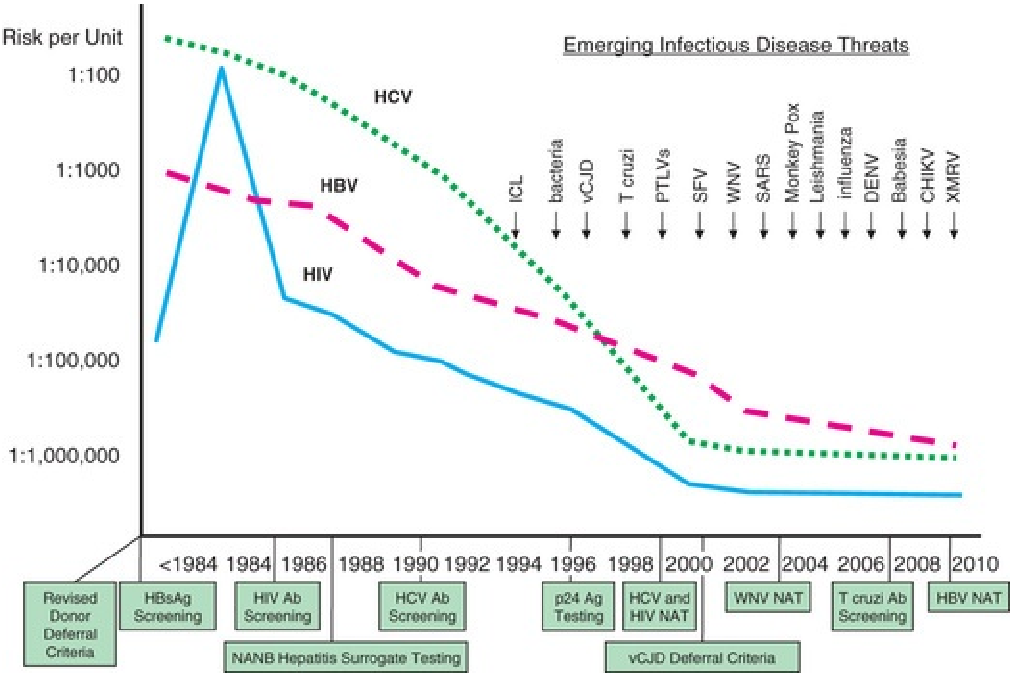

FIG. 501.1 **Risks of major transfusion-transmitted viruses related to interventions, and accelerating rate of emerging infectious diseases of concern to blood safety. Evolution of the risks of transmission by blood transfusion for human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Major interventions to reduce risks are shown below the time line on the *x* axis. Emerging infectious disease threats in the past 20 yr are shown above in the *top right quadrant* of the figure. Ab, Antibody; Ag, antigen; CHIKV, chikungunya virus; DENV, dengue virus; HBsAg, hepatitis B surface antigen; ICL, idiopathic CD4 T-lymphocytopenia; NANB, non-A, non-B hepatitis; NAT, nucleic acid amplification testing; PTLVs, primate T-lymphotropic viruses; SARS, severe acute respiratory syndrome; SFV, simian foamy virus; vCJD, variant Creutzfeldt-Jakob disease; WNV, West Nile virus; XMRV, xenotropic murine leukemia virus–related virus. (From Busch MP. Transfusion-transmitted viral infections: building bridges to transfusion medicine to reduce risks and understand epidemiology and pathogenesis. 2005 Emily Cooley Award Lecture, *Transfusion* 46:1624–1640, 2006.)**

Transfusion-associated cytomegalovirus (**CMV**) has been nearly eliminated by transfusion of leukocyte-reduced cellular blood products or by selection of blood collected from donors who are seronegative for antibody to CMV. Although it is logical to hypothesize that first collecting blood components from CMV-seronegative donors and then removing the white blood cells (WBCs) might further improve safety, little data are available to document the superior efficacy of this combined approach. However, in a recent prospective birth cohort study of premature infants with birthweight ≤1500 g, a combined approach of leukoreduction and CMV-seronegative cellular blood components yielded 0% transfusion transmission of CMV (15.3% cumulative incidence at 12 wk of maternal breast milk transmission from CMV-seropositive mothers) in >300 transfused infants studied. Similar uncontrolled reports of hematopoietic stem cell transplant patients found 0% transmission of CMV from leukoreduced blood products from donors of unknown CMV antibody status. Therefore, considerable care must be taken not to place children at risk of delayed or missed transfusions while awaiting/searching for blood from CMV-seronegative donors, then to leukoreduce (i.e., risks must not be taken for practices with no established benefits).

Further data on these 2 mitigation strategies revealed that large quantities of CMV viral material are present “free” in the plasma of healthy-appearing donors during the early phase of primary infection (while CMV antibodies are either absent [“window” phase] or are newly emerging and at low, inconsistently detected levels in plasma), rather than being leukocyte associated, as occurs with CMV as substantial quantities of IgG antibodies appear. As a result of this biology of CMV primary infection, plasma “free” virus will not be removed by leukoreduction during early infection, and CMV-seronegative donors who may be asymptomatic or deny symptoms of infection during blood donor screening will be misclassified as being CMV safe. They are not necessarily as safe because antibody is below the limits of detection, while plasma “free” CMV is plentiful during early infection. Because almost all plasma “free” CMV disappears and becomes almost exclusively cell associated, once donors are CMV seropositive with antibody present for several months, some propose that the best method to reduce CMV risk may be leukoreduction of blood from donors known to be CMV seropositive for at least 1 yr. However, data to prove the efficacy of this proposal are lacking, and in practice, several studies have shown that the most efficacious method currently available to prevent transfusion-transmitted CMV is to perform leukoreduction in the blood center/bank without regard for the CMV antibody status of the donor/unit (i.e., leukoreduction alone performed by the blood center/bank, not at the bedside, is sufficient in most cases).

Additional infectious risks include other types of **hepatitis** (A, B, E) and **retroviruses** (human T-cell lymphotropic virus types I and II, HIV-2), syphilis, parvovirus B19, Epstein-Barr virus, human herpesvirus 8, West Nile virus, yellow fever vaccine virus, malaria, babesiosis, *Anaplasma phagocytophilum* , Chagas disease, and Zika virus. Variant Creutzfeldt-Jacob disease has also been transmitted by blood transfusions in humans. All are reported very infrequently, but nonetheless provide the rationale to transfuse only when true benefits are likely.

Noninfectious Risks of Transfusion

Transfusion-associated risks of a noninfectious nature that may occur include hemolytic and nonhemolytic transfusion reactions, circulatory fluid overload, **graft-versus-host disease** (GVHD), electrolyte and acid-base imbalances, iron overload if repeated red blood cell (RBC) transfusions are needed long term, increased susceptibility to oxidant damage, exposure to plasticizers, hemolysis with T-antigen activation of RBCs, posttransfusion purpura, **transfusion-related acute lung injury** (TRALI), posttransfusion immunosuppression and immunomodulation, and alloimmunization (Fig. 501.2 ; see Table 501.1). The risk of TRALI may be reduced by avoiding transfusion of plasma or platelets from female donors, who were possibly alloimmunized to leukocyte antigens during pregnancy, or by selecting donors (e.g., males) who are likely to be negative for human leukocyte antigen (HLA) antibodies.

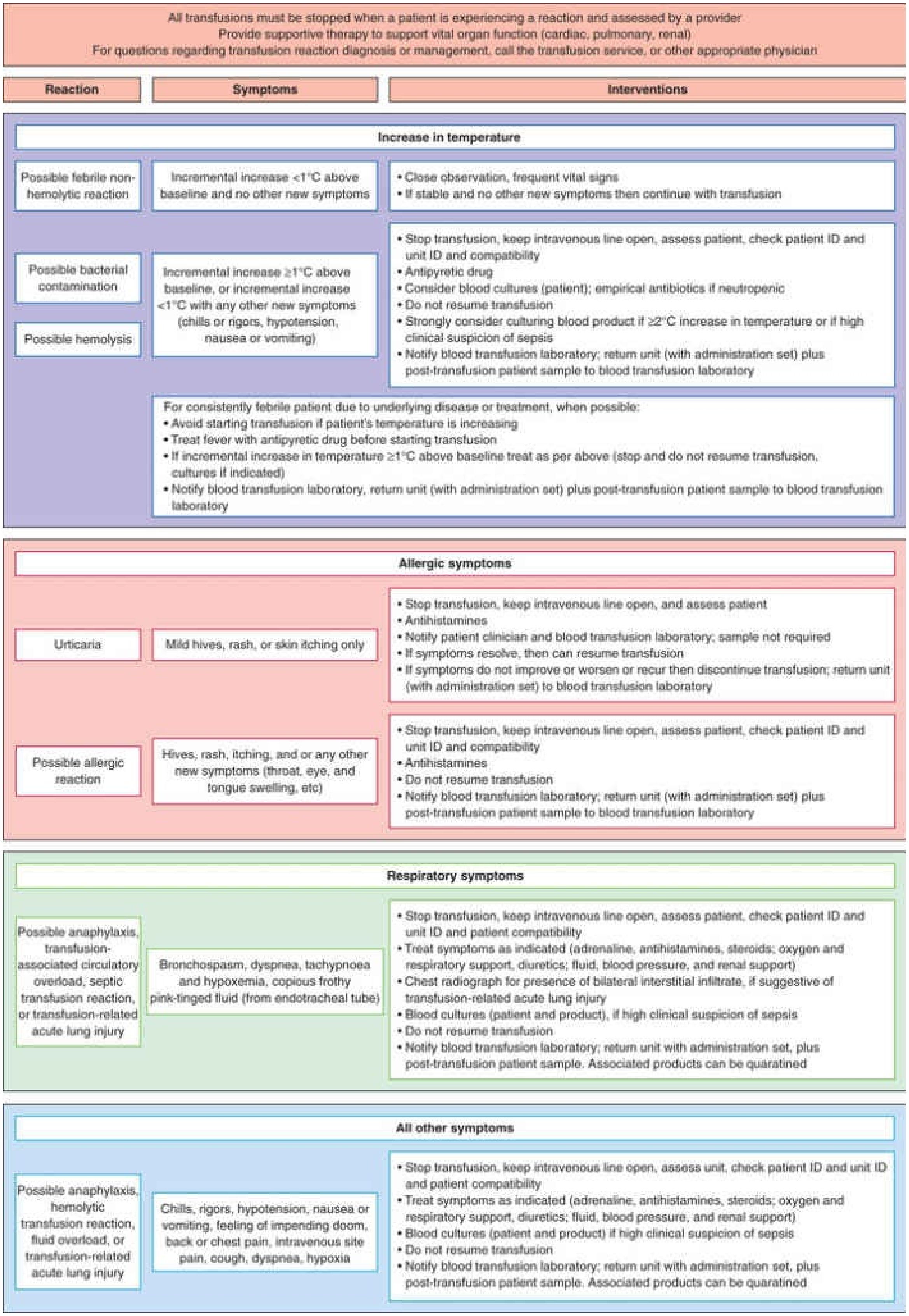

All transfusions must be stopped when a patient is experiencing a reaction and assessed by a provider
Provide supportive therapy to support vital organ function (cardiac, pulmonary, renal)
For questions regarding transfusion reaction diagnosis or management, call the transfusion service, or other appropriate physician

Reaction	Symptoms	Interventions
Increase in temperature		
Possible febrile non-hemolytic reaction	Incremental increase <1°C above baseline and no other new symptoms	• Close observation, frequent vital signs • If stable and no other new symptoms then continue with transfusion
Possible bacterial contamination Possible hemolysis	Incremental increase ≥1°C above baseline, or incremental increase <1°C with any other new symptoms (chills or rigors, hypotension, nausea or vomiting)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and compatibility • Antipyretic drug • Consider blood cultures (patient); empirical antibiotics if neutropenic • Do not resume transfusion • Strongly consider culturing blood product if ≥2°C increase in temperature or if high clinical suspicion of sepsis • Notify blood transfusion laboratory; return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory
	For consistently febrile patient due to underlying disease or treatment, when possible: • Avoid starting transfusion if patient's temperature is increasing • Treat fever with antipyretic drug before starting transfusion • If incremental increase in temperature ≥1°C above baseline treat as per above (stop and do not resume transfusion, cultures if indicated) • Notify blood transfusion laboratory, return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory	
Allergic symptoms		
Urticaria	Mild hives, rash, or skin itching only	• Stop transfusion, keep intravenous line open, and assess patient • Antihistamines • Notify patient clinician and blood transfusion laboratory; sample not required • If symptoms resolve, then can resume transfusion • If symptoms do not improve or worsen or recur then discontinue transfusion; return unit (with administration set) to blood transfusion laboratory
Possible allergic reaction	Hives, rash, itching, and or any other new symptoms (throat, eye, and tongue swelling, etc)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and compatibility • Antihistamines • Do not resume transfusion • Notify blood transfusion laboratory; return unit (with administration set) plus post-transfusion patient sample to blood transfusion laboratory
Respiratory symptoms		
Possible anaphylaxis, transfusion-associated circulatory overload, septic transfusion reaction, or transfusion-related acute lung injury	Bronchospasm, dyspnea, tachypnoea and hypoxemia, copious frothy pink-tinged fluid (from endotracheal tube)	• Stop transfusion, keep intravenous line open, assess patient, check patient ID and unit ID and patient compatibility • Treat symptoms as indicated (adrenaline, antihistamines, steroids; oxygen and respiratory support, diuretics; fluid, blood pressure, and renal support) • Chest radiograph for presence of bilateral interstitial infiltrate, if suggestive of transfusion-related acute lung injury • Blood cultures (patient and product), if high clinical suspicion of sepsis • Do not resume transfusion • Notify blood transfusion laboratory; return unit with administration set, plus post-transfusion patient sample. Associated products can be quaratined
All other symptoms		
Possible anaphylaxis, hemolytic transfusion reaction, fluid overload, or transfusion-related acute lung injury	Chills, rigors, hypotension, nausea or vomiting, feeling of impending doom, back or chest pain, intravenous site pain, cough, dyspnea, hypoxia	• Stop transfusion, keep intravenous line open, assess unit, check patient ID and unit ID and patient compatibility • Treat symptoms as indicated (adrenaline, antihistamines, steroids; oxygen and respiratory support, diuretics; fluid, blood pressure, and renal support) • Blood cultures (patient and product) if high clinical suspicion of sepsis • Do not resume transfusion • Notify blood transfusion laboratory; return unit with administration set, plus post-transfusion patient sample. Associated products can be quaratined

FIG. 501.2 **Transfusion reaction decision tree. Algorithm to guide assessment and actions to take when a transfusion reaction is initially identified. Actions should proceed from left to right. (From Delaney M, Wendel S, Bercovitz RS: Transfusion reactions: prevention, diagnosis, and treatment, *Lancet* 388:2825–2836, 2016, Fig 2).**

Immunologic adverse effects, including immunosuppression, immunomodulation, and alloimmunization, may be reduced by leukoreduction. Transfusion reactions and alloimmunization to RBC and leukocyte antigens seem to be uncommon in infants, perhaps because of developmental immaturity of the immune system or deficient cytokine production. When they do occur, adverse effects are seen primarily in massive transfusion settings, such as exchange transfusions and trauma or surgery, in which relatively large quantities of blood components are needed, but are rare when small-volume transfusions are usually given.

Premature infants are known to have immune dysfunction, but their relative risk of posttransfusion GVHD is controversial. The postnatal age of the infant, the number of immunocompetent lymphocytes in the transfusion product, the degree of HLA compatibility between donor and recipient, and other, poorly described phenomena determine which infants are truly at risk for GVHD. Regardless, many centers caring for preterm infants transfuse exclusively irradiated cellular products. As an alternative, pathogen-reduction technology has been documented to prevent GVHD and can substitute for irradiation. Directed donations with blood drawn from blood relatives must always be irradiated because of the risk of engraftment with transfused HLA-homozygous, haploidentical lymphocytes. Cellular blood products given as intrauterine or exchange transfusions should be irradiated, as should transfusions for patients with severe congenital immunodeficiency disorders (severe combined immunodeficiency syndrome and DiGeorge syndrome requiring heart surgery) and transfusions for recipients of hematopoietic progenitor cell transplants. Other groups who are potentially at risk but for whom no conclusive data are available include patients given T-cell antibody therapy (antithymocyte globulin or OKT3), those with organ allografts, those receiving immunosuppressive drug regimens, and those infected with HIV.

As an alternative, pathogen-reduction technology has been documented to prevent T-cell proliferation, and thus TA-GVHD may be used as a substitute for irradiation. Current practice uses **irradiation** from a cesium, cobalt, or linear acceleration source at doses ranging from 1,500 to 2,500 centigray; a maximum dose of 2,500 cGy is required to hit the center of the irradiation field and a minimum of 1,500 cGy delivered to any other portion of the cannister. All cellular blood components should be irradiated, except those frozen without a cryoprotectant agent and to be rendered as “acellular” products, such as plasma and cryoprecipitate, which do not require irradiation. Leukocyte reduction cannot be substituted for irradiation to prevent GVHD. However, as mentioned, pathogen-reduction technologies have been demonstrated to be efficacious.

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SECTION 7

Hemorrhagic and Thrombotic Diseases

OUTLINE

Chapter 502 Hemostasis
Chapter 503 Hereditary Clotting Factor Deficiencies (Bleeding Disorders)
Chapter 504 Von Willebrand Disease
Chapter 505 Hereditary Predisposition to Thrombosis
Chapter 506 Thrombotic Disorders in Children
Chapter 507 Postneonatal Vitamin K Deficiency
Chapter 508 Liver Disease
Chapter 509 Acquired Inhibitors of Coagulation
Chapter 510 Disseminated Intravascular Coagulation
Chapter 511 Platelet and Blood Vessel Disorders

CHAPTER 502

Hemostasis

J. Paul Scott, Veronica H. Flood, Leslie J. Raffini

Hemostasis is the process of blood clotting in areas of blood vessel injury. Over time, the clot is lysed by the fibrinolytic system, and normal blood flow is restored. If clotting is impaired, hemorrhage occurs. If clotting is excessive, thrombotic complications ensue. The hemostatic response needs to be rapid and regulated such that trauma does not trigger a systemic reaction but must initiate a rapid, localized response. When a platelet adheres to a site of vascular injury, the platelet surface provides a reaction surface where clotting factors bind. The active enzyme is brought together with its substrate and a catalytic cofactor on a reaction surface, accelerating reaction rates and providing activated products for reaction with clotting factors further down the coagulation cascade. Active clotting is controlled by negative feedback loops that inhibit the clotting process when the procoagulant process comes in contact with intact endothelium. The main components of the hemostatic process are the **vessel wall, platelets, coagulation proteins, anticoagulant proteins,** and **fibrinolytic system.** Most components of hemostasis are multifunctional; fibrinogen serves as the ligand between platelets during platelet aggregation and also as the substrate for thrombin that forms the fibrin clot. Platelets provide the reaction surface on which clotting reactions occur, form the plug at the site of vessel injury, and contract to constrict and limit clot size.

The Hemostatic Process

The intact vascular endothelium is the primary barrier against hemorrhage. The endothelial cells that line the vessel wall normally inhibit coagulation and provide a smooth surface that permits rapid blood flow.

After vascular injury, vasoconstriction occurs and flowing blood comes in contact with the subendothelial matrix. **Von Willebrand factor (VWF)** changes conformation and provides the glue to which the platelet VWF receptor, the glycoprotein Ib complex, binds, tethering platelets to sites of injury. Complex signaling occurs from the outside membrane receptor to intracellular pathways, activating the platelets and triggering secretion of storage granules containing adenosine diphosphate (ADP), serotonin, and stored plasma and platelet membrane proteins. On activation, the platelet receptor for fibrinogen, $\alpha IIb\beta_3$, is switched on ("inside out" signaling) to bind fibrinogen and triggers the aggregation and recruitment of other platelets to form the platelet plug. Multiple physiologic agonists can trigger platelet activation and aggregation, including ADP, collagen, thrombin, and arachidonic acid. Aggregation involves the interaction of specific receptors on the platelet surface with plasma hemostatic proteins, primarily fibrinogen.

One of the subendothelial matrix proteins that is exposed after vascular injury is *tissue factor* . Exposed tissue factor binds to factor VII and activates the *clotting cascade* (Fig. 502.1). The activated clotting factor then initiates the activation of the next sequential clotting factor in a systematic manner. Our understanding of the sequence of steps in the cascade followed assignment of the numerals for the clotting factors for the participant proteins, and thus the sequence seems "out of numerical order." During the process of platelet activation, internalized platelet phospholipids (primarily phosphatidylserine) become externalized and interact at 2 specific, rate-limiting steps in the clotting process—those involving the cofactors factor VIII (X-ase complex) and factor V (prothrombinase complex). Both these reactions are localized to the platelet surface and bring together the active enzyme, an activated cofactor, and the zymogen that will form the next active enzyme in the cascade. This sequence results in amplification of the process, which supplies a burst of clotting where it is physiologically needed. In vivo, autocatalysis of factor VII generates small amounts of VIIa continuously, so the system is always poised to act. Near the bottom of the cascade, the multipotent enzyme *thrombin* is formed. Thrombin converts fibrinogen into fibrin, activates factors V, VIII, and XI, and aggregates platelets. Activation of factor XI by thrombin amplifies further thrombin generation and contributes to inhibition of fibrinolysis. Thrombin also activates factor XIII. The stable fibrin-platelet plug is ultimately formed through clot retraction and cross linking of the fibrin clot by factor XIIIa.

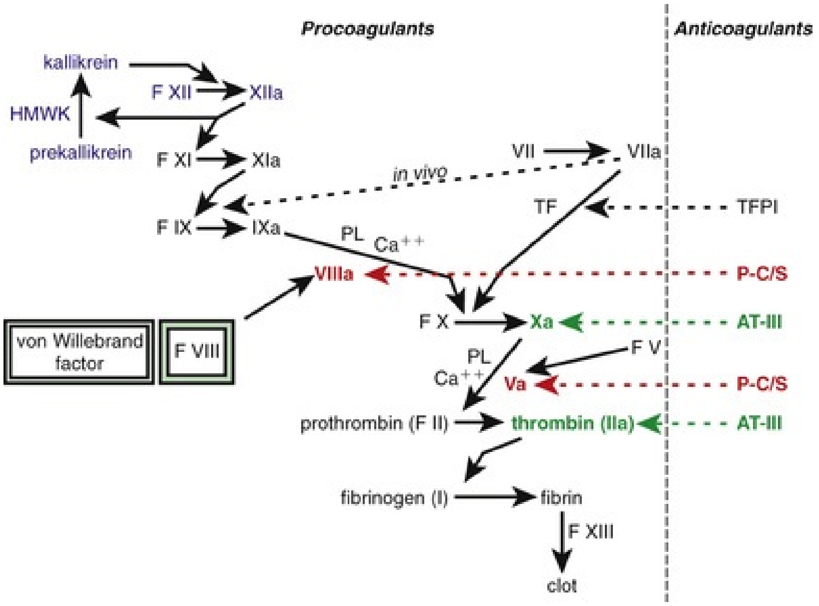

FIG. 502.1 The clotting cascade, with sequential activation and amplification of clot formation. Many of the factors (F) are activated by the clotting factors shown above them in the cascade. The activated factors are designated by the addition of an *a* . On the *right side,* the major anticoagulants and the sites that they regulate are shown: tissue factor pathway inhibitor (TFPI) regulates tissue factor (TF); factor VIIa, protein C, and protein S (P-C/S) regulate factors VIII and V; and antithrombin III (AT-III) regulates factor Xa and thrombin (factor IIa). The *dotted line* shows that, in vivo, TF and factor VIIa activate both factors IX and X, but that, in vitro, only the activation of factor X is measured. Unactivated factor VIII, when bound to its carrier protein, von Willebrand factor, is protected from protein C inactivation. When thrombin, or factor Xa activates factor VIII, it becomes unbound from von Willebrand factor, at which point it can participate with factor IXa in the activation of factor X in the presence of phospholipid (PL) and Ca^{++} (the “tenase” complex). Factor XIIIa cross-links the fibrin clot and thereby makes it more stable. Prekallikrein, high-molecular-weight kininogen (HMWK), and factor XII are shown in *blue* because they do not have a physiologic role in coagulation, although they contribute to the clotting time in partial thromboplastin time (PTT).

Virtually all procoagulant proteins are balanced by anticoagulant proteins that regulate or inhibit procoagulant function. Four clinically important, naturally occurring anticoagulants regulate the extension of the clotting process: antithrombin III (**AT III**), protein C, protein S, and tissue factor pathway inhibitor (**TFPI**). AT III is a serine protease inhibitor that regulates primarily factor Xa and thrombin and to a lesser extent, factors IXa, XIa, and XIIa. When thrombin in flowing blood encounters intact endothelium, thrombin binds to *thrombomodulin*, its endothelial receptor. The thrombin-thrombomodulin complex then converts **protein C** into activated protein C. In the presence of the cofactor **protein S** , activated protein C proteolyzes and inactivates factor Va and factor VIIIa. Inactivated factor Va is a functional anticoagulant that inhibits clotting. TFPI limits activation of factor X by factor VIIa and tissue factor and shifts the activation site of tissue factor and factor VIIa to that of factor IX (Fig.

502.2).

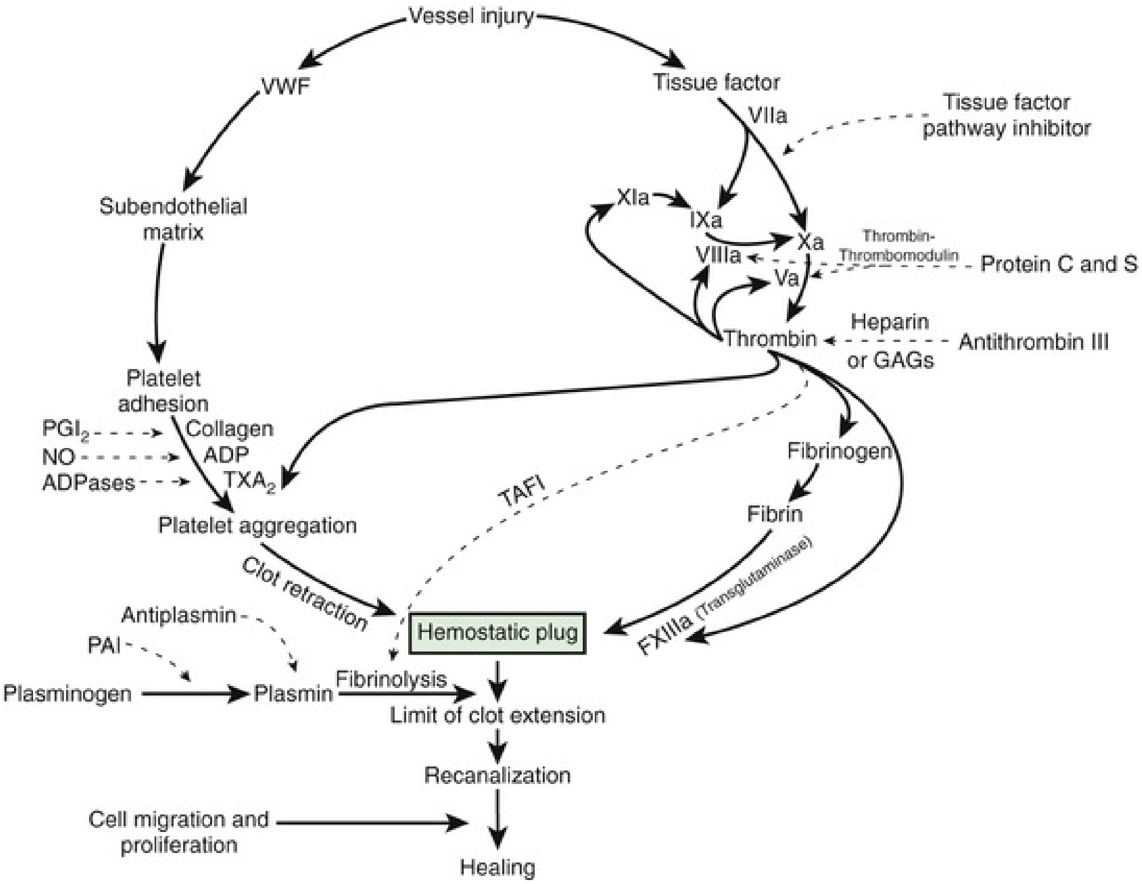
Vessel injury
VWF
Tissue factor
VIIa
Tissue factor pathway inhibitor
Subendothelial matrix
XIa
IXa
Xa
VIIIa
Va
Thrombin-Thrombomodulin
Protein C and S
Thrombin
Heparin or GAGs
Antithrombin III
Platelet adhesion
PGI_2
NO
ADPases
Collagen
ADP
TXA_2
Platelet aggregation
TAFI
Fibrinogen
Fibrin
FXIIIa (Transglutaminase)
Clot retraction
Hemostatic plug
Antiplasmin
PAI
Plasminogen
Plasmin
Fibrinolysis
Limit of clot extension
Recanalization
Cell migration and proliferation
Healing

FIG. 502.2 **The hemostatic mechanism. ADP, Adenosine diphosphate; GAGs, glycosaminoglycans; NO, nitric oxide; PGI_2 , prostacyclin (prostaglandin I_2); PAI, plasminogen activator inhibitor; TAFI, thrombin-activated fibrinolytic inhibitor; TXA_2 , thromboxane A_2 ; VWF, von Willebrand factor.**

Once a stable fibrin-platelet plug is formed, the fibrinolytic system limits its extension and also lyses the clot (**fibrinolysis**) to reestablish vascular integrity. Plasmin, generated from plasminogen by either urokinase-like or tissue-type plasminogen activator, degrades the fibrin clot. In the process of dissolving the fibrin clot, fibrin degradation products are produced. The fibrinolytic pathway is regulated by plasminogen activator inhibitors and α_2 -antiplasmin as well as by the thrombin-activatable fibrinolysis inhibitor. Finally, the flow of blood in and around the clot is crucial, because flowing blood returns to the liver, where activated clotting factor complexes are removed and new procoagulant and anticoagulant proteins are synthesized to maintain homeostasis of the hemostatic system.

Pathology

Congenital deficiency of an individual procoagulant protein leads to a bleeding disorder, whereas deficiency of an anticoagulant (clotting factor inhibitor) predisposes the patient to thrombosis. In acquired hemostatic disorders, there are frequently multiple problems with homeostasis that perturb and dysregulate hemostasis. A primary illness (sepsis) and its secondary effects (shock and acidosis) activate coagulation and fibrinolysis and impair the host's ability to restore normal hemostatic function. When sepsis triggers **disseminated intravascular coagulation,** platelets, procoagulant clotting factors, and anticoagulant proteins are consumed, leaving the hemostatic system unbalanced and prone to bleeding or clotting. Similarly, newborn infants and patients with severe liver disease have synthetic deficiencies of both procoagulant and anticoagulant proteins. Such dysregulation causes the patient to be predisposed to both hemorrhage and thrombosis with mild or moderate triggers that result in major alterations in the hemostatic process.

In the laboratory evaluation of hemostasis, parameters are manipulated to allow assessment of isolated aspects of hemostasis and limit the multifunctionality of some of its components. The coagulation process is studied in plasma anticoagulated with citrate to bind calcium, with added phospholipid to mimic the reaction surface normally provided by the platelet membrane and with a stimulus to trigger clotting. Calcium is added to restart the clotting process. This results in anomalies such that the in vivo physiologic pathway of clotting in which factor VIIa activates factor IX is bypassed; instead, in prothrombin time (PT), factor VIIa activates factor X. If this were truly the physiologic situation, there would be an in vivo bypass mechanism that would ameliorate severe factor VIII and factor IX deficiencies, the 2 most common severe bleeding disorders.

502.1

Clinical and Laboratory Evaluation of Hemostasis

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Keywords

coagulation factor
laboratory testing
PT
PTT
platelet aggregation
thrombin time
reptilase time
von Willebrand disease

Clinical History

For most hemostatic disorders, the clinical history provides the most useful information. To evaluate for a bleeding disorder, the history should determine the site or sites of bleeding, the severity and duration of hemorrhage, and the age at onset. Was the bleeding spontaneous, or did it occur after trauma? Was there a previous personal or family history of similar problems? Did the symptoms correlate with the degree of injury or trauma? Does bruising occur spontaneously? Are there lumps with bruises for which there is minimal trauma? If the patient had previous surgery or significant dental procedures, was there any increased bleeding? If a child or adolescent has had surgery that affects the mucosal surfaces, such as a tonsillectomy or major dental extractions, the absence of bleeding usually rules out a hereditary bleeding disorder. Delayed or slow healing of superficial injuries may suggest a hereditary bleeding disorder. In postpubertal females, it is important to take a careful menstrual history. Because some common bleeding disorders, such as **von Willebrand disease (VWD)** , have a fairly high prevalence, mothers and family members may have the same mild bleeding disorder and may not be cognizant that the child's menstrual history is abnormal. Women with mild VWD who have a moderate history of bruising frequently have a reduction in symptoms during pregnancy or after administration of oral contraceptives. Some medications, such as aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs), inhibit platelet function and increase bleeding symptoms in patients with a low platelet count or abnormal hemostasis. Standardized bleeding scores have been developed and are undergoing investigation for their sensitivity and specificity in children.

Outside the neonatal period, thrombotic disorders are relatively rare until adulthood. In the neonate, physiologic deficiencies of procoagulants and anticoagulants place the hemostatic mechanism at greater risk for imbalance, and clinical events can lead to either hemorrhage or thrombosis. If a child or teenager presents with deep vein thrombosis (DVT) or pulmonary embolism (PE), a detailed family history must be obtained to evaluate for DVT, PE, myocardial infarction (MI), or cerebrovascular accident (stroke) in other family members. The presence of **thrombosis** , especially in the absence of a provoking agent in the child or teenager, should induce the clinician to take a careful family history and consideration of evaluation for a hereditary or acquired predisposition to thrombosis.

Physical Examination

The physical examination should focus on whether bleeding symptoms are associated primarily with the mucous membranes or skin (*mucocutaneous* bleeding) or with the muscles and joints (*deep* bleeding). The examination should determine the presence of petechiae, ecchymoses, hematomas, hemarthroses, or mucous membrane bleeding. Patients with defects in platelet–blood vessel wall interaction (VWD or platelet function defects) usually have mucocutaneous bleeding, which may include epistaxis, menorrhagia, petechiae, ecchymoses, occasional hematomas, and less frequently, hematuria and gastrointestinal bleeding. Individuals with a clotting deficiency of factor VIII or IX (hemophilia A or B) have symptoms of deep bleeding into muscles and joints, with much more extensive ecchymoses and hematoma formation. Patients with mild VWD or other mild bleeding disorders may have no abnormal findings on physical examination. Individuals with disorders of the collagen matrix and vessel wall may have loose joints and lax skin associated with easy bruising (**Ehlers-Danlos syndrome**).

Patients undergoing evaluation for thrombotic disorders should be asked about swollen, warm, tender extremities (venous thrombosis), unexplained dyspnea or persistent “pneumonia,” especially in the absence of fever (PE), and varicosities and postphlebitic changes. Arterial thrombi usually cause an acute, dramatic impairment of organ function, such as stroke, MI, or a painful, white, cold extremity.

Laboratory Tests

In patients who have a positive bleeding history or who are actively hemorrhaging, a platelet count, PT, and partial thromboplastin time (PTT) should be performed as screening tests. In individuals with abnormal screening tests, further evaluation should be based on those results. In a patient with an abnormal bleeding history and a positive family history, normal screening tests should not preclude further laboratory evaluation, which may include a thrombin time, VWF testing, and platelet function studies. Historically, bleeding time and platelet function analysis (**PFA-100**) have been used as screening tests, but neither has proved to be useful in diagnosis of mild bleeding disorders.

There are no useful routine screening tests for *hereditary* thrombotic disorders. If the family history is positive or clinical thrombosis is unexplained, specific thrombophilia assays should be performed. Thrombosis is rare in children, and when it is present, the possibility of a hereditary predisposition should be considered (see Chapter 505).

Platelet Count

Platelet count is essential in the evaluation of the child with a positive bleeding history, because thrombocytopenia is the most common acquired cause of a bleeding diathesis in children. Patients with a platelet count of $>50 \times 10^9$ /L rarely have significant clinical bleeding. **Thrombocytosis** in children is usually reactive and is not associated with bleeding or thrombotic complications. Persistent, severe thrombocytosis in the absence of an underlying illness may require evaluation for the very rare pediatric presentation of essential thrombocythemia or polycythemia vera.

Prothrombin Time and Activated Partial Thromboplastin Time

Because clotting (coagulation) factors were named in the order of discovery, they do not necessarily reflect the sequential order of activation (Tables 502.1

and 502.2). In fact, factors III, IV, and VI were not subsequently found to be independent proteins; thus these terms are no longer used. Only 2 factors have commonly used names: fibrinogen (factor I) and prothrombin (factor II). The dual mechanisms of activating clotting have been termed the **intrinsic** (surface activation) and **extrinsic** (tissue factor–mediated) pathways. Study of the hemostatic mechanism is further complicated in that the interactions in vivo may use different pathways from those studied in clinical laboratory testing. PT measures the activation of clotting by tissue factor (thromboplastin) in the presence of calcium. Addition of tissue factor causes a burst of factor VIIa generation. The tissue factor–factor VIIa complex activates factor X. Whether factor X is activated by the intrinsic or the extrinsic pathway, factor Xa on the platelet phospholipid surface complexes with factor V and calcium (the "prothrombinase" complex) to activate prothrombin to thrombin (also referred to as *factor IIa*). Once thrombin is generated, fibrinogen is converted to a fibrin clot, the end-point of the reaction (see Fig. 502.2). PT is not prolonged with deficiencies of factors VIII, IX, XI, and XII. In most laboratories the normal PT value is 10-13 sec. PT has been standardized using the international normalized ratio (**INR**) so that values can be compared from one laboratory or instrument to another. This ratio is used to determine similar degrees of anticoagulation with vitamin K antagonists, such as warfarin.

Table 502.1

Coagulation (Clotting) Factors

CLOTTING FACTOR	SYNONYM	DISORDER
I	Fibrinogen	Congenital deficiency (afibrinogenemia) or dysfunction (dysfibrinogenemia)
II	Prothrombin	Congenital deficiency or dysfunction
V	Labile factor, proaccelerin	Congenital deficiency (parahemophilia)
VII	Stable factor or proconvertin	Congenital deficiency
VIII	Antihemophilic factor	Congenital deficiency is hemophilia A (classic hemophilia)
IX	Christmas factor	Congenital deficiency is hemophilia B (sometimes referred to as Christmas disease)
X	Stuart-Prower factor	Congenital deficiency
XI	Plasma thromboplastin antecedent	Congenital deficiency (sometimes referred to as hemophilia C)
XII	Hageman factor	Congenital deficiency is not associated with clinical symptoms
XIII	Fibrin-stabilizing factor	Congenital deficiency

Table 502.2

Reference Values for Coagulation Tests in Healthy Children[*]

TEST	28-31 Wk GESTATION [†]	30-36 Wk GESTATION	FULL TERM	1-5 Yr	6-10 Yr	11-18 Yr	ADULT
Screening Tests							
Prothrombin time (sec)	15.4 (14.6-16.9)	13.0 (10.6-16.2)	13.0 (10.1-15.9)	11 (10.6-11.4)	11.1 (10.1-12.0)	11.2 (10.2-12.0)	12 (11.0-14.0)
Activated partial thromboplastin time (sec)	108 (80-168)	53.6 (27.5-79.4) [‡] [§]	42.9 (31.3-54.3) [‡]	30 (24-36)	31 (26-36)	32 (26-37)	33 (27-40)
Procoagulants							
Fibrinogen	256 (160-550)	243 (150-373) [‡] [§]	283 (167-399)	276 (170-405)	279 (157-400)	300 (154-448)	278 (156-40)
Factor II	31 (19-54)	45 (20-77) [‡]	48 (26-70) [‡]	94 (71-116) [‡]	88 (67-107) [‡]	83 (61-104) [‡]	108 (70-146)
Factor V	65 (43-80)	88 (41-144) [§]	72 (34-108) [‡]	103 (79-127)	90 (63-116) [‡]	77 (55-99) [‡]	106 (62-150)
Factor VII	37 (24-76)	67 (21-113) [‡]	66 (28-104) [‡]	82 (55-116) [‡]	86 (52-120) [‡]	83 (58-115) [‡]	105 (67-143)
Factor VIII procoagulant	79 (37-126)	111 (5-213)	100 (50-178)	90 (59-142)	95 (58-132)	92 (53-131)	99 (50-149)
Von Willebrand factor	141 (83-223)	136 (78-210)	153 (50-287)	82 (60-120)	95 (44-144)	100 (46-153)	92 (50-158)
Factor IX	18 (17-20)	35 (19-65) [‡] [§]	53 (15-91) [‡]	73 (47-104) [‡]	75 (63-89) [‡]	82 (59-122) [‡]	109 (55-163)
Factor X	36 (25-64)	41 (11-71) [‡]	40 (12-68) [‡]	88 (58-116) [‡]	75 (55-101) [‡]	79 (50-117)	106 (70-152)
Factor XI	23 (11-33)	30 (8-52) [‡] [§]	38 (40-66) [‡]	97 (52-150) [‡]	86 (52-120)	74 (50-97) [‡]	97 (56-150)
Factor XII	25 (5-35)	38 (10-66) [‡] [§]	53 (13-93) [‡]	93 (64-129)	92 (60-140)	81 (34-137) [‡]	108 (52-164)
Prekallikrein	26 (15-32)	33 (9-89) [‡]	37 (18-69) [‡]	95 (65-130)	99 (66-131)	99 (53-145)	112 (62-162)
High-molecular-weight kininogen	32 (19-52)	49 (9-89) [‡]	54 (6-102) [‡]	98 (64-132)	93 (60-130)	91 (63-119)	92 (50-136)
Factor XIIIa [‖]		70 (32-108) [‡]	79 (27-131) [‡]	108 (72-143)	109 (65-151)	99 (57-140)	105 (55-155)
Factor XIIIb [‖]		81 (35-127) [‡]	76 (30-122) [‡]	113 (69-156) [‡]	116 (77-154) [‡]	102 (60-143)	98 (57-137)
Anticoagulants							
Antithrombin-III	28 (20-38)	38 (14-62) [‡] [§]	63 (39-87) [‡]	111 (82-139)	111 (90-131)	106 (77-132)	100 (74-126)
Protein C		28 (12-44) [‡] [§]	35 (17-	66 (40-	69 (45-	83 (55-	96 (64-128)

			53) ‡	92) ‡	93) ‡	111) ‡	
Protein S:							
Total (units/mL)		26 (14-38) ‡ §	36 (12-60) ‡	86 (54-118)	78 (41-114)	72 (52-92)	81 (61-113)
Free (units/mL)				45 (21-69)	42 (22-62)	38 (26-55)	45 (27-61)
Plasminogen (units/mL)		170 (112-248)	195 (125-265)	98 (78-118)	92 (75-108)	86 (68-103)	99 (77-122)
Tissue-type plasminogen activator (ng/mL)		8.48 (3.00-16.70)	9.6 (5.0-18.9)	2.15 (1.0-4.5) ‡	2.42 (1.0-5.0) ‡	2.16 (1.0-4.0) ‡	1.02 (0.68-1.36)
Antiplasmin (units/mL)		78 (40-116)	85 (55-115)	105 (93-117)	99 (89-110)	98 (78-118)	102 (68-136)
Plasminogen activator inhibitor-I		5.4 (0.0-12.2) ‡	6.4 (2.0-15.1)	5.42 (1.0-10.0)	6.79 (2.0-12.0) ‡	6.07 (2.0-10.0) ‡	3.60 (0.0-11.0)

[*] All factors except fibrinogen are expressed as units/mL (fibrinogen in mg/mL), in which pooled normal plasma contains 1 unit/mL. All data are expressed as the mean, followed by the upper and lower boundaries encompassing 95% of the normal population (shown in parentheses). Normal ranges above vary based on the reagents and instruments used.

[†] Levels for 19-27 wk and 28-31 wk gestation are from multiple sources and cannot be analyzed statistically.

[‡] Values are significantly different from those of adults.

[§] Values are significantly different from those of full-term infants.

[||] Value given as CTA (Committee on Thrombolytic Agents) units/mL. Normal ranges above vary based on the reagents and instruments used.

Data from Andrew M, Paes B, Johnston M: Development of the hemostatic system in the neonate and young infant, *Am J Pediatr Hematol Oncol* 12:95, 1990; and Andrew M, Vegh P, Johnston M, et al: Maturation of the hemostatic system during childhood, *Blood* 80:1998, 1992.

Partial Thromboplastin Time

The intrinsic pathway involves the initial activation of factor XII, which is accelerated by 2 other plasma proteins, prekallikrein and high-molecular-weight kininogen. In the clinical laboratory, factor XII is activated using a surface (silica or glass) or a contact activator, such as ellagic acid. Factor XIIa in turn activates factor XI to factor XIa, which then catalyzes factor IX to factor IXa. On the platelet phospholipid surface, factor IXa complexes with factor VIII and calcium to activate factor X (“tenase” complex).

This process is accelerated by interaction with phospholipid and calcium at the steps involving factors V and VIII. An isolated deficiency of a single clotting factor may result in isolated prolongation of PT, PTT, or both, depending on the location of the factor in the clotting cascade. This approach is useful in determining hereditary clotting factor deficiencies; however, in acquired hemostatic disorders encountered in clinical practice, more than 1 clotting factor is frequently deficient, so the relative prolongation of PT and PTT must be assessed.

Measurement of PTT as performed in the clinical laboratory is actually “activated” PTT; most refer to it as **PTT** . This test measures the initiation of clotting at the level of factor XII through sequential steps to the final clot end-point. It does not measure factor VII, factor XIII, or anticoagulants. PTT uses a contact activator (silica, kaolin, or ellagic acid) in the presence of calcium and phospholipid. Because of differences in reagents and laboratory instruments, the normal range for PTT varies among hospital laboratories. Normal ranges for PTT have much more interlaboratory variability than those for PT.

Thus, the mechanisms studied by PT and PTT allow the evaluation of clotting factor deficiencies, even though these pathways may not be the same as those occurring physiologically. In vivo, factor VIIa activates factors IX and X, but as routinely studied in the clinical laboratory, the pathway through which factor VIIa activates factor IX is not evaluated. If the tissue factor–factor VIIa complex activated only factor X, it would be difficult to explain why the most severe bleeding disorders are deficiencies of factor VIII (**hemophilia A**) and factor IX (**hemophilia B**). In vivo, thrombin is generated and feeds back to activate factor XI and accelerate the clotting process. The PTT can be prolonged by deficiencies of factor XII, prekallikrein, and high-molecular-weight kininogen, yet these deficiencies do not result in bleeding,

Thrombin Time

Thrombin time (TT) measures the final step in the clotting cascade, in which fibrinogen is converted to fibrin. The normal TT varies between laboratories but is usually 11-15 sec. Prolongation of TT occurs with reduced fibrinogen levels (*hypofibrinogenemia* or *afibrinogenemia*), with dysfunctional fibrinogen (*dysfibrinogenemia*), or in the presence of substances that interfere with fibrin polymerization, such as heparin and fibrin split products. If heparin contamination is a potential cause of prolonged TT, a reptilase time is usually ordered. Alternatively, heparinase can be added to the sample and TT repeated.

Reptilase Time

Reptilase time uses snake venom to clot fibrinogen. Unlike thrombin time, reptilase time is not sensitive to heparin and is prolonged only by reduced or dysfunctional fibrinogen and fibrin split products. Therefore, if TT is prolonged but reptilase time is normal, the prolonged TT is caused by heparin and does not indicate the presence of fibrin split products or reduced concentration or function of fibrinogen.

Mixing Studies

If there is unexplained prolongation of PT or PTT, a mixing study is usually performed. Normal plasma is added to the patient's plasma and the PT or PTT repeated. Correction of PT or PTT by 1:1 mixing with normal plasma suggests deficiency of a clotting factor, because a 50% level of individual clotting proteins is sufficient to produce normal PT or PTT. If the clotting time is not corrected or only partially corrected, an **inhibitor** is usually present. An inhibitor of clotting may be either a chemical similar to heparin that delays coagulation or an antibody directed against a specific clotting factor or the phospholipid used in clotting tests. In the inpatient setting the most common cause of a prolonged PTT is **heparin contamination** of the sample. The presence of heparin in the sample can be ruled in or out either by addition of *heparinase* to the sample and repeating the PTT. If the mixing study is not corrected or if its result becomes more prolonged and the patient has clinical bleeding, an inhibitor of a specific clotting factor (antibody directed against the factor), most often factor VIII, factor IX, or factor XI, may be present. If the patient has no bleeding symptoms and both PTT and the mixing study are prolonged, a **lupus-like anticoagulant** (see Chapter 503) is often present. Patients with these findings usually have a long PTT, do not bleed, and may have a clinical predisposition to excessive clotting.

Platelet Aggregation

When a qualitative platelet function defect is suspected, platelet aggregation testing is usually ordered. Platelet-rich plasma from the patient is activated with 1 of a series of agonists (ADP, epinephrine, collagen, thrombin or thrombin-receptor peptide, and ristocetin). Some platelet aggregometers measure specific adenosine triphosphate release from the platelets, as measured by the generation of luminescence via lumiaggregometry, and are more sensitive in detecting abnormalities of the platelet release reaction from storage granules. Repeat testing or testing of other symptomatic family members can help to determine the hereditary nature of the defect. Many medications, especially aspirin, other NSAIDs, and valproic acid, alter platelet function testing. Fig. 502.1 provides an approach to the differential diagnosis of many common bleeding disorders based on screening tests.

Testing for Thrombotic Predisposition

Hereditary predisposition to thrombosis is associated with a reduction of anticoagulant function (protein C, protein S, AT III); the presence of a factor V molecule that is resistant to inactivation by protein C (factor V Leiden); elevated levels of procoagulants (a mutation of the prothrombin gene); or a deficiency of fibrinolysis (plasminogen deficiency); and the rare metabolic disease homocystinuria (see Chapter 505).

Tests of the Fibrinolytic System

Euglobulin clot lysis time is a screening test used in some laboratories to assess fibrinolysis. More specific tests are available in most laboratories to determine the levels of plasminogen, plasminogen activator, and inhibitors of fibrinolysis. An increase in fibrinolysis may be associated with hemorrhagic symptoms, and a delay in fibrinolysis is associated with thrombosis.

Developmental Hemostasis

The normal newborn infant has reduced levels of most procoagulants and anticoagulants (see Table 502.2). In general, there is a more marked abnormality in the preterm infant. Although major differences exist in the normal ranges for newborn and preterm infants, these ranges vary greatly among laboratories based on the instruments and reagents used. During gestation, there is progressive maturation and increase of the clotting factors synthesized by the liver. The extremely premature infant has prolonged PT and PTT values as well as a marked reduction in anticoagulant protein levels (protein C, protein S, and AT III). Levels of fibrinogen, factors V and VIII, VWF, and platelets are near-normal throughout the later stages of gestation (see Chapter 124.4). Because protein C and protein S are physiologically reduced, factors V and VIII, which are present at normal levels at birth, are not balanced with their regulatory proteins. In contrast, the physiologic deficiency of vitamin K–dependent procoagulant proteins (factors II, VII, IX, and X) is partially balanced by the physiologic reduction of AT III. The net effect is that newborns (especially premature infants) are at increased risk for complications of bleeding, clotting, or both.

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CHAPTER 503

Hereditary Clotting Factor Deficiencies (Bleeding Disorders)

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Hemophilia A (factor VIII deficiency) and **hemophilia B** (factor IX deficiency) are the most common and serious congenital coagulation factor deficiencies. The clinical findings in hemophilia A and hemophilia B are virtually identical. **Hemophilia C** is the bleeding disorder associated with reduced levels of factor XI (see Chapter 503.2). Reduced levels of the *contact factors* (factor XII, high-molecular-weight kininogen, and prekallikrein) are associated with significant prolongation of *activated partial thromboplastin time* (aPTT; also referred to as **PTT**), but are not associated with hemorrhage, as discussed in Chapter 503.3 . Other, less common coagulation factor deficiencies are briefly discussed in subsequent subchapters.

503.1

Factor VIII or Factor IX Deficiency (Hemophilia A or B)

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Keywords

arthropathy
hemarthrosis
hemophilia
hemorrhage
inhibitor
tamponade
target joint

Deficiencies of factors VIII and IX are the most common severe inherited bleeding disorders.

Pathophysiology

Factors VIII and IX participate in a complex required for the activation of factor X. Together with phospholipid and calcium, they form the “tenase,” or factor X–activating, complex. Fig. 502.1 in Chapter 502 shows the clotting process as it occurs in the test tube, with factor X being activated by either the complex of factors VIII and IX or the complex of tissue factor and factor VII. In vivo, the complex of factor VIIa and tissue factor activates factor IX to initiate clotting. In the laboratory, prothrombin time (PT) measures the activation of factor X by factor VII and is therefore normal in patients with factor VIII or factor IX deficiency.

After injury, the initial hemostatic event is formation of the platelet plug, together with generation of the fibrin clot, which prevents further hemorrhage. In hemophilia A and B, clot formation is delayed and is not robust. Inadequate thrombin generation leads to failure to form a tightly cross-linked fibrin clot to support the platelet plug. Patients with hemophilia slowly form a soft, friable clot. When untreated bleeding occurs in a closed space, such as a joint, cessation of bleeding may be the result of **tamponade** . With open wounds, in which tamponade cannot occur, profuse bleeding may result in significant blood loss. The clot that is formed may be friable, and rebleeding occurs during the physiologic lysis of clots or with minimal new trauma.

Clinical Manifestations

Neither factor VIII nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus. Only 2% of neonates with hemophilia sustain intracranial hemorrhages, and 30% of male infants with hemophilia bleed with circumcision. Thus, in the absence of a positive family history (30% of hemophilia A occurs by spontaneous mutation), hemophilia may go undiagnosed in the newborn. Obvious symptoms, such as easy bruising, intramuscular hematomas, and hemarthroses, begin when the child starts to cruise. Bleeding from minor traumatic lacerations of the mouth (torn frenulum) may persist for hours or days and may cause the parents to seek medical evaluation. Even in patients with severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age. Although bleeding may occur in any area of the body, the hallmark of hemophilic bleeding is **hemarthrosis.** Bleeding into the joints may be induced by minor trauma; many hemarthroses are spontaneous. The earliest joint hemorrhages appear most often in the ankle. In the older child and adolescent, hemarthroses of the knees and elbows are also common. Whereas the child's early joint hemorrhages are recognized only after major swelling and fluid accumulation in the joint space, older children are frequently able to recognize bleeding before the physician does. They complain of a warm, tingling sensation in the joint as the first sign of an early joint hemorrhage. Repeated bleeding episodes into the same joint in a patient with severe hemophilia may result in a “target” joint. Recurrent bleeding may then become spontaneous because of the underlying pathologic changes in the joint.

Although most muscular hemorrhages are clinically evident because of localized pain or swelling, bleeding into the iliopsoas muscle requires specific mention. A patient may lose large volumes of blood into the iliopsoas muscle, verging on hypovolemic shock, with only a vague area of referred pain in the groin. The hip is held in a flexed, internally rotated position due to irritation of the iliopsoas. The diagnosis is made clinically from the inability to extend the hip but must be confirmed with ultrasonography or CT (Fig. 503.1). Life-threatening bleeding in the patient with hemophilia is caused by bleeding into vital structures (central nervous system, upper airway) or by exsanguination (external trauma, gastrointestinal or iliopsoas hemorrhage). Prompt treatment with clotting factor concentrate for these life-threatening hemorrhages is imperative. If head trauma is of sufficient concern to suggest radiologic evaluation, factor replacement should *precede* radiologic evaluation. Life-threatening hemorrhages require replacement therapy to achieve a level equal to that of normal plasma (100 IU/dL, or 100%).

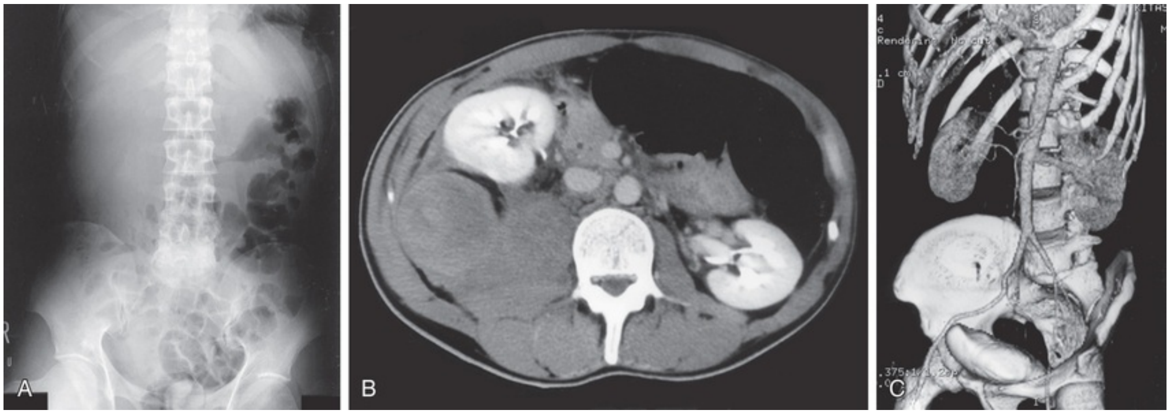

FIG. 503.1 **Massive hematoma into the iliopsoas muscle in a patient with hemophilia B. A 38 yr old man with severe deficiency of factor IX (hemophilia B) was admitted for right lower abdominal pain of progressively increasing severity and tenderness. He had had a common cold with severe cough and loss of appetite for approximately 1 wk. A, Abdominal radiograph shows presence of the psoas sign on the right side and left-shifted colon gas. B, CT scan shows massive hematoma in the right iliopsoas muscle, resulting in anterior translocation of the right kidney. C, Reconstructed 3-dimensional image shows more clearly the kidney translocation and the extended, but intact, large vessels. These are useful findings for the diagnostic procedures, because progressive right lower abdominal pain may closely simulate acute appendicitis. The hemorrhage was successfully managed by replacement of factor IX for 1 wk without any recurrence. The patient did not have any inhibitors to factor IX. (From Miyazaki K, Higashihara M: Massive hemorrhage into the iliopsoas muscle, *Intern Med* 44:158, 2005.)**

Patients with mild hemophilia who have factor VIII or factor IX levels >5 IU/dL usually do not have spontaneous hemorrhages. These individuals may experience prolonged bleeding after dental work, surgery, or injuries from moderate trauma and may not be diagnosed until they are older.

Laboratory Findings and Diagnosis

A reduced level of factor VIII or factor IX will result in a laboratory finding of a *prolonged PTT.* In severe hemophilia, the PTT value is usually 2-3 times the upper limit of normal. Results of the other screening tests of the hemostatic mechanism (platelet count, bleeding time, PT, thrombin time) are normal. Unless the patient has an inhibitor to factor VIII or IX, the mixing of normal plasma with patient plasma results in correction of PTT value. The specific assay for factors VIII and IX will confirm the diagnosis of hemophilia. If correction does not occur on mixing, an inhibitor may be present. In 25–35% of patients with hemophilia who receive infusions of factor VIII or factor IX, a factor-specific antibody may develop. These antibodies are directed against the active clotting site and are termed *inhibitors.* In such patients, the quantitative Bethesda assay for inhibitors should be performed to measure the antibody titer.

Differential Diagnosis

In young infants with severe bleeding manifestations, the differential diagnosis includes severe thrombocytopenia; severe platelet function disorders, such as Bernard-Soulier syndrome and Glanzmann thrombasthenia; type 3 (severe) von Willebrand disease; and vitamin K deficiency.

Genetics and Classification

Hemophilia occurs in approximately 1 : 5,000 males, with 85% having factor VIII deficiency and 10–15% having factor IX deficiency. Hemophilia shows no apparent racial predilection, appearing in all ethnic groups. The severity of hemophilia is classified on the basis of the patient's baseline level of factor VIII or factor IX, because factor levels usually correlate with the severity of bleeding symptoms. By definition, 1 IU of each factor is defined as that amount in 1 mL of normal plasma referenced against a standard established by the World Health Organization (WHO); thus, 100 mL of normal plasma has 100 IU/dL (100% activity) of each factor. For ease of discussion, we use the term *% activity* to refer to the percentage found in normal plasma (100% activity). Factor concentrates are also referenced against an international WHO standard, so treatment doses are usually referred to in IU. **Severe hemophilia** is characterized as having <1% activity of the specific clotting factor, and bleeding is often spontaneous. Patients with **moderate hemophilia** have factor levels of 1–5% and usually require mild trauma to induce bleeding. Individuals with **mild hemophilia** have levels >5%, may go many years before the condition is diagnosed, and frequently require significant trauma to cause bleeding. The hemostatic level for factor VIII is >30–40%, and for factor IX, it is >25–30%. The lower limit of levels for factors VIII and IX in normal individuals is approximately 50%.

The genes for factors VIII and IX are carried near the terminus of the long arm of the X chromosome and are therefore X-linked traits. The majority of patients with hemophilia have reduced clotting factor protein; 5–10% of those with hemophilia A and 40–50% of those with hemophilia B make a dysfunctional protein. Approximately 45–50% of patients with severe hemophilia A have the same mutation, in which there is an internal inversion within the factor VIII gene that results in production of no protein. This mutation can be detected in the blood of patients or carriers and in the amniotic fluid by molecular techniques. African Americans often have a different factor VIII haplotype, and this difference may be the reason that African Americans have higher inhibitor formation. Because of the multiple genetic causes of either factor VIII or factor IX deficiency, most cases of hemophilia are classified according to the amount of factor VIII or factor IX clotting activity. In the newborn, factor VIII values may be artificially elevated because of the acute-phase response elicited by the birth process. This artificial elevation may cause a mildly affected patient to have normal or near-normal levels of factor VIII. Patients with severe hemophilia do not have detectable levels of factor VIII. In contrast, factor IX levels are physiologically low in the newborn. If severe hemophilia is present in the family, an undetectable level of factor IX is diagnostic of severe hemophilia B. In some patients with mild factor IX deficiency, the presence of hemophilia can be confirmed only after several weeks of life.

Through lyonization of the X chromosome, some **female carriers** of hemophilia A or B have sufficient reduction of factor VIII or factor IX to produce mild bleeding disorders. Levels of these factors should be determined in all known or potential carriers to assess the need for treatment in the event of surgery or clinical bleeding.

Because factor VIII is carried in plasma by von Willebrand factor, the ratio of factor VIII to VWF is sometimes used to diagnose carriers of hemophilia but may give false-positive or false-negative results. When possible, specific genetic mutations should be identified in the propositus and used to test other family members who are at risk of either having hemophilia or being carriers.

Treatment

Early, appropriate therapy is the hallmark of excellent hemophilia care. When mild to moderate bleeding occurs, values of factor VIII or factor IX must be raised to hemostatic levels, in the 35–50% range. For life-threatening or major hemorrhages, the dose should aim to achieve levels of 100% activity.

Calculation of the dose of recombinant factor VIII (FVIII) or recombinant factor IX (FIX) is as follows:

$$\text{Dose of rFVIII (IU)} = \text{\% Desired (rise in FVIII)} \times \text{Body weight (kg)} \times 0.5$$

$$\text{Dose of rFIX (IU)} = \text{\% Desired (rise in plasma FIX)} \times \text{Body weight (kg)} \times 1.3$$

For factor VIII, the correction factor is based on the volume of distribution of factor VIII. For factor IX, the correction factor is based on the volume of distribution and the observed rise in plasma level after infusion of recombinant factor IX.

Table 503.1 summarizes the treatment of some common types of hemorrhage in a patient with hemophilia.

Table 503.1

Treatment of Hemophilia

TYPE OF HEMORRHAGE	HEMOPHILIA A	HEMOPHILIA B
Hemarthrosis*	50-60 IU/kg factor VIII concentrate † on day 1, then 20 IU/kg the following day. Consider every other day until joint function is normal or back to baseline. Consider prophylaxis.	80-100 IU/kg factor IX concentrate ‡ on day 1; then 40 IU/kg the following day. Consider every other day until joint function is normal or back to baseline. Consider prophylaxis.
Muscle or significant subcutaneous hematoma	50 IU/kg factor VIII concentrate; 20 IU/kg every other day treatment may be needed until resolved.	80 IU/kg factor IX concentrate ‡ ; 40 IU/kg every 2-3 days may be needed until resolved.
Mouth, deciduous tooth, or tooth extraction	20 IU/kg factor VIII concentrate † ; antifibrinolytic therapy § ; remove loose deciduous tooth.	40 IU/kg factor IX concentrate ‡ ; antifibrinolytic therapy § ; remove loose deciduous tooth.
Epistaxis	Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy § ; 20 IU/kg factor VIII concentrate † if this treatment fails. ‖	Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy § ; 30 IU/kg factor IX concentrate ‡ if this treatment fails.‖
Major surgery, life-threatening hemorrhage	50-75 IU/kg factor VIII concentrate; then initiate 25 IU/kg q8-12h to maintain trough level >50 IU/dL for 5-7 days; then 50 IU/kg q24h to maintain trough >25 IU/dL for 7 days; monitor factor VIII levels.	80-120 IU/kg factor IX concentrate ‡ , then 50-60 IU/kg q12-24h to maintain factor IX at >40 IU/dL for 5-7 days, and then at >30 IU/dL for 7 days; monitor factor IX levels.
Iliopsoas hemorrhage	50 IU/kg factor VIII concentrate; then 25 IU/kg q12h until asymptomatic; then 20 IU/kg every other day, for a total of 10-14 days.**	100 IU/kg factor IX concentrate ‡ ; then 50-60 IU/kg q12-24h to maintain factor IX at >40 IU/dL until patient is asymptomatic;

		then 40-50 IU every other day, for a total of 10-14 days.[**]
Hematuria	Bed rest; 1.5× maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected).	Bed rest; 1.5× maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate [‡] ; if not controlled, give prednisone (unless patient is HIV-infected).
Prophylaxis	20-40 IU/kg factor VIII concentrate every other day to achieve trough level ≥1%.	30-50 IU/kg factor IX concentrate [‡] every 2-3 days to achieve trough level ≥1%.

[*] For hip hemarthrosis, orthopedic evaluation for possible aspiration is advisable to prevent avascular necrosis of the femoral head.

[†] For mild or moderate hemophilia, desmopressin, 0.3 µg/kg, should be used instead of factor VIII concentrate, if the patient is known to respond with a hemostatic level of factor VIII; if repeated doses are given, monitor factor VIII levels for tachyphylaxis.

[‡] Stated doses apply for recombinant factor IX concentrate; different dosing may apply for long-acting recombinant factor IX concentrates or plasma-derived factor IX.

[§] Do not give antifibrinolytic therapy until 4-6 hr after a dose of prothrombin complex concentrate.

[||] Nonprescription coagulation-promoting products may be helpful.

[**] Repeat radiologic assessment should be performed before discontinuation of therapy.

HIV, Human immunodeficiency virus; IU, international units; q12-24h, every 12 to 24 hours.

Adapted from Di Paola J, Montgomery RR, Gill JC, Flood VH: Hemophilia and von Willebrand disease. In Orkin SH, Fisher DE, Ginsberg D, et al, editors: *Nathan and Oski's hematology of infancy and childhood,* ed 8, Philadelphia, 2015, Saunders Elsevier, pp 1028–1054.

With the availability of recombinant replacement products, *prophylaxis is the standard of care for most children with severe hemophilia*, to prevent spontaneous bleeding and early joint deformities. In addition to currently available recombinant factors, products are being developed to increase the plasma half-life and reduce the immunogenicity of hemostatic factors. A study comparing prophylaxis with aggressive episodic treatment provides evidence for the superiority of prophylaxis in preventing debilitating joint disease. If target joints develop, “secondary” prophylaxis is often initiated.

With mild factor VIII hemophilia, the patient's endogenously produced factor VIII can be released by the administration of **desmopressin acetate** . In patients with moderate or severe factor VIII deficiency, the stored levels of factor VIII in the body are inadequate, and desmopressin treatment is ineffective. A concentrated intranasal form of desmopressin acetate, not the enuresis or pituitary replacement dose, can also be used to treat patients with mild hemophilia A. The dose is 150 µg (1 spray) for children weighing <50 kg and 300 µg (2 sprays) for children and young adults weighing >50 kg. Most centers administer a trial of desmopressin to determine the level of factor VIII achieved after its infusion. Desmopressin is not effective in the treatment of factor IX–deficient hemophilia but is an effective and relatively less expensive treatment for mild factor VIII deficiency.

Preliminary trials of factor IX gene therapy are underway with some encouraging initial results. Mucosal bleeding may require adjunct use of an antifibrinolytic such as aminocaproic acid or tranexemic acid.

The bispecific, humanized monoclonal antibody **emicizumab** can bridge activated factor IX and factor X, thus restoring functional activated factor VIII activity in patients with hemophilia (with or without factor VIII inhibitors). Once-weekly prophylactic subcutaneous injections of emicizumab may be able to reduce the rate of bleeding in patients with or without factor VIII inhibitors.

Prophylaxis

Many patients are now given lifelong prophylaxis to prevent spontaneous joint bleeding. The **National Hemophilia Foundation** recommends that prophylaxis be considered optimal therapy for children with severe hemophilia. Usually, such programs are initiated with the 1st or 2nd joint hemorrhage. Young children often require the insertion of a central catheter to ensure venous access. Such programs are expensive but are highly effective in preventing or greatly limiting the degree of joint pathology; complications include central line infection and thrombosis. Treatment is usually provided every 2-3 days to maintain a measurable plasma level of clotting factor (1–2%) when assayed just before the next infusion (trough level). Newer long-acting formulations of factor IX are available that extend dosing to every week or every other week. Whether prophylaxis should be continued into adulthood has not yet been adequately studied. If moderate arthropathy develops, prevention of future bleeding will require higher plasma levels of clotting factors. In the older child who is not given primary prophylaxis, secondary prophylaxis is frequently initiated if a target joint develops.

Supportive Care

Although it is easy to tell parents that their child should avoid trauma, this advice is not practical in active children and adolescents. Toddlers are active, are curious about everything, and injure themselves easily. Effective measures include anticipatory guidance, including the use of car seats, seatbelts, and bike helmets and the avoidance of high-risk behaviors. Older boys should be counseled to avoid violent contact sports, but this issue is a challenge. Boys with severe hemophilia often sustain hemorrhages in the absence of known trauma. Early psychosocial intervention helps the family achieve a balance between overprotection and permissiveness. Patients with hemophilia should avoid aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) that affect platelet function. The child with a bleeding disorder should receive the appropriate vaccinations against hepatitis B, even though recombinant products may avoid exposure to transfusion-transmitted diseases. Patients exposed to plasma-derived products should be screened periodically for hepatitis B and C, HIV, and abnormalities in liver function.

Chronic Complications

Long-term complications of hemophilia A and B include chronic arthropathy, the development of an inhibitor to either factor VIII or factor IX, and the risk of transfusion-transmitted infectious diseases. Although an aggressive, or prophylactic, approach to treatment has reduced the problems of chronic arthropathy, these problems have not been eliminated.

Historically, **chronic arthropathy** has been the major long-term disability associated with hemophilia. The natural history of untreated hemophilia is one of cyclic recurrent hemorrhages into specific joints, including hemorrhages into the same (target) joint. In young children, the joint distends easily and a large volume of blood may fill the joint until tamponade ensues or therapy intervenes. After joint hemorrhage, proteolytic enzymes are released by white blood cells into the joint space, and heme iron induces macrophage proliferation, leading to inflammation of the synovium. The synovium thickens and develops frondlike projections into the joint that are susceptible to being pinched and may induce further hemorrhage. The cartilaginous surface becomes eroded and ultimately may even expose raw bone, leaving the joint susceptible to articular fusion. In the older patient with advanced arthropathy, bleeding into the target joint, with its thickened synovium, causes severe pain, because the joint may have little space to accommodate blood. Once a target joint is seen to be developing, the patient is usually given short- or long-term prophylaxis to prevent progression of the arthropathy and reduce inflammation.

Inhibitor Formation

Infusion of the deficient clotting factor may initiate an immune response in patients with either factor VIII or factor IX deficiency. Inhibitors are antibodies directed against factor VIII or factor IX that block the clotting activity. Failure of a bleeding episode to respond to appropriate replacement therapy is usually the first sign of an inhibitor. Less often, inhibitors are identified during routine follow-up screening for inhibitors. Inhibitors develop in approximately 25–35% of patients with hemophilia A but only 2–3% of patients with hemophilia B, many of whom make an inactive dysfunctional protein that renders them less susceptible to an immune response. Highly purified factor IX or recombinant factor IX seems to increase the frequency of inhibitor development, and some anti–factor IX inhibitors induce anaphylaxis. Many patients who have an inhibitor will lose it with continued regular infusions. Others have a higher titer of antibody with subsequent infusions and may need to go through **desensitization** (immune tolerance induction) programs, in which high doses of factor VIII for hemophilia A or factor IX for hemophilia B are infused in an attempt to saturate the antibody and permit the body to develop tolerance. Factor IX immune tolerance programs have resulted in nephrotic syndrome in some patients. Rituximab, corticosteroids, and other immunosuppressives have all been used as alternate therapy for patients with high inhibitor titers in whom immune tolerance programs have failed. If desensitization fails, bleeding episodes are treated with either recombinant factor VIIa or activated prothrombin complex concentrates (factor VIII inhibitor bypassing activity). The use of these products bypasses the inhibitor in many cases but may increase the risk of thrombosis. Emicizumab may be another approach for patients with inhibitors. Some patients with low titers of inhibitor can be treated with high-dose factor VIII during a bleeding episode. Patients with inhibitors require referral to a center that cares for many such patients and has a comprehensive hemophilia program. Some evidence suggests that inhibitor risk may be higher with recombinant factor compared with plasma-derived factor, but further studies are needed.

In the past, plasma-derived treatment products transmitted hepatitis B and C as well as HIV to large numbers of patients with hemophilia. In the era of recombinant products, the risk of acquiring such infections should be minimal, but patients should receive appropriate immunizations against hepatitis B. Those who are exposed to blood products should be monitored for transfusion-related infections. Reports have also identified the transmission of variant Creutzfeldt-Jakob disease to patients receiving therapeutic plasma and may warrant study of patients with hemophilia for prion transmission from plasma-derived factor concentrates.

Comprehensive Care

Patients with hemophilia are best managed through comprehensive hemophilia care centers. Such centers are dedicated to patient and family education and the prevention and treatment of the complications of hemophilia, including chronic joint disease and inhibitor development as well as infection (e.g., hepatitis B or C, HIV). Such centers involve a team that includes physicians, nurses, orthopedists, physical therapists, and psychosocial workers. Education remains crucial in hemophilia care, because patients who are receiving prophylaxis may be less “experienced” in recognizing bleeding episodes than affected children from previous eras.

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503.2

Factor XI Deficiency (Hemophilia C)

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Keywords

factor XI
fibrinolysis inhibitor
fresh-frozen plasma

Factor XI deficiency is an autosomal deficiency associated with mild to moderate bleeding symptoms. It is frequently encountered in Ashkenazi Jews but has been found in many other ethnic groups. In Israel, 1-3 per 1,000 individuals are homozygous for this deficiency.

The bleeding tendency is not as severe as in factor VIII or factor IX deficiency. The bleeding associated with factor XI deficiency is not correlated with the amount of factor XI. Some patients with severe deficiency may have minimal or no symptoms at the time of major surgery. Because factor XI augments thrombin generation and leads to activation of *thrombin-activatable fibrinolysis inhibitor,* surgical bleeding is more prominent in sites of high fibrinolytic activity such as the oral cavity. Unless the patient previously had surgery without bleeding, replacement therapy should be considered and given preoperatively, depending on the nature of the surgical procedure. No approved concentrate of factor XI is available in the United States; therefore the physician must use fresh-frozen plasma (FFP).

Bleeding during minor surgery can be controlled with local pressure. Patients undergoing dental extractions can be monitored closely and may benefit from treatment with a fibrinolytic inhibitor such as aminocaproic acid or tranexamic acid, with plasma replacement therapy used only if hemorrhage occurs. In a patient with homozygous deficiency of factor XI, PTT is often longer than it is in patients with either severe factor VIII or factor IX deficiency. The paradox of fewer clinical symptoms in combination with longer PTT is surprising, but it occurs because factor VIIa can activate factor IX in vivo. The deficiency of factor XI can be confirmed by specific factor XI assays. Plasma infusions of 1 IU/kg usually increase the plasma concentration by 2%. Thus, infusion of plasma at 10-15 mL/kg will result in a plasma level of 20–30%, which is usually sufficient to control moderate hemorrhage. Frequent infusions of plasma would be necessary to achieve higher levels of factor XI. Because the half-life of factor XI is usually ≥48 hr, maintaining adequate levels of factor XI usually is not difficult.

Chronic joint bleeding is rarely a problem in factor XI deficiency, and for most patients, the deficiency is a concern only at the time of major surgery unless there is a 2nd underlying hemostatic defect (e.g., von Willebrand disease).

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503.3

Deficiencies of the Contact Factors (Nonbleeding Disorders)

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Keywords

factor XII
high-molecular-weight kininogen
prekallikrein

Deficiency of the “contact factors”—factor XII, prekallikrein, and high-molecular-weight kininogen—causes prolonged PTT but no bleeding symptoms. Because these contact factors function at the step of initiation of the intrinsic clotting system by the reagent used to determine PTT, the PTT is markedly prolonged when these factors are absent. Thus, there is the paradoxical situation in which PTT is extremely prolonged with no evidence of clinical bleeding. It is important that individuals with these findings be well informed about the meaning of their clotting factor deficiency because they do not need treatment, even for major surgery.

503.4

Factor VII Deficiency

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Keywords

factor VII
epistaxis
menorrhagia

Factor VII deficiency is a rare autosomal bleeding disorder that is usually detected only in the homozygous state. Severity of bleeding varies from mild to severe with hemarthroses, spontaneous intracranial hemorrhage, and mucocutaneous bleeding, especially epistaxis (nosebleed) and menorrhagia. Patients with this deficiency have greatly prolonged PT but normal PTT. Factor VII assays show a marked reduction in factor VII. Because the plasma half-life of factor VII is 2-4 hr, therapy with FFP is difficult and is often complicated by fluid overload. A commercial concentrate of recombinant factor VIIa is effective in treating patients with factor VII deficiency.

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503.5

Factor X Deficiency

J. Paul Scott, Veronica H. Flood

Keywords

amyloidosis
factor X

Factor X deficiency is a rare (estimated 1 in 1 million) autosomal disorder with variable severity. Mild deficiency results in mucocutaneous and posttraumatic bleeding, whereas severe deficiency results in spontaneous hemarthroses and intracranial hemorrhages. Factor X deficiency is the result of either a quantitative deficiency or a dysfunctional molecule. A reduced factor X level is associated with prolongation of both PT and PTT. In patients with hereditary factor X deficiency, factor X levels can be increased with use of either FFP or prothrombin complex concentrate. The half-life of factor X is approximately 30 hr, and its volume of distribution is similar to that of factor IX. Thus, 1 unit/kg will increase the plasma level of factor X by 1%.

Although it is rarely a problem in pediatric patients, **systemic amyloidosis** may be associated with factor X deficiency, resulting from the adsorption of factor X on the amyloid protein. In the setting of amyloidosis, transfusion therapy often is not successful because of the rapid clearance of factor X.

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503.6

Prothrombin (Factor II) Deficiency

J. Paul Scott, Veronica H. Flood

Keywords

dysprothrombinemia
factor II
hypoprothrombinemia
prothrombin

Prothrombin deficiency is caused either by a markedly reduced prothrombin level (hypoprothrombinemia) or by functionally abnormal prothrombin (dysprothrombinemia). Laboratory testing in homozygous patients shows prolonged PT and PTT. Factor II, or prothrombin, assays show a greatly reduced prothrombin level. Mucocutaneous bleeding in infancy and posttraumatic bleeding later are common. Patients are treated with either FFP or, rarely, prothrombin complex concentrates. In prothrombin deficiency, FFP is useful, because the half-life of prothrombin is 3.5 days. Administration of 1 IU/kg of prothrombin will increase the plasma activity by 1%. Acquired factor II deficiency can be seen with a small percentage of lupus anticoagulants and is usually associated with significant bleeding.

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503.7

Factor V Deficiency

J. Paul Scott, Veronica H. Flood

Keywords

factor V
hematoma
menorrhagia
parahemophilia

Deficiency of factor V is an autosomal recessive, mild to moderate bleeding disorder that has also been termed **parahemophilia** . Hemarthroses occur rarely; mucocutaneous bleeding and hematomas are the most common symptoms. Severe menorrhagia is a frequent symptom in women. Laboratory evaluation shows prolonged PTT and PT. Specific assays for factor V show a reduction in factor V levels. FFP is the only currently available therapeutic product that contains factor V. Factor V is lost rapidly from stored FFP. Patients with severe factor V deficiency are treated with infusions of FFP at 10 mL/kg every 12 hr. Platelet transfusion is also an option because platelets contain factor V, perhaps explaining the lack of bleeding seen in many patients with factor V deficiency. Rarely, a patient with a negative family history of bleeding has an acquired antibody to factor V.

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503.8

Combined Deficiency of Factors V and VIII

J. Paul Scott, Veronica H. Flood

Keywords

factor V
factor VIII

Combined deficiency of factors V and VIII occurs secondary to the absence of an intracellular transport pathway that is responsible for transporting factors V and VIII from the endoplasmic reticulum to the Golgi compartments involving LMAN1 and MCFD2. This explains the paradoxical deficiency of 2 factors, one encoded on chromosome 1 and the other on the X chromosome. Bleeding symptoms are often milder than for hemophilia A and are treated with FFP to replace both factor V and factor VIII.

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503.9

Fibrinogen (Factor I) Deficiency

J. Paul Scott, Veronica H. Flood

Keywords

afibrinogenemia
dysfibrinogenemia
fibrinogen

Congenital afibrinogenemia is a rare autosomal recessive disorder characterized by an absence of fibrinogen. Patients with afibrinogenemia do not bleed as frequently as patients with hemophilia and rarely have hemarthroses. Affected patients may present in the neonatal period with gastrointestinal hemorrhage or hematomas after vaginal delivery. In addition to marked prolongation of PT and PTT, thrombin time is prolonged. In the absence of consumptive coagulopathy, an unmeasurable fibrinogen level is diagnostic. In addition to the quantitative deficiency of fibrinogen, a number of dysfunctional fibrinogens have been reported (**dysfibrinogenemia**). Rarely, patients with dysfibrinogenemia present with thrombosis.

A human fibrinogen concentrate is commercially available for therapy of bleeding episodes in afibrinogenemic patients. Because the plasma half-life of fibrinogen is 2-4 days, treatment with FFP or cryoprecipitate is also effective. The hemostatic level of fibrinogen is >60 mg/dL. Each bag of cryoprecipitate contains 100-150 mg of fibrinogen. Some clinical assays for fibrinogen are inhibited by high doses of heparin. Thus, a greatly prolonged thrombin time associated with a low fibrinogen level should be evaluated with determination of reptilase time. Prolonged reptilase time confirms that functional levels of fibrinogen are low and that heparin is not present.

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503.10

Factor XIII Deficiency (Fibrin-Stabilizing Factor or Transglutaminase Deficiency)

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Keywords

factor XIII
fibrin clot

Because factor XIII is responsible for the cross linking of fibrin to stabilize the fibrin clot, symptoms of delayed hemorrhage are secondary to instability of the clot. Typically, patients have trauma 1 day and then have a bruise or hematoma the next day. Clinical symptoms include mild bruising, delayed separation of the umbilical stump beyond 4 wk in neonates, poor wound healing, and recurrent spontaneous abortions in women. Rare kindreds with XIII deficiency with hemarthroses and intracranial hemorrhage have been described. Results of the usual screening tests for hemostasis are normal in patients with factor XIII deficiency. Screening tests for factor XIII deficiency are based on the observation that there is increased solubility of the clot because of the failure of cross linking. The normal clot remains insoluble in the presence of 5M urea, whereas in a patient with factor XIII deficiency, the clot dissolves. More specific assays for factor XIII are immunologic. The half-life of factor XIII is 5-7 days, and the hemostatic level is 2–3% activity. There is a heat-treated, lyophilized concentrate of coagulation factor XIII available to treat bleeding episodes or for prophylaxis.

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503.11

Antiplasmin or Plasminogen Activator Inhibitor Deficiency

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Keywords

antiplasmin
plasminogen activator inhibitor

Deficiency of either antiplasmin or plasminogen activator inhibitor, both of which are antifibrinolytic proteins, results in increased plasmin generation and premature lysis of fibrin clots. Affected patients have a mild bleeding disorder characterized by mucocutaneous bleeding but rarely have joint hemorrhages. Because results of the usual hemostatic tests are normal, further workup of a patient with a positive bleeding history should include *euglobulin clot lysis time* (if available), which measures fibrinolytic activity and yields a shortened result in the presence of these deficiencies. Specific assays for α_2 -antiplasmin and plasminogen activator inhibitor are available. Bleeding episodes are treated with FFP; bleeding in the oral cavity may respond to antifibrinolytic therapy.

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CHAPTER 504

Von Willebrand Disease

Veronica H. Flood, J. Paul Scott

Von Willebrand disease (**VWD**) is the most common inherited bleeding disorder, with an estimated prevalence cited at 1 : 100 to 1 : 10,000 depending on the criteria used for diagnosis. Patients with VWD typically present with mucosal bleeding. A family history of either VWD or bleeding symptoms and confirmatory laboratory testing are also required for the diagnosis of VWD.

Pathophysiology

VWD is caused by a defect in or deficiency of **von Willebrand factor (VWF)** . VWF has several functions in coagulation. First, VWF serves to tether platelets to injured subendothelium via binding sites for platelets and for collagen. Second, VWF serves as a carrier protein for **factor VIII (FVIII)** , protecting FVIII from degradation in plasma. VWF is stored in endothelial cells and in platelet Weibel-Palade bodies and circulates as a large, multimeric glycoprotein. Shear stress induces a conformational change in VWF that facilitates its ability to bind platelets through a binding site on platelet **glycoprotein Ib (GPIb)** . This enables VWF to recruit platelets to the site of clot formation, a function dependent on the high-molecular-weight (HMW) multimer forms of VWF.

VWD typically presents with mucosal bleeding, similar to that seen with other platelet defects. **Epistaxis, easy bruising,** and **menorrhagia** in women are common complaints. However, symptoms are variable and do not necessarily correlate well with VWF levels. Surgical bleeding, particularly with dental extractions or adenotonsillectomy, is another common presentation. Severe type 3 VWD may present with joint bleeds. Most patients will have a family history of bleeding. Women are more likely to be diagnosed with VWD because of the potential for symptoms with menorrhagia, but men and women are equally likely to have VWD. However, diagnosis based on symptoms may be difficult, since minor bruising and epistaxis are not uncommon in childhood. Significant unexplained bruising in infants and toddlers is more often from nonaccidental trauma than from an underlying bleeding disorder.

Classification

VWD may be caused by quantitative or qualitative defects in VWF. Mild to moderate quantitative defects are classified as type 1 VWD, whereas severe quantitative defects, in which there is no detectable VWF protein, are classified as type 3 VWD. The qualitative defects are grouped together as type 2 VWD.

Type 1 VWD is by far the most common type, accounting for 60–80% of all VWD patients. Typical symptoms include mucosal bleeding, such as epistaxis and menorrhagia, as well as easy bruising and potentially surgical bleeding. Guidelines from the National Heart, Lung and Blood Institute of the National Institutes of Health use a VWF level, as measured by the VWF antigen assay (**VWF:Ag**), of <30 IU/dL for diagnosis of VWD. Patients with VWF:Ag <30 IU/dL are most likely to have a genetic defect in VWF. Patients with VWF:Ag between 30 and 50 IU/dL are said to have “low VWF.” Whether or not this category truly represents VWD is a subject of some debate. Because some patients with VWF levels in this range do experience bleeding, many physicians elect to treat them, especially for surgical procedures such as tonsillectomy.

Patients with type 1 VWD may have low VWF as a result of increased clearance of their VWF, or **type 1C VWD** . Diagnosis of this subtype is important because treatment of these patients with desmopressin is likely to be ineffective, necessitating administration of VWF-containing products.

VWF levels can be influenced by external factors. Blood type has long been known to affect VWF, with lower VWF levels seen in people with blood group O. Stress, exercise, and pregnancy all increase VWF levels; therefore a single normal VWF level does not necessarily rule out the presence of VWD. Certain diseases, such as **hypothyroidism** *(* see Chapter 581 *)* , and medications, such as valproic acid, can lower VWF levels in affected patients. Repeat testing may be required to rule out or confirm a diagnosis of VWD.

Type 3 VWD is the most severe form and presents with symptoms similar to those seen in *mild hemophilia.* In type 3 VWD the VWF protein is completely absent. Type 3 VWD is seen at a frequency of approximately 1 in 1 million population. In addition to mucosal bleeding, patients may experience joint bleeds or central nervous system hemorrhage. Some physicians elect to treat patients with prophylaxis, or modified prophylaxis following injury, given that these patients typically have very low FVIII (<10 IU/dL). Because type 3 VWD is caused by a lack of VWF, treatment with VWF-containing concentrates is required.

Type 2A VWD is characterized by a defect in VWF multimerization and decreased VWF activity in terms of platelet binding. It is the most common of the type 2 variants, accounting for approximately 10% of VWD cases. Type 2A VWD can result from mutations that affect multimer assembly and processing, or mutations that result in increased proteolysis of secreted VWF. Some mutations affect both secretion and clearance of the VWF. Regardless of the mechanism, all type 2A VWD patients lack the HMW multimers, and therefore have reduced VWF activity, which results in bleeding. Symptoms are typically more severe than those seen in type 1 VWD. Desmopressin may have clinical efficacy for treatment of minor bleeding, but significant surgical challenges or major bleeding symptoms generally require a VWF-containing concentrate for treatment.

Type 2B VWD results from gain-of-function mutations that increase the ability of VWF to bind platelets. This leads to increased clearance of both VWF and platelets from circulation and results in the loss of HMW multimers and decreased VWF activity, similar to that seen in type 2A VWD. Special testing is therefore required to diagnose type 2B VWD, either by direct measurement of the increased platelet binding or by an increased response to low-dose ristocetin on platelet aggregation testing. Thrombocytopenia is not always present and may be more prominent during times of stress such as surgery or pregnancy. Desmopressin is relatively contraindicated in type 2B VWD, as it may accelerate VWF-platelet binding and clearance.

Platelet-type pseudo-VWD occurs when a mutation in platelet GPIb causes spontaneous binding to VWF and also presents with decreased VWF activity, loss of HMW multimers, and thrombocytopenia similar to type 2B VWD. Specific testing is required to distinguish the 2 conditions. Because the defect involves platelets, treatment generally requires platelet transfusion.

Type 2M VWD includes those patients with decreased VWF activity but normal (or near-normal) multimer distribution. This is generally caused by a defect in the ability of VWF to bind platelet GPIb, but this category also includes patients with defects in VWF-collagen interactions. Some minor bleeding in type 2M VWD may respond to desmopressin, but because type 2M

VWD is a functional defect, treatment with VWF-containing concentrates is usually required.

Type 2N VWD is characterized by a defect in the ability of VWF to bind FVIII. Some patients with type 2N VWD may be misdiagnosed as mild hemophilia, therefore a high index of suspicion for this diagnosis is required in patients with low FVIII and an absent family history of FVIII deficiency.

Laboratory Diagnosis

There are no reliable screening tests for VWD. Patients with significant bleeding may present with anemia, and some patients with type 2B VWD or platelet-type pseudo-VWD may have thrombocytopenia. The partial thromboplastin time may be prolonged if FVIII is low but especially in type 1 VWD it is often normal, precluding use of the PTT as a screening test. Platelet function analysis has been considered as a screening test for VWD, but suboptimal sensitivity and specificity render results difficult to interpret. Bleeding times are similarly unreliable in diagnosis of VWD.

Unfortunately, no single test can reliably diagnose VWD; therefore a panel of tests is usually required (Table 504.1). These include VWF:Ag, which measures the total amount of VWF protein present, and VWF activity test, typically using the *ristocetin cofactor* activity assay (**VWF:RCo**), which provides a measure of the amount of functional VWF. FVIII activity is also usually included in the workup. Another test measures VWF binding to platelet GPIb without ristocetin (**VWF:GPIbM**) but is not universally available. Collagen binding measures an additional function of VWF. Multimer distribution provides an assessment of HMW multimers. Table 504.2 summarizes the expected laboratory findings for each type of VWD. Fig. 504.1 provides more detailed analysis.

Table 504.1

Laboratory Testing for von Willebrand Disease (VWD)

TEST	ABBREVIATION	PURPOSE
VWF antigen	VWF:Ag	Measures total amount of VWF protein present.
VWF activity	VWF:RCo*	Assesses interaction of VWF and platelets as mediated by ristocetin.
VWF activity/antigen ratio	VWF:RCo/VWF:Ag	A decreased ratio (<0.7) is found in type 2A, type 2B, and type 2M VWD.
Factor VIII activity	FVIII	Measures circulating FVIII, which will be very low in type 2N and type 3 VWD.

Multimer distribution	VWF multimers	Allows visualization of VWF multimers, used to identify high-molecular-weight multimers, which will be absent in types 2A and 2B VWD.

[*] In some laboratories a GPIb-binding assay, the VWF:GPIbM, is available.

VWF, Von Willebrand factor.

Table 504.2

Classification of von Willebrand Disease

	TYPE 1	TYPE 3	TYPE 2A	TYPE 2B*	TYPE 2M	TYPE 2N
VWF:Ag	↓	Absent	↓	↓	↓	Normal or ↓
VWF:RCo	↓	Absent	↓↓	↓↓	↓↓	Normal or ↓
FVIII	Normal	↓↓	Normal or ↓	Normal or ↓	Normal or ↓	↓↓
Multimer distribution	Normal	Absent	Loss of HMWM	Loss of HMWM	Normal	Normal

[*] Platelet count is also usually decreased in type 2B VWD.

FVIII, factor VIII; HMWM, high-molecular-weight multimers; VWF:Ag, von Willebrand factor antigen; VWF:RCo, VWF ristocetin cofactor activity.

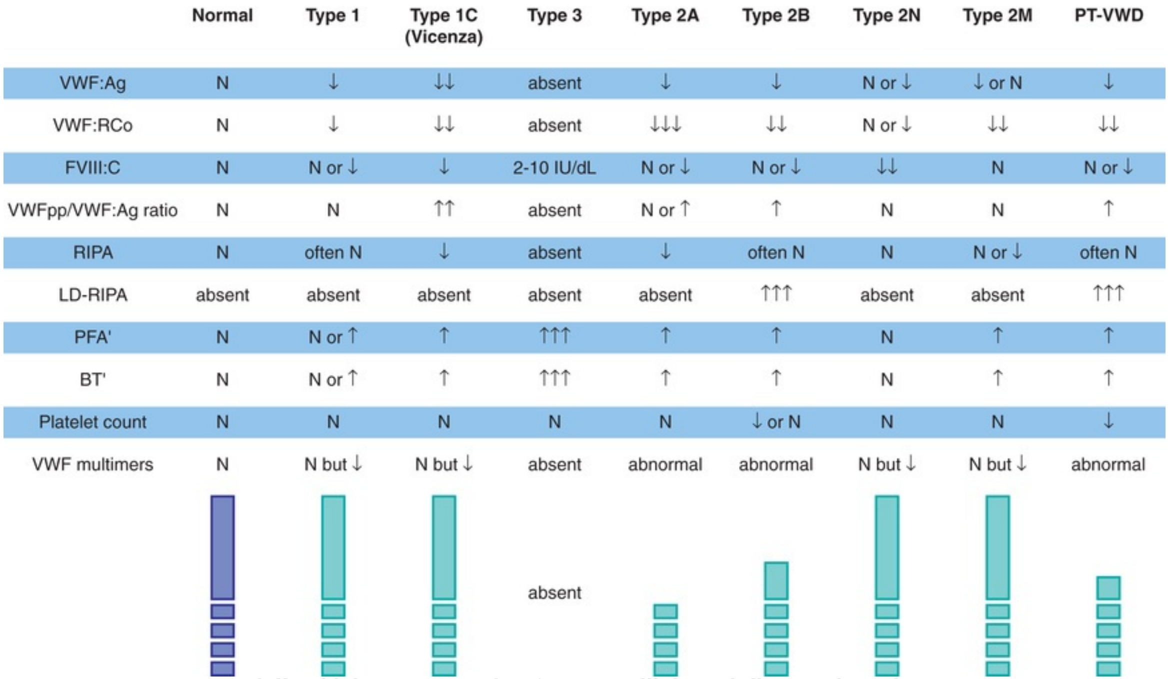

	Normal	Type 1	Type 1C (Vicenza)	Type 3	Type 2A	Type 2B	Type 2N	Type 2M	PT-VWD
VWF:Ag	N	↓	↓↓	absent	↓	↓	N or ↓	↓ or N	↓
VWF:RCo	N	↓	↓↓	absent	↓↓↓	↓↓	N or ↓	↓↓	↓↓
FVIII:C	N	N or ↓	↓	2-10 IU/dL	N or ↓	N or ↓	↓↓	N	N or ↓
VWFpp/VWF:Ag ratio	N	N	↑↑	absent	N or ↑	↑	N	N	↑
RIPA	N	often N	↓	absent	↓	often N	N	N or ↓	often N
LD-RIPA	absent	absent	absent	absent	absent	↑↑↑	absent	absent	↑↑↑
PFA'	N	N or ↑	↑	↑↑↑	↑	↑	N	↑	↑
BT'	N	N or ↑	↑	↑↑↑	↑	↑	N	↑	↑
Platelet count	N	N	N	N	N	↓ or N	N	N	↓
VWF multimers	N	N but ↓	N but ↓	absent	abnormal	abnormal	N but ↓	N but ↓	abnormal

FIG. 504.1 Specialized laboratory testing for von Willebrand disease (VWD). ↓, ↓↓, ↓↓↓, Relative decrease; ↑, ↑↑, ↑↑↑, relative increase; BT, bleeding time; FVIII:C, factor VIII coagulant activity; LD-RIPA, low-dose ristocetin-induced platelet aggregation; N, normal; N but ↓, normal but decreased in intensity; PFA, platelet function analysis; PT-VWD, platelet-type VWD; RIPA, ristocetin-induced platelet aggregation; VWF:Ag, von Willebrand factor antigen; VWF:RCo, VWF activity by ristocetin cofactor; VWF pp, VWF propeptide. (Courtesy of Dr. Robert R. Montgomery.)

Additional specialized testing may be employed to help determine the correct diagnosis. Specific testing for type 1C (clearance defects), type 2B, and type 2N VWD can confirm these diagnoses. Genetic diagnosis is not typically performed, partly because of the large size of the VWF gene and the large number of benign sequence variations. Large gene deletions are responsible for some cases of VWD and will not be detected on routine DNA sequencing. However, use of genetic diagnosis is increasing, particularly for types 2A, 2B, 2M, and 2N VWD.

Treatment

Treatment of VWD depends on the type of VWD present and the reason for treatment (Table 504.3). In general, type 1 VWD patients may be treated with **desmopressin** , which increases the amount of circulating VWF by release from storage. The exceptions are the rare type 1 patient who lacks a response to desmopressin and patients with type 1C VWD who do respond with an increase in VWF levels, but whose rapid clearance of circulating endogenous VWF results in a rapid return to baseline levels. Treatment of types 2 and 3 VWD requires **VWF-containing concentrates** similar to the treatment of hemophilia. Dosing depends on the type of VWD and the reason for treatment. Careful monitoring of VWF and FVIII levels is recommended to tailor treatment for surgeries and major trauma. For all types of VWD, adjunct therapy should be considered when possible, such as the use of antifibrinolytics for oral surgery or hormonal treatment for menorrhagia.

Table 504.3

Treatment of Von Willebrand Disease

TREATMENT	VWD TYPES	ROUTE	DOSING
Desmopressin*	Type 1 VWD Some type 2 VWD (use with caution)	IV or IN	0.3 µg/kg IV † 1 spray IN (<50 kg) 2 sprays IN (>50 kg)
Von Willebrand factor (VWF) concentrates ‡	Type 3 VWD Type 2 VWD Severe type 1 VWD (or type 1 clearance defects)	IV	40-60 ristocetin cofactor activity units/kg (adjust dose depending on baseline VWF level and desired peak VWF level). If recombinant VWF used, may need to administer additional recombinant FVIII for emergency treatment.
Antifibrinolytics	Mucosal bleeding, all types of VWD	PO or IV	Aminocaproic acid: 100 mg/kg PO loading dose followed by 50 mg/kg every 6 hr § Tranexamic acid: 1,300 mg PO 3 times daily for

			5 days

[*] Recommended treatment with Stimate brand nasal spray, as this form is concentrated to give 150 µg/spray. Other forms are much more dilute and will not result in desired increase in VWF.

[†] Maximum recommended dose is 20-30 µg/day.

[‡] Currently both Humate-P and Wilate are approved for treatment of VWD. Vonvendi is a recombinant VWF that is also approved for treatment of VWD, but does not contain FVIII.

[§] Maximum recommended dose is 24 g/day.

IN, Intranasal; IV, intravenous; PO, oral administration.

Alternate treatment strategies should also be considered, particularly for difficult symptoms or severe VWD. Hormonal therapy for women with menorrhagia, although not specific to VWD, can be very helpful in managing symptoms and improving quality of life. Local treatment of epistaxis, such as nasal cautery or packing, may be helpful in some circumstances. Iron therapy for patients with iron-deficiency anemia may also be required.

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CHAPTER 505

Hereditary Predisposition to Thrombosis

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Numerous inherited risk factors for thrombosis have been identified, but the majority of individuals who inherit one of these risk factors do not necessarily develop thrombosis during childhood. Identification of inherited risk factors that could be identified in the laboratory initially led to widespread testing of both children and adults with thrombosis. The clinical utility of performing such tests has been scrutinized, and it is important to understand the potential benefits and limitations of testing.

Table 505.1 lists the most common inherited **thrombophilias** and their prevalence in the general population. The inherited defects with the best understood pathogenic link include the factor V Leiden mutation, the prothrombin gene mutation, and deficiencies of protein C, protein S, and antithrombin III (AT III). Elevated levels of factor VIII (FVIII) and homocysteine are associated with thrombosis, but these thrombophilias are less well characterized and not necessarily genetically determined. Although additional alterations in coagulation have been associated with thrombotic risk, including elevated concentrations of factors IX and XI, heparin cofactor II deficiency, elevated lipoprotein (a), and dysfibrinogenemia, none has gained widespread acceptance in routine testing of children for inherited thrombophilia. In general, the prothrombotic tendency conferred by these defects is either a result of an increased procoagulant effect (prothrombin gene mutation, elevated FVIII, hyperhomocysteinemia) or a decreased anticoagulant effect (factor V Leiden mutation, deficiency of protein C, protein S, or AT III).

Table 505.1

Common Inherited Thrombophilias and Accompanying Diagnostic Laboratory Studies

THROMBOPHILIA	PREVALENCE IN WHITE POPULATION (%)	ODDS RATIO FOR FIRST EPISODE VTE IN CHILDHOOD*	LABORATORY STUDIES
Factor V Leiden mutation			DNA-based PCR assay (or screen with activated protein C resistance)
Heterozygote	3-7	3.8	
Homozygote	0.06-0.25	80-100	
Prothrombin 20210 mutation			DNA-based PCR assay
Heterozygote	1-3	2.6	
Homozygote	—	—	
Antithrombin III deficiency	0.02-0.04	9.4	Antithrombin activity via chromogenic or clotting assay
Protein S deficiency	0.03-0.13	5.8	Protein S activity via assay or immunologic assay of free and total protein S antigen
Protein C deficiency	0.2	7.7	Protein C activity via chromogenic or clotting assay
Hyperhomocysteinemia	—	—	Fasting homocysteine
Elevated factor VIII	—	—	Factor VIII activity via 1-stage clotting or chromogenic assay

[*] Data from Young G, Albisetti M, Bonduel M, et al: Impact of inherited thrombophilia on venous thromboembolism in children, *Circulation* 118:1373–1382, 2008.

PCR, Polymerase chain reaction; VTE, venous thromboembolism.

The **factor V Leiden mutation** is the result of a single nucleotide change at nucleotide 1765 within the factor V gene. This mutation causes factor Va to become resistant to inactivation by activated protein C and is the most common inherited risk factor for thrombosis. This defect is also known as *activated protein C resistance* . Approximately 5% of the U.S. white population is heterozygous for this mutation; it is less prevalent in other ethnic groups. Individuals who are heterozygous have a 5-7–fold increased risk of venous thrombosis, whereas homozygotes have a relative risk of 80-100. The baseline annual risk of thrombosis for young women of reproductive age is 1 per 12,500 and increases to 1:3,500 for those taking oral contraceptives. For young women who are heterozygous for the factor V Leiden mutation and are taking OCs, this baseline annual risk is increased 20-30–fold (relative risk) to approximately to 1:500 women.

The **prothrombin 20210 gene mutation** is a G-to-A transition in the 3′ untranslated region of the gene that results in increased levels of prothrombin messenger RNA. This variant is present in approximately 2% of U.S. whites. It is a weaker risk factor for venous thrombosis than factor V Leiden, with a relative risk of 2-3.

Deficiencies of protein C, protein S, and AT III , the natural anticoagulant proteins, are less common than the genetic mutations described previously but are associated with a stronger risk of thrombosis. Although heterozygous deficiencies do not often present during childhood, homozygous defects may result in significant symptoms in infancy. Neonates with *homozygous* deficiencies of AT III, protein C, or protein S may present with **purpura fulminans** . This rare condition is characterized by rapidly spreading purpuric skin lesions resulting from thromboses of the small dermal vessels, followed by bleeding into the skin. In addition, these infants may also develop cerebral thrombosis, ophthalmic thrombosis, disseminated intravascular coagulation, and large-vessel thrombosis. An infant with purpuric skin lesions of unknown cause should receive initial replacement with fresh-frozen plasma. Definitive diagnosis can be difficult in the sick premature neonate, who may have undetectable levels of these factors but not have a true genetic deficiency. Protein C and AT III concentrates are also available and have been demonstrated to be effective.

Both venous *and* arterial thromboses are common in young patients with **homocystinuria,** an inborn error of metabolism caused by deficiency of cystathione β-synthase. In this very rare condition, plasma levels of homocysteine exceed 100 μmol/L. Much more common are mild to moderate elevations of homocysteine, which may be acquired or associated with a polymorphism in the methylenetetrahydrofolate reductase (*MTHFR*) gene. Although moderate elevations of homocysteine have been associated with both venous and arterial thrombotic events, testing for polymorphisms in the *MTHFR* gene is not indicated because these polymorphisms are common and by themselves are not associated with venous thromboembolism. The pathogenic mechanisms for thrombosis in homocystinemia are not well understood.

Increased plasma concentrations of **factor VIII** (>150 IU/dL) appear to be regulated by both genetic and environmental factors and are associated with an increased risk of thrombosis. Although there is a strong component of heritability contributing to factor VIII levels, the molecular mechanisms responsible for elevated factor VIII are not well understood. Factor VIII is also considered to be an acute-phase reactant and may increase transiently during periods of inflammation.

Although interpretation of genetic studies (factor V Leiden and prothrombin gene mutations) is fairly straightforward, several challenges in interpretation of thrombophilia studies are unique to pediatric patients. Neonates have decreased concentrations of protein C, protein S, and AT III that increase rapidly over the 1st 6 mo of life; protein C concentrations remain below adult levels throughout much of childhood. It is important to use pediatric normal ranges when evaluating these values and recognize that often the normal range overlaps with heterozygous defects and that retesting may be required, particularly in young children. Several nongenetic factors may also influence the results of inherited thrombophilia testing, including acute thrombosis, infection, inflammation, hepatic dysfunction, nephrotic syndrome, medication, and vitamin K deficiency. In some patients the hereditary nature may be confirmed by testing the parents.

Thrombophilia testing is often considered during childhood in 2 situations: a child who develops thrombosis and a child who has relatives with thrombosis or thrombophilia. Thrombophilia testing rarely influences the acute management of a child with a thrombotic event. The majority of children who develop thrombosis have multiple, coexistent *acquired* risk factors (see Table 506.1 in Chapter 506); inherited thrombophilia is uncommon in this scenario, and testing is generally not warranted. However, inherited thrombophilia is more common in an otherwise healthy child or adolescent who develops a blood clot or in a child who develops unusual or recurrent thrombosis. Thrombophilia testing may be useful in these situations, because it may help explain why the child developed a blood clot. In some cases, identification of strong or combined defects may alter the duration of therapy. However, current treatment recommendations do not differ based on the presence or absence of an inherited thrombophilia.

The decision to perform thrombophilia testing in an otherwise healthy child with a **family history** of thrombosis or thrombophilia should be carefully considered, weighing the potential advantages and limitations of such an approach. Given that the absolute risk of thrombosis in children is extremely low (0.07/100,000), it is unlikely that an inherited thrombophilia will have any impact on clinical decision-making for a young child. The risk of thrombosis increases with age, so identification of a thrombophilic defect in an adolescent may guide thromboprophylaxis in high-risk situations (lower-extremity casting or prolonged immobility), inform the discussion about estrogen-based contraceptives, and promote lifestyle modification to avoid behavioral prothrombotic risk factors (sedentary lifestyle, dehydration, obesity, and smoking). Limitations of such testing include the cost as well as the potential for causing unnecessary anxiety or false reassurance.

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CHAPTER 506

Thrombotic Disorders in Children

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Advancements in the treatment and supportive care of critically ill children, coupled with a heightened awareness of genetic risk factors for **thrombosis** , have led to an increase in the diagnosis of **thromboembolic events (TEs)** in children. TEs are seen in pediatric tertiary care centers and may result in significant acute and chronic morbidity. Despite increasing in relative terms, TEs in children are still rare. Diagnosis and treatment are often extrapolated from adult data.

Epidemiology

Studies have confirmed a significant increase in the diagnosis of **venous thromboembolism (VTE)** in pediatric tertiary hospitals across the United States. Although the overall incidence of thrombosis in the general pediatric population is quite low (0.07/100,000), the rate of VTE in hospitalized children is 60 per 10,000 admissions. Infants <1 yr old account for the largest proportion of pediatric VTEs, with a 2nd peak during adolescence.

The majority of children who develop a TE have multiple risk factors that may be acquired, inherited, or anatomic (Table 506.1). The presence of a central venous catheter (CVC, peripherally inserted central venous catheter) is the most important risk factor for VTE in pediatric patients, associated with approximately 90% of neonatal VTE and 60% of childhood VTE. CVCs are often necessary for the care of premature neonates and children with acute and chronic diseases and are used for intravenous (IV) hyperalimentation, chemotherapy, dialysis, antibiotics, or supportive therapy. CVCs may damage the endothelial lining and/or cause blood flow disruption, increasing the risk of thrombosis. Many other acquired risk factors are associated with thrombosis, including trauma, infection, chronic medical illnesses, and medications. Cancer, congenital heart disease, and prematurity are the most common medical conditions associated with TEs.

Table 506.1

Risk Factors for Thrombosis

GENERAL
Indwelling catheter, including PICC lines
Infection
Trauma
Surgery
Cancer
Immobility
Cardiac disease/prosthetic valve
Systemic lupus
Rheumatoid arthritis
Inflammatory bowel disease
Polycythemia/dehydration
Nephrotic syndrome
Diabetes
Pregnancy
Obesity
Prematurity
Paroxysmal nocturnal hemoglobinuria
Antiphospholipid antibody syndrome
Thrombotic thrombocytopenic purpura
INHERITED THROMBOPHILIA
Factor V Leiden mutation
Prothrombin mutation
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Homocystinuria
Elevated factor VIII
Dysfibrinogenemia
ANATOMIC
Thoracic outlet obstruction (Paget-Schroetter syndrome)
Iliac vein compression syndrome (May-Thurner syndrome)
Absence of inferior vena cava
MEDICATIONS
Estrogen-containing contraceptives
Asparaginase
Heparin (heparin-induced thrombocytopenia)
Corticosteroids

PICC, Peripherally inserted central venous catheter.

Antiphospholipid antibody syndrome (APS) is a well-described syndrome in adults characterized by recurrent fetal loss and/or thrombosis. Antiphospholipid antibodies are associated with both venous and arterial thrombosis. The mechanism by which these antibodies cause thrombosis is not well understood. A diagnosis of APS requires the presence of both clinical and laboratory abnormalities (see Laboratory Testing). The laboratory abnormalities must be persistent for 12 wk. Because of the high risk of recurrence, patients with APS often require long-term anticoagulation. It is important to note that healthy children may have a *transient* lupus anticoagulant, often diagnosed because of a prolonged partial thromboplastin time (PTT) on routine preoperative testing. In this setting, transient antibodies may be associated with a recent viral infection and are not a risk factor for thrombosis. APS is noted in patients with **systemic lupus erythematosus** (see Chapter 183) and may also be associated with livedo reticularis, neuropsychiatric complications, thrombocytopenia, or anemia; these patients are often persistently positive for the antiphospholipid antibody. Catastrophic antiphospholipid syndrome is a rare and potentially fatal disorder characterized by rapid onset of multiorgan thrombosis and/or thrombotic microangiopathies.

Anatomic abnormalities that impede blood flow also predispose patients to thrombosis at an earlier age. Atresia of the inferior vena cava has been described in association with acute and chronic lower-extremity deep vein thrombosis (**DVT**). Compression of the left iliac vein by the overlying right iliac artery (**May-Thurner syndrome**) should be considered in patients who present spontaneously with left iliofemoral thrombosis, and thoracic outlet obstruction (**Paget-Schroetter syndrome**) frequently presents with effort-related axillary-subclavian vein thrombosis.

Clinical Manifestations

Extremity Deep Vein Thrombosis

Children with acute DVT often present with extremity pain, swelling, and discoloration. A history of a current or recent CVC in that extremity should be very suggestive. Many times, symptoms of CVC-associated thrombosis are more subtle and chronic, including repeated CVC occlusion or sepsis, or prominent venous collaterals on the chest, face, and neck.

Pulmonary Embolism

Symptoms of pulmonary embolism (**PE**) include shortness of breath, pleuritic chest pain, cough, hemoptysis, fever, and, in the case of massive PE, hypotension and right-sided heart failure. Based on autopsy studies in pediatric centers, PE is often undiagnosed, because young children are unable to describe their symptoms accurately and their respiratory deterioration may be masked by other conditions (see Chapter 436.1).

Cerebral Sinovenous Thrombosis

Symptoms may be subtle and may develop over many hours or days. Neonates with cerebral sinovenous thrombosis often present with seizures, whereas older children often complain of headache, vomiting, seizures, and focal signs. They may also have papilledema and abducens palsy. Older patients may have a concurrent sinusitis or mastoiditis that has contributed to the thrombosis.

Renal Vein Thrombosis

Renal vein thrombosis is the most common spontaneous VTE in neonates. Affected infants may present with hematuria, an abdominal mass, and thrombocytopenia. Infants of diabetic mothers are at increased risk for renal vein thrombosis, although the mechanism for the increased risk is unknown. Approximately 25% of cases are bilateral.

Peripheral Arterial Thrombosis

With the exception of stroke, the majority of arterial TEs in children are secondary to catheters, often in neonates related to umbilical artery lines or in patients with cardiac defects undergoing cardiac catheterization. Patients with an arterial thrombosis affecting blood flow to an extremity will present with a cold, pale, blue extremity with poor or absent pulses.

Stroke

Ischemic stroke typically presents with hemiparesis, loss of consciousness, or seizures. This condition may occur secondary to pathology that affects the intracranial arteries (e.g., sickle cell disease, vasculopathy, or traumatic arterial dissection) or may result from venous thrombi that embolize to the arterial circulation (placental thrombi, children with congenital heart disease or patent foramen ovale).

Rapidly Progressive Thrombosis (Thrombotic Storm)

Rapid progression or multifocal thrombosis is a rare complication of APS, heparin-induced thrombocytopenia with thrombosis, or thrombotic thrombocytopenia purpura during appropriate antithrombotic therapy. Multiorgan dysfunctions develop in the presence of small vessel occlusion and elevated D-dimer levels. Recurrences and **postthrombotic syndrome (PTS)** may occur. Treatment includes aggressive anticoagulation, often with direct thrombin inhibitors or fondaparinux, followed by prolonged warfarin therapy. In rare cases, plasmapheresis or immunosuppression may be warranted.

Diagnosis

Ultrasound with Doppler flow is the most commonly employed imaging study for the diagnosis of upper-extremity, or more often lower-extremity, VTE. Spiral CT is used most frequently for the diagnosis of PE (Fig. 506.1). Other diagnostic imaging options include CT and MR venography, which are noninvasive, although the sensitivity and specificity of these studies is not known. These studies may be particularly helpful in evaluating proximal or abdominal thrombosis. For the diagnosis of cerebral sinovenous thrombosis and acute ischemic stroke, the most sensitive imaging study is brain MRI with venography or diffusion-weighted imaging.

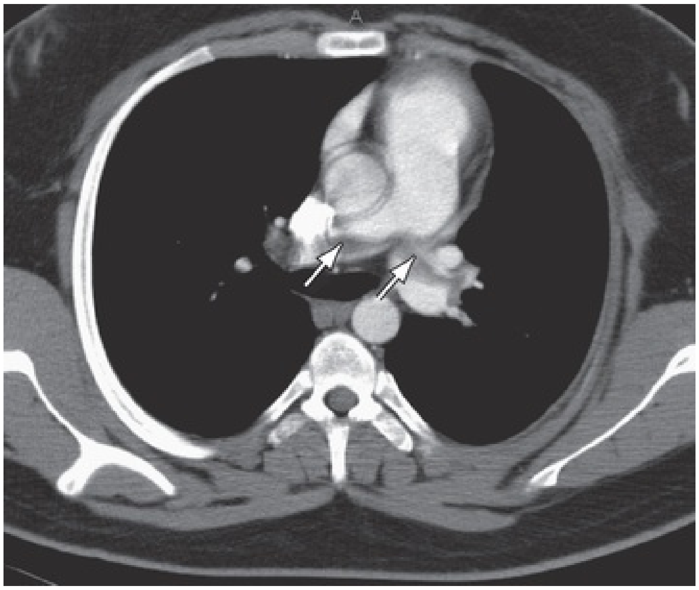

FIG. 506.1 Chest CT scan from 15 yr old male with large pulmonary embolism. There are large filling defects in both the right and the left main pulmonary artery.

Laboratory Testing

All children with a VTE should have a complete blood count and a baseline prothrombin time (PT) and PTT to assess their coagulation status. In adults with suspected DVT, the D-dimer level has a high negative predictive value, but the predictive value is not as well established for children. The D-dimer is a fragment produced when fibrin is degraded by plasmin and is a measure of fibrinolysis. Based on the clinical scenario, other laboratory studies, such as renal and hepatic function, may be indicated. Testing for APS includes evaluation for the lupus anticoagulant as well as anticardiolipin and anti–β_2 -glycoprotein antibodies, and should be considered in patients with inflammatory disorders or those who present with thrombosis and no other obvious risk factors.

There is debate regarding which patients should have testing for inherited risk factors. Thrombophilia testing rarely influences the acute management of a child with a thrombotic event. Identification of an inherited thrombophilia may influence the duration of treatment, particularly for those with a strong thrombophilia, and may aid in counseling patients about their risk of recurrence.

The evaluation and interpretation of coagulation studies in pediatric patients may be complicated by the developing hemostatic system and the differences in normal ranges between infants and adults (see Chapter 505).

Treatment

Therapeutic options for children with thrombosis include observation, anticoagulation, thrombolysis, and surgery. In premature neonates and critically ill children who are at high risk of bleeding, the potential benefits must be weighed against the risks, and close observation with repeat imaging may be an option. The majority of non-neonates with symptomatic thrombosis are treated with anticoagulant therapy. The goal of anticoagulation is to reduce the risk of embolism, halt clot extension, and prevent recurrence (see Chapter 506.1). Systemic or endovascular thrombolysis may be indicated for organ- or limb-threatening thrombosis. Surgery may be necessary for life- or limb-threatening thrombosis when there is a contraindication to thrombolysis. The optimal treatment for a child with acute ischemic stroke depends on the likely etiology and the size of the infarct. Children with sickle cell disease who develop stroke are treated with chronic red blood cell transfusions to reduce recurrence.

Complications

Complications of VTE include recurrent thrombosis (local or distant), and development of PTS. A thrombosed blood vessel may partially or fully recanalize or may remain occluded. Over time, an occluded deep vein may cause venous hypertension, resulting in blood flow being directed from the deep system into the superficial veins and potentially producing pain, swelling, edema, discoloration, and ulceration. This clinical picture is known as *postthrombotic syndrome* and may be chronically disabling. Several prospective studies in adults have shown PTS to be present in 17–50% of patients with a history of thrombosis. The likelihood of developing PTS is highest in the 1st 2 yr of life but continues to increase over time.

506.1

Anticoagulant and Thrombolytic

Therapy

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Keywords

anticoagulation
direct oral anticoagulant
DOAC
LMWH
low-molecular-weight heparin
thrombolysis
UFH
unfractionated heparin
warfarin embryopathy

Initial options for anticoagulation in children generally include unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), followed by LMWH or warfarin for outpatient management (Table 506.2). Several direct oral anticoagulants (DOACs) approved for treatment of TE in patients >18 yr old are currently in phase III clinical trials in children. These drugs act by inhibiting factor Xa or thrombin (Table 506.3). DOACs are recommended for acute and long term anticoagulant therapy for adults with VTE.

Table 506.2

Comparison of Antithrombotic Agents

	rTPA	**UNFRACTIONATED HEPARIN**	**WARFARIN**	**LMW HEPARIN (ENOXAPARIN)**
Indication	Recent onset of life- or limb-threatening thrombus	Acute or chronic thrombus, prophylaxis	Subacute or chronic thrombosis, thromboprophylaxis for cardiac valves	Acute or chronic thrombus, prophylaxis
Administration	IV continuous infusion	IV continuous infusion	PO once daily	SC injection twice daily

Monitoring	“Lytic state”: FDP or D-dimer	PTT	INR	Anti–factor Xa activity
Other	Higher risk of bleeding	Difficult to titrate; requires frequent dose adjustments; higher dose required in newborns	Heavily influenced by drug and diet	More stable and easy to titrate; concern of osteopenia with long-term use

FDP, Fibrin degradation products; INR, international normalized ratio; IV, intravenous; LMW, low-molecular-weight; PO, oral; PTT, partial thromboplastin time; rTPA, recombinant tissue-type plasminogen activator; SC, subcutaneous.

Table 506.3

Direct Oral Anticoagulants (DOACs)

	DABIGATRAN	**RIVAROXABAN**	**APIXABAN**	**EDOXABAN**	**BETRIXABAN**
Factor target	IIa	Xa	Xa	Xa	Xa
Half-life (hr)	12-17	5-13	8-14	10-14	20-30
Renal clearance (%)	80	33	25	35-50	5-7
Drug metabolism	P-glycoprotein	P-glycoprotein and *CYP34A*	P-glycoprotein and *CYP34A*	P-glycoprotein	P-glycoprotein
Drug reversal	Idarucizumab	Andexanet-alpha	Andexanet-alpha	Andexanet-alpha	Andexanet-alpha

The optimal duration of anticoagulation for children with TEs is not well established. Current guidelines recommend that neonates receive 6 wk to 3 mo of therapy for VTE, and that older children receive 3-6 mo of therapy. Patients with strong inherited thrombophilia, recurrent thrombosis, and APS may require indefinite anticoagulation.

Unfractionated Heparin

Both UFH and LMWH act by catalyzing the action of antithrombin III (AT III). UFH consists of large-molecular-weight polysaccharide chains that interact with AT III, catalyzing the inhibition of factor Xa and thrombin, as well as other serine proteases.

Heparin Dosing

Based on adult data, a therapeutic heparin dose achieves a prolongation of the PTT of 1.5-2.5 the upper limit of normal. A bolus dose of 75-100 units/kg results in a therapeutic PTT in the majority of children. This bolus should be followed by a continuous infusion. Initial dosing is based on age, with infants having the highest requirements. It is important to continue to monitor the PTT closely. In some situations, such as patients with a lupus anticoagulant, those with elevated factor VIII, or neonates, the PTT may not accurately reflect the degree of anticoagulation, and heparin can be monitored using a heparin anti-Xa level of 0.35-0.7 units/mL.

Heparin Complications

Maintaining the PTT in the therapeutic range can be difficult in young children for several reasons. The bioavailability of heparin is difficult to predict and may be influenced by plasma proteins. In many patients, this results in multiple dose adjustments requiring close monitoring with frequent venipuncture. UFH also requires continuous IV access, which may be difficult to maintain in young children.

The most common adverse effect related to heparin therapy is **bleeding** . This is well documented in the adult medical literature, and there are case reports of life-threatening bleeding in children treated with heparin. The true frequency of bleeding in pediatric patients receiving heparin has not been well established and is reported as 1–24%. If the anticoagulant effect of heparin must be reversed immediately, protamine sulfate may be administered to neutralize the heparin.

Other adverse effects include osteoporosis and **heparin-induced thrombocytopenia (HIT)** . Although rare in pediatric populations, HIT is a prothrombotic, immune-mediated complication in which antibodies develop to a complex of heparin and platelet factor 4. These antibodies result in platelet activation, stimulation of coagulation, thrombocytopenia, and in some cases, life-threatening thrombosis. If HIT is strongly suspected, heparin must be discontinued immediately. An alternative parenteral anticoagulant, such as argatroban or bivalirudin, may be used in this situation.

Low-Molecular-Weight Heparin

In contrast to UFH, LMWH contains smaller-molecular-weight polysaccharide chains. The interaction of the smaller chains with AT III results primarily in the inhibition of factor Xa, with less of an effect on thrombin. The several LMWHs available have variable inhibitory effects on thrombin. For this reason, the PTT is not a reliable measure of the anticoagulant effect of LMWH, and the anti–

factor Xa activity is used instead. Because of the ease of dosing and need for less monitoring, *LMWH is the most frequently used anticoagulant in pediatric patients*. The LMWH formulation that has been used most often in pediatric patients is enoxaparin.

Enoxaparin Dosing

The recommended standard starting dose of enoxaparin for infants <2 mo old is 1.5 mg/kg/dose subcutaneously every 12 hr and for patients >2 mo old, 1 mg/kg every 12 hr, although many centers use slightly higher doses for children <2 yr old. In general, peak levels are achieved 3-6 hr after injection. A therapeutic anti–factor Xa level, drawn 4 hr after the 2nd or 3rd dose, should be 0.5-1.0 IU/mL; the dose can be titrated to achieve this range. The elimination half-life of enoxaparin is 4-6 hr. Enoxaparin is cleared by the kidney and should be used with caution in patients with renal insufficiency. It should be avoided in patients with renal failure.

After an initial period of anticoagulation with heparin or LMWH, patients may continue to receive LMWH as an outpatient for the duration of therapy or may be transitioned to an oral anticoagulant such as warfarin.

Warfarin

Warfarin is an oral anticoagulant that competitively interferes with vitamin K metabolism, exerting its action by decreasing concentrations of the vitamin K–dependent coagulation factors II, VII, IX, and X, as well as protein C and protein S. Therapy should be started while a patient is anticoagulated with heparin or LMWH because of the risk of warfarin-induced skin necrosis. This transient hypercoagulable condition may occur when levels of protein C drop more rapidly than the procoagulant factors.

Dosing

Warfarin therapy is often initiated with a loading dose, with subsequent dose adjustments made according to a nomogram. When initiating warfarin therapy, UFH or LMWH should be continued until the international normalized ratio (INR) is therapeutic for 2 days. In most patients, this takes 5-7 days. The PT is used to monitor the anticoagulant effect of warfarin. Because the thromboplastin reagents used in PT assays have widely varying sensitivities, the PT performed in one laboratory cannot be compared to that performed in another laboratory. As a result, the INR was developed as a mechanism to standardize the variation in the thromboplastin reagent. The target INR range depends on the clinical situation. In general, a range of 2.0-3.0 is the target for the treatment of VTE. High-risk patients, such as those with mechanical heart valves, APS, or recurrent thrombosis, may require a higher target range.

Polymorphisms in *CYP2C9* and *VKORC1* affect the pharmacokinetics and pharmacodynamics of warfarin. Pharmacogenetic testing can identify wild-type responders, as well as those who are sensitive (increased risk of bleeding) and highly sensitive. Genotyping in adults may help select warfarin dose, monitor for bleeding, or choose a DOAC instead of warfarin for patients highly sensitive and at risk for hemorrhage.

Complications

As with the other anticoagulants, bleeding is the most common adverse effect. The risk of serious bleeding in children receiving warfarin for the treatment of VTE has been reported at 0.5% per year. Children who have supratherapeutic INR are at higher risk. There is considerable interpatient variation in dose. Diet, medications, and illness may influence the metabolism of warfarin, requiring frequent dose adjustments and laboratory studies. Numerous medications can affect the pharmacokinetics of warfarin by altering its clearance or rate of absorption. These effects can have a profound impact on the INR and must be considered when monitoring a patient receiving warfarin.

The strategies used to reverse warfarin therapy depend on the clinical situation and whether or not there is bleeding. Vitamin K can be administered to reverse the effect of warfarin but takes some time to have effect. If the patient is having significant bleeding, fresh-frozen plasma (FFP, 15 mL/kg) should be given along with the vitamin K. A nonactivated plasma-derived 4-factor prothrombin complex concentrate is approved for use in adults on vitamin K antagonists who have major bleeding.

Nonhemorrhagic complications are uncommon in children. Warfarin is a teratogen, particularly in the first trimester. **Warfarin embryopathy** is characterized by bone and cartilage abnormalities known as *chondrodysplasia punctata.* Affected infants may have nasal hypoplasia and excessive calcifications in the epiphyses and vertebrae.

Direct Oral Anticoagulants

Oral direct thrombin inhibitors (dabigatran) or inhibitors of factor Xa (apixaban, rivaroxaban, edoxaban) are approved agents for the prevention or treatment of thrombosis in patients >18 yr old (see Table 506.3). Fixed dosing, oral administration, no dietary interference with vitamin K, and no need to monitor laboratory tests, as well as initial results suggesting noninferiority to warfarin and fewer bleeding episodes, have favored the use of DOACs. Drugs are available to reverse the effects of DOACs if indicated. There is a paucity of evidence of their utility in children, although there are several ongoing clinical trials.

Thrombolytic Therapy

Although anticoagulation alone is often effective at managing thrombosis, more rapid clot resolution may be necessary or desirable. In these situations, a thrombolytic agent that can activate the fibrinolytic system is of potential benefit. The pharmacologic activity of thrombolytic agents depends on the conversion of endogenous plasminogen to plasmin. Plasmin is then able to degrade several plasma proteins, including fibrin and fibrinogen. Because of the high risk of bleeding, thrombolytic therapy is generally reserved for patients with life- or limb-threatening thrombosis.

Tissue plasminogen activator (TPA) is available as a recombinant product and has become the primary agent used for thrombolysis in children, although proper dose finding studies have not been performed.

Dosing

An extremely wide range of doses of TPA has been used for systemic therapy, and no consensus exists as to the optimal dose. Systemic TPA doses of 0.1-0.6 mg/kg/hr were previously recommended, although recent reports indicate successful therapy with fewer bleeding complications using prolonged infusions with very low doses—0.01-0.06 mg/kg/hr.

Monitoring

There is no specific laboratory test to document a “therapeutic range” for thrombolytic therapy. It is important to maintain the fibrinogen >100 mg/dL and the platelet count >75,000 × 10^9 /L during treatment. Supplementation of plasminogen using FFP is generally recommended in neonates before initiating thrombolysis because of their low baseline levels.

The clinical and radiologic response to thrombolysis should be closely monitored. The duration of therapy depends on the clinical response. Invasive procedures, including urinary catheterization, arterial puncture, and rectal temperatures, should be avoided.

The role of adjuvant UFH during thrombolytic therapy is controversial. Animal models have demonstrated that thrombolytic therapy can induce a procoagulant state with activation of the coagulation system, generation of thrombin, and extension or reocclusion of the thrombosis. In pediatric patients thought to be at low risk for bleeding, adjuvant UFH should be considered using doses of 10-20 units/kg/hr.

Complications

The most serious complication from thrombolysis is bleeding, which has been reported in 0–40% of patients. Absolute contraindications to thrombolysis include major surgery within 7 days, history of significant bleeding (intracranial, pulmonary, or gastrointestinal), peripartum asphyxia with brain damage, uncontrolled hypertension, and severe thrombocytopenia. In the event of serious bleeding, thrombolysis should be stopped and cryoprecipitate given to replace fibrinogen.

Thromboprophylaxis

There have been no formal trials of VTE prevention in children. Hospitalized adolescents with multiple risk factors for thrombosis who are immobilized for a prolonged period may benefit from prophylactic treatment with enoxaparin, 0.5 mg/kg every 12 hr (maximum 30 mg).

Antiplatelet Therapy

Inhibition of platelet function using agents such as aspirin is more likely to be protective against arterial TEs than VTEs. **Aspirin** , or acetylsalicylic acid

(ASA), exerts its antiplatelet effect by irreversibly inhibiting cyclooxygenase, preventing platelet thromboxane A_2 production. Aspirin is used routinely in children with Kawasaki disease and may also be useful in children with stroke, ventricular assist devices, and single-ventricle cardiac defects. The recommended dose of aspirin to achieve an antiplatelet effect in children is 1-5 mg/kg/day.

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CHAPTER 507

Postneonatal Vitamin K Deficiency

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Although “late” hemorrhagic disease has been reported in breastfed children, vitamin K deficiency occurring after the neonatal period is usually secondary to a lack of oral intake of vitamin K, alterations in the gut flora as a consequence of the long-term use of broad-spectrum antibiotics, liver disease, or malabsorption of vitamin K. Intestinal malabsorption of fats may accompany cystic fibrosis or biliary atresia and result in a deficiency of fat-soluble dietary vitamins, with reduced synthesis of vitamin K–dependent clotting factors (factors II, VII, IX, and X and proteins C and S). Prophylactic administration of water-soluble vitamin K orally is indicated in these patients (2-5 mg/24 hr for children and 5-10 mg/24 hr for adolescents and adults), or vitamin K may be administered at 1-2 mg intravenously. In patients with advanced cirrhosis, synthesis of many of the clotting factors may be reduced because of hepatocellular damage. In these patients, vitamin K may be ineffective. The anticoagulant properties of warfarin (Coumadin) depend on interference with vitamin K, with a concomitant reduction of factors II, VII, IX, and X. **Rat poison** (superwarfarin) produces a similar deficiency; vitamin K is a specific antidote.

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CHAPTER 508

Liver Disease

J. Paul Scott, Veronica H. Flood

Because all the clotting factors *except* factor VIII are produced exclusively in the liver, coagulation abnormalities are very common in patients with severe liver disease. Only 15% of such patients have significant clinical bleeding states, possibly because of concomitant reduction in anticoagulation proteins. The severity of the coagulation abnormality appears to be directly proportional to the extent of hepatocellular damage. The most common mechanism causing the defect is decreased synthesis of coagulation factors. Patients with severe liver disease characteristically have normal to increased (not reduced) levels of factor VIII activity in plasma. In some instances, **disseminated intravascular coagulation** (DIC; see Chapter 510) or **hyperfibrinolysis** may complicate liver disease, making laboratory differentiation of severe liver disease from DIC difficult.

Treatment of the coagulopathy of liver disease should be reserved for patients with clinical bleeding. Because a reduction in vitamin K–dependent coagulation factors is common in those with acute or chronic liver disease, vitamin K therapy can be given as a trial. Vitamin K can be given orally, subcutaneously, or intravenously (not intramuscularly) at a dose of 1 mg/24 hr for infants, 2-5 mg/24 hr for children, and 5-10 mg/24 hr for adolescents and adults. Inability to correct coagulopathy with vitamin K indicates that the coagulopathy may be caused by reduced levels of clotting factors that are not vitamin K–dependent and/or by inadequate production of precursor vitamin K proteins. Treatment for bleeding consists of factor replacement with **fresh-frozen plasma** (FFP) or **cryoprecipitate** . FFP (10-15 mL/kg) contains all clotting factors, but replacement of fibrinogen for severe hypofibrinogenemia may require cryoprecipitate at a dose of 1 unit per 5-10 kg body weight. In severe liver disease, it is often difficult to attain correction of abnormal clotting studies despite vigorous therapy with FFP and cryoprecipitate. Some patients with bleeding as a result of liver disease have responded to therapy with desmopressin, and others have responded to treatment with recombinant factor VIIa.

Frequently, severe liver disease is associated with moderate prolongation of bleeding time that is not corrected by vitamin K or plasma replacement. **Desmopressin** (0.3 µg/kg intravenously) is effective in shortening bleeding time and is used effectively to augment hemostasis before liver biopsy. In clinical trials of adults, recombinant factor VIIa has not been shown to be effective for the treatment of bleeding caused by severe liver disease.

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CHAPTER 509

Acquired Inhibitors of Coagulation

J. Paul Scott, Veronica H. Flood

Acquired circulating anticoagulants (**inhibitors**) are antibodies that react or cross-react with clotting factors or components used in coagulation screening tests (phospholipids), thereby prolonging screening tests, such as prothrombin time (PT) and partial thromboplastin time (PTT). Some of these anticoagulants are autoantibodies that react with phospholipid and thereby interfere with clotting in vitro *but not in vivo*. The most common form of these **antiphospholipid antibodies** has been referred to as the *lupus anticoagulant* (see Chapter 506.1). This anticoagulant is found in patients with systemic lupus erythematosus (SLE; see Chapter 183), in those with other collagen vascular diseases, and in association with HIV infection. In otherwise healthy children, spontaneous lupus-like inhibitors have developed transiently after incidental viral infection. These transient inhibitors are usually not associated with either bleeding or thrombosis.

Although the classic lupus anticoagulant is more often associated with a predisposition to thrombosis than with bleeding symptoms, bleeding symptoms in a patient with the lupus anticoagulant may be caused by **thrombocytopenia** , which may be a manifestation of the antiphospholipid syndrome or of lupus itself, or rarely, by a coexistent specific autoantibody against prothrombin (factor II). This antiprothrombin antibody does not inactivate prothrombin, but causes accelerated clearance of the protein, resulting in low levels of prothrombin.

Rarely, antibodies may arise spontaneously against a specific clotting factor, such as *factor VIII* or *von Willebrand factor* , similar to those seen more frequently in elderly patients. These patients are prone to excessive hemorrhage and may require specific treatment. In patients with a hereditary deficiency of a clotting factor (factor VIII or factor IX), antibodies may develop after exposure to transfused factor concentrates. These hemophilic inhibitory antibodies are discussed in Chapter 503.1 .

Laboratory Findings

Inhibitors against specific coagulation factors usually affect factors VIII, IX, and XI, or rarely prothrombin. Depending on the target of the antibody, PT and/or PTT may be prolonged. The mechanism by which the inhibitory antibody functions determines whether mixing patient plasma with normal plasma will normalize (correct) the clotting time. Patient plasma-containing antibodies directed against the active site of the clotting factor (factor VIII or factor IX) will not correct on 1 : 1 mixing with normal plasma, whereas antibodies that lead to increased clearance of the factor (prothrombin) will correct on 1 : 1 mixing. Specific factor assays are used to determine which factor is involved.

Treatment

Management of the bleeding patient with an inhibitor against factor VIII or IX is the same as for the patient with **hemophilia** who has an alloantibody against factor VIII or factor IX. Infusions of recombinant factor VIIa or activated prothrombin complex concentrate may be needed to control significant bleeding. Occasionally, high-dose coagulation factor VIII or IX may be effective. Immunosuppressive agents have been used “off label” to treat the inhibitor or reduce titers. Acute bleeding caused by an antiprothrombin antibody can often be treated with a plasma infusion and may benefit from a short course of corticosteroid therapy.

Asymptomatic spontaneous inhibitors that arise after a viral infection tend to disappear within a few weeks to months. Inhibitors seen with an underlying disease, such as SLE, often disappear when the primary disease is effectively treated.

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CHAPTER 510

Disseminated Intravascular Coagulation

J. Paul Scott, Leslie J. Raffini

Thrombotic microangiopathy refers to a heterogeneous group of conditions, including disseminated intravascular coagulation (**DIC**), that result in consumption of clotting factors, platelets, and anticoagulant proteins. Consequences of this process include widespread intravascular deposition of fibrin, leading to tissue ischemia and necrosis, a generalized hemorrhagic state, and microangiopathic hemolytic anemia.

Etiology

Any life-threatening severe systemic disease associated with hypoxia, acidosis, tissue necrosis, shock, or endothelial damage may trigger DIC (Table 510.1). Better understanding of the pathophysiology of hemostasis has led to an appreciation of the critical interaction of the coagulation pathways with the innate immune system and inflammatory response that likely contributes to the widespread dysregulation present in DIC. Activation and release of cytokines and chemokines alter endothelial function to a more prothrombotic state, enhancing the formation of microvascular thromboses, with resultant consumption of pro- and anticoagulant proteins. Excessive activation of clotting consumes both the physiologic anticoagulants (protein C, protein S, and AT III) and the procoagulants, resulting in a deficiency of factor V, factor VIII, prothrombin, fibrinogen, and platelets. Typically, the clinical result of this sequence of events is **hemorrhage** . The hemostatic dysregulation may also result in thromboses in the skin, kidneys, and other organs.

Table 510.1

Causes of Disseminated Intravascular Coagulation

INFECTIONS
Meningococcemia (purpura fulminans) Bacterial sepsis (staphylococcal, streptococcal, *Escherichia coli* , *Salmonella*) *Rickettsia* (Rocky Mountain spotted fever) Viruses (cytomegalovirus, herpes simplex, hemorrhagic fevers) Malaria Fungi
TISSUE INJURY
Central nervous system trauma (massive head injury) Multiple fractures with fat emboli Crush injury Profound shock or asphyxia Hypothermia or hyperthermia Massive burns
MALIGNANCY
Acute promyelocytic leukemia Acute monoblastic leukemia Widespread malignancies (neuroblastoma)
VENOM OR TOXIN
Snakebites Insect bites
MICROANGIOPATHIC DISORDERS
Severe thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome Giant hemangioma (Kasabach-Merritt syndrome)
GASTROINTESTINAL DISORDERS
Fulminant hepatitis Ischemic bowel Pancreatitis
HEREDITARY THROMBOTIC DISORDERS
Homozygous/compound heterozygous protein C, protein S, or AT III deficiency
NEWBORN
Maternal toxemia Bacterial or viral sepsis (group B streptococcus, herpes simplex virus) Abruptio placentae Severe respiratory distress syndrome Necrotizing enterocolitis Erythroblastosis fetalis Fetal demise of a twin
MISCELLANEOUS
Severe acute graft rejection Acute hemolytic transfusion reaction Severe collagen-vascular disease Kawasaki disease Heparin-induced thrombosis Infusion of activated prothrombin complex concentrates Hyperpyrexia/encephalopathy, hemorrhagic shock syndrome

Adapted from Montgomery RR, Scott IP: Hemostasis: diseases of the fluid phase. In Nathan DG, Oski FA, editors: *Hematology of infancy and childhood* , vol 2, ed 4, Philadelphia, 1993, Saunders.

Clinical Manifestations

DIC accompanies a severe systemic disease process, usually with **shock** . Bleeding frequently first occurs from sites of venipuncture or surgical incision. The skin may show petechiae and ecchymoses. Tissue necrosis may involve many organs and can be most spectacularly seen as infarction of large areas of skin, subcutaneous tissue, or kidneys. Anemia caused by hemolysis may develop rapidly because of microangiopathic hemolytic anemia.

Laboratory Findings

There is no well-defined sequence of events. Certain coagulation factors (factors II, V, and VIII; fibrinogen) and platelets may be consumed by the ongoing intravascular clotting process, with resultant prolongation of the prothrombin (PT), partial thromboplastin (PTT), and thrombin (TT) times. Platelet counts may be profoundly depressed. The blood smear may contain fragmented, burr- and helmet-shaped red blood cells (schistocytes). In addition, because the fibrinolytic mechanism is activated, *fibrinogen degradation products* (D-dimers) appear in the blood. The D-dimer is formed by fibrinolysis of a cross-linked fibrin clot. The D-dimer assay is as sensitive as the fibrinogen degradation product test and more specific for activation of coagulation and fibrinolysis.

Treatment

The 1st 2 steps in the treatment of DIC are the most critical: *treat the trigger* that caused DIC and *restore normal homeostasis* by correcting the shock, acidosis, and hypoxia that usually complicate DIC. If the underlying problem can be controlled and the patient can be stabilized, bleeding quickly ceases, and the abnormal laboratory findings improve. Blood components are used for replacement therapy in patients with hemorrhage and may consist of platelet infusions (for thrombocytopenia), cryoprecipitate (for hypofibrinogenemia), and/or fresh-frozen plasma (for replacement of other coagulation factors and natural inhibitors).

The role of **heparin** in DIC is limited to patients who have vascular thrombosis in association with DIC or who require prophylaxis because they are at high risk for venous thromboembolism. Such individuals should be treated as outlined in Chapter 506.1 , with careful attention to replacement therapy to maintain an adequate platelet count and thus limit bleeding complications.

The **prognosis** of patients with DIC is primarily dependent on the outcome of the treatment of the primary disease and prevention of end-organ damage.

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CHAPTER 511

Platelet and Blood Vessel Disorders

J. Paul Scott, Veronica H. Flood

Megakaryopoiesis

Platelets are nonnucleated cellular fragments produced by megakaryocytes (large polyploid cells) within the bone marrow and other tissues. When the megakaryocyte approaches maturity, budding of the cytoplasm occurs, and large numbers of platelets are liberated. Platelets circulate with a life span of 10-14 days. **Thrombopoietin (TPO)** is the primary growth factor that controls platelet production (Fig. 511.1). Levels of TPO appear to correlate inversely with platelet number and megakaryocyte mass. Levels of TPO are highest in the thrombocytopenic states associated with decreased marrow megakaryopoiesis and may be variable in states of increased platelet production.

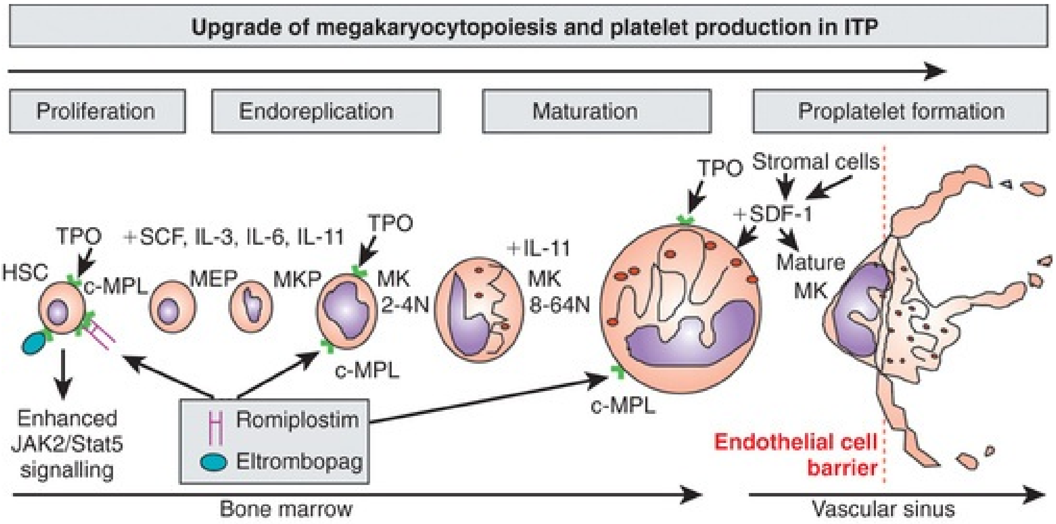
Upgrade of megakaryocytopoiesis and platelet production in ITP
Proliferation
Endoreplication
Maturation
Proplatelet formation
TPO
Stromal cells
+SDF-1
TPO
+SCF, IL-3, IL-6, IL-11
TPO
HSC
c-MPL
MEP
MKP
MK
2-4N
+IL-11
MK
8-64N
Mature
MK
c-MPL
c-MPL
Enhanced
JAK2/Stat5
signalling
Romiplostim
Eltrombopag
Endothelial cell
barrier
Bone marrow
Vascular sinus

FIG. 511.1 **Scheme of megakaryocytopoiesis and platelet production in idiopathic thrombocytopenic purpura (ITP). Hematopoietic stem cells (HSC) are mobilized and**

megakaryocyte (MK) and erythroid progenitors (MEP) accumulate with MK-committed progenitors (MKP), giving rise to mature MKs under control of thrombopoietin (TPO) working with chemokines, cytokines, and growth factors, including stem cell factor (SCF) and interleukin (IL)-3, IL-6, and IL-11. Endoreplication results in ploidy changes in MKs and increased chromosome number (up to 64N). Mature MKs migrate to the endothelial cell barrier delimiting the vascular sinus and, under the influence of stromal-derived factor-1 (SDF-1), give rise to proplatelets that protrude into the circulation and produce large numbers of platelets under hemodynamic determinants. Therapeutically given romiplostim and eltrombopag enter the marrow and join with TPO to stimulate megakaryocytopoiesis and platelet production. (From Nurden AT, Viallard JF, Nurden P: New-generation drugs that stimulate platelet production in chronic immune thrombocytopenic purpura, *Lancet* 373:1563, 2009.)

The platelet plays multiple hemostatic roles. The platelet surface possesses a number of important receptors for adhesive proteins, including **von Willebrand factor (VWF)** and fibrinogen, as well as receptors for agonists that trigger platelet aggregation, such as thrombin, collagen, and adenosine diphosphate (ADP). After injury to the blood vessel wall, the extracellular matrix containing adhesive and procoagulant proteins is exposed. Subendothelial collagen binds VWF, which undergoes a conformational change that induces binding of the platelet glycoprotein Ib (GPIb) complex, the VWF receptor. This process is called *platelet adhesion*. Platelets then undergo activation. During the process of activation, the platelets generate thromboxane A_2 from arachidonic acid via the enzyme cyclooxygenase. After activation, platelets release agonists, such as ADP, adenosine triphosphate (ATP), calcium ions (Ca^{2+}), serotonin, and coagulation factors, into the surrounding milieu. Binding of VWF to the GPIb complex triggers a complex signaling cascade that results in activation of the fibrinogen receptor, the major platelet integrin glycoprotein αIIb-β_3 (GPIIb-IIIa). Circulating fibrinogen binds to its receptor on the activated platelets, linking platelets in a process called *aggregation*. This series of events forms a hemostatic plug at the site of vascular injury. The serotonin and histamine that are liberated during activation increase local vasoconstriction. In addition to acting in concert with the vessel wall to form the platelet plug, the platelet provides the catalytic surface on which coagulation factors assemble and eventually generate thrombin through a sequential series of enzymatic cleavages. Lastly, the platelet contractile proteins and cytoskeleton mediate clot retraction.

Thrombocytopenia

The normal platelet count is 150-450 × 10^9 /L. *Thrombocytopenia* refers to a reduction in platelet count to <150 × 10^9 /L, although clinically significant bleeding is not seen until counts drop well below 50 × 10^9 /L. Causes of thrombocytopenia include decreased production on either a congenital or an acquired basis, sequestration of the platelets within an enlarged spleen or other organ, and increased destruction of normally synthesized platelets on either an immune or a nonimmune basis (Tables 511.1 and 511.2 and Fig. 511.2) (see Chapter 502).

Table 511.1

Differential Diagnosis of Thrombocytopenia in Children and Adolescents

Destructive Thrombocytopenias

Primary Platelet Consumption Syndromes

Immune thrombocytopenias

- Acute and chronic ITP
- Autoimmune diseases with chronic ITP as a manifestation
  - Cyclic thrombocytopenia
  - Autoimmune lymphoproliferative syndrome and its variants
  - Systemic lupus erythematosus
  - Evans syndrome
  - Antiphospholipid antibody syndrome
  - Neoplasia-associated immune thrombocytopenia
- Thrombocytopenia associated with HIV
- Neonatal immune thrombocytopenia
  - Alloimmune
  - Autoimmune (e.g., maternal ITP)
- Drug-induced immune thrombocytopenia (including heparin-induced thrombocytopenia)
- Posttransfusion purpura
- Allergy and anaphylaxis
- Posttransplant thrombocytopenia

Nonimmune thrombocytopenias

- Thrombocytopenia of infection
  - Bacteremia or fungemia
  - Viral infection
  - Protozoan
- Thrombotic microangiopathic disorders
  - Hemolytic-uremic syndrome
  - Eclampsia, HELLP syndrome
  - Thrombotic thrombocytopenic purpura
  - Bone marrow transplantation–associated microangiopathy
  - Drug induced (quinine, etc.)
- Platelets in contact with foreign material
- Congenital heart disease
- Drug-induced via direct platelet effects (ristocetin, protamine)
- Type 2B VWD or platelet-type VWD

Combined Platelet and Fibrinogen Consumption Syndromes

- Disseminated intravascular coagulation
- Kasabach-Merritt syndrome
- Hemophagocytic lymphohistiocytosis (inherited or acquired)

Impaired Platelet Production

Hereditary disorders

Acquired disorders
- Aplastic anemia
- Myelodysplastic syndrome
- Marrow infiltrative process—neoplasia
- Osteopetrosis
- Nutritional deficiency states (iron, folate, vitamin B_{12} , anorexia nervosa)
- Drug- or radiation-induced thrombocytopenia
- Neonatal hypoxia or placental insufficiency

Sequestration

Hypersplenism

Hypothermia

Burns

HELLP, Hemolysis, elevated liver enzymes, and low platelets; HIV, human immunodeficiency virus; ITP, immune thrombocytopenic purpura; VWD, von Willebrand disease.

From Wilson DB: Acquired platelet defects. In Orkin SH, Fisher DE, Ginsberg D, et al, editors: *Nathan and Oski's hematology of infancy and childhood,* ed 8, Philadelphia, 2015, Saunders Elsevier (Box 34.1, p 1077).

Table 511.2

Classification of Fetal and Neonatal Thrombocytopenias*

	CONDITION
Fetal	**Alloimmune thrombocytopenia**
	Congenital infection (e.g., CMV, toxoplasma, rubella, HIV)
	Aneuploidy (e.g., trisomy 18, 13, or 21, triploidy, Turner syndrome)
	Autoimmune condition (e.g., ITP, SLE)
	Severe Rh hemolytic disease
	Congenital/inherited (e.g., Wiskott-Aldrich, Noonan, Cornelia deLange, Jacobsen syndromes)
Early-onset neonatal (<72 hr)	**Placental insufficiency** (e.g., PET, IUGR, diabetes)
	Perinatal asphyxia
	Perinatal infection (e.g., *Escherichia coli* , GBS, herpes simplex)
	DIC
	Alloimmune thrombocytopenia
	Autoimmune condition (e.g., ITP, SLE)
	Congenital infection (e.g., CMV, toxoplasma, rubella, HIV)
	Thrombosis (e.g., aortic, renal vein)
	Bone marrow replacement (e.g., congenital leukemia)
	Kasabach-Merritt syndrome
	Metabolic disease (e.g., propionic and methylmalonic acidemia)
	Congenital/inherited (e.g., TAR, CAMT)
Late-onset neonatal (>72 hr)	**Late-onset sepsis**
	NEC
	Congenital infection (e.g., CMV, toxoplasma, rubella, HIV)
	Autoimmune
	Kasabach-Merritt syndrome
	Metabolic disease (e.g., propionic and methylmalonic acidemia)

	Congenital/inherited (e.g., TAR, CAMT)

[*] The most common conditions are shown in **bold** .

CAMT, Congenital amegakaryocytic thrombocytopenia; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation; GBS, group B streptococcus; HIV, human immunodeficiency virus; ITP, idiopathic thrombocytopenic purpura; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; PET, preeclampsia; SLE, systemic lupus erythematosus; TAR, thrombocytopenia with absent radii.

From Roberts I, Murray NA: Neonatal thrombocytopenia: causes and management, *Arch Dis Child Fetal Neonatal Ed* 88:F359–F364, 2003.

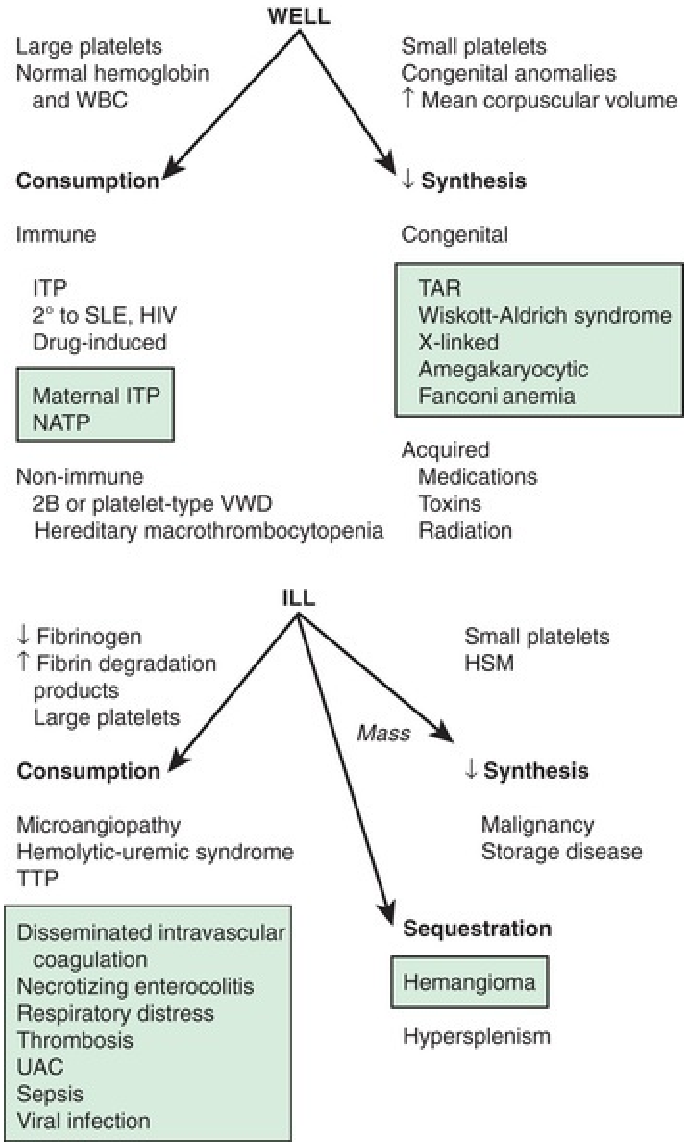
WELL
Large platelets
Normal hemoglobin and WBC
Small platelets
Congenital anomalies
↑ Mean corpuscular volume
Consumption
↓ Synthesis
Immune
ITP
2° to SLE, HIV
Drug-induced
Maternal ITP
NATP
Non-immune
2B or platelet-type VWD
Hereditary macrothrombocytopenia
Congenital
TAR
Wiskott-Aldrich syndrome
X-linked
Amegakaryocytic
Fanconi anemia
Acquired
Medications
Toxins
Radiation
ILL
↓ Fibrinogen
↑ Fibrin degradation products
Large platelets
Small platelets
HSM
Mass
Consumption
↓ Synthesis
Microangiopathy
Hemolytic-uremic syndrome
TTP
Disseminated intravascular coagulation
Necrotizing enterocolitis
Respiratory distress
Thrombosis
UAC
Sepsis
Viral infection
Malignancy
Storage disease
Sequestration
Hemangioma
Hypersplenism

FIG. 511.2 **Differential diagnosis of childhood thrombocytopenic syndromes. The syndromes initially are separated by their clinical appearance. Clues leading to the diagnosis are shown in *italics* . The mechanisms and common disorders leading to**

these findings are shown in the *lower part* of the figure. Disorders that commonly affect neonates are listed in the *shaded boxes* . HSM, Hepatosplenomegaly; ITP, idiopathic immune thrombocytopenic purpura; NATP, neonatal alloimmune thrombocytopenic purpura; SLE, systemic lupus erythematosus; TAR, thrombocytopenia–absent radius; TTP, thrombotic thrombocytopenic purpura; UAC, umbilical artery catheter; VWD, von Willebrand disease; WBC, white blood cell. (From Scott JP: Bleeding and thrombosis. In Kliegman RM, editor: *Practical strategies in pediatric diagnosis and therapy,* Philadelphia, 1996, Saunders, p 849; and Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: *Nelson essentials of pediatrics,* ed 5, Philadelphia, 2006, Elsevier/Saunders, p 716.)

511.1

Idiopathic (Autoimmune) Thrombocytopenic Purpura

J. Paul Scott, Veronica H. Flood

Keywords

idiopathic thrombocytopenic purpura
immune-mediated thrombocytopenic purpura
intracranial hemorrhage
ITP

The most common cause of acute onset of thrombocytopenia in an otherwise well child is (autoimmune) idiopathic thrombocytopenic purpura (**ITP**).

Epidemiology

In a small number of children, estimated at 1 in 20,000, 1-4 wk after exposure to a common viral infection, an autoantibody directed against the platelet surface develops with resultant sudden onset of thrombocytopenia. A recent history of viral illness is described in 50–65% of children with ITP. The peak age is 1-4 yr, although the age ranges from early in infancy to elderly. In childhood, males and females are equally affected. ITP seems to occur more often in late winter and spring after the peak season of viral respiratory illness.

Pathogenesis

The exact antigenic target for most such antibodies in most cases of childhood acute ITP remains undetermined, although in chronic ITP many patients demonstrate antibodies against αIIb-β_3 and GPIb. After binding of the antibody to the platelet surface, circulating antibody-coated platelets are recognized by the Fc receptor on splenic macrophages, ingested, and destroyed. Most common viruses have been described in association with ITP, including Epstein-Barr virus (EBV; see Chapter 281) and HIV (see Chapter 302). EBV-related ITP is usually of short duration and follows the course of infectious mononucleosis. HIV-associated ITP is usually chronic. In some patients, ITP appears to arise in children infected with *Helicobacter pylori* or rarely following vaccines.

Clinical Manifestations

The classic presentation of ITP is a previously healthy 1-4 yr old child who has sudden onset of generalized petechiae and purpura. The parents often state that the child was fine yesterday and now is covered with bruises and purple dots. There may be bleeding from the gums and mucous membranes, particularly with *profound thrombocytopenia* (platelet count $<10 \times 10^9$ /L). There is a history of a preceding viral infection 1-4 wk before the onset of thrombocytopenia. Findings on physical examination are normal, other than petechiae and purpura. *Splenomegaly, lymphadenopathy, bone pain, and pallor are rare.* A simple classification system from the United Kingdom has been proposed to characterize the severity of bleeding in ITP on the basis of symptoms and signs rather than platelet count, as follows:

1. No symptoms
2. Mild symptoms: bruising and petechiae, occasional minor epistaxis, very little interference with daily living
3. Moderate symptoms: more severe skin and mucosal lesions, more troublesome epistaxis and menorrhagia

4. Severe symptoms: bleeding episodes—menorrhagia, epistaxis, melena—requiring transfusion or hospitalization, symptoms interfering seriously with the quality of life

The presence of abnormal findings such as hepatosplenomegaly, bone or joint pain, remarkable lymphadenopathy other cytopenias, or congenital anomalies suggests other diagnoses (leukemia, syndromes). When the onset is insidious, especially in an adolescent, chronic ITP or the possibility of a systemic illness, such as **systemic lupus erythematosus** (SLE), is more likely.

Outcome

Severe bleeding is rare (<3% of cases in 1 large international study). In 70–80% of children who present with acute ITP, spontaneous resolution occurs within 6 mo. Therapy does not appear to affect the natural history of the illness. Fewer than 1% of patients develop an **intracranial hemorrhage** (ICH). Proponents of interventional therapy argue that the objective of early therapy is to raise the platelet count to $>20 \times 10^9$ /L and prevent the rare development of ICH. There is no evidence that therapy prevents serious bleeding. Approximately 20% of children who present with acute ITP go on to have chronic ITP. The outcome/prognosis may be related more to age; ITP in younger children is more likely to resolve, whereas development of chronic ITP in adolescents approaches 50%.

Laboratory Findings

Severe thrombocytopenia (platelet count $<20 \times 10^9$ /L) is common, and platelet size is normal or increased, reflective of increased platelet turnover (Fig. 511.3). In acute ITP the hemoglobin value, white blood cell (WBC) count, and differential count should be normal. Hemoglobin may be decreased if there have been profuse nosebleeds (epistaxis) or menorrhagia. Bone marrow examination shows normal granulocytic and erythrocytic series, with characteristically normal or increased numbers of megakaryocytes. Some of the megakaryocytes may appear to be immature and reflect increased platelet turnover. *Indications for bone marrow aspiration/biopsy* include an abnormal WBC count or differential or unexplained anemia, as well as history and physical examination findings suggestive of a bone marrow failure syndrome or malignancy. Other laboratory tests should be performed as indicated by the history and examination. HIV studies should be done in at-risk populations, especially sexually active teens. Platelet antibody testing is seldom useful in acute ITP. A direct antiglobulin test (Coombs) should be done if there is unexplained anemia, to rule out **Evans syndrome** (autoimmune hemolytic anemia and thrombocytopenia) (see Chapter 484). Evans syndrome may be idiopathic or an early sign of systemic lupus erythematosus, autoimmune lymphoproliferative syndrome or common variable immunodeficiency syndrome. An ANA should be considered in adolescents, especially with other features of SLE (see Chapter 183).

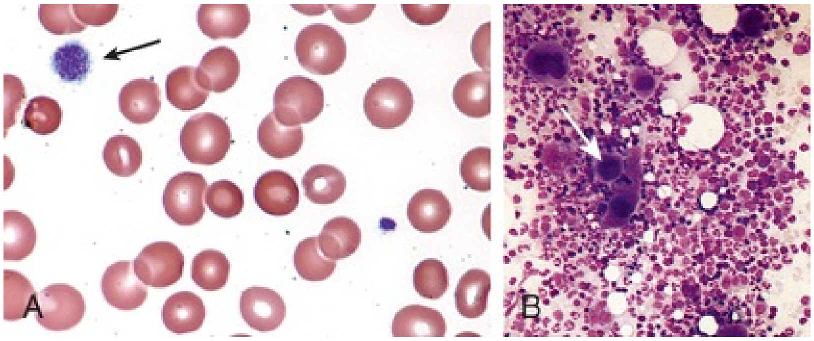

FIG. 511.3 Blood and marrow aspirate from child with idiopathic thrombocytopenic purpura. A, Blood smear shows large platelets. B, Bone marrow aspirate shows increased numbers of megakaryocytes, many of which appear immature. (From Blanchette V, Bolton-Maggs P: Childhood immune thrombocytopenic purpura: diagnosis and management, *Pediatr Clin North Am* 55:393–420, 2008, Fig 4, p 400.)

Diagnosis and Differential Diagnosis

The well-appearing child with moderate to severe thrombocytopenia, an otherwise normal complete blood cell count (CBC), and normal exam findings has a limited differential diagnosis that includes exposure to medication inducing drug-dependent antibodies, splenic sequestration because of previously unappreciated portal hypertension, and rarely, early aplastic processes, such as Fanconi anemia (see Chapter 495). Other than congenital thrombocytopenia syndromes (see Chapter 511.8), such as thrombocytopenia–absent radius (TAR) syndrome and MYH9-related thrombocytopenia, most marrow processes that interfere with platelet production eventually cause abnormal synthesis of red blood cells (RBCs) and WBCs and therefore manifest diverse abnormalities on the CBC. Disorders that cause increased platelet destruction on a nonimmune basis are usually serious systemic illnesses with obvious clinical findings such as **hemolytic-uremic syndrome** (HUS) and **disseminated intravascular coagulation** (DIC) (see Fig. 511.2 , and Table 510.1 in Chapter 510). Patients receiving heparin may develop heparin-induced thrombocytopenia. Isolated enlargement of the spleen suggests the potential for hypersplenism caused by liver disease or portal vein thrombosis. Autoimmune thrombocytopenia may be an initial manifestation of SLE, HIV infection, common variable immunodeficiency, and rarely, lymphoma or autoimmune lymphoproliferative syndrome. Wiskott-Aldrich syndrome must be considered in young males found to have thrombocytopenia with *small* platelets, particularly if there is a history of eczema and recurrent infection (see Chapter 152.2).

Treatment

A number of treatment options exist (Table 511.3), but there are no data showing that treatment affects either short- or long-term clinical outcome of ITP. Many patients with new-onset ITP have mild symptoms, with findings limited to petechiae and purpura on the skin, despite severe thrombocytopenia. Compared with untreated controls, treatment appears to be capable of inducing a more rapid rise in platelet count to the theoretically safe level of $>20 \times 10^9$ /L, although no data indicate that early therapy prevents ICH. Antiplatelet antibodies bind to transfused platelets as well as they do to autologous platelets. Thus, platelet transfusion in ITP is usually contraindicated unless life-threatening bleeding is present. Initial approaches to the management of ITP include the following:

Table 511.3

Treatment Options for Idiopathic Thrombocytopenic Purpura (ITP)

	PROS	CONS	COST
Observation	Does not expose patient to unnecessary medications	May increase parent and physician anxiety	Relatively inexpensive
IVIG	Rapid response in most cases	IV administration, side effects	Expensive
Corticosteroids	Oral, effective in 70–80% of patients, minimal side effects with short courses	Side effects, may not affect long term outcome	Inexpensive
Rituximab	Long-term remission in 40–60% of	IV administration, immune suppression,	Very

	patients	potential for reactivation of hepatitis	expensive
Splenectomy	Curative in 80% of patients	Requires surgery and anesthesia, lifelong risk of infection	Expensive
Thrombopoietin receptor agonists	Potential for oral administration, 40–60% of patients respond	Not curative, usually required long term, can cause elevated liver enzymes	Very expensive

IV, Intravenous; IVIG, intravenous immune globulin.

Adapted from Flood VH, Scott JP: Bleeding and thrombosis. In Kliegman R, Lye P, Bordini B, et al, editors: *Nelson pediatric symptom-based diagnosis,* Philadelphia, 2017, Saunders Elsevier.

1. No therapy other than education and counseling of the family and patient for patients with minimal, mild, and moderate symptoms, as defined earlier. This approach emphasizes the usually benign nature of ITP and avoids the therapeutic roller coaster that ensues once interventional therapy is begun. This approach is much less costly, and side effects are minimal. Observation is recommended by the American Society of Hematology guidelines for children with *only* mild bleeding symptoms such as bruising or petechiae.
2. Treatment with either IVIG or corticosteroids, particularly for children who present with *mucocutaneous* bleeding. As American Society of Hematology guidelines state, “A single dose of IVIG [intravenous immune globulin] (0.8-1.0 g/kg) or a short course of corticosteroids should be used as first-line treatment.” IVIG at a dose of 0.8-1.0 g/kg/day for 1-2 days induces a rapid rise in platelet count (usually $>20 \times 10^9$ /L) in 95% of patients within 48 hr. IVIG appears to induce a response by downregulating Fc-mediated phagocytosis of antibody-coated platelets. IVIG therapy is both expensive and time-consuming to administer. Additionally, after infusion, there is a high frequency of headaches and vomiting, suggestive of IVIG-induced aseptic meningitis.
3. Corticosteroid therapy has been used for many years to treat acute and chronic ITP in adults and children. Doses of prednisone at 1-4 mg/kg/24 hr appear to induce a more rapid rise in platelet count than in untreated patients with ITP. Corticosteroid therapy is usually continued for short course until a rise in platelet count to $>20 \times 10^9$ /L has been achieved to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis.

Each of these medications may be used to treat ITP exacerbations, which usually occur several weeks after an initial course of therapy. In the special case of ICH, multiple modalities should be used, including platelet transfusion, IVIG, high-dose corticosteroids, and prompt consultation by neurosurgery and surgery.

There is no consensus regarding the management of acute childhood ITP, except that patients who are bleeding significantly (<5% of children with ITP) should be treated. Intracranial hemorrhage remains rare, and there are no data showing that treatment actually reduces its incidence. *Mucosal bleeding* in particular is the most significant in terms of predicting severe bleeding.

The role of **splenectomy** in ITP should be reserved for 2 circumstances: (1) the older child (≥4 yr) with severe ITP that has lasted >1 yr (chronic ITP) and whose symptoms are not easily controlled with therapy and (2) when life-threatening hemorrhage (ICH) complicates acute ITP, if the platelet count cannot be corrected rapidly with transfusion of platelets and administration of IVIG and corticosteroids. Splenectomy is associated with a lifelong risk of overwhelming postsplenectomy infection caused by encapsulated organisms, increased risk of thrombosis, and the potential development of pulmonary hypertension in adulthood. As an alternative to splenectomy**, rituximab** has been used “off label” in children to treat chronic ITP. In 30–40% of children, rituximab has induced a partial or complete remission. Thrombopoietin receptor agonists have also been used to increase platelet count and are approved for pediatric use.

Chronic Autoimmune Thrombocytopenic Purpura

Approximately 20% of patients who present with acute ITP have persistent thrombocytopenia for >12 mo and are said to have *chronic* ITP. At that time, a careful reevaluation for associated disorders should be performed, especially for autoimmune disease (e.g., SLE), chronic infectious disorders (e.g., HIV), and nonimmune causes of chronic thrombocytopenia, such as type 2B and platelet-type von Willebrand disease, X-linked thrombocytopenia, autoimmune lymphoproliferative syndrome, common variable immunodeficiency syndrome, autosomal macrothrombocytopenia, and Wiskott-Aldrich syndrome (also X-linked). The presence of coexisting *H. pylori* infection should be considered and, if found, treated. Therapy should be aimed at controlling symptoms and preventing serious bleeding. In ITP the spleen is the primary site of both antiplatelet antibody synthesis and platelet destruction. Splenectomy is successful in inducing complete remission in 64–88% of children with chronic

ITP. This effect must be balanced against the lifelong risk of overwhelming postsplenectomy infection. This decision is often affected by quality-of-life issues, as well as the ease with which the child can be managed using medical therapy, such as IVIG, corticosteroids, IV anti-D, or rituximab. Two effective agents that act to stimulate thrombopoiesis, **romiplostim** and **eltrombopag** (see Fig. 511.1), are approved by the U.S. Food and Drug Administration (FDA) to treat adults and children with chronic ITP. Although these do not address the mechanism of action of ITP, the increase in platelet count may be enough to compensate for the increased destruction and allow the patient to have resolution of bleeding and maintain a platelet count >50 × 10^9 /L.

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511.2

Drug-Induced Thrombocytopenia

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Keywords

heparin
immune thrombocytopenia

A number of drugs are associated with immune thrombocytopenia as the result of either an immune process or megakaryocyte injury. Some common drugs used in pediatrics that cause thrombocytopenia include valproic acid, phenytoin, carbamazepine, sulfonamides, vancomycin, and trimethoprim-sulfamethoxazole. Heparin-induced thrombocytopenia (and rarely an associated thrombosis) is seldom seen in pediatrics, but it occurs when, after exposure to heparin, the patient has an antibody directed against the heparin–platelet factor 4 complex. Recommended treatment for heparin-induced thrombocytopenia includes direct thrombin inhibitors such as argatroban or danaparoid and removal of all sources of heparin, including line flushes.

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511.3

Nonimmune Platelet Destruction

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Keywords

hemolytic anemia
thrombotic microangiopathy

The syndromes of DIC (see Chapter 510), HUS (see Chapter 538.5), and thrombotic thrombocytopenic purpura (see Chapter 511.5) share the hematologic picture of a thrombotic microangiopathy in which there is RBC destruction and consumptive thrombocytopenia caused by platelet and fibrin deposition in the microvasculature. The microangiopathic hemolytic anemia is characterized by the presence of RBC fragments, including helmet cells, schistocytes, spherocytes, and burr cells.

511.4

Hemolytic-Uremic Syndrome

See Chapter 538.5 .

511.5

Thrombotic Thrombocytopenic Purpura

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Keywords

microangiopathic hemolytic anemia
renal failure
thrombotic microangiopathy

Thrombotic thrombocytopenic purpura (TTP) is a rare thrombotic microangiopathy characterized by the pentad of fever, microangiopathic hemolytic anemia, thrombocytopenia, abnormal renal function, and central nervous system (CNS) changes that is clinically similar to HUS (Table 511.4). Although TTP can be congenital, it usually presents in adults and occasionally in adolescents. Microvascular thrombi within the CNS cause subtle, shifting neurologic signs that vary from changes in affect and orientation to aphasia, blindness, and seizures. Initial manifestations are often nonspecific (weakness, pain, emesis); prompt recognition of this disorder is critical. Laboratory findings provide important clues to the diagnosis and show microangiopathic hemolytic anemia characterized by morphologically abnormal RBCs, with schistocytes, spherocytes, helmet cells, and an elevated reticulocyte count in association with thrombocytopenia. Coagulation studies are usually nondiagnostic. Blood urea nitrogen and creatinine are sometimes elevated. The **treatment** of acquired TTP is plasmapheresis (plasma exchange), which is effective in 80–95% of patients. Treatment with plasmapheresis should be instituted on the basis of thrombocytopenia and microangiopathic hemolytic anemia even if other symptoms are not yet present. Rituximab, corticosteroids, and splenectomy are reserved for refractory cases. *Caplacizumab,* an anti-VWF humanized immunoglobulin, blocks the interaction of ultralarge VWF multimers with platelets and many result in rapid resolution of acute TTP.

Table 511.4

ADAMTS13 Deficiency and Thrombotic Thrombocytopenic Purpura

DISEASE	PATHOPHYSIOLOGY	LAB FINDINGS	MANAGEMENT
Thrombotic thrombocytopenic purpura (TTP)	*Acquired* : Ab to ADAMTS13 *Congenital* : Inadequate ADAMTS13 production	Ab to ADAMTS13 ADAMTS13 <10%	*Acquired* : Plasmapheresis with plasma *Congenital* : Scheduled plasma infusions

Autoimmune TTP may be transient, recurrent, drug (ticlopidine, clopidogrel) associated, or seen in some pregnancy-associated cases of TTP.

ADAMTS13 mutations are often familial and chronic-relapsing RRP.

The majority of cases of TTP are caused by an autoantibody-mediated **deficiency of ADAMTS13** (a disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13) that is responsible for cleaving the high-molecular-weight multimers of VWF and appears to play a pivotal role in the evolution of the thrombotic microangiopathy (Fig. 511.4). In contrast, levels of the metalloproteinase in HUS are usually normal. *Congenital deficiency* of the metalloproteinase causes rare familial cases of TTP/HUS, usually manifested as recurrent episodes of thrombocytopenia, hemolytic anemia, and renal involvement, with or without neurologic changes, that often present in infancy after an intercurrent illness. Abnormalities of the complement system have now also been implicated in rare cases of familial TTP. ADAMTS13 deficiency can be treated by repeated infusions of fresh-frozen plasma.

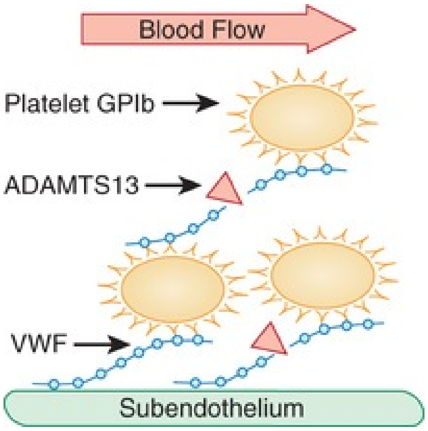

FIG. 511.4 **Pathogenesis of thrombotic thrombocytopenic purpura (TTP). The von Willebrand factor (VWF) multimers facilitate platelet adhesion to the subendothelium by binding to exposed connective tissue and then to platelet glycoprotein Ib (GPIb). In flowing blood shear stress unfolds ultralarge VWF multimers in the platelet-rich thrombus and enables ADAMTS13 to cleave a specific Tyr-Met bond in the 2nd of the 3 A domains in VWF subunits. Cleavage reduces VWF multimer size and limits thrombus growth. In the absence of ADAMTS13, VWF-dependent platelet accumulation continues and eventually results in microvascular thrombosis and TTP. (Courtesy of Dr. J. Evan Sadler, Washington University.)**

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511.6

Kasabach-Merritt Syndrome

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Keywords

hemangioma
hypofibrinogenemia
thrombocytopenia

See also Chapter 669 .

The association of a giant hemangioma with localized intravascular coagulation causing thrombocytopenia and hypofibrinogenemia is called Kasabach-Merritt syndrome. In most patients the site of the hemangioma is obvious, but retroperitoneal and intraabdominal hemangiomas may require body imaging for detection. Inside the hemangioma there is platelet trapping and activation of coagulation, with fibrinogen consumption and generation of fibrin(ogen) degradation products. Arteriovenous malformation within the lesions can cause heart failure. Pathologically, Kasabach-Merritt syndrome appears to develop more often as a result of a kaposiform hemangioendothelioma or tufted hemangioma rather than a simple hemangioma. The peripheral blood smear shows microangiopathic changes.

Multiple modalities have been used to treat Kasabach-Merritt syndrome, including propranolol, surgical excision (if possible), laser photocoagulation, high-dose corticosteroids, local radiation therapy, antiangiogenic agents such as interferon-α_2 , and vincristine. Over time, most patients who present in infancy have regression of the hemangioma. Treatment of the associated coagulopathy may benefit from a trial of antifibrinolytic therapy with ε-aminocaproic acid (Amicar) or anticoagulation with low-molecular-weight heparin.

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511.7

Sequestration

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Keywords

leukopenia
spleen
thrombocytopenia

Thrombocytopenia develops in individuals with massive splenomegaly because the spleen acts as a sponge for platelets and sequesters large numbers. Most such patients also have mild leukopenia and anemia on CBC. Individuals who have thrombocytopenia caused by splenic sequestration should undergo a workup to diagnose the etiology of splenomegaly, including infectious, inflammatory, infiltrative, neoplastic, obstructive, and hemolytic causes.

511.8

Congenital Thrombocytopenic Syndromes

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Keywords

congenital amegakaryocytic thrombocytopenia
MYH9
thrombocytopenia–absent radius syndrome
Wiskott-Aldrich syndrome

See Table 511.2 .

Congenital amegakaryocytic thrombocytopenia (CAMT) usually manifests within the 1st few days to week of life, when the child presents with petechiae and purpura caused by profound thrombocytopenia. CAMT is caused by a rare defect in hematopoiesis as a result of a mutation in the stem cell TPO receptor (MPL). Other than skin and mucous membrane abnormalities, findings on physical examination are normal. Examination of the bone marrow shows an absence of megakaryocytes. These patients often progress to marrow failure (aplasia) over time. Hematopoietic stem cell transplantation (HSCT) is curative.

Thrombocytopenia–absent radius (TAR) syndrome consists of thrombocytopenia (absence or hypoplasia of megakaryocytes) that presents in early infancy with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening (Fig. 511.5). Many such individuals also have other skeletal abnormalities of the ulna, radius, and lower extremities. *Thumbs are present* . Intolerance to cow's milk formula (present in 50%) may complicate management by triggering gastrointestinal bleeding, increased thrombocytopenia, eosinophilia, and a leukemoid reaction. The thrombocytopenia of TAR syndrome frequently remits over the 1st few yr of life. The molecular basis of TAR syndrome is linked to *RBM8A* . A few patients have been reported to have a syndrome of **amegakaryocytic thrombocytopenia with radioulnar synostosis** caused by a mutation in the *HOXA11* gene. Different from TAR syndrome, this mutation causes marrow aplasia.

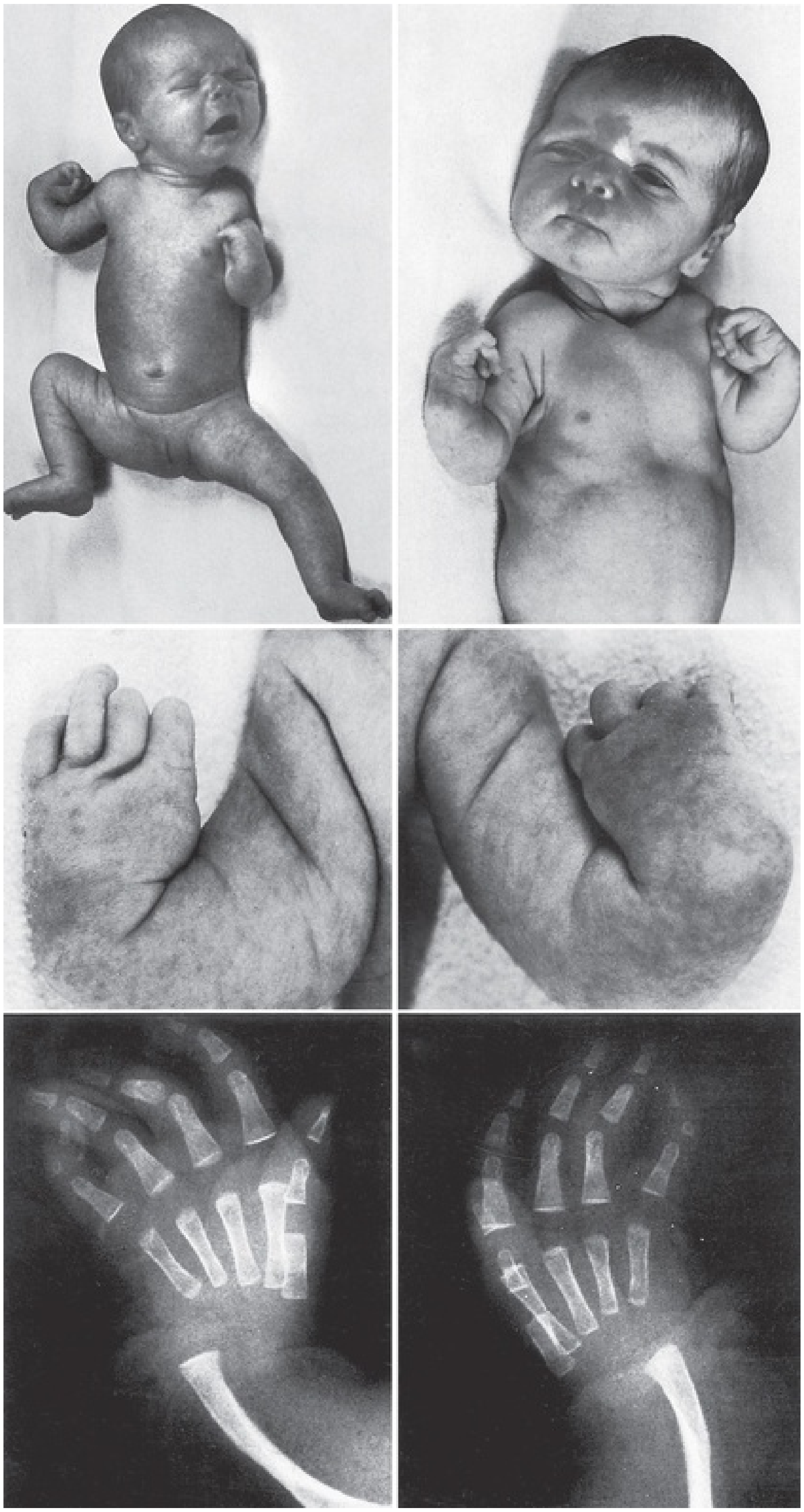

FIG. 511.5 A newborn, the first child of young, healthy parents, with fully expressed thrombocytopenia–absent radius (TAR) syndrome, including hypereosinophilia and anemia. Hypoplasia of the distal humeri and the shoulder girdles, bilateral hip dysplasia, mild talipes calcaneus, and clinodactyly of both little fingers are seen. This patient had a pronounced allergy to cow's milk, with exposure followed by diarrhea, vomiting, and decreased weight and platelet count, making a cow's milk–free diet

mandatory. A persistent depressed nasal bridge and development of pronounced bowed legs are seen. (From Wiedemann H-R, Kunze J, Grosse F-R, editors: *Clinical syndromes,* ed 3, [English translation], London, 1997, Mosby-Wolfe, p 430.)

Wiskott-Aldrich syndrome (WAS) is characterized by thrombocytopenia, with tiny platelets, eczema, and recurrent infection as a consequence of immune deficiency (see Chapter 152.2). WAS is inherited as an X-linked disorder, and the gene for WAS has been sequenced. The WAS protein appears to play an integral role in regulating the cytoskeletal architecture of both platelets and T lymphocytes in response to receptor-mediated cell signaling. The WAS protein is common to all cells of hematopoietic lineage. Molecular analysis of families with X-linked thrombocytopenia has shown that many affected members have a point mutation within the WAS gene, whereas individuals with the full manifestation of WAS have large gene deletions. Examination of the bone marrow in WAS shows the normal number of megakaryocytes, although they may have bizarre morphologic features. Transfused platelets have a normal life span. Splenectomy often corrects the thrombocytopenia, suggesting that the platelets formed in WAS have accelerated destruction. After splenectomy, these patients are at increased risk for overwhelming infection and require lifelong antibiotic prophylaxis against encapsulated organisms. Approximately 5–15% of patients with WAS develop lymphoreticular malignancies. Successful HSCT cures WAS. **X-linked macrothrombocytopenia** and **dyserythropoiesis** have been linked to mutations in the *GATA1* gene, an erythroid and megakaryocytic transcription factor.

MYH9-related thrombocytopenia comprises a number of diverse hereditary thrombocytopenia syndromes (e.g., Sebastian, Epstein, May-Hegglin, Fechtner) characterized by autosomal dominant macrothrombocytopenia, neutrophil inclusion bodies, and a variety of physical anomalies, including sensorineural deafness, renal disease, and eye disease. These have all been shown to be caused by different mutations in the *MYH9* gene (nonmuscle myosin-IIa heavy chain). The thrombocytopenia is usually mild and not progressive. Some other individuals with recessively inherited macrothrombocytopenia have abnormalities in chromosome 22q11. Mutations in the gene for glycoprotein Ibβ, an essential component of the platelet VWF receptor, can result in **Bernard-Soulier syndrome** (see Chapter 511.13).

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511.9

Neonatal Thrombocytopenia

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Keywords

maternal ITP
NATP
neonatal alloimmune thrombocytopenia

See also Chapter 124.4 .

Thrombocytopenia in the newborn rarely is indicative of a primary disorder of megakaryopoiesis. It is usually the result of systemic illness or transfer of maternal antibodies directed against fetal platelets (see Table 511.2). Neonatal thrombocytopenia often occurs in association with congenital viral infections, especially rubella, cytomegalovirus, protozoal infection (e.g., toxoplasmosis), and syphilis, and perinatal bacterial infections, especially those caused by gram-negative bacilli. Thrombocytopenia associated with DIC may be responsible for severe spontaneous bleeding. The constellation of marked thrombocytopenia and abnormal abdominal findings is common in necrotizing enterocolitis and other causes of necrotic bowel. Thrombocytopenia in an ill child requires a prompt search for viral and bacterial pathogens.

Antibody-mediated thrombocytopenia in the newborn occurs because of transplacental transfer of maternal antibodies directed against fetal platelets. **Neonatal alloimmune thrombocytopenic purpura (NATP)** is caused by the development of maternal antibodies against antigens present on fetal platelets that are shared with the father and recognized as foreign by the maternal immune system. This is the platelet equivalent of *Rh disease of the newborn* . The incidence of NATP is 1 in 4,000-5,000 live births. The clinical manifestations of NATP are those of an apparently well child who, within the 1st few days after delivery, has generalized petechiae and purpura. Laboratory studies show a normal maternal platelet count but moderate to severe thrombocytopenia in the newborn. Detailed review of the history should show no evidence of maternal thrombocytopenia. Up to 30% of infants with severe NATP may have ICH, either prenatally or in the perinatal period. Unlike Rh disease, first pregnancies may be severely affected. Subsequent pregnancies are often more severely affected than the first.

The **diagnosis** of NATP is made by checking for the presence of maternal alloantibodies directed against the father's platelets. Specific studies can be done to identify the target alloantigen. The most common cause is incompatibility for the platelet alloantigen HPA-1a. Specific DNA sequence polymorphisms have been identified that permit informative prenatal testing to identify at-risk pregnancies. The differential diagnosis of NATP includes transplacental transfer of maternal antiplatelet autoantibodies (maternal ITP), and, more commonly, viral or bacterial infection.

Treatment of NATP requires the administration of IVIG prenatally to the mother. Therapy usually begins in the second trimester and is continued throughout the pregnancy. Fetal platelet count can be monitored by percutaneous umbilical blood sampling. Delivery should be performed by cesarean section. After delivery, if severe thrombocytopenia persists, transfusion of 1 unit of platelets that share the maternal alloantigens (e.g., washed maternal platelets) will cause a rise in platelet counts to provide effective hemostasis. However, a random donor platelet transfusion is more likely to be readily available. Some centers have units available that may lack the antigens most often involved. After there has been one affected child, genetic counseling is critical to inform the parents of the high risk of thrombocytopenia in subsequent pregnancies.

Children born to mothers with idiopathic thrombocytopenic purpura **(maternal ITP)** appear to have a lower risk of serious hemorrhage than infants born with NATP, although severe thrombocytopenia may occur. The mother's preexisting platelet count may have some predictive value in that severe maternal thrombocytopenia before delivery appears to predict a higher risk of fetal thrombocytopenia. In mothers who have had splenectomy for ITP, the maternal platelet count may be normal and is not predictive of fetal thrombocytopenia.

Treatment includes prenatal administration of corticosteroids to the mother and IVIG and sometimes corticosteroids to the infant after delivery. Thrombocytopenia in an infant, whether a result of NATP or maternal ITP, usually resolves within 2-4 mo after delivery. The period of highest risk is the immediate perinatal period.

Two syndromes of congenital failure of platelet production often present in the newborn period. In **CAMT** the newborn manifests petechiae and purpura shortly after birth. Findings on physical examination are otherwise normal. Megakaryocytes are absent from the bone marrow. This syndrome is caused by a mutation in the megakaryocyte TPO receptor that is essential for development of all hematopoietic cell lines. Pancytopenia eventually develops, and HSCT is curative. **TAR syndrome** consists of thrombocytopenia that presents in early infancy, with bilateral radial anomalies of variable severity, ranging from mild changes to marked limb shortening. It frequently remits over the 1st few yr of life (see Chapter 511.8 and Fig. 511.4).

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511.10

Thrombocytopenia From Acquired Disorders Causing Decreased Production

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Keywords

aplastic anemia
leukemia
thrombocytopenia

Disorders of the bone marrow that inhibit megakaryopoiesis usually affect RBC and WBC production. Infiltrative disorders, including malignancies, such as acute lymphocytic leukemia, histiocytosis, lymphomas, and storage disease, usually cause either abnormalities on physical examination (lymphadenopathy, hepatosplenomegaly, or masses) or abnormalities of the WBC count, or anemia. Aplastic processes may present as isolated thrombocytopenia, although there are usually clues on the CBC (leukopenia, neutropenia, anemia, or macrocytosis). Children with constitutional aplastic anemia (Fanconi anemia) often (but not always) have abnormalities on examination, including radial anomalies, other skeletal anomalies, short stature, microcephaly, and hyperpigmentation. Bone marrow examination should be performed when thrombocytopenia is associated with abnormalities found on physical examination or on examination of the other blood cell lines.

511.11

Platelet Function Disorders

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Keywords

bleeding time
PFA-000
platelet function

There is no simple and reliable test to screen for abnormal platelet function. Bleeding time and the platelet function analyzer (PFA-100) have been used in the past, but neither has sufficient sensitivity or specificity to rule in or rule out a platelet defect. Bleeding time measures the interaction of platelets with the blood vessel wall and thus is affected by both platelet count and platelet function. The predictive value of bleeding time is problematic because bleeding time is dependent on a number of other factors, including the technician's skill and the patient's cooperation, often a challenge in the infant or young child. The PFA-100 measures platelet adhesion and aggregation in whole blood at high shear when the blood is exposed to either collagen-epinephrine or collagen-ADP. Results are reported as the closure time in seconds. The use of the PFA-100 as a screening test remains controversial and, like the bleeding time, lacks specificity. For patients with a positive history of bleeding suggestive of von Willebrand disease or platelet dysfunction, specific VWF testing and platelet function studies should be done, irrespective of the results of the bleeding time or PFA-100.

Platelet function in the clinical laboratory is measured using platelet aggregometry. In the aggregometer, agonists, such as collagen, ADP, ristocetin, epinephrine, arachidonic acid, and thrombin (or the thrombin receptor peptide), are added to platelet-rich plasma, and the clumping of platelets over time is measured by an automated machine. At the same time, other instruments measure the release of granular contents, such as ATP, from the platelets after activation. The ability of platelets to aggregate and their metabolic activity can be assessed simultaneously. When a patient is being evaluated for possible platelet dysfunction, it is critically important to exclude the presence of other exogenous agents and to study the patient, if possible, off all medications for 2 wk. Further evaluation using flow cytometric analysis or molecular testing is often necessary to make a more definitive diagnosis.

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511.12

Acquired Disorders of Platelet Function

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Keywords

aspirin
thrombocytopenia
uremia

A number of systemic illnesses are associated with platelet dysfunction, most frequently liver disease, kidney disease (uremia), and disorders that trigger increased amounts of fibrin degradation products. These disorders frequently cause prolonged bleeding time and are often associated with other abnormalities of the coagulation mechanism. *The most important element of management is to treat the primary illness.* If treatment of the primary process is not feasible, infusions of desmopressin have been helpful in augmenting hemostasis and correcting bleeding time. In some patients, transfusions of platelets and cryoprecipitate have also been helpful in improving hemostasis.

Many drugs alter platelet function. The most common drug in adults that alters platelet function is acetylsalicylic acid (*aspirin*). Aspirin irreversibly acetylates the enzyme cyclooxygenase, which is critical in the formation of thromboxane A_2 . Aspirin usually causes moderate platelet dysfunction that becomes more prominent if there is another abnormality of the hemostatic mechanism. In children, common drugs that affect platelet function include other nonsteroidal antiinflammatory drugs (NSAIDs), valproic acid, and high-dose penicillin. Specific agents to inhibit platelet function therapeutically include those that block the platelet ADP receptor (clopidogrel) and αIIb-β_3 receptor antagonists, as well as aspirin.

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511.13

Congenital Abnormalities of Platelet Function

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Keywords

Bernard-Soulier syndrome
dense body deficiency
Glanzmann thrombasthenia
gray platelet syndrome
Hermansky-Pudlak syndrome
MYH9
Quebec platelet syndrome
thrombocytopenia

Severe platelet function defects usually present with petechiae and purpura shortly after birth, especially after vaginal delivery. Defects in the platelet GPIb complex (the VWF receptor) or the αIIb-β_3 complex (the fibrinogen receptor) cause severe congenital platelet dysfunction. Although laboratory tests of platelet function are available, molecular characterization by genetic testing is rapidly progressing for platelet disorders.

Bernard-Soulier syndrome , a severe congenital platelet function disorder, is caused by absence or severe deficiency of the VWF receptor on the platelet membrane. This syndrome is characterized by thrombocytopenia, with giant platelets and greatly prolonged bleeding time (>20 min) or PFA-100 closure time. Patients may have significant mucocutaneous and gastrointestinal (GI) bleeding. Platelet aggregation tests show absent ristocetin-induced platelet aggregation but normal aggregation to all other agonists. Ristocetin induces the binding of VWF to platelets and agglutinates platelets. Results of studies of VWF are normal. The GPIb complex interacts with the platelet cytoskeleton; a defect in this interaction is believed to be the cause of the large platelet size. Bernard-Soulier syndrome is inherited as an autosomal recessive disorder. Causative genetic mutations are usually identified in the genes forming the GPIb complex of glycoproteins Ibα, Ibβ, V, and IX.

Glanzmann thrombasthenia is a congenital disorder associated with severe platelet dysfunction that yields prolonged bleeding time and a normal platelet count. Platelets have normal size and morphologic features on the peripheral blood smear, and closure times for PFA-100 or bleeding time are extremely abnormal. Aggregation studies show abnormal or absent aggregation with all agonists used except ristocetin, because ristocetin agglutinates platelets and does not require a metabolically active platelet. This disorder is caused by deficiency of the platelet fibrinogen receptor αIIb-β_3 , the major integrin complex on the platelet surface that undergoes conformational changes by inside-out signaling when platelets are activated. Fibrinogen binds to this complex when the platelet is activated and causes platelets to aggregate. Glanzmann thrombasthenia is caused by identifiable mutations in the genes for αIIb or β_3 and is inherited in an autosomal recessive manner. For both Bernard-Soulier syndrome and Glanzmann thrombasthenia, the **diagnosis** is confirmed by flow cytometric analysis of the patient's platelet glycoproteins. Bleeding in Glanzmann thrombasthenia may be quite severe and is typically mucocutaneous, including epistaxis, gingival, and GI bleeding. There are reports of curative therapy using stem cell transplant.

Hereditary deficiency of platelet storage granules occurs in 2 well-characterized but rare syndromes that involve deficiency of intracytoplasmic granules. **Dense body deficiency** is characterized by absence of the granules that contain ADP, ATP, Ca^{2+} , and serotonin. This disorder is diagnosed by the finding that ATP is not released on platelet aggregation studies and ideally is characterized by electron microscopic studies. **Hermansky-Pudlak syndrome** (with 9 subtypes) is a dense granule deficiency caused by defects in lysosomal storage. Affected patients present with oculocutaneous albinism and hemorrhage caused by the platelet defect; some patients also develop granulomatous colitis resembling Crohn disease or pulmonary fibrosis/interstitial lung disease (Table 511.5). **Chédiak-Higashi syndrome** also presents with a dense granule defect, immune dysfunction, and albinism (see Chapter 156). **Gray platelet syndrome** is caused by the absence of platelet α granules, resulting in large platelets that are large and appear gray on Wright stain of peripheral blood. In this rare syndrome, aggregation and release are absent with most agonists other than thrombin and ristocetin. Electron microscopic studies are diagnostic. Autosomal recessive gray platelet syndrome is mapped to defects in the *NBEAL2* gene, while autosomal dominant disease is associated with a mutation in *GFI1B* . **Quebec platelet syndrome** is caused by degradation of platelet α granules caused by defects in *PLAU* , a urokinase-type plasminogen activator. Treatment usually involves antifibrinolytic therapy.

Table 511.5

Comparison of 9 Types of Hermansky-Pudlak Syndrome

	1	2	3	4	5	6	7	8
Oculocutaneous albinism	Variable, mild-moderate: brown to white hair	Severe: lack of hair and iris pigment	Mild-moderate: light skin pigment	Severe: blonde hair, gray iris	Variable: light-brown hair, brown iris	Variable: iris heterochromia	Variable	V t s h b i
Platelet defect/bruising	+	+	+	+	+	+	+	+
Granulomatous colitis	+	−	−	+	−	+	+	-
Pulmonary fibrosis/ILD	+	+	−	+	−	−	−	-
Other symptoms		Neutropenia Failure to thrive Hypothyroidism CAH		Depression	High cholesterol			

+ , Present; −, absent; CAH, congenital adrenal hyperplasia; ILD, interstitial lung disease.

Other Hereditary Disorders of Platelet Function

Abnormalities in the pathways of platelet signaling/activation and release of granular contents cause a heterogeneous group of platelet function defects that are usually manifested as increased bruising, epistaxis, and menorrhagia. Symptoms may be subtle and are often made more obvious by high-risk surgery, such as tonsillectomy or adenoidectomy, or by administration of NSAIDs. In the laboratory, bleeding time is variable, and closure time as measured by the PFA-100 is frequently, but not always, prolonged. Platelet aggregation studies show deficient aggregation with 1 or 2 agonists and/or abnormal release of granular contents.

The formation of thromboxane from arachidonic acid (AA) after the activation of phospholipase is critical to normal platelet function. Deficiency or dysfunction of enzymes, such as cyclooxygenase and thromboxane synthase, which metabolize AA, causes abnormal platelet function. In the aggregometer, platelets from such patients do not aggregate in response to AA.

The most common platelet function defects are those characterized by variable bleeding time/PFA closure times and abnormal aggregation with 1 or 2 agonists, usually ADP and/or collagen. Some of these individuals have only decreased release of ATP from intracytoplasmic granules; the significance of this finding is debated.

Treatment of Patients With Platelet Dysfunction

Successful treatment depends on the severity of both the diagnosis and the hemorrhagic event. In all but severe platelet function defects, desmopressin, 0.3 µg/kg intravenously, may be used for mild to moderate bleeding episodes. In addition to its effect on stimulating levels of VWF and factor VIII, desmopressin corrects bleeding time and augments hemostasis in many individuals with mild to moderate platelet function defects. Antifibrinolytic therapy may be useful for mucosal bleeds. For individuals with Bernard-Soulier syndrome or Glanzmann thrombasthenia, platelet transfusions of 0.5-1 unit single donor platelets correct the defect in hemostasis and may be lifesaving. Rarely, antibodies develop to the deficient platelet protein, rendering the patient refractory to the transfused platelets. In such patients, the off-label use of recombinant factor VIIa has been effective, and this treatment is undergoing clinical trials. In both conditions, HSCT has been curative.

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511.14

Disorders of the Blood Vessels

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Keywords

collagen
platelet

vasculitis
vasculopathy

Disorders of the vessel walls or supporting structures mimic the findings of a bleeding disorder, although coagulation studies are usually normal. The findings of petechiae and purpuric lesions in such patients are often attributable to an underlying vasculitis or vasculopathy. Skin biopsy can be particularly helpful in elucidating the type of vascular pathology.

Henoch-Schönlein Purpura

See Chapter 192.1 .

Ehlers-Danlos Syndrome

See Chapter 679 .

Other Acquired Disorders

Scurvy, chronic corticosteroid therapy, and severe malnutrition are associated with “weakening” of the collagen matrix that supports the blood vessels. Therefore, these factors are associated with easy bruising, and particularly in the case of scurvy, bleeding gums and loosening of the teeth. Lesions of the skin that initially appear to be petechiae and purpura may be seen in vasculitic syndromes, such as SLE.

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SECTION 8

The Spleen

OUTLINE

Chapter 512 Anatomy and Function of the Spleen
Chapter 513 Splenomegaly
Chapter 514 Hyposplenism, Splenic Trauma, and Splenectomy

CHAPTER 512

Anatomy and Function of the Spleen

Amanda M. Brandow, Bruce M. Camitta

Anatomy

The splenic precursor is recognizable by 5 wk of gestation. At birth, the spleen weighs approximately 11 g. Thereafter, it enlarges until puberty, reaching an average weight of 135 g, and then diminishes in size during adulthood. Approximately 15% of patients will have an accessory spleen. The major splenic components are a lymphoid compartment *(white pulp)* and a filtering system *(red pulp)* . The white pulp consists of periarterial lymphatic sheaths of T lymphocytes with embedded germinal centers containing B lymphocytes. The red pulp has a skeleton of fixed reticular cells, mobile macrophages, partially collapsed endothelial passages (cords of Billroth), and splenic sinuses. A *marginal zone* rich in dendritic (antigen-presenting) cells separates the red pulp from the white pulp. The splenic capsule contains smooth muscle and contracts in response to epinephrine. Approximately 10% of the blood delivered to the spleen flows rapidly through a closed vascular network. The other 90% flows more slowly through an open system (the *splenic cords*), where it is filtered through 1-5 µm slits before entering the splenic sinuses.

Function

The unique anatomy and blood flow of the spleen enable it to perform reservoir, filtering, and immunologic functions. The spleen receives 5–6% of the cardiac output but normally contains only 25 mL of blood. It can retain much more when it enlarges, leading to **cytopenias** . Hematopoiesis is a major splenic function at 3-6 mo of fetal life but then disappears. *Splenic hematopoiesis* can be resumed in patients with myelofibrosis or severe hemolytic anemia. Factor VIII and one third of the circulating platelet mass are sequestered in the spleen and can be released by stress or epinephrine injection. **Thrombocytosis** and **leukocytosis** occur with loss of the splenic reservoir function. A high platelet count after the loss of splenic function or splenectomy is not associated with an increased risk of thrombosis in children.

Slow blood flow past macrophages and through small openings in the sinus walls facilitates the filtering functions of the spleen. Excess membrane is removed from young red blood cells (RBCs); loss of this function is characterized by target cells, poikilocytosis, and decreased osmotic fragility. The spleen is the primary site for destruction of old RBCs; this function is assumed by other reticuloendothelial cells after splenectomy. The spleen also removes damaged/abnormal RBCs (e.g., spherocytes, antibody-coated RBCs) and damaged/senescent platelets. Intracytoplasmic inclusions may be removed from RBCs without cell lysis. Functional or anatomic hyposplenia is characterized by continued circulation of cells containing nuclear remnants (**Howell-Jolly bodies**), denatured hemoglobin (**Heinz bodies**), and other debris in RBCs. This debris may appear as “pits” on indirect microscopy.

The spleen plays a large role in host defense against infection. The spleen is the largest lymphoid organ in the body and contains almost half the body's total immunoglobulin-producing B lymphocytes. The spleen processes foreign material to stimulate production of opsonizing antibody. Properdin and tuftsin are also produced in the spleen. Thus, young (nonimmune) or hyposplenic individuals are at increased risk for **sepsis** caused by pneumococci and other encapsulated bacteria. The spleen can also use phagocytosis to trap and destroy intracellular parasites. The spleen has a minor role in antibody response to intramuscularly or subcutaneously injected antigens but is required for early antibody production after exposure to intravenous antigens. The spleen may be an important site of antibody production in **immune thrombocytopenia purpura** .

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CHAPTER 513

Splenomegaly

Amanda M. Brandow, Bruce M. Camitta

Clinical Manifestations

A soft, thin spleen is palpable in 15% of neonates, 10% of normal children, and 5% of adolescents. In most individuals, the spleen must be 2-3 times its normal size before it is palpable. The spleen is best examined when standing on the right side of a supine patient by palpating across the abdomen as the patient inspires deeply or with the patient in the right lateral decubitus position. A splenic edge felt more than 2 cm below the left costal margin is abnormal. An enlarged spleen might descend into the pelvis; when splenomegaly is suspected, the abdominal examination should begin at a lower starting point. Superficial abdominal venous distention may be present when splenomegaly is a result of portal hypertension. Patients may also complain of left upper quadrant pain as the spleen enlarges. Radiologic detection or confirmation of splenic enlargement is done with ultrasonography, CT, or technetium-99m sulfur colloid scan. The latter also assesses splenic function.

Differential Diagnosis

Table 513.1 lists specific causes of splenomegaly. A thorough history with a focus on systemic complaints (fever, night sweats, malaise, weight loss) and a complete physical examination (with special attention to adenopathy), in combination with a complete blood count and careful review of the peripheral smear, can help guide diagnosis.

Table 513.1

Differential Diagnosis of Splenomegaly by Pathophysiology

ANATOMIC LESIONS

Cysts, pseudocysts
Hamartomas
Polysplenia syndrome
Hemangiomas and lymphangiomas
Hematoma or rupture (traumatic)
Peliosis

HYPERPLASIA CAUSED BY HEMATOLOGIC DISORDERS

Acute and Chronic Hemolysis *

Hemoglobinopathies (sickle cell disease in infancy with or without sequestration crisis and sickle variants, thalassemia major, unstable hemoglobins)
Erythrocyte membrane disorders (hereditary spherocytosis, elliptocytosis, pyropoikilocytosis)
Erythrocyte enzyme deficiencies (severe G6PD deficiency, pyruvate kinase deficiency)
Immune hemolysis (autoimmune and isoimmune hemolysis)
Paroxysmal nocturnal hemoglobinuria

Chronic Iron Deficiency

Extramedullary Hematopoiesis

Myeloproliferative diseases: CML, juvenile CML, myelofibrosis with myeloid metaplasia, polycythemia vera
Osteopetrosis
Patients receiving granulocyte and granulocyte-macrophage colony-stimulating factors

INFECTIONS †

Bacterial

Acute sepsis: *Salmonella typhi*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Staphylococcus aureus*
Chronic infections: infective endocarditis, chronic meningococcemia, brucellosis, tularemia, cat-scratch disease
Local infections: splenic abscess (*S. aureus*, streptococci, less often *Salmonella* spp., polymicrobial infection), pyogenic liver abscess (anaerobic bacteria, gram-negative enteric bacteria), cholangitis

Viral *

Acute viral infections
Congenital CMV, herpes simplex, rubella
Hepatitides A, B, and C; CMV
EBV
Viral hemophagocytic syndromes: CMV, EBV, HHV-6
HIV

Spirochetal

Syphilis, especially congenital syphilis
Leptospirosis

Rickettsial

Rocky Mountain spotted fever
Q fever
Typhus

Fungal/Mycobacterial

Miliary tuberculosis
Disseminated histoplasmosis
South American blastomycosis
Systemic candidiasis (in immunosuppressed patients)

Parasitic

Malaria
Toxoplasmosis, especially congenital
Toxocara canis, *Toxocara cati* (visceral larva migrans)
Leishmaniasis (kala-azar)

Schistosomiasis (hepatic-portal involvement)
Trypanosomiasis
Fascioliasis
Babesiosis

IMMUNOLOGIC AND INFLAMMATORY PROCESSES [*]

Systemic lupus erythematosus
Juvenile idiopathic arthritis
Mixed connective tissue disease
Systemic vasculitis
Serum sickness
Drug hypersensitivity, especially to phenytoin
Graft-versus-host disease
Sjögren syndrome
Cryoglobulinemia
Amyloidosis
Sarcoidosis
Autoimmune lymphoproliferative syndrome
Posttransplant lymphoproliferative disease
Large granular lymphocytosis and neutropenia
Histiocytosis syndromes
Hemophagocytic syndromes (nonviral, familial)

MALIGNANCIES

Primary: leukemia (acute, chronic), lymphoma, angiosarcoma, Hodgkin disease, mastocytosis
Metastatic

STORAGE DISEASES

Lipidosis (Gaucher disease, Niemann-Pick disease, infantile GM1 gangliosidosis)
Mucopolysaccharidoses (Hurler, Hunter-type)
Mucolipidosis (I-cell disease, sialidosis, multiple sulfatase deficiency, fucosidosis)
Defects in carbohydrate metabolism: galactosemia, fructose intolerance, glycogen storage disease IV
Sea-blue histiocyte syndrome
Tangier disease
Wolman disease
Hyperchylomicronemia type I, IV

CONGESTIVE DISEASE [*]

Heart failure
Intrahepatic cirrhosis or fibrosis
Extrahepatic portal (thrombosis), splenic, and hepatic vein obstruction (thrombosis, Budd-Chiari syndrome)

[*] Common.

[†] Chronic or recurrent infection suggests underlying immunodeficiency.

CML, Chronic myelogenous leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; G6PD, glucose-6-phosphate dehydrogenase; HHV-6, human herpesvirus 6; HIV, human immunodeficiency virus.

Pseudosplenomegaly

Abnormally long mesenteric connections may produce a *wandering* or ptotic spleen. An enlarged left lobe of the liver, a left upper quadrant mass, or a splenic hematoma may be mistaken for splenomegaly. Splenic **cysts** may contribute to splenomegaly or mimic it; these may be congenital (epidermoid) or acquired (pseudocyst) after trauma or infarction. Cysts are usually asymptomatic and are found on radiologic evaluation. **Splenosis** after splenic rupture or an accessory spleen (present in 15% of normal individuals) may also mimic splenomegaly; most are not palpable. The syndrome of **congenital polysplenism** includes cardiac defects, left-sided organ anomalies, bilobed lungs, biliary atresia, and pseudosplenomegaly (see Chapter 458.11).

Hypersplenism

Increased splenic function (sequestration or destruction of circulating cells) can result in peripheral blood **cytopenias** (thrombocytopenia, neutropenia, anemia), increased bone marrow activity, and splenomegaly. It is usually secondary to another disease and may be cured by treatment of the underlying condition or, if absolutely necessary, may be moderated by splenectomy.

Congestive Splenomegaly (Banti Syndrome)

Splenomegaly may result from obstruction in the hepatic, portal, or splenic veins leading to hypersplenism. Wilson disease (see Chapter 384.2), galactosemia (see Chapter 105.2), biliary atresia (see Chapter 383.1), and α_1 -antitrypsin deficiency (see Chapter 384) may result in hepatic inflammation, fibrosis, and vascular obstruction. Congenital abnormalities (absence or hypoplasia) of the portal or splenic veins may cause vascular obstruction. Septic omphalitis or thrombophlebitis (spontaneous or as a result of umbilical venous catheterization in neonates) may result in secondary obliteration of these vessels. Splenic venous flow may be obstructed by masses of sickled erythrocytes leading to infarction. When the spleen is the site of vascular obstruction, splenectomy cures hypersplenism. However, since obstruction usually is in the hepatic or portal systems, **portacaval shunting** may be more helpful, because both portal hypertension and thrombocytopenia contribute to variceal bleeding.

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CHAPTER 514

Hyposplenism, Splenic Trauma, and Splenectomy

Amanda M. Brandow, Bruce M. Camitta

Hyposplenism

Congenital absence of the spleen is associated with complex cyanotic heart defects, dextrocardia, bilateral trilobed lungs, and heterotopic abdominal organs (**Ivemark syndrome** ; see Chapter 458.11). Splenic function is usually normal in children with congenital polysplenia. **Functional hyposplenism** may occur in normal neonates, especially premature infants. Children with sickle cell hemoglobinopathies (see Chapter 489.1) may have splenic hypofunction as early as 6 mo of age. The spleen eventually autoinfarcts and becomes fibrotic and permanently nonfunctional. Functional hyposplenism may also occur in malaria (see Chapter 314), after irradiation to the left upper quadrant, and when the reticuloendothelial function of the spleen is overwhelmed (as in severe hemolytic anemia or metabolic storage disease). Splenic hypofunction has been reported occasionally in patients with autoimmune diseases (i.e., juvenile idiopathic arthritis, lupus, sarcoidosis), nephritis, inflammatory bowel disease, celiac disease, chronic hepatitis, Pearson syndrome, Fanconi anemia, and graft-versus-host disease (Table 514.1).

Table 514.1

Diseases Associated With Hyposplenism or Splenic Atrophy

CONGENITAL FORMS	AUTOIMMUNE DISORDERS
Normal and premature neonates	Systematic lupus erythematosus
Isolated congenital hypoplasia	Juvenile idiopathic arthritis

Ivemark syndrome Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome Hypoparathyroidism syndrome Stormorken syndrome Heterotaxia syndromes	Glomerulonephritis Granulomatosis with polyangiitis Goodpasture syndrome Sjögren syndrome Polyarteritis nodosa Thyroiditis Sarcoidosis
GASTROINTESTINAL DISORDERS	**INFECTIOUS DISEASES** HIV/AIDS Pneumococcal meningitis Malaria
Celiac disease Inflammatory bowel disease Whipple disease Dermatitis herpetiformis Intestinal lymphangiectasia Idiopathic chronic ulcerative enteritis	
HEPATIC DISORDERS	**IATROGENIC FORMS**
Active chronic hepatitis Primary biliary cirrhosis Hepatic cirrhosis and portal hypertension Alcoholism and alcoholic hepatopathy	Exposure to methyldopa High-dose steroids Total parenteral nutrition Splenic irradiation
HEMATOLOGIC AND ONCOLOGIC DISORDERS	**ALTERATION IN SPLENIC CIRCULATION**
Sickle cell disease (all genotypes) Bone marrow transplantation Chronic graft-versus-host disease Acute leukemia Chronic myeloproliferative disorders Fanconi syndrome Splenic tumors Mastocytosis	Thrombosis of splenic artery Thrombosis of splenic vein Thrombosis of celiac artery
	MISCELLANEOUS
	Amyloidosis

From Di Sabatino A, Carsetti R, Corazza GR: Post-splenectomy and hyposplenic states, *Lancet* 378(9785):86–97, 2011.

Splenic hypofunction is characterized by **RBC inclusions** in peripheral blood smears (Howell-Jolly or Heinz bodies), “pits**”** on interference microscopy, and poor uptake of technetium or other spleen scans (Table 514.2 and Fig. 514.1). Reduced immunoglobulin M memory B cells may also be detected and is a risk factor for overwhelming **sepsis** . Patients with functional hyposplenism or asplenia are at increased risk for sepsis from **encapsulated bacteria** and benefit from antibiotic prophylaxis and urgent evaluation when febrile.

Table 514.2

Diagnostic Techniques for and Features of Spleen Dysfunction

	DESCRIPTION	COMMENTS
Immunoglobulin M memory B cells	Cells dependent on spleen for survival. Produced in marginal zone.	Special tests required
Technetium-99m–labeled sulfur colloidal	Quantitation of splenic uptake of colloidal sulfur	Hypertrophy of the left hepatic lobe might be a limiting factor (this technique does not clearly show whether the

scintiscan	particles enables a fairly accurate static assessment of spleen function.	mass originated in the liver or the spleen in the presence of an overlapping hypertropic left hepatic lobe).
Technetium-99m–labeled or rubidium-81–labeled heat-damaged autologous erythrocyte clearance	Measurement of clearance time allows a dynamic evaluation of spleen function.	Preexisting erythrocyte defects, difficult erythrocyte incorporation of the radioisotope, and false-positive or false-negative results in relation to excessive or insufficient heat damage make the test not suitable for clinical practice.
Detection of Howell-Jolly bodies by staining	Erythrocytes with nuclear remnants Flow cytometry	No need for special equipment; inaccurate in the quantitation of splenic hypofunction.
Detection of pitted erythrocytes by phase-interference microscopy	Erythrocytes with membrane indentations (4% upper limit of the normal range)	Need for phase-interference microscopy; counts enable a wide range of measurements and correlate with radioisotopic methods.

From Di Sabatino A, Carsetti R, Corazza GR: Post-splenectomy and hyposplenic states, *Lancet* 378(9785):86-97, 2011 (Table 1).

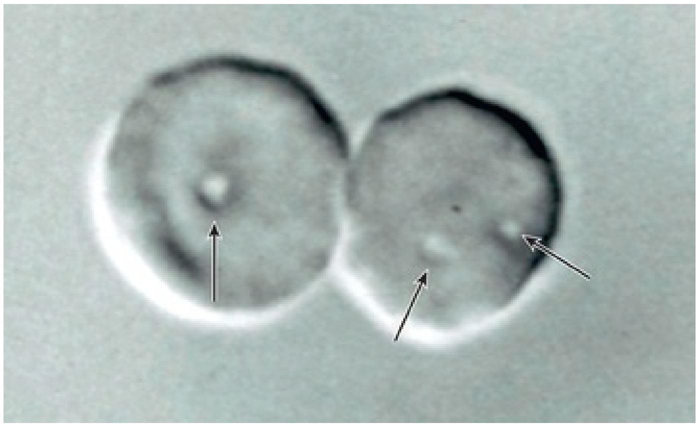

FIG. 514.1 Characteristic pitted erythrocytes in hyposplenism. A pitted erythrocyte is recognizable on phase-interference microscopy by the characteristic "pit" on the cell membrane *(arrows)* . (From Di Sabatino A, Carsetti R, Corazza GR: Post-splenectomy and hyposplenic states, *Lancet* 378[9785]:86-97, 2011, Fig 2.)

Splenic Trauma

Injury to the spleen may occur with abdominal trauma. Small splenic capsular tears may cause abdominal or referred left shoulder pain as a result of diaphragmatic irritation by blood. Larger tears result in more severe blood loss, with similar pain and signs of **hypovolemic shock** . Previously enlarged spleens (as in patients with infectious mononucleosis) are more likely to rupture with minor trauma. *Patients with splenomegaly should avoid contact sports and other* *activities that increase the risk of splenic trauma.* CT scan with intravenous contrast is the best imaging modality to assess splenic trauma.

Treatment of a small capsular injury should include careful observation with attention to changes in vital signs or abdominal findings, serial hemoglobin determinations, and the availability of prompt surgical intervention if a patient's condition deteriorates (see Chapter 82). RBC transfusion requirements should be minimal (<25 mL/kg/48 hr). These patients are usually hospitalized for 10-14 days and have their activities restricted for months. Laparotomy, with or without splenectomy, is indicated for more marked abdominal bleeding, in patients who have clinical instability or deterioration, or when other organ damage is suspected. Partial splenectomy and splenic repair should be substituted for total splenectomy when feasible to maintain some splenic immune function.

Splenectomy

Splenectomy should be limited to specific indications where medical therapy is (or has been) ineffective. These include traumatic splenic rupture, anatomic defects, severe transfusion-dependent hemolytic anemia, immune-mediated cytopenias, metabolic storage diseases, and secondary hypersplenism. *The major long-term risk of splenectomy is sudden, overwhelming postsplenectomy infections (sepsis or meningitis).* This risk is especially high in children <5 yr old at surgery. The risk of sepsis is less when splenectomy is performed for trauma, RBC membrane defects, and immune thrombocytopenia (2–4%) than when there is sickle cell anemia, thalassemia, or a preexisting immune deficiency (Wiskott-Aldrich syndrome, Hodgkin disease) or reticuloendothelial blockade (storage disease, severe hemolytic anemia) (8–30%). The overall risk is 2-5 per 1,000 asplenic patient-years, with a lifelong risk of overwhelming postsplenectomy infections of 5%; more than half occur within 2 yr after splenectomy, although the risk remains lifelong. The use of laparoscopic splenectomy has decreased surgical morbidity and hospitalization time.

Encapsulated bacteria, such as *Streptococcus pneumoniae* (>60% of cases), *Haemophilus influenzae*, and *Neisseria meningitidis*, account for >80% of cases of postsplenectomy sepsis. Because the spleen is responsible for filtering the blood and for early antibody responses, sepsis (with or without meningitis) can progress rapidly, leading to death within 12-24 hr of onset. Febrile splenectomized patients should be evaluated and treated promptly with antibiotics to cover the organisms previously mentioned. This treatment should be initiated at home if access to definitive medical care will be delayed. A broad-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended until specific antibiotic susceptibility and presence or absence of meningitis is known. Vancomycin (to cover penicillin-resistant pneumococci) should be initiated, depending on the illness severity and susceptibilities of pneumococci at the institution. Splenectomized patients are also at increased risk for contracting protozoal infections, such as malaria and babesiosis. Serious infection may occur after an animal bite (particularly dogs) and is caused by *Capnocytophaga canimorsus* or *C. cynodegmi* . Prophylactic antibiotics should be given after a bite potentially to prevent sepsis caused by these organisms (see Chapter 743).

Preoperative, intraoperative, and postoperative management may decrease the risk of postsplenectomy infection. It is important to be certain of the need for splenectomy and, if possible, to postpone the operation until the patient is ≥5 yr of age. *Pneumococcal, meningococcal, and H. influenzae conjugate vaccines given at least 14 days before splenectomy may reduce postsplenectomy sepsis.* The 7-valent (PCV7) was replaced by the 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13). Thus, depending on what primary pneumococcal vaccine was given, a single dose of PCV13 may be recommended. In addition, the 23-valent pneumococcal polysaccharide vaccine (Pneumovax) should be given at age ≥2 yr and a 2nd dose 5 yr later. Yearly influenza vaccine should also be given, because influenza infection is a risk factor for secondary pneumococcal infections. Prophylaxis with oral penicillin VK (125 mg twice daily for children <5 yr old; 250 mg twice daily for children ≥5 yr) should be given until at least 5 yr of age and for at least 2 yr after splenectomy. Although the greatest risk is in the immediate postoperative period, reports of deaths occurring years after splenectomy suggest that the risk (and the need for prophylaxis) may be lifelong. Lifelong prophylaxis should be strongly considered in patients who have had an invasive pneumococcal infection or who have an underlying immune deficiency. In children with sickle cell disease, penicillin prophylaxis should be started as soon as the diagnosis is made. Prophylaxis may be continued into adulthood for higher-risk patients, including those with a history of pneumococcal sepsis, but effectiveness in this older group has not been well documented.

In patients with traumatic injury, splenic repair or partial splenectomy should be considered in an attempt to preserve splenic function. Partial splenectomy or partial *splenic embolization* may be sufficient to ameliorate some forms of hemolytic anemia. Up to 50% of children whose spleen is removed because of trauma have spontaneous splenosis; *surgical splenosis* (distributing small pieces of spleen throughout the abdomen) may decrease the risk of sepsis in patients whose splenectomy is necessitated by trauma. However, in both these settings, the splenic tissue that regrows frequently has poor function.

In addition to postsplenectomy sepsis, splenectomized patients may be at risk for **thromboembolic complications** , including arterial and venous thrombosis and pulmonary hypertension. These findings have been reported regardless of the underlying reason for splenectomy and the postsplenectomy platelet count. Proposed mechanisms include loss of filtering function of the spleen, allowing abnormal RBCs to remain in the circulation and activate the coagulation cascade. Portal vein thrombosis has been reported as a complication of laparoscopic splenectomy.

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SECTION 9

The Lymphatic System

OUTLINE

Chapter 515 Anatomy and Function of the Lymphatic System
Chapter 516 Abnormalities of Lymphatic Vessels
Chapter 517 Lymphadenopathy

CHAPTER 515

Anatomy and Function of the Lymphatic System

Michael Kelly, Richard L. Tower II, Bruce M. Camitta

The lymphatic system participates in many biologic processes, including fluid homeostasis, absorption of dietary fat, and initiation of specific immune responses. This system includes circulating lymphocytes, lymphatic vessels, lymph nodes, spleen, tonsils, adenoids, Peyer patches, and thymus. *Lymph* is an ultrafiltrate of blood and is collected by lymphatic capillaries that are present in all organs where blood flows except the bone marrow and retina. Lymphatic capillaries form progressively larger vessels that drain regions of the body. The lymphatic vessels carry lymph to the *lymph nodes*, where it is filtered through sinuses, particulate matter and infectious organisms are phagocytosed, and antigens are presented to surrounding lymphocytes. These actions stimulate antibody production, T-cell responses, and cytokine secretion (see Chapter 149). Lymph is ultimately returned to the intravascular circulation.

The composition of lymph can vary with the site of lymph drainage. It is usually clear, but lymph drained from the intestinal tract may be milky (*chylous*) because of the presence of fats. The protein content is intermediate between an exudate and a transudate. The protein level may be increased with inflammation and in lymph drained from the liver or intestines. Lymph also contains variable numbers of lymphocytes and antigen-presenting cells.

Embryonic lymphatic development is a stepwise process that starts in the embryonic veins, where *lymphatic endothelial cell* (LEC) progenitors are initially specified. The differentiation and maturation of these progenitors continues as they bud from the veins to produce scattered primitive lymph sacs, from which most of the lymphatic vasculature is derived. *PROX1* gene expression is important to LEC specification, and studies have shown the critical importance of bone morphogenetic protein (BMP), Wnt, Notch, and vascular endothelial growth factor (VEGF) signaling pathways in lymphatic system development.

In contrast to the wealth of data describing the development of early lymphatic vessels, little is known about the establishment of organ-specific lymphatics at later stages. Studies using lineage-tracing technology suggest a venous and nonvenous origin of LECs giving rise to organ-specific lymphatics in the mesentery, skin, and heart. Until recently, the brain was thought to be devoid of lymphatics. However, lymphatic vessels that run parallel to the dural sinuses have now been identified. The embryonic origin of the meningeal lymphatics has not been determined. Whether signaling pathways important in early development are critical to the development of lymphatic networks in organs, and whether LECs of venous or nonvenous origins respond to injury, remain active areas of investigation.

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CHAPTER 516

Abnormalities of Lymphatic Vessels

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Lymphatic Malformations

Lymphatic malformations (LMs) can be isolated, generalized, or associated with syndromes and overgrowth and can occur as combined malformations with other vessel types (see International Society for the Study of Vascular Anomalies (**ISSVA**) classification; www.issva.org). LMs consist of dilated lymphatic channels or cysts lined by lymphatic endothelial cells (LECs). LMs are typically classified by *cyst size* (macrocystic, microcystic, mixed) and occur more frequently in the head, neck, and axilla.

Generalized lymphatic anomaly (GLA) is defined as a multifocal LM that involves soft tissues, abdominal and thoracic viscera, and often bone. Bone involvement in GLA is usually not progressive and typically spares the cortex. Chylous effusions involving the pleural, pericardial, and peritoneal spaces can occur.

Gorham-Stout disease (GSD; disappearing bone disease) is characterized by an LM involving single or multiple bones and leading to progressive cortical bone loss (also termed *vanishing bone syndrome*). LMs often involve soft tissue adjacent to bone and result in effusions in GSD as well.

Central conducting lymphatic anomalies are associated with intestinal dysmotility and, depending on the involved site, may result in chylothorax, pulmonary lymphangiectasia, chylous ascites, protein-losing enteropathy, cutaneous lesions, chylous leakage, and osseous changes from dilated intraosseous lymphatic channels. LMs are also associated with somatic mutations in *PIK3CA* , which often also produce other vascular malformations and regional tissue overgrowth.

Genetics

Somatic, hyperactivating *PIK3CA* mutations are present at low frequency (<10 %) in most isolated LMs and LMs that are part of a syndrome. These mutations are the same *PIK3CA* mutations found in many human cancers. It is not clear how the same somatic mutations cause such phenotypic diversity. However, activation of *PIK3CA* leads to increased signaling through the AKT/mTOR pathway, likely explaining the sensitivity of most LMs to sirolimus.

Treatment

A decision to treat an LM depends on the anatomic location, involvement of local structures, and symptoms. Referral to a specialized vascular anomalies clinic with the expertise to guide appropriate imaging and treatment decisions is recommended. For localized macrocystic LMs, **interventional radiology** (IR) with administration of sclerosing agents (OK432, ethanol, bleomycin) is most effective. For lesions involving skin and mucosa, laser treatments may be used. **Sirolimus** , an inhibitor of mammalian target of rapamycin (mTOR), has been shown to be effective when used alone or in combination with IR for complicated or extensive LMs. Propranolol has been effective in some patients.

Lymphangiectasia

Lymphangiectasia is no longer considered a unique entity and is grouped as either a GLA or channel-type LM according to ISSVA classification. Channel-type LM can result from hypoplasia of the cisternae chylae, lymph nodes, or central collecting ducts, leading to the obstruction of lymph flow from superficial to central collecting channels and resulting in dilation of superficial vessels (Fig. 516.1). Symptoms depend on the level of the obstruction and can include protein-losing enteropathy if the mesentery is involved or chylous effusions if obstruction occurs higher.

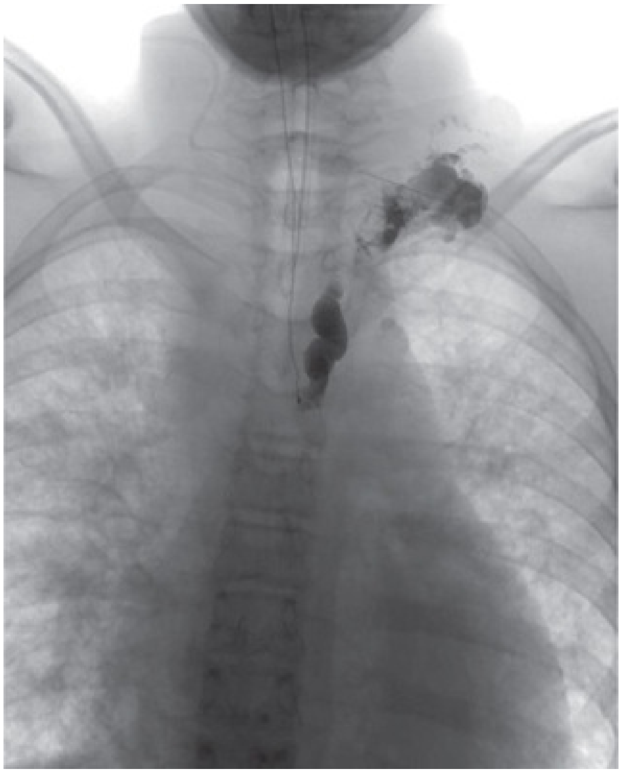

FIG. 516.1 **Intranodal lymphangiogram in 15 yr old boy with central conducting lymphatic anomaly and recurrent pericardial effusions. Stagnant flow is seen in the patulous superior portion of the thoracic duct. Direct puncture of the terminal portion demonstrates marked dilation with no spontaneous emptying.**

Lymphedema

Lymphedema is a localized swelling caused by impaired lymphatic flow and can be primary (congenital) or acquired. *Primary* lymphedemas are grouped as LMs because they result from dysgenesis of lymphatic networks during early development. Primary lymphedema may be found in Turner syndrome, Noonan syndrome, autosomal dominantly inherited Milroy disease, and other chromosomal abnormalities. Mutations in multiple genes, including the vascular endothelial growth factor receptor–3 gene (*VEGFR3*), *GJC2* , *PTPN14* , and *GATA2*, are associated with primary lymphedema (www.issva.org). Autosomal recessive, dominant or de novo mutations of *VEGFR3* produce Milroy disease. Mutations in other genes are associated with specific syndromes; *CCBE1* (Hennekam), *FOXC2* (lymphedema distichiasis), *SOX18* (hypotrichosis-telangiectasia-lymphedema), *KMT2D/MLL2*, and *KDM6A* (Kabuki). Unilateral or bilateral lower extremity lymphedema in an adolescent may be Meige disease.

Acquired obstruction of the lymphatics can result from tumor, postirradiation fibrosis, and postinflammatory scarring. **Filariasis** is an important cause of lymphedema in Africa, Asia, and Latin America. One third of the 120 million infected persons (primarily older adolescents and adults) have lymphedema or a hydrocele. Injury to the major lymphatic vessels can cause collection of lymph fluid in the abdomen (chylous ascites) or chest (chylothorax).

Untreated lymphedema can be disabling and is associated with immune dysfunction, inflammation, fibrosis, adipose tissue overgrowth, and **lymphangiosarcoma** . Current treatment modalities attempt to reduce localized swelling through massage, exercise, and compression. **Selenium** has been an effective adjuvant to physiotherapy in some adult patients following breast cancer treatment.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (**LAM**) is characterized by proliferation of lymphatic endothelial cells and smooth muscle cells in the lungs, leading to airway and lymphatic obstruction, cyst formation, pneumothorax, and respiratory failure. It may initially be mistaken for asthma. LAM occurs in young women and is associated with mutations in the tuberous sclerosis tumor-suppressor gene *TSC2* in one third of cases. Sirolimus stabilizes lung function, reduces symptoms, and improves life quality. Lung transplantation may be required.

Lymphangitis

Lymphangitis is an inflammation of the lymphatics that drain an area of infection. Tender, erythematous streaks extend proximally from the infected area. Regional nodes may also be tender. Group A streptococci and *Staphylococcus aureus* are the most common pathogens, and therapy should include antibiotics that treat these organisms.

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CHAPTER 517

Lymphadenopathy

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Palpable lymph nodes are common in pediatrics. Lymph node enlargement is caused by proliferation of normal lymphoid elements or by infiltration with malignant or phagocytic cells. In most patients, a careful history and a complete physical examination suggest the proper diagnosis.

Diagnosis

Is the mass a lymph node? Nonlymphoid masses (cervical rib, thyroglossal cyst, branchial cleft cyst or infected sinus, cystic hygroma, goiter, sternomastoid muscle tumor, thyroiditis, thyroid abscess, neurofibroma) occur frequently in the neck and less often in other areas. **Is the node enlarged?** Lymph nodes are not usually palpable in the newborn. With antigenic exposure, lymphoid tissue increases in volume. They are not considered enlarged until their diameter exceeds 1 cm for cervical and axillary nodes and 1.5 cm for inguinal nodes. Other lymph nodes usually are not palpable or visualized with plain radiographs.

What are the characteristics of the node? Acutely infected nodes are usually tender. There may also be erythema and warmth of the overlying skin. Fluctuance suggests abscess formation. *Tuberculous* nodes may be matted. With chronic infection, many of these signs are not present. Tumor-bearing nodes are usually firm and nontender and may be matted or fixed to the skin or underlying structures. Tumors or tumor-involved nodes are often present for >2 wk and may be associated with local extension (voice change, dysphagia) or systemic signs (fever, weight loss, night sweats).

Is the lymphadenopathy localized or generalized? *Generalized adenopathy* (enlargement of >2 noncontiguous node regions) is caused by systemic disease (Table 517.1) and is often accompanied by abnormal physical findings in other systems. In contrast, *regional adenopathy* is most frequently the result of infection in the involved node and/or its drainage area (Table 517.2). When caused by infectious agents other than bacteria, adenopathy may be characterized by atypical anatomic areas, a prolonged course, a draining sinus, lack of prior pyogenic infection, and unusual clues in the history (cat scratches, tuberculosis exposure, venereal disease). A firm, fixed node should always raise the question of malignancy, regardless of the presence or absence of systemic symptoms or other abnormal physical findings.

Table 517.1

Differential Diagnosis of Systemic Generalized Lymphadenopathy

INFANT	CHILD	ADOLESCENT
COMMON CAUSES		
Syphilis Toxoplasmosis CMV HIV	Viral infection EBV CMV HIV Toxoplasmosis	Viral infection EBV CMV HIV Toxoplasmosis Syphilis
RARE CAUSES		
Chagas disease Leukemia Tuberculosis Reticuloendotheliosis Lymphoproliferative disease Metabolic storage disease Histiocytic disorders	Serum sickness SLE, JIA Leukemia/lymphoma Tuberculosis Measles Sarcoidosis Fungal infection Plague Langerhans cell histiocytosis Chronic granulomatous disease Sinus histiocytosis Drug reaction	Serum sickness SLE, JIA Leukemia/lymphoma Hodgkin disease Lymphoproliferative disease Tuberculosis Histoplasmosis Sarcoidosis Fungal infection Plague Drug reaction Castleman disease

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; JIA, juvenile idiopathic arthritis (as Still disease); SLE, systemic lupus erythematosus.

From Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, Elsevier, p 863.

Table 517.2

Sites of Local Lymphadenopathy and Associated Diseases

CERVICAL

Oropharyngeal infection (viral or group A streptococcal, staphylococcal) Scalp infection/infestation (head lice) Mycobacterial lymphadenitis (tuberculosis and nontuberculous mycobacteria) Viral infection (EBV, CMV, HHV-6) Cat-scratch disease Toxoplasmosis Kawasaki disease Thyroid disease Kikuchi disease Sinus histiocytosis (Rosai-Dorfman disease) Autoimmune lymphoproliferative disease Periodic fever, aphthous stomatitis, pharyngitis, cervical adenopathy (PFAPA) syndrome
ANTERIOR AURICULAR
Conjunctivitis Other eye infection Oculoglandular tularemia Facial cellulitis Otitis media Viral infection (especially rubella, parvovirus)
SUPRACLAVICULAR
Malignancy or infection in the mediastinum (right) Metastatic malignancy from the abdomen (left) Lymphoma Tuberculosis
EPITROCHLEAR
Hand infection, arm infection[*] Lymphoma[†] Sarcoid Syphilis
INGUINAL
Urinary tract infection Venereal disease (especially syphilis or lymphogranuloma venereum) Other perineal infections Lower extremity suppurative infection Plague
HILAR[‡]
Tuberculosis[†] Histoplasmosis[†] Blastomycosis[†] Coccidioidomycosis[†] Leukemia/lymphoma[†] Hodgkin disease[†] Metastatic malignancy[*] Sarcoidosis[†] Castleman disease
AXILLARY
Cat-scratch disease Arm or chest wall infection Malignancy of chest wall Leukemia/lymphoma Brucellosis
ABDOMINAL
Malignancies

Mesenteric adenitis (measles, tuberculosis, *Yersinia* , group A streptococcus)

[*] Unilateral.

[†] Bilateral.

[‡] Not palpable, found on chest radiograph or CT.

CMV, Cytomegalovirus; CT, computed tomography; EBV, Epstein-Barr virus; HHV-6, human herpesvirus 6.

From Kliegman RM, Greenbaum LA, Lye PS: *Practical strategies in pediatric diagnosis and therapy* , ed 2, Philadelphia, 2004, Elsevier, p 864.

Treatment

Evaluation and treatment of lymphadenopathy is guided by the probable etiologic factor, as determined from the history and physical examination. Many patients with **cervical adenopathy** have a history compatible with viral infection and need no intervention. If bacterial infection is suspected, antibiotic treatment covering at least streptococci and staphylococci is indicated. Those who do not respond to oral antibiotics, as demonstrated by persistent swelling and fever, require intravenous (IV) antistaphylococcal antibiotics. If there is no response in 1-2 days, or if there are signs of airway obstruction or significant toxicity, ultrasound, CT, or MRI of the neck should be obtained. If *pus* is present, it may be aspirated, with CT or ultrasound guidance, or if it is extensive, it may require incision and drainage. Gram stain and culture of the pus should be obtained. The sizes of involved nodes should be documented before treatment. Failure to decrease in size within 10-14 days also suggests the need for further evaluation. This evaluation may include a complete blood cell count (CBC) with differential; Epstein-Barr virus, cytomegalovirus, *Toxoplasma,* and cat-scratch disease titers; anti–streptolysin O or anti-DNase B serologic tests; tuberculin skin test; and chest radiograph. If these are not diagnostic, consultation with an infectious diseases or oncology specialist may be helpful. Biopsy should be considered if there is persistent or unexplained fever, weight loss, night sweats, supraclavicular location, mediastinal mass, hard nodes, or fixation of the nodes to surrounding tissues. Biopsy may also be indicated if there is an increase in size over baseline in 2 wk, no decrease in size in 4-6 wk, no regression to “normal” in 8-12 wk, or if new signs and symptoms develop.

Differentiating benign disorders from a malignancy may initially be difficult. Hard, nontender, nonerythematous nodes involving multiple regions (including mediastinum and abdomen), hepatic or splenic enlargement, fever, night sweats, and weight loss suggest malignancy or a granulomatous process. Persistence of symptoms and lymphadenopathy >2 wk and certain locations (supraclavicular, mediastinal, abdominal) also suggest malignancy. Cytopenias and elevated blood lactate dehydrogenase are associated with malignancy and certain inflammatory disorders. Ultrasound is useful in distinguishing malignancy from reactive nodes. CT is helpful in identifying other affected nodes and organs; CT- or ultrasound-guided biopsy is helpful in determining the etiology.

517.1

Kikuchi-Fujimoto Disease (Histiocytic Necrotizing Lymphadenitis)

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Keywords

Kikuchi-Fujimoto disease
necrotizing lymphadenitis
lymphadenopathy

Kikuchi-Fujimoto disease is a rare, usually self-limiting disease that was originally reported in patients of Asian heritage. Cases are now described in all ethnic groups. Familial cases have been reported. The etiology is unknown, although viral and bacterial causes have been postulated. Autoimmune diseases such as systemic lupus erythematosus (SLE) have also been associated. The differential diagnosis includes lymphoma, tuberculosis, and SLE.

Presentation is varied and may include fever of unknown origin, but more often histiocytic necrotizing lymphadenitis presents as firm unilateral posterior cervical adenitis, fever, malaise, elevated erythrocyte sedimentation rate (ESR), atypical lymphocytosis, and leukopenia in children 8-16 yr of age. Nodes range in size from 0.5-6.0 cm, are painful or tender in only 50% of cases, may be multiple, and must be differentiated from lymphoma. Node involvement may occasionally be bilateral or present in axillary or supraclavicular nodes. Ultrasound usually shows multiple conglomerated, unilateral cervical lymphadenopathy with perinodal fat swelling and even size distribution.

The diagnosis is made by lymph node biopsy. Histologic features include necrosis with karyorrhexis, a histiocytic infiltrate, and plasmacytoid dendritic cells, showing CD123 and TCL1 nuclear reactivity and an absence of neutrophils. Kikuchi-Fujimoto disease usually resolves within 6 mo, although relapses have occurred up to 16 yr later. Therapy with systemic steroids is reserved for patients with severe symptoms. Rarely, the disease has been fatal.

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517.2

Sinus Histiocytosis With Massive Lymphadenopathy (Rosai-Dorfman

Disease)

Richard L. Tower II, Bruce M. Camitta

Keywords

emperipolesis
histiocyte
lymphadenopathy
Rosai-Dorfman disease
sinus histiocytosis

The uncommon, benign, and usually self-limited Rosai-Dorfman disease is a non-Langerhans cell histiocytosis that has a worldwide distribution but is more common in Africa and the Caribbean. The etiology is unknown, but immune dysfunction is suspected. It is not a single entity, but a pattern, and can be associated with neoplasia or immune disease. It can be sporadic or associated with inherited conditions. Some patients have gene variants in *KRAS* and *MAP2K1* . Patients present with massive bilateral, painless, mobile cervical adenopathy, along with fever, leukocytosis, high ESR, and polyclonal elevation of immunoglobulin G (hypergammaglobulinemia). Night sweats and weight loss are common. It rarely occurs at birth or in siblings, and males are affected more often than females.

Other nodal chains may be involved in sinus histiocytosis. Extranodal involvement occurs in 43% of cases. Soft tissue involvement has been reported in many organ systems. The most common sites are the skin, followed by the nasal cavity and sinuses, palate, orbit, bone, and central nervous system. Occasionally, autoantibodies to erythrocytes or synovium may be present. A biopsy that demonstrates pale histiocytes containing engulfed lymphocytes (**emperipolesis**), and immunoreactivity to S100 protein in large histiocytes, in conjunction with expected clinical features, is diagnostic. IgG4-positive cells are often abundant. The differential diagnosis includes Langerhans cell histiocytosis, myeloproliferative disorders, hyper-IgG4 syndrome, and lymphoma.

Therapy is usually not needed for this self-limited disease. However, Rosai-Dorfman disease may recur for many years. Disease is more widespread with higher fatality rates when associated with autoimmune disease. Life- or organ-threatening disease or exacerbations may respond to prednisone. Refractory cases have been treated with surgical excision. Radiation may be helpful in refractory orbital disease. Immunomodulating therapy, including interferon-α, 2-chlorodeoxyadenosine, clofarabine, imatinib, sirolimus, and rituximab, has been successful in some patients. Antibiotic therapy and chemotherapy have been unsuccessful.

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517.3

Castleman Disease

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Keywords

angiofollicular lymph node hyperplasia
HHV-8
lymphoproliferative
hyperplasia
multicentric Castleman disease
TAFRO syndrome

Castleman disease is an uncommon B-cell lymphoproliferative disorder and is also called **angiofollicular lymph node hyperplasia** . The underlying etiology is unknown, although an association with human herpesvirus 8 has been identified. HHV-8 may stimulate excessive production of interleukin-6 (IL-6). Invariant natural killer T cells are decreased in number and/or function. The disease usually presents in adolescents or young adults. Enlargement of a single node, most often in the mediastinum or abdomen, is the most common localized presentation. Other patients may have fever, night sweats, weight loss, and fatigue. Management includes surgery and/or radiation therapy.

Multicentric Castleman disease is a systemic B-cell lymphoproliferative disorder that causes lymphadenopathy, hepatosplenomegaly, fever, anemia, overexpression of IL-6, and polyclonal hypergammaglobulinemia. Multicentric Castleman disease may be associated with HIV infection, autoimmune disease–associated lymphadenopathy, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-proteins, and skin lesions). One uncommon presentation is **TAFRO syndrome** , consisting of thrombocytopenia, anasarca, fever, reticulum fibrosis, and organomegaly. Non-Hodgkin lymphoma may be concurrent or may develop because of disease progression. There is no standard treatment for multicentric Castleman disease. Deficiency of adenosine deaminase 2 (DADA2) may mimic Castleman disease. Therapeutic options include chemotherapy, corticosteroids, monoclonal antibodies to CD20 (rituximab), monoclonal antibodies to IL-6 (siltuximab), anti-IL-6–receptor antibodies (tocilizumab), antiviral agents, and interferon-α. Chemotherapy for diffuse large B-cell lymphoma and rituximab are currently the most common frontline therapies and have achieved durable remissions. Ganciclovir is the most active antiviral agent. Corticosteroids and anti-IL-6 therapies provide symptomatic relief, but symptoms often return after stopping therapy.

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PART XXI
Cancer and Benign Tumors

OUTLINE

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CHAPTER 518

Epidemiology of Childhood and Adolescent Cancer

Barbara L. Asselin

Cancer in patients younger than 20 yr is uncommon, with an age-adjusted annual incidence of 18.3 per 100,000 children age 0-19 yr, representing only approximately 1% of all new cancer cases in a year in the United States, or an estimated 16,000 new cases in 2017. This translates to nearly a 1 in 300 chance of developing cancer by age 20 yr. Although the relative 5 yr survival rates have improved from 61% in 1975–77 to 84.8% in 2007–13 in all age-groups 0-19 yr (Fig. 518.1), **malignant neoplasms** remain the leading cause of disease-related (noninjury) mortality (12%) among persons 1-19 yr of age, with 1,800-1,900 cancer-related deaths annually in the United States among children and adolescents 0-19 yr of age. The relative contribution of cancer to the overall mortality in infants 0-1 yr old and adolescents 15-19 yr old is lower than for children age 1-14 yr. The impressive improvements in survival over the past 3½ decades are attributed primarily to advances in treatment and enrollment in clinical trials for the majority of patients. Ongoing multiinstitutional cooperative clinical trials are investigating novel therapies and ways to improve survival rates further and decrease treatment-related long-term complications. Because increasingly more patients survive their disease, clinical investigations also are focusing on the quality of life among survivors and the late outcomes of therapy for pediatric and adult survivors of childhood cancer. The **National Cancer Institute** (NCI) estimated that in 2010 there were 380,000 persons alive (in all age-groups) who had survived childhood cancer, corresponding to 1 in 810 of persons younger than 20 yr and 1 in 1,000 persons 20-39 yr of age in the U.S. population.

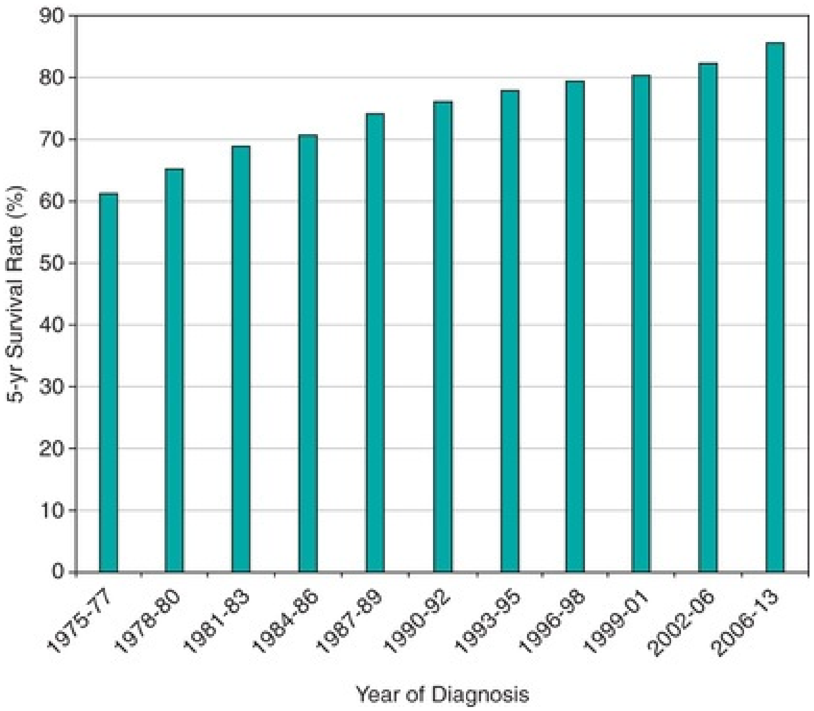

FIG. 518.1 **The 5-yr relative survival rates (%) by year of diagnosis of all cancers in children ≤19 yr old. The difference between the periods 1975–77 and 2006–13 is statistically significant ($p < 0.05$). Rates based on follow-up of patients into 2014 from Surveillance, Epidemiology, and End Results (SEER) database. (Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: *SEER Cancer Statistics Review, 1975–2014,* Section 29, Bethesda, MD, National Cancer Institute. http://seer.cancer.gov/csr/1975_2014/ . Based on November 2016 SEER data submission, posted to the SEER website, April 2017.)**

Pediatric malignancies differ greatly from adult malignancies in both prognosis and distribution by histology and tumor site. **Lymphohematopoietic cancers** (i.e., acute lymphoblastic leukemia, myeloid leukemia, Hodgkin and non-Hodgkin lymphomas) account for approximately 40%, **central nervous system cancers** for approximately 30%, and **embryonal tumors** and **sarcomas** for approximately 10% among the broad categories of childhood cancers (Table 518.1). In contrast, **epithelial tumors** of organs such as lung, colon, breast, and prostate, often seen among adults, are rare malignancies in children. Incidence patterns in the pediatric age-group show 2 peaks, in early childhood and in adolescence (Fig. 518.2). During the 1st yr of life, *embryonal tumors* such as neuroblastoma, nephroblastoma (Wilms tumor), retinoblastoma, rhabdomyosarcoma, hepatoblastoma, and medulloblastoma are most common (Figs. 518.3 and 518.4). These tumors are much less common in older children and adults after cell differentiation processes have slowed considerably. Embryonal tumors, acute leukemias, non-Hodgkin lymphomas, and gliomas peak in incidence from 2-5 yr of age. As children age, bone malignancies, Hodgkin disease, gonadal germ cell malignancies (testicular and ovarian carcinomas), and other carcinomas increase in incidence. Adolescence is a transitional period between the common early childhood malignancies and characteristic carcinomas of adulthood (Fig. 518.4).

Table 518.1

Age-Adjusted Incidence and Survival Rates of Malignant Neoplasms by Tumor Type in U.S. Children

	ANNUAL INCIDENCE RATES PER 1 MILLION CHILDREN, 2010–2014					**5-YR SURVIVAL (%), AGE ≤19 YR AT DIAGNOSIS, 2004–2011**
	Age <1 Yr	**Age 1-4 Yr**	**Age 5-9 Yr**	**Age 10-14 Yr**	**Age 15-19 Yr**	
All malignancies combined	234	219	128	142	228	83
Leukemia (ALL/AML)	51 (20/21)	93 (78/11)	44 (37/5)	35 (23/8)	36 (19/10)	83.5 (88/64)
Lymphoma (Hodgkin)	— (—)	8 (1)	16 (4)	26 (11)	49 (30)	93 (97)
CNS tumors	42	50	45	43	55.5	74
Neuroblastoma	51	21	4	1	1	78.5
Nephroblastoma/Wilms (renal cell carcinoma)	14 (—)	19.5 (—)	5.5 (—)	0.6 (0.6)	— (1.8)	90.5
Bone	—	2	6	14	14	71.5
Soft tissue sarcomas	16	11	9	12	16	72
Retinoblastoma	28	9	—	—	—	95
Hepatoblastoma (hepatic carcinoma)	13 (—)	6 (—)	— (—)	— (0.8)	— (0.8)	84
Germ cell tumors	20.5	3.5	3	7	31.5	92
Malignant epithelial cancer	—	2	5	17	54 29[*] /10 [†]	92 (99.5[*] /94 [†])

[*] Thyroid carcinoma.

[†] Malignant melanoma.

Based on the International Classification of Childhood Cancer (ICCC). Rates are per 1 million children and are age-adjusted to the 2000 U.S. standard population.

—, Indicates that the rate could not be calculated with <16 cases for the time interval.

ALL, Acute lymphoid leukemia; AML, acute myeloid leukemia; CNS, central nervous system.

Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: *SEER Cancer Statistics Review, 1975–2014,* Section 29, Bethesda, MD, National Cancer Institute. https://seer.cancer.gov/csr/1975_2014/ . Based on November 2016 SEER data submission, posted to SEER website, April 2017.

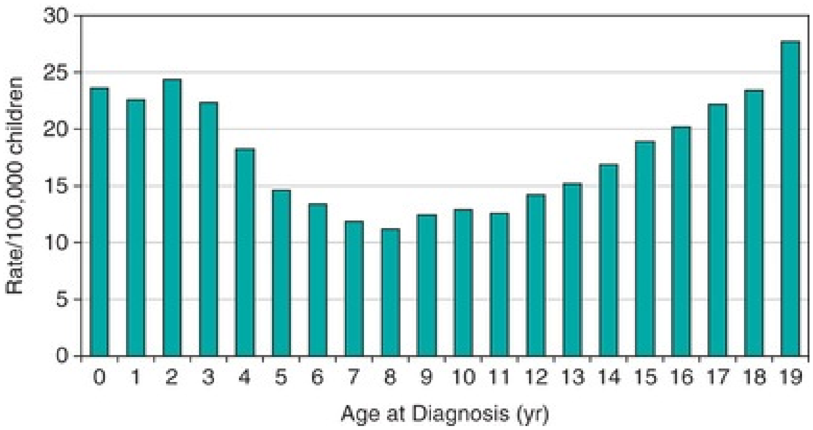

FIG. 518.2 Age-specific cancer incidence rates per 100,000 children within the United States. Rates based on data from 2010–2014 from SEER database. (Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: *SEER Cancer Statistics Review, 1975–2014,* Section 29, Bethesda, MD, National Cancer Institute. http://seer.cancer.gov/csr/1975_2014/ . Based on November 2016 SEER data submission, posted to the SEER website, April 2017.)

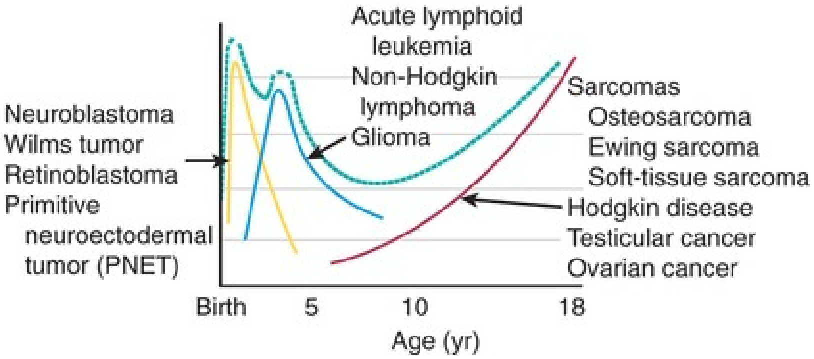

FIG. 518.3 Generalized incidence of the most common types of cancer in children by age. The cumulative incidence of all cancers is shown as a *dashed line* . (Courtesy of Archie Bleyer, MD.)

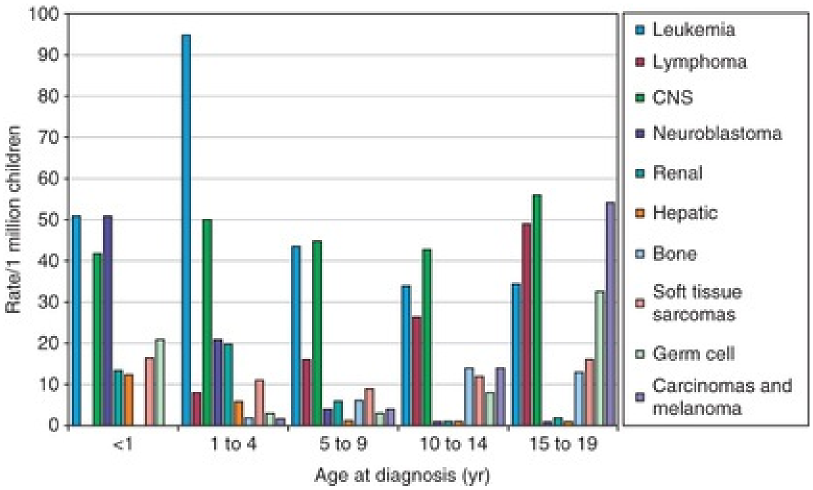

FIG. 518.4 SEER cancer incidence rates per 1 million children by International Classification of Childhood Cancer (ICCC) and age <20 yr. CNS, Central nervous system. (Data compiled from Howlader N, Noone AM, Krapcho M, et al, editors: *SEER Cancer Statistics Review, 1975–2014,* Section 29, Bethesda, MD, National Cancer Institute. http://seer.cancer.gov/csr/1975_2014/ . Based on November 2016 SEER data submission, posted to the SEER website, April 2017.)

Incidence rates also vary by *gender* (generally higher in boys vs girls), *race/ethnicity* (more common in whites), and between countries (data assembled by the International Agency for Research in Cancer in Lyon, France, http://www.iarc.fr/). These variations are not fully understood but likely reflect differences in genetic susceptibility and environmental exposures related to both known and unknown causes and risk factors for cancer (Table 518.2). Over the past 4 decades, 1975–2014, there has been some increase in the incidence of children and adolescents diagnosed with cancer, particularly in occurrence of leukemia and among adolescents. Interestingly, a similar increased incidence of malignancies diagnosed in childhood was observed between 1980 and 2010 in an international population-based registry study involving 62 countries. Reasons postulated to explain these increases include, but are not limited to, improved diagnosis, better record keeping, and development of data registries. Further analysis of trends among subpopulations, geographic variations, and incidence rates in high-income vs low-income countries are needed to clarify the role of *genetic ancestry, environmental factors*, and *technology* as explanations of these time trends in cancer in children.

Table 518.2

Known Risk Factors for Selected Childhood Cancers

CANCER TYPE	RISK FACTOR	COMMENTS
Acute lymphoid leukemia	Ionizing radiation	Although primarily of historical significance, prenatal diagnostic x-ray exposure increases risk. Therapeutic irradiation for cancer treatment also increases risk.
	Race	White children have a 2-fold higher rate than black children in the United States.
	Genetic factors*	Down syndrome is associated with an estimated 10-20–fold increased risk. NF1, Bloom syndrome, ataxia-telangiectasia, *TP53* mutations, and Langerhans cell histiocytosis, among others, are associated with an elevated risk.
	Birthweight	>4 kg increases risk.
Acute myeloid leukemias	Chemotherapeutic agents	Alkylating agents and epipodophyllotoxins increase risk.
	Genetic factors*	Down syndrome and NF1 are strongly associated. Familial monosomy 7 and several other genetic syndromes are also associated with increased risk.
Brain cancers	Therapeutic ionizing radiation to the head	With the exception of cancer radiation therapy, higher risk from radiation treatment is essentially of historical importance.
	Genetic factors*	NF1 is strongly associated with optic gliomas, and, to a lesser extent, with other central nervous system tumors. Tuberous sclerosis and several other genetic syndromes are associated with increased risk.
Hodgkin disease	Family history	Monozygotic twins and siblings of cases are at increased risk.
	Infections	EBV is associated with increased risk.
Non-Hodgkin lymphoma	Immunodeficiency	Acquired and congenital immunodeficiency disorders and immunosuppressive therapy increase risk.
	Infections	EBV is associated with Burkitt lymphoma in Africa.
Osteosarcoma	Ionizing radiation	Cancer radiation therapy and high radium exposure increase risk.
	Chemotherapy	Alkylating agents increase risk.
	Genetic factors*	Increased risk is apparent with Li-Fraumeni syndrome and hereditary retinoblastoma.
Ewing sarcoma	Race	White children have about a 9-fold higher incidence rate than black children in the United States.
Neuroblastoma		Neurocristopathies
Retinoblastoma	Genetic factors*	No established other risk factors
Wilms tumor	Congenital anomalies	Aniridia, Beckwith-Wiedemann syndrome, and other congenital and genetic conditions are associated with increased risk.
	Race	Asian children reportedly have about half the rates of white and black children.
Rhabdomyosarcoma	Congenital anomalies and genetic conditions	Li-Fraumeni syndrome and NF1 are believed to be associated with increased risk. There is some concordance with major birth defects.
Hepatoblastoma	Genetic factors*	Beckwith-Wiedemann syndrome, hemihypertrophy, Gardner syndrome, and family history of adenomatous polyposis are associated with increased risk.
Malignant germ cell tumors	Cryptorchidism	Cryptorchidism is a risk factor for testicular germ cell tumors.

[*] See Chapter 519 , Table 519.2 .

EBV, Epstein-Barr virus; NF1, neurofibromatosis type1.

Adapted from Ries LAG, Smith MA, Gurney JG, editors: Cancer incidence and survival among children and adolescents: United States, 1975–1995, SEER Program, NIH Pub No 99-4649, Bethesda, MD, 1999, National Cancer Institute. The publication and additional data are available on the SEER website, http://www.seer.cancer.gov .

Childhood cancer includes a diverse array of malignant tumors, termed “cancers,” and nonmalignant tumors arising from disorders of genetic processes involved in control of cellular growth and development. Although many genetic conditions are associated with increased risks for childhood cancer, such conditions are believed to account for 8–10% of all occurrences (see Chapter 519). The most notable germline genetic conditions that impart susceptibility to childhood cancer are Li-Fraumeni (*P53*) syndrome, neurofibromatosis types 1 and 2, Down syndrome, Beckwith-Wiedemann syndrome, tuberous sclerosis, von Hippel–Lindau disease, xeroderma pigmentosum, ataxia-telangiectasia, and nevus basal cell carcinoma syndrome. Consensus guidelines for surveillance screening in pediatric cancer predisposition syndromes were developed during a workshop of the Pediatric Cancer Working Group of the **American Association for Cancer Research** (AACR) and are available online through the AACR Open Access journal website (http://clincancerres.aacrjournals.org/content/23/11). The varying incidence patterns of individual childhood cancers around the world imply additional genetic and epidemiologic risk factors that remain uncharacterized.

Compared with adult epithelial tumors, an extremely small fraction of pediatric cancers appears to be explained by known **environmental exposures** (see Table 518.2). Ionizing radiation exposure and several chemotherapeutic agents explain only a small number of pediatric cases (see Chapter 736). The association between fetal exposures and pediatric cancer is largely not established, with the exception of maternal diethylstilbestrol intake during pregnancy and subsequent vaginal adenocarcinoma in adolescent daughters. Environmental exposures that have been studied without convincing evidence for a causal role include nonionizing power frequency electromagnetic fields, pesticides, parental occupational chemical exposures, dietary factors, in vitro fertilization, and environmental cigarette smoke. Viruses associated with certain pediatric cancers include **polyomaviruses** (BK, JC, SV40) associated with brain cancer and **Epstein-Barr virus** (EBV) associated with non-Hodgkin lymphoma, but the etiologic importance remains unclear.

The etiology of cancer in children still is poorly understood, and epidemiology studies demonstrate that the likely mechanisms are multifactorial, possibly resulting from potential interactions between genetic susceptibility traits and environmental exposures. Ongoing studies are investigating the role of **polymorphisms** of genes encoding enzymes, which function in the activation or metabolism of xenobiotics, protection of cells against oxidative stress, DNA repair, and/or immune modulation.

Curative therapy with chemotherapy, radiation, and/or surgery can adversely affect a child's development and result in serious long-term medical and psychosocial effects in childhood and adulthood. Potential adverse late effects include subsequent 2nd malignancy, early mortality, infertility, reduced stature, cardiomyopathy, pulmonary fibrosis, osteoporosis, neurocognitive impairment, affective disorders, and altered social functioning. Much has been learned about the incidence of late effects from large, multisite cohort studies such as the **Childhood Cancer Survivor Study** , an ongoing study of medical and psychosocial outcomes in survivors, which has provided data for the development of clinical care guidelines for survivors (http://www.survivorshipguidelines.org).

Given the relative rarity of specific types of childhood cancer and the sophisticated technology and expertise required for diagnosis, treatment, and monitoring of late effects, all children with cancer should be treated with standardized clinical protocols in pediatric clinical research settings whenever possible. Promoting such treatment, the **Children's Oncology Group** is a multiinstitutional research consortium that facilitates cooperative clinical, biologic, and epidemiologic research in more than 200 affiliated institutions in the United States, Canada, and other countries (http://childrensoncologygroup.org/). Coordinated participation in such research trials has been a major factor in the increased survival for many children with cancer. Such ongoing efforts are critical to better understand the etiology of childhood cancers, improve survival for malignancies with a poor prognosis, and maximize the quality of life for survivors.

Influencing the Incidence of Cancer

Pediatricians have a unique opportunity to educate children and adolescents and their parents regarding means of preventing cancer. There are only a few recognized environmental causes of childhood cancer that can be avoided or counteracted. One example is immunization against **hepatitis B** , which decreases the risk of hepatocellular carcinoma in adolescence and adulthood; another is **human papillomavirus** vaccination, which prevents cervical cancer and HPV-positive oropharyngeal cancers and anal cancers. Associations between cumulative radiation exposure from common diagnostic radiologic tests such as CT scans and an increased risk of malignancy later in life are of great concern for pediatricians. Guidelines to ensure the safe clinical use of diagnostic imaging are being evaluated (http://www.imagegently.org/). An objective of pediatric medicine is *to teach children how to adopt healthy lifestyles to reduce their risk of cancer during adulthood,* such as avoiding tobacco, alcohol, high-fat diets, and obesity. The earlier these habits are instilled, the greater the lifelong benefit and the more likely it will be present and sustained during adulthood.

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CHAPTER 519

Molecular and Cellular Biology of Cancer

Kristopher R. Bosse, Stephen P. Hunger

Cancer is a complex of diseases arising from alterations that can occur in a wide variety of genes. Multiple mutations, some germline but most acquired (somatic), are required for cells to become fully malignant. These mutations lead to alterations in normal cellular processes that control cell proliferation and survival, including signal transduction, cell-cycle control, DNA repair, cellular growth and differentiation, translational regulation, senescence, and apoptosis (programmed cell death).

Genes Involved in Oncogenesis

Two major classes of genes are implicated in the development of cancer: oncogenes and tumor-suppressor genes. **Protooncogenes** are cellular genes that are important for normal cellular function and code for various proteins, including transcription factors, growth factors, and growth factor receptors. These proteins are vital components in the network of signal transduction that regulate cell growth, division, and differentiation. Protooncogenes can be altered to form **oncogenes** —genes that, when translated, can result in the malignant transformation of a cell.

Oncogenes can be divided into 5 different classes based on their mechanisms of action. Changes in any of these normal cellular components can result in unchecked cell growth. Some oncogenes code for **growth factors** that bind to a receptor and stimulate the production of a protein. Other oncogenes code for **growth factor receptors** , which are proteins on the cell surface. When growth factors bind to a growth factor receptor, they can turn the receptor on or off.

Mutational or posttranslational modifications of the receptor can result in a receptor being permanently turned on, with consequent unregulated growth. **Signal transducers** or effectors make up another class. Signal transducers are responsible for taking the signal from the cell surface receptor to the cell nucleus. **Transcription factors** are molecules that bind to specific areas of the DNA and control transcription. MYC and MYCN are examples of transcription factors that when activated by mutation or amplification cause overstimulation of cell division. The final class of oncogenes **interferes with apoptosis** . Cells that no longer respond to the signal to die can lead to uncontrolled cell proliferation.

The 3 main mechanisms by which protooncogenes are activated are **amplification** , **mutation** , and **translocation** or **interstitial deletion** (Table 519.1). *MYC* or *MYCN*, which code for proteins that regulate transcription, are examples of protooncogenes that are activated by amplification. Patients with neuroblastoma in which the *MYCN* gene is amplified 10-300–fold have a worse clinical outcome. Point mutations can also activate protooncogenes. The *NOTCH1* protooncogene codes for a membrane-bound receptor integral to cell fate and differentiation pathways during normal development that undergoes proteolytic cleavage on ligand-induced activation, so that the protein can enter the nucleus and activate target gene transcription. *NOTCH1* is mutated in at least 50% of T-cell acute lymphoblastic leukemias, resulting in a constitutively activated protein important in leukemogenesis.

Table 519.1

Oncogene Activators of Pediatric Tumors

MECHANISM	CHROMOSOME	GENES	PROTEIN FUNCTION	TUMOR
Chromosomal translocation	t(9;22)	*BCR-ABL1*	Chimeric tyrosine kinase	CML, ALL
	t(1;19)	*TCF3 (E2A)-PBX1*	Chimeric transcription factor	ALL
	t(8;14)	*MYC-IGH*	Transcription factor	Burkitt lymphoma
	t(15;17)	*PML-RARα*	Chimeric transcription factor	APML
	11q23 and others (over 50 fusions partners)	*KMT2A (MLL)*	Regulation of gene expression	Infant leukemia, ALL, AML, treatment-related leukemias
	t(12;21)	*ETV6-RUNX1*	Chimeric protein	ALL
	t(2;13) or t(1;13)	*PAX3* or	Transcription factor	Rhabdomyosarcoma

		7-FOXO1		
	t(11;22)	*EWS-FLI1*	Transcription factor	Ewing sarcoma
Gene amplification	2p	*MYCN*	Transcription factor	Neuroblastoma
	7p	*EGFR*	Growth factor receptor, tyrosine kinase	Glioblastoma, lung cancer
Point mutation	1p or 12p	*NRAS* or *KRAS*	Guanosine triphosphatase	AML, ALL, JMML, rhabdomyosarcoma, neuroblastoma
	10q	*RET*	Tyrosine kinase	MEN2
	2p	*ALK*	Tyrosine kinase	Neuroblastoma
	9q	*NOTCH1*	Transmembrane receptor	ALL

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; CML, chronic myelogenous leukemia; JMML, juvenile myelomonocytic leukemia; MEN2, multiple endocrine neoplasia, type 2.

The 3rd mechanism by which protooncogenes become activated is chromosomal translocation or interstitial deletion. In some leukemias and lymphomas, transcription factor–controlling sequences are relocated in front of T-cell receptors or immunoglobulin genes, resulting in dysregulated transcription of these genes and leukemogenesis. A prominent example are translocations that bring *c-MYC* under control of the immunoglobulin heavy-chain gene (*IGH*) or the kappa (*IGκ*) or lambda (*IGλ*) light-chain genes in **Burkitt's lymphoma** . Chromosomal translocations that join genes from 2 different chromosomes or interstitial deletions or inversions within a chromosome can also result in **fusion genes** ; transcription of the fusion gene results in production of a chimeric protein with new and potentially oncogenic activity. Examples of cancers associated with fusion genes include the childhood solid tumors **Ewing sarcoma [t(11;22)]** and **alveolar rhabdomyosarcoma [t(2;13)** or **t(1;13)]** . These translocations result in novel messenger RNA transcripts that are useful as diagnostic markers. The best-described translocation in leukemia is the **Philadelphia chromosome t(9;22**), which produces the BCR-ABL1 protein found in chronic myelogenous leukemia and specific subtypes of acute lymphoblastic leukemia. BCR-ABL1 is a constitutively active tyrosine kinase. In addition, the protein is localized to the cytoplasm instead of the nucleus, exposing the kinase to a new spectrum of substrates.

Alteration in the regulation of tumor-suppressor genes is another mechanism involved in oncogenesis. Tumor-suppressor genes are important regulators of cellular growth and apoptosis. They have been called *recessive* oncogenes because the inactivation of both alleles of a tumor-suppressor gene is required for expression of a malignant phenotype.

Knudson's “2-hit” model of cancer development was based on the eye tumor retinoblastoma developing at a significantly younger age in children with the familial vs the sporadic form of the disease, and that tumors were often multifocal in familial cases but were almost always unifocal in sporadic cases. Knudson postulated that sporadic cases of retinoblastoma required somatic mutations to inactivate both copies of a gene, whereas in familial cases, children must inherit an inactivated allele from 1 parent and consequently only require the somatic inactivation of the 1 remaining normal allele. This hypothesis was proven correct 15 years later with the discovery of the *RB* tumor-suppressor gene.

Another major tumor-suppressor protein is **TP53** , which is known as the “guardian of the genome” because it detects the presence of chromosomal damage and prevents the cell from dividing until repairs have been made. In the presence of damage beyond repair, TP53 initiates apoptosis and the cell dies. More than 50% of all tumors have abnormal TP53 proteins. Mutations in the *TP53* gene are important in many cancers, including breast, colorectal, lung, esophageal, stomach, ovarian, and prostatic carcinomas, as well as gliomas, sarcomas, and some leukemias.

Syndromes Predisposing to Cancer

Several syndromes are associated with an increased risk of developing malignancies, which can be characterized by different mechanisms (Table 519.2). One mechanism involves the *inactivation of tumor-suppressor genes* such as *RB* in **familial retinoblastoma** . Interestingly, patients with retinoblastoma in which 1 of the alleles is inactivated throughout all the patient's cells are also at a very high risk for developing osteosarcoma. A familial syndrome, **Li-Fraumeni syndrome** , in which 1 mutant *TP53* allele is inherited, also has been described in patients who develop sarcomas, leukemias, adrenocortical carcinoma, and cancers of the breast, bone, lung, and brain. **Neurofibromatosis** (NF) is a condition characterized by the proliferation of cells of neural crest origin. NF patients are at a higher risk of developing nervous system tumors, breast cancer, leukemia, pheochromocytomas, and other tumors. NF is inherited in an autosomal dominant manner, although 50% of cases present without a family history and occur secondary to the high rate of spontaneous mutation of the *NF1* gene.

Table 519.2

Familial or Genetic Susceptibility to Malignancy

DISORDER	TUMOR/CANCER	COMMENT
CHROMOSOMAL DELETION/ANEUPLOIDY SYNDROMES		
Chromosome 11p deletion syndrome	Wilms tumor	Also known as WAGR syndrome (Wilms tumor, *a*niridia, *g*enitourinary abnormalities, mental *r*etardation); deletion typically includes *WT1* gene
Chromosome 13q deletion syndrome	Retinoblastoma, sarcoma	Associated with intellectual disability, characteristic craniofacial abnormalities; deletion typically includes *RB1* gene
Trisomy 21	ALL, AML, AMKL, TMD	Risk of ALL is increased 20-fold, risk of AMKL is increased 500-fold; high cure rates; more prone to chemotherapy toxicity; AMKL associated with *GATA1* mutations
Klinefelter syndrome (47, XXY)	Breast cancer, extragonadal germ cell tumors	
Trisomy 8	Myeloid neoplasms	Most commonly mosaic trisomy 8
Monosomy 5 or 7	AML, MDS	
CHROMOSOMAL INSTABILITY SYNDROMES		
Xeroderma pigmentosum	Basal cell and squamous cell carcinomas, melanoma	Autosomal recessive; failure to repair UV-damaged DNA; *XP* gene mutations
Fanconi anemia	AML, MDS, rare head, neck, and skin tumors, GI and GU cancers	Autosomal recessive; chromosome fragility; positive diepoxybutane (DEB) test result; mutations in *FANCX* gene family (includes at least 15 members)
Bloom syndrome	AML, MDS, ALL, lymphoma, and solid tumors	Associated with growth deficiency, malar rash; autosomal recessive; increase sister chromatid exchange (SCE); mutations in *BLM* gene; member of the RecQ helicase gene (unwinds DNA)
Ataxia-telangiectasia	Lymphoma, leukemia, less often central nervous system and other solid tumors	Associated with progressive ataxia, oculocutaneous telangiectasias; autosomal recessive; sensitive to radiation-induced DNA damage; increased risk of treatment-related morbidity; biallelic mutation in *ATM* tumor-suppressor gene
Nijmegen breakage syndrome	Leukemia, lymphoma	Associated with microcephaly, characteristic facies, immunodeficiency; biallelic mutations in *NBN* gene
Werner syndrome (progeria)	Soft tissue sarcomas, osteosarcoma, melanoma	Associated with accelerated aging; autosomal recessive; mutations in *WRN* gene
IMMUNODEFICIENCY SYNDROMES		
Wiskott-Aldrich syndrome	Lymphoma, leukemia	Associated with thrombocytopenia, eczema, and recurrent infections; X-linked recessive; *WASP* gene mutations
X-linked lymphoproliferative syndrome (XLP)	B-cell lymphoproliferative disease, lymphomas, HLH	Associated with fulminant and often fatal EBV infection; X-linked; mutations in the *SH2D1A* gene
X-linked agammaglobulinemia (XLA)	Lymphoproliferative disorders, colorectal cancer	Associated with absence of B cells; X-linked; mutations in *BTK* gene
Severe combined immunodeficiency (SCID)	Leukemia, lymphoma	X-linked or autosomal recessive; mutations in *IL2RG* and *ADA* genes
SYNDROMES ARISING FROM GENE MUTATIONS		

Neurofibromatosis 1	Neurofibroma, optic glioma, acoustic neuroma, astrocytoma, meningioma, pheochromocytoma, rhabdomyosarcoma, MPNST, neuroblastoma, leukemias	Associated with café-au-lait macules, axillary/inguinal freckling, Lisch nodules; autosomal dominant; mutations in tumor-suppressor gene *NF1*
Neurofibromatosis 2	Bilateral acoustic neuromas, meningiomas	Autosomal dominant; mutations in tumor-suppressor gene *NF2*
Tuberous sclerosis	Facial angiofibromas, renal cell carcinoma, renal angiomyolipomas, myocardial rhabdomyoma	Autosomal dominant; mutations in tumor suppressor gene *TSC1* or *TSC2*
Noonan syndrome	JMML, ALL, neuroblastoma, brain tumors	Associated with distinct facial features, short stature, and heart defects; autosomal dominant; caused by RAS/MAPK pathway mutations (most frequently *PTPN11*)
Gorlin-Goltz syndrome (nevoid basal cell carcinoma syndrome)	Multiple basal cell carcinomas, medulloblastoma	Associated with odontogenic keratocysts, skeletal and skin anomalies; autosomal dominant; mutations in *PTCH1 or SUFU* gene
Li-Fraumeni syndrome	Osteosarcoma, soft tissue sarcoma, acute leukemias, breast and brain cancer, adrenal cortical tumors	Autosomal dominant; mutations in *TP53* tumor-suppressor gene
Beckwith-Wiedemann syndrome (BWS)	Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma	Associated with macrosomia, macroglossia, hemihypertrophy, omphalocele; epigenetic/genomic alterations of chromosome 11p15
Von Hippel–Landau syndrome	Hemangioblastomas of the brain and retina, pheochromocytoma, renal cell carcinoma	Autosomal dominant; mutations of tumor-suppressor *VHL* gene
Multiple endocrine neoplasia, type 1 (Wermer syndrome)	Parathyroid, pancreatic islet cell and pituitary tumors	Associated with hyperparathyroidism, ZES; autosomal dominant; mutations in *MEN1* tumor suppressor gene
Multiple endocrine neoplasia syndrome, type 2A (Sipple syndrome)	Medullary thyroid carcinoma, parathyroid tumors, pheochromocytoma	Associated with hyperparathyroidism; autosomal dominant; mutations in *RET* gene
Multiple endocrine neoplasia type 2B (multiple mucosal neuroma syndrome)	Mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma	Associated with Marfan habitus, neuropathy; autosomal dominant; mutations in *RET* gene
Familial adenomatous polyposis (FAP)	Colorectal, thyroid, stomach and small intestinal cancer, hepatoblastoma	Associated with multiple colon polyps; autosomal dominant; mutations in *APC* gene
Juvenile polyposis syndrome	Colorectal, stomach, small intestinal and rectal cancer	Autosomal dominant; mutations in *BMPR1A* and *SMAD4* gene
Hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome)	Colorectal cancer, endometrial and stomach cancer, many other cancers	Autosomal dominant; mutations in DNA mismatch repair genes *MSH2, MLH1*, *PMS1*, *PMS2,* and *MSH6*
Turcot syndrome	Colorectal cancer, brain tumors (glioblastoma, medulloblastoma)	Autosomal dominant; mutations in *APC* or *MLH1* gene
Gardner syndrome	Colorectal cancer, other tumors similar to FAP	Subtype of FAP; autosomal dominant; mutations in *APC* gene
Peutz-Jeghers	Breast cancer, colorectal cancer	Associated with hamartomatous polyps of GI tract;

syndrome		freckling of mouth, lips, fingers, and toes; autosomal dominant; mutations in *STK11* gene
Hereditary hemochromatosis	Hepatocellular carcinoma	Autosomal dominant; mutations in *HFE* gene; malignancy associated with cirrhotic liver
Glycogen storage disease type 1 (von Gierke disease)	Hepatocellular carcinoma, liver adenomas	Autosomal recessive; mutations in *G6PC* or *SLC37A4* gene
Diamond-Blackfan anemia (DBA)	Colorectal and other GI cancers, AML, MDS, osteogenic sarcoma	Autosomal dominant; mutations in the small or large subunit-associated ribosomal protein genes (most often *RPS19*)
Shwachman-Diamond syndrome	AML, MDS	Associated with neutropenia, diarrhea, and failure to thrive; autosomal recessive; mutations in *SBDS* gene
DICER1 syndrome	Pleuropulmonary blastoma (PPB), cystic nephromas, ovarian-Sertoli-Leydig tumors, multinodular goiter	Autosomal dominant; associated with mutations in *DICER1* gene
Familial neuroblastoma	Neuroblastoma	Autosomal dominant; mutations in *ALK* or *PHOX2B* gene
Hereditary paraganglioma-pheochromocytoma syndrome (PGL/PCC)	Paraganglioma, pheochromocytomas	Autosomal dominant; mutations in the mitochondrial enzyme succinate dehydrogenase protein family (*SDHA, B, C,* or *D*)
Severe congenital or cyclic neutropenia	AML, MDS	Associated with increased bacterial infections; typically autosomal dominant; mutations in *ELANE* or *HAX1* (Kostmann syndrome) gene

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; AMKL, acute megakaryocytic leukemia; GI, gastrointestinal; GU, genitourinary; HLH, hemophagocytic lymphohistiocytosis; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; MPNST, malignant peripheral nerve sheath tumor; TMD, transient myeloproliferative disorder; ZES, Zollinger-Ellison syndrome.

A 2nd mechanism responsible for an inherited predisposition to develop cancer involves *defects in DNA repair.* Syndromes associated with an excessive number of broken chromosomes caused by repair defects include **Bloom syndrome** (short stature, photosensitive telangiectatic erythema), **ataxia-telangiectasia** (childhood ataxia with progressive neuromotor degeneration, ocular telangiectasias), and **Fanconi anemia** (short stature, skeletal and renal anomalies, pancytopenia). As a result of the decreased ability to repair chromosomal defects, cells accumulate abnormal DNA that results in significantly increased rates of cancer, especially leukemia. **Xeroderma pigmentosum** likewise increases the risk of skin cancer because of defects in repair to DNA damaged by ultraviolet light. These disorders display an autosomal recessive pattern.

The 3rd category of inherited cancer predisposition is characterized by *defects in immune surveillance.* This group includes patients with **Wiskott-Aldrich syndrome** , severe combined immunodeficiency, common variable immunodeficiency, and the X-linked lymphoproliferative syndrome. The most common types of malignancy in these patients are lymphoma and leukemia. Cure rates for immunodeficient children with cancer are much poorer than for immunocompetent children with similar malignancies, suggesting a role for the immune system in cancer treatment as well as in cancer prevention.

Genome-wide association studies (GWAS) in a diverse array of childhood tumors, including ALL and neuroblastoma, have defined common **single nucleotide polymorphisms (SNPs)** in genes that are associated with cancer predisposition and collectively define regions of the genome that are critical in tumorigenesis. These alterations may occur in the coding or noncoding regions of the genome and typically lead to a relatively modest increase in cancer risk (2-10–fold over background) compared to the cancer susceptibility syndromes previously discussed, which may be associated with a lifetime risk of 50–100% of developing cancer. Furthermore, **whole genome sequencing** efforts across diverse pediatric cancers have identified that at least 8% of children who develop malignancy have a germline cancer-predisposing gene mutation. Many of these predisposing mutations occur in children without a family history of cancer or a known cancer predisposition syndrome.

Other Factors Associated With Oncogenesis

Viruses

Several viruses have been implicated in the pathogenesis of malignancy. The association of the **Epstein-Barr virus (EBV)** with Burkitt lymphoma and nasopharyngeal carcinoma was identified more than 40 years ago, although EBV infection alone is not sufficient for malignant transformation. EBV is also associated with mixed cellularity and lymphocyte-depleted Hodgkin disease, as well as some T-cell lymphomas, which is particularly intriguing because EBV normally does not infect T lymphocytes. The most conclusive evidence for a role of EBV in lymphogenesis is the direct causal role of EBV for **B-cell lymphoproliferative disease** in immunocompromised persons, especially those with HIV infection or those receiving immunosuppression after organ transplantation. **Human herpesvirus 8 (HHV-8)** is associated with the development of Kaposi sarcoma.

Children who are chronically infected with **hepatitis B virus** (hepatitis B surface antigen positive) have a 100-fold increased risk of developing **hepatocellular carcinoma** . In adults the latency period between viral infection and development of hepatocellular carcinoma approaches 20 yr. However, in children who acquire the viral infection through perinatal transmission, the latency period can be as short as 6-7 yr. The additional factors that are required for the malignant transformation of virally infected hepatocytes are not clear. **Hepatitis C virus** infection is another risk factor for hepatocellular carcinoma and is also associated with a subset of B-cell non-Hodgkin's lymphomas such as splenic lymphoma.

Almost all cervical carcinomas are caused by **human papillomaviruses (HPVs)** . High-risk HPVs include types 16 and 18 but also types 31, 33, 34, 45, 52, and 58, which together cause >90% of cervical cancers. Vaccines against the major oncogenic subtypes are now available and are likely to save hundreds of millions of lives worldwide. The low-risk HPVs, including 6 and 11, that are commonly found in genital warts, are almost never associated with malignancies. Like other virus-associated cancers, the presence of HPV alone is not sufficient to cause malignant transformation. The mechanism by which the HPV-associated **oncoproteins HPV E6** and **E7** induce malignant transformation is thought to involve both the TP53 and the RB tumor-suppressor protein, as well as other pathways that are critical in cell cycle progression, maintenance of telomerase and genomic stability, and apoptosis.

Genomic Imprinting

The development of cancer has also been linked to *genomic imprinting*, which is the selective inactivation of 1 of 2 alleles of certain genes depending on parental origin. **Beckwith-Wiedemann syndrome (BWS)** , the most commonly identified imprinting disorder, is an overgrowth syndrome characterized by macrosomia, macroglossia, hemihypertrophy, omphalocele, and renal anomalies that is also associated with an increased risk of Wilms tumor, hepatoblastoma, rhabdomyosarcoma, neuroblastoma, and adrenocortical carcinoma. This increased risk in developing cancer is directly associated with changes in the promoter methylation patterns (or loss of heterozygosity) of imprinted genes on chromosome 11p15.5. Normally, the maternally derived *IGF2* (insulin-like growth factor receptor 2) allele at this genomic locus is inactivated, thus suppressing *IGF2* expression. However, children with BWS show a gain of methylation in this promoter region, which allows for expression from both maternal and paternal *IGF2* alleles, leading to growth factor overexpression. Concurrently, the neighboring maternal *H19* gene (which encodes ncRNA and miRNA critical in growth suppression), is silenced by this hypermethylation, ultimately resulting in a progrowth phenotype and predisposition to tumor development.

Telomerase

Telomeres are a series of tens to thousands of TTAGGG repeats at the ends of chromosomes that are important for stabilizing the chromosomal ends and limiting breakage, translocation, and loss of DNA material. With DNA replication there is a progressive shortening of telomere length, which is a hallmark of cellular aging and acts as replicative senescence signal. In a majority of cancers, *telomerase* (encoded by the *TERT* gene), an enzyme that adds telomeres to the ends of chromosomes, becomes activated, usually through mutations in the *TERT* promoter. The telomerase-driven maintenance of telomere length in tumors enables unrestrained cellular proliferation by relieving a main checkpoint to cellular life span.

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CHAPTER 520

Principles of Cancer Diagnosis

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Childhood cancer is uncommon and can manifest with symptoms seen with benign illnesses. The challenge for the pediatrician is to be alert to the clues suggesting a diagnosis of cancer. In addition to the classic manifestations, any *persistent, unexplained symptom or sign* should be evaluated as potentially emanating from a cancerous or precancerous condition. As part of the diagnostic evaluation, the pediatrician and pediatric oncologist must convey the possible diagnosis to the patient and family in a sensitive and informative manner.

Signs and Symptoms

The symptoms and signs of cancer are variable and nonspecific in pediatric patients. The types of cancer that occur during the 1st 20 yr of life vary dramatically as a function of age—more so than at any other comparable age range (see Chapter 518). Unlike cancers in adults, childhood cancers usually originate from the deeper, visceral structures and from the parenchyma of organs rather than from the epithelial layers that line the ducts and glands of organs and compose the skin. In children, dissemination of disease at diagnosis is common, and presenting symptoms or signs are often caused by systemic involvement. **Pain** was one of the initial presenting symptoms in >50% of children with cancer in one study. Infants and young children cannot express or localize their symptoms well.

Solid tumors may produce **mass effects** that are nonspecific, such as compression of the thoracic airways or superior vena cava (lymphoma), the optic chiasm and hypothalamic-pituitary region (craniopharyngioma), and the 4th ventricle (cerebellar astrocytoma). Another factor is the variability in the physiology and biology of the host related to growth and development during infancy, childhood, and adolescence.

The signs of cancer in children are often attributed to other causes before the malignancy is recognized. Delays in diagnosis are particularly problematic during late adolescence and are the result of a variety of factors prominent in this age-group, including loss of health insurance coverage.

Although there is no clearly established set of warning signs of cancer in young people, the most common cancers in children suggest some guidelines that may be helpful in early recognition of signs and symptoms of cancer (Table 520.1). Most of the symptoms and signs are not specific and might represent other possibilities in a differential diagnosis. Nonetheless, these clues encompass the common cancers of childhood and have been very useful in early detection.

Table 520.1

Common Manifestations of Childhood Malignancies

	SIGNS AND SYMPTOMS	**POTENTIAL ETIOLOGY**	**POSSIBLE ONCOLOGIC DIAGNOSIS**
Constitutional/systemic	Fever, persistent or recurrent infection, neutropenia	Bone marrow infiltration	Leukemia, neuroblastoma
	Fever of unknown origin, weight loss, night sweats	Lymphoma	Hodgkin and non-Hodgkin lymphoma
	Painless, persistent lymphadenopathy	Lymphoma, metastatic solid tumor	Leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, thyroid carcinoma
	Hypertension	Renal or adrenal tumor	Neuroblastoma, pheochromocytoma, Wilms tumor
	Soft tissue mass	Local or metastatic tumor	Ewing sarcoma, osteosarcoma, neuroblastoma, thyroid carcinoma, rhabdomyosarcoma, Langerhans cell histiocytosis
Neurologic/ophthalmologic	Headache with emesis, visual disturbances, ataxia, papilledema, cranial nerve palsies	Increased intracranial pressure	Primary brain tumor; metastasis
	Leukokoria (white pupil)	Retinal mass	Retinoblastoma
	Periorbital ecchymosis	Metastasis	Neuroblastoma
	Miosis, ptosis, heterochromia	Horner syndrome: compression of cervical sympathetic nerves	Neuroblastoma
	Opsoclonus myoclonus, ataxia	Neurotransmitters? Autoimmunity?	Neuroblastoma
	Exophthalmos, proptosis	Orbital tumor	Rhabdomyosarcoma, lymphoma, Langerhans cell histiocytosis
Respiratory/thoracic	Cough, stridor, pneumonia, tracheal-bronchial	Anterior mediastinal mass	Germ cell tumor, non-Hodgkin lymphoma, Hodgkin lymphoma

	compression; superior vena cava syndrome		
	Vertebral or nerve root compression; dysphagia	Posterior mediastinal mass	Neuroblastoma, neuroenteric cyst
Gastrointestinal	Abdominal mass	Adrenal, renal, or lymphoid tumor	Neuroblastoma, Wilms tumor, lymphoma
	Diarrhea	Vasoactive intestinal polypeptide	Neuroblastoma, ganglioneuroma
Hematologic	Pallor, anemia	Bone marrow infiltration	Leukemia, neuroblastoma
	Petechiae, thrombocytopenia	Bone marrow infiltration	Leukemia, neuroblastoma
Musculoskeletal	Bone pain, limp, arthralgia	Primary bone tumor, metastasis to bone	Osteosarcoma, Ewing sarcoma, leukemia, neuroblastoma
Endocrine	Diabetes insipidus, galactorrhea, poor growth	Neuroendocrine involvement of hypothalamus or pituitary gland	Adenoma, craniopharyngioma, prolactinoma, Langerhans cell histiocytosis

Adapted from Marcdante KJ, Kliegman RM, Jenson HB, et al, editors: *Nelson essentials of pediatrics,* ed 6, Philadelphia, 2011, Saunders, p 588.

Physical Examination

Physical examination findings in a child with malignancy are dependent on whether the cancer is systemic or localized. The cancers most common in children involve the **lymphohematopoietic system** . When the bone marrow is compromised by malignancy (e.g., leukemia, disseminated neuroblastoma), typical findings include pallor from anemia; bleeding, petechiae, or purpura from thrombocytopenia or coagulopathy; cellulitis or other localized infection from leukopenia; and skin nodules (especially in infants) and hepatosplenomegaly from malignant leukocytosis. Abnormalities found in lymphatic malignancies include peripheral **adenopathy** (Fig. 520.1) and signs of superior vena cava syndrome from an anterior mediastinal **mass** (Fig. 520.2), including respiratory distress, and facial and neck plethora and edema. Enlargement of cervical lymph nodes is common in children, but when persistent, progressive, and painless, it often suggests **lymphoma** . In particular, supraclavicular adenopathy suggests underlying malignancy.

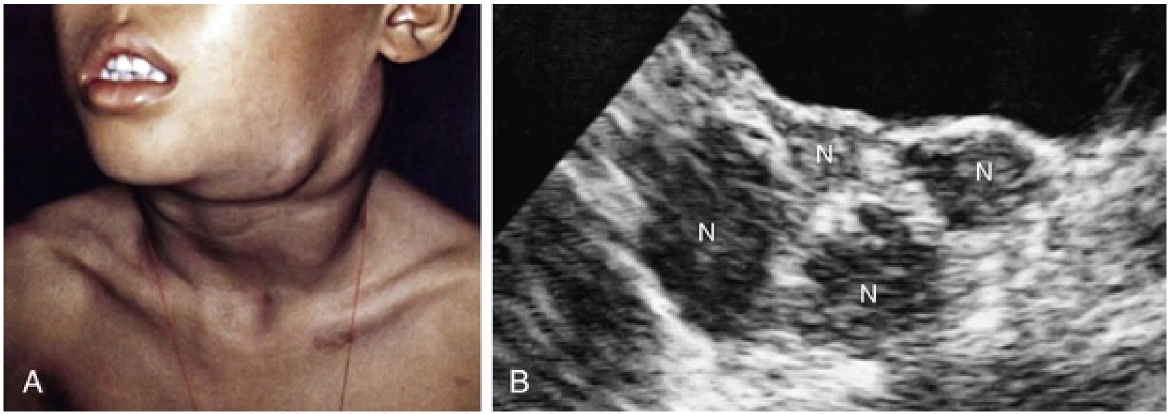

FIG. 520.1 Cervical lymphadenopathy. Manifestations on A, physical examination, and B, ultrasound examination. N, Abnormally enlarged lymph nodes. (From Sinniah D, D'Angio GJ, Chatten J, et al: *Atlas of pediatric oncology,* London, 1996, Arnold.)

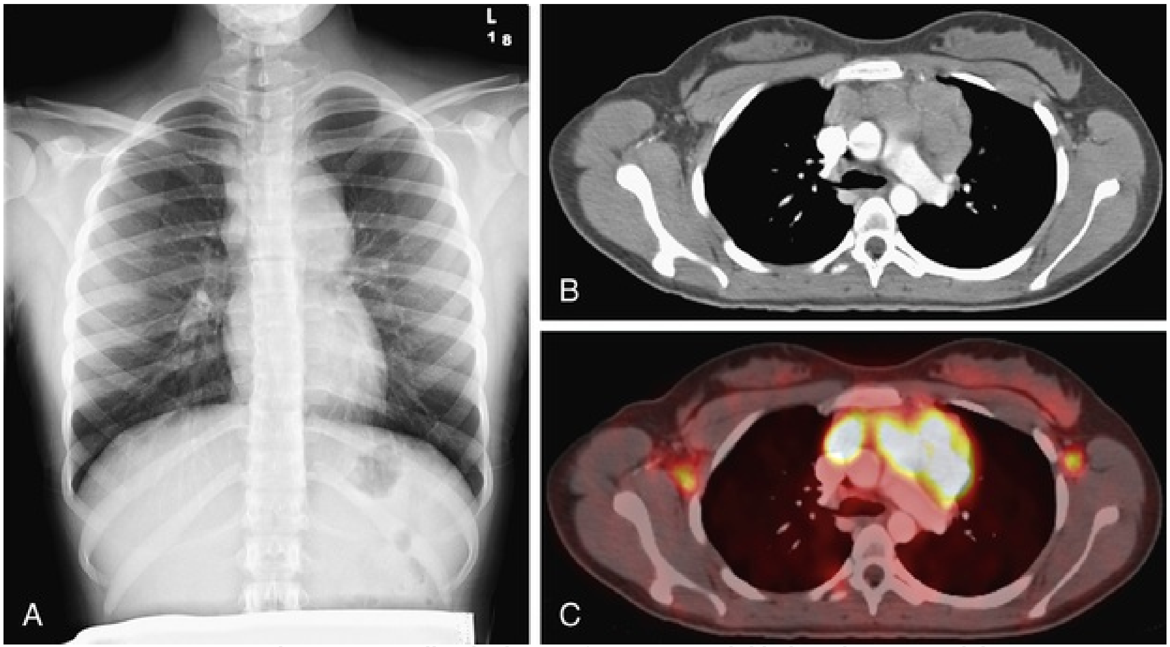

FIG. 520.2 Anterior upper mediastinal mass from non-Hodgkin lymphoma. A, Plain chest radiograph. B, CT scan. C, Positron emission tomography (PET) scan.

Abnormalities of the central nervous system (CNS) that can indicate cancer include decreased level of consciousness, cranial nerve palsies, ataxia, afebrile seizures, ptosis, decreased visual activity, neuroendocrine deficits, and increased intracranial pressure, which may be diagnosed by the presence of papilledema (Fig. 520.3). Any focal neurologic deficit in the motor or sensory system, especially a decrease in cranial nerve function, should prompt further investigation for malignancy.

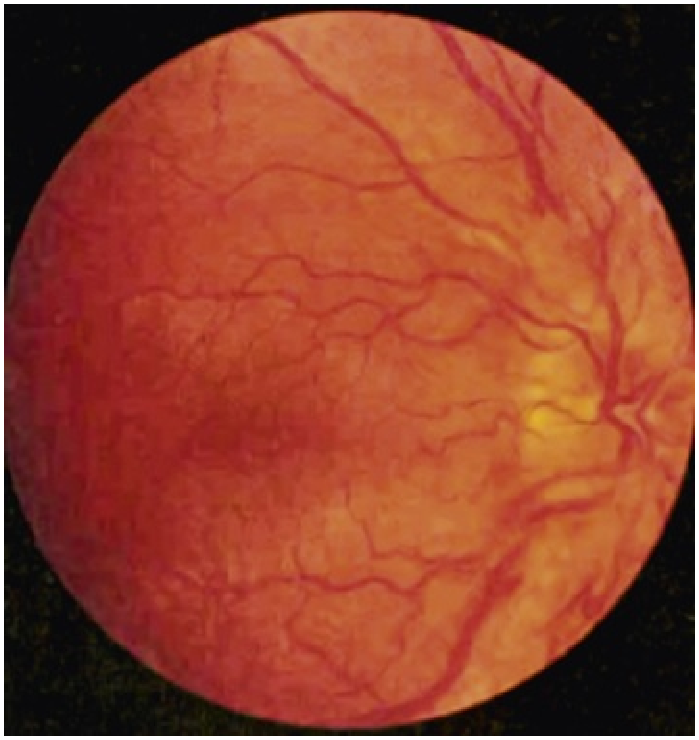

FIG. 520.3 **Papilledema on fundoscopic examination. (From Sinniah D, D'Angio GJ, Chatten J, et al: *Atlas of pediatric oncology,* London, 1996, Arnold.)**

Abdominal masses can be divided into upper, middle, and lower locations. Malignancies in the upper abdomen include Wilms tumor, neuroblastoma, hepatoblastoma, germ cell tumors, and sarcomas. Enlargement of the liver or spleen from leukemia can be mistaken for an upper abdominal mass. Mid-abdominal masses include non-Hodgkin lymphoma, neuroblastoma, germ cell tumors, and sarcomas. Lower abdominal masses include ovarian tumors, germ cell tumors, and sarcomas.

Rhabdomyosarcoma usually appears as an extremity mass, particularly in adolescents. These tumors can be deceptively benign in appearance, but as with all unexplained masses, require immediate attention. Sacrococcygeal masses in neonates are usually **teratomas** , which are usually benign but can undergo malignant transformation if not removed promptly. **Neuroblastoma** can present as “blueberry muffin” spots on the skin of neonates or as periorbital ecchymosis in older children.

Ophthalmologic presentation of malignancy includes a **white pupillary reflex** (Fig. 520.4) rather than the usual red reflection from incident light. A white pupillary reflex is essentially pathognomonic for retinoblastoma, although some benign conditions can mimic this finding. **Proptosis** can be produced by rhabdomyosarcoma, neuroblastoma, lymphoma, and Langerhans cell histiocytosis. Horner syndrome, iris heterochromia, and opsoclonus-myoclonus all suggest a diagnosis of neuroblastoma.

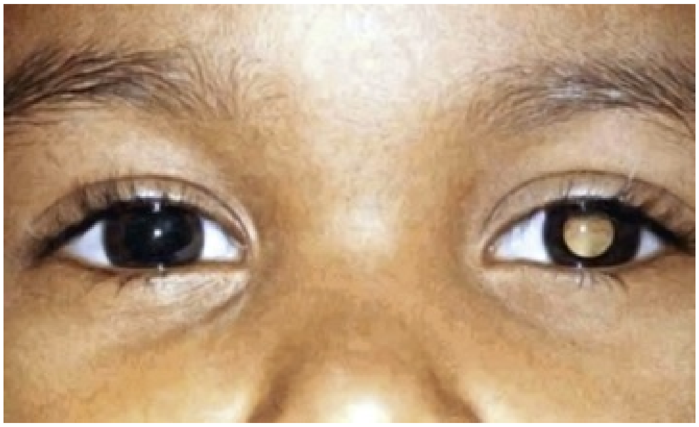

FIG 520.4 **White pupillary reflex in the left eye. (From Sinniah D, D'Angio GJ, Chatten J, et al: *Atlas of pediatric oncology,* London, 1996, Arnold.)**

Age-Related Manifestations

Because various types of cancer in children occur at specific ages, the physician should tailor the history and physical examination based on the age of the child. The **embryonal tumors** , including neuroblastoma, Wilms tumor, retinoblastoma, hepatoblastoma, and rhabdomyosarcoma, usually occur during the 1st 2 yr of life (see Fig. 518.4 in Chapter 518). From age 1-4 yr, **acute lymphoblastic leukemia** peaks in incidence. **Brain tumors** have a peak incidence in the 1st decade of life. **Non-Hodgkin lymphomas** are uncommon earlier than 5 yr of age but steadily increase thereafter. During adolescence, bone tumors, Hodgkin disease, and the gonadal and soft tissue sarcomas predominate. Hence, for infants and toddlers, special attention should be paid to the possibility of embryonal and intraabdominal tumors. Preschool-age and early school-age children showing compatible signs and symptoms should be specifically evaluated for **leukemia** . School-age children might present with lymphoma or with brain tumors. Adolescents require assessment for bone and soft tissue sarcomas and gonadal malignancies, as well as for Hodgkin lymphoma.

Early Detection

The prognosis of malignancy in children depends primarily on tumor type, extent of disease at diagnosis, and rapidity of response to treatment. Early diagnosis helps to ensure that appropriate therapy is given in a timely manner and thus optimizes the chances of cure. Because most physicians in general practice rarely encounter children with undiagnosed cancer, they should remember to investigate the possibility of malignancy, especially when they encounter an *atypical course* of a common childhood condition, *unusual manifestations* that do not fit common conditions, and any *persistent symptom* that defies diagnosis.

Delays in diagnosis are particularly likely in certain clinical situations. The cardinal symptom of both **osteosarcoma** and **Ewing sarcoma** is localized and usually persistent pain. Because these tumors occur during the 2nd decade of life, a time of increased physical activity, patients often assume the pain results from trauma. Prompt radiologic evaluation can help confirm the diagnosis. **Lymphoma** , especially during adolescence, often manifests as an anterior mediastinal mass. Symptoms such as chronic cough, unexplained shortness of breath, or “new-onset asthma” are typical with this presentation and are often overlooked. Tumors of the nasopharynx or middle ear can mimic infection. Prolonged, unexplained ear pain, nasal discharge, retropharyngeal swelling, and trismus should be investigated as possible signs of malignancy.

Early symptoms of **leukemia** may be limited to prolonged or unexplained low-grade fever or bone and joint pain. Blood counts with abnormalities in ≥2 cell lines might indicate the need for bone marrow examination, even when leukemic blast cells are not seen in the blood smear (see Table 520.1).

Mass screening for children with malignancy is not feasible. A screening program to detect early-stage neuroblastoma was successful in documenting more cases of the disease but had no impact on overall outcome. However, certain children are at increased risk for cancer and require an individualized plan to ensure early detection of malignancy. Select examples include children with certain chromosome abnormalities, such as Down syndrome, Klinefelter syndrome, and WAGR syndrome (Wilms tumor, *a* niridia, *g* enital abnormalities, mental *r* etardation); children with overgrowth syndromes, such as Beckwith-Wiedemann syndrome and hemihypertrophy; and children with certain inherited single-gene disorders, including retinoblastoma, *P53* mutations (Li-Fraumeni syndrome), familial adenomatous polyposis, and neurofibromatosis (see Table

519.2 in Chapter 519).

Ensuring the Diagnosis

When a malignant neoplasm is suspected, the immediate goal is to confirm the diagnosis. A tentative diagnosis can often be established on the basis of the patient's age, symptoms, and location of masses. Selected imaging techniques and tumor markers can facilitate the diagnostic approach (Table 520.2). Especially when a solid tumor is present, the pediatric oncologist, surgeon, and pathologist should work as a team to determine the site of biopsy, amount of tissue required, and whether fine-needle aspiration, percutaneous image-guided biopsy, incisional biopsy, or excisional biopsy and tumor resection are indicated. For select situations, at the time of the initial diagnostic procedure, plans for bone marrow aspiration and biopsy and placement of central venous access may be appropriate.

Table 520.2

Workup of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases

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MALIGNANCY	BONE MARROW ASPIRATE OR BIOPSY	CHEST X-RAY FILM	CT SCAN	MRI	PET SCAN	BONE SCAN	CSF ANALYSIS	SPECIFIC MARKERS
Leukemia	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	—	—	—	—	Yes	—
Non-Hodgkin lymphoma	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	Yes	—	Yes	Yes (selected cases)	Yes	—
Hodgkin lymphoma	Yes (in advanced stage)	Yes	Yes	—	Yes	No	—	—
CNS tumors	—	—	—	Yes	—	—	Yes (selected tumors)	—
Neuroblastoma	Yes (includes	—	Yes	Yes	—	Yes	—	Urine VMA,

	cytogenetics, molecular studies)							HVA
Wilms tumor	—	Yes	Yes	—	—	—	—	—
Rhabdomyosarcoma	Yes	Yes	Yes	Yes (select sites)	—	Yes	Yes (for parameningeal tumors only)	—
Osteosarcoma	—	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes	—	—
Ewing sarcoma	Yes (selected cases)	Yes	Yes (of chest)	Yes (for primary tumors)	Yes	Yes (Selected cases)	—	—
Germ cell tumors	—	Yes	Yes	Consider MRI of brain	—	—	—	AFP, HCG
Liver tumors	—	Yes	Yes	—	—	—	—	AFP
Retinoblastoma	Selected cases	—	Yes	Yes (includes brain)	—	Selected cases	Selected cases	—

AFP, α-Fetoprotein; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; HCG, human chorionic gonadotropin; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; VMA, vanillylmandelic acid.

Modified from Marcdante KJ, Kliegman RM, Jenson HB, et al, editors: *Nelson essentials of pediatrics,* ed 6, Philadelphia, 2011, Saunders, p 589.

Pathologic evaluation of pediatric malignancies requires appropriate handling of tissue so that multiple different techniques can be used. It is important that fresh tissue not be placed in formalin. Besides routine light microscopy, pathologic evaluation may include immunochemistry, flow cytometry, cytogenetics, and molecular genetic studies (e.g., fluorescence in situ hybridization and reverse-transcriptase polymerase chain reaction). Emerging technologies include DNA microarray analysis and cancer genome sequencing that can identify specific gene expression patterns and sequences in tumors. In time, these technologies might ensure more accurate classification and treatment.

Staging

Once a specific diagnosis is confirmed, studies to define the extent of the malignancy are necessary to determine prognosis and treatment. Table 520.2 outlines the minimum evaluation required for common pediatric malignancies. In addition, for many tumors (e.g., Wilms tumor, neuroblastoma, rhabdomyosarcoma) a surgical staging system is used. Surgical stage can be determined at the time of the initial diagnostic procedure or subsequently. For example, a patient who has abdominal surgery for possible Wilms tumor or neuroblastoma should have careful evaluation and biopsy of all adjacent lymph nodes. A child with rhabdomyosarcoma can require a subsequent biopsy of sentinel lymph nodes as determined by scintigraphy or dye injection adjacent to the primary tumor. The pathologist facilitates staging by examining margins of the specimen to determine residual tumor.

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CHAPTER 521

Principles of Cancer Treatment

Archie Bleyer, A. Kim Ritchey, Erika Friehling

Treatment of children with cancer begins with an absolute requirement for the correct diagnosis (including subtype), proceeds through accurate and thorough staging of the extent of disease and determination of prognostic subgroup, provides appropriate multidisciplinary and usually multimodal therapy, and requires assiduous evaluation for possible recurrent disease and late adverse effects of the disease and the therapies rendered. Throughout treatment, every child with cancer should have the benefit of the expertise of specialized teams of providers of pediatric cancer care, including pediatric oncologists, pathologists, radiologists, surgeons, radiotherapists, nurses, and support staff, including nutritionists, social workers, psychologists, pharmacists, other medical specialists, and teachers trained to work with seriously ill children.

The best chance for cure of cancer is during the initial course of treatment; the cure rates for patients with recurrent disease are much lower than those for patients with primary disease. All patients with cancer should be referred to an appropriate specialized center as soon as possible when the diagnosis of cancer is suspected. All such centers in North America are identified on the **Children's Oncology Group** website (http://www.childrensoncologygroup.org) and on the **National Cancer Institute** (NCI) cancer trials website (http://www.clinicaltrials.gov). In the United States, the NCI's Clinical Trials Cooperative Groups Program is associated with a >80% reduction in the incidence of mortality from childhood cancer despite an overall increase in cancer incidence during this interval (Fig. 521.1). After what appeared to be a plateau in the rate of decline in mortality in the early 2000s, there is evidence that the mortality rate continues to decline. Notably, a greater decline in mortality has been seen in the adolescent and young adult population when compared to children <15 yr old, reversing prior trends (Fig. 521.2). The most current information on treatment of all types of childhood cancer is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/pediatrictreatment).

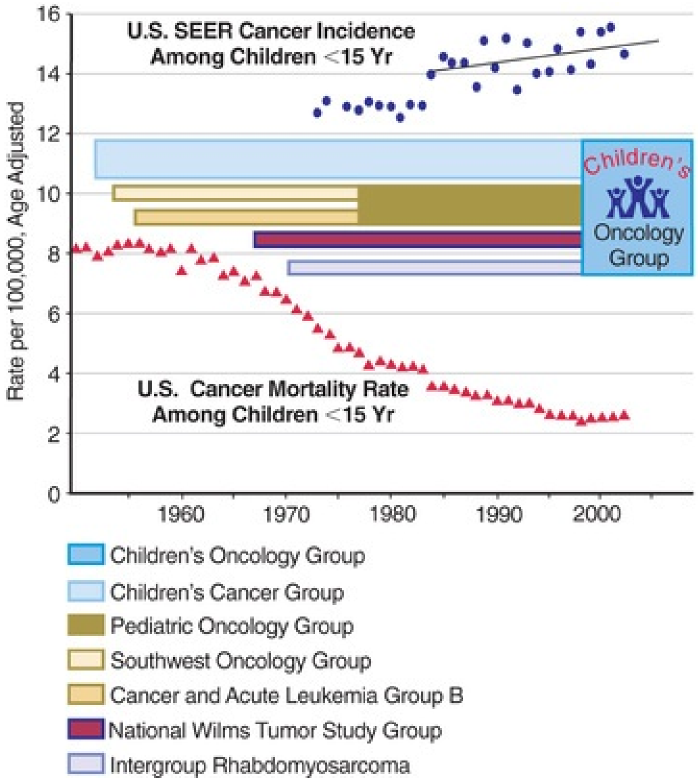

FIG. 521.1 Reduction in the national cancer mortality rate among children younger than 15 yr of age *(triangles)* in the United States as a direct consequence of the National Cooperative Group Program sponsored by the National Cancer Institute, and in comparison to the rising incidence of cancer before age 15 *(circles).* The *horizontal bars* indicate the duration of the existence of the national pediatric cancer cooperative groups, beginning with the Children's Cancer Group in 1955. Other groups are the Pediatric Oncology Group, which was derived from the Pediatrics Divisions of the Southwest Oncology Group and the Cancer and Acute Leukemia Group B; the National Wilms Tumor Study Group; and the Intergroup Rhabdomyosarcoma Study Group. In 2000 the 4 pediatric cooperative groups merged into the Children's Oncology Group. (Incidence and mortality rate data from Ries LAG, Eisner MP, Kosary CL, et al, editors: *SEER Cancer Statistics Review,* 1975–2002, Bethesda, MD, NCI [National Cancer Institute]; http://seer.cancer.gov/csr/1975_2002/ , based on November 2004 SEER [Surveillance Epidemiology and End Results] data submission. The mortality rate data are national rates, and the incidence data are derived from the SEER program, representing approximately 15% of the United States. The most current information on treatment of all types of childhood cancer is available in the PDQ [Physician Data Query] on the

NCI website, http://www.cancer.gov/cancertopics/pdq/pediatrictreatment .)

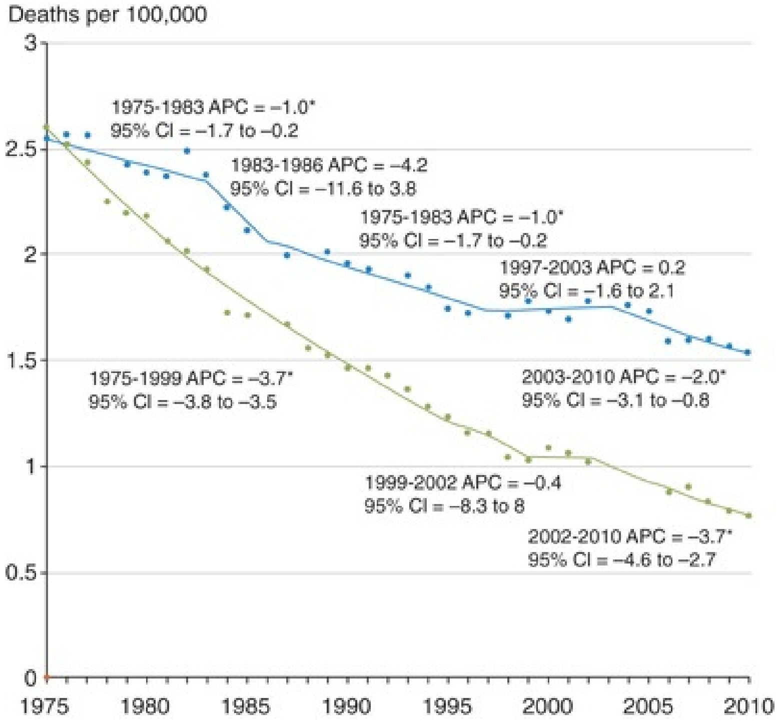

FIG. 521.2 Age-adjusted mortality trends for all malignant cancers among children <20 yr old in the United States from 1975 through 2010, along with annual percentage changes (APCs) for joinpoint segments. *Asterisk* indicates that the slope of the joinpoint segment is statistically different from zero ($p < .05$). The *green line* indicates leukemias and lymphomas, and the *blue line* indicates all other cancer sites; CI, confidence interval. (From Smith MA, Altekruse SF, Adamson PC, et al: Declining childhood and adolescent cancer mortality, *Cancer* 120:2497–2506, 2014.)

Diagnosis and Staging

Accurate diagnosis and staging of the extent of disease are imperative, especially for childhood cancers that have high cure rates, because the nature of therapy depends strongly on the type of cancer. In addition, **prognostic subgroups** based on the stage of disease have been established for most cancers that occur in children. Accordingly, children with a better prognosis are treated with less intensive therapy, including lower doses of chemotherapy or radiation therapy, a shorter duration of treatment, or elimination of at least 1 treatment modality (radiation therapy, chemotherapy, surgery). Accurate staging thus reduces the risk of excessive acute adverse effects and long-term complications of therapy in patients whose prognosis indicates that less therapy is required for cure. **Overtreatment** of patients with a more favorable prognosis is a definite risk if the patient is not referred to a cancer treatment center. Conversely, **undertreatment** also is a clear risk if the diagnosis and stage are not correct, resulting in a compromise of an otherwise high potential for cure.

Diagnostic imaging is a critical phase of evaluation in most children with solid tumors (i.e., cancers other than leukemia). MRI, CT, ultrasonography, scintigraphy (nuclear medicine scans), positron emission tomography (PET), and spectroscopy, as appropriate, all serve a clear purpose in the evaluation of children with cancer, not only before treatment to determine the extent of disease and the appropriate therapy but also during follow-up to determine whether the therapy was effective. In addition, response to treatment as determined by imaging techniques is being increasingly used to guide changes in the therapy.

Expertise in pathology and laboratory medicine provides critical diagnostic support and guides therapy in most children with cancer. Relatively noninvasive methods of obtaining tumor tissue (e.g., fine-needle aspiration, percutaneous image-guided biopsy) can be performed in pediatric centers with appropriate expertise in diagnostic imaging, interventional radiology, cytology, and anesthesia support. *Sentinel node mapping* is helpful in the staging of some children's cancers. Determining the adequacy of surgery by evaluating frozen sections of the surgical margins for tumor cells is essential in many tumor operations.

A Multimodal, Multidisciplinary Approach

Many pediatric subspecialties are involved in the evaluation, treatment, and management of children with cancer, including provision of primary therapy and supportive care services (Fig. 521.3). More than 2 of the primary modalities are often used together, with chemotherapy being the most widely used, followed, in order of use, by surgery, radiation therapy, and biologic agent therapy (Fig. 521.4).

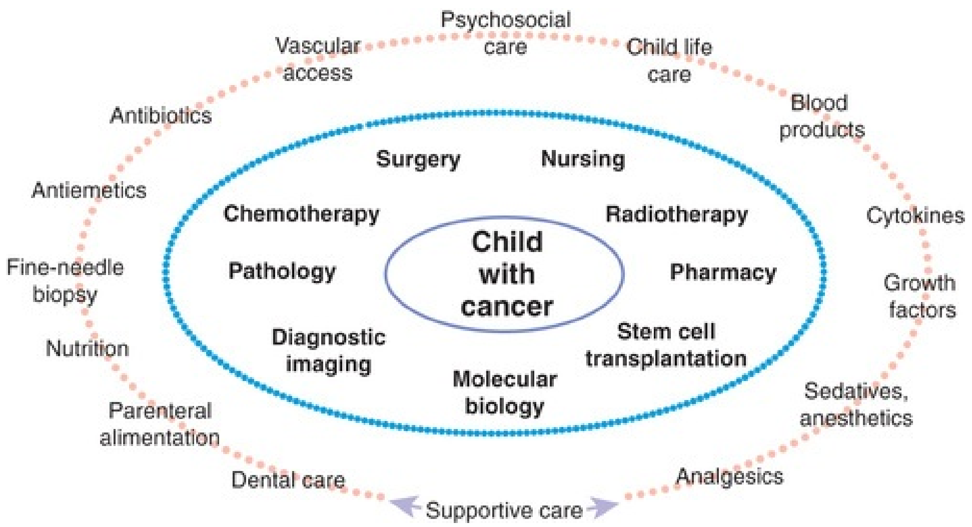
Psychosocial care
Vascular access
Child life care
Antibiotics
Blood products
Antiemetics
Cytokines
Fine-needle biopsy
Growth factors
Nutrition
Sedatives, anesthetics
Parenteral alimentation
Analgesics
Dental care
Supportive care
Surgery
Nursing
Chemotherapy
Radiotherapy
Pathology
Pharmacy
Child with cancer
Diagnostic imaging
Stem cell transplantation
Molecular biology

FIG. 521.3 Multidisciplinary care of children with cancer. The *inner circle* designates primary modalities, and the *outer ring* identifies supportive care elements to which all children with cancer have access.

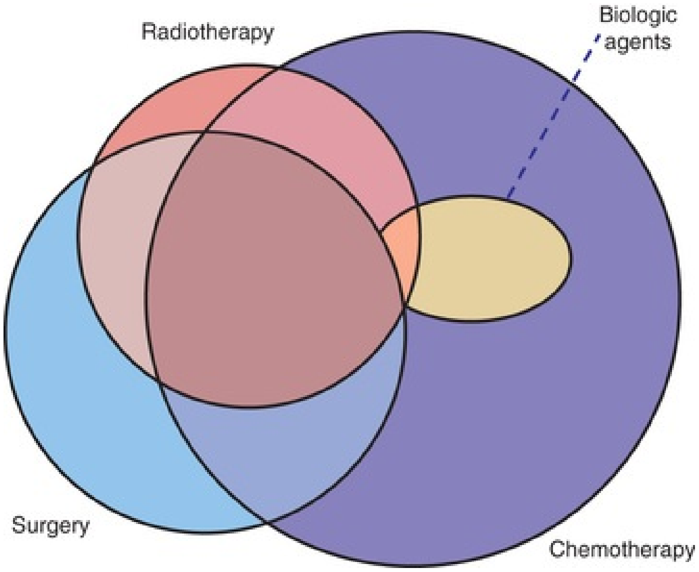
Radiotherapy
Biologic agents
Surgery
Chemotherapy

FIG. 521.4 The primary modalities of therapy used in the treatment of children with cancer. The relative sizes of the circles designate the approximate proportion of overall role in the management of pediatric cancers.

The **leukemias** that occur in childhood usually are managed with chemotherapy alone, with a small proportion of patients receiving cranial or craniospinal radiation therapy to prevent or treat overt central nervous system (CNS) leukemia. Children with **non-Hodgkin lymphoma** also are treated with chemotherapy alone, with the exception of radiation therapy for CNS involvement. Localized therapy with surgery or irradiation, or both, is an important component of treatment of most solid tumors, including **Hodgkin lymphoma** , but systemic multiagent chemotherapy usually is necessary because tumor dissemination generally is present even if undetectable. Chemotherapy alone usually is not adequate to eradicate gross residual tumors. Therefore, it is not unusual for children with malignant tumors to require treatment with all 3 modalities (see Fig. 521.4). Unfortunately, most treatments that are effective in children with cancer have a narrow therapeutic index (a low ratio of efficacy to toxicity). The acute and chronic adverse effects of these treatments can be minimized but not entirely avoided.

Biologic agent therapy has become an important modality in a few childhood cancers (see Fig. 521.4). This type of treatment generally refers to immunotherapy, biologic response modifiers, or endogenously occurring molecules that have therapeutic effects in supraphysiologic doses. Examples are retinoic acid therapy in acute promyelocytic leukemia, monoclonal antibody therapy for neuroblastoma and certain non-Hodgkin lymphomas, tyrosine kinase inhibitors such as imatinib mesylate for chronic myelogenous and Philadelphia chromosome–positive leukemias, and radioactive metaiodobenzylguanidine (MIBG) therapy for neuroblastoma. In addition, immune therapy directed at tumor cell antigens with modification of T-cell receptors (TCRs) or chimeric antigen receptors (CARs) have improved survival in patients with chemotherapy-resistant diseases (leukemia, lymphoma) and have shown promise in solid tumors and brain tumors.

Chemotherapy is used more widely in children than in adults because children better tolerate the acute adverse effects, and the malignant diseases that occur in childhood are more responsive to chemotherapy than are malignant diseases of adults. Radiation therapy is used sparingly in children because they are more vulnerable than adults to its late adverse effects.

Whenever possible, treatment is given on an outpatient basis. Children should remain living at home and in school as much as possible throughout treatment. Increasingly, pediatric cancer therapies are being administered to ambulatory patients, with the advent of such innovations as programmable infusion pumps, oral chemotherapeutic regimens, early discharge from hospital with intensive outpatient supportive care, and home healthcare services. Some patients miss a considerable amount of school in the 1st year after diagnosis because of the intensity of therapy or its adverse effects and the ensuing complications of the disease or therapy. Tutoring should be encouraged so that children do not fall behind in their schooling; counseling should be provided as appropriate. In-hospital school services should be provided for patients who must spend much of their time as inpatients receiving therapy for disease or for managing adverse effects.

Development of selective, highly effective therapy for cancer in both children and adults had been hindered by a lack of understanding of the molecular mechanisms that underlie malignant transformation. De novo or acquired *resistance* to chemotherapy and radiation therapy remains an obstacle to cure. Ongoing discoveries of molecular and cellular mechanisms that explain the cancer process have led to increasingly specific antineoplastic therapies, generally referred to as **molecularly targeted therapies** . Their most prominent feature is a relative lack of normal tissue toxicity, such that the additional therapeutic benefit occurs with minimum additional toxicity. Many of the new biologic agent therapies, such as imatinib and rituximab, fall into this category (Table 521.1). **Complementary** and **alternative remedies** are increasingly being provided by parents to their children with cancer, with or without knowledge of the medical professionals entrusted with the child's care (see Chapter 78). Many of these have not been evaluated by rigorous testing, and most are ineffective; some are toxic or interfere with the metabolism of other drugs.

Table 521.1

Protein Tyrosine Kinase Inhibitors and Monoclonal Antibodies

AGENT	TARGET	MALIGNANCY
Imatinib	BCR-ABL	CML Philadelphia chromosome–positive ALL
	PDGFRα	Hyper-eosinophilic syndrome Systemic mastocytosis
	PDGFRβ	CMML
	cKIT	Systemic mastocytosis Gastrointestinal stromal tumor
Dasatinib, nilotinib	BCR-ABL	CML Philadelphia chromosome–positive ALL
Gefitinib, erlotinib, cetuximab	EGFR	Non–small cell lung cancer
Rituximab	CD20	Non-Hodgkin lymphoma
Trastuzumab	ERBB2/HER-2	Breast cancer
Bevacizumab	VEGFR-1, -2	Non–small cell lung cancer Breast cancer Renal cell carcinoma Colorectal cancer

		Glioblastoma and other brain tumors

ALL, Acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia.

Discussing the Treatment Plan With the Patient and Family

The diagnostic and treatment plan must be carefully explained to parents and, if the child is old enough to understand, to the patient. Children should be given as much information as they can understand and would find useful or that information they express a desire or wish to know. Effects of treatment, such as the possible need to amputate a limb, loss of hair during chemotherapy, and possible temporary or permanent functional impairment, must be anticipated and fully discussed. The possibility and probability of death from cancer should be covered in an age-appropriate manner. It usually is necessary to repeat explanations several times before distraught family members fully understand. Throughout treatment, parents, patients, siblings, and medical staff will all need help in expressing feelings of anxiety, depression, guilt, and anger. The pediatrician, pediatric oncologist, and nurses should call on experienced professionals, including pediatric social workers, child psychologists and psychiatrists, child life specialists, and schoolteachers with special expertise in managing students with cancer, to assist when needed.

Treatments

Chemotherapy

The most widely used modality in pediatric cancer therapy is chemotherapy (see Fig. 521.4). Therapy usually involves a combination of drugs, such as VAC (vincristine, dactinomycin [Actinomycin D], and cyclophosphamide) and CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin/Adriamycin], vincristine [Oncovin], and prednisone). Sequential single-drug therapy rarely results in complete responses, and partial responses usually are infrequent and transient and grow progressively shorter in duration with each drug used. Combination chemotherapy is the standard when combinations of drugs with different mechanisms of action and nonoverlapping toxicities were first demonstrated to be effective in childhood leukemia. Most of the cytotoxic drugs for childhood cancer are selected from several classes of agents, including alkylating agents, antimetabolites, antibiotics, hormones, plant alkaloids, and topoisomerase inhibitors (Table 521.2). The increased metabolic and cell cycle activity of malignant cells makes them more susceptible to the cytotoxic effects of these types of agents (Fig. 521.5).

Table 521.2

Common Chemotherapeutic Agents Used in Children

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Methotrexate	Folic acid antagonist; inhibits dihydrofolate reductase	ALL, non-Hodgkin lymphoma, osteosarcoma, Hodgkin lymphoma, medulloblastoma	Myelosuppression, mucositis, stomatitis, dermatitis, hepatitis With long-term administration, osteopenia and bone fractures With high-dose administration, renal and CNS toxicity With intrathecal administration, arachnoiditis, leukoencephalopathy, and leukomyelopathy	Systemic administration may be PO, IM, or IV; also may be administered intrathecally. Plasma methotrexate levels must be monitored with high-dose therapy and when low doses are administered to patients with renal dysfunction, and leucovorin rescue applied accordingly.
6-Mercaptopurine (Purinethol)	Purine analog; inhibits purine synthesis	ALL	Myelosuppression, hepatic necrosis, mucositis; allopurinol increases toxicity.	Allopurinol inhibits metabolism.
Cytarabine (cytosine arabinoside; Ara-C)	Pyrimidine analog; inhibits DNA polymerase	ALL, AML, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, myelosuppression, conjunctivitis, mucositis, CNS dysfunction With intrathecal administration, arachnoiditis, leukoencephalopathy, and leukomyelopathy	Systemic administration may be PO, IM, or IV; may also be administered intrathecally.
Cyclophosphamide (Cytoxan)	Alkylates guanine; inhibits DNA synthesis	ALL, non-Hodgkin lymphoma, Hodgkin	Nausea, vomiting, myelosuppression, hemorrhagic cystitis,	Requires hepatic activation and thus is less

		lymphoma, soft tissue sarcoma, Ewing sarcoma, Wilms tumor, neuroblastoma	pulmonary fibrosis, inappropriate ADH secretion, bladder cancer, anaphylaxis	effective in presence of liver dysfunction. Mesna prevents hemorrhagic cystitis.
Ifosfamide (Ifex)	Alkylates guanine; inhibits DNA synthesis	Non-Hodgkin lymphoma, Wilms tumor, soft tissue sarcoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, CNS dysfunction, cardiac toxicity, anaphylaxis	Mesna prevents hemorrhagic cystitis.
Doxorubicin (Adriamycin), daunorubicin (Cerubidine), and idarubicin (Idamycin)	Binds to DNA, intercalation	ALL, AML, osteosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma	Nausea, vomiting, cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia	Dexrazoxane reduces risk of cardiotoxicity.
Dactinomycin	Binds to DNA, inhibits transcription	Wilms tumor, rhabdomyosarcoma, Ewing sarcoma	Nausea, vomiting tissue necrosis on extravasation, myelosuppression, radiosensitizer, mucosal ulceration	
Bleomycin (Blenoxane)	Binds to DNA, cleaves DNA strands	Hodgkin disease, non-Hodgkin lymphoma, germ cell tumors	Nausea, vomiting, pneumonitis, stomatitis, Raynaud phenomenon, pulmonary fibrosis, dermatitis	
Vincristine (Oncovin)	Inhibits microtubule formation	ALL, non-Hodgkin lymphoma, Hodgkin disease, Wilms tumor, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma	Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression	IV administration only; must not be allowed to extravasate.
Vinblastine (Velban)	Inhibits microtubule formation	Hodgkin lymphoma, non-Hodgkin lymphoma, Langerhans cell histiocytosis, CNS tumors	Local cellulitis, leukopenia	IV administration only; must not be allowed to extravasate.
L -Asparaginase	Depletion of L -asparagine	ALL; AML, when used in combination with cytarabine	Allergic reaction pancreatitis, hyperglycemia, platelet dysfunction and coagulopathy, encephalopathy	PEG-asparaginase now preferred to L -asparaginase.
Pegaspargase (Oncaspar)	Polyethylene glycol conjugate of L -	ALL	Indicated for prolonged asparagine depletion and	

	asparagine		for patients with allergy to L -asparaginase	
Prednisone and dexamethasone (Decadron)	Lymphatic cell lysis	ALL; Hodgkin lymphoma, non-Hodgkin lymphoma	Cushing syndrome, cataracts, diabetes, hypertension, myopathy, osteoporosis, avascular necrosis, infection, peptic ulceration, psychosis	
Carmustine (BiCNU)	Carbamylation of DNA; inhibits DNA synthesis	CNS tumors, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, delayed myelosuppression (4-6 wk); pulmonary fibrosis, carcinogenic stomatitis	Phenobarbital increases metabolism, decreases activity.
Carboplatin and cisplatin (Platinol)	Inhibits DNA synthesis	Osteosarcoma, neuroblastoma, CNS tumors, germ cell tumors	Nausea, vomiting, renal dysfunction, myelosuppression, ototoxicity, tetany, neurotoxicity, hemolytic-uremic syndrome, anaphylaxis	Aminoglycosides may increase nephrotoxicity.
Etoposide (VePesid)	Topoisomerase inhibitor	ALL, non-Hodgkin lymphoma, germ cell tumor, Ewing sarcoma	Nausea, vomiting, myelosuppression, secondary leukemia	
Tretinoin (all *trans*- retinoic acid) and isotretinoin (*cis* -retinoic acid; Accutane)	Enhances normal differentiation	Acute promyelocytic leukemia; neuroblastoma	Dry mouth, hair loss, pseudotumor cerebri, premature epiphyseal closure, birth defects	

ADH, Antidiuretic hormone; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CNS, central nervous system; IM, intramuscular; IV, intravenous; PEG, polyethylene glycol; PO, oral.

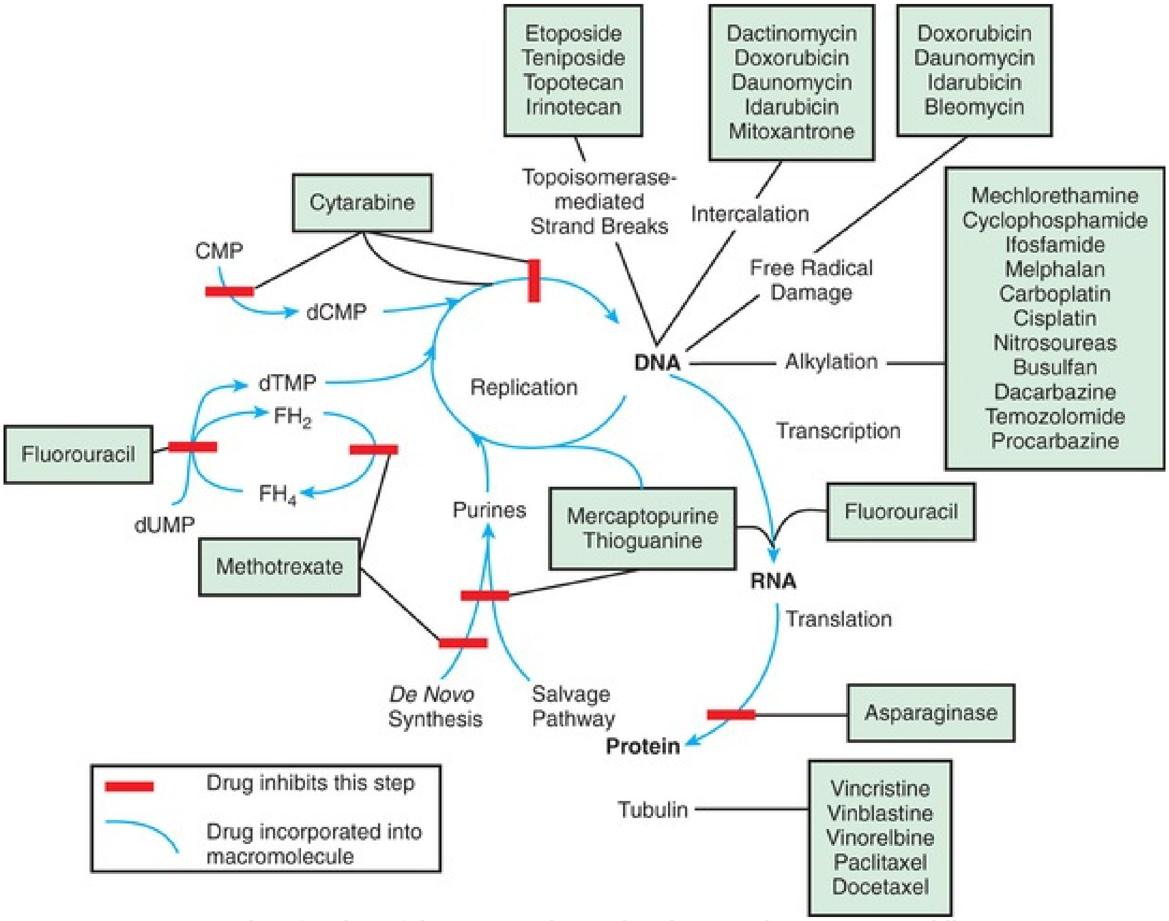
Etoposide
Teniposide
Topotecan
Irinotecan
Dactinomycin
Doxorubicin
Daunomycin
Idarubicin
Mitoxantrone
Doxorubicin
Daunomycin
Idarubicin
Bleomycin
Topoisomerase-mediated Strand Breaks
Intercalation
Free Radical Damage
Cytarabine
CMP
dCMP
dTMP
FH_2
FH_4
dUMP
Fluorouracil
Methotrexate
Replication
DNA
Alkylation
Mechlorethamine
Cyclophosphamide
Ifosfamide
Melphalan
Carboplatin
Cisplatin
Nitrosoureas
Busulfan
Dacarbazine
Temozolomide
Procarbazine
Transcription
Purines
Mercaptopurine
Thioguanine
Fluorouracil
RNA
Translation
De Novo Synthesis
Salvage Pathway
Protein
Asparaginase
Tubulin
Vincristine
Vinblastine
Vinorelbine
Paclitaxel
Docetaxel
Drug inhibits this step
Drug incorporated into macromolecule

FIG. 521.5 Site of action of the commonly used anticancer drugs. ***CMP,*** Cytidine monophosphate; ***dCMP,*** deoxycytidine monophosphate; ***dTMP,*** deoxythymidine monophosphate; ***dUMP,*** deoxyuridine monophosphate; ***FH2,*** dihydrofolate; ***FH4,*** tetrahydrofolate. (Redrawn from Adamson PC, Balis FM, Blaney SM: General principles of chemotherapy. In Pizzo PA, Poplack DG, editors: ***Principles and practice of pediatric oncology*** , ed 6, Philadelphia, 2011, Lippincott Williams & Wilkins, p 283.)

Because most antineoplastic agents are cell cycle dependent, their adverse effects usually are related to the proliferation kinetics of individual cell populations. Most susceptible are tissues or organs with high rates of cell turnover: bone marrow, oral and intestinal mucosa, epidermis, liver, and spermatogonia. The most common acute adverse effects are **myelosuppression** (with neutropenia and thrombocytopenia being the most problematic), immunosuppression, nausea and vomiting, hepatic dysfunction, upper and lower gastrointestinal mucositis, dermatitis, and alopecia. Fortunately, the tissues affected also recover relatively quickly, so that the acute adverse effects are usually reversible. Life-threatening effects of many chemotherapy agents include severe neutropenia with infection, fungemia or fungal pneumonia as a result of immunosuppression, and septicemia, not infrequently linked to indwelling intravascular devices (Table 521.3 ; see Chapters 205 and 206). **Cardiomyopathy** caused by anthracyclines (e.g., doxorubicin, daunorubicin) and **renal failure** from platinum-containing agents also may be life threatening or disabling.

Table 521.3

Infectious Complications of Malignancy

PREDISPOSING FACTOR	ETIOLOGY	SITE OF INFECTION	INFECTIOUS AGENTS
Neutropenia	Chemotherapy, bone marrow infiltration	Sepsis, shock, pneumonia, soft tissue, proctitis, mucositis	Viridans group streptococcus, *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Candida, Aspergillus,* anaerobic oral and rectal bacteria
Immunosuppression, lymphopenia, lymphocyte-monocyte dysfunction	Chemotherapy, corticosteroid	Pneumonia, meningitis, disseminated viral infection	*Pneumocystis jiroveci, Cryptococcus neoformans, Mycobacterium, Nocardia, Listeria monocytogenes, Candida, Aspergillus, Strongyloides, Toxoplasma,* varicella-zoster virus, cytomegalovirus, herpes simplex
Indwelling central venous catheter	Nutrition, administration of chemotherapy	Line sepsis, tract of tunnel, exit site	*S. epidermidis, S. aureus, Candida albicans, P. aeruginosa, Aspergillus, Corynebacterium , Enterococcus faecalis, Mycobacterium fortuitum, Propionibacterium acnes*

Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: *Nelson essentials of pediatrics,* ed 6, Philadelphia, 2011, Saunders.

Least susceptible to chemotherapy and radiation therapy are cells that do not replicate or that replicate slowly, such as neurons, muscle cells, connective tissue, and bone. However, children are not exempt from toxicities of these tissues, probably because they are still undergoing proliferation, although at a slower pace than other tissues, during growth and growth spurts.

Physically, children can endure the acute adverse effects of chemotherapy better than adults can in many ways. The *maximum tolerated dosage* in children, when expressed on the basis of body surface area or body weight, typically is greater than that in adults. A comparison of anticancer drugs tested in phase I trials in both adult and pediatric patients showed that the maximum tolerated dosage in children was greater than that in adults for 70% of the agents, equal to that in adults for 15%, and less than the adult dose for only 15% of the agents. For all the drugs that were compared, the mean pediatric maximum tolerated dosage was greater than the adult mean.

Tumor-directed immune therapies are evolving in the field of pediatric oncology. Tumor antigen–specific monoclonal antibodies have been incorporated into the standard therapy of neuroblastoma (anti–ganglioside GD_2). The antiangiogenic agent *bevacizumab* (monoclonal antibody against vascular endothelial growth factor A) shows promise in the treatment of CNS tumors, especially low-grade gliomas.

Immunotherapy , particularly adoptive cell transfer techniques, employs and enhances the patient's immune system to kill malignant cells. **Chimeric antigen receptor T cells (CAR-T cells)** are genetically engineered to make new TCRs that can then recognize and attach to an antigen on the tumor cell. This results in T-cell proliferation, cytolysis, and cytokine release with subsequent tumor cell death (Fig. 521.6). The B-cell antigen CD19 is the antigen targeted in children with acute lymphoblastic leukemia (ALL) and some adults with lymphoma. The response to therapy in children with chemotherapy-resistant ALL has been quite exciting; this therapy is U.S. Food and Drug Administration (FDA) approved for children with ALL. Other antigens may be targeted, including CD22, CD30 (lymphomas), CD171, GD2 (neuroblastoma), EGFR, and HER2 (glioblastoma).

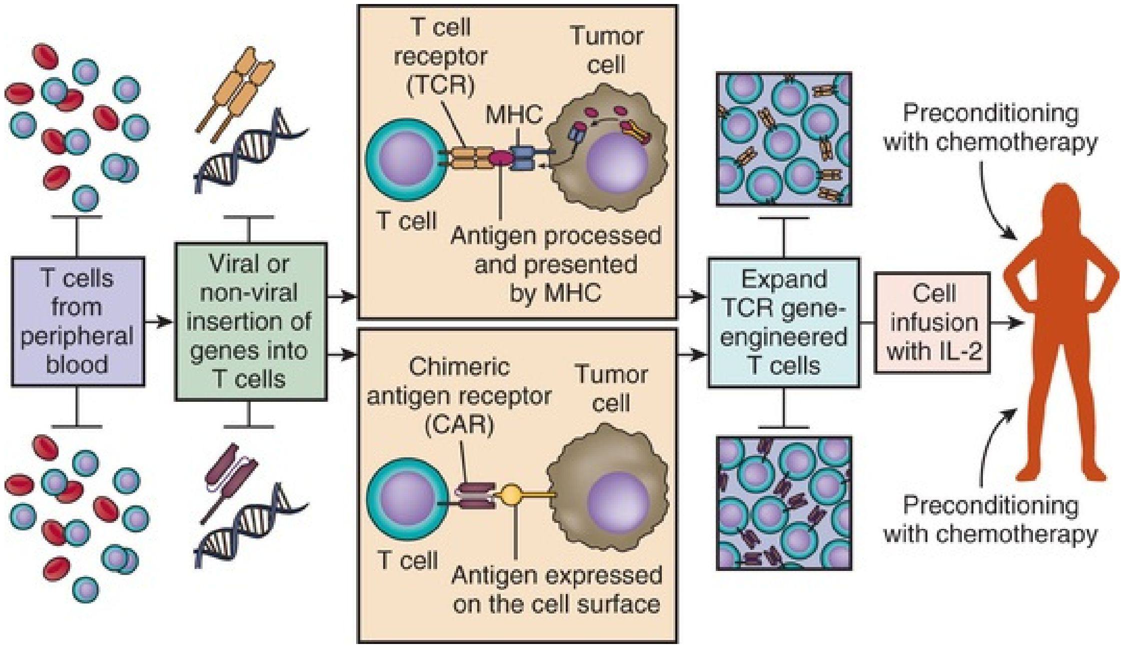
T cells from peripheral blood
Viral or non-viral insertion of genes into T cells
T cell receptor (TCR)
Tumor cell
MHC
T cell
Antigen processed and presented by MHC
Chimeric antigen receptor (CAR)
Tumor cell
T cell
Antigen expressed on the cell surface
Expand TCR gene-engineered T cells
Cell infusion with IL-2
Preconditioning with chemotherapy
Preconditioning with chemotherapy

FIG. 521.6 Chimeric antigen receptor (CAR) T cells and T-cell receptor (TCR) T cells are engineered to produce special receptors on their surfaces. They are then expanded in the laboratory and returned to the patient. IL, Interleukin; MHC, major histocompatibility complex. (Courtesy of National Cancer Institute. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells .)

Side effects of CAR-T therapy are common and potentially serious and are caused by the **cytokine release syndrome (CRS)** . Manifestations of CRS include hypotension, vascular leak, myalgias, cerebral edema, seizures, and confusion. Symptoms correlate with the extent of the tumor burden and require supportive care. *Tocilizumab*, an anti–interleukin-6 receptor monoclonal antibody, is the treatment of choice. B-cell aplasia may also develop and requires intravenous immune globulin (IVIG) replacement.

Surgery

Superb pediatric surgical and anesthesia services are indispensable for children with cancer. The pediatric surgeon's role varies, depending on the type of tumor. For **solid tumors** , complete resection with documented evidence of negative margins often is required for cure or long-term control. Considerable prolongation of life usually depends on the tumor's resectability and the actual extent of resection.

With the exception of brainstem tumors and retinoblastoma, all solid tumors in children require a tissue diagnosis; therefore biopsy of the suspected neoplasm is paramount. *Staging with sentinel node biopsies* has become the standard of care for several pediatric malignancies. Surgical expertise is essential for implantation of vascular access devices and removal and replacement of such devices when infection or thrombosis supervenes (see Chapter 206).

Increasingly, minimally invasive endoscopic surgical techniques are being used when indicated and, if the patient's condition permits, for biopsy and resection of tumor, direct ascertainment of residual disease and assessment of response, lysis of adhesions, and splenectomy.

Radiation Therapy

Radiation therapy is used sparingly in children, who are more susceptible than adults to the adverse delayed effects of ionizing radiation. A major advance in pediatric radiation therapy is the application of **conformal irradiation** to children with cancer. This technique, most often applied as **intensity-modulated radiation therapy** , spares normal tissue by conforming the radiation volume to the shape of the tumor, thereby enabling delivery of higher doses to the tumor with lower exposure of normal tissue adjacent to the tumor or in the path of the radiation beam. Another example is **proton-beam radiotherapy** , which has just begun to be more widely available for children with cancer. With more focused beams and better sedation and immobilization techniques, radiation therapy is becoming more common in children. Acute adverse effects from radiation therapy are less severe than those from chemotherapy and depend on which part of the body is irradiated and the means of administration. **Dermatitis** is the most common general adverse effect, because skin is always in the treatment field. Nausea and diarrhea are common subacute adverse effects with abdominal radiation therapy. **Mucositis** typically occurs to some extent whenever oral or intestinal mucosa is in the treatment volume. **Somnolence** is common with cranial irradiation. **Alopecia** occurs where hair is in the radiation field.

Most radiation therapy schedules require treatment 5 days per week for 4-7 wk, depending on the dose needed to control the tumor and on the amount and nature of normal tissue in the field. Most adverse effects are not noted until the 2nd half of the course of irradiation. Late effects can occur months to years after radiation therapy and usually are dose-limiting manifestations. The type of delayed toxicity also depends on the site of irradiation. Examples are impaired growth resulting from cranial or vertebral irradiation, endocrine dysfunction from midbrain irradiation, pulmonary or cardiac insufficiency from chest irradiation, strictures and adhesions from abdominal irradiation, and infertility from pelvic irradiation. Second malignancy can also develop in the radiation field, such as breast cancer from chest irradiation and brain tumors from CNS irradiation.

Acute Toxic Effects and Supportive Care

Adverse treatment effects that occur early in therapy can result in oncologic emergencies. These include metabolic disorders, bone marrow suppression, and compression by tumors on vital structures (Table 521.4). In **tumor lysis syndrome (TLS)** , uric acid, phosphate, and potassium are released in the circulation in large quantities from death of tumor cells. Hyperuricemia can lead to impairment of renal function, which further exacerbates the metabolic abnormalities. TLS can occur *before* therapy in patients with a large tumor burden (e.g., Burkitt lymphoma, lymphoblastic lymphoma, high–white blood cell count leukemia), but it is usually seen within 12-48 hr of initiating chemotherapy. TLS is infrequently reported in other tumors (Hodgkin lymphoma, neuroblastoma, hepatoblastoma). Before therapy is initiated, the serum levels of uric acid, electrolytes, calcium, phosphorus, and creatinine should be measured and adequate hydration ensured. *Allopurinol* (a xanthine oxidase inhibitor) should be started to prevent further accumulation of uric acid. In patients with established TLS with high uric acid levels or those at high risk for TLS, *rasburicase* (an enzyme that degrades uric acid) should be given instead of allopurinol. Symptomatic hyperkalemia and hyperphosphatemia with subsequent hypocalcemia can develop in the setting of inadequate renal function.

Table 521.4

Oncologic Emergencies

CONDITION	MANIFESTATIONS	ETIOLOGY	MALIGNANCY	TREATMENT
METABOLIC				
Hyperuricemia	Uric acid nephropathy	Tumor lysis syndrome	Lymphoma, leukemia	Allopurinol, alkalinize urine; hydration and diuresis, rasburicase
Hyperkalemia	Arrhythmias, cardiac arrest	Tumor lysis syndrome	Lymphoma, leukemia	Kayexalate, sodium bicarbonate, calcium gluconate, glucose, and insulin; check for pseudohyperkalemia from leukemic cell lysis in test tube
Hyperphosphatemia	Hypocalcemic tetany; metastatic calcification, photophobia, pruritus	Tumor lysis syndrome	Lymphoma, leukemia	Hydration, forced diuresis; stop alkalinization; oral aluminum hydroxide to bind phosphate
Hyponatremia	Seizure, lethargy (may also be asymptomatic)	SIADH; fluid, sodium losses in vomiting	Leukemia, CNS tumor	Restrict free water for SIADH; replace sodium if depleted
Hypercalcemia	Anorexia, nausea, polyuria, pancreatitis, gastric ulcers; prolonged PR, shortened QT interval	Bone resorption; ectopic parathormone, vitamin D, or prostaglandins	Metastasis to bone, rhabdomyosarcoma, leukemia	Hydration and furosemide diuresis; corticosteroids; calcitonin, bisphosphonates
HEMATOLOGIC				
Anemia	Pallor, weakness, heart failure	Bone marrow suppression or infiltration; blood loss	Any with chemotherapy	Packed red blood cell transfusion
Thrombocytopenia	Petechiae, hemorrhage	Bone marrow suppression or infiltration	Any with chemotherapy	Platelet transfusion
Disseminated intravascular coagulation	Shock, hemorrhage	Sepsis, hypotension, tumor factors	Promyelocytic leukemia, others	Fresh-frozen plasma; platelets, cryoprecipitate, treat

				underlying disorder
Neutropenia	Infection	Bone marrow suppression or infiltration	Any with chemotherapy	If febrile, administer broad-spectrum antibiotics, and filgrastim (G-CSF) if appropriate
Hyperleukocytosis (>100,000/mm^3)	Hemorrhage, thrombosis; pulmonary infiltrates, hypoxia; tumor lysis syndrome	Leukostasis; vascular occlusion	Leukemia	Leukapheresis; chemotherapy; hydroxyurea
Graft-versus-host disease	Dermatitis, diarrhea, hepatitis	Immunosuppression and nonirradiated blood products; bone marrow transplantation	Any with immunosuppression	Corticosteroids; cyclosporine; tacrolimus; antithymocyte globulin
SPACE-OCCUPYING LESIONS				
Spinal cord compression	Back pain ± radicular *Cord above T10:* symmetric weakness, increased deep tendon reflex; sensory level present; toes up *Conus medullaris (T10-L2):* symmetric weakness, increased knee reflexes; decreased ankle reflexes; saddle sensory loss; toes up or down *Cauda equina (below L2):* asymmetric weakness; loss of deep tendon reflex and sensory deficit; toes down	Metastasis to vertebra and extramedullary space	Neuroblastoma; medulloblastoma	MRI or myelography for diagnosis; corticosteroids; radiotherapy; laminectomy; chemotherapy
Increased intracranial pressure	Confusion, coma, emesis, headache, hypertension, bradycardia, seizures, papilledema, hydrocephalus; cranial nerves III and VI palsies	Primary or metastatic brain tumor	Neuroblastoma, astrocytoma; glioma	CT or MRI for diagnosis; corticosteroids; phenytoin; ventriculostomy tube; radiotherapy; chemotherapy
Superior vena cava syndrome	Distended neck veins plethora, edema of head and neck, cyanosis, proptosis, Horner syndrome	Superior mediastinal mass	Lymphoma	Chemotherapy; radiotherapy
Tracheal compression	Respiratory distress	Mediastinal mass compressing trachea	Lymphoma	Radiation, corticosteroids

CNS, Central nervous system; G-CSF, granulocyte colony-stimulating factor; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Adapted from Kliegman RM, Marcdante KJ, Jenson HB, et al, editors: *Nelson essentials of* *pediatrics* , ed 6, Philadelphia, 2011, Saunders, p 590.

Virtually all chemotherapy regimens can produce **myelosuppression** , as can malignancies that invade and replace bone marrow. Anemia can be corrected by transfusions of packed erythrocytes, and thrombocytopenia can be corrected by platelet infusions. Patients receiving immunosuppressive therapy should receive *irradiated* blood products to prevent graft-versus-host disease and leukoreduced blood products to prevent transfusion-associated reactions and infections. **Neutropenia** (neutrophil counts <500/µL) poses a risk of life-threatening infection. Febrile neutropenic patients should be hospitalized and treated with empirical broad-spectrum intravenous antimicrobial therapy pending the results of appropriate cultures of blood, urine, or any obvious sites of infection (see Chapter 205). Treatment is continued until fever resolves and the neutrophil count rises. If fever persists for more than 3-5 days while the patient is receiving broad-spectrum antibiotics, the possibility of fungal infection must be considered. Fungal infections caused by *Candida* and *Aspergillus* are common in immunosuppressed patients. Opportunistic organisms such as *Pneumocystis jiroveci* can produce fatal pneumonia. Prophylactic treatment with trimethoprim-sulfamethoxazole is given when severe or prolonged immunosuppression is anticipated.

Viruses of low pathogenicity can produce serious disease in the setting of immunosuppression caused by malignancy or its treatment. Patients should not be given live-virus vaccines. Children who are receiving chemotherapy and who are exposed to chickenpox should receive varicella-zoster immunoglobulin, or, if varicella-zoster immunoglobulin is not available, oral acyclovir should be considered. If clinical disease develops, the child should be hospitalized and treated with IV acyclovir.

Adequate **pain management** is critical. The World Health Organization (WHO) guidelines are particularly useful in the management of pain associated with cancer and cancer therapy (see Chapter 76).

Depending on the type of cancer therapy, patients can lose >10% body weight. Patients sometimes reduce their food intake because of temporary, treatment-associated nausea, stomatitis, and vomiting. Appetite loss is not a cause for alarm. **Malnutrition** is a particular risk in patients receiving radiation therapy involving the abdomen or the head and neck, intensive chemotherapy, or total body irradiation and high-dose chemotherapy before marrow transplantation. If oral supplementation proves inadequate, such patients may require enteral tube feedings or parenteral hyperalimentation.

Late Adverse Effects

Injury to tissues with low repair potential often results in long-lasting or permanent deficit. These effects can be either from the tumor or its treatment. For example, a brain or spinal tumor can leave the child with a permanent paresis or autonomic dysfunction; anthracycline-induced cardiomyopathy usually produces refractory cardiac dysfunction; and the leukoencephalopathy caused by intrathecal methotrexate and CNS radiation therapy often is only partially reversible. The type of late adverse effects depends on the child's age at treatment, the location(s) of the cancer, and the therapy administered. A good resource for the pediatrician, patient, and family who have to anticipate the possibilities is available at http://www.survivorshipguidelines.org .

Late adverse effects of therapy can cause substantial morbidity (Table 521.5). Successful surgical resection can result in loss of important functional structures. Irradiation can produce irreversible organ damage, with symptoms and functional limitations depending on the organ involved and the severity of the damage. Many problems related to radiation therapy do not become obvious until the patient is fully grown, such as asymmetry between irradiated and nonirradiated areas or extremities. Irradiation of fields that include endocrine organs can cause hypothyroidism, pituitary dysfunction, or infertility. In sufficient doses, cranial irradiation can produce neurologic dysfunction, and spinal irradiation can produce growth retardation.

Table 521.5

Late Effects and High-Risk Features of Childhood Cancer and Its Treatment

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
NEUROCOGNITIVE			
Neurocognitive deficits Functional deficits in: • Executive function • Sustained attention • Memory • Processing	Chemotherapy: • Methotrexate Radiation affecting brain: • Cranial • Ear/infratemporal • Total body irradiation (TBI)	Age <3 yr at time of treatment Female sex Supratentorial tumor Premorbid or family history of learning or attention problems Radiation doses >24 Gy Whole-brain irradiation	Acute lymphoblastic leukemia Brain tumor Sarcoma (head and neck or osteosarcoma)

speed • Visual-motor integration Learning deficits Diminished IQ Behavioral change			
NEUROSENSORY			
Hearing loss, sensorineural	Chemotherapy: • Cisplatin • Carboplatin Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher cisplatin dose (360 mg/m^2) Higher radiation dose impacting ear (>30 Gy) Concurrent radiation and cisplatin	Brain tumor Germ cell tumor Sarcoma (head and neck) Neuroblastoma Hepatoblastoma
Hearing loss, conductive Tympanosclerosis Otosclerosis Eustachian tube dysfunction	Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher radiation dose affecting ear (>30 Gy)	Brain tumor Sarcoma (head and neck)
Visual impairment Cataracts Lacrimal duct atrophy Xerophthalmia Retinopathy Glaucoma	Chemotherapy: • Busulfan • Glucocorticoids Radiation affecting eye: • Cranial • Orbital/eye • TBI	Higher radiation dose impacting eye (≥15 Gy for cataracts; >45 Gy for retinopathy and visual impairment)	Brain tumor Acute lymphoblastic leukemia Retinoblastoma Rhabdomyosarcoma (orbital) Allogeneic HSCT
Peripheral neuropathy, sensory	Chemotherapy: • Vincristine • Vinblastine • Cisplatin • Carboplatin	Higher cisplatin dose (≥300 mg/m^2)	Acute lymphoblastic leukemia Brain tumor Hodgkin lymphoma Germ cell tumor Non-Hodgkin lymphoma Sarcoma Neuroblastoma Wilms tumor Carcinoma
NEUROMOTOR			
Peripheral neuropathy, motor	Chemotherapy: • Vincristine • Vinblastine		Acute lymphoblastic leukemia Hodgkin lymphoma Non-Hodgkin lymphoma Sarcoma Brain tumor Neuroblastoma Wilms tumor
ENDOCRINE			
GH deficiency	Radiation affecting	Female sex	Acute

Precocious puberty	HPA: • Cranial • Orbital/eye	Radiation dose to HPA >18 Gy	lymphoblastic leukemia Sarcoma (facial) Carcinoma (nasopharyngeal)
Obesity	Ear/infratemporal Nasopharyngeal	Female sex Younger age (<4 yr)	Acute lymphoblastic leukemia
Hypothyroidism, central Gonadotropin deficiency Adrenal insufficiency, central	TBI	Radiation dose to HPA >18 Gy	Brain tumor Sarcoma (facial) Carcinoma (nasopharyngeal)
Hypothyroidism, primary	Neck, mantle irradiation	Radiation dose to thyroid >20 Gy	Hodgkin lymphoma
REPRODUCTIVE			
Gonadal dysfunction Delayed or arrested puberty Premature menopause Germ cell dysfunction or failure Infertility	Chemotherapy, alkylating: • Busulfan • Carmustine (BCNU) • Chlorambucil • Cyclophosphamide • Ifosfamide • Lomustine (CCNU) • Mechlorethamine • Melphalan • Procarbazine Radiation affecting reproductive system: • Whole abdomen (girls) • Pelvic • Lumbar/sacral spine (girls) • Testicular (boys) • TBI	Higher alkylating agent dose Alkylating agent conditioning for HSCT Radiation dose ≥15 Gy in prepubertal girls Radiation dose ≥10 Gy in pubertal girls For germ cell failure in boys, any pelvic irradiation For androgen insufficiency, gonadal irradiation, ≥20-30 Gy in boys	Acute lymphoblastic leukemia, high risk Brain tumor Hodgkin lymphoma, advanced or unfavorable Non-Hodgkin lymphoma, advanced or unfavorable Sarcoma Neuroblastoma Wilms tumor, advanced Autologous or allogeneic HSCT
CARDIAC			
Cardiomyopathy Arrhythmias	Chemotherapy: • Daunorubicin • Doxorubicin • Idarubicin	Female sex Age <5 yr at time of treatment Higher doses of chemotherapy (≥300 mg/m^2) Higher doses of cardiac radiation (≥30 Gy) Combined-modality therapy with cardiotoxic chemotherapy and irradiation	Hodgkin lymphoma Leukemia Non-Hodgkin lymphoma Sarcoma Wilms tumor Neuroblastoma
Cardiomyopathy Arrhythmias Pericardial fibrosis	Radiation affecting heart: • Chest • Mantle		

Valvular disease Myocardial infarction Atherosclerotic heart disease	• Mediastinum • Axilla • Spine • Upper abdomen		
PULMONARY			
Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	Chemotherapy: • Bleomycin • Busulfan • Carmustine (BCNU) • Lomustine (CCNU) Radiation impacting lungs: • Mantle • Mediastinum • Whole lung • TBI	Higher doses of chemotherapy Combined modality therapy with pulmonary toxic chemotherapy and irradiation	Brain tumor Germ cell tumor Hodgkin lymphoma Sarcoma (chest wall or intrathoracic) Autologous or allogeneic HCST
GASTROINTESTINAL			
Chronic enterocolitis Strictures Bowel obstruction	Radiation affecting gastrointestinal tract (≥30 Gy) Abdominal surgery	Higher radiation dose to bowel (≥45 Gy) Combined modality therapy with abdominal irradiation and radiomimetic chemotherapy (dactinomycin or anthracyclines) Combined modality therapy with abdominal surgery and irradiation	Sarcoma (retroperitoneal or pelvic primary)
HEPATIC			
Hepatic fibrosis Cirrhosis	Radiation affecting liver	Higher radiation dose or treatment volume (20-30 Gy to entire liver or ≥40 Gy to at least one third of liver)	Sarcoma Neuroblastoma
RENAL			
Renal insufficiency Hypertension Glomerular injury Tubular injury	Chemotherapy: • Ifosfamide • Cisplatin • Carboplatin Radiation affecting kidneys: • Whole abdomen • Upper abdominal fields • TBI		

GH, Growth hormone; HPA, hypothalamic-pituitary-adrenal axis; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation.

From Kurt BA, Armstrong GT, Cash DK, et al: Primary care management of the childhood cancer survivor, *J Pediatr* 152:458–466, 2008.

Chemotherapy also carries the risk of long-lasting organ damage. Of particular concern are **leukoencephalopathy** after high-dose methotrexate therapy; **infertility** in male patients treated with alkylating agents (e.g., cyclophosphamide); **myocardial damage** caused by anthracyclines; **pulmonary fibrosis** caused by bleomycin; **renal dysfunction** caused by ifosfamide, nitrosourea, or platinum agents; and **hearing loss** from cisplatin. Development of these sequelae may be dose related and usually is irreversible. Appropriate baseline and intermittent testing should be performed before these drugs are administered to ensure that there is no preexisting damage to the organs likely to be affected and to permit monitoring of the adverse effects of treatment-induced changes.

Perhaps the most serious late adverse effect is the occurrence of **second cancers** in patients successfully cured of a first malignancy. The risk appears to be cumulative, increasing by approximately 0.5% per year, resulting in approximately a 12% incidence at 25 yr after treatment. Patients who have been treated for childhood cancer should be examined annually with particular attention to possible late adverse effects of therapy, including second malignancies (Fig. 521.7).

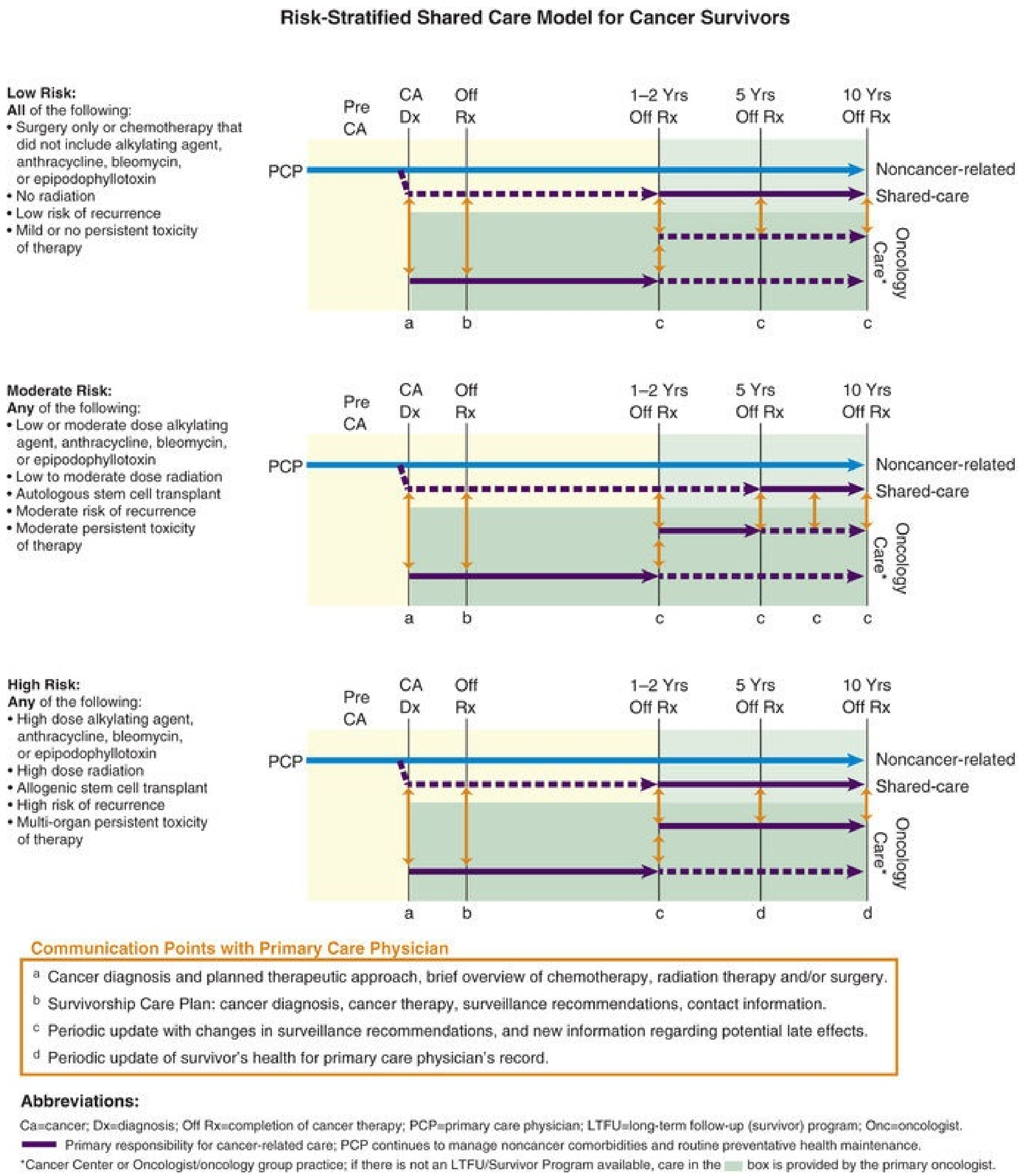
Risk-Stratified Shared Care Model for Cancer Survivors
Pre CA
CA Dx
Off Rx
1–2 Yrs Off Rx
5 Yrs Off Rx
10 Yrs Off Rx
PCP
Noncancer-related care
Shared-care
Oncology Care*
a
b
c
c
c
Pre CA
CA Dx
Off Rx
1–2 Yrs Off Rx
5 Yrs Off Rx
10 Yrs Off Rx
PCP
Noncancer-related care
Shared-care
Oncology Care*
a
b
c
c
c
c
Pre CA
CA Dx
Off Rx
1–2 Yrs Off Rx
5 Yrs Off Rx
10 Yrs Off Rx
PCP
Noncancer-related care
Shared-care
Oncology Care*
a
b
c
d
d

Low Risk:
All of the following:
- Surgery only or chemotherapy that did not include alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- No radiation
- Low risk of recurrence
- Mild or no persistent toxicity of therapy

Moderate Risk:
Any of the following:
- Low or moderate dose alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- Low to moderate dose radiation
- Autologous stem cell transplant
- Moderate risk of recurrence
- Moderate persistent toxicity of therapy

High Risk:
Any of the following:
- High dose alkylating agent, anthracycline, bleomycin, or epipodophyllotoxin
- High dose radiation
- Allogenic stem cell transplant
- High risk of recurrence
- Multi-organ persistent toxicity of therapy

Communication Points with Primary Care Physician

[a] Cancer diagnosis and planned therapeutic approach, brief overview of chemotherapy, radiation therapy and/or surgery.
[b] Survivorship Care Plan: cancer diagnosis, cancer therapy, surveillance recommendations, contact information.
[c] Periodic update with changes in surveillance recommendations, and new information regarding potential late effects.
[d] Periodic update of survivor's health for primary care physician's record.

Abbreviations:

Ca=cancer; Dx=diagnosis; Off Rx=completion of cancer therapy; PCP=primary care physician; LTFU=long-term follow-up (survivor) program; Onc=oncologist.
▬ Primary responsibility for cancer-related care; PCP continues to manage noncancer comorbidities and routine preventative health maintenance.
*Cancer Center or Oncologist/oncology group practice; if there is not an LTFU/Survivor Program available, care in the 🟩 box is provided by the primary oncologist.

FIG. 521.7 **Proposed risk-stratified shared care model for childhood cancer survivors. *Dark-blue solid line* denotes primary responsibility cancer-related care; risk stratification based on determination of the long-term follow-up staff. *CA,* Cancer; *DX,* diagnosis; *Onc,* oncologist; *PCP,* primary care provider; *RX,* therapy. (Adapted from McCabe MS, Partridge A, Grunfeld, E, Hudson MM: Risk-based health care, the cancer survivor, the oncologist, and the primary care physician, Semin Oncol 40:804–812, 2013; with data from Oeffinger KC, McCabe MS: Models for delivering survivorship care, J Clin Oncol 24:5117–5124, 2006.)**

Palliative Care

At all stages of caring for children with cancer, principles of palliative care should be applied to relieve pain and suffering and to provide comfort (see Chapter 7). **Pain** is a serious cause of suffering among patients with cancer. It may be the result of organ obstruction or compression or bone metastasis, or it may be neuropathic. Pain should be managed in a stepwise manner, as recommended by the WHO, in accordance with the principles of selecting the appropriate analgesic, prescribing the appropriate dosage, administering the drug by the appropriate route, and choosing an appropriate dosing schedule to prevent persistent pain and to relieve breakthrough pain (see Chapter 76). In addition, the dosage should be titrated aggressively while attempts are made to prevent, anticipate, and manage side effects. Adjuvant drugs and sequential trials of analgesic drugs should be considered.

The goals in the care of dying patients are to avoid distress for the patient, family, and caregivers; to provide care consistent with the patient's and family's wishes; and to comply with and advocate for clinical, cultural, and ethical standards.

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CHAPTER 522

The Leukemias

David G. Tubergen, Archie Bleyer, A. Kim Ritchey, Erika Friehling

The leukemias are the most common malignant neoplasms in childhood, accounting for approximately 31% of all malignancies that occur in children younger than 15 yr. Each year, leukemia is diagnosed in approximately 3,100 children and adolescents <20 yr old in the United States, an annual incidence of 4.5 cases per 100,000 children. Acute lymphoblastic leukemia (ALL) accounts for approximately 77% of cases of childhood leukemia, acute myelogenous leukemia (AML) for approximately 11%, chronic myelogenous leukemia (CML) for 2–3%, and juvenile myelomonocytic leukemia (JMML) for 1–2%. The remaining cases consist of a variety of acute and chronic leukemias that do not fit classic definitions for ALL, AML, CML, or JMML.

The leukemias may be defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to an unregulated clonal proliferation of cells. The progeny of these cells have a growth advantage over normal cellular elements because of their increased rate of proliferation and a decreased rate of spontaneous apoptosis. The result is a disruption of normal marrow function and, ultimately, marrow failure. The clinical features, laboratory findings, and responses to therapy vary depending on the type of leukemia.

522.1

Acute Lymphoblastic Leukemia

Erika Friehling, A. Kim Ritchey, David G. Tubergen, Archie Bleyer

Childhood acute lymphoblastic leukemia (**ALL**) was the first disseminated cancer shown to be curable. It actually is a heterogeneous group of malignancies with a number of distinctive genetic abnormalities that result in varying clinical behaviors and responses to therapy.

Epidemiology

Acute lymphoblastic leukemia is diagnosed in approximately 3,100 children and adolescents <20 yr old in the United States each year. ALL has a striking peak incidence at 2-3 yr of age and occurs more in boys than in girls at all ages. This peak age incidence was apparent decades ago in white populations in advanced socioeconomic countries, but it has since been confirmed in the black population of the United States as well. The disease is more common in children with certain chromosomal abnormalities, such as Down syndrome, Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia. Among identical twins, the risk to the second twin if one twin develops leukemia is greater than that in the general population. The risk is >70% if ALL is diagnosed in the first twin during the 1st yr of life and the twins shared the same (monochorionic) placenta. If the first twin develops ALL by 5-7 yr of age, the risk to the second twin is at least twice that of the general population, regardless of zygosity.

Etiology

In virtually all cases, the etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia (Table 522.1). Most cases of ALL are thought to be caused by postconception somatic mutations in lymphoid cells. However, the identification of the leukemia-specific fusion-gene sequences in archived neonatal blood spots of some children who develop ALL at a later date indicates the importance of in utero events in the initiation of the malignant process in some cases. The long lag period before the onset of the disease in some children, reported to be as long as 14 yr, supports the concept that additional genetic modifications are required for disease expression. Moreover, those same mutations have been found in neonatal blood spots of children who *never* go on to develop leukemia.

Table 522.1

Factors Predisposing to Childhood Leukemia

GENETIC CONDITIONS
Down syndrome
Fanconi anemia
Bloom syndrome
Diamond-Blackfan anemia
Shwachman-Diamond syndrome
Kostmann syndrome
Neurofibromatosis type 1
Ataxia-telangiectasia
Severe combined immune deficiency
Paroxysmal nocturnal hemoglobinuria
Li-Fraumeni syndrome
ENVIRONMENTAL FACTORS
Ionizing radiation
Drugs
Alkylating agents
Epipodophyllotoxin
Benzene exposure

Exposure to medical diagnostic radiation both in utero and in childhood is associated with an increased incidence of ALL. In addition, published descriptions and investigations of geographic clusters of cases have raised concern that environmental factors can increase the incidence of ALL. Thus far, no such factors other than radiation have been identified in the United States. In certain developing countries, there is an association between B-cell ALL (**B-ALL**) and Epstein-Barr virus (EBV) infections.

Cellular Classification

The classification of ALL depends on characterizing the malignant cells in the bone marrow to determine the morphology, phenotype as measured by cell membrane markers, and cytogenetic and molecular genetic features. **Morphology** is usually adequate alone to establish a diagnosis, but the other studies are essential for disease classification, which can have a major influence on the prognosis and the choice of appropriate therapy. The current system used is the World Health Organization (WHO) classification of leukemias. Phenotypically, surface markers show that approximately 85% of cases of ALL are classified as *B-lymphoblastic leukemia* (previously termed precursor B-ALL or pre–B-ALL), approximately 15% are *T-lymphoblastic leukemia*, and approximately 1% are derived from mature B cells. The rare leukemia of mature B cells is termed *Burkitt leukemia* and is one of the most rapidly growing cancers in humans, requiring a different therapeutic approach than other subtypes of ALL. A small percentage of children with leukemia have a disease characterized by surface markers of both lymphoid and myeloid derivation.

Chromosomal abnormalities are used to subclassify ALL into prognostic groups (Table 522.2). Many genetic alterations, including inactivation of tumor-suppressor genes and mutations that activate the *NOTCH1* or *RAS* pathways, have been discovered and in the future might be incorporated into clinical practice (Fig. 522.1).

Table 522.2

Common Chromosomal Abnormalities in Acute Lymphoblastic Leukemia of Childhood

SUBTYPE	CHROMOSOMAL ABNORMALITY	GENETIC ALTERATION	PROGNOSIS	INCIDENCE
B-ALL	Trisomies 4, 10, and 17	—	Favorable	25%
B-ALL	t(12;21)	*ETV6-RUNX1*	Favorable	20–25%
B-ALL	t(1;19)	*TCF3-PBX1*	None	5–6%
B-ALL	t(4;11)	*KMT2A(MLL)-AF4*	Unfavorable	2%
B-ALL	t(9;22)	*BCR-ABL*	Unfavorable	3%
Mature B-cell leukemia (Burkitt)	t(8;14)	*IGH-MYC*	None	1–2%
B-ALL	Hyperdiploidy	—	Favorable	20–25%
B-ALL	Hypodiploidy	—	Unfavorable	1%
T-ALL	t(10;14)	*TLX1/HOX11*	Favorable	5–10%
Infant	11q23	*KMT2A(MLL)* rearrangements	Unfavorable	2–10%

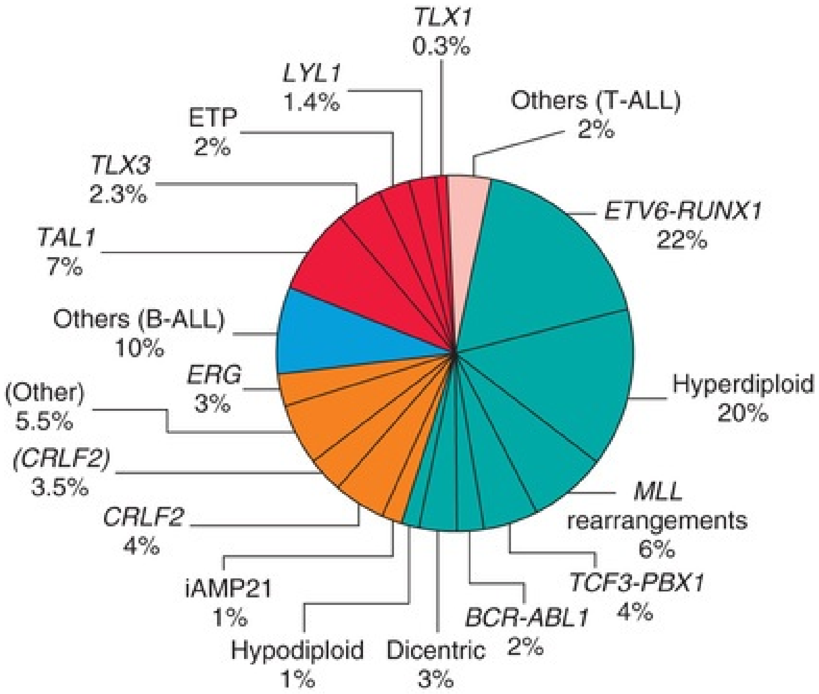

FIG. 522.1 **Estimated frequency of specific genotypes in childhood acute lymphoblastic leukemia (ALL).** ***Blue wedges*** **refer to B-ALL,** ***yellow*** **to recently identified subtypes of B-ALL, and** ***red wedges*** **to T-ALL. (From Mullighan CG: Genomic characterization of childhood acute lymphoblastic leukemia,** ***Semin Hematol*** **50:314–324, 2013.)**

The polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) techniques offer the ability to pinpoint molecular genetic abnormalities and can be used to detect small numbers of malignant cells at diagnosis as well as during follow-up (**minimal residual disease [MRD]** , see later) and are of proven clinical utility. The development of DNA microarray makes it possible to analyze the expression of thousands of genes in the leukemic cell. This technique promises to further enhance the understanding of the fundamental biology and to provide clues to the therapeutic approach of ALL.

Clinical Manifestations

The initial presentation of ALL usually is nonspecific and relatively brief. Anorexia, fatigue, malaise, irritability, and intermittent low-grade fever are often present. Bone or joint pain, particularly in the lower extremities, may be present. Less often, symptoms may be of several months’ duration, may be localized predominantly to the bones or joints, and may include joint swelling. Bone pain is severe and can wake the patient at night. As the disease progresses, signs and symptoms of **bone marrow failure** become more obvious with the occurrence of pallor, fatigue, exercise intolerance, bruising, oral mucosal bleeding or epistaxis, as well as fever, which may be caused by infection or the disease. Organ infiltration can cause lymphadenopathy, hepatosplenomegaly, testicular enlargement, or central nervous system (CNS) involvement (cranial neuropathies, headache, seizures). Respiratory distress may be caused by severe anemia or mediastinal node compression of the airways.

On **physical examination,** findings of pallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage can reflect bone marrow failure (see Chapter 520). The proliferative nature of the disease may be manifested as lymphadenopathy, splenomegaly, or, less often, hepatomegaly. Patients with bone or joint pain may have exquisite tenderness over the bone or objective evidence of joint swelling and effusion. Nonetheless, with marrow involvement, deep bone pain may be present, but tenderness will not be elicited. Rarely, patients show signs of increased intracranial pressure that indicate leukemic involvement of the CNS. These include papilledema (see Fig. 520.3), retinal hemorrhages, and cranial nerve palsies. Respiratory distress usually is related to anemia but can occur in patients as the result of a large anterior mediastinal mass (e.g., in the thymus or nodes). This problem is most frequently seen in adolescent boys with T-cell ALL. **T-ALL** also usually has a higher leukocyte count.

B-lymphoblastic leukemia is the most common immunophenotype, with onset at 1-10 yr of age. The median leukocyte count at presentation is 33,000/µL, although 75% of patients have counts <20,000/µL; thrombocytopenia is seen in 75% of patients and hepatosplenomegaly in 30–40% of patients. In all types of leukemia, CNS symptoms are seen at presentation in 5% of patients (10–15% have blasts in cerebrospinal fluid [CSF]). Testicular involvement is rarely evident at diagnosis, but prior studies indicate occult involvement in 25% of boys. There is no indication for testicular biopsy.

Diagnosis

The diagnosis of ALL is strongly suggested by peripheral blood findings that indicate bone marrow failure. **Anemia** and **thrombocytopenia** are seen in most patients. Leukemic cells might not be reported in the peripheral blood in routine laboratory examinations. Many patients with ALL present with total leukocyte counts of <10,000/µL. In such cases, the leukemic cells often are reported initially to be “atypical lymphocytes,” and it is only on further evaluation that the cells are found to be part of a malignant clone. When the results of an analysis of peripheral blood suggest the possibility of leukemia, the bone marrow should be examined promptly to establish the diagnosis. It is important that all studies necessary to confirm a diagnosis and adequately classify the type of leukemia be performed, including bone marrow aspiration and biopsy, flow cytometry, cytogenetics, and molecular studies.

ALL is diagnosed by a bone marrow evaluation that demonstrates >25% of the bone marrow cells as a homogeneous population of lymphoblasts. Initial evaluation also includes CSF examination. If lymphoblasts are found and the CSF leukocyte count is elevated, overt CNS or meningeal leukemia is present. This finding reflects a poorer stage and indicates the need for additional CNS and systemic therapies. The *staging lumbar puncture* (LP) may be performed in conjunction with the first dose of intrathecal chemotherapy, if the diagnosis of leukemia was previously established from bone marrow evaluation. An experienced proceduralist should perform the initial LP, because a traumatic LP is associated with an increased risk of CNS relapse.

Differential Diagnosis

The diagnosis of leukemia is readily made in the patient with typical signs and symptoms, anemia, thrombocytopenia, and elevated white blood cell (WBC) count with blasts present on smear. Elevation of the lactate dehydrogenase (LDH) is often a clue to the diagnosis of ALL. When only pancytopenia is present, aplastic anemia (congenital or acquired), myelofibrosis, and familial hemophagocytic lymphohistiocytosis should be considered. Failure of a single cell line, as seen in transient erythroblastopenia of childhood, immune thrombocytopenia, and congenital or acquired neutropenia, is rarely the presenting feature of ALL. A high index of suspicion is required to differentiate ALL from infectious mononucleosis in patients with acute onset of fever and lymphadenopathy and from juvenile idiopathic arthritis in patients with fever, bone pain but often no tenderness, and joint swelling. These presentations also can require bone marrow examination.

ALL must be differentiated from AML and other malignant diseases that invade the bone marrow and can have clinical and laboratory findings similar to ALL, including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and retinoblastoma.

Treatment

The single most important prognostic factor in ALL is the treatment: without effective therapy, the disease is fatal. Considerable progress has been made in overall survival for children with ALL since the 1970s through use of multiagent chemotherapeutic regimens, intensification of therapy, and selection of treatment based on relapse risk (Fig. 522.2). Survival is also related to age (Fig. 522.3) and subtype (Fig. 522.4).

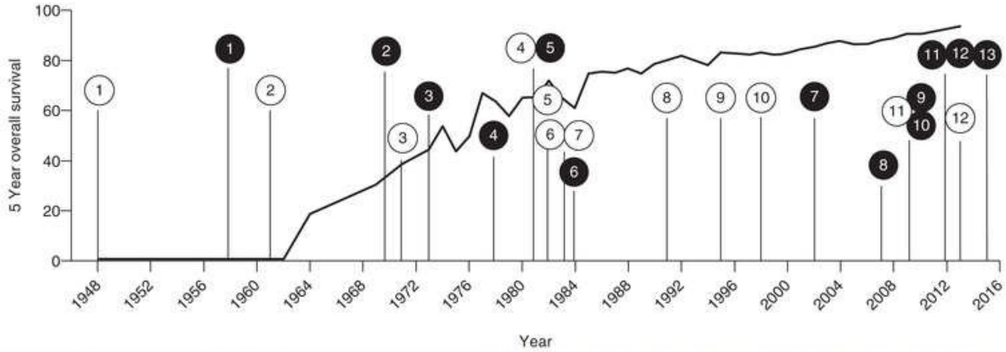

Landmark advances in treatment for pediatric ALL		
①	1948	"Transient remissions" induced by aminopterin
②	1961	First use of antimetabolites mercaptopurine and methotrexate
③	1971	Combination chemotherapy and effective CNS-directed therapy cure approximately 50% of patients
④	1981	Re-induction treatment improves outcomes
⑤	1982	Triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabine may effectively substitute for prophylactic cranial irradiation in some patients
⑥	1983	Postremission weekly high-dose asparaginase improves outcome
⑦	1983	Intermediate-dose methotrexate with leucovorin rescue decreases systemic and testicular relapses
⑧	1991	Dexamethasone is more effective than prednisone in preventing CNS relapse
⑨	1995	Inherited genetic polymorphisms in the gene encoding thiopurine methyltransferase influence mercaptopurine toxicity
⑩	1998	Individualized methotrexate dose improves outcome
⑪	2009	Effective systemic and intrathecal chemotherapy can eliminate the need for prophylactic cranial irradiation in all patients; imatinib improves outcome in Philadelphia chromosome-positive ALL
⑫	2013	First trial of chimeric antigen receptor (CAR)-T cell therapy

Landmark advances in understanding the biology of pediatric ALL		
❶	1958	First cytogenetic study in ALL
❷	1970	First report of Philadelphia chromosome-positvie ALL
❸	1973	First identification of T-cell ALL by spontaneous rosette formation with sheep erythrocytes
❹	1978	Classification of ALL by chromosome number >50 (hyperdiploidy) is associated with prolonged remission duration
❺	1981	Immunologic monitoring of residual leukemia
❻	1984	First identification of immunophenotype-specific chromosomal translocations: t(11;14) in T-cell ALL and t(1;19) in pre-B ALL
❼	2002	First genome-wide profiling of gene expression
❽	2007	First genome-wide study of changes in DNA copy number
❾	2009	Germline genetic variants associated with the development of ALL
❿	2009	Recognition of Philadelphia chromosome-like "Ph-like" ALL
⓫	2012	First whole-genome sequencing study to identify driver mutations in early T-cell precursor ALL
⓬	2012	Use of next-generation sequencing to enhance detection of minimal residual disease
⓭	2015	Whole genome analysis identified germline genetic mutations in predisposition genes

FIG. 522.2 **Landmark advances in pediatric acute lymphoblastic leukemia (ALL). 5-year overall survival data for pediatric ALL from the Surveillance, Epidemiology, and End Results (SEER) Program1 is overlaid with landmark advances in the treatment (white; left table) and in understanding the biology of pediatric ALL (black; right table). (From Heikamo EB, HonPui C: Next-generation evaluation and treatment of pediatric acute lymphoblastic leukemia. *J Pediatr* 203:14–24, 2018. Fig 1; and from Pui CH, Evans WE: A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin Hematol,* 50:185–196, 2013. Table 2.)**

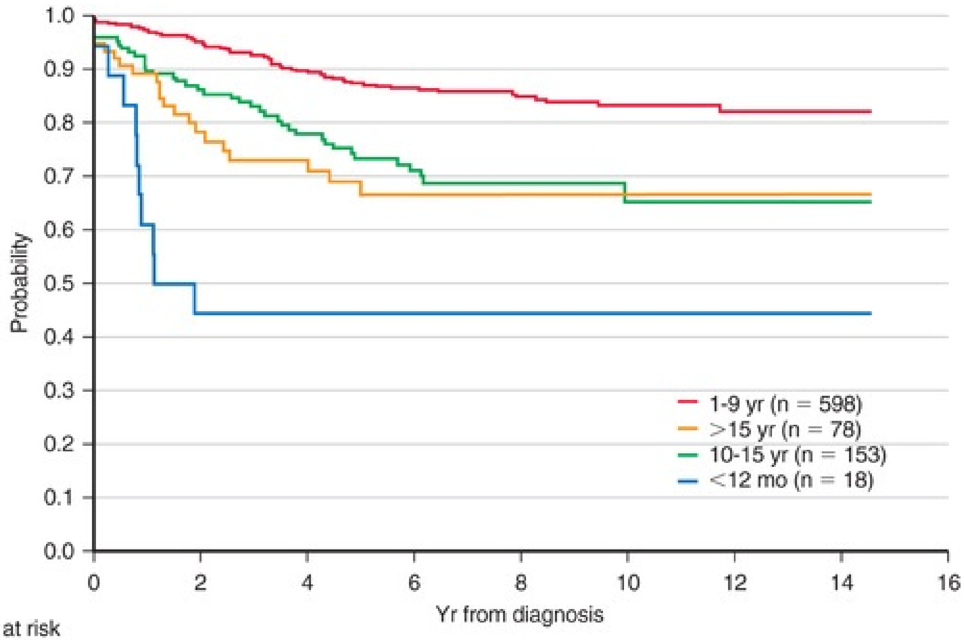

Number at risk									
<12 mo	18	11	8	8	6	1	1	0	0
1-9 yr	598	528	378	295	213	149	85	31	4
10-15 yr	153	130	100	77	50	26	11	6	1
>15 yr	78	60	40	29	20	7	1	0	0

FIG. 522.3 **Kaplan-Meier estimates of event-free survival according to age at diagnosis of acute lymphoblastic leukemia. (From Pui CH, Robinson LL, Look AT: Acute lymphoblastic leukaemia, *Lancet* 371:1030–1042, 2008.)**

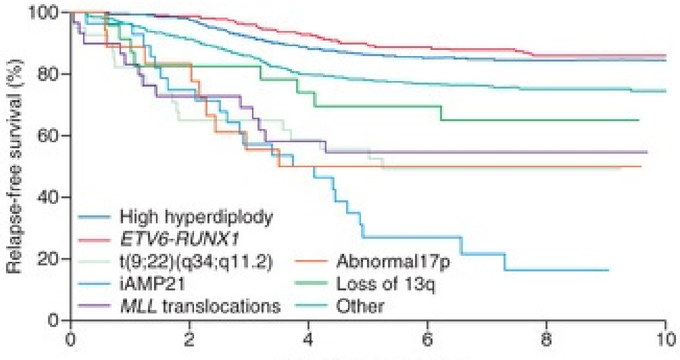

Number at risk						
High hyperdiplody	551	529	470	434	249	98
ETV6-RUNX1	365	355	331	301	167	47
t(9;22)(q34;q11.2)	42	22	19	14	8	2
iAMP21	28	21	14	6	1	0
MLL translocations	30	20	16	14	9	1
Abnormal17p	18	15	9	8	7	2
Loss of 13q	24	19	17	15	9	4
Other	644	567	483	440	258	105

FIG. 522.4 **Kaplan-Meier analysis of relapse-free survival according to biologic subtype of leukemia. (From Moorman AV, Ensor HM, Richards SM, et al: Prognostic effect of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: results from the UK Medical Research Council ALL97/99 randomised trial,**

***Lancet Oncol* 11:429–438, 2010.)**

Risk-directed therapy is the standard of current ALL treatment and accounts for age at diagnosis, initial WBC count, immunophenotypic and cytogenetic characteristics of blast populations, rapidity of early treatment response (i.e., how quickly the leukemic cells can be cleared from the marrow or peripheral blood), and assessment of MRD at the end of induction therapy. Different study groups use various factors to define risk, but age 1-10 yr and a leukocyte count <50,000/µL are used by the National Cancer Institute (NCI) to define standard risk. Children who are younger than 1 yr or older than 10 yr or who have an initial leukocyte count of >50,000/µL are considered to be *high risk.* Additional characteristics that adversely affect outcome include T-cell immunophenotype or a slow response to initial therapy. Chromosomal abnormalities, including hypodiploidy, the Philadelphia chromosome, and *KMT2A (MLL)* gene rearrangements, portend a poorer outcome. Other mutations, such as in the *IKZF1* gene, have been shown to be associated with a poor prognosis and may become important in treatment algorithms in the future. More favorable characteristics include a rapid response to therapy, hyperdiploidy, trisomy of specific chromosomes (4, 10, and 17), and rearrangements of the *ETV6-RUNX1* (formerly *TEL-AML1*) genes.

The outcome for patients at higher risk can be improved by administration of more intensive therapy despite the greater toxicity of such therapy. Infants with ALL, along with patients who present with specific chromosomal abnormalities, such as t(4;11), have an even higher risk of relapse despite intensive therapy. However, the poor outcome of Philadelphia chromosome–positive ALL with t(9;22) has been dramatically changed by the addition of imatinib to an intensive chemotherapy backbone. **Imatinib** is an agent specifically designed to inhibit the BCR-ABL kinase resulting from the translocation. With this approach, the event-free survival has improved from 30% to 70%. Clinical trials demonstrate that the prognosis for patients with a slower response to initial therapy may be improved by therapy that is more intensive than the therapy considered necessary for patients who respond more rapidly.

Most children with ALL are treated in clinical trials conducted by national or international cooperative groups. Standard treatment involves chemotherapy for 2-3 yr, and most achieve remission at the end of the induction phase. Patients in clinical remission can have MRD that can only be detected with specific molecular probes to translocations and other DNA markers contained in leukemic cells or specialized flow cytometry. MRD can be quantitative and can provide an estimate of the burden of leukemic cells present in the marrow. Higher levels of MRD present at the end of induction suggest a poorer prognosis and higher risk of subsequent relapse. MRD of >0.01% on the marrow on day 29 of induction is a significant risk factor for shorter event-free survival for all risk categories, compared with patients with negative MRD. Therapy for ALL intensifies treatment in patients with evidence of MRD at the end of induction.

Initial therapy, termed **remission induction** , is designed to eradicate the leukemic cells from the bone marrow. During this phase, therapy is given for 4 wk and consists of vincristine weekly, a corticosteroid such as dexamethasone or prednisone, and usually a single dose of a long-acting, pegylated asparaginase preparation. Patients at higher risk also receive daunomycin at weekly intervals. With this approach, 98% of patients are in *remission,* as defined by <5% blasts in the marrow and a return of neutrophil and platelet counts to near-normal levels after 4-5 wk of treatment. Intrathecal chemotherapy is always given at the start of treatment and at least once more during induction.

The second phase of treatment, **consolidation** , focuses on intensive CNS therapy in combination with continued intensive systemic therapy in an effort to prevent later CNS relapses. Intrathecal chemotherapy is given repeatedly by LP. The likelihood of later CNS relapse is thereby reduced to <5%, from historical incidence as high as 60%. A small percentage of patients with features that predict a high risk of CNS relapse may receive irradiation to the brain in later phases of therapy. This includes patients who at diagnosis have lymphoblasts in the CSF and either an elevated CSF leukocyte count or physical signs of CNS leukemia, such as cranial nerve palsy.

Subsequently, many regimens provide 14-28 wk of therapy, with the drugs and schedules used varying depending on the risk group of the patient. This period of treatment is often termed **intensification** and includes phases of aggressive treatment (**delayed intensification**) as well as relatively nontoxic phases of treatment (**interim maintenance**). Multiagent chemotherapy, including such medications as cytarabine, methotrexate, asparaginase, and vincristine, is used during these phases to eradicate residual disease.

Finally, patients enter the **maintenance** phase of therapy, which lasts for 2-3 yr, depending on the protocol used. Patients are given daily mercaptopurine and weekly oral methotrexate, usually with intermittent doses of vincristine and a corticosteroid.

A small number of patients with particularly poor prognostic features, such as those with induction failure or extreme hypodiploidy, may undergo bone marrow transplantation during the first remission.

Adolescents and **young adults** with ALL have an inferior prognosis compared to children <15 yr old. They often have adverse prognostic factors and require more intensive therapy. Patients in this age-group have a superior outcome when treated with pediatric rather than adult treatment protocols (Fig. 522.5). Although the explanation for these findings may be multifactorial, it is important that these patients be treated with pediatric treatment protocols, ideally in a pediatric cancer center.

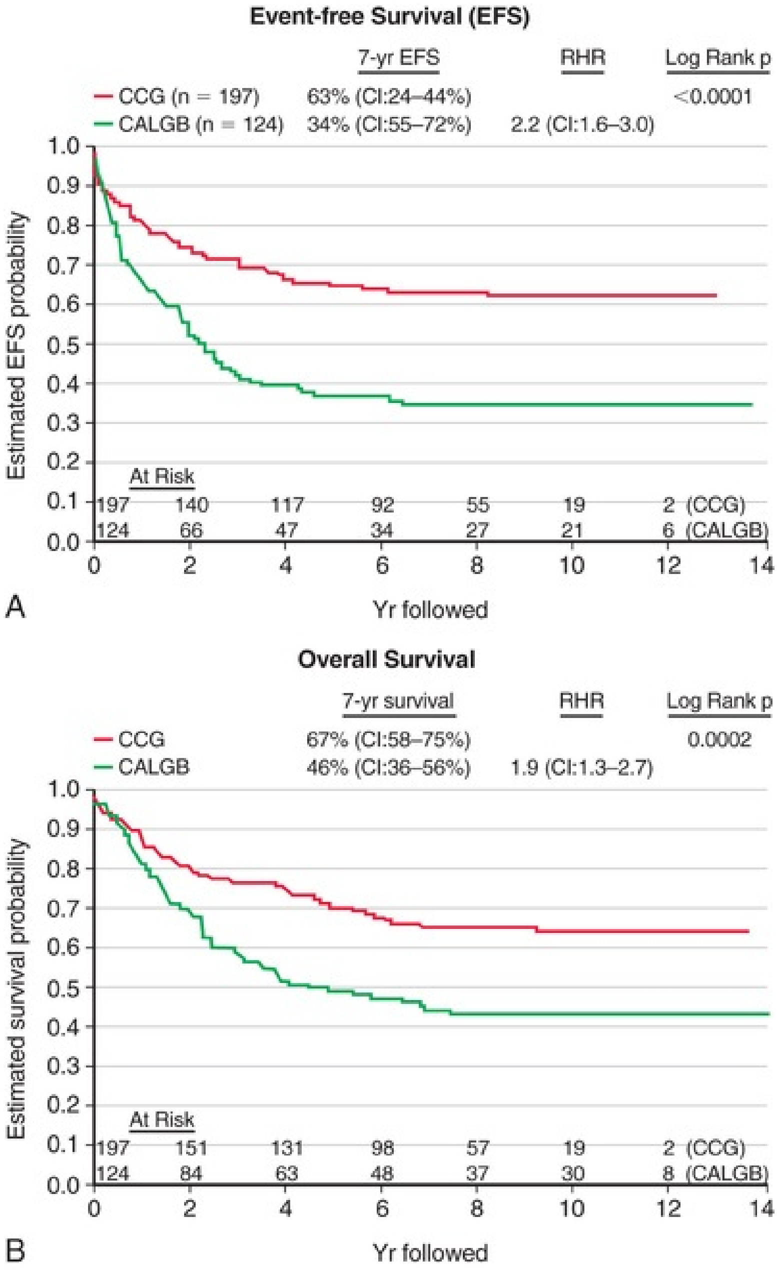

FIG. 522.5 **Comparison of event-free survival among Cancer and Leukemia Group B (CALGB) (adult protocol, *green line*) and Children's Cancer Group (CCG) (pediatric protocol, *red line*) patients. (From Stock W, La M, Sanford B, et al: What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies, *Blood* 112:1646–1654, 2008.)**

Genetic polymorphisms of enzymes important in drug metabolism may impact both the efficacy and the toxicity of chemotherapeutic medications. **Pharmacogenetic testing** of the thiopurine *S* -methyltransferase *(TPMT)* gene, which encodes one of the metabolizing enzymes of mercaptopurine, can identify patients who are *wild type* (normal TPMT enzyme activity), *heterozygous* (slightly decreased TPMT enzyme activity), or *homozygous* (low or absent enzyme activity). Decreased TPMT enzyme activity results in accumulation of a toxic metabolite of mercaptopurine and severe myelosuppression, requiring dose reductions of the chemotherapy (see Chapter 73). In the future, treatment also may be stratified by gene expression profiles of leukemic cells. In particular, gene expression arrays induced by exposure to a chemotherapeutic agent can predict which patients have drug-resistant ALL.

Treatment of Relapse

The major impediment to a successful outcome is **relapse** of the disease. Outcomes remain poor among those who relapse, with the most important prognostic indicators being time from diagnosis and site of relapsed disease. In addition, other factors, such as immunophenotype (T-ALL worse than B-ALL) and age at initial diagnosis, have prognostic significance.

Relapse occurs in the bone marrow in 15–20% of patients with ALL and carries the most serious implications, especially if it occurs during or shortly after completion of therapy. Intensive chemotherapy with agents not previously used in the patient followed by allogeneic stem cell transplantation can result in long-term survival for some patients with bone marrow relapse (see Chapter 161). **Chimeric antigen receptor** (CAR) T-cell technology will have an increasing role in the treatment of patients who have experienced a relapse of ALL (see Chapter 521).

The incidence of **CNS relapse** has decreased to <5% since introduction of preventive CNS therapy. CNS relapse may be discovered at a routine LP in the asymptomatic patient. Symptomatic patients with relapse in the CNS usually present with signs and symptoms of increased intracranial pressure and can present with isolated cranial nerve palsies. The diagnosis is confirmed by demonstrating the presence of leukemic cells in the CSF. The treatment includes intrathecal medication and cranial or craniospinal irradiation. Systemic chemotherapy also must be used, because these patients are at high risk for subsequent bone marrow relapse. Most patients with leukemic relapse confined to the CNS do well, especially those in whom the CNS relapse occurs longer than 18 mo after initiation of chemotherapy.

Testicular relapse occurs in <2% of boys with ALL, usually after completion of therapy. Such relapse occurs as painless swelling of 1 or both testes. The diagnosis is confirmed by biopsy of the affected testis. Treatment includes systemic chemotherapy and possibly local irradiation. A high proportion of boys with a testicular relapse can be successfully retreated, and the survival rate of these patients is good.

The most current information on treatment of childhood ALL is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/treatment/childALL/healthprofessional/).

Supportive Care

Close attention to the medical supportive care needs of the patients is essential in successfully administering aggressive chemotherapeutic programs. Patients with high WBC counts are especially prone to **tumor lysis syndrome** as therapy is initiated. The kidney failure associated with very high levels of serum uric acid can be prevented or treated with allopurinol or urate oxidase. Chemotherapy often produces severe myelosuppression, which can require erythrocyte and platelet transfusion and always requires a high index of suspicion and aggressive empirical antimicrobial therapy for sepsis in febrile children with neutropenia. Patients must receive prophylactic treatment for *Pneumocystis jiroveci* pneumonia during chemotherapy and for several months after completing treatment.

The successful therapy of ALL is a direct result of intensive and often toxic treatment. However, such intensive therapy can incur substantial academic, developmental, and psychosocial costs for children with ALL and considerable financial costs and stress for their families. Both long-term and acute toxicity effects can occur. An array of cancer care professionals with training and experience in addressing the myriad of problems that can arise is essential to minimize the complications and achieve an optimal outcome.

Prognosis

Improvements in therapy and risk stratification have resulted in significant increases in survival rates, with current data showing overall 5 yr survival of approximately 90% (Fig. 522.6). However, survivors are more likely to experience significant chronic medical conditions compared to siblings, including musculoskeletal, cardiac, and neurologic conditions. Overall, long-term management following ALL should be conducted in a clinic where children and adolescents can be followed by a variety of specialists to address the challenges of these unique patients.

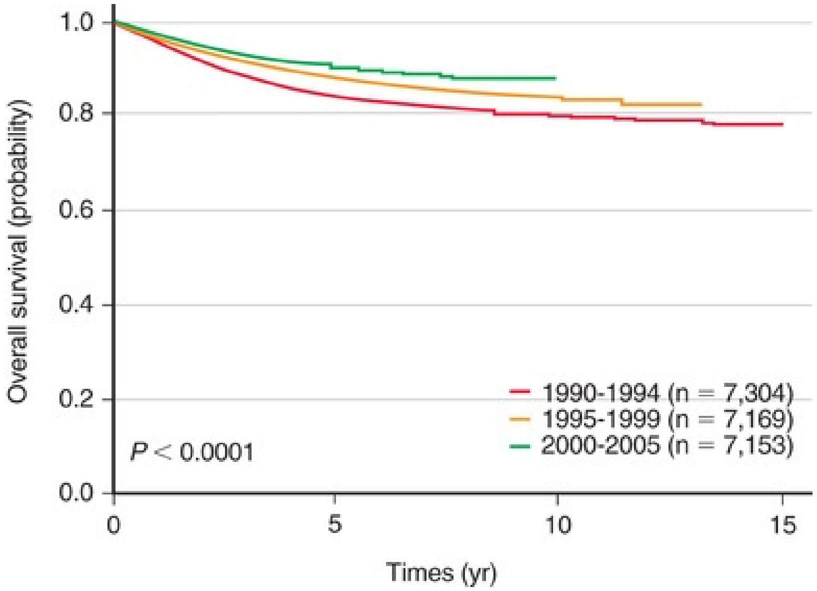

FIG. 522.6 **Overall survival probabilities by treatment era for patients with ALL in Children's Oncology Group trials in 1990–1994, 1995–1999, and 2000–2005. (From Hunger SP, Lu X, Devidas M, et al: Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group, *J Clin Oncol* 30:1663–1669, 2012.)**

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522.2

Acute Myelogenous Leukemia

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Keywords

AML
acute promyelocytic leukemia
AML
chloroma
tretinoin

Epidemiology

Acute myelogenous leukemia (**AML**) accounts for 11% of the cases of childhood leukemia in the United States; it is diagnosed in approximately 370 children annually. The relative frequency of AML increases in adolescence, representing 36% of cases of leukemia in 15-19 yr olds. **Acute promyelocytic leukemia (APL)** is a subtype that is more common in certain regions of the world, but the incidence of the other types is generally uniform. Several chromosomal abnormalities associated with AML have been identified, but no predisposing genetic or environmental factors can be identified in most patients (see Table 522.1). Nonetheless, a number of risk factors have been identified, including ionizing radiation, chemotherapeutic agents (e.g., alkylating agents, epipodophyllotoxin), organic solvents, paroxysmal nocturnal hemoglobinuria, and certain syndromes: Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, Li-Fraumeni syndrome, and neurofibromatosis type 1.

Cellular Classification

The characteristic feature of AML is that >20% of bone marrow cells on bone marrow aspiration or biopsy touch preparations constitute a fairly homogeneous population of blast cells, with features similar to those that characterize early differentiation states of the myeloid-monocyte-megakaryocyte series of blood cells. Current practice requires the use of flow cytometry to identify cell surface antigens and use of chromosomal and molecular genetic techniques for additional diagnostic precision and to aid the choice of therapy. The WHO has proposed a new classification system that incorporates morphology, chromosome abnormalities, and specific gene mutations. This system provides significant biologic and prognostic information (Table 522.3).

Table 522.3

WHO Classification of Acute Myeloid Neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities
• AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
• AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
• APL with *PML-RARA*
• AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
• AML with t(6;9)(p23;q34.1); *DEK-NUP214*
• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
• AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*
• *Provisional entity: AML with BCR-ABL1*
• AML with mutated NPM1
• AML with biallelic mutations of CEBPA
• *Provisional entity: AML with mutated RUNX1*
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
• AML with minimal differentiation
• AML without maturation
• AML with maturation
• Acute myelomonocytic leukemia
• Acute monoblastic/monocytic leukemia
• Pure erythroid leukemia
• Acute megakaryoblastic leukemia
• Acute basophilic leukemia
• Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
• Transient abnormal myelopoiesis

• Myeloid leukemia associated with Down syndrome Blastic plasmacytoid dendritic cell neoplasm

AML, Acute myelogenous leukemia; APL, acute promyelocytic leukemia.

Adapted from Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 127:2391–2405, 2016.

Clinical Manifestations

The production of symptoms and signs of AML is a result of replacement of bone marrow by malignant cells and caused by secondary bone marrow failure. Patients with AML can present with any or all of the findings associated with marrow failure in ALL. In addition, patients with AML present with signs and symptoms that are uncommon in ALL, including **subcutaneous nodules** or “blueberry muffin” lesions (especially in infants), infiltration of the gingiva (especially in monocytic subtypes), signs and laboratory findings of **disseminated intravascular coagulation** (especially indicative of APL), and discrete masses, known as **chloromas** or **granulocytic sarcomas** . These masses can occur in the absence of apparent bone marrow involvement and typically are associated with a t(8;21) translocation. Chloromas also may be seen in the orbit and epidural space.

Diagnosis

Analysis of bone marrow aspiration and biopsy specimens of patients with AML typically reveals the features of a hypercellular marrow consisting of a monotonous pattern of cells. Flow cytometry and special stains assist in identifying myeloperoxidase-containing cells, thus confirming both the myelogenous origin of the leukemia and the diagnosis. Some chromosomal abnormalities and molecular genetic markers are characteristic of specific subtypes of disease (Table 522.4).

Table 522.4

Prognostic Implications of Common Chromosomal Abnormalities in Pediatric Acute Myelogenous Leukemia

CHROMOSOMAL ABNORMALITY	GENETIC ALTERATION	USUAL MORPHOLOGY	PROGNOSIS
t(8;21)	*RUNX1-RUNX1T1*	Myeloblasts with differentiation	Favorable
inv(16)	*CBFB-MYHII*	Myeloblasts plus abnormal eosinophils with dysplastic basophilic granules	Favorable
t(15;17)	*PML-RARA*	Promyelocytic	Favorable
11q23 abnormalities	*KMT2A(MLL)* rearrangements	Monocytic	Unfavorable
FLT3 mutation	*FLT3* -ITD	Any	Unfavorable
del(7q), −7	Unknown	Myeloblasts without differentiation	Unfavorable

Adapted from Nathan DG, Orkin SH, Ginsburg D, et al, editors: *Nathan and Oski's hematology of infancy and childhood* , ed 6, Philadelphia, 2003, Saunders, p 1177.

Prognosis and Treatment

Aggressive multiagent chemotherapy is successful in inducing remission in approximately 85–90% of patients. Survival has increased dramatically since the 1970s, when only 15% of newly diagnosed patients survived, compared to a current survival rate of 60–70% with modern therapy (Fig. 522.7). Various induction chemotherapy regimens exist, typically including an anthracycline in combination with high-dose cytarabine. Targeting therapy to genetic markers may be beneficial (see Table 522.4). Up to 5% of patients die of either infection or bleeding before a remission can be achieved. Postremission therapy is chosen based on a combination of cytogenetic and molecular markers of the leukemia as well as the response to induction chemotherapy (MRD assessment). For selected patients with favorable prognostic features [t(8;21); t(15;17); inv(16)] and improved outcome with chemotherapy alone, stem cell transplantation is recommended only after a relapse. However, patients with unfavorable prognostic features (e.g., monosomies 7 and 5, 5q−, and 11q23 abnormalities) who have inferior outcome with chemotherapy might benefit from stem cell transplant in first remission. With improvements in supportive care, there is no longer a substantial difference in mortality when comparing matched-related stem cell transplants to matched-unrelated stem cell transplants for AML.

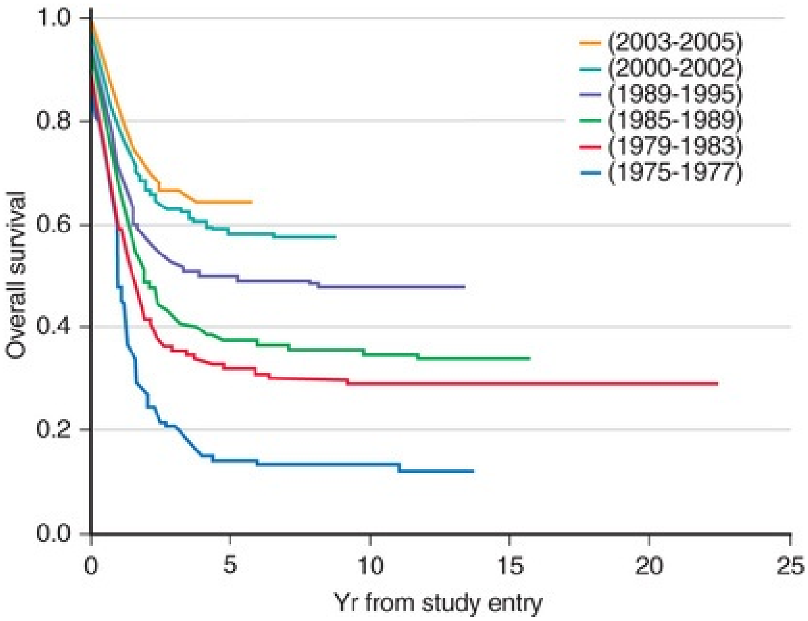

FIG. 522.7 **Overall survival showing incremental improvements over the last 40 years in Children's Oncology Group and legacy trials in childhood acute myelogenous leukemia (AML). (From Gamis AS, Alonzo TA, Perentesis JP, Meshinchi S, on behalf of the COG Acute Myeloid Leukemia Committee: Children's Oncology Group's 2013 blueprint for research: acute myeloid leukemia, *Pediatr Blood Cancer* 60:964–971, 2013.)**

Acute promyelocytic leukemia, characterized by a gene rearrangement involving the retinoic acid receptor [t(15;17); PML-RARA], is very responsive to **all-*trans* -retinoic acid (ATRA, tretinoin)** combined with anthracyclines and cytarabine. The success of this therapy makes marrow transplantation in first remission unnecessary for patients with this disease. Arsenic trioxide is an effective noncytotoxic therapy for APL. Data from trials in adults show promising results with the use of combined ATRA/arsenic without cytotoxic drugs as initial therapy for APL and would support a new trial of this regimen in children.

Increased supportive care is needed in patients with AML because the intensive therapy they receive produces prolonged bone marrow suppression with a very high incidence of serious infections, especially viridans streptococcal sepsis and fungal infection. These patients may require prolonged hospitalization, filgrastim (granulocyte colony-stimulating factor), and prophylactic antimicrobials.

The most current information on treatment of AML is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/treatment/childAML/healthprofessional).

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522.3

Down Syndrome and Acute Leukemia and Transient Myeloproliferative Disorder

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Keywords

Down syndrome
leukemia

myeloproliferative disorder

Acute leukemia occurs about 15-20 times more frequently in children with Down syndrome than in the general population (see Chapters 98.2 and 519). The ratio of ALL to AML in patients with Down syndrome is the same as that in the general population. The exception is during the 1st 3 yr of life, when AML is more common. In children with Down syndrome who have ALL, the expected outcome of treatment is slightly inferior to that for other children, a difference that can be partially explained by a lack of good prognostic characteristics, such as *ETV6-RUNX1* and trisomies, as well as genetic abnormalities that are associated with an inferior prognosis, such as *IKZF1* . Patients with Down syndrome demonstrate a remarkable sensitivity to methotrexate and other antimetabolites, resulting in substantial toxicity if standard doses are administered. However, in the case of AML, patients with Down syndrome have much better outcomes than non–Down syndrome children, with a >80% long-term survival rate. After induction therapy, these patients receive therapy that is less intensive to decrease toxicity while maintaining excellent cure rates.

Approximately 10% of neonates with Down syndrome develop a transient leukemia or **myeloproliferative disorder** characterized by high leukocyte counts, blast cells in the peripheral blood, and associated anemia, thrombocytopenia, and hepatosplenomegaly. These features usually resolve within the 1st 3 mo of life. Although these neonates can require temporary transfusion support, they do not require chemotherapy unless there is evidence of life-threatening complications. However, patients who have Down syndrome and who develop this transient myeloproliferative disorder require close follow-up, because 20–30% will develop typical leukemia (often **acute megakaryocytic leukemia**) by age 3 yr (mean onset, 16 mo). *GATA1* mutations (a transcription factor that controls megakaryopoiesis) are present in blasts from patients with Down syndrome who have transient myeloproliferative disease and also in those with leukemia (Fig. 522.8).

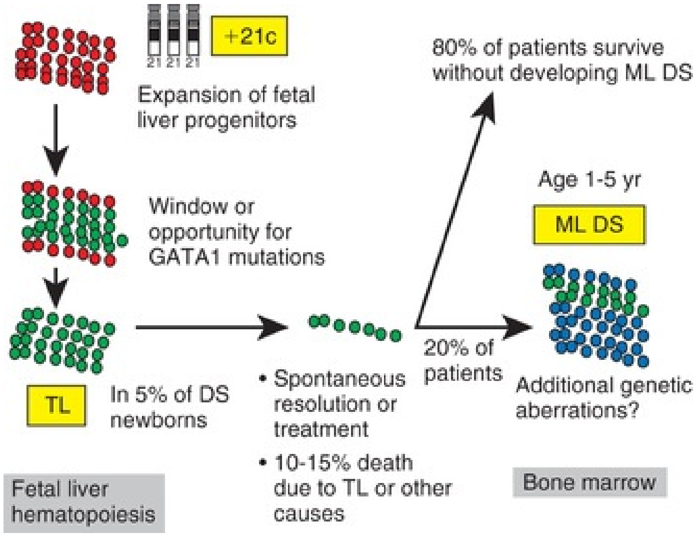
21 21 21
+21c
Expansion of fetal liver progenitors
Window or opportunity for GATA1 mutations
TL
In 5% of DS newborns
Fetal liver hematopoiesis
• Spontaneous resolution or treatment
• 10-15% death due to TL or other causes
80% of patients survive without developing ML DS
20% of patients
Age 1-5 yr
ML DS
Additional genetic aberrations?
Bone marrow

FIG. 522.8 Stepwise development of myeloid leukemia in Down syndrome (ML DS) following transient leukemia (TL). TL arises from expanded fetal liver progenitors as a result of constitutional trisomy 21, providing a window of opportunity for the occurrence of acquired mutations in the hematopoietic transcription factor GATA1. In most cases, TL spontaneously disappears, but some children need treatment because of severe TL-related symptoms. Approximately 20% of children with TL subsequently develop ML DS, which requires additional hits. (From Zwaan MC, Reinhardt D, Hitzler J, Vyas P: Acute leukemias in children with Down syndrome, *Pediatr Clin North Am* 55:53–70, 2008.)

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522.4

Chronic Myelogenous Leukemia

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Keywords

CML
imatinib
Philadelphia chromosome
tyrosine kinase inhibitor

Chronic myelogenous leukemia (**CML**) is a clonal disorder of the hematopoietic tissue that accounts for 2–3% of all cases of childhood leukemia. Approximately 99% of the cases are characterized by a specific translocation, t(9;22)(q34;q11), known as the **Philadelphia chromosome** , resulting in a *BCR-ABL* fusion protein**.**

The presenting symptoms of CML are nonspecific and can include fever, fatigue, weight loss, and anorexia. Splenomegaly also may be present, resulting in pain in the left upper quadrant of the abdomen. The diagnosis is suggested by a high WBC count with myeloid cells at all stages of differentiation in the peripheral blood and bone marrow. It is confirmed by cytogenetic and molecular studies that demonstrate the presence of the characteristic Philadelphia chromosome and the *BCR-ABL* gene rearrangement. This translocation, although characteristic of CML, is also found in a small percentage of patients with ALL.

The disease is characterized by an initial **chronic phase** in which the malignant clone produces an elevated leukocyte count with a predominance of mature forms but with increased numbers of immature granulocytes. In addition to leukocytosis, blood counts can reveal mild anemia and thrombocytosis. Typically, the chronic phase terminates 3-4 yr after onset, when the CML moves into the **accelerated** or “blast crisis” **phase** . At this point, the blood counts rise dramatically, and the clinical picture is indistinguishable from acute leukemia. Additional manifestations can occur, including neurologic symptoms from hyperleukocytosis, which causes increased blood viscosity with decreased CNS perfusion.

Imatinib (Gleevec), an agent designed specifically to inhibit the *BCR-ABL* tyrosine kinase, has been used in adults and children and has shown an ability to produce major cytogenetic responses in >70% of patients (see Table 522.1). Experience in children suggests it can be used safely with results comparable to those seen in adults. Second-generation tyrosine kinase inhibitors, such as **dasatinib and nilotinib** , have improved remission rates in adults and are now included in the first-line therapy in that population. While waiting for a response to the tyrosine kinase inhibitor, disabling or threatening signs and symptoms of CML can be controlled during the chronic phase with hydroxyurea, which gradually returns the leukocyte count to normal. *Treatment with a tyrosine kinase inhibitor is the current standard for pediatric CML.* While not considered curative at this time, prolonged responses can be seen and studies in adults have shown that in select cases, treatment with the tyrosine kinase inhibitor can be stopped. The role of potentially curative HLA-matched family donor stem cell transplant in management of pediatric CML is debated.

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522.5

Juvenile Myelomonocytic Leukemia

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Keywords

JMML
RAS mutation

Juvenile myelomonocytic leukemia (**JMML**), formerly termed **juvenile chronic myelogenous leukemia,** is a clonal proliferation of hematopoietic stem cells that typically affects children <2 yr old. JMML is rare, constituting <1% of all cases of childhood leukemia. Patients with this disease do not have the Philadelphia chromosome characteristic of CML. Patients with JMML present with rashes, lymphadenopathy, splenomegaly, and hemorrhagic manifestations. Analysis of the peripheral blood often shows an elevated leukocyte count with increased monocytes, thrombocytopenia, and anemia with the presence of erythroblasts. The bone marrow shows a myelodysplastic pattern, with blasts accounting for <20% of cells. Most patients with JMML have been found to have mutations that lead to activation of the *RAS* oncogene pathway, including *NRAS* , *NF1* , and *PTPN11* . Patients with **neurofibromatosis type 1** and **Noonan syndrome** have a predilection for this type of leukemia, since they have germline mutations involved in *RAS* signaling. JMML in the setting of Noonan syndrome is unique, with most patients having a spontaneous resolution. However, for most patients with JMML, stem cell transplantation offers the best opportunity for cure, but outcomes are still poor.

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522.6

Infant Leukemia

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Keywords

acute myelomonocytic leukemia
leukemia cutis

Approximately 2% of cases of leukemia during childhood occur before age 1 yr. In contrast to the situation in older children, the ratio of ALL in infants to AML is 2 : 1. Leukemic clones have been noted in cord blood at birth before symptoms appear, and in one case the same clone was noted in maternal cells (maternal-to-fetal transmission). Chromosome translocations can also occur in utero during fetal hematopoiesis, leading to malignant clone formation.

Several unique biologic features and a particularly poor prognosis are characteristic of ALL during infancy. More than 80% of the cases demonstrate rearrangements of the *KMT2A* (*MLL)* gene, found at the site of the 11q23 band translocation, the majority of which are the t(4;11). This subset of patients largely accounts for the very high relapse rate. These patients often present with hyperleukocytosis and extensive tissue infiltration producing organomegaly, including CNS disease. Subcutaneous nodules, known as **leukemia cutis** , and tachypnea caused by diffuse pulmonary infiltration by leukemic cells are observed more often in infants than in older children. The leukemic cell morphology is usually that of large, irregular lymphoblasts, with a phenotype negative for the CD10 (common ALL antigen) marker (pro-B), unlike most older children with B-ALL, who are $CD10^+$.

Very intensive chemotherapy programs, including stem cell transplantation, are being explored in infants with *KMT2A* (*MLL)* gene rearrangements, but none has yet proved satisfactory. Infants with leukemia who lack the 11q23 rearrangements have a prognosis similar to that of older children with ALL.

Infants with AML often present with CNS or skin involvement and have a subtype known as **acute myelomonocytic leukemia.** The treatment may be the same as that for older children with AML, with similar outcome. Meticulous supportive care is necessary because of the young age and aggressive therapy needed in these patients.

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CHAPTER 523

Lymphoma

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Lymphoma is the third most common cancer among U.S. children (≤14 yr old), with an annual incidence of 15 cases per 1 million children. It is the most common cancer in adolescents, accounting for >25% of newly diagnosed cancers in those 15-19 yr old. The 2 broad categories of lymphoma, Hodgkin lymphoma and non-Hodgkin lymphoma, have different clinical manifestations and treatments.*

523.1

Hodgkin Lymphoma

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Keywords

Epstein-Barr virus
EBV
HL
Lymphoma
immune therapy
Lugano classification

Reed-Sternberg cell

Hodgkin lymphoma (**HL**) is a malignant process involving the lymphoreticular system that accounts for 6% of childhood cancers. In the United States, HL accounts for approximately 5% of cancers in children ≤14 yr old; it accounts for approximately 15% of cancers in adolescents (15-19 yr), making HL the most common malignancy in this age-group.

Epidemiology

The worldwide incidence of HL is approximately 2-4 new cases/100,000 population/yr. There is a bimodal age distribution, with peaks at 15-35 yr of age and again after 50 yr. HL is the most common cancer seen in adolescents and young adults, and the 3rd most common in children <15 yr old. In developing countries, the early peak tends to occur before adolescence. A male predominance is found among young children but lessens with age. Infectious agents may be involved, such as human herpesvirus 6, cytomegalovirus, and **Epstein-Barr virus (EBV)** . The role of EBV is supported by prospective serologic studies. Infection with EBV confers a 4-fold higher risk of developing HL and may precede the diagnosis by years. EBV antigens have been demonstrated in HL tissues, particularly type II latent membrane proteins 1 and 2. Some studies have suggested that elevated copies of EBV by polymerase chain reaction (PCR) correspond to worse prognosis. The EBV antigens latent membrane protein (LMP) 1 and 2 have been used as targets for cytotoxic T-lymphocyte therapy in patient with relapsed/refractory HL.

Pathogenesis

The **Reed-Sternberg (RS) cell,** a pathognomonic feature of HL, is a large cell (15-45 µm in diameter) with multiple or multilobulated nuclei. This cell type is considered the hallmark of HL, although similar cells are seen in infectious mononucleosis, non-Hodgkin lymphoma, and other conditions. The RS cell is clonal in origin and arises from the germinal center B cells but typically has lost most B-cell gene expression and function. There is no single simple genetic aberration that leads to malignant transformation of the RS cell; rather, a combination of somatic mutations, chromosomal instability, and complex chromosomal rearrangements has been reported with no particular pattern or frequency. This typically leads to cell regulation defects such as constitutive activation of the nuclear factor (NF)-κB pathway or abnormal regulation of the Bcl-2 family of proteins. HL is characterized by a variable number of RS cells surrounded by an inflammatory infiltrate of lymphocytes, macrophages, plasma cells, and eosinophils in different proportions, depending on the HL histologic subtype. The interaction between the RS cell and these background inflammatory cells with their associated cytokine release is important in the development and progression of HL. Reactive infiltration of eosinophils and $CD68^+$ macrophages and increased concentrations of cytokines, such as interleukin (IL)-1 and IL-6 and tumor necrosis factor (TNF), are all associated with an unfavorable prognosis. Other factors associated with a worse prognosis include advanced stage, the presence of "B" symptoms, decreased response to therapy, and slow response to therapy. In addition, evidence of $CD8^+$ T cells surrounding the RS cell offers evidence of an important role in T-cell promotion of malignant cell survival, perhaps through the CD30 and CD40 ligands found on RS cells as well as immune checkpoint inhibition pathways. Other features that distinguish the histologic subtypes include various degrees of fibrosis and the presence of collagen bands, necrosis, or malignant reticular cells (Fig. 523.1). The distribution of subtypes varies with age.

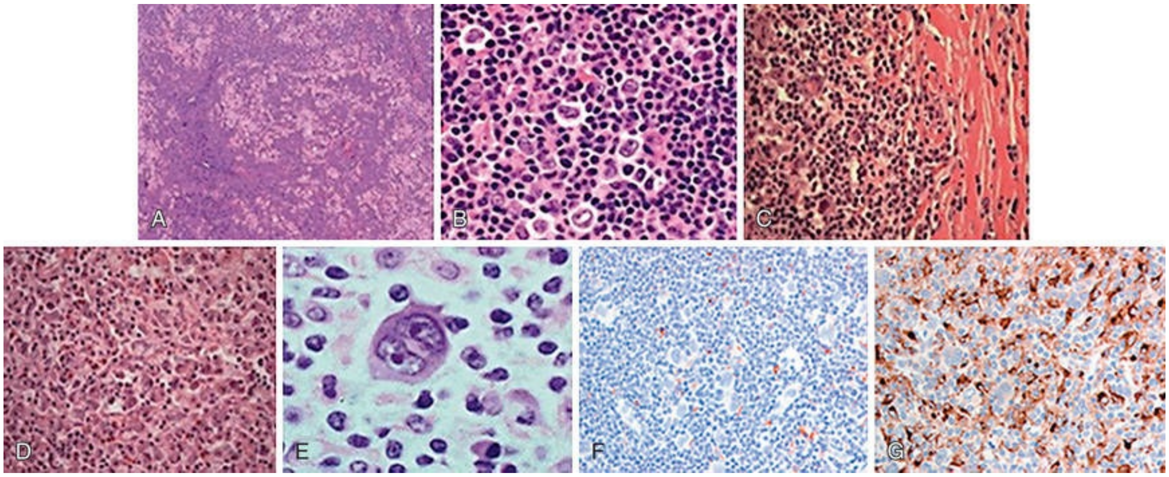

FIG. 523.1 **Histologic subtypes of Hodgkin lymphoma. A, Hematoxylin and eosin (H&E) stains of nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) demonstrating a nodular proliferation with a moth-eaten appearance. B, High-power view demonstrating the neoplastic L and H cells found in NLPHL. C, Classic Hodgkin lymphoma, nodular sclerosis subtype. Large mononuclear and binucleate Reed-Sternberg cells are seen admixed in the inflammatory cell background. D, Classic Hodgkin lymphoma, mixed cellularity subtype, demonstrating increased numbers of**

Reed-Sternberg cells in a mixed inflammatory background without sclerotic changes. E, High-power view of a classic Reed-Sternberg cell showing binucleate cells with prominent eosinophilic nucleoli and relatively abundant cytoplasm. F, Few CD68$^+$ macrophages in a treatment success patient. G, Many CD68$^+$ macrophages in a treatment failure patient.

The **Revised World Health Organization Classification of Lymphoid Neoplasms** includes 2 modifications of the older Rye system. HL appears to arise in lymphoid tissue and spread to adjacent lymph node areas in a relatively orderly manner (Table 523.1). Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow, or brain, and is usually associated with systemic symptoms.

Table 523.1

New World Health Organization (WHO)/Revised European–American Classification of Lymphoid Neoplasms for Hodgkin Lymphoma

- Nodular lymphocyte predominance
- Classical Hodgkin lymphoma
  - Lymphocyte rich
  - Mixed cellularity
  - Nodular sclerosis
  - Lymphocyte depletion

From Harris NL, Jaffe ES, Diebold J, et al: The World Health Organization classification of neoplastic diseases of the haematopoietic and lymphoid tissues: report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997, *Histopathology* 36:69–87, 2000.

Clinical Manifestations

Patients typically present with painless, nontender, firm, rubbery, cervical or supraclavicular lymphadenopathy and usually some degree of mediastinal involvement. Clinically detectable hepatosplenomegaly may be encountered. Depending on the extent and location of nodal and extranodal disease, patients may present with symptoms and signs of airway obstruction (dyspnea, hypoxia, cough), pleural or pericardial effusion, hepatocellular dysfunction, or bone marrow infiltration (anemia, neutropenia, or thrombocytopenia). Systemic symptoms**,** classified as **B symptoms** , that are considered important in staging are unexplained fever >38°C (100.4°F), weight loss >10% total body weight over 6 mo, and drenching night sweats. Less common and not considered of prognostic significance are symptoms of pruritus, lethargy, anorexia, or pain. Patients also exhibit immune system deficiencies that often persist during and after therapy.

Diagnosis

Any patient with persistent, unexplained lymphadenopathy unassociated with an obvious underlying inflammatory or infectious process should undergo chest radiography to identify the presence of a large mediastinal mass before undergoing lymph node biopsy (Fig. 523.2). Formal excisional biopsy is preferred over needle biopsy to ensure that adequate tissue is obtained, both for light microscopy and for appropriate immunohistochemical and molecular studies. Once the diagnosis of HL is established, extent of disease (stage) should be determined to allow selection of appropriate therapy (Table 523.2). Evaluation includes history, physical examination, and imaging studies, including chest radiograph; CT scans of the neck, chest, abdomen, and pelvis; and positron emission tomography (PET) scan (Fig. 523.3). Laboratory studies should include a complete blood cell count (CBC) to identify abnormalities that might suggest marrow involvement; erythrocyte sedimentation rate (ESR); and measurement of serum ferritin, which is of some prognostic significance and, if abnormal at diagnosis, serves as a baseline to evaluate the effects of treatment. A chest radiograph is particularly important for measuring the size of the mediastinal mass in relation to the maximal diameter of the thorax (see Fig. 523.2). This determines “bulk” disease and becomes prognostically significant. Chest CT more clearly defines the extent of a mediastinal mass if present and identifies hilar nodes and pulmonary parenchymal involvement, which may not be evident on chest radiographs (see Fig. 523.3). Bone marrow aspiration and biopsy should be performed to rule out advanced disease. Bone scans are performed in patients with bone pain and/or elevation of alkaline phosphatase. Fluorodeoxyglucose (FDG) PET imaging has advantages over traditional gallium scanning, with higher resolution, better dosimetry, less intestinal activity, and the potential to quantify disease. PET scans are essential as a prognostic tool in HL, enabling therapy to be reduced in those predicted to have a good outcome and identifying those at risk of relapse.

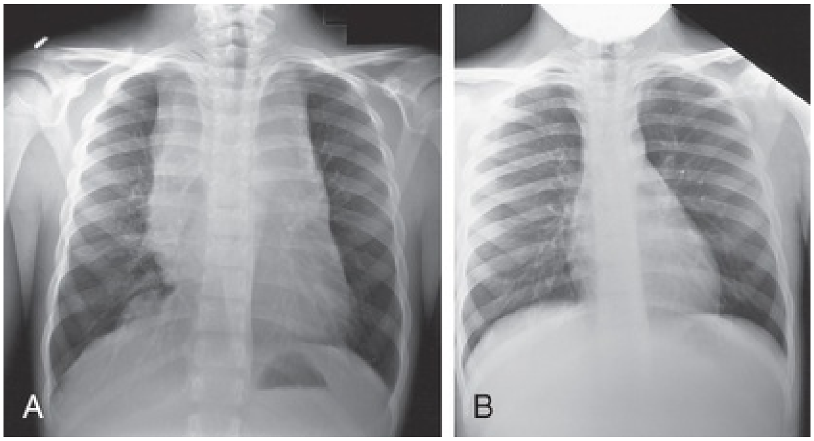

FIG. 523.2 **A,** Anterior mediastinal mass in a patient with Hodgkin disease before therapy. **B,** After 2 mo of chemotherapy, the mediastinal mass has disappeared.

Table 523.2

Lugano Classification for Hodgkin Lymphoma*

STAGE	INVOLVEMENT	EXTRANODAL STATUS
I	One node or group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky	II as above with "bulky" disease	Not applicable
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

* The absence or presence of fever >38°C (100.4°F) for 3 consecutive days, drenching night sweats, or unexplained loss of >10% of body weight in the 6 mo preceding admission are to be denoted in all cases by the suffix letter A or B, respectively.

From Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification, *J Clin Oncol* 32(27):3059–3067, 2014.

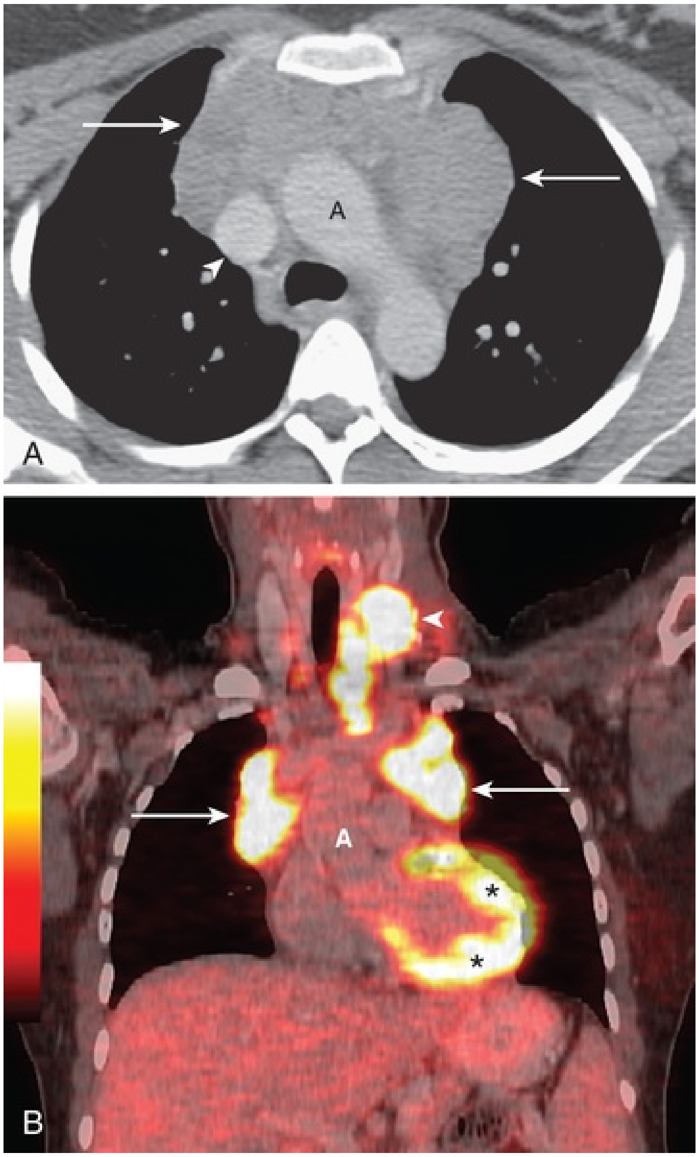

FIG. 523.3 **Hodgkin lymphoma in a young woman. A, CT shows a homogeneous anterior mediastinal mass *(arrows).* The *arrowhead* points to the superior vena cava. A, Ascending aorta. B, PET/CT in the coronal plane. The mass shows marked FDG activity *(arrows).* Note the associated left neck mass *(arrowhead).* The left ventricle activity *(asterisks)* is normal. (From Haaga JR, Boll DT, et al, editors: *CT and MRI of the whole body,* vol 1, Philadelphia, 2017, Elsevier, Fig 38-89, p 1065.)**

The staging classification currently used for HL was initially adopted at the **Ann Arbor Conference** in 1971 and was revised in 1989. The **Lugano classification** was developed in 2014 and incorporates standardized staging and response criteria for FDG-PET–avid lymphomas (see Table 523.2). HL can be subclassified into A or B categories: *A* is used to identify asymptomatic patients, and *B* is used for patients who exhibit any B symptoms. Extralymphatic disease resulting from direct extension of an involved lymph node region is designated by category *E* . A *complete response* in HL is defined as the complete resolution of disease on clinical examination and imaging studies, or at least 70–80% reduction of disease and a change from initial positivity to negativity on PET scanning, reflecting residual fibrosis, which is common.

Treatment

Multiple agents allow different mechanisms of action to have nonoverlapping toxicities so that full doses can be given to each patient. Chemotherapy and radiation therapy are both effective in the treatment of HL. Treatment of HL in pediatric patients is **risk adapted** and involves the use of combined chemotherapy with or without low-dose involved-field radiation therapy based on response. Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of *bulky nodal disease* . The development of effective multiagent combination chemotherapy and immunotherapy was a major milestone in the treatment of HL, resulting in a complete response rate of 70–80% and cure rate of 40–50% in patients with advanced-stage disease. However, this regimen also led to significant acute and long-term toxicity. The desire to reduce side effects and morbidity has stimulated attempts to reduce the intensity of chemotherapy, as well as radiation dose and volume. Combinations of chemotherapy have reduced the risk of secondary cancers. Also, current radiation therapy uses lower amounts of overall radiation in addition to narrowing the radiation treatment field to either involved-field or even involved-node irradiation. The current **Children's Oncology Group** trials are investigating whether radiation therapy can be eliminated altogether in patients who have a very good rapid early response to pre–radiation induction chemotherapy.

Chemotherapy agents used to treat children and adolescents with HL include cyclophosphamide, procarbazine, vincristine or vinblastine, prednisone or dexamethasone, doxorubicin, bleomycin, dacarbazine, etoposide, methotrexate, and cytosine arabinoside. The combination chemotherapy regimens in current use are based on **COPP** (cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone) or **ABVD** (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine), with the addition of prednisone, cyclophosphamide, and etoposide (**ABVE-PC** and **BEACOPP**) or **BAVD** (brentuximab vedotin, doxorubicin [Adriamycin], vincristine, dacarbazine) in various combinations for intermediate- and high-risk groups (Table 523.3).

Risk-adapted protocols are based on both staging criteria and rapidity of response to initial chemotherapy. The aim is to reduce total drug doses and treatment duration and to eliminate radiation therapy, if possible.

Table 523.3

Chemotherapy Regimens for Children, Adolescents, and Young Adults With Hodgkin Lymphoma

CHEMOTHERAPY REGIMEN	CORRESPONDING AGENTS
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine
ABVD-Rituxan	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine, rituximab
ABvVD	Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine
ABVE (DBVE)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide
VAMP	Vincristine, doxorubicin (Adriamycin), methotrexate, prednisone
OPPA ± COPP (females)	Vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
OEPA ± COPP (males)	Vincristine (Oncovin), etoposide, prednisone, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP/ABV	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), bleomycin, vinblastine
BEACOPP (advanced stage)	Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
CHOP	Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), prednisone
ABVE-PC (DBVE-PC)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, cyclophosphamide
ICE ± (Brentuximab)	Ifosfamide, carboplatin, etoposide ± brentuximab
Ifos/Vino ± (Brentuximab)	Ifosfamide, vinorelbine ± brentuximab

Agents such as those that disrupt the NF-κB pathway or monoclonal antibodies (mAbs) that target RS tumor cells, as well as the benign reactive cells that surround them, are currently being investigated. Ongoing clinical trials report encouraging results with anti-CD20 antibody (**rituximab**), particularly in nodular lymphocyte-predominant HL, for which trials in relapsed disease have shown an overall response rate of 94%. In addition, anti-CD30 agents are being used that are targeted to the RS cells themselves, where CD30 is abundantly expressed. **Brentuximab vedotin** is an antibody–drug conjugate approved by the U.S. Food and Drug Administration (FDA) to treat HL. It combines the chimeric anti-CD30 antibody brentuximab linked to the antimitotic agent monomethyl auristatin E. This agent shows impressive efficacy as single-agent therapy in refractory HL and is currently being tested as part of upfront therapy combined with chemotherapy in patients with newly diagnosed disease. Both brentuximab and rituximab have been combined with combination chemotherapy either alone or together in newly diagnosed patients, allowing for the elimination of toxic alkylator agents, topoisomerase inhibitors, bleomycin, and radiation in these patients. **EBV-specific cytotoxic T lymphocytes (CTLs)** can also be generated from allogeneic donors for patients with advanced HL (Fig. 523.4). In clinical trials, these cells show promising results, with enhanced antiviral activity and stabilization of disease. EBV-CTLs have been developed and are currently being investigated. These enhanced EBV-CTLs are designed to be LMP 1 and 2 specific and can be generated from second-party (in the case of bone marrow transplant recipients) or even third-party donors for patients with refractory disease. These approaches represent an exciting direction in adoptive cellular tumor immunology, and it remains to be determined whether CTLs will have improved cytotoxicity that can overcome inhibitory signals.

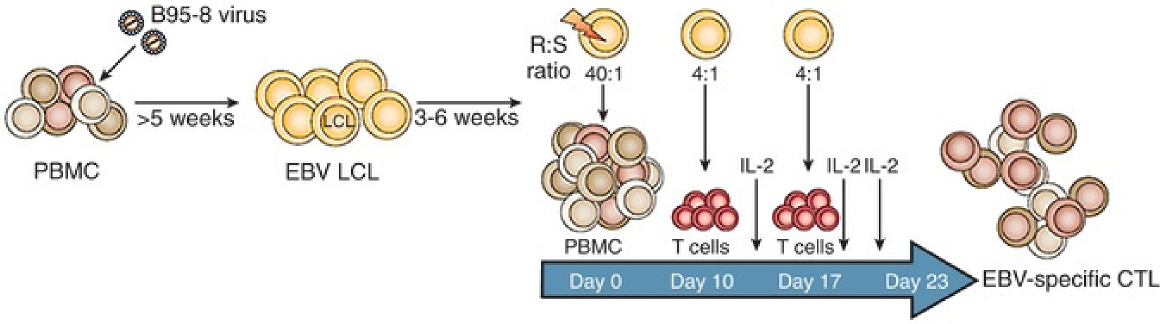

FIG. 523.4 Epstein-Barr virus (EBV)–specific cytotoxic T lymphocyte (CTL) production. EBV-transformed B-cell lymphoblastoid cell lines (LCLs) are prepared from the CTL donor by infection of peripheral blood mononuclear cells (PBMCs) with a clinical-grade laboratory strain of EBV (B95-8) in the presence of cyclosporine. Once the LCL is established (about 6 wk), it is irradiated and used to stimulate PBMCs from the same donor at a 40 : 1 PBMC/LCL ratio. At 9-12 days later and weekly thereafter, the T cells are restimulated with the LCL at a 4 : 1 ratio. Interleukin-2 is added 3 days after the 2nd stimulation and twice weekly thereafter. The CTLs should kill autologous LCLs but not autologous phytohemagglutinin blasts. Their specificity is donor dependent, and the CTLs may have specificity for any of the 10 latency-associated antigens and/or for early lytic cycle proteins expressed by a small fraction of the LCLs. These LCLs are grown in acyclovir to prevent the production of infectious virus by blocking the viral thymidine kinase. (Adapted from Bollard CM, Rooney CM, Heslop HE: T-cell therapy in the treatment of post-transplant lymphoproliferative disease, *Nat Rev Clin Oncol* 9:510–519, 2012, Fig 2.)

Relapse

Most relapses occur within the 1st 3 yr after diagnosis, but relapses as late as 10 yr have been reported. Relapse cannot be predicted accurately with this disease. Poor prognostic features include tumor bulk, stage at diagnosis, extralymphatic disease, and presence of B symptoms. Patients who achieve an initial chemosensitive response but relapse or progress before 12 mo from diagnosis are candidates for myeloablative chemotherapy and autologous stem cell transplantation, with or without radiation therapy. Retrospective studies show a significant decrease in relapse in patients with HL following allogeneic vs autologous stem cell transplant (18% vs 41%). Although in earlier studies there was no improvement in overall survival because of a high transplantation-related mortality, reduced-intensity conditioning or nonmyeloablative regimens are successful at reducing regimen-related morbidity and mortality associated with myeloablative allogeneic stem cell transplantation while still achieving a strong graft-versus-HL effect. For more difficult-to-treat refractory cases, radioimmunotherapy agents such as Zevalin and Bexxar are being trialed, often in combination with stem cell transplantation strategies. Both are monoclonal anti-CD20 antibodies to which a radioactive isotope is directly linked. Clinical trials show each to be more effective than rituximab in NHL patients, and there is some interest in studying their use in the CD20 subpopulation of HL patients. Tumors can evade the host immune system by exploiting immune checkpoint pathways, such as the CTL-associated protein 4 (CTLA-4) and **programmed-death 1 (PD-1)** pathways. PD-1 is a negative co-stimulatory receptor with increased expression reported on T cells. PD-1 is critical for suppression of T-cell activation, with binding of PD-L1 resulting in “T-cell exhaustion.” Blockade of this interaction renders previously anergic T cells responsive to antigen. Evidence has shown that antitumor immune responses can be improved by blocking immune checkpoint inhibitors in the tumor microenvironment. Phase I trials of the PD-1 blocking mAbs **nivolumab** and **pembrolizumab** have shown significant promise in refractory patients. Phase II clinical trials suggest that combining immunotherapy such as rituximab or brentuximab with PD-1 checkpoint blockade will be highly effective against relapsed lymphomas and well tolerated, without treatment-related adverse events. With the success seen in relapsed or refractory patients, PD-1 blockade, alone or in combination, likely will have a role in frontline therapy as well, and studies are currently in development.

Prognosis

With the use of current therapeutic regimens, patients with favorable prognostic factors and early-stage disease have an event-free survival (**EFS**) of 85–90% and an overall survival (**OS**) at 5 yr of >95%. Patients with advanced-stage disease have slightly lower EFS (80–85%) and OS (90%), respectively, although OS has approached 100% with dose-intense chemotherapy (Table 523.4). Prognosis after relapse depends on the time from completion of treatment to recurrence, site of relapse (nodal vs extranodal), and presence of B symptoms at relapse. Patients whose disease relapses >12 mo after chemotherapy alone or combined-modality therapy have the best prognosis, and their relapses usually respond to additional standard therapy, resulting in a long-term survival of 60–70%. A myeloablative autologous stem cell transplantation in patients with refractory disease or relapse within 12 mo of therapy results in a long-term survival rate of only 40–50%. Allogeneic stem cell transplantation has shown promise in patients with poor risk features at relapse/progression.

Table 523.4

Treatment Regimens and Outcome by Disease Staging

		LOCALIZED/LOW STAGE	**INTERMEDIATE**	**ADVANCED**
Hodgkin lymphoma	Treatment	*POG study 9426/GPOH-HD 95:* ABVD-type therapy ± IFRT (risk adapted based on early response to chemotherapy)	*Stanford/DAL-HD-90:* COPP-based or dose-intense multiagent chemotherapy + low-dose RT *POG 9426/CCG 5942:* ABVD-type therapy ± IFRT (risk adapted)	*POG 8725/DAL-HD-90:* Dose-intense multiagent chemotherapy + low-dose RT *HD9/HD12/CCG 59704:* Dose-intense BEACOPP ± IFRT
	Prognosis	5 yr EFS: 85-90% 5 yr OS: 95%	*Stanford/DAL-HD-90:* 5 yr EFS: 89-92% *POG 9426/CCG 5942:* 5 yr EFS: 84% 5 yr OS: 91%	*POG 8725:* 5-yr EFS: 72–89% (age based) *DAL-HD-90:* 5 yr EFS: 86% 5 yr OS: 85-90% *HD9/HD12/CCG 59704:* 5 yr EFS/OS: 88-93/~100%
Burkitt	Treatment	*FAB/LMB 96*	*FAB/LMB 96 Group B* therapy	*FAB/LMB 96:*

lymphoma and diffuse large B-cell lymphoma		*Group A therapy:* Complete surgical resection followed by 2 cycles of chemotherapy	with reduced cyclophosphamide and no maintenance therapy *COG ANHL01P1* : FAB/LMB Group B therapy + rituximab	standard-intensity Group C therapy: Reduction, induction, intensification, and maintenance therapy *COG ANHL01P1* : FAB/LMB Group C therapy + rituximab
	Prognosis	4 yr EFS: 98% (CI_{95} 94-99.5%) 4 yr OS: 99% (CI_{95} 96-99.9%)	*FAB/LMB96:* 4 yr EFS: 92% (CI_{95} 90-94%) 4 yr OS: 95% (CI_{95} 93-96%) *PMB DLBCL has worse prognosis (EFS/OS: 66/73%) *COG ANHL01P1:* 3 yr EFS 93% (CI_{95} 79-98%) 3 yr OS 95% (CI_{95} 83-99%)	*FAB/LMB96:* 4 yr EFS: BM+/CNS−: 91% ±3% BM−/CNS+: 85% ±6% BM+/CNS+: 66% ±7% *COG ANHL01P1:* 3 yr EFS/OS: BM+ or CNS+: 90% (CI_{95} 75-96%) CNS+: 93% (CI_{95} 61-99%)
Lymphoblastic lymphoma	Treatment	*NHL-BFM86/90/95:* *COG A5971:* ALL-type therapy × 2 yr without prophylactic cranial RT	No intermediate group; disease classified as localized (stages I/II) or advanced (stages III/IV)	*NHL-BFM86/90/95:* ALL-type therapy × 2 yr ± px CRT *CCG 5941:* Intensive chemotherapy × 1 yr + cranial RT if CNS + at diagnosis
	Prognosis	*COG A5971:* 5 yr EFS: 90 (CI_{95} 78-96%) 5 yr OS: 96 (CI_{95} 84-99%)	No intermediate group; see above	*NHL-BFM95:* 5 yr EFS: 90% ±3% (III), 95 ±5% (IV) *CCG 5941:* 5 yr EFS/OS: 78% ±5%/85% ±4%
Anaplastic large cell lymphoma	Treatment	*EICHNL ALCL 99:* Short intensive chemotherapy + HD MTX Completely resected stage I disease may be	No intermediate group; disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)	*ALCL 99, CCG 5941:* Short intensive chemotherapy + HD MTX *COG ANHL0131* : APO (doxorubicin,

		treated with surgery alone		prednisone, vincristine) ± vinblastine
	Prognosis	*EICHNL database:* 5 yr PFS: 89% (CI_{95} 82-96%) 5 yr OS: 94% (CI_{95} 89-99%)	No intermediate group; see above	*ALCL 99:* 2 yr EFS: 71% (CI_{95} 75-77%) 2 yr OS: 94% (CI_{95} 89-95%) *COG 5941:* 5 yr EFS 68% (CI_{95} 57-78%) 5 yr OS: 80% (CI_{95} 69-87%) *COH ANHL0131:* 2 yr EFS 79% (CI_{95} 71-88%) 2 yr OS 89% (CI_{95} 83-95%)

ABVD, Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; BM, bone marrow (involvement); CCG, Children's Cancer Group; CI_{95} , 95% confidence interval; CNS, central nervous system (involvement); COG, Children's Oncology Group; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; CRT, chemoradiotherapy; EFS, event-free survival; EICHNL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB, French-American-British; HD MTX, high-dose methotrexate; IFRT, involved field radiation therapy; LMB, Lymphome Malins de Burkit; MTX, methotrexate; NHL-BFM, non-Hodgkin lymphoma Berlin-Frankfurt-Munster; OS, overall survival; PFS, progression-free survival; PMB DLBCL, primary mediastinal B-cell diffuse large B-cell lymphoma; POG, Pediatric Oncology Group; px, prophylactic; RT, radiation therapy.

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523.2

Non-Hodgkin Lymphoma

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Keywords

anaplastic large cell lymphoma
BL
Burkitt lymphoma
diffuse large B-cell lymphoma
DLBCL
Immunotherapy
LBL
lymphoblastic lymphoma
mature B-cell lymphoma
NHL
tumor lysis syndrome

Non-Hodgkin lymphoma (**NHL**) accounts for approximately 60% of lymphomas in children and is the 2nd most common malignancy between ages 15 and 35 yr. The annual incidence of pediatric NHL in the United States is 750-800 cases/yr. In contrast to adult NHL, which is predominantly indolent, pediatric NHL is usually *high grade* . Although >70% of patients present with advanced disease, the prognosis has improved dramatically, with survival rates of 90–95% for localized disease and 80–95% for advanced disease.

Epidemiology

Although most children and adolescents with NHL present with de novo disease, a small number of patients have NHL secondary to specific etiologies, including inherited or acquired immunodeficiencies (e.g., severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome), virus-associated malignancy (e.g., HIV, EBV), and as part of genetic syndromes (e.g., ataxia-telangiectasia, Bloom syndrome). However, most children in North America and Europe in whom NHL develops have no obvious genetic or environmental etiology.

Pathogenesis

Three most prevalent subtypes of childhood and adolescent NHL with different treatment approaches are **lymphoblastic lymphoma (LBL), mature B-cell lymphoma** , and **anaplastic large cell lymphoma** (**ALCL** ; Figs. 523.5 and 523.6). LBL arises from precursor T lymphocytes and less often from precursor B lymphocytes, with biology and treatment approaches similar to acute lymphoblastic leukemia. Mature B-cell lymphomas comprise 2 main pathologies, **Burkitt lymphoma (BL)** and **diffuse large B-cell lymphoma (DLBCL)** . DLBCL is further divided into several subtypes: the *germinal center B-cell–like,* which carries a favorable prognosis and accounts for the vast majority of pediatric cases of DLBCL, and the subtypes with poorer prognosis, including *activated B-cell–like* and *primary mediastinal B-cell* subtypes. Interestingly, primary mediastinal B-cell subtype of DLBCL shares molecular signature more akin to Hodgkin lymphoma then germinal center–derived DLBCL. Most cases of ALCL are of mature T-cell origin, with a smaller percentage of null-cell and B-cell origin. Cellular surface markers can aid in differentiating NHL subtypes and also present opportunities for specific antibody targeted treatments. BL and DLBCL express the mature B-cell antigens CD20 (the target of rituximab), and CD22, while ALCL expresses the CD30 antigen (the target of the antibody conjugate brentuximab vedotin). Some pathologic subtypes have specific cytogenetic aberrations. Children with BL frequently have a driver genetic change involving the c-myc gene juxtaposed to an immunoglobulin chain in the form of translocations: t(8;14) (90%) or, less often, a t(2;8) or t(8;22) translocation (10%). Children with BL who have additional chromosomal aberrations such as 13q deletion or complex karyotype have a poorer prognosis. Unlike adult DLBCL, a higher proportion of pediatric DLBCL may also have c-myc dysregulation with t(8;14) translocation (30%) and often have a complex (80%) and aneuploid (80%) karyotype. Patients with ALCL usually have a driver t(2;5) translocation (90%), which results in the formation of a fusion gene encoding the constitutively active nucleophosmin–anaplastic lymphoma kinase (ALK) tyrosine kinase and can be targeted by the oral agent, crizotinib. T-cell LBL harbors many of the same cytogenetic abnormalities as T-cell acute lymphoblastic leukemia (T-ALL), including rearrangements with breakpoints at 14q11.2 involving the T-cell receptor and multiple other rearranged genes. Recent work by the Berlin-Frankfurt-Münster group has demonstrated that loss of heterozygosity at chromosome 6q defines a poor-risk subgroup of T-lymphoblastic lymphoma patients.

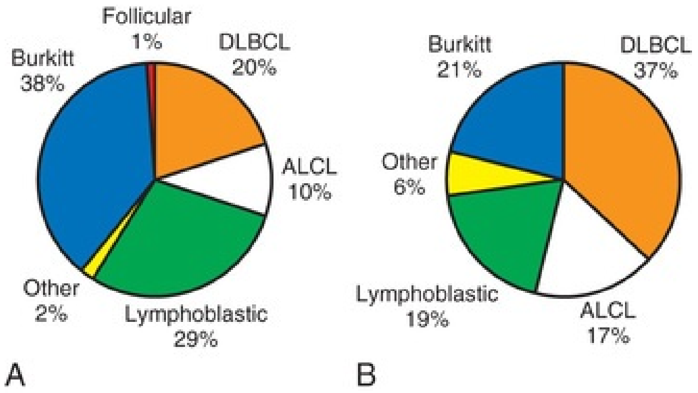

FIG. 523.5 **Incidence of non-Hodgkin lymphoma subtypes. A, In 0-14 yr old children. B, In 15-19 yr old adolescents. *ALCL* , Anaplastic large cell lymphoma; *DLBCL* , diffuse large B-cell lymphoma. (Adapted from Hochberg J, Waxman IM, Kelly KM, et al: Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma: state of the science, *Br J Haematol* 144:24–40, 2008.)**

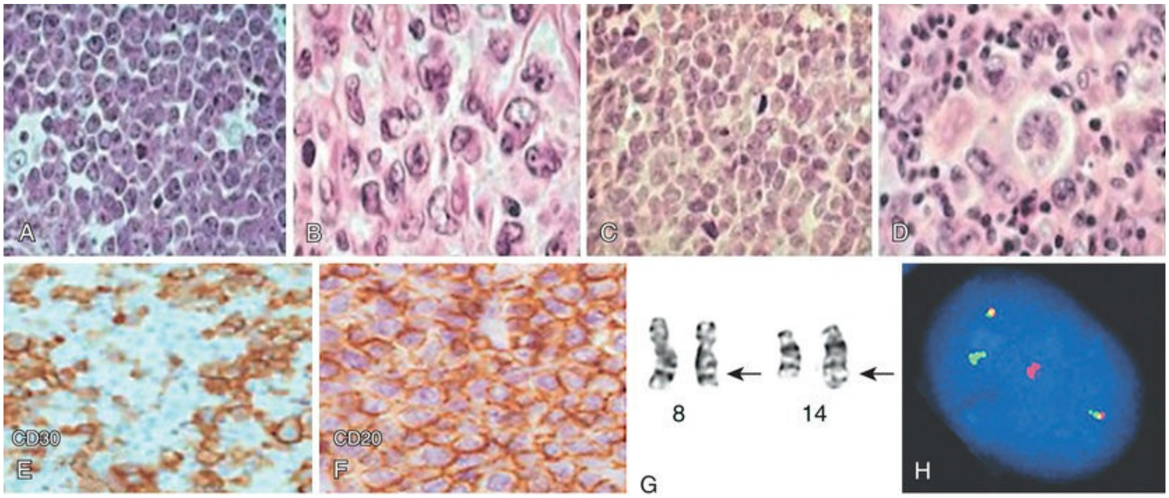

FIG. 523.6 Histologic subtypes of childhood and adolescent non-Hodgkin lymphoma. A-D, H&E stains showing morphology of Burkitt lymphoma (A, high power), diffuse large B-cell lymphoma (B, high power), precursor T-lymphoblastic lymphoma (C, high power), and anaplastic large cell lymphoma (D, high power). E and F, Characteristic surface markers for ALCL (CD30; E) and BL (CD20; F). G and H, Cytogenetic analysis of BL demonstrating t(8;14). G, Karyotype showing the conventional t(8;14)(q24;q32). H, Interphase fluorescence in situ hybridization showing a balanced translocation involving MYC and immunoglobulin (Ig) H loci. The chromosome 8 centromere is labeled with spectrum aqua, MYC probe is labeled with spectrum orange, and IgH is labeled with spectrum green. Two fusion signals are seen, as well as 1 red and 1 green, representing the normal chromosomes. (A-D, From Cairo MS, Raetz E, Lim MS, et al: Childhood and adolescent non-Hodgkin lymphoma: new insights in biology and critical challenges for the future, *Pediatr Blood Cancer* 45:753–769, 2005; E-H from Giulino-Roth, Cesarman E: Molecular biology of Burkitt lymphoma. In Robertson ES, editor, *Burkitt's lymphoma.* New York, 2012, Springer.)

Genomic studies have offered insights into NHL pathogenesis as well as elucidated potential targets for novel therapies. Gene expression profiling of T-LBL and T-ALL has implicated the activation of oncogenic transcription factors as a result of aberrant T-cell receptor gene rearrangement. One of the most frequently activated signaling pathways is NOTCH1, which may be amenable to therapeutic targeting with γ-secretase inhibitors. In BL and DLBCL, extensive genomic work has identified unique gene expression signatures that differentiate these 2 mature B-cell neoplasms. In addition, next-generation sequencing of BL has identified genetic lesions in *TCF3* and *ID3* , which lead to activation of the AKT/PI3 kinase pathway. Other genetic lesions that have been described in BL include loss of function of the chromatin remodeling genes *ARID1A* and *SMARCA4*. Importantly, many of these alterations are potentially targetable by agents that are in development.

Clinical Manifestations

The clinical manifestations of childhood and adolescent NHL depend primarily on pathologic subtype and sites of involvement. The current revised staging system used for NHL is the **International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS)** , which reflects our increasing ability to diagnose lower levels of organ involvement with disease. For instance, the older staging system (St. Jude/Murphy classification) did not account for molecular or flow cytometry involvement of bone marrow, which is now reflected in the new system (Tables 523.5A and 523.5B). Patients are further classified based on risk categories according to pediatric international cooperative group trials. Approximately 70% of patients with NHL present with advanced disease (stage III or IV), including extranodal disease with bone marrow and central nervous system (CNS) involvement. B symptoms of fever, weight loss, and night sweats can be seen, particularly in ALCL, but unlike HL, are not prognostic.

Table 523.5A

International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS)[*]

STAGE I
A single tumor with the exclusion of the mediastinum and abdomen. (N: nodal; EN: extranodal; bone (B) or skin (S): EN-B, EN-S)
STAGE II
A single extranodal tumor with regional node involvement. Two or more nodal areas on the same side of the diaphragm. A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable. (If malignant ascites or extension of the tumor to adjacent organs, it should be regarded as stage III.)
STAGE III
Two or more extranodal tumor(s) (including bone or skin: EN-B, EN-S) above and/or below the diaphragm. Two or more nodal areas above and below the diaphragm. Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic). Intraabdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection. (Except a primary gastrointestinal tract tumor [usually in the ileocecal region], with or without involvement of associated mesenteric nodes, that is completely resectable.) Any paraspinal or epidural tumor, whether or not other sites are involved. Single bone lesion with concomitant involvement of extranodal and/or nonregional nodal sites.
STAGE IV
Any of the above findings with initial involvement of the central nervous system (stage IV CNS), bone marrow (stage IV BM), or both (stage IV combined) based on conventional methods, see Table 523.5B . For each stage, type of examination and degree of BM and CNS involvement should be specified, using the abbreviations listed in Table 523.5B to identify involvement.

[*] Based on the classification proposed by Murphy (Murphy SB: Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults, *Semin Oncol* 7:332–339, 1980.)

From Rosolen A, Perkins SL, Pinkerton CR, et al: Revised International Pediatric Non-Hodgkin Lymphoma Staging System, *J Clin Oncol* 33(18):2112–2118, 2015.

Table 523.5B

Additional IPNHLSS Information*

BONE MARROW (BM) INVOLVEMENT
Stage IV disease, caused by BM involvement, is currently defined by morphologic evidence of ≥5% blasts or lymphoma cells by bone marrow aspiration. This applies to any histologic subtype and will be maintained in the IPNHLSS. However, for each stage, type and degree of BM involvement (by bone marrow aspiration) should be specified, using the abbreviations below to identify involvement: BMm = BM positive by morphology (specify % lymphoma cells). BMi = BM positive by immunophenotypic methods (immunohistochemical/flow cytometry analysis) (specify % lymphoma cells). BMc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells). BMmol = BM positive by molecular techniques (PCR based) (specify level of involvement). Same approach should be used for peripheral blood (PB) involvement (i.e., PBm, PBi, PBc, PBmol). *Note:* Definition of BM involvement should be obtained from analysis of bilateral BM aspirates and BM-biopsy.
CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT
CNS is considered involved in case of: 1. Any CNS tumor mass (identified by imaging techniques; i.e., CT, MRI). 2. In case of cranial nerve palsy that cannot be explained by extradural lesions. 3. In case of blasts morphologically identified in the cerebrospinal fluid (CSF). Condition that defines CNS positivity should be specified: CNS positive/mass; CNS positive/palsy; CNS positive/blasts. CSF status: CSF positivity is based on morphologic evidence of lymphoma cells. CSF should be considered positive when any number of blasts is detected. CSF unknown (e.g., not performed, technical difficulties). Similar to BM, type of CSF involvement should be described whenever possible: CSFm = CSF positive by morphology (specify the number of blasts/µL). CSFi = CSF positive by immunophenotype methods (immunohistochemical/flow cytometry analysis) (specify % lymphoma cells). CSFc = CSF positive by cytogenetic/FISH analysis (specify % lymphoma cells). CSFmol = CSF positive by molecular techniques (PCR based) (specify level of involvement).

* Until sufficient data are available, positron emission tomography (PET) should be used with caution for staging, and PET results should be compared and discussed in light of other, more consolidated imaging approaches.

FISH, Fluorescence in situ hybridization; PCR, polymerase chain reaction.

From Rosolen A, Perkins SL, Pinkerton CR, et al: Revised International Pediatric Non-Hodgkin Lymphoma Staging System, *J Clin Oncol* 33(18):2112–2118, 2015.

The primary site of tumor involvement and the pattern of metastasis vary by pathologic subtype. LBL typically manifests as a symptomatic mediastinal mass and also has a predilection for spreading to the bone marrow, CNS, and testes in males. BL commonly manifests as a diffuse leukemia presentation or massive abdominal (*sporadic* type) or head and neck (*endemic* type) tumor and can metastasize to the bone marrow or CNS. DLBCL usually manifests as either an abdominal or a mediastinal primary tumor and, rarely, disseminates to the bone marrow or CNS. ALCL manifests either as a primary cutaneous manifestation (10%) or as systemic disease (90%) with dissemination to liver, spleen, lung, or mediastinum. Bone marrow or CNS disease is rare in ALCL. Site-specific manifestations of NHL include painless, rapid lymph node enlargement; cough or dyspnea with thoracic involvement; superior mediastinal syndrome; ascites, increased abdominal girth or intestinal obstruction with an abdominal mass; nasal congestion, earache, hearing loss, or tonsil enlargement with Waldeyer ring involvement; and localized bone pain.

NHL can present as a life-threatening **oncologic emergency** . These manifestations are important to recognize because these patients require intensive supportive care and, in some cases, alternative treatment. **Superior mediastinal syndrome** can occur as a consequence of a large mediastinal mass causing obstruction of blood flow or respiratory airways. Spinal cord tumors can cause cord compression and acute paraplegias requiring emergent radiation therapy. **Tumor lysis syndrome (TLS)** can occur from rapid cell turnover, which is especially common in BL. TLS can result in severe metabolic abnormalities, including hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. This can rapidly lead to renal insufficiency/failure, as well as cardiac abnormalities, if not aggressively treated.

Laboratory Findings

Recommended laboratory and radiologic testing includes CBC; measurements of electrolytes, lactate dehydrogenase, uric acid, calcium, phosphorus, blood urea nitrogen, creatinine, bilirubin, alanine aminotransferase, and aspartate aminotransferase; bone marrow aspiration and biopsy; lumbar puncture with cerebrospinal fluid cytology, cell count, and protein; chest radiographs; and abdominal ultrasound for initial diagnosis. Staging relies on more detailed anatomic imaging, with CT for neck, chest, abdomen and pelvic imaging and MRI the preferred modality for suspected CNS disease of brain and spine (Fig. 523.7). PET scan, usually with radioactive fluorodeoxyglucose for functional imaging, is more sensitive and has replaced gallium imaging. It is also an excellent modality for judging treatment response to therapy. Tumor tissue (i.e., biopsy, bone marrow, cerebrospinal fluid, pleurocentesis/paracentesis fluid) should be tested by flow cytometry for immunophenotypic origin (T, B, or null) and cytogenetics (karyotype). Additional tests might include fluorescent in situ hybridization (FISH) or quantitative reverse-transcription polymerase chain reaction (RT-PCR) for specific genetic translocations, T- and B-cell gene rearrangement studies, and molecular profiling by oligonucleotide microarray or next-generation sequencing (NGS).

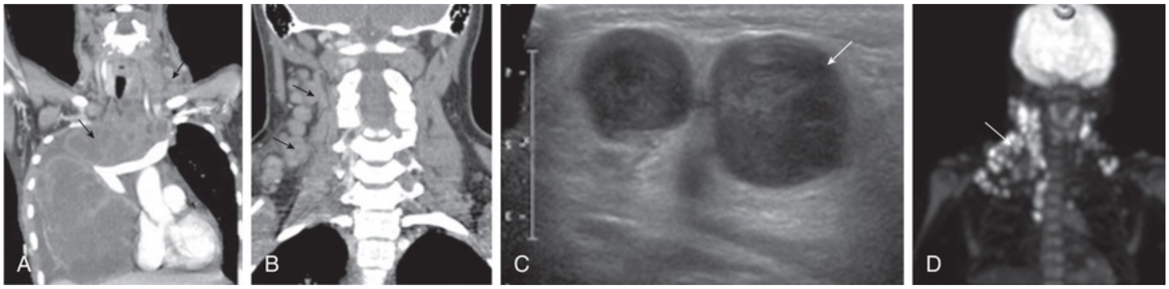

FIG. 523.7 **Lymphoma. Coronal postcontrast CT images demonstrate extensive cervical (A) and mediastinal (B) lymphadenopathy *(arrows)* . C, Sonographic image demonstrates 2 enlarged lymph nodes with abnormal internal morphology *(arrow)* . D, PET scan demonstrates metabolically active conglomeration of right-sided cervical lymph nodes *(arrow).* (From Haaga JR, Boll DT, et al, editors: *CT and MRI of the whole body,* vol 1, Philadelphia, 2017, Elsevier, Fig 26-15, p 768.)**

Treatment

The primary modality of treatment for childhood and adolescent NHL is *multiagent systemic chemotherapy and/or immunotherapy with intrathecal chemotherapy* (see Table 523.4). An international pediatric NHL response classification has been developed (IPNHLRC) (Tables 523.6A and 523.6B). Surgery is used mainly for diagnosis. Radiation therapy is used only in special circumstances, such as CNS involvement in LBL or the presence of acute superior mediastinal syndrome or paraplegias. Newly diagnosed patients, especially those with BL or LBL, are at high risk for TLS. These patients require vigorous hydration, frequent electrolyte monitoring, and either an xanthine oxidase inhibitor (e.g., allopurinol, 10 mg/kg/day orally in 3 divided doses daily) or a recombinant urate oxidase (e.g., rasburicase, 0.2 mg/kg/day intravenously once daily for up to 5 days). Recombinant urate oxidase is preferred in patients with a high risk of tumor lysis but is *contraindicated* in patients with a history of G6PD deficiency.

Table 523.6A

International Pediatric Non-Hodgkin Lymphoma Response Criteria (IPNHLRC)

Complete Response (CR): disappearance of all disease (3 designations)

1. Complete (CR):
    a. CT or MRI reveals no residual disease or new lesions.
    b. Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques, as described in "supporting data," Table 523.6B).
    c. Bone marrow (BM) and cerebrospinal fluid (CSF) morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 523.6B).
2. Complete Response, biopsy negative (CRb):
    a. Residual mass has no morphologic evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques, as described in Table 523.6B) with no new lesions by imaging examination.
    b. BM and CSF morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 523.6B).
    c. No new and/or progressive disease elsewhere.
3. Complete Response, unconfirmed (CRu):
    a. Residual mass is negative by FDG-PET; no new lesions by imaging examination.
    b. BM and CSF morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 523.6B).
    c. No new and/or progressive disease elsewhere.

Partial Response (PR): 50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) on CT or MRI. FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared to baseline). No new and/or PD. Morphologic evidence of disease may be present in the BM or CSF if present at diagnosis (detection of disease with more sensitive techniques, as described in Table 523.6B); however, there should be a 50% reduction in the percentage of lymphoma cells.

Minor Response (MR): Decrease in SPD is greater than 25% but less than 50% on CT or MRI. No new and/or PD. Morphologic evidence of disease may be present in the BM or CSF if present at diagnosis (detection of disease with more sensitive techniques, as described in Table 523.6B); however, there should be a 25–50% reduction in the percentage of lymphoma cells.

No Response (NR): For those who do not meet CR, PR, MR or PD criteria.

Progressive Disease (PD): For those with greater than 25% increase in the SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with an increase in lesional uptake from baseline, or the development of new morphologic evidence of disease in the BM or CSF.

FDG-PET, Fluorodeoxyglucose positron emission tomography.

From Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria, J Clin Oncol 33(18):2106–2111, 2015.

Table 523.6B

Supporting IPNHLRC Data

BONE MARROW (BM) INVOLVEMENT
BM involvement is currently defined by morphologic evidence of lymphoma cells. This applies to any histologic subtypes. Type and degree of BM involvement should be specified, using the abbreviations below: BMm = BM positive by morphology (specify % lymphoma cells).

BMi = BM positive by immunophenotypic methods (histochemical/flow cytometry analysis) (specify % lymphoma cells). BMc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells). BMmol= BM positive by molecular techniques. Same approach should be used for peripheral blood (PB) involvement (i.e., PBm, PBi, PBc, PBmol).
CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT
Cerebrospinal fluid (CSF) status: CSF positivity is based on morphologic evidence of lymphoma cells. CSF should be considered positive when any number of blasts is detected. CSF unknown (e.g., not performed, technical difficulties). Similar to BM, type of CSF involvement should be described whenever possible: CSFm = CSF positive by morphology (specify the number of blasts/μL). CSFi = CSF positive by immunophenotypic methods (histochemical/flow cytometry analysis) (specify % lymphoma cells). CSFc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells). CSFmol = CSF positive by molecular techniques.
RESIDUAL MASS (RM)
RMm = Tumor detected by standard morphologic evaluation. RMi = Tumor detected by immunophenotypic methods (immunohistochemical or flow cytometry analysis). RMc = Tumor detected by cytogenetic/FISH analysis. RMmol = Tumor detected by molecular techniques.

FISH, Fluorescence in situ hybridization.

From Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria, J Clin Oncol 33(18):2106–2111, 2015.

Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma

Pediatric BL and DLBCL (with the exception of mediastinal primary B cell) are treated with the same mature B-cell NHL chemoimmunotherapy regimens based on stage and risk stratification. For patients with localized disease, multiagent chemotherapy is given over 6 wk, and the prognosis is excellent. In the international FAB/LMB 96 (French-American-British Lymphoma, mature B cell) trial, patients with localized, completely resected disease received 2 cycles of COPAD (cyclophosphamide, vincristine, prednisone, and doxorubicin) resulting in a 4 yr OS of 99%. Advanced disease is usually treated with a 4-6 mo regimen of multiagent chemoimmunotherapy, such as FAB/LMB 96 protocol therapy or NHL-BFM (Berlin-Frankfurt-Munich) 95 protocol therapy with the addition of rituximab, with an OS of 79–90%. A subset of patients who likely require a different treatment approach has primary **mediastinal B-cell lymphoma (PMBCL)** . PMBCL is a histologic subtype that represents 2% of mature B-NHLs. Pediatric patients with PMBCL had an inferior outcome when treated with standard mature B-NHL protocols (EFS of only 66%). Alternative treatment strategies, including prolonged infusional chemotherapy, rituximab, and chimeric antigen receptor T cells expressing anti-CD19 mAbs, may benefit this group (see Chapter 521).

Rituximab is a mAb directed at CD20 that, when combined with standard chemotherapy, improves outcomes in adult patients with aggressive B-NHL (usually DLBCL). A window study of rituximab given to pediatric patients with newly diagnosed BL and DLBCL demonstrated its activity as a single agent with a response rate of 41%. Additionally, a Children's Oncology Group study examined the safety and pharmacokinetics of rituximab when added to standard chemotherapy for intermediate-risk patients. Rituximab was found to be safe, and survival in this cohort was the best reported to date (3 yr OS of 95%). In a similar cohort of CNS-positive patients, the addition of rituximab to the chemotherapy backbone resulted in a 93% EFS. An international randomized study of rituximab added to standard multiagent chemotherapy in advanced-stage pediatric patients was stopped early after the rituximab-containing arms had a clear improved EFS and is thus currently the standard of care in children and adolescents with advanced mature B-cell lymphoma.

Lymphoblastic Lymphoma

Localized or advanced LBL requires 12-24 mo of therapy, including chemotherapy, intrathecal therapy, and cranial radiation in CNS-positive lymphomas. The best results in advanced LBL have been obtained using therapeutic approaches mirroring those for childhood acute leukemia, including induction, consolidation, interim maintenance, and reinduction (advanced disease only) phases, as well as a year-long maintenance phase with 6-mercaptopurine and methotrexate. For patients with relapsed disease, the outcome is poor (OS of 10%), and novel treatments are needed. *Nelarabine*, a purine analog with significant T-lymphocyte toxicity, has completed testing in primary therapy for T-LBL, with results pending. In recent randomized testing, the oral proteasome inhibitor *bortezomib* was added to the prolonged chemotherapy in advanced T-LBL.

Anaplastic Large Cell Lymphoma

For patients who present with localized disease, surgical resection alone is sufficient. The majority of patients, however, have advanced disease, which requires multiagent chemotherapy. Various chemotherapy regimens have been studied, with similar outcomes and survival of 70–79%. CNS prophylaxis consists of intrathecal chemotherapy, although this may be omitted with the substitution of high-dose methotrexate.

Two novel targeted agents have shown substantial promise in early-phase trials in ALCL. The CD30 antibody–drug conjugate **brentuximab vedotin** and the ALK inhibitor **crizotinib** both have impressive activity and minimal toxicity in patients with relapsed ALCL. Given the high efficacy and low toxicity profile, it may be possible to use these agents in newly diagnosed patients to eliminate the reliance on, and toxicity of, conventional chemotherapy. The Children's Oncology Group is currently investigating the use of each of these agents in combination with chemotherapy in children with newly diagnosed advanced ALCL.

Relapsed Non-Hodgkin Lymphoma

Patients with NHL in whom progressive or relapsed disease develops require reinduction chemotherapy and may require either allogeneic or autologous stem cell transplantation (SCT). A notable exception is ALCL, where low-dose approaches such as prolonged vinblastine have been efficacious for some patients. The specific reinduction regimen or transplantation type depends on the pathologic subtype, previous therapy, site of reoccurrence, and stem cell donor availability. A number of novel reinduction approaches are being investigated, including a type II CD20 antibody, *obinutuzumab* , alone and in combination with chemotherapy, *ibrutinib,* a BTK inhibitor alone and in combination with chemotherapy, and *idelalisib,* a P13K delta inhibitor alone and in combination with chemotherapy. Although there are no randomized trials examining autologous vs allogeneic SCT for relapsed NHL, data from retrospective studies suggest that outcomes are similar, with the exception of LBL and ALCL, for which allogeneic SCT is superior, perhaps because of a graft-versus-lymphoma effect.

Because relapsed NHL can be difficult to treat, efforts have been made to identify those patients at higher risk of relapse to tailor the initial therapy. The measurement of minimal residual disease may serve as a prognostic marker and aid in risk stratification. Minimal residual disease is prognostic in ALCL and LBL. In ALCL, there is also evidence that a humoral response to the ALK kinase can be used to predict outcome, with a superior outcome in patients who mount an antibody titer to ALK. Minimal residual disease (MRD) measurement in intermediate-risk B-NHL is feasible and is currently being evaluated in an international trial.

Complications

Patients receiving multiagent chemotherapy for advanced disease are at acute risk for serious mucositis, infections, cytopenias that require red blood cell and platelet blood product transfusions, electrolyte imbalances, and poor nutrition. Long-term complications include the risk of growth retardation, cardiac toxicity, gonadal toxicity with infertility, and secondary malignancies.

Prognosis

The prognosis is excellent for most forms of childhood and adolescent NHL (see Table 523.4). Patients with localized disease have a 90–100% survival rate, and those with advanced disease have 80–95% survival. Since outcomes for pediatric patients with NHL have improved substantially, the focus has now shifted to minimizing the *long-term toxicity of therapy.* Novel targeted agents are desirable because they have the potential to improve outcomes and decrease the reliance on toxic conventional chemotherapy. An ongoing multiinstitutional study is testing the reduction of anthracyline to decrease short-term (mucositis) and long-term (cardiac health) complications of therapy by incorporation of immunotherapy in mature B-NHL, with promising results to date.

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523.3

Late Effects in Children and Adolescents With Lymphoma

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Keywords

cancer survivor
excess morbidity

The majority of patients with newly diagnosed HL and NHL have OS rates >90%. There are approximately 270,000 survivors of childhood cancer in the United States, or about 1 of every 640 adults between ages 20 and 40. However, this survival has often been achieved at the expense of an increased relative risk of long-term complications, including solid tumors, leukemia, cardiac disease, pulmonary complications, thyroid disease, and infertility. An analysis of >1,000 long-term childhood NHL survivors found increased rates of death >20 yr after treatment. A review of the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data over 25 yr follow-up demonstrates that the relative survival curves do not plateau after 10 yr following diagnosis of HL, but rather accelerate. This finding highlights the importance of late morbidity and mortality among survivors of lymphoma. The first **Childhood Cancer Survivor Study** , a retrospective cohort study of 10,397 cancer survivors, shows that 62.3% of survivors report at least 1 chronic condition, with 27.5% reporting severe or life-threatening conditions. The survivor's adjusted relative risk of a severe or life-threatening chronic condition, compared with that of a sibling, was 8.2 (95% confidence interval, 6.9-9.7). Studying disease-specific health outcomes, both HL and NHL were found to be associated with a cumulative incidence of chronic health conditions approaching 70–80%, with severe conditions reported in close to 50% of HL survivors (Fig. 523.8).

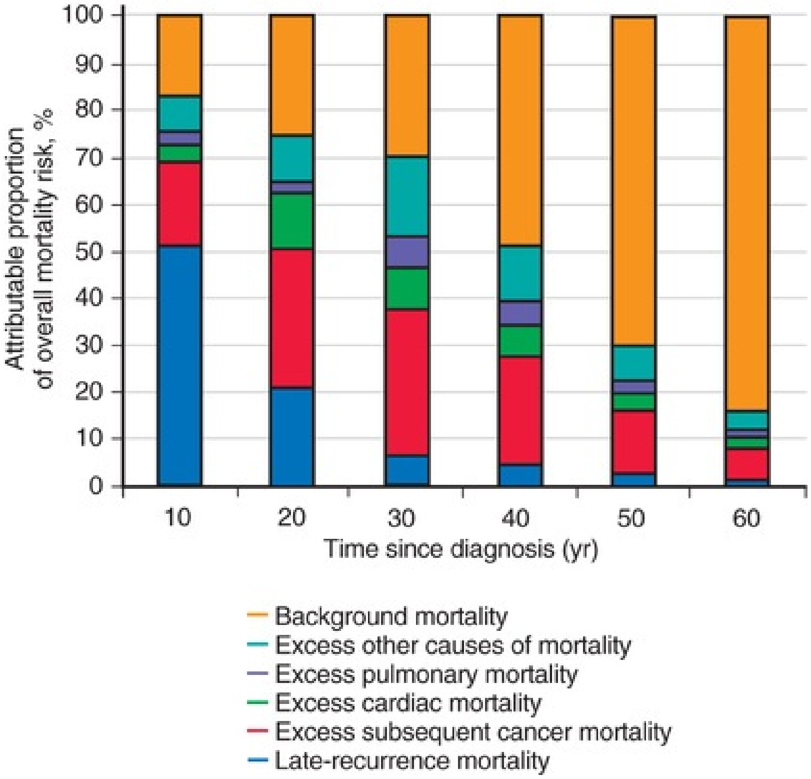

FIG. 523.8 Percentage of attributable proportions of overall mortality risk in survivors of childhood cancer. (Adapted from Yeh JM, Nekhlyudov L, Goldie SJ, et al: A model-based estimate of cumulative excess mortality in survivors of childhood cancer, *Ann Intern Med* 152[7]:409–417, 2010.)

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* The views expressed are the result of independent work and do not necessarily

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CHAPTER 524

Brain Tumors in Childhood

Wafik Zaky, Joann L. Ater, Soumen Khatua

Primary central nervous system (CNS) tumors are a heterogeneous group of diseases that collectively are the most common malignancy in childhood and adolescence. The overall mortality among this group approaches 30%. Patients with CNS tumors have the highest morbidity—primarily neurologic—of all children with malignancies. Outcomes have improved over time with innovations in neurosurgery, radiation therapy (particularly stereotactic conformal radiotherapy), chemotherapy, and immune therapy. The treatment approach for these tumors is multimodal. Surgery with complete resection, if feasible, is the foundation, with radiation therapy and chemotherapy used according to the diagnosis, patient age, and other factors

Etiology

The etiology of pediatric brain tumors is not well defined. A male predominance is noted in the incidence of medulloblastoma and ependymoma. **Familial syndromes** associated with an increased incidence of brain tumors account for approximately 5% of cases (Table 524.1). Cranial exposure to ionizing radiation also is associated with a higher incidence of brain tumors. There are sporadic reports of brain tumors within families without evidence of a heritable syndrome. The molecular events associated with tumorigenesis of pediatric brain tumors are not known.

Table 524.1

Familial Syndromes Associated With Pediatric Brain Tumors

SYNDROME	**CENTRAL NERVOUS SYSTEM MANIFESTATIONS**	**CHROMOSOME**	**GENE**
Neurofibromatosis type 1 (autosomal dominant)	Optic pathway gliomas, astrocytoma, malignant peripheral nerve sheath tumors, neurofibromas	17q11	*NF1*
Neurofibromatosis type 2 (autosomal dominant)	Vestibular schwannomas, meningiomas, spinal cord ependymoma, spinal cord astrocytoma, hamartomas	22q12	*NF2*
Von Hippel–Lindau (autosomal dominant)	Hemangioblastoma	3p25-26	*VHL*
Tuberous sclerosis (autosomal dominant)	Subependymal giant cell astrocytoma, cortical tubers	9q34	*TSC1*
		16q13	*TSC2*
Li-Fraumeni (autosomal dominant)	Astrocytoma, primitive neuroectodermal tumor	17q13	*TP53*
Cowden (autosomal dominant)	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease)	10q23	*PTEN*
Turcot (autosomal dominant)	Medulloblastoma	5q21	*APC*
	Glioblastoma	3p21	*hMLH1*
		7p22	*hPSM2*
Nevoid basal cell carcinoma Gorlin (autosomal dominant)	Medulloblastoma	9q31	*PTCH1*

Adapted from Kleihues P, Cavenee WK: *World Health Organization classification of tumors: pathology and genetics of tumors of the nervous system,* Lyon, 2000, IARC Press.

Epidemiology

Approximately 4,600 primary brain tumors are diagnosed each year in children and adolescents in the United States, with an overall annual incidence of approximately 47 cases per 1 million children <20 yr of age. The incidence of CNS tumors is highest in infants and children ≤5 yr old (approximately 52 cases/1 million children).

Pathogenesis

More than 100 histologic categories and subtypes of primary brain tumors are described in the World Health Organization (WHO) classification of CNS tumors. In children 0-14 yr old, the most common tumors are **pilocytic astrocytomas (PAs)** and **medulloblastoma/primitive neuroectodermal tumors (PNETs)** . In adolescents (15-19 yr), the most common tumors are pituitary/craniopharyngeal tumors and PAs (Fig. 524.1); congenital (neonatal) tumors have a distinct pattern (Table 524.2).

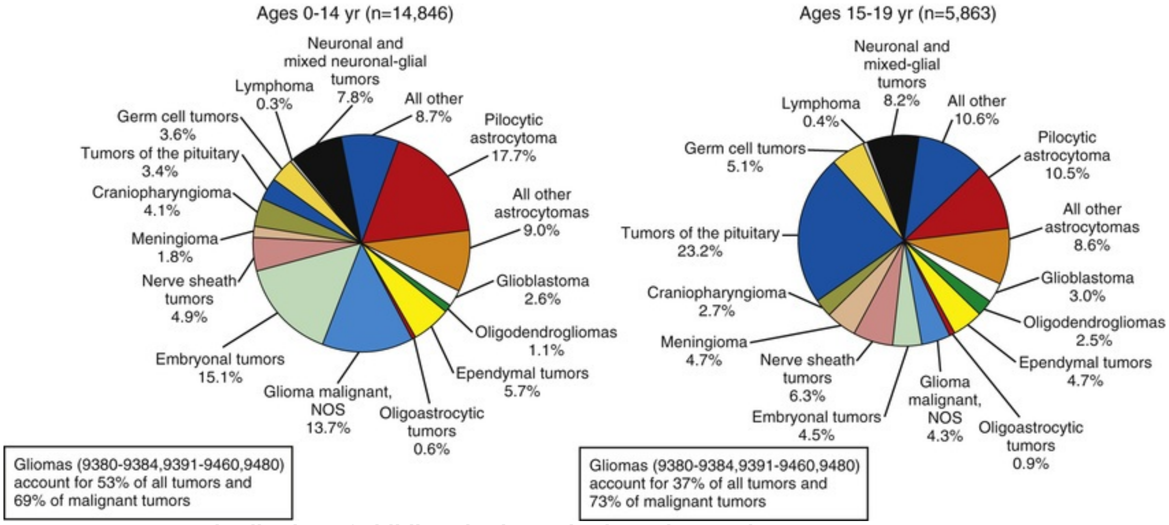

FIG. 524.1 **Distribution of childhood primary brain and central nervous system tumors by histology. NOS, Not otherwise specified. (From Dolecek TA, Propp JM, Stroup NE, Kruchko C: CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005–2009, *Neuro-Oncology* 14:v1–v49, 2012.)**

Table 524.2

Congenital and Neonatal Brain Tumors

- Germ cell tumors: teratoma (mature and immature)
- Choroid plexus tumors (papilloma and carcinoma)
- Embryonal tumors
  - Embryonal tumors with multilayered rosettes (formerly primitive neuroectodermal tumor)
  - Atypical teratoid/rhabdoid tumor
  - Medulloblastoma
- Astrocytic tumors
- Neuronal and mixed neuronal-glial tumors:
  - Desmoplastic infantile tumors (astrocytomas and gangliogliomas)

From Shekdar KV, Schwartz ES: Brain tumors in the neonate, *Neuroimag Clin North Am* 27:69–83, 2017.

The National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program reported a slight predominance of infratentorial tumor location (43.2%), followed by the supratentorial region (40.9%), spinal cord (4.9%), and multiple sites (11%) (Fig. 524.2 and Tables 524.3 and 524.4). There are age-related differences in primary location of tumor. During the 1st yr of life, supratentorial tumors predominate and most often include choroid plexus complex tumors and teratomas (see Table 524.2). In children 1-10 yr old, infratentorial tumors predominate because of the high incidence of juvenile PA and medulloblastoma. After 10 yr of age, supratentorial tumors again predominate, with diffuse astrocytomas most common (see Table 524.4). Tumors of the optic pathway and hypothalamus region, the brainstem, and the pineal-midbrain region are more common in children and adolescents than in adults.

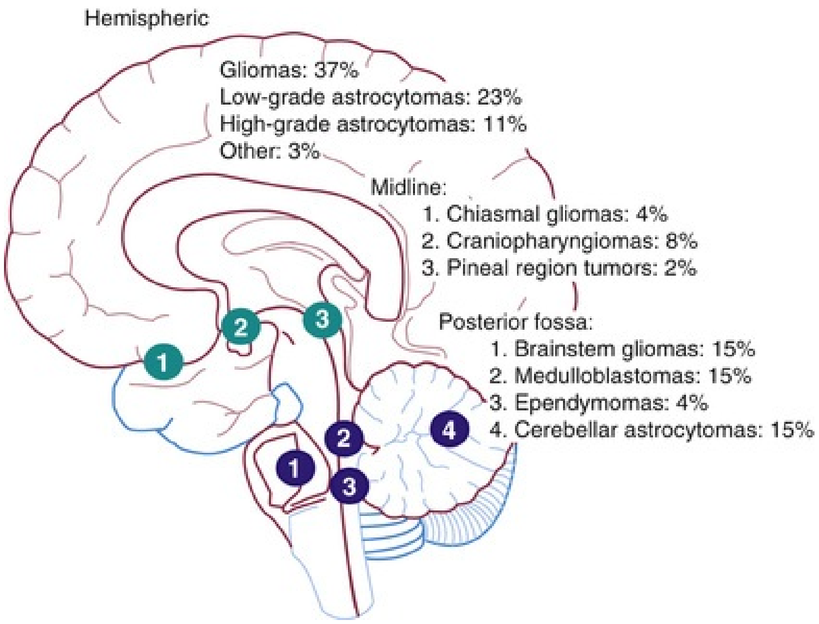
Hemispheric
Gliomas: 37%
Low-grade astrocytomas: 23%
High-grade astrocytomas: 11%
Other: 3%
Midline:
1. Chiasmal gliomas: 4%
2. Craniopharyngiomas: 8%
3. Pineal region tumors: 2%
Posterior fossa:
1. Brainstem gliomas: 15%
2. Medulloblastomas: 15%
3. Ependymomas: 4%
4. Cerebellar astrocytomas: 15%
1
2
3
1
2
3
4

FIG. 524.2 Childhood brain tumors occur at any location within the central nervous system. The relative frequency of brain tumor histologic types and the anatomic distribution are shown. (Redrawn from Albright AL: Pediatric brain tumors, *CA Cancer J Clin* 43:272–288, 1993.)

Table 524.3

Posterior Fossa Tumors of Childhood

TUMOR	RELATIVE INCIDENCE (%)	PRESENTATION	DIAGNOSIS	PROGNOSIS
Medulloblastoma	35-40	2-3 mo of headaches, vomiting, truncal ataxia	Heterogeneously or homogeneously enhancing 4th ventricular mass; may be disseminated	65–85% survival; dependent on stage/type; poorer (20–70%) in infants
Cerebellar astrocytoma	35-40	3-6 mo of limb ataxia; secondary headaches, vomiting	Cerebellar hemisphere mass, usually with cystic	90–100% survival in

			and solid (mural nodule) components	totally resected, pilocytic type
Brainstem glioma	10-15	1-4 mo of double vision, unsteadiness, weakness, and cranial nerve dysfunction, including facial weakness, swallowing dysfunction, and oculomotor abnormalities	Diffusely expanded, minimally or partially enhancing mass in 80%; 20% more focal tectal or cervicomedullary lesion	>90% mortality in diffuse tumors; better in localized
Ependymoma	10-15	2-5 mo of unsteadiness, headaches, double vision, and facial asymmetry	Usually enhancing, 4th ventricular mass with cerebellopontine predilection	>75% survival in totally resected lesions
Atypical teratoid/rhabdoid	>5 (10–15% of infantile malignant tumors)	As in medulloblastoma, but primarily in infants; often associated facial weakness and strabismus	As in medulloblastoma, but often more laterally extended	≤20% survival in infants

Adapted from Packer RJ, MacDonald T, Vezina G: Central nervous system tumors, *Pediatr Clin North Am* 55:121–145, 2008.

Table 524.4

Pediatric Supratentorial Brain Tumors With Key Features on Neuroimaging

TUMOR	KEY FEATURES
GLIAL CELL TUMORS	
Pilocytic astrocytoma	Most common primary tumor in children Excellent prognosis Cystic with enhancing mural nodule or solid mass Lack of significant vasogenic edema
Diffuse astrocytoma	Much less common in children than in adults Relatively ill-defined without contrast enhancement Dedifferentiation rarely seen in children
Anaplastic astrocytoma	Poorly circumscribed margins No hemorrhage or necrosis Usually no contrast enhancement
Glioblastoma	Rare in children Heterogeneous enhancement Necrosis and marked peritumoral edema
Subependymal giant cell tumor	Associated with the tuberous sclerosis complex Avid enhancement Virtually always in a lateral ventricle near foramen of Monro
Pleomorphic xanthoastrocytoma	Almost always supratentorial Solid components show avid enhancement Peripheral location abutting meningeal surface
Oligodendroglial tumors	Relatively well circumscribed, expanded cortex Enhancement and calcification less common than in adults High rCBV often found in low-grade tumors
Ependymoma	Half of supratentorial tumors are parenchymal Higher incidence of cysts than infratentorial ones

	Calcifications, hemorrhage and inhomogeneous enhancement ADC values usually higher than embryonal tumors
Angiocentric glioma	Superficial cortical lesions T1 hyperintensity is a characteristic but infrequent feature Usually no contrast enhancement
NEURONAL AND MIXED NEURONAL-GLIAL TUMORS	
Ganglioglioma	Most common in temporal lobes Mixed cystic and solid masses with avidly enhancing nodule Calcifications are common
Desmoplastic infantile tumors	Very rare, typically 18 mo of age or younger Predominantly cystic with solid nodules located near cortex Solid components may show low ADC values even if benign
Dysembryoplastic neuroepithelial tumors	Cortically based, favor temporal lobes 30% associated with cortical dysplasia May have a characteristic bubbly appearance Can rarely have nodular or ringlike enhancement
EMBRYONAL TUMORS	
Embryonal tumors not otherwise specified	Usually children <5 yr of age Large at presentation with little surrounding edema Intense and heterogeneous contrast enhancement Low ADC values
Atypical teratoid rhabdoid tumor	10% of CNS tumors in children <12 mo of age Rare aggressive neoplasms Large and predominantly solid with minimal edema Calcifications, hemorrhage, and cysts are common Moderate to marked enhancement and low ADC values

ADC, Apparent diffusion coefficient; CNS, central nervous system; rCBV, relative cerebral blood volume.

From Zamora C, Huisman TAGM, Izbudak I: Supratentorial tumors in pediatric patients, *Neuroimag Clin North Am* 27:39–67, 2017, pp 55-56.

Clinical Manifestations

The clinical presentation of the patient with a brain tumor depends on tumor location, tumor type, and patient age. Signs and symptoms are related to obstruction of cerebrospinal fluid (CSF) drainage paths by the tumor, leading to **increased intracranial pressure** (ICP) or causing focal brain dysfunction. In young children the diagnosis of a brain tumor may be delayed because the symptoms are similar to more common illnesses, such as gastrointestinal disorders, with associated vomiting. Infants with open cranial sutures may present with signs of increased ICP, such as vomiting, lethargy, and irritability, as well as the later finding of macrocephaly. The classic triad of headache, nausea, and vomiting as well as papilledema is associated with midline or **infratentorial tumors** . Headaches associated with brain tumors are often of new onset, persistent (but usually <6 mo), associated with either neurologic findings (papilledema, cognitive-behavioral changes, seizures, focal motor deficits), associated with emesis, and occur on awakening or wake the patient from sleep. Disorders of equilibrium, gait, and coordination occur with infratentorial tumors. **Torticollis** may occur in cases of cerebellar tonsil herniation. Blurred vision, diplopia, and nystagmus also are associated with infratentorial tumors. Tumors of the brainstem region may be associated with gaze palsy, multiple cranial nerve palsies, and upper motor neuron deficits (e.g., hemiparesis, hyperreflexia, clonus).

Supratentorial tumors are more frequently associated with focal motor weakness, focal sensory changes, language disorders, focal seizures, and reflex asymmetry. Infants with supratentorial tumors may present with premature hand preference. **Optic pathway tumors** manifest as visual and/or afferent oculomotor disturbances, such as decreased visual acuity, Marcus Gunn pupil (afferent pupillary defect), nystagmus, and/or visual field defects. Suprasellar region tumors and 3rd ventricular region tumors may manifest initially as **neuroendocrine deficits,** such as subacute development of obesity, abnormal linear growth velocity, diabetes insipidus, galactorrhea, precocious puberty, delayed puberty, and hypothyroidism. In fact, signs of endocrine dysfunction preceded symptoms of neuroophthalmologic dysfunction by an average of 1.9 yr, and their recognition as a possible sign of hypothalamic or pituitary neoplasm can hasten diagnosis and improve outcome. The **diencephalic syndrome,** which manifests as failure to thrive, emaciation despite normal caloric intake, and inappropriately normal or happy affect, occurs in infants and young children with tumors in these regions. **Parinaud syndrome** is seen with pineal region tumors and is manifested by paresis of upward gaze, pupillary caliber reactive to accommodation but not to light (pseudo–Argyll Robertson pupil), nystagmus to convergence or retraction, and eyelid retraction. Spinal cord tumors and spinal cord dissemination of brain tumors may manifest as long nerve tract motor and/or sensory deficits often localized to below a specific spinal level, bowel and bladder deficits, and back or radicular pain. The signs and symptoms of meningeal metastatic disease from brain tumors or leukemia include head or back pain and symptoms referable to compression of cranial nerves or spinal nerve roots.

Diagnosis

The evaluation of a patient in whom a brain tumor is suspected is an emergency

. Initial evaluation should include a complete history, physical (including ophthalmic) examination, and neurologic assessment with neuroimaging. For primary brain tumors, **MRI** with and without gadolinium is the neuroimaging standard. Tumors in the pituitary/suprasellar region, optic pathway, and infratentorium are better delineated with MRI than with CT. Patients with tumors of the midline and the pituitary/suprasellar/optic chiasmal region should undergo evaluation for **neuroendocrine dysfunction** . Formal ophthalmologic examination is beneficial in patients with optic path region tumors to document the impact of the disease on oculomotor function, visual acuity, and fields of vision. The suprasellar and pineal regions are preferential sites for germ cell tumors (Fig. 524.3). Both serum and CSF measurements of β–human chorionic gonadotropin (β-hCG), α-fetoprotein (AFP), and placental alkaline phosphatase can assist in the diagnosis of germ cell tumors. In tumors with a propensity for spreading to the leptomeninges, such as medulloblastoma/PNET, ependymoma, and germ cell tumors, lumbar puncture (LP) with cytologic analysis of the CSF is indicated; LP is *contraindicated* in patients with newly diagnosed hydrocephalus secondary to CSF flow obstruction, in those with tumors that cause supratentorial midline shift, and in patients with infratentorial tumors. LP in these patients may lead to brain herniation, resulting in neurologic compromise and death. Therefore, in children with newly diagnosed intracranial tumors and signs of increased ICP, the LP usually is delayed until surgery or shunt placement.

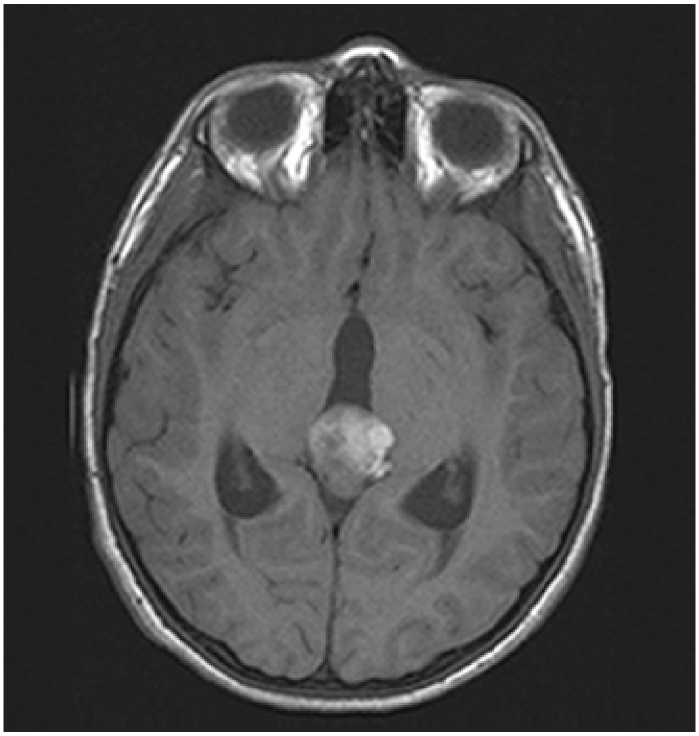

FIG. 524.3 Axial T1-weighted MR image with gadolinium in 10 yr old boy presenting with mixed germ cell tumor of the pineal region, with early onset of puberty, headaches, and elevated α-fetoprotein and β–human chorionic gonadotropin in the spinal fluid and serum.

Specific Tumors

Table 524.5 provides a classification of tumors of the central nervous system.

Table 524.5

WHO Classification of Central Nervous System (CNS) Tumors

DIFFUSE ASTROCYTIC AND OLIGODENDROGLIAL TUMORS	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wild type	9400/3
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wild type	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wild type	9440/3
Giant cell glioblastoma	9441/3

Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M-mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9451/3
Anaplastic oligodendroglioma, NOS	*9451/3*
Oligoastrocytoma, NOS	*9382/3*
Anaplastic oligoastrocytoma, NOS	*9382/3*
OTHER ASTROCYTIC TUMORS	
Pilocytic astrocytoma	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
EPENDYMAL TUMORS	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion-positive	9393/3*
Anaplastic ependymoma	9392/3
OTHER GLIOMAS	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
CHOROID PLEXUS TUMORS	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
NEURONAL AND MIXED NEURONAL-GLIAL TUMORS	
Dysembryoplastic neuroepithelial tumor	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumor	9509/1
Rosette-forming glioneuronal tumor	9509/1
Diffuse leptomeningeal glioneuronal tumor	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
TUMORS OF THE PINEAL REGION	
Pineocytoma	9361/1
Pineal parenchymal tumor of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumor of the pineal region	9395/3

EMBRYONAL TUMORS	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53* -mutant	9476/3*
Medulloblastoma, SHH-activated and TP53-wild type	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma, with extensive nodularity	9471/3
Medulloblastoma, large cell/anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumor with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumor with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumor, NOS	9473/3
Atypical teratoid/rhabdoid tumor	9508/3
CNS embryonal tumor with rhabdoid features	*9508/3*
TUMORS OF THE CRANIAL AND PARASPINAL NERVES	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0
Melanotic schwannoma	9560/1
Neurofibroma	9540/0
Atypical neurofibroma	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Hybrid nerve sheath tumors	
Malignant peripheral nerve sheath tumor	9540/3
Epithelioid MPNST	9540/3
MPNST with perineurial differentiation	9540/3
MENINGIOMAS	
Meningioma	9530/0
Meningothelial meningioma	9531/0
Fibrous meningioma	9532/0
Transitional meningioma	9537/0
Psammomatous meningioma	9533/0
Angiomatous meningioma	9534/0
Microcystic meningioma	9530/0
Secretory meningioma	9530/0
Lymphoplasmacyte-rich meningioma	9530/0
Metaplastic meningioma	9530/0
Chordoid meningioma	9538/1
Clear cell meningioma	9538/1
Atypical meningioma	9539/1
Papillary meningioma	9538/3
Rhabdoid meningioma	9538/3
Anaplastic (malignant) meningioma	9530/3

MESENCHYMAL, NONMENINGOTHELIAL TUMORS	
Solitary fibrous tumor/hemangiopericytoma**	
Grade 1	8815/0
Grade 2	8815/1
Grade 3	8815/3
Hemangioblastoma	9161/1
Hemangioma	9120/0
Epithelioid hemangioendothelioma	9133/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Ewing sarcoma/PNET	9364/3
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma	8850/3
Desmoid-type fibromatosis	8821/1
Myofibroblastoma	8825/0
Inflammatory myofibroblastic tumor	8825/1
Benign fibrous histiocytoma	8830/0
Fibrosarcoma	8810/3
Undifferentiated pleomorphic sarcoma/malignant fibrous histiocytoma	8802/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8890/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteochondroma	9210/0
Osteosarcoma	9180/3
MELANOCYTIC TUMORS	
Meningeal melanocytosis	8728/0
Meningeal melanocytoma	8728/1
Meningeal melanoma	8720/3
Meningeal melanomatosis	8728/3
LYMPHOMAS	
Diffuse large B-cell lymphoma of the CNS	9680/3
Immunodeficiency-associated CNS lymphomas	
AIDS-related diffuse large B-cell lymphoma	
EBV-positive diffuse large B-cell lymphoma, NOS	
Lymphomatoid granulomatosis	9766/1
Low-grade B-cell lymphomas of the CNS	
T-cell and NK/T-cell lymphomas of the CNS	
Anaplastic large cell lymphoma, ALK-positive	9714/3
Anaplastic large cell lymphoma, ALK-negative	9702/3
HISTIOCYTIC TUMORS	
Langerhans cell histiocytosis	9751/3
Erdheim-Chester disease	9750/1
Rosai-Dorfman disease	
Juvenile xanthogranuloma	
Histiocytic sarcoma	9755/3
GERM CELL TUMORS	

Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumor	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature teratoma	9080/0
Immature teratoma	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumor	9085/3
TUMORS OF THE SELLAR REGION	
Craniopharyngioma	9350/1
Adamantinomatous craniopharyngioma	9351/1
Papillary craniopharyngioma	9352/1
Granular cell tumor of the sellar region	9582/0
Pituicytoma	9432/1
Spindle cell oncocytoma	8290/0
METASTATIC TUMORS	

[*] These new codes were approved by the IARC/WHO Committee for ICD-O.

[**] Grading according to the 2013 *WHO Classification of Tumors of Soft Tissue and Bone.*

The morphology codes are from the *International Classification of Diseases for Oncology* (ICD-O) (742A). Behavior is coded /0 for benign tumors; /1 for unspecified, borderline, or uncertain behavior; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumors. The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions.

The *italicized* entries are provisional, i.e., the WHO Working Group thought there was insufficient evidence to recognize these as distinct disease entities at this time.

NOS, Not otherwise specified.

Adapted from Louis DN, Ohgaki H, Wiestler OD, Cavenee WK: *World Health Organization histological classification of tumours of the central nervous system,* 2016, International Agency for Research on Cancer, France.

Astrocytoma

Astrocytomas are a heterogeneous group of tumors that account for approximately 40% of pediatric CNS malignancies. These tumors occur throughout the CNS.

Low-grade astrocytomas (LGAs) , the predominant group of astrocytomas in childhood, are characterized by an indolent clinical course. **Pilocytic astrocytoma (PA)** is the most common astrocytoma in children, accounting for approximately 20% of all brain tumors. Based on clinicopathologic features using the WHO classification, PA is classified as a grade I tumor. Although PA can occur anywhere in the CNS, the classic sites are the cerebellum and the optic pathway region (Fig. 524.4). The classic but not exclusive neuroradiologic finding in PA is the presence of a contrast-enhancing nodule within the wall of a cystic mass. The microscopic findings include the biphasic appearance of bundles of compact fibrillary tissue interspersed with loose, microcystic, spongy areas. The presence of **Rosenthal fibers** (condensed masses of glial filaments occurring in compact areas) with low mitotic potentials helps establish the diagnosis. A small proportion of these tumors can progress and develop leptomeningeal spread, particularly in the optic pathway region and very rarely transform to higher-grade aggressive type. A PA of the optic nerve and chiasmal region is a relatively common finding in patients with neurofibromatosis type 1 (15% incidence).PA has activation of the MAPK pathway in the form of *BRAF* fusion or duplication and less often *BRAF* mutation (*V600E*). Other low-grade tumors occurring in the pediatric age-group with clinicopathologic characteristics similar to those of PA include pleomorphic xanthoastrocytoma, pilomyxoid astrocytoma, and subependymal giant cell astrocytoma.

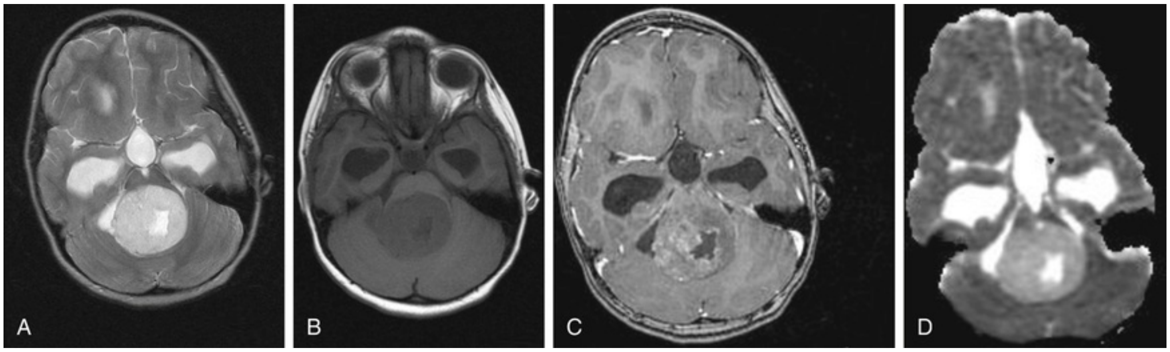

FIG. 524.4 MR images in 5 yr old girl presenting with headache and vomiting. There is a midline solid tumor, with cystic components compromising the cerebellar vermis. On the T2-weighted image (A) and the T1-weighted images without contrast (B) and with contrast (C), it is difficult to suggest the correct diagnosis. Looking at the ADC map (D), no restriction is seen, which is most consistent with a pilocytic astrocytoma. (From Lequin M, Hendrikse J: Advanced MR imaging in pediatric brain tumors, clinical applications, Neuroimag Clin North Am 27:167–190, 2017, Fig 1, p 169.)

The 2nd most common astrocytoma is **diffuse astrocytoma (DA),** which consists of a group of tumors characterized by a pattern of diffuse infiltration of tumor cells amidst normal neural tissue. DA accounts for 15% of brain tumors, with the fibrillary type the most common in children. Histologically, these low-grade tumors demonstrate greater cellularity, with few mitotic figures, nuclear pleomorphism, and microcysts. They occur anywhere in the CNS, with a predilection to supratentorial locations (Fig. 524.5). The characteristic MRI finding is a lack of enhancement after contrast infusion. Molecular genetic abnormalities found in DA include mutations of *P53* and overexpression of platelet-derived growth factor receptor α. Evolution of DA into malignant astrocytoma is associated with cumulative acquisition of multiple molecular abnormalities. Over activation of MAPK pathway was detected in DA in the form of *BRAF V600E* mutation and FGFR1 duplication.

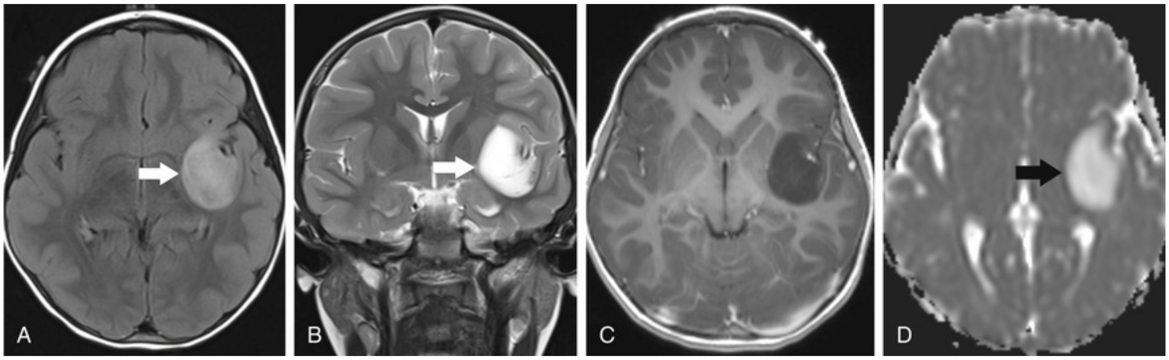

FIG. 524.5 **Diffuse astrocytoma. A, Axial FLAIR shows an infiltrative and expansile mass in the left insula and temporal lobe *(arrow).* B, Coronal T2-weighted MR image shows the lesion to be very bright (*arrow*). C, Axial postcontrast T1-weighted MR image demonstrates that the mass is markedly hypointense and does not enhance. D, The mass has high signal on the apparent diffusion coefficient map, in keeping with its low grade. (From Zamora C, Huisman TAGM, Izbudak I: Supratentorial tumors in pediatric patients, Neuroimag Clin North Am 27:39–67, 2017, Fig 4, p 44.)**

Pilomyxoid astrocytoma occurs most commonly in the hypothalamic/optic chiasmic region and carries a high risk of local as well as cerebrospinal spread. This astrocytoma affects young children and infants. It is classified as a WHO grade II tumor.

The **clinical management** of LGAs focuses on a multimodal approach incorporating surgery as the primary treatment, as well as radiation therapy and chemotherapy. With complete surgical resection, overall survival (OS) approaches 80–100%. In patients with partial resection, OS varies from 50–95%, depending on the anatomic location of the tumor. In the patient who has undergone partial tumor resection and has stable neurologic status, the current approach is to follow the patient closely by examination and imaging. With evidence of progression, a 2nd surgical resection should be considered. In patients in whom a 2nd procedure was less than complete or is not feasible, radiation therapy is beneficial. Radiation therapy is delivered to the tumor bed at a total cumulative dose ranging from 50-55 Gy. Modern surgical techniques and innovative radiation therapy methodology, including proton-beam radiation, may have a positive impact on the survival and clinical outcome of these patients.

The role of chemotherapy in the management of LGAs is evolving. Because of concerns regarding morbidity from radiation therapy in young children, several chemotherapy approaches have been evaluated, especially in children <10 yr old. Complete response to chemotherapy is uncommon; however, these approaches have yielded durable control of disease in 70–100% of patients. Patients with midline tumors in the hypothalamic/optic chiasmatic region have tended to do less well (Fig. 524.6). Taken together, the chemotherapy approaches have permitted delay and, potentially, avoidance of radiation therapy. Chemotherapy agents given singly or in combination for LGA include carboplatin, vincristine, lomustine, procarbazine, temozolomide, and vinblastine. Observation is the primary approach in clinical management of selected patients with LGAs that are biologically indolent (neurofibromatosis type 1 and midbrain astrocytoma). *Astrocytomas associated with tuberous sclerosis have responded to everolimus* (mammalian target of rapamycin inhibitor).

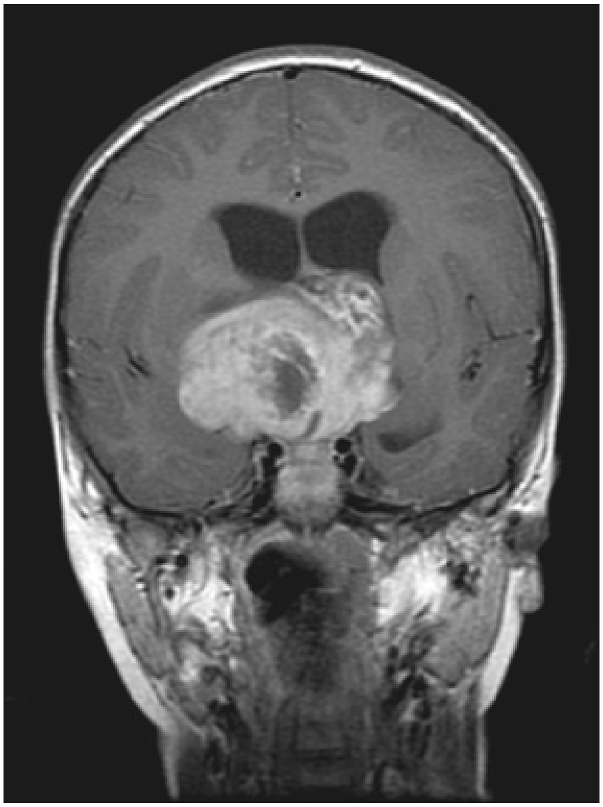

FIG. 524.6 Gadolinium-enhanced coronal view of a cystic juvenile pilocytic astrocytoma of the suprasellar region from 4 yr old child presenting with visual loss and headaches.

Malignant astrocytomas are less common in children and adolescents than in adults, accounting for 7–10% of all childhood brain tumors. Among this group, **anaplastic astrocytoma** (WHO grade III) (Fig. 524.7) is more common than **glioblastoma multiforme** (WHO grade IV) (Fig. 524.8). The histopathology of anaplastic astrocytomas demonstrates greater cellularity than that of LGA, with cellular and nuclear atypia, and the presence of mitoses. Characteristic histopathologic findings in glioblastoma multiforme include dense cellularity, high mitotic index, microvascular proliferation, and foci of tumor necrosis. Genome-wide DNA methylation patterns have now identified 5 molecular subgroups of pediatric high-grade glioma (HGG), these subgroups appear to have distinct cellular origins and biologic drivers. Common genetic alterations include gene mutations in histone *H3.3* or *H3.1* , *P53* , and *BRAF,* in addition to focal amplifications of oncogene (*PDGFRA* and *EGFR*) and deletions of tumor suppressor genes (*CDKN2A* and *CDKN2B*).

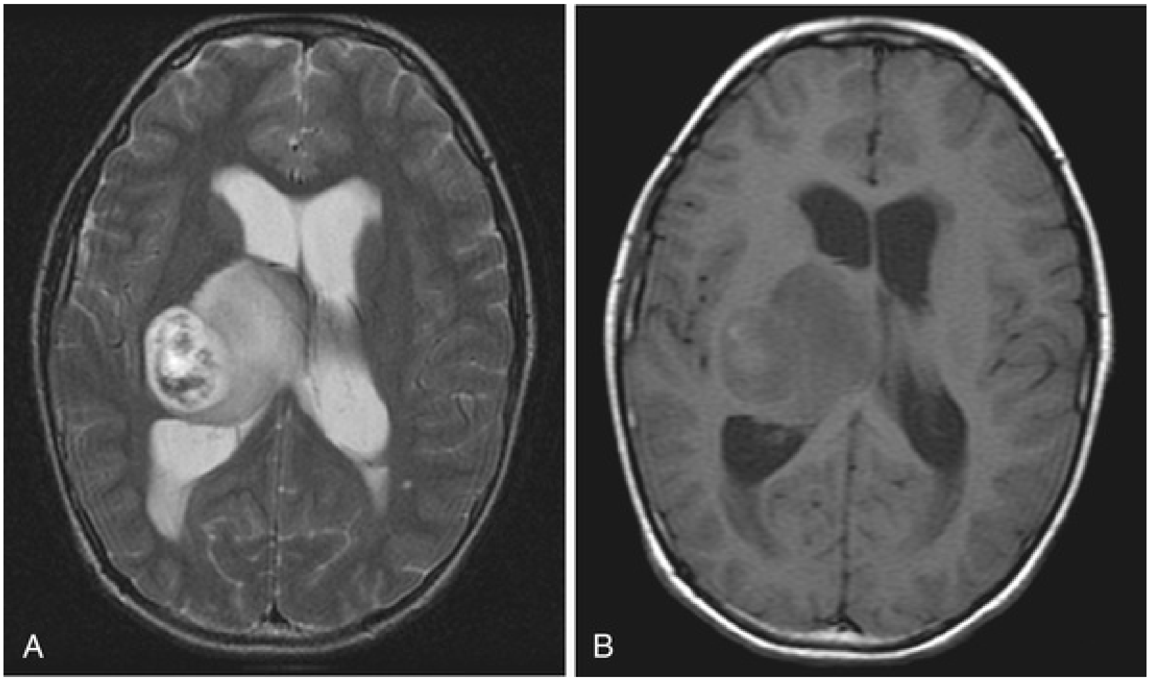

FIG. 524.7 **A,** Nonenhanced axial T2-weighted MR image of grade III astrocytoma of the right thalamus demonstrating diffuse hyperintensity and area of necrotic cyst formation. **B,** Gadolinium-enhanced sagittal T1-weighted MR image showing slight enhancement and hypodensity of grade III astrocytoma of the thalamus. This 14 yr old child presented with left arm and leg numbness and weakness and right-sided headaches.

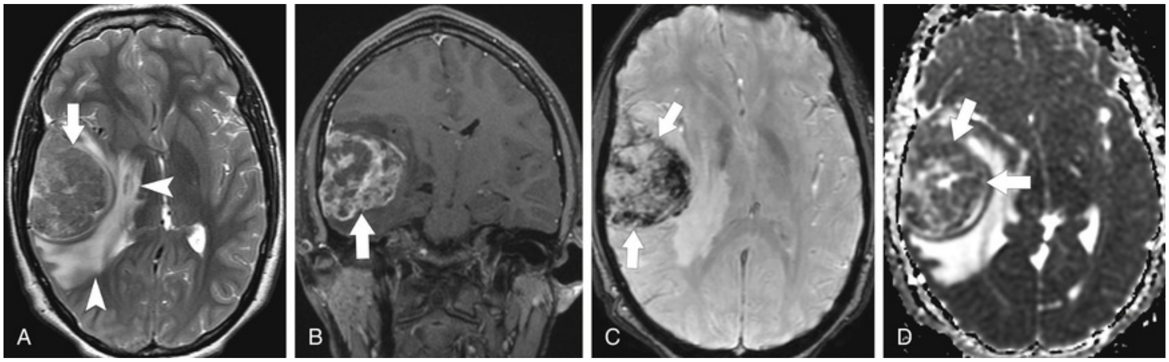

FIG. 524.8 **Glioblastoma. A, Axial T2-weighted MR image shows a heterogeneous mass that is predominantly hypointense to cortex and relatively well circumscribed (*arrow*). Note moderate peritumoral edema (*arrowheads*). B, Coronal postcontrast T1-weighted MR image heterogeneous but avid enhancement throughout the mass (*arrow*). C, Axial susceptibility-weighted MR image shows areas of increased susceptibility within the tumor caused by hemorrhage (*arrows*). D, Apparent diffusion coefficient map shows low signal within the lesion, in keeping with restricted diffusion (*arrows*). (From Zamora C, Huisman TAGM, Izbudak I: Supratentorial tumors in pediatric patients, Neuroimag Clin North Am 27:39–67, 2017, Fig 7, p 47.)**

Optimal therapeutic approaches for malignant astrocytomas have yet to be defined. Standard therapy continues to be surgical resection followed by involved-field radiation therapy. A study of adult glioblastoma showed significantly better survival with temozolomide during and after irradiation than with irradiation alone. Current therapeutic approaches incorporate novel chemotherapeutic agents with radiation therapy. Enrollment in a clinical trial may be the best therapeutic option in these tumors for which standard therapy is suboptimal. Immune therapy with chimeric antigen receptor T cells targeting the tumor antigen interleukin-13 receptor α holds promise as a therapy for glioblastomas.

Oligodendrogliomas are uncommon tumors of childhood. These infiltrating tumors occur predominantly in the cerebral cortex and originate in the white matter. Histologically, oligodendrogliomas consist of rounded cells with little cytoplasm and microcalcifications. Observation of a **calcified cortical mass** on CT in a patient presenting with a seizure is suggestive of oligodendroglioma. Treatment approaches are similar to those for infiltrating astrocytomas.

Ependymal Tumors

Ependymal tumors are derived from the ependymal lining of the ventricular system. **Cellular ependymoma** (WHO grade II) is the most common of these neoplasms, accounting for 10% of childhood tumors. Approximately 70% of ependymomas in childhood occur in the posterior fossa. The mean age of patients is 6 yr, with approximately 40% of cases occurring in children <4 yr old. The incidence of leptomeningeal spread approaches 10% overall. Clinical presentation can be insidious and often depends on the anatomic location of the tumor. MRI demonstrates a well-circumscribed tumor with variable and complex patterns of gadolinium enhancement, with or without cystic structures (Fig. 524.9). These tumors usually are noninvasive, extending into the ventricular lumen and/or displacing normal structures, sometimes leading to significant obstructive hydrocephalus. Histologic characteristics include perivascular pseudorosettes, ependymal rosettes, monomorphic nuclear morphology, and occasional nonpalisading foci of necrosis.

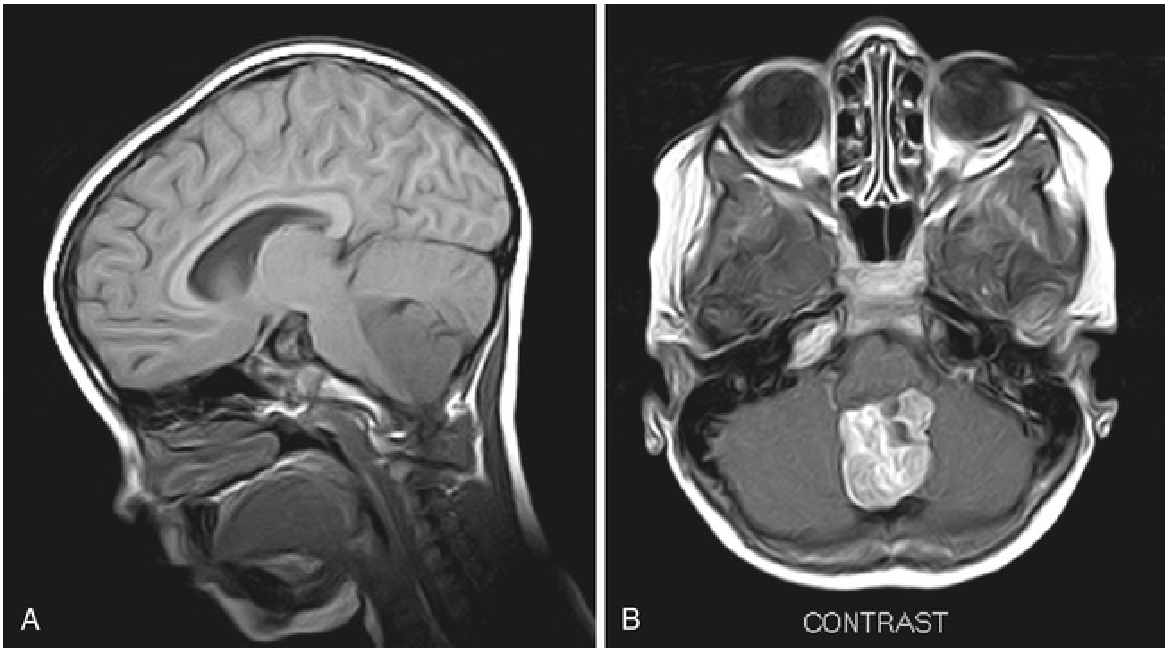

FIG. 524.9 **A,** Sagittal T1-weighted MR image of 6 yr old patient with ependymoma, demonstrating a hypointense mass within the 4th ventricle compressing the brainstem. **B,** Gadolinium-enhanced axial T1-weighted MR image of an ependymoma showing an enhancing mass within the 4th ventricle.

Other histologic subtypes include **anaplastic ependymoma** (WHO grade III), which is much less common in childhood and is characterized by a high mitotic index and histologic features of microvascular proliferation and pseudopalisading necrosis. **Myxopapillary ependymoma** (WHO grade I) is a slow-growing tumor arising from the filum terminale and conus medullaris and appears to be a biologically different subtype. Preliminary studies suggest that there are genetically distinct subtypes of ependymoma, exemplified by an association between alterations in the *NF2* gene and spinal ependymoma.

Surgery is the primary treatment modality, with *extent of surgical resection* a major prognostic factor. Two other major prognostic factors are *age,* with younger children having poorer outcomes, and *tumor location,* with localization in the posterior fossa, which often is seen in young children, associated with poorer outcomes. Surgery alone is rarely curative. Multimodal therapy incorporating irradiation with surgery has resulted in long-term survival in approximately 40% of patients with ependymoma undergoing gross total resection. Recurrence is predominantly local. The role of chemotherapy in multimodal therapy of ependymoma is still unclear. Current investigations are directed toward identification of optimal radiation dose, surgical questions addressing the use of second-look procedures after chemotherapy, and further evaluation of classic as well as novel chemotherapeutic agents. Genome-wide DNA methylation patterns have identified nine molecular subgroups in these tumors, across 3 anatomic compartments: supratentorial (ST), posterior fossa (PF), and spinal locations. Two subgroups (A and B) of PF ependymoma have been identified with distinct molecular and clinical characteristics, and use of targeted chemotherapy against these subtypes is now being evaluated.

Choroid Plexus Tumors

Choroid plexus tumors account for 2–4% of childhood CNS tumors. They are the most common CNS tumors in children <1 yr old and account for 10–20% of CNS tumors in infants. These tumors are intraventricular epithelial neoplasms arising from the choroid plexus. Children present with signs and symptoms of increased ICP. Infants may present with macrocephaly and focal neurologic deficits. In children, these tumors predominantly occur supratentorially in the lateral ventricles.

The group of choroid plexus tumors comprises **choroid plexus papillomas** (WHO grade I), **atypical choroid plexus papillomas** (WHO grade II), and **choroid plexus carcinomas** (WHO grade III). Choroid plexus papilloma is the most common of this group and is a well-circumscribed lesion with focal calcification on neuroimaging. Choroid plexus carcinoma is a malignant tumor with metastatic potential to seed into the CSF pathways. This malignancy has the histologic characteristics of nuclear pleomorphism, high mitotic index, necrosis, and increased cell density. MRI typically demonstrates a large, hyperdense, contrast-enhancing intraventricular mass with peritumoral edema, hemorrhage, and hydrocephalus. The tumor suppressor p53 is crucially involved in the biology of this cancer and may contribute to aggressive tumor behavior. Molecular data subclassify choroid plexus tumors into 3 distinct subgroups, with different molecular aberrations and clinical outcomes. These tumors are associated with the **Li-Fraumeni syndrome** .

After complete surgical resection, the frequency of cure for choroid plexus papilloma approaches 100%, whereas that for choroid plexus carcinoma approaches 20–40%. Reports suggest that radiation therapy and/or chemotherapy may lead to better disease control for choroid plexus carcinoma.

Embryonal Tumors

Embryonal tumors or **primitive neuroectodermal tumors (PNETs)** are the most common group of *malignant* CNS tumors of childhood, accounting for approximately 20% of pediatric CNS tumors. They have the potential to metastasize to the neuraxis and beyond. The group includes medulloblastoma, supratentorial PNET, ependymoblastoma, medulloepithelioblastoma, and atypical teratoid/rhabdoid tumor, all of which are histologically classified as WHO grade IV tumors.

Medulloblastoma accounts for 90% of embryonal CNS tumors and is a cerebellar tumor occurring predominantly in males and at a median age of 5-7 yr (Table 524.6). CT and MRI demonstrate a solid, homogeneous, contrast medium–enhancing mass in the posterior fossa causing 4th ventricular obstruction and hydrocephalus (Fig. 524.10). Up to 30% of patients with medulloblastoma present with neuroimaging evidence of leptomeningeal spread. Among a variety of diverse histologic patterns of this tumor, the most common is a monomorphic sheet of undifferentiated cells classically noted as small, blue, round cells. Neuronal differentiation is more common among these tumors and is characterized histologically by the presence of Homer Wright rosettes and immunopositivity for synaptophysin. An anaplastic variant is often more aggressive and may be associated with worse prognosis. Patients present with signs and symptoms of increased ICP (i.e., headache, nausea, vomiting, mental status changes, hypertension) and cerebellar dysfunction (i.e., ataxia, poor balance, dysmetria). Standard clinical staging evaluation includes MRI of the brain and spine, both preoperatively and postoperatively, as well as LP after the increased ICP has resolved. The **Chang staging** system, originally based on surgical information, has been modified to incorporate information from neuroimaging to identify risk categories. Clinical features that have consistently demonstrated prognostic significance include age at diagnosis, extent of disease, and extent of surgical resection. Patients <4 yr old have a poor outcome, partly as the result of a higher incidence of disseminated disease on presentation and past therapeutic approaches that have used less intense therapies. Patients with disseminated disease at diagnosis (M >0), including positive CSF cytologic result alone (M1), have a much poorer outcome than those with no dissemination (M0). Similarly, patients with gross residual disease after surgery have worse outcomes than those in whom surgery achieved gross total resection of disease.

Table 524.6

Summary of the Most Common Integrated Medulloblastoma Diagnoses, With Clinical Correlates

GENETIC PROFILE	HISTOLOGY	PROGNOSIS
Medulloblastoma, WNT-activated	Classic	Low-risk tumor; classic morphology found in almost all WNT-activated tumors
	Large cell/anaplastic (very rare)	Tumor of uncertain clinicopathologic significance
Medulloblastoma, SHH-activated, *TP52* -mutant	Classic	Uncommon high-risk tumor
	Large cell/anaplastic	High-risk tumor; prevalent in children age 7-17 yr
	Desmoplastic/nodular (very rare)	Tumor of uncertain clinicopathologic significance
Medulloblastoma, SHH-activated, *TP53* -wild type	Classic	Standard-risk tumor
	Large cell/anaplastic	Tumor of uncertain clinicopathologic significance
	Desmoplastic/nodular	Low-risk tumor in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumor of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumor
	Large cell/anaplastic	High-risk tumor
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumor; classic morphology found in almost all group 4 tumors
	Large cell/anaplastic (rare)	Tumor of uncertain clinicopathologic significance

Adapted from Louis DN, Ohgaki H, Wiestler OD, Cavenee WK: *World Health Organization histological classification of tumours of the central nervous system,* 2016, International Agency for Research on Cancer, France.

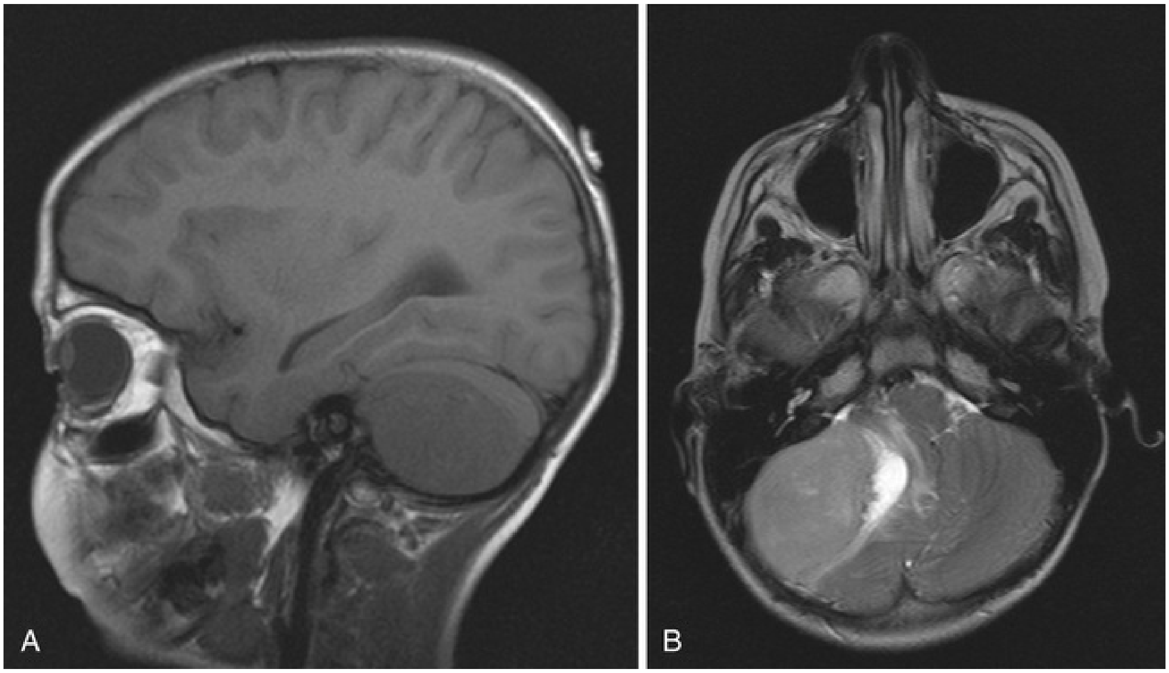

FIG. 524.10 **A,** Sagittal T1-weighted MR image shows hypointense mass involving the cerebellar hemisphere in 6 yr old child with desmoplastic variant of medulloblastoma. **B,** Axial T2-weighted MR image of the same child shows hyperintense mass involving the cerebellar hemisphere.

Cytogenetic and molecular genetic studies have demonstrated multiple abnormalities in medulloblastoma. The most common abnormality involves chromosome 17p deletions, which occur in 30–40% of all cases. These deletions are not associated with *P53* mutations. Several signaling pathways have been shown to be active in medulloblastomas, including the sonic hedgehog (SHH) pathway, predominately associated with the desmoplastic variants, and the WNT pathway, which can occur in up to 15% of cases and has been associated with improved survival. Integrative genomic studies have recently identified at least 4 distinct molecular subgroups of medulloblastoma—WNT, SHH, group 3, and group 4—which exhibit highly discriminate transcriptional, cytogenetic, and mutational spectra, in addition to divergent patient demographics and clinical behavior. These prognostic groups still must be validated in larger prospective studies, though the WNT subgroup is known to have the most favorable outcome.

A multimodal treatment approach is pursued in medulloblastoma, with surgery as the starting point of treatment. Medulloblastoma is sensitive to both chemotherapy and radiation therapy. With technologic advances in neurosurgery, neuroradiology, and radiation therapy, as well as identification of chemotherapy as an effective modality, the overall outcome among all patients approaches 60–

70%. Standard radiation treatment in standard-risk medulloblastoma incorporates craniospinal radiation at a total cumulative dose of 24 Gy, with a cumulative dose of 50-55 Gy to the tumor bed. Craniospinal radiation at this dose in children <3 yr old results in severe late neurologic sequelae, including microcephaly, learning disabilities, cognitive impairment, neuroendocrine dysfunction (growth failure, hypothyroidism, hypogonadism, absence/delay of puberty), and second malignancies. Similarly, in older children, late sequelae such as learning disabilities, neuroendocrine dysfunction, and second malignancies can occur.

These observations have resulted in stratification of treatment approaches into (1) patients <3 yr old; (2) standard-risk patients >3 yr old with surgical total resection and no disease dissemination (M0); and (3) high-risk patients >3 yr old with disease dissemination (M >0) and/or bulky residual disease after surgery. With the **risk-based approach** to treatment, children with high-risk medulloblastoma receive high-dose craniospinal radiation (36 Gy) with chemotherapy during and after radiation therapy. Since the dose of radiation depends on the risk stratification, complete staging with MRI of the spine before starting treatment is essential for the best chance of survival.

Approaches in young children (usually <3 yr) incorporate high-dose chemotherapy with peripheral stem cell reinfusion to avoid radiation therapy. OS in children with nonmetastatic medulloblastoma and gross total tumor resection approaches 85%. The presence of bulky residual tumor (56% survival) or metastases (38% survival) confers a poor prognosis. The molecular classification is being evaluated to stratify risk groups and tailor therapy accordingly. The WNT subgroup and nonmetastatic group 4 tumors are recognized as low-risk tumors that may qualify for reduced therapy. High-risk groups were defined as patients with metastatic SHH or group 4 tumors, where intensification of therapy is being profiled.

Supratentorial primitive neuroectodermal tumors (SPNETs) account for 2–3% of childhood brain tumors, primarily in children within the 1st decade of life. These tumors are similar histologically to medulloblastoma and are composed of undifferentiated or poorly differentiated neuroepithelial cells. Historically, patients with SPNETs have had poorer outcomes than those with medulloblastoma after combined-modality therapy. In current clinical trials, children with SPNETs are considered among the high-risk groups and receive dose-intense chemotherapy with craniospinal radiation therapy.

Atypical teratoid/rhabdoid tumor is a very aggressive embryonal malignancy that occurs predominantly in children <5 yr old and can occur at any location in the neuraxis. The histology demonstrates a heterogeneous pattern of cells, including rhabdoid cells that express epithelial membrane antigen and neurofilament antigen. The characteristic cytogenetic pattern is partial or complete deletion of chromosome 22q11.2 that is associated with mutation in the *INI1* gene. The relation between this mutation and tumorigenesis is unclear. Though the overall prognosis remains poor, intensive chemotherapy, focal radiation, and high-dose chemotherapy with stem cell rescue has shown a trend toward improved survival. This trend is noted more in patients who undergo complete resection of tumor and focal radiation. Newer data now suggest 3 molecular subtypes within this tumor, and the favorable response seen in some patients reaffirms the molecular intertumor heterogeneity

Pineal Parenchymal Tumors

The pineal parenchymal tumors are the most common malignancies after germ cell tumors that occur in the pineal region. These include **pineoblastoma** (Fig. 524.11), occurring predominantly in childhood; **pineocytoma** ; and the **mixed pineal-parenchymal tumors** . The therapeutic approach in this group of diseases is multimodal. There was significant concern regarding the location of these masses and the potential complications of surgical intervention. With developments in neurosurgical technique and surgical technology, the morbidity and mortality associated with these approaches have greatly decreased. Stereotactic biopsy of these tumors may be adequate to establish diagnosis; however, consideration should be given to total resection of the lesion before institution of additional therapy. Pineoblastoma, the more malignant variant, is considered a subgroup of childhood PNETs. Chemotherapy regimens incorporate cisplatin, cyclophosphamide (Cytoxan), etoposide (VP-16), and vincristine and/or lomustine. Data have shown that survival outcome of combined chemotherapy and radiation therapy in pineal-region PNETs approaches 70% at 5 yr, similar to that for medulloblastoma. Pineocytoma usually is approached with surgical resection.

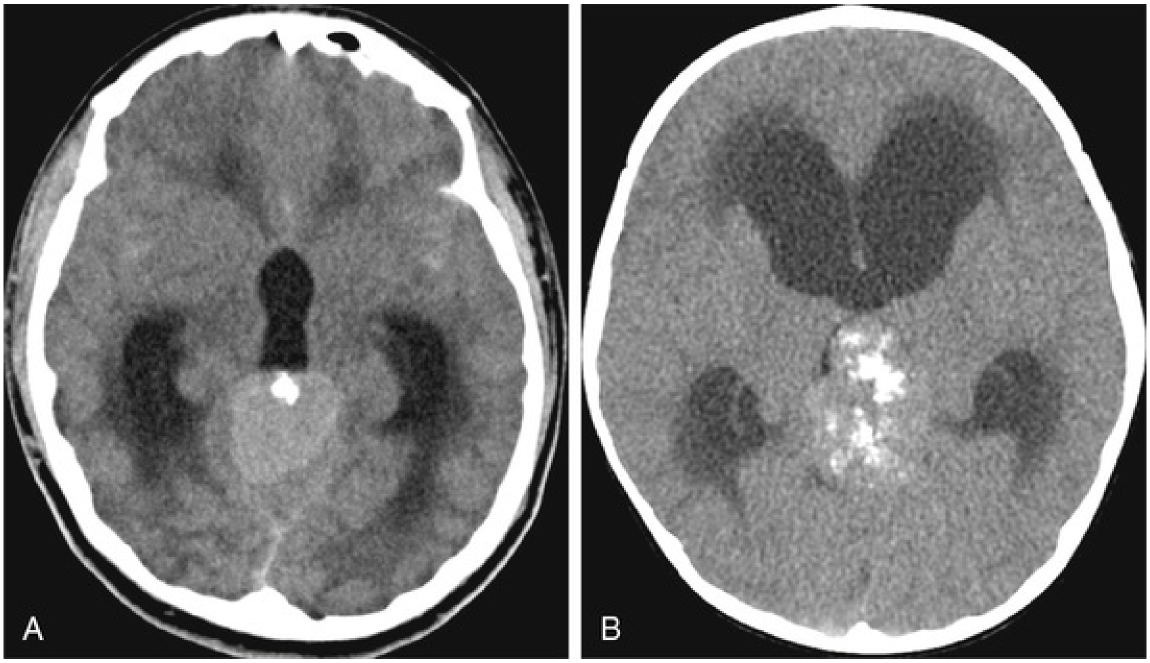

FIG. 524.11 Calcification pattern of germ cell tumor and pineoblastoma. A, Germ cell tumor with engulfment of the calcification within the pineal gland by the tumor. B, Pineoblastoma with exploded calcification along the periphery of the tumor. (From Tamrazi B, Nelson M, Bluml S: Pineal region masses in pediatric patients, Neuroimag Clin North Am 27:85–97, 2017, Fig 3, p 88.)

Craniopharyngioma

Craniopharyngioma (CP; WHO grade I) is a common tumor of childhood, accounting for 7–10% of all childhood tumors. Two histologic subtypes have been identified, **adamantinomatous** CP and **papillary** CP, each with specific origin and genetic alterations. *BRAF V600E* mutations were solely found in the papillary CP subgroup, which is a common type in adults, whereas *CTNNB1* mutations were exclusively detected in adamantinomatous CP, which is common in children. Children with CP often present with endocrinologic abnormalities (growth failure and delayed sexual maturation) and/or visual changes (decreased acuity or visual field abnormalities). These tumors are often large and heterogeneous, displaying both solid and cystic components, and occur within the suprasellar region. They are minimally invasive, adhere to adjacent brain parenchyma, and engulf normal brain structures. MRI demonstrates the solid tumor with cystic structures containing fluid of intermediate density, and CT may show calcifications (Fig. 524.12). Surgery is the primary treatment modality, with gross total resection curative. Controversy exists regarding the relative roles of surgery and radiation therapy in large, complex tumors.

Significant morbidity (panhypopituitarism, growth failure, visual loss) is associated with CPs and their therapy because of the anatomic location. There is no role for chemotherapy in CP.

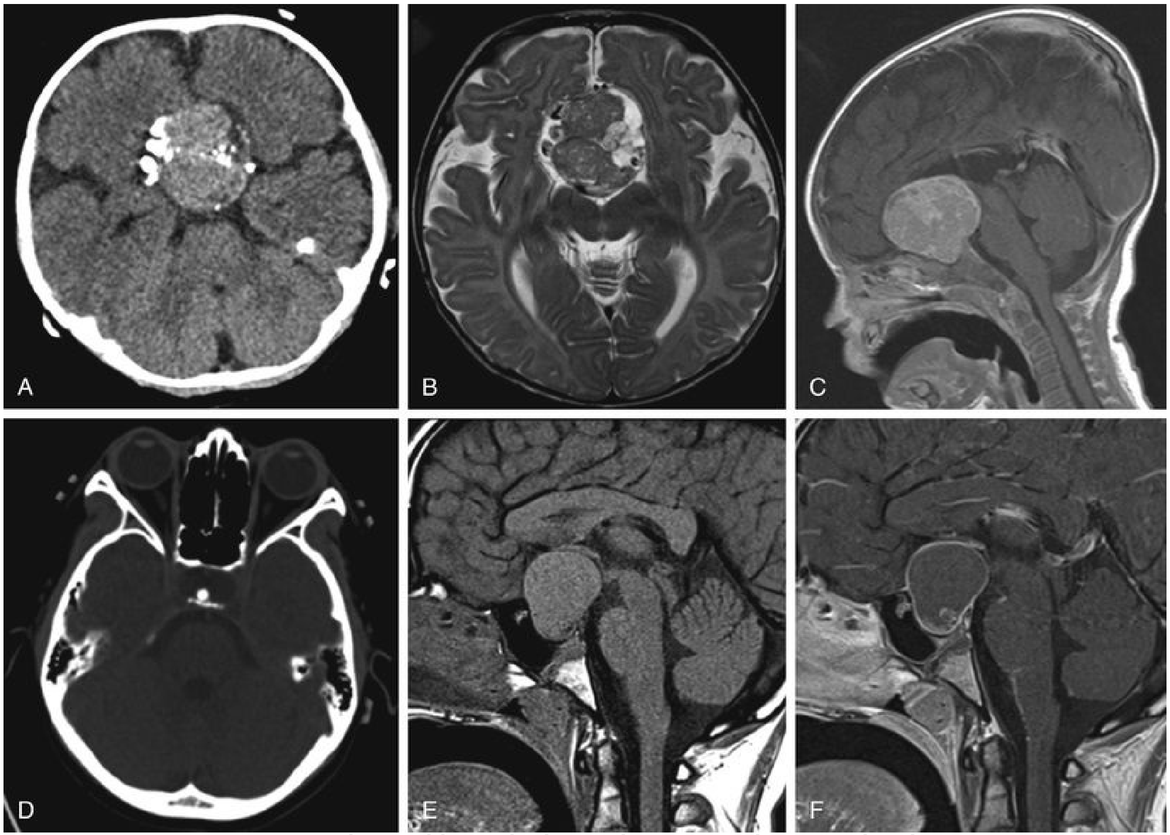

FIG. 524.12 Two patients with craniopharyngioma. A-C, The 1st patient has a predominantly solid sellar-suprasellar mass with internal calcifications, which are seen best on the axial CT image (A). The mass is predominantly T2 isointense to hypointense and there are few T2 hyperintense cystic components along the left aspect of the mass (B). The solid components show enhancement (C). D-F, The 2nd patient has a predominantly cystic sellar-suprasellar mass with internal calcification (D), intrinsic T1 hyperintensity of the cyst contents (E), and a thin rim of postcontrast enhancement (F). Both lesions result in posterior and superior displacement of the optic chiasm. (From Seeburg DP, Dremmen MHG, Huisman TAGM: Imaging of the sella and parasellar region in the pediatric population, Neuroimag Clin N Am 27:99–121, 2017, Fig 2, p 103.)

Germ Cell Tumors

Germ cell tumors of the CNS are a heterogeneous group and primarily tumors of childhood, arising predominantly in midline structures of the pineal and suprasellar regions (see Figs. 524.3 and 524.11). They account for 3–5% of pediatric brain tumors. The peak incidence of germ cell tumors occurs in children 10-12 yr old. Overall, there is a male preponderance, although there is a female preponderance for suprasellar tumors. Germ cell tumors occur multifocally in 5–10% of cases. This group of tumors is much more prevalent in Asian than in European populations. Delays in diagnosis can occur because these tumors have a particularly insidious course; the initial presenting symptoms may be subtle. As in peripheral germ cell tumors, the analysis of AFP and β-hCG levels may be useful in establishing the diagnosis and monitoring treatment response. Surgical biopsy is recommended to establish the diagnosis; however, secreting *germinomas* and *nongerminomatous germ cell tumors* may be diagnosed by protein marker elevations. Therapeutic approaches to germinomas and nongerminomatous germ cell tumors are different. Survival among patients with pure germinoma exceeds 90%. The postsurgical treatment of pure germinomas is somewhat controversial in defining the relative roles of chemotherapy and radiation therapy. Clinical trials have investigated the use of chemotherapy and reduced radiation and field after surgery in pure germinomas. The therapeutic approach to nongerminomatous germ cell tumors is more aggressive, combining more intense chemotherapy regimens with craniospinal radiation therapy. Survival rates among patients with nongerminomatous germ cell tumors are much lower than in those with germinoma, ranging from 40–70% at 5 yr. Trials have shown the benefit of the use of high doses of chemotherapy with peripheral blood stem cell rescue.

Tumors of the Brainstem

Tumors of the brainstem are a heterogeneous group and account for 10–15% of childhood primary CNS tumors. Outcome depends on tumor location, imaging characteristics, and the patient's clinical status. Patients with these tumors may present with motor weakness, cranial nerve dysfunction, cerebellar dysfunction, and signs of increased ICP. On the basis of MRI evaluation and clinical findings, tumors of the brainstem can be classified into 4 types: **focal** (5–10% of patients); **dorsally exophytic** (5–10%); **cervicomedullary** (5–10%); and **diffuse intrinsic pontine glioma (DIPG)** (70–85%) (Fig. 524.13). Surgical resection is the primary treatment approach for focal and dorsally exophytic tumors and leads to a favorable outcome. Histologically, these 2 groups usually are low-grade gliomas. Because of their location, cervicomedullary tumors may not be amenable to surgical resection but are sensitive to radiation therapy. DIPG, characterized by the diffuse, infiltrating grade II-IV glioma, is associated with a poor outcome independent of histologic diagnosis. These tumors are not amenable to surgical resection. Biopsy in children in whom MRI shows DIPG is controversial and is not recommended unless there are atypical radiographic findings suspicious for another diagnosis, such as infection, vascular malformation, myelination disorder, or metastatic tumor. Recent studies have unraveled the unique genetic makeup of this fatal brain cancer, with almost 80% found to harbor mutations in histone *H3.3* or *H3.1 (H3-K27M)* and 20% with mutations affecting the activin receptor gene (*ACVR1)*. Now, 3 molecularly distinct subgroups have been identified: H3-K27M, silent, and MYCN.

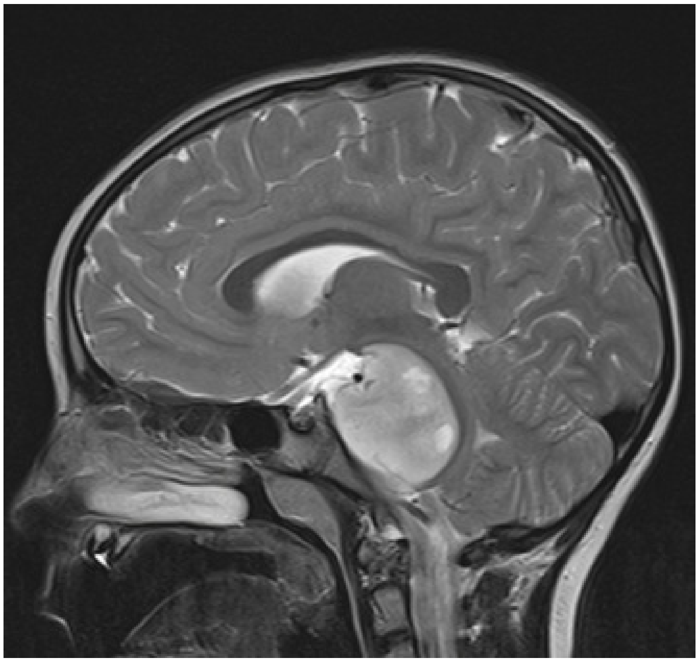

FIG. 524.13 T2-weighted sagittal MR image of a diffuse infiltrating pontine glioma in a 5 yr old girl presenting with headaches, left facial droop, and lethargy.

The standard treatment approach has been radiation therapy, and median survival with this treatment is 12 mo, at best. Use of chemotherapy, including high-dose chemotherapy with peripheral blood stem cell rescue, has not yet been of survival benefit in this group of patients. Current approaches include evaluation of investigational agents alone or in combination with radiation therapy, similar to approaches being pursued in patients with malignant gliomas.

Metastatic Tumors

Metastatic spread of other childhood malignancies to the brain is uncommon. Childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma can spread to the leptomeninges, causing symptoms of communicating hydrocephalus. **Chloromas** are collections of myeloid leukemia cells and can occur throughout the neuraxis. Rarely, brain parenchymal metastases occur from lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and clear cell sarcoma of the kidney. Therapeutic approaches are based on the specific histologic diagnosis and may incorporate radiation therapy, intrathecal chemotherapy, and systemic chemotherapy. **Medulloblastoma** is the childhood brain tumor that most often metastasizes extraneurally. Less often, extraneural metastases from malignant glioma, PNET, and ependymoma can occur. Ventriculoperitoneal shunts have been known to allow extraneural metastases, primarily within the peritoneal cavity but also systemically.

Complications and Long-Term Management

Data from the NCI SEER Program indicate that >70% of patients with childhood brain tumors will be long-term survivors. At least 50% of these survivors will experience chronic problems as a direct result of their tumors and treatment. These problems include chronic neurologic deficits (e.g., focal motor/sensory abnormalities), seizure disorders, neurocognitive deficits (e.g., developmental delays, learning disabilities), and neuroendocrine deficiencies (e.g., hypothyroidism, growth failure, delay/absence of puberty). These patients are also at significant risk for secondary malignancies. Supportive multidisciplinary interventions for children with brain tumors both during and after therapy may help improve the ultimate outcome. Optimal seizure management, physical therapy, endocrine management with timely growth hormone and thyroid replacement therapy, tailored educational programs, and vocational interventions can enhance the childhood brain tumor survivor's quality of life.

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CHAPTER 525

Neuroblastoma

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Neuroblastomas are embryonal cancers of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to intensive multimodal therapy. The causes of most cases remain unknown. Advances in the treatment of children with these tumors have improved outcomes, although many with aggressive forms of neuroblastoma still succumb to their disease despite intensive therapy.

Epidemiology

Neuroblastoma is the most common extracranial solid tumor in children and the most commonly diagnosed malignancy in infants. Approximately 600 new cases are diagnosed each year in the United States, accounting for 8–10% of childhood malignancies and one third of cancers in infants. Neuroblastoma accounts for >15% of the mortality from cancer in children. The median age of children at diagnosis of neuroblastoma is 22 mo, and 90% of cases are diagnosed by 5 yr of age. The incidence is slightly higher in boys and in Caucasian populations.

Pathology

Neuroblastoma tumors, which are derived from primordial neural crest cells, form a spectrum with variable degrees of neural differentiation, ranging from tumors with primarily undifferentiated small round cells (neuroblastoma) to tumors consisting of mature and maturing schwannian stroma with ganglion cells (ganglioneuroblastoma or ganglioneuroma). The tumors may resemble other **small round blue cell tumors,** such as rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma. The prognosis of children with neuroblastoma varies with the histologic features of the tumor, as dictated by the presence and amount of schwannian stroma, the degree of tumor cell differentiation, and the mitosis-karyorrhexis index.

Pathogenesis

The etiology of neuroblastoma in most cases remains unknown. Familial neuroblastoma accounts for 1–2% of all cases, is associated with a younger age at diagnosis, and is linked to mutations in the *PHOX2B* and *ALK* genes. The *BARD1* gene has also been identified as a major genetic contributor to neuroblastoma risk. Neuroblastoma is associated with other neural crest disorders, including Hirschsprung disease, central hypoventilation syndrome, neurofibromatosis type 1, and potentially congenital cardiovascular malformations (Table 525.1). Children with Beckwith-Wiedemann syndrome and hemihypertrophy also have a higher incidence of neuroblastoma. Increased incidence of neuroblastoma is associated with some maternal and paternal occupational chemical exposures, farming, and work related to electronics, although no single environmental exposure has been shown to directly cause neuroblastoma.

Table 525.1

Syndromes Associated With Neuroblastoma

SYNDROME	FEATURES
Pepper syndrome	Massive involvement of the liver with metastatic disease, with or without respiratory distress.
Horner syndrome	Unilateral ptosis, myosis, and anhidrosis associated with a thoracic or cervical primary tumor. Symptoms do not resolve with tumor resection.
Hutchinson syndrome	Limping and irritability in young child associated with bone and bone marrow metastases.
Opsoclonus-myoclonus–ataxia syndrome	Myoclonic jerking and random conjugate eye movements with or without cerebellar ataxia. Often associated with a biologically favorable and differentiated tumor. The condition is likely immune mediated, may not resolve with tumor removal, and often exhibits progressive neuropsychologic sequelae.
Kerner-Morrison syndrome	Intractable secretory diarrhea caused by tumor secretion of vasointestinal peptides. Tumors are generally biologically favorable.
Neurocristopathy syndrome	Neuroblastoma associated with other neural crest disorders, including congenital hypoventilation syndrome or Hirschsprung disease.

	Germline mutations in the paired homeobox gene *PHOX2B* have been identified in a subset of patients with this disease.
ROHHAD	Approximately 40% may have neural crest–derived tumors. Obesity and neurologic issues may be part of a paraneoplastic syndrome.

ROHHAD, Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation.

Adapted from Park JR, Eggert A, Caron H: Neuroblastoma: biology, prognosis, and treatment, *Pediatr Clin North Am* 55:97–120, 2008.

Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the *MYCN* (*N-myc*) protooncogene and tumor cell DNA content, or ploidy (Table 525.2). Amplification of *MYCN* is strongly associated with advanced tumor stage and poor outcomes. **Hyperdiploidy** confers better prognosis if the child is <18 mo old at diagnosis and if amplification of *MYCN* is not present. Other chromosomal abnormalities, including loss of heterozygosity of 1p, 11q, and 14q and gain of 17q, may be found in neuroblastoma tumors and have been associated with worse outcomes. In addition, many other biologic factors are associated with neuroblastoma outcomes, including tumor vascularity and the expression levels of nerve growth factor receptors (TrkA, TrkB), ferritin, lactate dehydrogenase, ganglioside GD2, neuropeptide Y, chromogranin A, CD44, multidrug resistance–associated protein, and telomerase. These factors and many others are under investigation in clinical trials to determine whether they can be used to reduce therapy for children predicted to fare well with minimal therapy or to intensify therapy for those predicted to be at high risk for relapse.

Table 525.2

International Neuroblastoma Risk Group (INRG) Pretreatment Classification Schema

INRG STAGE	AGE (mo)	HISTOLOGIC CATEGORY	GRADE OF TUMOR DIFFERENTIATION	*MYC-N*	11Q ABERRATION	PLOIDY	PRETRE RISK GR
L1/L2		GN Maturing GNB Intermixed					A (very lo
L1		Any, except GN Maturing or GNB Intermixed		NA			B (very lo
				Amplified			K (high)
L2	<18	Any,		NA	No		D (low)

		except GN Maturing or GNB Intermixed			Yes		G (interme
	≥18	GNB nodular neuroblastoma	Differentiating	NA	No		E (low)
					Yes		H (interme
			Poorly differentiated or undifferentiated	NA			H (interme
				Amplified			N (high)
M	<18			NA		Hyperdiploid	F (low)
	<12			NA		Diploid	I (interme
	12 to <18			NA		Diploid	J (interme
	<18			Amplified			O (high)
	≥18						P (high)
MS	<18			NA	No		C (very lo
					Yes		Q (high)
				Amplified			R (high)

GN, Ganglioneuroma; GNB, ganglioneuroblastoma; NA, not amplified.

From Pinto NR, Applebaum MA, Volchenboum SL, et al: Advances in risk classification and treatment strategies for neuroblastoma, *J Clin Oncol* 33(27):3008–3017, 2015 (Table 1).

Clinical Manifestations

Neuroblastoma may develop at any site of sympathetic nervous system tissue. Approximately half of neuroblastoma tumors arise in the adrenal glands, and most of the remainder originate in the paraspinal sympathetic ganglia. **Metastatic spread** , which is more common in children >1 yr old at diagnosis, occurs through local invasion or distant hematogenous or lymphatic routes. The most common sites of metastasis are the regional or distant lymph nodes, long bones and skull, bone marrow, liver, and skin. Lung and brain metastases are rare, occurring in <3% of cases.

The signs and symptoms of neuroblastoma reflect the tumor site and extent of disease and may mimic other disorders, which can result in a delayed diagnosis. Metastatic disease can cause a variety of signs and symptoms, including fever, irritability, failure to thrive, bone pain, cytopenias, bluish subcutaneous nodules, orbital proptosis, and periorbital ecchymoses (Fig. 525.1). Localized disease can manifest as an asymptomatic mass or can cause symptoms from mass effect, which in certain cases can result in spinal cord compression, bowel obstruction, and superior vena cava syndrome.

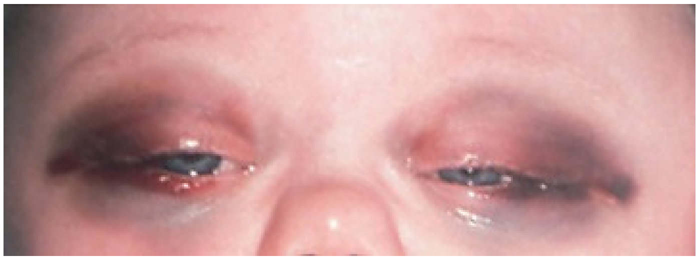

FIG. 525.1 Periorbital metastases of neuroblastoma with ecchymoses and proptosis.

Children with neuroblastoma can also present with associated neurologic signs and symptoms. Neuroblastoma originating in the superior cervical ganglion can result in **Horner syndrome.** Paraspinal neuroblastoma tumors can invade the neural foramina, causing spinal cord and nerve root compression. Neuroblastoma can also be associated with a paraneoplastic syndrome of autoimmune origin, termed **opsoclonus-myoclonus–ataxia syndrome** , in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination, and cognitive dysfunction. Some tumors produce catecholamines that can cause increased sweating and hypertension, and may release vasoactive intestinal peptide, causing a profound secretory diarrhea. Children with extensive tumors can also experience tumor lysis syndrome and disseminated intravascular coagulation. Infants <18 mo old also can present in unique fashion, termed **stage MS** (previously 4S; see later), with widespread subcutaneous tumor nodules, massive liver involvement, limited bone marrow disease, and a small primary tumor without bone involvement or other metastases. The stage MS disease can spontaneously regress. The enigmatic characteristics of neuroblastoma with paraneoplastic syndromes and spontaneous regression under some circumstances have led some researchers to suggest that neuroblastoma may originate as a neurodevelopmental disorder.

Diagnosis

Neuroblastoma is usually discovered as a mass or multiple masses on plain radiography, CT, or MRI (Figs. 525.2*A* and 525.3). The mass often contains calcification and hemorrhage that can allow it to be appreciated on plain radiography or CT. Prenatal diagnosis of perinatal neuroblastoma on maternal ultrasound scans is sometimes possible. Tumor markers, including the catecholamine metabolites homovanillic acid (HVA) and vanillylmandelic acid

(VMA), are elevated in the urine of approximately 95% of patients and help to confirm the diagnosis. A pathologic diagnosis is established from tumor tissue obtained by biopsy. Neuroblastoma can be confirmed without a primary tumor biopsy if small round blue tumor cells are observed in bone marrow samples (Fig. 525.4) and VMA or HVA levels are elevated in the urine.

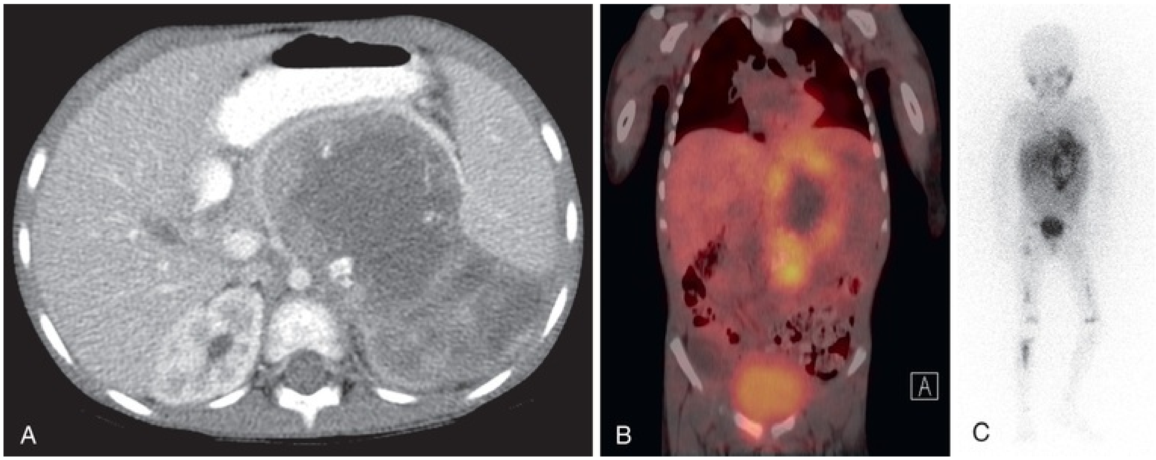

FIG. 525.2 **A,** CT scan of an abdominal neuroblastoma with central necrosis at diagnosis. **B,** Coronal fused CT and metaiodobenzylguanidine (MIBG) image of same child with extensive retroperitoneal mass and central necrosis, probably an adrenal primary with extensive lymph node involvement. **C,** MIBG-avid neuroblastoma with increased uptake of radiolabeled tracer can be detected in multiple sites of disease, including bone and soft tissue.

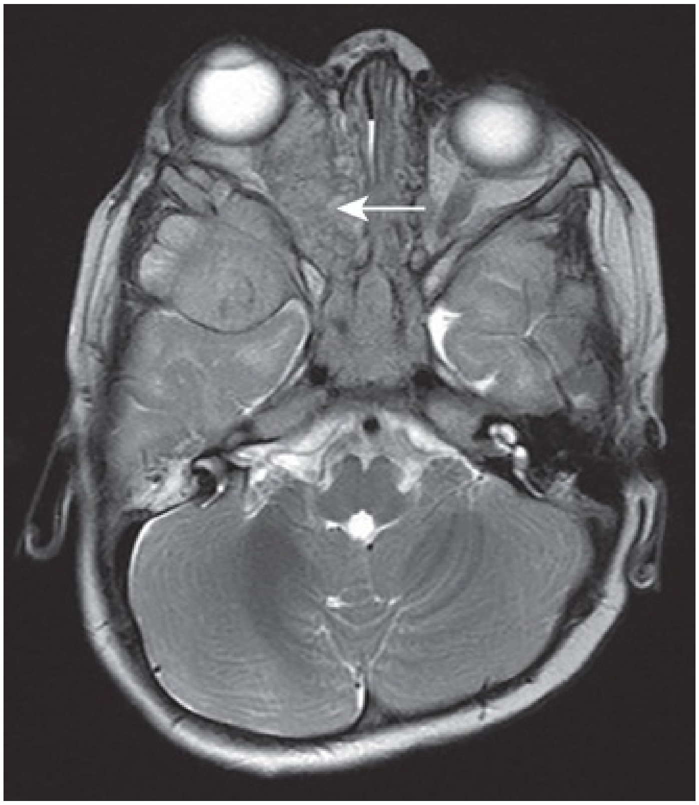

FIG. 525.3 Axial brain MRI scan after gadolinium enhancement. *White arrow* points to the hypointense intraorbital mass in the right orbit. (From Alaghband P, Long V: Periorbital ecchymosis, *J Pediatr* 168:245, 2016.)

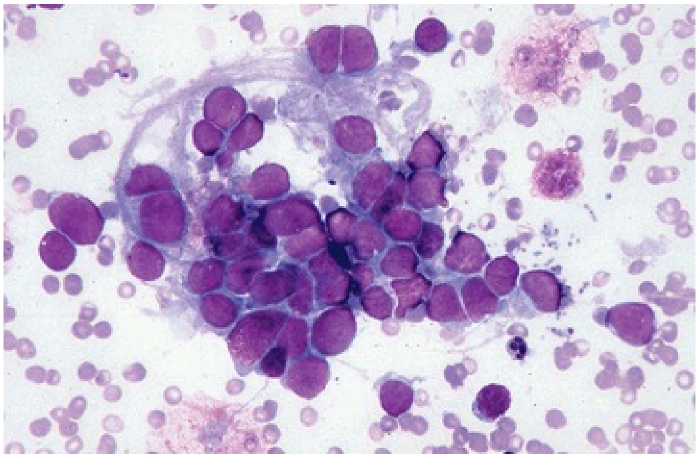

FIG. 525.4 Neuroblastoma cells aspirated from the bone marrow. Clumps of cells often contain 3 or more cells with or without evidence of rosette formation. Rosettes of cells surrounding an inner mass of fibrillary material are characteristic of neuroblastoma.

Evaluations for metastatic disease should include CT or MRI of the chest and abdomen, bone scans to detect cortical bone involvement, and at least 2 independent bone marrow aspirations and biopsies to evaluate for marrow disease. Iodine-123 metaiodobenzylguanidine (^{123} I-MIBG) studies should be used when available to better define the extent of disease (see Fig. 525.2*B* and *C*). PET combined with CT or MRI is another useful imaging method. MRI of the spine should be performed in cases with suspected or potential spinal cord compression, but imaging of the brain with either CT or MRI is not routinely performed unless dictated by the clinical presentation.

The **International Neuroblastoma Risk Group (INRG) Staging System (INSS)** is used to stage patients with neuroblastoma and is based on the extent of disease as determined by imaging at diagnosis. Extent of locoregional disease is based on specific local *image-defined risk factors* (IDRFs). **L1** tumors (previously classified as INSS stage 1) are localized and confined to 1 body compartment without any IDRFs. **L2** tumors (previously classified as INSS stages 2 and 3) refer to localized tumors with the presence of IDRFs. Disseminated tumors with metastases to bones, bone marrow, liver, distant lymph nodes, and other organs are staged as **M** (previously classified as INSS stage 4). Stage **MS** (previously stage 4S) refers to neuroblastoma in children <18 mo old with dissemination to liver, skin, or bone marrow without bone involvement and with a primary tumor that would otherwise be staged as L1 or L2.

Treatment

Treatment strategies for neuroblastoma have changed dramatically over the past 20 yr, with significant reduction in treatment intensity for children who have localized low-risk tumors and with continued increased treatment intensity and the addition of novel agents for treatment of children who have high-risk or recurrent disease. Patient age and tumor stage are combined with cytogenetic and molecular features of the tumor to determine the treatment risk group and estimated prognosis for each patient (see Table 525.2). Treatment for children with low-risk neuroblastoma typically includes surgery for stages L1 and L2 and observation for asymptomatic stage MS, with cure rates generally >90% without further therapy. Treatment with chemotherapy or radiation for the rare child with local recurrence can still be curative. Children with **spinal cord compression** at diagnosis may require urgent treatment with chemotherapy, surgery, or radiation to avoid neurologic damage. Stage MS neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy. Chemotherapy or resection of the primary tumor does not improve survival rates, but for infants with massive liver involvement and respiratory compromise, chemotherapy or radiation is used to alleviate symptoms. For children with stage MS neuroblastoma who require treatment for symptoms, the survival rate is 81%.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and in some cases, radiation therapy. The chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide, and doxorubicin given over several months. Radiation therapy is used for tumors with incomplete response to chemotherapy. Children with intermediate-risk neuroblastoma, including children with L2 disease and infants with M disease (both with favorable characteristics), have an excellent prognosis and >90% survival with this moderate treatment. In this intermediate-risk group, obtaining adequate diagnostic material for determination of the underlying biologic features of the tumor, such as the Shimada pathologic classification and *MYCN* gene amplification, is critical, so that children with unfavorable characteristics can receive more-aggressive treatment and those with favorable features can be spared excessive toxic therapy.

Children with **high-risk neuroblastoma** historically have had poor long-term survival rates between 25% and 35% with treatment that consisted of intensive chemotherapy, high-dose chemotherapy with autologous stem cell rescue, surgery, radiation, and 13-*cis* -retinoic acid (isotretinoin, Accutane). Induction chemotherapy for children with high-risk neuroblastoma includes combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. After completion of induction chemotherapy, resection of the residual primary tumor is followed by high-dose chemotherapy with autologous stem cell rescue and focal radiation therapy to tumor sites. A national cooperative group trial demonstrated significantly better survival with chemotherapy plus autologous stem cell rescue than with chemotherapy alone. The further addition of the differentiating agent 13-*cis* -retinoic acid following autologous stem cell transplantation resulted in further improvements in survival rates. In addition, a national clinical trial has demonstrated an increase in short-term survival rates with the addition of the monoclonal antibody (mAb) ch14.18 (**dinutuximab**), interleukin-2, and granulocyte-macrophage colony-stimulating factor to 13-*cis* -retinoic acid therapy. This mAb targets a diasialoganglioside, GD2, which has ubiquitous expression on neuroblastoma cells; incorporation of the mAb into consolidative therapy after autologous stem cell transplant improves the 2-yr event-free survival from 46.5% to 66.5%. Dinutuximab is approved by the U.S. Food and Drug Administration (FDA) as a standard of care for this subset of patients. The incorporation of tandem autologous stem cell transplant (2 separate autologous stem cell transplants with differing conditioning regimens) may further improve outcomes for patients with high-risk disease.

Cases of high-risk neuroblastoma are associated with frequent relapses, and children with recurrent neuroblastoma have a <50% response rate to alternative chemotherapy regimens. Therapies currently under investigation include new chemotherapeutic agents as well as novel therapies directed against critical intracellular signaling pathways, radiolabeled targeted agents (e.g., *therapeutic* ^{131} I-MIBG), immunotherapy, and antitumor vaccines.

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CHAPTER 526

Neoplasms of the Kidney

526.1

Wilms Tumor

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Keywords

abdominal mass
Beckwith-Weidemann syndrome
Denys-Drash syndrome
diffuse anaplasia
favorable histology
gain of 1q
loss of heterozygosity
nephroblastoma
renal tumor
nephrogenic rests
WAGR
Wilms tumor

Wilms tumor, also known as **nephroblastoma** , is the most common primary malignant *renal* tumor of childhood. It is the second most common malignant abdominal tumor in childhood after neuroblastoma. The most common sites of metastases are the lungs, regional lymph nodes, and liver. Histologically, the classic Wilms tumor is made up of varying proportions of blastemal, stromal, and epithelial cells, recapitulating stages of normal renal development. The treatment includes surgery and chemotherapy with or without radiotherapy. The use of multimodality treatment and multiinstitutional cooperative group trials has dramatically improved the cure rate of Wilms tumor from <30% to >90% (Table 526.1).

Table 526.1

Four-Year Outcomes for Patients With Wilms Tumor*

HISTOLOGY AND OTHER RISK FACTORS	STAGE	RECURRENCE-FREE SURVIVAL	OVERALL SURVIVAL
Favorable, age <2 yr, tumor <550 g, treated with nephrectomy only	I	84% at 5 yr	98% at 5 yr
Favorable, no LOH	I/II	91%	98%
Favorable, LOH 1p and 16q	I/II	75%	91%
Favorable, no LOH	III/IV	83%	92%
Favorable, LOH 1p and 16q	III/IV	66%	78%
Favorable, any LOH	V	61%	81%
Diffuse anaplasia	I	68%	79%
Diffuse anaplasia	II	83%	82%
Diffuse anaplasia	III	65%	67%
Diffuse anaplasia	IV	33%	33%

* Treated in the National Wilms Tumor Study-5 according to histology and stage.

LOH, Loss of heterozygosity.

Epidemiology

Wilms tumor accounts for 6% of pediatric malignancies and >95% of kidney tumors in children. In the United States, incidence of Wilms tumor is approximately 7 cases per 1 million children <15 yr of age per year, and about 650 new cases are diagnosed each year. Approximately 75% of the cases occur in children <5 yr old, with a peak incidence at 2-3 yr. It can arise in one or both kidneys; the incidence of bilateral Wilms tumors is 7%. The male/female ratio is 0.92 to 1 in unilateral disease and 0.6 to 1 in bilateral disease. Most cases are sporadic, but approximately 2% of patients have a family history. In 8–10% of patients, Wilms tumor is observed in the context of hemihypertrophy, aniridia, genitourinary anomalies, and a variety of rare syndromes, including **Beckwith-**

Weidemann syndrome (BWS) and **Denys Drash syndrome** (Table 526.2). An earlier age at diagnosis and an increased incidence of bilateral disease are generally observed in syndromic and familial cases.

Table 526.2

Syndromes Associated With Wilms Tumor

SYNDROME	CLINICAL CHARACTERISTICS	GENETIC ALTERATION
Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation (WAGR)	Aniridia, genitourinary abnormalities, mental retardation	Del 11p13 (*WT1* and *PAX6*)
Denys-Drash syndrome	Early-onset renal failure with renal mesangial sclerosis, male pseudohermaphrodism	*WT1* missense mutation
Beckwith-Wiedemann syndrome	Organomegaly (liver, kidney, adrenal, pancreas) macroglossia, omphalocele, hemihypertrophy	Unilateral paternal disomy, duplication of 11p15.5, loss of imprinting, mutation of *p57KIP57* Del 11p15.5 *IGF2* and *H19* imprinting control region
Frasier syndrome	Undermasculinized external genitalia, focal segmental glomerulosclerosis, gonadoblastoma	*WT1* intron 9 variants affecting splicing
Fanconi anemia	Bone marrow failure, short stature, microcephaly, café-au-lait spots, developmental delay	*BRCA2, PALB2*
Trisomy 18	Cognitive impairment, hypertonia, prominent occiput, micrognathia, low-set and malformed ears, overlapping fingers, ventricular septal defects	Trisomy 18
Perlman syndrome	Polyhydramnios, macrosomia, distinctive facial features, renal dysplasia, nephroblastomatosis, multiple congenital anomalies	*DIS3L2*

Etiology: Genetics and Molecular Biology

Wilms tumor is thought to be derived from incompletely differentiated renal mesenchyme, and tumors are typically composed of cells reminiscent of the undifferentiated and partially differentiated cells that normally arise from renal mesenchyme. Foci of benign, undifferentiated mesenchyme (**nephrogenic rests**) that persist abnormally in the kidney into postnatal life are observed in approximately 1% of children in the general population, but are present in up to 90% of children who have a family history of Wilms tumor, develop bilateral tumors, or display features of Wilms tumor–related syndromes. Nephrogenic rests usually regress or differentiate, but those that persist can become malignant.

The first identified Wilms tumor gene, *WT1* , located at 11p13, is homozygously mutated in 10–15% of tumors, resulting in loss of function of the encoded zinc finger transcription factor. The majority of *WT1* mutations are somatic; however, *WT1* mutations can also be germline. Germline truncating mutations are usually associated with Wilms tumor in the context of genitourinary anomalies or the **WAGR syndrome** (Wilms tumor, aniridia, genitourinary anomalies, mental retardation). Missense germline mutations are usually observed in children with Denys-Drash syndrome, resulting in early-onset renal failure. In instances of germline mutation, the wild-type allele present in the germline is mutated or lost in the tumor, resulting in loss of WT1 function. Somatic ablation of *WT1* in the developing mouse kidney results in a block in the differentiation of the metanephric mesenchyme. Interestingly, nephrogenic rests assessed from patients heterozygous for a germline *WT1* mutation are homozygous for the *WT1* mutation, with additional somatic mutations observed in the autologous tumors. The vast majority of *WT1* mutations are deletion/truncating mutations or missense mutations that affect amino acid residues critical for WT1 function.

The **Wnt signaling pathway** plays a critical role in regulating the differentiation of the fetal kidney. *CTNNB1* encodes β-catenin, which has a major regulatory point in this pathway, and *CTNNB1* mutations are observed in approximately 15% of Wilms tumors, very often those that have sustained *WT1* mutations. *WTX* , a gene located on the X chromosome that encodes a protein that also plays a role in Wnt pathway regulation, is mutated in approximately 20% of tumors. *CTNNB1* and *WTX* mutations are somatic.

Consistent with the etiology of Wilms tumor being grounded in aberrant kidney development, genes that regulate the proliferation and differentiation of kidney progenitors have been identified to be mutated in tumors. One class of genes encodes proteins essential for the biogenesis of mature miRNAs and are mutated in one fifth to one third of Wilms tumors. *DROSHA* missense mutations in the catalytic domains critical for the processing of pre-miRNA occur in approximately 10% of tumors. These are invariably heterozygous, and in vitro studies have supported a dominant-negative mechanism of action by which they impair miRNA biogenesis. Additionally, mutations genes encoding other components of the miRNA biogenesis pathway (*DICER, DGCR8 XPO5* , and *TARBP2*) are observed in Wilms tumor. *DICER1* mutations are usually missense mutations and can be somatic or germline. Germline *DICER1* mutations are observed, albeit infrequently, in Wilms tumor families and, more frequently, in families with pleuropulmonary blastoma. Mutations in these miRNA processing genes are associated with reduced expression of the Let-7 family of miRNAs.

An interrelated molecular pathway also critical for regulating progenitor proliferation and differentiation is the MYCN-SIX1/2-EYA1 pathway. Somatic mutations in *MYCN* , *SIX1* , and *SIX2* are observed in approximately 10% of tumors, with an additional approximately 15% of tumors displaying *MYCN* copy number increases.

The initial identification of *WT1* mutations in tumors demonstrated that aberrant transcriptional regulation (that can act in a variety of biologic processes) is important in the etiology of some Wilms tumors. This conclusion is underscored by the identification of mutations in genes encoding proteins that have roles in epigenetic regulation of transcription and transcriptional elongation. These include somatic mutations in *MLLT1* , *ARID1A* , and *SMARCA4,* at a frequency of approximately 4–5% each.

Somatic mutation of the p53 gene, *TP53* , is observed in approximately 5% of tumors and is associated with **anaplastic tumor** histology, a poor prognostic feature of Wilms tumor.

In approximately 70% of tumors, loss of heterozygosity (usually copy number neutral) or loss of imprinting at imprinted loci at 11p15 is observed. This epigenetic alteration often results in biallelic expression of *IGF2* , a normally imprinted gene that encodes insulin-like growth factor 2, in addition to the loss of imprinting of other 11p15 genes. Families with Beckwith-Weidemann syndrome, a somatic overgrowth syndrome in which predisposition to embryonal tumors (including Wilms tumor) is observed, have been genetically linked to 11p15, and microdeletions within the *IGF2* imprinting control region are present in BWS families in whom Wilms tumor is observed.

Allelic imbalances have been identified in Wilms tumors, particularly loss of heterozygosity at 1p and 16q, which has been associated with increased risk of recurrence. Gain of chromosome 1q was found to be associated with inferior survival in unilateral favorable-histology Wilms tumor.

In patients with a family history of Wilms tumor, predisposition is inherited as an autosomal dominant trait with incomplete penetrance. Predisposition to other tumor types or other phenotypes is not observed in the majority of these families. Germline mutations have been identified in a minority of families, and each of those genes identified (e.g., *WT1* , *DICER1* , *MYCN* , *REST* , *BRCA2*) is altered in <5% of Wilms tumor families.

Clinical Presentation

The most common initial clinical presentation for Wilms tumor is the incidental discovery of an asymptomatic **abdominal mass** by parents while bathing or clothing an affected child or by a physician during a routine physical examination (Table 526.3). At presentation, the mass can be quite large, because retroperitoneal masses can grow unhampered by strict anatomic boundaries. Functional defects in paired organs such as the kidney, with good functional reserve, are also unlikely to be detected early. Children with direct access to pediatricians vs generalists as primary caregivers are more likely to be diagnosed early and to have smaller tumors and less advanced stage at diagnosis. Hypertension is present in about 25% of patients at presentation and has been attributed to increased renin activity. Abdominal pain (40%), gross painless hematuria (18%), and constitutional symptoms such as fever, anorexia, and weight loss are other findings at diagnosis. Occasionally, rapid abdominal enlargement and anemia occur because of bleeding into the renal parenchyma or pelvis. Wilms tumor thrombus extends into the inferior vena cava (IVC) in 4–10% of patients and rarely into the right atrium; dislodgment of the intravascular tumor may produce a fatal **pulmonary embolism** . Patients might also have microcytic anemia from iron deficiency or anemia of chronic disease, polycythemia, elevated platelet count, and acquired deficiency of von Willebrand factor or factor VII deficiency.

Table 526.3

Differential Diagnosis of Abdominal and Pelvic Tumors in Children

TUMOR	PATIENT AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Wilms tumor	Preschool	Unilateral flank mass, aniridia, hemihypertrophy	Hematuria, polycythemia, thrombocytosis, elevated partial thromboplastin time
Neuroblastoma	Preschool	Gastrointestinal/genitourinary obstruction, raccoon eyes, myoclonus-opsoclonus, diarrhea, skin nodules	Increased urinary vanillylmandelic acid, homovanillic acid, or ferritin; stippled calcification in the mass
Non-Hodgkin lymphoma	>1 yr	Intussusception in >2 yr old	Increased lactate dehydrogenase; blood cytopenia caused by bone marrow involvement
Rhabdomyosarcoma	All	Gastrointestinal/genitourinary obstruction, abdominal pain, vaginal bleeding, paratesticular mass	Hypercalcemia; blood cytopenia caused by bone marrow involvement

Germ cell tumor/teratoma	Preschool, teenage	*Females:* Abdominal pain, vaginal bleeding *Males:* Testicular mass, new-onset hydrocele, sacrococcygeal mass/dimple	Increased β–human chorionic gonadotropin, increased α-fetoprotein
Hepatoblastoma	Birth-3 yr	Right upper quadrant mass, jaundice Early puberty in males	Increased α-fetoprotein
Hepatocellular carcinoma	School age, teenage	Right upper quadrant mass, jaundice, hepatitis B, cirrhosis	Increased α-fetoprotein

Diagnosis and Differential Diagnosis

An abdominal mass in a child should be considered malignant until diagnostic imaging, laboratory findings, and pathology can define its true nature (see Table 526.3). Imaging studies include plain abdominal radiography, abdominal ultrasonography (US), and CT of the abdomen to define the intrarenal origin of the mass and differentiate it from adrenal masses (e.g., neuroblastoma) and other masses in the abdomen. Abdominal US helps differentiate solid from cystic masses. Wilms tumor might show focal areas of necrosis or hemorrhage and hydronephrosis because of obstruction of the renal pelvis by the tumor. US with Doppler imaging of renal veins and the IVC is a useful first study to identify Wilms tumor, evaluate the collecting system, and demonstrate tumor thrombi in the renal veins and IVC. However, its routine use after CT has been performed is not required.

CT is useful to define the extent of the disease, integrity of the contralateral kidney, and metastasis (Figs. 526.1 and 526.2). MRI requires sedation in young children and is not routinely used. However, MRI may be helpful in defining an extensive tumor thrombus that extends up to the level of the hepatic veins, or even into the right atrium, and to distinguish Wilms tumor from nephrogenic rests. Chest CT is more sensitive than chest radiography to screen for pulmonary metastasis and is preferably performed before surgery, because effusions and atelectasis can confound the interpretation of postoperative imaging studies. A bone scan is performed if the histologic diagnosis confirms clear cell sarcoma of the kidney or rhabdoid tumor of the kidney, to look for bone metastasis. Brain imaging with CT or MRI is also obtained in cases of clear cell sarcoma or rhabdoid tumor of the kidney because these tumors can spread to the brain.

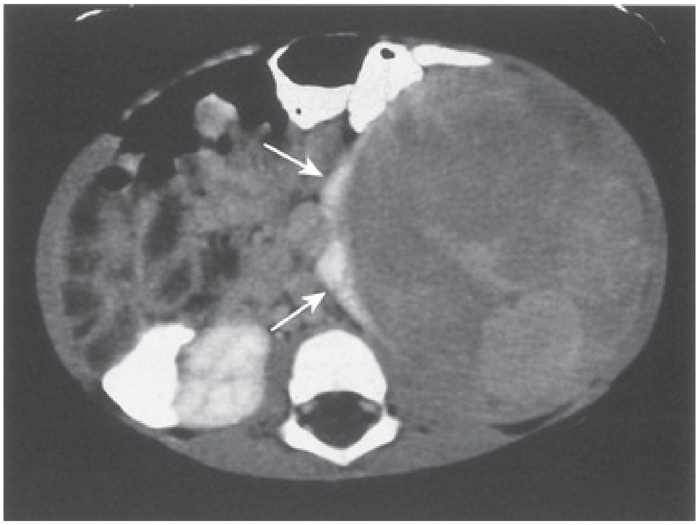

FIG. 526.1 **Large heterogeneous Wilms tumor in left kidney. The residual renal parenchyma is displaced medially *(arrows)* . (From Haaga JR, Boll DT, editors: *CT and MRI of the whole body,* vol II, ed 6, Philadelphia, 2017, Elsevier, Fig 54-84, p 1816.)**

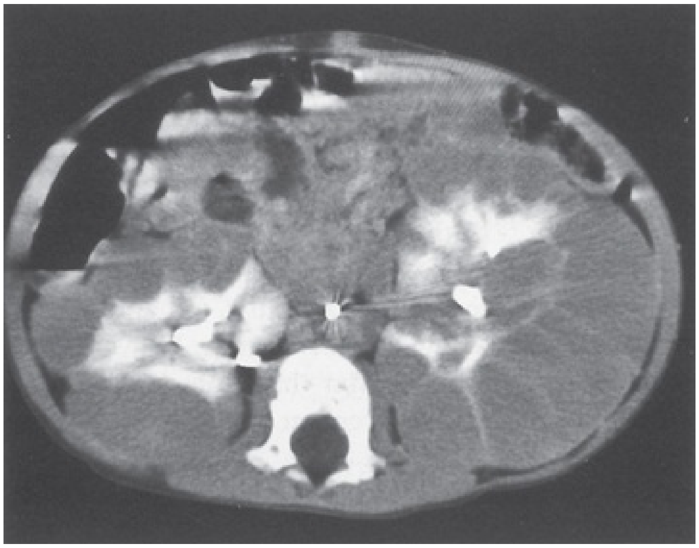

FIG. 526.2 **Multicentric and bilateral Wilms tumors. The tumors have a low density and compress residual enhancing renal tissue. (From Haaga JR, Boll DT, editors: *CT and MRI of the whole body,* vol II, ed 6, Philadelphia, 2017, Elsevier, Fig 54-86, p 1817.)**

Wilms tumor lesions are metabolically active and concentrate fluorodeoxyglucose (FDG). Regional spread and metastatic lesions can be visualized on positron emission tomography (PET)/CT scanning. The diagnosis is usually made by imaging studies and confirmed by histology at the time of nephrectomy. Although biopsy is a reliable diagnostic tool, it is discouraged since it results in disease upstaging. A core needle biopsy obtained through a posterior approach (to limit contamination of the peritoneal cavity) should be performed in cases of unusual presentation (>10 yr old, signs of infection, inflammation) or unusual imaging findings (significant adenopathy, no renal parenchyma seen, intratumoral calcification).

Treatment

Children's Oncology Group (COG) protocols and the **International Society of Pediatric Oncology (SIOP)** protocols differ in their initial treatment approach. *COG advocates upfront surgery* prior to initiating treatment, whereas *SIOP recommends preoperative chemotherapy.* Each approach has advantages and limitations, but they have similar outcomes. Early surgery provides accurate diagnosis and staging and can facilitate **risk-adapted therapy** . Preoperative chemotherapy can make surgery easier and reduces the risk of intraoperative tumor rupture and hemorrhage. Surgery entails a **radical nephrectomy** , with meticulous dissection to avoid rupture of the tumor capsule, and lymph node sampling despite the absence of abnormal nodes on preoperative imaging studies or intraoperative assessment. **Partial nephrectomy** is performed in patients with bilateral disease or those with unilateral Wilms tumor and predisposing syndrome such as the Denys-Drash and WAGR syndromes, to minimize the risk of future renal failure.

Prognostic factors for risk-adapted therapy include age, stage, tumor weight, and loss of heterozygosity at chromosomes 1p and 16q (Table 526.4). Histology plays a major role in risk stratification of Wilms tumor. Absence of anaplasia is considered a favorable histologic finding. Presence of anaplasia is further classified as focal or diffuse, both of which are unfavorable histologic findings.

Table 526.4

Children's Oncology Group (COG) Staging of Wilms Tumor

STAGE	DESCRIPTION
I	Tumor *confined to the kidney* and completely resected. Renal capsule or sinus vessels not involved. Tumor not ruptured or biopsied. Regional lymph nodes examined and negative.
II	Tumor extends *beyond the kidney* but is completely resected with negative margins and lymph nodes. At least 1 of the following has occurred: (a) penetration of renal capsule, (b) invasion of renal sinus vessels.
III	*Residual tumor* present following surgery confined to the abdomen, including gross or microscopic tumor; spillage of tumor preoperatively or intraoperatively; biopsy prior to nephrectomy, regional

	lymph node metastases; tumor implants on the peritoneal surface; extension of tumor thrombus into the inferior vena cava, including thoracic vena cava and heart.
IV	*Hematogenous metastases* (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region.
V	*Bilateral* renal involvement by tumor.

The COG has very specific drug dose and schedule recommendations for risk-adapted treatment of Wilms tumor. Patients with **favorable-histology** Wilms tumor have a good outcome and are generally treated in the outpatient setting. Nephrectomy alone is sufficient for patients <2 yr old with stage I disease and a tumor weight <550 g, resulting in a 5 yr event-free survival of 84% and a 5 yr overall survival of 98%. Patients with stage I and II disease receive chemotherapy with 2 drugs, vincristine and actinomycin D (also called dactinomycin), every 1-3 wk for a total of 18 wk (regimen **EE4A**). Patients with stage III or IV disease receive chemotherapy with 3 drugs (vincristine, doxorubicin, and actinomycin D) every 1-3 wk for a total of 24 wk (regimen **DD4A**) and radiation therapy. Patients with regional lymph node metastases, residual disease after surgery, or tumor rupture receive radiation therapy to the flank or abdomen, and those with lung metastases receive radiation therapy to the lungs. Rapid response of lung metastases to chemotherapy may eliminate the need for lung radiation. The loss of heterozygosity of both 1p and 16q and gain of 1q confers an adverse prognosis and deserves treatment intensification.

Anaplastic histology (focal and diffuse) accounts for approximately 11% of Wilms tumor cases. Patients with **diffuse anaplasia** have a particularly poor outcome and are treated with intensive chemotherapy regimens that include vincristine, cyclophosphamide, doxorubicin, etoposide, carboplatin, and ifosfamide, in addition to radiation therapy.

Recurrent Disease

Approximately 15% of favorable-histology and 50% of anaplastic-histology Wilms tumors relapse; most relapses occur early (within 2 yr of diagnosis). Factors associated with a favorable outcome after relapse include low stage (I/II) at diagnosis, treatment with vincristine and actinomycin D only, no prior radiotherapy, favorable histology, relapse to lung only, and interval from nephrectomy to relapse ≥12 mo. Patients with recurrent Wilms tumor who previously received only vincristine and actinomycin D had a 4 yr survival of approximately 80%, whereas those who previously received the 3-drug regimen of vincristine, actinomycin D, and doxorubicin had a 4 yr survival of only 50%.

Other agents used to treat recurrent Wilms tumor include doxorubicin, carboplatin, cyclophosphamide, ifosfamide, etoposide, and topotecan. **Metachronous** Wilms tumor may not represent tumor relapse but development of a new tumor in the opposite kidney.

Prognosis

Despite some adverse risk factors that decrease prognosis (metastases, unfavorable histology, recurrent disease, loss of heterozygosity of both 1p and 16q and gain of 1q), most children with Wilms tumor have a very favorable prognosis. Overall survival of children with Wilms tumor exceeds 90%, with some prognostic factors (low stage, favorable histology, young age, low tumor weight) conferring even better outcomes. Wilms tumor tops the list of common pediatric solid tumors in terms of favorable outcome.

Late Effects

Current strategies are successful, with relatively few long-term effects of therapy. Generally, late complications are a consequence of treatment type and intensity; the use of radiotherapy and anthracyclines increase the risk of these complications. Clinically significant late sequelae include musculoskeletal effects, cardiac toxicity, pulmonary disease, reproductive problems, renal dysfunction, and development of second malignant neoplasms such as leukemia and cancer of the digestive organs and breast (in females).

526.2

Other Pediatric Renal Tumors

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Keywords

bone metastasis
brain metastasis
clear cell sarcoma
hematuria
INI1
mesoblastic nephroma
nephrectomy
renal cell carcinoma
renal neoplasm
rhabdoid tumor
SMARCB1
translocation-type RCC

Mesoblastic Nephroma

Mesoblastic nephroma is the most common solid renal tumor identified in the *neonatal period* and the most frequent benign renal tumor in childhood. It represents approximately 5% of all pediatric renal tumors. Many cases are diagnosed with prenatal US and can manifest as polyhydramnios, hydrops, and premature delivery. Most patients are diagnosed before 3 mo of age, whereas Wilms tumor is *rarely diagnosed* before 6 mo. Male/female ratio is 1.5 : 1. Radical nephrectomy is the treatment of choice and may be sufficient by itself. Local recurrence is uncommon. Although rare, malignant variants do occur, marked by metastases to the lung, liver, heart, and brain.

Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (**CCSK**) is an uncommon renal neoplasm of childhood, with approximately 20 new cases diagnosed each year in North America. Peak incidence is between 1 and 4 yr of age, usually presenting as an abdominal mass. Gene expression profiles of CCSK suggest the cell of origin to be a renal mesenchymal cell with neural markers. Bone is the most common site of distant metastasis, followed by lung, abdomen, retroperitoneum, brain, and liver. Therefore, the staging workup should include a bone scan. With modern therapy, patients with stage I and II disease have an excellent prognosis (4 yr overall survival of 97–100%), whereas those with stage III and IV disease have a 4 yr overall survival of 89% and 45%, respectively.

Rhabdoid Tumor of the Kidney

Malignant rhabdoid tumor of the kidney (**MRTK**) has rhabdomyoblast-like morphology and is a rare but aggressive cancer. Hematuria is a common presenting feature. Both rhabdoid tumor of the kidney and central nervous system (CNS) atypical teratoid/rhabdoid tumors have deletions and mutations of the *SMARCB1/hSNF5/INI1* gene and are considered related. They tend to metastasize to the lungs and brain. Prognosis is poor with current therapeutic protocols. Younger age at diagnosis, advanced-stage disease, and CNS involvement are associated with a worse prognosis. The outcome of patients with MRTK is poor. Both the 4 yr relapse-free survival and overall survival for patients treated on the NWTS-5 were 50% for stage I, 33% for stages II and III, and 21% for stage IV.

Renal Cell Carcinoma

Although renal cell carcinoma (**RCC**) is the most prevalent renal tumor in adults, it is extremely rare in children, accounting for <10% of pediatric renal tumors. The annual incidence rate is approximately 4 cases per 1 million children. Although Wilms tumor is the predominant renal tumor in childhood, it is rare past early childhood, and RCC is the most prevalent renal malignancy during the 2nd decade of life. Several **genetic disorders** are associated with a predisposition to RCC, including von Hippel–Lindau disease, tuberous sclerosis, and hereditary leiomyomatosis. The most common subtype of RCC in children, the **translocation-type RCC** , is characterized by translocations most frequently involving the *TFE3* gene on chromosome Xp11.2 or the *TFEB* gene on chromosome 6p21. Renal medullary carcinoma is seen typically in young patients with sickle cell trait.

Children with RCC may present with frank hematuria, flank pain, and/or a palpable mass, although RCC can be asymptomatic and detected incidentally. RCC has a propensity to metastasize to the lungs, liver, and bone. Whereas local lymph node involvement is a poor prognostic indicator in adult RCC, the importance of nodal status in pediatric RCC is controversial. Nephrectomy alone may be adequate for early-stage RCC. Besides surgery, there is no established optimal treatment for childhood RCC; neither chemotherapy nor radiation therapy has demonstrated significant activity.

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CHAPTER 527

Soft Tissue Sarcomas

Carola A.S. Arndt

The annual incidence of soft tissue sarcomas is 8.4 cases per 1 million white children younger than 14 yr of age. Rhabdomyosarcoma accounts for more than 50% of soft tissue sarcomas. The prognosis most strongly correlates with age and extent of disease at diagnosis, primary tumor site and histology, and expression of the fusion protein PAX-FOXO1.

Rhabdomyosarcoma

Epidemiology

The most common pediatric soft tissue sarcoma, rhabdomyosarcoma, accounts for approximately 3.5% of childhood cancers. These tumors may occur at virtually any anatomic site but are usually found in the head and neck (25%), orbit (9%), genitourinary tract (24%), and extremities (19%); retroperitoneal and other sites account for the remainder of primary sites. The incidence at each anatomic site is related to both patient age and tumor type. Extremity lesions are more likely to occur in older children and to have alveolar histology. Rhabdomyosarcoma occurs with increased frequency in patients with **neurofibromatosis** and other family cancer predisposition syndromes such as **Li-Fraumeni syndrome** (Table 527.1).

Table 527.1

Comparative Features of Rhabdomyosarcoma

FEATURE	EMBRYONAL RHABDOMYOSARCOMA	ALVEOLAR RHABDOMYOSARCOMA
Age of	Usually <5 yr; patients with spindle cell	Affects all ages; more likely to be alveolar if

patient	variants are often adolescents	occurring in patients age ≥5 yr
Site of original tumor	Head and neck: orbit, cheek, mouth, pharynx, ear, temporal fossa, parotid region Abdomen: abdominal soft tissues, bile ducts (intrahepatic and extrahepatic), gallbladder Genitourinary tract: urinary bladder, prostate, vagina, cervix, uterus Scrotum: paratesticular soft tissues	Extremities: upper, particularly hand; lower, including thigh, calf, and foot, including thigh, calf, and foot Trunk; gluteal musculature, perianal region, chest wall, abdominal wall, paraspinal musculature Head: paranasal sinuses and base of skull
Genetic features	Loss of heterozygosity of short arm of chromosome 11 Imprinting abnormalities Heterogeneous expression pattern on gene expression array	*PAX3-FOXO1* fusion *PAX7-FOXO1* fusion Gene amplification Homogeneous expression pattern on gene expression array (for fusion-positive tumors)
Cytogenetic features	Gains of chromosomes 2, 7, 8, 11, 12, 13q21, and 20 Losses of 1p35-36.3, 6, 9q22, 14q21-32, and 17 Diploid or hyperdiploid	t(1;13)(p36;q14) t(2;13)(q35;q14) Diploid or near-tetraploid
Myogenin expression	Patchy expression: rare to 80% of nuclei	Strong diffuse nuclear reactivity in 80–100% of tumor cells

Adapted from Parham DM, Alaggio R, Coffin CM: Myogenic tumors in children and adolescents, *Pediatr Dev Path* 15(1):S211–S236, 2012 (Table 2, p 214).

Pathogenesis

Rhabdomyosarcoma is thought to arise from the same embryonic mesenchyme as striated skeletal muscle, although a large percentage of these tumors arise in areas lacking skeletal muscle (e.g., bladder, prostate, vagina). On the basis of light microscopic appearance, rhabdomyosarcoma belongs to the general category of **small, round cell tumors** , which includes Ewing sarcoma, neuroblastoma, and non-Hodgkin lymphoma. Definitive diagnosis of a pathologic specimen requires immunohistochemical studies using antibodies to skeletal muscle (desmin, muscle-specific actin, myogenin) and, in the case of alveolar histology, reverse-transcription polymerase chain reaction or fluorescent in situ hybridization for PAX-FOXO1 transcript.

Determination of the specific histologic subtype (and in current studies, fusion status, i.e., FOXO1 positive or negative) is important in treatment planning and assessment of prognosis. There are 3 recognized histologic subtypes. The **embryonal type** accounts for approximately 60% of all cases and has an intermediate prognosis. The **botryoid type,** a variant of the embryonal form in which tumor cells and an edematous stroma project into a body cavity like a bunch of grapes, is found most often in the vagina, uterus, bladder, nasopharynx, and middle ear. The **alveolar type** accounts for approximately 25–40% of cases and often is characterized by the presence of PAX-FOXO1 fusion transcript (Table 527.2). The tumor cells tend to grow in nests that often have cleft-like spaces resembling alveoli. Alveolar tumors occur most often in the trunk and extremities and carry the poorest prognosis. The **pleomorphic type** (adult form) is rare in childhood, accounting for <1% of cases.

Table 527.2

Genetic Disorders Associated With Rhabdomyosarcoma

DISORDER	GENETIC ABERRATION
Beckwith-Weidemann syndrome	Deletions and loss of heterozygosity at chromosome 11p15, particularly affecting *IGF2* , *CDKAIC* , *H19* , and/or *LIT1*
Gorlin syndrome (basal cell nevus syndrome)	*PTCH* gene mutation
Costello syndrome	*H-RAS* mutation
Neurofibromatosis 1	*NF1* mutation
Li-Fraumeni syndrome	*TP53* mutation
Mosaic variegated aneuploidy syndrome	*BUB1B* mutation
Nijmegen breakage syndrome (ataxia-telangiectasis syndrome variant 1)	*NBS* mutation
Rubinstein-Taybi syndrome	*CREBBP* mutation
Constitutional mismatch-repair/deficiency syndrome	*PSM2* mutation
Adenomatous polyposis coli	*APC* mutation
Hereditary retinoblastoma	*RB1* mutation
Familial pleuropulmonary blastoma syndrome	*DICER* mutation
Noonan syndrome	*PTPN11* mutation
Werner syndrome	*RECOL2* mutation

From Parham DM, Alaggio R, Coffin CM: Myogenic tumors in children and adolescents, *Pediatr Dev Path* 15(1):S211–S236, 2012 (Table 3, p 214).

Clinical Manifestations

The most common presenting feature of rhabdomyosarcoma is a mass that may or may not be painful. Symptoms are caused by displacement or obstruction of normal structures (Table 527.1). Origin in the nasopharynx may be associated with nasal congestion, mouth breathing, epistaxis, and difficulty with swallowing and chewing. Regional extension into the cranium can produce cranial nerve paralysis, blindness, and signs of increased intracranial pressure with headache and vomiting. When the tumor develops in the face or cheek, there may be swelling, pain, trismus, and, as extension occurs, paralysis of cranial nerves. Tumors in the neck can produce progressive swelling with neurologic symptoms after regional extension. Orbital primary tumors are usually diagnosed early in their course because of associated proptosis, periorbital edema, ptosis, change in visual acuity, and local pain. When the tumor arises in the middle ear, the most common early signs are pain, hearing loss, chronic otorrhea, or a mass in the ear canal; extensions of tumor produce cranial nerve paralysis and signs of an intracranial mass on the involved side. An unremitting croupy cough and progressive stridor can accompany rhabdomyosarcoma of the larynx. Because most of these signs and symptoms also are associated with common childhood conditions, clinicians must be alert to the possibility of tumor.

Rhabdomyosarcoma of the *trunk or extremities* often is first noticed after trauma and initially may be regarded as a **hematoma** . If the swelling does not resolve or increases, malignancy should be suspected. Involvement of the genitourinary tract can produce hematuria, obstruction of the lower urinary tract, recurrent urinary tract infections, incontinence, or a mass detectable on abdominal or rectal examination. *Paratesticular* tumor usually manifests as a painless, rapidly growing mass in the scrotum. *Vaginal* rhabdomyosarcoma may manifest as a grapelike mass of tumor tissue bulging through the vaginal orifice, known as **sarcoma botryoides** , and can cause urinary tract or large bowel symptoms. Vaginal bleeding or obstruction of the urethra or rectum may occur. Similar findings can be noted with uterine primaries.

Tumors in any location may disseminate early and cause symptoms of pain or respiratory distress associated with pulmonary metastases. Extensive bone involvement can produce symptomatic hypercalcemia. In such cases, it may be difficult to identify the primary lesion.

Diagnosis

Early diagnosis of rhabdomyosarcoma requires a high index of suspicion. The microscopic appearance is that of a small, round, blue cell tumor. Neuroblastoma, lymphoma, and Ewing sarcoma also are **small, round, blue cell tumors** from which suspected rhabdomyosarcomas must be differentiated. The differential diagnosis depends on the site of presentation. Definitive diagnosis is established by biopsy, microscopic appearance, and results of immunohistochemical stains and analysis of PAX/FOXO1 expression. A lesion in an extremity may be thought to be a hematoma or **hemangioma** ; an orbital lesion resulting in proptosis may be treated as an **orbital cellulitis** ; or bladder-obstructive symptoms may be missed. Adolescents may ignore or be embarrassed to mention paratesticular lesions for a long time. Unfortunately, several months often elapse between the initial symptoms and biopsy.

Diagnostic procedures are determined mainly by the area of involvement. CT or MRI is necessary for evaluation of the primary tumor site. With signs and symptoms in the head and neck area, radiographs should be examined for evidence of a tumor mass and for indications of bony erosion. MRI should be performed to identify intracranial extension or meningeal involvement and also to reveal bony involvement or erosion at the base of the skull. For abdominal and pelvic tumors, CT with a contrast agent or MRI can help delineate the tumor (Figs. 527.1 and 527.2). A radionuclide bone scan, chest CT, and bilateral bone marrow aspiration and biopsy should be performed to evaluate the patient for the presence of metastatic disease and to plan treatment. Certain low-risk patients may not need bone marrow evaluation. Fluorodeoxyglucose positron emission tomography will help enhance staging.

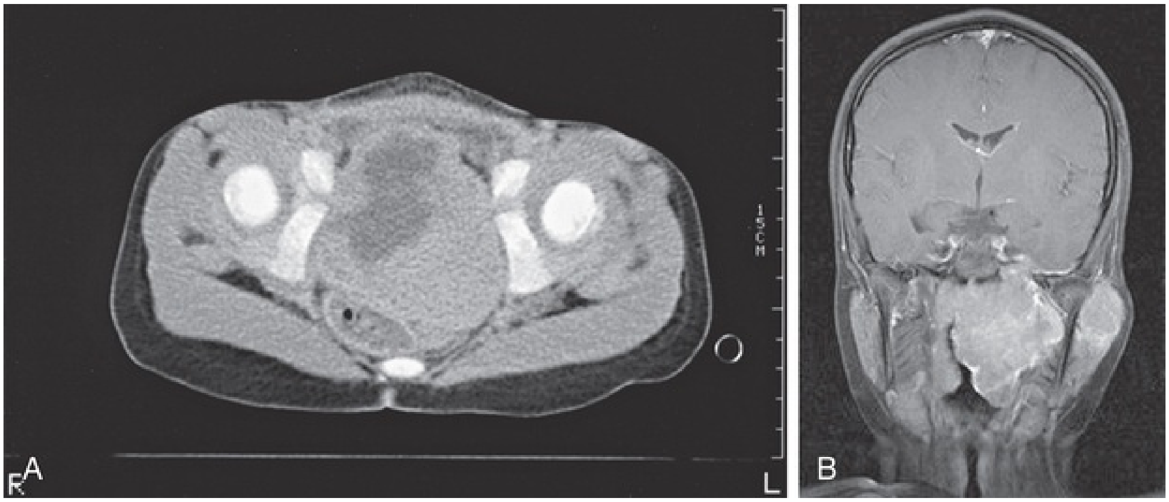

FIG. 527.1 **A,** Pelvic CT scan of child with bladder rhabdomyosarcoma. **B,** MR image of child with parameningeal rhabdomyosarcoma.

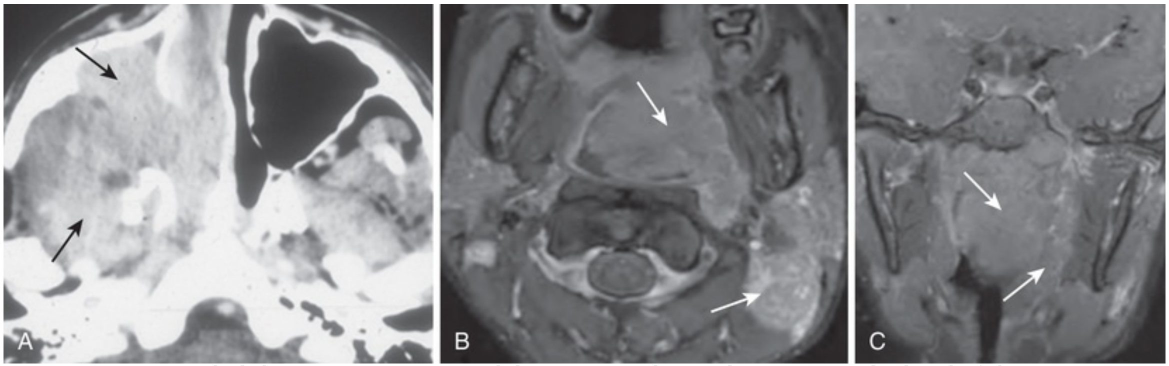

FIG. 527.2 Rhabdomyosarcoma. A, Axial contrast-enhanced CT scan at the level of the nasal cavity demonstrates a large, enhancing, aggressive soft tissue mass involving the right maxillary sinus and the infratemporal fossa *(arrows)* . B, Axial MR image, and C, coronal contrast-enhanced T1-weighted MR image, demonstrate an infiltrative mass involving the pharyngeal mucosal space, left infratemporal masticator space, skull base, and sphenoid sinus *(arrows).* (From Haaga JR, Boll DT, editors: *CT and MRI of the whole body,* ed 6, Philadelphia, 2017, Elsevier, Fig. 26-16, p 769.)

The most critical element of the diagnostic workup is *examination of tumor tissue* , which includes the use of special histochemical stains and immunostains. Molecular genetics also is important to detect fusion transcripts present in alveolar rhabdomyosarcoma (PAX-FOX1). Lymph nodes also should be sampled for the presence of disease spread, especially in tumors of the extremities and in boys >10 yr old with paratesticular tumors.

Treatment

Treatment is multidisciplinary and includes the pediatric oncologist, pediatric surgeon or other surgical subspecialist, and most often the radiation oncologist. Only if the tumor is able to be completely resected, with negative margins, without loss of function or major cosmetic deformity, should this be attempted initially. Unfortunately, most rhabdomyosarcomas are not completely resectable at initial diagnosis. Treatment is based on risk classification of the tumor, which is determined by the stage of tumor, the tumor histology and/or fusion status, and the amount of tumor that was surgically resected before chemotherapy (“surgical group”). Stage is dependent on primary site (favorable vs unfavorable), tumor invasiveness (T1 or T2), lymph node status, tumor size, and presence of metastasis. *Favorable sites* include female genital, paratesticular, and head and neck (nonparameningeal) regions; all other sites are considered unfavorable. Table 527.3 shows the Children's Oncology Group staging system for rhabdomyosarcoma.

Table 527.3

Staging System for Rhabdomyosarcoma

STAGE	SITE	T STAGE	SIZE	NODE STATUS	METASTASIS
1	Favorable	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Unfavorable	T1 or T2	a	N0 or Nx	M0
3	Unfavorable	T1 or T2	a b	N1 N0 or N1 or Nx	M0
4	Any	T1 or T2	a or b	N0 or N1 or Nx	M1

T1, Confined to anatomic site of origin; T2, extension and/or fixative to surrounding tissue.

Size: a, <5 cm in diameter; b, ≥5 cm in diameter.

Nodes: N0, regional nodes not involved; N1, regional nodes involved; Nx, regional node status unknown.

Metastases: M0, no distant metastases; M1, metastases present (includes positive cytology in cerebrospinal fluid, pleural fluid, or peritoneal fluid).

Patients should be offered enrollment in clinical trials. Table 527.4 shows risk stratification and outcomes. Patients with low-risk disease can be cured with minimal therapy consisting of vincristine and of actinomycin, with or without lower doses of cyclophosphamide; radiation therapy can be used in the case of residual disease after initial surgery. Treatment for patients with intermediate-risk disease consists of vincristine, actinomycin, cyclophosphamide, and irinotecan along with radiation. For patients with high-risk disease, approaches using intensive multiagent chemotherapy have not improved the outcome, and new approaches are being investigated.

Table 527.4

Risk Groups and Outcome for Rhabdomyosarcoma, Children's Oncology Group

RISK GROUP	STAGE/GROUP	HISTOLOGY	LONG-TERM EFS
Low, subset 1	Stage 1, Groups I-II Stage 1, Group III (orbit) Stage 2, Groups I-II	Embryonal	85–95%
Low, subset 2	Stage 1, Group III (nonorbit) Stage 3, Groups I-II	Embryonal	70–85%
Intermediate	Stage 2-3, Group III Stage 1-3, Groups I-III	Embryonal Alveolar	73% 65%
High	Stage 4, Group IV Stage 4, Group IV	Embryonal Alveolar	35% 15%

EFS, Event-free survival.

From Hawkins DS, Spunt SL, Skapek SX: Children's Oncology Group's 2013 blueprint for research: soft tissue sarcomas, *Pediatr Blood Cancer* 60:1001–1008, 2013 (Table I, p 1002).

Prognosis

Prognostic factors include age, stage, histology/fusion status, and primary site. Among patients with resectable tumor and favorable histology, 80–90% have prolonged disease-free survival. Unresectable tumor localized to certain favorable sites, such as the orbit, also has a high likelihood of cure. Approximately 65–70% of patients with incompletely resected tumor also achieve long-term disease-free survival. Patients with disseminated disease have a poor prognosis; only approximately 50% achieve remission, and fewer than 50% of these are cured. Older children have a poorer prognosis than younger children. For all patients, surveillance for late effects of cancer treatment is extremely important. Late effects include infertility from cyclophosphamide, late effects in the radiation field (e.g., bladder dysfunction, infertility, cataracts, impaired bone growth), and secondary malignancies.

Other Soft Tissue Sarcomas

The *nonrhabdomyosarcoma* soft tissue sarcomas constitute a heterogeneous group of tumors that account for 3% of all childhood malignancies (Table 527.5). Because they are relatively rare in children, much of the information about their natural history and treatment has been derived from studies in adult patients. In children, the median age at diagnosis is 12 yr, with a male/female ratio of 2.3 : 1. These tumors usually arise in the trunk or lower extremities. The most common histologic types are **synovial sarcoma** (42%), **fibrosarcoma** (13%), **malignant fibrous histiocytoma** (12%), and **neurogenic tumors** (10%). Molecular genetic studies often prove useful in diagnosis, because several of these tumors have characteristic chromosomal translocations. Tumor size, stage (clinical group), invasiveness, and histologic grade correlate with survival.

Table 527.5

Features of Most Common Types of Nonrhabdomyosarcoma Soft Tissue Sarcomas

TISSUE TYPE	TUMOR	NATURAL HISTORY AND BIOLOGY

Fibrous	Fibrosarcoma	Most common soft tissue sarcoma in children <1 yr old. Congenital fibrosarcoma is a low-grade malignancy that commonly arises in the extremities or trunk and rarely metastasizes. Surgical excision is treatment of choice; dramatic responses to preoperative chemotherapy may occur. In children >4 yr old, the natural history is similar to that in adults (5 yr survival rate of 60%). In patients with fibrosarcoma and *TRK* fusions, dramatic responses have occurred with new agents targeting *TRK* . Wide surgical excision and preoperative chemotherapy are typically used. Associated with t(12;15)(p13;q25) or trisomy 11, also +8, +17, +20.
Peripheral nerves	Neurofibrosarcoma	Also known as the malignant peripheral nerve sheath tumor. Develops in up to 16% of patients with neurofibromatosis type 1 (NF1); almost 50% occur in patients with NF1. Deletions of chromosome 22q11-q13 or 17q11 and p53 mutations have been reported. Usually arises in trunk and extremities and is locally invasive. Complete surgical excision is necessary for survival; response to chemotherapy is suboptimal.
Synovium	Synovial sarcoma	The most common nonrhabdomyosarcoma soft tissue sarcoma in some series. Often manifesting in the 3rd decade of life, but 33% of patients are <20 yr old. Typically arises around the knee or thigh and is characterized by a nonrandom translocation t(X;18)(p11;q11). Wide surgical excision is necessary. Radiation therapy is effective in microscopic residual disease, and ifosfamide-based therapy is active in advanced disease.
Unknown	Alveolar soft part sarcoma	Slow-growing tumor; tends to recur or to metastasize to lung and brain years after diagnosis. Often arises in the extremities and head and neck. Unresponsive to chemotherapy.

Surgery remains the mainstay of therapy, but a careful search for lung and bone metastases should be undertaken before surgical excision. Chemotherapy and radiation therapy should be considered for large, high-grade, and/or unresectable tumors. The role of chemotherapy for nonrhabdomyosarcoma soft tissue sarcomas is not as well defined as for rhabdomyosarcoma. Patients with large (>5 cm), high-grade, or unresectable or metastatic disease are treated with multiagent chemotherapy in addition to irradiation and/or surgery. Patients with completely resected small (<5 cm) tumors are generally treated with surgery alone and can be expected to have an excellent outcome regardless of whether the tumor is high or low grade.

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Parham DM, Alaggio R, Coffin CM. Myogenic tumors in children and adolescents. *Pediatr Dev Path* . 2012;15(1):S211–S236.

CHAPTER 528

Neoplasms of Bone

528.1

Malignant Tumors of Bone

Carola A.S. Arndt

Keywords

- Askin tumor
- Ewing sarcoma
- Li-Fraumeni syndrome
- osteosarcoma
- parosteal
- periosteal
- retinoblastoma
- Rothmund-Thomson syndrome
- small round blue cell tumor
- telangiectatic

The annual incidence of malignant bone tumors in the United States is approximately 7 cases per 1 million white children younger than 14 yr, with a slightly lower incidence in black children. **Osteosarcoma** is the most common primary malignant bone tumor in children and adolescents, followed by **Ewing sarcoma** (Table 528.1 and Fig. 528.1). In children <10 yr old, Ewing sarcoma is more common than osteosarcoma. Both tumor types are most likely to occur in the 2nd decade of life.

Table 528.1

Comparison of Features of Osteosarcoma and the Ewing Family of Tumors

FEATURE	OSTEOSARCOMA	EWING FAMILY OF TUMORS
Age	2nd decade	2nd decade
Race	All races	Primarily whites
Sex (M:F)	1.5 : 1	1.5 : 1
Predisposition	Retinoblastoma, Li-Fraumeni syndrome, Paget disease, radiotherapy	None known
Site	Metaphyses of long bones	Diaphyses of long bones, flat bones
Presentation	Local pain and swelling; often history of injury	Local pain and swelling; fever
Radiographic findings	Sclerotic destruction (less often lytic); sunburst pattern	Primarily lytic, multilaminar periosteal reaction (“onion-skinning”)
Differential diagnosis	Ewing sarcoma, osteomyelitis	Osteomyelitis, eosinophilic granuloma, lymphoma, neuroblastoma, rhabdomyosarcoma
Metastasis	Lungs, bones	Lungs, bones
Treatment	Chemotherapy	Chemotherapy
	Ablative surgery of primary tumor	Radiotherapy and/or surgery of primary tumor
Outcome	Without metastases, 70% cured; with metastases at diagnosis, ≤20% survival	Without metastases, 65–75% cured; with metastases at diagnosis, 20–30% survival

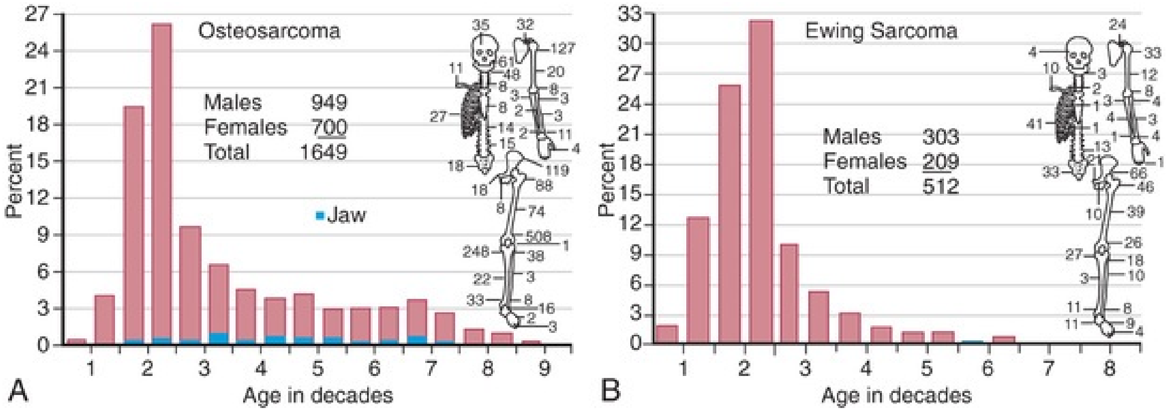

FIG. 528.1 **A,** Age and skeletal distribution of 1,649 cases of osteosarcoma in the Mayo Clinic files. **B,** Age and skeletal distribution of 512 cases of Ewing sarcoma in the Mayo Clinic files. (From Unni KK, editor: *Dahlin's bone tumors: general aspects and data on 11,087 cases,* ed 5, Philadelphia, 1996, Lippincott-Raven. Reprinted by permission of the Mayo Foundation.)

Osteosarcoma

Epidemiology

The annual incidence of osteosarcoma in the United States is 5.6 cases per 1 million children <15 yr old. The highest risk period for development of osteosarcoma is during the adolescent growth spurt, suggesting an association between rapid bone growth and malignant transformation. Patients with osteosarcoma are taller than their peers of similar age.

Pathogenesis

Although the cause of osteosarcoma is unknown, certain genetic or acquired conditions predispose patients to development of osteosarcoma. Patients with **hereditary retinoblastoma** have a significantly increased risk for development of osteosarcoma. The sites of osteosarcoma in these patients were initially thought to be only in previously irradiated areas, but later studies show them to arise in sites far from the original retinoblastoma radiation field. Predisposition to development of osteosarcoma in these patients may be related to loss of heterozygosity of the *RB* gene. Osteosarcoma also occurs in the **Li-Fraumeni syndrome** , which is a familial cancer syndrome associated with germline mutations of the *P53* gene. Kindreds with Li-Fraumeni syndrome have a spectrum of malignancies in first-degree relatives, including carcinoma of the breast, soft tissue sarcomas, brain tumors, leukemia, adrenocortical carcinoma, and other malignancies. **Rothmund-Thomson syndrome** is a rare condition associated with short stature, skin telangiectasia, small hands and feet, hypoplasticity or absence of the thumbs, and a high risk of osteosarcoma. Osteosarcoma also can be induced by irradiation for Ewing sarcoma, craniospinal irradiation for brain tumors, or high-dose irradiation for other malignancies. Other benign conditions that can be associated with malignant transformation to osteosarcoma include Paget disease, enchondromatosis, multiple hereditary exostoses, and fibrous dysplasia (see Chapter 528.2).

The pathologic diagnosis of osteosarcoma is made by demonstration of a highly malignant, pleomorphic, spindle cell neoplasm associated with the formation of malignant osteoid and bone. There are 4 pathologic subtypes of conventional high-grade osteosarcoma: osteoblastic, fibroblastic, chondroblastic, and telangiectatic. No significant differences in outcome are associated with the various subtypes, although the chondroblastic component of that subtype may not respond as well to chemotherapy. The role in prognosis of various genes, such as drug resistance–related genes, tumor-suppressor genes, and genes related to apoptosis, is being evaluated.

Telangiectatic osteosarcoma may be confused with aneurysmal bone cyst because of its lytic appearance on radiography. High-grade osteosarcoma typically arises in the diaphyseal region of long bones and invades the medullary cavity. It also may be associated with a soft tissue mass. Two variants of osteosarcoma, parosteal and periosteal, should be distinguished from conventional osteosarcoma because of their characteristic clinical features. **Parosteal osteosarcoma** is a low-grade, well-differentiated tumor that does not invade the medullary cavity and most frequently is found in the posterior aspect of the distal femur. Surgical resection alone often is curative in this lesion, which has a low propensity for metastatic spread. **Periosteal osteosarcoma** is a rare variant that arises on the surface of the bone but has a higher rate of metastatic spread than the parosteal type and an intermediate prognosis.

Clinical Manifestations

Pain, limp, and swelling are the most common presenting manifestations of osteosarcoma. Because these tumors occur most often in active adolescents, initial complaints may be attributed to a sports injury or sprain; any bone or joint pain not responding to conservative therapy within a reasonable time should be investigated thoroughly. Additional clinical findings may include limitation of motion, joint effusion, tenderness, and warmth. Results of routine laboratory tests, such as a complete blood cell count and chemistry panel, are usually normal, although alkaline phosphatase or lactate dehydrogenase values may be elevated.

Diagnosis

Bone tumor should be suspected in a patient who presents with deep bone pain, often causing nighttime awakening, and has a palpable mass with radiographs that demonstrate a lesion. The lesion may be mixed lytic and blastic in appearance, but new bone formation is usually visible. The classic radiographic appearance of osteosarcoma is the *sunburst pattern* (Fig. 528.2). When osteosarcoma is suspected, the patient should be referred to a center with experience in managing bone tumors. The biopsy and the surgery should be performed by the same surgeon so that the incisional biopsy site can be placed in a manner that will not compromise the ultimate limb salvage procedure. Tissue usually is obtained for molecular and biologic studies at the time of the initial biopsy. Before biopsy, MRI of the primary lesion and the entire bone should be performed to evaluate the tumor for its proximity to nerves and blood vessels, soft tissue and joint extension, and skip lesions. The metastatic workup includes CT of the chest and radionuclide bone scanning or positron emission tomography (PET) scan to evaluate for lung and bone or soft tissue metastases, respectively. The **differential diagnosis** of a lytic bone lesion includes histiocytosis, Ewing sarcoma, lymphoma, and bone cyst.

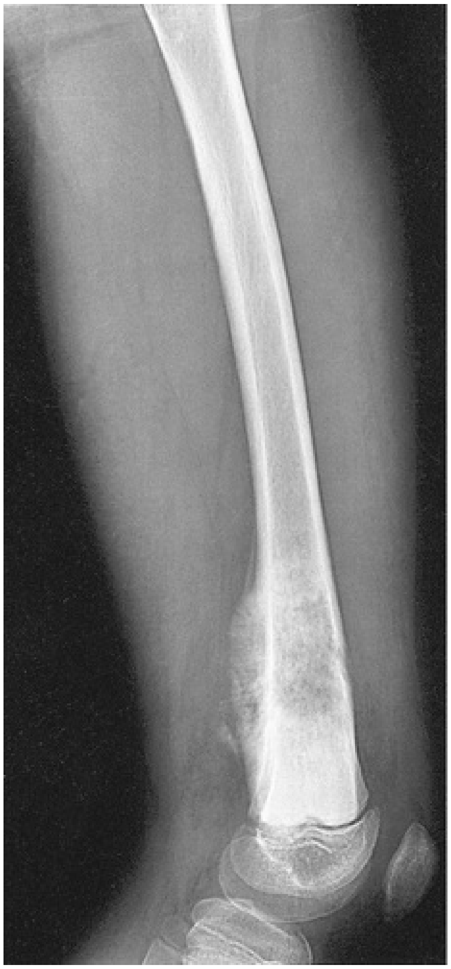

FIG. 528.2 Radiograph of an osteosarcoma of the femur with typical “sunburst” appearance of bone formation.

Treatment

With chemotherapy and surgery, 5 yr disease-free survival of patients with nonmetastatic extremity osteosarcoma is 65–75%. Complete surgical resection of the tumor is important for cure. The current approach is to treat patients with preoperative chemotherapy in an attempt to facilitate limb salvage operations and to treat micrometastatic disease immediately. Up to 80% of patients are able to undergo limb salvage operations after initial chemotherapy. It is important to resume chemotherapy as soon as possible after surgery. Lung metastases present at diagnosis should be resected by thoracotomies at some time during treatment. Active agents in use in multidrug chemotherapy regimens for conventional osteosarcoma include doxorubicin, cisplatin, methotrexate, and ifosfamide.

One of the most important prognostic factors in osteosarcoma is the *histologic response to chemotherapy* ; a poor histologic response is ≥10% viable tumor. **MAP** (methotrexate, doxorubicin, cisplatin) is the standard chemotherapy regimen for osteosarcoma. After limb salvage surgery, intensive rehabilitation and physical therapy are necessary to ensure maximal functional outcome. Intensification of therapy by addition of ifosfamide and etoposide in patients with poor histologic response after induction chemotherapy with MAP has not improved outcome.

For patients who require amputation, early prosthetic fitting and gait training are essential to enable patients to resume normal activities as soon as possible. Before definitive surgery, patients with tumors on weight-bearing bones should be instructed to use crutches to avoid stressing the weakened bones and causing pathologic fracture. The role of chemotherapy in parosteal and periosteal osteosarcomas is not well defined, and chemotherapy is generally reserved for use in patients with tumors that have a high-grade microscopic appearance.

Prognosis

Surgical resection alone is curative only for patients with low-grade parosteal osteosarcoma. Conventional osteosarcoma requires multiagent chemotherapy. Up to 75% of patients with nonmetastatic extremity osteosarcoma are cured with current multiagent treatment protocols. The prognosis is not as favorable for patients with pelvic tumors as for those with primary tumors in the extremities. From 20–30% of patients who have limited numbers of pulmonary metastases also can be cured with aggressive chemotherapy and resection of lung nodules.

Patients with bone metastases and those with widespread lung metastases have an extremely poor prognosis. Long-term follow-up of patients with osteosarcoma is important to monitor for late effects of chemotherapy, such as cardiotoxicity from anthracycline and hearing loss from cisplatin. Patients in whom late, isolated lung metastases develop may be cured with surgical resection of the metastatic lesions alone.

Ewing Sarcoma

Epidemiology

The incidence of Ewing sarcoma in the United States is 2.1 cases per 1 million children. It is rare among black children. Ewing sarcoma, an undifferentiated sarcoma of bone, also may arise from soft tissue. Treatment protocols for these tumors are the same whether the tumors arise in bone or soft tissue. Anatomic sites of primary tumors arising in bone are distributed evenly between the extremities and the central axis (pelvis, spine, and chest wall). Primary tumors arising in the chest wall are often referred to as **Askin tumors** .

Pathogenesis

Immunohistochemical staining assists in the diagnosis of Ewing sarcoma to differentiate it from **small, round, blue cell tumors** such as lymphoma, rhabdomyosarcoma, and neuroblastoma. Histochemical stains may react positively with certain neural markers on tumor cells (neuron-specific enolase and S-100), especially in peripheral primitive neuroectodermal tumors. Reactivity with muscle markers (e.g., desmin, actin) is absent. Additionally, MIC-2 (CD99) staining is usually positive. A specific chromosomal translocation, t(11;22) or a variant is found in most of the Ewing sarcoma family of tumors. Analysis for the translocation by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) analysis for the chimeric fusion gene products EWS/FLI1 or EWS/ERG (or other variants) are used routinely in diagnosis.

Clinical Manifestations

Symptoms of Ewing sarcoma are similar to those of osteosarcoma. Pain, swelling, limitation of motion, and tenderness over the involved bone or soft tissue are common presenting symptoms. Patients with huge chest wall primary tumors may present with respiratory distress. Patients with paraspinal or vertebral primary tumors may present with symptoms of cord compression. Ewing sarcoma often is associated with **systemic manifestations** , such as fever and weight loss, and may be accompanied by elevated inflammatory markers; patients may have undergone treatment for a presumptive diagnosis of osteomyelitis or a fever of unknown origin. Patients also may have a delay in diagnosis when their pain or swelling is attributed to a sports injury. Biopsy and tissue diagnosis should be considered for patients presenting with suspicious bone lesions, since even the gross appearance of Ewing sarcoma can appear similar to infection and the time course can be rapid. Surgical procedures for treatment of infection can contaminate the surgical field and impact treatment outcomes.

Diagnosis

The diagnosis of Ewing sarcoma should be suspected in a patient who presents with pain and swelling, with or without systemic symptoms, and with a radiographic appearance of a primarily lytic bone lesion with periosteal reaction, the characteristic **onion-skinning** (Fig. 528.3). A large, associated soft tissue mass often is visualized on MRI or CT (Fig. 528.4). The **differential diagnosis** includes osteosarcoma, osteomyelitis, Langerhans cell histiocytosis, primary lymphoma of bone, metastatic neuroblastoma, or rhabdomyosarcoma in the case of a pure soft tissue lesion. Patients should be referred to a center with experience in managing bone tumors for evaluation and biopsy. Thorough evaluation for metastatic disease includes CT of the chest, radionuclide bone scan or PET scan, and bone marrow aspiration and biopsy specimens from at least 2 sites. MRI of the tumor and the entire length of involved bone should be performed to determine the exact extension of the soft tissue and bony mass and the proximity of tumor to neurovascular structures. Studies are also using fluorodeoxyglucose (FDG) PET to evaluate response to therapy.

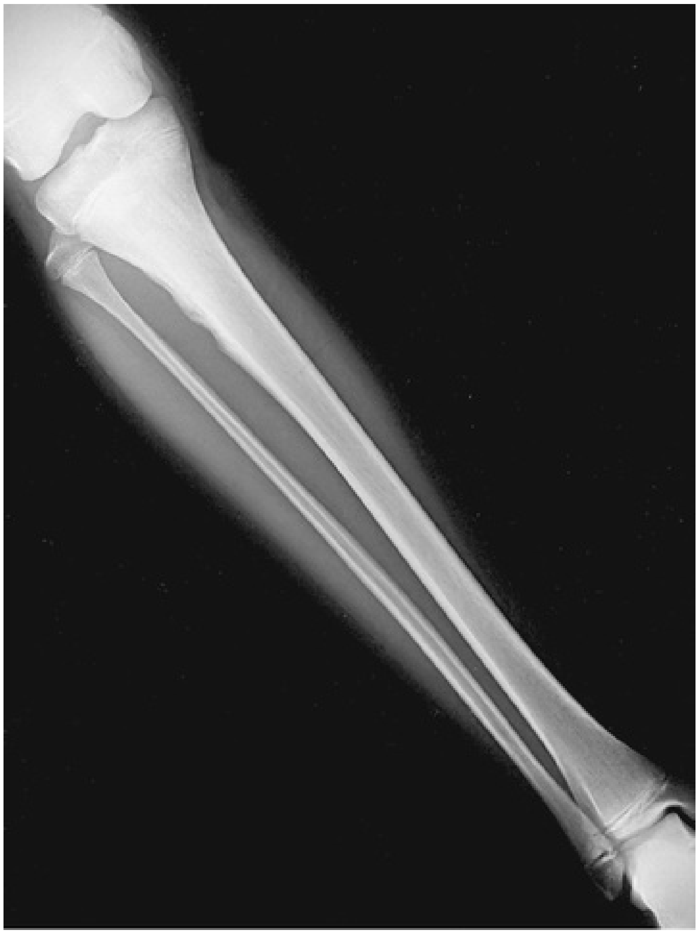

FIG. 528.3 Radiograph of tibial Ewing sarcoma showing periosteal elevation or “onion-skinning.”

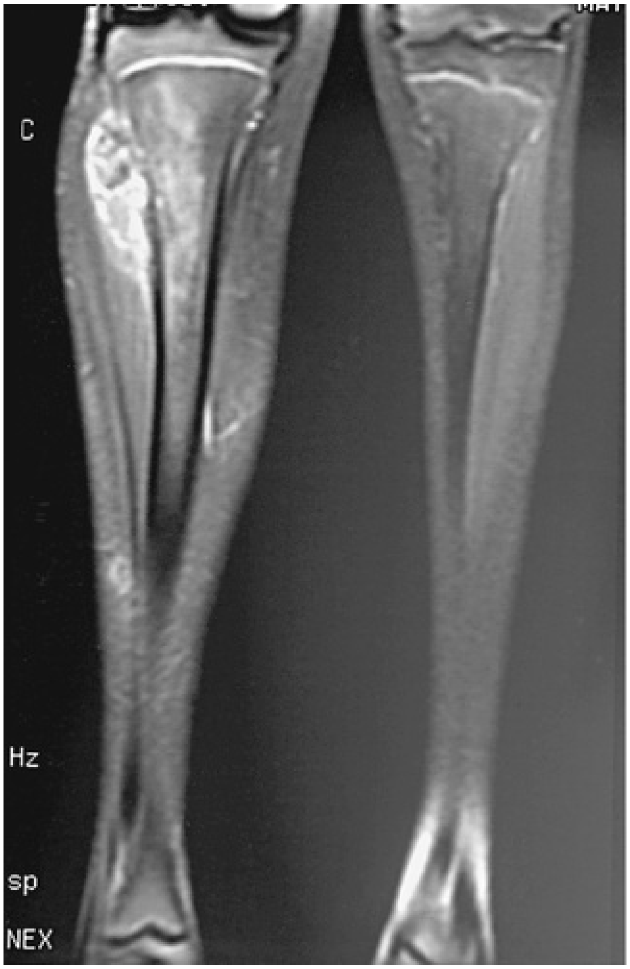

FIG. 528.4 MR image of tibial Ewing sarcoma showing a large associated soft tissue mass.

To avoid compromising an ultimate potential for limb salvage by a poorly planned biopsy incision, the same surgeon should perform the biopsy and the surgical procedure. CT-guided biopsy of the lesion often provides diagnostic tissue. It is important to obtain adequate tissue for special stains and molecular studies.

Treatment

Tumors of the Ewing sarcoma family are best managed with a comprehensive multidisciplinary approach in which the surgeon, chemotherapist, and radiation oncologist plan therapy. Multiagent chemotherapy is important because it can shrink the tumor rapidly and is usually given before local control is attempted. In North America, standard **chemotherapy** for nonmetastatic Ewing sarcoma includes vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide. Chemotherapy usually causes dramatic shrinkage of the soft tissue mass and rapid, significant pain relief. Patients with nonmetastatic Ewing sarcoma have a better outcome when treated on a 14-day rather than on a 21-day schedule. Current studies are evaluating the addition of *topoisomerase inhibitors* to standard chemotherapy, and the addition of insulin-like growth factor receptor inhibitors for patients with metastatic disease. An international cooperative group trial is evaluating whether myeloablative chemotherapy and stem cell rescue is superior to chemotherapy with lung irradiation for patients with pulmonary metastases.

Ewing sarcoma is considered a radiosensitive tumor, and local control may be achieved with **irradiation** or **surgery** . Radiation therapy is associated with a risk of radiation-induced second malignancies, especially osteosarcoma, as well as failure of bone growth in skeletally immature patients. Many centers prefer surgical resection, if possible, to achieve local control. It is important to provide the patient with crutches if the tumor is in a weight-bearing bone, to avoid a pathologic fracture before definitive local control. Chemotherapy should be resumed as soon as possible after surgery.

Prognosis

Patients with small, nonmetastatic, distally located extremity tumors have the best prognosis, with a cure rate of up to 75%. Patients with pelvic tumors have, until recently, had a much worse outcome. Patients with metastatic disease at diagnosis, especially bone or bone marrow metastases, have a poor prognosis, with <30% surviving long term. New approaches, such as very intensive chemotherapy with peripheral blood stem cell rescue, are being investigated in these patients.

Long-term follow-up of patients with Ewing sarcoma is important because of the potential for late effects of treatment, such as anthracycline cardiotoxicity; second malignancies, especially in the radiation field; and late relapses, even as long as 10 yr after initial diagnosis.

528.2

Benign Tumors and Tumor-Like Processes of Bone

Carola A.S. Arndt, A. Noelle Larson

Keywords

adamantinoma
bone cyst
chondroblastoma
chondromyxoid fibroma
enchondroma
exostosis
fibroma
fibrous dysplasia
Langerhans cell histiocytosis
Maffucci syndrome
McCune-Albright syndrome
multiple hereditary exostoses
Ollier disease
osteochondroma
osteoblastoma
osteofibrous dysplasia
osteoid osteoma
subungual exostosis
unicameral bone cyst

Benign bone lesions in children are common compared with the relatively rare malignant neoplasms of bone. A broad range of diagnostic possibilities must be considered when the physician is confronted with an undiagnosed bone lesion. Some lesions, although histologically benign, can be life threatening, whereas others can be locally destructive to bone. Many lesions represent an incidental finding that, if asymptomatic, can be observed. A group of benign characteristic lesions, including osteochondroma, nonossifying fibroma, unicameral bone cyst, and enchondroma, can readily be diagnosed on standard radiographs without additional imaging studies. Other conditions require further study to determine a diagnosis, when no single element in the history or diagnostic test is sufficient to rule out malignancy (Table 528.2). Benign lesions are usually painless but may be painful, especially if the lesion is causing local bone destruction or there is an impending pathologic fracture. **Night pain** that awakens a child suggests malignancy, but relief of such pain with aspirin is common with osteoid osteomas. Rapidly enlarging lesions usually are associated with malignancy, but several benign lesions, such as aneurysmal bone cysts, can enlarge faster than most malignancies. Several conditions, such as **osteomyelitis** , can simulate the appearance of bone tumors.

Table 528.2

Features of Pediatric Benign Bone Tumors

LESION	TYPICAL COURSE	MOST COMMON WORKUP TO CONFIRM DIAGNOSIS
Fibroma (nonossifying fibroma, fibrous cortical defect, metaphyseal fibrous defect)	Observation; surgery to treat fracture/impending fracture (rare, large lesions)	Radiographs
Enchondroma	Observation; treat if symptomatic.	Radiographs, occasionally MRI
Osteochondroma	Observation; excise if symptomatic.	Radiographs
Subungual exostosis	Symptoms warrant excision for most patients.	Radiographs
Unicameral/simple bone cyst	Observation; treat if fracture occurs to prevent further fractures.	Radiographs, occasionally MRI
Osteoid osteoma	NSAIDs; but symptoms warrant percutaneous ablation for most patients.	Radiographs, CT
Heterotopic ossification	Observation; if symptomatic, excise after bone is mature (>6 mo).	Radiographs, ± MRI, CT
Fibrous dysplasia	Observation; treat if pain or bony deformities.	Radiographs, ± MRI, ± biopsy
Chronic regional multifocal osteomyelitis (reactive bone condition)	Observation; medical treatment available if symptomatic; pathology is identical to osteomyelitis.	Radiographs, MRI; bone scan to look for other lesions; antibiotics to rule out osteomyelitis; biopsy
Langerhans cell histiocytosis	Variable; depends on extent of disease.	Skeletal survey, MRI, biopsy, workup to rule out systemic disease
Infection	Treat with prolonged antibiotics, typically some intravenously; surgery for joint/growth plate involvement, abscess, and chronic disease.	CRP, sedimentation rate, CBC with differential, blood cultures, radiographs, ± MRI, ± biopsy
Osteoblastoma	Locally aggressive, treat.	Radiographs, CT, MRI, biopsy
Aneurysmal bone cyst	Locally aggressive, treat.	Radiographs, MRI, biopsy
Chondroblastoma	Locally aggressive, treat.	Radiographs, MRI, biopsy
Chondromyxoid fibroma	Locally aggressive, treat.	Radiographs, MRI, biopsy

Osteofibroma dysplasia	Possibly locally aggressive; variable.	Radiographs, MRI, biopsy
Adamantinoma	Malignant, treat.	Radiographs, MRI, biopsy

CBC, Complete blood count; CRP, C-reactive protein; CT, computed tomography, MRI, magnetic resonance imaging; NSAIDs, nonsteroidal antiinflammatory drugs.

Many benign bone tumors are diagnosed incidentally or after pathologic **fracture** . Initial management of these fractures is similar to that of nonpathologic fractures in the same location. It is unusual for benign bone tumors to interfere with fracture healing, but the area of weakness typically remains, and refracture is common. Fractures rarely result in resolution of the tumor, which usually is treated after the fracture has healed. Fractures around the hip, however, frequently require immediate treatment to stabilize the femoral neck and restore anatomic alignment.

Radiographs of any suspected bone lesion should always be obtained in 2 planes. Additional studies may be necessary to help arrive at the correct diagnosis and to guide treatment. Although these lesions are benign, selected lesions require intervention. If biopsy is performed, both microbiology and pathology evaluations should always be obtained, and the possibility of malignancy should be taken into account when planning the biopsy tract. Needle biopsy is more likely to be nondiagnostic than open biopsy. Although open biopsy increases morbidity, treatment can sometimes be performed at the same operative setting based on intraoperative pathology.

Osteochondroma (exostosis) is one of the most common benign bone tumors in children. Because many are completely asymptomatic and unrecognized, the true incidence of this lesion is unknown. Osteochondromas develop in childhood, arising from the metaphysis of a long bone, particularly the distal femur, proximal humerus, and proximal tibia. The lesion enlarges with the child until skeletal maturity. Children usually present at 5-15 yr of age, when the child or parent notices a bony, nonpainful mass. Some are discovered because they are irritated by soft tissues rubbing over the lesion during athletic or other activities. Fracture is rare. Osteochondromas appear radiographically as stalks or broad-based projections from the surface of the bone, usually in a direction away from the adjacent joint (Fig. 528.5*A*). The bone is in continuity with the medullary canal. Invariably, the lesion is radiographically smaller than suggested by palpation because the cartilage cap covering the lesion is not seen. This cartilage cap may be up to 1 cm thick. Both the cortex of the bone and the marrow space of the involved bone are continuous with the lesion. Malignant degeneration to a chondrosarcoma is rare in children but occurs in up to 1% of adults. Routine removal is not performed unless the lesion is large enough to cause symptoms, such as pain or nerve compression, most frequently presenting as footdrop. Osteochondromas can be diagnosed by radiographs alone, and unless patients present with unusual symptoms such as night pain, further studies such as CT or MRI are not typically indicated. Patients should be referred to an orthopedic practice for counseling, but routine radiographic follow-up and treatment should be based on symptoms.

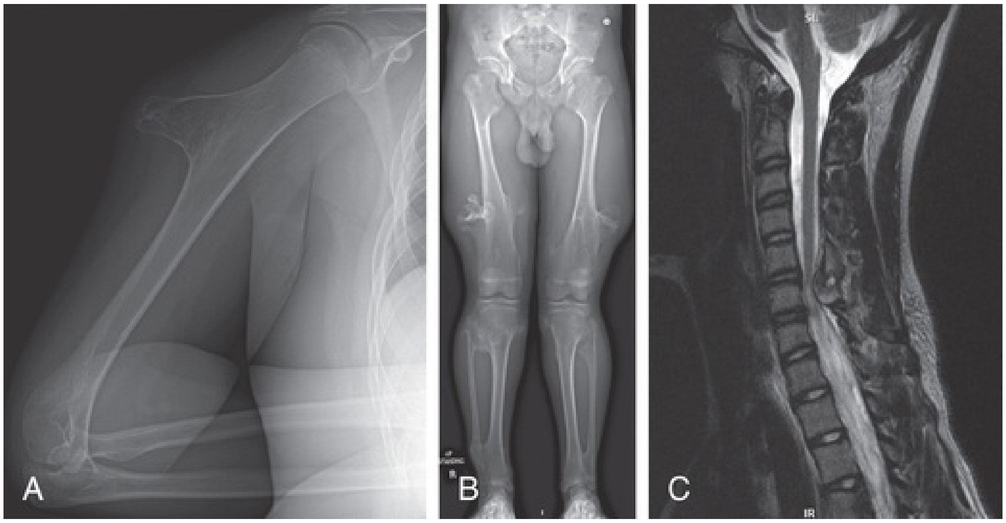

FIG. 528.5 **A,** Lateral radiograph of the right humerus showing isolated osteochondroma. Bone lesion is in continuity with the medullary canal and points away from the growth plate. **B,** Hip-to-ankle radiograph in a child with multiple hereditary exostoses (MHE) showing many osteochondromas about the knees and ankles. **C,** Sagittal T2-weighted MR image of the cervical spine in a 15 yr old female with MHE who underwent routine cervical screening MRI, which detected asymptomatic spinal stenosis caused by C6 osteochondroma. She underwent urgent decompression.

Multiple hereditary exostoses (MHE) is a related but rare condition characterized by the presence of multiple osteochondromas (Fig. 528.5*B*). Severely involved children can have short stature, limb-length inequality, premature partial physeal arrests, and deformity of both the upper and lower extremities, including genu valgum and dislocation of the radial head at the elbow. These children must be monitored carefully during growth by a pediatric orthopedist. Screening MRI of the entire spine is recommended during childhood to detect bony lesions growing into the canal, which can result in spinal cord compression and may occur in up to 20–30% of patients (Fig.

528.5*C*).

Subungual exostosis is an osteochondroma that forms underneath the nail bed in an otherwise healthy child. The nail bed may become discolored or raised, and the condition is typically painful (Fig. 528.6). It can be differentiated from a paronychia or ingrown toenail by radiographs, which show a bony protuberance under the nail bed. Treatment should be nail removal, surgical excision of the lesion, and nail bed repair. Despite surgical excision, recurrence can occur up to 5% of patients.

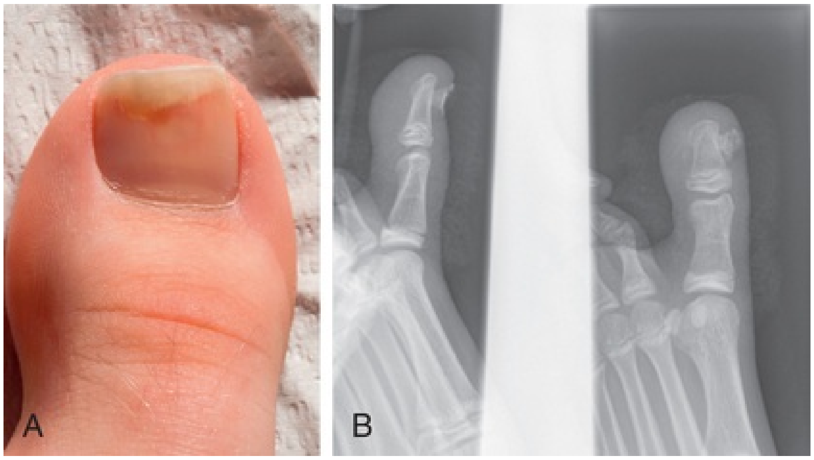

FIG. 528.6 **A,** Photograph of the great toe showing nail bed abnormality. **B,** Lateral and oblique views of the left great toe showing subungual exostosis. These lesions are typically painful and require surgical removal.

Enchondroma is a benign lesion of hyaline cartilage that occurs centrally in the bone. These lesions are asymptomatic and frequently occur in the hands. Most are discovered incidentally, although pathologic fractures often lead to the diagnosis. Radiographically, the lesions occupy the medullary canal, are radiolucent, and are sharply marginated. Punctate or stippled calcification may be present within the lesion, but this is much more common in adults than in children. Almost all enchondromas in children are solitary and small. Most can simply be observed, with curettage and bone grafting reserved for lesions that are symptomatic or large enough to weaken the bone structurally. Large lesions with extensive involvement may represent **low-grade chondrosarcoma** . Multifocal involvement is referred to as **Ollier disease** and can result in bone dysplasia, short stature, limb-length inequality, and joint deformity. Surgery may be necessary to correct or prevent such deformities. When multiple enchondromas are associated with angiomas of the soft tissue, the condition is referred to as **Maffucci syndrome** . A high rate of malignant transformation has been reported in both these multifocal conditions.

Chondroblastoma is a rare lesion usually found in the epiphysis of long bones. Most patients present in the 2nd decade with complaints of stiffness or mild to moderate pain in the adjacent joint. Common sites include the hip, shoulder, and knee. Muscle atrophy and local tenderness may be the only clinical findings. The lesion appears radiographically as a sharply marginated radiolucency within the epiphysis or apophysis, occasionally with metaphyseal extension across the physis. Proximity to the joint can cause deformity of the subchondral bone, an effusion, or erosion into the joint (Fig. 528.7). Recognition is important because most lesions can be cured with curettage and bone grafting before joint or physeal destruction occurs. Complete eradication with aggressive debridement is difficult because the lesion abuts the growth plate and joint surface. Recurrence is common, so ongoing monitoring is required. Pulmonary metastasis can also occur.

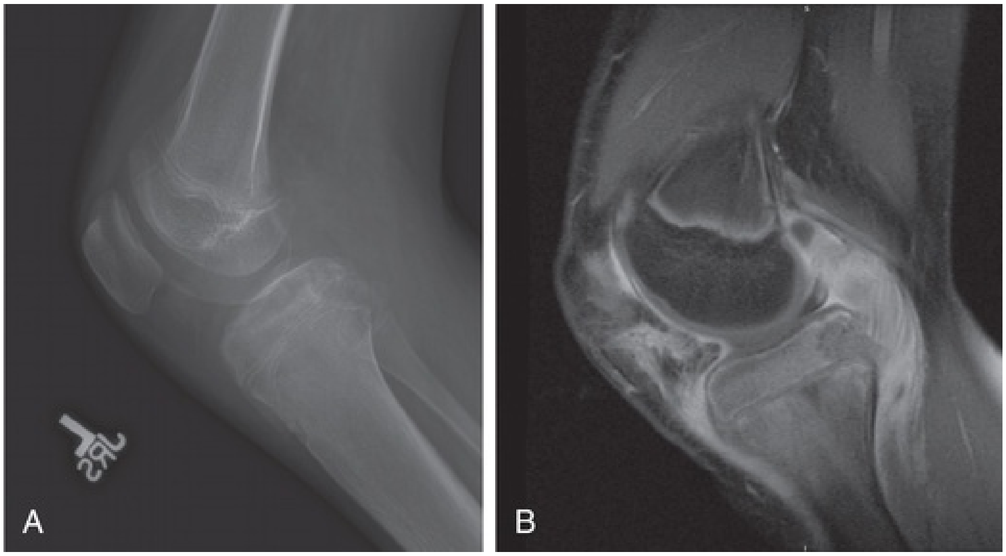

FIG. 528.7 **Chondroblastoma in 11 yr old girl with left tibial knee flexion contracture. A, Lateral radiograph shows epiphyseal lesion in the posterior proximal tibia. B, Sagittal MR image shows knee effusion and extension of the lesion into the posterior joint space. Patient underwent resection of the lesion and regained normal knee motion.**

Chondromyxoid fibroma is an uncommon benign bone tumor in children. This metaphyseal lesion usually causes pain and local tenderness, but occasionally is asymptomatic. Chondromyxoid fibroma appears radiographically as an eccentric, lobular, metaphyseal radiolucency with sharp, sclerotic, and scalloped margins. The lower extremity is involved most often. Treatment usually consists of curettage and bone grafting or en bloc resection.

Osteoid osteoma is a small benign bone tumor found in the proximal tibia and femur and the posterior elements of the spine. Most of these tumors are diagnosed between 5 and 20 yr of age. The clinical pattern is characteristic, consisting of unremitting and gradually increasing pain that often is worst at night and is relieved by nonsteroidal antiinflammatory drugs (NSAIDs). Boys are affected more often than girls. Vertebral lesions can cause scoliosis or symptoms that mimic a neurologic disorder. Examination can reveal a limp, atrophy, and weakness when the lower extremity is involved. Palpation and range of motion do not alter the discomfort. Radiographs may show cortical thickening, and CT shows distinctive findings, with a round or oval metaphyseal or diaphyseal lucency (0.5-1.0 cm in diameter) surrounded by dense sclerotic bone (Fig. 528.8). The central lucency, or *nidus*, shows intense uptake on bone scan. Approximately 25% of osteoid osteomas are not visualized on plain radiographs but can be identified with CT. Because of the small size of the lesion and its location adjacent to thick cortical bone, MRI is poor at diagnosing osteoid osteomas, revealing only extensive T2 signal change throughout the region. Treatment is directed at removing the lesion. Patients may be treated with NSAIDs, and the symptoms typically resolve within 1-2 yr. Most patients and families elect for treatment. Percutaneous treatments such as radiofrequency ablation and cryoablation have become the standard of care for routine lesions. There is still an occasional role for open surgical resection, if there is concern for osteomyelitis (**Brodie abscess**), or the lesion is close to articular cartilage or neurovascular structures.

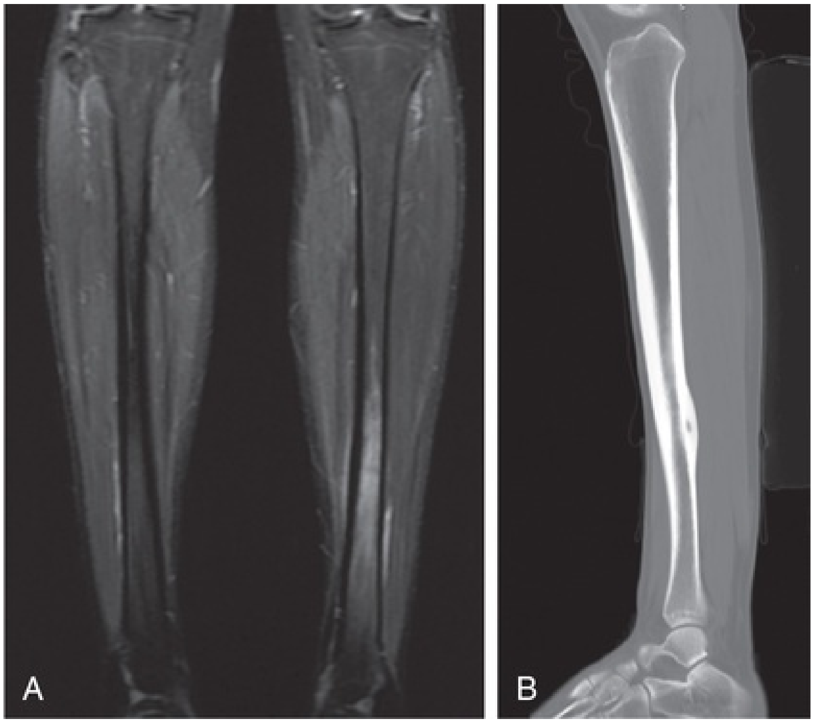

FIG. 528.8 MRI and CT in 15 yr old girl with left tibial night pain. A, Coronal T2-weighted MR of the bilateral tibias shows increased T2 signal change in the left tibia diaphysis. B, Sagittal CT scan shows cortically-based lesion <1 cm typical for osteoid osteoma. Patient was treated with percutaneous radiofrequency ablation.

Osteoblastoma is a locally destructive, progressively growing lesion of bone with a predilection for the vertebrae, although almost any bone may be involved. Most patients note the insidious onset of dull, aching pain, which may be present for months before patients seek medical attention. Spinal lesions can cause neurologic symptoms or deficits. The radiographic appearance is variable and less distinctive than that of other benign bone tumors. CT or MRI is indicated. Approximately 25% show features suggesting a malignant neoplasm, making biopsy necessary in many cases. Expansile spinal lesions often involve the posterior elements. Treatment involves curettage and bone grafting or en bloc excision. Surgical stabilization of the spine may be necessary.

Fibromas (nonossifying fibroma, fibrous cortical defect, metaphyseal fibrous defect) are fibrous lesions of bone that occur in up to 40% of children >2 yr old. They most likely represent a defect in ossification rather than a neoplasm and usually are asymptomatic. Most are discovered incidentally when radiographs are taken for other reasons, usually to rule out a fracture after trauma. Occasional pathologic fractures can occur through large lesions. Physical examination usually is unrevealing. Radiographs show a sharply marginated, eccentric lucency in the metaphysis or metaphyseal cortex (Fig.

528.9). Lesions may be multilocular and expansile, with extension from the cortex into the medullary bone. The long axis of the lesion runs parallel to that of the bone. Approximately 50% are bilateral or multiple. Because of the characteristic radiographic appearance, most lesions do not require axial imaging, biopsy, or treatment. If the child is asymptomatic, no further monitoring is needed for characteristic lesions. Spontaneous regression can be expected after skeletal maturity. Curettage and bone grafting may be considered for symptomatic lesions or lesions occupying >50% of the bone diameter, because of the risk of a pathologic fracture.

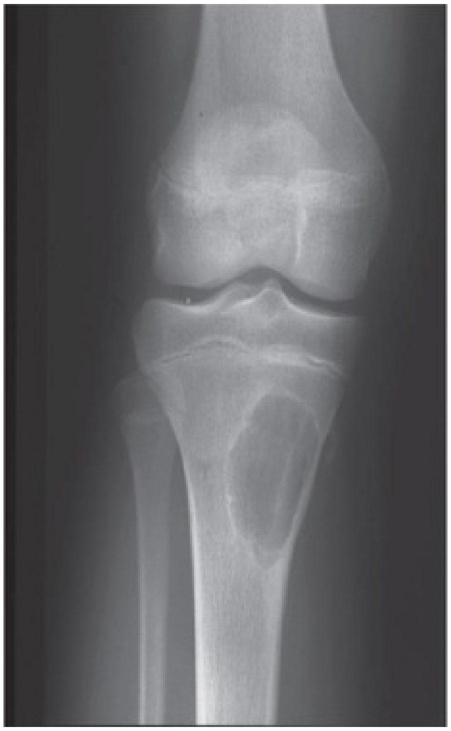

FIG. 528.9 Anteroposterior radiograph of the knee showing nonossifying fibroma, which was discovered incidentally.

Unicameral bone cysts can occur at any age in childhood but are rare in children <3 yr old and after skeletal maturity. The cause of these fluid-filled lesions is unknown. Spontaneous resolution after skeletal maturity is expected, although pathologic fracture can be a significant problem in the interim. Diagnosis usually follows a pathologic fracture (Fig. 528.10). Such fractures can occur with relatively minor trauma, such as with throwing or catching a ball. Unicameral bone cysts appear radiographically as solitary, centrally located lesions within the medullary portion of the bone. These cysts are most common in the proximal humerus or femur. They often extend to (but not through) the physis and are sharply marginated. The cortex expands, but this does not exceed the width of the adjacent physis. Treatment involves allowing the pathologic fracture to heal. Subsequently, humerus lesions can be observed or treated. Proximal femoral lesions are typically treated because of the risk of pathologic fracture. Treatments include aspiration and injection with methylprednisolone or injectable calcium phosphate. A recent randomized controlled trial (RCT) showed a 42% healing rate with corticosteroid injections (1-3, mean 1.7 injections) compared to injection of bone marrow aspirate (23% healing rate, 1-3 injections, 2.1 mean). Open biopsy and bone grafting with or without internal fixation can also be performed. Recurrence is common despite surgical treatment. Repeat injections are frequently necessary to treat recurrent lesions. Healing rates are higher with injection or surgical treatment compared to observation, and internal fixation is recommended for proximal femoral lesions given the high risk of fracture.

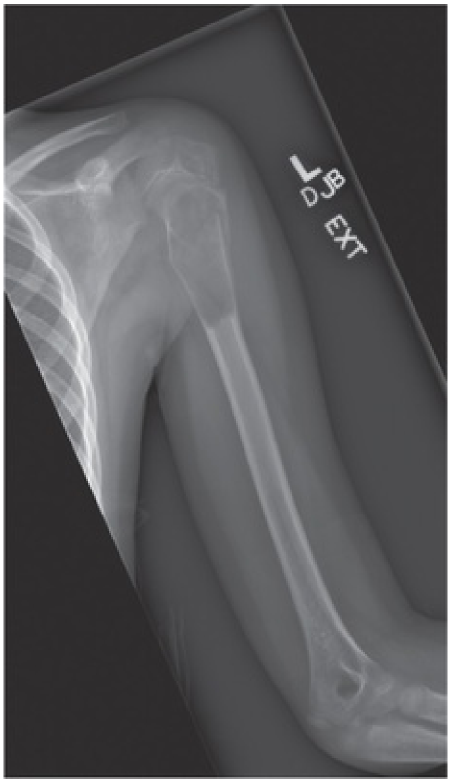

FIG. 528.10 External rotation view of the left humerus in a 9 yr old girl who presented with pain after falling off her bicycle. Imaging is consistent with

simple bone cyst.

Aneurysmal bone cyst (ABC) is a reactive lesion of bone typically seen in persons <20 yr old. The lesion is characterized by cavernous spaces filled with blood and solid aggregates of tissue. Although the femur, tibia, and spine are most often involved, this progressively growing, expansile lesion can develop in any bone. Radiographs show eccentric, lytic destruction and expansion of the metaphysis surrounded by a thin sclerotic rim of bone. Pain and swelling are common. Spinal involvement can lead to cord or nerve root compression and associated neurologic symptoms, including paralysis. Posterior elements of the spine are involved more often than the vertebral body. Unlike most other benign bone tumors, which usually are confined to a single bone, ABCs can involve adjacent vertebrae. Spinal lesions can require stabilization after excision. As with other benign tumors, attempts are made to preserve nerve roots and other vital structures. Rapid growth is characteristic and can lead to confusion with malignant neoplasms. ABCs can occur concomitantly with neoplasms, confounding pathology results from biopsy. Treatment consists of curettage and bone grafting or excision. Recurrence after surgical treatment occurs in 20–30% of patients, is more common in younger than older children, and usually occurs in the 1st 1-2 yr after treatment. Treatment approaches include percutaneous injection of doxycycline, which targets the specific MMP-upregulation pathway seen in ABCs and has shown promising preliminary results, particularly for recurrent or multiloculated lesions.

Fibrous dysplasia is a developmental abnormality characterized by fibrous replacement of cancellous bone. Lesions may be solitary or multifocal (**polyostotic**). Lesions may progress over time or may be stable. Some children are asymptomatic, although others have bone pain. Those with skull involvement might have swelling or exophthalmos. Pain and limp are characteristic of proximal femoral involvement, which also may indicate impending pathologic fracture. Limb-length discrepancy, bowing of the tibia or femur, and pathologic fractures may be presenting complaints. The triad of polyostotic disease, precocious puberty, and cutaneous pigmentation is known as **McCune-Albright syndrome** . Radiographic features of fibrous dysplasia include a lytic or ground-glass expansile lesion of the metaphysis or diaphysis. The lesion is sharply marginated and often is surrounded by a thick rim of sclerotic bone. Bowing, especially of the proximal femur, may be present. Treatment usually involves observation for asymptomatic lesions. Surgery is indicated for patients with progressive deformity, pain, or impending pathologic fractures. Bone grafting is not as successful in the treatment of fibrous dysplasia, because the lesion recurs within the grafted bone. Reconstructive surgical techniques with metal implants often are necessary to provide stability and treat pain, particularly in the proximal femur. In addition to surgical stabilization, bisphosphonate therapy has been used to treat bone pain, although a recent RCT showed improvement in regional bone mineral density but no change in pain scores.

Characteristic Lesions of the Tibia

Osteofibrous dysplasia affects the tibia in children. Most children present with anterior swelling or enlargement of the leg. Radiographs show solitary or multiple, lucent cortical diaphyseal lesions surrounded by sclerosis. Anterior bowing of the tibia often is present, and pathologic fracture can occur. The radiographic appearance closely resembles that of adamantinoma, a malignant neoplasm, making biopsy more common than with other benign bone tumors. Some believe osteofibrous dysplasia is a precursor lesion to adamantinoma. Treatment options include observation, excision and bone grafting, or wide resection.

Adamantinoma is a rare malignancy typically found in adults but occasionally in children. In contrast to osteofibrous dysplasia, the lesion involves the medullary canal. Wide resection is indicated, because radiation or chemotherapy has no known benefit in this slow-growing tumor.

Histiocytosis

Langerhans cell histiocytosis is a monostotic or polyostotic disease that can also involve the skin, liver, or other organs. Single-site disease should be distinguished from the other forms of Langerhans cell histiocytosis (**Hand-Schüller-Christian** or **Letterer-Siwe** variants), which can have a less favorable prognosis (see Chapter 534.1). Langerhans cell histiocytosis usually occurs during the 1st 3 decades of life and is most common in boys 5-10 yr old. The skull is most frequently affected, but any bone may be involved. Patients usually present with local pain and swelling. Marked tenderness and warmth often are present around the involved bone. Spinal lesions can cause pain, stiffness, and occasional neurologic symptoms. The classic spinal lesion is **vertebra plana**

with uniform compression or flattening of the vertebral body. The radiographic appearance of the skeletal lesions is similar in all forms of Langerhans cell histiocytosis but is variable enough to mimic many other benign and malignant lesions of bone as well as infection. The radiolucent lesions have well-defined or irregular margins with expansion of the involved bone and periosteal new bone formation. A skeletal survey is warranted because lesions may not be apparent on bone scan. *Polyostotic* involvement and the typical skull lesions strongly suggest the diagnosis of **eosinophilic granuloma** . Biopsy often is necessary to confirm the diagnosis because of the broad radiographic differential diagnosis. Treatment for isolated bone lesions includes curettage and bone grafting or observation. Observation for asymptomatic lesions is reasonable because most osseous lesions heal spontaneously and do not recur. Children with bone lesions should be evaluated for visceral involvement because multisystem organ disease may exist with the bone lesion and may not be obvious. Treatment of multisystem disease is more complex, often systemic, and may require chemotherapy. For multisystem disease, bone lesions frequently improve with systemic chemotherapy.

Diagnostic Considerations

Infection and fracture should always be considered in the differential diagnosis of tumor-like processes of bone. Young children cannot report a history of trauma, and nondisplaced fractures may not be apparent on radiographs until new bone formation is visible at 1-2 wk. Atypical or multiple fractures in various states of healing should prompt metabolic and child abuse workup. Bone infections are common in the pediatric orthopedic population, occurring in up to 1 in 10,000 healthy children. A child with a chronic bone infection may have normal inflammatory lab work and no constitutional symptoms. Thus, infection should always be considered for noncharacteristic bone lesions in children. **Eosinophilic granuloma** and **Ewing sarcoma** in particular may have features that resemble bone infection. Thus, cultures as well as pathology specimens should always be taken at biopsy and a high index of suspicion maintained.

Vascular Tumors of Bone

There is a wide spectrum of vascular bone tumors (Table 528.3), which, depending on severity, may produce local sclerosis or osteopenia. More severe lesions are locally aggressive and result in cortical destruction.

Table 528.3

Summary of Prognosis and Treatment of Vascular Bone Tumors

CLASSIFICATION	ENTITY	PROGNOSIS	TREATMENT
Benign	Hemangioma	100% survival, 0% metastasis	Treat symptoms
Intermediate	Epithelioid hemangioma	100% survival, 2% metastases, 9% local recurrence	Curettage or marginal excision
	Pseudomyogenic hemangioendothelioma	Limited follow-up, stable or progressive osseous disease	
Malignant	Epithelioid hemangioendothelioma	85% survival, 25% metastases	Wide resection
	Angiosarcoma	30% survival	Wide resection, consider systemic therapy

From van IJzendoorn DGP, Bovee JVMG: Vascular tumors of bone: the evolvement of a classification based on molecular developments. *Surg Pathol Clin* 10:621–635, 2017 (Table 1, p. 622).

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CHAPTER 529

Retinoblastoma

Nidale Tarek, Cynthia E. Herzog

Retinoblastoma is an embryonal malignancy of the retina and the most common intraocular tumor in children. Although the survival rate of children with retinoblastoma in the United States and developed countries is extremely high, retinoblastoma progresses to metastatic disease and death in >50% of children worldwide. Furthermore, the associated loss of vision and side effects of therapy are significant problems that remain to be addressed.

Epidemiology

Approximately 250-350 new cases of retinoblastoma are diagnosed each year in the United States, with no known racial or gender predilection. The cumulative lifetime incidence of retinoblastoma is approximately 1 in 20,000 live births, and retinoblastoma accounts for 4% of all pediatric malignancies. The median age at diagnosis is approximately 2 yr, and >90% of cases are diagnosed in children <5 yr old. Overall, 66–75% of children with retinoblastoma have unilateral tumors, with the remainder having bilateral retinoblastoma. Bilateral involvement is more common in younger children, particularly in those diagnosed before age 1 yr, and is always heritable. Risk of retinoblastoma may be increased in children conceived by in vitro fertilization.

Retinoblastoma can be either hereditary or sporadic. **Hereditary** cases usually are diagnosed at a younger age and are multifocal and bilateral, whereas **sporadic** cases are usually diagnosed in older children, who tend to have unilateral, unifocal involvement. The hereditary form is associated with loss of function of the **retinoblastoma gene *(RB1)*** via gene mutation or deletion. *RB1* is located on chromosome 13q14 and encodes the retinoblastoma protein, a tumor-suppressor protein that controls cell cycle phase transition and has roles in apoptosis and cell differentiation. Many different causative mutations have been identified, including translocations, deletions, insertions, point mutations, and epigenetic modifications such as gene methylation. The nature of the predisposing mutation can affect the penetrance and expressivity of retinoblastoma development.

According to Knudson's “2-hit” model of oncogenesis, 2 mutational events are required for retinoblastoma tumor development (see Chapter 519). In the hereditary form of retinoblastoma, the 1st mutation in *RB1* is inherited through germinal cells, and a 2nd mutation occurs subsequently in somatic retinal cells. Second mutations that lead to retinoblastoma often result in the loss of the normal allele and concomitant loss of heterozygosity. Parents and siblings of a child with a germline mutation should be referred to a genetic specialist for testing; most children with hereditary retinoblastoma have spontaneous new germinal mutations, and both parents have wild-type retinoblastoma genes. All first-degree relatives of children with known or suspected hereditary retinoblastoma should have retinal examinations to identify retinomas or retinal scars, which may suggest hereditary retinoblastoma even though malignant retinoblastoma did not develop. In the sporadic form of retinoblastoma, the 2 mutations occur in somatic retinal cells. Heterozygous carriers of oncogenic *RB1* mutations demonstrate variable phenotypic expression.

Pathogenesis

Histologically, retinoblastoma appears as a small, round, blue cell tumor with rosette formation (**Flexner-Wintersteiner rosettes**). It may arise in any of the nucleated layers of the retina and exhibit various degrees of differentiation. Retinoblastoma tumors tend to outgrow their blood supply, resulting in necrosis and calcification.

Endophytic tumors arise from the inner surface of the retina and grow into the vitreous and can also grow as tumors suspended within the vitreous itself, known as **vitreous seeding** . *Exophytic* tumors grow from the outer retinal layer and can cause retinal detachment. Diffuse infiltrating tumors grow intraretinally and remain flat; these are less common and can cause iris neovascularization. Tumors can also be both endophytic and exophytic. These tumors can also spread by direct extension to the choroid or along the optic nerve beyond the lamina cribrosa to the central nervous system, or by hematogenous or lymphatic spread to distant sites, including bones, bone marrow, and lungs.

Screening

Children with a positive family history of retinoblastoma should undergo a dilated eye examination under general anesthesia early in life and at regular interval until genetic testing is performed and results are available. Infants with a negative genetic test require no further screening; infants with a positive genetic test require regular screening ophthalmologic examinations until age 5 yr.

Clinical Manifestations

Retinoblastoma classically presents with **leukocoria,** a *white pupillary reflex* , which often is first noticed when a red reflex is not present at a routine newborn or well-child examination or in a flash photograph of the child (Fig. 529.1). Strabismus often is an initial presenting complaint. Decreased vision, orbital inflammation, hyphema, and pupil irregularity can occur with advancing disease. Pain can occur if secondary glaucoma is present. Only approximately 10% of retinoblastoma cases are detected by routine ophthalmologic screening in the context of a positive family history.

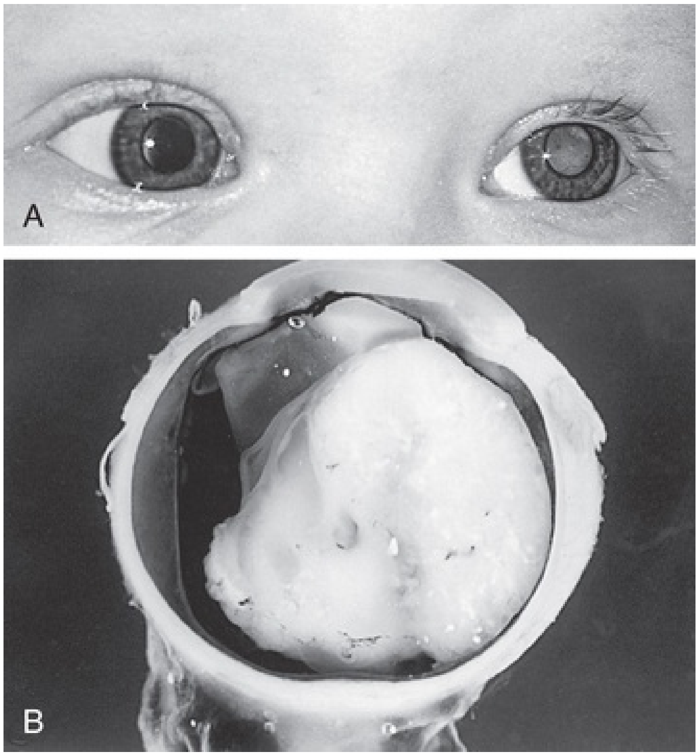

FIG. 529.1 **A,** Leukocoria noted in the left eye of a child presenting with retinoblastoma. **B,** A large white tumor mass noted within the posterior chamber of the enucleated eye. (From Shields JA, Shields CL: Current management of retinoblastoma, *Mayo Clin Proc* 69:50–56, 1994.)

Diagnosis

The diagnosis is established by the characteristic ophthalmologic findings of a chalky, white-gray retinal mass with a soft, friable consistency. Imaging studies are not diagnostic, and biopsies are contraindicated. Indirect ophthalmoscopy with slit-lamp evaluation can detect retinoblastoma tumors, but a complete evaluation requires an examination under general anesthesia by an experienced ophthalmologist to obtain complete visualization of both eyes, which also facilitates photographing and mapping of the tumors. Retinal detachment or vitreous hemorrhage can complicate the evaluation.

Orbital ultrasonography, CT, or MRI is used to evaluate the extent of intraocular disease and extraocular spread (Fig. 529.2). In approximately 5% of cases, a pineal area (primitive neuroectodermal) tumor is detected in a child with hereditary and bilateral retinoblastoma, a phenomenon known as **trilateral retinoblastoma** . MRI allows for better evaluation of optic nerve involvement. Metastatic disease is rarely present at diagnosis; evaluation of the cerebrospinal fluid and bone marrow for tumor metastasis and radionuclide bone scan are required only if indicated by other clinical, laboratory, or imaging findings.

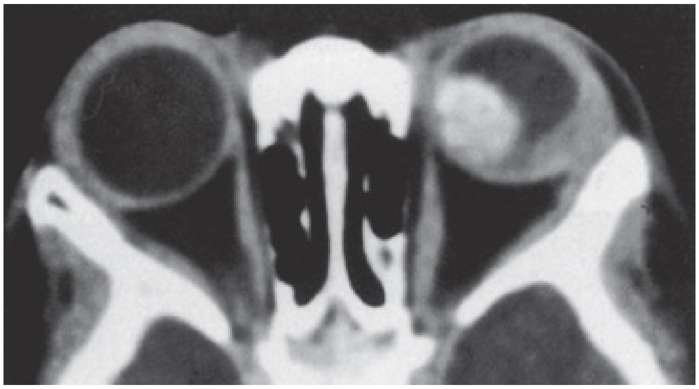

FIG. 529.2 Axial contrast-enhanced CT scan shows calcified retinoblastoma of the left eye. (From Haaga JR, Boll DT, et al, editors: *CT and MRI of the whole body,* ed 6, Philadelphia, 2017, Elsevier, Fig 20-32.)

The **differential diagnosis** of retinoblastoma includes other causes of leukocoria, including persistent hyperplastic primary vitreous, Coats disease, vitreous hemorrhage, cataract, endophthalmitis from *Toxocara canis* , choroidal coloboma, retinopathy of prematurity, and familial exudative vitreoretinopathy.

Treatment

Treatment is determined by the size and location of the tumors, if the disease is localized to the eye or has spread either to the brain or to the rest of the body, and whether the child has hereditary or sporadic disease. The primary goal of treatment is always cure; the secondary goals include preserving vision and the eye itself and decreasing the risk of late side effects, mainly secondary malignancies. As newer modalities for local control of intraocular tumors and more effective systemic chemotherapy have emerged, primary enucleation is being performed less often.

Most unilateral disease presents with a solitary, large tumor. **Enucleation** is performed if useful vision cannot be salvaged. With bilateral disease, chemoreduction in combination with **focal therapy** (laser photocoagulation or cryotherapy) has replaced the traditional approach of enucleation of the more severely affected eye and irradiation of the remaining eye. If feasible, small tumors can be treated with focal therapy with careful follow-up for recurrence or new tumor growth. Larger tumors often respond to multiagent **chemotherapy** , including carboplatin, vincristine, and etoposide given intravenously. The delivery of chemotherapy via the ophthalmic artery is becoming more common, as is delivery of intravitreal chemotherapy. If these approaches fail, **external-beam irradiation** should be considered, although this approach may result in significant orbital deformity and increased incidence of second malignancies in patients with germline *RB1* mutations. **Brachytherapy** , or *episcleral plaque radiotherapy,* is an alternative with less morbidity. Enucleation may be required for unresponsive or recurrent tumors. Alternative treatment options currently under investigation include other systemic chemotherapy agents, such as topotecan, and intense multiagent chemotherapy with autologous stem cell rescue for patients with metastatic disease.

Prognosis

Approximately 95% of U.S. children with retinoblastoma are cured with modern treatment. Current efforts using chemotherapy in combination with focal therapy are intended to preserve useful vision and avoid external-beam radiation or enucleation. Routine ophthalmologic examinations should continue until children are >7 yr old. Unfortunately, the diagnosis of retinoblastoma in many children from Third World countries is delayed, resulting in spread of the tumor outside the orbit. The prognosis for children with retinoblastoma that has spread outside the eye is poor. Trilateral retinoblastoma, disease involving both eyes and the pineal region, is almost universally fatal.

Children with germline *RB1* mutations are at significant risk for development of second malignancies, especially osteosarcoma, as well as soft tissue sarcomas and malignant melanoma. The risk of second malignancies is further increased by the use of radiation therapy. Other radiation-related late adverse effects include cataracts, orbital growth deformities, lacrimal dysfunction, and late retinal vascular injury.

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CHAPTER 530

Gonadal and Germ Cell Neoplasms

Cynthia E. Herzog, Winston W. Huh

Epidemiology

Malignant **germ cell tumors (GCTs)** and gonadal tumors are rare, with an incidence of 12 cases per 1 million persons younger than 20 yr. Most malignant tumors of the gonads in children are GCTs. The incidence varies according to age and sex, although the incidence of GCTs in adolescent males has increased over time. **Sacrococcygeal** tumors occur predominantly in infant females. **Testicular** GCTs occur predominantly before age 4 yr and after puberty. Klinefelter syndrome is associated with an increased risk of **mediastinal** GCTs. Down syndrome, undescended testes, infertility, testicular atrophy, testicular microlithiasis, testicular dysgenesis syndrome, and inguinal hernias are associated with an increased risk of **testicular cancer** . The risk of testicular cancer in patients with cryptorchidism is reduced but not eliminated if orchiopexy is performed before 13 yr of age. The risk of testicular GCT is increased in first-degree relatives and is highest among monozygotic twins.

Pathogenesis

The GCTs and non-GCTs arise from primordial germ cells and coelomic epithelium, respectively. Testicular and sacrococcygeal GCTs arising during early childhood characteristically have deletions at chromosome arms 1p and 6q and gains at 1q, and they lack the isochromosome 12p that is highly characteristic of malignant GCTs of adults. Testicular GCT also may demonstrate loss of imprinting. Ovarian GCTs from older females characteristically have deletions at 1p and gains at 1q and 21. Because GCTs may contain benign and mixed malignant elements in different areas of the tumor, extensive sectioning is essential to confirm the correct diagnosis. The many histologically distinct subtypes of GCTs include **teratoma** (mature and immature), endodermal sinus tumor, and embryonal carcinoma (Fig. 530.1). Non-GCTs of the ovary include epithelial (serous and mucinous) and sex cord–stromal tumors; non-GCTs of the testicle include sex cord–stromal (e.g., Leydig cell, Sertoli cell) tumors. *DICER1* mutations have been observed in nonepithelial ovarian cancers, especially in Sertoli-Leydig tumors. Table 530.1 provides a histologic classification of testicular GCTs.

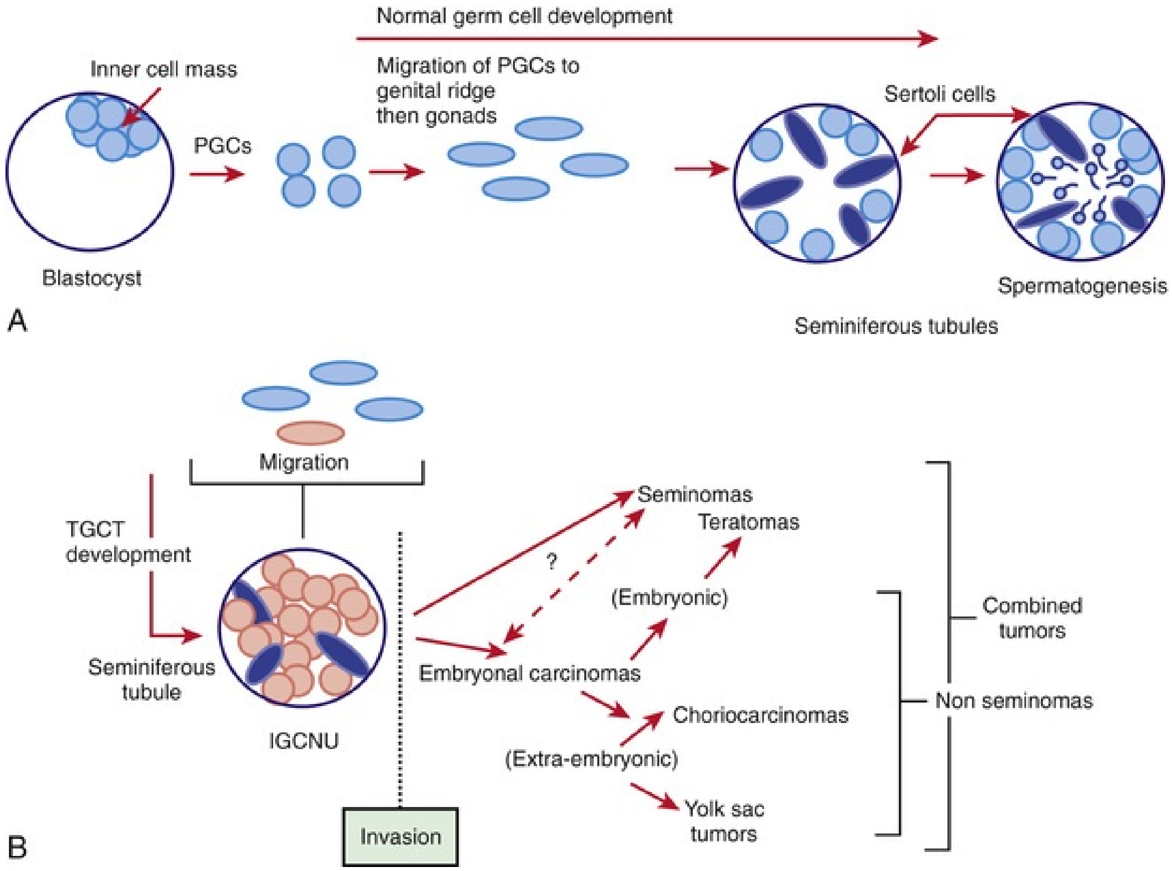
Normal germ cell development
Inner cell mass
Migration of PGCs to genital ridge then gonads
Sertoli cells
PGCs
Blastocyst
Spermatogenesis
Seminiferous tubules
A
Migration
TGCT development
Seminiferous tubule
IGCNU
Seminomas
Teratomas
?
(Embryonic)
Embryonal carcinomas
Choriocarcinomas
(Extra-embryonic)
Yolk sac tumors
Combined tumors
Non seminomas
Invasion
B

FIG. 530.1 **A,** Normal germ cell development. **B,** Model for the origin and histogenesis of different subtypes of testicular germ cell tumors. *IGCNU,* Intratubular germ cell neoplasia unclassified; *PGCs,* primary germ cells; *TGCT,* testicular germ cell tumor.

Table 530.1

Main Histologic Types of Testicular Germ Cell Tumors*

NONINVASIVE GERM CELL NEOPLASIA
Germ cell neoplasia in situ (GCNIS; previous synonyms: carcinoma in situ testis, intratubular germ cell neoplasia unclassified) Gonadoblastoma (in patients with disorders of sex development; tumor also contains sex cord–stromal elements)
GERM CELL TUMORS DERIVED FROM GCNIS
Seminoma Nonseminoma (nonseminomatous germ cell tumors) Embryonal carcinoma Teratoma (postpubertal type) Yolk sac tumor (postpubertal type) Choriocarcinoma and other trophoblastic tumors
GERM CELL TUMORS UNRELATED TO GCNIS
Childhood tumors Teratoma (prepubertal type) Yolk sac tumor (prepubertal type) Spermatocytic tumor (median age at diagnosis: approximately 50 yr)

[*] Based on updated WHO classification of tumors of the testis and paratesticular tissue.

Adapted from Raypert-De Meyts E, McGlynn KA, Okamoto, et al: Testicular germ cell tumours, *Lancet* 387:1762–1770, 2016 (panel, p 1763).

Clinical Manifestations and Diagnosis

The clinical presentation of germ cell neoplasms depends on location. Ovarian tumors often are quite large by the time they are diagnosed (Fig. 530.2). Extragonadal GCTs occur in the midline, including the suprasellar region, pineal region, neck, mediastinum, and retroperitoneal and sacrococcygeal areas (Fig. 530.3). Symptoms relate to mass effect, but the intracranial GCTs often present with anterior and posterior pituitary deficits (see Chapter 524).

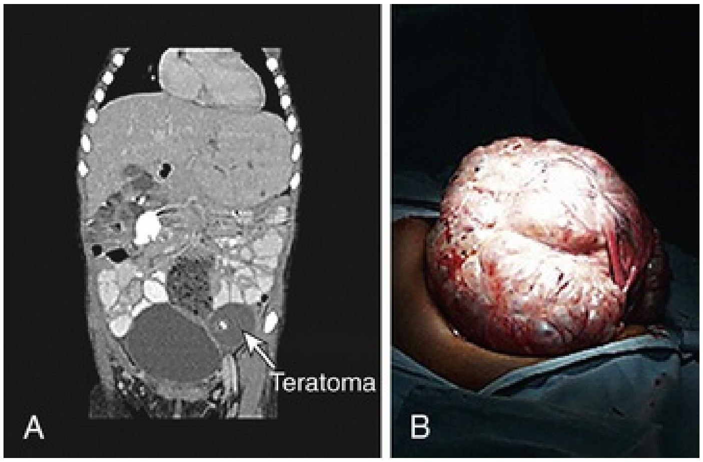

FIG. 530.2 **A,** Postnatal MR image showing a left ovarian teratoma with

bony calcification. **B,** Massive ovarian teratoma. (From Lakhoo K: Neonatal teratomas, *Early Hum Dev* 86(10):643–647, 2010.)

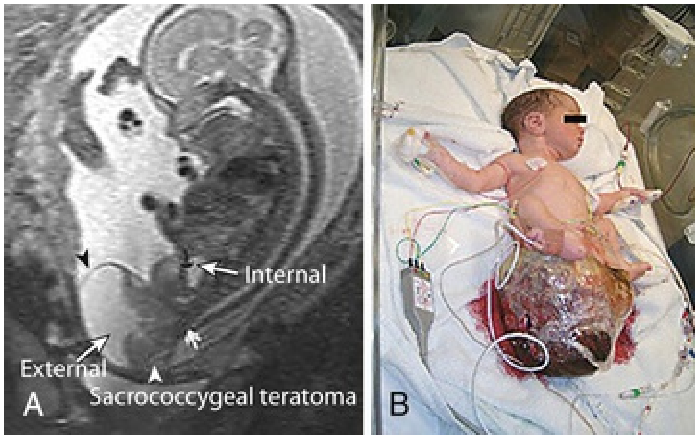

FIG. 530.3 **A,** Prenatal MR image showing sacrococcygeal teratoma with a small internal and large external component. **B,** Postnatal large, bleeding sacrococcygeal teratoma. (From Lakhoo K: Neonatal teratomas, *Early Hum Dev* 86(10):643–647, 2010.)

The serum α-fetoprotein (**AFP**) level is elevated with endodermal sinus tumors and may be minimally elevated with teratomas. Infants normally have higher levels of AFP, which usually falls to normal adult levels by about age 8 mo; consequently, high AFP levels must be interpreted with caution in this age-group. Elevation of the β subunit of human chorionic gonadotropin (**β-hCG**), which is secreted by syncytiotrophoblasts, is seen with choriocarcinoma and germinomas. Lactate dehydrogenase, although nonspecific, may be a useful marker. If elevated, these markers provide important confirmation of the diagnosis and provide a means to monitor the patient for tumor response and recurrence. Both serum and cerebrospinal fluid (CSF) should be assayed for these markers in patients with intracranial lesions.

Diagnosis begins with physical examination and imaging studies, including plain radiographs of the chest and ultrasonography of the abdomen. CT or MRI can further delineate the primary tumor. If germ cell malignancy is strongly suggested, preoperative staging with CT of the chest and bone scan is appropriate. Primary surgical resection is indicated for tumors deemed resectable. For older patients with testicular tumors, ipsilateral retroperitoneal lymph node sampling may be required to determine extent of disease and aid in treatment planning. Ovarian tumors also require detailed surgical evaluation, including lymph node removal and pelvic washings for cytologic analysis for peritoneal spread. Diagnosis of intracranial lesions can be established with imaging and AFP or β-hCG determinations of serum and CSF.

Gonadoblastomas often occur in patients with gonadal dysgenesis and all or parts of a Y chromosome. **Gonadal dysgenesis** is characterized by failure to fully masculinize the external genitalia. If this syndrome is diagnosed, imaging of the gonad with ultrasonography or CT is performed, and surgical resection of the tumor usually is curative. Prophylactic resection of dysgenetic gonads at the time of diagnosis is recommended, because gonadoblastomas, some of which contain malignant GCT elements, often develop. Gonadoblastomas may produce abnormal amounts of estrogen.

Teratomas occur in many locations, presenting as masses. They are not associated with elevated markers unless malignancy is present. The sacrococcygeal region is the most common site for teratomas. Sacrococcygeal teratomas occur most commonly in infants and may be diagnosed in utero or at birth, with most found in girls. The rate of malignancy in this location varies, ranging from <10% in children younger than 2 mo to >50% in children older than 4 mo.

Germinomas occur intracranially, in the mediastinum, and in the gonads. In the ovary, they are called **dysgerminomas,** and in the testis, they are called **seminomas.** They usually are tumor-marker–negative masses despite being malignant. Endodermal sinus or yolk sac tumor and choriocarcinoma appear highly malignant by histologic criteria. Both occur at gonadal and extragonadal sites. Embryonal carcinoma most often occurs in the testes. Choriocarcinoma and embryonal carcinoma rarely occur in the pure form and are usually found as part of a mixed malignant GCT.

Non–germ cell gonadal tumors are very uncommon in pediatrics and occur predominantly in the ovary. Epithelial carcinomas (usually an adult tumor), Sertoli-Leydig cell tumors, and granulosa cell tumors may occur in children. Carcinomas account for about one third of ovarian tumors in females <20 yr old; most of these occur in older teens and are of the serous or mucinous subtype. **Sertoli-Leydig cell tumors** and **granulosa cell tumors** produce hormones that can cause virilization, feminization, or precocious puberty, depending on pubertal stage and the balance between Sertoli cells (estrogen production) and Leydig cells (androgen production). Diagnostic evaluation usually focuses on the chief complaint of inappropriate sex steroid effect and includes hormone measurements, which reflect gonadotropin-independent sex steroid production.

Appropriate imaging also is performed to rule out a functioning gonadal tumor. Surgery usually is curative. No effective therapy for nonresectable disease has been found.

Treatment

Complete surgical excision of the tumor usually is indicated, except for patients with intracranial tumors, for whom the primary therapy consists of radiation therapy and chemotherapy. For testicular tumors, an inguinal approach is indicated, and complete resection should include the entire spermatic cord. When complete excision cannot be accomplished, preoperative chemotherapy is indicated, with second-look surgery. For teratomas, both mature and immature, and completely resected malignant tumors of the testes and ovary, surgery alone is the treatment. For ovarian tumors, unless the contralateral ovary is obviously also involved by tumor, a fertility-sparing surgery should be performed. Cisplatin-based chemotherapy regimens usually are curative in GCTs that cannot be completely resected, even if metastases are present. However, sex cord–stromal tumors tend to be refractory to chemotherapy. Except for GCTs of the central nervous system, radiation therapy is limited to those tumors that are not amenable to complete excision and are refractory to chemotherapy.

Prognosis

The overall cure rate for children with GCTs is >80%. **Age** is the most predictive factor of survival for extragonadal GCTs. Children >12 yr old have a 4-fold higher risk of death and a 6-fold higher risk if the tumor is thoracic. Histology has minimal effect on prognosis. Patients with nonresected extragonadal GCTs have a slightly worse prognosis.

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CHAPTER 531

Neoplasms of the Liver

Nidale Tarek, Cynthia E. Herzog

Hepatic tumors are rare in children. Primary tumors of the liver account for approximately 1% of malignancies in children younger than 15 yr, with an annual incidence of 1.6 cases per 1 million children in the United States. Between 50% and 60% of hepatic tumors in children are malignant, with >65% of these malignancies being **hepatoblastomas** and most of the remainder being **hepatocellular carcinomas** . Rare **hepatic malignancies** include embryonal sarcoma, angiosarcoma, malignant germ cell tumor, rhabdomyosarcoma of the liver, and undifferentiated sarcoma. More common childhood malignancies, such as neuroblastoma, Wilms tumor, and lymphoma, can metastasize to the liver. **Benign liver tumors** , which usually present in the 1st 6 mo of life, include hemangiomas, hamartomas, and hemangioendotheliomas.

Hepatoblastoma

Epidemiology

Approximately 100 new cases of hepatoblastoma are diagnosed each year in the United States. The incidence of hepatoblastoma has increased over the last 2 decades, probably related to increasing survival of very-low-birthweight premature infants. Hepatoblastoma occurs predominantly in children <3 yr old, and the median age of diagnosis is 1 yr. The etiology is unknown. Hepatoblastomas are associated with **familial adenomatous polyposis** . Alterations in the antigen-presenting cell/β-catenin pathway have been found in most of the tumors evaluated. Hepatoblastomas are also associated with **Beckwith-Wiedemann syndrome** (BWS), **hemihyperplasia** , and other somatic overgrowth syndromes. Increased expression of insulin-like growth factor 2 secondary to genetic mutations or epigenetic changes is implicated in hepatoblastoma development in patients with BWS. All children with BWS or hemihyperplasia should be routinely screened with α-fetoprotein (**AFP**) levels and abdominal ultrasounds. Prematurity/low birthweight is associated with increased incidence of hepatoblastoma, with the risk increasing as birthweight decreases. **Aicardi syndrome** , trisomy 18, and other trisomies have also been associated with increased risk of hepatoblastoma.

Pathogenesis

Hepatoblastoma arises from precursors of hepatocytes and is histologically classified as *whole epithelial* type, containing fetal or embryonal malignant cells (either as a mixture or as pure elements), and *mixed* type, containing both epithelial and mesenchymal elements. Histologic classification has a direct correlation with clinical outcome. The *pure fetal histology* subtype predicts a more favorable outcome, and the *small cell undifferentiated* subtype is associated with normal AFP levels and predicts a worse outcome.

Clinical Manifestations

Hepatoblastoma usually presents as a large, asymptomatic abdominal mass. It arises from the right lobe 3 times more often than the left and usually is unifocal. As the disease progresses, fatigue, fever, weight loss, anorexia, vomiting, and abdominal pain may ensue. Rarely, hepatoblastoma presents with hemorrhage secondary to trauma or spontaneous rupture. Metastatic spread of hepatoblastoma most often involves regional lymph nodes and the lungs.

Diagnosis

A biopsy of liver tumors is necessary to establish the diagnosis. A valuable serum tumor marker, AFP is used in the diagnosis and monitoring of hepatic tumors. AFP is normally elevated in the newborn period and then declines to <10 ng/mL by 1 yr of age. The AFP levels are elevated in almost all hepatoblastomas. Bilirubin and liver enzymes usually are normal. Anemia is common, and thrombocytosis occurs in approximately 30% of patients. Serologic testing for hepatitides B and C should be performed, but the results usually are negative in hepatoblastoma.

Diagnostic imaging should include plain radiographs and ultrasonography of the abdomen to characterize the hepatic mass. US can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest (Fig. 531.1).

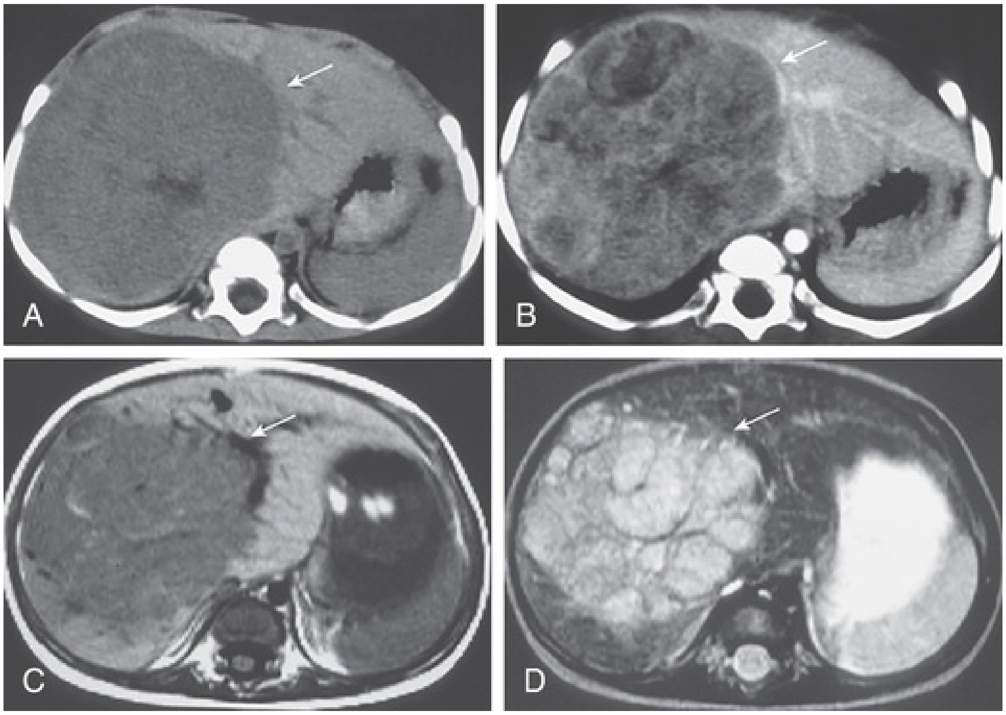

FIG. 531.1 **Hepatoblastoma in 3 yr old boy. A, Precontrast CT scan shows well-demarcated, heterogeneous hypodense mass *(arrow).* B, Postcontrast CT scan shows heterogeneous internal enhancement *(arrow)* . C and D, The mass *(arrow)* demonstrates heterogeneous hypointensity on T1-weighted (C) and hyperintensity on T2-weighted (D) MR images.**

Treatment

In general, the cure of malignant hepatic tumors in children depends on complete resection of the primary tumor (Fig. 531.2); as much as 85% of the liver can be resected, with hepatic regeneration noted within 3-4 mo after surgery. Treatment of hepatoblastoma is based on surgery and **systemic chemotherapy** using cisplatin in combination with vincristine and 5-fluorouracil (5-FU) or doxorubicin. The role of **radiation therapy** is questionable, because the effective antitumor dose exceeds the hepatic tolerance. Radiation therapy may have a role in shrinking unresectable disease or managing incompletely resected tumors. In 30% of cases, tumors are resectable at diagnosis; a safe attempt for initial gross total resection should be made, followed by adjuvant chemotherapy. Unresectable tumors with or without metastatic disease at presentation usually respond to chemotherapy; preresection chemotherapy is indicated, and excision of the primary tumor and extrahepatic disease should be attempted as soon as it becomes feasible, followed by additional chemotherapy. **Liver transplant** is a viable option for unresectable primary hepatic malignancies and results in good long-term survival. The pretransplant medical condition is an important predictor of outcome, and thus transplant is much more effective as the primary surgery than as salvage therapy. Alternative treatment options currently under investigation include other systemic chemotherapy agents such as carboplatin, ifosfamide, etoposide, and irinotecan. Other treatment approaches include transarterial chemoembolization, cryoablation, and radiofrequency ablation (RFA).

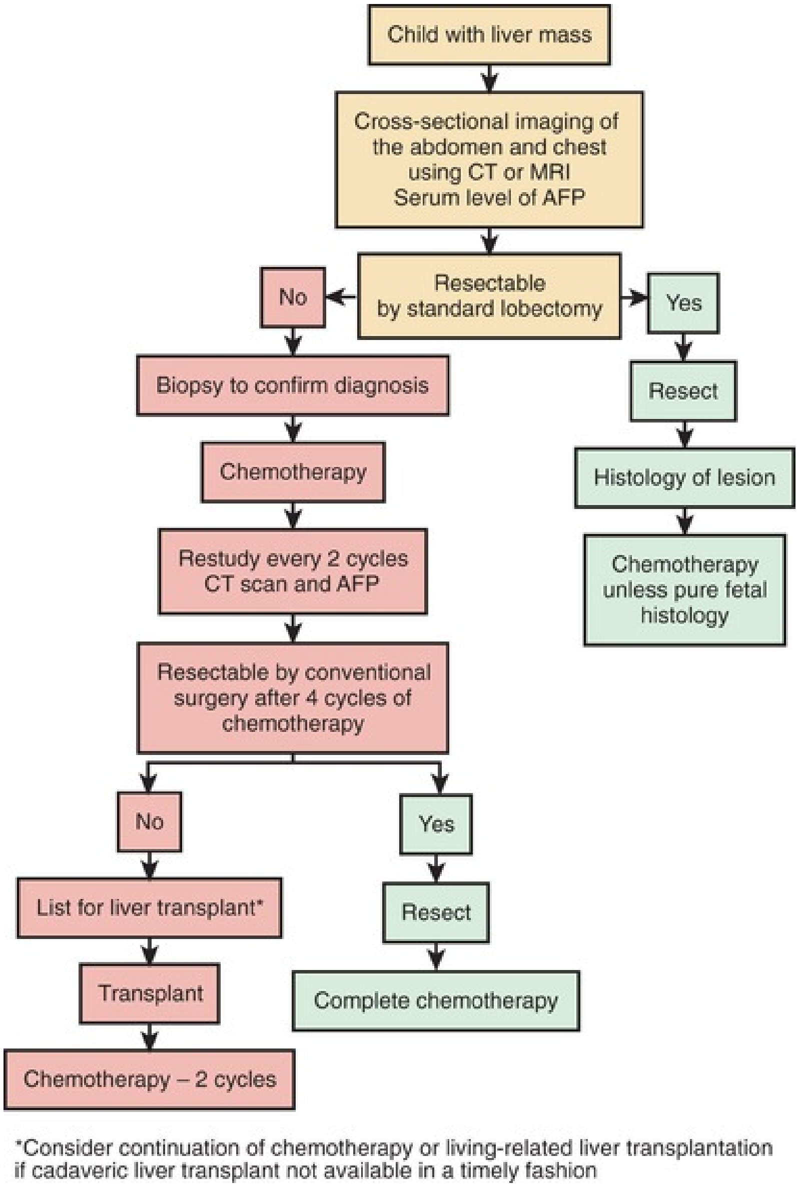
Child with liver mass
Cross-sectional imaging of the abdomen and chest using CT or MRI Serum level of AFP
Resectable by standard lobectomy
No
Yes
Biopsy to confirm diagnosis
Chemotherapy
Restudy every 2 cycles CT scan and AFP
Resectable by conventional surgery after 4 cycles of chemotherapy
No
Yes
List for liver transplant*
Transplant
Chemotherapy – 2 cycles
Resect
Complete chemotherapy
Resect
Histology of lesion
Chemotherapy unless pure fetal histology
*Consider continuation of chemotherapy or living-related liver transplantation if cadaveric liver transplant not available in a timely fashion

FIG. 531.2 Algorithm for the management of a child who presents with a hepatoblastoma. *AFP* , α-Fetoprotein. (From Tiao GM, Bobey N, Allen S, et al: The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation, *J Pediatr* 146:204–211, 2005.)

Prognosis

In low-stage tumors, survival rates >90% can be achieved with multimodal treatment, including surgery and adjuvant chemotherapy. With tumors unresectable at diagnosis, survival rates of approximately 60% can be obtained. Metastatic disease further reduces survival, but complete regression of disease often can be obtained with chemotherapy and surgical resection of the primary tumor and isolated pulmonary metastatic disease, resulting in survival rates of approximately 25%. Treatment-related long-term adverse effects include cardiac toxicity with doxorubicin and renal and ototoxicity with cisplatin.

Hepatocellular Carcinoma

Epidemiology

Hepatocellular carcinoma (**HCC**) occurs mostly in adolescents and often is associated with hepatitis B or C infection. It is more common in East Asia and other areas where hepatitis B is endemic; the incidence has decreased following the introduction of hepatitis B vaccination. In these areas, HCC also tends to occur in a bimodal pattern, with the younger age peak overlapping the age of hepatoblastoma presentation. HCC also occurs in the chronic form of hereditary tyrosinemia, galactosemia, glycogen storage disease, α_1 -antitrypsin deficiency, progressive familial intrahepatic cholestasis, and biliary cirrhosis. Alagille syndrome and aflatoxin B contamination of food are associated risk factors.

Pathogenesis

Hepatocellular carcinoma usually arises in an abnormal or cirrhotic liver and presents as a multicentric, invasive tumor consisting of large pleomorphic cells of epithelial origin. Compared to adults, cirrhosis in children is less common, and congenital liver disorders are more common. HCCs are classified as **classical** or **fibrolamellar** . The fibrolamellar variant occurs more often in adolescent and young adult patients and is not associated with cirrhosis. This variant has been reported to have a distinct translocation, *DNAJB1-PRKACA.* Although previous reports have suggested that the fibrolamellar type has a better prognosis than the classical, more recent data analysis refutes this. A rare subtype called **transitional liver tumor** occurs in older children and has clinical and histopathologic findings of both hepatoblastoma and HCC.

Clinical Manifestations

Hepatocellular carcinoma usually presents as a hepatic mass with abdominal distention and symptoms of anorexia, weight loss, and abdominal pain. HCC can present as an acute abdominal crisis with rupture of the tumor and hemoperitoneum. Metastatic spread usually involves regional lymph nodes and the lungs. The AFP level is elevated in approximately 60% of children with conventional HCC, but not in the fibrolamellar variant. Evidence of hepatitis B and C infection usually is found in endemic areas but not in Western countries or with the fibrolamellar type. Bilirubin usually is normal, but liver enzymes may be abnormal.

Diagnostic imaging should include plain radiographs and US of the abdomen to characterize the hepatic mass. US can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest.

Treatment

Complete tumor resection is crucial for curative treatment. Because of the multicentric origin of HCC and underlying liver disease, complete resection is accomplished in only 30-40% of cases. A gross total resection should be attempted at diagnosis when possible; combination chemotherapy following surgery is necessary. For unresectable tumors, **chemotherapy** followed by surgical assessment is essential; **liver transplant** is an option for unresectable tumors. Even with complete surgical resection, only 30% of children are long-term survivors. Chemotherapy, including cisplatin, doxorubicin, etoposide, and 5-FU, has shown some activity against this tumor, but improved long-term outcome has been difficult to achieve. **Sorafenib** , a small inhibitor of several tyrosine protein kinase, is a promising agent for the treatment of HCC. Other techniques are under study, including cryosurgery, RFA, transarterial chemoembolization, ethanol injection, and radiation therapy.

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CHAPTER 532

Benign Vascular Tumors

532.1

Hemangiomas

Cynthia E. Herzog

Keywords

Hemangioendothelioma
infantile hemangioma
Kasabach-Merritt syndrome
segmental hemangioma

Hemangiomas , the most common benign tumors of infancy, occur in approximately 5–10% of term infants (see Chapter 669). The risk of hemangioma is 3-5 times higher in girls than boys. The risk is doubled in premature infants and 10 times higher in offspring of women who had chorionic villus sampling. Hemangiomas can be present at birth but usually arise shortly after birth and grow rapidly during the 1st yr of life, with slowing of growth in the next 5 yr and involution by 10-15 yr of age.

Clinical Manifestations

More than 50% of all hemangiomas are located in the head and neck region.

Most are solitary lesions, but the presence of more than one cutaneous lesion increases the likelihood of visceral hemangiomas. The liver is the primary site of visceral involvement; other involved organs include the brain, intestines, and lung. Infantile hemangiomas can be differentiated from other lesions with which they may be confused by the expression of GLUT1. Most hemangiomas require no therapy, but approximately 10% cause significant impairment, and 1% are life threatening because of their location. Hemangiomas around the airway can cause airway obstruction, and those around the eyes can result in loss of vision. **Ulceration** is a common complication and can lead to secondary infection. With or without treatment, after involution of a hemangioma, residual skin abnormalities remain. Large hepatic hemangiomas or **hemangioendotheliomas** may result in hepatomegaly, anemia, thrombocytopenia, and high-output heart failure.

Kasabach-Merritt syndrome (or phenomenon; see Chapter 669) is characterized by a rapidly enlarging lesion, thrombocytopenia, microangiopathic hemolytic anemia, and coagulopathy as a result of platelet and red blood cell trapping and activation of the clotting system within the vasculature of the hemangioma. This syndrome is associated with kaposiform hemangioendotheliomas or tufted angiomas but not with infantile hemangiomas.

Cutaneous lesions usually can be diagnosed by typical appearance and rapid proliferation. **Segmental hemangiomas** , or those with geographic localization and some plaquelike features, recently have been shown to have a higher risk of complications and association with developmental abnormalities. A deep lesion may require imaging studies to help differentiate it from a lymphangioma. The presence of a midline hemangioma in the lumbosacral area indicates the need for an MRI to search for underlying asymptomatic neurologic abnormalities. Location also may dictate the need for an ophthalmologic or surgical consultation. An ultrasonographic scan or MRI of the liver should be performed if multiple cutaneous lesions are present.

Treatment

See Chapter 669 .

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532.2

Lymphangiomas and Cystic Hygromas

Cynthia E. Herzog

Keywords

cystic hygroma
lymphangioma

Lymphatic malformations , including lymphangiomas and cystic hygromas, which arise in the embryonic lymph sac, are the second most common benign vascular tumors in children, after hemangiomas. About half of lymphatic malformations are located in the head and neck area. Approximately 50% are present at birth, with most presenting by 2 yr of age. There is no gender predisposition. Spontaneous regression has been reported but is not typical.

Lymphatic malformations present as soft, painless masses that transilluminate if superficial. Intrathoracic lymphatic malformation can present as symptoms related to a mediastinal mass or pericardial or pleural effusion. Rapid enlargement can occur with infection or hemorrhage. Localized lesions may be surgically resected, but this can be difficult because of their infiltrative nature. **Recurrence** is common with incompletely resected lesions. Aspiration can provide temporary relief in an emergency, such as in the presence of dyspnea, but reaccumulation will occur. Treatment by intralesional injection of sclerosing agents, or OK432 (picibanil), as well as localized laser therapy, may be helpful. Systemic therapy with propranolol or sirolimus has shown benefit in patients unresponsive to local therapy.

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CHAPTER 533

Rare Tumors

533.1

Thyroid Tumors

Steven G. Waguespack

Keywords

- differentiated thyroid carcinoma
- DTC
- follicular thyroid carcinoma
- medullary thyroid carcinoma
- MTC
- multiple endocrine neoplasia
- MEN2A
- papillary thyroid carcinoma
- PTC
- thyroid cancer
- thyroid nodule
- *RET* mutation

See Chapter 585 .

Benign Thyroid Tumors

Benign thyroid tumors represent approximately 75% of all thyroid nodules presenting in the pediatric population. The workup of a suspected thyroid nodule includes the laboratory assessment of thyroid function, ultrasound (US) to assess characteristics of the nodule(s) and regional lymph nodes, and fine-needle aspiration biopsy under US guidance for cytopathologic diagnosis. Nuclear scintigraphy using radioactive iodine (^{123} I) or technetium 99m (^{99m} Tc)-pertechnetate is not recommended in the initial diagnostic evaluation, except in the event of a suppressed thyroid-stimulating hormone (TSH) level.

Malignant Thyroid Tumors

Pediatric thyroid malignancies are rare tumors that include **medullary thyroid carcinoma (MTC)** and the **differentiated thyroid carcinomas (DTCs)** , namely, **papillary thyroid carcinoma (PTC)** and **follicular thyroid carcinoma** . PTC represents the vast majority of thyroid cancers in children. The incidence of pediatric thyroid cancer has been rising, with 15-19 yr olds having the highest rate. With few exceptions, children with thyroid carcinoma have an excellent prognosis, with anticipated survival over decades, even in the presence of metastatic disease at diagnosis. *The major established risk factor for development of PTC is exposure to ionizing radiation.*

MTC is an uncommon disease in childhood that almost always occurs in the context of an autosomal dominant, hereditary endocrine tumor syndrome that arises secondary to activating mutations in the *RET* (*RE* arranged during *T* ransfection) protooncogene: **multiple endocrine neoplasia type 2a (MEN2A) or type 2b (MEN2B)** . In addition to the almost complete penetrance of MTC in the most common *RET* mutations, patients with MEN2A and MEN2B have up to a 50% lifetime risk of developing pheochromocytomas. Up to 20% of MEN2A patients will also develop primary hyperparathyroidism. Patients with MEN2B do not develop hyperparathyroidism but have a distinct clinical phenotype that includes a characteristic facial appearance, marfanoid body habitus, aerodigestive tract ganglioneuromatosis, and **oral mucosal neuromas** (Fig. 533.1). The diagnosis of MEN2B is often delayed (usually after the MTC has already metastasized) because its pathognomonic features are not apparent in very early childhood, although an inability to cry tears and constipation represent the earliest clues to diagnosis. MTC may be sporadic or familial without features of MEN 2A or 2B; it may also be associated with **Hirschsprung disease** .

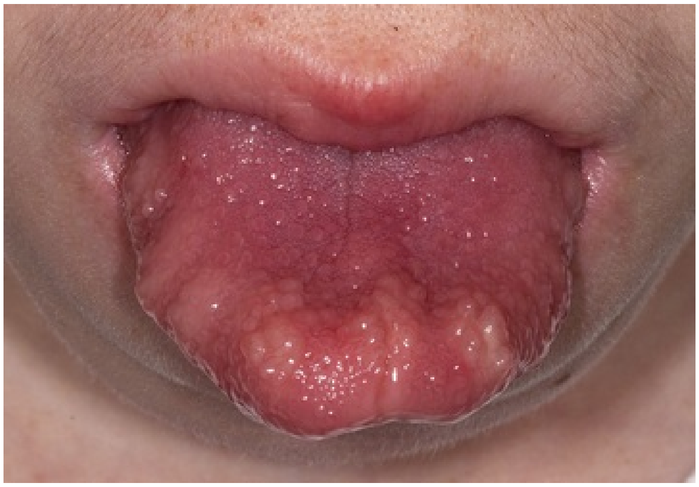

FIG. 533.1 Classic appearance of oral mucosal neuromas on the tongue in a boy with MEN2B secondary to the typical M918T mutation in the *RET* protooncogene.

Children with thyroid cancer usually present with an asymptomatic thyroid mass and/or cervical lymphadenopathy, although children with MEN2 are often diagnosed only after a positive genetic test result or, in the case of MEN2B, after the clinical phenotype is recognized. Lymph node metastases are present in most PTC cases, and lung metastases are identified in up to 20% of patients, primarily in those children with a high burden of neck disease. MTC also frequently metastasizes to cervical lymph nodes.

The **primary therapy** for thyroid cancer is a total thyroidectomy and a compartment-oriented lymph node dissection, as indicated, performed by a highly experienced thyroid cancer surgeon. In DTC, radioactive iodine (^{131} I) is used postoperatively to treat iodine-avid distant metastasis and unresectable residual neck disease. In PTC the routine use of ^{131} I is limited to higher-risk children who are most likely to benefit from treatment. Children with MTC do not require ^{131} I therapy. The TSH level is initially suppressed by giving supraphysiologic levothyroxine in the case of DTC, because TSH may stimulate DTC tumor growth; the TSH level is kept normal in MTC. The U.S. Food and Drug Administration (FDA) has approved oral tyrosine kinase inhibitors for the treatment of advanced MTC and DTC in adults, but these are rarely required in pediatric patients. Long-term follow-up involves monitoring of tumor markers (thyroglobulin/thyroglobulin antibody in DTC, calcitonin/carcinogenic embryonic antigen in MTC), as well as routine imaging, primarily neck US.

In MEN2, there are well-documented genotype-phenotype correlations, and the biologic aggressiveness of MTC depends on the hereditary setting in which it develops. With the availability of genetic testing for *RET* mutations, MTC has become one of the few malignancies that can be cured by **early thyroidectomy** before the cancer becomes metastatic. Recommendations regarding the age at surgery of children who are carriers of a *RET* mutation are evolving and incorporate clinical testing, especially calcitonin levels, as well as knowledge of the genotype and parent preference.

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533.2

Nasopharyngeal Carcinoma

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Keywords

EBV
Epstein-Barr virus
nasopharyngeal carcinoma

Nasopharyngeal carcinoma is rare in the pediatric population but is one of the most common nasopharyngeal tumors in pediatric patients. In adults, the incidence is highest in South China, but it is also high among the Inuit people and in North Africa and Northeast India. In China, this diagnosis is rare in the pediatric population, but in other populations, a substantial proportion of cases occur in the pediatric age-group, primarily in adolescents. It occurs in males twice as often as in females and is more common in blacks. In the pediatric population, the tumors are more frequently of **undifferentiated histology** and associated with **Epstein-Barr virus (EBV)** . Nasopharyngeal carcinoma is associated with specific human leukocyte antigen (HLA) types, and other genetic factors may play a role, especially in low-incidence populations.

Most pediatric patients present with advanced locoregional disease manifesting as cervical lymphadenopathy. Epistaxis, trismus, and cranial nerve deficits also may be present. The diagnosis is established from biopsy of the nasopharynx or cervical lymph nodes. In most cases the lactate dehydrogenase level is elevated, but this finding is nonspecific. CT or MRI evaluation of the head and neck is performed to determine the extent of locoregional disease. Chest radiography, CT, bone scan, and liver scan are used to evaluate for metastatic disease. Positron emission tomography (PET) scans appear to be useful for monitoring primary disease and looking for metastases. EBV DNA levels correlate with disease stage, have prognostic value, and can be used to monitor for recurrence.

Treatment is a combination of chemotherapy and irradiation. Cisplatin, given concurrently with radiation, with or without neoadjuvant cisplatin-based chemotherapy, is the standard treatment. The outcome depends on the extent of disease; patients with distant metastases have a very poor prognosis. Using intensity-modulated radiation therapy improves local control and reduces the late adverse effects associated with radiation therapy, including hormonal dysfunction, dental caries, fibrosis, and second malignancies. Use of proton therapy may result in further reduction of adverse effects.

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533.3

Adenocarcinoma of the Colon and Rectum

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Keywords

adenocarcinoma
attenuated FAP
colon cancer
colorectal cancer
CRC
familial adenomatous polyposis
FAP
hereditary nonpolyposis colon cancer
HNPCC

Colorectal carcinoma (CRC) is rare in the pediatric population, with an estimated incidence rate of approximately 1 case per 1 million. Even in patients with predisposing conditions, CRC usually does not present until late adolescence or adulthood. **Hereditary nonpolyposis colon cancer (HNPCC)** is an autosomal dominant disorder, with germline mutations in DNA mismatch repair genes *(MMR)* causing DNA repair errors and microsatellite instability. **Familial adenomatous polyposis (FAP)** and **attenuated FAP** are autosomal disorders, with germline mutations in the *APC* gene. In addition to CRC, patients with HNPCC, FAP, and attenuated FAP are predisposed to a number of extracolonic cancers. Desmoid tumors can occur in patients with FAP, whereas patients with HNPCC have an increased risk for tumors involving the genitourinary tract, stomach, and small intestine. *MYH* -associated polyposis, Peutz-Jeghers syndrome, and juvenile polyposis also predispose to CRC.

Genetic testing is available, and screening for cancer in HNPCC and FAP should begin during childhood or adolescence. Likewise, genetic evaluation for these conditions should be pursued in young patients presenting with colon cancer, even when there is no history of predisposing genetic conditions.

Presenting symptoms include bloody stools or melena, abdominal pain, weight loss, and changes in bowel patterns. In many cases, signs are vague, often resulting in a delay in diagnosis, sometimes not until the disease has reached an advanced stage. The histologic subtype differs from that seen in adults, with the majority of pediatric tumors being either **mucinous adenocarcinoma** or **signet ring cell carcinoma** . Pediatric patients also tend to present with more advanced disease. Treatment consists of surgical resection when possible, with chemotherapy for unresectable tumors. Adequate lymph node removal should be performed at surgical resection of primary tumor. Radiation therapy is useful in select cases. Pediatric patients have a worse overall prognosis compared to adult patients, but the reasons for this discrepancy are not clear.

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533.4

Adrenal Tumors

Steven G. Waguespack

Keywords

ACT
adrenocortical tumor
Beckwith-Wiedemann syndrome
Cushing syndrome
Li-Fraumeni syndrome
metanephrine
paraganglioma
PGL
PHEO
pheochromocytoma
virilization
von Hippel–Lindau disease

See Chapters 595 to 599 .

Adrenocortical tumors (ACTs) arise from the outer adrenal cortex, whereas **pheochromocytomas (PHEOs)** derive from the catecholamine-producing chromaffin cells of the adrenal medulla. When tumors arise from the parasympathetic and sympathetic paraganglia outside the adrenal medulla, they are called **paragangliomas (PGLs)** . The pathologic categorization of adrenal tumors as “benign” or “malignant” does not always correlate well with the clinical behavior, making it difficult to differentiate malignant from benign disease based on pathology alone. Therefore, long-term follow-up is warranted. Because of the significant association with genetic disease, genetic counseling is advised for all children diagnosed with an ACT or PHEO/PGL.

ACTs are very rare and tend to present before age 10 yr. They have a female predominance and are functional tumors in >90% of cases, primarily producing androgens and causing clinically apparent **virilization** , although cortisol hypersecretion can also occur. ACT may also present as an abdominal mass or pain. In children, ACTs are most frequently associated with **Li-Fraumeni syndrome** (germline inactivating mutations in the *TP53* tumor-suppressor gene) and **Beckwith-Wiedemann syndrome** (BWS), but they can also be seen in hemihyperplasia other than that seen as part of BWS, multiple endocrine neoplasia type 1 (MEN1), McCune-Albright syndrome, familial adenomatous polyposis, and very rarely, congenital adrenal hyperplasia. Unusual causes of bilateral nodular adrenocortical disease, which usually present with **Cushing syndrome** , include the Carney complex and macronodular adrenocortical hyperplasia.

PHEOs/PGLs are rare tumors that are more likely to be bilateral, malignant, and secondary to a heritable tumor syndrome when diagnosed in children. There is also a strong link between cyanotic congenital heart disease and PHEO/PGL. **Von Hippel–Lindau disease** is the most common genetic association in the pediatric population, followed by the **familial PGL syndromes (1, 2, 3, 4)** caused by mutations in the succinate dehydrogenase gene. MEN2 (types 2A and 2B) and neurofibromatosis type 1 (NF1) are also in the differential diagnosis but are more often associated with a PHEO diagnosis during adulthood. *Hypertension is usually sustained* in pediatric patients with PHEO/PGL, who may also lack the typical triad of headache, palpitations, and diaphoresis seen in adults. Attention-deficit hyperactivity disorder is also more prevalent in children with these tumors. The best screening test for PHEO/PGL is measurement of plasma and/or urine **metanephrine** levels. Imaging studies include CT, MRI, and metaiodobenzylguanidine (MIBG) or the more sensitive PET scans (Fig. 533.2).

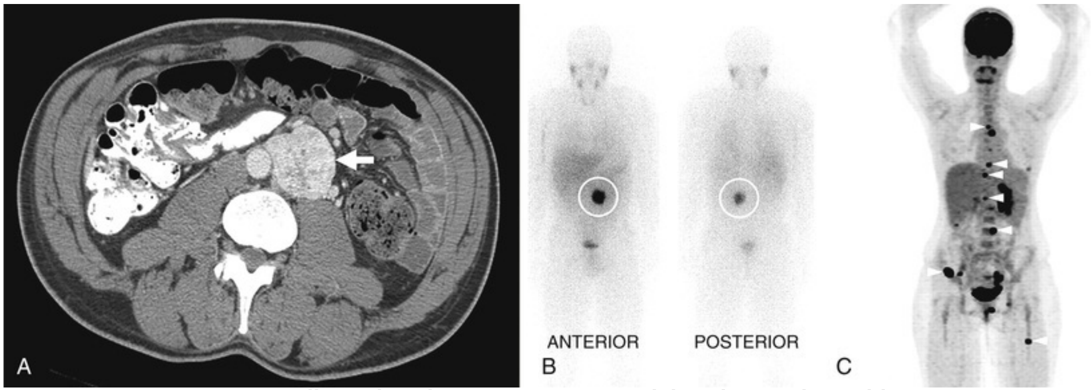

FIG. 533.2 Paraganglioma (PGL). A, Postcontrast axial CT in a patient with symptoms of catecholamine excess and a noradrenergic biochemical profile. PGL (*arrow*) is identified in a paraaortic location between the left renal artery and the origin of the inferior mesenteric artery in the region of the organs of Zuckerkandl. B, MIBG scan in the same patient, 24 hr after administration of ^{123}I-MIBG, demonstrating intense uptake in the tumor. C, ^{18}F-FDG PET scan in a patient with metastatic PGL and an *SDHB* mutation. Bony metastatic disease (*arrowheads*) predominates. (From Waguespack SG, Rich T, Grubbs E, et al: A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma, *J Clin Endocrinol Metab* 95:2023–2037, 2010, Fig 2).

The initial treatment of ACT and PHEO/PGL is *surgery by a surgeon* *experienced in the management of these tumors*. Children with PHEO/PGL require preoperative medical management with α and β blockade. **First-line medical therapy** for metastatic ACT includes mitotane and chemotherapy with cisplatin, etoposide, and doxorubicin. Metastatic PHEO/PGL has historically been treated with cyclophosphamide, vincristine, and dacarbazine. In cases of both ACT and PHEO/PGL, novel targeted agents are being studied for the treatment of advanced metastatic disease, which is typically nonresponsive to standard chemotherapeutic approaches. **Endocrine therapy** targeting hormonal overproduction may also be needed to palliate symptoms and improve quality of life.

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533.5

Desmoplastic Small Round Cell Tumor

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Keywords

DSRCT
Ewing tumor
Wilms tumor

Desmoplastic small round cell tumor (**DSRCT**) is a very rare and aggressive mesenchymal tumor that occurs predominantly in adolescent and young adult males. It is associated with a diagnostic chromosomal translocation between the Ewing tumor gene and the Wilms tumor gene, t(11;22)(p13;q12), creating a chimeric gene (*EWS-WT1*) that encodes a chimeric protein with oncogenic properties. Patients typically present at advanced stage with a bulky abdominal mass, multiple peritoneal and omental implants, and symptoms of abdominal sarcomatosis, including pain, ascites, intestinal obstruction, hydronephrosis, and weight loss. DSRCT mainly involves the abdominal cavity but can spread to the lymph nodes, liver, lungs, and bones. There is no standard treatment approach. Aggressive treatment with combination chemotherapy, debulking surgery, and whole abdominopelvic irradiation results almost universally in a poor outcome. Median survival ranges between 17 and 25 mo, and the 5 yr overall survival remains <20%. Although high-dose chemotherapy and autologous stem cell rescue demonstrated some benefit, this approach has been abandoned because of significant toxicity. Alternative treatment options currently under investigation include hyperthermic intraperitoneal chemotherapy and radioimmunotherapy with monoclonal antibodies targeting different surface antigens on tumor cells.

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CHAPTER 534

Histiocytosis Syndromes of Childhood

Stephan Ladisch

The childhood histiocytoses constitute a diverse group of disorders that are frequently severe in their clinical expression. These disorders are individually rare and are grouped together because they have in common a prominent proliferation or accumulation of cells of the monocyte-macrophage system of bone marrow (myeloid) origin. Although these disorders sometimes are difficult to distinguish clinically, accurate diagnosis is essential for facilitating progress in treatment. A systematic classification of the histiocytoses is based on histopathologic findings (Table 534.1). A thorough, comprehensive evaluation of a biopsy specimen obtained at diagnosis is critical. This evaluation includes studies such as immunostaining, molecular analysis, and electron microscopy that may require special sample processing.

Table 534.1

Classification of the Childhood Histiocytoses

	DISEASE	CELLULAR CHARACTERISTICS OF LESIONS	TREATMENT
LCH	Langerhans cell histiocytosis	Langerhans-like cells (CD1a positive, CD207 positive) with Birbeck granules (LCH cells)	Local therapy for isolated lesions; chemotherapy for disseminated disease
HLH	Familial (primary) hemophagocytic lymphohistiocytosis	Morphologically normal reactive macrophages with prominent erythrophagocytosis and $CD8^+$ T cells	Chemotherapy; allogeneic bone marrow transplantation
	Infection-associated (secondary) hemophagocytic syndrome*		
	Associated with albinism syndromes †		
	Associated with immunocompromised states		
	Associated with		

	autoimmune/autoinflammatory states		
Other	Juvenile xanthogranuloma	Characteristic vacuolated lesional histiocytes with foamy cytoplasm	None or excisional biopsy for localized disease; chemotherapy, radiotherapy for disseminated disease
	Rosai-Dorfman disease	Hemophagocytic histiocytes	None if localized; surgery for bulk reduction; chemotherapy if organ systems involvement
	Malignant histiocytosis	Neoplastic proliferation of cells with characteristics of monocytes-macrophages or their precursors	Antineoplastic chemotherapy, including anthracyclines
Other	Acute monocytic (myelogenous) leukemia [‡]	M5 by FAB classification	Antineoplastic chemotherapy
	ALK+ histiocytosis	Infiltration of large histiocytes, multinucleated with fine chromation; CD68, CD163, S100 protein, and ALK positive	Rare disorder of infants; treat with steroids and chemotherapy; may spontaneously regress.

[*] Also called secondary hemophagocytic lymphohistiocytosis.

[†] Chédiak-Higashi and Hermansky-Pudlak syndromes.

[‡] See Chapter 522.2 .

FAB, French-American-British; LCH, Langerhans cell histiocytosis; HLH, hemophagocytic lymphohistiocytosis.

Classification and Pathology

Three classes of childhood histiocytosis are defined, based on histopathologic findings. The best known is **Langerhans cell histiocytosis (LCH)** , previously called *histiocytosis X*. LCH includes the clinical entities of bone or skin limited disease, eosinophilic granuloma, **Hand-Schüller-Christian disease,** and **Letterer-Siwe disease.** The normal Langerhans cell is an antigen-presenting cell (APC) of the skin. The hallmark of LCH in all forms is the presence of a clonal proliferation of cells of the monocyte–dendritic cell lineage containing the characteristic electron microscopic findings of a Langerhans cell, the **Birbeck granule** . This tennis racket–shaped bilamellar granule, when seen in the cytoplasm of lesional cells in LCH, is diagnostic of the disease. The Birbeck granule expresses a newly characterized antigen, *langerin* (CD207), which itself is involved in antigen presentation to T lymphocytes. CD207 expression has been established to be uniformly present in LCH lesions and thus becomes an additional reliable diagnostic marker. It is more likely that the LCH cell is not actually a (differentiated) Langerhans cell but rather an immature cell of myeloid origin, possibly in an arrested state of development. The definitive diagnosis of LCH is established by demonstrating CD1a positivity of lesional cells, which can be done using fixed tissue (Fig. 534.1). Lesional cells must be distinguished from normal Langerhans cells of the skin, which are also CD1a positive but are only sparsely distributed and not diagnostic of LCH. The peripheral lesions usually leading to the diagnosis (e.g., skin, lymph node, bone) contain various proportions of Birbeck granule–containing CD1a-positive cells, lymphocytes, granulocytes, monocytes, and eosinophils.

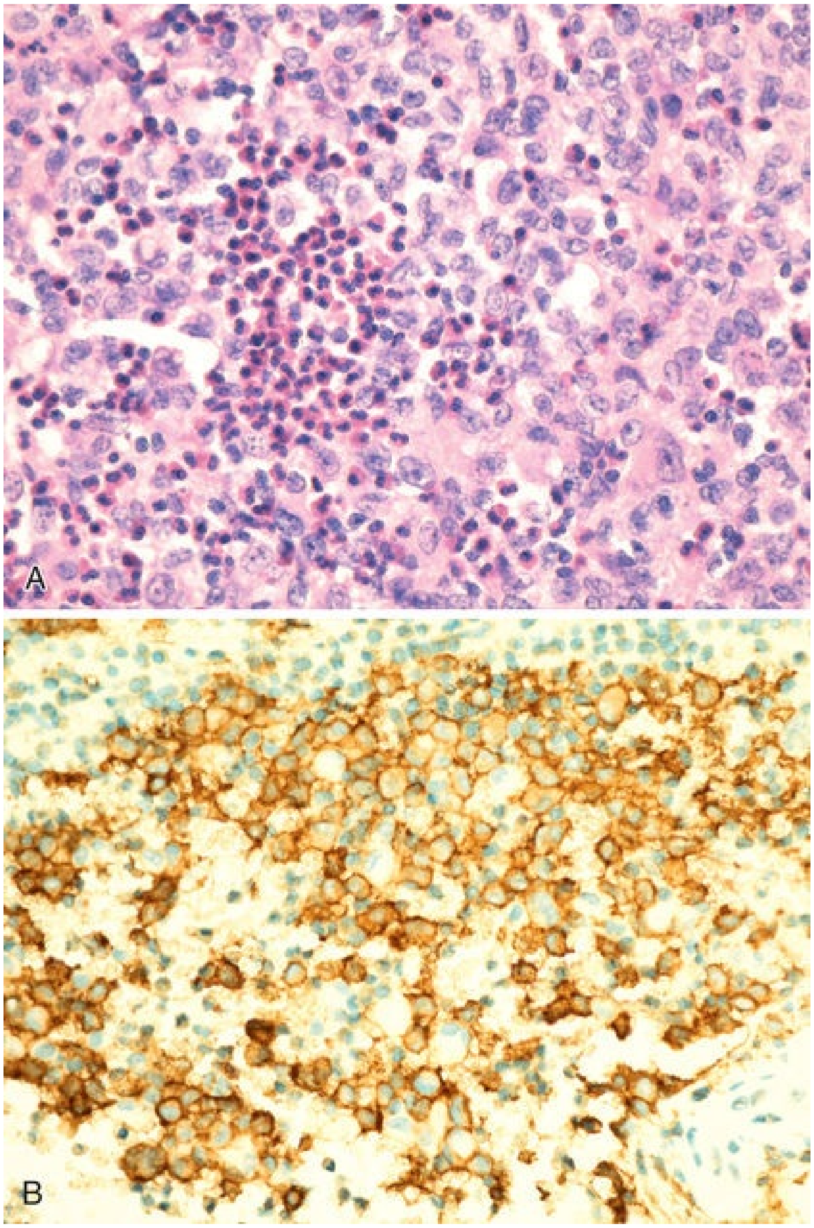

FIG. 534.1 **A,** Histopathology of Langerhans cell histiocytosis (LCH). Shown is the eosinophilic granuloma of a lytic bone lesion of the femoral head. Multiple LCH cells with characteristic grooved nuclei, as well as numerous eosinophils, are visible in this mixed infiltrate. **B,** CD1a staining, characteristic and diagnostic of lesions with LCH cells.

Clonality of individual lesions exists in some cases of LCH. Importantly, an activating somatic mutation of the *BRAF* gene (*V600E*) has been identified in many patients with LCH. Studies in patients negative for *BRAFV600E* have revealed mutations in other genes of the mitogen-activated protein kinase (MAPK) pathway, including *MAP2K1* and *ARAF* . With the majority of LCH patients having 1 or another of these activating mutations in the MAPK pathway, it has been suggested that LCH is driven by a disorder in MAPK signaling.

In contrast to the prominence of an APC in LCH, the other common form of histiocytosis is characterized by accumulation of activated APCs (macrophages and lymphocytes) and is known as **hemophagocytic lymphohistiocytosis (HLH)** . This diagnosis is the result of uncontrolled hemophagocytosis and uncontrolled activation (upregulation) of inflammatory cytokines with some similarities to the **macrophage activation syndrome** (see Table 180.6). Tissue infiltration by activated CD8 T lymphocytes, activated macrophages, and hypercytokinemia are classic features (Fig. 534.2). With the characteristic morphology of normal macrophages by light microscopy, these phagocytic cells (see Fig. 534.1) are CD163 positive but negative for the markers that are characteristic of LCH cells (Birbeck granules, CD1a, CD207).

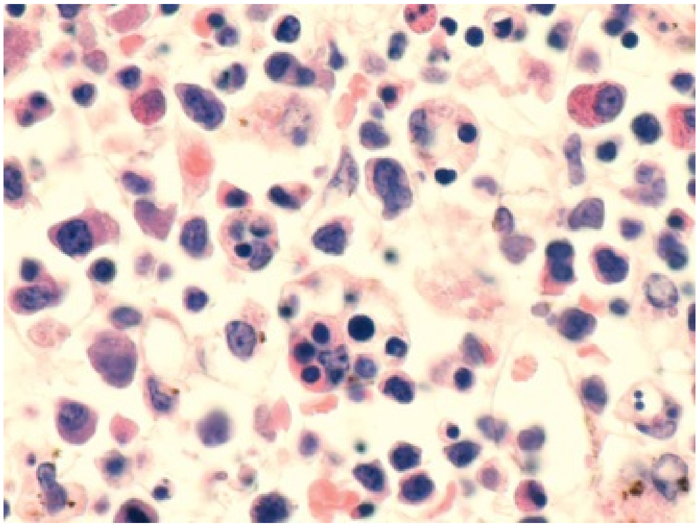

FIG. 534.2 **Bone marrow aspirate of a child with familial (genetically confirmed)**

hemophagocytic lymphohistiocytosis. Numerous characteristic hemophagocytic cells (which are CD163-positive macrophages) are seen ingesting various blood elements.

The 2 major forms of HLH have indistinguishable pathologic findings but are important to differentiate because of implications for treatment and prognosis. **Primary HLH** , originally named *familial erythrophagocytic lymphohistiocytosis,* is known as **familial hemophagocytic lymphohistiocytosis (FHLH)** . This disease is an autosomal recessive disorder and represents approximately 25% of patients with HLH (Table 534.2). Genes are known for 4 of the 5 familial HLH syndromes and other hereditary causes of HLH; these mutations affect the ability of T lymphocytes and natural killer (NK) cells to synthesize and release perforin and granzymes, thus reducing cytotoxic granule formation (Fig. 534.3). The other form of HLH, originally called *infection-associated hemophagocytic syndrome,* is recognized as **secondary HLH** (Table 534.3). Both disease processes affect multiple organs and are characterized by massive infiltrates of hyperactivated lymphocytes and activated phagocytic macrophages in the involved organs, with the lymphocytes serving as the driver of the resulting disease process.

Table 534.2

Hemophagocytic Lymphohistiocytosis

DISEASE	GENE	PROTEIN	PERCENTAGE OF FHLH	IMMUNE IMPAIRMENT	UNIQUE CLINICAL CHARACTERISTICS
FHLH-16	Unknown 9q21.3–22	Rare			
FHLH-2	*PRF1*	Perforin	~20–37, 50delT mainly in African American/African descent	Cytotoxicity; forms pores in APCs	
FHLH-3	*UNC13D*	Munc13–4	20–33	Cytotoxicity; vesicle priming	Increased incidence of CNS HLH
FHLH-4	*STX11*	Syntaxin	<5	Cytotoxicity; vesicle fusion	Mild recurrent HLH, colitis
FHLH-5	*STXBP2*	Syntaxin-binding protein 2	5–20	Cytotoxicity; vesicle fusion	Colitis, hypogammaglobulinemia
SYNDROMES WITH PARTIAL OCULOCUTANEOUS ALBINISM					
Griscelli syndrome	*RAB27A*	Rab27A	~5	Cytotoxicity; vesicle docking	Partial albinism, silver-gray hair
Chédiak-Higashi syndrome	*LYST*	Lyst	~2	Cytotoxicity; heterogeneous defects in NK cells	Partial albinism, bleeding tendency, recurrent infections

Hermansky-Pudlak syndrome type II	*AP3B1*	AP-3 complex subunit β_1	Rare	Cytotoxicity; vesicle trafficking	Partial albinism, bleeding tendency
EBV-DRIVEN AND RARE CAUSES					
XLP1	*SH2D1A*	SAP	~7	Signaling in cytotoxic NK and T cells	Hypogammaglobulinemia, lymphoma
XLP2	*BIRC4*	XIAP	~2	NK T-cell survival and NF-κB signaling	Mild recurrent HLH, colitis
ITK deficiency	*ITK*	ITK	Rare	IL-2 signaling in T cells	Hypogammaglobulinemia, autoimmunity, Hodgkin lymphoma
CD27 deficiency	*CD27*	CD27	Rare	Signal transduction in lymphocytes	Combined immunodeficiency, lymphoma
XMEN syndrome	*MAGT1*	MAGT1	Rare	Magnesium transporter, induced by TCR stimulation	Lymphoma, recurrent infections, CD4 T-cell lymphopenia

APCs, Antigen-presenting cells; CNS, central nervous system; EBV, Epstein-Barr virus; FHLH, familial hemophagocytic lymphohistiocytosis; HLH, hemophagocytic lymphohistiocytosis; ITK, interleukin (IL)-2–inducible T-cell kinase; NF-κB, nuclear factor–kappa B; NK, natural killer; TCR, T-cell receptor.

Adapted from Erker C, Harker-Murray, Talano JA: Usual and unusual manifestations of familial hemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis, *Pediatr Clin North Am* 64:91–109, 2017 (Table 1, p 95).

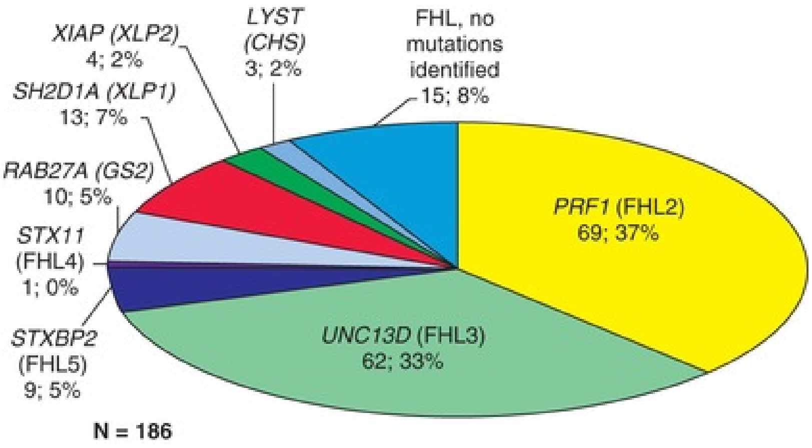

FIG. 534.3 **Different genetic subtypes in 171 patients with familial hemophagocytic lymphohistiocytosis (FHL) or FHL-related disease. For each subtype, the name of the gene, the abbreviation of the disease subtype, the absolute number, and the percentage are shown. Furthermore, we include as FHL one subgroup of 15 patients with either familial recurrence or refractory/recurrent disease despite specific therapy and/or repeatedly documented severe functional defect in degranulation or cytotoxicity assays. (From Cetica V, Sieni E, Pende D, et al: Genetic predisposition to hemophagocytic lymphohistiocytosis: report on 500 patients from the Italian registry, *J***

***Allergy Clin Immunol* 137:188–196, 2016, Fig 2, p 191.)**

Table 534.3

Infections Associated With Hemophagocytic Syndrome

VIRAL
Adenovirus
Cytomegalovirus (CMV)
Dengue virus
Epstein-Barr virus (EBV)
Enteroviruses
Herpes simplex viruses (HSV1, HSV2)
Human herpesviruses (HHV6, HHV8)
Human immunodeficiency virus (HIV)
Influenza viruses
Parvovirus B19
Varicella-zoster virus (VZV)
Hepatitis viruses
Measles
Parechovirus
BACTERIAL
Babesia microti
Brucella abortus
Enteric gram-negative rods
Haemophilus influenzae
Mycoplasma pneumoniae
Staphylococcus aureus
Streptococcus pneumoniae
Ehrlichia chaffeensis
FUNGAL
Candida albicans
Cryptococcus neoformans
Histoplasma capsulatum
Fusarium
MYCOBACTERIAL
Mycobacterium tuberculosis
RICKETTSIAL
Coxiella burnetii
Other rickettsial diseases
PARASITIC
Leishmania donovani
Plasmodium

From Nathan DG, Orkin SH, Ginsburg D, et al, editors: *Nathan and Oski's hematology of infancy and childhood* , ed 6, Philadelphia, 2003, Saunders, p 1381.

In primary HLH, genetic mutations in multiple different steps in granule formation and release by cytotoxic T cells have been identified (Fig. 534.4 , *bottom*). Mutations in the *PRF1* perforin gene or the *MUNC13-4* gene are the most common causes of defective function of the cytotoxic lymphocytes whose activity is inhibited in primary HLH. In an analogous way, a trigger can result in secondary HLH (Fig. 534.4, *top*). A myriad of both infectious and noninfectious processes can trigger secondary HLH (Tables 534.3 and 534.4 and Fig. 534.5). Examples of noninfectious triggers include drugs (e.g., phenytoin, highly active antiretroviral therapy), hematopoietic stem cell transplantation, chemotherapy, autoimmune diseases, inflammatory bowel disease, cancer, and immunodeficiency states (e.g., DiGeorge syndrome, Bruton agammaglobulinemia, severe combined immunodeficiency syndrome, chronic granulomatous disease).

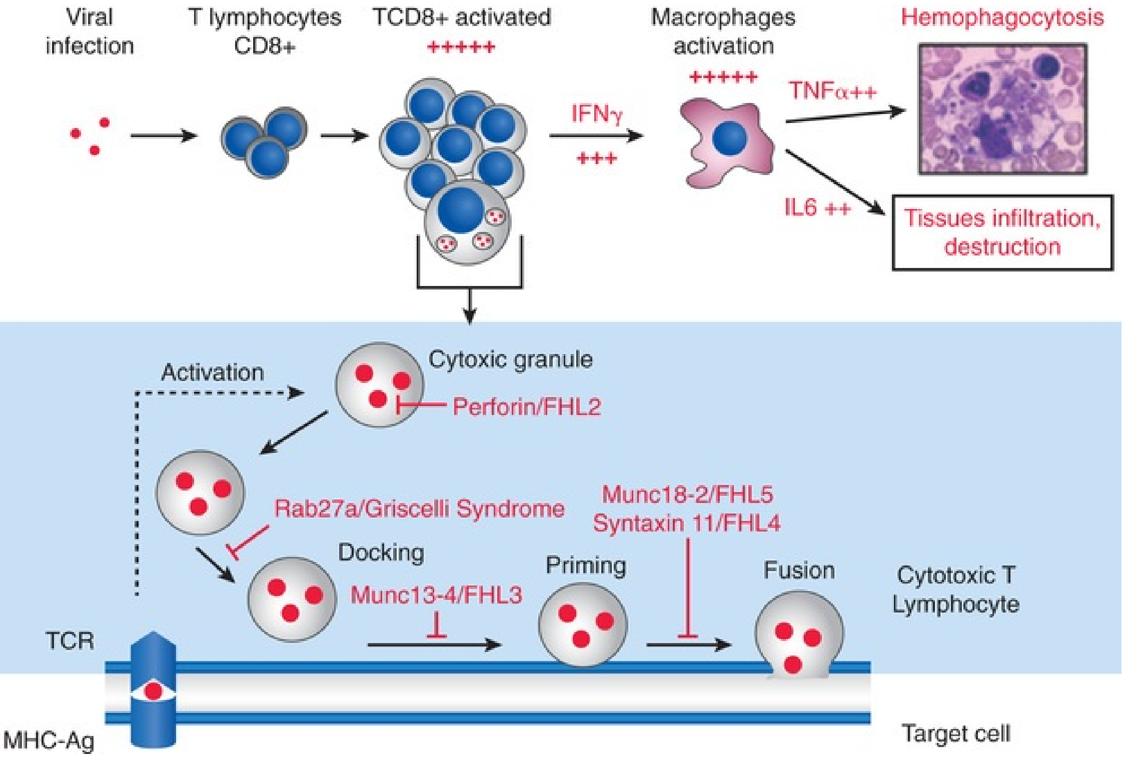
Viral infection
T lymphocytes CD8+
TCD8+ activated
+++++
IFNγ
+++
Macrophages activation
+++++
TNFα++
IL6 ++
Hemophagocytosis
Tissues infiltration, destruction
Activation
Cytoxic granule
Perforin/FHL2
Rab27a/Griscelli Syndrome
Munc18-2/FHL5
Syntaxin 11/FHL4
Docking
Munc13-4/FHL3
Priming
Fusion
Cytotoxic T Lymphocyte
TCR
MHC-Ag
Target cell

FIG. 534.4 Inborn errors in the cytotoxic activity of lymphocytes. Top, Schematic diagram of the immune mechanisms leading to the occurrence of a hemophagocytic syndrome. Following a viral infection, antigen-specific CD8$^+$ T lymphocytes undergo massive expansion and activation and secrete high levels of interferon (IFN)-γ. The overwhelming activated effector cells induce excessive macrophage activation and proinflammatory cytokine production, including tumor necrosis factor (TNF)-α and interleukin-6 (IL-6). Macrophages spontaneously phagocytose blood elements (platelets, red blood cells, and a polymorphonuclear cell shown here). Activated lymphocytes and macrophages infiltrate various organs, resulting in massive tissue necrosis and organ failure. Bottom, The genetic defects causing hemophagocytic lymphohistiocytic syndrome (HLH) affect a precise step of the cytotoxic machinery: granule content, docking, priming, or fusion. Only the defects causing Griscelli syndrome (GS) and familial hemophagocytic lymphohistiocytosis (FHL) are shown. MHC-Ag, Major histocompatibility complex antigen; TCR, T-cell receptor. (From

Pachlopnik Schmid J, Cote M, Menager MM, et al: Inherited defects in cytotoxic lymphocyte activity. *Immunol Rev* 235:10–23, 2010.)

Table 534.4

Spectrum of Diseases Characterized by Hemophagocytosis

- Primary HLH (see Table 534.2)
- HLH with immunodeficiency, autoinflammatory states (see Table 534.2)
- Infection-associated HLH (see Table 534.3)
- Malignancy-associated HLH
  - Lymphoma
  - Leukemia
- Macrophage activation syndrome (MAS) associated with autoimmune disease
  - Systemic-onset juvenile idiopathic arthritis
  - Systemic lupus erythematosus
  - Enthesitis-related arthritis
  - Inflammatory bowel disease

HLH, Hemophagocytic lymphohistiocytosis.

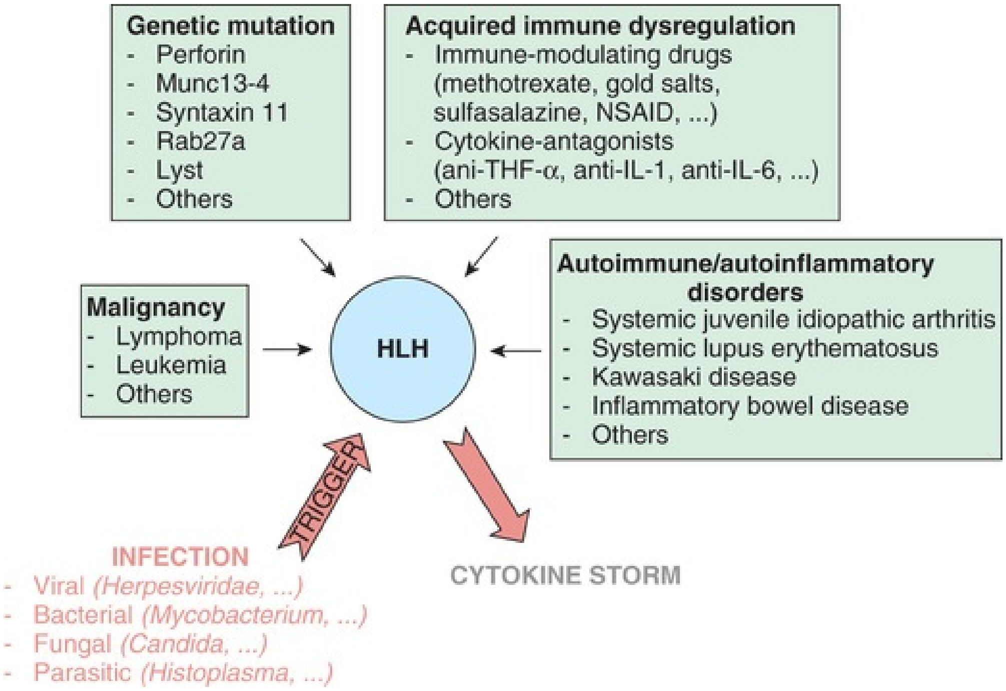
Genetic mutation
- Perforin
- Munc13-4
- Syntaxin 11
- Rab27a
- Lyst
- Others
Acquired immune dysregulation
- Immune-modulating drugs (methotrexate, gold salts, sulfasalazine, NSAID, ...)
- Cytokine-antagonists (ani-THF-α, anti-IL-1, anti-IL-6, ...)
- Others
Malignancy
- Lymphoma
- Leukemia
- Others
HLH
Autoimmune/autoinflammatory disorders
- Systemic juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Kawasaki disease
- Inflammatory bowel disease
- Others
TRIGGER
INFECTION
- Viral (Herpesviridae, ...)
- Bacterial (Mycobacterium, ...)
- Fungal (Candida, ...)
- Parasitic (Histoplasma, ...)
CYTOKINE STORM

FIG. 534.5 **Hemophagocytic lymphohistiocytosis (HLH) comprises a heterogeneous spectrum of disorders that all present with severe cytokine storm and life-threatening immunopathology. HLH can be caused by mutations in genes involved in granule-mediated cytotoxicity, but can also be acquired on a multitude of underlying autoimmune/autoinflammatory diseases or malignancies, with possible facilitation by**

immunomodulating therapies. Clinical manifestations of HLH are generally precipitated by an infection. NSAID, Nonsteroidal antiinflammatory drugs. (From Brisse E, Wouters CH, Matthys P: Hemophagocytic lymphohistiocytosis (HLH): a heterogeneous spectrum of cytokine-driven immune disorders, *Cytokine Growth Factor Rev* 26:263–280, 2015, Fig 2, p 267.)

In addition to these 2 most common forms of childhood histiocytosis (LCH and HLH), a number of rarer diseases are included under this rubric. **Juvenile xanthogranuloma (JXG)** is characterized by vacuolated histiocytes with foamy cytoplasm in lesions that evolve into mixed granulomas also containing eosinophils, lymphocytes, and other cells. **Erdheim-Chester disease (ECD)** predominantly affects adults. Surface markers suggest a link among LCH, JXG, and ECD; all 3 are dendritic cell diseases, with *BRAFV600E* mutations in the affected cells. Another rare form of histiocytosis is **Rosai-Dorfman disease** , also known as **sinus histiocytosis** with massive lymphadenopathy. Rosai-Dorfman disease is characterized by packing of sinusoids of the lymph nodes with hemophagocytic histiocytes, although extranodal involvement may also be present. Lastly, there is a group of unequivocal malignancies of cells of monocyte-macrophage lineage. By this definition, acute monocytic leukemia and true malignant histiocytosis are included among the class III histiocytoses (see Chapter 522). True neoplasms of Langerhans cells have been reported but are extremely rare.

534.1

Langerhans Cell Histiocytosis

Stephan Ladisch

Keywords

Birbeck granule
CD1a
CD207

hepatosplenomegaly
langerin
LCH
lymphadenopathy
MAPK pathway

Clinical Manifestations

Langerhans cell histiocytosis (LCH) has an extremely variable presentation. The skeleton is involved in 80% of patients and may be the only affected site, especially in children >5 yr old. **Bone lesions** may be single or multiple and are seen most often in the skull (Fig. 534.6). Other sites include the pelvis, femur, vertebra, maxilla, and mandible. Lesions may be asymptomatic or associated with pain and local swelling. Involvement of the spine may result in collapse of the vertebral body, which can be seen radiographically and may cause secondary compression of the spinal cord. In flat and long bones, osteolytic lesions with sharp borders occur, and no evidence exists of reactive new bone formation until the lesions begin to heal. Lesions that involve weight-bearing long bones may result in pathologic fractures. Chronically draining, infected ears are usually associated with destruction in the mastoid area. Bone destruction in the mandible and maxilla may result in teeth that appear to be free floating on radiographs. With response to therapy, healing is usually complete.

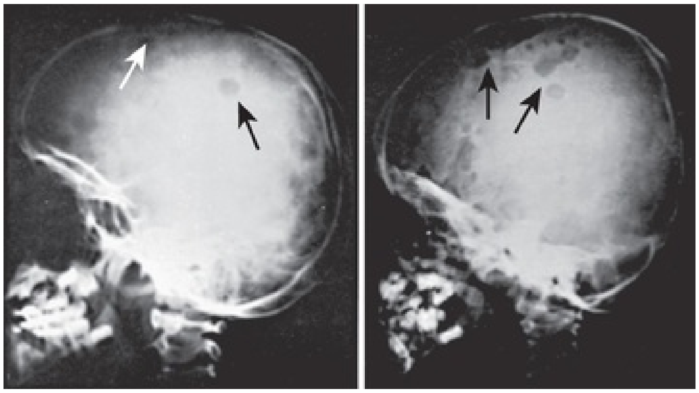

FIG. 534.6 **Skull radiographs from patients with Langerhans cell histiocytosis (LCH). Left, Patient was >2 yr old and had involvement limited to isolated bone lesions *(arrows).* She had a good recovery. Right, Patient was <2 yr old and had extensive bone disease *(arrows),* a febrile course, anemia, severe skin eruption, generalized lymphadenopathy, hepatosplenomegaly, pulmonary infiltrates, and a fatal outcome despite antitumor chemotherapy. These patients represent opposite ends of the clinical**

spectrum of LCH.

Approximately 50% of patients experience **skin involvement** (isolated or part of multisystem involvement) at some time during the course of disease, usually as a difficult-to-treat scaly, papular, seborrheic dermatitis of the scalp, diaper, axillary, or posterior auricular regions (Figs. 534.7 and 534.8). The lesions may spread to involve the back, palms, and soles. The exanthem may be petechial or hemorrhagic, even in the absence of thrombocytopenia. Localized or disseminated **lymphadenopathy** is present in approximately 33% of patients. **Hepatosplenomegaly** occurs in approximately 20% of patients. Various degrees of hepatic malfunction may occur, including jaundice and ascites.

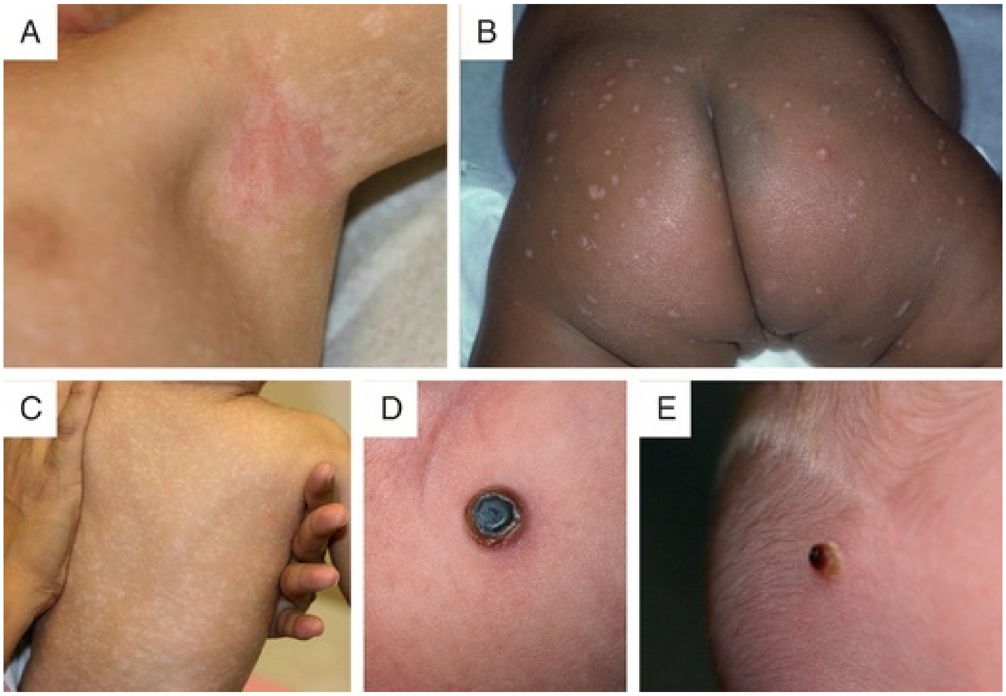

FIG. 534.7 Variable appearance of Langerhans cell histiocytosis of skin. A, Eczematous dermatitis. B, Hypopigmented, eroded papules. C, Hypopigmented macules. D and E, Crusted papulonodules. Presentation does not reflect presence or absence of multisystem disease. Despite similar appearance, the patient in D had a single lesion, whereas the patient in E had organ involvement. (From Simko SJ, Garmezy B, Abhyankar H, et al: Differentiating skin-limited and multisystem Langerhans cell histiocytosis, *J Pediatr* 165:990–996, 2014, Fig 3.)

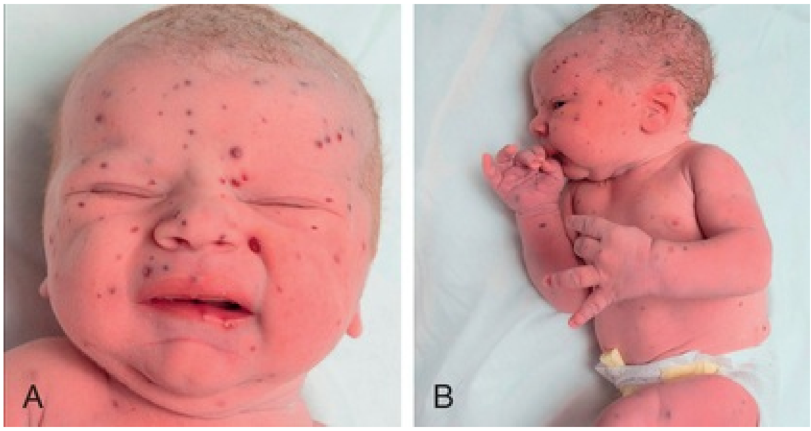

FIG. 534.8 **Langerhans cell histiocytosis presenting as "blueberry muffin" rash in neonate. Multiple firm, nonblanching, purple papules affecting A, the head and neck, and B, the body. (From Schmitt AR, Wetter DA, Camilleri MJ, et al: Langerhans cell histiocytosis presenting as a blueberry muffin rash, *Lancet* 390:155, 2017.)**

Exophthalmos, when present, often is bilateral and is caused by retroorbital accumulation of granulomatous tissue. Gingival mucous membranes may be involved with infiltrative lesions that appear superficially like candidiasis. Otitis media is present in 30–40% of patients; deafness may follow destructive lesions of the middle ear. In 10–15% of patients, **pulmonary infiltrates** are found on radiography. The lesions may range from diffuse fibrosis and disseminated nodular infiltrates to diffuse cystic changes (Fig. 534.9). Rarely, pneumothorax is a complication. If the lungs are severely involved, tachypnea and progressive respiratory failure may result.

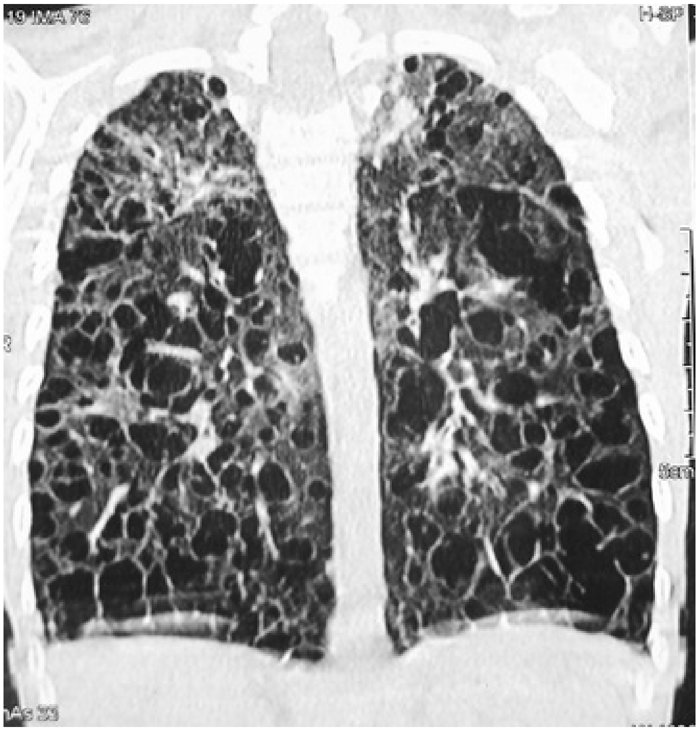

FIG. 534.9 High-resolution coronal CT image (lung window) reveals diffuse lung cysts with parenchymal destruction in bilateral lung fields. (From Chauhan L, Aggarwal N: Honey-comb Langerhans cell histiocytosis, *J Pediatr* 168:248, 2016, Fig 2.)

Pituitary dysfunction or hypothalamic involvement may result in growth retardation. In addition, patients may have diabetes insipidus; patients suspected of having LCH should demonstrate the ability to concentrate their urine before going to the operating room for a biopsy. Rarely, panhypopituitarism may occur. Primary hypothyroidism as a result of thyroid gland infiltration also may occur.

Patients with multisystem disease who are affected more severely are those who have systemic manifestations, including fever, weight loss, malaise, irritability, and failure to thrive. These systemic manifestations will distinguish patients at high risk of mortality (i.e., risk organ–positive patients) from patients at low risk of mortality (i.e., without systemic manifestations; risk organ–negative patients). The **risk organs** are liver, spleen, and the hematopoietic (bone marrow) system. The lung is not considered a risk organ. The distinction of risk-organ involvement is important for deciding the intensity of the treatment approach and has been addressed in standard treatment approaches for LCH, as delineated in the Histiocyte Society protocols. Bone marrow involvement may cause anemia and thrombocytopenia. Two uncommon but serious manifestations of LCH are hepatic involvement (leading to fibrosis and cirrhosis) and a peculiar central nervous system (CNS) involvement characterized by ataxia, dysarthria, and other neurologic symptoms. **Hepatic involvement** is associated with multisystem disease that is often already present at diagnosis. In contrast, the **CNS involvement** , which is progressive and histopathologically characterized by gliosis and has no known treatment, may be observed only many years after the initial diagnosis of LCH. These manifestations are not associated with LCH cells, Birbeck granules, CD1a positivity, or any other indication of LCH cell infiltration, raising questions about their pathogenesis.

After tissue biopsy, which is diagnostic and is easiest to perform on skin or bone lesions, a thorough clinical and laboratory evaluation should be undertaken. This should include a series of studies in all patients: complete blood cell count, liver function tests, coagulation studies, skeletal survey, chest radiograph, and measurement of urine osmolality. In addition, detailed evaluation of any organ system shown to be involved by physical examination or by these studies should be performed to establish the extent of disease before initiation of treatment.

Treatment and Prognosis

The clinical course of **single-system disease** (usually bone, lymph node, or skin) generally is benign, with a high chance of spontaneous remission. Therefore, treatment should be minimal and should be directed at arresting the progression of a bone lesion that could result in permanent damage before it resolves spontaneously. Curettage or, less often, corticosteroid injection or low-dose local radiation therapy (5-6 Gy) may accomplish this goal.

In contrast, **multisystem disease** requires treatment with systemic multiagent chemotherapy. Several different regimens have been proposed, but central elements are the inclusion of vinblastine and corticosteroids, both of which have been found to be very effective in treating LCH. Etoposide has been excluded from standard treatment of multisystem LCH, which is treated with multiple agents, designed to reduce mortality, reactivation of disease, and long-term consequences. The response rate to therapy is quite high, and mortality in severe LCH has been substantially reduced by multiagent chemotherapy, especially if the diagnosis is made accurately and expeditiously. The most recent treatment results associated with lengthened continuation therapy show a greater than 85% survival rate in severe (risk organ–positive) multisystem disease and a reduced rate of reactivation.

Experimental therapies are suggested only for unresponsive disease (often in very young children with multisystem disease and organ dysfunction who have not responded to multiagent initial treatment) and reactivation of risk organ–positive disease in risk organs, but not in reactivation of mild disease (any risk organ–negative reactivations). The approaches include immunosuppressive therapy with cyclosporine/antithymocyte globulin and possibly imatinib, 2-chlorodeoxyadenosine, clofarabine, and stem cell transplantation. With the discovery of the *BRAFV600E* mutation causing hyperactivation of the MAPK pathway in LCH cells, pharmacologic inhibition of BRAF and pharmacologic inhibition of MEK are being investigated as therapeutic approaches for resistant disease.

Late (fibrotic) complications, whether hepatic or pulmonary, are irreversible and require organ transplantation to be definitively treated. Current treatment approaches and experimental protocols for both LCH and HLH can be obtained at the Histiocyte Society website (http://www.histiocytesociety.org). An unresolved problem is treatment of the (usually late-onset) severe, progressive, and intractable LCH-associated **neurodegenerative syndrome** .

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534.2

Hemophagocytic Lymphohistiocytosis

Stephan Ladisch

Keywords

CD163 perforin
familial hemophagocytic lymphohistiocytosis
FHLH
hemophagocytosis
hemophagocytic lymphohistiocytosis
HLH
infection-associated hemophagocytic syndrome
macrophage activation syndrome
MUNC13-4
secondary HLH
stem cell transplantation

See Classification and Pathology at start of chapter .

Clinical Manifestations

Familial hemophagocytic lymphohistiocytosis (FHLH) and secondary hemophagocytic lymphohistiocytosis (HLH) have remarkably similar presentations, consisting of a generalized disease process, most often with fever (90–100%), maculopapular and/or petechial rash (10–60%), weight loss, and irritability. The initial clinical presentation can vary but is almost always very severe and, in the case of secondary HLH, may be camouflaged by a primary disease process. Acute presentations include septic shock, acute respiratory distress, seizures, and coma (because of CNS infiltration). Other features that are frequently present result from bone marrow involvement and pancytopenia or hepatic dysfunction.

Children with primary HLH are generally <1-2 yr old, and children with secondary HLH typically present at an older age, but both forms may present at any age. **Physical examination** often reveals hepatosplenomegaly (70–100%), lymphadenopathy (20–50%), respiratory distress (40–90%), jaundice, and symptoms of CNS involvement (50%) that are not unlike those of aseptic meningitis or acute demyelinating encephalomyelitis (see Chapter 618.4). MRI may demonstrate systemic T2-weighted/FLAIR hyperintensities in gray and white matter and in supratentorial and infratentorial regions. The cerebrospinal fluid (CSF) pleocytosis (50–90%) associated with CNS involvement in primary HLH is characterized by cells that are the same phagocytic macrophages found in the peripheral blood or bone marrow. Primary HLH is also generally associated with severe immunodeficiency.

The **diagnosis** of HLH is arrived at in 2 stages. The 1st stage is based on a set of 8 clinical and laboratory findings, with the presence of 5 of the 8 being diagnostic of HLH. The 8 findings, formulated by the Histiocyte Society, are fever, splenomegaly, cytopenia of 2 cell lines (in 90–100%), hypertriglyceridemia (80–100%) or hypofibrinogenemia (65–85%), hyperferritinemia (≥500 but often >10,000), extremely elevated soluble CD25 (interleukin-2 receptor), reduced or absent NK cell activity, and bone marrow, CSF, or lymph node evidence of hemophagocytosis (Table 534.5). The 2nd stage involves genetic analysis for mutations and is undertaken as quickly as possible, but generally requires some time to complete and should not interfere with initiation of treatment (Fig. 534.10). The genetic findings and family history will determine whether the diagnosis is (autosomal recessive) primary HLH or secondary HLH.

Table 534.5

Diagnostic Guidelines for Hemophagocytic Lymphohistiocytosis (HLH)

The diagnosis of HLH is established by fulfilling one of the following 2 criteria:

1. A molecular diagnosis consistent with HLH (e.g., *PRF* mutations, *SAP* mutations)
   or
2. Presence of 5 of the following 8 symptoms, signs, or laboratory abnormalities:
   - a. Fever
   - b. Splenomegaly
   - c. Cytopenia (affecting ≥2 cell lineages; hemoglobin ≤9 g/dL [or ≤10 g/dL for infants <4 wk old], platelets <100,000/µL, neutrophils <1,000/µL)
   - d. Hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (≤150 mg/dL)
   - e. Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
   - f. Low or absent natural killer cell cytotoxicity
   - g. Hyperferritinemia (≥500 ng/mL)
   - h. Elevated soluble CD25 (interleukin-2Rα chain; ≥2,400 U/mL)

Adapted from VerbskyJW, Grossman WJ: Hemophagocytic lymphohistiocytosis: diagnosis, pathophysiology, treatment, and future perspectives, *Ann Med* 38:20–31, 2006 (Table 1, p 21).

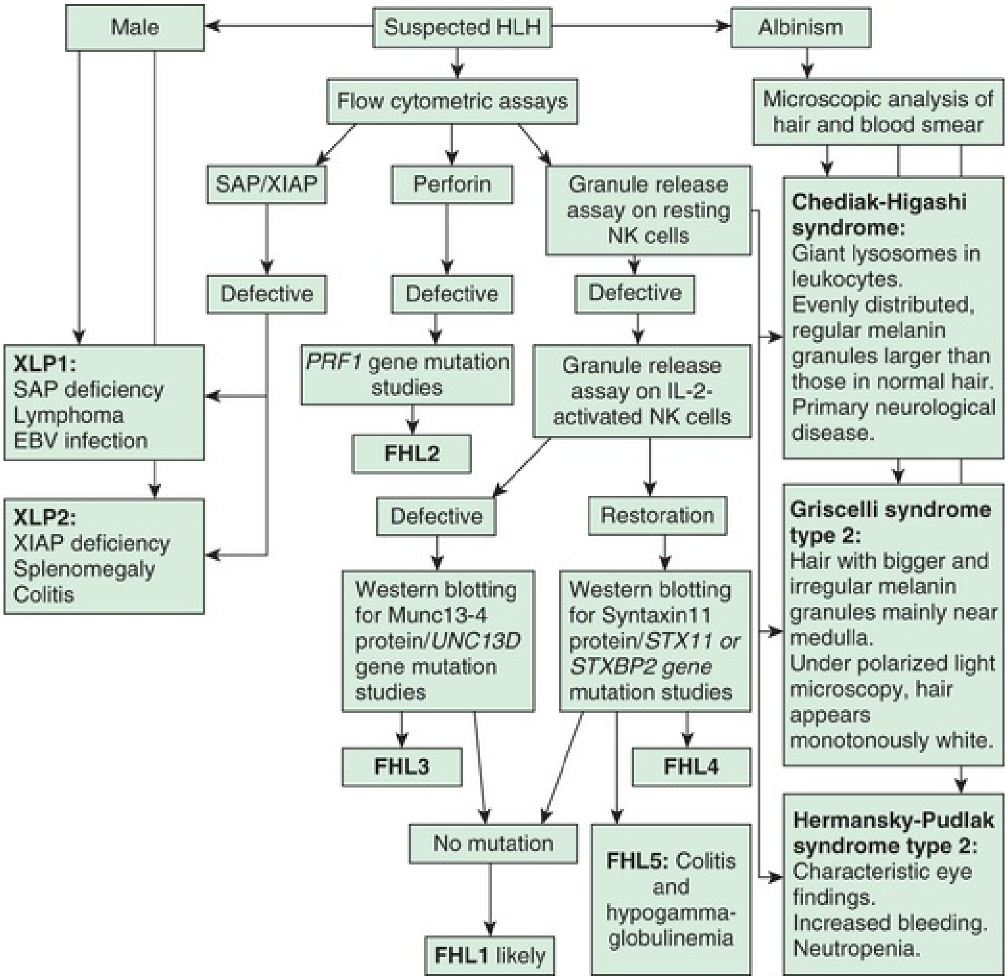

Suspected HLH
Male
Albinism
Flow cytometric assays
Microscopic analysis of hair and blood smear
SAP/XIAP
Perforin
Granule release assay on resting NK cells
Defective
Defective
Defective
Chediak-Higashi syndrome: Giant lysosomes in leukocytes. Evenly distributed, regular melanin granules larger than those in normal hair. Primary neurological disease.
XLP1: SAP deficiency Lymphoma EBV infection
PRF1 gene mutation studies
Granule release assay on IL-2-activated NK cells
FHL2
XLP2: XIAP deficiency Splenomegaly Colitis
Defective
Restoration
Griscelli syndrome type 2: Hair with bigger and irregular melanin granules mainly near medulla. Under polarized light microscopy, hair appears monotonously white.
Western blotting for Munc13-4 protein/*UNC13D* gene mutation studies
Western blotting for Syntaxin11 protein/*STX11 or STXBP2 gene* mutation studies
FHL3
FHL4
No mutation
FHL5: Colitis and hypogamma-globulinemia
Hermansky-Pudlak syndrome type 2: Characteristic eye findings. Increased bleeding. Neutropenia.
FHL1 likely

FIG. 534.10 **Algorithm for identification of genetic causes of hemophagocytic lymphohistiocytosis (HLH). The HLH algorithm is based on flow cytometry assays: all the patients fitting into HLH criteria, irrespective of age and clinical presentations, should be screened for perforin expression and granule release assay. All male patients should be screened for signaling lymphocyte activation molecule–associated protein (SAP) and X-linked inhibitor of apoptosis protein (XIAP) expression. For patients clinically presenting with albinism, microscopic analysis of hair and blood smear is essential for differential diagnosis of Chédiak-Higashi syndrome, Griscelli syndrome, and Hermansky-Pudlak syndrome. Based on the defect in expression of a particular protein identified, molecular characterization for the respective gene should be performed for confirmation of diagnosis. EBV, Epstein-Barr virus; FHL, familial hemophagocytic lymphohistiocytosis; NK, natural killer. (Adapted from Madkaikar M, Shabrish S, Desai M: Current updates on classification, diagnosis and treatment of hemophagocytic lymphohistiocytosis (HLH),** ***Indian J Pediatr*** **83:434–443, 2016.)**

Hemophagocytosis is not specific for HLH and should be considered in the context of the diagnostic criteria. No absolute clinical or laboratory distinction can be made between primary HLH and secondary HLH. In some subgroups of HLH, perforin assays may be normal. Similarly, some patients with primary FHLH have no known identifiable gene mutation.

In the absence of either (1) a documented genetic defect coupled with defective NK cell cytotoxicity or (2) frank hemophagocytosis, care should be taken in making the diagnosis of secondary HLH, given the implication to use cytotoxic chemotherapy. The nonspecific criteria (indicative of inflammation) used to diagnose HLH can also be seen in diseases that are not always associated with hemophagocytosis (e.g., overwhelming acute viral infection with appropriate T-cell activation), in which the cytotoxic and immunosuppressive therapy used in treating HLH might be contraindicated.

Macrophage activation syndrome , particularly in the context of systemic-onset juvenile idiopathic arthritis (JIA) or infection, has many similarities to HLH (see Chapter 180). Indeed, whole exome sequencing of patients with systemic-onset JIA or those with fatal influenza has revealed a higher-than-expected incidence of HLH genes. Other disorders in the **differential diagnosis** of HLH include sepsis, Wolman disease, osteopetrosis, autoimmune lymphoproliferative syndrome, neonatal hemochromatosis, Gaucher disease, combined immunodeficiency disease, and common variable immunodeficiency disease.

Treatment and Prognosis

Therapy for **primary HLH** (autosomal recessive genetic disease or familial occurrence) consists of a combination of etoposide, corticosteroids, cyclosporine, and intrathecal methotrexate, as described in the current Histiocyte Society HLH-1994 and HLH-2004 protocols. It should be stressed that pancytopenia and the presence of an infection are *not* contraindications to cytotoxic therapy. Some recommend antithymocyte globulin and cyclosporine for maintenance therapy. The goal is to reach the point of initiating **stem cell transplantation** . To date, this is the only known potentially curative treatment for primary HLH and is effective in achieving cure in >60% of patients. Chemotherapy is inadequate for sustained cure of primary HLH, which is ultimately fatal without transplantation.

In **secondary HLH** , it is critical that the underlying disease (e.g., infection, malignancy) be identified and successfully treated. The diagnostic distinction between primary HLH and secondary HLH sometimes can be based on the acute onset of secondary HLH in the presence of a documented infection. In this case, treatment of the underlying infection is coupled with supportive care. If the diagnosis is made in the setting of iatrogenic immunodeficiency, immunosuppressive treatment should be withdrawn and supportive care instituted along with specific therapy for the underlying infection. In many patients the prognosis is excellent without additional specific treatment other than treating the triggering infection. However, when a treatable infection or other cause cannot be documented, and when the clinical presentation is severe, the prognosis for secondary HLH is as poor as for primary HLH. These patients should receive the identical initial 8 wk chemotherapeutic approach, including etoposide, even in the face of cytopenias. In both primary and secondary HLH, the cytotoxic effect of etoposide on macrophages interrupts cytokine production, the hemophagocytic process, and the accumulation of macrophages, all of which may contribute to the pathogenesis of **infection-associated hemophagocytic syndrome** . A broad spectrum of infectious agents, including viruses (e.g., cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), fungi, protozoa, and bacteria, may trigger secondary HLH, often in the setting of immunodeficiency (see Table 534.3). A thorough evaluation for infection should be undertaken in immunodeficient patients with hemophagocytosis. The same syndrome may be identified in conjunction with a rheumatologic disorder (e.g., systemic lupus erythematosus, Kawasaki disease) or a neoplasm (e.g., leukemia). In these patients, effective treatment of the underlying disease (e.g., infection, cancer) is critical and may itself lead to ultimate resolution of the hemophagocytosis.

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534.3

Other Histiocytoses

Stephan Ladisch

Keywords

juvenile xanthogranuloma
Rosai-Dorfman disease

Other rare histiocytoses have been named for their clinical presentation. Examples include xanthogranuloma in juvenile xanthogranuloma (JXG) and striking lymphadenopathy in Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy). JXG may require systemic treatment with cytotoxic chemotherapy or potentially MAPK pathway inhibitors, reflecting the presence of a *BRAF* mutation. Rosai-Dorfman disease usually is not treated, although the massive lymphadenopathy may require intervention because of its tendency to cause physical obstruction. Acute monocytic leukemia and true malignant histiocytosis are included because they are unequivocal malignancies of the monocyte-macrophage lineage (see Chapter 522).

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PART XXII

Nephrology

OUTLINE

Section 1 Glomerular Disease

Section 2 Conditions Particularly Associated with Hematuria

Section 3 Conditions Particularly Associated with Proteinuria

Section 4 Tubular Disorders

SECTION 1

Glomerular Disease

OUTLINE

Chapter 535 Introduction to Glomerular Diseases

CHAPTER 535

Introduction to Glomerular Diseases

535.1

Anatomy of the Glomerulus

Edward J. Nehus

The kidneys lie in the retroperitoneal space slightly above the level of the umbilicus. They range in length and weight, respectively, from approximately 6 cm and 24 g in a full-term newborn to ≥ 12 cm and 150 g in an adult. The kidney (Fig. 535.1) has an outer layer, **the cortex,** which contains the glomeruli, proximal and distal convoluted tubules, and collecting ducts, and an inner layer, **the medulla,** that contains the straight portions of the tubules, the loops of Henle, the vasa recta, and the terminal collecting ducts (Fig. 535.2).

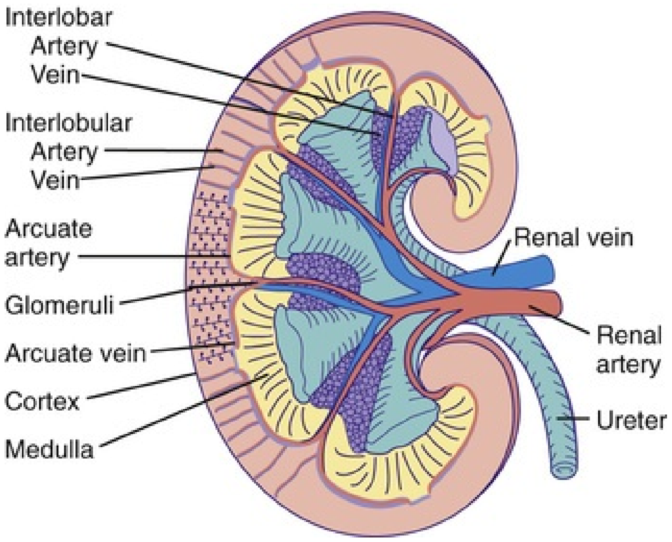
Interlobar
Artery
Vein
Interlobular
Artery
Vein
Arcuate artery
Glomeruli
Arcuate vein
Cortex
Medulla
Renal vein
Renal artery
Ureter

FIG. 535.1 Gross morphology of the renal circulation. (From Pitts RF: Physiology of the kidney and body fluids, ed 3, Chicago, 1974, Year Book Medical Publishers.)

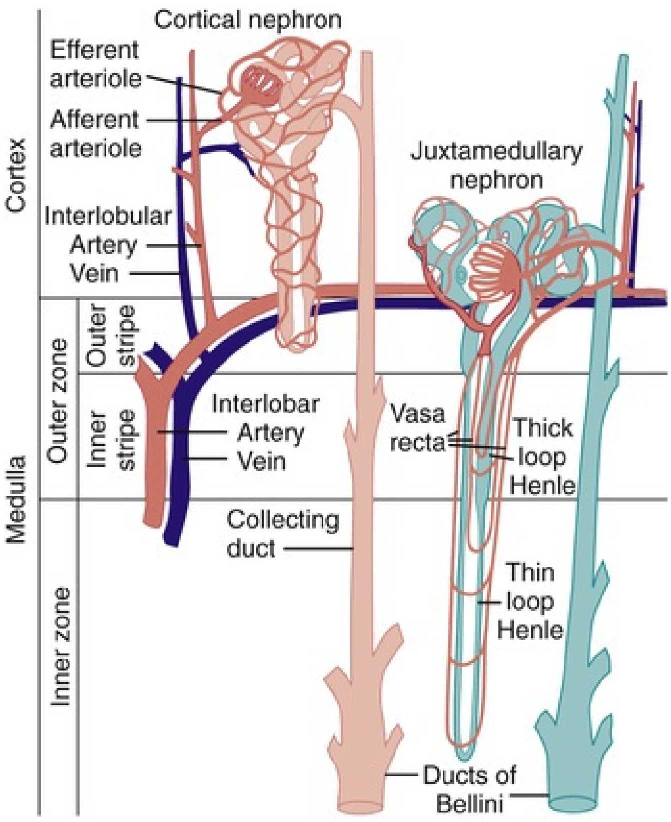
Cortical nephron
Efferent arteriole
Afferent arteriole
Cortex
Interlobular
Artery
Vein
Juxtamedullary nephron
Medulla
Outer zone
Outer stripe
Inner stripe
Inner zone
Interlobar
Artery
Vein
Vasa recta
Thick loop Henle
Collecting duct
Thin loop Henle
Ducts of Bellini

FIG. 535.2 Comparison of the blood supplies of cortical and juxtamedullary nephrons. (From Pitts RF: Physiology of the kidney and

body fluids, ed 3, Chicago, 1974, Year Book Medical Publishers.)

The blood supply to each kidney usually consists of a main renal artery that arises from the aorta, although multiple renal arteries can occur. The main artery divides into segmental branches within the medulla, becoming the interlobar arteries that pass through the medulla to the corticomedullary junction. At this point, the interlobar arteries branch to form the arcuate arteries, which run parallel to the surface of the kidney. Interlobular arteries originate from the arcuate arteries and give rise to the afferent arterioles of the glomeruli. Specialized muscle cells in the wall of the afferent arteriole and specialized distal tubular cells adjacent to the glomerulus (macula densa) form the juxtaglomerular apparatus that controls the secretion of renin. The afferent arteriole divides into the glomerular capillary network, which then recombines into the efferent arteriole (see Fig. 535.2). The juxtamedullary efferent arterioles are larger than those in the outer cortex and provide the blood supply, as the vasa recta, to the tubules and medulla.

Each kidney contains approximately 1 million **nephrons** (each consisting of a glomerulus and associated tubules). There is a large distribution of normal nephron numbers in humans, ranging from 200,000 to 1.8 million nephrons per kidney. This variation can have major pathophysiologic significance as a risk factor for the later development of hypertension and progressive renal dysfunction. In humans, the formation of nephrons is complete at 34-36 wk of gestation, but functional maturation with tubular growth and elongation continues during the 1st decade of life. Because new nephrons cannot be formed after birth, any disease that results in progressive loss of nephrons can lead to renal insufficiency. A decreased number of nephrons secondary to low birthweight, prematurity, and/or unknown genetic or environmental factors has been implicated as a significant risk factor for the development of primary hypertension and progressive renal dysfunction in adulthood. A low nephron number presumably results in hyperfiltration and eventual sclerosis of *overworked* nephron units.

The glomerular network of specialized capillaries serves as the filtering mechanism of the kidney. The glomerular capillaries are lined by endothelial cells (Fig. 535.3) and have very thin cytoplasm that contains many holes (fenestrations). The **glomerular basement membrane** (GBM) forms a continuous layer between the endothelial and mesangial cells on one side and the epithelial cells on the other. The membrane has three layers: a central electron-dense lamina densa; the lamina rara interna, which lies between the lamina densa and the endothelial cells; and the lamina rara externa, which lies between the lamina densa and the epithelial cells. The visceral epithelial cells cover the capillary and project cytoplasmic foot processes, which attach to the lamina rara externa. Between the foot processes are spaces or filtration slits. The **mesangium** (mesangial cells and matrix) lies between the glomerular capillaries on the endothelial cell side of the GBM and forms the medial part of the capillary wall. The mesangium may serve as a supporting, stalk-like structure for the glomerular capillaries and probably has a role in the regulation of glomerular blood flow, filtration, and the removal of macromolecules (such as immune complexes) from the glomerulus. The Bowman's capsule, which surrounds the glomerulus, is composed of a basement membrane, which is continuous with the basement membranes of the glomerular capillaries and the proximal tubules, and the parietal epithelial cells, which are adjacent to the visceral epithelium (Fig. 535.4).

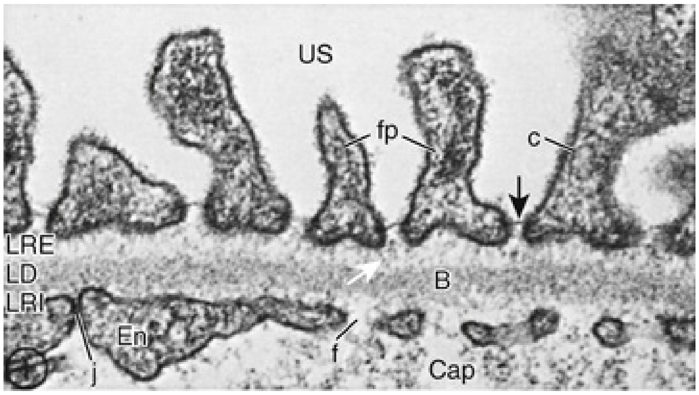

FIG. 535.3 Electron micrograph of the normal glomerular capillary (Cap) wall demonstrating the endothelium (En) with its fenestrations (f), the glomerular basement membrane (B) with its central dense layer, the lamina densa (LD), and adjoining lamina rara interna (LRI) and externa (LRE) *(white arrow),* and the epithelial cell foot processes (fp) with their thick cell coat (c). The glomerular filtrate passes through the endothelial fenestrae, crosses the basement membrane, and passes through the filtration slits *(black arrow)* between the epithelial cell foot processes to reach the urinary space (US) (×60,000). J is the junction between two endothelial cells. (From Farquhar MG, Kanwar YS: Functional organization of the glomerulus: state of the science in 1979. In Cummings NB, Michael AF, Wilson CB, editors: Immune mechanisms in renal disease, New York, 1982, Plenum.)

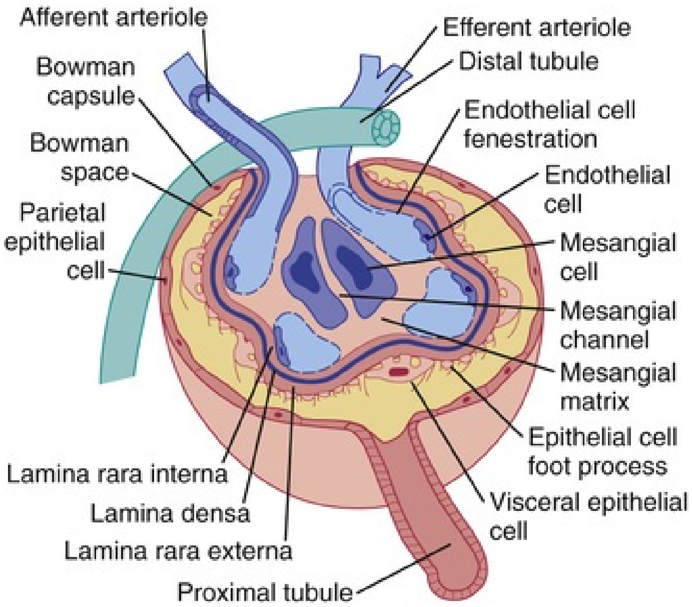
Afferent arteriole
Bowman capsule
Bowman space
Parietal epithelial cell
Efferent arteriole
Distal tubule
Endothelial cell fenestration
Endothelial cell
Mesangial cell
Mesangial channel
Mesangial matrix
Epithelial cell foot process
Visceral epithelial cell
Lamina rara interna
Lamina densa
Lamina rara externa
Proximal tubule

FIG. 535.4 Schematic depiction of the glomerulus and surrounding structures.

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Tufro A, Gulati A, et al. Development of glomerular circulation and function. Avner ED, Harmon WE, Niaudet P. *Pediatric nephrology* . ed 7. Springer-Verlag: Heidelberg, Germany; 2016:37–59.

535.2

Glomerular Filtration

Edward J. Nehus

Kidney function is best measured as the glomerular filtration rate (GFR). As the blood passes through the glomerular capillaries, the plasma is filtered through the glomerular capillary walls. Small plasma molecules filter freely (e.g., electrolytes, glucose, phosphate, urea, creatinine, peptides, low-molecular-weight proteins), whereas larger molecules are retained in the circulation (such as albumin and globulins). The filtrate is collected in Bowman's space and enters the tubules. There its composition is modified by tightly regulated secretion and absorption of solute and fluid by the multiple tubular segments of the nephron and the ductal system, until it exits the kidney, via the ureter, as urine.

Glomerular filtration is the net result of opposing forces applied across the capillary wall. The force for ultrafiltration (glomerular capillary hydrostatic pressure) is a result of systemic arterial pressure, modified by the tone of the afferent and efferent arterioles. The major force opposing ultrafiltration is glomerular capillary oncotic pressure, created by the gradient between the high concentration of plasma proteins within the capillary and the almost protein-free ultrafiltrate in Bowman's space. Filtration may be modified by the rate of glomerular plasma flow, the hydrostatic pressure within Bowman's space, and/or the permeability of the glomerular capillary wall.

Although glomerular filtration begins at approximately the 6th wk of fetal life, kidney function is not necessary for normal intrauterine homeostasis because the placenta serves as the major fetal excretory organ. After birth, the GFR increases until renal growth ceases (by age ~ 18-20 yr in most people). To compare GFRs of children and adults, the GFR is standardized to the body surface area (1.73 m^2) of an “ideal” 70-kg adult. Even after correction for surface area, the GFR of a child does not approximate adult values until the 3rd yr of life (Fig. 535.5). The GFR may be estimated by measurement of the serum creatinine level. Creatinine is derived from muscle metabolism. Its production is relatively constant, and its excretion is primarily through glomerular filtration, although tubular secretion can become important as the serum creatinine rises in renal insufficiency. In contrast to the concentration of blood urea nitrogen, which is affected by the state of hydration and nitrogen balance, the serum creatinine level is primarily influenced by muscle mass and the level of glomerular function. The serum creatinine is of value only in estimating the GFR under steady-state conditions. A patient can have a normal serum creatinine level with decreased renal function very shortly after the onset of acute kidney injury. In this clinical setting, serum creatinine may take days to reach the steady state. Furthermore, kidney function may fall up to 50% before a significant rise in serum creatinine occurs.

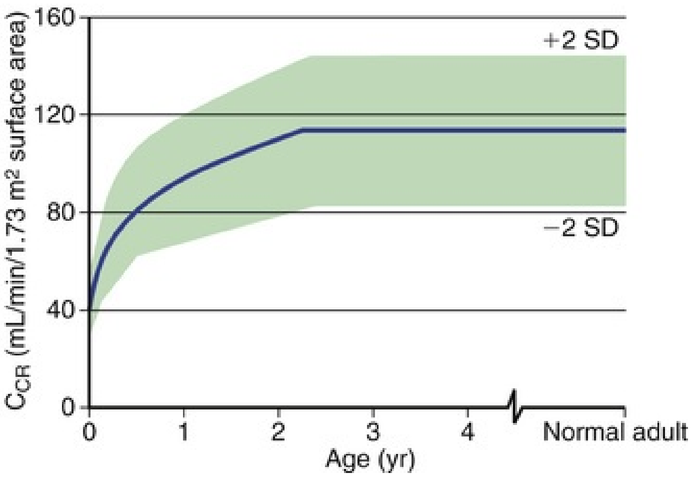

FIG. 535.5 Changes in the normal value of the glomerular filtration rate, as measured by the creatinine clearance (Ccr), when standardized to mL/min/1.73 m^2 of body surface area. The *solid line* depicts the mean, and the *shaded area* includes 2 SD. (From McCrory W: Developmental nephrology, Cambridge, MA, 1972, Harvard University Press.)

The precise measurement of the GFR is accomplished by quantitating the clearance of a substance that is freely filtered across the capillary wall and is neither reabsorbed nor secreted by the tubules. The clearance (C_s) of such a substance is the volume of plasma that, when completely cleared of the contained substance, would yield an equal quantity of that substance excreted in the urine over a specified time. Renal clearance is calculated by the following formula:

$$C_s\ (\text{mL/min}) = U_s\ (\text{mg/mL}) \times V\ (\text{mL/min}) / P_s\ (\text{mg/mL})$$

where C_s equals the clearance of substance s, U_s reflects the urinary concentration of s, V represents the urinary flow rate, and P_s equals the plasma concentration of *s.* To correct the clearance for individual body surface area, the formula is:

$$\text{Corrected clearance } (\text{mL/min}/1.73\ \text{m}^2) = C_s(\text{mL/min}) \times \frac{1.73}{\text{Surface area } (\text{m}^2)}$$

The GFR is optimally measured by the clearance of inulin, a fructose polymer having a molecular weight of approximately 5.7 kDa. Because the inulin clearance technique is cumbersome, radioisotopes are commonly used to measure GFR in clinical practice. GFR can be accurately determined by a single intravenous injection of a radioisotope, most commonly ^{99m} TC-DTPA, followed by timed monitoring of serum samples.

Because true measurement of the GFR is expensive and time consuming, the GFR is commonly estimated (eGFR) by the clearance of endogenous creatinine. Formulas that estimate creatinine clearance accurately in clinical settings have been useful tools in patient care. The “bedside” Schwartz formula is the most widely used pediatric formula and is based on the serum creatinine (Scr), patient height, and an empirical constant:

$$\text{eGFR} = 0.413 \times \text{height (cm)}/S_{cr}\ (\text{mg/dL})$$

The accuracy of GFR estimating equations can be further improved utilizing an additional endogenous marker, cystatin C, in addition to serum creatinine. Cystatin C is a 13.6-kDa protease inhibitor produced by nucleated cells that is freely filtered by the kidney. It continues to gain popularity as a clinical tool to provide an alternative to creatinine-based formulas, because it has distinct advantages in estimating the GFR. Unlike creatinine, cystatin C is not secreted by the renal tubules under any conditions. Furthermore, it is less affected by sex, age, and muscle mass than serum creatinine.

The absence of plasma proteins larger than the size of albumin from the glomerular filtrate confirms the effectiveness of the glomerular capillary wall as a filtration barrier. The endothelial cell, basement membrane, and epithelial cell of the glomerular capillary wall have size-selective properties that filter plasma molecules of different molecular weights. The molecular charge also determines the glomerular permeability, with negatively charged plasma proteins repelled by negatively charged sites of the glomerular capillary wall. The renal glomerulus is therefore capable of permitting the free filtration of water and other solutes while retaining plasma proteins of vital importance.

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535.3

Glomerular Diseases

Edward J. Nehus

Pathogenesis

Glomerular injury may be a result of genetic, immunologic, perfusion, or coagulation disorders. Genetic disorders of the glomerulus may result from mutations in DNA exons encoding proteins located within the glomerulus, interstitium, or tubular epithelium; mutations in regulatory genes controlling DNA transcription; abnormal posttranscriptional modification of RNA transcripts; or abnormal posttranslational modification of proteins. Immunologic injury to the glomerulus results in **glomerulonephritis,** which is a generic term for several diseases, but more precisely a histopathologic term defining inflammation of the glomerular capillaries. Evidence that glomerulonephritis is caused by immunologic injury includes morphologic and immunopathologic similarities to experimental immune-mediated glomerulonephritis; the demonstration of immune reactants (immunoglobulin, complement) in glomeruli; abnormalities in serum complement; and the finding of autoantibodies (anti-GBM) in some of these diseases (Fig. 535.6). There appear to be two major mechanisms of immunologic injury: glomerular deposition of circulating antigen–antibody immune complexes and interaction of antibody with glomerular antigens in situ. In the latter circumstance, the antigen may be a normal component of the glomerulus (the noncollagenous domain [NC-1] of type IV collagen, a putative antigen in human anti-GBM nephritis) or an antigen that has been deposited in the glomerulus.

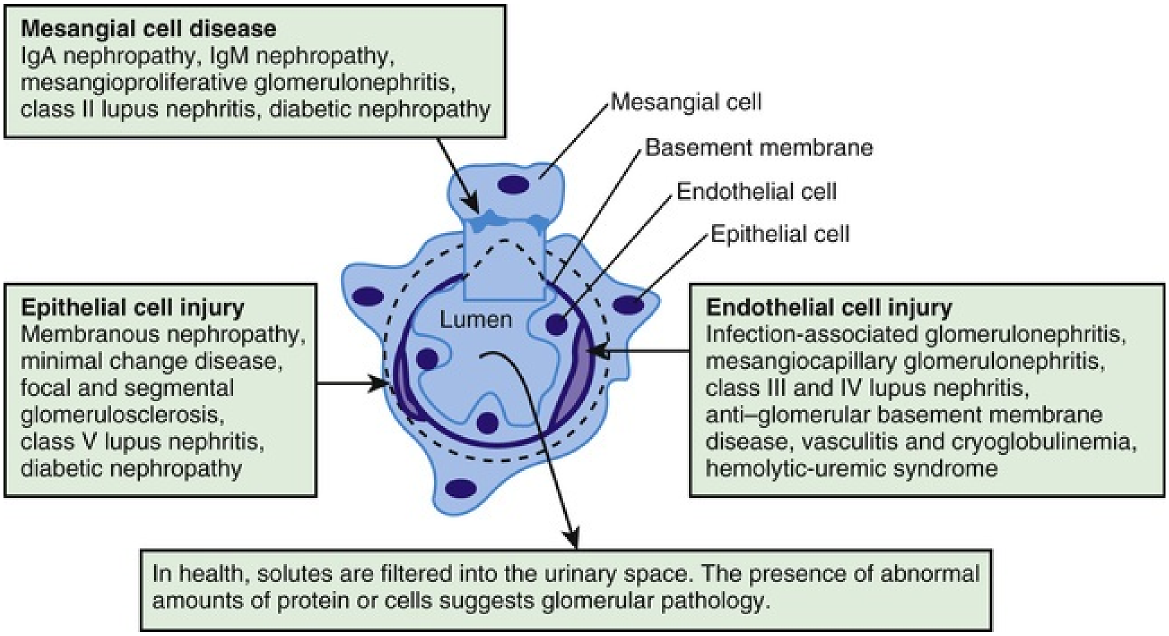
Mesangial cell disease
IgA nephropathy, IgM nephropathy, mesangioproliferative glomerulonephritis, class II lupus nephritis, diabetic nephropathy
Mesangial cell
Basement membrane
Endothelial cell
Epithelial cell
Lumen
Epithelial cell injury
Membranous nephropathy, minimal change disease, focal and segmental glomerulosclerosis, class V lupus nephritis, diabetic nephropathy
Endothelial cell injury
Infection-associated glomerulonephritis, mesangiocapillary glomerulonephritis, class III and IV lupus nephritis, anti–glomerular basement membrane disease, vasculitis and cryoglobulinemia, hemolytic-uremic syndrome
In health, solutes are filtered into the urinary space. The presence of abnormal amounts of protein or cells suggests glomerular pathology.

FIG. 535.6 Cellular location of injury during glomerulonephritis. Mesangial cells are directly exposed to the circulation. Deposition of immune complexes within these cells is typically seen in disorders such as immunoglobulin A (IgA) nephropathy; it results in proliferation and expansion of the cells, leading to hematuria, proteinuria, and renal impairment. Epithelial cells, in conjunction with basement membrane, allow filtration of plasma solutes but retard passage of cells and plasma proteins. Disease related to these cells is typified by the presence of subepithelial deposits and flattening of the foot processes that engage the basement membrane, resulting in disruption of the filtration barrier and proteinuria. Endothelial cell disease can result from deposition of immune complex (as

occurs in mesangiocapillary glomerulonephritis), attachment of antibody to the basement membrane (Goodpasture disease), or trauma and activation of coagulation (hemolytic-uremic syndrome). Endothelial cell proliferation and necrosis are accompanied by leukocyte accumulation, and rupture of the basement membrane, crescent formation, and disruption of glomerular architecture can develop. A nephritic or rapidly progressive presentation ensues. (From Chadban SJ, Atkins RC: Glomerulonephritis, Lancet 365:1797-1806, 2005.)

In **immune complex–mediated** diseases, antibody is produced against, and combines with, a circulating antigen that is usually unrelated to the kidney (see Fig. 535.6). The immune complexes accumulate in GBMs and activate the complement system, leading to immune injury. Acute serum sickness in rabbits is a model of immune complex-mediated glomerulonephritis, which is produced by a single intravenous injection of bovine albumin. Within 1 wk after injection, a rabbit produces antibody against bovine albumin, and the antigen remains in the blood in high concentration. Antigen-antibody immune complexes form in the circulation, accumulate in the glomerulus, and induce acute glomerulonephritis and vasculitis. The processes involved in glomerular localization are not well understood but include characteristics of the complex (concentration, charge, size) and/or the glomerulus (mesangial trapping, negatively charged capillary wall); hydrodynamic forces; and the influence of various chemical mediators (angiotensin II, prostaglandins).

With deposition of immune complexes in glomeruli, rabbits develop an acute proliferative glomerulonephritis. Immunofluorescence microscopy demonstrates granular **(lumpy-bumpy)** deposits containing immunoglobulin and complement in the glomerular capillary wall. Electron microscopic studies show these deposits to be on the epithelial side of the GBM and in the mesangium. For the next few days, as additional antibody enters the circulation, the antigen is ultimately removed from the circulation and the glomerulonephritis subsides.

An example of in situ antigen–antibody interaction is **anti–GBM antibody disease,** in which antibody reacts with antigen(s) of the GBM. Immunopathologic studies reveal linear deposition of immunoglobulin and complement along the GBM in Goodpasture syndrome (see Chapter 538.4) and certain types of rapidly progressive glomerulonephritis (see Chapter 537.7).

The inflammatory reaction that follows immunologic injury results from activation of one or more mediator pathways. The most important of these is the complement system, which has two initiating sequences: the classic pathway, which is activated by antigen–antibody immune complexes, and the alternative or properdin pathway, which is activated by polysaccharides and endotoxin. These pathways converge at C3; from that point on, the same sequence leads to lysis of cell membranes (see Chapter 159). The major noxious products of complement activation are produced after activation of C3 and include anaphylatoxin (which stimulates contractile proteins within vascular walls and increases vascular permeability) and chemotactic factors (C5a) that recruit neutrophils and perhaps macrophages to the site of complement activation, leading to consequent damage to vascular cells and basement membranes.

The coagulation system may be activated *directly,* after endothelial cell injury that exposes the thrombogenic subendothelial layer (thereby initiating the coagulation cascade), or it may be activated *indirectly,* after complement activation. Consequently, fibrin is deposited within glomerular capillaries or within Bowman's space as crescents. Activation of the coagulation cascade can also activate the kinin system, which produces additional chemotactic and anaphylatoxin-like factors.

Pathology

The glomerulus may be injured by several mechanisms, but it has only a limited number of histopathologic responses; different disease states can produce similar microscopic changes.

Proliferation of glomerular cells occurs in most forms of glomerulonephritis and may be generalized (involving all glomeruli) or focal (involving only some glomeruli and sparing others). Within a single glomerulus, proliferation may be diffuse (involving all parts of the glomerulus) or segmental (involving only one or more tufts, but not others). Proliferation commonly involves the endothelial and mesangial cells and is often associated with an increase in the mesangial matrix (see Fig. 535.6). Mesangial proliferation can result from deposition of immune complex within the mesangium. The resultant increase in cell size and number, and production of mesangial matrix, can increase the glomerular size and narrow the lumens of glomerular capillaries, leading to renal insufficiency.

Crescent formation in Bowman's space (capsule) is a result of proliferation of parietal epithelial cells and is often associated with clinical signs of renal dysfunction. Crescents develop in several forms of glomerulonephritis (termed **rapidly progressive** or **crescentic;** see Chapter 537.7) and are a characteristic response to deposition of fibrin in Bowman's space. Newly formed crescents contain fibrin, the proliferating epithelial cells of Bowman's space, basement membrane–like material produced by these cells, and macrophages that might have a role in the genesis of glomerular injury. Over the subsequent days to weeks, the crescent is invaded by connective tissue and becomes a fibroepithelial crescent. This process generally results in glomerular obsolescence and the clinical development of chronic renal failure. Crescent formation is often associated with glomerular cell death. The necrotic glomerulus has a characteristic eosinophilic appearance and usually contains nuclear remnants. Crescent formation is usually associated with generalized proliferation of the mesangial cells and with either immune complex or anti-GBM antibody deposition in the glomerular capillary wall.

Certain forms of acute glomerulonephritis show glomerular exudation of blood cells, including neutrophils, eosinophils, basophils, and mononuclear cells. The thickened appearance of GBM can result from a true increase in the width of the membrane (as seen in membranous glomerulopathy; see Chapter 537.5), from massive deposition of immune complexes that have staining characteristics similar to the membrane (as seen in systemic lupus erythematosus; see Chapter 538.2), or from the interposition of mesangial cells and matrix into the subendothelial space between the endothelial cells and the GBM. The last can give the basement membrane a split appearance, as seen in type I membranoproliferative glomerulonephritis (see Chapter 537.6) and other diseases.

Sclerosis refers to the presence of scar tissue within the glomerulus. Occasionally, pathologists use this term to refer to an increase in mesangial matrix.

Tubulointerstitial fibrosis is present in all patients who have glomerular disease and who develop progressive renal injury. This fibrosis is initiated by injury to either the glomeruli, which, if severe, may secondarily involve the tubules, or direct injury to the tubules themselves. Tubular injury recruits mononuclear cell infiltrate, which releases a variety of soluble factors that have fibrosis-promoting effects. Matrix proteins of the renal interstitium begin to accumulate, leading to eventual destruction of renal tubules and peritubular capillaries.

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SECTION 2

Conditions Particularly Associated with Hematuria

OUTLINE

Chapter 536 Clinical Evaluation of the Child With Hematuria

Chapter 537 Isolated Glomerular Diseases Associated With Recurrent Gross Hematuria

Chapter 538 Multisystem Disease Associated With Hematuria

Chapter 539 Tubulointerstitial Disease Associated With Hematuria

Chapter 540 Vascular Diseases Associated with Hematuria

Chapter 541 Anatomic Abnormalities Associated With Hematuria

Chapter 542 Lower Urinary Tract Causes of Hematuria

CHAPTER 536

Clinical Evaluation of the Child With Hematuria

Francisco X. Flores

Hematuria, defined as the persistent presence of more than 5 red blood cells (RBCs)/high power field (HPF) in uncentrifuged urine, occurs in 4–6% of urine samples from school-age children. Quantitative studies demonstrate that normal children can excrete more than 500,000 RBCs per 12-hr period; this increases with fever and/or exercise. In the clinical setting, qualitative estimates are provided by a urinary dipstick that uses a very sensitive peroxidase chemical reaction between hemoglobin (or myoglobin) and a colorimetric chemical indicator impregnated on the dipstick. Chemstrip (Boehringer Mannheim), a common commercially available dipstick, is very sensitive and capable of detecting 3-5 RBCs/HPF of unspun urine. The presence of 10-50 RBCs/µL may suggest underlying pathology, but significant hematuria is generally considered as > 50 RBCs/HPF. False-negative results can occur in the presence of formalin (used as a urine preservative) or high urinary concentrations of ascorbic acid (i.e., in patients with vitamin C intake > 2,000 mg/day). False-positive results may be seen in a child with an alkaline urine (pH > 8), or more commonly following contamination with oxidizing agents such as hydrogen peroxide used to clean the perineum before obtaining a specimen. Microscopic analysis of 10-15 mL of freshly voided and centrifuged urine is essential in confirming the presence of RBCs suggested by > 10 RBCs/HPF, or a 1+ positive urinary dipstick reading.

Red urine **without** RBCs is seen in a number of conditions (Table 536.1). Clinically significant heme-positive urine without RBCs may be caused by the presence of either hemoglobin or myoglobin. **Hemoglobinuria** without hematuria can occur in the presence of acute or chronic hemolysis. **Myoglobinuria** without hematuria occurs in the presence of rhabdomyolysis resulting from skeletal muscle injury and is generally associated with a 5-fold increase in the plasma concentration of creatinine kinase. Clinically innocuous heme-negative urine can appear red, cola colored, or burgundy, owing to ingestion of various drugs, foods (blackberries, beets), or dyes used in food and candy, whereas dark brown (or black) urine can result from various urinary metabolites.

Table 536.1

Other Causes of Red Urine

HEME POSITIVE
Hemoglobin Myoglobin
HEME NEGATIVE
Drugs
Adriamycin Chloroquine Deferoxamine Hydroxycobalamin Ibuprofen Iron sorbitol Levodopa Metronidazole Nitrofurantoin Phenazopyridine (Pyridium) Phenolphthalein Phenothiazines Phenytoin Quinine Rifampin Salicylates Sulfasalazine
Dyes (Vegetable/Fruit)
Beets Blackberries Blueberries Food and candy coloring Paprika Rhubarb
Metabolites
Homogentisic acid Melanin Methemoglobin Porphyrin Tyrosinosis Urates

Evaluation of the child with hematuria begins with a careful history, physical examination, and microscopic urinalysis. This information is used to determine the level of hematuria (upper vs lower urinary tract) and to determine the urgency of the evaluation based on symptomatology. Special consideration needs to be given to the family history, identification of anatomic abnormalities and malformation syndromes, presence of gross hematuria, and manifestations of hypertension, edema, or heart failure.

Table 536.2 lists causes of hematuria. Upper urinary tract sources of hematuria originate within the nephron (glomerulus, tubular system, or interstitium). Lower urinary tract sources of hematuria originate from the pelvocaliceal system, ureter, bladder, or urethra. Hematuria from within the glomerulus is often associated with brown, cola- or tea-colored, or burgundy urine, proteinuria > 100 mg/dL via dipstick, urinary microscopic findings of RBC casts, and deformed urinary RBCs (particularly acanthocytes). Hematuria originating within the tubular system may be associated with the presence of leukocytes or renal tubular casts. Lower urinary tract sources of hematuria may be associated with gross hematuria that is bright red or pink, terminal hematuria (gross hematuria occurring at the end of the urine stream), blood clots, normal urinary RBC morphology, and minimal proteinuria on dipstick (<100 mg/dL).

Table 536.2

Causes of Hematuria in Children

UPPER URINARY TRACT DISEASE
Isolated Renal Disease
Immunoglobulin (Ig) A nephropathy (Berger disease) Alport syndrome (hereditary nephritis) Thin glomerular basement membrane nephropathy Postinfectious GN (poststreptococcal GN)* Membranous nephropathy Membranoproliferative GN* Rapidly progressive GN Focal segmental glomerulosclerosis Anti–glomerular basement membrane disease Hereditary angiopathy with nephropathy, aneurysms, muscle cramps (HANAC)
Multisystem Disease
Systemic lupus erythematosus nephritis* Henoch-Schönlein purpura nephritis Granulomatosis with polyangiitis (formerly Wegener granulomatosis) Polyarteritis nodosa Goodpasture syndrome Hemolytic-uremic syndrome Sickle cell glomerulopathy HIV nephropathy
Tubulointerstitial Disease
Pyelonephritis

Interstitial nephritis Papillary necrosis Acute tubular necrosis
Vascular Disorders
Arterial or venous thrombosis Malformations (aneurysms, hemangiomas) Nutcracker syndrome Hemoglobinopathy (sickle cell trait/disease) Crystalluria
Anatomic Disorders
Hydronephrosis Cystic-syndromic kidney disease Polycystic kidney disease Multicystic dysplasia Tumor (Wilms tumor, rhabdomyosarcoma, angiomyolipoma, medullary carcinoma) Trauma
LOWER URINARY TRACT DISEASE
Inflammation (infectious and noninfectious) Cystitis Urethritis Urolithiasis Trauma Coagulopathy Heavy exercise Bladder tumor Factitious syndrome, factitious syndrome by proxy [†]

[*] Denotes glomerulonephritides presenting with hypocomplementemia.

[†] Formerly Munchausen syndrome and Munchausen syndrome by proxy.

GN, glomerulonephritis.

Patients with hematuria can present with a number of symptoms suggesting specific disorders. Tea- or cola-colored urine, facial or body edema, hypertension, and oliguria are classic symptoms of **glomerulonephritis.** Diseases commonly manifesting as glomerulonephritis include postinfectious glomerulonephritis, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis, Henoch-Schönlein purpura (HSP) nephritis, systemic lupus erythematosus (SLE) nephritis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyarteritis nodosa, Goodpasture syndrome, and hemolytic-uremic syndrome. A history of recent upper respiratory, skin, or gastrointestinal infection suggests postinfectious glomerulonephritis, hemolytic-uremic syndrome, or HSP nephritis. Rash and joint complaints suggest HSP or SLE nephritis.

Hematuria associated with glomerulonephritis is typically painless, but can be associated with flank pain when acute or unusually severe. Frequency, dysuria, and unexplained fevers suggest a urinary tract infection, whereas renal colic suggests nephrolithiasis. A flank mass can suggest hydronephrosis, renal cystic diseases, renal vein thrombosis, or tumor. Hematuria associated with headache, mental status changes, visual changes (diplopia), epistaxis, or heart failure suggests associated severe hypertension. Patients with hematuria and a history of trauma require immediate evaluation (see Chapter 82). Child abuse must always be suspected in the child presenting with unexplained perineal bruising and hematuria.

A careful family history is critical in the initial assessment of the child with hematuria given the numerous genetic causes of renal disorders. Hereditary glomerular diseases include hereditary nephritis (isolated Alport syndrome or with leiomyomatosis or macrothrombocytopenia); thin glomerular basement membrane disease; SLE nephritis; hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC); and IgA nephropathy (Berger disease). Other hematuric renal disorders with a hereditary component include both autosomal recessive and autosomal dominant polycystic kidney diseases, atypical hemolytic-uremic syndrome, urolithiasis, and sickle cell disease/trait.

Physical examination may also suggest possible causes of hematuria. The presence of hypertension, edema, or signs of heart failure suggests acute glomerulonephritis. Several malformation syndromes are associated with renal disease, including VATER (*v* ertebral body anomalies, *a* nal atresia, *t* racheo*e* sophageal fistula, and *r* enal dysplasia) syndrome. Abdominal masses may be caused by bladder distention in posterior urethral valves, hydronephrosis in ureteropelvic junction obstruction, polycystic kidney disease, or Wilms tumor. Hematuria seen in patients with neurologic or cutaneous abnormalities may be the result of a number of syndromic renal disorders, including tuberous sclerosis, von Hippel-Lindau syndrome, and Zellweger (cerebrohepatorenal) syndrome. Anatomic abnormalities of the external genitalia may be associated with hematuria and/or renal disease.

Patients with gross hematuria present additional challenges because of the associated parental anxiety. The most common cause of gross hematuria is bacterial or viral urinary tract infection. **Urethrorrhagia,** which is urethral bleeding in the absence of urine, is associated with dysuria and blood spots on underwear after voiding. This condition, which often occurs in prepubertal boys at intervals several months apart, has a benign self-limited course. Less than 10% of patients have evidence of glomerulonephritis. Recurrent episodes of gross hematuria suggest IgA nephropathy, Alport syndrome, or thin glomerular basement membrane disease. Dysuria and abdominal or flank pain are symptoms of idiopathic hypercalciuria, or urolithiasis. Table 536.3 lists common causes of gross hematuria; Fig. 536.1 outlines a general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. Asymptomatic patients with isolated microscopic hematuria should not undergo extensive diagnostic evaluation, because such hematuria is often transient and benign.

Table 536.3

Common Causes of Gross Hematuria

Urinary tract infection
Meatal stenosis with ulcer
Perineal irritation
Trauma
Urolithiasis
Hypercalciuria
Obstruction
Coagulopathy
Tumor
Glomerular disease
Postinfectious glomerulonephritis
Henoch-Schönlein purpura nephritis
IgA nephropathy
Alport syndrome (hereditary nephritis)
Thin glomerular basement membrane disease
Systemic lupus erythematosus nephritis

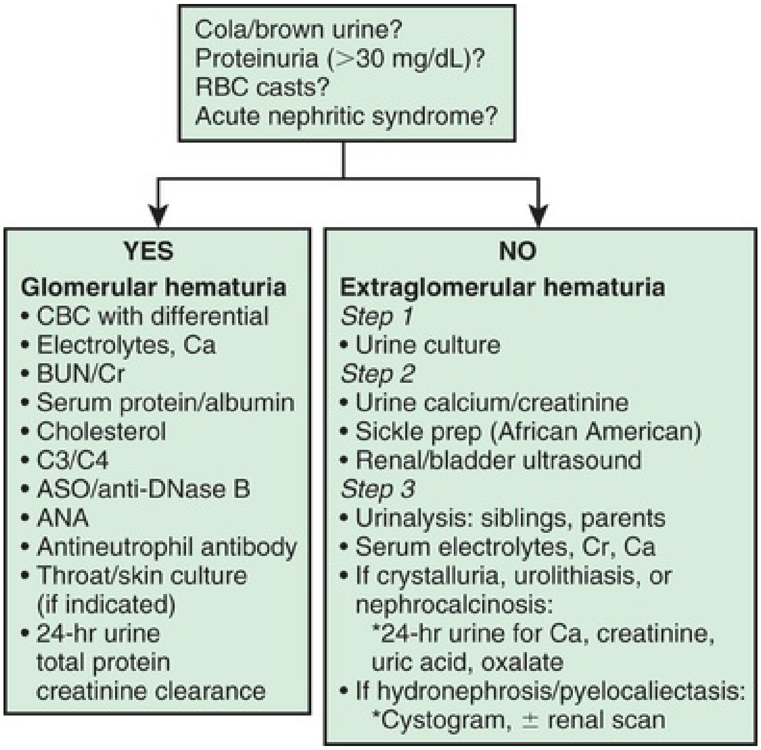
Cola/brown urine?
Proteinuria (>30 mg/dL)?
RBC casts?
Acute nephritic syndrome?
YES
Glomerular hematuria
• CBC with differential
• Electrolytes, Ca
• BUN/Cr
• Serum protein/albumin
• Cholesterol
• C3/C4
• ASO/anti-DNase B
• ANA
• Antineutrophil antibody
• Throat/skin culture (if indicated)
• 24-hr urine total protein creatinine clearance
NO
Extraglomerular hematuria
Step 1
• Urine culture
Step 2
• Urine calcium/creatinine
• Sickle prep (African American)
• Renal/bladder ultrasound
Step 3
• Urinalysis: siblings, parents
• Serum electrolytes, Cr, Ca
• If crystalluria, urolithiasis, or nephrocalcinosis:
*24-hr urine for Ca, creatinine, uric acid, oxalate
• If hydronephrosis/pyelocaliectasis:
*Cystogram, ± renal scan

FIG. 536.1 Diagnostic algorithm of the general approach to the laboratory and radiologic evaluation of the patient with glomerular or extraglomerular hematuria. ANA, antinuclear antibody; ASO, antistreptolysin O; BUN, blood urea nitrogen; C3/C4, complement; CBC, complete blood cell count; Cr, creatinine; RBC, red blood cell.

The child with completely asymptomatic isolated microscopic hematuria that persists on at least three urinalyses observed over a minimum of a 2-wk period poses a dilemma in regard to the degree of further diagnostic testing that should be performed. Significant disease of the urinary tract is uncommon with this clinical presentation. The initial evaluation of these children should include a urine culture followed by a spot urine for hypercalciuria with a calcium:creatinine ratio in culture-negative patients. In African-American patients, a sickle cell screen should be included. If these studies are normal, urinalysis of all first-degree relatives is indicated. Renal and bladder ultrasonography should be considered to rule out structural lesions such as tumor, cystic disease, hydronephrosis, or urolithiasis. Ultrasonography of the urinary tract is most informative in patients presenting with gross hematuria, abdominal pain, flank pain, or trauma. If these initial studies are normal, assessment of serum creatinine and electrolytes is recommended.

The finding of certain hematologic abnormalities can narrow the differential diagnosis. Anemia in this setting may be caused by hypervolemia with dilution associated with acute kidney injury; decreased RBC production in chronic kidney disease; hemolysis from hemolytic-uremic syndrome, a chronic hemolytic anemia, or SLE; blood loss from pulmonary hemorrhage, as seen in Goodpasture syndrome; or melena in patients with HSP or hemolytic-uremic syndrome. Inspection of the peripheral blood smear might reveal a microangiopathic process consistent with the hemolytic-uremic syndrome. The presence of autoantibodies in SLE can result in a positive Coombs test, the presence of antinuclear antibody, leukopenia, and multisystem disease. Thrombocytopenia can result from decreased platelet production (malignancies) or increased platelet consumption (SLE, idiopathic thrombocytopenic purpura, hemolytic-uremic syndrome, renal vein thrombosis, or congenital hepatic fibrosis with portal hypertension secondary to autosomal recessive polycystic kidney disease). Although urinary RBC morphology may be normal with lower tract bleeding and dysmorphic from glomerular bleeding, it is not sensitive enough to unequivocally delineate the site of hematuria. A bleeding diathesis is an unusual cause of hematuria, and coagulation studies are not routinely obtained unless a personal or family history suggests a bleeding tendency.

A voiding cystourethrogram is only required in patients with a urinary tract infection, renal scarring, hydroureter, or pyelocaliectasis. Cystoscopy is an unnecessary and costly procedure in most pediatric patients with hematuria, and carries the associated risks of anesthesia. This procedure should be reserved for evaluating the rare child with a bladder mass noted on ultrasound, urethral abnormalities caused by trauma, posterior urethral valves, or tumor. The finding of unilateral gross hematuria localized by cystoscopy is rare, but it can indicate a vascular malformation or another anatomic abnormality.

Children with persistent asymptomatic isolated hematuria and a completely normal evaluation should have their blood pressure and urine checked every 3 mo until the hematuria resolves. Referral to a pediatric nephrologist should be considered for patients with persistent asymptomatic hematuria greater than 1 yr in duration and is recommended for patients with nephritis (glomerulonephritis, tubulointerstitial nephritis), hypertension, renal insufficiency, urolithiasis or nephrocalcinosis, or a family history of renal disease such as polycystic kidney disease or hereditary nephritis. Renal biopsy is indicated for some children with persistent microscopic hematuria and for most children with recurrent gross hematuria associated with decreased renal function, proteinuria, or hypertension.

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CHAPTER 537

Isolated Glomerular Diseases Associated With Recurrent Gross Hematuria

Francisco X. Flores

Approximately 10% of children with gross hematuria have an acute or a chronic form of glomerulonephritis that may be associated with a systemic illness. The gross hematuria, which is usually characterized by brown or cola-colored urine, may be painless or associated with vague flank or abdominal pain. A presentation with gross hematuria is common within 1-2 days after the onset of an apparent viral upper respiratory tract infection in immunoglobulin (Ig) A nephropathy, and typically resolves within 5 days. This relatively short period contrasts with a latency period of 7-21 days occurring between the onset of a streptococcal pharyngitis or impetiginous skin infection and the development of postinfectious acute glomerulonephritis. Gross hematuria in these circumstances can last as long as 4-6 wk. Gross hematuria can also be seen in children with glomerular basement membrane (GBM) disorders such as hereditary nephritis (Alport syndrome [AS]) and thin GBM disease. These glomerular diseases can also manifest as microscopic hematuria and/or proteinuria without gross hematuria.

537.1

Immunoglobulin A Nephropathy (Berger Nephropathy)

Francisco X. Flores

IgA nephropathy is the most common chronic glomerular disease in children. It is characterized by a predominance of IgA within mesangial glomerular deposits in the absence of systemic disease. Its diagnosis requires a renal biopsy, which is performed when clinical features warrant confirmation of the diagnosis or characterization of the histologic severity, which might affect therapeutic decisions.

Pathology and Pathologic Diagnosis

Focal and segmental mesangial proliferation and an increased mesangial matrix are seen in the glomerulus (Fig. 537.1). Renal histology demonstrates mesangial proliferation that may be associated with epithelial cell crescent formation and sclerosis. IgA deposits in the mesangium are often accompanied by C3 complement (Fig. 537.2).

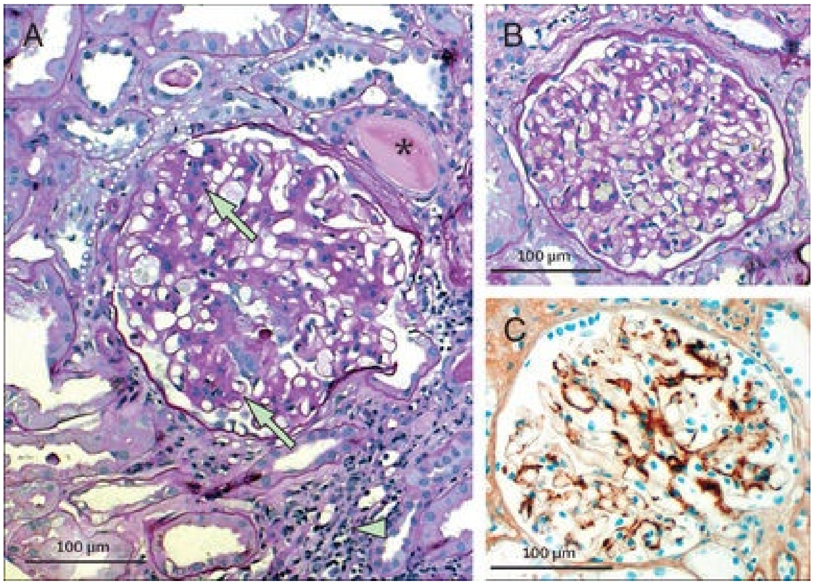

FIG. 537.1 IgA nephropathy. **A,** In IgA nephropathy, segmental areas *(arrows)* of mesangial hypercellularity and matrix expansion occur, characteristic of mesangioproliferative glomerulonephritis. Part of the glomerular tuft adheres to Bowman's capsule *(white dashed oval),*

constituting the starting point of a secondary focal segmental glomerulosclerosis lesion. Tubulointerstitial damage with leucocyte infiltrates, tubular atrophy and fibrosis *(arrowhead),* and tubular protein casts *(asterisk)* is also present. PAS stain. **B,** Other glomeruli in the same patient exhibit few pathologic abnormalities on light microscopy (PAS stain), but the characteristic mesangial granular IgA deposition **(C)** can be found in these glomeruli as well. (From Floege J, Amann K: Primary glomerulonephritides, Lancet 387:2036-2046, 2016, Fig. 2.)

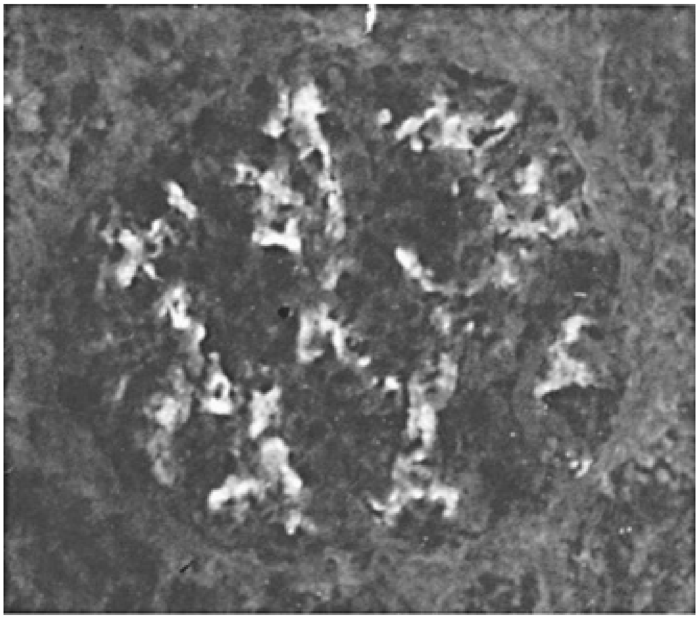

FIG. 537.2 Immunofluorescence microscopy of the biopsy specimen from a child with episodes of gross hematuria demonstrating mesangial deposition of IgA (×150).

IgA nephropathy is an immune complex disease initiated by excessive amounts of poorly galactosylated IgA_1 in the serum, causing the production of IgG and IgA autoantibodies. The abnormalities identified in the IgA system have also been observed in patients with Henoch-Schönlein purpura, and this finding lends support to the hypothesis that these two diseases are part of the same disease spectrum. Familial clustering of IgA nephropathy cases suggests the importance of genetic factors. Genome-wide linkage analysis suggests the linkage of IgA nephropathy to 6q22-23 in multiplex IgA nephropathy kindreds. Additional genomic studies demonstrate a high predisposition to IgA nephropathy in Southeast Asia, with the lowest prevalence in Africa.

Clinical and Laboratory Manifestations

IgA nephropathy is seen more often in male than in female patients. Although there are rare cases of rapidly progressive forms of the disease, the clinical presentation of childhood IgA nephropathy is often benign in comparison with that of adults. IgA nephropathy is an uncommon cause of end-stage renal failure during childhood. A majority of children with IgA nephropathy in the United States and Europe present with gross hematuria, whereas microscopic hematuria and/or proteinuria is a more common presentation in Japan. Other presentations include acute nephritic syndrome, nephrotic syndrome, or a combined nephritic-nephrotic picture. Gross hematuria often occurs within 1-2 days of onset of an upper respiratory or gastrointestinal infection, in contrast with the longer latency period observed in acute postinfectious glomerulonephritis, and may be associated with loin pain. Proteinuria is often < 1,000 mg/24 hr in patients with asymptomatic microscopic hematuria. Mild to moderate hypertension is most often seen in patients with nephritic or nephrotic syndrome, but is rarely severe enough to result in hypertensive emergencies. Normal serum levels of C3 in IgA nephropathy help to distinguish this disorder from postinfectious glomerulonephritis. Serum IgA levels have no diagnostic value because they are elevated in only 15% of pediatric patients.

Prognosis and Treatment

Although IgA nephropathy does not lead to significant kidney damage in most children, progressive disease develops in 20–30% of adult patients 15-20 yr after disease onset. Therefore, most children with IgA nephropathy do not display progressive renal dysfunction until adulthood, prompting the need for careful long-term follow-up. Poor prognostic indicators at presentation or follow-up include persistent hypertension, diminished renal function, and significant, increasing, or prolonged proteinuria. A more severe prognosis is correlated with histologic evidence of diffuse mesangial proliferation, extensive glomerular crescents, glomerulosclerosis, and diffuse tubulointerstitial changes, including inflammation and fibrosis.

The primary treatment of IgA nephropathy is appropriate blood pressure control and management of significant proteinuria. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are effective in reducing proteinuria and retarding the rate of disease progression when used individually or in combination. Fish oil, which contains antiinflammatory omega-3 polyunsaturated fatty acids, may decrease the rate of disease progression in adults. If a renin-angiotensin system (RAS) blockade proves ineffective and significant proteinuria persists, then addition of immunosuppressive therapy with corticosteroids is recommended. Corticosteroids reduce proteinuria and improve renal function in those patients with a glomerular filtration rate > 60 mL/min/m^2 . It remains unclear if the effects of glucocorticoids deter progression to end-stage renal failure to a degree to offset their significant side effects. To date, additional immunosuppression with cyclophosphamide or azathioprine has not appeared to be effective, but further randomized clinical trials are in progress. Tonsillectomy has been used as a treatment for IgA nephropathy in many countries, including Japan. Performing a tonsillectomy in the absence of significant tonsillitis in association with IgA nephropathy is currently not recommended until appropriate prospective, controlled trials have been performed and demonstrate efficacy. Targeted-release oral budesonide combined with RAS blockade has been shown in a pilot study to reduce proteinuria. Patients with IgA nephropathy may undergo successful kidney transplantation. Although recurrent disease is frequent, allograft loss caused by IgA nephropathy occurs in only 15–30% of patients.

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537.2

Alport Syndrome

Francisco X. Flores

Alport syndrome (AS), or hereditary nephritis, is a genetically heterogeneous disease caused by mutations in the genes coding for type IV collagen, a major component of basement membranes. These genetic alterations are associated with marked variability in the clinical presentation, natural history, and histologic abnormalities.

Genetics

Approximately 85% of patients have X-linked inheritance caused by a mutation in the *COL4A5* gene encoding the α5 chain of type IV collagen. Patients with a subtype of X-linked AS and diffuse **leiomyomatosis** demonstrate a contiguous mutation within the *COL4A5* and *COL4A6* genes that encodes the α5 and α6 chains, respectively, of type IV collagen. Autosomal recessive forms of AS in approximately 15% of patients are caused by mutations in the *COL4A3* and *COL4A4* genes on chromosome 2 encoding the α3 and α4 chains, respectively, of type IV collagen. An autosomal dominant form of AS linked to the *COL4A3*-*COL4A4* gene locus occurs in 5% of cases.

Fechtner syndrome (AS with macrothrombocytopenia) is an autosomal dominant disorder due to mutations in *MYH9* . Hereditary angiopathy with nephropathy-aneurysms-muscle cramps **(HANAC)** may initially resemble AS. HANAC is due to mutations in the *COL4A1* gene.

Pathology

Kidney biopsy specimens during the first decade of life will show only a few changes on light microscopy. Later, the glomeruli may develop mesangial proliferation and capillary wall thickening, leading to progressive glomerular sclerosis. Tubular atrophy, interstitial inflammation and fibrosis, and lipid-containing tubular or interstitial cells, called *foam cells*, develop as the disease progresses. Immunopathologic studies are usually nondiagnostic.

In most patients, electron microscopy reveals diffuse thickening, thinning, splitting, and layering of the glomerular and tubular basement membranes (Fig. 537.3). To confound the diagnosis, the ultrastructural analysis of the GBM in all genetic forms of AS may be completely normal, display nonspecific alterations, or demonstrate only uniform thinning.

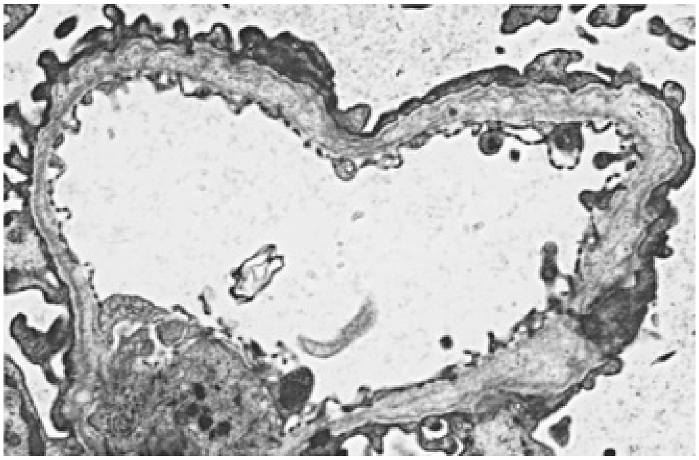

FIG. 537.3 Electron micrograph of a biopsy specimen from a child with AS depicting thickening, thinning, splitting, and layering of the GBM (×1,650). (From Yum M, Bergstein JM: Basement membrane nephropathy, Hum Pathol 14:996–1003, 1983.)

Clinical Manifestations

All patients with AS have asymptomatic microscopic hematuria, which may be intermittent in females and younger males. Single or recurrent episodes of gross hematuria commonly occurring 1-2 days after an upper respiratory infection are seen in approximately 50% of patients. Proteinuria is often seen in males but may be absent, mild, or intermittent in females. Progressive proteinuria, often exceeding 1 g/24 hr, is common by the second decade of life and can be severe enough to cause nephrotic syndrome.

Bilateral **sensorineural hearing loss,** which is never congenital, develops in 90% of hemizygous males with X-linked AS, 10% of heterozygous females with X-linked AS, and 67% of patients with autosomal recessive AS. This deficit begins in the high-frequency range but progresses to involve the hearing associated with normal speech, prompting the need for hearing aids. This progression of hearing loss seems to run parallel to the loss of renal function. Ocular abnormalities, which occur in 30–40% of patients with X-linked AS, include anterior lenticonus (extrusion of the central portion of the lens into the anterior chamber), macular flecks, and corneal erosions. Leiomyomatosis of the esophagus, tracheobronchial tree, and female genitals has been reported but is rare.

Diagnosis

A combination of a thorough family history, a screening urinalysis of first-degree relatives, an audiogram, and an ophthalmologic examination are critical in making the diagnosis of AS. The presence of anterior lenticonus is pathognomonic. AS is highly likely in the patient who has hematuria and at least two of the following characteristic clinical features: macular flecks, recurrent corneal erosions, GBM thickening and thinning, or sensorineural deafness. The absence of epidermal basement membrane staining for the α5 chain of type IV collagen in male hemizygotes and discontinuous epidermal basement membrane staining in female heterozygotes on skin biopsy is pathognomonic for X-linked AS and can preclude a diagnostic renal biopsy. Genetic testing is clinically available for X-linked AS and *COL4A5* mutations. Prenatal diagnosis is available for families with members who have X-linked AS and who carry an identified mutation.

Prognosis and Treatment

The risk of progressive renal dysfunction leading to end-stage renal disease (ESRD) is highest among hemizygotes and autosomal recessive homozygotes. ESRD occurs before age 30 yr in approximately 75% of hemizygotes with X-linked AS. The risk of ESRD in X-linked heterozygotes is 12% by age 40 yr and 30% by age 60 yr. Risk factors for progression are gross hematuria during childhood, nephrotic syndrome, and prominent GBM thickening. An intrafamilial variation in phenotypic expression results in significant differences in the age of ESRD among family members. No specific therapy is available to treat AS, although angiotensin-converting enzyme inhibitors (and possibly angiotensin-2 receptor inhibitors) can slow the rate of progression. Careful management of renal failure complications, such as hypertension, anemia, and electrolyte imbalance, is critical. Patients with ESRD are treated with dialysis and kidney transplantation (see Chapter 551). Approximately 5% of kidney transplantation recipients develop anti-GBM nephritis, which occurs primarily in males with X-linked AS who develop ESRD before age 30 yr.

Pharmacologic treatment of proteinuria with angiotensin-converting enzyme inhibition or angiotensin-2 receptor blockade has proven effective in other glomerular diseases and has also shown promise in AS. Screening of heterozygote carriers for significant renal disease in later adulthood and possible treatment of significant proteinuria is also recommended.

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537.3

Thin Basement Membrane Disease

Francisco X. Flores

Thin basement membrane disease (TBMD) is defined by the presence of persistent microscopic hematuria and isolated thinning of the GBM (and, occasionally, tubular basement membranes) on electron microscopy. Microscopic hematuria is often initially observed during childhood and may be intermittent. Episodic gross hematuria can also be present, particularly after a respiratory illness. Isolated hematuria in multiple family members without renal dysfunction is referred to as **benign familial hematuria.** Although most of these patients will not undergo renal biopsy, it is often presumed that the underlying pathology is TBMD. TBMD may be sporadic or transmitted as an autosomal dominant trait. Heterozygous mutations in the *COL4A3* and *COL4A4* genes, which encode the α3 and α4 chains of type IV collagen present in the GBM, result in TBMD. Rare cases of TBMD progress, and such patients develop significant proteinuria, hypertension, or renal insufficiency. Homozygous mutations in these same genes result in autosomal recessive AS. Therefore, in these rare cases, the absence of a positive family history for renal insufficiency or deafness would not necessarily predict a benign outcome. Consequently, monitoring patients with benign familial hematuria for progressive proteinuria, hypertension, or renal insufficiency is important throughout childhood and young adulthood.

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537.4

Acute Poststreptococcal Glomerulonephritis

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Group A β-hemolytic streptococcal infections are common in children and can lead to the postinfectious complication of acute glomerulonephritis (GN). Acute poststreptococcal glomerulonephritis (APSGN) is a classic example of the **acute nephritic syndrome** characterized by the sudden onset of gross hematuria, edema, hypertension, and renal dysfunction. It is one of the most common glomerular causes of gross hematuria in children and is a major cause of morbidity in group A β-hemolytic streptococcal infections.

Etiology and Epidemiology

APSGN follows infection of the throat or skin by certain *nephritogenic* strains of group A β-hemolytic streptococci. Epidemics and clusters of household (camps, military) cases occur throughout the world, and 97% of cases occur in less-developed countries. The overall incidence has decreased in industrialized nations, presumably as a result of improved hygienic conditions and the near eradication of streptococcal pyoderma. Poststreptococcal GN commonly follows streptococcal pharyngitis during cold-weather months and streptococcal skin infections or pyoderma during warm-weather months. Although epidemics of nephritis have been described in association with throat (serotypes M1, M4, M25, and some strains of M12) and skin (serotype M49) infections, this disease is most commonly sporadic.

Pathology

Glomeruli appear enlarged and relatively bloodless and show a diffuse mesangial cell proliferation, with an increase in mesangial matrix (Fig. 537.4). Polymorphonuclear leukocyte infiltration is common in glomeruli during the early stage of the disease. Crescents and interstitial inflammation may be seen in severe cases, but these changes are not specific for poststreptococcal GN. Immunofluorescence microscopy reveals a pattern of “lumpy-bumpy” deposits of immunoglobulin and complement on the glomerular basement membrane and in the mesangium. On electron microscopy, electron-dense deposits, or “humps,” are observed on the epithelial side of the glomerular basement membrane (Fig. 537.5).

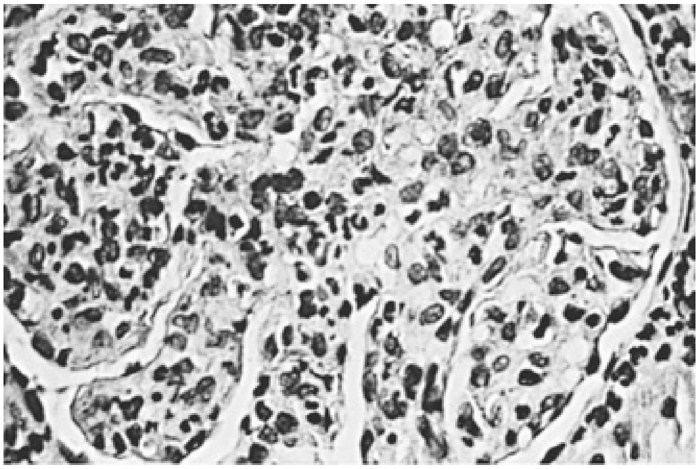

FIG. 537.4 Glomerulus from a patient with poststreptococcal glomerulonephritis appears enlarged and relatively bloodless and shows mesangial proliferation and exudation of neutrophils (×400).

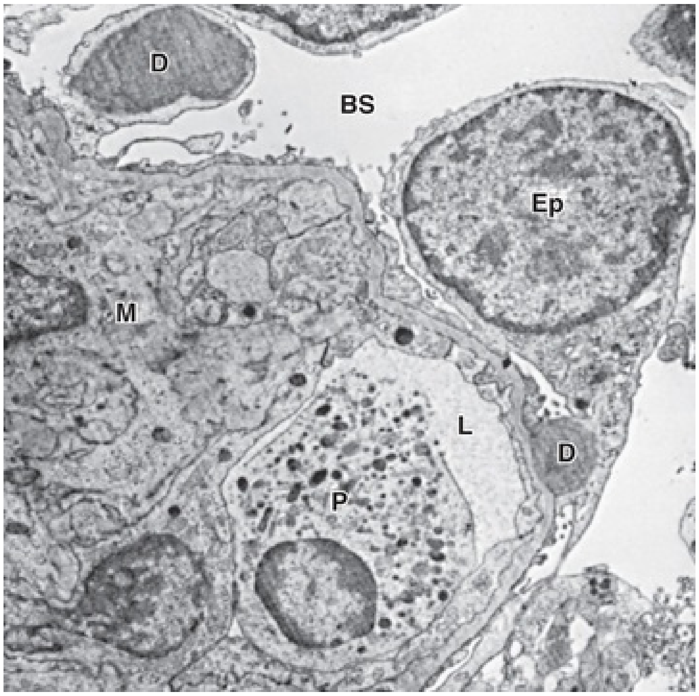

FIG. 537.5 Electron micrograph in poststreptococcal glomerulonephritis demonstrating electron-dense deposits (D) on the epithelial cell (Ep) side of the glomerular basement membrane. A polymorphonuclear leukocyte (P) is present within the lumen (L) of the capillary. BS, Bowman space; M, mesangium.

Pathogenesis

Morphologic studies and a depression in the serum complement (C3) level provide strong evidence that ASPGN is mediated by immune complexes. Circulating immune complex formation with streptococcal antigens and subsequent glomerular deposition is thought less likely to be a pathogenic mechanism. Molecular mimicry whereby circulating antibodies elicited by streptococcal antigens react with normal glomerular antigens, in situ immune complex formation of antistreptococcal antibodies with glomerular deposited antigen, and complement activation by directly deposited streptococcal antigens continue to be considered as probable mechanisms of immunologic injury.

Group A streptococci possess M proteins, and nephritogenic strains are related to the M protein serotype. The search for the precise nephritogenic antigen(s) that cause disease suggests that streptococcal pyogenic exotoxin (SPE) B and nephritis-associated streptococcal plasmin receptor are promising candidates. Both have been identified in glomeruli of affected patients, and in one study, circulating antibodies to SPE B were found in all patients. Cross-reactivity of SPE B and other M proteins with various components of the glomerular basement membrane also give evidence for molecular mimicry.

Clinical Manifestations

Poststreptococcal GN is most common in children ages 5-12 yr and uncommon before the age of 3 yr. The typical patient develops an acute nephritic syndrome 1-2 wk after an antecedent streptococcal pharyngitis or 3-6 wk after a streptococcal pyoderma. The history of a specific infection may be absent, because symptoms may have been mild or have resolved without patients receiving specific treatment or seeking the care of a medical provider.

The severity of kidney involvement varies from asymptomatic microscopic hematuria with normal renal function to gross hematuria with acute renal failure. Depending on the severity of renal involvement, patients can develop various degrees of edema, hypertension, and oliguria. Patients are at risk for developing encephalopathy and/or heart failure secondary to hypertension or hypervolemia. Hypertensive encephalopathy must be considered in patients with blurred vision, severe headaches, altered mental status, or new seizures. The effects of acute hypertension not only depend on the severity of hypertension but also the absolute change in comparison with the patient's baseline blood pressure and the rate at which it has risen. Respiratory distress, orthopnea, and cough may be symptoms of pulmonary edema and heart failure. Peripheral edema typically results from salt and water retention and is common; nephrotic syndrome develops in a minority (<5%) of childhood cases. Atypical presentations of APSGN include those with subclinical disease and those with severe symptoms but an absence of initial urinary abnormalities; in individuals who present with a purpuric rash, it is difficult to distinguish APSGN from Henoch-Schönlein purpura without a renal biopsy.

The acute phase generally resolves within 6-8 wk. Although urinary protein excretion and hypertension usually normalize by 4-6 wk after onset, persistent microscopic hematuria can persist for 1-2 yr after the initial presentation.

Diagnosis

Urinalysis demonstrates red blood cells, often in association with red blood cell casts, proteinuria, and polymorphonuclear leukocytes. A mild normochromic anemia may be present from hemodilution and low-grade hemolysis. The serum C3 level is significantly reduced in > 90% of patients in the acute phase, and returns to normal 6-8 wk after the onset. Although serum CH_{50} is commonly depressed, *C4 is most often normal in APSGN*, or only mildly depressed.

Confirmation of the diagnosis requires clear evidence of a prior streptococcal infection. A positive throat culture report might support the diagnosis or might represent the carrier state. A rising antibody titer to streptococcal antigen(s) confirms a recent streptococcal infection. The antistreptolysin O titer is commonly elevated after a pharyngeal infection but rarely increases after streptococcal skin infections. The best single antibody titer to document cutaneous streptococcal infection is the antideoxyribonuclease B level. If available, a positive streptozyme screen (which measures multiple antibodies to different streptococcal antigens) is a valuable diagnostic tool. Serologic evidence for streptococcal infections is more sensitive than the history of recent infections and far more sensitive than positive bacterial cultures obtained at the time of onset of acute nephritis.

Magnetic resonance imaging of the brain is indicated in patients with severe neurologic symptoms and can demonstrate **posterior reversible encephalopathy syndrome** in the parietooccipital areas on T2-weighted images. Chest x-ray is indicated in those with signs of heart failure or respiratory distress, or physical exam findings of a heart gallop, decreased breath sounds, rales, or hypoxemia.

The clinical diagnosis of poststreptococcal GN is quite likely in a child presenting with acute nephritic syndrome, evidence of recent streptococcal infection, and a low C3 level. However, it is important to consider other diagnoses such as systemic lupus erythematosus, endocarditis, membranoproliferative GN, and an acute exacerbation of chronic GN. Renal biopsy should be considered only in the presence of acute renal failure, nephrotic syndrome, absence of evidence of streptococcal infection, or normal complement levels. In addition, renal biopsy is considered when hematuria and proteinuria, diminished renal function, and/or a low C3 level persist more than 2 mo after onset. Persistent hypocomplementemia can indicate a chronic form of postinfectious GN or another disease such as membranoproliferative GN.

The differential diagnosis of poststreptococcal GN includes many of the causes of hematuria listed in Tables 536.2 and 537.1 , and algorithms to help with the diagnosis are presented in Figs. 537.6 and 537.7 . Acute postinfectious

GN can also follow other infections with coagulase-positive and coagulase-negative staphylococci, *Streptococcus pneumoniae*, and Gram-negative bacteria. The clinical course, histopathology, and laboratory features are similar to those described for APSGN. For some, the terms APSGN and acute postinfectious GN are used synonymously. Acute GN can occur after certain fungal, rickettsial, protozoan, parasitic, or viral diseases. Among the latter, influenza and parvovirus infections are particularly notable.

Table 537.1

Summary of Primary Renal Diseases That Manifest as Acute Glomerulonephritis

DISEASES	**POSTSTREPTOCOCCAL GLOMERULONEPHRITIS**	**IgA NEPHROPATHY**	**GOODPASTURE SYNDROME**	**IDIOPATHIC RA PROGRESSIVE GLOMERULON**
CLINICAL MANIFESTATIONS				
Age and sex	All ages, mean 7 yr, 2 : 1 male	10-35 yr, 2 : 1 male	15-30 yr, 6 : 1 male	Adults, 2 : 1 male
Acute nephritic syndrome	90%	50%	90%	90%
Asymptomatic hematuria	Occasionally	50%	Rare	Rare
Nephrotic syndrome	5–10%	Rare	Rare	10–20%
Hypertension	70%	30–50%	Rare	25%
Acute renal failure	50% (transient)	Very rare	50%	60%
Other	Latent period of 1-3 wk	Follows viral syndromes	Pulmonary hemorrhage; iron deficiency anemia	None
Laboratory findings	↑ ASO titers (70%) Positive streptozyme (95%) ↓C3-C9; normal C1, C4	↑ Serum IgA (50%) IgA in dermal capillaries	Positive anti-GBM antibody	Positive ANCA in
Immunogenetics	HLA-B12, D “EN” (9)*	HLA-Bw 35, DR4 (4)*	HLA-DR2 (16)*	None established
RENAL PATHOLOGY				
Light microscopy	Diffuse proliferation	Focal proliferation	Focal → diffuse proliferation with crescents	Crescentic GN
Immunofluorescence	Granular IgG, C3	Diffuse mesangial IgA	Linear IgG, C3	No immune deposi
Electron microscopy	Subepithelial humps	Mesangial deposits	No deposits	No deposits
Prognosis	95% resolve spontaneously 5% RPGN or slowly progressive	Slow progression in 25–50%	75% stabilize or improve if treated early	75% stabilize or i treated early
Treatment	Supportive	Uncertain (options include steroids,	Plasma exchange, steroids,	Steroid pulse thera

		fish oil, and ACE inhibitors)	cyclophosphamide	

* Relative risk.

ACE, angiotensin-converting enzyme; ANCA, antineutrophil cytoplasmic antibody; ASO, anti-streptolysin O; GBM, glomerular basement membrane; GN, glomerulonephritis; HLA, human leukocyte antigen; Ig, immunoglobulin; RPGN, idiopathic rapidly progressive glomerulonephritis.

(From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, 2/e, Philadelphia, 2004, Elsevier.)

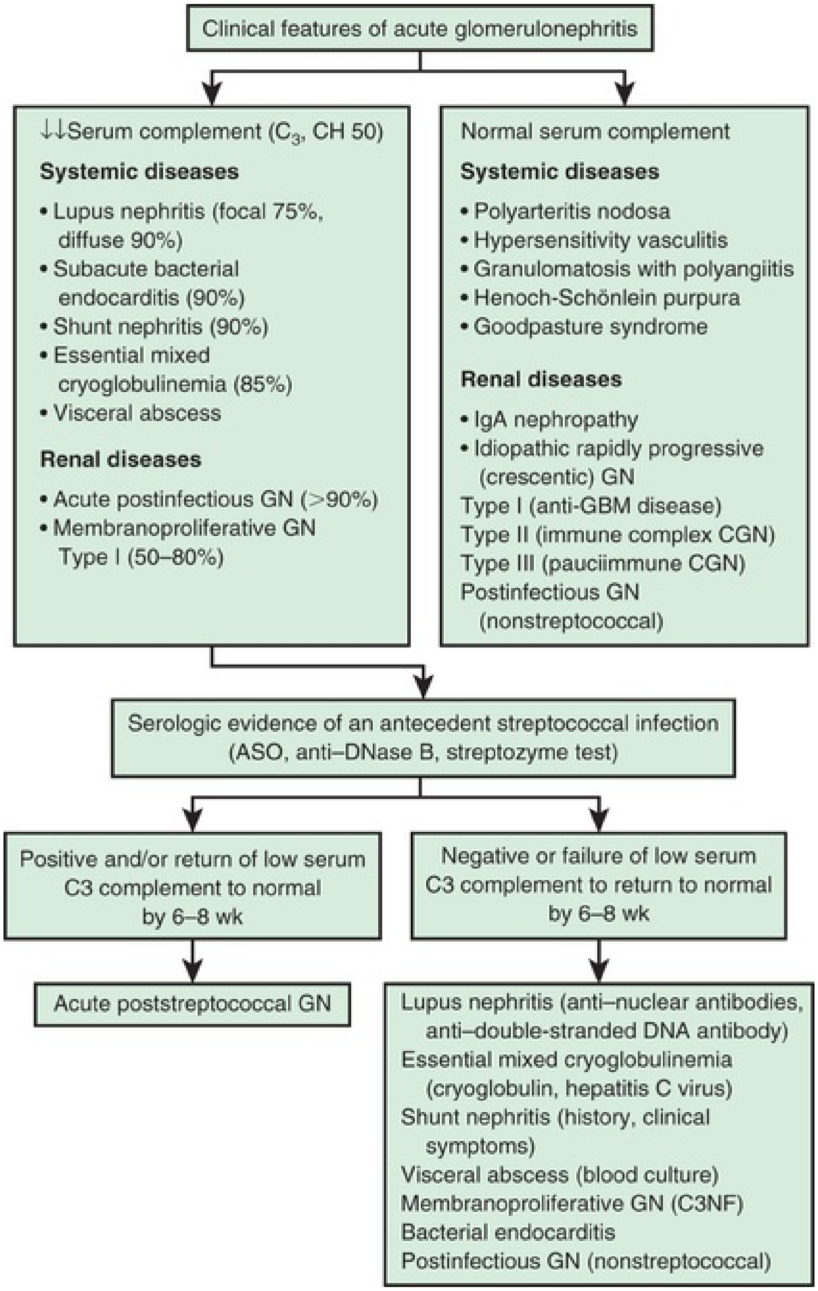
Clinical features of acute glomerulonephritis
↓↓Serum complement (C_3, CH 50)
Systemic diseases
• Lupus nephritis (focal 75%, diffuse 90%)
• Subacute bacterial endocarditis (90%)
• Shunt nephritis (90%)
• Essential mixed cryoglobulinemia (85%)
• Visceral abscess
Renal diseases
• Acute postinfectious GN (>90%)
• Membranoproliferative GN Type I (50–80%)
Normal serum complement
Systemic diseases
• Polyarteritis nodosa
• Hypersensitivity vasculitis
• Granulomatosis with polyangiitis
• Henoch-Schönlein purpura
• Goodpasture syndrome
Renal diseases
• IgA nephropathy
• Idiopathic rapidly progressive (crescentic) GN
Type I (anti-GBM disease)
Type II (immune complex CGN)
Type III (pauciimmune CGN)
Postinfectious GN (nonstreptococcal)
Serologic evidence of an antecedent streptococcal infection (ASO, anti–DNase B, streptozyme test)
Positive and/or return of low serum C3 complement to normal by 6–8 wk
Negative or failure of low serum C3 complement to return to normal by 6–8 wk
Acute poststreptococcal GN
Lupus nephritis (anti–nuclear antibodies, anti–double-stranded DNA antibody)
Essential mixed cryoglobulinemia (cryoglobulin, hepatitis C virus)
Shunt nephritis (history, clinical symptoms)
Visceral abscess (blood culture)
Membranoproliferative GN (C3NF)
Bacterial endocarditis
Postinfectious GN (nonstreptococcal)

FIG. 537.6 Differential diagnostic algorithm of acute glomerulonephritis (GN). ASO, anti–streptolysin O; GBM, glomerular basement membrane; NF, nuclear factor. (Adapted from Sulyok E: Acute proliferative glomerulonephritis. In Avner ED, Harmon WE, Niaudet P (eds): Pediatric Nephrology, 5/e. Philadelphia, 2004, Lippincott Williams & Wilkins, Fig. 30-4.)

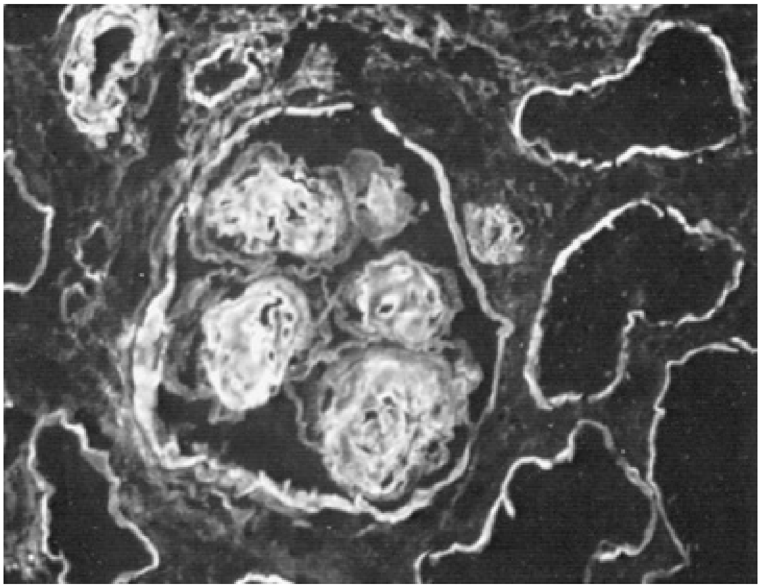

FIG. 537.7 Algorithm for diagnostic classification of glomerulonephritis (GN) that is known or suspected of being mediated by antibodies and complement. Note that the integration of light microscopy, immunofluorescence (IF) microscopy, electron microscopy, laboratory data, and clinical manifestations is required to precisely diagnose GN. ANCA, Anti–neutrophil cytoplasmic autoantibody; DDD, dense deposit disease; EGPA, eosinophilic granulomatosis with polyangiitis; GBM, glomerular basement membrane; GPA, granulomatosis with polyangiitis; IgA, immunoglobulin A; MPA, microscopic polyangiitis; MPGN, membranoproliferative glomerulonephritis. (From Pendergraft WF III, Nachman PH, Jennette JC, Falk RJ: Primary glomerular disease. In Skorecki K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's The Kidney, 10/e, Philadelphia, 2016, Elsevier, 2016, Fig. 33-35.)

Complications

Acute complications result from hypertension and acute renal dysfunction. Hypertension is seen in 60% of patients and is associated with hypertensive encephalopathy in 10% of cases. Although the neurologic sequelae are often reversible with appropriate management, severe prolonged hypertension can lead to intracranial bleeding. Other potential complications include heart failure, hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, seizures, and uremia. Acute renal failure can require treatment with dialysis.

Prevention

Early systemic antibiotic therapy for streptococcal throat and skin infections does not eliminate the risk of GN. Family members of patients with acute GN, especially young children, should be considered at risk and be cultured for group A β-hemolytic streptococci and treated if positive. Family pets, particularly dogs, have also been reported as carriers.

Treatment

Management is directed at treating the acute effects of renal dysfunction and hypertension (see Chapter 550.1). Although a 10-day course of systemic antibiotic therapy with penicillin is recommended to limit the spread of the nephritogenic organisms, antibiotic therapy does not affect the natural history of APSGN. This is unlike the GN seen in the context of ongoing or chronic infections, as noted in Chapter 538.1 . Sodium and fluid restriction, diuretics, and pharmacotherapy with calcium channel antagonists, vasodilators, or angiotensin-converting enzyme inhibitors are standard therapies used to treat hypertension.

Prognosis

Complete recovery occurs in > 95% of children with APSGN. Recurrences are extremely rare. Mortality in the acute stage can be avoided by appropriate management of acute renal failure, cardiac failure, and hypertension. Infrequently, the acute phase is severe and leads to glomerulosclerosis and chronic renal disease in < 2% of affected children.

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537.5

Membranous Nephropathy

Francisco X. Flores

Membranous nephropathy (MN), amongst the most common causes of nephrotic syndrome in adults, is a rare cause of nephrotic syndrome in children. MN is classified as the primary, idiopathic form, where there is isolated renal disease, or secondary MN, where nephropathy is associated with other identifiable systemic diseases or medications. In children, secondary MN is far more common than primary, idiopathic MN. The most common etiologies of secondary MN are systemic lupus erythematosus or chronic infections. Among the latter, chronic hepatitis B infection and congenital syphilis are the best characterized and recognized causes of MN. Other chronic infections have also been associated with MN, including malaria, which is likely the most common cause of nephrotic syndrome worldwide. Certain medications, such as penicillamine and gold, or chronic factor replacement in patients with hemophilia can also cause MN. Rare causes associated with MN include tumors, such as neuroblastoma, or other idiopathic systemic diseases. Identification of secondary causes of MN is critical, because removal of the offending agent or treatment of the causative disease often leads to resolution of the associated nephropathy and improves patient outcome.

Pathology

Glomeruli have diffuse thickening of the glomerular basement membrane (GBM), without significant cell proliferative changes. Immunofluorescence and electron microscopy typically demonstrate granular deposits of immunoglobulin G and C3 located on the epithelial side of the GBM. The GBM thickening presumably results from the production of membrane-like material in response to deposition of immune complexes (Fig. 537.8).

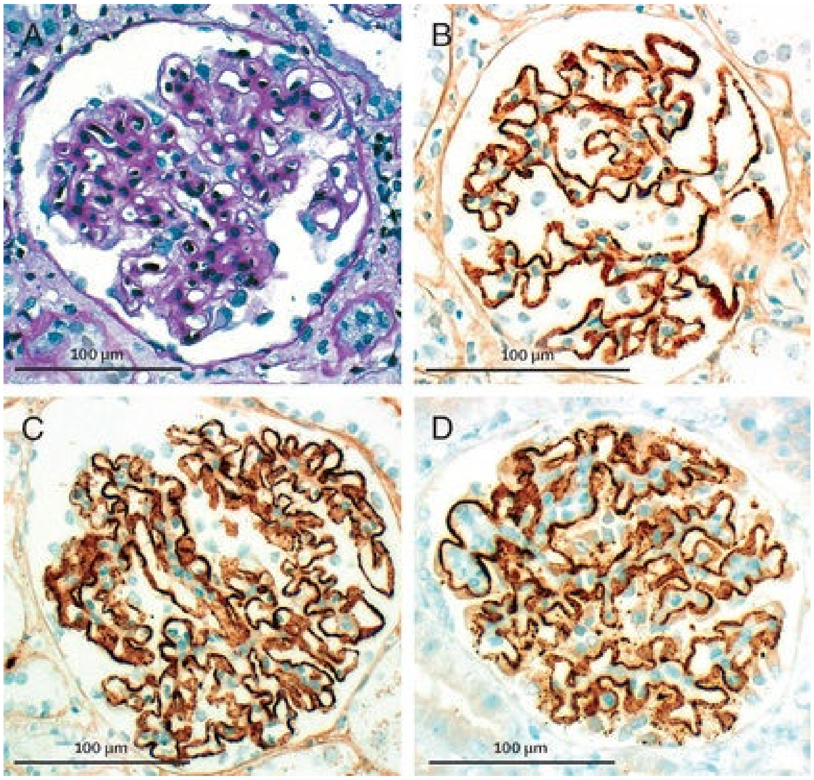

FIG. 537.8 Membranous glomerulonephritis. The PAS stain **(A)** shows slightly thickened glomerular basement membranes and prominent podocytes. On immunohistology, granular deposits of **(B)** IgG and **(C)** C3c can be found along the glomerular basement membrane, and pronounced de novo expression of **(D)** PLA2R is present on the podocytes. PLA2R, phospholipase A2 receptor. (From Floege J, Amann K: Primary glomerulonephritides, *Lancet* 387:2036-2046, 2016, Fig. 3.)

Pathogenesis

MN is believed to be caused by in situ immune complex formation. Therefore, antigens from the infectious agents or medications associated with secondary MN directly contribute to the pathogenesis of the renal disease. The causative antigen in idiopathic MN is not established, but the podocyte phospholipase A_2 receptor, present on normal podocytes, may be a target antigen in idiopathic MN. Antigen from this receptor is found in immune deposits extracted from glomeruli in patients with idiopathic MN. The majority of idiopathic MN patients have circulating antibody against this podocyte membrane antigen, as well as against several podocyte cytoplasmic antigens. Childhood MN may be associated with anticationic bovine serum albumin antibodies. In addition, neutral endopeptidase antigen may be the antigen in neonatal onset MN.

Clinical Manifestations

In children, MN is most common in the second decade of life, but it can occur at any age, including infancy. The disease usually manifests as nephrotic syndrome and accounts for 2–6% of all cases of childhood nephrotic syndrome. Most patients also have microscopic hematuria and only rarely present with gross hematuria. Approximately 20–30% of children have hypertension at presentation. A subset of patients with MN present with a major venous thrombosis, commonly renal vein thrombosis. This complication of nephrotic syndrome (see Chapter 545) is particularly common in patients with MN. Serum C3 and CH_{50} levels are normal, except in secondary forms such as in systemic lupus erythematosus, where levels may be depressed (see Fig. 537.6).

Diagnosis

MN might be suspected on clinical grounds, particularly in the setting of known risk factors for secondary forms of the disease. The diagnosis can only be established by renal biopsy. No serologic test is specific for MN, but finding an active carrier state for hepatitis B or congenital syphilis would make the diagnosis probable in the appropriate clinical setting. Common indications for renal biopsy leading to the diagnosis of MN include presentation with nephrotic syndrome in a child > 10 yr or unexplained persistent hematuria with significant proteinuria.

Prognosis and Treatment

The clinical course of idiopathic membranous glomerulopathy is variable. Children presenting with asymptomatic, low-grade proteinuria can enter remission spontaneously. Retrospective reports of children 1-15 yr after diagnosis, treated with a variety of regimens, indicate that 20% progress to chronic renal failure, 40% continue with active disease, and 40% achieve complete remission. Poor prognostic factors include male gender, high levels of proteinuria, reduced kidney function, and findings of glomerulosclerosis and tubular damage in the renal biopsy. Although no controlled trials have been performed in children, immunosuppressive therapy with an extended course of prednisone can be effective in promoting complete resolution of symptoms. The addition of chlorambucil or cyclophosphamide appears to provide further benefit to those not responding to steroids alone. Rituximab has shown significant promise in adults and has been proposed by some as the first-line treatment but has yet to be studied in a randomized controlled trial in any age-group. For those unresponsive to immunosuppression, or with mild clinical features, proteinuria can be reduced with angiotensin-converting enzyme inhibitors and probably with angiotensin-II–receptor blockers.

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537.6

Membranoproliferative Glomerulonephritis

Francisco X. Flores

Membranoproliferative glomerulonephritis (MPGN), also known as mesangiocapillary glomerulonephritis, most commonly occurs in older children or young adults. MPGN can be classified into primary (idiopathic) and secondary forms of glomerular disease. Secondary forms of MPGN are most commonly associated with subacute and chronic infection, including hepatitis B and C, syphilis, subacute bacterial endocarditis, and infected shunts, especially ventriculoatrial shunts (shunt nephritis) (Table 537.2). MPGN can also be one of the glomerular lesions seen in lupus nephritis (see Chapter 538.2).

Table 537.2

Secondary Causes of Membranoproliferative Glomerulonephritis (MPGN)

ASSOCIATED WITH INFECTION
Hepatitis B and C
Visceral abscesses
Infective endocarditis
Shunt nephritis
Quartan malaria
Schistosoma nephropathy
Mycoplasma infection
ASSOCIATED WITH RHEUMATOLOGIC DISEASE
Systemic lupus erythematosus
Scleroderma
Sjögren syndrome
Sarcoidosis
Mixed essential cryoglobulinemia with or without hepatitis C infection
Anti–smooth muscle syndrome
ASSOCIATED WITH MALIGNANCY
Carcinoma

  - Lymphoma
  - Leukemia

ASSOCIATED WITH AN INHERITED DISORDER

  - α_1 -Antitrypsin deficiency
  - Complement deficiency (C2 or C3), with or without partial lipodystrophy

From Pendergraft WF III, Nachman PH, Jennette JC, Falk RJ: Primary glomerular disease. In Skorecki K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's The Kidney, 10/e, Philadelphia, 2016, Elsevier, Table 32-12, p. 1049.

Pathology

Primary MPGN is defined by the histologic pattern of glomeruli as seen by light, immunofluorescence, and electron microscopy. Two subtypes have been defined on histologic criteria and are associated with different clinical phenotypes. **Type I MPGN** is most common. Glomeruli have an accentuated lobular pattern from diffuse mesangial expansion, endocapillary proliferation, and an increase in mesangial cells and matrix. The glomerular capillary walls are thickened, often with splitting from interposition of the mesangium. Crescents, if present, indicate a poor prognosis. Immunofluorescence microscopy reveals C3 and lesser amounts of immunoglobulin in the mesangium and along the peripheral capillary walls in a lobular pattern. Electron microscopy confirms numerous deposits in the mesangial and subendothelial regions.

Far less common is **type II MPGN,** also called dense deposit disease, which has similar light microscopic findings as type I MPGN. Differentiation from type I disease is by immunofluorescence and electron microscopy. In type II disease, C3 immunofluorescence typically is prominent, without concomitant immunoglobulin. By electron microscopy, the lamina densa in the glomerular basement membrane undergoes a very dense transformation, without evident immune complex–type deposits.

C3 glomerulonephritis (C3GN) is a related but separate diagnostic category. By light and electron microscopy C3GN usually has features indistinguishable from classic MPGN. Immunofluorescence studies distinguish between the two, with C3GN having only C3 deposition and MPGN having both C3 and immunoglobulin fluorescence.

Pathogenesis

Although the histology of **type I MPGN** produced by primary and secondary forms is indistinguishable, it appears that **type I** disease occurs when circulating immune complexes become trapped in the glomerular subendothelial space, which then causes injury, resulting in the characteristic proliferative response and mesangial expansion. Further evidence confirming this pathway to glomerular injury is the finding of complement activation through the classic pathway in as many as 50% of affected patients.

Type II MPGN appears *not* to be mediated by immune complexes. The pathogenesis of the disease is not known, but the characteristic finding of severely depressed serum complement levels suggests that deranged complement regulation might play a major role in the disease. A typical finding is markedly depressed serum C3 complement levels, with normal levels of other complement components. In many patients with type II MPGN, *C3 nephritic factor* (anti–C3 convertase antibody) is present. This factor activates the alternative complement pathway. In unusual cases, patients with type II MPGN demonstrate an associated systemic disease called **partial lipodystrophy,** where there is diffuse loss of adipose tissue and decreased complement in the presence of C3 nephritic factor. The correlation between the presence of C3 nephritic factor, complement levels, and disease presence or severity is not strong, indicating that the complement abnormalities alone are not sufficient to cause the disease.

Type II MPGN **(dense deposit disease)** is considered part of the broader spectrum of C3GN. The latter, as defined above pathologically, appears to be caused by primary dysregulation of the alternative or terminal cascade complement pathways.

Clinical Manifestations

MPGN is most common in the second decade of life, equally affects males and females, and is more common in Caucasian individuals. Systemic features may provide clues to which type of MPGN may be present, but the two histologic types of idiopathic MPGN are indistinguishable in terms of their renal manifestations. Patients present in equal proportions with nephrotic syndrome, acute nephritic syndrome (hematuria, hypertension, and some level of renal dysfunction), or persistent asymptomatic microscopic hematuria and proteinuria. Serum C3 complement levels are low in the majority of cases (see Fig. 537.6).

Differential Diagnosis

The differential diagnosis includes all forms of acute and chronic glomerulonephritis, including idiopathic and secondary forms, along with postinfectious glomerulonephritis. Postinfectious glomerulonephritis, far more common than MPGN, usually does not have nephrotic features but typically has hematuria, hypertension, renal dysfunction, and transiently low C3 complement, all features that may be seen with MPGN or C3GN. In contrast to MPGN and C3GN, where C3 levels usually remain persistently low, C3 returns to normal within 8-10 wk after the onset of postinfectious glomerulonephritis (see Chapter 537.4). The diagnosis of MPGN is made by renal biopsy. Indications for biopsy include nephrotic syndrome in an older child, significant proteinuria with microscopic hematuria, and hypocomplementemia lasting > 2 mo in a child with acute nephritis. If C3 but no immunoglobulin deposition is found in glomeruli with MPGN, genetic testing and functional assays to define defects of complement cascade regulation should be pursued.

Prognosis and Treatment

It is important to determine whether MPGN is idiopathic or secondary to a systemic disease, particularly lupus or chronic infection, because treatment of the causative disease can result in resolution of the MPGN. Untreated, idiopathic MPGN, regardless of type, has a poor prognosis. By 10 yr following onset, 50% of patients with MPGN have progressed to end-stage renal disease. By 20 yr following onset, up to 90% have lost renal function. Those with nephrotic syndrome and hypertension at the time of presentation progress to renal failure more rapidly. No definitive therapy exists, but several reports, including a randomized controlled trial, indicate that extended courses of alternate-day prednisone (for years) provide benefit. Some patients treated with steroids enter a complete clinical remission of their disease, but many have ongoing disease activity. Nevertheless, an extended course of prednisone is associated with significant preservation of renal function when compared with patients receiving no such treatment.

The prognosis of C3GN, separate from dense deposit disease (considered a part of C3GN by some) and other forms of classically defined MPGN is as yet hard to define, because reports of the outcome of such patients previously had been grouped in studies of all forms of MPGN (types I and II, and even a poorly characterized type III form not considered above). The apparent pathophysiology of C3GN promises that treatments targeting the interruption of complement activation pathways, such as complement factor H replacement or shutting down the terminal complement cascade by blocking C5 activation with eculizumab (anti–C5 antibody), could be beneficial in preventing the progression of renal disease.

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537.7

Rapidly Progressive (Crescentic) Glomerulonephritis

Francisco X. Flores

Rapidly progressive describes the clinical course of several forms of glomerulonephritis that have the unifying feature of a histopathologic finding of crescents in the majority of glomeruli (Fig. 537.9). The terms *rapidly progressive glomerulonephritis* (RPGN) and *crescentic glomerulonephritis* (CGN) are synonymous. The natural history of most forms of CGN is the rapid loss of the renal function.

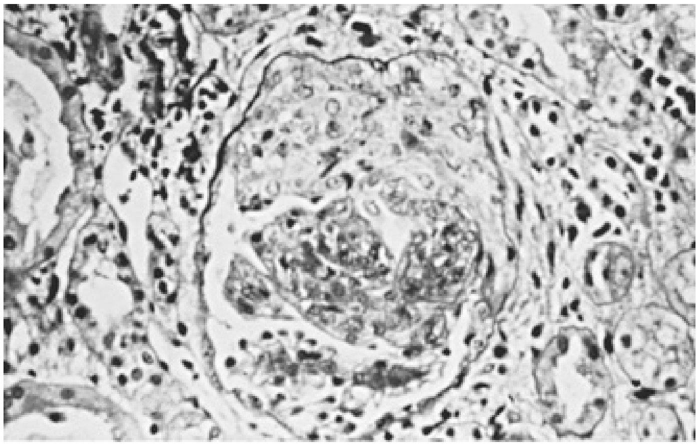

FIG. 537.9 Light micrograph of a biopsy specimen from a child with Henoch-Schönlein purpura glomerulonephritis demonstrating a crescent overlying the glomerulus (×180).

Classification

CGN can be a severe manifestation of essentially every defined primary and secondary glomerulonephritis (GN), but particular forms of GN are more likely to present as, or evolve into, RPGN (Table 537.3). If no underlying cause is identified by systemic features, serologic testing, or histologic examination, the disease is classified as idiopathic CGN. The incidence of specific etiologies of CGN in children varies widely; certain common themes are shared in all such reports. Patients with systemic vasculitis appear to be particularly prone to develop CGN. Patients with Henoch-Schönlein purpura (HSP), antineutrophil cytoplasmic antibody (ANCA-mediated GN (microscopic polyangiitis and granulomatosis with polyangiitis), and systemic lupus erythematosus account for the majority of patients with CGN. Postinfectious GN or endocarditis rarely progresses to CGN, but because it is the most common form of GN in childhood it accounts for a significant percentage of patients with CGN in most reports. Membranoproliferative GN and idiopathic disease make up most of the remaining cases of CGN. Immunoglobulin (Ig) A nephropathy, a common GN, only rarely is rapidly progressive. Goodpasture disease often has rapidly progressive GN as a component of the syndrome, but its rarity in childhood results in only a small percentage of children with CGN.

Table 537.3

Classification of Rapidly Progressive (Crescentic) Glomerulonephritis

PRIMARY
- Type I: Anti–glomerular basement membrane antibody disease, Goodpasture syndrome (with pulmonary disease)
- Type II: Immune complex mediated
- Type III: Pauci-immune (usually antineutrophil cytoplasmic antibody–positive)

SECONDARY
- Membranoproliferative glomerulonephritis
- Immunoglobulin A nephropathy, Henoch-Schönlein purpura
- Postinfectious glomerulonephritis
- Systemic lupus erythematosus
- Polyarteritis nodosa, hypersensitivity angiitis

From Appel GB, Radhakrishnan J: Glomerular disorders and nephrotic syndromes. In Goldman L, Schafer AI (eds): Goldman's Cecil medicine, 24/e, Philadelphia, 2012, Saunders, Table 122-3, p. 758.

Pathology and Pathogenesis

The hallmark of CGN is the histopathologic finding of epithelial crescents involving 50% or more glomeruli (see Fig. 537.9). Crescent formation, through proliferation of parietal epithelial cells in Bowman's space, may be the final pathway of any severe inflammatory glomerular injury. Podocytes and renal progenitor cells are involved in the pathogenesis of CGN. Fibrous crescents, in which proliferative cellular crescents are replaced by collagen, are a late finding. The immunofluorescence findings, as well as the pattern of any deposits by electron microscopy, can delineate the underlying glomerulopathy in CGN secondary to lupus, HSP nephritis, membranoproliferative glomerulonephritis, postinfectious GN, IgA nephropathy, or Goodpasture disease. Rare or absent findings by immunofluorescence and electron microscopy typify pauciimmune GN (granulomatosis with polyangiitis and microscopic polyangiitis) and idiopathic crescentic GN.

Clinical Manifestations

Most children present with acute nephritis (hematuria, various degrees of renal dysfunction, and hypertension) and usually have concomitant proteinuria, often with nephrotic syndrome. Occasional patients present late in the course of disease with oliguric renal failure. Extrarenal manifestations, such as pulmonary involvement, joint symptoms, or skin lesions, can help lead to the diagnosis of the underlying systemic disease causing the CGN.

Diagnosis and Differential Diagnosis

The diagnosis of CGN is made by obtaining a kidney biopsy. Delineation of the underlying etiology is reached by a combination of additional biopsy findings (described earlier), extrarenal symptoms and signs, and serologic testing, including the evaluation of antinuclear and anti-DS DNA antibodies, serum complement levels, anti-GBM antibodies, and ANCA titers. If the patient has no extrarenal manifestations and a negative serologic evaluation, and if the biopsy has no immune or electron microscopy deposits, the diagnosis is idiopathic, rapidly progressive CGN.

Prognosis and Treatment

The natural course of CGN is far more severe in the setting of other etiologies, including the idiopathic category, and progression to end-stage renal disease within weeks to months from the onset is common. Having a majority of fibrous crescents on a renal biopsy portends a poor prognosis, because the disease usually has progressed to irreversible damage. Although there are few controlled data, the consensus of most nephrologists is that the combination of high-dose corticosteroids and cyclophosphamide may be effective in preventing progressive renal failure in patients with systemic lupus erythematosus, HSP nephritis, granulomatosis with polyangiitis, and IgA nephropathy if given early in the course when acute cellular crescents predominate. Although such therapy can also be effective in the other diseases causing RPGN, renal outcomes in those settings are less favorable. Progression to end-stage renal disease often occurs despite aggressive immunosuppressive therapy. In combination with immunosuppression, plasmapheresis has been reported to benefit patients with Goodpasture disease. Plasmapheresis may also benefit patients with ANCA-associated CGN, in particular those with the most severe renal dysfunction and pulmonary hemorrhage at presentation. The possible benefits of plasmapheresis in other forms of RPGN are unclear.

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CHAPTER 538

Multisystem Disease Associated With Hematuria

Prasad Devarajan

Gross or microscopic hematuria may be associated with several multisystem disorders, including chronic systemic infections, systemic lupus erythematosus, Henoch-Schönlein purpura nephritis, Goodpasture disease, hemolytic-uremic syndrome, nephrotoxicity, and renal cortical necrosis. In most of these conditions, the presenting complaints pertain primarily to the underlying systemic illness, and hematuria often heralds or portends renal involvement (see Chapters 538.1 to 538.8).

538.1

Chronic Infections

Prasad Devarajan

Glomerulonephritis (GN) with hematuria is a recognized complication of various chronic infections. Classic examples that are uncommonly encountered today include bacterial endocarditis caused by viridans group streptococci and other organisms, and ventriculoatrial shunts infected with *Staphylococcus epidermidis*. Other infections, observed less commonly in children than in adults, include those due to HIV, hepatitis B virus, or hepatitis C virus; syphilis; and renal candidiasis. Parasitic infections associated with glomerular disease include malaria, schistosomiasis, leishmaniasis, filariasis, hydatid disease, trypanosomiasis, and toxoplasmosis. In each condition, the infecting organism has a low virulence and the host is chronically infected with a microbial antigen. In the presence of high levels of circulating antigen, the host's antibody response leads to the formation of **immune complexes** that are deposited in the kidneys and initiate glomerular inflammation. Foreign antigens can also stimulate an autoimmune response through the production of antibodies that cross-react with such antigens incorrectly recognized as glomerular structural components.

The renal histopathology in GN due to chronic infections can resemble poststreptococcal GN, membranous GN, or membranoproliferative GN. The clinical manifestations are generally those of an acute nephritic syndrome (active urinary sediment with hematuria, proteinuria, and granular and/or red blood cell casts, edema, hypertension) or nephrotic syndrome (proteinuria, edema, hypoalbuminemia). *The serum C3 and* CH_{50} *complement levels are often decreased due to activation of the classic complement pathway.*

In **HIV-associated nephropathy,** direct viral infection of nephrons occurs because renal cells express a variety of lymphocyte chemokine receptors that are essential for and facilitate viral invasion. The renal expression of HIV infection is quite variable and includes an immune complex injury and a direct cytopathic effect. The classic histopathologic lesion of HIV-associated nephropathy is *focal segmental glomerulosclerosis.* In the era of antiretroviral therapy, the decline in mortality from HIV disease has led to the increased recognition of renal disorders as an important long-term complication in children who survive perinatal HIV infection.

Hepatitis B virus (HBV) infection is a global public health problem. It is estimated that there are more than 350 million HBV carriers in the world.

Prompt eradication of any infection before severe glomerular injury occurs usually results in resolution of the GN associated with chronic infections. Progression to end-stage renal failure has been described but is uncommon. Spontaneous resolution of hepatitis B infection is common in children (30–50%) and results in remission of the glomerulopathy. Widespread use of hepatitis B vaccines has decreased the incidence of hepatitis B virus–related renal diseases. Also, with the new availability of direct-acting antivirals for hepatitis C virus, successful remission and even regression of glomerular lesions can be achieved if treatment is initiated at an early stage. Similarly, in patients with HIV-associated nephropathy, several clinical studies have demonstrated the overall improvement in kidney function with early initiation of antiretroviral therapy.

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538.2

Glomerulonephritis Associated With Systemic Lupus Erythematosus

Prasad Devarajan

Keywords

anti-nuclear antibody
glomerular deposits
Lupus nephritis
Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by fever, weight loss, dermatitis, hematologic abnormalities, arthritis, and involvement of the heart, lungs, central nervous system, and kidneys (see Chapter 183). Although SLE is less frequent in children, renal involvement (lupus nephritis) is more common and is more severe than that seen in adults. Lupus nephritis is the most important cause of morbidity and mortality in SLE.

Pathogenesis and Pathology

The hallmark of SLE is the abnormal production of pathogenic autoantibodies to self-antigens such as DNA (anti–double stranded DNA antibody [anti-dsDNA]) and nuclear proteins (antinuclear antibodies), driven by immune dysregulation and loss of self-tolerance. The antigen–antibody complexes accumulate in small vessels of many organs, where they incite a local inflammatory response by activating complement pathways and by binding to Fc receptors. Lupus nephritis is a result of the deposition of circulating immune complexes, as well as the direct binding of autoantibodies to glomerular components with resultant complement stimulation.

Kidney biopsy and evaluation of renal histopathology remain the gold standard for establishing the diagnosis of SLE nephritis and determining specific therapeutic regimens. The World Health Organization (WHO) classification of lupus nephritis has been employed in clinical trials since the 1980s, and is based on a combination of features, including light microscopy, immunofluorescence, and electron microscopy. In patients with **WHO class I nephritis** (minimal mesangial lupus nephritis)**,** no histologic abnormalities are detected on light microscopy but mesangial immune deposits are present on immunofluorescence or electron microscopy. In **WHO class II nephritis** (mesangial proliferative nephritis), light microscopy shows both mesangial hypercellularity and an increased matrix, along with mesangial deposits containing immunoglobulin and complement.

WHO class III nephritis and **WHO class IV nephritis** are interrelated lesions characterized by both mesangial and endocapillary lesions. Class III nephritis is defined by < 50% glomeruli with involvement and class IV has ≥ 50% glomerular involvement. Immune deposits are present in both the mesangium and subendothelial areas. A subclassification scheme helps grade the severity of the proliferative lesion based on whether the glomerular lesions are segmental (<50% glomerular tuft involved) or global (≥50% glomerular tuft involved). The WHO classification scheme also delineates whether there is a predominance of chronic disease versus active disease. Chronic injury results in glomerular sclerosis and is felt to be the consequence of significant proliferative disease seen in classes III and IV. Other signs of active disease include capillary walls that are thickened secondary to subendothelial deposits (creating the characteristic wire-loop lesion), necrosis, and crescent formation. WHO class IV nephritis is associated with poorer outcomes but can be successfully treated with aggressive immunosuppressive therapy.

WHO class V nephritis (membranous lupus nephritis) is less commonly seen as an isolated lesion and resembles idiopathic membranous nephropathy with subepithelial immune deposits. This lesion is often seen in combination with class III or IV proliferative nephritis, and if the membranous lesion is present in > 50% glomeruli, both classes are noted in the designation. This classification scheme also identifies cases with combinations of mixed classes III, IV, and V lesions, directing appropriate treatment for such patients.

A newer classification scheme proposed in 2004 by both the International Society of Nephrology and the Renal Pathology Society differs mainly in its subclassification of class IV into diffuse global and diffuse segmental lesions (Table 538.1). Although the newer classification is widely preferred, it should be noted that most available results of clinical trials are based on the WHO classification.

Table 538.1

Classification of Lupus Nephritis

Classification of Lupus Nephritis

CLASS	CLINICAL FEATURES
I. Minimal mesangial LN	No renal findings
II. Mesangial proliferative LN	Mild clinical renal disease; minimally active urinary sediment; mild to moderate proteinuria (never nephrotic) but may have active serology
III. Focal proliferative LN < 50% glomeruli involved A. Active A/C. Active and chronic C. Chronic	More active sediment changes; often active serology; increased proteinuria (>25% nephrotic); hypertension may be present; some evolve into class IV pattern; active lesions require treatment; chronic do not
IV. Diffuse proliferative LN (>50% glomeruli involved); all may be with segmental or global involvement (S or G) A. Active A/C. Active and chronic C. Chronic	Most severe renal involvement with active sediment, hypertension, heavy proteinuria (frequent nephrotic syndrome), often reduced glomerular filtration rate; serology very active. Active lesions require treatment
V. Membranous LN glomerulonephritis	Significant proteinuria (often nephrotic) with less active lupus serology
VI. Advanced sclerosing LN	More than 90% glomerulosclerosis; no treatment prevents renal failure

LN, lupus nephritis.

From Appel GB, Radhakrishnan J: Glomerular disorders and nephrotic syndromes. In Goldman L, Schafer AI (eds): Goldman's Cecil medicine, 24/e, St. Louis, 2012, Saunders, Table 123-7.

Transformation of the histologic lesions of lupus nephritis from one class to another is common. This is more likely to occur among inadequately treated patients and usually results in progression to a more severe histologic lesion.

Immunofluorescence microscopy is an essential component of the pathologic evaluation. Lupus nephritis is characterized by the granular deposition of all immunoglobulin isotypes (IgG, IgM, and IgA), as well as complements (C3, C4, and C1q) in the glomerular mesangium and capillary walls. This pattern of extensive glomerular immune deposition is referred to as full-house immune staining and is diagnostic of lupus nephritis.

Clinical Manifestations

Most children with SLE are adolescent females (female-to-male ratio of 5 : 1), and present with extrarenal manifestations. The relative risk of SLE is 3- to 7-fold higher in Asian, African-American, and Hispanic females compared with Caucasian females. Lupus nephritis in African-American and Hispanic populations also typically displays an increased severity and worse prognosis. Lupus nephritis affects 80% of pediatric patients with SLE, and although it commonly presents within the first year of diagnosis, may occur at any time during the course of the disease. The clinical findings in patients having milder forms of lupus nephritis (all class I and II, some class III) include hematuria, normal renal function, and proteinuria < 1 g/24 hr. Some patients with class III and all patients with class IV nephritis have hematuria and proteinuria, active urinary sediment with cellular casts, hypertension, reduced renal function, nephrotic syndrome, or acute kidney injury. The urinalysis may be normal on rare occasions in patients with proliferative lupus nephritis. Patients with class V nephritis commonly present with nephrotic syndrome.

Diagnosis

The diagnosis of SLE is confirmed by the detection of circulating antinuclear antibodies (ANA) and by demonstrating antibodies that react with native double-stranded DNA (anti-dsDNA). In most patients with active disease, C3 and C4 levels are depressed. In view of the lack of a clear correlation between the clinical manifestations and the severity of the renal involvement, renal biopsy should be performed in all patients with SLE who display even minor urinary abnormalities or other clinical evidence for renal disease. Histopathologic findings are used to determine the classification, severity, prognosis, and selection of specific immunosuppressive therapies.

Treatment

Children with SLE should be treated by experienced pediatric specialists in centers where medical and psychological support can be provided for patients and their families. At the present time, there are no randomized controlled trials to indicate the optimal treatment of lupus nephritis in children. Current therapies are largely based on the histology, clinical severity, and lessons learned from clinical trials of adults with lupus nephritis. Immunosuppression remains the cornerstone of therapy. The goal of immunosuppressive therapy in lupus nephritis is to produce both a clinical remission, defined as normalization of renal function and proteinuria, and a serologic remission, defined as normalization of anti-DNA antibody, C3, and C4 levels. Therapy is initiated in all patients with prednisone at a dose of 1-2 mg/kg/day in divided doses, followed by a slow steroid taper over 4-6 mo beginning 4-6 wk after achieving a serologic remission.

For patients with more severe forms of nephritis (WHO classes III and IV), more aggressive immunosuppressive regimens are required because corticosteroid therapy alone is insufficient to induce a remission. In general, such regimens are separated into two phases, namely, an induction phase and a maintenance phase. The most commonly employed induction therapy has been 6 consecutive monthly intravenous infusions of cyclophosphamide at a dose of 500-1,000 mg/m^2 . Pulse intravenous methylprednisolone (1,000 mg/m^2) is also used in addition to oral corticosteroids. Maintenance therapy previously consisted of additional cyclophosphamide (Cytoxan) infusions every 3 mo for 18 mo, which reduced the risk of progressive renal dysfunction. Serious side effects of cyclophosphamide have included infections, hair loss, hemorrhagic cystitis, and gonadal failure.

As an alternative induction therapy, in adult and pediatric clinical trials, mycophenolate mofetil was as efficacious as, or even superior to, cyclophosphamide, and is increasingly considered for use in children at a dosage of 600 mg/m^2 per dose twice daily. Maintenance therapy using mycophenolate mofetil or azathioprine is also as efficacious as intravenous cyclophosphamide and results in less-serious side effects. Mycophenolate mofetil is particularly more efficacious than cyclophosphamide in African-Americans. Major side effects of mycophenolate mofetil have included diarrhea, leucopenia, and teratogenicity. Azathioprine, at a single daily dose of 1.5-2.0 mg/kg, may be used as a steroid-sparing agent in patients with WHO class I or II lupus nephritis.

Rituximab, a chimeric monoclonal antibody specific for human CD20, is an alternative that has been shown to induce a remission in adults and children with proliferative lupus nephritis refractory to steroids and other immunosuppressants. Rituximab is used in cases where resistance to conventional treatment is demonstrated. Plasmapheresis is ineffective in lupus nephritis unless there is accompanying thrombotic thrombocytopenic purpura or antineutrophilic cytoplasmic antibody–associated disease. New therapies include belimumab, a fully humanized monoclonal antibody against a type II transmembrane protein that functions in the normal survival and differentiation of B cells; it has been approved by the FDA for use in SLE. Its role in lupus nephritis, either in combination with current therapies or to replace them, requires further study.

The optimal treatment for class V lupus nephritis remains unclear. On the one hand, the low risk of progression to end-stage renal disease when compared with proliferative forms of lupus nephritis has encouraged a less aggressive approach. On the other hand, patients with uncontrolled nephrotic syndrome due to class V lupus nephritis are at a high risk of morbidity, and may require more aggressive immunosuppression.

Hydrochloroquine is prescribed for most patients with SLE for extrarenal manifestations, but is thought to have a beneficial effect in maintaining the remission in lupus nephritis. It is a rational choice given its low side effect profile. Use of antihypertensive drugs to aggressively treat hypertension, as well as the specific use of drugs that block the renin–angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers) to reduce proteinuria, are also important adjuvant therapies that appear to decrease the long-term progression of renal disease.

Prognosis

Overall, renal survival (defined as chronic kidney disease without the need for end-stage renal disease therapy) is seen in 80% of patients 10 yr after the diagnosis of SLE nephritis. Patients with diffuse proliferative WHO class IV lupus nephritis, poor renal function at presentation, or persistent nephrotic-range proteinuria exhibit the highest risk for progression to end-stage renal disease. Concerns regarding the side effects of chronic immunosuppressive therapy and the risk of recurrent disease are lifelong. Close monitoring for the relapse of disease is critical to ensure maximally successful renal outcomes. Special care must be taken to minimize the risks of infection, osteoporosis, obesity, poor growth, hypertension, and diabetes mellitus associated with chronic corticosteroid therapy. Patients require counseling regarding the risk of malignancy or infertility, which may be increased in those receiving a cumulative dose of > 20 g of cyclophosphamide or other immunosuppressant therapies.

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538.3

Henoch-Schönlein Purpura Nephritis

Prasad Devarajan

Keywords

IgA vasculitis
polymeric immunoglobulin A
crescentic glomerulonephritis

Henoch-Schönlein purpura (HSP) is an idiopathic systemic immune complex–mediated vasculitis associated with IgA deposition within small-vessel walls. The current terminology for HSP is IgA vasculitis. It is the most common small-vessel vasculitis in children, with a peak incidence in early childhood (4-6 yr of age). Ninety percent of cases occur in children, with about half the cases preceded by an upper respiratory infection. It is characterized by a purpuric rash and commonly accompanied by arthritis and abdominal pain (see Chapter 192.1

). Approximately 50% of patients with HSP develop renal manifestations, which vary from asymptomatic microscopic hematuria to severe, progressive glomerulonephritis. HSP nephritis shares a similar pathogenesis and nearly identical renal histology with IgA nephropathy. Although the two are considered as distinct entities, many consider HSP nephritis and IgA nephropathy as part of the same clinical spectrum, and IgA nephropathy as one of the sequelae of HSP nephritis.

Pathogenesis and Pathology

The pathogenesis of HSP nephritis appears to be mediated by the deposition of polymeric immunoglobulin A (IgA) in glomeruli. This is analogous to the same type of IgA deposits seen in systemic small vessels in HSP, primarily those of the skin and intestine. Studies have identified defective glycosylation of the hinge region of IgA1 in patients with both HSP nephritis and IgA nephropathy. Recognition of the exposed hinge region of IgA1 by naturally occurring autoantibodies leads to formation of immune complexes that are deposited in the glomerular mesangium. Any mucosal infection or food antigen may trigger the increased production of pathogenic IgA1. IgA immune complexes are deposited throughout the body and activate pathways leading to necrotizing vasculitis. A skin biopsy characteristically shows leukocytoclastic vasculitis with IgA, C3, and fibrin deposition. The glomerular findings can be indistinguishable from those of IgA nephropathy. Pathognomonic IgA deposits are detected by immunofluorescence as the dominant immunoglobulin in the glomerular mesangium. Histologically, a broad spectrum of glomerular lesions that can range from mild mesangial and endocapillary proliferation to necrotic and crescentic changes from extracapillary proliferation can be seen.

Clinical and Laboratory Manifestations

The classic tetrad of HSP nephritis includes a palpable purpura, arthritis or arthralgia, abdominal pain, and evidence for renal disease. These may develop over a period of days to weeks and may vary in their order of presentation. Notably, not all of the tetrad are present in all patients. The nephritis associated with HSP usually follows the onset of the rash, often presenting weeks or even months after the initial nonrenal manifestations have resolved. Nephritis can be manifest at the initial presentation but only rarely before onset of the rash. Some degree of renal involvement occurs in approximately 50% of HSP cases, more commonly in older children (age > 8 yr confers a 3-fold greater risk for renal involvement). Most patients (80%) initially display only mild renal involvement, principally isolated microscopic hematuria without significant proteinuria. About 20% of patients can present with a more severe renal involvement, including a combined acute nephritic and nephrotic picture (hematuria, hypertension, renal insufficiency, significant proteinuria, and nephrotic syndrome). Older children (and adults) have a greater risk for more severe involvement. Initial mild renal involvement can also occasionally progress to more severe nephritis despite resolution of all other features of HSP. The severity of the systemic manifestations is not correlated with the severity of the nephritis. *Most patients who develop nephritis have urinary abnormalities by 1 mo, and nearly all have abnormalities by 3-6 mo after the onset of HSP* . Therefore, a urinalysis should be performed weekly in patients with HSP during the period of active clinical disease. Thereafter, a urinalysis should be performed once a month for up to 6 mo. If all urinalyses are normal during this follow-up interval, nephritis is unlikely to develop. If proteinuria, renal insufficiency, or hypertension develops along with hematuria, consultation with a pediatric nephrologist is indicated. Indications for a kidney biopsy in children with HSP nephritis include significant proteinuria (urine protein > 1 g/day or urine protein/creatinine ratio > 1.0), significant hypertension, or elevated serum creatinine.

Prognosis and Treatment

The prognosis of HSP nephritis for most patients is excellent. Spontaneous and complete resolution of the nephritis typically occurs in the majority of patients with mild initial manifestations (isolated hematuria with insignificant proteinuria). However, such patients uncommonly can progress to severe renal involvement, including development of chronic renal failure. Patients with acute nephritic or nephrotic syndrome at presentation have a guarded renal prognosis, particularly if they are found to have concomitant necrosis or substantial crescentic changes on renal biopsy. Untreated, the risk of developing chronic kidney disease, including end-stage renal disease, is 2–5% in all patients with HSP, but almost 50% in those with the most severe early renal clinical and histologic features.

No convincing randomized clinical studies or evidence-based guidelines exist for treatment of HSP nephritis. In particular, no studies have demonstrated any efficacy of short courses (weeks) of oral corticosteroids administered promptly after the onset of HSP in either preventing the development of nephritis or decreasing the severity of subsequent renal involvement. Tonsillectomy has been proposed as an intervention for HSP nephritis, but it also does not appear to have any measurable effect on the renal outcome. Mild HSP nephritis does not require treatment, because it usually resolves spontaneously.

The efficacy of treatment for moderate or severe HSP nephritis, which is far more likely to progress to chronic kidney disease, is more difficult to assess. Several uncontrolled studies have reported a significant benefit from aggressive immunosuppression (high-dose and extended courses of corticosteroids with azathioprine, mycophenolate mofetil, or cyclophosphamide) in patients with poor prognostic features on renal biopsy; such patients are at high risk of progressing to chronic kidney disease based on historical controls. Anecdotal reports of the treatment of high-risk patients with either plasmapheresis or rituximab have also indicated a potential benefit. Balancing the absence of controlled data with the severe side effects of aggressive therapies in patients with poor renal prognostic factors is difficult. Aggressive therapy with careful monitoring may be reasonable in those with the most severe HSP nephritis (>50% crescents on biopsy). One common approach in children with severe clinical renal involvement (nephrotic range proteinuria, elevated serum creatinine, hypertension) is the use of oral prednisone (1 mg/kg per day for 3 mo), along with angiotensin-converting enzyme inhibitors, followed by azathioprine or mycophenolate mofetil if severe clinical involvement persists. For children with severe histologic manifestations (>50% glomerular crescents), treatment with intravenous methylprednisolone pulses for 3 days, followed by a combination of oral prednisone (for 3 mo) and azathioprine or mycophenolate mofetil (extended course) may be considered. For children with the most severe histology (>75% glomerular crescents) and progressive renal failure, intravenous steroids plus plasmapheresis may be considered. If progression to end-stage renal disease occurs, renal transplantation is the treatment of choice. Deposition of IgA in the transplanted kidney is common, but most cases are subclinical and the overall graft survival is similar to that for other renal transplant recipients.

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538.4

Goodpasture Disease

Prasad Devarajan

Keywords

Antineutrophilic cytoplasmic antibody
Anti-GBM antibody
Goodpasture syndrome
rapidly progressive glomerulonephritis

Goodpasture disease is an autoimmune disease characterized by pulmonary hemorrhage, rapidly progressive glomerulonephritis, and elevated anti–glomerular basement membrane antibody titers. The disease results from an attack on these organs by antibodies directed against certain epitopes of type IV collagen, located within the alveolar basement membrane in the lung and glomerular basement membrane (GBM) in the kidney. An acquired conformational change in the noncollagenous 1 domain of the alpha 3-chain of type IV collagen leads to the production of pathologic autoantibodies. The high affinity of these antibodies to the GBM results in the characteristic rapidly progressive kidney disease. Infusion of human anti-GBM antibodies into animals reproduces the rapidly aggressive glomerulonephritis, confirming the high pathogenicity of these antibodies.

Pathology

Kidney biopsy shows crescentic glomerulonephritis in most patients. Immunofluorescence microscopy demonstrates the pathognomonic continuous linear deposition of immunoglobulin G along the GBM (Fig. 538.1).

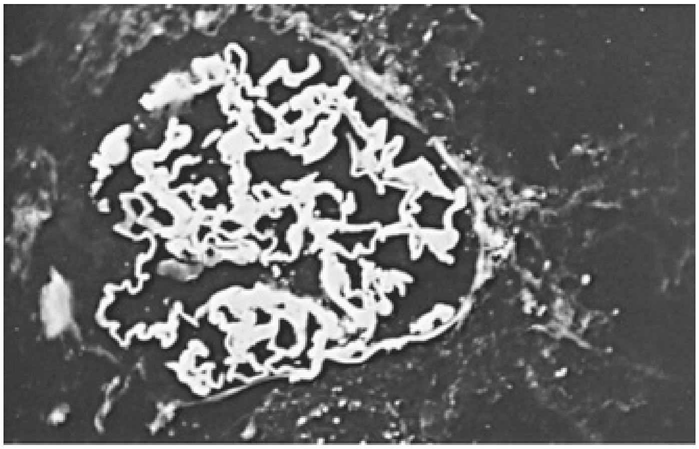

FIG. 538.1 Immunofluorescence micrograph demonstrating the continuous linear staining of immunoglobulin G along the glomerular basement membrane in Goodpasture disease (×250).

Clinical Manifestations

Goodpasture disease is rare in childhood. Patients usually present with hemoptysis from pulmonary hemorrhage that can be life-threatening. Concomitant renal manifestations include acute glomerulonephritis with hematuria, nephritic urinary sediment with cellular casts, proteinuria, and hypertension, which usually follow a rapidly progressive course. Renal failure commonly develops within days to weeks of the clinical presentation. Although fever may be present, other systemic complaints such as malaise or arthralgia are usually absent; their presence should raise suspicion for a systemic vasculitis. *Less commonly, patients can have anti-GBM nephritis manifesting as isolated, rapidly progressive glomerulonephritis without pulmonary hemorrhage.* In essentially all cases, anti-GBM antibody is present in the serum and/or the kidney, and the serum complement C3 level is normal. Antineutrophilic cytoplasmic antibody (ANCA) levels can be found to be elevated in 10–40% of patients, along with the anti-GBM antibody; such patients doubly positive for these autoantibodies have more severe disease at presentation. In general, anti-GBM antibody titers are correlated with the severity of the renal involvement. However, a kidney biopsy should be performed (unless contraindicated), since the accuracy of anti-GBM serology is variable, and renal biopsy provides additional histologic information that can guide therapy.

Diagnosis and Differential Diagnosis

The diagnosis is made by a combination of the clinical presentation of pulmonary hemorrhage with acute glomerulonephritis, the presence of serum antibodies directed against GBM (anti–type IV collagen in GBM), and characteristic renal biopsy findings. Other diseases that can cause a **pulmonary-renal syndrome** need to be considered and include systemic lupus erythematosus, Henoch-Schönlein purpura, nephrotic syndrome–associated pulmonary embolism, and ANCA-associated vasculitis (such as granulomatosis with polyangiitis and microscopic polyangiitis). These diseases are ruled out by the absence of other characteristic clinical features, kidney biopsy findings, and negative serologic studies for antibodies against nuclear (antinuclear antibody), DNA (anti-dsDNA), and neutrophil cytoplasmic components (ANCA antibody).

Prognosis and Treatment

Untreated, the prognosis of Goodpasture disease is poor. Treatment must be initiated emergently, as soon as the diagnosis is suspected. The prompt institution of plasmapheresis, high-dose intravenous methylprednisolone, and cyclophosphamide often induces remission and improves survival times. Initial therapy with plasmapheresis removes circulating anti-GBM antibodies, and initial immunosuppression with steroids and cyclophosphamide inhibits ongoing antibody production. Rituximab may be used as a substitute in cases where cyclophosphamide toxicity is encountered. Initial treatment is guided by the clinical response and serial anti-GBM titers. Retrospective cohort studies suggest that when this combination of treatments is started early, the majority of patients will have a good renal outcome. However, an initial presentation with oligoanuria, a high proportion of glomerular crescents, or kidney failure requiring dialysis predicts worse renal and patient survival rates. After the induction of remission, maintenance therapy with lower doses of prednisone and azathioprine (or mycophenolate mofetil) is continued for 6-9 mo. However, patients who survive the acute pulmonary hemorrhage and rapidly progressive glomerulonephritis can still progress to end-stage renal failure despite ongoing immunosuppressive therapy. For patients who progress, kidney transplantation is the treatment of choice. Relapse and recurrent disease after kidney transplantation are both uncommon.

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538.5

Hemolytic-Uremic Syndrome

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Keywords

complement dysregulation
Escherichia coli
Shiga toxin-producing E. coli (STEC)
thrombotic microangiopathy

Hemolytic-uremic syndrome (HUS) is a common cause of community-acquired acute kidney injury in young children. It is the most common form of **thrombotic microangiopathy (TMA)** in children. Like all TMAs, HUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. HUS has clinical features in common with thrombotic thrombocytopenic purpura (TTP) (see Chapter 511.05). The etiology and pathophysiology of the more common forms of HUS clearly delineate typical childhood HUS as separate from idiopathic TTP.

Etiology

The various etiologies of HUS and other related thrombotic microangiopathies allow classification into infection-induced, genetic, drug-induced, and HUS associated with systemic diseases characterized by microvascular injury (Table

538.2). The most common form of HUS is caused by Shiga toxin–producing *Escherichia coli* (STEC), which causes prodromal acute enteritis and is commonly termed STEC-HUS or **diarrhea-associated HUS.** In the subcontinent of Asia and in southern Africa, the toxin of *Shigella dysenteriae* type 1 is causative, whereas in Western countries, verotoxin or Shiga toxin–producing *E. coli* (STEC) is the usual cause. STEC-HUS accounts for about 90% of all HUS cases in childhood.

Table 538.2

Current Classification of Hemolytic-Uremic Syndromes and Thrombotic Microangiopathies

DIARRHEA-ASSOCIATED HUS
• STEC (*Escherichia coli* O157:H7) • STEC (*E.coli* 0121 and 0104:H4) • Non-STEC (*Shigella dysenteriae* type 1)
HUS SECONDARY TO SYSTEMIC INFECTIONS
• Neuraminidase *(Streptococcus pneumoniae)* • Human immunodeficiency virus • Influenza • Human herpes virus 6 • Parvovirus B19 • Malaria
ATYPICAL HUS DUE TO COMPLEMENT DYSREGULATION
• Factor H deficiency (mutations, autoantibodies) • Factor I deficiency (mutations) • Factor B (gain-of-function mutations) • Membrane cofactor (MCP) deficiency (mutations) • C3 deficiency (mutations, autoantibodies) • Thrombomodulin deficiency (mutations) • Anti–complement factor H antibody • Unknown
THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)
• Inherited ADAMTS13 deficiency (mutations) • Acquired ADAMTS13 deficiency (antibody-mediated) • Pregnancy-associated • Vitamin B_{12} deficiency
DRUG INDUCED
• Cyclosporine • Tacrolimus • Mithramycin • Quinine • Cocaine • Anti–vascular endothelial growth factor therapy
SYSTEMIC DISEASE ASSOCIATED
• Systemic lupus erythematosus • Coexisting nephropathies • Malignant hypertension

• Malignancies • Cobalamin C defect • Diacylglycerol kinase epsilon mutation
TRANSPLANT ASSOCIATED
• Stem cell transplant • Bone marrow transplant • Renal • Heart • Intestinal

Several serotypes of *E. coli* can produce the toxin; O157:H7 is most common in Europe and the Americas. A large epidemic of HUS in Europe was caused by Shiga toxin–producing *E. coli* O104:H4. The reservoir of STEC is the intestinal tract of domestic animals, usually cows. Disease commonly is transmitted by undercooked meat or unpasteurized (raw) milk and apple cider. Local outbreaks have followed the ingestion of undercooked, contaminated hamburger or other foods cross-contaminated on unwashed cutting boards at fast food restaurants; contaminated municipal water supplies; petting farms; and swimming in contaminated ponds, lakes, or pools. With broad food distribution, wider epidemics have been traced to lettuce, raw spinach, and bean sprouts contaminated with STEC. Less often, STEC has been spread by person-to-person contact within families or child care centers. A rare but distinct entity of infection-triggered HUS is related to neuraminidase-producing *Streptococcus pneumoniae*. HUS, typically severe, develops during acute infection with this organism, typically manifesting as pneumonia with empyema. A thrombotic microangiopathy, similar to HUS or TTP, also can occur in patients with untreated HIV infection and influenza infection.

Genetic forms of HUS (atypical, nondiarrheal) compose the second major category of the disease (see Table 538.2). Inherited deficiencies of either von Willebrand factor–cleaving protease (ADAMTS13) or complement factor H, I, or B can cause HUS. A specific genetic defect has not been identified in approximately 50% of familial cases transmitted in classic Mendelian autosomal dominant or recessive patterns. Some of these may be due to cobalamin C mutations. A major feature characteristic of genetic forms of HUS is the *absence* of a preceding diarrheal prodrome. Genetic forms of HUS can be indolent and unremitting once they become manifest, or they can have a relapsing pattern precipitated by an infectious illness. The latter feature likely explains the association of many infectious agents with HUS, particularly in reports published before the recognition of the unique pathophysiology of STEC and neuraminidase-producing pneumococci in causing HUS.

HUS can be superimposed on any disease associated with microvascular injury, including malignant hypertension, systemic lupus erythematosus, and antiphospholipid syndrome. It can also occur following bone marrow or solid organ transplantation, and may be triggered by the use of the calcineurin inhibitors cyclosporine and tacrolimus in that setting. Several other medications also can induce HUS (see Table 538.2).

Pathology

Kidney biopsies are only rarely performed in HUS because the diagnosis is usually established by clinical criteria and the risks of biopsy are significant during the active phase of the disease. Early glomerular changes include thickening of the capillary walls caused by swelling of endothelial cells and accumulation of fibrillar material between endothelial cells and the underlying basement membrane, causing narrowing of the capillary lumens. Platelet–fibrin thrombi are often seen in glomerular capillaries. Thrombi are also seen in afferent arterioles and small arteries with fibrinoid necrosis of the arterial wall, leading to renal cortical necrosis from vascular occlusion. Late findings include glomerular sclerosis and obsolescence secondary to either severe direct glomerular involvement or glomerular ischemia from arteriolar involvement.

Pathogenesis

Microvascular injury with endothelial cell damage is characteristic of all forms of TMA, including HUS. In the diarrhea-associated form of HUS, enteropathic organisms produce either Shiga toxin or the highly homologous Shiga-like verotoxin. These toxins are easily absorbed from the colonic mucosa into the systemic circulation, bind to endothelial cells in the glomerulus and elsewhere, and directly cause endothelial cell damage. Shiga toxin can also directly activate platelets to promote their aggregation. Mechanical injury to RBCs passing through the thrombotic microvasculature results in a severe nonimmune anemia with a negative direct Coombs test. In pneumococcal-associated HUS, neuraminidase cleaves sialic acid on membranes of endothelial cells, red cells, and platelets to expose the underlying cryptic Thomsen-Friedenreich (T) antigen. Endogenous immunoglobulin M (IgM) antibodies recognize and react with the T antigen to trigger hemolysis and anemia with a positive direct Coombs test.

The familial recessive and dominant forms of HUS, including the inherited deficiencies of ADAMTS13 and regulators of the complement cascade, probably predispose patients to developing HUS but do not cause the disease per se, because these patients might not develop HUS until later childhood or even adulthood. In such cases, HUS is often triggered by an inciting event such as an infectious disease. The absence of ADAMTS13 impairs cleavage of von Willebrand factor multimers, which enhances platelet aggregation. Factor H plays a central role in complement regulation, primarily arresting the amplification and propagation of complement activation. It is possible that mild endothelial injury that would normally resolve instead evolves to an aggressive microangiopathy because of the inherited deficiencies of these factors.

In each form of HUS, capillary and arteriolar endothelial injury in the kidney leads to localized thrombosis, particularly in glomeruli, causing a direct decrease in glomerular filtration. Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia. Microangiopathic hemolytic anemia results from mechanical damage to red blood cells as they pass through the damaged and thrombotic microvasculature.

Clinical Manifestations

HUS (diarrhea form) is most common in preschool and school-age children, but it can occur in adolescents and adults. In HUS caused by toxigenic *E. coli,* the onset of HUS occurs 5-7 days after the onset of gastroenteritis with fever, vomiting, abdominal pain, and diarrhea. The prodromal intestinal symptoms may be severe and require hospitalization, but they can also be relatively mild and considered trivial. The diarrhea is often bloody, but not necessarily so. Following the prodromal illness, the sudden onset of pallor, weakness, and lethargy heralds the onset of HUS, and it reflects the development of microangiopathic hemolytic anemia. Oliguria can be present in early stages but may be masked by ongoing diarrhea, because the prodromal enteritis often overlaps the onset of HUS, particularly with ingestion of large doses of toxin. Thus, patients with HUS can present with either significant dehydration or volume overload, depending on whether the enteritis or renal insufficiency from HUS predominates, and the amount of fluid that has been administered.

Patients with pneumococci-associated HUS usually are quite ill with pneumonia, empyema, and bacteremia when they develop HUS. The onset can be insidious in patients with the genetic forms of HUS, with HUS triggered by a variety of illnesses, including mild, nonspecific gastroenteritis or respiratory tract infections.

HUS can be relatively mild, or can progress to a severe and fatal multisystem disease. Leukocytosis, severe prodromal enteritis, hyponatremia, and antibiotic use portend a severe course, but no presenting features reliably predict the severity of HUS in any given patient. Patients with HUS who appear mildly affected at presentation can rapidly develop severe, multisystem, life-threatening complications. Renal insufficiency can be mild but also can rapidly evolve into severe oliguric or anuric renal failure. The combination of rapidly developing renal failure and severe hemolysis can result in life-threatening hyperkalemia. Severe acute kidney injury requiring dialysis develops in about 50% of patients with STEC-HUS. The duration of the dialysis requirement is usually about 2 wk. Volume overload, hypertension, and severe anemia can all develop soon after the onset of HUS, and together can precipitate heart failure. Direct cardiac involvement is rare, but pericarditis, myocardial dysfunction, or arrhythmias can occur without predisposing features of hypertension, volume overload, or electrolyte abnormalities.

The majority of patients with HUS have some central nervous system (CNS) involvement. Most have mild manifestations, with significant irritability, lethargy, or nonspecific encephalopathic features. Severe CNS involvement occurs in ≤ 20% of cases. Seizures and significant encephalopathy are the most common manifestations in those with severe CNS involvement, resulting from focal ischemia secondary to microvascular CNS thrombosis. Small infarctions in the basal ganglion and cerebral cortex have also been reported, but large strokes and intracranial hemorrhage are rare. Hypertension may produce an encephalopathy and seizures. Intestinal complications can be protean and include severe inflammatory colitis, ischemic enteritis, bowel perforation, intussusception, and pancreatitis. Patients can develop petechiae, but significant or severe bleeding is rare despite very low platelet counts.

Diagnosis and Differential Diagnosis

The diagnosis is made by the combination of microangiopathic hemolytic anemia with schistocytes, thrombocytopenia, and some degree of kidney involvement. The anemia can be mild at presentation, but it rapidly progresses. Thrombocytopenia is an invariable finding in the acute phase, with platelet counts usually 20,000-100,000/mm^3 . Partial thromboplastin and prothrombin times are usually normal. The Coombs test is negative, with the exception of pneumococci-induced HUS, where the Coombs test is usually positive. Leukocytosis is often present and significant. Urinalysis typically shows microscopic hematuria and low-grade proteinuria. The renal insufficiency can vary from mild elevations in serum blood urea nitrogen and creatinine to acute, anuric kidney failure.

The etiology of HUS is often clear with the presence of a diarrheal prodrome or pneumococcal infection. The presence or absence of toxigenic organisms on stool culture has little role in making the diagnosis of diarrhea-associated STEC-HUS. Only a minority of patients infected with those organisms develops HUS, and the organisms that cause HUS may be rapidly cleared. Therefore, the stool culture is often negative in patients who have diarrhea-associated HUS. If no history of diarrheal prodrome or pneumococcal infection is obtained, then evaluation for genetic forms of HUS should be considered, because those patients are at risk for recurrence, have a severe prognosis, and can benefit from a different therapy. Other causes of acute kidney injury associated with a microangiopathic hemolytic anemia and thrombocytopenia should be considered and excluded, such as systemic lupus erythematosus, malignant hypertension, and bilateral renal vein thrombosis. A kidney biopsy is rarely indicated to diagnose HUS.

Prognosis and Treatment

With early recognition and intensive supportive care, the mortality rate for diarrhea-associated HUS is < 5% in most major medical centers. Up to half of patients may require dialysis support during the acute phase of the disease. Recovery of platelet counts usually occurs first, followed by renal recovery about 5 days later, and finally by resolution of anemia. Most recover renal function completely, but of surviving patients, 5% remain dependent on dialysis, and up to 30% are left with some degree of chronic renal insufficiency. The prognosis for HUS not associated with diarrhea is more severe. Pneumococci-associated HUS causes increased patient morbidity (>80% require dialysis), with the mortality rate reported as 20%. The familial, genetic forms of HUS can be insidiously progressive or relapsing diseases and have a poor prognosis. Identification of specific factor deficiencies in some of these genetic forms provides an opportunity for directed therapy to improve the outcome.

The primary approach that has substantially improved an acute outcome in

HUS is early recognition of the disease, monitoring for potential complications, and meticulous supportive care. Supportive care includes careful management of fluid and electrolytes, including prompt correction of a volume deficit, control of hypertension, and early institution of dialysis if the patient becomes significantly oliguric or anuric, particularly with hyperkalemia. Early intravenous volume expansion before the onset of oliguria or anuria may be nephroprotective in diarrhea-associated HUS. Red cell transfusions are usually required because hemolysis can be brisk and recurrent until the active phase of the disease has resolved. In pneumococci-associated HUS, it is critical that any administered red cells be washed before transfusion to remove residual plasma, because endogenous IgM directed against the revealed T antigen can play a role in accelerating the pathogenesis of the disease. Platelets should generally not be administered, regardless of the platelet count, to patients with HUS because they are rapidly consumed by the active coagulation and theoretically can worsen the clinical course. Despite low platelet counts, serious bleeding is very rare in patients with HUS.

There is no evidence that any therapy directed at arresting the disease process of the most common, diarrhea-associated STEC-HUS provides benefit, and some can cause harm. Attempts have been made using anticoagulants, antiplatelet agents, fibrinolytic therapy, plasma therapy, immune globulin, and antibiotics. Anticoagulation, antiplatelet, and fibrinolytic therapies are specifically contraindicated because they increase the risk of serious hemorrhage. Antibiotic therapy to clear enteric toxigenic organisms (STEC) can result in increased toxin release, potentially exacerbating the disease, and therefore is not recommended. However, prompt treatment of causative pneumococcal infection is important. The European experience with *E. coli* O104:H4 in adults who were treated with azithromycin demonstrated more rapid elimination of the organism. Furthermore, in vitro evidence suggests that meropenem, rifaximin, and azithromycin downregulate the release and expression of Shiga toxin. Nonetheless, in children with *E. coli* O157:H7–associated HUS, antibiotics are still considered contraindicated.

Plasma infusion or plasmapheresis has been proposed for patients suffering severe manifestations of HUS with serious CNS involvement. There are no controlled data demonstrating the effectiveness of this approach, and it is specifically contraindicated in those with pneumococcal-associated HUS because it could exacerbate the disease. The use of plasma therapy in STEC-HUS was one of many treatment strategies during one of the largest reported outbreaks of STEC-HUS, which occurred in Europe in 2011. This outbreak was caused by an uncommon serotype (O104:H4) that had unique virulence factors. Thought initially to cause more severe disease, it differed epidemiologically from other STEC-HUS serotypes by affecting primarily healthy adults, rather than the usual pattern of affecting children and the elderly. Treatment in this epidemic included plasma exchange in most of the adult patients, as well as the use of eculizumab.

Eculizumab is an anti-C5 antibody that inhibits complement activation, a pathway that contributes to active disease in some forms of atypical familial HUS; this pathway may also contribute to the process in STEC-HUS. Eculizumab is FDA approved for the treatment of atypical HUS. Because of the risk of meningococcal disease in patients with defects in terminal complement components, it is recommended to give the meningococcal vaccine prior to giving eculizumab (if the patient has not been primarily immunized). Although initial reports suggested that eculizumab provided benefit in patients with diarrhea-associated HUS, subsequent systematic analysis showed no benefit from either plasma exchange or eculizumab.

Plasma therapy can be of substantial benefit to patients with identified deficits of ADAMTS13 or factor H. It may also be considered in patients with other genetic forms of HUS, such as the undefined familial (recessive or dominant) form or sporadic but recurrent HUS. In contrast to its use in STEC-HUS, eculizumab shows great promise in the treatment of atypical HUS, including HUS occurring following renal transplantation. Whether it should be combined with plasma therapy or used as a primary treatment of atypical HUS, is still undetermined.

Most patients with diarrhea-associated HUS recover completely, with little risk of long-term sequelae. Patients with hypertension, any level of renal insufficiency, or residual urinary abnormalities persisting a year after an episode of diarrhea-positive HUS (particularly significant proteinuria) require careful follow-up. Patients who have recovered completely with no residual urinary abnormalities after 1 yr are unlikely to manifest long-term sequelae. Because of some reports of late sequelae in such patients, annual examinations with a primary physician are still warranted.

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538.6

Toxic Nephropathy

Prasad Devarajan

Keywords

acute kidney injury
contrast-induced nephropathy
nephrotoxicity

Aberrant renal function often results from purposeful or accidental exposure to any number of diagnostic, biologic, or therapeutic agents that are potential or actual nephrotoxins. Among diagnostic agents, **contrast-induced nephropathy** is a common and generally reversible form of acute kidney injury that results from administration of radiocontrast media in predisposed individuals. Iodinated radiocontrast agents are generally well tolerated by most patients without significant adverse consequences. In volume-depleted patients or patients with underlying chronic kidney disease, their use poses a serious risk for the development of acute kidney injury with significant attendant morbidity and mortality. Contrast agents can lead to renal vasoconstriction as well as direct tubule cell injury. Contrast-induced nephropathy usually manifests as an increase in serum creatinine 1-2 days following exposure; most patients are not oliguric. In most cases, the serum creatinine normalizes in the next 3-7 days, and treatment is supportive.

Biologic nephrotoxins include venomous exposures from insects, reptiles, amphibians, and a wide variety of sea-dwelling animals. The most common forms of toxic nephropathy unfortunately relate to the exposure of children to pharmacologic agents, accounting for close to 20% of episodes of acute kidney injury occurring in children and adolescents. Age, underlying medical condition, genetics, exposure dose, and the concomitant use of other drugs all influence the likelihood of developing acute kidney injury. One common scenario is the use of nonsteroidal antiinflammatory agents (NSAIDs) in febrile children with concomitant dehydration. In this situation, NSAIDs can inhibit the production of intrarenal vasodilatory prostaglandins, thereby leading to decreased renal perfusion and acute kidney injury.

Table 538.3 summarizes the agents that commonly cause acute kidney injury and some of their clinical manifestations. Mechanisms of injury often help to explain the presentation; however, multiple toxic exposures in patients with complicated clinical histories often limit the ability to clearly establish clinical cause and effect. For example, diminished urine output may be the clinical hallmark of tubular obstruction caused by agents such as methotrexate or agents that cause acute tubular necrosis, such as amphotericin B or pentamidine. Alternatively, nephrogenic diabetes insipidus may be the critical clinical manifestation of agents that cause interstitial nephritis, such as lithium or cisplatin. Nephrotoxicity is often reversible if the noxious agent is promptly removed.

Table 538.3

Renal Syndromes Produced by Nephrotoxins

NEPHROTIC SYNDROME
Angiotensin-converting enzyme inhibitors
Gold salts
Interferon
Mercury compounds
Nonsteroidal antiinflammatory drugs
Penicillamine

NEPHROGENIC DIABETES INSIPIDUS

- Amphotericin B
- Cisplatin
- Colchicine
- Demeclocycline
- Lithium
- Methoxyflurane
- Propoxyphene
- Vinblastine

RENAL VASCULITIS

- Hydralazine
- Isoniazid
- Penicillins
- Propylthiouracil
- Sulfonamides
- Numerous other drugs that can cause a hypersensitivity reaction

THROMBOTIC MICROANGIOPATHY

- Cyclosporine A
- Oral contraceptive agents
- Mitomycin C

NEPHROCALCINOSIS OR NEPHROLITHIASIS

- Allopurinol
- Bumetanide
- Ethylene glycol
- Furosemide
- Melamine
- Methoxyflurane
- Topiramate
- Vitamin D

ACUTE KIDNEY INJURY

- Acetaminophen
- Acyclovir
- Aminoglycosides
- Amphotericin B
- Angiotensin-converting enzyme inhibitors
- Biologic toxins (snake, spider, bee, wasp)
- Cisplatin
- Cyclosporine
- Ethylene glycol
- Halothane
- Heavy metals
- Ifosfamide
- Lithium
- Methoxyflurane
- Nonsteroidal antiinflammatory drugs
- Radiocontrast agents
- Tacrolimus
- Vancomycin

OBSTRUCTIVE UROPATHY

- Sulfonamides

Acyclovir
Methotrexate
Protease inhibitors
Ethylene glycol
Methoxyflurane

FANCONI SYNDROME

Aminoglycosides
Chinese herbs (aristolochic)
Cisplatin
Heavy metals (cadmium, lead, mercury, and uranium)
Ifosfamide
Lysol
Outdated tetracycline

RENAL TUBULAR ACIDOSIS

Amphotericin B
Lead
Lithium
Toluene

INTERSTITIAL NEPHRITIS

Amidopyrine
p -Aminosalicylate
Carbon tetrachloride
Cephalosporins
Cimetidine
Cisplatin
Colistin
Copper
Cyclosporine
Ethylene glycol
Foscarnet
Gentamicin
Gold salts
Indomethacin
Interferon-α
Iron
Kanamycin
Lithium
Mannitol
Mercury salts
Mitomycin C
Neomycin
Nonsteroidal antiinflammatory drugs
Penicillins (especially methicillin)
Pentamidine
Phenacetin
Phenylbutazone
Poisonous mushrooms
Polymyxin B
Radiocontrast agents
Rifampin
Salicylate
Streptomycin
Sulfonamides

Tacrolimus
Tetrachloroethylene
Trimethoprim-sulfamethoxazole

Clinical use of potential nephrotoxins should be judicious. Necessity of exposure, dosing parameters, and the use of drug levels or pharmacogenomic data, when available, should always be considered. Caution is particularly mandated for patients with complex medical conditions that include preexisting renal disease, cardiac disease, diabetes, and/or complicated surgeries. Alternative approaches to imaging or the use of different pharmacologic options should be considered when possible. Imaging modalities such as ultrasonography, radionuclide scanning, or MRI may be preferable to contrast studies in some patients. Alternatively, a judicious volume expansion with or without the administration of *N* -acetylcysteine might offer renoprotection when radioiodinated contrast studies are critical. Pharmacologic agents with no known renal effects can often be substituted for known nephrotoxins with equal clinical efficacy. In all cases, simultaneous use of known nephrotoxins should be avoided whenever possible. The use of nephrotoxic agents represents one of the few modifiable risk factors for acute kidney injury, and promising new biomarkers for the early detection and modification of nephrotoxic injuries are currently becoming available. Use of the electronic health record for systematic surveillance for nephrotoxic medication exposure and acute kidney injury can also lead to sustained reductions in avoidable kidney injury.

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538.7

Cortical Necrosis

Prasad Devarajan

Keywords

acute kidney injury
acute renal failure
cortical necrosis

Background

Renal cortical necrosis is a rare cause of severe acute kidney injury occurring secondary to extensive ischemic damage of the renal cortex. Ischemic necrosis is due to markedly decreased renal arterial perfusion as a result of vascular spasm, microvascular injury, or intravascular coagulation. Renal cortical necrosis is usually bilateral and extensive, although focal and patchy forms have also been described. The medulla, the juxtamedullary cortex, and a thin rim of subcapsular cortex are usually spared. It occurs most commonly in neonates and in adolescents of childbearing age.

Etiology

In newborns, cortical necrosis is most commonly associated with hypoxic or ischemic insults caused by perinatal asphyxia, placental abruption, and twin–twin or fetal-maternal transfusion. Other causes include renal vascular thrombosis and severe congenital heart disease. After the neonatal period, cortical necrosis is most commonly seen in children with septic shock or severe hemolytic-uremic syndrome. In adolescents and women, cortical necrosis occurs in association with obstetric complications, including prolonged intrauterine fetal death, placental abruption, septic abortion, or amniotic fluid embolism.

Less-common causes of cortical necrosis include malaria, extensive burns, snakebites, infectious endocarditis, and medications (e.g., nonsteroidal antiinflammatory agents). Acute renal cortical necrosis has also been reported to occur in systemic lupus erythematosus–associated antiphospholipid antibody syndrome.

Pathogenesis

The presumed initiating factor in many cases is intense vasospasm of the small vessels. When prolonged, this leads to necrosis and thrombosis of the distal arterioles and glomeruli, with ensuing cortical necrosis. In hemolytic-uremic syndrome and septic abortion, endotoxin-mediated endothelial damage contributes to worsening vascular thrombosis.

Clinical Manifestations

Cortical necrosis clinically presents as severe acute kidney injury in patients with predisposing causes. Urine output is diminished and gross and/or microscopic hematuria may be present. Hypertension is common, and thrombocytopenia may be present as a result of renal microvascular injury.

Laboratory and Radiologic Findings

Laboratory results are consistent with acute kidney injury: an elevated blood urea nitrogen and creatinine, hyperkalemia, and metabolic acidosis. Anemia and thrombocytopenia are common. Urinalysis reveals hematuria with red cell or granular casts, and proteinuria.

Ultrasound examination with Doppler flow studies demonstrates decreased perfusion to both kidneys. Kidneys are enlarged in the initial stages, but cortical tissue becomes shrunken in the later stages. Thin cortical shells of calcification (tram lines) are a radiologic hallmark, but they develop only 4-5 wk after the initial insult.

CT scanning with contrast is the most sensitive imaging modality in renal cortical necrosis. Diagnostic features include absent opacification of the renal cortex and enhancement of subcapsular and juxtamedullary regions and of the medulla with absent excretion of contrast medium.

A radionuclide renal scan shows decreased uptake with significantly delayed or absent function. Renal scanning is the imaging technique of choice if contrast-enhanced CT scanning is not available or is contraindicated.

Treatment

The cornerstones of therapy for renal cortical necrosis are to restore hemodynamic stability, institute early dialysis, and treat the underlying cause. Most cases of renal cortical necrosis require initial treatment in an intensive care setting. It is important to prevent or treat the underlying cause of acute cortical necrosis, when possible. Therapy involves medical management of acute renal failure, often with the initiation of dialysis as indicated. Management is otherwise supportive and involves volume repletion, correction of asphyxia, and treatment of sepsis.

Prognosis

The most important prognostic factors include the extent of necrosis, duration of oligoanuria, and severity of the overall associated conditions. Untreated, renal cortical necrosis has a high mortality rate, exceeding 50%. Early initiation of dialysis significantly diminishes the mortality rate. Most patients require dialysis for variable but extended periods of time. Twenty to 40% of patients have partial recovery of renal function, the extent of which depends on the amount of preserved cortical tissue. All patients require long-term follow-up for chronic kidney disease.

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538.8

Coagulopathies and Thrombocytopenia

Prasad Devarajan

Gross or microscopic hematuria may be associated with inherited or acquired disorders of coagulation (hemophilia, disseminated intravascular coagulation, thrombocytopenia). In these cases, however, hematuria is not usually the presenting complaint or a major factor affecting the clinical management or outcome (see Chapters 502 to 511).

CHAPTER 539

Tubulointerstitial Disease Associated With Hematuria

Prasad Devarajan

Gross or microscopic hematuria may be associated with several disorders of the renal tubules and the interstitium (pyelonephritis, tubulointerstitial nephritis, papillary necrosis, acute tubular necrosis). However, except for papillary necrosis, hematuria is not usually the presenting complaint or a major factor affecting the clinical management or outcome (see Chapters 539.2 to 539.4).

539.1

Pyelonephritis

See Chapter 553 , Urinary Tract Infections.

539.2

Tubulointerstitial Nephritis

Prasad Devarajan

Keywords

acute kidney injury
drug-induced kidney disease
interstitial nephritis
juvenile nephronophthisis

Tubulointerstitial nephritis (TIN, also called interstitial nephritis) is the term applied to conditions characterized by tubulointerstitial inflammation and damage with relative sparing of glomeruli and vessels. Both acute and chronic primary forms exist. Acute TIN is characterized by an acute extensive lymphocytic inflammatory response and a rapid decline in renal function. Chronic TIN usually displays a protracted onset and also a chronic patchy lymphocytic infiltrate, interstitial fibrosis, and a slow deterioration in renal function. Secondary forms of interstitial nephritis can be associated with primary glomerular diseases, as well as systemic diseases affecting the kidney.

Acute Tubulointerstitial Nephritis

Pathogenesis and Pathology

The hallmarks of acute TIN are an extensive lymphocytic infiltration of the tubulointerstitium, interstitial edema, and varying degrees of tubular necrosis and regeneration. Eosinophils may be present, particularly in drug-induced TIN; occasionally, interstitial granulomas with giant cells occur. Glomeruli are usually normal in primary TIN. The pathogenesis is not fully understood, but a T-cell–mediated immune mechanism has been postulated. **Drugs are the most common cause of acute TIN in children.** A large number of medications, especially antimicrobials, anticonvulsants, and analgesics, have been implicated as etiologic agents (Table 539.1). Nonsteroidal antiinflammatory agents (NSAIDs), penicillins, and sulfonamides account for most cases. Drug-induced TIN is an idiosyncratic reaction that occurs in only a very small subset of patients who ingest the medication, typically with repeated exposure. Drugs of abuse (including synthetic cannabinoids, bath salts, ecstasy, anabolic steroids, inhaled solvents, heroin, and cocaine) are an increasingly common problem in certain populations. Other causes of acute TIN include infections, primary glomerular diseases, and systemic diseases such as systemic lupus erythematosus.

Table 539.1

Etiology of Interstitial Nephritis

ACUTE INTERSTITIAL NEPHRITIS

Drugs

- Antimicrobials
  - Penicillin derivatives
  - Cephalosporins
  - Sulfonamides
  - Trimethoprim-sulfamethoxazole
  - Ciprofloxacin
  - Tetracyclines
  - Vancomycin
  - Erythromycin derivatives
  - Rifampin
  - Amphotericin B
  - Acyclovir
- Anticonvulsants
  - Carbamazepine
  - Phenobarbital
  - Phenytoin
  - Sodium valproate

Drugs of Abuse

- Synthetic cannabinoids
- Bath salts
- Ecstasy
- Anabolic steroids
- Inhaled solvents
- Heroin
- Cocaine

Other Drugs

- Allopurinol
- All-*trans* -retinoic acid
- 5-Aminosalicylic acid
- Cimetidine
- Cyclosporine
- Diuretics
- Escitalopram
- Interferon
- Mesalazine
- Quetiapine
- Olanzapine
- Nonsteroidal antiinflammatory drugs
- Protease inhibitors
- Proton pump inhibitors
- Aristolochic acid (traditional Chinese herb)

Infections

- Adenovirus
- Bacteria associated with acute pyelonephritis

- BK virus
- *Brucella*
- Streptococcal species
- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis B virus
- Histoplasmosis
- Human immunodeficiency virus
- Hantavirus
- Leptospirosis
- *Toxoplasma gondii*

Disease-Associated

- Glomerulonephritis (e.g., systemic lupus erythematosus)
- Acute allograft rejection
- Tubulointerstitial nephritis and uveitis (TINU) syndrome

Idiopathic

CHRONIC INTERSTITIAL NEPHRITIS

Drugs and Toxins

- Analgesics
- Cyclosporine
- Lithium
- Heavy metals

Infections (See Acute Interstitial Nephritis)

- Disease-associated causes
  - Metabolic and hereditary
  - Cystinosis
  - Oxalosis
  - Fabry disease
  - Wilson disease
  - Sickle cell nephropathy
  - Alport syndrome
  - Juvenile nephronophthisis, medullary cystic disease

Immunologic

- Systemic lupus erythematosus
- Crohn disease
- Chronic allograft rejection
- Tubulointerstitial nephritis and uveitis (TINU) syndrome
- Antitubular basement disease

Urologic

- Posterior urethral valves
- Eagle-Barrett syndrome
- Ureteropelvic junction obstruction
- Vesicoureteral reflux

Miscellaneous

- Balkan nephropathy
- Radiation
- Sarcoidosis
- Neoplasm

Idiopathic

Clinical Manifestations

The classic presentation of acute TIN is fever, rash, and arthralgia in the setting of a rising serum creatinine. Acute TIN accounts for about 5% of pediatric acute kidney injury cases. Although the full clinical triad may be noted in drug-induced TIN, most patients with acute TIN do not demonstrate all of the typical features. The rash can vary from maculopapular to urticarial and is often transient. Patients often have nonspecific constitutional symptoms of nausea, vomiting, fatigue, and weight loss. Flank pain may be present, presumably secondary to stretching of the renal capsule from acute inflammatory enlargement of the kidney. If acute TIN is caused by a systemic disease such as systemic lupus erythematosus, the clinical presentation will be consistent with specific signs and symptoms of the underlying disease. Unlike the typical presentation of oliguric acute renal failure seen with glomerular diseases, 30–40% of patients with acute TIN are nonoliguric, and hypertension is less common. Peripheral eosinophilia can occur, especially with drug-induced TIN. Microscopic hematuria is invariably present, but significant hematuria or proteinuria > 1.5 g/day is uncommon. One exception is patients whose TIN is caused by nonsteroidal antiinflammatory drugs (NSAIDs), who can present with the nephrotic syndrome. Urinalysis can reveal white blood cell, granular, or hyaline casts, but red blood cell casts (a characteristic of glomerular disease) are absent. The presence of urine eosinophils is neither sensitive nor specific, being detected in only 25% of cases. Because of pyuria, the initial diagnosis may be a urinary tract infection.

Diagnosis

The diagnosis is usually based on the clinical presentation and laboratory findings. A renal biopsy will establish the correct diagnosis in cases where the etiology or clinical course confounds the diagnosis. A careful history of the timing of disease onset in relation to drug exposure is essential in suspected drug-induced TIN. Because of the immune-mediated nature of TIN, signs or symptoms generally appear within 1-2 wk following exposure. In children, antimicrobials are a common inciting agent. NSAIDs are an important cause of acute TIN in children, and volume depletion or underlying chronic renal disease can increase the risk of occurrence. Urinalysis and serial measurements of serum creatinine and electrolytes should be monitored. Renal ultrasonography, though not diagnostic, can demonstrate enlarged, echogenic kidneys. Removal of a suspected offending agent followed by spontaneous improvement in renal function is highly suggestive of the diagnosis, and additional testing is generally not performed in this setting. In more severe cases, in which the cause is unclear or the patient's renal function deteriorates rapidly, a renal biopsy is indicated.

Treatment and Prognosis

Treatment of acute TIN starts with eliminating the suspected causative drug or agent. Most patients with mild ATN recover kidney function when the inciting agent is discontinued. Other treatment includes supportive care directed at addressing complications of acute kidney injury, such as hyperkalemia or volume overload (see Chapter 550.1). Corticosteroid administration within 2 wk of the discontinuation of certain offending agents (e.g., NSAIDs or antibiotics) can hasten the recovery and improve the long-term prognosis in drug-induced TIN. Current recommendations favor the use of oral prednisone in children whose kidney function fails to improve after stopping the suspected agent. Intravenous methylprednisolone is used in severe cases. Mycophenolate mofetil has been found to be beneficial in steroid-unresponsive cases. Whether such therapies are indicated in other causes of TIN is not clear. For patients with prolonged renal insufficiency, the prognosis remains guarded, and severe acute TIN from any cause can progress to chronic TIN.

Chronic Tubulointerstitial Nephritis

In children, chronic TIN most commonly occurs in the context of (1) an underlying congenital urologic renal disease, such as obstructive uropathy or vesicoureteral reflux, or (2) an underlying metabolic disorder affecting the kidneys (see Table 539.1). Some commonly used drugs such as cyclosporine and tacrolimus also cause chronic TIN. Chronic TIN can occur as an idiopathic disease, although this is more common in adults.

The juvenile nephronophthisis (JN)–medullary cystic kidney disease complex (MCKD) is a group of inherited, genetically determined cystic renal diseases that share the common histologic finding of chronic TIN. At least 20 different genes are associated with JN, usually inherited as an autosomal recessive disease (Table 539.2). These genes only define 30% of cases, and new genes are being identified at a rapid pace. Although uncommon in the United States, JN causes 10–20% of pediatric cases of end-stage renal disease (ESRD) in Europe. Patients with JN typically present with polyuria, growth failure, unexplained anemia, and chronic renal failure in late childhood or adolescence.

As a **ciliopathy,** JN is often associated with extrarenal features such as retinal degeneration, hepatobiliary disease, cerebellar vermis hypoplasia, laterality defects, intellectual disability, and shortening of bones. These features are represented in a number of syndromes, such as **Senior-Løken syndrome (retinitis pigmentosa), Joubert syndrome** (**cerebellar vermis hypoplasia;** 22 subtypes), **Bardet-Biedl syndrome** (intellectual disability, obesity; 17 subtypes), **Jeune asphyxiating thoracic dystrophy** (shortening of the long bones, narrow rib cage; 11 subtypes), and many others. **MCKD** is an autosomal dominant disease that typically manifests in adulthood. **TIN with uveitis (TINU syndrome)** is a rare autoimmune syndrome of chronic TIN with bilateral anterior uveitis and bone marrow granulomas that occurs primarily in adolescent girls. Clinical manifestations include photophobia, ocular pain and redness, and visual impairment. Chronic TIN is seen in all forms of progressive renal disease, regardless of the underlying cause, and the severity of interstitial disease is the single most important factor predicting progression to ESRD.

Table 539.2

Summary of the *NPHP1* to *NPHP18, NHPH1L,* and *NPHP2L* Genes, Gene Products, Chromosomal Localization, Phenotypes, Extrarenal Symptoms, and Interaction Partners

GENE (PROTEIN)	CHROMOSOME	PHENOTYPE (MEDIAN AGE AT ESRD)	EXTRARENAL SYMPTOMS	INTERACTION PARTNERS
NPHP1 (nephrocystin-1)	2q13	NPHP (13 yr)	RP (10%), OMA (2%), JBTS (rarely)	Inversin, nephrocystin-3, nephrocystin-4, filamin A and B, tensin, β-tubulin, PTK2B
NPHP2/INVS (inversin)	9q31	Infantile NPHP (<4 yr)	RP (10%), LF, situs inversus, CHD	Nephrocystin-1, calmodulin, catenins, β-tubulin, APC2
NPHP3 (nephrocystin-3)	3q22	Infantile and adolescent NPHP	LF, RP (10%), situs inversus, MKS, CHD	Nephrocystin-1
NPHP4 (nephrocystin-4)	1p36	NPHP (21 yr)	RP (10%), OMA, LF	Nephrocystin-1, BCAR1, PTK2B
NPHP5/IQCB1 (nephrocystin-5)	3q21	NPHP (13 yr)	Early-onset RP	Calmodulin, RPGR, nephrocystin-6
NPHP6/CEP290 (nephrocystin-6/CEP290)	12q21	NPHP	JBTS, MKS	ATF4, nephrocystin-5, CC2D2A
NPHP7/GLIS2	16p	NPHP	—	—

(nephrocystin-7/GLIS2)				
NPHP8/RPGRIP1L (nephrocystin-8/RPGRIP1L)	16q	NPHP	JBTS, MKS	Nephrocystin-1
NPHP9/NEK8 (nephrocystin-9/NEK8)	17q11	Infantile NPHP	—	—
NPHP10/SDCCAG8 (nephrocystin-10/SDCCAG8)	1q43	Juvenile NPHP	RP (SLS), BBS-like	OFD1
TMEM67/MKS3/NPHP11 (nephrocystin-11/meckelin)	8q22.1	NPHP	JBTS, MKS, LF	MKS1, nephrocystin-1, nephrocystin-4, nephrocystin-6, nesprin-2, TMEM216
TTC21B//JBTS11/NPHP12 (nephrocystin-12/IFT139)	2q24.3	Early-onset NPHP, juvenile NPHP	JATD, MKS, JBTS, BBS-like	Ciliopathy modifier
WDR19/NPHP13 (nephrocystin-13/IFT144)	4p14	NPHP	JATD, SBS, CED, RP, Caroli, BBS-like	
ZNF423/NPHP14 (nephrocystin-14/ZNF423)	16q12.1	Infantile NPHP, PKD	JBTS, situs inversus	PARP1, nephrocystin-6,
CEP164/NPHP15 (nephrocystin-15 centrosomal protein 164 kDa)	11q23.3	NPHP (8 years)	RP, JBTS, LF, obesity	ATRIP, CCDC92, TTBK2, nephrocystin-3, nephrocystin-4, Dvl3
ANKS6/NPHP16 (nephrocystin-16/ANKS6)	9q22.33	NPHP, PKD	LF, situs inversus, cardiovascular abnormalities	INVS, nephrocystin-3, NEK8, HIF1AN, NEK7, BICC1
IFT172/NPHP17 (nephrocystin-17/IFT172)	2p23.3	NPHP	JATD, MZSDS, JBTS	IFT140, IFT80
CEP83/NPHP18 (nephrocystin-18/centrosomal protein 83 kDa)	12q22	Early-onset NPHP (3 yr)	Learning disability, hydrocephalus, LF	CEP164, IFT20
NPHP1L/XPNPEP3 (nephrocystin-1L/XPNPEP3)	22q13	NPHP	Cardiomyopathy, seizures	Cleaves LRRC50, ALMS1, nephrocystin-6
NPHP2L/SLC41A1 (nephrocystin-2L/SLC41A1)	1q32.1	NPHP	Bronchiectasis	

ATF4, activating transcription factor 4; APC2, anaphase-promoting complex 2; BCAR1, breast cancer antiestrogen resistance 1; CAD, cranioectodermal dysplasia; CC2D2A, coiled-coil and C2 domain containing 2A; CHD, congenital heart disease; JATD, Jeune asphyxiating thoracic dysplasia; JBTS, Joubert syndrome; LF, liver fibrosis; MKS, Meckel-Gruber syndrome; OMA, oculomotor apraxia; PTK2B, protein tyrosine kinase 2B; RP, retinitis pigmentosa; RPGR, retinitis pigmentosa GTPase regulator; SBS, Sensenbrenner syndrome.

From Wolf MTF: Nephronophthisis and related syndromes, Curr Opin Pediatr 27:201-211, 2015, Table 1.

Pathogenesis and Pathology

The pathophysiology of chronic TIN is undefined, but data suggest that, in addition to abnormal cilia structure and function in JN and MCKD, it is immune mediated. Cells making up the interstitial infiltrate appear to be a combination of native interstitial cells, inflammatory cells recruited from the circulation, and resident tubular cells that undergo epithelial-mesenchymal transformation. Grossly, kidneys can appear pale and small for age. Microscopically, tubular atrophy and “dropout” with interstitial fibrosis and a patchy lymphocytic interstitial inflammation are seen. Patients with JN often have characteristic small cysts in the corticomedullary region. In primary chronic TIN, glomeruli are relatively spared until late in the disease course. Patients with chronic TIN secondary to a primary glomerular disease have histologic evidence of the primary disease. Chronic TIN due to cyclosporine or tacrolimus use is characterized by tubular atrophy, “stripe” interstitial fibrosis, and vascular sclerosis.

Clinical Manifestations

The clinical features of chronic TIN are often nonspecific and can reflect signs and symptoms of slowly progressive chronic renal insufficiency (see Chapter 550). Fatigue, growth failure, polyuria, polydipsia, and enuresis are often present. Anemia that is seemingly disproportionate to the degree of renal insufficiency is common and is a particularly prominent feature in JN. Because tubular damage often leads to renal salt wasting, significant hypertension is unusual. Fanconi syndrome, proximal renal tubular acidosis, distal renal tubular acidosis, and hyperkalemic distal renal tubular acidosis can occur.

Extrarenal manifestations of nephronophthisis include ophthalmic, neurologic, hepatic, and skeletal disorders (Table 539.3).

Table 539.3

Extrarenal Manifestations Associated With Nephronophthisis and Resulting Syndromes Associated With *NPHP* Mutations

DISORDER	SYNDROME
OPHTHALMOLOGIC	

Retinitis pigmentosa	Senior-Løken syndrome (SLSN)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Alstrom (RP, obesity, DM type 2, hearing impairment)
	RHYNS (RP, hypopituitarism, skeletal dysplasia)
Oculomotor apraxia	Cogan syndrome
Nystagmus	Joubert syndrome/Joubert syndrome–related disorders
Coloboma	Joubert syndrome/Joubert syndrome–related disorders
NEUROLOGIC	
Encephalocele	Meckel-Gruber syndrome (occipital encephalocele, NPHP)
Vermis aplasia	Joubert syndrome/Joubert syndrome–related disorders
Hypopituitarism	RHYNS (RP, hypopituitarism, skeletal dysplasia)
HEPATIC	
Liver fibrosis	Boichis syndrome
	Meckel-Gruber syndrome (occipital encephalocele, NPHP)
	Arima syndrome (cerebro-oculo-hepato-renal syndrome)
	Joubert syndrome/Joubert syndrome–related disorders
SKELETAL	
Short ribs	Jeune syndrome/asphyxiating thoracic dystrophy
Cone-shaped epiphysis	Mainzer-Saldino syndrome
Postaxial polydactyly	Joubert syndrome/Joubert syndrome–related disorders
	Bardet-Biedl syndrome (NPHP, RP, obesity, deafness)
	Ellis van Creveld
Skeletal abnormalities	Sensenbrenner syndrome/cranioectodermal dysplasia
	Ellis van Creveld
OTHERS	
Situs inversus	
Cardiac malformation	
Bronchiectasis	
Ulcerative colitis	

From Wolf MT, Hildebrandt F: Nephronophthisis, Pediatr Nephrol 26:181-194, 2011.

Diagnosis

The diagnosis is suggested by signs or symptoms of renal tubular damage such as polyuria and an elevated serum creatinine value, coupled with a history suggestive of a chronic disease, such as long-standing enuresis or the presence of anemia resistant to iron therapy. Radiographic studies, in particular ultrasonography, can give additional evidence of chronicity, such as small, echogenic kidneys, corticomedullary microcysts suggesting JN, or findings of obstructive uropathy. A vesicocystourethrogram can demonstrate the presence of vesicoureteral reflux or bladder abnormalities. If JN is suspected, a molecular diagnosis is available. In instances in which the cause is unclear, a renal biopsy may be performed. In cases of advanced disease, a renal biopsy might not be diagnostic. Many end-stage kidney diseases display a common histologic appearance of tubular fibrosis and inflammation.

Treatment and Prognosis

Therapy is directed at maintaining the fluid and electrolyte balance and avoiding further exposure to nephrotoxic agents. Patients with obstructive uropathies can require salt supplementation and treatment with potassium-binding resin (Kayexalate). Prevention of infection by antibiotic prophylaxis can slow the progression of renal damage in appropriate patients. The prognosis in patients with chronic TIN depends in large part on the nature of the underlying disease. Patients with obstructive uropathy or vesicoureteral reflux can have a variable degree of renal damage and thus a variable course. ESRD can develop over months to years. Patients with JN uniformly progress to ESRD by adolescence. Patients with metabolic disorders can benefit from treatment when available.

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539.3

Papillary Necrosis

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Keywords

acute kidney injury
drug-induced kidney disease
renal papillary necrosis

Renal papillary necrosis (RPN) is a descriptive term applied to conditions that result in necrosis of the renal medullary pyramids and papillae. The hypoxic and hypertonic environment that normally prevails in the renal medullary region renders it especially vulnerable to ischemic necrosis. Common precipitating factors in children include shock, hypovolemia, hypoxia, pyelonephritis, urinary tract obstruction, and sickle cell hemoglobinopathies, Analgesic abuse and diabetes mellitus are additional important causes in adults. RPN can result in secondary infection, deposition of stones, and sloughing of papillae with resultant urinary tract obstruction. Both an acute progressive clinical course and a more chronic protracted form have been described. Patients most commonly present with flank pain and hematuria. Radiologic studies are key to establishing the diagnosis. Management is directed toward treating the underlying cause, ameliorating renal ischemia with hydration, and surgical relief of obstruction.

Pathogenesis and Pathology

RPN may be focal (involving only the papillary tips) or diffuse (involving the whole papilla and the innermost areas of the medulla). RPN may affect a single papilla or multiple papillae. Histologically, the tissue typically reveals classic coagulative necrosis, surrounded by an inflammatory response.

Even under normal conditions, the medullary region of the kidney subsists on a hypoxic precipice owing to low blood flow and countercurrent exchange of oxygen, although paradoxically housing nephron segments with very high energy requirements. The blood flow decreases even further as one approaches the innermost regions of the medulla and becomes marginal toward the apex and tips of the papillae. The already compromised blood supply is further attenuated in several pathophysiologic states, including the hypoxia from shock and dehydration, the intraluminal stasis of sickle cell nephropathy, the inflammation of pyelonephritis, the increased pressure of urinary tract obstruction, the microvascular changes of diabetes, and the direct damage from analgesics (including nonsteroidal antiinflammatory drugs). Approximately 15–30% of patients with sickle cell disease will encounter episodes of RPN during their lifetime.

Clinical Manifestations

The classic presentation of acute RPN is flank pain and renal colic, gross hematuria with clots and tissue debris, and fever with chills. Acute kidney injury, an increase in the serum creatinine, and oliguria are not common but may accompany the rapidly progressive form. Patients with the chronic indolent form may be asymptomatic, and may first present with the passage of sloughed papillae in the urine.

Diagnosis

The diagnosis of RPN is usually based on the history, clinical presentation, laboratory findings, and radiologic investigations. Contrast-enhanced CT scanning is the imaging modality of choice. In the acute phase, this method depicts several typical features, including clefts in the medulla, pelvic filling defects, nonenhanced lesions surrounded by rings of excreted material, medullary calcifications, and the presence of obstruction. If intravenous contrast is contraindicated, CT scanning without contrast or renal ultrasonography may be performed. These modalities are now replacing intravenous urography, which was the imaging method of choice in the past.

Treatment and Prognosis

Treatment of acute RPN starts with ameliorating the renal ischemia with intravenous hydration. In addition, it is important to treat the underlying cause, including appropriate medical management of shock, sepsis, pyelonephritis, or sickle cell disease. Cessation of any analgesics (including nonsteroidal antiinflammatory drugs) is critical. Patients with acute obstruction may require surgical intervention for relief.

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539.4

Acute Tubular Necrosis

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Keywords

acute kidney injury
acute renal failure
acute tubular necrosis
oliguria

Acute tubular necrosis (ATN) is a descriptive term applied to conditions that result in necrosis of the renal tubular epithelial cells. The hypoxic environment that normally prevails in the renal medullary region renders its nephron segments especially vulnerable to necrotic cell death. ATN frequently coexists with other forms of cell death, as well as cellular regeneration. Common precipitating factors in children include prolonged renal ischemia, sepsis, shock, hypovolemia, and nephrotoxic medications. ATN is the most common cause of **intrinsic acute kidney injury (AKI)** (see Chapter 550). ATN is clinically characterized by a rapid (within hours to days) decline in kidney function that leads to retention of waste products such as BUN and creatinine, fluid overload, and reduced urine output in many cases. Patients with hospital-acquired ATN frequently have no specific symptoms, and the diagnosis requires a high index of suspicion in predisposed individuals. Laboratory tests and radiologic studies are the key to establishing the diagnosis. Management is directed toward treating the underlying or precipitating cause, correction of imbalances in fluid, electrolyte, and acid-base status, avoidance of nephrotoxic medications, and treatment of complications.

Pathogenesis and Pathology

The pathologic findings are highly variable, depending on the etiology and the region of the kidney affected. In children with predominantly ischemic ATN, necrosis is relatively inconspicuous, whereas it is more widespread in nephrotoxic ATN. Because the medullary region of the kidney (including the straight segment of the proximal tubule and the medullary thick ascending limb of Henle's loop) normally subsists in a hypoxic environment owing to low blood flow and countercurrent exchange of oxygen, these nephron segments are usually the most severely affected. Typical findings include patchy areas of tubule cell necrosis with resultant loss of tubule epithelial cells and exposure of denuded basement membrane. Other forms of cell death, including apoptosis, necroptosis, and ferroptosis, occur simultaneously. Surviving proximal tubule cells show diffuse effacement and loss of the brush border and apical blebs. The distal nephron segments exhibit tubular dilatation with intraluminal casts. There is concomitant evidence for cellular regeneration and repair among freshly damaged tubule epithelial cells. Injury is aggravated by several pathophysiologic states, including the ischemia from sepsis, shock, and dehydration and the direct damage from nephrotoxic medications.

The significant decline in kidney function is often out of proportion to the observed patchy histologic changes. In addition to tubule cell necrosis, several other factors contribute to the decline in the glomerular filtration rate (GFR). First, a single collecting tubule drains multiple nephrons, such that obstruction of even a small number of collecting tubules results in failure of filtration from several nephrons. Second, obstruction aggravates the backflow of filtered tubular fluid into the vascular space across the denuded epithelium. Third, loss of the proximal tubular reabsorptive capacity results in increased delivery of sodium chloride to the macula densa, with activation of the tubuloglomerular feedback mechanisms that worsens the afferent arteriolar constriction. Fourth, many additional factors contribute to the pathogenesis of ATN, including changes in the microvascular blood flow, endothelial damage, and the activation of inflammatory pathways.

The pathophysiology and clinical course of ATN may be divided into three sequential phases, namely, initiation, maintenance, and recovery. The initiation phase occurs during the initial exposure to ischemia or nephrotoxins. Tubule cell damage begins to evolve, and the sloughed tubular cell debris results in obstruction of the tubular lumen. The combination of hypoperfusion and obstruction to the tubular fluid flow results in a fall in the GFR and urine output and a rise in serum creatinine levels. During the maintenance phase of ATN, renal tubule injury is established at its highest severity, the GFR and urine output become stabilized at a very low level, and the BUN and serum creatinine peak. It should be noted that ATN due to nephrotoxic medications is typically nonoliguric. This phase typically lasts for 1-2 wk but may extend to several weeks. Complications (e.g., metabolic, fluid, and electrolyte imbalances) typically occur during this phase. The recovery phase, also called the diuretic phase, is characterized by regeneration of lost tubule epithelial cells, repair of sublethally injured cells, and removal of intratubular casts by reestablishment of tubular fluid flow. It is clinically heralded by polyuria and a slow recovery of the GFR. Diuresis occurs because the rapidly increasing GFR precedes the complete recovery of the tubule cell structure and function, and can result in volume depletion if not recognized and treated promptly.

The most prevalent causes of ATN in neonates and older children are shown in Tables 539.4 and 539.5 , respectively.

Table 539.4

Prevalent Causes of Acute Tubular Necrosis in Neonates

MECHANISM	CAUSES
Ischemia	Perinatal asphyxia, respiratory distress syndrome, hemorrhage, congenital heart disease, sepsis, shock
Exogenous toxins	Aminoglycosides, maternal ingestion of angiotensin-converting enzyme inhibitors or nonsteroidal antiinflammatory drugs
Endogenous toxins	Hemoglobin (hemolysis), myoglobin (seizures)
Primary kidney disease	Renal vein thrombosis, renal artery thrombosis, polycystic kidney disease

Table 539.5

Prevalent Causes of Acute Tubular Necrosis in Older Children

Prevalent Causes of Acute Tubular Necrosis in Older Children

MECHANISM	CAUSES
Ischemia	Severe dehydration, hemorrhage, shock, sepsis, burns, major surgery, severe cardiac disease, prolonged cold ischemia time in kidney transplant
Exogenous toxins	Aminoglycosides, cisplatin, contrast agents, cyclosporine, tacrolimus, angiotensin-converting enzyme inhibitors, nonsteroidal antiinflammatory drugs
Endogenous toxins	Hemoglobin (hemolysis, extracorporeal circulation), myoglobin (crush injuries, seizures, influenza)
Primary kidney disease	Hemolytic-uremic syndrome, crescentic glomerulonephritis

Clinical Manifestations

ATN is largely asymptomatic, and the clinical diagnosis depends on having a high index of suspicion in children with etiologic risk factors. ATN most frequently manifests with a progressive accumulation of fluid, a serial elevation in the BUN and serum creatinine, and a reduction in urine output, in a predisposed patient who has been exposed to either ischemic or nephrotoxic injury. The evaluation requires a complete history directed toward the known causes of ATN, physical examination, laboratory testing, and renal imaging. A detailed history of all ingested drugs and medications is especially important. Although ATN is technically a histologic diagnosis, kidney biopsies are only rarely performed in children with this condition.

Signs of ATN on physical examination include edema, hypertension, and evidence of heart failure. Children with intravascular volume depletion exhibit tachycardia, hypotension, decreased skin turgor, and dry mucous membranes.

Diagnosis

The diagnosis of ATN is aided by laboratory findings and radiologic investigations. A freshly voided urine is typically positive for blood and protein, and microscopy reveals red blood cells and broad, muddy-brown granular casts. Heme-positive urine in the absence of red blood cells in the sediment should raise the suspicion for hemolysis or rhabdomyolysis. In ATN, the impaired renal reabsorptive and concentrating capacity typically results in a low urine specific gravity and a high urinary sodium and fractional excretion of sodium. The hallmark of ATN is a progressive increase in the serum creatinine and BUN. A mild-to-moderate anemia is common due to dilution and decreased erythropoiesis. A high anion gap metabolic acidosis results from impaired renal excretion of acids and decreased tubular reabsorption of bicarbonate. Several electrolyte disturbances may be encountered, including hyponatremia, hyperkalemia, hyperphosphatemia, hypocalcemia, and hypomagnesemia. If rhabdomyolysis is suspected, the diagnosis can be confirmed by the detection of urine myoglobin and elevated levels of serum creatine kinase. The diagnosis of nephrotoxicity may be aided by the determination of serum drug levels. Renal ultrasonography in ATN typically reveals enlarged echogenic kidneys. Prolonged severe ATN results in renal cortical necrosis and a reduction in kidney size.

Treatment and Prognosis (see also Chapter 550.1)

Treatment of ATN starts with ameliorating the renal ischemia by restoring and maintaining the intravascular volume with intravenous hydration. In addition, it is important to treat the underlying cause, including with appropriate medical management of shock, sepsis, or cardiac disease. Cessation of any potential nephrotoxic agent (including nonsteroidal antiinflammatory drugs) is critical. Dosages of all medications should be chosen based on the estimated GFR. Children with oliguria and volume overload may require fluid restriction and the judicious use of furosemide. Although furosemide can convert the clinical picture from an oliguric to a nonoliguric one (which can facilitate medical management), there is little evidence that it changes the course of ATN. Children with established ATN may not respond to furosemide and are at higher risk for ototoxicity. Common indications for dialysis in ATN include fluid overload that is unresponsive to diuretics or is a hindrance to the provision of adequate nutrition, hyperkalemia unresponsive to medical management, symptomatic acid-base imbalances, and refractory hypertension.

In the absence of multiorgan failure, most children with ATN eventually regain renal function to a large extent. In the context of severe multiorgan dysfunction, renal recovery is limited and morbidity and mortality rates remain high. Patients who recover from severe ATN remain at risk for subsequently developing chronic kidney disease.

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CHAPTER 540

Vascular Diseases Associated with Hematuria

540.1

Vascular Abnormalities

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Keywords

angiomyoma
arteriovenous malformations
hemangioma
nutcracker syndrome

Hemangiomas, hemangiolymphangiomas, angiomyomas, and arteriovenous malformations of the kidneys and lower urinary tract are rare causes of hematuria. It can present clinically with microscopic hematuria or gross hematuria with clots. When associated cutaneous vascular malformations are present, they can offer a clue to these underlying causes of hematuria. **Angiomyolipomas,** the most common benign solid tumors of the kidney, are composed of vascular, smooth muscle, and fatty tissue elements. They can rupture on occasion to cause severe hemorrhage. Angiomyolipomas are an important component of the **tuberous sclerosis complex** (see Chapter 614.2), which includes developmental delay, facial angiofibromas, and lung cysts. Renal colic can develop with any upper tract vascular abnormality that obstructs urinary drainage, induces an inflammatory response, or distends the renal capsule. The diagnosis may be confirmed by angiography or endoscopy.

Unilateral bleeding of varicose veins of the left ureter, resulting from compression of the left renal vein between the aorta and superior mesenteric artery (mesoaortic compression), is referred to as the **nutcracker syndrome.** Patients with this syndrome typically present with persistent microscopic hematuria (and, occasionally, recurrent gross hematuria) that may be accompanied by proteinuria, left lower abdominal pain, left flank pain, or orthostatic hypotension. The diagnosis requires a high degree of suspicion and is confirmed by Doppler ultrasonography, CT scanning, phlebography of the left renal vein, or MRI.

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540.2

Renal Vein Thrombosis

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Keywords

hypercoagulable states
nephrotic syndrome complications
renal vein thrombosis

Epidemiology

Renal vein thrombosis (RVT) occurs in two distinct clinical settings: (1) In newborns and infants, RVT is commonly associated with asphyxia, dehydration, shock, sepsis, congenital hypercoagulable states, central venous catheters, and maternal diabetes or preeclampsia. (2) In older children, RVT is seen in patients with nephrotic syndrome, cyanotic heart disease, inherited hypercoagulable states, sepsis, following kidney transplantation, and following exposure to angiographic contrast agents.

Pathogenesis

RVT begins in the intrarenal venous circulation and can then extend to the main renal vein and even the inferior vena cava. Thrombus formation is mediated by endothelial cell injury resulting from hypoxia, endotoxin, or contrast media. Other contributing factors include hypercoagulability from either nephrotic syndrome or mutations in genes that encode clotting factors (e.g., deficiencies of protein C, protein S, antithrombin, and factor V Leiden); hypovolemia and decreased venous blood flow associated with septic shock, dehydration, or nephrotic syndrome; and intravascular sludging caused by polycythemia.

Clinical Manifestations

The development of RVT is classically heralded by the sudden onset of gross hematuria and unilateral or bilateral flank masses. However, patients can also present with any combination of microscopic hematuria, flank pain, hypertension, or a microangiopathic hemolytic anemia with thrombocytopenia or oliguria. RVT is usually unilateral. Bilateral RVT results in acute kidney injury.

Diagnosis

The diagnosis of RVT is suggested by the development of hematuria and flank masses in patients seen in the high-risk clinical settings or with the predisposing clinical features noted above. Ultrasonography shows marked renal enlargement, and radionuclide studies reveal little or no renal function in the affected kidney(s). Doppler flow studies of the inferior vena cava and renal vein are essential to confirm the diagnosis. Contrast studies should be avoided to minimize the risk of further vascular damage.

Differential Diagnosis

The differential diagnosis of RVT includes other causes of hematuria that are associated with rapid development of microangiopathic hemolytic anemia or enlargement of the kidney(s). These include hemolytic-uremic syndrome, hydronephrosis, polycystic kidney disease, Wilms tumor, and intrarenal abscess or hematoma. All patients with RVT should be evaluated for congenital and acquired hypercoagulable states.

Treatment

The primary treatment of RVT starts with aggressive supportive intensive care, including correction of fluid and electrolyte imbalance and treatment of renal insufficiency. Recommendations include additional initial treatment of bilateral RVT with tissue plasminogen activator and unfractionated heparin followed by continued anticoagulation with unfractionated or low-molecular-weight heparin. Treatment recommendations for unilateral RVT with inferior vena cava extension include either unfractionated or low-molecular-weight heparin. There is no consensus as to whether unilateral RVT without extension should be managed with heparin or with supportive therapy alone. Aggressive treatment with thrombolytic agents in all of these clinical settings, as well as antithrombotic prevention of patients with documented thrombotic risk, remains controversial despite such recommendations given the significant risks of bleeding. Evidence-based data, particularly in children, do not exist despite such best-practice recommendations. Children with severe hypertension secondary to RVT who are refractory to antihypertensive medications may require nephrectomy.

Prognosis

Perinatal mortality rates from RVT have decreased significantly over the past 20 yr. Partial or complete renal atrophy is a common sequela of RVT in the neonate, leading to an increased risk of renal insufficiency, renal tubular dysfunction, and systemic hypertension. These complications are also seen in older children. However, recovery of renal function is not uncommon in older children with RVT resulting from nephrotic syndrome or cyanotic heart disease with correction of the underlying etiology. Long-term follow-up of infants and children with RVT by pediatric nephrologists is recommended for the monitoring of kidney function and the early detection of hypertension and chronic kidney disease

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540.3

Sickle Cell Nephropathy

Prasad Devarajan

Keywords

sickle cell disease
sickle cell trait

Gross or microscopic hematuria may be seen in children with sickle cell disease or sickle trait. Hematuria tends to resolve spontaneously in the majority of children. Clinically apparent renal involvement occurs more commonly in patients with sickle cell disease than in those with sickle cell trait with the exception of an association with renal cell carcinoma, which is more common in sickle cell trait.

Etiology

The renal manifestations of sickle cell nephropathy (SSN) are generally related to microthrombosis secondary to sickling in the relatively hypoxic, acidic, hypertonic renal medulla, where vascular stasis is normally present. Analgesic use, volume depletion with consequent prerenal failure, infection, and iron-related hepatic disease are independent contributing factors. Glomerular hyperfiltration, mediated by the intrarenal production of prostaglandins and synthesis of nitric oxide, is involved in the pathogenesis of proteinuria and kidney failure in SSN.

Pathology

Ischemia, papillary necrosis, and interstitial fibrosis are common pathologic findings in SSN. The specific sickle cell glomerular lesion consists of glomerular hypertrophy, with glomerulomegaly and distended capillaries. In addition, a variety of glomerular lesions are also found in SSN; most commonly these include focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and thrombotic microangiopathy. The pathophysiology of these specific glomerulonephritic lesions in SSN is poorly understood.

Clinical Manifestations

Clinical manifestations of SSN include polyuria caused by a urinary concentrating defect, renal tubular acidosis, and proteinuria associated with the glomerular lesions noted above.

Approximately 20–30% of patients with sickle cell disease develop proteinuria. Nephrotic-range proteinuria with or without clinically apparent nephrotic syndrome occurs in up to 30% of patients with SSN, and when present generally heralds progressive renal failure.

Treatment

Tubular manifestations have no specific treatment other than those recommended generally for patients with sickle cell disease. However, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor inhibitors can be used to reduce the urine protein excretion in patients with daily amounts exceeding 500 mg, and may slow the progression of renal failure. Gross hematuria secondary to papillary necrosis may respond to treatment with ε-aminocaproic acid or desmopressin acetate. Hydroxyurea and newer treatments for sickle cell disease (see Chapter 489.1) have decreased the manifestations of SSN in proportion to the other complications of the primary hemoglobinopathy.

Prognosis

SSN can eventually lead to hypertension, renal insufficiency, and progressive kidney failure. Dialysis and eventual kidney transplantation are successful treatment modalities when kidney failure is irreversible.

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540.4

Idiopathic Hypercalciuria

Prasad Devarajan

Keywords

crystalluria
kidney stones
hematuria

Idiopathic hypercalciuria, which may be inherited as an autosomal dominant disorder, can clinically present as recurrent gross hematuria, persistent microscopic hematuria, dysuria, crystalluria, or abdominal pain with or without kidney stone formation. Hypercalciuria can also accompany conditions resulting in hypercalcemia, such as hyperparathyroidism (see Chapter 591), vitamin D intoxication, immobilization, and sarcoidosis (see Chapter 190). Hypercalciuria may be associated with Cushing syndrome (see Chapter 597), corticosteroid therapy, tubular dysfunction secondary to Fanconi syndrome as occurs with Wilson disease (see Chapter 384.2), oculocerebrorenal syndrome, William syndrome, distal renal tubular acidosis, or Bartter syndrome (see Chapter 549.1). Hypercalciuria may also be seen in patients with Dent disease, which is an X-linked form of nephrolithiasis associated with hypophosphatemic rickets. Although microcrystal formation with consequent tissue irritation is believed to mediate symptoms, the precise mechanism by which hypercalciuria causes hematuria or dysuria is unknown.

Diagnosis

Hypercalciuria is diagnosed by a 24-hr urinary calcium excretion > 4 mg/kg. A screening test for hypercalciuria may be performed on a random urine specimen by measuring the calcium and creatinine concentrations. A spot urine calcium:creatinine ratio (mg/dL:mg/dL) > 0.2 suggests hypercalciuria in an older child. Normal ratios may be as high as 0.8 in infants < 7 mo of age.

Treatment

Left untreated, hypercalciuria leads to nephrolithiasis in approximately 15% of cases. Hypercalciuria has also been associated with an increased risk for development of low bone mineral density, as well as an increased incidence of urinary tract infections. Idiopathic hypercalciuria has been identified as a risk factor in 40% of children with kidney stones, and a low urinary citrate level has been associated as a risk factor in approximately 38% of this group. Oral thiazide diuretics can normalize urinary calcium excretion by stimulating calcium reabsorption in the proximal and distal tubules. Such therapy can lead to the resolution of gross hematuria or dysuria and can prevent nephrolithiasis. The precise indications for thiazide treatment (including its duration if initiated) remain controversial.

In patients with persistent gross hematuria or dysuria, therapy is initiated with hydrochlorothiazide at a dose of 1-2 mg/kg/24 hr as a single morning dose. The dose is titrated upward until the 24-hr urinary calcium excretion is < 4 mg/kg and clinical manifestations resolve. After 1 yr of treatment, hydrochlorothiazide is usually discontinued, but it may be resumed if gross hematuria, nephrolithiasis, or dysuria recurs. During hydrochlorothiazide therapy, the serum potassium level should be monitored periodically to avoid hypokalemia. Potassium citrate at a dose of 1 mEq/kg/24 hr may also be beneficial, particularly in patients with low urinary citrate excretion, a low urine pH, and symptomatic dysuria or crystalluria.

Sodium restriction is important because urinary calcium excretion parallels sodium excretion. Importantly, *dietary calcium restriction is not recommended* (except in children with a massive calcium intake > 250% of the recommended dietary allowance by dietary history) because calcium is a critical requirement for growth, and no evidence supports a relationship between decreased calcium intake and decreased urinary calcium levels. This is particularly important given the association of hypercalciuria in some patients with reduced bone mineral density. A number of uncontrolled, small-scale studies support a role for bisphosphonate therapy, which leads to a reduction in urinary calcium excretion and improvement in bone mineral density. Controlled studies are necessary to establish a clear role for such therapy in children with hypercalciuria.

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540.5

Nephrocalcinosis

See Chapter 562 .

CHAPTER 541

Anatomic Abnormalities Associated With Hematuria

541.1

Congenital Anomalies

Prasad Devarajan

Gross or microscopic hematuria may be associated with many different types of malformations of the urinary tract. The sudden onset of gross hematuria after minor trauma to the flank is often associated with ureteropelvic junction obstruction, cystic kidneys, or enlarged kidneys from any cause (see Chapter 555).

541.2

Autosomal Recessive Polycystic Kidney Disease

Prasad Devarajan

Keywords

end-stage renal disease
fibrocystin
infantile polycystic disease
Potter syndrome

Autosomal recessive polycystic kidney disease (ARPKD) (also known as ARPKD-congenital hepatic fibrosis [CHF]) is an autosomal recessive disorder occurring with an incidence of 1 : 10,000 to 1 : 40,000 and a gene carrier rate in the general population of 1/70. The gene for ARPKD *(PKHD1 [polycystic kidney and hepatic disease 1])* encodes fibrocystin, a large protein (>4,000 amino acids) with multiple isoforms.

Pathology

Both kidneys are markedly enlarged and grossly show innumerable small cysts throughout the cortex and medulla. Microscopic studies demonstrate dilated, ectatic collecting ducts radiating from the medulla to the cortex. The development of progressive interstitial fibrosis and tubular atrophy during the advanced stages of the disease eventually leads to renal failure. ARPKD causes dual-organ disease; hence, the term *ARPKD/congenital hepatic fibrosis*. Liver involvement is characterized by a basic ductal plate abnormality that leads to bile duct proliferation and ectasia, as well as progressive hepatic fibrosis.

Pathogenesis

Fibrocystin may form a multimeric complex with proteins of other primary genetic cystic diseases. It appears that altered intracellular signaling from these complexes, located at epithelial apical cell surfaces, intercellular junctions, and basolateral cell surfaces in association with the focal adhesion complex, is a critical feature of the disease pathophysiology.

Over 300 mutations in *PKHD1* (without identified specific hot spots) cause disease, and the same mutation can give variable degrees of disease severity in the same family. This clinical observation is consistent with preclinical data demonstrating many environmental and unknown genetic factors affecting disease expression. The false-negative rate for genetic diagnosis is approximately 10%. Limited available information suggests only a gross genotype–phenotype correlation: mutations that modify fibrocystin appear to cause less-severe disease than those that truncate fibrocystin.

Clinical Manifestations

The diagnosis is often made antenatally by the demonstration of oligohydramnios and bilateral enlarged kidneys on prenatal ultrasound. The typical infant presents with bilateral flank masses during the neonatal period or in early infancy. ARPKD may be associated with respiratory distress and spontaneous pneumothorax in the neonatal period. Perinatal demise (25–30%) appears to be associated with truncating mutations. Components of the **oligohydramnios complex (Potter syndrome),** including low-set ears, micrognathia, flattened nose, limb-positioning defects, and intrauterine growth restriction, may be present at death from pulmonary hypoplasia. Respiratory distress may also be secondary to large kidneys that compromise the diaphragm function. Hypertension is usually noted within the first few weeks of life, is often severe, and requires aggressive multidrug therapy for control. Oliguria and acute renal failure are uncommon, but transient hyponatremia, often in the presence of acute renal failure, often responds to diuresis. Renal function is usually impaired but may be initially normal in 20–30% of patients. Approximately 50% of patients with a neonatal-perinatal presentation develop end-stage renal disease (ESRD) by age 10 yr.

ARPKD is increasingly recognized in infants (and, rarely, in adolescents and young adults) with a mixed renal-hepatic clinical picture. Such children and young adults often present with predominantly hepatic manifestations in combination with variable degrees of renal disease. **Hepatic fibrosis** manifests as portal hypertension, hepatosplenomegaly, gastroesophageal varices, episodes of ascending cholangitis, prominent cutaneous periumbilical veins, reversal of portal vein flow, and thrombocytopenia. Congenital hepatic fibrosis may manifest with cholangiodysplastic changes or a frank Caroli type with marked intrahepatic bile duct dilation, affecting the whole liver or just one segment; biliary tract disease increases the risk of ascending cholangitis. Renal findings in patients with a hepatic presentation may range from asymptomatic abnormal renal ultrasonography to systemic hypertension and renal insufficiency. In the newborn, clinical evidence of liver disease by radiologic or clinical laboratory assessment is present in approximately 50% of children and believed to be universal by microscopic evaluation. Natural history studies of ARPKD patients presenting as infants and young children have classified this group in terms of the severity of their dual-organ phenotype: 40% have the severe kidney/severe liver phenotype and 20% each have the severe kidney/mild liver, severe liver/mild kidney, and mild kidney/mild liver phenotype.

Diagnosis

The diagnosis of ARPKD is strongly suggested by bilateral palpable flank masses in an infant with pulmonary hypoplasia, oligohydramnios, and hypertension and the absence of renal cysts by sonography of the parents (Fig. 541.1). Markedly enlarged and uniformly hyperechogenic kidneys with poor corticomedullary differentiation are commonly seen on ultrasonography (Fig. 541.2). The diagnosis is supported by clinical and laboratory signs of hepatic fibrosis, pathologic findings of ductal plate abnormalities seen on liver biopsy, anatomic and pathologic proof of ARPKD in a sibling, or parental consanguinity. The diagnosis can be confirmed by genetic testing. The differential diagnosis includes other causes of bilateral renal enlargement and/or cysts, such as multicystic dysplasia, hydronephrosis, Wilms tumor, and bilateral renal vein thrombosis (Tables 541.1 and 541.2).

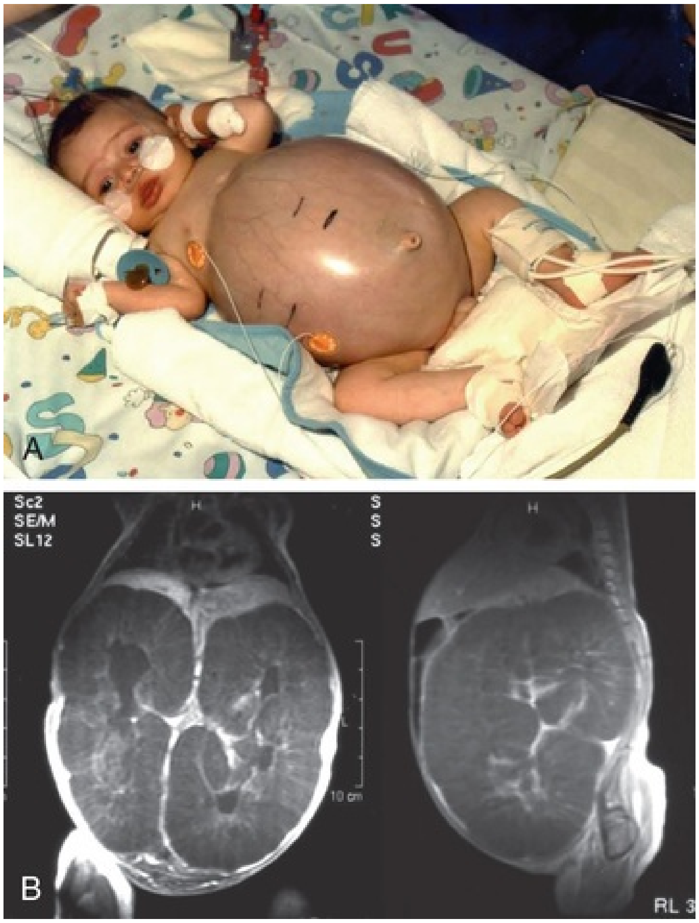

FIG. 541.1 A, Severe nephromegaly in a 3 mo old infant with autosomal recessive polycystic kidney disease, with x-rays (B). (From Bakkaloglu SA, Schaefer F: Disease of the kidney and urinary tract in children. In Skorecki K, Chertow GM, Marsden PA, et al. (eds): Brenner & Rector's the kidney, 10/e, Philadelphia, 2016, Elsevier, Fig. 74-6, p. 2320).

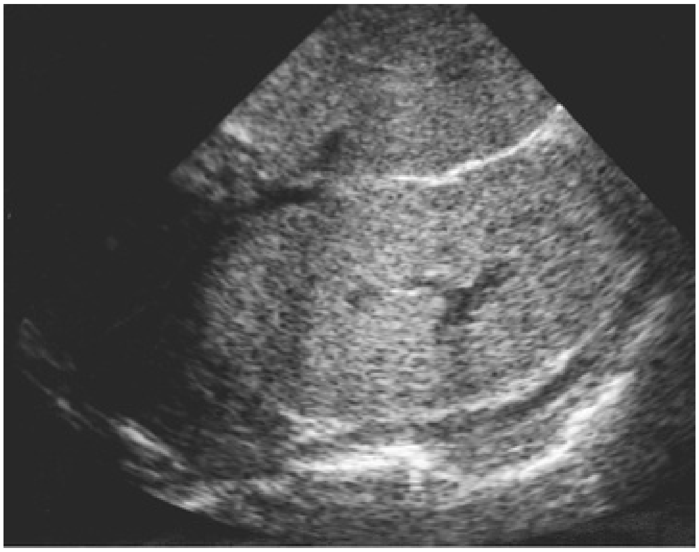

FIG. 541.2 Ultrasound examination of a neonate with autosomal recessive polycystic kidney disease demonstrating renal enlargement (9 cm) and increased diffuse echogenicity with complete loss of corticomedullary differentiation resulting from multiple small cystic interfaces.

Table 541.1

Comparison of Clinical Features of Cystic Kidney Diseases

DISEASE	INHERITANCE	FREQUENCY	GENE PRODUCT	AGE OF ONSET	CYST ORIGIN	RENOMEGA
ADPKD	AD	1:400-1,000	*PKD1* *PKD2*	20s and 30s; <2% before age 15 Occasional perinatal onset	Anywhere (including the Bowman capsule)	Yes
ARPKD	AR	1:6,000-10,000	*PKHD1*	First year of life; perinatal onset	Distal nephron, CD	Yes
ACKD	No	90% of ESRD patients at 8 yr	None	Years after onset of ESRD	Proximal and distal tubules	Rarely
Simple cysts	No	50% in those older than 40 yr	None	Adulthood	Anywhere (usually cortical)	No
Nephronophthisis	AR	1:80,000	Nephrocystins (NPHP1-9)	Childhood or adolescence	Medullary DCT	No
MCKD	AD	Rare	Uromodulin,	Adulthood	Medullary	No

			others		DCT	
MSK	No	1:5,000-20,000	None	30s	Medullary CD	No
Tuberous sclerosis	AD	1:10,000	Hamartin (TSC1) Tuberin (TSC2)	Childhood	Loop of Henle, DCT	Rarely
VHL syndrome	AD	1:40,000	VHL protein	20s	Cortical nephrons	Rarely
Oral-facial-digital syndrome	XD	1:250,000	OFD1 protein	Childhood or adulthood	Renal glomeruli	Rarely
Bardet-Biedl syndrome	AR	1:65,000-160,000	BBS 14	Adulthood	Renal calyces	Rarely

ACKD, acquired cystic kidney disease; AD, autosomal dominant; ADPKD, autosomal dominant polycystic kidney disease; AR, autosomal recessive; ARPKD, autosomal recessive polycystic kidney disease; CD, collecting duct; CNS, central nervous system; DCT, distal convoluted tubule; ESRD, end-stage renal disease; MCKD, medullary cystic kidney disease; MSK, medullary sponge kidney; UTI, urinary tract infection; VHL, von Hippel-Lindau; XD, X-linked dominant.

From Arnaout MA: Cystic kidney disease. In Goldman L, Schafer AI (eds): Goldman's Cecil medicine, 24/e, Philadelphia, 2012, Saunders, Table 129-1.

Table 541.2

Autosomal Recessive Polycystic Kidney Disease and Hepatorenal Fibrocystic Disease Phenocopies

DISEASE	GENE(S)	RENAL DISEASE	HEPATIC DISEASE	SYSTEMIC FEATURES
ARPKD	*PKHD1*	Collecting duct dilation	CHF; Caroli disease	No
ADPKD	*PKD1; PKD2*	Cysts along entire nephron	Biliary cysts; CHF (rare)	Yes: adults
NPHP	*NPHP1-NPHP16*	Cysts at the corticomedullary junction	CHF	+/−
Joubert syndrome and related disorders	*JBTS1-JBTS20*	Cystic dysplasia; NPHP	CHF; Caroli disease	Yes
Bardet-Biedl syndrome	*BBS1-BBS18*	Cystic dysplasia; NPHP	CHF	Yes
Meckel-Gruber syndrome	*MKS1-MKS10*	Cystic dysplasia	CHF	Yes
Oral-facial-digital	*OFD1*	Glomerular cysts	CHF (rare)	Yes

syndrome, type I				
Glomerulocystic disease	*PKD1; HNF1B; UMOD*	Enlarged; normal or hypoplastic kidneys	CHF (with PKD1 mutations)	+/−
Jeune syndrome (asphyxiating thoracic dystrophy)	*IFT80 (ATD2) DYNC2H1 (ADT3) ADT1, ADT4, ADT5*	Cystic dysplasia	CHF; Caroli disease	Yes
Renal-hepatic-pancreatic dysplasia (Ivemark II)	*NPHP3, NEK8*	Cystic dysplasia	Intrahepatic biliary dysgenesis	Yes
Zellweger syndrome	*PEX1-3;5-6;10-11;13;14;16;19;26*	Renal cortical microcysts	Intrahepatic biliary dysgenesis	Yes

CHF, congenital hepatic fibrosis; NPHP, nephronophthisis.

Modified from Guay-Woodford LM, Bissler JJ, Braun MC, et al: Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: report of an international conference, J Pediatr 165:611-617, 2014.

Nephronophthisis, an autosomal recessive disorder with renal fibrosis, tubular atrophy, and cyst formation, is a common cause of ESRD in children and adolescents (see Tables 541.1 and 541.2) (see also Chapter 539). Associated external findings include retinal degeneration (Senior-Loken syndrome), cerebellar ataxia (Joubert syndrome), and hepatic fibrosis (Boichis disease). Symptoms include polyuria (salt wasting, poor concentrating ability), failure to thrive, and anemia. Hypertension and edema are seen later when ESRD develops. Prenatal diagnostic testing using genetic linkage analysis or direct mutation analysis is available in families with a previously affected child.

Preimplantation genetic diagnosis with in vitro fertilization may avoid the birth of another affected child with ARPKD.

Treatment

The treatment of ARPKD is supportive. Aggressive ventilatory support is often necessary in the neonatal period secondary to pulmonary hypoplasia, hypoventilation, and the respiratory illnesses of prematurity. Careful management of hypertension (angiotensin-converting enzyme inhibitors, and other antihypertensive medications as needed), fluid and electrolyte abnormalities, osteopenia, and clinical manifestations of renal insufficiency are essential. Children with severe respiratory failure or feeding intolerance from enlarged kidneys can require unilateral or, more commonly, bilateral nephrectomies, prompting the need for renal replacement therapy. For many children approaching ESRD therapy, significant portal hypertension is present.

This in combination with the dramatic improvement in liver transplantation survival has led to consideration of dual renal and hepatic transplantation in a carefully selected group of patients. Dual transplantation thus avoids the later development of end-stage liver disease despite successful renal transplantation.

Prognosis

Mortality rates have improved dramatically, although approximately 30% of patients die in the neonatal period from complications of pulmonary hypoplasia. Neonatal respiratory support and renal replacement therapies have increased the 10-yr survival of children surviving beyond the first year of life to > 80%. The fifteen-year survival rate is currently estimated at 70–80%. Consideration of dual renal and hepatic transplantation and the development of disease-specific therapies for pediatric clinical trials will further positively impact the natural history of ARPKD. An important resource for families of patients is the ARPKD/CHF Alliance **(www.arpkdchf.org).**

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541.3

Autosomal Dominant Polycystic Kidney Disease

Prasad Devarajan

Keywords

intracranial aneurysms
polycystin

Autosomal dominant polycystic kidney disease (ADPKD), also known as adult-onset polycystic kidney disease, is the most common hereditary human kidney disease, with an incidence of 1/400 to 1/1,000. It is a systemic disorder with possible cyst formation in multiple organs (liver, pancreas, spleen, brain) and the development of saccular cerebral aneurysms.

Pathology

Both kidneys are enlarged and show large cortical and medullary cysts originating from all regions of the nephron.

Pathogenesis

Approximately 85% of patients with ADPKD have mutations that map to the *PKD1* gene on the short arm of chromosome 16, which encodes polycystin, a transmembrane glycoprotein. Another 10–15% of ADPKD mutations map to the *PKD2* gene on the long arm of chromosome 4, which encodes polycystin 2, a proposed nonselective cation channel. The majority of mutations appear to be unique to a given family. At present, a mutation can be found in 85% of patients with well-characterized disease. Approximately 8–10% of patients will have de novo, disease-causing mutations. Mutations of *PKD1* are associated with more severe renal disease than mutations of *PKD2* . The pathophysiology of the disease appears to be related to the disruption of normal multimeric cystoprotein complexes, with consequent abnormal intracellular signaling resulting in abnormal proliferation, tubular secretion, and cyst formation. Abnormal growth factor expression, coupled with low intracellular calcium and elevated cyclic adenosine monophosphate, appear to be important features leading to formation of cysts and progressive enlargement. Mutations in *GANAB* have been reported in *PKD1*- and *PKD2*- negative patients.

Clinical Presentation

The severity of renal disease and the clinical manifestations of ADPKD are highly variable. Symptomatic ADPKD most commonly occurs in the fourth or fifth decade of life. However, symptoms, including gross or microscopic hematuria, bilateral flank pain, abdominal masses, hypertension, and urinary tract infection, may be seen in neonates, children, and adolescents. With the increased utilization of abdominal sonography in the pediatric population, as well as ADPKD families requesting possible screening in their asymptomatic, at-risk offspring (with the passage of the Genetic Information Nondiscrimination Act in the United States), most children with ADPKD are diagnosed by abnormal renal sonography in the absence of symptoms. Renal ultrasonography usually demonstrates multiple bilateral macrocysts in enlarged kidneys (Fig. 541.3), although normal kidney size and unilateral disease may be seen in the early phase of the disease in children.

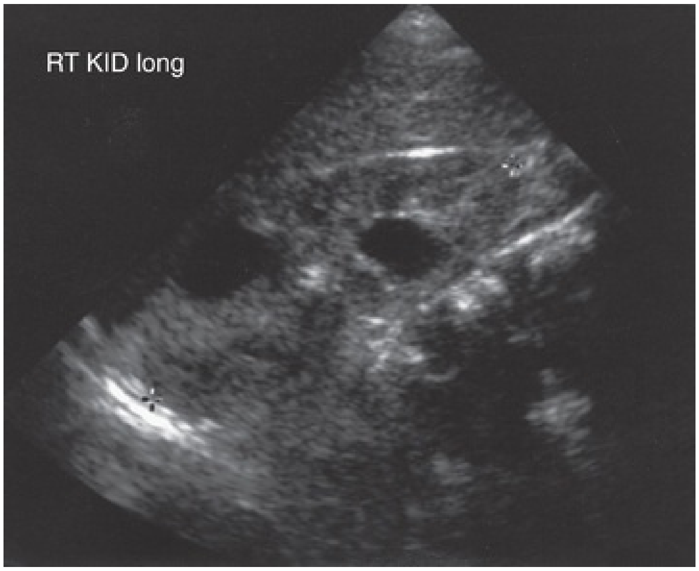

FIG. 541.3 Ultrasound examination of an 18 mo old boy with autosomal dominant polycystic kidney disease demonstrating renal enlargement (10 cm) and two large cysts.

ADPKD is a multiorgan disorder affecting many tissue types. Cysts may be asymptomatic but present within the liver, pancreas, spleen, and ovaries and when present help confirm the diagnosis in childhood. **Intracranial aneurysms,** which appear to segregate within certain families, have an overall prevalence of 15% and are an important cause of mortality in adults, but occasionally occur in children. Mitral valve prolapse is seen in approximately 12% of children; aortic and coronary artery aneurysms and aortic valve insufficiency are noted in affected adults. Hernias, bronchiectasis, and intestinal diverticula can also occur in these children.

Diagnosis

ADPKD is confirmed by the presence of enlarged kidneys with bilateral macrocysts in a patient with an affected first-degree relative. De novo mutations occur in 8–10% of patients with newly diagnosed disease. The diagnosis might be made in children before their affected parent, making parental renal sonography an important diagnostic test to be performed in families with no apparent family history. Among patients with genetically defined ADPKD, screening renal ultrasonography results may be normal in ≤ 20% by 20 yr of age and < 5% by 30 yr of age.

Prenatal diagnosis is suggested from the presence of enlarged kidneys with or without cysts on ultrasonography in families with known ADPKD. Prenatal DNA testing is available in families with affected members whose disease is caused by identified mutations in the *PKD1* or *PKD2* genes.

The differential diagnosis includes renal cysts associated with glomerulocystic kidney disease, tuberous sclerosis, and von Hippel-Lindau disease, which may be inherited in an autosomal dominant pattern (see Table 541.1). The neonatal manifestations of ADPKD and ARPKD may rarely be indistinguishable.

Treatment and Prognosis

Treatment of ADPKD is primarily supportive. Control of blood pressure is critical because the rate of disease progression in ADPKD correlates with the presence of hypertension. Angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists are agents of choice. Obesity, dietary salt and protein excess, caffeine ingestion, smoking, multiple pregnancies, and male gender appear to accelerate the disease progression. Older patients with a *family history of intracranial aneurysm rupture* should be screened for cerebral aneurysms.

Although neonatal ADPKD may be fatal, long-term survival of the patient and the kidneys is possible for children surviving the neonatal period. ADPKD that occurs initially in older children has a favorable prognosis, with normal renal function during childhood seen in > 80% of children. Pain may be a manifestation of infection, hemorrhage, cyst rupture, stones, or tumors and should be managed appropriately with pain medications and specifically based on its etiology.

Although disease-specific therapy is not yet available, clinical trials are in progress based on promising preclinical laboratory investigations. These potential therapies include renin–angiotensin blockade, vasopressin V_2 receptor antagonism (tolvaptan), and somatostatin analogues. A valuable resource for patients and their families is the Polycystic Kidney Disease Foundation (www.pkdcure.org).

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541.4

Trauma

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Keywords

rhabdomyolysis

Infants and children are more susceptible to renal injury following blunt or penetrating injury to the back or abdomen because of their decreased muscle mass “protecting” the kidney. Gross or microscopic hematuria, flank pain, and abdominal rigidity can occur; associated injuries may be present (see Chapter 82). In the absence of hemodynamic instability, most renal trauma can be managed nonoperatively. Urethral trauma can result from crush injury, often associated with a fractured pelvis or from direct injury. Such injury is suspected in the appropriate clinical setting when gross blood appears at the external urethral meatus. Rhabdomyolysis and consequent renal failure is another complication of crush injury that can be ameliorated by vigorous fluid resuscitation. There may be a relationship between microscopic hematuria and recreational accidents in individuals > 16 yr of age, none of whom exhibited hypotension or required surgical intervention.

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541.5

Renal Tumors

See Chapters 525 (Neuroblastoma) and 526 (Neoplasms of the Kidney).

CHAPTER 542

Lower Urinary Tract Causes of Hematuria

542.1

Infectious Causes of Cystitis and Urethritis

Prasad Devarajan

Gross or microscopic hematuria may be associated with bacterial, mycobacterial, or viral infections of the bladder (see Chapter 553).

542.2

Hemorrhagic Cystitis

Prasad Devarajan

Keywords

BK virus
cyclophosphamide
cystitis
hematuria
urinary tract infection

Hemorrhagic cystitis is defined as the presence of sustained hematuria and lower urinary tract symptoms (e.g., dysuria, frequency, urgency) in the absence of other bleeding conditions such as vaginal bleeding, a generalized bleeding condition, or a bacterial urinary tract infection. Depending on the severity, patients can present with microscopic or gross hematuria, often with clots. In severe forms, bleeding can lead to a significant decrease in blood hemoglobin levels and symptoms of lower urinary tract obstruction.

Hemorrhagic cystitis can occur in response to chemical toxins (cyclophosphamide, penicillins, busulfan, thiotepa, dyes, insecticides), viruses (adenovirus types 11 and 21 [see Chapter 289] and influenza A [see Chapter 285]), radiation, and amyloidosis. The polyoma BK virus (see Chapter 301) present latently in immunocompetent hosts, is associated with the development of drug-induced cystitis in immunosuppressed patients. The pediatric bone marrow transplantation population is particularly susceptible to hemorrhagic cystitis.

For chemical irritation related to the use of cyclophosphamide, hydration, bladder washes, and the use of mesna disulfide, which inactivates urinary cyclophosphamide metabolites, help to protect the bladder. Administration of oral cyclophosphamide in the morning followed by aggressive oral hydration throughout the remainder of the day is very effective in minimizing the risk of hemorrhagic cystitis. Treatment of hemorrhagic cystitis consists of a combination of intensive intravenous hydration, forced diuresis, analgesia, and spasmolytic drugs. Consultation with a urologist is recommended for more invasive measures if the cystitis does not respond to conservative measures. Gross hematuria associated with viral hemorrhagic cystitis usually resolves within 1 wk.

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542.3

Vigorous Exercise

Prasad Devarajan

Keywords

exercise-induced hematuria
post exertional hematuria
myoglobinuria
rhabdomyolysis
sports hematuria

Gross or microscopic hematuria can follow vigorous exercise. Exercise-induced hematuria is less common in females and can be associated with dysuria. Approximately 30–60% of runners completing marathons have dipstick-positive urine for blood. In limited follow-up, none appeared to have any significant urinary tract abnormalities. The color of the urine following vigorous exercise can vary from red to black. Blood clots may be rarely present in the urine. Findings on urine culture, intravenous pyelography, voiding cystourethrography, and cystoscopy are normal in most patients. This seems to be a benign condition, and the hematuria generally resolves within 48 hr after cessation of exercise. The absence of red blood cell casts or evidence of renal disease and the presence of dysuria and blood clots in some patients suggest that the source of bleeding lies in the lower urinary tract. **Rhabdomyolysis** with myoglobinuria or hemoglobinuria must be considered in the differential diagnosis when the condition is associated with symptoms in the appropriate clinical context. Hydronephrosis or other anatomic abnormalities must be considered in any child who presents with hematuria (particularly gross hematuria) after mild exercise or following mild trauma. Appropriate imaging studies are indicated in this setting.

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SECTION 3

Conditions Particularly Associated with Proteinuria

OUTLINE

Chapter 543 Clinical Evaluation of the Child With Proteinuria
Chapter 544 Conditions Associated With Proteinuria
Chapter 545 Nephrotic Syndrome

CHAPTER 543

Clinical Evaluation of the Child With Proteinuria

Francisco X. Flores

Normal Physiology

The charge and size selective properties of the glomerular capillary wall prevent significant amounts of albumin, globulin, and other large plasma proteins from entering the urinary space (see Chapter 535). Smaller proteins (low-molecular-weight proteins) do cross the capillary wall but are reabsorbed by the proximal tubule. A very small amount of protein that normally appears in the urine is the result of normal tubular secretion. The normally excreted protein mostly consists of Tamm-Horsfall protein (uromodulin), a protective glycoprotein secreted by the tubules that inactivates cytokines.

Pathophysiology of Proteinuria

Abnormal amounts of protein may appear in the urine from three possible mechanisms: **glomerular proteinuria,** which occurs as a result of disruption of the glomerular capillary wall; **tubular proteinuria,** a tubular injury or dysfunction that leads to ineffective reabsorption of mostly low-molecular-weight proteins; and **increased production of plasma proteins** —in multiple myeloma, rhabdomyolysis, or hemolysis—which may cause the production or release of very large amounts of protein that are filtered at the glomerulus and overwhelm the absorptive capacity of the proximal tubule.

Measurement of Urine Protein

Urine protein can be measured in random collected samples or in timed (e.g., 24 hr or overnight) samples. Tests to accurately quantify the urine protein concentration rely on precipitation with sulfosalicylic acid and measurement of turbidity (Table 543.1).

Table 543.1

Methods Available to Test for Proteinuria

METHOD	INDICATIONS	NORMAL RANGE	COMMENTS
Dipstick testing	Routine screening for proteinuria performed in the office	Negative or trace in a concentrated urine specimen (specific gravity: ≥1.020)	False-positive test can occur if urine is very alkaline (pH > 8.0) or very concentrated (specific gravity: >1.025)
24 hr urine for protein and creatinine[*] excretion	Quantitation of proteinuria (as well as creatinine clearances)	<100 mg/m^2 /24 hr or <150 mg/24 hr in a documented 24 hr collection	More accurate than spot urine analysis; inconvenient for patient; limited use in pediatric practice
Spot urine for protein/creatinine ratio—preferably on first morning urine specimen	Semiquantitative assessment of proteinuria	<0.2 mg protein/mg creatinine in children > 2 yr old <0.5 mg protein/mg creatinine in those 6–24 mo old	Simplest method to quantitate proteinuria; less accurate than measuring 24 hr proteinuria
Microalbuminuria	Assess risk of progressive glomerulopathy in patients with diabetes mellitus	<30 mg urine albumin per gram of creatinine on first morning urine	Therapy should be intensified in diabetics with microalbuminuria

[*] Note that in a 24 hr urine specimen, the creatinine content should be measured to determine whether the specimen is truly a 24 hr collection. The amount of creatinine in a 24 hr specimen can be estimated as follows: females, 15-20 mg/kg; males, 20-25 mg/kg.

Adapted from Hogg RJ, Portman RJ, Milliner D, et al: Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a Pediatric Nephrology Panel Established at the National Kidney Foundation Conference on Proteinuria, Albuminuria, Risk Assessment, Detection, and Elimination (PARADE), Pediatrics 105(6):1242-1249, 2000.

Urine Dipstick Measurement of Protein

The total protein concentration in urine can be estimated with chemically impregnated plastic strips that contain a pH-sensitive colorimetric indicator that changes color when negatively charged proteins, such as albumin, bind to it. Dipsticks primarily detect albuminuria and are less sensitive for other forms of proteins (low-molecular-weight proteins, Bence Jones protein, gamma globulins). Visual changes in the color of the dipstick are a semiquantitative measure of urinary protein concentration. The dipstick is reported as negative, trace (10-29 mg/dL), 1+ (30-100 mg/dL), 2+ (100-300 mg/dL), 3+ (300-1000 mg/dL), and 4+ (>1000 mg/dL). **False-positive** results can occur with a very high urine pH (>7.0), a highly concentrated urine specimen, contamination of the urine with blood, and the presence of pyuria or prolonged dipstick immersion. **False-negative** test results can occur in patients with a low urine pH (<4.5), dilute urine or a large volume of urine output, or in disease states in which the predominant urinary protein is not albumin.

Positive urine dipstick test for protein is considered to be present if there is more than a trace (10-29 mg/dL) in a urine sample in which the specific gravity is < 1.010. If the specific gravity is > 1.015, the dipstick must read ≥1+ (>30 mg/dL) to be considered clinically significant.

Because the dipstick reaction offers only a qualitative measurement of urinary protein excretion, children with persistent proteinuria should have proteinuria quantitated more precisely. **Timed (24 hr) urine collections** offer more precise information regarding urine protein excretion than a randomly performed dipstick test. Urinary protein excretion in the normal child is less than 100 mg/m^2 /day or a total of 150 mg/day. In neonates, normal urinary protein excretion is higher, up to 300 mg/m^2 , because of reduced reabsorption of filtered proteins. A reasonable upper limit of normal protein excretion in healthy children is 150 mg/24 hr. More specifically, normal protein excretion in children is defined as ≤ 4 mg/m^2 /hr; abnormal proteinuria is defined as excretion of 4-40 mg/m^2 /hr; and nephrotic-range proteinuria is defined as > 40 mg/m^2 /hr.

Timed urine collections are cumbersome to obtain, and the sensitivity and specificity of the test can be influenced by fluid intake, the volume of urine output, and the importance of including a complete collection without missed voids.

Urine Protein-to-Creatinine Ratio Measurement

Urine protein-to-creatinine ratio measurement of an untimed (spot) urine specimen has largely replaced timed urine collection. In children, urine protein-to-creatinine ratios have been shown to be significantly correlated with measurements of 24 hr urine protein and are useful to screen for proteinuria and to longitudinally monitor urine protein levels.

This ratio is calculated by dividing the urine protein concentration (mg/dL) by the urine creatinine concentration (mg/dL) to provide a simple measure. It should be ideally performed on a first morning voided urine specimen to eliminate the possibility of orthostatic (postural) proteinuria (see Chapter 544.2). A ratio of < 0.5 in children < 2 yr of age and < 0.2 in children > 2 yr of age suggests normal urinary protein excretion. A ratio greater than 2 suggests nephrotic-range proteinuria.

Clinical Considerations

The finding of proteinuria in children and adolescents in a single, non–first morning urine specimen is common, varying between 5% and 15%. The prevalence of persistent proteinuria on repeated testing is much less common. The challenge is to differentiate the child with proteinuria related to renal disease from the otherwise healthy child with transient or other benign forms of proteinuria. When proteinuria is detected it is important to determine if it is transient, orthostatic, or fixed in nature.

Microalbuminuria is defined as the presence of albumin in the urine above the normal level but below the detectable range of conventional urine dipstick methods. In adults, persistent microalbuminuria (defined as a urinary albumin excretion of 30-300 mg/g creatinine on at least 2-3 samples) is accepted as evidence of diabetic nephropathy and also a predictor of cardiovascular and renal disease. The mean level of urinary albumin excretion falls between 8 and 10 mg/g of creatinine in children > 6 yr of age. Similar to adults, microalbuminuria in children has been found to be associated with obesity and to predict, with reasonable specificity, the development of diabetic nephropathy in type 1 diabetes mellitus.

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CHAPTER 544

Conditions Associated With Proteinuria

544.1

Transient Proteinuria

Francisco X. Flores

Keywords

transient proteinuria

The majority of children found to have positive tests for protein on urinary dipsticks will have negative evaluations on repeated dipsticks and normal urinary protein if formally quantitated. Approximately 10% of children who undergo random urinalysis have proteinuria by a single dipstick measurement. Across the school-age spectrum, this finding occurs more commonly in adolescents than in younger children. In most cases, serial testing of the patient's urine demonstrates resolution of the abnormality. This phenomenon defines **transient proteinuria,** and its cause remains elusive. Defined contributing factors include a temperature > 38.3°C (101°F), exercise, dehydration, cold exposure, heart failure, recent use of epinephrine, seizures, or stress. Transient proteinuria usually does not exceed 1-2+ on the dipstick. No evaluation or therapy is needed for children with this benign condition, and it resolves spontaneously or as the cause resolves. Persistence of proteinuria, even if low grade, is not consistent with the diagnosis and suggests the need for additional evaluation.

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544.2

Orthostatic (Postural) Proteinuria

Francisco X. Flores

Orthostatic proteinuria is the most common cause of persistent proteinuria in school-age children and adolescents, occurring in up to 60% of children with persistent proteinuria. Children with this condition are usually asymptomatic, and the condition is discovered by routine urinalysis. Patients with orthostatic proteinuria excrete normal or minimally increased amounts of protein in the supine position. In the upright position, urinary protein excretion may be increased 10-fold, up to 1,000 mg/24 hr (1 g/24 hr). *Hematuria, hypertension, hypoalbuminemia, edema, and renal dysfunction are absent.*

In a child with persistent asymptomatic proteinuria, the initial evaluation should include an assessment for orthostatic proteinuria. It begins with the collection of a first morning urine sample, with subsequent testing of any urinary abnormalities by a complete urinalysis and determination of a spot urine protein-to-creatinine ratio. The correct collection of the first morning urine sample is critical. The child must fully empty the bladder before going to bed and then collect the first voided urine sample immediately upon arising in the morning. The absence of proteinuria (dipstick negative or trace for protein; and a normal ratio of urinary protein [mg/dL] to urinary creatinine [mg/dL] = [uPr/uCr] < 0.2) on the first morning urine sample for 3 consecutive days confirms the diagnosis of orthostatic proteinuria. No further evaluation is necessary, and the patient and family should be reassured of the benign nature of this condition. However, if there are other abnormalities of the urinalysis (e.g., hematuria), or if the urine uPr:uCr ratio is > 0.2, the patient should be referred to a pediatric nephrologist for a complete evaluation.

The cause of orthostatic proteinuria is unknown, although altered renal hemodynamics and partial left renal vein obstruction in the upright, lordotic position have been proposed as possible causes. An increased body mass index is recognized as a strong correlate of orthostatic proteinuria. Long-term follow-up studies in young adults suggest that orthostatic proteinuria is a benign process, but similar data are not available for children. Therefore, long-term follow-up of children is prudent. Patients should be monitored for the development of nonorthostatic proteinuria, particularly in the presence of hematuria, hypertension, or edema. Such findings may herald underlying kidney disease.

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544.3

Fixed Proteinuria

Francisco X. Flores

Keywords

Dent disease
glomerular proteinuria
tubular proteinuria

Children found to have fixed proteinuria on a first morning urine sample on three separate occasions should be further investigated. Fixed proteinuria is defined as a first morning urine sample that is ≥1+ on dipstick testing with a urine specific gravity > 1.015 or with a urine protein-to-creatinine ratio of ≥ 0.2. Fixed proteinuria indicates a potential kidney disease caused by either glomerular or tubular disorders.

Glomerular Proteinuria

The glomerular capillary wall consists of three layers: the fenestrated capillary endothelium, the glomerular basement membrane, and the podocytes (with foot processes and intercalated slit diaphragms) (Fig. 544.1). Glomerular proteinuria results from alterations in the permeability of any of the layers of the glomerular capillary wall to normally filtered proteins and occurs in a variety of renal diseases (Table 544.1). Glomerular proteinuria can range widely from < 1 g to > 30 g of protein in a 24 hr period. The podocyte is the predominant cell of injury in most glomerular diseases characterized by heavy proteinuria.

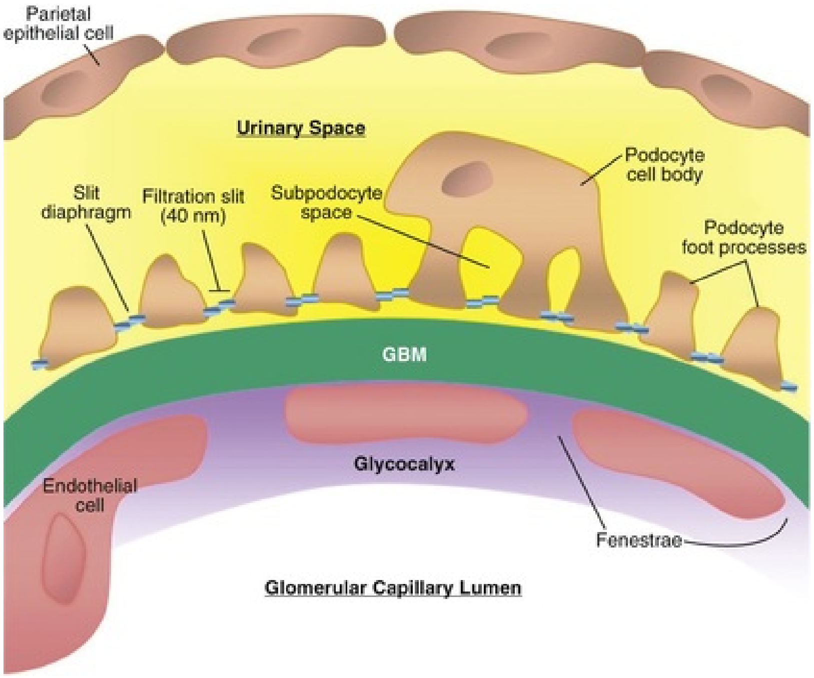
Parietal epithelial cell
Urinary Space
Podocyte cell body
Slit diaphragm
Filtration slit (40 nm)
Subpodocyte space
Podocyte foot processes
GBM
Glycocalyx
Endothelial cell
Fenestrae
Glomerular Capillary Lumen

FIG. 544.1 Glomerular capillary wall. The three layers of the capillary wall (glomerular endothelial cell, glomerular basement membrane [GBM], and podocyte) act as the glomerular filtration barrier (GFB), preventing proteins and large molecules from passing from the capillary lumen into the urinary space. The podocyte cell body lies within the urinary space, and the cell is attached to the GBM through foot processes. Adjacent foot processes are separated by the filtration slit, bridged by the slit diaphragm. Disruption of the GFB leads the passage of protein across the capillary wall, leading to proteinuria. (From Jefferson JA, Nelson PJ, Najafian B, Shankland SJ: Podocyte disorders: core curriculum 2011, Am J Kidney Dis 58:666-677, 2011, Fig. 1.)

Table 544.1

Causes of Proteinuria

Transient Proteinuria

- Fever
- Exercise
- Dehydration
- Cold exposure
- Congestive heart failure
- Seizure
- Stress
- Recent use of epinephrine

Orthostatic (Postural) Proteinuria

Glomerular Diseases Characterized by Isolated Proteinuria

- Idiopathic (minimal change) nephrotic syndrome
- Focal segmental glomerulosclerosis
- Secondary causes of nephrotic syndrome (see Chapter 545)
- Mesangial proliferative glomerulonephritis
- Membranous nephropathy
- Membranoproliferative glomerulonephritis
- Amyloidosis
- Diabetic nephropathy
- Sickle cell nephropathy

Glomerular Diseases With Proteinuria as a Prominent Feature

- Acute postinfectious glomerulonephritis (streptococcal, endocarditis, hepatitis B or C virus, HIV)
- Immunoglobulin A nephropathy
- Henoch-Schönlein purpura nephritis
- Lupus nephritis
- Serum sickness
- Alport syndrome
- Vasculitic disorders
- Reflux nephropathy

Tubular Diseases

- Cystinosis
- Fanconi syndrome
- Wilson disease
- Lowe syndrome
- Dent disease (X-linked recessive nephrolithiasis)
- Galactosemia
- Tubulointerstitial nephritis
- Acute tubular necrosis
- Renal dysplasia
- Polycystic kidney disease
- Reflux nephropathy
- Renal transplant rejection
- Drugs (aminoglycosides, cisplatin, penicillamine, lithium, nonsteroidal antiinflammatory drug, cyclosporine)
- Heavy metals (lead, gold, mercury)

Glomerular proteinuria should be suspected in any patient with a first morning urine protein-to-creatinine ratio > 1.0, or significant proteinuria of any degree, accompanied by hypertension, hematuria with active urine sediment, edema, or renal dysfunction (elevated blood urea nitrogen, creatinine). Disorders characterized primarily by proteinuria include idiopathic (minimal change disease) nephrotic syndrome, secondary causes of nephrotic syndrome, focal segmental glomerulosclerosis, mesangial proliferative glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, diabetic nephropathy, and obesity-related glomerulopathy. Other renal disorders that can include proteinuria as a prominent feature include acute postinfectious glomerulonephritis, immunoglobulin A nephropathy, systemic lupus erythematosus nephritis, Henoch-Schönlein purpura nephritis, and Alport syndrome.

The initial evaluation of a child with fixed proteinuria should include the measurement of serum creatinine and an electrolyte panel, first morning urine protein-to-creatinine ratio, serum albumin level, complement levels, and ANA. The child should be referred to a pediatric nephrologist for further evaluation and management. Renal biopsy is often necessary to establish a diagnosis and guide therapy.

In asymptomatic patients with low-grade proteinuria (urine protein-to-creatinine ratio between 0.2 and 1.0) in whom all other findings are normal, renal biopsy might not be indicated, because the underlying process may be transient or resolving or because specific pathologic features of a chronic kidney disease might not yet be apparent. Such patients should have periodic reevaluation (ideally every 4-6 mo unless the patient is or becomes symptomatic). The evaluation should consist of a physical examination with accurate blood pressure measurement, urinalysis, measurement of serum creatinine, and a repeat first morning urine protein-to-creatinine ratio. Indications for renal biopsy include increasing proteinuria (urine protein-to-creatinine ratio > 1.0) or the development of hematuria with active urine sediment, hypertension, or reduced renal function.

Tubular Proteinuria

A variety of renal disorders that primarily involve the tubulointerstitial compartment of the kidney can cause low-grade fixed proteinuria (urine protein-to-creatinine ratio 0.2 : 1.0). In the healthy state, large amounts of proteins of lower molecular weight than albumin are filtered by the glomerulus and reabsorbed in the proximal tubule. Injury to the proximal tubules can result in diminished reabsorptive capacity and the loss of these low-molecular-weight proteins in the urine.

Tubular proteinuria (see Table 544.1) may be seen in acquired and inherited disorders and may be associated with other defects of proximal tubular function, such as the Fanconi syndrome (glycosuria, phosphaturia, bicarbonate wasting, and aminoaciduria). Tubular proteinuria is a consistent finding among patients with the X-linked tubular syndrome, Dent disease, caused by mutations of the renal chloride channel.

Asymptomatic patients having persistent proteinuria generally have glomerular rather than tubular proteinuria. In occult cases, glomerular and tubular proteinuria can be distinguished by protein electrophoresis of the urine. In tubular proteinuria, little or no albumin is detected, whereas in glomerular proteinuria, the major protein is albumin.

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CHAPTER 545

Nephrotic Syndrome

Elif Erkan

Nephrotic syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic-range) proteinuria. Nephrotic-range proteinuria is defined as proteinuria > 3.5 g/24 hr or a urine protein:creatinine ratio > 2. The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein are hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol > 200 mg/dL).

Nephrotic syndrome affects 1-3 per 100,000 children < 16 yr of age. Without treatment, nephrotic syndrome in children is associated with a high risk of death, most commonly from infections. Fortunately, 80% of children with nephrotic syndrome respond to corticosteroid therapy. Although glucocorticoid therapy is standard therapy for nephrotic syndrome, neither the target cell nor the mechanism of action of steroids has been determined. Early referral to a pediatric nephrologist is recommended for initial management of nephrotic syndrome. However, continued care of these children is always a collaborative effort between the nephrologist and the primary care physician.

Etiology

Most children with nephrotic syndrome have a form of **primary** or idiopathic nephrotic syndrome (Table 545.1). Glomerular lesions associated with idiopathic nephrotic syndrome include minimal change disease (the most common), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulopathy, and membranous nephropathy (Table 545.2). These etiologies have different age distributions (Fig. 545.1). Nephrotic syndrome may also be **secondary** to systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, malignancy (lymphoma and leukemia), and infections (hepatitis, HIV, and malaria) (see Table 545.1). A number of **hereditary** proteinuria syndromes are caused by mutations in genes that encode critical protein components of the glomerular filtration apparatus (Table 545.3).

Table 545.1

Causes of Childhood Nephrotic Syndrome

IDIOPATHIC NEPHROTIC SYNDROME
Minimal change disease Focal segmental glomerulosclerosis Membranous nephropathy Glomerulonephritis associated with nephrotic syndrome–membranoproliferative glomerulonephritis, crescentic glomerulonephritis, immunoglobulin A nephropathy
GENETIC DISORDERS ASSOCIATED WITH PROTEINURIA OR NEPHROTIC SYNDROME (see also Table 545.3)
Nephrotic Syndrome (Typical)
Finnish-type congenital nephrotic syndrome (absence of nephrin) Focal segmental glomerulosclerosis (mutations in nephrin, podocin, *MYO1E* , α-actinin 4, TRPC6) Diffuse mesangial sclerosis (mutations in laminin β_2 chain) Denys-Drash syndrome (mutations in WT1 transcription factor) Congenital nephrotic syndrome with lung and skin involvement (integrin α-3 mutation) Mitochondrial disorders
Proteinuria With or Without Nephrotic Syndrome
Nail–patella syndrome (mutation in LMX1B transcription factor) Alport syndrome (mutation in collagen biosynthesis genes)
Multisystem Syndromes With or Without Nephrotic Syndrome
Galloway-Mowat syndrome Charcot-Marie-Tooth disease Jeune syndrome Cockayne syndrome Laurence-Moon-Biedl-Bardet syndrome
Metabolic Disorders With or Without Nephrotic Syndrome
Alagille syndrome α_1 -Antitrypsin deficiency Fabry disease Glutaric acidemia Glycogen storage disease Hurler syndrome Partial lipodystrophy Mitochondrial cytopathies Sickle cell disease
SECONDARY CAUSES OF NEPHROTIC SYNDROME
Infections
Endocarditis Hepatitides B, C HIV-1 Infectious mononucleosis Cytomegalovirus Malaria

Syphilis (congenital and secondary) Toxoplasmosis Tuberculosis Schistosomiasis Filariasis
Drugs
Captopril Penicillamine Gold Nonsteroidal antiinflammatory drugs Pamidronate, other bisphosphonates Interferon Mercury Heroin Lithium Rifampicin Sulfasalazine
Immunologic or Allergic Disorders
Vasculitis syndromes Castleman disease Kimura disease Bee sting Snake venom Food allergens Serum sickness Poison ivy, poison oak
Associated With Malignant Disease
Wilms Tumor
Lymphoma Pheochromocytoma Leukemia Thymoma Solid tumors
Glomerular Hyperfiltration
Oligomeganephronia Morbid obesity Adaptation to nephron reduction

Adapted from Eddy AA, Symons JM: Nephrotic syndrome in childhood, Lancet 362:629-638, 2003.

Table 545.2

Summary of Primary Renal Diseases That Manifest as Idiopathic Nephrotic Syndrome

FEATURES	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPR GLOMERULON
				Type I
DEMOGRAPHICS				
Age (yr)	2-6, some adults	2-10, some adults	40-50	5-15

Sex (male:female)	2 : 1	1.3 : 1	2 : 1	1:1
CLINICAL MANIFESTATIONS				
Nephrotic syndrome	100%	90%	80%	60%[*]
Asymptomatic proteinuria	0	10%	20%	40%
Hematuria (microscopic or gross)	10–20%	60–80%	60%	80%
Hypertension	10%	20% early	Infrequent	35%
Rate of progression to renal failure	Does not progress	10 yr	50% in 10-20 yr	10-20 yr
Associated conditions	Usually none	HIV, heroin use, sickle cell disease, reflux nephropathy	Renal vein thrombosis; medications; SLE; hepatitides B, C; lymphoma; tumors	None
GENETICS				
	None except in congenital nephrotic syndrome (see Table 545.3)	Podocin, α-actinin 4, TRPC6 channel, INF-2, MYH-9	None	None
LABORATORY FINDINGS				
	Manifestations of nephrotic syndrome ↑ BUN in 15–30% Normal complement levels	Manifestations of nephrotic syndrome ↑ BUN in 20–40% Normal complement levels	Manifestations of nephrotic syndrome Normal complement levels	Low complement levels—C1, C4, C3-C9
RENAL PATHOLOGY				
Light microscopy	Normal	Focal sclerotic lesions	Thickened GBM, spikes	Thickened GBM, proliferation
Immunofluorescence	Negative	IgM, C3 in lesions	Fine granular IgG, C3	Granular IgG, C3
Electron microscopy	Foot process fusion	Foot process fusion	Subepithelial deposits	Mesangial and subendothelial deposits
REMISSION ACHIEVED AFTER 8 WK OF ORAL CORTICOSTEROID THERAPY				
	90%	15–20%	Resistant	Not established/resista

[*] Approximate frequency as a cause of idiopathic nephrotic syndrome. Approximately 10% of cases of adult nephrotic syndrome are a result of various diseases that usually manifest as acute glomerulonephritis.

↑, Elevated; BUN, blood urea nitrogen; C, complement; GBM, glomerular basement membrane; Ig, immunoglobulin; SLE, systemic lupus erythematosus.

Modified from Couser WG: Glomerular disorders. In Wyngaarden JB, Smith LH, Bennett JC (eds): Cecil Textbook of medicine, 19/e, Philadelphia, 1992, WB Saunders, p. 560.

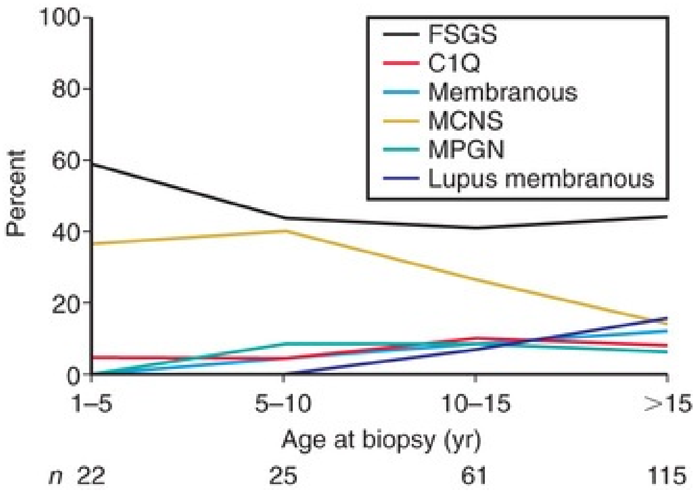

FIG. 545.1 Kidney biopsy results from 223 children with proteinuria referred for diagnostic kidney biopsy (Glomerular Disease Collaborative Network, J. Charles Jennette, MD, Hyunsook Chin, MS, and D.S. Gipson, 2007). C1Q, nephropathy; FSGS, focal segmental glomerulosclerosis; MCNS, minimal change nephrotic syndrome; MPGN, membranoproliferative glomerulonephritis; n, number of patients. (From Gipson DS, Massengill SF, Yao L, et al: Management of childhood onset nephrotic syndrome, Pediatrics 124:747-757, 2009.)

Table 545.3

Causative Genes and Histologic Patterns of Nephrotic Syndrome by Time of Disease Onset

CAUSE		INHERITANCE/LOCUS	GENE/PROTEIN	HISTOLOGIC FEATURES
CONGENITAL ONSET (0-3 MO)				
Isolated	Congenital nephrotic syndrome of the Finnish type (CNF)	AR	*NPHS1* /nephrin	Radial dilation of proximal tubule
	Recessive SRNS, type 2	AR	*NPHS2* /podocin	FSGS/MGC
	Recessive SRNS, type 3	AR	*NPHS3* /PLCE1	DMS
	Isolated DMS	AR	WT1	DMS
	Recessive SRNS	AR	COQ2	FSGS, collapsing
	Recessive SRNS + deafness	AR	COQ6	FSGS
	Dominant SRNS + deafness	AD/11q24	Unknown	FSGS
	DMS + neurologic findings	AR	ARHGDIA/Rho GDP dissociation inhibitor (GDI) alpha	DMS
	NS + lung and skin disease	AR	*ITGA3* /integrin alpha 3	DMS

	Steroid-sensitive nephrotic syndrome	AR/2p12-13.2	Unknown	MGC/FSGS
Syndromic	Denys-Drash syndrome	AD	WT1	DMS
	Pierson syndrome	AR	*LAMB2* /laminin-β2	FSGS
	Nail–patella syndrome	AD	*LMX1B* /LIM homeobox transcription factor-1β	
	Frasier syndrome	AD	WT1	FSGS
	Schimke immunoosseous dysplasia	AR	SMARCAL1	FSGS
	Epidermolysis bullosa + FSGS	AR	*ITGB4* /integrin-β4	FSGS
	Galloway-Mowat syndrome	AR	Unknown	MGC to FSGS
INFANCY-CHILDHOOD ONSET				
Genetic	Recessive SSNS	AR	*EMP2* /epithelial membrane protein 2	
	Recessive SRNS	AR	*NPHS2* /podocin	FSGS/MGC
	Recessive SRNS	AR	*NPHS1* /nephrin	FSGS/MGC
	Recessive SRNS	AR	*NPHS3* /PLCE1	DMS
	Isolated DMS	AD	*WT1*	DMS
	Recessive SRNS + deafness or intellectual disability	AR	*ARHGDIA*	DMS
	SRNS	AR	*MYOE1* /nonmuscle class I myosin E	FSGS
	SRNS	AR	*PTPRO/GLEPP1* protein tyrosine phosphatase receptor type O/glomerular epithelial protein-1	FSGS
JUVENILE-ADULT ONSET				
Genetic	SRNS	AR or sporadic	*NPHS2* (p.R229Q)	FSGS
	Familial SRNS	AD	*INF2* /formin family of actin-regulating proteins	FSGS
	FSGS, type 1	AD/19q13	*ACTN4* /α-actinin-4	FSGS
	FSGS, type 2	AD/11q21-22	*TRPC6* /transient receptor potential cation channel, subfamily C, member 6	FSGS
	FSGS, type 3	AR-AD/6p12	*CD2AP* /CD2-associated protein	FSGS
	SRNS	AR	*PTPRO/GLEPP1* protein tyrosine phosphatase receptor type O/glomerular epithelial protein-1	FSGS
	SRNS	AR	*ADCK4/* aarF domain-containing kinase 4	FSGS
	SRNS (no extrarenal symptoms)	AD or sporadic	*LMX1B* encodes homeodomain-containing transcription factor	FSGS

AD, autosomal dominant; AR, autosomal recessive; DMS, diffuse mesangial sclerosis; FSGS, focal segmental glomerulosclerosis; MGC, minimal glomerular changes; NS, nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome.

From Bakkaloglu SA, Schaefer F: Diseases of the kidney and urinary tract in children. In Skorecki

K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's the kidney, 10/e, Philadelphia, 2016, Elsevier, Table 74-2.

Pathogenesis

Role of the Podocyte

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. The podocyte plays a crucial role in the development of proteinuria and the progression of glomerulosclerosis (Fig. 545.2). The podocyte is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop. Foot processes are extensions of the podocyte that terminate on the glomerular basement membrane. The foot processes of a podocyte interdigitate with those from adjacent podocytes and are connected by a slit called the slit diaphragm. The podocyte functions as structural support of the capillary loop, is a major component of the glomerular filtration barrier to proteins, and is involved in synthesis and repair of the glomerular basement membrane. The slit diaphragm is one of the major impediments to protein permeability across the glomerular capillary wall. Slit diaphragms are not simple passive filters; they consist of numerous proteins that contribute to complex signaling pathways and play an important role in podocyte function. Important component proteins of the slit diaphragm include nephrin, podocin, CD2AP, and α-actinin 4. Podocyte injury or genetic mutations of genes producing podocyte proteins may cause nephrotic-range proteinuria (see Table 545.3). Genetic screening of 1,655 patients with steroid-resistant nephrotic syndrome and congenital nephrotic syndrome in the European PodoNet Registry Cohort has shown that mutations in *NPHS1, WT1,* and *NPHS2* were the most common. The proportion of patients with genetic mutations of podocyte genes decreased by age: 66% in patients with congenital nephrotic syndrome to 15–16% in school-age patients and adolescents.

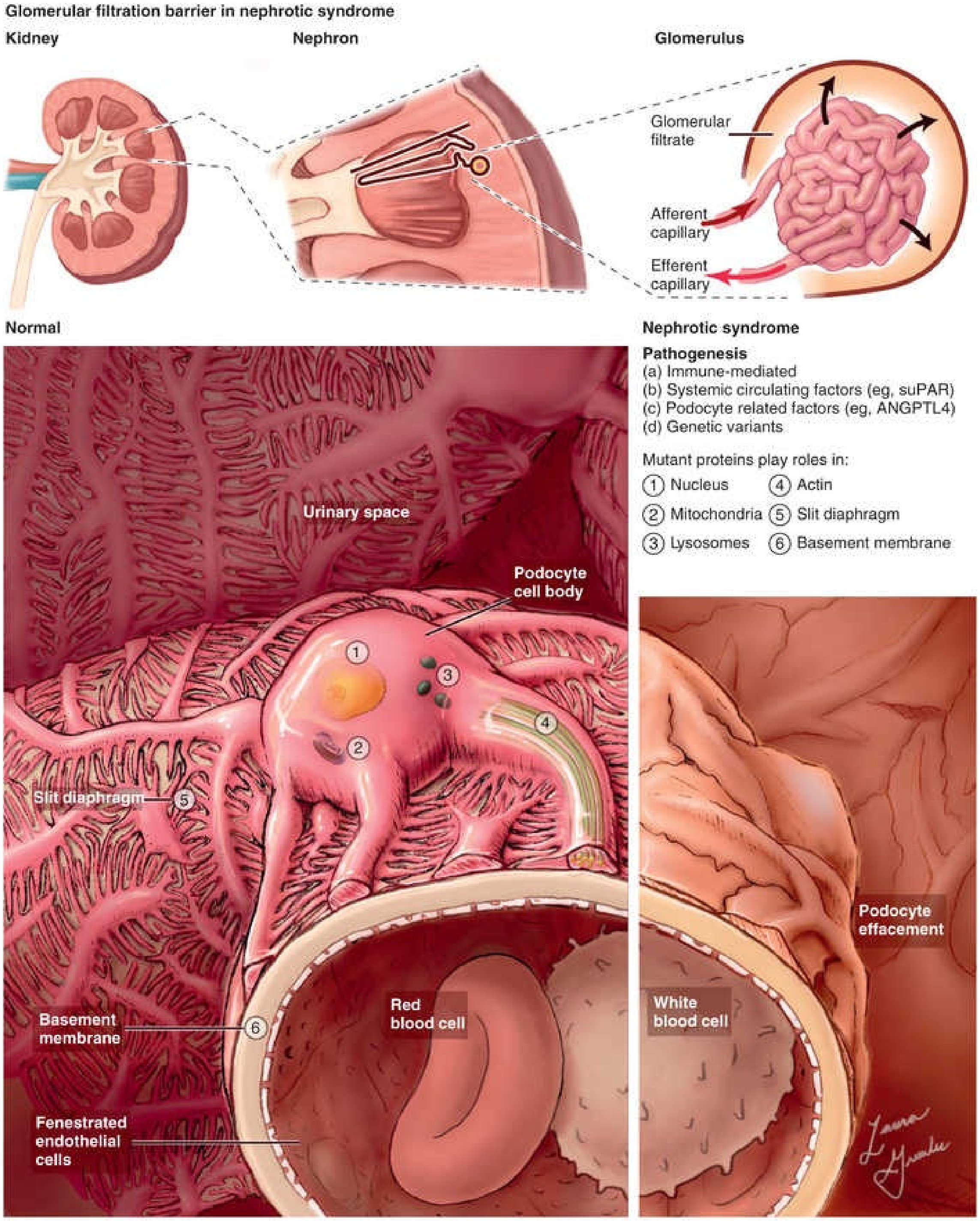
Glomerular filtration barrier in nephrotic syndrome
Kidney
Nephron
Glomerulus
Glomerular filtrate
Afferent capillary
Efferent capillary
Normal
Nephrotic syndrome
Pathogenesis
(a) Immune-mediated
(b) Systemic circulating factors (eg, suPAR)
(c) Podocyte related factors (eg, ANGPTL4)
(d) Genetic variants
Mutant proteins play roles in:
① Nucleus
② Mitochondria
③ Lysosomes
④ Actin
⑤ Slit diaphragm
⑥ Basement membrane
Urinary space
Podocyte cell body
①
②
③
④
Slit diaphragm ⑤
Basement membrane ⑥
Fenestrated endothelial cells
Red blood cell
White blood cell
Podocyte effacement

FIG. 545.2 The glomerular filtration barrier and pathogenesis of idiopathic nephrotic syndrome. Within the kidney is the glomerulus, a capillary tuft that filters the blood. The podocyte, glomerular basement membrane, and fenestrated glomerular endothelium form the glomerular filtration barrier, allowing the ultrafiltrate to enter the urinary space. The podocyte has extensive cellular extensions that interdigitate, and these foot processes are connected by the slit diaphragm. In nephrotic syndrome, there is extensive effacement of the podocytes and loss of this barrier to protein,

allowing excessive serum albumin to leak into the urine. The pathogenesis of idiopathic nephrotic syndrome is hypothesized to be either immune mediated, due to a systemic podocyte-derived circulating factor, or, in rarer or familial forms, a genetic variant. Numerous mutations are associated with steroid-resistant nephrotic syndrome that affect various parts of the podocyte itself or the other constituents of the glomerular basement membrane. These include mutations affecting the podocyte nucleus, mitochondria or lysosomes, the slit diaphragm or actin cytoskeleton, and the glomerular basement membrane. Nephrin, podocin, and CD2AP, for example, are essential components of a zipper-like structure spanning the interdigitating foot processes of the podocyte and the slit diaphragm and link directly with the podocyte actin cytoskeleton. The actin cytoskeleton is further supported by microfilaments that maintain structural stability and facilitate the dynamic nature of the podocyte structure and function. The importance of these microfilaments is evident because mutations in both α-actinin 4 and INF2, which are involved in actin regulation and polymerization, lead to FSGS. (From Noone DG, Iijima K, Parekh R: Idiopathic nephrotic syndrome in children, Lancet 392:61-72, 2018, Fig. 2.)

In idiopathic, hereditary, and secondary forms of nephrotic syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein leakiness across the glomerular capillary wall into the urinary space.

Role of the Immune System

Minimal change nephrotic syndrome (MCNS) may occur after viral infections and allergen challenges. MCNS has also been found to occur in children with Hodgkin lymphoma and T-cell lymphoma. That immunosuppression occurs with drugs such as corticosteroids and cyclosporine provides indirect additional evidence that the immune system contributes to the overall pathogenesis of the nephrotic syndrome.

Clinical Consequences of Nephrotic Syndrome

Edema

Edema is the most common presenting symptom of children with nephrotic syndrome. Despite its almost universal presence, there is uncertainty as to the exact mechanism of edema formation. There are two opposing theories, the *underfill hypothesis* and the *overfill hypothesis,* that have been proposed as mechanisms causing nephrotic edema.

The *underfill hypothesis* is based on nephrotic-range proteinuria that leads to a fall in the plasma protein level with a corresponding decrease in intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, generating edema. As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, results in increased sodium and water retention by the tubules. Sodium and water retention therefore occur as a consequence of intravascular volume depletion.

This hypothesis does not fit the clinical picture of some patients with edema caused by nephrotic syndrome who have clinical signs of intravascular volume overload, not volume depletion. Treating these patients with albumin alone may not be sufficient to induce a diuresis without the concomitant use of diuretics. Also, reducing the renin–aldosterone axis with mineralocorticoid receptor antagonists does not result in a marked increase in sodium excretion. With the onset of remission of MCNS, many children will have increased urine output before their urinary protein excretion is measurably reduced.

The *overfill hypothesis* postulates that nephrotic syndrome is associated with primary sodium retention, with subsequent volume expansion and leakage of excess fluid into the interstitium. There is accumulating evidence that the epithelial sodium channel in the distal tubule may play a key role in sodium reabsorption in nephrotic syndrome. The clinical weaknesses of this hypothesis are evidenced by the numerous nephrotic patients who present with an obvious clinical picture of intravascular volume depletion: low blood pressure, tachycardia, and elevated hemoconcentration. Furthermore, amiloride, an epithelial sodium channel blocker, used alone is not sufficient to induce adequate diuresis.

The goal of therapy should be a gradual reduction of edema with judicious use of diuretics, sodium restriction, and cautious use of intravenous albumin infusions, if indicated.

Hyperlipidemia

There are several alterations in the lipid profile in children with nephrotic syndrome, including an increase in cholesterol, triglycerides, low-density lipoproteins, and very-low-density lipoproteins. The high-density lipoprotein level remains unchanged or is low. In adults, this results in an increase in the adverse cardiovascular risk ratio, although the implications for children are not as serious, especially those with steroid-responsive nephrotic syndrome. Hyperlipidemia is thought to be the result of increased synthesis as well as decreased catabolism of lipids. Although commonplace in adults, the use of lipid-lowering agents in children is uncommon.

Increased Susceptibility to Infections

Children with nephrotic syndrome are especially susceptible to infections such as cellulitis, spontaneous bacterial peritonitis, and bacteremia. This occurs as a result of many factors, particularly hypoglobulinemia as a result of the urinary losses of immunoglobulin (Ig) G. In addition, defects in the complement cascade from urinary loss of complement factors (predominantly C3 and C5), as well as alternative pathway factors B and D, lead to impaired opsonization of microorganisms. Children with nephrotic syndrome are at significantly increased risk for infection with encapsulated bacteria and, in particular, pneumococcal disease. **Spontaneous bacterial peritonitis** presents with fever, abdominal pain, and peritoneal signs. Although *Pneumococcus* is the most frequent cause of peritonitis, Gram-negative bacteria also are associated with a significant number of cases. Children with nephrotic syndrome and fever or other signs of infection must be evaluated aggressively, with appropriate cultures drawn, and should be treated promptly and empirically with antibiotics. Peritoneal leukocyte counts > 250 cells/µL are highly suggestive of spontaneous bacterial peritonitis.

Hypercoagulability

Nephrotic syndrome is a hypercoagulable state resulting from multiple factors: vascular stasis from hemoconcentration and intravascular volume depletion, increased platelet number and aggregability, and changes in coagulation factor levels. There is an increase in hepatic production of fibrinogen along with urinary losses of antithrombotic factors such as antithrombin III and protein S. Deep venous thrombosis may occur in any venous bed, including the cerebral venous sinus, renal vein, and pulmonary veins. The clinical risk is low in children (2–5%) compared with adults but has the potential for serious consequences.

545.1

Idiopathic Nephrotic Syndrome

Elif Erkan

Keywords

focal segmental glomerulosclerosis
minimal change nephrotic syndrome
obesity
thromboembolism

Approximately 90% of children with nephrotic syndrome have idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is associated with primary glomerular disease without an identifiable causative disease or drug. Idiopathic nephrotic syndrome includes multiple histologic types: minimal change disease, mesangial proliferation, focal segmental glomerulosclerosis, membranous nephropathy, and membranoproliferative glomerulonephritis.

Pathology

In minimal change nephrotic syndrome (MCNS) (Σ85% of total cases of nephrotic syndrome in children), the glomeruli appear normal or show a minimal increase in mesangial cells and matrix. Findings on immunofluorescence microscopy are typically negative, and electron microscopy simply reveals effacement of the epithelial cell foot processes. More than 95% of children with minimal change disease respond to corticosteroid therapy.

Mesangial proliferation is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Immunofluorescence microscopy might reveal trace to 1+ mesangial IgM and/or IgA staining. Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

In **focal segmental glomerulosclerosis (FSGS),** glomeruli show lesions that are both focal (present only in a proportion of glomeruli) and segmental (localized to ≥ 1 intraglomerular tufts). The lesions consist of mesangial cell proliferation and segmental scarring on light microscopy (Fig. 545.3 and see Table 545.2). Immunofluorescence microscopy is positive for IgM and C3 staining in the areas of segmental sclerosis. Electron microscopy demonstrates segmental scarring of the glomerular tuft with obliteration of the glomerular capillary lumen. In a review of the kidney pathology slides of 138 patients with FSGS, the presence of a tip lesion (located at the 25% of the outer tuft next to the proximal tubule origin) was found to be correlated with Caucasian race and slower progression, whereas the collapsing variant of FSGS had the higher progression rate with a predilection for African Americans.

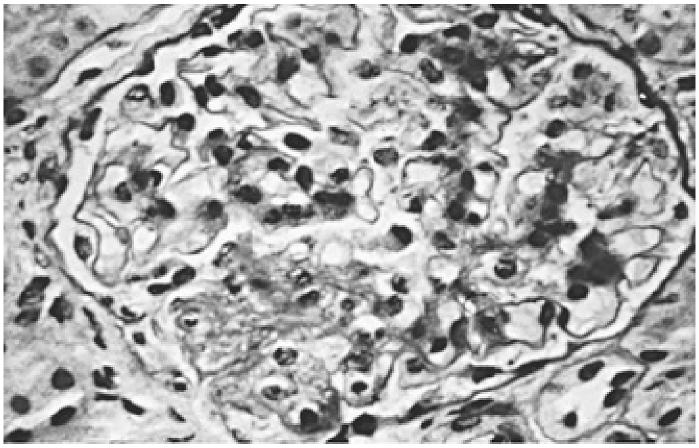

FIG. 545.3 Glomerulus from a patient with steroid-resistant nephrotic syndrome showing mesangial hypercellularity and an area of sclerosis in the lower portion (×250).

Lesions consistent with FSGS may be seen secondary to HIV infection, vesicoureteral reflux, and intravenous use of heroin and other drugs of abuse. Only 20% of patients with FSGS respond to prednisone. The disease is often progressive, ultimately involving all glomeruli with end-stage renal disease in most patients.

Minimal Change Nephrotic Syndrome

Clinical Manifestations

The idiopathic nephrotic syndrome is more common in males than in females (2 : 1) and most commonly appears between the ages of 2 and 6 yr (see Fig. 545.1). However, it has been reported as early as 6 mo of age and throughout adulthood. MCNS is present in 85–90% of patients < 6 yr of age. In contrast, only 20–30% of adolescents who present for the first time with nephrotic syndrome have MCNS. The more common cause of idiopathic nephrotic syndrome in this older age-group is FSGS. FSGS is the most common cause of end-stage renal disease in adolescents. The incidence of FSGS has been increasing; African Americans are considered an especially at-risk population.

The initial episode of idiopathic nephrotic syndrome, as well as subsequent relapses, may follow minor infections and, uncommonly, reactions to insect bites, beestings, or poison ivy.

Children usually present with mild edema, which is initially noted around the eyes and in the lower extremities. Nephrotic syndrome can initially be misdiagnosed as an allergic disorder because of the periorbital swelling that decreases throughout the day. With time, the edema becomes generalized, with the development of ascites, pleural effusions, and genital edema. Anorexia, irritability, abdominal pain, and diarrhea are common. Important features of minimal change idiopathic nephrotic syndrome are the absence of hypertension and gross hematuria (the so-called nephritic features).

The differential diagnosis of the child with marked edema includes protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis, and protein malnutrition. A diagnosis other than MCNS should be considered in children < 1 yr of age, with a positive family history of nephrotic syndrome, and/or the presence of extrarenal findings (e.g., arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency, and gross hematuria.

Diagnosis

Recommendations for the Initial Evaluation of Children With Nephrotic Syndrome

Confirming the Diagnosis of Nephrotic Syndrome.

The diagnosis of nephrotic syndrome is confirmed by urinalysis with the first morning urine protein:creatinine ratio and serum electrolytes, blood urea nitrogen, creatinine, albumin, and cholesterol levels; an evaluation to rule out secondary forms of nephrotic syndrome (children ≥ 10 yr) by the complement C3 level, antinuclear antibody, double-stranded DNA; hepatitis B and C and HIV in high-risk populations; and kidney biopsy (for children ≥ 12 yr, who are less likely to have MCNS).

The urinalysis reveals 3+ or 4+ proteinuria, and microscopic hematuria is present in 20% of children. A spot urine protein:creatinine ratio should be > 2.0. The serum creatinine value is usually normal, but it may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume. The serum albumin level is < 2.5 g/dL, and serum cholesterol and triglyceride levels are elevated. Serum complement levels are normal. A renal biopsy is not routinely performed if the patient fits the standard clinical picture of MCNS.

Treatment

Children with their first episode of nephrotic syndrome and mild to moderate edema may be managed as outpatients. Such outpatient management is not practiced in all major centers, because the time required for successful education of the family regarding all aspects of the condition can require a short period of hospitalization. The child's parents must be able to recognize the signs and symptoms of the complications of the disease and may be taught how to use a dipstick and interpret the results to monitor for the degree of proteinuria. Tuberculosis must be ruled out prior to starting immunosuppressive therapy with corticosteroids by placing a purified protein derivative or obtaining an interferon release assay, and confirming a negative result.

Children with onset of uncomplicated nephrotic syndrome between 1 and 8 yr of age are likely to have steroid-responsive MCNS, and steroid therapy may be initiated without a diagnostic renal biopsy. Children with features that make MCNS less likely (gross hematuria, hypertension, renal insufficiency, hypocomplementemia, or age < 1 yr or > 12 yr) should be considered for renal biopsy before treatment.

Use of Corticosteroids to Treat Minimal Change Nephrotic

Syndrome

Corticosteroids are the mainstay of therapy for MCNS. The treatment guidelines for corticosteroid use presented below are adapted from and based on the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines on glomerulonephritis.

Treatment of the Initial Episode of Nephrotic Syndrome

In children with presumed MCNS, prednisone or prednisolone should be administered as a single daily dose of 60 mg/m^2 /day or 2 mg/kg/day to a maximum of 60 mg daily for 4-6 wk followed by alternate-day prednisone (starting at 40 mg/m^2 qod or 1.5 mg/kg qod) for a period ranging from 8 wk to 5 mo, with tapering of the dose. The issue of the duration of steroid treatment has been controversial. Prolonged steroid treatment with a tapering schedule for 2-5 mo is advocated for decreasing the incidence of relapse based on recent multicenter trials. The Kidney Disease Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group recommends at least 12 wk of steroid treatment. When planning the duration of steroid therapy, the side effects of prolonged corticosteroid administration must be kept in mind. Approximately 80–90% of children respond to steroid therapy.

Definitions regarding the response to steroid therapy are as follows: **Response** is defined as the attainment of remission within the initial 4 wk of corticosteroid therapy. **Remission** consists of a urine protein:creatinine ratio of < 0.2 or $< 1+$ protein on urine dipstick testing for 3 consecutive days. Most children with minimal change disease respond to daily prednisone therapy fairly quickly, within the first 2-3 wk of treatment. **Relapse** is an increase in the first morning urine protein:creatinine ratio > 0.2 or a reading of 2+ and higher for 3 consecutive days on Albustix testing. **Frequently relapsing** is two or more relapses within 6 mo after the initial therapy or four relapses in a 12-mo period. **Steroid dependent** is a relapse during steroid tapering or a relapse within 2 wk of the discontinuation of therapy. **Steroid resistance** is the inability to induce remission within 4 wk of daily steroid therapy.

Managing the Clinical Sequelae of Nephrotic Syndrome

Edema.

Children with severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized. In addition to sodium restriction (<1,500 mg daily), water/fluid restriction may be necessary if the child is hyponatremic. A swollen scrotum may be elevated with pillows to enhance fluid removal by gravity. Diuresis may be augmented by the administration of loop diuretics (furosemide), orally or intravenously, *although extreme caution should be exercised.* Aggressive diuresis can lead to intravascular volume depletion and an increased risk for acute renal failure and intravascular thrombosis.

When a patient has severe generalized edema with evidence of intravascular volume depletion (e.g., hemoconcentration, hypotension, tachycardia), intravenous administration of 25% albumin (0.5-1.0 g albumin/kg) as a slow infusion followed by furosemide (1-2 mg/kg/dose intravenously) is sometimes necessary. Such therapy should be used only in collaboration with a pediatric nephrologist and mandates close monitoring of volume status, blood pressure, serum electrolyte balance, and renal function. Symptomatic volume overload, with hypertension, heart failure, and pulmonary edema, is a potential complication of parenteral albumin therapy, particularly when it is administered as a rapid infusions.

Dyslipidemia.

Dyslipidemia should be managed with a low-fat diet. Dietary fat intake should be limited to < 30% of calories with a saturated fat intake of < 10% calories. Dietary cholesterol intake should be < 300 mg/day. There are insufficient data to recommend the use of 3-hydroxy-3-methylgluataryl coenzyme A (HMG-CoA) reductase inhibitors routinely in children with dyslipidemia.

Infections.

Families of children with nephrotic syndrome should be counseled regarding the signs and symptoms of infections such as cellulitis, peritonitis, and bacteremia. If there is a suspicion of infection, a blood culture should be drawn prior to starting empirical antibiotic therapy. In the case of spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a paracentesis and sent for cell count, Gram stain, and culture. The antibiotic provided must be of broad enough coverage to include *Pneumococcus* and Gram-negative bacteria. A third-generation cephalosporin is a common choice of intravenous antibiotic.

Thromboembolism.

Children who present with the clinical signs of thromboembolism should be evaluated by appropriate imaging studies to confirm the presence of a clot. Studies to delineate a specific underlying hypercoagulable state are recommended. Anticoagulation therapy in children with thrombotic events appears to be effective—heparin, low-molecular-weight heparin, and warfarin are therapeutic options.

Obesity and Growth.

Glucocorticoids may increase the body mass index in children who are overweight when steroid therapy is initiated, and these children are more likely to remain overweight. Anticipatory dietary counseling is recommended. Growth may be affected in children who require long-term corticosteroid therapy. Steroid-sparing strategies may improve linear growth in children who require prolonged courses of steroids.

Relapse of Nephrotic Syndrome.

Relapse of nephrotic syndrome is defined as a urine protein:creatinine ratio of > 2 or ≥ 3+ protein on urine dipstick testing for 3 consecutive days. Relapses are common, especially in younger children, and are often triggered by upper respiratory or gastrointestinal infections. Relapses are usually treated similar to the initial episode, except that daily prednisone courses are shortened. Daily high-dose prednisone is given until the child has achieved remission, and the regimen is then switched to alternate-day therapy. The duration of alternate-day therapy varies depending on the frequency of relapses of the individual child. Children are classified as infrequent relapsers or frequent relapsers, and as being steroid dependent, based on the number of relapses in a 12-mo period or their inability to remain in remission following discontinuation of steroid therapy.

Steroid Resistance.

Steroid resistance is defined as the failure to achieve remission after 8 wk of corticosteroid therapy. Children with steroid-resistant nephrotic syndrome require further evaluation, including a diagnostic kidney biopsy, evaluation of kidney function, and quantitation of urine protein excretion (in addition to urine dipstick testing). Steroid-resistant nephrotic syndrome is usually caused by FSGS (80%), MCNS, or membranoproliferative glomerulonephritis.

Implications of Steroid-Resistant Nephrotic Syndrome.

Steroid-resistant nephrotic syndrome, and specifically FSGS, is associated with a 50% risk for end-stage kidney disease within 5 yr of diagnosis if patients do not achieve a partial or complete remission. Persistent nephrotic syndrome is associated with a poor patient-reported quality of life, hypertension, serious infections, and thromboembolic events. Children reaching end-stage kidney disease have a greatly reduced life expectancy compared with their peers.

Alternative Therapies to Corticosteroids in the Treatment of Nephrotic Syndrome.

Steroid-dependent patients, frequent relapsers, and steroid-resistant patients are candidates for alternative therapies, particularly if they have severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure). **Cyclophosphamide** prolongs the duration of remission and reduces the number of relapses in children with **frequently relapsing** and **steroid-dependent** nephrotic syndrome. The potential side effects of the drug (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility, increased risk of future malignancy) should be carefully reviewed with the family before initiating treatment. Cyclophosphamide (2 mg/kg) is given as a single oral dose for a total duration of 8-12 wk. Alternate-day prednisone therapy is often continued during cyclophosphamide administration. During cyclophosphamide therapy, the white blood cell count must be monitored weekly and the drug should be withheld if the count falls below 5,000/mm^3 . The cumulative threshold dose above which oligospermia or azoospermia occurs in boys is > 250 mg/kg.

Calcineurin inhibitors (cyclosporine or tacrolimus) are recommended as initial therapy for children with steroid-resistant nephrotic syndrome. Children must be monitored for side effects, including hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia. Mycophenolate can maintain remission in children with steroid-dependent or frequently relapsing nephrotic syndrome. Levamisole, an antihelmintic agent with immunomodulating effects that has been shown to reduce the risk of relapse in comparison to prednisone, is not available in the United States.

There are also data regarding prolonged remissions achieved with rituximab, the chimeric monoclonal antibody against CD20-targeting B cells, in children with steroid-dependent and/or steroid-resistant nephrotic syndrome. Randomized trials with rituximab have shown promising results of an up to 80% drug-free remission rate at 1 yr in patients with steroid-dependent nephrotic syndrome. However, rituximab is less effective in patients treated with calcineurin inhibitors and steroids and with multidrug-resistant nephrotic syndrome.

There are no data from randomized clinical trials directly comparing the various corticosteroid-sparing agents. Most children who respond to cyclosporine, tacrolimus, or mycophenolate therapy tend to relapse when the medication is discontinued. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be helpful as adjunct therapy to reduce proteinuria in steroid-resistant patients.

Immunizations in Children With Nephrotic Syndrome.

To reduce the risk of serious infections in children with nephrotic syndrome, give the full pneumococcal vaccination (with the 13-valent conjugant vaccine and 23-valent polysaccharide vaccine) and influenza vaccination annually to the child and their household contacts; defer vaccination with live vaccines until the prednisone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days. Live virus vaccines are contraindicated in children receiving corticosteroid-sparing agents such as cyclophosphamide or cyclosporine. Following close contact with varicella infection, give immunocompromised children taking immunosuppressive agents varicella-zoster immune globulin if available**;** immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child, but avoid direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts for 3-6 wk after vaccination.

Table 545.4 provides monitoring recommendations for children with nephrotic syndrome.

Table 545.4

Monitoring Recommendations for Children With Nephrotic Syndrome

DISEASE AND TREATMENT	HOME URINE PROTEIN	WEIGHT, GROWTH, BMI	BP	Cr	ELECTROLYTES	SERUM GLUCOSE	CBC	LIPID PROFILE	DR LE
DISEASE TYPE									
Mild (steroid responsive)	•	•	•						

Moderate (frequent relapsing, steroid dependent)	•	•	•	•				•	
Severe (steroid resistant)	•	•	•	•				•	
THERAPY									
Corticosteroids		•	•			•		•	
Cyclophosphamide				•			•		
Mycophenolate mofetil							•		
Calcineurin inhibitors			•	•	•	•		•	•
ACEIs/ARBs			•	•	•		•		
HMG-CoA reductase inhibitors								•	

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BP, blood pressure; CBC, complete blood count; CPK, creatine phosphokinase; Cr, creatinine; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LFTs, liver function tests; UA, urinalysis.

From Gipson DS, Massengill SF, Yao L, et al: Management of childhood onset nephrotic syndrome, Pediatrics 124:747-757, 2009.

Prognosis

Most children with steroid-responsive nephrotic syndrome have repeated relapses, which generally decrease in frequency as the child grows older. Although there is no proven way to predict an individual child's course, children who respond rapidly to steroids and those who have no relapses during the first 6 mo after diagnosis are likely to follow an infrequently relapsing course. It is important to indicate to the family that the child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease, that the disease is rarely hereditary, and that the child (in the absence of prolonged cyclophosphamide therapy) will remain fertile. To minimize the psychological effects of the condition and its therapy, children with idiopathic nephrotic syndrome should not be considered chronically ill and should participate in all age-appropriate childhood activities and maintain an unrestricted diet when in remission.

Children with steroid-resistant nephrotic syndrome, most often caused by FSGS, generally have a much poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end-stage renal disease requiring dialysis or kidney transplantation. Recurrent nephrotic syndrome develops in 30–50% of transplant recipients with FSGS.

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545.2

Secondary Nephrotic Syndrome

Elif Erkan

Keywords

Henoch-Schönlein purpura nephritis
leprosy

Nephrotic syndrome can occur as a secondary feature of many forms of glomerular disease. Membranous nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, and Henoch-Schönlein purpura nephritis can all have a nephrotic component (see Tables 545.1 and 545.3). Secondary nephrotic syndrome should be suspected in patients > 8 yr and those with hypertension, hematuria, renal dysfunction, extrarenal symptoms (e.g., rash, arthralgias, fever), or depressed serum complement levels. In certain areas of the world, malaria and schistosomiasis are the leading causes of nephrotic syndrome. Other infectious agents associated with nephrotic syndrome include hepatitis B virus, hepatitis C virus, filaria, leprosy, and HIV.

Nephrotic syndrome has been associated with malignancy, particularly in the adult population. In patients with solid tumors, such as carcinomas of the lung and gastrointestinal tract, the renal pathology often resembles membranous glomerulopathy. Immune complexes composed of tumor antigens and tumor-specific antibodies presumably mediate the renal involvement. In patients with lymphomas, particularly Hodgkin lymphoma, the renal pathology most often resembles MCNS. The proposed mechanism of the nephrotic syndrome is that the lymphoma produces a lymphokine that increases permeability of the glomerular capillary wall. Nephrotic syndrome can develop before or after the malignancy is detected, resolve as the tumor regresses, and return if the tumor recurs.

Nephrotic syndrome has also developed during therapy with numerous drugs and chemicals. The histologic picture can resemble membranous glomerulopathy (penicillamine, captopril, gold, nonsteroidal antiinflammatory drugs, mercury compounds), MCNS (probenecid, ethosuximide, methimazole, lithium), or proliferative glomerulonephritis (procainamide, chlorpropamide, phenytoin, trimethadione, paramethadione).

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545.3

Congenital Nephrotic Syndrome

Elif Erkan

Keywords

Denys-Drash syndrome
Galloway Mowat syndrome
hypercholesterolemia
Wilms tumor
Pierson syndrome
proteinuria,

Nephrotic syndrome (massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia) has a poorer prognosis when it occurs in the first year of life, when compared with nephrotic syndrome manifesting in childhood. Congenital nephrotic syndrome is defined as nephrotic syndrome manifesting at birth or within the *first 3 mo of life*. Congenital nephrotic syndrome may be classified as primary or as secondary to a number of etiologies such as in utero infections (cytomegalovirus, toxoplasmosis, syphilis, hepatitides B and C, HIV), infantile systemic lupus erythematosus, or mercury exposure.

Primary congenital nephrotic syndrome is due to a variety of syndromes inherited as autosomal recessive disorders (see Table 545.3). A number of structural and functional abnormalities of the glomerular filtration barrier causing congenital nephrotic syndrome have been elucidated. In a large European cohort of children with congenital nephrotic syndrome, 85% carried disease-causing mutations in four genes *(NPHS1*, *NPHS2*, *WT1*, and *LAMB2)*, the first three of which encode components of the glomerular filtration barrier. The Finnish type of congenital nephrotic syndrome is caused by mutations in the *NPHS1* or *NPHS2* gene, which encodes nephrin and podocin, critical components of the slit diaphragm. Affected infants most commonly present at birth with edema caused by massive proteinuria, and they are typically delivered with an enlarged placenta (>25% of the infant's weight). Severe hypoalbuminemia, hyperlipidemia, and hypogammaglobulinemia result from loss of filtering selectivity at the glomerular filtration barrier. Prenatal diagnosis can be made by the presence of elevated maternal and amniotic α-fetoprotein levels.

Denys-Drash syndrome is caused by mutations in the *WT1* gene, which results in abnormal podocyte function. Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumors.

Mutations in the *LAMB2* gene, seen in **Pierson syndrome,** lead to abnormalities of β_2 -laminin, a critical component of the glomerular and ocular basement membranes. In addition to congenital nephrotic syndrome, affected infants display bilateral microcoria (fixed narrowing of the pupil).

Galloway-Mowat syndrome is characterized by microcephaly with hiatal hernia and congenital nephrotic syndrome. Patients have distinctive kidney biopsy findings with loss of or poor basement membrane formation or permeation of their basement membranes with fibrils.

Regardless of the etiology of congenital nephrotic syndrome, the diagnosis is made clinically in newborns or infants who demonstrate severe generalized edema, poor growth and nutrition with hypoalbuminemia, increased susceptibility to infections, hypothyroidism (from urinary loss of thyroxin-binding globulin), and an increased risk of thrombotic events. Most infants have progressive renal insufficiency.

Treatment with albumin and diuretic infusions, providing high amounts of protein (3-4 g/kg), lipids, and a high caloric intake to maintain nutrition, along with vitamin and thyroid hormone replacement, has been the mainstream therapy for congenital nephrotic syndrome. Treatment of the congenital syndrome also consists of unilateral nephrectomy and use of angiotensin-converting enzyme inhibitors and/or indomethacin to decrease the proteinuria and glomerular filtration rate. Some centers prefer more aggressive therapy, including bilateral nephrectomy at 1-2 yr of age, weight > 7 kg, and initiation of peritoneal dialysis with subsequent kidney transplantation.

Secondary congenital nephrotic syndrome can resolve with treatment of the underlying cause, such as syphilis (Table 545.5). The management of primary congenital nephrotic syndrome includes intensive supportive care with intravenous albumin and diuretics, regular administration of intravenous γ-globulin, and aggressive nutritional support (often parenteral), while attempting to pharmacologically decrease urinary protein loss with angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors, or even unilateral nephrectomy. If conservative management fails and patients suffer from persistent anasarca or repeated severe infections, bilateral nephrectomies are performed, and chronic dialysis is initiated. Renal transplantation is the definitive treatment of congenital nephrotic syndrome, though recurrence of the nephrotic syndrome has been reported to occur after transplantation.

Table 545.5

Causes of Nephrotic Syndrome in Infants Younger Than 1 Year of Age

SECONDARY CAUSES
Infections
Syphilis Cytomegalovirus Toxoplasmosis Rubella Hepatitis B HIV Malaria
Drug Reactions
Toxins Mercury
Syndromes With Associated Renal Disease
Nail–patella syndrome Lowe syndrome Nephropathy associated with congenital brain malformation Denys-Drash syndrome: Wilms tumor Hemolytic-uremic syndrome Systemic lupus erythematosus
PRIMARY CAUSES
Congenital nephrotic syndrome Diffuse mesangial sclerosis Minimal change disease Focal segmental sclerosis Membranous nephropathy

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, 2/e, Philadelphia, 2004, Saunders, p. 418.

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SECTION 4

Tubular Disorders

OUTLINE

Chapter 546 Tubular Function
Chapter 547 Renal Tubular Acidosis
Chapter 548 Nephrogenic Diabetes Insipidus
Chapter 549 Inherited Tubular Transport Abnormalities
Chapter 550 Renal Failure
Chapter 551 Renal Transplantation

CHAPTER 546

Tubular Function

Bradley P. Dixon

Water and electrolytes are freely filtered at the level of the glomerulus. Thus, the electrolyte content of ultrafiltrate at the beginning of the proximal tubule is similar to that of plasma. Carefully regulated processes of tubular reabsorption and/or tubular secretion determine the final water content and electrolyte composition of urine. Bulk movement of solute tends to occur in the proximal portions of the nephron, and fine adjustments tend to occur distally (see Chapter 68).

Sodium

Sodium is essential in maintaining extracellular fluid balance and, thus, volume status. The kidney is capable of effecting large changes in sodium excretion in a variety of normal and pathologic states.

There are four main sites of sodium transport. Approximately 60% of sodium is absorbed in the proximal tubule by coupled transport with glucose, amino acids, and phosphate; 25% in the ascending loop of Henle (mediated by NKCC2, the bumetanide-sensitive sodium-potassium-2 chloride transporter); and 15% in the distal tubule (mediated by NCCT, the thiazide-sensitive sodium chloride cotransporter) and collecting tubule (mediated by ENaC, the epithelial sodium channel).

The urinary excretion of sodium normally approximates the sodium intake of 2-6 mEq/kg/24 hr for a child consuming a typical American diet, minus 1-2 mEq/kg/24 hr required for normal metabolic processes. However, in states of volume depletion (dehydration, blood loss) or decreased effective circulating blood volume (septic shock, hypoalbuminemic states, heart failure), there may be a dramatic decrease in urinary sodium excretion to as low as 1 mEq/L.

Changes in systemic volume status are detected by (1) baroreceptors in the atria, afferent arteriole, and carotid sinus and (2) by the macula densa, which detects changes in chloride delivery.

The major hormonal mechanisms mediating sodium balance include the renin–angiotensin–aldosterone axis, atrial natriuretic factor, and norepinephrine. Angiotensin II and aldosterone increase sodium reabsorption in the proximal tubule and distal tubule, respectively. Norepinephrine, released in response to volume depletion, does not directly act on tubular transport mechanisms but affects sodium balance by decreasing renal blood flow, thus decreasing the filtered load of sodium as well as stimulating renin release. With more severe volume depletion, antidiuretic hormone is also released (see Chapter 548). Sodium excretion is promoted by atrial natriuretic factor and suppression of renin.

Potassium

Extracellular potassium homeostasis is regulated because small changes in plasma potassium concentrations have dramatic effects on cardiac, neural, and neuromuscular function (see Chapter 68.4). Essentially, all filtered potassium is fully reabsorbed in the proximal tubule and ascending loop of Henle. Therefore, urinary excretion of potassium is completely dependent on tubular secretion by potassium channels present in the principal cells of the collecting tubule. Factors that promote potassium secretion include aldosterone, increased sodium delivery to the distal nephron, and increased urine flow rate.

Calcium

A significant portion of filtered calcium (70%) is reabsorbed in the proximal tubule. Additional calcium is reabsorbed in the ascending loop of Henle (20%) and the distal tubule and collecting duct (5–10%). Calcium is reabsorbed by passive movement between cells (paracellular absorption) in a process driven by sodium chloride reabsorption and potassium recycling into the lumen. In addition, calcium uptake is actively regulated by calcium receptors, specific transporters, and calcium channels. Factors that promote calcium reabsorption include parathyroid hormone (released in response to hypocalcemia), calcitonin, vitamin D, thiazide diuretics, and volume depletion (see Chapter 588). Factors that promote calcium excretion include volume expansion, increased sodium intake, and diuretics such as mannitol and furosemide.

Phosphate

The majority of filtered phosphate is reabsorbed in the proximal tubule by active transport coupled with sodium. Reabsorption is increased by dietary phosphorus restriction, volume contraction, and growth hormone. Parathyroid hormone and volume expansion increase phosphate excretion.

Magnesium

Approximately 25% of filtered magnesium is reabsorbed in the proximal tubule. Modulation of renal magnesium excretion occurs primarily in the ascending loop of Henle, with some contribution of the distal convoluted tubule. Magnesium is transported by the paracellular route similar to calcium, as well as through the transcellular route. Although specific magnesium transporters for transcellular absorption have been identified, the precise mechanisms by which they are regulated remain unclear.

Acidification and Concentrating Mechanisms

Acidification and concentration are addressed in the sections on renal tubular acidosis and nephrogenic diabetes insipidus, respectively (see Chapters 547 and 548).

Developmental Considerations

The tubular transport capabilities of neonates (especially premature infants) and young infants are less than those of adults. Although nephronogenesis (the formation of new glomerular/tubular units) is complete by about 36 wk of gestation, significant tubular maturation occurs during infancy. Renal tubular immaturity, a reduced glomerular filtration rate, a decreased concentrating gradient, and a diminished responsiveness to antidiuretic hormone are characteristic of young infants. These factors can contribute to impaired regulation of water, solute, and electrolyte and acid–base homeostasis, particularly during times of acute illness.

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CHAPTER 547

Renal Tubular Acidosis

Bradley P. Dixon

Renal tubular acidosis (RTA) is a disease state characterized by a non–anion gap (hyperchloremic) metabolic acidosis in the setting of a normal or near-normal glomerular filtration rate. There are four main types: proximal (type II) RTA, classic distal (type I) RTA, hyperkalemic (type IV) RTA, and a combined proximal and distal (type III). Proximal RTA results from impaired bicarbonate reabsorption and distal RTA from failure to secrete acid. Either of these defects may be inherited and persistent from birth or acquired, as is seen more commonly in clinical practice.

Normal Urinary Acidification

Kidneys contribute to the acid–base balance by reabsorption of filtered bicarbonate (HCO_3^-) and excretion of hydrogen ion (H^+) produced every day. Hydrogen ion secretion from tubule cells into the lumen is key in the reabsorption of HCO_3^- and the formation of titratable acid (H^+ bound to buffers such as HPO_4^{2-}) and ammonium ions (NH_4^+). Because loss of filtered HCO_3^- is equivalent to the addition of H^+ to the body, all filtered bicarbonate should be absorbed before dietary H^+ can be excreted. Approximately 90% of filtered bicarbonate is absorbed in the proximal tubule and the remaining 10% in the distal segments, mostly the thick ascending limb and outer medullary collecting tubule (Fig. 547.1). In the proximal tubule and thick ascending limb of the loop of Henle, H^+ from water is secreted by the Na^+ -H^+ exchanger on the luminal membrane. H^+ combines with filtered bicarbonate, resulting in the formation of H_2CO_3, which splits into water and CO_2 in the presence of carbonic anhydrase

IV. CO_2 diffuses freely back into the cell, combines with OH^- (from H_2O) to form HCO_3^- in the presence of carbonic anhydrase II, and returns to the systemic circulation via an Na^+-HCO_3^- cotransporter situated at the basolateral membrane of the cell. In the collecting tubule, H^+ is secreted into the lumen by H^+ ATPase (adenosine triphosphatase) and HCO_3^- is returned to the systemic circulation by the HCO_3^--Cl^- exchanger located on the basolateral membrane. The H^+ secreted proximally and distally in excess of the filtered HCO_3^- is excreted in the urine either as titratable acid ($H_2PO_4^-$) or as NH_4^+.

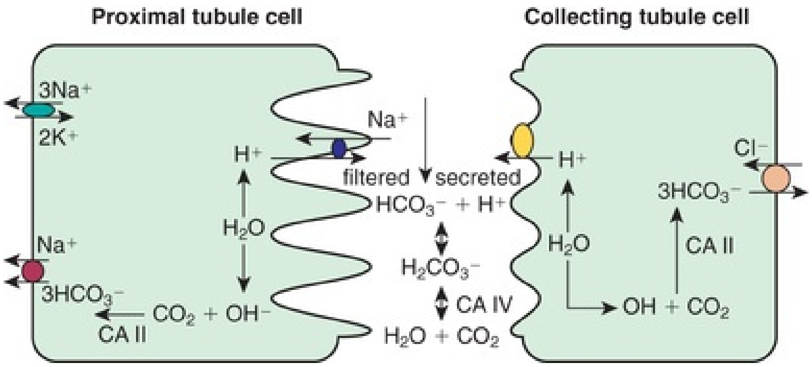

FIG. 547.1 Major cellular luminal events in acid–base regulation in the proximal and collecting tubule cells. In the proximal tubule, H^+, split from H_2O, is secreted into the lumen via Na^+/H^+ exchanger, and HCO_3^-, formed by combination of OH^- (split from H_2O) with CO_2 in the presence of carbonic anhydrase (CA) II, is returned to the systemic circulation by an Na^+-$3HCO_3^-$ cotransporter. Similarly, in the collecting tubule, H^+ is secreted into the lumen by an active H^+-ATPase (adenosine triphosphatase), and HCO_3^- is returned to the systemic circulation via an HCO_3^--Cl^- exchanger. H^+ secreted into the lumen combines with filtered HCO_3^- to form carbonic acid (H_2CO_3) and then CO_2 and H_2O in the presence of CA IV, which can be passively reabsorbed. (Modified from Rose BD, Post TW: Clinical physiology of acid-base and electrolyte disorders, ed 5/e, New York, 2001, McGraw-Hill.)

547.1

Proximal (Type II) Renal Tubular Acidosis

Bradley P. Dixon

Pathogenesis

Proximal RTA can be inherited and persistent from birth or occur as a transient phenomenon during infancy. Although rare, it may be primary and isolated. Proximal RTA usually occurs as a component of global proximal tubular dysfunction or **Fanconi syndrome,** which is characterized by low-molecular-weight proteinuria, glycosuria, phosphaturia, aminoaciduria, and proximal RTA. Table 547.1 outlines the causes of proximal RTA (pRTA) and Fanconi syndrome. Many of these causes are inherited disorders. In addition to **cystinosis** and **Lowe syndrome,** autosomal recessive and dominant pRTA are addressed further in this section. Other inherited forms of Fanconi syndrome include **galactosemia** (see Chapter 105.2), **hereditary fructose intolerance** (see Chapter 105.3), **tyrosinemia** (see Chapter 103.2), and **Wilson disease** (see Chapter 384.2). **Dent disease,** or X-linked nephrolithiasis, is discussed in Chapter 549.3 . In children, an important form of secondary Fanconi syndrome is exposure to medications such as ifosfamide, a component of many treatment regimens for Wilms tumor and other malignancies.

Table 547.1

Disorders With Dysfunction of Renal Acidification—Defective HCO_3^- Reclamation: Proximal Renal Tubular Acidosis

ISOLATED PURE BICARBONATE WASTING (UNASSOCIATED WITH FANCONI SYNDROME)
• Primary
• Inherited autosomal recessive with ocular abnormalities (missense mutations of *SLC4A4*)
• Autosomal dominant with short stature (mutation of *SLC9A3/* NHE3)
• Carbonic anhydrase deficiency, inhibition, or alteration
Drugs

        - Acetazolamide
        - Topiramate
        - Sulfanilamide
        - Mafenide acetate
        - Carbonic anhydrase II deficiency with osteopetrosis (mixed proximal and distal RTA type 3)

GENERALIZED (ASSOCIATED WITH FANCONI SYNDROME)

- Primary (without associated systemic disease)
    - Genetic
    - Sporadic
- Genetically transmitted systemic diseases
    - Cystinosis
    - Lowe syndrome
    - Wilson syndrome
    - Tyrosinemia
    - Galactosemia
    - Hereditary fructose intolerance (during fructose ingestion)
    - Metachromatic leukodystrophy
    - Pyruvate carboxylase deficiency
    - Methylmalonic acidemia
- Dysproteinemic states
    - Multiple myeloma
    - Monoclonal gammopathy
- Secondary hyperparathyroidism with chronic hypocalcemia
    - Vitamin D deficiency or resistance
    - Vitamin D dependency
- Drugs or toxins
    - Ifosfamide
    - Outdated tetracycline
    - 3-Methylchromone
    - Streptozotocin
    - Lead
    - Mercury
    - Amphotericin B (historical)
- Tubulointerstitial diseases
    - Sjögren syndrome
    - Medullary cystic disease
    - Renal transplantation
- Other renal and miscellaneous diseases
    - Nephrotic syndrome
    - Amyloidosis
    - Paroxysmal nocturnal hemoglobinuria

From DuBose TD Jr: Disorders of acid-base balance. In Skorecki K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's the kidney, 10/e, Philadelphia, 2016, Elsevier, 2016, Table17-7.

Autosomal Recessive Disease

Isolated **autosomal recessive pRTA** is caused by mutations in the gene encoding the sodium bicarbonate cotransporter NBC1. It manifests with ocular abnormalities (band keratopathy, cataracts, and glaucoma, often leading to blindness), short stature, enamel defects of the teeth, intellectual impairment, and occasionally basal ganglia calcification along with pRTA. An autosomal dominant pattern of inheritance has been identified in a single pedigree with nine members presenting with hyperchloremic metabolic acidosis, a normal ability to acidify urine, normal renal function, and growth retardation.

Cystinosis

Cystinosis is a systemic disease caused by a defect in the metabolism of cysteine that results in accumulation of cystine (an oxidized form of cysteine in which two cysteine molecules are joined together by their sulfhydryl groups through a disulfide bond) crystals in most of the major organs of the body, notably the kidney, liver, eye, and brain. It occurs at an incidence of 1 : 100,000 to 1 : 200,000. In certain populations, such as French Canadians, the incidence is much higher. At least three clinical patterns have been described. Young children with the most severe form of the disease *(infantile* or *nephropathic cystinosis)* present in the 1st or 2nd year of life with severe tubular dysfunction and growth failure. If the disease is not treated, the children develop end-stage renal disease by the end of their 1st decade. A milder form of the disease manifests in adolescents and is characterized by less-severe tubular abnormalities and a slower progression to renal failure. A benign adult form with ocular involvement but no renal involvement also exists.

Cystinosis is caused by mutations in the *CTNS* gene, which encodes the protein cystinosin. Cystinosin is thought to be an H^+ -driven lysosomal cystine transporter. Genotype–phenotype studies demonstrate that patients with severe nephropathic cystinosis carry mutations that lead to complete loss of cystinosin function. Patients with milder clinical disease have mutations that lead to the expression of partially functional protein. Patients with nephropathic cystinosis present with clinical manifestations reflecting their pronounced tubular dysfunction and Fanconi syndrome, including polyuria and polydipsia, growth failure, and rickets. Fever, caused by dehydration or diminished sweat production, is common. Patients are typically fair skinned and blond because of diminished pigmentation. Ocular presentations include photophobia, retinopathy, and impaired visual acuity. Patients also can develop hypothyroidism, hepatosplenomegaly, and delayed sexual maturation. With progressive tubulointerstitial fibrosis, renal insufficiency is invariant.

The diagnosis of cystinosis is suggested by the detection of cystine crystals in the cornea and confirmed by measurement of increased leukocyte cystine content. Prenatal testing is available for at-risk families.

Treatment of cystinosis is directed at correcting the metabolic abnormalities associated with Fanconi syndrome or chronic renal failure. In addition, specific therapy is available with cysteamine, which converts cystine to cysteine and a cysteine–cysteamine heterodimer. This facilitates lysosomal transport and decreases tissue cystine. Oral cysteamine does not achieve adequate levels in ocular tissues, so additional therapy with cysteamine eyedrops is required. Early initiation of the drug can prevent or delay deterioration of renal function. Patients with growth failure that does not improve with cysteamine might benefit from treatment with growth hormone. Kidney transplantation is a viable option in patients with renal failure. With prolonged survival, additional complications may become evident, including central nervous system abnormalities, muscle weakness, swallowing dysfunction, and pancreatic insufficiency. It is unclear whether long-term cysteamine therapy will decrease these complications.

Lowe Syndrome

Lowe syndrome *(oculocerebrorenal syndrome of Lowe)* is a rare X-linked disorder characterized by congenital cataracts, mental retardation, and Fanconi syndrome. The disease is caused by mutations in the *OCRL1* gene, which encodes the phosphatidylinositol polyphosphate 5-phosphatase protein. The abnormalities seen in Lowe syndrome are thought to be caused by abnormal transport of vesicles within the Golgi apparatus. Kidneys show nonspecific tubulointerstitial changes. Thickening of glomerular basement membrane and changes in proximal tubule mitochondria are also seen.

Patients with Lowe syndrome typically present in infancy with cataracts, progressive growth failure, hypotonia, and Fanconi syndrome. Significant low-molecular-weight proteinuria is common. Blindness and renal insufficiency often develop. Characteristic behavioral abnormalities are also seen, including tantrums, stubbornness, stereotypy (repetitive behaviors), and obsessions. There is no specific therapy for the renal disease or neurologic deficits. Cataract removal is generally required.

Clinical Manifestations of Proximal Renal Tubular Acidosis and Fanconi Syndrome

Patients with isolated, sporadic, or inherited pRTA present with growth failure in the 1st year of life. Additional symptoms can include polyuria, dehydration (from sodium loss), anorexia, vomiting, constipation, and hypotonia. Patients with primary Fanconi syndrome have additional symptoms, secondary to phosphate wasting, such as rickets. Those with systemic diseases present with additional signs and symptoms specific to their underlying disease. Urinalysis in patients with isolated pRTA is generally unremarkable. The urine pH is acidic (<5.5) because distal acidification mechanisms are intact in these patients. Urinary studies in patients with Fanconi syndrome demonstrate varying degrees of phosphaturia, aminoaciduria, glycosuria, uricosuria, and elevated urinary sodium or potassium. Depending on the nature of the underlying disorder, laboratory evidence of chronic renal insufficiency, including elevated serum creatinine, may be present.

547.2

Distal (Type I) Renal Tubular Acidosis

Bradley P. Dixon

Pathogenesis

Distal RTA can be sporadic or inherited. It can also occur as a complication of inherited or acquired diseases of the distal tubules. Primary or secondary causes of distal RTA can result from damaged or impaired functioning of one or more transporters or proteins involved in the acidification process, including the H^+/ATPase, the HCO_3^-/Cl^- anion exchangers, or the components of the aldosterone pathway. Because of impaired hydrogen ion excretion, the urine pH cannot be reduced to < 5.5, despite the presence of severe metabolic acidosis. Loss of sodium bicarbonate distally, owing to lack of H^+ to bind to in the tubular lumen (see Fig. 547.1), results in increased chloride absorption and hyperchloremia. Inability to secrete H$^+$ is compensated for by increased K$^+$ secretion distally, leading to hypokalemia. **Hypercalciuria** is usually present and can lead to nephrocalcinosis or nephrolithiasis. Chronic metabolic acidosis also impairs urinary citrate excretion. **Hypocitraturia** further increases the risk of calcium deposition in the tubules. Bone disease is common, resulting from mobilization of organic components from bone to serve as buffers to chronic acidosis.

Clinical Manifestations

Distal RTA shares features with those of pRTA, including non–anion gap metabolic acidosis and growth failure; distinguishing features of distal RTA include nephrocalcinosis and hypercalciuria. The phosphate and massive bicarbonate wasting characteristic of pRTA is generally absent. Table 547.2 lists the causes of primary and secondary distal RTA. Although inherited forms are rare, three specific inherited forms of distal RTA have been identified, including an autosomal recessive form associated with sensorineural deafness.

Table 547.2

Disorders With Dysfunction of Renal Acidification—Selective Defect in Net Acid Excretion: Classic Distal Renal Tubular Acidosis

PRIMARY DISORDERS	
Familial	
Autosomal dominant	
AE1 gene	
Autosomal recessive	
With deafness (*rdRTA1* or *ATP6V1B1* gene)	
Without deafness (*rdRTA2* or *ATP6V0A4*)	
Sporadic	
ENDEMIC DISORDERS	
Northeastern Thailand	
DISORDERS SECONDARY TO SYSTEMIC DISORDERS	
Autoimmune Diseases	
Hyperglobulinemic purpura	Fibrosing alveolitis
Cryoglobulinemia	Chronic active hepatitis
Sjögren syndrome	Primary biliary cirrhosis
Thyroiditis	Polyarteritis nodosa
HIV nephropathy	

Hypercalciuria and Nephrocalcinosis	
Primary hyperparathyroidism	Vitamin D intoxication
Hyperthyroidism	Idiopathic hypercalciuria
Medullary sponge kidney	Wilson disease
Fabry disease	Hereditary fructose intolerance
X-linked hypophosphatemia	
DRUG- AND TOXIN-INDUCED DISEASE	
Amphotericin B	Toluene
Cyclamate	Mercury
Hepatic cirrhosis	Vanadate
Ifosfamide	Lithium
Foscarnet	Classic analgesic nephropathy
TUBULOINTERSTITIAL DISEASES	
Balkan nephropathy	Kidney transplantation
Chronic pyelonephritis	Leprosy
Obstructive uropathy	Jejunoileal bypass with hyperoxaluria
Vesicoureteral reflux	
DISORDERS ASSOCIATED WITH GENETICALLY TRANSMITTED DISEASES	
Ehlers-Danlos syndrome	Hereditary elliptocytosis
Sickle cell anemia	Marfan syndrome
Medullary cystic disease Hereditary sensorineural deafness	Jejunal bypass with hyperoxaluria
Osteopetrosis with carbonic anhydrase II deficiency (mixed proximal and distal RTA type III)	Carnitine palmitoyltransferase deficiency

From DuBose TD Jr: Disorders of acid-base balance In Skorecki K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's the kidney, 10/e, Philadelphia, 2016, Elsevier, 2016, Table 17-9.

Medullary sponge kidney is a relatively rare sporadic disorder in children, although not uncommon in adults. It is characterized by cystic dilation of the terminal portions of the collecting ducts as they enter the renal pyramids. On ultrasound studies, patients often have medullary nephrocalcinosis. Although patients with this condition typically maintain normal renal function through adulthood, complications include nephrolithiasis, pyelonephritis, hyposthenuria (inability to concentrate urine), and distal RTA. Associations of medullary sponge kidney with Beckwith-Wiedemann syndrome or hemihypertrophy have been reported.

547.3

Hyperkalemic (Type IV) Renal Tubular Acidosis

Bradley P. Dixon

Pathogenesis

Type IV RTA occurs as the result of impaired aldosterone production *(hypoaldosteronism)* or impaired renal responsiveness to aldosterone *(pseudohypoaldosteronism).* Acidosis results because aldosterone has a direct effect on the H^+ /ATPase responsible for hydrogen secretion. In addition, aldosterone is a potent stimulant for potassium secretion in the collecting tubule; consequently, lack of aldosterone results in hyperkalemia. This further affects the acid–base status by inhibiting ammoniagenesis and, thus, H^+ excretion. Aldosterone deficiency typically occurs as a result of adrenal gland disorders such as Addison disease or some forms of congenital adrenal hyperplasia. In children, aldosterone unresponsiveness is a more common cause of type IV RTA. This can occur transiently, during an episode of acute pyelonephritis or acute urinary obstruction, or chronically, particularly in infants and children with a history of obstructive uropathy. The latter patients can have significant hyperkalemia, even in instances when renal function is normal or only mildly impaired. Rare examples of inherited forms of type IV RTA have been identified (Table 547.3).

Table 547.3

Disorders With Dysfunction of Renal Acidification—Generalized Abnormality of Distal Nephron With Hyperkalemia

MINERALOCORTICOID DEFICIENCY
Primary Mineralocorticoid Deficiency

• **Combined deficiency of aldosterone, desoxycorticosterone, and cortisol**
  • Addison disease
  • Bilateral adrenalectomy
  • Bilateral adrenal destruction
  • Hemorrhage or carcinoma
• **Congenital enzymatic defects**
  • 21-Hydroxylase deficiency
  • 3β-Hydroxydehydrogenase deficiency
  • Desmolase deficiency
• **Isolated (selective) aldosterone deficiency**
  • Chronic idiopathic hypoaldosteronism

  - Heparin (low-molecular-weight or unfractionated) administration in critically ill patient
  - Familial hypoaldosteronism
  - Corticosterone methyl oxidase deficiency types 1 and 2
  - Primary zona glomerulosa defect
  - Transient hypoaldosteronism of infancy
  - Persistent hypotension and/or hypoxemia
- **Angiotensin-converting enzyme inhibition**
  - Endogenous
  - Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Secondary Mineralocorticoid Deficiency

- **Hyporeninemic hypoaldosteronism**
  - Diabetic nephropathy
  - Tubulointerstitial nephropathies
  - Nephrosclerosis
  - Nonsteroidal antiinflammatory agents
  - Acquired immunodeficiency syndrome
  - Immunoglobulin M monoclonal gammopathy
  - Obstructive uropathy

MINERALOCORTICOID RESISTANCE

- **PHA I—autosomal dominant (human mineralocorticoid receptor defect)**

Renal Tubular Dysfunction (Voltage Defect)

- **PHA I—autosomal recessive**
- **PHA II—autosomal dominant**
- **Drugs that interfere with Na^+ channel function in the CCT**
  - Amiloride
  - Triamterene
  - Trimethoprim
  - Pentamidine
- **Drugs that interfere with Na^+ -K^+ -ATPase in the CCT**
  - Cyclosporine, tacrolimus
- **Drugs that inhibit aldosterone effect on the CCT**
  - Spironolactone
- **Disorders associated with tubulointerstitial nephritis and renal insufficiency**
  - Lupus nephritis
  - Methicillin nephrotoxicity
  - Obstructive nephropathy
  - Kidney transplant rejection
  - Sickle cell disease
  - Williams syndrome with uric acid nephrolithiasis

ATPase, adenosine triphosphatase; CCT, cortical collecting tubule; PHA I, PHA II, pseudohypoaldosteronism types 1 and 2.

From DuBose TD Jr: Disorders of acid-base balance. In Skorecki K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's the kidney, 10/e, Philadelphia, 2016, Elsevier, 2016, Table 17-11.

Clinical Manifestations

Patients with type IV RTA can present with growth failure in the 1st few years of life. Polyuria and dehydration (from salt wasting) are common. Rarely, patients (especially those with pseudohypoaldosteronism type 1) present with life-threatening hyperkalemia. Patients with obstructive uropathies can present acutely with signs and symptoms of pyelonephritis, such as fever, vomiting, and foul-smelling urine. Laboratory tests reveal a hyperkalemic non–anion gap metabolic acidosis. Urine may be alkaline or acidic. Elevated urinary sodium levels with inappropriately low urinary potassium levels reflect the absence of aldosterone effect.

Diagnostic Approach to Renal Tubular Acidosis

The first step in the evaluation of a patient with suspected RTA is to confirm the presence of a normal anion gap metabolic acidosis, identify electrolyte abnormalities, assess renal function, and rule out other causes of bicarbonate loss such as diarrhea (see Chapter 55) (Table 547.4). Metabolic acidosis associated with diarrheal dehydration is extremely common, and acidosis generally improves with correction of volume depletion. Patients with protracted diarrhea can deplete their total-body bicarbonate stores and can have persistent acidosis despite apparent restoration of volume status. In instances where a patient has a recent history of severe diarrhea, full evaluation for RTA should be delayed for several days to permit adequate time for reconstitution of total-body bicarbonate stores. If acidosis persists beyond a few days in this setting, additional studies are indicated.

Table 547.4

Contrasting Features and Diagnostic Studies in Renal Tubular Acidosis

FINDING	TYPE OF RENAL TUBULAR ACIDOSIS		
	Proximal	**Classic Distal**	**Generalized Distal Dysfunction**
Plasma [K^+]	Low	Low	High
Urine pH with acidosis	<5.5	>5.5	<5.5 or >5.5
Urine net charge	Negative	Positive	Positive
Fanconi lesion	Present with acquired pRTA	Absent	Absent
Fractional bicarbonate excretion	>10–15% during alkali therapy	2–5%	5–10%
U−BPco$_2$	Normal	Low	Low
Response to therapy	Least responsive	Responsive	Less responsive

Associated features	Fanconi syndrome	Nephrocalcinosis/hyperglobulinemia	Renal insufficiency

ATPase, adenosine triphosphatase; pRTA, proximal renal tubular acidosis; $U{-}BP_{CO_2}$, urine minus blood CO_2 pressure.

From DuBose TD Jr: Disorders of acid-base balance. In Skorecki K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's the kidney, 10/e, Philadelphia, 2016, Elsevier, 2016, Table 17-17.

Serum electrolytes, blood urea nitrogen, calcium, phosphorus, creatinine, and pH should be obtained by venipuncture. Traumatic blood draws (such as heel-stick specimens), small volumes of blood in adult-size specimen collection tubes, or a prolonged specimen transport time at room temperature can lead to falsely low bicarbonate levels, often in association with an elevated serum potassium value. True hyperkalemic acidosis is consistent with type IV RTA, whereas the finding of normal or low potassium suggests type I or II. The **blood anion gap** should be calculated using the formula $[Na^+] - [Cl^- + HCO_3^-]$. Values of < 12 demonstrate the absence of an anion gap. Values of > 20 indicate the presence of an anion gap. If such an anion gap is found, then other diagnoses (lactic acidosis, diabetic ketoacidosis, inborn errors of metabolism, ingested toxins) should be investigated. If tachypnea is noted, evaluation of an arterial blood gas may be appropriate to evaluate the possibility of a mixed acid–base disorder primarily involving respiratory and metabolic components. A detailed history, with particular attention to growth and development, recent or recurrent diarrheal illnesses, a family history of mental retardation, failure to thrive, end-stage renal disease, infant deaths, or miscarriages is essential. The physical examination should determine growth parameters and volume status as well as the presence of any dysmorphic features suggesting an underlying syndrome.

Once the presence of a non–anion gap metabolic acidosis is confirmed, the urine pH can help distinguish distal from proximal causes. A urine pH < 5.5 in the presence of acidosis suggests pRTA, whereas patients with distal RTA typically have a urine pH > 6.0. The **urine anion gap** ($[\text{urine } Na^+ + \text{urine } K^+] - \text{urine } Cl^-$) is sometimes calculated to confirm the diagnosis of distal RTA. A positive gap suggests a deficiency of ammoniagenesis and, thus, the possibility of a distal RTA. A negative gap is consistent with proximal tubule bicarbonate wasting (or gastrointestinal bicarbonate wasting). A urinalysis should also be obtained to determine the presence of glycosuria, proteinuria, or hematuria, suggesting more global tubular damage or dysfunction. Random or 24 hr urine calcium and creatinine measurements will identify hypercalciuria. Renal ultrasonography should be performed to identify underlying structural abnormalities such as obstructive uropathies, as well as to determine the presence of nephrocalcinosis (Fig. 547.2).

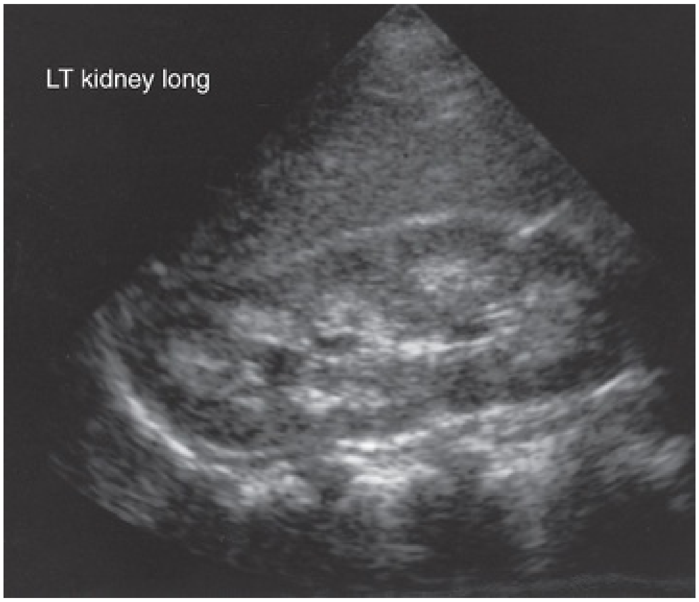

FIG. 547.2 Ultrasound examination of a child with distal RTA, demonstrating medullary nephrocalcinosis.

Treatment and Prognosis

The mainstay of therapy in all forms of RTA is bicarbonate replacement. Patients with pRTA often require large quantities of bicarbonate, up to 20 mEq/kg/24 hr, in the form of sodium bicarbonate or sodium citrate solution (Bicitra or Shohl solution). The base requirement for distal RTAs is generally in the range of 2-4 mEq/kg/24 hr, although individual patients' requirements can vary. Patients with Fanconi syndrome usually require phosphate supplementation. Patients with distal RTA should be monitored for the development of hypercalciuria. Those with symptomatic hypercalciuria (recurrent episodes of gross hematuria), nephrocalcinosis, or nephrolithiasis can require thiazide diuretics to decrease urine calcium excretion. Patients with type IV RTA can require chronic treatment for hyperkalemia with sodium–potassium exchange resin (i.e., sodium polystyrene sulfonate).

The prognosis of RTA depends to a large extent on the nature of any existing underlying disease. Patients with treated isolated proximal or distal RTA generally demonstrate improvement in growth, provided serum bicarbonate levels can be maintained in the normal range. Patients with systemic illness and Fanconi syndrome can have ongoing morbidity with growth failure, rickets, and signs and symptoms related to their underlying disease.

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547.4

Rickets Associated With Renal Tubular Acidosis

Bradley P. Dixon

Rickets may be present in primary RTA, particularly in pRTA due to the added features of hypophosphatemia and phosphaturia from generalized proximal tubular dysfunction. Bone demineralization without overt rickets usually is detected in distal (type I) RTA. This metabolic bone disease may be characterized by bone pain, growth retardation, osteopenia, and, occasionally, pathologic fractures.

Bone demineralization in distal RTA probably relates to dissolution of bone because the calcium carbonate in bone serves as a buffer against the metabolic acidosis due to the hydrogen ions retained by patients with RTA.

Administration of sufficient bicarbonate to reverse acidosis reverses bone dissolution and the hypercalciuria that is common in distal RTA. Proximal RTA is treated with both bicarbonate and oral phosphate supplements to heal rickets. Doses of phosphate similar to those used in familial hypophosphatemia or Fanconi syndrome may be indicated. Vitamin D is required to offset the secondary hyperparathyroidism that complicates oral phosphate therapy. Following therapy, growth in patients with type II (proximal) RTA is greater than in patients with primary Fanconi syndrome.

CHAPTER 548

Nephrogenic Diabetes Insipidus

Bradley P. Dixon

Nephrogenic diabetes insipidus (NDI) is a rare congenital or, more commonly, acquired, disorder of water metabolism characterized by an inability to concentrate urine, even in the presence of antidiuretic hormone (ADH). The most common pattern of inheritance in congenital NDI is as an X-linked recessive disorder. Rarely, affected females are seen, presumably secondary to nonrandom X-chromosome inactivation. Approximately 10% of cases of congenital NDI are inherited as autosomal dominant or recessive disorders, with males and females affected equally. The clinical phenotype of autosomal recessive forms is similar to that of the X-linked form. Secondary (acquired), either partial or complete, forms of NDI are not uncommon. They may be seen in many disorders affecting renal tubular function, including obstructive uropathies, acute or chronic renal failure, renal cystic diseases, interstitial nephritis, nephrocalcinosis, or toxic nephropathy caused by hypokalemia, hypercalcemia, lithium, or amphotericin B.

Pathogenesis

The ability to concentrate urine (and thus absorb water) requires the delivery of urine to the collecting tubule; an intact concentrating gradient in the renal medulla; and the ability to modulate water permeability in the collecting tubule by ADH. ADH (also called arginine vasopressin [AVP]), is synthesized in the hypothalamus and stored in the posterior pituitary. Under basal situations, the collecting tubule is impermeable to water. However, in response to increased serum osmolality (as detected by osmoreceptors in the hypothalamus) and/or severe volume depletion, ADH is released into the systemic circulation. It then binds to its receptor, vasopressin V_2 R (AVPR2), on the basolateral membrane of the collecting tubule cell. Binding of the hormone to its receptor activates a cyclic adenosine monophosphate–dependent cascade that results in movement of preformed water channels (aquaporin 2 [AQP2]) to the luminal membrane of the collecting duct, rendering it permeable to water.

Defects in the *AVPR2* gene cause the more common X-linked form of NDI. Mutations in the *AQP2* gene have been identified in patients with the rarer autosomal dominant and recessive forms. Prenatal testing is available for families at risk for X-linked NDI. Patients with secondary forms of NDI can have ADH resistance owing to defective aquaporin expression (as seen in lithium intoxication). Secondary ADH resistance usually occurs as the result of loss of the hypertonic medullary gradient as a result of solute diuresis or tubular damage, resulting in the inability to absorb sodium or urea.

Clinical Manifestations

Patients with congenital NDI typically present in the newborn period with massive polyuria, volume depletion, hypernatremia, and hyperthermia. Irritability and inconsolability are common features. Constipation and poor weight gain are also seen. After multiple episodes of hypernatremic dehydration in infancy, patients can have developmental delay and mental retardation, although this has become less common with cautious fluid resuscitation and gradual correction of hypernatremia. Enuresis, caused by large urine volumes, is common. Because of the need to consume large volumes of water during the day, patients often have diminished appetite and poor food intake. However, even with adequate caloric supplementation, patients still exhibit growth abnormalities. Patients with congenital NDI also exhibit behavioral problems, including hyperactivity and short-term memory problems. Patients with the secondary form generally present later in life, primarily with hypernatremia and polyuria. Associated symptoms such as developmental delay and behavioral abnormalities are less common in this latter group.

Diagnosis

The diagnosis is suggested in a male infant with polyuria, hypernatremia, and dilute urine. Simultaneous serum and urine osmolality measurements should be obtained. *If the serum osmolality value is 290 mOsm/kg or higher with a* *simultaneous urine osmolality value of < 290 mOsm/kg, a formal water deprivation test is not necessary.* Because the differential diagnosis includes causes of **central diabetes insipidus,** the inability to respond to ADH (and thus the presence of NDI) should then be confirmed by the administration of vasopressin (10-20 µg intranasally) followed by serial urine and serum osmolality measurements hourly for 4 hr. In patients with possible "partial" or secondary diabetes insipidus, in whom the initial serum osmolality value may be < 290 mOsm/kg, a water-deprivation test should be considered. Fluids should be withheld and urine and serum osmolalities measured periodically until the serum osmolality value is > 290 mOsm/kg; vasopressin is then given as before. Criteria for premature termination of a water-deprivation test include a decrease in body weight of > 3%. If NDI is confirmed or suspected, an additional evaluation should include a detailed history to assess possible toxic exposures, determination of renal function by serum creatinine and blood urea nitrogen levels, and renal ultrasonography to identify obstructive uropathies or cystic disease. Because of the massive urine output, patients with congenital NDI can have *nonobstructive hydronephrosis* of varying severity.

Treatment and Prognosis

Treatment of NDI includes maintenance of adequate fluid intake and access to free water, minimizing the urine output by limiting the solute load with a low-osmolar, low-sodium diet, and administering medications directed at decreasing the urine output. For infants, human milk or a low-solute formula, such as Similac PM 60/40, is preferred. Most infants with congenital NDI require gastrostomy or nasogastric feedings to ensure adequate fluid administration throughout the day and night. Sodium intake in older patients should be < 0.7 mEq/kg/24 hr**.** Thiazide diuretics (2-3 mg/kg/24 hr of hydrochlorothiazide) effectively induce sodium loss and stimulate proximal tubule reabsorption of water. Potassium-sparing diuretics, in particular, amiloride (0.3 mg/kg/24 hr in 3 divided doses), are often additionally indicated. Patients who have an inadequate response to diuretics alone might benefit from the addition of indomethacin (2 mg/kg/24 hr), which has an additive effect in reducing water excretion in some patients. Renal function must be monitored closely in such patients because indomethacin can cause deterioration in renal function over time. Patients with secondary NDI may not require medications but should have access to free water. Such patients should have the serum electrolytes and volume status monitored closely, particularly during periods of superimposed acute illnesses.

Prevention of recurrent dehydration and hypernatremia in patients with congenital NDI has significantly improved the neurodevelopmental outcome of these patients. However, behavioral issues remain a significant problem. In addition, chronic use of nonsteroidal antiinflammatory drugs can predispose patients to renal insufficiency. The prognosis of patients with secondary NDI generally depends on the nature of the underlying disease.

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CHAPTER 549

Inherited Tubular Transport Abnormalities

549.1

Bartter Syndrome

Bradley P. Dixon

Bartter syndrome is a group of disorders characterized by hypokalemic hypochloremic metabolic alkalosis with hypercalciuria and salt wasting (see Chapter 68). These disorders are currently classified by the anatomic site affected by the gene mutation (Tables 549.1 and 549.2). **Antenatal** Bartter syndrome (types I, II, and IV; also called hyperprostaglandin E syndrome) typically manifests in infancy and has a more severe phenotype than **classic** Bartter syndrome (type III); the perinatal onset includes maternal polyhydramnios, neonatal salt wasting, and severe episodes of recurrent dehydration. The milder phenotype, classic Bartter syndrome, manifests in childhood with failure to thrive and a history of recurrent episodes of dehydration. A phenotypically related disease, Gitelman syndrome, has a distinct genetic defect and is discussed in Chapter 549.2 (see Table 549.1). One distinct variant of antenatal Bartter syndrome is associated with sensorineural deafness (type IV). Bartter-like phenotypes have been noted in other diseases such as Kearns-Sayre syndrome.

Table 549.1

Types of Bartter Syndrome, Gitelman Syndrome, and Related Conditions

DISORDER	OMIM, GENE	GENE PRODUCT	INHERITANCE	FEATURES
BS VARIANTS				
BS I (ABS, HPES)	601678, *SLC12A1*	NKCC2	AR	Polyhydramnios, prematurity, hypokalemic hypochloremic alkalosis, nephrocalcinosis, with or without concentrating defect
BS II (ABS with transient hyperkalemia and acidosis, HPES)	241200, *KCNJ1*	ROMK1	AR	Polyhydramnios, prematurity, transient hyperkalemia and acidosis, then hypokalemic hypochloremic alkalosis, nephrocalcinosis, with or without concentrating defect
BS III (CBS)	607364, *CLCNKB*	ClC-Kb	AR; many sporadic	Variable age at presentation with severity corresponding to type of gene mutation; hypokalemic hypochloremic alkalosis
BS IVa and BS IVb (ABS or HPES with sensorineural deafness)	602522, *BSND* *CLCNKA*, *CLCNKB*	Barttin ClC-Ka and ClC-Kb	AR	Polyhydramnios, prematurity, hypokalemic hypochloremic alkalosis, sensorineural deafness, with or without concentrating defect
BS V (transient ABS)	300971, *MAGED2*	MAGED2	XR	Severe polyhydramnios, hypokalemic hypochloremic alkalosis with symptoms resolving within the first few months of life
AD hypocalcemic hypercalciuria	601199, *L125P*	CaSR	AD	Hypocalcemic hypocalciuria, hypokalemic hypochloremic alkalosis, suppressed PTH
GS VARIANTS				
GS	263800, *SLC12A3*	NCC	AR	Present in later childhood or adulthood with weakness, lethargy, carpopedal spasm, hypokalemic alkalosis, hypomagnesemia, hypermagnesuria and hypocalciuria
EAST syndrome (SeSAME)	612780, *Kir4.1*	KCNJ10	AR	Epilepsy, ataxia, sensorineural deafness, hypokalemic hypochloremic alkalosis
OTHER VARIANTS				
CLDN10 mutations	617579, *CLDN10*	Claudin-10	AR	Hypokalemic metabolic alkalosis with hypocalciuria but normal to elevated magnesium

AD, autosomal dominant; AR, autosomal recessive; CaSR, calcium-sensing receptor; ClC-Ka, chloride channel-Ka; ClC-Kb, chloride channel-Kb; MAGED, melanoma-associated antigen-D2; NCC, thiazide-sensitive NaCl cotransporter; NKCC2, furosemide-sensitive Na-K-2Cl cotransporter; OMIM, Online Mendelian Inheritance in Man; PTH, parathyroid hormone; ROMK, renal outer medullary K channel; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalances; XR, X-linked recessive.

From Fulchiero R, Seo-Mayer P: Bartter syndrome and Gitelman syndrome. Pediatr Clin North Am 66:121-134, 2019. Box 1.

Table 549.2

Features That Distinguish Bartter and Gitelman Syndrome Variants

VARIANT	AGE OF ONSET	SERUM K	SERUM Cl	SERUM Mg	SERUM RENIN, ALDOSTERONE	URINE Ca/Cr	OTHER DISTINCT FEATURES
BS I	AN	Low	Low	Normal	High, high	High	—
BS II	AN	High, then low	Low	Normal	High, high	High	Transient hyperkalemia
BS III	N, C, A	Low	Very low	Normal	High, high	Low, normal, or high	—
BS IVa, IVb	AN	Low	Low	Normal	High, high	Normal or High	Sensorineural deafness
BS V	AN	Low	Low	Normal	High, high	—	Transient features
Hypocalcemic hypercalciuria	—	Low	Low	Normal	High, high	High	Family history, hypocalcemia, suppressed PTH
GS	C, A	Low	Low	Low	High, high	Low	—
EAST syndrome	—	Low	Low	Low	High, high	Low	Epilepsy, ataxia, sensorineural deafness

A, adult; AN, antenatal; C, child; Ca/Cr, spot calcium to creatinine ratio; Mg, magnesium; N, neonate.

From Fulchiero R, Seo-Mayer P: Bartter syndrome and Gitelman syndrome. Pediatr Clin North Am 66:121-134, 2019. Box 3.

Pathogenesis

The biochemical features of Bartter syndrome, hypokalemic hypochloremic metabolic alkalosis with hypercalciuria, resemble those seen with chronic use of loop diuretics and reflect a defect in sodium, chloride, and potassium transport in the ascending loop of Henle. The loss of sodium and chloride, with resultant volume contraction, stimulates the renin–angiotensin II–aldosterone axis. Aldosterone promotes sodium uptake and potassium secretion, exacerbating the hypokalemia. It also stimulates hydrogen ion secretion distally, worsening the metabolic alkalosis. Hypokalemia stimulates prostaglandin synthesis, which further activates the renin–angiotensin II–aldosterone axis. Bartter syndrome has been associated with at least five distinct genetic defects in loop of Henle transporters (see Table 549.1). Each contributes, in some manner, to sodium and chloride transport. Mutations in the genes that encode the Na$^+$ /K$^+$ /2Cl$^-$

transporter (NKCC2, the site of action of furosemide), the luminal potassium channel (ROMK), combined chloride channel (CLC-Ka, CLC-Kb), or subunit of chloride channels (barttin) cause neonatal Bartter syndrome. Isolated defects in the genes that produce a specific basolateral chloride channel (ClC-Kb) cause classic Bartter syndrome.

Clinical Manifestations

A history of maternal polyhydramnios with or without prematurity may be elicited. Dysmorphic features, including triangular facies, protruding ears, large eyes with strabismus, and drooping mouth may be present on physical examination. Consanguinity suggests the presence of an autosomal recessive disorder. Older children can have a history of recurrent episodes of polyuria with dehydration, failure to thrive, nonspecific fatigue, dizziness, and chronic constipation. Older children may also present with muscle cramps and weakness secondary to chronic hypokalemia. The blood pressure is usually normal, although patients with the antenatal form can have severe salt wasting, resulting in dehydration and hypotension. Serum chemistry reveals the classic biochemical abnormalities of a **hypokalemic hypochloremic metabolic alkalosis.** The renal function is typically normal. Urinary calcium levels are typically elevated, as are urinary potassium and sodium levels. Serum renin, aldosterone, and prostaglandin E levels are often markedly elevated, particularly in the more severe antenatal form. Nephrocalcinosis, resulting from hypercalciuria, may be seen on ultrasound examination (types I and II).

Diagnosis

The diagnosis is usually made based on the clinical presentation and laboratory findings. The diagnosis in the neonate or infant is suggested by severe hypokalemia, usually < 2.5 mmol/L, with metabolic alkalosis. Hypercalciuria is typical; hypomagnesemia is seen in a minority of patients but is more common in Gitelman syndrome. Because features of Bartter syndrome resemble the chronic use of loop diuretics, diuretic abuse should be considered in the differential diagnosis, even in young children. Chronic vomiting and cystic fibrosis can also give a similar clinical picture but can be distinguished by the **measurement of urinary chloride,** which is elevated in Bartter syndrome and low in patients with chronic vomiting and cystic fibrosis. Kidneys demonstrate hyperplasia of the juxtaglomerular apparatus, although renal biopsy is rarely performed to diagnose this condition.

Treatment and Prognosis

Treatment of Bartter syndrome is directed at preventing dehydration, maintaining the nutritional status, and correcting hypokalemia. Potassium supplementation, usually in the form of potassium chloride to correct the concomitant chloride depletion and often at very high doses, is required. Even with appropriate therapy, serum potassium values might not normalize, particularly in patients with the neonatal form. Infants and young children require a high-sodium diet and, at times, sodium supplementation. Indomethacin, a prostaglandin inhibitor, can also be effective. If hypomagnesemia is present, magnesium supplementation is required. With close attention to electrolyte balance, volume status, and growth, the long-term prognosis is generally good. In a minority of patients, chronic hypokalemia, nephrocalcinosis, and chronic indomethacin therapy can lead to chronic interstitial nephritis and chronic renal failure.

549.2

Gitelman Syndrome

Bradley P. Dixon

Gitelman syndrome (often called a “Bartter syndrome variant”) is a rare autosomal recessive cause of hypokalemic hypochloremic metabolic alkalosis, with distinct features of **hypocalciuria** and **hypomagnesemia.** Patients with Gitelman syndrome typically present in late childhood or early adulthood (see Tables 549.1 and 549.2).

Pathogenesis

The biochemical features of Gitelman syndrome resemble those of chronic use of thiazide diuretics. Thiazides act on the sodium chloride cotransporter NCCT, present in the distal convoluted tubule. Through linkage analysis and mutational studies, defects in the gene encoding NCCT have been demonstrated in patients with Gitelman syndrome.

Clinical Manifestations

Patients with Gitelman syndrome typically present at a later age than those with Bartter syndrome and may have symptoms similar to older children with Bartter syndrome (see Chapter 549.1). Patients often have a history of recurrent muscle cramps and spasms, presumably caused by low serum magnesium levels, nocturia, polyuria, and occasional hypotension. They usually do not have a history of recurrent episodes of dehydration. Biochemical abnormalities include hypokalemia, metabolic alkalosis, and hypomagnesemia. The urinary calcium level is usually very low (in contrast to the elevated urinary calcium level often seen in Bartter syndrome), and the urinary magnesium level is elevated. Renin and aldosterone levels are usually normal, and prostaglandin E secretion is not elevated. Growth failure is less prominent in Gitelman syndrome than in Bartter syndrome.

Diagnosis

The diagnosis of Gitelman syndrome is suggested in an adolescent or adult presenting with hypokalemic hypochloremic metabolic alkalosis, hypomagnesemia, and hypocalciuria.

Treatment

Therapy is directed at correcting hypokalemia and hypomagnesemia with supplemental potassium and magnesium. Sodium supplementation or treatment with prostaglandin inhibitors is generally not necessary because patients typically do not have episodes of volume depletion or elevated prostaglandin E excretion.

549.3

Other Inherited Tubular Transport Abnormalities

Bradley P. Dixon

Inherited abnormalities in distinct transporters in each segment of the nephron have now been identified and the molecular defects have been characterized. Renal tubular acidosis and nephrogenic diabetes insipidus are discussed in detail in Chapters 547 and 548 , respectively. **Cystinuria** is an autosomal recessive disorder seen primarily in patients of Middle Eastern descent and is characterized by recurrent stone formation. The disease is caused by a defective high-affinity transporter for L -cystine and dibasic amino acids present in the proximal tubule.

Dent disease is an X-linked proximal tubulopathy with characteristic abnormalities that include low-molecular-weight proteinuria, hypercalciuria, and other features of Fanconi syndrome, such as glycosuria, aminoaciduria, and phosphaturia. Although some patients develop nephrocalcinosis, nephrolithiasis, progressive renal failure, and hypophosphatemic rickets, patients with Dent disease typically do not have proximal renal tubular acidosis or extrarenal manifestations. Loss-of-function mutations of the *CLCN5* gene, which encodes a renal Cl^- /H^+ antiporter (ClC-5), are reported in ~ 50–60% of patients with Dent disease. The genetic heterogeneity of Dent disease in some patients who exhibit mutations in the gene for OCRL1 (responsible for Lowe syndrome) also meet the criteria for Dent disease (~15% of patients): Dent-2 disease. Dent disease includes X-linked recessive nephrolithiasis with renal failure, X-linked recessive hypophosphatemic rickets, and idiopathic low-molecular-weight proteinuria seen in Japanese children.

Mutations in an extracellular basolateral calcium-sensing receptor, normally present in the loop of Henle, can cause a **dominant Bartter syndrome–like picture** (also known as Bartter syndrome type V). These patients’ predominant symptoms are hypocalcemia and suppressed parathyroid hormone function, which differentiates them from patients with Bartter syndrome.

In the distal convoluted tubule, gain-of-function mutations in *WNK1* and loss-of-function mutations in *WNK4,* both serine threonine kinases, lead to excessive NCCT-mediated salt reabsorption with the clinical picture of pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension, or **Gordon syndrome**), including volume expansion with hypertension, hyperkalemia, hyperchloremic metabolic acidosis, and hypercalciuria. Due to the excessive activation of the thiazide-sensitive NCCT, this disorder can be effectively treated with thiazide diuretics.

In the collecting duct, gain-of-function mutations of the gene that encodes the epithelial sodium channel (ENaC) cause an inherited form of hypertension, **Liddle syndrome.** Patients with this disorder have constitutive sodium uptake in the collecting duct, with hypokalemia and suppressed aldosterone. Due to the excessive activation of ENaC, potassium-sparing diuretics (specifically amiloride) are an effective treatment for Liddle syndrome. Conversely, loss-of-function mutations cause **pseudohypoaldosteronism,** characterized by severe sodium wasting and hyperkalemia as well as a distal (type IV) RTA (also discussed in Chapter 547.3). A variant of the latter disorder is associated with systemic abnormalities, including defects in sweat chloride, and can resemble cystic fibrosis.

Renal hypouricemia, a defect in the *SLC22A12* gene, presents with low serum uric acid levels and is complicated by exercise-induced acute renal failure. Patients have elevated urine uric acid levels and present with loin pain, nausea, and vomiting after exercise. Treatment is for acute renal failure and reducing the intensity of exercise.

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CHAPTER 550

Renal Failure

550.1

Acute Kidney Injury

Prasad Devarajan

Keywords

acute interstitial nephritis
acute tubular necrosis
continuous renal replacement therapy
glomerular filtration rate
glomerulonephritis
hemodialysis
peritoneal dialysis
prerenal azotemia
tumor lysis syndrome

Acute kidney injury (AKI) has been traditionally defined as an abrupt loss of kidney function leading to a rapid decline in the glomerular filtration rate (GFR), accumulation of waste products such as blood urea nitrogen (BUN) and creatinine, and dysregulation of extracellular volume and electrolyte homeostasis. The term AKI has largely replaced acute renal failure (ARF), because the latter designation overemphasizes the discrete event of a failed kidney. AKI embodies a continuum of renal dysfunction that ranges from a small increase in serum creatinine to complete anuric renal failure. AKI is a common problem afflicting all ages, the leading reason to seek inpatient nephrology consultation, and associated with serious consequences and unsatisfactory therapeutic options. The incidence of AKI varies from 2–5% of all hospitalizations to > 25% in critically ill infants and children. The etiology of AKI varies widely according to age, geographic region, and clinical setting. Functional AKI induced by dehydration is usually reversible with early fluid therapy. However, the prognosis for patients with structural AKI in the intensive care setting with multiorgan failure remains guarded.

A classification system proposed by the Kidney Disease Improving Global Outcomes (KDIGO) AKI Consensus Conference takes both serum creatinine and urine output criteria into account to define and stage AKI (Table 550.1). Thus, AKI is defined as:

Table 550.1

KDIGO Staging of Acute Kidney Injury

STAGE	SERUM CREATININE	URINE OUTPUT
1	1.5-1.9 times baseline, OR ≥0.3 mg/dL increase	<0.5 mL/kg/hr for 6-12 hr
2	2.0-2.9 times baseline	<0.5 mL/kg/hr for ≥ 12 hr
3	3.0 times baseline, OR SCr ≥ 4.0 mg/dL, OR Initiation of renal replacement therapy, OR eGFR < 35 mL/min per 1.73 m^2 (< 18 yr)	<0.3 mL/kg/hr for ≥ 24 hr, OR Anuria for ≥ 12 hr

Increase in serum creatinine by ≥ 0.3 mg/dL from baseline within 48 hr; *or*
Increase in serum creatinine to ≥ 1.5 times baseline within the prior 7 days; *or*
Urine volume ≤ 0.5 mL/kg/hr for 6 hr

Pathogenesis

AKI has been conventionally classified into three categories: prerenal, intrinsic renal, and postrenal (Table 550.2 and Fig. 550.1).

Table 550.2

Common Causes of Acute Kidney Injury

PRERENAL
Dehydration
Gastroenteritis
Hemorrhage
Burns
Sepsis
Capillary leak
Hypoalbuminemia
Cirrhosis
Abdominal compartment syndrome
Cardiac failure
Anaphylaxis
INTRINSIC RENAL
Glomerulonephritis
Postinfectious/poststreptococcal
Lupus erythematosus
Henoch-Schönlein purpura
Membranoproliferative
Anti–glomerular basement membrane
Hemolytic-uremic syndrome
Acute tubular necrosis
Cortical necrosis
Renal vein thrombosis
Rhabdomyolysis
Acute interstitial nephritis
Tumor infiltration
Toxin and drugs (see Table 550.3)
Tumor lysis syndrome
Vasculitis
POSTRENAL
Posterior urethral valves
Ureteropelvic junction obstruction
Ureterovesicular junction obstruction
Ureterocele
Tumors
Urolithiasis
Urethral strictures
Hemorrhagic cystitis
Neurogenic bladder
Anticholinergic drugs

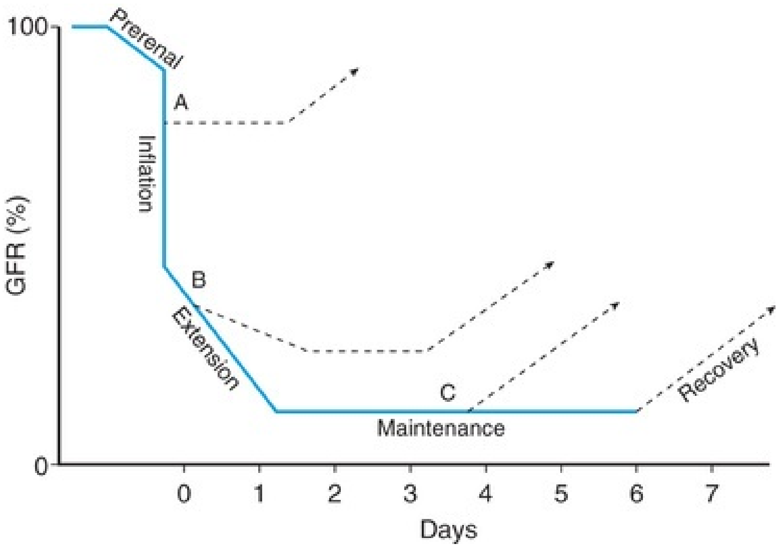

FIG. 550.1 Phases of acute kidney injury. GFR, glomerular filtration rate. (From Sutton TA, Fisher CJ, Molitoris BA: Microvascular endothelial injury and dysfunction during ischemic acute renal failure, Kidney Int 62:1539-1549, 2002.)

Prerenal AKI, also called *prerenal azotemia*, is characterized by a diminished effective circulating arterial volume, which leads to inadequate renal perfusion and a decreased GFR. Evidence of structural kidney damage is absent. Common causes of prerenal AKI include dehydration, sepsis, hemorrhage, severe hypoalbuminemia, and cardiac failure. If the underlying cause of the renal hypoperfusion is reversed promptly, renal function returns to normal. If hypoperfusion is sustained, intrinsic renal parenchymal damage can develop.

Intrinsic renal AKI includes a variety of disorders characterized by renal parenchymal damage, including sustained hypoperfusion and ischemia. Ischemic/hypoxic injury and nephrotoxic insults are the most common causes of intrinsic AKI in the United States and are more common with an underlying comorbid condition; most are associated with cardiac, oncologic, urologic, renal, and genetic disorders or prematurity (Table 550.3). Many forms of **glomerulonephritis,** including postinfectious glomerulonephritis, lupus nephritis, Henoch-Schönlein purpura nephritis, membranoproliferative glomerulonephritis, and anti–glomerular basement membrane nephritis, can also cause intrinsic AKI. Severe and prolonged ischemic/hypoxic injury and nephrotoxic insult lead to **acute tubular necrosis (ATN),** seen most often in critically ill infants and children. Mechanisms leading to ischemic AKI include hypotension/intravascular volume depletion (hemorrhage, third-space fluid losses, diarrhea), decreased effective intravascular volume (heart failure, cirrhosis, hepatorenal syndrome, peritonitis, abdominal compartment syndrome), vasodilation/vasoconstriction (sepsis, hepatorenal syndrome), renal artery obstruction (thrombosis, embolization, stenosis), intrarenal artery disease (vasculitis, hemolytic-uremic syndrome, sickle cell anemia, transplant rejection), and impaired renal blood flow (cyclosporine, tacrolimus, angiotensin-converting enzyme [ACE] inhibitors, angiotensin-receptor blocking agents, radiocontrast agents).

Table 550.3

Major Endogenous and Exogenous Toxins Causing Acute Tubular Injury

ENDOGENOUS TOXINS	EXOGENOUS TOXINS
MYOGLOBULINURIA	**ANTIBIOTICS**
Muscle breakdown—trauma, compression, electric shock, hypothermia, hyperthermia, seizures, exercise, burns Metabolic—hypokalemia, hypophosphatemia Infections—tetanus, influenza Toxins—isopropyl alcohol, ethanol, ethylene glycol, toluene, snake and insect bites, cocaine, heroin Drugs—HMG-CoA reductase inhibitors (statins), amphetamines, fibrates Inherited disease—deficiency of myophosphorylase, phosphofructokinase, carnitine palmitoyltransferase Autoimmune—polymyositis, dermatomyositis	Aminoglycosides Amphotericin B Antiviral agents—acyclovir, cidofovir, indinavir, foscarnet, tenofovir Pentamidine Vancomycin
	CHEMOTHERAPY
	Cisplatin Ifosfamide Plicamycin 5-Fluorouracil Cytarabine 6-Thioguanine Methotrexate
	CALCINEURIN INHIBITORS
	Cyclosporine Tacrolimus
HEMOGLOBINURIA	**ORGANIC SOLVENTS**
Mechanical—prosthetic valves, microangiopathic hemolytic anemia, extracorporeal circulation Drugs—hydralazine, methyldopa Chemicals—benzene, arsine, fava beans, glycerol, phenol Immunologic—transfusion reaction Genetic—G6PD deficiency, PNH	Toluene Ethylene glycol
	POISONS
	Snake venom Paraquat
	MISCELLANEOUS
	Radiocontrast media Intravenous immune globulin Nonsteroidal antiinflammatory drugs Oral phosphate bowel preparations
INTRATUBULAR OBSTRUCTION FROM CRYSTALLURIA OR PARAPROTEINS	
Tumor lysis syndrome HGPT deficiency Multiple myeloma Oxalate (ethylene glycol)	

G6PD, Glucose-6-phosphate dehydrogenase; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A; PNH, paroxysmal nocturnal hemoglobinuria.

From Sharfuddin AA, Weisbord SD, Palevsky PM, Molitoris BA: Acute kidney injury. In Skorecki K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's the kidney, 10/e, Philadelphia, 2016, Elsevier, Tab 31-5.

The typical pathologic feature of ATN is tubular cell necrosis, although significant histologic changes are not consistently seen in patients with clinical ATN. The mechanisms of injury in ATN can include alterations in intrarenal hemodynamics, tubular obstruction, and passive backleak of the glomerular filtrate across injured tubular cells into the peritubular capillaries.

Tumor lysis syndrome is a specific form of AKI related to spontaneous or chemotherapy-induced cell lysis in patients with lymphoproliferative malignancies. This disorder is primarily caused by obstruction of the tubules by uric acid crystals (see Chapters 522 and 523). **Acute interstitial nephritis** is another common cause of AKI and is usually a result of a hypersensitivity reaction to a therapeutic agent or various infectious agents (see Chapter 539.2).

Postrenal AKI includes a variety of disorders characterized by obstruction of the urinary tract. In neonates and infants, congenital conditions, such as posterior urethral valves and bilateral ureteropelvic junction obstruction, account for the majority of cases of AKI. Other conditions, such as urolithiasis, tumor (intraabdominal lesion or within the urinary tract), hemorrhagic cystitis, and neurogenic bladder, can cause AKI in older children and adolescents. In a patient with two functioning kidneys, obstruction must be bilateral to result in AKI. Relief of the obstruction usually results in recovery of renal function, except in patients with associated renal dysplasia or prolonged urinary tract obstruction.

Clinical Manifestations and Diagnosis

A carefully taken history is critical in defining the cause of AKI. An infant with a 3-day history of vomiting and diarrhea most likely has prerenal AKI caused by volume depletion, but hemolytic-uremic syndrome (HUS) must also be a consideration. A 6 yr old child with a recent pharyngitis who presents with periorbital edema, hypertension, and gross hematuria most likely has intrinsic AKI related to acute postinfectious glomerulonephritis. A critically ill child with a history of protracted hypotension or with exposure to nephrotoxic medications most likely has ATN. A neonate with a history of hydronephrosis seen on prenatal ultrasound studies and a palpable bladder most likely has congenital urinary tract obstruction, probably related to posterior urethral valves.

The physical examination must be thorough, with careful attention to volume status. Tachycardia, dry mucous membranes, and poor peripheral perfusion suggest an inadequate circulating volume and the possibility of prerenal AKI. Hypertension, peripheral edema, rales, and a cardiac gallop suggest volume overload and the possibility of intrinsic AKI from glomerulonephritis or ATN. The presence of a rash and arthritis might indicate systemic lupus erythematosus (SLE) or Henoch-Schönlein purpura nephritis. Palpable flank masses may be seen with renal vein thrombosis, tumors, cystic disease, or urinary tract obstruction.

Laboratory Findings

Laboratory abnormalities can include anemia (the anemia is usually dilutional or hemolytic, as in SLE, renal vein thrombosis, HUS); leukopenia (SLE, sepsis); thrombocytopenia (SLE, renal vein thrombosis, sepsis, HUS); hyponatremia (dilutional); metabolic acidosis; elevated serum concentrations of blood urea nitrogen, creatinine, uric acid, potassium, and phosphate (diminished renal function); and hypocalcemia (hyperphosphatemia).

The serum C3 level may be depressed (postinfectious glomerulonephritis, SLE, or membranoproliferative glomerulonephritis), and antibodies may be detected in the serum to streptococcal (poststreptococcal glomerulonephritis), nuclear (SLE), neutrophil cytoplasmic (granulomatosis with polyangiitis, microscopic polyarteritis), or glomerular basement membrane (Goodpasture disease) antigens.

The presence of hematuria, proteinuria, and red blood cell or granular urinary casts suggests intrinsic AKI, in particular glomerular disease and ATN. The presence of white blood cells and white blood cell casts with low-grade hematuria and proteinuria suggests tubulointerstitial disease. Urinary eosinophils may be present in some children with drug-induced tubulointerstitial nephritis.

Urinary indices may be useful in differentiating prerenal AKI from intrinsic AKI (Table 550.4). Patients whose urine shows an elevated specific gravity (>1.020), elevated urine osmolality (UOsm > 500 mOsm/kg), low urine sodium (UNa < 20 mEq/L), and fractional excretion of sodium < 1% (<2.5% in neonates) most likely have prerenal AKI. Those with a specific gravity of < 1.010, low urine osmolality (UOsm < 350 mOsm/kg), high urine sodium (UNa >

40 mEq/L), and fractional excretion of sodium > 2% (>10% in neonates) most likely have intrinsic AKI.

Table 550.4

Urinalysis, Urine Chemistries, and Osmolality in Acute Kidney Injury

	HYPOVOLEMIA	ACUTE TUBULAR NECROSIS	ACUTE INTERSTITIAL NEPHRITIS	GLOMERULONEPHRITIS	OBSTRUCTI
Sediment	Bland, may have hyaline casts	Broad, brownish granular casts	White blood cells, eosinophils, cellular casts	Red blood cells, red blood cell casts	Bland or blood
Protein	None or low	None or low	Minimal but may be increased with NSAIDs	Increased, > 100 mg/dL	Low
Urine sodium (mEq/L)*	<20	>40	>30	<20	<20 (acute) >40 (few days)
Urine osmolality (mOsm/kg)	>400	<350	<350	>400	<350
Fractional excretion of sodium % †	<1	>2 ‡	Varies	<1	<1 (acute) >1 (few days)

* The sensitivity and specificity of urine sodium of < 20 mEq/L in differentiating prerenal azotemia from acute tubular necrosis are 90% and 82%, respectively.

† Fractional excretion of sodium is the urine:plasma (U:P) ratio of sodium divided by U:P of creatinine ×100. The sensitivity and specificity of fractional excretion of sodium of < 1% in differentiating prerenal azotemia from acute tubular necrosis are 96% and 95%, respectively.

‡ The fractional excretion of sodium may be < 1% in acute tubular necrosis secondary to radiocontrast material or rhabdomyolysis.

NSAIDs, nonsteroidal antiinflammatory drugs.

From Singri N, Ahya SN, Levin ML: Acute renal failure, JAMA 289:747-751, 2003.

Chest radiography may reveal cardiomegaly, pulmonary congestion (fluid overload), or pleural effusions. Renal ultrasonography can reveal hydronephrosis and/or hydroureter, which suggest urinary tract obstruction, or nephromegaly, consistent with intrinsic renal disease. Renal biopsy can ultimately be required to determine the precise cause of AKI in patients who do not have clearly defined prerenal or postrenal AKI.

Although serum creatinine is used to measure kidney function, it is an insensitive and delayed measure of decreased kidney function following AKI. Other biomarkers under investigation include changes in plasma neutrophil gelatinase–associated lipocalin and cystatin C levels and urinary changes in neutrophil gelatinase-associated lipocalin, interleukin 18, and kidney injury molecule-1.

Treatment

Medical Management

Complications of acute kidney injury are noted in Table 550.5 . In infants and children with urinary tract obstruction, such as in a newborn with suspected posterior ureteral valves, a bladder catheter should be placed immediately to ensure adequate drainage of the urinary tract. The placement of a bladder catheter may also be considered in nonambulatory older children and adolescents to accurately monitor urine output during AKI; however, precautions to prevent iatrogenic infection should be taken.

Table 550.5

Common Complications of Acute Kidney Injury

METABOLIC	CARDIOPULMONARY	GASTROINTESTINAL	NEUROLOGIC	HEMATO
Hyperkalemia	Pulmonary edema	Nausea	Neuromuscular irritability	Anemia
Metabolic acidosis	Arrhythmias	Vomiting	Asterixis	Bleeding
Hyponatremia	Pericarditis	Malnutrition	Seizures	
Hypocalcemia	Pericardial effusion	Hemorrhage	Mental status changes	
Hyperphosphatemia	Hypertension			
Hypermagnesemia	Myocardial infarction			
Hyperuricemia	Pulmonary embolism			

From Sharfuddin AA, Weisbord SD, Palevsky PM, Molitoris BA: Acute kidney injury. In Skorecki K, Chertow GM, Marsden PA, et al (eds): Brenner & Rector's the kidney, 10/e, Philadelphia, 2016, Elsevier, Tab 31-14.

Determination of the volume status is of critical importance when initially evaluating a patient with AKI. If there is no evidence of volume overload or cardiac failure, the intravascular volume should be expanded by intravenous administration of isotonic saline, 20 mL/kg over 30 min. In the absence of blood loss or hypoproteinemia, colloid-containing solutions are not required for volume expansion. Severe hypovolemia may require additional fluid boluses (see Chapters 69 , 70 , and 88). Determination of the central venous pressure may be helpful if adequacy of the blood volume is difficult to determine. After volume resuscitation, hypovolemic patients generally void within 2 hr; failure to do so suggests intrinsic or postrenal AKI. Hypotension caused by sepsis requires vigorous fluid resuscitation followed by a continuous infusion of vasopressors.

Diuretic therapy should be considered only after the adequacy of the circulating blood volume has been established. Furosemide (2-4 mg/kg) may be administered as a single intravenous dose. Bumetanide (0.1 mg/kg) may be given as an alternative to furosemide. If urine output is not improved, then a continuous diuretic infusion may be considered. To increase renal cortical blood flow, many clinicians administer dopamine (2-3 µg/kg/min) in conjunction with diuretic therapy, although no controlled data support this practice. There is little evidence that diuretics or dopamine can prevent AKI or hasten recovery. Mannitol may be effective in the prevention of pigment (myoglobin, hemoglobin)-induced renal failure. Atrial natriuretic peptide may be of value in preventing or treating AKI, although there is little pediatric evidence to support its use.

If there is no response to a diuretic challenge, diuretics should be discontinued and fluid restriction is essential. Patients with a relatively normal intravascular volume should initially be limited to 400 mL/m^2 /24 hr (insensible losses) plus an amount of fluid equal to the urine output for that day. Extrarenal (blood, GI tract) fluid losses should be replaced, milliliter for milliliter, with appropriate fluids. Markedly hypervolemic patients can require further fluid restriction, omitting the replacement of insensible fluid losses, urine output, and extrarenal losses to diminish the expanded intravascular volume. Fluid intake, urine and stool output, body weight, and serum chemistries should be monitored on a daily basis.

In AKI, rapid development of **hyperkalemia** (serum potassium level > 6 mEq/L) can lead to cardiac arrhythmia, cardiac arrest, and death. The earliest electrocardiographic change seen in patients with developing hyperkalemia is the appearance of peaked T waves. This may be followed by widening of the QRS intervals, ST segment depression, ventricular arrhythmias, and cardiac arrest (see Chapter 450.2). Procedures to deplete body potassium stores should be initiated when the serum potassium value rises to > 6.0 mEq/L. Exogenous sources of potassium (dietary, intravenous fluids, total parenteral nutrition) should be eliminated. Sodium polystyrene sulfonate resin (Kayexalate), 1 g/kg, should be given orally or by retention enema. This resin exchanges sodium for potassium and can take several hours to take effect. A single dose of 1 g/kg can be expected to lower the serum potassium level by about 1 mEq/L. Resin therapy may be repeated every 2 hr, the frequency being limited primarily by the risk of sodium overload.

More severe elevations in serum potassium (>7 mEq/L), especially if accompanied by electrocardiographic changes, require emergency measures in addition to Kayexalate. The following agents should be administered:

Calcium gluconate 10% solution, 100 mg/kg/dose (maximum 3000 mg/dose)
Sodium bicarbonate, 1-2 mEq/kg intravenously, over 5-10 min
Regular insulin, 0.1 units/kg, with glucose 50% solution, 1 mL/kg, over 1 hr

Calcium gluconate counteracts the potassium-induced increase in myocardial irritability but does not lower the serum potassium level. Administration of sodium bicarbonate, insulin, or glucose lowers the serum potassium level by shifting potassium from the extracellular to the intracellular compartment. A similar effect has been reported with the acute administration of β-adrenergic agonists in adults, but there are no controlled data in pediatric patients. Because the duration of action of these emergency measures is just a few hours, persistent hyperkalemia should be managed by dialysis.

Mild **metabolic acidosis** is common in AKI because of the retention of hydrogen ions, phosphate, and sulfate, but it rarely requires treatment. If acidosis is severe (arterial pH < 7.15; serum bicarbonate < 8 mEq/L) or contributes to significant hyperkalemia, treatment is indicated. The acidosis should be corrected partially by the intravenous route, generally by giving enough bicarbonate to raise the arterial pH to 7.20 (which approximates a serum bicarbonate level of 12 mEq/L). The remainder of the correction may be accomplished by oral administration of sodium bicarbonate after normalization of the serum calcium and phosphorus levels. Correction of metabolic acidosis with intravenous bicarbonate can precipitate tetany in patients with renal failure because rapid correction of acidosis reduces the ionized calcium concentration.

Hypocalcemia is primarily treated by lowering the serum phosphorus level.

Calcium should not be given intravenously, except in cases of tetany, to avoid deposition of calcium salts into tissues. Patients should be instructed to follow a low-phosphorus diet, and phosphate binders should be orally administered to bind any ingested phosphate and increase the GI phosphate excretion. Common agents include sevelamer (Renagel), calcium carbonate (Tums tablets or Titralac suspension), and calcium acetate (PhosLo). Aluminum-based binders, commonly employed in the past, should be avoided because of the risk of aluminum toxicity.

Hyponatremia is most commonly a dilutional disturbance that must be corrected by fluid restriction rather than sodium chloride administration. Administration of hypertonic (3%) saline should be limited to patients with symptomatic hyponatremia (seizures, lethargy) or those with a serum sodium level < 120 mEq/L. Acute correction of the serum sodium to 125 mEq/L (mmol/L) should be accomplished using the following formula:

$$\begin{aligned}&\text{mEq sodium required}\\&\quad = 0.6 \times \text{weight in kg} \times (125 - \text{serum sodium in mEq/L}).\end{aligned}$$

AKI patients are predisposed to **GI bleeding** because of uremic platelet dysfunction, increased stress, and heparin exposure if treated with hemodialysis or continuous renal replacement therapy. Oral or intravenous H_2 blockers such as ranitidine are commonly administered to prevent this complication.

Hypertension can result from hyperreninemia associated with the primary disease process and/or expansion of the extracellular fluid volume and is most common in AKI patients with acute glomerulonephritis or HUS. Salt and water restriction is critical, and diuretic administration may be useful (see Chapter 472). Isradipine (0.05-0.15 mg/kg/dose, maximum dose 5 mg qid) may be administered for a relatively rapid reduction in blood pressure. Longer-acting oral agents such as calcium channel blockers (amlodipine, 0.1-0.6 mg/kg/24 hr qd or divided bid) or β blockers (labetalol, 4-40 mg/kg/24 hr divided bid or tid) may be helpful in maintaining control of the blood pressure. Children with severe symptomatic hypertension (hypertensive urgency or emergency) should be treated with continuous infusions of nicardipine (0.5-5.0 µg/kg/min), sodium nitroprusside (0.5-10.0 µg/kg/min), labetalol (0.25-3.0 mg/kg/hr), or esmolol (150-300 µg/kg/min) and converted to intermittently dosed antihypertensives when more stable.

Neurologic symptoms in AKI can include headache, seizures, lethargy, and confusion (encephalopathy). Potential etiologic factors include hypertensive encephalopathy, hyponatremia, hypocalcemia, cerebral hemorrhage, cerebral vasculitis, and the uremic state. Benzodiazepines are the most effective agents in acutely controlling seizures, and subsequent therapy should be directed toward the precipitating cause.

The **anemia** of AKI is generally mild (hemoglobin 9-10 g/dL) and primarily results from volume expansion (hemodilution). Children with HUS, SLE, active bleeding, or prolonged AKI can require transfusion of packed red blood cells if their hemoglobin level falls below 7 g/dL. In hypervolemic patients, blood transfusion carries the risk of further volume expansion, which can precipitate hypertension, heart failure, and pulmonary edema. Slow (4-6 hr) transfusion with packed red blood cells (10 mL/kg) diminishes the risk of hypervolemia. The use of fresh, washed red blood cells minimizes the acute risk of hyperkalemia, and the chronic risk of sensitization if the patient becomes a future candidate for renal replacement therapy. In the presence of severe hypervolemia or hyperkalemia, blood transfusions are most safely administered during dialysis or ultrafiltration.

Nutrition is of critical importance in children who develop AKI. In most cases, sodium, potassium, and phosphorus should be restricted. Protein intake should be moderately restricted while maximizing the caloric intake to minimize the accumulation of nitrogenous wastes. In critically ill patients with AKI, parenteral hyperalimentation with essential amino acids should be considered.

Dialysis

Indications for dialysis in AKI include the following:

Anuria/oliguria
Volume overload with evidence of hypertension and/or pulmonary edema refractory to diuretic therapy
Persistent hyperkalemia
Severe metabolic acidosis unresponsive to medical management
Uremia (encephalopathy, pericarditis, neuropathy)
Calcium:phosphorus imbalance, with hypocalcemic tetany that cannot be controlled by other measures

An additional indication for dialysis is the inability to provide adequate nutritional intake because of the need for severe fluid restriction. In patients with AKI, dialysis support may be necessary for days or for up to 12 wk. Many patients with AKI require dialysis support for 1-3 wk. Table 550.6 lists the advantages and disadvantages of the three types of dialysis.

Table 550.6

Comparison of Peritoneal Dialysis, Intermittent Hemodialysis, and Continual Renal Replacement Therapy

	PD	IHD	CRRT
BENEFITS			
Fluid removal	+	++	++
Urea and creatinine clearance	+	++	+
Potassium clearance	++	++	+
Toxin clearance	+	++	+
COMPLICATIONS			
Abdominal pain	+	−	−
Bleeding	−	+	+
Dysequilibrium	−	+	−
Electrolyte imbalance	+	+	+
Need for heparinization	−	+	+/−
Hyperglycemia	+	−	−
Hypotension	+	++	+
Hypothermia	−	−	+
Central line infection	−	+	+
Inguinal or abdominal hernia	+	−	−
Peritonitis	+	−	−
Protein loss	+	−	−
Respiratory compromise	+	−	−
Vessel thrombosis	−	+	+

PD, peritoneal dialysis; IHD, intermittent hemodialysis; CRRT, continual renal replacement therapy.

Adapted from Rogers MC: Textbook of pediatric intensive care, Baltimore, 1992, Williams & Wilkins.

Intermittent hemodialysis is useful in patients with a relatively stable hemodynamic status. This highly efficient process accomplishes both fluid and electrolyte removal in sessions of 3-4 hr using a pump-driven extracorporeal circuit and large central venous catheter. Intermittent hemodialysis may be performed 3-7 times per week based on the patient's fluid and electrolyte balance.

Peritoneal dialysis is most commonly employed in neonates and infants with

AKI, although this modality may be used in children and adolescents of all ages. Hyperosmolar dialysate is infused into the peritoneal cavity via a surgically or percutaneously placed peritoneal dialysis catheter. The fluid is allowed to dwell for 45-60 min and is then drained from the patient by gravity (manually or with the use of machine-driven cycling), accomplishing fluid and electrolyte removal. Cycles are repeated for 8-24 hr/day based on the patient's fluid and electrolyte balance. Anticoagulation is not necessary. Peritoneal dialysis is contraindicated in patients with significant abdominal pathology.

Continuous renal replacement therapy (CRRT) is useful in patients with an unstable hemodynamic status, concomitant sepsis, or multiorgan failure in the intensive care setting. CRRT is an extracorporeal therapy in which fluid, electrolytes, and small- and medium-size solutes are continuously removed from the blood (24 hr/day) using a specialized pump-driven machine. Usually, a double-lumen catheter is placed into the internal jugular or femoral vein. The patient is then connected to the pump-driven CRRT circuit, which continuously passes the patient's blood across a highly permeable filter.

CRRT may be performed in three basic fashions. In continuous venovenous hemofiltration, a large volume of fluid is driven by systemic or pump-assisted pressure across the filter, bringing with it by convection other molecules, such as urea, creatinine, phosphorus, and uric acid. The blood volume is reconstituted by an intravenous infusion of a replacement fluid having a desirable electrolyte composition similar to that of blood. Continuous venovenous hemofiltration dialysis uses the principle of diffusion by circulating dialysate in a countercurrent direction on the ultrafiltrate side of the membrane. No replacement fluid is used. Continuous hemodiafiltration employs both replacement fluid and dialysate, offering the most effective solute removal of all forms of CRRT.

Table 550.6 compares the relative risks and benefits of the various renal replacement therapies.

Prognosis

The mortality rate in children with AKI is variable and depends entirely on the nature of the underlying disease process rather than on the renal failure itself. Children with AKI caused by a renal-limited condition such as postinfectious glomerulonephritis have a very low mortality rate (<1%); those with AKI related to multiorgan failure have a very high mortality rate (>50%).

The prognosis for recovery of renal function depends on the disorder that precipitated AKI. Recovery of renal function is likely after AKI resulting from prerenal causes, ATN, acute interstitial nephritis, or tumor lysis syndrome. Complete recovery of renal function is unusual when AKI results from most types of rapidly progressive glomerulonephritis, bilateral renal vein thrombosis, or bilateral cortical necrosis. Medical management may be necessary for a prolonged period to treat the sequelae of AKI, including chronic renal insufficiency, hypertension, renal tubular acidosis, and urinary concentrating defect.

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550.2

Chronic Kidney Disease

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Keywords

Fluid and electrolyte management
CKD mineral and bone disease
Anemia
Hypertension
Proteinuria
Linear Growth
Progression
End stage renal disease
glomerular filtration rate
hyperfiltration injury
hyperlipidemia
hyperphosphatemia
hypertension
osteitis fibrosa cystica
osteodystrophy
proteinuria

Chronic kidney disease (CKD) is determined by the presence of kidney damage and level (or severity) of kidney function (glomerular filtration rate, or GFR; Tables 550.7 and 550.8). End-stage renal disease (ESRD) is an administrative term in the United States; it is used to define all patients who are treated with dialysis or kidney transplantation, and is a subset of patients with stage 5 CKD.

Table 550.7

Criteria for Definition of Chronic Kidney Disease (NKF KDOQI Guidelines)

Patient has chronic kidney disease (CKD) if either of the following criteria are present:
1. Kidney damage for ≥ 3 mo, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by one or more of the following features: • Abnormalities in the composition of the blood or urine • Abnormalities in imaging tests • Abnormalities on kidney biopsy 2. GFR < 60 mL/min/1.73 m^2 for ≥ 3 mo, with or without the other signs of kidney damage described above

NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

Table 550.8

Standardized Terminology for Stages of Chronic Kidney Disease (NKF KDOQI Guidelines)

STAGE	DESCRIPTION	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 or on dialysis

GFR, glomerular filtration rate; NKF KDOQI, National Kidney Foundation Kidney Disease Outcomes Quality Initiative.

The pediatric CKD prevalence is approximately 18 per 1 million children. The prognosis for the infant, child, or adolescent with CKD has improved dramatically since the 1970s, mostly because of improved medical management, dialysis techniques, and kidney transplantation. Yet, childhood-onset ESRD still carries significant morbidity and a 30-fold increased mortality rate as compared with healthy peers, with cardiovascular and infectious diseases as the leading causes of death.

Etiology

The etiology of pediatric CKD may be the result of congenital, acquired, inherited, or metabolic renal disease; causes of kidney disease in children are typically subdivided as being either nonglomerular or glomerular in origin (Table 550.9). The underlying cause correlates with the age at the time of diagnosis. In children < 5 yr of age, CKD is most commonly a result of congenital abnormalities of the kidney and urinary tract (i.e., renal hypoplasia, dysplasia, or obstructive uropathy) and is often diagnosed with prenatal ultrasonography. In children older than 5 yr of age, acquired or inherited forms of glomerulonephritis predominate.

Table 550.9

Etiologies of Pediatric Chronic Kidney Disease

NONGLOMERULAR	GLOMERULAR
Aplastic, hypoplastic, and dysplastic kidneys	Chronic glomerulonephritis (including focal segmental glomerulonephritis [FSGS])
Cystinosis	Congenital nephrotic syndrome (CNS)
Medullary cystic kidney disease/juvenile nephronophthisis	Hemolytic-uremic syndrome (HUS)
Obstructive uropathy (e.g., PUV, cloaca, neurogenic bladder)	Henoch-Schönlein nephritis (HSP nephritis)
Oxalosis	Idiopathic crescentic glomerulonephritis
Autosomal dominant and autosomal recessive polycystic kidney disease (ADPKD, ARPDK)	IgA nephropathy (IGAN)
Pyelonephritis/interstitial nephritis/reflux nephropathy	Membranoproliferative glomerulonephritis (MPGN)
Renal infarct	Membranous nephropathy
Syndrome of agenesis of abdominal musculature (Eagle-Barrett syndrome)	Sickle cell nephropathy
Wilms tumor	Systemic immunologic disease (e.g., SLE, Wegener granulomatosis)
	Hereditary nephritis (Alport syndrome)

Pathogenesis

In addition to progressive injury with ongoing structural or metabolic genetic diseases, renal injury can progress despite removal of the original insult.

Hyperfiltration injury may be an important final common pathway of glomerular destruction, independent of the underlying cause of renal injury. As nephrons are lost, the remaining nephrons undergo structural and functional hypertrophy characterized by an increase in glomerular blood flow. The driving force for glomerular filtration is thereby increased in the surviving nephrons. Although this compensatory hyperfiltration temporarily preserves total renal function, it can cause progressive damage to the surviving glomeruli, possibly by a direct effect of the elevated hydrostatic pressure on the integrity of the capillary wall and/or the toxic effect of increased protein traffic across the capillary wall. Over time, the remaining nephrons suffer an increased excretory burden, resulting in a vicious cycle of increasing glomerular blood flow and hyperfiltration injury.

Other pathologic etiologies of chronic kidney disease include proteinuria, hypertension, hyperphosphatemia, and hyperlipidemia. **Proteinuria** itself can contribute to renal functional decline. Proteins that traverse the glomerular capillary wall can exert a direct toxic effect on tubular cells and recruit monocytes and macrophages, enhancing the process of glomerular sclerosis and tubulointerstitial fibrosis. Uncontrolled **hypertension** can exacerbate the disease progression by causing arteriolar nephrosclerosis and by increasing the hyperfiltration injury. **Hyperphosphatemia** can increase the progression of disease by leading to calcium phosphate deposition in the renal interstitium and blood vessels. **Hyperlipidemia,** a common condition in CKD patients, can adversely affect glomerular function through oxidant-mediated injury.

CKD is viewed as a continuum of disease, with increasing biochemical and clinical manifestations as renal function deteriorates. Regardless of the etiology, the progression of tubulointerstitial fibrosis is the primary determinant of CKD progression.

Clinical Manifestations

Table 550.10 outlines the pathophysiologic manifestations of CKD. The clinical presentation of CKD is varied and depends on the underlying etiology and CKD stage (Fig. 550.2). CAKUT and some genetic forms of renal disease (i.e., familial nephronophthisis) demonstrate growth failure, vomiting, and polyuria with associated polydipsia. Urinary tract infection can also be common in those with urologic abnormalities. Glomerular forms of CKD often present with edema, hypertension, hematuria, and proteinuria; in severe forms of glomerulonephritis, malnutrition can be seen. As renal deterioration advances in severity, patients can develop uremic symptoms (i.e., worsening fatigue, weakness, nausea, vomiting, anorexia, and poor sleep patterns), as well as edema, hypertension, and other findings of fluid overload, regardless of the cause of CKD.

Table 550.10

Pathophysiology of Chronic Kidney Disease

MANIFESTATION	MECHANISMS
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium wasting	Solute diuresis Tubular damage
Urinary concentrating defect	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol (1,25OH$_2$ D) Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron, folate, and/or vitamin B$_{12}$ deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Decreased academic achievement, attention regulation, or executive functioning	Hypertension Low birth weight
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity Abnormal HDL-C
Cardiomyopathy	Hypertension Anemia Fluid overload
Glucose intolerance	Tissue insulin resistance

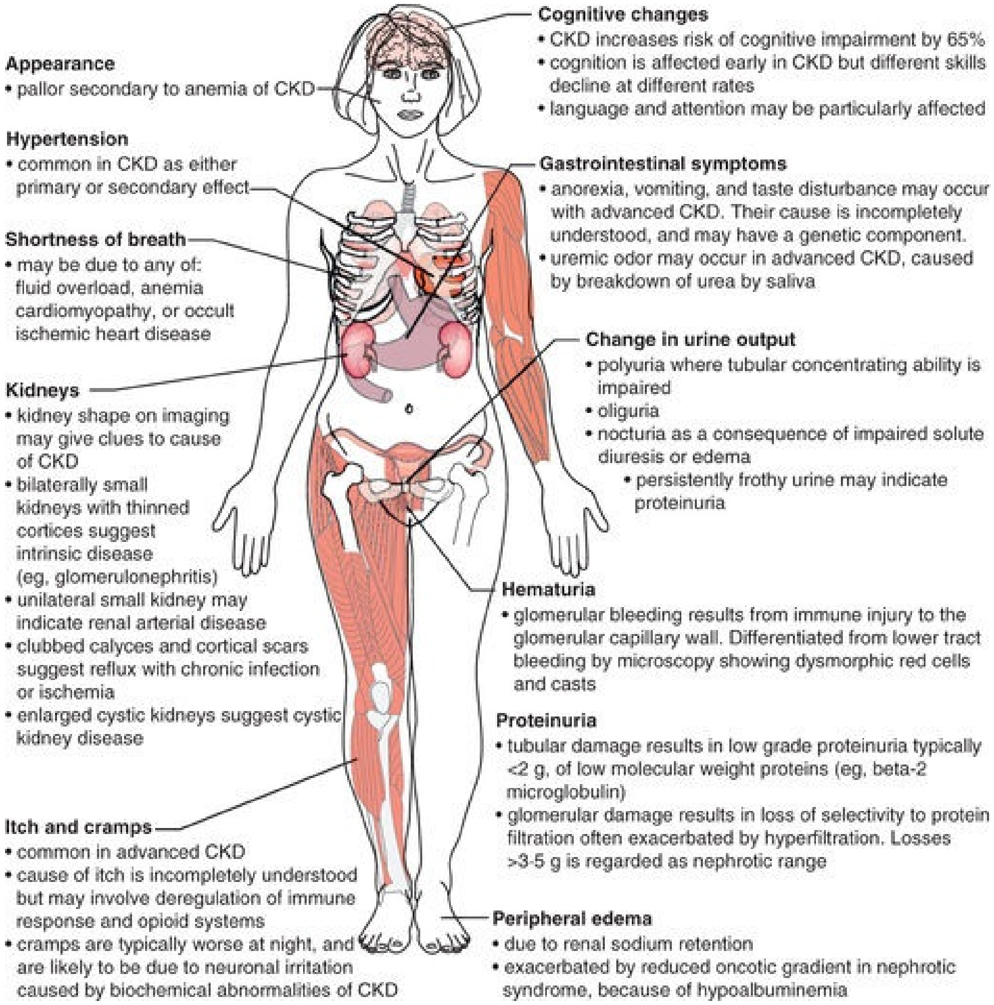
Appearance
• pallor secondary to anemia of CKD
Hypertension
• common in CKD as either primary or secondary effect
Shortness of breath
• may be due to any of: fluid overload, anemia cardiomyopathy, or occult ischemic heart disease
Kidneys
• kidney shape on imaging may give clues to cause of CKD
• bilaterally small kidneys with thinned cortices suggest intrinsic disease (eg, glomerulonephritis)
• unilateral small kidney may indicate renal arterial disease
• clubbed calyces and cortical scars suggest reflux with chronic infection or ischemia
• enlarged cystic kidneys suggest cystic kidney disease
Itch and cramps
• common in advanced CKD
• cause of itch is incompletely understood but may involve deregulation of immune response and opioid systems
• cramps are typically worse at night, and are likely to be due to neuronal irritation caused by biochemical abnormalities of CKD
Cognitive changes
• CKD increases risk of cognitive impairment by 65%
• cognition is affected early in CKD but different skills decline at different rates
• language and attention may be particularly affected
Gastrointestinal symptoms
• anorexia, vomiting, and taste disturbance may occur with advanced CKD. Their cause is incompletely understood, and may have a genetic component.
• uremic odor may occur in advanced CKD, caused by breakdown of urea by saliva
Change in urine output
• polyuria where tubular concentrating ability is impaired
• oliguria
• nocturia as a consequence of impaired solute diuresis or edema
• persistently frothy urine may indicate proteinuria
Hematuria
• glomerular bleeding results from immune injury to the glomerular capillary wall. Differentiated from lower tract bleeding by microscopy showing dysmorphic red cells and casts
Proteinuria
• tubular damage results in low grade proteinuria typically <2 g, of low molecular weight proteins (eg, beta-2 microglobulin)
• glomerular damage results in loss of selectivity to protein filtration often exacerbated by hyperfiltration. Losses >3-5 g is regarded as nephrotic range
Peripheral edema
• due to renal sodium retention
• exacerbated by reduced oncotic gradient in nephrotic syndrome, because of hypoalbuminemia

FIG. 550.2 Symptoms and signs of CKD. (From Webster AC, Nagler EV, Morton RL, Masson P: Chronic kidney disease, Lancet 389:1238-1252, 2017, Fig. 2.)

Physical examination in CKD should focus on overall growth and development, with special attention and/or evaluation of the blood pressure, as well as the skin (pallor) and the extremities (edema; bony abnormalities of rickets seen in untreated renal osteodystrophy).

Laboratory Findings

Laboratory findings can include elevations in blood urea nitrogen and serum creatinine in addition to hyperkalemia, hyponatremia (secondary to either renal salt wasting versus volume overload), hypernatremia (loss of free water), acidosis, hypocalcemia, hyperphosphatemia, and an elevation in uric acid.

Patients with heavy proteinuria can have hypoalbuminemia. A complete blood cell count may show a normochromic, normocytic anemia. Dyslipidemia is commonly seen. In children with glomerulonephritis, the urinalysis (UA) shows hematuria and proteinuria, whereas in children with congenital lesions such as renal dysplasia, the UA often has a low specific gravity with minimal other abnormalities.

Renal function can be measured or estimated by the GFR. Inulin clearance is the gold standard to measure the GFR, but it is no longer readily available. Other methods for measuring the GFR in clinical practice include using iohexol or various radioisotopes (^{99m} Tc-DTPA, ^{51} Cr-EDTA, or ^{125} Iothalamate). However, estimating the GFR by endogenous markers (e.g., creatinine and/or cystatin C) is the most utilized method to understand the severity of renal disease. A new bedside creatinine-based estimating equation of estimated GFR (mL/min/1.73 m^2) = 0.43 × height (cm)/serum creatinine (mg/dL) has been validated in a pediatric CKD population of children aged 1-16 yr and whose GFR was between 15 and 90 mL/min/1.73 m^2 .

Treatment and Management

CKD treatment is supportive, with an aim to screen for and treat various metabolic complications of CKD in hopes to improve the quality of life and potentially slow the progression of renal dysfunction. Children with CKD should be treated at a pediatric center capable of supplying multidisciplinary services, including medical, nursing, social service, nutritional, and psychological support.

CKD management requires close monitoring of blood studies, urine studies (including quantitative measurement for proteinuria using either a spot urine protein/urine creatinine ratio or 24 hr urine collection), and overall clinical symptomatology. Ambulatory blood pressure monitoring (ABPM) over 24 hr, the gold standard of blood pressure evaluation, is recommended in patients with renal disease to diagnose and treat hypertension, especially masked hypertension. Masked hypertension (defined as a normal office blood pressure but abnormal ABPM) is seen in up to 35% of pediatric predialysis CKD patients and carries a 4-fold increased risk of having left ventricular hypertrophy (LVH).

Nutrition

Nutritional management by a dietician experienced in pediatric renal patients is recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI). Patients should receive 100% of the estimated energy requirement for age, individually adjusted for the physical activity level, body mass index, and response in the rate of weight gain or loss. When oral supplemental nutrition with increased calories or fluid volume is insufficient, tube feeding (by nasogastric tubes or gastrostomy tubes) should be considered. Calories should be balanced between carbohydrate, unsaturated fat in physiologic ranges (per dietary reference intake [DRI]), and protein. Dietary protein restriction is not suggested for children with CKD because of the concern about adverse effects on growth and development; in fact, the recommended protein intake is often 100% (or more for those receiving dialysis) of the DRI for ideal weight for children. Children with CKD stages 2-5 should receive 100% of the DRI of vitamins and trace elements; water-soluble vitamin supplements are often required for patients receiving dialysis.

CKD Mineral and Bone Disorder (CKD-MBD)

Chronic kidney disease is characterized by systemic disorders of calcium, phosphorus, PTH, and vitamin D metabolism that can not only lead to bone disorders *(renal osteodystrophy)* but also *vascular and soft tissue calcification* (Fig. 550.3). Efforts have focused on the role of the hormone fibroblast growth factor 23 (FGF23) and its cofactor, Klotho, in CKD-MBD. An elevated FGF23 results in increased urinary phosphate excretion and suppression of 1-α-hydroxylase activity, leading to reduced 1,25-dihydroxycholecalciferol ($1,25OH_2$ D) values and increased PTH secretion. Elevated FGF23 is the first sign of altered osteocyte function in pediatric and adult CKD, is seen as early as CKD stage 2 (GFR 60-90 mL/min/1.73 m2), and occurs despite normal calcium, phosphorus, PTH, and $1,25OH_2$ D levels. With a continued loss of renal function, further FGF23 elevation results in the development of secondary hyperparathyroidism (low $1,25OH_2$ D, with hypocalcemia, hyperphosphatemia, and elevated PTH values).

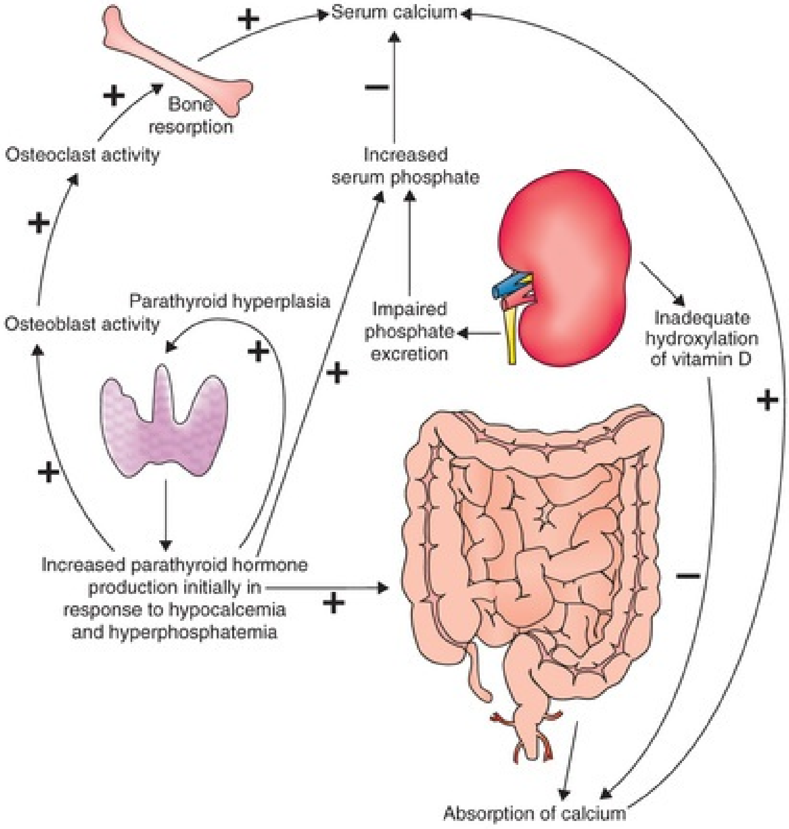
Serum calcium
+
Bone resorption
+
Osteoclast activity
−
Increased serum phosphate
+
Parathyroid hyperplasia
Osteoblast activity
+
+
Impaired phosphate excretion
Inadequate hydroxylation of vitamin D
+
+
Increased parathyroid hormone production initially in response to hypocalcemia and hyperphosphatemia
+
−
Absorption of calcium

FIG. 550.3 Pathophysiology of CKD mineral bone disease. (From Webster AC, Nagler EV, Morton RL, Masson P: Chronic kidney disease, Lancet 389:1238-1252, 2017, Fig. 4.)

Renal osteodystrophy is characterized by abnormalities in bone turnover (high versus low), mineralization, and bone volume. High-turnover bone disease, or *osteitis fibrosa cystica,* is the most common condition seen in advanced pediatric CKD, with characteristic laboratory findings (hypocalcemia, hyperphosphatemia, and elevated alkaline phosphatase and PTH values) and radiographic findings (subperiosteal bone resorption, metaphyseal widening). Clinical manifestations may include bone pain, fractures with minor trauma, and various bony abnormalities (rachitic changes, varus and valgus deformities of the long bones, and slipped capital femoral epiphyses, or SCFE). In contrast, low-turnover bone disease *(adynamic renal osteodystrophy)* is associated with PTH oversuppression, hypercalcemia, and low alkaline phosphatase activity; it is more commonly seen in pediatric dialysis patients receiving treatment for secondary hyperparathyroidism. Defective bone mineralization occurs in states of either high bone turnover (mixed lesion) or low to normal bone turnover (osteomalacia). In terms of bone volume, most pediatric CKD patients have normal to high bone volume on bone histomorphometry unless they were exposed to prolonged corticosteroid use.

Vascular calcification in CKD-MBD typically occurs within the vascular media, which is in contrast to the atherosclerotic plaques that form within the vascular intima in patients without renal disease but with traditional cardiovascular risk factors (hypertension, diabetes/obesity, cigarette smoking, and dyslipidemia). Vascular calcification in CKD has been associated with hypercalcemia, hyperphosphatemia, and an elevated calcium-phosphorus product ($Ca \times PO_4$;); yet, studies of adult and pediatric patients with mild to moderate CKD have noted findings of vascular calcification despite normal serum calcium and phosphorus values. The cause of vascular calcification in CKD is not completely understood and is being actively studied; the proposed pathophysiologic etiology involves the transition of vascular smooth muscle cells to osteoblast-like cells in response to trigger(s) that are currently unknown.

Treatment for CKD-MBD is guided by the clinical assessment of calcium, phosphorus, 25OH Vitamin D, and PTH. The goals of treatment are to normalize mineral metabolism with the goal of improving growth, reducing bone deformities and fragility, and reducing vascular and other soft tissue calcification. This is typically accomplished with reduced phosphorus intake, normalization of 25OH vitamin D, and use of active vitamin D sterol agents.

CKD patients of all ages should typically follow a low-phosphorus diet with the goal of maintaining age-appropriate serum phosphorus values. Infants should be provided with a low-phosphorus formula (Similac PM 60/40). Phosphate binders (given with meals) are used to enhance GI phosphate excretion, and at present are recommended to be started at the onset of hyperphosphatemia. **Phosphate binders** should be adjusted to maintain normal serum calcium and phosphorus levels, and to ensure that the recommended total daily intake of calcium is not exceeded. Phosphate binders can be either calcium-based (calcium carbonate, calcium acetate) or non–calcium-based (sevelamer and ferric citrate). Because aluminum may be absorbed from the GI tract and can lead to aluminum toxicity, aluminum-based binders should be avoided.

Correcting 25OH Vitamin D insufficiency can delay the onset of secondary hyperparathyroidism in predialysis CKD patients, and it improves bone mineralization. 25OH vitamin D provides a substrate for the formation of $1{,}25OH_2$ D, and has been shown to directly suppress PTH production at the level of the parathyroid gland. US-based pediatric CKD treatment guidelines define 25OH vitamin D sufficiency as a serum value of ≥ 30 ng/mL; **ergocalciferol** or

cholecalciferol are typically recommended to treat insufficient 25OH vitamin D.

Active vitamin D sterols have been traditionally indicated when (1) 1,25OH$_2$ D levels fall below the established goal range for the child's particular stage of CKD, (2) PTH levels increase above the established goal range for CKD stage (after correcting for insufficient 25OH vitamin D), or (3) in patients with elevated PTH levels and hypocalcemia. Vitamin D sterols increase calcium and phosphorus absorption from the GI tract and are effective in reducing PTH values. Calcitriol is the most well-known and studied active vitamin D sterol; newer agents such as paricalcitol and doxercalciferol have less intestinal calcium and phosphorus reabsorption and are used in CKD patients predisposed to hypercalcemia. The ideal PTH target at which to initiate and monitor active vitamin D sterol therapy is debated, particularly in the predialysis CKD population.

Fluid and Electrolyte Management

Infants and children with renal dysplasia may be polyuric, with significant urinary sodium and free water losses. These children benefit from high-volume, low-caloric-density feedings with sodium supplementation. Children with high blood pressure or edema benefit from sodium restriction and diuretic therapy. Fluid restriction is necessary in severe cases of nephrotic syndrome or when renal function worsens to the point of requiring dialysis.

Hyperkalemia can develop with severe deterioration in renal function, as well as in patients with moderate renal insufficiency who have excessive dietary potassium intake, severe acidosis, or hyporeninemic hypoaldosteronism (related to destruction of the renin-secreting juxtaglomerular apparatus). Hyperkalemia may be treated by the restriction of dietary potassium intake, administration of oral alkalinizing agents, and/or use of Kayexalate. Sodium zirconium and patiromer are additional oral agents used to treat hyperkalemia in adults.

Metabolic acidosis develops because of a decreased net acid excretion by the failing kidneys. Either **Bicitra** (1 mEq sodium citrate/mL) or **sodium bicarbonate tablets** (650 mg = 8 mEq of base) may be used to maintain the serum bicarbonate level ≥ 22 mEq/L.

Linear Growth

Short stature is a significant long-term sequela of childhood CKD. CKD results in an apparent growth hormone–resistant state, with elevated growth hormone levels but decreased insulin-like growth factor 1 levels and abnormalities of insulin-like growth factor–binding proteins.

Children with CKD who remain less than −2 SD for height despite optimal medical support (adequate caloric intake and effective treatment of renal osteodystrophy, anemia, and metabolic acidosis) may benefit from treatment with **recombinant human growth hormone** (rHuGH). rHuGH is given by daily subcutaneous injections and continues until the patient reaches the 50th percentile for midparental height, achieves a final adult height, or undergoes kidney transplantation. Long-term rHuGH treatment significantly improves the final adult height and induces persistent catch-up growth; some patients are able to achieve normal adult height.

Anemia

Anemia in patients with CKD is primarily the result of inadequate erythropoietin production by the failing kidneys and typically manifests when renal function falls below 40 mL/min/1.73 m^2 . Other contributory factors for anemia in CKD include iron, folic acid, and/or vitamin B_{12} deficiency, and decreased erythrocyte survival secondary to uremia.

Anemia in pediatric CKD patients is defined when the hemoglobin falls to < 5% for age and gender; alternatively, anemia can be defined when the hemoglobin falls to < 11g/dL (ages 0.5-5 yr of age), < 11.5 g/dL (5-12 yr of age), < 12 g/dL (females > 12 yr of age, males 12-15 yr of age), and < 13 g/dL (males > 15 yr of age). Once anemia is diagnosed, the recommendation is to investigate for deficiencies in iron and/or other vitamins (i.e., vitamin B_{12} , folate). **Iron supplementation** (oral or intravenous) is recommended for patients who demonstrate a transferrin saturation (TSAT) ≤ 20% and ferritin ≤ 100 ng/mL.

Erythropoiesis-stimulating agents (ESAs) have decreased the need for transfusion in CKD patients, especially those receiving hemodialysis. Erythropoietin and darbepoetin alfa are common prescribed ESAs. All patients receiving ESA therapy should be provided with either oral or intravenous iron supplementation. Patients who appear to be resistant to ESA should be evaluated for iron deficiency, occult blood loss, a chronic infection or inflammatory state, vitamin B_{12} or folate deficiency, or bone marrow fibrosis related to secondary hyperparathyroidism.

Hypertension and Proteinuria

Hypertension in pediatric CKD can be secondary to volume overload and/or excessive renin production due to glomerular disease. Both hypertension and proteinuria have been independently associated with more rapid CKD progression in various pediatric CKD observational studies. The ESCAPE trial demonstrated that more aggressive blood pressure control delays CKD progression. In this study, participants with 24 hr mean arterial pressure (MAP) < 50th percentile for age and sex by ABPM had a 35% risk reduction of reaching the composite outcome (doubling of serum creatinine, eGFR of < 10 mL/min/1.73 m^2 , or need for dialysis or kidney transplantation) as compared with those randomized to a conventional blood pressure target (MAP of 50–95% by ABPM); this effect was more notable in those with significant proteinuria.

Therapy for hypertension involves both dietary interventions and, often, pharmacologic agents. **Dietary sodium restriction** (< 2 g of sodium/24 hr) and lifestyle modifications that promote achieving a healthy weight are both important aspects of achieving good blood pressure control. Treatment guidelines recommend initiating pharmacologic antihypertensive therapy when systolic or diastolic blood pressures are > 90% for age, gender, and height. Once therapy is started, it is recommended to titrate medications to achieve a systolic and diastolic blood pressure < 50% for age, gender, and height, especially for those patients with proteinuria. **ACE inhibitors** (ACE; e.g., enalapril or lisinopril) and **angiotensin II receptor blockers** (ARB; e.g., losartan) are the antihypertensive medications of choice in all children with pediatric CKD, irrespective of the level of proteinuric renal disease, because of their potential ability to slow CKD and their superiority in controlling blood pressure as noted in various observational and research studies. It is important to closely monitor the renal function and electrolyte balance while using ACEs or ARBs, particularly in those with advanced CKD. **Thiazide** (hydrochlorothiazide, chlorothiazide) or **loop diuretics** (furosemide) can be helpful in controlling hypertension related to salt and fluid retention. Thiazides become ineffective when a patient's estimated GFR falls below 30 mL/min/1.73 m^2 . Calcium channel blockers (amlodipine), β-blockers (propranolol, atenolol), and centrally acting agents (clonidine) may be useful as adjunctive agents in children with CKD whose blood pressure cannot be controlled using dietary sodium restriction, ACE inhibitors, and diuretics.

Immunizations

Children with CKD should receive all standard immunizations according to the schedule used for healthy children, with an exception to withhold live virus vaccines (such as measles, mumps, rubella, varicella) from those receiving immunosuppressive medications (i.e., kidney transplant recipients and some patients with glomerulonephritis). It is critical to make every attempt to administer live virus vaccines before kidney transplantation. All children with CKD should receive a yearly influenza vaccine. Data from a number of studies suggest that children with CKD might respond suboptimally to immunizations.

Adjustment in Drug Dose

Drugs excreted by the kidneys might need to be dose adjusted in CKD patients to maximize their effectiveness and minimize the risk of toxicity. Strategies in dosage adjustment include lengthening of the interval between doses or decreasing the absolute dose, or both.

Progression of Disease

The timing of CKD progression from minimal renal injury to the onset of ESRD is variable. The median loss of GFR in children enrolled in the Chronic Kidney Disease in Children (CKiD) study is 1.5 mL/min/1.73 m^2 /yr (nonglomerular CKD etiology) versus 4.3 mL/min/1.73 m^2 /yr (glomerular CKD etiology). Nonmodifiable risk factors associated with more rapid CKD progression include older age, glomerular etiology of renal disease, CKD severity, and onset of puberty. In terms of potential modifiable risk factors (in addition to an elevated blood pressure), persistent nephrotic range proteinuria, anemia, and dyslipidemia, as well as no ACE/ARB use, were important predictors of CKD progression.

In addition to addressing and treating the risk factors as noted above, prompt treatment of infectious complications and episodes of dehydration can minimize additional loss of renal parenchyma. Other potentially beneficial recommendations include tobacco avoidance, prevention of obesity, and avoidance of potential nephrotoxic medications (which includes nonsteroidal antiinflammatory medicines, various illegal street drugs, and herbal and/or homeopathic medications or supplements).

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550.3

End-Stage Renal Disease

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Keywords

Dialysis
Hemodialysis
Peritoneal Dialysis

ESRD represents the state in which a patient's renal dysfunction has progressed to the point at which homeostasis and survival can no longer be sustained by maximal medical management. At this point, renal replacement therapy (dialysis or renal transplantation) becomes necessary. The ultimate goal for children with ESRD is successful kidney transplantation (see Chapter 551) because it provides the most normal lifestyle and improved mortality and morbidity rates.

In the United States, 75% of children with ESRD require dialysis prior to transplantation. It is recommended that plans for renal replacement therapy (RRT) be initiated when a child reaches stage 4 CKD (GFR < 30 mL/min/1.73 m^2). Indications for initiating maintenance dialysis include diuretic-resistant fluid overload, severe fluid restrictions that inhibit the ability to provide appropriate nutrition sufficient for linear growth, uncontrolled electrolyte abnormalities (hyperkalemia, hyperphosphatemia, metabolic acidosis), and subjective findings of uremia (fatigue, weakness, nausea, vomiting, anorexia, and poor sleep patterns), especially if these symptoms are negatively affecting academic performance. Dialysis initiation should be considered as the GFR approaches 10-15 mL/min/1.73 m^2 . Most nephrologists attempt to initiate dialysis early enough to prevent the development of severe fluid and electrolyte abnormalities, malnutrition, and uremic symptoms.

The dialysis modality selection must be individualized to fit the needs of each child.

In the United States, peritoneal dialysis is still the most utilized dialysis modality (~55%) as compared with hemodialysis (~44%); however, there is a temporal trend toward greater use of hemodialysis as the initial maintenance dialysis therapy. Age is a defining factor in dialysis modality selection: 85% of infants and children from birth to 5 yr of age initiate maintenance dialysis treatment using peritoneal dialysis, whereas 50% of children ≥ 13 yr of age initiate maintenance dialysis treatment with hemodialysis.

Peritoneal dialysis utilizes the patient's peritoneal membrane to transport fluid and solutes. Excess body water is removed by an osmotic gradient created by the relatively high dextrose concentration in the dialysis fluid; wastes are removed by diffusion from the peritoneal capillaries into the dialysis fluid. Access to the peritoneal cavity is achieved by a surgically inserted, tunneled catheter. Peritoneal dialysis may be provided either as continuous ambulatory peritoneal dialysis (CAPD) or as an automated therapy using a cycler (APD), which allows exchanges of peritoneal fluid to be performed automatically during sleep by a cycler machine. APD is the PD modality of choice in countries without cost restraints. Cycler-driven peritoneal dialysis therapy allows the child and family an uninterrupted day of activities (including decreased school interruption), a reduction in the number of dialysis catheter connections and disconnections (which decreases the risk of peritonitis), often less strict fluid and dietary restrictions, and a reduction in the time required by patients and parents to perform dialysis, reducing the risk of caregiver fatigue and burnout. Because peritoneal dialysis is not as efficient as hemodialysis, it must be performed at least 6 times per week. Contraindications to peritoneal dialysis use include anatomic abnormalities (e.g., significant surgical adhesions, omphalocele, gastroschisis, or bladder exstrophy), peritoneal injury (including injury secondary to previous severe peritoneal infections), or lack of an appropriate caregiver who can reliably perform peritoneal dialysis in the home.

Hemodialysis, unlike peritoneal dialysis, is usually performed in a hospital or outpatient clinic setting; home pediatric hemodialysis programs or programs that provide intensified hemodialysis are available but uncommon. Access to the child's circulation is achieved by a surgically created arteriovenous fistula (AVF), arteriovenous graft (AVG), or tunneled dual-lumen catheter. The internal jugular vein is the preferred catheter site; indwelling subclavian catheters can cause subclavian stenosis that limits that ability to utilize a future AVF or AVG in the ipsilateral arm. Each hemodialysis treatment is typically prescribed to provide appropriate solute clearance and fluid removal. Hemodialysis has historically been provided 3 times per week; however, more frequent dialysis treatments (up to 4-5 times per week) are seen in the United States. Intensified hemodialysis programs (such as short daily hemodialysis, intermittent nocturnal hemodialysis, and daily nocturnal hemodialysis) have demonstrated improved control of blood pressure, fluid overload, phosphorus, anemia, and improved growth. Many pediatric dialysis centers work with schools or have hospital-based teachers that can help hemodialysis patients stay on track academically. Contraindications to hemodialysis include inadequate vascular access.

Dialysis-associated infections (peritonitis, hemodialysis-related bloodstream infections) are the leading causes of hospitalization and the second-leading cause of death in pediatric dialysis patients.

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CHAPTER 551

Renal Transplantation

David K. Hooper, Charles D. Varnell Jr

Kidney transplantation is the optimal therapy for children with **end-stage renal disease (ESRD).** The life expectancy in children who receive a kidney transplant has steadily increased and is substantially better than for those who remain on dialysis (Fig. 551.1). Children and adolescents with ESRD have special needs that differ from adults, including the need to achieve normal growth and cognitive development. Successful transplantation leads to accelerated linear growth, allows for regular school attendance, and often eliminates the need for dietary restrictions. Improvements in surgical techniques and a reduction in the early complications of thrombosis have given young children the best long-term outcomes of all age-groups among transplant recipients. Following kidney transplantation, the most commonly encountered complications include acute or chronic allograft rejection, an increased risk for infections with both community-acquired and opportunistic organisms, and cardiovascular disease (hypertension, obesity, dyslipidemia). Providers must also be aware of the risks for malignancy and sequelae of chronic kidney disease (CKD).

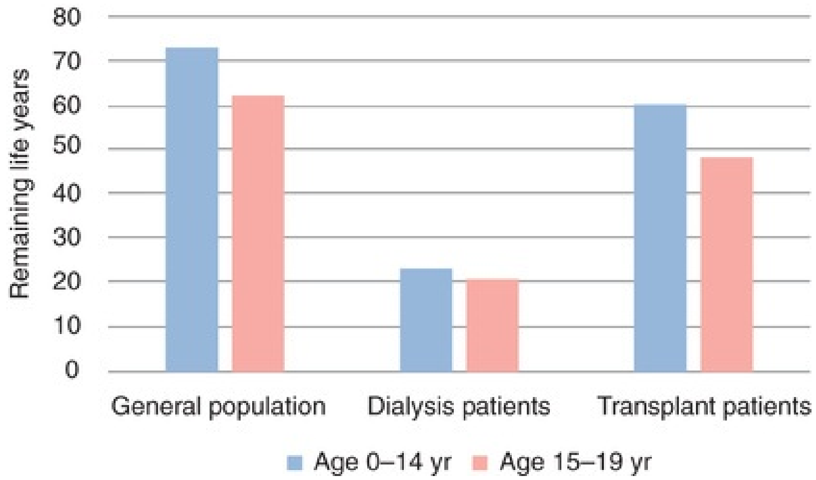

FIG. 551.1 Expected remaining years of life by end-stage renal disease treatment modality. (Adapted from United States Renal Data System. 2016 USRDS annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016.)

Incidence and Etiology of End-Stage Renal Disease

The incidence of ESRD in pediatric patients in the United States varies by age-group (Table 551.1), with an adjusted incident rate of 14.5 per million population for ages 0-21 yr. The etiology of ESRD in children also varies by age (Table 551.2 and Fig. 551.2). **Congenital anomalies of the kidney and urinary tract** account for more than 40% of children < 6 yr old awaiting a kidney transplant, whereas **glomerulonephritis** and **focal segmental glomerulosclerosis (FSGS)** account for more than 30% of such children over the age of 12 yr. In 2016, there were 747 kidney transplants performed in children < 18 yr of age in the United States, with 137 performed in children < 5 yr old, 124 in children ages 5-9 yr, 173 in children ages 10-13 yr, and 313 in children ages 14-17 yr. That same year, of the 5,739 children in the United States with ESRD, 4,375 (76%) had a functioning kidney transplant.

Table 551.1

Incident Rates of Reported ESRD in the United States

AGE RANGE (YR)	ADJUSTED INCIDENT RATES* PER MILLION POPULATION

0-4	10.7
5-9	6.6
10-13	11.4
14-17	15.8
18-21	29

[*] Rates are adjusted for age, sex, race, and ethnicity.

ESRD, end-stage renal disease.

United States Renal Data System. 2016 USRDS annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016.

Table 551.2

Common Causes of ESRD in Pediatric Transplant Recipients (N = 11186)

CAUSES	% OF RECIPIENTS
Aplasia, hypoplasia, dysplasia	15.8
Obstructive uropathy	15.3
Focal segmental glomerulosclerosis	11.7
Reflux nephropathy	5.1
Chronic glomerulonephritis	3.1
Polycystic disease	3.0
Medullary cystic disease	2.7
Congenital nephrotic syndrome	2.6
Hemolytic-uremic syndrome	2.6
Prune belly syndrome	2.5
Familial nephritis	2.2
Cystinosis	2.0
Idiopathic crescentic glomerulonephritis	1.7
MPGN type I	1.7
Pyelonephritis/interstitial nephritis	1.7
SLE nephritis	1.5
Renal infarct	1.3

ESRD, end-stage renal disease; MPGN, membranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus.

Data from the North American Pediatric Renal Trials and Collaborative Studies 2014 Annual Report, https://web.emmes.com/study/ped/ .

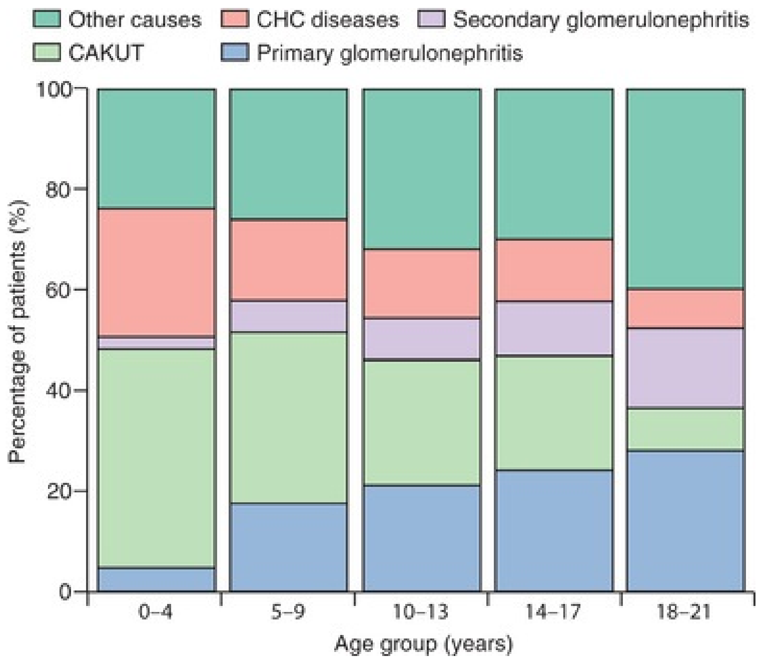

FIG. 551.2 Distribution of primary cause of end-stage renal disease, by age, in incident pediatric dialysis patients reported to USRDS in 2010–2014. The data reported here have been supplied by the USRDS (United States Renal Data System 2016 annual data report. Chapter 8 : ESRD among children, adolescents, and young adults. https://www.usrds.org/2016/view/v2_08.aspx , 2016). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. Government. USRDS, U,S, Renal Data System; CAKUT, congenital anomalies of the kidney and urinary tract; CHC, cystic, hereditary, and congenital. (From Rees L, Schaefer F, Schmitt CP, et al: Chronic dialysis in children and adolescents: challenges and outcomes. Lancet Child Adolesc Health 1:68-77, 2017, Fig. 1.)

Indications for Renal Transplantation

Renal transplantation is generally considered for any child when chronic renal replacement therapy is indicated. There are few absolute contraindications for pediatric kidney transplantation, yet relative contraindications arise when the combined risks of the transplant procedure itself and lifelong immunosuppression outweigh the benefits of improved health, longevity, and/or quality of life. Such relative contraindications include preexisting malignancy, primary or secondary immunodeficiency, chronic severe infection, inability to receive appropriate post-transplant care, or severe neurologic dysfunction where improvement in the quality of life and/or longevity is unlikely. In each scenario, the multidisciplinary team must weigh the risks and benefits of transplantation while accounting for the values of patients and caregivers. For instance, patients who have remission of malignancy for a minimum of 1-2 yr may be considered on an individual basis for kidney transplantation. Similarly, patients with autoimmune diseases resulting in ESRD (e.g., systemic lupus erythematosus) are candidates for transplantation after a period of immunologic quiescence of the primary disease.

In children, dialysis may be required before transplantation to optimize the nutritional and metabolic conditions, allow for quiescence of an underlying autoimmune disorder, achieve an appropriate size, or keep a patient stable until a suitable donor is available. Although successful transplantation with an adult-sized kidney has occurred in children < 10 kg and < 6 mo of age, recipients usually must weigh at least 8-10 kg to minimize the risk for vascular thrombosis and accommodate an adult-size kidney. This may require a period of dialysis support until the child is 12-18 mo of age.

Preemptive transplantation (i.e., transplantation without prior dialysis) accounts for ~ 25% of all pediatric renal transplants. It is the preferred approach when possible because of a small but incremental decrease in patient and allograft survival for every year spent on dialysis prior to transplant. Preemptive renal transplantation can and should therefore be considered in any child with stage IV or V CKD who is likely to require dialysis within 6-12 mo and/or has evidence of the adverse effects of CKD on his or her health or neurocognitive development. This requires early referral to a transplant center for evaluation of the candidate and potential donors. The transplant team must work with the recipient and caregivers to determine the optimal time for transplantation considering the risks and benefits posed to the recipient.

Characteristics of Kidney Donors and Recipients

Twenty-seven to 50% of pediatric kidney transplants come from **living donors,** depending on the age-group and year. The highest rates of transplantation are in children age 5-13 yr, with 18 live donor transplants and 31 **deceased donor** transplants performed per 100 dialysis patient-years. The Organ Procurement and Transplantation Network (OPTN) gives preference to children waiting for a deceased-donor renal transplant. From 2005 to 2014, children waitlisted before their 18th birthday were given priority for kidneys from young deceased donors age 5-35 yr. In 2014, a new policy was implemented to allocate priority to children based on projected organ survival using the **Kidney Donor Profile Index (KDPI),** which computes the projected allograft survival from 12 important donor characteristics. Under the new system, the top 35% of kidneys (KDPI < 35%) are preferentially allocated to children. Additional factors that determine the allocation include the time on dialysis or since listing (whichever is longest), a zero antigen mismatch, calculated panel-reactive antibody (cPRA), prior living donor, and 0 or 1 HLA-DR (human leukocyte antigen–antigen D–related) mismatch. Because of such policies, the median time on the waitlist for children (8-9 mo) is substantially lower than that for adults (3.5-4 yr).

Evaluation and Preparing for Kidney Transplantation

A comprehensive transplant evaluation includes a transplant surgeon, nephrologist, dietitian, social worker, psychologist, pharmacist, financial counselor, pretransplant nurse coordinator, and anesthesiologist. A urologist familiar with transplantation is also essential for patients with lower urinary tract anomalies. Important considerations for the transplant evaluation include considering the primary diagnosis and risk of recurrence; ensuring an adequate lower urinary tract for drainage of the transplanted kidney; diagnosing and treating infections; the presence of cardiovascular disease, anemia, and other sequelae of ESRD; and preparing the patient with immunizations prior to starting life-long immunosuppression.

Understanding the primary renal diseases is essential prior to kidney transplantation. For instance, a number of *primary renal diseases can recur* in a transplanted kidney, but this is not a contraindication to transplantation. Recurrent disease accounts for graft loss in almost 7% of primary transplantations and 10% of repeat transplants. **Primary FSGS** is known to recur in 30–60% of cases and substantially decreases allograft survival. Because **primary hyperoxaluria** is caused by enzymatic defects in the liver, unless kidney transplantation is accompanied by liver transplantation, the transplanted kidney will succumb to the same fate as the native kidneys. Histologic evidence of recurrent **membranoproliferative glomerulonephritis type I** varies widely, from 20–70%, and graft loss can occur in ≤ 30% of cases. Histologic recurrence of **membranoproliferative glomerulonephritis type II** occurs in virtually all cases, with graft loss in ≤ 50% cases. Histologic recurrence with mesangial immunoglobulin (Ig) A deposits is common and occurs in about half of the patients with **IgA nephropathy** and in approximately 30% of patients with **Henoch-Schönlein purpura,** yet it may not necessarily lead to premature allograft failure. **Congenital nephrotic syndrome** rarely recurs after transplantation, although patients can develop **antinephrin antibodies** and present with nephrotic syndrome. **Membranous nephropathy** occurs very rarely in children. The recurrence rate after kidney transplantation for patients who have been treated for **Wilms tumor** is approximately 13%. Although **Alport syndrome** does not recur following transplantation, approximately 3–4% of patients with Alport syndrome can develop de novo **anti–glomerular basement membrane (anti-GBM) glomerulonephritis** that may lead to graft loss.

Owing to the high risk of developing Wilms tumor, patients with **Denys-Drash syndrome** should undergo bilateral nephrectomy prior to transplantation. Other *indications for unilateral or bilateral native nephrectomies* include hyposthenuria with polyuria, significant proteinuria leading to coagulopathy, recurrent infection of the native kidneys, and severe hypertension resistant to medical management. Nephrectomies are also indicated in cases such as **polycystic kidney disease,** where the native kidneys may become so large that they cause feeding intolerability in infants or prevent space for a transplanted kidney. Finally, it is important to perform bilateral native nephrectomy or ureteral ligation in patients with **primary FSGS** to allow for surveillance of proteinuria and early identification and treatment of **recurrent FSGS.**

Urologic problems, such as **vesicoureteral reflux, posterior urethral valves,** and/or abnormal urinary bladders, should be addressed before surgery. Malformations and voiding abnormalities (e.g., neurogenic bladder, bladder dyssynergia, remnant posterior urethral valves, and urethral strictures) should be identified and repaired if possible. Children with urologic disease and renal dysplasia often require multiple operations to optimize the urinary tract anatomy and function. Such procedures include ureteric reimplantation to correct vesicoureteral reflux, bladder augmentation or reconstruction, urinary diversion (vesicostomy, ureterostomy, ileal conduit, continent appendicovesicostomy), and excision of ectopic ureteroceles. Good outcomes have been achieved in posterior urethral valve bladders by following a staged procedure of initial valve resection and bladder rehabilitation by a process of regimented double voiding and/or bladder cycling prior to transplantation.

A comprehensive nutritional assessment should be performed to ensure that an optimal nutritional status is achieved before transplant. Many children with ESRD require nutritional supplements to provide them with sufficient protein and calories. Infants and young children on dialysis often require nasogastric or gastrostomy tube feedings to overcome decreased oral intake from nausea and anorexia due to uremia.

Bone disease should be evaluated for and bone health optimized before transplantation. Uncontrolled secondary hyperparathyroidism may lead to urinary phosphate wasting, hypercalcemia, hypercalciuria, and/or nephrolithiasis posttransplant. A high calcium phosphorus product before transplantation leads to vascular stiffness and calcifications, increasing the risk for cardiovascular disease and difficult-to-control hypertension in the perioperative and posttransplant period.

In the United States, > 25% of the deaths in children on maintenance dialysis are a result of cardiovascular disease. Cardiac death is the leading cause of death in young adults after transplant in childhood. Therefore, evaluation of cardiac function, including echocardiography and electrocardiography, is required before kidney transplantation to ensure sufficient cardiac function to tolerate the large fluid load that accompanies kidney transplantation. Hypertension is common in ESRD and should be treated before transplant. If medical management is insufficient, bilateral nephrectomy may be considered to control the hyperreninemic response from the failing kidneys. Finally, patients with a history of obstructive uropathy and oligohydramnios in utero who survive to kidney transplant may have undiagnosed/unrecognized pulmonary hypertension, which should be evaluated prior to transplantation.

Anemia needs to be treated before transplantation. Most patients receive erythropoietin, folate, and iron to maintain goals for hemoglobin levels between 11 and 13 g/dL. Blood transfusions should be avoided if possible owing to concerns about sensitizing the patient to human leukocyte antigens before transplant. If a blood transfusion is required, patients should receive leukoreduced red blood cells.

Evaluation for hypercoagulable states is important before renal transplantation because venous thrombosis is an important cause of graft failure. Risk factors for graft thrombosis include surgical technique, perfusion and reperfusion injury of the graft, young donor age (<6 yr), young recipient (<5 yr), cold ischemia time > 24 hr, arterial hypotension, prior history of peritoneal dialysis, and/or hypoperfusion of an adult allograft transplanted into a small child. Particularly in the young recipient, there must be an evaluation for thrombosis of iliac vessels and inferior vena cava, especially if there is a history of previous surgery or central line placement. Children who have large protein losses, such as from nephrotic syndrome and/or peritoneal dialysis, can be at an increased risk for thrombosis because of protein loss, such as protein S, protein C, and antithrombin III. Doppler ultrasound, computed tomographic angiography, and magnetic resonance angiography have all been used to evaluate vessels. In order to minimize the risk of contrast-induced nephropathy associated with computed tomography contrast, patients with advanced CKD or ESRD not yet on dialysis should receive intravenous hydration before and after the study and acidosis should be corrected before giving contrast medium. If the patient is on dialysis, hemodialysis can be performed after the study for clearance of contrast medium. Magnetic resonance angiography has been used less owing to the concern about exposure to gadolinium and nephrogenic systemic fibrosis.

Infections must be identified, prevented, and treated before transplantation. Infectious diseases screening includes obtaining a complete history of the following: current or previous infections, all vaccinations, any occupational risks among family members (e.g., healthcare worker), household or other contacts with treatment for tuberculosis, travel within the past 2 yr or significant time spent in another country, bacille Calmette-Guérin, animal and/or insect exposure, sexual activity, and consumption of high-risk foods such as unpasteurized products. Screening includes a tuberculosis skin test (purified protein derivative) or interferon gamma release assay, cytomegalovirus IgG, Epstein-Barr virus (EBV) antibody panel, varicella titer, measles antibody, hepatitis B serologies, hepatitis C antibody, HIV, and toxoplasmosis. Additional testing for patients who live in or have visited endemic areas might include *Coccidioides* immunodiffusion, serology for *Strongyloides,* and/or antibody for *Histoplasma* antibody. Sexually active patients should also be screened for syphilis, gonorrhea, and *Chlamydia.*

It is recommended that all immunizations be current prior to transplantation. All live vaccines (measles-mumps-rubella and varicella) should be given prior to transplantation, and antibody titers should be checked for a response because these vaccines should not be given to immunosuppressed patients. Measles-mumps-rubella may be given as early as 6 mo of age. Inhaled (live-attenuated virus) influenza vaccine should not be given to transplant patients, family members, or healthcare providers.

Psychiatric evaluation should be performed before transplantation to evaluate the ability of patients and families to cope with the substantial stressors that accompany caring for a child with a kidney transplant. This evaluation should include screening for depression, substance abuse, and adherence so that problems can be identified and managed before kidney transplantation. If nonadherence is identified or anticipated, interventions should be in place before transplantation.

The ABO blood type must be confirmed twice before a patient is listed for kidney transplantation. Donors and recipients are currently matched for HLA-A, HLA-B, and HLA-DR antigens. In general, better-matched organs have improved survival times following kidney transplantation. Matching at the DR locus appears to be especially advantageous, though in the modern era of immunosuppression, successful 6 antigen mismatched transplants are performed routinely. All patients must be screened for preformed anti-HLA antibodies prior to kidney transplantation. The most common, sensitive, and specific method uses flow cytometry and single HLA-antigen beads. In this manner, a patient's panel-reactive antibody (PRA) can be assessed and is reported as the percentage of the population against which a recipient has anti-HLA antibodies. Patients can become sensitized by a prior transplant, blood transfusions, and/or pregnancy. Highly sensitized patients (PRA > 80%) may undergo desensitization with plasmapheresis, anti-CD 20 antibody, and/or proteasome inhibitors to expand the donor pool from which they can safely receive an organ.

Immunosuppression

Most pediatric kidney transplant centers employ induction immunosuppression at the time of transplant followed by lifelong maintenance immunosuppression with a calcineurin inhibitor and an antiproliferative agent with or without steroids.

Induction Therapy

Induction therapy is used in nearly all pediatric renal transplants to prevent early acute rejection. The OPTN Scientific Registry of Transplant Recipients (OPTN/SRTR) 2015 Annual Report indicates that the percentage of patients receiving T-cell–depleting induction therapy (rabbit antithymocyte globulin) is rising; the therapy was used in > 60% of kidney transplant recipients in 2015.

Use of an IL-2 receptor antagonist (basiliximab) has been stable at between 30% and 40% for the last 5 yr, and the rates of no induction therapy have declined to about 10%.

T-Cell Antibodies

Antithymocyte globulin is comprised of rabbit- or horse-derived polyclonal antibodies against human T-lymphocyte antigens that results in a rapid depletion of T lymphocytes. The infusion is generally started in the operating room prior to reperfusion of the transplant kidney. Most centers use this for standard induction therapy, but some limit its use to induction of sensitized high-risk patients or patients who have concerns for delayed graft function and want to avoid high calcineurin inhibitor levels in the early postoperative period. The standard dosage is 1.5 mg/kg/dose for 4-5 doses, with daily monitoring of lymphocyte, neutrophil, and platelet counts. Some centers monitor $CD3^+$ subsets and hold the dose if the $CD3^+$ count is below 20 $cells/mm^3$.

The monoclonal antibody OKT3 was previously used but has been removed from the market.

Interleukin-2 Receptor Antibodies

Basiliximab is currently the only monoclonal anti-CD25 antibody on the market. Daclizumab was also previously used but has been taken off the market owing to manufacturing deficits. These chimeric (murine/human) anti-CD25 antibodies prevent T-cell proliferation but do not cause T-cell depletion. Basiliximab is given in two doses of 10 mg for patients < 35 kg and 20 mg for patients ≥ 35 kg. The first dose should be given within 2 hr prior to the transplant surgery and the second dose on day 4. Patients tend to tolerate IL-2 receptor antagonists well with few side effects.

Other Induction Therapies

Alemtuzumab (Campath-1H) is a monoclonal antibody against CD52 present on T and B cells, monocytes, and natural killer cells. Some centers have used this induction antibody in steroid and calcineurin inhibitor-sparing protocols, but pediatric data are limited, and its use has been limited.

Other induction therapies for highly sensitized patients include targeting B cells and/or removing neutralizing antibodies by using rituximab against the CD20 epitope on early-lineage and intermediate-lineage B cells, proteasome inhibitors, and plasmapheresis and/or high-dose intravenous immunoglobulin for removing donor-specific antibodies.

Maintenance Immunosuppression

Lifelong maintenance immunosuppression is required in nearly all patients following kidney transplantation. The most common regimens include a calcineurin inhibitor (predominantly tacrolimus vs. cyclosporine) and an antiproliferative agent (predominantly mycophenolate mofetil vs. azathioprine) with or without corticosteroids. The mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus are sometimes used in place of the calcineurin inhibitor or antiproliferative agent. The rationale for combination therapy in children is to provide effective immunosuppression while minimizing the toxicity of any single drug.

Calcineurin Inhibitors

Despite the search for immunosuppression regimens that minimize calcineurin inhibitor exposure, tacrolimus remains the centerpiece of maintenance immunosuppression for the vast majority of pediatric patients in North America. The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2014 report indicates that nearly 80% of all recipients are taking a calcineurin inhibitor and > 90% of these are taking tacrolimus. The increasing use of tacrolimus in place of cyclosporine can be attributed to studies demonstrating better efficacy (fewer rejections and less reliance on steroids) and less severe cosmetic side effects, such as hypertrichosis, gingival hyperplasia, and coarsening facial features. This is especially relevant for adolescents, who are especially focused on appearance and for whom unwanted cosmetic side effects can become a barrier to immunosuppression adherence. Tacrolimus also appears to cause less dyslipidemia, though other side effects such as **new-onset diabetes after transplant (NODAT),** tremor, seizure, alopecia, and sleep disturbance seem to be more common in patients treated with tacrolimus. Despite the nearly complete replacement of cyclosporine with tacrolimus, there are select cases when cyclosporine is the preferred agent (e.g., to treat posttransplant recurrence of FSGS or conversion therapy in patients who develop NODAT).

Unfortunately, both calcineurin inhibitors have a narrow therapeutic index and can cause acute and chronic kidney injury. Also, many foods and drugs interact with the calcineurin inhibitor metabolism, requiring frequent therapeutic drug monitoring. A usual starting dose of tacrolimus is 0.1 to 0.15 mg/kg twice a day on the day of the transplant, targeting trough levels above 10 ng/mL for the first month and then tapering down to trough levels of 4-8 ng/mL by 6 mo. African American patients often require doses nearly twice as high as Caucasian patients to achieve similar drug levels. Most long-term immunosuppressive regimens attempt to limit calcineurin inhibitor dosing as much as possible, and the search for calcineurin inhibitor–sparing drug regimens remains an area of intense research.

Antiproliferative Agents

Most immunosuppression regimens for children following kidney transplantation include an antiproliferative agent. Mycophenolate mofetil (MMF) is the morpholinoethylester prodrug of mycophenolic acid, an inhibitor of de novo purine synthesis, and is part of the initial maintenance immunosuppression regimen in at least two thirds of U.S. pediatric renal transplant recipients. The absence of nephrotoxicity, cardiovascular risk (hypertension, dyslipidemia), and hepatotoxicity make it an attractive option for immunosuppression, and the fact that it has greater efficacy than azathioprine has enabled the use of lower doses of corticosteroids and/or calcineurin inhibitors. Primary toxicities include diarrhea and upset stomach, as well as leucopenia and anemia, affecting up to 40% of patients. These side effects are often transient and can be treated with a temporary dosage reduction, but persistent dose reductions have been associated with an increased risk of rejection. MMF is also associated with a high risk for birth defects, so its use in adolescent females necessitates two forms of birth control and regular pregnancy screening. The usual dose of MMF is 600 mg/m^2 in patients treated with cyclosporine. MMF metabolism is slower in patients treated concomitantly with tacrolimus, allowing for lower doses (450 mg/m^2) to be used.

Azathioprine, an analog of 6-mercaptopurine, is an alternative to MMF that also inhibits *de novo* purine synthesis and contributes to cell cycle arrest. It was the first medication approved for immunosuppression in kidney transplantation, yet in the last two decades, its use has declined because of the advent of newer immunosuppressive medications with purported greater efficacy. It is inexpensive and, unlike MMF, it can be administered once daily, so it is an attractive alternative for patients who struggle to take twice-daily medications. Bone marrow suppression is the primary toxicity, but gastrointestinal side effects are less common than with MMF, with the exception of pancreatitis, which has rarely been reported. Unlike MMF, it is not associated with birth defects and is an important alternative in pregnant patients. Enteric-coated mycophenolic acid is another alternative to MMF that may decrease upper gastrointestinal side effects in some patients.

Mammalian Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors (sirolimus more commonly than everolimus) are used primarily as adjunctive immunosuppression in combination with MMF in order to avoid tacrolimus toxicity or with tacrolimus and MMF to spare steroids. However, their use has fallen to only 5–10% of pediatric kidney transplant recipients by 1 yr posttransplant, perhaps owing to recent evidence suggesting a high rate of donor-specific antibodies and antibody-mediated rejection in patients taking mTOR inhibitors. Other toxicities, including a high rate of aphthous ulcers, dyslipidemia, poor wound healing, proteinuria, and diarrhea, have limited their use.

Corticosteroids

Corticosteroids remain integral to most immunosuppressive protocols despite their multifaceted toxicities. According to the 2015 OPTN/SRTR report, 60% of patients are treated with steroids at hospital discharge and at 1 yr posttransplant. The adverse effects of steroids are especially pronounced in children, for whom retarded skeletal growth, hypertension, obesity, diabetes mellitus, hyperlipidemia, osteopenia, and aseptic necrosis of bone (particularly the femoral heads) can have dire long-term consequences. Cosmetic side effects, such as cushingoid facies and acne, also become barriers to adolescents taking their medication. For these reasons, steroid-based regimens in children seek to minimize steroid exposure by starting with high-dose steroids as induction therapy and tapering down over several months to a lowest dose of 5-10 mg or 0.1 mg/kg daily. Other protocols call for a more rapid steroid taper over 1 wk to several months before stopping them altogether.

Several well-designed randomized controlled trials in children and adults have demonstrated that complete steroid avoidance can be safely achieved in patients with a low immunologic risk by using induction therapy with dual-maintenance immunosuppression comprised of tacrolimus and MMF. In general, steroid avoidance is associated with higher rates of rejection but also carries significant benefits for growth, hypertension, and dyslipidemia with no decrease in long-term allograft survival. Importantly, this approach appears to be safe and without increases in the generation of donor-specific antibody or histologic injury. Despite this evidence, data from the OPTN network suggest that steroid use is largely dependent on the center where the transplant is performed rather than the characteristics of the patient.

Other Agents

Belatacept is a fusion protein composed of the Fc fragment of a human IgG_1 linked to the extracellular domain of CTLA-4 (a molecule crucial for T-cell costimulation), which selectively blocks the process of T-cell activation. Belatacept is attractive for maintenance immunosuppression because it is a quick monthly infusion rather than a daily oral medication and it does not have many of the untoward side effects associated with calcineurin inhibitors, including and especially nephrotoxicity. Adult studies of belatacept have demonstrated similar rejection rates but significantly improved kidney function up to 10 yr following kidney transplantation compared with cyclosporine. Unfortunately, there is an unacceptably high rate of posttransplant lymphoproliferative disorder (PTLD) in EBV-naïve patients, which are most of the children receiving a kidney transplant. Studies in pediatrics are underway, the results of which are much anticipated.

Fluid Management in Infants and Small Children Following Kidney Transplantation

Maintenance of adequate blood flow to an adult-sized kidney in an infant or small child is crucial to avoid acute tubular necrosis (ATN) and graft loss from vascular thrombosis. The recipient aortic blood flow early after transplantation of an adult-size kidney more than doubles from the pretransplantation aortic blood flow. The maximum blood flow that can be obtained in an adult-size kidney transplanted into a small child is approximately 65% of what was in the donor. Low blood flow states, such as those with hypovolemia or hypotension, increase the risk for ATN, graft thrombosis, and graft nonfunction. Thus, in the postoperative period, patients are maintained on high fluid volumes.

Close attention is paid to the blood pressure and hydration status in the operating room in an attempt to reduce the incidence of delayed graft function. Typically, a central venous catheter is inserted to monitor the central venous pressure throughout the operation. A central venous pressure of 12-15 cm H_2O should be achieved before removing the vascular clamps; a higher central venous pressure may be desirable in the case of a small infant receiving an adult-size kidney. Dopamine may be started in the operating room and continued for 24-48 hr postoperatively to maintain a mean arterial blood pressure > 60 mm Hg. A blood transfusion with packed red blood cells may be required in very small recipients because the hemoglobin can drop as a result of sequestration of approximately 150-250 mL of blood in the transplanted kidney. Because an adult kidney transplanted into a small child can produce enormous amounts of urine, a fluid strategy that provides a constant rate for insensible losses (D10W at a rate of 400 mL/m^2 /day) and urine replacements helps to ensure adequate hydration of the adult kidney. Some transplant centers continue to provide infants with aggressive fluid management by nasogastric or gastrostomy tube feedings of at least 2500 mL/m^2 /day for up to 6 mo following transplant if the child is unable to take in sufficient volume by mouth.

Rejection of Kidney Transplant

Hyperacute rejection, caused by preformed antibodies against the donor HLA, ABO, or other antigens, occurs immediately on reperfusion of the allograft. The practice of prospective cross matching using complement-dependent cytotoxicity has virtually eliminated hyperacute rejection.

Acute cellular rejection (ACR) must be identified and treated promptly, although this may not be straightforward in the very young transplant recipient. Because most small children receive adult-size kidneys with a large renal reserve in comparison with their body mass, significant allograft dysfunction may be present with little or no increase in serum creatinine. Therefore, even subtle findings such as hypertension with low-grade fever or new proteinuria can indicate acute rejection and must be investigated. Late diagnosis and treatment of rejection are associated with a higher incidence of resistant rejections and graft loss. Most acute cellular rejections can be treated if detected early by using a short course (3-5 days) of high-dose intravenous steroids (10-30 mg/kg) followed by an oral steroid taper over the next several weeks and either increased maintenance immunosuppression or improved adherence, whichever is most appropriate. Steroid-resistant or high-grade rejection can be treated with thymoglobulin (1.5 mg/kg/day) for 7-14 days, high-dose tacrolimus (trough levels > 20 ng/dL for 1-2 wk), or local allograft irradiation. Following treatment for rejection, it is important to consider 3-12 mo of prophylaxis with trimethoprim/sulfamethoxazole to prevent *Pneumocystis jirovecii* pneumonia (PJP pneumonia), valganciclovir/valaciclovir to prevent cytomegalovirus/herpes reactivation, and nystatin to prevent oral candidiasis.

Antibody-mediated rejection (ABMR) consisting of anti-HLA donor-specific antibodies has become increasingly recognized as an important cause of kidney function decline and allograft loss. It can present acutely in the few weeks following transplantation in highly sensitized patients, or may develop chronically due to inadequate immunosuppression or poor adherence. Unlike acute cellular rejection, antibody-mediated rejection is much more difficult to treat and may require plasmapheresis, IVIG, anti-CD20 antibody infusions, and/or proteasome inhibitors. Studies have demonstrated that treatment is most likely to be successful if initiated within a few months of identifying new donor-specific antibodies.

Chronic rejection is the leading cause of graft loss and primarily results from immune and nonimmune injuries such as hypertension and diabetes. Children often have a gradual decline in their renal function and often have fixed proteinuria and hypertension. Despite initial excitement about the potential of MMF and sirolimus mitigating chronic graft injury, this has not translated readily into observable clinical benefits. Chronic ABMR has been implicated in this injury, as have non-HLA antibodies, which are areas of active investigation.

Kidney Biopsy

Kidney biopsy is the gold standard for the diagnosis of ACR or ABMR. Despite attempts to develop noninvasive biomarker panels, none has proven sensitive enough to rule out rejection. Many centers perform protocol biopsies at specific time points following transplantation to detect subclinical rejection; it has been reported in < 10% of biopsies.

Graft Survival of Kidneys

Survival rates for live-donor kidney allografts are superior to those for deceased-donor allografts. Living-donor kidneys generally have fewer HLA mismatches and less cold ischemia time and require less immunosuppression than deceased-donor kidneys. Furthermore, children must wait a median of 8-9 mo on the deceased-donor waitlist prior to receiving an organ. The OPTN/SRTR 2015 annual report showed that the death-censored 5-year allograft survival rate has improved from approximately 65% for deceased-donor transplants performed in the early 1990s to more than 80% for those performed in 2011, whereas the death-censored 5-year allograft survival rate for living-donor transplants has improved from approximately 73% to 90% over the same time period. For these reasons and because it expands the donor pool, living donation should be advocated at every opportunity.

Children < 10 yr of age have the best long-term graft and patient survival rates of all age-groups, and adolescents and young adults have the worst. Among patients with at least 1 yr of graft function, graft failure rates are stable at around 1.4 per 100 person-years until 10 yr of age, when rates increase, peaking at a maximum of 6.3 per 100 person-years at age 19 yr, regardless of the age at transplantation. A variety of factors likely account for such poor outcomes in adolescents and young adults, including the patient's changing physiology, a transition from pediatric to adult care, and a greater number of barriers to taking immunosuppressives. According to the NAPRTCS 2014 annual report, risk factors other than age for graft failure include African American race, previous transplant history, female gender, and dialysis before transplant. The three most common known causes of graft failure are chronic rejection (35.8%), acute rejection (13%), and vascular thrombosis (9.6%). Approximately 7% of patients had graft failure as a result of primary disease recurrence.

Complications of Immunosuppression

Since the mid-1990s, the incidence of acute rejection has decreased but the incidence of infection after transplantation has increased.

Pneumonia and urinary tract infection are the most common posttransplant bacterial infections. Urinary tract infections can progress rapidly to urosepsis and may be confused with episodes of acute rejection. Trimethoprim-sulfamethoxazole is used for urinary tract infection antibiotic prophylaxis as well as *Pneumocystis jirovecii* pneumonia prophylaxis for 3-6 mo after transplant (see Chapter 271).

The herpesviruses (cytomegalovirus, herpesvirus, varicella-zoster virus, and EBV) pose a special problem in view of their common occurrences in childhood (see Chapters 279 to 282). Many young children have not yet been exposed to these viruses, and because they lack protective immunity, their predisposition to serious primary infection is high. The incidence of cytomegalovirus seropositivity is approximately 30% in children > 5 yr of age and rises to approximately 60% in teenagers. Thus, the younger child is at a greater potential risk for serious infection when a cytomegalovirus-positive donor kidney is transplanted. About half of children are seronegative for EBV; most of them will become infected shortly after transplant. Most EBV infections are clinically silent but put transplant recipients at risk for posttransplant lymphoproliferative disease (PTLD) in the presence of immunosuppression. The incidence of these infections is higher in children who receive antibody induction therapy and after treatment of acute rejection. Antiviral prophylaxis with ganciclovir or valganciclovir for 3-12 mo after transplantation, especially in the higher-risk groups (recipient-negative, donor-positive), has been effective in reducing the incidence of clinical cytomegalovirus disease. Serial surveillance for these viruses by quantitative polymerase chain reaction for the viral load in the peripheral blood has also allowed educated minimization of immunosuppression with a resultant reduction in the viral burden. It is important to monitor for **PTLD** with routine examinations for lymphadenopathy, hepatosplenomegaly, and EBV screening.

Polyomavirus nephropathy is an important cause of allograft dysfunction; almost 30% of children have BK viruria (see Chapter 301), although allograft dysfunction occurs only in a small subset of patients (~5%). Early protocols focusing on screening for BK virus in the urine have proven ineffective at distinguishing patients who will develop BK nephropathy; rather, plasma BK monitoring has become the standard of care. Ultimately, a renal biopsy, with identification of BK virus by immunoperoxidase staining, is required to make the diagnosis of BK virus nephropathy with certainty. Reducing immunosuppression when plasma BK PCR levels start to rise is the main form of therapy. Cidofovir, leflunomide, and IVIG have all been used as adjunctive therapies.

Oral candidiasis is another important infection following kidney transplantation and can be prevented with oral nystatin four times daily or fluconazole once daily for the first 3 mo.

Hypertension, dyslipidemia, obesity, and posttransplant diabetes mellitus are other complications of immunosuppression and kidney transplantation that have been underrecognized and undertreated. Cardiovascular disease is the primary cause of premature death in young adults who had a kidney transplant in childhood, and uncontrolled blood pressure leads to premature allograft failure. Up to 80% of children have hypertension and up to 60% are uncontrolled despite multiple available therapies. The most recent guidelines suggest treating blood pressure to below the 90th percentile for age, gender, and height and below 130/80 mm Hg. Angiotensin-converting enzyme (ACE) inhibitors are the preferred first-line agents in patients with proteinuria; otherwise, either calcium channel blockers or ACE inhibitors can be used with other agents added as needed to achieve blood pressure control.

Although growth improves after transplantation, chronic steroid use does not allow a child to reach the full potential height. The use of recombinant human growth hormone in pediatric renal transplant recipients significantly improves the growth velocity and standard deviation score (SDS). Steroid minimization and withdrawal protocols have demonstrated growth benefits, and the steroid-avoidance data in children show significant catch-up growth at 5 yr after transplantation. It is thus likely that with a well-functioning kidney and no maintenance steroids, children might now be able to realize their full height potential.

Malignancy is an important problem following kidney transplantation for children. Lifelong immunosuppression confers at least a two-fold lifetime risk of developing cancer for solid-organ transplant recipients compared with the general population. The most common cancer to develop within 10 yr following kidney transplantation in children is **PTLD.** It occurs in 1–5% of pediatric kidney transplant recipients and is the most likely cancer to be encountered in childhood. Over the long term, skin cancers (basal cell carcinoma, cutaneous squamous cell carcinoma) are the most common malignancies, with an incidence of close to 15% by 15 yr posttransplant and increasing from there. Carcinomas other than skin carcinomas also arise at a rate far higher than in the general population. The prognosis is generally good for most of these malignancies when they are diagnosed early and treated appropriately. Any kidney transplant recipient must be assessed regularly for signs of malignancy and practice preventative measures such as using appropriate sunscreen products.

Developing good adherence behaviors with immunosuppressive medications is one of the most important challenges facing children and adolescents following kidney transplantation. Up to 43% of adolescents display some decreased adherence to their immunosuppressive regimen, which is thought to contribute to decreased allograft survival rates compared with other age-groups. Research demonstrates that a child's normal development, which includes establishing more independence, spending more time away from home, feeling invincible, and being vulnerable to cosmetic medication side effects, increases the barriers to taking immunosuppression medications. The literature about other chronic conditions suggests that systems-based approaches, in which clinicians partner with patients to identify and address adherence barriers, are most likely to improve adherence over the long term.

Long-Term Outcome of Kidney Transplantation

With advances in transplant care and treatment modalities and with diligent attention to the pediatric patient's psychosocial, educational, vocational, and developmental rehabilitation, the social and emotional functioning of the child and the child's family appears to return to the same level as before the illness within 1 yr of successful transplantation. Renal transplantation leads to improvement in linear growth in children. School function tests improve after renal transplantation. Most patients can reenter school and social activities after a short recovery time of 6-12 wk following surgery. A 3-yr follow-up shows that nearly 90% of children are in their appropriate school or job placement positions. Surveys of 10-yr survivors of pediatric kidney transplants report that most patients consider their health to be good, and they engage in appropriate social, educational, and sexual activities while experiencing a very good to excellent quality of life.

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PART XXIII

Urologic Disorders in Infants and Children

OUTLINE

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CHAPTER 552

Congenital Anomalies and Dysgenesis of the Kidneys

Jack S. Elder

Embryonic and Fetal Development

The kidney is derived from interaction between the ureteral bud and the metanephric blastema. During the 5th wk of gestation, the ureteral bud arises from the mesonephric (wolffian) duct and penetrates the metanephric blastema, which is an area of undifferentiated mesenchyme on the nephrogenic ridge. The ureteral bud undergoes a series of approximately 15 generations of divisions and by wk 20 of gestation forms the entire collecting system: the ureter, renal pelvis, calyces, papillary ducts, and collecting tubules. Signals from the mesenchymal cells induce ureteric bud formation from the wolffian duct as well as ureteric bud branching. Reciprocal signals from the ureteric bud and, later, from its branching tips induce mesenchymal cells to condense, proliferate, and convert into epithelial cells. Under the inductive influence of the ureteral bud, nephron differentiation begins during the 7th wk of gestation. By the 20th wk of gestation, when the collecting system is developed, approximately 30% of the nephrons are present. Nephrogenesis continues at a nearly exponential rate and is complete by the 36th wk of gestation. During nephrogenesis, the kidneys ascend to a lumbar site just below the adrenal glands. At least 16 signaling agents have been identified that regulate renal development. Defects in any of the signaling activities could cause a kidney not to form **(renal agenesis),** or to differentiate abnormally **(renal dysgenesis).** Dysgenesis of the kidney includes **aplasia, dysplasia, hypoplasia,** and certain forms of **renal cystic disease.**

The fetal kidneys play a minor role in the maintenance of fetal salt and water homeostasis. The rate of urine production increases throughout gestation; at term, volumes have been reported to be 50 mL/hr. The glomerular filtration rate is 25 mL/min/1.73 m^2 at term and triples by 3 mo postterm. The increase in the glomerular filtration rate is caused by a reduction in intrarenal vascular resistance and redistribution of intrarenal blood flow to the cortex, where more nephrons are located.

Renal Agenesis

Renal agenesis, or absent kidney development, can occur secondary to a defect of the wolffian duct, ureteric bud, or metanephric blastema. Unilateral renal agenesis has an incidence of 1 in 450-1,000 births. Unilateral renal agenesis often is discovered during the course of an evaluation for other congenital anomalies (VACTERL [vertebral defects, imperforate anus, congenital heart disease, tracheoesophageal fistula, renal and limb defects] syndrome; e.g., see Chapter 371). Its incidence is increased in newborns with a single umbilical artery. In true agenesis, the ureter and the ipsilateral bladder hemitrigone are absent. The contralateral kidney undergoes compensatory hypertrophy, to some degree prenatally but primarily after birth. Approximately 15% of these children have contralateral vesicoureteral reflux, and most males have an ipsilateral absent vas deferens because the wolffian duct is absent. Because the wolffian and müllerian ducts are contiguous, müllerian abnormalities in girls also are common. The **Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome** (1 in 4,000 to 1 in 10,000 female births) is a group of associated findings that may include vaginal aplasia, uterine maldevelopment, and normal ovaries. Two types are described—type I and type II. In type I, only müllerian aplasia occurs, whereas in type II, there are associated anomalies, most commonly unilateral renal agenesis or a horseshoe kidney, and skeletal anomalies are present in 10% (see Chapter 569). **Zinner syndrome** is considered the male counterpart of MRKH syndrome (Fig. 552.1). In this condition, males with unilateral renal agenesis (or a regressed multicystic dysplastic kidney) have an ipsilateral seminal vesicle cyst, and a possible epididymal cyst and dilated distal ureteral segment. These patients typically present in adolescence.

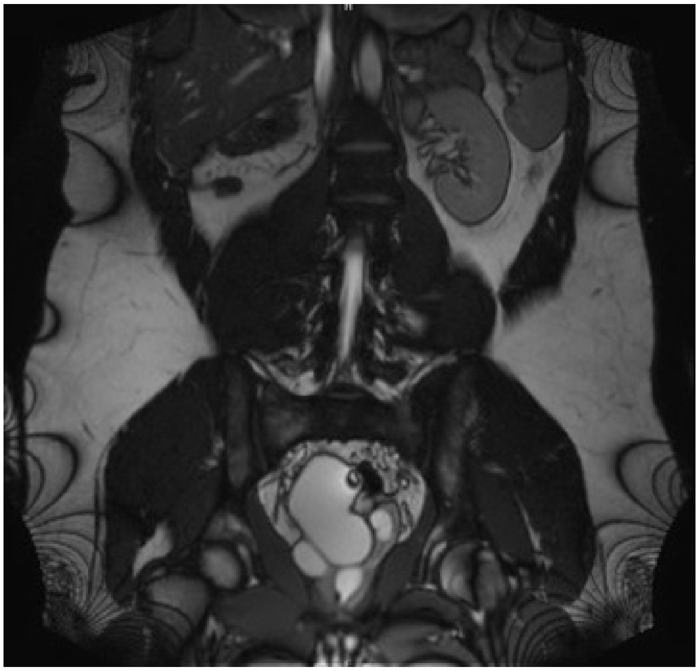

FIG. 552.1 Zinner syndrome; 17 yr old male with regressed right multicystic dysplastic kidney and dilated ectopic distal ureter draining into seminal vesicle cyst.

Renal agenesis is distinguished from aplasia, in which a nubbin of nonfunctioning tissue is seen capping a normal or abnormal ureter. This distinction may be difficult but usually is clinically insignificant. Unilateral renal agenesis is diagnosed in some patients based on the finding of an absent kidney on ultrasonography or renal scintigraphy (renal scan). Some of these patients were born with a hypoplastic kidney or a multicystic dysplastic kidney that underwent complete cyst regression. Although the specific diagnosis is not critical, if the finding of an absent kidney is based on an ultrasonogram, a functional imaging study such as a renal scan should be considered because some of these patients have an ectopic kidney in the pelvis. If there is a normal contralateral kidney, long-term renal function usually remains normal.

Bilateral renal agenesis is incompatible with extrauterine life and produces the **Potter syndrome.** Death occurs shortly after birth from pulmonary hypoplasia. The newborn has a characteristic facial appearance, termed *Potter facies* (Fig. 552.2). The eyes are widely separated with epicanthic folds, the ears are low set, the nose is broad and compressed flat, the chin is receding, and there are limb anomalies. Bilateral renal agenesis should be suspected when maternal ultrasonography demonstrates **oligohydramnios,** nonvisualization of the bladder, and absent kidneys. The incidence of this disorder is 1 in 3,000 births, with a male predominance, and represents 20% of newborns with the Potter phenotype. Other common causes of neonatal renal failure associated with the Potter phenotype include cystic renal dysplasia and obstructive uropathy. Less-common causes are autosomal recessive polycystic kidney disease (infantile), renal hypoplasia, and medullary dysplasia. Neonates with bilateral renal agenesis die of pulmonary insufficiency from pulmonary hypoplasia rather than renal failure (see Chapter 423).

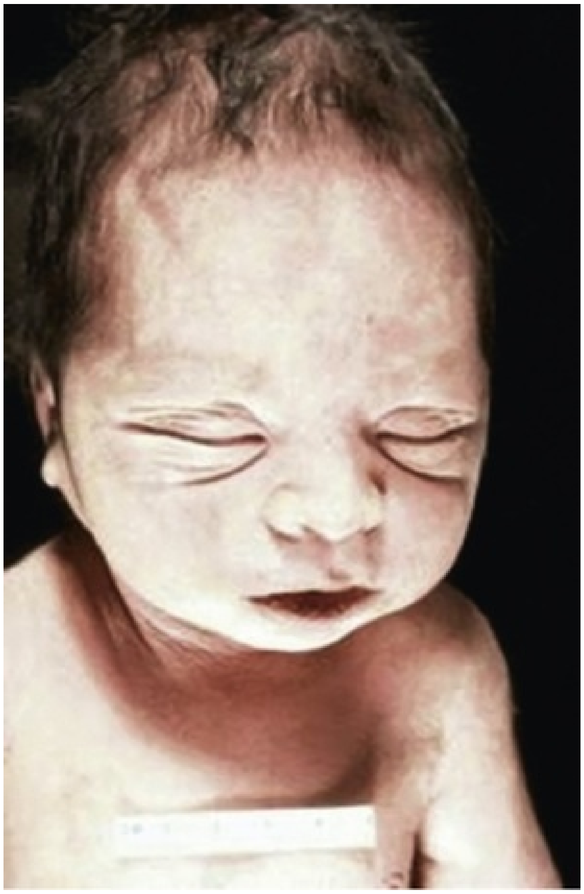

FIG. 552.2 Stillborn infant with renal agenesis exhibiting characteristic Potter facies.

The term **familial renal adysplasia** describes families in which renal agenesis, renal dysplasia, multicystic kidney (dysplasia), or a combination, occurs in a single family. This disorder has an autosomal dominant inheritance pattern with a penetrance of 50–90% and variable expression. Because of this association, some clinicians advise screening first-degree relatives of persons who have renal agenesis or dysplasia, but this is not standard practice.

Whether persons with a solitary kidney should avoid contact sports such as football and karate is unresolved. The arguments favoring participation are that there are other solitary organs (spleen, liver, and brain) that do not preclude participation in contact sports, and there have been only a few reports of persons losing a kidney from sports injuries. The arguments against such participation are that the contralateral normal kidney is hypertrophic and not as well protected by the ribs, and a serious renal injury could have serious lifelong consequences. The American Academy of Pediatrics recommends an “individual assessment for contact, collision, and limited-contact sports.”

Renal Dysgenesis: Dysplasia, Hypoplasia, and Cystic Anomalies

Renal dysgenesis refers to maldevelopment of the kidney that affects its size, shape, or structure. The three principal types of dysgenesis are dysplastic, hypoplastic, and cystic. Although dysplasia always is accompanied by a decreased number of nephrons (hypoplasia), the converse is not true: Hypoplasia can occur in isolation. When both conditions are present, the term **hypodysplasia** is preferred. The term **dysplasia** is technically a histologic diagnosis and refers to focal, diffuse, or segmentally arranged primitive structures, specifically primitive ductal structures, resulting from abnormal metanephric differentiation. Nonrenal elements, such as cartilage, also may be present. The condition can affect all or only part of the kidney. If cysts are present, the condition is termed **cystic dysplasia.** If the entire kidney is dysplastic with a preponderance of cysts, the kidney is referred to as a **multicystic dysplastic kidney** (MCDK) (Fig. 552.3).

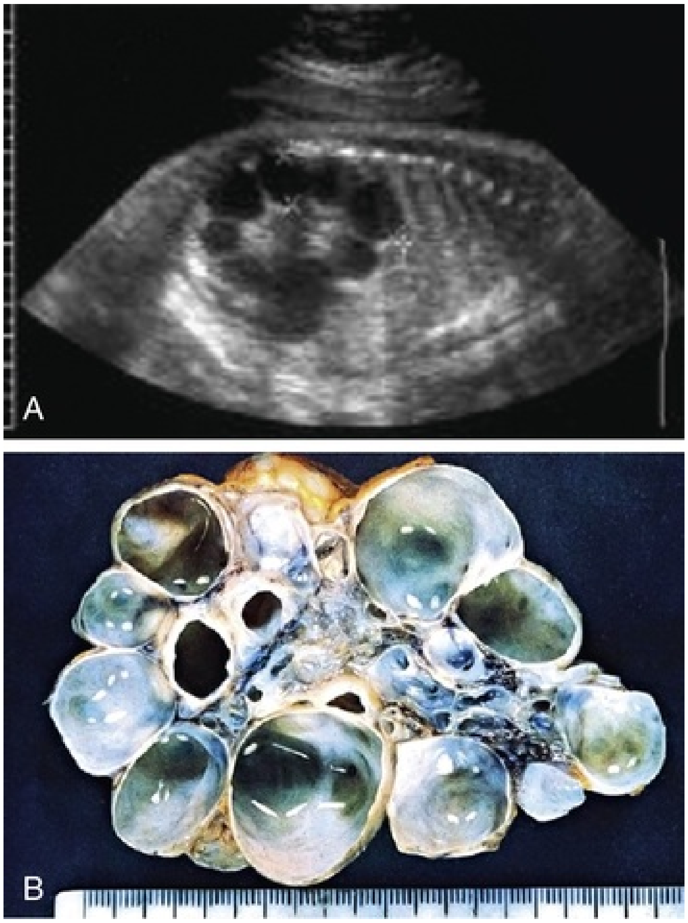

FIG. 552.3 **A,** Prenatal sonogram demonstrating multicystic dysplastic kidney. **B,** Surgical specimen.

The pathogenesis of dysplasia is multifactorial. The “bud” theory proposes that if the ureteral bud arises in an abnormal location, such as an ectopic ureter, there is abnormal penetration and induction of the metanephric blastema, which causes abnormal kidney differentiation, resulting in dysplasia. Renal dysplasia also can occur with severe obstructive uropathy early in gestation, as with the most severe cases of posterior urethral valves or in an MCDK, in which a portion of the ureter is absent or atretic.

MCDK is a congenital condition in which the kidney is replaced by cysts and does not function; it can result from ureteral atresia. Kidney size is highly variable. The incidence is approximately 1 in 2,000. Some clinicians incorrectly use the terms *multicystic kidney* and *polycystic kidney* interchangeably. However, polycystic kidney disease is an inherited disorder that may be autosomal recessive or autosomal dominant and affects both kidneys (see Chapter 541). MCDK usually is unilateral and generally is not inherited. Bilateral MCDKs are incompatible with life.

MCDK is the most common cause of an abdominal mass in the newborn, but the vast majority are nonpalpable at birth. In most cases, it is discovered incidentally during prenatal sonography. In some patients, the cysts are identified prenatally, but the cysts regress in utero and no kidney is identified on imaging at birth. Contralateral hydronephrosis is present in 5–10% of patients. Sonography shows the characteristic appearance of a kidney replaced by multiple cysts of varying sizes that do not communicate, and no identifiable parenchyma is present. In the past, most cases were confirmed with a renal scan, which should demonstrate nonfunction. However, presently the diagnosis of MCDK is usually straightforward based on the renal ultrasound, and a scan generally is unnecessary. In some patients, usually boys, a small nonobstructing ureterocele is present in the bladder (see Chapter 555). Although 15% have contralateral vesicoureteral reflux, it is usually low grade, and obtaining a voiding cystourethrogram also is unnecessary, unless there is significant contralateral hydronephrosis or the child develops an upper urinary tract infection. Management is controversial. Complete cyst regression occurs in nearly half of MCDKs by age 7 yr. The risk of associated hypertension is 0.2–1.2%, and the risk of Wilms tumor arising from an MCDK is approximately 1 in 1,200. Because neoplasms arise from the stromal rather than the cystic component, even if the cysts regress completely, the likelihood that the kidney could develop a neoplasm is not altered.

Because of the occult nature of these potential problems, some clinicians advise annual follow-up with sonography and blood pressure measurement. The most important aspect of follow-up is being certain that the solitary kidney is functioning normally. If there is an abdominal mass, the cysts enlarge, the stromal core increases in size, or hypertension develops, nephrectomy is recommended. In lieu of follow-up screening, laparoscopic nephrectomy may be performed.

Renal hypoplasia refers to a small nondysplastic kidney that has fewer than the normal number of calyces and nephrons. The term encompasses a group of conditions with an abnormally small kidney and should be distinguished from aplasia, in which the kidney is rudimentary. If the condition is unilateral, the diagnosis usually is made incidentally during evaluation for another urinary tract problem or hypertension. Bilateral hypoplasia usually manifests with signs and symptoms of chronic renal failure and is a leading cause of end-stage renal disease during the first decade of life. A history of polyuria and polydipsia is common. Urinalysis results may be normal. In a rare form of bilateral hypoplasia called **oligomeganephronia,** the number of nephrons is markedly reduced and those present are markedly hypertrophied.

The **Ask-Upmark kidney,** also termed **segmental hypoplasia,** refers to small kidneys, usually weighing not more than 35 g, with one or more deep grooves on the lateral convexity, underneath which the parenchyma consists of tubules resembling those in the thyroid gland. It is unclear whether the lesion is congenital or acquired. Most patients are 10 yr or older at diagnosis and have severe hypertension. Nephrectomy usually controls the hypertension.

Renal Cysts in Children

Although uncommon, there are many renal cystic disorders in children (Table 552.1). The most common is the **simple renal cyst** . The mean incidence is 0.22%; they are usually discovered incidentally during urinary tract imaging. Most are small and asymptomatic and do not require treatment, although follow-up imaging is recommended. If there are septations, irregular margins, calcifications, or a cluster of cysts, further evaluation may be indicated, however. The **Bosniak classification** of simple and complex renal cysts places various cystic lesions into four risk categories, and helps guide a decision on whether removal of a lesion is necessary. A **calyceal diverticulum** is an outpouching of the collecting system into the corticomedullary region of the kidney, and it usually arises from the fornix of a calyx, typically in the upper or lower pole. Typically, the infundibulum between the diverticulum and renal pelvis is narrow. Occasionally, calculi form within the lesion or it causes symptoms of flank pain, necessitating removal of the diverticulum.

Table 552.1

Cystic Diseases of the Kidney

INHERITABLE
Autosomal recessive (infantile) polycystic kidney disease
Autosomal dominant (adult) polycystic kidney disease
Juvenile nephronophthisis and medullary cystic disease complex
Juvenile nephronophthisis (autosomal recessive)
Medullary cystic disease (autosomal dominant)
Congenital nephrosis (familial nephrotic syndrome) (autosomal recessive)
Familial hypoplastic glomerulocystic disease (autosomal dominant)
Multiple malformation syndromes with renal cysts (e.g., tuberous sclerosis, von Hippel-Lindau disease)

NONHERITABLE

- Multicystic kidney (multicystic dysplastic kidney)
- Benign multilocular cyst (cystic nephroma)
- Simple cysts
- Medullary sponge kidney
- Sporadic glomerulocystic kidney disease
- Acquired renal cystic disease
- Calyceal diverticulum (pyelogenic cyst)

From Glassberg KI, Stephens FD, Lebowitz RL, et al: Renal dysgenesis and cystic disease of the kidney: a Report of the Committee on Terminology, Nomenclature and Classification, Section on Urology, American Academy of Pediatrics, J Urol 138[4]:1085-1092, 1987, Tab 2.

A **multilocular cyst (multilocular cystic nephroma)** is a lesion in the kidney that falls in a spectrum of diseases, along with multilocular cyst with partially differentiated Wilms tumor, multilocular cyst with nodules of Wilms tumor, or cystic Wilms tumor. The multilocular cyst is considered benign and is unrelated to the multicystic dysplastic kidney. More than 95% occur in children < 4 yr, and most are discovered during evaluation for an abdominal or flank mass. The lesion should be removed.

Anomalies in Shape and Position

During renal development, the kidneys normally ascend from the pelvis into their normal position behind the ribs. The normal process of ascent and rotation of the kidney may be incomplete, resulting in renal ectopia or nonrotation. The ectopic kidney may be in a pelvic, iliac, thoracic, or contralateral position. If the ectopia is bilateral, in 90% of persons the two kidneys fuse. The incidence of renal ectopia is approximately 1 in 900 (Fig. 552.4).

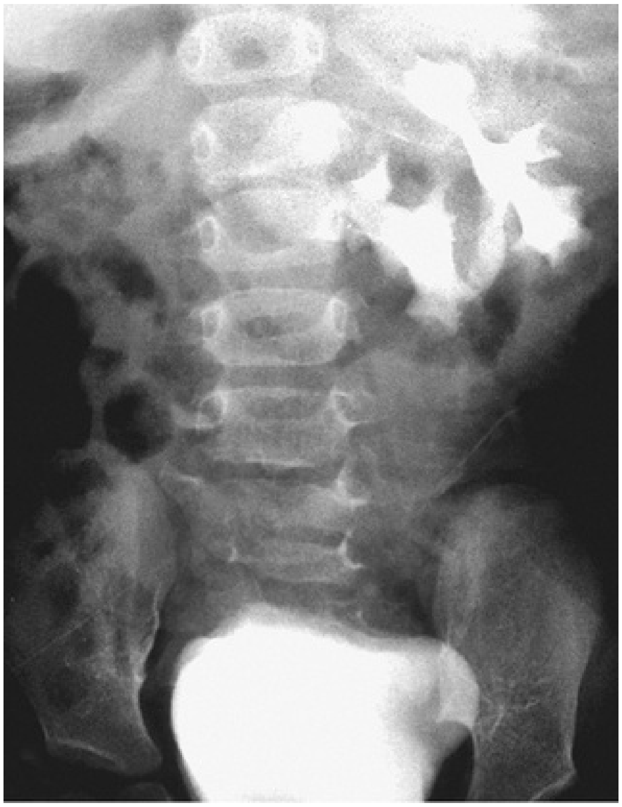

FIG. 552.4 Crossed renal ectopia. Intravenous urography shows both renal collecting systems to the left of the spine. Segmentation anomalies of the sacrum, which are subtle in this child, are one of the skeletal anomalies associated with renal ectopia. (From Slovis T, editor: Caffey's pediatric diagnostic imaging, ed 11, vol 2, Philadelphia, 2008, Mosby, Fig. 145-23A, p. 2244.)

Renal fusion anomalies are more common. The lower poles of the kidneys can fuse in the midline, resulting in a horseshoe kidney (Fig. 552.5); the fused portion is termed the *isthmus* and may be thick functioning parenchyma or a thin fibrous strand. Horseshoe kidneys occur in 1 in 400-500 births and are seen in 7% of patients with Turner syndrome. Horseshoe kidney is one of the many renal anomalies that occur in 30% of patients with Turner syndrome (see Chapter 604). Wilms tumors are four times more common in children with horseshoe kidneys than in the general population. Stone disease and hydronephrosis secondary to ureteropelvic junction obstruction are other potential late complications. The incidence of MCDK affecting one of the two sides of a horseshoe kidney also is increased. With crossed fused ectopia, one kidney crosses over to the other side and the parenchyma of the two kidneys is fused. Renal function usually is normal. Most commonly, the left kidney crosses over and fuses with the lower pole of the right kidney. The insertion of the ureter to the bladder does not change, and the adrenal glands remain in their normal positions. The clinical significance of this anomaly is that if renal surgery is necessary, the blood supply is variable and can make partial nephrectomy more difficult.

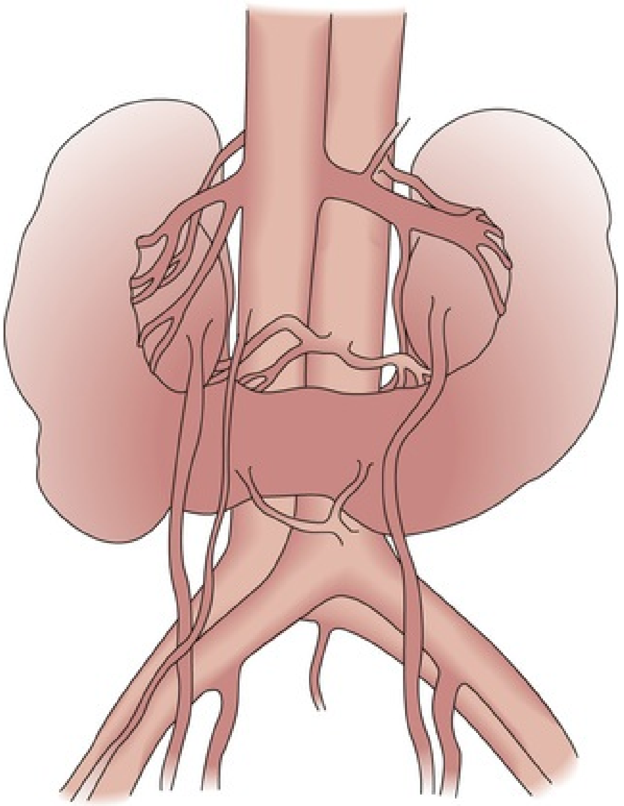

FIG. 552.5 Horseshoe kidney.

Associated Physical Findings

Upper urinary tract anomalies are more common in children with certain physical findings. The incidence of renal anomalies is increased if there is a single umbilical artery and an abnormality of another organ system (congenital heart disease). External ear anomalies (particularly if the child has multiple congenital anomalies), imperforate anus, and scoliosis are associated with renal anomalies. Infants with these physical findings should undergo a renal sonogram.

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CHAPTER 553

Urinary Tract Infections

Karen E. Jerardi, Elizabeth C. Jackson

Prevalence and Etiology

Urinary tract infections (UTIs) commonly occur in children of all ages, though the prevalence varies with age. UTIs are most common in children under age 1 yr; the prevalence of *afebrile* symptomatic UTIs in children over age 1 yr is ~8%; the prevalence in *febrile* infants is 7%. During the first yr of life, the male:female ratio is 2.8 : 5.4. Beyond 1-2 yr, there is a female preponderance, with a male:female ratio of 1 : 10. In males, most UTIs occur during the first year of life; UTIs are much more common in uncircumcised males, especially in the first yr of life, where the rate is 20% in febrile uncircumcised males under age 1 yr. In females, the first UTI usually occurs by the age of 5 yr, with peaks during infancy, toilet training, and onset of sexual activity.

UTIs are caused primarily by colonic bacteria. *Escherichia coli* (see Chapter 227) causes 54–67% of all UTIs, followed by *Klebsiella* spp. and *Proteus* spp., *Enterococcus*, and *Pseudomonas* (see Chapter 129). Other bacteria known to cause UTIs include *Staphylococcus saprophyticus*, group B streptococcus, and, less commonly, *Staphylococcus aureus*, *Candida* spp., and *Salmonella* spp.

UTIs have been considered a risk factor for the development of renal insufficiency or end-stage renal disease in children, although some have questioned the importance of UTI as an isolated risk factor, because only 2% of children with renal insufficiency report a history of UTI. Furthermore, many children receive antibiotics for fever without a specific diagnosis (e.g., treating a questionable otitis media), resulting in a partially treated UTI. Some children with end-stage renal disease diagnosed as reflux nephropathy actually have dysplasia associated with reflux rather than scarring caused by infection and reflux.

Clinical Manifestations and Classification

The two basic forms of UTIs (defined as symptoms and a positive culture) are **pyelonephritis** and **cystitis.** Focal pyelonephritis (lobar nephronia) and renal abscesses are less common.

Pyelonephritis

Pyelonephritis is characterized by any or all of the following: abdominal, back, or flank pain; fever; malaise; nausea; vomiting; and, occasionally, diarrhea. *Fever may be the only manifestation; particular consideration should occur for a temperature > 39°C without another source lasting more than 24 hr for males and more than 48 hr for females* . Newborns can show nonspecific symptoms, such as poor feeding, irritability, jaundice, and weight loss. Pyelonephritis is the most common serious bacterial infection in infants younger than 24 mo of age who have fever without an obvious focus (see Chapters 202 and 203). Involvement of the renal parenchyma is termed *acute pyelonephritis* (Figs. 553.1 and 553.2), whereas if there is no parenchymal involvement, the condition may be termed *pyelitis.* Acute pyelonephritis can result in renal injury, termed *pyelonephritic scarring.*

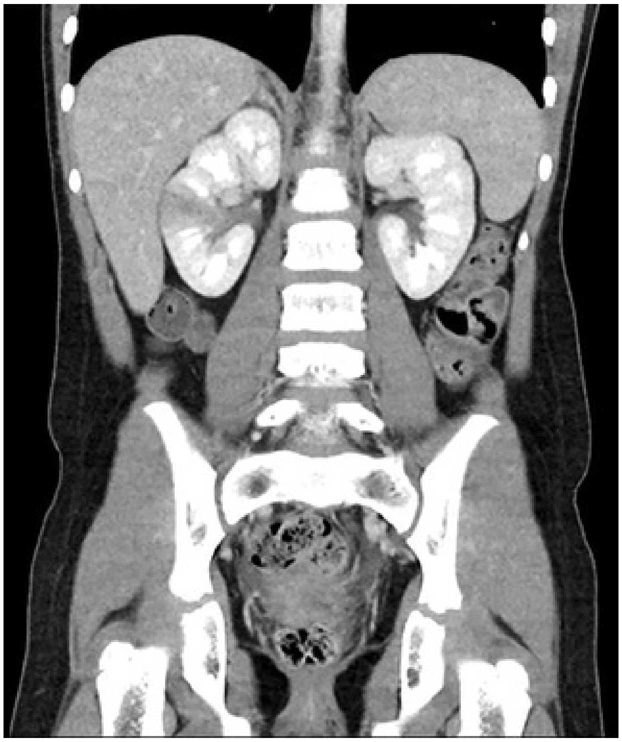

FIG. 553.1 Acute pyelonephritis seen as an area of decreased perfusion by CT scan done for abdominal pain and fever in a child who subsequently was shown to have no reflux by VCUG.

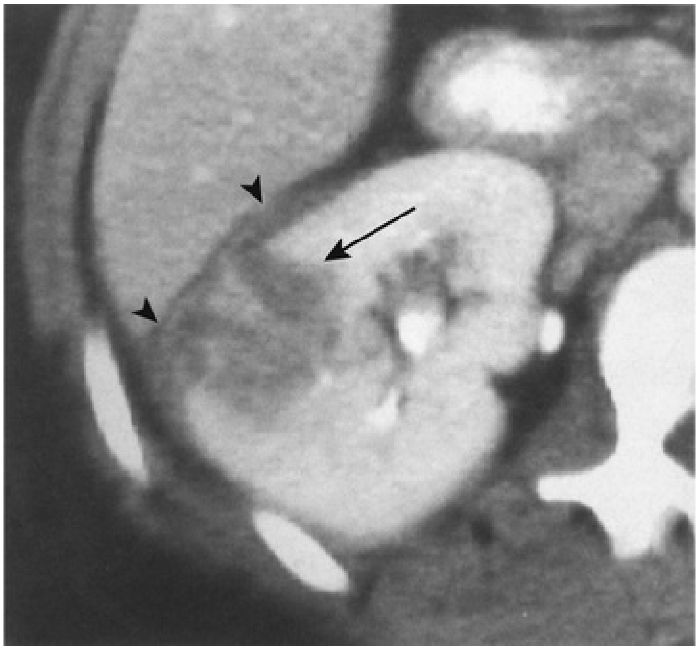

FIG. 553.2 Acute pyelonephritis with focal mass formation. The kidney

shows a rounded heterogeneous mass *(arrow)* with a poorly defined margin. Inflammatory changes in the adjacent perinephric fat and renal fascial thickening *(arrowheads)* are also present. (From Haaga JR, Boll DT [eds]: CT and MRI of the whole body, 6th ed, Philadelphia 2017, Elsevier; Fig. 54-131, p. 1833.)

Acute lobar nephronia (acute lobar nephritis) is a localized renal parenchymal mass caused by acute focal infection without liquefaction; it more commonly occurs in older children. It may be an early stage in the development of a renal abscess (Fig. 553.3). Manifestations are identical to those of pyelonephritis and include fever and flank pain. The epidemiology of the causative organism is also similar to that of pyelonephritis. *Renal abscess* typically occurs following hematogenous spread with *S. aureus* or can occur following a pyelonephritic infection caused by the usual uropathogens. Most abscesses are unilateral and right sided and can affect children of all ages (Fig. 553.4). Both acute lobar nephronia and renal abscess are associated with an increased risk of renal scarring. *Perinephric abscess* (see Fig. 553.3) can occur secondary to contiguous infection in the perirenal area (e.g., vertebral osteomyelitis, psoas abscess) or pyelonephritis that dissects to the renal capsule. It differs from renal abscess in that it is diffuse throughout the capsule and is not walled off, although it can develop septations. As with renal abscesses, the most common organisms are *S. aureus* and *E. coli.* A perinephric abscess may not communicate with the collecting system, and, thus, abnormal findings may not be seen on urinalysis or culture.

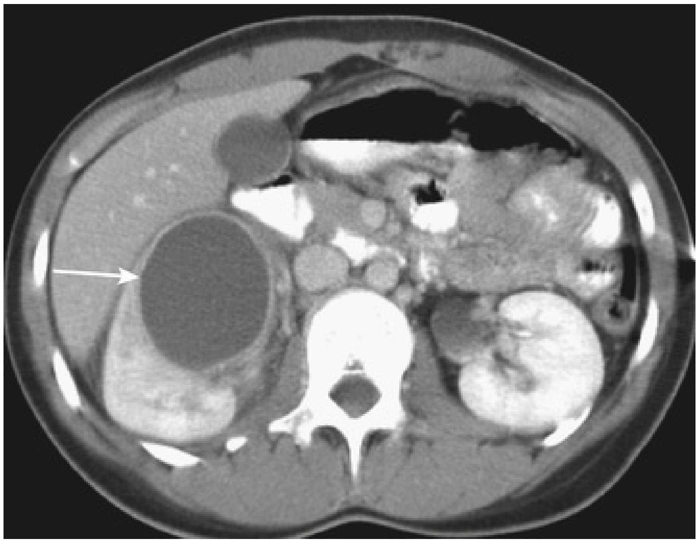

FIG. 553.3 Right renal abscess *(arrow)* shows a thick wall and low density (30 HU). Inflammatory stranding is present in the perinephric fat. (From Haaga JR, Boll DT [eds]: CT and MRI of the whole body, 6th ed, Philadelphia, 2017, Elsevier; Fig. 54-133, p. 1834.)

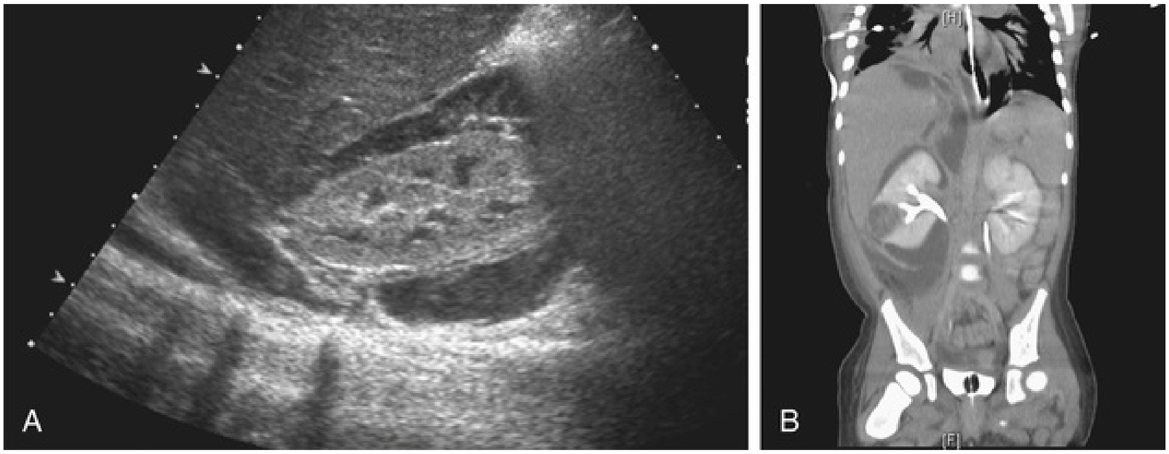

FIG. 553.4 **A,** Renal sonogram, 19 mo old girl with perirenal abscess secondary to methicillin-resistant *Staphylococcus aureus* . **B,** CT scan demonstrates extensive perinephric and focal intrarenal abscess. Patient underwent incision and drainage.

Xanthogranulomatous pyelonephritis is a rare type of renal infection characterized by granulomatous inflammation with giant cells and foamy histiocytes. It can manifest clinically as a renal mass or an acute or chronic infection. Renal calculi, obstruction, and infection with *Proteus* spp. or *E. coli* contribute to the development of this lesion, which usually requires total or partial nephrectomy.

Cystitis

Cystitis indicates that there is only bladder involvement; symptoms include dysuria, urgency, frequency, suprapubic pain, incontinence, and possibly malodorous urine. Cystitis does not cause high fever and does not result in renal injury. Malodorous urine is not specific for a UTI.

Acute hemorrhagic cystitis, though uncommon in children, is often caused by *E. coli;* it also has been attributed to adenovirus types 11 and 21. Adenovirus cystitis is more common in boys; it is self-limiting, with hematuria lasting approximately 4 days. Patients receiving immunosuppressive therapy (e.g., solid-organ or bone marrow transplantation) are at higher risk for hemorrhagic cystitis; adenoviruses and polyomaviruses (i.e., JC virus and BK virus) are important causes in immunocompromised populations (see Chapter 301). Other rare types of cystitis that may be confused with infection include *eosinophilic cystitis* or *interstitial cystitis*. Eosinophilic cystitis may present with hematuria, whereas interstitial cystitis may present with irritative voiding symptoms but a negative urine culture.

Pathogenesis and Pathology

Nearly all UTIs are ascending infections. The bacteria arise from the fecal flora, colonize the perineum, and enter the bladder via the urethra. In uncircumcised males, the bacterial pathogens arise from the flora beneath the prepuce. In some cases, the bacteria causing cystitis ascend to the kidney to cause pyelonephritis. Rarely, renal infection occurs by hematogenous spread, as in endocarditis or in some bacteremic neonates.

If bacteria ascend from the bladder to the kidney, acute pyelonephritis can occur. Normally, the simple and compound papillae in the kidney have an antireflux mechanism that prevents urine in the renal pelvis from entering the collecting tubules. However, some compound papillae, typically in the upper and lower poles of the kidney, allow intrarenal reflux. Infected urine stimulates an immunologic and inflammatory response, causing renal injury and scarring (Figs. 553.5 and 553.6). Children of any age with a febrile UTI can have acute pyelonephritis and subsequent renal scarring, but the risk is highest in those younger than 2 yr of age.

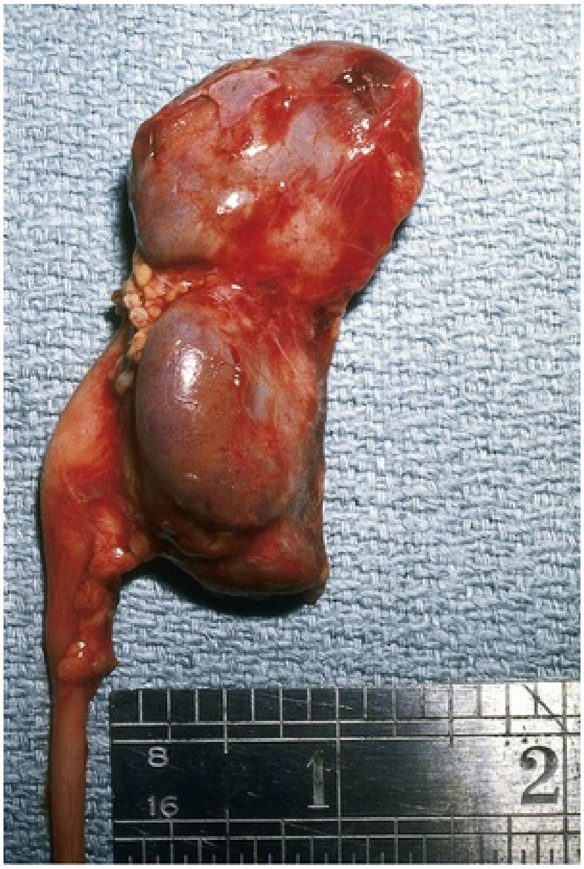

FIG. 553.5 Scarred kidney from recurrent pyelonephritis.

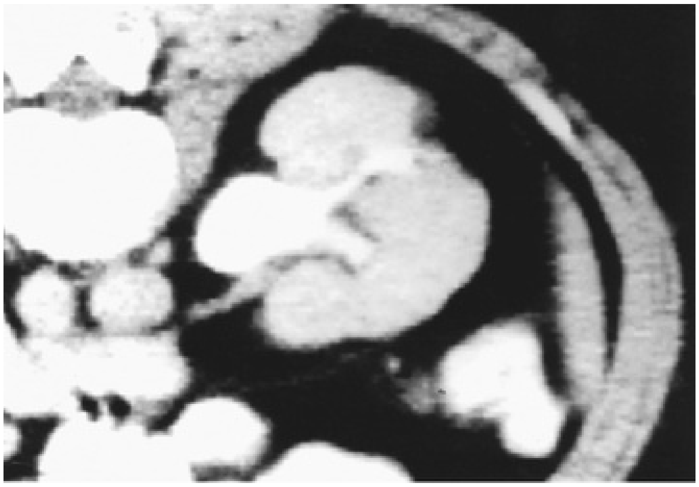

FIG. 553.6 CT scan showing an area of parenchymal thinning corresponding to an underlying calyx, characteristic of pyelonephritic scarring or reflux nephropathy.

Table 553.1 and Fig. 553.7 outline the host risk factors for UTI. Vesicoureteral reflux (VUR) is discussed in Chapter 554 . If there is grade III, IV, or V VUR and a febrile UTI, 90% have evidence of acute pyelonephritis on renal scintigraphy or other imaging studies. In females, UTIs often occur at the onset of toilet training because of bowel–bladder dysfunction that occurs at that age. The child is trying to retain urine to stay dry, yet the bladder may have uninhibited contractions forcing urine out. The resulting high-pressure, turbulent urine flow and incomplete bladder emptying both increase the likelihood of bacteriuria. *Bowel–bladder dysfunction* can arise in school-age children who refuse to use the school bathroom, creating a state of urinary retention. Obstructive uropathy resulting in hydronephrosis increases the risk of UTI because of urinary stasis. Specifically, patients who require clean intermittent catheterization due to neurogenic bladder dysfunction are at high risk for UTI, often from organisms with more antibiotic resistance. Constipation with fecal impaction can increase the risk of UTI because it can cause bladder dysfunction.

Table 553.1

Risk Factors for Urinary Tract Infection

Female gender
Uncircumcised male
Vesicoureteral reflux
Toilet training
Voiding dysfunction
Obstructive uropathy
Urethral instrumentation
Sources of external irritation (such as tight clothing, pinworm infestation)
Constipation
Anatomic abnormality (labial adhesion)
Neuropathic bladder
Sexual activity
Pregnancy

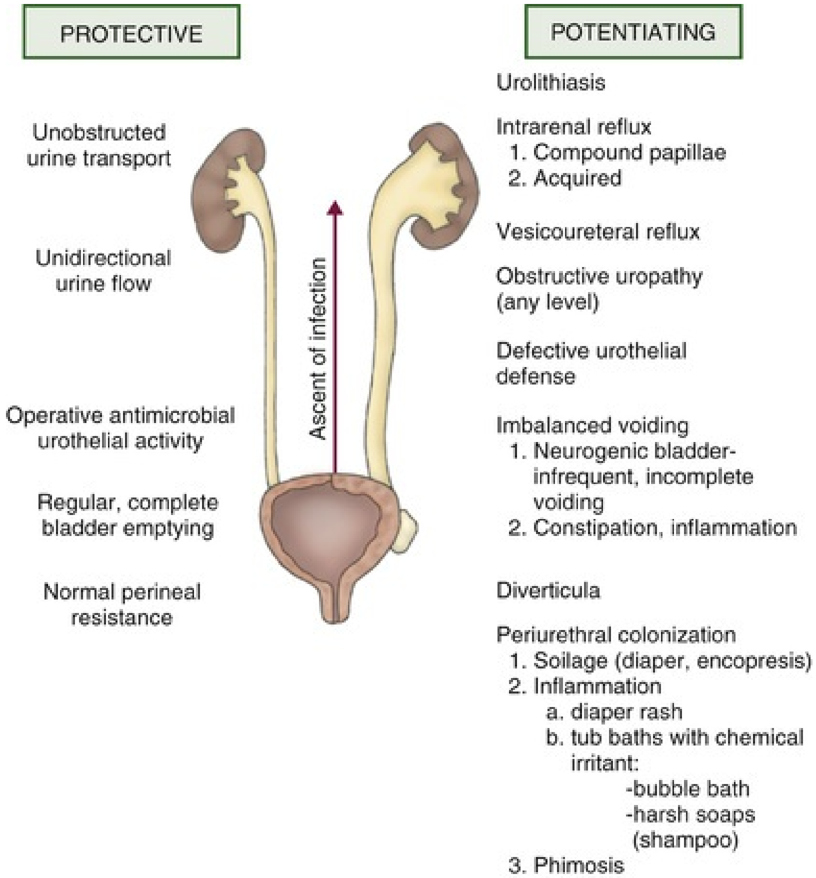
PROTECTIVE
POTENTIATING
Unobstructed urine transport
Unidirectional urine flow
Operative antimicrobial urothelial activity
Regular, complete bladder emptying
Normal perineal resistance
Ascent of infection
Urolithiasis
Intrarenal reflux
1. Compound papillae
2. Acquired
Vesicoureteral reflux
Obstructive uropathy (any level)
Defective urothelial defense
Imbalanced voiding
1. Neurogenic bladder-infrequent, incomplete voiding
2. Constipation, inflammation
Diverticula
Periurethral colonization
1. Soilage (diaper, encopresis)
2. Inflammation
a. diaper rash
b. tub baths with chemical irritant:
-bubble bath
-harsh soaps (shampoo)
3. Phimosis

FIG. 553.7 Host factors that protect the urinary tract from infection and abnormalities that potentiate the establishment of invasive bacterial infection. (From Holcomb III GW, Murphy JP, Ostlie DJ [eds]: Ashcraft's pediatric surgery, 6th ed, Philadelphia, 2014, Elsevier; Fig. 55-3, p. 735.)

The pathogenesis of UTI is based in part on the presence of bacterial pili or fimbriae on the bacterial surface. There are two types of fimbriae, type I and type II. Type I fimbriae are found in most strains of *E. coli*. Because attachment to target cells can be blocked by D -mannose, these fimbriae are referred to as *mannose sensitive*. They have no role in pyelonephritis. The attachment of type II fimbriae is not inhibited by mannose, and these are known as *mannose resistant*. These fimbriae are expressed by only certain strains of *E. coli*. The receptor for type II fimbriae is a glycosphingolipid that is present on both the uroepithelial cell membrane and red blood cells. The Gal 1-4 Gal oligosaccharide fraction is the specific receptor. Because these fimbriae can agglutinate by P blood group erythrocytes, they are known as P fimbriae. Bacteria with P fimbriae are more likely to cause pyelonephritis. Between 76% and 94% of pyelonephritogenic strains of *E. coli* have P fimbriae, compared with 19–23% of cystitis strains.

Other host factors for UTI include anatomic abnormalities precluding normal micturition, such as a labial adhesion. This lesion acts as a barrier and causes vaginal voiding. A neuropathic bladder can predispose to UTIs if there is incomplete bladder emptying and/or detrusor–sphincter dyssynergia or a resultant need for frequent catheterization. Sexual activity is associated with UTIs in females, due to introduction of bacteria near the urinary tract that can be exacerbated in part because of urethral irritation and incomplete bladder emptying following intercourse. The incidence of UTI in infants who are breastfed is lower than in those fed with formula.

The first step in an *E. coli* UTI is attachment of the bacteria to the mannose receptor on the umbrella cells, the cells lining the bladder. These bladder-lining cells may take the *E. coli* into the cell, where the bacteria replicate in the nutrient-rich environment, forming intracellular bacterial communities (IBCs). Within the IBCs, some of the *E. coli* fail to divide, becoming filamentous. Part of the bladder's defense against infection is to shed the lining cells with the IBCs; however, some IBCs break out from the cell and repopulate the urine. The filamentous forms can evade attack by polymorphonuclear white blood cells (WBCs) in the urine. When the lining of the bladder is shed, *E. coli* may be taken up in the cells of the bladder wall, where they form quiescent intracellular reservoirs (QIRs). The dormant QIRs are completely protected from antibiotics and may be a source of recurrent infections. Much current research is attempting to prevent the initial attachment of bacteria to the bladder wall that can lead to the IBCs and QIRs.

Diagnosis

UTIs may be suspected based on symptoms or findings on urinalysis, or both; *a urine culture is necessary for confirmation and appropriate therapy* . There are several ways to obtain a urine sample; some are more accurate than others. In toilet-trained children, a midstream urine sample usually is satisfactory; the introitus should be cleaned before obtaining the specimen. In uncircumcised males, the prepuce must be retracted; if the prepuce is not retractable, a voided sample may be unreliable and contaminated with skin flora. According to the 2011 American Academy of Pediatrics (AAP) Clinical Guideline for children 2-24 mo, in children who are not toilet trained, a catheterized or suprapubic aspirate urine sample should be obtained. Alternatively, the application of an adhesive, sealed, sterile collection bag after disinfection of the skin of the genitals can be useful only if the urinalysis or culture is negative; the negative predictive value for urinalysis from a "bag" specimen is 99%. However, a positive culture can result from skin contamination, particularly in females and uncircumcised males. If treatment is planned immediately after obtaining the urine culture, a bagged specimen should *not* be the method because of a high rate of contamination, often with mixed organisms. A suprapubic aspirate generally is unnecessary.

Nitrites and **leukocyte esterase** are often positive in infected urine. Bacteria generally require 4 hr for metabolism of nitrates to nitrites. Nitrites may not be detected in cases of UTI if the organism does not convert nitrates to nitrites (most notably enterococcus) or if the child has urinary frequency, where there may not be enough time for the conversion to nitrites (Table 553.2). In febrile infants less than 60 days old, the presence of pyuria, nitrites, or leukocyte esterase has a high sensitivity and specificity for a UTI.

Table 553.2

Sensitivity and Specificity of Components of Urinalysis, Alone and in Combination

TEST	SENSITIVITY (RANGE) %	SPECIFICITY (RANGE) %
Leukocyte esterase test	83 (67–94)	78 (64–92)
Nitrite test	53 (15–82)	98 (90–100)
Leukocyte esterase or nitrite positive	93 (90–100)	72 (58–91)
Microscopy (white blood cells)	73 (32–100)	81 (45–98)
Microscopy (bacteria)	81 (16–99)	83 (11–100)
Leukocyte esterase test, nitrite, or microscopy positive	99.8 (99–100)	70 (60–92)

From Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management: Clinical practice guideline. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics 128:595-610, 2011.

Microscopic hematuria is common in acute cystitis, but microhematuria alone does not suggest UTI. WBC casts in the urinary sediment suggest renal involvement, but in practice these are rarely seen. If the child is asymptomatic and the urinalysis result is normal, it is unlikely that there is a UTI. However, if the child is symptomatic, a UTI is possible, even if the urinalysis result is negative, and the urine culture should be monitored.

Pyuria (leukocytes on urine microscopy) suggests infection, but infection can occur in the absence of pyuria; this finding is more confirmatory than diagnostic (see Table 553.2). A WBC count on urinalysis above 3-6 WBCs/high-power-field is indicative of infection with a likelihood ratio of 10 in a symptomatic child. Conversely, pyuria can be present without UTI. Asymptomatic bacteriuria can also have pyuria.

Sterile pyuria (positive leukocytes, negative culture) may occur in partially treated bacterial UTIs, viral infections, urolithiasis, renal tuberculosis, renal abscess, UTI in the presence of urinary obstruction, urethritis as a consequence of a sexually transmitted infection (see Chapter 146), inflammation near the ureter or bladder (appendicitis, Crohn disease), Kawasaki disease (Chapter 471.1), schistosomiasis, neoplasm, renal transplant rejection, or interstitial nephritis (eosinophils). Prompt plating of the urine sample for culture is important, because if the urine sits at room temperature for more than 60 min, overgrowth of a minor contaminant can suggest a UTI when the urine might not be infected. Refrigeration is a reliable method of storing the urine until it can be cultured.

If the culture shows > 50,000 colony-forming units/mL of a single pathogen (suprapubic or catheter sample) and the urinalysis has pyuria or bacteriuria in a symptomatic child, the child is considered to have a UTI. In a bag sample, if the urinalysis result is positive and the patient is symptomatic, a catheter sample should be obtained for culture.

With acute renal infection, leukocytosis and neutrophilia are noted on the complete blood count (CBC); an elevated serum erythrocyte sedimentation rate, procalcitonin level, and C-reactive protein are common. However, these are all nonspecific markers of inflammation, and their elevation does not prove that the child has acute pyelonephritis. Bacteremia in the setting of pyelonephritis is reported to occur in 3–20% of patients and is most common in infants less than 90 days old (with rates decreasing with increasing age in the first 90 days) and in any child with obstructive uropathy. For these high-risk groups, particularly if the patient appears to be ill at presentation, blood cultures should be drawn before starting antibiotics, if possible.

Among children 2-24 mo, risk factors for females include white race, age younger than 12 mo, temperature > 39°C (102.2°F), fever for longer than 2 days, and absence of another source of infection. Risk factors for males include nonblack race, temperature > 39°C (102.2°F), fever for longer than 24 hr, and absence of another source of infection. Atypical features include failure to respond within 48 hr of appropriate antibiotics, poor urine flow, an abdominal flank or suprapubic mass, non–*E. coli* pathogen, urosepsis, and an elevated creatinine level.

Imaging Findings

Imaging is not needed to make the clinical diagnosis of UTI or pyelonephritis. If there is concern about acute lobar nephronia or renal abscess, imaging should be considered. Ultrasound is the first-line type of imaging for screening and will likely demonstrate an enlarged kidney with a possible mass in the case of acute lobar nephronia or renal abscess. CT scan is more sensitive and specific for lobar nephronia and will typically show a wedge-shaped, lower-density area after contrast administration. The more frequent use of imaging in patients with possible pyelonephritis is thought to be contributing to the increasing frequency of acute lobar nephronia diagnoses.

Treatment

Acute cystitis should be treated promptly to prevent possible progression to pyelonephritis. If the symptoms are severe, presumptive treatment is started pending results of the culture. If the symptoms are mild or the diagnosis is doubtful, treatment can be delayed until the results of culture are known, and the culture can be repeated if the results are uncertain. If treatment is initiated before the results of a culture and sensitivities are available, a 3- to 5-day course of therapy with trimethoprim-sulfamethoxazole (TMP-SMX) (6-12 mg TMP/kg/day in 2 divided doses) or trimethoprim is effective against many strains of *E. coli*. Nitrofurantoin (5-7 mg/kg/24 hr in 3-4 divided doses) also is effective and has the advantage of being active against *Klebsiella* and *Enterobacter* organisms. Amoxicillin (50 mg/kg/24 hr in 2 divided doses) also may be effective as initial treatment but has a high rate of bacterial resistance.

In **acute febrile UTIs** , the clinical symptoms of UTI and pyelonephritis are difficult to differentiate. Given this, it is reasonable to consider that given the presence of systemic symptoms, the infection has likely progressed to the kidneys and the patient should be treated for pyelonephritis. A course of antibiotics for 7-14 days that is capable of reaching significant tissue levels is preferable for pyelonephritis; oral and parental routes are equally efficacious. Children who are dehydrated, are vomiting, are unable to drink fluids, have complicated infection, or in whom urosepsis is a possibility should be admitted to the hospital for intravenous (IV) rehydration and IV antibiotic therapy. Local antimicrobial sensitivity patterns should be considered when selecting empirical antibiotic treatment. For hospitalized children, parenteral treatment with ceftriaxone (50 mg/kg/24 hr, not to exceed 2 g) or cefepime (100 mg/kg/24 hr q 12 h) or cefotaxime (100-150 mg/kg/24 hr in 3-4 divided doses) (when available) is a reasonable choice until culture results are back to determine whether a narrower-spectrum antibiotic can be used. If prior urine culture results have grown resistant or atypical organisms, other antibiotic choices may be prudent on a case-by-case basis.

Oral 3rd-generation cephalosporins such as cefixime are as effective as parenteral ceftriaxone against a variety of Gram-negative organisms other than *P. aeruginosa,* and these medications are considered by some authorities to be the treatment of choice for oral outpatient therapy. Cephalexin may also be considered given the increasing resistance of Gram-negative organisms to amoxicillin. Nitrofurantoin should not be used routinely in children with a febrile UTI, because it does not achieve significant renal tissue levels. The oral fluoroquinolone ciprofloxacin is an alternative agent for resistant microorganisms, particularly *P. aeruginosa,* in patients older than 17 yr; however, evidence suggests that the potential side effects of fluoroquinolones should be weighed against the benefits of this antibiotic selection. It also has been used on occasion for short-course therapy in younger children with *P. aeruginosa* UTIs. Levofloxacin is an alternative quinolone with a good safety profile in children. However, clinical treatment with fluoroquinolones in children should be used with caution because of potential cartilage damage. In some children with a febrile UTI, intramuscular injection of a loading dose of ceftriaxone followed by oral therapy with a third-generation cephalosporin is effective. This may be especially useful in children with vomiting or to allow families time to obtain the oral medication. *A repeat urine culture after the termination of treatment of a UTI is not routinely needed.* Urine cultures are typically negative within 24 hr of initiation of antibiotic therapy, and therefore a urine culture during treatment is almost invariably negative.

Acute Lobar Nephronia, Renal Abscess, and Perinephric Abscess

Acute lobar nephronia is treated with the same antibiotics as pyelonephritis. The duration of treatment is recommended for 14-21 days; one study suggested higher treatment failure in the group treated for the shorter duration. Children with a renal or perirenal abscess or with infection in obstructed urinary tracts can require surgical or percutaneous drainage in addition to antibiotic therapy and other supportive measures (see Fig. 553.4). Percutaneous drainage is typically attempted prior to surgical intervention. Immediate percutaneous drainage has been recommended when the abscess is larger than 3-5 cm; however, some patients have been managed successfully with IV antibiotics only. A 48-hr trial of IV antibiotics first before surgical drainage may be warranted in otherwise stable children. Small abscesses, less than 3 cm, may initially be treated with antibiotics alone. Few studies address the role of oral antibiotic therapy for renal abscess. Traditionally, patients received 10-14 days of IV antibiotics, followed by 2-4 wk of oral antibiotic therapy targeted against the known organism (or the likely causes of *E. coli* and *S. aureus* if the organism was unknown). The increasing use of oral antibiotics for other serious infections (e.g., osteomyelitis) suggests that an earlier transition to oral therapy for renal abscess is likely feasible. Kidney loss is reported to occur in 10–20% of cases of renal abscess. Perinephric abscesses may be managed with IV antibiotics alone or with percutaneous drainage if the area is large, causing impaired kidney function. Identification of a causative organism can be an additional advantage of percutaneous drainage of a perinephric abscess because the infection may remain isolated from the collecting system based on the location.

Other Potential Treatment or Prevention Options

There is interest in probiotic therapy, which replaces urogenital flora, as well as cranberry juice to prevent UTIs. Studies are beginning in the United States with a non-uropathogenic *E. coli* called Nissle 1917 already available in Europe. These bacteria may inhibit growth of other bacteria. Cranberry juice may prevent bacterial adhesion and biofilm formation, hypothesized to be via proanthocyanidin (PAC). Currently there is insufficient evidence regarding the use of these therapies to reduce UTIs.

The main consequences of chronic renal damage caused by pyelonephritis are arterial hypertension and end-stage renal insufficiency; when they are found, they should be treated appropriately (see Chapters 472 and 550). Even without chronic renal damage, the consequences of infections include lost days from school and work, uncomfortable symptoms, and exposure to antibiotics that change the healthy microbiome.

Imaging Studies in Children With a

Febrile UTI

The goal of imaging studies in children with a UTI is to identify anatomic abnormalities that predispose to infection, determine whether there is active renal involvement, and assess whether renal function is normal or at risk.

There are two *historical* approaches to imaging, the traditional “bottom-up” and “top-down” approaches.

1. The “bottom-up” method was a renal sonogram plus a voiding cystourethrogram (VCUG), which will identify upper and lower urinary tract abnormalities, including VUR, bladder–bowel dysfunction, and bladder abnormalities, such as a paraureteral diverticulum.
2. The “top-down” approach was intended to reduce the number of VCUG examinations. It begins with a dimercaptosuccinic acid (DMSA) renal scan, to identify areas of **acute pyelonephritis** (Fig. 553.8). The DMSA scan in younger children generally requires sedation. On DMSA, involved areas of the kidney are photopenic and the kidney is enlarged. Among children with a febrile UTI, approximately 50% have a positive DMSA scan; the proportion with acute pyelonephritis is 80–90% among those with dilating grades of reflux (III, IV, V). Of those with a positive scan, approximately 50% develop renal scarring in the areas of acute pyelonephritis. If the DMSA scan is positive, a VCUG is performed (Fig. 553.9) because 90% of children with dilating reflux have a positive DMSA scan. If reflux is identified, treatment is based on the perceived long-term risk of the reflux to the child (see Chapter 554).

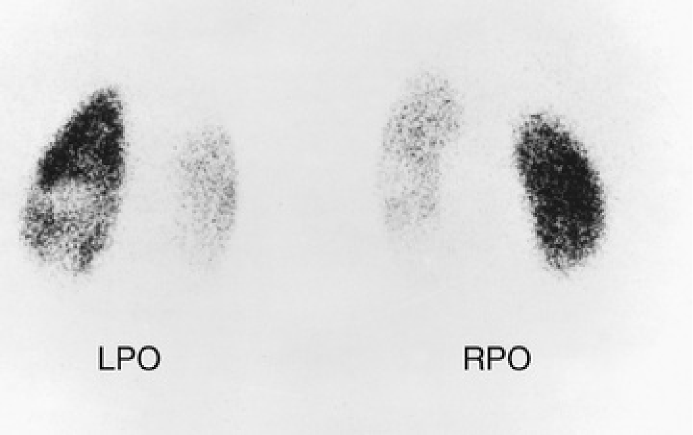

FIG. 553.8 DMSA renal scan showing bilateral photopenic areas

indicating acute pyelonephritis and renal scarring. LPO, left posterior oblique; RPO, right posterior oblique.

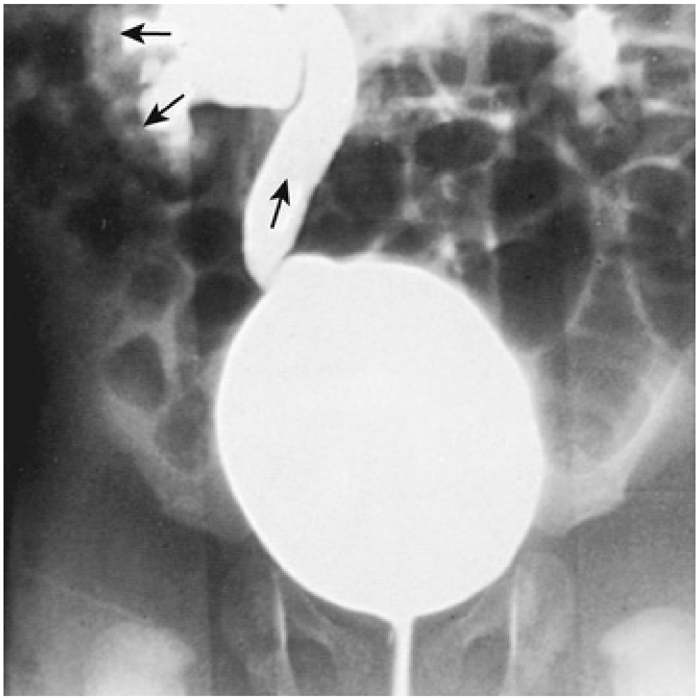

FIG. 553.9 Intrarenal reflux. VCUG in an infant boy with a history of a UTI. Note the right VUR with ureteral dilation, with opacification of the renal parenchyma representing intrarenal reflux.

The AAP practice parameter recommends initial ultrasound of the kidneys, ureters, and bladder for children 2-24 mo with a first episode of UTI. VCUG is indicated only if the ultrasound study indicates hydronephrosis, scarring or other findings suggestive of reflux or obstructive uropathy, or if the patient has other atypical complex features. Further, they recommend VCUG if the child has a recurrent febrile UTI (Table 553.3). This recommendation minimizing VCUG use highlights the importance of parental education to return for evaluation of subsequent fevers, so that the child can be promptly evaluated for a recurrent febrile UTI. The rate of renal scarring increases between days 2 and 3 of fever; this makes the prompt evaluation and appropriate treatment of a recurrent UTI important. The risk of scarring also increases with the number of episodes of pyelonephritis and with the grade of reflux.

Table 553.3

Guideline Recommendations for Diagnostic Evaluation Following a Febrile Urinary Tract Infection in Infants

GUIDELINE	ULTRASONOGRAPHY	VCUG	LATE DMSA SCAN
National Institute for Health and Care Excellence (NICE)*	(see Table 553.4)		
American Academy of Pediatrics	Yes	If abnormal ultrasonogram or febrile recurrence	No
Italian Society for Paediatric Nephrology (ISPN)	Yes	If abnormal ultrasonogram or if risk factors are present †	If abnormal ultrasonogram or VUR

* Upper urinary tract dilation on ultrasonography, poor urinary flow, infection with organism other than *E. coli* , or family history of vesicoureteral reflux.

† Abnormal antenatal ultrasonogram of fetal urinary tract, family history of reflux, septicemia, renal failure, age younger than 6 mo in a male infant, likely family noncompliance, incomplete bladder emptying, no clinical response to appropriate antibiotic therapy within 72 hr, or infection with organism other than *E. coli.*

VCUG, voiding cystourethrogram; DMSA, dimercaptosuccinic acid; VUR, vesicoureteral reflux.

The AAP guidelines address only febrile infections in children between the ages of 2 and 24 mo. Given the discomfort associated with imaging, other causes of infection in children older than 2 yr of age, and unclear optimal management of reflux in other age-groups, shared decision making with parents or guardians and the child, when appropriate, should be considered for children outside the ages of the guideline.

In children with a history of cystitis (dysuria, urgency, frequency, suprapubic pain), imaging is usually unnecessary. Instead, assessment and treatment of *bladder and bowel dysfunction* is important. This evaluation is also recommended in recurrent upper tract infections.

The AAP recommendation has resulted in a significant decrease in the number of VCUGs performed. However, the pediatric urologic community has raised numerous concerns regarding the recommendations. One concern is that many primary care physicians may generalize these recommendations, which were intended for children *2-24 mo* , to *all* children. Further, there is concern that the premise on which the AAP recommendations were made was that prophylaxis did not reduce the frequency of UTIs but that the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) showed a significant reduction in febrile UTIs in children with reflux on prophylaxis. However, given that the rates of renal scarring were unchanged in those receiving prophylaxis, the AAP reaffirmed the recommendations in 2016.

Similarly, in 2007, the NICE (National Institute for Health and Clinical Excellence, UK) guidelines for diagnosis, management, and imaging after UTI were released (Table 553.4). These recommendations divided children into those younger than 6 mo, 6 mo to 3 yr, and older than 3 yr of age. An initial ultrasound is recommended for children younger than 6 mo, and a VCUG is recommended only in children younger than age 6 mo with atypical features (non-*E. coli* , significant family history), recurrent UTI, or abnormal ultrasound findings. For children age 6 mo to 3 yr, an ultrasound and VCUG are recommended for those patients with atypical features or recurrent UTIs. No imaging is suggested for first-time, typical UTIs in this age-group. These recommendations are controversial because the methodology was not based on evidence but on expert opinion. In addition, there was no retrospective or prospective assessment of the potential of this approach to identify significant uropathology. There is evidence that a significant number of children with uropathology would not have been identified under these guidelines.

Table 553.4

Recommended Imaging Schedule for Children With Urinary Tract Infection

CHILD AGE AND TESTS	TYPE OF INFECTION		
	RESPONDS WELL TO TREATMENT WITHIN 48 HR	ATYPICAL INFECTION	RECURRENT INFECTION
CHILDREN YOUNGER THAN 6 MO OLD			
Ultrasound scan during acute infection	No	Yes	Yes
Ultrasound scan within 6 wk of infection	Yes	No	No
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	Consider if ultrasound scan abnormal	Yes	Yes
CHILDREN 6 MO TO 3 YR OLD			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan	No	No	Yes

within 6 wk of infection			
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	No	Not routine; consider if dilation on ultrasound, poor urine flow, non–*E. coli* infection, or family history of vesicoureteric reflux	
CHILDREN OLDER THAN AGE 3 YR			
Ultrasound scan during acute infection	No	Yes	No
Ultrasound scan within 6 wk of infection	No	No	Yes
DMSA scan 4-6 mo after acute infection	No	Yes	Yes
Micturating cystograms	No	No	No

DMSA, dimercaptosuccinic acid.

Adapted from National Institute for Health and Clinical Excellence. Urinary tract infection in children: diagnosis, treatment, and long-term management. NICE clinical guidelines, no. 54. London, 2007, RCOG Press, Tables 6-13, 6-14, and 6-15.

Prevention of Recurrences

In a child with recurrent UTIs, identification of predisposing factors is beneficial. Bowel and bladder dysfunction is a very important contributor to recurrent UTIs and is one of the main reasons for an increase in UTIs around the time of toilet training. Some children with UTIs may also have constipation (see Chapter 358.1). Behavioral modification, with treatment of constipation as described in Chapter 558 , often is effective. The first UTI gives the pediatrician a chance to investigate constipation. The Rome III criteria for constipation in the pediatric age-group standardize the definition of constipation.

Bladder dysfunction manifested by urgency, wetting, and especially “Vincent's curtsy” (females squat on their heels in response to an uninhibited bladder contraction) can predispose to UTI.

In toilet-trained children, a thorough history and use of urodynamic studies and measurement of postvoid residual volumes may be helpful in identifying children with bladder dysfunction that may contribute to UTIs. Tightening the pelvic floor during urination can sometimes be seen on a VCUG as a spinning-top urethra (Fig. 553.10). An ultrasound may document residual urine and possibly a thick bladder wall. Urodynamics may show an intermittent stream with increased activity in the pelvic floor muscles.

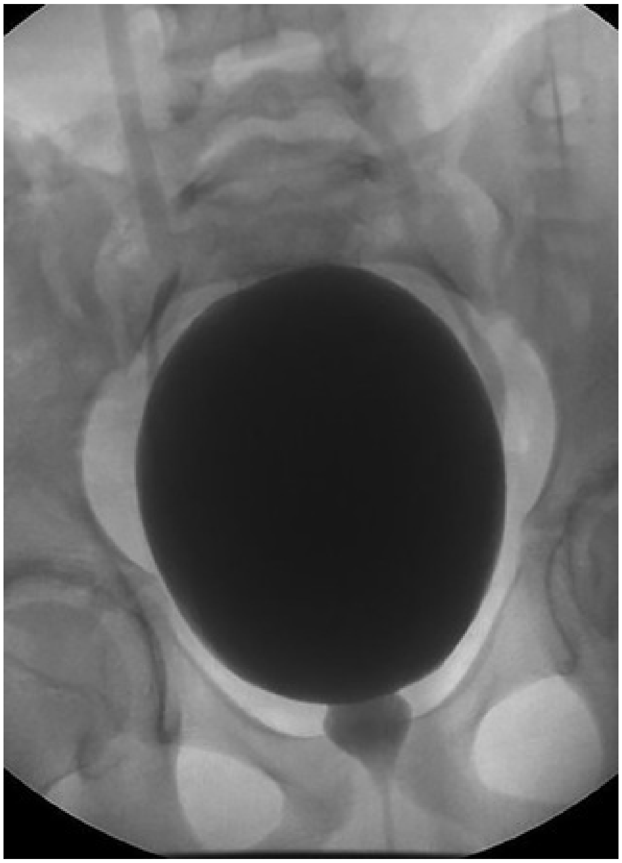

FIG. 553.10 This VCUG shows contraction of the pelvic floor and external sphincter during voiding, leading to a dilated posterior urethra and bilateral reflux.

The RIUVR study was a randomized trial of TMP-SMX prophylaxis for patients with a history of UTI and diagnosed VUR. Although the UTI recurrence rate was decreased by half from 30% in the group not receiving prophylaxis to 15% in those receiving prophylaxis, rates of renal scarring were the same in both groups. Additionally, the rates of UTI caused by resistant organisms increased in the group receiving prophylaxis. Taken together, although the use of prophylaxis can decrease rates of recurrence, the increase in antibiotic resistance, need for daily medication in children, and no change in renal scarring prevent firm recommendations for prophylaxis. The AAP does not recommend routine use of antibiotic prophylaxis in children with a first episode of pyelonephritis in an otherwise anatomically normal urinary tract. Urologic conditions that can cause recurrent UTIs that might benefit from long-term antibiotic prophylaxis include neuropathic bladder, urinary tract stasis and obstruction, severe VUR (see Chapter 554), and urinary calculi.

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CHAPTER 554

Vesicoureteral Reflux

Jack S. Elder

Vesicoureteral reflux (VUR) describes the retrograde flow of urine from the bladder to the ureter and kidney. The ureteral attachment to the bladder normally is oblique, between the bladder mucosa and detrusor muscle, creating a flap-valve mechanism that prevents VUR (Fig. 554.1). VUR occurs when the submucosal tunnel between the mucosa and detrusor muscle is short or absent. Affecting 1–2% of children, VUR usually is congenital and often is familial. VUR is present in approximately 30% of females who had a urinary tract infection and in 5–15% of infants with antenatal hydronephrosis.

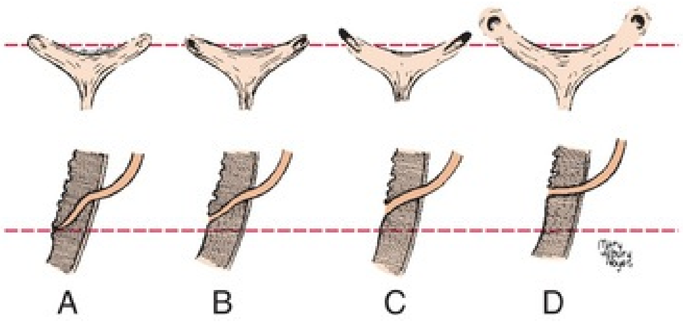

FIG. 554.1 Normal and abnormal configuration of the ureteral orifices. Shown from *left* to *right,* progressive lateral displacement of the ureteral orifices and shortening of the intramural tunnels. *Top,* Endoscopic appearance. *Bottom,* Sagittal view through the intramural ureter.

VUR predisposes to kidney infection (pyelonephritis) by facilitating the transport of bacteria from the bladder to the upper urinary tract (see Chapter 553). The inflammatory reaction caused by pyelonephritis can result in renal injury or scarring, also termed **reflux-related renal injury** or **reflux nephropathy.** In children with a febrile urinary tract infection (UTI), those with VUR are three times more likely to develop renal injury compared with those without VUR. Extensive renal scarring impairs renal function and can result in renin-mediated hypertension (see Chapter 472), renal insufficiency or end-stage renal disease (see Chapter 550), impaired somatic growth, and morbidity during pregnancy. Scarring associated with reflux may be present at birth or develop in the absence of infection if there is significant bladder–sphincter discoordination during voiding.

In the past, reflux nephropathy accounted for as much as 15–20% of end-stage renal disease in children and young adults. With greater attention to the management of UTIs and a better understanding of VUR, end-stage renal disease secondary to reflux nephropathy is uncommon. Reflux nephropathy remains a common cause of hypertension in children. VUR in the absence of infection or elevated bladder pressure (e.g., neuropathic bladder, posterior urethral valves) rarely causes renal injury.

Classification

VUR severity is graded using the International Reflux Study (IRS) Classification of I-V and is based on the appearance of the urinary tract on a contrast voiding cystourethrogram (VCUG) (Figs. 554.2 and 554.3). The higher the VUR grade the greater the likelihood of renal injury. VUR severity is an indirect indication of the degree of abnormality of the ureterovesical junction.

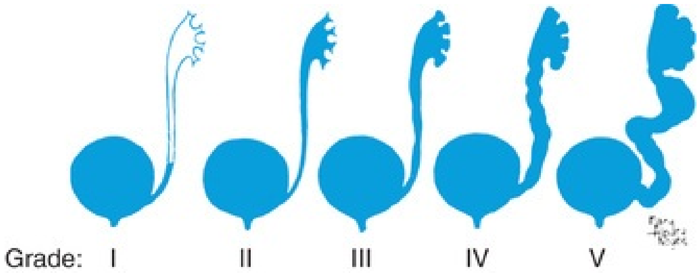

FIG. 554.2 Grading of VUR. Grade I: VUR into a nondilated ureter. Grade II: VUR into the upper collecting system without dilation. Grade III: VUR into a dilated ureter and/or blunting of the calyceal fornices. Grade IV: VUR into a grossly dilated ureter. Grade V: massive VUR, with significant ureteral dilation and tortuosity and loss of the papillary impression.

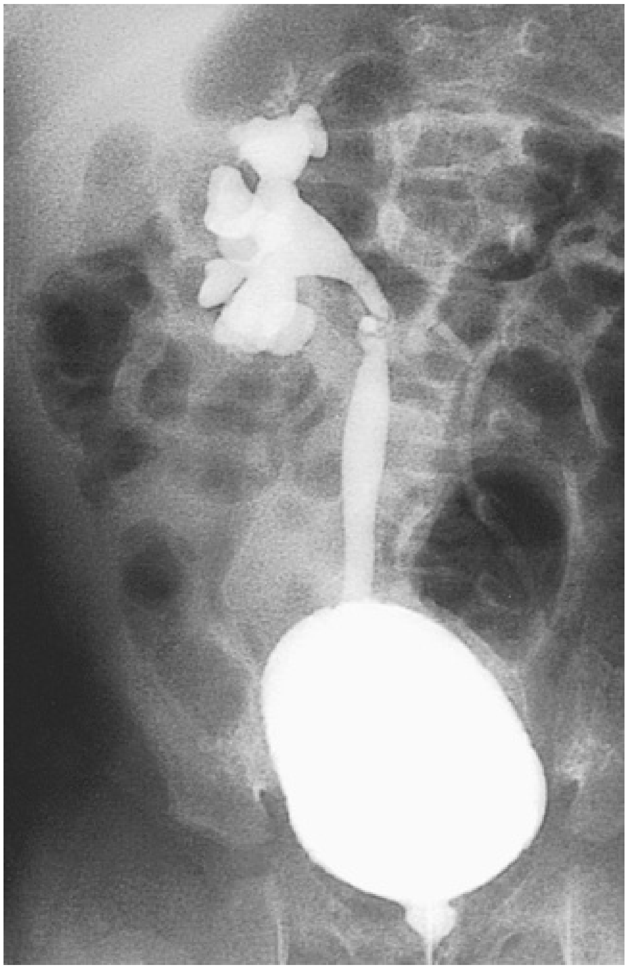

FIG. 554.3 VCUG showing grade IV right VUR.

VUR may be primary or secondary (Table 554.1). Bladder–bowel dysfunction can worsen preexisting VUR if there is a marginally competent ureterovesical junction. In the most severe cases, there is such massive VUR into the upper tracts that the bladder becomes overdistended. This condition, the **megacystis–megaureter syndrome,** occurs primarily in males and may be unilateral or bilateral (Fig. 554.4). Reimplantation of the ureters into the bladder to correct VUR corrects the condition.

Table 554.1

Classification of Vesicoureteral Reflux

TYPE	CAUSE
Primary	Congenital incompetence of the valvular mechanism of the vesicoureteral junction
Primary associated with other malformations of the	Ureteral duplication

ureterovesical junction	Ureterocele with duplication Ureteral ectopia Paraureteral diverticula
Secondary to increased intravesical pressure	Neuropathic bladder Nonneuropathic bladder dysfunction Bladder outlet obstruction
Secondary to inflammatory processes	Severe bacterial cystitis Foreign bodies Vesical calculi Clinical cystitis
Secondary to surgical procedures involving the ureterovesical junction	Surgery

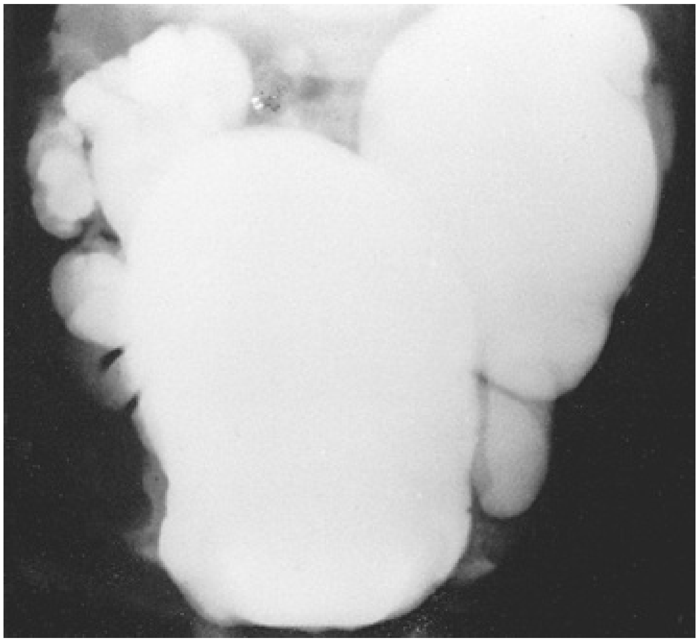

FIG. 554.4 VCUG in newborn boy with megacystis–megaureter syndrome. Note the massive ureteral dilation caused by high-grade VUR. The bladder is very distended. There was no urethral obstruction or neuropathic dysfunction.

Primary VUR appears to be an autosomal dominant inherited trait with variable penetrance. Approximately 35% of siblings of children with VUR also have VUR, and VUR is found in nearly half of newborn siblings. The likelihood of a sibling having VUR is independent of the grade of VUR or sex of the index child. Approximately 12% of asymptomatic siblings with VUR have evidence of renal scarring. In addition, 50% of children born to women with a history of VUR also have VUR. The American Urological Association Vesicoureteral Reflux Guidelines Panel stated that, in siblings of individuals with VUR, a

VCUG or radionuclide cystogram is recommended if there is evidence of a renal cortical abnormality or renal size asymmetry on sonography, or if the sibling has a history of UTI. Otherwise, screening is optional. VUR may be suggested on a prenatal ultrasound that demonstrates hydronephrosis or hydroureteronephrosis. Primary VUR is uncommon in African Americans.

Approximately 1 in 125 children has a **duplication** of the upper urinary tract, in which two ureters rather than one drain the kidney. Duplication may be partial or complete. In partial duplication, the ureters join above the bladder and there is one ureteral orifice. In complete duplication, the attachment of the lower pole ureter to the bladder is superior and lateral to the upper pole ureter. The valve-like mechanism for the lower pole ureter often is marginal, and VUR into the lower ureter occurs in as many as 50% of cases (Fig. 554.5). VUR occurs into both the lower and upper systems in some persons. With a duplication anomaly, some patients have an ectopic ureter, in which the upper pole ureter drains outside the bladder (see Chapter 555 and Figs. 555.6 and 555.7). If the ectopic ureter drains into the bladder neck, typically it is obstructed and refluxes. Duplication anomalies also are common in children with a ureterocele, which is a cystic swelling of the intramural portion of the distal ureter. These patients often have VUR into the associated lower pole ureter or the contralateral ureter. In addition, generally VUR is present when the ureter enters a bladder diverticulum (Fig. 554.6).

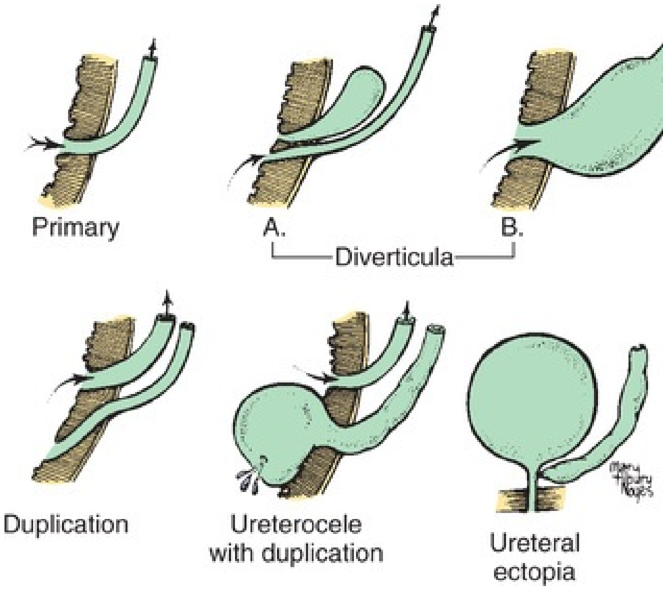

FIG. 554.5 Various anatomic defects of the ureterovesical junction

associated with VUR.

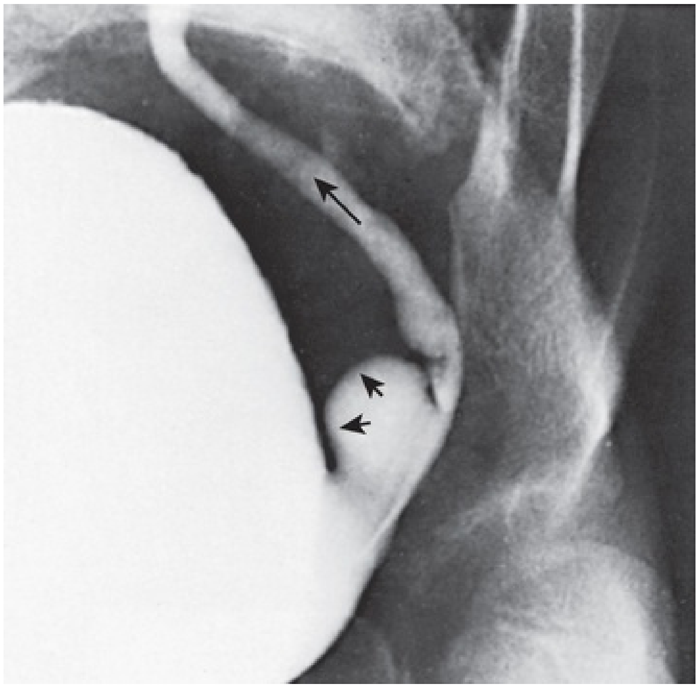

FIG. 554.6 VUR and bladder diverticulum. The VCUG demonstrates left VUR and a paraureteral diverticulum.

VUR is present at birth in 25% of children with **neuropathic bladder,** as occurs in myelomeningocele (see Chapters 557 and 609.4), sacral agenesis, and many cases of high imperforate anus. VUR is seen in 50% of males with posterior urethral valves. VUR with increased intravesical pressure (as in detrusor–sphincter discoordination or bladder outlet obstruction) can result in renal injury because of increased intravesical pressure transmitted to the upper urinary tract, even in the absence of infection.

Primary VUR occurs in association with several congenital urinary tract abnormalities. Of children with a multicystic dysplastic kidney or renal agenesis (see Chapter 552), 15% have VUR into the contralateral kidney, and 10–15% of children with a ureteropelvic junction obstruction have VUR into either the hydronephrotic kidney or the contralateral kidney.

Clinical Manifestations

VUR usually is discovered during evaluation for a UTI (see Chapter 553). Among these children, 80% are female, and the average age at diagnosis is 2-3 yr. In other children, a VCUG is performed during evaluation of bladder–bowel dysfunction, renal insufficiency, hypertension, or other suspected pathologic process of the urinary tract. Primary VUR also may be discovered during evaluation for antenatal hydronephrosis. In this select population, 80% of affected children are male, and the VUR grade usually is higher than in females whose VUR is diagnosed following a UTI. The UTI may be symptomatic, an isolated febrile event, or more often both febrile and symptomatic (abdominal pain, dysuria). Bladder and bowel dysfunction (constipation) may be present in 50% of children with reflux and a UTI.

Diagnosis

Diagnosis of VUR requires catheterization of the bladder, instillation of a solution containing iodinated contrast or a radiopharmaceutical, and radiologic imaging of the lower and upper urinary tract: a contrast VCUG or radionuclide cystogram, respectively. The bladder and upper urinary tracts are imaged during bladder filling and voiding. VUR occurring during bladder filling is termed *low-pressure* VUR; VUR during voiding is termed *high-pressure* VUR. VUR in children with low-pressure VUR is significantly less likely to resolve spontaneously than in children who exhibit only high-pressure VUR. Radiation exposure during a radionuclide cystogram is significantly less than that from a contrast VCUG. Low-dose radiation contrast VCUG provides more anatomic information, such as demonstration of a duplex collecting system, ectopic ureter, paraureteral (bladder) diverticulum, bladder outlet obstruction in boys, upper urinary tract stasis, and signs of voiding dysfunction, such as a “spinning-top” urethra in girls. The VUR grading system is based on the appearance on contrast VCUG, and the grade reported is the maximum grade observed during the study. For follow-up evaluation, some prefer the radionuclide cystogram because of the lower radiation exposure (Fig. 554.7), although it is difficult to determine whether the VUR severity has changed and the grading system for the radionuclide study is different than the standard IRS grading system.

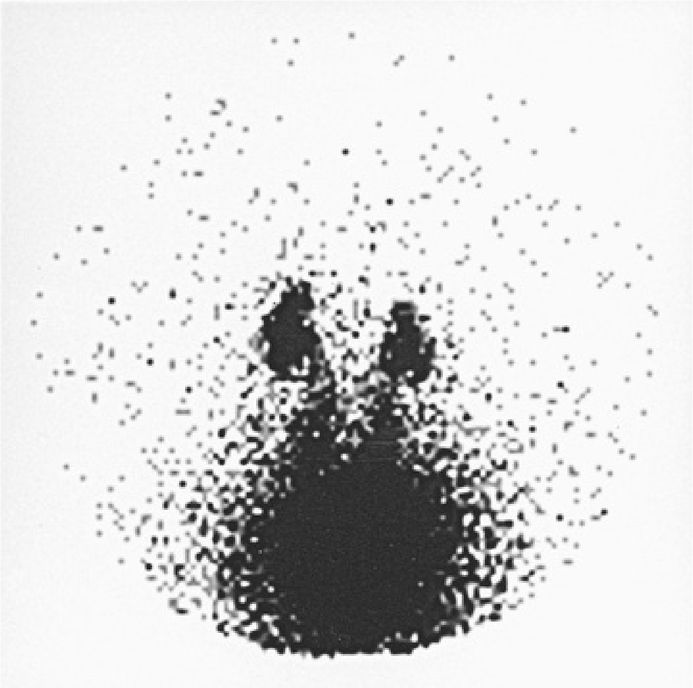

FIG. 554.7 Radionuclide cystogram shows bilateral VUR.

Children undergoing cystography may be psychologically traumatized by the catheterization. Careful preparation by caregivers, use of Child Life individuals, or administration of oral or nasal midazolam (for sedation and amnesia) or propofol before the study can result in a less-distressing experience.

Indirect cystography is a technique of detecting VUR without catheterization that involves injecting an intravenous radiopharmaceutical that is excreted by the kidneys, waiting for it to be excreted into the bladder, and imaging the lower urinary tract while the patient voids. This technique detects only 75% of VUR cases. Another technique, which avoids radiation exposure, involves instilling sonographic contrast medium through a urethral catheter. The kidneys are imaged sonographically to determine whether any of the material refluxes. This technique is investigational.

After VUR is diagnosed, assessment of the upper urinary tract is important. The goal of upper tract imaging is to assess whether renal scarring and associated urinary tract anomalies are present. Renal imaging typically is performed with a renal sonogram and/or renal scintigraphy (Fig. 554.8 ; see Chapter 553).

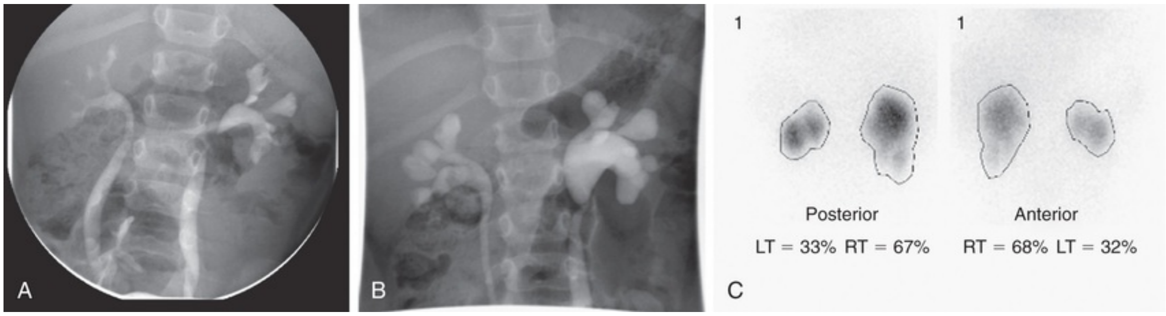

FIG. 554.8 **A,** VCUG in a 3 yr old girl with two febrile UTIs shows bilateral grade III VUR. **B,** At 5 yr, repeat VCUG shows worsening VUR and calyceal clubbing, indicating renal scarring. **C,** At 11 yr, she has developed renin-mediated hypertension. Dimercaptosuccinic acid (DMSA) renal scan shows significant VUR-related renal scarring.

The child should be evaluated for **bladder–bowel dysfunction** (also termed BBD), including urgency, frequency, diurnal incontinence, infrequent voiding, or a combination of these (see Chapter 553). Children with an overactive bladder often undergo a regimen of behavioral modification with timed voiding, treatment of constipation, and, on occasion, anticholinergic therapy.

After diagnosis, the child's height, weight, and blood pressure should be measured and monitored. If upper tract imaging shows renal scarring, a serum creatinine measurement should be obtained. The urine should be assessed for infection and proteinuria.

Natural History

The incidence of reflux-related renal scarring increases with VUR grade. With bladder growth and maturation, the VUR grade often resolves or improves. Lower grades of VUR are much more likely to resolve than are higher grades. For grades I and II VUR, the likelihood of resolution is similar regardless of age at diagnosis and whether it is unilateral or bilateral. For grade III, a younger age at diagnosis and unilateral VUR usually are associated with a higher rate of spontaneous resolution (Fig. 554.9). Bilateral grade IV VUR is much less likely to resolve than is unilateral grade IV VUR. Grade V VUR rarely resolves. The mean age at VUR resolution is 6 yr. BBD and grade III-V VUR are the most common risk factors for recurrent febrile UTI and new renal scarring.

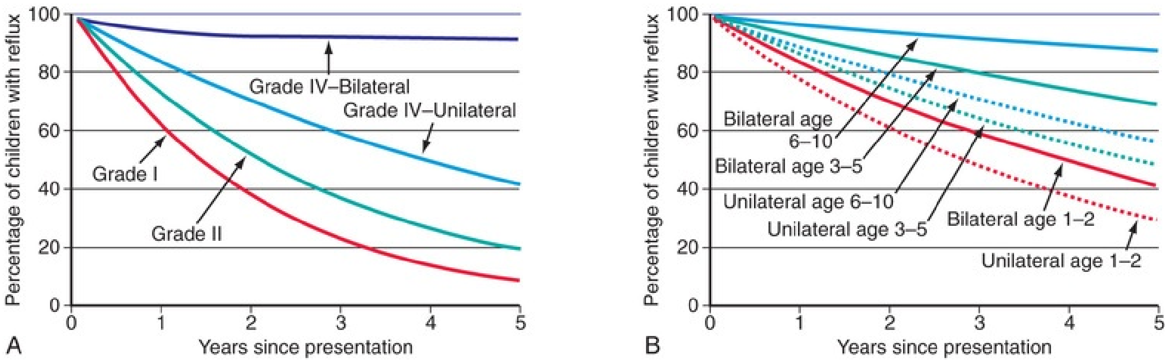

FIG. 554.9 **A,** Percentage chance of VUR persistence, grades I, II, and IV, for 1-5 yr after presentation. **B,** Percentage chance of VUR persistence by age at presentation, grade III, for 1-5 yr after presentation. (From Elder JS, Peters CA, Arant BS Jr, et al: Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children, J Urol 157:1846-1851, 1997.)

Sterile VUR does not usually cause renal injury in the absence of infection, but in situations with high-pressure VUR, as in children with posterior urethral valves, neuropathic bladder, and nonneurogenic neurogenic bladder (i.e., **Hinman syndrome**), sterile VUR can cause significant renal damage. Children with high-grade VUR who acquire a UTI are at significant risk for acute and recurrent pyelonephritis and new renal scarring (see Fig. 554.8).

Treatment

The goals of treatment are to prevent pyelonephritis, VUR-related renal injury, and other complications of VUR. Medical therapy is based on the principle that VUR often resolves over time and that if UTIs can be prevented, the morbidity or complications of VUR may be avoided without surgery. Medical therapy includes observation with behavioral modification or behavioral modification with antimicrobial prophylaxis in some patients. The basis for surgical therapy is that in selected children, ongoing VUR has caused or has significant potential for causing renal injury or other VUR-related complications, and that elimination of VUR minimizes the risk of these problems. Therapy for VUR should be individualized based on a particular patient's risk factors.

Observation

In children undergoing observation, therapeutic emphasis is directed at minimizing the risk of UTI by behavioral modification. These methods include timed voiding during the day, ensuring regular fecal elimination, increased fluid intake, periodic assessment of satisfactory bladder emptying, and prompt assessment and treatment of UTIs, particularly febrile UTIs. This approach is most appropriate for children with grades I and II VUR, and perhaps older children with persistent VUR and normal kidneys who have not experienced clinical pyelonephritis.

Antimicrobial Prophylaxis

In the past, daily antimicrobial prophylaxis was recommended as an initial approach to most children with VUR. Currently, many families express concern regarding the safety and benefit of prophylaxis. In addition, as a result of several prospective clinical trials, the benefit of prophylaxis has been questioned in children with VUR. The risk of recurrent UTI is highest in patients with grade III or IV reflux, those with BBD, and those whose first reflux-associated UTI was *febrile* rather than just symptomatic without fever. Antibiotic prophylaxis after a reflux-associated UTI decreases the risk of recurrent UTI but may increase the risk of developing resistant bacteria. In one study, antibiotic prophylaxis reduced the risk of new renal scars in children with grade III or IV reflux, while in another larger study, antibiotic prophylaxis did not affect the incidence of new renal scars in those with severe reflux (approximately 10% developed new scars regardless of prophylaxis).

Surgery

The purpose of surgical therapy is to minimize the risk of febrile UTI from ongoing VUR and nonsurgical therapy (observation or prophylaxis with follow-up testing). VUR can be corrected through a lower abdominal or inguinal incision (open), laparoscopically (with or without robotic assistance), or endoscopically with subureteral injection of a bulking agent.

Open surgical management involves modifying the abnormal ureterovesical attachment to create a 4 : 1 to 5 : 1 ratio of intramural ureter length: ureteral diameter. The operation can be performed from either outside or inside the bladder. When VUR is associated with severe ureteral dilation (i.e., megaureter), the ureter must be tailored or narrowed to a more normal size to allow a smaller length: width ratio for the intramural tunnel, and a corner of the bladder is attached to the psoas tendon, forming a *psoas hitch.* Most children can be discharged 1-2 days following the surgical procedure. If the refluxing kidney is poorly functioning, nephrectomy or nephroureterectomy is indicated. Minimally invasive approaches with laparoscopic and robotic-assisted laparoscopic ureteral reimplantation have been investigated and have been shown to have favorable success, but they are less successful than open surgery.

The success rate of conventional open ureteral reimplantation in children with primary VUR is > 95–98% for grades I-IV, with 2% experiencing persistent VUR and 1% having ureteral obstruction that requires correction. The success rate is so high that many pediatric urologists do not perform a postoperative VCUG unless the child develops clinical pyelonephritis. For grade V VUR, the success rate is approximately 80%. In lower grades of VUR, a failed reimplantation is most likely to occur in children with undiagnosed BBD. In children with secondary VUR (posterior urethral valves, neuropathic bladder), the success rate is slightly lower than with primary VUR. The risk of pyelonephritis in children with grades III and IV VUR is significantly lower following open surgical correction compared with medical management. Surgical repair will not reverse renal scarring or cause improvement in renal function.

Endoscopic repair of VUR involves injection of a bulking agent through a cystoscope just beneath the ureteral orifice, creating an effective flap-valve (Figs. 554.10 and 554.11). In 2001, the FDA approved the use of a biodegradable material, dextranomer microspheres suspended in hyaluronic acid (Dx-HA) (Deflux), for subureteral injection. The advantage of subureteral injection is that it is a noninvasive outpatient procedure (performed under general anesthesia) with no recovery time. The success rate is 70–80% and is highest for lower grades of VUR. If the first injection is unsuccessful, one or two repeat injections can be performed. The VUR recurrence rate is approximately 10–20%. In Europe and South America, a polyacrylamide hydrogel also is being used for endoscopic injection. The success rate with this product, which is not approved in the United States, is similar to Dx-HA, but the risk of reflux recurrence is significantly less.

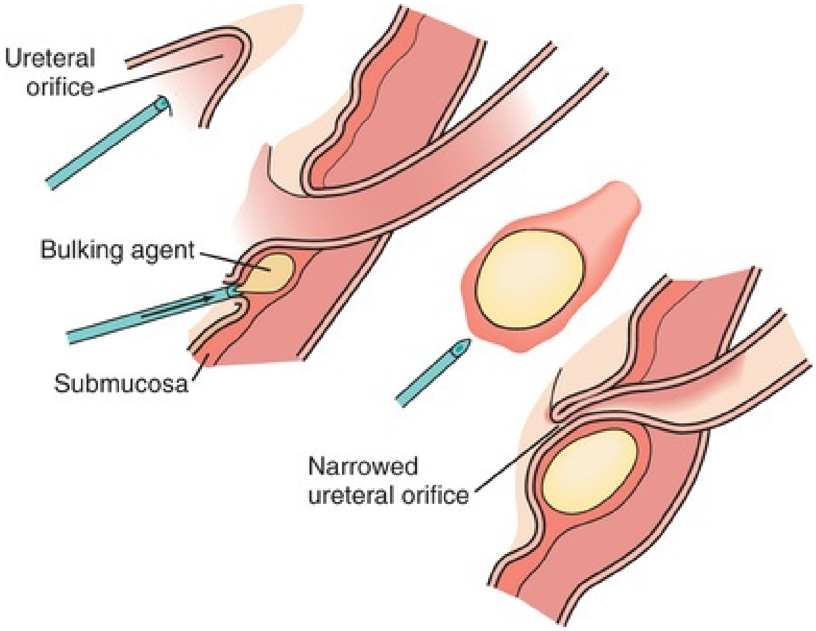
Ureteral orifice
Bulking agent
Submucosa
Narrowed ureteral orifice

FIG. 554.10 Endoscopic correction of VUR. Through a cystoscope, a needle is inserted into the submucosal plane deep to the ureteral orifice and a bulking agent is injected, creating a flap-valve to prevent VUR. (Adapted from Ortenberg J: Endoscopic treatment of vesicoureteral reflux in children, Urol Clin North Am 25:151-156, 1998.)

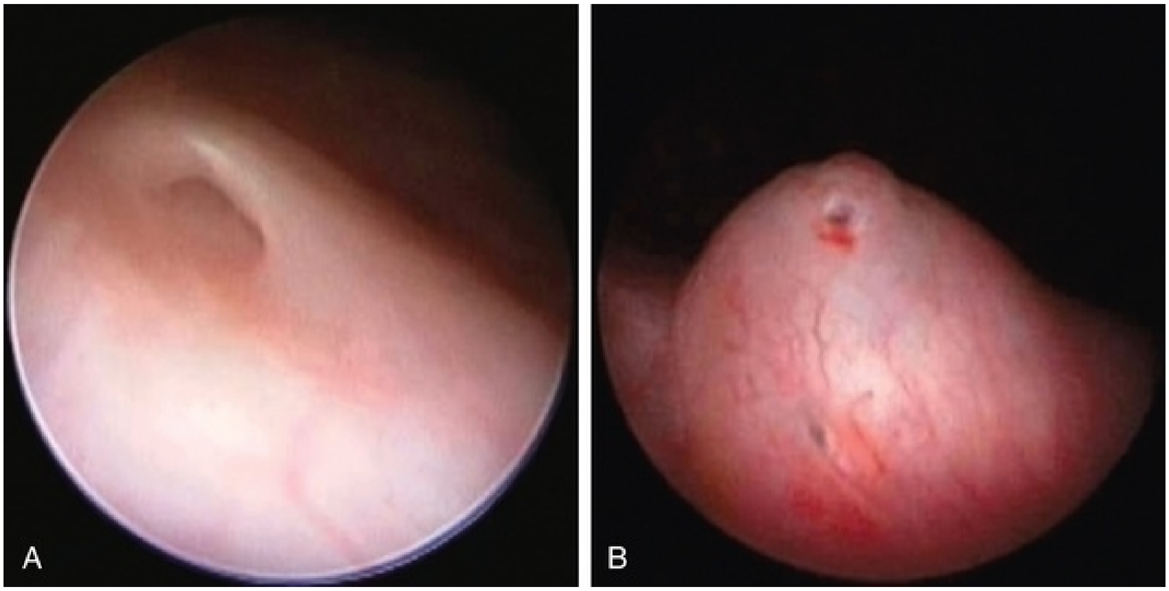

FIG. 554.11 **A,** Endoscopic view of right vesicoureteral refluxing ureter. **B,** The same ureter after subureteral injection of dextranomer microspheres.

Current Vesicoureteral Reflux Guidelines

The AUA evidence-based guidelines regarding VUR management were updated in 2017. In 2016 the European Association of Urology published expert opinion–based guidelines. Both societies’ recommendations were based on a risk assessment of children with VUR.

The long-standing belief regarding the benefit of antibiotic prophylaxis in children with VUR has been questioned. Multiple randomized, controlled prospective trials suggested that the risk of UTI in children with VUR is not reduced by prophylaxis. Most of the children in these trials had grades I-III VUR, and few younger than 1 yr old were studied. In contrast, the PRIVENT (Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts) trial from Australia showed significant benefit to prophylaxis in children with VUR. The Swedish VUR Trial in Children studied children younger than 2 yr of age with grades III and IV VUR; they compared antibiotic prophylaxis (nitrofurantoin) with observation and endoscopic injection therapy. Females in the surveillance group had a significantly higher incidence of febrile UTI and new renal scarring compared with the other treatment groups. The largest randomized trial (RIVUR [Randomized Intervention for Children with Vesicoureteral Reflux]) enrolled more than 600 children and demonstrated a reduction in the recurrence rate of UTIs but no reduction in the occurrence of renal scarring with antibiotic prophylaxis, but the prevalence of renal scarring at study entry was low.

Prophylaxis is recommended by the AUA in children at greatest risk for VUR-related renal injury (i.e., those < 1 yr of age). In addition, evaluation for bladder and bowel dysfunction is considered a standard part of initial and ongoing patient evaluation in children with VUR. Because children with bladder and bowel dysfunction and VUR are much more likely to have recurrent UTIs and renal scarring, prophylaxis is recommended for these children. In children with VUR who are being managed by surveillance, if a febrile UTI occurs, prophylaxis is recommended. The decision whether to recommend observation, medical therapy, or surgery is based on the risk of VUR to the patient, the likelihood of spontaneous resolution, and the parents’ and patient's preferences, and the family should understand the risks and benefits of each treatment approach.

Another aspect of VUR management pertains to screening. VUR is known to be a familial disorder with autosomal dominant transmission with variable penetrance. The advantage of early VUR detection is to implement treatment before a potentially damaging episode of clinical pyelonephritis. In siblings of an index patient with VUR, optional management includes screening of asymptomatic siblings or offspring with a renal ultrasound or VCUG. The AUA recommends that a VCUG should be obtained if a screening ultrasound demonstrated a renal abnormality or if the sibling had a UTI.

The AUA also determined that female newborns with renal pelvic dilation were more likely than male newborns to have VUR. The AUA recommended that a VCUG should be performed in neonates with grade 3-4 *antenatal* hydronephrosis (moderate to severe pelvocalyceal dilation), hydroureter, or an abnormal bladder. In children with less-severe renal pelvic dilation, an observational approach without screening for VUR, with prompt treatment of any UTI, is appropriate. However, the AUA also indicated that obtaining a VCUG is considered an appropriate option for neonates with lesser grades of hydronephrosis.

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CHAPTER 555

Obstruction of the Urinary Tract

Jack S. Elder

Most childhood obstructive lesions are congenital, although urinary tract obstruction can be caused by trauma, neoplasia, calculi, inflammatory processes, or surgical procedures. Obstructive lesions occur at any level from the urethral meatus to the calyceal infundibula (Table 555.1). The pathophysiologic effects of obstruction depend on its level, the extent of involvement, the child's age at onset, and whether it is acute or chronic.

Table 555.1

Types and Causes of Urinary Tract Obstruction

LOCATION	CAUSE
Infundibula	Congenital Calculi Inflammatory (tuberculosis) Traumatic Postsurgical Neoplastic
Renal pelvis	Congenital (infundibulopelvic stenosis) Inflammatory (tuberculosis) Calculi Neoplasia (Wilms tumor, neuroblastoma)
Ureteropelvic junction	Congenital stenosis Calculi Neoplasia Inflammatory Postsurgical Traumatic
Ureter	Congenital obstructive megaureter Midureteral structure Ureteral ectopia Ureterocele Retrocaval ureter Ureteral fibroepithelial polyps Ureteral valves

	Calculi Postsurgical Extrinsic compression Neoplasia (neuroblastoma, lymphoma, and other retroperitoneal or pelvic tumors) Inflammatory (Crohn disease, chronic granulomatous disease) Hematoma, urinoma Lymphocele Retroperitoneal fibrosis
Bladder outlet and urethra	Neurogenic bladder dysfunction (functional obstruction) Posterior urethral valves Anterior urethral valves Diverticula Urethral strictures (congenital, traumatic, or iatrogenic) Urethral atresia Ectopic ureterocele Meatal stenosis (males) Calculi Foreign bodies Phimosis Extrinsic compression by tumors Urogenital sinus anomalies

Etiology

Severe ureteral obstruction early in fetal life results in renal dysplasia, ranging from multicystic kidney, which is associated with ureteral or ureteropelvic junction (UPJ) atresia (see Fig. 552.3 in Chapter 552), to various degrees of histologic renal cortical dysplasia that are seen with less-severe obstruction. Chronic ureteral obstruction in late fetal life or after birth results in dilation of the ureter, renal pelvis, and calyces, with alterations of renal parenchyma ranging from minimal tubular changes to dilation of Bowman's space, glomerular fibrosis, and interstitial fibrosis. After birth, infection can complicate obstruction and worsen renal damage.

Prenatal screening with **ultrasonography** (US) may detect antenatal hydronephrosis (ANH), which is graded by the trimester and the anterior-posterior diameter of the renal pelvis (Table 555.2); most are mild. Table 555.3 notes the eventual etiology. Risk stratification for prenatal (Fig. 555.1) and postnatal (Fig. 555.2) urinary tract dilation helps plan for further evaluation and treatment.

Table 555.2

Definition of Antenatal Hydronephrosis by Anterior-Posterior Diameter

DEGREE OF ANTENATAL HYDRONEPHROSIS	SECOND TRIMESTER	THIRD TRIMESTER
Mild	4 to < 7 mm	7 to < 9 mm
Moderate	7 to ≤ 10 mm	9 to ≤ 15 mm
Severe	>10 mm	>15 mm

From Nguyen HT, Herndon CDA, Cooper C, et al: The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 6:212-231, 2010, Table 2, p. 215.

Table 555.3

The Etiology of Antenatal Hydronephrosis

ETIOLOGY	INCIDENCE
Transient hydronephrosis	41–88%
Ureteropelvic junction obstruction	10–30%
Vesicoureteral reflux	10–20%
Ureterovesical junction obstruction/megaureters	5–10%
Multicystic dysplastic kidney	4–6%
Posterior urethral valve/urethral atresia	1–2%
Ureterocele/ectopic ureter/duplex system	5–7%
Others: prune-belly syndrome, cystic kidney disease, congenital ureteric strictures, megalourethra	Uncommon

From Nguyen HT, Herndon CDA, Cooper C, et al: The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 6:212-231, 2010, Table 5, p. 217.

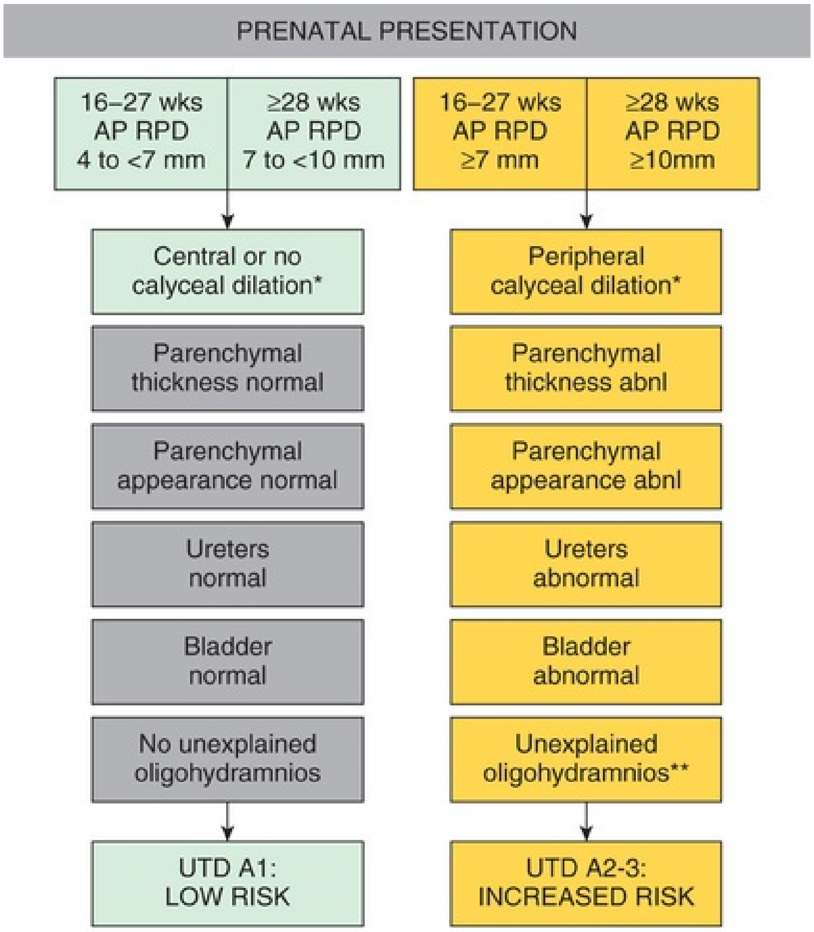
PRENATAL PRESENTATION
16–27 wks AP RPD 4 to <7 mm
≥28 wks AP RPD 7 to <10 mm
16–27 wks AP RPD ≥7 mm
≥28 wks AP RPD ≥10mm
Central or no calyceal dilation*
Parenchymal thickness normal
Parenchymal appearance normal
Ureters normal
Bladder normal
No unexplained oligohydramnios
UTD A1: LOW RISK
Peripheral calyceal dilation*
Parenchymal thickness abnl
Parenchymal appearance abnl
Ureters abnormal
Bladder abnormal
Unexplained oligohydramnios**
UTD A2-3: INCREASED RISK

*Central and peripheral calyceal dilation may be difficult to evaluate early in gestation

**Oligohydramnios is suspected to result from a GU cause

FIG. 555.1 Urinary tract dilation (UTD) risk stratification: prenatal presentation for UTD A1 (low risk) and UTD A2-3 (increased risk). Note: Classification is based on the presence of the most concerning feature. For example, a fetus with an ARPRD within the UTD A1 range but with peripheral calyceal dilation would be classified as UTD A2-3. (From Nguyen HT, Benson CB, Bromley B, et al: Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation [UTD classification system]. J Pediatr Urol 10:982-998, 2014, Fig. 3, p. 990.)

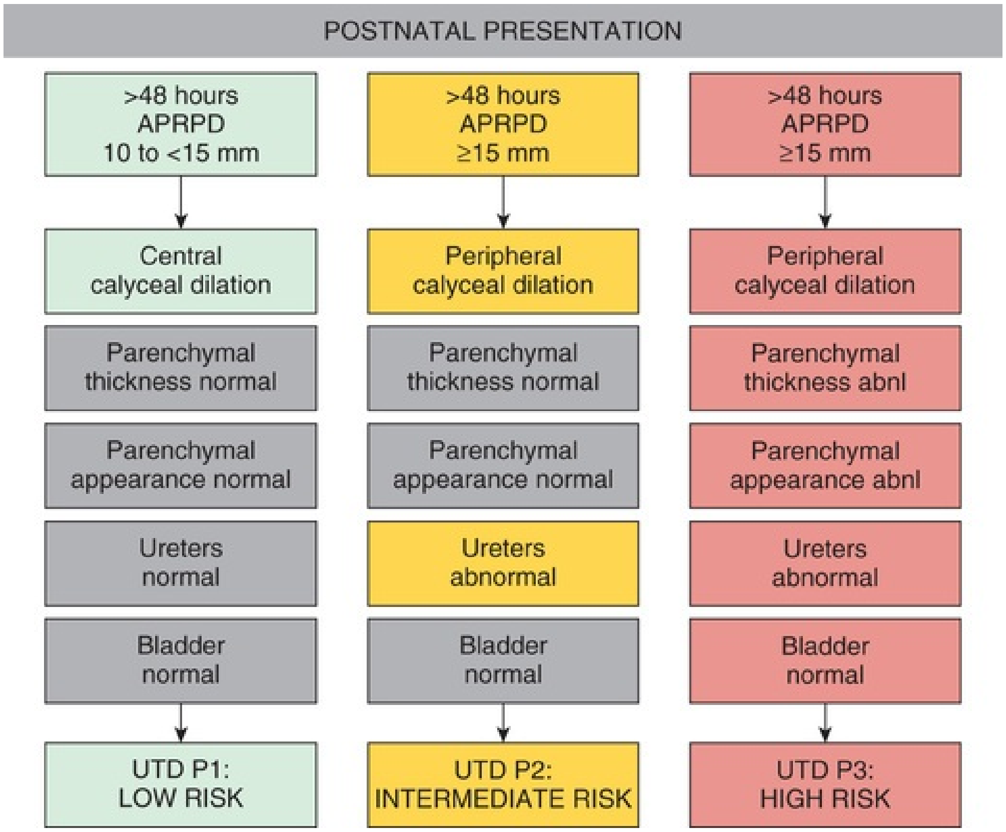
POSTNATAL PRESENTATION
>48 hours APRPD 10 to <15 mm
>48 hours APRPD ≥15 mm
>48 hours APRPD ≥15 mm
Central calyceal dilation
Peripheral calyceal dilation
Peripheral calyceal dilation
Parenchymal thickness normal
Parenchymal thickness normal
Parenchymal thickness abnl
Parenchymal appearance normal
Parenchymal appearance normal
Parenchymal appearance abnl
Ureters normal
Ureters abnormal
Ureters abnormal
Bladder normal
Bladder normal
Bladder normal
UTD P1: LOW RISK
UTD P2: INTERMEDIATE RISK
UTD P3: HIGH RISK

FIG. 555.2 Urinary tract dilation (UTD) risk stratification: postnatal presentation for UTD P1 (low risk), UTD P2 (intermediate risk), and UTD P3 (high risk). Note: Stratification is based on the most concerning US finding. For example, if the APRPD is in the UTD P1 range but there is peripheral calyceal dilation, the classification is UTD P2. Similarly, the presence of parenchymal abnormalities denotes a UTD P3 classification, regardless of APRPD measurement. (From Nguyen HT, Benson CB, Bromley B, et al: Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation [UTD classification system]. J Pediatr Urol 10:982-998, 2014, Fig. 6, p. 993.)

Clinical Manifestations

Obstruction of the urinary tract generally causes **hydronephrosis,** which typically is asymptomatic in its early phases. An obstructed kidney secondary to a **UPJ obstruction** or **ureterovesical junction obstruction** can manifest as a unilateral mass or cause upper abdominal or flank pain on the affected side. Pyelonephritis can occur because of urinary stasis. An upper urinary tract stone can occur, causing abdominal and flank pain and hematuria. With bladder outlet obstruction, the urinary stream may be weak; urinary tract infection (UTI; see

Chapter 553) is common. Many of these lesions are identified by antenatal US; an abnormality involving the genitourinary tract is suspected in as many as 1 in 50 fetuses (see Table 555.3).

Obstructive renal insufficiency can manifest itself by failure to thrive, vomiting, diarrhea, or other nonspecific signs and symptoms. In older children, **infravesical obstruction** can be associated with overflow urinary incontinence or a poor urine stream. **Acute ureteral obstruction** causes flank or abdominal pain; there may be nausea and vomiting. **Chronic ureteral obstruction** can be silent or can cause vague abdominal or typical flank pain with increased fluid intake.

Diagnosis

Urinary tract obstruction may be diagnosed prenatally by US, which typically shows hydronephrosis and occasionally a distended bladder. More complete evaluation, including imaging studies, should be undertaken in these children in the neonatal period.

In 2014, a multidisciplinary consensus conference that included pediatric urologists, pediatric nephrologists, pediatric radiologists, and maternal-fetal medicine specialists was convened to standardize the fetal evaluation and early postnatal management of babies with **antenatal hydronephrosis** (ANH). The US parameters include the anterior-posterior renal pelvic diameter (APRPD), **calyceal dilation,** whether the ANH involves the major and/or minor calyces, the parenchymal thickness and appearance, whether the ureter is normal or abnormal, and whether the bladder is normal or abnormal. Normal values for urinary tract dilation are the APRPD:

Antenatal	16-27 wk	<4 mm
	≥28 wk	<7 mm
Postnatal	(>48 hr)	<10 mm

Assuming there is no calyceal dilation, if the kidneys have a normal appearance and the ureter and bladder are normal, the study is considered normal.

The consensus group then categorized ANH into antenatal and postnatal risk groups. For antenatal ANH, there are two risk groups: low risk and high risk (see Fig. 555.1). For postnatal ANH, there are three risk groups: low risk, intermediate risk, and high risk (see Fig. 555.2). The panel recommended that all seven urinary tract parameters be described in a written report.

For antenatal presentation, if the APRPD is 4-7 mm at 16-27 wk or 7-10 mm at ≥ 28 wk and there is central or no calyceal dilation, the fetus is categorized as having urinary tract dilation **(UTD) A1** , **Low Risk** . In follow-up for UTD A1, the panel suggested one additional antenatal US at ≥ 32 wk, and after birth, a renal US at > 48 hr to 1 mo of age and a second renal US 6 mo later. Genetic screening is not indicated unless there are associated congenital malformations.

If the APRPD is ≥ 7 mm at 16-27 wk or ≥ 10 mm at ≥ 28 wk with any peripheral calyceal dilation or any other upper urinary tract abnormality, the fetus is classified as having **UTD A2-3,** or **Increased Risk** . The assigned risk is based on the most concerning feature. For UTD A2-3, the panel recommended a follow-up US in 4 to 6 wk, although with suspected posterior urethral valves (PUVs) or severe bilateral hydronephrosis, more frequent follow-up was recommended until delivery. Following delivery, a renal US after 48 hr but before 1 mo was suggested, again with more immediate evaluation if PUV is suspected or there is significant bilateral hydronephrosis. In addition, specialist consultation with pediatric urology or nephrology was recommended.

For postnatal presentation, at > 48 hr an APRPD < 10 mm is **Normal.** If the APRPD is 10-15 mm and there is central calyceal dilation but all other parameters are normal, the infant is classified as having **UTD P1, Low Risk** . Society of Fetal Urology (SFU) hydronephrosis grades 1 and 2 correspond to UTD P1. The panel recommends a follow-up renal US in 1 to 6 mo. A VCUG and antibiotic prophylaxis are optional, at the discretion of the clinician. A renal scan is not recommended.

If the postnatal APRPD is ≥ 15 mm and there is peripheral calyceal dilation and/or abnormal ureters, the infant is classified as having **UTD P2, Intermediate Risk** . SFU hydronephrosis grade 3 corresponds to UTD P2. The panel recommends a follow-up renal US in 1 to 3 mo. A VCUG, antibiotic prophylaxis, and a functional renal scan are optional, at the discretion of the clinician.

If the APRPD is ≥ 15 mm and there is peripheral calyceal dilation, abnormal parenchymal thickness, abnormal parenchymal appearance, abnormal ureters, and/or abnormal bladder, the infant is classified as having **UTD P3, High Risk** . SFU hydronephrosis grade 4 corresponds to UTD P3. The panel recommends a follow-up renal US in 1 mo. A VCUG and antibiotic prophylaxis are recommended. A functional renal scan is optional, at the discretion of the clinician (but is virtually always recommended).

Physical Findings

Urinary tract obstruction is often silent. In the newborn infant, a palpable abdominal mass most commonly is a hydronephrotic or multicystic dysplastic kidney. With PUVs, which constitutes an infravesical obstructive lesion in boys, a walnut-sized mass representing the bladder is palpable just above the pubic symphysis. A **patent draining urachus** also can suggest urethral obstruction. **Urinary ascites** in the newborn usually is caused by renal or bladder urinary extravasation secondary to PUVs. Infection and sepsis may be the first indications of an obstructive lesion of the urinary tract. The combination of infection and obstruction poses a serious threat to infants and children and generally requires parenteral administration of antibiotics and drainage of the obstructed kidney. Renal US should be performed in all children during the acute stage of an initial febrile UTI.

Imaging Studies

Renal Ultrasound

Hydronephrosis is the most common characteristic of obstruction (Fig. 555.3). Upper urinary tract dilation is not diagnostic of obstruction and often persists after surgical correction of a significant obstructive lesion. Dilation can result from vesicoureteral reflux, or it may be a manifestation of abnormal development of the urinary tract, even when there is no obstruction. Renal length, degree of caliectasis and parenchymal thickness, and presence or absence of ureteral dilation should be assessed. In addition to the UTD system, most pediatric urologists also grade the severity of hydronephrosis from 1-4 using the SFU grading scale (Table 555.4). The clinician should ascertain that the contralateral kidney is normal, and the bladder should be imaged to see whether the bladder wall is thickened, the lower ureter is dilated, and bladder emptying is complete. In acute or intermittent obstruction, the dilation of the collecting system may be minimal and US may be misleading.

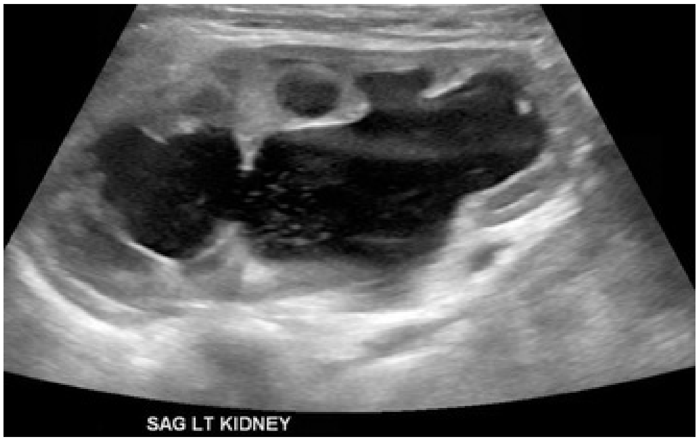

FIG. 555.3 US image of the left kidney with marked pelvic and calyceal dilation (grade 4 hydronephrosis) in a newborn with ureteropelvic junction obstruction.

Table 555.4

Society for Fetal Urology Grading System for Hydronephrosis

GRADE OF HYDRONEPHROSIS	RENAL IMAGE	
	CENTRAL RENAL COMPLEX	RENAL PARENCHYMAL THICKNESS
0	Intact	Normal
1	Slight splitting	Normal
2	Evident splitting, complex confined within renal border	Normal
3	Wide splitting, pelvis dilated outside renal border, calyces uniformly dilated	Normal
4	Further dilation of pelvis and calyces (calyces may appear convex)	Thin

After Maizels M, Mitchell B, Kass E, et al: Outcome of nonspecific hydronephrosis in the infant: a report from the registry of the Society for Fetal Urology, J Urol 152:2324-2327, 1994.

Voiding Cystourethrogram

In neonates and infants with congenital grade 3 or 4 hydronephrosis and in any child with ureteral dilation, a **contrast voiding cystourethrogram (VCUG)** should be obtained, because the dilation is secondary to vesicoureteral reflux in 15% of cases. In males, the VCUG also is performed to rule out urethral obstruction, particularly in cases of suspected PUVs. In older children, the urinary flow rate can be measured noninvasively with a urinary flowmeter; decreased flow with a normal bladder contraction suggests infravesical obstruction (e.g., PUVs, urethral stricture). When the urethra cannot be catheterized to obtain a VCUG, the clinician should suspect a urethral stricture or an obstructive urethral lesion. Retrograde urethrography with contrast medium injected into the urethral meatus helps delineate the anatomy of the urethral obstruction.

Radioisotope Studies

Renal scintigraphy is used to assess renal anatomy and function. The two most commonly used radiopharmaceuticals are mercaptoacetyl triglycine (MAG-3) and technetium-99m-labeled dimercaptosuccinic acid (DMSA). MAG-3, which is excreted by renal tubular secretion, is used to assess differential renal function, and when furosemide is administered, drainage also can be measured. DMSA is a renal cortical imaging agent and is used to assess differential renal function and to demonstrate whether renal scarring is present. It is used infrequently in children with obstructive uropathy.

In a MAG-3 diuretic renogram, a small dose of technetium-labeled MAG-3 is injected intravenously (Figs. 555.4 and 555.5). During the first 2-3 min, renal parenchymal uptake is analyzed and compared, allowing computation of differential renal function.

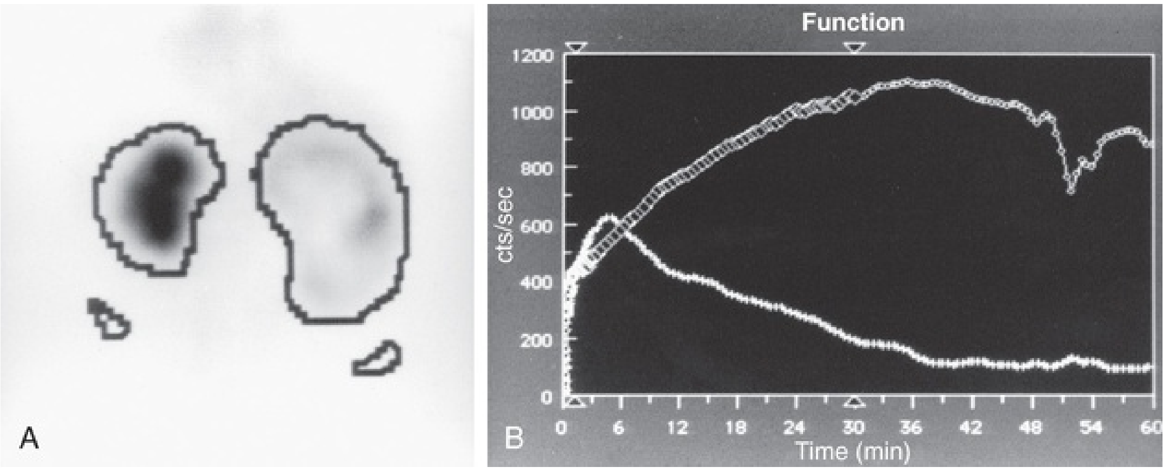

FIG. 555.4 MAG-3 diuretic renogram of a 6 wk old patient with severe right hydronephrosis. The right kidney is on the *right* side of the image. **A,** Differential renal function: left kidney 70%, right kidney 30%. **B,** After administration of furosemide, drainage from the left kidney was normal and

drainage from the right kidney was slow, consistent with right UPJ obstruction. Pyeloplasty was performed on the right kidney.

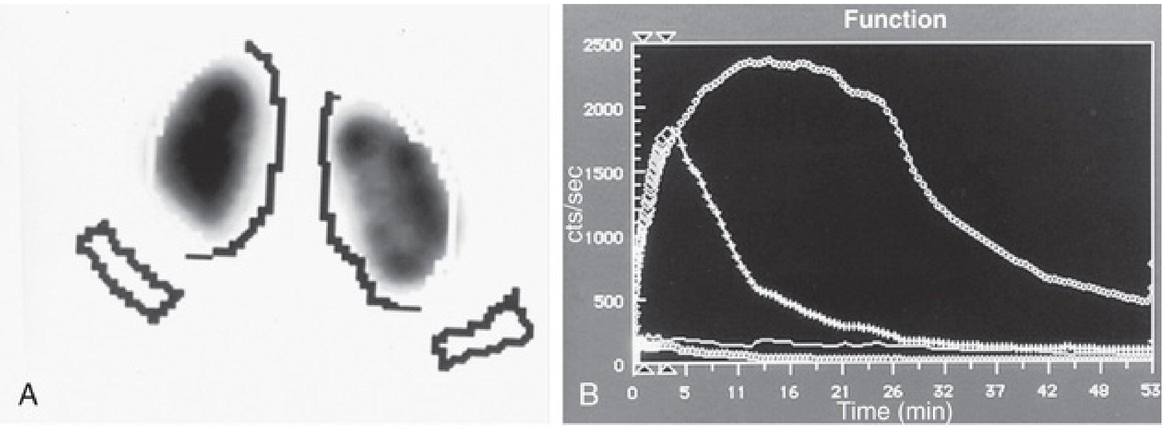

FIG. 555.5 **A,** MAG-3 diuretic renogram at 14 mo of age shows equal function in the two kidneys. **B,** Prompt drainage after the administration of furosemide.

Subsequently, excretion is evaluated. After 20 min, furosemide 1 mg/kg is injected intravenously, and the rapidity and pattern of drainage from the kidneys to the bladder are analyzed. If no obstruction is present, half of the radionuclide should be cleared from the renal pelvis within 10-15 min, termed the half-time ($t_{1/2}$). If there is significant upper tract obstruction, the $t_{1/2}$ usually is longer than 20 min. A $t_{1/2}$ of 15-20 min is indeterminate. An elevated $t_{1/2}$ is suggestive but not diagnostic of obstruction. The images generated usually provide an accurate assessment of the site of obstruction. Numerous variables affect the outcome of the diuretic renogram. Newborn kidneys are functionally immature, and, in the first mo of life, normal kidneys might not demonstrate normal drainage after diuretic administration. Patient dehydration prolongs parenchymal transit and can blunt the diuretic response. Giving an insufficient dose of furosemide can result in slow drainage. If vesicoureteral reflux is present, continuous bladder drainage is mandatory to prevent the radionuclide from refluxing from the bladder into the dilated upper tract, which would prolong the washout phase.

Magnetic Resonance Urography

Magnetic resonance (MR) urography also is used to evaluate suspected upper urinary tract pathology. The child is hydrated and given intravenous furosemide.

Gadolinium-diethylene tetrapentaacetic acid is injected, and routine T1-weighted and fat-suppressed fast spin-echo T2-weighted imaging is performed through the kidneys, ureters, and bladder. This study provides superb images of the pathology, and methodology permits assessment of differential renal function and drainage (Fig. 555.6). There is no radiation exposure; however, young children need sedation or anesthesia. It is used primarily when renal US and radionuclide imaging fail to delineate complex pathology.

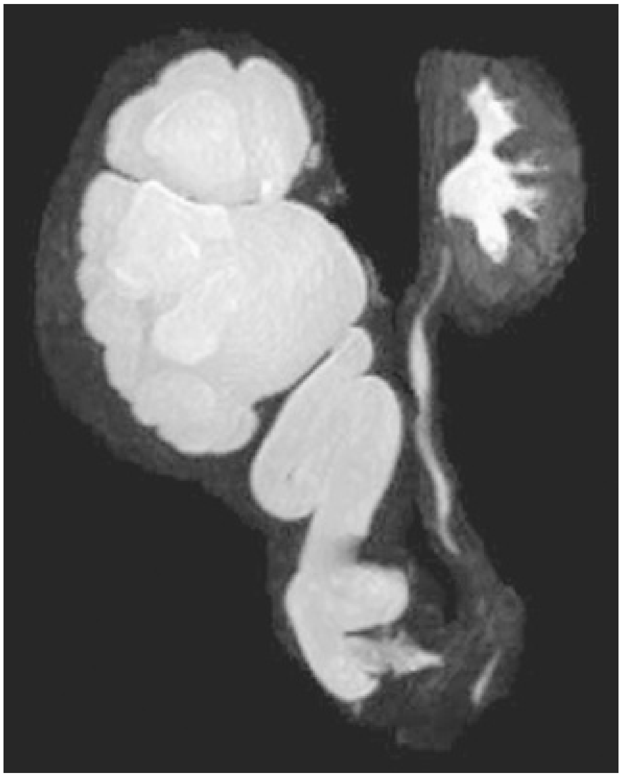

FIG. 555.6 MR urogram in boy with distal ureterovesical obstruction.

Computed Tomography

In children with a suspected ureteral calculus (see Chapter 562), noncontrast low-dose spiral CT of the abdomen and pelvis is a standard method of demonstrating whether a calculus is present, its location, and whether there is significant proximal hydronephrosis. This study may be ordered when a renal/bladder US is inconclusive. The disadvantage of CT is the significant radiation exposure, and it should be used only when the results will direct management decisions.

Ancillary Studies

In unusual cases, an **antegrade pyelogram** (insertion of a percutaneous nephrostomy tube and injection of contrast agent) can be performed to assess the anatomy of the upper urinary tract. This procedure usually requires general anesthesia. In addition, an **antegrade pressure-perfusion flow study** (Whitaker test) may be performed, in which fluid is infused at a measured rate, usually 10 mL/min. The pressures in the renal pelvis and the bladder are monitored during this infusion, and pressure differences exceeding 20 cm H_2O suggest obstruction. In other cases, cystoscopy with retrograde pyelography provides excellent images of the upper urinary tract (Fig. 555.7).

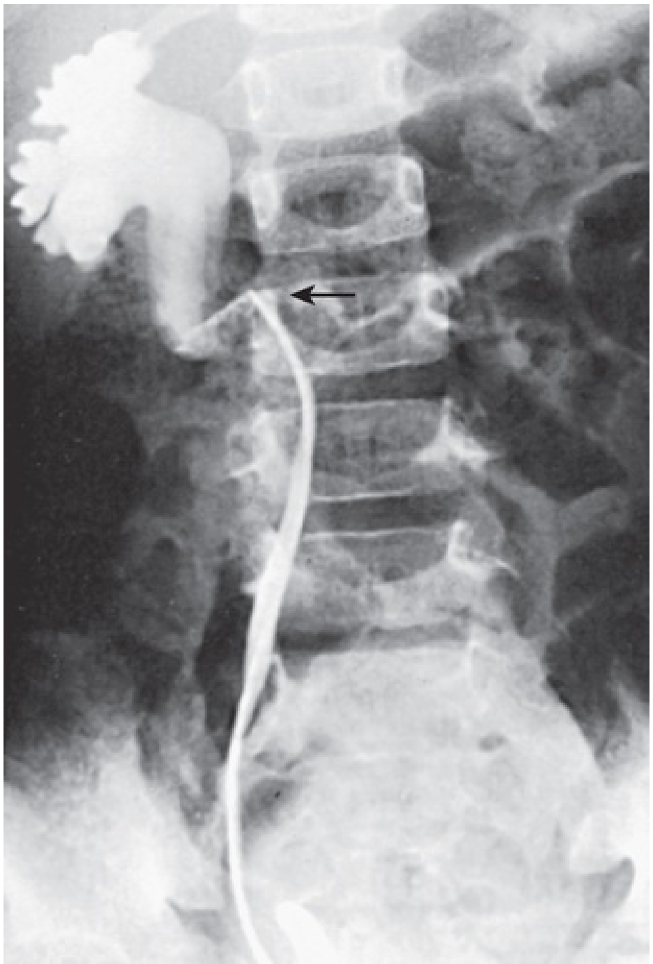

FIG. 555.7 Retrograde pyelogram showing medial deviation of a dilated

upper ureter to the level of the 3rd lumbar vertebra *(arrow),* characteristic of a retrocaval ureter.

Specific Types of Urinary Tract Obstruction and Their Treatment

Hydrocalycosis

The term *hydrocalycosis* refers to a localized dilation of the calyx caused by obstruction of its infundibulum, termed **infundibular stenosis.** This condition can be developmental in origin or secondary to inflammatory processes, such as UTI. It usually is discovered during evaluation for pain or UTI. The diagnosis of infundibular stenosis is usually established by sonograph and CT scan or MR urography.

Ureteropelvic Junction Obstruction

UPJ obstruction is the most common obstructive lesion in childhood and usually is caused by intrinsic stenosis (see Figs. 555.3 to 555.5). An accessory artery to the lower pole of the kidney also can cause extrinsic obstruction. The typical appearance on US is grade 3 or 4 hydronephrosis without a dilated ureter. UPJ obstruction most commonly manifests on antenatal sonography revealing fetal hydronephrosis; as a palpable renal mass in a newborn or infant; as abdominal, flank, or back pain; as a febrile UTI; or as hematuria after minimal trauma. Approximately 60% of cases occur on the left side; the male:female ratio is 2 : 1. *UPJ obstruction is bilateral in only 10% of cases* . In kidneys with UPJ obstruction, renal function may be significantly impaired from pressure atrophy, but approximately half of affected kidneys have relatively normal glomerular function. The anomaly is corrected by performing a pyeloplasty, in which the stenotic segment is excised, and the normal ureter and renal pelvis are reattached. Success rates are 91–98%. Pyeloplasty can be performed using laparoscopic techniques, often robotic-assisted using the da Vinci robot.

Lesser degrees of UPJ narrowing might cause mild hydronephrosis, which usually is nonobstructive, and typically these kidneys function normally. The spectrum of UPJ abnormalities has been referred to as **anomalous UPJ** . Another cause of mild hydronephrosis is fetal folds of the upper ureter, which also are nonobstructive.

The diagnosis can be difficult to establish in an asymptomatic infant in whom dilation of the renal pelvis is found incidentally in a prenatal US. After birth, the sonographic study is repeated to confirm the prenatal finding. A VCUG is necessary because 10–15% of patients have ipsilateral vesicoureteral reflux. Because neonatal oliguria can cause temporary decompression of a dilated renal pelvis, it is ideal to perform the first postnatal US after the 3rd day of life. Delaying the US may be impractical. If no dilation is found on the initial US, a repeat study should be performed at 1 mo of age. If the kidney shows grade 1 or 2 hydronephrosis and the renal parenchyma appears normal, a period of observation usually is appropriate, with sequential renal US studies to monitor the severity of hydronephrosis, and the hydronephrosis usually disappears. Antibiotic prophylaxis is *not* indicated for children with mild hydronephrosis. If the hydronephrosis is grade 3 or 4, spontaneous resolution is less likely, and obstruction is more likely to be present, particularly if the renal pelvic diameter is 3 cm. A diuretic renogram with MAG-3 is performed at 4-6 wk of age. If there is poor upper tract drainage or the differential renal function is poor, pyeloplasty is recommended. After pyeloplasty the differential renal function often improves, and improved drainage with furosemide stimulation is expected.

If the differential function on renography is normal and drainage is satisfactory, the infant can be followed with serial US studies, even with grade 4 hydronephrosis. If the hydronephrosis remains severe with no improvement, a repeat diuretic renogram after 6-12 mo can help in the decision between continued observation and surgical repair. Prompt surgical repair is indicated in infants with an abdominal mass, bilateral severe hydronephrosis, a solitary kidney, or diminished function in the involved kidney. In unusual cases in which the differential renal function is < 10% but the kidney has some function, insertion of a percutaneous nephrostomy tube allows drainage of the hydronephrotic kidney for a few weeks to allow reassessment of renal function. In older children who present with symptoms, the diagnosis of UPJ obstruction usually is established by US and diuretic renography.

The following entities should be considered in the differential diagnosis: megacalycosis, a congenital nonobstructive dilation of the calyces without pelvic or ureteric dilation; vesicoureteral reflux with marked dilation and kinking of the ureter; midureteral or distal ureteral obstruction when the ureter is not well visualized on the urogram; and retrocaval ureter.

Midureteral Obstruction

Congenital ureteral stenosis or a ureteral valve in the midureter is rare. It is corrected by excision of the strictured segment and reanastomosis of the normal upper and lower ureteral segments. A **retrocaval ureter** is an anomaly in which the upper right ureter travels posterior to the inferior vena cava. In this anomaly, the vena cava can cause extrinsic compression and obstruction. A retrograde pyelogram or MR urogram shows the right ureter to be medially deviated at the level of the 3rd lumbar vertebra (see Fig. 555.7). Surgical treatment consists of transection of the upper ureter, moving it anterior to the vena cava, and reanastomosing the upper and lower segments. Repair is necessary only when obstruction is present. Retroperitoneal tumors, fibrosis caused by surgical procedures, inflammatory processes (as in chronic granulomatous disease), and radiation therapy can cause acquired midureteral obstruction.

Ectopic Ureter

A ureter that drains outside the bladder is referred to as an ectopic ureter. This anomaly is three times as common in females as in males and usually is detected prenatally. The ectopic ureter typically drains the upper pole of a duplex collecting system (two ureters).

In females, approximately 35% of these ureters enter the urethra at the bladder neck, 35% enter the urethrovaginal septum, 25% enter the vagina, and a few drain into the cervix, uterus, Gartner duct, or a urethral diverticulum. Often the terminal aspect of the ureter is narrowed, causing hydroureteronephrosis. With the exception of the ectopic ureter entering the bladder neck, in females an ectopic ureter causes continuous urinary incontinence from the affected renal moiety. UTI is common because of urinary stasis.

In males, ectopic ureters enter the posterior urethra (above the external sphincter) in 47%, the prostatic utricle in 10%, the seminal vesicle in 33%, the ejaculatory duct in 5%, and the vas deferens in 5%. Consequently, in males, an ectopic ureter does not cause incontinence, and most patients present with a UTI or epididymitis.

Evaluation includes a renal US, VCUG, and renal scan, which demonstrates whether the affected segment has significant function. The US shows the affected hydronephrotic kidney or dilated upper pole and ureter down to the bladder (Fig. 555.8). If the ectopic ureter drains into the bladder neck (female), a VCUG usually shows reflux into the ureter. Otherwise, there is no reflux into the ectopic ureter, but there may be reflux into the ipsilateral lower pole ureter or contralateral collecting system.

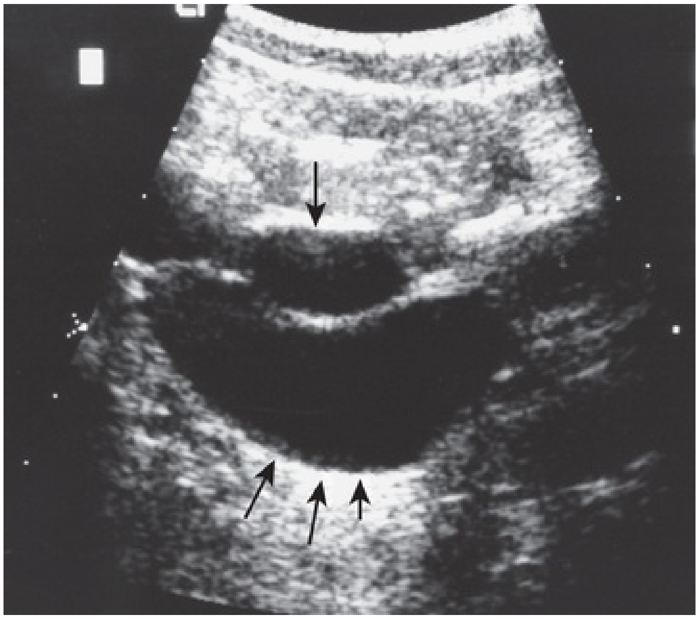

FIG. 555.8 Ultrasonographic image of the right dilated ureter *(bottom arrows)* extending behind and caudal to a nearly empty bladder *(top arrow)* in a girl with urinary incontinence and ectopic ureter draining into the vagina.

Treatment depends on the status of the renal unit drained by the ectopic ureter. If there is satisfactory function, ureteral reimplantation into the bladder or ureteroureterostomy (anastomosing the ectopic upper pole ureter into the normally inserting lower pole ureter) is indicated. If function is poor, partial or total nephrectomy is indicated. In many centers this procedure is done laparoscopically and often with robotic assistance using the da Vinci robot.

Ureterocele

A ureterocele is a cystic dilation of the terminal ureter and is obstructive because of a pinpoint ureteral orifice. Ureteroceles are much more common in females than in males. Affected children usually are discovered by prenatal US, but some present with a febrile UTI. Ureteroceles may be ectopic, in which case the cystic swelling extends through the bladder neck into the urethra, or orthotopic, in which case the ureterocele is entirely within the bladder. Both orthotopic and ectopic ureteroceles can be bilateral.

In females, ureteroceles nearly always are associated with ureteral duplication (Fig. 555.9), whereas in 50% of affected boys there is only one ureter. When associated with a duplication anomaly, the ureterocele drains the upper renal moiety, which commonly functions poorly or is dysplastic because of congenital obstruction. The lower pole ureter drains into the bladder superior and lateral to the upper pole ureter and may reflux.

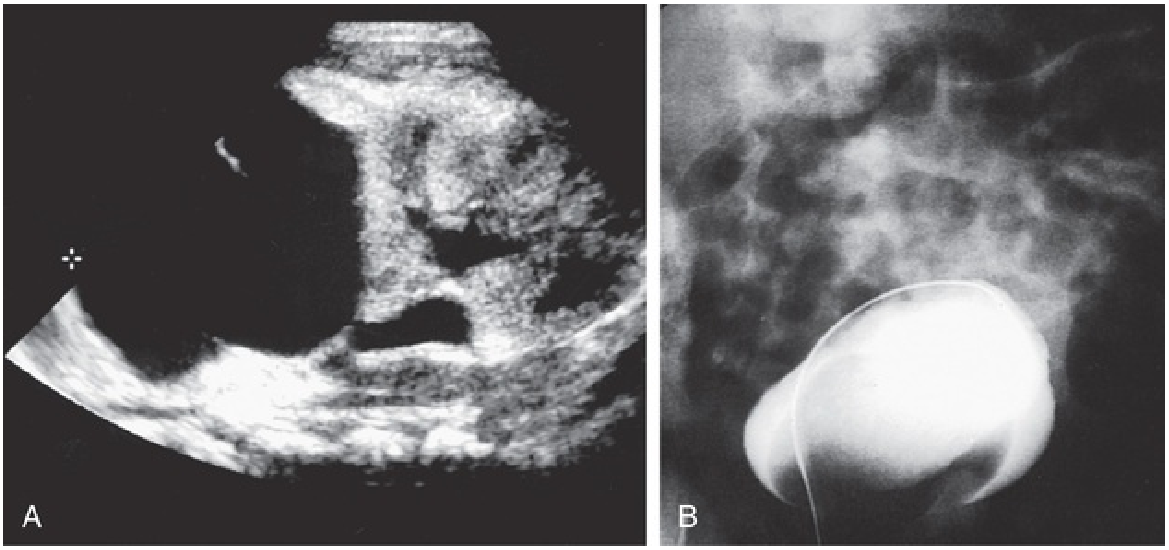

FIG. 555.9 **A,** Infant with ectopic ureterocele. US of the left kidney shows massive dilation of the upper pole and a normal lower pole. **B,** VCUG shows large ureterocele, draining the left upper pole, in the bladder. No reflux is present.

An **ectopic ureterocele** extends submucosally through the bladder neck into the urethra. Rarely, large ectopic ureteroceles can cause bladder outlet obstruction and retention of urine with bilateral hydronephrosis. In females, the ureterocele can prolapse from the urethral meatus. US is effective in demonstrating the ureterocele and whether the associated obstructed system is duplicated or single. VCUG usually shows a filling defect in the bladder, sometimes large, corresponding to the ureterocele, and it often shows reflux into the adjacent lower pole collecting system with typical findings of a “drooping lily” appearance to the kidney. Nuclear renal scintigraphy is most accurate in demonstrating whether the affected renal moiety has significant function.

Treatment of ectopic ureteroceles varies among different medical centers and depends on whether the upper pole functions on renal scan and whether there is reflux into the lower pole ureter. If there is nonfunction of the upper pole of the kidney and there is no reflux, treatment usually involves laparoscopic, robotic, or open excision of the obstructed upper pole and most of the associated ureter. If there is function in the upper pole or significant reflux into the lower pole ureter, or if the patient is septic from infection of the hydronephrotic kidney, then transurethral incision with cautery is appropriate initial therapy to decompress the ureterocele. Reflux into the incised ureterocele is common, and subsequent excision of the ureterocele and ureteral reimplantation usually is necessary. An alternative method is to perform an upper-to-lower ureteroureterostomy, allowing the obstructed upper pole ureter to drain through the normal lower ureter; this procedure often is performed with minimally invasive laparoscopic (robotic) technique or through a small incision.

Orthotopic ureteroceles are associated with duplicated or single collecting systems, and the orifice is in the expected location in the bladder (Fig. 555.10). These anomalies usually are discovered during an investigation for prenatal hydronephrosis or a UTI. US is sensitive for detecting the ureterocele in the bladder and hydroureteronephrosis. Transurethral incision of the ureterocele effectively relieves the obstruction, but it can result in vesicoureteral reflux, necessitating ureteral reimplantation later. Some prefer open excision of the ureterocele and reimplantation as the initial form of treatment. Small, simple ureteroceles discovered incidentally without upper tract dilation generally do not require treatment.

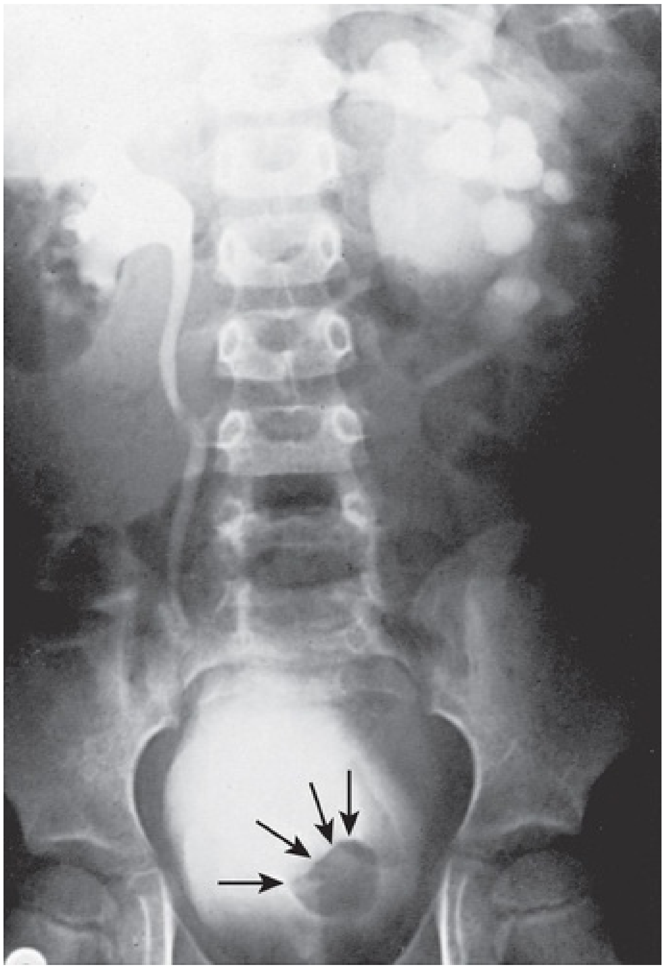

FIG. 555.10 Simple intravesical ureterocele. The excretory urogram shows left hydronephrosis and a round filling defect on the left side of the bladder corresponding to a simple ureterocele causing left ureteral obstruction. This lesion was treated by transurethral incision and drainage of the ureterocele.

Megaureter

Table 555.5 presents a classification of megaureters (dilated ureter). Numerous disorders can cause ureteral dilation, and many are nonobstructive.

Table 555.5

Classification of Megaureter

REFLUXING		OBSTRUCTED		NONREFLUXING AND NONOBSTRUCTED	
PRIMARY	SECONDARY	PRIMARY	SECONDARY	PRIMARY	SECONDARY

Primary reflux	Neuropathic bladder	Intrinsic (primary obstructed megaureter)	Neuropathic bladder	Nonrefluxing, nonobstructive	Diabetes insipidus
Megacystic-megaureter syndrome	Hinman syndrome	Ureteral valve	Hinman syndrome		Infection
Ectopic ureter	Posterior urethral valves	Ectopic ureter	Posterior urethral valves		Persistent after relief of obstruction
Prune-belly syndrome	Bladder diverticulum	Ectopic ureterocele	Ureteral calculus		
	Postoperative		Extrinsic		
			Postoperative		

Megaureters usually are discovered during antenatal sonography, postnatal UTI, hematuria, or abdominal pain. A careful history, physical examination, and VCUG identify causes of secondary megaureters and refluxing megaureters, as well as the prune-belly syndrome. Primary obstructed megaureters and nonobstructed megaureters probably represent varying degrees of severity of the same anomaly.

The **primary obstructed nonrefluxing megaureter** results from abnormal development of the distal ureter, with collagenous tissue replacing the muscle layer. Normal ureteral peristalsis is disrupted, and the proximal ureter widens. In most cases there is not a true stricture. On IVP or an MR urogram, the distal ureter is more dilated in its distal segment and tapers abruptly at or above the junction of the bladder (Fig. 555.11). The lesion may be unilateral or bilateral. Significant hydroureteronephrosis suggests obstruction. Megaureter predisposes to UTI, urinary stones, hematuria, and flank pain because of urinary stasis. In most cases, diuretic renography and sequential sonographic studies can reliably differentiate obstructed from nonobstructed megaureters. In most nonobstructed megaureters, the hydroureteronephrosis diminishes gradually (Fig. 555.12). Truly obstructed megaureters require surgical treatment, with excision of the narrowed segment, ureteral tapering, and reimplantation of the ureter. The results of surgical reconstruction usually are good, but the prognosis depends on preexisting renal function and whether complications develop.

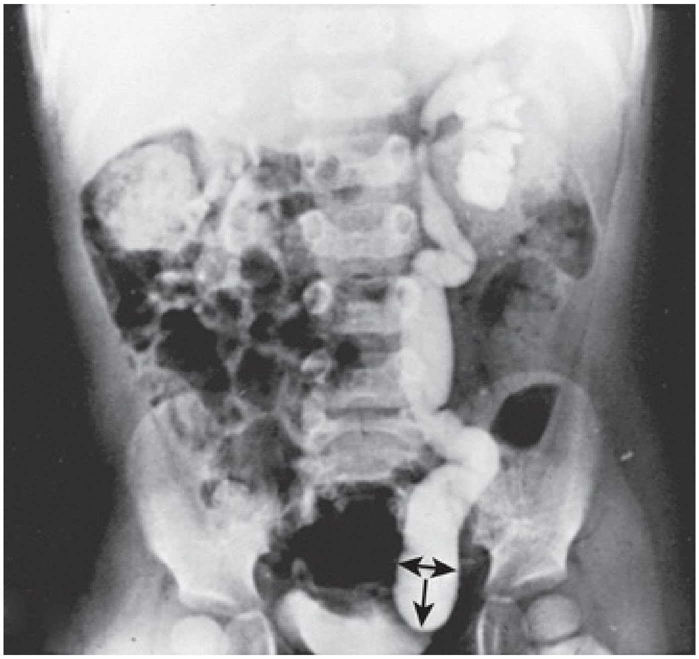

FIG. 555.11 Obstructed nonrefluxing megaureter. Excretory urogram in a girl with a history of a febrile UTI. The right side is normal. The left side reveals hydroureteronephrosis with predominant dilation of the distal ureter. Note the characteristic appearance of the distal ureter. There was no vesicoureteral reflux. The diagnosis of obstruction was confirmed by diuretic renography.

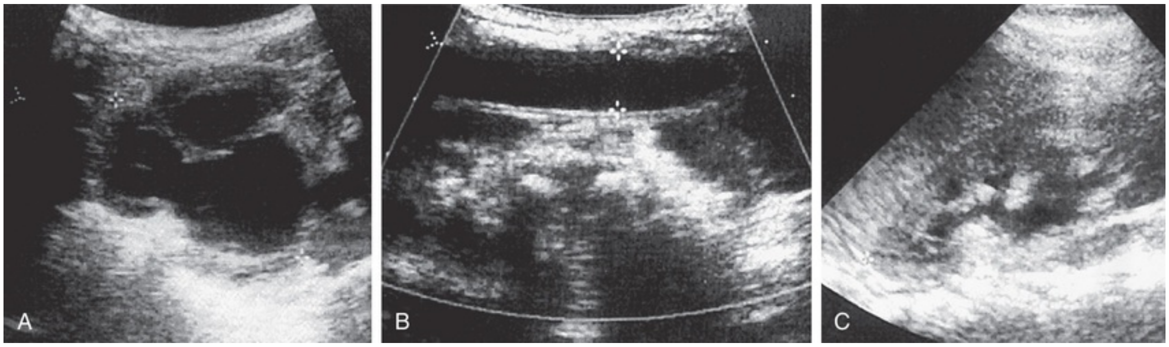

FIG. 555.12 Neonate with primary nonrefluxing megaureter. **A,** Renal US shows grade 4 hydronephrosis. **B,** Dilated ureter. Renal scan showed equal function with the contralateral kidney and satisfactory drainage with diuresis stimulation. **C,** Follow-up US at 10 mo shows complete resolution of hydronephrosis.

If differential renal function is normal (>45%) and the child is asymptomatic, it is safe to manage the patient with observation with serial US and periodic diuretic renography to monitor renal function and drainage. In children with grade 4 hydroureteronephrosis, prophylactic antimicrobial therapy should be prescribed, as these children are prone to upper UTI. If renal function deteriorates, upper urinary tract drainage slows, or UTI occurs, ureteral reimplantation is recommended. Approximately 25% of children with a nonrefluxing megaureter undergo ureteral reimplantation.

Prune-Belly Syndrome

Prune-belly syndrome, also called **triad syndrome** or **Eagle-Barrett syndrome,** occurs in approximately 1 in 40,000 births; 95% of affected children are male. The characteristic association of deficient abdominal muscles, undescended testes, and urinary tract abnormalities probably results from severe urethral obstruction in fetal life (Fig. 555.13). Oligohydramnios and pulmonary hypoplasia are common complications in the perinatal period. Many affected infants are stillborn. Urinary tract abnormalities include massive dilation of the ureters and upper tracts and a very large bladder, with a patent urachus or a urachal diverticulum. Most patients have vesicoureteral reflux. The prostatic urethra usually is dilated, and the prostate is hypoplastic. The anterior urethra may be dilated, resulting in a megalourethra. Rarely, there is urethral stenosis or atresia. The kidneys usually show various degrees of dysplasia, and the testes usually are intraabdominal. Malrotation of the bowel often is present. Cardiac abnormalities occur in 10% of cases; >50% have abnormalities of the musculoskeletal system, including limb abnormalities and scoliosis. In females, anomalies of the urethra, uterus, and vagina usually are present.

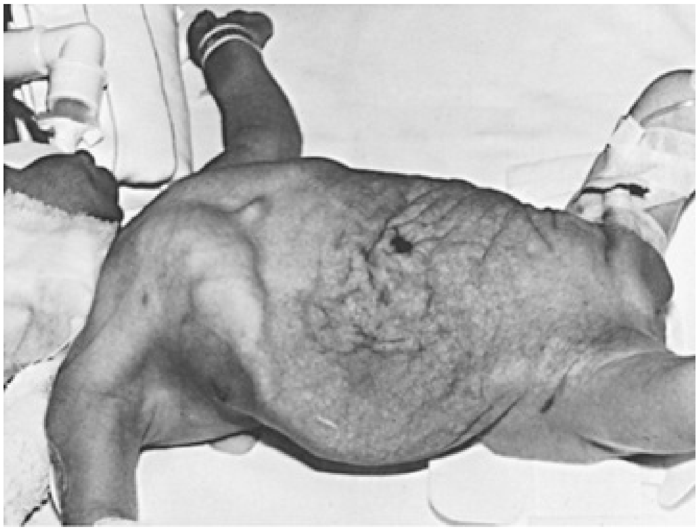

FIG. 555.13 Photograph of a 1,600-g newborn with the prune-belly syndrome. Note the lack of tonicity of the abdominal wall and the wrinkled appearance of the skin.

Many neonates with prune-belly syndrome have difficulty with effective bladder emptying because the bladder musculature is poorly developed, and the urethra may be narrowed. When no obstruction is present, the goal of treatment is the prevention of UTI with antibiotic prophylaxis. When obstruction of the ureters or urethra is demonstrated, temporary drainage procedures, such as a vesicostomy, can help to preserve renal function until the child is old enough for surgical reconstruction. Some children with prune-belly syndrome have been found to have classic or atypical PUVs. UTIs occur often and should be treated promptly. Correction of the undescended testes by orchidopexy can be difficult in these children because the testes are located high in the abdomen and surgery is best accomplished in the first 6 mo of life. Reconstruction of the abdominal wall offers cosmetic and functional benefits.

The prognosis ultimately depends on the degree of pulmonary hypoplasia and renal dysplasia. One third of children with prune-belly syndrome are stillborn or die in the first few mo of life because of pulmonary hypoplasia. As many as 30% of the long-term survivors develop end-stage renal disease from dysplasia or complications of infection or reflux and eventually require renal transplantation. Renal transplantation in these children offers good results.

Bladder Neck Obstruction

Bladder neck obstruction usually is secondary to ectopic ureterocele, bladder calculi, or a tumor of the prostate (rhabdomyosarcoma). The manifestations include difficulty voiding, urinary retention, UTI, and bladder distention with overflow incontinence. Apparent bladder neck obstruction is common in cases of PUVs, but it seldom has any functional significance. Primary bladder neck obstruction is extremely rare.

Posterior Urethral Valves

The most common cause of severe obstructive uropathy in children is PUVs, affecting 1 in 8,000 males. The urethral valves are tissue leaflets fanning distally from the prostatic urethra to the external urinary sphincter. A slit-like opening usually separates the leaflets. Valves are of unclear embryologic origin and cause varying degrees of obstruction. Approximately 30% of patients experience end-stage renal disease or chronic renal insufficiency. The prostatic urethra dilates, and the bladder muscle undergoes hypertrophy. Vesicoureteral reflux occurs in 50% of patients, and distal ureteral obstruction can result from a chronically distended bladder or bladder muscle hypertrophy. The renal changes range from mild hydronephrosis to severe renal dysplasia; their severity probably depends on the severity of the obstruction and its time of onset during fetal development. As in other cases of obstruction or renal dysplasia, there may be oligohydramnios and pulmonary hypoplasia.

Affected males with PUVs often are discovered prenatally when maternal US reveals bilateral hydronephrosis, a distended bladder, and, if the obstruction is severe, oligohydramnios. Prenatal bladder decompression by percutaneous vesicoamniotic shunt or open fetal surgery has been reported. Experimental and clinical evidence of the possible benefits of fetal intervention is lacking, and few affected fetuses are candidates. Prenatally diagnosed PUVs, particularly when discovered in the second trimester, carry a poorer prognosis than those detected in the third trimester following a normal second-trimester fetal US. In the male neonate, PUVs are suspected when there is a palpably distended bladder and the urinary stream is weak. If the obstruction is severe and goes unrecognized during the neonatal period, infants can present later in life with failure to thrive because of uremia or sepsis caused by infection in the obstructed urinary tract. With lesser degrees of obstruction, children present later in life with difficulty in achieving diurnal urinary continence or with UTI. The diagnosis is established with a VCUG (Fig. 555.14) or by perineal US.

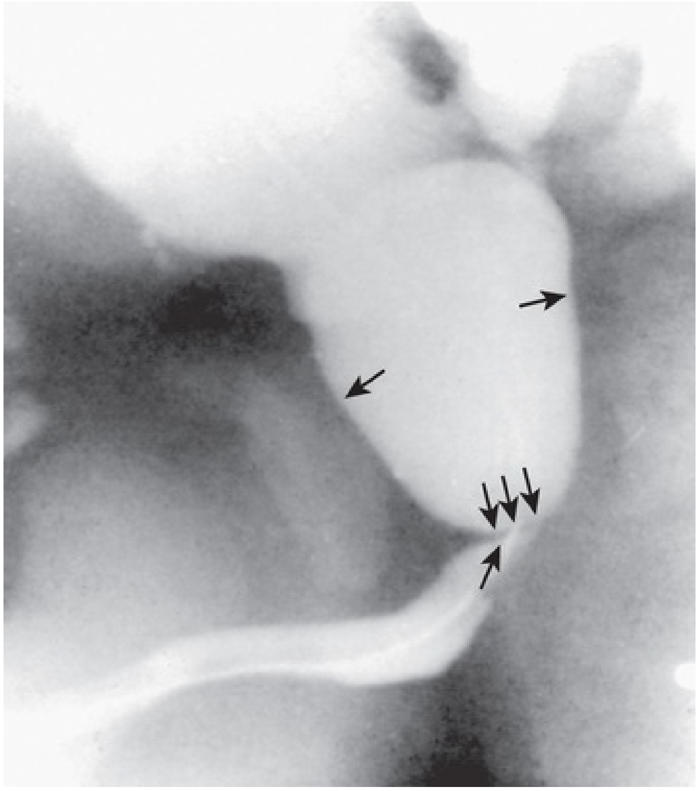

FIG. 555.14 VCUG in an infant with PUVs. Note the dilation of the prostatic urethra and the transverse linear filling defect corresponding to the valves.

After the diagnosis is established, renal function and the anatomy of the upper urinary tract should be carefully evaluated. In the healthy neonate, a small polyethylene feeding tube (No. 5 or No. 8 French) is inserted in the bladder and left for several days. Passing the feeding tube may be difficult because the tip of the tube can coil in the prostatic urethra. A sign of this problem is that urine drains around the catheter rather than through it. A Foley (balloon) catheter *should not be used* , because the balloon can cause severe bladder spasm, which can produce severe ureteral obstruction.

If the serum creatinine level remains normal or returns to normal, treatment consists of transurethral ablation of the valve leaflets, which is performed endoscopically under general anesthesia. If the urethra is too small for transurethral ablation, temporary vesicostomy is preferred, in which the dome of the bladder is exteriorized on the lower abdominal wall. When the child is older, the valves may be ablated and the vesicostomy closed.

If the serum creatinine level remains high or increases despite bladder drainage by a small catheter, secondary ureteral obstruction, irreversible renal damage, or renal dysplasia should be suspected. In such cases, a vesicostomy should be considered. Cutaneous pyelostomy rarely affords better drainage when compared with cutaneous vesicostomy, and the latter also allows continued bladder growth and gradual improvement in bladder wall compliance.

In the septic and uremic infant, lifesaving measures must include prompt correction of the electrolyte imbalance and control of the infection by appropriate antibiotics. Drainage of the upper tracts by percutaneous nephrostomy and hemodialysis may be necessary. After the patient's condition becomes stable, evaluation and treatment may be undertaken. PUVs are diagnosed in some older males because of a poor stream, diurnal incontinence, or a UTI; these males generally are treated by primary valve ablation.

Favorable prognostic factors include a normal prenatal US between 18 and 24 wk of gestation, a serum creatinine level < 0.8-1.0 mg/dL after bladder decompression, and visualization of the corticomedullary junction on renal sonography. In several situations, a “popoff valve” can occur during urinary tract development, which preserves the integrity of one or both kidneys. For example, 15% of males with PUVs have unilateral reflux into a nonfunctioning dysplastic kidney, termed the **VURD syndrome** (valves, unilateral reflux, dysplasia). In these males, the high bladder pressure is dissipated into the nonfunctioning kidney, allowing normal development of the contralateral kidney. In newborn males with urinary ascites, the urine generally leaks out from the obstructed collecting system through the renal fornices, allowing normal development of the kidneys. Unfavorable prognostic factors include the presence of oligohydramnios in utero, identification of hydronephrosis before 24 wk of gestation, a serum creatinine level > 1.0 mg/dL after bladder decompression, identification of cortical cysts in both kidneys, and persistence of diurnal incontinence beyond 5 yr of age.

The prognosis in the newborn is related to the child's degree of pulmonary hypoplasia and potential for recovery of renal function. Severely affected infants often are stillborn. Of those who survive the neonatal period, approximately 30% eventually require kidney transplantation and 15% have renal insufficiency. In some series, kidney transplantation in children with PUVs has a lower success rate than does transplantation in children with normal bladders, presumably because of the adverse influence of altered bladder function on graft function and survival.

After valve ablation, antimicrobial prophylaxis is beneficial in preventing UTI, because hydronephrosis to some degree often persists for many years.

These males should be evaluated annually with a renal US, physical examination including assessment of somatic growth and blood pressure, urinalysis, and determination of serum levels of electrolytes. Many males have significant polyuria resulting from a concentrating defect secondary to prolonged obstructive uropathy. If these children acquire a systemic illness with vomiting and/or diarrhea, urine output cannot be used to assess their hydration status. They can become dehydrated quickly, and there should be a low threshold for hospital admission for intravenous rehydration. Some of these patients have renal tubular acidosis, requiring oral bicarbonate therapy. If there is any significant degree of renal dysfunction, growth impairment, or hypertension, the child should be followed closely by a pediatric nephrologist. When vesicoureteral reflux is present, expectant treatment and prophylactic doses of antibacterial drugs are advisable. If breakthrough UTI occurs, surgical correction should be undertaken.

After treatment, males with urethral valves often do not achieve diurnal urinary continence as early as other males. Incontinence can result from a combination of factors, including uninhibited bladder contractions, poor bladder compliance, bladder atonia, bladder neck dyssynergia, or polyuria. Often these males require urodynamic evaluation with urodynamics or videourodynamics to plan therapy. Males with a poorly compliant bladder are at significant risk for ongoing renal damage, even in the absence of infection. Overnight catheter drainage has been shown to be beneficial in males with polyuria and can help preserve renal function. Urinary incontinence usually improves with age, particularly after puberty. Meticulous attention to bladder compliance, emptying, and infection can improve results in the future.

Urethral Atresia

The most severe form of obstructive uropathy in males is urethral atresia, a rare condition. In utero there is a distended bladder, bilateral hydroureteronephrosis, and oligohydramnios. In most cases, these infants are stillborn or succumb to pulmonary hypoplasia. Some males with prune-belly syndrome also have urethral atresia. If the urachus is patent, oligohydramnios is unlikely, and the infant usually survives. Urethral reconstruction is difficult, and most patients are managed with continent urinary diversion.

Urethral Hypoplasia

Urethral hypoplasia is a rare form of obstructive uropathy in males that is less severe than urethral atresia. In urethral hypoplasia, the urethral lumen is extremely small. Neonates with urethral hypoplasia typically have bilateral hydronephrosis and a distended bladder. Passage of a small pediatric feeding tube through the urethra is difficult or impossible. Usually a cutaneous vesicostomy must be performed to relieve upper urinary tract obstruction, and the severity of renal insufficiency is variable. The most severely affected males have end-stage renal disease. Treatment includes urethral reconstruction, gradual urethral dilation, or continent urinary diversion.

Urethral Stricture

Urethral strictures in males usually result from urethral trauma, either iatrogenic (catheterization, endoscopic procedures, previous urethral reconstruction) or accidental (straddle injuries, pelvic fractures). Because these lesions can develop gradually, the decrease in force of the urinary stream is seldom noticed by the child or the parents. More commonly, the obstruction causes symptoms of bladder instability, hematuria, or dysuria. Catheterization of the bladder usually is impossible. The diagnosis is made by a **retrograde urethrogram,** in which contrast is injected toward the bladder through a catheter inserted into the distal urethra. US also has been used to diagnose urethral strictures. Endoscopy is confirmatory. Endoscopic treatment of short strictures by direct-vision urethrotomy is often successful initially and results in a profoundly improved urinary stream, but often the stricture recurs. Longer strictures surrounded by periurethral fibrosis often require urethroplasty. Repeated endoscopic procedures generally should be avoided, because they can cause additional urethral damage. Noninvasive measurement of the urinary flow rate and pattern is useful for diagnosis and follow-up.

In females, true urethral strictures are rare because the female urethra is protected from trauma, particularly in childhood. In the past it was thought that a distal urethral ring commonly caused obstruction of the female urethra and UTI and that affected females benefited from urethral dilation. The diagnosis was suspected when a “spinning-top” deformity of the urethra was found in the VCUG (see Fig. 558.3 in Chapter 558) and was confirmed by urethral calibration. There is no correlation between the radiologic appearance of the urethra in the VCUG and the urethral caliber and no significant difference in urethral caliber between females with recurrent cystitis and normal age-matched controls. The finding usually is secondary to detrusor–sphincter discoordination. Consequently, urethral dilation in females rarely is indicated.

Anterior Urethral Valves and Urethral Diverticula in the Male

Anterior urethral valves are rare. The obstruction is not obstructing valve leaflets, as occurs in the posterior urethra. Rather, it is a urethral diverticulum in the penile urethra that expands during voiding. Distal extension of the diverticulum causes extrinsic compression of the distal penile urethra, causing urethral obstruction. There is usually a soft mass on the ventral surface of the penis at the penoscrotal junction. In addition, the urinary stream often is weak, and the physical findings associated with PUVs often are present. The diverticulum may be small and minimally obstructive, or, in other cases, may be severely obstructive and cause renal insufficiency. The diagnosis is suspected on physical examination and is confirmed by the VCUG. Treatment involves open excision of the diverticulum or transurethral excision of the distal urethral cusp. Urethral diverticulas occasionally occur after extensive hypospadias repair.

Fusiform dilation of the urethra or **megalourethra** can result from underdevelopment of the corpus spongiosum and support structures of the urethra. This condition is commonly associated with the prune-belly syndrome.

Male Urethral Meatal Stenosis

See Chapter 559 for information on urethral meatal stenosis in males.

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CHAPTER 556

Anomalies of the Bladder

Jack S. Elder

Bladder Exstrophy

Exstrophy of the urinary bladder occurs in approximately 1 in 35,000-40,000 births. The male:female ratio is 2 : 1. The severity ranges from simple **epispadias** (in males) to complete exstrophy of the cloaca involving exposure of the entire hindgut and the bladder (termed **cloacal exstrophy**).

Clinical Manifestations

Anomalies of the bladder are hypothesized to result when the mesoderm fails to invade the cephalad extension of the cloacal membrane; the extent of this failure determines the degree of the anomaly. In classic bladder exstrophy (Fig. 556.1), the bladder protrudes from the abdominal wall and its mucosa is exposed. The umbilicus is displaced downward, the pubic rami are widely separated in the midline, and the rectus muscles are separated. In males, there is complete epispadias with dorsal chordee, and the overall penile length is approximately half that of unaffected males. The scrotum typically is separated slightly from the penis and is wide and shallow. Undescended testes and inguinal hernias are common. Females also have epispadias, with separation of the two halves of the clitoris and wide separation of the labia. The anus is displaced anteriorly in both sexes, and there may be rectal prolapse. The pubic rami are widely separated. Persons with exstrophy tend to be shorter than normal.

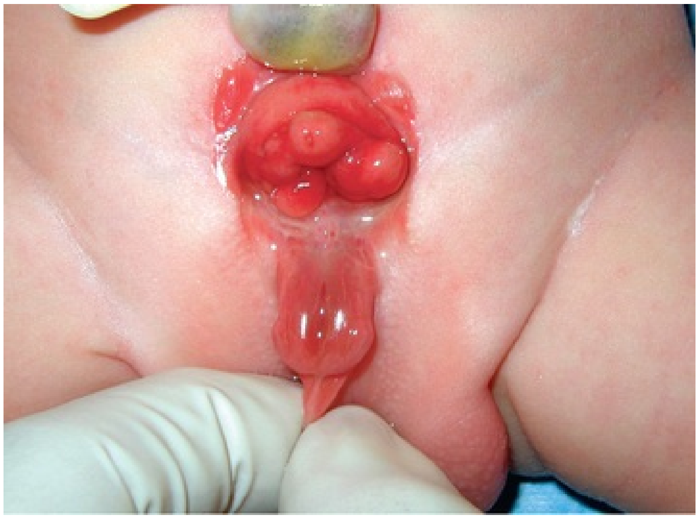

FIG. 556.1 Classic bladder exstrophy in a newborn male. The bladder is exposed in the midline, the umbilical cord is displaced caudad, the penis is epispadiac, and the scrotum is broad.

The consequences of untreated bladder exstrophy are total urinary incontinence and an increased incidence of bladder cancer, usually adenocarcinoma. The external and internal genital deformities cause sexual disability in both sexes, particularly in males. The wide separation of the pubic rami causes a characteristic broad-based gait but no significant disability. In classic bladder exstrophy, the upper urinary tracts usually are normal at birth.

Treatment

Management of bladder exstrophy should start at birth. The bladder should be covered with plastic wrap to keep the bladder mucosa moist. *Application of gauze or petroleum-gauze to the bladder mucosa should be avoided, because significant inflammation will result.* The infant should be transferred promptly to a center with pediatric urologic and pediatric anesthetic support for newborns with complex anomalies. These children are prone to *latex allergy,* and latex precautions should be practiced from birth, both in the nursery and in the operating room.

There are two surgical approaches: staged reconstruction and total single-stage reconstruction. Most babies also undergo bilateral iliac osteotomy, which allows the pubic symphysis to be approximated, which supports the bladder closure. In a staged reconstruction, the initial stage is bladder closure, the second stage (in males) is epispadias repair, and the final stage is bladder neck reconstruction.

The single-stage reconstruction attempts to reconstruct the entire malformation in a single procedure. When this operation is performed in the newborn, there is an increased risk of intraoperative penile injury and postoperative hydronephrosis, compared with the staged reconstruction. The complication rate is high with both approaches and there is no consensus on which is better.

Although bladder closure within 48 hr has been the standard in the past, many centers of excellence now defer the procedure for 1-2 wk to be certain that the appropriate multidisciplinary surgical and anesthetic teams are available. During bladder exstrophy closure, the abdominal wall is mobilized and the pubic rami are brought together in the midline following pelvic osteotomy. Early bladder closure can be performed in almost all neonates with classic bladder exstrophy. Treatment should be deferred in selected situations when surgical therapy would be excessively risky or complex, as in a premature baby or when it would have to be performed by inexperienced surgeons. In the staged approach, in males, epispadias repair usually is performed at 1-2 yr of age. At this point the child has total urinary incontinence because there is no functional external urinary sphincter. Most infants with bladder exstrophy have vesicoureteral reflux and should receive antibiotic prophylaxis. Typically, the bladder capacity is monitored every 12-24 mo using cystoscopy under anesthesia. The final stage of reconstruction involves creation of a sphincter muscle for bladder control and correction of vesicoureteral reflux. At this point the child is 3-6 yr old, the bladder capacity should be at least 80-90 mL, and the child must have gained rectal sphincter control.

Total single-stage reconstruction includes newborn closure of the bladder and bladder neck narrowing, abdominal wall closure, and, in males, correction of epispadias using a technique of penile disassembly, in which the two corpora cavernosa and the midline urethra are mobilized separately into three parts. Postoperatively, the infant's upper urinary tract is monitored closely for possible development of hydronephrosis and infection. Comparison of outcomes between the multistage and single-stage approaches is ongoing.

At puberty, often the pubic hair is distributed to the sides of the external genitals. A monsplasty can performed to provide a normal escutcheon.

Long-Term Prognosis

Long-term management of individuals born with bladder exstrophy includes monitoring of upper urinary tract appearance and function, UTI, continence, erectile function, and, in adults, sexual function and fertility.

The previously described plan of treatment has yielded a continence rate of 60–70% in a few centers, with < 15% deterioration of the upper urinary tract. This continence rate reflects not only successful reconstruction but also the quality and size of the bladder. From a functional standpoint, the reconstructed bladder neck does not relax during voiding as in a normal child; instead the patient must void by Valsalva.

Children who remain incontinent for more than 1 yr after bladder neck reconstruction or those who are ineligible for bladder neck reconstruction because of a small bladder capacity are candidates for an alternative reconstructive procedure to achieve dryness. In selected cases, cystoscopic injection of dextranomer or polydimethylsiloxane microspheres into the bladder neck can provide sufficient bladder neck coaptation to establish continence. Alternatively, if the child is not a candidate for endoscopic therapy, options include:

- Augmentation cystoplasty, in which the bladder is enlarged with a patch of small or large bowel to increase its capacity.
- Creation of a neobladder out of small and large bowel with placement of a continent abdominal stoma through which clean intermittent catheterization can be performed.
- Placement of an artificial urinary sphincter, with possible augmentation cystoplasty.
- Ureterosigmoidostomy, in which the ureters are detached from the bladder and sutured to the sigmoid colon; individuals void urine and stool from the rectum and rely on their anal sphincter for continence.
- Mainz II procedure, in which the sigmoid colon is reconfigured into a “bladder” into which the ureters

are connected; the patient voids 3-6 times daily through the rectum, and the stool tends to be more solid.

Ureterosigmoidostomy carries a significant risk of chronic pyelonephritis (see Chapter 553), upper urinary tract damage, metabolic acidosis resulting from absorption of hydrogen ion and chloride in the intestine, and at least a 15% long-term risk of colon carcinoma. Patients from less-developed countries often undergo the Mainz II procedure because the continence rate is high and pyelonephritis and upper tract changes are uncommon.

Late follow-up has shown that although adult males with exstrophy have a penis that is half normal length, they usually experience satisfactory sexual function. Fertility has been low, possibly because of iatrogenic injury to the secondary sexual organs during reconstruction. With artificial reproductive technology, nearly all affected men can be fertile. In adult females, fertility is not affected, but uterine prolapse during pregnancy is a problem. In adult females who have undergone a continent urinary diversion, delivery by cesarean section may be necessary.

Other Exstrophy Anomalies

Children with more complex cases of **cloacal exstrophy,** which has an incidence of 1 in 400,000, have an omphalocele and severe abnormalities of the colon and the rectum and often have short bowel syndrome (see Chapter 364.7), the most devastating anomaly managed by pediatric urologists. Approximately 50% of patients have an upper urinary tract anomaly, and 50% have spina bifida (see Chapter 609.2). Children with cloacal exstrophy do not achieve normal urine or stool continence. Reconstructive techniques result in a satisfactory outcome in most patients with permanent urinary diversion (either ileal conduit or continent urinary diversion) and a colostomy. Because the penis in males with cloacal exstrophy usually is diminutive, genital reconstruction in males with cloacal exstrophy has been unsatisfactory. Until recently, many specialists recommended assigning a female gender to such infants, but currently there is debate as to whether these children, who have a 46,XY karyotype and brain androgen imprinting in utero, can have a satisfactory female gender identity (see Chapter

133). Many assume male gender characteristics by adolescence. Decisions regarding gender assignment should be made jointly by the physicians caring for the infant (surgical team, pediatric endocrinologist, child psychiatrist, and ethicist) and family.

Epispadias is in the spectrum of exstrophy anomalies, affecting approximately 1 in 117,000 males and 1 in 480,000 females. In males, the diagnosis is obvious because the prepuce is distributed primarily on the ventral aspect of the penile shaft and the urethral meatus is on the dorsum of the penis. Distal epispadias in males (Fig. 556.2) usually is associated with normal urinary control and normal upper urinary tracts and should be repaired by 6-12 mo of age. In females, the clitoris is bifid, and the urethra is split dorsally (Fig. 556.3). In more severely affected males and in all females with epispadias, there is total urinary incontinence because the sphincter is incompletely formed, and there is wide separation of the pubic rami. These children require surgical reconstruction of the bladder neck, similar to the final management stage in children with classic bladder exstrophy.

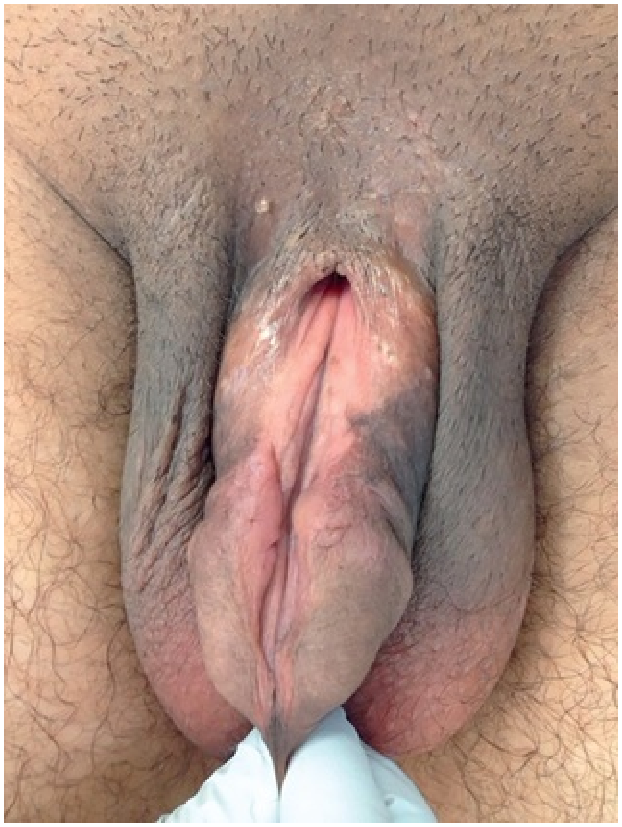

FIG. 556.2 Adolescent male with penopubic epispadias.

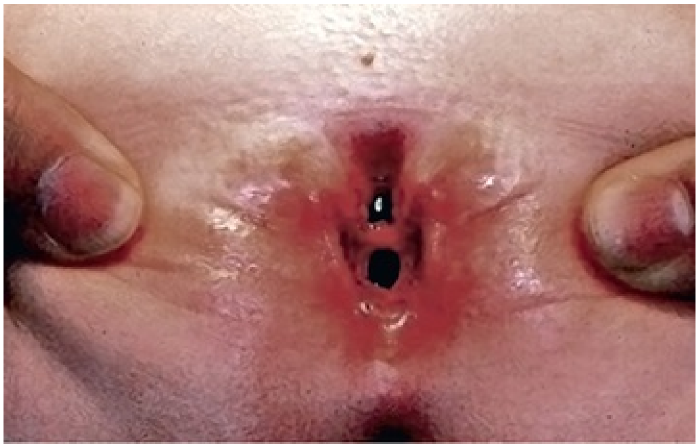

FIG. 556.3 Female with complete epispadias. (From Gearhart JP, Rink RC, Mouriquand PDE, editors: Pediatric urology, ed 2, Philadelphia, 2010, WB Saunders.)

Bladder Diverticula

Bladder diverticula develop as herniations of the bladder mucosa between defects of bladder smooth muscle fibers. Primary bladder diverticula usually develop at the ureterovesical junction and may be associated with vesicoureteral reflux, because the diverticulum interferes with the normal flap-valve attachment between the ureter and bladder. In rare circumstances, the diverticulum is so large that it interferes with normal micturition by obstructing the bladder neck. Bladder diverticula also commonly are associated with distal urethral obstructions such as posterior urethral valves or neurogenic bladder dysfunction. They occur commonly in children with connective tissue disorders, including Williams syndrome, Ehlers-Danlos syndrome, and Menkes syndrome (Fig. 556.4). Small diverticula require no treatment other than that of the primary disease, whereas large diverticula can contribute to inefficient voiding, residual urine, urinary stasis, and urinary tract infections and should be excised.

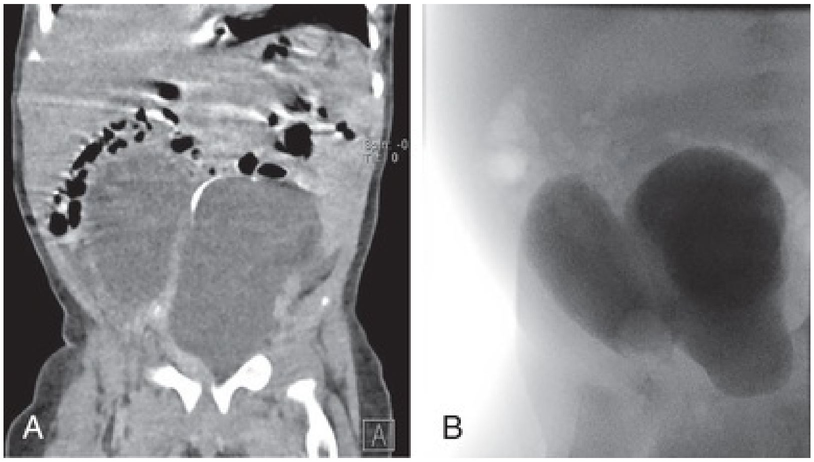

FIG. 556.4 Six-month-old male with abdominal mass. Ultrasound showed a large fluid-filled mass and normal kidneys. **A,** CT scan shows large bladder diverticulum on right side with ureter coursing between the diverticulum and the bladder. **B,** Voiding cystourethrogram demonstrates no reflux and large diverticulum on left side. Managed with diverticulectomy.

Urachal Anomalies

The urachus is an embryologic canal connecting the dome of the fetal bladder with the allantois, a structure that contributes to the formation of the umbilical cord. The lumen of the urachus is normally obliterated during embryonic development, transforming the urachus into a solid cord. Urachal abnormalities are more common in males than in females. A **patent urachus** can occur as an isolated anomaly or it may be associated with prune-belly syndrome or posterior urethral valves (see Chapter 555) (Fig. 556.5). A patent urachus results in continuous urinary drainage from the umbilicus. The tract should be excised. Another urachal anomaly is the **urachal cyst,** which can become infected. Typical symptoms and physical findings include suprapubic pain, fever, irritative voiding symptoms, and an infraumbilical mass, which can be erythematous. Diagnosis is made by ultrasonography or CT (Fig. 556.6). Treatment is intravenous antibiotic therapy and drainage and excision. Other urachal anomalies include the **vesicourachal diverticulum,** which is a diverticulum of the bladder dome, and **umbilical–urachal sinus,** which is a blind external sinus that opens at the umbilicus. These lesions should be excised.

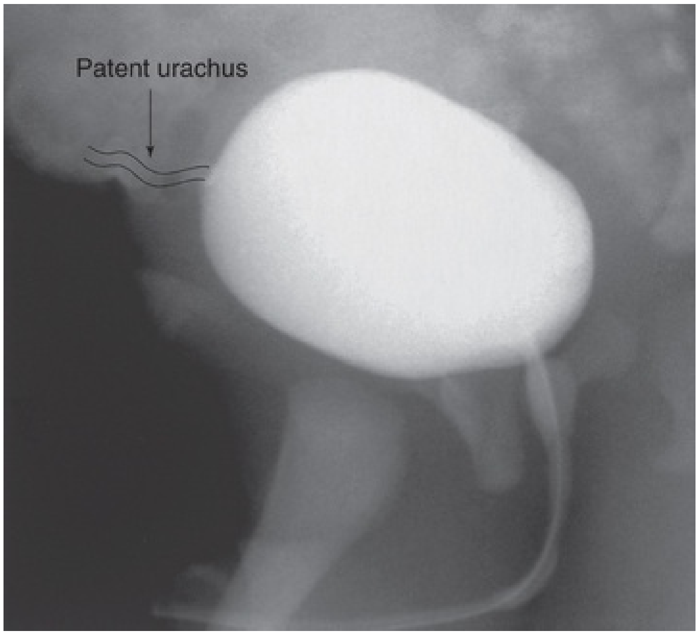

FIG. 556.5 Patent urachus. Vesicourethrogram image of patent urachus in a newborn. Retrograde contrast filling of patent canal with contrast pooling in umbilicus. (From Wein AJ, Kavoussi LR, Partin AW, Peters CA (eds): Campbell-Walsh urology, 11th ed, Vol 4, 2016, Elsevier, Philadelphia, Fig. 138-4, p. 3177.)

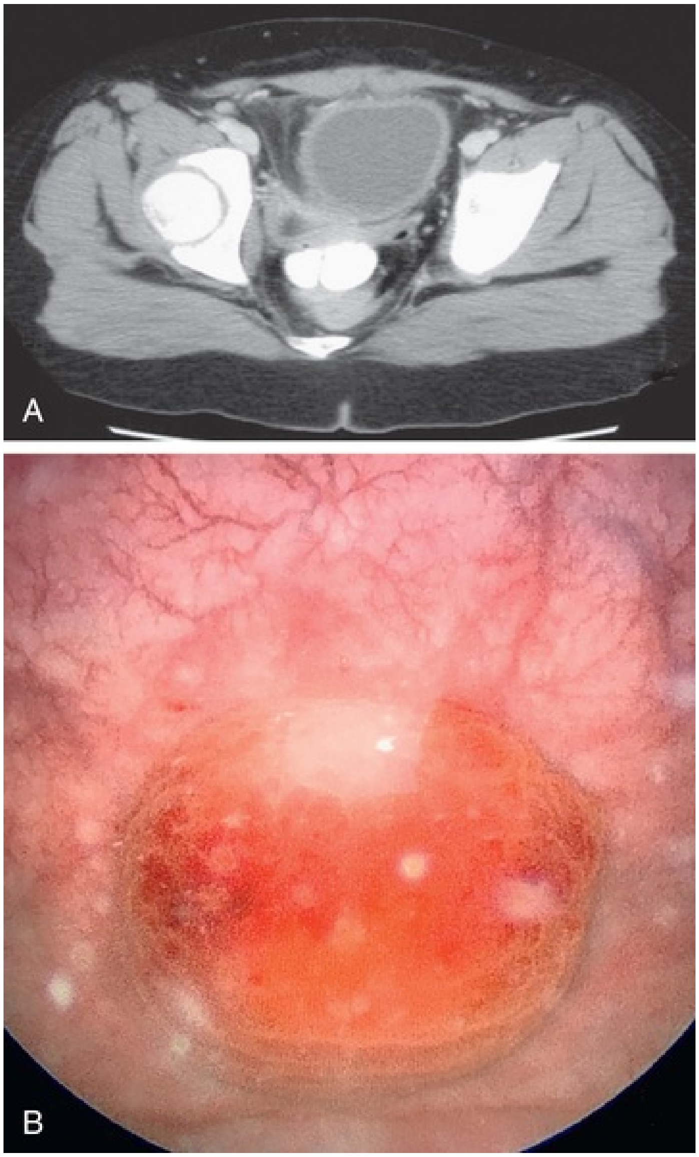

FIG. 556.6 **A,** CT scan demonstrating infected urachal abscess in an 8 yr old female. The condition was managed by drainage and excision. **B,** Cystoscopic view of 10 yr old female with new-onset daytime frequency and incontinence secondary to infected urachal cyst.

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CHAPTER 557

Neuropathic Bladder

Jack S. Elder

Neuropathic bladder dysfunction in children usually is congenital, generally resulting from neural tube defects or other spinal abnormalities. Acquired diseases and traumatic lesions of the spinal cord are less common. Central nervous system tumors, sacrococcygeal teratoma, spinal abnormalities associated with imperforate anus (see Chapter 371), and spinal cord trauma also can result in abnormal innervation of the bladder and/or sphincter (Table 557.1).

Table 557.1

Causes of Neuromuscular Dysfunction of the Lower Urinary Tract

CONGENITAL
Neural tube defect
Occult forms of neural tube defect (lipomeningocele and other spinal dysraphisms)
Sacral agenesis
Anorectal malformations
ACQUIRED
Extensive pelvic surgery
Central nervous system disorders
Cerebral palsy
Conditions of the brain (tumors, infarcts, encephalopathies)
Spinal cord disorders
Trauma
Transverse myelitis

From Wein AJ, Kavoussi LR, Partin AW, Peters CW (eds): Campbell-Walsh urology, 11th ed, Vol 4, Philadelphia, 2016, Elsevier, Box 142-1, p. 3273.

Neural Tube Defects

Neural tube defects, resulting from failure of the neural tube to close spontaneously between the third and fourth wk in utero, result in abnormalities of the vertebral column that affect spinal cord function, including myelomeningocele and meningocele (see Chapters 609.3 and 609.4). Specialized medical centers in the United States have performed antenatal myelomeningocele closure. Long-term results from one large clinical trial (the "MOMS trial"), have not shown a definite improvement in lower urinary tract function, although some children have demonstrated nearly normal bladder function, and overall there has been a significant reduction in the need for ventriculoperitoneal shunting.

Clinical Manifestations and Diagnosis

The most important urologic consequences of neuropathic bladder dysfunction associated with neural tube defects are urinary incontinence (see Chapter 558), urinary tract infections (UTIs; see Chapter 553), and hydronephrosis from vesicoureteral reflux (see Chapter 554) or detrusor–sphincter dyssynergia (see Chapter 558). Pyelonephritis and renal functional deterioration (see Chapter 553) are common causes of premature death in affected patients.

In the neonate, renal ultrasonography, assessment of postvoiding residual urine volumes, and a voiding cystourethrogram are performed after closure of the myelomeningocele. Approximately 10–15% of newborns with myelomeningocele have hydronephrosis, and renal malformations are common; 25% have vesicoureteral reflux. A urodynamic study also should be performed. In this study, the bladder is filled with saline, and the bladder volume, bladder pressure, abdominal pressure, and sphincter tone are measured until the patient voids. During bladder filling, the bladder might show (1) uninhibited (premature) contractions (termed hyperreflexia) at low volumes, (2) normal bladder volume with contraction at an appropriate volume, or (3) atonia (lack of bladder contraction). Bladder compliance or elasticity also may be abnormal (i.e., abnormally high bladder pressure during bladder filling). The sphincter can show (1) normal tonicity with relaxation during bladder contraction, (2) reduced or absent tonicity, or (3) normal or increased tonicity that increases significantly during a bladder contraction (termed detrusor–sphincter dyssynergia) (Fig. 557.1).

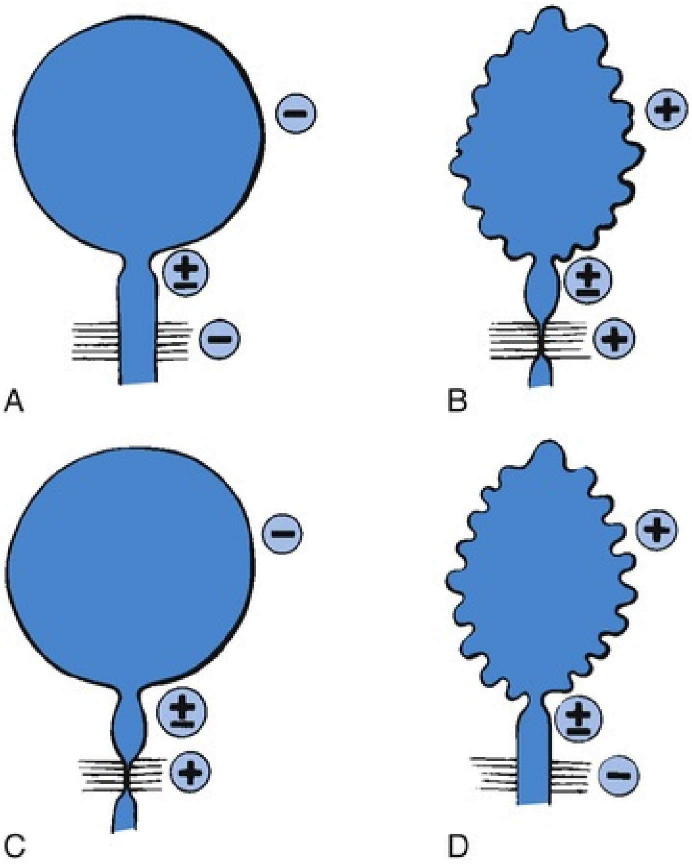

FIG. 557.1 Grouping of neuropathic bladder dysfunction according to the innervation, tonicity, and coordination of the detrusor and sphincters described by Guzman. This grouping is based on data from imaging studies, cystometrography, and electromyography of the sphincters. Patients in group B are at risk of developing reflux and hydronephrosis. For guidance in the treatment of incontinence, group A patients benefit from procedures that increase outlet resistance, group B patients from anticholinergics or bladder augmentation surgery, and group C patients from intermittent catheterization. Group D patients require both increased outlet resistance and pharmacologic or surgical bladder enlargement. Most patients require intermittent catheterization to empty. (Modified from Gonzalez R: Urinary incontinence. In Kelalis PK, King LR, Belman AB, editors: Clinical pediatric urology, Philadelphia, 1992, WB Saunders, p. 387.)

Renal Damage

Renal damage usually results from detrusor–sphincter dyssynergia. This dyssynergia causes functional obstruction of the bladder outlet, leading to bladder muscle hypertrophy and trabeculation, high intravesical pressure, and transmission of this high pressure into the upper urinary tracts, causing hydronephrosis (Fig. 557.2). Vesicoureteral reflux and UTI compound this problem, but severe hydronephrosis can result without reflux. Treatment includes reduction of bladder pressure with anticholinergic drugs (e.g., oxybutynin, 0.2 mg/kg/24 hr in 2 or 3 divided doses) and clean intermittent catheterization every 3-4 hr. If the child has vesicoureteral reflux or UTI, antimicrobial prophylaxis also is prescribed.

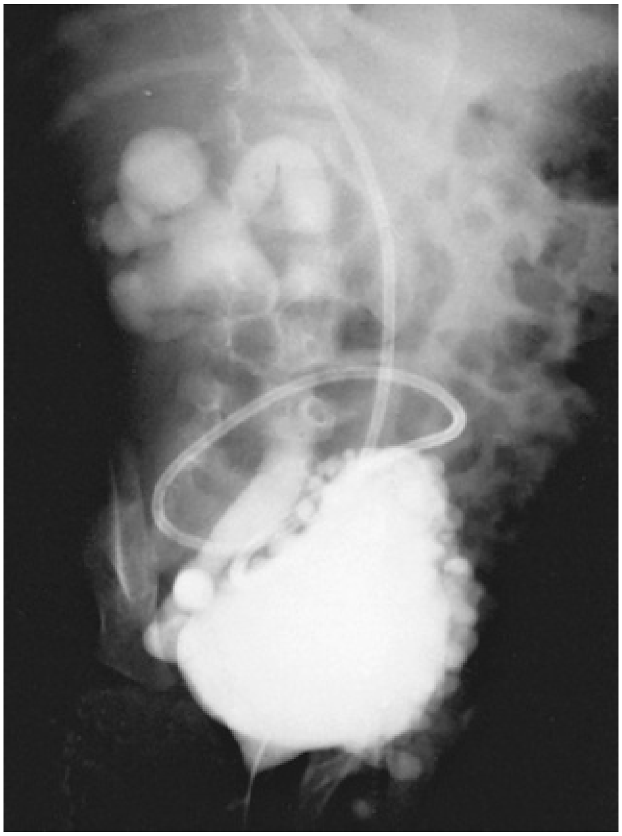

FIG. 557.2 Voiding cystourethrogram in an infant with myelodysplasia shows a severely trabeculated bladder with multiple diverticula and grade V (out of V) right vesicoureteral reflux. Evaluation showed severe detrusor–sphincter dyssynergia.

Temporary urinary diversion by cutaneous vesicostomy is an alternative in the newborn or infant with severe reflux, if intermittent catheterization is difficult, or if anticholinergic medications are not well tolerated. Another option for treating the severely trabeculated bladder is transurethral injection of botulinum toxin (Botox) into the detrusor muscle, which reduces bladder hypertonicity for approximately 6 mo and often needs to be repeated. A different approach in these children is to temporarily inactivate the tight sphincter by urethral overdilation or transurethral injection of botulinum toxin into the sphincter. In children with upper tract changes, continuous overnight bladder drainage allows significant bladder relaxation and can reduce bladder wall thickening and lessen hydronephrosis.

Clean intermittent catheterization and anticholinergic therapy cure reflux in up to 80% of children with grade I or II reflux. Children with more severe reflux often require subureteral endoscopic injection therapy (see Chapter 554) or open antireflux surgery followed by intermittent catheterization and anticholinergic drugs. In older children with myelomeningocele with high-grade reflux, UTI, and hydronephrosis, augmentation enterocystoplasty (enlarging the bladder with a patch of intestine) with intermittent catheterization may be necessary. This intervention allows a normal-capacity bladder with low bladder pressure and effective drainage of the bladder.

Urinary Incontinence

Incontinence in the child with neuropathic bladder can result from total or partial denervation of the sphincter, bladder hyperreflexia, poor bladder compliance, chronic urinary retention, or a combination of these factors.

Incontinence often is addressed at 4 to 5 yr and is tailored to the individual child. Nearly all children require clean intermittent catheterization to stay dry. This technique allows efficient bladder emptying with minimal risk of symptomatic UTI. The urinary tract should be reevaluated with renal ultrasonography, a voiding cystourethrogram, and a urodynamic study, including bladder capacity. If the external sphincter tone is sufficient and the bladder has adequate compliance, intermittent catheterization every 3-4 hr often is successful in keeping the child socially dry. If there are unstable bladder contractions, an anticholinergic medication such as oxybutynin chloride, hyoscyamine, or tolterodine is prescribed to increase bladder capacity. If there is sphincteric incompetence, α-adrenergic medications are prescribed to enhance outlet resistance. Bacteriuria is seen in up to 50% of children using intermittent self-catheterization, but it seldom causes symptoms. In the absence of reflux, there seems to be little cause for concern. Performing intermittent catheterization with a new catheter (hydrophilic or standard silicone) each time is also quite effective in preventing bacteriuria and avoids the need for antibiotic prophylaxis. With this treatment plan, 40–85% of patients are dry, depending on the definition of continence; some children wear a pad in their underwear or a diaper but feel that they are dry.

If there is persistent incontinence despite medical therapy, reconstructive urinary tract surgery nearly always can provide complete or satisfactory continence. If urethral resistance is low, bladder neck reconstructive procedures such as a periurethral sling often are successful. Alternatively, implantation of an artificial sphincter usually is successful. This sphincter consists of an inflatable cuff that is placed around the bladder neck, a pressure-regulating balloon implanted in the extraperitoneal space, and a pump mechanism that is implanted in the scrotum of boys and in the labia majora of girls. Squeezing the pump 3 to 4 times moves the fluid out of the inflatable urethral cuff and then the cuff slowly refills over the next 2 to 3 min.

If the bladder capacity or bladder compliance is low, or if there are persistent uninhibited contractions despite anticholinergic therapy, enlargement of the bladder with a patch of small or large intestine, termed augmentation cystoplasty or enterocystoplasty, is effective. These patients still need to perform clean intermittent catheterization. If urethral catheterization is difficult, a continent urinary stoma may be incorporated into the urinary tract reconstruction. A common method is the Mitrofanoff procedure (appendicovesicostomy), in which the appendix is isolated from the cecum on its vascular pedicle and is interposed between the bladder and abdominal wall to allow intermittent catheterization through a dry stoma. An ileal conduit with a bag on the abdominal wall is rarely used.

Complications of Augmentation Cystoplasty

Urinary Tract Infection

The urine may be colonized with Gram-negative bacteria, and attempts to sterilize the urine for prolonged periods usually fail. There is no evidence that chronic bacteriuria in patients who have had enterocystoplasty is associated with renal damage; therefore, only symptomatic UTIs should be treated.

Metabolic Acidosis

The enteric mucosal surface in contact with the urine absorbs ammonium, chloride, and hydrogen ions and loses potassium. Hyperchloremic metabolic acidosis can result, possibly requiring medical treatment (see Chapter 68).

Chronic acidosis can compromise skeletal growth. This condition is common with colocystoplasty but is uncommon with ileocystoplasty. Metabolic acidosis also is common in patients with compromised renal function. To overcome this limitation of enterocystoplasty in patients with chronic renal insufficiency, a composite augmentation using stomach and a small or large bowel gastric segment can be used. The stomach secretes chloride and hydrogen ions; thus, preexisting metabolic acidosis remains stable or improves.

Spontaneous Perforation

Perforation of the augmented bladder is a life-threatening complication that results most often from acute or chronic overdistention of the augmented bladder. Patients with this complication typically present with severe abdominal pain and signs of peritonitis. Prompt diagnosis and treatment with exploratory laparotomy and bladder closure are necessary. Meticulous adherence to the prescribed program of intermittent catheterization to avoid bladder overdistention is important.

Bladder Calculi

Bladder calculi have developed in as many as 70% of children followed for 10 yr after enterocystoplasty. The calculi develop in response to mucus that accumulates in the bladder and act as a nidus for stone formation. This complication can be prevented by daily irrigation of the bladder with sterile saline.

Malignant Neoplasm

Invasive transitional cell carcinoma has been reported in nearly 4.6% of patients undergoing enterocystoplasty (compared with a 2.6% risk in spina bifida patients without enterocystoplasty). The pathogenesis is uncertain, but there is speculation that it is related to bacteriuria and the bowel-bladder contact. The risk is highest following gastrocystoplasty. The risk increases 10 yr following enterocystoplasty. Although these patients probably should undergo screening, there are no guidelines or recommendations regarding this practice. It seems appropriate to advise yearly endoscopic examinations or urine cytologic studies beginning in the 10th postoperative yr.

Future Management

The development of a tissue-engineered bladder using a composite scaffold, which could be attached to the dome of the bladder to increase capacity and compliance, might help patients achieve continence (Fig. 557.3). Clinical trials are ongoing.

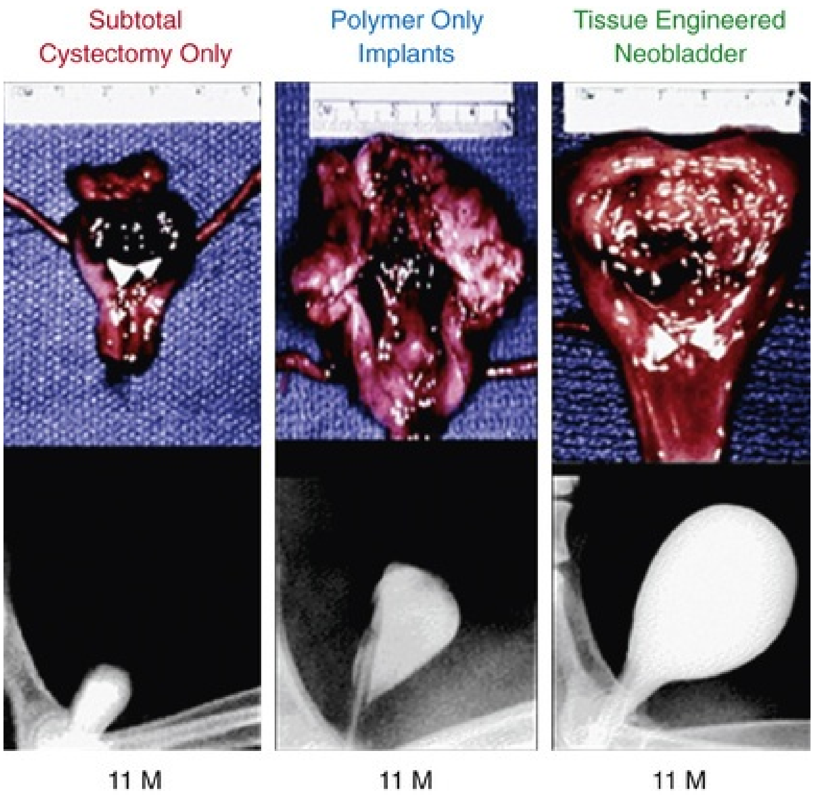

FIG. 557.3 Gross specimens and cystograms at 11 mo of the cystectomy-only, nonseeded controls, and cell-seeded tissue–engineered bladder replacements in dogs. The cystectomy-only bladder had a capacity of 22% of the preoperative value and a decrease in bladder compliance to 10% of the preoperative value. The nonseeded controls showed significant scarring and had a capacity of 46% of the preoperative value and a decrease in bladder compliance to 42% of the preoperative value. An average bladder capacity of 95% of the original precystectomy volume was achieved in the cell-seeded tissue–engineered bladder replacements, and the compliance showed almost no difference from preoperative values that were measured when the native bladder was present (106%). (From Atala A: Bioengineered tissues for urogenital repair in children, Pediatr Res 63:569-575, 2008.)

Associated Disorders

Constipation

Many patients with spina bifida also have bowel problems with constipation, and a vigorous bowel regimen is important. Some benefit from the Malone antegrade continence enema (MACE) procedure, in which the appendix is brought out to the skin to allow a catheter to be inserted into the cecum for antegrade enema. The stoma is continent, and an antegrade enema can be performed with tap water each day. This form of management allows the patient to be continent of stool and be more self-sufficient. An alternative to the MACE procedure is a percutaneous cecostomy, in which a button is placed into the cecum to allow an antegrade flush. The ACE and percutaneous cecostomy procedures can be performed laparoscopically.

Latex Allergy

Latex allergy is a very serious problem encountered by as many as half of patients with spina bifida and other urologic conditions who require clean intermittent catheterization and urinary tract reconstructive procedures. This immunoglobulin E–mediated allergy is acquired and is secondary to repeated exposure to the latex allergen. Latex allergy can manifest as watery eyes, sneezing, itching, hives, or anaphylaxis when blowing up a balloon or if an examiner is using latex gloves. Intraoperatively, a sensitized patient can experience anaphylactic shock. A latex-free environment should be provided for all children with spina bifida in the office, during hospitalization, and during operative procedures. Affected children also should wear a medical alert bracelet.

Occult Spinal Dysraphism

Approximately 1 in 4,000 patients have occult spinal dysraphism, a category that includes lipomeningocele, intradural lipoma, diastematomyelia, tight filum terminale, dermoid cyst-sinus, aberrant nerve roots, anterior sacral meningocele, and cauda equina tumor. More than 90% of patients have a cutaneous abnormality overlying the lower spine, including a small dimple, tuft of hair, dermal vascular malformation, or subcutaneous lipoma (Fig. 557.4). Often these children have high-arched feet, discrepancy in muscle size and strength between the legs, and a gait abnormality. Newborns and young infants often have a normal neurologic examination. Older children often have absent perineal sensation and back pain. Lower urinary tract function is abnormal in 40% of patients, including incontinence, recurrent UTI, and fecal soiling. The likelihood of a normal examination is inversely related to the child's age at surgical correction of the spinal lesion. In infants with abnormal urodynamics, 60% revert to normal; in older children, only 27% become normal. Management of the urinary tract in other children is similar to that described earlier for neural tube defects.

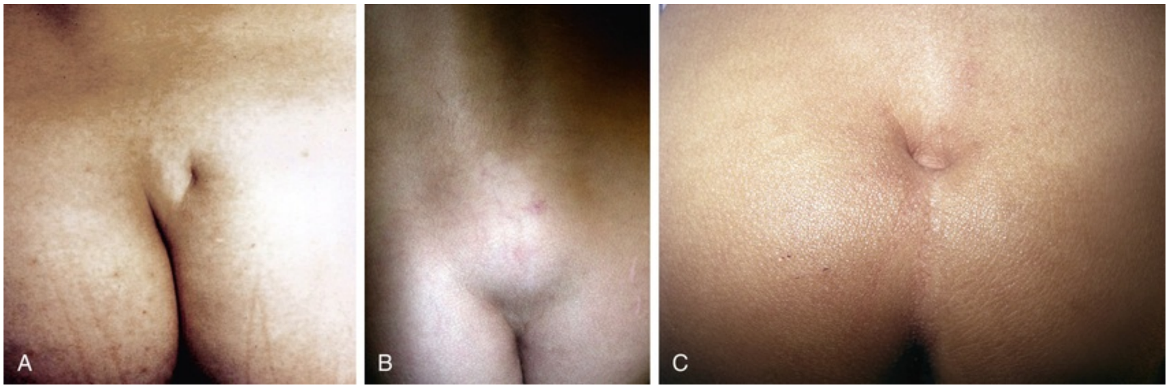

FIG. 557.4 **A,** Buttocks of teenage boy with tethered cord secondary to lipomeningocele. Note sacral dimple and deviation of gluteal fold to the left. **B,** Fat deposit over sacrum in girl with tethered cord secondary to lipomeningocele. **C,** Deep sacral pit in child with neuropathic bladder.

Sacral Agenesis

Sacral agenesis is defined as the absence of part or all of ≥ 2 lower vertebral bodies. This condition is more common in the offspring of women with diabetes. These children have a flattened buttock and a low, short gluteal cleft but usually have no orthopedic deformity, although some have high-arched feet. Palpation of the coccygeal area detects the absent vertebrae. Approximately 20% of cases are undetected until the age of 3-4 yr; many are diagnosed after unsuccessful toilet training. Urodynamic studies in these children show a variety of patterns, and most need clean intermittent catheterization and pharmacotherapy to stay dry.

Imperforate Anus

Approximately 30–45% of children with a high imperforate anus have a neuropathic bladder, often because of sacral agenesis. Newborns with imperforate anus should undergo a spinal ultrasound during their initial evaluation, and if these children have difficulty with toilet training, complete urologic evaluation with upper and lower urinary tract imaging and urodynamics should be performed. See Chapter 371 for further details.

Cerebral Palsy

Children with cerebral palsy (see Chapter 616.1) often have reasonable bladder control. However, they achieve continence at a later age than unaffected children. Overall, 25–50% are incontinent, and the risk is directly related to the severity of physical impairment. Their upper urinary tracts usually are normal. Urodynamic studies have shown that most have uninhibited bladder contractions. Timed voiding and anticholinergic therapy are usually effective. Upper urinary tract deterioration is uncommon, and clean intermittent catheterization rarely is necessary.

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CHAPTER 558

Enuresis and Voiding Dysfunction

Jack S. Elder

Normal Voiding and Toilet Training

Fetal voiding occurs by reflex bladder contraction in concert with simultaneous contraction of the bladder and relaxation of the sphincter. Urine storage results from sympathetic and pudendal nerve-mediated inhibition of detrusor contractile activity accompanied by closure of the bladder neck and proximal urethra with increased activity of the external sphincter. The infant has coordinated reflex voiding as often as 15-20 times/day. Over time, bladder capacity increases. In children up to the age of 14 yr, the mean bladder capacity in milliliters is equal to the age + 2 (in years) times 30 (e.g., the bladder capacity of a 6 yr old should be $[6+2]\times 30$ or 240 mL).

At 2-4 yr, the child is developmentally ready to begin toilet training. To achieve conscious bladder control, several conditions must be present: awareness of bladder filling; cortical inhibition (suprapontine modulation) of reflex (unstable) bladder contractions; ability to consciously tighten the external sphincter to prevent incontinence; normal bladder growth; and motivation by the child to stay dry. The transitional phase of voiding refers to the period when children are acquiring bladder control. Females typically acquire bladder control before males, and bowel control typically is achieved before bladder control.

A common condition in children is **bladder–bowel dysfunction (BBD)** . This term refers to disorders of bladder and/or bowel function. The old term for this condition was dysfunctional elimination syndrome.

Diurnal Incontinence

Daytime incontinence not secondary to neurologic abnormalities is common in children. At age 5 yr, 95% have been dry during the day at some time and 92% are dry consistently. At 7 yr, 96% are dry, although 15% have significant urgency at times. At 12 yr, 99% are dry consistently during the day. The most common causes of daytime incontinence are **overactive bladder (urge incontinence)** and **bladder–bowel dysfunction** . Table 558.1 lists the causes of diurnal incontinence in children.

Table 558.1

Causes of Urinary Incontinence in Childhood

Overactive bladder (urge incontinence or diurnal urge syndrome)
Infrequent voiding (underactive bladder)
Voiding postponement
Detrusor–sphincter discoordination
Nonneurogenic neurogenic bladder (Hinman syndrome)
Vaginal voiding
Giggle incontinence
Cystitis
Bladder outlet obstruction (posterior urethral valves)
Ectopic ureter and fistula
Sphincter abnormality (epispadias, exstrophy; urogenital sinus abnormality)
Neuropathic
Overflow incontinence
Traumatic
Iatrogenic
Behavioral
Combinations

The patient history should assess the pattern of incontinence, including the frequency of voiding, frequency of day and night urinary leakage, volume of urine lost during incontinent episodes, whether the incontinence is associated with urgency or giggling, whether it occurs after voiding, and whether the incontinence is continuous. In addition, whether the patient has a strong continuous urinary stream and sensation of incomplete bladder emptying should be assessed. A diary of when the child voids and whether the child is wet or dry is helpful. Other urologic problems, such as urinary tract infections (UTIs), vesicoureteral reflux, neurologic disorders, or a family history of renal duplication anomalies, should be assessed. Bowel habits also should be evaluated because incontinence is common in children with constipation and/or encopresis. Diurnal incontinence can occur in children with a history of sexual abuse or following bullying. Physical examination is directed at identifying signs of organic causes of incontinence. Short stature, hypertension, enlarged kidneys and/or bladder, constipation, labial adhesion, ureteral ectopy, back or sacral anomalies (see Fig. 557.4 in Chapter 557), and neurologic abnormalities should be documented.

Assessment tools include urinalysis, with culture if indicated; bladder diary (recorded times and volumes voided, whether wet or dry); postvoid residual urine volume (generally obtained by bladder scan); and the **Dysfunctional Voiding Symptom Score** (Fig. 558.1). An alternative to the Dysfunctional Voiding Symptom Score is the **Vancouver Nonneurogenic Lower Urinary Tract Dysfunction/Dysfunctional Elimination Syndrome** questionnaire. This questionnaire is a validated tool that consists of 14 questions scored on a 5-point Likert scale to assess lower urinary tract and bowel dysfunction. In most cases, a uroflow study with electromyography (noninvasive assessment of urinary flow pattern and measurement of external sphincter activity) is indicated. Another item that may be useful in children older than age 5 yr is the **Pediatric Symptom Checklist (PSC)** . The Pediatric Symptom Checklist is a brief screening questionnaire consisting of 35 questions that is used by pediatricians and other health professionals to improve the recognition and treatment of psychosocial problems in children.

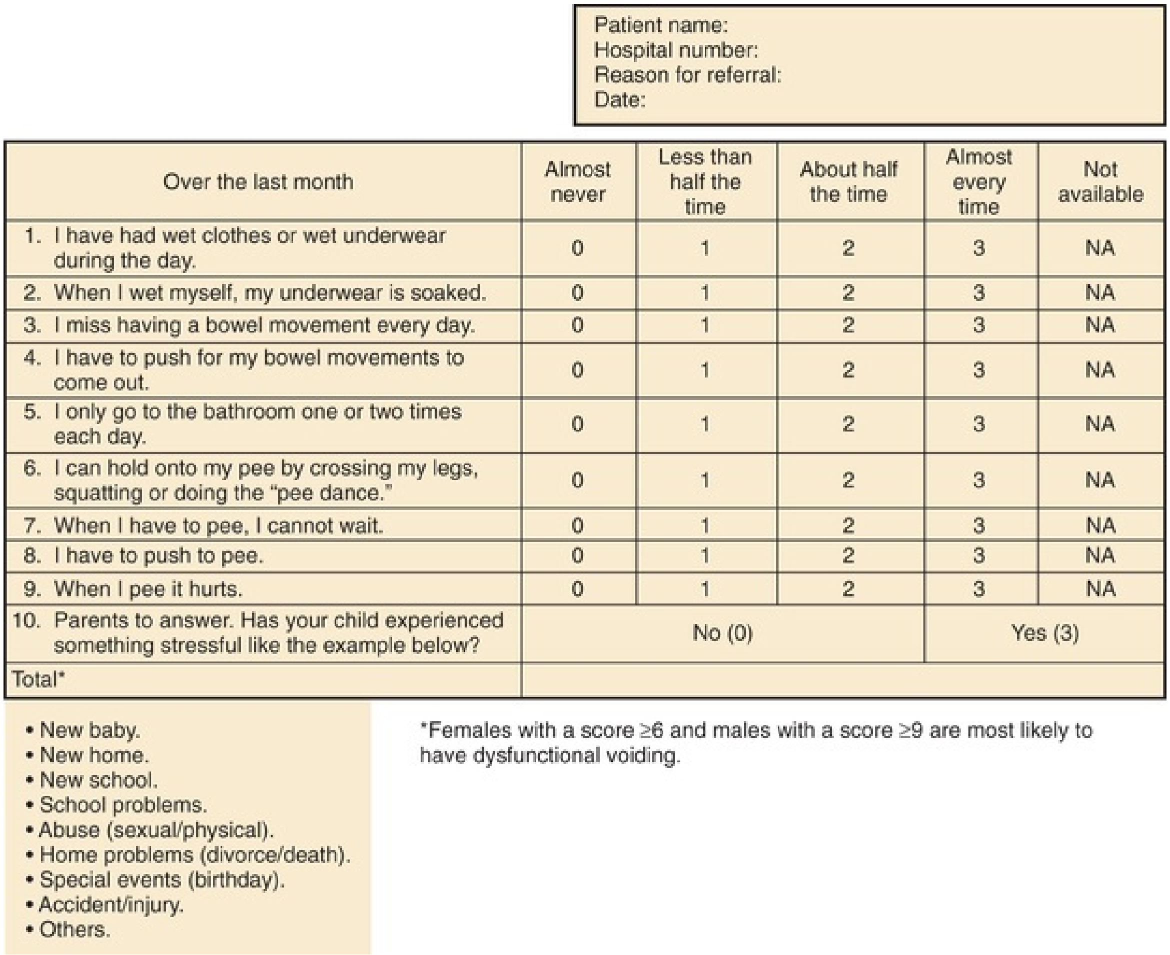

Patient name:
Hospital number:
Reason for referral:
Date:

Over the last month	Almost never	Less than half the time	About half the time	Almost every time	Not available
1. I have had wet clothes or wet underwear during the day.	0	1	2	3	NA
2. When I wet myself, my underwear is soaked.	0	1	2	3	NA
3. I miss having a bowel movement every day.	0	1	2	3	NA
4. I have to push for my bowel movements to come out.	0	1	2	3	NA
5. I only go to the bathroom one or two times each day.	0	1	2	3	NA
6. I can hold onto my pee by crossing my legs, squatting or doing the "pee dance."	0	1	2	3	NA
7. When I have to pee, I cannot wait.	0	1	2	3	NA
8. I have to push to pee.	0	1	2	3	NA
9. When I pee it hurts.	0	1	2	3	NA
10. Parents to answer. Has your child experienced something stressful like the example below?	No (0)			Yes (3)	
Total*					

- New baby.
- New home.
- New school.
- School problems.
- Abuse (sexual/physical).
- Home problems (divorce/death).
- Special events (birthday).
- Accident/injury.
- Others.

*Females with a score ≥6 and males with a score ≥9 are most likely to have dysfunctional voiding.

FIG. 558.1 Dysfunctional Voiding Symptom Score questionnaire. (From Farhat W, Bagli DJ, Capolicchio G, et al: The dysfunctional voiding scoring system: quantitative standardization of dysfunctional voiding symptoms in children, J Urol 164:1011–1015, 2000.)

Bowel function should be assessed also. The Bristol Stool Form Score (Fig. 558.2) should be recorded. In addition, the clinician should utilize the Rome III diagnostic criteria, which classify functional gastrointestinal disorders that do not have underlying structural or tissue-based causes. Children 4 yr of age or older are diagnosed as being constipated if they fulfill two or more of the following criteria over a period of 2 mo: two or fewer defecations in the toilet per week, at least one episode of fecal incontinence per week, a history of retentive posturing or excessive volitional stool retention, a history of painful or hard bowel movements, the presence of a large fecal mass in the rectum, and a history of large-diameter stools that obstruct the toilet.

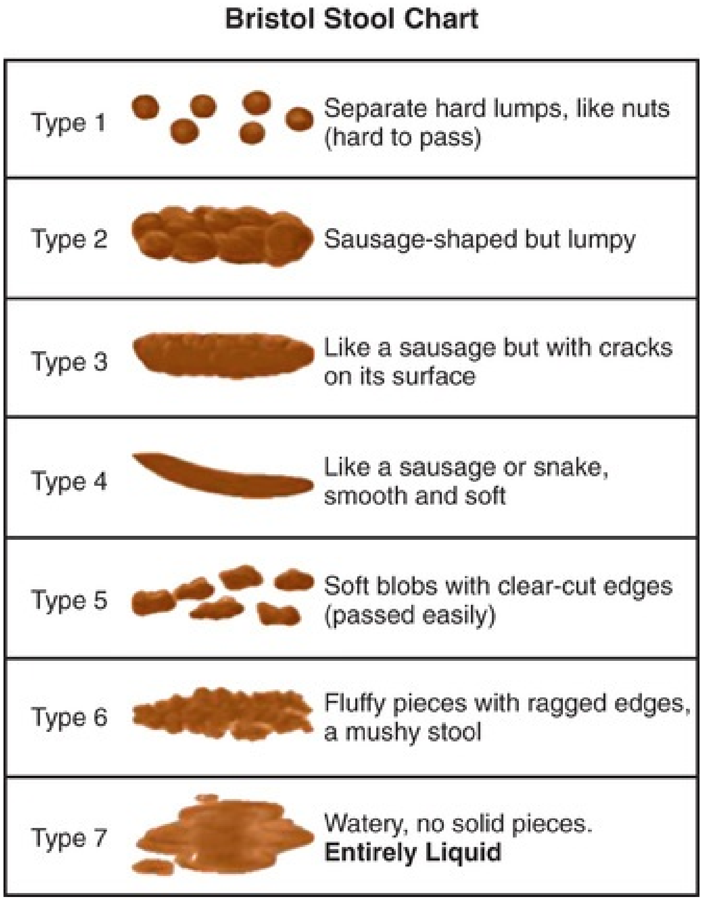

Bristol Stool Chart

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces. **Entirely Liquid**

FIG. 558.2 Bristol Stool Chart for evaluating bowel function.

Imaging is performed in children who have significant physical findings, those who have a family history of urinary tract anomalies or UTIs, and those who do not respond to therapy appropriately. A renal/bladder ultrasonogram with or without a voiding cystourethrogram is indicated. Urodynamics should be performed if there is evidence of neurologic disease and may be helpful if empirical therapy is ineffective. If there is any evidence of a neurologic disorder or if there is a sacral abnormality on physical examination, an MRI of the lower spine should be obtained.

Overactive Bladder (Diurnal Urge Syndrome)

Children with an overactive bladder typically exhibit urinary frequency, urgency, and urge incontinence. Often a female will squat down on her foot to try to prevent incontinence (termed *Vincent's curtsy*). The bladder in these children is functionally, but not anatomically, smaller than normal and exhibits strong uninhibited contractions. Approximately 25% of children with nocturnal enuresis also have symptoms of an overactive bladder. Many children indicate they do not feel the need to urinate, even just before they are incontinent. In females, a history of recurrent UTI is common, but incontinence can persist long after infections are brought under control. It is unclear if the voiding dysfunction is a sequela of the UTIs or if the voiding dysfunction predisposes to recurrent UTIs. In some females, voiding cystourethrography shows a dilated urethra (**spinning-top deformity** , Fig. 558.3) and narrowed bladder neck with bladder wall hypertrophy. The urethral finding results from inadequate relaxation of the external urinary sphincter. Constipation is common and should be treated, particularly with any child with Bristol Stool Score 1, 2, or 3.

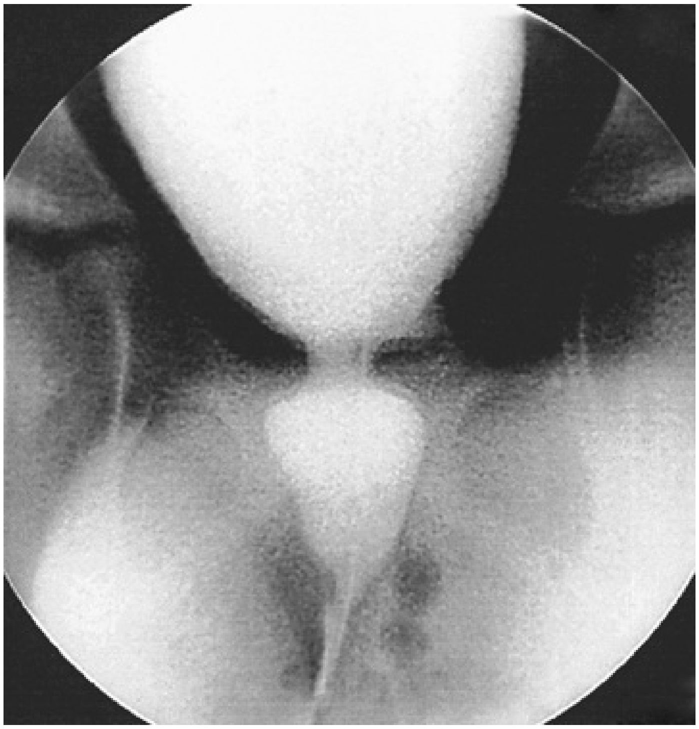

FIG. 558.3 Spinning-top deformity. Voiding cystourethrogram demonstrating dilation of the urethra with distal urethral narrowing and contraction of the bladder neck.

The overactive bladder nearly always resolves, but the time to resolution is highly variable, occasionally not until the teenage years. Initial therapy is timed voiding, every 1.5-2 hr. Treatment of constipation and UTIs is important. Another treatment is biofeedback, in which children are taught pelvic floor exercises **(Kegel exercises),** because daily performance of these exercises can reduce or eliminate unstable bladder contractions. Biofeedback often consists of 8-10 1-hr sessions and may include participation with animated computer games. Biofeedback also may include periodic uroflow studies with sphincter electromyography to be certain that the pelvic floor relaxes during voiding, and assessment of postvoid residual urine volume by sonography. Anticholinergic therapy often is helpful if bowel function is normal. Oxybutynin chloride is the only FDA-approved medication in children, but hyoscyamine, tolterodine, trospium, solifenacin, and mirabegron have demonstrated safety in children; these medications reduce bladder overactivity and may help the child achieve dryness. Treatment with an α-adrenergic blocker such as terazosin or doxazosin can aid in bladder emptying by promoting bladder neck relaxation; these medications also have mild anticholinergic properties. If pharmacologic therapy is successful, the dosage should be tapered periodically to determine its continued need. Children who do not respond to therapy should be evaluated urodynamically to rule out other possible forms of bladder or sphincter dysfunction. In refractory cases, other procedures such as sacral nerve stimulation (InterStim), percutaneous tibial nerve stimulation, and intravesical botulinum toxin injection have been effective in children.

If the child has constipation based on the criteria described above, treatment generally is initiated with polyethylene glycol powder, which has been shown to be safe in children and generally more effective than other laxative preparations.

Nonneurogenic Neurogenic Bladder (Hinman Syndrome)

Hinman syndrome is a very serious but uncommon disorder involving failure of the external sphincter to relax during voiding in children without neurologic abnormalities. Children with this syndrome, also called nonneurogenic neurogenic bladder, typically exhibit a staccato stream, day and night wetting, recurrent UTIs, constipation, and encopresis. Evaluation of affected children often reveals vesicoureteral reflux, a trabeculated bladder, and a decreased urinary flow rate with an intermittent pattern (Fig. 558.4). In severe cases, hydronephrosis, renal insufficiency, and end-stage renal disease can occur. The pathogenesis of this syndrome is thought to involve learning abnormal voiding habits during toilet training; the syndrome is rarely seen in infants. Urodynamic studies and magnetic resonance imaging of the spine are indicated to rule out a neurologic cause for the bladder dysfunction.

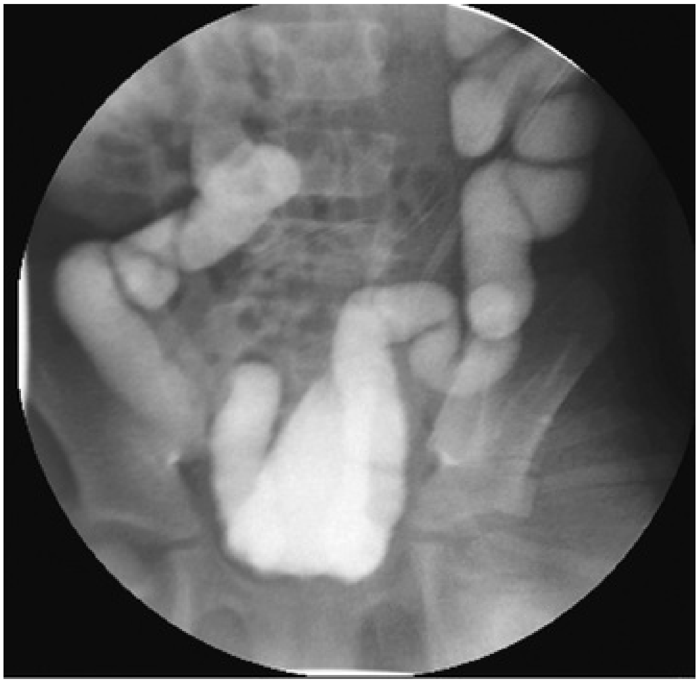

FIG. 558.4 Voiding cystourethrogram demonstrating severe bladder trabeculation and vesicoureteral reflux in a 12 yr old male with Hinman syndrome. The patient presented with day and night incontinence, had chronic renal failure, and underwent kidney transplantation.

The treatment usually is complex and can include anticholinergic and α-adrenergic blocker therapy, timed voiding, treatment of constipation, behavioral modification, and encouragement of relaxation during voiding. Biofeedback has been used successfully in older children to teach relaxation of the external sphincter. Botulinum toxin injection into the external sphincter can provide temporary sphincteric paralysis and thereby reduce outlet resistance. In severe cases, intermittent catheterization is necessary to ensure bladder emptying. In selected patients, external urinary diversion is necessary to protect the upper urinary tract. These children require long-term treatment and careful follow-up.

Infrequent Voiding (Underactive Bladder)

Infrequent voiding is a common disorder of micturition, usually associated with UTIs. Affected children, usually females, void only twice a day rather than the normal 4-7 times. With bladder overdistention and prolonged retention of urine, bacterial growth can lead to recurrent UTIs. Some of these children are constipated. Some also have occasional episodes of incontinence from overflow or urgency. The disorder is behavioral. If the child has UTIs, treatment includes antibacterial prophylaxis and encouragement of frequent voiding and complete emptying of the bladder by double voiding until a normal pattern of micturition is re-established.

Vaginal Voiding

In females with vaginal voiding, incontinence typically occurs after urination after the female stands up. Usually the volume of urine is 5-10 mL. One of the most common causes is labial adhesion (Fig. 558.5). This lesion, typically seen in young females, can be managed either by topical application of estrogen cream to the adhesion or lysis in the office. Some females experience vaginal voiding because they do not separate their legs widely during urination. These females typically are overweight and/or do not pull their underwear down to their ankles when they urinate. Management involves encouraging the female to separate the legs as widely as possible during urination. The most effective way to do this is to have the child sit backward on the toilet seat during micturition.

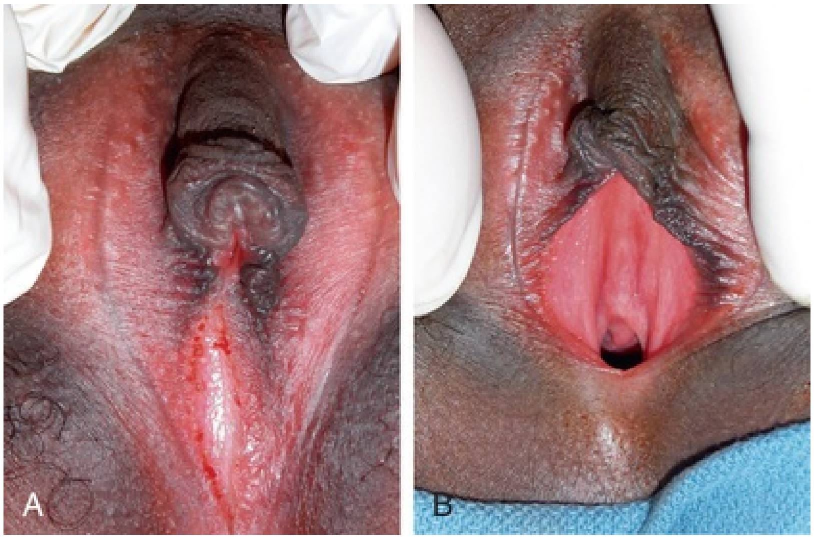

FIG. 558.5 **A,** Labial adhesion. Note the inability to visualize the urethral

meatus and vagina. **B,** Normal female external genitalia following lysis of labial adhesion.

Other Causes of Incontinence in Females

Ureteral ectopia, usually associated with a duplicated collecting system in females, refers to a ureter that drains outside the bladder, often into the vagina or distal urethra. It can produce urinary incontinence characterized by constant urinary dribbling all day, even though the child voids regularly. Sometimes the urine production from the renal segment drained by the ectopic ureter is small, and urinary drainage is confused with watery vaginal discharge. Children with a history of vaginal discharge or incontinence and an abnormal voiding pattern require careful study. The ectopic orifice usually is difficult to find. On ultrasonography or intravenous urography, one may suspect duplication of the collecting system (Fig. 558.6), but the upper collecting system drained by the ectopic ureter usually has poor or delayed function. CT scanning of the kidneys or an MR urogram should demonstrate subtle duplication anomalies. Examination under anesthesia for an ectopic ureteral orifice in the vestibule or the vagina may be necessary (Fig. 558.7). Treatment in these cases is either partial nephrectomy, with removal of the upper pole segment of the duplicated kidney and its ureter down to the pelvic brim, or ipsilateral ureteroureterostomy, in which the upper pole ectopic ureter is anastomosed to the normally positioned lower pole ureter. These procedures often are performed by minimally invasive laparoscopy with or without robotic assistance.

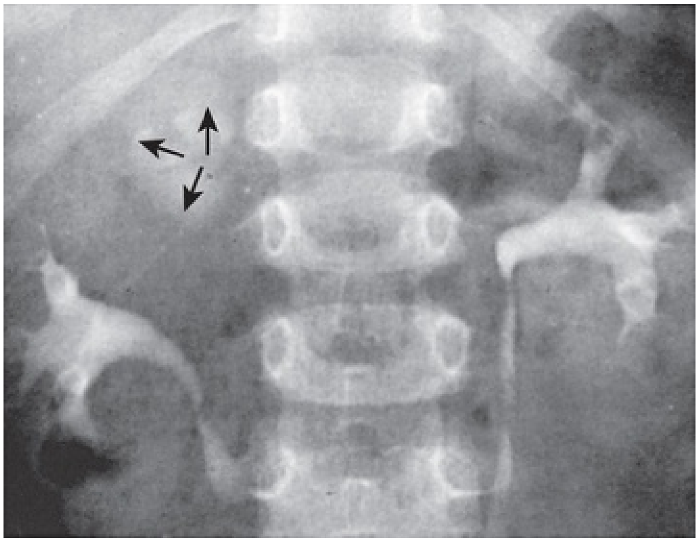

FIG. 558.6 Duplication of the right collecting system with ectopic ureter. Excretory urogram in a female presenting with a normal voiding pattern and constant urinary dribbling. The left kidney is normal, and the right side, well visualized, is the lower collecting system of a duplicated kidney. On the upper pole opposite the 1st and 2nd vertebral bodies, note the accumulation of contrast material corresponding with a poorly functioning upper pole drained by a ureter opening in the vestibule.

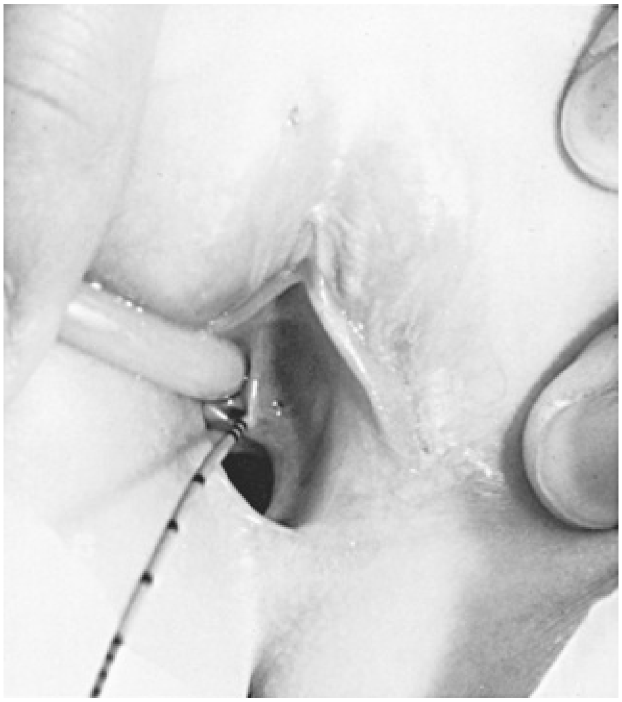

FIG. 558.7 This photograph shows an ectopic ureter entering the vestibule next to the urethral meatus. The thin ureteral catheter with transverse

marks has been introduced into this ectopic ureter. This female had a normal voiding pattern and constant urinary dribbling.

Giggle incontinence typically affects females 7-15 yr of age. The incontinence occurs suddenly during giggling, and the entire bladder volume is lost. The pathogenesis is thought to be sudden relaxation of the urinary sphincter. Anticholinergic medication and timed voiding occasionally are effective. The most effective treatment is low-dose methylphenidate, which seems to stabilize the external sphincter.

Total incontinence in females may be secondary to **epispadias** (see Fig. 556.2 in Chapter 556). This condition, which affects only 1 in 480,000 females, is characterized by separation of the pubic symphysis, separation of the right and left sides of the clitoris, and a patulous urethra. Treatment is bladder neck reconstruction; an alternative surgical therapy is placement of an artificial urinary sphincter to repair the incompetent urethra.

A short, incompetent urethra may be associated with certain urogenital sinus malformations. The diagnosis of these malformations requires a high index of suspicion and a careful physical examination of all incontinent females. In these cases, urethral and vaginal reconstruction often restores continence.

Voiding Disorders Without Incontinence

Some children have abrupt onset of severe urinary frequency, voiding as often as every 10-15 min during the day, without dysuria, UTI, daytime incontinence, or nocturia. The most common age for these symptoms to occur is 4-6 yr, after the child is toilet trained, and most are males. This condition is termed the **daytime frequency syndrome of childhood,** or **pollakiuria** . The condition is functional; no anatomic problem is detected. Often the symptoms occur just before a child starts kindergarten or if the child is having emotional family stress-related problems. These children should be checked for UTIs, and the clinician should ascertain that the child is emptying the bladder satisfactorily. Another contributing cause is constipation. Occasionally, pinworms cause these symptoms. The condition is self-limited, and symptoms generally resolve within 2-3 mo. Anticholinergic therapy rarely is effective.

Some children have the **dysuria–hematuria syndrome,** in which the child has dysuria without UTI but with microscopic or total gross hematuria (blood throughout the stream). This condition affects children who are toilet-trained and is often secondary to hypercalciuria. A 24-hr urine sample should be obtained and calcium and creatinine excretion assessed. A 24-hr calcium excretion of > 4 mg/kg is abnormal and deserves treatment with thiazides, because some of these children are at risk for urolithiasis. **Terminal hematuria** (blood at the end of the stream) occurs in males and typically is secondary to bladder–bowel dysfunction or urethral meatal stenosis. Cystoscopy is not indicated, and the condition usually resolves with treatment for constipation.

Nocturnal Enuresis

By 5 yr of age, 90–95% of children are nearly completely continent during the day, and 80–85% are continent at night. Nocturnal enuresis refers to the occurrence of involuntary voiding at night after 5 yr, the age when volitional control of micturition is expected. Enuresis may be primary (estimated 75–90% of children with enuresis; nocturnal urinary control never achieved) or secondary (10–25%; the child was dry at night for at least a few months and then enuresis developed). Overall, 75% of children with enuresis are wet only at night, and 25% are incontinent day and night. This distinction is important, because children with both forms are more likely to have an abnormality of the urinary tract. *Monosymptomatic enuresis* is more common than *polysymptomatic enuresis* (associated urgency, hesitancy, frequency, daytime incontinence).

Epidemiology

Approximately 60% of children with nocturnal enuresis are males. The family history is positive in 50% of cases. Although primary nocturnal enuresis may be polygenetic, candidate genes have been localized to chromosomes 12 and 13. If one parent was enuretic, each child has a 44% risk of enuresis; if both parents were enuretic, each child has a 77% likelihood of enuresis. Nocturnal enuresis without overt daytime voiding symptoms affects up to 20% of children at the age of 5 yr; it ceases spontaneously in approximately 15% of involved children every year thereafter. Its frequency among adults is < 1%.

Pathogenesis

The pathogenesis of primary nocturnal enuresis (normal daytime voiding habits) is multifactorial (Table 558.2).

Table 558.2

Nocturnal Enuresis

Causes

- Delayed maturation of the cortical mechanisms that allow voluntary control of the micturition reflex
- Defective sleep arousal
- Reduced antidiuretic hormone production at night, resulting in an increased urine output (nocturnal polyuria)
- Genetic factors, with chromosomes 12 and 13q the likely sites of the gene for enuresis
- Bladder factors (lack of inhibition, reduced capacity, overactive)
- Constipation
- Organic factors, such as urinary tract infection, obstructive uropathy, or sickle cell anemia nephropathy
- Sleep disorders
- Sleep-disordered breathing secondary to enlarged adenoids
- Psychological factors more often implicated in secondary enuresis

Other Features

- Enuresis can occur in any stage of sleep (but usually non–rapid eye movement sleep)
- All children are most difficult to arouse in the first third of the night and easiest to awaken in the last third, but enuretic children are more difficult to arouse than those with normal bladder control
- Enuretic children often are described as "soaking the bed"
- Family history in enuretic children often positive for enuresis
- Risk increased with developmental delay, attention-deficit/hyperactivity disorder, autism spectrum disorders

Clinical Manifestations and Diagnosis

A careful history should be obtained, especially with respect to fluid intake at night and the pattern of nocturnal enuresis. Children with diabetes insipidus (see Chapter 574), diabetes mellitus (see Chapter 607), and chronic renal disease (see Chapter 550) can have a high obligatory urinary output and a compensatory polydipsia. The family should be asked whether the child snores loudly at night. Many children with enuresis sleepwalk or talk in their sleep. A complete physical examination should include palpation of the abdomen and possibly a rectal examination after voiding to assess the possibility of a chronically distended bladder and constipation. The child with nocturnal enuresis should be examined carefully for neurologic and spinal abnormalities. There is an increased incidence of bacteriuria in enuretic females, and, if found, it should be investigated and treated (see Chapter 553), although this does not always lead to resolution of bedwetting. A urine sample should be obtained after an overnight fast and evaluated for specific gravity or osmolality to exclude polyuria as a cause of frequency and incontinence and to ascertain that the concentrating ability is normal. The absence of glycosuria should be confirmed. If there are no daytime symptoms, the physical examination and urinalysis are normal, and the urine culture is negative, further evaluation for urinary tract pathology generally is not warranted. A renal ultrasonogram is reasonable in an older child with enuresis or in children who do not respond appropriately to therapy.

Treatment

The best approach to treatment is to reassure the child and parents that the condition is self-limited and to avoid punitive measures that can affect the child's psychological development adversely. Fluid intake should be restricted to 2 oz after 6 or 7 PM . The parents should be certain that the child voids at bedtime. Avoiding extraneous sugar and caffeine after 5 PM also is beneficial. If the child snores and the adenoids are enlarged, referral to an otolaryngologist should be considered, because adenoidectomy can cure the enuresis in some cases.

Active treatment should be avoided in children younger than 6 yr of age, because enuresis is extremely common in younger children. Treatment is more likely to be successful in children approaching puberty compared with younger children. In addition, treatment is most likely to be effective in children who are motivated to stay dry and is less successful in children who are overweight. Treatment should be viewed as a facilitator that requires active participation by the child (e.g., a coach and an athlete).

The simplest initial measure is **motivational therapy** and includes a star chart for dry nights. Waking children a few hours after they go to sleep to have them void often allows them to awaken dry, although this measure is not curative. Some have recommended that children try holding their urine for longer periods during the day, but there is no evidence that this approach is beneficial. **Conditioning therapy** involves use of a loud auditory or vibratory alarm attached to a moisture sensor in the underwear. The alarm activates when voiding occurs and is intended to awaken children and alert them to void. This form of therapy has a reported success of 30–60%, although the relapse rate is significant. Often the auditory alarm wakes up other family members and not the enuretic child; persistent use of the alarm for several months often is necessary to determine whether this treatment is effective. Conditioning therapy tends to be most effective in older children. Another form of therapy to which some children respond is self-hypnosis. The primary role of psychological therapy is to help the child deal with enuresis psychologically and help motivate the child to void at night if he or she awakens with a full bladder.

Pharmacologic therapy is intended to treat the symptom of enuresis and thus is regarded as second line and is not curative. Direct comparisons of the moisture alarm with pharmacologic therapy favor the former because of lower relapse rates, although initial response rates are equivalent.

One form of treatment is **desmopressin acetate,** a synthetic analog of antidiuretic hormone that reduces urine production overnight. This medication is FDA-approved in children and is available as a tablet, with a dosage of 0.2-0.6 mg 2 hr before bedtime. In the past a nasal spray was used, but some children experienced hyponatremia and convulsions with this formulation, and the nasal spray is no longer recommended for nocturnal enuresis. Hyponatremia has not been reported in children using the oral tablets. Fluid restriction at night is important, and the drug should not be used if the child has a systemic illness with vomiting or diarrhea or if the child has polydipsia. Desmopressin acetate is effective in as many as 40% of children and is most effective in those approaching puberty. If effective, it should be used for 3-6 mo, and then an attempt should be made to taper the dosage. Some families use it intermittently (sleepovers, school trips, vacations) with success. If tapering results in recurrent enuresis, the child should return to the higher dosage. Few adverse events have been reported with the long-term use of desmopressin acetate.

For therapy-resistant enuresis or children with symptoms of an overactive bladder, **anticholinergic therapy** is indicated. Oxybutynin 5 mg or tolterodine 2 mg at bedtime often is prescribed. If the medication is ineffective, the dosage may be doubled. The clinician should monitor for constipation as a potential side effect.

A third-line treatment is **imipramine,** which is a tricyclic antidepressant. This medication has mild anticholinergic and α-adrenergic effects, reduces the urine output slightly, and also might alter the sleep pattern. The dosage of imipramine is 25 mg in children age 6-8 yr, 50 mg in children age 9-12 yr, and 75 mg in teenagers. Reported success rates are 30–60%. Side effects include anxiety, insomnia, and dry mouth, and heart rhythm may be affected. If there is any history of palpitations or syncope in the child, or sudden cardiac death or unstable arrhythmia in the family, long QT syndrome in the patient needs to be excluded. The drug is one of the most common causes of poisoning by prescription medication in younger siblings.

In unsuccessful cases, combining therapies often is effective. Alarm therapy plus desmopressin is more successful than either alone. The combination of oxybutynin chloride and desmopressin is more successful than either alone. Desmopressin and imipramine also may be combined.

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CHAPTER 559

Anomalies of the Penis and Urethra

Jack S. Elder

Hypospadias

Hypospadias is a urethral opening on the ventral surface of the penile shaft affecting 1 in 250 male newborns. Typically an isolated defect, its incidence is increased in many males with chromosomal abnormalities, anorectal malformation, and congenital heart disease. Usually, there is incomplete development of the prepuce, called a **dorsal hood,** in which the foreskin is on the sides and dorsal aspect of the penile shaft and deficient or absent ventrally. Some males with hypospadias, particularly those with proximal hypospadias, have **chordee,** in which there is ventral penile curvature during erection. The incidence of hypospadias appears to be increasing, possibly because of in utero exposure to estrogenic or antiandrogenic endocrine-disrupting chemicals (e.g., polychlorobiphenyls, phytoestrogens).

Clinical Manifestations

Hypospadias is classified according to the position of the urethral meatus after taking into account whether chordee is present (Fig. 559.1). The deformity is described as glanular (on the glans penis), coronal, subcoronal, midpenile, penoscrotal, scrotal, or perineal. Approximately 65% of cases are distal, 25% are subcoronal or midpenile, and 10% are proximal. In the most severe cases, the scrotum is bifid and sometimes there is moderate **penoscrotal transposition.** As many as 10% of affected males have a **megameatal variant of hypospadias** in which the foreskin is developed normally (megameatus intact prepuce variant) and there is either glanular or subcoronal hypospadias with a “fish mouth” meatus. These cases might not be diagnosed until after a circumcision is performed.

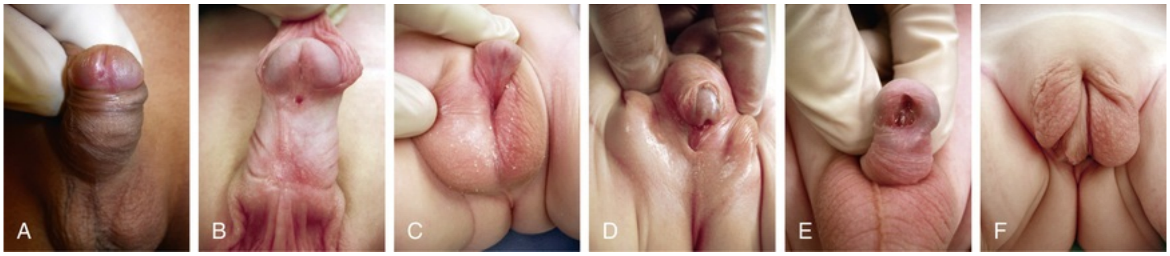

FIG. 559.1 Varying forms of hypospadias. **A,** Glanular hypospadias. **B,** Subcoronal hypospadias. Note the dorsal hood of foreskin. **C,** Penoscrotal hypospadias with chordee. **D,** Perineal hypospadias with chordee and partial penoscrotal transposition. **E,** Megameatal variant of hypospadias diagnosed following circumcision; note absence of hooded foreskin. **F,** Complete penoscrotal transposition with scrotal hypospadias.

Approximately 10% of males with hypospadias have an undescended testis; an inguinal hernia(s) also are common. In the newborn, the differential diagnosis of midpenile or proximal hypospadias associated with an undescended testis should include forms of a **disorder of sex development,** particularly mixed gonadal dysgenesis, partial androgen insensitivity, true hermaphroditism, and congenital adrenal hyperplasia in a female (see Chapter 594). In the latter condition, neither gonad is palpable. A karyotype should be obtained in patients with midpenile or proximal hypospadias and cryptorchidism (see Chapter 606). In males with proximal hypospadias, a voiding cystourethrogram should be considered because 5–10% of these children have a dilated **prostatic utricle,** which is a remnant of the müllerian system (see Chapter 569). The incidence of upper urinary tract abnormalities is low unless there are abnormalities of other organ systems.

Complications of untreated hypospadias include deformity of the urinary stream, typically ventral deflection or severe splaying; sexual dysfunction secondary to penile curvature; infertility if the urethral meatus is proximal; meatal stenosis (congenital), which is uncommon; and cosmetic appearance. The goal of hypospadias surgery is to correct the functional and cosmetic deformities. Whereas hypospadias repair is recommended for all males with midpenile and proximal hypospadias, some males with distal hypospadias have no functional abnormality and do not need surgical correction.

Treatment

Management begins in the newborn period. Circumcision should be avoided because the foreskin often is used in the repair in most cases. The ideal age for repair in a healthy infant is 6-12 mo because the risk of general anesthesia at this age is similar to older children; penile growth over the next several years is slow; the child does not remember the surgical procedure; and postoperative analgesic needs are less than in older children. With the exception of proximal hypospadias, virtually all cases are repaired in a single operation on an ambulatory basis. The most common repair involves tubularization of the urethral plate distal to the urethral meatus, with coverage by a vascularized flap from the foreskin, termed a tubularized incised plate repair. Proximal cases might require a 2-stage repair. The complication rate is low: 5% for distal hypospadias, 10% for midpenile hypospadias, and 40% for proximal hypospadias. The most common complications include urethrocutaneous fistula and meatal stenosis. Other complications include a deformed urinary stream, persistent penile curvature, and dehiscence of the hypospadias repair. Treatment of these complications generally is straightforward. In complex cases, a buccal mucosa graft from the mouth is used to create urethral mucosa. Repair of hypospadias is a technically demanding operation and should be performed by a surgeon with specialty training in pediatric urology and extensive experience.

Chordee Without Hypospadias

In some males, there is mild or moderate ventral penile curvature **(chordee)** and incomplete development of the foreskin **(dorsal hood),** but the urethral meatus is at the tip of the glans (Fig. 559.2). In most of these males, the urethra is normal but there is insufficient ventral penile skin or prominent, inelastic ventral bands of dartos fascia that prevent a straight erection. In some cases, the urethra is hypoplastic, and a formal urethroplasty is necessary for repair. The only sign of this anomaly in the neonate may be the hooded foreskin, and delayed repair under general anesthesia after 6 mo of age is recommended. **Lateral penile curvature** usually is caused by overgrowth or hypoplasia of a corporal (erectile) body and usually is congenital. Surgical repair is recommended at age 6-12 mo.

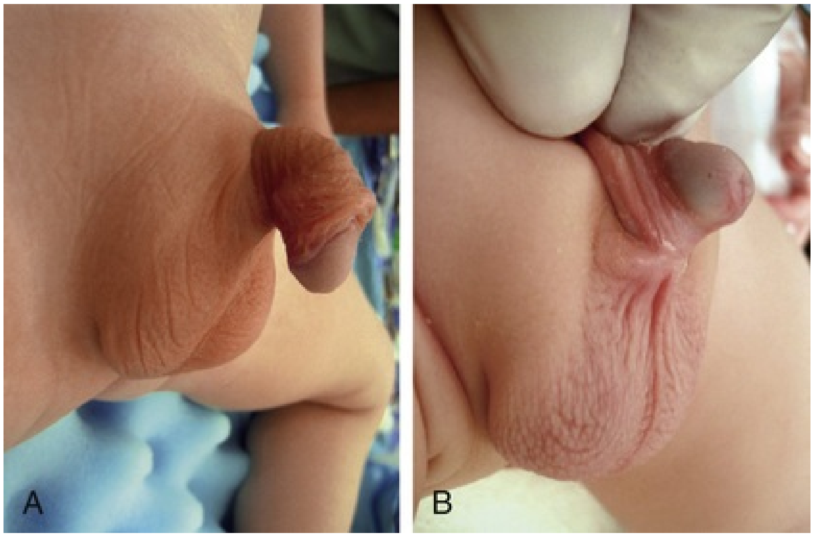

FIG. 559.2 **A** and **B,** Two examples of chordee without hypospadias. Note hooded foreskin and normal location of urethral meatus.

Phimosis and Paraphimosis

Phimosis refers to the inability to retract the prepuce. At birth, phimosis is physiologic. Over time, the adhesions between the prepuce and glans lyse and the distal phimotic ring loosens. In 80% of uncircumcised males, the prepuce becomes retractable by 3 yr of age. Accumulation of epithelial debris under the infant's prepuce is physiologic and does not mandate circumcision. In older males, phimosis may be physiologic, or may be pathologic from **lichen sclerosus (balanitis xerotica obliterans)** at the tip of the foreskin (Fig. 559.3A) and can affect the meatus also (see Fig. 559.3B). The prepuce might have been retracted forcefully on one or two occasions in the past, which can result in a cicatricial scar that prevents subsequent retraction of the foreskin. In males with persistent physiologic or pathologic phimosis, application of corticosteroid ointment to the tip of the foreskin two times daily for 1 mo loosens the phimotic ring in two thirds of cases. If there is ballooning of the foreskin during voiding or phimosis beyond 10 yr of age and topical corticosteroid therapy is ineffective, circumcision is recommended.

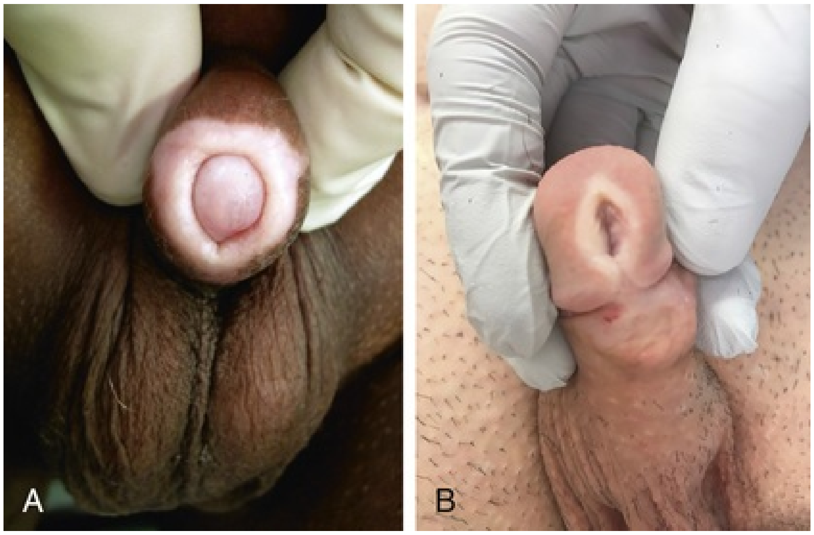

FIG. 559.3 **A,** Balanitis xerotica obliterans. Note whitish cicatricial plaque. **B,** Involvement of the urethral meatus necessitated a meatoplasty.

Paraphimosis occurs when the foreskin is retracted proximal to the coronal sulcus and the prepuce cannot be pulled back over the glans (Fig. 559.4). Painful venous stasis in the retracted foreskin results, with edema leading to severe pain and inability to reduce the foreskin (pull it back over the glans). Treatment includes lubricating the foreskin and glans and then simultaneously compressing the glans and placing distal traction on the foreskin to try to push the phimotic ring past the coronal sulcus. Topical application of granulated sugar has been reported to aid in reduction of edema by creation of an osmotic gradient, facilitating reduction of paraphimosis. In addition, injection of hyaluronidase into the edematous skin has been reported to result in immediate reduction in swelling. In rare cases, emergency circumcision under general anesthesia is necessary.

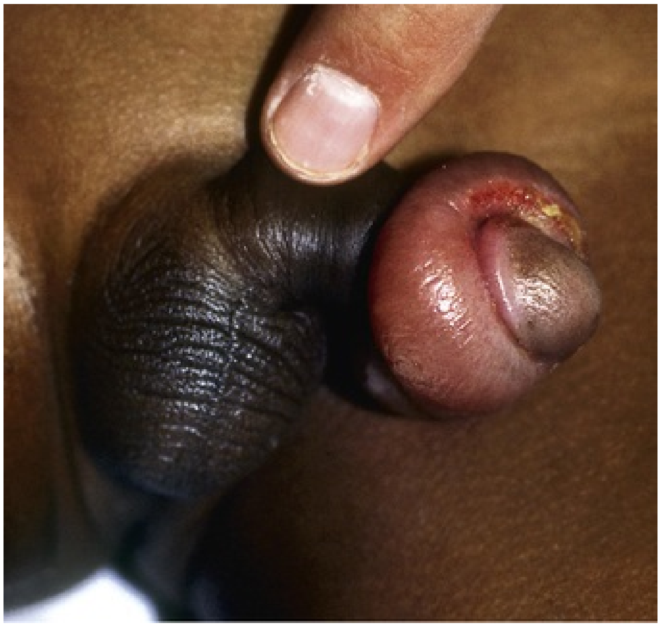

FIG. 559.4 Paraphimosis. The foreskin has been retracted proximal to the glans penis and is markedly swollen secondary to venous congestion.

Circumcision

In the United States, circumcision usually is performed for cultural reasons. In 2012, a multidisciplinary task force of the American Academy of Pediatrics stated that evidence indicates that the health benefits of newborn male circumcision outweigh the risks and that the procedure's benefits justify access to this procedure for families who choose it. Specific benefits identified included prevention of urinary tract infections (UTIs) and penile cancer and reducing the risk and transmission of some sexually transmitted infections, including HIV. The American College of Obstetricians and Gynecologists endorsed this policy statement. By contrast, European medical professional groups have been less likely to endorse this practice.

When performing a neonatal circumcision, local analgesia, such as a dorsal or penile ring block or application of EMLA (eutectic mixture of local anesthetics) cream (lidocaine 2.5% and prilocaine 2.5%) is recommended.

UTIs are 10-15 times more common in uncircumcised *infant* males than in circumcised infants, with the urinary pathogens arising from bacteria that colonize the space between the prepuce and glans. The risk of febrile UTI (see Chapter 553) is highest between birth and 6 mo, but there is an increased risk of

UTI until at least 5 yr of age. Many recommend circumcision in infants who are predisposed to UTI, such as those with congenital hydronephrosis and vesicoureteral reflux. Circumcision reduces the risk of sexually transmitted infections in adults (see Chapter 146), in particular HIV (see Chapter 302). There have been only a handful of reports of adult males who were circumcised at birth and subsequently acquired penile carcinoma, but in Scandinavian countries, where few males are circumcised and hygiene is good, the incidence of penile cancer is low.

Early and late complications after neonatal circumcision include bleeding, wound infection, meatal stenosis, secondary phimosis, removal of insufficient foreskin, and fibrous penile adhesions (skin bridge; Fig. 559.5); 0.2–3.0% of patients undergo a subsequent operative procedure. Males with a large hydrocele or hernia are at particular risk for secondary phimosis because the scrotal swelling tends to displace the penile shaft skin over the glans. Serious complications of newborn circumcision include sepsis, amputation of the distal part of the glans, removal of an excessive amount of foreskin, and urethrocutaneous fistula. Circumcision should not be performed in neonates with hypospadias, chordee without hypospadias, or a dorsal hood deformity (relative contraindication) or in those with a small penis (see Fig. 559.6). In males with a "wandering raphe" (see Fig. 559.6), in which the median raphe deviates to one side, there may be underlying penile torsion or hypospadias, and evaluation by a pediatric urologist is suggested before performing a circumcision.

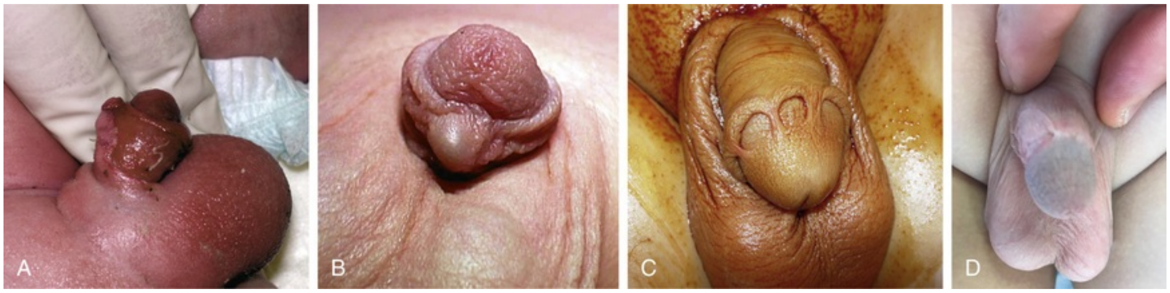

FIG. 559.5 Complications of circumcision. **A,** Denuded penile shaft. With local care, the penis healed and appeared normal. **B,** Midline epithelial inclusion cyst. **C** and **D,** Fibrous penile skin bridges.

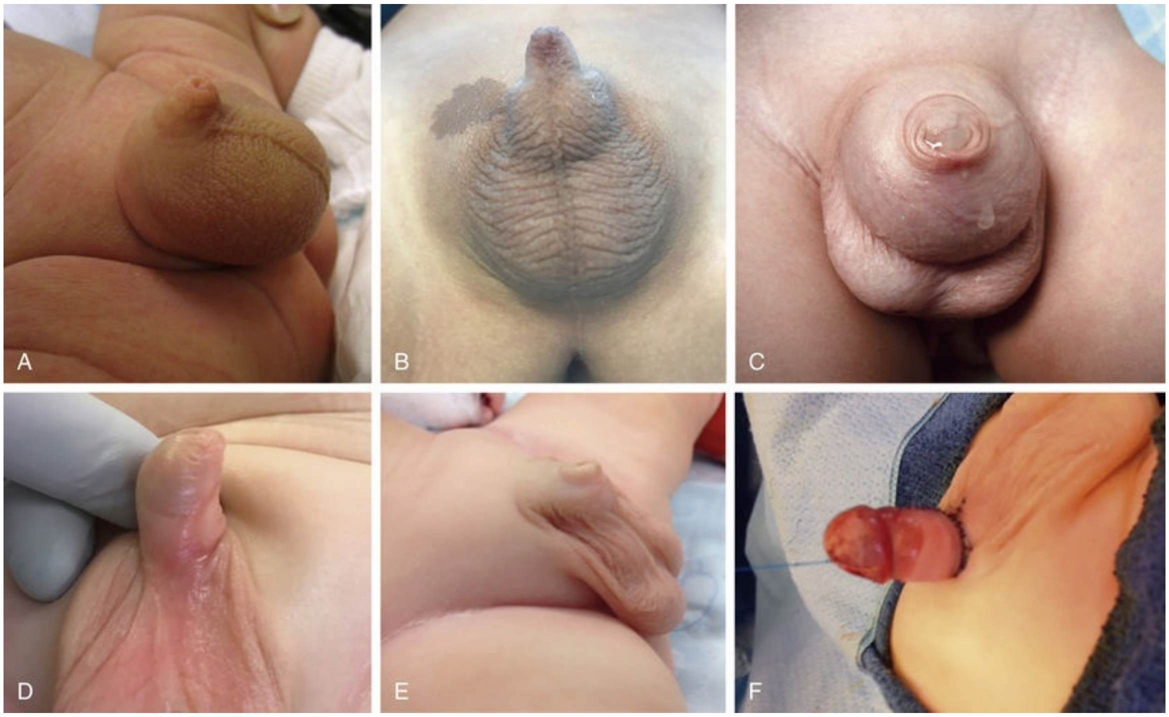

FIG. 559.6 Examples of congenital deformities in which neonatal circumcision is contraindicated. **A** and **B,** Hidden penis. **C,** Megaprepuce. **D,** Penile torsion to left side; note "wandering raphe." **E,** Webbed penis; note scrotal attachment to penile shaft. **F,** Same patient as in **E** following reconstruction at 6 mo.

Penile Torsion

Penile torsion, a rotational defect of the penile shaft, usually occurs in a counterclockwise direction, usually to the left side (see Fig. 559.6). In most cases, penile development is normal, and the condition is unrecognized until circumcision is performed or the foreskin is retractable. In many cases, the midline raphe of the penile shaft is deviated. Penile torsion also occurs in some males with hypospadias. The defect has primarily cosmetic significance, and correction is unnecessary if the rotation is < 60 degrees from the midline. The severity of penile torsion may lessen during infancy.

Inconspicuous Penis

The term *inconspicuous penis* refers to a penis that appears to be small. A **webbed penis** is a condition in which the scrotal skin extends onto the ventral penile shaft. This deformity represents an abnormality of the attachment between the penis and scrotum. Although the deformity might appear mild, if a routine circumcision is performed, the penis can retract into the scrotum, resulting in secondary phimosis **(trapped penis).** The concealed **(hidden or buried)** penis is a normally developed penis that is camouflaged by the suprapubic fat pad (Fig. 559.7). This anomaly may be congenital, iatrogenic after circumcision, or a result of obesity. Surgical correction is indicated for cosmetic reasons or if there is a functional abnormality with a splayed stream.

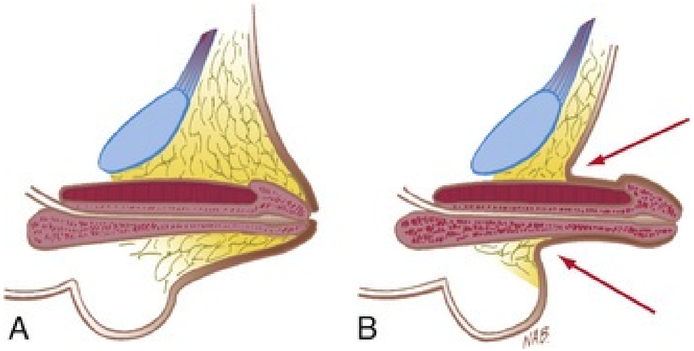

FIG. 559.7 Concealed penis **(A),** which may be visualized by retracting skin lateral to penile shaft **(B).** (From Wein AJ, Kavoussi LR, Novick AC, et al, editors: Campbell-Walsh urology, ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-4, p. 2339.)

A **trapped penis** is an acquired form of inconspicuous penis and refers to a phallus that becomes embedded in the suprapubic fat pad after circumcision (Fig. 559.8). This deformity can occur after neonatal circumcision in an infant who has significant scrotal swelling from a large hydrocele or inguinal hernia or after routine circumcision in an infant with a webbed penis. This complication can predispose to UTIs and can cause urinary retention. Initial treatment of a trapped penis should include topical corticosteroid cream, which often loosens the phimotic ring. In some cases, secondary repair is necessary at 6-9 mo.

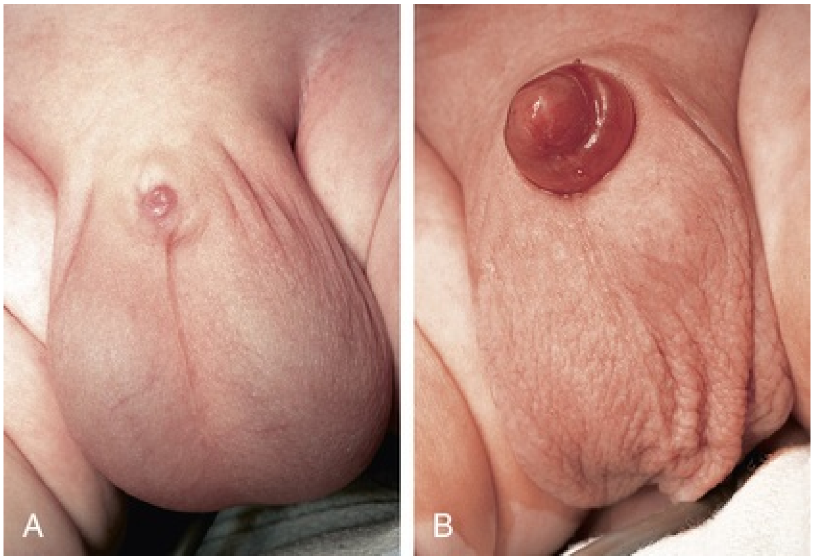

FIG. 559.8 **A,** Trapped (concealed) penis resulting from circumcision. **B,** Same patient after revision of circumcision. (From Wein AJ, Kavoussi LR, Novick AC, et al, editors: Campbell-Walsh urology, ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-2, p. 2340.)

Micropenis

Micropenis is defined as a normally formed penis that is at least 2.5 SD below the mean in size (Fig. 559.9). Typically, the ratio of the length of the penile shaft to its circumference is normal. The pertinent measurement is the *stretched penile length* , which is measured by stretching the penis and measuring the distance from the penile base under the pubic symphysis to the tip of the glans. The mean length of the term newborn penis is 3.5 ± 0.7 cm and the diameter is 1.1 ± 0.2 cm. The diagnosis of micropenis in a male newborn is if the stretched length is < 1.9 cm.

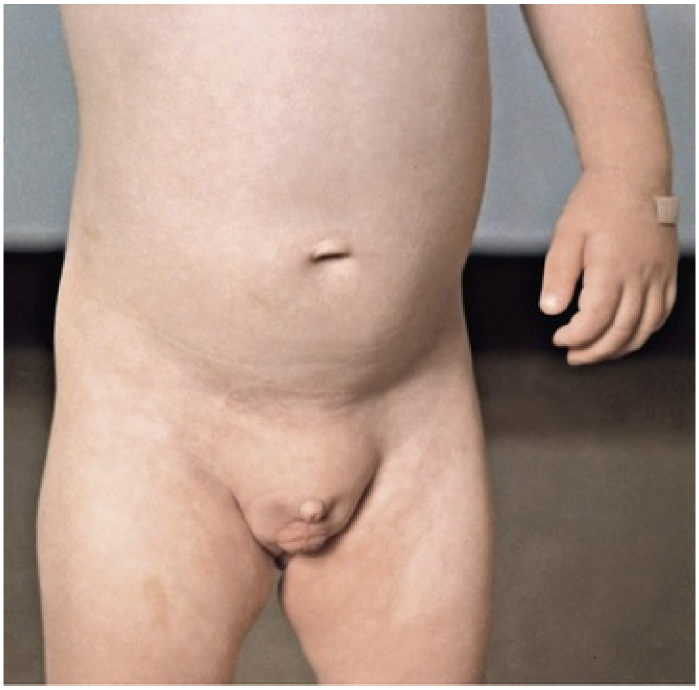

FIG. 559.9 Micropenis secondary to hypopituitarism in an 8 yr old boy. (From Wein AJ, Kavoussi LR, Novick AC, et al, editors: Campbell-Walsh urology, ed 9, Philadelphia, 2007, WB Saunders, Fig. 126-5a, p. 2341.)

Micropenis usually results from a hormonal abnormality that occurs after 14 wk of gestation. Common causes include hypogonadotropic hypogonadism, hypergonadotropic hypogonadism (primary testicular failure), and idiopathic micropenis. If growth hormone deficiency also is present, neonatal hypoglycemia can occur. The most common cause of micropenis is failure of the hypothalamus to produce an adequate amount of gonadotropin-releasing hormone, as typically occurs in Kallmann syndrome (see Chapter 601), Prader-Willi syndrome (see Chapter 98), and Lawrence-Moon-Bardet-Biedl syndrome. In some cases, there is growth hormone deficiency. Primary testicular failure can result from gonadal dysgenesis or rudimentary testes syndrome and also occurs in **Robinow syndrome** (characterized by hypoplastic genitalia, shortening of the forearms, frontal bossing, hypertelorism, wide palpebral fissures, short broad nose, long philtrum, small chin, brachydactyly, and a normal karyotype).

A pediatric endocrinologist, geneticist, and pediatric urologist should examine all children with these syndromes, with participation by medical ethics. Evaluation includes a karyotype, assessment of anterior pituitary function and testicular function, and MRI to determine the anatomic integrity of the hypothalamus and the anterior pituitary gland as well as the midline structure of the brain. One of the difficult questions is whether androgen therapy is essential during childhood, because androgenic stimulation of penile growth in a prepubertal male can limit the growth potential of the penis in puberty. Studies of small groups of men with micropenis suggest that many, although not all, have satisfactory sexual function. Consequently, a decision for gender reassignment is made infrequently.

Priapism

Priapism is a persistent penile erection at least 4 hr in duration that continues beyond, or is unrelated to, sexual stimulation. Typically, only the corpora cavernosa is affected. There are three subtypes:

◆ Ischemic (venoocclusive, low-flow) priapism is characterized by little or no cavernous blood flow, and cavernous blood gases are hypoxic, hypercapnic, and acidotic. The corpora are rigid and tender to palpation.

◆ Nonischemic (arterial, high-flow) priapism is caused by unregulated cavernous arterial inflow. Typically, the penis is neither fully rigid nor painful. There is often a history of antecedent trauma resulting in a cavernous artery–corpora cavernosa fistula.

◆ Stuttering (intermittent) priapism is a recurrent form of ischemic priapism with painful erections with intervening periods of detumescence.

The most common cause of priapism in children is sickle cell disease, which is characterized by a predominance of sickle cell hemoglobin (see Chapter 489.1). As many as 27.5% of children with sickle cell disease develop priapism. The priapism is generally related to a low-flow state, secondary to sickling of red blood cells within the sinusoids of the corpora cavernosa during normal erection, resulting in venous stasis. This situation results in decreased local oxygen tension and pH, which potentiates further stasis and sickling. Priapism typically occurs during sleep, when mild hypoventilatory acidosis depresses oxygen tension and pH in the corpora. There is typically significant corporal engorgement with sparing of the glans penis. If the spongiosum is involved, voiding may be impaired. Evaluation includes a complete blood count and serum chemistry. If the sickle cell status is unknown, hemoglobin electrophoresis should be performed. In some cases, corporal aspiration is performed to distinguish between a high-flow and low-flow state. Other causes of low-flow priapism include sildenafil ingestion and leukemia.

In priapism secondary to sickle cell disease, medical therapy includes exchange transfusion, intravenous hydration, alkalinization, pain management with morphine, and oxygen. The American Urological Association guideline on priapism also recommends concurrent intracavernous treatment beginning with corporal aspiration and irrigation with a sympathomimetic agent, such as phenylephrine. If priapism has been present for > 48 hr, ischemia and acidosis impair the intracavernous smooth muscle response to sympathomimetics. If irrigation and medical therapy are unsuccessful, a corporoglanular shunt should be considered. For stuttering priapism, administration of an oral α-adrenergic agent (pseudoephedrine) once or twice daily is first-line therapy. If this treatment is unsuccessful, an oral β-agonist (terbutaline) is recommended; a gonadotropin-releasing hormone analog plus flutamide is recommended as third-line therapy. Long-term follow-up of adults treated for sickle cell disease as children shows that satisfactory erectile function is inversely related to the patient's age at the onset of priapism and duration of priapism.

Nonischemic (high-flow) priapism most commonly follows perineal trauma, such as a straddle injury, that results in laceration of the cavernous artery. Typically, the aspirated blood is bright red, and the aspirate is similar to arterial blood. Color Doppler ultrasonography often demonstrates the fistula. The priapism can spontaneously resolve. If it does not, angiographic embolization is indicated.

Other Penile Anomalies

Agenesis of the penis affects approximately 1 in 10 million males. The karyotype is almost always 46, XY, and the usual appearance is that of a well-developed scrotum with descended testes and an absent penile shaft. Upper urinary tract abnormalities are common. In most cases, gender reassignment is recommended in the newborn period. **Diphallia** ranges from a small accessory penis to complete duplication.

Meatal Stenosis

Meatal stenosis is a condition that almost always is acquired and occurs after neonatal circumcision. Most probably, it probably results from inflammation of the denuded glans and is difficult to prevent. If the meatus is pinpoint, males void with a forceful, fine stream that goes a great distance. These males can experience dysuria, frequency, hematuria, or a combination of these conditions, typically at age 3-8 yr. UTI is uncommon. Other males have dorsal deflection of the urinary stream. Although the meatus may be small, hydronephrosis or voiding difficulty is extremely rare unless there is associated **balanitis xerotica obliterans** (see Fig. 559.3 ; chronic dermatitis of unknown etiology, generally involving the glans and prepuce, occasionally extending into the urethra). Treatment is meatoplasty, in which the urethral meatus is opened surgically; this procedure can be performed either under anesthesia as an outpatient or in the office using local anesthesia (EMLA cream) with or without sedation. Routine cystoscopy is unnecessary.

Other Male Urethral Anomalies

Parameatal urethral cyst manifests as an asymptomatic small cyst on one side of the urethral meatus. Treatment is excision under anesthesia. **Congenital urethral fistula** is a rare deformity in which a fistula is present from the penile urethra. It usually is an isolated abnormality. Treatment is fistula closure. **Megalourethra** is a large urethra that usually is associated with abnormal development of the corpus spongiosum. This condition is most commonly associated with prune-belly syndrome (see Chapter 555). **Urethral duplication** is a rare condition in which the two urethral channels lie in the same sagittal plane. There are many variations with complete and incomplete urethral duplication. These males often have a double stream. Most commonly, the dorsal urethra is small and the ventral urethra is of normal caliber. Treatment involves excision of the small urethra. **Urethral hypoplasia** is a rare condition in which the entire male urethra is extremely small but patent. In some cases, a temporary cutaneous vesicostomy is necessary for satisfactory urinary drainage. Either gradual enlargement of the urethra or major urethroplasty is necessary. **Urethral atresia** refers to maldevelopment of the urethra and nearly always is fatal unless the urachus remains patent throughout gestation.

Urethral Prolapse (Female)

Urethral prolapse occurs predominantly in black females 1-9 yr of age. The most common signs are bloody spotting on the underwear or diaper, although dysuria or perineal discomfort also can occur (Fig. 559.10). An inexperienced examiner can mistake the finding for sexual abuse. Initial therapy consists of application of estrogen cream 2-3 times daily for 3-4 wk and sitz baths. Manual lysis is recommended for females that fail medical therapy and is curative. In some cases, this can be performed in the office under local anesthesia.

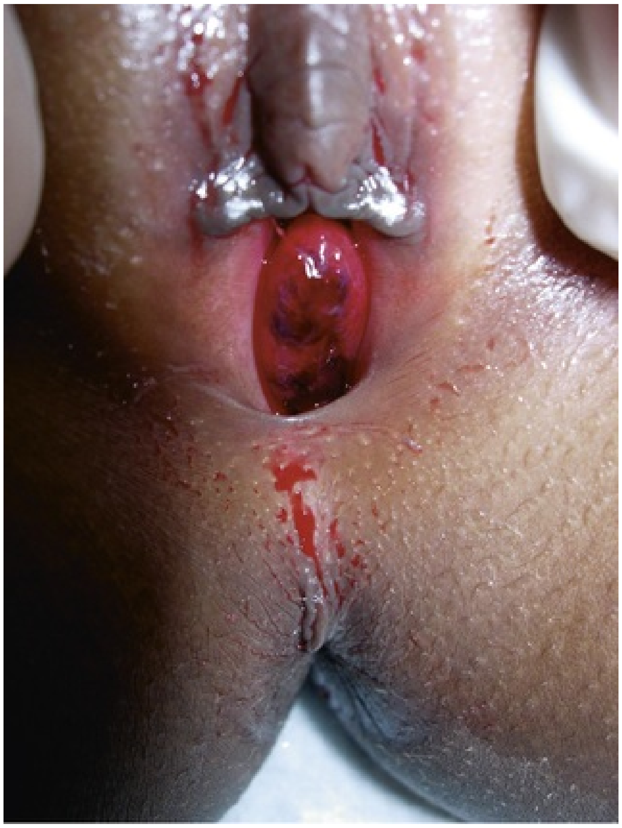

FIG. 559.10 Urethral prolapse in a 4 yr old African-American girl who had bloody spotting on her underwear.

Other Female Urethral Lesions

Paraurethral cyst results from retained secretions in the Skene glands secondary to ductal obstruction (Fig. 559.11). These lesions are present at birth, and most regress in size during the first 4-8 wk, although occasionally incision and drainage is necessary. A **prolapsed ectopic ureterocele** appears as a cystic mass protruding from the urethra and is a presenting symptom in 10% of females with a ureterocele, which is a cystic swelling of the terminal ureter (Fig. 559.12). Ultrasonography should be performed to visualize the upper urinary tracts to confirm the diagnosis. Usually, either the ureterocele is incised or an upper urinary tract reconstructive procedure is necessary.

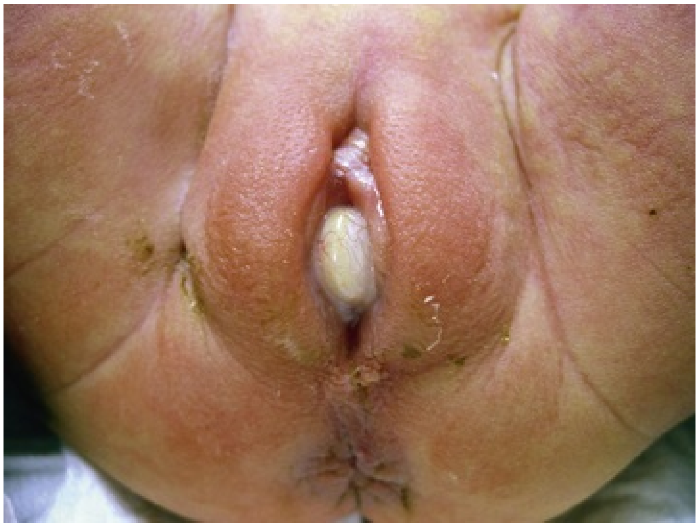

FIG. 559.11 Paraurethral cyst in a newborn girl.

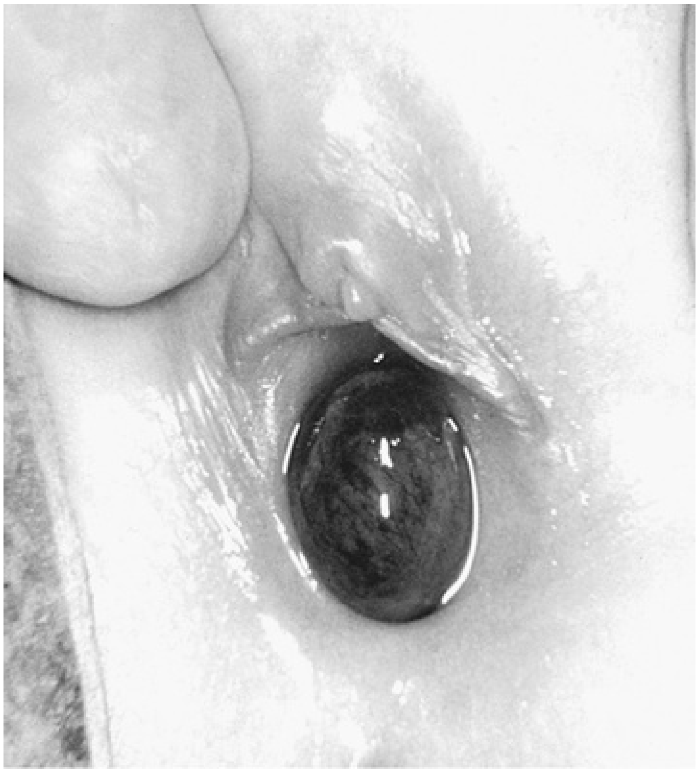

FIG. 559.12 Prolapsed ectopic ureterocele in a female infant. She had a nonfunctioning upper pole collecting system connected to the ureterocele.

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CHAPTER 560

Disorders and Anomalies of the Scrotal Contents

Jack S. Elder

Undescended Testis (Cryptorchidism)

The absence of a palpable testis in the scrotum indicates that the testis is undescended, absent, atrophic, or retractile.

Epidemiology

An undescended **(cryptorchid)** testis is the most common disorder of sexual differentiation in males. At birth, approximately 4.5% of males have an **undescended testis.** Because testicular descent occurs at 7-8 mo of gestation, 30% of premature male infants have an undescended testis; the incidence is 3.4% at term. As many as 50% of congenital undescended testes descend spontaneously during the first 3 mo of life, and by 6 mo the incidence decreases to 1.5%. Spontaneous descent occurs secondary to a temporary testosterone surge (termed a *minipuberty*) during the first 2 mo, which also results in significant penile growth. If the testis has not descended by 4 mo, it will remain undescended. Cryptorchidism is bilateral in 10% of cases. There is some evidence that the incidence of cryptorchidism is increasing. Although cryptorchidism usually is considered to be congenital, some older males have a scrotal testis that “ascends” to a low inguinal position, and therefore requires an orchiopexy. In addition, 1–2% of neonatal and young males undergoing hernia repair develop secondary cryptorchidism from scar tissue along the spermatic cord.

Pathogenesis

The process of testicular descent is regulated by an interaction among genetic, hormonal, and mechanical factors, including testosterone, dihydrotestosterone, müllerian-inhibiting factor, the gubernaculum, intraabdominal pressure, and the genitofemoral nerve. The testis develops in the abdomen at 7-8 wk of gestation. Insulin-like factor 3 controls the transabdominal phase. At 10-11 wk, the Leydig cells produce testosterone, which stimulates differentiation of the wolffian (mesonephric) duct into the epididymis, vas deferens, seminal vesicle, and ejaculatory duct. At 32-36 wk, the testis, which is anchored at the internal inguinal ring by the gubernaculum, begins its process of descent, and is controlled in part by calcium gene-related peptide produced by the genitofemoral nerve. The gubernaculum distends the inguinal canal and guides the testis into the scrotum. Following testicular descent, the patent processus vaginalis (hernia sac) normally involutes.

Clinical Manifestations

Undescended testes are classified as **abdominal** (which are nonpalpable), **peeping** (abdominal but can be pushed into the upper part of the inguinal canal), **inguinal, gliding** (can be pushed into the scrotum but retracts immediately to the pubic tubercle), and **ectopic** (superficial inguinal pouch or, rarely, perineal). Most undescended testes are palpable just distal to the inguinal canal over the pubic tubercle.

A **disorder of sex development** should be suspected in a newborn phenotypic male with bilateral nonpalpable testes, as the child could be a virilized female with congenital adrenal hyperplasia (see Chapter 594). In a male with midpenile or proximal hypospadias and a palpable undescended testis, a disorder of sexual development is present in 15%, and the risk is 50% if the testis is nonpalpable.

The potential **consequences of cryptorchidism** include poor testicular growth, infertility, testicular malignancy, associated hernia, torsion of the cryptorchid testis, and the possible psychological effects of an empty scrotum.

The undescended testis is normal at birth histologically with a plethora of germ cells, but pathologic changes occur by 6-12 mo. Delayed germ cell maturation, germ cell depletion, hyalinization of the seminiferous tubules, and reduced Leydig cell number are typical; these changes are progressive over time if the testis remains undescended. At puberty, an undescended testis has no viable sperm components. Although less severe, changes may occur in the contralateral descended testis after 4-7 yr. After treatment for a unilateral undescended testis, 85% of patients are fertile, which is slightly less than the 90% rate of fertility in an unselected population of adult males. In contrast, following bilateral orchiopexy, only 50–65% of patients are fertile.

The risk of a **germ cell malignancy** (see Chapter 530) developing in an undescended testis is four times higher than in the general population and is approximately 1 in 80 with a unilateral undescended testis and 1 in 40-50 for bilateral undescended testes. Testicular tumors are less common if the orchiopexy is performed before 10 yr of age, but they still occur, and adolescents should be instructed in testicular self-examination. The peak age for developing a malignant testis tumor is 15-45 yr. The most common tumor developing in an undescended testis in an adolescent or adult is a **seminoma** (65%); after orchiopexy, nonseminomatous tumors represent 65% of testis tumors. Orchiopexy seems to reduce the risk of seminoma. Whether early orchiopexy reduces the risk of developing cancer of the testis is controversial, but it is uncommon for testis tumors to occur if the orchiopexy was performed before age 2 yr. The contralateral scrotal testis is not at increased risk for malignancy.

An indirect inguinal hernia usually accompanies a congenital undescended testis but rarely is symptomatic. Torsion and infarction of the cryptorchid testis also are uncommon but can occur because of excessive mobility of undescended testes. Consequently, inguinal pain and/or swelling in a male with an undescended testis should raise the suspicion of an inguinal hernia or torsion of the undescended testis.

An *acquired* or **ascending undescended testis** occurs when a male has a descended testis at birth but during childhood, usually between 4-10 yr of age, the testis does not remain in the scrotum. Such males often have a history of a retractile testis. With testicular ascent on physical examination, the testis can often be manipulated into the upper scrotum, but there is obvious tension on the spermatic cord. This condition is speculated to result from incomplete involution of the processus vaginalis, restricting spermatic cord growth, resulting in the testis gradually moving out of its scrotal position during a male's somatic growth.

On physical examination of the scrotum, the child should be entirely undressed, to help him relax. The examiner should examine the patient's scrotum and inguinal canal using their dominant hand. The nondominant hand is positioned over the pubic tubercle and is pushed inferiorly toward the scrotum.

The examiner's dominant hand is used to try to palpate the testis. If the testis is nonpalpable, the *soap test* often is useful; soap is applied to the inguinal canal and the examiner's hand, significantly reducing friction and facilitating identification of an inguinal testis. In addition, pulling on the scrotum can pull a high inguinal testis into a palpable position. One soft sign that a testis is absent is contralateral testicular hypertrophy, but this finding is not 100% diagnostic.

Retractile testes may be misdiagnosed as undescended testes. Males older than age 1 yr often have a brisk cremasteric reflex, and if the child is anxious or ticklish during scrotal examination, the testis may be difficult to manipulate into the scrotum. Males should be examined with their legs in a relaxed frogleg position, and if the testis can be manipulated into the scrotum comfortably, it is probably retractile. It should be monitored every 6-12 mo with follow-up physical examinations, because it can become an acquired undescended testis. Overall, as many as one third of males with a retractile testis develop an acquired undescended testis requiring orchiopexy, and males younger than 7 yr of age at diagnosis of a retractile testis are at greatest risk. Although definitive data are not available, it is generally thought that males with a retractile testis are not at increased risk for infertility or malignancy.

Approximately 10% of undescended testes are **nonpalpable testes.** Of these, 50% are viable testes in the abdomen or high in the inguinal canal, and 50% are atrophic or absent, almost always in the scrotum, secondary to spermatic cord torsion in utero **(vanishing testis).** If the nonpalpable testis is abdominal, it will not descend after 3 mo of age. Although sonography often is performed to try to identify whether the testis is present, it rarely changes clinical management, because the abdominal testis and atrophic testis are not identified on sonography. Inguinal/scrotal sonography might be beneficial in obese males with a nonpalpable testis; in this clinical setting, the undescended testis often is nonpalpable, and an inguinal/scrotal sonogram can be beneficial in surgical planning. CT scanning is relatively accurate in demonstrating the presence of the testis, but the radiation exposure is significant. MRI is even more accurate, but the disadvantage is that general anesthesia or sedation is necessary in most young children. None of these imaging studies are 100% accurate and in general do not add significantly to clinical decision making by the pediatric urologist or pediatric surgeon. Consequently, routine use of imaging is discouraged. A diagnostic approach is noted in Figure 560.1 .

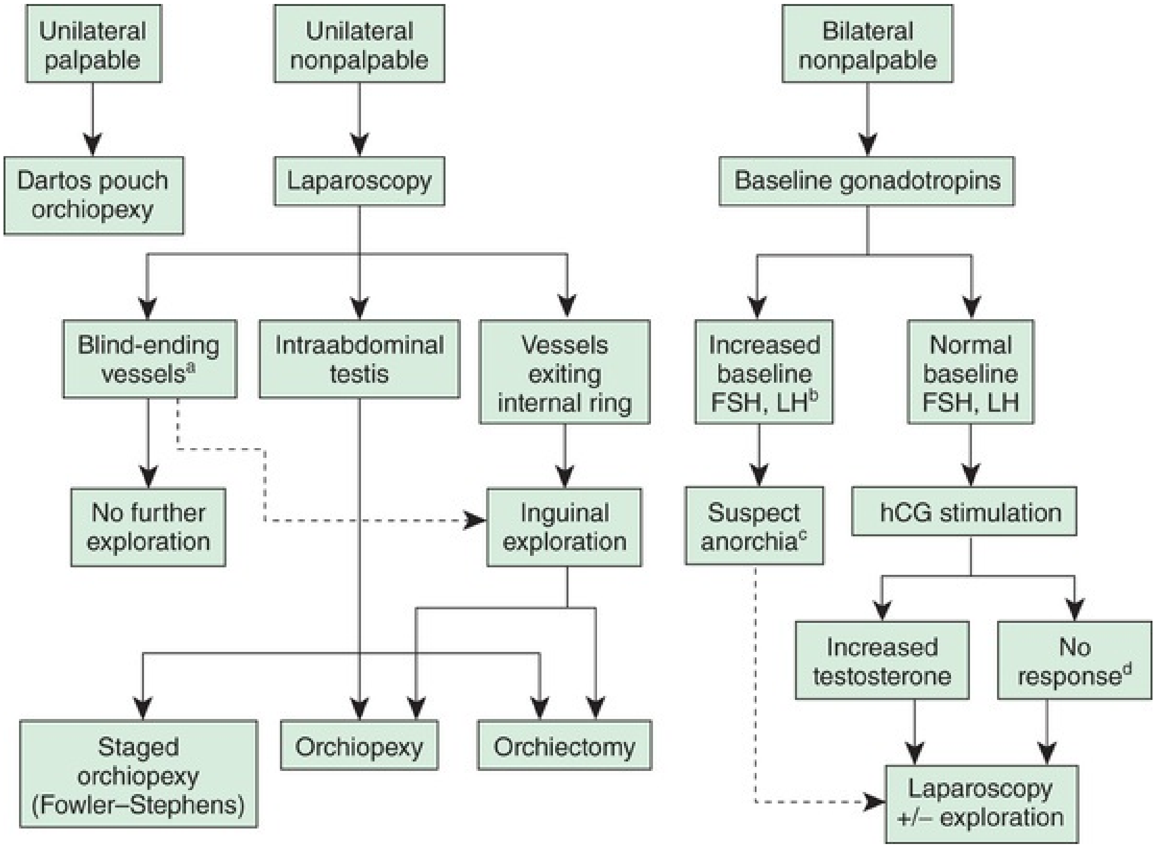
Unilateral palpable
Unilateral nonpalpable
Bilateral nonpalpable
Dartos pouch orchiopexy
Laparoscopy
Baseline gonadotropins
Blind-ending vessels[a]
Intraabdominal testis
Vessels exiting internal ring
Increased baseline FSH, LH[b]
Normal baseline FSH, LH
No further exploration
Inguinal exploration
Suspect anorchia[c]
hCG stimulation
Increased testosterone
No response[d]
Staged orchiopexy (Fowler–Stephens)
Orchiopexy
Orchiectomy
Laparoscopy +/– exploration

FIG. 560.1 Management algorithm for undescended testis. ***a,*** If blind-ending vessels are unequivocally identified, then there is no need for further exploration. ***b,*** Baseline FSH and LH levels are elevated if values are 3 SD above the mean. ***c,*** Increased suspicion of anorchia with elevated baseline FSH and LH levels; however, exploration is still warranted. ***d,*** Testicular remnant tissue may be present despite a negative hCG stimulation test; therefore, exploration for testicular remnant tissue should still be performed. FSH, follicle-stimulating hormone; LH, luteinizing hormone; hCG, human chorionic gonadotropin. (From Lee JJ, Dairiki Shortliffe LM: Undescended testes and testicular tumors. In Ashcraft's pediatric surgery, 6th ed, Philadelphia, 2014, Elsevier, Fig. 51-2, p. 692.)

Treatment

The congenital undescended testis should be treated surgically by 9-15 mo of age. With anesthesia by a pediatric anesthesiologist, surgical correction at 6 mo is appropriate, because spontaneous descent of the testis will not occur after 4 mo of age. Most testes can be brought down to the scrotum with an orchiopexy, which involves an inguinal incision, mobilization of the testis and spermatic cord, and correction of an indirect inguinal hernia. The procedure is typically performed on an outpatient basis and has a success rate of 98%. In some males with a testis that is close to the scrotum, a prescrotal orchiopexy can be performed. In this procedure, the entire operation is performed through a high scrotal incision. Often the associated inguinal hernia also can be corrected through this incision. Advantages of this approach over the inguinal approach include shorter operative time and less postoperative discomfort.

In males with a nonpalpable testis, diagnostic laparoscopy is performed in most centers. This procedure allows safe and rapid assessment of whether the testis is intraabdominal. In most cases, orchiopexy of the intraabdominal testis located adjacent to the internal inguinal ring is successful, but orchiectomy should be considered in more difficult cases or when the testis appears to be atrophic. A two-stage orchiopexy sometimes is needed in males with a high abdominal testis. Males with abdominal testes are managed with laparoscopic techniques at many institutions. Testicular prostheses are available for older children and adolescents when the absence of the gonad in the scrotum might have an undesirable psychological effect. The FDA has approved a saline testicular implant. Solid silicone "carving block" implants also are used (Fig. 560.2). Placement of testicular prostheses early in childhood is recommended for males with anorchia (absence of both testes).

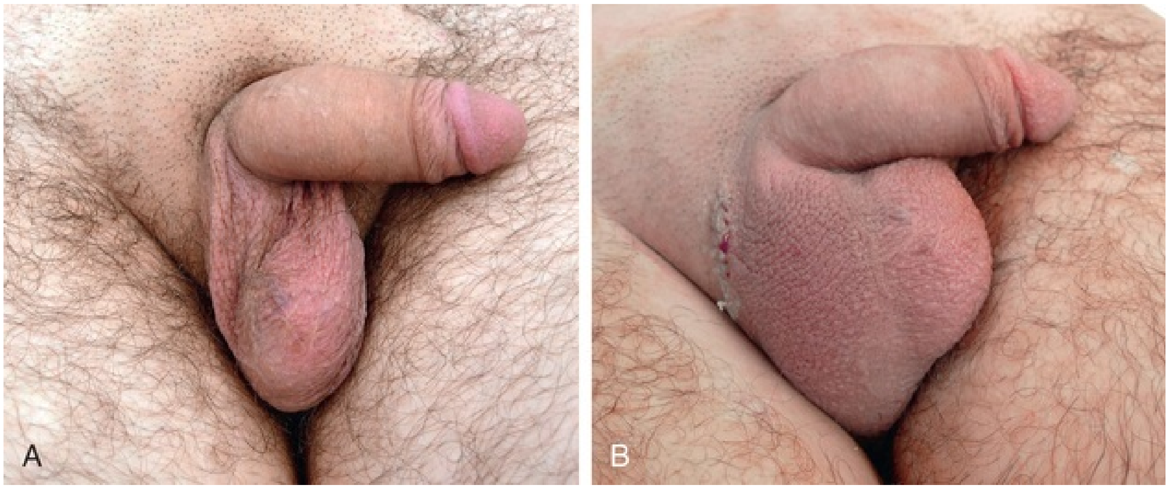

FIG. 560.2 **A,** Adolescent with solitary left testis. **B,** Appearance following implantation of right testicular prosthesis.

The American Urological Association released guidelines for the evaluation and treatment of males with an undescended testis in 2014. Table 560.1 summarizes the primary statements.

Table 560.1

American Urological Association Guidelines for Evaluation and Treatment of Males With an Undescended Testis

DIAGNOSIS

Primary care providers should palpate testes for quality and position at each recommended well-child visit. (Standard)

Providers should refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by 6 mo (corrected for gestational age) to an appropriate surgical specialist for timely evaluation. (Standard)

Providers should refer males with the possibility of newly diagnosed (acquired) cryptorchidism after 6 mo. (Standard)

Providers must immediately consult an appropriate specialist for all phenotypic male newborns with bilateral, nonpalpable testes for evaluation of a possible disorder of sex development (DSD). (Standard)

Providers should not perform ultrasound (US) or other imaging modalities in the evaluation of males with cryptorchidism before referral because these studies rarely assist in decision making. (Standard)

Providers should assess the possibility of a disorder of sex development (DSD) when there is increasing severity of hypospadias with cryptorchidism. (Recommendation)

In males with retractile testes, providers should monitor the position of the testes at least annually to monitor for secondary ascent. (Standard)

TREATMENT

Providers should not use hormonal therapy to induce testicular descent because evidence shows low response rates and lack of evidence for long-term efficacy. (Standard)

In the absence of spontaneous testicular descent by 6 mo (corrected for gestational age), specialists should perform surgery within the next year. (Standard)

In prepubertal males with nonpalpable testes, surgical specialists should perform examination under anesthesia to reassess for palpability of testes. If nonpalpable, surgical exploration and, if indicated, abdominal orchidopexy should be performed. (Standard)

In males with a normal contralateral testis, surgical specialists may perform an orchiectomy (removal of the undescended testis) if a male has a normal contralateral testis and either very short testicular vessels and vas deferens, dysmorphic or very hypoplastic testis, or postpubertal age. (Clinical Principle)

Providers should counsel males with a history of cryptorchidism and/or monorchidism and their parents regarding potential long-term risks and provide education on infertility and cancer risk. (Clinical Principle)

Adapted from Kolon TF, Herndon CDA, Baker LA, et al: Evaluation and treatment of cryptorchidism: AUA Guideline. http://www.auanet.org/common/pdf/education/clinical-guidance/Cryptorchidism.pdf

Scrotal Swelling

Scrotal swelling may be acute or chronic and painful or painless (Table 560.2). Abrupt onset of painful scrotal swelling necessitates prompt evaluation because some conditions, such as testicular torsion and incarcerated inguinal hernia, require emergency surgical management. Tables 560.3 and 560.4 show the differential diagnosis.

Table 560.2

Differential Diagnosis of Pediatric Adolescent Acute Scrotal Pain

- Appendage torsion
  - Appendix testis
  - Other appendage (epididymis, paradidymis, vas aberrans)
- Spermatic cord torsion
  - Intravaginal, acute or intermittent
  - Extravaginal
- Epididymitis
  - Infectious
    - Urinary tract infection
    - Sexually transmitted disease
    - Viral
  - Sterile or traumatic
- Scrotal edema or erythema
  - Diaper dermatitis, insect bite, or other skin lesions
  - Idiopathic scrotal edema
  - Henoch-Schönlein purpura
- Orchitis
  - Associated with epididymitis with or without abscess
  - Vasculitis (e.g., Henoch-Schönlein purpura)
  - Viral illness (mumps)
- Trauma
  - Hematocele or scrotal contusion or testis rupture
- Hernia or hydrocele
  - Inguinal hernia with or without incarceration
  - Communicating hydrocele
  - Encysted hydrocele with or without torsion
  - Associated with acute abdominal pathology (e.g., appendicitis, peritonitis)
- Varicocele
- Intrascrotal mass
  - Cystic dysplasia or tumor of testis
  - Epididymal cyst, spermatocele or tumor
  - Other paratesticular tumors
- Musculoskeletal pain from inguinal tendinitis or muscle strain
- Ilioinguinal neuropathy
- Genitofemoral nerve entrapment
- Referred pain (e.g., ureteral calculus or anomaly)

Modified from Palmer LS, Palmer JS: Management of abnormalities of the external genitalia in boys. In Wein AJ, Kavoussi LRR, Partin AW, Peters CA (eds): Campbell-Walsh Urology, 4th ed, Vol 4, Philadelphia, 2016, Elsevier, Box 146-2, p. 3388.

Table 560.3

Differential Diagnosis of Scrotal Masses in Males and Adolescents

PAINFUL
Testicular torsion
Torsion of appendix testis
Epididymitis
Trauma: ruptured testis, hematocele
Inguinal hernia (incarcerated)
Mumps orchitis
Testicular vasculitis
PAINLESS
Hydrocele
Inguinal hernia[*]
Varicocele[*]
Spermatocele[*]
Testicular tumor[*]
Henoch-Schönlein purpura[*]
Idiopathic scrotal edema

[*] May be associated with discomfort.

Table 560.4

Differential Diagnosis of Scrotal Swelling in Newborn Males

Hydrocele
Inguinal hernia (reducible)
Inguinal hernia (incarcerated)[*]
Testicular torsion[*]
Scrotal hematoma
Testicular tumor
Meconium peritonitis
Epididymitis[*]

[*] May be associated with discomfort.

Clinical Manifestations

A detailed history is helpful in determining the cause of the swelling and includes the onset of pain—with testicular torsion, the pain often is sudden in onset and may be associated with exercise or minor genital trauma; duration of pain; radiation of pain—inguinal discomfort is common with testicular torsion, inguinal hernia, or epididymitis, and associated flank pain can occur with passage of a ureteral calculus; previous episodes of similar pain, which are common in males with intermittent testicular torsion or inguinal hernia; nausea and vomiting, which are associated with testicular torsion and inguinal hernia; and irritative urinary symptoms, such as dysuria, urgency, and frequency, which indicate a urinary tract infection that can cause epididymitis. Some males report a recent history of scrotal trauma. There are multiple reports of familial testicular torsion. Males with lower urinary tract pathology such as urethral stricture or neuropathic bladder may be prone to epididymitis.

Physical examination may be difficult in males with a painful scrotum. Some have advocated performing a spermatic cord block or administering intravenous analgesia to facilitate the examination, but such measures usually are unnecessary. Scrotal wall erythema is common in testicular torsion, epididymitis, torsion of the appendix testis, and an incarcerated hernia. In males with a normal cremasteric reflex, testicular torsion is unlikely. Absence of a cremasteric reflex is nondiagnostic.

Laboratory Findings and Diagnosis

Pertinent laboratory studies include a urinalysis and culture. A positive urinalysis suggests bacterial epididymitis (uncommon before adolescence). Serum studies are not helpful in establishing a diagnosis unless a testicular malignancy is suspected. After initial evaluation, in males with testicular pain color Doppler ultrasonography often is helpful in establishing the diagnosis because it assesses whether testicular blood flow is normal, reduced, or increased (Fig. 560.3). If a hydrocele is present and the testis is nonpalpable, or if an abnormality of the testis is found, sonography also is indicated. Imaging studies are not 100% accurate; they should not be used to decide whether a male with testicular pain should be referred for urologic evaluation.

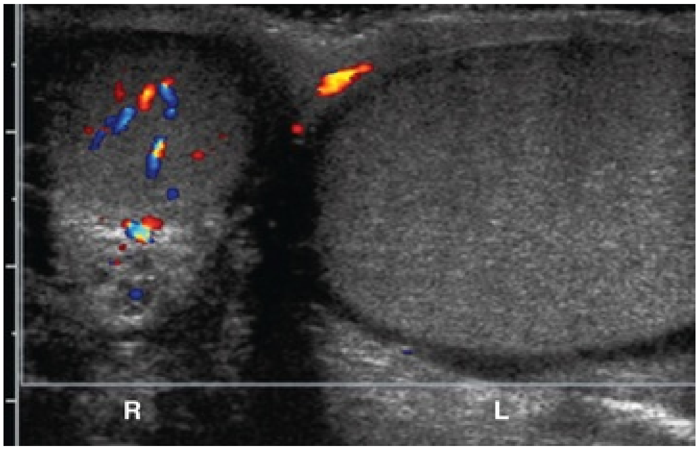

FIG. 560.3 Testicular torsion and axis change. A color Doppler ultrasound in the transverse plane shows color flow in the right testicle. The right testicle is oval to circular, because it has been evaluated in the transverse plane. The left testicle is elongated as if it is in the longitudinal plane. This axis change is the ultrasound equivalent of the worrisome clinical finding suggestive of torsion when accompanied by a history of sudden pain. Lack of color Doppler flow in the left testicle confirms a left testicular torsion. (From Coley BD, editor: Caffey's pediatric imaging, ed 12, Philadelphia, 2013, Elsevier, Fig. 126-13, p. 1300.)

Color Doppler ultrasonography allows assessment of testicular blood flow and testicular morphologic features. Accuracy is > 95% if the ultrasonographer is experienced and the patient is older than 2 yr old. A false-negative study (demonstrates normal testicular blood flow) can occur in a male with testicular torsion if the degree of torsion is < 360 degrees and the duration of torsion is short, because there may be continued testicular perfusion. In males < 1 yr of age, including neonates, blood flow may be difficult to demonstrate in 15% of normal testes.

Testicular (Spermatic Cord) Torsion

Etiology

Testicular torsion requires prompt diagnosis and treatment to salvage the testis. Torsion is the most common cause of severe testicular pain in males age 12 yr and older, and is uncommon before age 10 yr. It is caused by inadequate fixation of the testis within the scrotum, resulting from a redundant tunica vaginalis and abnormal gubernacular attachment, allowing excessive mobility of the testis. The abnormal attachment is termed a **bell clapper deformity** and may be bilateral. Following spermatic cord torsion, venous congestion occurs, and subsequently arterial flow is interrupted. The likelihood of testis survival depends on the duration and severity of torsion. Following 4-6 hr of absent blood flow to the testis, irreversible loss of spermatogenesis can occur. Torsion is familial in 10% of males.

Diagnosis

Testicular torsion produces acute pain and swelling of the scrotum. On examination, the scrotum is swollen, and the testis is exquisitely tender and often difficult to examine. The cremasteric reflex nearly always is absent. The position (lie) of the testis is abnormal, and the testis position often is high in the scrotum. In addition, often there is associated nausea and vomiting. The condition can be differentiated from an incarcerated hernia because swelling in the inguinal area typically is absent with torsion. If the pain duration is < 4-6 hr, manual detorsion may be attempted. In 65% of cases the torsed testis rotates inward, so detorsion should be attempted in the opposite direction (e.g., the left testis is rotated clockwise). Successful manual detorsion results in dramatic pain relief. In the emergency department, prompt scrotal ultrasound should be performed. In some centers, this is performed as a point of care procedure by the emergency department staff.

Some adolescents experience **intermittent testicular torsion** . These males report episodes of severe unilateral testicular pain that resolves spontaneously after 30-60 min. Treatment is elective bilateral scrotal orchiopexy (see Treatment).

Treatment

Treatment is prompt surgical exploration and detorsion. If the testis is explored within 6 hr of torsion, up to 90% of the gonads survive. Testicular salvage decreases rapidly with a delay of > 6 hr. If the degree of torsion is 360 degrees or less, the testis might have sufficient arterial flow to allow the gonad to survive, even after 24-48 hr. Following detorsion, the testis is fixed in the scrotum with nonabsorbable sutures, termed **scrotal orchiopexy,** to prevent torsion in the future. The contralateral testis also should be fixed in the scrotum because the predisposing anatomic condition often is bilateral. If the testis appears nonviable, orchiectomy is performed (Fig. 560.4A). The detorsed testis may undergo compartment syndrome, and following detorsion, despite blood flow to the testis, high intratesticular pressure may cause ischemia and necrosis. This condition has been treated intraoperatively by incising the tunica vaginalis (similar to a blunt testicular rupture) and placing a tunica vaginalis flap over the exposed tunica. Some adolescents do not undergo prompt evaluation and treatment and present with *late phase testicular torsion,* in which there is delayed diagnosis of torsion. Often the testis is high in the scrotum and nontender (see Fig. 560.4*B*). Fertility is reduced in adult males who experience spermatic cord torsion in adolescence, irrespective of whether detorsion or orchiectomy is performed.

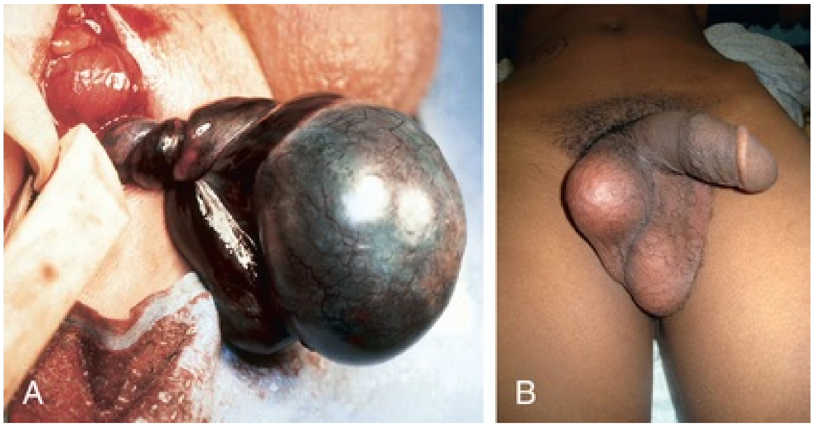

FIG. 560.4 **A,** Left testicular torsion in adolescent with acute scrotum; the testis is necrotic. **B,** "Late-phase torsion" in an adolescent with severe testicular pain 1 mo previously. Note absence of inflammation and high position of testis in scrotum.

Spermatic cord torsion also can occur in the fetus or neonate. This condition results from incomplete attachment of the tunica vaginalis to the scrotal wall and is "extravaginal." When torsion occurs just before delivery, the baby usually is born with a large, firm, nontender testis. Usually the ipsilateral hemiscrotum is ecchymotic (Fig. 560.5). In these cases, the testis rarely is viable because torsion was a remote event. However, the contralateral testis is at increased risk for torsion until 1-2 mo beyond term. The pediatric urology community is divided regarding whether immediate exploration is necessary in a male newborn who has suspected testicular torsion at birth, but if observation is recommended, the family needs to be counseled regarding the risk of contralateral spermatic cord torsion. If the initial exam is normal and the newborn subsequently develops scrotal swelling and erythema, and imaging is consistent with spermatic cord torsion, emergency scrotal exploration is indicated.

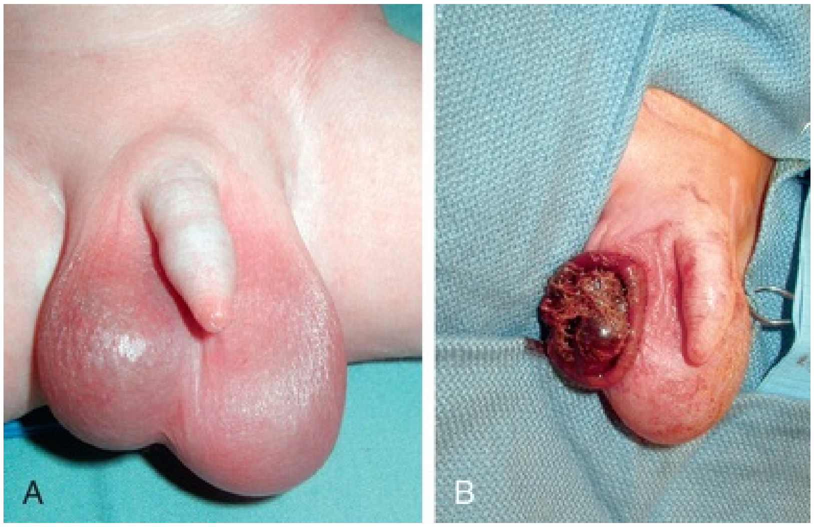

FIG. 560.5 **A** and **B,** Right testicular torsion in a newborn. The right hemiscrotum is darker, and the testis was indurated and enlarged.

Torsion of the Appendix Testis/Epididymis

Torsion of the appendix testis is the most common cause of testicular pain in males 4-10 yr but is uncommon in adolescents. The appendix testis is a stalk-like structure that is a vestigial embryonic remnant of the müllerian (paramesonephric) ductal system that is attached to the upper pole of the testis. When it undergoes torsion, progressive inflammation and swelling of the testis and epididymis occurs, resulting in testicular pain and scrotal erythema. The onset of pain usually is gradual. Palpation of the testis usually reveals a 3- to 5-mm tender indurated mass on the upper pole (Fig. 560.6A). In some cases, the appendage that has undergone torsion may be visible through the scrotal skin, termed the **“blue dot”** sign. In some males, distinguishing torsion of the appendix from testicular torsion is difficult. In such cases, color Doppler ultrasonography is useful because testicular blood flow is normal and shows hyperemia to the upper pole of the testis. In such cases, the radiologist often recognizes epididymal enlargement and makes the diagnosis of epididymitis, reflecting the inflammatory reaction (see Fig. 560.6*B*).

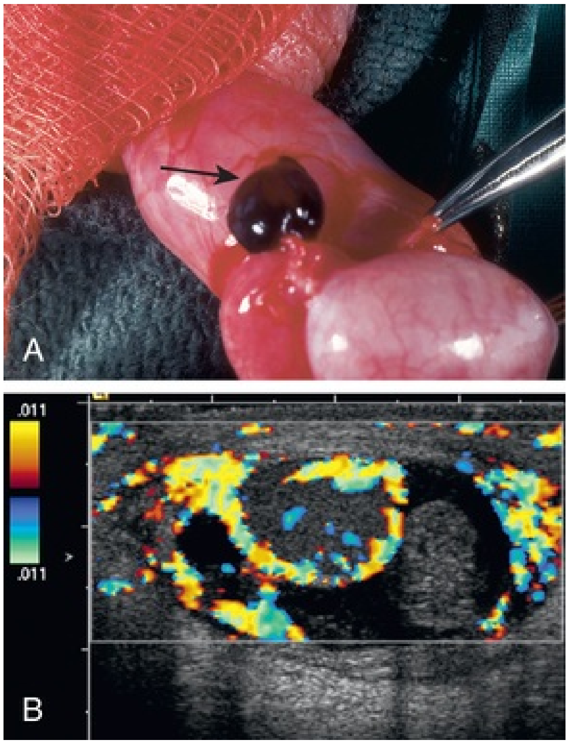

FIG. 560.6 **A,** Torsion of the appendix testis; the appendix testis is necrotic *(arrow).* **B,** Color Doppler scrotal sonogram showing hyperemia to the testis and absent flow to the appendix testis *(right side).* Symptoms resolved with medical therapy.

The natural history of torsion of the appendix testis is for the inflammation to resolve in 3-10 days. Nonoperative treatment is recommended, including bed rest for 24 hr and analgesia with nonsteroidal antiinflammatory medication for 5 days. If the diagnosis is uncertain, scrotal exploration is recommended.

Epididymitis

Acute bacterial inflammation of the epididymis is an ascending retrograde infection from the urethra, through the vas into the epididymis. This condition causes acute scrotal pain, erythema, and swelling. It is rare before puberty and should raise the question of a congenital abnormality of the wolffian duct, such as an ectopic ureter entering the vas. In younger males, the responsible organism is often *Escherichia coli* (see Chapter 227). After puberty, bacterial epididymitis becomes progressively more common and can cause acute painful scrotal swelling in young sexually active males. Urinalysis usually reveals pyuria. Epididymitis can be infectious (usually gonococcus or *Chlamydia* ; see Chapters 219 and 253), but often the organism remains undetermined. Additional etiologies include familial Mediterranean fever, enterovirus, and adenoviruses. Treatment consists of bed rest and antibiotics as indicated. Differentiation from torsion is straightforward with scrotal ultrasonography.

Henoch-Schönlein purpura (see Chapter 192.1) is a systemic vasculitis that involves multiple organ systems and that can involve the kidney and spermatic cord. When the spermatic cord is involved, typically there is bilateral painful scrotal swelling with purpuric lesions involving the scrotum. Scrotal sonography should show normal testicular blood flow. Treatment is directed toward systemic treatment of the Henoch-Schönlein purpura. Isolated testicular vasculitis is less common in Henoch-Schönlein purpura and, in such cases, polyarteritis nodosa should be suspected.

Varicocele

A **varicocele** is a congenital condition in which there is abnormal dilation of the pampiniform plexus in the scrotum, often described as a “bag of worms” (Fig. 560.7). Dilation of the pampiniform venous plexus results from valvular incompetence of the internal spermatic vein. Approximately 15% of adult males have a varicocele; of these, approximately 10–15% are subfertile. Varicocele is the most common (and virtually the only) surgically correctable cause of infertility in males. A varicocele is found in 10–15% of adolescent males, but it rarely is diagnosed in males younger than 10 yr old, because the varicocele becomes distended only after the increased blood flow associated with puberty occurs. Varicoceles occur predominantly on the left side, are bilateral in 2% of cases, and rarely involve the right side only. A varicocele in a male younger than age 10 yr or on the right side might indicate an abdominal or retroperitoneal mass; an abdominal sonogram or CT scan should be performed in such cases.

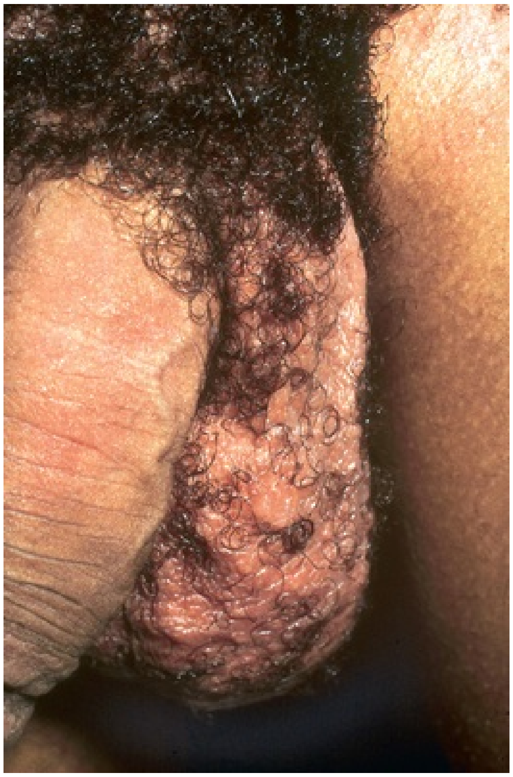

FIG. 560.7 Left varicocele in an adolescent male.

A varicocele typically is a painless paratesticular mass. Occasionally patients describe a dull ache in the affected testis. Usually the varicocele is not apparent when the patient is supine because it is decompressed; in contrast, the varicocele becomes prominent when the patient is standing and enlarges with a Valsalva maneuver. Many pediatricians do not routinely screen adolescents for a varicocele. Varicoceles typically are graded from 1-3 with the male standing: **grade 1** is palpable only with Valsalva (clinically insignificant); **grade 2** is palpable without Valsalva but is not visible on inspection; and **grade 3** is visible with inspection. Males with a grade 3 varicocele are at greatest risk for testicular growth arrest, particularly if the varicocele is larger than the testis. Testicular size should be documented with calipers, an orchidometer, or scrotal sonography, because if the affected left testis is significantly smaller than the right testis, spermatogenesis probably has been adversely affected. A **semen analysis** should be considered in sexually mature adolescents who are Tanner stage V.

The goal of varicocelectomy is to maximize future fertility. Surgical treatment of varicoceles is indicated in males with a significant disparity in testicular size, with pain in the affected testis, if the contralateral testis is diseased or absent, or with oligospermia on semen analysis. Following treatment, typically the involved testis enlarges and catches up with the normal testis over the following 1-2 yr. Varicocelectomy should also be considered in males with a large grade 3 varicocele, even if there is not a disparity in testicular size. Surgical repair is accomplished with a variety of techniques by ligation of the veins of the pampiniform plexus laparoscopically or through an inguinal or subinguinal incision (with or without an operating microscope) or by ligating the internal spermatic vein in the retroperitoneum. The operation is performed on an ambulatory basis.

Spermatocele

A **spermatocele** is a cystic lesion that contains sperm and is attached to the upper pole of the sexually mature testis. Spermatoceles usually are painless and are incidental findings on physical examination. Enlargement of the spermatocele or significant pain is an indication for removal.

Hydrocele

Etiology

A hydrocele is an accumulation of fluid in the tunica vaginalis (Fig. 560.8). Between 1% and 2% of neonates have a hydrocele. In most cases, the hydrocele is noncommunicating (the processus vaginalis was obliterated during development). In such cases, the hydrocele fluid disappears by 1 yr of age. If there is a persistently patent processus vaginalis, the hydrocele persists and may become larger during the day and is small in the morning. A rare variant of a hydrocele is the **abdominoscrotal hydrocele,** in which there is a large, tense hydrocele that extends into the lower abdominal cavity. In some older males, a noncommunicating hydrocele can result from an inflammatory condition within the scrotum, such as testicular torsion, torsion of the appendix testis, epididymitis, or testicular tumor. The long-term risk of a communicating hydrocele is the development of an inguinal hernia. Some older males and adolescents also develop a hydrocele. In some cases, hydrocele develop acutely after an episode of scrotal trauma or epididymoorchitis, whereas others develop more insidiously.

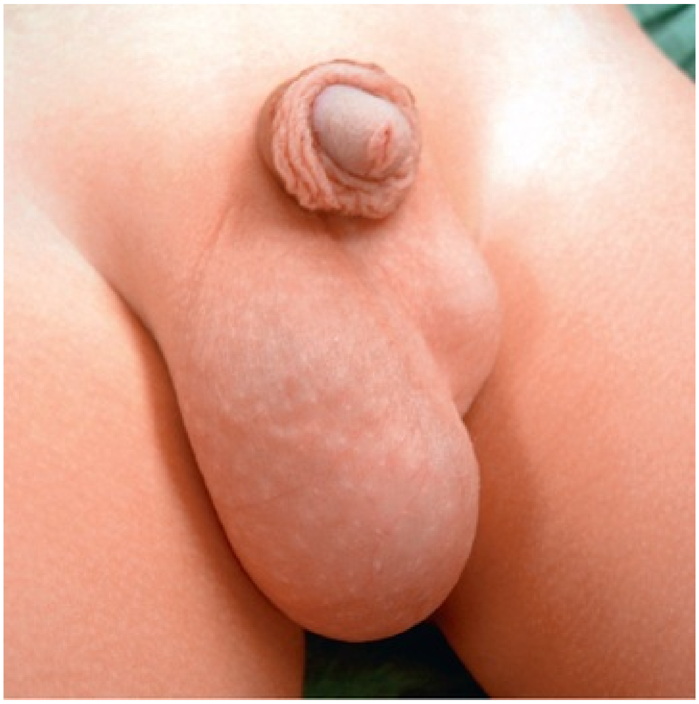

FIG. 560.8 Newborn with large right hydrocele.

Diagnosis

On examination, hydroceles are smooth and nontender. Transillumination of the scrotum confirms the fluid-filled nature of the mass. It is important to palpate the testis, because some young males develop a hydrocele in association with a testis tumor. If the testis is nonpalpable, a scrotal ultrasound should be performed to confirm that the testis is present and normal. If compression of the fluid-filled mass completely reduces the hydrocele, an inguinal hernia/hydrocele is the likely diagnosis.

Treatment

Most congenital hydroceles resolve by 12 mo of age following reabsorption of the hydrocele fluid. If the hydrocele is large and tense, however, early surgical correction should be considered, because it is difficult to verify that the child does not have a hernia, and large hydroceles rarely disappear spontaneously. Hydroceles persisting beyond 12-18 mo often are communicating and should be repaired. Surgical correction is similar to a herniorrhaphy (see Chapter 373). Through an inguinal incision, the spermatic cord is identified, the hydrocele fluid is drained, and a high ligation of the processus vaginalis is performed. If an older male has a large hydrocele, often diagnostic laparoscopy can be performed to determine whether there is a patent processus vaginalis, and if the internal ring is closed, then the hydrocele may be corrected with a scrotal incision.

Inguinal Hernia

Inguinal hernia is discussed in Chapter 373 .

Testicular Microlithiasis

Approximately 2–3% of pediatric scrotal ultrasound examinations demonstrate calcific depositions in the testis, termed testicular microlithiasis. Typically, it is found in males undergoing an examination for testicular pain, varicocele, or scrotal swelling. In adults, it is a common finding in males with infertility and with a germ cell tumor of the testis. In pediatric patients with microlithiasis, there are no guidelines for monitoring, but the condition should be monitored for changes in testicular size or induration, with follow-up ultrasound studies as indicated.

Testicular Tumor

Testicular and paratesticular tumors can occur at any age, even in the newborn. Approximately 35% of prepubertal testis tumors are malignant; most commonly they are yolk sac tumors, although rhabdomyosarcoma and leukemia also can occur in this age-group. In adolescents, 98% of painless solid testicular masses are malignant (see Chapter 530). Most manifest as a painless, hard testicular mass that does not transilluminate. Scrotal ultrasonography should be performed to confirm the finding of a testicular mass, and it can help to delineate the type of testis tumor. Serum tumor markers, including *α-fetoprotein* and *β-human chorionic gonadotropin,* should be drawn. Definitive therapy includes surgical exploration through an inguinal incision. In most cases, a radical orchiectomy, consisting of removal of the entire testis and spermatic cord, is performed. In a prepubertal male, if the ultrasonographic study or surgical exploration suggests that the tumor is localized and benign, such as a teratoma or an epidermoid cyst, testis-sparing surgery with removal only of the mass may be appropriate.

Testicular microlithiasis identified incidentally with ultrasonography may be a risk factor for future neoplasia.

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CHAPTER 561

Trauma to the Genitourinary Tract

Jack S. Elder

Etiology

Most injuries to the genitourinary tract in children result from blunt trauma during falls, athletic activities, or motor vehicle crashes (see Chapter 82). Children are at greater risk of blunt renal injury than are adults, because they have less body fat and because the kidneys are not located directly behind the ribs. Children with a preexisting renal anomaly, such as hydronephrosis secondary to a ureteropelvic junction obstruction, horseshoe kidney, or renal ectopia, also are at increased risk for renal injury. Blunt abdominal or flank trauma often causes a renal injury. Falling can cause a deceleration injury that results in an injury to the renal pedicle, interrupting blood flow to the kidney. If the bladder is full, blunt lower abdominal trauma can cause a bladder rupture. Rupture of the membranous urethra occurs in 5% of pelvic fractures. Straddle injuries usually are associated with trauma to the bulbous urethra.

Symptoms and signs of urinary tract injury include gross or microscopic hematuria, bleeding from the urethral meatus, abdominal or flank pain, a flank mass, fractured lower ribs or lumbar transverse processes, and a perineal or scrotal hematoma.

In more than 50% of cases, there also are major injuries to the brain, spinal cord, skeleton, lungs, or abdominal organs.

Diagnosis

Evaluation of the patient begins after an adequate airway has been established and the patient is hemodynamically stable (see Chapters 80 and 81). With significant abdominal injury, gross hematuria or >50 red blood cells per high-power field, or suspicion of renal injury (deceleration injury, flank pain or bruise), renal imaging is indicated (Fig. 561.1). The bladder should be catheterized unless blood is dripping from the urethral meatus, which is an indication of potential urethral injury. Passing the catheter in the presence of a urethral injury can increase the extent of the damage and convert a partial membranous urethral tear into a total disruption. In these patients, a retrograde urethrogram should be performed by injecting radiopaque contrast medium into the urethral meatus under fluoroscopy. Oblique radiographs demonstrate the extent of the injury and whether urethral continuity is preserved or has been disrupted.

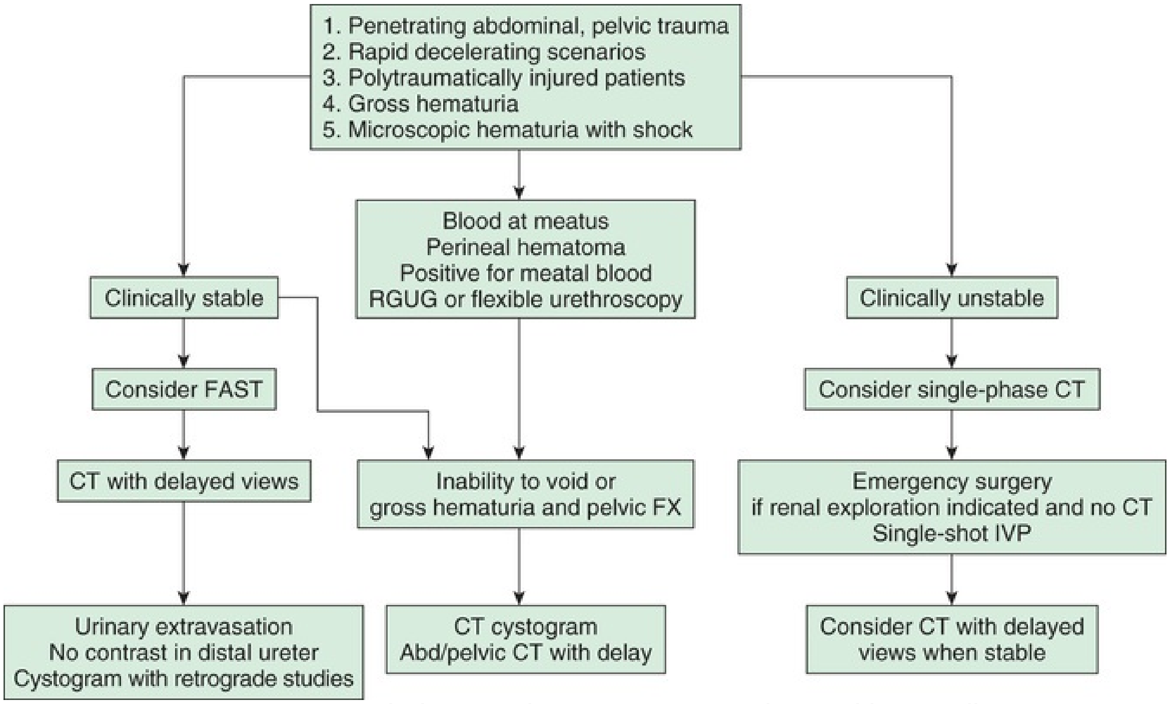
1. Penetrating abdominal, pelvic trauma
2. Rapid decelerating scenarios
3. Polytraumatically injured patients
4. Gross hematuria
5. Microscopic hematuria with shock
Clinically stable
Blood at meatus
Perineal hematoma
Positive for meatal blood
RGUG or flexible urethroscopy
Clinically unstable
Consider FAST
Consider single-phase CT
CT with delayed views
Inability to void or
gross hematuria and pelvic FX
Emergency surgery
if renal exploration indicated and no CT
Single-shot IVP
Urinary extravasation
No contrast in distal ureter
Cystogram with retrograde studies
CT cystogram
Abd/pelvic CT with delay
Consider CT with delayed
views when stable

FIG. 561.1 Recommended evaluation protocol for patients with a medical history or physical findings consistent with possible genitourinary injury. Abd, abdominal; CT, computed tomography; FAST, focused assessment with sonography for trauma; FX, fracture; IVP, intravenous pyelography; RGUG, retrograde urethrogram. (From Husmann DA: Pediatric genitourinary trauma. In Wein AJ, Kavoussi LR, Partin AW, Peters CA, editors: Campbell-Walsh urology, 11th ed, Vol 4, Philadelphia, 2016, Elsevier, Fig. 154-6, p. 3546.)

A 3-phase spiral CT scan should be performed to evaluate the kidneys, ureters, and bladder. The delayed images are important to detect renal extravasation of blood or urine. Prompt function of both kidneys without extravasation usually excludes significant renal injury. Renal injuries are classified according to the grading scale presented in Table 561.1 . Minor renal injuries are most common; these include contusion of the renal parenchyma and shallow cortical lacerations not involving the collecting system. Major renal injuries include deep lacerations involving the collecting system, the shattered kidney, and renal pedicle injuries (Fig. 561.2). Complete absence of function of one kidney without contralateral compensatory hypertrophy (indicating congenital absence) should be regarded as an indication of major injury to the renal pedicle. Renal angiography, once used for further evaluation of renal injuries, particularly if a renal pedicle injury is suspected, now is rarely used because such patients are often hemodynamically unstable, and management is not significantly affected by the findings. In some cases, a preexisting renal anomaly is demonstrated on the study. A ruptured ureteropelvic junction obstruction may be apparent if the kidney is intact but the distal ureter is not visualized.

Table 561.1

Grading of Renal Injuries

GRADE	DESCRIPTION
1	Renal contusion or subcapsular hematoma
2	Nonexpanding perirenal hematoma, < 1 cm parenchymal laceration, no urinary extravasation; all renal fragments viable; confined to renal retroperitoneum
3	Nonexpanding perirenal hematoma, > 1 cm parenchymal laceration, no urinary extravasation; renal fragments may be viable or devitalized
4	Laceration extending into the collecting system with urinary extravasation; renal fragments may be vital or devitalized *or* Injury to the main renal vasculature with contained hemorrhage
5	Completely shattered kidney; by definition, multiple major lacerations > 1 cm associated with multiple devitalized fragments *or* Injury to the main renal vasculature with uncontrolled hemorrhage, renal hilar avulsion

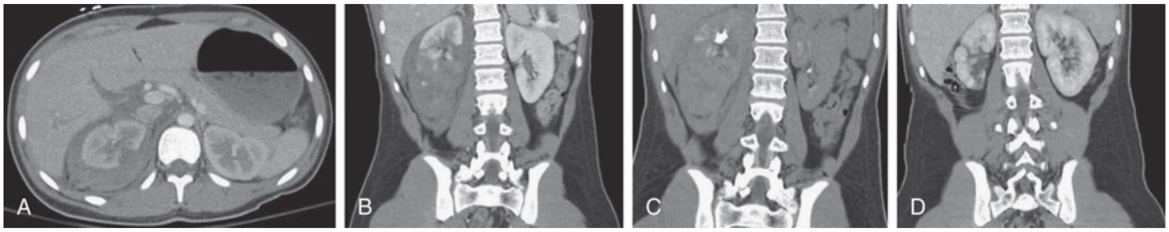

FIG. 561.2 Computed tomography (CT) images of grade 3 right renal trauma—acute, delayed, and at 3-month follow-up. **A,** Acute CT image of

grade 3 renal trauma showing laceration of more than 1 cm of midrenal pole with perinephric hematoma. **B,** Acute CT image coronal reconstruction of grade 3 renal trauma, with possible devitalization of the entire lower pole of the kidney. **C,** Two-hr delayed CT image coronal reconstruction of grade 3 renal trauma, with no urinary extravasation noted and lower pole with questionable devitalization versus contusion. **D,** CT image coronal reconstruction 3 mo after traumatic injury revealing parenchymal scarring at site of laceration with scarred but functional lower pole consistent with healed parenchyma following severe renal contusion. Scarring of lower pole was believed to have occurred with impoverished blood supply owing to severe contusion. (From Husmann DA: Pediatric genitourinary trauma. In Wein AJ, Kavoussi LR, Partin AW, Peters CA, editors: Campbell-Walsh urology, 11th ed, Vol 4, Philadelphia, 2016, Elsevier, Fig. 154-3, p. 3542.)

If there is a pelvic fracture, a urethral transection injury should be suspected, particularly in males. The risk is directly related to the number of broken pubic rami and whether there is separation of the pubic symphysis or displacement of the posterior pubic arch. Radiographic evaluation with retrograde urethrography should be performed if there is blood at the urethral or vaginal meatus, inability to void, and a perineal or penile hematoma.

Treatment

Minor renal injuries such as contusions are managed by bed rest and monitoring of vital signs until abdominal or flank discomfort and gross hematuria have resolved. Children with a major renal injury usually are admitted to an intensive care unit for continuous monitoring of vital signs and urine output. Intravenous antibiotics are also administered. These injuries also are managed nonoperatively, because Gerota's fascia often causes tamponade of bleeding from the kidney, and dramatic healing of the injured parenchyma can occur even with significant urinary extravasation.

Approximately 10% of children with a major renal injury undergo surgical exploration because of associated abdominal injuries, hemodynamic instability, persistent extravasation, or persistent hematuria or to correct a congenital renal deformity. It can be difficult to identify normal and devitalized parenchyma, and the likelihood of having to remove the kidney is significant. If the child is undergoing exploration for other abdominal injuries, the injured kidney is examined. If there is persistent extravasation because of intermittent ureteral obstruction from a blood clot, passage of a temporary double-J stent endoscopically between the bladder and kidney might allow resolution. If the renal pedicle is injured, nephrectomy is necessary. The kidney can be salvaged by emergency renal revascularization only if the kidney is explored within 2-3 hr of the injury. Virtually all penetrating injuries of the kidneys should be explored.

In addition to loss of renal function, the main long-term complication of renal injury is renin-mediated hypertension. Children who sustain significant renal injuries should have periodic measurement of blood pressure if they have any residual renal abnormality.

Ureteral injuries usually are iatrogenic. Injuries of the ureter by blunt or penetrating trauma require immediate surgical attention.

When the bladder can be catheterized, a static cystogram is obtained, infusing a contrast solution through the catheter by gravity, ideally using fluoroscopy. Flat and oblique views are often obtained; a postvoid film also should be obtained because, in some cases, extravasation may be hidden by the full bladder. An alternative is a CT cystogram, which is highly accurate in demonstrating a bladder injury.

Bladder ruptures can be intraperitoneal or extraperitoneal. All intraperitoneal ruptures require surgical repair. Minor extraperitoneal near-ruptures might be treated by catheter drainage but generally require surgical treatment.

Treatment of a **membranous urethral injury** is controversial. Erectile dysfunction, urethral stricture, and urinary incontinence are the major late complications of rupture of the membranous urethra, and therapy is directed at minimizing the risk of these problems. A large pelvic hematoma with tamponade often is present, and an immediate attempt to repair the injury can be technically difficult and result in significant hemorrhage. Many such injuries are managed initially by temporary suprapubic cystostomy, with continuous bladder drainage for 3-6 mo. Subsequently, open or endoscopic urethroplasty can be performed. Alternatively, some try to achieve urethral continuity under anesthesia and leave a urethral catheter for several months. These patients typically require subsequent open urethroplasty.

Penile injury is uncommon. Partial or complete glans amputation is a risk of newborn circumcision with a Mogen clamp. With immediate surgical repair, often the excised glans tissue can be replaced as a free graft. Some males who are in the process of toilet training sustain an injury to the glans penis if the lid of the toilet falls while they are urinating. These males often have a hematoma covering the distal half of the glans. Typically, they have no difficulty urinating and do not need extensive evaluation. Some male infants develop an inadvertent **hair coil tourniquet** or strangulation injury. Typically, a very narrow constriction is noted with severe distal penile swelling and pain. Identification and incision of the hair allows prompt resolution of the edema. The urethra and penile vascularity should be assessed after release of the hair coil. Adolescent males who indulge in extremely vigorous sexual intercourse may sustain rupture of one of the corporal bodies. These males have severe swelling of the penile shaft and require emergency exploration and repair. Males with penetrating injuries of the penis also require emergency debridement and repair.

Testicular injuries are relatively uncommon in children because of the small size of the testes and their mobility within the scrotum. Such injuries usually result from blunt trauma during athletic activity. Typically, these males have significant scrotal swelling, testicular pain, and tenderness (Fig. 561.3A). Ultrasonography demonstrates rupture of the tunica albuginea, which is the capsule of the testis, and surrounding hemorrhage. Prompt surgical treatment of testicular injuries increases the salvage rate (see Fig. 561.3*B*). An uncommon injury is the **zipper injury,** which can affect either the scrotum or foreskin. This problem generally occurs in males who do not wear underwear. The zipper can be cut with bone cutters or metal cutters. Sedation generally is unnecessary.

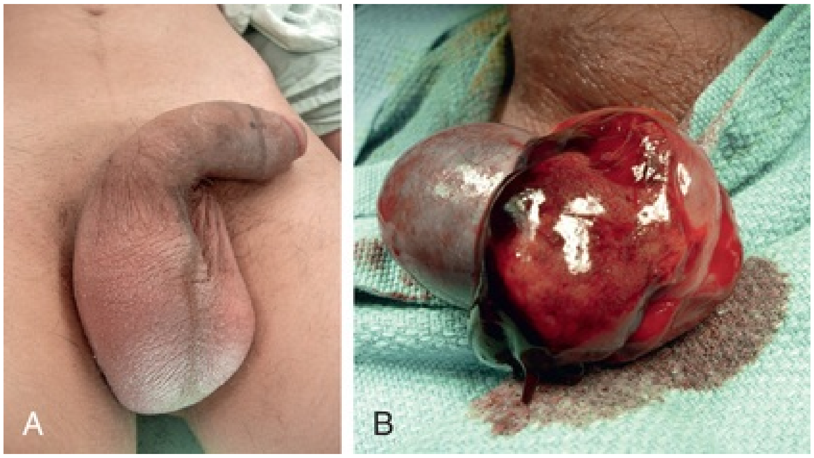

FIG. 561.3 **A,** Adolescent male with blunt right testicular injury. **B,** Tunica albuginea of testis is ruptured; the patient underwent debridement and closure of testicular capsule.

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CHAPTER 562

Urinary Lithiasis

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Urinary lithiasis in children is related to genetic, climatic, dietary, and socioeconomic factors. The incidence is increasing: In 1996, the rate of symptomatic nephrolithiasis was 7.9 in 10,000, whereas in 2007, it was 18.5 in 10,000. In the South, the incidence has increased 26% over the past 10 yr. Adolescents are 10 times more likely to have a symptomatic calculus compared with children 0-3 yr. The increase in stone disease in the United States is attributed to obesity and changes in dietary habits, such as increased sodium and fructose intake, and decreased calcium and water intake.

Urolithiasis is less common in the United States than in other parts of the world. In the United States, 1 in 685 pediatric hospital admissions is for stone disease. Approximately 7% of urinary calculi occur in children younger than 16 yr of age. In the United States, many children with stone disease have a metabolic abnormality. The exceptions are patients with a neuropathic bladder (see Chapter 557), who are prone to infection-initiated renal stones, and those who have urinary tract reconstruction with small or large intestine, which predisposes to bladder calculi. The incidence of metabolic stones is similar in males and females; they are most common in the southeastern United States and are uncommon in African Americans. In Southeast Asia, urinary calculi are endemic and are related to dietary factors. Contamination of infant formula with the organic base and illegally added nitrogen-containing food additive melamine was reported in China in 2008 as a cause.

Stone Formation

Nearly 90% of urinary stones contain calcium as a major constituent, and 60% are composed of calcium oxalate. Most *spontaneous* stones are composed of calcium, oxalate, or phosphate crystals; others are caused by uric acid, cystine, ammonium crystals, or phosphate crystals, or a combination of these substances (Table 562.1). The risk of stone formation increases in the presence of increasing concentrations of these crystals and is reduced with increasing concentrations of urinary inhibitors. Renal calculi develop from crystals that form on the calyx and aggregate to form a calculus. Bladder calculi may be stones that formed in the kidney and traveled down the ureter, or they can form primarily in the bladder.

Table 562.1

Classification of Urolithiasis

CALCIUM STONES (CALCIUM OXALATE AND CALCIUM PHOSPHATE)*

- Hypercalciuria
- Absorptive: increased Ca absorption from gut; types I and II
- Renal leak: decreased tubular reabsorption of Ca
- Resorptive
- Primary hyperparathyroidism (rare in children)
- Iatrogenic
- Loop diuretics
- Ketogenic diet
- Corticosteroids
- Adrenocorticotropic hormone administration
- Methylxanthines (theophylline, aminophylline)
- Distal renal tubular acidosis, type 1 (calcium phosphate)
- Hypocitraturia—citrate most important inhibitor of Ca crystallization
- Vitamin D excess
- Immobilization
- Sarcoidosis
- Cushing disease
- Hyperuricosuria
- Heterozygous cystinuria
- Hyperoxaluria (calcium oxalate)
- Primary hyperoxaluria, types 1 and 2
- Secondary hyperoxaluria
- Enteric hyperoxaluria

CYSTINE STONES

Cystinuria

STRUVITE STONES (MAGNESIUM AMMONIUM PHOSPHATE)

- Urinary tract infection (urea-splitting organism)
- Foreign body
- Urinary stasis

URIC ACID STONES

- Hyperuricosuria
- Lesch-Nyhan syndrome

- Myeloproliferative disorders
  - After chemotherapy
  - Inflammatory bowel disease

INDINAVIR STONES

MELAMINE

NEPHROCALCINOSIS

[*] Most common.

Low urine volume, low urine pH, calcium, sodium, oxalate, and urate are known to promote stone formation. Many inorganic (e.g., citrate, magnesium) and organic (e.g., glycosaminoglycans, osteopontin) substances are known to inhibit stone formation. Organic inhibitory compounds adsorb to the surface of the crystal, thereby inhibiting crystal growth and nucleation.

Stone formation depends on four factors: matrix, precipitation–crystallization, epitaxy, and the absence of inhibitors of stone formation in the urine. **Matrix** is a mixture of protein, nonamino sugars, glucosamine, water, and organic ash that makes up 2–9% of the dry weight of urinary stones and is arranged within the stones in organized concentric laminations. **Precipitation–crystallization** refers to supersaturation of the urine with specific ions composing the crystal. Crystals aggregate by chemical and electrical forces. Increasing the saturation of urine with respect to the ions increases the rate of nucleation, crystal growth, and aggregation and increases the likelihood of stone formation and growth. **Epitaxy** refers to the aggregation of crystals of different composition but similar lattice structure, thus forming stones of a heterogeneous nature. The lattice structures of calcium oxalate and monosodium urate have similar structures, and calcium oxalate crystals can aggregate on a nucleus of monosodium urate crystals. Urine also contains **inhibitors of stone formation,** including citrate, diphosphonate, and magnesium ion.

Clinical Manifestations

Children with urolithiasis usually have gross or microscopic hematuria. If the calculus causes ureteral or renal pelvic obstruction, then severe flank pain (renal colic) or abdominal pain occurs. The calculus typically causes obstruction at areas of narrowing of the urinary tract—the ureteropelvic junction, where the ureter crosses the iliac vessels, and the ureterovesical junction. The ureter progressively narrows distally, and its most narrow segment is the ureterovesical junction. The pain typically radiates anteriorly to the scrotum or labia. Often the pain is intermittent, corresponding to periods of obstruction of urine flow, which increases the pressure in the collecting system. If the calculus is in the distal ureter, the child can have irritative symptoms of dysuria, urgency, and frequency. If the stone passes into the bladder, the child usually becomes asymptomatic. If the stone is in the urethra, dysuria and difficulty voiding can result, particularly in males. Some children pass small amounts of gravel-like material. Stones can also be asymptomatic, although it is uncommon to pass a ureteral calculus without symptoms.

Diagnosis

Approximately 90% of urinary calculi are calcified to some degree and are radiopaque on a plain abdominal film. However, many calculi are only a few millimeters in diameter and are difficult to see, particularly if they are in the ureter. Struvite (magnesium ammonium phosphate) stones are radiopaque. Cystine, xanthine, and uric acid calculi may be radiolucent but often are slightly opacified. Some children have **nephrocalcinosis,** which is calcification of the renal tissue itself. Nephrocalcinosis is seen most commonly in premature neonates receiving furosemide, which causes hypercalciuria, and in children with medullary sponge kidney.

In a child with suspected renal colic, there are multiple imaging options. The most accurate study is an unenhanced spiral CT scan of the abdomen and pelvis (Fig. 562.1). This study takes only a few minutes to perform, has 96% sensitivity and specificity in delineating the number and location of calculi, and demonstrates whether the involved kidney is hydronephrotic. Currently, pediatric imaging centers use low-dose CT, which is similar to three chest x-rays. An alternative is to obtain a plain radiograph of the abdomen and pelvis plus a renal ultrasonogram. These studies can demonstrate hydronephrosis and possibly the calculus on the radiograph; however, the calculus is not visualized on sonography unless it is adjacent to the bladder or in the renal pelvis. In addition, renal calculi < 3 mm typically are not seen. Consequently, the clinician needs to carefully balance the risks of CT imaging against the lower sensitivity of the plain abdominal film plus sonography.

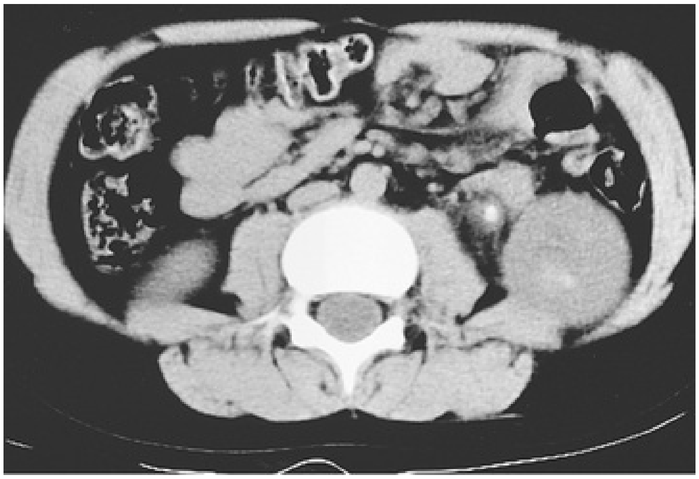

FIG. 562.1 Noncontrast CT scan of the midabdomen in a male infant with cystinuria shows a left-sided calculus at the ureteropelvic junction with proximal hydronephrosis.

In a child with an already-diagnosed calculus, serial plain x-rays or renal ultrasonography can be used to follow the status of the calculus, such as whether it has grown or diminished in size or has moved. If a child has a renal pelvic calculus, a ureteropelvic junction obstruction should be suspected. In some cases, it can be difficult to determine whether hydronephrosis in such a child is secondary to an obstructing stone, ureteropelvic junction obstruction, or both.

Any material that resembles a calculus should be sent for analysis by a laboratory that specializes in identifying the components of urinary calculi.

Metabolic Evaluation

A metabolic evaluation for the most common predisposing factors should be undertaken in all children with urolithiasis, bearing in mind that structural, infectious, and metabolic factors often coexist. This evaluation should not be undertaken in a child who is in the process of passing a stone, because the altered diet and hydration status, as well as the effect of obstruction on the kidney, can alter the results of the study. Table 562.2 lists the basic laboratory studies required, and Table 562.3 shows the normal values for 24-hr urine collections. In children with hypercalciuria, further studies of calcium excretion with dietary calcium restriction and calcium loading are necessary.

Table 562.2

Laboratory Tests Suggested for Evaluation of Urolithiasis

SERUM

- Calcium
- Phosphorus
- Uric acid
- Electrolytes and anion gap
- Creatinine
- Alkaline phosphatase

URINE

- Urinalysis
- Urine culture
- Calcium:creatinine ratio
- Spot test for cystinuria
- 24 hr collection for:
- Creatinine clearance
- Calcium
- Phosphate
- Oxalate
- Uric acid
- Dibasic amino acids (if cystine spot test result is positive)

Table 562.3

Urine Chemistry: Normal Values

URINE CONSTITUENT	AGE	RANDOM	TIMED	COMMENTS
Calcium	0-6 mo	<0.8 mg/mg creat	<4 mg/kg/24 hr	Prandial variation
	7-12 mo	<0.6 mg/mg creat		Sodium-dependent
	≥2 yr	<0.21 mg/mg creat		
Oxalate*	<1 yr	0.15-0.26 mmol/mmol creat	≥2 yr: <0.5 mmol/1.73 m^2 /24 hr	Random urine mmol/mmol highly age-dependent
	1-<5 yr	0.11-0.12 mmol/mmol creat		Excretion rate/1.73 m^2 constant through childhood and adulthood
	5-12 yr	0.006-0.15 mmol/mmol creat		
	>12 yr	0.002-0.083 mmol/mmol creat		
Uric acid	Term infant	3.3 mg/dL GFR †	<815 mg/1.73 m^2 /24 hr	Excretion rate/1.73 m^2 from >1 yr age; constant through childhood
	>3 yr	<0.53 mg/dL GFR		
Magnesium	>2 yr	<0.12 mg/mg creat	<88 mg/1.73 m^2 /24 hr	Excretion rate/1.73 m^2 constant through childhood
Citrate		>400 mg/g creat		Limited data available for children
Cystine		<75 mg/g creat	<60 mg/1.73 m^2 /24 hr	Cystine >250 mg/g creat suggests homozygous cystinuria

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[*] Oxalate oxidase assay.

[†] (mg/dL uric acid) (serum creatinine concentration/urine creatinine concentration).

creat, Creatinine; GFR, glomerular filtration rate.

From Milliner DS: Urolithiasis. In Avner ED, Harmon WE, Naiudet P, editors: Pediatric nephrology, ed 5, Philadelphia, 2004, Lippincott Williams & Wilkins, p. 1103, with permission.

Pathogenesis of Specific Renal Calculi

Calcium Oxalate and Calcium Phosphate Calculi

Most urinary calculi in children in the United States are composed of calcium oxalate and/or calcium phosphate. The most common metabolic abnormality in these patients is **normocalcemic hypercalciuria.** Between 30% and 60% of children with calcium stones have hypercalciuria without hypercalcemia. Other metabolic aberrations that predispose to stone disease include hyperoxaluria, hyperuricosuria, hypocitruria, heterozygous cystinuria, hypomagnesuria, hyperparathyroidism, and renal tubular acidosis (see Chapter 547).

Hypercalciuria may be absorptive, renal, or resorptive. The primary disturbance in absorptive hypercalciuria is intestinal hyperabsorption of calcium. In some children, an increase in 1,25-dihydroxyvitamin D is associated with the increased calcium absorption, whereas in others, the process is independent of vitamin D. **Renal hypercalciuria** refers to impaired renal tubular reabsorption of calcium (see Chapter 540.4). Renal leak of calcium causes mild hypocalcemia, which triggers an increased production of parathyroid hormone, with increased intestinal absorption of calcium and increased mobilization of calcium stores. Resorptive hypercalciuria is uncommon and is found in patients with primary hyperparathyroidism. Excess parathyroid hormone secretion stimulates intestinal absorption of calcium and mobilization of calcium stores. Table 562.4 summarizes the metabolic evaluation of children with hypercalciuria.

Table 562.4

Metabolic Evaluation of Children With Hypercalciuria

TYPE	SERUM	RESTRICTED CALCIUM	FASTING CALCIUM	CALCIUM LOAD	PARATHYROID

	CALCIUM	(URINE)	(URINE)	(URINE)	HORMONE (SERUM)
Absorptive	N	N or I	N	I	I
Renal	N	I	I	I	N
Resorptive	I	I	I	I	I

I, increased; N, normal.

Hyperoxaluria is another potentially important cause of calcium stones. Oxalate increases the solubility product of calcium oxalate crystallization 7-10 times more than calcium. Consequently, hyperoxaluria significantly increases the likelihood of calcium oxalate precipitation. Oxalate is found in high concentration in tea, coffee, spinach, and rhubarb. Primary hyperoxaluria is a rare autosomal recessive disorder that can be subclassified into glycolic aciduria and L -glyceric aciduria. Most patients with primary hyperoxaluria have glycolic aciduria; oxalic and glycolic acids are increased in the urine of affected persons. Both defects cause increased endogenous production of oxalate, with hyperoxaluria, urolithiasis, nephrocalcinosis, and injury to the kidneys. Death from renal failure occurs by age 20 yr in untreated patients. **Oxalosis,** defined as extrarenal deposition of calcium oxalate, occurs when renal insufficiency is present with elevated plasma oxalate. Calcium oxalate deposits appear first in blood vessels and bone marrow, and with time they appear throughout the body. Secondary hyperoxaluria is more common and can occur in patients with increased intake of oxalate and oxalate precursors such as vitamin C, in those with pyridoxine deficiency, and in children with intestinal malabsorption.

Enteric hyperoxaluria refers to disorders such as inflammatory bowel disease (see Chapter 362), pancreatic insufficiency (see Chapter 377), and biliary disease (see Chapter 383), in which there is gastrointestinal malabsorption of fatty acids, which bind intraluminal calcium and form salts that are excreted in the feces. Normally, calcium forms a complex with oxalate to reduce oxalate absorption, but if calcium is unavailable, there is increased absorption of unbound oxalate.

Hypocitraturia refers to a low excretion of citrate, which is an important inhibitor of calcium stone formation. Citrate acts as an inhibitor of calcium urolithiasis by forming complexes with calcium, increasing the solubility of calcium in the urine, and inhibiting the aggregation of calcium phosphate and calcium oxalate crystals. Disorders such as chronic diarrhea, intestinal malabsorption, and renal tubular acidosis can cause hypocitraturia. It may also be idiopathic.

Renal tubular acidosis (RTA) is a syndrome involving a disturbance of acid–

base balance within the kidney that can be classified into three types, one of which predisposes to renal calculi that typically are calcium phosphate (see Chapter 547). In type 1 RTA, the distal nephron does not secrete hydrogen ion into the distal tubule. The urine pH is never < 5.8, and hyperchloremic hypokalemic acidosis results. Patients acquire nephrolithiasis, nephrocalcinosis, muscle weakness, and osteomalacia. Type 1 RTA can be an autosomal dominant disorder, but more often it is acquired and associated with systemic diseases such as Sjögren syndrome, Wilson disease, primary biliary cirrhosis, and lymphocytic thyroiditis, or it results from amphotericin B, lithium, or toluene (an organic solvent associated with glue sniffing).

From 5–8% of patients with **cystic fibrosis** (see Chapter 432) have urolithiasis. Typically, the stones are calcium, and they often become manifest in adolescence or young adulthood. Microscopic nephrocalcinosis also occurs in younger children with the disease. These patients do not have hypercalciuria, and the propensity for urolithiasis has been speculated to result from an inability to excrete a sodium chloride load or from intestinal malabsorption.

Other disorders can play a role in causing calcium stones. **Hyperuricosuria** may be related to the epitactic growth of calcium oxalate crystals around a nucleus of uric acid crystals or to the action of uric acid as a counterinhibitor of urinary mucopolysaccharides, which inhibit calcium oxalate crystallization. Heterozygous **cystinuria** is found in some patients with calcium stones. The mechanism is unknown but may be similar to that of uric acid. Sarcoidosis (see Chapter 190) causes an increased sensitivity to vitamin D_3 and thus an increased absorption of calcium from the gastrointestinal tract. In Lesch-Nyhan syndrome (see Chapter 108), there is excessive uric acid synthesis. These patients are more likely to form uric acid stones, but some of these stones may be calcified. **Immobility** can cause hypercalciuria by mobilization of calcium stores. High-dose corticosteroids can cause hypercalciuria and calcium oxalate precipitation. Furosemide, which is administered in the neonatal intensive care unit, also can cause severe hypercalciuria, urolithiasis, and nephrocalcinosis.

In some children, calcium calculi are idiopathic. A complete metabolic evaluation must be performed before this diagnosis is made.

Cystine Calculi

Cystinuria accounts for 1% of renal calculi in children. The condition is a rare autosomal recessive disorder of the epithelial cells of the renal tubule that prevents absorption of the four dibasic amino acids (cystine, ornithine, arginine, lysine) and results in excessive urinary excretion of these products. The only known complication of this familial disease is the formation of calculi, because of the low solubility of cystine. The patients usually have acidic urine, which leads to a higher rate of precipitation. In the homozygous patient, the daily excretion of cystine usually exceeds 500 mg, and stone formation occurs at an early age. Heterozygotes excrete 100-300 mg/day and typically do not have clinical urolithiasis. The sulfur content of cystine gives these stones their faint radiopaque appearance.

Struvite Calculi

Urinary tract infections (see Chapter 553) caused by urea-splitting organisms (most often *Proteus* spp., and occasionally *Klebsiella* spp., *Escherichia coli, Pseudomonas* spp., and others) result in urinary alkalinization and excessive production of ammonia, which can lead to the precipitation of magnesium ammonium phosphate (struvite) and calcium phosphate. In the kidney, the calculi often have a staghorn configuration, filling the calyces. The calculi act as foreign bodies, causing obstruction, perpetuating infection, and causing gradual kidney damage. Patients with struvite stones also can have metabolic abnormalities that predispose to stone formation. These stones often are seen in children with neuropathic bladder, particularly those who have undergone a urinary tract reconstructive procedure (see Chapter 557). Struvite stones also can form in the reconstructed bladder of children who have undergone augmentation cystoplasty or continent urinary diversion.

Uric Acid Calculi

Calculi containing uric acid represent < 5% of all cases of lithiasis in children in the United States but are more common in less-developed areas of the world. Hyperuricosuria with or without hyperuricemia is the common underlying factor in most cases. The stones are radiolucent on x-ray. The diagnosis should be suspected in a patient with persistently acid urine and urate crystalluria.

Hyperuricosuria can result from various inborn errors of purine metabolism that lead to overproduction of uric acid, the end product of purine metabolism in humans. Children with the Lesch-Nyhan syndrome and patients with glucose-6-phosphatase deficiency (see Chapter 105) form urate calculi as well. In children with short-bowel syndrome (see Chapter 364.7), and particularly those with ileostomies, chronic dehydration and acidosis sometimes are complicated by uric acid lithiasis.

One of the most common causes of uric acid lithiasis is the rapid turnover of purine with some tumors and myeloproliferative diseases. The risk of uric acid lithiasis is especially great when treatment of these diseases causes rapid breakdown of nucleoproteins. Uric acid calculi or “sludge” can fill the entire upper collecting system and cause renal failure and even anuria. Urates also are present within calcium-containing stones. In these cases, more than one predisposing factor for stone formation can exist.

Indinavir Calculi

Indinavir sulfate is a protease inhibitor approved for treating HIV infection (see Chapter 302). Up to 4% of patients acquire symptomatic nephrolithiasis. Most of the calculi are radiolucent and are composed of indinavir-based monohydrate, although calcium oxalate and/or phosphate have been present in some. After each dose, 12% of the drug is excreted unchanged in the urine. The urine in these patients often contains crystals of characteristic rectangles and fan-shaped or starburst crystals. Indinavir is soluble at a pH of < 5.5. Consequently, dissolution therapy by urinary acidification with ammonium chloride or ascorbic acid should be considered.

Nephrocalcinosis

Nephrocalcinosis refers to calcium deposition within the renal tissue. Often nephrocalcinosis is associated with urolithiasis. The most common causes are furosemide (administered to premature neonates), distal RTA, hyperparathyroidism, medullary sponge kidney, hypophosphatemic rickets, sarcoidosis, cortical necrosis, hyperoxaluria, prolonged immobilization, Cushing syndrome, hyperuricosuria, monogenetic causes of hypertension, and renal candidiasis.

Treatment

In a child with a renal or ureteral calculus, the decision whether to remove the stone depends on its location, size, and composition (if known) and whether obstruction and/or infection is present. Pain is managed with nonsteroidal antiinflammatory drugs or, less often, opiates. Small ureteral calculi often pass spontaneously, although the child might experience severe renal colic. The narrowest segment of the ureter is the ureterovesical junction. Calculi <5 mm will pass 80–90% of the time. An α-adrenergic blocker, such as tamsulosin, 0.4 mg at bedtime, may facilitate stone passage by decreasing ureteral pressure below the stone and decreasing the frequency of the peristaltic contractions of the obstructed ureter. This intervention is termed medical expulsive therapy. In many cases, passage of a ureteral stent past the stone endoscopically relieves pain and dilates the ureter sufficiently to allow the calculus to pass. In cases such as children with a uric acid calculus or an infant with a furosemide-associated calculus, dissolution alkaline therapy may be effective.

If the calculus does not pass or seems unlikely to pass or if there is associated urinary tract infection, removal is necessary (Table 562.5). Lithotripsy of bladder, ureteral, and small renal pelvic calculi using the holmium laser through a flexible or rigid ureteroscope is quite effective. Extracorporeal shock wave lithotripsy has been successfully applied to children with renal and ureteral stones, with a success rate of > 75%. Another alternative is percutaneous nephrostolithotomy, in which access to the renal collecting system is obtained percutaneously and the calculi are broken down by ultrasonic lithotripsy. In cases in which these modalities are unsuccessful, an alternative is laparoscopic removal; this procedure can be performed using the da Vinci robot.

Table 562.5

Primary Surgical Treatment Options vs Stone Size and Location

STONES	SHOCK WAVE LITHOTRIPSY	URETEROSCOPY	PERCUTANEOUS NEPHROLITHOTOMY
RENAL			
<1 cm	Most common	Optional	Optional
1-2 cm	Most common	Optional	Optional
>2 cm	Optional	Rare	Most common
LOWER POLE			
<1 cm	Most common	Optional	Optional
>1 cm	Optional	Optional	Most common
URETERAL			
Proximal	Most common	Optional	Occasional
Distal	Optional	Most common	Rare

From Durkee CT, Balcom A: Surgical management of urolithiasis, Pediatr Clin North Am 53:465–

477, 2006.

Stone Prevention

In children with urolithiasis, the underlying metabolic disorder should be addressed (Table 562.6). Because lithiasis results from elevated concentrations of specific substances in the urine, maintaining a continuous high urine output by maintaining a high fluid intake often is an effective method of preventing further stones. The high fluid intake should be continued at night, and usually it is necessary for the child to get up at least once at night to urinate and drink more water. A daily fluid intake of 2-2.5 L in adolescent stone formers is recommended, with greater intake during summer months.

Table 562.6

Suggested Therapy for Urolithiasis Caused by Metabolic Abnormalities

METABOLIC ABNORMALITY	INITIAL TREATMENT	SECOND-LINE TREATMENT
Hypercalciuria	Reduction of dietary Na+	Potassium citrate
	Dietary calcium at RDA	Neutral phosphate
	Thiazides	
Hyperoxaluria	Adjustment of dietary oxalate	Neutral phosphate*
	Potassium citrate	Magnesium
		Pyridoxine*
Hypocitric aciduria	Potassium citrate	
	Bicarbonate	
Hyperuricosuria	Alkalinization	Allopurinol
Cystinuria	Alkalinization	Tiopronin (Thiola)
	Reduction of dietary Na+	D -Penicillamine
		Captopril

[*] Initial therapy in primary hyperoxaluria.

RDA, recommended dietary allowance.

From Milliner DS: Urolithiasis. In Avner ED, Harmon WE, Niaudet P, editors: Pediatric nephrology, ed 5, Philadelphia, 2004, Lippincott Williams & Wilkins, p. 1104, with permission.

Dietary sodium intake in children has increased significantly because of increased consumption of salty, processed foods. High sodium intake increases urinary excretion of calcium and may result in hypocitraturia. In addition, increased salt intake induces metabolic acidosis. To compensate for the acid load, the kidneys conserve anions, including urinary citrate, which contributes to hypocitraturia. Reduction in dietary intake of sodium and increased potassium intake is indicated.

Although counterintuitive, low-calcium diets are less effective in the treatment of calcium stones than diets containing normal amounts of calcium and limited amounts of sodium and animal protein. Low-sodium, low-protein diets reduce urinary calcium and oxalate excretion. Children with stone disease should avoid excess calcium intake. However, children require calcium for bone development, and recommendations for daily calcium intake vary by age. *Consequently, calcium restriction in children should be avoided.* Thiazide diuretics also reduce renal calcium excretion. The addition of potassium citrate, an inhibitor of calcium stones, with a dosage of 1-2 mEq/kg/24 hr is beneficial. An excellent source of citrate is lemonade, because 4 oz of lemon juice contains 84 mEq of citric acid. A daily mixture of 4 oz of reconstituted lemon juice in 2 L of water and sweetened to taste should significantly increase the urinary citrate level. In difficult cases, neutral orthophosphate should be given also, although it is poorly tolerated.

In patients with uric acid stones, allopurinol is effective. Allopurinol is an inhibitor of xanthine oxidase and is effective in reducing the production of both uric acid and 2,8-dihydroxyadenine and can help control the recurrence of both types of stones. In addition, urinary alkalinization with sodium bicarbonate or sodium citrate is beneficial. The urine pH should be ≥6.5 and can be monitored at home by the family.

Maintaining a high urine pH can also prevent the recurrence of cystine calculi. Cystine is much more soluble when the urinary pH is > 7.5, and alkalinization of urine with sodium bicarbonate or sodium citrate is effective. Another important medication is D -penicillamine, which is a chelating agent that binds to cysteine or homocysteine, increasing the solubility of the product. Although poorly tolerated by many patients, it has been reported to be effective in dissolving cystine stones and in preventing recurrences when hydration and urinary alkalinization fail. *N* -Acetylcysteine appears to have low toxicity and may be effective in controlling cystinuria, but long-term experience with it is lacking.

Treatment of type 1 RTA involves correcting the metabolic acidosis and replacing lost potassium and sodium. Sodium or potassium citrate therapy, or both, is necessary. When the metabolic acidosis is corrected, the urinary citrate excretion returns to normal.

Treatment of primary hyperoxaluria involves liver transplantation because the defective enzymes are hepatic. Ideally, this procedure is performed before renal failure occurs. In the most severe cases, kidney transplantation is also necessary.

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PART XXIV

Gynecologic Problems of Childhood

OUTLINE

Chapter 563 Gynecologic History and Physical Examination

Chapter 564 Vulvovaginitis

Chapter 565 Vaginal Bleeding in the Prepubertal Child

Chapter 566 Breast Concerns

Chapter 567 Polycystic Ovary Syndrome and Hirsutism

Chapter 568 Gynecologic Neoplasms and Adolescent Prevention Methods for Human Papillomavirus

Chapter 569 Vulvovaginal and Müllerian Anomalies

Chapter 570 Gynecologic Care for Girls With Special Needs

Chapter 571 Female Genital Mutilation

CHAPTER 563

Gynecologic History and Physical Examination

Kathryn C. Stambough, Diane F. Merritt

History

The approach to both the history and physical examination of a child is often a collaborative effort that involves the child, her caregiver, and the provider. With a preverbal or very young patient, clinicians obtain the majority of the history from a parent or caregiver. Even for the very young patient, developmentally appropriate social questions directed to the patient can put her at ease and help to develop cooperation and rapport that will facilitate a subsequent examination. Specific patient, caregiver, or provider concerns about vaginal discharge or bleeding, pruritus, external genital lesions, or abnormalities should direct a problem-focused history. In a patient presenting with vaginal bleeding, questions should focus on recent growth and development, signs of pubertal progression, trauma, vaginal discharge, medication exposure, and any history of foreign objects in the vagina. For complaints of vulvovaginal irritation, pruritus, or discharge, questions should concentrate on perineal hygiene, the onset and duration of symptoms, the presence and quality of discharge, exposure to skin irritants, recent antibiotic use, travel, presence of medical comorbidities or infections in the patient and her family members, and other systemic symptoms of illness or skin conditions. Throughout the history, the patient should be encouraged to ask her own questions. Occasionally, the child is brought to the clinician because she or her parents have concerns about anatomic findings, developmental changes, or congenital anomalies. It helps to understand the family's concerns and if a specific reason, event, or family history raised the need for a gynecologic consultation.

Gynecologic Examination

The physical examination of the patient should be tailored to the child's age, complaint, and any other concerns elicited in the history. The menstrual period should be included with an assessment of other vital signs as age appropriate.

Neonates

The delivering obstetrician should briefly examine the external genitals of female infants to confirm the patency of the vagina and assess the presence of any obvious genital anomalies. The pediatrician's newborn examination should note any abnormal findings such as ambiguous genitalia, imperforate hymen, urogenital abnormalities, abdominal mass, or inguinal hernia that might herald a gynecologic problem.

Placing the infant in the supine position with thighs flexed against the abdomen allows visualization of the neonate's external genitals. Estrogenic effects commonly notable in neonates include prominence of the labia majora and a white vaginal discharge. The labia minora and hymen may protrude slightly from the vestibule. A small amount of neonatal vaginal bleeding from endometrial sloughing following maternal hormone withdrawal might occur. Bleeding that is excessive or persistent beyond 1 mo of life requires further evaluation. Breast buds may be palpable at the time of the neonatal examination but should regress in the 1st mo of life; occasionally, nipple discharge occurs.

The vaginal orifice may be difficult to see. Gentle lateral traction on the labia majora usually allows complete visualization of the hymen and vaginal orifice. The hymen should be evaluated for patency. Most hymenal variations—imperforate, microperforate, septate—do not require treatment during the neonatal period (Fig. 563.1). Variations should be noted and readdressed in subsequent visits. The hymen originates from the urogenital sinus. The uterus and vagina originate from the müllerian ducts. The concomitant renal malformations seen with müllerian anomalies are not associated with hymenal anomalies. Hymenal polyps seen in newborns typically regress in size as the maternal estrogen effects subside. Cervicovaginal mucus secretions can accumulate behind the blocked outflow tract of an imperforate hymen and manifest as a mucocolpos. *In this instance and if urinary obstruction occurs, correction of the imperforate hymen in the neonatal period is indicated* .

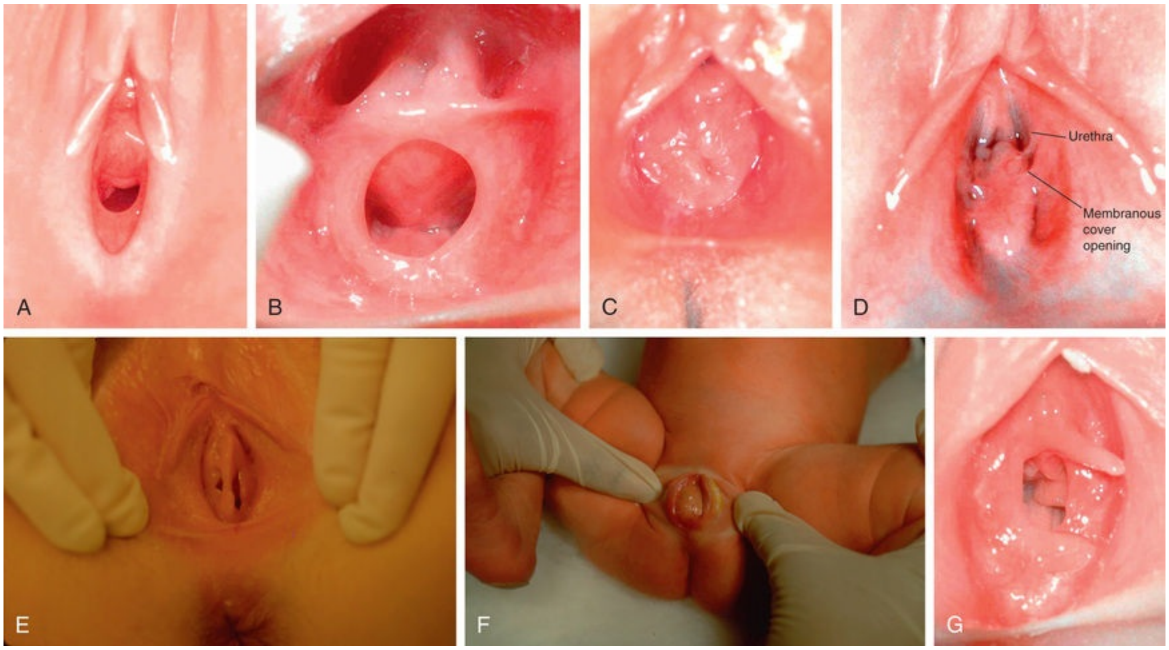

FIG. 563.1 Types of hymens. **A,** Crescentic. **B,** Annular. **C,** Redundant. **D,** Microperforate. **E,** Septated. **F,** Imperforate. **G,** Hymeneal tags. (A through F, from Perlman SE, Nakajima ST, Hertweck SP, editors: Clinical protocols in pediatric adolescent gynecology. London, 2004, Parthenon Publishing Group. G from McCann JJ, Kerns DL, editors: The child abuse atlas, Evidentia Learning, 2018, www.childabuseatlas.com .)

The clitoris may appear large in proportion to the other genital structures, especially in premature infants. If the clitoris appears enlarged, the clitoral width should be measured; values > 6 mm in a newborn indicate a need for further evaluation. *If clitoromegaly and ambiguous genitals are present, the obstetrician and pediatrician should immediately obtain expert consultation for evaluation of the infant and to counsel the parents.* Congenital adrenal hyperplasia is the most common cause of ambiguous genitals (accounting for > 90% of cases), and the salt-wasting forms can lead to rapid dehydration with subsequent fluid and electrolyte imbalance (see Chapter 594). Delay in the diagnosis and treatment of congenital adrenal hyperplasia may be life-threatening.

In the neonate, the ovaries are < 1 cm in diameter and average 1 cm^3 in volume. Antenatal or postnatal abdominopelvic ultrasound might reveal small simple ovarian cysts, which represent normal follicles. Because of the abdominal location of ovaries in the neonate, ovarian enlargement can manifest as a palpable abdominal mass. Large cysts (>4-5 cm) or those of a complex nature pose the risk of ovarian torsion, hemorrhage into the cyst, or, uncommonly, an ovarian tumor. A nonresolving or enlarging neonatal ovarian cyst warrants expert consultation. If the mass causes respiratory compromise or gastrointestinal obstruction, decompression is usually performed. Cyst aspiration can give temporary relief, but it is not recommended, because the fluid aspirated is not reliable for diagnosis and fluid may reaccumulate. If a cystectomy is done for appropriate clinical indications, the cyst wall should be surgically excised to prevent reaccumulation of fluid and to provide a pathologic diagnosis, the remaining ovarian tissue should be left in situ, and the contralateral ovary should be inspected. Preservation of normal ovarian tissue is recommended for all benign lesions, and salpingo-oophorectomy should not be performed unless clinically indicated.

Infants and Prepubertal Girls

As the maternal estrogen effect subsides, the genitals of the female infant change in appearance. The labia begin to flatten. The hymenal membrane loses its redundancy and becomes translucent. The hypoestrogenic prepubertal vaginal epithelium appears thin, red, and sensitive to the touch. The vaginal mucosa of young children can have longitudinal ridges running along the axis of the vagina at 3 o'clock, 6 o'clock, and 9 o'clock, which can cause small protrusions on the hymen at these locations. The cervix usually appears flat and flush with the vaginal vault. During infancy, the uterus regresses in size and does not return to its birth size until the 5th or 6th yr. The prepubertal cervix:fundus ratio is 2:1.

As puberty approaches, the child experiences increasing endocrine activity of the hypothalamus, pituitary gland, adrenal gland, and ovaries (see Chapter 577). The labia majora begin to fill out, and the labia minora thicken and elongate as a result of increased estrogen levels. The hymen thickens and becomes more redundant. Clear or white physiologic secretions may be present. Breast buds begin to appear, either bilateral or initially unilateral with subsequent development of the contralateral breast. Pubic hair begins to appear.

Indications for Genital Examination

Genitourinary complaints or suspected genitourinary pathology warrants assessment of the external and internal genitals of pediatric patients, specifically in cases of vaginal bleeding, vaginal discharge, vulvar trauma, presence of a foreign body, perineal or pelvic masses, vulvovaginal ulcerative or inflammatory lesions, congenital anomalies, or suspected sexual abuse.

Preparation

The genital examination in prepubertal girls requires a gentle, patient approach to maximize cooperation and minimize fear and embarrassment. A clear, simple explanation of what the exam involves can facilitate the child's comfort and cooperation. The presence of a parent or caregiver during the entire examination provides reassurance for most children. For the older prepubertal patient, the physician may discuss whether the patient wishes to have a family member present during the examination. Even in the presence of the caregiver, the examiner should speak directly to the child. Prior to initiating any part of the examination, the provider should explicitly verify with both the patient and her caregiver that the caregiver has given permission for the examination. This provides an opportunity to explain to the child the privacy of body parts and who may examine or touch those areas. It is useful to educate the patient and caregiver about the basic anatomy and hygiene of the external genital area. Before each step of the examination, the physician should explain what will occur. Allowing an older child the option of watching her examination with a handheld mirror may contribute to her comfort and understanding. Forcible restraint is never indicated; if optimal evaluation is not possible, the clinician must assess the acuity of the complaint and pathology and determine the potential need for a multivisit examination or an examination under anesthesia.

Positioning

A variety of techniques and positions can facilitate the genital examination in prepubertal patients. Children younger than 4 yr of age can be placed on the parent or caregiver's lap with the child's legs straddling the parent's thighs (Fig. 563.2). If the child permits, she may be positioned on the table in the supine position with the hips fully abducted and the feet together in the frog-leg (diamond or butterfly) position. Older children may prefer to use the stirrups. The head of the examination table should be raised so that eye contact can be maintained with the patient throughout the examination. When the child is supine, grasping the labia majora along the inferior portion between the thumb and index finger and gently pulling outward and posteriorly (labial traction) allows visualization of the vaginal introitus. Alternatively, the child may be placed in the knee–chest position with elevation of the buttocks and hips (see Fig. 563.2). This position provides exposure of the inferior portion of the hymen, the lower vagina, and possibly the upper vagina and cervix but has the disadvantage of having the child face away from the examiner.

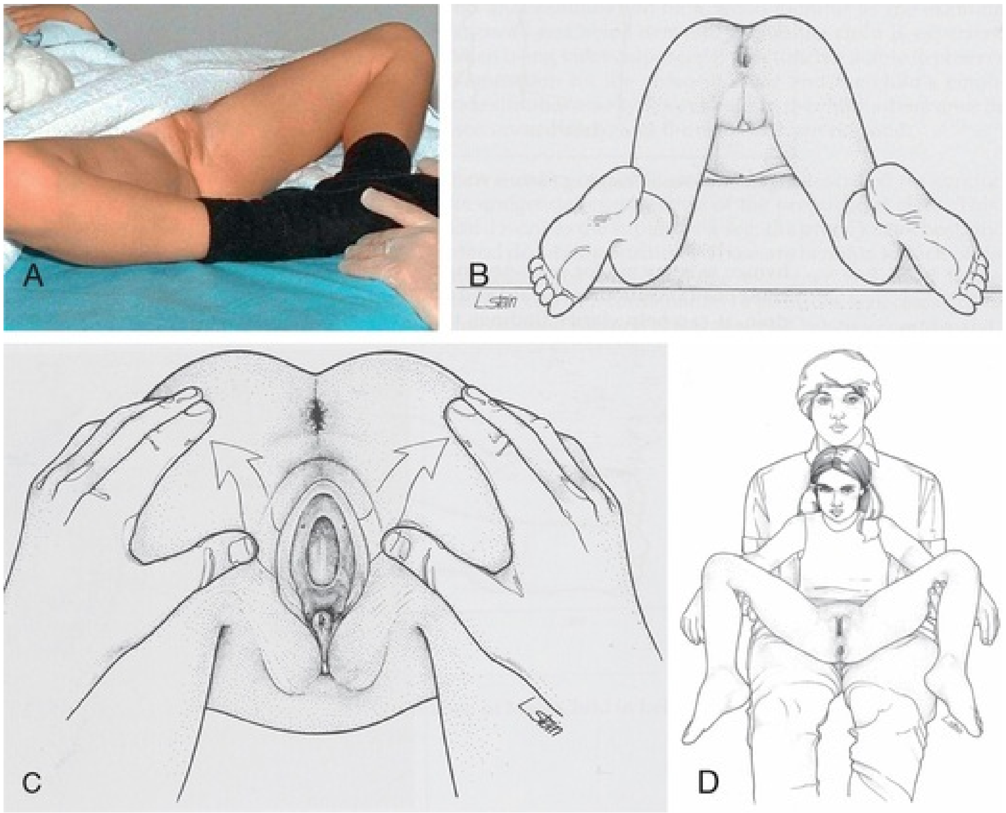

FIG. 563.2 Different exam positions for performing a gynecologic exam on a child. **A,** Frog-leg position. **B,** Knee–chest position. **C,** Prone position. **D,** Sitting on mom's lap. (A from McCann JJ, Kerns DL. The child abuse atlas, Evidentia Learning, 2018, www.childabuseatlas.com ; B, C, and D from Finkel MA, Giardino AP (eds): Medical examination of child sexual abuse: a practical guide, 2nd ed. Thousand Oaks, 2002, CA, 2002, pp. 46-64.)

Some extremely cooperative children tolerate a vaginoscopic examination in an outpatient office setting for better intravaginal assessment. The endoscope (either a cystoscope or a hysteroscope) is placed in the vagina and the labia are gently opposed, allowing the vagina to distend with water. This technique permits visualization of the vagina and cervix, allowing for the evaluation of an injury, lesion, and anatomic variant or for the presence of a foreign body. Application of 2% lidocaine gel at the introitus makes the insertion easier and less irritating for the patient. If a more complete examination is indicated or if the child is too young, frightened, or unable to cooperate, an examination under anesthesia is recommended.

Documentation

Clinicians should thoroughly and accurately document genital exam findings in the medical record, reserving conclusions and diagnostic terms for the impression and plan portion of the documentation rather than in the description of exam findings. Each structure visualized should be noted (e.g., clitoris, labia majora, labia minora, urethra, vestibule, and rectum) with attention to describing normal appearance and any anatomic variations (e.g., the configuration of the hymen as annular, crescentic, etc.). Describing any findings or lesions using a clock-face method provides a consistent reference point; a sketch or magnified photograph may also be helpful. Future examiners will rely on this documentation as a record with which they compare their findings and note any variances. Changes should be noted in any follow-up examinations.

Adolescents

Some teens prefer to initially meet and discuss the reason for their visit with the provider without their parent or guardian present, and this request should be honored (see Chapter 137). A majority of the time, obtaining a history from an adolescent begins with meeting the patient and her parent or caregiver together to review her history and the reason for the visit and to explain the concepts of confidentiality and privacy. Familiarity with local laws governing limitations to confidential services should guide the protection of the adolescent and her parents' rights to information access and privacy. The Guttmacher Institute provides an up-to-date listing of state and federal laws in the United States affecting access to medical care (https://www.guttmacher.org/geography/united-states). Brief discussions of normal pubertal development and menstruation can reassure both patients and their parents or guardians and provide valuable education on appropriate menstrual flow, menstrual hygiene, and the duration and frequency of bleeding. Introducing the menstrual diary as an invaluable tool for the teen can help patients, parents, and clinicians identify abnormal bleeding patterns that might require further evaluation. Many applications are available for tracking menstrual periods on a smart phone or computer.

After the initial interview with the teen and her parent or caregiver, the confidential and sensitive portion of the history, particularly sexual history and alcohol, tobacco, and drug use, is taken with the teen alone. Such a request could be phrased as follows: "I would like to give your daughter an opportunity to ask any questions she might have privately, so would you mind stepping out of the room for a moment?" Concerns for the presence of vaginal discharge, the potential for sexually transmitted infections, pregnancy, or menstrual aberration should be explored. Teens and their parents should be informed of the proper use and accessibility of condoms, all contraceptive methods, and emergency contraception.

Resources for educating adolescents regarding their first pelvic examination and in-depth sexual history and psychosocial screening tools are available. These include the North American Society for Pediatric and Adolescent Gynecology (http://www.naspag.org), the American Academy of Pediatrics (http://www.aap.org), the Society for Adolescent Health and Medicine (http://www.adolescenthealth.org), and the American College of Obstetricians and Gynecologists (http://acog.org/Patients).

Pelvic Examination

Table 563.1 presents the indications for the first pelvic examination in adolescents. If an adolescent does not meet one of the criteria listed in Table 563.1 , the American College of Obstetricians and Gynecologists recommends that the first gynecologic encounter occur between the ages of 13 and 15 yr (Table 563.2), with attention toward anticipatory guidance focusing on normal pubertal development and menstruation. Patients should undergo screening for sexually transmitted infection with each new sexual partner. With the availability of urine and vaginal swab nucleic acid amplification testing for *Chlamydia* and gonorrhea, sexually transmitted infection screening does not necessitate a speculum exam.

Table 563.1

Suggested Indications for Pelvic Examination in Adolescents

Age 21 yr for initial Pap test
Unexplained menstrual irregularities, including pubertal aberrations (especially delayed puberty)
Severe dysmenorrhea
Unexplained abdominal or pelvic pain
Unexplained dysuria
Abnormal vaginal discharge
Placement of intrauterine device
Removal of foreign body
Inability to place tampons

Data from American College of Obstetricians and Gynecologists: The initial reproductive health visit; Committee Opinion No. 598. Obstet Gynecol 123:1143-1147, 2014.

Table 563.2

Recommendations for First Gynecologic Evaluation

Between 13 and 15 yr of age
First gynecologic encounter focuses on patient education; pelvic examination is generally not indicated
First pelvic examination with Pap test at 21 yr of age, unless otherwise indicated by Table 563.1

Prior to the initiation of a physical examination, all young women should be offered the choice of having a medical attendant, family member, or friend present during her examination. At the initial gynecologic exam, the physician should explain the process in understandable terms. A thorough evaluation begins with an assessment of body mass index, blood pressure, menstruation status, thyroid, lymph nodes, breast development, abdominal exam, and skin. The external genitals should be examined with the patient in the dorsal lithotomy position while communication is maintained between the physician and patient. Elevating the head of the examination table allows the teen and her examiner to maintain eye contact. The teen can hold a mirror to follow along with the examination, and she should be encouraged to ask questions. Inspection of the vulva is followed by inspection of the Bartholin, urethral, and Skene glands. The clitoris, normally 2-4 mm in width, is then assessed; a clitoris wider than 10 mm, especially in the presence of other signs of virilization, suggests a need for further evaluation. The hymenal anatomy should also be evaluated. Throughout the examination, the proper nomenclature for genital anatomy should be emphasized with the teen to empower her to use proper wordage with the avoidance of slang when referring to her body.

Because the initial Papanicolaou test is deferred until 21 yr of age and cultures for sexually transmitted infections can be obtained from urine or vaginal swabs, the need for a speculum exam is decreasing in this age-group. If a speculum exam is indicated, use an appropriately sized speculum, such as the Huffman (½ in wide × 4 in long) or Pedersen (⅞ in wide × 4 in long) speculum. Shorter speculums will not allow visualization of the entire vaginal canal. The adolescent patient should be reassured that the exam may be uncomfortable but should not be painful and that her request to stop or wait will be honored. Encouraging the patient to watch with a hand-held mirror facilitates patient education and can be empowering. She may be told before the insertion of the speculum that she will experience a pressure sensation. Before touching the introitus, it may be useful to touch the inner thigh with the speculum. Compression of the urethra anteriorly should be avoided. Gentle pressure with a finger for displacement of the fourchette posteriorly further facilitates proper speculum placement. After visualization of the vagina and cervix, specimens should be obtained as indicated. A bimanual examination, sometimes with a single digit, allows palpation of the vaginal walls and cervix and bimanual assessment of the uterus and adnexa. Reassurance of normal findings throughout the examination should be provided, and normal variants to anatomy should be pointed out to the teen as they are encountered (e.g., asymmetric labia minora).

Following the examination, it is appropriate to review the exam findings with the teen (and her parent) and initiate a collaborative discussion of the management plan. Encouraging the adolescent to participate in decision making empowers her to undertake responsibility for her health, may strengthen compliance with the medical plan, and will acknowledge her as a unique individual.

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CHAPTER 564

Vulvovaginitis

Helen M. Oquendo Del Toro, Holly R. Hoefgen

Vulvovaginitis is the most common gynecologic-based problem for prepubertal children, with a reported incidence of 17–50%. It is most typically caused by either inadequate or excessive hygiene or chemical irritants. The age of presentation peaks at 4 and 8 yr of age. The condition is usually improved by hygiene measures and education of the caregivers and child.

Etiology

Vulvitis refers to external genital pruritus, burning, redness, or rash. **Vaginitis** implies inflammation of the vagina, which can manifest as a discharge with or without an odor or bleeding. These may occur simultaneously as **vulvovaginitis.** When a child presents with vulvovaginitis, the history should include questions on hygiene (wiping from front to back) and information about possible exposure to chemical irritants (bath soaps, bubble bath, laundry detergents, swimming pools, or hot tubs). A detailed history of recent diarrhea, perianal itching, or nighttime itching is important. The possibility of foreign objects being placed into the vagina should also be asked, although the young child is unlikely to remember or recall. However, approximately 75% of cases of vulvovaginitis in children are nonspecific for a variety of reasons, including their lack of vaginal estrogenization and resulting atrophy and alkalinic pH, poor perianal hygiene, and the proximity of the anus to the vagina, which is without geographic barriers given the flattened labia and lack of pubic hair (Fig. 564.1 and Table 564.1).

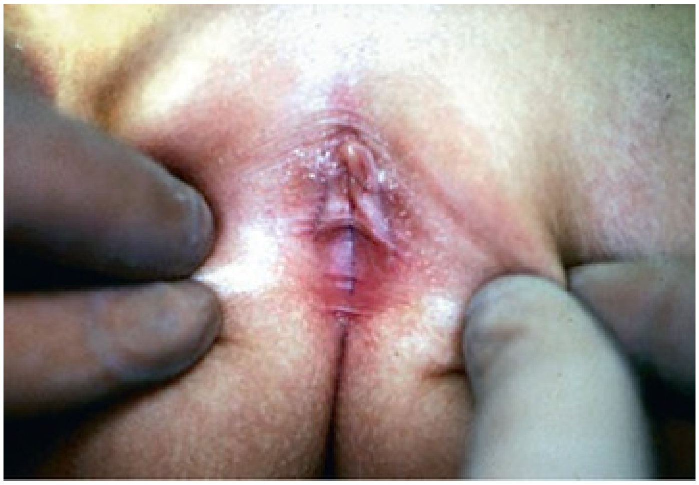

FIG. 564.1 Labial adhesions. (Photo courtesy of Diane F. Merritt, MD.)

Table 564.1

Specific Vulvar Disorders in Children

CONDITION	PRESENTATION	DIAGNOSIS	TREATMENT
Molluscum contagiosum (Fig. 564.8)	1- to 5-mm discrete, skin-colored, dome-shaped, umbilicated lesions with a central cheesy plug	Diagnosis usually is made by visual inspection.	The disease generally is self-limited and the lesions can resolve spontaneously. Treatment choices in children may include cryosurgery, laser, application of topical anesthetic and curettage, podophyllotoxin, and topical silver nitrate. Use of topical 5% imiquimod cream and 10% potassium hydroxide has been reported with similar effects.
Condyloma acuminata	Skin-colored papules, some with a shaggy, cauliflower-like appearance	Diagnosis usually is made by visual inspection. Biopsy should be reserved for when the diagnosis is in question. Human papillomavirus DNA testing is not helpful.	Many lesions in children resolve spontaneously, “wait and see” often utilized in children (60 days). Topical treatment with imiquimod cream and podophyllotoxin is the most studied (daily qhs 3 times/wk × 16 wk, wash 6-10 hr after application). General anesthesia is usually required for surgical/ablative procedures (cryotherapy, laser therapy, electrocautery); reserve for symptomatic or large lesions. Other treatments have been utilized in adults, including trichloroacetic acid, 5-fluorouracil, sine catechins, topical cidofovir, and cimetidine. The efficacy and safety of these treatments in children has not been established.
Herpes simplex	Blisters that break, leaving tender ulcers	Visual inspection confirmed by culture from lesion.	*Infants:* Acyclovir 20 mg/kg body weight IV q8 hr × 21 days for disseminated and central nervous system disease or × 14 days for disease limited to the skin and mucous membranes. *Genital/mucocutaneous disease:* Age 3 mo–2 yr: 15 mg/kg/day IV divided in q8h × 5-7 days. Age 2-12 yr (1st episode): Same as above or 1,200

			mg/day divided in q8h dosing × 7-10 days. Age 2-12 yr (recurrence): 1,200 mg/day in q8h dosing or 1,600 mg/day in bid dosing × 5 days (give 3-5 days for children older than 12 yr).
Labial agglutination (see Fig. 564.1)	May be asymptomatic or can cause vulvitis, urinary dribbling, urinary tract infection, or urethritis	Diagnosis is made by visual inspection of the adherent labia, often with a central semitranslucent line.	Does not require treatment if the patient is asymptomatic. *Symptomatic patients:* Topical estrogen cream or betamethasone ointment applied alone or in combination daily for 6 wk directly to the line of adhesion, using a cotton swab while applying gentle labial traction. Estrogen should be interrupted if breast budding occurs. Mechanical or surgical separation of the adhesions is rarely indicated. The adhesions usually resolve in 6-12 wk; unless good hygiene measures are followed, recurrence is common. To decrease the risk of recurrence, an emollient (petroleum jelly, A and D ointment) should be applied to the inner labia for 1 mo or longer at bedtime.
Lichen sclerosus (see Fig. 564.4)	A sclerotic, atrophic, parchment-like plaque with an hourglass or keyhole appearance of vulvar, perianal, or perineal skin, subepithelial hemorrhages may be misinterpreted as sexual abuse or trauma. The patient can experience perineal itching, soreness, or dysuria.	Diagnosis usually is made by visual inspection. Biopsy should be reserved for when the diagnosis is in question.	Ultrapotent topical corticosteroids are the first-line therapy (clobetasol propionate ointment 0.05%) once or twice a day for 4-8 wk. Once symptoms are under control, the patient should be tapered off the drug unless therapy is required for a flare-up. In many girls, the condition resolves with puberty; however, this is not always the case and patients may require long-term follow-up. Immunomodulators can be used: tacrolimus 1% (applied once daily) and pimecrolimus 1% (applied twice daily for 3 mo, then every other day).
Psoriasis	Children are more likely than adults to have vulvar psoriasis noted as pruritic, well-demarcated, nonscaly, brightly erythematous, symmetric plaques. The classic extragenital lesions are similar but with	Diagnosis may be confirmed by locating other affected areas on the scalp or in nasolabial folds or behind the ears.	Vulvar lesions may be treated with low- to medium-potency topical corticosteroids, increasing strength as necessary.

	a silver scaly appearance.		
Atopic dermatitis	Chronic cases can result in crusty, weepy lesions that are accompanied by intense pruritus and erythema. Scratching often results in excoriation of the lesions and secondary bacterial or candidal infection.	It may be seen in the vulvar area but characteristically affects the face, neck, chest, and extremities.	Children with this condition should avoid common irritants and use topical corticosteroids (such as 1% hydrocortisone) for flare-ups. If dry skin is present, lotion or bath oil can be used to seal in moisture after bathing.
Contact dermatitis	Erythematous, edematous, or weepy vulvar vesicles or pustules can result, but more often the skin appears inflamed.	Associated with exposure to an irritant, such as perfumed soaps, bubble bath, talcum powder, lotions, elastic bands of undergarments, or disposable diaper components.	Avoidance of irritant. Topical corticosteroids for flare-ups.
Seborrheic dermatitis	Erythematous and greasy, yellowish scaling on vulva and labial crural folds associated with greasy dandruff-type rash of scalp, behind ears and face.	Diagnosis usually is made by visual inspection.	Gentle cleaning, topical clotrimazole with 1% hydrocortisone added.
Vitiligo (see Fig. 564.5)	Sharply demarcated hypopigmented patches, often symmetric in vaginal and anal regions. May be present in periphery at body orifices and extensor surfaces.	Clinical. Test for associated illness if clinically warranted (thyroid disease, Addison disease, pernicious anemia, diabetes mellitus).	If desired, treat limited lesions with low-potency corticosteroids or tacrolimus. See dermatologist for extensive lesions.

Epidemiology

Infectious vulvovaginitis, where a specific pathogen is isolated as the cause of symptoms, is most commonly associated with fecal or respiratory pathogens, and cultures may reveal *Escherichia coli* (see Chapter 227), *Streptococcus pyogenes* (Chapter 210), *Staphylococcus aureus* (see Chapter 208), *Haemophilus influenzae* (see Chapter 221), *Enterobius vermicularis* (Chapter 320), and, rarely, *Candida* spp. (see Chapter 261). These organisms may be transmitted by the child using improper toilet hygiene and manually from the nasopharynx to the vagina. The children present with perianal redness, introital inflammation, and often a yellow-green or mildly bloody discharge. They may be observed to be grabbing their genital area or "digging" in their underwear, which is usually stained with yellow-brown discharge. Attempts to treat these bacterial etiologies with antifungal medication will fail and often the antifungal product will lead to more irritation. Table 564.2 gives specific treatment recommendations based on the bacteria localized.

Table 564.2

Antibiotic Recommendations for Specific Vulvovaginal Infections

ETIOLOGY	TREATMENT
Streptococcus pyogenes *Streptococcus pneumoniae*	Penicillin V, 250 mg PO bid-tid × 10 days Amoxicillin. 50 mg/kg/day (max: 500 mg/dose) divided into 3 doses daily × 10 days Erythromycin ethyl succinate, 30-50 mg/kg/day (max: 400 mg/dose) divided into 4 doses daily TMP-SMX. 6-10 mg/kg/day (TMP component) divided into 2 doses daily × 10 days Clarithromycin. 7.5 mg/kg bid (max: 1 g/day) × 5-10 days Reoccurrence most likely from asymptomatic pharyngeal carriage in child or family member. However, failure of penicillin regimens can occur. For penicillin resistance: Rifampin 10 mg/kg every 12 hr × 2 days
Staphylococcus aureus	Topical mupirocin 2% 3 times daily to the affected skin area If systemic therapy required: Amoxicillin-clavulanate, 45 mg/kg/day (amoxicillin) PO divided into 2 or 3 doses daily × 7 days (first-line treatment because of high penicillin resistance) Extensive resistance to common antibiotics noted, recommend susceptibility testing for further antibiotic use MRSA: TMP-SMX double-strength 8-10 mg/kg/day; culture abscesses, incision and drainage
Haemophilus influenzae	Amoxicillin, 40 mg/kg/day divided into 3 doses daily × 7 days Cases of treatment failure or nonencapsulated H. influenzae, amoxicillin–clavulanate is recommended.
Yersinia	TMP-SMX 6 mg/kg (TMP component) daily for 3 days
Shigella	TMP-SMX 10/50 mg/kg/day (max: 160/600) divided into 2 doses daily × 5 days Ampicillin 50-100 mg/kg/day divided into 4 doses daily (adult max: 4 g/day) × 5 days Azithromycin 12 mg/kg (max: 500) × 1 day, then 6 mg/kg/day (max: 250 mg) × 4 days (in areas of high resistance to above regimens or when sensitivities are unknown) For resistant organisms: Ceftriaxone 50-75 mg/kg/day IV or IM divided into 1 or 2 doses (max: 2 g/day) × 2-5 days

Chlamydia trachomatis	Children weighing < 45 kg: Erythromycin base or ethylsuccinate 50 mg/kg/day PO divided into 4 daily doses × 14 days Children weighing > 45 kg but age younger than 8 yr: azithromycin 1 g PO in a single dose Children age older than 8 yr (treat per adult regimens): Preferred regimens: Azithromycin 1 g PO in a single dose or Doxycycline 100 mg PO twice daily × 7 days Alternative regimens: Erythromycin base 500 mg PO 4 times daily × 7 days Erythromycin ethylsuccinate 800 mg PO 4 times daily × 7 days Levofloxacin 500 mg PO daily × 7 days Ofloxacin 300 mg PO twice daily for 7 days
Neisseria gonorrhoeae	Children weighing < 45 kg: Ceftriaxone, 125 mg IM in a single dose Children weighing ≥ 45 kg: Dual therapy: Treat with adult regimen of 250 mg IM in a single dose and azithromycin 1 g orally in single dose Children with bacteremia or arthritis: Ceftriaxone, 50 mg/kg (max dose for children weighing < 45 kg: 1 g) IM or IV in a single dose daily × 7 days Dual treatment: Addition of either azithromycin 1 g PO in a single dose or doxycycline 100 mg PO twice daily × 7 days to the above regimens may assist in hindering the development of antibiotic resistance. Note: The CDC removed cefixime 400 mg PO in a single dose from recommended medications because of increasing resistance; however, can be used as part of a dual therapy if ceftriaxone is unavailable.
Trichomonas	Metronidazole, 15-30 mg/kg/day tid (max: 250 mg tid) × 5-7 days or Tinidazole 50 mg/kg (≤2 g) as a single dose for children older than 3 yr
Pinworms *(Enterobius vermicularis)*	Mebendazole (Vermox), 1 chewable 100-mg tablet, repeated in 2 wk or Albendazole, 100 mg for child younger than age 2 yr or 400 mg for older child, repeated in 2 wk Pyrantel pamoate 10 mg/kg in a single administration

MRSA, methicillin-resistant *Staphylococcus aureus;* TMP-SMX, trimethoprim-sulfamethoxazole.

Neisseria gonorrhoeae or *Chlamydia trachomatis* also are causes of specific infectious vulvovaginitis (see Chapter 146). Management of prepubertal children who have **sexually transmitted infections** requires close cooperation between clinicians and child-protection authorities. Official investigations for sexual abuse, when indicated, should be initiated promptly (see Chapter 16). If acquired after the neonatal period, some diseases (e.g., gonorrhea, syphilis, and chlamydia) are virtually 100% indicative of sexual contact. For other diseases (e.g., human papillomavirus infection and herpes simplex virus), the association with sexual contact is not as clear. Presumptive treatment for prepubertal children who have been sexually assaulted or abused is not recommended, because (1) the incidence of most sexually transmitted infections in children is low after abuse/assault, (2) prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, and (3) regular follow-up of children usually can be ensured. Although *Trichomonas vaginalis* can be transmitted vertically and can be seen in children up to 1 yr of age, it is an uncommon cause of specific infectious vulvovaginitis in the unestrogenized prepubertal girl.

Other causes of specific infectious vulvovaginitis include *Shigella* (see Chapter 226), which often manifests with a blood-tinged purulent discharge, and *Yersinia enterocolitica* (see Chapter 230). *Candida* infections (yeast) commonly cause diaper rash, but they are unlikely to cause vaginitis in children because the alkaline pH of the prepubertal vagina does not support fungal infections. Diabetic or immunocompromised children and children taking prolonged antibiotics may be at increased risk for fungal vaginitis. Pinworms are the most common helminthic infestation in the United States, with the highest rates in school-age and preschool children. Perianal itching can lead to excoriation and, rarely, bleeding.

Clinical Manifestations

Diaper Dermatitis

Diaper dermatitis is the most common dermatologic problem in infancy and occurs in half of all diaper-wearing infants and children. The moisture and contact with urine and feces irritates the skin, and colonization with *Candida* spp. increases the severity of the dermatitis. First-line treatment includes hygiene measures such as increasing the frequency of diaper changes, allowing the infant to be diaper free, frequent bathing, and application of water-repellant barriers such as zinc oxide. If diaper dermatitis persists after these conservative measures, or if the classic satellite lesions of *Candida* are present, treatment with a topical antifungal can decrease the inflammation.

Physiologic Leukorrhea

Neonates and peripubertal girls can present with a white or clear or mucus discharge, which is a physiologic effect of estrogen. Some girls may complain of the moisture and mucus. Hygiene measures including baths may help but an explanation should reassure the patient and her mother.

Labial Agglutination

Labial agglutination (labial adhesions) are described most frequently in infants and young children. This phenomenon is thought to be secondary to an inflammatory response in the labia minora in combination with a hypoestrogenic state. Diagnosis is usually done on routine genital examination. Asymptomatic patients usually require no intervention. **First-line therapy** in patients with difficulty voiding, persistent infections, or pain includes topical estrogen (Premarin or Estrace cream 0.01%) or a topical steroid (Betamethasone 0.05% ointment) applied twice daily to the midline raphe under gentle traction. Surgical correction is rarely necessary, but recurrence is common until the age of puberty.

Genital Ulcers

Acute genital ulceration of the vulva (Fig. 564.2) is described in young adolescents who are not sexually active and can occur in association with oral aphthous ulcers. Although initially linked to infectious causes such as Epstein-Barr virus, cytomegalovirus, mycoplasma, mumps, and influenza A, these ulcers may also be idiopathic vulvar aphthoses. Other potential etiologies include inflammatory bowel disease, Behçet disease, pemphigoid, Stevens-Johnson syndrome, drug eruption, or mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome.

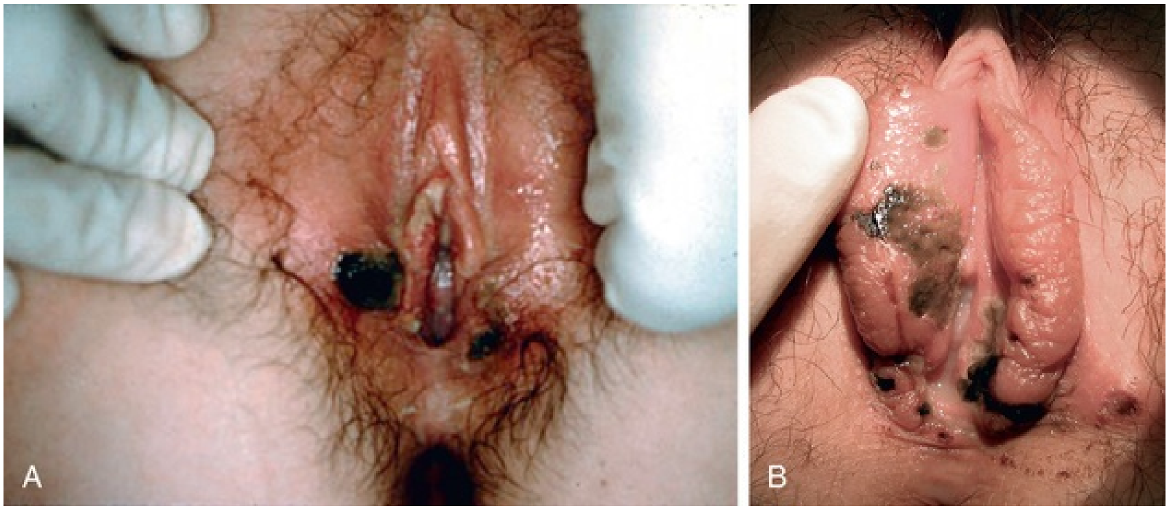

FIG. 564.2 Aphthous ulcers. (Photo courtesy of Diane F. Merritt, MD.)

These lesions usually appear on the mucosal surfaces of the introitus as painful red or white lesions that evolve into sharply demarcated red-rimmed ulcers with a necrotic or eschar-like base. The time course is generally 10-14 days until remission occurs. The lesions are quite painful, and pain management and urinary diversion with a Foley catheter may be necessary. Patients with acute genital ulcers show a fairly consistent picture of flu-like prodromal symptoms, including fever, nausea, and abdominal pain. Dysuria and vulvar pain are common complaints as well. One third of patients present with a history of or develop oral ulcerations. Evaluation includes culture for herpes simplex virus to exclude this etiology. Special testing for systemic disease depends on the history. Biopsies are usually nondiagnostic because they yield acute and chronic inflammatory changes. Fig. 564.3 outlines the suggested evaluation and management of initial and recurrent disease. Evaluation for Behçet disease (see Chapter 186) using the International Study Group diagnostic guidelines should be considered with recurrent or severe cases (see Table 564.1 for other common etiologies). **Treatment of acute genital ulcers** should include topical Xylocaine 2% jelly, sitz baths, good hygiene, and acetaminophen. Nonsteroidal antiinflammatory drug avoidance is suggested because of a possible causative link. Hospitalization may be required for pain management not controlled with oral narcotics or urinary retention requiring Foley catheterization, or if whirlpool debridement should hygiene become difficult. Antibiotic treatment is not required, unless evidence of bacterial superinfection exists or the patient is immunocompromised. Insufficient evidence exists to recommend whether oral steroid treatment is effective but may be helpful in the setting of recurrent outbreaks and extensive disease. Ultrapotent topical steroids (clobetasol 0.05% ointment) are beneficial in oral aphthous ulcers and may prove helpful in acute genital ulcers as well.

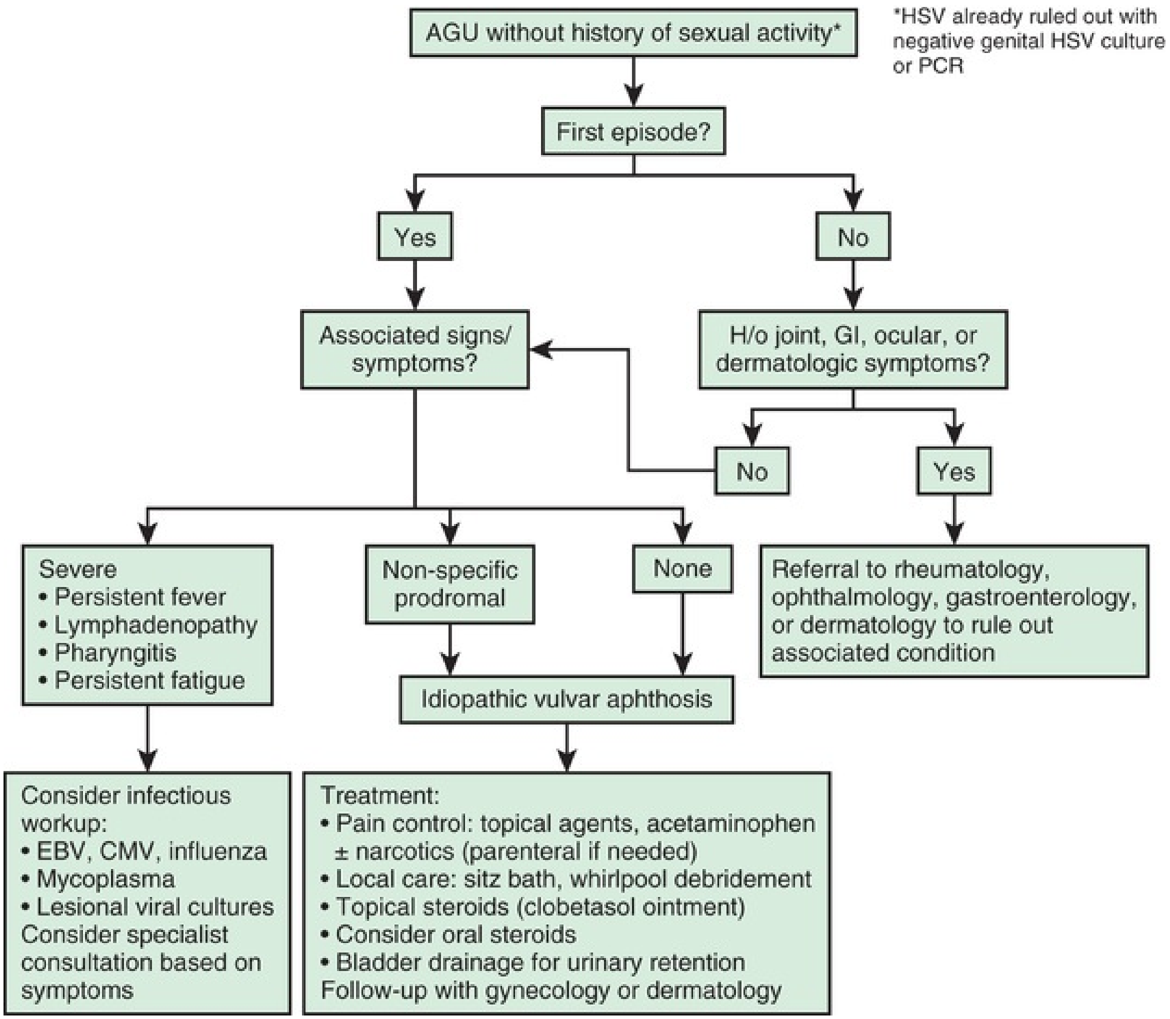
AGU without history of sexual activity*
*HSV already ruled out with negative genital HSV culture or PCR
First episode?
Yes
No
Associated signs/ symptoms?
H/o joint, GI, ocular, or dermatologic symptoms?
No
Yes
Severe
• Persistent fever
• Lymphadenopathy
• Pharyngitis
• Persistent fatigue
Non-specific prodromal
None
Referral to rheumatology, ophthalmology, gastroenterology, or dermatology to rule out associated condition
Idiopathic vulvar aphthosis
Consider infectious workup:
• EBV, CMV, influenza
• Mycoplasma
• Lesional viral cultures
Consider specialist consultation based on symptoms
Treatment:
• Pain control: topical agents, acetaminophen ± narcotics (parenteral if needed)
• Local care: sitz bath, whirlpool debridement
• Topical steroids (clobetasol ointment)
• Consider oral steroids
• Bladder drainage for urinary retention
Follow-up with gynecology or dermatology

FIG. 564.3 Algorithm for evaluation and management of acute genital ulcers in non–sexually active young girls. (From Rosman IS, Berk DR, Bayliss SJ, et al: Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations. Pediatr Dermatol 29(2);147-153, 2012.)

Dermatoses

Dermatologic conditions often affect the vulvar area in children; it is important to determine if the girl presenting with vulvar irritation has a skin condition elsewhere on the body. **Lichen sclerosus** is commonly seen in the anogenital region and has a characteristic appearance of white skin changes associated with areas of erosion, ulceration, and petechiae. This disease can cause severe discomfort and most commonly presents with vulvar or perianal pruritus, dysuria, and constipation. Patients may also present without any symptoms, which may lead to underrecognition and undertreatment. If untreated, lichen sclerosus can lead to destruction and scarring of normal genital architecture, including labial resorption, obliteration of the clitoris, narrowing of the introitus, and painful fissures that may become secondarily infected. Once thought to resolve with puberty, this theory is now controversial, and many postmenarchal adolescents still suffer from disease (Fig. 564.4). **Lichen sclerosis** may be treated with potent topical steroids, such as clobetasol propionate 0.05% applied once or twice daily until the symptoms resolve, and then tapered down through lower-dose topical steroids. Topical calcineurin inhibitors such as tacrolimus and pimecrolimus have been used in the treatment of lichen sclerosis. Patients should be followed every 6-12 mo to evaluate for recurrence (Fig. 564.5).

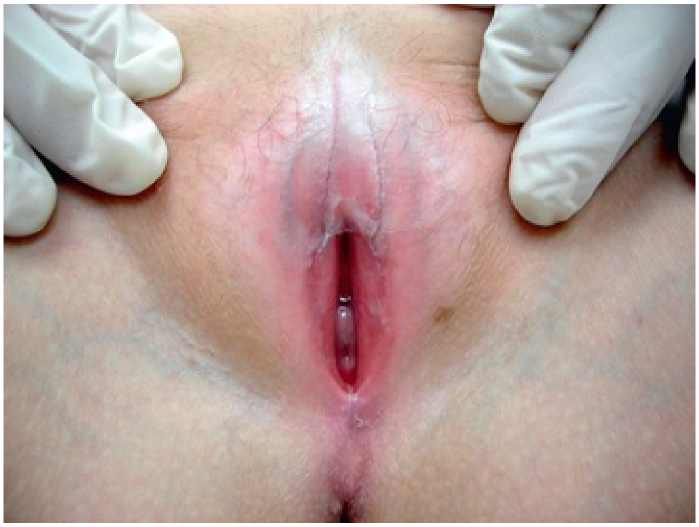

FIG. 564.4 Lichen sclerosus. (Photo courtesy of Diane F. Merritt, MD.)

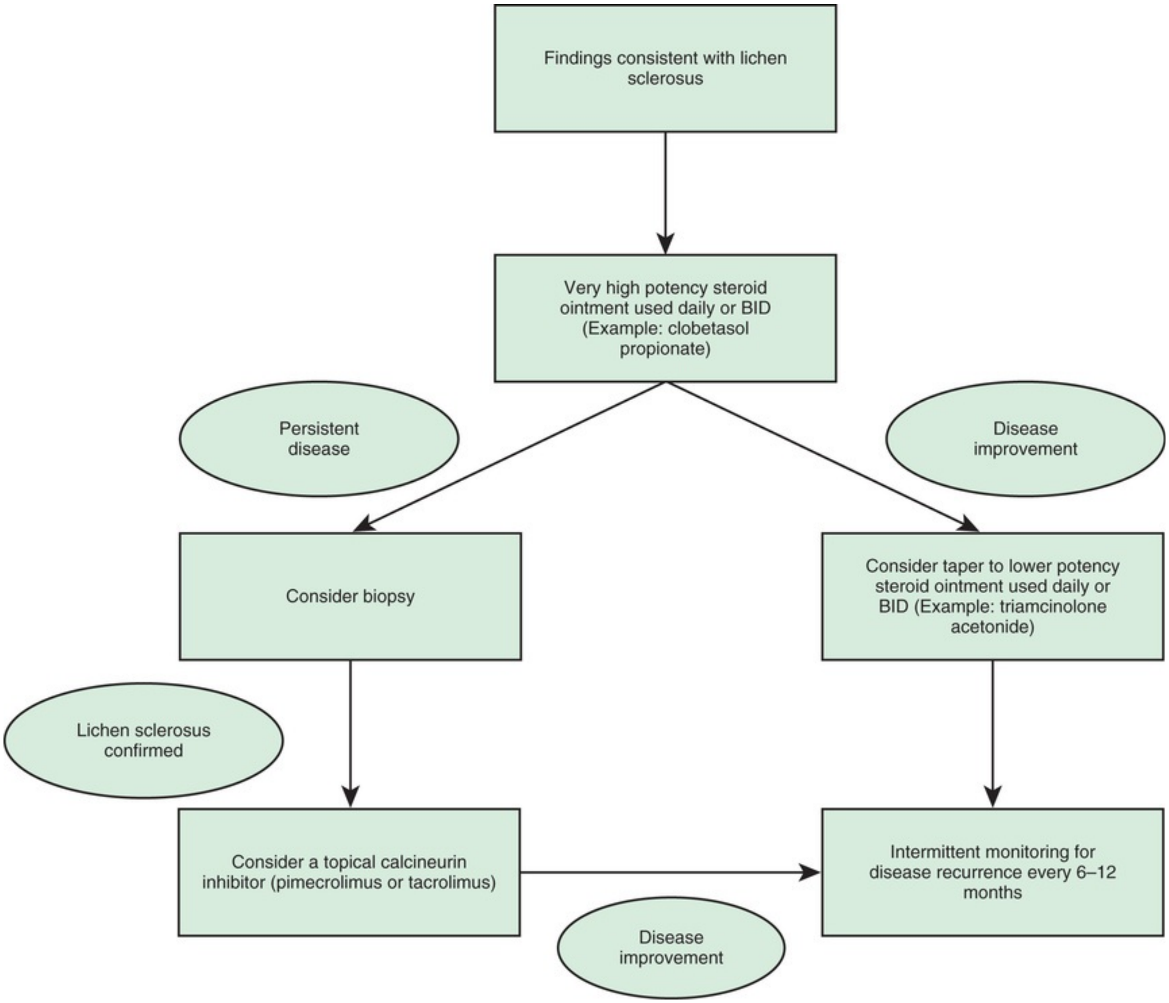
Findings consistent with lichen sclerosus
Very high potency steroid ointment used daily or BID (Example: clobetasol propionate)
Persistent disease
Disease improvement
Consider biopsy
Consider taper to lower potency steroid ointment used daily or BID (Example: triamcinolone acetonide)
Lichen sclerosus confirmed
Consider a topical calcineurin inhibitor (pimecrolimus or tacrolimus)
Intermittent monitoring for disease recurrence every 6–12 months
Disease improvement

FIG. 564.5 Management algorithm for lichen sclerosus. (From Bercaw-Pratt JL, Boardman LA, Simms-Cendan JS: Clinical recommendation: pediatric lichen sclerosus. J Pediatr Adolesc Gynecol 27:111-116, 2014, Fig. 2.)

Vitiligo is an acquired skin depigmentation resulting from an autoimmune process directed at epidermal melanocytes. Lesions appear as sharply demarcated patches of pigment loss, often symmetrically located around the vagina and anal area. Similar lesions of hypopigmentation can be found surrounding body orifices and extensor surfaces (Fig. 564.6). Although the diagnosis is clinical, there is an association with other autoimmune or endocrine disorders (hypothyroidism, Graves disease, Addison disease, pernicious anemia, insulin-dependent diabetes mellitus) and the workup should include evaluation for at least thyroid dysfunction. Mild topical corticosteroid cream or ointment may be prescribed for children. Dermatologists may offer immunomodulators (tacrolimus) and phototherapy.

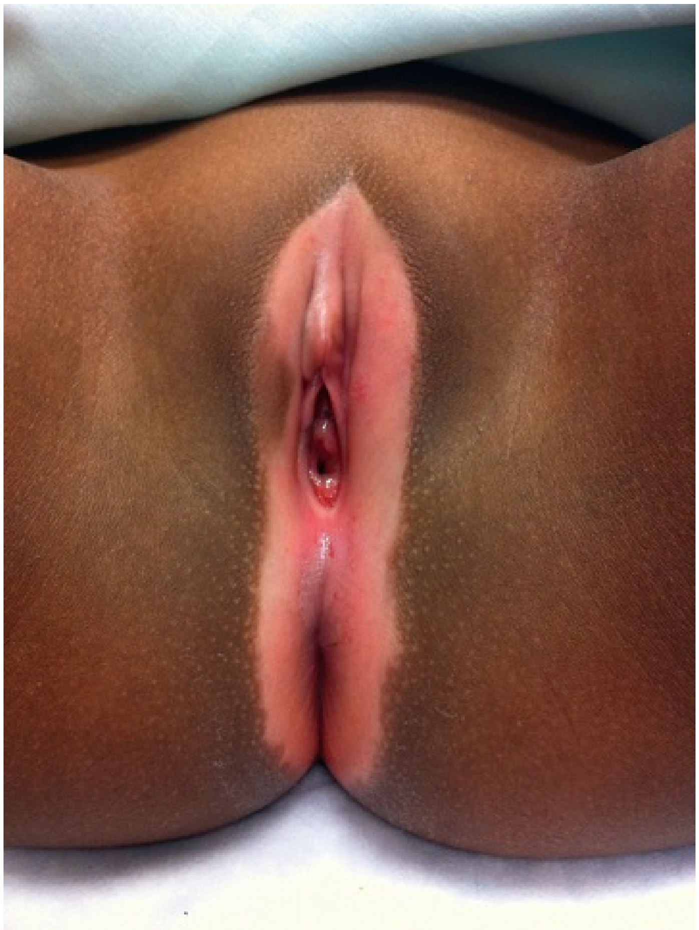

FIG. 564.6 Vitiligo. (Photo courtesy of Diane F. Merritt, MD.)

Vulvar psoriasis presents as pruritic, well-demarcated, erythematous, symmetric plaques that involve the vulva, perineum, and/or gluteal folds. Lesions on the mons pubis may have the more characteristic scaly appearance. The classic signs of psoriasis may also be appreciated with pitting nail beds, posterior auricular erythema, or a silvery scaling rash found elsewhere on the body. Many of the treatments used in adults may not be appropriate in children. Psoriasis may be treated with moisturizers, topical steroids, and light therapy. Teens may be treated with coal tar, retinoids, tacrolimus, and calcipotriene, which is a derivative of vitamin D_3 .

Diagnosis and Differential Diagnosis

Children with symptoms of vulvovaginitis often have had previous evaluations and treatment failures. Cultures with sensitivities to test for specific pathogens may be obtained with cotton swabs or urethral (Calgiswab) swabs moistened with nonbacteriostatic saline. Use of a swab can cause discomfort or, rarely, minimal bleeding. The premoistened swab can be placed vertically between the labia minora to collect secretions, as it is not necessary to place the swab into the vagina. Testing for gonorrhea and chlamydia may be done by culture or by nucleic acid amplification testing, depending on institutional or state and Centers for Disease Control guidelines. Tests for *Shigella* and *H. influenzae* might require special media and collection procedures.

If **pinworms** (see Chapter 320) are suspected, transparent adhesive tape or an anal swab should be applied to the anal region in the morning before defecation or bathing and then placed on a slide. Eggs seen on microscopic examination confirm the diagnosis, and sometimes the pinworms can be seen at the anal verge. Clinical history is often more indicative of disease than physical exam, and a negative tape test does not rule out this pathogen as a cause.

If the vaginal discharge is serosanguineous, if a foul odor is present, or if the discharge fails to respond to hygiene measures, consider presence of a vaginal foreign body (Fig. 564.7). If inspection suggests the presence of a foreign body, the vagina can be irrigated, or an examination under anesthesia may reveal the foreign body. Vaginal irrigation may occasionally lead to expulsion of the foreign body; in cases where this does not occur, vaginoscopy is an excellent diagnostic tool and can be performed in an unsedated cooperative patient in an outpatient setting, or under general anesthesia if necessary. Using a cystoscope with saline or water irrigation to gravity, insert the endoscopic device into the vagina, gently oppose the labia, the vagina will distend, and the entire vaginal cavity and cervix may be easily assessed.

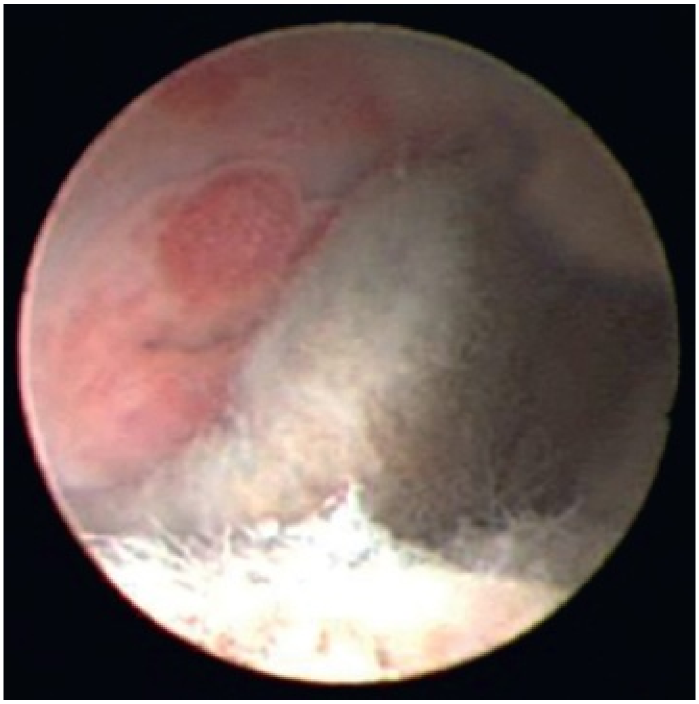

FIG. 564.7 Vaginal foreign body as seen through vaginoscope. (Photo courtesy of Diane F. Merritt, MD.)

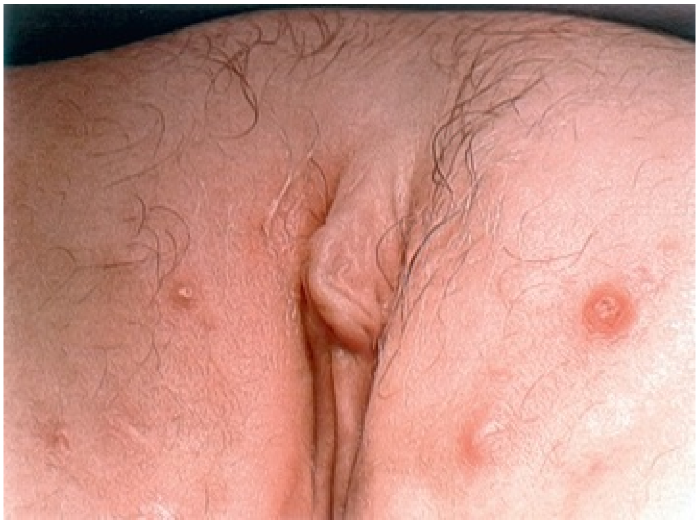

FIG. 564.8 Molluscum contagiosum. (Photo courtesy of Diane F. Merritt, MD.)

Treatment and Prevention

The treatment of specific vulvovaginitis should be directed at the organism causing the symptoms (see Table 564.1). Treatment of nonspecific vulvovaginitis includes sitz baths and avoidance of irritating or harsh soaps and chemicals and tight clothing that abrades the perineum. External application of bland emollient barriers such as nonprescription diaper rash medications and petroleum jelly may be helpful. Proper perineal hygiene is critical for long-term improvement. Younger children need supervised perineal hygiene, and caregivers should be advised to wipe the genital area from front to back. Use of a warm moistened washcloth or diaper wipe is helpful after initially wiping with toilet tissue. Girls should wear cotton underwear and limit time spent in tights, leotards, jeggings, tight jeans, and wet swimsuits. Soaking in warm clean bathwater for 15-min intervals (no shampoo or bubble bath) is soothing and helps with cleaning the area. Parents should be counseled to avoid all scented, antiseptic, and deodorant-based soaps, and to eliminate the use of fabric softeners or dryer sheets when laundering undergarments.

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CHAPTER 565

Vaginal Bleeding in the Prepubertal Child

Morgan P. Welebir, Diane F. Merritt

Vaginal bleeding in infants and prepubescent children should always be evaluated. Although physiologic bleeding may start as early as the first week of life, when circulating maternal estrogen diminishes and stimulates endometrial sloughing, there are many pathologic etiologies that require expeditious workup. Common causes include vulvovaginitis, dermatologic conditions, vaginal foreign bodies, and urethral prolapse; less common are the effects of endogenous or exogenous estrogen; and the least common but most worrisome sources include neoplasms and trauma.

Although many cases of pediatric vaginal bleeding are idiopathic, most of these instances are attributed to **vulvovaginitis** (see Chapter 564) stemming from transmission of respiratory, oral, fecal, or sexually communicated pathogens that may present with serosanguineous vaginal drainage (e.g., *Streptococcus, Shigella*) or vulvar irritation. Age-appropriate anatomic and physiologic factors put prepubertal girls at higher risk of developing vulvovaginitis. The protective barrier of fully developed labia is absent, leaving the vaginal introitus exposed to the external environment. The hypoestrogenized vagina is marked by an alkaline milieu that is prone to infection, lacking the protective acidic pH afforded by the lactobacilli colonization that occurs with puberty. Routine handwashing, improved perineal hygiene (e.g., wiping from front to back, use of wet wipes after bowel movements, proper cleansing of genitalia during baths) and avoidance of topical irritants, chemicals, and perfumed or deodorant soaps and bubble baths, will reduce nonspecific vulvovaginitis. Topical application of bland emollient barriers (e.g., over-the-counter diaper rash ointments, petroleum jelly) may be protective against and mitigate symptoms of external irritation. Antibiotics should be employed in the event of recurrent or persistent infections where a specific pathogen has been identified (see Table 564.2 in Chapter 564).

Vulvar dermatoses may initially present with bleeding. **Lichen sclerosus** (see Table 564.1 and Fig. 564.4 in Chapter 564) is characterized by chronic inflammation, intense pruritus, loss of normal architecture, and thinning and whitening of vulvar and perianal skin, often in a butterfly or keyhole distribution. Petechiae or blood blisters can complicate the classic clinical picture, leading to a mistaken assumption of sexual trauma. A tissue biopsy can provide a definitive diagnosis but is not usually necessary in prepubertal children. The first-line treatment is ultrapotent topical steroids (e.g., clobetasol propionate 0.05%). Appropriate timing and duration of application is practitioner dependent, but guidelines suggest treating children similarly to adults by starting with daily application for 4 wk or until symptoms resolve, tapering to alternate days for 4 wk, and finally twice weekly for 4 wk. Follow-up evaluations for response should start at 3 mo. In the event of flare-ups, long-term maintenance therapy may be initiated, as side effects are rare.

Vaginal foreign bodies are a common finding in children presenting with blood-tinged and foul-smelling discharge. Quick identification and removal of the foreign body avoids potential complications, including recurrent urinary tract infections, dermatologic abnormalities, vaginal perforation, or fistula formation. The most common object found in the prepubertal vagina is retained toilet paper. If physical exam in knee–chest or frog-leg position reveals the object, an attempt at removal in the office can be made using warm water flushes through a syringe equipped with a small feeding tube. If the object is not visible, irrigation is unlikely to remove it and examination under anesthesia and vaginoscopy are often required. Direct visualization via vaginoscopy facilitates extraction of an object, as well as evaluation for potential sites of injury or unrelated sources of bleeding.

Several urologic conditions may have a mixed clinical picture suspicious for vaginal bleeding, including **gross hematuria** (see Chapter 536) and **urethral prolapse** (see Chapter 559) (Fig. 565.1). Prolapse involves protrusion of urethral mucosa through the external meatus, resulting in a friable hemorrhagic mass that often obscures the adjacent vaginal introitus. Predisposing factors include hypoestrogenic state, neuromuscular diseases, urethral anomalies, fascial defects, trauma and chronic increases in intraabdominal pressure (e.g., recurrent valsalva related to constipation or forceful coughing). **Treatment of prolapse** is conservative, involving twice-daily sitz baths followed by topical application of estrogen cream (e.g., Estrace 0.01%) at the affected area for 2 wk. If on reevaluation the prolapse remains, application should be continued until complete resolution is achieved. Surgical excision is rarely necessary and reserved primarily for management of necrotic tissue.

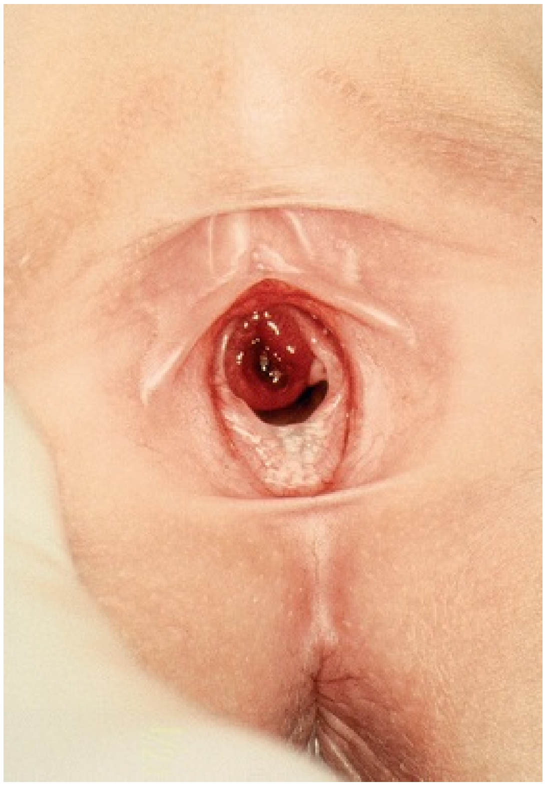

FIG. 565.1 Prepubertal urethral prolapse with high crescent-shaped hymen. (From Lara-Torre E, Valea FA: Pediatric and adolescent gynecology: gynecologic examination, infections, trauma, pelvic mass, precocious puberty. In Lobo RA, Gershenson DM, Lentz GM, Valea FA, editors: Comprehensive gynecology, 7th ed, St. Louis, 2017, Elsevier, Figure 12.6, p. 227.)

Vaginal bleeding may be a presenting sign of **precocious puberty** (see Chapter 578), defined as premature pubertal development occurring 2.0-2.5 SD earlier than the average age in the general population. A formal evaluation should be conducted if pubic hair or breast development occurs rapidly or initiates before age 7 yr in non–African-American girls and before age 6 yr in African-American girls. The most common source of premature development is **gonadotropin-dependent** or **central precocious puberty** (see Chapter subsection 578.1), resulting in early enhancement of pulsatile release of hypothalamic gonadotropic-releasing hormone (GnRH) that stimulates ovarian follicular growth and subsequent estrogen production. **Gonadotropin-independent** or **peripheral precocious puberty** occurs less commonly and in the absence of hypothalamic influence, with estrogen being a product of ovarian or adrenal tumors, or McCune Albright syndrome. In both instances, elevated estrogen levels lead to a thickened endometrium capable of shedding as in menses.

Evaluation of precocious puberty starts by examining for secondary sex characteristics and documenting the Tanner stage of breast and pubic hair development using the **Sexual Maturation Index** (see Chapter 132). Plotting height and weight on a growth chart may assist in identifying accelerated growth velocity. Supportive laboratory findings include elevated serum luteinizing hormone levels, but the gold standard remains measurement of gonadotropin levels after stimulation with GnRH or a GnRH receptor agonist. Estradiol levels greater than 100 pg/mL can indicate either the presence of premature ovarian follicles or a peripheral tumor (e.g., ovarian germ cell tumor). A pelvic ultrasound should be used to evaluate for ovarian or adrenal pathology, as well as uterine maturation in response to estrogen. However, premature ovarian follicles typically produce estrogen for a very short period, in quantities just sufficient to stimulate growth and shedding of the endometrium. Follicular involution and return of estrogen to prepubertal levels may occur before an ultrasound can be obtained. Other supportive radiologic findings include x-rays establishing advanced bone age and a brain MRI demonstrating a mass in the context of central precocious puberty. If indicated, central precocious puberty can be suppressed with leuprolide injections or histrelin implants. Peripheral tumors (i.e., ovarian germ cell tumors) are treated by excision, staging, and chemo or radiation therapy in line with oncologic protocols.

Differential diagnoses of vaginal bleeding attributed to premature estrogenization must also include exposure to **exogenous estrogens,** including hormonal contraceptives, certain foods, beauty products, and plastics. Ingesting large quantities of Bisphenol A (BPA), a product that may leach into the contents of plastic cups and bottles, is known to convey an estrogenic effect, though the impact remains unknown. Treatment involves elimination of any problematic sources of estrogen from the patient's daily use.

Juvenile hypothyroidism (see Chapter 581) commonly causes pubertal delay, but severe cases may present with premature breast development, vaginal bleeding, and abdominal distention secondary to ovarian enlargement and ascites. The mechanism for this condition is unclear, but it has been proposed that elevated levels of thyroid-stimulating hormone cross-react with follicle-stimulating hormone receptors, resulting in follicle maturation and estradiol production. Treatment with thyroid hormone replacement (e.g., Levothyroxine) results in improvement and ultimately reversal of symptoms.

Neoplasms of the vulva and vagina (see Chapter 568) are rare causes of bleeding in the pediatric patient. **Infantile hemangiomas** are the most common benign vascular neoplasm of infancy, affecting up to 5% of all infants. Most lesions initially proliferate before resolving spontaneously and seldom require intervention. However, on identifying a perineal hemangioma, a neurologic assessment should be performed due to an association with spinal dysraphism. If a persistent lesion is superficial, application of topical beta-blockers (e.g., Timolol 0.5%) 2-3 times daily for 6-12 mo has demonstrated good response rates. A small, well-demarcated but deep lesion may require intralesional injection of corticosteroids (e.g., triamcinolone 10-14 mg/mL) serially at 4-wk intervals until resolution. As with all systemic steroid therapies, injections should be limited to the minimum necessary to avoid complications. If conservative therapies fail, laser ablation and surgical excision may be employed. Vaginal polyps may result in bleeding, and expedient excision and pathologic evaluation is recommended.

Malignant gynecologic neoplasms (see Chapter 568) are a source of pediatric genital bleeding that requires scrupulous evaluation and timely management. Primary **endodermal sinus** (i.e., **yolk sac**) **tumors** of the vagina are exceedingly rare, but early diagnosis is imperative given the malignancy's aggressive nature and poor prognosis. **Rhabdomyosarcoma** is the most common soft tissue sarcoma of childhood; 3% arise from the uterus or vagina. The embryonal variant is responsible for uterine sarcomas, whereas the embryonal subvariant sarcoma botryoides is found in the vagina. Both endodermal sinus and sarcomatous tumors arise primarily in the first 3 yr of life, presenting on examination with a cystic or polypoid mass, bloody discharge, and occasionally urinary retention. Treatment consists of a multimodal approach, including surgery, radiation, and chemotherapy per oncologic guidelines.

Vulvovaginal trauma is an especially concerning cause of pediatric genital bleeding. Most traumatic injuries are accidental, but physical and sexual abuse must be ruled out (see Chapter subsection 16.1). **Straddle injuries,** sustained by abrupt contact with the metal frame of a bicycle or a slip-and-fall onto the edge of a bathtub or pool, may result in bruising, hematomas, or lacerations (Fig.

565.2). Accidental trauma usually spares the hymen and vagina, instead affecting the external impact-absorbing tissue of the mons and labia. *However, a physical finding consistent with external injuries does not exclude the need to rule out involvement of internal genital structures. If there are no eyewitnesses to the injury, if the history does not clarify or support the clinical findings, and especially if there is a hymenal laceration, abuse must be considered in the differential diagnosis and a forensic interview of the patient and family conducted.* If after initial inspection a penetrative injury is suspected, further examination and imaging are necessary to assess for potential damage to the urethra, bladder, anus, or intraabdominal structures. An examination under anesthesia may be needed to fully assess and repair extensive injuries, while minor lacerations in a cooperative child may potentially be repaired using local anesthesia. If the patient can void spontaneously, nonexpanding hematomas can be observed and treated with ice, pressure, and pain medications. Large expanding hematomas may require drainage, ligation of bleeding vessels, and placement of a closed suction drain if the overlying skin is showing signs of necrosis. A Foley catheter should be placed in all children who are having difficulty with voiding secondary to the injury.

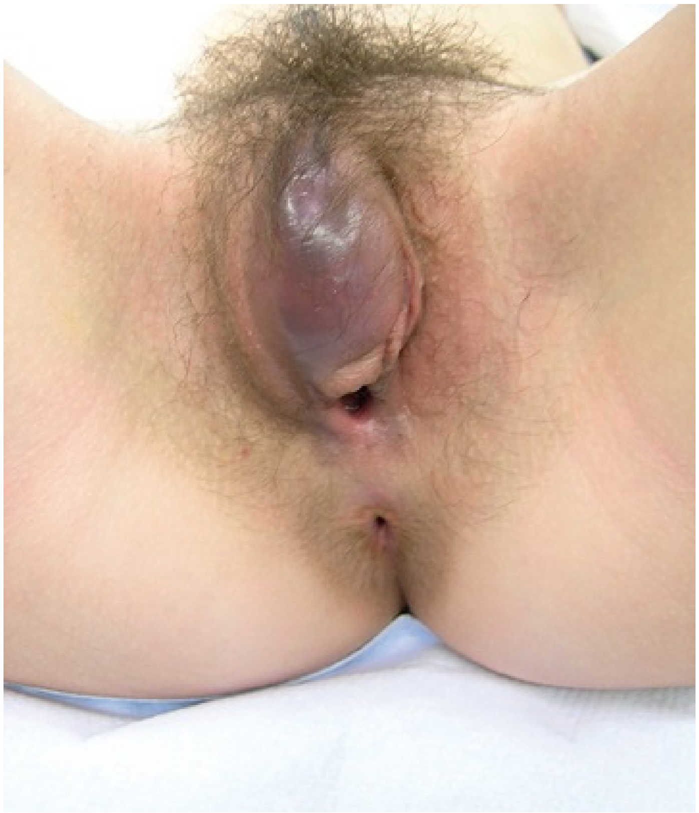

FIG. 565.2 Vulvar hematoma in an adolescent female as a result of a straddle injury. (From Mok-Lin EY, Laufer MR: Management of vulvar hematomas: use of a word catheter. J Pediatr Adolesc Gynecol 22(5):e156-e158, 2009.)

Vaginal bleeding in the infant or prepubertal girl is distressing to the patient and their family, and can result from a wide spectrum of pathologic conditions or traumatic incidents. A detailed history and thorough physical examination must be done to identify the source of bleeding, and a management plan established efficiently. Presentations suspicious for trauma or abuse should involve the appropriate healthcare staff and authorities from an early stage, with findings meticulously documented. If an intervention is indicated to manage bleeding, regardless of its source, the risks and benefits of any therapy should be reviewed carefully with the family before initiation.

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CHAPTER 566

Breast Concerns

Lindsay N. Conner, Diane F. Merritt

Presenting concerns of girls with breast disorders typically include the development or appearance of their breasts, breast pain, nipple discharge, or concerns about the presence of a mass. Although children and adolescents are very unlikely to have malignant or life-threatening breast problems, this population of patients should be referred to practitioners who have experience and familiarity with the immature and developing breast to avoid overtreatment with unnecessary diagnostic or surgical procedures.

Breast Development

Development of the breast begins around wk 5 of gestation, when the ectoderm on the anterior body wall thickens into two ridges known as the **mammary ridges.** They extend from the area of the developing axilla to the area of the developing inguinal canal. The ridge above and below the area of the pectoralis muscle recedes in utero, leaving the **mammary primordium** , which is the origin of the lactiferous ducts. The initial lactiferous ducts form between wk 10 and 20 and become interspersed through the developing mesenchyme, which becomes the fibrous and fatty portions of the breast. The **breast bud** , under the stimulation of maternal estrogen, becomes palpable at wk 34 of gestation. This breast bud regresses within the first month of life once estrogen stimulation is no longer present. The **areola** appears at 5 mo of gestation, and the nipple is seen shortly after birth. It is initially depressed or inverted, and later becomes elevated.

Thelarche, or the onset of pubertal breast development, is hormonally mediated and normally occurs between the ages of 8 and 13 yr. The initiation of thelarche and progression in females is affected by race, with normal thelarche occurring earlier in African American girls than in white or Asian girls. This occurs when the hypothalamus releases gonadotropin-releasing hormone, which stimulates the pituitary gland to produce follicle-stimulating hormone and luteinizing hormone. These hormones then stimulate the ovaries to produce estradiol, which leads to breast development.

Once thelarche is initiated, normal development of the breast occurs over 2-4 yr and is classified by the **sexual maturity rating system** (also known as **Tanner staging**) into five stages (see Chapter 132). Maturation can sometimes occur asymmetrically owing to fluctuation of the hormonal environments and various end-organ sensitivities. Lack of development by age 13 yr is considered delayed and warrants endocrinology evaluation. **Menarche** usually occurs ~2 yr after initiation of breast development.

Breast Evaluation

Breast evaluation should be included in the annual examination of all children and adolescents. Assessment of the newborn includes breast size, nipple position, presence of accessory nipples, and nipple discharge. Assessment of the prepubertal girl includes inspection and palpation of the chest wall for masses, pain, nipple discharge, and signs of **premature thelarche.** Examination of the adolescent is performed with the patient in the supine position; the arm ipsilateral to the breast that is being examined should be placed next to the patient's head. The breast tissue is examined with the flat pads of the middle fingers, and the examiner should palpate all of the breast tissue in a uniform manner. The sexual maturity rating should be noted and the axillary, supraclavicular, and infraclavicular nodes evaluated for lymphadenopathy. The areola should be compressed to assess for nipple discharge.

Breast Self-Awareness

Controversy exists as to the utility of breast self-examination in the adolescent population. Experts believe that it might be ill-advised to encourage breast self-examination in the adolescent because of a potential for unnecessary anxiety and possible unwarranted treatment in a population that is at low risk for malignant disease. The American College of Obstetricians and Gynecologists (ACOG) endorses breast self-awareness, which is defined as a women's awareness of the normal appearance and feel of her breasts. This can include breast self-examination, and instruction should be considered for high-risk patients. Adolescents should be educated to report any changes in their breasts or concerns to their healthcare providers.

Abnormal Development

Neonatal Breast Abnormalities

The condition in which breasts enlarge in the newborn period is **neonatal breast hypertrophy.** This is quite common in term infants of either sex and can occur as a result of elevated circulating maternal endogenous steroid hormones in late gestation. As maternal estrogen levels fall, prolactin levels can increase and the breasts can produce a clear or cloudy (milk-like) nipple discharge ("witch's milk") in male and female infants. Repeated manipulation of the breast can exacerbate the condition, so it should be discouraged. On occasion, the hypertrophy is associated with **mastitis** caused by a staphylococcal or streptococcal infection; parenteral antibiotics should be administered.

Precocious Puberty

Premature thelarche is usually an isolated benign condition and is more common than previously thought. In one study, patients with a sexual maturity rating of 2 or greater at 7 yr of age were evident in 10.4% of white, 23.4% of black non-Hispanic, and 14.9% of Hispanic girls. However, it may also be the first symptom of **precocious puberty.** Precocious puberty occurs in 14–18% of girls with premature thelarche (see Chapter 578). Serial examinations, with particular emphasis on growth velocity, secondary sex characters such as pubic hair, pigmentation of the labia or areola, or vaginal bleeding are imperative to identify precocious puberty. Unless there are associated signs of precocious puberty, the parents should be reassured and the child should be followed. If persistent maturation is noted, further workup should be performed to exclude central nervous system disorders or possible adrenal or gonadal neoplasm.

Amastia

Complete absence of the breast, or **amastia,** is rare and is thought to occur from lack of formation of or obliteration of the mammary ridge. Amastia is usually unilateral and can be congenital or associated with systemic disorders (e.g., ectodermal dysplasia), endocrine disorders (e.g., congenital adrenal hyperplasia, gonadal dysgenesis, hypogonadotropic hypogonadism), or novel gene mutations. It can be associated with anomalies of the underlying mesoderm, such as abnormal pectoralis muscles seen in **Poland syndrome** (aplasia of the pectoralis muscles, rib deformities, webbed fingers, and radial nerve aplasia) (Fig. 566.1). Amastia or hypomastia can also be iatrogenic, resulting from injuries sustained during thoracotomy, chest tube placement, radiotherapy, severe burns, and inappropriate biopsy of the breast bud. Treatment is surgical correction.

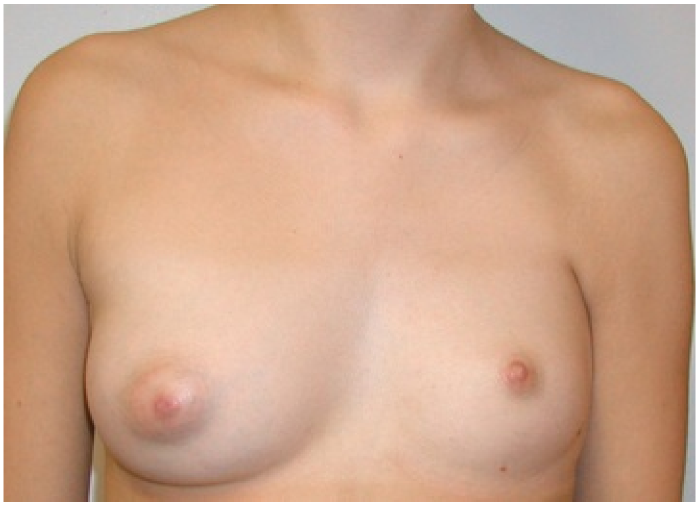

FIG. 566.1 Preoperative frontal view of a patient with left breast hypoplasia secondary to Poland syndrome. (From Laberge LC, Bortoluzzi PA: Correction of breast asymmetry in teenagers. In Hall-Findlay EJ, Evans GRD, editors: Aesthetic and reconstructive surgery of the breast. London, 2010, Elsevier, Fig 39.14.)

Polymastia and Polythelia

Supernumerary breast tissue **(polymastia)** and accessory nipples **(polythelia)** occur in approximately 1–6% of the population (Fig. 566.2). The abnormally placed tissue can be seen anywhere along the mammary ridges as a result of incomplete involution but is usually noted on the chest, upper abdomen, or just inferior to the normally positioned breast. There is an association between polythelia and anomalies of the urinary and cardiovascular system. Surgical excision of the accessory breasts or nipple is not usually needed. Resection of accessory tissue may be warranted if the patient has pain or for cosmetic reasons.

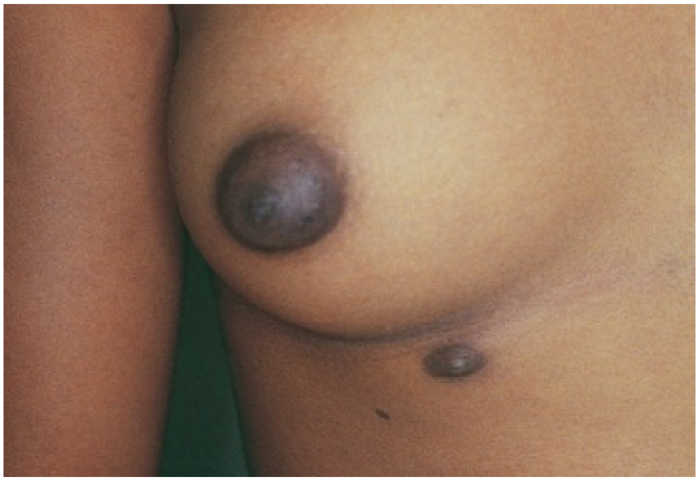

FIG. 566.2 Accessory nipple located inferior to the right breast. (From Swartz MH: Textbook of physical diagnosis, ed 7, Philadelphia, 2014, Elsevier, Fig 13-5.)

Breast Asymmetry and Hypomastia

Some degree of asymmetry is normal in women, and it may be more pronounced during puberty while the breasts are developing. Hypoplasia of the breasts varies in degree from a nearly total absence of breast tissue to well-formed breasts that are considered by the patient to be too small. There are several causes for poor or absent breast development. The onset of breast development may be delayed with normal secondary sex characters; the breasts develop slowly but are normal in all other respects; a patient's family history might include late breast development. Other causes include ovarian dysfunction, hypothyroidism, and chest wall irradiation or surgery. **Hypoplastic breast tissue** can also be associated with a tuberous breast anomaly. Treatment depends on the underlying cause. Patients with mild asymmetry and with no other associated pathology should be reassured. If a girl has marked breast asymmetry, she may be initially offered the option of using padding for the underdeveloped breast. She may also choose to explore surgical correction after reaching 18 yr of age (see the section on Cosmetic Surgery).

Juvenile or Virginal Hypertrophy

Spontaneous massive growth of the breasts during puberty and adolescence is thought to be the result of excessive end-organ sensitivity to gonadal hormones, although both the hormone receptors and serum estradiol levels are normal. The underlying cause, if any, should be determined and removed (Table 566.1). When growth is extreme, it is termed **macromastia** or **gigantomastia.** It is more commonly bilateral, often occurs over a brief period, and most commonly affects adolescent girls (Fig. 566.3). Physical and psychological problems can affect posture and quality of life. Strong emotional support should be provided because this can affect an adolescent's self-esteem at a vulnerable time in her psychological development. Management should be individualized and may range from reassurance or the use of supportive brassieres to reduction mammoplasty or even mastectomy. Medical therapy, such as tamoxifen, is available to slow breast growth in extreme cases until surgery can be performed and/or after surgery in cases of reoccurrence.

Table 566.1

Differential Diagnosis of Macromastia

Juvenile hypertrophy
Tumors of the breast
Giant fibroadenoma
Hamartoma
Cystosarcoma phyllodes
Carcinoma
Hormonally active tumors
Ovarian granulosa cell tumor
Ovarian follicular cysts
Adrenal cortical tumors
Exogenous hormones
Estrogen
Testosterone
Gonadotropins
Corticosterone
Medications
Cannabis

From Desilva N, Brandt M: Breast disorders in children and adolescents. In Sanfilippo J, Lara-Torre E, editors: Clinical pediatric and adolescent gynecology, London, 2008, Taylor & Francis.

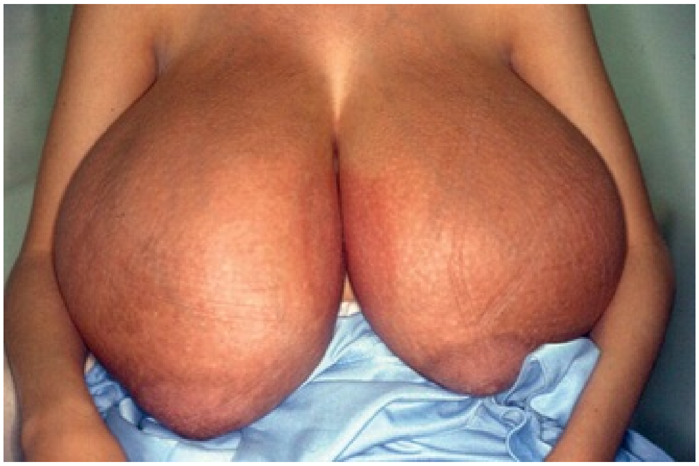

FIG. 566.3 Virginal mammary hypertrophy in a 12 yr old female. (From Al-Saif AA, Al-Yahya GM, Al-Qattan MM: Juvenile mammary hypertrophy: is reduction mammoplasty always feasible? J Plast Reconstr Aesthet Surg 62:1470–1472, 2009, Fig. 1.)

Infections

Mastitis is the most common infection of the breast. Although it is most common in lactating mothers, it can occur in young infants and adolescents. **Neonatal mastitis** is an infection that usually occurs in the first 2 mo after delivery in term or near-term infants. Adolescents can develop **nonlactational mastitis** or a **breast abscess** as a result of irritation of the skin (e.g., acne lesions of the chest, shaving, or nipple stimulation), trauma, a foreign body (e.g., piercing), or ductal abnormality (such as ductal ectasia). *Staphylococcus aureus* (see Chapter 208.1) or anaerobic bacilli *(bacteroides)* are the offending organisms in almost all cases, and methicillin-resistant *S. aureus* coverage should be considered in communities where the prevalence is high. Owing to the potential for breast abscess, the neonatal population should be treated with parenteral antibiotics for methicillin-resistant *S. aureus* or guided by Gram staining and culture. Adolescents may be initially treated with warm compresses, analgesics, and oral antibiotics. The choice of antibiotic may be directed by Gram staining and culture of nipple discharge or fluid collections obtained from sonographically directed fine-needle aspiration. Ultrasound guidance may also be utilized to direct drainage of breast abscesses. If incision and drainage is performed, a small periareolar incision is most cosmetic.

Trauma and Inflammation

Breast trauma is common in adolescent girls participating in contact sports. The trauma usually takes the form of contusion or **hematoma** and can resolve spontaneously or may be associated with late cystic changes in the breast or fibrosis with retraction of the skin or the nipple over the injured area. When diagnosed with a hematoma, short-term follow-up by ultrasound is recommended to ensure resolution.

Nipple Discharge

Nipple discharge must be carefully evaluated and a distinction made among **galactorrhea** (milky white discharge), blood, or other discharge (Table 566.2). A careful history and physical examination directed at the possible etiologies of galactorrhea will help the practitioner determine the etiology. Examination of the discharge assists in diagnosis. Benign conditions are usually associated with a milky, sticky, thick discharge; infection is associated with a purulent discharge; **intraductal papilloma** and cancer are associated with a serous, serosanguineous, or bloody discharge. Preoperative evaluations by mammography, hemoccult, ductography, and cytology are poor predictors of the histologic diagnosis. Therefore, patients with pathologic nipple discharge should undergo biopsy for accurate diagnosis.

Table 566.2

Common Causes of Nipple Discharge

Pregnancy
Hormones (oral contraceptives, estrogen, progesterone)
Blood pressure drugs (methyldopa, verapamil)
Tricyclic antidepressants
Tranquilizers (antipsychotics)

Antinausea drugs (metoclopramide)
Herbs (nettle, fennel, blessed thistle, anise, fenugreek seed)
Illicit drugs (marijuana, opiates)
Stimulation of the breast (sexual or from exercise)
Thyroid abnormalities
Chronic emotional stress
Hypothalamic tumors
Chest wall conditions
Herpes zoster
Trauma
Burns
Tumors
Breast conditions
Mammary duct ectasia
Chronic cystic mastitis
Intraductal cysts
Intraductal papillomas

Galactorrhea

Causes of galactorrhea include medications, street drugs, herbal supplements, oral contraceptives, hyperprolactinemia, hypothyroidism, renal disease, breast stimulation, nerve damage to the chest wall, and spinal cord injuries (Tables 566.3 and 566.4). Cytologic evaluation of milky nipple discharge is not recommended. Serum pregnancy testing, prolactin levels, and thyroid levels are obtained to rule out pregnancy (in the postpubertal adolescent), a pituitary prolactinoma, and/or the presence of a thyroid abnormality. If the prolactin level is elevated, visual field studies and a head MRI might reveal the presence of a pituitary adenoma (see Chapter 576). Treatment is directed by results of the history, physical exam, and lab studies. Patients should be instructed to avoid nipple stimulation and stop any offending drugs. Hypothyroidism should be treated and prolactin tumors managed with appropriate medical or surgical care. Treatment of galactorrhea (not thyroid related) consists primarily of dopamine agonists such as bromocriptine or cabergoline. Surgical intervention, usually transsphenoidal hypophysectomy, is rarely required.

Table 566.3

Causes of Hyperprolactinemia

PITUITARY DISEASE
Prolactinomas
Acromegaly
Empty sella syndrome
Lymphocytic hypophysitis
Cushing disease
HYPOTHALAMIC DISEASE
Craniopharyngiomas
Meningiomas
Dysgerminomas
Nonsecreting pituitary adenomas
Other tumors
Sarcoidosis
Eosinophilic granuloma
Neuraxis irradiation
Vascular disorders
Pituitary stalk section
MEDICATIONS
See Table 566.4
NEUROGENIC DISORDERS
Chest wall lesions
Spinal cord lesions
Breast stimulation
OTHER CAUSES
Pregnancy
Hypothyroidism
Chronic renal failure
Cirrhosis
Pseudocyesis
Adrenal insufficiency
Ectopic disorders
Polycystic ovary syndrome
Idiopathic disorders

From Molitch ME: Prolactinoma. In Melmed S, editor: The pituitary, 2nd ed. Malden, MA, 2002, Blackwell, pp. 455-495.

Table 566.4

Pharmacologic Agents Affecting Prolactin Concentrations

Stimulators
Anesthetics, including cocaine
Psychoactive drugs
Phenothiazines
Tricyclic antidepressants
Opiates
Chlordiazepoxide
Amphetamines
Diazepam
Haloperidol
Fluphenazine
Chlorpromazine
Selective serotonin reuptake inhibitors
Hormones
Estrogen
Oral-steroid contraceptives
Thyrotropin-releasing hormone
Antihypertensives
α-Methyldopa
Reserpine
Verapamil
Dopamine receptor antagonists
Metoclopramide
Antiemetics
Sulpiride
Promazine
Perphenazine
Others
Cimetidine
Cyproheptadine
Protease inhibitors
Inhibitors

L-Dopa
Dopamine
Bromocriptine
Pergolide
Cabergoline
Depot bromocriptine

From Shoupe D, Mishell DR Jr: Hyperprolactinemia: diagnosis and treatment. In Lobo RA, Mishell DR Jr, Paulson RJ, Shoupe D, editors: Mishell's textbook of infertility, contraception and reproductive endocrinology, 4th ed. Cambridge, MA, 1997, Blackwell Scientific.

Bloody Discharge

Cytologic assessment of bloody discharge should be performed. In adolescent athletes, bloody discharge may be due to chronic nipple irritation **(jogger's nipple),** discharge from the ducts of Montgomery (on the edge of the areola, not through the nipple), or **ductal ectasia.** Surgical consultation for a mass is indicated because intraductal breast papillomas have occurred in adolescents. However, there have been no reported cases of breast cancer in infants. Bloody nipple discharge in infants is most likely from mammary duct ectasia, and if the following studies are normal (prolactin, estradiol, thyrotropin, and ultrasound), then watchful waiting may be appropriate.

Mastalgia

The most common causes of breast pain in adolescents are exercise and benign breast changes. Physiologic swelling and tenderness occur on a cyclic basis, most commonly during the premenstrual phase, and are secondary to hormonal stimulation and resulting proliferative changes. Hormonal imbalance can cause exaggerated responses in the breast tissue, especially in the upper and outer quadrants. Nodularity, poorly localized tenderness, and a soreness radiating to the axilla and arm are usual accompanying findings. The preferable term for these changes is **benign breast changes** rather than fibrocystic disease. Treatments recommended for this condition and exercise-induced pain include a firm, supportive sports-type bra, heat, and analgesics. Oral contraceptives often improve the breast pain. A course of nonsteroidal antiinflammatory drugs is also effective. Methylxanthines (e.g., caffeine in coffee, tea, carbonated drinks, and chocolate) and smoking should be eliminated. Evening primrose oil and vitamin E are popular but unproven treatments.

Breast Masses

Peripubertal Masses

A mass in the developing breast can be of concern to the adolescent and her family. Initial breast development at the onset of thelarche can be asymmetric and thus mistaken for a "mass." The breast bud is palpable in these cases and should be distinguishable. Such asynchronous thelarche should be recognized to avoid biopsy and potential injury to the maturing breast. If there is any question, ultrasound can be used to evaluate for a mass. Unilateral thelarche has also been reported as a side effect of cimetidine and is reversible when the medication is stopped. Lymph nodes within the axilla, axillary tail, and breast parenchyma can become clinically palpable. This is usually a reactive process secondary to viral illness or vaccination.

Common Adolescent Breast Masses

Table 566.5 shows the differential diagnosis for breast masses in the adolescent patient. The patient should be questioned about the variation in symptoms with the menstrual cycle, associated symptoms such as nipple discharge, recent trauma to the breast, family history of breast masses or cancer, and history of chest radiation or malignancy. Because breast cancer in the adolescent is extremely rare, masses can be expectantly managed for extended periods with little concern for malignancy in this population.

Table 566.5

Breast Masses in the Adolescent Girl

BENIGN
Fibroadenoma
Fibrocystic changes or cysts
Unilateral thelarche

Hemangioma
Intramammary lymph node
Fat necrosis
Abscess
Mastitis
Lipoma
Hematoma
Hamartoma
Macromastia (juvenile hypertrophy)
Galactocele
Intraductal papilloma
Juvenile papillomatosis
Lymphangioma
MALIGNANT
Malignant cystosarcoma phyllodes
Breast carcinoma
Metastatic disease
Lymphoma, neuroblastoma, sarcoma, rhabdomyosarcoma, acute leukemia

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Data from Dehner LP, Hill DA, Deschryver K: Pathology of the breast in children, adolescents, and young adults, Semin Diagn Pathol 16:235-247, 1999; Simmons PS: Diagnostic considerations in breast disorders of children and adolescents, Obstet Gynecol Clin North Am 19:91-102, 1992; and Divasta AD, Weldon C, Labow BI: The breast examination and lesions. In Emans SJ, Laufer MR, Goldstein DP, editors: Pediatric and adolescent gynecology, ed 6, Philadelphia, 2012, Lippincott Williams & Wilkins, pp. 405-420.

The most common solid mass seen in adolescent girls is the **fibroadenoma.** Fibroadenomas are most often located in the upper outer quadrant of the breast. The average size is 2-3 cm, and 10–25% of patients have multiple lesions. The physical examination is usually diagnostic because these lesions are well circumscribed, rubbery, mobile, and not tender. In equivocal cases, an ultrasound may be helpful in making the diagnosis.

Fibroadenomas can develop because of a local exaggerated response to estrogen stimulation, and they can enlarge during the menstrual cycle. Approximately 10% of fibroadenomas regress spontaneously. The option of expectantly managing the patient until adulthood should be considered because the risk of primary cancer is very low in this population. If expectant management is chosen, serial ultrasounds every 6-12 mo may be done to ensure that the mass does not have malignant characteristics on imaging and that it is not enlarging or changing in contour until it starts regressing, at which time the ultrasounds can be done at longer intervals. Approximately 4% of fibroadenomas grow, and so excisional biopsy is recommended when a mass looks suspicious, has complex ultrasonographic signs, is larger than 4-5 cm (because of the risk of giant fibroadenoma or **phyllodes tumor**), or is causing anxiety to the patient or her family. Combined estrogen–progesterone birth control pills have been found to be protective of fibroadenomas.

Cysts are very common masses seen in the pediatric breast. Cysts vary in size over the course of a menstrual cycle, so a patient with a possible cyst should be reexamined a few weeks after the initial evaluation to see if the mass is still present. If a mass persists, then it may be imaged by sonography or aspirated with a needle to evaluate if it truly is a cyst. If the cyst demonstrates an anechoic structure with imperceptible wall and posterior acoustic enhancement on ultrasound, it is most likely a benign diagnosis. If the cyst appears thick-walled and/or has internal echoes, consider a complicated cyst, abscess, galactocele, or focal ductal ectasia. Aspirated fluid that is clear may be discarded. Bloody fluid and other aspirated material should be sent for cytologic examination. Cystic lesions that resolve with aspiration should be reevaluated in 3 mo. If they recur, they should be evaluated with sonography.

Malignant Masses

Primary breast cancer is extremely rare in adolescents. Surveillance Epidemiology and End Results data from 2011-2015 for female invasive breast cancer established an age-specific rate at ages 15-19 yr of 0.1/100,000 and at ages 20-24 yr of 1.6/100,000. Although malignancy is rare, lesions with suspicious imaging findings (e.g., irregular shape/microlobulated/spiculated margin) or progressive growth should undergo cytologic or histologic examination.

Phyllodes tumors, constituting 0.3–1% of fibroepithelial neoplasms of the breast, are extremely rare. They are generally classified as low grade, intermediate grade, or high grade (malignant). They are characterized by asymmetric breast enlargement in association with a firm, mobile, circumscribed mass. The mass can mimic a giant fibroadenoma. The tumor often grows rapidly and can become quite large. The majority of these tumors have a favorable prognosis, but malignant phyllodes has been reported to recur both locally and with metastases. Excision with 1-cm margins is the preferred initial therapy in adolescent patients, regardless of the histologic classification of the lesion.

Juvenile papillomatosis is a marker for increased breast cancer risk in family members, and in patients with this condition, up to 15% may have a juvenile secretory carcinoma. Treatment of juvenile papillomatosis is total resection of the lesion with preservation of the breast.

Invasive secretory carcinoma is the most common subtype of invasive breast cancer in children. The tumor is usually a small (<3 cm), nonpainful mass. Treatment consists of surgical excision with sentinel node biopsy, with the potential for chemotherapy dependent upon the extent of the disease.

Secondary cancers in adolescents with previous therapeutic radiation to the chest or with malignancies with the potential to metastasize to the breast should be monitored more closely for breast masses. Rhabdomyosarcoma is the most common to metastasize to the breast. Other malignancies include neuroblastoma, melanoma, renal cell carcinoma and Ewing sarcoma. Breast tumors also may be the first manifestation of relapse (extramedullary) in acute lymphoblastic leukemia.

In young women with risk factors predisposing to breast cancer (family history, genetic mutation, known extramammary malignancy, or prior mantle irradiation), a biopsy is required regardless of imaging findings.

Imaging of Breast Masses

Because the dense breast tissue of the adolescent obstructs the visualization of a palpable mass, mammography is not advised for this age-group. **Ultrasonography** is the imaging modality of choice for breast abnormalities in the pediatric population given the diagnostic specificity and lack of ionizing radiation. Of note, the ultrasound appearance of the breast at various Tanner stages is critical knowledge for the radiologist. Color Doppler ultrasound can be useful in evaluating breast abnormalities such as fibroadenomas or abscesses. CT/MR is reserved for evaluation of the disease extent.

Recommendations for Daughters of Women With Breast Cancer

Risk Reduction

There are a limited number of things that young women can do to lower their risk of breast cancer. The American Cancer Society recommends regular physical activity, limiting alcohol, eliminating cigarette smoking, and maintaining a healthy weight. Some studies have shown that breastfeeding for at least 1 yr may slightly lower the breast cancer risk.

Screening Procedures

Women in their 20s and 30s should have a clinical breast exam as part of a periodic (regular) health exam by a health professional at least every 1-3 yr. After age 40 yr, women should have a breast exam by a health professional every year and ACOG recommends screening mammogram every year for as long as they are in good health.

In young adults with known *BRCA* mutations, the recommended surveillance includes a clinical breast exam semiannually, as well as annual mammography plus magnetic resonance imaging beginning at age 25 yr or sooner, based on the earliest age of onset in the family. Women who have 1st-degree relatives with these mutations but who are untested are generally managed as if they carry these mutations until their *BRCA* status is known.

For those who underwent thoracic radiation between 10 and 30 yr (typically for lymphoma), annual mammography and MRI plus screening breast exams every 6-12 mo should be performed beginning 8-10 yr after treatment or at age 25 yr.

Genetic Testing in Children

Genetic testing for mutations in cancer susceptibility genes in children is particularly complex. Both parents and providers may request or recommend testing for minor children; however, many experts (including the American Society of Clinical Oncology) recommend that unless there is evidence that the test result will influence the medical management of the child or adolescent, genetic testing should be deferred until legal adulthood (18 yr or older) because of concerns about autonomy, potential discrimination, and possible psychosocial effects.

Cosmetic Surgery

Breast reduction mammoplasty may be desired by adolescents in order to relieve severe back, neck, and shoulder pain, and breast augmentation may be desired for reconstruction of congenital conditions with deformity, severe asymmetry, or as an elective procedure. ACOG recommends that when adolescents seek breast surgery, the first step should be education and reassurance regarding normal variations in anatomy, growth, and development for the patient and her family. Nonsurgical alternatives for comfort and appearance should be emphasized (e.g., pads or prostheses to wear with clothes) and knowledge regarding indications and timing of surgical intervention and referral should be provided. Last, assessment of the adolescent's physical and emotional maturity level must be performed, as well as screening for **body dysmorphic disorder.**

The American Society of Plastic Surgeons supports the recommendations made by ACOG, specifically highlighting that adolescents be at least 18 yr of age before undergoing the surgery and have a realistic understanding of the potential results, as well as the possible need for additional surgery. Currently, saline-filled implants are the only type of implant approved by the U.S. Food and Drug Administration for females < 22 yr. Saline-filled implants typically have a 10-yr lifespan.

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CHAPTER 567

Polycystic Ovary Syndrome and Hirsutism

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Polycystic Ovary Syndrome

Etiology and Definition

Polycystic ovary syndrome (PCOS) is a common disorder of reproductive hormone function that is characterized by the triad of oligoovulation or anovulation, clinical or biochemical hyperandrogenism, and ovaries with a polycystic morphology on ultrasound examination (≥12 follicles in 1 ovary and/or ovarian volume > 10 mm^3 by Rotterdam criteria). Various expert groups prioritize these elements differently for establishing the diagnosis, and few require the presence of all 3 (Table 567.1). Hyperandrogenism with ovulatory dysfunction (with exclusion of other causes) is most often considered sufficient for diagnosis in the United States. Abnormalities commonly associated with PCOS include obesity, insulin resistance, and the metabolic syndrome, but the phenotype is variable, and affected individuals may display none of these. The disorder, affecting 5–20% of women of reproductive age, depending on diagnostic criteria used, typically emerges in adolescence when a normal menstrual pattern is not established and there is clinical evidence of androgen excess. In addition, 10–25% of women with no signs of clinical PCOS may have an isolated finding of polycystic ovaries by ultrasonography; they may be considered as polycystic-appearing ovaries (PAO) or polycystic ovarian morphology (PCOM). Some may be at risk for developing PCOS in the future.

Table 567.1

Diagnostic Criteria for Polycystic Ovary Syndrome

Diagnostic Criteria for Polycystic Ovary Syndrome

NATIONAL INSTITUTES OF HEALTH CRITERIA	ROTTERDAM CRITERIA	ANDROGEN EXCESS SOCIETY
Oligoovulation or anovulation *and* Clinical or biochemical hyperandrogenism	Two of 3 of the following: Oligoovulation or anovulation Polycystic ovaries on ultrasonography (12 or more follicles in a single ovary or ovarian volume of > 10 mm^3 in 1 ovary) Clinical and/or biochemical hyperandrogenism	Clinical or biochemical hyperandrogenism and at least 1 of the following: Polycystic ovaries *or* Oligoovulation or anovulation

Pathology, Pathogenesis, and Genetics

PCOS has a high concordance rate in twins, and in some studies either epigenetic or dominant inheritance patterns are observed. Nonetheless, a consistent hereditary pattern has not been identified.

Gonadotropic dysregulation with increased luteinizing hormone (LH) pulsatility and abnormally high ratios of circulating LH to follicle-stimulating hormone (FSH) are found in many patients with PCOS. Increased *ovarian* production of androgen in response to LH and impaired folliculogenesis owing to lower FSH are attributed to this gonadotropic pattern. Abnormal regulation of gonadotropin-releasing hormone agonist and gonadotropin secretion are more likely a reflection of the abnormal hormonal milieu of the syndrome rather than an explanation for its origin (Fig. 567.1). An increased ratio of circulating levels of LH:FSH is *not* a diagnostic criterion for PCOS.

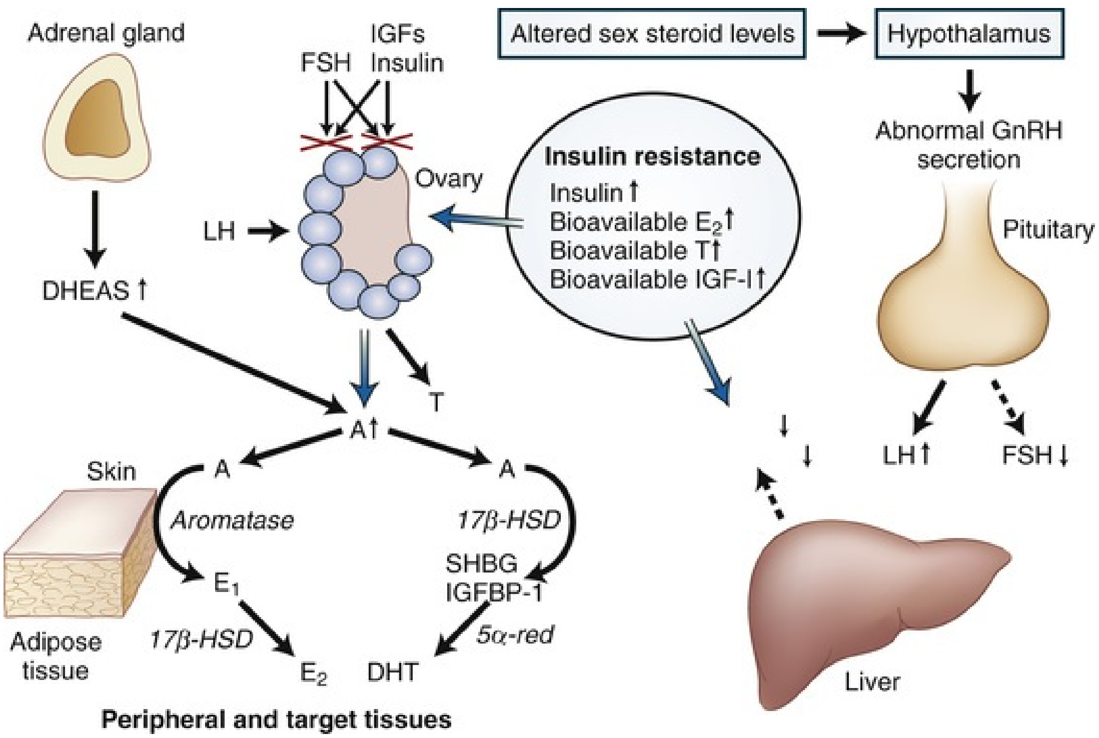
Adrenal gland
DHEAS ↑
IGFs
FSH
Insulin
Ovary
LH
Altered sex steroid levels
Hypothalamus
Abnormal GnRH secretion
Insulin resistance
Insulin ↑
Bioavailable E_2 ↑
Bioavailable T ↑
Bioavailable IGF-I ↑
Pituitary
T
A ↑
A
A
Skin
Aromatase
17β-HSD
E_1
SHBG
IGFBP-1
↓
↓
LH ↑
FSH ↓
Adipose tissue
17β-HSD
5α-red
E_2
DHT
Liver
Peripheral and target tissues

FIG. 567.1 Pathologic mechanisms in polycystic ovary syndrome (PCOS). A deficient in vivo response of the ovarian follicle to physiologic quantities of follicle-stimulating hormone (FSH), possibly because of an impaired interaction between signaling pathways associated with FSH and insulin-like growth factors (IGFs) or insulin, may be an important defect responsible for anovulation in PCOS. Insulin resistance associated with increased circulating and tissue levels of insulin and bioavailable estradiol (E_2), testosterone (T), and IGF-I gives rise to abnormal hormone production in a number of tissues. Oversecretion of luteinizing hormone (LH) and decreased output of FSH by the pituitary, decreased production of sex hormone–binding globulin (SHBG) and IGF-binding protein 1 (IGFBP-1) in the liver, increased adrenal secretion of dehydroepiandrosterone sulfate (DHEAS), and increased ovarian secretion of androstenedione (A) all contribute to the feed-forward cycle that maintains anovulation and androgen excess in PCOS. Excessive amounts of E_2 and T arise primarily from the conversion of A in peripheral and target tissues. T is converted to the potent steroids estradiol or DHT (dihydrotestosterone). Reductive 17β-hydroxysteroid dehydrogenase (17β-HSD) enzyme activity may be conferred by protein products of several genes with overlapping functions; 5α-reductase (5α-red) is encoded by at least two genes, and aromatase is encoded by a single gene. GnRH, gonadotropin-releasing hormone. (From Bulun SE: Physiology and pathology of the female reproductive axis. In Melmed S, Polonsky KS, Larsen PR, editors: Williams textbook of endocrinology, ed 13, Philadelphia, 2016, Elsevier, Fig 17-30.)

Alterations in activities of steroidogenic enzymes that would explain *ovarian androgenic* hyperfunction are seen in PCOS subjects, but they are not consistently present in all patients, and it is unclear whether these alterations are a cause of PCOS or are a consequence of ovarian dysregulation. The mass of ovarian stromal cells responsible for androgen production is increased, and surgery that reduces this ovarian component (ovarian wedge resection, or laparoscopic ablative procedures) reduces circulating androgen levels and often restores ovarian cyclicity. Patients with hyperandrogenic congenital or adult-onset adrenal hyperplasia exhibit PCOS-like ovarian dysfunction that can be reversed by reducing the *adrenal-derived* androgens with glucocorticoid therapy. A primary role for androgen excess in the pathophysiology of all instances of PCOS seems unlikely; many patients have minimal hyperandrogenism, and elimination of androgen excess (with gonadotropin-releasing hormone agonists) does not affect associated insulin resistance.

Measures of insulin resistance are greater and more prevalent among women with PCOS than controls even when accounting for body mass index (BMI). Insulin enhances ovarian androgen production directly and contributes to elevations of free testosterone levels through its suppression of hepatic production of sex steroid–binding globulin. Treatment with insulin sensitivity–enhancing agents that can reduce insulin levels is associated with modest reductions in measures of androgen excess and, in some patients, restoration of regular ovulation. The association of insulin resistance with weight might explain the appearance of features of PCOS among some women who gain weight, as well as the resolution of PCOS among affected women who lose weight.

Clinical Manifestations

PCOS, a lifelong disorder, commonly becomes manifest as puberty progresses, but its onset can occur later, during young adulthood. Clinical hallmarks are menstrual abnormalities and manifestations of *hyperandrogenism*, but the severity of the disorder is variable (Table 567.2). Ovulation is typically irregular or absent, and menses are consequently irregular or absent. When menstrual bleeding does occur, it may be anovulatory bleeding, which is often heavy and/or protracted, resulting from an extended period of unopposed endometrial growth. Alternatively, bleeding can be relatively normal in character as a consequence of a preceding ovulation. Protracted spells of anovulation, with accompanying unopposed estrogen, is a risk factor for endometrial hyperplasia, and more severe premalignant and frankly malignant changes may eventuate. Hyperandrogenism is most commonly manifest as hirsutism, which is graded by the extent and locations of excessive male pattern hair growth (Fig. 567.2).

Table 567.2

Phenotypes for Polycystic Ovary Syndrome Based on 2003 Rotterdam Criteria

SIGNS, RISKS, AND PREVALENCE	SEVERE PCOS	HYPERANDROGENISM AND CHRONIC ANOVULATION	OVULATORY PCOS	MILD PCOS
Periods	Irregular	Irregular	Normal	Irregular
Ovaries on ultrasonography	Polycystic	Normal	Polycystic	Polycystic
Androgen concentrations	High	High	High	Mildly raised
Insulin concentrations	Increased	Increased	Increased	Normal
Risks	Potential long-term	Potential long-term	Unknown	Unknown
Prevalence in affected women	61%	7%	16%	16%

PCOS, polycystic ovary syndrome.

From Norman RJ, Dewailly D, Legro RS, et al: Polycystic ovary syndrome, Lancet 370:685-696, 2007.

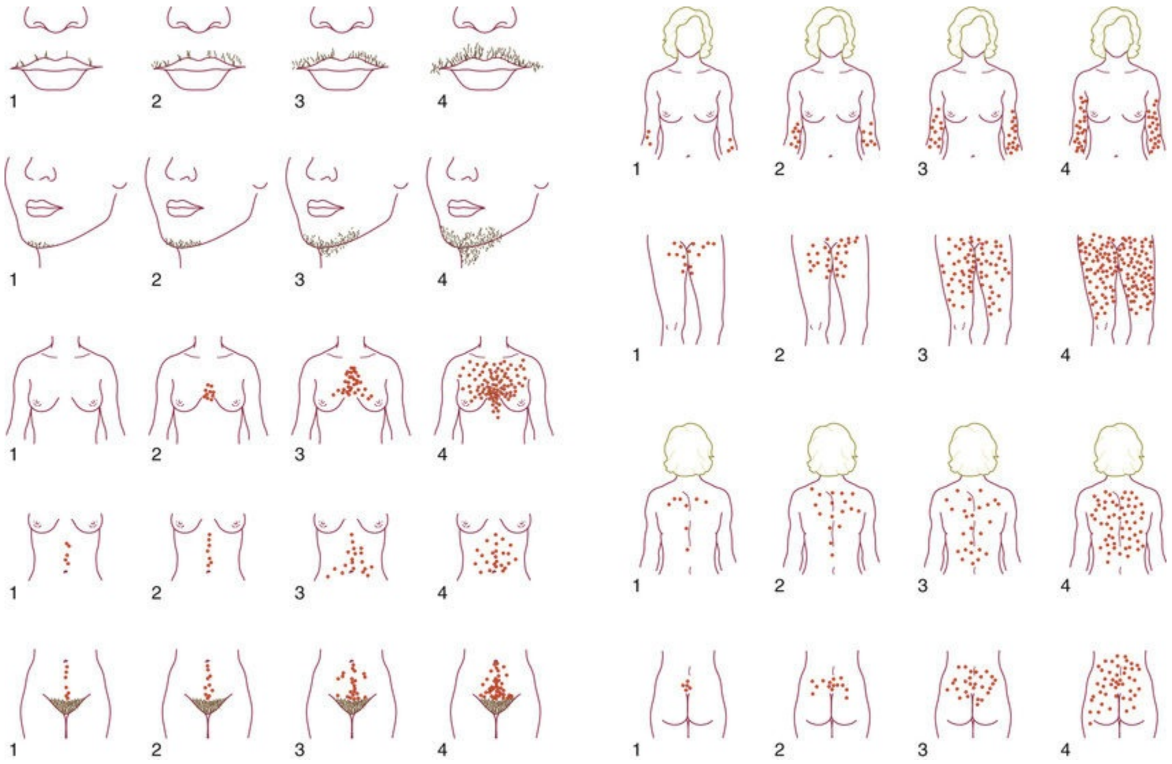

FIG. 567.2 Modified Ferriman Gallwey score. (Modified from Hatch R, Rosenfield RL, Kim MH, et al: Hirsutism: implications, etiology and management, Am J Obstet Gynecol 1981;140[7]:815-830.)

The diagnosis of PCOS in adolescents may be made on the basis of a lack of resolution of the developmentally usual pattern of anovulatory menstrual cycles present in the first 2 postmenarchal yr. Less commonly, the diagnosis is made in the setting of primary amenorrhea. Serum androgen levels may be elevated, and clinical findings of androgen excess are common, although distinction of normal androgenic expressions of puberty (acne, mild hirsutism) from early manifestations of PCOS may be difficult. Diagnosis in adolescents should be made with caution because of the hormonal changes that occur during puberty. Some suggest waiting 3 yr after menarche and require all 3 Rotterdam criteria.

Obesity is common among affected women. In some patients, expression of features of PCOS is conditional on elevation of BMI and reversible with weight loss. However, there is a subset of patients who present with a “lean” PCOS phenotype, and thus absence of excess weight should not preclude consideration of the PCOS diagnosis. PCOS is associated with an increased prevalence of insulin resistance and type 2 diabetes independent of the tendency for many affected patients to have an elevated BMI. Additionally, PCOS confers a substantial and specific increase in risk for metabolic syndrome (hyperlipidemia, insulin resistance, type 2 diabetes) in adolescent girls after accounting for BMI.

Laboratory Findings, Diagnosis, and Differential Diagnosis

The diagnosis of PCOS requires exclusion of disorders that would otherwise account for hyperandrogenism and anovulation. Serum 17-hydroxyprogesterone should be measured when there is clear androgen excess to screen for **adult-onset 21-hydroxylase deficiency** (see Chapter 594). In the adolescent with amenorrhea but minimal hyperandrogenic findings, consideration should be given to functional hypothalamic suppression as a result of excessive exercise and/or dieting, and a careful history taken to rule out such behavioral patterns. All patients should be clinically evaluated for Cushing syndrome, and biochemical evaluation is indicated when clinical findings, including hypertension and/or characteristic exam features, are suggestive (see Chapter 595). The two disorders have in common a tendency for overweight and varying degrees of insulin resistance and androgen excess, but they differ in that Cushing syndrome demonstrates muscle wasting as a result of catabolism.

Evidence for androgen excess that is *rapid in onset and/or severe,* especially if masculinizing, warrants measurement of androgens (total testosterone, dehydroepiandrosterone [DHEAS]) to exclude the possibility of an *androgen-secreting adrenal or ovarian tumor.* The laboratory evaluation is completed with the exclusion of hyperprolactinemia, premature ovarian failure, and thyroid disease as causes of anovulation: determinations of prolactin, FSH, and thyroid-stimulating hormone, respectively.

The diagnosis of PCOS is confirmed from the constellation of oligoovulation or anovulation, androgen excess (clinically or with biochemical confirmation), and typical ovarian morphology on ultrasound. Various experts weigh these 3 features differently and do not, as a rule, require the presence of all (see Table 567.1). Young women often exhibit the ovarian appearance of PCOS without any other evidence, and not all patients with PCOS by the criteria of hyperandrogenism and ovulatory disruption exhibit ovarian changes typical of PCOS. Ultrasound study to diagnose PCOS is not always required if oligoovulation and features of androgen excess are present. Clinical androgen excess (particularly acne) often appears in late puberty and does not necessarily signal PCOS. Nevertheless, young women with persistent oligoovulation or anovulation, accompanied by androgen excess, will likely have persistence of these symptoms and should be considered to have PCOS.

Insulin resistance is common among women with PCOS, and although not requisite for diagnosis, it should be considered when PCOS is likely. Adolescents with hyperandrogenemia and anovulation should be evaluated for diabetes or impaired glucose tolerance with a 2-hr (75-g glucose load) glucose tolerance test.

Complications and Long-Term Outlook

Fertility management, prevention of endometrial cancer, and reduction in the likelihood and severity of the common accompanying risk for the metabolic syndromes are long-term tasks for the PCOS patient and her healthcare providers (Table 567.3). Notwithstanding its reversibility with weight loss in some patients and a tendency to ameliorate in some women later in reproductive life, PCOS usually requires management throughout the reproductive years. Young patients should be counseled that modern fertility management allows most affected women to have children without great difficulty, and they should also know that the disorder does not confer reliable protection from unintended pregnancy. Endometrial cancer can develop as early as the 3rd decade in women with PCOS who are not managed with progestins or ovulation induction; patients should understand the importance of long-term strategies for endometrial protection. Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome are more common among obese adolescents with PCOS; their prevalence increases over time. Weight control through diet and lifestyle measures, detection and management of impaired glucose tolerance and diabetes, and management of abnormal lipids are targets for long-term management.

Table 567.3

Lifelong Health Complications of Polycystic Ovary Syndrome

PRENATAL OR CHILDHOOD	ADOLESCENCE, REPRODUCTIVE YEARS	POSTMENOPAUSAL
REPRODUCTIVE		
Premature adrenarche Early menarche	Menstrual irregularity Hirsutism Acne Infertility Endometrial cancer Miscarriage Pregnancy complications	Delayed menopause?
METABOLIC		
Abnormal fetal growth	Obesity Impaired glucose tolerance Insulin resistance Dyslipidemia Type 2 diabetes	Obesity Impaired glucose tolerance Insulin resistance Dyslipidemia Type 2 diabetes
OTHER		
	Sleep apnea Fatty liver Depression	Cardiovascular disease?

From Norman RJ, Dewailly D, Legro RS, et al: Polycystic ovary syndrome, Lancet 370:685-696, 2007.

Treatment

Management focuses on the menstrual abnormalities, symptoms of androgen excess, and associated metabolic changes. Weight loss through lifestyle change, use of hormonal contraceptive agents for menstrual regulation as well as androgen suppression, antiandrogens as adjuncts for hirsutism treatment, and insulin-sensitizing agents are common components of treatment.

Lifestyle Changes

Comprehensive lifestyle programs for overweight and obese *women* with PCOS aimed at fitness and weight loss can yield high rates of restoration of normal menstrual function, reduction of the free androgen index, reduction in measures of insulin resistance, and improvements in serum lipids. Limited data show similar benefits from such interventions for obese *adolescents* with PCOS. Successful weight loss programs for adolescents with PCOS using both psychological and nutritional counseling do result in improved menstrual function.

Hormonal Contraceptives

Combined (estrogen and progestin) hormonal contraceptive medications are considered first-line therapy for adults not desiring fertility and for adolescents (see Chapter 143). Adolescents with PCOS are at risk for unintended pregnancy; their fertility would be expected to be reduced relative to that of their peers, but they are still at risk for pregnancy.

Avoidance of hyperplastic endometrial states resulting from unopposed estrogen and management of abnormal uterine bleeding in anovulatory episodes can be accomplished with the use of combined hormonal contraceptives. The progestational component inhibits endometrial proliferation, and the schedule of pill administration predictably regulates menstrual bleeding. The estrogenic component of the combined oral contraceptive elevates circulating sex hormone–binding globulin, which reduces free and bioavailable testosterone levels. Both of the hormonal elements in oral contraceptives combine to suppress gonadotropic (particularly LH) stimulation of ovarian androgen production. DHEAS levels, often contributory to hyperandrogenemia in PCOS, are usually decreased by combined contraceptive use. Products with less-androgenic progestational components (drospirenone, desogestrel) may provide better relief from androgenic symptoms.

Using hormonal contraception that is well tolerated in long-term use is more important than using a product with a particular progestational component. Products with reduced frequency and duration of pill-free intervals can provide superior androgen suppression and a welcome decrease in frequency of bleeding episodes. Depot medroxyprogesterone acetate for contraception, endometrial protection, and androgen suppression may be a suitable alternative to combined hormonal contraceptives; it provides even more profound suppression of ovarian androgen production, but it does not elevate sex hormone–binding globulin. Low-dose progestin-only regimens (oral minipills, implantable progestational contraceptives, and progestin-releasing intrauterine devices) also provide effective endometrial protection but would be expected to provide only partial and/or inconsistent androgen suppression, would not elevate sex hormone–binding globulin, and have not been shown to be consistently helpful in regard to abnormal bleeding patterns.

Patients without the need for management of hyperandrogenic symptoms or contraception are often treated with periodic use of oral progestins to induce predictable menstrual bleeding and prevent endometrial hyperplasia and malignancy. Twelve-day courses of medroxyprogesterone acetate 10 mg daily or norethindrone acetate 5 mg daily are effective and safe for this purpose when taken every 1-2 mo.

Metformin

Metformin is a biguanide medication used to treat type 2 diabetes, its only FDA-approved indication. It has been used in a variety of settings and with differing objectives for patients with PCOS. Metformin exerts its principal effect by reducing hepatic production of glucose and limiting intestinal absorption of glucose. A subset of women with PCOS resume regular ovulation and menses when treated with metformin, obviating the need for progestational therapy to protect endometrial health or medications to induce ovulation. For some patients, the resulting normal reproductive function is appealing regardless of interest in fertility.

Metformin reduces insulin resistance and the levels of androgens. Its extended use can reduce the likelihood of development of impaired glucose tolerance or the progression of impaired glucose tolerance to type 2 diabetes; these effects are not yet proved for patients with PCOS. It should not be used in the presence of renal or hepatic impairment. Typical dosing is 1,500-2,000 mg/day, achieved through gradual increments because gastrointestinal intolerance is common. Long-acting preparations are helpful when gastrointestinal intolerance is a problem.

The use of metformin in the treatment of PCOS depends on the patient's goals and preference. For the treatment of hyperandrogenic symptoms, metformin effects may be modest compared with other available agents. There are no empirical data supporting the theoretical benefits of long-term use of metformin in adolescents with PCOS and obesity compared with the outcomes achieved with weight loss and oral contraceptive medications. Use of metformin as a first-line agent is favored by some experts, in part for improvement in serum measures of intermediate outcomes, and in part because of evidence in other populations of reduced progression of insulin resistance. There is no evidence for a long-term benefit for clinical outcomes of adding metformin to treatment for women managed primarily with oral contraceptives. For adolescents receiving metformin as a first-line medication, progestational management (combined contraceptives or periodic progestins) will still be necessary for those not resuming ovulatory function and oral contraceptives may still be an important adjunct for management of clinical hyperandrogenism and/or contraception.

Antiandrogens

Antiandrogenic medications may be added to other therapies or used alone for the treatment of hirsutism. These agents are usually used adjunctively with ovarian hormonal suppression, in part because of better reduction in hirsutism when antiandrogens are combined with ovarian suppression but also to reduce the risk of unintended embryonic or fetal exposure. The highly active androgen antagonist and progestin, cyproterone, is available in Europe and in Canada as a single agent for treatment of hirsutism or in combination with ethinyl estradiol as an oral contraceptive with enhanced antiandrogenic profile. In the United States, spironolactone is the most commonly used antiandrogen. Spironolactone antagonizes androgens at their receptor and also impairs androgen synthesis. Doses of 100-200 mg daily are commonly used. Other agents that have been studied are finasteride, a 5α-reductase inhibitor, and flutamide, a nonsteroidal and highly specific androgen receptor antagonist. These are rarely used because of lack of evidence of superior effectiveness, cost, and, in the case of flutamide, the potential for hepatotoxicity.

Hirsutism

Hirsutism is defined as abnormally increased terminal (mature, heavy, dark) hair growth in areas of the body where hair growth is normally androgen dependent (see Chapter 682). Its presence is a result of the combination of the extent of androgenic stimulation and familial regional follicle sensitivity to androgens, which varies considerably among ethnic groups. Patients' cosmetic concerns generally determine whether findings of hirsutism are a matter for clinical investigation and treatment. Hirsutism as an isolated finding is to be distinguished from **masculinization.** The latter includes alteration in muscle mass, clitoral enlargement, and voice change, generally manifesting as a rapid evolution (over months). *Masculinization mandates a search for a neoplastic source of androgen.* Elevations of testosterone or DHEAS commonly indicate an ovarian or adrenal androgen source, respectively; specific imaging and occasionally selective catheterization studies are indicated.

Hirsutism without masculinization is common. The potential causes to consider are PCOS (when there is hyperandrogenism and anovulation), benign functional androgen excess (measurable hyperandrogenism without anovulation), idiopathic hirsutism (increased hair in androgen-dependent areas without measurable androgen excess), and adult-onset adrenal hyperplasia. Patients can be primarily distinguished by evidence of an ovulatory disorder by menstrual history, and for those with absent or irregular menses, a diagnosis of PCOS can be made. The remainder, for whom adult-onset adrenal hyperplasia and PCOS have been excluded, either have normal androgen levels with enhanced end-organ sensitivity owing to familial or ethnic predisposition or have a functional and benign overproduction of ovarian androgens. Measures of androgens (testosterone, DHEAS) may be normal or mildly elevated in the latter group. Testosterone suppresses circulating sex-steroid binding globulin, so states of testosterone overproduction might not be accompanied by elevated measures of total testosterone, although estimates of "free" or "bioavailable" testosterone reveal hyperandrogenism. Measures of unbound testosterone distinguish idiopathic hirsutism from mild benign hyperandrogenic states; making this distinction contributes little to patient management and adds cost. Idiopathic hirsutism (without evidence of androgen excess) usually responds to antiandrogen or androgen suppression therapy similarly to hirsutism associated with elevated androgens and anovulation (PCOS), and benign hyperandrogenism not associated with PCOS.

If hirsutism is present, and clinical evaluation excludes neoplasm, adult-onset adrenal hyperplasia, and Cushing syndrome, then management for symptoms of hyperandrogenism (regardless of whether measures of circulating androgens are elevated or not) can proceed as for patients with PCOS (Table 567.4). Estrogen and progestin suppression of ovarian function, with or without added antiandrogen treatment, is the mainstay of therapy for these patients. Androgen suppression and/or antagonism results in gradual regression of the size and productivity of follicles in androgen-sensitive areas of the face and body, and these changes will evolve over successive and months-long generations of hair growth and shedding. Patients should therefore be advised that the effects of medical therapy accrue slowly, over many months.

Table 567.4

Treatment of Hirsutism

SYSTEMIC THERAPIES
Suppression of Androgen Production
Combined oral contraceptives (ethinyl estradiol + progestin with low androgenic activity)
Androgen Blockers
Spironolactone
Finasteride
Flutamide
Cyproterone acetate (not available in United States)
COSMETIC STRATEGIES
Temporary Measures
Shaving, bleaching, chemical depilation
Permanent Measures
Electrolysis Laser therapy

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CHAPTER 568

Gynecologic Neoplasms and Adolescent Prevention Methods for Human Papillomavirus

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Overview of Gynecologic Malignancies in Children and Adolescents

After injuries, cancer is the most common cause of death in children and adolescents, with the highest death rate in the 5 to 14 yr old age-group. Although rare, gynecologic malignancies can be followed by infertility, depression, and a poor self-image, which may be lifelong or cause long-term morbidity.

The most common type of gynecologic malignancy found in children and adolescents is of ovarian origin and usually manifests as an abdominal or pelvic mass, acute or chronic lower abdominal pain, or menstrual difficulties. The diagnostic workup includes a physical exam; laboratory tests including a urine pregnancy test, hormone levels, tumor markers, and imaging, with transabdominal ultrasonography being the preferred initial method. The differential diagnosis includes gynecologic tumors, other organ-based tumors, and ovarian functional, physiologic, inflammatory/infectious, or pregnancy-related processes. Although the majority of ovarian neoplasms are benign, ~ 9–33% of all childhood or adolescent ovarian neoplasms are malignant and have higher associated rates of morbidity and mortality. Ovarian neoplasms constitute 1.3% of all childhood malignancies, but account for 60–70% of all gynecologic malignancies in this age-group, with germ cell tumors being the most common type of neoplasm. Less often, the vagina or cervix is a site of malignant lesions in children, with a few specific tumors having their greatest incidence in this population. Vulvar and endometrial malignancies in children and adolescents are exceedingly rare.

Impact of Cancer Therapy on Fertility

The treatment of gynecologic cancer, depending on the type and extent of disease, may include fertility-sparing cytoreductive surgery with adjuvant chemotherapy, definitive surgery including bilateral salpingo-oophorectomy, and comprehensive surgical staging, radiation, and/or secondary salvage surgery. Fertility-sparing surgery is defined as unilateral salpingo-oophorectomy, lymphadenectomy, and omentectomy, whereas maximal cytoreduction includes hysterectomy and contralateral salpingo-oophorectomy. For malignant ovarian germ cell tumors, the most common adolescent gynecologic malignancy, the use of fertility-sparing surgery is increasingly seen as the gold standard. This approach achieves a good prognosis, and the majority of patients achieve normal hormonal function and future pregnancies; it does not seem to be associated with lower progression-free survival, overall survival, or mortality rates compared with those of radical surgery.

Platinum-based chemotherapeutic regimens are most often used for malignant ovarian tumors. The need for chemotherapy and radiation therapy is associated with acute ovarian failure, premature menopause, and infertility (Table 568.1). Risk factors include older age, abdominal or spinal radiation, and certain chemotherapeutic drugs, such as alkylating agents (cyclophosphamide, busulfan). Uterine irradiation is associated with infertility, spontaneous pregnancy loss, and intrauterine growth restriction. The vagina, bladder, ureters, urethra, and rectum can also be injured by radiation. Vaginal shortening, vaginal stenosis, urinary tract fistulas, and diarrhea are important side effects of pelvic irradiation for pelvic cancers. Pregnancy outcomes appear to be influenced by prior chemotherapy and radiation treatment; 15% of all childhood cancer survivors have infertility. Cancer survivors have an increased rate of spontaneous abortions, premature deliveries, and low birthweight infants compared with their normal healthy siblings. No data support an increased incidence of congenital malformations in offspring.

Table 568.1

Effect of Cancer Treatment on the Development of

Amenorrhea

TREATMENT	AGENT/MODALITY	IMPACT	TREATMENT FOR
Protocols containing nonalkylating agents or lower levels of alkylating agents	ABVD, CHOP, COP, multiagent therapies for leukemia	**LOWER RISK** < 20% of women develop amenorrhea posttreatment	Non-Hodgkin lymphoma Leukemia
Protocols containing	Multiagent therapies using vincristine	**VERY LOW/NO RISK** No effect on menses	Leukemia Lymphomas
Protocols containing	Procarbazine MOPP and BEACOPP 3 cycles > 6 cycles	**HIGH RISK** More than 80% develop amenorrhea posttreatment	Hodgkin lymphoma
Protocols containing	Temozolomide or BCNU + cranial radiation	**HIGH RISK** More than 80% develop amenorrhea posttreatment	Brain tumor
Abdominal or pelvic radiation	10-15 Gy in prepubertal girls 5-10 Gy in postpubertal girls	**INTERMEDIATE RISK** 30–70% of women develop amenorrhea posttreatment	Acute lymphoblastic leukemia Brain tumor Neuroblastoma Non-Hodgkin lymphoma Hodgkin lymphoma Spinal tumor Wilms' tumor
Whole abdominal or pelvic radiation	>15 Gy in prepubertal girls >10 Gy in postpubertal girls > 6 Gy in adult women	**HIGH RISK** More than 80% develop amenorrhea posttreatment	
Total cyclophosphamide	5 g/m^2 in women > 30 yr 7.5 g/m^2 in women and girls < 20 yr	**HIGH RISK** More than 80% develop amenorrhea posttreatment	Non-Hodgkin lymphoma
Any alkylating agent + pelvic radiation	E.g., busulfan, carmustine, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine	**HIGH RISK** More than 80% develop amenorrhea posttreatment	Ovarian cancer Sarcoma
Any alkylating agent + total body irradiation	E.g., busulfan, carmustine, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine	**HIGH RISK** More than 80% develop amenorrhea posttreatment	Lymphomas Myelomas Choriocarcinoma Ewing sarcoma, neuroblastoma
Any cancer requiring bone		**HIGH RISK**	Hodgkin

marrow transplant/stem cell transplant		More than 80% develop amenorrhea posttreatment	lymphoma Non-Hodgkin lymphoma Acute myeloid leukemia Chronic myeloid leukemia Myeloma Acute lymphoid lymphoma Chronic lymphoid lymphoma Some solid tumors (e.g., breast, ovarian, kidney, brain)

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; COP, cyclophosphamide, vincristine, prednisone; MOPP, mechlorethamine, vincristine, prednisone, procarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BCNU, carmustine; Gy, gray.

Adapted from Female Fertility Preservation © LIVESTRONG, a registered trademark of the LIVESTRONG Foundation. https://www.livestrong.org/we-can-help/just-diagnosed/female-fertility-preservation .

Advancements in oncologic treatments have led to improvements in childhood cancer survival rates. Unfortunately, with this comes an increase in short- and long-term adverse effects, including gonadotoxicity and infertility. Recommendations state that the individualized risk of infertility should be discussed prior to gonadotoxic therapies and options of fertility preservation should be made available to all patients, with referrals to reproductive specialists and mental health professionals as appropriate. Multiple recommendations specifically address the pediatric population, stating that parents/guardians should be allowed to act for and consent in the interest of their minor children.

Mature oocyte and embryo cryopreservation is a standard of care preservation option available to postpubertal females with ample time prior to treatment to allow for ovarian stimulation (2-6 wk). Ovarian tissue cryopreservation (OTC) remains experimental and may be offered as part of a research protocol. It is the only available option for prepubertal females and allows a secondary preservation option for postpubertal females with time-limiting treatment plans. There have been over 60 live births from orthotopic transplantation of cryopreserved ovarian tissue, mostly in adult women. Live births have occurred in women whose tissue was cryopreserved prior to menarche. The safety and feasibility of OTC and transplantation following nonsterilizing chemotherapy and in select leukemia survivors have been favorable. Laparoscopic ovarian transposition can be used prior to radiation therapy where a high risk of ovarian radiation exposure is expected. Hormone suppression with GnRH analogs has been investigated as a means of fertility preservation, but evidence is lacking as to its efficacy. Uterine transplantation is another method under experimental investigation that may become a treatment option in the future.

Gonadotoxicity can also lead to premature ovarian insufficiency, which is associated with an increased risk for cardiovascular complications, osteoporosis, and difficulties with sexual function. Risks and benefits of hormonal therapy need to be addressed as appropriate.

Ovarian Neoplasms

Neonatal and Pediatric Ovarian Cysts

Normal follicles or physiologic ovarian cysts are seen by ultrasound examination of the ovaries in all healthy neonates, infants, and prepubertal girls. The incidence of functional ovarian cysts increases with puberty. Most of these are < 2 cm in diameter and not pathologic. In the fetal and neonatal period, physiologic follicular cysts form as a result of maternal estrogen stimulation; they are common and identified by antenatal ultrasonography. In fetal imaging, care should be taken to determine the organ of origin of any cyst because the differential diagnosis of a fetal cystic mass includes renal, ureteral, and gastrointestinal masses. Fetal and neonatal ovarian cysts may be simple or complex and unilateral or bilateral. Most evidence seems to indicate that simple neonatal ovarian cysts will resolve spontaneously and should be followed with observation. Because of the risk of ovarian torsion and resultant antenatal autoamputation of the ovary, treatment modalities have been developed to prevent ovarian torsion, including ultrasound-guided laparoscopic cystectomy, aspiration, and detorsion, with the goal of ovarian preservation. Oophorectomy should be avoided.

Children with an ovarian mass might have no symptoms, and the mass may be detected incidentally or during a routine examination. They may also present with abdominal pain that may be accompanied by nausea, vomiting, or urinary frequency or retention. The cyst's most common complication, **ovarian torsion,** can result in loss of the ovary. Large cysts (>4-5 cm); those with complex characteristics, including fluid-debris levels, clots, septations, or solid components; or any ovarian cyst in premenarchal girls with associated signs or symptoms of hormonal stimulation deserves prompt evaluation. When surgery is necessary, laparoscopic detorsion and ovarian preservation should be the goal because recurrence and the need for repeat surgery is rare.

Functional Cysts

Over the course of several menstrual cycles, a **dominant follicle** forms and increases in size. Following ovulation, the dominant follicle becomes a corpus luteum that, if it bleeds, is termed a **hemorrhagic corpus luteum.** These can become symptomatic owing to size or peritoneal irritation, and they have a characteristic complex appearance on ultrasound. Expectant management for a presumed functional or hemorrhagic cyst is appropriate. Physiologic cysts are usually ≤ 5 cm and resolve over the course of 6-8 wk or several menstrual cycles during subsequent ultrasound imaging without the need for any intervention. Monophasic oral contraceptives can be used to suppress future follicular development to prevent formation of additional cysts. Cysts that persist beyond 3 cycles are generally not physiologic and should be further evaluated.

Teratomas

The most common ovarian neoplasm in children and adolescents is the **mature cystic teratoma (dermoid cyst).** Most are benign and contain mature tissue of ectodermal (skin, hair, sebaceous glands, neuroectodermal tissue), mesodermal (muscle, bone, cartilage, fat, teeth), and/or endodermal (thyroid, salivary, respiratory, gastrointestinal) origin. The majority of benign teratomas are diagnosed by ultrasound, where characteristic findings include fluid-fluid levels, Rokitansky nodules, cysts, and hyperechoic regions; on abdominal radiograph, calcification is often a hallmark. These tumors may be asymptomatic and found incidentally, or they can manifest as a mass or with abdominal pain (associated with torsion or rupture). If the major component of the dermoid is thyroid tissue (struma ovarii), hyperthyroidism can be the clinical presentation, and if the tumor contains carcinoid tissue, carcinoid syndrome can be the presentation. Benign teratomas can be observed if they are asymptomatic and small (<5 cm); when they are large or symptomatic, they should be carefully resected to prevent torsion or rupture, with preservation of as much normal ovarian tissue as possible. Oophorectomy (and salpingo-oophorectomy) for this benign lesion is excessive treatment. During surgery, both ovaries should be evaluated (≤10% of cases are bilateral), and if there is any question about the nature of the lesion, the specimen should be evaluated by a pathologist, either grossly or by frozen section, because malignant transformation of mature teratomas can occasionally occur.

An **immature teratoma** of the ovary is an uncommon tumor, accounting for < 1% of ovarian teratomas. In contrast to the mature cystic teratoma, which is encountered most often during the reproductive years but occurs at all ages, the immature teratoma has a specific age incidence, occurring most commonly in the first 2 decades of life. By definition, an immature teratoma contains immature embryonal elements, which are most commonly neuroepithelial but may arise from any germ layer. An association of dermoid tumors with neural elements and **anti–N-methyl-D -aspartase receptor (anti-NMDAR) encephalitis** has been reported. Patients may present with flu-like symptoms and progress to psychiatric and cognitive symptoms, autonomic instability, and seizure activity (Chapter 616.4).

Immature teratomas present similarly to mature teratomas, with pelvic pain or a mass, but have differentiating imaging findings. Because the lesion is rarely bilateral in its ovarian involvement, the present method of therapy consists of unilateral salpingo-oophorectomy with wide sampling of peritoneal/omental implants and iliac and retroperitoneal lymph nodes.

Cystadenomas

Serous, mucinous, and mixed serous/endometrioid or mucinous/endometrioid **cystadenomas** are the second most common benign ovarian tumor in adolescents, representing 10–28% of adolescent tumors. These tumors often have both solid and cystic components and may secrete tumor markers, including CEA, Ca-125, and Ca 19-9. These cystic lesions can become very large, yet with care, the tumor can be resected, preserving normal ovarian tissue for future reproductive potential. Recurrence rates may be as high as 11% and thus surveillance should continue postoperatively.

Endometriomas

Endometriosis is a syndrome defined by the presence of ectopic endometrial tissue usually located within the pelvis and abdomen but outside of the uterus.

The principal clinical symptoms in adolescents consist of severe menstrual pain and pelvic pain, but may also include menorrhagia, abnormal uterine bleeding, and gastrointestinal, genitourinary, or constitutional symptoms. Diagnosis is often delayed as other etiologies are considered or assigned and a high clinical suspicion should be maintained. Although endometriosis has a variable presentation, it is associated with **endometriomas** in 16–40% of adolescent cases; they may be unilateral or bilateral. Endometriomas (chocolate cysts) form when the ovaries are involved and are collections of old blood and hemosiderin within an endometrium-lined cyst. They have a typical homogeneous “ground glass” echogenic appearance on ultrasound and are more common in adults than in adolescents. Conservative management (suppressive therapy with ovulation suppression, nonsteroidal antiinflammatory drugs, combined oral contraceptives, or progestin therapy) and ovarian cystectomy with preservation of as much functioning ovary as possible is recommended for adolescents. Recurrence of endometriosis occurs more commonly in adolescents than adults, and future fertility is associated with stage of disease.

Pelvic Inflammatory Disease and Tuboovarian Abscess

Pelvic inflammatory disease (PID) complicated by a **tuboovarian abscess (TOA)** should be considered in a sexually active adolescent with an adnexal mass and pain on examination (see Chapter 146). These patients also typically exhibit fever with leukocytosis and cervical motion tenderness and may additionally complain of vaginal discharge, nausea, and abnormal vaginal bleeding. TOAs are usually clearly seen on transvaginal ultrasound, but pelvic CT imaging may be used for uncertain cases. Treatment of PID with TOA consists of inpatient administration of intravenous antibiotics. After 48-72 hr of treatment with antibiotics alone, patients with TOAs who do not respond or who worsen should undergo imaging-guided abscess drainage. This conservative management is recommended as long as the patient continues to improve. When the patient is worsening or sepsis occurs, only experienced gynecologic surgeons familiar with bowel surgery should undertake exploration and resection of pelvic abscesses due to the challenges of encountering anatomic distortion, other organ involvement, and friable tissue planes.

Adnexal Torsion

Adnexal torsion of the ovary and/or fallopian tube is the fifth most common gynecologic emergency and occurs more often in children and adolescents than in adults. It can occur in individuals with normal adnexa but more often occurs in adnexa enlarged by cystic (follicular, tubal) changes or ovarian (teratoma, cystadenoma) neoplasms. When torsion occurs, the venous outflow is obstructed first, and the fallopian tube and/or ovary swells and becomes hemorrhagic. Once the arterial flow is interrupted, necrosis begins and if untreated, may result in pelvic thrombophlebitis, hemorrhage, infection, peritonitis, and autoamputation of the adnexa. It is not known how long torsed adnexa will remain viable. A female patient may present with acute lower abdominal pain, either episodic or constant, which may be accompanied by nausea, vomiting, bowel/bladder symptoms, and peritonitis. Pelvic ultrasound imaging studies most commonly show unilateral enlargement of an adnexa and may or may not demonstrate the presence of Doppler flow, free pelvic fluid, the “whirlpool sign,” or a “beak sign.” Prompt surgical intervention (laparoscopic detorsion) is warranted if clinical suspicion is high. Detorsion of the adnexa and observation for viability is recommended, as even necrotic-appearing ovaries usually recover function and may demonstrate Doppler flow and follicular development as soon as 6 wk postoperatively with excellent long-term preservation of fertility. Cystectomy should be completed if possible to reduce the risk of recurrent torsion. Removal of the fallopian tube and/or ovary should be reserved for cases of grossly necrotic tissue and those associated with malignant tumors demonstrated on intraoperative frozen section pathology. Oophoropexy (plication) of the affected and the contralateral adnexa remains controversial.

Ovarian Malignancies

Ovarian cancer is very uncommon in children; only 1.3% of all ovarian cancers are diagnosed in patients < 20 yr old. Surveillance, Epidemiology, and End Results (SEER) age-adjusted incident rates, 2011-2015 are ≤ 0.8/100,000 at age 0-14 yr and 1.5/100,000 at age 15-19 yr; mortality rates are 0.1/100,000 for girls ≤ 19 yr. **Germ cell tumors** are the most common and originate from primordial germ cells that then develop into a number of heterogeneous tumor types, including **dysgerminomas** (the most common malignant germ cell tumor of the ovary with the best prognosis), malignant teratomas, **yolk sac tumors** (also referred to as **endodermal sinus tumors**), embryonal carcinomas, mixed cell neoplasms, and **gonadoblastomas** (commonly associated with chromosomal abnormalities). Immature teratomas and yolk sac tumors are more aggressive malignancies than dysgerminomas and occur in a significantly higher proportion of younger girls (10-20 yr of age). **Sex-cord stromal tumors** include benign **thecomas** and **fibromas,** as well as malignant **Sertoli-Leydig cell tumors** (presenting with clinical evidence of androgen excess) and **juvenile granulosa cell tumors** (presenting with precocious puberty and excess estrogen) (Table 568.2). Imaging may demonstrate large, complex cystic structures with calcifications, fat, or vascularization, as well as pelvic ascites. **Tumor markers** such as α-fetoprotein, carcinoembryonic antigen, antigen Ca-125, inhibin B, human chorionic gonadotropin, and lactate dehydrogenase are used for diagnosis and treatment surveillance (Table 568.3).

Table 568.2

Malignant Ovarian Tumors in Children and Adolescents

TUMOR	OVERALL 5-YR SURVIVAL	CLINICAL FEATURES
GERM CELL TUMORS		
Dysgerminoma	85%	10–20% bilateral Most common ovarian malignancy Gonadal dysgenesis/androgen insensitivity Sensitive to chemotherapy/radiation
Immature teratoma	97–100%	All 3 germ layers present
Endodermal sinus tumor	80%	Almost always large (>15 cm) Schiller-Duval bodies
Choriocarcinoma	30%	Rare Can mimic ectopic pregnancy
Embryonal carcinoma	25%	Endocrinologic symptoms (precocious puberty) Highly malignant
Gonadoblastoma	100%	Primary amenorrhea Virilization 45,X or 45,X/46,XY mosaicism
SEX CORD STROMAL TUMORS		
Juvenile granulosa stroma cell tumor	92%	Produce estrogen Menstrual irregularities Isosexual precious pseudopuberty Call-Exner bodies rare
Sertoli-Leydig cell tumor	70–90%	Virilization in 40% Produce testosterone
Lipoid cell tumors	~80%	Rare heterogeneous group with lipid-filled parenchyma
Gynandroblastoma	90% or greater	Rare low-grade mixed tumors that produce either estrogen or androgen

Table 568.3

Serum Tumor Markers

TUMOR	CA-125	AFP	hCG	LDH	E2	T	INHIBIN	MIS	VEGF	DHEA
Epithelial tumor	+									
Immature teratoma	+	+			+					+
Dysgerminoma			+	+	+					
Endodermal sinus tumor		+								
Embryonal carcinoma		+	+		+					
Choriocarcinoma			+							
Mixed germ cell		+	+	+						
Granulosa cell tumor	+				+		+	+		
Sertoli-Leydig						+	+			
Gonadoblastoma					+	+	+			+
Theca-fibroma									+	

AFP, α-fetoprotein; CA-125, cancer antigen 125; DHEA, dehydroepiandrostenedione; E2, estradiol; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; T, testosterone; MIS, müllerian-inhibiting substance; VEGF, vascular endothelial growth factor.

Tumor staging is done according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines and is imperative for informing treatment decisions. Treatment for stage Ia dysgerminomas and stage I immature teratomas is resection. For stage Ic or higher tumors, treatment is surgical excision followed by postoperative chemotherapy that usually consists of bleomycin, etoposide, and cisplatin. Radiotherapy is sometimes administered for disease recurrence in dysgerminomas, but it is otherwise not included in routine treatment. In rare cases, a second-look laparotomy with secondary cytoreduction may be indicated for neoplasms with teratomatous elements or for those incompletely resected. For unresectable tumors or for patients who cannot undergo surgery, neoadjuvant chemotherapy is an option. Recurrences are treated with chemotherapy. Germ cell tumors may recur in up to 10% of cases, and thus yearly follow-up ultrasound is recommended.

Epithelial ovarian cancers account for 19% of ovarian masses in the pediatric population, with a total of 5–16% being malignant and 30–40% being considered borderline or of low malignant potential with atypical proliferative cells but no stromal invasion. Epithelial ovarian tumors manifest almost exclusively after puberty. Common presenting symptoms include dysmenorrhea, abdominal pain, abdominal distention, nausea and vomiting, and vaginal discharge, and the antigen Ca-125 is almost always elevated. Treatment involves surgical oophorectomy, pelvic washings, and biopsies of suspicious omental, peritoneal, and lymph node lesions, with adjuvant chemotherapy for patients with FIGO stage II-IV disease. Given the young age of this population, although this is not the standard of care for adult patients, fertility-sparing surgery is recommended for stage I cancer to conserve the contralateral ovary and uterus if they appear normal. Data suggest that in patients with early-stage disease, such an approach with appropriate surgical staging results in optimal outcomes, but is not recommended for stage II-IV disease due to the high rate of recurrence. The number of term pregnancies and use of oral contraceptives decrease the risk of invasive epithelial ovarian cancer. Young women with a family history of ovarian cancer should seriously consider using long-term oral contraceptives for the preventive benefits when pregnancy is not being sought.

Uterine Malignancies

Rhabdomyosarcomas are the most common type of soft tissue sarcoma occurring in patients < 20 yr of age (see Chapter 527) and the third most common pediatric solid tumor, accounting for 5–15% of all solid tumors in children. They can develop in any organ or tissue in the body except bone, and roughly 3% originate from the uterus or vagina. Of the various histologic subtypes, embryonal rhabdomyosarcomas in the female patient most often occur in the genital tract of infants or young children. They are rapidly growing entities that can cause the tumor to be expelled through the cervix, with subsequent complications such as uterine inversion or large cervical polyps. Irregular vaginal bleeding may be another presenting clinical symptom. They are defined histologically by the presence of mesenchymal cells of skeletal muscle in various stages of differentiation intermixed with myxoid stroma. A genetic link has been found between Li-Fraumeni cancer susceptibility syndrome, Beckwith-Wiedemann syndrome, pleuropulmonary blastoma, Costello syndrome, Noonan syndrome, and neurofibromatosis type I. Treatment recommendations are based on protocols coordinated by the Intergroup Rhabdomyosarcoma Study Group and consist of a multimodal approach including radiation therapy and chemotherapy. Vincristine, adriamycin-D, and cyclophosphamide (VAC) with or without radiation therapy make up the first line of treatment. Intensity-modulated radiation therapy and proton beam radiotherapy are used to reduce the therapy burden and long-term toxicity. Resection rates are now very low, due to the risk of losing the form and function of local tissue; chemotherapy with restrictive surgery and adjunctive irradiation has enabled many patients to retain the uterus while achieving excellent long-term survival rates.

Leiomyosarcomas and **leiomyomas** are extremely rare, occurring in < 2 in 10 million individuals in the pediatric and adolescent age-groups, although their numbers are increasing among pediatric patients with AIDS. They usually involve the spleen, lung, or gastrointestinal tract, but they could also originate from uterine smooth muscle. Epstein-Barr virus pathogenesis has been shown in AIDS and solid-organ transplant patient populations (see Chapter 281). Despite treatment that demands complete surgical resection (and chemotherapy for the sarcomas), they tend to recur frequently.

Endometrial stromal sarcoma and **endometrial adenocarcinoma** of the uterine corpus are extremely rare in children and adolescents, with the only case reports noted in the literature. Vaginal bleeding is not associated. Sexual precocity is a common presenting sign. Treatment consists of hysterectomy, removal of both ovaries, and appropriate surgical staging, followed by adjunctive radiotherapy and/or chemotherapy, depending on the operative findings.

Vaginal Malignancies

Sarcoma botryoides is a variant of embryonal rhabdomyosarcoma that occurs most commonly in the vagina of pediatric patients. Sarcoma botryoides tends to arise in the anterior wall of the vagina and manifests as a protruding submucosal lesion that is grape-like in appearance; if it is located at the cervix, it could resemble a cervical polyp or polypoid mass. Vaginal bleeding is often a presenting clinical symptom. These lesions were formerly treated with exenterative procedures; however, equal success has occurred with fertility-sparing surgery (polypectomy, conization, local excision, and robot-assisted radical trachelectomy) and adjuvant multiagent chemotherapy with or without radiotherapy. A combination of vincristine, actinomycin-D, and cyclophosphamide (VAC) has been shown to be effective. Outcomes depend on the tumor size, extent of disease at the time of diagnosis, and histologic subtype. The 5-yr survival rates for patients with clinical stages I-IV were 83%, 70%, 52%, and 25%, respectively.

Vaginal adenosis can lead to the development of **clear cell adenocarcinoma** of the vagina in females exposed to diethylstilbestrol (DES) in utero. At present, pregnant women at risk for miscarriage are no longer treated with DES, and thus fewer adolescent girls and young women are at risk for this unusual tumor. Vaginal adenosis has also been shown to be associated with Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), although in these cases, there has been no progression to clear cell adenocarcinoma.

The most common subtype of GCT is the **endodermal sinus tumor,** also known as a yolk sac tumor, which occurs in the vagina of infants. This disease usually occurs in infants and rarely is seen in children < 3 yr of age at the time of presentation. Combination surgery and chemotherapy is appropriate; however, survival rates are poor. Treatment effect and recurrence monitoring can be done with serum alpha-fetoprotein levels.

Benign **papillomas** and **hemangiomas** can arise in the vagina of children and result in vaginal bleeding.

Vulvar Malignancies

Any questionable vulvar lesion should be biopsied and submitted for histologic examination. Lipoma, liposarcoma, and malignant melanoma of the vulva have been reported in young patients. The most common lesion is likely **condyloma acuminata,** the proliferation of squamous epithelial cells, associated with the **human papillomavirus (HPV)** (see Chapter 293). Anogenital lesions are most commonly caused by HPV 6 and 11. The diagnosis is usually made by visual inspection. Preventive measures include HPV vaccination. Treatment consists of observation for spontaneous regression, topical trichloroacetic acid, local cryotherapy, electrocautery, excision, and laser ablation. Some products used to treat skin lesions in adults have not been approved for children, including provider application of podophyllin resin and home application of imiquimod, podofilox, and sinecatechins ointment.

Cervical Malignancies and Their Prevention

Cervical cancer is preventable by the HPV vaccine; the CDC recommends HPV vaccination for boys and girls beginning at age 11 or 12. **HPV vaccines** offer the best protection if all scheduled vaccine doses are administered before the patient is sexually active. In 2016, the CDC recommended two doses of the 9vHPV vaccine for persons starting the series before their 15th birthday (usually 11-12 yr of age). The second dose of HPV vaccine should be given 6-12 mo after the first dose. Adolescents who receive their two doses less than 5 mo apart will require a third dose of HPV vaccine. Teens and young adults who start the series at ages 15 through 26 yr still need three doses of the HPV vaccine. Also, three doses are still recommended for people with certain immunocompromising conditions ages 9 through 26 yr. HPV vaccination is recommended for HIV-infected females and males ages 9 through 26 yr. For children who were sexually abused, immunization should start at age 9 yr. In October 2018, the U.S. Food and Drug Administration approved expanding the use of HPV 9-valent vaccine to include women and men 27-45 yr.

Although vaccination prior to exposure is ideal, female patients should be vaccinated even if sexually exposed. Pap testing and screening for HPV DNA or HPV antibody are not required before vaccination. The American Congress of Obstetrics and Gynecology recommends that cervical cancer screening of women who have been immunized against HPV should not differ from that of nonimmunized women. Smoking cessation, condom use, and limiting the number of sexual partners also lowers the risk for cervical cancer.

The adolescent population presents a unique challenge to cervical cancer screening, because the prevalence of HPV infection is high; it is recommended that adolescents be managed conservatively and should not receive Pap smear screening until age 21 yr regardless of age of onset of sexual intercourse. The screening Pap test looks for precancerous cell changes that may become cancerous if not treated appropriately. In adolescents ages 15-19 yr, HPV cumulative incidence rates after initiation of sexual activity are reported as 17% at 1 yr and 35.7% at 3 yr. Correlating with the natural history of an HPV infection, > 90% of low-grade intraepithelial HPV-associated lesions regress within this age-group, giving the presence of HPV in this population less clinical significance. The overall incidence of a high-grade lesion on Pap test in the adolescent population remains low (0.7%); cervical cancer is uncommon in the adolescent age-group. In the United States, the Surveillance, Epidemiology, and End Results Cancer Statistics Review 1975-2015 published by the National Cancer Institute reports that cervical cancer in patients <20 yr makes up 0.1% of all new cases, with no cases reported in patients <20 yr from 2011-2015. Therefore, Pap screening should not be offered before age 21; colposcopy for minor cytologic abnormalities within this age group should be highly discouraged because it will not produce any clinical benefit. If an HPV test is done in adolescents, the results should not be acted on. *There is one exception: Sexually active immunocompromised (HIV-positive patients or organ transplant recipients) adolescents should undergo screening twice within the 1st yr after* *diagnosis and annually thereafter* . Table 568.4 demonstrates management recommendations for abnormal cytologic results for adolescents who are screened in error and immunocompromised sexually active adolescents who are screened.

Table 568.4

Management of Cytologic Abnormalities in Adolescents Who Are Screened in Error and Immunocompromised Women Less Than 21 Years of Age

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CYTOLOGY RESULT	MANAGEMENT RECOMMENDATION	HPV TESTING?	COLPOSCOPY?
ASCUS	Repeat cytologic testing in 1 yr	No	At 1 yr follow-up if HGSIL or greater result At 2 yr follow-up if persistent ASCUS or greater
LGSIL	Repeat cytologic testing in 1 yr	No	At 1 yr follow-up if HGSIL or greater result At 2 yr follow-up if ASCUS or greater
HGSIL	If colposcopy is unsatisfactory or if CIN is ungraded: excisional procedure If colposcopy is satisfactory: • If no CIN1-3: Pap and colposcopy q6mo until 2 yr are negative. **If persistent HGSIL without CIN1-3 identified, then excisional procedure at 2 yr** • If CIN1: (ASCUS/LGSIL protocol) • If CIN2, CIN2-3: Pap or colposcopy q6mo until 2 yr is negative, or else rebiopsy at 1 yr, treat if persistent at 2 yr • If CIN3: excisional procedure	No	Yes, immediately
ASC-H or AGC	There are no specific recommendations in regard to adolescents; see ASCCP guidelines for adults Endometrial biopsy is not advised in adolescents	No	Yes, immediately

Note: Cryotherapy and laser ablation are acceptable treatment options only for biopsy-proven CIN2+ lesion and satisfactory colposcopic examination.

AGC, atypical glandular cells; ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-H, atypical squamous cell changes, high grade; ASCUS, atypical squamous cell changes of undetermined significance; CIN, cervical dysplasia; HGSIL, high-grade squamous intraepithelial dysplasia; LGSIL, low-grade squamous intraepithelial dysplasia; Pap, Papanicolaou smear.

Data from Saslow D, Solomon D, Lawson HW, et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer, J Low Genit Tract Dis 16(3):175-204, 2012.

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CHAPTER 569

Vulvovaginal and Müllerian Anomalies

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Embryology

Cellular differentiation, duct elongation, fusion, resorption, canalization, and programmed cell death are all involved in the sequence of events that occur in a developing embryo and early fetus to create a normal reproductive system. Myriad gonadal, müllerian, and/or vulvovaginal anomalies can result from interruption of the intricate sequence or functions of any one of these processes during formation of the reproductive system (Table 569.1). Genetic, epigenetic, enzymatic, and environmental factors all have some role in the process (Table 569.2).

Table 569.1

Müllerian Anomalies

ANOMALY	DESCRIPTION
Hydrocolpos	Accumulation of mucus or nonsanguineous fluid in the vagina
Hematocolpos	Accumulation of blood in the vagina
Hematometra	Accumulation of blood in the uterus
Hydrosalpinx	Accumulation of serous fluid in the fallopian tube, often an end result of pyosalpinx
Didelphic uterus	Two cervices, each associated with one uterine horn
Bicornuate uterus	One cervix associated with two uterine horns
Unicornuate uterus	One cervix and one uterine horn, the result of failure of one müllerian duct to descend

Table 569.2

Heritable Disorders Associated With Müllerian Anomalies

MODE OF INHERITANCE	SYNDROME	ASSOCIATED MÜLLERIAN DEFECT
Autosomal dominant	Camptobrachydactyly	Longitudinal vaginal septa
	Hand-foot-genital	Incomplete müllerian fusion
Autosomal recessive	McKusick-Kaufman	Transverse vaginal septa
	Johanson-Blizzard	Longitudinal vaginal septa
	Renal-genital-middle ear anomalies	Vaginal atresia
	Fraser	Incomplete müllerian fusion
	Uterine hernia	Persistent müllerian duct derivatives
Polygenic/multifactorial	Mayer-Rokitansky-Küster-Hauser	Müllerian aplasia
X-linked	Uterine hernia	Persistent müllerian duct derivatives

Phenotypic sexual differentiation, especially during formation of the vulvovaginal and müllerian systems, is determined from genetic (46,XX), gonadal, and hormonal influences (see Chapter 600). Gonadal development determines the progression or regression of the genital ducts and subsequent hormonal production and, thus, the external genitalia. Critical areas in the SRY region (sex-determining region on the Y chromosome) are believed to be the factors that drive the development of a testis from a primitive gonad as well as spermatogenesis. The testis begins to develop between 6 and 7 wk of gestation, first with Sertoli cells followed by Leydig cells, and testosterone production begins at approximately 8 wk of gestation. The genital tract begins to differentiate later than the gonads. The differentiation of the wolffian ducts begins with an increase in testosterone, and the local action of testosterone activates development of the epididymis, vas deferens, and seminal vesicle. Further male genital duct and external genital structures depend on the conversion of testosterone to dihydrotestosterone.

In a 46,XX embryo, female sexual differentiation occurs about 2 wk later than gonadal differentiation in the male. Because the ovaries develop prior to and separately from the müllerian ducts, females with müllerian ductal anomalies usually have normal ovaries and steroid hormone production. The regression of the wolffian ducts results from the lack of local gonadal testosterone production, and the persistence of the **müllerian** (or paramesonephric) **ducts** results from the absence of **antimüllerian hormone** (or müllerian-inhibiting substance) production. The müllerian ducts continue to differentiate into the fallopian tubes, uterus, and upper one third of the vagina without interference from antimüllerian hormone. There are complex interactions among the mesonephric, paramesonephric, and metanephric ducts early in embryonic development, and normal development of the müllerian system depends on such interaction. If this process is interrupted, coexisting müllerian and renal anomalies are often discovered in the female patient at the time of evaluation. Although most müllerian defects seem sporadic, familial recurrence or clustering has been observed, which strongly supports the influence of genetic factors. Differentiation along the female pathway is often referred to as the *default pathway,* but it is an extremely intricate process regulated by numerous gene products, including *SRY* , *SF-1* , *WTI* , *SOX9* , *Wnt-4* , *GATA4* , *DAX-1* , *BMP4* , and *HOX* . One of the most well described genes includes the *HOX* gene family, which is comprised of regulatory molecules that encode highly conserved transcription factors and regulate the developmental axis of the female reproductive tract during the embryonic period (Fig. 569.1).

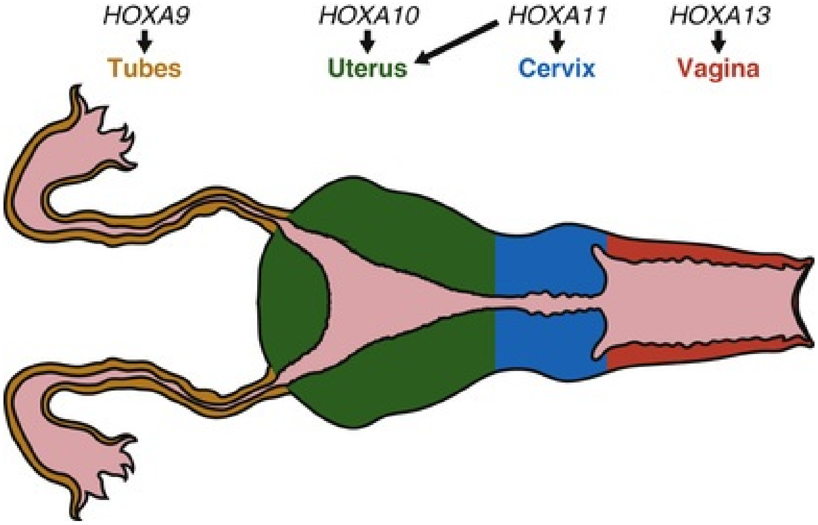

FIG. 569.1 *HOX* code of the developing müllerian system. (Adapted from Taylor HS: The role of HOX genes in the development and function of the female reproductive tract. Semin Reprod Med 2000; 18[1]:81-9.)

By 10 wk of gestation, the caudal portions of the müllerian ducts fuse together in the midline to form the uterus, cervix, and upper vagina, in a Y-shaped structure, with the open upper arms of the Y forming the primordial fallopian tubes. Initially, the müllerian ducts are solid cords that gradually canalize as they grow along and cross the mesonephric ducts ventrally and fuse in the midline. The mesonephric ducts caudally open into the **urogenital sinus,** and the müllerian ducts contact the dorsal wall of the urogenital sinus, where proliferation of the cells at the point of contact form the müllerian tubercle. Cells between the müllerian tubercle and the urogenital sinus continue to proliferate, forming the vaginal plate. At the same time of the midline fusion of the müllerian ducts, the medial walls begin to degenerate and resorption occurs to form the central cavity of the uterovaginal canal. Uterine septal resorption is thought to occur in a caudal to cephalad direction and to be complete at approximately 20 wk of gestation. This theory has been scrutinized because some anomalies do not fit the standard classification system; and it is possible that septal resorption starts at some point in the middle and proceeds in both directions. At approximately 16 wk of gestation, the central cells of the vaginal plate desquamate and resorption occurs, forming the vaginal lumen. The lumen of the vagina is initially separated from the urogenital sinus by a thin hymenal membrane. The hymenal membrane undergoes apoptosis and central resorption and is usually perforate before birth.

Epidemiology

Müllerian anomalies can include abnormalities in portions or all of the fallopian tubes, uterus, cervix, and vagina (Fig. 569.2). True estimates of prevalence are difficult because of the varied presentations and asymptomatic nature of some of the anomalies. Imaging techniques have made significant contributions to uterovaginal anomaly diagnoses, which has increased reporting of anomalies and led to additional combinations of anomalies. Most estimate that müllerian anomalies are present in 2–4% of the female population. The incidence increases in women with a history of adverse pregnancy outcomes or infertility: 5–10% of infertile women undergoing hysterosalpingogram, 5–10% of women with recurrent pregnancy loss, 15% of women with primary amenorrhea, and 25% or more of women with late miscarriages and/or preterm delivery have müllerian defects.

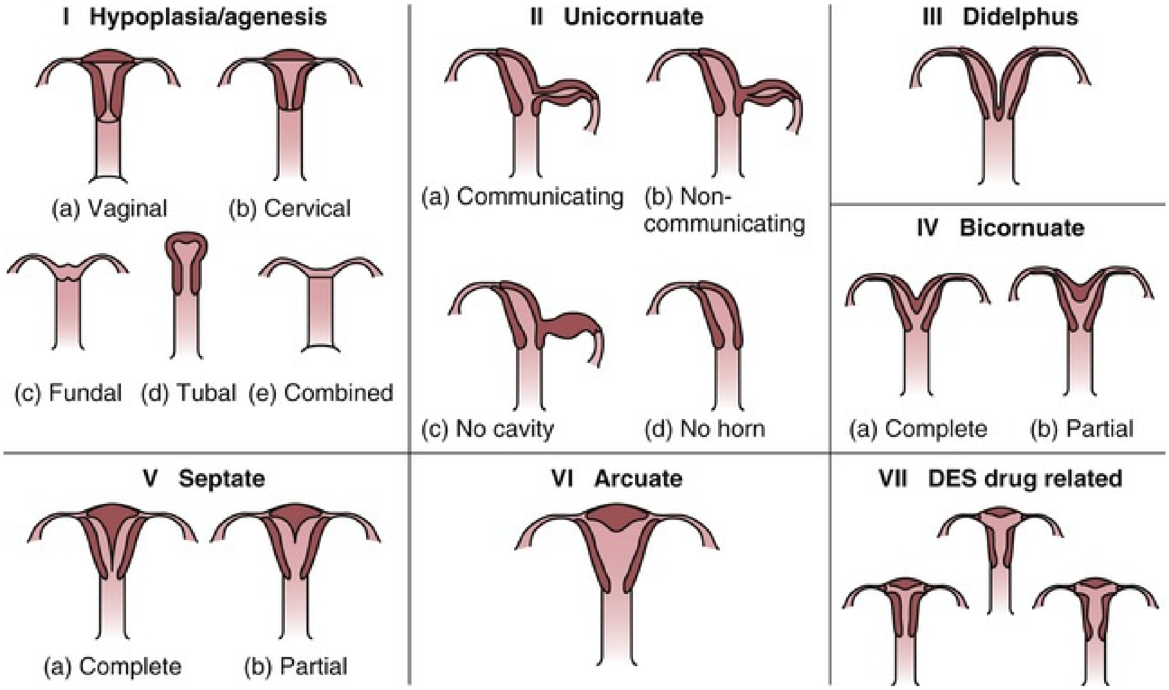
I Hypoplasia/agenesis
(a) Vaginal
(b) Cervical
(c) Fundal
(d) Tubal
(e) Combined
II Unicornuate
(a) Communicating
(b) Non-communicating
(c) No cavity
(d) No horn
III Didelphus
IV Bicornuate
(a) Complete
(b) Partial
V Septate
(a) Complete
(b) Partial
VI Arcuate
VII DES drug related

FIG. 569.2 Classification system of müllerian duct anomalies developed by the American Society of Reproductive Medicine. (From Gholoum S, Puligandla PS, Hui T, et al: Management and outcome of patients with combined vaginal septum, bifid uterus, and ipsilateral renal agenesis [Herlyn-Werner-Wunderlich syndrome]. J Pediatr Surg 41:987–992, 2006, Fig. 3.)

Clinical Manifestations

Vulvovaginal and müllerian anomalies can manifest at a variety of chronologic time points during a female's life: from infancy, through childhood and adolescence, and during adulthood (see Table 569.1). The majority of external genitalia malformations manifest at birth, and often even subtle deviations from normal in either a male or female newborn warrant evaluation. Structural reproductive tract abnormalities can be seen at birth or can cluster at menarche or any time during a woman's reproductive life. Some müllerian anomalies are asymptomatic, whereas others can cause gynecologic, obstetric, or infertility issues.

Clinical manifestations and treatments depend on the specific type of müllerian anomaly and are varied. There may be a pelvic mass, which may or may not be associated with symptoms. A mass bulging at the introitus or within the vagina indicates complete or partial **outflow tract obstruction.** A newborn can present with no evidence of a vaginal opening. An adolescent can present with cyclic pelvic pain either in association with **primary amenorrhea** or several months after the onset of menarche. Patients also may be asymptomatic until they present with miscarriage, pregnancy loss, or preterm delivery. When presentation is acutely symptomatic, emergency management may be required. Obstruction can result from a number of distinct anomalies, including an **imperforate hymen,** a **transverse vaginal septum,** a distal **vaginal agenesis,** or a **noncommunicating rudimentary horn.** As menstrual fluid accumulates proximal to the obstruction, the resulting **hematocolpos** (Fig. 569.3) and **hematometra** cause cyclic pain or a pelvic mass.

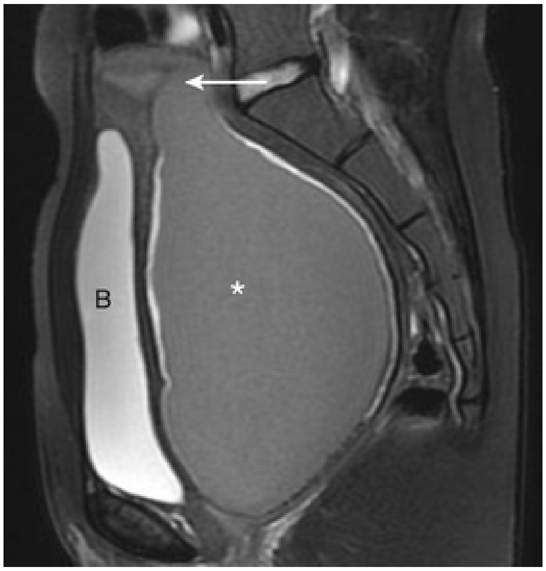

FIG. 569.3 Sagittal MRI of pelvis showing large-volume hematocolpos (asterisk). B, bladder; arrow, hematometra.

Prenatal or neonatal presentation of hydrometrocolpos from distal vaginal obstruction produces fluid accumulation in the vagina and uterus and presents as a lower abdominal mass with or without associated acute urinary tract obstruction. **Hydrometrocolpos with polydactyly** may be a result of two autosomal recessive disorders: **McKusick-Kaufman syndrome** (with associated congenital heart disease) and **Bardet-Biedl syndrome** (with obesity, learning disabilities, retinitis pigmentosa, renal anomalies).

Adolescent patients can present with acute obstruction of the outflow tract because of a müllerian anomaly, which requires emergency evaluation and surgical treatment. A small percentage of females can present with concomitant urinary retention caused by an altered urethral angle or pressure on the sacral plexus. Urinary hesitancy and incomplete emptying symptoms may be present before abdominopelvic pain increases from the obstruction in a patient of any age. Some menstruating adolescents may present with increasing cyclic abdominopelvic pain with their menses due to an obstructed hemivagina with uterine didelphys and ipsilateral renal agenesis **(OHVIRA).**

Laboratory Findings

Several radiographic studies have been used, often in combination, to aid in diagnosis including ultrasound, hysterosalpingogram, sonohysterography (saline-infusion sonography), and magnetic resonance imaging (MRI). Historically laparoscopy and hysteroscopy were the gold standard for evaluation of müllerian anomalies but this has changed over time. The least invasive initial study for a young adolescent with cyclic pain, a pelvic mass, or amenorrhea would be a pelvic ultrasound; *MRI is considered standard of care and best suited for complex anomalies because of its noninvasive, high-quality capabilities* . MRI is the most sensitive and specific imaging technique used for evaluating müllerian anomalies because it can image nearly all reproductive structures, blood flow, external contours, junctional zone resolution on T2-weighted images, and associated renal and other anomalies. MRI also has a high correlation with surgical findings because of its multiplanar capabilities and high spatial resolution. Three-dimensional ultrasound is another useful diagnostic tool and may be superior to traditional pelvic ultrasound and hysterosalpingogram but may not be easily accessible. Evaluation of the external contour of the uterus is important for differentiating types of uterine anomalies. This often requires a combination of radiologic modalities for the uterine cavity, external contour, and possible tubal patency. Diagnostic laparoscopy or hysteroscopy may be necessary depending on the presentation, but it is used less with the advancement of MRI and other imaging modalities.

Diagnosis of müllerian anomalies should include a physical exam, MRI with or without pelvic ultrasound, and renal and skeletal inspections for associated anomalies. Renal anomalies are noted in 30–40% and skeletal anomalies are associated in 10–15% of patients with müllerian anomalies. Unilateral renal agenesis occurs in 15% of patients. The most common skeletal anomalies are vertebral. Patients usually have a normal female karyotype (46,XX), but several familial segregations and gene mutations and/or abnormal karyotypes have been reported 5–8% of the time (Table 569.2). Most malformations are sporadic, with a polygenic mechanism and multifactorial etiology.

Uterine Anomalies

Anomalous development of the uterus may be symmetric or asymmetric and/or obstructed or nonobstructed. Patients can present with primary amenorrhea or have either irregular or regular menstrual cycles. There may be an asymptomatic pelvic mass or dysmenorrhea. In adolescents and adults, pregnancy loss can cause the first suspicion of a uterine anomaly. Treatment is highly specific to the specific anomaly.

Septate Uterus

A **uterine septum** is the most common müllerian anomaly, accounting for just over half of all abnormalities, and it is the most common structural uterine anomaly. After the two müllerian ducts fuse in the midline, resorption must occur to unify the endometrial cavities; failure of this process results in some degree of uterine septum. It can vary in length from just below the fundus to beyond the cervix, depending on the amount of caudal resorption, but is generally defined as > 1 cm. A **septate uterus** has a normal external uterine contour, which is what distinguishes it from a bicornuate or didelphic uterus. An MRI can help delineate between a predominantly fibrous septum and a muscular or myometrial septum. Because the septum may be poorly vascularized, a septate uterus is the most significant anomaly associated with pregnancy loss, as well as other untoward pregnancy outcomes. Hysteroscopic metroplasty (septal excision) is generally recommended in the setting of a previous pregnancy loss. Controversy still exists regarding whether a woman should have such a surgical procedure without a previous pregnancy loss. Correction of uterine septum improves the prognosis in patients with a history of adverse obstetric outcomes (i.e., spontaneous abortions, preterm delivery). The length of the septum might not correlate with the frequency or occurrence of untoward pregnancy outcomes. Differentiating precisely between bicornuate and septate uteri is extremely important to determine effective and safe treatment plans.

Bicornuate Uterus

Both müllerian ducts develop and elongate in this anomaly, but they do not completely fuse in the midline. The vagina and external cervix are normal, but the extent of division of the two endometrial cavities can vary, depending on the extent of failed fusion between the cervix and the fundus. Bicornuate uteri are also associated with increased preterm labor and delivery, malpresentation, and miscarriage. This anomaly accounts for ~ 10–20% of müllerian anomalies and a significant percentage of uterine anomalies. Presently there is no pregnancy outcome data to provide evidence to support unification of a uterine duplication, and expectant management should be encouraged.

Unicornuate Uterus and Rudimentary Horns

A **unicornuate uterus** results from a normal creation of a fallopian tube, functional uterus, cervix, and vagina from one müllerian duct. The other side fails to develop, resulting in either absence of the contralateral müllerian duct or a rudimentary horn. There is a 30–40% association of renal anomalies. If a rudimentary horn is identified, it is important to determine whether functional endometrium is present (usually with T2-weighted MRI images). About two thirds of rudimentary horns are noncommunicating, some with a fibrous band connecting the two structures. Rudimentary horns can also communicate with the contralateral uterus. A fertilized ovum can implant and develop within a rudimentary horn. Pregnancies within a rudimentary horn are incompatible with expectant management, and rupture of the horn could be life-threatening. Rupture tends to occur at a later gestation than with an ectopic pregnancy, and hemorrhage is severe. Patients with rudimentary horns with functioning endometrium can also present with pain caused by accumulating menses. Because the contralateral uterine horn has a normal outflow pathway, these patients present with cyclic pain and/or a mass, not primary amenorrhea. Pregnancies that arise in a unicornuate uterus are associated with increased preterm labor and delivery, malpresentation, and miscarriage. The patient should be counseled regarding these increased obstetric risks and be offered a preconception consult with a high-risk obstetric physician to best manage her pregnancy.

Uterine Didelphys

A **uterine didelphys** is the result a complete failure of fusion and represents 5%

of müllerian anomalies. There are two fallopian tubes, two completely separate uterine cavities, two cervices, and often two vaginal canals or two partial canals because of an associated longitudinal vaginal septum (75% of the time). At times, the longitudinal septum attaches to one sidewall and obstructs one side of the vagina (or hemivagina) (Fig. 569.4). Evaluation for renal anomalies should be pursued because they are common as well. The combination of uterine didelphys, obstructed hemivagina, and ipsilateral renal agenesis is a variant of the broad spectrum of müllerian anomalies that is referred to as the **Herlyn-Werner-Wunderlich syndrome** or **obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome.** Adolescents with this disorder usually present with abdominal pain shortly after menarche. Although there still may be a risk of adverse pregnancy outcomes with a uterine didelphys (preterm labor, malpresentation), overall pregnancy outcomes are good and are associated with less risk than in other uterine anomalies, but preconception counseling and a consult with a high-risk obstetric physician should be offered.

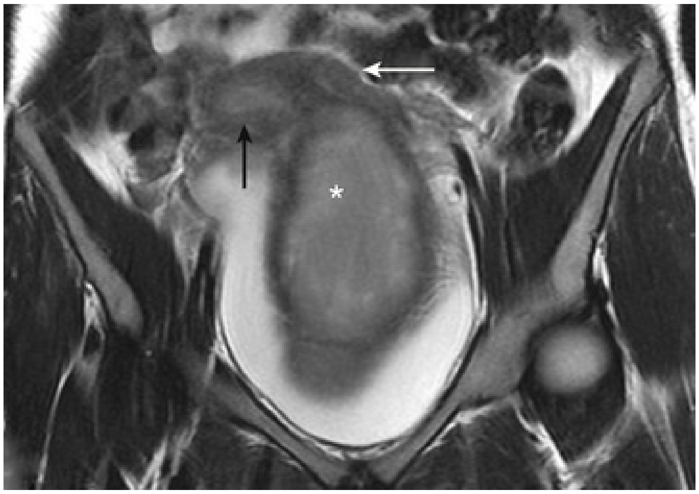

FIG. 569.4 Coronal MRI demonstrating large-volume hematocolpos (asterisk) in a case of uterine didelphys with longitudinal vaginal septum. Black arrow, obstructed right uterus resulting in hematometra; white arrow, unobstructed left uterus.

Arcuate Uterus

An **arcuate uterus** is a uterine cavity that has a small midline septum, from lack of a small amount of resorption (<1 cm), and sometimes a slight indentation of the uterine fundus. An arcuate uterus might represent a variant of normal rather than a müllerian anomaly. Untoward pregnancy outcomes are rare, and *surgical correction is not warranted* .

Treatment

Treatment depends on the specific anomaly. Hysteroscopic surgical resection is widely supported for uterine septa. If a septate uterus extends through the cervical canal, many choose to leave this cervical portion of the septum because of concerns for future incompetence, although case reports indicate that incisions have been done with uneventful follow-up. Most would support the incision of a uterine septum in the clinical setting of pregnancy loss, but some would also support prophylactic metroplasty without a history of miscarriage, especially before in vitro fertilization.

A noncommunicating horn with functional endometrium should be resected to improve the quality of life or prevent future complications. Opinions vary as to whether resection of a communicating horn or one with no functional endometrium is warranted. Any surgical resection of a rudimentary horn requires careful surgical technique to protect the ipsilateral ovarian blood supply and the myometrium of the remaining unicornuate uterus.

Although metroplasty had been advocated with didelphic and bicornuate uteri and a history of poor pregnancy outcomes in the past, currently most clinicians feel there is not enough evidence to support such a complicated procedure. Any obstruction to the outflow tract must be relieved; this can necessitate creation of a vaginal window or excision of a hemivaginal septum.

Vaginal Anomalies

Abnormalities of the Hymen

An **imperforate hymen** is the most common obstructive anomaly, and familial occurrences have been reported (see Fig. 563.1). Its incidence is most often reported as approximately 1 in 1,000. In the newborn period and early infancy, it may be diagnosed by a bulging membrane caused by a **mucocolpos** from maternal estrogen stimulation of the vaginal mucosa. This can eventually reabsorb if it is not too large or symptomatic. More often it is diagnosed at the time of menarche, when menstrual fluid accumulates **(hematocolpos).** The clinical manifestations often are a bulging blue-black membrane, pain, primary amenorrhea, and normal secondary sex characters. A mucocolpos or hematocolpos may obstruct urinary outflow. Depending on the circumstance, patients might have cyclic abdominal pain or a pelvic mass. Other hymenal abnormalities have been reported. A normal hymen can have various configurations (annular, crescentic). Some hymenal membranes do not undergo complete resorption or perforation, resulting in a microperforate, cribriform, or septate-shaped hymen. Infants and children vary in age as to when these are recognized, but hymenal anomalies are often discovered after menarche when it is difficult for an adolescent to place or remove a tampon.

Congenital Absence of the Vagina and Mayer-Rokitansky-Küster-Hauser Syndrome

Vaginal agenesis or **atresia** results when the vaginal plate fails to canalize. On physical exam it appears as an extremely foreshortened vagina, sometimes referred to as a *vaginal dimple.* Isolated (partial) vaginal agenesis involves an area of aplasia between the distal vaginal portion and a normal upper vagina, cervix, and uterus. These patients present with cryptomenorrhea and eventually have cyclic pain caused by obstructed outflow. Each subsequent menses distends the upper vagina with menstrual blood. On initial presentation it may be confused with a low transverse septum or imperforate hymen, and therefore clear delineation of the anomaly with appropriate imaging is critical before attempting surgical repair. Surgical repair and reconstruction is complicated and best performed with consultation of specialists with expertise in managing these anomalies.

Uterine and **vaginal agenesis** often occur together because of their close association during development, when müllerian ductal development fails early in the process. The most common cause of vaginal agenesis is **Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome,** with an incidence reported at 1 in 4,000-5,000 female births. After gonadal dysgenesis, müllerian agenesis is the second most common cause of primary amenorrhea. The etiology is believed to be multigenetic and multifactorial. This condition is present at birth but often not diagnosed until mid-adolescence. Women with MRKH have normal ovarian function and undergo normal secondary sexual development at puberty but do not have a menstrual cycle (primary amenorrhea). The range and severity of MRKH syndrome can vary greatly and the disorder may be type I (isolated) or type II, involving additional organ systems including the renal and skeletal systems. Absence of the vagina and uterus has significant anatomic, physiologic, and psychological implications for the patient and family, and counseling is recommended. Although most patients with müllerian agenesis have small rudimentary müllerian bulbs, approximately 2–7% of patients can have active endometrium within these uterine structures. These patients will often present with cyclic pelvic pain. MRI is often necessary to determine if any small uterine remnant is present (often located on the pelvic sidewall or near the ovaries) and to clearly delineate the anomaly. Laparoscopy is not necessary to diagnosis müllerian agenesis but may be useful in the treatment of rudimentary uterine horns, particularly when removal of obstructed uterine structures or associated endometriosis is indicated for pelvic pain. Any diagnosis of müllerian agenesis must be differentiated from **androgen insensitivity** ; the karyotype, serum testosterone levels, and pubic hair distribution help distinguish between the two because testosterone levels and adrenarche will be normal in women with MRKH.

Abnormalities involving other organ systems occur in association with MRKH type II, or müllerian duct aplasia, renal dysplasia, and cervical somite anomalies (MURCS) association. The most common are urinary tract anomalies (15–40%) primarily involving unilateral absence of a kidney, a horseshoe or pelvic kidney, and skeletal anomalies (5–10%), which primarily involve vertebral development but can also include cardiac anomalies and hearing impairment, and these should be evaluated at the time of diagnosis.

Longitudinal Vaginal Septa

Longitudinal vaginal septa represent failure of complete canalization of the vagina. These often occur in the presence of uterine anomalies as noted earlier.

Transverse Vaginal Septa (Vertical Fusion Defects)

Vertical fusion defects can result in a transverse septum, which may be imperforate and associated with hematocolpos or hematometra in adolescents or with mucocolpos in infants. These are much less common anomalies, reportedly found in 1 in 80,000 females. Patients commonly present with primary amenorrhea and cyclical abdominal pain around the time of menarche. However, patients who have a small opening in the transverse septa might present with prolonged vaginal drainage and **mucopurulent** or **sanguineous discharge.** Transverse vaginal septa can vary in location (15–20% occur in the lower third, but the majority are in the middle or upper third of the vagina) and thickness (but are generally ≤ 1 cm). High locations, thicker septa, and narrow vaginal orifices present challenging surgical cases.

Transverse vaginal septa may be associated with other congenital anomalies, although this occurs less often than with müllerian agenesis. These patients have a functional normal uterus, unlike women with MRKH syndrome. There is also an increased incidence of endometriosis secondary to retrograde menstruation.

Evaluation of transverse vaginal septa includes careful pelvic examination and pelvic imaging, usually with MRI and ultrasound, to delineate the anatomic abnormalities. MRI is especially helpful to determine the thickness of the septum and presence of a cervix and for surgical planning. Diagnosis and treatment plans should be made as soon as possible after menarche, because significant accumulation of hematometra and/or hematosalpinx could affect future reproductive success by negatively affecting uterine and/or tubal function. Alternately, menstrual suppression is another option to enable adolescent patients time to mature psychologically and participate in the treatment phase of the resection of the transverse septum.

Treatment

An imperforate hymen requires resection to prevent or relieve the outflow tract obstruction. Many approach it with a horizontal, lunate or cruciate incision, excision of excess tissue, and approximation of the mucosal edges. Repair should be done at time of diagnosis if the patient is symptomatic, although the lesion may be repaired any time during infancy, childhood, or adolescence. Elective surgery with general anesthesia is discouraged in the very young. Elective hymenal excision in the prepubertal child will heal best if topical estrogen is placed at the site for a few days. Elective excision of an imperforate hymen can be performed after age 1-2 yr through puberty, but ideally prior to menses. Variants in the hymen with microperforations or hymenal septa may interfere with tampon use, and resection of this tissue is usually electively performed using local anesthesia or sedation according to patient preference.

Treatment of congenital absence of the vagina is usually delayed until the patient. The nonsurgical approach is the most common first-line therapy and is recommended by the American College of Obstetricians and Gynecologists because it is safer, patient-controlled, more cost effective than surgery, and successful in 90-96% of patients. If done correctly it is possible to achieve a functional vaginal length (6-8 cm), width, and physiologic angle for intercourse in about 6-8 wk of therapy. When the ultimate size that accommodates coitus is reached, then the patient must use the dilator or have coitus with a frequency that maintains adequate length.

Surgical approaches require more expertise and often some postoperative vaginal dilation to ensure a functional result. Controversy exists among surgical subspecialties, because pediatric surgeons and pediatric urologists often recommend creating the neovagina in infancy. Pediatric gynecologists and reproductive endocrinologists believe better outcomes result from creating the neovagina when the young woman is interested in sexual activity and can participate in the decision to have surgery and in her own postoperative recovery. There is no consensus as to the best surgical option; the most-used procedures include two surgical approaches followed by dilators or an approach using a loop of bowel out of which to construct a vagina. Surgery should be reserved for the rare patient for whom primary dilator therapy was unsuccessful or for those who request surgery after a thorough informed consent. Referral to centers with expertise should be offered.

Future options for having children should be addressed including adoption and gestational surrogacy. Assisted reproductive techniques using ovum retrieval, fertilization, and implantation of embryos into gestational carriers (surrogates) have been successful. Female offspring usually have normal reproductive tracts. Uterine transplantation has resulted in live births, but given limited data, this procedure is currently considered experimental. Opportunities for family building enables adolescents, young women, and their families to appreciate the potential for becoming parents and help cope with the diagnosis of MRKH and its implications.

Surgical resection of transverse vaginal septa should be undertaken only by surgeons with expertise. Some surgeons advocate waiting for one or more menstrual cycles or using preoperative dilators from below to increase the depth and circumference of the distal vagina and to allow menstrual blood to accumulate and dilate the upper portion of the vagina. Complete resection of the septum, with primary anastomosis of the upper and lower mucosal segments, should be attempted. A vaginal stent is sometimes placed postoperatively in the vagina to maintain patency and allow squamous epithelialization of the upper vagina and cervix. Follow-up dilation may be necessary after the stent is removed. Careful preoperative assessment is important because surgeons who begin a case believing they are operating on an imperforate hymen can find themselves in entirely different and more complex surgical planes. Regardless of the approach, vaginoplasty is often best deferred until the patient is mature and physically and psychologically prepared to participate in the healing process and postoperative dilator treatments. It can be challenging to differentiate a low transverse septum from distal vaginal agenesis. If by rectal examination the distal vagina cannot be palpated close to the anal sphincter, the patient should be allowed to continue to menstruate to distend the upper vagina to within 3 cm of the anal sphincter. This enables the surgeon to dissect up to the lower vagina and perform a pull-through procedure, anastamosing the upper vagina to the introitus. Proper timing and surgical execution yield excellent outcomes.

Longitudinal vaginal septa themselves do not lead to adverse reproductive outcomes but may be symptomatic in a patient, causing dyspareunia, traumatic bleeding with intercourse, difficulties with tampon insertion, or impedance during vaginal birth. Such complaints can warrant a resection of the vaginal septa. In a small number of patients, there may be unilateral obstruction of a hemivagina, which would require incision and resection. There may be OHVIRA (Herlyn-Werner-Wunderlich syndrome), which requires a carefully planned incision and resection of the septum to maintain patency of the upper tract.

Cervical Anomalies

Congenital atresia or complete agenesis of the uterine cervix is extremely rare and often manifests at puberty with amenorrhea and pelvic pain. It is associated with significant renal anomalies in 5–10% of patients. A pelvic MRI is often warranted to completely define the abnormality. Usually, pain and obstruction are significant and a hysterectomy is necessary. Attempts to reconnect the uterus to the vagina are rarely successful and are associated with significant morbidity and reoperation rates. As with most müllerian anomalies, the ovaries usually remain normal and future reproduction can still occur through the use of in vitro fertilization and a gestational carrier.

Vulvar and Other Anomalies

Complete Vulvar Duplication

Duplication of the vulva is a rare congenital anomaly that is seen in infancy and consists of two vulvas, two vaginas, and two bladders, a didelphic uterus, a single rectum and anus, and two renal systems.

Labial Asymmetry and Hypertrophy

With the onset of puberty the labia minora enlarge and grow to an adult size. A woman's labia can vary in size and shape. Asymmetry of the labia, where the right and left labia are different in size and appearance, is a normal variant. Some women are uncomfortable with what they perceive to be their asymmetric or enlarged labia minora and complain about self-consciousness and discomfort while wearing tight clothing, exercising, or having sex. The mature labia minora can protrude beyond the labia majora and this normal variant can be functionally or psychologically bothersome. Local irritation, problems of personal hygiene with bowel movements or menses, or interference with sexual intercourse or while sitting or exercising have resulted in requests for labial reduction. Patients may find on-line procedures advertised to reduce uneven or enlarged labia minora. Education and reassurance is very important for adolescents who have concerns about the appearance of their labia. The American College of Obstetricians and Gynecologists does not support performing such surgery unless there is significant congenital malformation. Surgical alteration of the labia that is not necessary to the health of the adolescent less than age 18 is considered a violation of federal criminal law. Complications of labial surgery include loss of sensation, keloid formation, and dyspareunia.

Clitoral Abnormalities

Agenesis of the clitoris is rare. Clitoral duplication has been reported, often associated with cloacal and bladder exstrophy. Exposure to male hormones will result in clitoral enlargement and is often a sign of a testosterone-producing tumor or use of exogenous steroids.

Cloacal Anomalies

Cloacal anomalies are rare lesions representing a common urogenital sinus into which the gastrointestinal, urinary, and vaginal canals all exit. Usually there is an abnormality in all or some of the processes of fusion of the müllerian ducts, development of the sinovaginal bulbs, or development of the vaginal plate. The single opening (cloaca) requires surgical correction, which is often done very early in life, preferably by a multidisciplinary pediatric surgical team.

Ductal Remnants

Even though the opposite duct regresses in both sexes, there can sometimes be a small portion of either the müllerian or wolffian duct that remains in either the male or female, respectively. Such remnants can form cysts, which is what makes them clinically visible during surgery, examination, or imaging. Most do not cause pain, although torsion of some has been reported, and small asymptomatic ones usually do not require resection. The most commonly reported are hydatid of Morgagni cysts (remnant of a wolffian duct arising from the fallopian tube), cysts of the broad ligament, and Gartner's duct cysts, which can form an ectopic ureter or be found along the cervix or vaginal walls.

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CHAPTER 570

Gynecologic Care for Girls With Special Needs

Elisabeth H. Quint

Adolescence presents challenges for all children and their families, but particularly so for teens with special needs and their families. The start of menstrual periods, the mood changes associated with puberty, the concerns about sexual activity with possible unplanned pregnancies, and worries about safety and abuse may present teens with disabilities and their families with additional issues.

Sexuality and Sexual Education

Adolescents with special needs can have physical and/or developmental disabilities. These young women are often seen as asexual by their families, care providers, and society and therefore sexual education might not have been provided or considered necessary. Physically disabled teens are as likely to be sexually active as nondisabled teens. The care provider needs to assess the teen's knowledge of anatomy and sexuality, her social knowledge of relationships, and her ability to consent to sexual activity. Education regarding HIV and other sexually transmitted infections, disease prevention, and contraception, including emergency contraception, should be offered at a developmentally appropriate level. Teens with disabilities may be more at risk for isolation and depression during adolescence.

Abuse

The risk for sexual abuse in teens with disabilities is difficult to estimate.

Screening for abuse is mandatory. Studies show that teens with physical disabilities are just as sexually active as their nondisabled counterparts but that more of their activity is nonvoluntary. Patients with cognitive impairment are often taught to be cooperative, which may make them more vulnerable to coercion. Abuse prevention education can include the No! Go! Tell! model. For teens with limited verbal capacity or developmental delay, abuse may be very hard to detect. The care provider needs to be vigilant in looking for signs on physical exam, such as unexplained bruises or scratches, or changes in behavior, such as regression, which may be indications of sexual abuse in those adolescents (see Chapters 16.1 and 145).

Pelvic Examination

An internal pelvic exam is rarely indicated in teens that are not sexually active, as Papanicolaou smears are not recommended to start until age 21. An external genital exam can be performed, if there are vulvar issues such as discharge, irregular bleeding, suspicion for abuse, or foreign body. The frog-leg position is usually favored over the use of stirrups. If the vagina or cervix needs to be clearly visualized for a medical indication, an exam under anesthesia by a gynecologist should be considered. Testing for sexually transmitted infections can be accomplished by urine testing or vaginal swabs (see Chapter 146).

Menstruation

Irregular menstruation is common in teenagers, especially during the first 5 yr after menarche, because of immaturity of the hypothalamic–pituitary–ovarian axis and subsequent anovulation (see Chapter 142). Several conditions in teens with disabilities are associated with an even higher risk of irregular cycles. Teens with Down syndrome have a higher incidence of thyroid disease. There is a higher incidence of reproductive issues, including polycystic ovarian syndrome in teens with epilepsy or those taking certain antiepileptic drugs. Antipsychotic medication can cause hyperprolactinemia, which can affect menstruation.

For teens with disabilities, the main issue with menstrual cycles, whether they are regular, irregular, or heavy, is the impact of menstruation on the patient's life, her health, and her ability to perform her normal activities. The history should focus on this aspect, and menstrual calendars may be helpful to document the cycles, behavior, and impact of treatments. Most adolescents who self-toilet can learn to use menstrual hygiene products appropriately. Premenarchal anticipatory guidance is recommended, but hormonal treatment before menarche should be avoided.

The evaluation for abnormal bleeding is the same as for all teens. Areas requiring particular attention for the girl with special needs are the consideration of menstrual suppression for hygiene or cyclical behavioral issues, like crying, tantrums, or withdrawal. A request for birth control, especially coming from a caregiver and not from the teen, requires an evaluation of the teen's ability to consent to sexual activity and the safety of her environment. Guidelines for abnormal bleeding include menses that are too heavy (in excess of 1 pad/hr for several hours in a row), too long (> 7 days), or too frequent (< 20 days apart).

Treatment of Menstruation

If after documenting the impact of the regular or irregular cycles on the patient's well-being (often through menstrual or behavioral charting for several months), the care provider, patient, and family decide on menstrual intervention, several options are available. Menstrual regulation is not different from that in the nondisabled teenager in general, although there are some special considerations. Goals for treatment can be to decrease the heaviness of flow, regulate cycles to predictable bleeding, relieve pain or cyclical behavior symptoms, provide contraception, and/or obtain amenorrhea. Menstrual suppression leading to complete amenorrhea is usually difficult to obtain and infrequent scheduled bleeds may be easier to manage than unpredictable spotting, a common side effect of any suppressive treatment, for certain patients. After treatment has started, continue to monitor bleeding, ideally with continued menstrual or behavior calendars.

Nonhormonal Methods

If menorrhagia or dysmenorrhea (occasionally leading to cyclical behavior changes in nonverbal teens) is the main concern, the patient can be started on nonsteroidal antiinflammatory drugs. These can decrease the flow by up to 20% in adequate doses and can be used alone or in combination with other treatments.

Estrogen-Containing Methods

Oral Contraceptives

Cyclical oral contraceptives usually lead to regular, lighter cycles with less cramping. Extended cycling through continuous use of oral contraceptives can suppress cycles, with amenorrhea rates improving with time. Some unpredictable spotting is usually unavoidable, and often teens with special needs prefer to have predictable cycles several times a year. A chewable oral contraceptive is available for those with swallowing issues.

Contraceptive Ring

The contraceptive ring is usually used in a pattern of 3 wk on and 1 wk off, but it can be used (off-label) in a continuous 4-wk pattern, which can lead to less bleeding. However, the contraceptive ring may be difficult to use for a teen with dexterity problems, and help with placement has obvious privacy issues.

Contraceptive Patch

The weekly patch can also be used in a continuous fashion. Some teens with developmental disabilities remove their patch erratically, and placement out of reach (e.g., on buttocks or shoulder) is advised.

Estrogen Use, Venous Thromboembolism, and Mobility Issues

Whether immobility and wheelchair use can lead to an increased risk of venous–thrombolic events (VTEs) in association with estrogen-containing contraceptives remains controversial. The risk of thrombosis with the use of combined hormonal contraceptives by adolescents who are immobile or who have limited mobility has not been studied. Immobility per se is not a contraindication to estrogen-containing contraceptives; however, it may increase the risk of VTE, according to the Centers for Disease Control and Prevention medical eligibility criteria for contraception released in 2016. There are limited data to support the concern that higher-dose oral estrogen and the third- and fourth-generation progestin preparations may have a higher risk for venous thromboembolism. It is important to obtain a thorough and extended family history for hypercoagulability before initiating estrogen therapy. Careful use of lower-dose (30 or 20 μg) ethinyl estradiol preparations after appropriate counseling may be advisable, and third-generation progestin combinations should only be used if other methods have failed.

Progestin-Only Methods

Intramuscular Medroxyprogesterone Acetate

Intramuscular medroxyprogesterone acetate (DMPA) has long been used for menstrual suppression. Two issues are particularly relevant to teens with disabilities. Studies documenting a decrease in bone density associated with longer-term use of DMPA and a black box warning by the FDA have raised concerns about use of these products in young women, although research indicates that the bone density improves after the medication is stopped. For teens with mobility issues or those with very low body weight who are already at risk for low bone density, decreased bone density is a real concern, although the risk of fractures is unclear. Adequate calcium and vitamin D is recommended. The second issue for teens with mobility issues is weight gain associated with DMPA, especially among obese teens, which can lead to transfer and mobility issues. The potential health risks associated with the effects of DMPA on bone density must be balanced against the need for menstrual suppression and the likelihood of unintended pregnancy. Weight should be monitored closely. Routine bone density scanning (dexa) is not recommended in adolescents.

Oral Progestins

Continuous oral progestins can also be very effective in obtaining amenorrhea. The progesterone-only pill causes significant irregular spotting, so if full suppression is the goal, then other progestins can be used daily, such as norethindrone 2.5 or 5 mg or micronized progesterone 200 mg.

Progesterone Intrauterine Device

The 5-yr levonorgestrel–intrauterine device has now been used for many teenagers for contraception, as well as heavy menses. Teens with special needs might require anesthesia for insertion if the exam is very difficult because of discomfort, contractures, or a narrow vagina. Checking for strings in a clinic setting may be challenging; however, the intrauterine device location can be confirmed by sonography. There may be a significant amount of irregular bleeding and spotting in the 1st several months, but there is 20% amenorrhea after insertion and up to 50% amenorrhea after 1 yr of use. The bleeding profile of the newer and smaller 3-yr levonorgestrel–intrauterine device may not be as helpful for menstrual suppression; the amenorrhea rates from the initial studies by the manufacturer are 6% at 1 yr, but more studies are needed.

Implants

Progestin subdermal implants have relatively low amenorrhea rates and higher rates of unscheduled bleeding; therefore, they are not recommended as first-line treatment for menstrual suppression for teens with special needs. They also require significant patient cooperation for insertion.

Hormones and Antiepileptic Drugs

Certain enzyme-inducing seizure medications can interfere with estrogen-containing contraceptives, change their contraceptive effectiveness, and/or lead to intermittent bleeding. Higher estrogen dose or shorter injection intervals for DMPA may be considered. The only antiepileptic medication that is affected by combined oral contraceptives is lamotrigine; consequently, the dose of that medication may need to be adjusted if used in conjunction with hormones.

Surgical Methods

Surgical procedures such as endometrial ablation, a procedure where the lining of the uterus is surgically removed, and hysterectomy are available for treatment of abnormal periods in adults, but they should only rarely be used in extreme situations for teenagers where all other methods have failed and the patient's health is severely compromised by her cycles. Endometrial ablation only leads to amenorrhea approximately 30% of the time and has a higher failure rate in women younger than 40 yr of age, and it is not recommended in this population. Ethical considerations around these methods leading to infertility and consent issues are complicated, and state law varies on this topic.

Contraception

See also Chapter 143 .

The menstrual management methods discussed above can also be used for contraception, and if a request for birth control is made, an evaluation of the patient's ability to consent to sexual activity and the safety of her environment should be done. The method chosen should be the safest method for her situation with the highest protection rate. Therefore a long-acting reversible contraceptive method may be advisable. Sexually transmitted infections and condom use should be addressed with the teen and specific guidelines on how to obtain condoms and negotiate their use may be needed. A discussion about emergency contraception is recommended, as well as ways to help the teen obtain this if indicated.

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CHAPTER 571

Female Genital Mutilation

Deborah Hodes, Sarah M. Creighton

Background

Female genital mutilation (FGM) is a human rights issue affecting girls and women worldwide. It is defined by the World Health Organization (WHO) as procedures that remove or damage the external female genital organs for no medical reason. UNICEF (United Nations International Children's Emergency Fund) estimated in 2016 that at least 200 million women and girls in 30 countries have undergone FGM. There has been a decline in the prevalence of FGM, but current trends suggest that actual numbers will rise due to population growth. FGM is most commonly performed in Africa, the Middle East, and Asia, with new data suggesting an estimated 40 million girls in Indonesia have undergone FGM. However, the migration of FGM-practicing communities means that FGM is a global problem, although there is scant data on the practice in high-income countries. FGM is almost always carried out on children, and pediatricians must be familiar with the identification of FGM, the impact upon health, and how to protect girls from this widespread form of child abuse.

FGM has no health benefits and can cause lifelong damage to physical and psychological health. The WHO has classified FGM into 4 types, depending on the extent and type of genital tissue removed (Table 571.1). The traditional practitioner performs FGM without anesthetic or sterile conditions, and in some countries it is done as part of a wider ritual related to early child marriage. The child is restrained whilst the external genitalia are removed or damaged using a knife, scalpel, or other sharp instrument. An increasing number of procedures are performed at a younger age, and the WHO estimates that up to 17% are performed by health professionals. Table 571.2 lists potential risks and protective factors for FGM.

Table 571.1

Summary of WHO Classification of FGM

Type 1 : Clitoridectomy: partial or total removal of the clitoris (a small sensitive and erectile part of the female genitals) and in rare cases only the prepuce (the fold of skin surrounding the clitoris)
Type 2 : Excision: partial or total removal or the clitoris and labia minora with or without removal of the labia majora (the labia are the “lips” that surround the vagina)
Type 3 : Infibulation: narrowing of the vaginal opening through the creation of a covering seal. The seal is formed by cutting and repositioning the labia minora or majora with or without removal of the clitoris.
Type 4 : Other: all other harmful procedures to the genitalia for nonmedical reasons (e.g., pricking, piercing, incision, scraping, and cauterizing the genital area).

From the World Health Organization Female Genital Mutilation Fact sheet. http://www.who.int/mediacentre/factsheets/fs241/en/ . Updated February 2017.

Table 571.2

Factors That Influence Whether or Not a Child May Have FGM

RISK FACTORS
Mother or sister cut
Isolated mother
Grandmother influential
Little information and discussion about FGM
PROTECTIVE FACTORS
Discussing with husband or friend
Knowing the law has been implemented
TV, global debate, media
Men's attitude and knowledge
Knowing an uncut person

Complications

Immediate complications of FGM include hemorrhage and infection. Deaths have been reported, although numbers are unknown. Infections include immediate wound infection, tetanus, and gangrene. FGM has been implicated in the transmission of blood-borne infections due to the use of shared and unsterile tools. Although procedure-related blood-borne infection is probable, there are no good studies to confirm this; infections such as hepatitis B and HIV are endemic in areas where FGM is prevalent. FGM leads to obstetric, gynecologic, and psychological consequences in adult women. Gynecologic symptoms include painful and unsightly scarring, clitoral cysts, and recurrent urinary infections. Menstrual difficulties and infertility are reported, although the underlying mechanisms of these are unclear apart from type 3 FGM, where the vagina is narrowed. FGM damages sexual function by removing sensitive sexual tissue and narrowing the vagina. Mental health problems such as anxiety and depression have been linked to FGM. FGM also has a detrimental impact on obstetric outcomes for both the mother and baby, leading to increased risks of postpartum hemorrhage, perineal trauma, and perinatal death.

Clinical Management of FGM

Most pediatricians will not see a child who is acutely unwell due to FGM. Management of FGM in the acute situation should include assessment for blood loss, sepsis, and urinary retention and treatment with antibiotics, analgesia, tetanus toxoid, and urinary catheterization. Pediatricians are more likely to see a child in whom FGM has been found during the investigation of other symptoms, such as recurrent urinary tract infections and vulvovaginitis. FGM may also be alleged by the child or family member or concerns may be raised by other health and social care professionals, particularly if the mother herself has undergone FGM and she has little support from her husband (see Table 571.2). Pediatricians may be asked to confirm FGM on genital examination; it should be performed using a colposcope for magnification and video documentation, which can be used for peer review and a court of law. The examination must be done in a sensitive and gentle manner by an appropriately trained clinician and in an age-appropriate setting. It is often assumed that FGM will be obvious. However whilst type 3 FGM, in which the vagina is sealed, is usually easy to detect, other types of FGM can be more difficult to diagnose. This is particularly true for type 4 FGM, which may comprise a prick or small scratch on or adjacent to the clitoris and may heal without a trace. General assessment of the child's health should include screening for blood-borne viruses.

If the child has type 3 FGM, then a deinfibulation procedure will be required at some point. Deinfibulation is a minor surgical procedure to divide any scar tissue that obscures the vaginal introitus. If the child is asymptomatic, this can be deferred until adolescence or prior to sexual activity. Deinfibulation procedures are usually performed under a local anesthetic in adult women, but in children a brief general anesthetic is more appropriate. The psychological impact of FGM on a child may be severe, and flashbacks and nightmares have been reported.

Input from a child psychologist or psychotherapist with experience in working with children with FGM and their families should be available. If a child is confirmed to have FGM, then other children in the family may be at risk, and local safeguarding pathways should be activated. Pediatricians must be advocates against FGM and contribute to training healthcare workers who may treat patients and promoting local and national policies against it, as well as supporting legislation to end the practice.

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PART XXV

The Endocrine System

OUTLINE

Section 1 Disorders of the Hypothalamus and Pituitary Gland
Section 2 Disorders of the Thyroid Gland
Section 3 Disorders of the Parathyroid Gland
Section 4 Disorders of the Adrenal Gland
Section 5 Disorders of the Gonads
Section 6 Diabetes Mellitus in Children

SECTION 1

Disorders of the Hypothalamus and Pituitary Gland

OUTLINE

Chapter 572 Hormones of the Hypothalamus and Pituitary
Chapter 573 Hypopituitarism
Chapter 574 Diabetes Insipidus
Chapter 575 Other Abnormalities of Arginine Vasopressin Metabolism and Action
Chapter 576 Hyperpituitarism, Tall Stature, and Overgrowth Syndromes
Chapter 577 Physiology of Puberty
Chapter 578 Disorders of Pubertal Development

CHAPTER 572

Hormones of the Hypothalamus and Pituitary

Eric I. Felner, Briana C. Patterson

The pituitary gland is the major regulator of an elaborate hormonal system. The pituitary gland receives signals from the hypothalamus and responds by sending pituitary hormones to target glands. The target glands produce hormones that provide negative feedback at the level of the hypothalamus and pituitary (Figs. 572.1 and 572.2). This feedback mechanism enables the pituitary to regulate the amount of hormone released into the bloodstream by the target glands. The pituitary's central role in this hormonal system and its ability to interpret and respond to a variety of signals have led to its designation as the *master gland* . Table 572.1 lists hypothalamic and pituitary hormones and their functions.

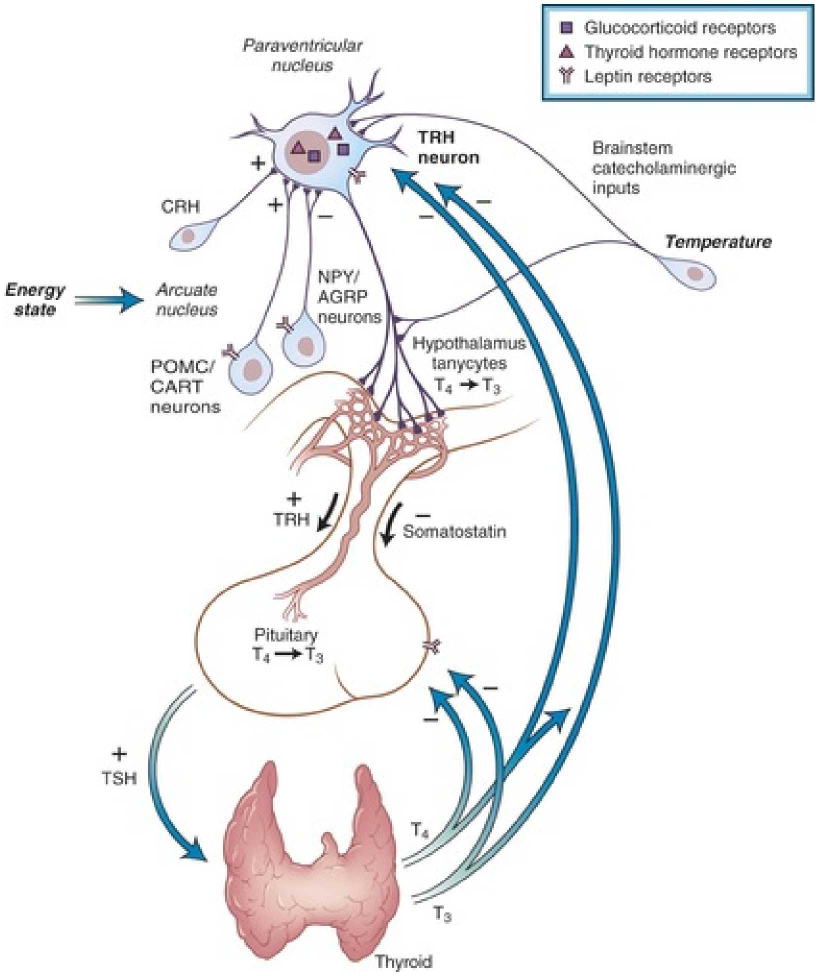
■ Glucocorticoid receptors
▲ Thyroid hormone receptors
Leptin receptors
Paraventricular nucleus
TRH neuron
Brainstem catecholaminergic inputs
Temperature
CRH
+
+
–
–
–
Energy state
Arcuate nucleus
NPY/ AGRP neurons
POMC/ CART neurons
Hypothalamus tanycytes $T_4 \rightarrow T_3$
+ TRH
– Somatostatin
Pituitary $T_4 \rightarrow T_3$
+ TSH
–
–
T_4
T_3
Thyroid

FIG. 572.1 Regulation of the hypothalamic-pituitary-thyroid axis. *AGRP,* Agouti-related peptide; *CART,* cocaine- and amphetamine-regulated transcript; *CRH,* corticotropin-releasing hormone; *NPY,* neuropeptide Y; *POMC,* proopiomelanocortin; T_3 , triiodothyronine; T_4 , thyroxine; *TRH,* thyrotropin-releasing hormone; *TSH,* thyrotropin. (From Low MJ: Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier. Fig. 7.9.)

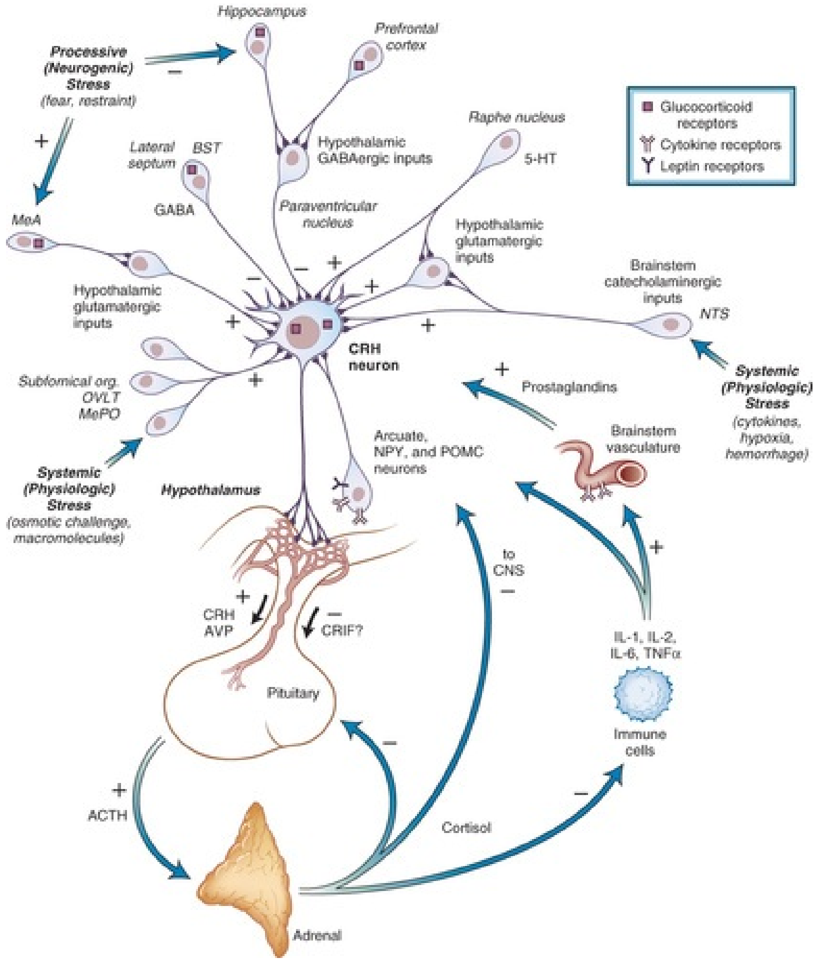
Hippocampus
Prefrontal cortex
Processive (Neurogenic) Stress
(fear, restraint)
−
+
MeA
Lateral septum
BST
GABA
Hypothalamic GABAergic inputs
Paraventricular nucleus
Raphe nucleus
5-HT
Glucocorticoid receptors
Cytokine receptors
Leptin receptors
Hypothalamic glutamatergic inputs
Hypothalamic glutamatergic inputs
Brainstem catecholaminergic inputs
NTS
CRH neuron
Subfornical org.
OVLT
MePO
Systemic (Physiologic) Stress
(cytokines, hypoxia, hemorrhage)
Prostaglandins
Brainstem vasculature
Arcuate, NPY, and POMC neurons
Systemic (Physiologic) Stress
(osmotic challenge, macromolecules)
Hypothalamus
to CNS
CRH
AVP
CRIF?
Pituitary
IL-1, IL-2, IL-6, TNFα
Immune cells
ACTH
Cortisol
Adrenal

FIG. 572.2 Regulation of the hypothalamic-pituitary-adrenal axis. *ACTH,* Adrenocorticotropic hormone; *AVP,* arginine vasopressin; *BST,* bed nucleus of the stria terminalis; *CNS,* central nervous system; *CRH,* corticotropin-releasing hormone; *CRIF,* corticotropin release–inhibiting factor; *GABA,* γ-aminobutyric acid; *5-HT,* 5-hydroxytryptamine; *IL-1,* interleukin 1; *MeA,* medial amygdala; *MePO,* medial preoptic nucleus; *NPY,* neuropeptide Y; *NTS,* nucleus of the tractus solitarius; *OVLT,* organum vasculosum of the lamina terminalis; *POMC,* proopiomelanocortin; *TNF-α,* tumor necrosis factor-α. (From Low MJ: Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier. Fig. 7.18.)

Table 572.1

Hormones of the Hypothalamus and Pituitary Gland

HORMONES	LOCATION	S/I	FUNCTION
ACTH	Anterior pituitary	S	Production and secretion of GCs, MCs, and androgens from adrenal gland
ADH	Posterior	S	Reabsorption of water into the bloodstream via renal collecting ducts

	pituitary		
CRH	Hypothalamus	S	Secretion of ACTH
Dopamine	Hypothalamus	I	Secretion of PRL
FSH (females)	Anterior pituitary	S	Secretion of estrogen from ovary
FSH (males)	Anterior pituitary	S	Production of sperm from testis
GH	Anterior pituitary	S	Secretion of IGF-1
GHRH	Hypothalamus	S	Secretion of GH
Ghrelin	Hypothalamus	S	Secretion of GH
GnRH	Hypothalamus	S	Secretion of FSH and LH
LH (females)	Anterior pituitary	S	Ovulation and development of the corpus luteum
LH (males)	Anterior pituitary	S	Production and secretion of testosterone
Oxytocin	Posterior pituitary	S	Contractions of uterus at birth and release of milk from breast
PRL	Anterior pituitary	S	Promotion of milk synthesis
Somatostatin	Hypothalamus	I	Secretion of GH and TSH
TRH	Hypothalamus	S	Secretion of TSH and PRL
TSH	Anterior pituitary	S	Secretion of T_4 and T_3

ACTH, Adrenocorticotropic hormone; *ADH,* antidiuretic hormone; *CRH,* corticotropin-releasing hormone; *FSH,* follicle-stimulating hormone; *GC,* glucocorticoids; *GH,* growth hormone; *GHRH,* growth hormone–releasing hormone; *GnRH,* gonadotropin-releasing hormone; *IGF-1,* insulin-derived growth factor 1; *LH,* luteinizing hormone; *MC,* mineralocorticoids; *PRL,* prolactin; *S/I,* stimulate/inhibit; T_3 , triiodothyronine; T_4 , thyroxine; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone (thyrotropin).

Anatomy

The pituitary gland is located at the base of the skull in a saddle-shaped cavity of the sphenoid bone called the *sella turcica.* The bony structure protects and surrounds the pituitary bilaterally and inferiorly. The dura, a dense layer of connective tissue, forms the roof of the sella. An external layer of the dura continues into the sella to form its lining. As a result, the pituitary is extradural and is not normally in contact with cerebrospinal fluid. The pituitary gland is connected to the hypothalamus by the pituitary stalk. The pituitary gland is composed of an anterior (adenohypophysis) and a posterior (neurohypophysis) lobe. The anterior lobe constitutes approximately 80% of the gland.

Embryology

The anterior pituitary gland originates from the Rathke pouch as an invagination of the oral ectoderm. It then detaches from the oral epithelium and becomes an individual structure of rapidly proliferating cells. By 6 wk of gestation, the connection between the Rathke pouch and the oropharynx is completely obliterated, and the pouch establishes a direct connection with the downward extension of the hypothalamus, which gives rise to the pituitary stalk. Persistent remnants of the original connection between the Rathke pouch and the oral cavity can develop into **craniopharyngiomas** (see Chapter 524), the most common type of tumor in this area.

Vascular Supply

The arterial blood supply of the pituitary gland originates from the internal carotid via the inferior, middle, and superior hypophyseal arteries. This network of vessels forms a unique portal circulation connecting the hypothalamus and pituitary. The branches of the superior hypophyseal arteries penetrate the stalk and form a network of vessels that traverse the pituitary stalk and terminate in a network of capillaries within the anterior lobe. It is through this portal venous system that hypothalamic hormones are delivered to the anterior pituitary gland. Anterior pituitary hormones, in turn, are secreted into a secondary plexus of portal veins that drain into the dural venous sinuses.

Anterior Pituitary Cell Types

A series of sequentially expressed transcriptional activation factors directs the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. The consequences of mutations in several of these genes are evident in human forms of multiple pituitary hormone deficiency. Five cell types in the anterior pituitary produce 6 peptide hormones. Somatotropes produce growth hormone (GH), lactotropes produce prolactin (PRL), thyrotropes make thyroid-stimulating hormone (TSH), corticotropes express proopiomelanocortin (POMC), the precursor of adrenocorticotropic hormone (ACTH), and gonadotropes express luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Growth Hormone

Human GH is a 191-amino-acid single-chain polypeptide that is synthesized, stored, and secreted by somatotropes in the pituitary. Its gene *(GH1)* is the first in a cluster of 5 closely related genes on the long arm of chromosome 17 (q22-24). The 4 other genes *(CS1, CS2, GH2,* and *CSP)* have >90% sequence identity with the *GH1* gene.

GH is secreted in a pulsatile fashion under the regulation of hypothalamic hormones. The alternating secretion of GH-releasing hormone, which stimulates GH release, and somatostatin, which inhibits GH release, accounts for the rhythmic secretion of GH. Peaks of GH occur when peaks of GH-releasing hormone coincide with troughs of somatostatin. **Ghrelin,** a peptide produced in the arcuate nucleus of the hypothalamus and in much greater quantities by the stomach, also stimulates GH secretion. In addition to the 3 hypothalamic hormones, physiologic factors play a role in stimulating and inhibiting GH. Sleep, exercise, physical stress, trauma, acute illness, puberty, fasting, and hypoglycemia stimulate the release of GH, whereas hyperglycemia, hypothyroidism, and glucocorticoids inhibit GH release (Fig. 572.3).

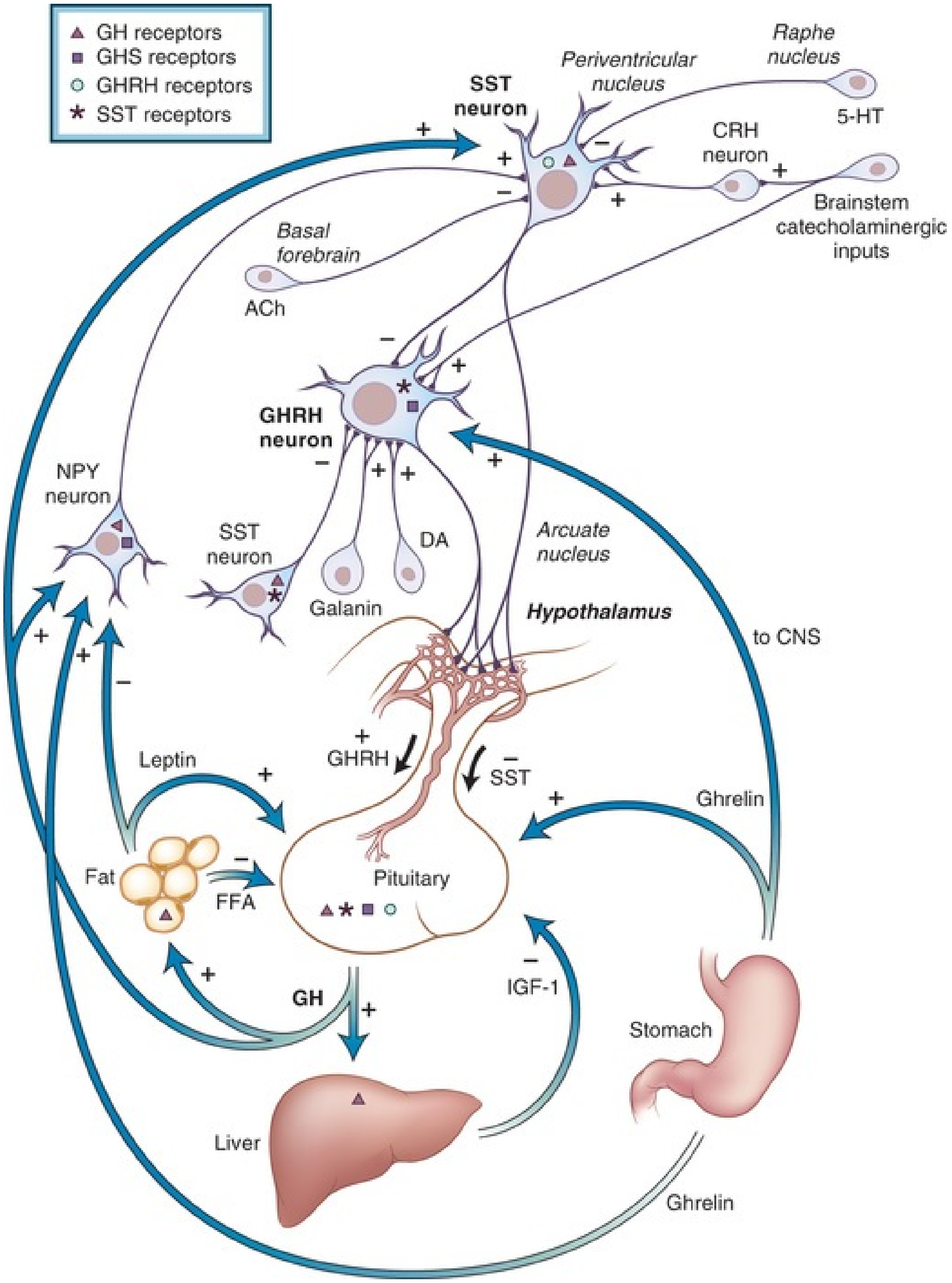

▲ GH receptors
■ GHS receptors
○ GHRH receptors
★ SST receptors
SST neuron
Periventricular nucleus
Raphe nucleus
5-HT
CRH neuron
Brainstem catecholaminergic inputs
Basal forebrain
ACh
GHRH neuron
NPY neuron
SST neuron
Galanin
DA
Arcuate nucleus
Hypothalamus
to CNS
Leptin
GHRH
SST
Ghrelin
Fat
FFA
Pituitary
GH
IGF-1
Stomach
Liver
Ghrelin
+
−

FIG. 572.3 Regulation of the hypothalamic-pituitary-growth hormone *(GH)* axis. GH secretion by the pituitary is stimulated by GH-releasing hormone *(GHRH)* and is inhibited by somatostatin *(SST).* Negative feedback control of GH secretion is exerted at the pituitary level by insulin-like growth factor 1 *(IGF-1)* and by free fatty acids *(FFAs)* . GH itself exerts a short-loop negative feedback through activation of SST neurons in the hypothalamic periventricular nucleus. These SST neurons directly synapse on arcuate GHRH neurons and project axon collaterals to the median eminence. Neuropeptide Y *(NPY)* neurons in the arcuate nucleus also indirectly modulate GH secretion by integrating peripheral GH, leptin, and ghrelin

signals and projecting to periventricular SST neurons. Ghrelin is secreted from the stomach and is a natural ligand for the GH secretagogue *(GHS)* receptor that stimulates GH secretion at both the hypothalamic and pituitary levels. On the basis of indirect pharmacologic data, it appears that release of GHRH is stimulated by galanin, γ-aminobutyric acid *(GABA)* , and α_2 -adrenergic and dopaminergic inputs and inhibited by SST. Secretion of SST is inhibited by muscarinic acetylcholine *(ACh)* and 5-HT-1D receptor ligands and increased by β_2 -adrenergic stimuli and corticotropin-releasing hormone *(CRH)* . *CNS,* Central nervous system; *DA,* dopamine; *5-HT,* serotonin (5-hydroxytryptamine). (From Low MJ: Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier. Fig. 7.22.)

GH binds to receptor molecules on the surface of target cells. The GH receptor is a 620-amino-acid, single-chain molecule with an extracellular domain, a single membrane-spanning domain, and a cytoplasmic domain. Proteolytically cleaved fragments of the extracellular domain circulate in plasma and act as a GH-binding protein. As in other members of the cytokine receptor family, the cytoplasmic domain of the GH receptor lacks intrinsic kinase activity; instead, GH binding induces receptor dimerization and activation of a receptor-associated Janus kinase (Jak2). Phosphorylation of the kinase and other protein substrates initiates a series of events that leads to alterations in nuclear gene transcription. The signal transducer and activator of transcription 5b (STAT5b) plays a critical role in linking receptor activation to changes in gene transcription.

The biologic effects of GH include increases in linear growth, bone thickness, soft tissue growth, protein synthesis, fatty acid release from adipose tissue, insulin resistance, and blood glucose. The mitogenic actions of GH are mediated through increases in the synthesis of **insulin-like growth factor** 1 (IGF-1), formerly named *somatomedin C* , a 70-amino-acid single-chain peptide coded for by a gene on the long arm of chromosome 12. IGF-1 has considerable homology to insulin. Circulating IGF-1 is synthesized primarily in the liver and formed locally in mesodermal and ectodermal cells, particularly in the growth plates of children, where its effect is exerted by paracrine or autocrine mechanisms. Circulating levels of IGF-1 are related to blood levels of GH and to nutritional status. IGF-1 circulates bound to several different binding proteins. The major one is a 150-kDa complex (IGF-BP3) that is decreased in GH-deficient children. Human recombinant IGF-1 might have therapeutic potential in conditions characterized by end-organ resistance to GH such as Laron syndrome and the development of antibodies to administered GH. IGF-2 is a 67-amino-acid single-chain protein that is coded for by a gene on the short arm of chromosome 11. It has homology to IGF-1. Less is known about its physiologic role, but it appears to be an important mitogen in bone cells, where it occurs in a concentration many times higher than that of IGF-1.

Prolactin

PRL is a 199-amino-acid peptide made in pituitary lactotropes. The regulation of PRL is unique because PRL is consistently secreted unless it is actively inhibited by dopamine, a peptide produced by neurons in the hypothalamus. Disruption of the hypothalamus or pituitary stalk can result in elevated PRL levels. Dopamine antagonists, states of primary hypothyroidism, administration of thyrotropin-releasing hormone (TRH), and pituitary tumors result in increased serum levels of PRL. Dopamine agonists and processes causing destruction of the pituitary cause reduced levels of PRL.

The primary physiologic role for PRL is the initiation and maintenance of lactation. PRL prepares the breasts for lactation and stimulates milk production postpartum. During pregnancy, PRL stimulates the development of the milk secretory apparatus, but lactation does not occur because of the high levels of estrogen and progesterone. After delivery, the estrogen and progesterone levels drop and physiologic stimuli such as suckling and nipple stimulation signal PRL release and initiate lactation.

Thyroid-Stimulating Hormone

TSH consists of 2 glycoprotein chains (α, β) linked by hydrogen bonding: the α-subunit, which is composed of 89 amino acids and is identical to other glycoproteins (FSH, LH, and human chorionic gonadotropin), and the β-subunit, composed of 112 amino acids, that is specific for TSH.

TSH is stored in secretory granules and released into circulation primarily in response to TRH, which is produced by the hypothalamus. TRH is released from the hypothalamus into the hypothalamic-pituitary portal system and ultimately stimulates TSH release from pituitary thyrotropes. TSH stimulates release of thyroxine (T_4) and triiodothyronine (T_3) from the thyroid gland through the formation of cyclic adenosine monophosphate and the G protein second messenger system. In addition to the negative feedback inhibition by T_3, the release of TRH and TSH is inhibited by dopamine, somatostatin, and glucocorticoids.

Deficiency of TSH results in inactivity and atrophy of the thyroid gland, whereas excess TSH results in hypertrophy and hyperplasia of the thyroid gland.

Adrenocorticotropic Hormone

ACTH is a 39-amino-acid single-chain peptide that is derived by proteolytic cleavage from **POMC** , a 240-amino-acid precursor glycoprotein product of the pituitary gland. POMC also contains the sequences for the *lipotropins* , *melanocyte-stimulating hormones* (α, β, γ), and β-*endorphin* .

Secretion of ACTH is regulated by corticotropin-releasing hormone (CRH), a 41-amino-acid peptide found predominantly in the median eminence but also in other areas in and outside of the brain. ACTH is secreted in a diurnal pattern. It acts on the adrenal cortex to stimulate cortisol synthesis and secretion. ACTH and cortisol levels are highest in the morning at the time of waking, are low in the late afternoon and evening, and reach their nadir 1-2 hr after beginning sleep. ACTH also appears to be the principal pigmentary hormone in humans. Similar to TRH and TSH, CRH and ACTH function through the formation of cyclic adenosine monophosphate and the G protein second messenger system. Although CRH is the primary regulator of ACTH secretion, other hormones play a role. Arginine vasopressin, oxytocin, angiotensin II, and cholecystokinin stimulate release of CRH and ACTH, whereas atrial natriuretic peptide and opioids inhibit release of CRH and ACTH. Similar to the feedback inhibition T_3 has on TRH and TSH, cortisol also inhibits CRH and ACTH. Physiologic conditions, such as stress, fasting, and hypoglycemia, also stimulate release of CRH and ACTH.

Luteinizing Hormone and Follicle-Stimulating Hormone

Gonadotropic hormones include 2 glycoproteins, LH and FSH. They contain the same α subunit as TSH and human chorionic gonadotropin but distinct β subunits. Receptors for FSH on the ovarian granulosa cells and on testicular Sertoli cells mediate FSH stimulation of follicular development in the ovary and of gametogenesis in the testis. On binding to specific receptors on ovarian theca cells and testicular Leydig cells, LH promotes luteinization of the ovary and

Leydig cell function of the testis (Fig. 572.4). The receptors for LH and FSH belong to a class of receptors with 7 membrane-spanning protein domains. Receptor occupancy activates adenylyl cyclase through the mediation of G proteins.

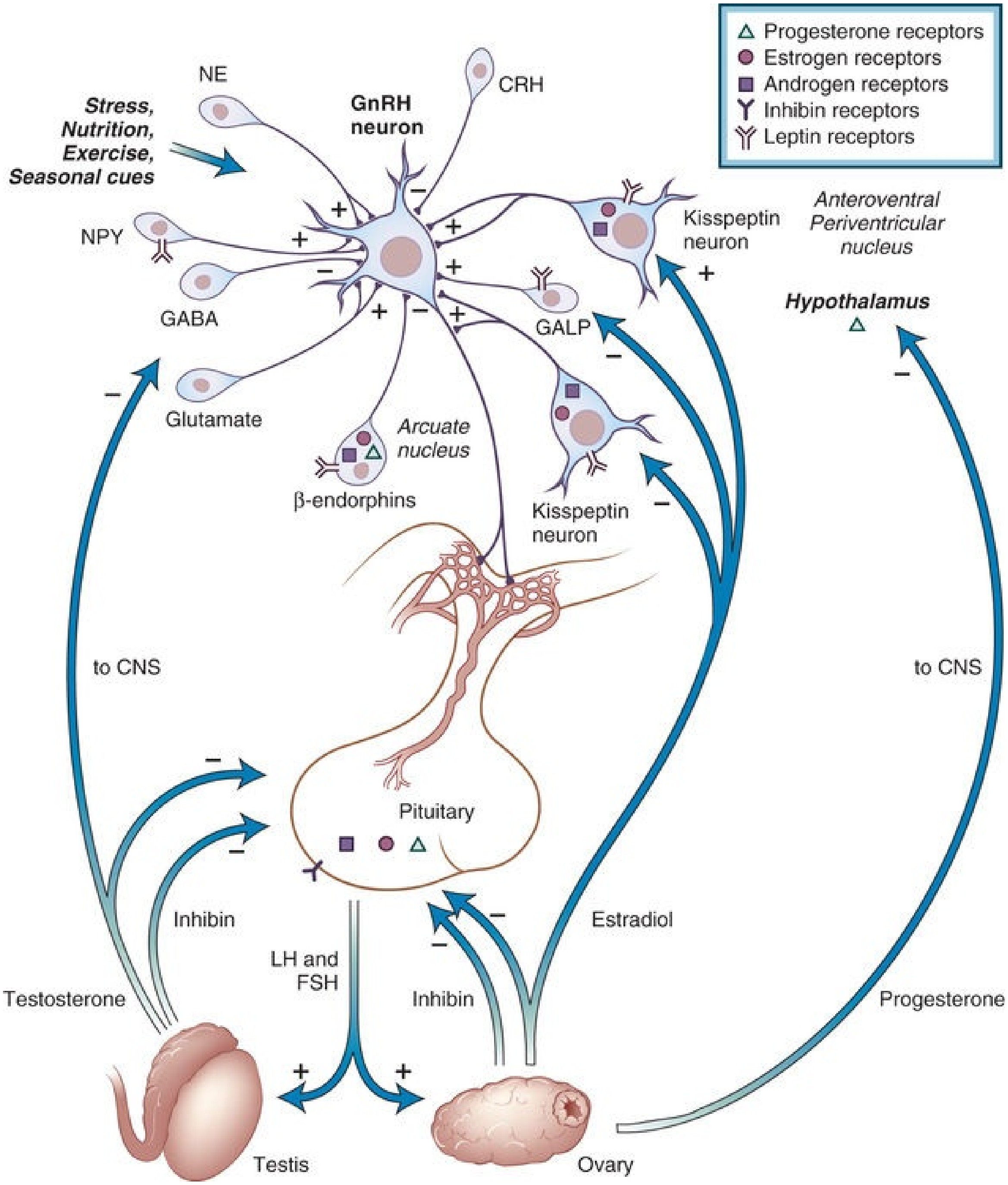

△ Progesterone receptors
● Estrogen receptors
■ Androgen receptors
Y Inhibin receptors
Leptin receptors
NE
GnRH neuron
CRH
Stress, Nutrition, Exercise, Seasonal cues
NPY
GABA
Glutamate
Arcuate nucleus
β-endorphins
Kisspeptin neuron
Anteroventral Periventricular nucleus
Hypothalamus
GALP
Kisspeptin neuron
to CNS
Pituitary
to CNS
Inhibin
Testosterone
LH and FSH
Inhibin
Estradiol
Progesterone
Testis
Ovary
+
−

FIG. 572.4 Regulation of the hypothalamic-pituitary-gonadal axis.

Schematic diagram of the hypothalamic-pituitary-gonadal axis showing neural systems that regulate gonadotropin-releasing hormone *(GnRH)* secretion and feedback of gonadal steroid hormones at the level of the hypothalamus and pituitary. *CNS,* Central nervous system; *CRH,* corticotropin-releasing hormone; *FSH,* follicle-stimulating hormone; *GABA* , γ-aminobutyric acid; *GALP,* galanin-like peptide; *LH,* luteinizing hormone; *NE,* norepinephrine; *NPY,* neuropeptide Y. (From Low MJ: Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier. Fig. 7.30.)

LH-releasing hormone, a decapeptide, has been isolated, synthesized, and widely used in clinical studies. Because it leads to the release of LH and FSH from the same gonadotropic cells, it appears that it is the only gonadotropin-releasing hormone.

Secretion of LH is inhibited by androgens and estrogens, and secretion of FSH is suppressed by gonadal production of inhibin, a 31-kDa glycoprotein produced by the Sertoli cells. Inhibin consists of α and β subunits joined by disulfide bonds. The β-β dimer (activin) also occurs, but its biologic effect is to stimulate FSH secretion. The biologic features of these more recently identified hormones are being delineated. In addition to its endocrine effect, activin has paracrine effects in the testis. It facilitates LH-induced testosterone production, indicating a direct effect of Sertoli cells on Leydig cells.

Posterior Pituitary Cell Types

The posterior lobe of the pituitary is part of a functional unit, the neurohypophysis, that consists of the neurons of the supraoptic and paraventricular nuclei of the hypothalamus; neuronal axons, which form the pituitary stalk; and neuronal terminals in the median eminence or in the posterior lobe. Arginine vasopressin (antidiuretic hormone [ADH]) and oxytocin are the 2 hormones produced by neurosecretion in the hypothalamic nuclei and released from the posterior pituitary. They are octapeptides and differ by only 2 amino acids.

Antidiuretic Hormone

ADH regulates water conservation at the level of the kidney by increasing the permeability of the renal collecting duct to water. ADH stimulates translocation of water channels through its interaction with vasopressin 2 receptors in the collecting duct, which act through G proteins to increase adenylyl cyclase activity and increase permeability to water. V2 receptors also mediate the von Willebrand factor and tissue plasminogen activator. At higher concentrations, ADH activates V1 receptors in smooth muscle cells and hepatocytes and exerts pressor and glycogenolytic effects through mobilization of intracellular calcium stores. Separate V3 receptors mediate stimulation of ACTH secretion. These effects involve phosphatidylinositol hydrolysis rather than cyclic adenosine monophosphate production.

ADH and its accompanying protein neurophysin II are encoded by the same gene. A single preprohormone is cleaved, and the 2 are transported to neurosecretory vesicles in the posterior pituitary. The 2 are released in equimolar amounts.

ADH has a short half-life and responds quickly to changes in hydration. The stimuli for its release are increased plasma osmolality, perceived by osmoreceptors in the hypothalamus, and decreased blood volume, perceived by baroreceptors in the carotid sinus of the aortic arch.

Oxytocin

Oxytocin stimulates uterine contractions at the time of labor and delivery in response to distention of the reproductive tract and stimulates smooth muscle contraction in the breast during suckling, which results in milk let-down. Studies suggest that oxytocin also plays a role in orgasm, social recognition, pair bonding, anxiety, trust, love, and maternal behavior. Most recently, through the interaction with its G protein–coupled receptor in pancreatic and adipose tissue, oxytocin appears to play a significant role in appetite regulation and obesity by inducing anorexia.

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CHAPTER 573

Hypopituitarism

Briana C. Patterson, Eric I. Felner

Hypopituitarism denotes underproduction of 1 or multiple pituitary hormones. Affected children have postnatal growth impairment and other endocrine deficiencies that are specifically corrected by hormone replacement. The incidence of congenital hypopituitarism is thought to be between 1 in 4,000 and 1 in 10,000 live births. There is an epidemiologic association between hypopituitarism and breech delivery, but the causal relationship is not understood. With expanding knowledge of the genes that direct pituitary development or hormone production, an increasing proportion of cases can be attributed to specific genetic disorders. Mutations in 7 candidate genes account for 13% of isolated growth hormone deficiency (IGHD) and 20% of multiple pituitary hormone deficiency (MPHD) cases. The likelihood of finding mutations is increased by consanguinity and occurrence in siblings or across generations; however, in most cases of IGHD and MPHD, no specific genetic cause can be identified. The genes, hormonal phenotypes, associated abnormalities, and modes of transmission for such established genetic disorders are shown in Tables 573.1 and 573.3 through 573.5 . Acquired hypopituitarism usually has a later onset and different causes (Table 573.2).

Multiple Pituitary Hormone Deficiency

Genetic Forms (Table 573.1)

Sequentially expressed transcriptional activation factors direct the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. Mutations produce different forms of MPHD. *PROP1* and *POU1F1* genes are expressed fairly late in pituitary development only in cells of the anterior pituitary and result in hypopituitarism without anomalies of other organ systems. The *HESX1*, *LHX3*, *LHX4*, *OTX2*, *SOX3*, and *PITX2* genes are expressed at earlier stages and are not restricted to the pituitary. Mutations in these genes tend to produce phenotypes that extend beyond hypopituitarism to include abnormalities in other organs, and the degree of hypopituitarism is typically variable.

Table 573.1

Etiologic Classification of Congenital and Genetic Forms of Multiple Pituitary Hormone Deficiency

GENE OR LOCATION	PHENOTYPE	INHERITANCE
GENETIC FORMS		
POU1F1 (PIT1)	GH, PRL deficiencies, variable TSH deficiency	R, D
PROP1	GH, TSH, PRL, LH, FSH deficiencies, variable ACTH deficiency, variable AP	R
LHX3	GH, TSH, PRL, LH, FSH deficiencies, variable AP, ±short neck, limited neck rotation, sensorineural deafness	R
LHX4	GH, TSH, ACTH deficiencies, small AP, EPP, variable Arnold-Chiari, cerebellar abnormalities	D
TPIT	ACTH, severe neonatal form	R
HESX1	GH deficiency, variable for others, small AP, EPP, optic nerve hypoplasia; septo-optic dysplasia	R, D
SOX2	LH, FSH, variable GH, anophthalmia, microphthalmia, esophageal atresia, sensorineural hearing loss	D
SOX3	Variable deficiencies, ±MR, EPP, small AP and stalk, developmental delay	XL
PITX2	Axenfeld-Rieger syndrome	D
GLI2	Hypopituitarism, holoprosencephaly, midline defects, polydactyly	D
GLI3	Hall-Pallister syndrome, hypopituitarism	D
SHH (Sonic Hedgehog)	GH deficiency with single central incisor	D
OTX12	GH or combined deficiencies Anophthalmia or microphthalmia, coloboma, developmental delay	D
TBX19	ACTH, neonatal hypoglycemia or cholestatic jaundice	R
TGIF, SHH, CDON, GPR161, PROKR2	*Pituitary stalk interruption syndrome* : thin or absent pituitary stalk, hypoplasia of adenohypophysis, ectopic neurohypophysis, neonatal hypoglycemia, cholestasis, micropenis	Holoprosencephaly related gene group
UNCERTAIN ETIOLOGY		
Congenital absence of pituitary		
Optic nerve hypoplasia syndrome/septo-optic dysplasia	Optic nerve hypoplasia, nystagmus, absent septum pellucidum, pituitary hypoplasia	

ACTH, Adrenocorticotropic hormone; *AP,* anterior pituitary; *D,* dominant; *EPP,* ectopic posterior pituitary; *FSH,* follicle-stimulating hormone; *GH,* growth hormone; *LH,* luteinizing hormone; *MR,* mental retardation; *PRL,* prolactin; *R,* recessive; *TSH,* thyroid-stimulating hormone; *XL,* X-linked.

PROP1

PROP1 (prophet of *PIT1*) is found in the nuclei of somatotropes, lactotropes, and thyrotropes. Its roles include turning on *POU1F1* expression and downregulating *HESX1* expression. Although no genetic mutation can be identified in most patients with MPHD, mutations of *PROP1* are the most common explanation for recessive MPHD and are 10 times as common as the combined total of mutations in other pituitary transcription factor genes. Deletions of 1 or 2 base pairs in exon 2 are most common, followed by missense, nonsense, and splice-site mutations. Anterior pituitary hormone deficiencies are seldom evident in the neonatal period. The median age at diagnosis of growth hormone (GH) deficiency is around 6 yr. Recognition of thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and adrenocorticotropic hormone (ACTH) deficiencies is delayed relative to recognition of GH deficiency. Anterior pituitary size is small in most patients, but in others there is progressive enlargement of the pituitary.

POU1F1 (PIT1)

POU1F1 (formerly *PIT1*) was identified as a nuclear protein that binds to the GH and prolactin promoters. It is necessary for emergence and mature function of somatotropes, lactotropes, and thyrotropes. Dominant and recessive mutations in *POU1F1* are responsible for complete deficiencies of GH and prolactin and variable TSH deficiency. Affected patients exhibit nearly normal fetal growth but experience severe growth failure in the 1st yr of life. With normal production of LH and FSH, puberty develops spontaneously, although at a later than normal age. These patients are not at risk for development of ACTH deficiency. Anterior pituitary size is normal to small.

HESX1

The *HESX1* gene is expressed in precursors of all 5 cell types of the anterior pituitary early in embryologic development. Mutations result in heterogeneous phenotypes with defects in development of the optic nerve and pituitary. The anterior pituitary may be hypoplastic or aplastic, and the posterior pituitary may be orthotopic or ectopic. Patients may have IGHD or MPHDs, with or without the optic nerve hypoplasia syndrome, which is also called **septo-optic dysplasia** (incomplete development of the septum pellucidum with optic nerve hypoplasia and pituitary insufficiency). However, the great majority of patients with optic nerve hypoplasia syndrome do not have *HESX1* mutations.

LHX3 and *LHX4*

The phenotype produced by recessive loss-of-function mutations of the *LHX3* gene resembles that produced by *PROP1* mutations. There are deficiencies of GH, prolactin, TSH, LH, and FSH but not ACTH. Some affected persons show enlargement of the anterior pituitary. The first patients to be described had the unusual findings of a short neck and a rigid cervical spine. Dominantly inherited mutations in the structurally similar *LHX4* gene consistently produce GH deficiency, with the variable presence of TSH and ACTH deficiencies. Additional findings can include a very small V -shaped pituitary fossa, Chiari I malformation, and an ectopic posterior pituitary.

Other Congenital Forms

Pituitary hypoplasia can occur as an isolated phenomenon or in association with more extensive developmental abnormalities such as anencephaly or holoprosencephaly. Midline facial anomalies (cleft lip, palate; see Chapter 336) or the finding of a solitary maxillary central incisor indicate a high likelihood of GH or other anterior or posterior hormone deficiency (Fig. 573.1). At least 12 genes have been implicated in the complex genetic etiology of **holoprosencephaly** . The **Hall-Pallister syndrome** is caused by dominant loss of function mutations in the *GLI3* gene. Absence of the pituitary gland is accompanied by hypothalamic hamartoma, polydactyly, nail dysplasia, bifid epiglottis, imperforate anus, and anomalies of the heart, lungs, and kidneys. The combination of anophthalmia and hypopituitarism has been associated with mutations in the *SIX6*, *SOX2*, and *OTX2* genes.

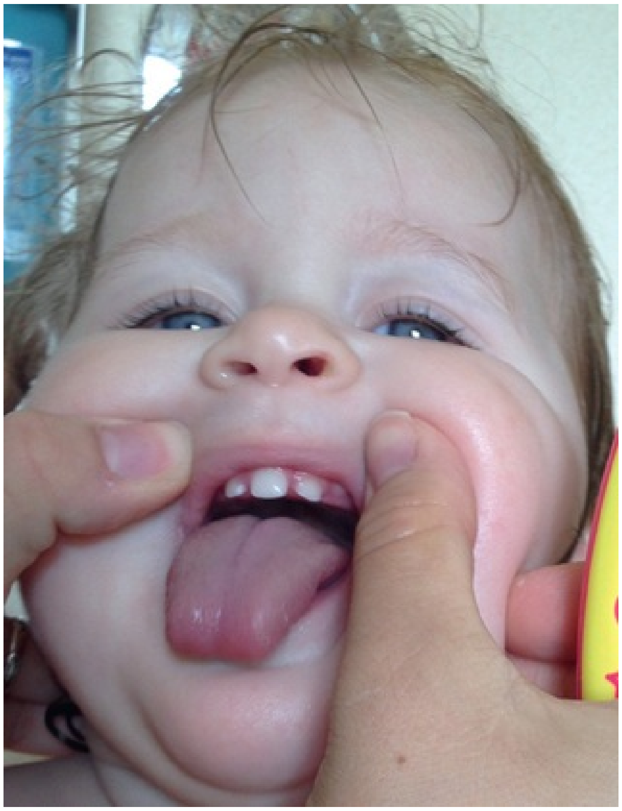

FIG. 573.1 Solitary median maxillary central incisor at age 16 mo. (From Giannopoulou EZ, Rohrer T, Hoffmann P, et al: Solitary median maxillary central incisor, *J Pediatr* 167:770, 2015. Fig. 2).

The optic nerve hypoplasia syndrome or **septo-optic dysplasia** may be detected due to clinical observation of nystagmus and visual impairment in infancy. Neuroimaging demonstrates optic nerve and brain abnormalities and is associated with anterior and/or posterior pituitary hormone deficiencies in up to 75% of the cases (Fig. 573.2). Although these patients often show the triad of a small anterior pituitary gland, an attenuated pituitary stalk, and an ectopic posterior pituitary bright spot, the primary etiology of the hypopituitarism in this condition is thought to be hypothalamic dysfunction. GH deficiency is the most commonly observed hormone deficiency, and other anterior pituitary hormone deficiencies are less common. Diabetes insipidus is reported in only about 5% of cases. The etiology is likely multifactorial and may involve interaction between genetic and environmental factors. In the vast majority of cases, no single gene defect can be identified.

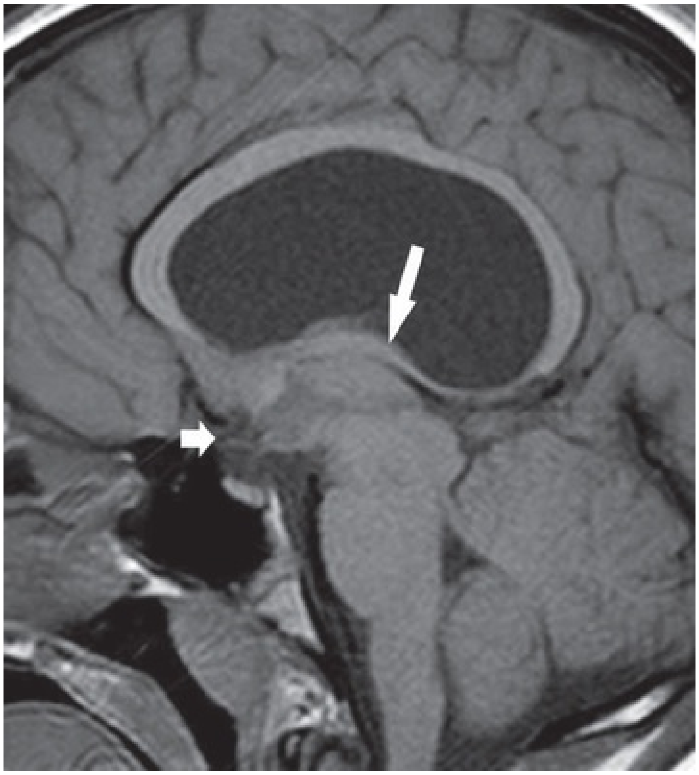

FIG. 573.2 Septo-optic dysplasia with agenesis of the septum pellucidum. Sagittal T1-weighted MR image shows that fornices are inferiorly positioned *(arrow)* . The optic apparatus is hypoplastic *(short arrow)* ; there is no identifiable neurohypophysis. (From Rollins N: Congenital brain malformations. In Coley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 13, Philadelphia, 2019, Elsevier. Fig. 31.13.)

Severe, early-onset MPHD including deficiency of ACTH is often associated with the triad of anterior pituitary hypoplasia, absence or attenuation of the pituitary stalk, and an ectopic posterior pituitary bright spot on MRI. Most cases are sporadic, and there is a male predominance. Some are from abnormalities of the *SOX3* gene, located on the X chromosome.

Acquired Forms

Any lesion that damages the hypothalamus, pituitary stalk, or anterior pituitary can cause pituitary hormone deficiency (Table 573.2). Because such lesions are not selective, multiple hormonal deficiencies are usually observed. Diabetes insipidus is more frequent in acquired than in congenital hypopituitarism. The most common lesion is the craniopharyngioma (see Chapter 524). Central nervous system germinoma, eosinophilic granuloma (histiocytosis), tuberculosis, sarcoidosis, toxoplasmosis, meningitis, pituitary abscess, and aneurysms can also cause hypothalamic-hypophyseal destruction. Children treated with radiation therapy for central nervous system or nasopharyngeal tumors are at increased risk for GH deficiency and other pituitary hormone deficiencies to the extent that the radiation field includes the hypothalamus and/or pituitary, even if the tumor itself is remote from the pituitary and hypothalamus. The magnitude of the risk and the timing of the emergence of pituitary hormone deficiencies depend on the dose of radiation to the hypothalamic-pituitary axis and the duration of elapsed time after radiotherapy is complete. High doses of radiation (>50 Gy) are likely to produce GH deficiency sooner than 1 yr after irradiation, whereas other anterior pituitary hormone deficiencies may not appear until later. GH production appears to be particularly vulnerable to the effects of irradiation, even at lower doses, whereas deficiencies of ACTH, gonadotropins, and TRH/TSH occur with declining frequency and typically occur at higher doses of radiation. Irradiation alone does not typically result in diabetes insipidus. Traumatic brain injury, including abusive head trauma, motor vehicle accidents, and chronic repetitive head injury, is an increasingly recognized cause of pituitary dysfunction due to damage to the pituitary, its stalk, or the hypothalamus.

Table 573.2

Causes of Acquired Pituitary Insufficiency

TRAUMATIC
• Surgical resection • Radiation damage • Traumatic brain injury
INFILTRATIVE/INFLAMMATORY
• Primary hypophysitis • Lymphocytic • Granulomatous • Xanthomatous • Secondary hypophysitis • Sarcoidosis • Langerhans cell histiocytosis • Infections • Granulomatosis with polyangiitis • Takayasu disease • Hemochromatosis
INFECTIONS
• Tuberculosis • *Pneumocystis jirovecii* infection • Fungal (histoplasmosis, aspergillosis) • Parasites (toxoplasmosis) • Viral (cytomegalovirus)
VASCULAR

• Pregnancy related • Aneurysm • Apoplexy • Diabetes • Hypotension • Arteritis • Sickle cell disease
NEOPLASTIC
• Pituitary adenoma • Parasellar mass • Rathke cyst • Dermoid cyst • Meningioma • Germinoma • Ependymoma • Glioma • Craniopharyngioma • Hypothalamic hamartoma, gangliocytoma • Pituitary metastatic deposits • Hematologic malignancy • Leukemia • Lymphoma
FUNCTIONAL
• Nutritional • Caloric restriction • Malnutrition • Excessive exercise • Critical illness • Acute illness • Chronic renal failure • Chronic liver failure • Hormonal • Hyperprolactinemia • Hypothyroidism • Drugs • Anabolic steroids • Glucocorticoid excess • GnRH agonists • Estrogen • Dopamine • Somatostatin analog • Thyroid hormone excess

Modified from Kaiser U, Ho KKY: Pituitary physiology and diagnostic evaluation. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier. Table 8.5, p. 193.

Isolated Growth Hormone Deficiency and Insensitivity

Genetic Forms of Growth Hormone Deficiency

IGHD is caused by abnormalities of the GH-releasing hormone receptor, GH genes, and genes located on the X chromosome (Table 573.3).

Table 573.3

Established Genetic Defects of the GH-IGF Axis Resulting in Isolated GH Deficiency, GH Insensitivity, or IGF-1 Deficiency

MUTANT GENE	INHERITANCE	PHENOTYPE
ISOLATED GROWTH HORMONE DEFICIENCY		
GHRHR	AR	Type IB form of IGHD; low levels of GH production, but less severe than type 1A IGHD; may also be caused by mutations in *GH1*
GHS-R	AD	GHD and ISS
GH1	AR	Type IA form of IGHD, in utero growth retardation; absent GH production due to gene deletion, antibodies to GH develop over time during treatment
GH1	AR	Type IB form of IGHD; low levels of GH production, but less severe than Type 1A IGHD; may also be caused by mutations in *GHRHR*
GH1	AD	Type II form of IGHD; dominant negative mutations in GH1 which decrease GH secretion
BTK	XL	Type III form of IGHD; hypogammaglobulinemia
GH1	AD	Bioinactive GH molecule; rare, dominant negative mutation in *GH1* that interferes with GHR signaling
GROWTH HORMONE INSENSITIVITY		
GHR	AR, AD	IGF-I deficiency; high GH level; normal, decreased or increased GHBP (depending on which domain of the receptor is affected); unresponsive to GH treatment
IGF-1 DEFICIENCY		
IGF1	AR	IGF-1 deficiency; IUGR and postnatal growth failure, sensorineural deafness, insulin resistance, microcephaly
STAT5b	AR	IGF-1 deficiency, variable immune defect, hyperprolactinemia, chronic pulmonary infections, eczema
ALS	AR	IGF-1 deficiency; variable postnatal growth failure, delayed puberty

AD, Autosomal dominant; *ALS,* acid labile subunit; *AR,* autosomal recessive; *GH,* growth hormone; *GHBP,* GH-binding protein; *GHRHR,* GH-releasing hormone receptor; *IGF,* insulin-like growth factor; *IGHD,* isolated GHD; *ISS,* idiopathic short stature; *IUGR,* intrauterine growth retardation; *XL,* X-linked.

Modified from Sperling MA: Pediatric Endocrinology, ed 4, Philadelphia, 2014, Elsevier. Table 10.3, p. 333.

Growth Hormone–Releasing Hormone Receptor

Recessive loss-of-function mutations in the receptor for GH-releasing hormone interfere with proliferation of somatotropes during pituitary development and disrupt the most important signals for release of GH. The anterior pituitary is small, in keeping with the observation that somatotropes normally account for >50% of pituitary volume. There is some compromise of fetal growth followed by severe compromise of postnatal growth.

GH1

The *GH1* gene is one of a cluster of 5 genes on chromosome 17q22-24. This cluster arose through successive duplications of an ancestral GH gene. Unequal crossing over at meiosis has produced a variety of gene deletions. Small deletions (<10 kb) remove only the *GH1* gene, whereas large deletions (45 kb) remove 1 or more of the adjacent genes (*CSL*, *CS1*, *GH2*, and *CS2*). The growth phenotype is identical with deletion of *GH1* alone or *GH1* together with 1 or more of the adjacent genes. Loss of the *CS1*, *GH2*, and *CS2* genes without loss of *GH1* causes deficiency of chorionic somatomammotropin and placental GH in the maternal circulation, but it does not result in fetal or postnatal growth retardation. Most children with *GH1* gene deletions respond very well to recombinant GH treatment, but some develop antibodies to GH and cease growing.

Recessively transmitted mutations in the *GH1* gene produce a similar phenotype. Missense, nonsense, and frameshift mutations have been described. Autosomal dominant IGHD is also caused by mutations in *GH1*. The mutations usually involve splice-site errors in intron 3 and result in a variant protein that lacks the amino acids normally encoded by exon 3. Accumulation of this protein interferes with the processing, storage, and secretion of the normal GH protein and may result in additional deficiencies of TSH and/or ACTH. There are several reports of mutations in *GH1* that lead to variant proteins with reduced biological activity.

X-Linked Isolated Growth Hormone Deficiency

Two loci on the X chromosome have been associated with hypopituitarism. The first lies at Xq21.3-q22 in the region of the Bruton thymidine kinase *(BTK)* gene. Mutations in this region produce hypogammaglobulinemia and IGHD. The second locus maps farther out on the long arm, at Xq24-q27.1, a region containing the *SOX2* transcription factor gene. Abnormalities in this locus have been linked to IGHD with intellectual disability, as well as to MPHD with the triad of pituitary hypoplasia, missing pituitary stalk, and ectopic posterior pituitary gland.

Acquired Forms

The GH axis is more susceptible to disruption by acquired conditions than are other hypothalamic-pituitary axes. Recognized causes of acquired GH deficiency include the use of radiotherapy for malignancy, meningitis, histiocytosis, and trauma.

Children who receive radiotherapy for central nervous system tumors, leukemia, or total body irradiation prior to hematopoietic stem cell transplant are at risk for developing GH deficiency. Spinal irradiation results in disproportionately poor growth of the axial skeleton relative to the appendicular skeleton; this defect is not remediable with GH treatment. Growth typically slows during radiation therapy or chemotherapy, may improve for 1-2 yr after cancer treatment, and then declines with the development of GH deficiency. The dose and frequency of radiotherapy are important determinants of hypopituitarism. GH deficiency is almost universal 5 yr after therapy with a total dose ≥35 Gy. More subtle defects are seen with doses around 20 Gy. Deficiency of GH is the most common defect, but deficiencies of TSH and ACTH can also occur. Cranial irradiation may result in precocious puberty in conjunction with GH deficiency. The clinician is likely to encounter children in the 8- to 10-yr age range who are growing at rates that are normal for chronological age but subnormal for stage of pubertal development.

Growth Hormone Insensitivity

Abnormalities of the Growth Hormone Receptor

GH insensitivity is caused by disruption of pathways distal to production of GH (Table 573.4). **Laron syndrome** involves mutations of the GH receptor. Children with this condition clinically resemble those with severe IGHD. Birth length tends to be about 1 SD below the mean, and severe short stature with lengths >4 SD below the mean is present by 1 yr of age. Resting and stimulated GH levels tend to be high and insulin-like growth factor (IGF) 1 levels are low.

The GH receptor has an extracellular GH-binding domain, a transmembrane domain, and an intracellular signaling domain. Mutations in the extracellular domain interfere with binding of GH. Serum GH-binding protein activity, representing the circulating form of the membrane receptor for GH, is generally low. Mutations in the transmembrane domain can interfere with anchoring of the receptor to the plasma membrane. In these cases, circulating GH-binding protein activity is normal or high. Mutations in the intracellular domain interfere with JAK/STAT signaling.

Table 573.4

Proposed Classification of Growth Hormone Insensitivity

PRIMARY GH INSENSITIVITY (HEREDITARY DEFECTS)
GH receptor defect (may be positive or negative for GH-binding protein)
• Extracellular mutation (e.g., Laron syndrome)
• Cytoplasmic mutation
• Intracellular mutation
GH signal transduction defects (distal to cytoplasmic domain of GH receptor)
• Stat5b mutations
Insulin-like growth factor-1 defects
• IGF-1 gene deletion
• IGF-1 transport defect (ALS mutation)
• IGF-1 receptor defect
Bioinactive GH molecule (responds to exogenous GH)
SECONDARY GH INSENSITIVITY (ACQUIRED DEFECTS)
• Circulating antibodies to GH that inhibit GH action
• Antibodies to the GH receptor
• GH insensitivity caused by malnutrition, liver disease, catabolic states, diabetes mellitus
• Other conditions that cause GH insensitivity

ALS, Acid-labile subunit; *GH,* growth hormone; *IGF,* insulin-like growth factor.

From Sperling MA: Pediatric Endocrinology, ed 4, Philadelphia, 2014, Elsevier. Box 10.4.

Postreceptor Forms of Growth Hormone Insensitivity

Some children with severe growth failure, high GH and low IGF-1 levels, and normal GH-binding protein levels have abnormalities distal to the GH binding and activation of the GH receptor. Several have been found to have mutations in the gene encoding signal transducer and activator of transcription 5b (STAT5b). Disruption of this key intermediate connecting receptor activation to gene transcription produces growth failure similar to that seen in Laron syndrome.

These patients also suffer from *immunodeficiency* and chronic pulmonary infections, consistent with important roles for STAT5b in interleukin cytokine signaling.

IGF-1 Gene Abnormalities

Abnormalities of the *IGF-1* gene produce severe prenatal and postnatal growth impairment. Microcephaly, intellectual disability, and deafness are present in patients with exon deletion and a missense mutation. These patients can be expected to respond to recombinant IGF-1 treatment.

Insulin-Like Growth Factor–Binding Protein Abnormalities

Mutation of the gene encoding the acid-labile subunit of the circulating 165-kDa IGF-1, IGF-BP3, acid-labile subunit complex has been associated with short stature. Total IGF-1 levels were very low. The index case, with homozygosity for an acid-labile subunit mutation, did not show an increase in IGF-1 levels or an increase in growth rate during GH treatment.

IGF-1 Receptor Gene Abnormalities

Mutations of the IGF-1 receptor also compromise prenatal and postnatal growth. The phenotype does not appear to be as severe as that seen with absence of IGF-1. Adult heights are closer to the normal range, and affected patients do not have intellectual disability or deafness.

Clinical Manifestations

Congenital Hypopituitarism

The child with hypopituitarism is usually of normal size and weight at birth, although those with MPHD and genetic defects of the *GH1* or *GHR* gene have birth lengths that average 1 SD below the mean. Children with severe defects in GH production or action typically fall more than 4 SD below the mean for length by 1 yr of age. Those with less-severe deficiencies grow at rates below the 25th percentile for age and gradually diverge from normal height percentiles. Delayed closure of the epiphyses permits growth beyond the normal age when growth should be complete. Features of GH insensitivity, including Laron syndrome, are noted in Table 573.5 .

Table 573.5

Clinical Features of Growth Hormone Insensitivity, Including Classic Laron Syndrome

GROWTH AND DEVELOPMENT
Near-normal birthweight
Slightly decreased birthweight
Severe postnatal growth failure
Delayed bone age (may be advanced relative to height age)
Micropenis in childhood; normal for body size in adults
Puberty may be delayed 3-7 yr
Normal sexual function and fertility
OTHER PHYSICAL CHARACTERISTICS
Sparse hair (before age 7 yr)
Frontal bossing
Normal head circumference
Small facies (resulting in craniofacial disproportion)
Hypoplastic nasal bridge
Shallow orbits
Delayed dentition
Blue sclerae
High-pitched voice
Hip dysplasia
Limited extension in elbows
LATE FINDINGS/OTHER COMPLICATIONS
Hypoglycemia in infants and children (fasting symptoms in some adults)
Delayed walking and motor milestones
Avascular necrosis of femoral head
Thin, prematurely aged skin
Osteopenia

From Sperling MA: *Pediatric endocrinology* , ed 4, Philadelphia, 2014, Elsevier. Box 10.5.

Infants with congenital defects of the pituitary or hypothalamus may present with neonatal emergencies such as apnea, cyanosis, or severe hypoglycemia with or without seizures. Prolonged neonatal cholestatic jaundice is common. It involves elevation of conjugated and unconjugated bilirubin and may be associated with giant cell neonatal hepatitis. Nystagmus can suggest septo-optic dysplasia (see Chapter 591). Micropenis in boys provides an additional diagnostic clue. Deficiency of GH may be accompanied by hypoadrenalism (see Chapter 593) and hypothyroidism (see Chapter 581), as well as gonadotropin deficiency (see Chapters 601.2 and 604.2).

On physical examination, the head is round and the face is short and broad. The frontal bone is prominent, and the bridge of the nose is depressed and saddle shaped. The nose is small, and the nasolabial folds are well developed. The mandible and the chin are underdeveloped, and the teeth, which erupt late, are often crowded. The neck is short and the larynx is small. The voice is high-pitched and remains high after puberty. The extremities are well proportioned, with small hands and feet. *Weight for height is usually normal, but an excess of body fat and a deficiency of muscle mass contribute to a pudgy appearance.* The genitals are usually small for age, and sexual maturation may be delayed or absent. Facial, axillary, and pubic hair usually is lacking, and the scalp hair is fine. Intelligence is usually normal for age, unless there are other structural brain abnormalities, and the children may seem precocious compared with children of a similar size.

Acquired Hypopituitarism

The child is normal initially, and manifestations similar to those seen in idiopathic pituitary growth failure gradually appear and progress. When complete or almost complete destruction of the pituitary gland occurs, signs of pituitary insufficiency are present. Atrophy of the adrenal cortex, thyroid, and gonads results in loss of weight, asthenia, sensitivity to cold, mental torpor, and absence of sweating. Sexual maturation fails to take place or regresses if already present. There may be atrophy of the gonads and genital tract with amenorrhea and loss of pubic and axillary hair. There is a tendency to hypoglycemia. Growth slows dramatically. Diabetes insipidus (see Chapter 574) may be present but can by obscured by the development of central adrenal insufficiency.

If the lesion is an expanding tumor, symptoms such as headache, vomiting, visual disturbances, pathologic sleep patterns, decreased school performance, seizures, polyuria, and growth failure can occur. Slowing of growth can antedate neurologic signs and symptoms, especially with craniopharyngioma. In other cases, evidence of pituitary insufficiency may first appear after surgical intervention. In children with craniopharyngioma, visual field defects, optic atrophy, papilledema, obesity, and cranial nerve palsy are common.

Laboratory Findings

GH deficiency should be suspected in children with severe postnatal growth failure (Table 573.6). Criteria for short stature include height below the 1st percentile for age and sex or height >2 SD below sex-adjusted mid-parent height. Acquired GH deficiency can occur at any age, and when it is of acute onset, height may be within the normal range. In both congenital and acquired

GH deficiency, height velocity will be low relative to sex- and bone age–matched peers. A strong clinical suspicion is important in establishing the diagnosis because laboratory measures of GH sufficiency lack specificity. Observation of low serum levels of IGF-1 and the GH-dependent IGF-BP3 can be helpful, but IGF-1 and IGF-BP3 levels should be matched to normal values for skeletal age rather than chronological age. Values in the upper part of the normal range for age effectively exclude GH deficiency. IGF-1 values in the lower part of the normal range may occur in normally growing children, children with impaired nutrition, or in those with hypopituitarism. The expected range for IGF-1 in normal and GH-deficient children overlaps somewhat during infancy and early childhood. IGF-1 levels in isolation should not be used to diagnose GH deficiency.

Table 573.6

Evaluation of Suspected Growth Hormone Deficiency

History	• Birth weight and length • Obstetric complications • Neonatal hypoglycemia • Prolonged neonatal jaundice/giant cell hepatitis • Review of systems for systemic illness • Diet history
Physical exam	• Linear growth failure (may be the only clinical feature present) Proportionate short stature Low height velocity • Weight for length appropriate or increased • Micropenis in males • Small midface • High-pitched voice • Delayed dental eruption
Imaging	• Radiologic evaluation of bone age • Central nervous system imaging to evaluate the hypothalamus/pituitary and to exclude other conditions
Laboratory evaluation	• Measurements of IGF-1 and IGF-binding protein levels • Assess thyroid function • Exclude chronic medical illness CBC, metabolic profile, inflammatory markers, celiac testing, urinalysis • Determination of peak GH levels after stimulation test
Treatment Considerations	• Replacement with rhGH • Dosage adjustment IGF-1 Height velocity Pubertal status Body weight • Predictors of improved response to treatment Early initiation of treatment Higher rhGH dose

	• Monitor during treatment Height velocity IGF-1 levels Glucose metabolism Skeletal age Thyroid function, adrenal function

GH, Growth hormone; *IGF,* insulin-like growth factor; *rhGH,* human recombinant growth hormone.

Definitive diagnosis of GH deficiency traditionally requires demonstration of absent or low levels of GH in response to stimulation, but provocative testing may be omitted if the patient has the expected auxologic findings, a documented hypothalamic or pituitary defect, and at least one other pituitary hormone deficiency. A variety of provocative tests have been devised that rapidly increase the level of GH in normal children. These include administration of insulin, arginine, clonidine, levodopa, or glucagon. Because thyroid hormone is a prerequisite for normal GH synthesis, it must always be assessed before provocative GH testing. In chronic GH deficiency, the demonstration of subnormal linear growth, a delayed skeletal age, and low peak levels of GH (<10 ng/mL) in each of 2 provocative tests are compatible with GH deficiency. In acute GH deficiency, a high clinical suspicion of GH deficiency and low peak levels of GH (<10 ng/mL) in each of 2 provocative tests are compatible with GH deficiency. This rather arbitrary cutoff point is higher than the criteria used for diagnosis of adult GH deficiency. There is no consensus regarding adoption of criteria that take into account age, sex, and GH assay characteristics. Some studies indicate that many GH-sufficient prepubertal children fail to achieve GH values >10 ng/mL with 2 pharmacologic tests; pre-test, short-term sex steroid priming has been proposed to increase the diagnostic specificity of this testing.

In addition to establishing the diagnosis of GH deficiency, it is necessary to examine other pituitary functions. Levels of TSH, free thyroxine or total thyroxine with T_3 resin uptake, ACTH, cortisol, gonadotropins, and gonadal steroids might provide evidence of other pituitary hormonal deficiencies. Antidiuretic hormone deficiency may be established by appropriate studies.

Radiologic Findings

Neurologic imaging should be obtained when the cause of hypopituitarism is not known. CT is appropriate for recognizing suprasellar calcification associated with craniopharyngiomas and bony changes accompanying histiocytosis. MRI provides a much more detailed view of hypothalamic and pituitary anatomy.

Many cases of severe early-onset MPHD show the triad of a small anterior pituitary gland, a missing or attenuated pituitary stalk, and an ectopic posterior pituitary bright spot at the base of the hypothalamus (Fig. 573.3). Subnormal anterior pituitary height, implying a small anterior pituitary, is common in genetic and idiopathic causes of IGHD. Craniopharyngiomas are common, and pituitary adenomas are rare in children as causes of acquired hypopituitarism. Both hypoplastic and markedly enlarged anterior pituitary glands are seen in patients with *PROP1* or *LHX3* mutations.

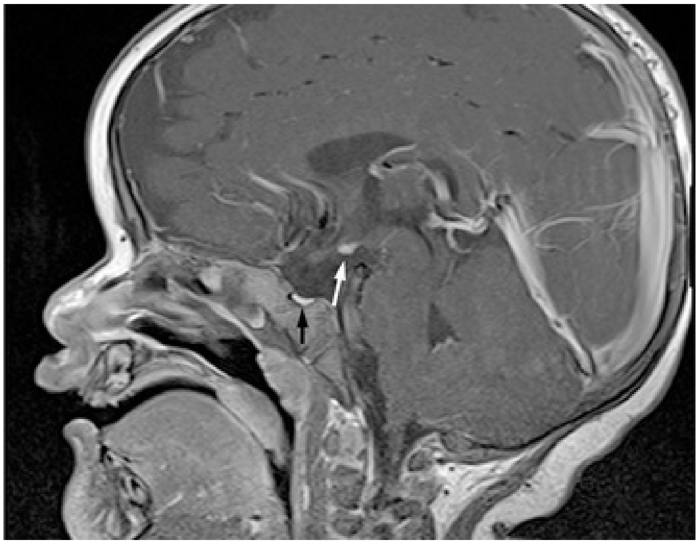

FIG. 573.3 Sagittal T1-weighted magnetic resonance imaging shows an ectopic posterior pituitary *(white arrow)* and a small anterior pituitary *(black arrow)* . (From Giannopoulou EZ, Rohrer T, Hoffmann P, et al: Solitary median maxillary central incisor, *J Pediatr* 167:770, 2015. App Fig. 1.)

Skeletal maturation may be assessed with a plain film of the hand (bone age) and is delayed in patients with IGHD and may be even more delayed when there is combined GH and TSH deficiency. Dual-photon x-ray absorptiometry shows deficient bone mineralization, deficiencies in lean body mass, and a corresponding increase in adiposity, but it is not routinely recommended in the evaluation of pediatric GH deficiency.

Differential Diagnosis

The causes of growth disorders are numerous. Differential diagnosis can be summarized broadly as follows: hormonal disorders, chronic illness, undernutrition, genetic conditions, nonsyndromic family trait, and constitutional delay of growth and development. Hormonal disorders include primary hypothyroidism and Cushing disease. Systemic conditions, such as inflammatory bowel disease, celiac disease, occult renal disease, and anemia must be considered. *Patients with systemic conditions often have a greater deficit of weight than length.* Severe psychosocial deprivation may result in growth failure that mimics GH deficiency. Many syndromic genetic conditions include short stature as a manifestation. Some genetic conditions, such as Turner syndrome and *SHOX* gene defects have variable phenotypes, and isolated short stature may be the clinical presentation.

Some otherwise normal children are short (i.e., >2.25 SD below the mean for age) and grow 5 cm/yr or less but have normal levels of GH in response to provocative tests and normal spontaneous episodic secretion; this is often termed *idiopathic short stature* . Most of these children show increased rates of growth when treated with GH in doses comparable with those used to treat children with hypopituitarism. Plasma levels of IGF-1 in these patients may be normal or low. Several groups of treated children have achieved final or near-final adult heights. Different studies have found changes in adult height that range from −2.5 to +7.5 cm compared with pretreatment predictions. There are no methods that can reliably predict which of these children will become taller in adulthood as a result of GH treatment and which will have compromised adult height.

Diagnostic strategies for distinguishing between permanent GH deficiency and other causes of impaired growth are imperfect. Children with a combination of genetic short stature and constitutional delay of growth have short stature, below-average growth rates, and delayed bone ages. Many of these children exhibit minimal GH secretory responses to provocative stimuli. When children in whom idiopathic or acquired GH deficiency is diagnosed are treated with human GH (hGH) and retested as adults, the majority have peak GH levels within the normal range.

Constitutional Growth Delay

Constitutional growth delay is one of the variants of normal growth commonly encountered by the pediatrician. Length and weight measurements of affected children are normal at birth, and growth is normal for the first 4-12 mo of life. Height is sustained at a lower percentile during childhood. The pubertal growth spurt is delayed, so their growth rates continue to decline after their classmates have begun to accelerate. Detailed questioning often reveals other family members (often 1 or both parents) with histories of short stature in childhood, delayed puberty, and eventual normal stature. IGF-1 levels tend to be low for chronological age but within the normal range for bone age. GH responses to provocative testing tend to be lower than in children with a more typical timing of puberty. The prognosis for these children to achieve normal adult height is guarded. Predictions based on height and bone age tend to overestimate eventual height to a greater extent in boys than in girls. Boys with >2 yr of pubertal delay can benefit from a short course of testosterone therapy to hasten puberty after 14 yr of age. The cause of this variant of normal growth is thought to be persistence of the relatively hypogonadotropic state of childhood.

Treatment

Recombinant hGH (rhGH) has been available by prescription since the 1980s. Multiple brands are marketed in the United States. They are therapeutically equivalent, with the major differences consisting of proprietary devices for subcutaneous injection and availability of solubilized liquid forms versus powders needing reconstitution before injection. At present, none of the products are available in long-acting forms; clinical trials to develop such products are underway.

The U.S. Food and Drug Administration (FDA) has approved 8 pediatric indications for rhGH treatment to promote linear growth. They are GH deficiency, Turner syndrome, chronic renal failure before transplantation, idiopathic short stature, small-for-gestational-age short stature, Prader-Willi syndrome, *SHOX* gene abnormality, and Noonan syndrome. FDA approval for a given indication does not ensure that a patient's insurance carrier will approve payment for the drug. Treatment should be started as soon as possible to narrow the gap in height between patients and their classmates during childhood and to have the greatest effect on mature height. The recommended initial dose of rhGH for treatment of GH deficiency is 0.16-0.24 mg/kg/wk (22 to 35 µg/kg/day). Higher doses have been used during puberty and for non-GH deficiency indications. RhGH is administered subcutaneously once daily. Maximal response to rhGH occurs in the 1st yr of treatment. Growth velocity during this 1st yr is typically above the 95th percentile for age. With each successive year of treatment, the growth rate tends to decrease. If growth rate drops below the 25th percentile, adherence should be evaluated before the dose is increased. IGF-1 may be measured as an objective assessment of adherence. GH therapy should be continued until near-final height is achieved. Criteria for stopping GH treatment include a decision by the patient that he or she is tall enough, a growth rate <1 inch/yr, and a bone age >14 yr in girls and >16 yr in boys.

Concurrent treatment with rhGH and a gonadotropin-releasing hormone agonist has been used in the hope that interruption of puberty will delay epiphyseal fusion and prolong growth. This strategy can increase adult height. It can also increase the discrepancy in physical maturity between GH-deficient children and their age peers and can impair bone mineralization. There have also been attempts to forestall epiphyseal fusion in boys by giving aromatase inhibitors, which inhibit the enzyme responsible for converting androgens to estrogens, and clinical trials to determine the efficacy of this approach are underway.

Some patients develop either primary or central hypothyroidism while under treatment with GH. Similarly, there is a risk of developing adrenal insufficiency as an associated component of hypopituitarism. If unrecognized, this can be fatal. *Periodic evaluation of thyroid and adrenal function is indicated for all patients diagnosed with GH deficiency.*

RhGH treatment may enhance the growth of non–GH-deficient children as well. Intensive investigation is in progress to determine the full spectrum of short children who may benefit from treatment with GH. The FDA approval for use of GH in idiopathic short stature specifies a height below the 1.2 percentile (−2.25 SD) for age and sex, a predicted height below the 5th percentile, and open epiphyses. Studies of the effect of GH treatment on adult height suggest a median gain of 2-3 inches, depending on dose and duration of treatment.

In children with MPHD, replacement should also be directed at other hormonal deficiencies. In TSH-deficient patients, thyroid hormone is given in full replacement doses. In ACTH-deficient patients, hydrocortisone should be prescribed in physiologic doses, about 8-12 mg/m^2 /day. Individualized dose adjustment is needed to minimize the risk of side effects associated with excess glucocorticoid administration and prevent symptoms of adrenal insufficiency. Increased doses are required to provide stress coverage during illness, or during and after surgical procedures. In patients with a deficiency of gonadotropins, gonadal steroids are given when bone age reaches the age at which puberty usually takes place. For infants with micropenis, one or two 3-mo courses of monthly intramuscular injections of 25 mg of testosterone cypionate or testosterone enanthate can bring the penis to normal size without an inordinate effect on osseous maturation.

Recombinant IGF-1 (mecasermin) is approved for use in the United States for primary IGF-1 deficiency. It is given subcutaneously twice a day. Side effects are similar to rhGH, except that mecasermin can cause hypoglycemia. The risk of hypoglycemia is reduced by giving the injections concurrently with a meal or snack. In some situations, its use may be more efficacious than use of GH. These conditions include abnormalities of the GH receptor and *STAT5b* genes that alter GH signaling downstream. It may have utility for severe GH deficiency in the rare patients who have developed clinically significant antibodies to administered rhGH. However, mecasermin is not an indicated treatment for the majority of patients with GH deficiency.

Complications and Adverse Effects of Growth Hormone Treatment

GH treatment influences glucose homeostasis. Fasting and postprandial insulin levels are characteristically low before treatment, and they normalize during GH replacement. GH treatment is associated with an increase in the risk for type 2 diabetes and no significant increase in the risk for type 1 diabetes.

Concerns have been raised about the safety of GH treatment in children who become deficient after treatment of brain tumors, leukemia, and other neoplasms. Long-term studies show no increase in risk of recurrence of craniopharyngioma, other brain tumors, or leukemia. At least 3 studies indicate an increased risk of second neoplasms in cancer survivors treated with GH.

An unconfirmed study documents an increased risk of hemorrhagic stroke and a 30% increase in mortality among young adults who received GH in childhood, particularly if the GH dose exceeds 0.35 mg/kg/wk (50 µg/kg/day).

Other reported side effects include pseudotumor cerebri, slipped capital femoral epiphysis, gynecomastia, coarsening of features, and worsening of scoliosis. The risk of late development of Creutzfeldt-Jakob disease was limited to recipients of contaminated lots of extracted pituitary GH. No comparable risks have been seen with rhGH, which is the only pharmacologic form of hGH currently in clinical use.

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CHAPTER 574

Diabetes Insipidus

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Diabetes insipidus (DI) manifests clinically with polyuria and polydipsia and can result from either vasopressin deficiency (central DI) or vasopressin insensitivity at the level of the kidney (nephrogenic DI [NDI]). Both central DI and NDI can arise from inherited defects of congenital or neonatal onset or can be secondary to a variety of causes (Table 574.1).

Table 574.1

Causes of Hypotonic Polyuria

CENTRAL (NEUROGENIC) DIABETES INSIPIDUS
Congenital (congenital malformations, autosomal dominant, arginine vasopressin [AVP] neurophysin gene mutations) Drug or toxin induced (ethanol, diphenylhydantoin, snake venom) Granulomatous (histiocytosis, sarcoidosis) Neoplastic (craniopharyngioma, germinoma, lymphoma, leukemia, meningioma, pituitary tumor; metastases) Infectious (meningitis, tuberculosis, encephalitis) Inflammatory, autoimmune (lymphocytic infundibuloneurohypophysitis) Trauma (neurosurgery, deceleration injury) Vascular (cerebral hemorrhage or infarction, brain death) Idiopathic
OSMORECEPTOR DYSFUNCTION
Granulomatous (histiocytosis, sarcoidosis) Neoplastic (craniopharyngioma, pinealoma, meningioma, metastases) Vascular (anterior communicating artery aneurysm or ligation, intrahypothalamic hemorrhage) Other (hydrocephalus, ventricular or suprasellar cyst, trauma, degenerative diseases) Idiopathic
INCREASED AVP METABOLISM
Pregnancy
NEPHROGENIC DIABETES INSIPIDUS
Congenital (X-linked recessive, AVP V2 receptor gene mutations, autosomal recessive or dominant, aquaporin-2 water channel gene mutations) Drug induced (demeclocycline, lithium, cisplatin, methoxyflurane) Hypercalcemia Hypokalemia

Infiltrating lesions (sarcoidosis, amyloidosis) Vascular (sickle cell anemia) Mechanical (polycystic kidney disease, bilateral ureteral obstruction) Solute diuresis (glucose, mannitol, sodium, radiocontrast dyes) Idiopathic
PRIMARY POLYDIPSIA
Psychogenic (schizophrenia, obsessive-compulsive behaviors) Dipsogenic (downward resetting of thirst threshold, idiopathic or similar lesions, as with central DI)

DI , Diabetes insipidus.

From Verbalis JG: Disorders of water balance. In Skorecki K, Chertow GM, Marsden PA, et al, editors: *Brenner & Rector's the kidney* , ed 10, Philadelphia, 2016, Elsevier, 2016. Table 16.2.

Physiology of Water Balance

The control of extracellular tonicity (osmolality) and volume within a narrow range is critical for normal cellular structure and function (see Chapter 68.2). Extracellular fluid tonicity is regulated almost exclusively by water intake and excretion, whereas extracellular volume is regulated by sodium intake and excretion. The control of plasma tonicity and intravascular volume involves a complex integration of endocrine, neural, behavioral, and paracrine systems (Fig. 574.1). Vasopressin, secreted from the posterior pituitary, is the principal regulator of tonicity, with its release largely stimulated by increases in plasma tonicity. Volume homeostasis is largely regulated by the renin-angiotensin-aldosterone system, with contributions from both vasopressin and the natriuretic peptide family.

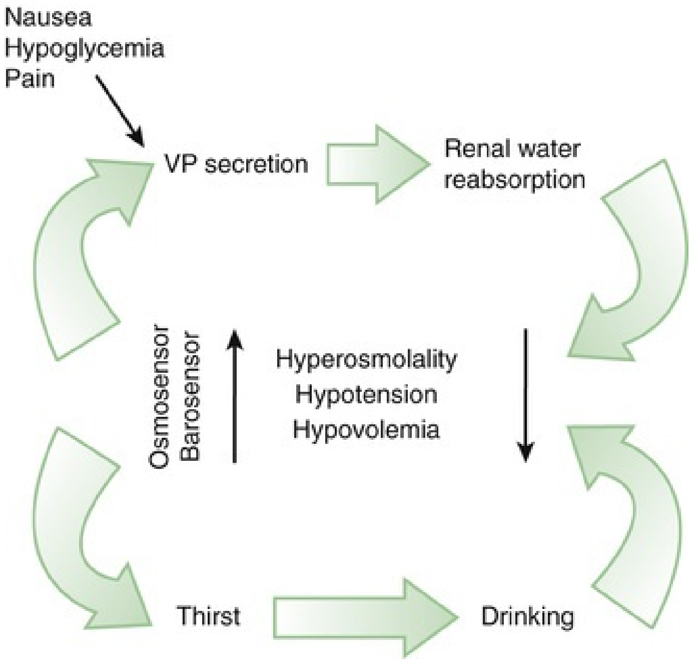

FIG. 574.1 Regulation of vasopressin *(VP)* secretion and serum osmolality. Hyperosmolality, hypovolemia, and hypotension are sensed by osmosensors, volume sensors, and barosensors, respectively. These stimulate both VP secretion and thirst. VP, acting on the kidney, causes increased reabsorption of water (antidiuresis). Thirst causes increased water ingestion. The results of these dual negative feedback loops cause a reduction in hyperosmolality or in hypotension or hypovolemia. Additional stimuli for VP secretion include nausea, hypoglycemia, and pain. (From Muglia LJ, Srivasta A, Majzoub JA: Disorders of the posterior pituitary. In Sperling MA, editor: *Pediatric endocrinology* , ed 4, Philadelphia, 2014, Elsevier, Fig. 11.6.)

Vasopressin, a 9-amino-acid peptide, has both antidiuretic and vascular pressor activity and is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. It is transported to the posterior pituitary via axonal projections, where it is stored awaiting release into the systemic circulation. The half-life of vasopressin in the circulation is 5 min. In addition to responding to osmotic stimuli, vasopressin is secreted in response to significant decreases in intravascular volume and pressure (minimum of 8% decrement) via afferent baroreceptor pathways arising from the aortic arch (carotid sinus) and volume receptor pathways in the cardiac atria and pulmonary veins. Osmotic and hemodynamic stimuli interact synergistically.

The sensation of thirst and the release of vasopressin are regulated by cortical and hypothalamic neurons. The thirst threshold is approximately 10 mOsm/kg higher (i.e., 293 mOsm/kg) than the osmotic threshold for vasopressin release.

Consequently, under conditions of hyperosmolality, vasopressin is released before thirst is initiated, allowing ingested water to be retained. Subsequently, anticipation of water ingestion by cortical and vasopressin-secreting neurons leads to a decrease in vasopressin release immediately before water ingestion, presumably to prevent subsequent hyponatremia. Chemoreceptors present in the oropharynx also downregulate vasopressin release following water ingestion. In addition, thirst drive decreases even before the ingested fluid lowers blood osmolality, presumably to prevent overdrinking leading to hyponatremia.

Vasopressin exerts its principal effect on the kidney via V2 receptors located primarily in the collecting tubule, the thick ascending limb of the loop of Henle, and the periglomerular tubules. The human V2 receptor gene is located on the long arm of the X chromosome (Xq28) at the locus associated with **congenital, X-linked, vasopressin-resistant DI.** Activation of the V2 receptor results in increases in intracellular cyclic adenosine monophosphate, which leads to the insertion of the aquaporin-2 water channel into the apical (luminal) membrane. This allows water movement along its osmotic gradient into the hypertonic inner medullary interstitium from the tubule lumen and excretion of concentrated urine. In contrast to aquaporin-2, aquaporin-3 and aquaporin-4 are expressed on the basolateral membrane of the collecting duct cells and aquaporin-1 is expressed in the proximal tubule. These channels may also contribute to urinary concentrating ability.

Atrial natriuretic peptide , initially isolated from cardiac atrial muscle, has a number of important effects on salt and water balance, including stimulation of natriuresis, inhibition of sodium resorption, and inhibition of vasopressin secretion. Atrial natriuretic peptide is expressed in endothelial cells and vascular smooth muscle, where it appears to regulate relaxation of arterial smooth muscle. Atrial natriuretic peptide is also expressed in the brain, along with other natriuretic family members; the physiologic role of these factors has yet to be defined.

Approach to the Patient With Polyuria, Polydipsia, and Hypernatremia

The cause of pathologic polyuria or polydipsia (exceeding 2 L/m^2 /24 hr) may be difficult to establish in children. Infants can present with irritability, failure to thrive, and intermittent fever. Patients with suspected DI should have a careful history taken, which should quantify the child's daily fluid intake and output and establish the voiding pattern, nocturia, and primary or secondary enuresis. A complete physical examination should establish the patient's hydration status, and the physician should search for evidence of visual and central nervous system dysfunction, as well as for other pituitary hormone deficiencies.

If pathologic polyuria or polydipsia is present, the following should be obtained: serum for osmolality, sodium, potassium, blood urea nitrogen, creatinine, glucose, and calcium; urine for osmolality, specific gravity, and glucose determination. The diagnosis of DI is established if the serum osmolality is >300 mOsm/kg, and the urine osmolality is <300 mOsm/kg. DI is unlikely if the serum osmolality is <270 mOsm/kg or the urine osmolality is >600 mOsm/kg. If the patient's serum osmolality is <300 mOsm/kg (but >270 mOsm/kg) and pathologic polyuria and polydipsia are present, a water deprivation test is indicated to establish the diagnosis of DI and to differentiate central from nephrogenic causes.

In the inpatient postneurosurgical setting, central DI is likely if hyperosmolality (serum osmolality >300 mOsm/kg) is associated with urine osmolality less than serum osmolality. It is important to distinguish between polyuria resulting from postsurgical central DI and polyuria resulting from the normal diuresis of fluids received intraoperatively. Both cases may be associated with a large volume (>200 mL/m^2 /hr) of dilute urine, although in patients with DI, the serum osmolality is high in comparison with patients undergoing postoperative diuresis.

Causes of Hypernatremia

Hypernatremia is discussed in Chapter 68.3 .

Central Diabetes Insipidus

Central DI can result from multiple etiologies, including genetic mutations in the vasopressin gene; trauma (accidental or surgical) to vasopressin neurons; congenital malformations of the hypothalamus or pituitary; neoplasms; infiltrative, autoimmune, and infectious diseases affecting vasopressin neurons or fiber tracts; and increased metabolism of vasopressin. In approximately 10% of children with central DI, the etiology is idiopathic. Other pituitary hormone deficiencies may be present (see Chapter 573). Over time, up to 35% of those with idiopathic central DI will develop other hormone deficiencies or have an underlying etiology identified.

Autosomal dominant central DI usually occurs within the first 5 yr of life and results from mutations in the vasopressin gene, *AVP* . A number of mutations can cause gene-processing defects in a subset of vasopressin-expressing neurons, which have been postulated to result in endoplasmic reticulum stress and cell death. **Wolfram syndrome,** which includes DI, diabetes mellitus, optic atrophy, and deafness, also results in vasopressin deficiency. Mutations in 2 genes, which give rise to endoplasmic reticulum proteins, are associated with this condition. Congenital brain abnormalities (see Chapter 609) such as **optic nerve hypoplasia syndrome** with agenesis of the corpus callosum, the Niikawa-Kuroki syndrome, holoprosencephaly, and familial pituitary hypoplasia with absent stalk may be associated with central DI and defects in thirst perception *(adipsia).* Empty sella syndrome, possibly resulting from unrecognized pituitary infarction, can be associated with DI in children.

Trauma to the base of the brain and neurosurgical intervention in the region of the hypothalamus or pituitary are common causes of central DI. The **triphasic response** following surgery refers to an initial phase of transient DI, lasting 12-48 hr, followed by a 2nd phase of syndrome of inappropriate antidiuretic hormone secretion (SIADH), lasting up to 10 days, which may be followed by permanent DI. The initial phase may be the result of local edema interfering with normal vasopressin secretion; the 2nd phase results from unregulated vasopressin release from dying neurons, whereas in the 3rd phase, permanent DI, results if more than 90% of the neurons have been destroyed.

Given the anatomic distribution of vasopressin neurons over a large area within the hypothalamus, tumors causing DI must either be very large and infiltrative or be strategically located near the base of the hypothalamus, where vasopressin axons converge before their entry into the posterior pituitary. Germinomas and pinealomas typically arise in this region and are among the most common primary brain tumors associated with DI. Germinomas can be very small and undetectable by MRI for several years following the onset of polyuria. Quantitative measurement of α-fetoprotein and β-human chorionic gonadotropin, often secreted by germinomas, should be performed in children with idiopathic or unexplained DI, in addition to serial MRI scans. Craniopharyngiomas and optic gliomas can also cause central DI when they are very large, although this is more often a postoperative complication of the treatment for these tumors (see Chapter 524). Hematologic malignancies, such as acute myelocytic leukemia, can cause DI via infiltration of the pituitary stalk and sella.

Langerhans cell histiocytosis (see Chapter 534.1) and lymphocytic hypophysitis are common types of infiltrative disorders causing central DI, with **hypophysitis** as the cause in 50% of cases of "idiopathic" central DI. Infections involving the base of the brain (see Chapter 621), including meningitis (meningococcal, cryptococcal, listerial, toxoplasmal), congenital cytomegalovirus infection, and nonspecific inflammatory diseases of the brain may give rise to central DI that is often transient. Drugs associated with the inhibition of vasopressin release include ethanol, phenytoin, opiate antagonists, halothane, and α-adrenergic agents.

Nephrogenic Diabetes Insipidus

NDI can result from genetic or acquired causes. Genetic causes are less common but more severe than acquired forms of NDI. The polyuria and polydipsia associated with genetic NDI usually occur within the 1st several weeks of life but may become apparent only after weaning or with longer periods of nighttime sleep. Many infants initially present with fever, vomiting, and dehydration. Failure to thrive may be secondary to the ingestion of large amounts of water, resulting in caloric malnutrition. Long-standing ingestion and excretion of large volumes of water can lead to nonobstructive hydronephrosis, hydroureter, and megabladder.

Congenital X-linked NDI results from inactivating mutations of the vasopressin V2 receptor, *AVPR2* . **Congenital autosomal recessive NDI** results from defects in the aquaporin-2 gene, *AQP2* . An **autosomal dominant form of NDI** is associated with processing mutations of the aquaporin-2 gene.

Acquired NDI can result from hypercalcemia or hypokalemia and is associated with lithium, demeclocycline, foscarnet, clozapine, amphotericin, methicillin, and rifampin. Impaired renal concentrating ability can also be seen with ureteral obstruction, chronic renal failure, polycystic kidney disease, medullary cystic disease, Sjögren syndrome, and sickle cell disease. Decreased protein or sodium intake or excessive water intake, as in primary polydipsia, can lead to diminished tonicity of the renal medullary interstitium and NDI.

Treatment of Central Diabetes Insipidus

Fluid Therapy

With an intact thirst mechanism and free access to oral fluids, a person with complete DI can maintain plasma osmolality and sodium in the high normal range, although at great inconvenience. Neonates and young infants are often best treated solely with fluid therapy, given their requirement for large volumes (~3 L/m^2 /24 hr) of nutritive fluid. The use of vasopressin analogs in patients with obligate high fluid intake is difficult given the risk of life-threatening hyponatremia. Although not FDA approved, the use of diluted parenteral and lyophilized long-acting vasopressin analog DDAVP (desmopressin) has been successfully administered to infants with central DI both subcutaneously and orally without causing severe hyponatremia. Patients with both central and NDI should ingest a diet without excessive solute (e.g., sodium chloride) to help decrease urine output when vasopressin action wanes.

Vasopressin Analogs

Treatment of central DI in older children is best accomplished with the use of DDAVP. DDAVP is available in an intranasal preparation (onset 5-10 min) and as tablets (onset 15-30 min). The intranasal preparation of DDAVP (10 µg/0.1 mL) can be administered by rhinal tube (allowing dose titration) or by nasal spray (10 µg/puff). Use of DDAVP oral tablets requires at least a 10-fold increase in the dosage compared with the intranasal preparation. Oral dosages of 25-300 µg every 8-12 hr are safe and effective in children. The appropriate dosage and route of administration is determined empirically based on the desired length of antidiuresis and patient preference. The use of oral DDAVP for the treatment of enuresis in older children should be regarded as a temporizing measure, given it does not affect the underlying condition, and should be used with great caution given the risk of hyponatremia if water intake exceeds the capacity for renal clearance. To prevent water intoxication, patients should have at least 1 hr of urinary breakthrough between doses each day and be advised to drink only in response to thirst sensation, if present. The use of DDAVP nasal spray for childhood enuresis is no longer approved due to its risk of causing hyponatremia.

Aqueous Vasopressin

Central DI of acute onset following neurosurgery is best managed with continuous administration of synthetic aqueous vasopressin (Pitressin). Under most circumstances, total fluid intake must be limited to 1 L/m^2 /24 hr during antidiuresis. A typical dosage for intravenous vasopressin therapy is 1.5 mU/kg/hr, which results in a blood vasopressin concentration of approximately 10 pg/mL. On occasion, following hypothalamic (but not transsphenoidal) surgery, higher initial concentrations of vasopressin may be required to treat acute DI, which has been attributed to the release of a vasopressin inhibitory substance. Vasopressin concentrations >1,000 pg/mL should be avoided because they can cause cutaneous necrosis, rhabdomyolysis, cardiac rhythm disturbances, and hypertension. Postneurosurgical patients treated with vasopressin infusion should be switched from intravenous to oral fluids as soon as possible to allow thirst sensation, if intact, to help regulate osmolality.

Treatment of Nephrogenic Diabetes Insipidus

The treatment of acquired NDI focuses on eliminating, if possible, the underlying disorder, such as offending drugs, hypercalcemia, hypokalemia, or ureteral obstruction. Congenital NDI is often difficult to treat. The main goals are to ensure the intake of adequate calories for growth and to avoid severe dehydration. Foods with the highest ratio of caloric content to osmotic load (Na <1 mmol/kg/24 hr) should be ingested to maximize growth and to minimize the urine volume required to excrete the solute load. However, even with the early institution of therapy, growth failure and developmental disabilities are common.

Pharmacologic approaches to the treatment of NDI include the use of thiazide diuretics and are intended to decrease the overall urine output. Thiazides appear to induce a state of mild volume depletion by enhancing sodium excretion at the expense of water and by causing a decrease in the glomerular filtration rate, which results in proximal tubular sodium and water reabsorption. Indomethacin and amiloride may be used in combination with thiazides to further reduce polyuria. High-dose DDAVP therapy, in combination with indomethacin, has been used in some subjects with NDI. This treatment could prove useful in patients with genetic defects in the V2 receptor associated with a reduced binding affinity for vasopressin.

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CHAPTER 575

Other Abnormalities of Arginine Vasopressin Metabolism and Action

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Hyponatremia (serum sodium <130 mEq/L) in children is usually associated with severe systemic disorders and is most often a result of intravascular volume depletion, excessive salt loss, or hypotonic fluid overload, especially in infants (see Chapter 68).

The initial approach to the patient with hyponatremia begins with determination of the volume status. A careful review of the patient's history, physical examination (including changes in weight), and vital signs helps to determine whether the patient is hypovolemic or hypervolemic. Supportive evidence includes laboratory data such as serum electrolytes, blood urea nitrogen, creatinine, uric acid, urine sodium, specific gravity, and osmolality (see Chapter 68 ; Tables 575.1 and 575.2).

Table 575.1

Differential Diagnosis of Hyponatremia

DISORDER	INTRAVASCULAR VOLUME STATUS	URINE SODIUM
Systemic dehydration	Low	Low
Decreased effective plasma volume	Low	Low
Primary salt loss (nonrenal)	Low	Low
Primary salt loss (renal)	Low	High
SIADH	High	High
Cerebral salt wasting	Low	Very high
Decreased free water clearance	Normal or high	Normal or high
Primary polydipsia	Normal or high	Normal
Runner's hyponatremia	Low	Low
NSIAD	High	High
Pseudohyponatremia	Normal	Normal
Factitious hyponatremia	Normal	Normal

NSIAD , Nephrogenic syndrome of inappropriate antidiuresis; *SIADH* , syndrome of inappropriate antidiuretic hormone secretion.

Table 575.2

Clinical Parameters to Distinguish Among Syndrome of Inappropriate Antidiuretic Hormone Secretion, Cerebral Salt Wasting, and Central Diabetes Insipidus

CLINICAL PARAMETER	SIADH	CEREBRAL SALT WASTING	CENTRAL DI
Serum sodium	Low	Low	High
Urine output	Normal or low	High	High
Urine sodium	High	Very high	Low
Intravascular volume status	Normal or high	Low	Low
Vasopressin level	High	Low	Low

DI , Diabetes insipidus; *SIADH* , syndrome of inappropriate antidiuretic hormone secretion.

Causes of Hyponatremia

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by hyponatremia, an inappropriately concentrated urine (>100 mOsm/kg), normal or slightly elevated plasma volume, normal-to-high urine sodium, and low serum uric acid. SIADH is uncommon in children, and most cases result from excessive administration of vasopressin in the treatment of central diabetes insipidus. It can also occur with encephalitis, brain tumors, head trauma, psychiatric disease, prolonged nausea, pneumonia, tuberculous meningitis and AIDS and in the postictal phase following generalized seizures (Table 575.3). SIADH is the cause of the hyponatremic 2nd phase of the triphasic response seen after hypothalamic-pituitary surgery. It is found in up to 35% of patients 1 wk after surgery and can result from retrograde neuronal degeneration with cell death and vasopressin release. Common drugs that have been shown to increase vasopressin secretion or mimic vasopressin action, resulting in hyponatremia, include oxcarbazepine, carbamazepine, chlorpropamide, vinblastine, vincristine, and tricyclic antidepressants.

Table 575.3

Disorders Associated With Syndrome of Inappropriate Antidiuretic Hormone Secretion

CARCINOMAS	PULMONARY DISORDERS	CENTRAL NERVOUS SYSTEM DISORDERS	OTHER DISORDERS
Thymoma Lymphoma Ewing sarcoma Oropharyngeal tumor	Viral pneumonia Bacterial pneumonia Pulmonary abscess Tuberculosis Aspergillosis Positive pressure breathing Asthma Pneumothorax Cystic fibrosis	Encephalitis (viral or bacterial) Meningitis (viral, bacterial, tuberculous, fungal) Head trauma Brain abscess Guillain-Barré syndrome Subarachnoid hemorrhage or subdural hematoma Cerebellar and cerebral atrophy Cavernous sinus thrombosis Neonatal hypoxia Shy-Drager syndrome Rocky Mountain spotted fever Delirium tremens Cerebrovascular accident (cerebral thrombosis or hemorrhage) Acute psychosis Peripheral neuropathy Multiple sclerosis	AIDS Prolonged exercise Idiopathic (in older individuals) Nephrogenic Acute intermittent porphyria

Modified from Verbalis JG: Disorders of water balance. In Skorecki K, Chertow GM, Marsden PA, et al, editors: *Brenner & Rector's the kidney* , ed 10, Philadelphia, 2016, Elsevier. Table 16.6.

Nephrogenic Syndrome of Inappropriate Antidiuresis

Gain-of-function mutations in the V2 vasopressin receptor gene, *AVPR2*, have been described in male infants presenting with an SIADH-like clinical picture with undetectable vasopressin levels. Activating mutations in the aquaporin-2 gene, *AQP2*, might also give rise to the same syndrome but have not yet been described.

Systemic Dehydration

The initial manifestation of systemic dehydration is often hypernatremia and hyperosmolality, which subsequently lead to the activation of vasopressin secretion and a decrease in water excretion. As dehydration progresses, hypovolemia and/or hypotension become a major stimulus for vasopressin release, further decreasing free water clearance. Excessive free water intake with ongoing salt loss can also produce hyponatremia. Urinary sodium excretion is low (usually <10 mEq/L) owing to a low glomerular filtration rate and concomitant activation of the renin-angiotensin-aldosterone system, unless primary renal disease or diuretic therapy is present.

Primary Salt Loss

Hyponatremia can result from the primary loss of sodium chloride as seen in specific disorders of the kidney (congenital polycystic kidney disease, acute interstitial nephritis, chronic renal failure), gastrointestinal tract (gastroenteritis), and sweat glands (cystic fibrosis). The hyponatremia is not solely caused by the salt loss, because the latter also causes hypovolemia, leading to an increase in vasopressin. Mineralocorticoid deficiency (hypoaldosteronism), pseudohypoaldosteronism (genetic or sometimes seen in children with urinary tract obstruction or infection), and diuretics can also result in loss of sodium chloride. Low aldosterone states are associated with salt wasting, hypovolemia, hyponatremia, hyperkalemia, and failure to thrive (Table 575.4).

Table 575.4

Genetic Mutations Associated With Hypoaldosteronism/Pseudohypoaldosteronism (Type IV Renal Tubular Acidosis)

GENE CHROMOSOME OMIM	PATHOPHYSIOLOGY	MUTATION–CLINICAL MANIFESTATIONS–OMIM–INHERITANCE
PRIMARY HYPOALDOSTERONISM		
CYP21A2 —cytochrome P450, subfamily XXIA, polypeptide 2 6p21.3 613815	P450c21—steroid 21-hydroxylase that converts 17 α-hydroxyprogesterone to 11-deoxycortisol and progesterone to 11-deoxycorticosterone in the adrenal zona fasciculata	Loss-of-function mutations decrease synthesis of cortisol and aldosterone, the latter resulting in the salt-losing form of classical congenital adrenal hyperplasia, AR–201910
CYP11B2 —cytochrome P450, subfamily XIB, polypeptide 2 8q21 124080	P450c11B2—aldosterone synthase/corticosterone methyoxidase types I and II expressed only in the zona glomerulosa; hydroxylates deoxycorticosterone at carbon-11 and corticosterone at carbon-18 and oxidizes 18-hydroxycorticosterone to aldosterone	Loss-of-function mutations associated with severe salt loss and volume depletion but not with abnormalities of genital formation or glucocorticoid synthesis AR (CMOI 203400; CMOII 610600)
PSEUDOHYPOALDOSTERONISM TYPE I		
NR3C2 —nuclear receptor subfamily	Ligand-activated nuclear transcription factor that transmits aldosterone-mediated control of gene	Loss-of-function mutations lead to mineralocorticoid resistance and

3, group C, member 2 (MR-mineralocorticoid receptor), 4q31.1 600983	expression by binding to the mineralocorticoid response element in the promoter region of the target gene	pseudohypoaldosteronism type I, AD–177735
SCNN1A —sodium channel, non–voltage-gated, α-subunit 12p13.31 600228	Inactivating mutation of α-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
SCNN1B —sodium channel, non–voltage-gated, β-subunit 16p12.2 600760	Inactivating mutation of β-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
SCNN1G —sodium channel, non–voltage-gated, γ-subunit 16p12.2 600761	Inactivating mutation of γ-subunit of the epithelial sodium channel	Pseudohypoaldosteronism type I, AR–264350
PSEUDOHYPOALDOSTERONISM TYPE II		
WNK4 —protein kinase, lysine-deficient 4 17q21.31 601844	Multifunctional serine-threonine protein kinase whose substrate is SLC12A3, the thiazide-sensitive sodium/chloride cotransporter (NCCT)—OMIM 600968—that also regulates lysosomal degradation of NCCT and endocytosis of the KCNJ1 potassium channel	Pseudohypoaldosteronism type IIB, AD–614491
WNK1 —protein kinase, lysine-deficient 1 12p13.33 605232	Serine-threonine protein kinase that inactivates WNK4 by phosphorylating its kinase domain	Pseudohypoaldosteronism type IIC, AD–614492
KLH3 —Kelch-like 3 5q31.2 605775	Adaptor protein within the ubiquitination sequence that links WNK1 and WNK4 to CUL3	Pseudohypoaldosteronism type IID, AD/AR–614495
CUL3 —Cullin 3 2q36.2 603136	Scaffold protein that links to RING-box E3 ligase facilitating WNK4 ubiquitination and proteasomal destruction of WNK4	Pseudohypoaldosteronism type IIE, AD–614496

AD , Autosomal dominant; *AR* , autosomal recessive; *CMO* , corticosterone methyloxidase; *OMIM* , Online Mendelian Inheritance in Man.

From Root AW: Disorders of aldosterone synthesis, secretion, and cellular function, *Curr Opin Pediatr* 26:480–486, 2014. Table 1.

Decreased Effective Plasma Volume

Hyponatremia can result from decreased effective plasma volume, as found in congestive heart failure, cirrhosis, nephrotic syndrome, positive pressure mechanical ventilation, severe burns, bronchopulmonary dysplasia in neonates, cystic fibrosis with obstruction, and severe asthma. The resulting decrease in cardiac output leads to reduced water and salt excretion, as with systemic dehydration, and an increase in vasopressin secretion. In patients with impaired cardiac output and elevated atrial volume (congestive heart failure, lung disease), atrial natriuretic peptide concentrations are elevated further, leading to hyponatremia by promoting natriuresis. However, owing to the marked elevation of aldosterone in these patients, their urine sodium remains low (<20 mEq/L) despite this. Unlike dehydrated patients, these patients also have excess total body sodium from activation of the renin-angiotensin-aldosterone system and can demonstrate peripheral edema as well.

Primary Polydipsia (Increased Water Ingestion)

In patients with normal renal function, the kidney can excrete dilute urine with an osmolality as low as 50 mOsm/kg. To excrete a daily solute load of 500 mOsm/m^2 , the kidney must produce 10 L/m^2 of urine per day. Therefore, to avoid hyponatremia, the maximum amount of water a person with normal renal function can consume daily is 10 L/m^2 . However, neonates cannot dilute their urine to this degree, putting them at risk for water intoxication if water intake exceeds 4 L/m^2 /day (approximately 60 mL/hr in a newborn). Infants may develop transient hyponatremic seizures after being fed pure water without electrolytes rather than breast milk or formula.

Decreased Free Water Clearance

Hyponatremia as a consequence of decreased renal free water clearance, even in the absence of an increase in vasopressin secretion, can result from adrenal insufficiency or thyroid deficiency or can be related to a direct effect of drugs on the kidney. Both mineralocorticoids and glucocorticoids are required for normal free water clearance in a vasopressin-independent manner. In patients with unexplained hyponatremia, adrenal and thyroid insufficiency should be considered. In addition, patients with coexisting adrenal failure and diabetes insipidus might have no symptoms of the latter until glucocorticoid therapy unmasks the need for vasopressin replacement. Certain drugs can inhibit renal water excretion through direct effects on the nephron, thus causing hyponatremia; these drugs include high-dose cyclophosphamide, vinblastine, cisplatinum, carbamazepine, and oxcarbazepine.

Cerebral Salt Wasting

Cerebral salt wasting is a controversial topic and appears to be the result of hypersecretion of atrial natriuretic peptide and is seen primarily with central nervous system disorders, including brain tumors, head trauma, hydrocephalus, neurosurgery, cerebrovascular accidents, and brain death. Hyponatremia is accompanied by elevated urinary sodium excretion (often >150 mEq/L), excessive urine output, hypovolemia, normal or high uric acid, suppressed vasopressin, and elevated atrial natriuretic peptide concentrations (>20 pmol/L). Thus it is distinguished from SIADH, in which normal or decreased urine output, euvolemia, only modestly elevated urine sodium concentration, and an elevated vasopressin level occur. The distinction between cerebral salt wasting and SIADH is important because the treatment of the 2 disorders differs markedly. However, its existence has been questioned because few patients with the suspected syndrome have documented hypovolemia and thus might truly have SIADH.

Runner's Hyponatremia

Excess fluid ingestion during long-distance running (e.g., marathon running) can result in severe hyponatremia from hypovolemia-induced activation of arginine vasopressin secretion coupled with excessive water ingestion and is correlated with weight gain, long racing time, and extremes of body mass index.

Pseudohyponatremia and Other Causes of Hyponatremia

Pseudohyponatremia can result from hypertriglyceridemia (see Chapter 68.3). Elevated lipid levels result in a relative decrease in serum water content. As electrolytes are dissolved in the aqueous phase of the serum, they appear low when expressed as a fraction of the total serum volume. However, as a fraction of serum water, electrolyte content is normal. Modern laboratory methods that measure sodium concentration directly, independent of sample volume, do not cause this anomaly. Factitious hyponatremia can result from obtaining a blood sample downstream to the site of intravenous hypotonic fluid infusion.

Hyponatremia is also associated with hyperglycemia, which causes the influx of water into the intravascular space. Serum sodium decreases by 1.6 mEq/L for every 100 mg/dL increment in blood glucose >100 mg/dL. Glucose is not ordinarily an osmotically active agent and does not stimulate vasopressin release, probably because it can equilibrate freely across plasma membranes. However, in the presence of insulin deficiency and hyperglycemia, glucose acts as an osmotic agent, presumably because its normal intracellular access to osmosensor sites is prevented. Under these circumstances, an osmotic gradient exists, stimulating vasopressin release.

Treatment

Patients with systemic dehydration and hypovolemia should be rehydrated with salt-containing fluids such as normal saline or lactated Ringer solution. Because of activation of the renin-angiotensin-aldosterone system, the administered sodium is avidly conserved, and water diuresis quickly ensues as volume is restored and vasopressin concentrations decrease. Under these conditions, caution must be taken to prevent a too-rapid correction of hyponatremia (with a goal increase of <0.5 mEq/L/hr), which can result in central pontine myelinolysis characterized by discrete regions of axonal demyelination and the potential for irreversible brain damage.

Hyponatremia from a decrease in effective plasma volume caused by cardiac, hepatic, renal, or pulmonary dysfunction is more difficult to reverse. The most effective therapy is treatment of the underlying systemic disorder. For example, patients weaned from positive pressure ventilation undergo a prompt water diuresis and resolution of hyponatremia as cardiac output is restored and vasopressin concentrations decrease. Vaptans are a class of small-molecule arginine vasopressin V2 receptor antagonists (aquaretics) useful for the treatment of hypervolemic hyponatremia associated with severe congestive heart failure and chronic liver failure. Although these agents successfully increase plasma sodium, they also lead to increased thirst and plasma vasopressin levels, which can limit their effectiveness, can increase serum sodium more rapidly than is safe, and are not FDA approved for use in children.

Patients with hyponatremia from primary salt loss require supplementation with sodium chloride and fluids. Initially, intravenous replacement of urine volume with fluid containing sodium chloride, 150-450 mEq/L depending on the degree of salt loss, may be necessary; oral salt supplementation may be required subsequently. This treatment contrasts with that of SIADH, in which water restriction without sodium supplementation is the mainstay.

Emergency Treatment of Hyponatremia

The development of acute hyponatremia (onset <12 hr) or a serum sodium concentration <120 mEq/L may be associated with lethargy, psychosis, coma, or generalized seizures, especially in younger children. Acute hyponatremia can cause cell swelling and lead to neuronal dysfunction or to cerebral herniation. *The emergency treatment of cerebral dysfunction resulting from acute hyponatremia includes water restriction and can require rapid correction with hypertonic 3% sodium chloride*. If hypertonic saline treatment is undertaken, the serum sodium should be raised only high enough to cause an improvement in mental status and, in no case, faster than 0.5 mEq/L/hr or 12 mEq/L/24 hr.

Treatment of Syndrome of Inappropriate Antidiuretic Hormone

Chronic SIADH is best treated by oral fluid restriction. With full antidiuresis (urine osmolality of 1,000 mOsm/kg), a normal daily obligate renal solute load of 500 mOsm/m^2 would be excreted in 500 mL/m^2 water. This, plus a daily nonrenal water loss of 500 mL/m^2 , would require that oral fluid intake be limited to 1,000 mL/m^2 /24 hr to avoid hyponatremia. In young children, this degree of fluid restriction might not provide adequate calories for growth. In this situation, a vaptan such as tolvaptan, although not FDA approved in children and may cause initial correction of hyponatremia at too rapid a rate, may allow sufficient fluid intake for normal growth without concomitant hyponatremia. Urea has also been safely used to induce an osmotic diuresis in infants and children.

Treatment of Cerebral Salt Wasting

Treatment of patients with cerebral salt wasting consists of restoring intravascular volume with sodium chloride and water, as for the treatment of other causes of systemic dehydration. The underlying cause of the disorder, which is usually due to acute brain injury, should also be treated if possible. Treatment involves the ongoing replacement of urine sodium losses volume for volume.

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CHAPTER 576

Hyperpituitarism, Tall Stature, and Overgrowth Syndromes

Omar Ali

Hyperpituitarism

Primary hypersecretion of pituitary hormones rarely occurs in the pediatric population and should be distinguished from secondary hyperpituitarism, which occurs as a physiologic response to target hormone deficiencies resulting in decreased hormonal feedback, such as in hypogonadism, hypoadrenalism, or hypothyroidism. In secondary hyperpituitarism, chronic pituitary hypersecretion occurs in response to target hormone deficiencies and leads to pituitary hyperplasia, which can enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such enlargements should not be confused with primary pituitary tumors; they disappear and elevated pituitary hormone levels readily suppress to normal when the underlying hormone deficiency is treated by replacement of end-organ hormones.

Primary hypersecretion of pituitary hormones by adenoma is relatively uncommon in childhood. The most commonly diagnosed adenoma during childhood is prolactinoma, followed by corticotropinoma, and then somatotropinoma, which secrete prolactin, corticotropin, and growth hormone (GH), respectively. There are a handful of case reports of thyrotropinoma in children and adolescents. There are no pediatric reports of gonadotropinoma, but hypothalamic hamartomas that secrete excess gonadotropin-releasing hormone are one of the causes of precocious puberty. In very rare cases, pituitary hyperplasia can also occur in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome secondary to corticotropin-releasing hormone excess or in children with acromegaly secondary to growth hormone–releasing hormone (GHRH) produced by a variety of systemic tumors.

The monoclonal nature of most pituitary adenomas implies that most originate from a clonal event in a single cell. In some cases, the pituitary tumors result from stimulation with hypothalamic-releasing hormones and in other instances, as in **McCune-Albright syndrome** (MAS), the tumor is caused by activating mutations of the *GNAS1* gene that codes for the α subunit of G_s α, a guanine nucleotide-binding protein. The clinical presentation typically depends on the pituitary hormone that is hypersecreted. In addition, disruptions of growth regulation and/or sexual maturation are common, as a result of either hormone hypersecretion or local compression by the tumor. MAS also features polyostotic fibrous dysplasia of bone and café-au-lait spots in a distinct distribution.

Tall Stature

The normal distribution of height predicts that 2.3% of the population will be taller than 2 SD (97.7%) above the mean. The social acceptability and even desirability of tallness (heightism) makes tall stature an uncommon patient complaint in clinical practice. It is exceptionally unusual for males to seek medical attention regarding excessive height. Females (or their parents) were historically more likely to approach a physician with concern about tall stature, but even in girls this complaint has become less frequent as tallness has become more acceptable and socially desirable in adult women. Concern about side effects of estrogen treatment and reports of dissatisfaction among adult women subjected to this treatment have also led to a decline in the use of estrogen to limit adult height in girls who do happen to feel they are excessively tall.

Differential Diagnosis of Tall Stature

Table 576.1 lists the causes of tall stature at birth and then in childhood and adolescence. Fig. 576.1 shows an approach to diagnosis.

Table 576.1

Differential Diagnosis of Tall Stature and Overgrowth Syndromes

FETAL OVERGROWTH
Maternal diabetes mellitus

Cerebral gigantism (Sotos syndrome: *NSD1*) Weaver syndrome *(EZH2)* Beckwith-Wiedemann syndrome Other IGF-2 excess syndromes Marshall-Smith syndrome *(NFIX)*
POSTNATAL OVERGROWTH LEADING TO CHILDHOOD OR ADULT TALL STATURE
Nonendocrine Causes
Familial (constitutional) tall stature Exogenous obesity Cerebral gigantism (Sotos syndrome: *NSD1*) Weaver syndrome Perlman syndrome Simpson-Golabi-Behmel syndrome (*GPC3, GPC4*) Marfan syndrome Homocystinuria Beckwith-Wiedemann syndrome Klinefelter syndrome (XXY) Other syndromes with extra X or Y chromosomes Overgrowth syndromes with intellectual disability (*DNMT3A, CHD8, HIST1H1E, EED*)
Endocrine Causes
Excess GH secretion due to adenomas (pituitary gigantism) X-linked acrogigantism (Xq26.3 duplication) McCune-Albright syndrome or MEN associated with excess GH secretion Aromatase deficiency and estrogen receptor defects Precocious puberty (initial acceleration, ultimate short stature) Hyperthyroidism (acceleration, but not adult tall stature)

ACTH , Adrenocorticotropic hormone; *GH* , growth hormone; *IGF* , insulin-like growth factor; *MEN* , multiple endocrine neoplasia.

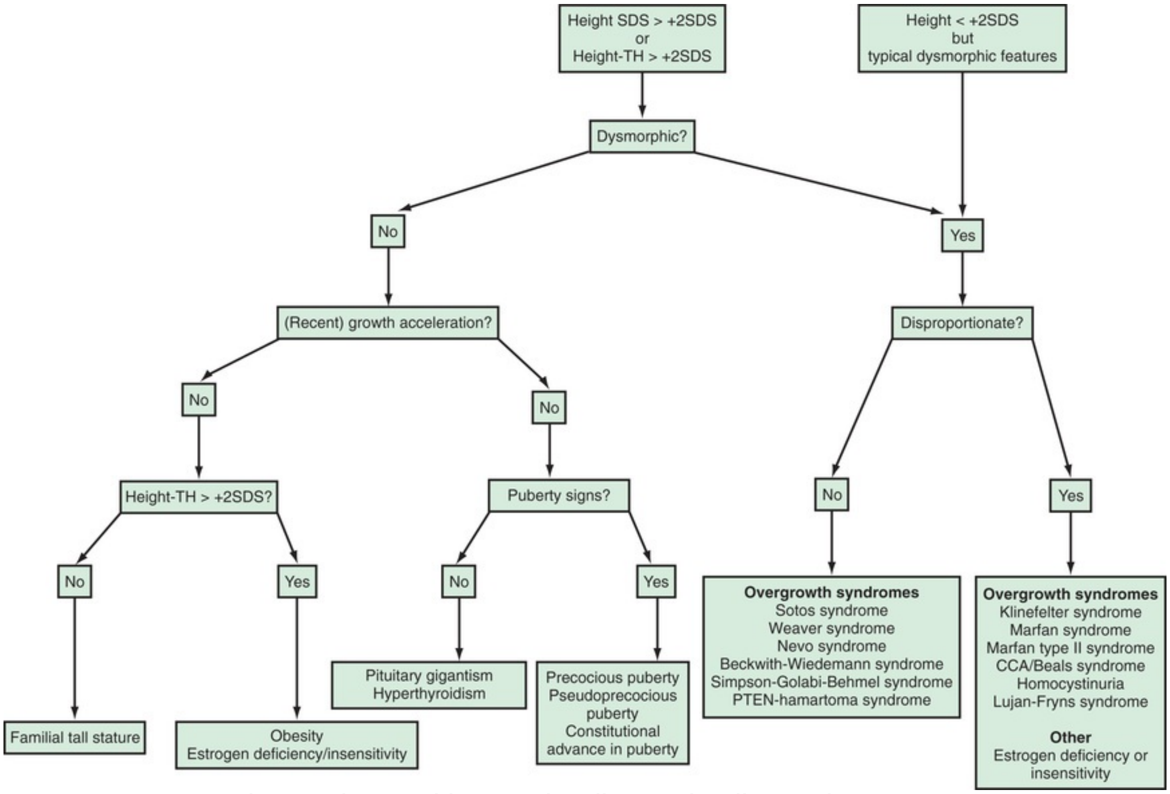
Height SDS > +2SDS
or
Height-TH > +2SDS
Height < +2SDS
but
typical dysmorphic features
Dysmorphic?
No
Yes
(Recent) growth acceleration?
Disproportionate?
No
No
Height-TH > +2SDS?
Puberty signs?
No
Yes
No
Yes
No
Yes
No
Yes
Familial tall stature
Obesity
Estrogen deficiency/insensitivity
Pituitary gigantism
Hyperthyroidism
Precocious puberty
Pseudoprecocious puberty
Constitutional advance in puberty
Overgrowth syndromes
Sotos syndrome
Weaver syndrome
Nevo syndrome
Beckwith-Wiedemann syndrome
Simpson-Golabi-Behmel syndrome
PTEN-hamartoma syndrome
Overgrowth syndromes
Klinefelter syndrome
Marfan syndrome
Marfan type II syndrome
CCA/Beals syndrome
Homocystinuria
Lujan-Fryns syndrome
Other
Estrogen deficiency or insensitivity

FIG. 576.1 Diagnostic algorithm for the differential diagnosis of tall stature and overgrowth syndromes. Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; *SDS* , standard deviation score. (From Neylon OM, Werther GA, Sabin MA: Overgrowth syndromes. *Curr Opin Pediatr* 24:505–511, 2012, Fig. 1, p. 507.)

Overgrowth in the Fetus and Neonate

Maternal diabetes is the most common cause of infants being large for gestational age. Even in the absence of clinical symptoms or a family history, the birth of a large-for-gestational-age infant should lead to evaluation for maternal (or gestational) diabetes.

Overgrowth syndromes: A group of disorders associated with excessive somatic growth and growth of specific organs has been described and is collectively referred to as overgrowth syndromes. These disorders are caused in many cases by excess production and availability of insulin-like growth factor 2 (IGF-2) encoded by the gene *Igf2.* The best described of these syndromes is the **Beckwith-Wiedemann syndrome** (BWS), which is an overgrowth malformation syndrome that occurs with an incidence of 1 : 13,700 births, equal in males and females. It is caused by genetic or epigenetic abnormalities in the

11p15 chromosomal region, with most cases being due to epigenetic abnormalities (loss or gain of DNA methylation) of 2 imprinting control regions, IC1 and IC2. Other causes include mutations, gene duplication, and loss of heterozygosity in this region. The imprinted genes involved in BWS and associated childhood tumors include, in addition to *Igf2,* the gene *H19,* which is involved in *Igf2* suppression, as well as *WT-1* (the Wilms tumor gene), cyclin-dependent kinase inhibitor 1C (CDKN1C), potassium channel voltage-gated KQT-like subfamily member 1 (KCNQ1), and KCNQ1-overlapping transcript 1 (KCNQ1OT1, or long QT intronic transcript 1, LIT1).

Approximately 15% of cases are familial, while the rest appear to be sporadic.

Clinical features include eye proptosis with periorbital fullness, mid-glabellar capillary malformation (nevus flammeus), earlobe creases and pits, and macrosomia, including macroglossia, hepatosplenomegaly, nephromegaly, and omphalocele. They also have hypoglycemia secondary to hyperinsulinemia as a result of pancreatic β-cell hyperplasia. These children are predisposed to embryonal tumors, including Wilms tumor, hepatoblastoma, neuroblastoma, and adrenocortical carcinoma. Management focuses on the omphalocele, airway issues (a result of macroglossia), and neonatal hypoglycemia. Cancer risk is high until 8 yr of age, and regular surveillance with abdominal ultrasound and measurement of α-fetoprotein is recommended every 3 mo until age 8 yr. Thereafter, renal ultrasound is recommended every 1-2 yr as medullary sponge kidney and nephrocalcinosis may develop later.

Mutations in *GPC3* , a glypican gene (which codes for an IGF-2-neutralizing membrane receptor), cause the related **Simpson-Golabi-Behmel** overgrowth syndrome. Other syndromic causes of fetal overgrowth include **Costello syndrome, Weaver syndrome, Sotos syndrome, and Perlman syndrome.**

Overgrowth in Childhood or Adolescence

Normal variant, familial, or constitutional tall stature is by far the most common cause of tall stature. Almost invariably, a family history of tall stature can be obtained, and no organic pathology is present. The child is often taller than the child's peers throughout childhood and enjoys excellent health. There are no abnormalities in the physical examination, and laboratory studies, if obtained, are negative.

Exogenous obesity is associated with rapid linear growth and relatively early onset of puberty (more so in girls). Bone age is accelerated leading to relative tall stature in childhood but adult height is typically normal.

Klinefelter syndrome (XXY syndrome) is a relatively common (1 in 500-1,000 live male births) chromosomal abnormality associated with tall stature, learning disabilities (including requirement for speech therapy), gynecomastia, and decreased upper body:lower body segment ratio. Affected boys can have hypotonia, clinodactyly, and hypertelorism. The testes are invariably small, although androgen production by Leydig cells is often in the low-normal range. Spermatogenesis and Sertoli cell function are defective and lead to infertility. Other genital abnormalities include relatively small phallus and an increased incidence of hypospadias, and cryptorchidism.

XYY syndrome is associated with tall stature, severe acne in adolescence, increased incidence of learning disabilities, and behavioral problems, particularly impulsivity. Intelligence is usually in the normal range, but may be 10-15 IQ points lower than their siblings. Oher rare chromosomal abnormalities in which an excess number of X or Y chromosomes is present (e.g., XXX, XXXY, XYYY) are also associated with increased height.

Marfan syndrome is an autosomal dominant connective tissue disorder consisting of tall stature, arachnodactyly, thin extremities, increased arm span, and decreased upper body:lower body segment ratio (see Chapter 702). Additional abnormalities include ocular abnormalities (e.g., lens subluxation), hypotonia, kyphoscoliosis, cardiac valvular deformities, and aortic root dilation.

Homocystinuria is an autosomal recessive inborn error of amino acid metabolism caused by a deficiency of the enzyme cystathionine synthetase. It is characterized by intellectual disability when untreated, and many of its clinical features resemble Marfan syndrome, particularly ocular manifestations (see Chapter 85).

Sotos Syndrome (Cerebral Gigantism)

Children with cerebral gigantism (also known as Sotos syndrome) are above the 90th percentile for both length and weight at birth and may also have an increased head size. In other cases, macrocrania becomes more apparent postnatally. Most cases of Sotos syndrome are caused by mutations in the *NSD1* (nuclear receptor SET domain-containing protein 1) gene, but in the Japanese population most cases are attributable to microdeletions of the 5q35 region that includes this gene. Inheritance is autosomal dominant, but 95% of cases are a result of new mutations. Incidence is estimated to be approximately 1 in 14,000 live births. The *NSD1* gene is thought to play a role in epigenetic regulation, but the exact mechanisms by which mutations lead to the features of Sotos syndrome are not yet understood.

Although it is characterized by rapid growth, there is no evidence that Sotos syndrome is caused by endocrine dysregulation. Growth is markedly rapid; by 1 yr of age, affected infants are taller than the 97th percentile in height. Accelerated growth continues for the first 4-5 yr and then returns to a normal rate (Fig. 576.2). Puberty usually occurs at the expected time but may occur slightly early. Adult height is usually in the upper-normal range.

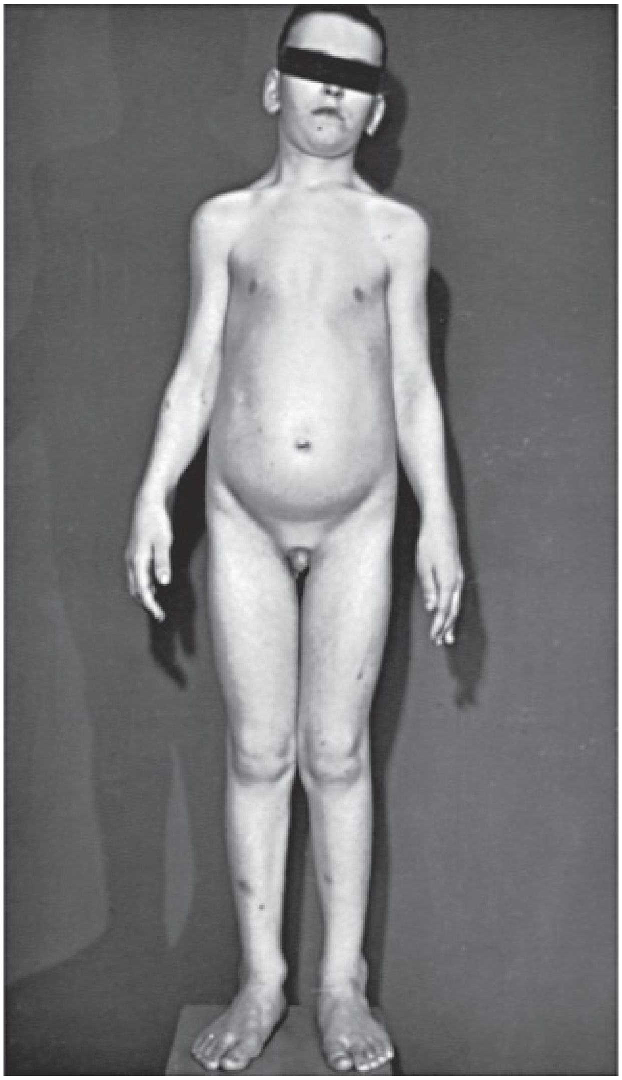

FIG. 576.2 Cerebral gigantism (Sotos syndrome) in an 8 yr old boy. The height age was 12 yr, and the bone age was 12 yr. IQ was 60. The electroencephalogram had abnormal findings. Note the prominence of the forehead and jaw and the large hands and feet. Sexual development was

consistent with chronological age. Hormone study results were normal. The adult height was 208 cm (6 ft 10 in); his sexual development was normal. He wears size 18 shoes.

Clinically the syndrome is characterized by a large (macrocephaly) dolichocephalic head, prominent forehead and jaw, hypertelorism, antimongoloid slant of the palpebral fissures, high-arched palate, and large hands and feet with thickened subcutaneous tissue. Clumsiness and awkward gait are also noted, and affected children have great difficulty in sports, in learning to ride a bicycle, and in other tasks requiring coordination. Some degree of developmental disability affects most patients; in some affected children, perceptual deficiencies may predominate. Many different types of nonfebrile seizures have been reported and up to 25% of patients with Sotos syndrome have seizures at some point in their life. Affected patients may be at somewhat increased risk for neoplasms, including neuroblastoma, hepatoblastoma, and leukemia, with a lifetime risk of between 2% and 4%. Osseous maturation is usually compatible with the patient's height, although advanced bone age has been reported. Scoliosis develops in up to 30% of cases, usually starting in school-age children. GH, IGF-1, and other endocrine studies are usually normal; there is no distinctive laboratory or radiologic marker for the syndrome. Abnormal electroencephalograms are common; imaging studies often reveal an enlarged ventricular system, but intracranial pressure is normal. Genetic testing for *NSD1* mutations (or fluorescence in situ hybridization for 5q35 microdeletions in Japanese patients) is available and should be routinely used. Management is symptomatic and includes paying special attention to developmental and behavioral problems (which tend to improve with age), scoliosis, and seizure disorder. No specific treatment is needed for the overgrowth itself. There is no consensus on the need for cancer surveillance at this time.

Table 576.2 notes additional features of genetic overgrowth syndromes.

Table 576.2

Overgrowth Syndromes

SYNDROME	CLINICAL FEATURES	GENETIC ETIOLOGY	TUMOR SURVEILLANCE
Beckwith-Wiedemann syndrome	Hypoglycemia, large tongue, ear pits, omphalocele or umbilical hernia, hemihyperplasia, organomegaly, high risk	Various genetic and epigenetic abnormalities in 11p15, most commonly in	Tumor surveillance until at least age 8 yr

	of embryonal tumors till age 8	the IC2 region	
Perlman syndrome	Macrosomia, unusual facies, nephroblastosis, severe hypotonia, very high risk of Wilms tumor	*DIS3L2* (DIS3 Like 3′-5′ Exoribonuclease 2) mutations (autosomal recessive)	Tumor surveillance
Simpson-Golabi-Behmel syndrome	Coarse facial features, macroglossia, central groove lower lip, supernumerary nipples, cardiac and skeletal defects	*GPC3 (* glypican 3*)* mutations (X-linked recessive)	Tumor surveillance justified
Sotos syndrome	Excessive growth in first 4 yr, dolichocephaly, macrocrania, typical facies, long limbs, seizures, hypotonia	*NSD1* deletion or mutation (autosomal dominant) Rare familial cases *NFIX* (Nuclear Factor I X) mutations may cause related Malan syndrome	Routine tumor screening not recommended
Weaver syndrome	Broad forehead, hypertelorism, small chin, long philtrum, camptodactyly, redundant nuchal skin, heart and brain defects	*EZH2* (Enhancer of zeste homolog 2) gene mutations in some cases	Routine tumor screening not recommended
PTEN-hamartoma syndromes (including Bannayan-Ruvalcaba-Riley)	Macrocephaly, hypotonia, pigmented skin, penile macules, lipomas, seizures	Sporadic or autosomal dominant *PTEN* mutations	Tumor surveillance recommended
PI3K-Related syndromes	Brain overgrowth (megalencephaly), microgyria, cutaneous vascular malformations, syndactyly, seizures, developmental delay	Mutations in various PI3K-related genes, including P|I3R2, AKT3, CCND2, PIK3CA etc.	Tumor surveillance recommended
Marfan syndrome	Facial gestalt, lens dislocation, arachnodactyly, scoliosis, pectus carinatum or excavatum, aortic root dilation	*FBN1* (Fibrillin 1) mutations (Autosomal dominant)	None
Loeys-Dietz syndrome	Marfan-like habitus, aortic root dilation, aortic dissection, vasculopathy (more aggressive than Marfan)	Autosomal dominant, TGF-β pathway genes including *TGFBR1* , *TGFBR2* , *SMAD3*, *TGFB2*	None
Homocystinuria	Marfan-like habitus Developmental delay Lens dislocation	*CBS* gene (Cystathionine β-synthase) autosomal recessive	None
Lujan syndrome	Marfanoid habitus plus intellectual disability, no eye or cardiovascular anomalies	*MED12* (Mediator Complex Subunit 12) gene X-linked recessive	None

Hyperthyroidism in adolescents is associated with rapid growth but normal final adult height. It is almost always caused by Graves disease and is much more common in girls (see Chapter 584).

Precocious puberty, whether mediated centrally (increased gonadotropin secretion) or peripherally (increased secretion of androgens or estrogens, or both), results in accelerated linear growth during childhood, mimicking the pubertal growth spurt (Chapter 578). Because skeletal maturation is also advanced, adult height is often compromised.

Although delayed puberty may be associated with short stature in childhood, as with constitutional delay, failure to eventually enter puberty and complete sexual maturation can result in sustained growth during adult life, with ultimate tall stature. In both males and females, epiphyseal fusion is mediated by estrogen (produced from testosterone and other androgens via aromatization), so rare defects in the aromatase enzyme or the estrogen receptor can lead to failure of epiphyseal fusion and ultimate tall stature, with growth continuing well into adulthood as epiphyses fail to fuse.

Diagnostic evaluation: The purpose of the diagnostic evaluation of tall stature is to distinguish the commonly occurring, normal variant, constitutional variety from the rare pathologic conditions. Often, when the history suggests familial tall stature and the physical examination is entirely normal, no laboratory tests are indicated. It is valuable to obtain a bone age radiograph to be able to predict adult height, which serves as a basis for discussions with the family and for management decisions. If the history suggests any of the aforementioned disorders or the physical examination reveals abnormalities, additional laboratory tests should be obtained. IGF-1 and IGF-binding protein-3 (IGFBP-3) are excellent screening tests for GH excess and can be verified with a glucose suppression test. Laboratory evidence of GH excess mandates MRI evaluation of the pituitary. Chromosome analysis is useful in males, especially when the ratio of upper to lower body segment is decreased or when developmental disability is present, to rule out Klinefelter syndrome. If Marfan syndrome or homocystinuria is suspected from the physical examination, referral to a cardiologist and an ophthalmologist should be made. Thyroid function tests are useful to diagnose or rule out hyperthyroidism when this disorder is suspected.

Treatment of Normal Variant Tall Stature

Reassurance of the family and the patients is the key to the management of normal variant tall stature. The use of the bone age to predict adult height might provide some comfort for them, as will general supportive discussions on the social acceptability of this condition. Although treatment is possible for females and males with excessive growth, its use should be restricted to patients with predicted adult height >3-4 SD above the mean (79 inches or 200 cm in males, 73 inches or 185 cm in females) *and* evidence of significant psychosocial impairment.

Sex steroids have been used in the treatment of tall stature and are designed to accelerate puberty and to promote epiphyseal fusion; these are therefore of little benefit when given in late puberty. The lack of extensive experience with this form of therapy and the risks of estrogen or androgen treatment for tall stature should be carefully weighed and discussed with the family and treatment should be discouraged except in the most extreme cases. Detailed discussion with the child at the child's level is also advisable as up to 40% of those who underwent such treatments are dissatisfied as adults and feel they were not sufficiently consulted about this course of action. Therapy is initiated ideally before puberty or in early puberty (no later than bone age of 14). In the extremely rare instances where treatment is desired, testosterone enanthate is used at a dose of 250-500 mg intramuscularly every 2 wk for 6 mo in males. In females, oral estrogens in various doses have been used to reduce the predicted height, but average height reduction may be only 1.1-2.4 cm. Therapy must begin before the bone age has reached 12 yr. In the rare case where treatment is advised, oral ethinyl estradiol has been used at a dose of 0.15-0.5 mg/day until cessation of growth occurs. Short-term side effects have included benign breast disease, cholelithiasis, hypertension, menstrual irregularities, weight gain, nausea, limb pain, galactorrhea, and thrombosis. Reduced fertility later in life may be a potential long-term complication. An alternative to sex-steroid therapy is the use of epiphysiodesis (destruction of the growth plates) around the knee to limit linear growth, but this intervention also remains controversial and its long-term safety profile and psychological risks and benefits remain unknown.

Excess Growth Hormone Secretion and Pituitary Gigantism

In young persons with open epiphyses, overproduction of GH results in **gigantism;** in persons with closed epiphyses, the result is **acromegaly.** Often some acromegalic features are seen with gigantism, even in children and adolescents. After closure of the epiphyses, the acromegalic features become more prominent.

Gigantism is rare, with only several hundred reported cases worldwide to date. Genetic mutations are now recognized as being present in about half the cases, though many are sporadic (indicating new mutations). In a recent large series, detailed genetic testing revealed mutations in the AIP (aryl hydrocarbon receptor interacting protein) gene in 29% of cases, X-linked acrogigantism (X-LAG) due to microdeletions at Xq26.3 in 10% and MAS in 5% of the cases. No genetic abnormality was identified in 54% of the cases. Although GH secreting adenomas eventually develop in up to 60% of patients with MEN1, most of these occur in adults and therefore cause acromegaly rather than gigantism. Increased GH secretion and GH-secreting adenomas may also be seen in **neurofibromatosis, tuberous sclerosis** , and **Carney complex** .

Clinical features: The cardinal clinical feature of gigantism is longitudinal growth acceleration secondary to GH excess. The usual manifestations consist of coarse facial features and enlarging hands and feet. In young children, rapid growth of the head can precede linear growth. Some patients have behavioral and visual problems. In most recorded cases, the abnormal growth became evident at puberty, but the condition has been established as early as the newborn period in 1 child and at 21 mo of age in another. Giants have rarely been reported to grow to a height of over 8 ft. In some cases, the patient may present with local effects of the pituitary tumor (headache, visual field defects, and other pituitary hormone deficiencies) as the main complaint, and there is at least 1 report of a patient presenting with diabetic ketoacidosis induced by GH excess. The presentation of gigantism is usually dramatic, unlike the insidious onset of acromegaly in adults.

Pituitary adenomas secreting GH are more common in males but females may present at an earlier age. Tumors with AIP mutations are more common in males, are larger and invasive, and secrete GH or prolactin. **X-LAG syndrome** is a recently recognized cause of familial pituitary adenomas and in these patients the rapid growth begins in infancy and is more frequent in females. Patients with **MAS** will usually exhibit other features of MAS, including polyostotic fibrous dysplasia, café au lait spots, and precocious puberty. Pituitary tumors secrete extremely high levels of GH (up to 1,500 µg/L has been reported) and approximately 50% of pituitary adenomas also exhibit hyperprolactinemia because they secrete both GH and prolactin. Adenomas can compromise other anterior pituitary function through growth or cystic degeneration. Secretion of gonadotropins, thyrotropin, or corticotropin may be impaired. Delayed sexual maturation or hypogonadism can occur. When GH hypersecretion is accompanied by gonadotropin deficiency, accelerated linear growth can persist for decades. In some cases, the tumor spreads outside the sella, invading the sphenoid bone, optic nerves, and brain. GH-secreting tumors in pediatric patients are more likely to be locally invasive or aggressive than are those in adults.

Acromegalic features consist chiefly of enlargement of the distal parts of the body, but manifestations of abnormal growth involve all portions. The circumference of the skull increases, the nose becomes broad, and the tongue is often enlarged, with coarsening of the facial features. The mandible grows excessively, and the teeth become separated. Visual field defects and neurologic abnormalities are common; signs of increased intracranial pressure appear later. The fingers and toes grow chiefly in thickness. There may be dorsal kyphosis. Fatigue and lassitude are early symptoms. GH levels are elevated and occasionally exceed 100 ng/mL. There is usually no suppression of GH levels by the hyperglycemia of a glucose tolerance test and IGF-1 and IGFBP-3 levels are consistently elevated in acromegaly and pituitary gigantism.

Diagnosis

Most children with tall stature do not have pituitary gigantism and other etiologies of rapid linear growth such as genetic tall stature, precocious puberty, and hyperthyroidism should be carefully excluded. Coexisting findings (e.g., dysmorphic facial features, neurocognitive problems, hemihypertrophy) may suggest syndromic or chromosomal causes of tall stature, such as Sotos, Weaver, Klinefelter, or XYY syndrome. GH hypersecretion can be screened for by testing IGF-1 and IGFBP-3 levels. An elevated IGF-1 level in a patient with appropriate clinical suspicion usually indicates GH excess. Potential confusion can arise in the evaluation of normal adolescents because significantly higher IGF-1 levels occur during puberty than in adulthood, so the IGF-1 level must be age and gender matched. Serum IGFBP-3 levels are also sensitive markers of GH elevations and will be elevated in almost all cases. If IGF-1 and/or IGFBP-3 levels are elevated, then the next step is to test for GH excess by doing an oral glucose-suppression test. The gold standard for the diagnosis of GH excess in adults is the failure to suppress serum GH levels to <1 ng/dL at any time during a 2 hr oral glucose tolerance test with 1.75 g/kg oral glucose challenge (maximum: 75 g). GH levels may not be suppressed to this level in normal adolescents and a cutoff of 5 ng/mL may be more appropriate in this age group. If laboratory findings suggest GH excess, the presence of a pituitary adenoma should be confirmed by MRI of the brain. In rare cases, a pituitary mass is not identified. This might be from an occult pituitary microadenoma or ectopic production of GHRH or GH. CT is acceptable when MRI is unavailable.

Treatment

The goals of therapy are to remove or shrink the pituitary mass, to restore GH and secretory patterns to normal, to restore IGF-1 and IGFBP-3 levels to normal, to retain the normal pituitary secretion of other hormones, and to prevent recurrence of disease.

For well-circumscribed pituitary adenomas, trans-sphenoidal surgery is the treatment of choice and may be curative. The tumor should be removed completely. The likelihood of surgical cure depends greatly on the surgeon's expertise as well as on the size and extension of the mass. Intraoperative GH measurements can improve the results of tumor resection. Trans-sphenoidal surgery to resect the tumors is as safe in children as in adults. At times, a transcranial approach might be necessary. The primary goal of treatment is to normalize GH and IGF-1 levels. GH levels (<1 ng/mL within 2 hr after a glucose load) and serum IGF-1 levels (age-adjusted normal range) are the best tests to define a biochemical cure.

If GH secretion and IGF-1 levels are not normalized by surgery, the options include pituitary irradiation and medical therapy. Further growth of the tumor is prevented by irradiation in >99% of patients. The main disadvantage is the delayed efficacy in decreasing GH levels. GH is reduced by approximately 50% from the initial concentration by 2 yr, by 75% by 5 yr, and approaches 90% by 15 yr. Multiple pituitary hormone deficiency is a predictable outcome, occurring in 40–50% of patients 10 yr after irradiation.

Surgery fails to cure a significant number of patients and radiotherapy may not work fast enough, so medical therapy has an important role in treating patients with GH excess. Treatment is effective and well tolerated with GH antagonists, long-acting somatostatin analogs, and in some cases, by dopamine agonists.

Pegvisomant is a GH-receptor antagonist that competes with endogenous GH for binding to the GH receptor. It effectively suppresses GH and IGF-1 levels in patients with acromegaly caused by pituitary tumors as well as ectopic GHRH hypersecretion. Normalization of IGF-1 levels occurs in up to 90% of patients treated daily with this drug for 3 mo or longer. The adult dosage is 10-40 mg via subcutaneous injection once daily, although twice-weekly protocols have also been reported as highly successful. IGF-1 levels and hepatic enzymes must be monitored. Combined therapy with somatostatin analogs and weekly pegvisomant injections also is effective. Pediatric experience is limited, but case reports indicate that it can successfully suppress IGF-1 levels when used in doses of 10-30 mg/day.

The somatostatin analogs are frequently effective in the treatment of patients with GH excess. Octreotide suppresses GH to <2.5 ng/mL in 65% of patients with acromegaly and normalizes IGF-1 levels in 70%. The effects of octreotide are well sustained over time. Tumor shrinkage also occurs with octreotide but is generally modest. Consistent GH suppression can be obtained with a continuous SC pump infusion of octreotide or with long-acting formulations, including long-acting octreotide and lanreotide. Octreotide injection in the pediatric population has been used at doses of 1-40 µg/kg/24 hr. In adults the long-acting form is used in a dose of 10-40 mg every month, but no pediatric dose range has been established.

For patients with both GH and prolactin oversecretion, dopamine agonists, such as bromocriptine and cabergoline, which bind to pituitary dopamine type 2 receptors and may also suppress GH secretion, may also be considered. Prolactin levels are often adequately suppressed, but GH levels and IGF-1 levels are rarely normalized with this treatment modality alone. Tumor shrinkage occurs in a minority of patients. The effectiveness of these agents may be additive to that of octreotide. Cabergoline therapy at doses of 0.25-4.0 mg/wk (given 1-2 times per wk) has been used in adults with acromegaly, and because of its less-frequent dosing and lower incidence of side effects as compared to bromocriptine, this is now considered the dopamine agonist of choice in both adults and children. Side effects can include nausea, vomiting, abdominal pain, arrhythmias, nasal stuffiness, orthostatic hypotension, sleep disturbances, and fatigue.

Hypersecretion of Other Pituitary Hormones

Prolactinoma

Prolactin-secreting pituitary adenomas are the most common pituitary tumors in adolescents. With the advent of MRI, more of these tumors, particularly microadenomas (<1 cm in diameter), are being detected. The most common presenting manifestations are headache, primary or secondary amenorrhea, and galactorrhea. The disorder affects more than twice as many girls as boys; most patients have undergone normal puberty before becoming symptomatic. Only a few have delayed puberty. In some kindreds with type I multiple endocrine neoplasia, prolactinomas are the presenting feature during adolescence. Familial cases as well as sporadic cases with *de novo* mutations of the AIP gene and X-LAG are being recognized more often as genetic testing becomes more common.

Prolactin levels may be elevated mildly (40-50 ng/mL) or markedly (10,000-15,000 ng/mL) and there is correlation between tumor size and prolactin levels. Most prolactinomas in children are large (macroadenomas), cause the sella to enlarge, and, in some cases, cause visual field defects. Approximately 30% of patients with macroadenomas develop other pituitary hormone deficiencies, particularly GH deficiency. Alternatively, prolactin-secreting adenomas might also stain for and secrete excess GH and/or thyroid-stimulating hormone.

Prolactinomas should not be confused with the hyperprolactinemia and pituitary hyperplasia that can occur in patients with primary hypothyroidism, which is readily treated with thyroid hormone (see Chapter 581). Moderate elevations (<200 ng/mL) of prolactin are also associated with a variety of medications (antipsychotics, metoclopramide, phenothiazines, verapamil), with pituitary stalk dysfunction such as can occur with craniopharyngioma, with chronic stress (rarely > 40 ng/mL), with nipple stimulation, and may remain idiopathic in some cases.

In some cases, extreme hyperprolactinemia is associated with a hook effect that leads to factitiously low values on blood tests. In cases where clinical features are compatible with hyperprolactinemia, serial dilution of the lab specimen should be done to rule out this kind of measurement error. On the other hand, patients may have factitiously elevated prolactin levels on immunoassay as a result of the presence of prolactin polymers and dimers (macroprolactinemia) that are not physiologically active. In cases where an elevated prolactin is detected in an asymptomatic patient, unnecessary diagnostic work-up and treatment can be avoided by performing polyethylene glycol precipitation to exclude the presence of macroprolactinemia, which is clinically benign.

In most patients where the hyperprolactinemia is secondary to an adenoma, it can be effectively treated with dopamine agonists. Treatment leads to lowering of prolactin levels and tumor shrinkage in the vast majority of patients. Because of its greater efficacy and lower incidence of side effects, cabergoline is considered the drug of choice for treatment of hyperprolactinemia. The usual protocol is to begin with 0.25 mg twice weekly and then increase as needed to 1 mg twice weekly. Higher doses may be needed in some patients but should be carefully monitored; high doses used for long periods in older patients with Parkinsonism are associated with cardiac valvular abnormalities though this has not been reported with the doses used in pediatric hyperprolactinemia; monitoring of cardiac valves with echocardiography may be advisable if high doses are used for a prolonged period.

When dopamine agonist treatment has been unsuccessful in lowering the serum prolactin concentration or the size of the adenoma, and when symptoms or signs attributable to hyperprolactinemia or adenoma size persist during treatment, trans-sphenoidal surgery may be considered. Very rare cases of malignant prolactinomas may require chemotherapy with temozolomide, but a cure is difficult in such cases.

Corticotropinoma

Corticotropinoma is very rare in children, and its peak occurrence is at age 14 yr. **Cushing disease** refers specifically to an adrenocorticotropic hormone–producing pituitary adenoma that stimulates excess cortisol production and secretion. It is more common than primary adrenal causes of Cushing syndrome, except in younger children (younger than 5 yr of age), in whom adrenal carcinomas and adrenal activating mutations of MAS are rare but dominant causes of the syndrome. Adenomas causing Cushing disease are almost always microadenomas with a diameter of <5 mm and are significantly smaller than all other types of adenomas at presentation. The most sensitive indicator of excess glucocorticoid secretion in children is growth failure, which generally precedes other manifestations. Patients develop weight gain that tends to be centripetal rather than generalized. Pubertal arrest, hypertension, large purplish striae, fatigue, and depression are also common. In prepubertal children, males are more frequently affected than females.

Midnight salivary cortisol measurements can be used as a screening test for cortisol excess, but confirmation requires at least 1 additional test (either 24 hr urinary free cortisol or an overnight dexamethasone suppression test). Location of the microadenoma is usually determined by MRI, and bilateral inferior petrosal sinus sampling may be needed in difficult cases. Trans-sphenoidal surgery is the treatment of choice for Cushing disease in children. Initial remission rates of 70–98% of patients and long-term success rates of 50–98% are reported. Residual transient hypoadrenalism is often observed after surgery, lasting as long as 30 mo. Pituitary radiotherapy is used if cortisol levels remain elevated and/or adrenocorticotropic hormone levels continue to be detectable. Successful treatment may not correct the height deficit, and GH deficiency may be present after treatment and should be treated as required.

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CHAPTER 577

Physiology of Puberty

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Between early childhood and approximately 8-9 yr of age (prepubertal stage), the hypothalamic-pituitary-gonadal axis is dormant, as reflected by undetectable serum concentrations of luteinizing hormone (LH) and sex hormones (estradiol in girls, testosterone in boys). One to 3 yr before the onset of clinically evident puberty, low serum levels of LH during sleep become demonstrable. This sleep-entrained LH secretion occurs in a pulsatile fashion and reflects endogenous episodic discharge of hypothalamic gonadotropin-releasing hormone (GnRH). Nocturnal pulses of LH continue to increase in amplitude and, to a lesser extent, in frequency as clinical puberty approaches. This pulsatile secretion of gonadotropins is responsible for enlargement and maturation of the gonads and the secretion of sex hormones. The appearance of the secondary sex characteristics in early puberty is the visible culmination of the sustained, active interaction occurring among hypothalamus, pituitary, and gonads in the peripubertal period. By mid-puberty, LH pulses become evident even during the daytime and occur at about 90- to 120-min intervals. A 2nd critical event occurs in middle or late adolescence in girls in whom cyclicity and ovulation occur. A positive feedback mechanism develops whereby increasing levels of estrogen in midcycle cause a distinct increase of LH.

The increasing secretion of hypothalamic GnRH in a pulsatile fashion thus underlies the onset of pubertal development. The *GnRH pulse generator* is regulated by multiple neuropeptides, including glutamic acid, kisspeptin, neurokinin-B (stimulatory); γ-aminobutyric acid, preproenkephalin, and dynorphin (inhibitory). Mutations of the *KISS1 R* (previously known as *GPR54*, a G protein–coupled receptor gene whose ligand is kisspeptin) are a rare cause of autosomal recessive hypogonadotropic hypogonadism (loss-of-function mutations) or precocious puberty (gain-of-function mutations). The (maternally) imprinted gene makorin RING finger protein 3 *(MKRN3)* has been described as a *brake* for the onset of puberty. Loss-of-function mutations of this gene are responsible for paternally transmitted familial precocious puberty in both sexes.

The interpretation of the hormonal changes of puberty is complex. Issues in interpreting LH and follicle-stimulating hormone (FSH) measurements include the presence of multiple gonadotropin isoforms, immunoassay-related variability, and problems inherent to their pulsatile secretion which mandates serial sampling in plasma. In addition, important sex differences exist in the maturation of the hypothalamus and pituitary gland because serum LH concentrations tend to increase earlier in the course of the pubertal process in males than in females. Adrenocortical androgens also have a role in sexual maturation. Serum levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to increase at approximately 6-8 yr of age, before any increase in LH or sex hormones and before the earliest physical changes of puberty are apparent; this process has been called adrenarche. DHEAS is the most abundant adrenal C-19 steroid in the blood, and its serum concentration remains fairly stable over 24 hr. A single measurement of this hormone is commonly used as a marker of adrenal androgen secretion. Although adrenarche typically antedates the onset of onset of gonadal activity (gonadarche) by a few years, the 2 processes do not seem to be causally related, because adrenarche and gonadarche are dissociated in conditions such as central precocious puberty and adrenocortical failure.

The effects of gonadal steroids (testosterone in males, estradiol in females) on bone growth and osseous maturation are critical. Both aromatase deficiency and estrogen receptor defects result in delayed epiphyseal fusion and tall stature in affected males. These observations suggest that estrogens, rather than androgens, are responsible for the process of bone maturation that ultimately leads to epiphyseal fusion and cessation of growth. Estrogens also mediate the increased production of growth hormone, which along with a direct effect of sex steroids on bone growth, is responsible for the pubertal growth spurt.

The age of onset of puberty varies and is more closely correlated with osseous maturation than with chronological age (Chapters 26 and 132). In females, the **breast bud** (thelarche) is usually the first sign of puberty (10-11 yr), followed by the appearance of **pubic hair** (pubarche) 6-12 mo later. The interval to the onset of **menstrual activity** (menarche) is usually 2-2.5 yr but may be as long as 6 yr. In the United States, at least one sign of puberty is present in approximately 95% of females by 12 yr of age and in 99% of females by 13 yr of age. Peak height velocity occurs early (at breast stage II–III, typically between 11 and 12 yr of age) in females and always precedes menarche. The mean age of menarche is about 12.75 yr. However, there are wide variations in the sequence of changes involving growth spurt, breast bud, pubic hair, and maturation of the internal and external genitalia.

In males, **growth of the testes** (≥4 mL in volume or 2.5 cm in longest diameter) and thinning of the scrotum are the first signs of puberty (11-12 yr). These are followed by pigmentation of the scrotum and growth of the penis and by **pubarche** . Appearance of **axillary hair** usually occurs in mid-puberty. In males, unlike in females, acceleration of growth begins after puberty is well underway and is maximal at genital stage IV-V (typically between 13 and 14 yr of age). In males, the growth spurt occurs approximately 2 yr later than in females, and growth may continue beyond 18 yr of age.

Genetic and environmental factors affect the timing for the onset of puberty. Population-based studies in the United States and Europe have suggested secular trends for earlier onset of puberty over the past few decades in females and, to a lesser degree, in males. African American, and to a less extent Hispanic, females appear to be more advanced in the development of secondary sex characteristics for age than white females. However, the timing of menarche has advanced only marginally (2.5-4 mo) in white females and slightly more so (up to 6 mo) in African-American females. The Copenhagen Puberty Study showed that the earlier onset of breast development observed in females examined in 2006-2008 than those seen in 1991-1993 (means 10.9 yr vs. 9.9 yr) was not associated with different levels of gonadotropins or estradiol when females of similar chronological ages were compared between the 2 groups. Hence earlier breast development may not simply reflect earlier activation or maturation of the hypothalamic-pituitary-gonadal axis but could also stem from other factors such as increased adiposity or increased exposure to certain environmental agents. Positive correlations between the degree of adiposity and earlier pubertal development in girls have, indeed, been reported. Conversely, female athletes in whom leanness and strenuous physical activity have coexisted from early childhood frequently exhibit a marked delay in puberty or menarche, and they frequently have oligomenorrhea or amenorrhea as adults (Chapter 711). Pubertal delay is also prevalent in males who are physically very active. Thus energy balance is closely related to the activity of the GnRH pulse generator and the mechanisms initiating and sustaining puberty, possibly via hormonal signals such as leptin or other adipokines.

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CHAPTER 578

Disorders of Pubertal Development

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Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 yr in females and 9 yr in males. The variation in the age of the onset of puberty in normal children, particularly of different ethnicities, makes this definition somewhat arbitrary. It remains in use by most clinicians.

Depending on the primary source of the hormonal production, precocious puberty may be classified as **central** (also known as **gonadotropin dependent,** or **true**) or **peripheral** (also known as **gonadotropin independent** or **precocious pseudopuberty)** (Table 578.1). **Central** precocious puberty (CPP) is always isosexual and stems from hypothalamic-pituitary-gonadal activation with ensuing sex hormone secretion and progressive sexual maturation. In **peripheral** precocious puberty, some of the secondary sex characters appear, but there is no activation of the normal hypothalamic-pituitary-gonadal interplay. In this latter group, the sex characteristics may be isosexual or heterosexual (contrasexual) (Chapters 600 to 606).

Table 578.1

Classification of Sexual Precocity

TRUE PRECOCIOUS PUBERTY OR COMPLETE ISOSEXUAL PRECOCITY (GNRH-DEPENDENT SEXUAL PRECOCITY OR PREMATURE ACTIVATION OF THE HYPOTHALAMIC GNRH PULSE GENERATOR)

Idiopathic true precocious puberty
CNS tumors
Optic glioma associated with neurofibromatosis type 1
    Hypothalamic astrocytoma
Other CNS disorders
    Developmental abnormalities including hypothalamic hamartoma of the tuber cinereum
    Encephalitis
    Static encephalopathy
    Brain abscess

  - Sarcoid or tubercular granuloma
  - Head trauma
  - Hydrocephalus
  - Arachnoid cyst
  - Myelomeningocele
  - Vascular lesion
  - Cranial irradiation
- True precocious puberty after late treatment of congenital virilizing adrenal hyperplasia or other previous chronic exposure to sex steroids
- True precocious puberty due to mutations:
  - in *KISS1R/GRP54* gene
  - in *KISS1* gene
  - *MKRN3* gene

INCOMPLETE ISOSEXUAL PRECOCITY (HYPOTHALAMIC GNRH-INDEPENDENT)

Males

- Gonadotropin-secreting tumors
  - hCG-secreting CNS tumors (e.g., chorioepitheliomas, germinoma, teratoma)
  - hCG-secreting tumors located outside the CNS (hepatoma, teratoma, choriocarcinoma)
- Increased androgen secretion by adrenal or testis
  - Congenital adrenal hyperplasia (CYP21 and CYP11B1 deficiencies)
  - Virilizing adrenal neoplasm
  - Leydig cell adenoma
  - Familial testotoxicosis (sex-limited autosomal dominant pituitary gonadotropin-independent precocious Leydig cell and germ cell maturation)
  - Cortisol resistance syndrome

Females

- Ovarian cyst
- Estrogen-secreting ovarian or adrenal neoplasm
- Peutz-Jeghers syndrome with SCTAT

Both Sexes

- McCune-Albright syndrome
- Hypothyroidism
- Iatrogenic or exogenous sexual precocity (including inadvertent exposure to estrogens in food, drugs, or cosmetics)

VARIATIONS OF PUBERTAL DEVELOPMENT

- Premature thelarche
- Premature isolated menarche
- Premature adrenarche
- Adolescent gynecomastia in boys
- Macroorchidism

CONTRASEXUAL PRECOCITY

Feminization in Males

- Adrenal neoplasm
- Chorioepithelioma
- CYP11B1 deficiency
- Testicular neoplasm (Peutz-Jeghers syndrome)
- Increased extraglandular conversion of circulating adrenal androgens to estrogen
- Iatrogenic (exposure to estrogens)

Virilization in Females

- Congenital adrenal hyperplasia
  - CYP21 deficiency
  - CYP11B1 deficiency
  - 3β-HSD deficiency
- Virilizing adrenal neoplasm (Cushing syndrome)
- Virilizing ovarian neoplasm (e.g., arrhenoblastoma)

Iatrogenic (exposure to androgens)
Cortisol resistance syndrome
Aromatase deficiency

CNS , Central nervous system; *CYP11B1* , 11-hydroxylase; *CYP21* , 21-hydroxylase; *GnRH* , gonadotropin-releasing hormone; *hCG* , human chorionic gonadotropin; *3β-HSD* , 3β-hydroxysteroid dehydrogenase 4,5-isomerase; *KISS1R/GPR54* , kisspeptin/G protein–coupled receptor 54; *SCTAT* , sex cord tumor with annular tubules.

Modified from Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier, Table 25.25, p 1163.

Peripheral precocious puberty can also induce maturation of the hypothalamic-pituitary-gonadal axis and trigger the onset of central puberty. This mixed type of precocious puberty occurs commonly in conditions such as congenital adrenal hyperplasia, McCune-Albright syndrome, and familial male-limited precocious puberty, when the bone age reaches the pubertal range (10.5-12.5 yr).

578.1

Central Precocious Puberty

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Keywords

Central precocious puberty
Peripheral precocious puberty
Rapidly progressive puberty
Highly sensitive LH assays

CPP is defined by the onset of breast development before the age of 8 yr in females and by the onset of testicular development (volume ≥ 4 mL) before the age of 9 yr in males, as a result of the early activation of the hypothalamic-pituitary-gonadal axis. It occurs 5- to 10-fold more frequently in females than in males and is usually sporadic. Although at least 90% of females have an idiopathic form, a structural central nervous system (CNS) abnormality may occur in 25–75% of males with CPP. Genetic forms of CPP, such as the paternally transmitted type due to a mutation of the *MKRN3* gene, have been recently described. A high prevalence of CPP has been reported in females adopted from developing countries, particularly if adopted several months or years after birth, possibly related to undefined nutritional or environmental factors.

Clinical Manifestations

Sexual development may begin at any age and generally follows the sequence observed in normal puberty. In females, early menstrual cycles may be more irregular than they are with normal puberty. The initial cycles are usually anovulatory, but pregnancy has been reported as early as 5.5 yr of age (Fig. 578.1). In males, testicular biopsies have shown stimulation of all elements of the testes, and spermatogenesis has been observed as early as 5-6 yr of age. In affected females and males, height, weight, and height velocity are accelerated. The increased rate of bone maturation results in early closure of the epiphyses, and compromised adult height, particularly if puberty begins at a very early age. Historically, approximately 30% of females and an even larger percentage of males achieved a height below the 5th percentile as adults without treatment. Mental development is usually compatible with chronological age. Emotional behavior and mood swings are common, but serious psychological problems are rare.

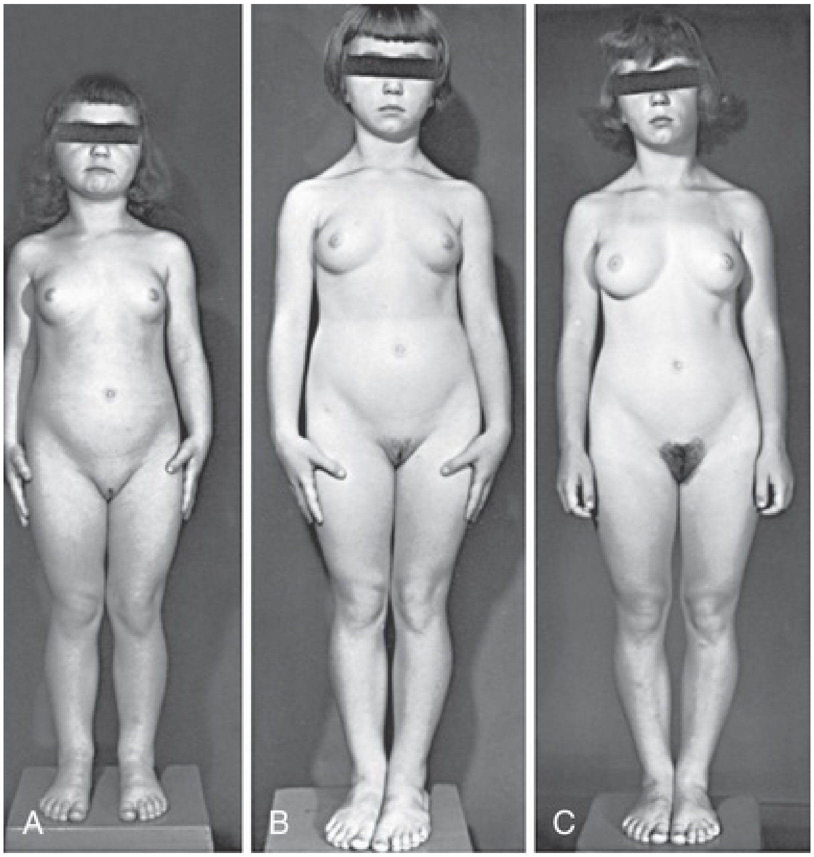

FIG. 578.1 Natural course of idiopathic central precocious puberty. Patient **(A)** at $3\frac{11}{12}$, **(B)** at $5\frac{8}{12}$, and **(C)** at $8\frac{1}{2}$ yr of age. Breast development and vaginal bleeding began at $2\frac{1}{2}$ yr of age. Bone age was $7\frac{1}{2}$ yr at $3\frac{11}{12}$ and 14 yr at 8 yr of age. Intelligence and dental age were normal for chronological age. Growth was completed at 10 yr; ultimate height was 142 cm (56 in). No effective therapy was available at the time this patient sought medical attention.

Although the clinical course is variable, 3 main patterns of pubertal progression can be identified. Most females (particularly those younger than 6 yr of age at the onset) and a large majority of males have rapidly progressive puberty, characterized by rapid physical and osseous maturation, leading to a loss of height potential. An increasing percentage of females (older than 6 yr of age at the onset with an idiopathic form), and rarely males, have a slowly progressive variant, characterized by parallel advancement of osseous maturation and linear growth, with preserved height potential. Very rarely, central puberty may regress spontaneously (unsustained CPP). This variability in the natural course of sexual precocity underscores the need for longitudinal observation at the onset of sexual development, before treatment is considered.

Laboratory Findings

Sex hormone concentrations are usually appropriate for the stage of puberty in both sexes (Table 578.2). Despite the availability of sensitive and specific (liquid chromatography/tandem mass spectrometry) assays for sex hormones, serum estradiol concentrations are low or undetectable in the early phase of sexual precocity in females, as they are in normal puberty. In males, serum testosterone levels are usually detectable or clearly elevated by the time the parents seek medical attention, provided that an early morning blood sample is obtained. With the use of highly sensitive immunofluorometric and chemiluminescent assays, serum LH concentrations are undetectable in prepubertal children in random blood samples but become detectable in 50–75% of females and a higher percentage of males with CPP. Unfortunately, a number of hospitals use only moderately sensitive immunoenzymatic assays for LH and often insensitive assays for estradiol and testosterone, which decrease the diagnostic sensitivity of these measurements. Measurement of LH in serial blood samples obtained during sleep has greater diagnostic power than measurement in a single random sample, and it typically reveals a well-defined pulsatile secretion of LH. Administration of gonadotropin-releasing hormone (GnRH stimulation test, intravenously) or a GnRH agonist (leuprolide stimulation test, subcutaneously) is a helpful diagnostic tool, particularly for males, in whom a pubertal LH response (LH peak >5 IU/L) with predominance of LH over follicle-stimulating hormone (FSH) tends to occur early in the course of precocious puberty. In females with sexual precocity, however, the nocturnal LH secretion and the LH response to GnRH or GnRH agonist may be quite low at breast stages II to early III (LH peak, <5 IU/L), and the LH to FSH ratio may remain low until mid-advanced puberty. In such females with low LH response, the central nature of sexual precocity can be proven by detecting pubertal levels of estradiol (>50 pg/mL) 20-24 hr after stimulation with leuprolide.

Table 578.2

Differential Diagnosis of Sexual Precocity

DISORDER	PLASMA GONADOTROPINS	LH RESPONSE TO GNRH	SERUM SEX STEROID CONCENTRATION	GONADAL SIZE	MISCELLANE
GONADOTROPIN DEPENDENT					
True (central)	Prominent LH pulses	Pubertal LH	Pubertal values of	Normal pubertal	MRI of brain to

precocious puberty	(premature reactivation of GnRH pulse generator)	response initially during sleep	testosterone or estradiol	testicular enlargement or ovarian and uterine enlargement	out CNS tumor other abnormali
GONADOTROPIN INDEPENDENT					
Males					
Chorionic gonadotropin-secreting tumor in males	High hCG, low LH	Prepubertal LH response	Pubertal value of testosterone	Slight to moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; of brain if chori gonadotropin-secreting CNS t suspected
Leydig cell tumor in males	Suppressed	No LH response	High testosterone	Irregular, asymmetric enlargement of testes	
Familial, male-limited precocious puberty (FMPP, “testotoxicosis”)	Suppressed	No LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm but smaller than expected for pubertal development; spermatogenesis occurs	Activating muta of the LHCG receptor; autoso dominant transmission
Virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in CYP21 deficiency or elevated 11-deoxycortisol in CYP11B1 deficiency	Testes prepubertal	Autosomal reces variable severity of onset; may ha salt loss in CYP deficiency or hypertension in CYP11B1 defici
Virilizing adrenal tumor	Prepubertal	Prepubertal LH response	High DHEAS, DHEA, and/or androstenedione values	Testes prepubertal	CT, MRI, or US abdomen
Females					
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Prepubertal LH response	Very high estradiol	Ovarian enlargement on physical examination, CT, MRI, or US	Tumor often pal on physical examination
Follicular cyst	Suppressed	Prepubertal LH response	Prepubertal to very high estradiol	Ovarian enlargement on physical examination, CT, MRI, or US	Single or recurr episodes of men and/or breast development; exclude McCun Albright syndro
Feminizing adrenal tumor	Suppressed	Prepubertal LH response	High estradiol, variable DHEAS increase	Ovaries prepubertal	Unilateral adren mass
Nonclassical congenital	Prepubertal	Prepubertal LH response	Elevated 17-OHP in basal or corticotropin-	Ovaries prepubertal	Autosomal reces

adrenal hyperplasia			stimulated state		
In Both Sexes					
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroid pubertal. Estradiol may be quite high in girls.	Ovarian enlargement (asymmetrical) on US; slight (usually symmetrical) testicular enlargement	Skeletal survey/ scan for polyost fibrous dysplasi skin examinatio café au lait spots
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal; FSH response flat	Estradiol may be pubertal	Testicular enlargement; ovaries cystic	TSH and prolac elevated; T_4 low
INCOMPLETE PRECOCITY/VARIATIONS OF PUBERTY					
Premature thelarche	Prepubertal	Prepubertal LH	Prepubertal or early pubertal estradiol response	Ovaries prepubertal	Onset usually be 3 yr of age
Premature adrenarche (males)	Prepubertal	Prepubertal LH response	Prepubertal testosterone; DHEAS, or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Testes prepubertal	Onset usually af yr of age; more frequent in CNS injured children
Premature adrenarche (females)	Prepubertal	Prepubertal LH response	Prepubertal estradiol; DHEAS or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Ovaries prepubertal	Onset usually af yr of age; more frequent in brair injured children

CNS , Central nervous system; *CT* , computed tomography; *CYP* , P450 cytochrome isoenzyme; *DHEAS* , dehydroepiandrosterone sulfate; *FSH,* follicle-stimulating hormone; *GnRH* , gonadotropin-releasing hormone; *hCG* , human chorionic gonadotropin; *LH* , luteinizing hormone; *MRI* , magnetic resonance imaging; *17-OHP* , 17-hydroxyprogesterone; T_4 , thyroxine; *TSH* , thyrotropin; *US* , ultrasonography.

Modified from Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier, Table 25.41, pp 1196–1197.

Osseous maturation is variably advanced, often more than 2-3 SD. Pelvic ultrasonography in females reveals progressive enlargement of the ovaries, followed by enlargement of the fundus and then of the whole uterus to pubertal size. An MRI scan usually demonstrates physiologic enlargement of the pituitary gland, as seen in normal puberty; it may also reveal CNS pathology (see Chapter 578.2).

Differential Diagnosis

Organic CNS causes of central sexual precocity are more likely in males, and in females who have rapid breast development, estradiol greater than 30 pg/mL, or are younger than 6 yr of age. All children in these categories should undergo MRI scans of the brain and pituitary gland. Criteria for ordering brain imaging in females older than 6 yr are controversial, although some authorities recommend MRI scans for *all children* with CPP.

Gonadotropin-independent causes of isosexual precocious puberty must be considered in the differential diagnosis (see Tables 578.1 and 578.2). For females, these include tumors of the ovaries, autonomously functioning ovarian cysts, feminizing adrenal tumors, McCune-Albright syndrome, and exogenous sources of estrogens. In males, congenital adrenal hyperplasia, adrenal tumors, Leydig cell tumors, human chorionic gonadotropin (hCG)–producing tumors, exposure to exogenous androgens, and familial male precocious puberty should be considered.

Treatment

Virtually all males and the large subgroup of females with rapidly progressive precocious puberty are candidates for treatment. Females with slowly progressive idiopathic CPP do not seem to benefit in terms of height prognosis from GnRH agonist therapy. Former small-for-gestational-age infants may be at greater risk of short stature as adults and may require more aggressive treatment of precocious puberty, possibly in conjunction with human growth hormone (hGH) therapy. Certain patients require treatment predominantly for psychologic or social reasons, including children with special needs and very young females at risk of early menarche.

The observation that the pituitary gonadotropic cells require pulsatile, rather than continuous, stimulation by GnRH to maintain the ongoing release of gonadotropins provides the rationale for using GnRH agonists for treatment of CPP. By virtue of being more potent, and having a longer duration of action than native GnRH, these GnRH agonists (after a brief period of stimulation) desensitize the gonadotropic cells of the pituitary to the stimulatory effect of endogenous GnRH and effectively halt the progression of central sexual precocity.

Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentration of the drug for weeks or months, constitute the preparations of choice for treatment of CPP. In the United States, the available preparations include: (a) leuprolide acetate *(Lupron Depot Ped)*, in a dose of 0.2-0.3 mg/kg

(7.5-15 mg) intramuscularly once every 4 wk; (b) longer-acting preparations of depot-leuprolide, allowing for injections (11.25 or 30 mg IM) every 90 days; (c) histrelin *(Supprelin LA)*, a subcutaneous 50-mg implant with effects lasting at least 12 mo; and (d) triptorelin (Triptodur), 22.5 mg IM every 6 months. Other preparations such as goserelin acetate (*Zoladex*) are approved for treatment of precocious puberty in other countries. Recurrent sterile fluid collections at the sites of injections are an uncommon local side effect and occur in less than 1–3% of patients treated with depot-leuprolide. Breakage or malfunction of the histrelin implant is very rare. Other available treatment options, usually reserved for children who cannot tolerate the products listed previously, include subcutaneous injections of aqueous leuprolide, given once or twice daily (total dose 60 mcg/kg/24 hr), or intranasal administration of the GnRH agonist nafarelin (Synarel), 800 mcg bid. The potential for irregular compliance with daily administration, as well as the variable absorption of the intranasal route for nafarelin, may limit the long-term benefit of the latter preparations on adult height. GnRH antagonists, including novel oral compounds, have not been investigated sufficiently in children and are not FDA approved.

Treatment results in decrease of the growth rate, generally to age-appropriate values, and an even greater decrease of the rate of osseous maturation. Some children, particularly those with greatly advanced (pubertal) bone age, may show marked deceleration of their growth rate and an arrest in the rate of osseous maturation. Treatment results in enhancement of the predicted height, although the actual adult height of patients followed to epiphyseal closure has, historically, been approximately 1 SD less than their mid–parental height. In females, breast size may regress in those with Tanner stage II-III development but tends to remain unchanged in females with late stage III-V development or may even increase slightly because of progressive adipose tissue deposition. The amount of glandular tissue decreases. Pubic hair usually remains stable in females or may progress slowly during treatment, reflecting the gradual increase in adrenal androgens. Menses, if present, cease. Pelvic sonography demonstrates a decrease of the ovarian and uterine size. In males, there is decrease of testicular size, variable regression of pubic hair, and decrease in the frequency of erections. Except for a reversible decrease in bone density (of uncertain clinical significance), no serious adverse effects of GnRH analogs have been reported in children treated for sexual precocity. If treatment is effective, the serum sex hormone concentrations decrease to prepubertal levels (testosterone, <10-20 ng/dL in males; estradiol, <5-10 pg/mL in females). The serum LH and FSH concentrations, as measured by sensitive immunometric assays, decrease to less than 1 IU/L in most patients, although rarely does the LH return to truly prepubertal levels (<0.1 IU/L). Moreover, the incremental FSH and LH responses to GnRH stimulation decrease to less than 2-3 IU/L. Serum LH, FSH and sex hormone levels are suppressed more completely and evenly by the histrelin implant than by GnRH agonist injections. Therapy is typically discontinued at a pubertal chronological age, after which puberty resumes promptly. In females, menarche generally appears at an average of 18 mo (range 6-24 mo) after cessation of IM therapy and somewhat earlier after removal of the histrelin implant. The addition of hGH to GnRH agonists has been used on an investigational basis in children with precocious puberty, markedly advanced bone age, and prediction of short stature. The available, albeit limited, data indicate that combined therapy may increase the adult height.

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578.2

Precocious Puberty Resulting from Organic Brain Lesions

Wassim Chemaitilly, Luigi R. Garibaldi

Keywords

Central precocious puberty
Peripheral precocious puberty
Rapidly progressive puberty
Highly sensitive LH assays
GnRH analog
Contrasexual precocity
Isosexual precocity

Etiology

Hypothalamic hamartomas are the most common brain lesion causing CPP (Fig. 578.2). This congenital malformation consists of ectopically located neural tissue, within which glial cells can produce transforming growth factor-α (TGF-α), which has the potential to activate the GnRH pulse generator. On MRI, it appears as a small pedunculated mass attached to the tuber cinereum or the floor of the 3rd ventricle or, less often, as a sessile mass (Fig. 578.3) that remains static in size over years.

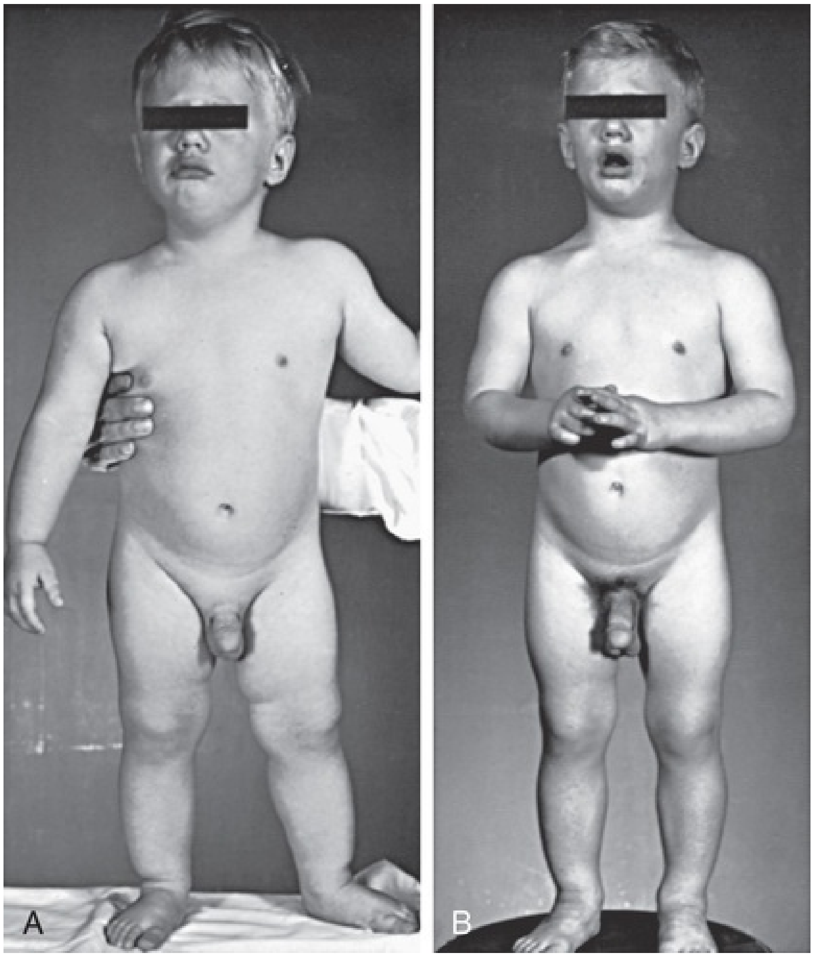

FIG. 578.2 Natural course of precocious puberty with central nervous system lesion. Photographs at 1.5 **(A)** and 2.5 **(B)** yr of age. Accelerated growth, muscular development, osseous maturation, and testicular development were consistent with the degree of secondary sexual maturation. In early infancy, the patient began having frequent spells of rapid, purposeless motion; later in life, he had episodes of uncontrollable laughing with ocular movements. At 7 yr, he exhibited emotional lability, aggressive behavior, and destructive tendencies. Although a hypothalamic hamartoma had been suspected, it was not established until CT scanning became available when the patient was 23 yr of age. Epiphyses fused at 9 yr of age; final height was 142 cm (56 in). At 24 yr of age, he developed an embryonal cell carcinoma of the retroperitoneum.

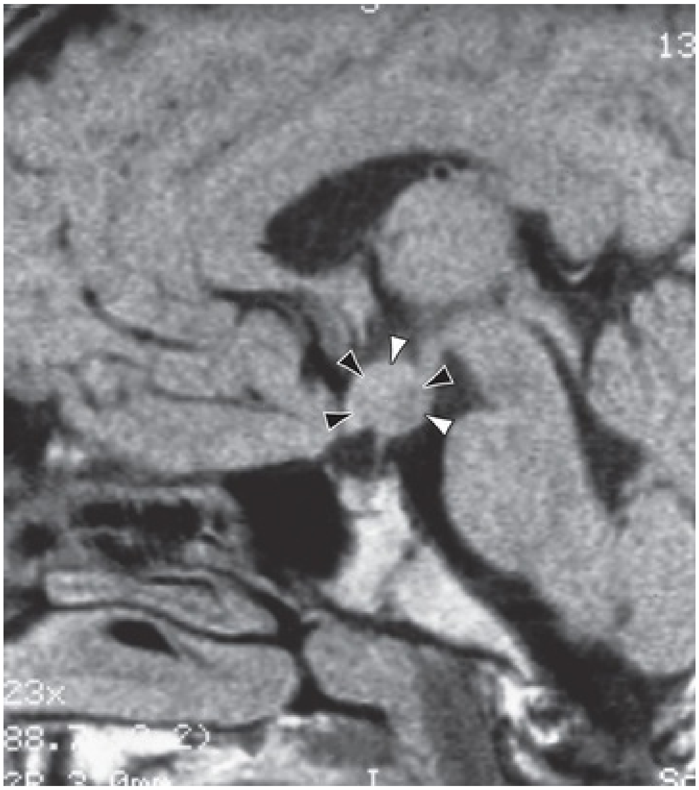

FIG. 578.3 MRI of a central nervous system lesion in a child with central precocious puberty. A 6 yr old girl was referred for stage IV breast development and growth acceleration. Serum luteinizing hormone and estradiol concentrations were in the adult range. The midsagittal T1-weighted image shows an isointense hypothalamic mass *(arrowheads),* typical of a hamartoma. (From Sharafuddin M, Luisiri A, Garibaldi LR, et al: MR imaging diagnosis of central precocious puberty: importance of changes in the shape and size of the pituitary gland, *Am J Roentgenol* 162:1167–1173, 1994.)

A wide variety of other CNS lesions or insults, usually involving the hypothalamus by scarring, invasion, or pressure, have been associated with gonadotropin-dependent sexual precocity (see Table 578.1). They include postencephalitic scars, tuberculous meningitis, tuberous sclerosis, severe head trauma, and hydrocephalus, either isolated or associated with myelomeningocele. Gonadotropin-dependent precocious puberty occurs in 26–29% of children with tumors developing within or near the hypothalamus or optic pathways. Low-grade gliomas, the most common types of such neoplasms, are highly prevalent (15–20%) in children with neurofibromatosis type 1 (NF-1) and constitute the main etiologic factor for the central sexual precocity encountered in a small subset (approximately 3%) of children with NF-1.

About 50% of the tumors in the pineal region are germ cell tumors or astrocytomas; the remainder consists of a wide variety of histologically distinct tumor types. Pineal or hypothalamic germ cell tumors can cause CPP in males, by secreting hCG, which stimulates the LH receptors in the Leydig cells of the testes (see Chapter 578.5).

Clinical Manifestations

Hypothalamic hamartomas remain static in size or grow slowly, can be associated with gelastic or psychomotor seizures, but most often produce no signs other than precocious puberty. This is often rapidly progressive sexual precocity in very young children. For lesions causing neurologic symptoms, the neuroendocrine manifestations may be present for 1-2 yr before the tumor can be detected radiologically. Hypothalamic signs or symptoms such as diabetes insipidus, adipsia, hyperthermia, unnatural crying or laughing, obesity, and cachexia should suggest the possibility of an intracranial lesion. Visual signs (proptosis, decreased visual acuity, visual field defects) may be the first manifestation of an optic glioma.

The sexual precocity is always *isosexual* , and the endocrine patterns are generally those found in children without demonstrable organic lesions. In conditions other than hypothalamic hamartoma, GH deficiency can occur and may be masked by the growth-promoting effect of the increased sex hormone levels. The pubertal staging of males treated with gonadotoxic modalities such as high-dose alkylating agents or testicular radiotherapy should not rely on testicular volume measurements because these are affected by treatment-induced germ cell and Sertoli depletion. Pubic hair development, scrotal thinning, and penile size may be better indicators, and providers should not hesitate to measure serum LH and testosterone levels when in doubt.

Treatment

GnRH agonists (depot-forms or implant) are the treatment of choice of tumor-induced CPP. In a subset of patients with hypothalamic hamartoma and associated intractable gelastic or psychomotor seizures, stereotactic radiation therapy (Gamma Knife surgery) may be more effective and carries fewer risks than neurosurgical intervention. For other neurologic lesions, therapy depends on the nature and location of the pathologic process. Combined GH therapy should be considered for patients with associated GH deficiency. The final height outcome will also depend on other factors such as the burden of disease from the primary tumor, side effects of cancer treatments, and associated chronic health conditions

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578.3

Precocious Puberty Following Irradiation of the Brain

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Keywords

- Tumoral causes of precocious puberty
- Brain irradiation and puberty
- Peripheral precocious puberty (gonadotropin-independent precocious puberty)
- GnRH analog

Children treated with cranial radiotherapy at a wide range of doses (18-50 Gy) have an increased risk of developing gonadotropin-dependent precocious puberty. The prevalence of this condition in children treated with radiotherapy for tumors located outside of the hypothalamic pituitary or optic pathways region has been reported at 6.6%. Hydrocephalus, young age at exposure to radiation (<5 yr), female sex, and increased BMI are additional risk factors. This condition is often associated with GH deficiency and at times with other conditions (spinal irradiation, hypothyroidism) adversely affecting the adult height prognosis. Unless careful attention is paid to early signs of pubertal development in these children, the combination of GH deficiency and the growth-promoting effect of sex steroids often result in a normal growth rate at the expense of a rapidly advancing bone age and impaired adult height potential. The pubertal staging of males treated with gonadotoxic modalities such as high-dose alkylating agents or testicular radiotherapy should not rely on testicular volume measurements (see Chapter 578.2).

Treatment

GnRH analogs are effective in arresting pubertal progression, but concomitant GH (and/or thyroid hormone) deficiency should be diagnosed and treated promptly to improve the adult height prognosis.

Paradoxically, hypopituitarism with gonadotropin deficiency may subsequently develop as a late effect of high-dose CNS irradiation in patients with or without a history of precocious puberty, and it may require substitution therapy with sex steroids.

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578.4

Syndrome of Precocious Puberty and Hypothyroidism

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Keywords

Tumoral causes of precocious puberty
Brain irradiation and puberty
Peripheral precocious puberty (gonadotropin-independent precocious puberty)
GnRH analog

The onset of puberty is usually delayed in children with mild forms of hypothyroidism. However, up to 50% of children with profound, untreated hypothyroidism of long duration may paradoxically develop precocious puberty. **Hashimoto thyroiditis** is frequently the cause of such forms of hypothyroidism. Patients have the usual manifestations of hypothyroidism (see Chapter 581); the symptoms may be difficult to recognize in children with special needs. Children with precocious puberty due to hypothyroidism have, contrary to other children with sexual precocity, decreased growth velocity and delayed bone age. Females may present with breast development and menstrual bleeding; the latter may occur even in females with minimal breast enlargement. Pelvic sonography may reveal large, multicystic ovaries. Males have testicular enlargement associated with modest or no penile enlargement. No pubic hair development occurs in either females or males. Enlargement of the sella, which is typical of long-standing primary hypothyroidism, may be demonstrated by skull film or MRI. Plasma levels of thyroid-stimulating hormone (TSH) are markedly elevated, often greater than 500 µU/mL, and those of prolactin and estradiol are mildly elevated. Although serum FSH is low and LH is undetectable, when measured by specific assays, the massively elevated concentrations of TSH appear to interact with the FSH receptor (specificity spillover), thus inducing FSH-like effects in the absence of LH effects on the gonads. The FSH-like effect suffices to induce estradiol secretion by the ovaries, whereas in males, testicular enlargement occurs without substantial testosterone secretion. Treatment of the hypothyroidism results in rapid return to normal of the biochemical and clinical manifestations. Possible progression to central puberty with rapid bone age advancement may occur in the months following the initiation of thyroid hormone replacement, a complication that would justify delaying puberty with GnRH analogs. Macroorchidism (testicular volume >30 mL) may persist in adult males despite adequate levothyroxine therapy. Children with a high risk of primary hypothyroidism, especially those with special needs such as patients with trisomy 21, should be screened at least annually, via measurement of serum free T_4 and TSH levels.

578.5

Chorionic Gonadotropin-Secreting Tumors

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Keywords

Tumoral causes of precocious puberty
Brain irradiation and puberty
Peripheral precocious puberty (gonadotropin-independent precocious puberty)
GnRH analog

hCG-secreting tumors are a rare cause of precocious puberty in males. Secretion of hCG activates LHCG receptors in the Leydig cells causing testosterone production and virilization with minimal testicular enlargement. Testicular histology reveals interstitial cell hyperplasia with no spermatogenesis. Plasma levels of testosterone are elevated, whereas those of FSH and LH, as measured by specific assays, are low. Females with hCG-secreting tumors do not present with precocious puberty because the ovarian production of estradiol cannot occur in the absence of FSH stimulation.

Hepatic Tumors

All reported cases of hepatoblastoma causing isosexual precocious puberty have been in males, with the average age of onset of 2 yr (range 4 mo to 8 yr). An enlarged liver or mass in the right upper quadrant should suggest the diagnosis. Plasma levels of hCG and α-fetoprotein (AFP) are usually markedly elevated and serve as useful markers for following the effects of therapy. As with other carcinomas of the liver, the prognosis for survival beyond 1-2 yr from the time of diagnosis is poor.

Intracranial Tumors

Nongerminomatous or mixed germ cell tumors, choriocarcinomas, teratomas, teratocarcinomas, and others account for <5% of intracranial tumors, are usually located in the neurohypophyseal area or the pineal area, and may cause precocious puberty in males if they secrete hCG; the mass effect can infrequently cause precocious puberty in females. Marked elevations of hCG and AFP often occur in the cerebrospinal fluid, although elevations in the blood may be modest. Treatment includes radiation, chemotherapy, and debulking surgery.

Tumors in Other Locations

Very rare locations include mediastinum, gonads, or even adrenal glands. Mediastinal germ cell tumors have been reported to cause precocious puberty in males with Klinefelter syndrome.

Peripheral Precocious Puberty

The adrenal causes of peripheral precocious puberty are discussed in Chapter 594 , and the gonadal causes are discussed in Chapters 602 and 605 .

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578.6

McCune-Albright Syndrome

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Keywords

Peripheral precocious puberty
McCune-Albright syndrome

Familial male limited puberty

McCune-Albright syndrome, or precocious puberty with polyostotic fibrous dysplasia and abnormal pigmentation, is a syndrome of endocrine dysfunction associated with patchy cutaneous pigmentation and fibrous dysplasia of the skeletal system. It is a rare condition with a prevalence between 1/100,000 and 1/1,000,000. A classical cause of peripheral precocious puberty, it is characterized by autonomous hyperfunction of 1 or more glands (which may include pituitary, thyroid, and adrenal glands). An activating missense mutation in the GNAS1 gene encoding the α-subunit of G_S , the G protein that stimulates cyclic adenosine monophosphate (cAMP) formation, results in activation of receptors (ACTH, TSH, FSH, and LH receptors) that operate via a cAMP-dependent mechanism, as well as cell proliferation. Because the mutation is postzygotic rather than genomic, it is expressed differently in different tissues (somatic mosaicism), hence the variability of clinical expression and the limited reliability of genetic testing from leukocyte DNA and unaffected tissues. Precocious puberty has been described predominantly in females (Fig. 578.4) and is characterized by recurrent ovarian cysts, bouts of estrogen secretion, and vaginal bleeding in the face of modest breast development. The age at onset in females is usually 3-6 yr but has been reported as early as 4-6 mo of age. Serum levels of LH and FSH are suppressed, with no response to GnRH stimulation. Estradiol levels fluctuate from low to markedly elevated (>300 pg/mL), are often cyclic, and may correlate with the size of the cysts. In males, precocious puberty is less commonly recognized. Unlike ovarian enlargement in females, testicular enlargement in males is often symmetric. It is followed by the appearance of phallic enlargement and pubic hair, as in normal puberty. Testicular histology has shown foci or nodules (often sonographically detectable) of Leydig cell hyperplasia. In females and males, when the bone age reaches the usual pubertal age range, gonadotropin secretion begins, CPP ensues and overrides the antecedent (gonadotropin-independent) puberty. In females, menses become more regular, but often not completely so, and fertility has been documented.

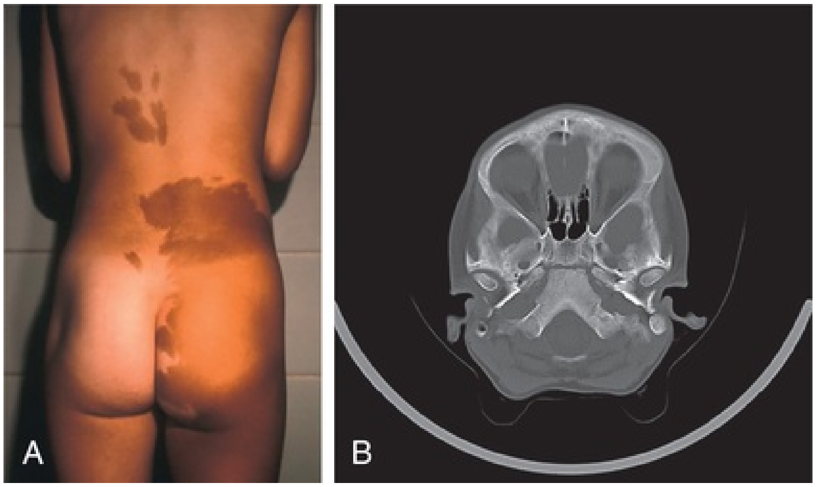

FIG. 578.4 Precocious puberty with McCune-Albright syndrome (MAS). **A,** A girl presented at 5 yr of age with early stage III breast development and vaginal bleeding. Note the extensive café-au-lait skin patches, some of which did not cross the midline. **B,** A girl presented with recurring episodes of mild breast enlargement and vaginal bleeding associated with ovarian cysts, starting at age 7 mo. She had no skin lesions, negative skeletal survey and bone scan at age 4 yr. The diagnosis of MAS was established at 5 yr of age, when prominence of her left forehead and supraorbital ridge prompted a CT scan which revealed unilateral thickening of the skull bones **(B)** . Skull lesions are often hyperostotic, whereas long bone lesions usually have a lytic, "ground-glass" appearance.

Pubertal progression is variable in these patients. Functioning ovarian cysts often disappear spontaneously; aspiration or surgical excision of cysts is rarely indicated. For those females with persistent or recurrent estradiol secretion, aromatase inhibitors (which inhibit the final step of estrogen biosynthesis) such as letrozole (1.25-2.5 mg/day p.o.) have proven safe and effective in limiting the estrogen effects on pubertal and osseous maturation. The same compounds have also been used in males, in combination with antiandrogens. These medications are not approved by the FDA for this indication. Associated therapy with long-acting analogs of GnRH is indicated only for young children whose puberty has shifted from a gonadotropin-independent to a predominantly gonadotropin-dependent mechanism. Ovarian torsion is a disturbing complication of large ovarian cysts.

Extragonadal Manifestations

The hyperthyroidism that occurs in this condition is usually clinically mild or subclinical, unlike that observed in Graves disease. Mildly elevated triiodothyronine levels, suppressed TSH levels, and nodular abnormalities on ultrasound have been reported. Thyroidectomy is rarely necessary.

Cushing syndrome due to bilateral nodular adrenocortical hyperplasia has occurred only in neonates or young infants. ACTH levels are low, and cortisol is elevated and not suppressible by dexamethasone. The condition may resolve spontaneously; if not, treatment is bilateral adrenalectomy.

Increased secretion of GH occurs uncommonly and is manifested clinically by gigantism or acromegaly. The growth rate is increased (even in the absence of precocious puberty); serum levels of GH are elevated, increase during sleep, and are poorly suppressed by oral glucose. Serum levels of prolactin are increased in most patients. Fewer than 50% of the patients have a demonstrable pituitary tumor. Treatment includes octreotide or lanreotide, long-acting somatostatin analogs, to lower the elevated GH levels; or pegvisomant, to antagonize the effect of GH at the receptor level.

Fibrous dysplasia of (usually) multiple bones (polyostotic) represents a major cause of morbidity in this syndrome (Fig. 578.5). The base of the skull and the proximal femurs are most commonly involved, but any bone can be affected. Even in the absence of deformities, a CT scan of the cranium is recommended by several investigators. The prognosis is favorable for longevity, but deformities, repeated fractures, pain, and occasional cranial nerve compression may result from the bony lesions. Bone pain often responds to IV pamidronate or other bisphosphonates. Extensive bony lesions may be associated with phosphaturia, due to oversecretion of FGF 23, leading to rickets or osteomalacia. Extraglandular manifestations of this syndrome are rare, but cardiovascular and hepatic involvement (severe neonatal cholestasis) may be life threatening.

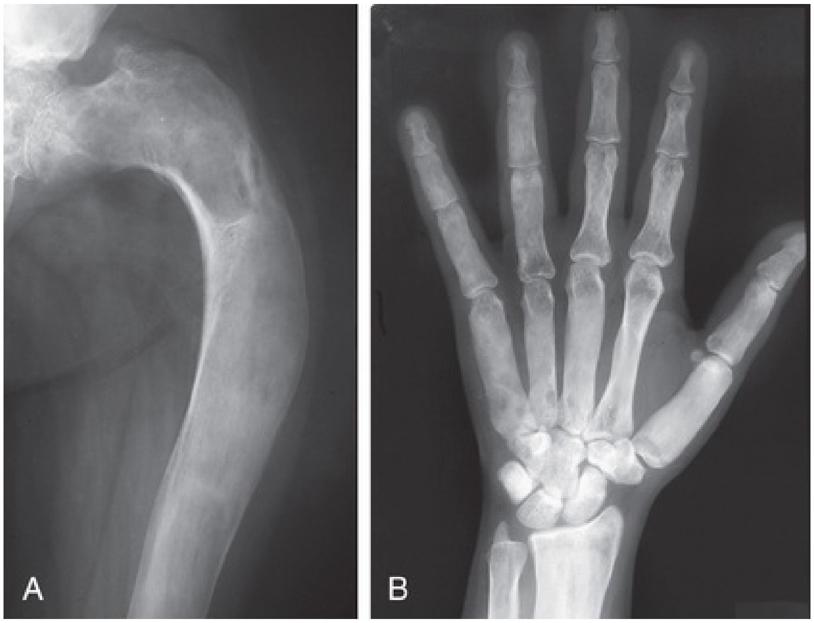

FIG. 578.5 Polyostotic fibrous dysplasia in a 22 yr old woman. **(A)** The femur is expanded and bowed with a “shepherd's crook” deformity. The femoral trabeculae are replaced by “ground-glass” matrix. **(B)** Diffuse sclerosis is seen in the hand and wrist with mild expansion and indistinct transition from cortex to medullary space. (From Thapa MM, Kaste SC, Meyer JS: Soft tissue bone tumors. In Coley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 13, Philadelphia, 2018, Elsevier, Fig. 138.31.)

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578.7

Familial Male Gonadotropin-Independent Precocious Puberty

Wassim Chemaitilly, Luigi R. Garibaldi

Keywords

Atypical thelarche
Atypical adrenarche
Incomplete puberty
Variants of puberty
Familial male gonadotropin-independent precocious puberty
Premature thelarche
Premature pubarche (premature adrenarche)
Premature menarche

This rare, autosomal dominant form of peripheral precocious puberty is transmitted from affected males and unaffected female carriers of the gene to their male offspring. Signs of puberty appear by 2-3 yr of age. The testes are only slightly enlarged. Testicular biopsies show Leydig cell maturation and, sometimes, marked hyperplasia. Maturation of seminiferous tubules may be present. Testosterone levels are variably elevated, often markedly so, even above the adult male range; however, baseline levels of LH are prepubertal, pulsatile secretion of LH is absent, and LH does not respond to stimulation with GnRH or GnRH agonist. The cause for activation of Leydig cells independently of gonadotropin stimulation is a missense mutation of the LHCG receptor leading to constitutive activation of cAMP production. Osseous maturation may be markedly advanced; when it reaches the pubertal age range, hypothalamic maturation shifts the mechanism of pubertal development to a gonadotropin-dependent one. This sequence of events is similar to that occurring in children with McCune-Albright syndrome (Chapter 578.6) or in those with congenital adrenal hyperplasia (Chapter 576).

Gonadotropin-independent precocious puberty has been diagnosed in a few unrelated males with **type IA pseudohypoparathyroidism** who had a single mutation of the G_s α protein. This mutation is inactivating at normal body temperature and causes pseudohypoparathyroidism, but in the cooler temperature of the testes, it is constitutionally activating, resulting in adenyl cyclase stimulation and production of testosterone. Although this mutation differs from the constitutive LH receptor mutation, which usually causes familial male gonadotropin-independent precocious puberty, the end result is the same.

Treatment

Young males have been successfully treated with ketoconazole (10-15 mg/kg/day in 8-hr divided doses), an antifungal drug that inhibits C-17,20-lyase and testosterone synthesis. Other investigators use a combination of antiandrogens (such as spironolactone 50-100 mg b.i.d., flutamide 125-250 mg daily or b.i.d, or bicalutamide 25-50 mg daily) and aromatase inhibitors (letrozole 2.5 mg/day, or anastrozole 1 mg/day) because estrogens derived from androgens stimulate bone maturation. These medications are unable to revert the serum testosterone to the normal (prepubertal) concentrations or completely offset the unfavorable effects of the elevated sex hormones. They slow down, but do not halt, the progression of puberty and may not improve the height prognosis. Males whose GnRH pulse generator has matured require combined therapy with GnRH agonists.

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578.8

Incomplete (Partial) Precocious

Development

Wassim Chemaitilly, Luigi R. Garibaldi

Keywords

Atypical thelarche
Atypical adrenarche
Incomplete puberty
Variants of puberty
Familial male gonadotropin-independent precocious puberty
Premature thelarche
Premature pubarche (premature adrenarche)
Premature menarche

Isolated development of the breasts in females and growth of sexual hair in both sexes without other signs of puberty are the 2 most common forms of incomplete precocity and not unusual in a pediatric practice.

Premature Thelarche

This term applies to a sporadic, transient condition of isolated breast development that most often appears in the first 2 yr of life. In some females, breast development is present at birth and persists. It may be unilateral or asymmetric and often fluctuates in degree. Growth and osseous maturation are normal or slightly advanced. The genitalia show no evidence of estrogenic stimulation. Breast development may regress after 2 yr, often persists for 3-5 yr, and is rarely progressive. Menarche occurs at the expected age, and reproduction is normal. Basal serum levels of FSH and the FSH response to GnRH stimulation may be greater than that seen in normal controls. Plasma levels of LH and estradiol are typically undetectable. Pelvic ultrasound reveals normal-sized ovaries, but a few small (<9 mm) cysts are not uncommon.

In some females, breast development may be associated with definite evidence of systemic estrogen effects, such as growth acceleration or bone age advancement. Pelvic sonography may reveal enlarged ovaries and/or uterus. This condition, referred to as **exaggerated or atypical thelarche,** differs from CPP because it spontaneously regresses. Leuprolide or GnRH stimulation elicits a robust FSH response, a low LH response, and (after leuprolide only) a moderate estradiol increment at 24 hr (average 60-90 pg/mL). The pathogenesis of typical and exaggerated forms of thelarche is unclear. Delayed inactivation of the hypothalamic-pituitary-ovarian axis, which is active during the prenatal and early postnatal period, increased peripheral sensitivity to estrogens, and other possibilities are unproven hypotheses. In addition to a detailed history, a bone age should be obtained if there are any unusual features. Random serum concentrations of FSH, LH, and estradiol are generally low and not diagnostic. Pelvic ultrasound examination or leuprolide stimulation testing are occasionally indicated. Continued observation is important because the condition cannot be readily distinguished from true precocious puberty. Regression and recurrence suggest functioning follicular cysts. Occurrence of thelarche in children older than 3 yr of age most often is caused by a condition other than benign premature thelarche.

Premature Pubarche (Adrenarche)

This term has traditionally applied to the appearance of sexual hair before the age of 8 yr in females or 9 yr in males without other evidence of maturation. It is much more frequent in females than in males. The higher prevalence of this condition in African-American and, to a smaller extent, Latino females in comparison to white females may suggest that the cutoff age for the definition of *premature* should be adjusted for different ethnic groups on epidemiologic data. Hair appears on the mons and labia majora in females, and perineal and scrotal area in males; axillary hair generally appears later. Adult-type axillary odor is common. Affected children are often slightly advanced in height and osseous maturation. Premature adrenarche is an early maturational event of adrenal androgen production. It coincides with precocious maturation of the zona reticularis, an associated decrease in 3β-hydroxysteroid dehydrogenase activity, and an increase in C-17, 20-lyase activity. These enzymatic changes result in increased basal and ACTH-stimulated serum concentrations of the Δ^5 -steroids (17-hydroxypregnenolone and dehydroepiandrosterone [DHEA]) and, to a lesser extent, of the Δ^4 -steroids (particularly androstenedione) compared with age-matched control subjects. The levels of these steroids and of dehydroepiandrosterone sulfate (DHEAS) are usually comparable with those of older children in the early stages of normal puberty. Idiopathic premature adrenarche is a slowly progressive condition that requires no therapy. However, a subset of patients presents with **atypical premature adrenarche** characterized by one or more features of systemic androgen effect, such as marked growth acceleration, clitoral (females) or phallic (males) enlargement, cystic acne, and advanced bone age (2 SD greater than the mean for age). In this subgroup, an ACTH stimulation test with measurement of serum 17-hydroxyprogesterone concentration is indicated to rule out **nonclassical congenital adrenal hyperplasia** due to 21-hydroxylase deficiency. The prevalence of nonclassical 21-hydroxylase deficiency is approximately 3–6% of unselected children with precocious pubarche; other enzyme defects (i.e., 3β-hydroxysteroid dehydrogenase or 11β-hydroxylase deficiencies) are extremely rare. Although idiopathic premature adrenarche has been considered a benign condition, longitudinal observations suggest that approximately 50% of females with premature adrenarche are at high risk for **hyperandrogenism** and **polycystic ovary syndrome,** alone or more often in combination with other components of the so-called metabolic syndrome (insulin resistance possibly progressing to type 2 diabetes mellitus, dyslipidemia, hypertension, increased visceral fat) as adults. Whether the unfavorable progression to pubertal hyperandrogenism can be prevented by insulin-sensitizing agents (metformin 850-2000 mg/day) or lifestyle interventions (diet, exercise) remains to be proven in large studies. An increased risk of premature adrenarche and the metabolic syndrome has been documented in children born small for their gestational age. This appears to be associated with insulin resistance and decreased β-cell reserve, perhaps as a consequence of fetal undernutrition.

Premature Menarche

This is a rare entity, much less frequent than premature thelarche or premature adrenarche, and is a diagnosis of exclusion. In females with isolated vaginal bleeding in the absence of other secondary sexual characteristics, more common causes such as vulvovaginitis, a foreign body (typically associated with malodorous discharge), or sexual abuse, and uncommon causes such as urethral prolapse and sarcoma botryoides must be carefully excluded. Most females with idiopathic premature menarche have only 1-3 episodes of bleeding; puberty occurs at the usual time, and menstrual cycles are normal. Plasma levels of gonadotropins are low, but estradiol levels may be occasionally elevated, probably owing to episodic ovarian estrogen secretion associated with ovarian follicular cysts that can be detected on ultrasound.

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578.9

Medicational Precocity

Luigi R. Garibaldi, Wassim Chemaitilly

Keywords

- Delayed puberty
- Constitutional delay of growth and puberty
- Hypergonadotrophic hypogonadism
- Hypogonadotrophic hypergonadism

Various medicaments can induce the appearance of secondary sexual characteristics (i.e., peripheral precocious puberty). Examples include the accidental ingestion of estrogens (including contraceptive pills) and the administration of anabolic steroids. Exogenous estrogens may produce a darkening of the areola that is not usually seen in central sexual precocity. The most common cause of medicational precocity is currently related to the widespread use of testosterone gels or creams, which are applied to the skin for treatment of male hypogonadism, with ensuing virilization of children and women following skin contact. Systemic absorption from the skin area of a male relative where the gel/cream was applied may result in serum testosterone levels in the 50-100 mg/dL range in children.

Less commonly, estrogens in cosmetics, hair creams, and breast augmentation creams cause breast development in females and gynecomastia in males, via percutaneous absorption. Lavender and tea tree oils have been associated with prepubertal gynecomastia in several reports. Genistein, a compound from soy, has estrogenic activity in mice, but data in humans are conflicting. The physical changes disappear after cessation of exposure to the hormones. A careful history focused on exploring the possibility of accidental exposure to, or ingestion of, sex hormones is important.

578.10

Delayed or Absent Puberty*

Peter M. Wolfgram

Keywords

Delayed puberty
Constitutional delay of growth and puberty
Hypergonadotrophic hypogonadism
Hypogonadotrophic hypergonadism

For Hypofunction of Testis see Chapter 601 .

For Hypofunction of Ovaries see Chapter 604 .

Delayed puberty is the failure of development of any pubertal feature by 13 yr of age in females or by 14 yr of age in males. A lower cutoff may be appropriate in a child with a strong familial pattern of early puberty.

Differential Diagnosis

Delay or absence of puberty is caused by:

- constitutional delay: a variant of normal
- hypogonadotropic hypogonadism: low gonadotropin levels as a result of a defect of the hypothalamus and/or pituitary gland (Tables 578.3 and 578.4)

Table 578.3

Classification of Delayed Puberty and Sexual Infantilism

Idiopathic (Constitutional) Delay in Growth and Puberty (Delayed Activation of Hypothalamic LRF Pulse Generator)
Hypogonadotropic Hypogonadism: Sexual Infantilism Related to Gonadotropin Deficiency
CNS DISORDERS
Tumors
Craniopharyngiomas Germinomas Other germ cell tumors Hypothalamic and optic gliomas Astrocytomas Pituitary tumors (including MEN-1, prolactinoma)
Other Causes
Langerhans histiocytosis Postinfectious lesions of the CNS Vascular abnormalities of the CNS Radiation therapy Congenital malformations especially associated with craniofacial anomalies Head trauma Lymphocytic hypophysitis
ISOLATED GONADOTROPIN DEFICIENCY
Kallmann syndrome With hyposmia or anosmia Without anosmia LHRH receptor mutation Congenital adrenal hypoplasia (*DAX1* mutation) Isolated LH deficiency Isolated FSH deficiency Prohormone convertase 1 deficiency (PCI)
IDIOPATHIC AND GENETIC FORMS OF MULTIPLE PITUITARY HORMONE DEFICIENCIES INCLUDING PROP1 MUTATION

MISCELLANEOUS DISORDERS
Prader-Willi syndrome Laurence-Moon and Bardet-Biedl syndromes Functional gonadotropin deficiency Chronic systemic disease and malnutrition Sickle cell disease Cystic fibrosis Acquired immunodeficiency syndrome (AIDS) Chronic gastroenteric disease Chronic renal disease
Malnutrition Anorexia nervosa Bulimia Psychogenic amenorrhea Impaired puberty and delayed menarche in female athletes and ballet dancers (exercise amenorrhea) Hypothyroidism Diabetes mellitus Cushing disease Hyperprolactinemia Marijuana use Gaucher disease
Hypergonadotropic Hypogonadism
MALES
The syndrome of seminiferous tubular dysgenesis and its variants (Klinefelter syndrome) Other forms of primary testicular failure Chemotherapy Radiation therapy Testicular steroid biosynthetic defects Sertoli-only syndrome LH receptor mutation Anorchia and cryptorchidism Trauma/surgery
FEMALES
The syndrome of gonadal dysgenesis (Turner syndrome) and its variants XX and XY gonadal dysgenesis Familial and sporadic XX gonadal dysgenesis and its variants Familial and sporadic XY gonadal dysgenesis and its variants Aromatase deficiency Other forms of primary ovarian failure Premature menopause Radiation therapy Chemotherapy Autoimmune oophoritis Galactosemia Glycoprotein syndrome type 1 Resistant ovary FSH receptor mutation LH/hCG resistance Polycystic ovarian disease Trauma/surgery Noonan or pseudo-Turner syndrome Ovarian steroid biosynthetic defects

CNS , Central nervous system; *FSH,* follicle-stimulating hormone; *hCG* , human chorionic gonadotropin; *LHRH* , luteinizing hormone–releasing hormone; *LRF* , luteinizing hormone–

releasing factor; *MEN* , multiple endocrine neoplasia.

From Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams Textbook of Endocrinology* , ed 13, Philadelphia, 2016, Elsevier, Table 25.15, p. 1129.

Table 578.4

Molecular Basis for Developmental Disorders Associated with Hypogonadotropic Hypogonadism

GENE	PHENOTYPE	COMPLEX PHENOTYPE
ISOLATED HYPOGONADOTROPIC HYPOGONADISM		
Kallmann Syndrome or Normosmic IHH (With the Same Mutant Gene)		
KAL1 (Xp22.3)	X-linked Kallmann syndrome	Anosmia/hyposmia, renal agenesis, dyskinesia
FGFR1 (KAL2) (8p11.2)	Autosomal dominant Kallmann syndrome (± recessive)	Anosmia/hyposmia, cleft lip/palate
FGF8 (ligand for FGFR1) (10q25)		
NELF (9p34.3)	Autosomal dominant (?) Kallmann syndrome	
PROK2 (3p21.1)	Autosomal recessive Kallmann syndrome	
PROKR2 * (20p12.3)		
CHD7 (8p12.1)	Autosomal dominant (some)	CHARGE syndrome includes hyposmia
Normosmic Isolated Hypogonadotropic Hypogonadism		
GNRH1 (8p21-11.2)	Autosomal recessive	
GNRHR * (4q13.2-3)	Autosomal recessive (± dominant)	
GPR54 * (19p13.3)	Autosomal recessive	
SNRPN		Prader-Willi syndrome
Lack of function of paternal 15q11-q13 region or maternal uniparental disomy		Obesity
LEP (7q31.3)	Autosomal recessive	Obesity
LEPR (1p31)	Autosomal recessive	Obesity
NR0B1 (DAX1) (X21.3-21.2)	X-linked recessive	Adrenal hypoplasia
TAC3 (12q13-12)	Autosomal recessive	
TACR3 (4q25)	Autosomal recessive	
Multiple Pituitary Hormone Deficiencies		
PROP1 (POU1F1)	Autosomal recessive GH, PRL, TSH, and LH/FSH (less commonly, later-onset ACTH deficiency)	
HESX1 (RPX)	Autosomal recessive; and heterozygous mutations	Septo-optic dysplasia
	Multiple pituitary deficiencies including diabetes insipidus, but LH/FSH uncommon	
LHX3	Autosomal recessive GH, PRL, TSH, FSH/LH	Rigid cervical spine

PHF6	X-linked; GH, TSH, ACTH, LH/FSH	Börjeson-Lehmann syndrome: mental retardation; facies

[*] AG-protein–coupled receptor.

ACTH , Adrenocorticotropic hormone; *CHD7* , chromatin-remodeling factor; *DAX1* , dosage-sensitive sex reversal-adrenal hyperplasia congenita critical region on the X chromosome, gene 1; *FGF* , fibroblast growth factor; *FSH* , follicle-stimulating hormone; *GH* , growth hormone; *GNRH* , gonadotropin-releasing hormone; *GPR54* , kisspeptin G protein–coupled receptor 54; *HESX1* , homeobox gene expressed in ES cells; *IHH* , idiopathic hypogonadotropic hypogonadism; *LEP* , leptin; *LH* , luteinizing hormone; *LHX3* , lim homeobox gene 3; *NELF* , nasal embryonic luteinizing hormone–releasing factor; *NR0B1* , nuclear receptor family 0, group B, member 1; *PHF6* , plant homeodomain–like finger gene; *PRL* , prolactin; *PROK2* , prokineticin 2; *PROP1* , prophet of Pit-1; R, receptor; *SNRPN* , small nuclear ribonucleoprotein polypeptide SmN; *TAC3* , neurokinin 3; *TSH* , thyroid-stimulating hormone.

From Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier, Table 25.19, p 1138.

- hypergonadotropic hypogonadism: high gonadotropin levels as a result of a lack of negative feedback because of a gonadal problem (see Tables 578.3 and 578.4). Females may have isolated absence of adrenarche with normal breast development.

Constitutional Delay of Growth and Puberty

This is the most common cause of delayed puberty and is thought to be a normal variant. It is usually diagnosed in males, probably as a result of ascertainment bias of referral patterns. The cause is unknown, but approximately 50% of affected patients have a first-degree relative with delayed puberty and/or late growth. This tendency can occur in a child of the same gender as the affected parent or in a child of the opposite gender. An affected child typically presents in early adolescence, when peers are beginning to develop and having growth spurts, but the patient is not. The patient's height is usually at or below the 3rd percentile (see Chapter 573). In the classical case, the affected child had a normal length at birth, a slowdown in height velocity between 6 mo and 2 yr of age that resulted in short stature, and a normal or near-normal height velocity thereafter along the child's current height percentile. The physical examination findings are unremarkable and, depending on the age, the child may have delayed puberty. The cardinal diagnostic result is a bone age that is moderately delayed in comparison with chronologic age. There may also be a history of delayed dentition. Without intervention, final adult height usually reaches or approximates the target height range. However, children with constitutional delay may have a blunted pubertal growth spurt in relation to their peers and therefore may not reach their genetic target height range.

Hypogonadotropic Hypogonadism

A variety of CNS insults may disrupt production of gonadotropins. The GnRH pulse generator may be disrupted by an interfering substance, such as excess prolactin (with or without hypothyroidism), or by stress, chronic illness, malnutrition, or excessive physical activity. The hypothalamic arcuate nucleus may be damaged by trauma, radiation, infection, infiltration, increased intracranial pressure, or surgery. The most common mass lesions are craniopharyngiomas, gliomas, and cysts. Congenital conditions or malformations may have allowed enough GnRH for infantile development but not enough for pubertal needs.

Kallmann Syndrome

This is the combination of impaired or absence of sense of smell and gonadotropin deficiency. Other features include color blindness, atrial septal defects, and renal structural anomalies (unilateral renal agenesis). The X-linked form is caused by a mutation of the *KAL* gene; there are autosomal recessive and autosomal dominant forms.

LH and FSH deficiencies may also be isolated or caused by multiple pituitary hormone deficiencies. The latter condition may be a result of pituitary damage from trauma, radiation, infection, sickle cell disease, compression by infiltrate or tumor, or autoimmune processes. In differentiating primary pituitary deficiency from that secondary to hypothalamic deficiency, the clinician should remember that all pituitary hormones except prolactin are stimulated by hypothalamic-releasing hormones; prolactin is inhibited by hypothalamic prolactin inhibitory factor. Therefore, if all pituitary hormones, including prolactin, are deficient, the problem is in the pituitary gland. If prolactin levels are present or even elevated but the other pituitary hormones are deficient, the problem is above the pituitary gland, in the stalk or hypothalamus. In the case of isolated LH and FSH deficiencies, the primary abnormality may lie within the pituitary or hypothalamic neurons producing GnRH; there is evidence of primary abnormalities being further upstream. In particular, defects in molecules required for proper migration of GnRH neurons (including the *KAL* gene) or lack of necessary signaling to GnRH-producing neurons (defects in kisspeptin or Neurokinin B and their receptors) can result in LH and FSH deficiency through inappropriate GnRH secretion.

Hypergonadotropic Hypogonadism: Males

If the testes are small, they may have been damaged by torsion, sickle cell disease, infection, autoimmune disease, chemotherapy, or radiation and may not be able to respond to LH and FSH stimulation. If the bone age is greater than 10 yr and the hypothalamus has probably matured, the serum LH and FSH may then be high.

When the testis size is prepubertal and LH is present, but testosterone is not increasing, there may be a problem with the LH receptor.

Klinefelter Syndrome

This occurs in 1 : 500 males and is often associated with a 47,XXY karyotype; common features include reduced intelligence, adolescent gynecomastia (often pronounced), and small, firm testes. The testes rarely exceed 5 mL in volume (approximately 25% of the average adult volume). Patients, often tall and thin with an eunuchoid habitus, may have delayed puberty. Virilization may be incomplete, the phallus is often smaller than average, and infertility is near 100%.

Hypergonadotropic Hypogonadism: Females

In this condition, the ovary may be unable to synthesize estrogen (an inherited metabolic defect, possibly associated with excess adrenal mineralocorticoid and hypertension), the ovary may not be formed normally (dysgenesis), or the ovary may have been damaged by any of the factors listed for testicular damage and by galactosemia.

The ovary may be intact but may not be stimulated by gonadotropins. Gonadotropins are present but not effective if there is an FSH receptor problem.

Turner Syndrome

The 2 most common features of Turner syndrome are short stature (involving the limbs to a greater degree than the trunk) and ovarian insufficiency. Lymphedema and a webbed neck are diagnostic features present in a neonate. Additional features include shield chest, increased carrying angle (cubitus valgus), short 4th metacarpal, hypoplastic nails, renal anomalies, and left-sided heart defects (coarctation of the aorta, bicuspid mitral valve, etc.). Approximately 50% of affected girls have no stigmata except short stature and thus are typically identified later. About 20% may have spontaneous puberty with functioning ovaries for at least a short period of time, which is in large part dependent on the child's karyotype, but the infertility rate is greater than 99%.

Females with Delayed or Absent Adrenarche

If a female has advanced breast development but no androgen signs, she may have a deficiency of androgen receptors, as occurs in **androgen insensitivity syndrome** (testicular feminization). In females, the androgens come predominantly from the adrenal glands (adrenarche). If the bone age has not passed 8 yr, when DHEAS generally increases, adrenarche may simply be delayed (delayed adrenarche). However, if bone age is advanced, there is a deficiency in androgen production. In addition, there may be an inherited problem in androgen synthesis from an enzyme deficiency, or the adrenal may be damaged secondary to autoimmune, infectious, or hypoxic injury. In these latter conditions, other signs of adrenal insufficiency would be evident.

Diagnostic Approach to Delayed Puberty

A normal growth rate with delayed, but not absent puberty, and a family history of late blooming suggests the diagnosis of constitutional delay of growth and puberty, which is the most commonly encountered cause. A bone age that correlates with the patient's pubertal status confirms the clinical impression; no other testing is necessary.

Initial evaluation should include:

- medical history: trauma, illness, medications (e.g., stimulants, chemotherapy), radiation, infection, malnutrition, autoimmune problems, sickle cell disease status, stresses, growth records, galactosemia

◆ review of symptoms: vision problems, headache, vomiting, inability to detect odors (hyposmia or anosmia), age at onset of androgen signs, age at onset of estrogen signs, small genitalia at birth, signs of primary adrenal insufficiency such as hyperpigmentation, need for deodorant, need to wash hair more frequently

◆ family history: timing of maternal and paternal growth and pubertal development; siblings and cousins with delayed development

◆ physical examination: signs of chronic disease, temperature, blood pressure, height, weight, head circumference, dental age, tanning (hyperpigmentation), pubic and axillary hair, adult body odor, skin and hair oils, visual fields, optic discs, ability to detect odors, breast development, vaginal cornification/discharge, penis size, scrotal development, testicular volume, pubic hair stages, neurologic status, affect or mood, intellectual ability, dysmorphic features

Initial laboratory evaluation screens for chronic disease (complete blood cell count, chemistry profile, sedimentation rate), hypothyroidism (free thyroxine and TSH), and hyperprolactinemia (prolactin level) should be obtained. If growth is slow, the clinician should measure insulin-like growth factor-1 level (marker of basal GH activity) and consider GH testing. The clinician should measure testosterone levels in males and estradiol levels in females.

Measurements of random FSH and LH and results of a GnRH stimulation test may differentiate between hypogonadotropic hypogonadism and primary gonadal failure (Figs. 578.6 and 578.7). Elevated gonadotropin levels support a diagnosis of primary gonadal failure. Chromosomal karyotyping is then performed (Klinefelter syndrome in males and Turner syndrome in females). GnRH stimulation testing, with measurement of serum LH levels over 1-2 hr, is often used. Its rationale is based on the fact that a child in puberty has a significant rise in serum LH over baseline. Unfortunately, the GnRH test is not helpful in distinguishing between constitutional delay and hypogonadotropic hypogonadism because, in both cases, the LH response is blunted secondary to lack of endogenous GnRH priming of the gonadotrophs. However, the child with constitutional delay eventually develops an appropriate pubertal response to GnRH stimulation testing.

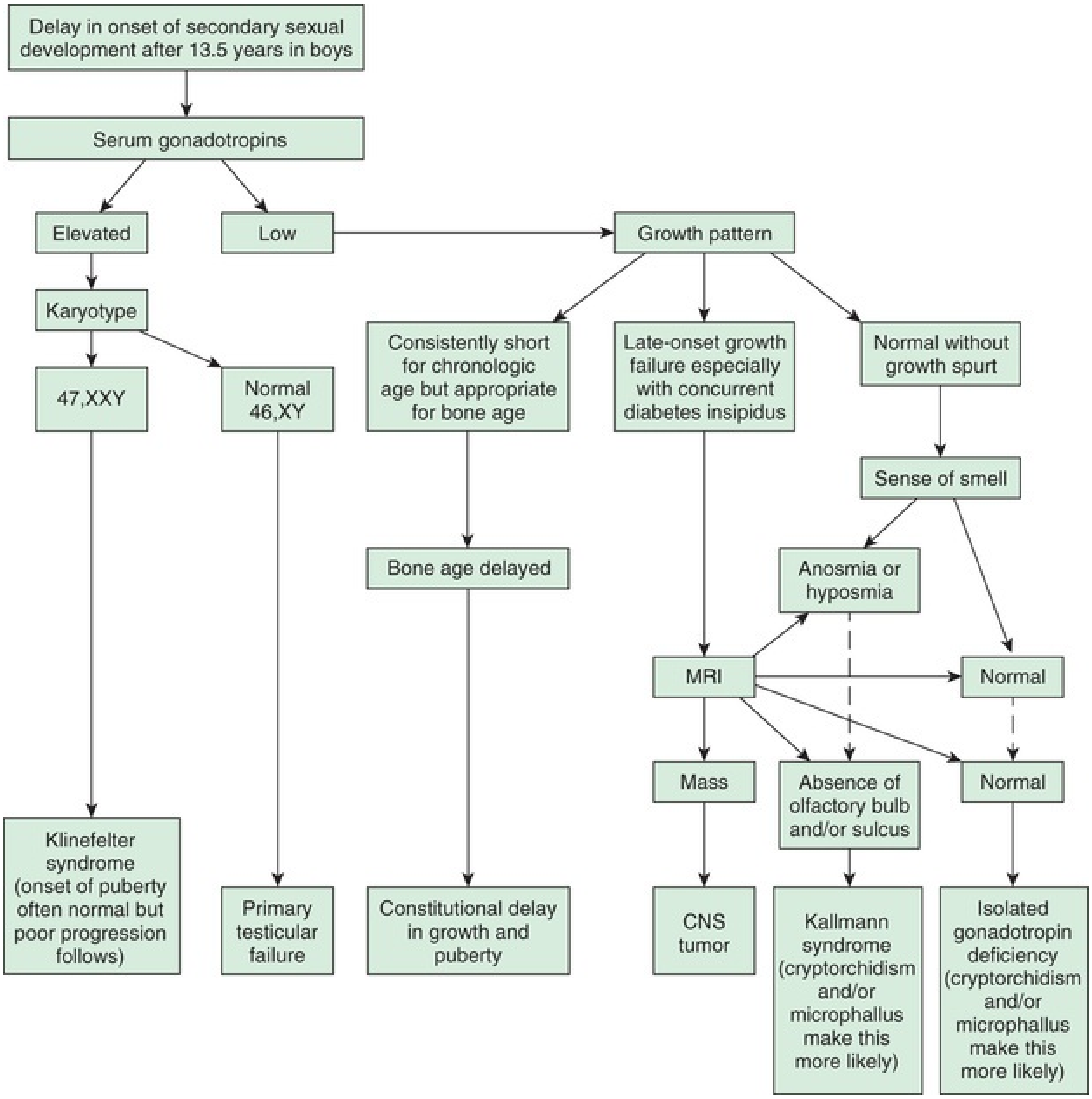
Delay in onset of secondary sexual development after 13.5 years in boys
Serum gonadotropins
Elevated
Low
Growth pattern
Karyotype
47,XXY
Normal 46,XY
Consistently short for chronologic age but appropriate for bone age
Late-onset growth failure especially with concurrent diabetes insipidus
Normal without growth spurt
Sense of smell
Bone age delayed
Anosmia or hyposmia
MRI
Normal
Mass
Absence of olfactory bulb and/or sulcus
Normal
Klinefelter syndrome (onset of puberty often normal but poor progression follows)
Primary testicular failure
Constitutional delay in growth and puberty
CNS tumor
Kallmann syndrome (cryptorchidism and/or microphallus make this more likely)
Isolated gonadotropin deficiency (cryptorchidism and/or microphallus make this more likely)

FIG. 578.6 Diagnostic algorithm for the evaluation of delayed puberty in males. *CNS* , Central nervous system; *MRI* , magnetic resonance imaging. (From Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier, Fig. 25.48.)

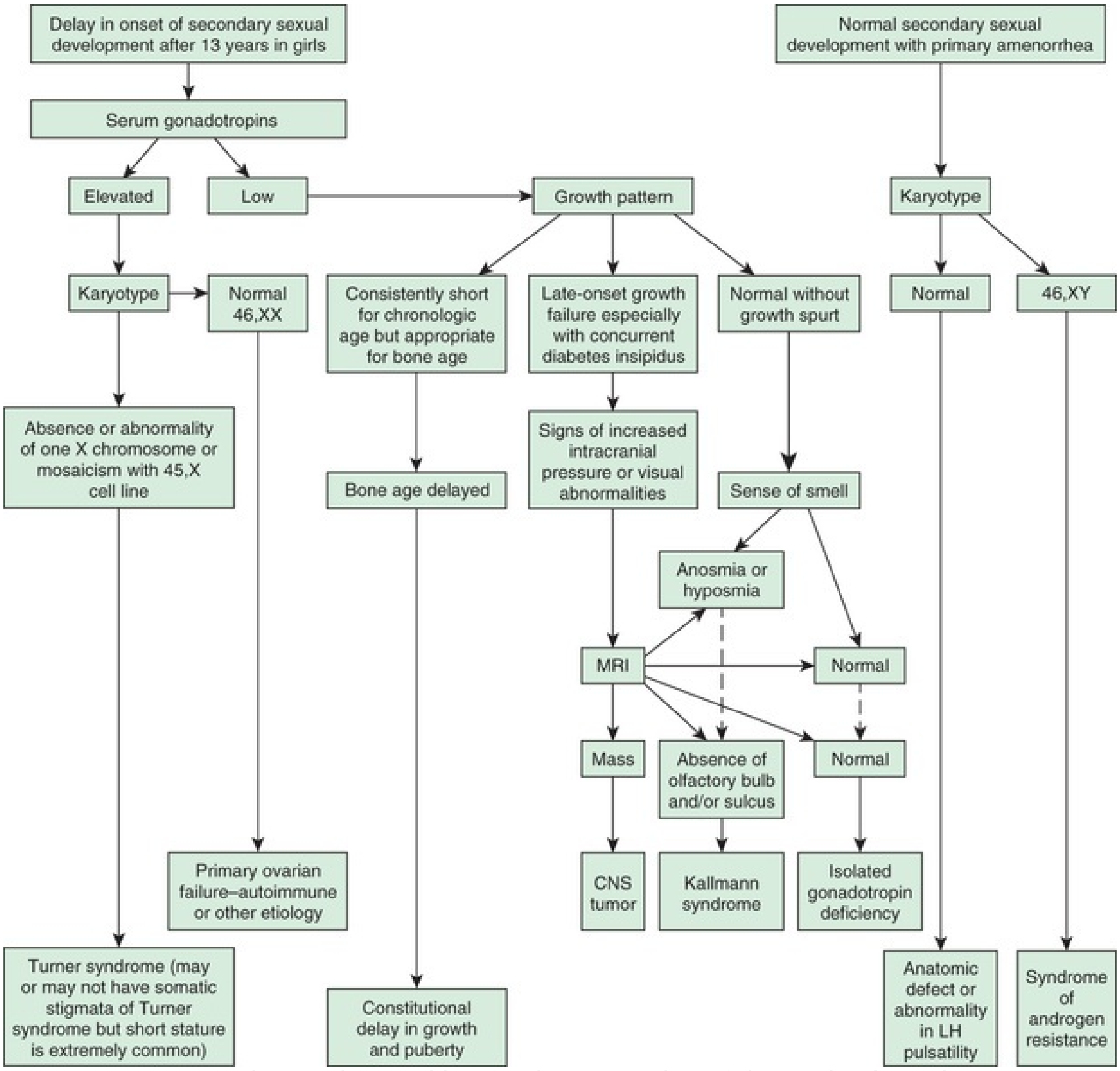
Delay in onset of secondary sexual development after 13 years in girls
Serum gonadotropins
Elevated
Low
Growth pattern
Normal secondary sexual development with primary amenorrhea
Karyotype
Karyotype
Normal 46,XX
Consistently short for chronologic age but appropriate for bone age
Late-onset growth failure especially with concurrent diabetes insipidus
Normal without growth spurt
Normal
46,XY
Absence or abnormality of one X chromosome or mosaicism with 45,X cell line
Bone age delayed
Signs of increased intracranial pressure or visual abnormalities
Sense of smell
Anosmia or hyposmia
MRI
Normal
Mass
Absence of olfactory bulb and/or sulcus
Normal
Primary ovarian failure–autoimmune or other etiology
CNS tumor
Kallmann syndrome
Isolated gonadotropin deficiency
Turner syndrome (may or may not have somatic stigmata of Turner syndrome but short stature is extremely common)
Constitutional delay in growth and puberty
Anatomic defect or abnormality in LH pulsatility
Syndrome of androgen resistance

FIG. 578.7 Diagnostic algorithm for the evaluation of delayed puberty in females. *CNS* , Central nervous system; *MRI* , magnetic resonance imaging. (From Styne DM, Grumbach MM: Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier, Fig. 25.49, p 1157.)

If Kallmann syndrome is being considered, a magnetic resonance imaging scan may show abnormalities in the olfactory region. If a 46,XX female has unexplained ovarian failure, antiovarian antibodies are obtained and müllerian-inhibiting substance can also be used in girls to assess ovarian follicle reserve and potential fertility. An hCG stimulation test to evaluate ability to produce testosterone and a serum level of müllerian-inhibiting substance (secreted by Sertoli cells) are useful for determining whether functional testicular tissue is present.

Treatment of Delayed Puberty

If delayed puberty is physiologic, there is no medical necessity for initiating sex steroid replacement. Watchful waiting is usually the appropriate course of action. Adolescent males with constitutional delay of growth and puberty who are short, underdeveloped, and psychologically compromised frequently benefit from a short course of testosterone therapy. This is usually given as long-acting intramuscular testosterone, at a dosage of 50-100 mg every 3-4 wk for a course ranging between 3 and 12 mo. Treatment is generally begun at about 13 yr of age and, if possible, when the testes are about 6-8 mL in volume. These doses stimulate height and weight gain, allow adequate virilization (increased pubic and axillary hair growth and penile enlargement), and do not typically suppress pituitary FSH and LH secretion, thereby allowing simultaneous endogenous pubertal progression (testicular enlargement). This narrows the physical gap between the patient and peers, without causing undue advancement of bone age. Acne is the principal side effect, and the adult height is not altered. It is the hope that at the conclusion of treatment, the male will continue to grow and develop rapidly with the testosterone treatment perceived as a jump starter of endogenous puberty. A short course of low-dose anabolic steroids, such as oxandrolone or fluoxymesterone, can also be used in prepubertal and pubertal males, and low-dose estradiol has been used in prepubertal and pubertal females with constitutional delay.

Treatment of hypogonadism is aimed at mimicking normal physiology with stepwise replacement of testosterone in males and estrogen and progesterone in females. For males with hypogonadism, low-dose parenteral testosterone is initiated at 50 mg every 3-4 wk, with increases in 50-mg increments made over a 2-3 yr period. Most adult men receive 200 mg every 3-4 wk, which is based on the daily adult male testosterone production rate of 6 mg. Some adult men are treated with 300 mg every 2 wk. Adult men can use testosterone by patch, which is often associated with local irritation, or by gel, but, typically in growing adolescents, intramuscular testosterone is prescribed.

For females, daily estrogen therapy is given for 1 yr. This can be either in the form of conjugated estrogens (Premarin) at 0.3 mg daily for the first 6 mo and 0.625 mg daily for the second 6 mo, or with an analogous schedule of ethinyl estradiol replacement or through a weekly applied 17β-estradiol patch. This duration does not place the uterus at undue risk for hyperplasia and malignancy, but after 2 yr of therapy (or if spotting occurs prior), progesterone should be added. Options to consider when adding progesterone include continuing the purely estrogen containing pills (conjugated estrogens or ethinyl estradiol) or the 17β-estradiol patches in conjunction with oral medroxyprogesterone acetate (Provera) or switching the patient over to conventional oral contraceptives. If the patient is not put on a conventional oral contraceptive, the estrogen (pill or patch) is prescribed days 1-23 of the calendar month with addition of medroxyprogesterone acetate on days 10-23. With this approach, withdrawal bleeding generally occurs between day 23 and the end of the month, although there can be some variability in the timing between patients.

Patients of either sex with hypogonadotropic hypogonadism are potentially fertile, but sex-steroid therapy alone is ordinarily not sufficient to initiate gametogenesis, although there are rare cases in males in which testosterone replacement alone has stimulated spermatogenesis. The general approach to fertility induction in either sex involves addition of either cyclical gonadotropin therapy or pump-driven GnRH therapy at the age of desired conception. *Finally, if hypogonadotropic hypogonadism is present as one component of hypopituitarism, it is critical to adequately replace all deficient hormones.* In contrast, patients with primary hypogonadism have intrinsic gonadal damage and are normally infertile.

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[*] Portions of this chapter were previously published in Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis* . Philadelphia, 2018, Elsevier.

SECTION 2

Disorders of the Thyroid Gland

OUTLINE

Chapter 579 Thyroid Development and Physiology

Chapter 580 Disorders of Thyroxine-Binding Globulin

Chapter 581 Hypothyroidism

Chapter 582 Thyroiditis

Chapter 583 Goiter

Chapter 584 Thyrotoxicosis

Chapter 585 Carcinoma of the Thyroid

Chapter 586 Autoimmune Polyglandular Syndromes

Chapter 587 Multiple Endocrine Neoplasia Syndromes

CHAPTER 579

Thyroid Development and Physiology

Ari J. Wassner, Jessica R. Smith

Fetal Development

The fetal thyroid arises from an outpouching of the foregut at the base of the tongue (foramen cecum). It migrates to its normal location over the thyroid cartilage by 8-10 wk of gestation. The thyroid bilobed shape is recognized by 7 wk of gestation, and characteristic thyroid follicle cell and colloid formation is seen by 10 wk. Thyroglobulin synthesis occurs from 4 wk, iodine trapping occurs by 8-10 wk, and thyroxine (T_4) and, to a lesser extent, triiodothyronine (T_3) synthesis and secretion occur from 12 wk of gestation. There is evidence that several transcription factors—including NKX2.1, FOXE1, and PAX8—are important in thyroid gland morphogenesis and differentiation, and possibly also in its caudal migration to its final location. These factors bind to the promoters of the thyroglobulin and thyroperoxidase (TPO) genes and so influence thyroid hormone production. Hypothalamic neurons synthesize thyrotropin-releasing hormone (TRH) and thyrotropin (TSH) secretion is evident by 10-12 wk of gestation. Maturation of the hypothalamic-pituitary-thyroid axis occurs over the second half of gestation, but normal feedback relationships are not mature until 1-3 mo of postnatal life. Other transcription factors, including PROP1 and POU1F1, are important for differentiation and growth of thyrotrophs, along with somatotrophs and lactotrophs.

Thyroid Physiology

The main function of the thyroid gland is to synthesize T_4 and T_3 . The only known physiologic role of iodine is in the synthesis of these hormones. The daily recommended dietary allowance of iodine is 110-130 µg for infants, 90-120 µg for children, and 150 µg for adolescents and adults.

The median iodine intake in the United States decreased by approximately 50% between the 1970s (320 µg/L) and the 1990s (145 µg/L), but it appears to have stabilized (2009-2010 = 144 µg/L). Whatever the chemical form ingested, iodine eventually reaches the thyroid gland as its ionized form, iodide [I^-]. Thyroid tissue has an avidity for iodide and is able to trap (with a gradient of 100 : 1), transport, and concentrate it in the follicular lumen for synthesis of thyroid hormone. Entry of iodide from the circulation into the thyroid follicular cell is carried out by the sodium–iodide symporter (NIS). Iodide diffuses across the cell to the apical membrane where it is transported into the colloid via pendrin (and likely at least one other unidentified transporter).

To form thyroid hormone, trapped inorganic iodide must be organified onto tyrosine residues of thyroglobulin in the follicular lumen. This reaction is catalyzed by TPO and requires H_2O_2 produced by the enzyme DUOX2, the expression of which depends in turn on dual oxidase maturation factor 2 (DUOXA2). Thyroglobulin is a large homodimeric glycoprotein with a molecular weight of approximately 660 kDa that contains 138 tyrosine residues. Iodination of about 14 of these tyrosines forms monoiodotyrosine (MIT) or diiodotyrosine (DIT). Two molecules of DIT then couple to form one molecule of T_4 , or one molecule of DIT and one of MIT couple to form T_3 . Once formed, hormones remain stored as part of thyroglobulin in the colloid of the follicular lumen until ready to be secreted from the thyroid. T_4 and T_3 are liberated when the follicular cell endocytoses colloid and the thyroglobulin is degraded by endosomal proteases and peptidases.

In adults, the thyroid secretes approximately 85 µg of T_4 and 6-7 µg of T_3 daily. Only 20% of circulating T_3 is secreted by the thyroid, while the remainder is produced by deiodination of T_4 in extrathyroidal tissues by iodotyrosine deiodinases (types 1 and 2). In the pituitary and brain, approximately 80% of required T_3 is produced locally from T_4 by type 2 deiodinase. Although it is present in the blood only about one-fiftieth the concentration of T_4 , T_3 is the physiologically active thyroid hormone because it binds the thyroid hormone receptor with 10- to 15-fold greater affinity than T_4 .

Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation, and affect carbohydrate, lipid, and vitamin metabolism. Entry of T_4 and T_3 into cells is facilitated by specific thyroid hormone transporters, of which the most important is monocarboxylate transporter 8 (MCT8). Once inside the cell, T_4 is converted to T_3 by type 1 or 2 deiodinase. Intracellular T_3 then enters the nucleus and binds to thyroid hormone receptors. Thyroid hormone receptors are members of the steroid hormone receptor superfamily that includes receptors for glucocorticoid, androgen, estrogen, progesterone, vitamin D, and retinoids. Four thyroid hormone receptor isoforms (α_1 , α_2 , β_1 , and β_2) are expressed in different tissues, although it is unknown whether $TR\alpha_2$ has any physiologic function. Thyroid hormone receptors consist of a ligand-binding domain that binds T_3 , a hinge region, and a DNA-binding domain (zinc finger) that binds to thyroid hormone receptor response elements. Binding of T_3 to the thyroid hormone receptor causes recruitment of co-activator molecules, transcription of messenger RNA, and protein synthesis. Thus the multiple levels of regulation of thyroid hormone signaling, including deiodination, transmembrane transport, and thyroid hormone receptor expression allow tissue-specific modulation of thyroid hormone action in the face of a given level of circulating T_4 .

Approximately 70% of circulating T_4 is bound to thyroxine-binding globulin (TBG), and most of the remainder is bound to albumin and prealbumin (also called *transthyretin*). Only 0.03% of serum T_4 is unbound and comprises free T_4 . Approximately 50% of circulating T_3 is bound to TBG and 50% is bound to albumin, while only 0.3% of T_3 is unbound or free T_3 . Because the concentration or binding of TBG is altered in many clinical circumstances, its status must be considered when interpreting total T_4 or T_3 levels.

Thyroid Regulation

The thyroid is regulated by TSH, a glycoprotein hormone secreted by the anterior pituitary. Binding to the TSH receptor activates adenylate cyclase in the thyroid gland and stimulates all steps of thyroid hormone biosynthesis, from uptake of iodine to release of thyroid hormones (see Fig. 572.1). TSH is a heterodimer composed of α and β subunits. The α subunit is common to luteinizing hormone, follicle-stimulating hormone, and chorionic gonadotropin, while the specificity of each hormone is conferred by the unique β subunit. TSH synthesis and release are stimulated by TRH, a tripeptide that is synthesized in the hypothalamus and secreted into the pituitary. In states of decreased thyroid hormone, TSH and TRH are increased, while increased thyroid hormone inhibits TSH and TRH production. Although TSH levels can be measured in serum, circulating levels of TRH are very low outside the neonatal period.

Further control of the level of circulating thyroid hormones occurs in the periphery. In many nonthyroidal illnesses, circulating T_3 levels fall due to decreased extrathyroidal production of T_3 by type 1 deiodinase and increased inactivation of T_4 (to reverse T_3) and T_3 (to T_2) by type 3 deiodinase. These changes may be induced by factors such as fasting, chronic malnutrition, acute illness, and certain drugs. Although levels of T_3 may be significantly decreased, levels of free T_4 and TSH may remain normal. The decreased levels of T_3 may be a physiologic adaptation, resulting in decreased rates of oxygen consumption, of substrate use, and of other catabolic processes.

579.1

Thyroid Hormone Studies

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Serum Thyroid Hormones

Methods are available to measure all the thyroid hormones in serum: T_4 , free T_4 , T_3 , and free $T_{3.}$ The metabolically inert reverse T_3 (rT_3 or 3,5′,3′-triiodothyronine) is also present in serum, but measuring rT_3 is rarely clinically useful. Direct free T_4 assays are widely available and are generally reliable in healthy patients; however, these assays may be unreliable during acute illness or with severe abnormalities of thyroid hormone binding. Therefore, in such situations it may be preferable to measure total T_4 and an index of TBG binding, or to measure free T_4 by the gold standard technique of equilibrium dialysis.

Many free T_3 assays are poorly standardized, and their clinical utility is limited. Age must be considered in interpreting all thyroid hormone results, particularly in the neonate.

Thyroglobulin is a glycoprotein that is secreted through the apical surface of the thyroid follicular cell into the colloid. Small amounts escape into the circulation and are measurable in serum. Levels of thyroglobulin increase with TSH stimulation and decrease when TSH is suppressed. Serum thyroglobulin levels are increased in the neonate, in patients with Graves disease and other forms of autoimmune thyroid disease, and in those with endemic goiter. Marked elevations of thyroglobulin can also occur in patients with differentiated carcinoma of the thyroid. Athyreotic infants have markedly reduced levels of thyroglobulin in serum.

Serum TSH levels are the most sensitive test for primary thyroid dysfunction. Serum TSH levels are elevated in primary hypothyroidism and suppressed in hyperthyroidism. After the neonatal period, normal levels of TSH are < 5 mIU/L. In central (secondary) hypothyroidism, serum TSH is either low or inappropriately in the normal range despite a low serum T_4 or free T_4 level. Although it may be normal in concentration, TSH is less biologically active in patients with central hypothyroidism. The availability of sensitive assays for TSH and free T_4 obviates the need for TRH stimulation in the diagnosis of most patients with thyroid disorders.

Fetal and Newborn Thyroid

Fetal serum T_4 and free T_4 increase progressively from midgestation to approximately 9.5 µg/dL and 1.4 ng/dL, respectively, at term. Fetal levels of T_3 are low before 20 wk and then gradually increase to approximately 60 ng/dL at term. Reverse T_3 levels, however, are high in the fetus (300 ng/dL at 30 wk) and decrease to 200 ng/dL at term. Serum levels of TSH gradually increase to 6 mIU/L at term. Approximately one third of maternal T_4 crosses the placenta to the fetus. Maternal T_4 plays a role in fetal development, especially that of the brain, before the synthesis of fetal thyroid hormone begins. Therefore, a hypothyroid fetus may be partially protected until delivery by maternal T_4 if the mother is euthyroid but may be at risk for neurologic injury if the mother is hypothyroid. The amount of T_4 that crosses the placenta generally is not sufficient to interfere with a diagnosis of congenital hypothyroidism in the neonate.

At birth, there is an acute release of TSH, with peak serum concentrations reaching 70-100 mIU/L 30 min following delivery in full-term infants. A rapid decline occurs over the ensuing 24 hr, and a more gradual decline over the next 5 days to <10 mIU/L. The acute increase in TSH produces a dramatic increase in levels of T_4 to approximately 16 µg/dL and of T_3 to approximately 300 ng/dL in about 4 hr. This T_3 appears to be largely derived from increased peripheral conversion of T_4 to T_3 . T_4 levels gradually decrease during the first 2 wk of life to 10-12 µg/dL. T_3 levels decline during the 1st wk of life to below 200 ng/dL. Serum free T_4 levels are 0.9-2.3 ng/dL in infancy and decline to 0.7-1.8 ng/dL in childhood. Serum free T_3 concentrations are approximately 180-760 pg/dL in infancy and decline to 230-650 pg/dL in childhood. Reverse T_3 levels remain high for 2 wk (200 ng/dL) and decrease by 4 wk to around 50 ng/dL. In preterm infants, changes in thyroid function after birth are qualitatively similar to but quantitatively smaller than in full-term infants. Serum T_4 and T_3 levels are decreased in proportion to gestational age and birth weight.

Serum Thyroxine-Binding Globulin

The thyroid hormones are transported in plasma bound primarily to TBG, a glycoprotein synthesized in the liver. Estimation of TBG binding is occasionally necessary because it is increased or decreased in a variety of clinical situations, with effects on the level of total T_4 and T_3 . TBG binds approximately 70% of T_4 and 50% of T_3 . TBG levels increase in pregnancy, in the newborn period, with hepatitis, and with administration of estrogens (oral contraceptives), selective estrogen receptor modulators, heroin or methadone, mitotane, and 5-fluorouracil. TBG levels decrease with androgens, anabolic steroids, glucocorticoids, nicotinic acid, and L -asparaginase. These effects are the results of modulation of hepatic synthesis of TBG. TBG levels may be markedly decreased owing to decreased production with hepatocellular disease, or due to massive protein loss in the gut (protein-losing enteropathies) or the urine (congenital nephrotic syndrome). Decreased or increased levels of TBG also occur as genetic traits (see Chapter 580).

Some drugs, including furosemide, salicylates, nonsteroidal antiinflammatory drugs, and heparin, as well as free fatty acids, inhibit binding of T_4 and T_3 to TBG. In addition, phenytoin, carbamazepine, phenobarbital, and rifampin can decrease T_4 levels by stimulating hepatic cytochrome P450-mediated conjugation and excretion of T_4 .

Radionuclide Studies

The availability of highly sensitive tests of thyroid function has decreased the necessity for radioiodine uptake studies except in specific clinical situations. The ability of the thyroid to take up and organify iodine can be evaluated by measuring the uptake of radioactive isotope ^{123} I (half-life: 13 hr) using doses of radioiodine (0.1-0.5 mCi) that are only a fraction of those used with ^{131} I. Technetium (^{99m} Tc) is a useful radioisotope for children because, in contrast to iodine, it is trapped but not organified by the thyroid and has a half-life of only 6 hr. Thyroid scanning may be indicated to assess for possible thyroid dysgenesis and to detect ectopic thyroid tissue, and to evaluate possible autonomous (hot) thyroid nodules. Diagnostic studies should be performed with ^{99m} Tc pertechnetate or ^{123} I because they have the advantages of lower radiation exposure and high-quality scintigrams. Radioiodine treatment for children with Graves hyperthyroidism or differentiated thyroid cancer employs ^{131} I, which has a longer half-life (8 days) and greater cytotoxic effect.

Thyroid Ultrasonography

Thyroid ultrasound can determine the location, size, and shape of the thyroid gland, as well as the characteristics of thyroid nodules. Ultrasound can also be used to evaluate infants with suspected thyroid dysgenesis, but its sensitivity is user-dependent, and it will not reliably detect ectopic thyroid glands. Ultrasound examinations are useful in identifying normal thyroid gland position in children with suspected thyroglossal duct cysts. In children with autoimmune thyroiditis, ultrasound may reveal heterogeneous echotexture. Ultrasound examinations are more accurate than physical examination in estimating thyroid gland size and assessing thyroid nodules. Certain characteristics of thyroid nodules, such as irregular margins, microcalcifications, hypoechogenicity, and taller-than-wide shape increase the likelihood that a thyroid nodule is malignant, although none of these features is 100% sensitive or specific.

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CHAPTER 580

Disorders of Thyroxine-Binding Globulin

Ari J. Wassner, Jessica R. Smith

Abnormalities in levels of thyroxine-binding globulin (TBG) are not associated with clinical disease and do not require treatment. They are usually uncovered by a chance finding of abnormally low or high levels of thyroxine (T_4) and may be a source of confusion in the diagnosis of hypothyroidism or hyperthyroidism.

Congenital TBG deficiency is an X-linked dominant trait. It is most often discovered through screening programs for neonatal hypothyroidism that measure levels of T_4 as the primary screening test. Affected patients have low levels of total T_4 (usually <4 µg/dL) and elevated triiodothyronine (T_3) resin uptake, but levels of free T_4 and thyrotropin (TSH) are normal. The diagnosis is confirmed by the finding of absent or low serum levels of TBG. No treatment is required, but testing may be indicated in potentially affected family members to avoid the incorrect diagnosis of hypothyroidism in the future. TBG deficiency occurs in 1 in 1,700 male newborns, 36% of whom have TBG levels <1 mg/dL. Milder forms of TBG deficiency occur in approximately 1 in 15,000 female newborns, who are heterozygous carriers. Complete TBG deficiency (serum TBG <0.5 mg/dL) in females is extremely rare. More than 40 different mutations have been reported in the TBG gene that result in either decreased TBG levels or reduced affinity of TBG for T_4 . **Acquired** causes of TBG deficiency are listed in Table 580.1 .

Table 580.1

Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

DECREASED TBG	INCREASED TBG

Androgens	Estrogens
Anabolic steroids	Selective estrogen receptor modulators
Glucocorticoids	Pregnancy
Hepatocellular disease	Hepatitis
Severe illness	Porphyria
Nephrotic syndrome	Heroin, methadone
Protein-losing enteropathy	Mitotane
Nicotinic acid	5-Flurouracil
L -Asparaginase	Perphenazine

TBG excess is also a benign X-linked dominant anomaly, occurring in approximately 1 in 25,000 persons. It has been recognized primarily in adults, but newborn screening programs may uncover the condition in the neonate. The level of T_4 is elevated, T_3 is variably elevated, TSH and free T_4 are normal, and T_3 resin uptake is decreased. Elevated serum levels of TBG confirm the diagnosis. Affected neonates have been found to have levels of T_4 as high as 95 µg/dL, which decrease to 20-30 µg/dL after 2-3 wk. Such high levels of T_4 may be related in part to the normal elevation of TBG in neonates, presumably an effect of maternal estrogens. Affected patients are euthyroid, but family studies may be indicated to alert other affected family members. Acquired causes of TBG excess are listed in Table 580.1 .

Familial dysalbuminemic hyperthyroxinemia is an autosomal dominant disorder that may be mistaken for hyperthyroidism. Patients have an abnormal albumin variant with a markedly increased affinity for T_4 that leads to increased serum concentrations of T_4 . Levels of T_3 are normal or slightly elevated. However, levels of free T_4 , free T_3 , and TSH are normal, and affected patients are euthyroid.

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CHAPTER 581

Hypothyroidism

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Hypothyroidism is a state of insufficient circulating thyroid hormone. Hypothyroidism almost always results from deficient production of thyroid hormone caused either by a defect in the thyroid gland itself (primary hypothyroidism) or a by reduced thyrotropin (TSH) stimulation (central or secondary hypothyroidism; Table 581.1). Hypothyroidism may be present from birth (congenital) or may be acquired, although some acquired cases are due to congenital defects in which the onset of hypothyroidism is delayed.

Table 581.1

Etiologic Classification of Congenital Hypothyroidism

PRIMARY HYPOTHYROIDISM
Defect of thyroid development (dysgenesis)
• Agenesis
• Hypoplasia
• Ectopia
Defects in Thyrotropin (TSH) responsiveness
• TSH receptor-blocking antibodies
• Mutation in TSH receptor (TSHR)
• Defects in Gsα (GNAS)—pseudohypoparathyroidism
Defect in thyroid hormone synthesis (dyshormonogenesis)
• Defective iodide uptake into follicular cell: sodium–iodide symporter (NIS)
• Defective iodide transport from follicular cell into colloid: Pendred syndrome (SLC26A4)
• Iodide organification defects: thyroperoxidase (TPO), dual oxidase 2 (DUOX2), dual oxidase maturation factor 2 (DUOXA2)
• Thyroglobulin synthesis defect: thyroglobulin (TG)
• Deiodination defect: iodotyrosine deiodinase (IYD)
• Thyroid hormone transport defect: monocarboxylate transporter 8 (SLC16A2)—X-linked
Iodine deficiency (endemic goiter)
Iodine excess
Maternal medications
• Iodides, amiodarone
• Methimazole, propylthiouracil

• Radioactive iodine (131I)
CENTRAL (SECONDARY) HYPOTHYROIDISM
Isolated TSH deficiency • Mutation in TSH β-subunit (TSHβ)—depending on mutation measured TSH level may be low, normal, or elevated • Mutation in TRH receptor (TRHR) • Mutation in IGFS1—X-linked central hypothyroidism and macroorchidism (prolactin deficiency and variable GH deficiency) Multiple pituitary hormone deficiencies • Mutation in POU1F1—deficiency of TSH, GH, and prolactin • Mutation in PROP1—deficiency of TSH, GH, LH, FSH, prolactin, and variably ACTH • Mutation in HESX1—variable deficiencies of TSH, GH, LH, FSH, prolactin, and ACTH • Mutations in other genes: OTX2, LHX3, LHX4, SOX3, FGF8, FGFR1, GLI2, LEPR

ACTH , Adrenocorticotropic hormone; *FSH* , follicle-stimulating hormone; *GH* , growth hormone; *LH* , luteinizing hormone; *TRH* , thyrotropin-releasing hormone.

Congenital Hypothyroidism

Most cases of congenital hypothyroidism are caused by abnormal formation of the thyroid gland (thyroid dysgenesis), and a minority are due to inborn errors of thyroid hormone synthesis (dyshormonogenesis) or other rarer causes. Most infants with congenital hypothyroidism are detected by newborn screening programs in the 1st few wk after birth, before any obvious clinical signs or symptoms develop. In areas with no screening program, severely affected infants usually manifest features within the 1st wk of life, but in infants with milder hypothyroidism, clinical manifestations may not be evident for months.

Epidemiology

The incidence of congenital hypothyroidism based on nationwide programs for neonatal screening was initially reported at 1 in 4,000 infants worldwide. Over the past few decades, the apparent incidence has increased to about 1 in 2,000, primarily because more stringent screening algorithms have resulted in the detection of milder cases of hypothyroidism. Studies from the United States report that the incidence is lower in African Americans and higher in Asian Americans and Pacific Islanders, Hispanics, and Native Americans as compared with white infants.

Etiology

See Table 581.1 .

Primary Hypothyroidism

Thyroid Dysgenesis.

Thyroid dysgenesis is the most common cause of permanent congenital hypothyroidism, accounting for 80–85% of cases. In approximately 33% of cases of dysgenesis, no thyroid tissue is present (**agenesis**). In the other 66% of infants, rudiments of thyroid tissue are present, either in the normal position (**hypoplasia**) or in an **ectopic** location anywhere along the embryologic path of descent of the thyroid, from the base of the tongue (lingual thyroid) to the normal position. Thyroid dysgenesis occurs twice as commonly in females as in males.

The cause of thyroid dysgenesis is largely unknown. Thyroid dysgenesis is usually sporadic, but familial cases have been reported. Thyroid developmental anomalies, such as thyroglossal duct cysts and thyroid hemiagenesis, are present in 8–10% of first-degree relatives of infants with thyroid dysgenesis. However, whether this represents a true genetic susceptibility is unclear, particularly given the high degree of discordance for thyroid dysgenesis among monozygotic twins.

About 2–5% of cases of thyroid dysgenesis are caused by genetic defects in 1 of several transcription factors important for thyroid morphogenesis and differentiation, including NKX2.1 (formerly TTF1), FOXE1 (formerly TTF2), and PAX8. NKX2.1 is expressed in the thyroid, lung, and central nervous system, and recessive mutations in *NKX2-1* cause thyroid dysgenesis, respiratory distress, and neurologic problems (including chorea and ataxia) despite early thyroid hormone treatment. Recessive mutations in *FOXE1* cause thyroid dysgenesis, spiky or curly hair, cleft palate, and sometimes choanal atresia and bifid epiglottis (**Bamforth-Lazarus syndrome**). PAX8 is expressed in the thyroid and kidney, and dominant *PAX8* mutations are associated with thyroid dysgenesis and kidney and ureteral malformations.

Inactivating mutations in the thyrotropin receptor *(TSHR)* have been described in patients with congenital hypothyroidism, including thyroid agenesis or hypoplasia. *TSHR* mutations may be homozygous, or they may be heterozygous with or without a concurrent mutation in another congenital hypothyroidism gene (such as *DUOX2* or *TG* ; see later). Infants with a severe TSHR defect have elevated TSH levels and are detected by newborn screening, whereas patients with a mild defect may remain euthyroid without treatment.

Congenital hypothyroidism can also occur in infants with pseudohypoparathyroidism type 1a. These patients have somatic inactivating mutations of the G-protein stimulatory α-subunit G_s α (GNAS), leading to impaired signaling of the TSH receptor (see Chapter 590).

Defects in Thyroid Hormone Synthesis (Dyshormonogenesis).

A variety of defects in the biosynthesis of thyroid hormone account for 15% of cases of permanent congenital hypothyroidism detected by neonatal screening programs (1 in 30,000-50,000 live births). These defects are usually transmitted in an autosomal recessive manner. Because the thyroid gland responds normally to elevated TSH stimulation, a **goiter** is almost always present. When the synthetic defect is incomplete, the onset of hypothyroidism may be delayed for years.

Defective Iodide Transport.

Defective iodide uptake is very rare and is caused by mutations in the sodium–iodide symporter (NIS) responsible for concentrating iodide in the thyroid gland. Among the cases reported, it has been found in 9 related infants of the Hutterite sect, and approximately 50% of the cases are from Japan. Consanguinity is a factor in approximately 30% of cases.

In the past, clinical hypothyroidism with or without a goiter often developed in the 1st few mo of life, and the condition has been detected in neonatal screening programs. However, in Japan the onset of goiter and hypothyroidism may be delayed past 10 yr of age, perhaps because of the very high iodine content of the Japanese diet.

In this disorder, the mechanism for concentrating iodide is defective in the thyroid and salivary glands. In contrast to other defects of thyroid hormone synthesis, uptake of radioiodine and pertechnetate is low. A reduced saliva:serum ratio of ^{123}I will support the diagnosis, which is confirmed by finding a mutation in the *NIS* gene. This condition responds to treatment with large doses of potassium iodide, but treatment with levothyroxine is preferable.

Pendred syndrome is an autosomal recessive disorder composed of sensorineural deafness and goiter. Pendred syndrome is caused by a mutation in the chloride–iodide transport protein pendrin *(SLC26A4)* that is expressed in the thyroid gland and the cochlea. Pendrin allows transport of iodide across the apical membrane of the follicular cell into the colloid where it undergoes organification and incorporation into the tyrosine residues on thyroglobulin. Patients with a mutation in the pendrin gene have impaired iodide organification and a positive perchlorate discharge test. Mutations in pendrin are a relatively common genetic cause of sensorineural deafness, but some patients diagnosed due to their hearing disorder have no goiter or thyroid dysfunction. This finding has fueled speculation that pendrin is not the sole apical iodine transporter in the thyroid, but to date no other such transporter has been identified.

Defects of Iodine Organification.

Defects of iodine organification are the most common type of thyroid hormone synthetic defects. After iodide is taken up by the thyroid, it is rapidly oxidized to reactive iodine, which is then incorporated into tyrosine residues on thyroglobulin. These reactions are catalyzed by the critical enzyme thyroperoxidase (TPO) and requires locally generated $H_2 O_2$ and hematin (a cofactor). Defects can occur in any of these components, and there is considerable clinical and biochemical heterogeneity. In the Dutch neonatal screening program, 23 infants were found with a complete organification defect (1 in 60,000 live births), but its prevalence in other areas is unknown. A characteristic finding in patients with this defect is a marked discharge of thyroid radioactivity when perchlorate or thiocyanate is administered 2 hr after administration of a test dose of radioiodine (perchlorate discharge of 40–90% of radioiodine compared with <10% in normal persons). Numerous mutations in the TPO gene have been reported in children with congenital hypothyroidism.

The enzyme dual oxidase 2 (DUOX2) produces the $H_2 O_2$ required for iodide organification. *DUOX2* mutations can cause permanent or transient congenital hypothyroidism. Previously, it was thought that monoallelic *DUOX2* mutations cause transient disease and biallelic mutations cause permanent disease, but the reverse has been observed in some cases, and this relationship remains unclear. *DUOX2* mutations have been reported in 15–40% of patients with apparent dyshormonogenesis, with mutation rates as high as 50–60% in studies from China and South Korea. Dual oxidase maturation factor 2 (DUOXA2) is required to express DUOX2 enzymatic activity, and recessive mutations in *DUOXA2* are a rare cause of congenital hypothyroidism.

Defects of Thyroglobulin Synthesis.

Defects of thyroglobulin synthesis are characterized by congenital hypothyroidism with goiter and absent or low levels of circulating thyroglobulin. More than 40 different mutations in the thyroglobulin gene *(TG)* have been described.

Defects in Deiodination.

Monoiodotyrosine and diiodotyrosine are normally released from thyroglobulin along with thyroxine (T_4) and triiodothyronine (T_3). The *IYD* gene (formerly *DEHAL1*) encodes the thyroidal enzyme iodotyrosine deiodinase, which deiodinates these intermediates and allows the liberated iodide to be recycled into thyroid hormone synthesis. Urinary excretion of monoiodotyrosine and diiodotyrosine in patients with rare mutations in *IYD* rapidly causes them to develop severe iodine deficiency, leading to hypothyroidism and goiter that may present soon after birth or may be delayed for months or years.

Defects in Thyroid Hormone Transport.

Passage of thyroid hormone into the cell is facilitated by specific plasma membrane transporters. Mutations in the transporter MCT8 *(SLC16A2)*, located on the X-chromosome, impair the movement of T_4 and T_3 into cells. This leads to severe neurologic manifestations including profound developmental delay, reduced muscle mass, dysarthria, athetoid movements, and hypotonia that evolves to spastic paraplegia (**Allan-Herndon-Dudley syndrome**). This syndrome is also characterized by elevated serum T_3 levels but low serum T_4 levels and normal or mildly elevated serum TSH levels.

Thyrotropin Receptor–Blocking Antibodies.

Maternal TSHR–blocking antibodies (TRBAbs) cause about 2% of cases of congenital hypothyroidism detected by neonatal screening programs (1 in 50,000-100,000 infants). Transplacentally acquired maternal TRBAb inhibits binding of TSH to its receptor in the neonate. This condition should be suspected whenever there is a history of maternal autoimmune thyroid disease, including chronic lymphocytic thyroiditis or Graves disease, maternal hypothyroidism, or transient congenital hypothyroidism in previous siblings. However, TRBAbs can cause congenital hypothyroidism in the absence of any maternal history. When suspected, maternal levels of TRBAb (measured as thyrotropin-binding inhibitory immunoglobulin [TBII]) should be measured during pregnancy. Affected infants and their mothers also can have TSHR–stimulating antibodies and TPO antibodies. Ultrasonography will typically demonstrate a normally positioned but small thyroid gland; however, thyroid tissue will often not be detected by scintigraphy with technetium pertechnetate or ^{123}I because impaired TSHR function suppresses thyroidal iodine uptake. Serum thyroglobulin levels are also low. Treatment with levothyroxine is required initially, but remission of hypothyroidism occurs in approximately 3-6 mo, once the TRBAb are cleared from the infant circulation. Correct diagnosis of this cause of congenital hypothyroidism prevents unnecessary protracted treatment and alerts the clinician to possible recurrences in future pregnancies. The prognosis is generally favorable, but developmental delay may occur in patients whose mothers had unsuspected (and untreated) hypothyroidism caused by TRBAb during pregnancy.

Radioiodine Administration.

Neonatal hypothyroidism can occur when radioiodine is administered as treatment for Graves disease or thyroid cancer to a mother during (a usually unrecognized) pregnancy. The fetal thyroid is capable of trapping iodide by 70-75 days of gestation. Therefore a pregnancy test must be performed in any woman of childbearing age before ^{131}I is given, regardless of menstrual history or reported history of contraception. Administration of radioactive iodine to lactating women is also contraindicated because it is excreted in breast milk.

Iodine Exposure.

Congenital hypothyroidism can result from fetal exposure to *excessive* iodides. Perinatal exposure can occur with the use of iodine antiseptic to prepare the skin for caesarian section or to paint the cervix before delivery. Hypothyroidism has also been reported in exclusively breastfed infants born to mothers who consume large amounts of iodine daily (up to 12 mg) in the form of nutritional supplements or who consume large quantities of iodine-rich seaweed. Iodine-induced hypothyroidism is transient once the exposure is discontinued and must not be mistaken for other forms of congenital hypothyroidism. In the neonate, especially in those of low birthweight (LBW), topical iodine-containing antiseptics used in nurseries and perioperatively can cause transient hypothyroidism, which may be detected by newborn screening tests. In older children, excess iodine may be present proprietary preparations used to treat asthma or in amiodarone, an antiarrhythmic drug with high iodine content. In most of these instances, goiter is present (see Chapter 583).

Iodine Deficiency (Endemic Goiter).

See Chapter 583.3 .

Iodine deficiency or endemic goiter is the most common cause of congenital hypothyroidism worldwide. The recommended intake of iodine in adults is 150 µg daily, increasing to 220 µg daily during pregnancy to allow for fetal iodine requirements. Despite efforts at universal iodization of salt in many countries, economic, political, and practical obstacles continue to prevent realization of this goal. Although the U.S. population is generally iodine sufficient, approximately 15% of women of reproductive age are iodine deficient. Borderline iodine deficiency is more likely to cause problems in preterm infants who depend on a maternal source of iodine for normal thyroid hormone production and who often receive insufficient dietary iodine from common preterm infant formulas that are low in iodine.

Central (Secondary) Hypothyroidism

Thyrotropin and Thyrotropin-Releasing Hormone Deficiency.

Deficiency of TSH and central hypothyroidism can occur in any condition associated with developmental defects of the pituitary or hypothalamus (see Chapter 573). Central hypothyroidism occurs in 1 in 16,000-30,000 infants, but many cases are not detected by neonatal screening, particularly because many screening programs are designed to detect only primary hypothyroidism. The majority (75%) of affected infants have multiple pituitary hormone deficiencies and may present with hypoglycemia, persistent jaundice, micropenis or cryptorchidism (in males), or midline defects such as midline cleft lip or palate or midface hypoplasia.

Congenital TSH deficiency may be caused by mutations in genes coding for transcription factors essential to pituitary development or thyrotroph cell differentiation. *POU1F1* mutations cause deficiency of TSH, growth hormone, and prolactin. Patients with *PROP1* mutations also have deficiency of TSH, growth hormone, and prolactin, as well as deficiency of luteinizing hormone and follicle-stimulating hormone and variable deficiency of adrenocorticotropic hormone. *HESX1* mutations are associated with TSH, growth hormone, prolactin, and adrenocorticotropic hormone deficiencies and are found in some patients with optic nerve hypoplasia (septo-optic dysplasia syndrome; see Chapter 609).

Isolated congenital deficiency of TSH is rare. The most common genetic cause is a mutation in *IGSF1* , a gene of unclear function, resulting in a syndrome of X-linked congenital central hypothyroidism and macroorchidism. Prolactin deficiency is usually present, and some patients also have growth hormone deficiency. Patients with mutations in the gene encoding the TSH β-subunit *(TSHB)* have central hypothyroidism with very low TSH levels, although in some cases TSH levels are normal or even elevated. In some of these cases, levels of the TSH α-subunit are elevated. Mutations in the gene for the TRH receptor *(TRHR)* is a very rare cause of congenital central hypothyroidism reported in a few families. In this condition, both TSH and prolactin fail to respond to TRH stimulation.

Thyroid Function in Preterm and Low Birthweight Infants

Postnatal thyroid function in preterm and LBW infants is qualitatively similar but quantitatively reduced compared with that of term infants. The cord blood T_4 concentration is decreased in proportion to gestational age and birthweight. The postnatal TSH surge is reduced, and very premature or very LBW infants experience a decrease in serum T_4 in the 1st wk of life, in contrast to term infants in whom T_4 increases during this time. The serum T_4 gradually increases to the range observed in term infants by about 6 wk of life. However, serum free T_4 concentrations seem less affected than total T_4 , and free T_4 levels may be normal when measured by the gold standard technique of equilibrium dialysis. Preterm and LBW infants also have a higher incidence of delayed TSH elevation and apparent transient primary hypothyroidism. Mechanisms underlying these changes in thyroid function in preterm and LBW infants may include immaturity of the hypothalamic-pituitary-thyroid axis; loss of the maternal contribution of thyroid hormone normally present in the 3rd trimester; severe illness and complications of prematurity; and exposure to medications that can affect thyroid function (e.g., dopamine and glucocorticoids).

Clinical Manifestations

Before neonatal screening programs, congenital hypothyroidism was rarely recognized in the newborn because most affected infants are asymptomatic at birth, even if there is complete agenesis of the thyroid gland. This is due to transplacental passage of maternal T_4 , which provides fetal levels that are approximately 33% of normal at birth. Despite this maternal contribution of T_4 , infants with primary hypothyroidism have elevated TSH levels and most have low T_4 levels, and so will be identified by newborn screening programs.

Because symptoms are usually not present at birth, the clinician depends on neonatal screening tests for the diagnosis of congenital hypothyroidism . However, some infants escape newborn screening, and laboratory errors occur, so pediatricians must still be alert for symptoms and signs of hypothyroidism if they develop. Birthweight and length are normal, but head size may be slightly increased because of myxedema of the brain. The anterior and posterior fontanels are open widely, and the presence of this sign at birth may be a clue to early recognition of congenital hypothyroidism (only 3% of normal newborns have a posterior fontanel wider than 0.5 cm). Prolonged jaundice (indirect hyperbilirubinemia) may be present due to delayed maturation of hepatic glucuronide conjugation. Affected infants cry little, sleep much, have poor appetites, and are generally sluggish. Feeding difficulties, especially sluggishness, lack of interest, somnolence, and choking spells during nursing, may be present during the 1st mo of life. Respiratory difficulties, partly caused by macroglossia, include apneic episodes, noisy respirations, and nasal obstruction. There may be constipation that does not usually respond to treatment. The abdomen is large, and an umbilical hernia is often present. The temperature may be subnormal (often <35°C/95°F), and the skin may be cold and mottled, particularly on the extremities. Edema of the genitals and extremities may be present. The pulse is slow, and heart murmurs, cardiomegaly, and asymptomatic pericardial effusion are common. Macrocytic anemia is often present. Because symptoms appear gradually and may be nonspecific, the clinical diagnosis of neonatal hypothyroidism is often delayed.

Approximately 10% of infants with congenital hypothyroidism have associated congenital anomalies. Cardiac anomalies are most common, but anomalies of the nervous system and eye have also been reported. Infants with congenital hypothyroidism may have associated hearing loss. Mutations in certain genes involved in thyroid gland development result in congenital hypothyroidism with other syndromic features (Table 581.2). Mutations in *NKX2-1* are characterized by congenital hypothyroidism, respiratory distress, and ataxia or choreoathetosis. Mutations in *FOXE1* present with congenital hypothyroidism, spiky or curly hair, and cleft palate. Mutations in *PAX8* cause congenital hypothyroidism and genitourinary anomalies, including renal agenesis.

Table 581.2

Genes and Thyroid Development

GENE	THYROID PHENOTYPE	OTHER FEATURES
TTF-2/FOXE-1	Athyreosis	Cleft palate, choanal atresia, kinky hair, bifid epiglottis
TTF-1/NKX2.1	Athyreosis to normal gland	Respiratory distress syndrome, developmental delays/hypotonia, ataxia/choreoathetosis
PAX-8	Athyreosis to normal gland	Cysts within thyroid remnants, kidney, and urinary tract malformations
GLIS3	Athyreosis to normal gland	Congenital glaucoma, deafness, liver/kidney, and pancreatic abnormalities
TSHR	Athyreosis to normal gland	None
NKX2.5	Athyreosis, ectopy	Cardiac defects

FOXE-1 , Forkhead box E1; *GLIS3* , GLIS family zinc finger 3; *PAX-8* , paired box 8; *TSHR* , thyroid stimulating hormone receptor; *TTF-1* , transcription termination factor 1; *TTF-2* , transcription termination factor 2.

From Kim G, Nandi-Munshi D, Diblasi CC: Disorders of the thyroid gland. In Gleason CA, Juul SE, editors: *Avery's diseases of the newborn* , ed 10, Philadelphia, 2018, Elsevier. Table 98.3, p 1396.

If congenital hypothyroidism goes undetected and untreated, the clinical manifestations progress. Delay of physical and mental development becomes more severe over time, and by 3-6 mo of age the clinical picture is fully developed (Fig. 581.1). When there is only partial deficiency of thyroid hormone, the symptoms may be milder and their onset delayed. Although breast milk contains significant amounts of thyroid hormones, particularly T_3 , it is inadequate to protect the breastfed infant with congenital hypothyroidism, and it has no effect on neonatal thyroid screening tests.

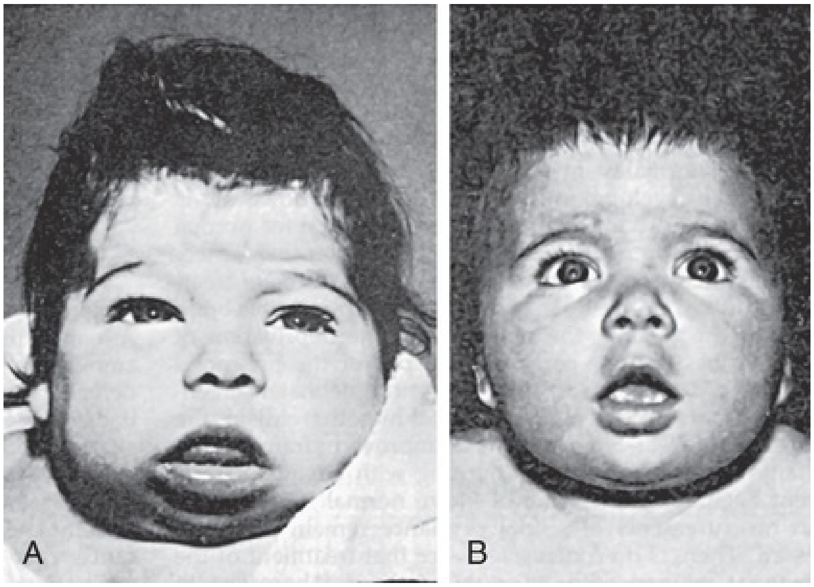

FIG. 581.1 Congenital hypothyroidism in an infant 6 mo of age. The infant ate poorly in the neonatal period and was constipated. She had persistent nasal discharge and a large tongue, was very lethargic, and had no social smile and no head control. **(A)** Notice the puffy face, dull expression, and hirsute forehead. Tests revealed a negligible uptake of radioiodine. Osseous development was that of a newborn. **(B)** Four months after treatment, note the decreased puffiness of the face, the decreased hirsutism of the forehead, and the alert appearance.

In the patient with untreated congenital hypothyroidism, growth will be stunted, extremities are short, and head size is normal or increased. The anterior fontanel is large and the posterior fontanel may remain open. The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow and the eyelids are swollen. The mouth is kept open, and the thick, broad tongue protrudes. Dentition will be delayed. The neck is short and thick, and there may be deposits of fat above the clavicles and between the neck and shoulders. The hands are broad and the fingers are short. The skin is dry and scaly, and there is little perspiration. Myxedema occurs particularly in the skin of the eyelids, the back of the hands, and the external genitalia. The skin shows general pallor with a sallow complexion. Carotenemia can cause a yellow discoloration of the skin, but the sclerae remain white. The scalp is thickened, and the hair is coarse, brittle, and scanty. The hairline reaches far down on the forehead, which usually appears wrinkled, especially when the infant cries.

Development is usually delayed. Hypothyroid infants appear lethargic and are late in acquiring gross and fine motor skills. The voice is hoarse, and they do not learn to talk. The degree of physical and intellectual delay increases with age.

Sexual maturation may be delayed or even absent.

The muscles are usually hypotonic, but in rare instances generalized muscular pseudohypertrophy occurs **(Kocher-Debré-Sémélaigne syndrome).** Affected older children can have an athletic appearance because of pseudohypertrophy, particularly in the calf muscles. Its pathogenesis is unknown; nonspecific histochemical and ultrastructural changes seen on muscle biopsy return to normal with treatment. Males are more prone to development of the syndrome, which has been observed in siblings born from a consanguineous mating. Affected patients have hypothyroidism of longer duration and severity.

Some infants with mild congenital hypothyroidism have normal thyroid function at birth and are not identified by newborn screening programs. In particular, some children with ectopic thyroid tissue (lingual, sublingual, subhyoid) produce adequate amounts of thyroid hormone for a variable length of time (even years) until the abnormal thyroid tissue fails. Affected children come to clinical attention because of a growing mass at the base of the tongue or in the midline of the neck, usually at the level of the hyoid. Occasionally, thyroid ectopy is associated with **thyroglossal duct cysts** . Surgical removal of ectopic thyroid tissue from a euthyroid patient usually results in hypothyroidism, because most such patients have no other thyroid tissue.

Laboratory Findings

In countries where newborn screening is performed, this is the most important method for identifying infants with congenital hypothyroidism. Blood obtained by heel-prick between 1 and 5 days of life is placed on a filter paper card and sent to a central screening laboratory. Most screening programs measure the level of TSH, which detects infants with primary hypothyroidism, including some with milder disease in whom TSH but T_4 is normal. However, this approach may not detect rarer disorders such as central hypothyroidism or congenital primary hypothyroidism with delayed TSH elevation. Some screening programs begin by measuring levels of T_4 , followed by reflex measurement of TSH when the T_4 is low. This approach identifies infants with primary hypothyroidism, some infants with central hypothyroidism or delayed TSH elevation, and also infants with thyroxine-binding globulin deficiency (a benign variant). All newborn screening results should be interpreted based on the normal range of values for the age of the patient, particularly in the 1st wk of life (Table 581.3). Regardless of the approach used for screening, some infants escape detection because of technical or human errors, and clinicians must remain vigilant for clinical manifestations of hypothyroidism.

Table 581.3

Thyroid Function Tests

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
THYROID THYROGLOBULIN, SERUM			
Cord blood	14.7-101.1 ng/mL	×1	14.7-101.1 µg/L
Birth to 35 mo	10.6-92.0 ng/mL	×1	10.6-92.0 µg/L
3-11 yr	5.6-41.9 ng/mL	×1	5.6-41.9 µg/L
12-17 yr	2.7-21.9 ng/mL	×1	2.7-21.9 µg/L
THYROID-STIMULATING HORMONE, SERUM			
Premature Infants (28-36 wk)			
1st wk of life	0.7-27.0 mIU/L	×1	0.7-27.0 mIU/L
Term Infants			
Birth to 4 days	1.0-17.6 mIU/L	×1	1.0-17.6 mIU/L
2-20 wk	0.6-5.6 mIU/L	×1	0.6-5.6 mIU/L
5 mo-20 yr	0.5-5.5 mIU/L	×1	0.5-5.5 mIU/L
THYROXINE-BINDING GLOBULIN, SERUM			
Cord blood	1.4-9.4 mg/dL	×10	14-94 mg/L
1-4 wk	1.0-9.0 mg/dL	×10	10-90 mg/L
1-12 mo	2.0-7.6 mg/dL	×10	20-76 mg/L
1-5 yr	2.9-5.4 mg/dL	×10	29-54 mg/L
5-10 yr	2.5-5.0 mg/dL	×10	25-50 mg/L
10-15 yr	2.1-4.6 mg/dL	×10	21-46 mg/L
Adult	1.5-3.4 mg/dL	×10	15-34 mg/L
THYROXINE, TOTAL, SERUM			
Full-Term Infants			
1-3 days	8.2-19.9 µg/dL	×12.9	106-256 nmol/L
1 wk	6.0-15.9 µg/dL	×12.9	77-205 nmol/L
1-12 mo	6.1-14.9 µg/dL	×12.9	79-192 nmol/L
Prepubertal Children			
1-3 yr	6.8-13.5 µg/dL	×12.9	88-174 nmol/L
3-10 yr	5.5-12.8 µg/dL	×12.9	71-165 nmol/L
Pubertal Children and Adults			
>10 yr	4.2-13.0 µg/dL	×12.9	54-167 nmol/L
THYROXINE, FREE, SERUM			
Full term (3 days)	2.0-4.9 ng/dL	×12.9	26-63.1 pmol/L
Infants	0.9-2.6 ng/dL	×12.9	12-33 pmol/L
Prepubertal children	0.8-2.2 ng/dL	×12.9	10-28 pmol/L
Pubertal children and adults	0.8-2.3 ng/dL	×12.9	10-30 pmol/L
THYROXINE, TOTAL, WHOLE BLOOD			
Newborn screen (filter paper)	6.2-22 µg/dL	×12.9	80-283 nmol/L
TRIIODOTHYRONINE, FREE, SERUM			
Cord blood	20-240 pg/dL	×0.01536	0.3-0.7 pmol/L
1-3 days	180-760 pg/dL	×0.01536	2.8-11.7 pmol/L

1-5 yr	185-770 pg/dL	×0.01536	2.8-11.8 pmol/L
5-10 yr	215-700 pg/dL	×0.01536	3.3-10.7 pmol/L
10-15 yr	230-650 pg/dL	×0.01536	3.5-10.0 pmol/L
>15 yr	210-440 pg/dL	×0.01536	3.2-6.8 pmol/L
TRIIODOTHYRONINE RESIN UPTAKE TEST (RT$_3$ U), SERUM			
Newborn	26–36%	×0.01	0.26-0.36 fractional uptake
Thereafter	26–35%	×0.01	0.26-0.35 fractional uptake
TRIIODOTHYRONINE, TOTAL, SERUM			
Cord blood	30-70 ng/dL	×0.0154	0.46-1.08 nmol/L
1-3 days	75-260 ng/dL	×0.0154	1.16-4.00 nmol/L
1-5 yr	100-260 ng/dL	×0.0154	1.54-4.00 nmol/L
5-10 yr	90-240 ng/dL	×0.0154	1.39-3.70 nmol/L
10-15 yr	80-210 ng/dL	×0.0154	1.23-3.23 nmol/L
>15 yr	115-190 ng/dL	×0.0154	1.77-2.93 nmol/L

Adapted from Nicholson JF, Pesce MA: Reference ranges for laboratory tests and procedures. In Behrman RE, Kliegman RM, Jenson HB, editors: *Nelson textbook of pediatrics* , ed 17, Philadelphia, 2004, WB Saunders, pp 2412–2413; TSH from Lem AJ, de Rijke YB, van toor H, et al: Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age, *J Clin Endocrinol Metab* 97:3170–3178, 2012; free T$_3$ from Elmlinger MW, Kuhnel W, Lambrecht H-G, et al: Reference intervals from birth to adulthood for serum thyroxine (T$_4$), triiodothyronine (T$_3$), free T$_3$, free T$_4$, thyroxine binding globulin (TBG), and thyrotropin (TSH), *Clin Chem Lab Med* 39:973–979, 2001.

Several groups of patients deserve vigilance for congenital hypothyroidism. Infants with trisomy 21 or cardiac defects have an increased risk of congenital hypothyroidism. Monozygotic twins are usually *discordant* for congenital hypothyroidism, but if they are monochorionic, fetal hypothyroidism in the affected twin may be compensated by the normal twin through their shared fetal circulation. In such cases, the affected twin may go undetected on newborn screening in the 1st days of life and present later with untreated hypothyroidism. Preterm and LBW neonates have an increased incidence of congenital hypothyroidism and are more likely to have delayed TSH elevation that may be missed on initial screening. Therefore, in all of these groups of infants, many newborn screening programs perform a routine 2nd test 2-6 wk after birth.

Patients with congenital hypothyroidism have low serum levels of T$_4$ and free T$_4$. Serum levels of T$_3$ are often normal and are not helpful for diagnosis. If primary hypothyroidism is present, levels of TSH are elevated, often to >100 mU/L. Serum levels of thyroglobulin are usually low in infants with thyroid agenesis, defects of the TSH receptor (including *TSHR* mutations and TRBAb), or defects in the synthesis or secretion of thyroglobulin itself. In contrast, thyroglobulin levels are usually elevated in patients with thyroid ectopy and other defects of thyroid hormone synthesis, but there is a wide overlap of ranges.

Delay of osseous development can be shown radiographically at birth in approximately 60% of congenitally hypothyroid infants and indicates some deficiency of thyroid hormone during intrauterine life. The distal femoral and proximal tibial epiphyses, normally present at birth, are often absent (Fig. 581.2*A*). In untreated patients, the discrepancy between chronologic age and osseous development increases over time. The epiphyses often have multiple foci of ossification (epiphyseal dysgenesis; see Fig. 581.2*B*). Deformity (beaking) of the 12th thoracic or 1st or 2nd lumbar vertebra is common. X-rays of the skull show large fontanels and wide sutures, and intersutural (wormian) bones are common. The sella turcica may be enlarged and round, and in rare instances, there may be bony erosion and thinning. Formation and eruption of teeth can be delayed. Cardiac enlargement or pericardial effusion may be present.

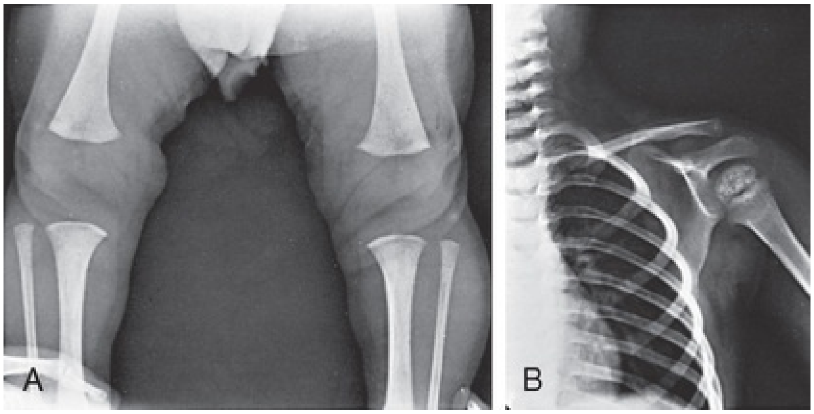

FIG. 581.2 Congenital hypothyroidism. **(A)** Absence of distal femoral epiphyses in a 3 mo old infant who was born at term. This is evidence for onset of the hypothyroid state during fetal life. **(B)** Epiphyseal dysgenesis in the head of the humerus in a 9 yr old girl who had been inadequately treated with thyroid hormone.

Scintigraphy can help to define the underlying cause in infants with congenital hypothyroidism, but treatment should not be delayed to obtain such imaging. ^{123}I–sodium iodide is superior to ^{99m}Tc–sodium pertechnetate for this purpose. Scintigraphy will demonstrate an ectopic thyroid gland, but the absence of uptake in disorders of the TSH receptor (including TRBAb) or NIS may be mistaken for thyroid agenesis. On the other hand, ultrasonographic examination of the thyroid can document presence or absence of an anatomically normal gland, but it can miss some ectopic glands detectable by scintigraphy. Demonstration of ectopic thyroid tissue is diagnostic of thyroid dysgenesis and establishes the need for lifelong treatment. Failure to demonstrate any thyroid tissue suggests thyroid agenesis. A normally located thyroid gland with normal or increased uptake indicates a defect in thyroid hormone synthesis. In the past, patients with goitrous congenital hypothyroidism (presumably due to dyshormonogenesis) have undergone extensive evaluation including scintigraphy, perchlorate discharge tests, kinetic studies, chromatography, and studies of thyroid tissue, to determine the biochemical nature of the defect. Currently, many can be evaluated by genetic studies looking for a suspected defect in the thyroid hormone biosynthetic pathway; however, attempting to define the precise genetic etiology may be costly, is unsuccessful in at least 40% of cases, and may have little effect on clinical management.

Treatment

Levothyroxine (L -T_4) given orally is the treatment for congenital hypothyroidism. Although T_3 is the biologically active form of thyroid hormone, 80% of circulating T_3 is derived from deiodination of circulating T_4 , and therefore treatment with L -T_4 alone restores normal serum levels of T_4 and T_3 . The recommended initial dose of L -T_4 is 10-15 µg/kg/day (37.5-50 µg/day for most term infants), and within this range the starting dose can be adjusted based on the severity of hypothyroidism. Newborns with more severe hypothyroidism, as judged by a serum T_4 <5 µg/dL and/or imaging studies confirming aplasia, should be started at the higher end of the dosage range. Rapid normalization of thyroid function (ideally within 2 wk) is important in achieving optimal neurodevelopmental outcome.

L -T_4 should be prescribed only in tablet form in the United States; there is an approved liquid L -T_4 preparation in Europe. Tablets should be crushed and mixed with a small volume (1-2 mL) of liquid. *L -T_4 tablets should not be mixed with soy protein formulas, concentrated iron, or calcium, because these can inhibit L -T_4 absorption* . Although it is recommended to administer L -T_4 on an empty stomach and avoid food for 30-60 min, this is not practical in an infant. As long as the method of administration is consistent, dosing can be adjusted based on serum thyroid test results to achieve the desired treatment goals. One trial has suggested that brand-name L -T_4 may be superior to generic formulations in children with severe congenital hypothyroidism.

Levels of serum T_4 or free T_4 and TSH should be monitored at recommended intervals (every 1-2 mo in the 1st 6 mo of life, and then every 2-4 mo between 6 mo and 3 yr of age). The goals of treatment are to maintain serum TSH in the reference range for age and the serum free T_4 or total T_4 in the upper half of the reference range for age (see Table 581.3). Care should be taken to avoid undertreatment or overtreatment, both of which may be related to adverse neurodevelopmental outcomes including decreased intelligence quotient (IQ).

About 35% of infants with congenital hypothyroidism and a normally located thyroid gland have transient disease and do not require lifelong therapy. In patients who might have transient disease, a trial of L -T_4 for 4 wk may be undertaken after 3 yr of age for 3-4 wk to assess whether the TSH rises significantly, indicating the presence of permanent hypothyroidism. This is unnecessary in infants with proven thyroid dysgenesis or in those who have previously manifested elevated levels of TSH after 6-12 mo of therapy because of poor medication adherence or an inadequate dose of T_4 .

Prognosis

Thyroid hormone is critical for normal neurodevelopment, particularly in the early postnatal months. Prompt diagnosis and treatment of congenital hypothyroidism in the 1st wk of life is essential to prevent irreversible brain damage and results in normal growth and development. In most infants detected by newborn screening, verbal development, psychomotor development, and global IQ scores are similar to those of unaffected siblings or classmate controls. However, the most severely affected infants—those with the lowest T_4 levels and most delayed skeletal maturation—may have reduced IQ and other neuropsychologic sequelae such as incoordination, hypotonia or hypertonia, or problems with attention or speech despite early diagnosis and adequate treatment. Psychometric testing can show problems with vocabulary and reading comprehension, arithmetic, and memory. Approximately 10% of children have a neurosensory hearing deficit. Outcome studies in adults who were diagnosed and treated as neonates reveal delayed social development, lower self-esteem, and a lower health-related quality of life. The latter appears to be related to those individuals with lower neurocognitive outcome and associated congenital malformations.

Delay in diagnosis or treatment, failure to correct rapidly the initial hypothyroxinemia, inadequate treatment, or poor adherence to treatment in the first 2-3 yr of life may result in variable degrees of brain damage. Without treatment, severely affected infants have profound intellectual disability and growth retardation. When hypothyroidism develops after 2 yr of age, the outlook for neurodevelopment is much better even if diagnosis and treatment are delayed, which illustrates how critically dependent brain development is on thyroid hormone in the 1st yr of life.

Acquired Hypothyroidism

Epidemiology

Hypothyroidism occurs in approximately 0.3% (1 in 333) of school-age children. *Subclinical hypothyroidism* (defined as an elevated TSH with normal T_4 or free T_4) is more common, occurring in approximately 2% of adolescents. Autoimmune thyroid disease is the most common cause of acquired hypothyroidism: 6% of children age 12-19 yr have evidence of autoimmune thyroid disease, and females are twice as likely to be affected as males. Although this condition typically arises in adolescence, it may present as early as the 1st yr of life.

Etiology

The most common cause of acquired hypothyroidism (Table 581.4) is **chronic lymphocytic thyroiditis** (also called Hashimoto or autoimmune thyroiditis; see Chapter 582). Children with trisomy 21, Turner syndrome, Klinefelter syndrome, celiac disease, or type 1 diabetes mellitus are at higher risk for associated autoimmune thyroid disease (see Chapter 582), as are those with **autoimmune polyglandular syndromes (APSs** ; see Chapter 586 **).** APS type 1 (APS-1) is a rare autosomal recessive disorder caused by mutations in the *AIRE* gene. It is classically characterized by the triad of mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency. Autoimmune thyroiditis is a less common feature (~10%), as are type 1 diabetes mellitus, primary hypogonadism, pernicious anemia, vitiligo, alopecia, nephritis, hepatitis, and gastrointestinal dysfunction. APS type 2 (APS-2) is far more common than APS-

1, and its pathogenesis remains an obscure combination of genetic and environmental factors. APS-2 may consist of any combination of autoimmune thyroiditis (~70%), type 1 diabetes mellitus, celiac disease, or less-common manifestations such as primary adrenal insufficiency, primary hypogonadism, pernicious anemia, and vitiligo. Patients with any of these other autoimmune conditions are at increased risk of developing hypothyroidism. For example, about 20% of children with **type 1 diabetes mellitus** develop thyroid autoantibodies, and about 5% become hypothyroid.

Table 581.4

Etiologic Classification of Acquired Hypothyroidism

- Autoimmune
  - Chronic lymphocytic thyroiditis (Hashimoto thyroiditis)
  - Autoimmune polyglandular syndromes types 1 and 2 (APS-1, APS-2)
  - Celiac disease
  - IPEX
- Drug-induced
  - Excess iodide: amiodarone, nutritional supplements, expectorants
  - Anticonvulsants: oxcarbazepine, phenytoin, phenobarbital, valproate
  - Antithyroid drugs: methimazole, propylthiouracil
  - Miscellaneous: lithium, rifampin, tyrosine kinase inhibitors, interferon-α, stavudine, thalidomide, aminoglutethimide, dopamine, amiodarone, tetracycline
- Postablative
  - Irradiation (e.g., cancer therapy, bone marrow transplant)
  - Radioactive iodine (^{131}I)
  - Thyroidectomy
- Systemic infiltrative disease
  - Cystinosis
  - Langerhans cell histiocytosis
- Inactivation of thyroid hormone by large liver hemangiomas (type 3 deiodinase)
- Decreased sensitivity to thyroid hormone (*MCT8*, *SEC16A2*, *THRA*, *THRB* mutations)
- Hypothalamic-pituitary disease (often with multiple pituitary hormone deficiencies)
  - Central nervous system tumors (e.g., craniopharyngioma)
  - Meningoencephalitis
  - Cranial irradiation
  - Head trauma
  - Langerhans cell histiocytosis

IPEX, Immunodysregulation polyendocrinopathy X-linked.

In children with **trisomy 21** , thyroid autoantibodies develop in approximately 30% and subclinical or overt hypothyroidism occurs in approximately 15–20%. In girls with **Turner syndrome** , thyroid autoantibodies develop in approximately 40% and subclinical or overt hypothyroidism occurs in approximately 15–30%, rising with increasing age. Additional autoimmune conditions with an increased risk of hypothyroidism include immune dysregulation–polyendocrinopathy–enteropathy–X-linked syndrome (IPEX) and IPEX-like disorders, immunoglobulin G_4 –related diseases, Sjögren syndrome, and multiple sclerosis. **Williams syndrome** is associated with subclinical hypothyroidism, but this does not appear to be autoimmune and thyroid autoantibodies are absent.

Medications can cause acquired hypothyroidism. Some medications containing iodides (e.g., expectorants or nutritional supplements) may cause hypothyroidism through the Wolff-Chaikoff effect (see Chapter 583). Amiodarone, a drug used for cardiac arrhythmias and consisting of 37% iodine by weight, causes hypothyroidism in approximately 20% of treated children. Children treated with amiodarone should have serial monitoring of thyroid function.

Anticonvulsants, including phenytoin, phenobarbital, and valproate, may cause thyroid dysfunction, usually in the form of subclinical hypothyroidism. In some cases, this is due to their effect of stimulating hepatic cytochrome P450 metabolism and excretion of T_4 . The anticonvulsant oxcarbazepine can cause central (secondary) hypothyroidism. Children with Graves disease treated with antithyroid drugs (methimazole or propylthiouracil) can develop hypothyroidism. Additional drugs that can produce hypothyroidism include lithium, rifampin, tyrosine kinase inhibitors, interferon-α, stavudine, thalidomide, and aminoglutethimide.

Children who receive **therapeutic irradiation** , such as for Hodgkin disease or other head and neck malignancies or prior to bone marrow transplantation, are at risk for thyroid damage and hypothyroidism. Approximately 30% of such children acquire elevated TSH levels within a year after therapy, and another 15–20% progress to hypothyroidism within 5-7 yr. Central hypothyroidism may develop in up to 10% of children receiving craniospinal irradiation. **Radioactive iodine** ablative treatment or **thyroidectomy** for Graves disease or thyroid cancer results in hypothyroidism, as can removal of ectopic thyroid tissue. Thyroid tissue in a thyroglossal duct cyst may constitute the only source of thyroid hormone, and in this case excision of the cyst results in hypothyroidism. Ultrasonographic examination or a radionuclide scan before surgery is indicated in these patients.

Children with **nephropathic cystinosis,** a disorder characterized by intralysosomal storage of cystine in body tissues, acquire impaired thyroid function. Hypothyroidism is usually subclinical but may be overt, periodic assessment of TSH levels is indicated. By 13 yr of age, two thirds of these patients require L -T_4 replacement.

Histiocytic infiltration of the thyroid in children with **Langerhans cell histiocytosis** (see Chapter 534.1) can result in hypothyroidism. Children with chronic **hepatitis C infection** are at risk for subclinical hypothyroidism that does not appear to be autoimmune.

Consumptive hypothyroidism can occur in children with large **hemangiomas** of the liver. These tumors may express massive amounts of the enzyme type 3 deiodinase, which converts T_4 and T_3 , respectively, to the inactive metabolites reverse T_3 and diiodothyronine (T_2). Hypothyroidism occurs when the increased secretion of thyroid hormones is insufficient to compensate for their rapid inactivation.

Some patients with mild forms of congenital hypothyroidism (thyroid dysgenesis or genetic defects in thyroid hormone synthesis) do not develop clinical manifestations until childhood. Although these conditions are often detected by newborn screening, very mild defects can escape detection and present later with apparent acquired hypothyroidism.

Any **hypothalamic** or **pituitary** disease can cause acquired central hypothyroidism (see Chapter 573). TSH deficiency may be the result of a hypothalamic-pituitary tumor (craniopharyngioma is most common in children) or of treatment for a tumor. Other causes include cranial irradiation, head trauma, or infiltrative diseases affecting the pituitary gland such as Langerhans cell histiocytosis.

Clinical Manifestations

Slowing of growth is usually the first clinical manifestation of acquired hypothyroidism, but this sign often goes unrecognized (Figs. 581.3 and 581.4). Goiter is a common presenting feature. In chronic lymphocytic thyroiditis, the thyroid is typically nontender and firm, with a rubbery consistency and pebbly (bosselated) surface. Weight gain is mostly caused by fluid retention (myxedema), not true obesity. Myxedematous changes of the skin, constipation, cold intolerance, decreased energy, and an increased need for sleep develop insidiously. School performance usually does not suffer, even in severely hypothyroid children. Additional features may include bradycardia, muscle weakness or cramps, nerve entrapment, and ataxia. Skeletal maturation is delayed, often strikingly, and the degree of delay reflects the duration of the hypothyroidism. Adolescents typically have delayed puberty. Older adolescent females may have menometrorrhagia, and some may develop galactorrhea because of increased TRH stimulating prolactin secretion. In fact, long-standing primary hypothyroidism can result in enlargement of the pituitary gland, sometimes leading to headaches and vision problems. This is believed to be the result of thyrotroph hyperplasia but may be mistaken for a pituitary tumor, particularly a prolactinoma if prolactin is elevated (see Chapter 573). Rarely, young children with profound hypothyroidism may develop secondary sex characteristics (pseudoprecocious puberty), including breast development or vaginal bleeding in girls and testicular enlargement in males. It is hypothesized that this phenomenon results from abnormally high concentrations of TSH binding and stimulating the follicle-stimulating hormone receptor.

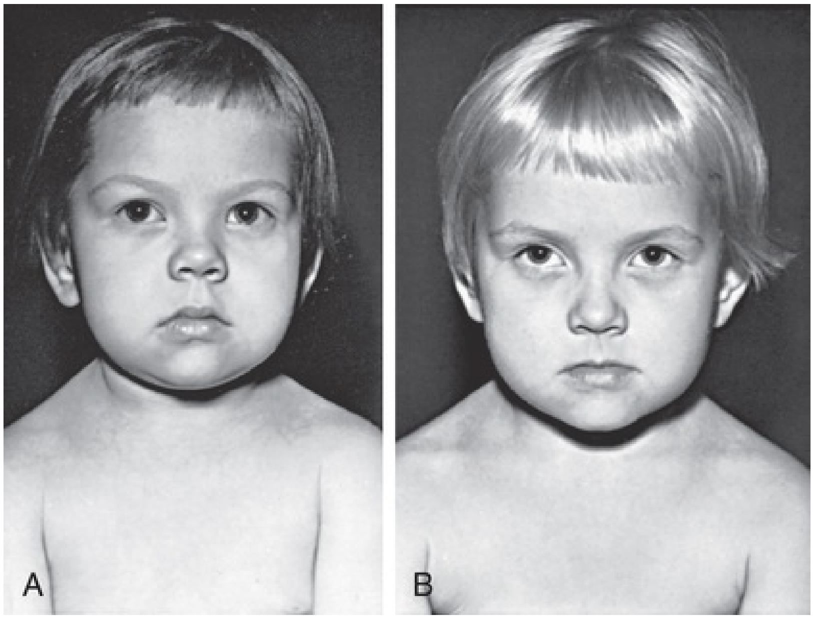

FIG. 581.3 **(A)** Acquired hypothyroidism in a girl 6 yr of age. She was treated with a wide variety of hematinics for refractory anemia for 3 yr. She had almost complete cessation of growth, constipation, and sluggishness for 3 yr. The height age was 3 yr; the bone age was 4 yr. She had a sallow complexion and immature facies with a poorly developed nasal bridge. Serum cholesterol, 501 mg/dL; radioiodine uptake, 7% at 24 hr; protein-bound iodine *(PBI),* 2.8 mg/dL. **(B)** After therapy for 18 mo, note the nasal development, increased luster and decreased pigmentation of hair, and maturation of the face. The height age was 5.5 yr; the bone age was 7 yr. There was a decided improvement in her general condition. Menarche occurred at 14 yr. The ultimate height was 155 cm (61 in). She graduated from high school. The disorder was well controlled with daily L -thyroxine.

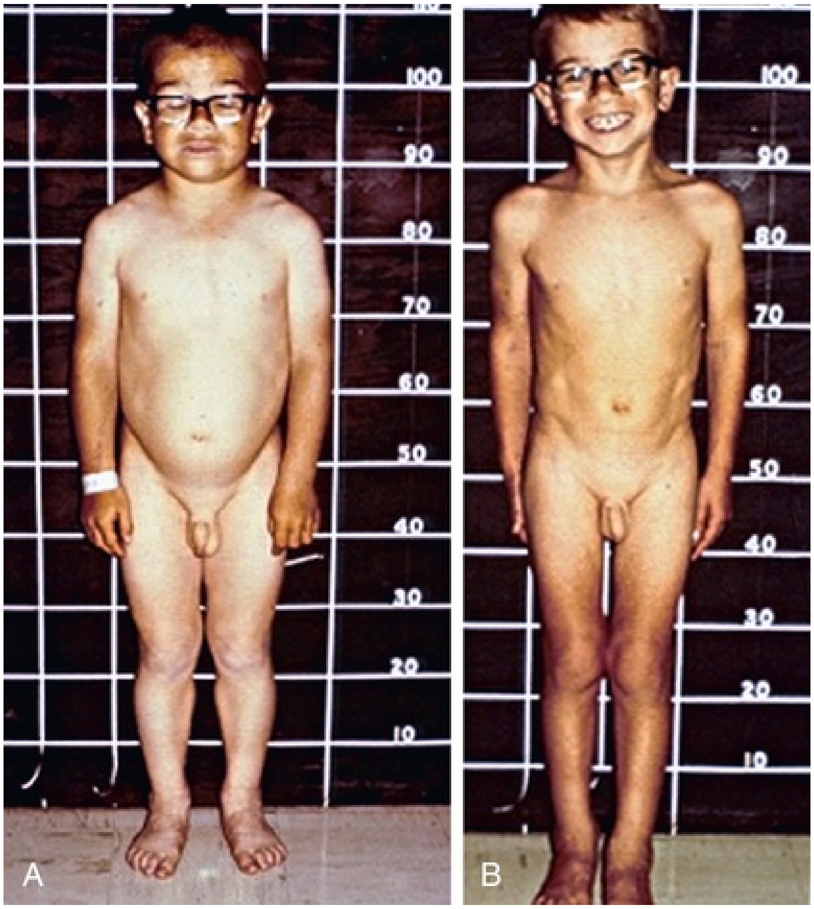

FIG. 581.4 **(A)** This 12 yr old boy with hypothyroidism has short stature (108 cm, <3rd percentile), generalized myxedema, sleepy expression, protuberant abdomen, and coarse hair. Body proportions are immature for his age (1.25:1). **(B)** Same boy 4 mo after treatment. His height increased by 4 cm, and there is a marked change in body habitus owing to loss of myxedema, improved muscle tone, and bright facial expression. (From LaFranchi SH: Hypothyroidism, *Pediatr Clin North Am* 26:33–51, 1979.)

Laboratory abnormalities in hypothyroidism may include hyponatremia, macrocytic anemia, hypercholesterolemia, and elevated creatine phosphokinase. Table 581.5 lists the complications of severe hypothyroidism, all of which normalize with adequate replacement of $T_{4.}$

Table 581.5

Clinical Presentation and Implications of Hypothyroidism

	PRESENTATION	SIGNS AND IMPLICATIONS
General metabolism	Weight gain, cold intolerance, fatigue	Increase in body mass index, low metabolic rate, myxedema,* hypothermia*
Cardiovascular	Fatigue on exertion, shortness of breath	Dyslipidemia, bradycardia, hypertension, endothelial dysfunction or increased intima–media thickness,* diastolic dysfunction,* pericardial effusion,* hyperhomocysteinemia,* electrocardiogram changes*
Neurosensory	Hoarseness of voice, decreased taste, vision, or hearing	Neuropathy, cochlear dysfunction, decreased olfactory and gustatory sensitivity
Neurologic and psychiatric	Impaired memory, paresthesia, mood impairment	Impaired cognitive function, delayed relaxation of tendon reflexes, depression,* dementia,* ataxia,* carpal tunnel syndrome and other nerve entrapment syndromes,* myxedema coma*
Gastrointestinal	Constipation	Reduced esophageal motility, nonalcoholic fatty liver disease,* ascites (very rare)
Endocrinologic	Infertility and subfertility, menstrual disturbance, galactorrhea	Goiter, glucose metabolism dysregulation, infertility, sexual dysfunction, increased prolactin, pituitary hyperplasia*
Musculoskeletal	Muscle weakness, muscle cramps, arthralgia	Creatine phosphokinase elevation, Hoffman syndrome,* osteoporotic fracture* (most probably caused by overtreatment)
Hemostasis and hematologic	Bleeding, fatigue	Mild anemia, acquired von Willebrand disease,* decreased protein C and S,* increased red cell distribution width,* increased mean platelet volume*
Skin and hair	Dry skin, hair loss	Coarse skin, loss of lateral eyebrows,* yellow palms of the hand,* alopecia areata*
Electrolytes and kidney function	Deterioration of kidney function	Decreased estimated glomerular filtration rate, hyponatremia*

* Uncommon presentation.

From Chaker L, Bianco AC, Jonklaas J, et al: Hypothyroidism, *Lancet* 390:1550–1560, 2017, Table 1.

Diagnostic Studies

Children with suspected hypothyroidism should undergo measurement of serum TSH and free T_4 . Because the normal range for thyroid tests varies by age and is different in children than in adults, it is important to compare results to age-specific reference ranges (see Table 581.3). Detection of thyroglobulin or TPO antibodies is diagnostic of chronic lymphocytic (autoimmune) thyroiditis as the etiology. In cases of goiter resulting from autoimmune thyroiditis, ultrasonography typically shows diffuse enlargement and heterogeneous echotexture; however, ultrasonography generally is not indicated unless the physical exam raises suspicion for a thyroid nodule. A bone age x-ray at diagnosis may suggest the duration and severity of hypothyroidism based on the degree of bone age delay.

Treatment and Prognosis

L -T_4 is the treatment for children with hypothyroidism. The dose on a weight basis gradually decreases with age. For children age 1-3 yr, the average daily L -T_4 dose is 4-6 µg/kg; for age 3-10 yr, 3-5 µg/kg; and for age 10-16 yr, 2-4 µg/kg. Treatment should be monitored by measuring serum TSH every 4-6 mo, as well as 4-6 wk after any change in dosage, and TSH should be maintained in the age-specific reference range. In young children (under age 3 yr), serum free T_4 should also be measured and ideally maintained in the upper half of the age-specific reference range. In older children with primary hypothyroidism, serum free T_4 need not be measured routinely but may be helpful in certain situations, such as to assess for poor adherence to medication. In children with central hypothyroidism, in which TSH levels by definition do not reflect systemic thyroid status, serum free T_4 alone should be monitored and maintained in the upper half of the age-specific reference range.

During the 1st yr of treatment, deterioration of schoolwork, poor sleeping habits, restlessness, short attention span, and behavioral problems may develop, but these issues are transient and more easily managed if families are forewarned about them. Some practitioners feel that these symptoms may be partially ameliorated by starting at a lower dose of L -T_4 and advancing slowly. The development of persistent headaches or vision changes should prompt an evaluation for pseudotumor cerebri, a rare complication following initiation of L -T_4 treatment in older children (age 8-13 yr).

In older children, after catch-up growth is complete, the growth rate provides a good index of the adequacy of therapy. In children with long-standing hypothyroidism, catch-up growth may be incomplete and final adult height may be irremediably compromised (see Fig. 581.4).

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CHAPTER 582

Thyroiditis

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Thyroiditis refers to any disorder that causes inflammation of the thyroid gland. Thyroiditis can be acute or chronic and can be categorized by etiology, pathology, and/or clinical features. Painful thyroiditis is typically due to infection or trauma, whereas painless thyroiditis is often autoimmune-mediated or due to drug exposure.

Depending on the etiology and phase of illness, patients with thyroiditis may be euthyroid, hypothyroid, or thyrotoxic. The classic pattern of thyroid function changes in transient forms of thyroiditis (such as subacute thyroiditis and painless thyroiditis) is thyrotoxicosis, followed by hypothyroidism and then restoration of euthyroidism. The thyrotoxicosis (elevated thyroid hormone levels) caused by thyroiditis is not due to increased thyroid hormone synthesis (in contrast to Graves disease) but rather to leakage of preformed thyroid hormone into the circulation from the damaged gland, which can last up to 60 days. In some cases, hypothyroidism can persist after transient thyroiditis.

Treatment for patients with thyroiditis is typically aimed at alleviating the pain and addressing the symptoms of the thyrotoxicosis such as tachycardia, palpations, and tremors. Non-steroidal anti-inflammatory drugs (NSAIDs) are usually effective in alleviating thyroid tenderness. If pain is severe, a short course of steroids (prednisone) can be considered. Given that the thyrotoxicosis is due to release of preformed thyroid hormone, antithyroid drugs are usually not effective. Rather, treatment with β-blockers (atenolol or propranolol) to help control the cardiovascular symptoms is useful. Thyroid function tests should be monitored every 6-8 wk, and if hypothyroidism is prolonged or overtly symptomatic, then replacement with thyroid hormone can be considered.

Thyroiditis With Pain

Acute infectious (suppurative) thyroiditis is uncommon in children. It is typically preceded by a respiratory infection or pharyngitis, and the left lobe is more often affected. The infection may be caused by gram positive or gram negative organisms, and abscess formation can occur. The most common organism is α-hemolytic streptococci and *Staphylococcus aureus* followed by gram negative organisms and anaerobic bacteria. Other pathogens including mycobacteria, fungi, and pneumocystis cause more indolent infection and occur mostly in immunocompromised patients. Recurrent episodes or detection of mixed bacterial flora suggests that the infection arises from a **piriform sinus fistula** or, less commonly, from a **thyroglossal duct** remnant. Acute infectious thyroiditis is characterized by sudden onset of neck pain, tenderness of the gland, swelling, erythema, dysphagia, and decreased range of motion of the neck. Fever, chills, sore throat, and leukocytosis are commonly present. Thyroid function is usually normal, but thyrotoxicosis can occur due to leakage of preformed thyroid hormone. Thyroid ultrasound can visualize an abscess if present, and fine needle aspiration can help to identify the responsible microorganisms. When abscesses form, incision and drainage and administration of parenteral antibiotics are indicated. After the infection subsides, a CT scan with contrast is indicated to search for a fistulous tract, and if one is found, surgical removal is typically required.

Subacute thyroiditis (de Quervain disease, subacute granulomatous thyroiditis) is thought to have a viral or post-viral etiology and is usually transient. It typically presents with low-grade fever, minimal thyroid tenderness, and laboratory evidence of thyrotoxicosis (suppressed TSH and elevated T_4 and T_3) caused by leakage of preformed thyroid hormone from the inflamed gland into the circulation. Mild symptoms of thyrotoxicosis may be present, but radioiodine uptake is depressed in the thyrotoxic phase. The erythrocyte sedimentation rate (ESR) is increased. The course is variable but usually characterized by four phases: thyrotoxic, euthyroid, hypothyroid, and remission to euthyroidism usually occurring in several months. There is a strong association with HLA-B35.

Radiation thyroiditis can occur in children who are treated with radioiodine for Graves disease. Thyroid pain and tenderness can develop 2-5 days later due to radiation-induced destruction of the thyroid follicular cells and subsequent release of preformed thyroid hormone. The neck pain is responsive to antiinflammatory therapies.

Palpation- or trauma-induced thyroiditis can be a result of direct trauma to the thyroid gland, typically from surgery, accidental trauma, biopsy, or rarely vigorous palpation of the thyroid gland.

Thyroiditis Without Pain

Chronic Lymphocytic Thyroiditis (Hashimoto Thyroiditis, Autoimmune Thyroiditis)

Chronic lymphocytic thyroiditis is the most common cause of thyroid disease in children and adolescents and accounts for many of the formerly designated *adolescent* or *simple* goiters. It is also the most common cause of acquired hypothyroidism, with or without goiter. One to 2% of school-age children and 6–8% of adolescents have positive antithyroid antibodies as evidence of autoimmune thyroid disease.

Etiology

This typical organ-specific autoimmune disease results from inheritance of susceptible genes involved in immunoregulation and from environmental triggers, both as yet poorly characterized. Early in the disease, there may be thyroid hyperplasia only. This is followed by infiltration of lymphocytes and plasma cells between the follicles and subsequent follicular atrophy. Lymphoid follicle formation with germinal centers is almost always present, and the degree of atrophy and fibrosis of the follicles varies. Certain human leukocyte antigen (HLA) haplotypes (HLA-DR4, HLA-DR5) are associated with an increased risk of goiter and thyroiditis, and others (HLA-DR3) are associated with the atrophic variant of thyroiditis.

A variety of different autoantibodies to thyroid antigens are also present. Thyroperoxidase antibodies (TPO-Abs) or thyroglobulin antibodies (Tg-Abs) are demonstrable in the sera of 95% of children with chronic lymphocytic thyroiditis and in many patients with Graves disease. TPO-Abs are involved in activation of the complement cascade and in antibody-dependent, cell-mediated cytotoxicity. Tg-Abs do not appear to play a role in the autoimmune destruction of the gland. Thyrotropin receptor-blocking antibodies (TRBAb) may cause thyroid atrophy and have been demonstrated in 18% of patients with severe hypothyroidism

(TSH > 20 mU/L) caused by autoimmune thyroiditis. Antibodies to pendrin, an apical membrane protein on thyroid follicular cells, have been demonstrated in 80% of children with autoimmune thyroiditis. Antibodies also have been found against the sodium–iodide symporter (NIS), but their pathogenic role is unclear.

Clinical Manifestations

The disorder is 4-6 times more common in females than in males. It can occur during the first 3 yr of life but becomes more common after 6 yr of age and reaches its peak incidence during adolescence. The most common clinical manifestations are goiter and growth deceleration. The goiter can appear insidiously and may be variable in size. In most patients, the thyroid is diffusely enlarged, firm, and nontender. In approximately 30% of patients, the gland is asymmetric. Most affected children are clinically euthyroid and asymptomatic. Some children have clinical signs and symptoms of hypothyroidism, but others who appear clinically euthyroid have laboratory evidence of overt hypothyroidism. Some children have manifestations suggestive of thyrotoxicosis, such as tremulousness, irritability, increased sweating, and hyperactivity, and laboratory evaluation may show that they are in the Hashitoxic phase of disease, characterized by thyrotoxicosis due to autoimmune thyroid destruction. Ophthalmopathy can occur in autoimmune thyroiditis even in the absence of Graves disease.

The clinical course is variable. The goiter might spontaneously regress, or it might persist unchanged for years while the patient remains euthyroid. Most children who are euthyroid at presentation remain euthyroid, although a percentage of patients acquire hypothyroidism gradually within months or years. In children who initially have subclinical hypothyroidism (elevated serum TSH, normal free thyroxine [T_4]), approximately 35% revert to euthyroidism, 50% continue to have subclinical hypothyroidism, and approximately 15% develop overt hypothyroidism (elevated serum TSH, subnormal free T_4) over 5 years.

Familial clusters of chronic lymphocytic thyroiditis are common, and the incidence in siblings or parents of affected children may be as high as 25%. TPO-Abs and Tg-Abs in these families appear to be inherited in an autosomal dominant fashion, with reduced penetrance in males. The concurrence within families of patients with chronic lymphocytic thyroiditis, hypothyroidism, and Graves disease provides evidence for a basic relationship among these three conditions.

The disorder is associated with many other autoimmune disorders. Autoimmune thyroiditis occurs in 10% of patients with **type 1 autoimmune polyglandular syndrome (APS-1),** characterized by autoimmune polyendocrinopathy, candidiasis, and ectodermal dysplasia **(APECED)** . Patients with APS-1 have at least 2 of the triad of hypoparathyroidism, Addison disease, and mucocutaneous candidiasis. This rare autosomal recessive disorder occurs in childhood and is caused by mutations in the autoimmune regulator *(AIRE)* gene (see Chapter 586).

Autoimmune thyroid disease occurs in 70% of patients with **type 2 autoimmune polyglandular syndrome (APS-2)** . APS-2 consists of the association of autoimmune thyroiditis with Addison disease (Schmidt syndrome), type 1 diabetes mellitus (Carpenter syndrome), or other autoimmune conditions including pernicious anemia, vitiligo, and alopecia. TPO-Abs are found in approximately 20% of Caucasian and 4% of African American children with type 1 diabetes mellitus. APS-2 typically occurs in later childhood or early adulthood. Its cause is unknown but may be related to predisposing genetic factors that are shared among these autoimmune conditions (see Chapter 586). Autoimmune thyroiditis has also been described in children with **immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome** , which includes early-onset diabetes and colitis (see Chapter 586).

Chronic lymphocytic thyroiditis occurs frequently in patients with celiac disease and those with certain chromosomal disorders, particularly Turner syndrome (8–30%) and Down syndrome (7–10%). Males with Klinefelter syndrome also appear to be at risk for autoimmune thyroid disease.

Table 582.1 compares the characteristics of chronic lymphocytic thyroiditis to other thyroiditis syndromes.

Table 582.1

Characteristics of Thyroiditis Syndromes

CHARACTERISTIC	CHRONIC LYMPHOCYTIC THYROIDITIS	PAINLESS THYROIDITIS	SUBACUTE THYROIDITIS	ACUTE INFECTIOUS THYROIDITIS	FIBROUS THYROIDI
Sex ratio (F:M)	4-6 : 1	2 : 1	5 : 1	1 : 1	3-4 : 1
Cause	Autoimmune	Autoimmune	Unknown (probably viral)	Infectious (bacterial)	Unknown
Pathologic findings	Lymphocytic infiltration, germinal centers, fibrosis	Lymphocytic infiltration	Giant cells, granulomas	Abscess formation	Dense fibros

Thyroid function	Usually euthyroidism; some hypothyroidism	Hyperthyroidism, hypothyroidism, or both	Hyperthyroidism, hypothyroidism, or both	Usually euthyroidism	Usually euthyroidis
TPO antibodies	High titer, persistent	High titer, persistent	Low titer, or absent, or transient	Absent	Usually pres
ESR	Normal	Normal	High	High	Normal
24 hr ^{123}I uptake	Variable	<5%	<5%	Normal	Low or nor

ESR , erythrocyte sedimentation rate; ^{123}I, iodine 123; *TPO* , thyroid peroxidase.

Data from Farwell AP, Braverman LE: Inflammatory thyroid disorders. *Otolaryngol Clin North Am* 4:541–556, 1996.

Laboratory Findings

Thyroid function tests are often normal, although the level of TSH may be slightly or even moderately elevated in some patients with a normal free T_4 level, a pattern termed *subclinical hypothyroidism.* The fact that children with chronic lymphocytic thyroiditis often have goiters despite having normal TSH levels indicates that the goiter is caused primarily by the lymphocytic infiltration of the gland. Young children with chronic lymphocytic thyroiditis have serum TPO-Abs, but Tg-Abs are positive in <50%. TPO-Abs and Tg-Abs are found equally in adolescents with chronic lymphocytic thyroiditis. When both tests are used, approximately 95% of patients with thyroid autoimmunity are detected. Levels in children and adolescents are lower than those in adults with chronic lymphocytic thyroiditis, and repeated measurements are indicated in questionable instances because titers might increase later in the course of the disease. In adolescent females with overt hypothyroidism, measurement of TSH receptor antibodies may identify patients at future risk of having babies with transient congenital hypothyroidism.

Thyroid scintigraphy and ultrasonography usually are not needed. If they are done, thyroid scintigraphy reveals irregular, patchy, and overall decreased radioisotope uptake. Thyroid ultrasonography shows heterogeneous echogenicity along with an increased number of benign-appearing hyperplastic lymph nodes in the neck. The definitive diagnosis can be established by biopsy of the thyroid, which is rarely clinically indicated.

Treatment

If there is evidence of overt hypothyroidism (elevated TSH with low free T_4), treatment with levothyroxine is indicated at doses specific for size and age. The goiter usually shows some decrease in size but can persist for years. In a euthyroid patient, treatment with suppressive doses of levothyroxine is unlikely to lead to a significant decrease in size of the goiter. Antibody levels fluctuate in both treated and untreated patients and persist for years. Because the disease is self-limited in some instances, the need for continued therapy may be reevaluated periodically, particularly after growth and pubertal development are complete. Untreated patients should also be checked periodically. There is some controversy about the management of patients with subclinical hypothyroidism. This condition has not been demonstrated to have clinically significant adverse effects, but studies are small and of limited quality. Therefore many clinicians prefer to treat such children until growth and puberty are complete, and then reevaluate their thyroid function.

Other Causes of Thyroiditis

Painless thyroiditis (silent thyroiditis) is characterized primarily by transient thyrotoxicosis, followed sometimes by hypothyroidism, and then recovery. It accounts for 1 to 5% of cases of thyrotoxicosis. It can also occur in the postpartum period as well as in response to certain types of drugs (see below).

Drug-induced thyroiditis can be due to specific drugs including lithium, amiodarone, interferon-α, interleukin-2, and tyrosine kinase inhibitors. Patients taking lithium are susceptible to both lithium-induced hypothyroidism and painless thyroiditis. Amiodarone is an antiarrhythmic containing a high concentration of iodine, and it can cause two types of thyrotoxicosis. Type 1 is true hyperthyroidism (overproduction of thyroid hormone) and is typically seen in patients with underlying thyroid autoimmunity. Type 2 is a destructive thyroiditis and causes excessive release of preformed thyroid hormone.

Fibrous thyroiditis (invasive or Riedel thyroiditis) is very rare in children and is characterized by extensive fibrosis and macrophage and eosinophil infiltration of the thyroid gland. The thyroid becomes enlarged, hard, and affixed to surrounding structures. Typically, thyroid function tests are normal, and fine needle aspiration may reveal mononuclear cells and fibrous tissue. However, a biopsy is typically required to confirm the diagnosis. Glucocorticoids may alleviate symptoms.

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CHAPTER 583

Goiter

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A goiter is an enlargement of the thyroid gland. A normal thyroid volume is approximately 1 mL at birth and increases with age and body mass index. The rule of thumb can be used to evaluate the size of the thyroid in older children (>5 yr) with each lobe of the child's thyroid gland approximating the size of the distal phalanx of the child's thumb. Children with an enlarged thyroid can have normal function of the gland **(euthyroidism),** underproduction of thyroid hormone **(hypothyroidism),** or overproduction of thyroid hormone **(hyperthyroidism).**

Goiter may be congenital or acquired, endemic or sporadic. A goiter often results from increased pituitary secretion of thyrotropin thyroid-stimulating hormone (TSH) in response to decreased circulating levels of thyroid hormone. The most common causes of pediatric goiter are inflammation (chronic lymphocytic thyroiditis) and, in endemic areas, iodine deficiency (endemic goiter). Other causes include inborn errors in thyroid hormone synthesis (dyshormonogenesis), thyrotropin receptor–stimulating antibodies (TRSAb) in Graves disease, maternal ingestion of antithyroid drugs, goitrogens, activating mutations of the TSH receptor, or disorders of inappropriate TSH secretion. Thyroid enlargement can also result from thyroid nodules or other infiltrative processes. Most goiters are discovered incidentally by the patient or a caregiver, or on physical examination. Detection of a goiter should prompt an investigation of its cause and assessment of thyroid function.

583.1

Congenital Goiter

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Keywords

congenital hypothyroidism
dyshormonogenesis
Graves
iodine deficiency

Congenital goiter is usually sporadic and results from a defect in fetal thyroxine (T_4) synthesis that leads to neonatal hypothyroidism and goiter. This defect may be intrinsic to the fetal thyroid or may be caused by administration of antithyroid drugs (methimazole or propylthiouracil) or iodides during pregnancy for the treatment of maternal thyrotoxicosis. These drugs cross the placenta and can interfere with fetal synthesis of thyroid hormone. The neonatal consequences are most severe when overtreatment with antithyroid drugs also causes concomitant hypothyroidism in the mother, thereby reducing the supply of maternal thyroid hormone available to the fetus. Fetal effects can occur even with relatively low-dose doses of antithyroid drugs; therefore, all women treated with such drugs in the third trimester should undergo serum thyroid studies at birth, even if they appear clinically euthyroid. Administration of thyroid hormone to affected infants may be indicated for clinical hypothyroidism or to reduce goiter size (particularly if causing airway obstruction). Hypothyroidism due to maternal antithyroid drugs is transient, and thyroid hormone may be safely discontinued after the antithyroid drug has been excreted by the neonate, usually after 1-2 wk. In addition to antithyroid drugs, other medications containing significant amounts of iodine can cause congenital goiter, including amiodarone and some proprietary cough preparations used to treat asthma.

Enlargement of the thyroid at birth may occasionally be sufficient to cause respiratory distress that interferes with nursing and can even cause death. The head may be maintained in extreme hyperextension. In pregnant women who are overtreated with antithyroid drugs, the prenatal diagnosis of even massive fetal goiter can often be corrected by withdrawal or dose reduction of the maternal medication, with or without intra-amniotic thyroid hormone injection. When postnatal respiratory obstruction is severe, partial thyroidectomy rather than tracheostomy is indicated (Fig. 583.1).

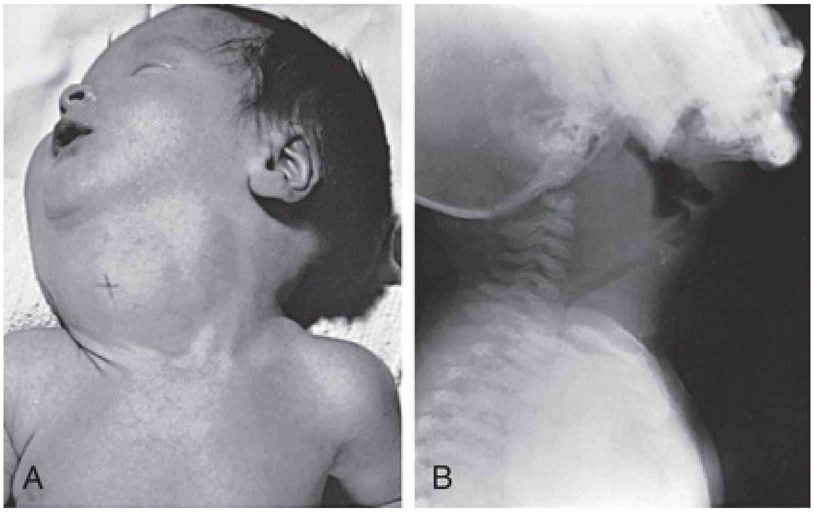

FIG. 583.1 Congenital goiter in infancy. **A,** Large congenital goiter in an infant born to a mother with thyrotoxicosis who had been treated with iodides and methimazole during pregnancy. **B,** A different infant, 6 wk old, with increasing respiratory distress and cervical mass since birth. The operation revealed a large goiter that almost completely encircled the trachea. Notice the anterior deviation and posterior compression of the trachea. Partial thyroidectomy completely relieved the symptoms. It is apparent why a tracheostomy is not adequate treatment for these infants. The cause for the goiter was not found.

Goiter is almost always present in the infant with neonatal Graves hyperthyroidism. Thyroid enlargement results from transplacental passage of maternal TSH receptor-stimulating antibodies (see Chapter 584.2). These goiters usually are not large, and the infant manifests clinical symptoms of hyperthyroidism. The mother often has a history of Graves disease, but occasionally, the diagnosis of maternal Graves disease may be discovered through the evaluation of neonatal hyperthyroidism. Activating mutations of the TSH receptor are also a rare cause of congenital goiter with hyperthyroidism.

In cases of congenital goiter and hypothyroidism in which no cause is identifiable from the maternal or medication history, an **intrinsic defect in synthesis of thyroid hormone** (dyshormonogenesis) should be suspected.

Neonatal screening programs find congenital hypothyroidism caused by such a defect in about 1 in 30,000 infants. Treatment with thyroid hormone should be initiated immediately. If a specific defect is suspected, genetic testing to identify a mutation may be considered (see Chapter 581). Monitoring subsequent pregnancies with ultrasonography can be useful in detecting fetal goiters (see Chapter 115).

Pendred syndrome is characterized by familial goiter and neurosensory deafness. The syndrome is caused by a mutation in *SLC26A4* , which encodes the pendrin chloride–iodide transporter expressed in the thyroid gland and cochlea. Pendrin defects result in abnormal iodide organification in the thyroid and can cause a goiter at birth, but the more common presentation is sensorineural hearing loss with development of a euthyroid goiter later in life.

Iodine deficiency as a cause of congenital goiter is rare in developed countries but persists in endemic areas (see Chapter 583.3). More important is the recognition that severe iodine deficiency early in pregnancy can cause neurologic damage during fetal development, even in the absence of goiter. This is true because iodine deficiency can cause maternal as well as fetal hypothyroidism, reducing the protective transfer of maternal thyroid hormones to the fetus.

When a palpable "goiter" is lobulated, asymmetric, firm, or unusually large, a teratoma in or near the thyroid must be considered in the differential diagnosis (see Chapter 585).

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583.2

Intratracheal Goiter

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Keywords

trachea

One of the many potential ectopic locations of thyroid tissue is within the trachea. When present, intraluminal thyroid tissue lies beneath the tracheal mucosa and is often continuous with the normally located extratracheal thyroid gland. Both eutopic and ectopic thyroid tissue are susceptible to goitrous enlargement. Therefore, when airway obstruction is associated with a goiter, it must be ascertained whether the obstruction is extratracheal or intratracheal. If obstructive manifestations are mild, administration of sodium levothyroxine usually decreases the size of the goiter. When symptoms are severe, surgical removal of the intratracheal goiter is indicated.

583.3

Endemic Goiter and Cretinism

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Keywords

iodine
cretinism
hypothyroidism

Etiology

Goiter caused by iodine deficiency is termed endemic goiter, while cretinism refers to the clinical manifestations of severe hypothyroidism in early life. The association of dietary iodine deficiency with endemic goiter and cretinism is well established. The thyroid gland can overcome a moderate deficiency of iodine by increasing the efficiency of thyroid hormone synthesis. Iodine liberated in peripheral tissues is returned rapidly to the gland, which increases the rate of thyroid hormone synthesis and produces a higher proportion of triiodothyronine (T_3) to thyroxine (T_4). This increased activity is achieved by compensatory thyroid hypertrophy and hyperplasia (goiter). In areas of severe iodine deficiency, these compensatory mechanisms are insufficient, and hypothyroidism can result. Estimates from the World Health Organization indicate that nearly 2 billion individuals currently have insufficient iodine intake, including one third of the world's school-age children. Thus, despite great progress in the global effort to reduce iodine deficiency, it remains the leading cause of preventable intellectual disability worldwide.

Because seawater is rich in iodine, the iodine content of fish and shellfish is high. As a result, endemic goiter is rare in coastal populations. Iodine is deficient in the water and native foods in the Pacific West and the Great Lakes regions of the United States. Deficiency of dietary iodine is even greater in certain Alpine valleys, the Himalayas, the Andes, the Congo, and the highlands of Papua New Guinea. Iodized salt provides excellent prophylaxis against iodine deficiency, and in the United States and many other countries that have introduced salt iodization programs, endemic goiter has effectively disappeared. Further iodine intake in the United States is contributed by iodates used in baking, iodine-containing coloring agents, and iodine-containing disinfectants used in the dairy industry. The United States recommended dietary allowance of iodine is as follows:

- Infants under 6 mo: 110 µg/day
- Infants 7-12 mo: 130 µg/day
- Children 1-8 yr: 90 µg/day
- Children 9-13 yr: 120 µg/day
- Children 14 yr and older: 150 µg/day
- Pregnant women: 220 µg/day
- Lactating women: 290 µg/day

While the overall dietary iodine intake in the United States is considered adequate, the most recent NHANES (National Health and Nutrition Examination Survey) from 2007 to 2010 reports that the median urinary iodine concentration among pregnant U.S. women has dropped to <150 µg/L. This indicates mild iodine deficiency and highlights the risk of iodine deficiency reemergence in industrialized countries as salt intake decreases. These risks can be mitigated by the continued monitoring of iodine status, the adjustment of salt iodization levels, and the targeted supplementation of vulnerable subpopulations (e.g., promotion of iodine-containing prenatal vitamins).

Clinical Manifestations

In mild iodine deficiency, thyroid enlargement generally is not noticeable except when demand for thyroid hormone synthesis is increased, such as during rapid growth in adolescence and pregnancy. In regions of moderate iodine deficiency, goiter observed in school children can disappear with maturity and reappear during pregnancy or lactation. Iodine-deficient goiters are more common in girls than in boys. In areas where iodine deficiency is severe, as in the hyperendemic highlands of Papua New Guinea, nearly half the population has large goiters, and endemic cretinism is common (Fig. 583.2).

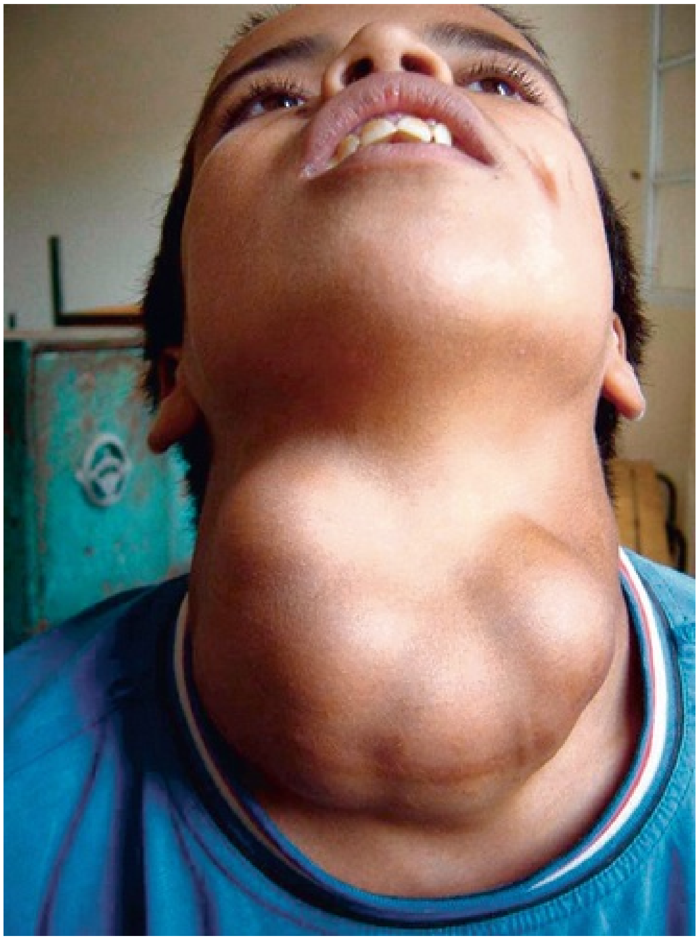

FIG. 583.2 A 14 yr old boy with a large nodular goiter was seen in 2004, in an area of severe iodine-deficiency disorders in northern Morocco. He had tracheal and esophageal compression and hoarseness, probably as a result of damage to the recurrent laryngeal nerves. (From Zimmermann MB, Jooste PL, Pandav CS: Iodine-deficiency disorders, *Lancet* 372:1251–1262, 2008, Fig. 2.)

Serum T_4 levels are often low in persons with endemic goiter, although clinical hypothyroidism is rare. This is true in Papua New Guinea, the Congo, the Himalayas, and South America. Despite low serum T_4 levels, serum TSH concentrations are often normal or only moderately increased due to elevated circulating levels of T_3 . In fact, T_3 levels are elevated even in patients with normal T_4 levels, reflecting the fact that iodine deficiency leads to preferential secretion of T_3 by the thyroid and an adaptive increase in peripheral T_4 to T_3 conversion.

Endemic cretinism is the most serious consequence of iodine deficiency and occurs only in geographic association with endemic goiter. The term *endemic* *cretinism* includes 2 different but overlapping syndromes: a **neurologic type** and a **myxedematous type.** The incidence of the 2 types varies among different populations. In Papua New Guinea, the neurologic type occurs almost exclusively, whereas in the Congo, the myxedematous type predominates. However, both types are found in all endemic areas, and some persons have intermediate or mixed features.

The **neurologic syndrome** is characterized by intellectual disability, deaf-mutism, disturbances in standing and gait, and pyramidal signs such as clonus of the foot, the Babinski sign, and patellar hyperreflexia. Affected persons are goitrous, but have little or no impaired thyroid function and have normal pubertal development and adult stature. Persons with the **myxedematous syndrome** also are intellectually challenged, deaf, and have neurologic symptoms, but in contrast to the neurologic type, they have delayed growth and sexual development, myxedema, and absence of goiter. Serum T_4 levels are low and TSH levels are markedly elevated. Delayed skeletal maturation may extend into the 3rd decade or later. Ultrasonographic examination shows thyroid atrophy.

Pathogenesis

The pathogenesis of the **neurologic syndrome** is attributed to maternal iodine deficiency and hypothyroxinemia during pregnancy, leading to fetal and postnatal hypothyroidism. Although some investigators have attributed brain damage to a direct effect of elemental iodine deficiency in the fetus, most believe the neurologic symptoms are caused by combined fetal and maternal hypothyroxinemia. There is evidence for the presence of thyroid hormone receptors in the fetal brain as early as 7 wk of gestation. Although the normal fetal thyroid gland does not begin to produce significant amounts of thyroid hormone until midgestation, there is measurable T_4 in the coelomic fluid as early as 6 wk, almost certainly of maternal origin. These lines of evidence support a role for maternal thyroid hormone in fetal brain development in the first trimester. In addition, there is evidence of transplacental passage of maternal thyroid hormone into the fetus, which normally might ameliorate the effects of fetal hypothyroidism on the developing nervous system in the second half of pregnancy. Thus, iodine deficiency in the mother affects fetal brain development both in the first trimester and throughout pregnancy. Intake of iodine after birth is often sufficient for normal or only minimally impaired thyroid function.

The pathogenesis of the **myxedematous syndrome** leading to thyroid atrophy is less well understood. Searches for additional environmental factors that might provoke continuing postnatal hypothyroidism have led to incrimination of selenium deficiency, goitrogenic foods, thiocyanates, and *Yersinia* (Table 583.1). Studies from western China suggest that thyroid autoimmunity might play a role. Some have suggested that TSH receptor-blocking immunoglobulins of the type found rarely in infants with sporadic congenital hypothyroidism may play a role in myxedematous cretinism with thyroid atrophy, but not in euthyroid cretinism; however, another study failed to replicate these findings, and the potential role of TSH receptor-blocking immunoglobulins remains unclear.

Table 583.1

Goitrogens and Their Mechanism

GOITROGEN	MECHANISM
FOODS	
Cassava, lima beans, linseed, sorghum, sweet potato	Contain cyanogenic glucosides that are metabolized to thiocyanates that compete with iodine for uptake by the thyroid
Cruciferous vegetables (cabbage, kale, cauliflower, broccoli, turnips)	Contain glucosinolates; metabolites compete with iodine for uptake by the thyroid
Soy, millet	Flavonoids impair thyroid peroxidase activity
INDUSTRIAL POLLUTANTS	
Perchlorate	Competitive inhibitor of the sodium–iodine symporter, decreasing iodine transport into the thyroid
Others (e.g., disulfides from coal processes)	Reduce thyroidal iodine uptake
Smoking	Smoking during breastfeeding is associated with reduced iodine concentrations in breast milk; high serum concentration of thiocyanate from smoking might compete with iodine for active transport into the secretory epithelium of the lactating breast
NUTRIENTS	
Selenium deficiency	Accumulated peroxides can damage the thyroid, and deiodinase deficiency impairs thyroid hormone activation
Iron deficiency	Reduces heme-dependent thyroperoxidase activity in the thyroid and may blunt the efficacy of iodine prophylaxis
Vitamin A deficiency	Increases TSH stimulation and goiter through decreased vitamin A–mediated suppression of the pituitary TSH-β gene

TSH , thyroid-stimulating hormone.

From Zimmermann MB, Jooste PL, Pandav CS: Iodine-deficiency disorders, *Lancet* 372:1251–1262, 2008, Table 1.

Treatment

In many developing countries, administration of a single intramuscular injection of iodinated poppy seed oil to women prevents iodine deficiency during future pregnancies for approximately 5 yr. This form of therapy given to children younger than 4 yr of age with myxedematous cretinism results in a euthyroid state in 5 mo. Older children respond poorly and adults not at all to iodized oil injections, indicating an inability of the thyroid gland to synthesize hormone; these patients require treatment with T_4 . Through the efforts of the World Health Organization and its program of universal salt iodization, the number of households worldwide with access to adequately iodized salt has increased from <10% in 1990 to 70% in 2012. In the Xinjiang province of China, where the usual methods of iodine supplementation had failed, iodination of irrigation water has increased iodine levels in soil, animals, and human beings. In other countries, iodinated salt in school meal programs gives children the dietary iodine they need. Nevertheless, political, economic, and practical obstacles have limited penetration of iodized food into regular diets around the world.

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583.4

Acquired Goiter

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Keywords

hypothyroidism
thyrotoxicosis
thyroiditis
iodine
Hashimoto

Acquired goiter is usually sporadic and may develop from a variety of causes. Patients are typically euthyroid but may be either hypothyroid or hyperthyroid. The most common cause of acquired goiter is chronic lymphocytic thyroiditis (see Chapter 582). Rarer causes in children include painless sporadic thyroiditis and subacute or painful thyroiditis (de Quervain disease; see Chapter 582).

Excess iodide ingestion and certain drugs (amiodarone and lithium) can cause goiter, as can congenital defects in thyroid hormonogenesis. The occurrence of the disorder in siblings, onset in early life, and possible association with hypothyroidism (goitrous hypothyroidism) are important clues to the diagnosis of congenital dyshormonogenesis.

Iodide Goiter

Excessive iodine administration can result in a goiter. Iodine is found in expectorants for chronic reactive airways disease or cystic fibrosis. Most children with iodine-induced goiters have underlying chronic lymphocytic thyroiditis or a subclinical inborn error in thyroid hormone synthesis. In a normal thyroid gland, the acute administration of large doses of iodine inhibits the organification of iodine and the synthesis of thyroid hormone (Wolff-Chaikoff effect). This effect is short-lived and does not lead to permanent hypothyroidism. When iodine administration continues, an autoregulatory mechanism limits iodide trapping, permitting the level of iodide in the thyroid to decrease and normal organification to resume. In patients with iodine-induced goiter, this escape does not occur, usually because of an underlying abnormality in thyroid hormone synthesis.

Iodine-Deficiency Goiter

Iodine deficiency is the most common cause of endemic goiter worldwide, but supplementation with iodized salt has nearly eradicated this entity in the United States. A severely iodine-restricted diet can result in a goiter and hypothyroidism in children and adolescents, or in neonates born to mothers with severe iodine deficiency (urine iodine concentration <50 mcg/L). Children with moderate or severe iodine deficiency and goiter have subclinical or mild hypothyroidism, but their serum T_3 concentrations may be normal or high because of preferential thyroidal T_3 secretion. They can be treated with either iodine or levothyroxine supplementation.

Goitrogens

Certain foods contain goitrogenic substances (see Table 583.1). These substances are unlikely to cause goiter when consumed alone but can contribute to goiter formation when iodine intake is marginal.

Lithium carbonate can cause a goiter and hypothyroidism in children. Lithium decreases T_4 and T_3 synthesis and release; the mechanism producing the goiter or hypothyroidism is similar to that described for iodide goiter . Lithium and iodide act synergistically to produce goiter, so their combined use should be avoided.

Amiodarone, a drug used to treat cardiac arrhythmias, can cause thyroid dysfunction with goiter because it is rich in iodine. It is also an inhibitor of type 1 deiodinase, preventing conversion of T_4 to T_3 . Amiodarone can cause hypothyroidism, particularly in patients with underlying autoimmune thyroid disease. In other patients, it can cause thyrotoxicosis through either transient thyroiditis or the Jod-Basedow effect (iodine-induced hyperthyroidism).

Simple Goiter (Colloid Goiter)

Some children with euthyroid goiters have simple goiters, a condition of unknown cause not associated with hypothyroidism or hyperthyroidism and not caused by inflammation or neoplasia. Simple goiter is more common in girls, may be familial, and has its peak incidence during adolescence. Histologic examination of the thyroid either is normal or reveals variable follicular size, dense colloid, and flattened epithelium. The size of the goiter is variable. It can occasionally be firm, asymmetric, or nodular. Levels of TSH are normal or low, thyroid scintigraphy is normal, and thyroid antibodies are absent. Differentiation from lymphocytic thyroiditis might not be possible without a biopsy, but biopsy is usually not indicated. Simple goiters usually decrease in size gradually over several years, without treatment. Patients should be reevaluated periodically because some have antibody-negative chronic lymphocytic thyroiditis and therefore are at risk for changes in thyroid function (see Chapter 582).

Multinodular Goiter

Multinodular goiter is usually encountered as a firm goiter with a lobulated surface and one or more palpable nodules. Areas of cystic change, hemorrhage, and fibrosis may be present. The incidence of this condition has decreased markedly with the use of iodine-enriched salt. Ultrasonographic examination can reveal multiple nodules that are nonfunctioning on thyroid scintigraphy. Thyroid studies are usually normal. Some children with chronic lymphocytic thyroiditis develop multinodular goiter, and in such cases TSH may be elevated and thyroid antibodies may be present. Children can develop toxic multinodular goiter, characterized by a suppressed TSH and hyperthyroidism. The condition can occur in children with **McCune-Albright syndrome** or with TSH receptor–activating mutations. If hypofunctioning nodules within a multinodular goiter grow to significant size (≥1 cm), then fine-needle aspiration should be considered to rule out malignancy (see Chapter 585).

Toxic Goiter (Hyperthyroidism)

See Chapter 584 .

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CHAPTER 584

Thyrotoxicosis

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Although the terms hyperthyroidism and thyrotoxicosis are often interchanged in the literature, they are not synonymous. **Hyperthyroidism** specifically refers to the synthesis and secretion of excess thyroid hormone from the thyroid gland; in contrast, **thyrotoxicosis** refers to any state of excess circulating thyroid hormone (and its clinical manifestations) regardless of its source. This distinction is physiologically and clinically relevant because different therapies may be indicated depending on the mechanism of thyroid hormone excess.

Graves disease is the most common cause of hyperthyroidism in children (Table 584.1). Graves disease is an autoimmune disorder that results in the production of **thyrotropin (TSH) receptor–stimulating antibodies (TRSAbs)** that bind and activate the G protein–coupled **TSH receptor (TSHR**) to cause increased thyroid hormonogenesis and diffuse glandular growth. Etiologies of nonautoimmune hyperthyroidism include hyperfunctioning thyroid nodules and germline gain-of-function mutations in the TSHR (either autosomal dominant or sporadic). Hyperthyroidism can also occur in patients with **McCune-Albright syndrome** as a result of an activating mutation of the stimulatory α-subunit of the G-protein. These patients can also develop a multinodular goiter. Other rare causes of hyperthyroidism include iodine-induced hyperthyroidism, TSH-secreting adenomas, toxic multinodular goiters, and hyperfunctioning thyroid carcinoma. Thyrotoxicosis not due to hyperthyroidism (i.e., not due to overproduction of thyroid hormone by the gland) can be caused by thyroiditis (see Chapter 582) or ingestion of exogenous thyroid hormone (thyrotoxicosis factitia).

Table 584.1

Pathogenic Mechanisms and Causes of Thyrotoxicosis

Cause	
Thyrotoxicosis with hyperthyroidism (normal or high radioactive iodine uptake)	
Effect of increased thyroid stimulators	
TSH-receptor antibody	Graves disease
Inappropriate TSH secretion	TSH-secreting pituitary adenoma; pituitary resistance to thyroid hormone
Excess hCG secretion	Trophoblastic tumors (choriocarcinoma or hydatidiform mole); hyperemesis gravidarum
Autonomous thyroid function	
Activating mutations in TSH receptor or G_s α protein	Solitary hyperfunctioning adenoma; multinodular goiter; familial nonautoimmune hyperthyroidism
Thyrotoxicosis without hyperthyroidism (low radioactive iodine uptake)	
Inflammation and release of stored hormone	
Autoimmune destruction of thyroid gland	Silent (painless) thyroiditis; postpartum thyroiditis
Viral infection*	Subacute (painful) thyroiditis (de Quervain thyroiditis)
Toxic drug effects	Drug-induced thyroiditis (amiodarone, lithium, interferon-α)
Bacterial or fungal infection	Acute suppurative thyroiditis
Radiation	Radiation thyroiditis
Extrathyroidal source of hormone	
Excess intake of thyroid hormone	Excess exogenous thyroid hormone (iatrogenic or factitious)
Ectopic hyperthyroidism (thyroid hormone produced outside the thyroid gland)	Struma ovarii; functional thyroid cancer metastases
Ingestion of contaminated food	Hamburger thyrotoxicosis
Exposure to excessive iodine	
Jod-Basedow effect	

* Etiology is not definitive.

G_s α , G protein alpha subunit; *hCG* , human chorionic gonadotropin; *TSH* , thyroid-stimulating hormone.

From De Leo S, Lee SY, Braverman LE: Hyperthyroidism, *Lancet* 388:906–916, 2016, Table 1.

Laboratory evaluation of primary hyperthyroidism reveals suppression of serum TSH and elevation of serum total thyroxine (T_4) and total triiodothyronine (T_3) levels. Hyperthyroidism caused by inappropriate TSH secretion is usually due to a dominant-negative mutation in thyroid hormone receptor-β *(THRB)* resulting in **resistance to thyroid hormone (RTH)** . TSH-secreting pituitary tumors are extremely rare in the pediatric population. In infants born to mothers with Graves disease, hyperthyroidism is transitory and resolves when TRSBAb are cleared from the neonate's circulation. Choriocarcinoma, hydatidiform mole, struma ovarii, and functional thyroid cancer can cause hyperthyroidism in adults but are rarely diagnosed in children.

584.1

Graves Disease

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Keywords

hyperthyroidism
goiter
thyrotoxicosis
ophthalmopathy
methimazole
propylthiouracil
iodine
Graves

Epidemiology

Graves disease occurs in approximately 0.02% of children (1 : 5,000) and is the most common cause of pediatric hyperthyroidism. Only 5% of all patients with hyperthyroidism are younger than 15 yr of age. Graves disease has a peak incidence in the 11-15 yr old age group, and there is a 5 : 1 female:male ratio. Many children with Graves disease have a family history of autoimmune thyroid disease. Although rare, Graves disease has been reported between 6 wk and 2 yr of age in children born to mothers without a history of hyperthyroidism.

Etiology

Enlargement of the thymus, splenomegaly, lymphadenopathy, peripheral lymphocytosis, and infiltration of the thyroid gland and retro-orbital tissues with lymphocytes and plasma cells are well-established findings in Graves disease. In the thyroid gland, T-helper cells ($CD4^+$) predominate in dense lymphoid aggregates; in areas of lower cell density, cytotoxic T cells ($CD8^+$) predominate. The percentage of activated B lymphocytes infiltrating the thyroid is higher than in peripheral blood. A postulated failure of T suppressor cells allows expression of T helper cells sensitized to the TSH antigen to interact with B cells. These cells differentiate into plasma cells that produce **TRSAbs** . TRSAbs bind to the TSHR and stimulate production of cyclic adenosine monophosphate (cAMP), resulting in thyroid hyperplasia and unregulated thyroid hormone synthesis. In some patients with Graves disease, **TSH receptor–blocking antibodies (TRBAbs)** are produced that bind to but do not activate the TSHR. The clinical course of the disease correlates to the ratio between stimulating and blocking antibodies.

The ophthalmopathy that occurs in Graves disease appears to be caused by antibodies against antigens shared by both the thyroid and retro-orbital tissue. TSHR have been identified in retro-orbital adipocytes and might represent a target for antibodies. TRSAbs bind to the extraocular muscles and orbital fibroblasts and stimulate the synthesis of glycosaminoglycans and cytokines. Although 50–75% of children with Graves disease have some eye finding, the symptoms are much milder than in adults.

In whites, Graves disease is associated with human leukocyte antigen (HLA)-B8 and HLA-DR3; the latter carries a 7-fold relative risk for Graves disease. Graves disease is also associated with other HLA-D3–related disorders, such as Addison disease, type 1 diabetes mellitus, myasthenia gravis, and celiac disease (Table 584.2). Systemic lupus erythematosus, rheumatoid arthritis, vitiligo, idiopathic thrombocytopenic purpura, and pernicious anemia have also been described in children with Graves disease. In family clusters, the condition associated most commonly with Graves disease is autoimmune thyroiditis. In Japanese children, Graves disease is associated with different HLA haplotypes: HLA-DRB1*0405 and HLA-DQB1*0401. In the Chinese population the RNASET2-FGFR1OP-CCR6 region at 6q27 and an intergenic region at 4p14 are important susceptibility loci. Polymorphisms in the *TSHR* gene and numerous immunomodulatory genes—including *FOXP3* , *IL2RA* , *CD40* , *CTLA4* , *PTPN22* , and *FCRL3* —have also been associated with increased susceptibility to Graves disease.

Table 584.2

Conditions Associated With Hyperthyroidism

Type 1 diabetes mellitus
Addison disease
Vitiligo
Psoriasis
Trisomy 21
Turner syndrome
Pernicious anemia
Alopecia areata
Myasthenia gravis
Celiac disease
Rheumatoid arthritis

Clinical Manifestations

The clinical course of Graves disease is highly variable, and children typically take longer to remit than adults. Because symptoms develop gradually, the interval between onset and diagnosis is typically 6-12 mo and may be longer in prepubertal children compared with adolescents.

Many of the signs and symptoms of Graves disease in children are similar to those in adults (Fig. 584.1 and Table 584.3). However, the earliest signs and most pronounced differences in children may be related to growth and neuropsychologic systems. Tremulousness, headaches, mood disturbances, behavioral swings, difficulties with sleep, decrease in attention span, hyperactivity, and a decline in school performance are all common findings in childhood, and many hyperthyroid children are referred for evaluation of attention-deficit/hyperactivity disorder (ADHD).

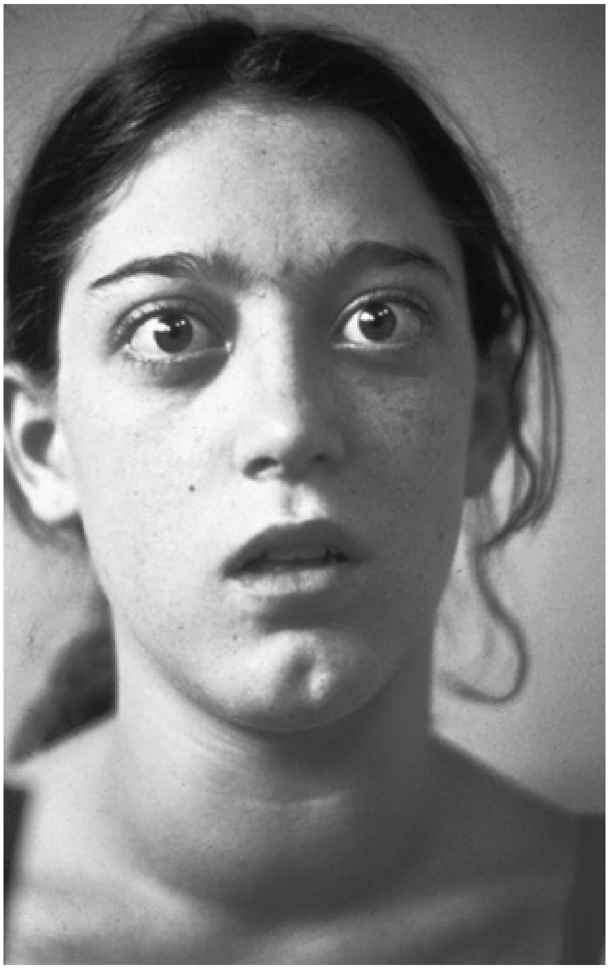

FIG. 584.1 A 15 yr old girl with classic Graves disease. Clinical features include a goiter and exophthalmos. She was treated with antithyroid drugs, to which she had a good response.

Table 584.3

Clinical Manifestation of Thyrotoxicosis

	SYMPTOMS	SIGNS
Constitutional	Weight loss despite increased appetite; heat-related symptoms (heat intolerance, sweating, and polydipsia)	Weight loss
Neuromuscular	Tremor; nervousness; anxiety; fatigue; weakness; disturbed sleep; poor concentration	Tremor of the extremities; hyperactivity; hyperreflexia; pelvic and girdle muscle weakness
Cardiovascular	Palpitations	Tachycardia; systolic hypertension
Pulmonary	Dyspnea, shortness of breath	Tachypnea
Gastrointestinal	Hyperdefecation; nausea, vomiting	Abdominal tenderness
Skin	Increased perspiration	Warm and moist skin
Reproductive		Menstrual disturbances

Ocular (Graves disease)	Diplopia; sense of irritation in the eyes; eyelid swelling; retro-orbital pain or discomfort	Proptosis; eyelid retraction and lag; periorbital edema; conjunctival injection and chemosis; ophthalmoplegia

From De Leo S, Lee SY, Braverman LE: Hyperthyroidism, *Lancet* 388:906–916, 2016, Table 2.

Children with hyperthyroidism may show acceleration in growth velocity and advanced skeletal maturation. The effect on growth may be more pronounced if hyperthyroidism presents earlier in childhood. With antithyroid drug (ATD) treatment, growth velocity, and bone age approach a more normal pattern. There may also be an increase in appetite with either failure to gain weight or overt weight loss. Polyuria and more frequent defecation (although not usually frank diarrhea) contribute to changes in weight. Due to the increased risk of comorbid autoimmune disorders, screening for type 1 diabetes, celiac disease, and inflammatory bowel disease should be considered in patients who present with these symptoms.

The age of the onset of puberty does not appear to be altered by hyperthyroidism; however, menarchal females can develop secondary amenorrhea. Hyperthyroidism is also associated with increased aromatization of androgens to estrogens, but gynecomastia does not occur in males.

Most children with Graves disease have a diffuse goiter, but the size of the thyroid is variable. It is typically smooth and without nodules. A bruit can occasionally be auscultated over a markedly enlarged gland. If exophthalmos is present, it is typically mild. Ocular manifestations can produce pain, eyelid erythema, chemosis, decreased extraocular muscle function, and decreased visual acuity (corneal or optic nerve involvement) (Table 584.4). In children with thyrotoxicosis, the identification of these signs of ophthalmopathy on physical examination in the setting of diffuse goiter is highly suggestive of the diagnosis of Graves disease. Stare and lid lag are common eye findings caused by increased sympathetic activity and can be seen in thyrotoxicosis of any cause, not only Graves disease (Fig. 584.2). In general, ocular symptoms in children with Graves disease tend to be milder than in adults, and they improve with the restoration of euthyroidism.

Table 584.4

Clinical Assessment of the Patient With Graves Ophthalmopathy

ACTIVITY MEASURES *

• Spontaneous retrobulbar pain • Pain on attempted up or down gaze • Redness of the eyelids • Redness of the conjunctivae • Swelling of the eyelids • Inflammation of the caruncle and/or plica • Conjunctival edema
SEVERITY MEASURES
• Lid aperture (distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed, and with distant fixation) • Swelling of the eyelids (absent/equivocal, moderate, severe) • Redness of the eyelids (absent/present) • Redness of the conjunctivae (absent/present) • Conjunctival edema (absent, present) • Inflammation of the caruncle or plica (absent, present) • Exophthalmos (measured in millimeters using the same Hertel exophthalmometer and the same intercanthal distance for an individual patient) • Subjective diplopia score [†] • Eye muscle involvement (ductions in degrees) • Corneal involvement (absent/punctate keratopathy/ulcer) • Optic nerve involvement (best corrected visual acuity, color vision, optic disk, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected

[*] Based on the classic features of inflammation in Graves ophthalmopathy.

[†] Subjective diplopia score: 0, no diplopia; 1, intermittent (i.e., diplopia in primary position of gaze, when tired or when first awakening); 2, inconstant (i.e., diplopia at extremes of gaze); 3, constant (i.e., continuous diplopia in primary or reading position).

The clinical activity score (CAS) is the sum (1 point each) of all items present; a CAS ≥ 3/7 indicates active ophthalmopathy.

From Davies TF, Laurberg P, Bahn RS: Hyperthyroid disorders. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors: *Williams textbook of endocrinology* , ed 13, Philadelphia, 2016, Elsevier, Table 12.4.

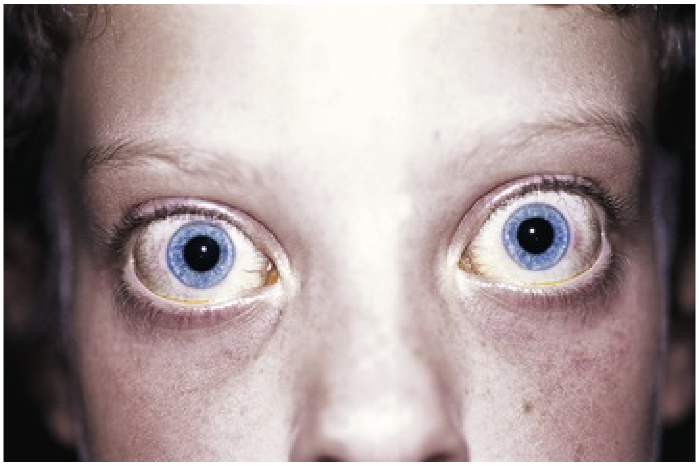

FIG. 584.2 Retraction of upper eyelids in the primary gaze (Dalrymple

sign). (From Kanski JJ: *Systemic diseases and the eye: signs and differential diagnosis* , London, 2001, Mosby.)

Children with hyperthyroidism have an increase in cardiac output. Tachycardia, palpitations, increased systolic blood pressure, and a widened pulse pressure are common cardiac manifestations, whereas cardiac enlargement and insufficiency, and atrial fibrillation are rare complications.

The skin is smooth and flushed, with excessive sweating. Occasionally, vitiligo or psoriasis can be present. Graves dermopathy is rare in children and typically responsive to steroids. Proximal muscular weakness is common. Thyroid hormone stimulates bone resorption, leading to low bone density and an increased fracture risk in patients with chronic hyperthyroidism. Bone density returns to normal with treatment.

Thyroid storm is an extreme form of hyperthyroidism manifested by a severe biochemical derangement, hyperthermia, tachycardia, heart failure, and restlessness (Table 584.5). There may be rapid progression to delirium, coma, and death. Precipitating events include trauma, infection, radioactive iodine (RAI) treatment, or surgery.

Table 584.5

Diagnostic Criteria for Thyroid Storm

	POINTS
TEMPERATURE°F (°C)	
99-99·9 (37·2-37·7)	5
100-100·9 (37·8-38·2)	10
101-101·9 (38·3-38·8)	15
102-102·9 (38·9-39·4)	20
103-103·9 (39·4-39·9)	25
≥104·0 (>40·0)	30
CENTRAL NERVOUS SYSTEM EFFECTS	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
GASTROINTESTINAL–HEPATIC DYSFUNCTION	
Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
CARDIOVASCULAR DYSFUNCTION	
Tachycardia	
90-109	5
110-119	10

120-129	15
130-139	20
≥140	25
Congestive Heart Failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Atrial Fibrillation	
Absent	0
Present	10
Precipitating History	
Absent	0
Present	10

In adults, a score ≥45 is highly suggestive of thyroid storm; a score of 25-44 is suggestive of impending thyroid storm; a score of <25 is unlikely to represent thyroid storm. Data are from Burch and Wartofsky.

From De Leo S, Lee SY, Braverman LE: Hyperthyroidism, *Lancet* 388:906–916, 2016, Table 3.

Laboratory Findings

In Graves disease, serum TSH is suppressed and free T_4 and T_3 are elevated. Most patients with newly diagnosed Graves disease have measurable thyrotropin receptor antibodies (TSHR-Abs). TSHR-Abs can be measured by either of 2 methods. Thyroid-stimulating immunoglobulin (TSI) is a functional assay measuring the presence of antibodies capable of stimulating TSHR-mediated cAMP generation (TRSAb). Thyrotropin-binding inhibitory immunoglobulin (TBII) is a binding assay measuring antibody binding to the TSHR, regardless of receptor-stimulating (TRSAb) or receptor-blocking (TRBAb) activity. In a patient with thyrotoxicosis, both assays are 96–97% sensitive and 99% specific for Graves disease.

When the diagnosis cannot be established by history, physical examination, and laboratory evaluation, RAI uptake can be measured. ^{123}I is the radionucleotide of choice for thyroid uptake and scintigraphy. The RAI uptake (typically assessed at 4 and 24 hr after isotope administration) is elevated in Graves disease, whereas it is low in other causes of thyrotoxicosis like thyroiditis or exogenous thyroid hormone ingestion. If scintigraphy is also performed, the increased RAI uptake in Graves disease is present diffusely throughout the gland, whereas focally increased uptake is observed in hyperfunctioning thyroid nodules.

Differential Diagnosis

Diagnosis of thyrotoxicosis is straightforward once the diagnosis is considered. Elevated serum levels of T_4 or free T_4 and T_3 in association with suppressed levels of TSH are diagnostic (see Table 584.1). The combination of diffuse goiter and prolonged thyrotoxicosis (>8 wk) is nearly always caused by Graves disease, and the presence of circulating TSHR-Abs or characteristic eye or skin changes is diagnostic.

In cases of thyrotoxicosis in which the etiology is not clear, ^{123} I radioiodine uptake can be used to distinguish hyperthyroidism (increased uptake) from other causes of thyrotoxicosis, which will determine the appropriateness of antithyroid medication. If a discrete thyroid nodule is palpated, ^{123} I scintigraphy should be performed to assess the possibility of a hyperfunctioning nodule. Some children with toxic multinodular goiter may have either a TSHR–activating mutation or McCune-Albright syndrome. If precocious puberty, polyostotic fibrous dysplasia, or café-au-lait macules are present, then McCune-Albright syndrome is likely.

Patients with thyroid hormone resistance (see later) have elevated levels of free T_4 and T_3 , but levels of TSH are inappropriately elevated or normal. They must be differentiated from patients with TSH-secreting pituitary tumors who have elevated serum levels of the common α-subunit shared by TSH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (hCG). Most other causes of elevated serum T_4 are uncommon but can result in erroneous diagnosis. Patients with **elevated thyroxine-binding globulin** levels or **familial dysalbuminemic hyperthyroxinemia** have high serum T_4 but normal levels of free T_4 and TSH and are clinically euthyroid. Rare patients with mutations in *SLC16A2* (encoding the MCT8 thyroid hormone transporter) or *THRA* (encoding thyroid hormone receptor α) can present with high serum T_3 , inappropriately normal or high TSH, and low or low-normal serum T_4 concentrations.

When thyrotoxicosis is caused by exogenous thyroid hormone (thyrotoxicosis factitia), levels of free T_4 and TSH are the same as those seen in Graves disease but, in contrast to Graves disease, thyroid size is small, serum thyroglobulin is very low, and ^{123} I radioiodine uptake is suppressed.

Treatment

Antithyroid Drugs

Most pediatric endocrinologists recommend initial medical therapy of Graves disease using antithyroid drugs (ATDs) rather than radioiodine ablation or near-total thyroidectomy, although radioiodine is gaining acceptance as initial treatment in children older than 10 yr of age. Each therapeutic option has advantages and disadvantages (Table 584.6). Methimazole is the first line ATD for children with Graves disease and functions by blocking the organification of iodide necessary to synthesize thyroid hormone. Methimazole has a long serum half-life (6-8 hr) that allows once- or twice-daily dosing. Propylthiouracil is a similar ATD that is effective in hyperthyroidism, but its use is not recommended in children due to its potential to cause liver failure.

Table 584.6

Treatments for Graves Disease

TREATMENT	ADVANTAGE	DISADVANTAGE	COMMENT
Antithyroid drugs	Noninvasive Less initial cost No risk of permanent hypothyroidism Possible remission	Remission rate 30–50% (with long-term treatment) Adverse drug reactions Drug compliance required	First line treatment in children and adolescents and in pregnancy Initial treatment in severe cases or preoperative preparation
Radioactive iodine (^{131}I)	Cure of hyperthyroidism Most cost-effective	Permanent hypothyroidism Might worsen ophthalmopathy Pregnancy must be deferred for 6-12 mo, mother cannot breastfeed; small potential risk of exacerbation of hyperthyroidism	No evidence for infertility, birth defects, or secondary cancers with currently recommended doses
Surgery	Rapid, effective (especially in patients with large goiter)	Most invasive therapy Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Permanent hypothyroidism Most costly therapy Pain, surgical scar	Potential use in pregnancy if major side effect from antithyroid drugs Useful when coexisting suspicious nodule is present or thyromegaly is massive Option for patients who do not desire radioiodine

From Cooper DS: Hyperthyroidism, *Lancet* 362:459–468, 2003.

Adverse reactions can occur with ATDs, and although most are mild, some are life threatening. Minor adverse effects occur in approximately 10–20% of patients, and severe adverse effects occur in 2–5%. Reactions most commonly occur in the first 3 mo of therapy but can occur at any time during therapy. Transient urticarial rashes are common and may be managed with antihistamines or by a short period off therapy followed by restarting ATD. Agranulocytosis is a severe adverse reaction that occurs in 0.1–0.5% of patients and can lead to fatal infections. Therefore patients on methimazole should stop this medication and have a white blood count checked during any episode of significant fever, pharyngitis, or oral ulcers. On the other hand, transient, asymptomatic granulocytopenia (<2,000/mm^3) is a common finding in Graves disease; it is not a harbinger of agranulocytosis and is not a reason to discontinue treatment. Other severe reactions include hepatitis (0.2–1.0%), a lupus-like polyarthritis syndrome, glomerulonephritis, and antineutrophilic cytoplasmic antibody–positive vasculitis. Severe liver disease, including liver failure requiring transplantation, has been reported with propylthiouracil. The most common liver disease associated with methimazole is cholestatic jaundice, which is reversible when the drug is discontinued. Patients with severe adverse effects should be treated with radioiodine or thyroidectomy. In rare instances in which hyperthyroidism is severe and methimazole cannot be used, a short course of propylthiouracil may be offered to restore euthyroidism prior to definitive therapy. Both methimazole and propylthiouracil have been associated with congenital malformations in infants exposed to these drugs in utero. Methimazole exposure may be associated with aplasia cutis, omphalocele, choanal atresia, and urinary system malformations, whereas propylthiouracil may be associated with malformations of the head, neck, and urinary system.

The initial dosage of methimazole is 0.5-1.0 mg/kg/24 hr (max 40 mg/day) administered once or twice daily. Smaller initial dosages should be used in early childhood. Careful surveillance is required after treatment is initiated. Rising serum levels of TSH of greater than normal indicates overtreatment and warrants a dose reduction. Clinical response becomes apparent in 3-4 wk, and adequate control is typically evident within 3-4 mo. The dose is decreased to the minimal level required to maintain a euthyroid state.

Most studies report a remission rate of approximately 25% after 2 yr of ATD treatment in children. Some studies find that longer treatment is associated with higher remission rates of 30–50% after 4-10 yr of drug treatment. Relapses usually occur within 6-12 mo after therapy has been discontinued. In case of relapse, ATD therapy may be resumed or definitive therapy with either radioiodine or thyroidectomy can be pursued. In general, adolescents, males, those with a higher body mass index, and those with small goiters and modestly elevated T_3 levels are thought to have earlier remissions; however, this has not been proven in large studies, because TRSAbs tend to persist for a longer period of time in children than in adults with Graves disease.

Thyroid hormones potentiate the actions of catecholamines, including tachycardia, tremor, excessive sweating, lid lag, and stare. To help control cardiovascular symptoms, a β-adrenergic blocking agent such as propranolol or atenolol is a useful supplement to ATDs. However, these agents do not alter thyroid function or exophthalmos. Table 584.7 lists additional therapies for **thyroid storm** .

Table 584.7

Management of Thyroid Storm in Adolescents

GOAL	TREATMENT
Inhibition of thyroid hormone formation and secretion	Propylthiouracil, 400 mg every 8 hr PO/IV/NGT Saturated solution of potassium iodide, 3 drops every 8 hr
Sympathetic blockade	Propranolol, 20-40 mg every 4-6 hr or 1 mg IV slowly (repeat doses until heart rate slows); not indicated in patients with asthma or heart failure that is not rate related
Glucocorticoid therapy	Prednisone 20 mg bid
Supportive therapy	Intravenous fluids (depending on indication: glucose, electrolytes, multivitamins) Temperature control (cooling blankets, acetaminophen; avoid salicylates) O_2 if required Digitalis for heart failure and to slow ventricular response; pentobarbital for sedation Treatment of precipitating event (e.g., infection)

From Goldman L, Ausiello D, editors: *Cecil textbook of medicine* , ed 22, Philadelphia, 2004, WB Saunders, p 1401.

Definitive Therapy

Radioiodine ablation or thyroidectomy is indicated when medical management is not possible due to patient nonadherence or severe side effects of ATDs, when an adequate trial of medical management has failed to result in remission, or if the patient prefers definitive therapy.

Radioiodine ablation with ^{131} I is an effective therapy for Graves disease in children. In patients with severe thyrotoxicosis, euthyroidism should be restored with methimazole prior to radioiodine ablation to deplete the gland of preformed hormone and reduce the risk of a thyrotoxic flare from radiation thyroiditis. If a patient is taking an ATD, it must be stopped 3-5 days before radioiodine administration to avoid inhibition of uptake. The goal of radioiodine ablation is to administer a sufficient dose of radioiodine to ensure complete ablation of thyroid tissue. Many centers measure radioiodine uptake before treatment and use this to calculate an ^{131} I dose that delivers an absorbed thyroid dose of >150 μCi/g thyroid tissue (based on thyroid gland mass estimated by clinical examination or ultrasound). Alternatively, an empiric fixed ^{131} I dose (usually 10-15 mCi) can be offered. The theoretical advantage of calculated doses is that they define for each individual patient the lowest administered dose that achieves the therapeutic target. This benefit is most important in small children, because the absorbed radiation dose to the bone marrow and other normal tissues is inversely proportional to body size. Based upon this concept and theoretical modeling of radiation exposure, current consensus guidelines recommend that ^{131} I therapy be avoided in children younger than 5 yr of age and used in children between 5 and 10 yr of age if the administered dose is <10 mCi. As with other Graves therapies, radioiodine ablation has a low failure rate (5–20%). Patients with persistent hyperthyroidism more than 6 mo after their first ^{131} I therapy can be offered retreatment.

Thyroidectomy is a safe procedure when performed by an experienced surgeon. Thyroid surgery should be done only after the patient has been rendered euthyroid with methimazole over 2-3 mo. A saturated solution of potassium iodide (SSKI; 1-3 drops, 2-3 times per day) may be added for 7-14 days before surgery to decrease the vascularity of the gland. In expert hands, complications of surgical treatment are rare and include hypoparathyroidism (transient or permanent) and paralysis of the vocal cords. When surgery is elected, total or near-total thyroidectomy should be performed rather than a less extensive subtotal resection. The incidence of recurrence is low, and patients become hypothyroid postoperatively. Referral to a surgeon with extensive experience in thyroidectomy and a low personal complication rate is paramount.

Graves **ophthalmopathy** usually remits gradually and independently of the hyperthyroidism, but control of ophthalmopathy is facilitated by maintaining consistent euthyroidism. Severe ophthalmopathy can require treatment with high-dose glucocorticoids, orbital radiotherapy, or orbital decompression surgery. Teprotumumab, a human monoclonal antibody against the insulin-like growth factor 1 receptor IGF-1R has been effective in adults with ophthalmopathy. Cigarette smoking is a risk factor for thyroid eye disease and should be avoided or discontinued to avoid progression of eye involvement.

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584.2

Congenital Hyperthyroidism

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Keywords

Graves
McCune-Albright
thyrotoxicosis
resistance to thyroid hormone

Etiology and Pathogenesis

Neonatal Graves disease is caused by transplacental passage of TRSAbs from mothers with a history of Graves disease. These mothers can have active Graves disease, Graves disease in remission, or a prior history of Graves disease treated with radioiodine ablation or thyroidectomy. Occasionally, there is a maternal history of chronic lymphocytic thyroiditis with hypothyroidism. High levels of TRSAb typically result in classic neonatal hyperthyroidism, but if the mother has been treated with ATDs, the onset of hyperthyroid symptoms may be delayed by 3-7 days until the ATD is metabolized by the neonate. If TRBAbs are also present, the onset of hyperthyroidism may also be delayed for several weeks, or neonatal hypothyroidism may even develop.

Neonatal hyperthyroidism occurs in approximately 2% of infants born to mothers with a history of Graves disease. In utero, fetal tachycardia and goiter may suggest the diagnosis, and close ultrasound surveillance is recommended in mothers with uncontrolled hyperthyroidism, particularly in the 3rd trimester. Elevated serum titers of TRSAb (more than 3 times the upper limit of normal) or a history of a prior child with neonatal thyroid dysfunction increases the likelihood of neonatal Graves disease.

Neonatal Graves disease typically remits spontaneously within 6-12 wk but can persist longer, depending on the titer and rate of clearance of the TRSAbs (and TRBAbs, if present). Rarely, classic neonatal Graves disease may not remit but persist for several yr or longer. These children typically have a family history of Graves disease. In these infants, the transfer of maternal TRSAbs exacerbates the infantile onset of autonomous Graves disease.

Clinical Manifestations

Many infants born with neonatal Graves disease are premature and have intrauterine growth restriction. Many infants also have goiter, and occasionally tracheal compression can occur if the goiter is very large. Other signs and symptoms of neonatal Graves disease include low birth weight, stare, periorbital edema, retraction of the eyelids, hyperthermia, irritability, diarrhea, feeding difficulties, poor weight gain, tachycardia, heart failure, hypertension, hepatomegaly, splenomegaly, cholestasis, jaundice, thrombocytopenia, and hyperviscosity (Fig. 584.3). Laboratory evaluation shows suppressed serum TSH and elevated serum levels of T_4 , free $T_{4,}$ and T_3 . TRSAbs are markedly elevated at birth and typically resolve within 3 mo of life. If symptoms and signs are not immediately recognized and treated, cardiac failure and death can occur. Craniosynostosis and developmental delay can be permanent sequelae of the hyperthyroidism.

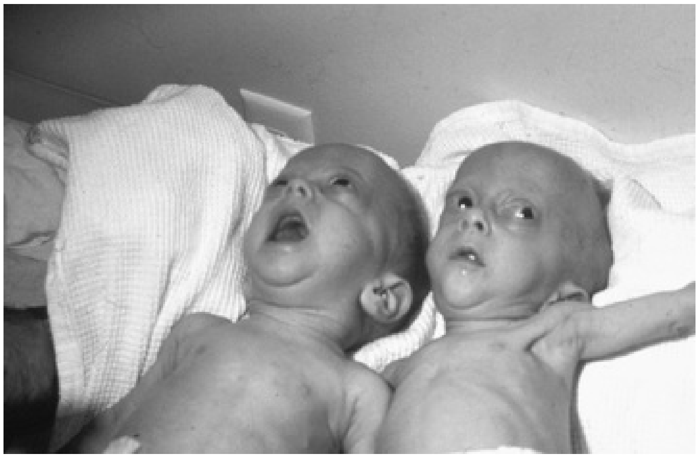

FIG. 584.3 Twin boys with neonatal hyperthyroidism confirmed by abnormal thyroid function tests. Clinical features include lack of subcutaneous tissue owing to a hypermetabolic state and a wide-eyed, anxious stare. They were given the diagnosis of neonatal Graves disease, but, in fact, their mother did not have Graves disease; they had persistent, not transient, hyperthyroidism. At age 8 yr, they were treated with radioiodine. They are now believed to have had some other form of neonatal hyperthyroidism, such as a constitutive activation of the thyroid-stimulating hormone receptor.

Treatment

Treatment should be initiated at the onset of symptoms to avoid short-term and long-term complications. Therapy consists of methimazole (0.5-1.0 mg/kg/24 hr given every 12 hr) and oral or intravenous administration of a nonselective β-adrenergic blocker such as propranolol to decreases sympathetic hyperactivity. In refractory cases, Lugol solution or potassium iodide (1-2 drops per day) can be added. The first dose of iodide should be given at least 1 hr after the 1st dose of ATD to prevent the iodide from being used for further thyroid hormone synthesis. If thyrotoxicosis is severe and progresses to heart failure, parenteral fluid therapy, corticosteroids, and digitalization may be indicated. Once serum thyroid hormone levels begin to decrease, antithyroid medications should be gradually tapered to keep the infant euthyroid. Occasionally, a block-and-replace method with concurrent ATD and thyroid hormone replacement therapy may be required to ensure euthyroidism.

Most cases of neonatal Graves disease remit by 3 mo of age, but occasionally neonatal hyperthyroidism persists into childhood. Typically, there is a family history of hyperthyroidism. Neonatal hyperthyroidism without evidence for autoimmune disease in mother or infant may be caused by a mutation in the *TSHR* gene that results in constitutive activation of the receptor. This can be transmitted in an autosomal dominant manner or can occur sporadically. Neonatal hyperthyroidism has also been reported in patients with McCune-Albright syndrome because of an activating mutation of the stimulatory α-subunit of the G-protein. Under these circumstances, hyperthyroidism recurs when ATDs are discontinued, and these children eventually must be treated with radioiodine or surgery.

Prognosis

Advanced osseous maturation, microcephaly, and cognitive impairment occur when treatment is delayed. Intellectual development is normal in most treated infants with neonatal Graves disease, although some manifest neurocognitive problems from in utero hyperthyroidism. In some infants, in utero hyperthyroidism appears to suppress the hypothalamic-pituitary-thyroid feedback mechanism and they develop transient or permanent central hypothyroidism that requires thyroid hormone replacement. Neurocognitive development should be monitored throughout childhood.

Resistance to Thyroid Hormone

This *autosomal dominant* disorder is caused by mutations in the ***THRB*** gene. Because this receptor mediates the normal feedback of thyroid hormone on the hypothalamus and pituitary, patients have elevated serum levels of T_4 and T_3 but serum TSH levels are inappropriately normal or elevated. Goiter is almost always present, but symptoms of thyroid dysfunction are highly variable among individuals. There may be clinical features of hypothyroidism such as developmental delay, growth retardation, and delayed skeletal maturation, as well as certain clinical features of hyperthyroidism like tachycardia and hyperreflexia. Affected children also have an increased association of learning disabilities and ADHD. The clinical symptoms, goiter, and elevated thyroid hormone levels may be mistaken for Graves disease, but resistance to thyroid hormone (RTH) is confirmed by the presence of normal or elevated (not suppressed) TSH levels. This condition must also be differentiated from a pituitary TSH-secreting tumor, which is not familial and in which serum levels of the TSH α-subunit are elevated. Elevated levels of T_4 on newborn screening should suggest the possibility of RTH.

More than 100 distinct mutations in *THRB* have been identified in patients with RTH, and genotype-phenotype correlation is poor even amongst affected members of the same family. Nearly all mutations have a dominant-negative effect in which the mutant receptor interferes with normal receptor action, leading to disease even in heterozygotes. Individuals carrying 2 mutant alleles are severely affected. A very rare *autosomal recessive* form of this disorder has been reported in individuals homozygous for a deletion of the *THRB* gene.

Treatment is usually not required unless growth and skeletal retardation are present. Different therapies, including levothyroxine and triiodothyroacetic acid, have been successful in some patients. Symptoms of hyperthyroidism can be treated with **β** -blockers, but ATDs or radioiodine ablation are generally not used because they increase TSH levels and goiter size.

Although RTH due to *THRB* mutations has been recognized for decades, the first patients with mutations in the *THRA* gene have been reported only recently. These mutations, too, are dominant negative and cause disease in heterozygous carriers. Clinical symptoms suggest those of untreated primary hypothyroidism, including skeletal dysplasia with short stature and macrocephaly, developmental delay, constipation, bradycardia, and macrocytic anemia. Serum thyroid function tests show subtle abnormalities of low or low-normal T_4 , high or high-normal

T_3 (with elevated T_3 /T_4 ratio), and normal TSH, as well as the unique finding of markedly low reverse T_3 . Treatment has not been clearly established for this condition.

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CHAPTER 585

Carcinoma of the Thyroid

Jessica R. Smith, Ari J. Wassner

Epidemiology

Carcinoma of the thyroid is rare in childhood, with an annual incidence in children younger than 15 yr of approximately 4-5 in 100,000 cases. The incidence of childhood thyroid cancer increases with age and peaks in adolescence. Females are more commonly affected than males. Compared to adults, childhood thyroid cancers are characterized by significantly higher rates of metastasis and recurrence. Despite often being metastatic at discovery, pediatric thyroid cancers usually have an indolent course and with adequate treatment, most patients have a favorable outcome.

Pathogenesis

At all ages, the vast majority of differentiated thyroid cancers are of follicular cell origin and, in North America, **papillary carcinoma** (85–90%) is the most common subtype. While their histologic features are similar, thyroid cancers of childhood are genetically distinct from their adult counterparts. Although about 70% of adults with papillary thyroid cancer exhibit pathogenic somatic mutations in *BRAF* or *RAS*, these mutations are uncommon in children with papillary thyroid cancer. In contrast, *RET-PTC* translocations, which result in chimeric proteins containing the tyrosine kinase domains of RET fused to the regulatory sequences of ubiquitously expressed genes such as *H1* and *ELE1*, are often found in childhood thyroid cancers. After papillary thyroid cancer, **follicular carcinoma** (10%) is the next most common type of childhood thyroid cancer. **Medullary carcinoma** (2%) and anaplastic thyroid cancers are relatively rare. Of note, only thyroid cancers of follicular cell origin (papillary and follicular carcinomas) respond to the adjunctive therapies of ^{131} I therapy and thyrotropin (TSH) suppression.

Up to 10% of cases of follicular cell–derived thyroid cancers are familial, and these are usually inherited in an autosomal dominant manner. **Familial syndromes** associated with an increased risk of thyroid neoplasia include *PTEN* hamartoma tumor syndromes (Cowden, Bannayan-Riley-Ruvalcaba, and Proteus syndromes) characterized by macrocephaly, mucocutaneous lesions (fibromas), and breast cancer and endometrial tumors; and familial adenomatous polyposis (mutation in the *APC* gene). Germline mutations in *DICER1* are also a cause of pediatric thyroid neoplasia. The evaluation of a child with thyroid nodule should include a medical and family history to assess for features of these syndromes.

The thyroid gland of children is very sensitive to exposure to external radiation, particularly at very young ages. There probably is no lower threshold dose; however, 1 Gy of radiation exposure results in a 7.7-fold increased relative risk of thyroid cancer. In past decades, approximately 80% of children with cancer of the thyroid had received inappropriate therapeutic irradiation of the neck and adjacent areas during infancy for benign conditions such as enlarged thymus, hypertrophied tonsils and adenoids, hemangiomas, nevi, eczema, tinea capitis, and cervical adenitis. With the discontinuation of irradiation for benign conditions, this cause of thyroid cancer has vanished. However, the long-term survival of children who have received appropriate therapeutic irradiation of areas of the neck for neoplastic disease has made this cause of thyroid cancer and nodules increasingly prevalent. Increased radiation dose, younger age at time of treatment, and female sex are factors that increase the risk of thyroid cancer. The relative risk of thyroid cancer is highest after radiation doses of 5-30 Gy, above which the excess risk declines but does not disappear. Long-term risk data for cancer are sparse, but 15–50% of children who have received irradiation and chemotherapy for Hodgkin disease, leukemia, bone marrow transplantation, brain tumors, and other malignancies of the head and neck have elevated levels of TSH within the 1st yr of therapy, and 5–20% progress to hypothyroidism during the next 5-7 yr. Most large groups of treated children have a 10–30% incidence of benign thyroid nodules and an increased incidence of thyroid cancer. The latter begins to appear within 3-5 yr after radiation treatment and reaches a peak in 15-25 yr. It is unknown whether there is a period after which no more tumors develop. Administration of ^{131} I for diagnostic or therapeutic purposes does not appear to increase the risk of thyroid cancer.

Thyroid cancer has been reported in children with congenital goiter or ectopic thyroid tissue. In these patients and in children with autoimmune thyroiditis and hypothyroidism, chronic TSH stimulation may play a pathogenic role. It is unclear if the course of thyroid cancer differs in these patients compared to the general population. From a practical standpoint, nodules that are detected in the context of these disorders should be fully evaluated for cancer risk as in other children.

Clinical Manifestations

A *painless nodule* in the anterior neck is the usual presentation of thyroid cancer. Rapid growth and large nodule size, firmness, fixation to adjacent tissues, hoarseness, dysphagia, or neck lymphadenopathy should heighten the concern for thyroid cancer. Cervical lymph node metastasis is common, so any unexplained cervical lymph node enlargement warrants examination of the thyroid.

The lungs are the most common site of distant metastasis. There may be no clinical manifestations referable to pulmonary metastases, and pulmonary function testing may be normal even with widespread macroscopic metastases. Radiologically, they appear as diffuse miliary or nodular infiltrations, typically greatest in the posterior basal portions. Metastases may be mistaken for tuberculosis, histoplasmosis, or sarcoidosis. Other sites of metastasis include the mediastinum, axilla, long bones, skull, and brain. Almost all children with thyroid cancer are euthyroid, but rarely the carcinoma is functional and produces symptoms of hyperthyroidism.

Diagnosis

Patients usually present with a neck mass and virtually all have a thyroid nodule of significant size upon ultrasound. While several imaging features are significantly associated with thyroid cancer risk, none have sufficient negative predictive value to forgo tissue diagnosis. Because papillary thyroid cancer is characterized by nuclear abnormalities that are well identified by cytology, fine-needle aspiration is the most appropriate method for evaluating children with nodules. In most cases, operative pathology is required to confirm the diagnosis of thyroid cancer and to determine the extent of disease.

Treatment

The primary therapy for thyroid cancer is surgical resection. Because intrathyroidal spread is common in papillary thyroid cancer, near-total thyroidectomy is the recommended approach. Prior to surgery, neck ultrasonography should be performed to assess for sonographically abnormal lymph nodes. Suspicious lymph nodes may be biopsied preoperatively to determine the appropriateness and extent of initial lymph node dissection. Depending on the clinical situation, adjunctive therapy with both TSH suppression (dosing levothyroxine to lower serum TSH and deprive residual thyroid cancer cells of this growth factor) and ^{131} I therapy (to ablate the normal thyroid remnant and/or to treat residual thyroid cancer) may be recommended.

Prognosis

Although lymph node and distant metastasis are more common in the pediatric population, most children with thyroid cancer have an excellent outcome. Families should be counseled that the response to ^{131} I therapy is slow and that repeated treatments and years of care may be required to eliminate the disease. Many patients who are unable to achieve complete cure can be maintained in the well state with stable or slowly progressive cancer burden. For rare children with aggressive cancers that progress despite the optimization of conventional therapies, newer options, such as oral tyrosine kinase inhibitors, are available. Psychosocial supports must be available, including access to social work and other mental health professionals.

Thyroid cancer can recur years or decades after initial presentation. For this reason, children with thyroid cancer require lifelong monitoring for disease progression. For most patients, serum thyroglobulin is a sensitive and specific cancer marker. However, in patients who have circulating thyroglobulin autoantibodies, such as those with Hashimoto thyroiditis, thyroglobulin levels may be difficult to interpret accurately. Because of this, thyroglobulin autoantibodies must always be measured whenever serum thyroglobulin is assayed to confirm the latter's reliability. As most thyroid cancer recurrences are local, surveillance should also include serial neck ultrasounds. Patients with higher recurrence risk or distant metastases may benefit from additional anatomic imaging studies and from extended surveillance studies performed during TSH stimulation.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) arises from the parafollicular cells (C cells) of the thyroid and accounts for approximately 2% of thyroid malignancies in children. The majority of MTC cases are sporadic, but approximately 25% are hereditary as part of the syndrome of multiple endocrine neoplasia type 2 (MEN2; see Chapter 587). Activating mutations in the *RET* proto-oncogene are responsible for the majority of cases of MTC. These mutations occur in the germline in patients with MEN2, but somatic *RET* mutations may be present in some sporadic cases of MTC.

The most common presentation of sporadic MTC is an asymptomatic, palpable thyroid nodule. When the tumor occurs sporadically it is usually unicentric, but in the familial form it may be multicentric. MTC begins as hyperplasia of the parafollicular cells (*C cell hyperplasia*), which is often present in thyroid glands removed prophylactically from patients with MEN2. The diagnosis of MTC can also be made by cytology after fine needle aspiration (FNA) of a thyroid nodule. Because C cells produce calcitonin, a high calcitonin concentration in a FNA specimen or in a patient's serum can be helpful to confirm the diagnosis of MTC. The diagnosis of MTC warrants genetic testing for a germline *RET* mutation, and in mutation-positive patients screening for pheochromocytoma and hyperparathyroidism should be obtained prior to anesthesia for thyroidectomy.

The most important treatment for MTC is surgical resection. Preoperative evaluation should include neck ultrasound to search for potential lymph node metastases. Baseline serum levels of calcitonin and carcinoembryonic antigen (CEA) should also be measured preoperatively; higher levels are correlated with a greater likelihood of metastatic disease. Surgical treatment includes total thyroidectomy and lymph node dissection of any involved lymph node compartments. Complete resection is often curative, but this can be difficult to achieve in patients with metastatic disease. Surveillance with neck ultrasound and serum levels of calcitonin and CEA can assess for the presence or progression of residual disease. Other treatment modalities employed for advanced or metastatic disease include external beam radiation, radiofrequency ablation, and tyrosine kinase inhibitors such as vandetanib or cabozantinib.

585.1

Thyroid Nodules

Jessica R. Smith, Ari J. Wassner

The frequency of thyroid nodules increases with age. While sonographically detectable nodules are present in 19–67% of randomly selected adults, the estimated frequency of nodules in children is only 0.05–2.0%. Although early pediatric series cited extremely high rates of cancer in thyroid nodules (up to 70%), more recent studies of children report lower cancer prevalence (around 20–26%) that is closer to the 5–15% prevalence observed in adults. *Thus, when a thyroid nodule is discovered in a child, parents should be counseled that the majority of nodules are benign.*

Benign disorders that can occur as a solitary thyroid mass include benign adenomatous or colloid nodules, as well as a variety of congenital cysts (Table 585.1). A thyroid mass that appears suddenly or enlarges rapidly can indicate hemorrhage into a cyst or benign adenoma.

Table 585.1

Etiologic Classification of Solitary Thyroid Nodules

- Lymphoid follicle, as part of chronic lymphocytic thyroiditis
- Thyroid developmental anomalies
  - Intrathyroidal thyroglossal duct cyst
  - Intrathyroidal ectopic thymus
- Thyroid abscess (acute infectious thyroiditis)
- Simple cyst
- Neoplasms
  - Benign
    - Colloid (adenomatous) nodule
    - Follicular adenoma
    - Hyperfunctioning (toxic) adenoma
    - Lymphohemangioma
  - Malignant
    - Papillary carcinoma
    - Follicular carcinoma
    - Anaplastic carcinoma
    - Medullary carcinoma

Nonthyroidal
  Lymphoma
  Teratoma

Evaluation of a child with a thyroid nodule should begin by measuring serum TSH. In patients who present with a suppressed serum TSH, thyroid scintigraphy (preferably using ^{123} I or ^{99m} Tc-pertechnetate) should be performed to assess the possibility of a hyperfunctioning thyroid nodule, which is generally not malignant. All other patients should proceed directly to ultrasound and, if a discrete nodule(s) of significant size is documented by this imaging, it should be biopsied by ultrasound-guided FNA (Fig. 585.1). FNA cytology may be interpreted as benign, positive for papillary thyroid cancer, indeterminate, or nondiagnostic. When an initial biopsy is nondiagnostic, an adequate sample can usually be obtained by repeating the aspiration. Multiple categorization systems exist, and most North American centers follow the Bethesda System for interpretation of thyroid cytology. The predictive value of thyroid FNA varies between institutions. In most high-volume centers, the “positive for papillary thyroid cancer” category corresponds to a >98% likelihood of cancer and, in that context, near-total thyroidectomy is appropriate. In children with unilateral nodule(s) of indeterminate cytology, lobectomy is commonly performed; this is followed by completion thyroidectomy if lobectomy pathology shows a significant cancer. Patients with cytologically benign nodules can be offered surveillance with serial neck imaging.

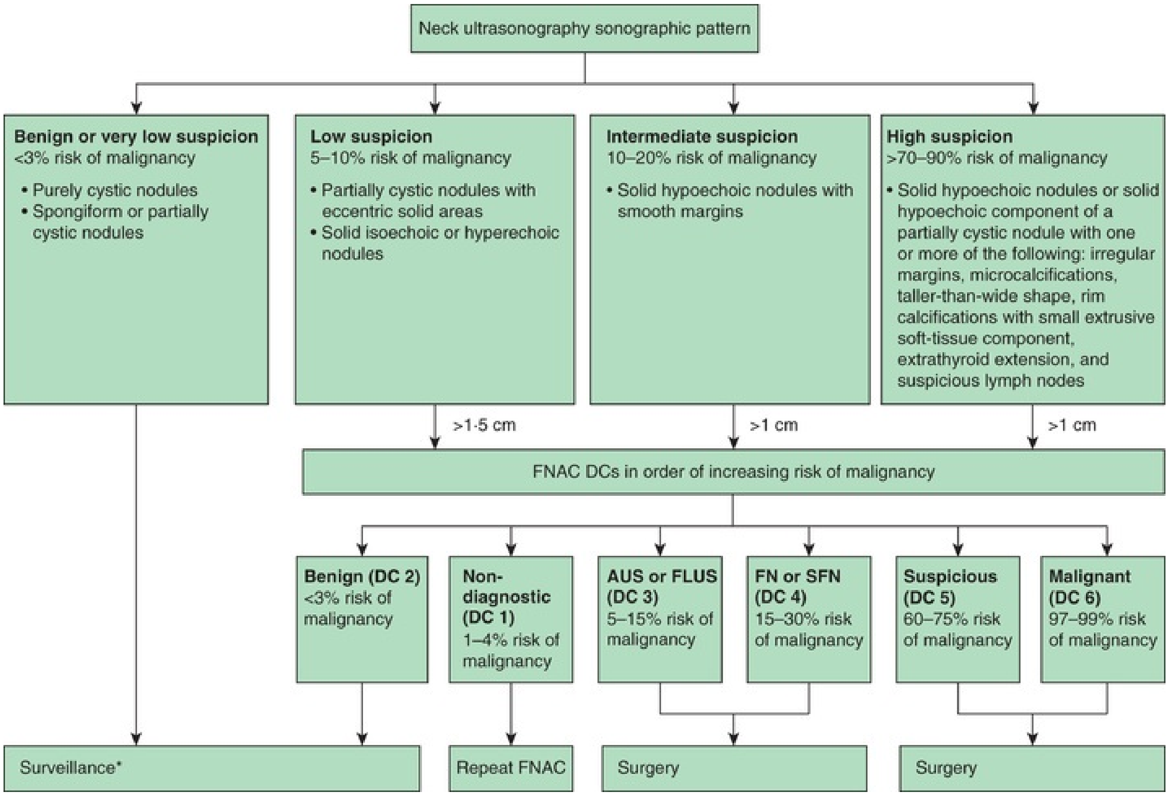
Neck ultrasonography sonographic pattern
Benign or very low suspicion
<3% risk of malignancy
• Purely cystic nodules
• Spongiform or partially cystic nodules
Low suspicion
5–10% risk of malignancy
• Partially cystic nodules with eccentric solid areas
• Solid isoechoic or hyperechoic nodules
Intermediate suspicion
10–20% risk of malignancy
• Solid hypoechoic nodules with smooth margins
High suspicion
>70–90% risk of malignancy
• Solid hypoechoic nodules or solid hypoechoic component of a partially cystic nodule with one or more of the following: irregular margins, microcalcifications, taller-than-wide shape, rim calcifications with small extrusive soft-tissue component, extrathyroid extension, and suspicious lymph nodes
>1·5 cm
>1 cm
>1 cm
FNAC DCs in order of increasing risk of malignancy
Benign (DC 2)
<3% risk of malignancy
Non-diagnostic (DC 1)
1–4% risk of malignancy
AUS or FLUS (DC 3)
5–15% risk of malignancy
FN or SFN (DC 4)
15–30% risk of malignancy
Suspicious (DC 5)
60–75% risk of malignancy
Malignant (DC 6)
97–99% risk of malignancy
Surveillance*
Repeat FNAC
Surgery
Surgery

FIG. 585.1 Management algorithm for thyroid nodules on the basis of sonographic patterns and cytology diagnostic categories of the Bethesda System. *Fine-needle aspiration can be considered (1) for nodules with very low suspicion sonographic pattern and the largest diameter greater than 2 cm; and (2) if there are suspicious clinical findings (e.g., firm mass, neck pain, cough, voice change, and a history of childhood neck irradiation or familial thyroid cancer), regardless of the sonographic appearances. *AUS,* Atypia of undetermined significance; *DC,* diagnostic category; *FLUS,* follicular lesion of undetermined significance; *FN,* follicular neoplasm; *FNAC,* fine-needle aspiration cytology; *SFN,* suspicious for follicular neoplasm. (From Cabanillas ME, McFadden DG, Durante C: Thyroid cancer, *Lancet* 388:2783–2794, 2016, Fig. 2.)

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CHAPTER 586

Autoimmune Polyglandular Syndromes

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An **autoimmune polyglandular syndrome (APS)** occurs when autoimmunity is directed at multiple glands and/or nonendocrine organs, sometimes in association with immunodeficiency. Endocrine glands and other organs commonly affected by APS have unique autoantigens that increase these tissues' susceptibility to damage by an untamed immune response. Most autoimmune endocrinopathies are caused by cell-mediated immunity from autoreactive T cells. Although antibodies to 1 or more autoantigens are commonly associated with specific autoimmune endocrinopathies, in most cases these autoantibodies are not directly pathogenic but rather are markers of immune dysregulation. A notable exception is Graves disease, which is caused by autoantibodies that directly activate the thyrotropin hormone receptor (TSHR).

APS, due to monogenic disorders of immune dysregulation (including APS type 1 [APS-1]), have heritable lesions in key aspects of immune tolerance (Table 586.1). Polygenic disorders associated with APS (APS type 2 [APS-2]) and some chromosomal abnormalities (e.g., trisomy 21) also result in an aberrant immune response that produces multiorgan autoimmunity. Finally, nongenetic factors (e.g., immune checkpoint inhibitors for cancer therapy) may lead to autoimmune polyglandular disease. While APS is uncommon, patients can experience significant lifetime morbidity, particularly if the syndrome is not identified early and managed appropriately. There may be 1-2 decades between the presentations of the first and subsequent endocrinopathy. The presence of primary hypoparathyroidism, primary adrenal insufficiency, neonatal type 1 diabetes mellitus, chronic mucocutaneous candidiasis, or a family history should raise particular suspicion for APS.

Table 586.1

Autoimmune Polyglandular Syndromes

AUTOIMMUNE POLYGLANDULAR SYNDROME	**MONOGENIC APS**			
	APS-1	**IPEX**	***CTLA4***	***LRBA***
EPIDEMIOLOGY AND GENETICS				
Incidence	<1 : 100,000	Rare	Rare	Rare
Onset	Infancy	Infancy	Infancy	Infancy
Male-to-female ratio	1 : 1	Males only		
Inheritance	Autosomal recessive (most)	X-linked	Autosomal dominant	Autosomal
Genetic abnormality	AIRE	*FOXP3*	*CLTA4*	*LRBA*
Mechanism of disease	Central tolerance	Treg development	Treg suppression	Treg suppr
CLINICAL FEATURES				
Classic Phenotype	Candidiasis	Enteropathy	Enteropathy	Enteropath
	Hypoparathyroidism	Type 1 diabetes mellitus in infancy	Cytopenia	Respirator
	Addison disease	Eczematous dermatitis	Lymphocytic aggregates	Organome
			Hypogammaglobulinemia	Hypogam
Endocrinopathies				
Adrenal insufficiency	60–90%			
Thyroid	10–40%	Common	15%	10%
Type 1 diabetes mellitus	5–20%	Common	Rare	5%
Hypoparathyroidism	80–90%			
Gonadal insufficiency	5–60%			
Hypophysitis	Rare			
Hypothalamic dysfunction				
Hyperprolactinemia				
GH axis, skeletal				
Nonendocrine Disease				
Immune Dysregulation				
Candida infection	75–100%	Rare		
Other infections	Asplenism (10–20%)	Bacterial (rare)	Common	Common r
Gastrointestinal				
Malabsorption, enteropathy	10–20%	Common	80%	60%
GI autoimmunity	10–15%			10%
Autoimmune hepatitis	10–15%	Rare		
Integumentary/Rheumatologic			Psoriasis or other skin (20%)	

Vitiligo	5–15%			5%
Eczema, allergic disease		Common		10%
Alopecia	25%			
Ectodermal dysplasia	75%			
Arthritis		Rare	15%	10%
Other	Keratoconjunctivitis (5–20%) Periodic fever (15%)	Cytopenias (common) Nephritis (rare)	Cytopenia (60%) Lung disease (60%)	Cytope Myasth (rare)

AUTOIMMUNE POLYGLANDULAR SYNDROME	**OTHER APS AND APS-LIKE CONDITIONS**				
	APS-2	**TURNER SYNDROME**	**KLINEFELTER SYNDROME**	**DOWN SYNDROME**	**DIGEORGE SYNDROME**
EPIDEMIOLOGY AND GENETICS					
Incidence	1-2/10,000	1 : 2,500 females	1 : 1,000 males	1 : 700	1 : 4,000
Onset	Adulthood	Congenital	Congenital	Congenital	Congenital
Male-to-female ratio	1 : 3	Females only	Males only		
Inheritance	Polygenic	N/A	N/A	N/A (most)	Autosomal dominant
Genetic abnormality	*HLA, MICA, PTPN22, CTLA4, NALP1*	46, X	47, XXY	Trisomy 21	22q11.2 del
Mechanism of disease	Multifactorial	Multifactorial	Multifactorial	Multifactorial	T-cell development defects
CLINICAL FEATURES					
Classic Phenotype	Addison disease	Short stature	Tall stature	Hypotonia	Absent thymus
	Autoimmune thyroid disease	Ovarian insufficiency	Testicular insufficiency	Epicanthal folds	Congenital hea disease
	Type 1 diabetes mellitus	Webbed neck	Gynecomastia	Brushfield spots	Hypocalcemia
		Coarctation of the aorta		Single palmar crease	Developmental delay
				Developmental delay	
Endocrinopathies					
Adrenal insufficiency	70–100%		Rare		
Thyroid	70%	15–20%	1%	15%	5%
Type 1 diabetes mellitus	40–50%	2%	2%	1–10%	Rare
Hypoparathyroidism	None				30%
Gonadal insufficiency	3–10%	90%	Common		
Hypophysitis	Rare				
Hypothalamic dysfunction					
Hyperprolactinemia					
GH axis, skeletal		Short stature	Tall stature	Short stature	Short stature
Nonendocrine disease					
Immune Dysregulation					
Candida infection	None				
Other infections					Thymic

					dysplasia/aplas
Gastrointestinal		IBD (1%)			
Malabsorption, enteropathy	Rare				
GI autoimmunity	2–25%	Rare		5%	
Autoimmune hepatitis	Rare				
Integumentary/Rheumatologic		Psoriasis (rare)			
Vitiligo, other skin	4–5%	Rare			
Eczema, allergic disease					
Alopecia	2%	Rare		Rare	
Ectodermal dysplasia	None				
Arthritis		Rare	1%		Rare
Other		Lymphedema	Lupus, Sjogren and multiple sclerosis (rare)	Congenital heart disease	Congenital heart disease T-cell deficiency Cytopenias (rare)

CMV, cytomegalovirus; EBV, Epstein-Barr virus; GH, growth hormone; GI, gastrointestinal; IBD, inflammatory bowel disease; VZV, varicella zoster virus.

Modified from Nambam B, Winter WE, Schatz DA: IgG4 antibodies in autoimmune polyglandular disease and IgG4-related endocrinopathies: pathophysiology and clinical characteristics. *Curr Opin Pediatr* 26:493–499, 2014, Table 1, p. 494 and Verbsky JW, Chatila TA: Immune dysregulation, polyendocrinopathy, enteropathy, X–linked (IPEX) and IPEX–related disorders: an evolving web of heritable autoimmune diseases. *Curr Opin Pediatr* 25:708–715, 2013, Table 1, p. 709.

Monogenic Autoimmune Polyglandular Syndromes

The number of recognized monogenic defects of immune regulatory mechanisms leading to APS has grown substantially in the past decade (see Table 586.1). The best-characterized monogenic APS are caused by mutations that primarily affect central immune tolerance (APS-1) or regulatory T cell development (immune dysregulation polyendocrinopathy enteropathy X-linked, or IPEX). Other monogenic APS (the so-called IPEX-like disorders) are due to defects in regulatory T cell suppression or signaling.

Autoimmune Polyglandular Syndrome Type 1

APS-1, the archetypal monogenic polyendocrinopathy syndrome, is caused by loss of function mutations in the autoimmune regulator gene *(AIRE)* on chromosome 21q22.3. *AIRE* plays a critical role in the presentation of self-antigens to developing T cells in the thymus, which normally leads to central immune tolerance by inducing apoptosis of T cells specific for these autoantigens (negative selection). *AIRE* also plays a role in the development of regulatory T cells (see Chapter 149). Therefore patients with APS-1 develop autoreactive T cells and autoantibodies directed at multiple tissues. APS-1 is a rare disorder but is more common in certain founder populations, including Iranian Jews, Sardinians, Finns, and Norwegians, with a reported prevalence ranging from 1 in 9,000 to 1 in 90,000. It is inherited in an autosomal recessive pattern, although sporadic and autosomal dominant cases have been reported. APS-1 is also referred to by the clinically descriptive name **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).**

APS-1 is defined by the presence of at least 2 of the 3 primary clinical features (Whitaker's triad) of chronic mucocutaneous candidiasis, primary hypoparathyroidism and primary adrenal insufficiency. These three conditions tend to emerge over time—candidiasis before around 5 yr of age, hypoparathyroidism around 10 yr, and adrenal insufficiency around 15 yr—but the precise order and age of onset of each component are highly variable. Most patients develop additional autoimmune manifestations over time, with skin and gastrointestinal disorders tending to emerge before age 20 yr and other endocrine disorders after the 2nd decade (see Table 586.1). Sex, ancestry, and specific *AIRE* mutations may correlate with an increased risk for certain manifestations.

Nearly every endocrine gland may be affected by immune dysregulation in APS-1. The most commonly affected glands include the parathyroids and adrenals (about 80% each), with less frequent involvement of the gonads (ovarian insufficiency in 70% of females; testicular insufficiency in 30% of males), thyroid (20%), pancreatic beta-cells (10%), and pituitary (less than 5%). Nonendocrine autoimmunity affects a wide range of tissues and may appear before the first endocrinopathy is detected clinically. The most commonly affected tissues are the teeth and nails, with ectodermal dystrophy present the majority of patients (80%). Other affected tissues include the gastrointestinal tract (about 15% each for malabsorption, autoimmune hepatitis, and pernicious anemia), skin (vitiligo in 15%), and hair follicle (alopecia in 25%). APS-1 patients are at increased risk of infections, possibly related to a combination of cytokine autoantibodies, splenic dysfunction, and poor gut integrity.

Mucocutaneous candidiasis is very common (70–100%) and can lead to esophageal cancer if not detected and treated. Esophageal cancer, autoimmune hepatitis, adrenal crisis, and severe hypocalcemia are important causes of mortality in APS-1 patients.

The diagnosis of APS-1 is generally made clinically. Patients with APS-1 should have regular screening for the development of new autoimmune manifestations. The importance of such screening is illustrated by reports of unexplained death in APS-1 patients or their siblings, presumably due to undiagnosed autoimmune manifestations (such as adrenal insufficiency). Multiple autoantibodies may be detectable in patients with APS-1 (Table 586.2). While some of these are also present in the corresponding single-organ autoimmune endocrinopathy (e.g., 21-hydroxylase autoantibodies in adrenal insufficiency), other antibodies are unique to APS-1. Moreover, the clinical utility of measuring organ-specific autoantibodies for predicting the onset of endocrine gland failure in APS-1 is variable. Therefore clinical suspicion, laboratory screening, and education about symptoms of evolving endocrinopathies and other autoimmune disease are paramount regardless of autoantibody status.

Table 586.2

Autoantibodies Present in Autoimmune Polyglandular Syndromes and in Isolated Autoimmune Endocrinopathies

TISSUE OR GLAND	AUTOANTIGEN	DISEASE MANIFESTATION	NOTE
AUTOIMMUNE ENDOCRINOPATHIES			
Adrenal	CYP21A2, CYP11A1, CYP17A1	Primary adrenal insufficiency	Of the adrenal autoantibodies, CYP21A2 most strongly associated with adrenal insufficiency. Higher risk of progression to adrenal insufficiency in children with positive adrenal autoantibodies (over 80%) compared to adults (near 20%). Adrenal autoantibodies detected in 50% pediatric hypoparathyroidism and 1% pediatric type 1 diabetes mellitus.
Thyroid	TPO, Tg	Hashimoto thyroiditis (hypothyroidism)	Frequently positive without clinical thyroid disease
	TSHR	Graves disease (hyperthyroidism)	Only endocrine autoantibody that directly causes autoimmune endocrinopathy
Pancreatic beta cell	IA-2, GAD65, insulin, ZnT8	Type 1 diabetes mellitus	Risk of type 1 diabetes mellitus increases with the number of positive autoantibodies; IA-2, but not GAD65, autoantibodies associated with time to type 1 diabetes mellitus diagnosis in APS-1

Parathyroid	NALP5, CaSR	Hypoparathyroidism	NALP5 antibodies are present only in hypoparathyroidism due to APS-1
Gonad	CYP11A1, CYP17A1, NALP5, and TSGA10	Gonadal insufficiency	CYP11A1 antibodies associated with gonadal insufficiency in APS-1
Pituitary	TDRD6	Hypophysitis	Poorly predictive of clinical pituitary disease
NONENDOCRINE DISEASE			
Cytokines	IFN-ω, IFN-α, IL-22, IL-17F	APS-1	IFN-ω autoantibodies are 100% sensitive and 99% specific for APS-1; IL-22 autoantibodies associated with time to diagnosis and diagnosis of candidiasis in APS-1
Gastric	IF, H+/K+ ATPase	Pernicious anemia, autoimmune gastritis	IF autoantibodies associated with time to B12 deficiency in APS-1
Small intestine	TTG, gliadin	Celiac disease	
Gastrointestinal	TPH, GAD65	Intestinal dysfunction	TPH autoantibodies associated with time to intestinal dysfunction in APS-1. Both autoantibodies associated with diagnosis of intestinal dysfunction in APS-1.
Liver	CYP1A2, TPH, AADC	Autoimmune hepatitis	TPH autoantibodies associated with diagnosis of autoimmune hepatitis in APS-1
Skin melanocytes	Tyrosinase, SOX9, SOX10, AADC	Vitiligo	
Hair follicle	Tyrosine hydroxylase	Alopecia	
Lung	KCNRG, BPIFB1	Interstitial lung disease	Both autoantibodies present in 90–100% of APS-1 patients with interstitial lung disease, and are associated with time to diagnosis.

AADC, aromatic L-amino acid decarboxylase; BPIFB1, bactericidal/permeability-increasing fold-containing B1; CaSR, calcium sensing receptor; CYP11A1, side chain cleavage enzyme; CYP17A1, 17-α-hydroxylase; CYP1A2, cytochrome P450 1A2; CYP21A2, 21-hydroxylase; GAD65, glutamic acid decarboxylase; IA-2, islet antigen-2; IF, intrinsic factor; IFN, interferon; IL, interleukin; KCNRG, potassium channel-regulating protein; NALP5, NACHT leucine-rich-repeat protein 5; TDRD6, tudor domain containing protein 6; Tg, thyroglobulin; TPH, tryptophan hydroxylase; TPO, thyroid peroxidase; TSGA10, testis-specific gene 10 protein; TSHR, thyroid-stimulating hormone receptor; TTG, tissue transglutaminase; ZnT8, zinc transporter 8.

Three autoantibodies may eventually prove to have diagnostic value in APS-1, although they are not yet in clinical use. Autoantibodies to NALP5 are associated with hypoparathyroidism only in patients with APS-1 but not in isolated autoimmune or idiopathic hypoparathyroidism. Therefore patients with hypoparathyroidism and NALP5 antibodies should be further evaluated for APS-1. Autoantibodies to Th17 cytokines (especially interleukin-22 and interleukin-17F) are correlated with and may play a pathogenic role in APS-1 associated candidiasis. Autoantibodies to interferons (particularly interferon-ω and interferon-α) are present in virtually all patients with clinical APS-1 and are highly specific for the diagnosis, making this potentially an optimal diagnostic test for APS-1 itself. At present, confirmation of the diagnosis can be obtained by sequencing the *AIRE* gene, which is indicated for any patient with classic features, or an incomplete picture with supportive evidence. *AIRE* mutations can be detected by genetic testing in the majority of patients with clinical APS-1. Knowledge of the causative mutation facilitates genetic counseling and testing of family members.

Treatment of individual endocrinopathies, other autoimmune diseases, and associated infections are reviewed separately in the relevant chapters. Immunosuppression for the underlying immune dysregulation of APS-1 is problematic because of the coexistence of candidiasis and immunodeficiency, but this has been used in selected patients with specific autoimmune manifestations.

Immune Dysregulation-Polyendocrinopathy-Enteropathy X-Linked

IPEX is caused by loss-of-function mutations in the *FOXP3* gene, which is located on the X-chromosome (Xp11.23) (see Chapter 152). The inactivation of FOXP3 results in impaired peripheral immune tolerance due to impaired development of regulatory T cells and the emergence of autoreactive T cells. The endocrinopathies most commonly associated with IPEX are early-onset type 1 diabetes mellitus and autoimmune thyroiditis. Any diagnosis of type 1 diabetes mellitus before 6-9 mo of age should prompt consideration of a monogenic APS or a genetic cause of beta-cell dysfunction. Patients with IPEX often have autoimmune enteropathy and eczematous dermatitis; they may also have other autoimmunity (e.g., liver, kidney, cytopenias) and allergic dysregulation (e.g., food allergy, peripheral eosinophilia). Therapy of IPEX consists of immune modulation with immunosuppressants (e.g., glucocorticoids, tacrolimus), novel therapeutics (e.g., abatacept), or stem cell transplantation.

Other Monogenic Immune Dysregulation Disorders

Several other disorders involve failure of peripheral tolerance and emergence of autoimmunity, often with some degree of immunodeficiency. These disorders include loss-of-function mutations in CD25 *(IL2RA)*, *LRBA* , *CTLA4* , *STAT5b* , and gain-of-function mutations in *STAT1* that are pathophysiologically similar to IPEX. Broadly, patients with these IPEX-like disorders tend to be at high risk of type 1 diabetes mellitus and autoimmune thyroiditis (see Table 586.1). They also have multiple nonendocrine diseases, especially autoimmunity and immunodeficiency affecting the skin, lungs, and gastrointestinal tract. STAT5b participates in the IL2/STAT5 signal transduction axis necessary for growth hormone signaling, and may also affect prolactin secretion; therefore patients with STAT5b defects may have nonautoimmune growth hormone insensitivity and hyperprolactinemia in addition to immune dysregulation, hypergammaglobulinemia, and multiple autoimmunity. *STAT1* gain-of-function mutations inhibit the normal production of Th17 cytokines, which leads to chronic mucocutaneous candidiasis. These patients also have increased risk of infection, squamous cell cancer, enteropathy, and arterial aneurysms. Patients with CD25 defects are also at increased risk of infection due to the role of IL-2 signaling in Th17 responses.

Polygenic Autoimmune Polyglandular Syndrome (APS-2)

APS-2 is a clinical syndrome defined by the presence of two or more syndrome-specific endocrinopathies: autoimmune primary adrenal insufficiency (Addison disease), autoimmune thyroid disease (Hashimoto thyroiditis or Graves disease) and/or type 1 diabetes mellitus. Some classification systems subdivide APS-2 according to the particular glands affected (e.g., subtype 2, 3, and 4 if adrenal, thyroid, or neither gland) or other autoimmune manifestations present (e.g., subtype 3A, 3B, and 3C if additional endocrine, gastrointestinal, or systemic autoimmunity). However, because there is no clear pathophysiological distinction between these subtypes, we consider them collectively as APS-2. Still, when describing the characteristics of APS-2, it is important to acknowledge some degree of overlap between patients with clinical APS-2 and those with a single clinical endocrinopathy but evidence of additional autoimmunity (such as autoantibodies) who may go on to be classified APS-2.

Unlike monogenic APS, which generally manifest by early childhood with a mendelian inheritance pattern, APS-2 usually becomes apparent after the 2nd decade in a patient with a personal history of autoimmune endocrinopathy and a family history of autoimmune disease. APS-2 is most common in middle-aged females (prevalence near 1 : 20,000). Primary gonadal insufficiency, vitiligo, alopecia, and chronic atrophic gastritis (with or without pernicious anemia) can occur, but autoimmune hypoparathyroidism and candidiasis are *not typical* of APS-2.

While Addison disease is uncommon (prevalence near 1 : 10,000), patients with this condition are at high risk of developing additional endocrine autoimmunity constituting APS-2, with evidence of additional subclinical or clinical autoimmunity reported in up to two thirds. About half of patients with Addison disease have comorbid autoimmune thyroid disease (Schmidt syndrome), and 15% have type 1 diabetes mellitus (Carpenter syndrome). Other autoimmune manifestations each affecting 5–10% of patients include Graves disease, ovarian insufficiency, alopecia, vitiligo, pernicious anemia, or positive celiac autoantibodies. APS-2 develops less frequently in patients with type 1 diabetes mellitus than in those with Addison disease, but additional autoimmunity is still frequent. In these patients, autoimmune thyroid disease and gastrointestinal autoimmunity (each in about 20% of patients) are much more common than comorbid adrenal disease (in <1%). Because thyroxine and cortisol affect insulin sensitivity, metabolism, and appetite, unexplained hypoglycemia or deterioration in glycemic control may be the first clinical sign of APS-2 in a patient with preexisting type 1 diabetes mellitus. Unexplained hypoglycemia may also signal the onset of celiac disease. Indeed, **celiac disease** often precedes the onset of autoimmune endocrinopathies including type 1 diabetes mellitus, hypothyroidism, and Addison disease.

The development of APS-2 among those with isolated autoimmune thyroid disease is relatively infrequent. Nevertheless, the clinician should consider the possibility of adrenal insufficiency prior to treating autoimmune primary hypothyroidism in a patient with features suggestive of APS-2, as thyroid hormone replacement may precipitate adrenal crisis in this setting. As in APS-1, autoantibodies to specific tissues may be detectable and may prompt functional screening prior to the onset of overt clinical disease (see Table 586.2); however, the predictive value of these autoantibodies for the development of clinical disease is variable.

Aberrant T cell responses likely play a role in pathogenesis of multiple gland destruction seen in APS-2. Risk of autoimmunity directed against the adrenal glands, thyroid gland, and islet cells appears to be shared across certain human leukocyte antigen (HLA) haplotypes and other immune-related genetic loci, though the magnitude of this risk varies substantially for each endocrinopathy. The prevalence of HLA-D3 and HLA-D4 alleles is increased in patients with APS-2, and they appear to confer an increased risk for development of this disease. Particular alleles of the major histocompatibility complex class I chain–related genes A and B *(MICA* and *MICB)* also are associated with APS-2. Polymorphisms in other genes (e.g., *PTPN22* , *CTLA4*) have been associated with individual autoimmune endocrinopathies that constitute APS-2, but the contribution of these genes to the pathogenesis of APS-2 itself is uncertain. Although not well defined, there are also likely environmental factors that predispose to or promote the development of autoimmunity in genetically susceptible individuals, and many of the risk factors associated with endocrine and nonendocrine autoimmunity overlap (see individual chapters on these diseases for more detailed discussions of risk factors).

Chromosomal Abnormalities Associated With Autoimmune Polyglandular Syndrome

Many genetic syndromes involving chromosomal deletions, duplications, and other copy number variations are associated with an increased risk of autoimmunity, and especially endocrine autoimmunity affecting the thyroid and pancreatic beta cells (see Table 586.1). These include Turner syndrome, Klinefelter syndrome, DiGeorge (22q11.2 deletion) syndrome, and trisomy 21. Males with Klinefelter syndrome and females with Turner syndrome have an increased risk of autoimmunity in multiple systems, including autoimmune endocrine disease. The mechanism of autoimmunity in trisomy 21 remains unclear, although differences in *AIRE* gene expression, HLA-susceptibility, and autoantibody profiles have been described. Thymic dysplasia is a typical feature of DiGeorge syndrome, and the resulting immune dysregulation may play a role in the increased risk of autoimmunity in this disorder. Patients with genetic syndromes and chromosomal abnormalities may have nonautoimmune endocrinopathies such as abnormal growth, primary gonadal failure, and primary hypoparathyroidism.

Mitochondrial disease has been rarely associated with autoimmune endocrinopathy/polyendocrinopathy syndromes. Kearns-Sayre syndrome (progressive external ophthalmoplegia, retinal pigmentation, cardiac conduction defects) has been associated with autoimmune thyroid, adrenal disease, and diabetes. Other mitochondrial gene mutations including MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes) are associated with single endocrine disorders such as gonadal failure, hypogonadism, hypoparathyroidism, Addison disease, and type 1 diabetes mellitus.

Nongenetic Autoimmune Causes of Multiple Endocrinopathy

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (**ROHHAD**) is a rare pediatric syndrome diagnosed by its cardinal clinical features. ROHHAD usually presents with rapid weight gain in a previously healthy child (age of onset between 1 and 9 yr). The clinical picture evolves to include autonomic deficits (e.g., ophthalmologic findings, gastrointestinal dysmotility, thermal dysregulation, bradycardia), central hypoventilation, and variable hypothalamic dysfunction that may include central hypothyroidism, growth hormone deficiency, hyperprolactinemia, or hyponatremia (Chapter 60.1). The hypothesis that ROHHAD has an autoimmune paraneoplastic etiology is supported by the presence of markers of immune-mediated injury, its response to immunosuppressive therapy in some patients, and its association with neuroendocrine tumors (NETs). However, such tumors are present in only 40% of patients and tumor removal may not affect disease progression. To date, a genetic cause of ROHHAD has not been discovered.

Novel immune-modulating biological compounds are used increasingly in the treatment of malignancies and immune disorders. Antitumor drugs that inhibit immune checkpoints such as CLTA4, PD1, and PDL1 are associated with acute onset of multiple autoimmune endocrinopathies including hypophysitis with hypopituitarism, type 1 diabetes mellitus, primary adrenal insufficiency, and thyroiditis. Anti-CD52 antibodies used in the treatment of multiple sclerosis have been linked to the development of Graves disease and other antibody-mediated autoimmune diseases (e.g., immune thrombocytopenic purpura). Preexisting autoimmunity may be a risk factor for developing autoimmune disease after exposure to a wide range of immunomodulatory therapies.

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CHAPTER 587

Multiple Endocrine Neoplasia Syndromes

Ari J. Wassner, Jessica R. Smith

Multiple endocrine neoplasia (MEN) syndromes are characterized by the development of tumors in 2 or more endocrine glands. These syndromes are divided clinically into 2 main types based on the specific endocrine organs involved (Table 587.1). MEN type 1 is characterized by tumors of the parathyroid glands, anterior pituitary, and endocrine pancreas. In contrast, MEN type 2 is characterized by medullary thyroid cancer and pheochromocytoma. Both types of MEN are generally inherited in autosomal dominant manner, but sporadic cases can occur.

Table 587.1

Manifestations of Multiple Endocrine Neoplasia Syndromes

MEN1	MEN2A	MEN2B
Pituitary adenomas		
Prolactin Growth hormone Adrenocorticotrophic hormone Nonfunctional	Medullary thyroid carcinoma	Medullary thyroid carcinoma
PANCREATIC NEUROENDOCRINE TUMORS		
Insulinoma Gastrinoma Nonfunctional	Pheochromocytoma	Pheochromocytoma
Hyperparathyroidism	Hyperparathyroidism	Mucosal neuromas Marfan-like habitus

MEN, Multiple endocrine neoplasia.

Multiple Endocrine Neoplasia Type 1

Multiple endocrine neoplasia type 1 (MEN1) most commonly presents in the 4th or 5th decade of life, but endocrine tumors can develop as early as 5 yr of age. The most frequently involved endocrine tissues include the parathyroid glands, pituitary, and cells of the endocrine pancreas.

Primary hyperparathyroidism due to a parathyroid adenoma or multigland hyperplasia is the most common manifestation of MEN1, with a lifetime cumulative incidence of 90–95%. In children with MEN1, hyperparathyroidism usually presents after 10 yr of age and is typically the first endocrine disorder to develop (in about 50% of cases). The diagnosis and management of hyperparathyroidism are discussed in Chapter 591 . In patients with MEN1, bilateral surgical exploration is generally recommended over focused minimally invasive approaches because of the tendency for multiple parathyroid glands to be hyperplastic. In such cases, subtotal (3- or 3.5-gland) parathyroidectomy may be required. MEN1 may be present in 15–70% of pediatric cases of primary hyperparathyroidism, and this syndrome should be considered in any child or adolescent with primary hyperparathyroidism, particularly if multigland hyperplasia is present.

Pituitary adenomas are the presenting feature of pediatric MEN1 in about 20% of cases and usually occur after age 10 yr, although they have been reported in patients as young as 5 yr. While these adenomas most commonly secrete prolactin (60–70%), a few secrete growth hormone (5–10%) or adrenocorticotrophic hormone (5%), and the remainder are nonfunctioning (~25%). Diagnosis and management are similar to that of sporadic pituitary adenomas, except that adenomas associated with MEN1 may be more locally aggressive and are more likely to co-secrete multiple pituitary hormones (see Chapter 576).

Patients with MEN1 can develop neoplasia of various enteropancreatic endocrine cells. Such tumors may occur in up to 70% of patients by adulthood but are found in only about 30% of affected children. Insulinomas are the most common pancreatic tumor in children with MEN1, occurring in 10–15% of cases, and present with symptoms of hypoglycemia. These tumors may present before age 10 yr and often occur before age 20 yr. While gastrinomas represent over 50% of pancreatic tumors in adults with MEN1, they are rare in children (~2%). The increasing use of screening imaging has revealed that nonfunctioning pancreatic neuroendocrine tumors may be as or more common than insulinomas in adolescents with MEN1. Rarer pancreatic tumors can secrete other hormones such as glucagon or vasoactive intestinal peptide (VIP).

MEN1 is also associated with a number of other rare tumors. Adrenocortical tumors in children with MEN1 may be benign or malignant, and they may be nonfunctional or hypersecrete cortisol, androgens, or aldosterone. Pheochromocytomas have rarely been reported. Meningiomas, carcinoid tumors, and neuroendocrine tumors of the thymus, bronchopulmonary tree, or stomach can also occur. Older patients with MEN1 frequently manifest cutaneous angiofibromas or collagenomas, which are benign but may be a useful diagnostic clue.

The diagnosis of MEN1 can be made clinically based on the presence of at least 2 of the classical endocrine tumor types (parathyroid, pituitary, pancreas), or the presence of one of these tumors in a 1st-degree relative of a patient with known MEN1. Genetic testing can be used to confirm a clinical diagnosis of MEN1 or to diagnose the condition preclinically in a relative of an affected individual. The *MEN1* gene on chromosome 11q13 encodes the tumor-suppressor menin. A single germline inactivating mutation in *MEN1* is inherited but is not sufficient to cause tumorigenesis alone; a second somatic mutation that inactivates the remaining normal allele then leads to tumor formation in a specific tissue. For this reason, MEN1 is generally inherited in autosomal dominant fashion, although sporadic mutations account for about 10% of cases. Over 1,000 *MEN1* mutations have been described, including deletions and mutations in noncoding regions; therefore genetic testing should include analysis for deletions in patients in whom MEN1 sequencing does not reveal a mutation.

Multiple Endocrine Neoplasia Type 2

Multiple endocrine neoplasia type 2 (MEN2) is a rare genetic disorder that occurs in about 1 in 2 million individuals and is characterized by development of medullary thyroid carcinoma (MTC) and pheochromocytoma. MEN2 is an autosomal dominant disorder caused by activating mutations in the *RET* proto-oncogene, a tyrosine kinase that is encoded on chromosome 10q11.2. The clinical features of the syndrome are related to some extent on the specific *RET* mutation present, although disease manifestations can vary even among family members carrying the same mutation.

Multiple Endocrine Neoplasia Type 2A

Multiple endocrine neoplasia type 2A (MEN2A) is characterized by MTC, pheochromocytoma, and primary hyperparathyroidism. At least 50 different *RET* mutations have been described in patients with MEN2A, the vast majority occurring in exons 10 or 11 (codons 609, 611, 618, 620, or 634) in the *RET* extracellular domain. Essentially all patients with MEN2A develop MTC, but the occurrence of other manifestations is more variable. MTC, or its precursor C-cell hyperplasia, is usually the first manifestation to occur, but the age at which it develops is variable. Pheochromocytomas are often bilateral and may be multiple, and they usually develop in the 3rd decade or later but may occur in childhood. Hyperparathyroidism is caused by hyperplasia that may involve one or more parathyroid glands. Hyperparathyroidism occurs at an average age of about 30 yr but can occur in childhood or adolescence. Mutations in *RET* codon 634 confer a relatively high risk of pheochromocytoma and hyperparathyroidism compared to mutation at other sites.

Additional clinical conditions associated with MEN2A include cutaneous lichen amyloidosis and Hirschsprung disease. Cutaneous lichen amyloidosis is a dermatologic lesion consisting of pruritic hyperpigmented papules that are usually distributed in the interscapular region and on extensor surfaces. These skin lesions may develop before MTC and may provide an early clue to the diagnosis of MEN2A. Some patients with Hirschsprung disease have mutations in *RET* , particularly in exon 10. Although the *RET* mutations that cause Hirschsprung disease are generally loss-of-function mutations, some of these mutations can nevertheless cause MEN2A. Therefore individuals with Hirschsprung disease who carry such a *RET* mutation should be evaluated for MEN2A.

Multiple Endocrine Neoplasia Type 2B

Multiple endocrine neoplasia type 2B (MEN2B) is characterized by MTC and pheochromocytoma, but not hyperparathyroidism. Rather, the distinguishing features of MEN2B are the presence of multiple neuromas and a characteristic phenotype that includes Marfan-like habitus. Nearly all patients with MEN2B have a specific missense mutation (M918T) in the tyrosine kinase catalytic domain of *RET* . While MEN2B can be inherited, about 75% of cases are caused by de novo mutations.

MTC in MEN2B can develop in infancy and is typically aggressive, with a tendency to metastasize early to local and distant sites. Pheochromocytomas occur in about half of patients. The neuromas of MEN2B can occur throughout the digestive tract, most commonly on the tongue, buccal mucosa, lips, and conjunctivae. Diffuse proliferation of nerves and ganglion cells is found in mucosal, submucosal, myenteric, and subserosal plexuses throughout the digestive tract and may be associated with gastrointestinal symptoms. Peripheral neurofibromas and café-au-lait patches may be present. Affected individuals may be tall, with arachnodactyly and a Marfan-like appearance, including scoliosis, pectus excavatum, pes cavus, and muscular hypotonia. The eyelids may be thickened and everted, lips thickened, and jaw prognathic. Feeding difficulties, poor sucking, diarrhea, constipation, and failure to thrive can begin in infancy or early childhood, many years before the appearance of neuromas or endocrine symptoms.

Familial Medullary Thyroid Carcinoma

The familial occurrence of MTC without other clinical manifestations of MEN2 has been termed familial medullary thyroid carcinoma (FMTC). *RET* mutations are commonly present in individuals with FMTC, and while a few families appear to have truly isolated MTC, in other cohorts the pattern of apparent FMTC may represent MEN2A in which other manifestations have not yet occurred or have not been diagnosed. Therefore FMTC is generally regarded as a form of MEN2A, and evaluation for other manifestations of MEN2A is warranted in patients with FMTC.

Management of Multiple Endocrine Neoplasia Type 2

Genetic testing of affected family members often leads to the diagnosis of MEN2 in a child prior to the development of any disease manifestations. MTC is nearly certain to develop in these individuals, and while thyroidectomy is curative if performed prior to the development of MTC or while it is still localized to the thyroid gland, the prognosis is poorer once MTC has metastasized beyond the thyroid. Therefore prophylactic thyroidectomy is required in most individuals with MEN2. However, the timing of prophylactic thyroidectomy must be determined for each patient based on balancing the likelihood of developing metastatic MTC against the need to minimize the risks of surgery, which are higher in younger children.

Factors influencing the risk of MTC include the specific *RET* mutation present, the history of MTC in the family, and serum levels of calcitonin. The first two are not entirely predictive, as MTC behavior can vary significantly even in family members with the same mutation. Nevertheless, some *RET* mutations are associated with more aggressive, earlier-onset MTC, and consensus guidelines generally categorize *RET* mutations as highest risk (M918T, usually associated with MEN2B), high risk (codon 634 and 883 mutations), or moderate risk (other mutations) for MTC. Patients at highest risk should have a thyroidectomy within the first year of life. Those with high-risk mutations should have a thyroidectomy at 5 yr of age, or earlier if calcitonin levels begin to rise. Patients with moderate risk should be monitored by neck ultrasound and serum calcitonin levels beginning at age 5 yr, and thyroidectomy should be performed if calcitonin levels rise. However, the timing of surgery may be influenced by other factors, including family history or the family's desire to avoid prolonged monitoring and proceed with thyroidectomy. Thyroidectomy should be performed by an experienced thyroid surgeon, especially in the youngest patients, to minimize the risk of surgical complications. Prophylactic thyroidectomy reduces morbidity and mortality from MTC in patients with MEN2, many of whom are found to have C-cell hyperplasia, or even MTC, at the time of prophylactic thyroidectomy. The management of MTC is described in detail in Chapter 585 .

Screening for pheochromocytoma and hyperparathyroidism should be performed in children with MEN2. The age at which screening should commence depends on the specific RET mutation (11 yr for high- and highest-risk mutations; 16 yr for moderate-risk mutations). Management of pheochromocytoma (see Chapter 598) and hyperparathyroidism (see Chapter 591) are discussed elsewhere.

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SECTION 3

Disorders of the Parathyroid Gland

OUTLINE

Chapter 588 Hormones and Peptides of Calcium Homeostasis and Bone Metabolism

Chapter 589 Hypoparathyroidism

Chapter 590 Pseudohypoparathyroidism

Chapter 591 Hyperparathyroidism

CHAPTER 588

Hormones and Peptides of Calcium Homeostasis and Bone Metabolism

Daniel A. Doyle

Parathyroid hormone (PTH) and vitamin D are the principal regulators of calcium homeostasis (see Chapters 64 and 723). Calcitonin and PTH-related peptide (PTHrP) are important primarily in the fetus.

Parathyroid Hormone

PTH is an 84-amino-acid chain (95 kDa), but its biologic activity resides in the 1st 34 residues. In the parathyroid gland, a pre-pro-PTH (115-amino-acid chain) and a pro-PTH (90 amino acids) are synthesized. Pre-pro-PTH is converted to pro-PTH and pro-PTH to PTH. PTH (consisting of amino acids 1-84) is the major secretory product of the gland, but it is rapidly cleaved in the liver and kidney into smaller COOH-terminal, mid-region, and NH_2 -terminal fragments.

The occurrence of these fragments in serum has led to the development of a variety of assays. The 1-34 aminoterminal (N-terminus) fragments possess biologic activity but are present in low amounts in the circulation; assay of these fragments is most useful for detecting acute secretory changes. The carboxyterminal (C-terminus) and midregion fragments, although biologically inert, are cleared more slowly from the circulation and represent 80% of plasma immunoreactive PTH; concentrations of the C-terminal fragment are 50-500 times the level of the active hormone. The C-terminal assays are effective in detecting hyperparathyroidism, but because C-terminal fragments are removed from the circulation by glomerular filtration, these assays are less useful for evaluating the secondary hyperparathyroidism characteristic of renal disease. Only certain sensitive radioimmunoassays for PTH can differentiate the subnormal concentrations that occur in hypoparathyroidism from normal levels.

When serum levels of calcium fall, the signal is transduced through the calcium-sensing receptor, and secretion of PTH increases (Fig. 588.1). PTH stimulates activity of 1α-hydroxylase in the kidney, enhancing production of 1,25-dihydroxycholecalciferol, also written as $1,25(OH)_2 D_3$. The increased level of $1,25(OH)_2 D_3$ induces synthesis of a calcium-binding protein (calbindin-D) in the intestinal mucosa, with resultant absorption of calcium. PTH also mobilizes calcium by directly enhancing bone resorption, an effect that requires $1,25(OH)_2 D_3$. The effects of PTH on bone and kidney are mediated through binding to specific receptors on the membranes of target cells and through activation of a transduction pathway involving a G-protein coupled to the adenylate cyclase system (see Chapter 572).

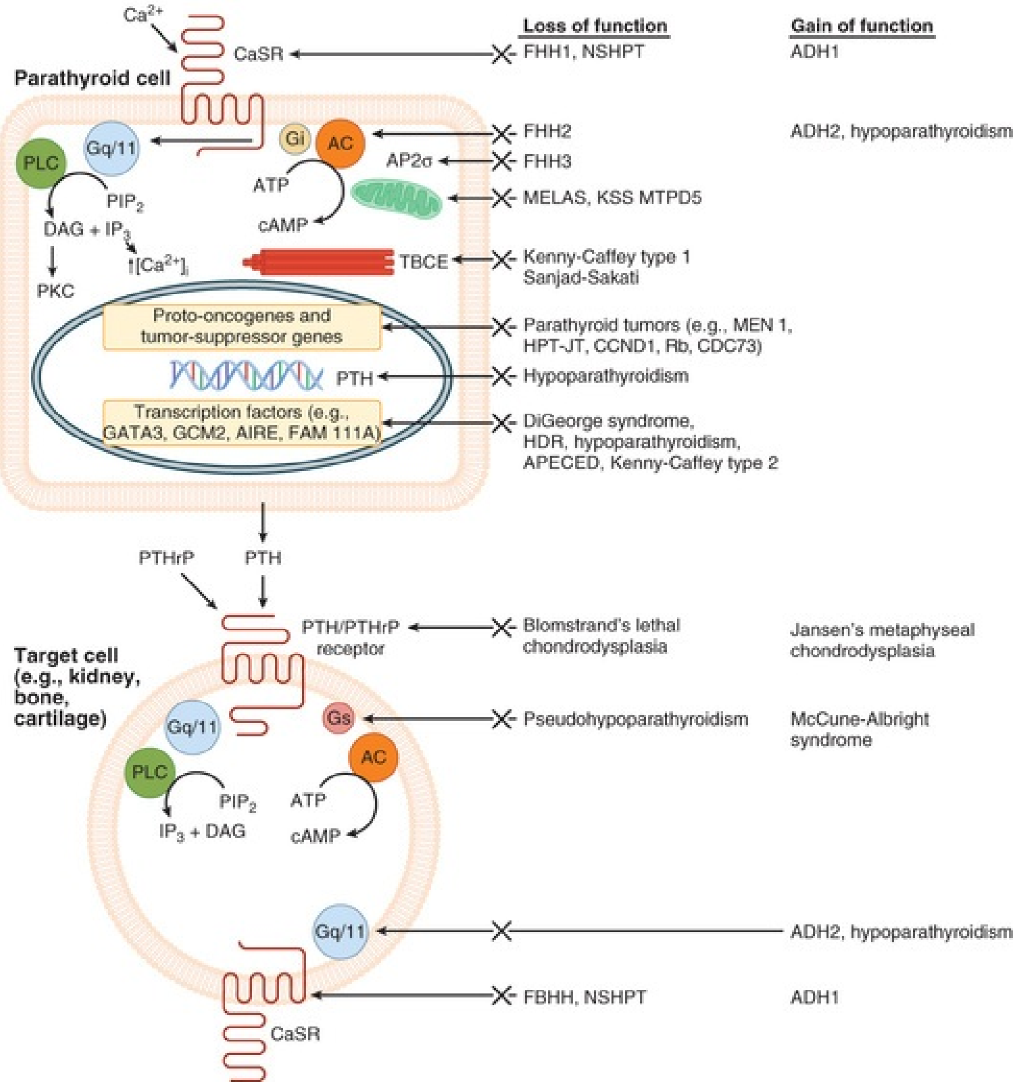

Ca^{2+}
CaSR
Parathyroid cell
Loss of function
Gain of function
FHH1, NSHPT
ADH1
Gq/11
PLC
Gi
AC
FHH2
ADH2, hypoparathyroidism
AP2σ
FHH3
ATP
MELAS, KSS MTPD5
PIP_2
$DAG + IP_3$
cAMP
↑$[Ca^{2+}]_i$
PKC
TBCE
Kenny-Caffey type 1
Sanjad-Sakati
Proto-oncogenes and tumor-suppressor genes
Parathyroid tumors (e.g., MEN 1, HPT-JT, CCND1, Rb, CDC73)
PTH
Hypoparathyroidism
Transcription factors (e.g., GATA3, GCM2, AIRE, FAM 111A)
DiGeorge syndrome, HDR, hypoparathyroidism, APECED, Kenny-Caffey type 2
PTHrP
PTH
PTH/PTHrP receptor
Blomstrand's lethal chondrodysplasia
Jansen's metaphyseal chondrodysplasia
Target cell (e.g., kidney, bone, cartilage)
Gq/11
Gs
Pseudohypoparathyroidism
McCune-Albright syndrome
AC
PLC
PIP_2
ATP
$IP_3 + DAG$
cAMP
Gq/11
ADH2, hypoparathyroidism
FBHH, NSHPT
ADH1
CaSR

FIG. 588.1 Schematic representation of some of the components involved in calcium homeostasis. Alterations in extracellular calcium are detected by the calcium-sensing receptor *(CaSR)* , which is a 1078−amino acid G protein−coupled receptor. The PTH/PTHrP receptor, which mediates the actions of PTH and PTHrP, is also a G protein−coupled receptor. Thus Ca^{2+} , PTH, and PTHrP involve G protein−coupled signaling pathways, and interaction with their specific receptors can lead to activation of Gs, Gi, and Gq, respectively. Gs stimulates adenylcyclase *(AC)* , which catalyzes the formation of cyclic adenosine monophosphate *(cAMP)* from adenosine triphosphate *(ATP)* . Gi inhibits AC activity. cAMP stimulates protein kinase A *(PKA)* , which phosphorylates cell-specific substrates. Activation of Gq stimulates phospholipase C *(PLC)* , which catalyzes the hydrolysis of the phosphoinositide *(PIP_2)* to inositol triphosphate *(IP_3)* , which then increases intracellular calcium, and diacylglycerol *(DAG)* , activating protein kinase C *(PKC)* . These proximal signals modulate downstream pathways, which results in specific physiologic effects. Loss of function in several genes, shown with their respective sites of action on the right, has been identified in specific disorders of calcium homeostasis. (From Thakker RV:

The parathyroid glands, hypercalcemia and hypocalcemia. In Goldman L, Schafer AI, editors: *Goldman-Cecil medicine,* ed 25, Philadelphia, 2016, Elsevier, p. 1651, Fig. 245.2.)

The calcium-sensing receptor regulates the secretion of PTH and the reabsorption of calcium by the renal tubules in response to alterations in serum calcium concentrations. The gene for the receptor is located on chromosome 3q13.3-q21 and encodes a cell surface protein that is expressed in parathyroid glands and kidneys and belongs to the family of G-protein–coupled receptors. In the normally functioning calcium-sensing receptor, hypocalcemia induces increased secretion of PTH and hypercalcemia depresses PTH secretion. Loss-of-function mutations cause an increased set point with respect to serum calcium, resulting in hypercalcemia and in the conditions of familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Acquired hypocalciuric hypercalcemia may be a result of autoantibodies to the calcium-sensing receptor and manifests with hypercalcemia and hyperparathyroidism. Gain-of-function mutations result in depressed secretion of PTH in response to hypocalcemia, leading to the syndrome of familial hypocalcemia with hypercalciuria (see Fig. 588.1).

Parathyroid Hormone–Related Peptide

PTHrP is homologous to PTH only in the 1st 13 amino acids of its amino terminus, 8 of which are identical to PTH. Its gene is on the short arm of chromosome 12 and that of PTH is on the short arm of chromosome 11.

PTHrP, like PTH, activates PTH receptors in kidney and bone cells and increases urinary cyclic adenosine monophosphate and renal production of $1,25(OH)_2 D_3$. It is produced in almost every type of cell of the body, including every tissue of the embryo at some stage of development. PTHrP is critical for normal fetal development. Inactivating mutations of the receptor for PTH/PTHrP results in a lethal bone disorder characterized by short limbs and markedly advanced bone maturation known as *Blomstrand chondrodysplasia* (see Fig. 588.1). PTHrP appears to have a paracrine or autocrine role because serum levels are low except in a few clinical situations. Cord blood contains levels of PTHrP that are 3-fold higher than in serum from adults; it is produced by the fetal parathyroid glands and appears to be the main agent stimulating maternal-fetal calcium transfer. PTHrP appears to be essential for normal skeletal maturation of the fetus, which requires 30 g of calcium during a normal gestation. During pregnancy, maternal absorption of calcium increases from about 150 mg daily to 400 mg during the 2nd trimester.

As in cord blood, PTHrP levels are increased during lactation and in patients with benign breast hypertrophy. Breast milk and pasteurized bovine milk have levels of PTHrP that are 10,000 times higher than those of normal plasma. Most instances of the hormonal **hypercalcemia** syndrome of malignancy are caused by elevated concentrations of PTHrP.

Vitamin D

See Chapter 64 .

Calcitonin

Calcitonin is a 32-amino-acid polypeptide. Its gene is on chromosome 11p and is tightly linked to that of PTH. The gene for calcitonin encodes 3 peptides: calcitonin, a 21-amino-acid carboxyterminal flanking peptide (katacalcin), and a calcitonin gene–related peptide. Katacalcin and calcitonin are cosecreted in equimolar amounts by the parafollicular cells (C cells) of the thyroid gland. Calcitonin appears to be of little consequence in children and adults because very high levels in patients with medullary carcinoma of the thyroid (a tumor arising from the C cells) do not cause hypercalcemia. In the fetus, however, circulating levels are high and appear to augment bone metabolism and skeletal growth; these high levels are probably stimulated by the normally high fetal calcium levels. Unlike the high levels in cord blood and circulating concentrations in young children, levels in older children and adults are low. Infants and children with congenital hypothyroidism (and presumed deficiency of C cells) have lower levels of calcitonin than normal children.

Its action appears to be independent of PTH and vitamin D. Its main biologic effect appears to be the inhibition of bone resorption by decreasing the number and activity of bone-resorbing osteoclasts. This action of calcitonin is the rationale for its use in treatment of Paget disease. Calcitonin is synthesized in other organs, such as the gastrointestinal tract, pancreas, brain, and pituitary. In these organs, calcitonin is thought to behave as a neurotransmitter to impose a local inhibitory effect on cell function.

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CHAPTER 589

Hypoparathyroidism

Daniel A. Doyle

Etiology

Hypocalcemia is common in neonates between 12 and 72 hr of life, especially in premature infants, in infants with asphyxia, and in infants of diabetic mothers (**early neonatal hypocalcemia** ; see Chapter 119.4 ; Table 589.1 and Fig. 589.1). After the 2nd to 3rd day and during the 1st wk of life, the type of feeding also is a determinant of the level of serum calcium (**late neonatal hypocalcemia**). The role played by the parathyroid glands in these hypocalcemic infants is unclear, although functional immaturity of the parathyroid glands is invoked as 1 pathogenetic factor. In a group of infants with **transient idiopathic hypocalcemia** (1-8 wk of age), serum levels of parathyroid hormone (PTH) are significantly lower than those in normal infants. It is possible that the functional immaturity is a manifestation of a delay in development of the enzymes that convert glandular PTH to secreted PTH; other mechanisms are possible.

Table 589.1

Causes of Hypocalcemia

I. Neonatal
  A. Maternal Disorders
    Diabetes mellitus
    Toxemia of pregnancy
    Vitamin D deficiency
    High intake of alkali or magnesium sulfate
    Use of anticonvulsants
    Hyperparathyroidism
  B. Neonatal Disorders
    Low birthweight: prematurity, intrauterine growth restriction
    Peripartum asphyxia, sepsis, critical illness
    Hyperbilirubinemia, phototherapy, exchange transfusion

    - Hypomagnesemia, hypermagnesemia
    - Acute/chronic renal failure
    - Nutrients/medications: high phosphate intake, fatty acids, phytates, bicarbonate infusion, citrated blood, anticonvulsants, aminoglycosides
    - Hypoparathyroidism
    - Vitamin D deficiency or resistance
    - Osteopetrosis type II
- II. Hypoparathyroidism
  - A. Congenital
    - 1. Transient neonatal
    - 2. Congenital hypoparathyroidism
      - a. Familial isolated hypoparathyroidism
      - (1) Autosomal recessive hypoparathyroidism (GCMB, PTH)
      - (2) Autosomal dominant hypoparathyroidism (CaSR)
      - (3) X-linked hypoparathyroidism *(SOX3)*
      - b. DiGeorge syndrome *(TBX1)*
      - c. Sanjad-Sakati syndrome (short stature, retardation, dysmorphism; HRD); Kenny-Caffey syndrome 1 (short stature, medullary stenosis) *(TBCE)*
      - d. Barakat syndrome (sensorineural deafness, renal dysplasia; HDR) *(GATA3)*
      - e. Lymphedema-hypoparathyroidism-nephropathy, nerve deafness
      - f. Mitochondrial disorders (Kearns-Sayre, Pearson, MELAS)
    - 3. Insensitivity to PTH
      - a. Blomstrand chondrodysplasia *(PTHR1)*
      - b. Pseudohypoparathyroidism type IA *(GNAS)*
      - Pseudohypoparathyroidism type IB
      - Pseudohypoparathyroidism type IC
      - Pseudohypoparathyroidism type II
      - Pseudopseudohypoparathyroidism
      - c. Acrodysostosis with hormone resistance *(PRKAR1A)*
      - d. Hypomagnesemia
    - 4. CaSR-activating mutation
      - a. Sporadic
      - b. Autosomal dominant (G protein subunit α11 mutation)
  - B. Acquired
    - 1. Autoimmune polyglandular syndrome type I (*AIRE* gene mutation)
    - 2. Activating antibodies to the CaSR
    - 3. Postsurgical, radiation destruction
    - 4. Infiltrative—excessive iron (hemochromatosis, thalassemia) or copper (Wilson disease) deposition; granulomatous inflammation, neoplastic invasion; amyloidosis, sarcoidosis
    - 5. Maternal hyperparathyroidism
    - 6. Hypomagnesemia/hypermagnesemia
- III. Vitamin D Deficiency
- IV. Other Causes of Hypocalcemia
  - A. Calcium Deficiency
    - 1. Nutritional deprivation
    - 2. Hypercalciuria
  - B. Disorders of Magnesium Homeostasis
    - 1. Congenital hypomagnesemia
    - 2. Acquired
      - a. Acute renal failure
      - b. Chronic inflammatory bowel disease, intestinal resection
      - c. Diuretics
  - C. Hyperphosphatemia
    - 1. Renal failure
    - 2. Phosphate administration (intravenous, oral, rectal)
    - 3. Tumor cell lysis

    4. Muscle injuries (crush, rhabdomyolysis)
  D. Miscellaneous
    1. Hypoproteinemia
    2. Hyperventilation
    3. Drugs: furosemide, aminoglycosides, bisphosphonates, calcitonin, anticonvulsants, ketoconazole, antineoplastic agents (plicamycin, asparaginase, cisplatinum, cytosine arabinoside, doxorubicin), citrated blood products
    4. Hungry bone syndrome
    5. Acute and critical illness: sepsis, acute pancreatitis, toxic shock
      a. Organic acidemia: propionic, methylmalonic, isovaleric

HDR, hypoparathyroidism, sensorineural deafness, and renal anomaly; HRD, hypoparathyroidism, retardation, dysmorphism; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episode; PTH, parathyroid hormone.

Modified from Root AW, Diamond Jr FB: Disorders of mineral homeostasis in children and adolescents. In Sperling MA, editor: *Pediatric endocrinology* , ed 4, Philadelphia, 2014, Elsevier, Table 18.2A.

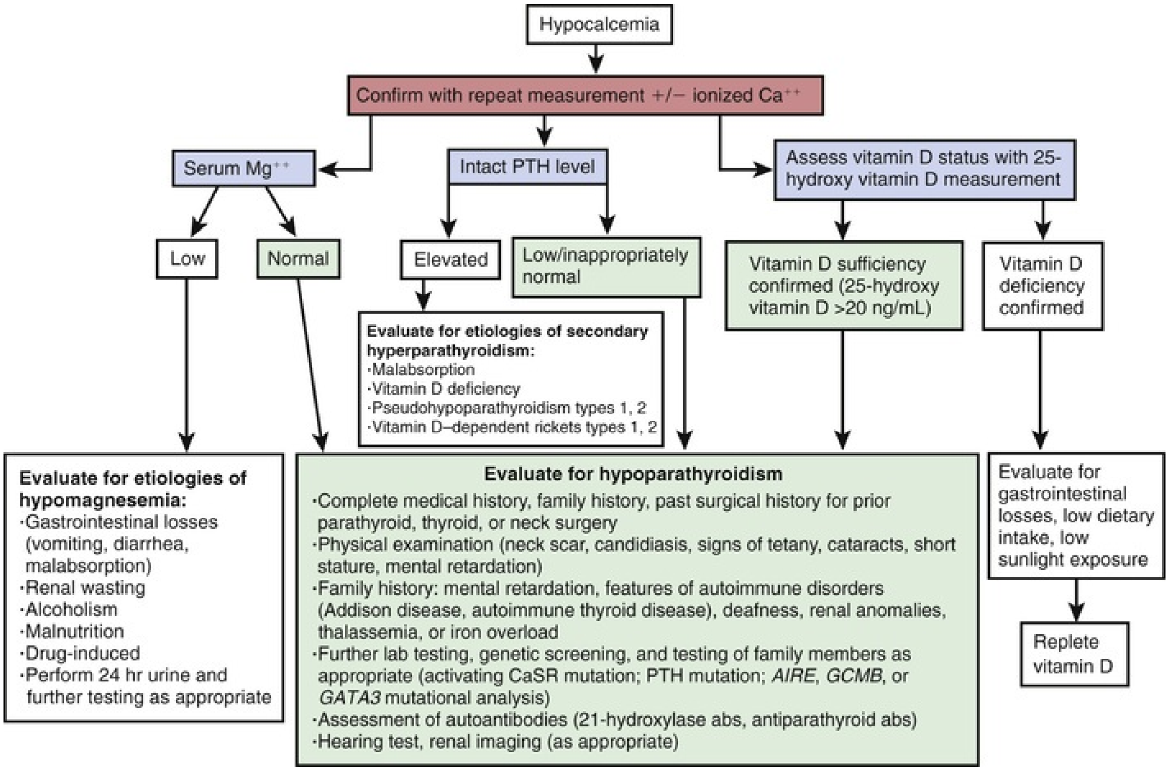
Hypocalcemia
Confirm with repeat measurement +/− ionized Ca^{++}
Serum Mg^{++}
Intact PTH level
Assess vitamin D status with 25-hydroxy vitamin D measurement
Low
Normal
Elevated
Low/inappropriately normal
Vitamin D sufficiency confirmed (25-hydroxy vitamin D >20 ng/mL)
Vitamin D deficiency confirmed
Evaluate for etiologies of secondary hyperparathyroidism:
·Malabsorption
·Vitamin D deficiency
·Pseudohypoparathyroidism types 1, 2
·Vitamin D–dependent rickets types 1, 2
Evaluate for etiologies of hypomagnesemia:
·Gastrointestinal losses (vomiting, diarrhea, malabsorption)
·Renal wasting
·Alcoholism
·Malnutrition
·Drug-induced
·Perform 24 hr urine and further testing as appropriate
Evaluate for hypoparathyroidism
·Complete medical history, family history, past surgical history for prior parathyroid, thyroid, or neck surgery
·Physical examination (neck scar, candidiasis, signs of tetany, cataracts, short stature, mental retardation)
·Family history: mental retardation, features of autoimmune disorders (Addison disease, autoimmune thyroid disease), deafness, renal anomalies, thalassemia, or iron overload
·Further lab testing, genetic screening, and testing of family members as appropriate (activating CaSR mutation; PTH mutation; AIRE, GCMB, or GATA3 mutational analysis)
·Assessment of autoantibodies (21-hydroxylase abs, antiparathyroid abs)
·Hearing test, renal imaging (as appropriate)
Evaluate for gastrointestinal losses, low dietary intake, low sunlight exposure
Replete vitamin D

FIG. 589.1 **Evaluation of hypocalcemia. Abs, autoantibodies; CaSR, calcium-sensing receptor; PTH, parathyroid hormone. (From Bilezikian JP, Khan A, Potts Jr JT, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. *J Bone Miner Res* 26:2317–2337, 2011, Fig. 1.)**

Aplasia or Hypoplasia of the Parathyroid Glands

Aplasia or hypoplasia of the parathyroid glands is often associated with the **DiGeorge/velocardiofacial syndrome** . This syndrome occurs in 1 in 4,000 newborns. In 90% of patients, the condition is caused by a deletion of chromosome 22q11.2. Approximately 25% of these patients inherit the chromosomal abnormality from a parent. Neonatal hypocalcemia occurs in 60% of affected patients, but it is transitory in the majority; hypocalcemia can recur or can have its onset later in life. Associated abnormalities of the 3rd and 4th pharyngeal pouches are common; these include conotruncal defects of the heart in 25%, velopharyngeal insufficiency in 32%, cleft palate in 9%, renal anomalies in 35%, and aplasia of the thymus with severe immunodeficiency in 1%. This syndrome has also been reported in a small number of patients with a deletion of chromosome 10p13, in infants of diabetic mothers, and in infants born to mothers treated with retinoic acid for acne early in pregnancy.

X-Linked Recessive Hypoparathyroidism

Familial clusters of hypoparathyroidism with various patterns of transmission have been described. In 2 large North American pedigrees, this disorder appears to be transmitted by an X-linked recessive gene located on Xq26-q27. In these families, the onset of afebrile seizures characteristically occurs in infants from 2 wk to 6 mo of age. The absence of parathyroid tissue after detailed examination of a boy with this condition suggests a defect in embryogenesis.

Autosomal Recessive Hypoparathyroidism With Dysmorphic Features

Autosomal recessive hypoparathyroidism with dysmorphic features has been described in Middle Eastern children. Parental consanguinity occurred for almost all of several dozen affected patients. Profound hypocalcemia occurs early in life, and dysmorphic features include microcephaly, deep-set eyes, beaked nose, micrognathia, and large floppy ears. Intrauterine and postnatal growth restriction are severe, and cognitive impairment is common. The putative gene is on chromosome 1q42-43. The autosomal recessive form of hypoparathyroidism that occurs with type I polyglandular autoimmune disease is described subsequently. In a few patients with autosomal recessive inheritance of isolated hypoparathyroidism, mutations of the *PTH* gene have been found.

Hypoparathyroidism, Sensorineural Deafness, and Renal Anomaly Syndrome

Hypoparathyroidism, sensorineural deafness, and renal anomaly occur owing to mutations of the *GATA3* gene. The protein encoded by this gene is essential in the development of the parathyroids, auditory system, and kidneys. The *GATA3* gene is located at chromosome 10p14 and is nonoverlapping with the DiGeorge critical region at 10p13 (see Fig. 588.1). *Congenital ichthyosis and HDR have also been reported.*

Suppression of Neonatal Parathyroid Hormone Secretion Because of Maternal Hyperparathyroidism

Neonatal PTH secretion can be suppressed by maternal hyperparathyroidism, resulting in transient hypocalcemia in the newborn infant. It appears that neonatal hypocalcemia results from suppression of the fetal parathyroid glands by exposure to elevated levels of calcium in maternal and hence fetal serum. Tetany usually develops within 3 wk but may be delayed by 1 mo or more if the infant is breastfed. Hypocalcemia can persist for weeks or months. When the cause of hypocalcemia in an infant is unknown, measurements of calcium, phosphorus, and PTH should be obtained from the mother. Most affected mothers are asymptomatic, and the cause of their hyperparathyroidism is usually a parathyroid adenoma.

Autosomal Dominant

Hypoparathyroidism

Patients with autosomal dominant hypoparathyroidism have an activating (gain-of-function) mutation of the Ca^{2+} -sensing receptor, forcing the receptor to an on state with subsequent depression of PTH secretion even during hypocalcemia. The patients have hypercalciuria. The hypocalcemia is usually mild and might not require treatment beyond childhood (see Fig. 588.1).

Hypoparathyroidism Associated With Mitochondrial Disorders

Mitochondrial DNA mutations in Kearns-Sayre syndrome, MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) syndrome, and in mitochondrial trifunctional protein–deficiency syndrome is associated with hypoparathyroidism. A diagnosis of mitochondrial cytopathy should be considered in patients with unexplained symptoms, such as ophthalmoplegia, sensorineural hearing loss, cardiac conduction disturbances, and tetany (see Fig. 588.1).

Surgical Hypoparathyroidism

Removal or damage of the parathyroid glands can complicate thyroidectomy. Hypoparathyroidism has developed even when the parathyroid glands have been identified and left undisturbed at the time of operation. This may be the result of interference with the blood supply or of postoperative edema and fibrosis. Symptoms of tetany can occur abruptly postoperatively and may be temporary or permanent. In some instances, symptoms develop insidiously and go undetected until months after thyroidectomy. Occasionally, the first evidence of surgical hypoparathyroidism may be the development of cataract. The status of parathyroid function should be carefully monitored in all patients undergoing thyroidectomy.

Deposition of iron pigment or of copper in the parathyroid glands (thalassemia, Wilson disease) can also produce hypoparathyroidism.

Autoimmune Hypoparathyroidism

An autoimmune mechanism for hypoparathyroidism is strongly suggested by the finding of parathyroid antibodies and by its frequent association with other autoimmune disorders or organ-specific antibodies. Autoimmune hypoparathyroidism is often associated with Addison disease and chronic mucocutaneous candidiasis. The association of at least 2 of these 3 conditions has been classified as **autoimmune polyglandular disease type I** (see Chapter 586). It is also known as autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy (APECED). This syndrome is inherited in an autosomal recessive fashion and is not related to any single human leukocyte antigen–associated haplotype. One-third of patients with this syndrome have all 3 components; 66% have only 2 of 3 conditions. The candidiasis almost always precedes the other disorders (70% of cases occur in children younger than 5 yr of age); the hypoparathyroidism (90% of cases occur after 3 yr of age) usually occurs before Addison disease (90% of cases occur after 6 yr of age). A variety of other disorders, including alopecia areata or totalis, malabsorption disorder, pernicious anemia, gonadal failure, chronic active hepatitis, vitiligo, and insulin-dependent diabetes, occur at various times. Some of these associations might not appear until adult life. Autoimmune thyroid disease is a rare concomitant finding.

Affected siblings can have the same or different constellations of disorders (hypoparathyroidism, Addison disease). The disorder is exceptionally prevalent among Finns and Iranian Jews. The gene for this disorder is designated *AIRE* (autoimmune regulator); it is located on chromosome 21q22. It appears to be a transcription factor that plays an essential role in the development of immunologic tolerance. Patients with Addison disease as part of polyendocrinopathy syndrome type I have demonstrated adrenal-specific autoantibody reactivity directed against the side-chain cleavage enzyme.

Idiopathic Hypoparathyroidism

The term *idiopathic hypoparathyroidism* should be reserved for the small residuum of children with hypoparathyroidism for whom no causative mechanism can be defined. Most children in whom onset of hypoparathyroidism occurs after the 1st few years of life have an **autoimmune condition.** Autoantibodies to the extracellular domain of the calcium-sensing receptor have been identified in some patients with acquired hypoparathyroidism. One should always consider incomplete forms of DiGeorge syndrome or an activating calcium-sensing receptor mutation in the differential diagnosis.

Clinical Manifestations

There is a spectrum of parathyroid deficiencies with clinical manifestations varying from no symptoms to those of complete and long-standing deficiency. Mild deficiency may be revealed only by appropriate laboratory studies. Muscular pain and cramps are early manifestations; they progress to numbness, stiffness, and tingling of the hands and feet. There may be only a positive Chvostek or Trousseau sign or laryngeal and carpopedal spasms. Convulsions with or without loss of consciousness can occur at intervals of days, weeks, or months. These episodes can begin with abdominal pain, followed by tonic rigidity, retraction of the head, and cyanosis. Hypoparathyroidism is often mistaken for epilepsy. Headache, vomiting, increased intracranial pressure, and papilledema may be associated with convulsions and might suggest a brain tumor.

In patients with long-standing hypocalcemia, the teeth erupt late and irregularly. Enamel formation is irregular, and the teeth may be unusually soft. The skin may be dry and scaly, and the nails might have horizontal lines. Mucocutaneous candidiasis, when present, antedates the development of hypoparathyroidism; the candidal infection most often involves the nails, the oral mucosa, the angles of the mouth, and less often, the skin; it is difficult to treat.

Cataracts in patients with long-standing untreated disease are a direct consequence of hypoparathyroidism; other autoimmune ocular disorders such as keratoconjunctivitis can also occur. Manifestations of Addison disease, lymphocytic thyroiditis, pernicious anemia, alopecia areata or totalis, hepatitis, and primary gonadal insufficiency may also be associated with those of hypoparathyroidism.

Permanent physical and mental deterioration occurs if initiation of treatment is long delayed.

Laboratory Findings

The serum calcium level is low (5-7 mg/dL), and the phosphorus level is elevated (7-12 mg/dL). Blood levels of ionized calcium (usually approximately 45% of the total) more nearly reflect physiologic adequacy but also are low. The serum level of alkaline phosphatase is normal or low, and the level of $1,25(OH)_2 D_3$ is usually low, but high levels have been found in some children with severe hypocalcemia. The level of magnesium is normal but should always be checked in hypocalcemic patients. Levels of PTH are low when measured by immunometric assay. Radiographs of the bones occasionally reveal an increased density limited to the metaphyses, suggesting heavy metal poisoning, or an increased density of the lamina dura. Radiographs or CT scans of the skull can reveal calcifications in the basal ganglia. There is a prolongation of the QT interval on the electrocardiogram, which disappears when the hypocalcemia is corrected. The electroencephalogram usually reveals widespread slow activity; the tracing returns to normal after the serum calcium concentration has been within the normal range for a few weeks, unless irreversible brain damage has occurred or unless the parathyroid insufficiency is associated with epilepsy. When hypoparathyroidism occurs concurrently with Addison disease, the serum level of calcium may be normal, but hypocalcemia appears after effective treatment of the adrenal insufficiency.

Treatment

Emergency treatment of neonatal tetany consists of intravenous injections of 5-10 mL or 1-3 mg/kg of a 10% solution of calcium gluconate (elemental calcium 9.3 mg/mL) at the rate of 0.5-1.0 mL/min while the heart rate is monitored and a total dose not to exceed 20 mg of elemental calcium/kg. Additionally, 1,25-dihydroxycholecalciferol (calcitriol) should be given. The initial dosage is 0.25 µg/24 hr; the maintenance dosage ranges from 0.01-0.10 µg/kg/24 hr to a maximum of 1-2 µg/24 hr. Calcitriol has a short half-life and should be given in 2 equal divided doses; it has the advantages of rapid onset of effect (1-4 days) and rapid reversal of hypercalcemia after discontinuation in the event of overdosage (calcium levels begin to fall in 3-4 days). Calcitriol is supplied as an oral solution.

An adequate intake of calcium should be ensured. Supplemental calcium can be given in the form of calcium gluconate or calcium glubionate to provide 800 mg of elemental calcium daily, but it is rarely essential. Foods with high phosphorus content such as milk, eggs, and cheese should be reduced in the diet.

Clinical evaluation of the patient and frequent determinations of the serum calcium levels are indicated in the early stages of treatment to determine the requirement for calcitriol or vitamin D_2 . If hypercalcemia occurs, therapy should be discontinued and resumed at a lower dose after the serum calcium level has returned to normal. In long-standing cases of hypercalcemia, repair of cerebral and dental changes is not likely. Pigmentation, lowering of blood pressure, or weight loss can indicate adrenal insufficiency, which requires specific treatment. Patients with autosomal dominant hypocalcemic hypercalciuria can develop nephrocalcinosis and renal impairment if treated with vitamin D.

Differential Diagnosis

Magnesium deficiency must be considered in patients with unexplained hypocalcemia. Concentrations of serum magnesium <1.5 mg/dL (1.2 mEq/L) are usually abnormal. Familial hypomagnesemia with secondary hypocalcemia has been reported in approximately 50 patients, most of whom developed tetany and seizures at 2-6 wk of age. Administration of calcium is ineffective, but administration of magnesium promptly corrects both calcium and magnesium levels. Oral supplements of magnesium are necessary to maintain levels of magnesium in the normal range. Two genetic forms have been described. One is caused by an autosomal recessive gene on chromosome 9, resulting in a specific defect in absorption of magnesium. The other is caused by an autosomal dominant gene on chromosome 11q23, resulting in renal loss of magnesium.

Hypomagnesemia also occurs in malabsorption syndromes such as Crohn disease and cystic fibrosis. Patients with autoimmune polyglandular disease type I and hypoparathyroidism can also have concurrent steatorrhea and low magnesium levels. Therapy with aminoglycosides causes hypomagnesemia by increasing urinary losses.

It is not clear how low levels of magnesium lead to hypocalcemia. Evidence suggests that hypomagnesemia impairs release of PTH and induces resistance to the effects of the hormone, but other mechanisms also may be operative.

Poisoning with inorganic phosphate leads to hypocalcemia and tetany. Infants administered large doses of inorganic phosphates, either as laxatives or as sodium phosphate enemas, have had sudden onset of tetany, with serum calcium levels <5 mg/dL and markedly elevated levels of phosphate. Symptoms are quickly relieved by intravenous administration of calcium. The mechanism of the hypocalcemia is not clear (see Chapter 68.6).

Hypocalcemia can occur early in the course of treatment of acute lymphoblastic leukemia. Hypocalcemia is usually associated with hyperphosphatemia resulting from destruction of lymphoblasts.

Episodic symptomatic hypocalcemia occurs in the **Kenny-Caffey syndrome,** which is characterized by medullary stenosis of the long bones, short stature, delayed closure of the fontanel, delayed bone age, and eye abnormalities. Idiopathic hypoparathyroidism and abnormal PTH levels have been found. Autosomal dominant and autosomal recessive modes of inheritance have been reported. Mutations of the *TBCE* gene (1q43-44) perturb microtubule organization in diseased cells.

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CHAPTER 590

Pseudohypoparathyroidism

Daniel A. Doyle

In contrast to the situation in hypoparathyroidism, in pseudohypoparathyroidism (PHP, also known as Albright hereditary osteodystrophy) the parathyroid glands are normal or hyperplastic and they can synthesize and secrete parathyroid hormone (PTH). Serum levels of immunoreactive PTH are elevated even when the patient is hypocalcemic and may be elevated when the patient is normocalcemic. Neither endogenous nor administered PTH raises the serum levels of calcium or lowers the levels of phosphorus. The genetic defects in the **hormone receptor adenylate cyclase system** are classified into various types depending on the phenotypic and biochemical findings (Table 590.1).

Table 590.1

Clinical, Biochemical, and Genetic Features of Hypoparathyroid and Pseudohypoparathyroid Disorders

	HYPOPARATHYROIDISM	PSEUDOHYPOPARATHYROIDISM				
		PHP 1a	**PPHP**	**PHP 1b**	**PHP 1c**	**PHP 2**
AHO manifestations	No	Yes	Yes	No	Yes	No
Serum calcium	↓	↓	N	↓	↓	↓
Serum PO_4	↑	↑	N	↑	↑	↑
Serum PTH	↓	↑	N	↑	↑	↑
Response to PTH:						
Urinary cAMP[*] (Chase-Aurbach test)	↑	↓	↑	↓	↓	↑
Urinary PO_4 (Ellsworth-Howard test)	↑	↓	↑	↓	↓	↓
G_s α activity	N	↓	↓	N	N	N
Inheritance	AD, AR, X	AD	AD	AD	AD	Sporadic
Molecular defect	PTH, CaSR, GATA3, Gcm2, others	GNAS1	GNAS1	GNAS1[†]	?Adenyl cyclase	?cAMP targets
Other hormonal resistance	No	Yes	No	No	Yes	No

[*] Plasma cyclic adenosine monophosphate (cAMP) responses are similar to those of urinary cAMP.

[†] Involves deletions that are located upstream of GNAS1.

↓, decreased; ↑, increased; ?, presumed, but not proved; AD, autosomal dominant; AHO, Albright's hereditary osteodystrophy; AR, autosomal recessive; N, normal; PHP, pseudoparathyroidism; PPHP, pseudopseudoparathyroidism; PTH, parathyroid hormone; X, X-linked.

From Thakker RV: The parathyroid glands, hypercalcemia and hypocalcemia. In Goldman L, Schafer AI, editors: *Goldman-Cecil medicine* , ed 25. Philadelphia, 2016, Elsevier, Table 245-8.

Type Ia

Type Ia accounts for the majority of patients with PHP. Affected patients have a genetic defect of the α subunit of the stimulatory guanine nucleotide-binding protein (G_s α). This coupling factor is required for PTH bound to cell surface receptors to activate cyclic adenosine monophosphate (cAMP). Heterogeneous mutations of the G_s α gene have been documented; the gene is located on chromosome 20q13.2. Deficiency of the G_s α subunit is a generalized cellular defect and accounts for the association of other endocrine disorders with type Ia PHP. The defect is inherited as an autosomal dominant trait, and the paucity of father-to-son transmissions is thought to be a result of decreased fertility in males.

Tetany is often the presenting sign. Affected children have a short, stocky build and a round face. *Brachydactyly with dimpling of the dorsum of the hand is usually present.* The second metacarpal is involved least often. As a result, the index finger occasionally is longer than the middle finger. Likewise, the second metatarsal is only rarely affected. There may be other skeletal abnormalities such as short and wide phalanges, bowing, exostoses, and thickening of the calvaria. These patients often have calcium deposits and metaplastic bone formation subcutaneously. Moderate degrees of cognitive impairment, calcification of the basal ganglia, and lenticular cataracts are common in patients whose disease is diagnosed late.

Some members of affected kindreds may have the usual anatomic stigmata of PHP, but serum levels of calcium and phosphorus are normal despite reduced G_s α activity; however, PTH levels may be slightly elevated. Such patients have been labeled as having **pseudopseudohypoparathyroidism** ***or PHP1C*** **.** Transition from normocalcemia to hypocalcemia often occurs with increasing age of the patient. These phenotypically similar but metabolically dissimilar patients may be in the same family and have the same mutations of G_s α protein. It is not known what other factors cause clinically overt hypocalcemia in some affected patients and not in others. There is evidence that the G_s α mutation is paternally transmitted in pseudopseudohypoparathyroidism and maternally transmitted in patients with type Ia disease. The gene may be imprinted in a tissue-specific manner *and have different methylation patterns* .

In addition to resistance to PTH, resistance to other G-protein–coupled receptors for thyroid-stimulating hormone (TSH), gonadotropins, and glucagon can result in various metabolic effects. Clinical hypothyroidism is uncommon, but basal levels of TSH are elevated and thyrotropin-releasing hormone–stimulated TSH responses are exaggerated. Moderately decreased levels of thyroxine and increased levels of TSH have been demonstrated by newborn thyroid-screening programs, leading to the detection of type Ia PHP in infancy. In adults, gonadal dysfunction is common, as manifested by sexual immaturity, amenorrhea, oligomenorrhea, and infertility. Each of these abnormalities can be related to deficient synthesis of cAMP secondary to a deficiency of G_s α, but it is not clear why resistance to other G-protein–dependent hormones (corticotropin, vasopressin) is much less affected.

Serum levels of calcium are low, and those of phosphorus and alkaline phosphatase are elevated. Clinical diagnosis can be confirmed by demonstration of a markedly attenuated response in urinary phosphate and cAMP after intravenous infusion of the synthetic 1-34 fragment of human PTH (teriparatide acetate). Definitive diagnosis is established by demonstration of the mutated G protein.

Type Ia With Precocious Puberty

Two boys have been reported with both type Ia PHP and gonadotropin-independent precocious puberty (see Chapter 578.7). They were found to have a temperature-sensitive mutation of the G_s protein. Thus, at normal body temperature (37°C), the G_s is degraded, resulting in PHP, but in the cooler temperature of the testes (33°C) the G_s mutation results in constitutive activation of the luteinizing hormone receptor and precocious puberty.

Type Ib

Affected patients have normal levels of G protein activity and a normal phenotypic appearance. These patients have tissue-specific resistance to PTH but not to other hormones. Serum levels of calcium, phosphorus, and immunoreactive PTH are the same as those in patients with type Ia PHP. These patients also show no rise in cAMP in response to exogenous administration of PTH. Bioactive PTH is not increased. The pathophysiology of the disorder in this group of patients is caused by paternal uniparental isodisomy of chromosome 20q and resulting *GNAS1* methylation. This, along with the loss of the maternal *GNAS1* gene, leads to PTH resistance in the proximal renal tubules, which leads to impaired mineral ion homeostasis.

Acrodysostosis With Hormone Resistance

Patients with acrodysostosis resemble those with PHP type Ia, but defects in the G_s α subunit are not present. Instead, in 1 subgroup of patients there is a defect in the gene encoding *PRKAR1A* , the cAMP-dependent regulatory subunit of protein kinase A that confers resistance to multiple hormones, including PTH. Another subgroup has a defect in a phosphodiesterase gene *Pde4d* . This subgroup also carries the phenotype of PHP type Ia but rarely exhibits the hormone resistance. *Acroscyphodysplasia is a distinctive form of metaphyseal dysplasia characterized by the distal femoral and proximal tibial epiphyses embedded in cup-shaped, large metaphyses known as metaphyseal scypho or cup deformity and is a phenotypic variation of PHP and acrodysostosis.*

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CHAPTER 591

Hyperparathyroidism

Daniel A. Doyle

Excessive production of parathyroid hormone (PTH) can result from a primary defect of the parathyroid glands such as an **adenoma** or hyperplasia **(primary hyperparathyroidism).**

More often, the increased production of PTH is compensatory, usually aimed at correcting hypocalcemic states of diverse origins **(secondary hyperparathyroidism).** In vitamin D–deficient rickets and the malabsorption syndromes, intestinal absorption of calcium is deficient but hypocalcemia and tetany may be averted by increased activity of the parathyroid glands. In **pseudohypoparathyroidism,** PTH levels are elevated because a mutation in the G_s α protein interferes with response to PTH. Early in chronic renal disease, hyperphosphatemia results in a reciprocal fall in the calcium concentration with a consequent increase in PTH, but in advanced stages of renal failure, production of $1,25(OH)_2 D_3$ is also decreased, leading to worsening hypocalcemia and further stimulation of PTH. In some instances, if stimulation of the parathyroid glands has been sufficiently intense and protracted, the glands continue to secrete increased levels of PTH for months or years after kidney transplantation, with resulting hypercalcemia.

Etiology

Childhood hyperparathyroidism is uncommon. Onset during childhood is usually the result of a single benign **adenoma** . It usually becomes manifested after 10 yr of age. There have been a number of kindreds in which multiple members have hyperparathyroidism transmitted in an autosomal dominant fashion. Most of the affected family members are adults, but children have been involved in approximately 30% of the pedigrees. Some affected patients in these families are asymptomatic, and disease is detected only by careful study. In other kindreds, hyperparathyroidism occurs as part of the constellation known as the **multiple endocrine neoplasia** (MEN) syndromes (see Chapter 587) or of the hyperparathyroidism–jaw tumor syndrome.

Neonatal severe hyperparathyroidism is a rare disorder. Symptoms develop shortly after birth and consist of anorexia, irritability, lethargy, constipation, and failure to thrive. Radiographs reveal subperiosteal bone resorption, osteoporosis, and pathologic fractures. Symptoms may be mild, resolving without treatment, or can have a rapidly fatal course if diagnosis and treatment are delayed. Histologically, the parathyroid glands show diffuse hyperplasia. Affected siblings have been observed in some kindreds, and parental consanguinity has been reported in several kindreds. Most cases have occurred in kindreds with the clinical and biochemical features of **familial hypocalciuric hypercalcemia.** Infants with neonatal severe hyperparathyroidism may be homozygous or heterozygous for the mutation in the Ca^{2+} -sensing receptor gene, whereas most persons with 1 copy of this mutation exhibit autosomal dominant familial hypocalciuric hypercalcemia.

MEN type I (see Chapter 587) is an autosomal dominant disorder characterized by hyperplasia or neoplasia of the endocrine pancreas (which secretes gastrin, insulin, pancreatic polypeptide, and occasionally glucagon), the anterior pituitary (which usually secretes prolactin), and the parathyroid glands. In most kindreds, hyperparathyroidism is usually the presenting manifestation, with a prevalence approaching 100% by 50 yr of age and occurring only rarely in children younger than 18 yr of age. With appropriate DNA probes, it is possible to detect carriers of the gene with 99% accuracy at birth, avoiding unnecessary biochemical screening programs.

The gene for MEN type I is on chromosome 11q13; it appears to function as a tumor-suppressor gene and follows the two-hit hypothesis of tumor development. The first mutation (germinal) is inherited and is recessive to the dominant allele; this does not result in tumor formation. A second mutation (somatic) is required to eliminate the normal allele, which then leads to tumor formation.

Hyperparathyroidism–jaw tumor syndrome is an autosomal dominant disorder characterized by parathyroid adenomas and fibro-osseous jaw tumors. Affected patients can also have polycystic kidney disease, renal hamartomas, and Wilms tumor. Although the condition affects adults primarily, it has been diagnosed as early as age 10 yr.

MEN type II may also be associated with hyperparathyroidism (see Chapter 587).

Transient neonatal hyperparathyroidism has occurred in a few infants born to mothers with hypoparathyroidism (idiopathic or surgical) or with pseudohypoparathyroidism. In each case, the maternal disorder had been undiagnosed or inadequately treated during pregnancy. The cause of the condition is chronic intrauterine exposure to hypocalcemia with resultant hyperplasia of the fetal parathyroid glands. In the newborn, manifestations involve the bones primarily, and healing occurs between 4 and 7 mo of age.

Clinical Manifestations

At all ages, the clinical manifestations of hypercalcemia of any cause include muscle weakness, fatigue, headache, anorexia, abdominal pain, nausea, vomiting, constipation, polydipsia, polyuria, weight loss, and fever. When hypercalcemia is of long duration, calcium may be deposited in the renal parenchyma (nephrocalcinosis), with progressively diminished renal function. Renal calculi can develop and can cause renal colic and hematuria. Osseous changes can produce pain in the back or extremities, disturbances of gait, genu valgum, fractures, and tumors. Height can decrease from compression of vertebrae; the patient can become bedridden. Detection of completely asymptomatic patients is increasing with the advent of automated panel assays that include serum calcium determinations.

Abdominal pain is occasionally prominent and may be associated with acute pancreatitis. Parathyroid crisis can occur, manifested by serum calcium levels >15 mg/dL and progressive oliguria, azotemia, stupor, and coma. In infants, failure to thrive, poor feeding, and hypotonia are common. Cognitive impairment, convulsions, and blindness can occur as sequelae of long-standing hypercalcemia. Psychiatric manifestations include depression, confusion, dementia, stupor, and psychosis.

Laboratory Findings

The serum calcium level is elevated; 39 of 45 children with adenomas had levels >12 mg/dL. The hypercalcemia is more severe in infants with parathyroid hyperplasia; concentrations ranging from 15 to 20 mg/dL are common, and values as high as 30 mg/dL have been reported. Even when the total serum calcium level is borderline or only slightly elevated, ionized calcium levels are often increased. The serum phosphorus level is reduced to approximately 3 mg/dL or less, and the level of serum magnesium is low. The urine can have a low and fixed specific gravity, and serum levels of nonprotein nitrogen and uric acid may be elevated. In patients with adenomas who have skeletal involvement, serum phosphatase levels are elevated, but in infants with hyperplasia the levels of alkaline phosphatase may be normal even when there is extensive involvement of bone.

Serum levels of intact PTH are elevated, especially in relation to the level of calcium. Calcitonin levels are normal. Acute hypercalcemia can stimulate calcitonin release, but with prolonged hypercalcemia, hypercalcitoninemia does not occur.

The most consistent and characteristic radiographic finding is resorption of subperiosteal bone, best seen along the margins of the phalanges of the hands. In the skull, there may be gross trabeculation or a granular appearance resulting from focal rarefaction; the lamina dura may be absent. In more advanced disease, there may be generalized rarefaction, cysts, tumors, fractures, and deformities. Approximately 10% of patients have radiographic signs of rickets. Radiographs of the abdomen can reveal renal calculi or nephrocalcinosis.

Differential Diagnosis

Other causes of hypercalcemia can result in a similar clinical pattern and must be differentiated from hyperparathyroidism (Table 591.1 and Fig. 591.1). A low serum phosphorus level with hypercalcemia is characteristic of primary hyperparathyroidism; elevated levels of PTH are also diagnostic. With hypercalcemia of any cause except hyperparathyroidism and familial hypocalciuric hypercalcemia, PTH levels are suppressed. Pharmacologic doses of corticosteroids lower the serum calcium level to normal in patients with hypercalcemia from other causes but generally do not affect the calcium level in patients with hyperparathyroidism.

Table 591.1

Causes of Hypercalcemia

- I. Neonate/Infant
  - A. Maternal Disorders
    - 1. Excessive vitamin D ingestion, hypoparathyroidism, pseudohypoparathyroidism
  - B. Neonate/Infant
    - 1. Iatrogenic: excessive intake of calcium, vitamin D, vitamin A
    - 2. Phosphate depletion
    - 3. Subcutaneous fat necrosis
    - 4. Williams-Beuren syndrome (del7q11.23/*BAZ1B*) (transient receptor potential; 3-channel defect)
    - 5. Neonatal severe hyperparathyroidism *(CaSR)*
    - 6. Metaphyseal chondrodysplasia, Murk-Jansen type *(PTH1R)*
    - 7. Idiopathic infantile hypercalcemia *(CYP24A1)* (25-hydroxyvitamin D 24-hydroxylase)
    - 8. Persistent parathyroid hormone–related protein
    - 9. Lactase/disaccharidase deficiency *(LCT)*
    - 10. Infantile hypophosphatasia *(TNSALP)*
    - 11. Mucolipidosis type II *(GNPTAB)*
    - 12. Blue diaper syndrome
    - 13. Antenatal Bartter syndrome types 1 and 2 *(SLC12A1, KCNJ1)*
    - 14. Distal renal tubular acidosis
    - 15. IMAGe syndrome *(CDKN1C)*
    - 16. Post bone marrow transplantation for osteopetrosis
    - 17. Endocrinopathies: primary adrenal insufficiency, severe congenital hypothyroidism, hyperthyroidism
- II. Hyperparathyroidism
  - A. Sporadic
    - 1. Parathyroid hyperplasia, adenoma, carcinoma
  - B. Familial
    - 1. Neonatal severe hyperparathyroidism *(CaSR)*
    - 2. Multiple endocrine neoplasia, type I *(MEN1)*
    - 3. Multiple endocrine neoplasia, type IIA *(RET)*
    - 4. Multiple endocrine neoplasia, type IIB *(RET)*
    - 5. Multiple endocrine neoplasia, type IV *(CDKN1B)*
    - 6. McCune-Albright syndrome *(GNAS)*
    - 7. Familial isolated hyperparathyroidism 1 *(CDC73)*
    - 8. Familial isolated hyperparathyroidism 2 (jaw tumor syndrome) *(CDC73)*
    - 9. Familial isolated hyperparathyroidism 3
    - 10. Jansen metaphyseal dysplasia *(PTH1R)*
  - C. Secondary/Tertiary
    - 1. Postrenal transplantation
    - 2. Chronic hyperphosphatemia
  - D. Hypercalcemia of malignancy
    - 1. Ectopic production of parathyroid hormone–related peptide
    - 2. Metastatic dissolution of bone
- III. Familial Hypocalciuric Hypercalcemia
  - A. Familial Hypocalciuric Hypercalcemia I *(CaSR)*
    - 1. Loss-of-function mutations in *CaSR*
      - a. Monoallelic: familial benign hypercalcemia
      - b. Biallelic: neonatal severe hyperparathyroidism
  - B. Familial Hypocalciuric Hypercalcemia II *(GNA11)*
  - C. Familial Hypocalciuric Hypercalcemia III, Oklahoma Variant *(AP2S1)*
  - D. *CaSR* -blocking autoantibodies
- IV. Excessive Calcium or Vitamin D
  - A. Milk-Alkali Syndrome
  - B. Exogenous Ingestion of Calcium or Vitamin D or Topical Application of Vitamin D (calcitriol or analog)
  - C. Ectopic Production of Calcitriol Associated with Granulomatous Diseases (sarcoidosis, cat-scratch fever; tuberculosis, histoplasmosis, coccidioidomycosis, leprosy; human immunodeficiency virus; cytomegalovirus; chronic inflammatory bowel disease)
  - D. Neoplasia

    1. Primary bone tumors
    2. Metastatic tumors with osteolysis
    3. Lymphoma, leukemia
    4. Dysgerminoma
    5. Pheochromocytoma
    6. Tumors secreting parathyroid hormone–related peptide, growth factors, cytokines, prostaglandins, osteoclast-activating factors
  E. Williams-Beuren Syndrome (del7q11.23)
V. Immobilization
VI. Other Causes
  A. Drugs: Thiazides, Lithium, Vitamin A and Analogs, Calcium, Alkali, Antiestrogens, Aminophylline
  B. Total Parenteral Nutrition
  C. Endocrinopathies: Hyperthyroidism, Congenital hypothyroidism, Addison disease, Pheochromocytoma
  D. Vasoactive Intestinal Polypeptide–Secreting Tumor
  E. Acute or Chronic Renal Failure/Administration of Aluminum
  F. Hypophosphatasia
  G. Juvenile Idiopathic Arthritis: Cytokine Mediated

Adapted from Lietman SA, Germain-Lee EL, Levine MA: Hypercalcemia in children and adolescents. *Curr Opin Pediatr* 22:508–515, 2010; Benjamin RW, Moats-Staats BM, Calikoglu A, et al: Hypercalcemia in children. *Pediatr Endocrinol Rev* 5:778–784, 2008; Davies JH: A practical approach to the problems of hypercalcaemia. *Endocr Dev* 16:93–114, 2009.

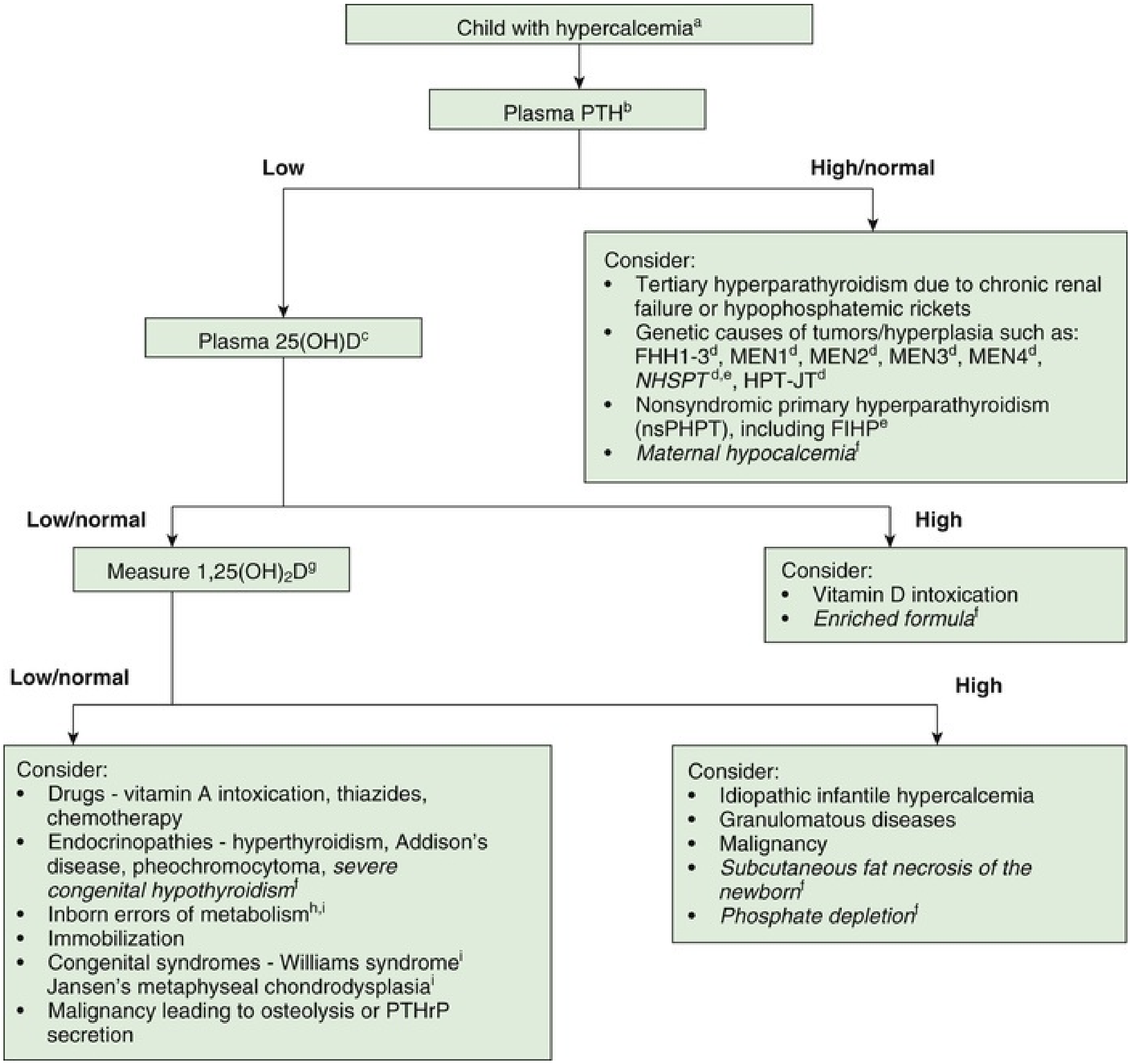
Child with hypercalcemia[a]
Plasma PTH[b]
Low
High/normal
Consider:
• Tertiary hyperparathyroidism due to chronic renal failure or hypophosphatemic rickets
• Genetic causes of tumors/hyperplasia such as: FHH1-3[d], MEN1[d], MEN2[d], MEN3[d], MEN4[d], NHSPT[d,e], HPT-JT[d]
• Nonsyndromic primary hyperparathyroidism (nsPHPT), including FIHP[e]
• Maternal hypocalcemia[f]
Plasma 25(OH)D[c]
Low/normal
High
Measure 1,25(OH)$_2$D[g]
Consider:
• Vitamin D intoxication
• Enriched formula[f]
Low/normal
High
Consider:
• Drugs - vitamin A intoxication, thiazides, chemotherapy
• Endocrinopathies - hyperthyroidism, Addison's disease, pheochromocytoma, severe congenital hypothyroidism[f]
• Inborn errors of metabolism[h,i]
• Immobilization
• Congenital syndromes - Williams syndrome[i] Jansen's metaphyseal chondrodysplasia[i]
• Malignancy leading to osteolysis or PTHrP secretion
Consider:
• Idiopathic infantile hypercalcemia
• Granulomatous diseases
• Malignancy
• Subcutaneous fat necrosis of the newborn[f]
• Phosphate depletion[f]

FIG. 591.1 Clinical approach to investigation of causes of hypercalcemia in a child. [a] Confirm hypercalcemia, defined as plasma (or serum) adjusted calcium >10.5 mg/dL (2.60 mmol/L) or ionized calcium >5.25 mg/dL (1.32 mmol/L). [b] PTH, parathyroid hormone. [c] 25(OH)D, 25-hydroxyvitamin D. [d] FHH1-3, familial hypocalciuric hypercalcemia types 1-3; MEN1, multiple endocrine neoplasia type 1; MEN2, multiple endocrine neoplasia type 2; MEN3, multiple endocrine neoplasia type 3; MEN4, multiple endocrine neoplasia type 4; NSHPT, neonatal severe primary hyperparathyroidism; HPT-JT, hyperparathyroid-jaw tumor syndrome. [e] Familial isolated hyperparathyroidism. [f] Conditions affecting neonates (shown in italics). [g] 1,25(OH)$_2$ D, 1,25-dihydroxyvitamin D. [h] Inborn errors of metabolism, for example, hypophosphatasia, congenital lactase deficiency (CLD), and blue diaper syndrome. [i] These syndromes may be associated with dysmorphic features, for example, Williams syndrome, Jansen's metaphyseal chondrodysplasia, hypophosphatasia. (From Stokes VJ, Nielsen MF, Hannan FM, Thaller RV: Hypercalcemic disorders in children. *J Bone Miner Res* 32(11):2157–2170, 2017, Fig. 2, p. 2160.)

Treatment

Surgical exploration is indicated in all instances. All glands should be carefully inspected; if an adenoma is discovered, it should be removed; very few instances of carcinoma are known in children. Most neonates with severe hypercalcemia require total parathyroidectomy; less-severe hypercalcemia remits spontaneously in others. Still others have been treated successfully with bisphosphonates and calcimimetics. The patient should be carefully observed postoperatively for the development of hypocalcemia and tetany; intravenous administration of calcium gluconate may be required for a few days. The serum calcium level then gradually returns to normal, and, under ordinary circumstances, a diet high in calcium and phosphorus must be maintained for only several months after operation.

CT, real-time ultrasonography, and subtraction scintigraphy using sestamibi/technetium-pertechnetate alone and in combination have proved effective in localizing a single **adenoma** versus diffuse hyperplasia in 50–90% of adults. Parathyroid surgeons often rely on intraoperative selective venous sampling with intraoperative assay of PTH for localizing and removing the source of increased PTH secretion.

Prognosis

The prognosis is good if the disease is recognized early and there is appropriate surgical treatment. When extensive osseous lesions are present, deformities may be permanent. A search for other affected family members is indicated.

591.1

Other Causes of Hypercalcemia

Daniel A. Doyle

Familial Hypocalciuric Hypercalcemia (Familial Benign Hypercalcemia)

Patients with familial hypocalciuric hypercalcemia are usually asymptomatic, and the hypercalcemia is identified by chance during routine investigation for other conditions. The parathyroid glands are normal, PTH levels are inappropriately normal, and subtotal parathyroidectomy does not correct the hypercalcemia. Serum levels of magnesium are high normal or mildly elevated. The ratio of calcium-to-creatinine clearance is usually decreased despite hypercalcemia.

The disorder is inherited in an autosomal dominant manner and is caused by a mutant gene on chromosome 3q2. Penetrance is near 100%, and the disorder can be diagnosed early in childhood by serum and urinary calcium concentrations. Detection of other affected family members is important to avoid inappropriate parathyroid surgery. The defect is an inactivating mutation in the Ca^{2+} -sensing receptor gene. This G-protein–coupled receptor senses the level of free Ca^{2+} in the blood and triggers the pathway to increase extracellular Ca^{2+} in the face of hypocalcemia. This receptor functions in the parathyroid and kidney to regulate calcium homeostasis; inactivating mutations lead to an increased set point with respect to serum Ca^{2+} , resulting in mild to moderate hypercalcemia in heterozygotes.

Granulomatous Diseases

Hypercalcemia occurs in 30–50% of children with sarcoidosis and less often in patients with other granulomatous diseases such as tuberculosis. Levels of PTH are suppressed, and levels of $1,25(OH)_2 D_3$ are elevated. The source of **ectopic $1,25(OH)_2 D_3$** is the activated macrophage, through stimulation by interferon-α from T lymphocytes, which are present in abundance in granulomatous lesions. Unlike renal tubular cells, the 1α-hydroxylase in macrophages is unresponsive to homeostatic regulation. Oral administration of prednisone (2 mg/kg/24 hr) lowers serum levels of $1,25(OH)_2 D_3$ to normal and corrects the hypercalcemia.

Hypercalcemia of Malignancy

Hypercalcemia often occurs in adults with a wide variety of solid tumors but is identified much less often in children. It has been reported in infants with malignant rhabdoid tumors of the kidney or congenital mesoblastic nephroma and in children with neuroblastoma, medulloblastoma, leukemia, Burkitt lymphoma, dysgerminoma, and rhabdomyosarcoma. Serum levels of PTH are rarely elevated. In most patients, the hypercalcemia associated with malignancy is caused by elevated levels of parathyroid hormone–related peptide and not PTH. Rarely, tumors produce $1,25(OH)_2 D_3$ or PTH ectopically.

Miscellaneous Causes of Hypercalcemia

Hypercalcemia can occur in infants with **subcutaneous fat necrosis.** Levels of PTH are normal. In one infant, the level of $1,25(OH)_2 D_3$ was elevated and biopsy of the skin lesion revealed granulomatous infiltration, suggesting that the mechanism of the hypercalcemia was akin to that seen in patients with other granulomatous disease. In another infant, although the level of $1,25(OH)_2 D_3$ was normal, PTH was suppressed, suggesting the hypercalcemia was not related to PTH. Treatment with prednisone is effective.

Hypophosphatasia, especially the severe infantile form, is usually associated with mild to moderate hypercalcemia (see Chapter 724). Serum levels of phosphorus are normal, and those of alkaline phosphatase are subnormal. The bones exhibit rachitic-like lesions on radiographs. Urinary levels of phosphoethanolamine, inorganic pyrophosphate, and pyridoxal 5′-phosphate are elevated; each is a natural substrate to a tissue-nonspecific (liver, bone, kidney) alkaline phosphatase enzyme. Missense mutations of the tissue-nonspecific alkaline phosphatase enzyme gene result in an inactive enzyme in this autosomal recessive disorder.

Idiopathic hypercalcemia of infancy is manifested by failure to thrive and hypercalcemia during the 1st yr of life, followed by spontaneous remission. Serum levels of phosphorus and PTH are normal. The condition has been defined as resulting from increased absorption of calcium from decreased degradation of $1,25(OH)_2 D_3$. Mutations in the *CYP24A1* gene that encodes 25-hydroxyvitamin D 24-hydroxylase, the key enzyme in $1,25(OH)_2 D_3$ degradation, cause excessive levels of the active vitamin D metabolite, which, in turn, causes hypercalcemia in a subset of infants who receive supplemental vitamin D. An excessive rise in the level of $1,25(OH)_2 D_3$ in response to PTH administration has been reported years after the hypercalcemic phase.

Approximately 10% of patients with **Williams syndrome** also inconsistently exhibit associated infantile hypercalcemia. The phenotype consists of feeding difficulties, slow growth, elfin facies (small mandible, prominent maxilla, upturned nose), renovascular disorders, and a gregarious “cocktail party” personality. Cardiac lesions include supravalvular aortic stenosis, peripheral pulmonic stenosis, aortic hypoplasia, coronary artery stenosis, and atrial or ventricular septal defects. **Nephrocalcinosis** can develop if hypercalcemia persists. The IQ score of 50-70 is curiously accompanied by enhanced quantity and quality of vocabulary, auditory memory, and social use of language. A contiguous gene deletion syndrome with a submicroscopic deletion at chromosome 7q11.23, which includes deletion of one elastin allele, occurs in 90% of patients and seems to account for the vascular problems. Definitive diagnosis can be established by specific fluorescence in situ hybridization. The hypercalcemia and central nervous system symptoms may be caused by deletion of adjacent genes. Hypercalcemia has been successfully controlled with either prednisone or calcitonin.

Hypervitaminosis D resulting in hypercalcemia from drinking milk that has been incorrectly fortified with excessive amounts of vitamin D has been reported. Not all patients with hypervitaminosis D develop hypercalcemia. Affected infants can manifest failure to thrive, nephrolithiasis, poor renal function, and osteosclerosis. Serum levels of 25(OH)D are a better indicator of hypervitaminosis D than levels of $1,25(OH)_2\ D_3$ because 25(OH)D has a longer half-life.

Prolonged immobilization can lead to hypercalcemia and occasionally to decreased renal function, hypertension, and encephalopathy. Children who have hypophosphatemic rickets and undergo surgery with subsequent long-term immobilization are at risk for hypercalcemia and should therefore have their vitamin D supplementation decreased or discontinued.

Jansen-type metaphyseal chondrodysplasia is a rare genetic disorder characterized by short-limbed dwarfism and severe but asymptomatic hypercalcemia (see Chapter 714). Circulating levels of PTH and parathyroid hormone–related peptide are undetectable. These patients have an activating PTH–parathyroid hormone–related peptide receptor mutation that results in aberrant calcium homeostasis and abnormalities of the growth plate.

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SECTION 4

Disorders of the Adrenal Gland

OUTLINE

Chapter 592 Physiology of the Adrenal Gland
Chapter 593 Adrenocortical Insufficiency
Chapter 594 Congenital Adrenal Hyperplasia and Related Disorders
Chapter 595 Adrenocortical Tumors and Masses
Chapter 596 Virilizing and Feminizing Adrenal Tumors
Chapter 597 Cushing Syndrome
Chapter 598 Primary Aldosteronism
Chapter 599 Pheochromocytoma

CHAPTER 592

Physiology of the Adrenal Gland

592.1

Histology and Embryology

Perrin C. White

Keywords

zona glomerulosa
zona fasciculata
zona reticularis
aldosterone
mineralocorticoid
cortisol
glucocorticoid
adrenocorticotropic hormone (ACTH)

The adrenal gland is composed of 2 endocrine tissues: the medulla and the cortex. The chromaffin cells of the adrenal medulla are derived from neuroectoderm, whereas the cells of the adrenal cortex are derived from mesoderm. Mesodermal cells also contribute to the development of the gonads. The adrenal glands and gonads have certain common enzymes involved in steroid synthesis; an inborn error in steroidogenesis in 1 tissue can also be present in the other.

The adrenal cortex of the older child or adult consists of 3 zones: the **zona glomerulosa** , the outermost zone located immediately beneath the capsule; the **zona fasciculata** , the middle zone; and the **zona reticularis** , the innermost zone, lying next to the adrenal medulla. The zona fasciculata is the largest zone, constituting approximately 75% of the cortex; the zona glomerulosa constitutes approximately 15% and the zona reticularis approximately 10%. Glomerulosa cells are small, with a lower cytoplasmic:nuclear ratio, an intermediate number of lipid inclusions, and smaller nuclei containing more condensed chromatin than the cells of the other 2 zones. The cells of the zona fasciculata are large, with a high cytoplasmic:nuclear ratio and many lipid inclusions that give the cytoplasm a foamy, vacuolated appearance. The cells are arranged in radial cords. The cells of the zona reticularis are arranged in irregular anastomosing cords. The cytoplasmic:nuclear ratio is intermediate, and the compact cytoplasm has relatively little lipid content.

The zona glomerulosa synthesizes **aldosterone** , the most potent natural **mineralocorticoid** in humans. The zona fasciculata produces **cortisol** , the most potent natural **glucocorticoid** in humans, and the zona fasciculata and zona reticularis synthesize the adrenal androgens.

The adrenal medulla consists mainly of neuroendocrine (chromaffin) cells and glial (sustentacular) cells with some connective tissue and vascular cells. Neuroendocrine cells are polyhedral, with abundant cytoplasm and small, pale-staining nuclei. Under the electron microscope, the cytoplasm contains many large secretory granules that contain catecholamines. Glial cells have less cytoplasm and more basophilic nuclei.

The primordium of the fetal adrenal gland can be recognized at 3-4 wk of gestation just cephalad to the developing mesonephros. At 5-6 wk, the gonadal ridge develops into the steroidogenic cells of the gonads and adrenal cortex; the adrenal and gonadal cells separate, the adrenal cells migrate retroperitoneally, and the gonadal cells migrate caudad. At 6-8 wk of gestation, the gland rapidly enlarges, the cells of the inner cortex differentiate to form the fetal zone, and the outer subcapsular rim remains as the definitive zone. The primordium of the adrenal cortex is invaded at this time by sympathetic neural elements that differentiate into the chromaffin cells capable of synthesizing and storing catecholamines. Catechol *O* -methyltransferase, which converts norepinephrine to epinephrine, is expressed later in gestation. By the end of the 8th wk of gestation, the encapsulated adrenal gland is associated with the upper pole of the kidney. By 8-10 wk of gestation, the cells of the fetal zone are capable of active steroidogenesis.

In the full-term infant, the combined weight of both adrenal glands is 7-9 g. At birth, the inner fetal cortex makes up approximately 80% of the gland and the outer true cortex 20%. Within a few days the fetal cortex begins to involute, undergoing a 50% reduction by 1 mo of age. Conversely, the adrenal medulla is relatively small at birth and undergoes a proportionate increase in size over the first 6 mo after birth. By 1 yr, the adrenal glands each weigh < 1 g. Adrenal growth thereafter results in adult adrenal glands reaching a combined weight of 8 g. The zonae fasciculata and glomerulosa are fully differentiated by about 3 yr of age. The zona reticularis is not fully developed until puberty.

Adrenocorticotropic hormone (ACTH) is essential for fetal adrenal growth and maturation; feedback regulation of ACTH by cortisol is apparently established by 8-10 wk of gestation. Additional factors important in fetal growth and steroidogenesis include placental chorionic gonadotropins and a number of peptide growth factors produced by the placenta and fetus.

Several transcription factors are critical for the development of the adrenal glands. The 3 transcription factors associated with adrenal hypoplasia in humans are steroidogenic factor-1 (*SF-1;* NR5A1), *DAX-1* (dosage-sensitive sex reversal, adrenal hypoplasia congenita, X chromosome; NR0B1), and the *GLI3* oncogene. Disruption of *SF-1* , encoded on chromosome 9q33, results in gonadal and often adrenal agenesis, absence of pituitary gonadotropes, and an underdeveloped ventral medial hypothalamus. In-frame deletions and frameshift and missense mutations of this gene are associated with 46,XX ovarian insufficiency and 46,XY gonadal dysgenesis. Mutations in the *DAX1* gene, encoded on Xp21, result in adrenal hypoplasia congenita and hypogonadotropic hypogonadism (see Chapter 593.1). Mutations in *GLI3* on chromosome 7p13 cause Pallister-Hall syndrome, other features of which include hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly.

The postnatal adrenal cortex is not static but, in fact, is continually regenerated from a population of stem or progenitor cells under the adrenal capsule. These cells move radially inward (i.e., centripetally) and can differentiate into zona glomerulosa or fasciculata cells as needed in response to the appropriate trophic stimuli (see Chapter 592.3). Several signaling pathways, including sonic hedgehog and Wnt, regulate this process. Sonic hedgehog expression is restricted to the peripheral cortical cells that do not express high levels of steroidogenic genes but give rise to the underlying differentiated cells of the cortex. Wnt/β-catenin signaling maintains the undifferentiated state and adrenal fate of adrenocortical stem/progenitor cells, in part through induction of its target genes *DAX1* and inhibin-α, respectively. Adrenal tumors can result from constitutive activation of the Wnt signaling pathway (see Chapter 597).

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592.2

Adrenal Steroid Biosynthesis

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Keywords

Cholesterol
scavenger receptor class B

type I (SR-BI)
steroidogenic acute regulatory (StAR)
cholesterol side-chain cleavage enzyme
cytochrome P450
3β-hydroxysteroid dehydrogenase
steroid 21-hydroxylase
P450 oxidoreductase
deoxycorticosterone
aldosterone synthase
17α-hydroxylase
17-hydroxyprogesterone
steroid 11β-hydroxylase
11β-hydroxysteroid dehydrogenase type 2

Cholesterol is the starting substrate for all steroid biosynthesis (Fig. 592.1). Although adrenal cortex cells can synthesize cholesterol de novo from acetate, circulating plasma lipoproteins provide most of the cholesterol for adrenal cortex hormone formation. Receptors for both low-density lipoprotein and high-density lipoprotein cholesterol are expressed on the surface of adrenocortical cells; the receptor for high-density lipoprotein is termed **scavenger receptor class B, type I (SR-BI)** . Patients with homozygous familial hypercholesterolemia who lack low-density lipoprotein receptors have only mildly impaired adrenal steroidogenesis, suggesting that high-density lipoprotein is the more important source of cholesterol. Cholesterol is stored as cholesteryl esters in vesicles and subsequently hydrolyzed by cholesteryl ester hydrolases to liberate free cholesterol for steroid hormone synthesis.

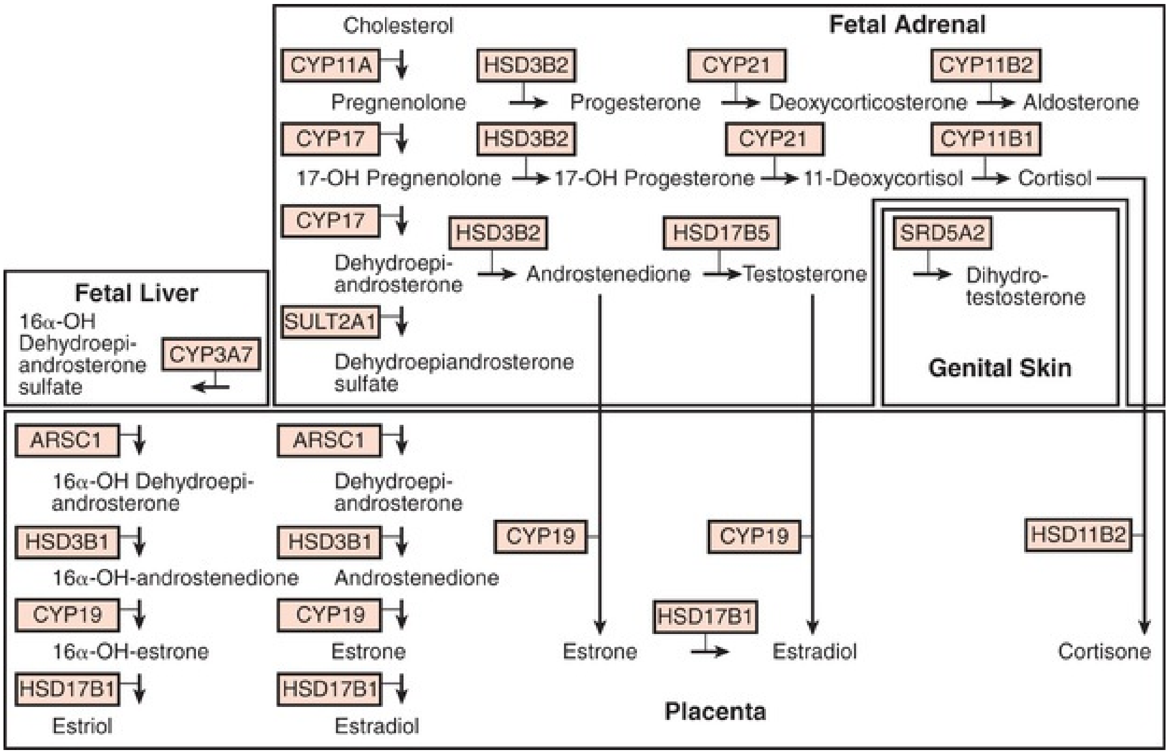
Cholesterol
Fetal Adrenal
CYP11A
HSD3B2
CYP21
CYP11B2
Pregnenolone
Progesterone
Deoxycorticosterone
Aldosterone
CYP17
HSD3B2
CYP21
CYP11B1
17-OH Pregnenolone
17-OH Progesterone
11-Deoxycortisol
Cortisol
CYP17
HSD3B2
HSD17B5
SRD5A2
Dehydroepi-androsterone
Androstenedione
Testosterone
Dihydro-testosterone
Fetal Liver
16α-OH Dehydroepi-androsterone sulfate
CYP3A7
SULT2A1
Dehydroepiandrosterone sulfate
Genital Skin
ARSC1
ARSC1
16α-OH Dehydroepi-androsterone
Dehydroepi-androsterone
HSD3B1
HSD3B1
CYP19
CYP19
HSD11B2
16α-OH-androstenedione
Androstenedione
CYP19
CYP19
HSD17B1
16α-OH-estrone
Estrone
Estrone
Estradiol
Cortisone
HSD17B1
HSD17B1
Estriol
Estradiol
Placenta

FIG. 592.1 Steroid biosynthesis and metabolism during gestation. Conversions within the fetal adrenal cortex, fetal liver, male (i.e., testosterone-exposed) genital skin, and placenta are denoted by *arrows;* the enzyme mediating each conversion is also shown. Enzymatic conversions in the adrenal cortex are the same postnatally as prenatally, but cortisol and aldosterone biosynthesis are more prominent, and normally little testosterone is synthesized. Many of the involved enzymes are cytochromes P450 (CYPs). Adrenal enzymes include CYP11A, cholesterol side-chain cleavage enzyme (P450scc in older terminology); HSD3B2, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 2; CYP 17, 17β-hydroxylase/17,20-lyase (P450c17); CYP21, 21-hydroxylase (P450c21); CYP11B1, 11β-hydroxylase (P450c11); CYP11B2, aldosterone synthase (P450aldo; this enzyme mediates successive 11β-hydroxylase, 18-hydroxylase, and 18-oxidase reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone). Other enzymes important in the fetoplacental unit include ARSC1, arylsulfatase; CYP19, aromatase (P450arom); HSD3B1, 3β-hydroxysteroid dehydrogenase/ Δ5,Δ4 isomerase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; HSD17B1 and HSD17B5 are 2 different 17-hydroxysteroid dehydrogenase enzymes; SRD5A2, steroid 5α-reductase type 2; SULT2A1, steroid sulfotransferase.

The rate-limiting step of adrenal steroidogenesis is importation of cholesterol across the mitochondrial outer and inner membrane. This requires several proteins, particularly the **steroidogenic acute regulatory (StAR)** protein. The StAR protein has a very short half-life, and its synthesis is rapidly induced by trophic factors (corticotropin); thus, it is the main short-term (minutes to hours) regulator of steroid hormone biosynthesis.

At the mitochondrial inner membrane, the side chain of cholesterol is cleaved to yield pregnenolone. This is catalyzed by the **cholesterol side-chain cleavage enzyme** (cholesterol desmolase, side-chain cleavage enzyme, P450scc, CYP11A1; the last term is the current systematic nomenclature), **a cytochrome P450** (CYP) enzyme. Like other P450s, this is a membrane-bound hemoprotein with a molecular mass of approximately 50 kDa. It accepts electrons from a reduced nicotinamide adenine dinucleotide phosphate–dependent mitochondrial electron transport system consisting of 2 accessory proteins, adrenodoxin reductase (a flavoprotein) and adrenodoxin (a small protein containing nonheme iron). P450 enzymes use electrons and O_2 to hydroxylate the substrate and form H_2O. In the case of cholesterol side-chain cleavage, 3 successive oxidative reactions are performed to cleave the C20,22 carbon bond. Pregnenolone then diffuses out of mitochondria and enters the endoplasmic reticulum. The subsequent reactions that occur depend on the zone of the adrenal cortex.

Zona Glomerulosa

In the zona glomerulosa, pregnenolone is converted to progesterone by **3 β-hydroxysteroid dehydrogenase** type 2, an oxidized nicotinamide adenine dinucleotide-dependent enzyme of the short-chain dehydrogenase type. Progesterone is converted to 11-deoxycorticosterone by **steroid 21-hydroxylase** (P450c21, CYP21), which is another P450. Like other P450s in the endoplasmic reticulum, it uses an electron transport system with only 1 accessory protein, **P450 oxidoreductase** .

Deoxycorticosterone then reenters mitochondria and is converted to aldosterone by **aldosterone synthase** (P450aldo, CYP11B2), a P450 enzyme structurally related to cholesterol desmolase. Aldosterone synthase also carries out 3 successive oxidations: 11β-hydroxylation, 18-hydroxylation, and further oxidation of the 18-methyl carbon to an aldehyde.

Zona Fasciculata

In the endoplasmic reticulum of the zona fasciculata, pregnenolone and progesterone are converted by **17α-hydroxylase** (P450c17, CYP17) to 17-hydroxypregenolone and **17-hydroxyprogesterone,** respectively. This enzyme is not expressed in the zona glomerulosa, which consequently cannot synthesize 17-hydroxylated steroids. 17-hydroxypregnenolone is converted to 17-hydroxyprogesterone and 11-deoxycortisol by the same 3β-hydroxysteroid and 21-hydroxylase enzymes, respectively, as are active in the zona glomerulosa. Thus, inherited disorders in these enzymes affect both aldosterone and cortisol synthesis (see Chapter 594). Finally, 11-deoxycortisol reenters mitochondria and is converted to cortisol by **steroid 11β-hydroxylase** (P450c11, CYP11B1). This enzyme is closely related to aldosterone synthase but has low 18-hydroxylase and nonexistent 18-oxidase activity. Thus, under normal circumstances the zona fasciculata cannot synthesize aldosterone.

Zona Reticularis

In the zona reticularis and to some extent in the zona fasciculata, the 17-hydroxylase (CYP17) enzyme has an additional activity, cleavage of the 17,20 carbon–carbon bond. This converts 17-hydroxypregnenolone to dehydroepiandrosterone (DHEA). DHEA is converted to androstenedione by HSD3B. This may be further converted in other tissues to testosterone and estrogens.

Fetoplacental Unit

Steroid synthesis in the fetal adrenal varies during gestation (see Figs. 592.1 and 592.2). Shortly after the fetal adrenal gland forms (wk 8-10), it efficiently secretes cortisol, which is able to negatively feed back on the fetal pituitary and hypothalamus to suppress ACTH secretion. This is a critical time for differentiation of the external genitalia in both sexes (see Chapter 594.1); to prevent virilization, the female fetus must not be exposed to high levels of androgens of adrenal origin, and placental aromatase activity must remain low during this time to minimize conversion of testosterone to estradiol in male fetuses, which would interfere with masculinization. After wk 12, HSD3B activity in the fetal adrenal gland decreases and steroid sulfokinase activity increases. Thus, the major steroid products of the midgestation fetal adrenal gland are DHEA and DHEA sulfate (DHEAS) and, by 16α-hydroxylation in the liver, 16α-hydroxy DHEAS. Aromatase activity increases in the placenta at the same time, and steroid sulfatase activity is high as well. Thus, the placenta uses

DHEA and DHEAS as substrates for estrone and estradiol and 16α-OH DHEAS as a substrate for estriol. Cortisol activity is low during the 2nd trimester, which might serve to prevent premature secretion of surfactant by the developing fetal lungs; surfactant levels can affect the timing of parturition. As term approaches, fetal cortisol concentration increases as a result of increased cortisol secretion and decreased conversion of cortisol to cortisone by **11β-hydroxysteroid dehydrogenase type 2** (HSD11B2). Low levels of aldosterone are produced in midgestation, but aldosterone secretory capacity increases near term.

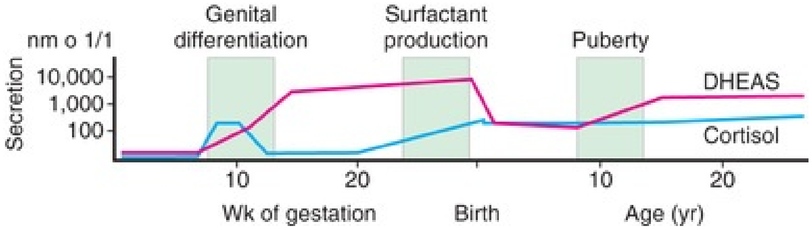

FIG. 592.2 Relative levels of cortisol and dehydroepiandrosterone sulfate secretion by the fetal adrenal cortex during gestation as well as postnatally. Approximate times of several events are shown. Vertical axis is logarithmic, but values are approximate. Horizontal axis is not to scale.

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592.3

Regulation of the Adrenal Cortex

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Keywords

proopiomelanocortin
arginine vasopressin
adenylate cyclase
cyclic adenosine monophosphate
familial glucocorticoid deficiency
renin–angiotensin system
renin
angiotensin-converting enzyme
angiotensin II
inositol triphosphate
diacylglycerol
protein kinase C
adrenarche

Regulation of Cortisol Secretion

Glucocorticoid secretion is regulated mainly by ACTH (corticotropin), a 39-amino-acid peptide that is produced in the anterior pituitary (see Fig. 572.2). It is synthesized as part of a larger-molecular-weight precursor peptide known as **proopiomelanocortin** . This precursor peptide is also the source of β-lipotropin. ACTH and β-lipotropin are cleaved further to yield α- and β-melanocyte–

stimulating hormone, corticotropin-like intermediate lobe peptide, γ-lipotropin, β- and γ-endorphin, and enkephalin (see Chapter 572).

ACTH is released in secretory bursts of varying amplitude throughout the day and night. The normal diurnal rhythm of cortisol secretion is caused by the varying amplitudes of ACTH pulses. Pulses of ACTH and cortisol occur every 30-120 min, are highest at about the time of waking, are low in late afternoon and evening, and reach their lowest point 1 or 2 hr after sleep begins.

Corticotropin-releasing hormone (CRH), synthesized by neurons of the parvicellular division of the hypothalamic paraventricular nucleus, is the most important stimulator of ACTH secretion. **Arginine vasopressin** (AVP) augments CRH action. Neural stimuli from the brain cause the release of CRH and AVP (see Chapter 572). AVP and CRH are secreted in the hypophyseal-portal circulation in a pulsatile manner. This pulsatile secretion appears to be responsible for the pulsatile (ultradian) release of ACTH. The circadian rhythm of corticotropin release is probably induced by a corresponding circadian rhythm of hypothalamic CRH secretion, regulated by the suprachiasmatic nucleus with input from other areas of the brain. Cortisol exerts a negative feedback effect on the synthesis and secretion of ACTH, CRH, and AVP. ACTH inhibits its own secretion, a feedback effect mediated at the level of the hypothalamus. Thus, the secretion of cortisol is a result of the interaction of the hypothalamus, pituitary, and adrenal glands and other neural stimuli.

ACTH acts through a specific G-protein–coupled receptor (also termed melanocortin receptor-2, encoded by the *MCR2* gene) to activate **adenylate cyclase** and increase levels of **cyclic adenosine monophosphate.** Cyclic adenosine monophosphate has short-term (minutes to hours) effects on cholesterol transport into mitochondria by increasing expression of StAR protein. The long-term effects (hours to days) of ACTH stimulation are to increase the uptake of cholesterol and the expression of genes encoding the enzymes required to synthesize cortisol. These transcriptional effects occur at least in part through increased activity of protein kinase A, which phosphorylates several transcriptional regulatory factors. MC2R trafficking and signaling are dependent on the MC2R accessory protein (MRAP). Mutations in either MC2R or MRAP can cause **familial glucocorticoid deficiency** (see Chapter 593).

Regulation of Aldosterone Secretion

The rate of aldosterone synthesis, which is normally 100- to 1,000-fold less than that of cortisol synthesis, is regulated mainly by **the renin–angiotensin system** and by potassium levels, with ACTH having only a short-term effect. In response to decreased intravascular volume, renin is secreted by the juxtaglomerular apparatus of the kidney. **Renin** is a proteolytic enzyme that cleaves angiotensinogen (renin substrate), an α_2 -globulin produced by the liver, to yield the inactive decapeptide angiotensin I. **Angiotensin-converting enzyme** in the lungs and other tissues rapidly cleaves angiotensin I to the biologically active octapeptide **angiotensin II.** Cleavage of angiotensin II produces the heptapeptide angiotensin III. Angiotensins II and III are potent stimulators of aldosterone secretion; angiotensin II is a more potent vasopressor agent. Angiotensins II and III occupy a G-protein–coupled receptor activating phospholipase C. This protein hydrolyzes phosphatidylinositol bisphosphate to produce **inositol triphosphate** and **diacylglycerol,** which raise intracellular calcium levels and activate **protein kinase C** and calmodulin-activated kinases. Similarly, increased levels of extracellular potassium depolarize the cell membrane and increase calcium influx through voltage-gated L-type calcium channels. Phosphorylation of transcriptional regulatory factors by calmodulin-activated kinases increases transcription of the aldosterone synthase (CYP11B2) enzyme required for aldosterone synthesis.

Regulation of Adrenal Androgen Secretion

The mechanisms by which the adrenal androgens DHEA and androstenedione are regulated are not completely understood. **Adrenarche** is a maturational process in the adrenal gland that results in increased adrenal androgen secretion between the ages of 5 and 20 yr. The process begins before the earliest signs of puberty and continues throughout the years when puberty is occurring. Histologically, it is associated with the appearance of the zona reticularis. Whereas ACTH stimulates adrenal androgen production acutely and clearly is the primary stimulus for cortisol release, additional factors have been implicated in the stimulation of the adrenal androgens. These include a relative decrease in expression of HSD3B2 in the zona reticularis and possibly increases in 17,20-lyase activity owing to phosphorylation of CYP17 or increased cytochrome b5 expression.

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592.4

Adrenal Steroid Hormone Actions

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Keywords

gluconeogenesis
epinephrine

norepinephrine
hypercalcemia
osteoporosis
psychosis
weight loss
hypotension
hyponatremia
hyperkalemia
serum and glucocorticoid-regulated kinase
apparent mineralocorticoid excess syndrome
dihydrotestosterone
estrone
estradiol
congenital adrenal hyperplasia
premature adrenarche
adrenal tumors
Cushing syndrome
prednisone, prednisolone
dexamethasone

Steroid hormones act through several distinct receptors corresponding to the known biologic activities of the steroid hormones: glucocorticoid, mineralocorticoid, progestin, estrogen, and androgen. These receptors belong to a larger superfamily of nuclear transcription factors that include, among others, thyroid hormone and retinoic acid receptors. They have a common structure that includes a carboxyterminal ligand-binding domain and a midregion DNA-binding domain. The latter domain contains 2 zinc fingers, each of which consists of a loop of amino acids stabilized by 4 cysteine residues chelating a zinc ion.

Unliganded glucocorticoid and mineralocorticoid receptors are found mainly in the cytosol in complexes with other proteins. Hormone molecules diffuse through the cell membrane and bind receptors, changing their conformation and causing them to release their cytosolic binding proteins and translocate to the nucleus, where they bind DNA at specific hormone-response elements. Bound receptors can recruit other transcriptional coregulatory factors to DNA.

Whereas different steroids can share bioactivities because of their ability to bind to the same receptor, a given steroid can exert diverse biologic effects in different tissues. The diversity of hormonal responses is determined by the different genes that are regulated by each hormone in different tissues. Additionally, different combinations of coregulators are expressed in different tissues, allowing each steroid hormone to have many different effects. Moreover, enzymes can increase or decrease the affinity of steroids for their receptors and thus modulate their activity. 11β-Hydroxysteroid dehydrogenase type 1 (HSD11B1) converts cortisone, which is not a ligand for the glucocorticoid receptor, to cortisol, which is an active glucocorticoid. This increases local glucocorticoid concentrations in several tissues, especially the liver, where glucocorticoids maintain hepatic glucose output (see Chapter 593.4). Overexpression of this enzyme in adipose tissue can predispose to development of obesity. Conversely, HSD11B2 oxidizes cortisol to cortisone, particularly in the kidney, preventing mineralocorticoid receptors from being occupied by high levels of cortisol (see Chapter 593.4).

Although corticosteroid receptors mainly act in the nucleus, some responses to both glucocorticoids and mineralocorticoids begin within minutes, an interval too short to be accounted for by increased gene transcription and protein synthesis. Such nongenomic effects can in some cases be mediated by cell membrane–associated isoforms of the classic glucocorticoid and mineralocorticoid receptors, which can couple to a variety of rapid intracellular signaling pathways such as G proteins. Direct interactions with other proteins, such as ion channels, have been documented as well, particularly in the nervous system.

Actions of Glucocorticoids

Glucocorticoids are essential for survival. The term *glucocorticoid* refers to the glucose-regulating properties of these hormones. However, glucocorticoids have multiple effects on carbohydrate, lipid, and protein metabolism. They also regulate immune, circulatory, and renal function. They influence growth, development, bone metabolism, and central nervous system activity.

In stress situations, glucocorticoid secretion can increase up to 10-fold. This increase is believed to enhance survival through increased cardiac contractility, cardiac output, sensitivity to the pressor effects of catecholamines and other pressor hormones, work capacity of the skeletal muscles, and capacity to mobilize energy stores.

Metabolic Effects

The primary action of the glucocorticoids on carbohydrate metabolism is to increase glucose production by increasing hepatic **gluconeogenesis** . Glucocorticoids also increase cellular resistance to insulin, thereby decreasing entry of glucose into the cell. This inhibition of glucose uptake occurs in adipocytes, muscle cells, and fibroblasts. In addition to opposing insulin action, glucocorticoids can work in parallel with insulin to protect against long-term starvation by stimulating glycogen deposition and production in liver. Both hormones stimulate glycogen synthetase activity and decrease glycogen breakdown. Glucocorticoid excess can cause hyperglycemia, and glucocorticoid deficiency can cause hypoglycemia.

Glucocorticoids increase free fatty acid levels by enhancing lipolysis, decreasing cellular glucose uptake, and decreasing glycerol production, which is necessary for reesterification of fatty acids. This increase in lipolysis is also stimulated through the permissive enhancement of lipolytic action of other factors such as epinephrine. This action affects adipocytes differently according to their anatomic locations. In the patient with glucocorticoid excess, fat is lost in the extremities but it is increased in the trunk (centripetal obesity), neck, and face (moon facies). This may involve effects on adipocyte differentiation.

Glucocorticoids generally exert a catabolic or antianabolic effect on protein metabolism. Proteolysis in fat, skeletal muscle, bone, lymphoid, and connective tissue increases amino acid substrates that can be used in gluconeogenesis. Cardiac muscle and the diaphragm are almost entirely spared from this catabolic effect.

Circulatory and Renal Effects

Glucocorticoids have a positive inotropic influence on the heart, increasing the left ventricular work index. Moreover, they have a permissive effect on the actions of **epinephrine** and **norepinephrine** on both the heart and the blood vessels. In the absence of glucocorticoids, decreased cardiac output and shock can develop; in states of glucocorticoid excess, hypertension is often observed. This may be a result of activation of the mineralocorticoid receptor (see Chapter 593.4), which occurs when renal HSD11B2 is saturated by excessive levels of glucocorticoids.

Growth

In excess, glucocorticoids inhibit linear growth and skeletal maturation in children, apparently through direct effects on the epiphyses. However, glucocorticoids are also necessary for normal growth and development. In the fetus and neonate, they accelerate the differentiation and development of various tissues, including the hepatic and gastrointestinal systems, as well as the production of surfactant in the fetal lung. Glucocorticoids are often given to pregnant women at risk for delivery of premature infants in an effort to accelerate these maturational processes.

Immunologic Effects

Glucocorticoids play a major role in immune regulation. They inhibit synthesis of glycolipids and prostaglandin precursors and the actions of bradykinin. They also block secretion and actions of histamine and proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, and interleukin-6), thus diminishing inflammation. High doses of glucocorticoids deplete monocytes, eosinophils, and lymphocytes, especially T cells. They do so at least in part by inducing cell-cycle arrest in the G_1 phase and by activating apoptosis through glucocorticoid receptor–mediated effects. The effects on lymphocytes are primarily exerted on T-helper 1 cells and hence on cellular immunity, whereas the T-helper 2 cells are spared, leading to a predominantly humoral immune response. Pharmacologic doses of glucocorticoids can also decrease the size of immunologic tissues (spleen, thymus, and lymph nodes).

Glucocorticoids increase circulating polymorphonuclear cell counts, mostly by preventing their egress from the circulation. Glucocorticoids decrease diapedesis, chemotaxis, and phagocytosis of polymorphonuclear cells. Thus, the mobility of these cells is altered such that they do not arrive at the site of inflammation to mount an appropriate immune response. High levels of glucocorticoids decrease inflammatory and cellular immune responses and increase susceptibility to certain bacterial, viral, fungal, and parasitic infections.

Effects on Skin, Bone, and Calcium

Glucocorticoids inhibit fibroblasts, leading to increased bruising and poor wound healing through cutaneous atrophy. This effect explains the thinning of the skin and striae that are seen in patients with Cushing syndrome.

Glucocorticoids have the overall effect of decreasing serum calcium and have been used in emergency therapy for certain types of **hypercalcemia** . This hypocalcemic effect probably results from a decrease in the intestinal absorption of calcium and a decrease in the renal reabsorption of calcium and phosphorus. Serum calcium levels, however, generally do not fall below normal because of a secondary increase in parathyroid hormone secretion.

The most significant effect of long-term glucocorticoid excess on calcium and bone metabolism is **osteoporosis.** Glucocorticoids inhibit osteoblastic activity by decreasing the number and activity of osteoblasts. Glucocorticoids also decrease osteoclastic activity but to a lesser extent, leading to low bone turnover with an overall negative balance. The tendency of glucocorticoids to lower serum calcium and phosphate levels causes secondary hyperparathyroidism. These actions decrease bone accretion and cause a net loss of bone mineral.

Central Nervous System Effects

Glucocorticoids readily penetrate the blood–brain barrier and have direct effects on brain metabolism. They decrease certain types of central nervous system edema and are often used to treat increased intracranial pressure. They stimulate appetite and cause insomnia with a reduction in rapid eye movement sleep. There is an increase in irritability and emotional lability, with an impairment of memory and ability to concentrate. Mild to moderate glucocorticoid excess for a limited period often causes a feeling of euphoria or well-being, but glucocorticoid excess and deficiency can both be associated with clinical depression. Glucocorticoid excess produces **psychosis** in some patients.

Glucocorticoid effects in the brain are mediated largely through interactions with both the mineralocorticoid and glucocorticoid receptors (sometimes referred to in this context as type I and type II corticosteroid receptors, respectively). Activation of type II receptors increases sensitivity of hippocampal neurons to the neurotransmitter serotonin, which might help explain the euphoria associated with high doses of glucocorticoids. Glucocorticoids suppress release of CRH in the anterior hypothalamus, but they stimulate it in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, where it can mediate fear and anxiety states. Glucocorticoids and other steroids might have nongenomic effects by modulating activities of both γ-aminobutyric acid and *N* -methyl-ᴅ -aspartate receptors.

Actions of Mineralocorticoids

The most important mineralocorticoids are aldosterone and, to a lesser degree, 11-deoxycorticosterone; corticosterone and cortisol are normally not important as mineralocorticoids unless secreted in excess. Mineralocorticoids have more limited actions than glucocorticoids. Their major function is to maintain intravascular volume by conserving sodium and eliminating potassium and hydrogen ions. They exert these actions in the kidney, gut, and salivary and sweat glands. Aldosterone can have distinct effects in other tissues. Mineralocorticoid receptors are found in the heart and vascular endothelium, and aldosterone increases myocardial fibrosis in heart failure.

Mineralocorticoids have their most important actions in the distal convoluted tubules and cortical collecting ducts of the kidney, where they induce reabsorption of sodium and secretion of potassium. In the medullary collecting duct, they act in a permissive fashion to allow vasopressin to increase osmotic water flux. Thus, patients with mineralocorticoid deficiency can develop **weight loss** , **hypotension** , **hyponatremia** , and **hyperkalemia** , whereas patients with mineralocorticoid excess can develop hypertension, hypokalemia, and metabolic alkalosis (see Chapters 593-596).

The mechanisms by which aldosterone affects sodium excretion are incompletely understood. Most effects of aldosterone are presumably due to changes in gene expression mediated by the mineralocorticoid receptor, and indeed levels of subunits of both the Na^+ , K^+ -adenosine triphosphatase and the epithelial sodium channel increase in response to aldosterone. Additionally, aldosterone increases expression of the **serum and glucocorticoid-regulated kinase** , which indirectly reduces turnover of epithelial sodium channel subunits and thus increases the number of open sodium channels.

The mineralocorticoid receptor has similar affinities in vitro for cortisol and aldosterone, yet cortisol is a weak mineralocorticoid in vivo. This discrepancy results from the action of HSD11B2, which converts cortisol to cortisone. Cortisone is not a ligand for the receptor, whereas aldosterone is not a substrate for the enzyme. Pharmacologic inhibition (as occurs with excessive consumption of licorice) or genetic deficiency of this enzyme allows cortisol to occupy renal mineralocorticoid receptors and produce sodium retention and hypertension; the genetic condition is termed **apparent mineralocorticoid excess syndrome** .

Actions of the Adrenal Androgens

Many actions of adrenal androgens are exerted through their conversion to active androgens or estrogens such as **testosterone** , **dihydrotestosterone** , **estrone** , and **estradiol** . In males, <2% of the biologically important androgens are derived from adrenal production, whereas in females approximately 50% of androgens are of adrenal origin. The adrenal contribution to circulating estrogen levels is mainly important in pathologic conditions such as feminizing adrenal tumors. Adrenal androgens contribute to the physiologic development of pubic and axillary hair during normal puberty. They also play an important role in the pathophysiology of **congenital adrenal hyperplasia** , **premature adrenarche** , **adrenal tumors,** and **Cushing syndrome** (see Chapters 594 , 595 , and 597).

In humans, circulating levels of DHEA and DHEAS, the chief adrenal androgens, reach a peak in early adulthood and then decline. This has led to speculation that some age-related physiologic changes might be reversed by DHEA administration, and beneficial effects have been suggested (but not proved) on insulin sensitivity, bone mineral density, muscle mass, cardiovascular risk, obesity, cancer risk, autoimmunity, and the central nervous system.

Synthetic Corticosteroids

Many synthetic analogs of cortisone and hydrocortisone are available. **Prednisone** and **prednisolone** are derivatives with an additional double bond in ring A. Similar to cortisone, prednisone is not an active steroid but it is converted to prednisolone by HSD11B1 in the liver. Prednisone and prednisolone are 4-5 times as potent in antiinflammatory and carbohydrate activity but have slightly less effect on retention of water and sodium than cortisol. Halogenated derivatives have different effects. Betamethasone and **dexamethasone** have 25-40 times the glucocorticoid potency of cortisol but have little mineralocorticoid effect. These analogs are usually used in pharmacologic doses for their antiinflammatory or immunosuppressive properties. The antiinflammatory activity of fludrocortisone is about 15 times that of hydrocortisone, but fludrocortisone is more than 125 times as active a mineralocorticoid; it is used to treat aldosterone deficiency.

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592.5

Adrenal Medulla

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Keywords

catecholamines
dopamine
norepinephrine
epinephrine
chromaffin tissue
metanephrine
normetanephrine
pheochromocytomas

The principal hormones of the adrenal medulla are the physiologically active **catecholamines** : **dopamine, norepinephrine, and epinephrine** (Fig. 592.3). Catecholamine synthesis also occurs in the brain, in sympathetic nerve endings, and in **chromaffin tissue** outside the adrenal medulla. Metabolites of catecholamines are excreted in the urine, principally 3-methoxy-4-hydroxymandelic acid, **metanephrine** , and **normetanephrine** . Urinary metanephrines and catecholamines are measured to detect **pheochromocytomas** of the adrenal medulla and sympathetic nervous system (see Chapter 598).

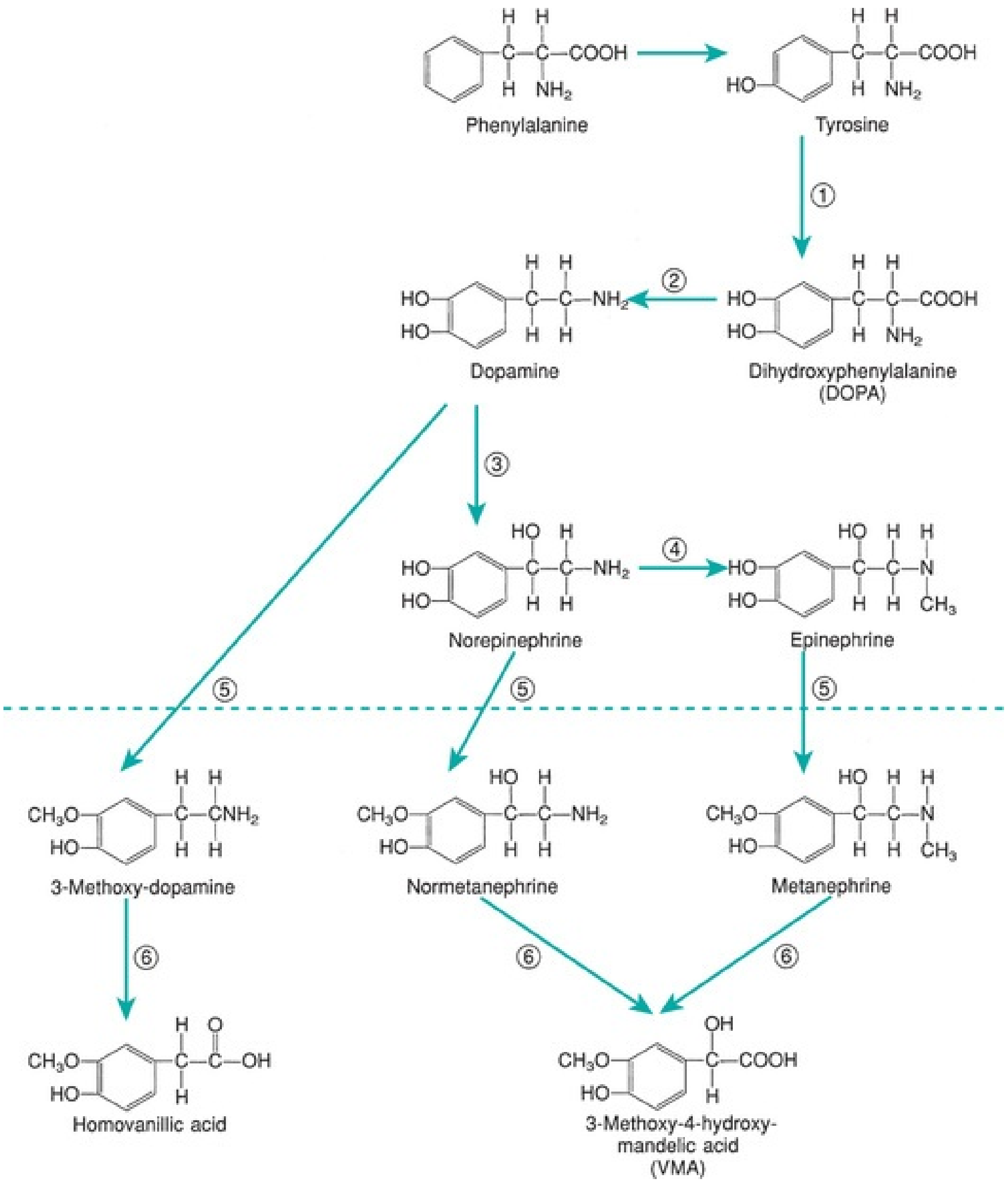
Phenylalanine
Tyrosine
①
②
Dopamine
Dihydroxyphenylalanine (DOPA)
③
④
Norepinephrine
Epinephrine
⑤
⑤
⑤
3-Methoxy-dopamine
Normetanephrine
Metanephrine
⑥
⑥
⑥
Homovanillic acid
3-Methoxy-4-hydroxy-mandelic acid (VMA)

FIG. 592.3 Biosynthesis (above *dashed line*) and metabolism (below *dashed line*) of the catecholamines norepinephrine and epinephrine. Enzymes: *1,* tyrosine hydroxylase; *2,* dopa decarboxylase; *3,* dopamine β-oxidase; *4,* phenylethanolamine-*N* -methyltransferase; *5,* catechol *O* -methyltransferase; *6,* monoamine oxidase.

The proportions of epinephrine and norepinephrine in the adrenal gland vary with age. In early fetal stages, there is practically no epinephrine; at birth, norepinephrine remains predominant. However in adults, norepinephrine accounts for only 10–30% of the pressor amines in the medulla.

The effects of catecholamines are mediated through a series of G-protein–coupled adrenergic receptors. Both epinephrine and norepinephrine raise the mean arterial blood pressure, but only epinephrine increases cardiac output. By increasing peripheral vascular resistance, norepinephrine increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate and, by decreasing the peripheral vascular resistance, decreases the diastolic pressure. The hyperglycemic and calorigenic effects of norepinephrine are much less pronounced than are those of epinephrine.

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CHAPTER 593

Adrenocortical Insufficiency

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In primary adrenal insufficiency, congenital or acquired lesions of the adrenal cortex prevent production of cortisol and often aldosterone (Table 593.1). Acquired primary adrenal insufficiency is termed **Addison disease** . Dysfunction of the anterior pituitary gland or hypothalamus can cause a deficiency of corticotropin (adrenocorticotropic hormone [ACTH]) and lead to hypofunction of the adrenal cortex, termed *secondary adrenal insufficiency;* the term *tertiary adrenal insufficiency* is sometimes used to denote cases arising from hypothalamic dysfunction (Table 593.2).

Table 593.1

Causes of Primary Adrenal Insufficiency

	PATHOGENESIS OR GENETICS	CLINICAL FEATURES IN ADDITION TO ADRENAL INSUFFICIENCY
CONGENITAL ADRENAL HYPERPLASIA		
21-Hydroxylase deficiency	*CYP21A2* mutations	Hyperandrogenism
11β-Hydroxylase deficiency	*CYP11B1* mutations	Hyperandrogenism, hypertension
3β-Hydroxysteroid dehydrogenase type 2 deficiency	*HSD3B2* mutations	Ambiguous genitalia in males, postnatal virilization in females
17α-Hydroxylase deficiency	*CYP17A1* mutations	XY sex reversal, pubertal delay in both sexes, hypertension
P450 oxidoreductase deficiency	*POR* mutations	Skeletal malformation (Antley-Bixler syndrome), abnormal genitalia
P450 side-chain cleavage deficiency	*CYP11A1* mutations	XY sex reversal
Congenital lipoid adrenal hyperplasia	*STAR* mutations	XY sex reversal
OTHER GENETIC DISORDERS		
Adrenoleukodystrophy	*ABCD1* mutations	Weakness, spasticity, dementia, blindness,

or adrenomyeloneuropathy		quadriparesis. Adrenomyeloneuropathy is a milder variant of adrenoleukodystrophy with slower progression
Triple A syndrome (Allgrove syndrome)	*AAAS* mutations	Achalasia, alacrima, cognitive deficits, neuromuscular deficits, hyperkeratosis
Smith-Lemli-Opitz syndrome	*DHCR7* mutations	Craniofacial malformations, developmental delay growth failure, cholesterol deficiency
Wolman disease	*LIPA* mutations	Bilateral adrenal calcification, hepatosplenomegaly
Kearns-Sayre syndrome	Mitochondrial DNA deletions	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrine disorders
Pallister-Hall syndrome	*GLI3* mutations	hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly
IMAGe syndrome	*CDKN1C* or POLE mutations	Intrauterine growth retardation, metaphyseal dysplasia, genital abnormalities
Adrenal Hypoplasia Congenita		
X-linked	*NR0B1* mutations	Hypogonadotropic hypogonadism in males
Xp21 contiguous gene syndrome	Deletion of genes for Duchenne muscular dystrophy, glycerol kinase, and *NR0B1*	Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation
SF-1 linked	*NR5A1* mutations	XY sex reversal
Familial Glucocorticoid Deficiency or Corticotropin Insensitivity Syndromes		
Type 1	*MC2R* mutations	Tall stature, characteristic facial features, such as hypertelorism and frontal bossing
Type 2	*MRAP* mutations	
Variant of familial glucocorticoid deficiency	*MCM4* mutations	Growth failure, increased chromosomal breakage, natural killer cell deficiency
Variant of familial glucocorticoid deficiency	*NNT* mutations	
AUTOIMMUNE		
Isolated	Sporadic; associations with *HLA-DR3-DQ2, HLA-DR4-DQ8, MICA, CTLA4, PTPN22, CIITA, CLEC16A*	None
APS type 1 (APECED)	*AIRE* mutations	Chronic mucocutaneous candidosis, hypoparathyroidism, other autoimmune diseases
APS type 2	Sporadic; associations with *HLA-DR3, HLA-DR4, CTLA4*	Thyroid autoimmune disease, type 1 diabetes, other autoimmune diseases
APS type 4	Sporadic; associations with *HLA-DR3, CTLA4*	Other autoimmune diseases (autoimmune gastritis, vitiligo, coeliac disease, alopecia), excluding thyroid disease and type 1 diabetes
INFECTIOUS		
Tuberculous adrenalitis	Tuberculosis	Tuberculosis-associated manifestations in other organs
AIDS	HIV-1	Other AIDS-associated diseases
Fungal adrenalitis	Histoplasmosis, cryptococcosis, coccidioidomycosis	Opportunistic infections
Meningococcal sepsis (Waterhouse-Friderichsen syndrome)	*Neisseria meningitidis*	

African trypanosomiasis	*Trypanosoma brucei*	Other trypanosomiasis-associated organ involvement
OTHER ACQUIRED CAUSES		
Bilateral adrenal hemorrhage	Meningococcal sepsis (Waterhouse-Friderichsen syndrome), primary antiphospholipid syndrome, traumatic birth, anticoagulation	Symptoms and signs of underlying disease
Bilateral adrenal metastases	Mainly cancers of the lung, stomach, breast, and colon	Symptoms and signs of underlying disease
Bilateral adrenal infiltration	Primary adrenal lymphoma, amyloidosis, hemochromatosis, sarcoidosis (rare)	Symptoms and signs of underlying disease
Bilateral adrenalectomy		Symptoms and signs of underlying disease
DRUG INDUCED		
Mitotane (o,p-DDD)	Cytotoxicity	None, unless related to drug
Aminoglutethimide	Inhibition of cholesterol side chain cleavage enzyme (CYP11A1)	None, unless related to drug
Trilostane	Inhibition of 3β-hydroxysteroid dehydrogenase type 2	None, unless related to drug
Etomidate	Inhibition of 11β-hydroxylase (CYP11B1)	None, unless related to drug
Ketoconazole, fluconazole	Inhibition of mitochondrial cytochrome P450 enzymes (e.g., CYP11A1, CYP11B1)	None, unless related to drug

AAAS , Achalasia, adrenocortical insufficiency, alacrima syndrome; *ABCD* , ATP-binding cassette, subfamily D; *ABCG5* , ATP-binding cassette, subfamily G, member 5; *ABCG8* , ATP-binding cassette, subfamily G, member 8; *APECED* , autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; *APS* , autoimmune polyendocrinopathy syndrome; *CIITA* , class II transactivator; *CTLA-4* , cytotoxic T-lymphocyte antigen 4; *DHCR7* , 7-dehydrocholesterol reductase; *HLA* , human leukocyte antigen; *IMAGe* , *i*ntrauterine growth restriction (IUGR), *m*etaphyseal dysplasia, *a*drenal hypoplasia congenita (AHC), and *ge*nitourinary abnormalities; *LIPA* , lipase A; *MC2R* , melanocortin 2 receptor; *MCM4* , minichromosome maintenance complex component 4; *MICA* , major histocompatibility complex class I chain-related gene A; *MRAP* , melanocortin 2 receptor accessory protein; *PTPN22* , protein tyrosine phosphatase, nonreceptor type 22; *StAR* , steroidogenic acute regulatory protein.

Adapted from Charmandari E, Nicolaides NC, Chrousos GP: Adrenal insufficiency, *Lancet* 383:2152–2164, 2014, Table 1, pp. 2153–2154.

Table 593.2

Causes of Secondary Adrenal Insufficiency

ETIOLOGIES		CLINICAL MANIFESTATIONS IN ADDITION TO ADRENAL INSUFFICIENCY
DRUG INDUCED		
Abrupt cessation of glucocorticoid therapy (systemic or	Suppression of CRH and ACTH secretion leading to atrophy of the adrenal cortex	Primary disease-associated symptoms

topical)		
OTHER ACQUIRED CAUSES		
Hypothalamic or pituitary tumors	Adenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, rarely carcinomas, metastasis	Panhypopituitarism[*] ; primary disease-associated symptoms
Traumatic brain injury		Panhypopituitarism[*] ; primary disease-associated symptoms
Hypothalamic or pituitary surgery or irradiation		Panhypopituitarism[*] ; primary disease-associated symptoms
Infections or infiltrative processes	Lymphocytic hypophysitis, hemochromatosis, tuberculosis, meningitis, sarcoidosis, actinomycosis, histiocytosis X, Wegener granulomatosis	Panhypopituitarism[*] ; primary disease-associated symptoms
Pituitary apoplexy (when occurring in a peripartum mother, termed Sheehan syndrome)	High blood loss or hypotension	Abrupt onset of severe headache, visual disturbance, nausea, vomiting; panhypopituitarism[*] ; primary disease-associated symptoms
CONGENITAL OR GENETIC CAUSES		
Abnormal Central Nervous System Development		
Anencephaly	Multiple	Primary disease-associated symptoms
Holoprosencephaly	Multiple	Primary disease-associated symptoms
Combined Pituitary Hormone Deficiency (CPHD) [†]		
CPHD2	Mutations in *PROP1* (paired-like homeobox 1)	Panhypopituitarism; corticotropin deficiency occurs in adolescence
CPHD3	Mutations in *LHX3* (LIM homeobox 3)	Panhypopituitarism; deafness, short neck
CPHD4	Mutations in *LHX4* (LIM homeobox 4)	Panhypopituitarism; small sella, cerebellar defects
Septo-optic dysplasia, CPHD5	Mutations in *HESX1* (HESX homeobox 1)	Panhypopituitarism; septo-optic dysplasia (blindness owing to hypoplastic optic nerves, absence of the septum pellucidum); developmental delay
CPHD6	Mutations in *OTX2* (orthodenticle homeobox 2)	Panhypopituitarism; ectopic posterior pituitary gland
X-linked panhypopituitarism	Mutations in *SOX3* (SRY [sex-determining region Y] box 3)	Panhypopituitarism; infundibular hypoplasia, developmental delay
Other Genetic Syndromes Affecting Corticotropin Secretion		
Congenital proopiomelanocortin deficiency	Mutations in *POMC* (proopiomelanocortin)	Early-onset severe obesity, hyperphagia, red hair
Prohormone convertase 1/3 deficiency	Mutations in *PC1* (prohormone convertase 1/3)	Obesity, malabsorption or diarrhea, hypogonadotropic hypogonadism
Isolated ACTH (corticotropin) deficiency	Mutations in *TBX19* (T-box 19)	
Prader-Willi syndrome	Deletion or silencing of genes on the parental copy of genes within the imprinted chromosome region 15q11-q13 including *SNRPN* (small nuclear ribonucleoprotein polypeptide N) and *NDN* (necdin, melanoma antigen	Dysmorphic features, hypotonia, developmental delay, obesity, growth hormone deficiency, hypogonadotropic hypogonadism

	[MAGE] family member)	

[*] The associated anterior and/or posterior hormone deficiencies may vary.

[†] CPHD1 (mutations in *POUF1*) is not associated with corticotropin deficiency.

593.1

Primary Adrenal Insufficiency

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Keywords

adrenoleukodystrophy
Cryptorchidism
contiguous gene deletion
Pallister-Hall syndrome
very-long-chain fatty acids
peroxisomes
Zellweger (cerebrohepatorenal) syndrome
Familial glucocorticoid deficiency
melanocyte receptor accessory protein
achalasia
alacrima (triple A or Allgrove syndrome)
Type I autoimmune polyendocrinopathy (APS-1)
Chronic mucocutaneous candidiasis
hypoparathyroidism
familial hypercholesterolemia
Smith-Lemli-Opitz syndrome
Wolman disease
antiadrenal cytoplasmic antibodies
Type II autoimmune polyendocrinopathy (APS-2)

Waterhouse-Friderichsen syndrome
Ketoconazole
Etomidate
adrenal crisis
Hyperpigmentation
Hyponatremia
Hyperkalemia
cosyntropin

Primary adrenal insufficiency in children is most frequently caused by genetic conditions that are often but not always manifested in infancy and less often by acquired problems such as autoimmune conditions (Table 593.3). Susceptibility to autoimmune conditions often has a genetic basis, and so these distinctions are not absolute.

Table 593.3

Frequencies of Etiologies of Primary Adrenal Insufficiency

ETIOLOGY	%	AGE AT DIAGNOSIS
Congenital adrenal hyperplasia	59	Infancy
Autoimmune	16	Childhood-adolescence
APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)	6	Childhood-adolescence
Adrenoleukodystrophy	4	Childhood-adolescence
Isolated glucocorticoid deficiency	4	Infancy
Idiopathic	4	Childhood
Syndromes	3	Infancy
X-linked adrenal hypoplasia congenita	2	Infancy-childhood
Hemorrhage	1	Infancy

Data from Perry R, Kecha O, Paquette J, et al: Primary adrenal insufficiency in children: twenty years' experience at the Sainte-Justine Hospital, Montreal, *J Clin Endocrinol Metab* 90:3243–3250, 2005; Hsieh S, White PC: Presentation of primary adrenal insufficiency in childhood, *J Clin Endocrinol Metab* 96:E925–E928, 2011.

Inherited Etiologies

Inborn Defects of Steroidogenesis

The most common causes of adrenocortical insufficiency in infancy are the salt-losing forms of congenital adrenal hyperplasia (see Chapter 594). Approximately 75% of infants with 21-hydroxylase deficiency, almost all infants with lipoid adrenal hyperplasia, and most infants with a deficiency of 3β-hydroxysteroid dehydrogenase manifest salt-losing symptoms in the newborn period because they are unable to synthesize either cortisol or aldosterone.

Adrenal Hypoplasia Congenita

Adrenal hypoplasia congenita (AHC) is a relatively frequent cause of adrenal failure in males, along with congenital adrenal hyperplasia, autoimmune disease, and adrenoleukodystrophy (ALD). The name of the disorder notwithstanding, AHC is predominantly a failure of development of the definitive zone of the adrenal cortex; the fetal zone may be relatively normal. Consequently, adrenal insufficiency generally becomes evident as the fetal zone involutes postnatally (see Chapter 592), with onset in infancy or in the first 2 yr of life but occasionally in later childhood or even adulthood. In some cases, aldosterone deficiency becomes evident before cortisol deficiency.

The disorder is caused by mutation of the *DAX1 (NR0B1)* gene, a member of the nuclear hormone receptor family, located on Xp21. Males with AHC often do not undergo puberty, owing to hypogonadotropic hypogonadism caused by the same mutated *DAX1* gene. **Cryptorchidism,** sometimes noted in these males, is probably an early manifestation of hypogonadotropic hypogonadism, but often testicular function in infants is normal, with a typical or even an unusually prolonged testosterone surge in the 1st mo of life.

AHC occasionally occurs as part of a *contiguous gene deletion* syndrome together with Duchenne muscular dystrophy, glycerol kinase deficiency, cognitive impairment, or a combination of these conditions.

Other Genetic Causes of Adrenal Hypoplasia

The transcription factor SF-1 is required for adrenal and gonadal development (see Chapter 592). Males with a heterozygous mutation in SF-1 *(NR5A1)* have impaired development of the testes despite the presence of a normal copy of the gene on the other chromosome and can appear to be female, similar to patients with lipoid adrenal hyperplasia (see Chapter 594). Rarely, such patients also have adrenal insufficiency.

Adrenal hypoplasia is also occasionally seen in patients with **Pallister-Hall syndrome** caused by mutations in the GLI3 oncogene.

Adrenoleukodystrophy

In ALD, adrenocortical deficiency is associated with demyelination in the central nervous system (see Chapters 104.2 and 617.3). High levels of **very-long-chain fatty acids** are found in tissues and body fluids, resulting from their impaired β-oxidation in the peroxisomes.

The most common form of ALD is an X-linked disorder with various presentations. The most common clinical picture is of a degenerative neurologic disorder appearing in childhood or adolescence and progressing to severe dementia and deterioration of vision, hearing, speech, and gait, with death occurring within a few years. Neurologic symptoms may be subtle at onset, sometimes consisting only of behavioral changes or deteriorating academic performance. Generalized but incomplete alopecia, resembling that of chemotherapy, is a characteristic but inconsistent finding. A milder form of X-linked ALD is adrenomyeloneuropathy, which begins in later adolescence or early adulthood. Patients may have evidence of adrenal insufficiency before, at the time of, or after neurologic symptoms develop, often with years separating their presentation. X-linked ALD is caused by mutations in the *ABCD1* gene located on Xq28. The gene encodes a transmembrane transporter involved in the importation of very-long-chain fatty acids into **peroxisomes** . More than 400 mutations have been described in patients with X-linked ALD. Clinical phenotypes can vary even within families, perhaps owing to modifier genes or other unknown factors. There is no correlation between the degree of neurologic impairment and severity of adrenal insufficiency. Prenatal diagnosis by DNA analysis and family screening by very-long-chain fatty acid assays and mutation analysis are available. Women who are heterozygous carriers of the X-linked ALD gene can develop symptoms in midlife or later; adrenal insufficiency is rare.

Neonatal ALD is a rare autosomal recessive disorder. Infants have neurologic deterioration and have or acquire evidence of adrenocortical dysfunction. Most patients have severe, progressive cognitive impairment and die before 5 yr of age. This disorder is a subset of **Zellweger (cerebrohepatorenal) syndrome** , in which peroxisomes do not develop at all owing to mutations in any of several genes (*PEX5, PEX1, PEX10, PEX13,* and *PEX26*) controlling the development of this organelle.

Familial Glucocorticoid Deficiency

Familial glucocorticoid deficiency is a form of chronic adrenal insufficiency characterized by isolated deficiency of glucocorticoids, elevated levels of ACTH, and generally normal aldosterone production, although salt-losing manifestations as are present in most other forms of adrenal insufficiency occasionally occur. Patients mainly have hypoglycemia, seizures, and increased pigmentation during the 1st decade of life. The disorder affects both sexes equally and is inherited in an autosomal recessive manner. There is marked adrenocortical atrophy with relative sparing of the zona glomerulosa. Mutations in the gene for the ACTH receptor *(MCR2)* have been described in approximately 25% of these patients, most of which affect trafficking of receptor molecules from the endoplasmic reticulum to the cell surface. Another 20% of cases are caused by mutations in *MRAP,* which encodes a **melanocyte receptor accessory protein** required for this trafficking. Mutations at new genetic loci have been identified, including the minichromosome maintenance-deficient 4 homolog *(MCM4)* and nicotinamide nucleotide transhydrogenase *(NNT).* These genes are involved in DNA replication and antioxidant defense, respectively. Patients with *MCM4* mutations also have growth failure, increased chromosomal breakage, and natural killer cell deficiency.

Another syndrome of ACTH resistance occurs in association with **achalasia** of the gastric cardia and **alacrima (triple A** or **Allgrove syndrome).** These patients often have a progressive neurologic disorder that includes autonomic dysfunction, intellectual disability, motor neuropathy, and occasional deafness. This syndrome is also inherited in an autosomal recessive fashion, and the *AAAS* gene has been mapped to chromosome 12q13. The encoded protein, aladin, might help to regulate nucleocytoplasmic transport of other proteins.

Type I Autoimmune Polyendocrinopathy Syndrome

Although autoimmune Addison disease most often occurs sporadically (see section on “Autoimmune Addison Disease ” in this chapter), it can occur as a component of 2 syndromes, each consisting of a constellation of autoimmune disorders (see Chapter 582). **Type I autoimmune polyendocrinopathy syndrome (APS-1),** also known as *autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy* (APECED) syndrome, is inherited in a mendelian autosomal recessive manner, whereas APS-2 (see section on “Autoimmune Addison Disease ” in this chapter) has complex inheritance.

Chronic mucocutaneous candidiasis is most often the first manifestation of APS-1, followed by **hypoparathyroidism** and then by Addison disease, which typically develops in early adolescence. Other closely associated autoimmune disorders include gonadal failure, alopecia, vitiligo, keratopathy, enamel hypoplasia, nail dystrophy, intestinal malabsorption, and chronic active hepatitis. Hypothyroidism and type 1 diabetes mellitus occur in less than 10% of affected patients. Some components of the syndrome continue to develop as late as the 5th decade. Patients with APS-1 may have autoantibodies to the adrenal cytochrome P450 enzymes CYP21, CYP17, and CYP11A1. The presence of such antibodies indicates a high likelihood of the development of Addison disease or, in female patients, ovarian failure. Adrenal failure can evolve rapidly in APS-1; death in patients with a previous diagnosis and unexplained deaths in siblings of patients with APS-1 have been reported, indicating the need to closely monitor patients with APS-1 (or any child with hypoparathyroidism of unknown etiology) and to thoroughly evaluate apparently unaffected siblings of patients with this disorder.

The gene affected in APS-1 is designated autoimmune regulator-1 *(AIRE1);* it has been mapped to chromosome 21q22.3. The *AIRE1* gene encodes a transcription factor that controls the expression of many proteins within the thymus, thus playing a critical role in the generation of immune tolerance. Many different mutations in the *AIRE1* gene have been described in patients with APS-1, with 2 mutations (*R257X* and a 3-bp deletion) being most common. There has been autosomal dominant transmission in 1 kindred owing to a specific missense mutation (G228W).

Disorders of Cholesterol Synthesis and Metabolism

Patients with disorders of cholesterol synthesis or metabolism, including abetalipoproteinemia with deficient lipoprotein B–containing lipoproteins (such as low-density lipoprotein), and homozygous **familial hypercholesterolemia** , with impaired or absent low-density lipoprotein receptors, have mildly impaired adrenocortical function. Heterozygous familial hypercholesterolemia patients have normal adrenocortical function which is unaffected by treatment with statin (HMG-CoA reductase inhibitor) drugs. Adrenal insufficiency has been reported in patients with **Smith-Lemli-Opitz syndrome** , an autosomal recessive disorder manifesting with facial anomalies, microcephaly, limb anomalies, and developmental delay (see Chapter 104.3). Mutations in the gene coding for sterol Δ^7 -reductase, mapped to 11q12-q13, resulting in impairment of the final step in cholesterol synthesis with marked elevation of 7-dehydrocholesterol, abnormally low cholesterol, and adrenal insufficiency, have been identified in Smith-Lemli-Opitz syndrome. **Wolman disease** is a rare autosomal recessive disorder caused by mutations in the gene encoding human lysosomal acid lipase on chromosome 10q23.2-23.3. Cholesteryl esters accumulate in lysosomes in most organ systems, leading to organ failure. Infants during the 1st or 2nd mo of life have hepatosplenomegaly, steatorrhea, abdominal distention, and failure to thrive. Adrenal insufficiency and bilateral adrenal calcification are present, and death usually occurs in the 1st yr of life.

Corticosteroid-Binding Globulin Deficiency and Decreased Cortisol-Binding Affinity

Corticosteroid-binding globulin deficiency and decreased cortisol-binding affinity result in low levels of plasma cortisol but normal urinary free cortisol and normal plasma ACTH levels. A high prevalence of hypotension and fatigue has been reported in some adults with abnormalities of corticosteroid-binding globulin deficiency.

Acquired Etiologies

Autoimmune Addison Disease

The most common cause of Addison disease is autoimmune destruction of the glands. The glands may be so small that they are not visible at autopsy, and only remnants of tissue are found in microscopic sections. Usually, the medulla is not destroyed, and there is marked lymphocytic infiltration in the area of the former cortex. In advanced disease, all adrenocortical function is lost, but early in the clinical course, isolated cortisol deficiency can occur. Most patients have **antiadrenal cytoplasmic antibodies** in their plasma; 21-hydroxylase (CYP21) is the most commonly occurring biochemically defined autoantigen.

Addison disease can occur as a component of 2 autoimmune polyendocrinopathy syndromes. Type I (APS-1) was discussed previously. **Type II autoimmune polyendocrinopathy (APS-2)** consists of Addison disease associated with autoimmune thyroid disease (Schmidt syndrome) or type 1 diabetes (Carpenter syndrome). Gonadal failure, vitiligo, alopecia, and chronic atrophic gastritis, with or without pernicious anemia, can occur. Frequencies of the human leukocyte antigen (HLA)-D3 and HLA-D4 alleles are increased in these patients and appear to confer an increased risk for development of this disease; particular alleles at the major histocompatibility complex class I chain–related genes A and B *(MICA* and *MICB)* also are associated with this disorder. Polymorphisms in genes involved in other autoimmune disorders have been inconsistently associated with primary adrenal insufficiency, and their contribution to its pathogenesis must be regarded as uncertain. These include the class II, major histocompatibility complex, transactivator *(CIITA),* C-type lectin domain family 16, member A (*CLEC16A*), and protein tyrosine phosphatase, nonreceptor type 22 *(PTPN22).* The disorder is most common in middle-aged women and can occur in many generations of the same family. Antiadrenal antibodies, specifically antibodies to the CYP21, CYP17, and CYP11A1 enzymes, are also found in these patients. Autoimmune adrenal insufficiency may also be seen in patients with celiac disease and mitochondrial gene mutations.

Infection

Tuberculosis was a common cause of adrenal destruction in the past but is currently much less prevalent. The most common infectious etiology for adrenal insufficiency is meningococcemia (see Chapter 218); adrenal crisis from this cause is referred to as the **Waterhouse-Friderichsen syndrome.** Patients with AIDS can have a variety of subclinical abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, but frank adrenal insufficiency is rare. However, drugs used in the treatment of AIDS can affect adrenal hormone homeostasis.

Drugs

Ketoconazole , an antifungal drug, can cause adrenal insufficiency by inhibiting adrenal enzymes. Mitotane (o,p′-DDD), used in the treatment of adrenocortical carcinoma and refractory Cushing syndrome (see Chapters 595 and 597), is cytotoxic to the adrenal cortex and can also alter extraadrenal cortisol metabolism. Signs of adrenal insufficiency occur in a substantial percentage of patients treated with mitotane. **Etomidate** , used in the induction and maintenance of general anesthesia, inhibits 11β-hydroxylase (CYP11B1), and a single induction dose can block cortisol synthesis for 4-8 hr or longer. This may be problematic in severely stressed patients, particularly if repeated doses are used in a critical care setting. Abiraterone acetate, an androgen biosynthesis inhibitor which is used to treat metastatic prostate carcinoma, inhibits cortisol biosynthesis but leaves corticosterone biosynthesis unimpaired. This drug is not currently encountered in pediatric practice. Although not themselves a cause of adrenal insufficiency, rifampicin and anticonvulsive drugs such as phenytoin and phenobarbital reduce the effectiveness and bioavailability of corticosteroid replacement therapy by inducing steroid metabolizing enzymes in the liver.

Hemorrhage Into Adrenal Glands

Hemorrhage into adrenal glands can occur in the neonatal period as a consequence of a difficult labor (especially breech presentation), or its etiology might not be apparent (Fig. 593.1). An incidence rate of 3 in 100,000 live births has been suggested. The hemorrhage may be sufficiently extensive to result in death from exsanguination or hypoadrenalism. An abdominal mass, anemia, unexplained jaundice, or scrotal hematoma may be the presenting sign. Often, the hemorrhage is asymptomatic initially and is identified later by calcification of the adrenal gland. Fetal adrenal hemorrhage has also been reported. Postnatally, adrenal hemorrhage most often occurs in patients being treated with anticoagulants. It can also occur as a result of child abuse.

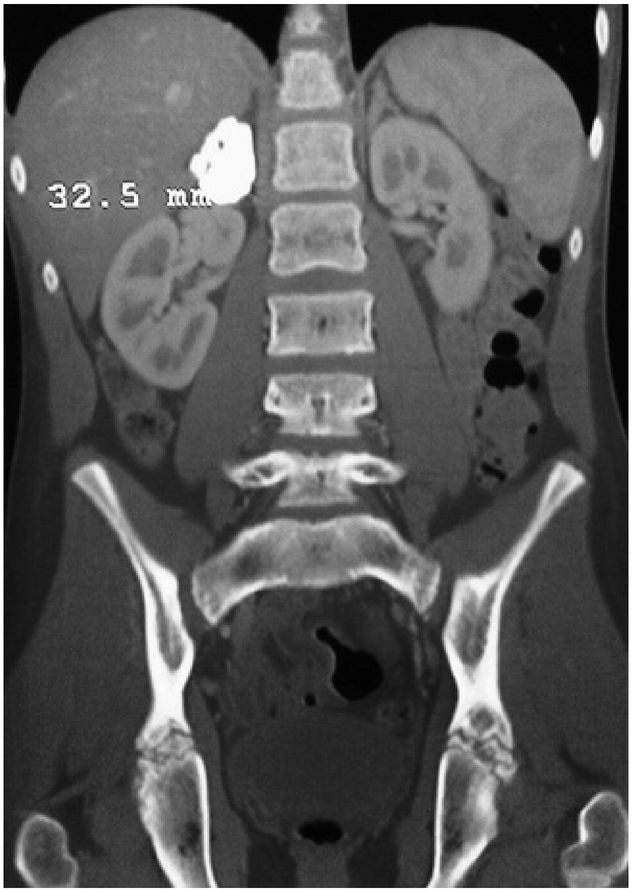

FIG. 593.1 Coronal plane of contrast-enhanced computed tomography confirming intraadrenal localization of a round hyperdense lesion compatible with a large calcification. (From Llano JP, Beaufils E, Nicolino M: Uncommon cause of large paravertebral calcification in a child, *J Pediatr* 162:881, 2013, Fig. 2.)

Clinical Manifestations

Primary adrenal insufficiency leads to cortisol and often aldosterone deficiency. The signs and symptoms of adrenal insufficiency are most easily understood in the context of the normal actions of these hormones (see Chapter 592 ; Table 593.4).

Table 593.4

Clinical Manifestations and Biochemical Findings in Adrenal Insufficiency

	PREVALENCE

	PATHOPHYSIOLOGIC MECHANISM	**(%)***
SYMPTOMS		
Fatigue	Glucocorticoid deficiency	90
Anorexia, weight loss	Glucocorticoid deficiency	90
Nausea, vomiting	Glucocorticoid deficiency, mineralocorticoid deficiency	90
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency	20
Myalgia or joint pain	Glucocorticoid deficiency	
SIGNS		
Low blood pressure, orthostatic hypotension	Mineralocorticoid deficiency, glucocorticoid deficiency	70–100
Skin or mucosal hyperpigmentation (primary adrenal insufficiency only)	Excess of proopiomelanocortin-derived peptides	70
LABORATORY FINDINGS		
Hyponatremia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to decreased free water excretion)	90
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency	50
Hypoglycemia	Glucocorticoid deficiency	30
Ketosis	Glucocorticoid deficiency	30
Low random cortisol level	Glucocorticoid deficiency	80
Eosinophilia, lymphocytosis	Glucocorticoid deficiency	
High ACTH level (primary adrenal insufficiency only)	Glucocorticoid deficiency	100
High plasma renin activity (primary adrenal insufficiency only)	Mineralocorticoid deficiency	100

* Prevalence data are for primary insufficiency only. Blanks indicate that no pediatric prevalence data are available.

Data from Hsieh S, White PC: Presentation of primary adrenal insufficiency in childhood, *J Clin Endocrinol Metab* 96:E925–E928, 2011.

Cortisol deficiency decreases cardiac output and vascular tone; moreover, catecholamines such as epinephrine have decreased inotropic and pressor effects in the absence of cortisol. These problems are initially manifested as orthostatic hypotension in older children and can progress to frank shock in patients of any age. They are exacerbated by aldosterone deficiency, which results in hypovolemia owing to decreased resorption of sodium in the distal nephron.

Hypotension and decreased cardiac output decrease glomerular filtration and thus decrease the ability of the kidney to excrete free water. Vasopressin (AVP) is secreted by the posterior pituitary in response to hypotension and also as a direct consequence of lack of inhibition by cortisol. These factors decrease plasma osmolality and lead in particular to hyponatremia. Hyponatremia is also caused by aldosterone deficiency and may be much worse when both cortisol and aldosterone are deficient.

In addition to hypovolemia and hyponatremia, aldosterone deficiency causes hyperkalemia by decreasing potassium excretion in the distal nephron. Cortisol deficiency alone does not cause hyperkalemia.

Cortisol deficiency decreases negative feedback on the hypothalamus and pituitary, leading to increased secretion of ACTH. Hyperpigmentation is caused by ACTH and other peptide hormones (γ-melanocyte–stimulating hormone) arising from the ACTH precursor proopiomelanocortin. In patients with a fair complexion, the skin can have a bronze cast. Pigmentation may be more prominent in skin creases, mucosa, and scars. In dark-skinned patients, it may be most readily appreciated in the gingival and buccal mucosa.

Hypoglycemia is a feature of adrenal insufficiency. It is often accompanied by ketosis as the body attempts to use fatty acids as an alternative energy source. Ketosis is aggravated by anorexia, nausea, and vomiting, all of which occur frequently.

The clinical presentation of adrenal insufficiency depends on the age of the patient, whether both cortisol and aldosterone secretion are affected, and to some extent on the underlying etiology. The most common causes in early infancy are inborn errors of steroid biosynthesis, sepsis, AHC, and adrenal hemorrhage. Infants have a relatively greater requirement for aldosterone than do older children, possibly owing to immaturity of the kidney and also to the low sodium content of human breast milk and infant formula. Hyperkalemia, hyponatremia, and hypoglycemia are prominent presenting signs of adrenal insufficiency in infants. Ketosis is not consistently present because infants generate ketones less well than do older children. Hyperpigmentation is not usually seen because this takes weeks or months to develop, and orthostatic hypotension is obviously difficult to demonstrate in infants.

Infants can become ill very quickly. There may be only a few days of decreased activity, anorexia, and vomiting before critical electrolyte abnormalities develop.

In older children with Addison disease, symptoms include muscle weakness, malaise, anorexia, vomiting, weight loss, and orthostatic hypotension. These may be of insidious onset. It is not unusual to elicit, in retrospect, an episodic history spanning years with symptoms being noticeable only during intercurrent illnesses. Such patients can present with acute decompensation **(adrenal crisis)** during relatively minor infectious illnesses. *Some of these patients have been initially misdiagnosed with chronic fatigue syndrome, postmononucleosis syndrome, chronic Lyme disease, or psychiatric disorders (depression or anorexia nervosa).*

Hyperpigmentation is often, but not necessarily, present. **Hyponatremia** is present at diagnosis in almost 90% of patients. **Hyperkalemia** tends to occur later in the course of the disease in older children than in infants and is present in only half of patients at diagnosis. *Normal potassium levels must never be presumed to rule out primary adrenal insufficiency.*

Hypoglycemia and ketosis are common. Thus the clinical presentation can be easily confused with gastroenteritis or other acute infections. Chronicity of symptoms can alert the clinician to the possibility of Addison disease, but this diagnosis should be considered in any child with orthostatic hypotension, hyponatremia, hypoglycemia, and ketosis. Salt craving is seen in primary adrenal insufficiency with mineralocorticoid deficiency. Fatigue, myalgias, fever, eosinophilia, lymphocytosis, hypercalcemia, and anemia may be noted with glucocorticoid deficiency.

Laboratory Findings

Hypoglycemia, ketosis, hyponatremia, and hyperkalemia have been discussed. An electrocardiogram is useful for quickly detecting hyperkalemia in a critically ill child. Acidosis is often present, and the blood urea nitrogen level is elevated if the patient is dehydrated.

Cortisol levels are sometimes at the low end of the normal range but are invariably low when the patient's degree of illness is considered. ACTH levels are high in primary adrenal insufficiency but can take time to be reported by the laboratory. Similarly, aldosterone levels may be within the normal range but inappropriately low considering the patient's hyponatremia, hyperkalemia, and hypovolemia. Plasma renin activity is elevated. Blood eosinophils may be increased in number, but this is rarely useful diagnostically.

Urinary excretion of sodium and chloride are increased and urinary potassium is decreased, but these are difficult to assess in random urine samples. Accurate interpretation of urinary electrolytes requires more-prolonged (24 hr) urine collections and knowledge of the patient's sodium and potassium intake.

The **most definitive** test for adrenal insufficiency is measurement of serum levels of cortisol before and after administration of ACTH; resting levels are low and do not increase normally after administration of ACTH (Table 593.5). Occasionally, normal resting levels that do not increase after administration of ACTH indicate an absence of adrenocortical reserve. A low initial level followed by a significant response to ACTH can indicate secondary adrenal insufficiency.

Traditionally, this test has been performed by measuring cortisol levels before and 30 or 60 min after giving 0.250 mg of **cosyntropin** (ACTH 1-24) by rapid intravenous infusion. Aldosterone will transiently increase in response to this dose of ACTH and may also be measured. A low-dose test (1 µg ACTH 1-24/1.73 m^2) is a more sensitive test of pituitary-adrenal reserve but has somewhat lower specificity (more false-positive tests).

Table 593.5

Proposed Diagnostic Criteria for Autoimmune Addison Disease

1. Basal cortisol < 3 µg/dL (83 nmol/L) and/or ACTH > 100 pg/mL (22 pmol/L) at 8-9 AM or serum cortisol less than 18 µg/dL (500 nmol/L) 30 or 60 min after an intravenous injection of 250 µg synthetic ACTH.
2. Normal or reduced adrenal gland volume on computed tomography (CT) and magnetic resonance imaging (MRI) and the absence of calcifications on abdominal x-ray or CT.
3. Anticortex adrenal antibodies or high titers of anti-21OH antibodies.
4. Exclusion of other causes of primary adrenal insufficiency: genetic (clinical signs or symptoms: achalasia, alacrimia, deafness or hypogonadotrophic hypogonadism in males or genotyping); adrenoleukodystrophy (levels of very-long-chain fatty acids within the normal range); infectious diseases (tuberculosis, paracoccidiomycosis, histoplasmosis, HIV or CMV); drugs (mitotane, ketoconazole, rifampin, etc.); adrenal hemorrhage or thrombosis; neoplasias; infiltrative (sarcoidosis, amyloidosis or hemochromatosis).
5. Other concomitant autoimmune condition(s) (Hashimoto thyroiditis, pernicious anemia, rheumatologic autoimmune disease, autoimmune disease, autoimmune hemocytopenia and others).

Definitive diagnosis: 1, 2, 3, and 4.

Probable diagnosis: 1, 2, 4, and 5.

From Neto RAB, Freire de Carvalho J: Diagnosis and classification of Addison's disease (autoimmune adrenalitis), *Autoimmune Rev* 13:408–411, 2014, Table 3.

Differential Diagnosis

Upon presentation, Addison disease often needs to be distinguished from more acute illnesses such as gastroenteritis with dehydration or sepsis. Additional testing is directed at identifying the specific cause for adrenal insufficiency. When congenital adrenal hyperplasia is suspected, serum levels of cortisol precursors (17-hydroxyprogesterone) should be measured along with cortisol in an ACTH stimulation test (see Chapter 594) (Fig. 593.2). Elevated levels of very-long-chain fatty acids are diagnostic of ALD (see Chapter 617.3). Many genetic etiologies for primary adrenal insufficiency may be identified by direct genetic testing, but it can take many weeks for results to become available. The presence of antiadrenal antibodies suggests an autoimmune pathogenesis. Patients with autoimmune Addison disease must be closely observed for the development of other autoimmune disorders. In children, hypoparathyroidism is the most commonly associated disorder, and it is suspected if hypocalcemia and elevated phosphate levels are present.

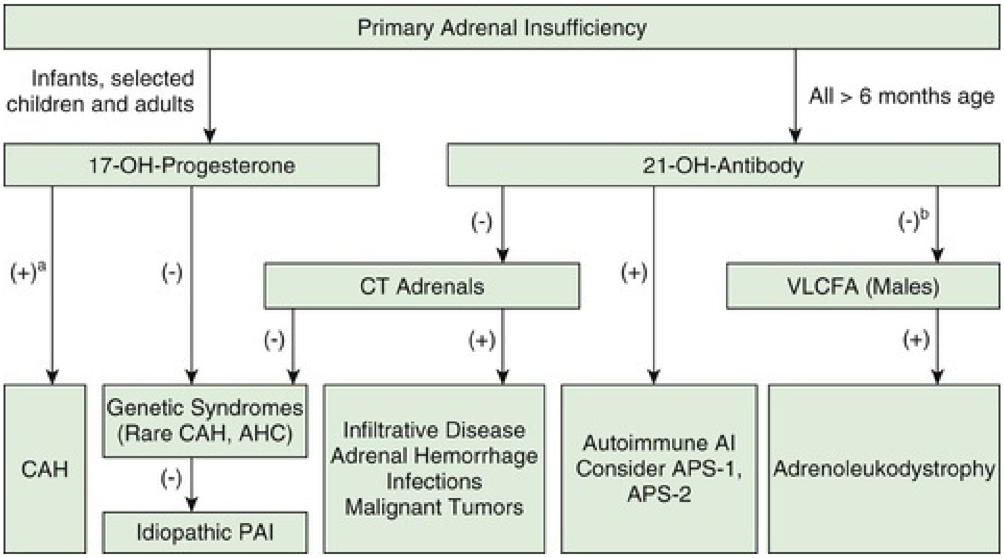
Primary Adrenal Insufficiency
Infants, selected children and adults
All > 6 months age
17-OH-Progesterone
21-OH-Antibody
(+)a
(-)
(-)
(-)b
(+)
CT Adrenals
VLCFA (Males)
(-)
(+)
(+)
CAH
Genetic Syndromes (Rare CAH, AHC)
(-)
Idiopathic PAI
Infiltrative Disease
Adrenal Hemorrhage
Infections
Malignant Tumors
Autoimmune AI
Consider APS-1, APS-2
Adrenoleukodystrophy

FIG. 593.2 Algorithm for the diagnostic approach to the patient with primary adrenal insufficiency (PAI). The most common causes of PAI are autoimmune destruction of the adrenal cortex in adults and congenital adrenal hyperplasia (CAH) in children. These etiologies can be screened for using 21-hydroxylase antibodies and a baseline serum 17-hydroxyprogesterone level, respectively. Males with negative 21-hydroxylase antibodies should be tested for adrenoleukodystrophy with plasma VLCFAs. If these diagnoses are excluded, a CT scan of the adrenals may reveal evidence of adrenal infiltrative processes or metastases, but this is of low yield in children and adolescents. The individual's clinical picture and family history may render some steps in the algorithm redundant or suggest specific genetic syndromes. The latter includes subtypes of autoimmune polyglandular syndromes or specific rare genetic disorders where adrenal failure is part of a broader phenotype. *AHC* , Adrenal hypoplasia congenita; *AI* , adrenal insufficiency; *VLCFA* , very-long-chain fatty acid. [a] 17-OH-progesterone >1,000 ng/dL is diagnostic for 21-OH deficiency (14). [b] VLCFA should be measured in the initial evaluation of preadolescent boys. (Adapted from Husebye ES, Allolio B, Arlt W, et al: Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency, *J Intern Med* 275:104–115, 2014, with permission John Wiley & Sons, Inc.)

Ultrasonography (which requires an experienced operator), CT, or MRI can help to define the size of the adrenal glands.

Treatment

Treatment of acute adrenal insufficiency must be immediate and vigorous. If the diagnosis of adrenal insufficiency has not been established, a blood sample should be obtained before therapy to determine electrolytes, glucose, ACTH, cortisol, aldosterone, and plasma renin activity. If the patient's condition permits, an ACTH stimulation test can be performed while initial fluid resuscitation is underway. An intravenous solution of 5% glucose in 0.9% saline should be administered to correct hypoglycemia, hypovolemia, and hyponatremia. Hypotonic fluids (e.g., 5% glucose in water or 0.2% saline) must be avoided because they can precipitate or exacerbate hyponatremia. If hyperkalemia is severe, it can require treatment with intravenous calcium and/or bicarbonate, intrarectal potassium-binding resin (sodium polystyrene sulfonate, Kayexalate), or intravenous infusion of glucose and insulin. A water-soluble form of hydrocortisone, such as hydrocortisone sodium succinate, should be given intravenously. As much as 10 mg for infants, 25 mg for toddlers, 50 mg for older children, and 100 mg for adolescents should be administered as a bolus and a similar total amount given in divided doses at 6-hr intervals for the first 24 hr. These doses may be reduced during the next 24 hr if progress is satisfactory. Adequate fluid and sodium repletion is achieved by intravenous saline administration, aided by the mineralocorticoid effect of high doses of hydrocortisone.

Particular caution should be exercised in the rare patient with concomitant adrenal insufficiency and hypothyroidism, because thyroxine can increase cortisol clearance. Thus an adrenal crisis may be precipitated if hypothyroidism is treated without first ensuring adequate glucocorticoid replacement.

After the acute manifestations are under control, most patients require chronic replacement therapy for their cortisol and aldosterone deficiencies. Hydrocortisone (cortisol) may be given orally in daily doses of 10 mg/m^2 /24 hr in 3 divided doses; some patients require 15 mg/m^2 /24 hr to minimize fatigue, especially in the morning. Timed-release preparations of hydrocortisone are undergoing clinical trials but are not yet generally available. Subcutaneous infusion of hydrocortisone with an insulin pump has also been examined in clinical trials; although this has the advantage that it can very closely mimic normal diurnal variation in cortisol secretion, it is very expensive and has not yet entered routine clinical practice. Equivalent doses (20–25% of the hydrocortisone dose) of prednisone or prednisolone may be divided and given twice daily. ACTH levels may be used to monitor adequacy of glucocorticoid replacement in primary adrenal insufficiency; in congenital adrenal hyperplasia, levels of precursor hormones are used instead. Blood samples for monitoring should be obtained at a consistent time of day and in a consistent relation to (i.e., before or after) the hydrocortisone dose. Normalizing ACTH levels is unnecessary and can require excessive doses of hydrocortisone; in general, morning ACTH levels high in the normal range to 3-4 times normal are satisfactory. Because untreated or severely undertreated patients can acutely decompensate during relatively minor illnesses, assessment of symptoms (or lack thereof) must not be used as a substitute for biochemical monitoring. During situations of stress, such as periods of infection or minor operative procedures, the dose of hydrocortisone should be increased 2-3–fold. Major surgery under general inhalation anesthesia requires high intravenous doses of hydrocortisone similar to those used for acute adrenal insufficiency.

If aldosterone deficiency is present, fludrocortisone, a synthetic mineralocorticoid, is given orally in doses of 0.05-0.2 mg daily. Measurements of plasma renin activity are useful in monitoring the adequacy of mineralocorticoid replacement. Chronic overdosage with glucocorticoids leads to obesity, short stature, and osteoporosis, whereas overdosage with fludrocortisone results in hypertension and occasionally hypokalemia.

Replacement of dehydroepiandrosterone (DHEA) in adults remains controversial; prepubertal children do not normally secrete large amounts of DHEA. Many adults with Addison disease complain of having decreased energy, and replacing DHEA can improve this problem, particularly in women in whom adrenal androgens represent approximately 50% of total androgen secretion.

Additional therapy might need to be directed at the underlying cause of the adrenal insufficiency in regard to infections and certain metabolic defects. Therapeutic approaches to ALD include administration of glycerol trioleate and glycerol trierucate (Lorenzo's oil), bone marrow transplantation, and lovastatin (see Chapter 617.3).

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593.2

Secondary and Tertiary Adrenal Insufficiency

Perrin C. White

Keywords

septo-optic dysplasia
Prader-Willi syndrome

Etiology

Abrupt Cessation of Administration of Corticosteroids

Secondary adrenal insufficiency most commonly occurs when the HPA axis is suppressed by prolonged administration of high doses of a potent glucocorticoid and that agent is suddenly withdrawn or the dose is tapered too quickly. Patients at risk for this problem include those with leukemia, asthma (particularly when patients are transitioned from oral to inhaled corticosteroids), and collagen vascular disease or other autoimmune conditions and those who have undergone tissue transplants or neurosurgical procedures. The maximal duration and dosage of glucocorticoid that can be administered before encountering this problem is not known, but it is assumed that high-dose glucocorticoids (the equivalent of >10 times physiologic cortisol secretion) can be administered for at least 1 wk without requiring a subsequent taper of dose. On the other hand, when high doses of dexamethasone are given to children with leukemia, it can take 6 mo or longer after therapy is stopped before tests of adrenal function return to normal. Signs and symptoms of adrenal insufficiency are most likely in patients who are subsequently subjected to stresses such as severe infections or additional surgical procedures.

Corticotropin (Adrenocorticotropic Hormone) Deficiency

Pituitary or hypothalamic dysfunction can cause corticotropin deficiency (see Chapter 573), usually associated with deficiencies of other pituitary hormones such as growth hormone and thyrotropin. Destructive lesions in the area of the pituitary, such as craniopharyngioma and germinoma, are the most common causes of corticotropin deficiency. In many cases the pituitary or hypothalamus is further damaged during surgical removal or radiotherapy of tumors in the midline of the brain. Traumatic brain injury (see Chapter 728) frequently causes pituitary dysfunction, especially in the 1st days after the injury. However, corticotropin deficiency is difficult to detect then owing to frequent use of high doses of dexamethasone to minimize brain swelling, and permanent corticotropin deficiency is unusual after traumatic brain injury. In rare instances, autoimmune hypophysitis is the cause of corticotropin deficiency.

Congenital lesions of the pituitary also occur. The pituitary alone may be affected, or additional midline structures may be involved, such as the optic nerves or septum pellucidum. The latter type of abnormality is termed **septo-optic dysplasia,** or de Morsier syndrome (see Chapter 609.9). More severe developmental anomalies of the brain, such as anencephaly and holoprosencephaly, can also affect the pituitary. These disorders are usually sporadic, although a few cases of autosomal recessive inheritance have occurred. Isolated deficiency of corticotropin has been reported, including in several sets of siblings. Patients with multiple pituitary hormone deficiencies caused by mutations in the *PROP1* gene have been described with progressive ACTH/cortisol deficiency. Isolated deficiency of corticotropin-releasing hormone has been documented in an Arab kindred as an autosomal recessive trait.

Up to 60% of children with **Prader-Willi syndrome** (see Chapter 98.8) have some degree of secondary adrenal insufficiency as assessed by provocative testing with metyrapone, although diurnal cortisol levels are normal. The clinical significance of this finding is uncertain, but it might contribute to the relatively high incidence of sudden death with infectious illness that occurs in this population. Although it is not yet a standard of care, some endocrinologists advocate treating patients who have Prader-Willi syndrome with hydrocortisone during febrile illness.

Clinical Presentation

Aldosterone secretion is unaffected in secondary adrenal insufficiency because the adrenal gland is, by definition, intact and the renin-angiotensin system is not involved. Thus signs and symptoms are those of cortisol deficiency. Newborns often have hypoglycemia. Older children can have orthostatic hypotension or weakness. Hyponatremia may be present.

When secondary adrenal insufficiency is the consequence of an inborn or acquired anatomic defect involving the pituitary, there may be signs of associated deficiencies of other pituitary hormones. The penis may be small in male infants if gonadotropins are also deficient. Infants with secondary hypothyroidism are often jaundiced. Children with associated growth hormone deficiency grow poorly after the 1st yr of life.

Some children with pituitary abnormalities have hypoplasia of the midface. Children with optic nerve hypoplasia can have obvious visual impairment. They usually have a characteristic wandering nystagmus, but this is often not apparent until several months of age.

Laboratory Findings

Because the adrenal glands themselves are not directly affected, the diagnosis of secondary adrenal insufficiency is sometimes challenging. Historical gold standard dynamic tests include insulin-induced hypoglycemia, which provides a potent stress to the entire HPA axis. This test requires constant attendance by a physician and is considered by many endocrinologists to be too dangerous for routine use. A second gold standard test uses metyrapone, a specific inhibitor of steroid 11β-hydroxylase (CYP11B1) to block cortisol synthesis, thus removing the normal negative feedback of cortisol on ACTH secretion. There are several protocols for this test; one version administers 30 mg/kg of metyrapone orally at midnight, with a blood sample obtained for cortisol and 11-deoxycortisol (the substrate for 11β-hydroxylase) at 8 AM . A low cortisol level (<5 µg/dL) demonstrates adequate suppression of cortisol synthesis, and an 11-deoxycortisol level >7 µg/dL indicates that ACTH has responded normally to the cortisol deficiency by stimulating the adrenal cortex. This test should be used with caution outside the research setting because it can precipitate adrenal crises in patients with marginal adrenal function; the drug is not available in all locales.

Currently, the most commonly used test to diagnose secondary adrenal insufficiency **is low-dose ACTH stimulation testing** (1 µg/1.73 m^2 of cosyntropin given intravenously), the rationale being that there will be some degree of atrophy of the adrenal cortex if normal physiologic ACTH stimulation is lacking. Thus this test may be falsely negative in cases of acute compromise of the pituitary (e.g., injury or surgery). Such circumstances rarely pose a diagnostic dilemma; in general, this test provides excellent sensitivity and specificity. Although assays vary somewhat, a threshold cortisol level of 18-20 μg/dL 30 min after cosyntropin administration may be used to dichotomize normal and abnormal responses.

Currently, there seems to be little reason to use stimulation with corticotropin-releasing hormone instead of ACTH; although the corticotropin-releasing hormone test has the theoretical advantage of testing the ability of the anterior pituitary to respond to this stimulus by secreting ACTH (thus distinguishing secondary and tertiary adrenal insufficiency), in practice it does not provide improved sensitivity and specificity, and the agent is not as widely available.

Treatment

Iatrogenic secondary adrenal insufficiency (caused by chronic glucocorticoid administration) is best avoided by use of the smallest effective doses of systemic glucocorticoids for the shortest period of time. When a patient is thought to be at risk, tapering the dose rapidly to a level equivalent to or slightly less than the physiologic replacement (~10 mg/m^2 /24 hr of hydrocortisone) and further tapering over several weeks can allow the adrenal cortex to recover without the patient developing signs of adrenal insufficiency. Patients with anatomic lesions of the pituitary should be treated indefinitely with glucocorticoids. Mineralocorticoid replacement is not required. In patients with panhypopituitarism, treating cortisol deficiency can increase free water excretion, thus unmasking central diabetes insipidus. Electrolytes must be monitored carefully when initiating cortisol therapy in panhypopituitary patients.

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593.3

Adrenal Insufficiency in the Critical Care Setting

Perrin C. White

Keywords

meningococcemia
etomidate
septic shock
syndrome of inappropriate antidiuretic hormone secretion

Etiology

Adrenal insufficiency in the context of critical illness is encountered in up to 20–50% of pediatric patients, often as a transient condition. In many cases, it is considered to be functional or relative in nature, meaning that cortisol levels are within normal limits but cannot increase sufficiently to meet the demands of critical illness. The causes are heterogeneous, and some were discussed in Chapter 593.1 . They include adrenal hypoperfusion from shock, particularly septic shock, as is often seen in meningococcemia. Inflammatory mediators during septic shock, particularly interleukin-6, can suppress ACTH secretion, directly suppress cortisol secretion, or both. Etomidate, used as sedation for intubation, inhibits steroid 11β-hydroxylase and thus blocks cortisol biosynthesis. Neurosurgical patients with closed head trauma or with tumors that involve the hypothalamus or pituitary might have ACTH deficiency in the context of panhypopituitarism. Some children have been previously treated with systemic corticosteroids (e.g., children with leukemia) and have suppression of the HPA axis for that reason. In the intensive care nursery, premature infants have not yet developed normal cortisol biosynthetic capacity and thus may not be able to secrete adequate amounts of this hormone when ill.

Clinical Manifestations

Cortisol is required for catecholamines to have their normal pressor effects on the cardiovascular system (see Chapters 592.4 and 592.5). Accordingly, adrenal insufficiency is often suspected in hypotensive patients who do not respond to intravenous pressor agents. Patients may be at increased risk for hypoglycemia or a presentation resembling the syndrome of inappropriate antidiuretic hormone secretion, but these conditions commonly occur in the context of sepsis, and the contribution of adrenal insufficiency may be difficult to distinguish.

Laboratory Findings

Although low random cortisol levels in severely stressed patients are certainly abnormal, very high levels are also associated with a poor outcome in such patients; the latter situation presumably reflects a maximally stimulated adrenal cortex with diminished reserve. ACTH (cosyntropin) stimulation testing is generally considered the best way to diagnose adrenal insufficiency in this setting (see Chapter 593.1); evidence suggests that the low-dose (1 µg/1.73 m^2) test may be superior to the 250 µg standard dose test, although this remains controversial. In general, a peak cortisol level <18 µg/dL or an increment of <9 µg/dL from baseline is considered suggestive for adrenal insufficiency in this context. In evaluating cortisol levels, it should be remembered that cortisol in the circulation is normally mostly bound to cortisol-binding globulin; in hypoproteinemic states, total cortisol levels may be decreased, whereas free cortisol levels might be normal. It may be prudent to measure free cortisol before initiating treatment when total cortisol is low and albumin is <2.5 g/dL, but such measurements are not readily available in all institutions.

Treatment

There are limited data regarding treatment efficacy in critically ill children. Based on studies of both children and adults, it is likely that moderate stress doses of hydrocortisone (e.g., 50 mg/m^2 /day) improve responses to pressor agents in patients with shock and documented adrenal insufficiency. It is uncertain if there is a beneficial effect on overall survival. There seems to be no benefit in using pharmacologic doses of potent synthetic glucocorticoids such as dexamethasone.

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593.4

Altered End-Organ Sensitivity to Corticosteroids

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Keywords

glucocorticoid receptor
apparent mineralocorticoid excess
autosomal dominant
autosomal recessive
pseudohypoaldosteronism type 2
cystic fibrosis–like pulmonary symptoms
licorice
nephrocalcinosis
nephrogenic diabetes insipidus
rhabdomyolysis
Liddle syndrome
activating mutations
ubiquitin
proteosome

Diseases can result from altered actions of hormones at their physiologic targets. These may be caused by abnormal metabolism of hormones, mutations in hormone receptors, or defects in cellular effectors (such as ion channels) that are targets of hormone action.

Generalized Glucocorticoid Resistance

Etiology

Patients with generalized glucocorticoid resistance have target-tissue insensitivity to glucocorticoids. The condition is usually inherited in an autosomal dominant manner, but sporadic cases occur. Impairment of normal negative feedback of cortisol at the levels of the hypothalamus and pituitary activates the HPA axis, with consequent increases in ACTH and cortisol concentrations. Generalized glucocorticoid resistance is caused by mutations in the **glucocorticoid receptor** (encoded by the *NR3C1* gene) that impair its action by interfering with ligand binding, DNA binding, transcriptional activation, or some combination of these. Most mutations are heterozygous; glucocorticoid receptors usually bind DNA as dimers, and 3 out of every 4 dimers will contain at least 1 abnormal receptor molecule when a heterozygous mutation is present.

Clinical Manifestations

The excess ACTH secretion causes adrenal hyperplasia with increased production of adrenal steroids with mineralocorticoid activity, including cortisol, deoxycorticosterone, and corticosterone, and also androgens and precursors, including androstenedione, DHEA, and DHEA sulfate. The high cortisol concentrations do not cause Cushing syndrome (see Chapter 597) because of the insensitivity to glucocorticoids; conversely, most signs and symptoms of adrenal insufficiency are absent except for the frequent occurrence of chronic fatigue and occasional anxiety (neonatal hypoglycemia was reported in one very unusual patient with a homozygous null mutation). On the other hand, the mineralocorticoid and androgen receptors are normally sensitive to their ligands. Signs of mineralocorticoid excess, such as hypertension and hypokalemic alkalosis, are frequently noted. The increased concentrations of adrenal androgens may cause ambiguous genitalia in females and gonadotropin-independent precocious puberty in children of either gender; acne; hirsutism, and infertility in both sexes; menstrual irregularities in females; and oligospermia in males. Testicular adrenal rest tumors and ACTH-secreting pituitary adenomas occasionally occur.

Laboratory Findings

The diagnosis of generalized glucocorticoid resistance is suggested by elevated serum cortisol concentrations and increased 24-hr urinary free cortisol excretion in the absence of Cushing syndrome. Levels of other adrenal steroids are also increased. Plasma concentrations of ACTH may be normal or high. The circadian pattern of ACTH and cortisol secretion is preserved, although at higher-than-normal concentrations, and there is resistance of the HPA axis to dexamethasone suppression. Sequencing of the *NR3C1* gene can confirm the diagnosis but is not routinely available.

Differential Diagnosis

Generalized glucocorticoid resistance should be distinguished from relatively mild cases of Cushing syndrome (whether caused by a pituitary adenoma or adrenal tumor, see Chapter 595); the latter is more likely to be associated with excessive weight gain or poor linear growth. Adrenocortical tumors may secrete mineralocorticoids such as deoxycorticosterone and also androgens, but ACTH levels are often suppressed and of course the tumor can usually be visualized with appropriate imaging techniques. Congenital adrenal hyperplasia (see Chapter 594), particularly 11β-hydroxylase deficiency, may present with hypertension and signs of androgen excess, but in that condition cortisol levels are low and levels of cortisol precursors (17-hydroxyprogesterone, 11-deoxycortisol) are elevated. Obese patients may be hypertensive and have hyperandrogenism, but cortisol secretion should be readily suppressed by dexamethasone.

Treatment

The goal of treatment is to suppress the excess secretion of ACTH, thereby suppressing the increased production of adrenal steroids with mineralocorticoid and androgenic activity. This requires administration of high doses of a pure glucocorticoid agonist such as dexamethasone (typically ~20-40 µg/kg/day) with careful titration to suppress endogenous corticosteroid secretion without causing signs of glucocorticoid excess such as excessive weight gain or suppression of linear growth.

Cortisone Reductase Deficiency

Etiology

Levels of active glucocorticoids in target tissues are modulated by 2 isozymes of 11β-hydroxysteroid dehydrogenase. The HSD11B2 isozyme converts cortisol to an inactive metabolite, cortisone; the 2 steroids differ in the presence of an 11β-hydroxyl versus an 11-oxo group, respectively. Mutations in this enzyme cause the syndrome of **apparent mineralocorticoid excess** (discussed later in this chapter). Conversely, the HSD11B1 isozyme converts cortisone to cortisol, and so it is sometimes referred to as cortisone reductase. This isozyme is expressed at high levels in glucocorticoid target tissues, particularly the liver, where it ensures adequate levels of active glucocorticoids (cortisol and corticosterone) to meet metabolic demands without requiring excessive adrenal cortisol secretion.

The HSD11B1 isozyme is located in the endoplasmic reticulum (i.e., it is a microsomal enzyme) and functions as a dimer. It accepts electrons from reduced nicotine–adenine dinucleotide phosphate, which is generated within the endoplasmic reticulum by hexose-6-phosphate dehydrogenase, an enzyme distinct from cytoplasmic glucose-6-phosphate dehydrogenase.

Apparent cortisone reductase deficiency is caused by homozygous mutations in hexose-6-phosphate dehydrogenase that prevent generation of reduced nicotine–adenine dinucleotide phosphate within the endoplasmic reticulum and thus starve HSD11B1 of its essential cofactor for the reductase reaction. Very rare patients have been reported to have heterozygous mutations in the *HSD11B1* gene itself and thus have “true” cortisone reductase deficiency; because the enzyme functions as a homodimer, heterozygous mutations are able to impair three fourths of all dimers.

Clinical Manifestations

Because circulating cortisone is not converted to cortisol, the circulating half-life of cortisol is decreased and the adrenal cortex must secrete additional cortisol to compensate. This leads to adrenocortical overactivity analogous to, but generally much milder than, that seen in generalized glucocorticoid resistance. This is usually not severe enough to cause hypertension, presenting instead with mild to moderate signs of androgen excess such as hirsutism, oligomenorrhea or amenorrhea, and infertility in females and precocious pseudopuberty (axillary and pubic hair, and penile enlargement, but not testicular enlargement) in males.

Laboratory Findings

The ratio of cortisol to cortisone in blood is lower than usual. The same is true of urinary metabolites, typically measured as a ratio of the sum of the tetrahydrocortisol and allotetrahydrocortisol excretion to that of tetrahydrocortisone. These determinations are best accomplished by gas chromatography followed by mass spectrometry and are available in specialized reference laboratories. Absolute levels of cortisol and ACTH are within normal limits.

Differential Diagnosis

Cortisone reductase deficiency has to be distinguished from, and is much less common than, other causes of androgen excess such as polycystic ovarian syndrome and nonclassical congenital adrenal hyperplasia as a result of 21-hydroxylase deficiency.

Treatment

Treatment is aimed at decreasing adrenal overactivity and thus reducing secretion of androgens. This can be accomplished by administration of hydrocortisone.

Altered End-Organ Sensitivity to Mineralocorticoids

Pseudohypoaldosteronism

Etiology

Pseudohypoaldosteronism type 1 (PHA1) is a monogenic disease in which aldosterone action is deficient and patients are thus unable to resorb urinary sodium or excrete potassium properly. There are 2 forms. A relatively mild **autosomal dominant** form is caused by mutations in the *NR3C2* gene encoding the human mineralocorticoid receptor. A heterozygous mutation is sufficient to cause disease because the mineralocorticoid receptor interacts with DNA as a dimer, and three fourths of the dimers are defective in individuals carrying heterozygous mutations (assuming mutant protein is synthesized). A more-severe **autosomal recessive** form is usually the result of homozygous mutations in the α *(SCNN1A)*, β *(SCNN1B)*, or γ *(SCNN1G)* subunits of the epithelial Na^+ channel, but 1 reported case of severe autosomal recessive disease was caused by homozygous mutations in *NR3C2* .

PHA1 should not be confused with **pseudohypoaldosteronism type 2** , a rare Mendelian syndrome characterized by hyperkalemia and, in contrast to PHA1, by hypertension from excessive renal salt reabsorption. This disorder is caused by mutations in the renal regulatory kinases WNK1 and WNK4 or components of an E3 ubiquitin ligase complex Kelch-like 3 (KLHL3) and Cullin 3 (CUL3).

Clinical Manifestations

Infants with PHA1 present with hyperkalemia, hyponatremia, hypovolemia, hypotension, and failure to thrive. In more-severe (usually autosomal recessive) cases, salt loss is not confined to the kidney but instead occurs from most epithelia. Mothers may report that the skin of their affected infants tastes salty. Some infants suffer from *cystic fibrosis–like pulmonary symptoms*. It is often difficult to control electrolyte abnormalities in patients with the autosomal recessive form, leading to frequent hospitalizations and a need for close clinical monitoring.

It is noteworthy that signs and symptoms of aldosterone deficiency tend to remit as the patients get older, particularly in the autosomal dominant form. This is similar to what is seen in actual aldosterone deficiency as occurs in the salt-losing forms of congenital adrenal hyperplasia or aldosterone synthase deficiency. The kidney matures after early infancy to become more efficient at excreting potassium, and although breast milk and infant formula are low in sodium, the normal adult Western diet is relatively high in sodium, thus compensating for the renal salt wasting.

Laboratory Findings

Infants have marked hyperkalemia and hyponatremia. Both plasma renin and aldosterone are markedly elevated. Levels of cortisol and ACTH are normal. If hypovolemia is severe, patients may develop prerenal azotemia. With severe hyperkalemia, the electrocardiogram may include tall peaked T or ventricular tachycardia.

Differential Diagnosis

PHA in infants should be distinguished from other causes of hyperkalemia and hyponatremia. These include renal failure of any cause, congenital adrenal hyperplasia, aldosterone synthase deficiency, and other causes of adrenocortical insufficiency such as AHC. Patients with renal failure will have elevated blood urea nitrogen and creatinine, but these may also be seen in severely dehydrated patients with PHA or adrenal insufficiency. Patients with any form of adrenal insufficiency in this clinical context will have low or low-normal aldosterone levels (with elevated plasma renin), in contrast to the elevated aldosterone levels seen in PHA. Patients with congenital adrenal hyperplasia have elevated levels of steroid precursors such as 17-hydroxyprogesterone (in patients with 21-

hydroxylase deficiency), and patients with most forms of adrenal insufficiency have elevated ACTH levels.

Treatment

Infants must be given sodium supplementation (initially intravenous and then oral or enteral), typically approximately 8 mEq/kg/day. Potassium levels in the infant formula often need to be reduced, which may be accomplished by mixing the formula with polystyrene resin (Kayexalate) and then decanting the formula prior to feeding. Fludrocortisone, a synthetic mineralocorticoid, may be efficacious in milder autosomal dominant cases if administered in high doses (titrating up to ~0.5 mg daily). Significant electrolyte abnormalities require treatment with intravenous normal saline and rectal polystyrene resin. Severe hyperkalemia may require glucose and insulin infusions to control.

Apparent Mineralocorticoid Excess

Etiology

The syndrome of apparent mineralocorticoid excess is an autosomal recessive disorder caused by mutations in the *HSD11B2* gene encoding the type 2 isozyme of 11β-hydroxysteroid dehydrogenase. The mineralocorticoid receptor actually has nearly identical affinities for aldosterone (the main mineralocorticoid hormone) and cortisol, yet cortisol is normally only a weak mineralocorticoid in vivo. This is because HSD11B2 is expressed along with the mineralocorticoid receptor in most target tissues such as the renal cortical collecting duct epithelium. It converts cortisol to cortisone, which is not an active steroid, thus preventing it from occupying the mineralocorticoid receptor. In contrast, aldosterone is not a substrate for the enzyme because its 11β-hydroxyl group forms a hemiketal with the 18-aldehyde group of the steroid and is thus not accessible to the enzyme. Thus, in the absence of HSD11B2, cortisol is able to efficiently occupy the mineralocorticoid receptor, and because cortisol concentrations are normally far higher than those of aldosterone, this results in signs and symptoms of mineralocorticoid excess.

A similar clinical picture occurs with excessive consumption of **licorice** or licorice-flavored chewing tobacco; licorice contains compounds including glycyrrhetinic and glycyrrhizic acids that inhibit HSD11B2. Carbenoxolone, an antihypertensive drug that is not marketed in the United States, has similar effects.

Clinical Manifestations

Affected infants often have some degree of intrauterine growth restriction, with birthweights of 2 kg typical for term infants. Infants and children often fail to thrive. Severe hypertension (to ~200/120 mm Hg) is almost always present. In some patients, the hypertension tends to be labile or paroxysmal with severe emotional stress as a precipitating factor. Complications of hypertension have included cerebrovascular accidents. Several patients have died during infancy or adolescence, either from electrolyte imbalances leading to cardiac arrhythmias or from vascular sequelae of hypertension. Hypokalemic alkalosis can eventually cause **nephrocalcinosis** (often visible on renal ultrasound) and **nephrogenic diabetes insipidus** leading to polyuria and polydipsia. Deleterious effects on muscle range from elevations in serum creatine phosphokinase to frank **rhabdomyolysis** . Electrocardiograms show left ventricular hypertrophy.

Laboratory Findings

Hypokalemia and alkalosis are common but not consistently present. Sodium levels are generally in the upper part of the reference range. Aldosterone and renin levels are very low because the hypertension and hypervolemia are independent of aldosterone concentrations. Serum cortisol and ACTH levels are generally within normal limits. The serum half-life of cortisol is increased, but the test for this requires a radioactive tracer and is not clinically available. Total urinary excretion of cortisol metabolites is markedly decreased. The urinary ratio of free cortisol to free cortisone is elevated, as is the ratio of urinary tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone.

Differential Diagnosis

The differential diagnosis includes other forms of severe childhood hypertension such as renal artery anomalies, but relatively few conditions present with suppressed renin and aldosterone levels. **Liddle syndrome** (see below) has a similar presentation but no abnormalities in the steroid profile, typically has an autosomal dominant mode of inheritance, and does not respond to treatment with mineralocorticoid receptor antagonists. Hypertensive forms of congenital adrenal hyperplasia (see Chapter 594) also have suppressed renin and aldosterone levels, but they present with signs of androgen excess (11β-hydroxylase deficiency) or androgen deficiency (17α-hydroxylase deficiency); the latter can be difficult to appreciate in young children. The steroid profiles in congenital adrenal hyperplasia differ from those seen in apparent mineralocorticoid excess syndrome.

Patients with severe Cushing syndrome may have high enough cortisol levels to overwhelm renal HSD11B2, leading to severe hypertension with alterations in urinary cortisol-to-cortisone ratios. This occurs most often in patients with the ectopic ACTH syndrome. This generally does not present a diagnostic dilemma, because other signs of Cushing syndrome are present including high cortisol levels.

Treatment

Treatment includes a low-salt diet, potassium supplementation, and mineralocorticoid receptor blockade with spironolactone or eplerenone; a sodium channel blocker, such as amiloride or triamterene may work at least as well. In principle, suppression of cortisol secretion with dexamethasone (which does not bind the mineralocorticoid receptor) should work, but in practice it is much less effective than mineralocorticoid receptor blockade.

Liddle Syndrome

Etiology

Liddle syndrome is a form of hypertension and hypokalemia that is clinically similar to the syndrome of apparent mineralocorticoid excess, but it is inherited in an autosomal dominant manner. It is caused by **activating mutations** in the β *(SCNN1B)* or γ *(SCNN1G)* subunits of the epithelial sodium channel. Most of these mutations prevent the channel subunits from being ligated to ubiquitin and targeted to the proteasome for degradation, a process that is normally regulated indirectly by aldosterone. The net effect is to increase the number of open channels at the apical surface of epithelial cells of the renal collecting duct, thus facilitating sodium resorption and potassium excretion. This disorder is thus the exact opposite of the autosomal recessive form of pseudohypoaldosteronism discussed previously.

Clinical Manifestations, Laboratory Findings, and Differential Diagnosis

Liddle syndrome is characterized by severe early-onset hypertension and by hypokalemia, which may not be persistent. Aldosterone and renin levels are suppressed but all steroid hormone levels are normal.

The differential diagnosis is the same as that for apparent mineralocorticoid excess.

Treatment

The mainstays of treatment are a low-salt diet, potassium supplementation, and a sodium channel blocker such as amiloride or triamterene. Mineralocorticoid receptor antagonists such as spironolactone are ineffective.

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CHAPTER 594

Congenital Adrenal Hyperplasia and Related Disorders

Perrin C. White

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of cortisol biosynthesis (normal adrenal steroidogenesis is discussed in Chapter 592). Cortisol deficiency increases secretion of corticotropin (adrenocorticotropic hormone [ACTH]), which, in turn, leads to adrenocortical hyperplasia and overproduction of intermediate metabolites. Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess; incomplete virilization or precocious puberty in affected males; and virilization or sexual infantilism in affected females (Figs. 594.1 and 594.2 , Table 594.1).

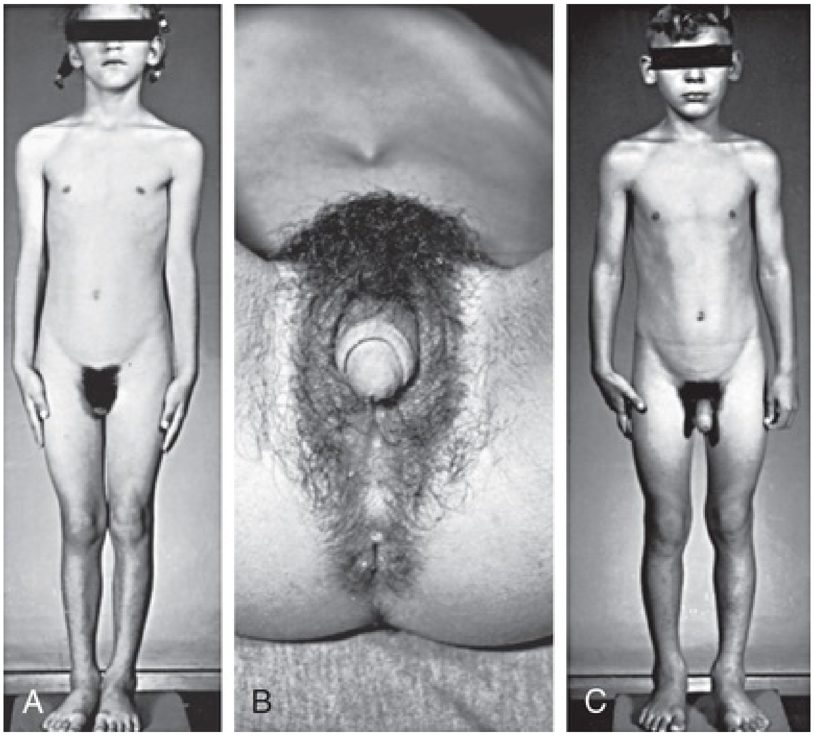

FIG. 594.1 **A,** A 6 yr old girl with congenital virilizing adrenal hyperplasia. The height age was 8.5 yr, and the bone age was 13 yr. **B,** Notice the clitoral enlargement and labial fusion. **C,** Her 5 yr old brother was not considered to be abnormal by the parents. The height age was 8 yr, and the bone age was 12.5 yr.

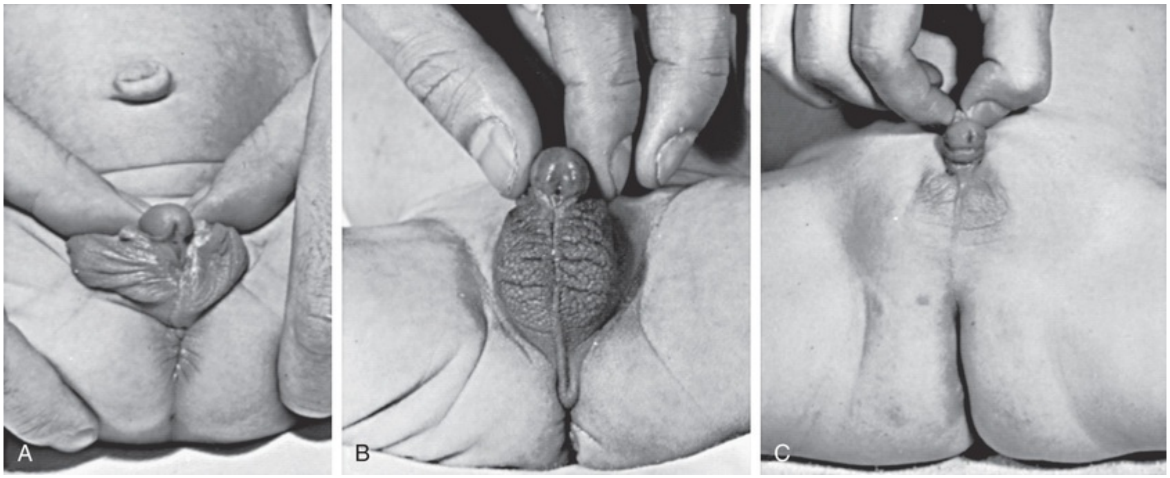

FIG. 594.2 Three virilized females with untreated congenital adrenal hyperplasia. All were erroneously assigned male sex at birth, and each had a normal female sex-chromosome complement. Infants **A** and **B** had the salt-wasting form and received the diagnosis early in infancy. Infant **C** was referred at 1 yr of age because of bilateral cryptorchidism. Notice the

completely penile urethra; such complete masculinization in females with adrenal hyperplasia is rare; most of these infants have the salt-wasting form.

Table 594.1

Diagnosis and Treatment of Congenital Adrenal Hyperplasia

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
21-Hydroxylase deficiency, classic form	*CYP21* 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ACTH ↑↑ Baseline and ACTH-stimulated 17-hydroxy-progesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	*CYP21* 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	*CYP11B1* 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH	Glucocorticoid (hydrocortisone) replacement
			↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency, classic form	*HSD3B2* 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated Δ5 steroids	Glucocorticoid (hydrocortisone) replacement

			(pregnenolone, 17-hydroxypregnenolone, DHEA)	
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/17,20-lyase deficiency	*CYP17* 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH ↑ DOC, corticosterone Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids
Congenital lipoid adrenal hyperplasia	*STAR* 8p11.2	Glucocorticoid deficiency	↑ ACTH Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement

				consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑ LH, ↓ estradiol (after puberty)	Estrogen replacement
P450 oxidoreductase deficiency	*POR* 7q11.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑ Pregnenolone, ↑ progesterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in males and females	↑ Serum androgens prenatally, ↓ androgens and estrogens at puberty	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Maternal virilization Antley-Bixler syndrome	Decreased ratio of estrogens to androgens	

↓, Decreased; ↑, increased; ↑↑, markedly increased; *ACTH* , Adrenocorticotropic hormone; *DHEA* , dehydroepiandrosterone; *DOC* , 11-deoxycorticosterone; *FSH* , follicle-stimulating hormone; *hCG* , human chorionic gonadotropin; *LH* , luteinizing hormone.

594.1

Congenital Adrenal Hyperplasia Caused by 21-Hydroxylase Deficiency

Perrin C. White

Keywords

salt-wasting
simple virilizing disease
classic 21-hydroxylase deficiency
nonclassic
Ehlers-Danlos syndrome

newborn screening
rapid somatic growth
accelerated skeletal maturation
testicular adrenal rest tumors
nonclassic 21-hydroxylase deficiency
Hirsutism
acne
menstrual disorders
infertility
17-hydroxyprogesterone

Etiology

More than 90% of CAH cases are caused by 21-hydroxylase deficiency. This P450 enzyme (CYP21, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone and 11-deoxycortisol, respectively (see Fig. 592.1 in Chapter 592). These conversions are required for synthesis of aldosterone and cortisol, respectively. Both hormones are deficient in the most-severe, **salt-wasting** form of the disease. Slightly less-severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed **simple virilizing disease** . These 2 forms are collectively termed **classic 21-hydroxylase deficiency** . Patients with **nonclassic** disease have relatively mildly elevated levels of androgens and may be asymptomatic or have signs of androgen excess at any time after birth. Clinical presentation is dependent, in part, on the genotype (see later, Genetics) (Table 594.2).

Table 594.2

Genotype-Phenotype Correlations in Congenital Adrenal Hyperplasia Owing to 21-Hydroxylase Deficiency

MUTATION GROUP	A	B	C
Enzymatic activity, % normal	Nil	1–2%	20–50%
CYP21 mutations (phenotype generally corresponds to the least affected allele)	Gene deletion Exon 3 del 8 bp Exon 6	I172N	P30L V281L P453S

	cluster Q318X R356W		
	Intron 2 splice[*]		
Severity	Salt wasting	Simple virilizing	Nonclassic
Aldosterone synthesis	Low	Normal	Normal
Age at diagnosis (without newborn screening)	Infancy	Infancy (females) Childhood (males)	Childhood to adulthood, or asymptomatic
Virilization	Severe	Moderate to severe	None to mild
Incidence	1/20,000	1/50,000	1/500

[*] This mutation is associated with both salt wasting and simple virilizing disease.

Epidemiology

Classic 21-hydroxylase deficiency occurs in approximately 1 in 15,000-20,000 births in most populations. Approximately 70% of affected infants have the salt-losing form, whereas 30% have the simple virilizing form of the disorder. In the United States, CAH is less common in African Americans compared with white children (1 : 42,000 vs 1 : 15,500). Nonclassic disease has a prevalence of approximately 1 in 1,000 in the general population but occurs more frequently in specific ethnic groups such as Ashkenazi Jews and Hispanics.

Genetics

There are 2 steroid 21-hydroxylase genes—*CYP21P (CYP21A1P, CYP21A)* and *CYP21 (CYP21A2, CYP21B)* —which alternate in tandem with 2 genes for the 4th component of complement (C4A and C4B) in the human leukocyte antigen (HLA) major histocompatibility complex on chromosome 6p21.3 between the HLA-B and HLA-DR loci. Many other genes are located in this cluster. *CYP21* is the active gene; *CYP21P* is 98% identical in DNA sequence to *CYP21* but is a pseudogene because of 9 different mutations. Although almost 300 mutations have been reported, more than 90% of mutant alleles causing 21-hydroxylase deficiency are the result of recombinations between *CYP21* and *CYP21P.* Approximately 20% are deletions generated by unequal meiotic crossing-over between *CYP21* and *CYP21P,* whereas the remainder are nonreciprocal transfers of deleterious mutations from *CYP21P* to *CYP21*, a phenomenon termed gene conversion.

The deleterious mutations in *CYP21P* have different effects on enzymatic activity when transferred to *CYP21*. Several mutations completely prevent synthesis of a functional protein, whereas others are missense mutations (they result in amino acid substitutions) that yield enzymes with 1–50% of normal activity. Disease severity correlates well with the mutations carried by an affected individual; for example, patients with salt-wasting disease usually carry mutations on both alleles that completely destroy enzymatic activity. Patients are frequently compound heterozygotes for different types of mutations (i.e., 1 allele is less-severely affected than the other), in which case the severity of disease expression is largely determined by the activity of the less-severely affected of the 2 alleles.

Closely adjacent to, but on the opposite DNA strand from, *CYP21* is the tenascin-X *(TNX)* gene, which encodes a connective tissue protein. Rarely, deletions of *CYP21* extend into *TNX* . Such patients may have a contiguous gene syndrome (see Chapter 98.1) consisting of CAH and **Ehlers-Danlos syndrome** (see Chapters 511 and 678).

Pathogenesis and Clinical Manifestations

Aldosterone and Cortisol Deficiency

Because both cortisol and aldosterone require 21-hydroxylation for their synthesis, both hormones are deficient in the most-severe, salt-wasting form of the disease. This form constitutes approximately 70% of cases of classic 21-hydroxylase deficiency. The signs and symptoms of cortisol and aldosterone deficiency, and the pathophysiology underlying them, are essentially those described in Chapter 593 . These include progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia, and hyperkalemia. These problems typically first develop in affected infants at approximately 10-14 days of age. Without treatment, shock, cardiac arrhythmias, and death may occur within days or weeks.

CAH differs from other causes of primary adrenal insufficiency in that precursor steroids accumulate proximal to the blocked enzymatic conversion. Because cortisol is not synthesized efficiently, ACTH levels are high, leading to hyperplasia of the adrenal cortex and levels of precursor steroids that may be hundreds of times normal. In the case of 21-hydroxylase deficiency, these precursors include 17-hydroxyprogesterone and progesterone. Progesterone and perhaps other metabolites act as antagonists of the mineralocorticoid receptor and thus may exacerbate the effects of aldosterone deficiency in untreated patients.

It is not unusual for children with classic CAH to require hospitalization for intercurrent illnesses during childhood. This is most likely to occur in the first 2 yr of life and to be precipitated by gastroenteritis, because such illnesses may cause fluid and electrolyte losses and vomiting may interfere with medication dosing. Children requiring high fludrocortisone doses are most likely to be hospitalized, presumably because those patients have the greatest propensity to salt wasting.

Prenatal Androgen Excess

The most important problem caused by accumulation of steroid precursors is that 17-hydroxyprogesterone is shunted into the pathway for androgen biosynthesis, leading to high levels of androstenedione that are converted outside the adrenal gland to testosterone. This problem begins in affected fetuses by 8-10 wk of gestation and leads to abnormal genital development in females (see Figs. 594.1 and 594.2).

The external genitalia of males and females normally appear identical early in gestation (see Chapter 600). Affected females who are exposed in utero to high levels of androgens of adrenal origin have masculinized external genitalia (see Figs. 594.1 and 594.2). This is manifested by enlargement of the clitoris and by partial or complete labial fusion. The vagina usually has a common opening with the urethra (urogenital sinus). The clitoris may be so enlarged that it resembles a penis; because the urethra opens below this organ, some affected females may be mistakenly presumed to be males with hypospadias and cryptorchidism. The severity of virilization is usually greatest in females with the salt-losing form of 21-hydroxylase deficiency (see Table 594.2). The internal genital organs are normal, because affected females have normal ovaries and not testes and thus do not secrete antimüllerian hormone.

Prenatal exposure of the brain to high levels of androgens may influence subsequent sexually dimorphic behaviors in affected females. Females may demonstrate aggressive play behavior, tend to be interested in masculine toys such as cars and trucks, and often show decreased interest in playing with dolls. Women may have decreased interest in maternal roles. There is an increased frequency of homosexuality in affected females. Nonetheless, most function heterosexually and do not have gender identity confusion or dysphoria. It is unusual for affected females to assign themselves a male role except in some with the severest degree of virilization.

Male infants appear normal at birth. Thus the diagnosis may not be made in males until signs of adrenal insufficiency develop. Because patients with this condition can deteriorate quickly, infant males are more likely to die than infant females. For this reason, all 50 American states and many countries have instituted **newborn screening** for this condition (see section on “Newborn Screening” in Chapter 594.2).

Postnatal Androgen Excess

Untreated or inadequately treated children of both sexes develop additional signs of androgen excess after birth. Males with the simple virilizing form of 21-hydroxylase deficiency often have a delayed diagnosis because they appear normal and rarely develop adrenal insufficiency.

Signs of androgen excess include **rapid somatic growth** and **accelerated skeletal maturation** . Thus affected patients are tall in childhood, but premature closure of the epiphyses causes growth to stop relatively early, and adult stature is stunted (see Fig. 594.1). Muscular development may be excessive. Pubic and axillary hair may appear, and acne and a deep voice may develop. The penis, scrotum, and prostate may become enlarged in affected males; however, the **testes are usually prepubertal** in size so that they appear small relative to the enlarged penis. Occasionally, ectopic adrenocortical cells in the testes of patients become hyperplastic similarly to the adrenal glands, producing **testicular adrenal rest tumors** (see Chapter 602). The clitoris may become further enlarged in affected females (see Fig. 594.1). Although the internal genital structures are female, breast development and menstruation may not occur unless the excessive production of androgens is suppressed by adequate treatment.

Similar but usually milder signs of androgen excess may occur in **nonclassic 21-hydroxylase deficiency** (see Table 594.2). In this attenuated form, cortisol and aldosterone levels are normal and affected females have normal genitals at birth. Males and females may present with precocious pubarche and early development of pubic and axillary hair. **Hirsutism, acne, menstrual disorders, and infertility** may develop later in life, but many females and males are completely asymptomatic.

Adrenomedullary Dysfunction

Development of the adrenal medulla requires exposure to the extremely high cortisol levels normally present within the adrenal gland. Thus patients with classic CAH have abnormal adrenomedullary function, as evidenced by blunted epinephrine responses, decreased blood glucose, and lower heart rates with exercise. Ability to exercise is unimpaired, and the clinical significance of these findings is uncertain. Adrenomedullary dysfunction may exacerbate the cardiovascular effects of cortisol deficiency in untreated or undertreated patients.

Laboratory Findings

See Table 594.1 .

Patients with salt-losing disease have typical laboratory findings associated with cortisol and aldosterone deficiency, including hyponatremia, hyperkalemia, metabolic acidosis, and, often, hypoglycemia, but these abnormalities can take 10-14 days or longer to develop after birth. Blood levels of **17-hydroxyprogesterone** are markedly elevated. However, levels of this hormone are high during the first 2-3 days of life even in unaffected infants and especially if they are sick or premature. After infancy, once the circadian rhythm of cortisol is established, 17-hydroxyprogesterone levels vary in the same circadian pattern, being highest in the morning and lowest at night. Blood levels of cortisol are usually low in patients with the salt-losing type of disease. They are often normal in patients with simple virilizing disease but inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels. In addition to 17-hydroxyprogesterone, levels of androstenedione and testosterone are elevated in affected females; testosterone is not elevated in affected males, because normal infant males have high testosterone levels compared with those seen later in childhood. Levels of urinary 17-ketosteroids and pregnanetriol are elevated but are now rarely used clinically because blood samples are easier to obtain than 24-hr urine collections. ACTH levels are elevated but have no diagnostic utility over 17-hydroxyprogesterone levels. Plasma levels of renin are elevated, and serum aldosterone is inappropriately low for the renin level. However, renin levels are high in normal infants in the 1st few wk of life.

Diagnosis of 21-hydroxylase deficiency is most reliably established by measuring 17-hydroxyprogesterone before and 30 or 60 min after an intravenous bolus of 0.125-0.25 mg of cosyntropin (ACTH 1-24). Nomograms exist that readily distinguish normals and patients with nonclassic and classic 21-hydroxylase deficiency. Heterozygous carriers of this autosomal recessive disorder tend to have higher ACTH-stimulated 17-hydroxyprogesterone levels than genetically unaffected individuals, but there is significant overlap between subjects in these 2 categories. However, in infants with frank electrolyte abnormalities or circulatory instability, it may not be possible or necessary to delay treatment to perform this test, as levels of precursors will be sufficiently elevated on a random blood sample to make the diagnosis.

Genotyping is clinically available and may help to confirm the diagnosis, but it is expensive and may take weeks. Because the gene conversions that generate most mutant alleles may transfer more than one mutation, at least 1 parent should also be genotyped to determine which mutations lie on each allele.

Differential Diagnosis

Disorders of sexual development are discussed more generally in Chapter 606 . The initial step in evaluating an infant with ambiguous genitalia is a thorough physical examination to define the anatomy of the genitals, locate the urethral meatus, palpate the scrotum or labia and the inguinal regions for testes (palpable gonads almost always indicate the presence of testicular tissue and thus that the infant is a genetic male), and look for any other anatomic abnormalities. Ultrasonography is helpful in demonstrating the presence or absence of a uterus and can often locate the gonads. A rapid karyotype (such as fluorescence in situ hybridization of interphase nuclei for X and Y chromosomes) can quickly determine the genetic sex of the infant. These results are all likely to be available before the results of hormonal testing and together allow the clinical team to advise the parents as to the genetic sex of the infant and the anatomy of internal reproductive structures. Injection of contrast medium into the urogenital sinus of a virilized female demonstrates a vagina and uterus, and many surgeons use this information to formulate a plan for surgical management.

Prenatal Diagnosis

Prenatal diagnosis of 21-hydroxylase is possible late in the 1st trimester by analysis of DNA obtained by chorionic villus sampling or during the 2nd trimester by amniocentesis. This is usually done because the parents already have an affected child. Most often, the *CYP21* gene is analyzed for frequently occurring mutations; more rare mutations may be detected by DNA sequencing.

Newborn Screening

Because 21-hydroxylase deficiency is often undiagnosed in affected males until they have severe adrenal insufficiency, all states in the United States and many other countries have instituted newborn screening programs. These programs analyze **17-hydroxyprogesterone** levels in dried blood obtained by heelstick and absorbed on filter paper cards; the same cards are screened in parallel for other congenital conditions, such as hypothyroidism and phenylketonuria. Potentially affected infants are typically quickly recalled for additional testing (electrolytes and repeat 17-hydroxyprogesterone determination) at approximately 2 wk of age. Infants with salt-wasting disease often have abnormal electrolytes by this age but are usually not severely ill. Thus screening programs are effective in preventing many cases of adrenal crisis in affected males. The nonclassic form of the disease is not reliably detected by newborn screening, but this is of little clinical significance because adrenal insufficiency does not occur in this type of 21-hydroxylase deficiency.

The main difficulty with current newborn screening programs is that to reliably detect all affected infants, the cutoff 17-hydroxyprogesterone levels for recalls are set so low that there is a very high frequency of false-positive results (i.e., the test has a low positive predictive value of as little as 1%). This problem is worst in premature infants. Positive predictive value can be improved by using cutoff levels based on gestational age and by using more specific 2nd-tier screening methods such as liquid chromatography followed by tandem mass spectrometry.

Treatment

Glucocorticoid Replacement

Cortisol deficiency is treated with glucocorticoids. Treatment also suppresses excessive production of androgens by the adrenal cortex and thus minimizes problems such as excessive growth and skeletal maturation and virilization. This often requires larger glucocorticoid doses than are needed in other forms of adrenal insufficiency, typically 15-20 mg/m^2 /24 hr of hydrocortisone daily administered orally in 3 divided doses. Affected infants usually require dosing at the high end of this range. Double or triple doses are indicated during periods of stress, such as infection or surgery. Glucocorticoid treatment must be continued indefinitely in all patients with classic 21-hydroxylase deficiency but may not be necessary in patients with nonclassic disease unless signs of androgen excess are present. Therapy must be individualized. It is desirable to maintain linear growth along percentile lines; crossing to higher height percentiles may suggest undertreatment, whereas loss of height percentiles often indicates overtreatment with glucocorticoids. Overtreatment is also suggested by excessive weight gain. Pubertal development should be monitored by periodic examination, and skeletal maturation is evaluated by serial radiographs of the hand and wrist for bone age. Hormone levels, particularly 17-hydroxyprogesterone and androstenedione, should be measured early in the morning, before taking the morning medications, or at a consistent time in relation to medication dosing. In general, desirable 17-hydroxyprogesterone levels are in the high-normal range or several times normal; low-normal levels can usually be achieved only with excessive glucocorticoid doses. Alternative delivery modalities have undergone small clinical trials, including delayed release hydrocortisone tablets and the use of a continuous subcutaneous insulin infusion device (insulin pump) to deliver hydrocortisone in a pattern more closely approximating the normal diurnal variation in cortisol secretion. At present, these approaches have not entered clinical practice.

Menarche occurs at the appropriate age in most females in whom good control has been achieved; it may be delayed in females with suboptimal control. Children with simple virilizing disease, particularly males, are frequently not diagnosed until 3-7 yr of age, at which time skeletal maturation may be 5 yr or more in advance of chronological age. In some children, especially if the bone age is 12 yr or more, spontaneous central (i.e., gonadotropin-dependent) puberty may occur when treatment is instituted, because therapy with hydrocortisone suppresses production of adrenal androgens and thus stimulates release of pituitary gonadotropins if the appropriate level of hypothalamic maturation is present. This form of superimposed true precocious puberty may be treated with a gonadotropin hormone–releasing hormone analog such as leuprolide (see Chapter 578.1).

Males with 21-hydroxylase deficiency who have had inadequate corticosteroid therapy may develop **testicular adrenal rest tumors** , which usually regress with increased steroid dosage. Testicular MRI, ultrasonography, and color flow Doppler examination help to define the character and extent of disease. Testis-sparing surgery for steroid-unresponsive tumors has been reported.

Mineralocorticoid Replacement

Patients with salt-wasting disease (i.e., aldosterone deficiency) require mineralocorticoid replacement with fludrocortisone. Infants may have very high mineralocorticoid requirements in the 1st few mo of life, usually 0.1-0.3 mg daily in 2 divided doses but occasionally up to 0.4 mg daily, and often require sodium supplementation (sodium chloride, 8 mmol/kg) in addition to the mineralocorticoid. Older infants and children are usually maintained with 0.05-0.1 mg daily of fludrocortisone. In some patients, simple virilizing disease may be easier to control with a low dose of fludrocortisone in addition to hydrocortisone even when these patients have normal aldosterone levels in the absence of mineralocorticoid replacement. Therapy is evaluated by monitoring of vital signs; tachycardia and hypertension are signs of overtreatment with mineralocorticoids. Serum electrolytes should be measured frequently in early infancy as therapy is adjusted. Plasma renin activity is a useful way to determine adequacy of therapy; it should be maintained in or near the normal range but not suppressed.

Additional approaches to improve outcome have been proposed but have not yet become the standard of care. These include an antiandrogen such as flutamide to block the effects of excessive androgen levels, and/or an aromatase inhibitor such as anastrozole, which blocks conversion of androgens to estrogen and thus retards skeletal maturation, a process that is sensitive to estrogens in both males and females. Aromatase inhibitors generally should not be used in pubertal females because they will retard normal puberty and may expose the ovaries to excessive levels of gonadotropins. Growth hormone, with or without luteinizing hormone–releasing hormone agonists to retard skeletal maturation, has been suggested to improve adult height.

Surgical Management of Ambiguous Genitals

Significantly virilized females usually undergo surgery between 2 and 6 mo of age. If there is severe clitoromegaly, the clitoris is reduced in size, with partial excision of the corporal bodies and preservation of the neurovascular bundle; however, moderate clitoromegaly may become much less noticeable even without surgery as the patient grows. Vaginoplasty and correction of the urogenital sinus usually are performed at the time of clitoral surgery; revision in adolescence is often necessary.

Risks and benefits of surgery should be fully discussed with parents of affected females. There is limited long-term follow-up of functional outcomes in patients who have undergone modern surgical procedures. It appears that female sexual dysfunction increases in frequency and severity in those with the most significant degrees of genital virilization and with the degree of enzymatic impairment (prenatal androgen exposure) caused by each patient's mutations (see Table 594.2). Sex assignment of infants with disorders of sexual differentiation (including CAH) is usually based on expected sexual functioning and fertility in adulthood with early surgical correction of the external genitalia to conform with the sex assignment. Gender dysphoria is not common with CAH; it occurs mostly in females with the salt-wasting form of the disease and the greatest degree of virilization.

Lay and medical opponents of genital surgery for other disorders of sexual differentiation bring up the concern that it ignores any prenatally biased gender role predisposition from androgen exposure and precludes the patient from having any decision as to the patient's own preferred sexual identity and what surgical correction of the genitals should be performed. They advocate that treatment should be aimed primarily at educating the patient, family, and others about the medical condition, its treatment, and how to deal with the intersex condition. They propose that surgery should be delayed until the patient decides on what, if any, correction should be performed. Not all lay groups support delayed surgery and many agree with appropriate surgery during infancy. Severely virilized genotypic (XX) females raised as males have generally functioned well in the male gender as adults.

In adolescent and adult females with poorly controlled 21-hydroxylase deficiency (hirsutism, obesity, amenorrhea), bilateral laparoscopic adrenalectomy (with hormone replacement) may be an alternative to standard medical hormone replacement therapy, but because the adrenal glands have been removed, patients treated in this way may be more susceptible to acute adrenal insufficiency if treatment is interrupted. Moreover, they may exhibit signs of elevated ACTH levels such as abnormal pigmentation.

Prenatal Treatment

Besides genetic counseling, the main goal of prenatal diagnosis is to facilitate prenatal treatment of affected females. Mothers with pregnancies at risk may be given dexamethasone, a steroid that readily crosses the placenta, in an amount of 20 µg/kg prepregnancy maternal weight daily in 2 or 3 divided doses. This suppresses secretion of steroids by the fetal adrenal, including secretion of adrenal androgens. If started by 6 wk of gestation, it ameliorates virilization of the external genitals in affected females. Chorionic villus biopsy is then performed to determine the sex and genotype of the fetus; therapy is continued only if the fetus is an affected female. DNA analysis of fetal cells isolated from maternal plasma for sex determination and *CYP21* gene analysis may permit earlier identification of the affected female fetus. Treatment should be considered only in affected female fetuses. Children exposed to this therapy have slightly lower birthweights. Effects on personality or cognition, such as increased shyness, have been suggested but not consistently observed. At present there is insufficient information to determine whether the long-term risks are acceptable, particularly in the males and unaffected females who derive no direct benefit from the treatment. Maternal side effects of prenatal treatment have included edema, excessive weight gain, hypertension, glucose intolerance, cushingoid facial features, and severe striae. Consensus statements from professional societies recommend that prenatal treatment be carried out only under institutional protocols, but it is sometimes offered as an option outside the research setting by high-risk obstetricians in some locales.

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594.2

Congenital Adrenal Hyperplasia Caused by 11β-Hydroxylase Deficiency

Perrin C. White

Keywords

hypertensive

Etiology

Deficiency of 11β-hydroxylase is caused by a mutation in the *CYP11B1* gene located on chromosome 8q24. *CYP11B1* mediates 11-hydroxylation of 11-deoxycortisol to cortisol. Because 11-deoxycortisol is not converted to cortisol, levels of corticotropin are high. In consequence, precursors—particularly 11-deoxycortisol and deoxycorticosterone—accumulate and are shunted into androgen biosynthesis in the same manner as occurs in 21-hydroxylase deficiency. The adjacent *CYP11B2* gene encoding aldosterone synthase is generally unaffected in this disorder, so patients are able to synthesize aldosterone normally.

Epidemiology

11β-Hydroxylase deficiency accounts for approximately 5% of cases of adrenal hyperplasia; its incidence in the general population has been estimated as 1 in 250,000 to 1 in 100,000. The disorder occurs relatively frequently in Israeli Jews of North African origin (1 in 15,000-17,000 live births). In this ethnic group, almost all alleles carry an Arg448 to His (R448H) mutation in *CYP11B1* , but many other mutations have been identified. This disorder presents in a classic, severe form and very rarely in a nonclassic, milder form.

Clinical Manifestations

Although cortisol is not synthesized efficiently, aldosterone synthetic capacity is normal, and some corticosterone is synthesized from progesterone by the intact aldosterone synthase enzyme. Thus it is unusual for patients to manifest signs of adrenal insufficiency such as hypotension, hypoglycemia, hyponatremia, and hyperkalemia. Approximately 65% of patients become **hypertensive,** although this can take several years to develop. Hypertension is probably a consequence of elevated levels of deoxycorticosterone, which has mineralocorticoid activity. Infants may transiently develop signs of mineralocorticoid deficiency after treatment with hydrocortisone is instituted. This is presumably from sudden suppression of deoxycorticosterone secretion in a patient with atrophy of the zona glomerulosa caused by chronic suppression of renin activity.

All signs and symptoms of androgen excess that are found in 21-hydroxylase deficiency may also occur in 11β-hydroxylase deficiency.

Laboratory Findings

Plasma levels of 11-deoxycortisol and deoxycorticosterone are elevated. Because deoxycorticosterone and some metabolites have mineralocorticoid activity, plasma renin activity is suppressed. Consequently, aldosterone levels are low even though the ability to synthesize aldosterone is intact. Hypokalemic alkalosis occasionally occurs.

Treatment

Patients are treated with hydrocortisone in doses similar to those used for 21-hydroxylase deficiency. Mineralocorticoid replacement is sometimes transiently required in infancy but is rarely necessary otherwise. Hypertension often resolves with glucocorticoid treatment but may require additional therapy if it is of long standing. Calcium channel blockers may be beneficial under these circumstances.

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594.3

Congenital Adrenal Hyperplasia Caused by 3β-Hydroxysteroid Dehydrogenase Deficiency

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Perrin C. White

Keywords

salt-wasting crises
incomplete virilization

Etiology

Deficiency of 3β-hydroxysteroid dehydrogenase (3β-HSD) occurs in fewer than 2% of patients with adrenal hyperplasia. This enzyme is required for conversion of Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, dehydroepiandrosterone [DHEA]) to Δ4 steroids (progesterone, 17-hydroxyprogesterone, and androstenedione). Thus deficiency of the enzyme results in decreased synthesis of cortisol, aldosterone, and androstenedione but increased secretion of DHEA (see Fig. 592.1 in Chapter 592). The 3β-HSD isozyme expressed in the adrenal cortex and gonad is encoded by the *HSD3B2* gene located on chromosome 1p13.1. More than 30 mutations in the *HSD3B2* gene have been described in patients with 3β-HSD deficiency.

Clinical Manifestations

Because cortisol and aldosterone are not synthesized in patients with the classic form of the disease, infants are prone to **salt-wasting crises.** Because androstenedione and testosterone are not synthesized, **males are incompletely virilized.** Varying degrees of hypospadias may occur, with or without bifid scrotum or cryptorchidism. Because DHEA levels are elevated and this hormone is a weak androgen, females are mildly virilized, with slight to moderate clitoral enlargement. Postnatally, continued excessive DHEA secretion can cause precocious adrenarche. During adolescence and adulthood, hirsutism, irregular menses, and polycystic ovarian disease occur in females. Males manifest variable degrees of hypogonadism, although appropriate male secondary sexual development may occur. However, a persistent defect of testicular 3β-HSD is demonstrated by the high Δ5:Δ4 steroid ratio in testicular effluent.

Laboratory Findings

The hallmark of this disorder is the marked elevation of the Δ5 steroids (such as 17-hydroxypregnenolone and DHEA) preceding the enzymatic block. Patients may also have elevated levels of 17-hydroxyprogesterone because of the extraadrenal 3β-HSD activity that occurs in peripheral tissues; these patients may be mistaken for patients with 21-hydroxylase deficiency. The ratio of 17-hydroxypregnenolone:17-hydroxyprogesterone is markedly elevated in 3β-HSD deficiency, in contrast to the decreased ratio in 21-hydroxylase deficiency. Plasma renin activity is elevated in the salt-wasting form.

Differential Diagnosis

It is not unusual for children with premature adrenarche, or women with signs of androgen excess, to have mild to moderate elevations in DHEA levels. It has been suggested that such individuals have *nonclassic 3 β-HSD deficiency* . Mutations in the *HSD3B2* gene are usually not found in such individuals, and a nonclassic form of this deficiency must actually be quite rare. The activity of 3β-HSD in the adrenal zonae fasciculata and reticularis, relative to CYP17 (17-hydroxylase/17,20-lyase) activity, normally decreases during adrenarche to facilitate DHEA synthesis, and so modest elevations in DHEA in preteenage children or women usually represent a normal variant.

Treatment

Patients require glucocorticoid and mineralocorticoid replacement with hydrocortisone and fludrocortisone, respectively, as in 21-hydroxylase deficiency. Incompletely virilized genetic males in whom a male sex of rearing is contemplated may benefit from several injections of 25 mg of a depot form of testosterone every 4 wk early in infancy to increase the size of the phallus. They may also require testosterone replacement at puberty.

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594.4

Congenital Adrenal Hyperplasia Caused by 17-Hydroxylase Deficiency

Perrin C. White

Keywords

hypertension
hypokalemia
incomplete virilization
failure of sexual development

Etiology

Less than 1% of CAH cases are caused by 17-hydroxylase deficiency, but the condition is apparently more common in Brazil and China. A single polypeptide, CYP17, catalyzes 2 distinct reactions: 17-hydroxylation of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, and the 17,20-lyase reaction mediating conversion of 17-hydroxypregnenolone to DHEA and, to a lesser extent, 17-hydroxyprogesterone to Δ4-androstenedione. DHEA and androstenedione are steroid precursors of testosterone and estrogen (see Fig. 592.1 in Chapter 592). The enzyme is expressed in both the adrenal cortex and the gonads and is encoded by a gene on chromosome 10q24.3. Most mutations affect both the hydroxylase and lyase activities, but rare mutations can affect either activity alone.

Mutations in genes other than *CYP17* can have the same phenotype as 17,20-lyase deficiency (i.e., deficient androgen synthesis with normal cortisol synthesis). These include an accessory electron transfer protein, cytochrome-b_5 , and mutations in 2 aldo-keto reductases, AKR1C2 and AKR1C4. These AKR1C isozymes normally catalyze 3α-HSD activity, which allows synthesis of the potent androgen dihydrotestosterone through an alternative backdoor biosynthetic pathway that does not include testosterone as an intermediate.

Clinical Manifestations and Laboratory Findings

Patients with 17-hydroxylase deficiency cannot synthesize cortisol, but their ability to synthesize corticosterone is intact. Because corticosterone is an active glucocorticoid, patients do not develop adrenal insufficiency. Deoxycorticosterone, the immediate precursor of corticosterone, is synthesized in excess. This can cause **hypertension, hypokalemia,** and suppression of renin and aldosterone secretion, as occurs in 11β-hydroxylase deficiency. In contrast to 11β-hydroxylase deficiency, patients with 17-hydroxylase deficiency are unable to synthesize sex hormones. Affected **males are incompletely virilized** and present as phenotypic females (but gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity. Affected females usually present with **failure of sexual development** at the expected time of **puberty.** 17-Hydroxylase deficiency in females must be considered in the differential diagnosis of primary hypogonadism (see Chapter 604). Levels of deoxycorticosterone are elevated, and renin and aldosterone are consequently suppressed. Cortisol and sex steroids are unresponsive to stimulation with

ACTH and human chorionic gonadotropin, respectively.

Patients with isolated 17,20-lyase deficiency have deficient androgen synthesis with normal cortisol synthesis and therefore do not become hypertensive.

Treatment

Patients with 17-hydroxylase deficiency require glucocorticoid replacement with hydrocortisone to suppress secretion of deoxycorticosterone and thus control hypertension. Additional antihypertensive medication may be required. Females require estrogen replacement at puberty. Genetic males may require either estrogen or androgen supplementation depending on the sex of rearing. Because of the possibility of malignant transformation of abdominal testes, as is more commonly encountered with androgen insensitivity syndrome (see Chapter 606.2), genetic males with severe 17-hydroxylase deficiency being reared as females require gonadectomy at or before adolescence.

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594.5

Lipoid Adrenal Hyperplasia

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Keywords

phenotypically female

Etiology

Lipoid adrenal hyperplasia is a rare disorder, most frequently found in Japanese persons. Patients with this disorder exhibit marked accumulation of cholesterol and lipids in the adrenal cortex and gonads, associated with severe impairment of all steroidogenesis. Lipoid adrenal hyperplasia is usually caused by mutations in the gene for steroidogenic acute regulatory protein (StAR), a mitochondrial protein that promotes the movement of cholesterol from the outer to the inner mitochondrial membrane. However, mutations in the *CYP11A1* gene (which encodes the cholesterol side chain cleavage enzyme) have been reported in several patients.

Some cholesterol is able to enter mitochondria even in the absence of StAR, so it might be supposed that this disorder would not completely impair steroid biosynthesis. However, the accumulation of cholesterol in the cytoplasm is cytotoxic, eventually leading to death of all steroidogenic cells in which StAR is normally expressed. This occurs prenatally in the adrenals and testes. The ovaries do not normally synthesize steroids until puberty, so cholesterol does not accumulate and the ovaries can retain the capacity to synthesize estrogens until adolescence.

Although estrogens synthesized by the placenta are required to maintain pregnancy, the placenta does not require StAR for steroid biosynthesis. Thus mutations of StAR are not prenatally lethal.

Clinical Manifestations

Patients with lipoid adrenal hyperplasia are usually unable to synthesize any adrenal steroids. Thus affected infants are likely to be confused with those with adrenal hypoplasia congenita. Salt-losing manifestations are typical, and many infants die in early infancy. Genetic males are unable to synthesize androgens and thus are **phenotypically female** but with gonads palpable in the labia majora or inguinal areas. Genetic females appear normal at birth and may undergo feminization at puberty with menstrual bleeding. They, too, progress to hypergonadotropic hypogonadism when accumulated cholesterol kills granulosa (i.e., steroid synthesizing) cells in the ovary.

Laboratory Findings

Adrenal and gonadal steroid hormone levels are low in lipoid adrenal hyperplasia, with a decreased or absent response to stimulation (ACTH, human chorionic gonadotropin). Plasma renin levels are increased.

Imaging studies of the adrenal gland demonstrating massive adrenal enlargement in the newborn help to establish the diagnosis of lipoid adrenal hyperplasia.

Treatment

Patients require glucocorticoid and mineralocorticoid replacement. Genetic males are usually assigned a female sex of rearing; thus both genetic males and females require estrogen replacement at the expected age of puberty.

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594.6

Deficiency of P450 Oxidoreductase (Antley-Bixler Syndrome)

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Keywords

maternal virilization
Antley-Bixler syndrome
luteoma of pregnancy

Etiology, Pathogenesis, and Clinical Manifestations

P450 oxidoreductase (POR; gene located on chromosome 7q11.3) is required for the activity of all microsomal cytochrome P450 enzymes (see Chapter 592), including the adrenal enzymes CYP17 and CYP21. Thus complete POR deficiency abolishes all microsomal P450 activity. This is embryonically lethal in mice and presumably also in humans. Patients with mutations that decrease but do not abolish POR activity have partial deficiencies of 17-hydroxylase and 21-hydroxylase activities in the adrenals. A single recurrent mutation A287P (alanine-287 to proline) is found on approximately 40% of alleles.

Deficiency of 17-hydroxylase leads to incomplete masculinization in males; 21-hydroxylase deficiency may lead to virilization in females. In addition, aromatase *(CYP19)* activity in the placenta is decreased, leading to unopposed action of androgens produced by the fetal adrenal. This exacerbates virilization of female fetuses and may **virilize the mother** of an affected fetus as well. Although it is puzzling that affected females could be virilized despite a partial deficiency in *CYP17* (which is required for androgen biosynthesis), an alternative (backdoor) biosynthetic pathway is used in which 17-hydroxyprogesterone is converted to 5α-pregnane-3α,17α-diol-20-one, a metabolite that is a much better substrate for the 17,20-lyase activity of *CYP17* than the usual substrate, 17-hydroxypregnenolone (see Chapter 592). The metabolite is then converted in several enzymatic steps to dihydrotestosterone, a potent androgen.

Because many other P450 enzymes are affected, patients often (but not invariably) have other congenital anomalies collectively referred to as **Antley-Bixler syndrome.** These include craniosynostosis; brachycephaly; frontal bossing; severe midface hypoplasia with proptosis and choanal stenosis or atresia; humeroradial synostosis; medial bowing of ulnas; long, slender fingers with camptodactyly; narrow iliac wings; anterior bowing of femurs; and malformations of the heart and kidneys. Studies of mutant mice suggest that the metabolic defects responsible for these anomalies include defective metabolism of retinoic acid, leading to elevated levels of this teratogenic compound, and deficient biosynthesis of cholesterol.

Epidemiology

The prevalence is not known with certainty. It must be rare compared with 21-hydroxylase deficiency but might occur at similar frequencies to the other forms of CAH.

Laboratory Findings

Serum steroids that are not 17- or 21-hydroxylated are most increased, including pregnenolone and progesterone. 17-Hydroxy, 21-deoxysteroids are also increased, including 17-hydroxypregnenolone, 17-hydroxyprogesterone, and 21-deoxycortisol. Urinary steroid metabolites may be determined by quantitative mass spectrometry. Metabolites excreted at increased levels include pregnanediol, pregnanetriol, pregnanetriolone, and corticosterone metabolites. Urinary cortisol metabolites are decreased. Genetic analysis demonstrates mutations in the *POR* gene.

Differential Diagnosis

This disorder must be distinguished from other forms of CAH, particularly 21-hydroxylase deficiency in females, which is far more common and has similar laboratory findings. Suspicion for *POR* deficiency may be raised if the mother is virilized or if the associated abnormalities of Antley-Bixler syndrome are present. Conversely, virilization of both the mother and her daughter can result from a **luteoma of pregnancy** , but in this case postnatal abnormalities of corticosteroid biosynthesis should not be observed. Antley-Bixler syndrome may also occur without abnormalities of steroid hormone biosynthesis, resulting from mutations in the fibroblast growth factor receptor FGFR2.

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594.7

Aldosterone Synthase Deficiency

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Keywords

hyponatremia
hyperkalemia
metabolic acidosis
Adrenal hypoplasia congenital
Pseudohypoaldosteronism

Etiology

This is an autosomal recessive disorder in which conversion of corticosterone to aldosterone is impaired; a group of Iranian Jewish patients has been the most thoroughly studied. The majority of cases result from mutations in the *CYP11B2* gene coding for aldosterone synthase; however, linkage to *CYP11B2* has been excluded in other kindreds. When not caused by *CYP11B2* mutations, the disorder has been termed *familial hyperreninemic hypoaldosteronism type 2;* the causative gene or genes have not yet been identified.

Aldosterone synthase mediates the 3 final steps in the synthesis of aldosterone from deoxycorticosterone (11β-hydroxylation, 18-hydroxylation, and 18-oxidation). Although 11β-hydroxylation is required to convert deoxycorticosterone to corticosterone, this conversion can also be catalyzed by the related enzyme, CYP11B1, located in the fasciculata, which is unaffected in this disorder. For the same reason, these patients have normal cortisol biosynthesis.

The disease has been classified into 2 types, termed *corticosterone methyloxidase deficiency types I and II.* They differ only in levels of the immediate precursor of aldosterone, 18-hydroxycorticosterone; levels are low in type I deficiency and elevated in type II deficiency. These differences do not correspond in a simple way to particular mutations and are of limited clinical importance.

Clinical Manifestations

Infants with aldosterone synthase deficiency may have severe electrolyte abnormalities with **hyponatremia, hyperkalemia,** and **metabolic acidosis.**

Because cortisol synthesis is unaffected, infants rarely become as ill as untreated infants with salt-losing forms of CAH such as 21-hydroxylase deficiency. Thus some infants escape diagnosis. Later in infancy or in early childhood they may exhibit failure to thrive and poor growth. Adults often are asymptomatic, although they may develop electrolyte abnormalities when depleted of sodium through procedures such as bowel preparation for a barium enema.

Laboratory Findings

Infants have elevated plasma renin activity. Aldosterone levels are decreased; they may be at the lower end of the normal range but are always inappropriately low for the degree of hyperkalemia or hyperreninemia. Corticosterone levels are often elevated.

Some, but not all, patients have marked elevation of 18-hydroxycorticosterone; however, low levels of this steroid do not exclude the diagnosis. In those kindreds in which 18-hydroxycorticosterone levels are elevated in affected individuals, this biochemical abnormality persists in adults even when they have no electrolyte abnormalities.

Differential Diagnosis

It is important to distinguish aldosterone synthase deficiency from primary adrenal insufficiency in which both cortisol and aldosterone are affected (including salt-wasting forms of CAH), because the latter condition is usually associated with a much greater risk of shock and hyponatremia. This becomes apparent after the appropriate laboratory studies. **Adrenal hypoplasia congenita** may initially present with aldosterone deficiency; all male infants with apparently isolated aldosterone deficiency should be carefully monitored for subsequent development of cortisol deficiency. **Pseudohypoaldosteronism** (see Chapter 593.4) may have similar electrolyte abnormalities and hyperreninemia, but aldosterone levels are high, and this condition usually does not respond to fludrocortisone treatment.

Treatment

Treatment consists of giving enough fludrocortisone (0.05-0.3 mg daily) or sodium chloride, or both, to return plasma renin levels to normal. With increasing age, salt-losing signs usually improve and drug therapy can often be discontinued.

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594.8

Glucocorticoid-Suppressible Hyperaldosteronism

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Keywords

low-renin hypertension

Etiology

Glucocorticoid-suppressible hyperaldosteronism (glucocorticoid-remediable aldosteronism, familial hyperaldosteronism type I) is an autosomal dominant form of **low-renin hypertension** in which hyperaldosteronism is rapidly suppressed by glucocorticoid administration. This unusual effect of glucocorticoids suggests that aldosterone secretion in this disorder is regulated by ACTH instead of by the renin-angiotensin system. In addition to abnormally regulated secretion of aldosterone, there is marked overproduction of 18-hydroxycortisol and 18-oxocortisol. The synthesis of these steroids requires both 17-hydroxylase (CYP17) activity, which is expressed only in the zona fasciculata, and aldosterone synthase (CYP11B2) activity, which is normally expressed only in the zona glomerulosa. Together, these features imply that aldosterone synthase is being expressed in a manner similar to the closely related enzyme steroid 11-hydroxylase *(CYP11B1)*. The disorder is caused by unequal meiotic crossing-over events between the *CYP11B1* and *CYP11B2* genes, which are closely linked on chromosome 8q24. An additional “chimeric” gene is produced, having regulatory sequences of *CYP11B1* juxtaposed with coding sequences of *CYP11B2*. This results in the inappropriate expression of a *CYP11B2* -like enzyme with aldosterone synthase activity in the adrenal fasciculata.

Clinical Manifestations

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension, typically approximately 30 mm Hg higher than unaffected family members of the same age. Others have more symptomatic hypertension with headache, dizziness, and visual disturbances. A strong family history of early-onset hypertension or early strokes may alert the clinician to the diagnosis. Some patients have chronic hypokalemia, but this is not a consistent finding and is usually mild.

Laboratory Findings

Patients have elevated plasma and urine levels of aldosterone and suppressed plasma renin activity. *Hypokalemia is not consistently present.* Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol are markedly increased. The hybrid *CYP11B1/CYP11B2* gene can be readily detected by molecular genetic methods.

Differential Diagnosis

This condition should be distinguished from primary aldosteronism based on bilateral hyperplasia or an aldosterone-producing adenoma (see Chapter 598). Most cases of primary aldosteronism are sporadic, although several affected kindreds have been reported. Patients with primary aldosteronism may also have elevated levels of 18-hydroxycortisol and 18-oxocortisol, and these biochemical tests should be used cautiously when attempting to distinguish primary and glucocorticoid-suppressible aldosteronism. By definition, a therapeutic trial of dexamethasone should suppress aldosterone secretion only in glucocorticoid-suppressible hyperaldosteronism, and genetic testing should identify the hybrid gene of glucocorticoid-suppressible hyperaldosteronism if it is present.

Treatment

Glucocorticoid-suppressible hyperaldosteronism is managed by daily administration of a glucocorticoid, usually dexamethasone, 25 µg/kg/day in divided doses. If necessary, effects of aldosterone can be blocked with a potassium-sparing diuretic such as spironolactone, eplerenone, or amiloride. Hypertension resolves in patients in whom the hypertension is not severe or of long standing. If hypertension is long standing, additional antihypertensive medication may be required, such as a calcium channel blocker.

Genetic Counseling

Because of the autosomal dominant mode of inheritance, at-risk family members should be investigated for this easily treated cause of hypertension.

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CHAPTER 595

Adrenocortical Tumors and Masses

Perrin C. White

Epidemiology

Adrenocortical tumors are rare in childhood, with an incidence of 0.3-0.5 cases per 1 million child-years. They occur in all age groups but most commonly in children younger than 6 yr of age and are slightly more frequent (1.6-fold) in females. In 2–10% of cases, the tumors are bilateral. Almost half of childhood adrenocortical tumors are carcinomas. Mutations in many genes can influence the risk of developing adrenal tumors (Table 595.1).

Table 595.1

Genes Involved in Adrenal Neoplasia

SYNDROME	ADRENAL NEOPLASIA TYPE	GENE MUTATION	OTHER PHENOTYPE
Li-Fraumeni syndrome	Adrenocortical carcinoma	*TP53*	Sarcoma, choroid plexus tumor, brain cancer, early breast cancer, leukemia, lymphoma
Multiple endocrine neoplasia type 1	Diffuse hyperplasia, nodular hyperplasia, adrenal adenoma, adrenocortical carcinoma	*MENIN*	Foregut neuroendocrine tumors, pituitary tumors, parathyroid hyperplasia or tumors, collagenoma, angiofibroma
Lynch syndrome	Adrenocortical carcinoma	*MSH2, MSH6, MLH1, PMS2*	Colorectal cancer, endometrial cancer, sebaceous neoplasms, ovarian cancer, pancreatic cancer, brain cancer
Beckwith-Wiedemann syndrome	Adrenal adenoma, adrenocortical carcinoma	*IGF2, CDKN1C* , *H19* methylation changes on 11p15	Macrosomia, hemihypertrophy, macroglossia, omphalocele, ear pits; Wilms tumor, hepatoblastoma
Familial adenomatous polyposis coli	Bilateral macronodular adrenal hyperplasia, aldosterone-producing	*APC*	Intestinal polyps, colon cancer, duodenal carcinoma, thyroid cancer, desmoid tumor, supernumerary teeth, congenital hypertrophy of

	adenoma, adrenocortical carcinoma		the retina, osteoma, epidermoid cysts
Neurofibromatosis type 1	Adrenocortical carcinoma, pheochromocytoma	*NF1*	Malignant peripheral nerve sheet tumor, café-au-lait spots, neurofibroma, optic glioma, Lisch nodule, skeletal abnormalities
Carney complex	Primary pigmented nodular adrenal disease, adrenocortical carcinoma	*PRKAR1A*	large-cell calcifying Sertoli cell tumors, thyroid adenoma, myxoma, somatotroph pituitary adenoma, lentigines
	Primary pigmented nodular adrenal disease	*PDE8B or PDE11A*	
Overexpression of steroidogenic factor-1	Adrenal adenoma, adrenocortical carcinoma	*Somatic amplification of NR5A1*	
McCune-Albright syndrome	Nodular hyperplasia, cortisol-secreting adenoma	*Activating somatic mosaic mutation of GNAS*	Hyperfunction of bone (producing fibrous dysplasia), gonads, thyroid, and pituitary.
	Cortisol-secreting adenomas	*Activating somatic mutations in PRKACA*	
Genetic causes of excess cortisol and aldosterone secretion	Hypertrophy of zona glomerulosa, aldosterone-producing adenoma	*Germline or somatic activating mutation in KCNJ5*	
	Aldosterone-producing adenoma	*Germline and somatic activating mutations in CACNA1D*	
	Aldosterone-producing adenoma	*Somatic mutations in ATP1A1 or ATP2B3*	
von Hippel-Landau syndrome	Pheochromocytoma	*VHL*	Retinal and central nervous system hemangioblastomas, renal clear cell carcinomas
Multiple endocrine neoplasia syndromes MEN2A and MEN2B	Pheochromocytoma	*RET*	Medullary thyroid carcinoma and parathyroid tumors; type 2B also may include multiple mucosal neuromas and intestinal ganglioneuromas, a marfanoid habitus, and other skeletal abnormalities
	Pheochromocytoma, often malignant	*SDHB, SDHD, SDHC*	Paragangliomas, sometimes associated with gastrointestinal stromal tumors and/or pulmonary chondromas (Carney-Stratakis dyad or triad)

Tumors may be associated with hemihypertrophy, usually occurring during the 1st few years of life. They are also associated with other congenital defects, particularly genitourinary tract and central nervous system abnormalities and hamartomatous defects.

595.1

Adrenocortical Carcinoma

Perrin C. White

Keywords

Hemihypertrophy
Adrenocortical carcinoma
Li-Fraumeni syndrome
Beckwith-Wiedemann syndrome
Multiple endocrine neoplasia type 1
Lynch syndrome

Etiology

The incidence of adrenocortical carcinoma is increased in several familial cancer syndromes resulting from abnormalities in genes that encode transcription factors implicated in cell proliferation, differentiation, senescence, apoptosis, and genomic instability. These include tumor protein 53 *(TP53)* , menin (the *MEN1* gene involved in multiple endocrine neoplasia type 1), the *APC* gene involved in familial adenomatous polyposis (FAP) coli, and the *PRKAR1A* gene encoding a cyclic adenosine monophosphate–dependent protein kinase regulatory subunit (also see Chapter 597).

Germline mutations in *TP53* (on chromosome 17p13.1) occur in 50–80% of children with adrenocortical carcinoma. They have been found in patients with isolated adrenal carcinoma as well as in patients with familial clustering of unusual malignancies (choroid plexus tumors, sarcomas, early-onset breast cancers, brain cancers, and leukemias); this latter condition is termed **Li-Fraumeni syndrome.** A 15-fold increased incidence of childhood adrenocortical tumors is found in southern Brazil, associated with a R337H mutation in *TP53* .

Overexpression of insulin-like growth factor 2 (encoded by *IGF2* , on chromosome 11p15.5) occurs in 80% of sporadic childhood adrenocortical tumors, as well as in those associated with **Beckwith-Wiedemann syndrome,** in which there is loss of the normal imprinting of genes in this chromosomal region. However, <1% of patients with Beckwith-Wiedemann syndrome develop an adrenocortical carcinoma. Further implicating insulin-like growth factors (IGFs) in pathogenesis, many pediatric adrenocortical tumors overexpress the IGF receptor, IGF1R.

Mutations in the *MENIN* gene on chromosome 11q13 cause **multiple endocrine neoplasia type 1** . Approximately 10% of MEN1 patients have adrenocortical tumors, of which ~14% are malignant.

Adrenocortical carcinomas also occur in patients with **Lynch syndrome** , a hereditary cancer syndrome (mainly colorectal and endometrial cancer) caused by mutations in genes involved in DNA mismatch repair. Finally, occasional adrenocortical carcinomas occur in patients with FAP, neurofibromatosis type 1, Werner syndrome, and Carney complex.

Overexpression of steroidogenic factor-1 (SF1, encoded by the NR5A1 gene), a transcription factor required for adrenal development (see Chapter 592) is associated with decreased overall survival and recurrence-free survival when it occurs in adults with adrenocortical carcinomas, but it is seen in most pediatric adrenocortical tumors, where it does not seem to have prognostic significance. Conversely, the messenger RNA encoding the nephroblastoma overexpressed (NOV) protein (also termed cysteine-rich protein 61, or connective tissue growth factor, or NOV gene-3) is significantly downregulated in childhood adrenocortical tumors. NOV is a selective proapoptotic factor for human adrenocortical cells, suggesting that abnormal apoptosis may play a role in childhood adrenocortical tumorigenesis.

Clinical Manifestations

Symptoms of endocrine hyperfunction are present in 80–90% of children with adrenal tumors. Tumors that secrete cortisol and aldosterone are discussed in Chapters 597 and 599 ; sex steroid secretion is discussed in the next section. Other tumors are detected as a consequence of symptoms related to local tumor growth, such as abdominal pain, or as incidental findings on abdominal imaging.

Tumors can usually be detected by ultrasonography, CT, or MRI. Preoperatively, the presence of metastatic disease should be determined by MRI or CT of the chest, abdomen, and pelvis. Because these tumors are metabolically active, ^{18}F-fluorodeoxyglucose PET/CT has very good sensitivity and specificity in distinguishing benign from malignant lesions, but it cannot distinguish adrenocortical carcinomas from other metabolically active tumors such as metastases, lymphoma, or pheochromocytoma. Radiochemical imaging of these tumors by positron emission tomography with ^{11}C-metomidate or single photon emission CT with ^{123}I-iodometomidate have been proposed but are not routinely available.

Pathologic Findings

Differentiation between benign and malignant tumors by histologic criteria (architecture, cytologic atypia, mitotic activity, atypical mitotic figures) is usually not possible; almost all pediatric adrenocortical tumors would be classified as malignant by the criteria used to classify adult tumors. Size is a useful prognostic factor, with tumors weighing less than 200 g, 200-400 g, and >400 g being classified as low, intermediate, and high risk (>10 cm diameter has also been suggested as a high-risk category). Incomplete resection and gross local invasion or metastasis are also associated with a poor prognosis. However, most tumors occurring in children younger than 4 yr of age fall into favorable prognostic categories.

Differential Diagnosis

For functioning tumors, the differential diagnoses are those of the main presenting signs and symptoms. The differential diagnosis for Cushing syndrome is discussed in Chapter 597 . For virilizing signs, the differential includes virilizing forms of adrenal hyperplasia (see Chapter 596) and factitious exposure to androgens, such as topical testosterone preparations. The differential diagnosis for hormonally inactive adrenocortical adenomas includes pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma (very rare in children). Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Not infrequently, a low level of autonomous cortisol secretion is detected that does not cause clinically apparent symptoms; this condition is sometimes referred to as subclinical Cushing syndrome.

Treatment

Functioning adrenocortical tumors should be removed surgically. There are no data on which to base a recommendation regarding nonfunctioning childhood incidentalomas; in adults, such tumors may be closely observed with imaging and repeat biochemical studies if smaller than 4 cm in diameter, but it is not certain that this is prudent in small children. Adrenalectomy may be performed either transperitoneally or laparoscopically. Some adrenocortical neoplasms are highly malignant and metastasize widely, but cure with regression of masculinizing or Cushingoid features may follow removal of less malignant, encapsulated tumors. Postoperatively, patients should be closely monitored biochemically, with frequent determinations of adrenal androgen levels and imaging studies. Recurrent symptoms or biochemical abnormalities should prompt a careful search for metastatic disease. Metastases primarily involve liver, lung, and regional lymph nodes. The majority of metastatic recurrences appear within 1 yr of tumor resection. Repeat surgical resection of metastatic lesions should be performed if possible and adjuvant therapy instituted. Radiation therapy has not been generally helpful. Antineoplastic agents such as cisplatin and etoposide, ifosfamide and carboplatin, and 5-fluorouracil and leucovorin have had limited use in children, and their success is not established. Therapy with o,p′-DDD (mitotane), an adrenolytic agent, may relieve the symptoms of hypercortisolism or virilization in recurrent disease. Treatment with higher doses of mitotane for more than 6 mo is associated with improved survival. Other agents that interfere with adrenal steroid synthesis, such as ketoconazole, aminoglutethimide, and metyrapone, may also relieve symptoms of steroid excess but do not improve survival.

A neoplasm of 1 adrenal gland may produce atrophy of the other because excessive production of cortisol by the tumor suppresses adrenocorticotropic hormone stimulation of the normal gland. Consequently, adrenal insufficiency may follow surgical removal of the tumor. This situation can be avoided by giving 10-25 mg of hydrocortisone every 6 hr, starting on the day of operation gradually decreased postoperatively. Adequate quantities of water, sodium chloride, and glucose also must be provided.

595.2

Adrenal Incidentaloma

Perrin C. White

Adrenal masses are discovered with increasing frequency in patients undergoing abdominal imaging for reasons unrelated to the adrenal gland. There are no published data on the frequency of the occurrence of such tumors in childhood. They are likely to be infrequent, being found in approximately 7% of autopsies of persons older than age 70 yr but in <1% of those younger than age 30 yr. They are detected in 1–4% of abdominal CT examinations in adults.

The unexpected discovery of such a mass presents the clinician with a dilemma in terms of diagnostic steps to undertake and treatment interventions to recommend. The differential diagnosis of adrenal incidentaloma includes benign lesions such as cysts, hemorrhagic cysts, hematomas, and myelolipomas. These lesions can usually be identified on CT or MRI. If the nature of the lesion is not readily apparent, additional evaluation is required. Included in the differential diagnosis of lesions requiring additional evaluation are benign adenomas, pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma. Benign, hormonally inactive adrenocortical adenomas make up the majority of incidentalomas. Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Functional tumors require removal. If the adrenal mass is nonfunctional and larger than 4-6 cm, recommendations are to proceed with surgical resection of the mass. Lesions of 3 cm or less should be followed clinically with periodic reimaging. Treatment must be individualized; nonsecreting adrenal incidentalomas may enlarge and become hyperfunctioning. Nuclear scan, and occasionally fine-needle aspiration, may be helpful in defining the mass.

595.3

Adrenal Calcification

Perrin C. White

Keywords

Tuberculosis
Waterhouse-Friderichsen syndrome
Wolman disease

Calcification within the adrenal glands may occur in a wide variety of situations, some serious and others of no obvious consequence. Adrenal calcifications are often detected as incidental findings in radiographic studies of the abdomen in infants and children. The physician may elicit a history of anoxia or trauma at birth. Hemorrhage into the adrenal gland at or immediately after birth is probably the most common factor that leads to subsequent calcification (see Fig. 593.1 in Chapter 593). Although it is advisable to assess the adrenocortical reserve of such patients, there is rarely any functional disorder.

Neuroblastomas, ganglioneuromas, adrenocortical carcinomas, pheochromocytomas, and cysts of the adrenal gland may be responsible for calcifications, particularly if hemorrhage has occurred within the tumor. Calcification in such lesions is almost always unilateral.

In the past, tuberculosis was a common cause both of calcification within the adrenals and of Addison disease. Calcifications may also develop in the adrenal glands of children who recover from the Waterhouse-Friderichsen syndrome; such patients are usually asymptomatic. Infants with Wolman disease, a rare lipid disorder caused by a deficiency of lysosomal acid lipase, have extensive bilateral calcifications of the adrenal glands (see Chapter 104.4).

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CHAPTER 596

Virilizing and Feminizing Adrenal Tumors

Perrin C. White

Clinical Manifestations

Virilization is the most common presenting symptom in children with adrenocortical tumors, occurring in 50–80%. In males, the clinical picture is similar to that of simple virilizing congenital adrenal hyperplasia: accelerated growth velocity and muscle development, acne, penile enlargement, and the precocious development of pubic and axillary hair. In females, virilizing tumors of the adrenal gland cause masculinization of a previously normal female with clitoral enlargement, growth acceleration, acne, deepening of the voice, and premature pubic and axillary hair development.

Conversely, adrenal tumors can occasionally (<10%) secrete high levels of estrogens as a result of overexpression of CYP19 (aromatase). Gynecomastia in males or premature thelarche in girls is often the initial manifestation. Growth and development may be otherwise normal, or concomitant virilization may occur.

In addition to virilization, 15–40% of children with adrenocortical tumors also have Cushing syndrome (see Chapter 597). Whereas isolated virilization occurs relatively frequently, children with adrenal tumors usually do not have Cushing syndrome alone.

Laboratory Findings

Serum levels of dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione are usually elevated, often markedly. Serum levels of testosterone are often increased, usually as a result of peripheral conversion of androstenedione, but infants with predominantly testosterone-secreting adenomas have been reported. Levels of estrone and estradiol are elevated in tumors from patients with feminizing signs. Urinary 17-ketosteroids (sex steroid metabolites) are also increased but are no longer routinely measured. Many adrenocortical tumors have a relative deficiency of 11β-hydroxylase activity and secrete increased amounts of deoxycorticosterone; these patients are hypertensive, and their tumors are often malignant.

Differential Diagnosis

For functioning tumors, the differential diagnoses are those of the main presenting signs and symptoms. The differential diagnosis for Cushing syndrome is discussed in Chapter 597 . For virilizing signs, the differential includes virilizing forms of adrenal hyperplasia (see Chapter 594) and factitious exposure to androgens, such as topical testosterone preparations. The differential diagnosis for hormonally inactive adrenocortical adenomas includes pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma (very rare in children). Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Not infrequently, a low level of autonomous cortisol secretion is detected that does not cause clinically apparent symptoms; this condition is sometimes referred to as “subclinical” Cushing syndrome.

Treatment

Functioning adrenocortical tumors should be removed surgically. There are no data on which to base a recommendation regarding nonfunctioning childhood incidentalomas; in adults, such tumors may be closely observed with imaging and repeat biochemical studies if smaller than 4 cm in diameter, but it is not certain that this is prudent in small children. Adrenalectomy may be performed either transperitoneally or laparoscopically. Some adrenocortical neoplasms are highly malignant and metastasize widely, but cure with regression of masculinizing or Cushingoid features may follow removal of less malignant, encapsulated tumors. Postoperatively, patients should be closely monitored biochemically, with frequent determinations of adrenal androgen levels and imaging studies. Recurrent symptoms or biochemical abnormalities should prompt a careful search for metastatic disease. Metastases primarily involve liver, lung, and regional lymph nodes. The majority of metastatic recurrences appear within 1 yr of tumor resection. Repeat surgical resection of metastatic lesions should be performed if possible and adjuvant therapy instituted. Radiation therapy has not been generally helpful. Antineoplastic agents such as cisplatin and etoposide, ifosfamide and carboplatin, and 5-fluorouracil and leucovorin have had limited use in children, and their success is not established. Therapy with o,p′-DDD (mitotane), an adrenolytic agent, may relieve the symptoms of hypercortisolism or virilization in recurrent disease. Treatment with higher doses of mitotane for more than 6 mo is associated with improved survival. Other agents that interfere with adrenal steroid synthesis, such as ketoconazole, aminoglutethimide, and metyrapone, may also relieve symptoms of steroid excess but do not improve survival.

A neoplasm of one adrenal gland may produce atrophy of the other because excessive production of cortisol by the tumor suppresses adrenocorticotropic hormone stimulation of the normal gland. Consequently, adrenal insufficiency may follow surgical removal of the tumor. This situation can be avoided by giving 10-25 mg of hydrocortisone every 6 hr, starting on the day of operation and weaned over 3-4 days postoperatively. Adequate quantities of water, sodium chloride, and glucose also must be provided.

CHAPTER 597

Cushing Syndrome

Perrin C. White

Cushing syndrome is the result of abnormally high blood levels of cortisol or other glucocorticoids. This can be iatrogenic or the result of endogenous cortisol secretion, a result of either an adrenal tumor or of hypersecretion of corticotropin (adrenocorticotropic hormone [ACTH]) by the pituitary (Cushing disease) or by a tumor (Table 597.1).

Table 597.1

Etiologic Classification of Adrenocortical Hyperfunction

EXCESS ANDROGEN
Congenital adrenal hyperplasia 21-Hydroxylase (P450c21) deficiency 11β-Hydroxylase (P450c11) deficiency 3β-Hydroxysteroid dehydrogenase defect (deficiency or dysregulation) Tumor
EXCESS CORTISOL (CUSHING SYNDROME)
Bilateral adrenal hyperplasia Adenoma Hypersecretion of corticotropin (Cushing disease) Ectopic secretion of corticotropin Exogenous corticotropin Adrenocortical nodular dysplasia Pigmented nodular adrenocortical disease (Carney complex) Tumor McCune-Albright syndrome
EXCESS MINERALOCORTICOID
Primary hyperaldosteronism Aldosterone-secreting adenoma Bilateral micronodular adrenocortical hyperplasia Glucocorticoid-suppressible aldosteronism Tumor Deoxycorticosterone excess Congenital adrenal hyperplasia 11β-Hydroxylase (P450c11)

17α-Hydroxylase (P450c17) Tumor Apparent mineralocorticoid excess (deficiency of 11β-hydroxysteroid dehydrogenase type 2)
EXCESS ESTROGEN
Tumor

Etiology

The most common cause of Cushing syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. This rarely represents a diagnostic challenge, but management of hyperglycemia, hypertension, weight gain, linear growth retardation, and osteoporosis often complicates therapy with corticosteroids.

Endogenous Cushing syndrome is most often caused in infants by a functioning adrenocortical tumor (see Chapter 595). Patients with these tumors often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone.

Although extremely rare in infants, the most common etiology of endogenous Cushing syndrome in children older than 7 yr of age is **Cushing disease** , in which excessive ACTH secreted by a **pituitary adenoma** causes bilateral adrenal hyperplasia. Such adenomas are often too small to detect by imaging techniques and are termed **microadenomas** . They consist principally of chromophobe cells and frequently show positive immunostaining for ACTH and its precursor, proopiomelanocortin. Whereas the vast majority of such tumors are sporadic, a small number occur in kindreds with **familial isolated pituitary adenoma syndrome** . This syndrome, which is caused by mutations in the aryl hydrocarbon receptor interacting protein *(AIP)* gene, accounts for perhaps 2% of pituitary adenomas; more commonly tumors with *AIP* mutations secrete growth hormone or prolactin, and only rarely do they secrete ACTH. Similarly, multiple endocrine neoplasia type 1 (MEN1) patients, who by definition have mutations in the MEN1 (menin) gene, may develop pituitary tumors, but these are typically prolactinomas. Other genes have also been implicated (Fig. 597.1).

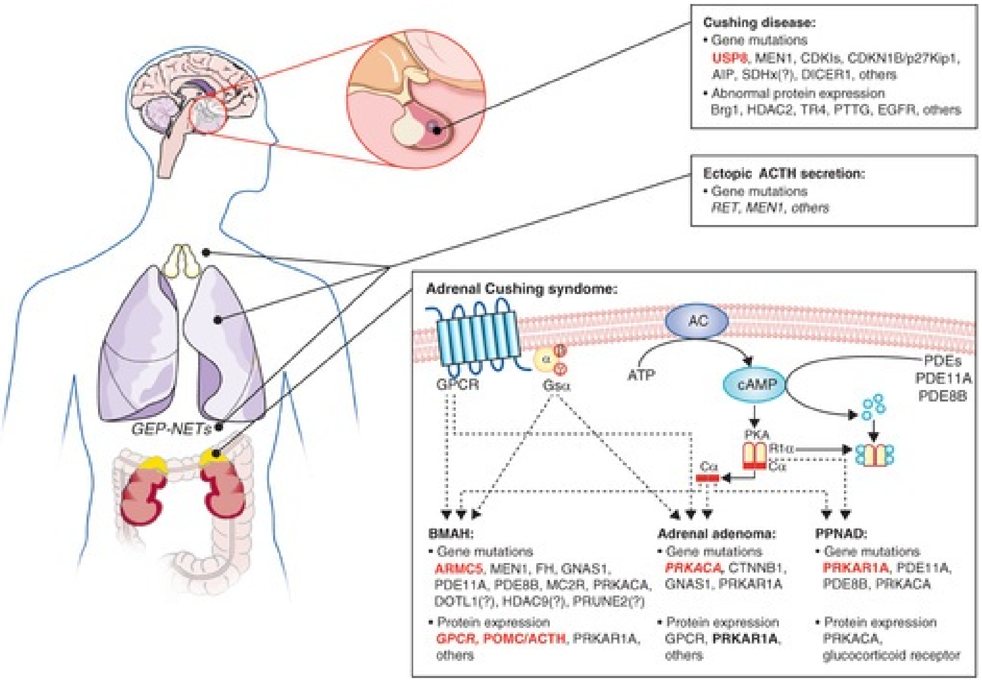
Cushing disease:
• Gene mutations
USP8, MEN1, CDKIs, CDKN1B/p27Kip1, AIP, SDHx(?), DICER1, others
• Abnormal protein expression
Brg1, HDAC2, TR4, PTTG, EGFR, others
Ectopic ACTH secretion:
• Gene mutations
RET, MEN1, others
GEP-NETs
Adrenal Cushing syndrome:
AC
GPCR
Gsα
α
ATP
cAMP
PDEs
PDE11A
PDE8B
PKA
R1α
Cα
Cα
BMAH:
• Gene mutations
ARMC5, MEN1, FH, GNAS1, PDE11A, PDE8B, MC2R, PRKACA, DOTL1(?), HDAC9(?), PRUNE2(?)
• Protein expression
GPCR, POMC/ACTH, PRKAR1A, others
Adrenal adenoma:
• Gene mutations
PRKACA, CTNNB1, GNAS1, PRKAR1A
• Protein expression
GPCR, PRKAR1A, others
PPNAD:
• Gene mutations
PRKAR1A, PDE11A, PDE8B, PRKACA
• Protein expression
PRKACA, glucocorticoid receptor

FIG. 597.1 Summary of genetic and molecular mechanisms implicated in Cushing syndrome. For each cause, the various genetic mutations or abnormal protein expression believed to play a part in the pathophysiology are shown. The most frequent mechanisms are highlighted in red; the well characterized mechanisms are highlighted in bold characters, and other potential mechanisms are in normal characters; a question mark shows an unconfirmed association or genetic predisposition. Please refer to the text for explanation of the various genetic defects under each diagnostic category. *AC,* Adenylate cyclase; *ACTH,* adrenocorticotropic hormone; *BMAH,* bilateral macronodular adrenal hyperplasia; *Cα,* catalytic subunit of PKA; *GPCR,* G-protein-coupled receptor; *PDEs,* phosphodiesterases; *PKA,* protein kinase A; *PPNAD,* primary pigmented nodular adrenocortical disease; *Rlα,* type 1α regulatory subunit of PKA. (From Lacroix A, Feelders RA, Stratakis CA, et al: Cushing's syndrome, *Lancet* 386:913–927, 2015, Fig. 1).

ACTH-dependent Cushing syndrome may also result from ectopic production of ACTH, although this is uncommon in children. Ectopic ACTH secretion in children is associated with islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangiopericytoma, Wilms tumor, and thymic carcinoid. Hypertension is more common in the ectopic ACTH syndrome than in other forms of Cushing syndrome, because very high cortisol levels may overwhelm 11β-hydroxysteroid dehydrogenase in the kidney (see Chapter 593) and thus have an enhanced mineralocorticoid (salt-retaining) effect.

Several syndromes are associated with the development of multiple autonomously hyperfunctioning nodules of adrenocortical tissue, rather than single adenomas or carcinomas (Chapter 595). In many cases they are caused by mutations in genes in the cAMP-mediated signaling pathway by which ACTH normally regulates cortisol secretion. **Primary pigmented nodular adrenocortical disease** (PPNAD) is a distinctive form of ACTH-independent Cushing syndrome. It may occur as an isolated event or, more commonly, as a familial disorder with other manifestations. The adrenal glands are small and have characteristic multiple, small (<4 mm in diameter), pigmented (black) nodules containing large cells with cytoplasm and lipofuscin; there is cortical atrophy between the nodules. This adrenal disorder occurs as a component of **Carney complex** , an autosomal dominant disorder also consisting of centrofacial lentigines and blue nevi; cardiac and cutaneous myxomas; pituitary, thyroid, and testicular tumors; and pigmented melanotic schwannomas. Carney complex is inherited in an autosomal dominant manner, although sporadic cases occur. Genetic loci for Carney complex have been mapped to the gene for the type 1α regulatory subunit of protein kinase A (PRKAR1A) on chromosome 17q22-24 and less frequently to chromosome 2p16. Patients with Carney complex and PRKAR1A mutations generally develop PPNAD as adults, and those with the disorder mapping to chromosome 2 (and most sporadic cases) develop PPNAD less frequently and later. Conversely, children presenting with PPNAD as an isolated finding rarely have mutations in PRKAR1A, or subsequently develop other manifestations of Carney complex. Some patients with isolated PPNAD have mutations in the *PDE8B* or *PDE11A* genes encoding different phosphodiesterase isozymes. In contrast, activating somatic mutations have been documented in the PRKACA catalytic subunit of protein kinase A in cortisol-secreting adenomas.

ACTH-independent Cushing syndrome with nodular hyperplasia and adenoma formation occurs rarely in cases of **McCune-Albright syndrome** , with symptoms beginning in infancy or childhood. McCune-Albright syndrome is caused by a somatic mutation of the *GNAS* gene encoding the G protein, G_s α, through which the ACTH receptor (MCR2) normally signals. This results in inhibition of guanosine triphosphatase activity and constitutive activation of adenylate cyclase, thus increasing levels of cyclic adenosine monophosphate. When the mutation is present in adrenal tissue, cortisol and cell division are stimulated independently of ACTH. Other tissues in which activating mutations may occur are bone (producing fibrous dysplasia), gonads, thyroid, and pituitary. Clinical manifestations depend on which tissues are affected.

The genes causing nodular adrenocortical hyperplasia that have been identified thus far all produce overactivity of the ACTH signaling pathway either by constitutively activating G_s α (McCune-Albright syndrome), by reducing the breakdown of cyclic adenosine monophosphate and thus increasing its intracellular levels (mutations of *PDE8B* or *PDE11A*), or by disrupting the regulation of the cyclic adenosine monophosphate–dependent enzyme, protein kinase A (PRKAR1A mutations).

Additionally, adrenocortical lesions including diffuse hyperplasia, nodular hyperplasia, adenoma, and rarely carcinoma may occur as part of the MEN1 syndrome (see Chapter 591), an autosomal dominant disorder, in which there is homozygous inactivation of the menin (MEN1) tumor-suppressor gene on chromosome 11q13.

Clinical Manifestations

Signs of Cushing syndrome have been recognized in infants younger than 1 yr of age. The disorder appears to be more severe and the clinical findings more dramatic in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon facies). Generalized obesity is common in younger children. In children with adrenal tumors, signs of abnormal masculinization occur frequently; accordingly, there may be hirsutism on the face and trunk, pubic hair, acne, deepening of the voice, and enlargement of the clitoris in girls. Growth is impaired, with length falling below the 3rd percentile, except when significant virilization produces normal or even accelerated growth. Hypertension is common and may occasionally lead to heart failure. An increased susceptibility to infection may also lead to sepsis.

In older children, in addition to obesity, short stature is a common presenting feature. Gradual onset of obesity and deceleration or cessation of growth may be the only early manifestations. Older children most often have more severe obesity of the face and trunk compared with the extremities. Purplish striae on the hips, abdomen, and thighs are common. Pubertal development may be delayed, or amenorrhea may occur in girls past menarche. Weakness, headache, and emotional lability may be prominent. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Osteoporosis is common and may cause pathologic fractures.

Laboratory Findings

Cortisol levels in blood are normally highest at 8 AM and decrease to less than 50% by midnight, except in infants and young children in whom a diurnal rhythm is not always established. In patients with Cushing syndrome, this circadian rhythm is lost; midnight cortisol levels >4.4 µg/dL strongly suggest the diagnosis. It is difficult to obtain diurnal blood samples as part of an outpatient evaluation, but cortisol can be measured in saliva samples, which can be obtained at home at the appropriate times of day. Elevated nighttime salivary cortisol levels raise suspicion for Cushing syndrome.

Urinary excretion of free cortisol is increased. This is best measured in a 24 hr urine sample and is expressed as a ratio of micrograms of cortisol excreted per gram of creatinine. This ratio is independent of body size and completeness of the urine collection.

A single-dose dexamethasone suppression test is often helpful; a dose of 25-30 µg/kg (maximum: 2 mg) given at 11 PM results in a plasma cortisol level of less than 5 µg/dL at 8 AM the next morning in normal individuals but not in patients with Cushing syndrome. It is prudent to measure the dexamethasone level in the same blood sample to ensure the adequacy of dosing.

A glucose tolerance test is often abnormal but is of no diagnostic utility. Levels of serum electrolytes are usually normal, but potassium may be decreased, especially in patients with tumors that secrete ACTH ectopically.

After the diagnosis of Cushing syndrome has been established, it is necessary to determine whether it is caused by a pituitary adenoma, an ectopic ACTH-secreting tumor, or a cortisol-secreting adrenal tumor (Fig. 597.2). ACTH concentrations are usually suppressed in patients with cortisol-secreting tumors and are very high in patients with ectopic ACTH-secreting tumors but may be normal in patients with ACTH-secreting pituitary adenomas. After an intravenous bolus of corticotropin-releasing hormone, patients with ACTH-dependent Cushing syndrome have an exaggerated ACTH and cortisol response, whereas those with adrenal tumors show no increase in ACTH and cortisol. The 2-step dexamethasone suppression test consists of administration of dexamethasone, 30 and 120 µg/kg/24 hr in 4 divided doses, on consecutive days. In children with pituitary Cushing syndrome, the larger dose, but not the smaller dose, suppresses serum levels of cortisol. Typically, patients with ACTH-independent Cushing syndrome do not show suppressed cortisol levels with dexamethasone.

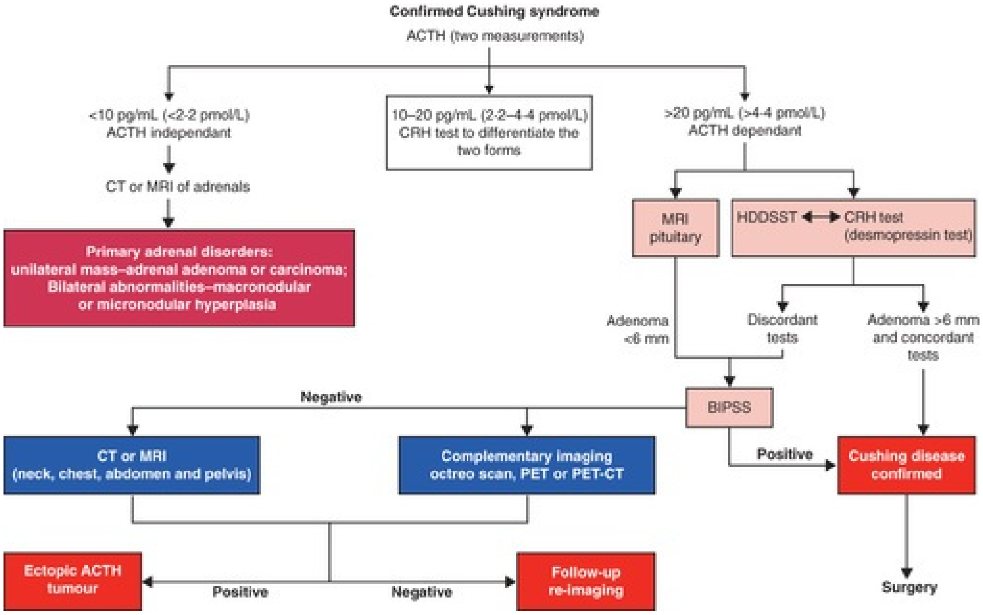
Confirmed Cushing syndrome
ACTH (two measurements)
<10 pg/mL (<2·2 pmol/L)
ACTH independant
10–20 pg/mL (2·2–4·4 pmol/L)
CRH test to differentiate the two forms
>20 pg/mL (>4·4 pmol/L)
ACTH dependant
CT or MRI of adrenals
Primary adrenal disorders:
unilateral mass–adrenal adenoma or carcinoma;
Bilateral abnormalities–macronodular
or micronodular hyperplasia
MRI pituitary
HDDSST
CRH test
(desmopressin test)
Adenoma <6 mm
Discordant tests
Adenoma >6 mm and concordant tests
Negative
BIPSS
Positive
CT or MRI
(neck, chest, abdomen and pelvis)
Complementary imaging
octreo scan, PET or PET-CT
Cushing disease confirmed
Ectopic ACTH tumour
Positive
Negative
Follow-up re-imaging
Surgery

FIG. 597.2 Clinical decision-making flow chart for the differential diagnosis of confirmed Cushing syndrome of different causes. *ACTH* , Adrenocorticotropic hormone; *BIPSS* , bilateral inferior petrosal sinus sampling; *CRH* , corticotropin-releasing hormone; *HDDSST* , high dose dexamethasone suppression test. (From Lacroix A, Feelders RA, Stratakis CA, et al: Cushing's syndrome, *Lancet* 386:913–927, 2015, Fig. 3).

CT detects virtually all adrenal tumors larger than 1.5 cm in diameter. MRI may detect ACTH-secreting pituitary adenomas, but many are too small to be seen; the addition of gadolinium contrast increases the sensitivity of detection. Bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after corticotropin-releasing hormone administration may be required to localize the tumor when a pituitary adenoma is not visualized; this is not routinely available in many centers, and moreover may be of decreased specificity in children.

Differential Diagnosis

Cushing syndrome is frequently suspected in children with obesity, particularly when striae and hypertension are present. Children with simple obesity are usually tall, whereas those with Cushing syndrome are short or have a decelerating growth rate. Although urinary excretion of cortisol is often elevated in simple obesity, salivary nighttime levels of cortisol are usually normal, and cortisol secretion is suppressed by oral administration of low doses of dexamethasone.

Elevated levels of cortisol and ACTH without clinical evidence of Cushing syndrome occur in patients with generalized glucocorticoid resistance (see Chapter 593.4). Affected patients may be asymptomatic or exhibit hypertension, hypokalemia, and precocious pseudopuberty; these manifestations are caused by increased mineralocorticoid and adrenal androgen secretion in response to elevated ACTH levels. Mutations in the glucocorticoid receptor have been identified.

Treatment

Transsphenoidal pituitary microsurgery is the treatment of choice in pituitary Cushing disease in children. The overall success rate with follow-up of less than 10 yr is 60–80%. Low postoperative serum or urinary cortisol concentrations predict long-term remission in the majority of cases. Relapses are treated with reoperation or pituitary irradiation.

Cyproheptadine, a centrally acting serotonin antagonist that blocks ACTH release, has been used to treat Cushing disease in adults; remissions are usually not sustained after discontinuation of therapy. This agent is rarely used in children. Inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, aminoglutethimide, etomidate) have been used preoperatively to normalize circulating cortisol levels and reduce perioperative morbidity and mortality. Mifepristone, a glucocorticoid receptor antagonist, has been used in a limited number of cases.

Pasireotide, a somatostatin analog, can inhibit ACTH secretion, and is approved for use in adults with persistent disease after surgery or in whom surgery is contraindicated.

If a pituitary adenoma does not respond to treatment or if ACTH is secreted by an ectopic metastatic tumor, the adrenal glands may need to be removed. This can often be accomplished laparoscopically. Adrenalectomy may lead to increased ACTH secretion by an unresected pituitary adenoma, evidenced mainly by marked hyperpigmentation; this condition is termed **Nelson syndrome.**

Management of patients undergoing adrenalectomy requires adequate preoperative and postoperative replacement therapy with a corticosteroid. Tumors that produce corticosteroids usually lead to atrophy of the normal adrenal tissue, and replacement with cortisol (10 mg/m^2 /24 hr in 3 divided doses after the immediate postoperative period) is required until there is recovery of the hypothalamic-pituitary-adrenal axis. Postoperative complications may include sepsis, pancreatitis, thrombosis, poor wound healing, and sudden collapse, particularly in infants with Cushing syndrome. Substantial catch-up growth, pubertal progress, and increased bone density occur, but bone density remains abnormal and adult height is often compromised. The management of adrenocortical tumors is discussed in Chapter 595 .

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CHAPTER 598

Primary Aldosteronism

Perrin C. White

Primary aldosteronism encompasses disorders caused by excessive aldosterone secretion independent of the renin–angiotensin system. These disorders are characterized by **hypertension** , **hypokalemia** , and suppression of the renin–angiotensin system.

Etiology

Aldosterone-secreting adenomas are unilateral and have been reported in children as young as 3.5 yr of age. They are very rarely malignant. Bilateral micronodular adrenocortical hyperplasia tends to occur in older ages. Primary aldosteronism due to unilateral adrenal hyperplasia may also occur. Glucocorticoid-suppressible hyperaldosteronism is discussed in Chapter 594.8 .

Epidemiology

These conditions are thought to be rare in children, but they may account for 5–10% of cases of hypertension in adults. Although usually sporadic, kindreds with several affected members have been reported. Genetic linkage to chromosome 7p22 has been identified in some of these kindreds, but the involved gene has not yet been identified. Mutations in the *KCNJ5* gene on chromosome 11q24 (encoding G protein-gated inward rectifier potassium channel 4) have been identified in several kindreds; these mutations (G151R and G151E) altered channel selectivity, producing increased Na^+ conductance and membrane depolarization, which increases aldosterone production and proliferation of adrenal glomerulosa cells. Moreover, such mutations have been identified in a subset of sporadic aldosterone-producing adenomas. Germline and somatic mutations have also been reported in the CACNA1D gene encoding a voltage-sensitive calcium channel, and somatic mutations in ATP1A1 and ATP2B3, respectively encoding sodium-potassium and calcium ATPases. The majority of aldosterone producing adenomas have mutations that activate the Wnt/β-catenin signaling pathway, either in β-catenin itself, or in the *APC* gene, which regulates this pathway.

Clinical Manifestations

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension. Others have severe hypertension (up to 240/150 mm Hg), with headache, dizziness, and visual disturbances. Chronic hypokalemia, if present, may lead to polyuria, nocturia, enuresis, and polydipsia. Muscle weakness and discomfort, tetany, intermittent paralysis, fatigue, and growth failure affect children with severe hypokalemia.

Laboratory Findings

Hypokalemia occurs frequently. Serum pH and the carbon dioxide and sodium concentrations may be elevated and the serum chloride and magnesium levels decreased. Serum levels of calcium are normal, even in children who manifest tetany. The urine is neutral or alkaline, and urinary potassium excretion is high. Plasma levels of aldosterone may be normal or elevated. Aldosterone concentrations in 24 hr urine collections are always increased. Plasma levels of renin are persistently low.

The diagnostic test of choice for primary aldosteronism is controversial. Both renin and aldosterone levels may vary by time of day, posture, and sodium intake, making it difficult to establish consistent reference ranges. It is desirable to establish a consistent sampling protocol, for example, at midmorning after the patient has been sitting for 15 min. If possible, antihypertensive drugs or other medications that can affect aldosterone or renin secretion should be avoided for several weeks prior to testing, including diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clonidine, and nonsteroidal antiinflammatory agents. Patients taking these agents may need to be changed to α-adrenergic blockers or calcium channel blockers that have smaller effects on the biochemical measurements. The ratio of plasma aldosterone concentration to renin activity is always high, and this represents a cost-effective screening test for primary aldosteronism. Aldosterone does not decrease with administration of saline solution or fludrocortisone, and renin does not respond to salt and fluid restriction. Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol may be increased but not to the extent seen in glucocorticoid-suppressible hyperaldosteronism.

Differential Diagnosis

Primary aldosteronism should be distinguished from glucocorticoid-suppressible hyperaldosteronism (see Chapter 594.8), which is specifically treated with glucocorticoids. An autosomal dominant pattern of inheritance should raise suspicion for the latter disorder. Glucocorticoid-suppressible hyperaldosteronism is diagnosed by dexamethasone suppression tests or by specific genetic testing. More generally, primary aldosteronism should be distinguished from other forms of hypertension by means of the testing previously discussed.

Treatment

The treatment of an aldosterone-producing adenoma is surgical removal. This is performed primarily by laparotomy and adrenalectomy; successful enucleation of aldosterone-producing adenomas, as well as laparoscopic adrenalectomy, has been reported. Hyperaldosteronism caused by bilateral adrenal hyperplasia is treated with the mineralocorticoid antagonists spironolactone (1-3 mg/kg/day to a maximum of 100 mg/day) or eplerenone (25-100 mg/day in 2 divided doses), often normalizing blood pressure and serum potassium levels. There is greater experience with spironolactone, but this agent has antiandrogenic properties that may be unacceptable in pubertal males. Eplerenone is a more specific antimineralocorticoid that is safe in children, but there is little specific experience with primary aldosteronism in the pediatric age group. As an alternative, an epithelial sodium channel blocker, such as amiloride, may be used, with other antihypertensive agents added as necessary. In patients whose condition cannot be controlled medically, unilateral adrenalectomy may be considered.

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CHAPTER 599

Pheochromocytoma

Perrin C. White

Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells. The most common site of origin (approximately 90%) is the adrenal medulla; however, tumors may develop anywhere along the abdominal sympathetic chain and are likely to be located near the aorta at the level of the inferior mesenteric artery or at its bifurcation. They also appear in the periadrenal area, urinary bladder or ureteral walls, thoracic cavity, and cervical region. Ten percent occur in children, in whom they present most frequently between 6 and 14 yr of age. Tumors vary from 1 to 10 cm in diameter; they are found more often on the right side than on the left. In more than 20% of affected children, the adrenal tumors are bilateral; in 30–40% of children, tumors are found in both adrenal and extraadrenal areas or only in an extraadrenal area.

Etiology

Pheochromocytomas may be associated with genetic syndromes such as **von Hippel-Lindau disease,** as a component of **multiple endocrine neoplasia** (MEN) syndromes MEN2A and MEN2B, and more rarely in association with **neurofibromatosis (type 1) or tuberous sclerosis.** The classic features of von Hippel-Landau syndrome, which occurs in 1 in 36,000 individuals, include retinal and central nervous system hemangioblastomas, renal clear cell carcinomas, and pheochromocytomas, but kindreds differ in their propensity to develop pheochromocytoma; in some kindreds, pheochromocytoma is the only tumor to develop. Germline mutations in the *VHL* tumor-suppressor gene on chromosome 3p25-26 have been identified in patients with this syndrome. Mutations of the *RET* protooncogene on chromosome 10q11.2 have been found in families with MEN2A and MEN2B. Patients with MEN2 are at risk of developing medullary thyroid carcinoma and parathyroid tumors; approximately 50% develop pheochromocytoma, with patients carrying mutations at codon 634 of the *RET* gene being at particularly high risk. Mutations are present in the *NF1* gene on chromosome 17q11.2 in neurofibromatosis type 1 patients.

Pheochromocytomas may occur in kindreds along with paragangliomas, particularly at sites in the head and neck. Such families typically carry mutations in the *SDHB* , *SDHD* , and, rarely, the *SDHC* genes encoding subunits of the mitochondrial **enzyme succinate dehydrogenase** . These mutations lead to intracellular accumulation of succinate, an intermediate of the Krebs cycle, which inhibits α-ketoglutarate–dependent dioxygenases and results in epigenetic alterations that affect expression of genes involved in cell differentiation. Approximately 50% of tumors with SDHB mutations are malignant.

In addition to associations with other tumors in MEN-2 patients, pheochromocytomas and paragangliomas can occur in association with **gastrointestinal stromal tumors** (GISTs; the association is termed the Carney-Stratakis dyad) and/or pulmonary chondromas (Carney-Stratakis triad) and adrenocortical tumors. These associations have heterogenous genetic etiologies but often involve mutations in SDH genes.

Clinical Manifestations

Pheochromocytomas detected by surveillance of patients who are known carriers of mutations in tumor-suppressor genes may be asymptomatic. Otherwise, patients are detected owing to hypertension, which results from excessive secretion of metanephrines, epinephrine and norepinephrine. All patients have hypertension at some time. Paroxysmal hypertension should particularly suggest pheochromocytoma as a diagnostic possibility, but in contrast to adults, the hypertension in children is more often sustained rather than paroxysmal. When there are paroxysms of hypertension, the attacks are usually infrequent at first, but become more frequent and eventually give way to a continuous hypertensive state. Between attacks of hypertension, the patient may be free of symptoms. During attacks, the patient complains of headache, palpitations, abdominal pain, and dizziness; pallor, vomiting, and sweating also occur. Seizures and other manifestations of hypertensive encephalopathy may occur. In severe cases, precordial pains radiate into the arms; pulmonary edema and cardiac and hepatic enlargement may develop. Symptoms may be exacerbated by exercise, or with use of nonprescription medications containing stimulants such as pseudoephedrine. Patients have a good appetite but because of the hypermetabolic state may not gain weight, and severe cachexia may develop. Polyuria and polydipsia can be sufficiently severe to suggest diabetes insipidus. Growth failure may be striking. The blood pressure may range from 180 to 260 mm Hg systolic and from 120 to 210 mm Hg diastolic, and the heart may be enlarged. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate, and arterial constriction.

Laboratory Findings

The urine may contain protein, a few casts, and occasionally glucose. Gross hematuria suggests that the tumor is in the bladder wall. Polycythemia is occasionally observed. The diagnosis is established by demonstration of elevated blood and 24 hr urinary levels of total metanephrines.

Pheochromocytomas produce norepinephrine and epinephrine. Normally, norepinephrine in plasma is derived from both the adrenal gland and adrenergic nerve endings, whereas epinephrine is derived primarily from the adrenal gland. In contrast to adults with pheochromocytoma in whom both norepinephrine and epinephrine are elevated, children with pheochromocytoma predominantly excrete norepinephrine in the urine. Total urinary metanephrine excretion usually exceeds 300 µg/24 hr. Urinary excretion of metanephrines (particularly normetanephrine) is also increased (see Fig. 592.3 in Chapter 592). Daily urinary excretion of these compounds by unaffected children increases with age. Although urinary excretion of vanillylmandelic acid (3-methoxy-4-hydroxymandelic acid), the major metabolite of epinephrine and norepinephrine, is increased, vanilla-containing foods and fruits can produce falsely elevated levels of this compound, which therefore is no longer routinely measured.

Elevated levels of free catecholamines and metanephrines can also be detected in plasma. In children, the best sensitivity and specificity are obtained by measuring plasma normetanephrine using gender-specific pediatric reference ranges, with plasma norepinephrine being next best. Plasma metanephrine and epinephrine are not reliably elevated in children. Additionally, the patient should be instructed to abstain from caffeinated drinks, and to avoid acetaminophen, which can interfere with plasma normetanephrine assays. If possible, the blood sample should be obtained from an indwelling intravenous catheter, to avoid acute stress associated with venipuncture.

Most tumors in the area of the adrenal gland are readily localized by CT or

MRI (Fig. 599.1), but extraadrenal tumors may be difficult to detect. ^{123} I-metaiodobenzylguanidine (MIBG) is taken up by chromaffin tissue anywhere in the body and is useful for localizing small tumors. PET-CT or PET-MRI with MIBG, DOPA, succinate, or FDG is highly sensitive and a more favored imaging approach (Fig. 599.2) for difficult to localize tumors. Venous catheterization with sampling of blood at different levels for catecholamine determinations is now only rarely necessary for localizing the tumor.

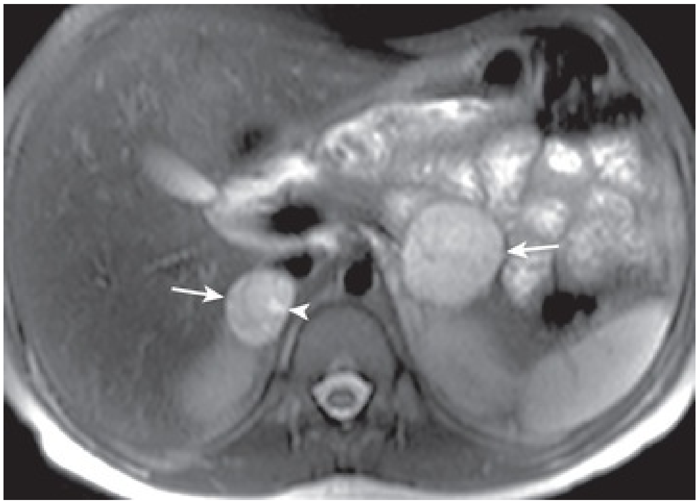

FIG. 599.1 Bilateral pheochromocytoma in an 11 yr old boy with von Hippel-Lindau disease and arterial hypertension. An axial fat-suppressed T2-weighted magnetic resonance image shows bilateral adrenal masses *(arrows),* larger on the left. The masses are hyperintense with small cystic change on the right medially. (From Navarro OM, Daneman A: Acquired conditions. In Coley BD, editor: *Caffey's Pediatric diagnostic imaging* , ed 12, Philadelphia, 2013, Elsevier, Fig. 123.9.)

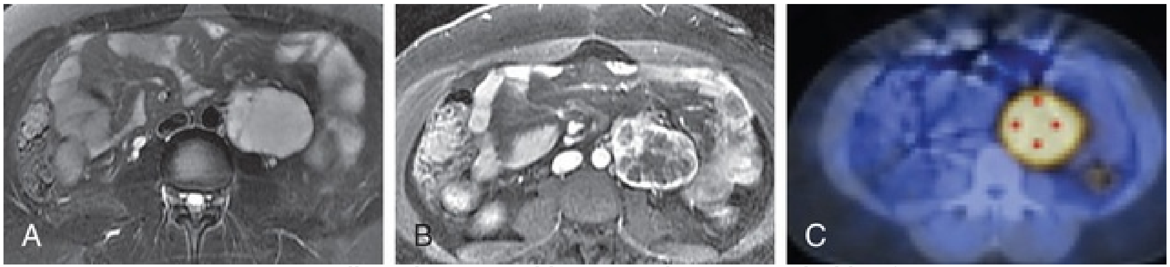

FIG. 599.2 **Paraganglioma in a 30 yr old woman who presented with refractory hypertension. A, Axial T2-weighted MRI shows homogeneously T2-hyperintense left periaortic mass just above the level of the aortic bifurcation (Zuckerkandl organ), illustrating the "light bulb" T2-bright appearance of pheochromocytomas and**

paragangliomas. B, Axial contrast-enhanced T1-weighted MRI demonstrates heterogeneous enhancement within the mass. C, ^{123} I-MIBG fused SPECT/CT axial image shows diffuse uptake within the tumor, compatible with paraganglioma. (From Ho LM: Adrenal glands. In Haaga JR, Boll D, editors: *CT and MRI of the whole body* , ed 6, Philadelphia, 2017, Elsevier, Fig. 53-18.)

Differential Diagnosis

Various causes of hypertension in children must be considered, such as renal or renovascular disease; coarctation of the aorta; hyperthyroidism; Cushing syndrome; deficiencies of 11β-hydroxylase, 17α-hydroxylase, or 11β-hydroxysteroid dehydrogenase (type 2 isozyme); primary aldosteronism; adrenocortical tumors; and, rarely, essential hypertension (see Chapter 472). A nonfunctioning kidney may result from compression of a ureter or of a renal artery by a pheochromocytoma. Paroxysmal hypertension may be associated with porphyria or familial dysautonomia. Cerebral disorders, diabetes insipidus, diabetes mellitus, and hyperthyroidism must also be considered in the differential diagnosis. Hypertension in patients with neurofibromatosis may be caused by renal vascular involvement or by concurrent pheochromocytoma.

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma frequently produce catecholamines, but urinary levels of most catecholamines are higher in patients with pheochromocytoma, although levels of dopamine and homovanillic acid are usually higher in neuroblastoma. Secreting neurogenic tumors often produce hypertension, excessive sweating, flushing, pallor, rash, polyuria, and polydipsia. Chronic diarrhea may be associated with these tumors, particularly with ganglioneuroma, and at times may be sufficiently persistent to suggest celiac disease.

Treatment

These tumors must be removed surgically, but careful preoperative, intraoperative, and postoperative management is essential. Manipulation and excision of these tumors result in marked increases in catecholamine secretion that increase blood pressure and heart rate. Therefore, preoperative *α- and β-adrenergic blockade* are required. Because these tumors are often multiple in children, a thorough transabdominal exploration of all the usual sites offers the best opportunity to find them all. Appropriate choice of anesthesia and *expansion of blood volume with appropriate fluids before and during surgery* are critical to avoid a precipitous drop in blood pressure during operation or within 48 hr postoperatively. Surveillance must continue postoperatively.

Although these tumors often appear malignant histologically, the only accurate indicators of malignancy are the presence of metastatic disease or local invasiveness that precludes complete resection, or both. Approximately 10% of all adrenal pheochromocytomas are malignant. Such tumors are rare in childhood; pediatric malignant pheochromocytomas occur more frequently in extraadrenal sites and are often associated with mutations in the *SDHB* gene encoding a subunit of succinate dehydrogenase. Prolonged follow-up is indicated because functioning tumors at other sites may be manifested many years after the initial operation. Examination of relatives of affected patients may reveal other individuals harboring unsuspected tumors that may be asymptomatic.

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SECTION 5

Disorders of the Gonads

OUTLINE

Chapter 600 Development and Function of the Gonads
Chapter 601 Hypofunction of the Testes
Chapter 602 Pseudoprecocity Resulting From Tumors of the Testes
Chapter 603 Gynecomastia
Chapter 604 Hypofunction of the Ovaries
Chapter 605 Pseudoprecocity Resulting From Lesions of the Ovary
Chapter 606 Disorders of Sex Development

CHAPTER 600

Development and Function of the Gonads

Patricia A. Donohoue

Genetic Control of Embryonic Gonadal Differentiation

Gonadal differentiation is a complex, multistep process that requires the sequential action and interaction of multiple gene products.

Early in the 1st trimester, the undifferentiated, bipotential fetal gonad begins as a thickening of the urogenital ridge, near the developing kidney and adrenal cortex. At 6 wk of gestation, the gonad contains germ cells, stromal cells that will become Leydig cells in the testes, or theca, interstitial, or hilar cells in the ovaries; and supporting cells that will develop into Sertoli cells in testes or granulosa cells in ovaries. In males, the *SRY* gene (**s** ex-determining **r** egion on the **Y** chromosome) is transiently expressed, followed by a sequential upregulation of a number of testis-specific genes. In the absence of SRY, the bipotential gonad will be able to develop into an ovary. Ovarian development is also characterized by expression of ovary-specific genes during the same time period. One such gene is *R-spondin1* . During the gestation time period of 6-9 wk, a number of genes are upregulated to the same degree in both the testis and the ovary, including *WNT4* and *CTNNB1* .

A chromosome complement of 46,XX is necessary for the development of **normal ovaries.** Both the long and short arms of the X chromosome contain genes for normal ovarian development. The DSS (**d** osage **s** ensitive/**s** ex reversal) locus associated with the *DAX1* (**D** SS **a** drenal hypoplasia on the **X** chromosome) gene, which is defective in 46,XY patients with X-linked congenital adrenal hypoplasia and hypogonadotropic hypogonadism, is a member of the nuclear receptor superfamily and acts as a repressor of male gene expression. The *DAX1* gene product acts by binding to a related nuclear receptor SF-1 (**s** teroidogenic **f** actor-1). *In vitro* , the signaling gene *WNT4* stimulates expression of *DAX1* , resulting in the suppression of androgen synthesis in XX females. The WNTs are ligands that activate receptor-mediated signal transduction pathways and are involved in modulating gene expression as well as cell behavior, adhesion, and polarity. Once developed, the ovary requires FAX12 to preserve its differentiation and stability. A key to its role in humans was elucidated by loss-of-function mutation of the *WNT4* gene that was found in an 18 yr old 46,XX woman. She had absence of müllerian-derived structures (uterus and fallopian tubes), unilateral renal agenesis, and clinical signs of androgen excess.

Mutations of the Wilms tumor 1 *(WT1)* gene, including alternative splicing, may also impact sex differentiation. *WT1* mutations are associated with the **Denys-Drash syndrome** (early-onset renal failure with abnormal external genitalia and Wilms tumor). Haploinsufficiency of a 3-amino-acid (KTS) form of *WT1* has been implicated in the gonadal dysgenesis of patients with **Fraser syndrome** (late-onset progressive glomerulopathy and 46,XY gonadal dysgenesis). Mutations in the *FOXL2* and *SF-1* genes are associated with ovarian failure. Mutation of the *R-spondin1* gene has been described in individuals with 46,XX DSD (**d** isorder of **s** ex **d** evelopment). Other autosomal genes also play a role in normal ovarian organogenesis and testicular development. Several conditions of gonadal dysgenesis are associated with gross abnormalities of both autosomes and sex chromosomes. A deletion affecting the short arm of the X chromosome produces the typical somatic anomalies of Turner syndrome.

Development of the testis requires the short arm of the Y chromosome; this contains the *SRY* gene, which is required for testicular differentiation. During male meiosis, the Y chromosome must segregate from the X chromosome so that both X and Y chromosomes do not occur in the same spermatozoa. The major portion of the Y chromosome is composed of Y-specific sequences that do not pair with the X chromosome. However, a minor portion of the Y chromosome shares sequences with the X chromosome and pairing does occur in this region. The genes and sequences in this area recombine between the sex chromosomes, behaving like autosomal genes. Therefore, the term *pseudoautosomal region* is used to describe this portion of the chromosome, and the term indicates genetic behavior of these genes relative to pairing and recombinational events. The *SRY* gene is localized to the 35-kb portion proximal to the pseudoautosomal region of the Y chromosome. It contains a high-mobility group (HMG) nonhistone protein (HMG box), supporting SRY's role as a transcriptional regulator of other genes involved in sex differentiation. The gonadal ridge forms at around 33 days of gestation. SRY is detected at 41 days, peaks at 44 days when testis cords are first visible, and persists into adulthood.

Other genes that are found on autosomes are important in this process. *SOX9* , a *SRY* -related gene containing a region homologous with the HMG box 9 of *SRY* , is located on chromosome 17. Mutations of this gene result in XY sex reversal and camptomelic dysplasia. *SF-1* on chromosome 9q33 is important in adrenal and gonadal development, as well as the development of gonadotropin-releasing hormone–secreting neurons in the hypothalamus. *WTI* , especially the KST isoform on chromosome 11p13, is needed for early gonadal, adrenal, and renal development. Fibroblast growth factor-9, GATA-4, XH-2, and SOY9 are also important.

When genetic recombination events on sex chromosomes extend beyond the pseudoautosomal region, X- and Y-specific DNA may be transferred between the chromosomes. Such aberrant recombinations result in X chromosomes carrying *SRY* , resulting in **XX males** , or Y chromosomes that have lost *SRY* , resulting in **XY females** . SRY acts as a transcriptional regulator to increase cellular proliferation, attract interstitial cells from adjacent mesonephros into the genital ridge, and stimulate testicular Sertoli cell differentiation. Sertoli cells act as an organizer of steroidogenic and germ cell lines and produce **antimüllerian hormone** (AMH) that causes the female duct system to regress. Table 600.1 lists additional genes involved in sex development, and if abnormal result in DSD.

Table 600.1

Genes Mutated in Disorders of Sex Development

GENE	PROTEIN	OMIM #	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTER GENITA
46,XY DSD							
DISORDERS OF GONADAL (TESTICULAR) DEVELOPMENT: SINGLE GENE DISORDERS							
WT1	TF	607102	11p13	AD	Dysgenetic testis	±	Female o ambiguo
SF1 (NR5A1)	Nuclear receptor TF	184757	9q33	AD/AR	Dysgenetic testis	±	Female o ambiguo

SRY	TF	480000	Yp11.3	Y	Dysgenetic testis or ovotestis	±	Female o ambiguou
SOX9	TF	608160	17q24-25	AD	Dysgenetic testis or ovotestis	±	Female o ambiguou
DHH	Signaling molecule	605423	12q13.1	AR	Dysgenetic testis	+	Female
ATRX	Helicase (? chromatin remodeling)	300032	Xq13.3	X	Dysgenetic testis	–	Female, ambiguou male
ARX	TF	3003382	Xp22.13	X	Dysgenetic testis	–	Ambiguo
Gata4	TF	615542	8p23.1	AD in XY subjects	Dysgenetic testes	_	Ambiguo
DISORDERS OF GONADAL (TESTICULAR) DEVELOPMENT: CHROMOSOMAL CHANGES INVOL GENES							
DMRT1	TF	602424	9p24.3	Monosomic deletion	Dysgenetic testis	±	Female o ambiguou
DAX1 (NR0B1)	Nuclear receptor TF	300018	Xp21.3	dupXp21	Dysgenetic testis or ovary	±	Female o ambiguou
WNT4	Signaling molecule	603490	1p35	dup1p35	Dysgenetic testis	+	Ambiguo
DISORDERS IN HORMONE SYNTHESIS OR ACTION							
LHGCR	G-protein receptor	152790	2p21	AR	Testis	–	Female, ambiguou micropen
DHCR7	Enzyme	602858	11q12-13	AR	Testis	–	Variable
StAR	Mitochondrial membrane protein	600617	8p11.2	AR	Testis	–	Female
CYP11A1	Enzyme	118485	15q23-24	AR	Testis	–	Female o ambiguou

HSD3B2	Enzyme	201810	1p13.1	AR	Testis	–	Ambiguo
CYP17	Enzyme	202110	10q24.3	AR	Testis	–	Female ambiguou micropen
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Testis	–	Male or ambiguou
HSD17B3	Enzyme	605573	9q22	AR	Testis	–	Female o ambiguou
SRD5A2	Enzyme	607306	2p23	AR	Testis	–	Ambiguo or microp
AKR1C4	Enzyme	600451	10p15.1	Unclear	Testis	–	Ambiguo or microp
AKR1C2	Enzyme	600450	10p15.1	Unclear	Testis	–	Ambiguo or microp
AMH	Signaling molecule	600957	19p13.3-13.2	AR	Testis	+	Normal m
AHM-receptor	Serine-threonine kinase transmembrane receptor	600956	12q13	AR	Testis	–	Normal m
Androgen receptor	Nuclear receptor TF	3130700	Xq11-12	X	Testis	–	Female, ambiguou micropen or norma male
46,XX DSD							
DISORDERS OF GONADAL (OVARIAN) DEVELOPMENT							
SRY	TF	480000	Yp11.3	Translocation	Testis or ovotestis	–	Male or ambiguou

SOX9	TF	608160	17q24	dup17q24	ND	–	Male or ambiguou
R spondin-1	TF	610644	1p34.3	AR	Ovotestis	±	Male or ambiguou
ANDROGEN EXCESS							
HSD3B2	Enzyme	201810	1p13	AR	Ovary	+	Clitorime
CYP21A2	Enzyme	201910	6p21-23	AR	Ovary	+	Ambiguo
CYP11B1	Enzyme	20210	8q21-22	AR	Ovary	+	Ambiguo
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Ovary	+	Ambiguo
CYP19	Enzyme	107910	15q21	AR	Ovary	+	Ambiguo
Glucocorticoid receptor	Nuclear receptor TF	138040	5q31	AR	Ovary	+	Ambiguo

ACTH , Adrenocorticotropin; *AD* , autosomal dominant (often *de novo* mutation); *AR* , autosomal recessive; *CAH* , congenital adrenal hyperplasia; *ND* , not determined; *OMIM #* , Online Mendelian Inheritance in Man number; *TF* , transcription factor; *WAGR* , Wilms, aniridia, genital anomalies, and retardation; *X* , X-chromosomal; *Y* , Y-chromosomal. Chromosomal rearrangements likely to include key genes are included.

From Lee PA, Houk CP, Ahmed SF, et al: International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex, *Pediatrics* 118:e488–e500, 2006; with additional data from Baxter RM, Arboleda VA, Lee H, et al: Exome sequencing for the diagnosis of 46,XY disorders of sex development, *J Clin Endocrinol Metab* 100:e333–e344, 2015; and Lourenco D, Brauner R, Rybczynska M, et al: Loss-of-function mutation in *GATA4* causes anomalies of human testicular development, *PNAS* 108:1597–1602, 2011.

Development of the ovary was once thought to be a passive process in the absence of SRY. Although the morphologic changes in the developing ovary are less marked than in the testis, there are a number of sequentially expressed genes and pathways that are required for complete ovarian development as well as maintenance of ovarian integrity postnatally. One of these genes is *R-spondin1* , which if mutated can result in testicular or ovotesticular development in 46,XX individuals. Some peptides in the Wnt-signaling pathway may antagonize testicular development. This effect may be mediated by β-catenin signaling, which is required for suppressing testicular features. Once developed, the ovary requires FAX12 to preserve its differentiation and stability.

Function of the Testes

Levels of placental chorionic gonadotropin peak at 8-12 wk of gestation and stimulate the fetal Leydig cells to secrete testosterone, the main hormonal product of the testis (Fig. 600.1). By way of 2 different biosynthetic pathways, the more potent metabolite of testosterone, dihydrotestosterone (DHT) is produced. In the originally described pathway, testosterone is converted by the enzyme 5α-reductase to DHT. In a more recently described pathway, DHT is produced from androstanediol. The early fetal period of DHT production and action is critical for normal and complete virilization of the XY fetus. Defects in this process lead to different forms of atypical male development (see Chapter 606.2). After virilization occurs, fetal levels of testosterone decrease but are maintained at lower levels in the latter half of pregnancy by luteinizing hormone (LH) secreted by the fetal pituitary; this LH-mediated testosterone secretion is required for continued penile growth, and to some degree also for testicular descent.

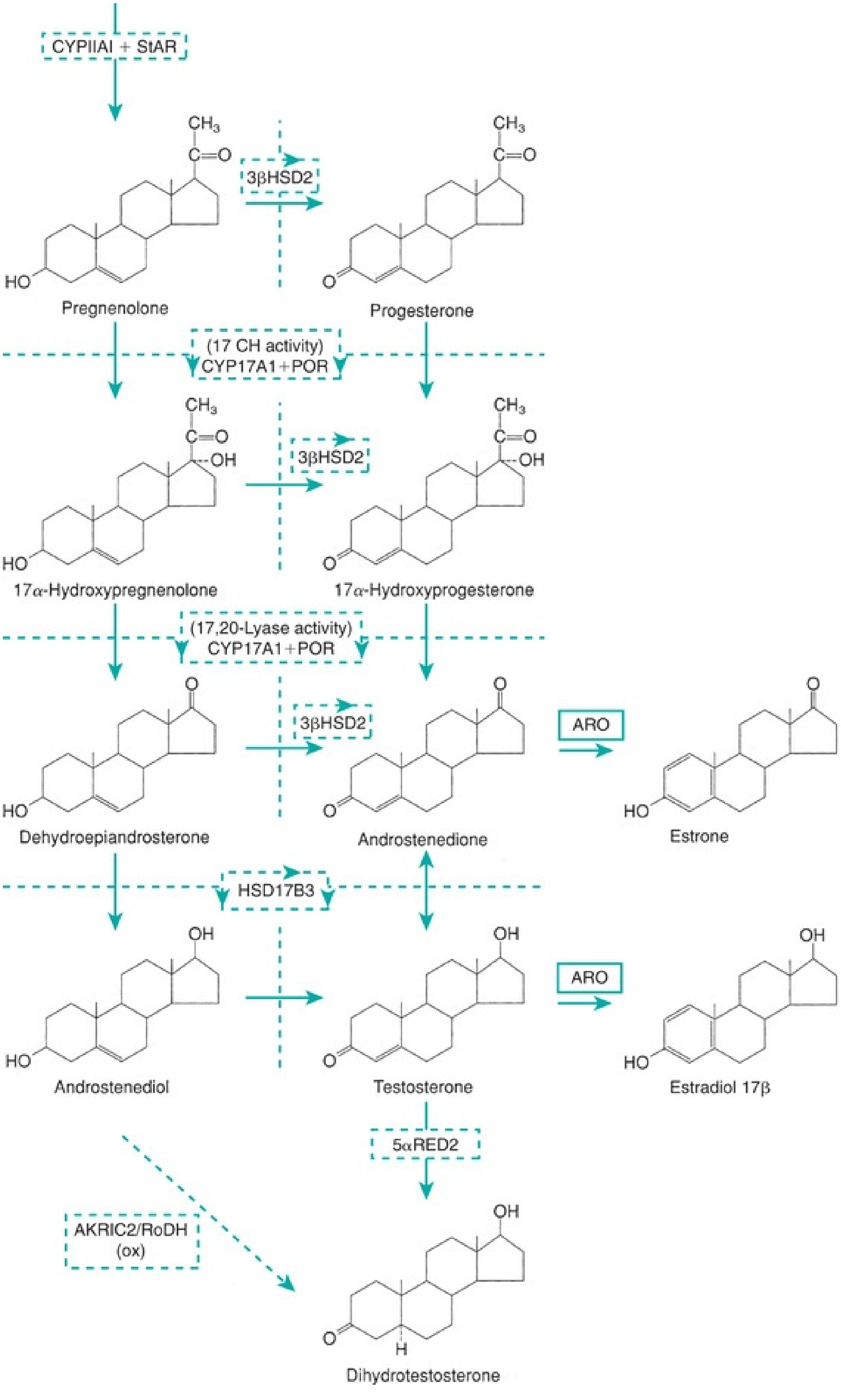
CYPIIAI + StAR
CH_3
C=O
3βHSD2
CH_3
C=O
HO
Pregnenolone
O
Progesterone
(17 CH activity)
CYP17A1+POR
CH_3
C=O
OH
3βHSD2
CH_3
C=O
OH
HO
17α-Hydroxypregnenolone
O
17α-Hydroxyprogesterone
(17,20-Lyase activity)
CYP17A1+POR
O
3βHSD2
O
ARO
O
HO
Dehydroepiandrosterone
O
Androstenedione
HO
Estrone
HSD17B3
OH
OH
ARO
OH
HO
Androstenediol
O
Testosterone
HO
Estradiol 17β
5αRED2
AKRIC2/RoDH
(ox)
OH
O
H
Dihydrotestosterone

FIG. 600.1 Biosynthesis of sex steroids. *Dashed lines* indicate enzymatic defects associated with 46,XY disorders of sex development. *3β-HSD2* , 3β-hydroxysteroid dehydrogenase type 2; *AKR1C2/RoDH (Ox)* , one of the enzymes in the alternative androgen biosynthetic pathway; *ARO,* aromatase; *CYP17A1,* the enzyme that catalyzes both 17α-hydroxylase (17-OH) and 17,20-lyase activities; *HSD17B3,* enzyme that catalyzes the 17-ketoreductase reaction; *POR,* P450 oxidoreductase; *StAR,* steroidogenic acute regulatory protein.

As part of the normal transition from intrauterine to extrauterine life, perhaps related to the sudden withdrawal of maternal and placental hormones, newborns and young infants experience a transient surge of gonadotropins and sex steroids. This is the so-called minipuberty.

In males, LH and testosterone peak at 1-2 mo of age and then decline to reach prepubertal levels by 4-6 mo of age. Follicle-stimulating hormone (FSH), along with inhibin B, peak at 3 mo and decline to prepubertal levels by 9 and 15 mo, respectively. The LH rise is more dominant than that of FSH.

The neonatal surge may be important for postnatal maturation of the gonads, stabilization of male external genitalia, and perhaps also for gender identity and sexual behaviors. The postnatal surge in LH and testosterone is absent or blunted in infants with hypopituitarism, cryptorchidism, and complete androgen insensitivity syndrome. The development of nocturnal pulsatile secretion of LH marks the beginning of puberty.

Within specific target cells, 6–8% of testosterone is converted by 5α-reductase to DHT, the more potent androgen (see Fig. 600.1), and approximately 0.3% is acted on by aromatase to produce estradiol. Approximately half of circulating testosterone is bound to sex hormone–binding globulin and half to albumin; only 2% circulates in the free form. Plasma levels of sex hormone–binding globulin are low at birth, rise rapidly during the first 10 days of life, and then remain stable until the onset of puberty. Thyroid hormone may play a role in this physiologic increase because neonates with athyreosis (absence of the thyroid gland) have very low levels of sex hormone–binding globulin.

AMH (previously referred to as *müllerian inhibitory substance*), **inhibin** , and **activin** are members of the transforming growth factor-β (TGF-β) superfamily of growth factors. This group, which has more than 45 members, also includes bone morphogenetic proteins. Members of the TGF-β superfamily are involved in the regulation of developmental processes and multiple diverse human disease states, including chondrodysplasias and cancer.

AMH, a homodimeric glycoprotein hormone encoded by a gene on chromosome 19, is the earliest secreted product of the Sertoli cells of the fetal testis. Produced as a prohormone, its carboxyterminal fragment is cleaved to make it active. *AMH* transcription is initiated by *SOX9* acting through the HMG box, while its expression is upregulated by SF-1 binding to its promoter and further interacting with *SOX9* , *WT1* , and *GATA4.* AMH binds to 2 distinct serine/threonine receptors, each having a single transmembrane domain. The activated type 1 receptor signals to the SMAD family of intracellular mediators.

The gene for the AMH receptor (on chromosome 12) is expressed in Sertoli cells. In the female, it is expressed in fetal müllerian duct cells and in fetal and postnatal granulosa cells. During sex differentiation in males, AMH causes involution of the müllerian (paramesonephric) ducts, which are embryologic precursors of the cervix and uterus. It works in concert with SF-1 to cause involution of the fallopian tubes.

AMH is secreted in males by Sertoli cells during both fetal and postnatal life. In females, it is secreted by granulosa cells from 36 wk of gestation to menopause but at lower levels. The serum concentration of AMH in males is highest at birth, whereas in females it is highest at puberty. After puberty, both sexes have similar serum concentrations of AMH. Its role in postnatal life is not yet fully characterized.

Inhibin is another glycoprotein hormone secreted by the Sertoli cells of the testes and granulosa and theca cells of the ovary. Inhibin A consists of an α-subunit disulfide linked to the β-A subunit, whereas inhibin B consists of the same α subunit linked to the β-B subunit. Activins are dimers of the B subunits, either homodimers (BA/BA, BB/BB) or heterodimers (BA/BB). Inhibins selectively inhibit whereas activins stimulate pituitary FSH secretion. By means of immunoassays specific for inhibin A or B, it has been shown that inhibin A is absent in males and is present mostly in the luteal phase in women. Inhibin B is the principal form of inhibin in males and in females during the follicular phase. Inhibin B may be used as a marker of Sertoli cell function in males. FSH stimulates inhibin B secretion in females and males, but only in males is there also evidence for gonadotropin-independent regulation. Levels of inhibin B are potentially informative in children with various forms of gonadal and pubertal disorders. In males with delayed puberty, inhibin B may be a useful screening test to differentiate between constitutional delay of puberty and hypogonadotropic hypogonadism. In hypogonadotropic hypogonadism, the serum inhibin B level is very low to undetectable.

Like inhibin and activin, follistatin (a single-chain glycosylated protein) is produced by gonads and other tissues such as the hypothalamus, kidney, adrenal gland, and placenta. Follistatin inhibits FSH secretion principally by binding activins, thereby blocking the effects of activins at the level of both ovary and pituitary.

Many additional peptides act as mediators of the development and function of the testis. They include neurohormones such as growth hormone–releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, oxytocin, arginine vasopressin, somatostatin, substance P, and neuropeptide Y; growth factors such as insulin-like growth factors and insulin-like growth factor–binding proteins, TGF-β, and fibroblast, platelet-derived, and nerve growth factors; vasoactive peptides; and immune-derived cytokines such as tumor necrosis factor and interleukins 1, 2, 4, and 6.

Clinical patterns of pubertal changes vary widely (see Chapters 26 and 577 covering pubertal maturation). In 95% of males, enlargement of the genitals begins between 9.5 and 13.5 yr of age, reaching maturity at 13-17 yr of age. In a minority of normal males, puberty begins after 15 yr of age. In some males, pubertal development is completed in less than 2 yr, but in others it may take longer than 4.5 yr. Pubertal development and the adolescent growth spurt occur at an older age in males than in females by approximately 2 yr.

The median age of sperm production (spermarche) is 14 yr. This event occurs in midpuberty as judged by pubic hair, testis size, evidence of growth spurt, and testosterone levels. Nighttime levels of FSH are in the adult male range at the time of spermarche; the 1st conscious ejaculation occurs at about the same time.

Function of the Ovaries

In the normal female, the undifferentiated gonad can be identified histologically as an ovary by 10-11 wk of gestation, after the upregulation of *R-spondin1* . Oocytes are present from the 4th mo of gestation and reach a peak of 7 million by 5 mo of gestation. For normal maintenance, oocytes need granulosa cells to form primordial follicles. Functional FSH (but not LH) receptors are present in oocytes of primary follicles during follicular development. Two normal X chromosomes are needed for maintenance of oocytes. In contrast to somatic cells, in which only 1 X chromosome is active, both Xs are active in germ cells. At birth, the ovaries contain approximately 1 million active follicles, which decrease to 0.5 million by menarche. Thereafter, they decrease at a rate of

1,000/mo, and at an even higher rate after the age of 35 yr.

The hormones of the fetal ovary are provided in most part by the fetoplacental unit. As in males, peak gonadotropin secretion occurs in fetal life and then again at 2-3 mo of life, with the lowest levels at about 6 yr of age. By contrast to males, the FSH surge predominates over LH in females. FSH peaks around 3-6 mo of age, declines by 12 mo, but remains detectable for 24 mo. Under LH influence, estradiol peaks at 2-6 mo of age. The inhibin B response is variable, peaking between 2 and 12 mo and remaining above prepubertal levels until 24 mo. In both infancy and childhood, gonadotropin levels are higher in females than in males.

The most important estrogens produced by the ovary are estradiol-17β (E_2) and estrone (E_1); estriol is a metabolic product of these 2, and all 3 estrogens may be found in the urine of mature females. Estrogens also arise from androgens produced by the adrenal gland and both the female and male gonads (see Fig. 600.1). This conversion explains why in certain types of disorders of sex differentiation in males, feminization occurs at puberty. In 17-ketosteroid reductase deficiency, for example, the enzymatic block results in markedly increased secretion of androstenedione, which is converted in the peripheral tissues to estradiol and estrone. These estrogens, in addition to those directly secreted by the testis, result in gynecomastia. Estradiol produced from testosterone in the complete androgen insensitivity syndrome causes complete feminization in these XY individuals.

Estrogen regulates a host of functionally different activities in multiple tissues. There are at least 2 distinct estrogen receptors with different expression patterns. The ovary also synthesizes progesterone, the main progestational steroid; the adrenal cortex and testis also synthesize progesterone where it is a precursor for other adrenal and testicular hormones.

A host of other hormones with autocrine, paracrine, and intracrine effects have been identified in the ovary. They include inhibins, activins, relaxin, and the growth factors insulin-like growth factor-1 (IGF-1), TGF-α and TGF-β, and cytokines.

Plasma levels of estradiol increase slowly but steadily with advancing sexual maturation and correlate well with clinical evaluation of pubertal development, skeletal age, and rising levels of FSH. Levels of LH do not rise until secondary sexual characteristics are well developed. Estrogens, like androgens, inhibit secretion of both LH and FSH (negative feedback). In females, estrogens also provoke the surge of LH secretion that occurs in the mid–menstrual cycle and stimulates ovulation. The capacity for this positive feedback is another maturational milestone of puberty.

The average age at menarche in American females is approximately 12.5-13 yr, but the range of normal is wide, and 1–2% of normal females have not menstruated by 16 yr of age. The age at onset of pubertal signs varies, with studies suggesting earlier ages than previously thought, especially in the U.S. African-American population (see Chapter 577). Menarche generally correlates closely with skeletal age. Maturation and closure of the epiphyses is estrogen-dependent, as demonstrated by a very tall 28 yr old, normally masculinized male with continued growth as a result of incomplete closure of the epiphyses, who had complete estrogen insensitivity caused by an estrogen-receptor defect.

Diagnostic Testing

Sensitive and specific assays for pituitary and gonadal hormones that can be measured in small amounts of blood have contributed to rapid advances in the understanding of normal and abnormal hypothalamic-pituitary-gonadal interactions. In male infants, measurements of LH, FSH, and testosterone can detect pituitary and testicular defects. Leydig cell integrity in childhood can be determined by the testosterone response following human chorionic gonadotropin administration. One protocol is to inject 5,000 IU IM daily for 3 days; other protocols are available. The integrity, as well as the maturity, of the hypothalamic-pituitary-gonadal axis in males and females can be assessed by measuring serial sex steroid, LH, and FSH levels after the subcutaneous administration of the gonadotropin-releasing hormone analog leuprolide. An ultrasensitive LH assay has been shown to differentiate between males with delayed puberty and those with complete, but not partial, hypogonadotropic hypogonadism.

The normal range for inhibin B levels has been established in infant males. Inhibin B may be a marker of spermatogenesis and also of tumors such as granulosa cell tumors. Inhibins may be involved in tumor suppression. Estrogen-receptor assays may be clinically useful in the management of various ovarian cancers. AMH measurements are useful in the evaluation of children with nonpalpable gonads and disorders of sex development.

Therapeutic Use of Sex Steroids

The estrogenic effects of polyhalogenated aromatic hydrocarbons may in part be a result of inhibition of estradiol sulfation by estrogen sulfotransferase, an important pathway of estradiol inactivation. Naturally occurring estrogens administered orally are rapidly destroyed by gastrointestinal and liver enzymes; accordingly, they are usually given as conjugates or esters. The most widely used oral preparations are equine conjugated estrogens (Premarin) and ethinyl estradiol. Estrogen-containing skin patches for transdermal absorption are also widely used. With improvements in the understanding of estrogen and estrogen-receptor interactions, a new class of compounds called *selective estrogen-receptor modulators* has been synthesized. For example, raloxifene, a nonsteroidal benzothiophene derivative, acts as an estrogen agonist in bone and liver and as an estrogen antagonist in breast and uterus.

Androgens, such as testosterone, are generally injected intramuscularly as long-acting esters (enanthate or cypionate, most commonly) because of their potency and steady response. Transdermal testosterone patches and a cutaneously applied gel have been used mostly in adults with hypogonadism because of the difficulty in titrating the doses needed during childhood and adolescence. Oral preparations, such as methyltestosterone or fluoxymesterone, do not produce so potent an androgenic response and may be hepatotoxic. Testosterone undecenoate, another oral preparation, is used in Europe but not in the United States. Sublingual (microspheres or pellets) and buccal (absorption via the buccal mucosa) preparations of testosterone are reportedly in development.

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CHAPTER 601

Hypofunction of the Testes

Omar Ali, Patricia A. Donohoue

Testicular hypofunction during fetal life can be a component of some types of **disorders of sex development** (see Chapter 606.2) and may lead to varying degrees of ambiguous genitalia. After birth, neonates undergo minipuberty with relatively high levels of gonadotropins and sex steroids, but this phenomenon is transient and its absence does not lead to any obvious clinical findings. Because prepubertal children normally do not produce significant amounts of testosterone and are not yet producing sperm, there are no discernible effects of testicular hypofunction in this age group. Testicular hypofunction from the age of puberty onward may lead to testosterone deficiency, infertility, or both. Such hypofunction may be primary in the testes **(primary hypogonadism)** or secondary to deficiency of pituitary gonadotropic hormones **(secondary hypogonadism).** Both types may be caused by inherited genetic defects or acquired causes, and in some cases the etiology may be unclear, but the level of the lesion (primary or secondary) is usually well defined; patients with primary hypogonadism have elevated levels of gonadotropins (hypergonadotropic); those with secondary hypogonadism have inappropriately low or absent levels (hypogonadotropic). Table 601.1 details the etiologic classification of male hypogonadism (see also Fig. 578.6).

Table 601.1

Etiologic Classification of Male Hypogonadism

HYPERGONADOTROPIC HYPOGONADISM (PRIMARY HYPOGONADISM; TESTES)
Congenital
Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) resistance Mutations in steroid synthetic pathways Gonadal dysgenesis Klinefelter syndrome (47,XXY)

Noonan syndrome (*PTPN-11* gene mutation in many cases) Cystic fibrosis (infertility)
Acquired
Cryptorchidism (some cases) Vanishing testes Chemotherapy Radiation Infection (e.g., mumps) Infarction (testicular torsion) Trauma
HYPOGONADOTROPIC HYPOGONADISM (SECONDARY HYPOGONADISM; HYPOTHALAMIC-PITUITARY)
Congenital
Genetic defects causing Kallmann syndrome and/or normosmic hypogonadotropic hypogonadism (HH) Other genetic disorders associated with HH: leptin gene, leptin receptor, DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), SF-1 (steroidogenic factor-1) Inherited syndromes: Prader-Willi, Bardet-Biedl, Laurence-Moon-Biedl, Alström Isolated HH at pituitary level (gonadotropin-releasing hormone receptor, FSH and LH β-subunit) Multiple pituitary hormone deficiencies: septo-optic dysplasia (*HESX-1* in some cases) and other disorders of pituitary organogenesis (e.g., *PROP1, LHX3, LHX4, SOX-3*) Idiopathic
Acquired
Anorexia nervosa Drug use Malnutrition Chronic illness, especially Crohn disease Hyperprolactinemia Pituitary tumors Pituitary infarction Infiltrative disorders (e.g., histiocytosis, sarcoidosis) Hemosiderosis and hemochromatosis Radiation

601.1

Hypergonadotropic Hypogonadism in the Male (Primary Hypogonadism)

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Keywords

Klinefelter syndrome
testicular regression
cryptorchidism
chemotherapy
radiation therapy
orchitis
autoimmunity
Noonan syndrome

Etiology

Some degree of testicular function is essential in the development of phenotypically male newborns. If testicular function is present, sex differentiation is normally complete by the 14th wk of intrauterine life. Hypogonadism may occur after phenotypically male genitalia have developed for a variety of reasons; genetic or chromosomal anomalies may lead to testicular hypofunction that does not become apparent until the time of puberty, when these males may have delayed or incomplete pubertal development. In other cases, normally developed testes may be damaged by infarction, trauma, radiation, chemotherapy, infections, infiltration, or other causes after sexual differentiation has occurred. In some cases, genetic defects may predispose to atrophy or maldescent, or torsion or infarction or may lead to progressive testicular damage and atrophy after a period of normal development. If testicular compromise is global, both testosterone secretion and fertility (sperm production) are likely to be affected. Even when the primary defect is in testosterone production, low levels of intratesticular testosterone will frequently lead to infertility. The reverse is not necessarily true. Defects in sperm production and in the storage and transit of sperm may not be associated with low testosterone levels; infertility may thus be seen in patients with normal testosterone levels, normal libido, and normal secondary sexual characteristics.

Various degrees of primary hypogonadism also occur in a significant percentage of patients with chromosomal aberrations, as in **Klinefelter syndrome, males with more than 1 X chromosome** , and **XX males.** These chromosomal anomalies are associated with other characteristic findings. Noonan syndrome is associated with cryptorchidism and infertility, but other (nongonadal) features dominate its clinical picture.

Congenital Anorchia or Testicular Regression Syndrome

Males in whom the external genitalia have developed normally (or nearly normally) and paramesonephric (müllerian) duct derivatives (uterus, fallopian tubes) are absent have obviously had testicular function for at least some part of gestation. If their testes cannot be palpated at birth, they are said to have **cryptorchidism.** In most such cases, the testes are undescended or retractile, but in some cases no testes are found in any location, even after extensive investigation. This syndrome of absence of testes in a phenotypic male with a normal 46,XY karyotype (indicating that there was some period of testicular function in intrauterine life) is known as *vanishing testes* , *congenital anorchia* , or **testicular regression syndrome.**

Testicular regression syndrome is not uncommon. Cryptorchidism occurs in 1.5–9% of male births; in 10–20% of these cases, the testes are impalpable. Of children with impalpable testes, up to 50% may have no detectable testes after extensive investigation. Most cases appear to be sporadic and are thought to be a result of torsion or vascular accidents. The incompletely descended testis may be more prone to torsion, and this may be one of the causes of vanishing testes. Most cases are sporadic, but in a subset of patients testicular regression syndrome occurs in monozygotic twins or in families with other affected individuals, suggesting a genetic etiology. Some cases are associated with micropenis, and in these cases the testicular loss probably occurred after the 14th wk but well before the time of birth, or this may indicate a preexisting dysfunction of male hormonal development. Low levels of testosterone (<10 ng/dL) and markedly elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are found in the early postnatal months; thereafter levels of gonadotropins tend to decrease even in agonadal children, rising to very high levels again as the pubertal years approach. Stimulation with human chorionic gonadotropin (hCG) fails to evoke an increase in the level of testosterone. *Serum levels of antimüllerian hormone (AMH) are undetectable or low.* All patients with undetectable testes should be tested for AMH and should undergo an hCG stimulation test. If the results indicate that no testicular tissue is present (absent AMH and no rise in testosterone after hCG stimulation), then the diagnosis of testicular regression syndrome is confirmed. If testosterone secretion is demonstrated, then imaging with abdominal magnetic resonance imaging (MRI) and/or surgical exploration is indicated. A small fibrotic nodule may be found at the end of the spermatic cord in many cases of testicular regression syndrome. Treatment of male hypogonadism (primary or secondary) is discussed in Chapter 601.2 . There is no possibility of normal fertility in these patients.

Chemotherapy and Radiation-Induced Hypogonadism

Testicular damage is a frequent consequence of chemotherapy and radiotherapy for cancer. The frequency and extent of damage depend on the agent used, total dose, duration of therapy, and posttherapy interval of observation. Another important variable is age at therapy; germ cells are less vulnerable in prepubertal than in pubertal and postpubertal males. Chemotherapy is most damaging if more than 1 agent is used. Although many chemotherapeutic agents produce azoospermia and infertility, Leydig cell damage (leading to low testosterone levels) is less common. In many cases the damage is transient and sperm counts recover after 12-24 mo. It has been suggested that prepubertal testes are less prone to damage than pubertal testes, but the evidence is not conclusive. The use of alkylating agents such as cyclophosphamide in prepubertal children may not impair pubertal development, even though there may be biopsy evidence of germ cell damage. Cisplatin causes transient azoospermia or oligospermia at lower doses, whereas higher doses (400-600 mg/m^2) can cause permanent infertility. Interleukin 2 can depress Leydig cell function, whereas interferon-α does not seem to affect gonadal function. Both chemotherapy and radiotherapy are associated with an increase in the percentage of abnormal gametes, but data concerning the outcomes of pregnancies after such therapy have *not* shown any increase in genetically mediated birth defects, possibly because of selection bias against abnormal sperm.

Radiation damage is dose-dependent. Temporary oligospermia can be seen with doses as low as 0.1 Gy, with permanent azoospermia seen with doses greater than 2 Gy. Recovery of spermatogenesis can be seen as long as 5 yr (or more) after irradiation, with higher doses leading to slower recovery. Leydig cells are more resistant to irradiation. Mild damage as determined by elevated LH levels can be seen with up to 6 Gy; doses greater than 30 Gy cause hypogonadism in most patients. Whenever possible, testes should be shielded from irradiation. Testicular function should be carefully evaluated in adolescents after multimodal treatment for cancer in childhood. Replacement therapy with testosterone and counseling concerning fertility may be indicated. The storage of sperm prior to chemotherapy or radiation treatment in postpubertal males is an option. Even in those cases where sperm counts are abnormal, recovery is possible, though the chances of recovery decline with increasing dose of radiation. If sperm counts remain low, fertility is still possible in some cases with testicular sperm extraction and intracytoplasmic sperm injection.

Sertoli Cell–Only Syndrome

Small testes and azoospermia are seen in patients with the extremely rare Sertoli cell–only syndrome (germ cell aplasia, or **Del Castillo syndrome**). These patients have no germ cells in the testes but usually have normal testosterone production and present as adults with the complaint of infertility. Typically patients have small testes and elevated FSH levels with normal LH and testosterone. They may have gynecomastia due to FSH stimulation of aromatase activity. Inhibin B levels may be decreased when compared with individuals with normal spermatogenesis. Most cases are sporadic and idiopathic, but deletions involving the azoospermia factor (AZF) region of the Y chromosome (Yq11) may be found in some cases.

Other Causes of Testicular Hypofunction

Atrophy of the testes may follow damage to the vascular supply as a result of manipulation of the testes during surgical procedures for correction of cryptorchidism or as a result of bilateral torsion of the testes. **Cryptorchidism** is a common condition (found in 3% of male children at birth, decreasing to 1% by age 6 mo) and current guidelines stress the importance of treatment before age 12 mo (or even earlier) in order to maximize future fertility. But it is clear that a small percentage of cases will develop fertility issues even when surgical treatment is successful and is completed within the 1st yr of life. These cases may represent intrauterine damage, surgical damage, or genetic defects in testicular development and are therefore included among the causes of testicular hypofunction.

Acute orchitis is common in pubertal or adult males with mumps and may lead to subfertility in 13% of cases, though infertility is rare. Testosterone secretion usually remains normal. The incidence of mumps orchitis in postpubertal males has increased in some areas as a result of a decrease in measles, mumps, and rubella vaccination uptake. Autoimmune polyendocrinopathy may be associated with primary hypogonadism (associated with anti-P450scc antibodies), but this appears to be more common in females.

Testicular Dysgenesis Syndrome

The incidence of testicular cancer has increased in many developed societies, while the incidence of cryptorchidism, hypospadias, low sperm counts, and sperm abnormalities also appears to have increased in some but not all studies. It has been proposed that all these trends are linked by prenatal testicular dysgenesis. The hypothesis is that some degree of testicular dysgenesis develops in intrauterine life from genetic as well as environmental factors and is associated with increased risk of cryptorchidism, hypospadias, hypofertility, and testicular cancer. The environmental influences that have been implicated in this syndrome include environmental chemicals that act as endocrine disruptors, such as bisphenol A and phthalates (components of many types of plastics), several pesticides, phytoestrogens or mycoestrogens, and other chemicals. The fact that these lesions can be reproduced in some animal models by environmental chemicals has led to efforts to remove these chemicals from products used by infants and pregnant mothers and from the environment in general. Nonetheless the evidence is only suggestive and not conclusive.

Clinical Manifestations

Primary hypogonadism may be suspected at birth if the testes and penis are abnormally small. Normative data are available for different populations. The condition often is not noticed until puberty, when secondary sex characteristics fail to develop. Facial, pubic, and axillary hair is scant or absent; there is neither acne nor regression of scalp hair; and the voice remains high pitched. The penis and scrotum remain infantile and may be almost obscured by pubic fat; the testes are small or not palpable. Fat accumulates in the region of the hips and buttocks and sometimes in the breasts and on the abdomen. The epiphyses close later than normal; therefore the extremities are long. The span may be several inches longer than the height, and the distance from the symphysis pubis to the soles of the feet (lower segment) is much greater than that from the symphysis to the vertex (upper segment). The proportions of the body are described as **eunuchoid.** The ratio of the upper to lower segment is considerably less than

0.9. Many individuals with milder degrees of hypogonadism may be detected only by appropriate studies of the pituitary-gonadal axis. Examination of the testes should be performed routinely by the pediatrician; testicular volumes as determined by comparison with standard orchidometers or by measurement of linear dimensions should be recorded.

Diagnosis

Levels of serum FSH and, to a lesser extent, of LH are elevated to greater than age-specific normal values in early infancy (when minipuberty normally occurs and the gonadotropins are normally disinhibited). This is followed by a time when even agonadal children may not exhibit significant elevation in gonadotropins, indicating that the gonadotropins are also suppressed at this stage by some mechanism independent of feedback inhibition by gonadal hormones. In the latter half of childhood and several years prior to the onset of puberty, this inhibition is released and gonadotropin levels again rise above age-based normals in subjects with primary hypogonadism. These elevated levels indicate that even in the prepubertal child there is an active hypothalamic-gonadal feedback relationship. After the age of 11 yr, FSH and LH levels rise significantly, reaching the castrate range. Measurements of random plasma testosterone levels in prepubertal males are not helpful because they are ordinarily low in normal prepubertal children, rising during puberty to attain adult levels. During puberty, these levels, when measured in an early-morning blood sample, correlate better with testicular size, stage of sexual maturity, and bone age than with chronological age. In patients with primary hypogonadism, testosterone levels remain low at all ages. There is an attenuated rise or no rise at all after administration of hCG, in contrast to normal males in whom hCG produces a significant rise in plasma testosterone at any stage of development.

AMH is secreted by the Sertoli cells, and this secretion is suppressed by testosterone. As a result, AMH levels are elevated in prepubertal males and suppressed at onset of puberty. Males with primary hypogonadism continue to have elevated AMH levels in puberty. Detection of AMH may be used in prepubertal years as an indicator of the presence of testicular tissue (e.g., in patients with bilateral cryptorchidism). Inhibin B is also secreted by the Sertoli cells, is present throughout childhood, and rises at onset of puberty (more in males than in females). It may be used as another marker of the presence of testicular tissue in bilateral cryptorchidism and as a marker of spermatogenesis (e.g., in delayed puberty, cancer survivors, and patients with Noonan syndrome). Bone age x-rays are useful to document delayed bone age in patients with constitutional growth delay as well as primary hypogonadism.

Noonan Syndrome

Etiology

The term *Noonan syndrome* has been applied to males and females with normal karyotypes who have certain phenotypic features that occur also in females with Turner syndrome (although the genetic causes are completely distinct) (see Chapter 98.4). Noonan syndrome occurs in 1 in 1,000-2,500 live births. Approximately 20% of the cases are familial and exhibit autosomal dominant inheritance. Males and females are equally affected. Several mutations in the renin–angiotensin system (RAS)–mitogen-activated protein kinase (MAPK) pathway can cause Noonan syndrome and other related disorders and such mutations are currently detected in approximately 70% of the cases of Noonan syndrome. Missense mutations in *PTPN11* —a gene on chromosome 12q24.1 encoding the nonreceptor protein tyrosine phosphatase SHP-2—are seen in about half the cases. Mutations in other genes in this pathway, including *SHOC2* , *CBL* , *SOS1* , *KRAS* , *NRAS* , *BRAF* , and *RAF1* as well as duplications of the 12q24 region are also seen. Phenotypic features of Noonan syndrome therefore overlap with other syndromes involving the RAS-MAPK pathway, such as Leopard syndrome, Costello syndrome, and cardiofaciocutaneous syndrome.

Clinical Manifestations

The most common abnormalities are short stature, webbing of the neck, pectus carinatum or pectus excavatum, cubitus valgus, right-sided congenital heart disease, and characteristic facies. Hypertelorism, epicanthus, downward-slanting palpebral fissures, ptosis, micrognathia, and ear abnormalities are common. Other abnormalities such as clinodactyly, hernias, and vertebral anomalies occur less frequently. The mean IQ of school-age children with Noonan syndrome is subnormal at 86, with a range of 53-127. Verbal IQ tends to be better than performance IQ. High-frequency sensorineural hearing loss is common. The cardiac defect is most often pulmonary valvular stenosis, hypertrophic cardiomyopathy, or atrial septal defect. Hepatosplenomegaly and several hematologic diseases—including low clotting factors XI and XII, acute lymphoblastic leukemia, and chronic myelomonocytic leukemia—are noted. Noonan-like features can be part of the phenotypic variation of the *NF1* (neurofibromatosis) gene mutation, possibly because of common involvement of the RAS-MAPK pathway in both diseases. Males frequently have cryptorchidism and small testes. Testosterone secretion may be low or normal, but spermatogenesis may be affected even in those with normal testosterone (and normal secondary sexual characteristics). Serum inhibin-B is a useful marker of Sertoli cell function in these patients. Puberty is delayed, and adult height is achieved by the end of the second decade; it usually reaches the lower limit of the normal population. Prenatal diagnosis should be suspected in fetuses with normal karyotype, edema, or hydrops and short femoral length.

Treatment

Human growth hormone results in improvement in growth velocity in many Noonan syndrome patients, comparable to that seen in patients with Turner syndrome, and studies show a mean increase in height standard deviation score ranging from 1.3 to 1.7, corresponding to 9.5-13 cm for males and 9.0-9.8 cm for females. Many patients with Noonan syndrome reach normal height without growth hormone therapy, but treatment is recommended for those who fall below the 3rd percentile for height. The recommended dose is up to 66 µg/kg/day of recombinant growth hormone. Patients with Noonan syndrome and demonstrable *PTNP11* mutations grow less well and are less responsive to growth hormone treatment than those without mutations. They have lower insulin-like growth factor-1 and higher growth hormone levels, suggesting partial growth hormone resistance because of post–receptor-signaling defects. Treatment of male hypogonadism is discussed in Chapter 601.2 .

Klinefelter Syndrome

See also Chapter 98 .

Etiology

Klinefelter syndrome is the most common sex chromosomal aneuploidy in males, with an incidence of 0.1–0.2% in the general population (1 in 500-1,000) and rising to 4% among infertile males and 10–11% in those with oligospermia or azoospermia. Approximately 80% of them have a 47,XXY chromosome complement, whereas mosaics and higher degrees of poly-X are seen in the remaining 20%. Even with as many as 4 X chromosomes, the Y chromosome determines a male phenotype. The chromosomal aberration most often results from meiotic nondisjunction of an X chromosome during parental gametogenesis; the extra X chromosome is maternal in origin in 54% and paternal in origin in 46% of patients. A national study in Denmark revealed a prenatal prevalence of 213 per 100,000 male fetuses, but in adult men the prevalence was only 40 per 100,000, suggesting that only 1 in 4 adult males with Klinefelter syndrome was diagnosed. The incidence of KS increases with maternal age and possibly also with paternal age.

Clinical Manifestations

In patients who do not have a prenatal diagnosis, the diagnosis is rarely made before puberty because of the paucity or subtlety of clinical manifestations in childhood. Behavioral or psychiatric disorders may be apparent long before defects in sexual development. These children tend to have learning disabilities and deficits in *executive function* (concept formation, problem solving, task switching, and planning), and the condition should be considered in males with psychosocial, learning, or school adjustment problems. Affected children may be anxious, immature, or excessively shy and tend to have difficulty in social interactions throughout life. In a prospective study, a group of children with 47,XXY karyotypes identified at birth exhibited relatively mild deviations from normal during the first 5 yr of life. None had major physical, intellectual, or emotional disabilities; some were inactive, with poorly organized motor function and mild delay in language acquisition. Problems often first become apparent after the child begins school. Full-scale IQ scores may be normal, with verbal IQ being somewhat decreased. Verbal cognitive defects and underachievement in reading, spelling, and mathematics are common. By late adolescence, many males with Klinefelter syndrome have generalized learning disabilities, most of which are language based. Despite these difficulties, most complete high school.

The patients tend to be tall, slim, and have a specific tendency to have long legs (disproportionate to the arms, and longer than those seen with other causes of hypogonadism), but body habitus can vary markedly. The testes tend to be small for age, but this sign may become apparent only after puberty, when normal testicular growth fails to occur. The phallus tends to be smaller than average, and cryptorchidism is more common than in the general population. Bone mineral density may be low in adults with Klinefelter syndrome, and this correlates with lower testosterone levels.

Pubertal development may be delayed, although some children undergo apparently normal or nearly normal virilization. Despite normal testosterone levels, serum LH and FSH concentrations and their responses to gonadotropin-releasing hormone (GnRH) stimulation are elevated starting at around 13 yr of age. Approximately 80% of adults have **gynecomastia;** they have sparser facial hair, most shaving less often than daily. The most common testicular lesions are spermatogenic arrest and Sertoli cell predominance. The sperm have a high incidence of sex chromosomal aneuploidy. Azoospermia and infertility are usual, although rare instances of fertility are known. It is now clear that germ cell numbers and sperm counts are higher in early puberty and decline with age. Testicular sperm extraction followed by intracytoplasmic sperm injection can result in the birth of healthy infants, with success rates declining with increasing age. In nonmosaic Klinefelter patients, most testicular sperm (94%) have a normal pattern of sex chromosome segregation, indicating that meiotic checkpoints can remove most aneuploid cells. Antisperm antibodies have been detected in 25% of tested specimens.

There is an increased incidence in adulthood of central adiposity, metabolic syndrome, pulmonary disease, varicose veins, and cancer of the breast. Among 93 unselected **male breast cancer** patients, 7.5% were found to have Klinefelter syndrome. Mediastinal germ cell tumors have been reported; some of these tumors produce hCG and cause precocious puberty in young males. They may also be associated with leukemia, lymphoma, and other types of hematologic neoplasia. The highest cancer risk (relative risk: 2.7) occurs in the 15-30 yr age group. A large cohort study in Britain demonstrated an overall significantly increased standardized mortality ratio (1.5), with increases in deaths from diabetes, epilepsy, peripheral and intestinal vascular sufficiency, pulmonary embolism, and renal disease. Mortality from ischemic heart disease was decreased. In adults, structural brain abnormalities correlate with cognitive deficits.

In adults with XY/XXY mosaicism, the features of Klinefelter syndrome are decreased in severity and frequency. Children with mosaicism have a better prognosis for virilization, fertility, and psychosocial adjustment.

Klinefelter Variants and Other Poly-X Syndromes

When the number of X chromosomes exceeds 2, the clinical manifestations, including intellectual disability and impairment of virilization, are more severe. Height decreases with increasing number of X chromosomes. The XXYY variant is the most common variant (1 in 18,000-40,000 male births). In most, intellectual disability occurs with IQ scores between 60 and 80, but 10% have IQs greater than 110. The XXYY male phenotype is not distinctively different from that of the XXY patient except that XXYY adults tend to be taller than the average XXY patient. The 49,XXXXY variant is sufficiently distinctive to be detected in childhood. Its incidence is estimated to be 1 in 80,000-100,000 male births. The disorder arises from sequential nondisjunction in meiosis. Affected patients are severely cognitively impaired and have short necks and typical coarse facies. The eyes are wide-set, with a mild upward slant of the fissures as well as epicanthus and strabismus; the nose is upturned, wide, and flat; also noted is a large open mouth and large malformed ears. The testes are small and may be undescended, the scrotum is hypoplastic, and the penis is very small. Defects suggestive of Down syndrome (short, incurved terminal 5th phalanges, single palmar creases, and hypotonia) and other skeletal abnormalities (including defects in the carrying angle of the elbows and restricted supination) are common. The most frequent radiographic abnormalities are radioulnar synostosis or dislocation, elongated radius, pseudoepiphyses, scoliosis or kyphosis, coxa valga, and retarded bone age. Most patients with such extensive changes have a 49,XXXXY chromosome karyotype; several mosaic patterns have also been observed: 48,XXXY/49,XXXXY; 48,XXXY/49,XXXXY/50,XXXXXY; and 48,XXXY/49,XXXXY/50,XXXXYY. Prenatal diagnosis of a 49,XXXXY infant has been reported. The fetus had intrauterine growth retardation, edema, and cystic hygroma colli.

The 48,XXXY variant is relatively rare. The characteristic features are generally less severe than those of patients with 49,XXXXY and more severe than those of 47,XXY patients. Mild intellectual disability, delayed speech and motor development, and immature but passive and pleasant behavior are associated with this condition.

Very few patients have been described with 48,XYYY and 49,XXYYY karyotypes. Dysmorphic features and cognitive impairment are common to both.

Laboratory Findings

Most males with Klinefelter syndrome go through life undiagnosed. The chromosomes should be examined in all patients suspected of having Klinefelter syndrome, particularly those attending child guidance, psychiatric, and cognitive disability clinics. In infancy, inhibin B and AMH levels are normal but testosterone levels are lower than in controls. Before 10 yr of age, males with 47,XXY Klinefelter syndrome have normal basal plasma levels of FSH and LH. Responses to gonadotropin-stimulating hormone and to hCG are normal. The testes show normal growth early in puberty, but by midpuberty the testicular growth stops, gonadotropins become elevated, and testosterone levels are slightly low. Inhibin B levels are normal in early puberty, decrease in late puberty, and are low in adults with the syndrome. Elevated levels of estradiol, resulting in a high ratio of estradiol to testosterone, account for the development of gynecomastia during puberty. Sex hormone–binding globulin levels are elevated, further decreasing free testosterone levels. A long androgen receptor polyglutamine (CAG) repeat length is associated with the more severe phenotype, including gynecomastia, small testes, and short penile length.

Testicular biopsy before puberty may reveal only deficiency or absence of germinal cells. After puberty, the seminiferous tubular membranes are hyalinized and there is adenomatous clumping of Leydig cells. Sertoli cells predominate. Azoospermia is characteristic, and infertility is the rule.

Management

Males known to have Klinefelter syndrome should be monitored closely for speech, learning, and behavioral problems; they should be referred for early evaluation and treatment as needed. Testosterone, LH, and FSH levels should be checked at 11-12 yr of age; replacement therapy with a testosterone preparation is recommended once FSH and LH begin to rise above normal. Fasting glucose, lipids, and hemoglobin A_{1C} should also be obtained, as these children are at risk for central adiposity and metabolic syndrome. A baseline dual-energy x-ray absorptiometry scan to assess bone density is also recommended by some authorities. Although testosterone treatment will normalize testosterone levels, stimulate the development of secondary sexual characteristics, increase bone mass and muscle mass, and improve body composition, it will *not* improve fertility (and will, in fact, suppress spermatogenesis). There is some evidence that it also improves mood and may have a positive effect on cognition and social functioning, but the findings are not conclusive at this time. Either long-acting testosterone injections or a daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are not frequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly every 3-4 wk, with 50-mg increments every 6-9 mo until a maintenance dose for adults (200-250 mg every 3-4 wk) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older males, larger initial doses and increments can achieve more rapid virilization. The various transdermal preparations differ somewhat from each other and standard references should be consulted for recommendations regarding dosage and mode of application.

Gynecomastia may be treated with aromatase inhibitors (which will also increase endogenous testosterone levels), but medical treatment is not always successful and plastic surgery may be needed. Fertility is usually not an issue in the pediatric age group, but adults can father children using testicular sperm extraction followed by intracytoplasmic sperm injection. Because sperm counts decrease rapidly after the onset of puberty in children with Klinefelter syndrome, sperm banking during early puberty is an option that can be discussed with a fertility specialist. Sperm counts can be stimulated using hCG treatment prior to testicular sperm extraction. Therapy, counseling, and psychiatric services should be provided as needed for learning difficulties and psychosocial disabilities.

XX Males

This disorder is thought to occur in 1 in 20,000 newborn males. Affected individuals have a male phenotype, small testes, a small phallus, and no evidence of ovarian or müllerian duct tissue. They appear, therefore, to be *distinct from* those with the ovotesticular disorder of sexual development. Undescended testes and hypospadias occur in a minority of patients. Infertility occurs in practically all cases, and the histologic features of the testes are essentially the same as in Klinefelter syndrome. Patients with the condition usually come to medical attention in adult life because of hypogonadism, gynecomastia, or infertility. Hypergonadotropic hypogonadism occurs secondary to testicular failure. A few cases have been diagnosed perinatally as a result of discrepancies between prenatal ultrasonography and karyotype findings.

In 90% of XX males with normal male external genitalia, one of the X chromosomes carries the *SRY* (sex-determining region on the Y chromosome) gene. The exchange from the Y to the X chromosome occurs during paternal meiosis, when the short arms of the Y and X chromosomes pair. XX males inherit one maternal X chromosome and one paternal X chromosome containing the translocated male-determining gene. A few cases of 46,XX males with 9P translocations have also been identified. Most XX males who are identified before puberty have hypospadias or a micropenis; this group of patients may lack Y-specific sequences, suggesting other mechanisms for virilization. Fluorescent in situ hybridization and primed in situ labeling have been used to identify small *SRY* DNA segments. Yp fragment abnormalities may result in sexually ambiguous phenotypes.

45,X Males

In a few male patients recognized with a 45,X karyotype, Yp sequences are translocated to an autosomal chromosome. In one instance, the terminal short arm of the Y chromosome was translocated onto an X chromosome. In another, *SRY/autosomal* translocation was postulated. A male with the 45,X karyotype and Leri-Weill dyschondrosteosis, *SHOX* gene loss, and an SRY to Xp translocation has also been described.

47,XXX Males

A Japanese male with poor pubic hair development, hypoplastic scrotal testes (4 mL), normal penis and normal height, gynecomastia, and severe cognitive impairment had 47,XXX karyotype caused by an abnormal X-Y interchange during paternal meiosis and X-X nondisjunction during maternal meiosis.

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601.2

Hypogonadotropic Hypogonadism in the Male (Secondary Hypogonadism)

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Keywords

hypogonadotropic hypogonadism
hypopituitarism
Kallmann syndrome
radiation therapy
constitutional delay

In hypogonadotropic hypogonadism (HH), lack of gonadal function is secondary to deficiency of one or both gonadotropins: FSH or LH. The primary defect may lie either in the anterior pituitary or in the hypothalamus. Hypothalamic etiologies result in deficiency of GnRH. The testes are normal but remain in the prepubertal state because stimulation by gonadotropins is lacking. The disorder may be recognized in infancy but is much more commonly recognized because of marked pubertal delay. Rarely, patients with an inherited form of HH may go through puberty and may present with hypogonadism as adults.

Etiology

HH may be genetic or acquired (Table 601.2). Several different genes can cause inherited forms of HH; the affected genes may be upstream of GnRH, at the level of GnRH receptors, or at the level of gonadotropin production. In addition, various genetic defects in transcription factors—such as POUF-1, LHX-3, LHX-4, and HESX-1—lead to defects in pituitary development and multiple pituitary hormone deficiencies, including deficiency of gonadotropins. Acquired pituitary gonadotropin deficiency may develop from various lesions in the hypothalamic-pituitary region (e.g., tumors, infiltrative disease, autoimmune disease, trauma, stroke).

Table 601.2

Forms of Congenital Hypogonadotropic Hypogonadism and Differential Diagnosis

FORMS OF CHH
GnRH Deficiency and Defective Sense of Smell
• Kallmann syndrome
Isolated GnRH Deficiency (Normal Sense of Smell)
• Normosmic CHH
Complex Syndromes Including CHH or KS
• Combined pituitary hormone deficiency
• Septo-optic dysplasia
• CHARGE syndrome
• Adrenal hypoplasia congenita with HH
• Waardenburg syndrome
• Bardet-Biedl syndrome
• Gordon Holmes syndrome
• Others
DIFFERENTIAL DIAGNOSIS
Functional Causes
• Malnutrition and/or malabsorption
• Any chronic disease (e.g., IBS or asthma)
• Celiac disease
• Eating disorders
• Excessive exercise
Systemic Causes
• Hemochromatosis
• Sarcoidosis
• Histiocytosis
• Thalassemia
Acquired Causes
• Pituitary adenomas and/or brain tumors
• Rathke cleft cyst
• Pituitary apoplexy
• Radiation (brain or pituitary)
• Medication induced (such as by steroids, opiates, or chemotherapy)

CHARGE , coloboma, heart defects, atresia of choanae, retardation of growth and/or development, genital and/or urinary defects, ear anomalies or deafness; *CHH* , congenital hypogonadotropic hypogonadism; *GnRH* , gonadotropin-releasing hormone; *HH* , hypogonadotropic hypogonadism; *IBS* , irritable bowel syndrome; *KS* , Kallmann syndrome

From Boehm U, Bouloux PM, Dattani MT, et al: European consensus statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment, *Nat Rev* 11:547–564, 2015, Box 2.

Isolated Gonadotropin Deficiency

Isolated gonadotropin deficiency in which other pituitary hormone levels are normal is more likely to be from defects in the secretion of GnRH from the hypothalamus rather than defects in gonadotropin synthesis in the pituitary. It affects approximately 1 in 10,000 males and 1 in 50,000 females and encompasses a heterogeneous group of entities. Many cases are associated with anosmia, and this combination of anosmia and HH defines Kallmann syndrome.

Kallmann syndrome is the most common form of HH and is genetically heterogeneous, with autosomal recessive, X-linked, and autosomal dominant forms of inheritance. Clinically it is characterized by its association with anosmia or hyposmia; 85% of the cases appear to be autosomal and 15% are X-linked. The **X-linked** form (KAL1) is caused by mutations of the *KAL1* gene at Xp22.3. This leads to failure of olfactory axons and GnRH-expressing neurons to migrate from their common origin in the olfactory placode to the brain. The *KAL* gene product anosmin-1, an extracellular 95-kDa matrix glycoprotein, facilitates neuronal growth and migration. The *KAL* gene is also expressed in various parts of the brain, facial mesenchyme, and mesonephros and metanephros, thus explaining some of the associated findings in patients with Kallmann syndrome, such as synkinesia (mirror movements), hearing loss, midfacial defects, and renal agenesis.

Some kindreds contain anosmic individuals *with or without* hypogonadism; others contain hypogonadal individuals who are anosmic. Cleft lip and palate, hypotelorism, median facial clefts, sensorineural hearing loss, unilateral renal aplasia, neurologic deficits, and other findings occur in some affected patients. When Kallmann syndrome is caused by terminal or interstitial deletions of the Xp22.3 region, it may be associated with other contiguous gene syndromes, such as steroid sulfatase deficiency, chondrodysplasia punctata, X-linked ichthyosis, or ocular albinism.

The **autosomal dominant** form of Kallmann syndrome (KAL2) occurs in up to 10% of patients and is caused by a loss-of-function mutation in the fibroblast growth factor receptor 1 *(FGFR1)* gene. Cleft lip and palate are associated with KAL2 but not with KAL1. Oligodontia and hearing loss may occur with both KAL1 and KAL2.

A variety of other genes—including *FGF8* , *PROK2/PROKR2* , *NELF* , *CHD7* (responsible for CHARGE [coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies] syndrome, which includes hypogonadism in its phenotype), *HS6ST1* , *WDR11* , and *SEMA3A*— are associated with defects in neuronal migration that can result in Kallmann syndrome; but in about 70% of patients the affected gene remains undefined, although this percentage continues to drop as genetic testing advances.

Hypogonadotropic Hypogonadism Without Anosmia

A specific genetic defect is not found in most cases of normosmic idiopathic hypogonadotropic hypogonadism (IHH), but the list of genes associated with this disorder is growing; mutations in the genes *KISS1/KISS1R* , *TAC3/TACR3* and *GNRH1/GNRHR* lead to abnormalities in the secretion and action of GnRH and are seen exclusively in patients with normosmic IHH. Mutations in *FGFR1* , *FGF8* , *PROKR2* , *CHD7* , and *WDR11* more commonly present with anosmia/hyposmia (Kallmann syndrome) but are also associated with normosmic IHH in some cases. It appears that kisspeptin (the gene product of the *KISS1* gene) and its G protein–coupled receptor (GPCR54) play an important role in triggering puberty in humans and act downstream of the leptin receptor in this pathway. Rare cases of leptin deficiency and leptin receptor defects are also associated with HH. In addition, starvation and anorexia are associated with hypogonadism, most likely acting via the leptin pathway.

There are no known human mutations of the *GnRH* gene, but several families with mutations in the GnRH receptor have been described. These mutations account for 2–14% of idiopathic HH without anosmia. The severity of the defect is variable, and many patients will respond to high-dose GnRH with increased gonadotropin secretion, indicating that the receptor defect is partial.

Mutations in gonadotropin genes are extremely rare. Mutations in the common α-subunit are not known in humans. Mutations in the LH-β subunit have been described in a few individuals and may lead to low, absent, or elevated LH levels, depending on the mutation. Defects in the FSH-β subunit may be the cause of azoospermia in a few rare cases.

Children with *X-linked adrenal hypoplasia congenital (AHC) have associated HH as a result of impaired GnRH secretion.* In these patients, there is a mutation of the *DAX1* gene at Xp21.2-21.3. Conditions occasionally associated with AHC occur in these patients because of the contiguous gene syndrome and include glycerol kinase deficiency, Duchenne muscular dystrophy, and ornithine transcarbamoyltransferase deficiency. Most males with *DAX1* mutations develop

HH in adolescence, although a patient with adult-onset adrenal insufficiency and partial HH and 2 females with HH and delayed puberty have also been described, the latter as part of extended families including males with classic HH. The *DAX1* gene defect is, however, rare in patients with delayed puberty or HH without at least a family history of adrenal failure (see Chapter 594).

It should be noted that genotype–phenotype correlations in IHH appear to be complex, and pedigrees with digenic or oligogenic inheritance have been described. The same genetic defect may be associated with Kallmann syndrome, normosmic IHH, additional birth defects, delayed normal puberty, or an apparently normal phenotype. This variability has been observed more frequently in kindreds with mutations in *FGF8/FGFR1* and in *PROK2/PROKR2* ligand-receptor pairs and may result from other interacting genes, epigenetic effects, or environmental factors.

Other Disorders With Hypogonadotropic Hypogonadism

HH has been observed in a few patients with polyglandular autoimmune syndrome, in some with elevated melatonin levels, and in those with a variety of other syndromes, such as Bardet-Biedl, Prader-Willi, multiple lentigines, and several ataxia syndromes. In rare cases, HH is associated with complex chromosomal abnormalities.

Hypogonadotropic Hypogonadism Associated With Other Pituitary Hormone Deficiencies

Defects in pituitary transcription factors—such as PROP-1, HESX-1, LHX-4, SOX-3, and LHX-3—lead to multiple pituitary deficiencies including HH. Most of these present with multiple pituitary hormone deficiency in infancy, but some cases (especially with *PROP-1* mutations) may present with hypogonadism or hypoadrenalism in adult life. Growth hormone is almost always affected in multiple pituitary hormone deficiency, but thyroid-stimulating hormone and adrenocorticotropic hormone may be spared in some cases. In patients with organic lesions in or near the pituitary, the gonadotropin deficiency is usually pituitary in origin. Microphallus (<2.5 cm at term) in the newborn male with growth hormone deficiency suggests the possibility of gonadotropin deficiency.

Diagnosis

Levels of gonadotropins and gonadal steroids are normally elevated for up to 6 mo after birth (minipuberty); if the diagnosis of HH is suspected in early infancy, these levels will be found to be inappropriately low. By the 2nd half of the 1st yr of life, these levels normally decline to being nearly undetectable and remain suppressed until late childhood. Therefore routine lab tests cannot distinguish HH from normal suppression of gonadotropins in this age group. At the normal age of puberty, these patients fail to show clinical signs of puberty or a normal increase in LH and FSH levels. Children with constitutional delay of growth and puberty will have the same clinical picture and similar lab findings (these cases are far more common than true HH, especially in males), and their differentiation from patients with HH is extremely difficult. Dynamic testing with GnRH or hCG may *not* be able to distinguish these groups in a reliable manner. A testosterone level greater than 50 ng/dL (1.7 nmol/L) generally indicates that normal puberty is likely, but a lower level does not reliably distinguish these groups. At least one study shows that an inhibin B level of <35 pg/mL in Tanner stage 1 and <65 pg/mL in Tanner stage 2 may be able to distinguish IHH from constitutional delay in males.

Insulin-like growth factor-1, thyroid-stimulating hormone, free thyroxine, and morning cortisol levels should be checked to assess the status of other anterior pituitary hormones; dynamic testing for growth hormone deficiency and adrenal insufficiency may be necessary if these are abnormal or equivocal. HH is very likely if the patient has evidence of another pituitary deficiency, such as a deficiency of growth hormone, particularly if it is associated with adrenocorticotropic hormone deficiency. *Hyperprolactinemia* is a known cause of delayed puberty and should be excluded by determination of serum prolactin levels in all patients. The presence of *anosmia* usually indicates permanent gonadotropin deficiency, but occasional instances of markedly delayed puberty (18-20 yr of age) have been observed in anosmic individuals. Although anosmia may be present in the family or in the patient from early childhood, its existence is rarely volunteered, and direct questioning is necessary in all patients with delayed puberty. Formal olfactometry, such as the University of Pennsylvania Smell Identification Test, is advisable to determine if partial degrees of hyposmia are present, because IHH patients display a broad spectrum of olfactory function.

In the absence of family history, it may not be possible to make the diagnosis of HH with certainty, but the diagnosis will become more and more likely as puberty is delayed further beyond the normal age. If pubertal delay persists beyond age 18 yr with low 8 AM testosterone levels and inappropriately low gonadotropins (normal values are inappropriately low in this setting), then the patient can be presumptively diagnosed with HH. *An MRI of the brain is indicated* to look for tumors and other anomalies in the hypothalamic-pituitary region. Genetic testing for pituitary transcription factors and several of the genes involved in isolated HH is also available and should be performed when possible. A renal ultrasound is recommended in patients with Kallmann syndrome because of its association with unilateral renal agenesis. Some authorities also recommend obtaining a baseline bone-density evaluation.

Treatment

Constitutional delay of puberty should be ruled out before a diagnosis of HH is established and treatment is initiated. Testicular volume of less than 4 mL by 14 yr of age occurs in approximately 3% of males, but true HH is a rare condition. Even relatively moderate delays in sexual development and growth may result in significant psychologic distress and require attention. Initially an explanation of the variations characteristic of puberty and reassurance suffice for the majority of males. If by 15 yr of age no clinical evidence of puberty is apparent and the testosterone level is <50 ng/dL, a brief course of testosterone may be recommended. Various regimens are used, including testosterone enanthate 100 mg intramuscularly once monthly for 4-6 mo or 150 mg once monthly for 3 mo. Some practitioners use oral oxandrolone, which has the theoretical advantage that it is not aromatized and may have less effect on bone age advancement (though definitive evidence of advantage is lacking). Oral oxandrolone may cause hepatic dysfunction and liver function tests should be monitored if it is used. Treatment is not necessary in all cases of constitutional delay, but if used it is usually followed by normal progression through puberty, and this may differentiate constitutional delay in puberty from isolated gonadotropin deficiency. The age of initiation of this treatment must be individualized.

Once a diagnosis of HH has been made, treatment with testosterone will induce secondary sexual characteristics but will *not* stimulate testicular growth or spermatogenesis. Treatment with gonadotropins (either as a combination of hCG and human menopausal gonadotropins or as GnRH pulse therapy) will lead to testicular development, including spermatogenesis, but it is much more complex to manage, so in most cases testosterone treatment is the best option. Either long-acting testosterone injections or a daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are infrequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly or subcutaneously every 3-4 wk, with 50 mg increments every 6-9 mo until a maintenance dose for adults (200-250 mg every 3-4 wk) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older males, larger initial doses and increments can achieve more rapid virilization.

Treatment with gonadotropins is more physiologic but is expensive and complex, so it is less commonly used in adolescence. This treatment may be attempted in adult life when fertility is desired. The treatment schedule varies from 1,250 to 5,000 IU hCG in combination with 12.5-150 IU human menopausal gonadotropins 3 times per week intramuscularly. It may require up to 2 yr of treatment to achieve adequate spermatogenesis in adults. Recombinantly produced gonadotropins (LH and FSH) are also able to stimulate gonadal growth and function but are much more expensive. Treatment with GnRH (when available) is the most physiologically appropriate, but it requires the use of a subcutaneous infusion pump to deliver appropriately pulsed therapy because continuous exposure to GnRH will suppress gonadotropins rather than stimulate them. In some cases, patients with GnRH defects also have pituitary or testicular dysfunction (a dual defect) and may fail to respond adequately to GnRH or gonadotropin treatment. The rare patient with isolated LH deficiency can be treated effectively using hCG injections.

It has been found that up to 10% of patients diagnosed with HH (with or without anosmia) may exhibit spontaneous reversal of hypogonadism with sustained normal gonadal function after treatment has been discontinued; this may even occur in patients with known genetic mutations in various genes, including *FGFR1* , *PROK2* , *GNRH* , *CHD7* , and *TAC/TACR3* . Such recovery is more likely in patients who show an increase in testicular volume during treatment or when treatment has been discontinued. Therefore a brief trial of interruption of treatment is justified in patients with idiopathic HH. However, the recovery of gonadal function may not be lifelong.

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CHAPTER 602

Pseudoprecocity Resulting From Tumors of the Testes

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Leydig cell tumors of the testes are rare causes of precocious pseudopuberty (gonadotropin-independent puberty) and cause asymmetric enlargement of the testes. Leydig cells are sparse before puberty and tumors derived from them are more common in the adult. However, rare cases do occur in children; the youngest reported case was in a 1-yr-old male. Although up to 10% of adult tumors may be malignant, metastasizing malignant tumors have not been reported in children, and pediatric Leydig cell tumors are usually unilateral and benign. Some tumors may be due to somatic activating mutations of the luteinizing hormone receptor.

The clinical manifestations are those of puberty in the male; onset usually occurs at 5-9 yr of age. Unilateral pubarche due to local hormone action has been described. Gynecomastia may occur. The tumor of the testis can usually be readily felt; the contralateral unaffected testis is normal in size for the age of the patient.

Plasma levels of testosterone are markedly elevated, and follicle-stimulating hormone and luteinizing hormone levels are suppressed. Ultrasonography may aid in the detection of small nonpalpable tumors. Fine-needle aspiration biopsy may help define the diagnosis.

Treatment consists of surgical removal of the affected testis. These tumors are generally resistant to chemotherapy. Progression of virilization ceases after removal of the tumor, and partial reversal of the signs of precocity may occur.

Testicular adrenal rests may develop into tumors that mimic Leydig cell tumors. Adrenal rest tumors are usually bilateral and occur in children with inadequately controlled congenital adrenal hyperplasia, usually of the salt-losing variety, during adolescence or young adult life. The stimulus for the growth of the adrenal rests is inadequate corticosteroid suppressive therapy causing excess adrenocorticotropic hormone secretion; treatment with adequate doses almost always results in their regression. These tumors are histologically similar to primary Leydig cell tumors, but definite evidence of their origin may be achieved by demonstrating their 21-hydroxylase activity. Misdiagnosis of these tumors as primary Leydig cell tumors may lead to unnecessary orchidectomy and should be avoided.

Fragile X syndrome (see Chapter 98.5) is caused by the amplification of a polymorphic CGG repeat in the 5′ untranslated region of the *FMRI* gene at Xp17.3. The gene encodes an RNA-binding protein that is highly expressed in the brain and the testis. In otherwise normal individuals, 6-50 CGG repeats are present in the gene; the presence of 50-200 repeats (permutation) is associated with mild intellectual disability and other abnormalities, and the presence of more than 200 repeats (fragile X mutation) is associated with the classic fragile X syndrome. Permutations are present in 1 in 1,000 white males, and mutations are found in 1 in 4,000-8,000. A cardinal characteristic of the condition is testicular enlargement (*macroorchidism*), reaching 40-50 mL after puberty. Although the condition has been recognized in a child as young as 5 mo of age, affected boys younger than 6 yr of age rarely have testicular enlargement; by 8-10 yr of age, most have testicular volumes greater than 3 mL. The testes are enlarged bilaterally, are not nodular, and are histologically normal. Results of hormonal studies are normal. Direct DNA analysis searching for CGG repeat sequences permits definitive diagnosis.

Large-cell calcifying Sertoli cell tumors of the testes (usually associated with Carney complex) and **sex cord tumors with annular tubules** (frequently associated with Peutz-Jeghers syndrome) are extremely rare Sertoli cell tumors that may be a cause of breast development in young males. These tumors often occur bilaterally, are multifocal, and are detectible by ultrasonography. Excessive production of aromatase (P450arom), the enzyme that converts testosterone to estradiol, causes feminization of these males. Because these tumors are usually benign, they may be left in place if they are not causing pain; the gynecomastia can be treated with aromatase inhibitors.

In males with *unilateral cryptorchidism*, the contralateral testis is approximately 25% larger than normal for age. Testicular enlargement has also been noted in males with Henoch-Schönlein purpura and lymphangiectasia. Epidermoid and dermoid cysts of the testes have been reported rarely.

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CHAPTER 603

Gynecomastia

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Gynecomastia, the proliferation of mammary glandular tissue in the male, is a common condition. True gynecomastia (the presence of glandular breast tissue) must be distinguished from pseudogynecomastia, which is the result of accumulation of adipose tissue in the area of the breast that is commonly seen in overweight males. True gynecomastia is characterized by the presence of a palpable fibroglandular mass at least 0.5 cm in diameter that is located concentrically beneath the nipple and areolar region.

Physiologic Forms of Gynecomastia

Gynecomastia occurs in many newborn males as a result of normal stimulation by maternal estrogen; the effect usually disappears in a few weeks. It is then extremely rare in prepubertal males, in whom it should always be investigated to identify the cause, but it again becomes common during normal puberty.

Neonatal Gynecomastia

Transient gynecomastia occurs in 60–90% of male newborns secondary to exposure to estrogens during pregnancy. Breast development may be asymmetrical, and galactorrhea is seen in approximately 5%. Most cases resolve within 4-8 wk of birth, but a few can last as long as 12 mo.

Pubertal Gynecomastia

During early puberty to midpuberty, up to 70% of males develop various degrees of subareolar hyperplasia of the breasts. Incidence peaks at 14 yr of age, at

Tanner stage 3-4 and at a testicular volume of 5-10 mL. Physiologic pubertal gynecomastia may involve only one breast; it is not unusual for both breasts to enlarge at disproportionate rates or at different times. Tenderness of the breast is common but transitory. Spontaneous regression may occur within a few months; it rarely persists longer than 2 yr. Significant psychosocial distress may be present, especially in obese males with relatively large breasts.

The cause is thought to be an imbalance between estrogen and androgen action at the level of breast tissue. Testing usually fails to reveal any significant difference in circulating estrogen and androgen levels between affected and unaffected males, but minor degrees of imbalance in free hormone levels may still be present. Other hormones, including leptin and luteinizing hormone, may directly stimulate breast development and may play a role in pubertal gynecomastia. Some cases may be caused by an increased sensitivity to estrogens and/or relative androgen resistance in the affected tissue. As androgen levels continue to rise in later puberty, *most cases resolve and no specific treatment is needed.*

Pathologic Gynecomastia

Monogenic forms of gynecomastia are extremely rare. Familial gynecomastia has occurred in several kindreds as an X-linked or autosomal dominant sex-limited trait. Some of these cases were found to be caused by constitutive activation of the P450 aromatase enzyme (*CYP19A1* gene), leading to increased peripheral conversion of C-19 steroids to estrogens (increased aromatization). A report of this syndrome in a father and his son and daughter suggests autosomal dominant inheritance. Excess aromatase activity was shown in skin fibroblasts and transformed lymphocytes in vitro.

Exogenous sources of estrogens are an important cause of gynecomastia in prepubertal children. Very small amounts of estrogens can cause gynecomastia in male children and accidental exposure may occur by inhalation, percutaneous absorption, or ingestion. Common sources of estrogens include oral contraceptive pills and oral and transdermal estrogen preparations. Gynecomastia has been reported in workers involved in the manufacture of estrogens and even in the children of such workers. Gynecomastia can also occur secondary to exposure to medications that decrease the level of androgens (especially free androgens), increase estradiol, or displace androgens from breast androgen receptors. Spironolactone, alkylating agents, anabolic steroids, human chorionic gonadotropin, ketoconazole, cimetidine, and androgen inhibitors such as flutamide are all associated with the occurrence of gynecomastia. Weaker associations are seen with a large number of other medications and drugs of abuse—including opiates, alcohol, and marijuana—although the association with marijuana may not be as strong as previously thought. Lavender, tea tree oils, and excessive consumption of soy are also implicated as possible causes of prepubertal gynecomastia.

Klinefelter syndrome and other causes of *male hypogonadism* are strongly associated with gynecomastia. Significant gynecomastia is seen in 50% of adolescents with Klinefelter syndrome; it is also seen in other conditions characterized by male undervirilization, including partial androgen insensitivity syndrome and 17-ketosteroid reductase deficiency. Gynecomastia has also been observed in children with congenital virilizing adrenal hyperplasia (11β-hydroxylase deficiency) and with Leydig cell tumors of the testis or with feminizing tumors of the adrenal gland. Several males with Peutz-Jeghers syndrome and gynecomastia had sex cord tumors of the testes. The testes may not be enlarged in these cases and the tumor is usually multifocal and bilateral. Excessive aromatase production accounts for the gynecomastia. When gynecomastia is associated with galactorrhea, a prolactinoma should be considered. Hyperthyroidism alters the ratio of androgen to estrogen by increasing bound androgen and decreasing the free testosterone; this may result in gynecomastia in up to 40% of cases. Gynecomastia is also seen in malnourished patients after restoration of normal nutrition (refeeding syndrome), in whom it may result from hepatic dysfunction or abnormal activation of the gonadotropin axis.

Evaluation of Gynecomastia

In pubertal cases a detailed history and physical examination may be all that is needed to exclude rare pathologic causes. Historical evaluation should include family history of male relatives with gynecomastia, history of liver or renal disease, use of medications or drugs of abuse, and exposure to herbal and cosmetic products that may contain phytoestrogens. Physical examination should include special attention to the breasts (looking for overlying skin changes, fixation, local lymphadenopathy, and nipple discharge) as well as a testicular exam. No laboratory evaluation is indicated in routine cases with no other associated abnormality; however, all prepubertal cases as well as pubertal cases with suspicious features should be investigated. Initial laboratory evaluation should include thyroid function tests (to rule out hyperthyroidism), testosterone, estradiol, human chorionic gonadotropin, luteinizing hormone, and prolactin levels. Most cases of hyperprolactinemia are associated with galactorrhea, but there are a few reports of hyperprolactinemia causing gynecomastia without associated galactorrhea. Because of circadian variation, these levels should ideally be obtained in the morning. Other tests that may be indicated in selected cases include a karyotype, dehydroepiandrosterone sulfate, and liver and renal function tests. Gonadotropin levels may be a useful screen for Klinefelter syndrome and will be elevated in pubertal males with this condition. If they are elevated, a karyotype should be performed.

Treatment

Treatment in case of benign pubertal gynecomastia usually consists of reassuring the boy and his family of the physiologic and transient nature of the phenomenon. When the enlargement is striking and persistent and causes serious emotional disturbance to the patient, specific treatment may be justified. Unfortunately, medical treatment is generally ineffective in long-standing cases. Early cases respond better to medical treatment, but it is then harder to justify as most cases will resolve spontaneously. Agents that have been used for medical treatment include androgens, aromatase inhibitors, and estrogen antagonists. The effectiveness of synthetic androgens is variable and side effects are a concern, so these are rarely used in pediatrics. Aromatase inhibitors have a physiologic rationale, but placebo-controlled trials have been disappointing. Estrogen antagonists like tamoxifen and raloxifene are more effective, with raloxifene being the superior agent in at least one well-designed trial. If medical treatment is attempted, it should be in early cases (<12 mo standing) using raloxifene (in a dose of 60 mg/day) or tamoxifen (10-20 mg/day) for 3-9 mo, with the understanding that success rates are generally low in severe cases and that mild cases will likely resolve on their own without treatment.

In those cases where breast development is excessive (Tanner stages 3-5), causes significant psychologic distress, and fails to regress in 18-24 mo, **surgical removal of the enlarged breast tissue may be indicated,** particularly in males who have completed or nearly completed pubertal development. Careful examination and laboratory testing to exclude nonphysiologic causes are advisable before proceeding to surgery.

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CHAPTER 604

Hypofunction of the Ovaries

Alvina R. Kansra, Patricia A. Donohoue

Hypofunction of the ovaries can be either primary or central in etiology. It may be caused by congenital failure of development, postnatal destruction (primary or hypergonadotropic hypogonadism), or lack of central stimulation by the pituitary and/or hypothalamus (secondary or tertiary hypogonadotropic hypogonadism). **Primary ovarian insufficiency** (hypergonadotropic hypogonadism), which is also termed *premature ovarian failure* (POF), is characterized by the arrest of normal ovarian function before 40 yr of age. Certain genetic mutations have been identified that can result in primary ovarian insufficiency. Hypofunction of the ovaries because of a lack of central stimulation (hypogonadotropic hypogonadism) can be associated with other processes, such as multiple pituitary hormone deficiencies and some chronic diseases. Table 604.1 details the etiologic classification of ovarian hypofunction (see also Fig. 578.7).

Table 604.1

Etiologic Classification of Ovarian Hypofunction

Hypogonadotropic Hypogonadism
Hypothalamic
Genetic defects • Kallmann syndrome KAL1, FGFR1, FGF8, PROK2, PROKR2, CHD7, WDR11, NELF, SEMA3A • Other gene defects: leptin, leptin receptor, KISS-1 (deficiency of kisspeptin), DAX-1, TAC3 (deficiency of neurokinin B), TACR3, SEMA7A • Inherited syndromes: Prader-Willi, Bardet-Biedl, and others • Marked constitutional growth delay Acquired defects (reversible) • Anorexia nervosa • Drug use • Malnutrition • Chronic illness, especially Crohn disease

• Hyperprolactinemia
Pituitary
Genetic defects • Isolated gonadotropin deficiency (GnRH receptor, FSH, and LH β-subunit) • Septo-optic dysplasia (*HESX-1* defect in some cases) • Disorders of pituitary organogenesis (*PROP1, LHX3, LHX4, SOX-3,* etc.) Acquired defects • Pituitary tumors • Pituitary infarction • Infiltrative disorders (histiocytosis, sarcoidosis) • Hemosiderosis and hemochromatosis • Radiation
Hypergonadotropic Hypogonadism
Genetic
Follicle-stimulating hormone and luteinizing hormone resistance Mutations in steroidogenic pathways 46,XX gonadal dysgenesis Turner syndrome and its variants Noonan syndrome (PTPN-11 gene) SF-1 gene mutations Galactosemia Fragile X–associated disorders Bloom syndrome Werner syndrome Ataxia-telangiectasia Fanconi anemia
Acquired
Chemotherapy Radiation Autoimmune ovarian failure from autoimmune polyendocrine syndromes 1 and 2

604.1

Hypergonadotropic Hypogonadism in the Female (Primary Hypogonadism)

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Keywords

primary ovarian insufficiency
ovarian failure
Turner Syndrome
gonadal dysgenesis
Noonan Syndrome
autoimmunity
chemotherapy
radiation therapy

Diagnosis of hypergonadotropic hypogonadism before puberty is difficult. Except in the case of Turner syndrome, most affected patients have no prepubertal clinical manifestations.

Turner Syndrome

Turner described a syndrome consisting of sexual infantilism, webbed neck, and cubitus valgus in adult females (see Chapter 98). Ullrich described a female with short stature and many of the same phenotypic features. The term *Ullrich-Turner syndrome* is frequently used in Europe but is infrequently used in the United States, where the condition is called Turner syndrome. The syndrome is defined as the combination of the characteristic phenotypic features accompanied by complete or partial absence of the second X chromosome with or without mosaicism.

Pathogenesis

Half the patients with Turner syndrome have a 45,X chromosomal complement. Approximately 15% of patients are mosaics for 45,X and a normal cell line (45,X/46,XX). Other mosaics with isochromosomes, 45,X/46,X,i(Xq); with rings, 45,X/46,X,r(X); or with fragments, 45,X/46fra, occur less often. Mosaicism is commonly detected when more than 1 tissue is examined. The single X is of maternal origin in nearly 80% of 45,X patients. The mechanism of chromosome loss is unknown, and the risk for the syndrome does not increase with maternal age. The genes involved in the Turner phenotype are X-linked genes that escape inactivation. A major locus involved in the control of linear growth has been mapped within the pseudoautosomal region of the X chromosome (PAR1). *SHOX*, a homeobox-containing gene of 170 kb of DNA within the PAR1, is thought to be important for controlling growth in children with Turner syndrome, Leri-Weill syndrome, and, rarely, in patients having idiopathic short stature. Genes for the control of normal ovarian function are postulated to be on Xp and perhaps 2 supergenes on Xq.

Turner syndrome occurs in approximately 1 in 1,500-2,500 liveborn females. The frequency of the 45,X karyotype at *conception* is approximately 3%, but 99% of these are spontaneously aborted, accounting for 5–10% of all abortuses. Mosaicism (45,X/46,XX) occurs in a proportion higher than that seen with any other aneuploid state, but the mosaic Turner constitution is rare among the abortuses; these findings indicate preferential survival for mosaic forms.

The normal fetal ovary contains approximately 7 million oocytes, but these begin to disappear rapidly after the 5th mo of gestation. At birth, there are only 2 million (1 million active follicles); by menarche, there are 400,000-500,000; and at menopause, 10,000 remain. In the absence of 1 X chromosome, this process is accelerated, and nearly all oocytes are gone by 2 yr of age. In aborted 45,X fetuses, the number of primordial germ cells in the gonadal ridge appears to be normal, suggesting that the normal process of oocyte loss is accelerated in patients with Turner syndrome. Eventually, the ovaries are described as streaks and consist only of connective tissue, with very few germ cells present.

Clinical Manifestations

Many patients with Turner syndrome are recognizable at birth because of a characteristic edema of the dorsa of the hands and feet and loose skinfolds at the nape of the neck. Low birthweight and decreased birth length are common (see Chapter 98). Clinical manifestations in childhood include webbing of the neck, a low posterior hairline, small mandible, prominent ears, epicanthal folds, high arched palate, a broad chest presenting the illusion of widely spaced nipples, cubitus valgus, and hyperconvex fingernails. The diagnosis is often first suspected at puberty when breast development fails to occur.

Short stature , the cardinal finding in virtually all females with Turner syndrome, may be present with little in the way of other clinical manifestations. The linear growth deceleration begins in infancy and early childhood, gets progressively more pronounced in later childhood and adolescence, and results in significant adult short stature. Sexual maturation (breast development) fails to occur at the expected age; however, signs of adrenarche (pubic hair) are normally present. Among untreated patients with Turner syndrome, the mean adult height is 143-144 cm in the United States and most of northern Europe but 140 cm in Argentina and 147 cm in Scandinavia (Fig. 604.1). The height is well correlated with the midparental height (average of the parents’ heights adjusted for child's sex). Specific growth curves for height have been developed for females with Turner syndrome.

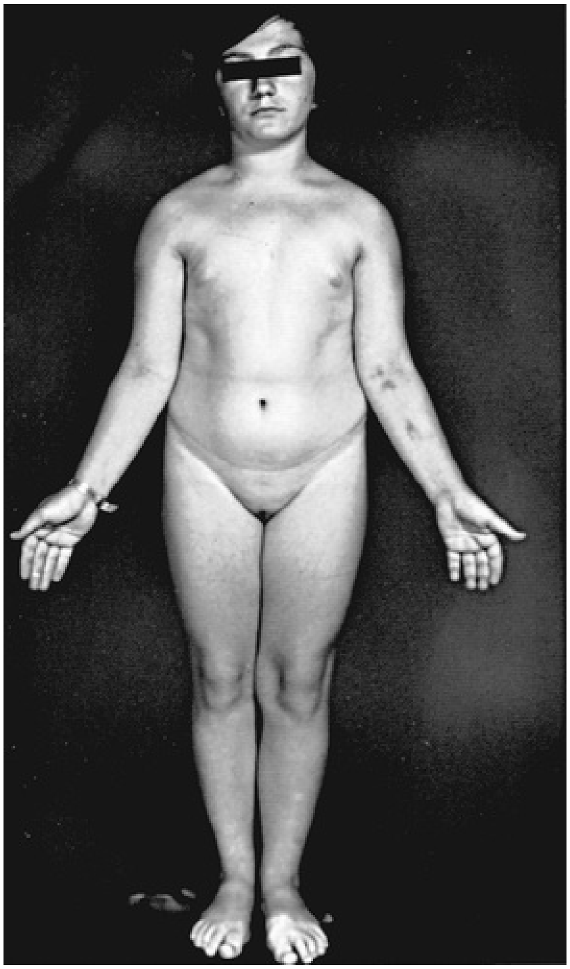

FIG. 604.1 Turner syndrome in a 15 yr old female exhibiting failure of sexual maturation, short stature, cubitus valgus, and a goiter. There is no webbing of the neck. Karyotyping revealed 45,X/46,XX chromosome complement.

Associated **cardiac defects** are common. In females with Turner syndrome, life-threatening consequences of X-chromosome haploinsufficiency involve the cardiovascular system. There is a 4-5–fold increase in the rate of premature mortality secondary to congenital heart disease and premature coronary heart disease in adults with Turner syndrome. Clinically silent cardiac defects, mainly bicuspid aortic valve but also ascending aortic dilation, coarctation of the aorta, and partial anomalous pulmonary venous connections, are present in patients with Turner syndrome. Regardless of the age, all patients with Turner syndrome at the time of diagnosis need comprehensive cardiovascular evaluation by a cardiologist specializing in congenital heart disease. Complete cardiologic evaluation, including echocardiography, reveals isolated nonstenotic bicuspid aortic valves in one third to one half of patients. In later life, bicuspid aortic valve disease can progress to dilation of the aortic root. Less-frequent defects include aortic coarctation (20%), aortic stenosis, mitral valve prolapse, and anomalous pulmonary venous drainage. In one study, 38% of patients with 45,X chromosomes had cardiovascular malformations compared with 11% of those with mosaic monosomy X; the most common were aortic valve abnormalities and aortic coarctation. Webbed neck in patients with or without recognized chromosome syndromes is associated with both flow-related and non–flow-related heart defects. Among patients with Turner syndrome, those with webbed necks have a much greater chance of having coarctation of the aorta than do those without webbed necks. Transthoracic echocardiogram in young females is adequate if cardiac anatomy is clearly seen; otherwise magnetic resonance angiographic screening studies should be considered in asymptomatic individuals with Turner syndrome. During adolescence, and certainly before pregnancy (when possible) is contemplated, repeat cardiac evaluation should be considered even in those without prior findings of cardiac abnormalities. Blood pressure should be routinely monitored even in the absence of cardiac or renal lesions and especially in those with suggestions of aortic root dilation. Cardiac MRI is a valuable tool to detect and monitor aortic root dilation.

Renal ultrasound should be performed in all females with Turner syndrome at diagnosis. One fourth to one third of patients have **renal malformations** on ultrasonographic examination (50% of those with 45,X karyotypes). The more serious defects include pelvic kidney, horseshoe kidney, double collecting system, complete absence of 1 kidney, and ureteropelvic junction obstruction. Some of the malformations may increase the risk of hypertension and urinary tract infection. Idiopathic hypertension is also common. Females with Turner syndrome who had normal baseline renal ultrasound findings did not develop renal disease during a follow-up period averaging 6 yr.

When the ovaries were examined by ultrasonography, older studies found a significant decrease in percentage of detectable ovaries from infancy to later childhood. A subsequent report found no such age-related differences in a cross-sectional and longitudinal study; 27–46% of patients had detectable ovaries at various ages; 76% of those with X mosaicism and 26% of those with 45,X karyotypes had detectable ovaries.

Sexual maturation usually fails to occur, but 10–20% of females have spontaneous breast development, and a small percentage may have menstrual periods. Primary gonadal failure is associated with early onset of adrenarche (elevation in dehydroepiandrosterone sulfate) but delayed pubarche (pubic hair development). Spontaneous pregnancies have been reported in menstruating patients with Turner syndrome. Premature menopause, increased risk of miscarriage, and offspring with increased risk of trisomy 21 have been reported. A woman with a 45,X/46,X,r(X) karyotype treated with hormone replacement therapy had 3 pregnancies, resulting in a normal 46,XY male infant, a spontaneous abortion, and a healthy term female with Turner syndrome 45,X/46,Xr(X).

Antithyroid antibodies (thyroid peroxidase and/or thyroglobulin antibodies) occur in 30–50% of patients. The prevalence increases with advancing age. **Autoimmune thyroid disease,** with or without the presence of a goiter, occurs in 10–30% of patients. Age-dependent abnormalities in carbohydrate metabolism characterized by abnormal glucose tolerance and insulin resistance and, only rarely, frank type 2 diabetes occur in older patients with Turner syndrome. Impaired insulin secretion has been described in 45,X women. Cholesterol levels are elevated in adolescence, regardless of body mass index or karyotype.

Inflammatory bowel disease (both Crohn disease and ulcerative colitis), gastrointestinal bleeding because of abnormal mesenteric vasculature, and delayed gastric emptying time have all been reported. Screening for celiac disease is recommended because the risk of celiac disease is increased in Turner syndrome, with 4–6% of individuals affected. Although autoimmune diseases have been associated with Turner syndrome, the prevalence of type 1 diabetes with Turner syndrome is not very high.

Sternal malformations can be detected by lateral chest radiography. An increased carrying angle at the elbow is usually not clinically significant. Scoliosis occurs in approximately 10% of adolescent females. Congenital hip dysplasia occurs more commonly than in the general population. Reported eye findings include anterior segment dysgenesis and keratoconus. Pigmented nevi become more prominent with age; melanocytic nevi are common. Essential hyperhidrosis, torus mandibularis, and alopecia areata occur rarely.

Recurrent bilateral otitis media develops in approximately 75% of patients. Sensorineural hearing deficits are common, and the frequency increases with age. Problems with gross and fine motor sensory integration, failure to walk before 15 mo of age, and early language dysfunction often raise questions about developmental delay, but intelligence is normal in most patients. However, cognitive impairment does occur in patients with 45,X/46,X,r(X); the ring chromosome is unable to undergo inactivation and leads to 2 functional X chromosomes.

Special attention should be given to psychosocial development in females with Turner syndrome. In general, behavior is normal in females with Turner syndrome, but they are at an increased risk for social isolation, immaturity, and anxiety. Other conditions, such as dyslexia, nonverbal learning disability, and attention-deficit disorder, have been reported in females with Turner syndrome. In adults, deficits in perceptual spatial skills are more common than they are in the general population. Some unconfirmed data suggest the existence of an imprinted X-linked locus that affects cognitive function such as verbal and higher-order executive function skills. These functions are apparently better when the X is paternal in origin.

The prevalence of mosaicism depends in large part on the techniques used for studying chromosomal patterns. The use of fluorescent in situ hybridization and reverse transcription–polymerase chain reaction (PCR) has increased the reported prevalence of mosaic patterns to as high as 60–74%.

Mosaicism involving the Y chromosome occurs in 5%. A population study using PCR with 5 different primer sets found Y chromosome material in 12.2%. **Gonadoblastoma** among Y-positive patients occurred in 7–10%. Therefore the recommendation is that prophylactic gonadectomy should be performed even in the absence of MRI or CT evidence of tumors. The recommended timing of this procedure is at the time of diagnosis, but this may need to be reevaluated in the future. The gonadoblastoma locus on the Y chromosome (GBY) maps close to the Y centromere. The presence of only the SRY (sex-determining region on the Y chromosome) locus is not sufficient to confer increased susceptibility for the development of gonadoblastoma. A detailed study of 53 patients with Turner syndrome by nested PCR excluded low-level Y mosaicism in almost all cases. A 2nd round of PCR detected SRY on the distal short arm of the Y chromosome in only 2 subjects. Therefore routine PCR for Y chromosome detection for the purpose of assigning gonadoblastoma risk is not indicated. High-throughput quantitative genotyping may provide an effective and inexpensive method for the identification of X chromosome abnormalities and Y chromosome material identification.

In patients with 45,X/46,XX mosaicism, the clinical abnormalities are attenuated and fewer; short stature is as frequent as it is in the 45,X patient and may be the only manifestation of the condition other than ovarian failure (see Fig. 604.1).

Laboratory Findings

Chromosomal analysis must be considered routinely in short females. In a systematic search, using Southern blot analysis of leukocyte DNA, Turner syndrome was detected in 4.8% of females referred to an endocrinology service because of short stature. Patients with a marker chromosome in some or all cells should be tested for DNA sequences at or near the centromere of the Y chromosome for GBY.

Ultrasonography of the heart, kidneys, and ovaries is indicated after the diagnosis is established. The most common skeletal abnormalities are shortening of the 4th metatarsal and metacarpal bones, epiphyseal dysgenesis in the joints of the knees and elbows, Madelung deformity, scoliosis, and, in older patients, inadequate osseous mineralization.

Plasma levels of gonadotropins, particularly follicle-stimulating hormone (FSH), are markedly elevated to greater than those of age-matched controls during infancy; at 2-3 yr of age, a progressive decrease in levels occurs until they reach a nadir at 6-8 yr of age, and by 10-11 yr of age, they rise to adult castrate levels.

Thyroid peroxidase antibodies and thyroglobulin antibodies should be checked periodically to detect autoimmune thyroiditis, and, if positive, levels of thyroxine and thyroid-stimulating hormone should be obtained. Turner syndrome females should be screened for **celiac disease** by measuring tissue transglutaminase immunoglobulin A antibodies. Initial testing should be done around age 4 yr and repeated every 2-5 yr. Extensive studies have failed to establish that growth hormone deficiency plays a primary role in the pathogenesis of the growth disorder. Defects in normal secretory patterns of growth hormone are seen in adolescents because of a lack of gonadal steroids, but not in younger females with Turner syndrome. In vitro, monocytes and lymphocytes show decreased sensitivity to insulin-like growth factor 1.

Treatment

Treatment with recombinant human growth hormone increases height velocity and ultimate stature in most, but not all, children with Turner syndrome. Many females achieve heights of greater than 150 cm with early initiation of treatment. In a large, multicenter, placebo-controlled clinical trial, 99 patients with Turner syndrome who started receiving growth hormone at a mean age of 10.9 yr at doses between 0.27 and 0.36 mg/kg/wk achieved a mean height of 149 cm, with nearly one third reaching heights greater than 152.4 cm (60 in). In the Netherlands, higher doses of growth hormone (up to 0.63 mg/kg/wk in the 3rd yr of treatment) resulted in 85% of the subjects reaching adult heights in the normal range for the Dutch reference population. Growth hormone treatment should be initiated in early childhood and/or when there is evidence of height velocity attenuation on specific Turner syndrome growth curves. Growth hormone therapy does not significantly aggravate carbohydrate tolerance and does not result in marked adverse events in patients with Turner syndrome. Serum levels of insulin-like growth factor 1 should be monitored if the patient is receiving high doses of growth hormone. If the insulin-like growth factor 1 levels are significantly elevated, the dose of growth hormone may need to be reduced. Treatment with growth hormone can cause excessive growth of the hands and feet in some females with Turner syndrome.

Oxandrolone has also been used to treat the short stature associated with Turner syndrome, either alone or in combination with growth hormone. This synthetic anabolic steroid has weak androgenic effects, and patients should be monitored for signs of pubarche, as well as hepatotoxicity. The latter is rare.

Replacement therapy with estrogens is indicated, but there is little consensus about the optimal age at which to initiate treatment. The psychological preparedness of the patient to accept therapy must be considered. The improved growth achieved by females treated with growth hormone in childhood permits initiation of estrogen replacement at 12-13 yr. Delaying estrogen therapy to optimize height potential until 15 yr of age, as previously recommended, seems unwarranted. This change to starting earlier estrogen therapy was considered because of the psychological importance of age-appropriate pubertal maturation. In addition, delaying estrogen therapy could be deleterious for bone health and potentially other aspects of the child's health. Low-dose estrogen replacement at 12 yr of age permits a normal pace of puberty without interfering with the positive effect of growth hormone on the final adult height. Estrogen therapy improves verbal and nonverbal memory in females with Turner syndrome. In young women with age-appropriate pubertal development who achieve normal height, health-related quality-of-life questionnaires have yielded normal results.

Many forms of estrogen are available. Oral estrogens had been mostly used in the past. Transdermal patches are increasing in popularity. This is because transdermal patches bypass the 1st hepatic metabolism, thereby requiring only a small amount of estrogen to attain the adequate levels for its function. For oral preparations, a conjugated estrogen (Premarin), 0.15-0.625 mg daily, or micronized estradiol (Estrace), 0.5 mg given daily for 3-6 mo, is usually effective in inducing puberty. The recommendations for transdermal patch therapy are 6.25 µg daily that is gradually increased over 2 yr to the adult dose of 100-200 µg daily. The estrogen may be cycled (taken on days 1-23) or not. A progestin (Provera) is added (taken on days 10-23) in a dose of 5-10 mg daily. In the week after the progestin, withdrawal bleeding usually occurs. Combination oral contraceptive pills may also be used for hormone replacement therapy.

Prenatal chromosome analysis for advanced maternal age has revealed a frequency of 45,X/46,XX that is 10 times higher than when diagnosed postnatally. Most of these patients have no clinical manifestations of Turner syndrome, and levels of gonadotropins are normal. Awareness of this mild phenotype is important in counseling patients.

Psychosocial support for these females is an integral component of treatment. A comprehensive psychological education evaluation is recommended either at the time of Turner syndrome diagnosis, depending on the patient's age, when any of the components of behavior or cognition become obvious, or immediately preceding school entry. The Turner Syndrome Society, which has local chapters in the United States and similar groups in Canada and other countries, provides a valuable support system for these patients and their families, in addition to that given by the healthcare team.

Successful pregnancies have been carried to term using ovum donation and in vitro fertilization. Adolescents with few signs of spontaneous puberty may have ovaries with follicles. There remains a future possibility of using cryopreserved ovarian tissue with immature oocytes before the regression of the ovaries for the future pregnancies. In adult women with Turner syndrome, there seems to be a high prevalence of undiagnosed bone mineral density, lipid, and thyroid abnormalities. Glucose intolerance diminished 1st-phase insulin response, elevated blood pressure, and lowered fat-free mass are common. Glucose tolerance worsens, but fat-free mass and blood pressure and general physical fitness improve with sex hormone replacement. The neurocognitive profile of adult women is unaffected by estrogen status.

XX Gonadal Dysgenesis

Some phenotypically and genetically normal females have gonadal lesions identical to those in 45,X patients but without somatic features of Turner syndrome; their condition is termed pure gonadal dysgenesis or pure ovarian dysgenesis.

The disorder is rarely recognized in prepubertal children because the external genitals are normal, no other abnormalities are visible, and growth is normal. At pubertal age, sexual maturation fails to take place. Plasma gonadotropin levels are elevated. Delay of epiphyseal fusion may result in a *eunuchoid* habitus. Pelvic ultrasonography reveals streak ovaries.

Affected siblings, parental consanguinity, and failure to uncover mosaicism all point to female-limited autosomal recessive inheritance. The disorder appears to be especially frequent in Finland (1 in 8,300 liveborn females). In this population, several mutations in the FSH receptor gene (on chromosome 2p) were demonstrated as the cause of the condition. By contrast, FSH receptor gene mutations were not detected in Mexican women with 46,XX gonadal dysgenesis. In some patients, XX gonadal dysgenesis has been associated with sensorineural deafness (**Perrault syndrome**). A patient with this condition and concomitant growth hormone deficiency and virilization has also been reported. There may be distinct genetic forms of this disorder. **Müllerian agenesis,** or the **Mayer-Rokitansky-Küster-Hauser** syndrome, which is second to gonadal dysgenesis as the most common cause of primary amenorrhea, occurring in 1 in 4,000-5,000 females, has been reported in association with 46,XX gonadal dysgenesis in a 17 yr old adolescent with primary amenorrhea and lack of breast development. One case of dysgerminoma with syncytiotrophoblastic giant cells was reported. An 18 yr old woman with primary amenorrhea and an absence of müllerian-derived structures, unilateral renal agenesis, and clinical signs of androgen excess, a phenotype resembling the Mayer-Rokitansky-Küster-Hauser syndrome, was found to have a loss-of-function mutation in the *WNT4* gene. Treatment consists of estrogen replacement therapy.

45,X/46,XY Gonadal Dysgenesis

45,X/46,XY gonadal dysgenesis, also called **mixed gonadal dysgenesis,** has extreme phenotypic variability postnatally that may extend from a Turner-like syndrome to a male phenotype with a penile urethra; it is possible to delineate 3 major clinical phenotypes. Short stature is a major finding in all affected children. Ninety percent of prenatally diagnosed cases have a normal male phenotype.

Some patients have no evidence of virilization; they have a female phenotype and often have the somatic signs of Turner syndrome. The condition is discovered prepubertally when chromosomal studies are made in short females or later when chromosomal studies are made because of failure of sexual maturation. Fallopian tubes and uterus are present. The gonads consist of intraabdominal undifferentiated streaks; chromosomal study of the streak often reveals an XY cell line. The streak gonad differs somewhat from that in females with Turner syndrome; in addition to wavy connective tissue, there are often tubular or cordlike structures, occasional clumps of granulosa cells, and, frequently, mesonephric or hilar cells.

Some children have mild virilization manifested only by prepubertal clitoromegaly. Normal müllerian structures are present, but at puberty virilization occurs. These patients usually have an intraabdominal testis, a contralateral streak gonad, and bilateral fallopian tubes.

Many 45,X/46,XY children present with frank ambiguity of the genitals in infancy (Fig. 604.2). A testis and vas deferens are found on one side in the labioscrotal fold, and a streak gonad is identified on the contralateral side. Despite the presence of a testis, fallopian tubes are often present bilaterally. An infantile or rudimentary uterus is often present.

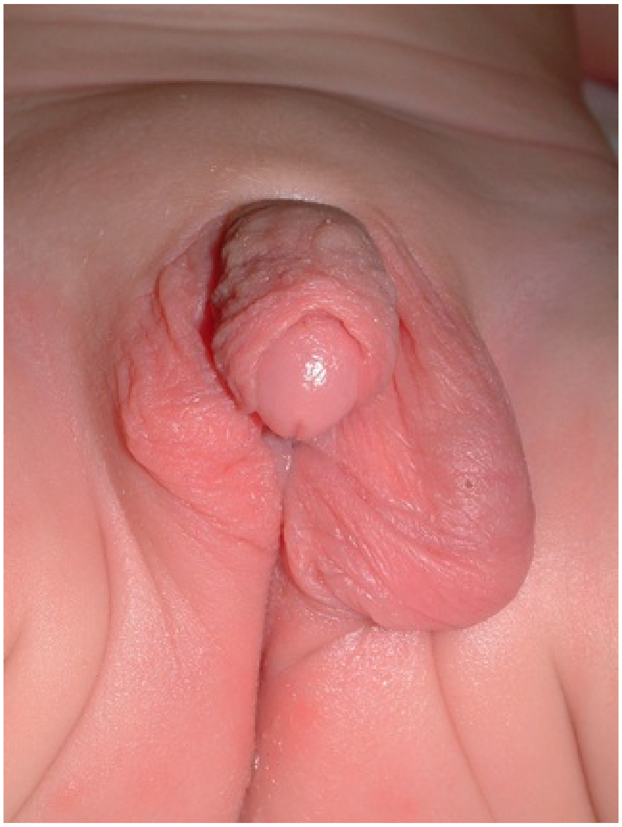

FIG. 604.2 A 45,X/46XY neonate with sex chromosome disorder of sex development was noted at birth to have male-appearing external genitalia with a phallus measured at 2.5 × 1.2 cm and penoscrotal hypospadias. The left gonad was palpable in incompletely fused scrotum, whereas the right gonad was not palpable. Gonadal biopsy revealed a testis on the left side and streak gonad on the right. The diagnosis was mixed gonadal dysgenesis. (From Remeithi SA, Wherret DK: Disorders of sexual development. In Martin RJ, Fanaroff AA, Walsh MC, editors: *Fanaroff & Martin's neonatal-perinatal medicine* , ed 10, Philadelphia, 2015, Elsevier, Fig. 98–13).

Other genotypes and phenotypes have been described in mixed gonadal dysgenesis. Approximately 25% of 200 analyzed patients have a dicentric Y chromosome (45,X/46,X,dic Y). In some patients the Y chromosome may be represented by only a fragment (45,X/45,X +fra); application of Y-specific probes can establish the origin of the fragment. It is not clear why the same genotype (45,X/46,XY) can result in such diverse phenotypes. Mutations in the *SRY* gene have been described in some patients.

Children with a female phenotype present no problem in gender of rearing. Patients who are only slightly virilized are usually assigned a female gender of rearing before a diagnosis is established. Patients with ambiguity of the genitals are often clinically indistinguishable from patients with various types of 46,XY disorders of sex development (46,XY DSD). In some instances, there may need to be careful consideration regarding sex of rearing. Factors that may influence this decision include short stature, the need for surgical genital reconstruction, the presence of müllerian structures, and the need for gonadectomy because of predisposition of the gonad to the development of malignancy. In some patients followed to adulthood, the putative normal testis proves to be dysgenetic with eventual loss of Leydig and Sertoli cell function (see Chapter 601). In an analysis of 22 patients with mixed gonadal dysgenesis, no significant associations or correlations were found between internal and external phenotypes or endocrine function and gonadal morphologic features. The sex of rearing was determined by the appearance of the external genitalia. In 11 patients, basal and human chorionic gonadotropin–stimulated testosterone levels were lower than in control subjects.

Gonadal tumors, usually **gonadoblastomas,** occur in approximately 25% of these children. As described previously, a gonadoblastoma locus has been localized to a region near the centromere of the Y chromosome (GBY). These germ cell tumors are preceded by the changes of carcinoma in situ. Accordingly, both gonads should be removed in all patients reared as females, and the undifferentiated gonad should be removed in the patients reared as males.

There is no correlation among the proportion of 45,X/46,XY cell lines in either blood or fibroblasts with the phenotype. In the past, all patients came to clinical attention because of their abnormal phenotypes. However, 45,X/46,XY mosaicism is found in approximately 7% of fetuses, with true chromosome mosaicism encountered prenatally. Of 76 infants with 45,X/46,XY mosaicism diagnosed prenatally, 72 had a normal male phenotype, 1 had a female phenotype, and only 3 males had hypospadias. Of 12 males whose gonads were examined, only 3 were abnormal. These data must be taken into account when counseling a family in which a 45,X/46,XY infant is discovered prenatally.

XXX, XXXX, and XXXXX Females

XXX Females

The 47,XXX (trisomy) chromosomal constitution is the most frequent extra–X chromosome abnormality in females, occurring in almost 1 in 1,000 liveborn females. In 68%, this condition is caused by maternal meiotic nondisjunction, but most 45,X and half of 47,XXY constitutions are caused by paternal sex chromosome errors. The phenotype is that of a normal female; affected infants and children are not recognized based on the genital appearance.

Sexual development and menarche are normal. Most pregnancies have resulted in normal infants. By 2 yr of age, delays in speech and language become evident and lack of coordination, poor academic performance, and immature behavior are seen in some. These females tend to be tall, manifest behavior disorders, and often require special education classes. Using high-resolution MRI, 10 47,XXX subjects had lower amygdala volumes than 20 euploid controls; 10 47,XXY subjects had even lower amygdala volumes. In a review of 155 females, 62% were physically normal. There is marked variability within the syndrome, and a small proportion of affected females are well coordinated, socially outgoing, and academically superior.

XXXX and XXXXX Females

The great majority of females with these rare karyotypes have been intellectually challenged. Commonly associated defects are epicanthal folds, hypertelorism, clinodactyly, transverse palmar creases, radioulnar synostosis, and congenital heart disease. Sexual maturation is often incomplete and may not occur at all. Nevertheless, 3 women with the tetra-X syndrome gave birth, but no pregnancies were reported in 49,XXXXX women. Most 48,XXXX women tend to be tall, with an average height of 169 cm, whereas short stature is a common feature of the 49,XXXXX phenotype.

Noonan Syndrome

Females with Noonan syndrome show certain anomalies that also occur in females with 45,X Turner syndrome, but they have normal 46,XX chromosomes (see Chapter 98.4). The most common abnormalities are the same as those described for males with Noonan syndrome (see Chapter 601). Short stature is one of the cardinal signs of this syndrome. The phenotype differs from Turner syndrome in several respects. Cognitive impairment is often present, the cardiac defect is most often pulmonary valvular stenosis or an atrial septal defect rather than an aortic defect, normal sexual maturation usually occurs but is delayed by 2 yr on average, and premature ovarian failure (POF) has been reported. Growth hormone therapy is approved by the FDA for use in Noonan syndrome patients with short stature.

Other Ovarian Defects

Some young women with no chromosomal abnormality are found to have streak gonads that may contain only occasional or no germ cells. Gonadotropins are increased. Cytotoxic drugs, especially alkylating agents such as cyclophosphamide and busulfan, procarbazine, etoposide, and exposure of the ovaries to irradiation for the treatment of malignancy are frequent causes of ovarian failure. Young women with Hodgkin disease demonstrate that combination chemotherapy and pelvic irradiation may be more deleterious than either therapy alone. Teenagers are more likely than older women to retain or recover ovarian function after irradiation or combined chemotherapy; normal pregnancies have occurred after such treatment. Treatment regimens may result in some ovarian damage in most females treated for cancer. The median lethal dose for the human oocyte is estimated to be approximately 4 Gy; doses as low as 6 Gy have produced primary amenorrhea. Ovarian transposition before abdominal and pelvic irradiation in childhood can preserve ovarian function by decreasing the ovarian exposure to less than 4-7 Gy.

Autoimmune ovarian failure occurs in 60% of children older than 13 yr of age with type I autoimmune polyendocrinopathy (Addison disease, hypoparathyroidism, mucocutaneous candidiasis). This condition, also known as *polyglandular autoimmune disease* type 1, is rare worldwide but not in Finland, where, as a result of a founder gene effect, it occurs in 1 in 25,000 people. The gene for this disorder is located on chromosome 21 and is associated with human leukocyte antigen (HLA) DR5. In patients with polyglandular autoimmune disease type 1 and ovarian failure, an association with HLA-A3 has been described. Affected females may not develop sexually, or secondary amenorrhea may occur in young women. The ovaries may have lymphocytic infiltration or appear simply as streaks. Most affected patients have circulating steroid cell antibodies and autoantibodies to 21-hydroxylase. Among patients with polyglandular autoimmune syndromes, 5% were found to have hypogonadism.

The condition also occurs in young women as an isolated event or in association with other autoimmune disorders, leading to secondary amenorrhea (POF). It occurs in 0.2–0.9% of women younger than 40 yr of age. POF is a heterogeneous disorder with many causes: chromosomal, genetic, enzymatic, infectious, and iatrogenic. When associated with autoimmune adrenal disease, steroid cell autoantibodies are usually present. These antibodies react with P450scc, 17α-OH, or 21-OH enzymes. When associated with an entire host of endocrine and nonendocrine autoimmune diseases and not adrenal autoimmunity, steroid cell autoantibodies are rarely found. A second autoimmune disorder, often subclinical, is found in 10–39% of adult patients with POF; these may include autoimmune thyroid disease, type 1 diabetes, SLE, inflammatory bowel disease, immune thrombocytopenia or hemolytic anemia, celiac disease, myasthenia gravis, and rheumatoid arthritis. One 17 yr old with idiopathic thrombocytopenic purpura and 47,XXX chromosomes had autoimmune POF. Patients with POF do not have the neurocognitive defects found in Turner syndrome patients.

Galactosemia, particularly the classical form of the disease, usually results in ovarian damage, beginning during intrauterine life. Levels of FSH and luteinizing hormone (LH) are elevated early in life. Ovarian damage may be caused by deficient uridine diphosphate-galactose (see Chapter 105). The **Denys-Drash syndrome,** caused by a *WT1* mutation, can result in ovarian dysgenesis.

Ataxia-telangiectasia may be associated with ovarian hypoplasia and elevated gonadotropins; the cause is unknown. Gonadoblastomas and dysgerminomas have occurred in a few females.

Hypergonadotropic hypogonadism has been postulated to also occur because of the resistance of the ovary to both endogenous and exogenous gonadotropins (Savage syndrome). This condition occurs also in women with POF. Antiovarian antibodies or FSH receptor abnormalities may cause this condition. Mutation of the FSH receptor gene has been reported as an autosomal recessive condition (see Chapter 600). A few females with 46,XX chromosomes presenting in primary amenorrhea with elevated gonadotropin levels were found to have inactivating mutations of the LH receptor gene. This suggests that LH action is needed for normal follicular development and ovulation. Other genetic defects associated with ovarian failure include mutations in the gene encoding transcription factor *SF-1* , *FOXL2, GNAS, CYP17,* and *CYP19.*

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604.2

Hypogonadotropic Hypogonadism in the Female (Secondary Hypogonadism)

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Keywords

hypopituitarism
prolactin
radiation therapy
constitutional delay

Hypofunction of the ovaries can result from failure to secrete normal pulses of the gonadotropins LH and FSH. Hypogonadotropic hypogonadism may occur if the hypothalamic-pituitary-gonadal axis is interrupted either at the hypothalamic or pituitary level. The mechanisms that result in hypogonadotropic hypogonadism include failure of the hypothalamic LH–releasing hormone (also known as *gonadotropin-releasing hormone*) pulse generator or inability of the pituitary to respond with secretion of LH and FSH. It is often difficult to distinguish between marked constitutional delay and hypogonadotropic hypogonadism.

Etiology

Hypopituitarism

Hypogonadotropic hypogonadism is most commonly seen with multiple pituitary hormone deficiencies resulting from malformations (e.g., septo-optic dysplasia, other midline defects), pituitary transcription factor defects such as in PROP-1, or lesions of the pituitary that are acquired postnatally. Familial isolated gonadotropin deficiency associated with anosmia (Kallmann syndrome) may occur in females. Many other genetic causes for hypogonadotropic hypogonadism have been identified. A gene important in LH-releasing hormone secretion is named *KISS* (encoding the protein kisspeptin), which is suggested to play a significant role in the development of the LH-releasing hormone–secreting cells. Another set of genes recently implicated in hypogonadotropic hypogonadism are the genes for neurokinin B *(TAC3)* and its receptor *(TAC3R)* .

In children with idiopathic hypopituitarism, the defect is usually found in the hypothalamus. In these patients, administration of gonadotropin-releasing hormone results in increased plasma levels of FSH and LH, establishing the integrity of the pituitary gland.

Hypogonadotropic hypogonadism is less common than hypergonadotropic hypogonadism. Ovarian function may be abnormal when associated with LH excess, a condition known as polycystic ovarian syndrome (Stein-Leventhal syndrome; see Chapter 567).

Isolated Deficiency of Gonadotropins

This heterogeneous group of disorders is evaluated more fully with the use of the gonadotropin-releasing hormone analog stimulation test rather than a single measurement of gonadotropin levels. In most children the pituitary gland is normal, and the defect causing gonadotropin deficiency resides in the hypothalamus. Patients with hyperprolactinemia, most often caused by a pituitary prolactin-secreting adenoma, often have suppression of gonadotropin secretion. If breast development has occurred, then galactorrhea and amenorrhea are frequently seen.

Several sporadic instances of anosmia with hypogonadotropic hypogonadism have been reported. **Anosmic** hypogonadal females have also been reported in kindreds with Kallmann syndrome, but hypogonadism more frequently affects the males in these families. Mutations in the gene for the β-subunit of FSH and LH have been reported.

Some autosomal recessive disorders, such as the Laurence-Moon-Biedl, multiple lentigines, and Carpenter syndromes, appear in some instances to include gonadotropic hormone deficiency. Patients with Prader-Willi syndrome usually have some degree of hypogonadotropic hypogonadism. Females with severe thalassemia may have gonadotropin deficiency from pituitary damage caused by chronic iron overload secondary to multiple transfusions. Anorexia nervosa frequently results in hypogonadotropic hypogonadism. The rare patients described with leptin deficiency or leptin receptor defects have failure of pubertal maturation because of gonadotropin deficiency.

Diagnosis

The diagnosis may be apparent in patients with other deficiencies of pituitary tropic hormones, but, as in males, it is difficult to differentiate isolated hypogonadotropic hypogonadism from physiologic delay of puberty. Repeated measurements of FSH and LH, particularly during sleep, may reveal the rising levels that herald the onset of puberty. Stimulation testing with gonadotropin-releasing hormone or one of its analogs may help to establish the diagnosis. Morbidity for both men and women with hypogonadism includes infertility and an increased risk of osteoporosis.

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CHAPTER 605

Pseudoprecocity Resulting From Lesions of the Ovary

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Females with signs of early puberty may, in rare circumstances, have a lesion of the ovary as the etiology. These include tumors or cysts that secrete estrogenic, androgenic, or both types of hormones. In these patients the sex steroid production is not mediated by pituitary gonadotropin secretion, and thus they are said to produce pseudoprecocity.

Ovarian tumors are rare in the pediatric population, occurring at a rate of less than 3 in 100,000. Most ovarian masses are benign, but 10–30% may be malignant. If they occur before 8 yr of age they may cause signs of puberty. Ovarian malignancies, the most common genital neoplasms in adolescence, account for only 1% of childhood cancers. More than 60% are germ cell tumors, most of which are dysgerminomas that can secrete tumor markers and sex hormones (see Chapter 530). Five to 10% of germ cell tumors occur in phenotypic females with abnormal gonads associated with the presence of a Y chromosome. The next most common are epithelial cell tumors (20%), and nearly 10% are sex cord/stromal tumors (granulosa, Sertoli cell, and mesenchymal tumors). Multiple tumor markers can be seen in ovarian tumors, including α-fetoprotein, human chorionic gonadotropin, carcinoembryonic antigen, oncoproteins, p105, p53, *KRAS* mutations, cyclin D_1 , epidermal growth factor–related proteins and receptors, cathepsin B, and others. Variable levels of inhibin–activin subunit gene expression have been detected in ovarian tumors.

Functioning lesions of the ovary consist of benign cysts or malignant tumors. The majority synthesize estrogens; a few synthesize androgens. The most common estrogen-producing ovarian tumor causing precocious puberty is the granulosa cell tumor. Other tumors that can cause precocious puberty are thecomas, luteomas, mixed types, theca-lutein and follicular cysts, and other ovarian tumors (i.e., teratoma, choriocarcinoma, and dysgerminoma).

Estrogenic Lesions of the Ovary

These lesions cause isosexual precocious sexual development but account for only a small percentage of all cases of precocity. Benign ovarian follicular cysts are the most common tumors associated with isosexual precocious puberty in females; they may rarely be gonadotropin dependent. Gonadotropin-independent follicular cysts that produce estrogen are often associated with the McCune-Albright syndrome.

Juvenile Granulosa Cell Tumor

In childhood, the most common neoplasm of the ovary with estrogenic manifestations is the granulosa cell tumor, although it makes up only 1–10% of all ovarian tumors. These tumors have distinctive histologic features that differ from those encountered in older women (adult granulosa cell tumor). The cells have high mitotic activity, follicles are often irregular, Call-Exner bodies are rare, and luteinization is frequent. The tumor may be solid or cystic, or both. It usually is benign. In a few instances, this tumor has been associated with multiple enchondromas **(Ollier disease)** and, in fewer still, with multiple subcutaneous hemangiomas **(Maffucci syndrome).**

Clinical Manifestations and Diagnosis

The juvenile granulosa cell tumor has been observed in newborns and may manifest with sexual precocity at 2 yr of age or younger; about half these tumors occurred before 10 yr of age. The mean age at diagnosis is 7.5 yr. The tumors are almost always unilateral. The breasts become enlarged, rounded, and firm, and the nipples prominent. The external genitals resemble those of a normal girl at puberty, and the uterus is enlarged. A white vaginal discharge is followed by irregular or cyclic menstruation. However, ovulation does not occur. The presenting manifestation may be abdominal pain or swelling. Pubic hair is usually absent unless there is mild virilization.

A mass is readily palpable in the lower portion of the abdomen in most children by the time sexual precocity is evident. However, the tumor may be small and escape detection even on careful rectal and abdominal examination; the tumors may be detected by ultrasonography, but multidetector CT scans are most sensitive. Most such tumors (90%) are diagnosed at very early stages of malignancy.

Plasma estradiol levels are markedly elevated. Plasma levels of gonadotropins are suppressed and do not respond to gonadotropin-releasing hormone analog stimulation. Levels of antimüllerian hormone, inhibin B, and α-fetoprotein may be elevated. Activating mutations of G_S α are seen in 30%, and GATA-4 expression is retained in the more aggressive tumors while antimüllerian hormone levels are inversely proportional to tumor size. Osseous development is moderately advanced. Several case reports showing the association of 45,X/46,XY karyotype and ambiguous genitalia with ovarian granulosa tumor have been published.

Treatment and Prognosis

The tumor should be removed as soon as the diagnosis is established. Prognosis is excellent because fewer than 5% of these tumors in children are malignant. However, advanced-stage tumors behave aggressively and require difficult decisions regarding surgical approaches as well as the use of irradiation and chemotherapy. In adults with granulosa cell tumors, p53 expression is associated with unfavorable prognosis. Vaginal bleeding immediately after removal of the tumor is common. Signs of precocious puberty abate and may disappear within a few months after the operation. The secretion of estrogens returns to normal.

Sex cord tumor with annular tubules is a distinctive tumor, thought to arise from granulosa cells, that occurs primarily in patients with Peutz-Jeghers syndrome. These tumors are multifocal, bilateral, and usually benign. The presence of calcifications aids ultrasonographic detection. Increased aromatase production by these tumors results in gonadotropin-independent precocious puberty. Inhibin A and B levels are elevated and decrease after tumor removal. In one study, 9 of 13 sex cord/stromal tumors exhibited follicle-stimulating hormone receptor mutations, suggesting a role for such mutation in the development of these tumors.

Chorioepithelioma has been reported only rarely. This highly malignant tumor is thought to arise from a preexisting teratoma. The usually unilateral tumor produces large amounts of human chorionic gonadotropin, which stimulates the contralateral ovary to secrete estrogen. Elevated levels of human chorionic gonadotropin are diagnostic.

Follicular Cyst

Small ovarian cysts (<0.7 cm in diameter) are common in prepubertal children. At puberty and in females with true isosexual precocious puberty, larger cysts (1-6 cm) are often seen; these are secondary to stimulation by gonadotropins. However, similar larger cysts occur occasionally in young females with precocious puberty in the absence of luteinizing hormone and follicle-stimulating hormone. Because surgical removal or spontaneous involution of these cysts results in regression of pubertal changes, there is little doubt that they are its cause. The mechanism of production of these autonomously functioning cysts is unknown. Such cysts may form only once, or they may disappear and recur, resulting in waxing and waning of the signs of precocious puberty. They may be unilateral or bilateral. The sexual precocity that occurs in young females with **McCune-Albright syndrome** is usually associated with autonomous follicular cysts caused by a somatic-activating mutation of the G_S α-protein occurring early in development (see Chapter 578.6). Gonadotropins are suppressed, and estradiol levels are often markedly elevated, but they may fluctuate widely and even temporarily may return to normal. Gonadotropin-releasing hormone analog stimulation fails to evoke an increase in gonadotropins. Ultrasonography is the method of choice for the detection and monitoring of such cysts. Aromatase inhibitors are shown to be the mainstay of the therapy in females with McCune-Albright syndrome and persistent estradiol elevation. A short period of observation to ascertain the lack of spontaneous resolution is advisable before cyst aspiration or cystectomy is considered. Cystic neoplasms must be considered in the differential diagnosis.

Androgenic Lesions of the Ovary

Virilizing ovarian tumors are rare at all ages but particularly so in prepubertal females. **Arrhenoblastoma** has been reported as early as 14 days of age, but few cases have been reported in females younger than 16 yr of age.

The **gonadoblastoma** occurs exclusively in dysgenetic gonads, particularly in phenotypic females who have a Y chromosome or a Y fragment in their genotype (46,XY; 45,X/46,XY; 45,X/46,X-fra). There is a proposed gonadoblastoma locus on the Y chromosome (GBY). The tumors may be bilateral. Virilization occurs with some but not all tumors. The clinical features are the same as those seen in patients with virilizing adrenal tumors and include accelerated growth, acne, clitoral enlargement, and growth of sexual hair. A palpable, abdominal mass is found in about 50% of patients. Plasma levels of testosterone and androstenedione are elevated, and gonadotropins are suppressed. Ultrasonography, CT, and MRI usually localize the lesion. The dysgenetic gonad of phenotypic females with a Y chromosome or fragment of Y chromosome containing GBY should be removed prophylactically. When a unilateral tumor is removed, the contralateral dysgenetic gonad should also be removed. Association of gonadoblastoma and WAGR (Wilms, aniridia, genitourinary anomalies, mental retardation) syndrome is also reported in the literature. In an immunohistochemical study of 2 gonadoblastomas, expressions of *WT1*, *p53*, and *MIS* , as well as inhibin, were all demonstrated.

Virilizing manifestations occur occasionally in females with **juvenile granulosa cell tumors.** Adrenal rests and hilum cell tumors rarely lead to virilization. Activating mutations of G-protein genes have been described in ovarian (and testicular) tumors. G_S α mutations, usually seen in gonadal tumors associated with **McCune-Albright syndrome,** were also noted in 4 of 6 Leydig cell tumors (3 ovarian, 1 testicular). Two granulosa cell tumors and 1 thecoma of 10 ovarian tumors studied were found to have *GIP-2* mutations.

Sertoli-Leydig cell tumors, rare sex cord/stromal neoplasms, constitute less than 1% of ovarian tumors. The average age at diagnosis is 25 yr; less than 5% of these tumors occur before puberty. α-Fetoprotein levels may be mildly elevated. In one 12 mo old with Sertoli-Leydig cell tumor presenting with isosexual precocity, the only detectable tumor marker was the serum inhibin level, with elevations in both A and B subunits. Five-yr survival rates are 70–90%.

Of 102 consecutive patients who underwent surgery because of ovarian masses over a 15-yr period, the presenting symptoms were acute abdominal pain in 56% and abdominal or pelvic mass in 22%. Of 9 children whose cause for surgery was presumed malignancy, 3 had dysgerminomas, 2 had teratomas, 2 had juvenile granulosa cell tumors, 1 had a Sertoli-Leydig cell tumor, and 1 had a yolk sac tumor.

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CHAPTER 606

Disorders of Sex Development

Patricia A. Donohoue

Sex Differentiation

See also Chapter 600 .

Differentiation and development of the gonads and genitalia are largely complete in the 1st half of gestation.

In normal differentiation, the final form of all sexual structures is consistent with normal sex chromosomes (either XX or XY). A 46,XX complement of chromosomes, as well as genetic factors such as DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), the signaling molecule WNT-4, and R-Spondin1, are among the many needed for the development of normal ovaries. Development of the male phenotype is potentially more complex. It requires a Y chromosome and, specifically, an intact *SRY* (sex-determining region on the Y chromosome) gene, which, in association with genes such as *SOX9*, *SF-1* (steroidogenic factor-1), *WT1* (Wilms tumor 1), and others (see Chapter 600), directs the undifferentiated gonad to become a testis. Aberrant recombinations may result in X chromosomes carrying *SRY,* resulting in XX males, or Y chromosomes that have lost *SRY,* resulting in XY females. Epigenetic causes of abnormal sex differentiation have been shown in plants, invertebrates, and vertebrates and will likely also contribute to human disorders of sex development (DSDs).

Antimüllerian hormone (AMH) causes the müllerian (paramesonephric) ducts to regress; in its absence, they persist as the uterus, fallopian tubes, cervix, and upper vagina. AMH activation in the testes probably requires the *SF-1* gene. By about 8 wk of gestation, the Leydig cells of the testis begin to produce testosterone. During this critical period of male differentiation, testosterone secretion is stimulated by placental human chorionic gonadotropin (hCG), which peaks at 8-12 wk. In the latter half of pregnancy, lower levels of testosterone are maintained by luteinizing hormone (LH) secreted by the fetal pituitary. Testosterone produced locally initiates development of the ipsilateral wolffian (mesonephric) duct into the epididymis, vas deferens, and seminal vesicle. Complete development of the external genitalia also requires dihydrotestosterone (DHT), the more active metabolite of testosterone. DHT is produced largely from circulating testosterone and is necessary to fuse the genital folds to form the penis and scrotum. DHT is produced from testosterone via the action of the enzyme 5α-reductase. DHT is also produced through an alternative biosynthetic pathway from androstanediol, and this pathway must be intact for normal and complete prenatal virilization to occur. Fig. 606.1 illustrates the production of steroid hormones in various glands, and the integrated pathways to the synthesis of DHT. A functional androgen receptor, produced by an X-linked gene, is required for testosterone and DHT to induce these androgen effects.

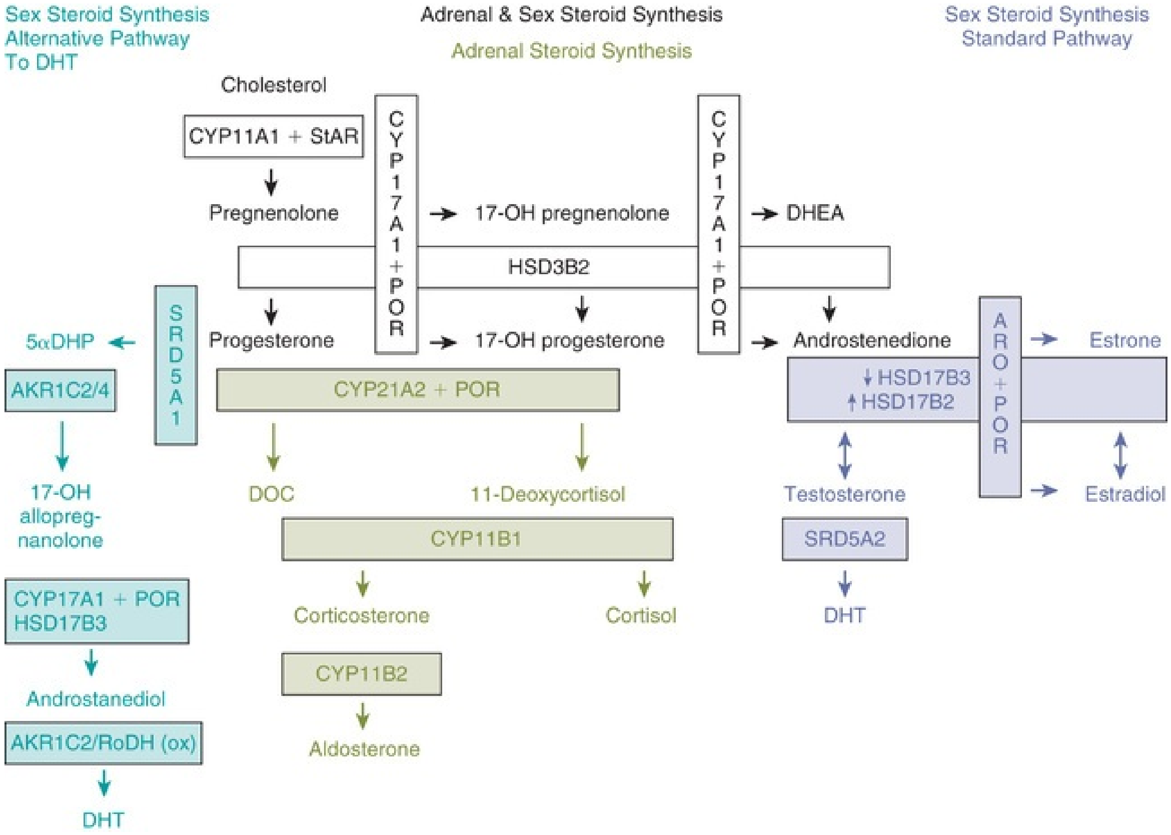
Sex Steroid Synthesis
Alternative Pathway
To DHT
Adrenal & Sex Steroid Synthesis
Adrenal Steroid Synthesis
Sex Steroid Synthesis
Standard Pathway
Cholesterol
CYP11A1 + StAR
Pregnenolone
CYP17A1 + POR
17-OH pregnenolone
DHEA
HSD3B2
Progesterone
17-OH progesterone
Androstenedione
5αDHP
SRD5A1
AKR1C2/4
CYP21A2 + POR
↓HSD17B3
↑HSD17B2
AROM + POR
Estrone
Estradiol
Testosterone
17-OH allopreg-nanolone
DOC
11-Deoxycortisol
CYP11B1
SRD5A2
DHT
CYP17A1 + POR
HSD17B3
Corticosterone
Cortisol
CYP11B2
Aldosterone
Androstanediol
AKR1C2/RoDH (ox)
DHT

FIG. 606.1 **Steroidogenic pathways enzyme names and activities. CYP11A1 : cholesterol side chain cleavage. Enzyme activities include 20-hydroxylase, 22-hydroxylase and 20,22-lyase. CYP17A1 : activities include 17α-hydroxylase and 17,20-lyase. 3βHSD2 (HSD3B2): activities include 3 β-hydroxysteroid dehydrogenase (type 2) and D5D4-isomerase. CYP21A2 : activity is 21-hydroxylase. CYP11B1 : activity is 11β-**

hydroxylase. CYP11B2 : activities include 18-hydroxylase (CMOI) and 18-dehydrogenase (CMOII). SRD5A1 : activity is 5α-reductase type 1. SRD5A2 : activity is 5α-reductase type 2. HSD17B2 : activity is 17 β-hydroxysteroid dehydrogenase type 2. HSD17B3 : activity is 17 β-hydroxysteroid dehydrogenase type 3. AKR1C2 /4(red): activities are 3α-reductase types 1 and 3. AKR1C2 /ToDH 9ox : activities are 3α-reductase and 3-hydroxyepimerase. *ARO:* aromatase; *CMOI* , corticosterone methyl oxidase type 1; *CMOII* , corticosterone methyl oxidase type 2;*DHEA* , dehydroepiandrosterone; *DHT* , dihydrotestosterone; *5αDHP* , 5α dihydroprogesterone. (Adapted from Kim MS, Donohoue PA: Adrenal disorders. In: Kappy MS, Allen DB, Geffner ME, editors: *Pediatric practice endocrinology,* ed 2, New York, 2014, McGraw Hill, and From Flück CE, Meyer-Böni M, Pandey AV, et al: Why boys will be boys: two pathways of fetal testicular androgen biosynthesis are needed for male sexual differentiation, *Am J Hum Genet* 89:201–218, 2011).

In the XX fetus with normal long and short arms of the X chromosome, the bipotential gonad develops into an ovary by about the 10th-11th wk. This occurs only in the absence of SRY, testosterone, and AMH and requires a normal gene in the dosage-sensitive/sex-reversal locus DAX1, the WNT-4 molecule, and R-Spondin1. A female external phenotype develops in the absence of fetal gonads. However, the male phenotype development requires androgen production and action. Estrogen is unnecessary for normal prenatal sexual differentiation, as demonstrated by 46,XX patients with aromatase deficiency and by mice without estradiol receptors.

Chromosomal aberrations may result in ambiguity of the external genitalia. Conditions of aberrant sex differentiation may also occur with the XX or XY genotype. The appropriate term for what was previously called *intersex* is **DSD.** This term defines a condition “in which development of chromosomal, gonadal, or anatomical sex is atypical.” It is increasingly preferable to use the term “atypical genitalia” rather than “ambiguous genitalia.” Tables 606.1 and 606.2 compare previous terms with their revised etiologic classification nomenclature. Table 600.1 in Chapter 600 lists some of the many genes that may be mutated in various forms of DSD. Gender fluidity (nonconformity) has become a socially and, in New York State, legally accepted concept and is often expressed by self-identified people as intersex. New York State has an intersex category on its birth certificate. Partial androgen insensitivity, 5α-reductase deficiency, and mixed gonadal dysgenesis are often associated with gender dissatisfaction and an intersex designation may help with future self-identification once the child is mature.

Table 606.1

Revised Nomenclature

PREVIOUS	**CURRENTLY ACCEPTED**
Intersex	Disorders of sex development (DSDs)
Male pseudohermaphrodite	46,XY DSD
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	46,XY DSD
46,XY intersex	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	46,XX DSD
46,XX intersex	46,XX DSD
True hermaphrodite	Ovotesticular DSD
Gonadal intersex	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

From Lee PA, Houk CP, Ahmed SF, et al: Consensus statement on management of intersex disorders, *Pediatrics* 118:e488–e500, 2006, Table 1.

Table 606.2

Etiologic Classification of Disorders of Sex Development

46,XX DSD
Androgen Exposure
Fetal/Fetoplacental Source 21-Hydroxylase (P450c21 or CYP21) deficiency 11β-Hydroxylase (P450c11 or CYP11B1) deficiency 3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency Cytochrome P450 oxidoreductase (POR deficiency) Aromatase (P450arom or CYP19) deficiency Glucocorticoid receptor gene mutation Maternal source Virilizing ovarian tumor Virilizing adrenal tumor Androgenic drugs
Disorder of Ovarian Development
XX gonadal dysgenesis Testicular DSD (SRY+, SOX9 duplication)
Undetermined Origin
Associated with genitourinary and gastrointestinal tract defects
46,XY DSD
Defects in Testicular Development
Denys-Drash syndrome (mutation in *WT1* gene) WAGR syndrome (Wilms tumor, aniridia, genitourinary malformation, retardation) Deletion of 11p13 Campomelic syndrome (autosomal gene at 17q24.3-q25.1) and *SOX9* mutation XY pure gonadal dysgenesis (Swyer syndrome) Mutation in *SRY* gene XY gonadal agenesis Unknown cause
Deficiency of Testicular Hormones

Leydig cell aplasia Mutation in LH receptor Lipoid adrenal hyperplasia (P450scc or CYP11A1) deficiency; mutation in StAR (steroidogenic acute regulatory protein) 3β-HSD II deficiency 17-Hydroxylase/17,20-lyase (P450c17 or CYP17) deficiency Persistent müllerian duct syndrome because of antimüllerian hormone gene mutations or receptor defects for antimüllerian hormone
Defect in Androgen Action
Dihydrotestosterone deficiency because of 5α-reductase II mutations or *AKR1C2/AKR1C4* mutations Androgen receptor defects: Complete androgen insensitivity syndrome Partial androgen insensitivity syndrome (Reifenstein and other syndromes) Smith-Lemli-Opitz syndrome (defect in conversion of 7-dehydrocholesterol to cholesterol, DHCR7)
Ovotesticular DSD
XX XY XX/XY chimeras
Sex Chromosome DSD
45,X (Turner syndrome and variants) 47,XXY (Klinefelter syndrome and variants) 45,X/46,XY (mixed gonadal dysgenesis, sometimes a cause of ovotesticular DSD) 46,XX/46,XY (chimeric, sometimes a cause of ovotesticular DSD)

DSD , Disorders of sex development.

Data from Lee PA, Houk CP, Ahmed SF, et al: Consensus statement on management of intersex disorders, *Pediatrics* 118:e488–e500, 2006.

The definition of atypical or ambiguous genitalia, in a broad sense, is any case in which the external genitalia do not appear completely male or completely female. Although there are standards for genital size dimensions, variations in size of these structures do not always constitute ambiguity.

Development of the external genitalia begins with the potential to be either male or female (Fig. 606.2). Virilization of a female, the most common form of DSD, results in varying phenotypes (Fig. 606.3) that develop from the basic bipotential genital appearances of the embryo (see Fig. 606.2).

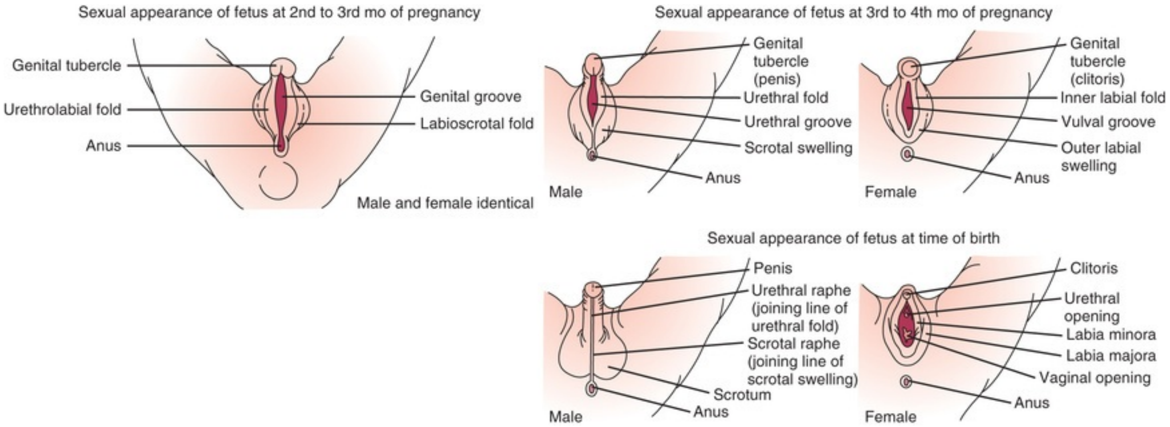
Sexual appearance of fetus at 2nd to 3rd mo of pregnancy
Genital tubercle
Urethrolabial fold
Anus
Genital groove
Labioscrotal fold
Male and female identical
Sexual appearance of fetus at 3rd to 4th mo of pregnancy
Genital tubercle (penis)
Urethral fold
Urethral groove
Scrotal swelling
Anus
Male
Genital tubercle (clitoris)
Inner labial fold
Vulval groove
Outer labial swelling
Anus
Female
Sexual appearance of fetus at time of birth
Penis
Urethral raphe (joining line of urethral fold)
Scrotal raphe (joining line of scrotal swelling)
Scrotum
Anus
Male
Clitoris
Urethral opening
Labia minora
Labia majora
Vaginal opening
Anus
Female

FIG. 606.2 Schematic demonstration of differentiation of normal male and female genitalia during embryogenesis. (From Zitelli BJ, Davis HW: *Atlas of pediatric physical diagnosis* , ed 4, St. Louis, 2002, Mosby, p 328.)

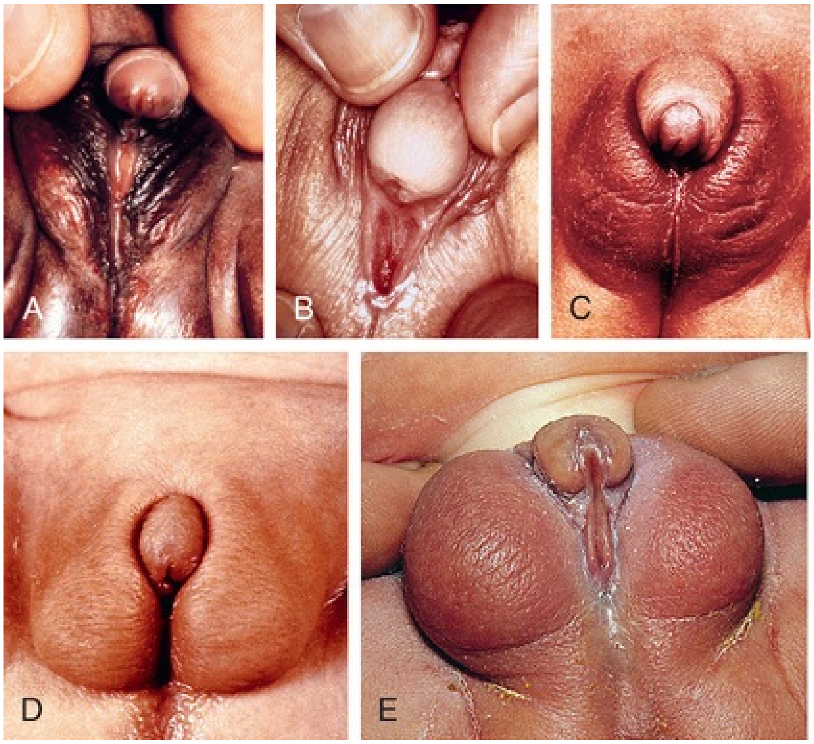

FIG. 606.3 Examples of atypical genitalia. These cases include ovotesticular disorder of sexual development **(A)** and congenital virilizing adrenal hyperplasia **(B-E).** (**B-D,** Courtesy D. Becker, MD, Pittsburgh. From Zitelli BJ, Davis HW: *Atlas of pediatric physical diagnosis* , ed 4, St. Louis, 2002, Mosby, p 329.)

Diagnostic Approach to the Patient With Atypical or Ambiguous Genitalia

The appearance of the external genitalia is rarely diagnostic of a particular disorder and thus does not often allow distinction among the various forms of DSD. The most common forms of 46,XX DSD are virilizing forms of congenital adrenal hyperplasia. It is important to note that in 46,XY DSD, the specific diagnosis is not found in up to 50% of cases; partial androgen insensitivity syndrome (PAIS) and pure gonadal dysgenesis are common identifiable etiologies in XY DSD. At 1 center with a large experience, the etiologies of DSD in 250 patients older than 25 yr were compiled. The 6 most common diagnoses accounted for 50% of the cases. These included virilizing congenital adrenal hyperplasia (14%), androgen insensitivity syndrome (AIS; 10%), mixed gonadal dysgenesis (8%), clitoral/labial anomalies (7%), hypogonadotropic hypogonadism (6%), and 46,XY small-for-gestational-age males with hypospadias (6%). Potential diagnostic clues are noted in Tables 606.3 and 606.4
.

Table 606.3

Associations of Genital Abnormalities

ABNORMAL CHARACTERISTICS	EXAMPLES OF ASSOCIATED DISORDERS
MALE-APPEARING GENITALIA	
Micropenis	Growth hormone or luteinizing hormone deficiency
	Testosterone deficiency (in 2nd and 3rd trimesters)
	Partial androgen insensitivity
	Syndrome: idiopathic
Hypospadias (more severe)	Disorders of gonadal development
	46,XX DSD
	Ovotesticular DSD
	46,XX or 46,XY DSD
	Syndrome: idiopathic
Impalpable gonads	Anorchia
	Persistent müllerian duct syndrome
	46,XX DSD with 21- or 11β-hydroxylase deficiency
	Cryptorchidism
Small gonads	47,XXY, 46,XX DSD
	Dysgenetic or rudimentary testes
Inguinal mass (uterus or tube)	Persistent müllerian duct syndrome, dysgenetic testes
FEMALE-APPEARING GENITALIA	
Clitoromegaly	XX with 21- or 11β-hydroxylase or 3β-hydroxy dehydrogenase

	deficiency
	Other 46,XX DSD
	Gonadal dysgenesis, dysgenetic testes, ovotesticular DSD
	46,XY DSD
	Tumor infiltration of clitoris
	Syndrome: idiopathic
Posterior labial fusion	As for clitoromegaly
Palpable gonad(s)	Gonadal dysgenesis, dysgenetic testes, ovotesticular DSD
	46,XY DSD
Inguinal hernia or mass	As for palpable gonad(s)

DSD , Disorders of sex development.

From Al Remeithi S, Wherrett DK: Disorders of sex development. In Martin RJ, Fanaroff AA, Walsh MC, editors: *Fanaroff & Martin's neonatal-perinatal medicine* , ed 10, Philadelphia, 2015, Elsevier, Table 98.3.

Table 606.4

Key Points in Evaluation of Infants With Disorders of Sexual Development

Identification of syndromic features in physical exam	Craniosynostosis and other synostosis in POR deficiency Cleft palate and 2nd-3rd toe syndactyly in Smith-Lemli-Opitz (SLO) syndrome Pierre Robin sequence or campomelia for SOX9 mutations Kidney abnormalities or dysfunction in WTI or WNT4 mutations Cardiac abnormalities in Turner syndrome, mixed gonadal dysgenesis or GATA4 mutations Adrenal insufficiency in cases of SLO, NR5A1 (SF-1) mutations, POR deficiency or congenital adrenal hyperplasia or hypoplasia forms Polyneuropathy in DHH mutations Chondrodysplasia in HHAT mutations Blepharophimosis/ptosis in FOXL2 mutations
Evaluation of internal genitalia to conclude about exposure to AMH using pelvic ultrasound or MRI	**NORMAL UTERUS IN:** 46,XY complete gonadal dysgenesis (CGD) 46,XX CGD 46,XX with androgen exposure (i.e., virilizing forms of CAH) Turner syndrome **ABNORMAL UTERUS IN:** 46,XY PGD (partial gonadal dysgenesis) Mixed gonadal dysgenesis **ABSENT UTERUS IN:** 46, XY DSD with androgen synthesis defects and androgen action defects 46,XX testicular DSD

POR , P450 oxidoreductase.

Modified from Rodriguez-Buritica D: Overview of genetics of disorders of sexual development, *Curr Opin Pediatr* 27:675–684, 2015, Table 1.

The potential of not finding a diagnosis in patients with DSD and the resulting lack of specific management emphasizes the need for thorough diagnostic evaluations. These include biochemical characterization of possible steroidogenic enzymatic defects in each patient with genital ambiguity. The parents need counseling about the potentially complex nature of the baby's condition and guidance as to how to deal with their well-meaning but curious friends and family members. The evaluation and management should be carried out by a multidisciplinary team of experts that includes pediatric endocrinology, pediatric surgery/urology, pediatric radiology, newborn medicine, genetics, and psychology. Once the sex of rearing has been agreed on by the family and team, treatment can be organized. Genetic counseling should be offered when the specific diagnosis is established.

After a complete history and physical exam, the common diagnostic approach includes multiple steps, described in the following outline. These steps are usually performed simultaneously rather than waiting for results of 1 test prior to performing another, because of the sensitive and sometimes urgent nature of the condition. Careful attention to the presence of physical features other than the genitalia is crucial to determine if a diagnosis of a particular multisystem syndrome is possible. These are described in more detail in Chapters 606.1 , 606.2 , and 606.3 later. Table 606.5 summarizes many of the features of commonly encountered causes of DSD. Exome sequencing is quite useful in the diagnostic evaluation, especially in 46, XY DSD, and may become a 1st line diagnostic test.

Table 606.5

Atypical Genitalia: Steps in Establishing the Diagnosis

	21-OH DEFICIENCY	GONADAL DYSGENESIS WITH Y CHROMOSOME	OVOTESTICULAR DSD	PARTIAL ANDROGEN INSENSITIVITY	BLOCK IN TESTOSTERON SYNTHESIS
CLINICAL FEATURE					
Palpable gonad(s)	–	±	±	+	+
Uterus present*	+	+	Usually	–	–
Increased skin	±	–	–	–	–

pigmentation					
Sick baby	±	–	–	–	±
Dysmorphic features	–	±	–	–	–
DIAGNOSTIC CONSIDERATIONS					
Serum 17-OHP	Elevated	Normal	Normal	Normal	Normal
Electrolytes	Possibly abnormal	Normal	Normal	Normal	Possibly abnormal
Karyotype	46,XX	45,X/46,XY or others	46,XX	46,XY	46,XY
Testosterone response to hCG	NA	Positive	Normal or reduced	Positive response	Reduced or absent
Gonadal biopsy	NA	Dysgenetic gonad	Ovotestis	Normal testis with ± Leydig cell hyperplasia	Normal testis
Other testing				Genital skin fibroblast culture	Measure
				For AR assay	Testosterone
				Or DNA screening for AR mutations in blood cells	Precursors

[*] As determined by ultrasound, MRI, or rectal examination.

AR , Androgen receptor; *DSDs* , disorders of sex development; *hCG* , human chorionic gonadotropin; *21-OH* , 21-hydroxylase; *17-OHP* , 17-hydroxyprogesterone; *NA* , not applicable.

Adapted from Donohoue PA, Saenger PH: Ambiguous genitalia. In Finberg L, Kleinman RE, editors: *Saunders manual of pediatric practice,* Philadelphia, 2002, WB Saunders, p 874.

Diagnostic tests include the following:

1. Blood karyotype, with rapid determination of sex chromosomes (in many centers this is available within 24-48 hr).
2. Other blood tests
    a. Screen for congenital adrenal hyperplasia: cortisol biosynthetic precursors and adrenal androgens (particularly 17-hydroxyprogesterone and androstenedione for 21-hydroxylase deficiency, the most common form). In the United States, all 50 states have a newborn screen for 21-hydroxylase deficiency.
    b. Screen for androgen biosynthetic defects with serum levels of androgens and their precursors
    c. Assess for gonadal response to gonadotropin stimulation to screen for the presence and function of testicular gonadal tissue: obtain serum levels of testosterone and DHT before

    and after IM injections of hCG.
  - d. Molecular genetic analyses for SRY (sex-determining region of the Y chromosome), other Y-specific loci, and when needed, other single gene defects associated with DSD
  - e. Gonadotropin (LH and follicle-stimulating hormone [FSH]) levels
3. The internal anatomy of patients with ambiguous genitalia can be defined with 1 or more of the following studies:
  - a. Voiding cystourethrogram
  - b. Endoscopic examination of the genitourinary tract
  - c. Pelvic ultrasound; renal and adrenal ultrasound
  - d. Pelvic MRI
  - e. Exploratory laparoscopy to locate and characterize/biopsy the gonads

606.1

46,XX DSD

Patricia A. Donohoue

Keywords

congenital adrenal hyperplasia
maternal virilization

The genotype is XX and the gonads are ovaries, but the external genitalia are virilized. There is no significant prenatal AMH production because the gonads are ovaries. Thus the uterus, fallopian tubes, and cervix develop. The varieties and causes of this condition are relatively few. Most instances result from exposure of the female fetus to excessive *exogenous* or *endogenous* androgens during intrauterine life. The changes consist principally of virilization of the external genitalia (clitoral hypertrophy and labioscrotal fusion).

Congenital Adrenal Hyperplasia

See Chapter 594.1 .

This is the most common cause of atypical genital and of 46,XX DSD. Females with the 21-hydroxylase and 11-hydroxylase defects are the most highly virilized, although minimal virilization also occurs with the type II 3β-hydroxysteroid dehydrogenase defect (see Fig. 606.3). Female patients with salt-losing congenital adrenal hyperplasia due to 21-hydroxylase deficiency tend to have more virilization than do patients with non–salt-losing CAH. Masculinization may be so complete that a penile urethra results, and the patient may appear to be a male with bilateral cryptorchidism.

Aromatase Deficiency

In 46,XX females, the rare condition of aromatase deficiency during fetal life leads to 46,XX DSD and results in hypergonadotropic hypogonadism at puberty because of ovarian failure to synthesize estrogen.

Examples of this condition include 2 46,XX infants who had enlargement of the clitoris and posterior labial fusion at birth. In one instance, maternal serum and urinary levels of estrogen were very low and serum levels of androgens were high. Cord serum levels of estrogen were also extremely low, and levels of androgen were elevated. The 2nd patient also had virilization of unknown cause since birth, but the aromatase deficiency was not diagnosed until 14 yr of age, when she had further virilization and failed to go into puberty. At that time, she had elevated levels of gonadotropins and androgens but low estrogen levels, and ultrasonography revealed large ovarian cysts bilaterally. These 2 patients demonstrate the important role of aromatase in the conversion of androgens to estrogens. Additional female and male patients with aromatase deficiency as a consequence of mutations in the *aromatase gene (CYP19)* are known. Two siblings with this gene defect were described, both of whom had tall stature due to lack of estrogen-mediated epiphyseal fusion. The 28 yr old XX proband was 177.6 cm tall (+2.5 SD) after having received hormonal replacement therapy. Her 24 yr old brother was 204 cm tall (+3.7 SD) and had a bone age of 14 yr. Low-dose estradiol replacement, carefully adjusted to maintain normal age-appropriate levels, may be indicated for affected females, even prepubertally.

Cortisol Resistance Due to Glucocorticoid Receptor Gene Mutation

A 9 yr old female with 46,XX disorder of sexual development, thought to be caused by 21-hydroxylase deficiency (congenital adrenal hyperplasia) since the age of 5 yr, had elevated cortisol levels both at baseline and after dexamethasone, hypertension, and hypokalemia, suggestive of the diagnosis of generalized glucocorticoid resistance. A novel homozygous mutation in exon 5 of the glucocorticoid receptor was demonstrated. In this Brazilian family, the condition was autosomal recessive. Virilization occurs due to excess ACTH stimulation of adrenal steroid production, because the glucocorticoid receptor defect is also present in the pituitary gland, which senses inadequate cortisol effect to provide negative feedback.

P450 Oxidoreductase Deficiency

Cytochrome P450 oxidoreductase (POR), encoded by a gene on 7q11.2, is a cofactor required for normal enzymatic activity of the microsomal 21- and 17-hydroxylases. POR deficiency thus causes partial combined P450C17 and P450C21 steroidogenic defects. Females are born with ambiguous genitalia, but as opposed to classic CAH, the virilization does not progress postnatally and androgen levels are normal or low. Males may be born undervirilized. Both may exhibit bony abnormalities seen in **Antley-Bixler syndrome** . Conversely, in a series of Antley-Bixler syndrome patients, those with ambiguous genitalia and disordered steroidogenesis had cytochrome POR deficiency. Those without genital ambiguity with normal steroidogenesis had fibroblast growth factor receptor 2 *(FGFR2)* mutations. The cardinal features of Antley-Bixler syndrome include craniosynostosis, severe midface hypoplasia, proptosis, choanal atresia/stenosis, frontal bossing, dysplastic ears, depressed nasal bridge, radiohumeral synostosis, long bone fractures and femoral bowing, and urogenital abnormalities.

Virilizing Maternal Tumors

Rarely, the female fetus has been virilized by a maternal androgen-producing tumor. In a few cases, the lesion was a benign adrenal adenoma, but all others were ovarian tumors, particularly androblastomas, luteomas, and Krukenberg tumors (Table 606.6). **Maternal virilization** may be manifested by enlargement of her clitoris, acne, deepening of the voice, decreased lactation, hirsutism, and elevated levels of androgens. In the infant, there is enlargement of the clitoris of varying degrees, often with labial fusion. Mothers of children with unexplained 46,XX DSDs should undergo physical examination and measurements of their own levels of plasma testosterone, dehydroepiandrosterone (DHEA) sulfate, and androstenedione.

Table 606.6

Sources of Maternal-Derived Androgens

ENDOGENOUS	**EXOGENOUS**
Benign	**Synthetic Androgens**
Luteoma of pregnancy	Danazol
Adrenal adenoma	Progestins (medroxyprogesterone acetate)
Hyperreactio luteinalis	Potassium-sparing diuretics
Thecoma/fibroma	
Stromal hyperthecosis	
Brenner tumor	
Serous cystadenoma	
Mature cystic teratoma (dermoid cyst)	
MALIGNANT	
Metastatic carcinomas (Krukenberg tumor)	
Sex-cord stromal tumors—granulosa cell and Sertoli-Leydig tumors	
Adrenal cortical carcinoma	
Cystadenocarcinoma	
Hilar cell tumor	

From Auchus RJ, Chang AY: 46,XX DSD: the masculinised female, *Best Pract Res Clin Endocrinol Metab* 24:219–242, 2010, Table 2.

Exposure to Androgenic Drugs by Women During Pregnancy

Testosterone and 17-methyltestosterone have been reported to cause 46,XX DSDs in some instances (see Table 606.6). The greatest number of cases has resulted from the use of certain progestational compounds for the treatment of threatened abortion. These progestins have since been replaced by nonvirilizing ones.

Infants with virilization and 46,XX chromosomes and caudal anomalies have been reported for whom no virilizing agent could be identified. In such instances, the disorder is usually associated with other congenital defects, particularly of the urinary and gastrointestinal tracts. Y-specific DNA sequences, including SRY, are absent. In 1 case, a scrotal raphe and elevated testosterone levels were found, but the cause remains unknown.

SF-1 Mutations

In a worldwide study of patients with **46,XX ovotesticular DSD** , a specific mutation in SF-1 was identified, p.Arg92Trp. Functional studies showed that the mutant probably interfered with inhibition of testicular development. In 1 family with a maternally transmitted mutation, the mother had early menopause. Multiple other SF-1 mutations have been reported to cause isolated ovarian insufficiency, some associated with 46,XY DSDs in their offspring.

46,XX Testicular DSD

In this condition, also known called **XX male** , the gonads are testicular and virilization is typically incomplete. Infertility and/or gonadal failure may develop after childhood. Many cases are due to translocation of SRY sequences onto one of the X chromosomes, often paired with duplication of SOX-9. The appropriate sex of rearing may be difficult to determine.

46,XX Gonadal Dysgenesis

These females typically present at puberty with normal female genitalia and lack of breast development and hypergonadotropic hypogonadism. Normal müllerian structures are present, but ovaries are absent or streaks.

Undetermined/Unknown

Rarely, 46,XX DSDs can be associated with other congenital anomalies, especially those of the GU or GI tract, and are thus multifactorial in origin. These include cloacal exstrophy and MURCS association (müllerian hypoplasia, renal agenesis, and cervicothoracic somite abnormalities). Isolated deficiency of müllerian development is known as **Meyer-Rokitansky-Küster-Hauser**

syndrome .

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606.2

46,XY DSD

Patricia A. Donohoue

Keywords

congenital adrenal hyperplasia
testosterone synthetic defects
congenital Wilms Tumor syndromes
androgen insensitivity syndrome
gonadoblastoma
gonadal dysgenesis

In this condition the genotype is XY but the external genitalia are either not completely virilized, are ambiguous (atypical), or are completely female. When gonads can be found, they typically contain *testicular* elements; their development ranges from rudimentary to normal. Because the process of normal virilization in the fetus is so complex, it is not surprising that there are many varieties and causes of 46,XY DSD. The etiology of 46,XY DSD is not identified in up to 50% of cases.

Defects in Testicular Differentiation

The 1st step in male differentiation is conversion of the bipotential gonad into a testis. In the XY fetus, if there is a deletion of the short arm of the Y chromosome or of the *SRY* gene, male differentiation does not occur. The phenotype is female; müllerian ducts are well developed because of the absence of AMH, and gonads consist of undifferentiated streaks. By contrast, even extreme deletions of the long arm of the Y chromosome (Yq−) have been found in normally developed males, most of whom are azoospermic and have short stature. This indicates that the long arm of the Y chromosome normally has genes that prevent these manifestations. In many syndromes in which the testes fail to differentiate, Y chromosomes are morphologically normal on karyotyping.

Wilms Tumor Suppressor Gene (WT1) Mutations: Denys-Drash, Frasier, and WAGR Syndromes

Denys-Drash Syndrome : The constellation of nephropathy with ambiguous genitalia and **bilateral Wilms tumor** is the major phenotype of this syndrome. Most reported cases have been 46,XY. Müllerian ducts are often present, indicating a global deficiency of fetal testicular function. Patients with a 46,XX karyotype have normal external genitalia. The onset of proteinuria in infancy progresses to **nephrotic syndrome** and end-stage renal failure by 3 yr of age, with focal or diffuse mesangial sclerosis being the most consistent histopathologic finding. Wilms tumor usually develops in children younger than 2 yr of age and is frequently bilateral. Gonadoblastomas have also been reported.

Several mutations of the *WT1* gene, located on chromosome 11p13, have been found. *WT1* functions as a tumor-suppressor gene and a transcription factor and is expressed in the genital ridge and fetal gonads. Nearly all reported mutations have been near or within the zinc finger–coding region. One report found a zinc finger domain mutation in the *WT1* alleles of a patient with no genitourinary abnormalities, suggesting that some cases of sporadic Wilms tumor may carry the *WT1* mutation.

Frasier Syndrome: Different mutations of the *WT1* gene, constitutional heterozygote mutations at intron 9, have been described in Frasier syndrome**,** a condition of nonspecific focal and segmental glomerulosclerosis, 46,XY gonadal dysgenesis, and frequent gonadoblastoma, but *without* Wilms tumor.

WAGR Syndrome: This acronym refers to a contiguous gene syndrome consisting of Wilms tumor, aniridia, genitourinary malformations, and retardation (WAGR). These children have a deletion of one copy of chromosome 11p13, which may be visible on karyotype analysis. The deleted region encompasses the aniridia gene *(PAX6)* and the Wilms tumor-suppressor gene

(WT1). Only the 46,XY patients have genital abnormalities, ranging from cryptorchidism to severe deficiency of virilization. Gonadoblastomas have developed in the dysgenetic gonads. Wilms tumor usually occurs by 2 yr of age. Some cases also had unexplained obesity, raising the question of an obesity-associated gene in this region of chromosome 11 and naming the syndrome WAGRO.

Campomelic Syndrome

See Chapter 714 .

This form of **short-limbed skeletal dysplasia** is characterized by anterior bowing of the femur and tibia, small, bladeless scapulae, small thoracic cavities, and 11 pairs of ribs, along with malformations of other organs. It is usually lethal in early infancy. Approximately 75% of reported 46,XY patients exhibit a completely **female phenotype;** the external and internal genitalia are female. Some 46,XY patients have ambiguous genitalia. The gonads appear to be ovaries but histologically may contain elements of both ovaries and testes.

The gene responsible for the condition is *SOX9* (SRY-related HMG [high-mobility group]-box gene) and is on 17q24-q25. This gene is structurally related to *SRY* and also directly regulates development of the type II collagen gene *(COL2A1)* . The same mutations may result in different gonadal phenotypes. Gonadoblastoma was reported in a patient with this condition. The inheritance is autosomal dominant.

SF-1 (Also Known as *Ad4BP* or *NR5A1*) Defects and 46,XY DSD

Adrenal insufficiency and 46,XY gonadal dysgenesis have been described in patients with mutations of the *SF-1* gene. In some of these patients, if the mother shares the *SF-1* mutation, she has premature ovarian insufficiency, as was also described in mothers of infants with 46,XX DSD. SF-1–related 46,XY DSD may also occur in the absence of adrenal insufficiency and may resemble PAIS.

46,XY sex reversal has also been described in patients with deletions of parts of autosomal loci on chromosomes 2q, 9p, and 10q.

XY Pure Gonadal Dysgenesis (Swyer Syndrome)

The designation pure distinguishes this condition from forms of gonadal dysgenesis that are of chromosomal origin and associated with somatic anomalies. Affected patients have normal stature and a **female phenotype,** including vagina, uterus, and fallopian tubes, but at pubertal age, breast development and menarche fail to occur. None of the other phenotypic features associated with 45,X (Turner syndrome) are present. Patients present at puberty with hypergonadotropic primary amenorrhea. Familial cases suggest an X-linked or a sex-limited dominant autosomal transmission. Most of the patients examined have had mutations of the *SRY* gene. The gonads consist of almost totally undifferentiated streaks despite the presence of a cytogenetically normal Y chromosome. The primitive gonad cannot accomplish any testicular function, including suppression of müllerian (paramesonephric) ducts. There may be hilar cells in the gonad capable of producing some androgens; accordingly, some virilization, such as clitoral enlargement, may occur at the age of puberty. The streak gonads may undergo neoplastic changes, such as gonadoblastomas and dysgerminomas, and should be removed as soon as the diagnosis is established, regardless of the age of the patient.

Pure gonadal dysgenesis also occurs in XX individuals.

XY Gonadal Agenesis Syndrome (Embryonic Testicular Regression Syndrome)

In this rare syndrome, the external genitalia are slightly ambiguous but more nearly **female.** Hypoplasia of the labia; some degree of labioscrotal fusion; a small, clitoris-like phallus; and a perineal urethral opening are present. No uterus, no gonadal tissue, and usually no vagina can be found. At the age of puberty, no sexual development occurs and gonadotropin levels are elevated. Most children have been reared as females. In several patients with XY gonadal agenesis in whom no gonads could be found on exploration, significant rises in testosterone followed stimulation with hCG, indicating Leydig cell function somewhere. Siblings with the disorder are known.

It is presumed that testicular tissue was active long enough during fetal life for AMH to inhibit development of müllerian ducts but not long enough for testosterone production to result in virilization. In 1 patient, no deletion of the Y chromosome was found by means of Y-specific DNA probes. Testicular degeneration seems to occur between the 8th and 12th fetal wk. Regression of the testis before the 8th wk of gestation results in Swyer syndrome; between the

14th and 20th wk of gestation, it results in the rudimentary testis syndrome; and after the 20th wk, it results in anorchia.

In **bilateral anorchia,** sometimes referred to as *vanishing testes syndrome* , testes are absent, but the **male phenotype** is complete; it is presumed that tissue with fetal testicular function was active during the critical period of genital differentiation but that sometime later it was damaged. Bilateral anorchia in identical twins and unilateral anorchia in identical twins and in siblings suggest a genetic predisposition. Coexistence of anorchia and the gonadal agenesis syndrome in a sibship is evidence for a relationship between the disorders. *SRY* defects have not yet been reported for patients with anorchia.

A retrospective review of urologic explorations revealed absent testes in 21% of 691 testes. Of those, 73% had blind-ending cord structures with the suggested site of the vanishing testes being the inguinal canal (59%), abdomen (21%), superficial inguinal ring (18%), and scrotum (2%). It was suggested that the presence of cord structures on laparoscopy should prompt inguinal exploration because viable testicular tissue was found in 4 of these children. No hormonal data (hCG stimulation tests, AMH levels) were reported.

Defiency of Testicular Hormone Production

Several genetic defects have been delineated in the enzymatic synthesis of testosterone by the fetal testis, and a defect in Leydig cell differentiation has been described. These defects produce 46,XY males with inadequate masculinization (see Fig. 600.3). Because levels of testosterone are normally low before puberty, an hCG stimulation test may be needed in children to assess the ability of the testes to synthesize testosterone.

Leydig Cell Aplasia

Patients with aplasia or hypoplasia of the Leydig cells usually have **female phenotypes,** but there may be mild virilization. Testes, epididymis, and vas deferens are present; the uterus and fallopian tubes are absent because of normal production of AMH. There is no breast development at puberty, but pubic hair development may be normal due to the production of adrenal androgens. Plasma levels of testosterone are low and do not respond to hCG; LH levels are elevated.

The Leydig cells of the testes are absent or markedly deficient. The defect may involve a lack of functional receptors for LH. In children, hCG stimulation is necessary to differentiate the condition from the AISs. There is male-limited autosomal recessive inheritance. The human LH/chorionic gonadotropin (CG) receptor is a member of the G-protein–coupled superfamily of receptors that contains 7 transmembrane domains. Several inactivating mutations of the LH/CG receptor have been described in males with hypogonadism suspected of having Leydig cell hypoplasia or aplasia.

High serum LH and low FSH were noted in 1 male with hypogonadism owing to a mutation in the gene for the β-subunit of FSH (see Table 601.1).

Lipoid Adrenal Hyperplasia

See Chapter 594 .

This is the most severe form of congenital adrenal hyperplasia, and it derives its name from the appearance of the enlarged adrenal glands resulting from accumulation of cholesterol and cholesterol esters. The rate-limiting process in steroidogenesis is the transport of free cholesterol through the cytosol to the inner mitochondrial membrane, where the P450 side-chain cleavage enzyme (P450scc; CYP11A1) acts. Cholesterol transport into mitochondria is mediated by the steroidogenic acute regulatory protein (StAR). StAR is a 30-kDa protein essential for steroidogenesis and is encoded by a gene on chromosome 8p11.2. The mitochondrial content of StAR increases between 1 and 5 hr after adrenocorticotropic hormone stimulation, long after the acute adrenocorticotropic hormone–induced increase in steroidogenesis. This has led some to suggest that extramitochondrial StAR might also be involved in the acute response to adrenocorticotropic hormone. Most patients with lipoid CAH have mutations in the gene encoding StAR, and a few have mutations in CYP11A1.

All serum steroid levels are low or undetectable, whereas ACTH and plasma renin levels are quite elevated. The phenotype is female in both genetic females and males. Genetic males have no müllerian structures because the testes can produce normal AMH but no steroid hormones. These children present with acute adrenal crisis and salt wasting in infancy. Most patients are 46,XY. In a few patients, ovarian steroidogenesis is present at puberty.

The regulatory role of StAR-independent steroidogenesis is illustrated by 46,XX 4 mo old twins with lipoid adrenal hyperplasia. One died at 15 mo because of cardiac complications related to coarctation of the aorta. The adrenal glands had characteristic lipid deposits. The surviving twin had spontaneous puberty with feminization at 11.5 yr and menarche at 13.8 yr. When restudied at the age of 15 yr, a homozygous frameshift-inactivating mutation in her *StAR* gene was discovered. This and the fact that she survived as an infant until 4 mo of age without replacement therapy with detectable serum aldosterone levels support the hypothesis that StAR-independent steroidogenesis was able to proceed until enough intracellular lipid accumulated to destroy steroidogenic activity. Partial defects in only partially virilized males and delayed onset of salt wasting have been described. Complete CYP11A1 defects may be incompatible with life because only this enzyme can convert cholesterol to pregnenolone, which then becomes progesterone, a hormone essential for the maintenance of normal mammalian pregnancy. Heterozygous mutation in *CYP11A1* was described in a 4 yr old with 46,XY sex reversal and late-onset form of lipoid adrenal hyperplasia. At 6-7 wk of gestation, when maternal corpus luteum progesterone synthesis stops, the placenta, which does not express StAR, produces progesterone by StAR-independent steroidogenesis using the CYP11A1 enzyme system.

3β-Hydroxysteroid Dehydrogenase Deficiency

Males with this form of congenital adrenal hyperplasia (see Chapter 594) have various degrees of hypospadias, with or without bifid scrotum and cryptorchidism and, rarely, a complete female phenotype. Affected infants usually develop salt-losing manifestations shortly after birth. Incomplete defects, occasionally seen in males with premature pubarche, as well as late-onset nonclassic forms, have been reported. These children have point mutations of the gene for type II 3β-hydroxysteroid enzyme, resulting in impairment of steroidogenesis in the adrenals and gonads; the impairment may be unequal between adrenals and gonads. Normal pubertal changes in some males could be explained by the normally present type I 3β-hydroxysteroid dehydrogenase present in many peripheral tissues. Infertility is frequent. There is no correlation between degree of salt wasting and degree of phenotypic abnormality.

Deficiency of 17-Hydroxylase/17,20-Lyase

A single enzyme (CYP17A1) encoded by a single gene on chromosome 10q24.3

has both 17-hydroxylase and 17,20-lyase activities in adrenal and gonadal tissues (see Chapter 594). Many different genetic mutations have been reported. Genetic males usually have a complete female phenotype or, less often, various degrees of undervirilization from labioscrotal fusion to perineal hypospadias and cryptorchidism. Pubertal development fails to occur in both genetic sexes.

In the classical disorder, there is decreased synthesis of cortisol by the adrenals and of sex steroids by the adrenals and gonads. Levels of the steroid precursor with mineralocorticoid activity, deoxycorticosterone, as well as corticosterone, are markedly increased and lead to the hypertension and hypokalemia characteristic of this form of 46,XY DSD. Although levels of cortisol are low, the elevated ACTH and corticosterone levels prevent symptomatic cortisol deficiency. The renin–aldosterone axis is suppressed because of the strong mineralocorticoid effect of elevated deoxycorticosterone. Virilization does not occur at puberty; levels of testosterone are low, and those of gonadotropins are increased. Because fetal production of AMH is normal, no müllerian duct remnants are present. In XY phenotypic females, gonadectomy and replacement therapy with hydrocortisone and sex steroids are indicated.

The defect follows autosomal recessive inheritance. Affected XX females are usually not detected until young adult life, when they fail to experience normal pubertal changes and are found to have hypertension and hypokalemia. This condition should be suspected in patients presenting with primary amenorrhea and hypertension whose chromosomal complement is either 46,XX or 46,XY.

Some patients originally described as having isolated 17,20 lyase deficiency were subsequently shown to have a defect in the production of DHT due to deficiency of enzymes in the alternative pathway of DHT synthesis (described in further detail later).

Deficiency of 17-Ketosteroid Reductase

This enzyme, also called *17β-hydroxysteroid dehydrogenase* , catalyzes the final step in testosterone biosynthesis. It is necessary to convert androstenedione to testosterone, DHEA to androstenediol, and estrone to estradiol. Deficiency of 17-ketosteroid reductase in the fetal testis causes the male fetus to have complete or near-complete female phenotype. Müllerian ducts are absent, and a shallow vagina is present. The diagnosis is based on the ratio of androstenedione to testosterone. In prepubertal children, stimulation with hCG may be necessary to make the diagnosis.

The defect is inherited in an autosomal recessive fashion. At least 4 different types of 17β-hydroxysteroid dehydrogenase are recognized, each coded by a different gene on different chromosomes. Type III is the enzyme responsible for testicular production of testosterone. This defect is more common in a highly inbred Arab population in Gaza than it is in other populations. The gene for the disorder is at 9q22 and is expressed only in the testes, where it converts androstenedione to testosterone. Most patients are diagnosed at puberty because of virilization and the failure to menstruate. Testosterone levels at puberty may approach normal, presumably as a result of peripheral conversion of androstenedione to testosterone; at this time, some patients may spontaneously adopt a male gender role.

Type I 17β-hydroxysteroid dehydrogenase, encoded by a gene on chromosome 17q21, converts estrone to estradiol and is found in placenta, ovary, testis, liver, prostate, adipose tissue, and endometrium. Type II, whose gene is on chromosome 16q24, reverses the reactions of types I and III (converting testosterone to androstenedione and estrone to estradiol, respectively). Type IV is similar in action to type II. A late-onset form of 17-ketosteroid reductase deficiency presents as gynecomastia in young adult males.

Persistent Müllerian Duct Syndrome

In this disorder, there is persistence of müllerian (paramesonephric) duct derivatives in otherwise completely virilized males. Cases have been reported in siblings and identical twins. Cryptorchidism is present in 80% of affected males; and during surgery for this or inguinal hernia, the condition is discovered when a fallopian tube and uterus are found. The degree of müllerian development is variable and may be asymmetric. Testicular function is normal in most, but testicular degeneration has been reported. Some affected males acquire testicular tumors after puberty. In a study of 38 families, 16 families had defects in the AMH gene, located on the short arm of chromosome 19. Affected patients had low AMH levels. In 16 families with high AMH levels, the defect was in the AMH type II receptor gene, with 10 of 16 having identical 27-bp deletions on exon 10 in at least 1 allele.

Treatment consists of removal of as many of the müllerian structures as possible without causing damage to the testis, epididymis, or vas deferens.

Defects in Androgen Action

In the following group of disorders, fetal synthesis of testosterone is normal and defective virilization results from inherited abnormalities in androgen action.

Dihydrotestosterone Deficiency

Decreased production of DHT in utero results in marked ambiguity of external genitalia of affected males. Biosynthesis and peripheral action of testosterone are normal.

The phenotype most commonly associated with this condition results in males who have a small phallus, bifid scrotum, urogenital sinus with perineal hypospadias, and a blind vaginal pouch (Fig. 606.4). Testes are in the inguinal canals or labioscrotal folds and are normal histologically. There are no müllerian structures. Wolffian structures—the vas deferens, epididymis, and seminal vesicles—are present. Most affected patients have been identified initially as females. At puberty, *virilization occurs* ; the phallus enlarges, the testes descend and grow normally, and spermatogenesis occurs. There is no gynecomastia. Beard growth is scanty, acne is absent, the prostate is small, and recession of the temporal hairline fails to occur. Virilization of the wolffian duct is caused by the action of testosterone itself, although masculinization of the urogenital sinus and external genitals depends on the action of DHT during the critical period of fetal masculinization. Growth of facial hair and of the prostate also appears to be DHT dependent.

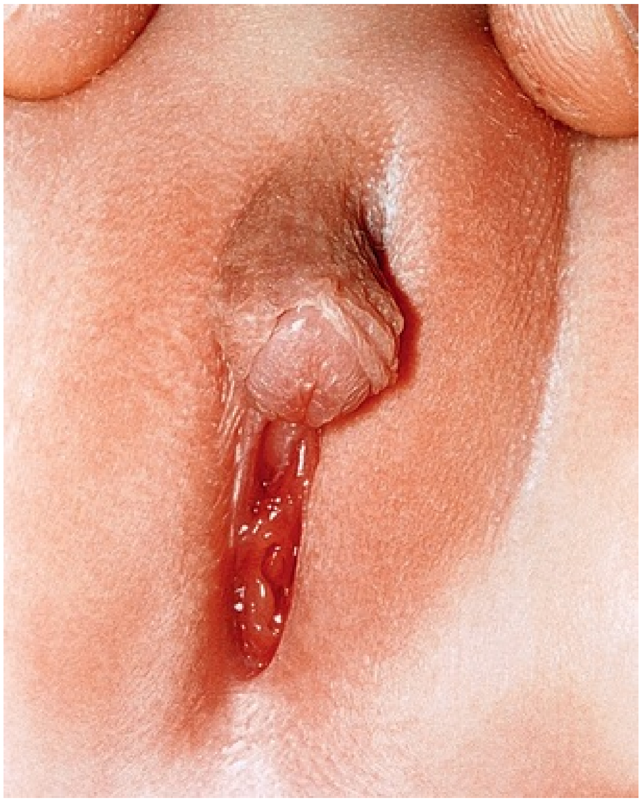

FIG. 606.4 5α-Reductase deficiency. (From Wales JKH, Wit JM, Rogol AD: *Pediatric endocrinology and growth* , ed 2, Philadelphia, 2003, WB Saunders, p 165.)

The adult height reached is close to that of the father and other male siblings. There is significant phenotypic heterogeneity. This has led to a classification of such patients into 5 types of **steroid 5α-reductase deficiency (SRD)** .

Several different gene defects of SRD5A2 (the 5α-reductase type 2 gene leading to SRD) have been identified, located on the short arm of chromosome 2, in patients from throughout the world. Familial clusters have been reported from the Dominican Republic, Turkey, Papua New Guinea, Brazil, Mexico, and the Middle East. There is no reliable correlation between genotype and phenotype.

The disorder is inherited as an autosomal recessive trait but is limited to males; normal homozygous females with normal fertility indicate that in females DHT has no clinically significant role in sexual differentiation or in ovarian function later in life. The clinical diagnosis should be made as early as possible in infancy. It is important to distinguish this from PAIS, because patients with PAIS are far less sensitive to androgen than are patients with SRD. The biochemical diagnosis of SRD is based on finding normal serum testosterone levels, normal or low DHT levels with markedly increased basal and especially hCG-stimulated testosterone: DHT ratios (>17), and high ratios of urinary etiocholanolone to androsterone. Children with androgen insensitivity have normal hepatic 5α reduction and thus a normal ratio of tetrahydrocortisol to 5α-tetrahydrocortisol, as opposed to those with SRD.

It is important to note that many but not all children with SRD reared as females in childhood have changed to male around the time of puberty. It appears that exposures to testosterone in utero, neonatally, and at puberty have variable contributions to the formation of male gender identity. Much more needs to be learned about the influences of hormones such as androgens, as well as the influences of cultural, social, psychologic, genetic, and other biologic factors in gender identity and behavior. Infants with this condition should be reared as males whenever practical. Treatment of male infants with DHT results in phallic enlargement.

Another cause of DHT deficiency is a block in an alternative pathway of DHT synthesis. Patients previously thought to have 46,XY DSD because of isolated 17,20-lyase deficiency have subsequently been characterized as having mutations in the *AKR1C2* gene (3α-reductase type 3) or both the *AKR1C2* and *AKR1C4* (3α-reductase type 4) genes (see Fig. 606.1). These findings showed that both the classical and alternative pathways to DHT must be intact for normal prenatal virilization.

Androgen Insensitivity Syndromes

The AISs are the most common forms of male DSDs, occurring with an estimated frequency of 1/20,000 genetic males. This group of heterogeneous X-linked recessive disorders is caused by more than 150 different mutations in the androgen receptor gene, located on Xq11-12: single point mutations resulting in amino acid substitutions or premature stop codons, frameshift and premature terminations, gene deletions, and splice-site mutations.

Clinical Manifestations

The clinical spectrum of patients with AISs, all of whom have a 46,XY chromosomal complement, range from phenotypic females (in *complete* AIS) to males with various forms of ambiguous genitalia and undervirilization (*partial* AIS, or clinical syndromes such as **Reifenstein syndrome**) to phenotypically normal-appearing males with infertility. In addition to normal 46,XY chromosomes, the presence of testes and normal or elevated testosterone and LH levels are common to all such children (Figs. 606.5 and 606.6).

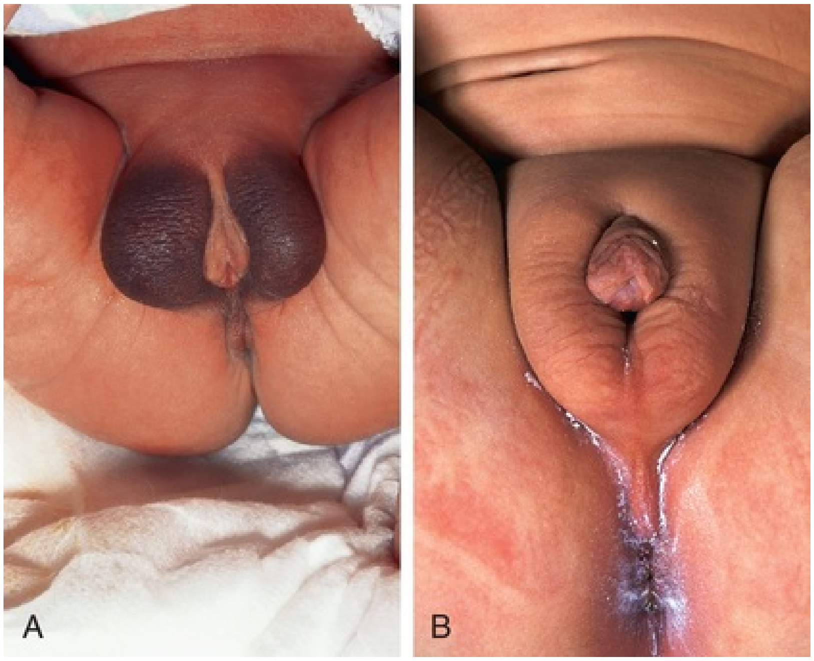

FIG. 606.5 **A,** Partial androgen insensitivity with descended testes in bifid labioscrotal folds. **B,** Less-severe partial androgen insensitivity with severe hypospadias and maldescent of testes. (From Wales JKH, Wit JM, Rogol AD: *Pediatric endocrinology and growth* , ed 2, Philadelphia, 2003, WB Saunders, p 165.)

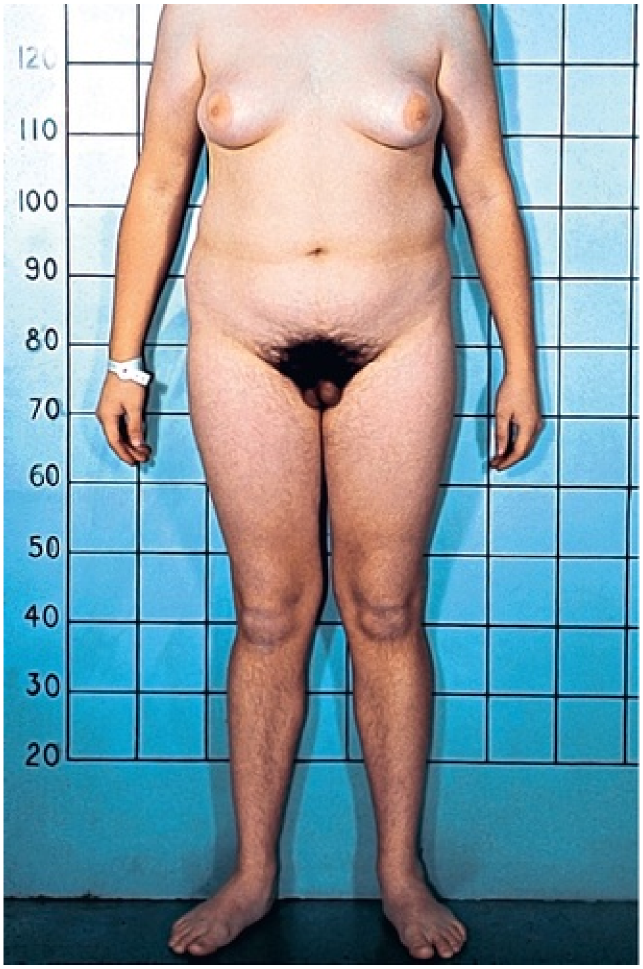

FIG. 606.6 Partial androgen insensitivity syndrome at adolescence, male sex of rearing. Note gynecomastia from peripheral aromatase conversion of testosterone to estrogen. Abundant pubic hair implies only partial resistance. (From Wales JKH, Wit JM, Rogol AD: *Pediatric endocrinology and growth* , ed 2, Philadelphia, 2003, WB Saunders, p 165.)

In **complete androgen insensitivity syndrome (CAIS),** an extreme form of failure of virilization, genetic males appear female at birth and are invariably reared accordingly. The external genitalia are female. The vagina ends blindly in a pouch, and the uterus is absent as a result of the normal production and effect of AMH by the testes. In about one third of patients, unilateral or bilateral fallopian tube remnants are found. The testes are usually intraabdominal but may descend into the inguinal canal; they consist largely of seminiferous tubules. At puberty, there is normal development of breasts and the habitus is female, but menstruation does not occur and sexual hair is absent. Adult heights are commensurate with those of normal males despite profound congenital deficiency of androgenic effects.

The testes of affected adult patients produce normal male levels of testosterone, which are converted to normal levels of DHT. Failure of normal male differentiation during fetal life reflects a defective response to androgens at that time. The absence of androgenic effects is caused by a striking resistance to the action of endogenous or exogenous testosterone at the cellular level.

Prepubertal females with this disorder are often detected when inguinal masses prove to be testes or when a testis is unexpectedly found during herniorrhaphy. Approximately 1–2% of females with an inguinal hernia prove to have this disorder. In infants, elevated LH levels should suggest the diagnosis. In older children and adults, **amenorrhea** is the usual presenting symptom. In prepubertal children, the condition must be differentiated from other types of XY undervirilized males in which there is complete feminization. These include XY gonadal dysgenesis (Swyer syndrome), true agonadism, Leydig cell aplasia including LH receptor defects, and 17-ketosteroid reductase deficiency. All these conditions, unlike CAIS, are characterized by **low levels of testosterone** as neonates and during adult life and by failure to respond to hCG during the prepubertal years.

Although patients with CAIS have unambiguously female external genitals at birth, those with **PAIS** have a wide variety of phenotypic presentations, ranging from **perineoscrotal hypospadias,** bifid scrotum, and cryptorchidism to extreme undervirilization appearing as clitoromegaly and labial fusion. Some forms of PAIS are known as specific syndromes. Patients with **Reifenstein syndrome** have incomplete virilization characterized by hypogonadism, severe hypospadias, and gynecomastia (see Fig. 606.6). **Gilbert-Dreyfus** and **Lubs** syndromes are also classified as PAISs. In all cases, abnormalities in the androgen receptor gene have been identified. Table 606.7 lists other causes of a PAIS-like syndrome.

Table 606.7

Causes of a Partial Androgen Insensitivity Syndrome-Like Phenotype

DEFECTS IN ANDROGEN PRODUCTION
• Partial gonadal dysgenesis   • Mutations in *SRY, NR5A1, WT1* • Mutations of the luteinizing hormone receptor • Biosynthetic enzyme deficiencies • 17,20-Lyase deficiency • P450 oxidoreductase deficiency

• 17β-hydroxysteroid dehydrogenase deficiency type 3 • 5α-Reductase deficiency type 2
GENETIC
• Klinefelter syndrome • Smith-Lemli-Opitz syndrome • Denys-Drash syndrome • Frasier syndrome
PAIS
• Mutations of the androgen receptor gene • Normal androgen receptor gene with fetal growth restriction

NR5A1 , Nuclear receptor subfamily 5 A1; *PAIS* , partial androgen insensitivity syndrome; *SRY* , sex-determining region Y; *WT1* , Wilms tumor 1.

From Hughes IA, Davies JD, Bunch TI, et al: Androgen insensitivity syndrome, *Lancet* 380:1419–1428, 2012, Panel 1.

Diagnosis

The diagnosis of patients with PAIS may be particularly difficult in infancy. The postnatal surge in testosterone and LH is diminished in those with CAIS but not in those with PAIS. In some, especially those sufficiently virilized in infancy, the diagnosis is not suspected until puberty, when there is inadequate virilization with lack of facial hair or voice change and the appearance of gynecomastia. Azoospermia and infertility are common. Increasingly, androgen receptor defects are being recognized in adults who have a small phallus and testes and infertility. A single-amino-acid substitution in the androgen receptor was reported in a large Chinese family in whom some affected members were fertile whereas others had gynecomastia and/or hypospadias. Production of insulin-like growth factor 2 and insulin-like growth factor–binding protein-2, but not insulin-like growth factor–binding protein-3, by genital skin fibroblasts is decreased in CAIS compared with normal genital skin fibroblasts, suggesting a possible role for the insulin-like growth factor system in modulating androgen action.

Treatment and Prognosis

In patients with CAIS whose sexual orientation is unambiguously female, the testes should be removed as soon as they are discovered. Laparoscopic removal of Y chromosome–bearing gonads has been performed in patients with AIS and in those with gonadal dysgenesis. In one third of patients, malignant tumors, usually seminomas, develop by 50 yr of age. Several teenage females have acquired seminomas. Replacement therapy with estrogens is indicated at the age of puberty.

Normal breasts develop in affected females who have not had their testes removed by the age of puberty. In these individuals, production of estradiol results from aromatase activity on testicular testosterone. The absence of androgenic activity also contributes to the feminization of these women.

The psychosexual and surgical management of patients with PAIS is extremely complex and depends in large part on the presenting phenotype. Osteopenia is recognized as a late feature of AIS.

Molecular analyses have suggested that phenotype may depend in part on somatic mosaicism of the androgen receptor gene. This was based on the case of a 46,XY patient who had a premature stop codon in exon 1 of the androgen receptor gene but who also had evidence of virilization (pubic hair and clitoral enlargement) explained by the discovery of the wild-type alleles on careful examination of the sequencing gel. The presence of mosaicism shifts the phenotype to a higher degree of virilization than expected from the genotype of the mutant allele alone.

Genetic counseling is difficult in families with androgen receptor gene mutation. In addition to lack of genotype–phenotype correlations, there is a high rate (27%) of de novo mutations in families.

Sex hormone–binding globulin reduction after exogenous androgen administration (stanozolol) correlates with the severity of the receptor defect and may become a useful clinical tool. Successful therapy with supplemental androgens has been reported in patients with PAIS and various mutations of the androgen receptor in the DNA-binding domain and the ligand-binding domain.

Mutated androgen receptors are also reported in patients with spinal and bulbar muscular atrophy in whom clinical manifestations including testicular atrophy, infertility, gynecomastia, and elevated LH, FSH, and estradiol levels usually manifest between the 3rd and 5th decades of life. Androgen receptor mutations have also been described in patients with prostate cancer.

Undetermined Causes

Other XY undervirilized males display great variability of the external and internal genitalia and various degrees of phallic and müllerian development. Testes may be histologically normal or rudimentary, or there may only be 1. No recognized cause is identified in up to 50% of children with 46,XY DSDs. Some ambiguity of the genitalia is associated with a wide variety of chromosomal aberrations, which must always be considered in the differential diagnosis, the most common being the 45,X/46,XY syndrome (see Chapter 604.1). It may be necessary to karyotype several tissues to establish mosaicism. Other complex genetic syndromes, many resulting from single gene mutations, are associated with varying degrees of ambiguity of the genitalia, particularly in the male. These entities must be identified on the basis of the associated extragenital malformations.

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder caused by mutations in the sterol Δ7-reductase gene located on chromosome 11q12-q13. It is characterized by prenatal and postnatal growth retardation, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the 2nd-3rd toes, and severe cognitive impairment (see Chapter 104.3). Its incidence is 1 in 20,000-30,000 live births in populations of northern and central European origin; 70% are male. Genotypic males usually have genital ambiguity and, occasionally, partial sex reversal with female genital ambiguity or complete sex reversal with female external genitalia. Müllerian duct derivatives are usually absent. Affected 46,XX patients have normal genitalia. Two types of Smith-Lemli-Opitz syndrome have been recognized. The **classical form (type I)** described earlier and the acrodysgenital syndrome, which is usually lethal within 1 yr and is associated with severe malformations, postaxial polydactyly, and extremely abnormal external genitalia **(type II)** . Pyloric stenosis is associated with Smith-Lemli-Opitz syndrome type I and Hirschsprung disease with type II. Cleft palate, skeletal abnormalities, and 1 case of a lipoma of the pituitary gland have been seen in **type II** cases. Some authors believe in a spectrum of disease severity rather than in the above classification. Low plasma cholesterol with elevated 7-dehydrocholesterol, its precursor, are found in types I and II, and the levels do not correlate with severity. Maternal apolipoprotein E values do seem to correlate with severity. The most common prenatal expression of Smith-Lemli-Opitz syndrome is intrauterine growth retardation (see Chapter 104.3 for treatment).

46,XY DSD subjects also have been described in siblings with the α-thalassemia/mental retardation syndrome.

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606.3

Ovotesticular DSD

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Keywords

ovotestes
chimeras

In ovotesticular DSD, both ovarian and testicular tissues are present, either in the same or in opposite gonads. Affected patients have ambiguous genitalia, varying from normal female with only slight enlargement of the clitoris to almost normal male external genitalia (see Fig. 606.3*A*).

Approximately 70% of all patients have a 46,XX karyotype. Ninety-seven percent of affected patients of African descent are 46,XX. Fewer than 10% of persons with ovotesticular DSD are 46,XY. Approximately 20% have 46,XX/46,XY mosaicism. Half of these are derived from more than 1 zygote and are chimeras (chi 46,XX/46,XY). The presence of paternal and both maternal alleles for some blood groups is demonstrated. An ovotesticular DSD chimera, 46,XX/46,XY, was reported as resulting from embryo amalgamation after in vitro fertilization. Each embryo was derived from an independent, separately fertilized ovum.

Examination of 46,XX ovotesticular DSD patients with Y-specific probes has detected fewer than 10% with a portion of the Y chromosome including the *SRY* gene. Ovotesticular DSD is usually sporadic, but a number of siblings have been reported. The cause of most cases of ovotesticular DSD is unknown.

The most frequently encountered gonad in ovotesticular DSD is an ovotestis, which may be bilateral. If unilateral, the contralateral gonad is usually an ovary but may be a testis. The ovarian tissue is normal, but the testicular tissue is dysgenetic. The presence and function of testicular tissue can be determined by measuring basal and hCG-stimulated testosterone levels, as well as AMH levels. Patients who are highly virilized and have had adequate testicular function with no uterus are usually reared as males. If a uterus exists, virilization is often mild and testicular function minimal; assignment of female sex may be indicated. Selective removal of gonadal tissue inconsistent with sex of rearing may be indicated. In a few families, 46,XY ovotesticular DSD subjects and 44,XX males have been described in the same sibship.

Defects in R-Spondin1, encoded by the *RSPO1* gene, have been described in 46,XX ovotesticular DSD. Defects in SF-1 have been described in both XX and XY ovotesticular DSD.

Pregnancies with living offspring have been reported in 46,XX ovotesticular DSD individuals reared as females, but very few males with ovotesticular DSD have fathered children. Approximately 5% of patients will develop gonadoblastomas, dysgerminomas, or seminomas.

Diagnosis and Management of Disorders of Sex Development

In the neonate, ambiguity of the genitals requires immediate attention to decide on the sex of rearing as early in life as possible. The family of the infant needs to be informed of the child's condition as early, completely, compassionately, and honestly as possible. Caution must be used to avoid feelings of guilt, shame, and discomfort. Guidance needs to be provided to alleviate both short-term and long-term concerns and to allow the child to grow up in a completely supportive environment. The initial care is best provided by a team of professionals that includes neonatologists and pediatric specialists, endocrinologists, radiologists, urologists, psychologists, and geneticists, all of whom remain focused foremost on the needs of the child. Management of the potential psychologic upheaval that these disorders can generate in the child or the family is of paramount importance and requires physicians and other healthcare professionals with sensitivity, training, and experience in this field.

While awaiting the results of chromosomal analysis, pelvic ultrasonography is indicated to determine the presence of a uterus and ovaries**.** Presence of a uterus and absence of palpable gonads usually suggest a virilized XX female; however, as described previously, these structures may also be found in 46,XY DSD. A search for the source of virilization should be undertaken; this includes studies of adrenal hormones to rule out varieties of congenital adrenal hyperplasia, and studies of androgens and estrogens occasionally may be necessary to rule out aromatase deficiency. Virilized XX females are generally (but not always) reared as females even when highly virilized.

The absence of a uterus, with or without palpable gonads, often indicates an undervirilized male and an XY karyotype. Measurements of levels of gonadotropins, testosterone, AMH, and DHT are necessary to determine whether testicular production of androgen is present and is normal. Undervirilized males who are totally feminized may be reared as females. Certain significantly feminized infants, such as those with 5α-reductase deficiency, may be reared as males because these children virilize normally at puberty. Sixty percent of individuals with 5α-reductase deficiency assigned as female in infancy live as males as adults. An infant with a comparable degree of feminization resulting from an androgen receptor defect, such as CAIS, may be successfully reared as a female.

When receptor disorders are suspected in the XY male with a small phallus (micropenis), a course of 3 monthly intramuscular injections of testosterone enanthate (25-50 mg) may assist in the differential diagnosis of androgen insensitivity, as well as in treatment of the small phallus.

In some mammals, the female exposed to androgens prenatally or in early postnatal life exhibits nontraditional sexual behavior in adult life. Most, but not all, females who have undergone fetal masculinization from congenital adrenal hyperplasia or from maternal progestin therapy have female sexual identity, although during childhood they may appear to prefer male playmates and activities over female playmates and feminine play with dolls in mothering roles.

In the past it was thought that surgical treatment of ambiguous genitalia to create a female appearance, particularly when a vagina is present, was more successful than construction of male genitalia. Considerable controversy exists regarding these decisions. Sexual functioning is to a large extent more dependent on neurohormonal and behavioral factors than the physical appearance and functional ability of the genitalia. Similarly, controversy exists regarding the timing of the performance of invasive and definitive procedures, such as surgery. Whenever possible without endangering the physical or psychologic health of the child, an expert multidisciplinary team should consider deferring elective surgical repairs and gonadectomies until the child can participate in the informed consent for the procedure. One study of children (59 males and 18 females) with gender dysphoria but without documentation of genomic or enzymologic abnormalities indicated that most of these children no longer have gender dysphoria after completion of puberty. Among those who do, homosexuality and bisexuality are the most frequent diagnoses.

For patients with DSD who have Y-chromosome material and intraabdominal gonads, gonadectomy is generally recommended because of the risk of gonadal tumors, many of which are malignant.

The pediatrician, pediatric endocrinologist, and psychologist, along with the appropriate additional specialists, should provide ongoing compassionate, supportive care to the patient and the patient's family throughout childhood, adolescence, and adulthood. Support groups are available for families and patients with many of the conditions discussed.

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SECTION 6

Diabetes Mellitus in Children

OUTLINE

Chapter 607 Diabetes Mellitus

CHAPTER 607

Diabetes Mellitus

607.1

Classification of Diabetes Mellitus

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Keywords

type 1 diabetes
type 2 diabetes
monogenic diabetes
insulin resistance
pancreatic beta-cells
diabetes autoantibodies

Diabetes mellitus (DM) is a common, chronic, metabolic disease characterized by hyperglycemia as a cardinal biochemical feature. The major forms of diabetes are differentiated by insulin deficiency vs insulin resistance: **type 1 diabetes mellitus (T1DM**) results from deficiency of insulin secretion because of pancreatic β-cell damage; **type 2 diabetes mellitus (T2DM)** is a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β-cell impairment. T1DM is the most common endocrine-metabolic disorder of childhood and adolescence, with important consequences for physical and emotional development. Individuals with T1DM confront serious lifestyle alterations, including an absolute daily requirement for exogenous insulin, the need to monitor their own glucose level, and the need to pay attention to dietary intake. Morbidity and mortality stem from a constant potential for acute metabolic derangements and from long-term complications. Potential acute complications include the development of hypoglycemia related to insulin excess or hyperglycemic ketoacidosis from insulin deficiency. Long-term complications typically manifest in adulthood and are related to the adverse effects of chronic hyperglycemia and associated metabolic abnormalities on tissues and organ systems. This can result in microvascular diseases such as retinopathy, nephropathy, and neuropathy, and macrovascular complications such as ischemic heart disease and arterial obstruction with gangrene of the extremities.

DM is not a single entity but rather a heterogeneous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance through deficient insulin production or action. The American Diabetes Association has proposed a diabetes classification system that includes 4 categories: type 1 diabetes, type 2 diabetes, other specific types, and gestational diabetes. An expanded list of diabetes etiologies is provided in Table 607.1 . The current criteria for the diagnosis of diabetes are provided in Table 607.2 . A thorough clinical history and physical exam are often sufficient to determine the etiology, however in some cases additional testing may be required.

Table 607.1

Etiologic Classifications of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction ultimately leading to complete insulin deficiency)
    A. Immune mediated
    B. Idiopathic
II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
    A. Typical
    B. Atypical
III. Other specific types
    A. Genetic defects of β-cell function (monogenic diabetes)
        i. Neonatal diabetes
        1. Mutations leading to transient neonatal diabetes (*PLAGL1/HYMAI*, *ZFP57*, *ABCC8*, *KCNJ11*, *HNF1* β)
        2. Mutations leading to permanent neonatal diabetes (ABCC8, KCNJ11, GCK, IPF1, PTF1A, FOXP3, EIF2AK3, GATA6)
        ii. MODY (maturity-onset diabetes of the young) syndromes
        1. MODY 1 chromosome 20, *HNF4α*
        2. MODY 2 chromosome 7, *GCK*
        3. MODY 3 chromosome 12q24.2, *HNF1α*, *TCF-1*

    4. MODY 4 chromosome 13q12.1, *IPF-1 (PDX1)*
    5. MODY 5 chromosome 17, *HNF1β*, *TCF-2*
    6. MODY 6 chromosome 2q32, *neuro-*D_1/β_2
    7. MODY 7 chromosome 2p25, *KLF11*
    8. MODY 8 chromosome 9q34, *CEL*
    9. MODY 9 chromosome 7q32, *PAX4*
    10. MODY 10 chromosome 11p15.5, *INS*
    11. MODY 11 chromosome 8p23, *BLK*
  iii. Mitochondrial DNA mutations (includes 1 form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, and maternally inherited diabetes and deafness)
  iv. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness):
    1. WFS1-Wolframin—chromosome 4p
    2. Wolfram locus 2—chromosome 4q22-24
    3. Wolfram mitochondrial
  v. Thiamine responsive megaloblastic anemia and diabetes
B. Genetic defects of insulin action
  i. Type A insulin resistance
  ii. Donohue syndrome
  iii. Rabson-Mendenhall syndrome
  iv. Lipoatrophic diabetes syndromes
C. Other genetic syndromes associated with diabetes (insulin resistance or deficiency)
  i. Down syndrome
  ii. Turner syndrome
  iii. Klinefelter syndrome
  iv. Prader-Willi syndrome
  v. Bardet-Biedl syndrome
  vi. Alström syndrome
  vii. Werner syndrome
D. Other autoimmune syndromes associated with diabetes
  i. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)
  ii. Autoimmune polyendocrinopathy syndromes (APS)
    1. APS-1 (APCED)
    2. APS-2
  iii. Stiff person syndrome
  iv. Anti-insulin receptor antibodies
E. Drug or chemical induced
  i. Antirejection—cyclosporine, sirolimus
  ii. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)
  iii. L-Asparaginase
  iv. β-Adrenergic blockers
  v. Vacor (rodenticide)
  vi. Phenytoin (Dilantin)
  vii. α-Interferon
  viii. Diazoxide
  ix. Nicotinic acid
  x. Pentamidine
F. Diseases of exocrine pancreas
  i. Cystic fibrosis
  ii. Trauma/pancreatectomy
  iii. Pancreatitis/ionizing radiation
  iv. Hemochromatosis
  v. Fibrocalculous pancreatopathy
G. Infections
  i. Congenital rubella
  ii. Cytomegalovirus
  iii. Hemolytic-uremic syndrome

H. Endocrinopathies associated with diabetes
    i. Cushing (hypercortisolism)
    ii. Acromegaly (growth hormone excess)
    iii. Pheochromocytoma
    iv. Glucagonoma
    v. Somatostatinoma
    vi. Aldosteronoma
IV. Gestational Diabetes

Modified from Sperling MA, Tamborlane WV, Battelino T, et al: Diabetes mellitus. In Sperling MA, editor: *Pediatric endocrinology* , ed 4, Philadelphia, 2014, Elsevier, Box 19-1.

Table 607.2

Diagnostic Criteria for Dysglycemia and Diabetes Mellitus

DYSGLYCEMIA	DIABETES MELLITUS
Impaired fasting glucose:	
Fasting (at least 8 hr) plasma glucose 100-125 mg/dL (5.6-7.0 mmol/L)	Fasting (at least 8 hr) plasma glucose ≥ 126 mg/dL (7.0 mmol/L) ***Or***
Impaired glucose tolerance:	
2 hr plasma glucose during OGTT ≥ 140 mg/dL (7.8 mmol/L), but < 200 mg/dL (11.1 mmol/L)	2 hr plasma glucose during OGTT ≥ 200 mg/dL (11.1 mmol/L) ***Or***
Prediabetes:	
Hemoglobin A1c 5.7–6.4% (39-47 mmol/mol)	Hemoglobin A1c ≥ 6.5% (48 mmol/mol) ***Or***
	Symptoms[*] of diabetes mellitus plus random or casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L) [†]

[*] Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.

[†] Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia.

OGTT, oral glucose tolerance test.

Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, *Diabetes Care* 20 (Suppl 1):S5, 1999; and American Diabetes Association. Standards in Medical Care of Diabetes-2017. *Diabetes Care* 40 (Suppl 1):S11–S24, 2017

Type 1 Diabetes Mellitus

Formerly called insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes, T1DM is characterized by low or absent levels of endogenously produced insulin and by dependence on exogenous insulin to prevent development of ketoacidosis, an acute life-threatening complication of T1DM. The natural history includes 4 distinct stages: (1) preclinical β-cell autoimmunity with progressive defect of insulin secretion, (2) onset of clinical diabetes, (3) transient remission honeymoon period, and (4) established diabetes during which there may occur acute and/or chronic complications and decreased life expectancy. The onset occurs predominantly in childhood, with a median age of 7-15 yr, but it may present at any age. The incidence of T1DM has steadily increased in nearly all parts of the world (Fig. 607.1). T1DM is characterized by autoimmune destruction of pancreatic islet β-cells. Both genetic susceptibility and environmental factors contribute to the pathogenesis. Susceptibility to T1DM is genetically controlled by alleles of the major histocompatibility complex (MHC) class II genes expressing human leukocyte antigens (HLAs). Autoantibodies to β-cell antigens including islet cell cytoplasm (ICA), insulin autoantibody (IAA), glutamic acid decarboxylase (GADA), islet antigen 2 (IA-2A, formerly ICA512), and zinc transporter 8 (ZnT8A) are detected in serum from affected subjects. These can be detected months to years prior to clinical onset of T1DM. In some children and adolescents with apparent T1DM, the β-cell destruction is not immune mediated. This subtype of diabetes occurs in patients of African or Asian origin and is distinct from known causes of β-cell destruction such as drugs or chemicals, viruses, mitochondrial gene defects, pancreatectomy, and ionizing radiation. These individuals may have ketoacidosis, but they have extensive periods of remission with variable insulin deficiency, similar to patients with T2DM. Patients with T1DM require lifelong treatment with insulin.

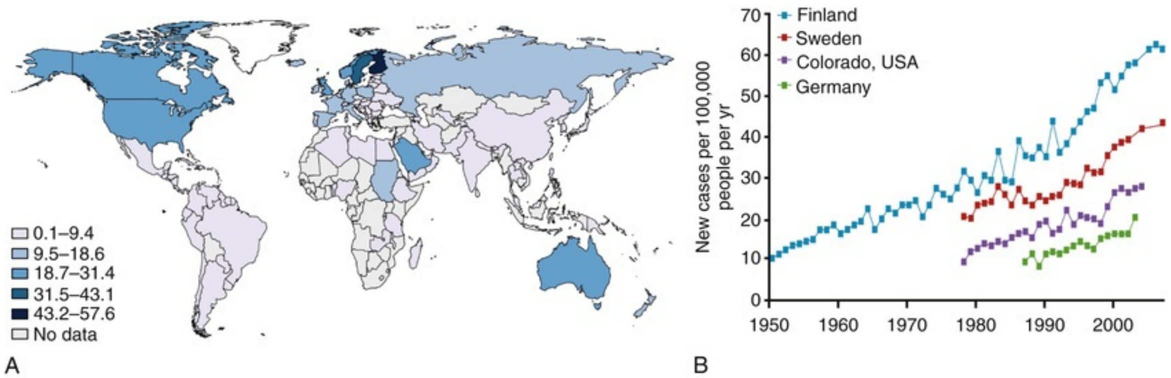

FIG. 607.1 Incidence of T1DM in children ages 0-14 yr, by geographical region and over time. **A,** Estimated global incidence of T1DM, by region, in 2011. **B,** Time-based trends for the incidence of T1DM in children ages 0-14 yr in areas with high or high-intermediate rates of disease. (From Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes. *Lancet* 383:69–78, 2014, Fig. 1.)

Type 2 Diabetes Mellitus

Formerly known as adult-onset diabetes mellitus or non–insulin-dependent diabetes mellitus, T2DM develops as a result of insulin resistance and progressive non-autoimmune β-cell failure. While T2DM has long been the most prevalent form of diabetes in adults, the dramatic rise in childhood obesity over the past few decades has led to a markedly increased incidence of this disease in children and adolescents. Pediatric T2DM may account for up to 80% of the new cases of diabetes in high-risk populations such as obese adolescents of African or Hispanic population ancestry (see Chapter 60). It is now apparent that childhood onset T2DM differs from adult disease in that it is associated with a more rapid decline in β-cell function and the earlier development of T2DM-related complications.

The presentation of T2DM is typically more insidious than that with T1DM. In contrast to patients with T1DM who are usually ill at the time of diagnosis and whose presentation rarely spans more than a few weeks, children with T2DM often seek medical care because of excessive weight gain and fatigue as a result of insulin resistance and/or the incidental finding of glycosuria during routine physical examination. A history of polyuria and polydipsia is not always a cardinal clinical feature in these patients. **Acanthosis nigricans** (dark pigmentation of skin creases in the nape of the neck especially), a sign of insulin resistance, is present in the majority of patients with T2DM and is accompanied by a relative hyperinsulinemia at the time of the diagnosis. However, the serum insulin elevation is usually disproportionately lower than that of age-, weight-, and sex-matched nondiabetic children and adolescents, suggesting a state of insulin insufficiency. Healthy lifestyle interventions and treatment with metformin remain the cornerstones of T2DM treatment in children and adolescents; however, insulin therapy is often required to control hyperglycemia. There is a strong heritable component to T2DM, although the genetic basis remains poorly understood. Population-based studies have linked T2DM risk with polymorphisms in a large number of genes related to insulin secretion, insulin action, energy expenditure, and birthweight; however, the collective contribution of these variants to overall T2DM risk remains low at <20%.

Other Specific Types of Diabetes

Monogenic Diabetes

The term monogenic diabetes is used to refer to a heterogeneous group of single-gene disorders resulting in impaired insulin secretion. This category encompasses **maturity-onset diabetes of the young (MODY)** as well as **transient or permanent neonatal diabetes (TND or PND**). Characteristics of monogenic diabetes can include age of onset prior to 6 mo (for TND or PND), development of hyperglycemia prior to age 25 yr of age, and strong family history of diabetes. Monogenic etiologies are estimated to comprise anywhere from 1% to 10% of all diabetes cases, with the uncertainty related to the clinical difficulty in differentiating these cases from T1DM and T2DM. Monogenic forms of diabetes may present with hyperglycemia, and consequent polyuria and polydipsia, or may be diagnosed simply by routine screening. Extra-pancreatic manifestations vary by genetic defect (see Table 607.19), and can include hepatic, renal, and CNS manifestations. Treatment is guided by genetic diagnosis and clinical course, with some forms being responsive to oral sulfonylureas and others requiring insulin replacement. *Children diagnosed with diabetes prior to 6 mo of age should have genetic testing for TND/PND, and older individuals with diabetes not characteristic of T1DM or T2DM in the setting of a family history of diabetes should have MODY genetic testing.* A comparison of the 4 types of diabetes is noted in Table 607.3 .

Table 607.3

Key Features of Diabetes in Pediatric Patients

	TYPE 1 DIABETES	TYPE 2 DIABETES	MATURITY-ONSET DIABETES IN THE YOUNG	NEONATAL DIABETES
Age at diagnosis	6 mo-18 yr	Puberty; rarely younger than 10 yr	Younger than 25 yr	Younger than 6 mo
Causes and genetic factors	Autoimmune; genetic predisposition (HLA and other genes)	Obesity; genetic and ethnic predisposition	Autosomal dominant; HNF1A, HNF4A, GCK, HNF1B (rare)	KCNJ11, ABCC8, INS, and other genes
Associated features	Lean or weight loss at diagnosis; thyroid autoimmunity;	Obesity; acanthosis nigricans; polycystic ovarian syndrome; hypertension; hyperlipidemia; fatty liver disease; family history	Lean or weight loss at diagnosis; GCK mutations are asymptomatic	Failure to thrive

	celiac disease			
Diabetic ketoacidosis at presentation	Yes; about 25%	Yes; 5–20%	No	Yes
Treatment	Insulin	Lifestyle modification; metformin; insulin	Sulfonylurea; no treatment for GCK mutations	Sulfonylurea for KCJN11 and ABCC8 mutations; insulin for other mutations

From Cameron FJ, Wherrett DK: Care of diabetes in children and adolescents: controversies, changes, and consensus. *Lancet* 385:2096–2104, 2015, Table 1.

Other Etiologies of Diabetes

Examples include diabetes secondary to exocrine pancreatic diseases (cystic fibrosis), other endocrine diseases (Cushing syndrome), infection, and ingestion of certain drugs or poisons (the rodenticide Vacor). In organ transplantation survivors, there is a linkage between cyclosporine and tacrolimus and posttransplantation DM, ascribed to a number of mechanisms. Certain genetic syndromes, including those with abnormalities of the insulin receptor or the immune system are also included in this category.

Prediabetes

The term prediabetes is used to identify individuals with abnormalities in blood glucose homeostasis who are at increased risk for the development of diabetes (see Table 607.2). Prediabetes is defined by **impaired fasting glucose** (IFG, fasting glucose 100-125 mg/dL [5.6-6.9 mmol/L]), **impaired glucose tolerance** (IGT, 2 hr postprandial glucose 140-199 mg/dL (7.8-11 mmol/L), or hemoglobin A$_{1c}$ (HbA$_{1c}$) values of 5.7–6.4% (39-47 mmol/mol). A fasting glucose concentration of 99 mg/dL (5.5 mmol/L) is the upper limit of normal. This choice is near the level above which acute-phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of the development of microvascular and macrovascular complications. Many individuals with IFG are euglycemic in their daily lives and may have normal or nearly normal HbA$_{1c}$ levels. Individuals with IFG often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized oral glucose tolerance test.

Prediabetes is not a clinical entity but rather a risk factor for future diabetes and cardiovascular disease. This may be observed as an intermediate stage in any of the disease processes listed in Table 607.1 . Prediabetes is often associated with the **insulin resistance syndrome** (also known as **metabolic syndrome**), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride or low- or high-density lipoprotein type, or both, and hypertension. Insulin resistance is directly involved in the pathogenesis of T2DM.

607.2

Type 1 Diabetes Mellitus (Immune Mediated)

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Keywords

type 1 diabetes
monogenic diabetes
autoimmune polyendocrine syndrome
major histocompatibility complex
hygiene hypothesis
microbiome
autoimmunity
diabetic ketoacidosis
insulin pumps
closed-loop systems
continuous glucose monitoring systems
hemoglobin A1c
diabetic retinopathy
diabetic nephropathy
diabetic neuropathy
diabetic osteopathy
islet cell transplantation

Epidemiology

T1DM accounts for approximately 10% of all cases of diabetes in all ages, affecting up to 3 million people in the United States and more than 15 million people in the world. A study using population-based estimates of diabetes incidence and prevalence indicated that approximately 15,000 youths are diagnosed with T1DM each year. While T1DM accounts for most cases of diabetes in childhood, it is not limited to this age group; new cases continue to present in adult life and between 25 and 50% of individuals with T1DM present as adults. The incidence of T1DM is highly variable among different ethnic groups (see Fig. 607.1). The overall age-adjusted incidence of T1DM varies from 0.7 in 100,000 per year in Karachi (Pakistan) to more than 40 in 100,000 per year in Finland. The incidence of T1DM is increasing in most (but not all) populations and this increase appears to be most marked in populations where the incidence of autoimmune diseases was historically low. Data from Western European diabetes centers suggest that the annual rate of increase in T1DM incidence is 2–5%, whereas some central and eastern European countries demonstrate an even more rapid increase—up to 9%. The rate of increase is greatest among the youngest children. In the United States, the overall prevalence of diabetes among school-age children is approximately 1.9 in 1,000, increasing from a prevalence of 1 in 1,430 children at 5 yr of age to 1 in 360 children at 16 yr of age. Among African Americans, the occurrence of T1DM is 30–60% of that seen in American whites. The annual incidence of new cases in the United States is approximately 19.7 in 100,000 among youth younger than 10 yr and 18.6 in 100,000 of those older than 10 yr. It is estimated that 30,000 new cases occur each year in the United States, affecting 1 in 300 children and as many as 1 in 100 adults during the life span. Rates are similar or higher in most Western European countries and significantly lower in Asia and Africa.

Females and males are almost equally affected, with a modest male preponderance in some populations (Western European/U.S.) and a female preponderance in others (Japanese); there is no apparent correlation with socioeconomic status. Peaks of presentation occur in 2 age groups: at 5-7 yr of age and at the time of puberty. The 1st peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the 2nd peak may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion (which antagonizes insulin). The understanding of the cause of diabetes or of its increased incidence remains elusive. A growing number of cases are presenting between 1 and 2 yr of age, especially in high-risk groups; the average age of presentation is older in low-risk populations. Low-risk groups that migrate to a high-risk country seem to acquire the increased risk of that country. On the other hand, there can be marked differences in incidence rates in various ethnic groups within the same country; for example, incidence rates (per 100,000) in the 10-14 yr age group in the United States range from a low of 7.1 in Native Americans, to 17.6 in Hispanics, 19.2 in African Americans, and 32.9 in whites.

Genetics

There is a clear familial clustering of T1DM, with prevalence in siblings approaching 8%, whereas the prevalence in the general population in the United States is only 0.4%. Risk of T1DM is also increased when a parent has T1DM and this risk differs between the 2 parents; the risk is 3–4% if the mother is affected but 5–6% when the father is affected. In monozygotic twins, the concordance rate ranges from 30% to 65%, whereas dizygotic twins have a concordance rate of 6–10%. Because the concordance rate of dizygotic twins is higher than the sibling risk, factors other than the shared genotypes (e.g., the shared intrauterine environment) may play a role in increasing the risk in dizygotic twins. Furthermore, the genetic susceptibility for T1DM in the parents of an affected child is estimated at 3%. It should be kept in mind that although there is a large genetic component in T1DM, 85% of newly diagnosed type 1 diabetic patients do not have a family member with T1DM. Thus, we cannot rely on family history to identify patients who may be at risk for the future development of T1DM as most cases will develop in individuals with no such family history.

Monogenic Type 1 Diabetes Mellitus

Classic single-gene defects are an extremely rare cause of autoimmune mediated T1DM. The **IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome** is caused by mutations of the *FOXP3* and other genes. The *FOXP3* (forkhead box P3) is a gene involved in immune system responses. A member of the FOX protein family, *FOXP3* appears to function as the master regulator in the development and function of regulatory T cells. These mutations lead to the lack of a major population of regulatory T lymphocytes with resulting overwhelming autoimmunity and development of diabetes (as early as 2 days of age) in approximately 80% of the children with this disorder.

Wolfram syndrome (DIDMOD: diabetes insipidus, diabetes mellitus, optic atrophy, deafness) is an autosomal recessive disease due predominantly to mutations in the *WFS1* gene and is a progressive neurodegenerative disease. Case definition requires the presence of T1DM and optic atrophy. This syndrome may be present in ~5% of patients with T1DM.

APS-1 (autoimmune polyendocrinopathy syndrome type 1) is caused by mutations of the *AIRE* (autoimmune regulator) gene, leading to abnormalities in expression of peripheral antigens within the thymus and/or abnormalities of negative selection in the thymus. This results in widespread autoimmunity. Approximately 18% of children with this syndrome develop T1DM.

Genes Altering the Risk of Autoimmune Type 1 Diabetes Mellitus

The risk of developing T1DM is modified by the influence of several risk loci. The genomic region with by far the greatest contribution to the risk of T1DM is the MHC on chromosome 6p21. Outside of the MHC, genome wide association studies have identified T1DM to be associated with at least 100 different single nucleotide polymorphisms, from which about 50 genes have emerged as potentially causal. Notable high-risk loci include insulin *(INS)* , protein tyrosine phosphatase nonreceptor type 22 *(PTPN22)* , interleukin 2 receptor α subunit (*IL2RA),* cytotoxic T-lymphocyte antigen 4 *(CTLA4)* , interferon-induced with helicase C domain 1 *(IFIH1),* v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 *(ERBB3),* and BCL2-associated agonist of cell death (*BAD.)* The contribution of each non-MHC locus to T1DM risk is small, making individual variants less useful for predicting the genetic risk of T1DM in a given patient. However, the determination of genetic risk scores from both MHC and non-MHC variants has shown promise in the ability to discriminate T1DM from T2DM in individuals and may one day become a clinically useful tool. On balance, the known functions of these genes suggest the primary etiologic pathways of diabetes, namely, HLA class II and class I molecules binding, T and β-cell activation, innate pathogen viral responses, chemokine and cytokine signaling, and T regulatory and antigen-presenting cell functions.

Major Histocompatibility Complex/Human Leukocyte Antigen Encoded Susceptibility to

Type 1 Diabetes Mellitus

The MHC is a large genomic region that contains a number of genes related to immune system function in humans. These genes are further divided into HLA classes I, II, III, and IV genes. Class II genes are the ones most strongly associated with risk of T1DM, but some of the risk associated with various HLA types is a result of variation in genes in HLA classes other than class II. Overall, genetic variation in the HLA region can explain 40–50% of the genetic risk of T1DM.

Some of the known associations include the HLA DR3/4-DQ2/8 genotype; compared to a population prevalence of T1DM of approximately 1 in 300, DR3/4-DQ2/8 newborns from the general population have a 1 in 20 genetic risk. This risk of development of T1DM is even higher when the high-risk HLA haplotypes are shared with a sibling or parent with T1DM. Thus, if 1 sibling has T1DM and shares the same high-risk DR3/4-DQ2/8 haplotype with another sibling, then the risk of autoimmunity in the other sibling is 50%. Moreover, this risk approaches 80% when siblings share both HLA haplotypes identical by descent. This is known as the *relative paradox* and points to the existence of other shared genetic risk factors (most likely in the extended HLA haplotype).

With advances in genotyping, further discrimination is possible and we can identify more specific risk ratios for specific haplotypes. For example, the DRB1*0401-DQA1*0301g-DQB1*0302 haplotype has an odds ratio (OR) of 8.39, whereas the DRB1*0401-DQA1*0301g-DQB1*0301 has an OR of 0.35, implicating the DQB1*0302 allele as a critical susceptibility allele. There are some dramatically protective DR-DQ haplotypes (e.g., DRB1*1501-DQA1*0102-DQB1*0602 [OR = 0.03], DRB1*1401-DQA1*0101-DQB1*0503 [OR = 0.02], and DRB1*0701-DQA1*0201-DQB1*0303 [OR = 0.02]). The DR2 haplotype (DRB1*1501-DQA1*0102-DQB1*0602) is dominantly protective and is present in 20% of the general population but is seen in only 1% of patients with T1DM.

Role of Aspartate at Position 57 in DQB1

DQB1*0302 (high risk for diabetes) differs from DQB1*0301 (protective against diabetes) only at position 57, where it lacks an aspartic acid residue. The DQB1*0201 allele (increased risk for diabetes) also lacks aspartic acid at position 57, and it has been proposed that the presence of aspartate at this position alters the protein recognition and protein binding characteristics of this molecule. Although the absence of aspartate at this position appears to be important in most studies on white individuals, it does not have the same role in Korean and Japanese populations. Moreover, certain low-risk DQB1 genotypes also lack aspartic acid at position 57, including DQB1*0302/DQB1*0201 (DR7) and DQB1*0201 (DR3)/DQB1*0201 (DR7). Thus, the presence of aspartate at this position is usually, but not always, protective in white populations but not necessarily in other populations.

Role of Human Leukocyte Antigen Class I

Although the alleles of class II HLA genes appear to have the strongest associations with diabetes, recent genotyping studies and analyses of pooled data have identified associations with other elements in the HLA complex, especially HLA-A and HLA-B. The most significant association is with HLA-B39, which confers high risk for T1DM in 3 different populations, makes up the majority of the signal from HLA-B, and is associated with a lower age of onset of the disease.

Non-MHC/HLA Genes Associated With T1DM Risk

The second locus found to be associated with risk of T1DM was localized to a region upstream of the insulin gene *(INS)*. Susceptibility in this region has been primarily mapped to a variable number of tandem repeats approximately 500 bp upstream of the insulin gene. This highly polymorphic region consists of anywhere from 30 to several hundred repeats of a 14-15 bp unit sequence (ACAGGGGTCTGGGG). The high-risk allele has been found to be associated with lower insulin and mRNA production in the thymus, suggesting a possible mechanism for decreased immune tolerance to insulin. A number of candidate genes linked to T1DM susceptibility have also been associated with increased risk of other autoimmune disease. These include the genes *PTPN22*, *IL2RA*, *CTLA4*, and *IFIH1*, which are involved in immune system regulation. Others, such as *ERBB3* and *BAD* are thought to be associated with cell apoptosis.

Environmental Factors

That ~50% of monozygotic twins are discordant for T1DM, the variation seen in urban and rural areas populated by the same ethnic group, the change in incidence that occurs with migration, the increase in incidence that has been seen in almost all populations in the last few decades, and the occurrence of seasonality all provide evidence that environmental factors also play a significant role in the causation of T1DM.

Viral Infections

It is possible that various viruses do play a role in the pathogenesis of T1DM, but no single virus, and no single pathogenic mechanism, stands out in the environmental etiology of T1DM. Instead, a variety of viruses and mechanisms may contribute to the development of diabetes in genetically susceptible hosts. Invoked mechanisms involve direct infection of β-cells by viruses resulting in lysis and release of self-antigens, direct viral infection of antigen-presenting cells causing increased expression of cytokines, and molecular mimicry, which is the notion that viral antigens exhibit homology to self-epitopes.

Congenital Rubella Syndrome

The clearest evidence of a role for viral infection in human T1DM is seen in congenital rubella syndrome. Prenatal infection with rubella is associated with β-cell autoimmunity in up to 70%, with development of T1DM in up to 40% of infected children. The time lag between infection and development of diabetes may be as high as 20 yr. T1DM after congenital rubella is more likely in patients that carry the higher-risk genotypes. Interestingly, there appears to be no increase in risk of diabetes when rubella infection develops after birth or when live-virus rubella immunization is used.

Enteroviruses

Studies show an increase in evidence of enteroviral infection in patients with T1DM and an increased prevalence of enteroviral RNA in prenatal blood samples from children who subsequently develop T1DM. In addition, there are case reports of association between enteroviral infection and subsequent T1DM, but the true significance of these infections remains unknown at this time.

Mumps Virus

It has been variably observed that mumps infection leads to the development of β-cell autoimmunity with high frequency and to T1DM in some cases. Although mumps may play a role in some cases of diabetes, the fact that T1DM diabetes incidence has increased steadily in several countries after universal mumps vaccination was introduced and that the incidence is extremely low in several populations where mumps is still prevalent indicates that mumps alone is not a major causal factor in diabetes.

The Hygiene Hypothesis: Possible Protective Role of Infections

Although some viral infections may increase the risk of T1DM, infectious agents may also play a protective role against diabetes. The hygiene hypothesis states that T1DM is a disease of industrialized countries, where the observation that there are fewer infections implies that the immune system is less-well trained for its main task, namely host defense. Some call this theory the *microbial deprivation hypothesis* . The hygiene hypothesis states that lack of exposure to childhood infections may increase an individual's chances of developing autoimmune diseases, including T1DM. Rates of T1DM and other autoimmune disorders are generally lower in underdeveloped nations with a high prevalence of childhood infections and tend to increase as these countries become more developed. The incidence of T1DM differs almost 6-fold between Russian Karelia and Finland, even though both are populated by genetically related populations and are adjacent to each other and at the same latitude. The incidence of autoimmunity in the 2 populations varies inversely with immunoglobulin (Ig) E antibody levels, and IgE is involved in the response to parasitic infestation. All these observations indicate that decreased exposure to certain parasites and other microbes in early childhood may lead to an increased risk of autoimmunity in later life, including autoimmune diabetes. On the other hand, retrospective case-control studies have been equivocal at best and direct evidence of protection by childhood infections is still lacking.

Gastrointestinal Microbiome

There has been great interest in better understanding the role of the gastrointestinal microbiome on health. There is emerging evidence from both animal and human studies that the gut microbiome is altered in T1DM, however a cause and effect relationship has yet to be established. Human studies have found that the gut microbiome in T1DM has decreased diversity of microbial species and contains fewer butyrate-producing organisms compared to healthy controls. Butyrate is a short-chain fatty acid that is thought to be antiinflammatory and may have a role in protecting the gut epithelium either directly or indirectly through an effect to increase mucin production. Theoretically, a disruption in epithelial integrity (the so-called leaky gut) could trigger inflammation and an enhanced autoimmune response as a result of increased entry of pathogenic or dietary antigens into the bloodstream. Early, small-scale prospective studies in infants and children at high risk for T1DM have shown an imbalance favoring species including *Bacteroides dorei* and *Bacteroides vulgatus* among individuals who went on to develop T1DM autoantibodies or disease compared to those who did not. A larger study across 6 different study sites in The Environmental Determinants of Diabetes in the Young (TEDDY) study identified significant geographic differences in fecal microbiome composition, highlighting the challenges in this field of study. Another gastrointestinal–T1DM relationship is noted in the co-occurrence of celiac disease with T1DM. Both are autoimmune disorders with each having disease-specific autoantibodies, and that immune-based predisposition may lead to both diseases. Alternately, intestinal mucosal injury may trigger events that lead to T1DM.

Diet

Dietary exposure may modify T1DM risk; however, a definitive link between any single dietary exposure and T1DM development has not been found. Early studies supported an association between early milk and/or gluten introduction and T1DM risk; however, subsequent studies have been inconsistent and in many cases refuted these findings. Furthermore, the majority of interventions studied have not shown an effect of delayed gluten exposure or the use of hydrolyzed formula to reduce the risk for development of T1DM autoantibodies of disease. A 2016 meta-analysis of both interventional and observational studies concluded that there was no association between early exposure of gluten or milk protein and risk of T1DM. Some, but not all, studies have suggested that breastfeeding lowers the risk of T1DM. The potential mechanism for a protective effect of breast milk is not well understood but could be related to a beneficial effect of breast milk on the infant immune system or an indirect effect such as reduced exposure to other dietary antigens early in life. Timing of solid food introduction may modify T1DM risk, as seen in a report from the Diabetes Autoimmunity Study in the Young (DAISY) which found that both early (before 4 mo of age) and late (after 6 mo of age) introduction of solid foods predicted development of T1DM.

Other dietary factors that have been suggested at various times as playing a role in T1DM risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E. Vitamin D is biologically plausible (it has a role in immune regulation), and deficiency is more common in northern countries like Finland where T1DM incidence is highest; however most observational studies have failed to find associations between vitamin D level or supplementation and T1DM risk. Interventional studies to assess effect of vitamin D supplementation on T1DM risk are lacking.

Psychologic Stress

Several studies show an increased prevalence of stressful psychologic situations among children who subsequently developed T1DM. Whether these stresses only aggravate preexisting autoimmunity or whether they can actually trigger autoimmunity through epigenetic mechanisms remains unknown.

Pathogenesis and Natural History of Type 1 Diabetes Mellitus

In T1DM, a genetically susceptible host develops autoimmunity against the host's own β-cells. What triggers this autoimmune response is complex and multifactorial. In some (but not all) patients, this immune mediated process results in progressive destruction of β-cells until a critical mass of β-cells is lost and insulin deficiency develops. Insulin deficiency, in turn, leads to the onset of clinical signs and symptoms of T1DM. At the time of diagnosis, if viable β-cells are still present and produce some insulin, there may be a partial remission of the disease (honeymoon period) but over time, more β-cell mass is destroyed, despite any regeneration and/or persistence of β-cell, and the patient becomes totally dependent on exogenous insulin for survival (Fig. 607.2). Over time, some of these patients develop secondary complications of diabetes that appear, in part, to be related to how well-controlled the diabetes has been. Thus, the natural history of T1DM involves some or all of the following stages, with 2 distinct identifiable stages prior to onset of symptoms:

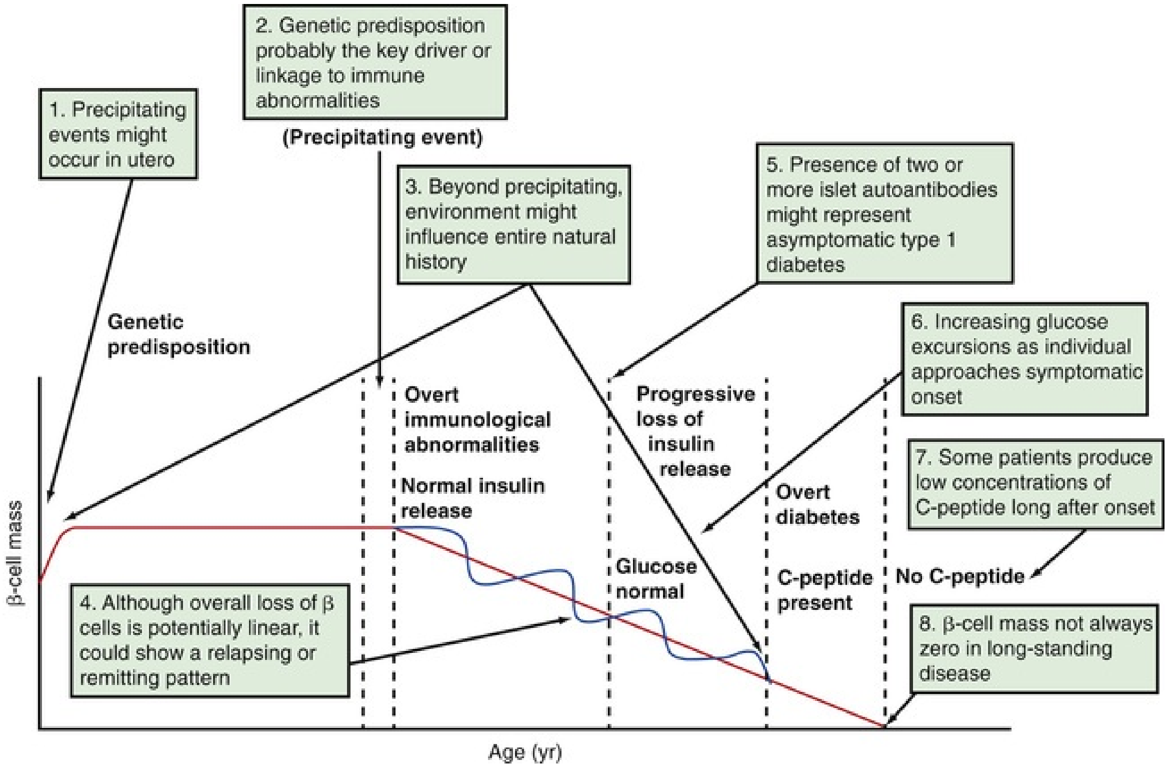
1. Precipitating events might occur in utero
2. Genetic predisposition probably the key driver or linkage to immune abnormalities
(Precipitating event)
3. Beyond precipitating, environment might influence entire natural history
5. Presence of two or more islet autoantibodies might represent asymptomatic type 1 diabetes
6. Increasing glucose excursions as individual approaches symptomatic onset
7. Some patients produce low concentrations of C-peptide long after onset
8. β-cell mass not always zero in long-standing disease
4. Although overall loss of β cells is potentially linear, it could show a relapsing or remitting pattern
Genetic predisposition
Overt immunological abnormalities
Normal insulin release
Progressive loss of insulin release
Glucose normal
Overt diabetes
C-peptide present
No C-peptide
β-cell mass
Age (yr)

FIG. 607.2 The natural history of T1DM—a 25 yr old concept revisited. A recreation of the model of T1DM, originally proposed in 1986, is shown in *black.* Additions and conjectures based on recent knowledge gains are shown in *green* . (From Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes. *Lancet* 383:69–78, 2014, Fig. 4.)

1. presence of 2 or more islet autoantibodies with normoglycemia and presymptomatic; can last years to decades
2. β-cell autoimmunity with dysglycemia and presymptomatic; shorter
3. Onset of symptomatic disease; usually quite brief, weeks, rarely months
4. Transient remission, usually within weeks of onset, may last 6-12 mo
5. Established disease, lifelong
6. Development of complications, quite variable

Initiation of Autoimmunity

Genetic susceptibility to T1DM is determined by several genes (see Genetics below), with the largest contribution coming from variants in the HLA system. Nonetheless even with the highest-risk haplotypes, most carriers will *not* develop T1DM. Even in monozygotic twins, the concordance is 30 to as high as 70%. The observed rise in incidence of T1DM, and particularly so in younger children within an essentially genetically stable patient population implies that something has accordingly changed in the environment. A number of factors, including maternal and intrauterine environmental influences, route of neonatal delivery, foods and diet in infancy, viral infections, lack of exposure to certain infections and antibiotic use, host microbiome, even psychologic stress, are implicated in the pathogenesis of T1DM, but their exact role and the mechanism by which they trigger or aggravate autoimmunity remains uncertain. What is clear is that markers of autoimmunity are much more prevalent than clinical T1DM, indicating that initiation of autoimmunity is a necessary but not a sufficient condition for T1DM. While so far no conclusive triggering factor has been identified, it seems that in most cases of T1DM that are diagnosed in childhood, the onset of autoimmunity occurs very early in life. In a majority of the children diagnosed before age 10 yr, the first signs of autoimmunity appear before age 2 yr. Development of autoimmunity is associated with the appearance of several autoantibodies. IAAs are usually the first to appear in young children, followed by glutamic acid decarboxylase 65 kDa, and later by tyrosine phosphatase insulinoma–associated 2 and zinc transporter 8 antibodies. The earliest antibodies are predominantly of the IgG_1 subclass. Not only is there spreading of autoimmunity to more antigens (IAA, and then glutamic acid decarboxylase 65 and insulinoma-associated 2 and zinc transporter 8) but there is also epitope spreading within 1 antigen. Initial glutamic acid decarboxylase 65 antibodies tend to be against the middle region or the carboxyl-terminal region, whereas aminoterminal antibodies usually appear later and are less common in children.

Preclinical Autoimmunity With Progressive Loss of β-Cell Function

In nearly all patients, the appearance of autoimmunity is followed by progressive or eventual destruction of β-cells (Figs. 607.3 and 607.4). Antibodies are a marker for the presence of autoimmunity, but the actual damage to the β-cells is primarily T-cell mediated (see Fig. 607.4). Histologic analysis of the pancreas from patients with recent-onset T1DM reveals insulitis, with an infiltration of the islets of Langerhans by mononuclear cells, including T and B lymphocytes, monocytes/macrophages, and natural killer cells. In the nonobese diabetic mouse, a similar cellular infiltrate is followed by linear loss of β-cells until they completely disappear. But it appears that the process in human T1DM is not necessarily linear and there may be an undulating downhill course, with remissions and relapses, in the development of T1DM.

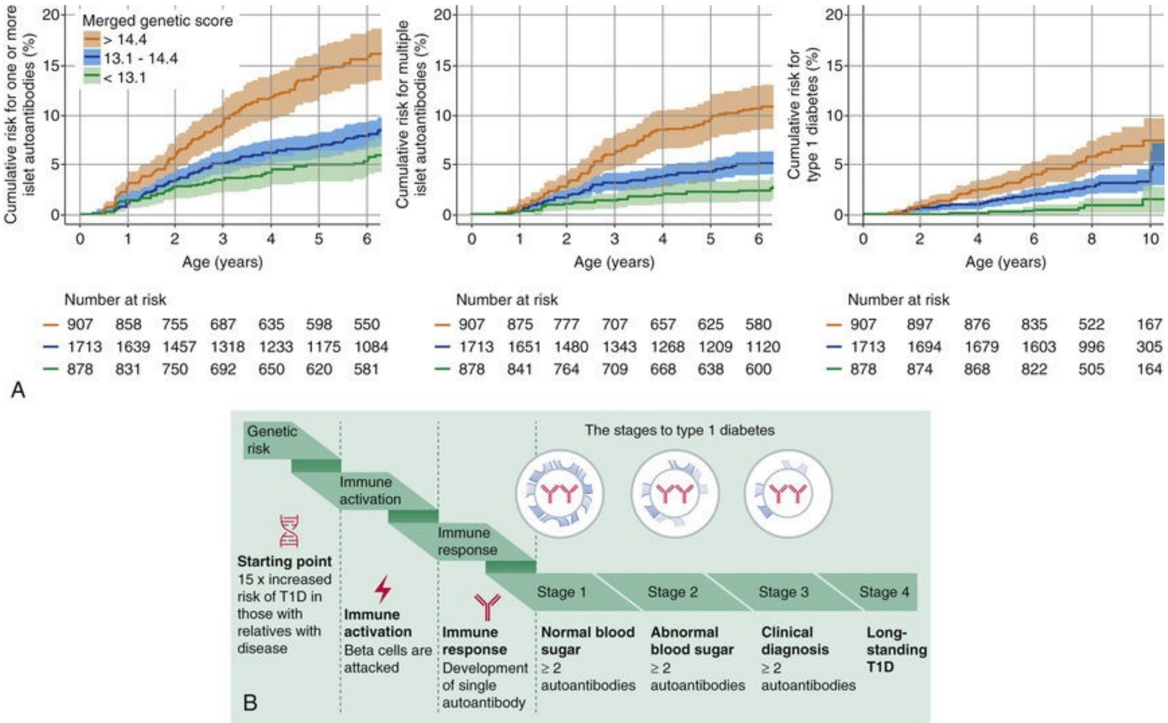

FIG. 607.3 **Factors contributing and disease progression to type 1 diabetes. A, Cumulative risks of one or more islet autoantibody, multiple islet autoantibody, and type 1 diabetes development in TEDDY children with the HLA DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8 genotype stratified by their merged score. The cumulative risk of developing 1 or more islet autoantibodies *(left graph)* , multiple islet autoantibodies *(middle graph)* , and type 1 diabetes (*right graph, y-* axis) is shown relative to age in years (*x* -axis) and was calculated using the Kaplan±Meier method. Curves are shown for children with genetic scores in the upper *(orange line)* , lower *(green line)* , and two middle *(blue line)* quartiles. The shaded areas represent the 95% confidence interval of the cumulative risk. The numbers at risk indicate the number of children included in the analysis at each age. B, Type 1 diabetes progression and stages of type 1 diabetes. Stage 1 is the start of type 1 diabetes, marked by individuals having 2 or more diabetes-related autoantibodies and normal blood sugar concentrations. In stage 2, individuals have dysglycemia without symptoms. Stage 3 is the time of clinical diagnosis. T1D, type 1 diabetes. (A, from Bonifacio E, Beyerlein A, Hippich M, et al: Genetic scores to stratify risk of developing multiple islet autoantibodies and type 1 diabetes” a prospective study in children. *PLoS Med* 15(4):e1002548. Fig. 4; B, from Greenbaum CJ,**

Speake C, Krischer J, et al: Strength in numbers: opportunities for enhancing the development of effective treatments for type 1 diabetes—the TrialNet experience. *Diabetes* 67(7):1216–1225, 2018.)

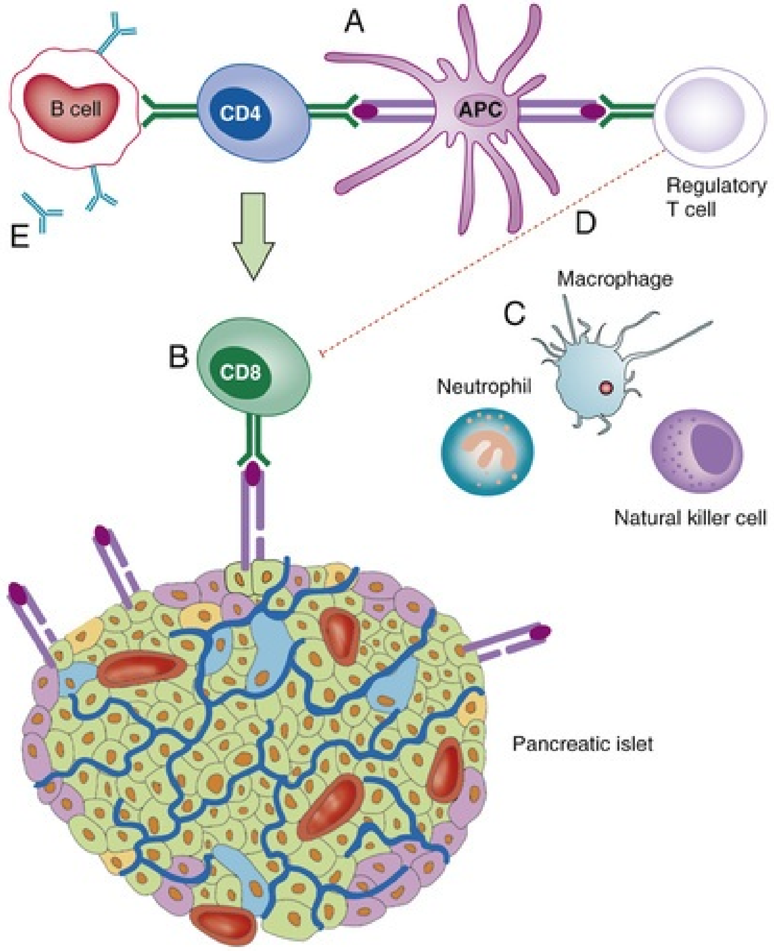

FIG. 607.4 **The immunopathogenesis of type 1 diabetes. The development of type 1 diabetes is thought to be initiated by the presentation of β-cell peptides by antigen-presenting cells *(APCs)* . APCs bearing these autoantigens migrate to the pancreatic lymph nodes where they interact with autoreactive CD4+ T lymphocytes, which in turn mediate the activation of autoreactive CD8+ T cells *(A)* . These activated CD8+ T cells return to the islet and lyse β cells expressing immunogenic self-antigens on major histocompatibility complex class I surface molecules *(B)* . β-Cell destruction is further exacerbated by the release of proinflammatory cytokines and reactive oxygen species from innate immune cells (macrophages, natural killer cells, and neutrophils) *(C*). This entire process is amplified by defects in regulatory T lymphocytes, which do not effectively suppress autoimmunity *(D)* . Activated T cells within the pancreatic lymph node also stimulate B lymphocytes to produce autoantibodies against β-cell proteins. These autoantibodies can be measured in circulation and are considered a defining biomarker of type 1 diabetes *(E)* . (From DiMeglio LA, Evans-Molina C, Oram RA: Type 1 diabetes. *Lancet* 391:2449–2458, 2018, Fig. 3.)**

Role of Autoantibodies

Even though T1DM does not occur as a direct consequence of autoantibody formation, the risk of developing clinical disease increases dramatically with an increase in the number of antibodies; only 30% of children with 1 antibody will progress to diabetes, but this risk increases to 70% at 10 yr when 2 antibodies are present and 90% when 3 are present (see Fig. 607.3). The risk of progression also varies with the intensity of the antibody response and those with higher antibody titers are more likely to progress to clinical disease. Another factor that appears to influence progression of β-cell damage is the age at which autoimmunity develops; children in whom IAAs appeared within the 1st 2 yr of life rapidly developed anti–islet cell antibodies and progressed to diabetes more frequently than children in whom the first antibodies appeared between ages 5 and 8 yr.

Role of Genetics in Disease Progression

In a large study of healthy children, the appearance of single antibodies is relatively common and usually transient and does not correlate with the presence of high-risk HLA alleles, but those carrying high-risk HLA alleles are more likely to develop multiple antibodies and progress to disease. Similarly, the appearance of antibodies is more likely to predict diabetes in those with a family history of diabetes versus those with no family history of T1DM. Thus it may be the case that environmental factors can induce transient autoimmunity in many children, but those with genetic susceptibility are more likely to see progression of autoimmunity and eventual development of diabetes.

Role of Environmental Factors

Environmental factors may also act as accelerators of T1DM after the initial appearance of autoimmunity. This is evident from the fact that the incidence of T1DM can vary several-fold between populations that have the same prevalence of autoimmunity. For instance, the incidence of T1DM in Finland is almost 4-fold higher than in Lithuania, but the incidence of autoimmunity is similar in both countries.

The fact that all children with evidence of autoimmunity and of autoreactive T cells do not progress to diabetes indicates that there are checkpoints at which the autoimmune process can be halted or reversed before it progresses to full-blown diabetes.

Onset of Clinical Disease

Patients with progressive β-cell destruction will eventually present with clinical T1DM. It was thought that 90% of the total β-cell mass is destroyed by the time clinical disease develops, but later studies have revealed that this is not always the case. It appears that β-cell destruction is more rapid and more complete in younger children, while in older children and adults the proportion of surviving β-cells is greater (10–20% in autopsy specimens) and some β-cells (about 1% of the normal mass) survive up to 30 yr after the onset of diabetes. Because autopsies are usually done on patients who died of diabetic ketoacidosis (DKA), these figures may underestimate the actual β-cell mass present at diagnosis. Functional studies indicate that up to 40% of the insulin secretory capacity may be preserved in adults at the time of presentation of T1DM. Ultrasensitive assays indicate that C-peptide production is measurable decades after onset of T1DM. The fact that newly diagnosed diabetic individuals may still have a significant surviving β-cell mass is important because it raises the possibility of *secondary* prevention of T1DM. Similarly, the existence of viable β-cells years or decades after initial presentation indicates that even patients with long-standing diabetes may be able to exhibit some recovery of β-cell function if the autoimmune destructive process could be halted and if islet cell regeneration could occur.

Prediction and Prevention

Autoimmunity precedes clinical T1DM, and indicators of maturing autoimmune responses may be useful markers for disease prediction. Individuals at risk for T1DM can be identified by a combination of genetic, immunologic, and metabolic markers. The most informative genetic locus, HLA class II, confers about half of the total genetic risk but has a low positive predictive value (PPV) when used in the general population. Autoantibodies provide a practical readout of β-cell autoimmunity, are easily sampled in venous blood, and have become the mainstay of T1DM prediction efforts. By comparison, and even though T lymphocytes mediate beta cell destruction, T cells are rare in blood, and assays of their function have been difficult to standardize and validate. In the first-degree relatives of patients with T1DM, the number of positive autoantibodies can help estimate the risk of developing T1DM: low risk (single autoantibodies: PPV of 2–6%), moderate risk (2 autoantibodies: PPV of 21–40%), and high risk (>2 autoantibodies: PPV of 59–80%) over a 5 yr period. In children carrying the

T1DM highest-risk genotype (HLA-DQB1*0201-DQA1*05/DQB1*0302-DQA1*03), insulitis is almost 10 times more frequent (PPV 21%) than in children with other genotypes (PPV 2.2%). But while autoantibodies are useful for the prediction of T1DM in the relatives of patients with T1DM, outside of that obvious population, the screening of the general population would be required to identify healthy subjects at risk of T1DM. Indeed, ~90% of individuals with new-onset T1DM have no family background of T1DM. Screening the general population is difficult to justify, in part, because the observed autoantibody prevalence greatly exceeds the low disease prevalence in nonrelatives, leading to high false-positive rates.

Pathophysiology

Insulin performs a critical role in the storage and retrieval of cellular fuel. Its secretion in response to feeding is exquisitely modulated by the interplay of neural, hormonal, and substrate-related mechanisms to permit controlled disposition of ingested foodstuff as energy for immediate or future use. Insulin levels must be lowered to then mobilize stored energy during the fasted state. Thus, in normal metabolism, there are regular swings between the postprandial, high-insulin anabolic state and the fasted, low-insulin catabolic state that affect liver, muscle, and adipose tissue (Table 607.4). T1DM is a progressive low-insulin catabolic state in which feeding does not reverse, but rather exaggerates, these catabolic processes. With moderate insulinopenia, glucose utilization by muscle and fat decreases and *postprandial* hyperglycemia appears. At even lower insulin levels, the liver produces excessive glucose via glycogenolysis and gluconeogenesis, and *fasting* hyperglycemia begins. Hyperglycemia produces an osmotic diuresis (glycosuria) when the renal threshold is exceeded (180 mg/dL; 10 mmol/L). The resulting loss of calories and electrolytes, as well as the worsening dehydration, produces a physiologic stress with hypersecretion of stress hormones (epinephrine, cortisol, growth hormone, and glucagon). These hormones, in turn, contribute to the metabolic decompensation by further impairing insulin secretion (epinephrine), by antagonizing its action (epinephrine, cortisol, growth hormone), and by promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, growth hormone, and cortisol) while decreasing glucose utilization and glucose clearance (epinephrine, growth hormone, cortisol).

Table 607.4

Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue*

	HIGH PLASMA INSULIN (POSTPRANDIAL STATE)	LOW PLASMA INSULIN (FASTED STATE)
Liver	Glucose uptake	Glucose production
	Glycogen synthesis	Glycogenolysis
	Absence of gluconeogenesis	Gluconeogenesis
	Lipogenesis	Absence of lipogenesis
	Absence of ketogenesis	Ketogenesis
Muscle	Glucose uptake	Absence of glucose uptake
	Glucose oxidation	Fatty acid and ketone oxidation
	Glycogen synthesis	Glycogenolysis
	Protein synthesis	Proteolysis and amino acid release
Adipose tissue	Glucose uptake	Absence of glucose uptake
	Lipid synthesis	Lipolysis and fatty acid release
	Triglyceride uptake	Absence of triglyceride uptake

[*] Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, untreated, results in exaggerated fasting.

The combination of insulin deficiency and elevated plasma values of the counterregulatory hormones is also responsible for accelerated lipolysis and impaired lipid synthesis, with resulting increased plasma concentrations of total lipids, cholesterol, triglycerides, and free fatty acids. The hormonal interplay of insulin deficiency and glucagon excess shunts the free fatty acids into ketone body formation; the supra-normal rate of formation of these ketone bodies, principally β-hydroxybutyrate and acetoacetate, exceeds the capacity for peripheral utilization and renal excretion. Accumulation of these keto acids results in metabolic acidosis (DKA) and compensatory rapid deep non-dyspneic breathing in an attempt to excrete excess CO_2 (Kussmaul respiration). Acetone, formed by non-enzymatic conversion of acetoacetate, is responsible for the characteristic fruity odor of the breath. Ketones are excreted in the urine in association with cations and thus further increase losses of water and electrolyte and bicarbonate regenerating ability. With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose.

Clinical Manifestations

The classic clinical manifestations of new onset diabetes in children reflect the hyperglycemic and catabolic physiologic state and include polyuria, polydipsia, polyphagia, and weight loss. Other common symptoms include fatigue, weakness, and a general feeling of malaise. Patients presenting with more advanced disease will exhibit signs of **DKA** including dehydration, nausea, vomiting, lethargy, altered mental status, and in extreme cases, coma. If the diagnosis is not recognized, the progression of symptoms follows a predictable course from early intermittent polyuria, to sustained polyuria and weight loss, followed by development of DKA. In most cases, this initial progression occurs over a period of weeks rather than months.

Initially, when only insulin reserve is limited, occasional asymptomatic postprandial hyperglycemia occurs. As insulin secretory capacity declines, blood glucose levels begin to rise. When the blood glucose increases above the renal threshold, intermittent polyuria and/or nocturia begins. With further β-cell loss, chronic hyperglycemia causes a more persistent diuresis, which often includes nocturnal enuresis in younger children. Female patients may develop vulvovaginal candidiasis from the chronic glycosuria. Eventually, daily losses of water and glucose may be as high as 5 L and 250 g, respectively, representing 1,000 calories, or 50%, of the average daily caloric intake. These losses trigger compensatory polydipsia and polyphagia; however progressive dehydration and weight loss will inevitably ensue unless treatment is initiated.

When the disease continues to progress, ketoacids begin to accumulate. At this stage in the disease, rapid clinical deterioration is possible. Ketoacids produce abdominal pain, nausea, and emesis and thereby impede the patient's ability to maintain sufficient oral replacement of urinary water losses. Dehydration accelerates, as manifested by weakness, orthostasis, and further weight loss. As in any hyperosmotic state, the degree of dehydration may be clinically underestimated because intravascular volume is conserved at the expense of intracellular volume. Signs and symptoms of advanced ketoacidosis include Kussmaul respirations (deep, heavy, non-labored rapid breathing), fruity breath odor (acetone), prolonged corrected Q-T interval, diminished neurocognitive function, and coma. Approximately 20–40% of children with new-onset diabetes progress to DKA before diagnosis.

Clinical progression typically happens more quickly in younger children, owing to either more aggressive autoimmune destruction of β-cells and/or to lower β-cell mass. Disease onset in infancy is associated with a greater likelihood of DKA at presentation. Weight loss in younger children and individuals with more rapidly progressive disease will be comprised mostly of acute fluid loss, whereas weight loss in adolescents and individuals with slowly progressive disease will also include significant fat and lean mass deficits as a result of prolonged starvation. In any child, the progression of symptoms may be accelerated by the stress of an intercurrent illness or trauma, when counterregulatory (stress) hormones counter the limited insulin secretory capacity.

Diagnosis

The diagnosis of T1DM is usually straightforward (see Table 607.2). Although most symptoms are nonspecific, the most important clue is an inappropriate polyuria in any child with signs of dehydration and poor weight gain. Hyperglycemia can be identified quickly from capillary blood by use of a glucometer; glycosuria and ketonuria can readily be determined by urine dipstick. Non-fasting blood glucose greater than 200 mg/dL (11.1 mmol/L) with typical symptoms is diagnostic with or without ketonuria. In the obese child, T2DM must be considered (see Type 2 Diabetes Mellitus later). Once hyperglycemia is confirmed, it is prudent to determine whether DKA is present (especially if ketonuria is found) by checking a venous blood sample for bicarbonate and pH, and also to evaluate for electrolyte abnormalities—even if signs of dehydration are minimal. A baseline hemoglobin A_{1c} (HbA_{1c}) will be confirmatory and allows an estimate of the duration of hyperglycemia and provides an initial value by which to compare the effectiveness of subsequent therapy. Falsely low HbA_{1c} levels are noted in hemolytic anemias, pure red cell aplasia, blood transfusions, and anemias associated with hemorrhage, cirrhosis, myelodysplasias, or renal disease treated with erythropoietin. Baseline HbA_{1c} may be higher in African Americans than whites.

Testing for autoimmunity (by assessment of T1DM autoantibodies) (see Chapter 607.1) should be considered in cases where the differentiation between T1DM and T2DM is not apparent and in cases where there is a strong family history suggestive of monogenic diabetes. The presence of other autoimmune diseases associated with T1DM should be sought at or shortly after diagnosis, including celiac disease (by tissue transglutaminase immunoglobulin A [IgA] and total IgA) and autoimmune hypothyroidism (by thyroid-stimulating hormone [TSH] and free or total thyroxine). Because significant physiologic perturbations can affect thyroid and celiac screening tests, individuals with only mild abnormalities should have tests repeated after several weeks prior to instituting therapy. In addition, since there is an increased risk of cardiovascular disease associated with diabetes, it is also recommended to obtain a fasting lipid profile in children ≥10 yr of age once glucose control has been established.

Rarely, a child has transient hyperglycemia with glycosuria while under substantial physical stress or illness. This usually resolves permanently during recovery from the stressors. **Stress-produced hyperglycemia** can reflect a limited insulin reserve temporarily revealed by **elevated** counterregulatory hormones. A child with temporary hyperglycemia should therefore be monitored for the development of symptoms of persistent hyperglycemia and be tested with an HbA_{1c} if such symptoms occur. Formal testing in a child who remains clinically asymptomatic is not necessary.

Routine screening procedures, such as postprandial determinations of blood glucose or screening oral glucose tolerance tests have yielded low detection rates in healthy, asymptomatic children, even among those considered at risk, such as siblings of diabetic children. Accordingly, such screening procedures are not recommended in children.

Treatment

Therapy is tailored to the degree of insulinopenia at presentation. Most children with new-onset T1DM have mild to moderate symptoms, have minimal dehydration with no history of emesis, and have not progressed to ketoacidosis. They can be started on subcutaneous insulin therapy directly. About 20–40% of children with new-onset diabetes present in DKA, which can be arbitrarily classified as mild, moderate, or severe (Table 607.5), and the range of symptoms depends on the degree of ketoacidosis. Cardinal biochemical abnormalities include elevations in blood and urine ketones, an increased anion gap, a decreased serum bicarbonate (or total CO_2) and pH, and an elevated effective serum osmolality. Hyponatremia is commonly present with hyperglycemia and is the result of an osmotic dilution as water shifts into the extracellular fluid. Potassium and phosphate depletion is common after prolonged polyuria but may be masked by acidosis which leads to extracellular shifting of these ions.

Table 607.5

Classification of Diabetic Ketoacidosis

	NORMAL	MILD	MODERATE	SEVERE*
CO_2 (mEq/L, venous) †	20-28	16-20	10-15	<10
pH (venous) †	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

* Severe hypernatremia (corrected Na >150 mEq/L) would also be classified as severe diabetic ketoacidosis.

† CO_2 and pH measurement are method dependent; normal ranges may vary.

Treatment of Diabetic Ketoacidosis

Severe insulinopenia (or lack of effective insulin action) results in a physiologic cascade of events in 3 general pathways:

1. Excessive glucose production coupled with reduced glucose utilization raises serum glucose. This produces an osmotic diuresis, with loss of fluid and electrolytes, dehydration, and activation of the renin–angiotensin–aldosterone axis with accelerated potassium loss. When glucose elevation and dehydration are severe and persist for several hours, the risk of cerebral edema increases.
2. Increased catabolic processes result in cellular losses of sodium, potassium, and phosphate.
3. Increased release of free fatty acids from peripheral fat stores supplies substrate for hepatic ketoacid production. When ketoacids accumulate, buffer systems are depleted, and a metabolic acidosis ensues.

Therapy must address both the initiating event in this cascade (insulinopenia) and the subsequent physiologic disruptions.

Reversal of DKA is associated with inherent risks that include hypoglycemia, hypokalemia, and cerebral edema. Any protocol must be used with caution and close monitoring of the patient. Adjustments based on sound medical judgment may be necessary for any given level of DKA (Tables 607.6 and 607.7).

Table 607.6

Diabetic Ketoacidosis Treatment Protocol

TIME	THERAPY	COMMENTS
1st hr	10-20 mL/kg IV bolus 0.9% NaCl or LR Insulin drip at 0.05 to 0.10 units/kg/hr	Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral edema
2nd hr until DKA resolution	0.45% NaCl: plus continue insulin drip 20 mEq/L KPhos and 20 mEq/L KAc 5% glucose if blood sugar <250 mg/dL (14 mmol/L)	$\text{IV rate} = \frac{85\text{ mL/kg} + \text{maintenance} - \text{bolus}}{23\text{ hr}}$ If K <3 mEq/L, give 0.5-1.0 mEq/kg as oral K solution *or* increase IV K to 80 mEq/L
Variable	Oral intake with subcutaneous insulin	No emesis; CO_2 ≥16 mEq/L; normal electrolytes
Note that the initial IV bolus is considered part of the total fluid allowed in the 1st 24 hr and is subtracted before calculating the IV rate.		
Maintenance (24 hr) = 100 mL/kg (for the first 10 kg) + 50 mL/kg (for the second 10 kg) + 25 mL/kg (for all remaining kg)		
Sample calculation for a 30-kg child:		
1st hr = 300 mL IV bolus 0.9% NaCl or LR		
$\text{2nd and subsequent hr} = \frac{(85\text{ mL} \times 30) + 1750\text{ mL} - 300\text{ mL}}{23\text{ hr}} = \frac{175\text{ mL}}{\text{hr}}$ (0.45% NaCl with 20 mEq/L KPhos and 20 mEQ/LKAc)		

DKA, diabetic ketoacidosis; I/O, input and output (urine, emesis); K, potassium; KAc, potassium acetate; KPhos, potassium phosphate; LR, lactated Ringer solution; NaCl, sodium chloride; NPO, nothing by mouth.

Table 607.7

Starting Doses of Subcutaneous Insulin (units/kg/day)

	NO DIABETIC KETOACIDOSIS	DIABETIC KETOACIDOSIS
Prepubertal	0.25-0.50	0.75-1.0
Pubertal	0.50-0.75	1.0-1.2
Postpubertal	0.25-0.50	0.8-1.0

Hyperglycemia and Dehydration

Insulin must be given to promote movement of glucose into cells, to subdue hepatic glucose production, and to halt the movement of fatty acids from the periphery to the liver. An initial insulin bolus does not speed recovery and may increase the risk of hypokalemia and hypoglycemia. *Therefore, insulin infusion is typically begun without an insulin bolus at a rate of 0.1 units/kg/hr.* This approximates maximal insulin output in normal subjects during an oral glucose tolerance test. Rehydration also lowers glucose levels by improving renal perfusion and enhancing renal excretion. The combination of these therapies usually causes a rapid initial decline in serum glucose levels. Persistent decreases in serum glucose of >100 mg/dL/hr may increase the risk of cerebral edema, therefore careful monitoring of serum glucose and adjustment of the dextrose concentration of the IV fluids is essential. As a general rule of thumb, the dextrose concentration of the IV fluid should be 5% (D5) once serum glucose falls below ~300 mg/dL and 10% once glucose is below 200 mg/dL. The use of a 2-bag system is the preferred approach for managing the dextrose concentrations of the infused IV fluid during DKA (see Table 607.6). A 2-bag system consists of 2 IV bags of identical electrolyte concentrations, where 1 bag contains 0% dextrose (normal saline) and the other contains 10% dextrose in normal saline. The fluids are administered via a Y-site and can be easily titrated to infuse fluids ranging from 0% to 10% dextrose.

Once glucose decreases below ~180 mg/dL (10 mmol/L), the osmotic diuresis stops and rehydration accelerates without further increase in the infusion rate. *Repair of hyperglycemia occurs well before correction of acidosis* . Therefore, insulin is still needed to control fatty acid release and ketosis after normal glucose levels are reached. If serum glucose levels fall below 100 mg/dL despite infusion of D10 containing IV fluids, the IV insulin rate can then be decreased from 0.1 units/kg/hr.

Repair of fluid deficits must be tempered by the potential risk of cerebral edema. It is prudent to approach any child in any hyperosmotic state with cautious rehydration. The effective serum osmolality ($E_{osm} = 2 \times [Na_{uncorrected}] + [glucose]$) is an accurate index of tonicity of the body fluids, reflecting intracellular and extracellular hydration better than measured plasma osmolality. It is calculated with sodium and glucose in mmol/L. This value is usually elevated at the beginning of therapy and should steadily normalize. A rapid decline, or a slow decline to a subnormal range, may indicate an excess of free water entering the vascular space and an increasing risk of cerebral edema. Therefore, patients should not be allowed oral fluids until rehydration is well underway and significant electrolyte shifts are no longer likely. Limited ice chips may be given as a minimal oral intake. All fluid intake and output should be closely monitored.

Calculation of fluid deficits using clinical signs is difficult in children with DKA because intravascular volume is better maintained in the hypertonic state. For any degree of tachycardia, delayed capillary refill, decreased skin temperature, or orthostatic blood pressure change, the child with DKA will be more dehydrated than the child with a normotonic fluid deficit. There remains uncertainty as to the ideal protocol for IV fluid rehydration protocol in DKA. Typically, an initial intravenous bolus of 10-20 mL/kg of glucose-free isotonic sodium salt solution such as Ringer lactate or 0.9% sodium chloride is given over 1 to 2 hr. Further fluid boluses should be given only for hemodynamically unstable patients. This bolus is given as isotonic saline because the patient is inevitably hypertonic, keeping most of the initial infusion in the intravascular space. Subsequent fluid replacement then consists of 0.45% or 0.9% sodium chloride infused at a rate calculated to replace the fluid deficit (after subtracting initial fluid bolus) over 24-48 hr plus maintenance. The fluid deficit can be calculated empirically if a recent weight is available, estimated at 5–10% of body weight based upon clinical severity, or by assuming a standard water deficit (85 mL/kg). Practically, this is generally equivalent to a rate of ~1.5× maintenance which can be substituted for simplicity in most situations.

The initial serum sodium is usually normal or low because of the osmolar dilution of hyperglycemia and the effect of an elevated sodium-free lipid fraction. An estimate of the reconstituted, or “true,” serum sodium for any given glucose level above 100 mg/dL (5.6 mmol/L) is calculated as follows:

$$[\mathrm{Na}^+] + (1.6\ \mathrm{mEq/L\ Na}^+\ \text{for every } 100\ \mathrm{mg/dL}\ \text{glucose in excess of } 100)$$

or

$$[\mathrm{Na}^{+}]+\left(\frac{\dfrac{1.6\ \mathrm{mEq}}{\mathrm{L\ Na^{+}\ for\ every\ 5.6\ mmol}}}{\mathrm{L\ glucose}}\ \text{in excess of } 5.6\right)$$

The sodium should increase by approximately 1.6 mmol/L for each 100 mg/dL decline in the glucose. The corrected sodium is usually normal or slightly elevated and indicates moderate hypernatremic dehydration. If the corrected value is greater than 150 mmol/L, severe hypernatremic dehydration may be present and may require slower fluid replacement. The sodium should steadily increase with therapy. *Declining sodium may indicate excessive free water accumulation and increased risk of cerebral edema.*

Catabolic Losses

Both the metabolic shift to a catabolic predominance and the acidosis move potassium and phosphate from the cell to the serum. The osmotic diuresis, the kaliuretic effect of the hyperaldosteronism, and the ketonuria then accelerate renal losses of potassium and phosphate. Sodium is also lost with the diuresis, but free water losses are greater than isotonic losses. With prolonged illness and severe DKA, total body losses can approach 10-13 mEq/kg of sodium, 5-6 mEq/kg of potassium, and 4-5 mEq/kg of phosphate. These losses continue for several hours during therapy until the catabolic state is reversed and the diuresis is controlled. For example, 50% of infused sodium may be lost in the urine during IV therapy. Even though the sodium deficit may be repaired within 24 hr intracellular potassium and phosphate may not be completely restored for several days.

Although patients with DKA have a total body potassium deficit, the initial serum level is often normal or elevated. This is caused by the movement of potassium from the intracellular space to the serum, both as part of the ketoacid buffering process and as part of the catabolic shift. These effects are reversed with therapy, and potassium returns to the cell. Improved hydration increases renal blood flow, allowing for increased excretion of potassium in the elevated aldosterone state. The net effect is often a dramatic decline in serum potassium levels, especially in severe DKA. This can precipitate changes in cardiac conductivity, flattening of T waves, and prolongation of the QRS complex and can cause skeletal muscle weakness or ileus. The risk of myocardial dysfunction is increased with shock and acidosis. Potassium levels must be closely followed and electrocardiographic monitoring continued until DKA is substantially resolved. Potassium should be added to the IV fluids once serum potassium declines below 5.5 mEq/L and titrated as outlined in Table 607.6 . A 1 : 1 mixture of potassium chloride (or acetate) and potassium phosphate is typically used. Rarely, the IV insulin must be temporarily held if serum potassium levels drop below 3 mEq/L. It is unclear whether phosphate deficits contribute to symptoms of DKA such as generalized muscle weakness. In pediatric patients, a deficit has not been shown to compromise oxygen delivery via a deficiency of 2,3-diphosphoglycerate. In most cases, the inclusion of potassium phosphate as outlined above will be sufficient; however additional IV supplementation with potassium phosphate can be used if needed.

Pancreatitis (usually mild) is occasionally seen with DKA, especially if prolonged abdominal distress is present; serum amylase and lipase may be elevated. If the serum lipase is not elevated, the amylase is likely nonspecific or salivary in origin. Serum creatinine adjusted for age may be falsely elevated owing to interference by ketones in the autoanalyzer methodology. An initial elevated value rarely indicates renal failure and should be rechecked when the child is less ketonemic. Blood urea nitrogen may be elevated with prerenal azotemia and should be rechecked as the child is rehydrated. Mildly elevated creatinine or blood urea nitrogen is not a reason to withhold potassium therapy if good urinary output is present.

Ketoacid Accumulation

Low insulin infusion rates (0.02-0.05 units/kg/hr) are usually sufficient to stop peripheral release of fatty acids, thereby eliminating the flow of substrate for ketogenesis. Therefore, the initial infusion rate may be decreased if blood glucose levels go below 100 mg/dL (5.5 mmol/L) despite the addition of glucose to the infusion. Ketogenesis continues until fatty acid substrates already in the liver are depleted, but this production declines much more quickly without new substrate inflow. Bicarbonate buffers, regenerated by the distal renal tubule and by metabolism of ketone bodies, steadily repair the acidosis once ketoacid production is controlled. *Bicarbonate therapy may increase the risk of hypokalemia and cerebral edema so should be considered only in situations with severe acidosis unresponsive to standard DKA management.*

There should be a steady increase in pH and serum bicarbonate as therapy progresses. Kussmaul respirations should abate and abdominal pain resolve. Persistent acidosis may indicate inadequate insulin or fluid therapy, infection, or rarely lactic acidosis. Urine ketones may be positive after ketoacidosis has resolved because the nitroprusside reaction routinely used to measure urine ketones by dipstick measures only acetoacetate. During DKA, most excess ketones are β-hydroxybutyrate, which increases the normal ratio to acetoacetate from 3 : 1 to as high as 8 : 1. With resolution of the acidosis, β-hydroxybutyrate converts to acetoacetate, which is excreted into the urine and detected by the dipstick test. Therefore, persistent ketonuria may not accurately reflect the degree of clinical improvement and should not be relied on as an indicator of therapeutic failure. β-Hydroxybutyrate can be measured from serum and even by bedside capillary ketometer and is used in some protocols to monitor resolution of DKA and help determine when to transition from IV to subcutaneous insulin administration.

All patients with known diabetes presenting in DKA should be checked for initiating events (infection, poor compliance, trauma) that may have triggered the metabolic decompensation.

Diabetic Ketoacidosis Protocol

See Tables 607.6 and 607.7 .

Even though DKA can be of variable severity, a common approach to all cases simplifies the therapeutic regimen and can be safely used for most children. Fluids are best calculated based on weight, not body surface area (m^2), because heights are rarely available for the acutely critically ill child. Children with milder DKA recover in 10-20 hr (and need less total IV fluid before switching to oral intake), whereas those with more severe DKA may require up to 36 hr with this protocol. Any child can be easily transitioned to oral intake and subcutaneous insulin when DKA has resolved (total CO_2 > 15 mEq/L; pH > 7.30; sodium stable between 135 and 145 mEq/L; anion gap closed; no emesis). A dose of long-acting insulin is given (or continuous subcutaneous infusion started via pump) and the insulin drip is discontinued approximately 30 min later. Typically, transition is timed to occur around mealtime so that short-acting insulin can be given as well. Frequent (every 2-3 hr) short-acting insulin bolusing may need to be given until ketosis resolves.

A flow sheet is mandatory for accurate monitoring of changes in acidosis, electrolytes, fluid balance, and clinical status, especially if the patient is transferred from the emergency department to an inpatient setting with new caretakers. This flow sheet is best implemented by a central computer system, which allows for rapid update and wide availability of results, as well as rule-driven highlighting of critical values. A paper flow sheet suffices if it stays with the patient, is kept current, and is reviewed frequently by the physician. Any flow sheet should include columns for serial electrolytes, pH, glucose, and fluid balance. Blood glucose should be tested every hour and electrolytes should be tested every 1-2 hr for children with severe DKA and every 3-4 hr for those with mild to moderate DKA.

Cerebral Edema

The mortality rate of cerebral edema complicating the treatment of DKA has declined with the standardization of treatment protocols; however, it still remains a major cause of morbidity and mortality in children and adolescents with T1DM. Despite the clinical significance of this complication, its etiology remains incompletely understood. A case-control study of DKA suggested that baseline acidosis and abnormalities of sodium, potassium, and blood urea nitrogen concentrations were important predictors of risk of cerebral edema. Early bolus administration of insulin and high volumes of fluid were also identified as risk factors. The incidence of cerebral edema in children with DKA has not changed over the past 15-20 yr, despite the widespread introduction of gradual rehydration protocols during this interval. Radiographic imaging is frequently unhelpful in making the diagnosis of cerebral edema. Consequently, each patient must be closely monitored. For all but the mildest cases, this includes frequent neurologic checks for any signs of increasing intracranial pressure, such as a change of consciousness, depressed respiration, worsening headache, bradycardia, apnea, pupillary changes, papilledema, posturing, and seizures. *In the event of the development of cerebral edema, immediate interventions should include elevation of the head of the bed, reduction in IV fluid rate, and the administration of mannitol (typically 1 g/kg infused intravenously over 20 min)*. Physicians must also keep informed of the laboratory changes; hypokalemia or hypoglycemia can occur rapidly. Children with moderate to severe DKA have a higher overall risk and should be treated in a hospital environment where appropriate monitoring can occur.

Nonketotic Hyperosmolar Coma

This syndrome is characterized by severe hyperglycemia (blood glucose >800 mg/dL; 44 mmol/L), absence of or only slight ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma, and various neurologic signs that may include grand mal seizures, hyperthermia, hemiparesis, and positive Babinski signs. Respirations are usually shallow, but coexistent metabolic (lactic) acidosis may be manifested by Kussmaul breathing. Serum osmolarity is commonly 350 mOsm/kg or greater. This condition is uncommon in children although may be increasing in frequency with the rise in the incidence of T2DM. Among adults, mortality rates are high, possibly in part because of delays in recognition and institution of appropriate therapy. In children, there has been a high incidence of preexisting neurologic injury. Profound hyperglycemia may develop over a period of days and, initially, the obligatory osmotic polyuria and dehydration may be partially compensated for by increasing fluid intake. With progression of disease, *thirst becomes impaired* , possibly because of alteration of the hypothalamic thirst center by hyperosmolarity and, in some instances, because of a preexisting defect in the hypothalamic osmoregulating mechanism.

The low production of ketones is attributed mainly to the hyperosmolarity, which in vitro blunts the lipolytic effect of epinephrine and the antilipolytic effect of residual insulin; blunting of lipolysis by the therapeutic use of β-adrenergic blockers may contribute to the syndrome. Depression of consciousness is closely correlated with the degree of hyperosmolarity in this condition as well as in DKA. Hemoconcentration may also predispose to cerebral arterial and venous thromboses before therapy is initiated.

Treatment of nonketotic hyperosmolar coma is directed at rapid repletion of the vascular volume deficit with normal saline, and *very slow correction* of the hyperosmolar state. The fluid deficit should be estimated at 12–15% of body weight. Additional normal saline boluses may be required to reduce tachycardia and poor perfusion. One-half isotonic saline (0.45% NaCl; may use normal saline) is administered at a rate estimated to replace 50% of the volume deficit in the 1st 12 hr, and the remainder is administered during the ensuing 24 hr. The rate of infusion and the saline concentration are titrated to result in a slow decline of serum osmolality. When the blood glucose concentration approaches 300 mg/dL, the hydrating fluid should be changed to 5% dextrose in 0.225% NaCl. Approximately 20 mEq/L of potassium chloride should be added to each of these fluids to prevent hypokalemia. Serum potassium and plasma glucose concentrations should be monitored at 2 hr intervals for the 1st 12 hr and at 4 hr intervals for the next 24 hr to permit appropriate adjustments of administered potassium and insulin.

Insulin can be given by continuous intravenous infusion only after serum glucose levels no longer decline with fluid administration. The IV insulin should be initiated at a low dose of 0.025-0.05 units/kg/hr and titrated to achieve a slow decline in serum glucose of 50-75 mg/dL/hr (2.8-4.2 mmol/L/hr). The presence of ketosis or more severe acidosis may necessitate earlier insulin initiation.

Initiation of Subcutaneous Insulin Therapy

Excellent diabetes control involves many goals: to maintain blood glucose and HbA_{1c} levels as close to normal without causing hypoglycemia, to eliminate polyuria and nocturia, to prevent ketoacidosis, to permit normal growth and development and avoid development of diabetes related complications—all while minimizing the impact on lifestyle. The specific components of therapy include initiation and adjustment of insulin, extensive teaching of the child and caretakers, and reestablishment of the life routines. Each aspect should be addressed early in the overall care.

Insulin Therapy

Insulin therapy is initiated at the time of diagnosis for all patients with T1DM. The starting dose may range from 0.4 to 1.2 units/kg/day and is calculated based on a number of factors including age, pubertal stage, and presence or absence of DKA. Typically, prepubertal children presenting *without* DKA can be started on a dose of 0.4-0.5 units/kg/day. Overweight pubertal adolescents presenting with DKA may need up to 1-1.2 units/kg/day. Insulin requirements in infancy vary tremendously, from <0.2 units/kg/day to >1 unit/kg day. Table 607.7 shows typical starting ranges for total daily insulin dose (units/kg/day) in children.

The precise optimal insulin dose can only be determined empirically, after beginning with the above-mentioned starting doses, with frequent self-monitored blood glucose levels and insulin adjustment by the diabetes team. Many children with new-onset diabetes have some residual β-cell function (the honeymoon period), which is associated with reduced exogenous insulin needs shortly after starting on treatment. Residual β-cell function usually fades within a few months and is reflected as a steady increase in insulin requirements and wider glucose excursions.

The initial insulin schedule should be directed toward the optimal degree of glucose control in an attempt to duplicate the activity of the β-cell. There are inherent limits to our ability to mimic the β-cell. Exogenous insulin does not have a first pass to the liver, whereas 50% of pancreatic portal insulin is taken up by the liver, a key organ for the disposal of glucose. Absorption of an exogenous dose continues despite hypoglycemia, whereas endogenous insulin secretion ceases and serum levels quickly lower with a normally rapid clearance. The absorption rate from an injection varies by injection site and patient activity level, whereas endogenous insulin is secreted directly into the portal circulation. Despite these fundamental physiologic differences, acceptable glucose control can be obtained with insulin analogs used in a **basal-bolus regimen** . Basal-bolus regimens can be accomplished with multiple daily injections (MDIs), where a slow-onset, long-duration background insulin is given once or twice daily for between-meal glucose control (basal) and a rapid-onset insulin is given with meals to provide carbohydrate coverage and correct hyperglycemia. Alternatively, an **insulin pump** can be used, where a rapid-onset insulin is used to provide both basal (via continuous infusion) and bolus (at mealtimes and as needed for hyperglycemia) coverage. The doses of short-acting insulin include 2 components: **carbohydrate ratio** (typically expressed as 1 unit of insulin for a set number of grams of carbohydrates) and **insulin sensitivity factor** (ISF, also referred to as “correction factor,” and typically expressed as 1 unit of insulin will decrease blood sugar by a set number of mg/dL). Formulas for calculating the basal dose, carbohydrate ratio, and ISF from the total daily insulin dose are provided in Tables 607.8 , 607.9 , and 607.10 .

Table 607.8

Calorie Needs for Children and Young Adults

AGE	kcal REQUIRED/kg BODY WEIGHT*
CHILDREN	
0-12 mo	120
1-10 yr	100-75
YOUNG WOMEN	
11-15 yr	35
≤16 yr	30
YOUNG MEN	
11-15 yr	80-55 (65)

16-20 yr	
Average activity	40
Very physically active	50
Sedentary	30

[*] Gradual decline in calories per unit weight as age increases.

Numbers in parentheses are means.

From *Nutrition guide for professionals: diabetes education and meal planning,* Alexandria, VA, and Chicago, IL, 1988, The American Diabetes Association and The American Dietetic Association.

Table 607.9

Summary of Nutrition Guidelines for Children and/or Adolescents With Type 1 Diabetes Mellitus

NUTRITION CARE PLAN		
Promotes optimal compliance.		
Incorporates goals of management: normal growth and development, control of blood glucose, maintenance of optimal nutritional status, and prevention of complications. Uses staged approach.		
NUTRIENT RECOMMENDATIONS AND DISTRIBUTION		
NUTRIENT	**(%) OF CALORIES**	**RECOMMENDED DAILY INTAKE**
Carbohydrate	Will vary	High fiber, especially soluble fiber; optimal amount unknown
Fiber	>20 g/day	
Protein	12–20	
Fat	<30	
Saturated	<10	
Polyunsaturated	6–8	
Monounsaturated	Remainder of fat allowance	
Cholesterol		300 mg
Sodium		Avoid excessive; limit to 3,000-4,000 mg if hypertensive
ADDITIONAL RECOMMENDATIONS		
Energy: If using measured diet, reevaluate prescribed energy level at least every 3 mo. *Protein:* High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore, 12–20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful. *Alcohol:* Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school. *Snacks:* Snacks vary according to individual needs (generally 3 snacks per day for children; midafternoon and bedtime snacks for junior high children or teens). *Alternative sweeteners:* Use of a variety of sweeteners is suggested. *Educational techniques:* No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required. *Eating disorders:* Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder. *Exercise:* Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.		

From Connell JE, Thomas-Doberson D: Nutritional management of children and adolescents with insulin-dependent diabetes mellitus: a review by the Diabetes Care and Education Dietetic Practice Group, *J Am Diet Assoc* 91:1556, 1991.

Table 607.10

Target Premeal and 30-Day Average Blood Glucose Ranges and the Corresponding Hemoglobin A_{1c} for Each Age Group

AGE GROUP (yr)	TARGET PREMEAL BG RANGE (mg/dL)	30-DAY AVERAGE BG RANGE (mg/dL)	TARGET HbA_{1c} (%)
<5	100-200	180-250	7.5–9.0
5-11	80-150	150-200	6.5–8.0
12-15	80-130	120-180	6.0–7.5
16-18	70-120	100-150	5.5–7.0

In our laboratory, the nondiabetic reference range for HbA_{1c} is 4.5-5.7% (95% confidence interval).

BG, blood glucose; HbA_{1c} , hemoglobin A_{1c} .

All preanalog insulins form hexamers, which must dissociate into monomers subcutaneously before being absorbed into the circulation. Thus a detectable effect for **regular insulin** is delayed by 30-60 min after injection. This, in turn, requires delaying the meal 30-60 min after the injection for optimal effect—a delay rarely attained in a busy child's life. Regular insulin has a wide peak and a long tail for bolus insulin. This profile limits postprandial glucose control, produces prolonged peaks with excessive hypoglycemic effects between meals, and increases the risk of nighttime hypoglycemia. **Neutral protamine Hagedorn (NPH,** also known as insulin isophane) is an intermediate-acting insulin with inherent limitations as a basal insulin because it does not achieve a peakless background insulin level. This produces a significant hypoglycemic effect during the midrange of the duration. Thus, it is often difficult to predict their interaction with fast-acting insulins. When regular insulin is combined with NPH, the composite insulin profile poorly mimics normal endogenous insulin secretion. Lente and ultralente insulins were other intermediate-acting insulins that have since been discontinued.

Lispro, aspart, and glulisine insulin are rapid-onset analogs that are absorbed much quicker because they do not form hexamers. They provide discrete pulses with onset of action in as little as 10 min, with little if any overlap and short tail effect. This allows better control of postmeal glucose increase and reduces between-meal or nighttime hypoglycemia. Other ultra-fast-acting insulin analogs are being developed that promise even faster onset of action, a feature that may make these insulins especially useful in insulin pumps and closed-loop systems.

The **long-acting analogs glargine, detemir, and degludec** have been designed to provide longer duration of action, ranging from ~20 hr (glargine) to ~40 hr (degludec). Glargine forms a precipitate after subcutaneous injection, detemir binds to circulating albumin, and degludec forms di-hexamers—all of which lead to stabilization of the hexameric structure, slower disassociation into insulin monomers, and prolonged duration of action. The result is a flatter 24 hr profile, making it easier to predict the combined effect of a rapid bolus (lispro, aspart, or glulisine) on top of the basal insulin and thereby create a more physiologic pattern of insulin effect. Postprandial glucose elevations are better controlled, and between-meal and nighttime hypoglycemia are reduced. An illustration of the insulin effect profiles of the currently available short- and long-acting insulins is provided in Figs. 607.5 and 607.6 .

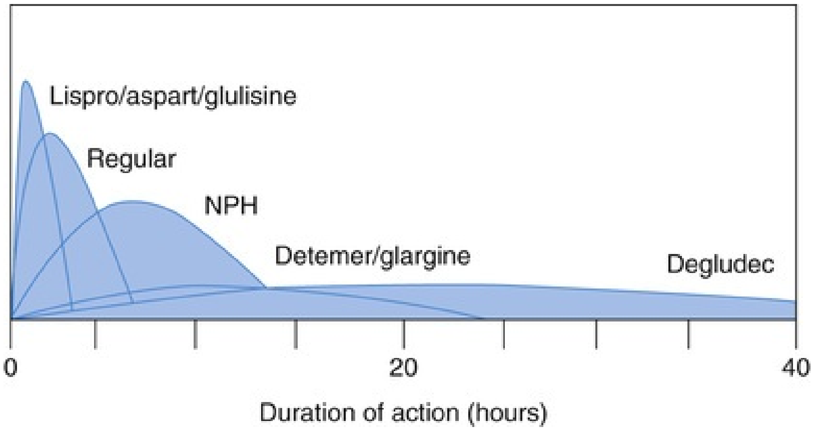

FIG. 607.5 **Approximate insulin effect profiles. The following relative peak effect and duration units are used: lispro/aspart/glulisine, peak 20 for 4 hr; regular, peak 15 for 7 hr; neutral protamine Hagedorn *(NPH)* peak 12 for 12 hr; detemir/glargine, peak 5 for 20-24 hr; degludec peak 5 for 42 hr.**

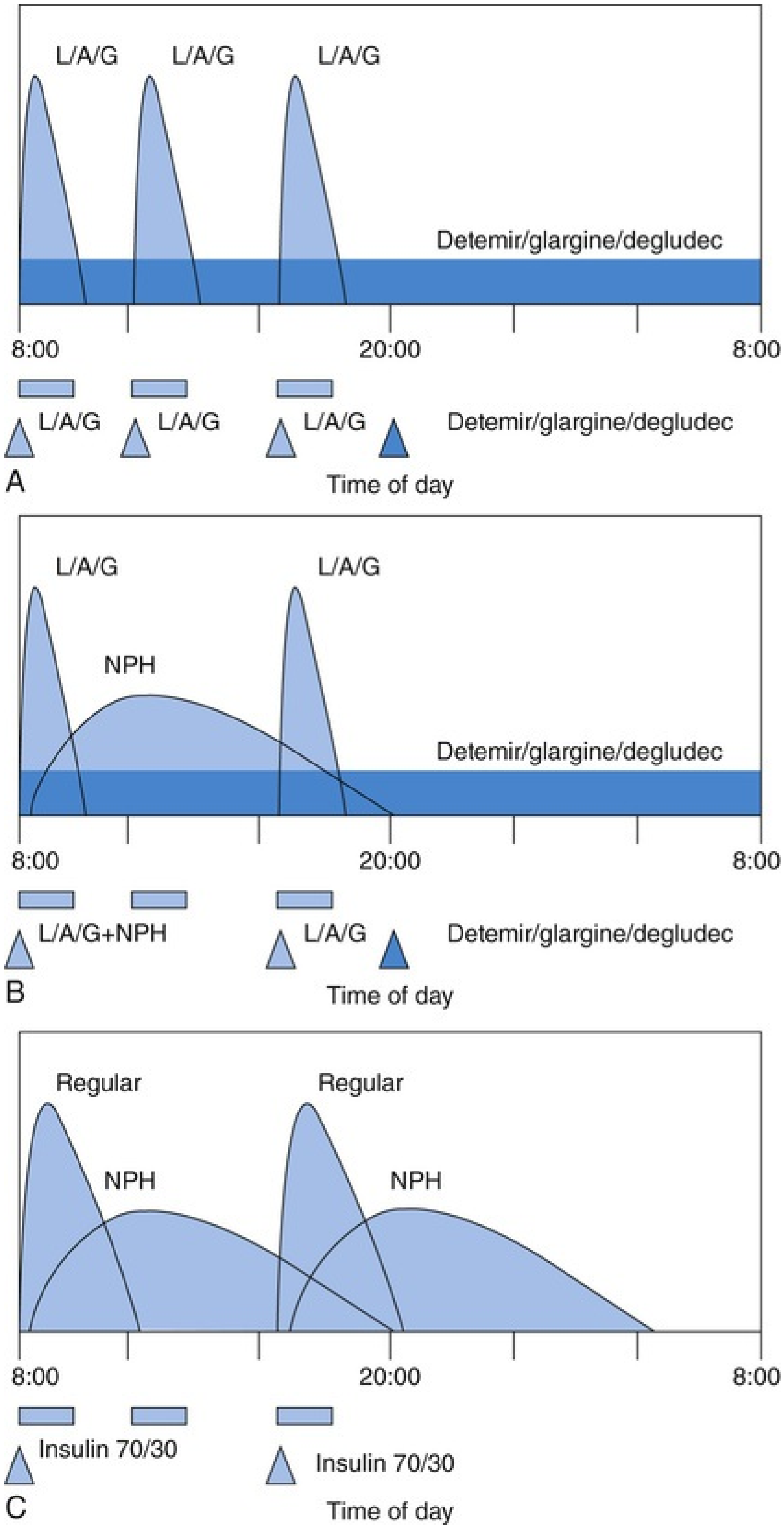

FIG. 607.6 Approximate composite insulin effect profiles of various insulin dosing strategies. Meals are shown as rectangles below time axis. Injections are shown as labeled *triangles; L/A/G,* lispro, aspart, glulisine. All profiles are idealized using average absorption and clearance rates. In typical clinical situations, these profiles vary among

patients. A given patient has varying rates of absorption depending on the injection site, physical activity, and other variables. A, Basal Bolus Regimen: A short-acting insulin (lantus/aspart/glulisine) is injected before meals and a long-acting basal insulin (glargine/detemir/degludec) is injected at bedtime. Additional short-acting insulin is given to cover between-meal snacks as needed (not shown). For patients on insulin pumps, the composite insulin profile is similar, however the basal insulin coverage is provided by a continuous infusion of short-acting insulin. B, Three Daily Injection Regimen: A short-acting insulin (lantus/aspart/glulisine) and neutral protamine Hagedorn *(NPH)* are injected with breakfast (the 2 types of insulin can be drawn up into 1 syringe for administration with a single injection), a short-acting insulin is injected with dinner, and a long-acting basal insulin (glargine/detemir/degludec) is injected at bedtime. Because NPH is not a peakless insulin, this regimen is associated with greater risk of hypoglycemia compared to the basal bolus regimen show in Fig. 607.6A but does offer the advantage of eliminating the need for an injection at lunchtime. C, Twice Daily Injection Regime: The use of a premixed insulin containing a short- and an intermediate-acting insulin that is given twice daily is sometimes necessary for families that are unable to manage more complex dosing regimens. Insulin 70/30 is 1 such product that combines regular and NPH insulins. This produces the least physiologic profile, with large excesses before lunch and during the early night, combined with poor coverage before supper and breakfast.

At diagnosis, the basal dose of long-acting insulin is typically calculated to provide 50% of the total daily dose, with the remainder provided with bolus doses of short-acting insulin at mealtimes (calculations used to determine insulin doses are provided in Table 607.7). Over time the ratio of basal to bolus will typically shift downward and will be affected by the magnitude of carbohydrate intake (especially during adolescence). Some infants and toddlers may do well with a higher percentage of their daily insulin provided as basal. There is considerable individual variability in the duration of action of long-acting insulins, and some younger children and obese adolescents will require twice daily dosing of glargine. It is presumed that the availability of degludec will eliminate the need for twice daily dosing of basal insulin in the majority of patients, but more clinical experience is needed. Both long- and short-acting insulins are available for administration via multi-dose insulin pens, which are generally easier to use compared to a traditional syringe and vial approach.

Some families may be unable to administer 4 daily injections. In these cases, a compromise may be needed. A 3-injection regimen combining NPH with a rapid analog bolus at breakfast, a rapid-acting analog bolus at supper, and glargine at bedtime may provide fair glucose control and eliminate the need for an injection at school. Further compromise to a 2-injection regimen may occasionally be needed and frequently involves use of premixed insulin preparations that include both rapid- and intermediate-acting insulins (e.g., 70/30). For this regimen, 70% of the TDD is typically provided with breakfast and 30% of TDD with dinner. An illustration of commonly used insulin regimens is shown in Fig. 607.6 .

Insulin Pump Therapy

Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps provides a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared with conventional insulin injection regimens. Insulin pump models can be programmed with a patient's personal insulin dose algorithms, including the **insulin to carbohydrate ratio** and the **ISF** (also called the correction factor) for premeal glucose levels. At mealtimes, the patient enters the blood glucose level (or it is automatically transmitted from a linked glucometer) and the carbohydrate content of the meal, and the pump computer will calculate the proper insulin bolus dose. Although CSII frequently improves metabolic control, this may not always be the case. The degree of glycemic control is mainly dependent on how closely patients adhere to the principles of diabetes self-care, regardless of the type of intensive insulin regimen. One benefit of pump therapy may be a reduction in severe hypoglycemia and associated seizures. Randomized trials comparing multiple daily insulin regimens using glargine insulin and CSII in children with T1DM demonstrate similar metabolic control and frequency of hypoglycemic events. Most patients will initiate therapy with insulin pens; timing of transition to an insulin pump can be individualized per patient preference as soon as 6-12 mo after diagnosis.

Continuous Glucose Monitoring Systems

Continuous glucose monitoring systems (CGMs) consist of a subcutaneous glucose sensor that continuously measures interstitial fluid glucose levels and a receiver to collect and display glucose data. CGMs reduce but do not eliminate the need for fingerstick blood glucose checking, as calibrations with capillary blood glucose readings are required at least every 12 hr. The current generation of CGMs report blood glucose levels to the patient/caregiver in real time and can be integrated with smartphones/watches for remote monitoring. To avoid hypoglycemia the CGM system sounds an alarm once a critical low blood sugar threshold is reached. Additional alerts can be set to notify users of hyperglycemia or rapid rates of change in glucose levels. Short-term studies indicate clinical benefits of these devices as compared to conventional methods of blood glucose monitoring, when used by motivated and well-informed patients. A limitation of CGM-only systems is that they require the user to respond to the alert, interpret the data, and intervene to prevent hypo- or hyperglycemic episodes. Users may sleep through alarms at night, or develop alarm fatigue and choose to ignore alerts, both of which ultimately reduce the clinical benefit of these devices.

Closed-Loop Systems

A closed-loop system allows for direct communication between the continuous glucose sensor and insulin pump for automatic adjustment of insulin infusion rates in response to glucose levels (Fig. 607.7). A fully closed-loop system would be completely independent of the user and theoretically could improve glycemic control through the early identification and response to glucose perturbation and also by minimizing the opportunity for human error in insulin dosing. Both single-hormone (insulin only) and bi-hormone (insulin and glucagon) systems are undergoing clinical investigation.

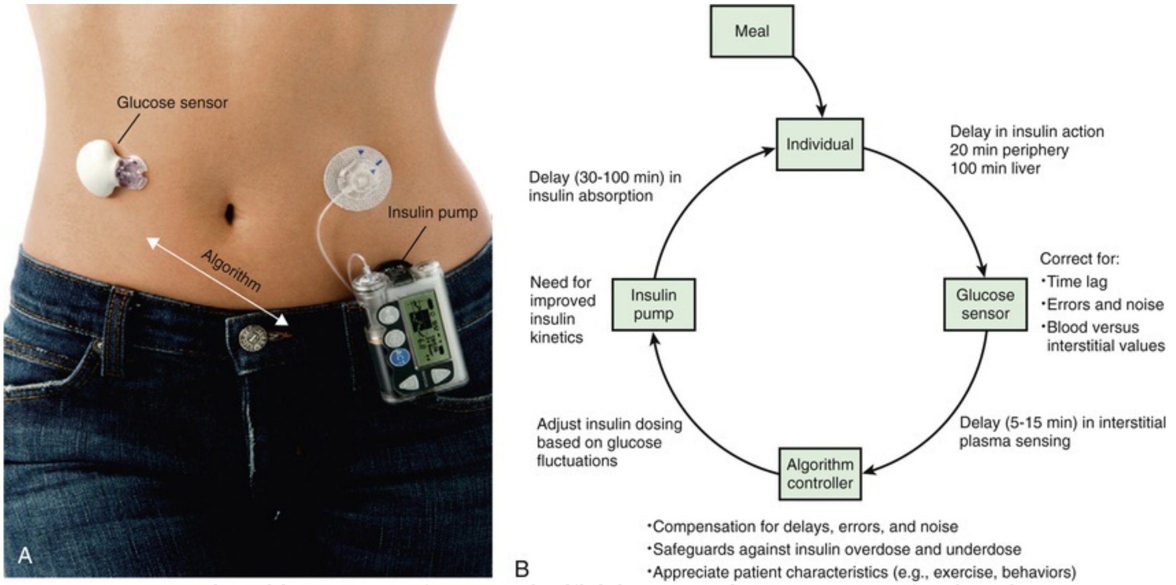
Glucose sensor
Insulin pump
Algorithm
A
B
Meal
Individual
Delay in insulin action
20 min periphery
100 min liver
Delay (30-100 min) in
insulin absorption
Correct for:
•Time lag
•Errors and noise
•Blood versus
interstitial values
Need for
improved
insulin
kinetics
Insulin
pump
Glucose
sensor
Adjust insulin dosing
based on glucose
fluctuations
Delay (5-15 min) in interstitial
plasma sensing
Algorithm
controller
•Compensation for delays, errors, and noise
•Safeguards against insulin overdose and underdose
•Appreciate patient characteristics (e.g., exercise, behaviors)

FIG. 607.7 **Closed-loop system for T1DM (artificial pancreas). A, Prototype of a closed-loop system. B, Components of a closed-loop system. Three potential delays in the system include glucose sensing in interstitial fluid, insulin absorption (depends on use of rapid vs. regular insulin), and insulin action in peripheral tissues and liver. (From Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes. *Lancet* 383:69–78, 2014, Fig. 5.)**

The first closed-loop type system to be approved by the FDA was the Medtronic MiniMed 530G System, a sensor-augmented system that automatically suspends insulin infusion for 2 hr in response to glucose levels that fall below a low glucose threshold. The device alarms to alert the user that the threshold suspend feature is engaged and can be overridden. Insulin infusion then resumes at the programmed basal rate after 2 hr. The newest closed-loop system to be FDA approved (in 2016) is the Medtronic MiniMed 670G system, a hybrid closed-loop system that uses an algorithm to adjust the rate of basal insulin infusion in response to glucose levels. Users must still calculate carbohydrates and bolus for mealtimes (hence the designation “hybrid”). There is emerging evidence from short-term clinical trials that the use of hybrid closed-loop systems can improve glycemic control, minimize glucose fluctuation, and reduce hypoglycemia compared to sensor-augmented systems. Current issues hampering full implementation of this technology include limitations in the accuracy and precision of interstitial fluid glucose sensing and the need for short-acting insulins with more rapid onset of action.

Adjunct Pharmacotherapy

Pramlintide acetate, a synthetic analog of amylin, may be of therapeutic value combined with insulin therapy. In adolescents, it has been shown to decrease postprandial hyperglycemia, insulin dosage, gastric emptying, and HbA_{1c} levels. It is given as a subcutaneous dose before meals. Metformin, an oral anti-hyperglycemic commonly used to treat T2DM is sometimes used clinically as an adjunct therapy in T1DM patients with evidence of significant insulin resistance (i.e., obesity, insulin requirements >1.2 units/kg/day, acanthosis nigricans on exam). A clinical trial investigating the addition of metformin in overweight adolescents with T1DM did not find a sustained effect of metformin to lower HbA_{1c} but did show a reduction in daily insulin dose and BMI. Reports from observational studies are likewise mixed. These agents would typically not be started at diagnosis of T1DM.

Basic and Advanced Diabetes Education

Therapy consists not only of initiation and adjustment of insulin dose but also of education of the patient and family. Teaching is most efficiently provided by experienced diabetes educators and nutritionists. In the acute phase, the family must learn the basics, which includes monitoring the child's blood glucose and urine and/or blood ketones, preparing and injecting the correct insulin dose subcutaneously at the proper time, recognizing and treating low blood glucose reactions, and having a basic meal plan. Most families are trying to adjust psychologically to the new diagnosis of diabetes in their child and thus have a limited ability to retain new information. Written materials covering these basic topics help the family during the 1st few days.

Children and their families are also required to complete advanced self-management classes to facilitate implementation of flexible insulin management. These educational classes will help patients and their families acquire skills for managing diabetes during athletic activities and sick days. Likewise, further patient and caregiver education with a diabetes educator familiar with diabetes technology is imperative when adding a CGM or transitioning to an insulin pump.

Nutritional Management

Nutrition plays an essential role in the management of patients with T1DM. This is of critical importance during childhood and adolescence, when appropriate energy intake is required to meet the needs for energy expenditure, growth, and pubertal development. There are no special nutritional requirements for the diabetic child other than those for optimal growth and development. Nutritional requirements for the child are outlined on the basis of age, sex, weight, activity, and food preferences. Cultural ethnic considerations must also be integrated into the nutrition plan.

Total recommended caloric intake is based on size or surface area and can be obtained from standard tables (see Tables 607.8 and 607.9). The caloric mixture should comprise approximately 55% carbohydrate, 30% fat, and 15% protein, but must be individualized to meet specific patient needs. Approximately 70% of the carbohydrate content should be derived from complex carbohydrates such as starch; intake of sucrose and highly refined sugars should be limited. Complex carbohydrates require prolonged digestion and absorption and thereby raise plasma glucose levels slowly, whereas glucose from refined sugars, including carbonated beverages, is rapidly absorbed and may cause wide swings in the metabolic pattern. The consumption of sugar-sweetened beverages including soda and juice should be discouraged. Priority should be given to total calories and total carbohydrates consumed rather than the source. Carbohydrate counting has become a mainstay in the nutrition education and management of patients with T1DM. Patients and their families are provided with information regarding the carbohydrate contents of different foods and food label reading. This allows patients to adjust their insulin dosage to their mealtime carbohydrate intake. The use of carbohydrate counting and insulin to carbohydrate ratios as a part of an MDI regimen allow for less-rigid meal planning. Flexibility in the use of insulin in relation to carbohydrate content of food improves the quality of life.

Diets with high fiber content are useful in improving control of blood glucose. Daily recommended fiber intake can be determined using the equation:

$$\text{Age in years} + 5 = \text{grams of fiber per day}$$

Moderate amounts of sucrose consumed with fiber-rich foods such as whole-grain bread may have no more glycemic effect than their low-fiber, sugar-free equivalents. Saturated fat intake may increase in patients with T1DM who reduce carbohydrate consumption in an attempt to avoid taking insulin doses by ingesting carbohydrate-free foods. Total energy from fat should not exceed 35%, and education should be provided such that <10% of total energy should come from saturated and trans fats. Dietary fats derived from animal sources should be reduced and replaced by polyunsaturated fats from vegetable sources. Substituting vegetable oil for animal oils or butter in cooking, and lean cuts of meat, poultry, and fish for fatty meats can help to achieve these goals. The intake of cholesterol is also reduced by these measures. These simple measures may reduce serum low-density lipoprotein cholesterol, a predisposing factor to atherosclerotic disease. Table 607.9 summarizes current nutritional guidelines for T1DM.

Each child/family can and should select a diet based on personal taste with the help of the physician or dietitian (or both). Emphasis should be placed on lifestyle changes to promote adherence to a healthy, balanced diet on daily basis. Occasional excesses (treats) are permissible but should be limited just as for any child without diabetes. Adjustments in meal planning must constantly be made to meet the needs as well as the desires of each child. A consistent eating pattern with appropriate supplements for exercise, the pubertal growth spurt, and pregnancy in an adolescent with diabetes is important for metabolic control.

Monitoring

Success in the daily management of the child with diabetes can be measured by the competence acquired by the family, and subsequently by the child, in assuming responsibility for daily self-care. Their initial and ongoing instruction in conjunction with their supervised experience can lead to a sense of confidence in adjusting in insulin dosage for dietary deviations, for unusual physical activity, and for some intercurrent illnesses. Such acceptance of responsibility should make them relatively independent of the physician for their ordinary care. The physician must maintain ongoing interested supervision and shared responsibility with the family and the child.

Self-monitoring of blood glucose is an essential component of managing diabetes. Effective monitoring often also includes other factors that influence blood glucose such as insulin dose, physical activity, dietary changes, hypoglycemia, and illness. A record of these items may be valuable in interpreting the self-monitoring of blood glucose, prescribing appropriate adjustments in insulin doses, and teaching the family. If there are discrepancies in the self-monitoring of blood glucose and other measures of glycemic control (such as the HbA_{1c}), the clinician should attempt to clarify the situation in a manner that does not undermine their mutual confidence.

Daily blood glucose monitoring is accomplished using test strips impregnated with glucose oxidase that permit blood glucose measurement from a drop of blood. A portable calibrated reflectance meter can approximate the blood glucose concentration accurately. Glucometers contain a memory chip enabling recall of each measurement and the ability to calculate measurement average over a given interval and display the pattern on a computer screen. Such information is a useful educational tool for verifying degree of control and modifying recommended regimens. A small, spring-loaded device that automates capillary bloodletting (lancing device) in a relatively painless fashion is commercially available. Parents and patients should be taught to use these devices and measure blood glucose at least 4 times daily—before breakfast, lunch, and supper, and at bedtime. When insulin therapy is initiated and when adjustments are made that may affect the overnight glucose levels, self-monitoring of blood glucose should also be performed at 12 midnight and 3 AM to detect nocturnal hypoglycemia. *Current recommended blood glucose targets are 90-130 mg/dL before meals and 90-150 mg/dL before bedtime* ; however glycemic goals must be individualized to the patient based on age, hypoglycemia risk, and other factors.

Blood glucose measurements that are consistently at or outside these limits, in the absence of an identifiable cause such as exercise or dietary indiscretion, are an indication for a change in the insulin dose. If the fasting blood glucose is high, the evening dose of long-acting insulin (or the early morning/overnight basal rate for insulin pump users) is increased by 10–20% and/or additional fast-acting insulin coverage for bedtime snack may be considered. If the noon glucose level exceeds set limits, the morning fast-acting insulin to carbohydrate ratio is increased by 10–20%. If the pre-supper glucose is high, the noon fast-acting insulin to carbohydrate ratio is increased by 10–20%. If the pre-bedtime glucose is high, the pre-supper fast-acting insulin to carbohydrate ratio is increased by 10–15%. The ISF can be increased by 10–20% if it is found that insulin corrections given for hyperglycemia do not normalize glucose levels as expected. Similarly, reductions in the insulin type and dose should be made if the corresponding blood glucose measurements are consistently below desirable limits.

A minimum of 4 daily blood glucose measurements should be performed. However, some children and adolescents may need to have more frequent blood glucose monitoring based on their level of physical activity and history of frequent hypoglycemic reactions. Families should be encouraged to become sufficiently knowledgeable about managing diabetes. They can maintain near-normal glycemia for prolonged periods by self-monitoring of blood glucose levels before and 2 hr after meals, and in conjunction with MDI of insulin, adjusted as necessary.

In 2016, the FDA granted the first approval for the use of CGMs to replace fingerstick blood glucose checking for the monitoring and treatment of diabetes in children 2 yr of age and older. CGMs are minimally invasive and entail the placement of a small, subcutaneous catheter that can be easily worn by adults and children. The system provides information that allows the patient and healthcare team to adjust the insulin regimen and the nutrition plan to improve glycemic control. CGMs can be helpful in detecting asymptomatic nocturnal hypoglycemia as well as in lowering HbA_{1c} values without increasing the risk for severe hypoglycemia. Although there are potential pitfalls in CGMs use, including suboptimal compliance, human error, incorrect technique, and sensor failure, the implementation of CGMs in ambulatory diabetes practice allows the clinician to diagnose abnormal glycemic patterns in a more precise manner.

Glycosylated Hemoglobin (HbA_{1c})

A reliable index of long-term glycemic control is provided by measurement of glycosylated hemoglobin. HbA_{1c} represents the fraction of hemoglobin to which glucose has been non-enzymatically attached in the bloodstream. The formation of glycosylated hemoglobin is a slow reaction that is dependent on the prevailing concentration of blood glucose; it continues irreversibly throughout the red blood cell's life span of approximately 120 days. The higher the blood glucose concentration and the longer the red blood cell's exposure to it, the higher the fraction of glycosylated hemoglobin, which is expressed as a percentage of total hemoglobin. Because a blood sample at any given time contains a mixture of red blood cells of varying ages, exposed for varying times to varying blood glucose concentrations, an HbA_{1c} measurement reflects the average blood glucose concentration from the preceding 2-3 mo. For some patients, it may be helpful to translate HbA_{1c} into estimated average glucose (eAG) using the following equation:

$$eAG = 28.7 * HbA_{1c} - 46.7$$

When measured by standardized methods to remove labile forms, HbA_{1c} is not influenced by an isolated episode of hyperglycemia.

It is currently recommended that HbA_{1c} measurements be obtained 3-4 times/yr to obtain a profile of long-term glycemic control. The lower the HbA_{1c} level, the more likely it is that microvascular complications such as retinopathy and nephropathy will be less severe, delayed in appearance, or even avoided altogether. Depending on the method used for determination, HbA_{1c} values may be spuriously elevated in thalassemia (or other conditions with elevated hemoglobin F) and spuriously lower in sickle cell disease (or other conditions with high red blood cell turnover). Fructosamine can be used instead of HbA_{1c} in these patients. Although values of HbA_{1c} may vary according to the method used for measurement, in individuals without diabetes the HbA_{1c} is usually less than 6%. The HbA_{1c} target for all children with diabetes is $<7.5\%$; for those over 18 yr it is $\leq 7.0\%$.

Exercise

No form of exercise, including competitive sports, should be forbidden to the child with diabetes. A major complication of exercise in patients with diabetes is the presence of a hypoglycemic reaction during or within hours after exercise. If hypoglycemia does not occur with exercise, adjustments in diet or insulin are not necessary, and glucoregulation is likely to be improved through the increased utilization of glucose by muscles. One contributing factor to hypoglycemia with exercise is an increased rate of absorption of insulin from its injection site. Higher insulin levels dampen hepatic glucose production so that it is inadequate to meet the increased glucose utilization of exercising muscle. Regular exercise also improves glucoregulation by increasing insulin receptor number. In patients who are in poor metabolic control, vigorous exercise may precipitate ketoacidosis because of the exercise-induced increase in the counterregulatory hormones.

Benefits of Improved Glycemic Control

The Diabetes Control and Complications Trial (DCCT) established conclusively the association between higher glucose levels and long-term microvascular complications. Intensive management produced dramatic reductions of retinopathy, nephropathy, and neuropathy by 47–76%. The data from the adolescent cohort demonstrated the same degree of improvement and the same relationship between the outcome measures of microvascular complications.

The beneficial effect of intensified treatment was determined by the degree of blood glucose normalization, independently of the type of intensified treatment used. Frequent blood glucose monitoring was considered an important factor in achieving better glycemic control for the intensively treated adolescents and adults. Patients who were intensively treated had individualized glucose targets, frequent adjustments based on ongoing capillary blood glucose monitoring, and a team approach that focused on the person with diabetes as the prime initiator of ambulatory care. Care was constantly adjusted toward reaching normal or near-normal glycemic goals while avoiding or minimizing severe episodes of hypoglycemia. Teaching emphasized a preventive approach to blood glucose fluctuations with constant readjustment to counterbalance any high or low blood glucose readings. Target blood glucose goals were adjusted upward if hypoglycemia could not be prevented.

Total *duration* of diabetes contributes to development and severity of complications. Nonetheless, many professionals have concerns about applying the results of the DCCT to preschool-age children, who often have hypoglycemia unawareness with unique safety issues, and to prepubertal school-age children, who were not included in the DCCT. When the DCCT ended in

1993, researchers continued to study more than 90% of participants. The follow-up study, called Epidemiology of Diabetes Interventions and Complications (EDIC), assessed the incidence and predictors of cardiovascular disease events such as heart attack, stroke, or needed heart surgery, as well as diabetic complications related to the eye, kidney, and nerves. The EDIC demonstrated that intensive blood glucose control reduced risk of any cardiovascular disease event by 42%. In addition, intensive therapy reduced risk of nonfatal heart attack, stroke, or death from cardiovascular causes by 57%.

Hypoglycemic Reactions

Hypoglycemia is the major limitation to tight control of glucose levels. Once injected, insulin absorption and action are independent of the glucose level, thus creating a unique risk of hypoglycemia from an unbalanced insulin effect. Insulin analogs may help reduce but cannot eliminate this risk. Most children with T1DM can expect *mild* hypoglycemia each week, *moderate* hypoglycemia a few times each year, and *severe* hypoglycemia every few years. These episodes are usually not predictable, although exercise, delayed meals or snacks, and wide swings in glucose levels increase the risk. Infants and toddlers are at higher risk for hypoglycemia because they have more variable meals and activity levels, are unable to recognize early signs of hypoglycemia, and are limited in their ability to seek a source of oral glucose to reverse the hypoglycemia. The very young have an increased risk of permanently reduced cognitive function as a long-term sequela of severe hypoglycemia. For these reasons, a more relaxed degree of glucose control may be tolerated in infants and young children.

Hypoglycemia can occur at any time of day or night. Early symptoms and signs (mild hypoglycemia) may occur with a sudden decrease in blood glucose to levels that do not meet standard criteria for hypoglycemia in children without diabetes. The child may show pallor, sweating, apprehension or fussiness, hunger, tremor, and tachycardia, all as a result of the surge in catecholamines as the body attempts to counter the excessive insulin effect. Behavioral changes such as tearfulness, irritability, and aggression are more prevalent in children. As glucose levels decline further, cerebral glucopenia occurs with drowsiness, personality changes, mental confusion, and impaired judgment (moderate hypoglycemia), progressing to inability to seek help and seizures or coma (severe hypoglycemia). Prolonged severe hypoglycemia can result in a depressed sensorium or stroke-like focal motor deficits that persist after the hypoglycemia has resolved. Although permanent sequelae are rare, severe hypoglycemia is frightening for the child and family and can result in significant reluctance to attempt even moderate glycemic control afterward.

Important counterregulatory hormones in children include growth hormone, cortisol, epinephrine, and glucagon. The latter 2 seem more critical in the older child. Many older patients with long-standing T1DM lose their ability to secrete glucagon in response to hypoglycemia. In the young adult, epinephrine deficiency may also develop as part of a general autonomic neuropathy. This substantially increases the risk of hypoglycemia because the early warning signals of a declining glucose level are as a result of catecholamine release. Recurrent hypoglycemic episodes associated with tight metabolic control may aggravate partial counterregulatory deficiencies, producing a syndrome of hypoglycemia unawareness and reduced ability to restore euglycemia (hypoglycemia-associated autonomic failure). Avoidance of hypoglycemia allows some recovery from this unawareness syndrome.

The most important factors in the management of hypoglycemia are an understanding by the patient and family of the symptoms and signs of the reaction and an anticipation of known precipitating factors such as gym or sports activities. Tighter glucose control increases the risk. Families should be taught to look for typical hypoglycemic scenarios or patterns in the home blood glucose log, so that they may adjust the insulin dose and avert predictable episodes. A source of emergency glucose should be available at all times and places, including at school and during visits to friends. If possible, it is important to document the hypoglycemia before treating, because some symptoms may not always be from hypoglycemia. Any child suspected of having a moderate to severe hypoglycemic episode should be treated before testing. It is important not to give too much glucose in response to hypoglycemia; 15 g should be given as juice or a sugar-containing beverage or candy, and the blood glucose checked 15-20 min later. Patients, parents, and teachers should also be instructed in the administration of glucagon when the child cannot take glucose orally. An injection kit should be kept at home and school. The intramuscular dose of glucagon is 0.5 mg if the child weighs less than 20 kg and 1.0 mg if more than 20 kg. This produces a brief release of glucose from the liver. Glucagon often causes emesis, which precludes giving oral supplementation if the blood glucose declines after the glucagon effects have waned. Caretakers must then be prepared to take the child to the hospital for IV glucose administration, if necessary. Minidose glucagon (10 µg/yr of age up to a maximum of 150 µg subcutaneously) is effective in treating hypoglycemia in children with blood glucose less than 60 mg/dL who fail to respond to oral glucose and remain symptomatic. Glucagon is reconstituted as per standard instructions, then drawn up for subcutaneous objection using a standard insulin syringe, whereby 1 unit is the equivalent of 10 mcg of glucagon.

Dawn Phenomenon and Somogyi Phenomenon

There are several reasons that blood glucose levels increase in the early morning hours before breakfast. The most common is a simple decline in insulin levels. This usually results in routinely elevated morning glucose. The **dawn phenomenon** is thought to be mainly caused by overnight growth hormone secretion and increased insulin clearance. It is a normal physiologic process seen in most adolescents without diabetes, who compensate with more insulin output. A child with T1DM cannot compensate. The dawn phenomenon is usually recurrent and modestly elevates most morning glucose levels. Rarely, high morning glucose is caused by the **Somogyi phenomenon,** a theoretical rebound from late-night or early-morning hypoglycemia, thought to be from an exaggerated counterregulatory response. It is unlikely to be a common cause, in that most children remain hypoglycemic (do not rebound) once nighttime glucose levels decline. CGMs may help clarify a child's ambiguously elevated morning glucose levels.

Behavioral/Psychologic Aspects and Eating Disorders

Diabetes in a child affects the lifestyle and interpersonal relationships of the entire family. Feelings of anxiety and guilt are common in parents. Similar feelings, coupled with denial and rejection, are equally common in children, particularly during the rebellious teenage years. Family conflict has been associated with poor treatment adherence and poor metabolic control among youths with T1DM. On the other hand, it has been shown that shared responsibility is consistently associated with better psychologic health, good self-care behavior, and good metabolic control, whereas responsibility assumed by either the child or parent alone does not have outcomes that are equally successful. In some cases, links of shared responsibility to health outcomes were stronger among older adolescents. However, no specific personality disorder or psychopathology is characteristic of diabetes; similar feelings are observed in families with children who have other chronic diseases.

Cognitive Function

There is increasing agreement that children with T1DM are at higher risk of developing small differences in cognitive abilities compared to healthy age-matched peers. Evidence suggests that early-onset diabetes (younger than 7 yr) is associated with cognitive difficulties compared to late-onset diabetes and healthy controls. The cognitive difficulties observed were primarily learning and memory skills (both verbal and visual) and attention/executive function skills. It is likely that the impact of diabetes on pediatric cognition appears shortly after diagnosis. Indeed, it has been observed that early-onset diabetes and longer duration of diabetes in some children with diabetes adversely affect their school performance and educational achievements.

Coping Styles

Children and adolescents with T1DM are faced with a complex set of developmental changes as well as shifting burdens of the disease. Adjustment problems might affect psychologic well-being and the course of the disease by impacting self-management and leading to poor metabolic control. Coping styles refer to typical habitual preferences for ways of approaching problems and might be regarded as strategies that people generally use to cope across a wide range of stressors. Problem-focused coping refers to efforts directed toward rational management of a problem, and it is aimed at changing the situation causing distress. On the other hand, emotion-focused coping implies efforts to reduce emotional distress caused by the stressful event and to manage or regulate emotions that might accompany or result from the stressor. In adolescents with diabetes, avoidance coping and venting emotions have been found to predict poor illness-specific self-care behavior and poor metabolic control. Patients who use more mature defenses and exhibit greater adaptive capacity are more likely to adhere to their regimen. Coping strategies seem to be age dependent, with adolescents using more avoidance coping than younger children with diabetes.

Nonadherence

Family conflict, anger, sadness, or denial, and feelings of anxiety or loss of control find expression in nonadherence to instructions regarding nutritional and insulin therapy and in noncompliance with self-monitoring. When adolescents externalize behavior problems, such behaviors interfere with adherence and may result in deterioration of glycemic control. Such externalizing behaviors are very common, whereas repeated omission of insulin resulting in ketoacidosis in the same individual are less common, and episodes of deliberate overdosage with insulin resulting in hypoglycemia are even less prevalent. They may, however, be pleas for psychologic help or be manipulative attempts to escape an environment perceived as undesirable or intolerable; occasionally, they may be manifestations of suicidal intent. Frequent admissions to the hospital for ketoacidosis or hypoglycemia should arouse suspicion of an underlying emotional conflict. Overprotectiveness on the part of parents is common and often is not in the best interest of the adolescent patient. Feelings of being different or of being alone, or both, are common and must be acknowledged. Tailoring the insulin administration, as well as timing of meals and blood sugar tests may support individual lifestyle choices. Aggregating what they know about type 1 and type II diabetes, families and patients worry about the risk of complications from diabetes and about the decreased life span. Unfortunately, misinformation abounds about the risks of the development of diabetes in siblings or offspring and of pregnancy in young diabetic women. Even appropriate information may cause further anxiety.

All of these issues must be spoken about at the outset, and many of these problems can be averted through continued empathic counseling based on correct information, focusing on normality and on planning to be a productive member of society. Recognizing the potential impact of these problems and that feelings of isolation and frustration tend to be lessened by the sharing of common problems, peer discussion groups have been organized in many locales. Summer camps for diabetic children afford an excellent opportunity for learning and sharing under expert supervision. Education about the pathophysiology of diabetes, insulin dose, technique of administration, nutrition, exercise, and hypoglycemic reactions can be reinforced by medical and paramedical personnel. The presence of numerous peers with similar problems offers new insights to the diabetic child. Residential treatment for children and adolescents with difficult to manage T1DM is an option available only in some centers.

Anxiety and Depression

It has been shown that there are significant correlations between poor metabolic control and depressive symptoms, a high level of anxiety, or a previous psychiatric diagnosis. In a similar way, poor metabolic control is related to higher levels of personal, social, school maladjustment, or family environment dissatisfaction. It is estimated that 20–26% of adolescent patients may develop major depressive disorder. The prevalence of depression is 2-fold greater than controls in children with diabetes and 3-fold greater in adolescents. Additionally, the prevalence of all psychopathology is altogether greater in people with diabetes. The course characteristics of depression in young diabetic subjects and psychiatric control subjects appear to be similar. However, eventual propensity of diabetic youths for more protracted depressions is greater. There is also a higher risk of recurrence among young diabetic females. On balance, anxiety and depression play an important and complex role in T1DM; their relationship to metabolic control does not yet appear clear. Therefore, the healthcare providers managing a child or adolescent with diabetes should be aware of their pivotal role as counselor and advisor and should closely monitor the mental health of patients with diabetes. Accordingly, the recommendation is screening for anxiety and/or depression in subjects exhibiting symptoms, using a validated screening tool, followed by the appropriate referral to mental health providers when warranted.

Fear of Self-Injecting and Self-Testing

Extreme fear of self-injecting insulin (*injection phobia*) is likely to compromise glycemic control as well as emotional well-being. Likewise, fear of finger pricks can be a source of distress and may seriously hamper self-management. Children and adolescents may either omit insulin dosing or refuse to rotate their injection sites because repeated injection in the same site is associated with less pain sensation. Failure to rotate injection sites results in subcutaneous scar formation (lipohypertrophy). Insulin injection into the lipohypertrophic skin is usually associated with poor insulin absorption, consequent frustration with lack of expected glucose control, and/or insulin leakage with resultant suboptimal glycemic control. Children and adolescents with injection phobia and fear of self-testing can be counseled by a trained behavioral therapist and benefit from such techniques as desensitization and biofeedback to attenuate pain sensation and psychologic distress associated with these procedures. Another possibility is to consider using an indwelling subcutaneous soft cannula to minimize the discomfort of repeated injections.

Eating Disorders

Treatment of T1DM involves constant monitoring of food intake. In addition, improved glycemic control is sometimes associated with increased weight gain. In adolescent females, these 2 factors, along with individual, familial, and socioeconomic factors, can lead to an increased incidence of both nonspecific and specific eating disorders, which can disrupt glycemic control and increase the risk of long-term complications. Eating disorders and subthreshold eating disorders are almost twice as common in adolescent females with T1DM as in their nondiabetic peers. The reports of the frequencies of specific (anorexia or bulimia nervosa) eating disorders vary from 1.0 to 6.9% among female patients with T1DM. The prevalence of nonspecific and subthreshold eating disorders is 9% and 14%, respectively. Approximately 11% of T1DM adolescent females take less insulin than prescribed in order to lose weight. Among adolescent females with T1DM and an eating disorder, approximately 42% of patients misuse insulin, whereas the estimates of insulin misuse prevalence in subthreshold and nondisordered eating groups are 18% and 6%, respectively. Although there is little information regarding the prevalence of eating disorders among male adolescents with T1DM, available data suggest normal eating attitudes in most. Among healthy adolescent males who participate in wrestling, however, the drive to lose weight has led to the seasonal, transient development of abnormal eating attitudes and behaviors, which may lead to insulin dose omission in order to lose weight.

When behavioral/psychologic problems and/or eating disorders are assumed to be responsible for poor adherence with the medical regimen, referral for psychologic evaluation and management is indicated. Behavioral therapists and psychologists usually form part of the pediatric diabetes team in most centers and can help assess and manage emotional and behavioral disorders in diabetic children. Evaluation of nurse-delivered motivational enhancement with and without cognitive behavior therapy in adults revealed that combined therapy resulted in modest improvement in glycemic control. However, motivational enhancement therapy alone did not improve glycemic control. While in some studies the effect of therapist-delivered motivational enhancement therapy on glycemic control in adolescents with T1DM lasted only as long as intensive individualized counseling continued, in other studies, motivational interviewing was shown to be an effective method of facilitating changes in a teenager's behavior with T1DM with corresponding improvement in glycemic control.

Management During Infections

Although infections are no more common in diabetic children than in nondiabetic ones, they can often disrupt glucose control and may precipitate DKA. In addition, the diabetic child is at increased risk of dehydration if hyperglycemia causes an osmotic diuresis or if ketosis causes emesis. Counterregulatory hormones associated with stress blunt insulin action and elevate glucose levels. If anorexia occurs from ketosis, lack of caloric intake increases the risk of hypoglycemia. Although children younger than 3 yr of age tend to become hypoglycemic and older children tend toward hyperglycemia, the overall effect is unpredictable. Therefore, frequent blood glucose monitoring, monitoring of urine and/or blood ketones, and adjustment of insulin doses are essential elements of **sick day guidelines** (Table 607.11).

Table 607.11

Guidelines for Sick Day Management

URINE KETONE STATUS	GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN		COMMENT
	INSULIN	CORRECTION DOSES*	
Negative or small †	q2 hr	q2 hr for glucose > 250 mg/dL	Check ketones every other void
Moderate to large ‡	q1 hr	q1 hr for glucose > 250 mg/dL	Check ketones each void; go to hospital if emesis occurs

[*] Give insulin based on individualized dosing schedule. Also give usual dose for carbohydrate intake if glucose >150 mg/dL.

[†] For home serum ketones <1.5 mmol/L per commercial kit.

[‡] For home serum ketones >1.5 mmol/L.

Basal insulin: glargine or detemir basal insulin should be given at the usual dose and time. NPH and Lente should be reduced by half if blood glucose <150 mg/dL and the oral intake is limited.

Oral fluids: sugar-free if blood glucose >250 mg/dL (14 mmol/L); sugar-containing if blood glucose <250 mg/dL.

Call physician or nurse if blood glucose remains elevated after 3 extra doses; if blood glucose remains <70 mg/dL and child cannot take oral supplement; if dehydration occurs.

The overall goals are to maintain hydration, control glucose levels, and avoid ketoacidosis. This can usually be done at home if proper sick day guidelines are followed and with telephone contact with healthcare providers. The development of ketones in a patient on insulin pump therapy may be a sign of infusion failure and the infusion set should be changed. The family should seek advice if home treatment does not control ketosis, hyperglycemia, or hypoglycemia, or if the child shows signs of dehydration or has persistent vomiting. A child with significant ketosis and emesis should be seen in the emergency department for a general examination, to evaluate hydration, and to determine whether ketoacidosis is present by checking serum electrolytes, glucose, pH, and total CO_2 . A child whose blood glucose declines to less than 50-60 mg/dL (2.8-3.3 mmol/L) and who cannot maintain oral intake may need IV glucose, especially if further insulin is needed to control ketosis.

Management During Surgery

Surgery can disrupt glucose control in the same way as can intercurrent infections. Stress hormones associated with the underlying condition as well as with surgery itself cause insulin resistance. This increases glucose levels, exacerbates fluid losses, and may initiate DKA. On the other hand, caloric intake is usually restricted, which decreases glucose levels. The net effect is as difficult to predict as during an infection. Vigilant monitoring and frequent insulin adjustments are required to maintain euglycemia and avoid ketosis.

For the majority of elective and other smaller surgical procedures, patients can simply be continued on their typical home basal regimens. This includes injection of the usual dose of long-acting insulin at the usual time for patients on shots. Patients on pumps can simply wear the pump during the surgery, if approved by hospital policy. Blood sugar should be monitored hourly during the procedure and peri-operatively; hyperglycemia can be corrected using the standard home ISF, and IV dextrose can be provided as needed for hypoglycemia. For major procedures, trauma, or situations where a prolonged period of decreased oral intake is expected postoperatively, it is advisable to manage insulin requirements with an IV insulin drip (Table 607.12). IV insulin is typically started at a dose of 0.03 units/kg/hour for patients who are euglycemic at the time of surgery. Serum glucose levels should be followed every hour operatively and peri-operatively, and the insulin dose and/or the dextrose concentration of the IV fluids can be adjusted as needed. In patients who are found to be hyperglycemic preoperatively (serum glucose > 250 mg/dL), it is advisable to check for ketones prior to starting surgery. If significant ketosis is identified, surgery should be delayed (if possible) until the ketosis can be treated and resolved. Postoperatively, the patient should not be discharged until blood glucose levels are stable and oral intake is tolerated.

Table 607.12

Guidelines for Intravenous Insulin Coverage During Surgery

BLOOD GLUCOSE LEVEL (mg/dL)	INSULIN INFUSION (units/kg/hr)	BLOOD GLUCOSE MONITORING
<120	0.00	1 hr
121-200	0.03	2 hr
200-300	0.06	2 hr
300-400	0.08	1 hr*
400	0.10	1 hr*

* Check urine ketones.

An infusion of 5% glucose and 0.45% saline solution with 20 mEq/L of potassium acetate is given at 1.5 times maintenance rate.

Long-Term Complications: Relation to Glycemic Control

Complications of DM include microvascular complications, such as retinopathy and nephropathy; macrovascular complications, including coronary artery disease, cerebrovascular disease, and peripheral vascular disease; peripheral and autonomic neuropathies; and diabetic osteopathy manifesting as increased risk for osteoporosis and fracture.

Diabetic Retinopathy

Diabetic retinopathy is the leading cause of blindness in the United States in adults age 20-65 yr. The risk of diabetic retinopathy after 15 yr duration of diabetes is 98% for individuals with T1DM and 78% for those with T2DM. Rates for diabetic retinopathy range from close to 15% to up to 30%. Lens opacities (caused by glycation of tissue proteins and activation of the polyol pathway) are present in at least 5% of those younger than age 19 yr. Metabolic control has an impact on the development of this complication, as prevalence rates are substantially higher with increased duration of diabetes, and higher HbA_{1c} , blood pressure, and cholesterol. Independent of duration, the prevalence of diabetic retinopathy is higher in T1DM. However, genetic factors also have a role, because only 50% of patients develop proliferative retinopathy. The earliest clinically apparent manifestations of diabetic retinopathy are classified as nonproliferative or background diabetic retinopathy—microaneurysms, dot and blot hemorrhages, hard and soft exudates, venous dilation and beading, and intraretinal microvascular abnormalities. These changes do not impair vision. The more severe form is proliferative diabetic retinopathy, which manifests by neovascularization, fibrous proliferation, and preretinal and vitreous hemorrhages. Proliferative retinopathy, if not treated, is relentlessly progressive and impairs vision, leading to blindness. The mainstay of treatment is panretinal laser photocoagulation. In advanced diabetic eye disease—manifested by severe vitreous hemorrhage or fibrosis, often with retinal detachment—vitrectomy is an important therapeutic modality. Eventually, the eye disease becomes quiescent, a stage termed involutional retinopathy. A separate subtype of retinopathy is diabetic maculopathy, which is manifested by severe macular edema impairing central vision. Focal laser photocoagulation may be effective in treating diabetic maculopathy.

Guidelines suggest that diabetic patients have an initial dilated and comprehensive examination by an ophthalmologist shortly after the diagnosis of diabetes is made in patients with T2DM, and within 3-5 yr after the onset of T1DM (but not before age 10 yr). Any patients with visual symptoms or abnormalities should be referred for ophthalmologic evaluation. Subsequent evaluations for both T1DM and T2DM patients should be repeated every 1-2 yr as recommended by an eye-care professional experienced in the diagnosis and management of diabetic retinopathy (Table 607.13).

Table 607.13

Screening Guidelines

	INITIAL TESTING	FREQUENCY	TEST
Thyroid disease	At diagnosis	Every 1-2 yr or sooner if symptoms	TSH, thyroid antibodies
Celiac	At diagnosis	Within 2 yr and again at 5 yr or sooner if symptoms	IgA and TTG

Hypertension	At diagnosis	Each visit	Elevated BP based on ≥ 90th% for age, sex, height on 3 separate occasions
Dyslipidemia	≥10 yr of age at diagnosis once glucose control established	If abnormal annually; every 5 yr if initially normal	Goal LDL-C < 100 mg/dL
Nephropathy	At puberty or age ≥ 10 yr whichever comes first, if T1DM ≥ 5 yr	Annually	Albuminuria; urine albumin to creatinine ratio
Retinopathy	T1DM ≥ 3-5 yr when ≥ 10 yr or puberty, whichever comes first	Annually	Dilated eye exam
Neuropathy	At puberty or ≥ 10 year, whichever earlier if T1DM > 5 yr	Annually	Foot exam

BP, blood pressure; IgA, immunoglobulin A; TSH, thyroid-stimulating hormone; TTG, tissue transglutaminase.

Data from American Diabetes Association: Children and adolescents: standards of medical care in diabetes—2018. *Diabetes Care* 41(Suppl 1):S126–S136, 2018.

Diabetic Nephropathy

Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD) in the United States. Most ESRD from diabetic nephropathy is preventable. Diabetic nephropathy affects 20–30% of patients with T1DM and 15–20% of T2DM patients 20 yr after onset. The mean 5 yr life expectancy for patients with diabetes-related ESRD is less than 20%. The increased mortality risk in long-term T1DM may be due to nephropathy, which may account for approximately 50% of deaths. The risk of nephropathy increases with duration of diabetes (up until 25-30 yr duration, after which this complication rarely begins), degree of metabolic control, and genetic predisposition to essential hypertension. Only 30–40% of patients affected by T1DM eventually experience ESRD. The glycation of tissue proteins results in glomerular basement membrane thickening. The course of diabetic nephropathy is slow. An increased urinary albumin excretion rate of 30-300 mg/24 hr (20-200 µg/min) —**microalbuminuria** —can be detected and constitutes an early stage of nephropathy from intermittent to persistent (incipient), which is commonly associated with glomerular hyperfiltration and blood pressure elevation. As nephropathy evolves to early overt stage with proteinuria (albumin excretion rate > 300 mg/24 hr, or > 200 µg/min), it is accompanied by hypertension. Advanced-stage nephropathy is defined by a progressive decline in renal function (declining glomerular filtration rate and elevation of serum blood urea and creatinine), progressive proteinuria, and hypertension. Progression to ESRD is recognized by the appearance of uremia, the nephritic syndrome, and the need for renal replacement (transplantation or dialysis).

Screening for diabetic nephropathy is a routine aspect of diabetes care (see Table 607.13). The American Diabetes Association recommends yearly screening for individuals with T2DM and yearly screening for those with T1DM after 5 yr duration of disease with a random spot urine sample for albumin to creatinine ratio. Abnormal results should be confirmed by 2 additional specimens on separate days because of the high variability of albumin excretion in patients with diabetes. Short-term hyperglycemia, strenuous exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient elevation in urinary albumin excretion. There is marked day-to-day variability in albumin excretion, so at least 2 of 3 collections done in a 3-6 mo period should show elevated levels before microalbuminuria is diagnosed and treatment is started. Once albuminuria is diagnosed, a number of factors attenuate the effect of hyperfiltration on kidneys: (1) meticulous control of hyperglycemia, (2) aggressive control of systemic blood pressure, (3) selective control of arteriolar dilation by use of angiotensin-converting enzyme inhibitors (thus decreasing transglomerular capillary pressure), and (4) dietary protein restriction (because high protein intake increases the renal perfusion rate). Tight glycemic control will delay the progression of microalbuminuria and slow the progression of diabetic nephropathy. Previous extensive therapy of diabetes has a persistent benefit for 7-8 yr and may delay or prevent the development of diabetic nephropathy.

Diabetic Neuropathy

Both the peripheral and autonomic nervous systems can be involved, and diabetic neuropathy can present in both children and adolescents. The etiology of diabetic neuropathy remains incompletely understood and the impact of hyperglycemia on its development remains uncertain. Observational studies done in the years prior to the era of intensive insulin therapy for T1DM generally reported higher incidence of neuropathy compared to more recent studies. However, several recent studies have found that the development of preclinical and symptomatic peripheral diabetic neuropathy in childhood was not strongly associated with either glycemic control or duration of disease. The polyol pathway, nonenzymatic glycation, and/or disturbances of myoinositol metabolism, affecting 1 or more cell types in the multicellular constituents of the peripheral nerve, have been hypothesized to have an inciting role. Other factors, such as possible direct neurotrophic effects of insulin, insulin-related growth factors, nitric oxide, and stress proteins, may also contribute to the development of neuropathy. Using quantitative sensory testing, abnormal cutaneous thermal perception is a common finding in both upper and lower limbs in neurologically asymptomatic young diabetic patients. Heat-induced pain threshold in the hand is correlated with the duration of the diabetes. There is no correlation between quantitative sensory testing scores and metabolic control. Subclinical motor nerve impairment as manifested by reduced sensory nerve conduction velocity and sensory nerve action potential amplitude have been detected in as many as 10–58% of children with diabetes. An early sign of autonomic neuropathy, such as decreased heart rate variability, may present in adolescents with a history of long-standing disease and poor metabolic control. A number of therapeutic strategies have been attempted with variable results. These treatment modalities include (1) improvement in metabolic control, (2) use of aldose reductase inhibitors to reduce by-products of the polyol pathway, (3) use of α-lipoic acid (an antioxidant) that enhances tissue nitric oxide and its metabolites, (4) use of anticonvulsants (e.g., lorazepam, valproate, gabapentin, carbamazepine, pregabalin, phenytoin, tiagabine, and topiramate) for treatment of neuropathic pain, and (5) use of antidepressants (amitriptyline, imipramine, and selective serotonin reuptake inhibitors). Additional medications include antiarrhythmics such as lidocaine, topical analgesics, and nonsteroidal antiinflammatory drugs.

Skeletal Effects of Type 1 Diabetes Mellitus

It has become apparent that the skeleton is adversely affected by diabetes, with T1DM patients at greater risk for skeletal complications than those with T2DM. T1DM is associated with an increased risk of fracture that first becomes evident in childhood and persists across the entire lifespan. This includes a dramatically increased hip fracture risk in adults, ranging from 2- to 7-fold higher than patients without diabetes, depending upon the population studied. Most, but not all, studies have shown T1DM to be associated with low bone mineral density. This differs from T2DM, where bone density is normal or even above average as a result of increased mechanical loading in association with obesity. The deficits in bone density do not appear to be sufficient to explain the degree of increased fracture risk, leading to the hypothesis that bone quality may be impaired as well. The mechanism(s) underlying diabetic related osteopathy is poorly understood and presumed to be multi-factorial. Most, but not all studies show association between poor glycemic control and adverse skeletal outcomes, suggesting a role for hyperglycemia and/or insulin deficiency. Chronic exposure to hyperglycemia may weaken bone strength through the accumulation of advanced glycation end products (AGEs) in bone. Other factors hypothesized to impair bone health in diabetes include chronic inflammation, abnormalities in the growth hormone-insulin-like growth factor 1 (IGF-1) axis, and abnormalities in bone mineral metabolism including excess urinary calcium loss. Currently, there are no standard guidelines for bone health screening in children. Assessment of bone density by DXA and markers of bone mineral metabolism is recommended in adults with fracture history and other risk factors for osteoporosis. Dietary education should reinforce the importance of meeting the RDA for calcium and vitamin D intake from diet and supplements.

Other Complications

The **Mauriac syndrome** is a rare complication related to chronic under-insulinization that is characterized by growth failure and hepatomegaly due to excess glycogen accumulation in the liver. It has become much less common since longer-acting insulins have become available. Clinical features of Mauriac syndrome include moon face, protuberant abdomen, proximal muscle wasting, and enlarged liver from fat and glycogen infiltration. The syndrome of limited joint mobility is frequently associated with the early development of diabetic microvascular complications, such as retinopathy and nephropathy, which may appear before 18 yr of age. In the past decade or 2, the prevalence of limited joint mobility has significantly decreased, which is attributed to the improved overall metabolic control of children and adolescents with T1DM.

Prognosis

T1DM is a serious, chronic disease. It has been estimated that the average life span of individuals with diabetes is approximately 10 yr shorter than that of the nondiabetic population, but with improved care, that figure is lessening consistently. Although diabetic children eventually attain a height within the normal adult range, puberty may be delayed, and the final height may be less than the genetic potential. From studies in identical twins, it is apparent that despite seemingly satisfactory control, the diabetic twin manifests delayed puberty and a substantial reduction in height when onset of disease occurs before puberty. These observations indicate that, in the past, conventional criteria for judging control were inadequate and that adequate control of T1DM was almost never achieved by routine means.

The continued development of closed-loop systems that may one day regulate glycemic control with minimal human input is one approach to the resolution of these long-term problems. In selected individuals, nearly normal patterns of blood glucose and other indices of metabolic control, including HbA_{1c} , have been maintained in short-term studies. Currently, this approach should be reserved for highly motivated families who are alert to the potential complications, such as mechanical failure of the infusion device causing hyperglycemia or hypoglycemia and infection at the site of catheter insertion.

The changing pattern of metabolic control is having a profound influence on reducing the incidence and the severity of certain complications. For example, after 20 yr of diabetes, there was a decline in the incidence of nephropathy in T1DM in Sweden among children whose disease was diagnosed in 1971–75 compared with in the preceding decade. In addition, in most patients with microalbuminuria in whom it was possible to obtain good glycemic control, microalbuminuria disappeared. This improved prognosis is directly related to metabolic control.

Pancreas and Islet Transplantation and Regeneration

In an attempt to cure T1DM, transplantation of a segment of the pancreas or of isolated islets has been performed in adults. These procedures are both technically demanding and associated with the risks of disease recurrence and complications of rejection or its treatment by immunosuppression. Long-term complications of immunosuppression include the development of malignancy. Some antirejection drugs, notably cyclosporine and tacrolimus, are toxic to the islets of Langerhans, impairing insulin secretion and even causing diabetes. Hence, segmental pancreas transplantation is generally only performed in association with transplantation of a kidney for a patient with ESRD due to diabetic nephropathy in which the immunosuppressive regimen is indicated for the renal transplantation. Several thousand such transplants have been performed in adults. With experience and better immunosuppressive agents, functional survival of the pancreatic graft may be achieved for up to several years, during which time patients may be in metabolic control with no or minimal exogenous insulin and reversal of some of the microvascular complications. However, because children and adolescents with DM are not likely to have ESRD from their diabetes, pancreas transplantation as a primary treatment in children cannot be recommended.

Islet cell transplantation is challenging because of limited survival of the transplanted cells and because of rejection. An islet transplantation strategy (Edmonton protocol) infused isolated pancreatic islets into the portal vein of adults with T1DM, along with immunosuppressive medications that had lower side-effect profiles than other drugs. While lasting insulin independence was initially low, engraftment and insulin independence have improved over the last decade, and over a thousand patients having undergone the procedure. There has been improved islet engraftment by the use of improved induction and maintenance immunosuppression. Still, in 5 yr follow-up studies, only ~10% maintain insulin independence, with an average duration of insulin independence in all of only about 15 mo. Long-term challenges remain the toxicity of immunosuppression, the limited procurement of viable tissue, and funding and limitations of engraftment itself.

Alternative means of generating β-cells are being sought from islet expansion, encapsulated islet xenografts, human islet cell-lines, and stem cells. Regeneration of islets is an approach that could potentially cure T1DM because β-cell mass is actually dynamically regulated.

607.3

Type 2 Diabetes Mellitus

David R. Weber, Nicholas Jospe

Formerly known as non–insulin dependent diabetes or adult-onset diabetes, T2DM is a heterogeneous disorder, characterized by peripheral insulin resistance and failure of the β-cell to keep up with increasing insulin demand. Patients with T2DM have relative rather than absolute insulin deficiency. Generally, they are not ketosis prone, but ketoacidosis is the initial presentation in 5–10% of affected subjects. The specific etiology is not known, but these patients do not have autoimmune destruction of β-cells, nor do they have any of the known causes of secondary diabetes (Table 607.14).

Table 607.14

Characteristics at Presentation for Type 1, Type 2, and Monogenic Diabetes

	TYPE 1 DIABETES	TYPE 2 DIABETES	MATURITY-ONSET DIABETES OF THE YOUNG
Age of onset during childhood and adolescence	Any	Rarely before puberty	Any
Weight status	Any	Rarely with normal weight	Any
Symptomatic (polyuria, polydipsia, weight loss)	Nearly universal	Two-thirds	Common
Duration of symptoms before presentation	<1 month	Frequently >1 month	Any
Diabetic ketoacidosis at presentation	Common	Rare (6–11%)	..
Family history of diabetes before age 40	Uncommon	Strong family history for type 2 diabetes	Very strong family history, classically in 3 generations
Acanthosis nigricans	Rare	Common (86%)	..
Ethnicity	Any	Predominantly black or minority ethnicity	Any
Diabetes-associated antibodies (IA2,	Positive in	Negative (<10%)	Negative (<1%)

glutamate decarboxylase, insulin)	majority		
Genetic mutation in *HNF1A*, *GCK* , or*HNF4A*	Negative	Negative	Nearly universal
Complications at presentation	Very rare	Common	Rare

IA2, tyrosine phosphatase-related islet antigen 2.

From Viner R, White B, Christie D: Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. *Lancet* 389:2252–2260, 2017.

Natural History

T2DM is considered a polygenic disease aggravated by environmental factors, with low physical activity and excessive caloric intake. Most patients are obese, although the disease can occasionally be seen in normal weight individuals. Asians in particular appear to be at risk for T2DM at lower degrees of total adiposity. Some patients may not necessarily meet overweight or obese criteria for age and gender despite abnormally high percentage of body fat in the abdominal region. Obesity, in particular central obesity, is associated with the development of insulin resistance. In addition, patients who are at risk for developing T2DM exhibit decreased glucose-induced insulin secretion. Obesity does not lead to the same degree of insulin resistance in all individuals and even those who develop insulin resistance do not necessarily exhibit impaired β-cell function. Thus, many obese individuals have some degree of insulin resistance but compensate for it by increasing insulin secretion. Those individuals who are unable to adequately compensate for insulin resistance by increasing insulin secretion develop IGT and IFG (usually, although not always, in that order). Hepatic insulin resistance leads to excessive hepatic glucose output (failure of insulin to suppress hepatic glucose output), while skeletal muscle insulin resistance leads to decreased glucose uptake in a major site of glucose disposal. Over time hyperglycemia worsens, a phenomenon that has been attributed to the deleterious effect of chronic hyperglycemia (glucotoxicity) or chronic hyperlipidemia (lipotoxicity) on β-cell function and is often accompanied by increased triglyceride content and decreased insulin gene expression. At some point, blood glucose elevation meets the criteria for diagnosis of T2DM (see Table 607.2), but most patients with T2DM remain asymptomatic for months to years after this point because hyperglycemia is moderate and symptoms are not as dramatic as the polyuria and weight loss at presentation of T1DM. Weight gain may even continue. The prolonged hyperglycemia may be accompanied by the development of microvascular and macrovascular complications. Among the differences between T2DM in children and adults is a faster decline in beta cell function and insulin secretion, as well as faster development of diabetes complications. In time, β-cell function can decrease to the point that the patient has absolute insulin deficiency and becomes dependent on exogenous insulin. In T2DM, insulin deficiency is rarely absolute, so patients usually do not need insulin to survive. Nevertheless, at the time of diagnosis, glycemic control can be best improved by exogenous insulin. Although DKA is uncommon in patients with T2DM, it can occur and is usually associated with the stress of another illness such as severe infection. DKA tends to be more common in African American patients than in other ethnic groups. Although it is generally believed that autoimmune destruction of pancreatic β-cells does not occur in T2DM, autoimmune markers of T1DM—namely, glutamic acid decarboxylase antibody, ICA512, and insulin-associated autoantibody—may be positive in up to one third of the cases of adolescent T2DM. The presence of these autoimmune markers does not rule out T2DM in children and adolescents. At the same time, because of the general increase in obesity, the presence of obesity does not preclude the diagnosis of T1DM. Although the majority of newly diagnosed children and adolescents can be confidently assigned a diagnosis of T1DM or T2DM, a few exhibit features of both types and are difficult to classify.

Epidemiology

The Search for Diabetes in Youth (SEARCH) study found that the prevalence of T2DM in the 10-19 yr old age group in the United States was 0.24/1000 in 2009. The incidence of T2DM in children has risen dramatically in recent years, from 9 cases per 100,000 youth in 2002 to 12.5 cases per 100,000 in 2011. Certain ethnic groups appear to be at higher risk; for example, Native Americans, Hispanic Americans, and African Americans (in that order) have higher incidence rates than white Americans (Fig. 607.8). Although a majority of children presenting with diabetes still have T1DM, the percentage of children presenting with T2DM is increasing and represents up to 50% of the newly diagnosed children in some centers.

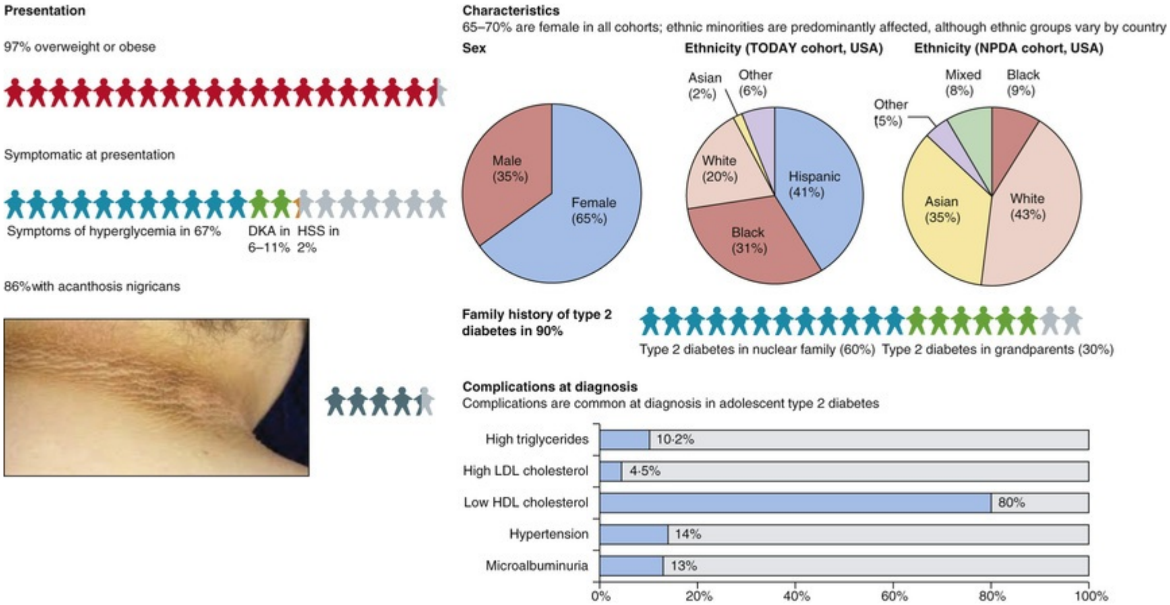

FIG. 607.8 **Features of adolescent type 2 diabetes at diagnosis. DKA, diabetic ketoacidosis. HHS, hyperglycemic hyperosmolar syndrome. (From Viner R, White B, Christie D: Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. *Lancet* 389:2252–2260, 2017.)**

Prevalence in the rest of the world varies widely and accurate data are not available for many countries, but it is clear that the prevalence is increasing in every part of the world. Asians in general seem to develop T2DM at lower body mass index levels than Europeans. In conjunction with their low incidence of T1DM, this means that T2DM accounts for a higher proportion of childhood diabetes in many Asian countries.

The epidemic of T2DM in children and adolescents parallels the emergence of the obesity epidemic. Although obesity itself is associated with insulin resistance, diabetes does not develop until there is some degree of failure of insulin secretion. Thus, when measured, insulin secretion in response to glucose or other stimuli is always lower in persons with T2DM than in control subjects matched for age, sex, weight, and equivalent glucose concentration.

Genetics

T2DM has a strong genetic component; concordance rates among identical twins are in the 40–80% range, but there is not a simple Mendelian pattern. It should be kept in mind, however, that twinning itself increases the risk of T2DM (because of intrauterine growth restriction) and this may distort estimates of genetic risk. Monozygotic twins have a lifetime concordance of T2DM of around 70%, indicating that shared environmental factors (including the prenatal environment) may play a large role in the development of T2DM, and dizygotic twins have a lifetime concordance of around 20–30%. The genetic basis for T2DM is complex and incompletely defined; no single identified defect predominates, as does the HLA association with T1DM. Genome-wide association studies have now identified certain genetic polymorphisms that are associated with increased T2DM risk in most populations studied; the most consistently identified are variants of the TCF7L2 (transcription factor 7—like 2) gene, which may have a role in β-cell function. Other identified risk alleles include variants in *PPARG* and *KCNJ11-ABCC8* as well as many others. But to date, and together, all these identified variants explain only a small portion (probably less than 20%) of the population risk of diabetes and in many cases the mechanism by which these polymorphisms confer risk of T2DM is not clear so far. It is hoped that these will provide clues to the vexing problem of disease pathophysiology and address new venues for therapy.

Epigenetics and Fetal Programming

Low birthweight and intrauterine growth restriction are associated with increased risk of T2DM. This risk appears to be higher in low-birthweight infants who gain weight more rapidly in the 1st few years of life. These findings have led to the formulation of the *thrifty phenotype* hypothesis, which postulates that poor fetal nutrition somehow programs these children to maximize storage of nutrients and makes them more prone to future weight gain and development of diabetes. Epigenetic modifications may play a role in this phenomenon, given that so few of the known T2DM genes are associated with low birthweight, but the detailed molecular mechanisms involved have yet to be determined. Whatever the exact mechanism, altered methylation profiles and/or transcriptional dysregulation and histone modifications, prenatal and early childhood environments play an important role in the pathogenesis of T2DM and may do so by epigenetic modification of the DNA (in addition to other factors).

Environmental and Lifestyle-Related Risk Factors

Obesity is the most important lifestyle factor associated with development of

T2DM. This, in turn, is associated with the intake of high-energy foods, physical inactivity, TV viewing (screen time), and low socioeconomic status (in developed countries). Maternal smoking also increases the risk of diabetes and obesity in the offspring. Increasingly, exposure to land pollutants and air pollutants is demonstrated to contribute to insulin resistance. The lipophilic nature of these organic pollutants and their consequent storage in adipose tissue may promote obesity and insulin resistance. In addition, sleep deprivation and psychosocial stress are associated with increased risk of obesity in childhood and with IGT in adults, possibly via over-activation of the hypothalamic-pituitary-adrenal axis. Many antipsychotics (especially the atypical antipsychotics like olanzapine and quetiapine) and antidepressants (both tricyclic antidepressants and newer antidepressants like fluoxetine and paroxetine) induce weight gain. In addition to the risk conferred by increased obesity, some of these medications may also have a direct role in causing insulin resistance, β-cell dysfunction, leptin resistance, and activation of inflammatory pathways. To complicate matters further, there is evidence that schizophrenia and depression themselves increase the risk of T2DM and the metabolic syndrome, independent of the risk conferred by drug treatment. As a result, both obesity and T2DM are more prevalent in this population. Furthermore, with increasing use of antipsychotics and antidepressants in the pediatric population, this association is likely to become stronger.

Clinical Features

In the United States, T2DM in children is more likely to be diagnosed in Native American, Hispanic American, and African American youth, with the highest incidence being reported in Pima Indian youth. While cases may be seen as young as 4 yr of age, most are diagnosed in adolescence and incidence increases with increasing age. Family history of T2DM is present in practically all cases. Typically, patients are obese and present with mild symptoms of polyuria and polydipsia, or are asymptomatic and T2DM is detected on screening tests. Presentation with DKA occurs in up to 10% of cases. Physical examination frequently reveals the presence of acanthosis nigricans, most commonly on the neck and in other flexural areas. Other findings may include striae and an increased waist to hip ratio. Laboratory testing reveals elevated HbA_{1c} levels. Hyperlipidemia characterized by elevated triglycerides and low-density lipoprotein cholesterol levels is commonly seen in patients with T2DM at diagnosis. Consequently, lipid screening is indicated in all new cases of T2DM. As well, the current recommendation is that blood pressure measurement, random urine albumin to creatinine ratio, and a dilated eye examination should be performed at diagnosis. Because hyperglycemia develops slowly, and patients may be asymptomatic for months or years after they develop T2DM, screening for T2DM is recommended in high-risk children (Table 607.15). The American Diabetes Association recommends that all youth who are overweight and have at least 2 other risk factors be tested for T2DM beginning at age 10 yr or at the onset of puberty and every 2 yr after that. Risk factors include family history of T2DM in first- or second-degree relatives, history of gestational diabetes in the mother, belonging to certain ethnic groups (i.e., Native American, African American, Hispanic, or Asian/Pacific Islander groups), and having signs of insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome). The current recommendation is to use fasting blood glucose as a screening test, but some authorities now recommend that HbA_{1c} be used as a screening tool. In borderline or asymptomatic cases, the diagnosis may be confirmed using a standard oral glucose tolerance test, but this test is not required if typical symptoms are present or fasting plasma glucose or HbA_{1c} is clearly elevated on 2 separate occasions.

Table 607.15

Testing for Type 2 Diabetes in Children

- Criteria[*]

  Overweight (body mass index >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

  Plus

  Any 2 of the following risk factors:
  - Family history of type 2 diabetes in 1st- or 2nd-degree relative
  - Race/ethnicity (Native American, African American, Hispanic, Asian/Pacific Islander)
  - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)
- Age of initiation: age 10 yr or at onset of puberty if puberty occurs at a younger age
- Frequency: every 2 yr
- Test: fasting plasma glucose preferred

[*] Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

From Type 2 diabetes in children and adolescents. American Diabetes Association, *Diabetes Care* 23:386, 2000. Reproduced by permission.

Treatment

T2DM is a progressive syndrome that gradually leads to complete insulin deficiency during the patient's life. A systematic approach for treatment of T2DM should be implemented according to the natural course of the disease, including adding insulin when hypoglycemic oral agent failure occurs. Nevertheless, lifestyle modification (diet and exercise) is an essential part of the treatment regimen, and consultation with a dietitian is usually necessary. This is particularly so because the largest pediatric clinical trial to date, the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY study), showed that oral agent monotherapy did not maintain lasting glucose control in close to half of those with T2DM.

There is no particular dietary or exercise regimen that has been conclusively shown to be superior and practitioners recommend a low-calorie, low-fat diet and 30-60 min of physical activity at least 5 times/wk. The ultimate goal is to bring the BMI below the 85% for age and gender, with attention to weight reduction versus maintenance depending on the age of the subject. Screen time should be limited to 1-2 hr/day. Children with T2DM often come from household environments with a poor understanding of healthy eating habits. Commonly observed behaviors include skipping meals, heavy snacking, and excessive daily television viewing, video game playing, and computer use. Adolescents engage in non–appetite-based eating (i.e., emotional eating, television-cued eating, boredom) and cyclic dieting (“yo-yo” dieting). Treatment in these cases is frequently challenging and may not be successful unless the entire family buys into the need to change their unhealthy lifestyle.

It is recommended, unless insulin needs to be used at the outset, that oral hypoglycemic agents be introduced at the time of diagnosis (Tables 607.16 and 607.17). Patients who present with DKA or with markedly elevated HbA_{1c} (>9.0%) will require treatment with insulin using protocols similar to those used for treating T1DM. Once blood glucose levels are under control, most cases can be managed with oral hypoglycemic agents and lifestyle interventions, but some patients will continue to require insulin therapy. Ongoing care should include periodic review of weight and BMI, diet, and physical activity, blood glucose monitoring, and monitoring of HbA_{1c} at 3 mo intervals. Frequency of home glucose monitoring can range from 3 to 4 times daily for those on multiple daily insulin injections, to twice daily for those on a stable insulin long-acting regimen or metformin.

Table 607.16

Summary of Medications

MEDICATIONS	CLASS	MECHANISM OF ACTION	ROUTE	FDA-APPROVED AGE
Pramlintide	Amylin analogue	Increases satiety, slows gastric emptying, and suppresses postprandial glucagon secretion, resulting in decreased postmeal glucose excursions	Subcutaneous injection	>18 yr
Metformin	Biguanide	Improves hepatic insulin sensitivity. Increases GLP-1 and PYY	Oral	10-18 yr
Colesevelam*	Bile acid sequestrant	Increases GLP-1 secretion and may increase peripheral insulin sensitivity	Oral	>10 yr †
Alogliptin* Linagliptin* Saxagliptin* Sitagliptin*	DPP-4 inhibitors	Inhibits DPP-4 from degrading GLP-1 and GIP	Oral	>18 yr
Albiglutide Dulaglutide Exenatide* Liraglutide*	Glucagon-like peptide agonists	Increase release of GLP-1, which stimulates release of insulin	Subcutaneous injection	>18 yr
Afrezza	Rapid-acting insulin	Pulmonary absorption of regular human insulin into systemic circulation	Inhaled	>18 yr
Degludec*	Long-acting insulin	Addition of hexadecanoic acid to lysine allows for multihexamer depot for slow insulin release	Subcutaneous injection	Awaiting new drug application to FDA
Detemir	Long-acting insulin	Addition of a fatty acid to lysine facilitates insulin binding to albumin resulting in slow insulin release	Subcutaneous injection	≥6 yr
Glargine u300	Long-acting insulin	Substitution of glycine and addition of 2 arginines at the carboxy terminal causes crystallization at physiologic pH resulting in slow insulin release	Subcutaneous injection	>18 yr for the u300 (300 units/mL) form >5 yr for the u100 (100 units/mL) form
Peglispro*	Long-acting insulin	Reversal of lysine and proline at the carboxy terminal with the addition of PEG results in slow insulin release	Subcutaneous injection	Awaiting new drug application to FDA ≥3 yr for the nonpegylated lispro
Nateglinide Repaglinide	Meglitinides	Causes rapid secretion of insulin by acting on the ATP sensitive potassium channel of pancreatic beta cells	Oral	>18 yr
Canagliflozin Dapagliflozin	Sodium-glucose	Promotes renal excretion of glucose at the level of the proximal tubule causing an	Oral	>18 yr

Empagliflozin[*]	cotransporter 2 inhibitors	osmotic diuresis		

[*] Ongoing clinical trials in pediatrics.

[†] Lipid lowering only, www.accessdata.fda.gov .

ATP, adenosine triphosphate; GIP, glucose-dependent insulinotropic peptide; PEG, polyethylene glycol; PYY, peptide YY.

From Meehan C, Silverstein J: Treatment options for type 2 diabetes in youth remain limited. *J Pediatr* 170:20–27, 2016.

Table 607.17

Existing and Future Glucose-Lowering Therapeutic Options by Organ or Organ System

	PATHOPHYSIOLOGICAL DEFECT	**GLUCOSE-LOWERING THERAPY**	
		Existing	**Future (Phase 1-3 Clinical Trials)**
Pancreatic β cell	Loss of cell mass and function; impaired insulin secretion	Sulfonylureas; meglitinides	Imeglimin
Pancreatic α cell	Dysregulated glucagon secretion; increased glucagon concentration	GLP-1 receptor agonist	Glucagon-receptor antagonists
Incretin	Diminished incretin response	GLP-1 receptor agonist; DPP-IV inhibitors	Oral GLP-1 receptor agonist; once-weekly DPP-IV inhibitors
Inflammation	Immune dysregulation	GLP-1 receptor agonist; DPP-IV inhibitors	Immune modulators; antiinflammatory agents
Liver	Increased hepatic glucose output	Metformin; pioglitazone	Glucagon-receptor antagonists
Muscle	Reduced peripheral glucose uptake; insulin resistance	Metformin; pioglitazone	Selective PPAR modulators
Adipose tissue	Reduced peripheral glucose uptake; insulin resistance	Metformin; pioglitazone	Selective PPAR modulators; FGF21 analogues; fatty acid receptor agonists
Kidney	Increased glucose reabsorption caused by upregulation of SGLT-2 receptors	SGLT-2 inhibitors	Combined SGLT-1/-2 inhibitors
Brain	Increased appetite; lack of satiety	GLP-1 receptor agonist	GLP-1-glucagon-gastric inhibitory peptide dual or triple agonists
Stomach or intestine	Increased rate of glucose absorption	GLP-1 receptor agonist; DPP-IV inhibitors; alpha-glucosidase inhibitors; pramlintide	SGLT-1 inhibitors
Colon (microbiome)	Abnormal gut microbiota	Metformin; GLP-1 receptor agonist; DPP-IV inhibitors	Probiotics

DPP-IV inhibitors, dipeptidyl peptidase-IV inhibitors; FGF21, fibroblast growth factor 21; GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide-1; PPAR, peroxisome proliferator-activated receptor; SGLT-1/SGLT-2 inhibitors, sodium glucose co-transporter-1/sodium glucose co-transporter-2 inhibitors.

From Chatterjee S, Khunti K, Davies MJ: Type 2 diabetes. *Lancet* 389:2239–2250, 2017, Table 1.

The most commonly used and the only FDA-approved oral agent for the treatment of T2DM in children and adolescents is metformin. Renal function must be assessed before starting metformin as impaired renal function has been associated with potentially fatal lactic acidosis. Significant hepatic dysfunction is also a contraindication to metformin use, although mild elevations in liver enzymes may not be an absolute contraindication. The usual starting dose is 500 mg once daily, with dinner to minimize the potential for side effects. This may be increased to a maximum dose of 2,000 mg/day. Abdominal symptoms are common early in the course of treatment, but in most cases they will resolve with time.

Other agents such as thiazolidinediones, sulfonylureas, acarbose, pramlintide, incretin mimetics, and sodium-glucose transport protein inhibitors are being used routinely in adults but are not used as commonly in pediatrics. While the number of classes of glucose-lowering medications has close to tripled in the past years, these have not been readily studied for use in children, nor therefore approved. Lastly, they have relatively weak glucose-lowering effects. Sulfonylureas are widely used in adults, but experience in pediatrics is limited. Sulfonylureas cause insulin release by closing the potassium channel (K_{ATP}) on β-cells. They are occasionally used when metformin monotherapy is unsuccessful or contraindicated for some reason (use in certain forms of neonatal diabetes is discussed in the section on neonatal diabetes). Thiazolidinediones are not approved for use in pediatrics. Pramlintide (Symlin) is an analog of IAPP (islet amyloid polypeptide), which is a peptide that is co-secreted with insulin by the β-cells and acts to delay gastric emptying, suppress glucagon, and possibly suppress food intake. It is not yet approved for pediatric use. Incretins are gut-derived peptides like GLP-1, GLP-2, and GIP (glucose-dependent insulinotropic peptide, previously known as gastric inhibitory protein) that are secreted in response to meals and act to enhance insulin secretion and action, suppress glucagon production, and delay gastric emptying (among other actions). GLP-1 analogs (e.g., exenatide) and agents that prolong endogenous GLP-1 action (e.g., sitagliptin) are now available for use in adults but are not yet approved for use in children; they may be associated with side effects such as hepatic injury and pancreatitis. The sodium-glucose transport protein (SGLT-2) inhibitors are a new class of glucose-lowering drugs. They act by blocking glucose reabsorption in the proximal renal tubule, but their effect is of course limited by the amount of glucose delivered to the tubule. As of this writing, these drugs are being studied in the pediatric population and may thus soon be approved for use. Lastly, bariatric surgical therapy, such as gastric bypass or banding, is not yet recommended for youth with T2DM, and while the experience is limited, it is growing such that long-term outcomes will be forthcoming. Guidelines are emerging that suggest that bariatric surgery may be indicated in certain conditions in late adolescence with BMI > 40 kg/m^2 .

Complications

In the SEARCH study of diabetes in youth, 92% of the patients with T2DM had 2 or more elements of the metabolic syndrome (hypertension, hypertriglyceridemia, decreased high-density lipoprotein, increased waist circumference), including 70% with hypertension. In addition, the incidence of microalbuminuria and diabetic retinopathy appears to be higher in T2DM than it is in T1DM. In the SEARCH study, the incidence of microalbuminuria among patients who had T2DM of less than 5 yr duration was 7–22%, while retinopathy was present in 18.3%. Thus, all adolescents with T2DM should be screened for hypertension and lipid abnormalities. Screening for microalbuminuria and retinopathy may be indicated even earlier than it is in T1DM. Treatment guidelines are the same as those for children with T1DM. Sleep apnea and fatty liver disease are being diagnosed with increasing frequency and may necessitate referral to the appropriate specialists. Complications associated with all forms of diabetes and recommendations for screening are noted in Table 607.13 ; Table 607.18 lists additional conditions particularly associated with T2DM.

Table 607.18

Monitoring for Complications and Comorbidities

CONDITION	SCREENING TEST	COMMENT
Hypertension	Blood pressure	
Fatty liver	Aspartate aminotransferase, alanine aminotransferase, possibly liver ultrasound	
Polycystic ovary syndrome	Menstrual history, assessment for androgen excess with free/total testosterone, dehydroepiandrosterone sulfate	
Microalbuminuria	Urine albumin concentration and albumin to creatinine ratios	

Dyslipidemia	Fasting lipid profile (total, low-density lipoprotein, high-density lipoprotein cholesterol, triglycerides)	Obtain at diagnosis and every 2 yr
Sleep apnea	Polysomnography: Sleep study to assess overnight oxygen saturation, airflow, heart rate, electromyography, and eye movements	

From Liu L, Hironaka K, Pihoker C: Type 2 diabetes in youth, *Curr Probl Pediatr Adolesc Health Care* 34:249–280, 2004.

Prevention

The difficulties in achieving good glucose control and preventing diabetes complications make prevention a compelling strategy. This is particularly true for T2DM, which is clearly linked to modifiable risk factors (obesity, a sedentary lifestyle). The Diabetes Prevention Program was designed to prevent or delay the development of T2DM in adult individuals at high risk by virtue of IGT. The Diabetes Prevention Program results demonstrated that intensified lifestyle or drug intervention in individuals with IGT prevented or delayed the onset of T2DM. The results were striking. Lifestyle intervention reduced the diabetes incidence by 58%; metformin reduced the incidence by 31% compared with placebo. The effects were similar for men and women and for all racial and ethnic groups. Lifestyle interventions are believed to have similar beneficial effects in obese adolescents with IGT. Screening is indicated for at-risk patients (see Table 607.13).

607.4

Other Specific Types of Diabetes

David R. Weber, Nicholas Jospe

Keywords

monogenic diabetes
maturity onset diabetes of youth (MODY)

transient neonatal diabetes
permanent neonatal diabetes
lipoatrophy
Hashimoto disease
celiac disease
Addison disease
cystic fibrosis related diabetes
autoimmune polyendocrine syndrome

Most cases of diabetes in children as well as adults fall into the 2 broad categories of type 1 and type 2 diabetes, but between 1% and 10% of cases are caused by single-gene disorders. These disorders include hereditary defects of β-cell function and insulin action, as well as rare forms of mitochondrial diabetes.

Genetic Defects of β-Cell Function

Transient Neonatal Diabetes Mellitus

Neonatal diabetes is transient in approximately 50% of cases, but after an interim period of normal glucose tolerance, 50–60% of these patients develop permanent diabetes (at an average age of 14 yr). There are also reports of patients with classic T1DM who formerly had transient diabetes as a newborn. It remains to be determined whether this association of transient diabetes in the newborn followed much later in life by classic T1DM is a chance occurrence or causally related (Fig. 607.9).

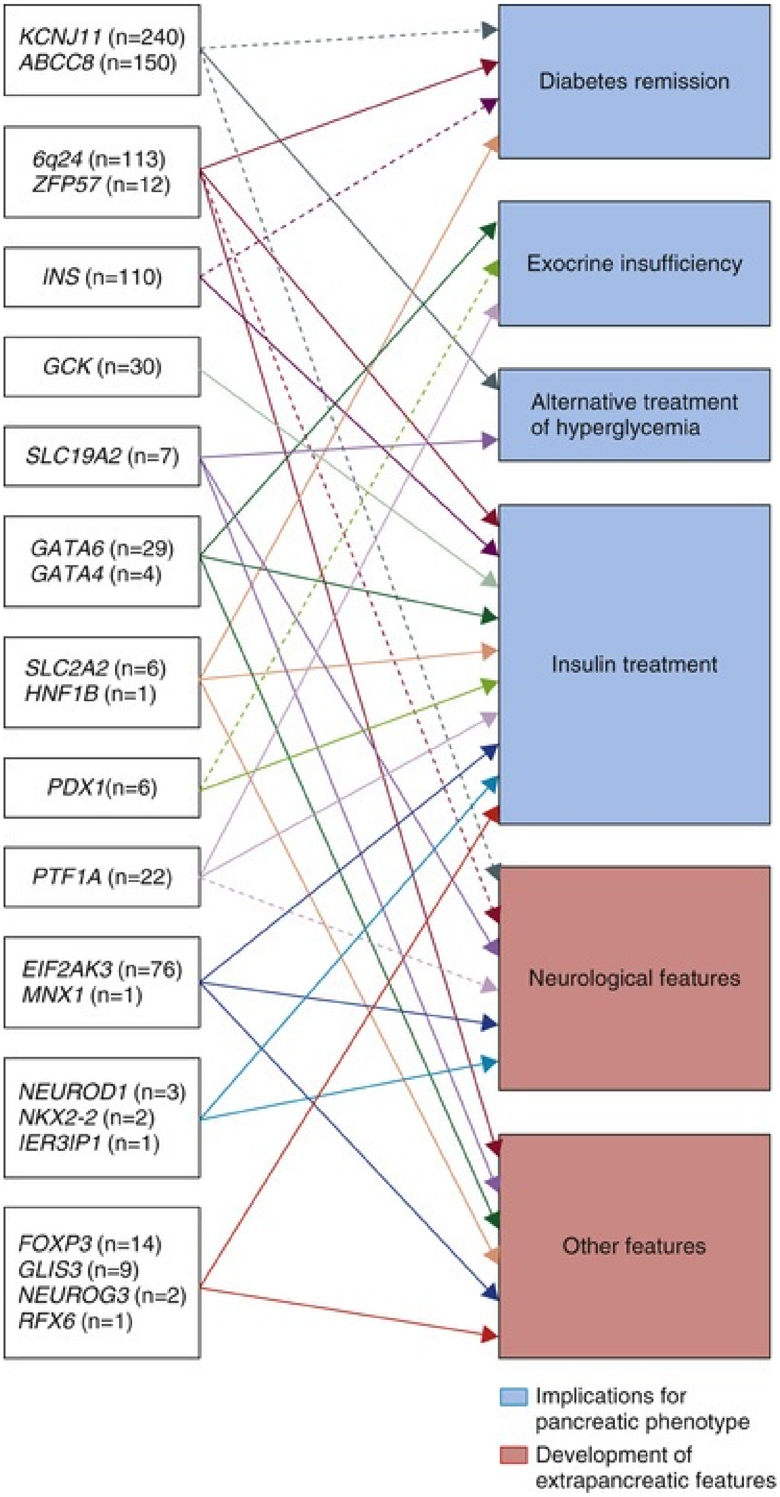
KCNJ11 (n=240)
ABCC8 (n=150)
6q24 (n=113)
ZFP57 (n=12)
INS (n=110)
GCK (n=30)
SLC19A2 (n=7)
GATA6 (n=29)
GATA4 (n=4)
SLC2A2 (n=6)
HNF1B (n=1)
PDX1(n=6)
PTF1A (n=22)
EIF2AK3 (n=76)
MNX1 (n=1)
NEUROD1 (n=3)
NKX2-2 (n=2)
IER3IP1 (n=1)
FOXP3 (n=14)
GLIS3 (n=9)
NEUROG3 (n=2)
RFX6 (n=1)
Diabetes remission
Exocrine insufficiency
Alternative treatment of hyperglycemia
Insulin treatment
Neurological features
Other features
🟦 Implications for pancreatic phenotype
🟥 Development of extrapancreatic features

FIG. 607.9 **A genetic diagnosis guides clinical management. Schematic representation of genetic causes of neonatal diabetes and the implications of this genetic diagnosis. *n* indicates the number of patients identified with mutations in each of the genes in the 1,020 neonatal diabetes patient cohort. Solid arrows indicate implications for most mutations in the genes. Dashed arrows indicate the implications for specific mutations. (From De Franco E, Flanagan SE, Houghton JAL, et al: The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet* 386:957–963, 2015, Fig. 3.)**

The syndrome of **transient DM** in the newborn infant has its onset in the 1st wk of life and persists several weeks to months before spontaneous resolution. Median duration is 12 wk. It occurs most often in infants who are small for gestational age and is characterized by hyperglycemia and pronounced glycosuria, resulting in severe dehydration and, at times, metabolic acidosis, but with only minimal or no ketonemia or ketonuria. There may also be findings such as umbilical hernia or large tongue. Insulin responses to glucose or tolbutamide are low to absent; basal plasma insulin concentrations are normal. After spontaneous recovery, the insulin responses to these same stimuli are brisk and normal, implying a functional delay in β-cell maturation with spontaneous resolution. Occurrence of the syndrome in consecutive siblings has been reported. About 70% of cases are due to abnormalities of an imprinted locus on chromosome 6q24, resulting in overexpression of paternally expressed genes such as pleomorphic adenoma gene–like 1 *(PLAGL1/ZAC)* and hydatidiform mole associated and imprinted *(HYMAI)*. Most of the remaining cases are caused by mutations in K_{ATP} channels. Mutations in K_{ATP} channels also cause many cases of PND, but there is practically no overlap between the mutations that lead to transient neonatal DM and those causing permanent neonatal DM. This syndrome of transient neonatal DM should be distinguished from the severe hyperglycemia that may occur in hypertonic dehydration; that usually occurs in infants beyond the newborn period and responds promptly to rehydration with minimal or no requirement for insulin.

Administration of insulin is mandatory during the active phase of DM in the newborn. Rehydration and IV insulin is usually required initially; transition to subcutaneous insulin can occur once clinically stable. A variety of regimens including intermediate or long-acting insulin given in 1-2 daily doses or continuous insulin therapy with an insulin pump have been used successfully. The starting dose is typically 1-2 units/kg/day but will need to be adjusted based upon blood glucose levels. Attempts at gradually reducing the dose of insulin may be made as soon as recurrent hypoglycemia becomes manifested or after 2 mo of age. Genetic testing is now available for 6q24 abnormalities as well as potassium channel defects and should be obtained on all patients, and recurrence risk assessment by a genetic counselor is recommended.

Permanent Neonatal Diabetes Mellitus

Permanent DM in the newborn period is caused, in approximately 50% of the cases, by mutations in the *KCNJ11* (potassium inwardly rectifying channel J, member 11) and *ABCC8* (adenosine triphosphate–binding cassette, subfamily C, member 8) genes (see Figs. 607.9 and 607.10). These genes code for the Kir6.2 and SUR1 subunits of the adenosine triphosphate–sensitive potassium channel, which is involved in an essential step in insulin secretion by the β-cell. Some cases are caused by pancreatic agenesis as a result of homozygous mutations in the *IPF-1* gene (where heterozygous mutations cause MODY4); homozygous mutations in the glucokinase gene (where heterozygous mutations cause MODY2); and mutations in the insulin gene. Almost all these infants are small at birth because of the role of insulin as an intrauterine growth factor. Instances of affected twins and families with more than 1 affected infant have been reported. Infants with permanent neonatal DM may be initially euglycemic and typically present between birth and 6 mo of life (mean age of presentation is 5 wk). There is a spectrum of severity and up to 20% have neurologic features. The most severely affected patients have the syndrome of *d* evelopmental delay, *e* pilepsy and *n* eonatal *d* iabetes (**DEND syndrome**). Less-severe forms of DEND are labeled intermediate DEND or i-DEND.

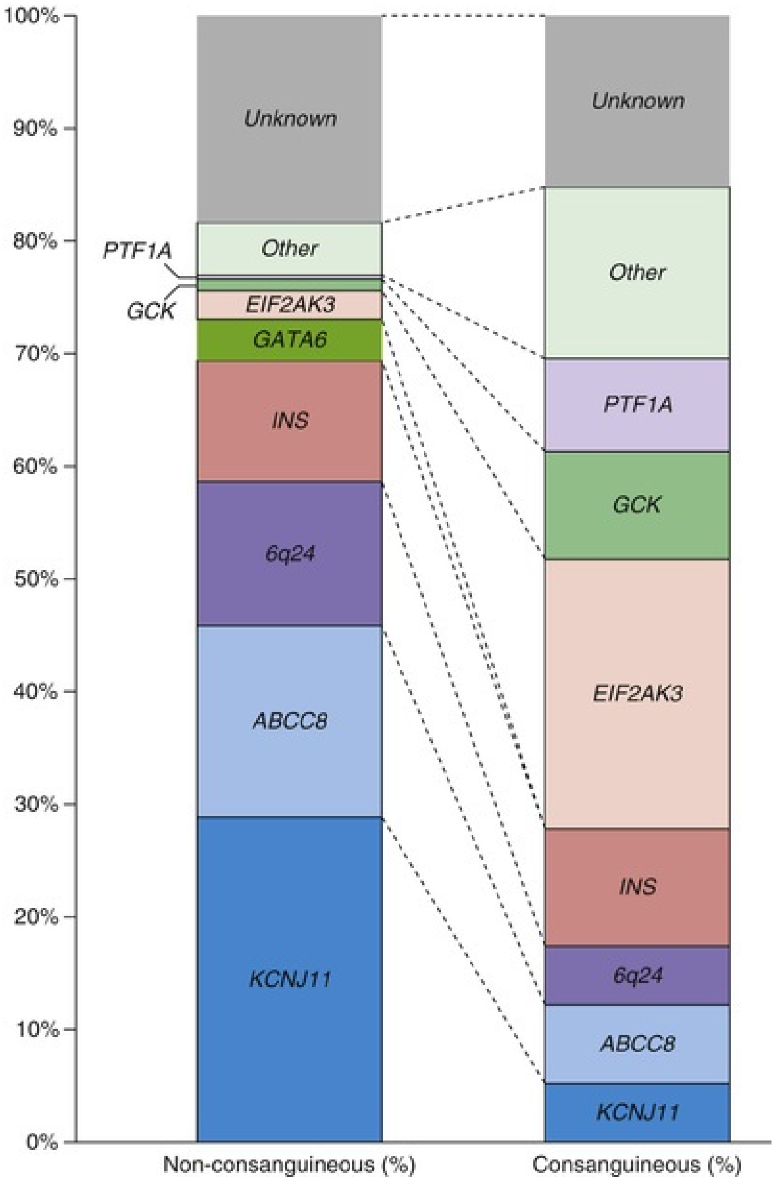

FIG. 607.10 Different genetic causes of neonatal diabetes in patients born to non-consanguineous and consanguineous parents. Comparison of genetic causes of neonatal diabetes in non-consanguineous (*n* = 790) and consanguineous groups (*n* = 230). Consanguinity is defined by parents being second cousins or more closely related or by the presence of 1·56% or higher total homozygosity. Genes mutated in fewer than 2·5% of patients in both cohorts were grouped in the other category. (From De Franco E, Flanagan SE, Houghton JAL, et al: The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet* 386:957–963, 2015, Fig. 2.)

Activating mutations in the *KCNJ11* gene (encoding the adenosine triphosphate–sensitive potassium channel subunit Kir6.2) are associated with both transient neonatal DM and permanent neonatal DM, with particular mutations being associated with each phenotype. More than 90% of these patients respond to sulfonylureas (at higher doses than those used in T2DM), but patients with severe neurologic disease may be less responsive. Mutations in the *ABCC8* gene (encoding the SUR1 subunit of this potassium channel) were thought to be less likely to respond to sulfonylureas (because this is the subunit that binds sulfonylurea drugs), but some of these mutations are reported to respond and patients have been successfully switched from insulin to oral therapy. Several protocols for switching the patient from insulin to glibenclamide are available and patients are usually stabilized on doses ranging from 0.4 to 1 mg/kg/day. Because approximately 50% of neonatal diabetics have K-channel mutations that can be switched to sulfonylurea therapy, with dramatic improvement in glycemic control and quality of life, *all patients with diabetes diagnosed before 6 mo of age (and perhaps even those diagnosed before 12 mo of age) should have genetic testing.*

Maturity-Onset Diabetes of Youth

Several forms of diabetes are associated with **monogenic defects in β-cell function** . Before these genetic defects were identified, this subset of diabetics was diagnosed on clinical grounds and described by the term MODY. This subtype of DM consists of a group of heterogeneous clinical entities that are characterized by onset before 25 yr, autosomal dominant inheritance, and a primary defect in insulin secretion. Strict criteria for the diagnosis of MODY include diabetes in at least 3 generations with autosomal dominant transmission and diagnosis before age 25 yr in at least 1 affected subject. Mutations have been found in at least 11 different genes, accounting for the dominantly inherited monogenic defects of insulin secretion, for which the term MODY is used. The American Diabetes Association groups these disorders together under the broader category of *genetic defects of β-cell function* . Eleven of these defects typically meet the clinical criteria for the diagnosis of MODY and are listed in Table 607.19 . Just 3 of them (MODY2, MODY3, and MODY5) account for 90% of the cases in this category in European populations, but the distribution may be different in other ethnic groups. Except for MODY2 (which is caused by mutations in the enzyme glucokinase), all other forms are caused by genetic defects in various transcription factors (see Table 607.19).

Table 607.19

Summary of MODY Types and Special Clinical Characteristics

	GENE MUTATED	FUNCTION	SPECIAL FEATURE
MODY1	*HNF4 α*	Transcription factor	Decreased levels of triglycerides, apolipoproteins AII and CIII (5–10% of MODY), neonatal hypoglycemia, very sensitive to sulfonylureas
MODY2	Glucokinase *(GCK)*	Enzyme, glucose sensor	Hyperglycemia of early onset but mild and nonprogressive; common (30–70% MODY)
MODY3	*HNF1 α*	Transcription factor	Decreased renal absorption of glucose and consequent glycosuria; common (30–70% of cases of MODY); very sensitive to sulfonylureas
MODY4	*IPF-1*	Necessary for pancreatic development	Homozygous mutation causes pancreatic agenesis
MODY5	*HNF1β*	Transcription factor	Renal malformations; associated with uterine abnormalities, hypospadias, joint laxity, and learning difficulties, pancreatic atrophy, pancreatic exocrine insufficiency; 5–10% of MODY
MODY6	*NEUROD1*	Differentiation factor in the development of pancreatic islets	Extremely rare
MODY7	*KFL11*	Zinc finger transcription factor	Early-onset type II diabetes mellitus
MODY8	*CEL*	Bile salt–dependent lipase	Hyperglycemia; fecal elastase deficiency; exocrine pancreatic atrophy
MODY9	*PAX4*	Transcription factor	
MODY10	*INS*	Insulin gene	Usually associated with neonatal diabetes
MODY11	*BLK*	B-lymphocyte tyrosine kinase	Early-onset T1DM without autoantibodies

View full size

MODY, maturity-onset diabetes of the young.

From Nakhla M, Polychronakos C: Monogenic and other unusual causes of diabetes mellitus, *Pediatr Clin North Am* 52:1637–1650, 2005.

MODY2

This is the second most common form of MODY and accounts for approximately 15–30% of all patients diagnosed with MODY. **Glucokinase** plays an essential role in β-cell glucose sensing and heterozygous mutations in this gene lead to mild reductions in pancreatic β-cell response to glucose. Homozygotes with the same mutations are completely unable to secrete insulin in response to glucose and develop a form of PND. Patients with heterozygous mutations have a higher threshold for insulin release but are able to secrete insulin adequately at higher blood glucose levels (typically 125 mg/dL [7 mmol/L] or higher). This results in a relatively mild form of diabetes (HbA_{1c} is usually less than 7%), with mild fasting hyperglycemia and IGT in the majority of patients. MODY2 may be misdiagnosed as T1DM in children, gestational diabetes in pregnant women, or well-controlled T2DM in adults (see Table 607.14). An accurate diagnosis is important because most cases are not progressive, and except for gestational diabetes, may not require treatment. When needed, they can usually be treated with small doses of exogenously administered insulin. Treatment with oral agents (sulfonylureas and related drugs) can be successful and may be more acceptable to many patients.

MODY3

Patients affected with mutations in the transcription factor hepatocyte nuclear factor-1α show abnormalities of carbohydrate metabolism varying from IGT to severe diabetes and often progressing from a mild to a severe form over time. They are also prone to the development of vascular complications. This is the most common MODY subtype and accounts for 50–65% of all cases. These patients are very sensitive to the action of sulfonylureas and can usually be treated with relatively low doses of these oral agents, at least in the early stages of the disease. In children, this form of MODY is sometimes misclassified as T1DM and treated with insulin. Evaluation of autoimmune markers helps to rule out T1DM; genetic testing for MODY is now available and is indicated in patients with relatively mild diabetes and a family history suggestive of autosomal dominant inheritance. Accurate diagnosis can lead to avoidance of unnecessary insulin treatment and specific genetic counseling.

Less Common Forms of Monogenic Diabetes

Hepatocyte nuclear factor-4α (MODY1), insulin promoter factor (IPF)-1, also known as (PDX-1) (MODY4), hepatocyte nuclear factor 1β/TCF2 (MODY5), and NeuroD1 (MODY6) are all transcription factors that are involved in β-cell development and function and mutations in these lead to various rare forms of MODY. In addition to diabetes they can also have specific findings unrelated to hyperglycemia; for example, MODY1 is associated with low triglyceride and lipoprotein levels and MODY5 is associated with renal cysts and renal dysfunction. In terms of treatment, MODY1 and MODY4 may respond to oral sulfonylureas, but MODY5 does not respond to oral agents and requires treatment with insulin. NeuroD1 defects are extremely rare and not much is known about their natural history.

Primary or secondary defects in the glucose transporter-2, which is an insulin-independent glucose transporter, may also be associated with diabetes. Diabetes may also be a manifestation of a polymorphism in the glycogen synthase gene. This enzyme is crucially important for storage of glucose as glycogen in muscle. Patients with this defect are notable for marked insulin resistance and hypertension, as well as a strong family history of diabetes. Another form of IDDM is the **Wolfram syndrome** . Wolfram syndrome 1 is characterized by diabetes insipidus, DM, optic atrophy, and deafness—thus, the acronym **DIDMOAD** . Some patients with diabetes appear to have severe insulinopenia, whereas others have significant insulin secretion as judged by C-peptide. The overall prevalence is estimated at 1 in 770,000 live births. The sequence of appearance of the stigmata is as follows: non-autoimmune IDDM in the 1st decade, central diabetes insipidus and sensorineural deafness in two-third to three-quarters of the patients in the 2nd decade, renal tract anomalies in about half of the patients in the 3rd decade, and neurologic complications such as cerebellar ataxia and myoclonus in half to two-thirds of the patients in the 4th decade. Other features include primary gonadal atrophy in the majority of males and a progressive neurodegenerative course with neurorespiratory death at a median age of 30 yr. Some (but not all) cases are caused by mutations in the *WFS-1* (wolframin) gene on chromosome 4p. Wolfram syndrome 2 has early-onset optic atrophy, DM, deafness, and a shortened life span but no diabetes insipidus; the associated gene is *CISD2* . Other forms of Wolfram syndrome may be caused by mutations in mitochondrial DNA.

Mitochondrial Gene Defects

Point mutations in mitochondrial DNA are associated with the cause of **maternally inherited DM and deafness** . The most common mitochondrial DNA mutation in these cases is the point mutation m.3243A>G in the transfer RNA leucine gene. This mutation is identical to the mutation in MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome), but this syndrome is not associated with diabetes; the phenotypic expression of the same defect varies. Diabetes in most of these cases presents insidiously but approximately 20% of patients have an acute presentation resembling T1DM. The mean age of diagnosis of diabetes is 37 yr, but cases have been reported as young as 11 yr; not all patients have deafness. This mutation has been estimated to be present in 1.5% of Japanese diabetics, which may be higher than the prevalence in other ethnic groups. Metformin should be avoided in these patients because of the theoretical risk of severe lactic acidosis in the presence of mitochondrial dysfunction. Some children with mitochondrial DNA mutations affecting complex I and/or complex IV may also develop diabetes.

Abnormalities of the Insulin Gene

Diabetes of variable degrees may also result from mutations in the insulin gene that impair the effectiveness of insulin at the receptor level. Insulin gene defects are exceedingly rare and may be associated with relatively mild diabetes or even normal glucose tolerance. Diabetes may also develop in patients with faulty processing of proinsulin to insulin (an autosomal dominant defect). These defects are notable for the high concentration of insulin as measured by radioimmunoassay, whereas MODY and glucose transporter-2 defects are characterized by relative or absolute deficiency of insulin secretion for the prevailing glucose concentrations.

Genetic Defects of Insulin Action

Various genetic mutations in the insulin receptor can impair the action of insulin at the insulin receptor or impair postreceptor signaling, leading to insulin resistance. The mildest form of the syndrome with mutations in the insulin receptor was previously known as **type A insulin resistance.** This condition is associated with hirsutism, hyperandrogenism, and cystic ovaries in females, without obesity. Acanthosis nigricans may be present and life expectancy is not significantly impaired. More severe forms of insulin resistance are seen in 2 mutations in the insulin receptor gene that cause the pediatric syndromes of **Donohue syndrome** (formerly called leprechaunism) and **Rabson-Mendenhall syndrome.**

Donohue Syndrome

This is a syndrome characterized by intrauterine growth restriction, fasting hypoglycemia, and postprandial hyperglycemia in association with profound resistance to insulin; severe hyperinsulinemia is seen during an oral glucose tolerance test. Various defects of the insulin receptor have been described, thereby attesting to the important role of insulin and its receptor in fetal growth and possibly in morphogenesis. Many of these patients die in the 1st year of life. Potential treatments include high-dose insulin, metformin, and continuous IGF-1 via insulin pump.

Rabson-Mendenhall Syndrome

This entity is defined by clinical manifestations that appear to be intermediate between those of acanthosis nigricans with insulin resistance type A and Donohue syndrome. The features include extreme insulin resistance, acanthosis nigricans, abnormalities of the teeth and nails, and pineal hyperplasia. It is not clear whether this syndrome is entirely distinct from Donohue syndrome; however, by comparison, patients with Rabson-Mendenhall tend to live significantly longer. Therapies with modest benefit have included IGF-1 and leptin.

Lipoatrophic Diabetes

Various forms of lipodystrophy are associated with insulin resistance and diabetes (Table 607.20). **Familial partial lipoatrophy, or lipodystrophy,** is associated with mutations in the *LMNA* gene, encoding nuclear envelope proteins lamin A and C. **Severe congenital generalized lipoatrophy** is associated with mutations in the seipin and *AGPAT2* genes, but the mechanism by which these mutations lead to insulin resistance and diabetes is not known.

Table 607.20

Clinical and Biochemical Features of Inherited Lipodystrophies

SUBTYPE	CONGENITAL GENERALIZED LIPODYSTROPHY		FAMILIAL PARTIAL LIPODYSTROPHY	
	BSCL1	**BSCL2**	**FPLD2**	**FPLD3**
Defective gene	*AGPAT2*	*BSCL2*	*LMNA*	*PPARG*
Clinical onset	Soon after birth	Soon after birth	Puberty	Usually puberty, but may present in younger children
Fat distribution	Generalized absence	Generalized absence	Loss of limb and gluteal fat; typically excess facial and nuchal fat; trunk fat often lost	Loss of limb and gluteal fat; preserved facial and trunk fat
Cutaneous features	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women
Musculoskeletal	Acromegaloid	Acromegaloid	Frequent muscle	Nil specific

	features common	features common	hypertrophy; some have overlap features of muscular dystrophy	
Nonalcoholic fatty liver disease	Severe	Severe	Yes	Yes
Dyslipidemia	Severe associated with pancreatitis	Severe associated with pancreatitis	Yes, may be severe	Yes, may be severe
Insulin resistance	Severe early onset	Severe early onset	Severe	Severe; early onset in some
Diabetes onset	<20 yr	<20 yr	Variable; generally later in men than women	Variable; generally later in men than women
Hypertension	Common	Common	Common	Very common
Other		Mild mental retardation possible		

From Semple RK, Savage DB, Halsall DJ, O'Rahilly S: Syndromes of severe insulin resistance and/or lipodystrophy. In Weiss RE, Refetoff S, editors: *Genetic diagnosis of endocrine disorders,* Philadelphia, 2010, Elsevier, Table 4.2.

Stiff-Person Syndrome

This is an extremely rare autoimmune central nervous system disorder that is characterized by progressive stiffness and painful spasms of the axial muscles and very high titers of glutamic acid decarboxylase antibodies. About one third of the patients also develop T1DM.

Systemic Lupus Erythematosus

In rare cases, patients with systemic lupus erythematosus may develop autoantibodies to the insulin receptor, leading to insulin resistance and diabetes.

Cystic Fibrosis–Related Diabetes

See Chapter 432 .

As patients with cystic fibrosis (CF) live longer, an increasing number are being diagnosed with **cystic fibrosis–related diabetes (CFRD).** Females appear to have a somewhat higher risk of CFRD than males and prevalence increases with increasing age until age 40 yr (there is a decline in prevalence after that, presumably because only the healthiest CF patients survive beyond that age). There is an association with pancreatic insufficiency and there may be a higher risk in patients with class I and class II CF transmembrane conductance regulator mutations. A large multicenter study in the United States reported prevalence (in all ages) of 17% in females and 12% in males. Cross-sectional studies indicate that the prevalence of IGT may be significantly higher than this and up to 65% of children with CF have diminished 1st phase insulin secretion, even when they have normal glucose tolerance. In Denmark, oral glucose tolerance screening of the entire CF population demonstrated no diabetes in patients younger than 10 yr, diabetes in 12% of patients age 10-19 yr, and diabetes in 48% of adults age 20 yr and older. At a Midwestern center where routine annual oral glucose tolerance screening is performed, only about half of children and a quarter of adults were found to have normal glucose tolerance.

Patients with CFRD have features of both T1DM and T2DM. In the pancreas, exocrine tissue is replaced by fibrosis and fat and many of the pancreatic islets are destroyed. The remaining islets demonstrate diminished numbers of β-, α-, and pancreatic polypeptide-secreting cells. Secretion of the islet hormones insulin, glucagon, and pancreatic polypeptide is impaired in patients with CF in response to a variety of secretagogues. This pancreatic damage leads to slowly progressive insulin deficiency, of which the earliest manifestation is an impaired 1st phase insulin response. As patients age, this response becomes progressively delayed and less robust than normal. At the same time, these patients develop insulin resistance due to chronic inflammation and the intermittent use of corticosteroids. Insulin deficiency and insulin resistance lead to a very gradual onset of IGT that eventually evolves into diabetes. In some cases, diabetes may wax and wane with disease exacerbations and the use of corticosteroids. The clinical presentation is similar to that of T2DM in that the onset of the disease is insidious and the occurrence of ketoacidosis is rare. Islet antibody titers are negative. Microvascular complications do develop but may do so at a slower rate than in typical T1DM or T2DM. Macrovascular complications do not appear to be of concern in CFRD, perhaps because of the shortened life span of these patients. Several factors unique to CF influence the onset and the course of diabetes. For example: (1) frequent infections are associated with waxing and waning of insulin resistance; (2) energy needs are increased because of infection and pulmonary disease; (3) malabsorption is common, despite enzyme supplementation; (4) nutrient absorption is altered by abnormal intestinal transit time; (5) liver disease is frequently present; (6) anorexia and nausea are common; (7) there is a wide variation in daily food intake based on the patient's acute health status; and (8) both insulin and glucagon secretion are impaired (in contrast to autoimmune diabetes, in which only insulin secretion is affected).

IGT and CFRD are associated with poor weight gain and there is evidence that treatment with insulin improves weight gain and slows the rate of pulmonary deterioration. Because of these observations, the CF Foundation/American Diabetes Association/Pediatric Endocrine Society guidelines recommend that routine diabetes screening of all children with CF begin at age 10 yr. Despite debate over the ideal screening modality, the current recommendation is the 2 hr glucose tolerance test, though it is possible that simply obtaining a single 2 hr postprandial glucose value may be sufficient. When hyperglycemia develops, the accompanying metabolic derangements are usually mild, and relatively low doses of insulin usually suffice for adequate management. Basal insulin may be started initially, but basal-bolus therapy similar to that used in T1DM will eventually be needed. Dietary restrictions are minimal as increased energy needs are present and weight gain is usually desired. Ketoacidosis is very uncommon but may occur with progressive deterioration of islet cell function. IGT is not necessarily an indication for treatment, but patients who have poor growth and inadequate weight gain may benefit from the addition of basal insulin even if they do not meet the criteria for diagnosis of diabetes.

Endocrinopathies

The endocrinopathies listed in Table 607.1 are only rarely encountered as a cause of diabetes in childhood. They may accelerate the manifestations of diabetes in those with inherited or acquired defects in insulin secretion or action.

Drugs

High-dose oral or parenteral steroid therapy usually results in significant insulin resistance leading to glucose intolerance and overt diabetes. The immunosuppressive agents cyclosporin and tacrolimus are toxic to β-cells, causing IDDM in a significant proportion of patients treated with these agents. Their toxicity to pancreatic β-cells was one of the factors that limited their usefulness in arresting ongoing autoimmune destruction of β-cells. Streptozotocin and the rodenticide Vacor are also toxic to β-cells, causing diabetes.

There are no consensus guidelines regarding treatment of **steroid-induced hyperglycemia** in children. Many patients on high-dose steroids have elevated blood glucose during the day and evening but become normoglycemic late at night and early in the morning. In general, significant hyperglycemia in an inpatient setting is treated with short-acting insulin on an as-needed basis. Basal insulin may be added when fasting hyperglycemia is significant. Outpatient treatment can be more difficult, but when treatment is needed, protocols similar to the basal-bolus regimens used in T1DM are used.

Genetic Syndromes Associated With Diabetes Mellitus

A number of rare genetic syndromes associated with IDDM or carbohydrate intolerance have been described (see Table 607.1). These syndromes represent a broad spectrum of diseases, ranging from premature cellular aging, as in the **Werner** and **Cockayne** syndromes (see Chapter 109) to excessive obesity associated with hyperinsulinism, resistance to insulin action, and carbohydrate intolerance, as in the **Prader-Willi syndrome** (see Chapters 97 and 98). Some of these syndromes are characterized by primary disturbances in the insulin receptor or in antibodies to the insulin receptor without any impairment in insulin secretion. Although rare, these syndromes provide unique models to understand the multiple causes of disturbed carbohydrate metabolism from defective insulin secretion or from defective insulin action at the cell receptor or postreceptor level.

Autoimmune Diseases Associated With T1DM

IPEX Syndrome

IPEX (immunodysregulation, polyendocrinopathy, and enteropathy, X-linked) is a genetic syndrome leading to autoimmune disease. In most patients with IPEX, mutations in the *FOXP3* (forkhead box P3) gene, a specific marker of natural and adaptive regulatory T cells, leads to severe immune dysregulation and rampant autoimmunity. Autoimmune diabetes develops in > 90% of cases, usually within the 1st few weeks of life and is accompanied by enteropathy, failure to thrive, and other autoimmune disorders.

Autoimmune Polyendocrine Syndromes

Autoimmune polyendocrine syndrome type 1 (APS-1, also known as APCED) is a syndrome of multiple endocrinopathy related to genetic mutation in the *AIRE* gene. It typically first manifests in infancy with recurrent mucocutaneous candidiasis, followed variably by hypocalcemia (autoimmune hypoparathyroidism), adrenal insufficiency (Addison disease), T1DM, hypothyroidism (Hashimoto), celiac disease, and other autoimmune conditions. Much more common is APS-2, which typically refers to the presence of Addison disease plus 1 other autoimmune disease. Alternate definitions consider the presence of any 2 autoimmune diseases to be consistent with the diagnosis of APS-2. Regardless, it is clear that any patient with an autoimmune disease is at increased risk for the development of T1DM (and any patient with T1DM is at increased risk of other autoimmune disease) and should be counseled regarding the signs/symptoms of new-onset diabetes. See Table 607.13 for recommendations regarding screening tests to look for other autoimmune disease in patients with T1DM.

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis) is frequently associated with T1DM in children (see Chapter 582). About 20% of insulin-dependent diabetic patients have thyroid antibodies in their serum; the prevalence is 2-20 times greater than in control populations. Only a small proportion of these patients acquire clinical hypothyroidism; the interval between diagnosis of diabetes and thyroid disease averages about 5 yr. **Celiac disease,** which is caused by hypersensitivity to dietary gluten, is another autoimmune disorder that occurs with significant frequency in children with T1DM (see Chapter 364.2). It is estimated that approximately 7–15% of children with T1DM develop celiac disease within the 1st 6 yr of diagnosis, and the incidence of celiac disease is significantly higher in children younger than 4 yr of age and in females. Young children with T1DM and celiac disease can present with gastrointestinal symptoms (abdominal cramping, diarrhea, constipation, gastroesophageal reflux), growth failure as a consequence of suboptimal weight gain, unexplained hypoglycemic reactions because of nutrient malabsorption, and less commonly hypocalcemia due to severe vitamin D malabsorption; in some cases the disease can be asymptomatic.

When diabetes and thyroid disease coexist, the possibility of autoimmune adrenal insufficiency should be considered. It may be heralded by decreasing insulin requirements, increasing pigmentation of the skin and buccal mucosa, salt craving, weakness, asthenia and postural hypotension, or even frank adrenal crisis. This syndrome is unusual in the 1st decade of life, but it may become apparent in the 2nd decade or later.

Circulating antibodies to gastric parietal cells and to intrinsic factor are 2-3 times more common in patients with T1DM than in control subjects. The presence of antibodies to gastric parietal cells is correlated with atrophic gastritis and antibodies to intrinsic factor are associated with malabsorption of vitamin B_{12} . However, megaloblastic anemia is rare in children with T1DM.

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PART XXVI

The Nervous System

OUTLINE

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Chapter 610 Deformational Plagiocephaly

Chapter 611 Seizures in Childhood

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CHAPTER 608

Neurologic Evaluation

Nina F. Schor

History

A detailed history is the cornerstone of neurologic assessment. Although parents may be the primary informants, most children older than 3-4 yr can contribute to their history and should be questioned. The history should begin with the chief complaint and its significance in the context of normal development (see Chapters 20-26). The latter step is critical because a 13 mo old who cannot walk may be normal, whereas a 4 yr old who cannot walk might have a serious neurologic condition.

Next, the history of the present illness should provide a chronologic outline of the patient's symptoms, with attention paid to location, quality, intensity, duration, associated features, and alleviating or exacerbating factors. It is essential to perform a review of systems, because abnormalities of the central nervous system (CNS) often manifest with vague, nonfocal symptoms that may be misattributed to other organ systems (e.g., vomiting, constipation, urinary incontinence). A detailed history might suggest that vomiting is as a result of increased intracranial pressure (ICP) rather than gastritis or that constipation and urinary incontinence are caused by a spinal cord tumor rather than behavioral stool withholding. In addition, a systemic illness may produce CNS manifestations, as do lupus erythematosus (seizures, psychosis, demyelination) or mitochondrial disorders (developmental delay, strokes, hypotonia).

Following the chief complaint and history of the present illness, the physician should obtain a complete birth history, particularly if a congenital or perinatal disorder is suspected. The birth history should begin with a review of the pregnancy, including specific questions about common complications, such as pregnancy-induced hypertension, preeclampsia, gestational diabetes, vaginal bleeding, infections, and falls. It is important to quantify any cigarette, alcohol, or drug (prescription, herbal, illicit) use. Inquiring about fetal movement might provide clues to an underlying diagnosis, because decreased or absent fetal activity can be associated with chromosomal anomalies and CNS or neuromuscular disorders. Finally, any abnormal ultrasound or amniocentesis results should be noted.

The mother's labor history should address the gestational age at birth and mode of delivery (spontaneous vaginal, vacuum- or forceps-assisted, cesarean section) and should comment on the presence or absence of fetal distress. If delivery was by cesarean section, it is essential to record the indication for surgery.

The birth weight, length, and head circumference provide useful information about the duration of a given problem, as well as insights into the uterine environment. Parents can usually provide a reliable history of their child's postnatal course; however, if the patient was resuscitated or had a complicated hospital stay, it is often helpful to obtain the hospital records. The physician should inquire about the infant's general well-being, feeding and sleeping patterns, and activity level and the nature of the infant's cry. If the infant had jaundice, it is important to determine both the degree of jaundice and how it was managed. Features of neurologic dysfunction at full term include inability to breathe spontaneously; poor, uncoordinated suck; or the need for an inordinate amount of time to feed or a requirement for gavage feeding. Again, it is important to consider the developmental context, because all of these issues would be expected in premature infants, particularly those with a very low birthweight. Double-checking the newborn screening results may provide a clue to abnormal neurologic manifestations in an infant.

A major component of the neurologic history is the **developmental assessment** (see Chapters 20-26 and 28). Careful evaluation of a child's social, cognitive, language, fine motor skills, and gross motor skills is required to distinguish normal development from either an isolated or a global (i.e., in two or more domains) developmental delay. A static abnormality in development from birth suggests a congenital, intrauterine, or perinatal cause, but a loss of skills **(regression)** over time strongly suggests an underlying degenerative disease of the CNS, such as an inborn error of metabolism. The ability of parents to recall the precise timing of their child's developmental milestones is extremely variable. It is often helpful to request old photographs of the child or to review the baby book, where the milestones may have been dutifully recorded. In general, parents are aware when their child has a developmental problem, and the physician should show appropriate concern. Table 608.1 outlines the upper limits of normal for attaining specific developmental milestones. Chapter 28 includes a comprehensive review of developmental screening tests and their interpretation.

Table 608.1

Screening Scheme for Developmental Delay: Upper Range

AGE (mo)	GROSS MOTOR	FINE MOTOR	SOCIAL SKILLS	LANGUAGE
3	Supports weight on forearms	Opens hands spontaneously	Smiles appropriately	Coos, laughs
6	Sits momentarily	Transfers objects	Shows likes and dislikes	Babbles
9	Pulls to stand	Pincer grasp	Plays pat-a-cake, peek-a-boo	Imitates sounds
12	Walks with 1 hand held	Releases an object on command	Comes when called	1-2 meaningful words
18	Walks upstairs with assistance	Feeds self from a spoon	Mimics actions of others	At least 6 words
24	Runs	Builds a tower of 6 blocks	Plays with others	2- to 3-word sentences

Next, the family history must be reviewed. Most parents are cooperative in securing medical information about family members, particularly if it might have relevance for their child. The history should document the age and history of neurologic disease, including developmental delay, epilepsy, migraine, stroke, and inherited disorders, for all first- and second-degree relatives. It is important to inquire directly about miscarriages or fetal deaths and to document the sex of the relevant embryo or fetus, as well as the gestational age at the time of demise. When available, the results of postmortem examinations should be obtained, because they can have a direct bearing on the patient's condition. The parents should be questioned about their ethnic backgrounds, because some genetic disorders occur more commonly within specific populations (e.g., Tay-Sachs disease in the Ashkenazi Jewish population). They should also be asked if there is any chance that they could be related to each other, because the incidence of metabolic and degenerative disorders of the CNS is increased significantly in children of **consanguineous** marriages.

The social history should detail the child's current living environment, as well as the child's relationship with other family members. It is important to inquire about recent stressors, such as divorce, remarriage, birth of a sibling, or death of a loved one, because they can affect the child's behavior. If the child is in daycare or school, one should document the child's academic and social performance, paying particular attention to any abrupt changes. Academic performance can be assessed by asking about the child's latest report card, and peer relationships can be evaluated by having the child name his or her best friends. Any child who is unable to name at least two or three playmates might have abnormal social development. In some cases, discussions with the daycare worker or teacher provide useful ancillary data.

Neurologic Examination

The neurologic examination begins during the interview. Indirect observation of the child's appearance and movements can yield valuable information about the presence of an underlying disorder. For instance, it may be obvious that the child has dysmorphic facies, an unusual posture, or an abnormality of motor function manifested by a hemiparesis or gait disturbance. The child's behavior while playing and interacting with his or her parents may also be telling. A normal child usually plays independently early in the visit but then engages in the interview process. A child with attention-deficit/hyperactivity disorder might display impulsive behavior in the examining room, and a child with neurologic impairment might exhibit complete lack of awareness of the environment. Finally, note should be made of any unusual odors about the patient, because some metabolic disorders produce characteristic scents (e.g., the musty smell of phenylketonuria or the sweaty feet smell of isovaleric acidemia). If such an odor is present, it is important to determine whether it is persistent or transient, occurring only with illnesses.

The examination should be conducted in a nonthreatening, child-friendly setting. The child should be allowed to sit where the child is most comfortable, whether it be on a parent's lap or on the floor of the examination room. The physician should approach the child slowly, reserving any invasive, painful, or discomforting tests for the end of the examination (e.g., measurement of head circumference, gag reflex). In the end, the more that the examination seems like a game, the more the child will cooperate. Because the neurologic examination of an infant requires a somewhat modified approach from that of an older child, these two groups are considered separately (see Chapters 21 , 22 , and 113 vs Chapters 23-26).

Mental State

Age aside, the neurologic examination should include an assessment of the patient's mental state in terms of both the level of arousal and the interaction with the environment. Premature infants born at < 28 wk of gestation do not have consistent periods of alertness, whereas slightly older infants arouse from sleep with gentle physical stimulation. Sleep–wake patterns are well developed at term. Because the level of alertness of a neonate depends on many factors, including the time of the last feeding, room temperature, and gestational age, serial examinations are critical when evaluating for changes in neurologic function. An older child's mental state can be assessed by watching the child play. Having the child tell a story, draw a picture, or complete a puzzle can also be helpful in assessing cognitive function. Memory can be evaluated informally as patients recount their personal information, as well as more formally by asking them to register and recall three objects or perform a digit span.

Head

Correct measurement of the **head circumference** is important. It should be performed at every visit for patients younger than 3 yr and should be recorded on a suitable head growth chart. To measure, a nondistensible plastic measuring tape is placed over the mid-forehead and extended circumferentially to include the most prominent portion of the occiput. If the patient's head circumference is abnormal, it is important to document the head circumferences of the parents and siblings. Errors in the measurement of a newborn skull are common due to scalp edema, overriding sutures, and the presence of cephalohematomas. The average rate of head growth in a healthy premature infant is 0.5 cm in the first 2 wk, 0.75 cm in the 3rd wk, and 1.0 cm in the 4th wk and every week thereafter until the 40th wk of development. The head circumference of an average term infant measures 34-35 cm at birth, 44 cm at 6 mo, and 47 cm at 1 yr of age (see Chapters 21 and 22).

If the brain is not growing, the skull will not grow; therefore, a small head frequently reflects a small brain, or **microcephaly.** Microcephaly may develop in utero or postnatally and may, for example, be related to intrauterine infection or drug exposure or to perinatal or postnatal injury. Conversely, a large head may be associated with a large brain, or **macrocephaly,** which is most commonly familial but may be from a disturbance of growth, neurocutaneous disorder (e.g., neurofibromatosis), chromosomal defect (e.g., Klinefelter syndrome), or storage disorder. Alternatively, the head size may be increased secondary to hydrocephalus (Fig. 608.1) or chronic subdural hemorrhages. In the latter case, the skull tends to assume a square or box-like shape, because the long-standing presence of fluid in the subdural space causes enlargement of the middle fossa.

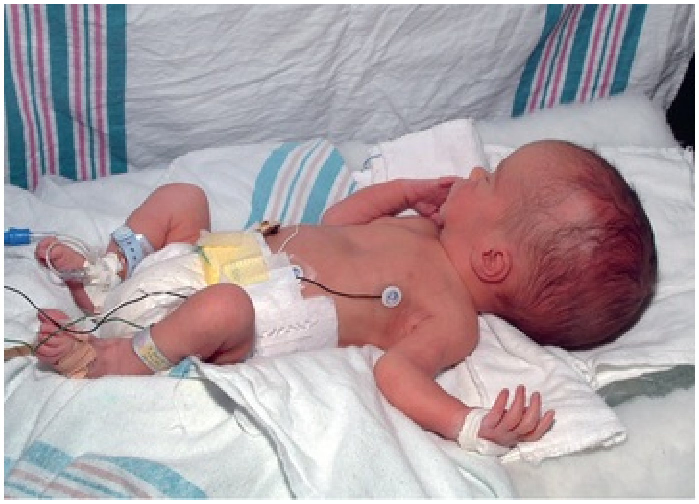

FIG. 608.1 Congenital hydrocephalus. Note the enlarged cranium and prominent scalp veins.

The shape of the head should be documented carefully. Plagiocephaly, or flattening of the skull, can be seen in normal infants but may be particularly prominent in hypotonic or weak infants, who are less mobile. A variety of abnormal head shapes can be seen when cranial sutures fuse prematurely, as in the various forms of inherited **craniosynostosis** (see Chapter 609.12).

An infant has two **fontanels** at birth: a diamond-shaped anterior fontanel at the junction of the frontal and parietal bones that is open at birth, and a triangular posterior fontanel at the junction of the parietal and occipital bones that can admit the tip of a finger or may be closed at birth. If the posterior fontanel is open at birth, it should close over the ensuing 6-8 wk; its persistence suggests underlying hydrocephalus or congenital hypothyroidism. The anterior fontanel varies greatly in size, but it usually measures approximately 2 × 2 cm. The average time of closure is 18 mo, but the fontanel can close normally as early as 9 mo. A very small or absent anterior fontanel at birth might indicate craniosynostosis or microcephaly, whereas a very large fontanel can signify a variety of problems. The fontanel is normally slightly depressed and pulsatile and is best evaluated by holding the infant upright while the infant is asleep or feeding. A bulging fontanel is a potential indicator of increased ICP, but vigorous crying can cause a protuberant fontanel in a normal infant.

Inspection of the head should include observation of the venous pattern, because increased ICP and thrombosis of the superior sagittal sinus can produce marked venous distention. Dysmorphic facial features can indicate a neurodevelopmental aberration. Likewise, cutaneous abnormalities, such as cutis aplasia or abnormal hair whorls, can suggest an underlying brain malformation or genetic disorder.

Palpation of a newborn's skull characteristically reveals **molding** of the skull accompanied by **overriding sutures** —a result of the pressures exerted on the skull during its descent through the pelvis. Marked overriding of the sutures beyond the early neonatal period is cause for alarm, because it suggests an underlying brain abnormality. Palpation additionally might reveal bony bridges between sutures **(craniosynostosis),** cranial defects, or, in premature infants, softening of the parietal bones **(craniotabes).**

Auscultation of the skull is an important adjunct to the neurologic examination. **Cranial bruits** may be noted over the anterior fontanel, temporal region, or orbits, and are best heard using the diaphragm of the stethoscope. Soft symmetric bruits may be discovered in normal children younger than 4 yr of age or in association with a febrile illness. Demonstration of a loud or localized bruit is usually significant and warrants further investigation, because it may be associated with severe anemia, increased ICP, or arteriovenous malformations of the middle cerebral artery or vein of Galen. It is important to exclude murmurs arising from the heart or great vessels, because they may be transmitted to the cranium.

Cranial Nerves

Olfactory Nerve (Cranial Nerve I)

Anosmia, or loss of smell, most commonly occurs as a transient abnormality in association with an upper respiratory tract infection or allergies. Permanent causes of anosmia include head trauma with damage to the ethmoid bone or shearing of the olfactory nerve fibers as they cross the cribriform plate, tumors of the frontal lobe, intranasal drug use, and exposure to toxins (acrylates, methacrylates, cadmium). Occasionally, a child who recovers from purulent meningitis or develops hydrocephalus has a diminished sense of smell. Rarely, anosmia is congenital, in which case it can occur as an isolated deficit or as part of Kallmann syndrome, a familial disorder characterized by hypogonadotropic hypogonadism and congenital anosmia. Although not a routine component of the examination, smell can be tested reliably as early as the 32nd wk of gestation by presenting a stimulus and observing for an alerting response or withdrawal, or both. Care should be taken to use appropriate stimuli, such as coffee or peppermint, as opposed to strongly aromatic substances (e.g., ammonia inhalants) that stimulate the trigeminal nerve. Each nostril should be tested individually by pinching shut the opposite side.

Optic Nerve (Cranial Nerve II; see also Part XXVIII)

Assessment of the optic disc and retina (see Chapters 637 , 648 , and 649) is a critical component of the neurologic examination. Although the retina is best visualized by dilating the pupil, most physicians do not have ready access to mydriatic agents at the bedside; therefore, it may be necessary to consult an ophthalmologist in some cases. Mydriatics should not be administered to patients whose pupillary responses are being followed as a marker for impending cerebral herniation or to patients with glaucoma or cataracts. When mydriatics are used, both eyes should be dilated, because unilateral papillary fixation and dilation can cause confusion and worry in later examiners unaware of the pharmacologic intervention. Examination of an infant's retina may be facilitated by providing a nipple or soother and by turning the head to one side. The physician gently strokes the patient to maintain arousal while examining the closer eye. An older child should be placed in the parent's lap and should be distracted by bright objects or toys. The color of the optic nerve is salmon-pink in a child but may be gray-white in a newborn, particularly if the newborn has fair coloring. This normal finding can cause confusion and can lead to the improper diagnosis of optic atrophy.

Disc edema refers to swelling of the optic disc, and **papilledema** specifically refers to swelling that is secondary to increased ICP. Papilledema rarely occurs in infancy because the skull sutures can separate to accommodate the expanding brain. In older children, papilledema may be graded according to the Frisen scale (Fig. 608.2). Disc edema must be differentiated from **papillitis,** or inflammation of the optic nerve. Both conditions manifest with enlargement of the blind spot, but visual acuity and color vision tend to be spared in early papilledema in contrast to what occurs in optic neuritis.

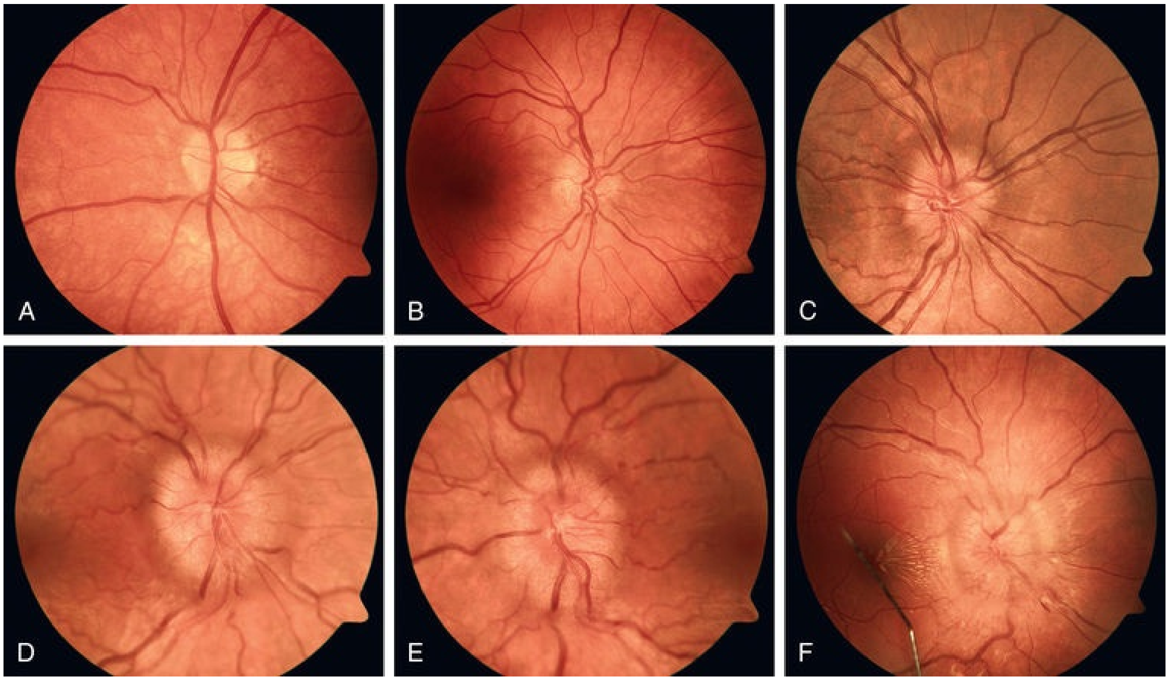

FIG. 608.2 Stages of papilledema (Frisen scale). **A,** Stage 0: Normal optic disc. **B,** Stage 1: Very early papilledema with obscuration of the nasal border of the disc only, without elevation of the disc borders. **C,** Stage 2: Early papilledema showing obscuration of all borders, elevation of the nasal border, and a complete peripapillary halo. **D,** Stage 3: Moderate papilledema with elevation of all borders, increased diameter of the optic nerve head, obscuration of vessels at the disc margin, and a peripapillary halo with finger-like extensions. **E,** Stage 4: Marked papilledema characterized by elevation of the entire nerve head and total obscuration a segment of a major blood vessel on the disc. **F,** Stage 5: Severe papilledema with obscuration of all vessels and obliteration of the optic cup. Note also the nerve fiber layer hemorrhages and macular exudate. (**A-C** courtesy Dr. Deborah Friedman; **D-F** courtesy Flaum Eye Institute, University of Rochester.)

Retinal hemorrhages occur in 30–40% of all full-term newborn infants. The hemorrhages are more common after vaginal delivery than after cesarean section and are not associated with birth injury or with neurologic complications. They disappear spontaneously by 1-2 wk of age. The presence of retinal hemorrhages beyond the early neonatal period should raise a concern for nonaccidental trauma.

Vision

A full description of the age-appropriate evaluation of vision can be found in Chapter 637 . Evaluation of vision in the premature infant presents unique challenges. At 28 wk of corrected gestational age, a premature infant blinks in response to a bright light, and at 32 wk, the infant maintains eye closure until the light source is removed. The pupil reacts to light by 29-32 wk of corrected gestational age; however, the pupillary response is often difficult to evaluate, because premature infants resist eye opening and have poorly pigmented irises. A normal 37-wk infant turns the head and eyes toward a soft light, and a term infant is able to fix on and follow a target, such as the examiner's face.

Oculomotor (Cranial Nerve III), Trochlear (Cranial Nerve IV), and Abducens (Cranial Nerve VI) Nerves

The globe is moved by six extraocular muscles, which are innervated by the oculomotor, trochlear, and abducens nerves. These muscles and nerves can be assessed by having the patient follow an interesting toy or the examiner's finger in the six cardinal directions of gaze. The physician observes the range and nature (conjugate vs disconjugate, smooth vs choppy or saccadic) of the eye movements, particularly noting the presence and direction of any abnormal eye movements. Premature infants older than 25 wk of gestational age and comatose patients can be evaluated using the oculocephalic (doll's eye) maneuver, in which the patient's head is quickly rotated to evoke reflex eye movements. If the brainstem is intact, rotating the patient's head to the right causes the eyes to move to the left and vice versa. Similarly, rapid flexion and extension of the head elicits vertical eye movement.

Disconjugate gaze can result from extraocular muscle weakness; cranial nerve (CN) III, IV, or VI palsies; or brainstem lesions that disrupt the medial longitudinal fasciculus. Infants who are younger than 2 mo can have a slightly disconjugate gaze at rest, with one eye horizontally displaced from the other by 1 or 2 mm **(strabismus).** Vertical displacement of the eyes requires investigation because it can indicate trochlear nerve (CN IV) palsy or **skew deviation** (supranuclear ocular malalignment that is often associated with lesions of the posterior fossa). Strabismus is discussed further in Chapter 641 .

The oculomotor nerve innervates the superior, inferior, and medial recti, as well as the inferior oblique and levator palpebrae superioris muscles. Complete paralysis of the oculomotor nerve causes ptosis, dilation of the pupil, displacement of the eye outward and downward, and impairment of adduction and elevation. The trochlear nerve supplies the superior oblique muscle, which depresses and intorts the globe during activities such as reading and walking downstairs. Patients with an isolated paralysis of the trochlear nerve often have a compensatory head tilt away from the affected side, which helps to alleviate their diplopia. The abducens nerve innervates the lateral rectus muscle; its paralysis causes medial deviation of the eye with an inability to abduct beyond the midline. Patients with increased ICP often respond positively when questioned about double vision **(diplopia)** and exhibit incomplete abduction of the eyes on lateral gaze as a result of partial palsies of nerve VI. This false-localizing sign occurs because CN VI has a long intracranial course, making it particularly susceptible to being stretched. **Internuclear ophthalmoplegia,** caused by a lesion in the medial longitudinal fasciculus of the brainstem, which functionally serves the conjugate gaze by connecting CN VI on one side to CN III on the other, results in paralysis of the medial rectus function in the adducting eye and nystagmus in the abducting eye.

When there is a subtle eye movement abnormality, the **red glass test** may be helpful in localizing the lesion. To perform this test, a red glass is placed over one of the patient's eyes and the patient is instructed to follow a white light in all directions of gaze. The child sees one red/white light in the direction of normal muscle function but notes a separation of the red and white images that is greatest in the plane of action of the affected muscle.

In addition to gaze palsies, the examiner might encounter a variety of adventitious movements. **Nystagmus** is an involuntary, rapid movement of the eye that may be subclassified as being **pendular,** in which the two phases have equal amplitude and velocity, or **jerk,** in which there is a fast and a slow phase. Jerk nystagmus can be further characterized by the direction of its fast phase, which may be left-, right-, up-, or downbeating; rotatory; or mixed. Many patients have a few beats of nystagmus with extreme lateral gaze **(end-gaze nystagmus),** which is of no consequence. Pathologic horizontal nystagmus is most often congenital, drug-induced (e.g., alcohol, anticonvulsants), or a result of vestibular system dysfunction. By contrast, vertical nystagmus is often associated with structural abnormalities of the brainstem and cerebellum. **Ocular bobbing** is characterized by a downward jerk followed by a slow drift back to primary position and is associated with pontine lesions. **Opsoclonus** describes involuntary, chaotic, conjugate oscillations of the eyes, which are often seen in the setting of neuroblastoma or viral infection.

Trigeminal Nerve (Cranial Nerve V)

The three divisions of the trigeminal nerve—ophthalmic, maxillary, and mandibular—convey information about facial protopathic (pain, temperature) and epicritic (vibration, proprioception) sensation. Each modality should be tested and compared with the contralateral side. In patients who are uncooperative or comatose, the integrity of the trigeminal nerve can be assessed by the corneal reflex, elicited by touching the cornea with a small pledget of cotton and observing for symmetric eye closure, and nasal tickle, obtained by stimulating the nasal passage with a cotton swab and observing for symmetric grimace. An absent reflex may be because of a sensory defect (trigeminal nerve) or a motor deficit (facial nerve). The motor division of the trigeminal nerve can be tested by examining the masseter, pterygoid, and temporalis muscles during mastication, as well as by evaluation of the jaw jerk.

Facial Nerve (Cranial Nerve VII)

The facial nerve is a predominantly motor nerve that innervates the muscles of facial expression, the buccinator, platysma, stapedius, and stylohyoid muscles and the posterior belly of the digastric muscle. It also has a separate division, called the chorda tympani, that contains sensory, special sensory (taste), and parasympathetic fibers. Because the portion of the facial nucleus that innervates the upper face receives bilateral cortical input, lesions of the motor cortex or corticobulbar tract have little effect on upper face strength. Rather, such lesions manifest with flattening of the contralateral nasolabial fold or drooping of the corner of the mouth. Conversely, lower motor neuron or facial nerve lesions tend to involve upper and lower facial muscles equally. Facial strength can be evaluated by observing the patient's spontaneous movements and by asking the patient to mimic a series of facial movements (e.g., smiling, raising the eyebrows, inflating the cheeks). A facial nerve palsy may be congenital; idiopathic **(Bell palsy);** or secondary to trauma, demyelination (Guillain-Barré syndrome), infection (Lyme disease, herpes simplex virus, HIV), granulomatous disease, neoplasm, or meningeal inflammation or infiltration. Facial nerve lesions that are proximal to the junction with the chorda tympani will result in an inability to taste substances with the anterior two thirds of the tongue. If necessary, taste can be tested by placing a solution of saline or glucose on one side of the extended tongue. Normal children can identify the test substance in < 10 sec. Other findings that may be associated with facial nerve palsy include hyperacusis, resulting from stapedius muscle involvement, and impaired tearing.

Vestibulocochlear Nerve (Cranial Nerve VIII)

The vestibulocochlear nerve has two components within a single trunk: the vestibular nerve, which innervates the semicircular canals of the inner ear and is involved with equilibrium, coordination, and orientation in space, and the cochlear nerve, which innervates the cochlea and subserves hearing.

Dysfunction of the vestibular system results in **vertigo,** the sensation of environmental motion. On examination, patients with vestibular nerve dysfunction typically have nystagmus, in which the fast component is directed away from the affected nerve. With their arms outstretched and eyes closed, their limbs tend to drift toward the injured side. Likewise, if they march in place, they slowly pivot toward the lesion **(Fukuda stepping test).** On Romberg and tandem gait testing, they tend to fall toward the abnormal ear. Vestibular function can be further evaluated with **caloric testing.** Before testing, the tympanic membrane should be visualized to ensure that it is intact and unobstructed. In an obtunded or comatose patient, 30-50 mL of ice water is then delivered by syringe into the external auditory canal with the patient's head elevated 30 degrees. If the brainstem is intact, the eyes deviate toward the irrigated side. A much smaller quantity of ice water (2 mL) is used in awake, alert patients to avoid inducing nausea. In normal subjects, introduction of ice water produces eye deviation toward the stimulated labyrinth followed by nystagmus with the fast component away from the stimulated labyrinth.

Because hearing is integral to normal language development, the physician should inquire directly about hearing problems. Parents’ concern is often a reliable indicator of hearing impairment and warrants a formal audiologic assessment with either audiometry or brainstem auditory evoked potential testing (see Chapter 655). Even in the absence of parents’ concern, certain children warrant formal testing within the first month of life, including those with a family history of early-life or syndromic deafness or a personal history of prematurity, severe asphyxia, exposure to ototoxic drugs, hyperbilirubinemia, congenital anomalies of the head or neck, bacterial meningitis, and congenital TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus) infections. For all other infants and children, a simple bedside assessment of hearing is usually sufficient. Newborns might have subtle responses to auditory stimuli, such as changes in breathing, cessation of movement, or opening of the eyes and/or mouth. If the same stimulus is presented repeatedly, normal neonates cease to respond, a phenomenon known as *habituation.* By 3-4 mo of age, infants begin to orient to the source of sound. Hearing-impaired toddlers are visually alert and appropriately responsive to physical stimuli but might have more frequent temper tantrums and abnormal speech and language development.

Glossopharyngeal Nerve (Cranial Nerve IX)

The glossopharyngeal nerve conveys motor fibers to the stylopharyngeus muscle; general sensory fibers from the posterior third of the tongue, pharynx, tonsil, internal surface of the tympanic membrane, and skin of the external ear; special sensory (taste) fibers from the posterior third of the tongue; parasympathetic fibers to the parotid gland; and general visceral sensory fibers from the carotid bodies. The nerve is tested by stimulating one side of the lateral oropharynx or soft palate with a tongue blade and observing for symmetric elevation of the palate **(gag reflex).** An isolated lesion of CN IX is rare because it runs in close proximity to CN X. Potential causes of injury and/or dysfunction include birth trauma, ischemia, mass lesions, motor neuron disease, retropharyngeal abscess, and Guillain-Barré syndrome.

Vagus Nerve (Cranial Nerve X)

The vagus nerve has ten terminal branches: meningeal, auricular, pharyngeal, carotid body, superior laryngeal, recurrent laryngeal, cardiac, pulmonary, esophageal, and gastrointestinal. The pharyngeal, superior laryngeal, and recurrent laryngeal branches contain motor fibers that innervate all of the muscles of the pharynx and larynx, with the exception of the stylopharyngeus (CN IX) and tensor veli palatini (CN V) muscles. Thus, unilateral injury of the vagus nerve results in weakness of the ipsilateral soft palate and a hoarse voice; bilateral lesions can produce respiratory distress as a result of vocal cord paralysis, as well as nasal regurgitation of fluids, pooling of secretions, and an immobile, low-lying soft palate. Isolated lesions to the vagus nerve may be a complication of thoracotomies or may be seen in neonates with type II Chiari malformations. If such a lesion is suspected, it is important to visualize the vocal cords. In addition to motor information, the vagus nerve carries somatic afferents from the pharynx, larynx, ear canal, external surface of the tympanic membrane, and meninges of the posterior fossa; visceral afferents; taste fibers from the posterior pharynx; and preganglionic parasympathetics.

Accessory Nerve (Cranial Nerve XI)

The accessory nerve innervates the sternocleidomastoid (SCM) and trapezius muscles. The left SCM acts to turn the head to the right side and vice versa;

acting together, the SCMs flex the neck. The trapezius acts to elevate the shoulder. Lesions to the accessory nerve result in atrophy and paralysis of the ipsilateral SCM and trapezius muscles, with resultant depression of the shoulder. Because several cervical muscles are involved in head rotation, unilateral SCM paresis might not be evident unless the patient is asked to rotate the head against resistance. Skull base fractures or lesions, motor neuron disease, myotonic dystrophy, and myasthenia gravis commonly produce atrophy and weakness of these muscles; congenital torticollis is associated with SCM hypertrophy.

Hypoglossal Nerve (Cranial Nerve XII)

The hypoglossal nerve innervates the tongue. Examination of the tongue includes assessment of its bulk and strength, as well as observation for adventitious movements. Malfunction of the hypoglossal nucleus or nerve produces atrophy, weakness, and fasciculations of the tongue. If the injury is unilateral, the tongue deviates toward the side of the injury; if it is bilateral, tongue protrusion is not possible and the patient can have difficulty swallowing **(dysphagia).** Werdnig-Hoffmann disease (infantile spinal muscular atrophy, or spinal muscular atrophy type 1) and congenital anomalies in the region of the foramen magnum are the principal causes of hypoglossal nerve dysfunction.

Motor Examination

The motor examination includes assessment of muscle bulk, tone, and strength, as well as observation for involuntary movements that might indicate central or peripheral nervous system pathology.

Bulk

Decreased muscle bulk **(atrophy)** may be secondary to disuse or to diseases of the lower motor neuron, nerve root, peripheral nerve, or muscle. In most cases, neurogenic atrophy is more severe than myogenic atrophy. Increased muscle bulk **(hypertrophy)** is usually physiologic (e.g., body builders). **Pseudohypertrophy** refers to muscle tissue that has been replaced by fat and connective tissue, giving it a bulky appearance with a paradoxical reduction in strength, as in Duchenne muscular dystrophy.

Tone

Muscle tone, which is generated by an unconscious, continuous, partial contraction of muscle, creates resistance to passive movement of a joint. Tone varies greatly based on a patient's age and state. At 28 wk of gestation, all four extremities are extended and there is little resistance to passive movement. Flexor tone is visible in the lower extremities at 32 wk and is palpable in the upper extremities at 36 wk; a normal term infant's posture is characterized by flexion of all four extremities.

There are three key tests for assessing postural tone in neonates: the traction response, vertical suspension, and horizontal suspension (Fig. 608.3 ; see Chapters 113 and 120). To evaluate the **traction response,** the physician grasps the infant's hands and gently pulls the infant to a sitting position. Normally, the infant's head lags slightly behind the infant's body and then falls forward upon reaching the sitting position. To test **vertical suspension,** the physician holds the infant by the axillae without gripping the thorax. The infant should remain suspended with the infant's lower extremities held in flexion; a hypotonic infant will slip through the physician's hands. With **horizontal suspension,** the physician holds the infant prone by placing a hand under the infant's abdomen. The head should rise and the limbs should flex, but a hypotonic infant will drape over the physician's hand, forming a U shape. Assessing tone in the extremities is accomplished by observing the infant's resting position and passively manipulating the infant's limbs. When the upper extremity of a normal term infant is pulled gently across the chest, the elbow does not quite reach the mid-sternum **(scarf sign),** whereas the elbow of a hypotonic infant extends beyond the midline with ease. Measurement of the **popliteal angle** is a useful method for documenting tone in the lower extremities. The examiner flexes the hip and extends the knee. Normal term infants allow extension of the knee to approximately 80 degrees. Similarly, tone can be evaluated by flexing the hip and knee to 90 degrees and then internally rotating the leg, in which case the heel should not pass the umbilicus.

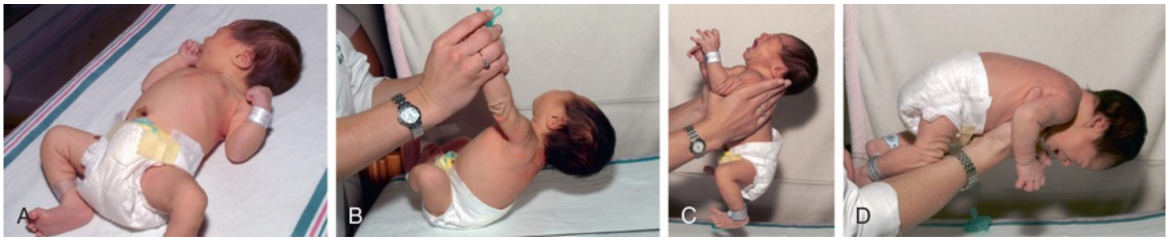

FIG. 608.3 Normal tone in a full-term neonate. **A,** Flexed resting posture**.**

B, Traction response. **C,** Vertical suspension. **D,** Horizontal suspension.

Abnormalities of tone include spasticity, rigidity, and hypotonia. (Paratonia, which is rarely seen in the pediatric population, is not discussed here.) **Spasticity** is characterized by an initial resistance to passive movement, followed by a sudden release, referred to as the **clasp-knife** phenomenon. Because spasticity results from upper motor neuron dysfunction, it disproportionately affects the upper-extremity flexors and lower-extremity extensors and tends to occur in conjunction with disuse atrophy, hyperactive deep tendon reflexes, and extensor plantar reflexes **(Babinski sign).** In infants, spasticity of the lower extremities results in scissoring of the legs upon vertical suspension. Older children can present with prolonged commando crawling or toe-walking. **Rigidity,** seen with lesions of the basal ganglia, is characterized by resistance to passive movement that is equal in the flexors and extensors regardless of the velocity of movement **(lead pipe).** Patients with either spasticity or rigidity might exhibit **opisthotonos** , defined as severe hyperextension of the spine caused by hypertonia of the paraspinal muscles (Fig. 608.4), although similar posturing can be seen in patients with Sandifer syndrome (gastroesophageal reflux or hiatal hernia associated with torsional dystonia). **Hypotonia** refers to abnormally diminished tone and is the most common abnormality of tone in neurologically compromised neonates. A hypotonic infant is floppy and often assumes a frog-leg posture at rest. Hypotonia can reflect pathology of the cerebral hemispheres, cerebellum, spinal cord, anterior horn cell, peripheral nerve, neuromuscular junction, or muscle.

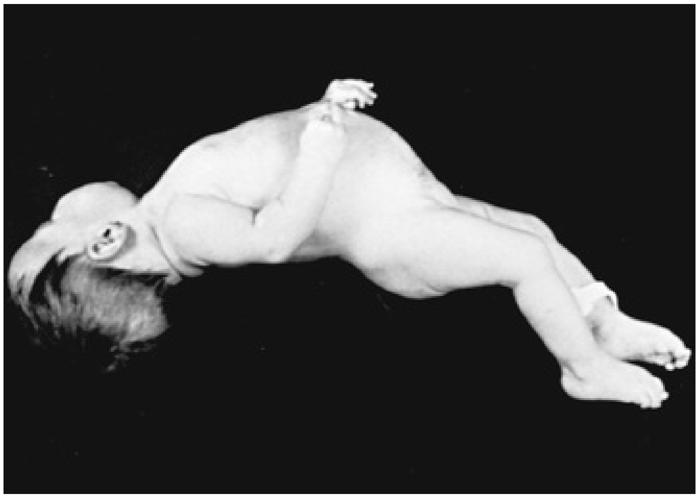

FIG. 608.4 Opisthotonos in a brain-injured infant.

Strength

Older children are usually able to cooperate with formal strength testing, in which case muscle power is graded on a scale of 0-5 as follows: 0 = no contraction; 1 = flicker or trace of contraction; 2 = active movement with gravity eliminated; 3 = active movement against gravity; 4 = active movement against gravity and resistance; 5 = normal power. An examination of muscle power should include all muscle groups, including the neck flexors and extensors and the muscles of respiration. It is important not only to assess individual muscle groups, but also to determine the pattern of weakness (i.e., proximal vs distal; segmental vs regional). Testing for **pronator drift** can be helpful in localizing the lesion in a patient with weakness. This test is accomplished by having the patient extend his or her arms away from the body with the palms facing upward and the eyes closed. *Together, pronation and downward drift of an arm indicate a lesion of the contralateral corticospinal tract.*

Because infants and young children are not able to participate in formal strength testing, they are best assessed with functional measures. Proximal and distal strength of the upper extremities can be tested by having the child reach overhead for a toy and by watching the child manipulate small objects. In infants younger than 2 mo, the physician can also take advantage of the palmar grasp reflex in assessing distal power and the Moro reflex in assessing proximal power. Infants with decreased strength in the lower extremities tend to have diminished spontaneous activity in their legs and are unable to support their body weight when held upright. Older children may have difficulty climbing or descending steps, jumping, or hopping. They might also use their hands to climb up their legs when asked to rise from a prone position, a maneuver called **Gowers sign** (Fig. 608.5).

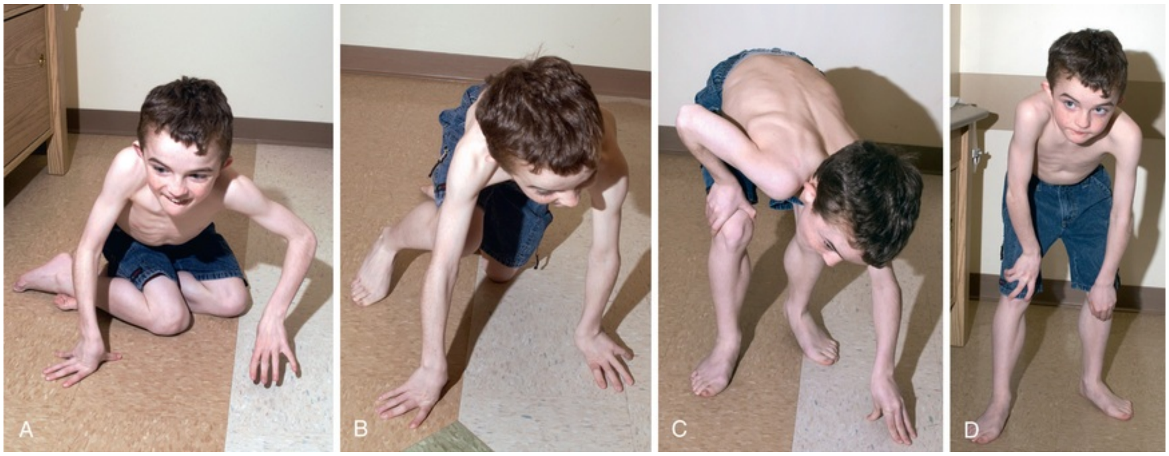

FIG. 608.5 **A-D,** Gowers sign in a boy with hip girdle weakness because of Duchenne muscular dystrophy. When asked to rise from a prone position, the patient uses his hands to walk up his legs to compensate for proximal lower extremity weakness.

Involuntary Movements

Patients with lower motor neuron or peripheral nervous system lesions might have **fasciculations,** which are small, involuntary muscle contractions that result from the spontaneous discharge of a single motor unit and create the illusion of a bag of worms under the skin. Because most infants have abundant body fat, muscle fasciculations are best observed in the tongue in this age-group.

Most other involuntary movements, including tics, dystonia, chorea, and athetosis, stem from disorders of the basal ganglia. Tremor seems to be an exception, as it is thought to be mediated by cerebellothalamocortical pathways. Further detail on the individual movement disorders is provided in Chapter 615 .

Sensory Examination

The sensory examination is difficult to perform on an infant or uncooperative child and has a relatively low yield in terms of the information that it provides. A gross assessment of sensory function can be achieved by distracting the patient with an interesting toy and then touching the patient with a cotton swab in different locations. Normal infants and children indicate an awareness of the stimulus by crying, withdrawing the extremity, or pausing briefly; however, with repeated testing, they lose interest in the stimulus and begin to ignore the examiner. It is critical, therefore, that any areas of concern are tested efficiently and, if necessary, reexamined at an appropriate time.

Fortunately, isolated disorders of the sensory system are less common in the very young pediatric population than in the adult population, so detailed sensory testing is rarely warranted. Furthermore, most patients who are old enough to voice a sensory complaint are also old enough to cooperate with formal testing of light touch, pain, temperature, vibration, proprioception, and corticosensation (e.g., stereognosis, 2-point discrimination, extinction to double simultaneous stimulation). A notable exception is when the physician suspects a spinal cord lesion in an infant or young child and needs to identify a sensory level. In such situations, observation might suggest a difference in color, temperature, or perspiration, with the skin cool and dry below the level of injury. Lightly touching the skin above the level can evoke a squirming movement or physical withdrawal. Other signs of spinal cord injury include decreased anal sphincter tone and strength and absence of the superficial abdominal, anal wink, and cremasteric reflexes.

Reflexes

Deep Tendon Reflexes and the Plantar Response

Deep tendon reflexes are readily elicited in most infants and children. In infants, it is important to position the head in the midline when assessing reflexes, because turning the head to one side can alter reflex tone. Reflexes are graded from 0 (absent) to 4+ (markedly hyperactive), with 2+ being normal. Reflexes that are 1+ or 3+ can be normal as long as they are symmetric. Sustained clonus is always pathologic, but infants younger than 3 mo old can have 5-10 beats of clonus, and older children can have 1-2 beats of clonus, provided that it is symmetric.

The ankle jerk is hardest to elicit, but it can usually be obtained by passively dorsiflexing the foot and then tapping on either the Achilles tendon or the ball of the foot. The knee jerk is evoked by tapping the patellar tendon. If this reflex is exaggerated, extension of the knee may be accompanied by contraction of the contralateral adductors **(crossed adductor response).** Hypoactive reflexes generally reflect lower motor neuron or cerebellar dysfunction, whereas hyperactive reflexes are consistent with upper motor neuron disease, although acute upper motor neuron injury can result in hypoactive or absent deep tendon reflexes. The plantar response is obtained by stimulation of the lateral aspect of the sole of the foot, beginning at the heel and extending to the base of the toes. The **Babinski sign,** indicating an upper motor neuron lesion, is characterized by extension of the great toe and fanning of the remaining toes. Too vigorous stimulation may produce withdrawal, which may be misinterpreted as a Babinski sign. Plantar responses have limited diagnostic utility in neonates, because they are mediated by several competing reflexes and can be either flexor or extensor, depending on how the foot is positioned. Asymmetry of the reflexes or plantar response is a useful lateralizing sign in infants and children.

Primitive Reflexes

Primitive reflexes appear and disappear at specific times during development (Table 608.2), and their absence or persistence beyond those times signifies CNS dysfunction. Although many primitive reflexes have been described, the Moro, grasp, tonic neck, and parachute reflexes are the most clinically relevant. The **Moro reflex** is elicited by supporting the infant in a semierect position and then allowing the infant's head to fall backward onto the examiner's hand. A normal response consists of symmetric extension and abduction of the fingers and upper extremities, followed by flexion of the upper extremities and an audible cry. An asymmetric response can signify a fractured clavicle, brachial plexus injury, or hemiparesis. Absence of the Moro reflex in a term newborn is ominous, suggesting significant dysfunction of the CNS. The **grasp response** is elicited by placing a finger in the open palm of each hand; by 37 wk of gestation, the reflex is strong enough that the examiner can lift the infant from the bed with gentle traction. The **tonic neck reflex** is produced by manually rotating the infant's head to one side and observing for the characteristic fencing posture (extension of the arm on the side to which the face is rotated and flexion of the contralateral arm). An obligatory tonic neck response, in which the infant becomes stuck in the fencing posture, is always abnormal and implies a CNS disorder. The **parachute reflex,** which occurs in slightly older infants, can be evoked by holding the infant's trunk and then suddenly lowering the infant as if he or she were falling. The arms will spontaneously extend to break the infant's fall, making this reflex a prerequisite to walking.

Table 608.2

Timing of Selected Primitive Reflexes

REFLEX	ONSET	FULLY DEVELOPED	DURATION
Palmar grasp	28 wk gestation	32 wk gestation	2-3 mo postnatal
Rooting	32 wk gestation	36 wk gestation	Less prominent after 1 mo postnatal

Moro	28-32 wk gestation	37 wk gestation	5-6 mo postnatal
Tonic neck	35 wk gestation	1 mo postnatal	6-7 mo postnatal
Parachute	7-8 mo postnatal	10-11 mo postnatal	Remains throughout life

Coordination

Ataxia refers to a disturbance in the smooth performance of voluntary motor acts and is usually the result of cerebellar dysfunction. Lesions to the cerebellar vermis result in unsteadiness while sitting or standing **(truncal ataxia).** Affected patients might have a wide-based gait or may be unable to perform tandem gait testing. Lesions of the cerebellar hemispheres cause appendicular ataxia, which may be apparent as the patient reaches for objects and performs finger-to-nose and heel-to-shin movements. Other features of cerebellar dysfunction include errors in judging distance **(dysmetria),** inability to inhibit a muscular action **(rebound),** impaired performance of rapid alternating movements **(dysdiadochokinesia),** intention tremor, nystagmus, scanning dysarthria, hypotonia, and decreased deep tendon reflexes. Acute ataxia suggests an infectious or postinfectious, endocrinologic, toxic, traumatic, vascular, or psychogenic process, and chronic symptoms suggest a metabolic, neoplastic, or degenerative process.

Station and Gait

Observation of a child's station and gait is an important aspect of the neurologic examination. Normal children can stand with their feet close together without swaying; however, children who are unsteady may sway or even fall. On gait testing, the heels should strike either side of an imaginary line, but children with poor balance tend to walk with their legs farther apart to create a more stable base. Tandem gait testing forces patients to have a narrow base, which highlights subtle balance difficulties.

There are a variety of abnormal gaits, many of which are associated with a specific underlying etiology. Patients with a **spastic gait** appear stiff-legged like a soldier. They may walk on tiptoe as a result of tightness or contractures of the Achilles tendons, and their legs may scissor as they walk. A **hemiparetic gait** is associated with spasticity and circumduction of the leg, as well as decreased arm swing on the affected side. **Cerebellar ataxia** results in a wide-based, reeling gait like that of a drunk person, whereas **sensory ataxia** results in a wide-based **steppage gait,** in which the patient lifts the legs up higher than usual in the swing phase and then slaps the foot down. A **myopathic,** or waddling, **gait** is associated with hip girdle weakness. Affected children often develop a compensatory lordosis and have other signs of proximal muscle weakness, such as difficulty climbing stairs. During gait testing, the examiner might also note hypotonia or weakness of the lower extremities; extrapyramidal movements, such as dystonia or chorea; or orthopedic deformities, such as pelvic tilt, genu recurvatum, varus or valgus deformities of the knee, pes cavus (high arches) or pes planus (flat feet), and scoliosis.

General Examination

Examination of other organ systems is essential because myriad systemic diseases affect the nervous system. Dysmorphic features can indicate a genetic syndrome (see Chapter 95). Heart murmurs may be associated with rheumatic fever (Sydenham chorea), cardiac rhabdomyoma (tuberous sclerosis), cyanotic heart disease (cerebral abscess or thrombosis), and endocarditis (cerebral vascular occlusion). Hepatosplenomegaly can suggest an inborn error of metabolism, storage disease, HIV infection, or malignancy. Cutaneous lesions may be a feature of a neurocutaneous syndrome (see Chapter 614).

Special Diagnostic Procedures

Lumbar Puncture and Cerebrospinal Fluid Examination

Examination of the cerebrospinal fluid (CSF) and measurement of the pressure it creates in the subarachnoid space are essential in confirming the diagnosis of meningitis, encephalitis (autoimmune, infectious), and idiopathic intracranial hypertension (previously referred to as pseudotumor cerebri), and it is often helpful in assessing subarachnoid hemorrhage; demyelinating, degenerative, and collagen vascular diseases; and intracranial neoplasms. Having an experienced assistant who can position, restrain, and comfort the patient is critical to the success of the procedure.

The patient should be situated in a lateral decubitus or seated position with the neck and legs flexed to enlarge the intervertebral spaces. As a rule, sick neonates should be maintained in a seated position to prevent problems with ventilation and perfusion. Regardless of the position chosen, it is important to make sure that the patient's shoulders and hips are straight to prevent rotating the spine.

Once the patient is situated, the physician identifies the appropriate interspace by drawing an imaginary line from the iliac crest downward perpendicular to the vertebral column. In adults, lumbar punctures are usually performed in the L3-L4 or L4-L5 interspaces. Next, the physician dons a mask, gown, and sterile gloves. The skin is thoroughly prepared with a cleansing agent, and sterile drapes are applied. The skin and underlying tissues are anesthetized by injecting a local anesthetic (e.g., 1% lidocaine) at the time of the procedure or by applying a eutectic mixture of lidocaine and prilocaine (EMLA) to the skin 30 min before the procedure. A 22-gauge, 1.5- to 3.0-inch, sharp, beveled spinal needle with a properly fitting stylet is introduced in the midsagittal plane and directed slightly cephalad. The physician should pause frequently, remove the stylet, and assess for CSF flow. Although a pop can occur as the needle penetrates the dura, it is more common to experience a subtle change in resistance.

Once CSF has been detected, a manometer and 3-way stopcock can be attached to the spinal needle to obtain an opening pressure. If the patient was seated as the spinal needle was introduced, the patient should be moved carefully to a **lateral decubitus position** with the head and legs extended before the manometer is attached. In children between 1 and 18 yr of age, the reference range parameter for abnormally elevated opening pressure, determined as the 90th percentile for all patients in the reference population, is 28 cm of water. The threshold for an abnormally reduced pressure in the 10th percentile is 11.5 cm of water. The most common cause of an elevated opening pressure is an agitated patient. Sedation and a high body mass index can also increase the opening pressure (Chapter 623).

Contraindications to performing a lumbar puncture include suspected mass lesion of the brain, especially in the posterior fossa or above the tentorium and causing shift of the midline; suspected mass lesion of the spinal cord; symptoms and signs of impending cerebral herniation in a child with probable meningitis; critical illness (on rare occasions); skin infection at the site of the lumbar puncture; and thrombocytopenia with a platelet count of $< 20 \times 10^9$ /L. If optic disc edema or focal findings suggest a mass lesion, a rapid CT scan of the head should be obtained before proceeding with lumbar puncture to prevent uncal or cerebellar herniation as the CSF is removed. In the absence of these findings, routine head imaging is not warranted. The physician should also be alert to clinical signs of impending herniation, including alterations in the respiratory pattern (e.g., hyperventilation, Cheyne-Stokes respirations, ataxic respirations, respiratory arrest), abnormalities of pupil size and reactivity, loss of brainstem reflexes, and decorticate or decerebrate posturing. If any of these signs are present or the child is so ill that the lumbar puncture might induce cardiorespiratory arrest, blood cultures should be drawn and supportive care, including antibiotics, should be initiated. Once the patient has stabilized, it may be possible to perform a lumbar puncture safely.

Normal CSF contains up to 5/mm^3 white blood cells, and a newborn can have as many as 15/mm^3 . Polymorphonuclear cells are always abnormal in a child, but 1-2/mm^3 may be present in a normal neonate. An elevated polymorphonuclear count suggests bacterial meningitis or the early phase of aseptic meningitis (see Chapter 621). CSF lymphocytosis can be seen in aseptic, tuberculous, or fungal meningitis; demyelinating diseases; brain or spinal cord tumor; immunologic disorders, including collagen vascular diseases; and chemical irritation (following myelogram, intrathecal methotrexate).

Normal CSF contains no red blood cells; thus, their presence indicates a traumatic tap or a subarachnoid hemorrhage. Progressive clearing of the blood between the first and last samples indicates a traumatic tap. Bloody CSF should be centrifuged immediately. A clear supernatant is consistent with a bloody tap, whereas **xanthochromia** (yellow color that results from the degradation of hemoglobin) suggests a subarachnoid hemorrhage. Xanthochromia may be absent in bleeds < 12 hr old, particularly when laboratories rely on visual inspection rather than spectroscopy. Xanthochromia can also occur in the setting of hyperbilirubinemia, carotenemia, and markedly elevated CSF protein.

The normal CSF protein is 10-40 mg/dL in a child and as high as 120 mg/dL in a neonate. The CSF protein falls to the normal childhood range by 3 mo of age. The CSF protein may be elevated in many processes, including infectious, immunologic, vascular, and degenerative diseases; blockage of CSF flow; as well as tumors of the brain (primary CNS tumors, systemic tumors metastatic to the CNS, infiltrative acute lymphoblastic leukemia) and spinal cord. With a traumatic tap, the CSF protein is increased by approximately 1 mg/dL for every 1,000 red blood cells/mm^3 . Elevation of CSF immunoglobulin G, which normally represents approximately 10% of the total protein, is observed in subacute sclerosing panencephalitis, in postinfectious encephalomyelitis, and in some cases of multiple sclerosis. If the diagnosis of multiple sclerosis is suspected, the CSF should be tested for the presence of oligoclonal bands.

The CSF glucose content is approximately 60% of the blood glucose in a healthy child. To prevent a spuriously elevated blood:CSF glucose ratio in a case of suspected meningitis, it is advisable to collect the blood glucose before the lumbar puncture when the child is relatively calm. Hypoglycorrhachia is found in association with diffuse meningeal disease, particularly bacterial and tubercular meningitis. Widespread neoplastic involvement of the meninges, subarachnoid hemorrhage, disorders involving the glucose transporter protein type 1 (e.g., GLUT1 deficiency), fungal meningitis, and, occasionally, aseptic meningitis can produce low CSF glucose as well.

A Gram stain of the CSF is essential if there is a suspicion for bacterial meningitis; an acid-fast stain and India ink preparation can be used to assess for tuberculous and fungal meningitis, respectively. CSF is then plated on different culture media depending on the suspected pathogen. When indicated by the clinical presentation, it can also be helpful to assess for the presence of specific antigens or polymerase chain reaction studies (e.g., *Neisseria meningitidis* , *Haemophilus influenzae* type b, or *Streptococcus pneumoniae*) or to obtain antibody or polymerase chain reaction studies (e.g., herpes simplex virus-1 and -2, West Nile virus, Zika, enteroviruses). In noninfectious cases, levels of CSF metabolites, such as lactate, amino acids, and enolase, can provide clues to the underlying metabolic disease.

Neuroradiologic Procedures

Skull x-rays have limited diagnostic utility. They can demonstrate fractures, bony defects, intracranial calcifications, or indirect evidence of increased ICP. Acutely increased ICP causes separation of the sutures, whereas chronically increased ICP is associated with erosion of the posterior clinoid processes, enlargement of the sella turcica, and increased convolutional markings.

Cranial ultrasonography is the imaging method of choice for detecting intracranial hemorrhage, periventricular leukomalacia, and hydrocephalus in infants with patent anterior fontanels. Ultrasound is less sensitive than either cranial CT scanning or MRI for detecting hypoxic–ischemic injury, but the use of color Doppler or power Doppler sonography, both of which show changes in regional cerebral blood flow velocity, improve its sensitivity. In general, ultrasound is not a useful technique in older children, although it can be helpful intraoperatively when placing shunts, locating small tumors, and performing needle biopsies.

Cranial CT is a valuable diagnostic tool in the evaluation of many neurologic emergencies, as well as some nonemergent conditions. It is a noninvasive, rapid procedure that can usually be performed without sedation. CT scans use conventional x-ray techniques, meaning that they produce ionizing radiation. Because children younger than 10 yr of age are several times more sensitive to radiation than adults, it is important to consider whether imaging is actually indicated and, if it is, whether an ultrasound or MRI might be the more appropriate study. In the emergency setting, a noncontrast CT scan can demonstrate skull fractures, pneumocephalus, intracranial hemorrhages, hydrocephalus, and impending herniation. If the noncontrast scan reveals an abnormality and an MRI cannot be performed in a timely fashion, nonionic contrast should be used to highlight areas of breakdown in the blood–brain barrier (e.g., abscesses, tumors) and/or collections of abnormal blood vessels (e.g., arteriovenous malformations). CT is less useful for diagnosing acute infarcts in children, because radiographic changes might not be apparent for up to 24 hr. Some subtle signs of early (<24 hr) infarction include sulcal effacement, blurring of the gray–white junction, and the hyperdense middle cerebral artery sign (increased attenuation in the middle cerebral artery that is often associated with thrombosis). In the routine setting, CT imaging can be used to demonstrate intracranial calcifications or, with the addition of 3-dimensional reformatting, to evaluate patients with craniofacial abnormalities or craniosynostosis. Although other pathologic processes may be visible on CT scan, *MR is generally preferred because it provides a more detailed view of the anatomy without exposure the patient to ionizing radiation* (Table 608.3).

Table 608.3

Preferred Imaging Procedures in Neurologic Diseases

ISCHEMIC INFARCTION OR TRANSIENT ISCHEMIC ATTACK
CT/CTA (head and neck) ± CT perfusion for patients who are unstable or are potential candidates for tissue plasminogen activator or other acute interventions
Otherwise, MRI/MRA (head and neck) with and without gadolinium and with diffusion-weighted images
If the examination findings localize to the anterior circulation, carotid ultrasound should be performed rather than neck CTA or MRA
Obtain an MRV if the infarct does not follow an arterial distribution
CT or MRI can detect infarcts more than 24 hr old, although MRI is generally preferred to avoid exposure to ionizing radiation
INTRAPARENCHYMAL HEMORRHAGE
CT if < 24 hr; MRI if > 24 hr

MRI and MRA to assess for underlying vascular malformation, tumor, etc.

Catheter angiography if MRA is nondiagnostic

ARTERIOVENOUS MALFORMATION

CT for acute hemorrhage; MRI and MRA with and without gadolinium as early as possible

Catheter angiography if noninvasive imaging is nondiagnostic

CEREBRAL ANEURYSM

CT without contrast for acute subarachnoid hemorrhage

MRA or CTA to identify the aneurysm

Catheter angiography may be necessary in some cases

TCD to detect vasospasm

HYPOXIC–ISCHEMIC BRAIN INJURY

Ultrasound in infants

If ultrasound is negative or there is a discrepancy between the clinical course and the sonogram, obtain an MRI

In older children, CT if unstable; otherwise, MRI

MRS can show a lactate peak even in the absence of structural abnormalities and can be useful for prognostication purposes

METABOLIC DISORDERS

MRI, particularly T2-weighted and FLAIR images

Diffusion-weighted images may be useful in distinguishing acute and chronic changes

MRS, SPECT, and PET may be useful in certain disorders

HYDROCEPHALUS

Ultrasound (in infants), CT with and without contrast, or MR with and without gadolinium for diagnosis of communicating hydrocephalus

MR with and without gadolinium for diagnosis of noncommunicating hydrocephalus

Ultrasound (in infants) or CT to follow ventricular size in response to treatment

HEADACHE

CT with and without contrast or MRI with and without gadolinium if a structural disorder is suspected (MRI is preferred in nonemergent situations because it does not involve ionizing radiation and provides a better view of the parenchyma)

HEAD TRAUMA

CT without contrast initially

MRI after initial assessment and treatment if clinically indicated. Diffusion tensor imaging and/or diffusion kurtosis sequences may be useful to detect subtle white matter abnormalities

EPILEPSY

MRI with and without gadolinium. Thin slices through the mesial temporal lobes may be helpful if a temporal focus is suspected

PET

Interictal SPECT

BRAIN TUMOR

MRI with and without gadolinium

MRS

PET

MULTIPLE SCLEROSIS

MRI with and without gadolinium

Obtain sagittal FLAIR images

MENINGITIS OR ENCEPHALITIS

CT without and with contrast before lumbar puncture if there are signs of increased ICP on examination

MRI with and without gadolinium after initial assessment and treatment for patients with complicated meningitis or encephalitis

BRAIN ABSCESS

MRI with and without gadolinium

Diffusion-weighted images and MRS can help to differentiate abscess from necrotic tumor

If the patient is unstable, CT with and without contrast followed by MRI with and without contrast when feasible

MOVEMENT DISORDERS

MRI with and without gadolinium

PET

DaTscan (SPECT scan using ioflupane iodine-123 as the contrast agent for detecting dopamine transporters in suspected parkinsonian syndromes)

CTA, computed tomographic angiography; FLAIR, fluid-attenuated inversion recovery; ICP, intracranial pressure; MRA, magnetic resonance angiography; MRS, magnetic resonance spectroscopy; MRV, magnetic resonance venography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler ultrasonography.

Cranial CT angiography is a useful tool for visualizing vascular structures and is accomplished by administering a tight bolus of iodinated contrast through a large-bore intravenous catheter and then acquiring CT images as the contrast passes through the arteries.

Brain MRI is a noninvasive procedure that is well suited for detecting a variety of abnormalities, including those of the posterior fossa and spinal cord. MR scans are highly susceptible to patient motion artifact; consequently, many children younger than age 8 yr require sedation to ensure an adequate study. The need for sedation has decreased in some centers as MRI technology improves and allows for faster performance of studies, and as visual distraction techniques are better designed to be used by a child while in the MRI scanner. Because the American Academy of Pediatrics recommends that infants be kept nothing by mouth (NPO) for 4 hr or longer and older children for 6 hr or longer before deep sedation, it is often difficult to obtain an MRI on an infant or young child in the acute setting. MRI can be used to evaluate for congenital or acquired brain lesions, migrational defects, dysmyelination or demyelination, posttraumatic gliosis, neoplasms, cerebral edema, and acute stroke (see Table 608.3). Paramagnetic MR contrast agents (e.g., gadolinium-diethylenetriaminepentaacetic acid [DTPA]) are efficacious in identifying areas of disruption in the blood–brain barrier, such as those occurring in primary and metastatic brain tumors, meningitis, cerebritis, abscesses, and active demyelination. **MR angiography** and **MR venography** provide detailed images of major intracranial vasculature structures and assist in the diagnosis of conditions such as stroke, vascular malformations, and cerebral venous sinus thrombosis. MR angiography is the procedure of choice for infants and young children due to the lack of ionizing radiation and contrast; however, CT angiography may be preferable in older children because it is faster and can eliminate the need for sedation; it is particularly useful for looking at blood vessels in the neck, where there is less interference from bone artifact than in the skull-encased brain.

Functional MRI is a noninvasive technique used to map neuronal activity during specific cognitive states and/or sensorimotor functions. Data are usually based on blood oxygenation, although they can also be based on local cerebral blood volume or flow. Functional MRI is useful for presurgical localization of critical brain functions and has several advantages over other functional imaging techniques. Specifically, functional MRI produces high-resolution images without exposure to ionizing radiation or contrast, and it allows coregistration of functional and structural images.

Proton MR spectroscopy (MRS) is a molecular imaging technique in which the unique neurochemical profile of a preselected brain region is displayed in the form of a spectrum. Many metabolites can be detected, the most common of which are *N* -acetylaspartate, creatine and phosphocreatine, choline, myoinositol, and lactate. Changes in the spectral pattern of a given area can yield clues to the underlying pathology, making MRS useful in the diagnosis of inborn errors of metabolism, as well as the preoperative and posttherapeutic assessment of intracranial tumors. MRS can also detect areas of cortical dysplasia in patients with epilepsy, because these patients have low *N* -acetylaspartate:creatine ratios. Finally, MRS may be useful in detecting hypoxic–ischemic injury in newborns in the first day of life, because the lactate peak enlarges and the *N* -

acetylaspartate peak diminishes before MRI sequences become abnormal.

Catheter angiography is the gold standard for diagnosing vascular disorders of the CNS, such as arteriovenous malformations, aneurysms, arterial occlusions, and vasculitis. A 4-vessel study is accomplished by introducing a catheter into the femoral artery and then injecting contrast media into each of the internal carotid and vertebral arteries. Because catheter angiography is invasive and requires general anesthesia, it is typically reserved for treatment planning of endovascular or open procedures and for cases in which noninvasive imaging results are not diagnostic.

Positron emission tomography (PET) provides unique information on brain metabolism and perfusion by measuring blood flow, oxygen uptake, and/or glucose consumption. PET is an expensive technique that is most often used in the context of epilepsy surgery programs. PET-MRI is an emerging clinical modality of particular use in epilepsy surgery evaluation and neuro-oncology. Pediatric PET-MRI is largely used in the research setting, although at least one children's hospital in the United States has been pioneering its clinical use. **Single-photon emission CT** using ^{99m} Tc hexamethylpropyleneamine oxime is a sensitive and inexpensive technique to study regional cerebral blood flow. Single-photon emission CT is particularly useful in assessing for vasculitis, herpes encephalitis, dysplastic cortex, and recurrent brain tumors. Positron emission tomography MRI is only available in a few pediatric centers in the United States; it provides better resolution and tissue definition than single-photon emission CT.

Electroencephalography

An electroencephalogram (EEG) provides a continuous recording of electrical activity between reference electrodes placed on the scalp. Although the genesis of the electrical activity is not certain, it likely originates from postsynaptic potentials in the dendrites of cortical neurons. Even with amplification of the electrical activity, not all potentials are recorded because there is a buffering effect of the scalp, muscles, bone, vessels, and subarachnoid fluid. EEG waves are classified according to their frequency as delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-20 Hz). These waves are altered by many factors, including age, level of alertness, eye closure, drugs, and disease states.

The normal waking EEG is characterized by the posterior dominant rhythm—a sinusoidal, 8- to 12-Hz rhythm that is most prominent over the occipital region in a state of relaxed wakefulness with the eyes closed. This rhythm first becomes apparent at 3-4 mo of age, and most children have achieved the adult frequency of 8-12 Hz by age 8 yr.

Normal sleep is divided into 3 stages of non–rapid eye movement sleep—designated N1, N2, and N3—and rapid eye movement sleep. N1 corresponds to drowsiness, and N3 represents deep, restorative, slow-wave sleep. Rapid eye movement sleep is rarely captured during a routine EEG but may be seen on an overnight recording. The American Electroencephalography Society Guideline and Technical Standards states that “sleep recordings should be obtained whenever possible”; however, it appears that sleep deprivation—not sleep during the EEG—is what increases the yield of the study, particularly in children with one or more clinically diagnosed seizures and in children older than 3 yr of age.

EEG abnormalities can be divided into two general categories: epileptiform discharges and slowing. Epileptiform discharges are paroxysmal spikes or sharp waves, often followed by slow waves, which interrupt the background activity. They may be focal, multifocal, or generalized. Focal discharges are often associated with cerebral dysgenesis or irritative lesions, such as cysts, slow-growing tumors, or glial scar tissue; generalized discharges typically occur in children with structurally normal brains. Generalized discharges can occur as an epilepsy trait in children who have never had a seizure and, by themselves, are not an indication for treatment. Epileptiform activity may be enhanced by activation procedures, including hyperventilation and photic stimulation.

As with epileptiform discharges, slowing can be either focal or diffuse. Focal slowing should raise a concern for an underlying functional or structural abnormality, such as an infarct, hematoma, or tumor. Diffuse slowing is the hallmark of encephalopathy and is usually secondary to a widespread disease process or toxic–metabolic insult.

Long-term video EEG monitoring provides a precise characterization of seizure types, which allows specific medical or surgical management. It facilitates more accurate differentiation of epileptic seizures from paroxysmal events that mimic epilepsy, including recurrent psychogenic seizure-like attacks. Long-term EEG monitoring can also be useful during medication adjustments.

Evoked Potentials

An evoked potential is an electrical signal recorded from the CNS following the presentation of a specific visual, auditory, or sensory stimulus. Stimulation of the visual system by a flash or patterned stimulus, such as a black-and-white checkerboard, produces **visual evoked potentials** (VEPs), which are recorded over the occiput and averaged in a computer. Abnormal VEPs can result from lesions to the visual pathway anywhere from the retina to the visual cortex. Many demyelinating disorders and neurodegenerative diseases, such as Tay-Sachs, Krabbe, or Pelizaeus-Merzbacher disease, or neuronal ceroid lipofuscinoses show characteristic VEP abnormalities. Flash VEPs can also be helpful in evaluating infants who have sustained an anoxic injury; however, detection of an evoked potential does not necessarily mean that the infant will have functional vision.

Brainstem auditory evoked responses (BAERs) provide an objective measure of hearing and are particularly useful in neonates and in children who have failed, or are uncooperative with, audiometric testing. BAERs are abnormal in many neurodegenerative diseases of childhood and are an important tool in evaluating patients with suspected tumors of the cerebellopontine angle. BAERs can be helpful in assessing brainstem function in comatose patients, because the waveforms are unaffected by drugs or by the level of consciousness; however, they are not accurate in predicting neurologic recovery and outcome.

Somatosensory evoked potentials (SSEPs) are obtained by stimulating a peripheral nerve (peroneal, median) and then recording the electrical response over the cervical region and contralateral parietal somatosensory cortex. SSEPs determine the functional integrity of the dorsal column–medial lemniscal system and are useful in monitoring spinal cord function during operative procedures for scoliosis, aortic coarctation, and myelomeningocele repair. SSEPs are abnormal in many neurodegenerative disorders and are the most accurate evoked potential in the assessment of neurologic outcome following a severe CNS insult.

Specific and General Genetic and Metabolic Testing

Children with intellectual disability or developmental delay are often evaluated with metabolic and/or genetic testing. Newborn screening study results should be rechecked before new studies are done. Specific accompanying features of the child's history and physical examination may point to a particular disorder or group of disorders, allowing for specific genetic or metabolic testing or for chromosomal studies to be fruitful. Whole-exome sequencing is often used in situations in which these studies are negative or there are no distinguishing features of the child's history or physical examination that point to a particular subgroup of diagnoses.

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CHAPTER 609

Congenital Anomalies of the Central Nervous System

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Central nervous system (CNS) malformations are grouped into neural tube defects (NTDs) and associated spinal cord malformations; encephaloceles; disorders of structure specification (gray matter structures, neuronal migration disorders, disorders of connectivity, and commissure and tract formation); disorders of the posterior fossa, brainstem, and cerebellum; disorders of brain growth and size; and disorders of skull growth and shape. Classification of these conditions into syndromic, nonsyndromic, copy number variations, and single-gene etiologies is also important. These disorders can be isolated findings or a consequence of environmental exposures. Elucidation of single-gene and copy number variations (deletions) causes has outpaced our understanding of the epigenetic and environmental mechanisms that cause these malformations.

These disorders are heterogeneous in their presentation. Common presentations and clinical problems include disorders of head size and/or shape; hydrocephalus; fetal ultrasonographic brain abnormalities; neonatal encephalopathy and seizures; developmental delay, cognitive impairment, and intellectual disability; hypotonia, motor impairment, and cerebral palsy; seizures, epilepsy, and drug-resistant epilepsy; cranial nerve dysfunction; and spinal cord dysfunction.

609.1

Neural Tube Defects

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Hydrocephalus

Neural tube defects (NTDs) account for the largest proportion of congenital anomalies of the CNS and result from failure of the neural tube to close spontaneously between the 3rd and 4th wk of in utero development. Although the precise cause of NTDs remains unknown, evidence suggests that many factors, including hyperthermia, drugs (valproic acid), malnutrition, low red cell folate levels, chemicals, maternal obesity or diabetes, and genetic determinants (mutations in folate-responsive or folate-dependent enzyme pathways) can adversely affect normal development of the CNS from the time of conception. In some cases, an abnormal maternal nutritional state or exposure to radiation before conception increases the likelihood of a congenital CNS malformation. The major NTDs include spina bifida occulta, meningocele, myelomeningocele, encephalocele, anencephaly, caudal regression syndrome, dermal sinus, tethered cord, syringomyelia, diastematomyelia, and lipoma involving the conus medullaris and/or filum terminale and the rare condition iniencephaly.

The human nervous system originates from the primitive ectoderm that also develops into the epidermis. The ectoderm, endoderm, and mesoderm form the three primary germ layers that are developed by the 3rd wk. The endoderm, particularly the notochordal plate and the intraembryonic mesoderm, induces the overlying ectoderm to develop the neural plate in the 3rd wk of development (Fig. 609.1*A*). Failure of normal induction is responsible for most NTDs, as well as disorders of prosencephalic development. Rapid growth of cells within the neural plate causes further invagination of the neural groove and differentiation of a conglomerate of cells, the neural crest, which migrate laterally on the surface of the neural tube (see Fig. 609.1*B*). The notochordal plate becomes the centrally placed notochord, which acts as a foundation around which the vertebral column ultimately develops. With formation of the vertebral column, the notochord undergoes involution and becomes the nucleus pulposus of the intervertebral disks. The neural crest cells differentiate to form the peripheral nervous system, including the spinal and autonomic ganglia and the ganglia of cranial nerves V, VII, VIII, IX, and X. In addition, the neural crest forms the leptomeninges, as well as Schwann cells, which are responsible for myelination of the peripheral nervous system. The dura is thought to arise from the paraxial mesoderm. In the region of the embryo destined to become the head, similar patterns exist. In this region, the notochord is replaced by the prechordal mesoderm.

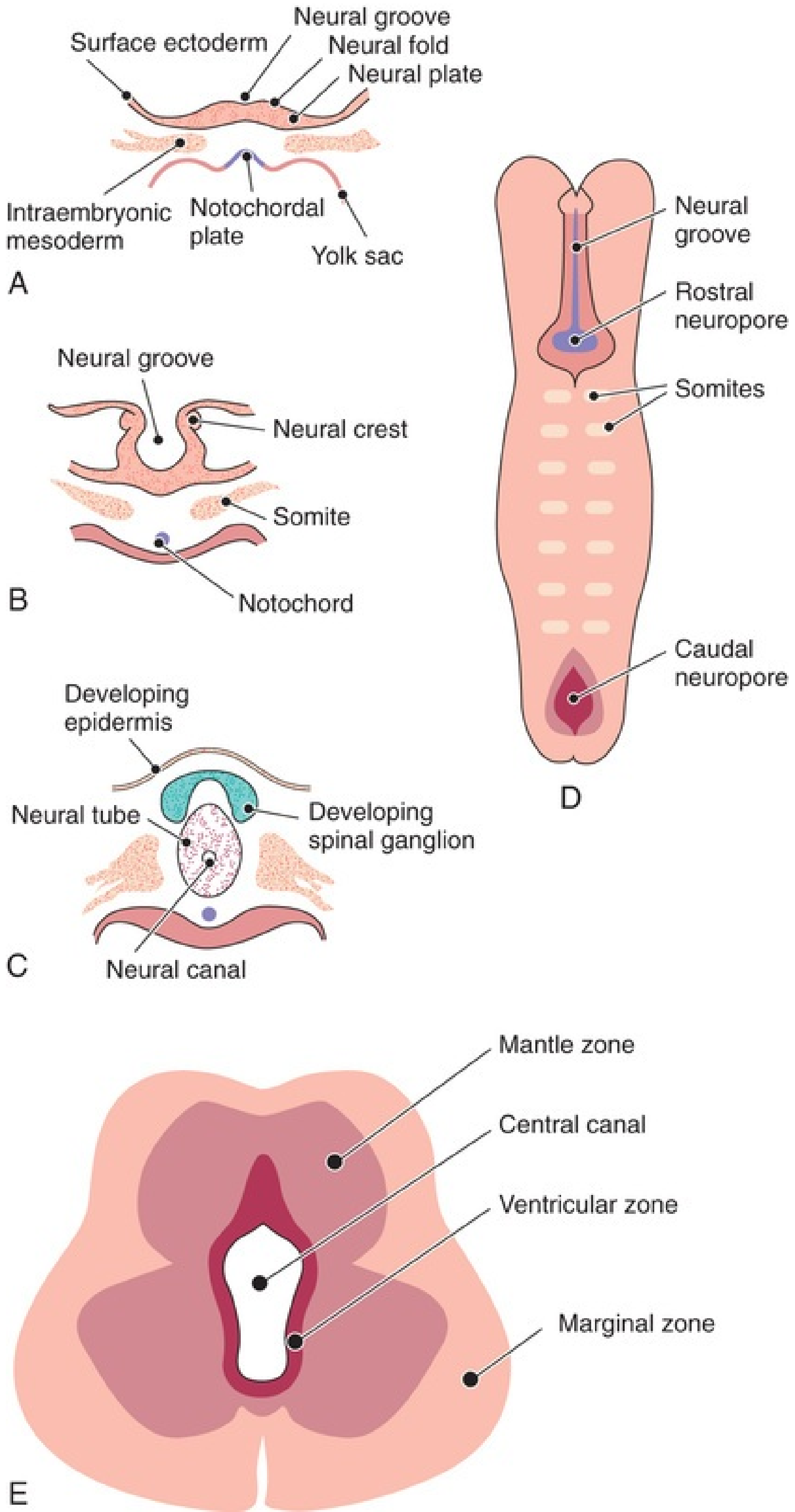
Surface ectoderm
Neural groove
Neural fold
Neural plate
Intraembryonic mesoderm
Notochordal plate
Yolk sac
A
Neural groove
Neural crest
Somite
Notochord
B
Developing epidermis
Neural tube
Developing spinal ganglion
Neural canal
C
Neural groove
Rostral neuropore
Somites
Caudal neuropore
D
Mantle zone
Central canal
Ventricular zone
Marginal zone
E

FIG. 609.1 Diagrammatic illustration of the developing nervous system. **A,** Transverse sections of the neural plate during the 3rd wk. **B,** Formation of the neural groove and the neural crest. **C,** The neural tube is developed. **D,** Longitudinal drawing showing the initial closure of the neural tube in the

central region. **E,** Cross-sectional drawing of the embryonic neural tube (primitive spinal cord).

In the 3rd wk of embryonic development, invagination of the neural groove is completed and the neural tube is formed by separation from the overlying surface ectoderm (see Fig. 609.1*C*). Initial closure of the neural tube is accomplished in the area corresponding to the future junction of the spinal cord and medulla and moves rapidly both caudally and rostrally. For a brief period, the neural tube is open at both ends, and the neural canal communicates freely with the amniotic cavity (see Fig. 609.1*D*). Failure of closure of the neural tube allows excretion of fetal substances (α-fetoprotein [AFP], acetylcholinesterase) into the amniotic fluid, serving as biochemical markers for an NTD. *Prenatal screening of maternal serum for AFP in the 16th-18th wk of gestation is an effective method for identifying pregnancies at risk for fetuses with NTDs in utero*. Normally, the rostral end of the neural tube closes on the 23rd day and the caudal neuropore closes by a process of secondary neurulation by the 27th day of development, before the time that many women realize they are pregnant.

The embryonic neural tube consists of three zones: ventricular, mantle, and marginal (see Fig. 609.1*E*). The ependymal layer consists of pluripotential, pseudostratified, columnar neuroepithelial cells. Specific neuroepithelial cells differentiate into primitive neurons or neuroblasts that form the mantle layer. The marginal zone is formed from cells in the outer layer of the neuroepithelium, which ultimately becomes the white matter. Glioblasts, which act as the primitive supportive cells of the CNS, also arise from the neuroepithelial cells in the ependymal zone. They migrate to the mantle and marginal zones and become future astrocytes and oligodendrocytes. It is likely that microglia originate from mesenchymal cells at a later stage of fetal development when blood vessels begin to penetrate the developing nervous system.

609.2

Spina Bifida Occulta (Occult Spinal Dysraphism)

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Spina bifida occulta is a common anomaly consisting of a midline defect of the vertebral bodies without protrusion of the spinal cord or meninges. Most patients are asymptomatic and lack neurologic signs, and the condition is usually of no consequence. Some consider the term *spina bifida occulta* to denote merely a posterior vertebral body fusion defect, as opposed to a true spinal dysraphism. This simple defect does not have an associated spinal cord malformation. Other clinically more significant forms of closed spinal cord malformations are more correctly termed **occult spinal dysraphism.** In most of these cases, there are cutaneous manifestations such as a hemangioma, discoloration of the skin, pit, lump, dermal sinus, or hairy patch (Figs. 609.2 and 609.3). A spine x-ray in simple spina bifida occulta shows a defect in closure of the posterior vertebral arches and laminae, typically involving L5 and S1; there is no abnormality of the meninges, spinal cord, or nerve roots. Occult spinal dysraphism is often associated with more significant developmental abnormalities of the spinal cord, including syringomyelia, diastematomyelia, lipoma, fatty filum, dermal sinus, and/or a tethered cord. A spine x-ray in these cases might show bone defects or may be normal. All cases of occult spinal dysraphism are best investigated with MRI (Fig. 609.4 and see Fig. 609.3). Initial screening in the neonate may include ultrasonography, but MRI is more accurate at any age.

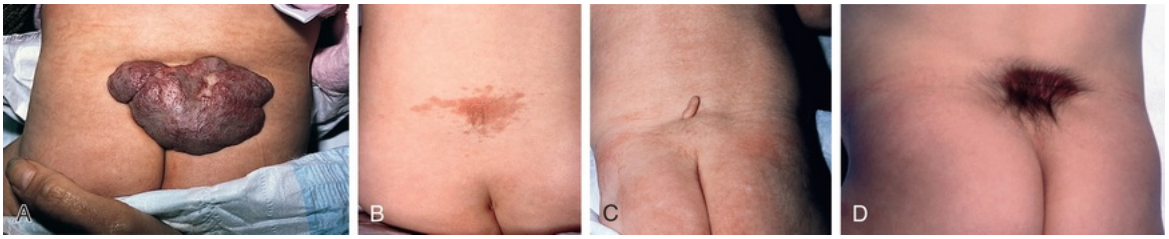

FIG. 609.2 Clinical aspects of congenital median lumbosacral cutaneous lesions. **A,** Midline sacral hemangioma in a patient with an occult lipomyelomeningocele. **B,** Capillary malformation with a subtle patch of hypertrichosis in a patient with a dermal sinus. **C,** Human tail with underlying lipoma in an infant with lipomyelomeningocele. **D,** Midline area of hypertrichosis (faun tail) overlying a patch of hyperpigmentation. (***A-C*** from Kos L, Drolet BA: Developmental abnormalities. In Eichenfield LF, Frieden IJ, Esterly NB, editors: Neonatal dermatology, ed 2, Philadelphia, 2008, WB Saunders. D from Spine and spinal cord: developmental disorders. In Schapira A, editor: Neurology and clinical neuroscience,

Philadelphia, 2007, Mosby.)

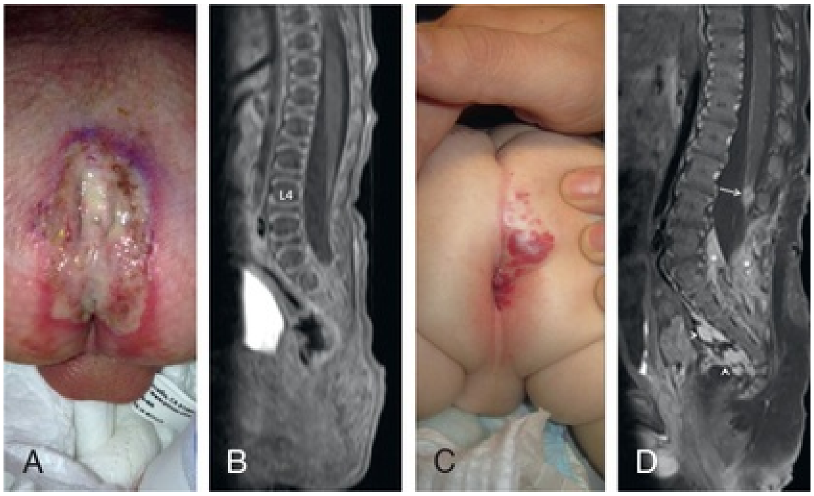

FIG. 609.3 **A,** Lumbosacral ulcerative plaque with surrounding red vascular rim was noted on initial examination. **B,** Midline sagittal contrast-enhanced, T1-weighted, fat-saturated image of the lumbosacral spine at presentation reveals low-lying conus at L4 vertebral level suggestive of tethered cord. **C,** Recurrence of lumbosacral hemangioma after discontinuation of oral propranolol. **D,** Midline sagittal contrast-enhanced, T1-weighted, fat-saturated image of the lumbosacral spine at 6 mo of age shows new nodular enhancing lesion at the lower end of the conus *(arrow)* compatible with intrathecal hemangioma. In addition, there is a large hemangioma in the epidural space in the sacral spinal canal *(asterisks)* with presacral extension *(arrowheads).* (From Yu J, Maheshwari M, Foy AB, et al: Neonatal lumbosacral ulceration masking lumbosacral and intraspinal hemangiomas associated with occult spinal dysraphism, J Pediat 175:211-215, 2016.)

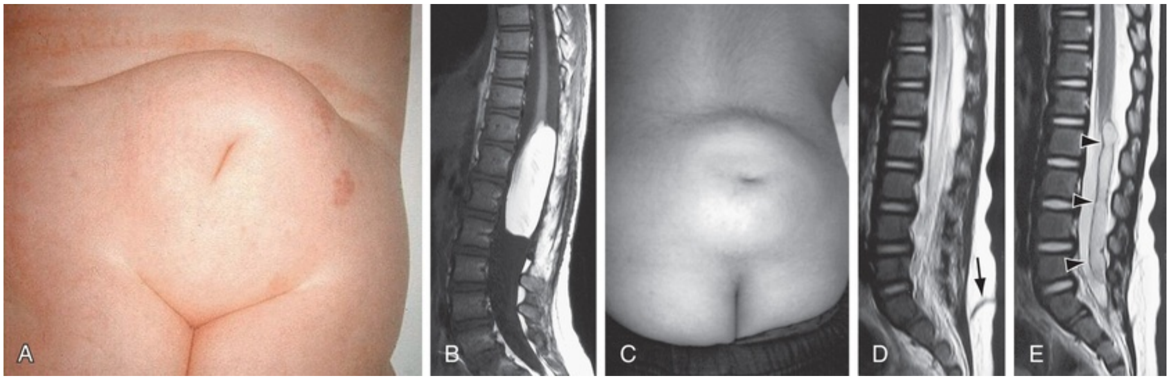

FIG. 609.4 Clinical features and imaging findings associated with occult

spinal dysraphism. **A,** Lumbosacral lipoma. The subcutaneous lipoma is in continuity with the spinal cord via a defect in the underlying muscles, bone, and dura. **B,** Sagittal T1-weighted image shows huge intradural lipoma, merging with the conus medullaris superiorly. **C,** Lipoma and central dermal sinus. **D** and **E,** Dermal sinus with dermoid on an 8 yr old girl. Slightly parasagittal T2-weighted image shows sacral dermal sinus coursing obliquely downward in subcutaneous fat *(arrow* in **D**). Midsagittal T2-weighted image shows huge dermoid in the thecal sac *(arrowheads),* extending upward to the tip of the conus medullaris **(E).** The mass gives a slightly lower signal than CSF and is outlined by a thin low-signal rim. (***A*** from Thompson DNP: Spinal dysraphic anomalies: classification, presentation and management, Paed Child Health 24:431-438, 2014, Fig. 4; ***B, D,*** and ***E*** from Rossi A, Biancheri R, Cama A, et al: Imaging in spine and spinal cord malformations, Eur J Radiol 50(2):177-200, 2004, Fig. 9a; and ***C*** from Jaiswal AK, Garg A, Mahapatra AK: Spinal ossifying lipoma, J Clin Neurosci 12:714-717, 2005, Fig. 1.)

A **dermoid sinus** usually forms a small skin opening, which leads into a narrow duct, sometimes indicated by protruding hairs, a hairy patch, or a vascular nevus. Dermoid sinuses occur in the midline at the sites where meningoceles or encephaloceles can occur: the lumbosacral region or occiput, respectively, and occasionally in the cervical or thoracic area. Dermoid sinus tracts can pass through the dura, acting as a conduit for the spread of infection. Recurrent meningitis of occult origin should prompt careful examination for a small sinus tract in the posterior midline region, including the back of the head. Lumbosacral sinuses are usually above the gluteal fold and are directed cephalad. The tethered spinal cord syndrome may also be an associated problem. Diastematomyelia commonly has bony abnormalities that require surgical intervention along with untethering of the spinal cord.

An approach to imaging of the spine in patients with cutaneous lesions is noted in Table 609.1 .

Table 609.1

Cutaneous Lesions Associated With Occult Spinal Dysraphism

IMAGING INDICATED
Subcutaneous mass or lipoma Hairy patch Dermal sinus or cyst Atypical dimples (deep, > 5 mm, > 25 mm from anal verge) Vascular lesion, e.g., hemangioma or telangiectasia Skin appendages or polypoid lesions, e.g., skin tags, tail-like appendages Scar-like lesions (aplasia cutis)

IMAGING UNCERTAIN

Hyperpigmented patches
Deviation of the gluteal fold

IMAGING NOT REQUIRED

Simple dimples (< 5 mm, < 25 mm from anal verge)
Coccygeal pits

From Williams H: Spinal sinuses, dimples, pits and patches: what lies beneath? Arch Dis Child Educ Pract Ed 91:ep75-ep80, 2006.

609.3

Meningocele

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A meningocele is formed when the meninges herniate through a defect in the posterior vertebral arches or the anterior sacrum. The spinal cord is usually normal and assumes a normal position in the spinal canal, although there may be tethering of the cord, syringomyelia, or diastematomyelia. A fluctuant midline mass that might transilluminate occurs along the vertebral column, usually in the lower back. Most meningoceles are well covered with skin and pose no immediate threat to the patient. Careful neurologic examination is mandatory. Orthopedic and urologic examination should also be considered. In asymptomatic children with normal neurologic findings and full-thickness skin covering the meningocele, surgery may be delayed or sometimes not performed.

Before surgical correction of the defect, the patient must be thoroughly examined with the use of plain x-rays, ultrasonography, and MRI to determine the extent of neural tissue involvement, if any, and associated anomalies, including diastematomyelia, lipoma, and a possible clinically significant tethered spinal cord. Urologic evaluation usually includes cystometrogram to identify children with neurogenic bladder who are at risk for renal deterioration. Patients with leaking cerebrospinal fluid (CSF) or a thin skin covering should undergo immediate surgical treatment to prevent meningitis. A cranial CT scan or an MRI of the head is recommended for children with a meningocele because of the association with hydrocephalus in some cases. An anterior meningocele projects into the pelvis through a defect in the sacrum. Symptoms of constipation and bladder dysfunction develop owing to the increasing size of the lesion. Female patients might have associated anomalies of the genital tract, including a rectovaginal fistula and vaginal septa. Plain x-rays demonstrate a defect in the sacrum, and CT scanning or MRI outlines the extent of the meningocele and any associated anomalies.

609.4

Myelomeningocele

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Myelomeningocele represents the most severe form of dysraphism, a so-called aperta or open form, involving the vertebral column and spinal cord; it occurs with an incidence of approximately 1 in 4,000 live births.

Etiology

The cause of myelomeningocele is unknown, but as with all neural tube closure defects, including anencephaly, a genetic predisposition exists; the risk of recurrence after one affected child is 3–4% and increases to 10% with two prior affected children. Both epidemiologic evidence and the presence of substantial familial aggregation of anencephaly, myelomeningocele, and craniorachischisis indicate heredity, on a polygenic basis, as a significant contributor to the etiology of NTDs. Nutritional and environmental factors have a role in the etiology of myelomeningocele as well.

Folate is intricately involved in the prevention and etiology of NTDs. Folate functions in single-carbon transfer reactions and exists in many chemical forms. Folic acid (pteroylmonoglutamic acid), which is the most oxidized and stable form of folate, occurs rarely in food but is the form used in vitamin supplements and in fortified food products, particularly flour. Most naturally occurring folates (food folate) are pteroylpolyglutamates, which contain 1-6 additional glutamate molecules joined in a peptide linkage to the γ-carboxyl of glutamate. Folate coenzymes are involved in DNA synthesis, purine synthesis, generation of formate into the formate pool, and amino acid interconversion; the conversion of homocysteine to methionine provides methionine for the synthesis of *S* -adenosylmethionine (SAMe, an agent important for in vivo methylation). Mutations in the genes encoding the enzymes involved in homocysteine metabolism may play a role in the pathogenesis of meningomyelocele. These enzymes include 5,10-methylenetetrahydrofolate reductase, cystathionine β-synthase, and methionine synthase. An association between a thermolabile variant of 5,10-methylenetetrahydrofolate reductase and mothers of children with NTDs might account for up to 15% of preventable NTDs. Maternal periconceptional use of folic acid supplementation reduces the incidence of NTDs in pregnancies at risk by at least 50%. *To be effective, folic acid supplementation should be initiated before conception and continued until at least the 12th wk of gestation, when neurulation is complete.* The mechanisms by which folic acid prevents NTDs remain poorly understood.

Prevention

See also Chapter 62.6 .

The United States Public Health Service recommends that all women of childbearing age who can become pregnant take 0.4 mg of folic acid daily. If, however, a pregnancy is planned in high-risk women (previously affected child), supplementation should be started with 4 mg of folic acid daily, beginning 1 mo before the time of the planned conception. The modern diet provides about half the daily requirement of folic acid. To increase folic acid intake, fortification of flour, pasta, rice, and cornmeal with 0.15 mg folic acid per 100 g was mandated in the United States and Canada in 1998. The added folic acid is insufficient to maximize the prevention of preventable NTDs. Therefore, informative educational programs and folic acid vitamin supplementation remain essential for women planning a pregnancy and possibly for all women of childbearing age. In addition, women should also strive to consume food folate from a varied diet. Certain drugs, including drugs that antagonize folic acid, such as trimethoprim and the anticonvulsants carbamazepine, phenytoin, phenobarbital, and primidone, increase the risk of myelomeningocele. The anticonvulsant valproic acid causes NTDs in approximately 1–2% of pregnancies when administered during pregnancy. Some epilepsy clinicians recommend that all female patients of childbearing potential who take anticonvulsant medications also receive folic acid supplements. There may be a threshold for ideal red blood cell folate levels (900-1,000 nmol/L), which is associated with a markedly reduced risk of NTDs.

Clinical Manifestations

Myelomeningocele produces dysfunction of many organs and structures, including the skeleton, skin, and gastrointestinal and genitourinary tracts, in addition to the peripheral nervous system and the CNS. A myelomeningocele may be located anywhere along the neuraxis, but the lumbosacral region accounts for at least 75% of the cases. The extent and degree of the neurologic deficit depend on the location of the myelomeningocele and the associated lesions. A lesion in the low sacral region causes bowel and bladder incontinence associated with anesthesia in the perineal area but with no impairment of motor function. Newborns with a defect in the midlumbar or high lumbothoracic region typically have either a sac-like cystic structure covered by a thin layer of partially epithelialized tissue (Fig. 609.5) or an exposed flat neural placode without overlying tissues. When a cyst or membrane is present, remnants of neural tissue are visible beneath the membrane, which occasionally ruptures and leaks CSF.

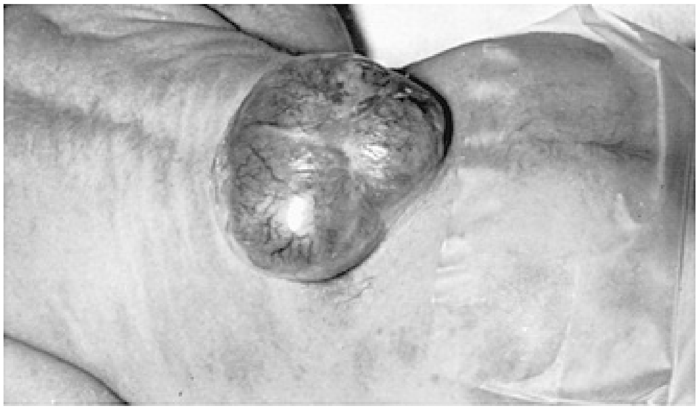

FIG. 609.5 A lumbar myelomeningocele is covered by a thin layer of skin.

Examination of the infant shows a flaccid paralysis of the lower extremities, an absence of deep tendon reflexes, a lack of response to touch and pain, and a high incidence of lower-extremity deformities (clubfeet, ankle and/or knee contractures, and subluxation of the hips). Some children have constant urinary dribbling and a relaxed anal sphincter. Other children do not leak urine and in fact have a high-pressure bladder and sphincter dyssynergy. Myelomeningocele above the midlumbar region tends to produce lower motor neuron signs because of abnormalities and disruption of the conus medullaris and above spinal cord structures.

Infants with myelomeningocele typically have an increased neurologic deficit as the myelomeningocele extends higher into the thoracic region. These infants sometimes have an associated kyphotic gibbus that requires neonatal orthopedic correction. Patients with a myelomeningocele in the upper thoracic or cervical region usually have a very minimal neurologic deficit and, in most cases, do not have hydrocephalus. They can have a neurogenic bladder and bowel.

Hydrocephalus in association with a **type II Chiari malformation** develops in at least 80% of patients with myelomeningocele who have not undergone fetal surgery. Generally, patients with sacral myelomeningocele have a very low risk of hydrocephalus. The possibility of hydrocephalus developing after the neonatal period should always be considered, no matter what the spinal level. Ventricular enlargement may be indolent and slow growing or may be rapid, causing a bulging anterior fontanel, dilated scalp veins, setting-sun appearance of the eyes, irritability, and vomiting in association with an increased head circumference. Approximately 15% of infants with hydrocephalus and Chiari II malformation develop symptoms of hindbrain (brainstem) dysfunction, including difficulty feeding, choking, stridor, apnea, vocal cord paralysis, pooling of secretions, and spasticity of the upper extremities, which, if untreated, can lead to death. This **Chiari crisis** is caused by downward herniation of the medulla and cerebellar tonsils through the foramen magnum, as well as endogenous malformations in the cerebellum and brainstem, causing dysfunction.

Treatment

Management and supervision of a child and family with a myelomeningocele require a multidisciplinary team approach, including surgeons, other physicians, and therapists, with one individual (often a pediatrician) acting as the advocate and coordinator of the treatment program. The news that a newborn child has a devastating condition such as myelomeningocele causes parents to feel considerable grief and anger. They need time to learn about the condition and its associated complications and to reflect on the various procedures and treatment plans. A knowledgeable individual in an unhurried and nonthreatening setting must give the parents the facts, along with general prognostic information and management strategies and timelines. If possible, discussions with other parents of children with NTDs are helpful in resolving important questions and issues.

Surgery is often done within a day or so of birth but can be delayed for several days (except when there is a CSF leak) to allow the parents time to begin to adjust to the shock and to prepare for the multiple procedures and inevitable problems that lie ahead. Evaluation of other congenital anomalies and renal function can also be initiated before surgery. Most pediatric centers aggressively treat the majority of infants with myelomeningocele. After repair of a myelomeningocele, most infants require a shunting procedure for hydrocephalus. If symptoms or signs of hindbrain dysfunction appear, early surgical decompression of the posterior fossa is indicated. Clubfeet can require taping or casting.

Careful evaluation and reassessment of the genitourinary system is an important component of management. Teaching the parents and, ultimately, the patient, to regularly catheterize a neurogenic bladder is a crucial step in maintaining a low residual volume and bladder pressure that prevents urinary tract infections and reflux, which can lead to pyelonephritis, hydronephrosis, and bladder damage. *Latex-free catheters and gloves must be used to prevent development of latex allergy.* Periodic urine cultures and assessment of renal function, including serum electrolytes and creatinine as well as renal scans, vesiculourethrograms, renal ultrasonograms, and cystometrograms, are obtained according to the risk status and progress of the patient and the results of the physical examination. This approach to urinary tract management has greatly reduced the need for urologic diversionary procedures and has decreased the morbidity and mortality associated with progressive renal disease in these patients. Some children can become continent with bladder augmentation at a later age.

Although incontinence of fecal matter is common and is socially unacceptable during the school years, it does not pose the same organ-damaging risks as urinary dysfunction, but occasionally fecal impaction and/or megacolon develop. Many children can be bowel-trained with a regimen of timed enemas or suppositories that allows evacuation at a predetermined time once or twice a day. Special attention to low anorectal tone and enema administration and retention is often required. Appendicostomy for antegrade enemas may also be helpful (see Chapter 354).

Functional ambulation is the wish of each child and parent and may be possible, depending on the level of the lesion and on intact function of the iliopsoas muscles. Almost every child with a sacral or lumbosacral lesion obtains functional ambulation; approximately half the children with higher defects ambulate with the use of braces, other orthotic devices, and canes. Ambulation is often more difficult as adolescence approaches and body mass increases. *Deterioration of ambulatory function, particularly during earlier years, should prompt referral for evaluation of tethered spinal cord and other neurosurgical issues.*

In utero surgical closure of a spinal lesion has been successful (Chapter 115.8). There is a lower incidence of hindbrain abnormalities and hydrocephalus (fewer shunts) as well as improved motor outcomes. This suggests that the defects may be progressive in utero and that prenatal closure might prevent the development of further loss of function. In utero diagnosis is facilitated by maternal serum alpha-fetoprotein (AFP) screening and by fetal ultrasonography (see Chapter 115.7).

Prognosis

For a child who is born with a myelomeningocele and who is treated aggressively, the mortality rate is 10–15%, and most deaths occur before age 4 yr, although life-threatening complications occur at all ages. At least 70% of survivors have normal intelligence, but learning problems and seizure disorders are more common than in the general population. Previous episodes of meningitis or ventriculitis adversely affect intellectual and cognitive function. Because myelomeningocele is a chronic disabling condition, periodic and consistent multidisciplinary follow-up is required for life. Renal dysfunction is one of the most important determinants of mortality.

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609.5

Encephalocele

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Two major forms of dysraphism affect the skull, resulting in protrusion of tissue through a bony midline defect, called **cranium bifidum.** A cranial meningocele consists of a CSF-filled meningeal sac only, and a cranial encephalocele contains the sac plus cerebral cortex, cerebellum, or portions of the brainstem. Microscopic examination of the neural tissue within an encephalocele often reveals abnormalities. The cranial defect occurs most commonly in the occipital region at or below the inion, but in certain parts of the world, frontal or nasofrontal encephaloceles (transethmoidal, sphenoethmoidal, sphenomaxillary, sphenoorbital, transsphenoidal) are more common. Some frontal lesions are associated with a cleft lip and palate. These abnormalities are one tenth as common as neural tube closure defects involving the spine. The etiology is presumed to be similar to that for anencephaly and myelomeningocele; examples of each are reported in the same family.

Infants with a cranial encephalocele are at increased risk for developing hydrocephalus because of **aqueductal stenosis, Chiari malformation,** or the **Dandy-Walker syndrome.** Examination might show a small sac with a pedunculated stalk or a large cyst-like structure that can exceed the size of the cranium. The lesion may be completely covered with skin, but areas of denuded lesion can occur and require urgent surgical management. Transillumination of the sac can indicate the presence of neural tissue. A plain x-ray of the skull and cervical spine is indicated to define the anatomy of the cranium and vertebrae. Ultrasonography is most helpful in determining the contents of the sac. MRI or CT further helps define the spectrum of the lesion. Children with a cranial meningocele generally have a good prognosis, whereas patients with an encephalocele are at risk for vision problems, microcephaly, intellectual disability, and seizures. Generally, children with neural tissue within the sac and associated hydrocephalus have the poorest prognosis.

Cranial encephalocele is often part of a syndrome. **Meckel-Gruber syndrome** is a rare autosomal recessive condition that is characterized by an occipital encephalocele, cleft lip or palate, microcephaly, microphthalmia, abnormal genitalia, polycystic kidneys, and polydactyly. Determination of maternal serum AFP levels and ultrasound measurement of the biparietal diameter, as well as identification of the encephalocele itself, can diagnose encephaloceles in utero. Fetal MRI can help define the extent of associated CNS anomalies and the degree of brain herniated into the encephalocele.

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609.6

Anencephaly

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An anencephalic infant presents a distinctive appearance with a large defect of the calvarium, meninges, and scalp associated with a rudimentary brain, which results from failure of closure of the rostral neuropore, the opening of the anterior neural tube. The primitive brain consists of portions of connective tissue, vessels, and neuroglia. The cerebral hemispheres and cerebellum are usually absent, and only a residue of the brainstem can be identified. The pituitary gland is hypoplastic, and the spinal cord pyramidal tracts are missing due to the absence of the cerebral cortex. Additional anomalies, including folding of the ears, cleft palate, and congenital heart defects, occur in 10–20% of cases. Most anencephalic infants die within several days of birth.

The incidence of **anencephaly** approximates 1 in 1,000 live births; the greatest incidence is in Ireland, Wales, and Northern China. The recurrence risk is approximately 4% and increases to 10% if a couple has had two previously affected pregnancies. Many factors, in addition to genetics, are implicated as a cause of anencephaly, including low socioeconomic status, nutritional and vitamin deficiencies, and a large number of environmental and toxic factors. It is very likely that several noxious stimuli interact on a genetically susceptible host to produce anencephaly. The incidence of anencephaly has been decreasing since the 1990s. Approximately 50% of cases of anencephaly have associated polyhydramnios. Couples who have had an anencephalic infant should have successive pregnancies monitored, including with amniocentesis, determination of AFP levels, and ultrasound examination, between the 14th and 16th wk of gestation. Prenatal folic acid supplementation decreases the risk of this condition.

609.7

Disorders of Neuronal Migration

Stephen L. Kinsman, Michael V. Johnston

Disorders of neuronal migration can result in minor abnormalities with little or no clinical consequence (small heterotopia of neurons) or devastating abnormalities of CNS structure and/or function (intellectual disability, seizures, **lissencephaly,** and **schizencephaly,** particularly the open-lip form) (Fig. 609.6). One of the most important mechanisms in the control of neuronal migration is the radial glial fiber system that guides neurons to their proper site. Migrating neurons attach to the radial glial fiber and then disembark at predetermined sites to form, ultimately, the precisely designed 6-layered cerebral cortex. Another important mechanism is the tangential migration of progenitor neurons destined to become cortical interneurons. The severity and the extent of the disorder are related to numerous factors, including the timing of a particular insult and a host of environmental and genetic contributors. Some cortical malformations may be from somatic mutations, as exemplified by kinesin gene mutations in patients with **pachygyria.**

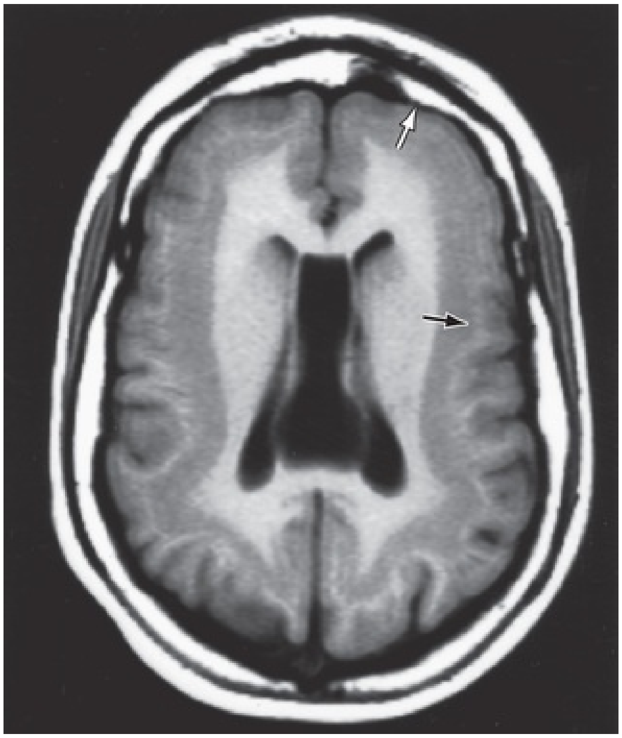

FIG. 609.6 T1-weighted MRI scan demonstrating band heterotopia. A thin layer of white matter *(black arrow)* lies between the band of heterotopic gray matter and the cortical surface. Failure of cortical organization with lissencephaly is present in both frontal lobes *(white arrow).*

Lissencephaly

Lissencephaly, or agyria, is a rare disorder that is characterized by the absence of cerebral convolutions and a poorly formed sylvian fissure, giving the appearance of a 3- to 4-mo fetal brain. The condition is probably a result of faulty neuroblast migration during early embryonic life and is usually associated with enlarged lateral ventricles and heterotopias in the white matter. In some forms, there is a 4-layered cortex, rather than the usual 6-layered one, with a thin rim of periventricular white matter and numerous gray heterotopias visible by microscopic examination. Milder forms of lissencephaly also exist.

These infants present with failure to thrive, microcephaly, marked developmental delay, and often a severe seizure disorder. Ocular abnormalities are common, including hypoplasia of the optic nerve and microphthalmia. Lissencephaly can occur as an isolated finding, but it is associated with **Miller-Dieker syndrome** in approximately 15% of cases. These children have characteristic facies, including a prominent forehead, bitemporal hollowing, anteverted nostrils, a prominent upper lip, and micrognathia. Approximately 70% of children with Miller-Dieker syndrome have visible or submicroscopic chromosomal deletions of 17p13.3.

The gene *LIS-1* (lissencephaly 1) that maps to chromosome region 17p13.3 is deleted in patients with Miller-Dieker syndrome. CT and MRI scans typically show a smooth brain with an absence of sulci (Fig. 609.7). *Doublecortin* is an X chromosome gene that causes lissencephaly when mutated in males and subcortical band heterotopia when mutated in females. Other important forms of lissencephaly include the **Walker-Warburg** variant and other cobblestone cortical malformations.

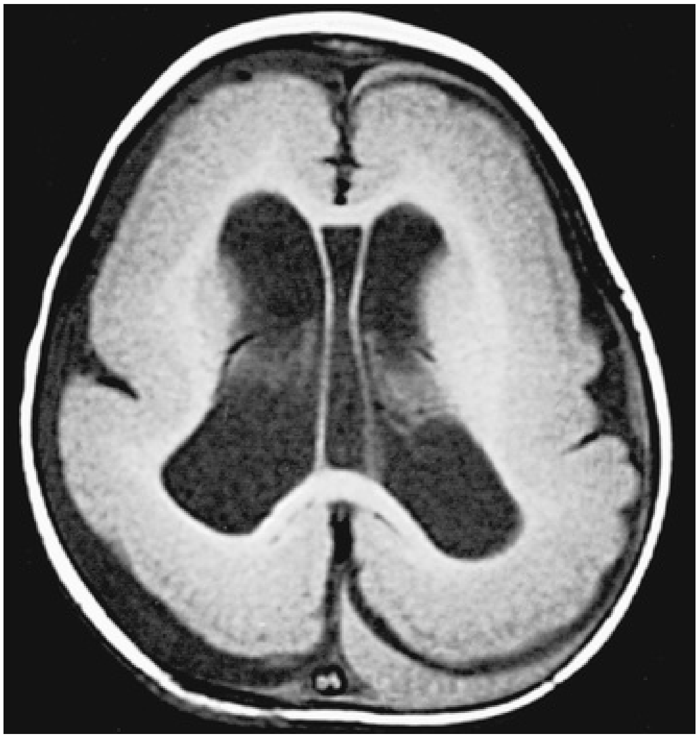

FIG. 609.7 MRI of an infant with lissencephaly. Note the absence of cerebral sulci and the maldeveloped sylvian fissures associated with enlarged ventricles.

Schizencephaly

Schizencephaly is the presence of unilateral or bilateral clefts within the cerebral hemispheres due to an abnormality of morphogenesis (Fig. 609.8). The cleft may be fused or unfused and, if unilateral and large, may be confused with a porencephalic cyst. Not infrequently, the borders of the cleft are surrounded by abnormal brain, particularly microgyria. MRI is the study of choice for elucidating schizencephaly and associated malformations.

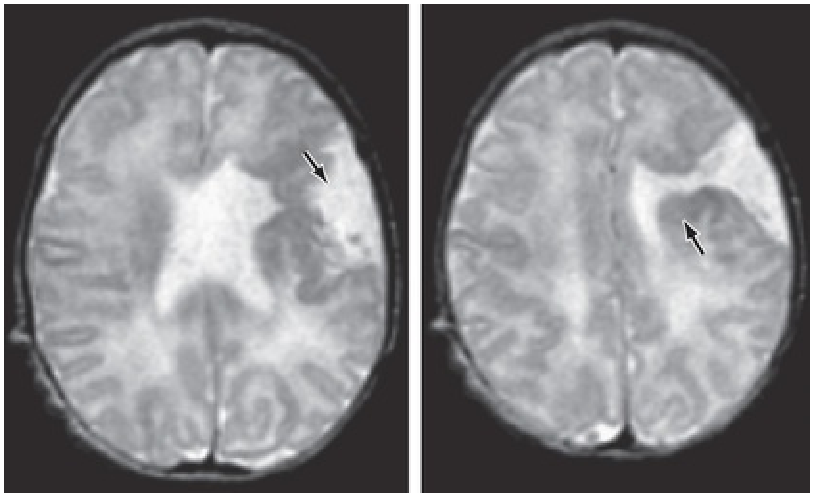

FIG. 609.8 Unilateral schizencephaly shown on axial MR images of the brain. Example of an open-lip schizencephaly with a cleft communicating between the ventricle and the extraaxial cranial space *(arrow on left panel).* Many of these clefts are lined with abnormal gray matter *(arrow on right panel).*

When the clefts are bilateral, many patients are severely intellectually challenged, with seizures that are difficult to control, and microcephaly with spastic quadriparesis. Some cases of bilateral schizencephaly are associated with **septooptic dysplasia** and endocrinologic disorders. Unilateral schizencephaly is a common cause of congenital hemiparesis. It remains controversial whether genetic causes of schizencephaly exist. Some gene mutations are seen in cases of familial schizencephaly.

Neuronal Heterotopias

Subtypes of neuronal heterotopias include **periventricular nodular heterotopias, subcortical heterotopia** (including band-type), and marginal glioneuronal heterotopias. Intractable seizures are a common feature. Several genes have been identified that are a cause of these conditions.

Polymicrogyrias

Polymicrogyria is characterized by an augmentation of small convolutions separated by shallow enlarged sulci (Fig. 609.9). Epilepsy, including drug-resistant forms, is a common feature. Truncation of the *KBP* gene has been implicated in a family with multiple members with polymicrogyria; other disorders are noted in Table 609.2 .

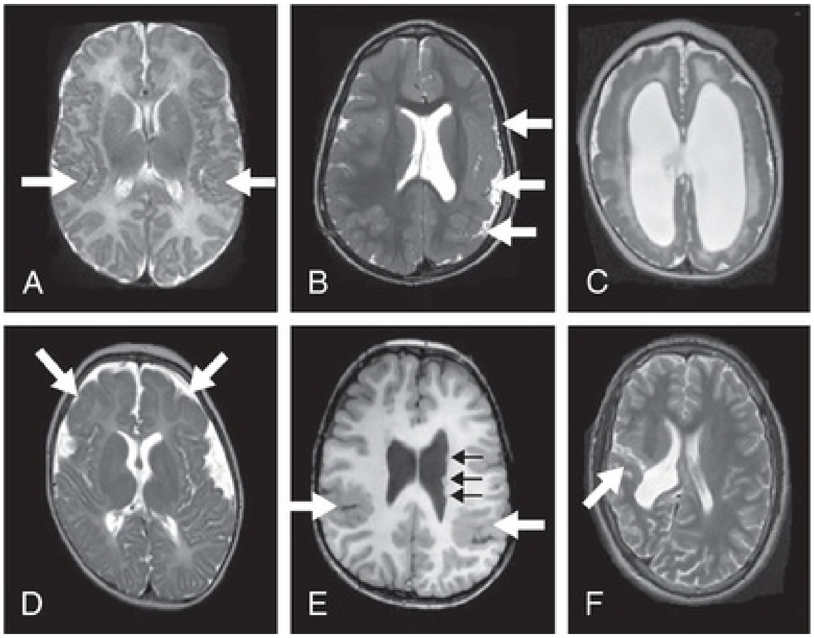

FIG. 609.9 MRI of common subtypes of polymicrogyria. All images are either axial T1- or T2-weighted. **A,** Bilateral perisylvian PMG with microgyri visible around both sylvian fissures *(arrows)* and insulae. The white matter appears bright because the patient is a neonate. **B,** Unilateral perisylvian PMG with PMG maximal in the left perisylvian region, extending anteriorly and posteriorly beyond the immediate perisylvian region *(arrows).* **C,** Bilateral generalized PMG, bright white matter, and dilated lateral ventricles with periventricular low signal suggestive of calcification in a child with congenital cytomegalovirus infection. **D,** Bilateral frontal PMG with subtle

irregular PMG throughout both frontal lobes *(arrows).* **E,** Bilateral perisylvian PMG *(white arrows)* with periventricular nodular gray matter heterotopia *(black arrows).* **F,** A small right hemisphere containing a full-thickness cleft lined by PMG *(arrow)* consistent with schizencephaly. (From Stutterd CA, Leventer RJ: Polymicrogyria: a common and heterogeneous malformation of cortical development, Am J Med Genet (Semin Med Genet) 166C:227-239, 2014, Fig. 1.)

Table 609.2

Named Syndromes in Which Polymicrogyria Has Been Reported Multiple Times

SYNDROME	PMG PATTERN	OTHER FEATURES	GENETIC BASIS
Aicardi	Variable, multifocal	Agenesis of corpus callosum, retinal lacunae	X-linked: gene unknown
Chudley-McCullough	Frontal	Sensorineural hearing loss, hydrocephalus, agenesis of corpus callosum	*GPSM2* mutations
DiGeorge/velocardiofacial	Perisylvian, unilateral or bilateral	Cardiac defects, parathyroid hypoplasia, facial dysmorphism, thymus hypoplasia	22q11.2 deletion
Ehlers–Danlos	Perisylvian and frontal	Skin fragility, cutaneous extensibility, joint laxity, bruising	Multiple genes
Kabuki make-up (Niikawa–Kuroki)	Perisylvian	Facial dysmorphism, digital anomalies, skeletal anomalies, microcephaly	*MLL2* and *KDM6A* mutations
Knobloch	Frontal	Eye abnormalities, occipital skull defects	*COL18A1* mutations
Leigh and other mitochondrial disorders, including PDH deficiency	Variable	Multiple CNS abnormalities, lactic acidosis, neurodegeneration, ocular abnormalities	Mitochondrial, including respiratory chain disorders
Meckel–Gruber	Variable	Occipital meningoencephalocele, arrhinencephaly, polycystic kidneys, polydactyly, bile duct abnormalities	Autosomal recessive, multiple genes
Megalencephaly-capillary malformation-polymicrogyria (MCAP)	Variable	Macrocephaly, vascular malformations, syndactyly, occasional hyperelasticity or thick skin	*PIK3CA* mutations
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH)	Variable	Macrocephaly, polydactyly	*PIK3R2* and *AKT3* mutations
Warburg-Micro	Frontal	Microcephaly, cataracts, microcornea, optic atrophy, hypogenitalism, hypoplasia of corpus callosum	*RAB3GAP* mutations
Oculocerebrocutaneous (Delleman)	Frontal	Orbital anomalies, skin defects, and multiple brain anomalies	Possibly autosomal dominant, gene unknown
Pena–Shokeir	Variable	IUGR, camptodactyly, multiple ankyloses, facial dysmorphism, pulmonary hypoplasia	Autosomal recessive, multiple genes
Sturge–Weber	Underlying cortical	Facial hemangioma, glaucoma	Somatic mutations in *GNAQ*

	angiomatosis		
Thanatophoric dysplasia	Temporal	Skeletal anomalies, hypoplastic lungs, megalencephaly	Autosomal dominant, multiple genes
Zellweger and other peroxisomal disorders	Generalized	White matter dysmyelination, facial dysmorphism, intrahepatic biliary dysgenesis, stippled epiphyses, renal cysts	Peroxisomal (*PEX* , *PXMP,* and *PXR* gene family mutations)

From Stutterd CA, Leventer RJ: Polymicrogyria: a common and heterogeneous malformation of cortical development. Am J Med Genet (Semin Med Genet) 166C:227-239, 2014, Table 1.

Focal Cortical Dysplasias

Focal cortical dysplasias consist of abnormal cortical lamination in a discrete area of cortex. High-resolution, thin-section MRI can reveal these areas sometimes in the setting of drug-resistant epilepsy.

Porencephaly

Porencephaly is the presence of cysts or cavities within the brain that result from developmental defects or acquired lesions, including infarction of tissue. True porencephalic cysts are most commonly located in the region of the sylvian fissure and typically communicate with the subarachnoid space or the ventricular system, or both. They represent developmental abnormalities of cell migration and are often associated with other malformations of the brain, including microcephaly, abnormal patterns of adjacent gyri, and encephalocele. Affected infants tend to have many problems, including intellectual disability, spastic hemiparesis or quadriparesis, optic atrophy, and seizures.

Several risk factors for porencephalic cyst formation have been identified, including hemorrhagic venous infarctions; various thrombophilias such as protein C deficiency and factor V Leiden mutations; perinatal alloimmune thrombocytopenia; von Willebrand disease; maternal warfarin use; maternal cocaine use; congenital infections; trauma such as amniocentesis; and maternal abdominal trauma. Mutations in the *COL4A1* and *COL4A2* genes have been described in cases of familial porencephaly.

Pseudoporencephalic cysts characteristically develop during the perinatal or postnatal period and result from abnormalities (infarction, hemorrhage) of arterial or venous circulation. These cysts tend to be unilateral, do not communicate with a fluid-filled cavity, and are not associated with abnormalities of cell migration or CNS malformations. Infants with pseudoporencephalic cysts present with hemiparesis and focal seizures in the first year of life and sometimes present with neonatal encephalopathy or as a floppy newborn or infant.

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609.8

Agenesis of the Corpus Callosum

Stephen L. Kinsman, Michael V. Johnston

Agenesis of the corpus callosum consists of a heterogeneous group of disorders that vary in expression from severe intellectual and neurologic abnormalities to the asymptomatic and normally intelligent patient (Fig. 609.10). The corpus callosum develops from the commissural plate that lies in proximity to the anterior neuropore. Either a direct insult to the commissural plate or disruption of the genetic signaling that specifies and organizes this area during early embryogenesis can cause agenesis of the corpus callosum.

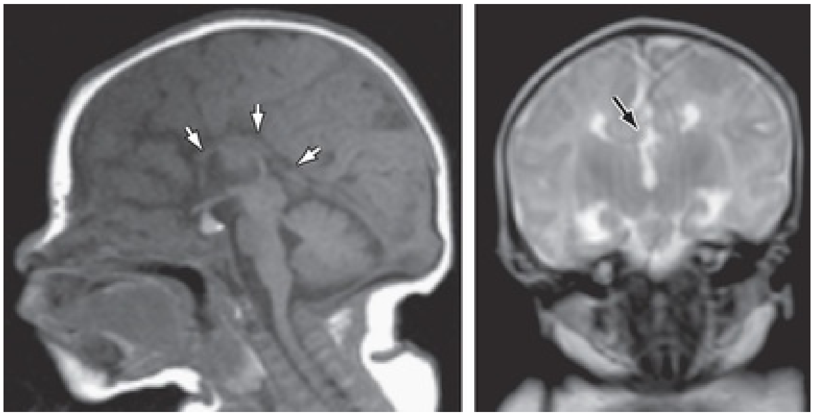

FIG. 609.10 Agenesis of the corpus callosum shown on MR images of the brain. Sagittal *(left panel)* and coronal *(right panel)* views of an infant show the total absence of a midsagittal white matter structure *(left panel, arrows).* The coronal view *(right panel)* demonstrates (despite some motion artifact) the absence of a structure bridging the two hemispheres *(area under arrow).*

When agenesis of the corpus callosum is an isolated phenomenon, the patient may still be normal. When it is accompanied by brain anomalies from cell migration defects, such as heterotopias, polymicrogyria, and pachygyria (broad, wide gyri), patients often have significant neurologic abnormalities, including intellectual disability, microcephaly, hemiparesis or diplegia, and seizures.

The anatomic features of agenesis of the corpus callosum are best depicted on

MRI and include widely separated frontal horns with an abnormally high position of the third ventricle between the lateral ventricles. MRI precisely outlines the extent of the corpus callosum defect. Absence of the corpus callosum may be inherited as an X-linked recessive trait or as an autosomal dominant trait and on occasion as an autosomal recessive trait. The condition may be associated with specific chromosomal disorders, particularly trisomy 8 and trisomy 18. Single-gene mutations have been described in multiple genes causing agenesis of the corpus callosum. So too have copy number variations (deletions) been identified but usually when agenesis is associated with other anomalies. Agenesis of the corpus callosum is also seen in some metabolic disorders (Table 609.3).

Table 609.3

Disorders Associated With Agenesis of the Corpus Callosum[*]

DISORDER	SALIENT FEATURES
WITH IDENTIFIED GENES [†]	
Andermann syndrome *(KCC3)*	ACC, progressive neuropathy, and dementia
Donnai-Barrow syndrome *(LRP2)*	Diaphragmatic hernia, exomphalos, ACC, deafness
Frontonasal dysplasia *(ALX1)*	ACC, bilateral extreme microphthalmia, bilateral oblique facial cleft
XLAG *(ARX)*	Lissencephaly, ACC, intractable epilepsy
Microcephaly *(TBR2)*	ACC, polymicrogyria
Microcephaly with simplified gyral pattern and ACC *(WDR62)*	
Mowat-Wilson syndrome *(ZFHX1B)*	Hirschsprung disease, ACC
Pyridoxine-dependent epilepsy *(ALDH7A1)*	ACC, seizures, other brain malformations
Pyruvate dehydrogenase deficiency *(PDHA1, PDHB, PDHX)*	ACC with other brain changes
ACC with fatal lactic acidosis *(MRPS16)*	Complexes I and IV deficiency, ACC, brain malformations
HSAS/MASA syndromes *(L1CAM)*	Hydrocephalus, adducted thumbs, ACC, MR
ACC SEEN CONSISTENTLY (NO GENE YET IDENTIFIED)	
Acrocallosal syndrome	ACC, polydactyly, craniofacial changes, MR
Aicardi syndrome	ACC, chorioretinal lacunae, infantile spasms, MR
Chudley-McCullough syndrome	Hearing loss, hydrocephalus, ACC, colpocephaly
FG syndrome	MR, ACC, craniofacial changes, macrocephaly
Genitopatellar syndrome	Absent patellae, urogenital malformations, ACC
Temtamy syndrome	ACC, optic coloboma, craniofacial changes, MR
Toriello-Carey syndrome	ACC, craniofacial changes, cardiac defects, MR
Vici syndrome	ACC, albinism, recurrent infections, MR
ACC SEEN OCCASIONALLY (PARTIAL LIST) [‡]	
ACC with spastic paraparesis *(SPG11, SPG15)*	Progressive spasticity and neuropathy, thin corpus callosum
Craniofrontonasal syndrome	Coronal craniosynostosis, facial asymmetry, bifid nose
Fryns syndrome	CDH, pulmonary hypoplasia, craniofacial changes

Marden-Walker syndrome	Blepharophimosis, micrognathia, contractures, ACC
Meckel-Gruber syndrome	Encephalocele, polydactyly, polycystic kidneys
Nonketotic hyperglycinemia *(GLDC, GCST, GCSH)*	ACC, cerebral and cerebellar atrophy, myoclonus, progressive encephalopathy
Microphthalmia with linear skin defects	Microphthalmia, linear skin markings, seizures
Opitz G syndrome	Pharyngeal cleft, craniofacial changes, ACC, MR
Orofaciodigital syndrome	Tongue hamartoma, microretrognathia, clinodactyly
Pyruvate decarboxylase deficiency	Lactic acidosis, seizures, severe MR and spasticity
Rubinstein-Taybi syndrome	Broad thumbs and great toes, MR, microcephaly
Septooptic dysplasia (de Morsier syndrome)	Hypoplasia of septum pellucidum and optic chiasm
Sotos syndrome	Physical overgrowth, MR, craniofacial changes
Warburg micro syndrome	Microcephaly, microphthalmia, microgenitalia, MR
Wolf-Hirschhorn syndrome	Microcephaly, seizures, cardiac defects, 4p−

[*] Reliable incidence data are unavailable for these very rare syndromes.

[†] Gene symbols in parentheses.

[‡] Many of these also may consistently have a thin dysplastic corpus callosum, such as Sotos syndrome or agenesis of the corpus callosum (ACC) with spastic paraparesis (SPG11). The overlap between ACC and these conditions is still under investigation. Other gene symbols are omitted from this section.

4p−, deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf-Hirschhorn patients; ACC, agenesis of the corpus callosum; ARX, Aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; HSAS/MASA, X-linked hydrocephalus/mental retardation, aphasia, shuffling gait, and adducted thumbs; KCC3, KCl cotransporter 3; L1CAM, L1 cell adhesion molecule; MR, mental retardation; MRPS16, mitochondrial ribosomal protein S16; SPG11, spastic paraplegia 11; XLAG, X-linked lissencephaly with absent corpus callosum and ambiguous genitalia; ZFHX1B, zinc finger homeobox 1b.

From Sherr EH, Hahn JS: Disorders of forebrain development. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's Pediatric Neurology, 5th ed., Philadelphia, 2012, WB Saunders, Table 23-2.

Aicardi syndrome represents a complex disorder that affects many systems and is typically associated with agenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms. Patients are almost all female, suggesting a genetic abnormality of the X chromosome (it may be lethal in males during fetal life). Seizures become evident during the first few months and are typically resistant to anticonvulsants. An electroencephalogram shows independent activity recorded from both hemispheres as a result of the absent corpus callosum and often shows hemihypsarrhythmia. All patients have severe intellectual disability and can have abnormal vertebrae that may be fused or only partially developed (hemivertebra). Abnormalities of the retina, including circumscribed pits or lacunae and coloboma of the optic disc, are the most characteristic findings of Aicardi syndrome.

Colpocephaly refers to an abnormal enlargement of the occipital horns of the ventricular system and can be identified as early as the fetal period. It is often associated with agenesis of the corpus callosum, but it can occur in isolation. It is also associated with microcephaly. It can also be seen in anatomic megalencephaly, such as is associated with **Sotos syndrome.**

Holoprosencephaly

Holoprosencephaly is a developmental disorder of the brain that results from defective formation of the prosencephalon and inadequate induction of forebrain structures. The abnormality, which represents a spectrum of severity, is classified into three groups: alobar, semilobar, and lobar, depending on the degree of the cleavage abnormality (Fig. 609.11). A fourth type, the middle interhemispheric fusion variant or **syntelencephaly,** involves a segmental area of noncleavage, actually a nonseparation, of the posterior frontal and parietal lobes. Facial abnormalities, including cyclopia, synophthalmia, cebocephaly, single nostril, choanal atresia, solitary central incisor tooth, and premaxillary agenesis are common in severe cases, because the prechordal mesoderm that induces the ventral prosencephalon is also responsible for induction of the median facial structures. Milder facial abnormalities are seen in milder forms. Alobar holoprosencephaly is characterized by a single ventricle, an absent falx, and nonseparated deep cerebral nuclei. Care must be taken not to overdiagnose holoprosencephaly based on ventricular abnormalities alone. Evidence of nonseparated midline deep-brain structures, such as caudate, putamen, globus pallidus, and hypothalamus, is the critical element for diagnosis.

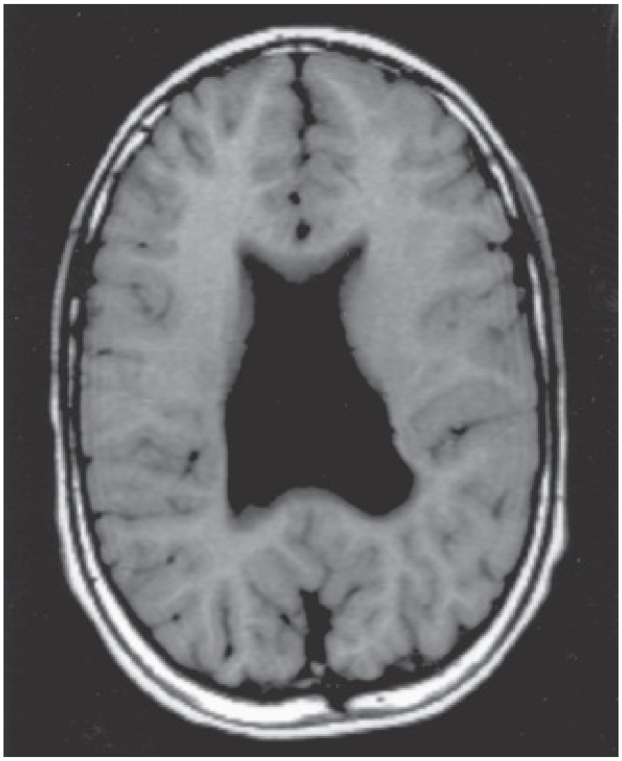

FIG. 609.11 Lobar holoprosencephaly. T1-weighted MRI scan demonstrates failure of separation of the hemispheres and a persistent fused ventricle.

Affected children with the alobar type have high mortality rates, but some live for years. Mortality and morbidity with milder types are more variable, and morbidity is less severe. Care must be taken not to prognosticate severe outcomes in all cases. The incidence of holoprosencephaly ranges from 1 in 5,000-16,000 live births. A prenatal diagnosis can be confirmed by ultrasonography after the 10th wk of gestation for more severe types, but fetal MRI at later gestational ages gives far greater anatomic, and therefore diagnostic, precision.

The cause of holoprosencephaly is often not identified. There appears to be an association with maternal diabetes. Chromosomal abnormalities, including deletions of chromosomes 7q and 3p, 21q, 2p, 18p, and 13q, as well as trisomy 13 and 18, account for upward of 50% of all cases. Mutations in the *sonic hedgehog* gene at 7q have been shown to cause holoprosencephaly. *Gene Reviews* lists 14 single-gene causes. Clinically, it is important to look for associated anomalies, because many syndromes are associated with holoprosencephaly.

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609.9

Agenesis of the Cranial Nerves and Dysgenesis of the Posterior Fossa

Stephen L. Kinsman, Michael V. Johnston

The classification of disorders of development of the cranial nerve, brainstem, and cerebellum remains anatomic, but future classification systems will likely be based on the molecular biology of brain development based on the genes involved and the roles they play in orchestrating brain architecture.

Congenital Cranial Dysinnervation Disorders

Absence of the cranial nerves or the corresponding central nuclei has been described in several conditions and includes optic nerve defects, congenital ptosis, Marcus Gunn phenomenon (sucking jaw movements causing simultaneous eyelid blinking; this congenital synkinesis results from abnormal innervation of the trigeminal and oculomotor nerves), defects of the trigeminal and auditory nerves, and defects of cranial nerves IX, X, XI, and XII. Increased understanding of these disorders and their genetic causes has led to the term *congenital cranial dysinnervation disorders.*

Optic nerve hypoplasia can occur in isolation or as part of the septooptic dysplasia complex (de Morsier syndrome). Septooptic dysplasia can be caused by a mutation in the *HESX1* gene. **Möbius syndrome** is characterized by bilateral facial weakness, which is often associated with paralysis of the abducens nerve. Hypoplasia or agenesis of brainstem nuclei, as well as absent or decreased numbers of muscle fibers, has been reported. Affected infants present in the newborn period with facial weakness, causing feeding difficulties owing to a poor suck. The immobile, dull facies might give the incorrect impression of intellectual impairment; the prognosis for normal development is excellent in most cases. The facial appearance of Möbius syndrome has been improved by facial surgery.

Duane retraction syndrome is characterized by congenital limitation of horizontal globe movement and some globe retraction on attempted adduction and is believed to be the result of abnormal innervation by the oculomotor nerve to the lateral rectus muscle. Abnormalities of cranial nerve development have been demonstrated in this condition.

Less common than Duane retraction syndrome and Möbius syndrome are the group of disorders known as **congenital fibrosis of the extraocular muscles.** Congenital fibrosis of the extraocular muscles is characterized by severe restriction of eye movements and ptosis from abnormal oculomotor and trochlear nerve development and/or from abnormalities of extraocular muscle innervation.

Brainstem and Cerebellar Disorders

Disorders of the posterior fossa structures include abnormalities not only of the brainstem and cerebellum, but also of the CSF spaces. Commonly encountered malformations include Chiari malformation, Dandy-Walker malformation, arachnoid cysts, mega cisterna magna, persisting Blake pouch, Joubert syndrome, rhombencephalosynapsis, Lhermitte-Duclos disease, and the pontocerebellar hypoplasias.

Chiari malformation is the most common malformation of the posterior fossa and hindbrain. It consists of herniation of the cerebellar tonsils though the foramen magnum (see Fig. 609.14). Often, there is also an associated developmental abnormality of the bones of the skull base leading to a small posterior fossa. Cases can be either asymptomatic or symptomatic. Chiari malformations may be isolated or seen in patients with Ehlers-Danlos syndrome, cystinosis, or other bone of connected tissue disorders. When symptoms develop, they often do not do so until late childhood. Symptoms include headaches that are worse with straining and other maneuvers that increase intracranial pressure. Symptoms of brainstem compression such as diplopia, oropharyngeal dysfunction, spasticity, tinnitus, and vertigo can occur. Obstructive hydrocephalus and/or syringomyelia can also occur (see Fig. 609.14).

Dandy-Walker malformation is part of a continuum of posterior fossa anomalies that include cystic dilation of the fourth ventricle, hypoplasia of the cerebellar vermis, hydrocephalus, and an enlarged posterior fossa with elevation of the lateral venous sinuses and the tentorium. Extracranial anomalies are also seen. Variable degrees of neurologic impairment are usually present. The etiology of Dandy-Walker malformation includes chromosomal abnormalities, single gene disorders, and exposure to teratogens.

Arachnoid cysts of the posterior fossa can be associated with hydrocephalus. Mega cisterna magna is characterized by an enlarged CSF space inferior and dorsal to the cerebellar vermis and when present in isolation may be considered a normal variant. Persisting Blake pouch is a cyst that obstructs the subarachnoid space and is associated with hydrocephalus.

Joubert syndrome is an autosomal recessive disorder (ciliopathy) with significant genetic heterogeneity that is associated with cerebellar vermis hypoplasia and the pontomesencephalic **molar tooth sign** (a deepening of the interpeduncular fossa with thick and straight superior cerebellar peduncles) (Fig. 609.12). It is associated with hypotonia, ataxia (as toddler), characteristic breathing abnormalities including episodic apnea and hyperpnea (which improves with age), global developmental delay, nystagmus, strabismus, ptosis, and oculomotor apraxia. There can be many associated systemic features (Joubert syndrome and related disorders), including progressive retinal dysplasia (Leber congenital amaurosis), coloboma, congenital heart disease, microcystic kidney disease, liver fibrosis, polydactyly, tongue protrusion, and soft tissue tumors of the tongue (Fig. 609.13).

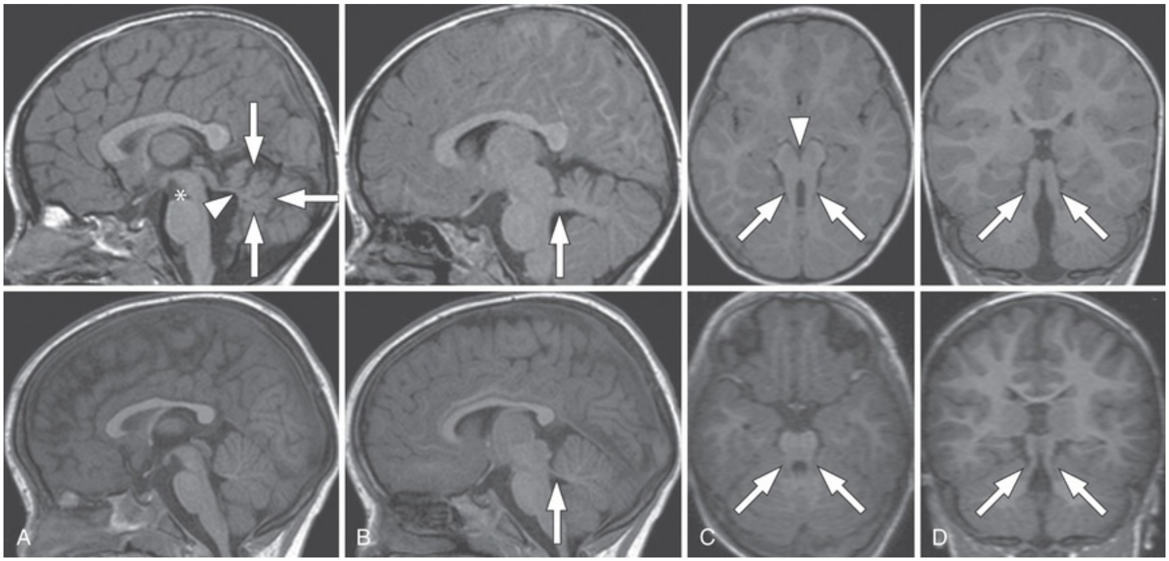

FIG. 609.12 Neuroimaging findings in a 2 yr old child with pure Joubert syndrome *(upper panels)* compared with a healthy control *(lower panels).* **A,** Parasagittal T1-weighted image shows the thickened, elongated, and horizontally oriented superior cerebellar peduncles *(white arrow).* **B,** Midsagittal T1-weighted image demonstrates a moderate hypoplasia and dysplasia of the cerebellar vermis *(white arrows)* with secondary distortion and enlargement of the fourth ventricle with rostral shifting of the fastigium *(white arrowhead).* A deepened interpeduncular fossa is also noted. **C,** Axial T1-weighted image at the level of the pontomesencephalic junction shows the molar tooth sign with a deepened interpeduncular fossa *(white arrowhead)* and elongated, thickened, and horizontally oriented superior cerebellar peduncles *(white arrows).* Additionally, the cerebellar vermis appears to be hypoplastic and its remnants dysplastic. **D,** Coronal T1-weighted image reveals the thickened superior cerebellar peduncles *(white arrows).* (From Romani M, Micalizzi ***A*** **,** Valente EM: Joubert syndrome: congenital cerebellar ataxia with the molar tooth, Lancet Neurol 12:894-905, 2013, Fig. 1.)

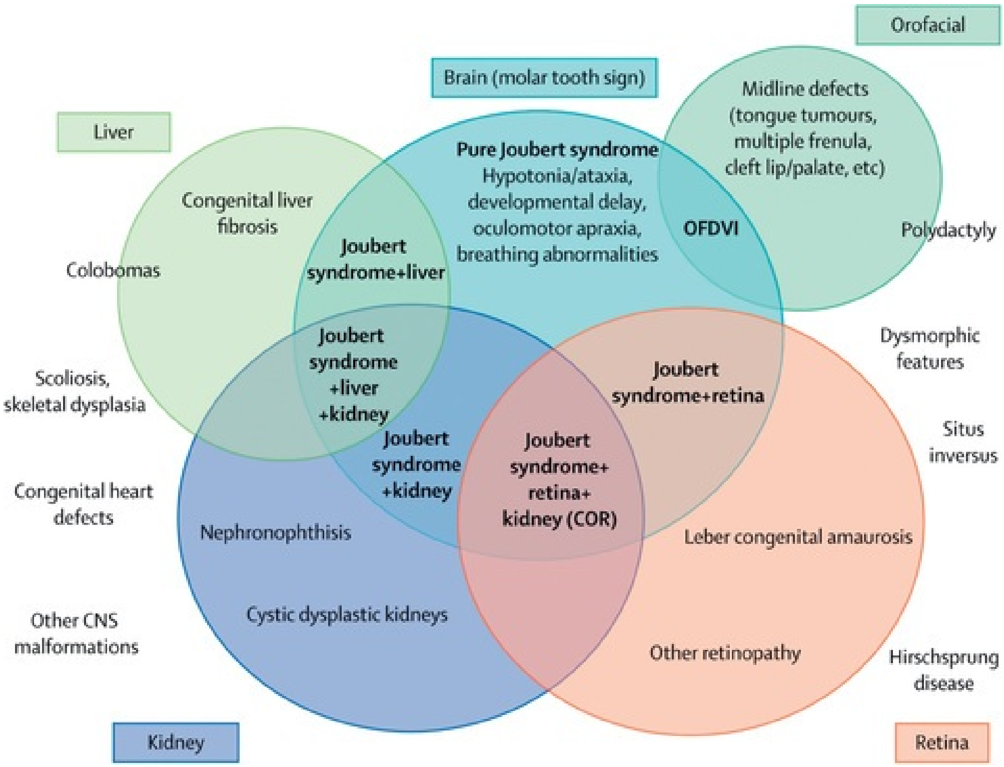
Orofacial
Brain (molar tooth sign)
Liver
Midline defects (tongue tumours, multiple frenula, cleft lip/palate, etc)
Pure Joubert syndrome
Hypotonia/ataxia, developmental delay, oculomotor apraxia, breathing abnormalities
OFDVI
Polydactyly
Congenital liver fibrosis
Joubert syndrome+liver
Colobomas
Joubert syndrome +liver +kidney
Dysmorphic features
Joubert syndrome+retina
Scoliosis, skeletal dysplasia
Situs inversus
Joubert syndrome +kidney
Joubert syndrome+ retina+ kidney (COR)
Congenital heart defects
Nephronophthisis
Leber congenital amaurosis
Cystic dysplastic kidneys
Other CNS malformations
Other retinopathy
Hirschsprung disease
Kidney
Retina

FIG. 609.13 Spectrum of organ involvement in Joubert syndrome and classification in clinical subgroups *(in bold).* Chorioretinal colobomas are more frequently found in the subgroup of Joubert syndrome with liver involvement but can be present also in other subgroups. Similarly, polydactyly (especially if preaxial or mesoaxial) is invariably present in the orofaciodigital type VI subgroup, but postaxial polydactyly is frequently observed also in association with other Joubert syndrome phenotypes. Other clinical features outside the circles occur more rarely, without a specific association to a clinical subgroup. CNS, central nervous system; COR, cerebellooculorenal; K, kidney involvement; L, liver involvement; MTS, molar tooth sign; OFDVI, orofaciodigital type VI syndrome. (From Romani M, Micalizzi A, Valente EM: Joubert syndrome: congenital cerebellar ataxia with the molar tooth, Lancet Neurol 12:894-905, 2013, Fig. 3.)

Rhombencephalosynapsis is an absent or small vermis associated with a nonseparation or fusion of the deep midline cerebellar structures. Ventriculomegaly or hydrocephalus is often seen. There is a variable clinical presentation from normal function to cognitive and language impairments, epilepsy, and spasticity. **Lhermitte-Duclos disease** is a dysplastic gangliocytoma of the cerebellum leading to focal enlargement of the cerebellum and macrocephaly, cerebellar signs, and seizures.

Pontocerebellar hypoplasias are a group of disorders characterized by impairment of cerebellar and pontine development together with histopathologic features of neuronal death and glial replacement. Clinical features tend to be nonspecific and include hypotonia, feeding difficulties, developmental delay, and breathing difficulties. Classification, associations, and causes include type I (with features of anterior horn cell involvement), type II (with extrapyramidal features, seizures, and acquired microcephaly), Walker-Warburg syndrome, muscle–eye–brain disease, congenital disorders of glycosylation type 1A, mitochondrial cytopathies, teratogen exposure, congenital cytomegalovirus infection, 3-methylglutaconic aciduria, PEHO syndrome (progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy), autosomal recessive cerebellar hypoplasia in the Hutterite population, lissencephaly with cerebellar hypoplasia, and other subtypes of pontocerebellar hypoplasia.

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609.10

Microcephaly

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Microcephaly is defined as a head circumference that measures more than 3 SD below the mean for age and sex. This condition is relatively common, particularly among developmentally delayed children. Although there are many causes of microcephaly, abnormalities in neuronal migration during fetal development, including heterotopias of neuronal cells and cytoarchitectural derangements, are often found. Microcephaly may be subdivided into two main groups: primary (genetic) microcephaly and secondary (nongenetic) microcephaly. A precise diagnosis is important for genetic counseling and for prediction of future pregnancies.

Etiology

Primary microcephaly refers to a group of conditions that usually have no associated malformations and that follow a mendelian pattern of inheritance or are associated with a specific genetic syndrome. Affected infants are usually identified at birth because of a small head circumference. The more common types include familial and autosomal dominant microcephaly and a series of chromosomal syndromes that are summarized in Table 609.4 . Primary microcephaly is also associated with seven gene loci, and at least seven single etiologic genes have been identified; the condition has autosomal recessive inheritance. Many X-linked causes of microcephaly are caused by gene mutations that lead to severe structural brain malformations, such as lissencephaly, holoprosencephaly, polymicrogyria, cobblestone dysplasia, neuronal heterotopia, and pontocerebellar hypoplasia; these findings should be sought on MRI. Secondary microcephaly results from a large number of noxious agents that can affect a fetus in utero or an infant during periods of rapid brain growth, particularly the first 2 yr of life, pregnancy-associated Zika virus infection being the most recent example.

Table 609.4

Causes of Microcephaly

CAUSES	CHARACTERISTIC FINDINGS
PRIMARY (GENETIC)	
Familial (autosomal recessive)	Incidence 1 in 40,000 live births Typical appearance with slanted forehead, prominent nose and ears; severe mental retardation and prominent seizures; surface convolutional markings of the brain; poorly differentiated and disorganized cytoarchitecture
Autosomal dominant	Nondistinctive facies, upslanting palpebral fissures, mild forehead slanting, and prominent ears Normal linear growth, seizures readily controlled, and mild or borderline mental retardation
Syndromes	
Down (trisomy 21)	Incidence 1 in 800 live births Abnormal rounding of occipital and frontal lobes and a small cerebellum; narrow superior temporal gyrus, propensity for Alzheimer neurofibrillary alterations, ultrastructure abnormalities of cerebral cortex
Edward (trisomy 18)	Incidence 1 in 6,500 live births Low birthweight, microstomia, micrognathia, low-set malformed ears, prominent occiput, rocker-bottom feet, flexion deformities of fingers, congenital heart disease, increased gyri, heterotopias of neurons
Cri-du-chat (5 p-)	Incidence 1 in 50,000 live births Round facies, prominent epicanthic folds, low-set ears, hypertelorism, characteristic cry No specific neuropathology
Cornelia de Lange	Prenatal and postnatal growth delay; synophrys; thin, downturning upper lip Proximally placed thumb
Rubinstein-Taybi	Beaked nose, downward slanting of palpebral fissures, epicanthic folds, short stature, broad thumbs and toes
Smith-Lemli-Opitz	Ptosis, scaphocephaly, inner epicanthic folds, anteverted nostrils Low birthweight, marked feeding problems
SECONDARY (NONGENETIC)	
Congenital Infections	
Zika virus	Small for dates, ocular anomalies
Cytomegalovirus	Small for dates, petechial rash, hepatosplenomegaly, chorioretinitis, deafness, mental retardation, seizures CNS calcification and microgyria
Rubella	Growth retardation, purpura, thrombocytopenia, hepatosplenomegaly, congenital heart disease, chorioretinitis, cataracts, deafness Perivascular necrotic areas, polymicrogyria, heterotopias, subependymal cavitations
Toxoplasmosis	Purpura, hepatosplenomegaly, jaundice, convulsions, hydrocephalus, chorioretinitis, cerebral calcification
Drugs	
Fetal alcohol	Growth retardation, ptosis, absent philtrum and hypoplastic upper lip, congenital heart

	disease, feeding problems, neuroglial heterotopia, disorganization of neurons
Fetal hydantoin	Growth delay, hypoplasia of distal phalanges, inner epicanthic folds, broad nasal ridge, anteverted nostrils
Other Causes	
Radiation	Microcephaly and mental retardation most severe with exposure before 15th wk of gestation
Meningitis/encephalitis	Cerebral infarcts, cystic cavitation, diffuse loss of neurons
Malnutrition	Controversial cause of microcephaly
Metabolic	Maternal diabetes mellitus and maternal hyperphenylalaninemia
Hyperthermia	Significant fever during first 4-6 wk has been reported to cause microcephaly, seizures, and facial anomalies Pathologic studies show neuronal heterotopias Further studies show no abnormalities with maternal fever
Hypoxic–ischemic encephalopathy	Initially diffuse cerebral edema; late stages characterized by cerebral atrophy and abnormal signals on MRI

Acquired microcephaly can be seen in conditions such as Rett, Seckel, and Angelman syndromes and in encephalopathy syndromes associated with severe seizure disorders.

Clinical Manifestations and Diagnosis

A thorough family history should be taken, seeking additional cases of microcephaly or disorders affecting the nervous system. It is important to measure a patient's head circumference at birth to diagnose microcephaly as early as possible. A very small head circumference implies a process that began early in embryonic or fetal development. An insult to the brain that occurs later in life, particularly beyond the age of 2 yr, is less likely to produce severe microcephaly. Serial head circumference measurements are more meaningful than a single determination, particularly when the abnormality is minimal or the microcephaly is acquired. The head circumference of each parent and sibling should be recorded.

Laboratory investigation of a microcephalic child is determined by the history and physical examination. If the cause of the microcephaly is unknown, the mother's serum phenylalanine level should be determined. High phenylalanine serum levels in an asymptomatic mother can produce marked brain damage in an otherwise normal nonphenylketonuric infant. Newborn screening in the United States will detect most of these cases. A karyotype and/or array comparative genomic hybridization (chromosome microarray) study is obtained if a chromosomal syndrome is suspected or if the child has abnormal facies, short stature, and additional congenital anomalies. MRI is useful in identifying structural abnormalities of the brain, such as lissencephaly, pachygyria, and polymicrogyria, and CT scanning is useful to detect intracerebral calcification. Additional studies include a fasting plasma and urine amino acid and organic acid analysis; serum ammonia determination; *to* xoplasmosis, *r* ubella, *c* ytomegalovirus, and *h* erpes simplex (TORCH) titers as well as HIV testing of the mother and child; and a urine sample for the culture of cytomegalovirus. Zika virus–specific testing is also indicated when the infant is born in a high-risk environment or a parent has a history of travel to endemic areas. Single-gene mutations as a cause of both primary microcephaly and syndromic microcephaly are being increasingly identified.

Treatment

Once the cause of microcephaly has been established, the physician must provide accurate and supportive genetic and family counseling. Because many children with microcephaly are also intellectually challenged, the physician must assist with placement in an appropriate program that will provide for maximal development of the child (see Chapter 53).

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609.11

Hydrocephalus

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Hydrocephalus is not a specific disease; it represents a diverse group of conditions that result from impaired circulation and/or absorption of CSF or, in rare circumstances, from increased production of CSF by a choroid plexus papilloma (Tables 609.5 and 609.6). Because megalencephaly is often discovered as part of an evaluation for hydrocephalus in children with macrocephaly, it is included in this section.

Table 609.5

Causes of Pediatric Hydrocephalus

CAUSE		PROPOSED MECHANISM
ACQUIRED HYDROCEPHALUS		
Inflammatory		
Subarachnoid hemorrhage or infection	Arachnoid scar	Dysfunctional subarachnoid space
Intraventricular hemorrhage or infection	Ependymal scar	Ventricular obstruction
Neoplasm		
Parenchymal brain tumor	Mass effect	Ventricular obstruction
Spinal cord tumor	Altered CSF composition	Dysfunctional subarachnoid space
Disseminated tumor	Tumors with meningeal infiltration, e.g., primitive neuroectodermal tumor	Dysfunctional subarachnoid space
Choroid plexus tumor	Altered CSF composition	Dysfunctional subarachnoid space
Choroid plexus tumor	Mass effect	Ventricular obstruction
Choroid plexus tumor or hyperplasia	Altered choroid plexus function	CSF overproduction or hyperdynamic intraventricular pulsations
Vascular		
Vascular malformation	Ventricular obstruction, e.g., vein of Galen malformation; venous hypertension, e.g., arteriovenous malformation	Ventricular obstruction; decreased venous compliance or decreased CSF absorption
Disordered cerebral venous function	Extrinsic venous obstruction, e.g., skeletal dysplasias; intrinsic venous obstruction, e.g., venous sinus thrombosis; idiopathic venous dysfunction, e.g., congenital idiopathic hydrocephalus	Decreased venous compliance or decreased CSF absorption
CONGENITAL OR DEVELOPMENTAL HYDROCEPHALUS		
Congenital aqueduct stenosis	Third ventricle outlet obstruction	Ventricular obstruction
Neural tube defects, e.g., myelomeningocele and Chiari II malformation	Third or fourth ventricle outlet obstruction; altered venous compliance; arachnoid or ependymal scar	Variable

Posterior fossa malformations	Fourth ventricle outlet obstruction, e.g., Dandy-Walker complex; Chiari I malformation	Ventricular obstruction
Developmental cysts	Mass effect	Ventricular obstruction
Congenital foramen of Monro atresia	Lateral ventricle outlet obstruction	Ventricular obstruction

From Kahle KT, Kulkarni AV, Limbick Jr DD, Warf BC: Hydrocephalus in children. Lancet 387:788-798, 2016, Table 1.

Table 609.6

Genetic Abnormalities Associated With Pediatric Hydrocephalus

PUTATIVE GENETIC LINK	
X-linked hydrocephalus with aqueduct stenosis (307000)	*L1CAM*
Nonsyndromic autosomal recessive hydrocephalus (HYC; 236600 [HYC1]; 615219 [HYC2])	*CCDC88C* ; *MPDZ*
Fried-type syndromic mental retardation (304340)	*AP1S2*
Walker-Warburg syndrome (multiple subtypes)	*POMT1* ; *POMT2* ; *POMGNT1* ; and others
Neural tube defects (folate-sensitive [601634] and insensitive [182940] forms)	Multiple susceptibility genes involved in planar-cell polarity, e.g., *FUZ, VANGL1/2, CCL2* , and others; folate-sensitive neural tube defects associated with genes in folate synthesis pathway (*MTR, MTRR, MTHFR, MTHFD*)
Primary ciliary dyskinesias and other ciliopathies (including the many heterogeneous subtypes of Meckel-Gruber syndrome and Joubert syndrome)	Multiple genes involved in cilia structure, function, and regulation, e.g., *CC2D2A, TMEM67, MKS1* , and others
RAS-opathies, e.g., neurofibromatosis type 1, Noonan syndrome, Costello syndrome, cardiofaciocutaneous syndrome	*NF1* ; Ras-Raf-MEK-ERK pathway genes, e.g., *KRAS, BRAF, PTPN11* , and others
VACTERL-H (association of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies plus hydrocephalus; 276950)	*PTEN*
X-linked VACTERL-H (300515)	*FANCB*

Numbers given are Online Mendelian Inheritance in Man (OMIM) identifiers.

Kahle KT, Kulkarni AV, Limbick Jr DD, Warf BC: Hydrocephalus in children. Lancet 387:788-798, 2016, Table 2.

Physiology

The CSF is formed primarily in the ventricular system by the choroid plexus, which is situated in the lateral, third, and fourth ventricles. Although most CSF is produced in the lateral ventricles, approximately 25% originates from extrachoroidal sources, including the capillary endothelium within the brain parenchyma. There is active neurogenic control of CSF formation because adrenergic and cholinergic nerves innervate the choroid plexus. Stimulation of the adrenergic system diminishes CSF production, whereas excitation of the cholinergic nerves may double the normal CSF production rate. In a normal child, approximately 20 mL/hr of CSF is produced. The total volume of CSF approximates 50 mL in an infant and 150 mL in an adult. Most of the CSF is extraventricular. The choroid plexus forms CSF in several stages; through a series of intricate steps, a plasma ultrafiltrate is ultimately processed into a secretion, the CSF.

CSF flow results from the pressure gradient that exists between the ventricular system and venous channels. Intraventricular pressure may be as high as 180 mm H_2O in the normal state, whereas the pressure in the superior sagittal sinus is in the range of 90 mm H_2O. Normally, CSF flows from the lateral ventricles through the foramina of Monro into the third ventricle. It then traverses the narrow aqueduct of Sylvius, which is approximately 3 mm long and 2 mm in diameter in a child, to enter the fourth ventricle. The CSF exits the fourth ventricle through the paired lateral foramina of Luschka and the midline foramen of Magendie into the cisterns at the base of the brain. Hydrocephalus resulting from obstruction within the ventricular system is called obstructive or noncommunicating hydrocephalus. The CSF then circulates from the basal cisterns posteriorly through the cistern system and over the convexities of the cerebral hemispheres. CSF is absorbed primarily by the arachnoid villi through tight junctions of their endothelium by the pressure forces that were noted earlier. CSF is absorbed to a much lesser extent by the lymphatic channels directed to the paranasal sinuses, along nerve root sleeves, and by the choroid plexus itself. Hydrocephalus resulting from obliteration of the subarachnoid cisterns or malfunction of the arachnoid villi is called nonobstructive or communicating hydrocephalus.

Pathophysiology and Etiology

Obstructive or noncommunicating hydrocephalus develops most commonly in children because of an abnormality of the aqueduct of Sylvius or a lesion in the fourth ventricle. Aqueductal stenosis results from an abnormally narrow aqueduct of Sylvius that is often associated with branching or forking. In a small percentage of cases, aqueductal stenosis is inherited as a sex-linked recessive trait. These patients occasionally have minor neural tube closure defects, including spina bifida occulta. Rarely, aqueductal stenosis is associated with neurofibromatosis. Aqueductal gliosis can also give rise to hydrocephalus. As a result of neonatal meningitis or a subarachnoid hemorrhage in a premature infant, the ependymal lining of the aqueduct is interrupted and a brisk glial response results in complete obstruction. Intrauterine viral infections can also produce aqueductal stenosis followed by hydrocephalus, and mumps meningoencephalitis has been reported as a cause in a child. A vein of Galen malformation can expand to become large and, because of its midline position, obstruct the flow of CSF. Lesions or malformations of the posterior fossa are prominent causes of hydrocephalus, including posterior fossa brain tumors, Chiari malformation, and the Dandy-Walker syndrome.

Nonobstructive or communicating hydrocephalus most commonly follows a subarachnoid hemorrhage, which is usually a result of intraventricular hemorrhage in a premature infant. Blood in the subarachnoid spaces can cause obliteration of the cisterns or arachnoid villi and obstruction of CSF flow. Pneumococcal and tuberculous meningitis have a propensity to produce a thick, tenacious exudate that obstructs the basal cisterns, and intrauterine infections can also destroy the CSF pathways. Leukemic infiltrates can seed the subarachnoid space and produce communicating hydrocephalus. Tumors or arteriovenous malformations in the spinal cord or cauda equina are uncommon etiologies of communicating hydrocephalus.

Clinical Manifestations

The clinical presentation of hydrocephalus is variable and depends on many factors, including the age at onset, the nature of the lesion causing obstruction, and the duration and rate of increase of the intracranial pressure. In an infant, an accelerated rate of enlargement of the head is the most prominent sign. In addition, the anterior fontanel is wide open and bulging, and scalp veins can be dilated. The forehead is broad, and the eyes might deviate downward because of impingement of the dilated suprapineal recess on the brainstem tectum, producing the setting-sun eye sign. Long-tract signs, including brisk tendon reflexes, spasticity, clonus (particularly in the lower extremities), and Babinski sign, are common due to stretching and disruption of the corticospinal fibers originating from the leg region of the motor cortex. In an older child, the cranial sutures are less accommodating, so that the signs of hydrocephalus may be subtler. Irritability, lethargy, poor appetite, and vomiting are common to both age-groups, and headache is a prominent symptom in older patients. A gradual change in personality and deterioration in academic productivity suggest a slowly progressive form of hydrocephalus. With regard to other clinical signs, serial measurements of the head circumference often indicate an increased velocity of growth. Percussion of the skull might produce a cracked pot sound or Macewen sign, indicating separation of the sutures. A foreshortened occiput suggests Chiari malformation, and a prominent occiput suggests the Dandy-Walker malformation. Papilledema, abducens nerve palsies, and pyramidal tract signs, which are most evident in the lower extremities, are apparent in many cases.

Chiari malformation consists of two major subgroups. Type I typically produces symptoms during adolescence or adult life and is usually not associated with hydrocephalus. Patients complain of recurrent headache, neck pain, urinary frequency, and progressive lower extremity spasticity. The deformity consists of displacement of the cerebellar tonsils into the cervical canal (Fig. 609.14). Syrinx of the spinal cord, especially in the cervical region, should be looked for on MRI imaging. Although the pathogenesis is unknown, a prevailing theory suggests that obstruction of the caudal portion of the fourth ventricle during fetal development is responsible.

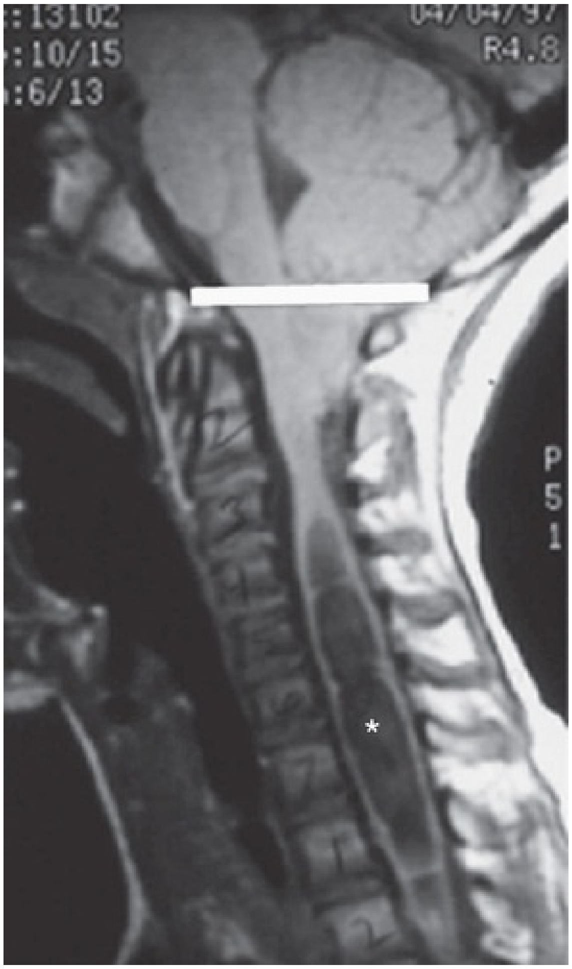

FIG. 609.14 Sagittal MR scan of a patient with Chiari malformation type I. Cerebellar tonsils are displaced through the foramen magnum *(white bar)* to the lower aspect of C2 with clear crowding at the foramen. A syrinx *(white asterisk)* is visible extending from C3 to T2. (From Yassari R, Frim D: Evaluation and management of the Chiari malformation type 1 for the primary care pediatrician, Pediatr Clin North Am 51:477-490, 2004.)

The type II Chiari malformation is characterized by progressive hydrocephalus with a myelomeningocele. This lesion represents an anomaly of the hindbrain, probably owing to a failure of pontine flexure development during embryogenesis, and results in elongation of the fourth ventricle and kinking of the brainstem, with displacement of the inferior vermis, pons, and medulla into the cervical canal (Fig. 609.15). Approximately 10% of type II malformations produce symptoms during infancy, consisting of stridor, weak cry, and apnea, which may be relieved by shunting or by decompression of the posterior fossa. A more indolent form consists of abnormalities of gait, spasticity, and increasing incoordination (including the arms and hands) during childhood.

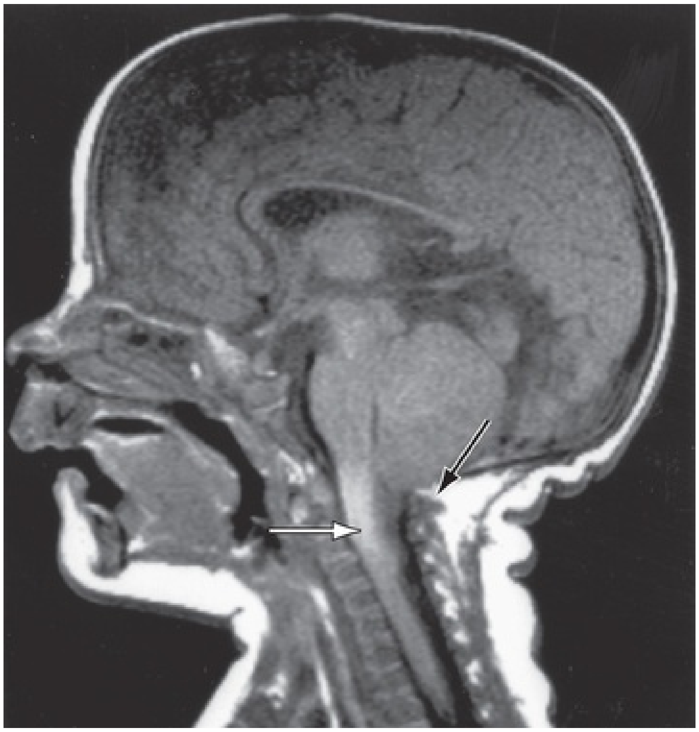

FIG. 609.15 A midsagittal T1-weighted MRI of a patient with type II Chiari malformation. The cerebellar tonsils *(white arrow)* have descended below the foramen magnum *(black arrow).* Note the small, slit-like fourth ventricle, which has been pulled into a vertical position.

Plain skull radiographs show a small posterior fossa and a widened cervical canal. CT scanning with contrast and MRI display the cerebellar tonsils protruding downward into the cervical canal and the hindbrain abnormalities. The anomaly is treated by surgical decompression, but asymptomatic or mildly symptomatic patients may be managed conservatively.

The Dandy-Walker malformation consists of a cystic expansion of the fourth ventricle in the posterior fossa and midline cerebellar hypoplasia, which results from a developmental failure of the roof of the fourth ventricle during embryogenesis (Fig. 609.16). Approximately 90% of patients have hydrocephalus, and a significant number of children have associated anomalies, including agenesis of the posterior cerebellar vermis and corpus callosum. Infants present with a rapid increase in head size and a prominent occiput. Most children have evidence of long-tract signs, cerebellar ataxia, and delayed motor and cognitive milestones, probably due to the associated structural anomalies. The Dandy-Walker malformation is managed by shunting the cystic cavity (and on occasion the ventricles as well) in the presence of hydrocephalus.

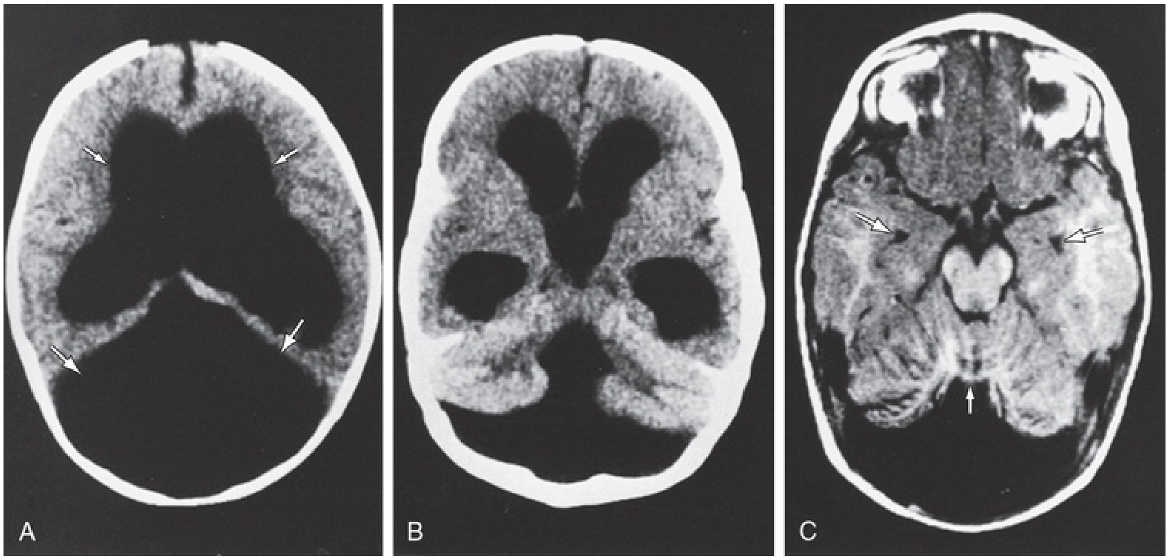

FIG. 609.16 Dandy-Walker cyst. **A,** Axial CT scan (preoperative) showing large posterior fossa cyst (Dandy-Walker cyst; *large arrows*) and dilated lateral ventricles *(small arrows),* a complication secondary to CSF pathway obstruction at the fourth ventricular outlet. **B,** Same patient, with a lower axial CT scan showing splaying of the cerebellar hemispheres by the dilated fourth ventricle (Dandy-Walker cyst). The dilated ventricles proximal to the fourth ventricle again show CSF obstruction caused by the Dandy-Walker cyst. **C,** MRI of the same patient showing decreased size of the Dandy-Walker cyst and temporal horns *(arrows)* after shunting. The incomplete vermis *(small arrow)* now becomes recognizable.

Diagnosis and Differential Diagnosis

Investigation of a child with hydrocephalus begins with the history. Familial cases suggest X-linked or autosomal hydrocephalus secondary to aqueduct stenosis (Fig. 609.17). A past history of prematurity with intracranial hemorrhage, meningitis, or mumps encephalitis is important to ascertain. Multiple café-au-lait spots and other clinical features of neurofibromatosis point to aqueductal stenosis as the cause of hydrocephalus.

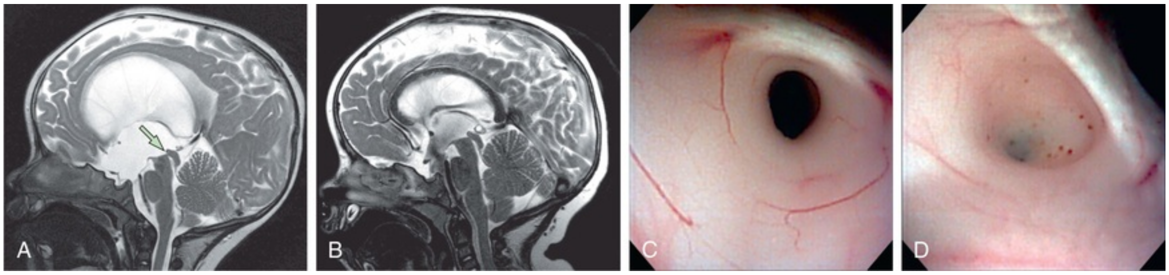

FIG. 609.17 Aqueduct stenosis. **A,** Sagittal brain T2-weighted MRI of infant with hydrocephalus secondary to congenital aqueduct stenosis. *Arrow* indicates point of obstruction. **B,** Same patient after endoscopic third ventriculostomy; note dark flow void indicating flow across endoscopic third ventriculostomy. **C,** Endoscopic view of healthy patent aqueduct. **D,** Endoscopic view of obstructed aqueduct in aqueduct stenosis; note posterior commissure at dorsal margin of the aqueduct ostium in both **A** and **B.** (From Kahle KT, Kulkarni AV, Limbick Jr DD, Warf BC: Hydrocephalus in children, Lancet 387:788-798, 2016, Fig.1.)

Examination includes careful inspection, palpation, and auscultation of the skull and spine. The occipitofrontal head circumference is recorded and compared with previous measurements. The size and configuration of the anterior fontanel are noted, and the back is inspected for abnormal midline skin lesions, including tufts of hair, lipoma, or angioma that might suggest spinal dysraphism. The presence of a prominent forehead or abnormalities in the shape of the occiput can suggest the pathogenesis of the hydrocephalus. A cranial bruit is audible in association with many cases of vein of Galen arteriovenous malformation. Transillumination of the skull is positive with massive dilation of the ventricular system or in the Dandy-Walker syndrome. Inspection of the eyegrounds is mandatory because the finding of chorioretinitis suggests an intrauterine infection, such as toxoplasmosis, as a cause of the hydrocephalus. Papilledema is observed in older children but is rarely present in infants because the cranial sutures separate as a result of the increased pressure.

Plain skull films typically show separation of the sutures, erosion of the posterior clinoids in an older child, and an increase in convolutional markings (beaten-silver appearance) on the inside of the skull with long-standing increased ICP. The CT scan and/or MRI along with ultrasonography in an infant are the most important studies to identify the specific cause and severity of hydrocephalus.

The head might appear enlarged (and can be confused with hydrocephalus) secondary to a thickened cranium resulting from chronic anemia, rickets, osteogenesis imperfecta, and epiphyseal dysplasia. Chronic subdural collections can produce bilateral parietal bone prominence. MRI has revealed the common occurrence of benign external hydrocephalus, a growth-limited condition where intervention is rarely required. Various metabolic and degenerative disorders of the CNS produce megalencephaly as a result of abnormal storage of substances within the brain parenchyma. These disorders include lysosomal diseases (Tay-Sachs disease, gangliosidosis, and the mucopolysaccharidoses), the aminoacidurias (maple syrup urine disease), and the leukodystrophies (metachromatic leukodystrophy, Alexander disease, Canavan disease). In addition, cerebral gigantism (Sotos syndrome), other overgrowth syndromes, and neurofibromatosis are characterized by increased brain mass. Familial megalencephaly is inherited as an autosomal dominant trait and is characterized by delayed motor milestones and hypotonia but normal or near-normal intelligence. Measurement of the parents' head circumferences is necessary to establish the diagnosis.

Megalencephaly

Megalencephaly is an anatomic disorder of brain growth defined as a brain weight:volume ratio of more than the 98th percentile for age (or ≥ 2 SD above the mean) that is usually accompanied by macrocephaly (an occipitofrontal circumference > 98th percentile). Various storage and degenerative diseases are associated with megalencephaly, but anatomic and genetic causes exist as well. The most common cause of anatomic megalencephaly is benign familial megalencephaly. This condition is easily diagnosed by a careful family history and measurement of the parents' head circumferences (occipitofrontal circumferences). On the other hand, macrocephaly is a known feature of more than 100 syndromes.

Anatomic megalencephaly is usually apparent at birth, and head growth continues to run parallel to the upper percentiles. Sometimes, in some syndromes, an increased occipitofrontal circumference is the presenting sign. Neuroimaging is critical in identifying the various structural and gyral abnormalities seen in syndromic macrocephaly and determining whether anatomic megalencephaly exists.

Common megalencephaly-associated macrocephaly syndromes include syndromes with prenatal and/or postnatal somatic overgrowth, such as the Sotos, Simpson-Golabi-Behmel, fragile X, Weaver, macrocephaly–cutis marmorata telangiectatica congenita, and Bannayan-Ruvalcaba-Riley syndromes, and syndromes without somatic overgrowth, such as the FG, Greig cephalopolysyndactyly, acrocallosal, and Gorlin syndromes.

Sotos syndrome (cerebral gigantism) is the most common megalencephalic syndrome, with 50% of patients having prenatal macrocephaly and 100% of patients having macrocephaly by age 1 yr. Early postnatal overgrowth normalizes by adulthood. Facial features include high forehead with frontal bossing, sparse hair in the frontoparietal region, downslanting palpebral fissures, apparent hypertelorism, long narrow face, prominent mandible, and malar flushing. Hypotonia, poor coordination, and speech delay are common. Most children show cognitive impairment, ranging from mild to severe.

Hydranencephaly

Hydranencephaly may be confused with hydrocephalus. The cerebral hemispheres are absent or represented by membranous sacs with remnants of frontal, temporal, or occipital cortex dispersed over the membrane. The midbrain and brainstem are relatively intact (Fig. 609.18). The cause of hydranencephaly is unknown, but bilateral occlusion of the internal carotid arteries during early fetal development would explain most of the pathologic abnormalities. Affected infants can have a normal or enlarged head circumference at birth that grows at an excessive rate postnatally. Transillumination shows an absence of the cerebral hemispheres. The child is irritable, feeds poorly, develops seizures and spastic quadriparesis, and has little or no cognitive development. A ventriculoperitoneal shunt prevents massive enlargement of the cranium.

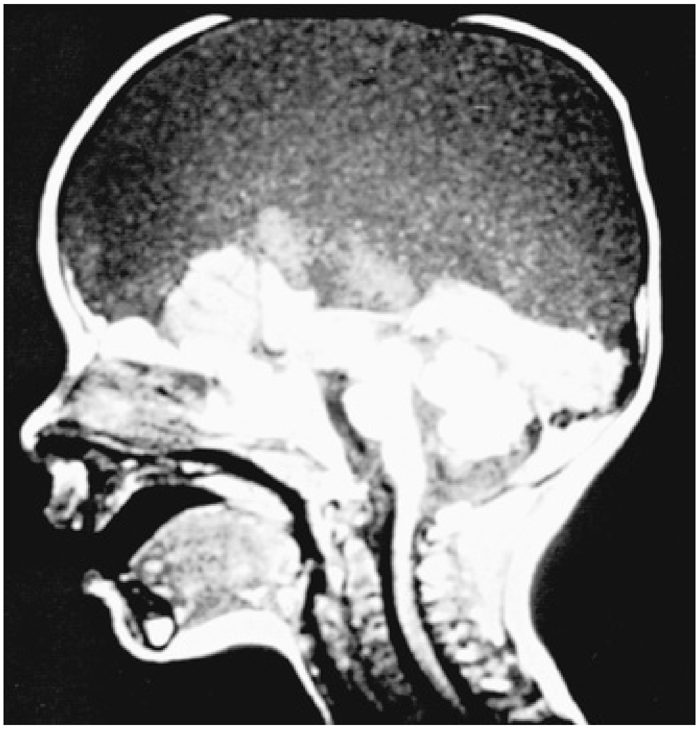

FIG. 609.18 Hydranencephaly. MRI scan showing the brainstem and spinal cord with remnants of the cerebellum and cerebral cortex. The remainder of the cranium is filled with CSF.

Treatment

Therapy for hydrocephalus depends on the cause. Medical management, including the use of acetazolamide and furosemide, can provide temporary relief by reducing the rate of CSF production, but long-term results have been disappointing. Most cases of hydrocephalus require extracranial shunts, particularly a ventriculoperitoneal shunt. Endoscopic third ventriculostomy has evolved as a viable approach and criteria have been developed for its use, but the procedure might need to be repeated to be effective. Ventricular shunting may be avoided with this approach. The major complications of shunting are occlusion (characterized by headache, papilledema, emesis, mental status changes) and bacterial infection (fever, headache, meningismus), usually caused by *Staphylococcus epidermidis*. With meticulous preparation, the shunt infection rate can be reduced to < 5%. The results of intrauterine surgical management of fetal hydrocephalus have been poor (possibly because of the high rate of associated cerebral malformations in addition to the hydrocephalus) except for some promise in cases of hydrocephalus associated with fetal meningomyelocele.

Prognosis

The prognosis depends on the cause of the dilated ventricles and not on the size of the cortical mantle at the time of operative intervention, except in cases in which the cortical mantle has been severely compressed and stretched. Hydrocephalic children are at increased risk for various developmental disabilities. The mean intelligence quotient is reduced compared with the general population, particularly for performance tasks as compared with verbal abilities. Many children have abnormalities in memory function. Vision problems are common, including strabismus, visuospatial abnormalities, visual field defects, and optic atrophy with decreased acuity secondary to increased ICP. The visual evoked potential latencies are delayed and take some time to recover after correction of the hydrocephalus. Although most hydrocephalic children are pleasant and mild mannered, some children show aggressive and delinquent behavior. Accelerated pubertal development in patients with shunted hydrocephalus or myelomeningocele is relatively common, possibly because of increased gonadotropin secretion in response to increased ICP. It is imperative that hydrocephalic children receive long-term follow-up in a multidisciplinary setting.

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609.12

Craniosynostosis

Stephen L. Kinsman, Michael V. Johnston

Craniosynostosis is defined as premature closure of the cranial sutures and is classified as primary or secondary. It is associated with varying types of abnormal skull shape. Primary craniosynostosis refers to closure of one or more sutures owing to abnormalities of skull development, whereas secondary craniosynostosis results from failure of brain growth and expansion and is not discussed here. The incidence of primary craniosynostosis approximates 1 in 2,000 live births. The cause is unknown in the majority of children; however, genetic syndromes account for 10–20% of cases. Deformational forces appear important in occipital and frontal plagiocephaly in many cases. Early detection of posterior skull shape is critical and allows successful intervention to be offered in the form of physical therapy for torticollis and other positional asymmetries that lead to plagiocephaly.

Development and Etiology

The bones of the cranium are well developed by the 5th mo of gestation (frontal, parietal, temporal, and occipital) and are separated by sutures and fontanels. The brain grows rapidly in the first several years of life and is normally not impeded because of equivalent growth along the suture lines. The cause of craniosynostosis is unknown, but the prevailing hypothesis suggests that abnormal development of the base of the skull creates exaggerated forces on the dura that act to disrupt normal cranial suture development. Genetic factors have been identified for some isolated and for many syndromic causes of craniosynostosis (Table 609.7 and Fig. 609.19). Untreated maternal hyperthyroidism is also associated with craniosynostosis.

Table 609.7

Commonly Used Clinical Genetic Classifications of Craniosynostoses

DISORDER	CAUSE
ISOLATED CRANIOSYNOSTOSIS	
Morphologically described	Unknown, uterine constraint, or *FGFR3* mutation
SYNDROMIC CRANIOSYNOSTOSIS	
Antler-Bixler syndrome	*FGFR2, POR*
Apert syndrome	Usually one of two mutations in *FGFR2*
Beare-Stevenson syndrome	Mutation in *GFGR2* or *FGFR3*
Baller-Gerold syndrome	Mutation in *TWIST* heterogeneous
Carpenter syndrome	*RAB23* in most
Craniofrontonasal dysplasia	*EFNB1*
Crouzon syndrome	Numerous different mutations at *FGFR2*
Crouzonomesodermoskeletal syndrome	Mutation in *FGFR3*
Jackson-Weiss syndrome	Mutation in *FGFR2*
Muenke syndrome	Mutation in *FGFR3*
Pfeiffer syndrome	Mutation in *FGFR1* or numerous mutations in *FGFR2*
Saethre-Chotzen syndrome	Mutation in *TWIST*
Shprintzen-Goldberg syndrome	Mutation in *FBEN1*

Modified from Ridgway EB, Weiner HL: Skull deformities, Pediatr Clin North Am 51:359–387, 2004.

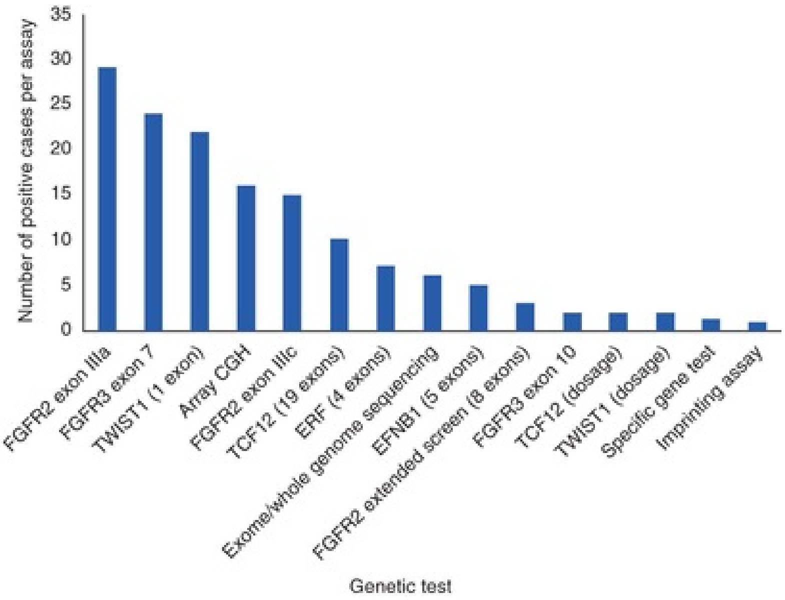

FIG. 609.19 Genetic testing in craniosynostosis. The tests are arranged hierarchically, with those yielding the highest number of diagnoses at the left. (From Wilkie AOM, Johnson D, Wall SA: Clinical genetics of craniosynostosis, Curr Opin Pediatr 29:622-628, 2017, Fig. 2.)

Clinical Manifestations and Treatment

Most cases of craniosynostosis are evident at birth and are characterized by a skull deformity that is a direct result of premature suture fusion. Palpation of the suture reveals a prominent bony ridge, and fusion of the suture may be confirmed by plain skull roentgenograms, CT scan, or bone scan in ambiguous cases (Table 609.8).

Table 609.8

Epidemiology and Clinical Characteristics of the Common Craniosynostoses

TYPE	EPIDEMIOLOGY	SKULL DEFORMITY	CLINICAL PRESENTATION
Sagittal	Most common CSO affecting a single suture, 80% male	Dolichocephaly or scaphocephaly (boat-shaped)	Frontal bossing, prominent occiput, palpable keel ridge. OFC normal and reduced biparietal diameter
Coronal	18% of CSO, more common in girls Associated with Apert syndrome (with syndactyly)	Unilateral: plagiocephaly Bilateral: brachycephaly,	Unilateral: flattened forehead on affected side, flat checks, nose deviation on normal side; higher supraorbital margin leading to

	and Crouzon disease, which includes abnormal sphenoid, orbital, and facial bones (hypoplasia of the midface)	acrocephaly	harlequin sign on radiograph and outward rotation of orbit can result in amblyopia Bilateral: broad, flattened forehead. In Apert syndrome accompanied by syndactyly and in Crouzon disease by hypoplasia of the midface and progressive proptosis
Lambdoid	10–20% of CSO, M:F ratio 4 : 1	Lambdoid/occipital plagiocephaly; right side affected in 70% of cases	Unilateral: flattening of occiput, indentation along synostotic suture, bulging of ipsilateral forehead leading to rhomboid skull, ipsilateral ear is anterior and inferior Bilateral: brachycephaly with bilateral anteriorly and inferiorly displaced ears
Metopic	Association with 19p chromosome abnormality	Trigonocephaly	Pointed forehead and midline ridge, hypotelorism
Multiple		Oxycephaly	Tower skull with undeveloped sinuses and shallow orbits, and elevated intercranial pressure

CSO, craniosynostosis; OFC, occipital–frontal circumference.

From Ridgway EB, Weiner HL: Skull deformities, Pediatr Clin North Am 51:359–387, 2004.

Premature closure of the sagittal suture produces a long and narrow skull, or **scaphocephaly,** the most common form of craniosynostosis. Scaphocephaly is associated with a prominent occiput, a broad forehead, and a small or absent anterior fontanel. The condition is sporadic, is more common in males, and often causes difficulties during labor because of cephalopelvic disproportion. Scaphocephaly does not produce increased ICP or hydrocephalus, and results of neurologic examination of affected patients are normal.

Frontal plagiocephaly is the next most common form of craniosynostosis and is characterized by unilateral flattening of the forehead, elevation of the ipsilateral orbit and eyebrow, and a prominent ear on the corresponding side. The condition is more common in females and is the result of premature fusion of a coronal and sphenofrontal suture. Surgical intervention produces a cosmetically pleasing result. When imaging does not reveal a closed suture, positional factors are of primary importance.

Occipital plagiocephaly is most often a result of positioning during infancy and is more common in an immobile child or a child with a disability, but fusion or sclerosis of the lambdoid suture can cause unilateral occipital flattening and bulging of the ipsilateral frontal bone.

Trigonocephaly is a rare form of craniosynostosis caused by premature fusion of the metopic suture. These children have a keel-shaped forehead and hypotelorism and are at risk for associated developmental abnormalities of the forebrain. Milder forms of metopic ridging are more common.

Turricephaly refers to a cone-shaped head from premature fusion of the coronal, and often sphenofrontal and frontoethmoidal, sutures. The **kleeblattschädel deformity** is a peculiarly shaped skull that resembles a cloverleaf. Affected children have very prominent temporal bones, and the remainder of the cranium is constricted. Hydrocephalus is a common complication.

Premature fusion of only one suture rarely causes a neurologic deficit. In this situation, the sole indication for surgery is to enhance the child's cosmetic appearance, and the prognosis depends on the suture involved and on the degree of disfigurement. Neurologic complications, including hydrocephalus and increased ICP, are more likely to occur when two or more sutures are prematurely fused, in which case operative intervention is essential. The role of early repositioning efforts and therapy for torticollis and the use of cranial molding devices are beyond the scope of this review.

The most prevalent genetic disorders associated with craniosynostosis include Crouzon, Apert, Carpenter, Chotzen, and Pfeiffer syndromes. **Crouzon syndrome** is characterized by premature craniosynostosis and is inherited as an autosomal dominant trait. The shape of the head depends on the timing and order of suture fusion but most often is a compressed back-to-front diameter or **brachycephaly** resulting from bilateral closure of the coronal sutures. The orbits are underdeveloped, and ocular proptosis is prominent. Hypoplasia of the maxilla and orbital hypertelorism are typical facial features.

Apert syndrome has many features in common with Crouzon syndrome. Apert syndrome is usually a sporadic condition, although autosomal dominant inheritance can occur. It is associated with premature fusion of multiple sutures, including the coronal, sagittal, squamosal, and lambdoid sutures. The facies tend to be asymmetric, and the eyes are less proptotic than in Crouzon syndrome. Apert syndrome is characterized by syndactyly of the 2nd, 3rd, and 4th fingers, which may be joined to the thumb and the 5th finger. Similar abnormalities often occur in the feet. All patients have progressive calcification and fusion of the bones of the hands, feet, and cervical spine.

Carpenter syndrome is inherited as an autosomal recessive condition, and the many fusions of sutures tend to produce the kleeblattschädel skull deformity. Soft tissue syndactyly of the hands and feet is always present, and intellectual disability is common. Additional but less common abnormalities include congenital heart disease, corneal opacities, coxa valga, and genu valgum.

Chotzen syndrome is characterized by asymmetric craniosynostosis and plagiocephaly. The condition is the most prevalent of the genetic syndromes and is inherited as an autosomal dominant trait. It is associated with facial asymmetry, ptosis of the eyelids, shortened fingers, and soft tissue syndactyly of the 2nd and 3rd fingers.

Pfeiffer syndrome is most often associated with turricephaly. The eyes are prominent and widely spaced, and the thumbs and great toes are short and broad. Partial soft tissue syndactyly may be evident. Most cases appear to be sporadic, but autosomal dominant inheritance has been reported.

Mutations of the fibroblast growth factor receptor (FGFR) gene family have been shown to be associated with phenotypically specific types of craniosynostosis. Mutations of the *FGFR1* gene located on chromosome 8 result in Pfeiffer syndrome; a similar mutation of the *FGFR2* gene causes Apert syndrome. Identical mutations of the *FGFR2* gene can result in both Pfeiffer and Crouzon phenotypes.

Each of the genetic syndromes poses a risk of additional anomalies, including hydrocephalus, increased ICP, papilledema, optic atrophy resulting from abnormalities of the optic foramina, respiratory problems secondary to a deviated nasal septum or choanal atresia, and disorders of speech and deafness. Craniectomy is mandatory for management of increased ICP, and a multidisciplinary craniofacial team is essential for the long-term follow-up of affected children. Craniosynostosis may be surgically corrected with good outcomes and relatively low morbidity and mortality, especially for nonsyndromic infants.

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CHAPTER 610

Deformational Plagiocephaly

Matthew P. Fahrenkopf, Nicholas S. Adams, Robert J. Mann, John A. Girotto

Deformational plagiocephaly (DP), also known as positional plagiocephaly, is the development of cranial flattening and asymmetry in the infant *as a result of extrinsic molding forces placed on the skull, such as consistently sleeping on the same area of the head* . Since the suggestion was made to place sleeping infants on their backs for the prevention of the sudden infant death syndrome, the incidence of DP has risen dramatically, and this has caused concern for parents and clinicians in the primary care setting.

Epidemiology and Etiology

Incidence

The incidence is 46.6%, utilizing the Argenta classification and looking at a socioeconomically and ethnically diverse patient population, with an average age of 2.25 mo. This incidence is higher than in previous reports, where it was found to peak between 7 wk of age (22.1%) and 4 mo of age (19.7%), and then decrease over the next 3 yr (7% at 12 mo and 3.3% at 24 mo). It generally resolves completely by 2-3 yr of age.

Infants cannot reposition their heads in the first few weeks of life and are not able to hold their heads up until about 4 mo of age. It is for this reason that DP is most severe around 4 mo of age. It is also during this time that an infant's head circumference is rapidly increasing: about 2 cm/mo in the first 3 mo, 1 cm/mo from 4-6 mo of age, and 0.5 cm/mo after 6 mo of age. At around 6 mo of age, infants have developed head control, and this ability to actively reposition their head allows for the gradual improvement of the cranial shape because of pressure offloading and continued brain growth.

Risk Factors

Congenital torticollis, positional preference when sleeping, and lower levels of activity are especially prominent in patients with DP. Table 610.1 delineates other risk factors. Many of these risk factors cannot be prevented, but sleeping supine with the head always turned to the same side has been found to predict DP independent of the other factors, and this *can* be prevented. There may be an association between developmental delay and DP. Although not causal, studies have found significant differences in gross motor development, such as sitting up, crawling, and rolling back to side, between babies with and without DP. Familial demographics, such as lower maternal education, primiparity, more prenatal education, and siblings with cranial asymmetries may also be predictive of the development of DP. The increase of DP with those mothers receiving more prenatal education is considered related to the emphasis placed on sudden infant death syndrome and the back to sleep campaign.

Table 610.1

Factors That Increase the Risk for Deformational Plagiocephaly

- Male
- First-born child
- Prematurity
- Limited passive neck rotation at birth (e.g., congenital torticollis)
- Developmental delay
- Sleep position is supine at birth and at 6 wk
- Bottle feeding only
- Tummy time < 3 times/day
- Lower activity level, slower milestone achievement
- Sleeping with head to same side, positional preference

Causes

Prenatal causes of DP include uterine compression and intrauterine constraint, such as occurs with oligohydramnios or multifetus gestation. Postnatal causes of DP include infant sleeping position and congenital muscular torticollis.

Muscular torticollis is a condition that is present in as many as 1 in 6 newborns and causes continuous tightening of muscles in the neck, preventing passive rotation. It is thought that this condition typically precedes the development of cranial deformity. However, head position preference may result from cervical asymmetry that leads to torticollis and later flattening of a side of the skull from acquired positional preference (see Chapter 700.1). Muscular and positional issues lead to nonsynostotic plagiocephaly rather than the opposite. Given that DP results from more time spent on one side of the head and that torticollis (and other neck muscle imbalances) are likely to lead to this disproportional partitioning of time, they are most likely causes, not effects, of DP.

Sleeping position plays a major role in the incidence of DP. When an infant continuously sleeps with the same part of the skull resting on a flat surface, a continuous force is placed in this area. During this time of rapid skull development, the growth is inhibited at the area where it rests on a hard surface, causing a flat spot. Because of this inhibition, growth is increased in opposite directions, causing a deformation that can be distinguished from other types of plagiocephaly.

Examination and Differentiating Between Deformational Plagiocephaly and Craniosynostosis

An abnormal head shape in an infant is distressing for parents. DP is a clinical diagnosis. Management also requires accurate counseling about its cause and treatment. It is especially important to be able to rule out **craniosynostosis** as a primary cause for cranial asymmetry in infants, because management of this condition is very different from that of DP and requires immediate referral to a craniofacial surgeon for evaluation (see Chapter 609.12). Craniosynostosis occurs in approximately 1 in 2,000 live births and results in plagiocephaly as a consequence of the early closure of skull sutures. Craniosynostosis must be distinguished from DP because the management is different. Lambdoidal craniosynostosis, although extremely rare (1 in 300,000 live births), presents with features most similar to those of DP. It can be distinguished from DP by a variety of historical and physical findings. Bilateral coronal synostosis also presents very similarly to posterior DP.

History and Physical Examination

Tables 610.2 and 610.3 outline the key components of the history and physical examination.

Table 610.2

Important Historical and Physical Factors in the Evaluation of a Patient With Plagiocephaly

	DEFORMATIONAL	SYNOSTOTIC
Birth history	Intrauterine compression First-born child	Typically no complications
Head shape at birth	Typically normal	Can be irregular
Age at which shape irregularity first noticed	Usually in first few months of life	Can be at birth
How patient prefers to sleep	Same side, same position Same even during naps	Variable
Bald spot	Yes	No
Motor development for age	If age is atypical for deformational plagiocephaly, motor development is typically slow for age Torticollis present History of limited activity or mobility	Varies depending on presence of concomitant syndrome
Tummy time	Decreased	Suggested time
Signs or symptoms of increasing intracranial pressure	No	Possible

Table 610.3

Key Differences Between Synostotic (Craniosynostosis) and Deformational Plagiocephaly

	DEFORMATIONAL PLAGIOCEPHALY	CRANIOSYNOSTOSIS
Causes	External forces applied to the skull Prenatal: uterine compression, intrauterine constrained Postnatal: congenital torticollis, sleeping position	Premature fusion of 1 or more cranial sutures
Common types	Lateral Posterior	Bilateral coronal Sagittal Metopic
Common distinguishing features	Normal round head shape at birth Parallelogram shape to head Ipsilateral ear anteriorly displaced No palpable bony ridges or open fontanels	Can have abnormal head shape at birth Trapezoid shape to head Ipsilateral ear posteriorly displaced Palpable bony ridges
Management	Repositioning Physical therapy Helmet in some cases	Surgery Helmet in some cases

Adapted from Nield LS, Brunner MD, Kamat D: The infant with a misshapen head, Clin Pediatr (Phila) 46:292–298, 2007, Tables 1 and 2.

Observation of cranial shape as well as ear displacement are the first steps. It is critical to observe the child anteriorly, laterally, and from a vertex view. When cranial shape is viewed from above, DP typically looks like a **parallelogram,** and the ear on the same side of the flat or bald spot is **displaced anteriorly.** In lambdoidal craniosynostosis, the head has a trapezoid shape and the ear on the same side as the flat spot is posteriorly displaced (Fig. 610.1). It is important to note that the ear position, though more likely to be anterior in DP and posterior in lambdoidal craniosynost1osis, may present anteriorly in both conditions.

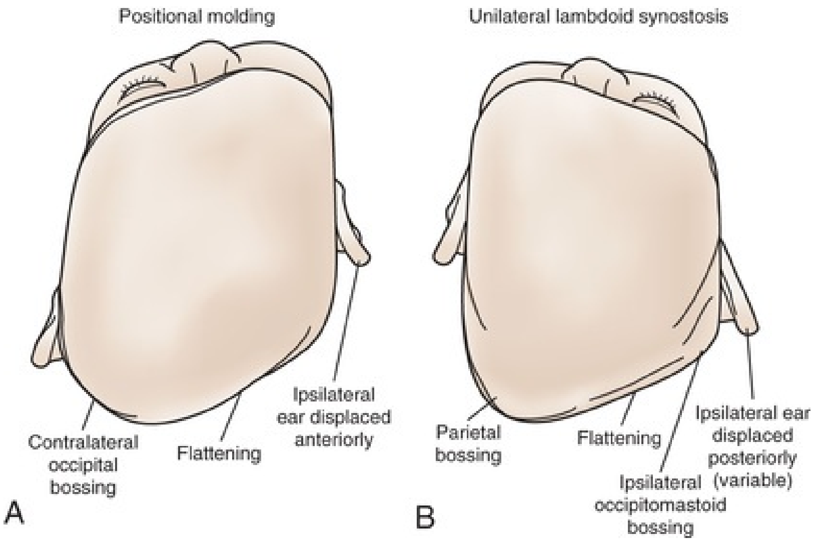
Positional molding
Unilateral lambdoid synostosis
Contralateral occipital bossing
Flattening
Ipsilateral ear displaced anteriorly
A
Parietal bossing
Flattening
Ipsilateral occipitomastoid bossing
Ipsilateral ear displaced posteriorly (variable)
B

FIG. 610.1 Differentiating physical findings between deformational plagiocephaly and craniosynostosis. Vertex views. **A,** Right-sided deformational plagiocephaly exhibiting a parallelogram head shape. **B,** Right-sided lambdoid craniosynostosis exhibiting a trapezoid-like head shape. (From Lin AY, Losee JE: Pediatric plastic surgery. In Zitelli BJ, McIntire SC, Norwalk AJ, editors: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 6th ed, Philadelphia, 2012, Elsevier, Fig. 22-5.)

Palpation will help to differentiate these two conditions. Craniosynostosis presents with palpable ridges along the suture, whereas DP does not. Additionally, patients with craniosynostosis will not have mobile calvarial bones. This can be tested by applying gentle pressure on two adjacent skull bones separated by a suspected synostotic suture. If the plates do not move relative to each other, then the suspicion for craniosynostosis is raised.

Verifying neck muscle tone and range of motion is a key part of the examination because it helps in evaluating motor development and in diagnosing congenital torticollis. Resistance to passive motion raises the concern for torticollis. Decreased tone should prompt further evaluation of motor development. Infants do not gain the muscle control to turn or lift their heads until approximately 4 mo of age, and delays in motor development could increase the infant's risk of DP at later ages than those at which it usually occurs. Decreased range of motion can also be seen in cervical spine abnormalities, although this is rare. Early recognition of these conditions is critical in treatment, management, and outcome.

Accurate and consistent measurements will help to distinguish etiologies and manage infants presenting with an abnormally shaped skull. Along with the usual head circumference measurements, the clinician should also measure cranial width, length, and transcranial diagonal diameter (as shown in Fig. 610.2), which is best performed with calipers. These measurements allow the clinician to diagnose, determine severity, and monitor the plagiocephaly:

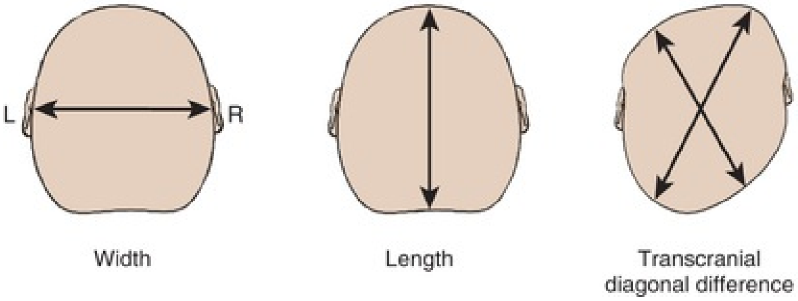

FIG. 610.2 Cranial measurements. (Modified from Looman WS, Flannery AB: Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis, J Pediatr Health Care 26:242–250, 2012, Table 1.)

◆ *Cranial length:* Distance from the most prominent point between the eyebrows to the most prominent point of the occiput

◆ *Width:* Maximum transverse diameter, horizontal

◆ *Cephalic index* (cranial index): Ratio of the cranial width to the cranial length

- *Occipital-frontal transcranial diameter:* Find the points on either side of the head where the deformation is the worst (two on the right, two on the left), then measure the diagonal distances between these points
- *Transdiagonal difference* (transcranial diagonal difference): The difference between two transcranial diagonal diameters
- *Cranial vault asymmetry:* Ratio of oblique measurements. This is difficult to implement because different physicians and authors propose varying points to use for these measurements

One technology for the evaluation of the severity and improvement over time of DP is the 3-dimensional photographic system. Advantages of this system include an easy and comfortable ability to image in an unbiased manner. Similarly, the use of laser scanners for the prefabrication scans for helmets is frequently employed by orthotists.

After observations and measurements, the clinician can determine the type and severity of the DP (Table 610.4 and Fig. 610.3). For *lateral DP*, bossing of the occiput occurs opposite the flattened deformity and the ear on the same side as the flat area can be anteriorly displaced. This type of DP is typically associated with infants who have torticollis or a head position preference to one side. Transdiagonal diameter is typically abnormal in this type of plagiocephaly, and this measurement is the gold standard for determining severity.

Table 610.4

Diagnostic Guide for Determining Type and Severity of Lateral and Posterior Deformational Plagiocephaly

	POSTERIOR DEFORMATIONAL

<table>
<tr><th></th><th>LATERAL DEFORMATIONAL PLAGIOCEPHALY</th><th colspan="4">PLAGIOCEPHALY (BRACHYCEPHALY)</th></tr>
<tr><td colspan="6">DETERMINING TYPE BASED ON CLINICAL FINDINGS</td></tr>
<tr><td>Occiput (vertex view)</td><td>Ipsilateral occipital flattening; contralateral occipital bossing</td><td colspan="4">Uniform occipital flattening</td></tr>
<tr><td>Ear position (vertex view)</td><td>Ipsilateral ear may be anteriorly displaced</td><td colspan="4">Normal</td></tr>
<tr><td>Face, forehead (anterior, lateral, and vertex views)</td><td>May be normal; more severe cases may present with the following: mandibular asymmetry, ipsilateral frontal bossing, contralateral forehead flattening, ipsilateral cheek anteriorly displaced</td><td colspan="4">Temporal bossing, increase in vertical height in severe cases</td></tr>
<tr><td>Other</td><td>Torticollis, head position preference</td><td colspan="4">Large size, history of limited activity or limited mobility</td></tr>
<tr><td colspan="6">DETERMINING SEVERITY</td></tr>
<tr><td>Mild</td><td>TDD 3-10 mm</td><td>Type I</td><td>Flattening restricted to back of the skull</td><td>CI: 0.82-0.9</td><td>Central posterior deformity (ping-pong ball depression)</td></tr>
<tr><td rowspan="2">Moderate</td><td rowspan="2">TDD 10-12 mm</td><td>Type II</td><td>Malposition of ear</td><td rowspan="2">CI: 0.9-1.0</td><td rowspan="2">Central posterior deformity and widening of posterior skull</td></tr>
<tr><td>Type III</td><td>Forehead deformity</td></tr>
<tr><td rowspan="2">Severe</td><td rowspan="2">TDD > 12 mm</td><td>Type IV</td><td>Malar deformity</td><td rowspan="2">CI: > 1.0</td><td rowspan="2">Vertical head, head growth, or temporal bossing</td></tr>
<tr><td>Type V</td><td>Vertical or temporal skull growth</td></tr>
</table>

CI, cephalic index (cranial index); TDD, transcranial diagonal diameter difference.

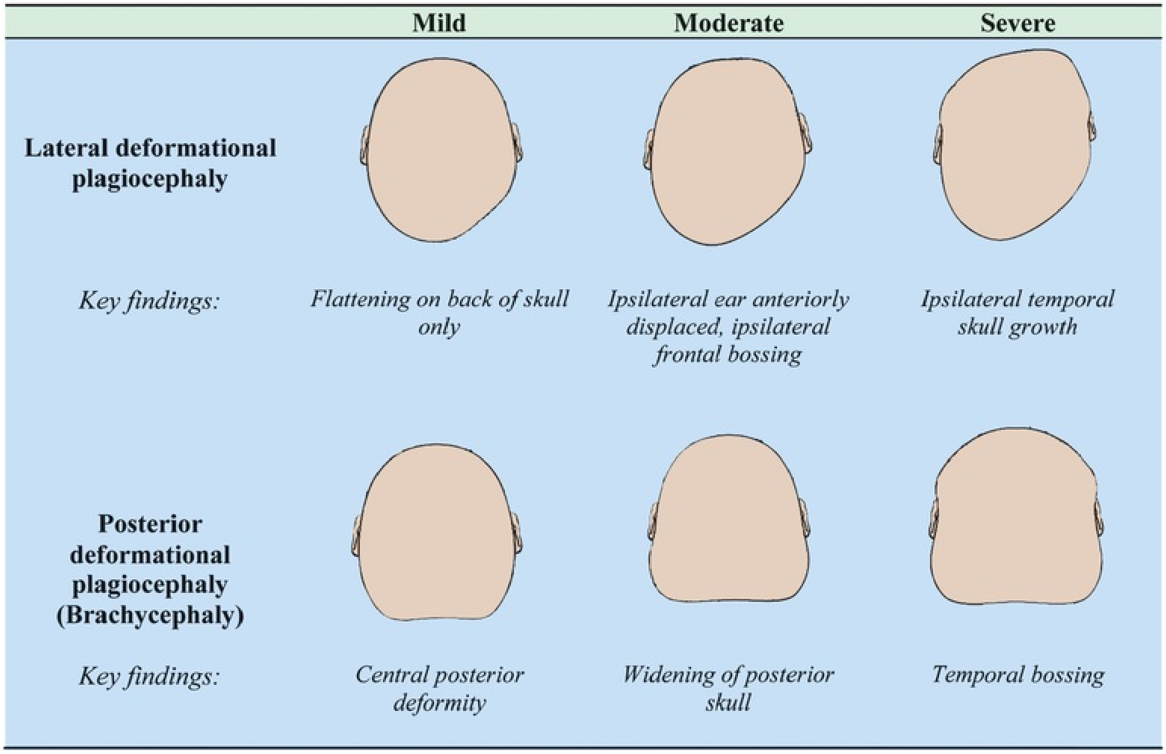
Mild
Moderate
Severe
Lateral deformational plagiocephaly
Key findings:
Flattening on back of skull only
Ipsilateral ear anteriorly displaced, ipsilateral frontal bossing
Ipsilateral temporal skull growth
Posterior deformational plagiocephaly (Brachycephaly)
Key findings:
Central posterior deformity
Widening of posterior skull
Temporal bossing

FIG. 610.3 Types of deformational plagiocephaly. (From Looman WS, Flannery AB: Evidence-based care of the child with deformational plagiocephaly, part I: assessment and diagnosis, J Pediatr Health Care 26:242–250, 2012, Fig. 1.)

In *posterior DP*, the occiput is uniformly flattened, temporal bossing can occur, and the ears are normal. It is usually associated with large head size and a history of limited activity or mobility. The cephalic index is increased with posterior DP.

Time and accurate exam records can help in management. If deformation is worsening when DP typically begins to demonstrate improving head shape, craniosynostosis should be suspected.

Treatment

Prevention

The sleep position should be monitored and varied. Alternating the infant's head to face the head and foot of the crib on alternate nights will allow the infant to sleep facing into the room without always lying on the same side of the head. Consistently alternating the sleeping position early on allows the infant to have equal time on both sides of the occiput, and the infant will become used to this pattern. Infants who have an obvious positional preference for a particular side will take more time and make more effort to purposefully reposition themselves counter to their preference. Parents must be counseled in the benefit of this strategy in preventing bald spots or flat spots that can progress to cranial deformity.

Tummy time is the term used to describe the infant's awake time spent lying on the stomach. The suggested amount of tummy time is 10-15 min at least 3 times a day. Reassure parents that sleep is the only time during which the prone position should be avoided, and educate the parents as to the benefits for the infant of awake prone positioning to help progression of motor development.

Treatment Options

Cranial asymmetry from DP does not usually spontaneously improve, nor do the more severe manifestations of facial and ear asymmetry disappear. Once a flat spot develops, it is unlikely that the infant will be able to overcome the pull to lie on the same spot in time to allow for reversal of the asymmetry.

Watch-and-wait management is not recommended in infants with DP. Evidence suggests that, at a minimum, repositioning and physiotherapy should be initiated as soon as asymmetry is observed.

Repositioning and physiotherapy (RPPT) include the counseling and teaching of parents about positional changes and tummy time for their child, as well as the referral to physical therapy in the case of congenital torticollis. RPPT is the optimal treatment choice for patients younger than 4 mo of age who have mild or moderately severe DP. The earliest types of behavioral modifications can be as simple as increasing tummy time or repositioning the infant's crib such that everything interesting in the room is on the side opposite the DP.

Molding therapy (helmet therapy) is the use of an orthotic helmet to promote the resolution of cranial asymmetry while the infant's head is still rapidly growing. Orthotic helmets do not actively mold the skull; rather, they protect the areas that are flat and allow the child to grow into the flat spot. Helmet therapy achieves correction 3 times faster and better than repositioning alone. This therapy is still debated because of its expense, time requirements, coverage, and side effects (irritation, rashes, and pressure sores). Combined treatment with helmet therapy and RPPT is the most beneficial management of infants older than 4 mo with severe DP or with worsening of mild or moderate DP trialed on RPPT. Infants with severe DP should be considered for helmet therapy at any age.

Studies suggest helmet therapy should be started for significant DP between 4 and 8 mo and continued for 7-8 mo. Parents should be counseled on the commitment involved in this treatment because helmets need to be worn up to 23 hr per day Noncompliance has been documented in 80% of study patient populations in as little as 4 mo.

There are risk factors associated with failure of RRPT and helmet therapy. Table 610.5 provides a list of these risk factors by treatment modality. These are important to consider when prescribing treatment regimens to families, in order to give the patient the best chance at a successful outcome.

Table 610.5

Risk Factors for Failure of Conservative and Helmet Therapy in the Treatment of Deformational Plagiocephaly

CONSERVATIVE THERAPY	HELMET THERAPY
Poor compliance Advanced age* Presence of torticollis Presence of developmental delay Increases severity of cranial deformity at time of therapy (via cranial ratio and diagonal difference)	Advanced age* Poor compliance

* Advanced age is defined as older than 6 mo.

Patients with **craniosynostosis** require surgery. Sometimes, a molding helmet can be used as an adjunctive therapy after surgery but never as monotherapy.

Outcomes

Outcomes may be better when helmet therapy is started before 6 mo of age; infants starting therapy later than that do not achieve the same degree of normal head measurements as those whose helmet therapy is started before 6 mo of age. Significant improvements in asymmetry are usually obvious at 4-11 wk after initiation of helmet therapy. An 8-yr review, analyzing 4,378 patients at the Children's Hospital of Chicago, found complete correction in 77.1% of patients undergoing conservative (RRPT) therapy and 94.4% of patients treated with helmet therapy.

Studies in patients with a median follow-up age of 9 yr found that 75% of cases had what both parents and patients considered to be a normal head appearance. Nine percent of patients and 4% of parents noted residual asymmetry that they considered significant. Though some literature hints at more satisfaction and less anxiety in parents of helmeted children, there is evidence to suggest that the treatment modality and outcome make no difference regarding parents' long-term satisfaction.

There is a small but growing body of literature that suggests conservative therapy (RRPT) may be as effective as helmet therapy for correcting certain cases of DP. Generalization of these findings to larger populations is not currently possible. The studies are too few, have low participation rates, exclude severe skull deformations, and have low overall complete corrections.

Cognitive and academic outcomes may be different depending on the side of deformity. Poorer academic performance and greater speech abnormalities were found in patients with left-sided deformities than in those with right-sided deformities. This manifested as double the number of patients with expressive speech abnormalities and triple the number of special education needs. It is unclear what the underlying mechanism is; treatment differences were apparently not a factor. In general, children with DP and without comorbid conditions are usually developmentally normal, healthy children. This is in contrast to craniosynostosis, in which increases in intracranial pressure may have deleterious effects on central nervous system function.

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CHAPTER 611

Seizures in Childhood

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A seizure is a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. The International League Against Epilepsy (ILAE) operational classification of seizure types divides epileptic seizures into four categories based on the presumed mode of seizure onset: focal, generalized, unknown onset, and unclassified (Table 611.1). In **focal** (formerly known as partial) **seizures,** the first clinical and electroencephalographic (EEG) changes suggest initial activation of a system of neurons limited to part of one cerebral hemisphere. Focal seizures can be described as motor or nonmotor seizures and are further characterized by preserved or impaired consciousness, which is used synonymously with the term **awareness.** Simple partial seizure is an outdated term that refers to a focal seizure with no alteration in consciousness; the current term is **focal aware seizure.** Complex partial seizure is also an outdated term that denotes focal seizures with altered awareness of the surroundings; they are currently referred to as **focal seizures with impaired awareness.** In **generalized seizures,** the first clinical and EEG changes indicate synchronous involvement of all of both hemispheres. A seizure may be labeled as being of **unknown onset** if there is not enough clinical information available to determine if the seizure is focal or generalized. If the clinical characteristics of a seizure are unusual and a determination of onset cannot be made despite an adequate workup, the seizure may be labeled as **unclassified.** Approximately 30% of patients who have a first afebrile seizure later develop epilepsy; the risk is approximately 20% if the neurologic exam, EEG, and neuroimages are normal.

Table 611.1

Types of Epileptic Seizures

SEIZURE TYPES
Focal-Onset Seizures
Motor Onset
Tonic
Clonic
Atonic
Myoclonic
Hyperkinetic
Epileptic spasms
Automatisms
Non–Motor Onset
Behavior arrest
Sensory
Cognitive
Emotional
Autonomic
Awareness Descriptor
Aware
Impaired awareness
Generalization Descriptor
Focal to bilateral tonic-clonic (*previously called secondary generalized seizure*)
Generalized-Onset Seizures
Motor
Tonic-clonic
Tonic
Clonic
Atonic
Myoclonic
Myoclonic-atonic
Myoclonic-tonic-clonic
Epileptic spasms
Non–Motor (Absence)
Typical
Atypical
Myoclonic
Eyelid myoclonia
Unknown-Onset Seizures
Motor
Tonic-clonic
Epileptic spasms
Non–Motor
Behavior arrest
Unclassified Seizures

Modified from Fisher RS, Cross JH, French, JA, et al: Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology, Epilepsia 58(4):522-530, 2017.

Febrile seizures are a separate category (see Chapter 611.1). **Acute symptomatic** or **provoked seizures** occur secondary to an acute problem affecting brain excitability, such as an electrolyte imbalance; most children with these types of seizures do well. However, sometimes these seizures signify major structural, inflammatory, or metabolic disorders of the brain, such as meningitis, encephalitis, acute stroke, or brain tumor. Consequently, the prognosis depends on the underlying disorder, including its reversibility or treatability and the likelihood of developing epilepsy from it. An **unprovoked seizure** is one that is not an acute symptomatic seizure. A **remote symptomatic seizure** is one that is considered to be secondary to a distant brain injury, such as an old stroke.

Reflex seizures are a type of seizure precipitated by a sensory stimulus. These types of seizures can be caused by a variety of stimuli, including visual (flickering lights, patterns, reading), auditory (music), somatosensory, or proprioceptive stimuli; praxis; eating; bathing in hot water; or being startled (see Chapter 609.11).

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The clinical diagnosis of epilepsy usually requires the occurrence of at least one unprovoked epileptic seizure with either a second such seizure or enough EEG and clinical information to convincingly demonstrate an enduring predisposition to develop recurrences. For epidemiologic and, commonly, for clinical purposes, epilepsy is considered present when two or more unprovoked seizures occur in a time frame of longer than 24 hr. Approximately 4–10% of children experience at least one seizure (febrile or afebrile) in the first 16 yr of life. The cumulative lifetime incidence of epilepsy is 3%, and more than half of the disorders start in childhood. The annual prevalence is 0.5–1.0%. Thus, the occurrence of a single seizure or of febrile seizures does not necessarily imply the diagnosis of epilepsy. **Seizure disorder** is a general term that is usually used to include any one of several disorders, including epilepsy, febrile seizures, and, possibly, single seizures and symptomatic seizures secondary to metabolic, infectious, or other etiologies (e.g., hypocalcemia, meningitis).

An **epileptic syndrome** is a disorder that manifests as one or more specific seizure types and has a specific age of onset and a specific prognosis. Several types of epileptic syndromes can be distinguished (Tables 611.2 and 611.3 ; Fig. 611.1). This category has to be distinguished from the category of epileptic seizures that refers to single events rather than to clinical syndromes. In general, the seizure type is the primary determinant of the medications to which the patient is likely to respond, and the epilepsy syndrome determines the prognosis one could expect. An **epileptic encephalopathy** is an epilepsy syndrome in which there is a severe EEG abnormality that is thought to result in cognitive and other impairments. **Developmental encephalopathy** denotes a disorder in which the underlying etiology (e.g., a specific gene mutation) contributes to a developmental delay independently of the patient's seizure burden and/or EEG abnormalities. The terms epileptic and developmental encephalopathy can be combined (i.e., **developmental epileptic encephalopathy**) in specific situations where both the EEG abnormalities and the underlying etiology contribute to the patient's developmental delay.

Table 611.2

Classification of Epilepsy Syndromes With an Indication of Age of Onset, Duration of Active Epilepsy, Prognosis, and Therapeutic Options

SPECIFIC SYNDROMES	AGE RANGE AT ONSET	AGE AT REMISSION	PROGNOSIS	MONOTHERAPY OR ADD-ON[*]	POSSIBLE ADD-ON [†]	SURGERY
NEONATAL						
Benign neonatal seizures	Newborn	Newborn	Good	LEV, TPM, PB	—	No
Early myoclonic encephalopathy and Ohtahara syndrome	Newborn infant	Poor, Ohtahara syndrome evolves into West syndrome	Ominous	PB, steroids, VGB	BZD, ZON, TPM, LEV, ketogenic diet	No
Benign familial neonatal convulsions	Newborn to young infant	Newborn to young infant	Good	LEV, TPM, PB	—	No
INFANCY						
Benign infantile seizures (nonfamilial)	Infant	Infant	Good	LEV, TPM, PB	—	No
Benign familial infantile convulsions	Infant	Infant	Good	LEV, TPM, OXC, CBZ, PB	—	No
Epilepsy of infancy with migrating focal seizures	Infant	No remission	Ominous	LEV, PB, OXC, CBZ, PHT, TPM, QND	BZD, bromides LAC, VPA, ZON	No
West syndrome	Infant	Variable	Variable	ACTH, steroids, VGB	BZD, FBM, IVIG, TPM, ZON, ketogenic diet	Lesionecto cortical res
Dravet syndrome (severe myoclonic	Infant	No remission	Severe	CLB, stiripentol, VPA (only after age 2 yr)	BZD, TPM, LEV, ZON, ketogenic diet	No

epilepsy in infancy)						
Benign myoclonic epilepsy in infancy	3 mo-3 yr	3-5 yr	Variable	LEV, TPM, BZD	VPA, ZON	No
CHILDHOOD						
Benign childhood epilepsy with centrotemporal spikes	3-13 yr	16 yr	Good	OXC, CBZ, LEV, VPA	LAC, PER	No
Early and late-onset idiopathic occipital epilepsy	2-8 yr; 6-17 yr	12 yr or younger; 18 yr	Good	OXC, CBZ, LEV, VPA	LAC, PER	No
Autosomal dominant nocturnal frontal lobe epilepsy	Childhood		Variable	OXC, CBZ, LEV	CLB, PB, PHT, LAC, PER, GBP, TPM	No
Familial lateral temporal lobe epilepsy	Childhood to adolescence		Variable	OXC, CBZ, LEV	CLB, PB, PHT, GBP, TPM, VPA, LAC, PER	No except cases
Generalized epilepsies with febrile seizures plus	Childhood to adolescence		Variable	ESM, LTG, LEV, VPA (depending on seizure type)	CLB, TPM, PER	No
Mesial temporal lobe epilepsy with hippocampal sclerosis	School-age or earlier	Long- lasting	Variable	OXC, CBZ, LEV	CLB, GBP, LAC, PB, PER, PHT, ZON, TPM, VPA	Temporal resection
Rasmussen syndrome	6-12 yr	Progressive	Ominous	LEV, OXC, CBZ, Plasmapheresis, immunoglobulins	LAC, PB, PER, PHT, TPM	Functional hemisphere
Hemiconvulsion–hemiplegia syndrome	1-5 yr	Chronic	Severe	OXC, CBZ, LEV	CLB, GBP, LAC, PB, PER, PHT, ZON, TPM, VPA	Functional hemisphere
Epilepsy with myoclonic astatic seizures	3-5 yr	Variable	Variable	ESM, TPM, VPA, LEV, ZON	BZD, ketogenic diet, LTG, PER, steroids	No
Childhood absence epilepsy	5-6 yr	10-12 yr	Good	ESM, LTG, VPA	Acetazolamide, CZP, ketogenic diet, ZON	No
Epilepsy with myoclonic absences	1-12 yr	Variable	Guarded	ESM, VPA, CZP	ZON, LTG	No
Lennox-Gastaut syndrome	3-10 yr	No remission	Severe	CLB, LTG, RFD, TPM, VPA	BZD, FBM, IVIG, PER, steroids, ZON, ketogenic diet	Callosotom
Landau-Kleffner syndrome	3-6 yr	8-12 yr	Guarded	Nocturnal DZP, steroids, VPA, LEV	CLB, ESM, IVIG, LTG,	Multiple su transection

					ketogenic diet	rarely lesionector
Epilepsy with continuous spike waves during slow-wave sleep	4-7 yr	8-12 yr	Guarded	Nocturnal DZP, steroids, VPA, LEV	CLB, ESM, IVIG, LTG, ketogenic diet	No
Other visual-sensitive epilepsies	2-5 yr	Unclear	Variable	VPA	BZD, LEV, LTG, ZON	No
Febrile seizures	3-5 yr	3-6 yr	Good	BZD (only as needed for febrile periods if frequent febrile seizures)	—	No
JUVENILE ONSET						
Juvenile absence epilepsy	10-12 yr	Usually lifelong	Good	ESM, LTG, VPA	Same as in childhood absence epilepsy	No
Juvenile myoclonic epilepsy	12-18 yr	Usually lifelong	Good	LEV, TPM, VPA	BZD, LTG, PB, PER, PRM, ZON	No
Epilepsy with generalized tonic-clonic seizures only	12-18 yr	Usually lifelong	Good	LEV, LTG, TPM, VPA	BZD, CBZ, PER, ZON	No
Idiopathic photosensitive occipital lobe epilepsy	10-12 yr	Unclear	Variable	VPA, LEV	BZD, LTG, ZON	No
Progressive myoclonic epilepsies (Unverricht-Lundborg, Lafora, ceroid lipofuscinoses, etc.)	Late infant to adolescent	Progressive	Ominous	TPM, VPA, ZON, LEV	BZD, PB, CLB, PER, ketogenic diet	No
VARIABLE AGE OF ONSET						
Mesial temporal lobe epilepsy defined by location and cause	Variable	Long-lasting	Variable	LEV, OXC, CBZ, TPM, VPA	PHT, PB, CLB, GBP, LAC, PER, ZON	Lesionecto cortical res
Mesial temporal lobe epilepsy defined by specific causes	Variable	Long-lasting	Variable	LEV, OXC, CBZ, TPM, VPA	CLB, GBP, LAC, PB, PER, PHT, ZON	Temporal resection
Startle epilepsy	Variable	Long-lasting	Guarded	OXC, CBZ, LEV, TPM, VPA	CLB, LEV, PB, PHT, ZON, GBP	Lesionecto cortical res in some
Reflex seizures	Variable	n/a		LEV, VPA	LTG, ZON	No
Drug or other chemically induced seizures	Variable	n/a		Withdraw offending agent	—	No
Immediate and	Variable	n/a		LEV, PHT	—	No

early posttraumatic seizures						

[*] Reflects current trends in practice, which may be off-label and may not be FDA-approved for that indication. Order of listing does not necessarily imply preference of use in that order. See Table 611.8 for FDA indications.

[†] May apply to selected cases only. Vagus nerve stimulation has been used for all types of refractory seizures and epilepsy types but has been FDA-approved as an adjunct therapy in patients 4 yr or older with medically refractory partial-onset seizures.

ACTH, adrenocorticotropic hormone; BZD, benzodiazepine; CBZ, carbamazepine; CLB, clobazam; DZP, diazepam; ESM, ethosuximide; FBM, felbamate; GBP, gabapentin; IVIG, intravenous immunoglobulin; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; n/a, not applicable; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; PRM, primidone; QND, quinidine; RFD, rufinamide; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZON, zonisamide.

Modified from Guerrini R: Epilepsy in children, Lancet 367:499–524, 2006; and Parisi P, Verrotti A, Paolino MC, et al: “Electro-clinical syndromes” with onset in the pediatric age group: the highlights of the clinical-EEG, genetic, and therapeutic advances, Ital J Pediatr 37:58, 2011.

Table 611.3

Selected Genes Causing Epilepsy Syndromes, Epileptic Encephalopathies, and Developmental Encephalopathies[*] [†]

EPILEPTIC CONDITIONS	GENE	PROTEIN
INFANTILE ONSET		
Adenosuccinate lyase deficiency	*ADSL*	Adenylosuccinate lyase
Benign familial neonatal seizures	*KCNQ2*	Potassium voltage-gated channel
	KCNQ3	Potassium voltage-gated channel
Benign familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Cerebral folate deficiency	*FOLR1*	Folate receptor alpha
Early familial neonatal infantile seizures	*SCN2A*	Sodium channel protein type 2α
Early infantile epileptic encephalopathy (EIEE)	*ARX (EIEE1)*	Aristaless-related homeobox
	CDKL5 (EIEE2)	Cyclin-dependent kinase-like 5
	SLC25A22 (EIEE3)	Mitochondrial glutamate carrier 1
	STXBP1 (EIEE4)	Syntaxin-binding protein 1
	SPTAN1 (EIEE5)	α_2 -Spectrin
	SCN1A (EIEE6)	Sodium-channel protein type 1α
	KCNQ2 (EIEE7)	Potassium voltage-gated channel
	ARHGEF9 (EIEE8)	Rho guanine nucleotide exchange factor 9
	PDCH19 (EIEE9)	Protocadherin-19
	PNKP (EIEE10)	Bifunctional polynucleotide phosphatase/kinase
	SCN2A (EIEE11)	Sodium-channel protein type 2α

	PLCβ1 (EIEE12)	Phospholipase C β1
	SCN8A (EIEE13)	Sodium-channel, voltage-gated, type VIII, alpha subunit
	KCNT1 (EIEE14)	Potassium-channel subfamily T, member 1
	ST3GAL3 (EIEE15)	ST3 beta-galactoside alpha-2,3-sialyltransferase 3
	TBC1D24 (EIEE16)	TBC1 domain family, member 24
	GNAO1 (EIEE17)	Guanine nucleotide-binding protein G(o) subunit alpha
	SZT2 (EIEE18)	Seizure threshold 2 homolog
	GABRA1 (EIEE19)	Gamma-aminobutyric acid receptor subunit alpha-1
	PIGA (EIEE20)	Phosphatidylinositol N-acetylglucosaminyltransferase subunit A
	NECAP1 (EIEE21)	Adaptin ear-binding coat-associated protein 2
	SLC35A2 (EIEE22)	UDP-galactose translocator
	DOCK7 (EIEE23)	Dedicator of cytokinesis 7
	HCN1 (EIEE24)	Potassium/sodium hyperpolarization–activated cyclic nucleotide-gated channel 1
	SLC13A5 (EIEE25)	Solute carrier family 13 (sodium-dependent citrate transporter), member 5
	KCNB1 (EIEE26)	Potassium voltage-gated channel, Shab-related subfamily, member 1
	GRIN2B (EIEE27)	NMDA receptor subtype 2B
	WWOX (EIEE28)	WW domain–containing oxidoreductase
	AARS (EIEE29)	Alanyl-tRNA synthetase
	SIK1 (EIEE30)	Salt inducible kinase 1
	DNM1 (EIEE31)	Dynamin-1
	KCNA2 (EIEE32)	Potassium voltage-gated channel subfamily A member 2
	EEF1A2 (EIEE33)	Elongation factor 1-alpha 2
	SLC12A5 (EIEE34)	Potassium–chloride transporter member 5
	ITPA (EIEE35)	Inosine triphosphate pyrophosphatase
	ALG13 (EIEE36)	Asparagine-linked glycosylation 13 homolog
Tuberous sclerosis	*TSC1*	Hamartin
	TSC2	Tuberin
Glucose transporter deficiency	*SLC2A1*	Solute carrier family 2, facilitated glucose transporter member 1
Pyridoxine dependent epilepsy	*ALDH7A1*	α-Aminoadipic semialdehyde dehydrogenase (antiquitin)

Polymerase G–related disorders	*POLG*	DNA polymerase subunit gamma-1
X-linked intellectual disability and epilepsy	*ATP6AP2*	Renin receptor
P5P-dependent epilepsy	*PNPO*	Pyridoxine-5′-phosphate oxidase
Generalized epilepsy with febrile seizures plus (early onset)	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
Microcephaly with early-onset intractable seizures and developmental delay (MCSZ)	*PNKP*	Bifunctional polynucleotide phosphatase/kinase
CHILDHOOD ONSET		
17q21.31 microdeletion syndrome	*KANSL1*	KAT8 regulatory nonspecific lethal (NSL) complex subunit 1
Angelman/Angelman-like/Pitt–Hopkins syndromes	*UBE3A*	Ubiquitin protein ligase E3A
	SLC9A6	Sodium/hydrogen exchanger 6
	MBD5	Methyl-CpG-binding domain protein 5
	TCF4	Transcription factor 4
	NRXN1	Neurexin-1
	CNTNAP2	Contactin-associated protein-like 2
Childhood-onset epileptic encephalopathies	*SCN1A*	Sodium channel protein type 1α
	PCDH19	Protocadherin-19
	SLC2A1	Solute carrier family 2, facilitated GTM1
	POLG	DNA polymerase subunit γ1
	SCN2A	Sodium channel protein type 2α
Creatine deficiency syndromes	*GAMT*	Guanidinoacetate *N* -methyltransferase
Early-onset absence seizures, drug-resistant epilepsy of multiple types at times with movement disorder	*GATM*	Glycine amidinotransferase, mitochondrial
Epilepsy with variable learning and behavioral disorders	*GRIN2A*	Glutamate receptor ionotropic, *N* -methyl-ᴅ -aspartate (NMDA) 2A
	SYN1	Synapsin-1
Generalized epilepsy with febrile seizure plus	*SCN1A*	Sodium channel protein type 1α
	SCN1B	Sodium channel protein type 1β
	GABRG2	γ-Aminobutyric acid receptor subunit γ2
	SCN2A	Sodium channel protein type 1α
Juvenile myoclonic epilepsy (more commonly presents in adolescence)	*EFHC1*	EF-hand domain–containing protein 1
	CACNB4	Voltage-dependent L-type calcium channel
	GABRA1	γ-Aminobutyric acid receptor subunit α1
Autosomal dominant nocturnal frontal lobe epilepsies (present in childhood through adulthood)	*CHRNA4*	Neuronal acetylcholine receptor α4
	CHRNB2	Neuronal acetylcholine receptor β2
	CHRNA2	Neuronal acetylcholine receptor α2
	CRH	Corticotropin releasing hormone
	DEPDC5	DEP domain containing 5
	KCNT1	Potassium sodium-activated channel subfamily T, member 1
Mowat–Wilson syndrome	*ZEB2*	Zinc finger E-box–binding homeobox 2

Neuronal ceroid lipofuscinosis (NCL)	*CLN1 (PPT1)*	Palmitoyl-protein thioesterase 1
	CLN2 (TPP2)	Tripeptidyl-peptidase 1
	CLN3	Battenin
	CLN4 (DNAJC5)	Cysteine-string protein alpha
	CLN5	Ceroid-lipofuscinosis neuronal protein 5
	CLN6	Ceroid-lipofuscinosis neuronal protein 6
	CLN7 (MFSD8)	Major facilitator superfamily domain-containing protein 8
	CLN8	Ceroid-lipofuscinosis neuronal protein 8
	CLN9	Ceroid-Lipofuscinosis, neuronal 9
	CLN10 (CTSD)	Cathepsin D
	CLN11 (GRN)	Granulin precursor
	CLN12 (ATP13A2)	ATPase 13A2
	CLN13 (CTSF)	Cathepsin F
	CLN14 (KCTD7)	BTB/POZ domain–containing protein KCTD7
Progressive myoclonic epilepsy (different forms present from infancy through adulthood)	*ATN1 (DRPLA)*	Atrophin 1
	CSTB	Cystatin-B
	CLN1-14	Multiple proteins causing neuronal ceroid lipofuscinosis
	EPM2A	Laforin
	EPM2B/NHLRC1	NHL repeat–containing protein 1 (Malin)
	GOSR2	Golgi snap receptor complex member 2
	PRICKLE1	Prickle-like protein 1
	SCARB2	Scavenger receptor class B member 2
Rett/atypical Rett syndromes	*MECP2*	Methyl CpG binding protein 2
	CDKL5	Cyclin-dependent kinase-like 5
	FOXG1	Forkhead box protein G1
	MBD5	Methyl-CpG–binding domain protein 5
	MEF2C	Myocyte-specific enhancer factor 2C
ADOLESCENT ONSET		
Juvenile myoclonic epilepsy (JME)	See Childhood-Onset JME	
Progressive myoclonic epilepsy (PME)	See Childhood-Onset PME	
Autosomal dominant nocturnal frontal lobe epilepsies (AD-NFLE)	See Childhood-Onset AD-NFLE	
Autosomal dominant lateral temporal lobe epilepsy (usually presents in adulthood)	*LGI1*	Leucine-rich glioma-inactivated protein 1

[*] Note that the same gene (different mutations) often appears as causing different epilepsy syndromes.

[†] The presence of most of these genes can be determined by means of commercially available, targeted single-gene sequencing, commercially available gene panels, or whole-exome sequencing (http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=genetests).

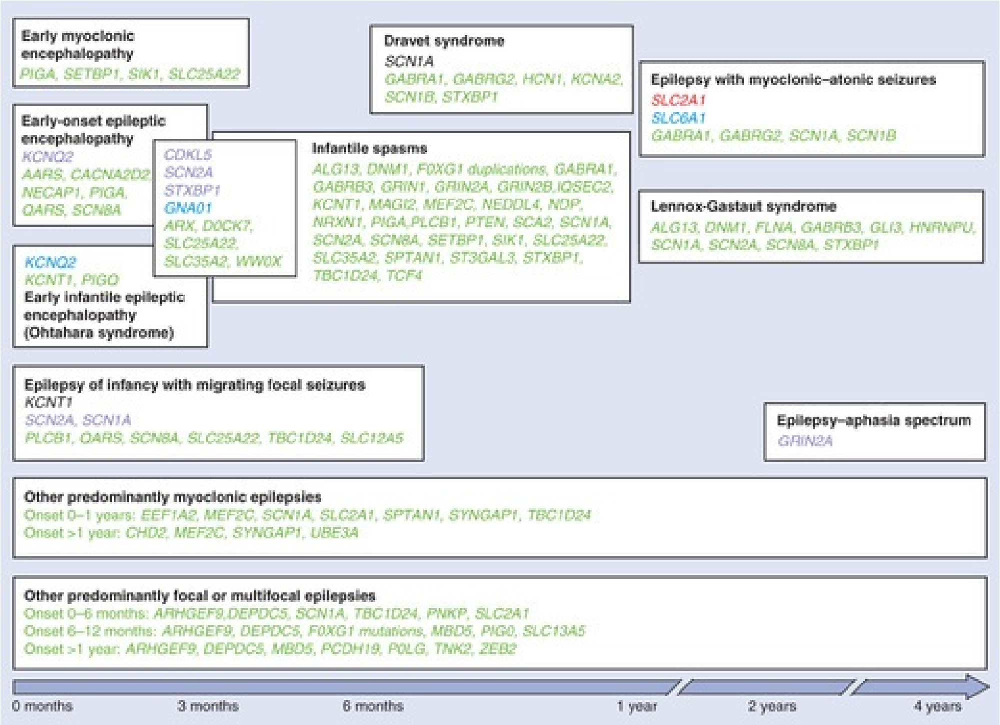
Early myoclonic encephalopathy
PIGA, SETBP1, SIK1, SLC25A22
Dravet syndrome
SCN1A
GABRA1, GABRG2, HCN1, KCNA2, SCN1B, STXBP1
Epilepsy with myoclonic–atonic seizures
SLC2A1
SLC6A1
GABRA1, GABRG2, SCN1A, SCN1B
Early-onset epileptic encephalopathy
KCNQ2
AARS, CACNA2D2, NECAP1, PIGA, QARS, SCN8A
CDKL5
SCN2A
STXBP1
GNA01
ARX, D0CK7, SLC25A22, SLC35A2, WW0X
Infantile spasms
ALG13, DNM1, F0XG1 duplications, GABRA1, GABRB3, GRIN1, GRIN2A, GRIN2B,IQSEC2, KCNT1, MAGI2, MEF2C, NEDDL4, NDP, NRXN1, PIGA,PLCB1, PTEN, SCA2, SCN1A, SCN2A, SCN8A, SETBP1, SIK1, SLC25A22, SLC35A2, SPTAN1, ST3GAL3, STXBP1, TBC1D24, TCF4
Lennox-Gastaut syndrome
ALG13, DNM1, FLNA, GABRB3, GLI3, HNRNPU, SCN1A, SCN2A, SCN8A, STXBP1
KCNQ2
KCNT1, PIGO
Early infantile epileptic encephalopathy (Ohtahara syndrome)
Epilepsy of infancy with migrating focal seizures
KCNT1
SCN2A, SCN1A
PLCB1, QARS, SCN8A, SLC25A22, TBC1D24, SLC12A5
Epilepsy–aphasia spectrum
GRIN2A
Other predominantly myoclonic epilepsies
Onset 0–1 years: EEF1A2, MEF2C, SCN1A, SLC2A1, SPTAN1, SYNGAP1, TBC1D24
Onset >1 year: CHD2, MEF2C, SYNGAP1, UBE3A
Other predominantly focal or multifocal epilepsies
Onset 0–6 months: ARHGEF9,DEPDC5, SCN1A, TBC1D24, PNKP, SLC2A1
Onset 6–12 months: ARHGEF9, DEPDC5, F0XG1 mutations, MBD5, PIG0, SLC13A5
Onset >1 year: ARHGEF9, DEPDC5, MBD5, PCDH19, P0LG, TNK2, ZEB2
0 months
3 months
6 months
1 year
2 years
4 years

FIG. 611.1 Genetic causes, and proportion of cases caused by each gene, including only nonchromosomal, nonmalformative, and nonmetabolic disorders. Only genes with more than one case reported are included. *Black font* denotes genes that account for at least 50% of cases, *purple font* 10–50% of cases, and *red font* 5–10% of cases. *Blue font* denotes genes that account for less than 5% of cases, and *green font* denotes genes that account for an unknown percentage of cases. (From McTague A, Howell KB, Cross JH, et al: The genetic landscape of the epileptic encephalopathies of infancy and childhood, Lancet 15:304-316, 2016.)

The ILAE Task Force on Classification has proposed a multilevel framework for categorizing epilepsies (Table 611.4). This framework should help guide therapeutic decisions and also assist with prognostication. At the most basic level (level 1), a patient's epilepsy can be classified by seizure type (focal, generalized, focal and generalized, or unknown). At the next level (level 2), based on available clinical data and known seizure types, an epilepsy type can be assigned (focal, generalized, focal and generalized, or unknown). At the next level (level 3), if further clinical data are available and based on supporting studies (e.g., EEG and/or MRI), the diagnosis of a specific epilepsy syndrome can be made (e.g., juvenile myoclonic epilepsy). Concurrent to this classification paradigm, the associated comorbidities and the underlying cause for the epilepsy must also be considered. If categorized by etiology, epilepsies are grouped into genetic, structural, metabolic, immune, infectious, or unknown categories. It is important to note that these categories are not mutually exclusive and a patient's epilepsy may have multiple concurrent etiologies (e.g., genetic and structural). At the final level (level 4) of categorizing and diagnosing the epilepsy, the epilepsy syndrome, the underlying etiology, and associated comorbidities are taken into account.

Table 611.4

Diagnostic and Classification Scheme of Epilepsies

Level 1: Determine if the event was an epileptic seizure and, if so, characterize the seizure type or types based on available clinical information as focal, generalized, or unknown. (Refer to Table 611.1 for more detailed characterizations.)

Level 2: Determine the type of epilepsy the patient has (focal, generalized, focal and generalized, or unknown).

Level 3: Determine if the epilepsy fits into a particular epilepsy syndrome (refer to Tables 611.1 to 611.3).

Level 4: Establish a unifying diagnosis that takes into account the epilepsy syndrome, underlying etiologies, and associated comorbidities.

The etiology for the epileptic seizures should be considered at **all** levels of an epilepsy diagnosis as listed above, etiologic categories:

Genetic
Structural
Metabolic
Immune
Infectious
Unknown

Comorbidities should be considered at **all** levels of an epilepsy diagnosis. These can include developmental delay, psychiatric symptoms, behavioral issues, academic difficulties, movement abnormalities, and many others.

Modified from Scheffer IE, Berkovic S, Capovilla G, et al: ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology, Epilepsia 58(4):512-521, 2017.

Genetic epilepsy (previously also referred to as idiopathic epilepsy) implies that the epilepsy syndrome is the direct result of a known or presumed genetic defect(s) that is not causative of a brain structural or metabolic disorder other than the epilepsy. This category encompasses *genetic generalized epilepsies* (previously called idiopathic generalized epilepsies), such as childhood absence epilepsy, as well as epilepsies caused by a known gene defect, such as the Dravet syndrome, which is most commonly caused by mutations in the *SCN1A* gene. **Structural epilepsy** (previously called symptomatic epilepsy) refers to an epilepsy syndrome caused by an underlying structural brain disorder that may or may not be genetic. This includes etiologies such as old stroke or hypoxic-ischemic injury, as well as epilepsy secondary to tuberous sclerosis (which is also genetic in etiology). **Immune-mediated epilepsy** is an important category that describes epilepsies occurring secondary to immune-mediated central nervous system (CNS) inflammation. This group of disorders warrants special attention because immunotherapies such as steroids and intravenous immunoglobulin may be the first-line treatments. **Autoimmune encephalitides** such as anti-NMDA receptor encephalitis and anti-LG1 limbic encephalitis are examples of immune-mediated epilepsies. **Infectious epilepsy** describes epilepsies secondary to chronic infectious conditions such as tuberculosis and HIV rather than acute infections such as bacterial meningitis or herpes simplex virus (HSV) encephalitis.

The older terms cryptogenic epilepsy and presumed symptomatic epilepsy refer to an epilepsy syndrome in which there is a presumed underlying brain disorder causing the epilepsy and affecting neurologic function but the underlying disorder is not known; the disorder is now referred to as **unknown epilepsy,** designating that the underlying cause of the epilepsy is still unknown.

Evaluation of the First Seizure

The initial evaluation of an infant or a child during or shortly after a suspected seizure should include an assessment of the adequacy of the airway, ventilation, and cardiac function, as well as measurement of temperature, blood pressure, and glucose concentration (many emergency rooms can measure the glucose with electrolytes as a point-of-care stat test). For acute evaluation of the first seizure, the physician should search for potentially life-threatening causes of seizures, such as meningitis, systemic sepsis, unintentional or nonaccidental intentional head trauma, and ingestion of drugs of abuse or accidental ingestion of drugs or other toxins. The history should aim to determine if the event was a seizure or not and to define factors that might have promoted the convulsion and to provide a detailed description of the seizure and the child's postictal state.

The subsequent step in an evaluation is to determine whether the seizure has a focal onset or is generalized. **Focal seizures** could include forceful turning of the head and eyes to one side, unilateral clonic movements beginning in the face or extremities, or a sensory disturbance, such as paresthesia or pain localized to a specific area. Focal seizures in an adolescent or adult usually indicate a localized lesion, whereas these seizures during childhood are often either secondary to a lesion or the result of a genetic, formerly known as idiopathic, epilepsy. Focal seizures in a neonate may be seen because of focal lesions such as perinatal stroke or because of a metabolic abnormality such as hypocalcemia that results in focal seizures that may not generalize due to immaturity of the brain connections. Focal and generalized motor seizures may be tonic-clonic, tonic, clonic, myoclonic, or atonic. **Tonic seizures** are characterized by increased tone or rigidity (usually lasting 2 sec up to several minutes), and **atonic seizures** are characterized by flaccidity and lack of movement. **Clonic seizures** consist of rhythmic, fast muscle contractions and slightly longer relaxations; **myoclonus** is a shock-like contraction of a muscle of < 50 msec that is often repeated. The duration of the seizure and state of consciousness (retained or impaired) should be documented. The history should determine whether an **aura** preceded the convulsion and the behavior the child was exhibiting immediately preceding the seizure. Auras can take the form of a number of sensations, including visual (e.g., flashing lights or seeing colors or complex visual hallucinations), somatosensory (tingling), olfactory, auditory, vestibular, or experiential (e.g., déjà vu, déjà vécu feelings) sensations, depending on the precise localization of the origin of the seizures. The most common aura experienced by children consists of epigastric discomfort or pain and a feeling of fear. The posture of the patient, presence or absence and distribution of cyanosis, vocalizations, loss of sphincter control (more commonly of the urinary bladder), and postictal state (including sleep, headache, and hemiparesis) should be noted. The provider taking the history should ask specifically about each of the above symptoms as appropriate because caretakers may not spontaneously report them.

In addition to clarifying the seizure semiology, a detailed history is crucial in identifying an underlying cause for the seizure. Reported personality changes or symptoms of increased intracranial pressure can suggest an intracranial tumor. Similarly, a history of cognitive regression can suggest a degenerative or metabolic disease. A history of prenatal or perinatal distress or of developmental delay can suggest etiologic congenital or perinatal brain dysfunction. Acute to subacute personality changes, psychiatric symptoms, and/or associated movement abnormalities may suggest an autoimmune etiology.

The examination of a child with a seizure disorder should also be geared toward the search for an organic cause. The child's head circumference, length, and weight are plotted on a growth chart and compared with previous measurements. A careful general and neurologic examination should be performed. A funduscopic exam should be performed to evaluate for the presence of papilledema, optic neuritis, retinal hemorrhages, uveitis, chorioretinitis, coloboma, or macular changes, as well as retinal phakoma. The finding of unusual facial features or of associated physical findings such as hepatosplenomegaly may point to an storage disease or inborn error of metabolism as the cause of the neurologic disorder. The presence of a **neurocutaneous disorder** may be indicated by the presence of vitiliginous ash leaf–type lesions usually better seen using an ultraviolet light (Wood lamp); of adenoma sebaceum, shagreen patches, or retinal phakomas (tuberous sclerosis); of multiple café-au-lait spots (neurofibromatosis); or of V1- or V2-distribution nevus flammeus (Sturge-Weber syndrome) (see Chapter 614).

Localizing neurologic signs, such as a subtle **hemiparesis** with hyperreflexia, an equivocal or positive Babinski sign, and pronator drifting of an extended arm with eyes closed, might suggest a contralateral hemispheric structural lesion, such as a slow-growing glioma, as the cause of the seizure disorder. Unilateral growth arrest of the thumbnail, hand, or extremity in a child with a focal seizure disorder suggests a chronic condition, such as a porencephalic cyst, arteriovenous malformation, or cortical atrophy of the opposite hemisphere.

In an acute setting such as the emergency department, the decision to pursue further laboratory testing, including serum electrolytes, a complete blood count, and/or urine toxicology tests, should be made on a case-by-case basis that takes into account the patient's clinical history and examination. Electrocardiography (ECG) to rule out long QT or other cardiac dysrhythmias and other tests directed at disorders that could mimic seizures may be needed (see Chapter 612). A lumbar puncture is usually of limited value in an acute workup of a *nonfebrile* seizure unless the history or examination is concerning for an infectious or inflammatory process or if there is clinical concern for intracranial bleeding despite normal brain imaging. *A routine EEG should be performed in all cases of a first unprovoked nonfebrile seizure to help predict the risk of seizure recurrence.* If the patient's neurologic status has returned to baseline, the EEG can often be done on an outpatient basis even though the yield may be slightly lower because the EEG has been delayed. Emergent brain imaging with a head CT or brain MRI is usually performed if the seizure was focal, if there are postictal focal deficits on neurologic exam, or if the patient's status is not returning to baseline; in patients with trauma preceding the seizure; and in patients with a high-risk medical history. In other situations, the yield of emergent imaging identifying an abnormality that warrants emergent intervention is less than 1%. *Brain MRI is preferred over a CT scan, and performing it on a nonemergent basis should be considered in most patients.* CT is useful if a rapid study is needed to look for trauma, a mass, or signs of increased intracranial pressure. In select situations, such as when the clinical and

EEG manifestations are consistent with a genetic generalized epilepsy such as childhood absence epilepsy, a brain MRI may not be necessary. Gadolinium (contrast) does not need to be routinely used when performing the brain MRI unless there is clinical suspicion of a neoplasm, vascular malformation, abscess, or another infectious or inflammatory process. Further details regarding the approach to a first seizure are included in Chapter 611.2 .

611.1

Febrile Seizures

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Keywords

simple febrile seizure
complex febrile seizure
febrile status epilepticus
febrile infection–related (or refractory) epilepsy (FIRES)
generalized epilepsy with febrile seizures plus (GEFS+)
severe myoclonic epilepsy of infancy
Dravet syndrome

Febrile seizures are seizures that occur between the ages of 6 and 60 mo (peak 12-18 mo) with a temperature of 38°C (100.4°F) or higher, that are not the result of CNS infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. A **simple febrile seizure** is a primary generalized, usually tonic-clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-hr period. A **complex febrile seizure** is more prolonged (>15 min), and/or is focal, and/or recurs within 24 hr. **Febrile status epilepticus** is a febrile seizure lasting longer than 30 min. Most patients with simple febrile seizures have a very short postictal state and usually return to their baseline normal behavior and consciousness within minutes of the seizure. **Febrile infection–related** (or **refractory**) **epilepsy (FIRES)** is a very different disorder seen predominantly in older (>5 yr) usually male children and associated with an encephalitis-like illness but without an identifiable infectious agent. Children with FIRES were previously normal but subsequently develop difficult-to-treat epilepsy.

Between 2% and 5% of neurologically healthy infants and children experience at least one, usually simple, febrile seizure. Simple febrile seizures do not have an increased risk of mortality even though they are concerning to the parents. Complex febrile seizures may have an approximately 2-fold long-term increase in mortality rates, as compared with the general population, over the subsequent 2 yr, probably secondary to a coexisting pathology. There are no long-term adverse effects of having one or more simple febrile seizures. Compared with age-matched controls, patients with febrile seizures do not have any increase in the incidence of abnormalities of behavior, scholastic performance, neurocognitive function, or attention. Children who develop later epilepsy, however, might experience such difficulties. Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after two or more episodes, and in 50% of infants younger than 1 yr of age at febrile seizure onset. Several factors affect the recurrence risk (Table 611.5). Although approximately 15% of children with epilepsy have had febrile seizures, only 5% (range 1–33%, dependent on risk factors) of children who experience febrile seizures proceed to develop epilepsy later in life. There are several predictors of epilepsy after febrile seizures (Table 611.6).

Table 611.5

Risk Factors for Recurrence of Febrile Seizures*

MAJOR
Age < 1 yr Duration of fever < 24 hr Fever 38-39°C (100.4-102.2°F)
MINOR
Family history of febrile seizures Family history of epilepsy Complex febrile seizure Daycare Male gender Lower serum sodium at time of presentation

[*] Having no risk factors carries a recurrence risk of approximately 12%; one risk factor, 25–50%;

two risk factors, 50–59%; three or more risk factors, 73–100%.

Table 611.6

Risk Factors for Occurrence of Subsequent Epilepsy After a Febrile Seizure[*]

RISK FACTOR	RISK FOR SUBSEQUENT EPILEPSY
Simple febrile seizure	1%
Recurrent febrile seizures	4%
Complex febrile seizures (>15 min in duration or recurrent within 24 hr)	6%
Fever < 1 hr before febrile seizure	11%
Family history of epilepsy	18%
Complex febrile seizures (focal)	29%
Neurodevelopmental abnormalities	33%

[*] Having more than one risk factor is at least in part additive.

Genetic and Other Factors Leading to Febrile Seizures

The genetic contribution to the incidence of febrile seizures is manifested by a positive family history for febrile seizures in many patients. In some families, the disorder is inherited as an autosomal dominant trait, and multiple single genes that cause the disorder have been identified in such families. However, in most cases the disorder appears to be polygenic, and many genes predisposing to it remain to be identified. Genes associated with febrile seizures include *SCN1A, SCN1B, SCN9A*, and *CPA6*. In terms of other etiologies, a dysregulation between the proinflammatory IL-1β, IL-6, and IL-8 cytokines and antiinflammatory ILR-1A cytokines has been associated with **febrile status epilepticus.** A decreased ILR-1A/IL-8 ratio (suggestive of an overall proinflammatory state) is predictive of hippocampal abnormalities on MRI done after febrile status epilepticus. The ILR-1A/IL-8 ratio may thus prove to be a potential biomarker for identifying febrile seizure patients who may be at higher risk for developing mesial temporal lobe epilepsy later in life.

Almost any type of epilepsy can be preceded by febrile seizures. A few epilepsy syndromes typically start with febrile seizures; these are **generalized epilepsy with febrile seizures plus** (GEFS+), **severe myoclonic epilepsy of infancy** (SMEI or **Dravet syndrome**), and, in many patients, temporal lobe epilepsy secondary to mesial temporal sclerosis. **GEFS+** is an autosomal dominant syndrome with a highly variable phenotype. Onset is usually in early childhood, and remission is usually in mid-childhood. It is characterized by multiple febrile seizures and by several subsequent types of afebrile generalized seizures, including generalized tonic-clonic, absence, myoclonic, atonic, or myoclonic astatic seizures with variable degrees of severity. A focal febrile seizures plus epilepsy variant, in which the seizures are focal rather than generalized, has also been described.

Dravet syndrome is the most severe of the phenotypic spectrum of febrile seizure–associated epilepsies. It constitutes a distinct entity, the onset of which is in infancy. It is initially characterized by febrile and afebrile unilateral clonic seizures that recur every 1 or 2 mo. These early seizures are typically induced by fever, but they differ from the usual febrile convulsions in that they are more prolonged, more frequent, and focal and recur in clusters. Seizures subsequently start to occur with lower fevers and then without fever. During the second year of life, myoclonus, atypical absences, and focal seizures occur frequently and developmental delay usually follows. This syndrome is usually caused by a de novo mutation, although rarely it is inherited in an autosomal dominant manner or may be inherited from a nonaffected carrier parent. Mutations in the *SCN1A* gene are the most common cause of Dravet syndrome (causing ~ 80% of all cases). The same gene is mutated in the GEFS+ spectrum; however, in Dravet syndrome the mutations lead to loss of function and thus to a more severe phenotype. There are several milder variants of Dravet syndrome that manifest some but not all of the above features and that are referred to as Dravet syndrome spectrum or SMEI-Borderland. Rarely the *GABRG2, SCN1B,* and *SCN2A* genes may cause Dravet syndrome; however, in 10–20% of the cases a specific gene mutation is not identified.

The majority of patients who had prolonged febrile seizures and encephalopathy after vaccination and who had been presumed to have suffered from vaccine encephalopathy (seizures and psychomotor regression occurring after vaccination and presumed to be caused by it) turn out to have Dravet syndrome mutations, indicating that their disease is caused by the mutation and not secondary to the vaccine. This has raised doubts about the very existence of the entity termed vaccine encephalopathy.

Evaluation

Fig. 611.2 delineates the general approach to the patient with febrile seizures. Each child who presents with a febrile seizure requires a detailed history and a thorough general and neurologic examination. Febrile seizures often occur in the context of otitis media; roseola and human herpesvirus (HHV) 6 infections; and infections with norovirus, enteroviruses, *Shigella*, or similar agents, making the evaluation more demanding. In patients with febrile status epilepticus, HHV-6B (more frequently) and HHV-7 infections account for 30% of the cases.

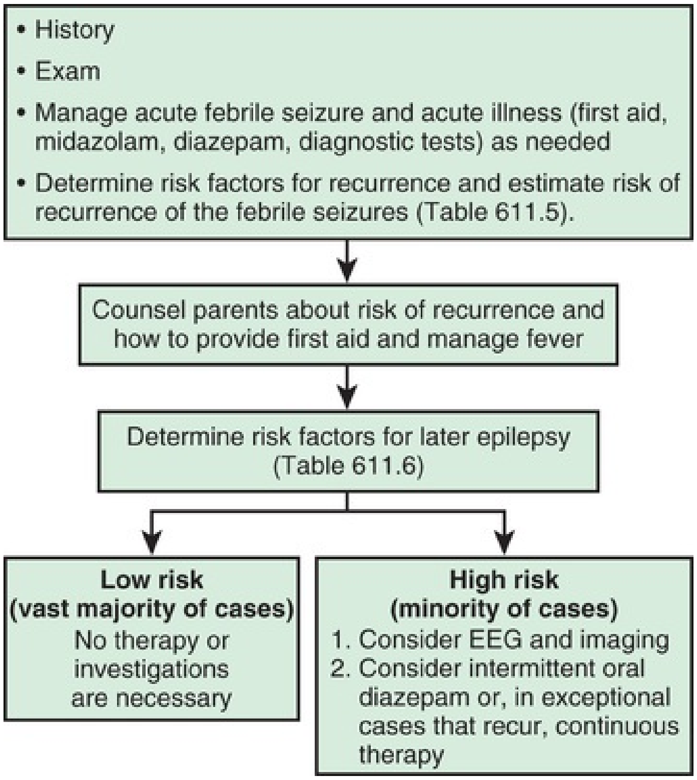
• History
• Exam
• Manage acute febrile seizure and acute illness (first aid, midazolam, diazepam, diagnostic tests) as needed
• Determine risk factors for recurrence and estimate risk of recurrence of the febrile seizures (Table 611.5).
Counsel parents about risk of recurrence and how to provide first aid and manage fever
Determine risk factors for later epilepsy (Table 611.6)
Low risk (vast majority of cases)
No therapy or investigations are necessary
High risk (minority of cases)
1. Consider EEG and imaging
2. Consider intermittent oral diazepam or, in exceptional cases that recur, continuous therapy

FIG. 611.2 Treatment algorithm for the management of febrile seizures. (Modified from Mikati MA, Rahi A: Febrile seizures: from molecular biology to clinical practice, Neurosciences [Riyadh] 10:14-22, 2004.)

Lumbar Puncture

Meningitis should be considered in the differential diagnosis, and lumbar puncture should be performed for all infants younger than 6 mo of age who present with fever and seizure, if the child is ill-appearing, or at any age if there are clinical signs or symptoms of concern. A lumbar puncture is an option in a child 6-12 mo of age who is deficient in *Haemophilus influenzae* type b and *Streptococcus pneumoniae* immunizations or for whom the immunization status is unknown. A lumbar puncture is an option in children who have been pretreated with antibiotics. In patients presenting with febrile status epilepticus, a nontraumatic lumbar puncture rarely shows cerebrospinal fluid (CSF) pleocytosis (96% have < 3 nucleated cells in the CSF) with a concurrently normal CSF protein and glucose. Pleocytosis suggests bacterial or viral infection.

Electroencephalogram

If the child is presenting with the first simple febrile seizure and is otherwise neurologically healthy, an EEG need not be performed as part of the evaluation. An EEG would not predict the future recurrence of febrile seizures or epilepsy even if the result is abnormal. Spikes during drowsiness are often seen in children with febrile seizures, particularly those older than age 4 yr, and these do not predict later epilepsy. EEGs performed within 2 wk of a febrile seizure often have nonspecific slowing, usually posteriorly. Thus, in many cases, if an EEG is indicated, it is delayed until or repeated after more than 2 wk have passed. An EEG should, therefore, generally be restricted to special cases in which epilepsy is highly suspected (see Table 611.6), and, generally, it should be used to delineate the type of epilepsy rather than to predict its occurrence. If an EEG is done, it should be performed for at least 20 min in wakefulness and in sleep according to international guidelines to avoid misinterpretation and drawing of erroneous conclusions. At times, if the patient does not recover immediately from a seizure, an EEG can help distinguish between ongoing seizure activity and a prolonged postictal state. After febrile status epilepticus, focal EEG slowing over the temporal lobe increases the chance that the patient may have medial temporal sclerosis on follow-up.

Blood Studies

Blood studies (serum electrolytes, calcium, phosphorus, magnesium, and a complete blood count) are not routinely recommended in the workup of a child with a first simple febrile seizure. Blood glucose should be measured initially and with prolonged postictal obtundation or with poor oral intake (prolonged fasting). Serum electrolyte values may be abnormal in children after a febrile seizure, but this should be suggested by precipitating or predisposing conditions elicited in the history and reflected in the physical examination. If clinically indicated (e.g., dehydration), these tests should be performed. A low sodium level is associated with a higher risk of recurrence of the febrile seizure within the following 24 hr.

Neuroimaging

A CT or MRI is not recommended in evaluating the child after a first simple febrile seizure. The workup of children with complex febrile seizures needs to be individualized. This can include an EEG and neuroimaging, particularly if the child is neurologically abnormal. Approximately 10% of children with febrile status epilepticus are reported to have unilateral or, less frequently, bilateral swelling of their hippocampus acutely; subsequent long-term hippocampal atrophy is evident in about 71% of those who had the acute findings. Whether these patients will ultimately develop temporal lobe epilepsy remains to be determined.

Treatment

In general, antiepileptic therapy, continuous or intermittent, is not recommended for children with one or more simple febrile seizures. Parents should be counseled about the relative risks of recurrence of febrile seizures and recurrence of epilepsy, educated on how to handle a seizure acutely, and given emotional support. If the seizure lasts for longer than 5 min, acute treatment with lorazepam, midazolam, or diazepam is needed (see Chapter 611.8 for acute management of seizures and status epilepticus). Rectal diazepam is often prescribed to families to be used at home as a rescue medication if a febrile seizure lasts longer than 5 min (see Table 611.15 for dosing). Alternatively, buccal or intranasal midazolam may be used. In cases of frequently recurring febrile seizures, intermittent oral clonazepam (0.01 mg/kg every 8-12 hr up to a maximum dose of 1.5 mg/day) or oral diazepam (0.33 mg/kg every 8 hr) can be given during febrile illnesses. Such therapies help reduce, but do not eliminate, the risks of recurrence of febrile seizures. Historically, continuous therapy with the AEDs phenobarbital or valproic acid was occasionally used to prevent febrile seizures. However, in the vast majority of cases, use of continuous therapy is not justified, due to the risk of side effects and lack of demonstrated long-term benefits, even if the recurrence rate of febrile seizures is expected to be decreased by these drugs.

Antipyretics can decrease the discomfort of the child but do not reduce the risk of having a recurrent febrile seizure. Chronic antiepileptic therapy may be considered for children with a high risk for later epilepsy. The possibility of future epilepsy does not change with or without antiepileptic therapy. Iron deficiency is associated with an increased risk of febrile seizures, and thus screening for that problem and treating it appears appropriate.

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611.2

Unprovoked Seizures

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Keywords

auras
tonic
clonic
myoclonic
atonic
astatic
drop attack
head drop
axial spasms
epilepsia partialis continua
absence seizures
typical absences
atypical absences
Lennox-Gastaut syndrome
juvenile absences
epilepsy syndrome

History and Examination

Evaluation of a first-time seizure was discussed earlier in this chapter. It entails stabilization of the patient if the child presents during or shortly after the seizure. A careful history and examination are done to accurately characterize the seizure, exclude acute intervenable causes, and attempt to determine the underlying etiology of the seizure.

Differential Diagnosis

This involves consideration of nonepileptic paroxysmal events (see Chapter 612), determination of the seizure type as classified by the ILAE system (see Table 611.1), and consideration of potential underlying etiologies. Some seizures might begin with **auras,** which are sensory experiences reported by the patient and are not observed externally.

Motor seizures can be **tonic, clonic, myoclonic, atonic,** or **astatic. Astatic** seizures often follow myoclonic seizures and cause a very momentary loss of tone with a sudden fall. **Atonic** seizures, on the other hand, are usually longer, and the loss of tone often develops more slowly. Sometimes it is difficult to distinguish among tonic, myoclonic, atonic, or astatic seizures based on the history alone when the family reports only that the patient falls; in such cases, the seizure may be described as a **drop attack.** Loss of tone or myoclonus in only the neck muscles results in a milder seizure referred to as a **head drop.** Tonic, clonic, tonic–clonic, myoclonic, and atonic seizures can be focal (including one limb or one side only), focal with secondary generalization, or primary generalized. Epileptic spasms, or **axial spasms** (these terms being preferred over infantile spasms because the spasms can occur beyond infancy), consist of flexion or extension of the truncal and extremity musculature that is sustained for 1-2 sec, shorter than the duration seen in tonic seizures, which last longer than 2 sec. Focal motor clonic and/or myoclonic seizures that persist for days, months, or even longer are termed **epilepsia partialis continua.**

Absence seizures are generalized seizures consisting of staring, unresponsiveness, and eye flutter lasting usually for a few seconds. **Typical absences** are associated with 3-Hz spike-and–slow-wave discharges and with childhood absence epilepsy, which has a good prognosis. **Atypical absences** are associated with 1- to 2-Hz spike-and–slow-wave discharges, and with head atonia and myoclonus during the seizures. They occur in **Lennox-Gastaut syndrome** and similar syndromes, which have a poor prognosis. **Juvenile absences** are similar to typical absences but are associated with 4- to 5-Hz spike-and–slow-wave discharges and often occur in juvenile myoclonic epilepsy. Seizure type and other EEG and clinical manifestations determine the type of **epilepsy syndrome** with which a particular patient is afflicted (see Tables 611.2 and 611.3 ; see also Chapters 611.3 and 611.4).

A family history of certain forms of epilepsy, such as benign familial neonatal seizures, can suggest the specific epilepsy syndrome. More often, however, different members of a family with a positive history of epilepsy have different types of epilepsy. Specific findings on physical exam may point to an underlying disorder causing the seizure, such as tuberous sclerosis, Sturge-Weber syndrome, neurofibromatosis, or other brain malformations.

Long-Term Approach to the Patient and Additional Testing

The approach to the patient with epilepsy is based on the diagnostic scheme proposed by the ILAE Task Force on Classification and Terminology and presented in Table 611.4 . Most epilepsy syndromes are potentially caused by any one of multiple underlying or still undetermined etiologies. However, in addition, there are many epilepsy syndromes that are associated with specific gene mutations (see Table 611.3 and Fig. 611.1). Different mutations of the same gene can result in different epilepsy syndromes, and mutations of different genes can cause the same epilepsy syndrome phenotype. The clinical use of gene testing in the diagnosis and management of childhood epilepsy has been limited to patients manifesting specific underlying malformational, metabolic, or degenerative disorders; patients with severe named epilepsy syndromes (such as West and Dravet syndromes and progressive myoclonic epilepsies); and patients with syndromes of mendelian inheritance (see Tables 611.2 and 611.3).

In patients with drug-resistant epilepsy, or in infants with new-onset epilepsy in whom the initial testing did not reveal an underlying etiology, a full metabolic workup, including amino acids, organic acids, biotinidase, and CSF studies, is needed. Additional testing can include, depending on the case, some or most of the following:

1. Measurement of serum lactate, pyruvate, acyl carnitine profile, creatine, very-long-chain fatty acids, and guanidino-acetic acid.
2. Blood and serum sometimes need to be tested for white blood cell lysosomal enzymes, serum coenzyme Q levels, and serum copper and ceruloplasmin levels (for Menkes syndrome).
3. Serum immune isoelectric focusing is performed for carbohydrate-deficient transferrin.
4. CSF glucose testing looks for glucose transporter deficiency, and the CSF can be examined for cells and proteins (for parainfectious and

postinfectious syndromes, and for Aicardi-Goutières syndrome, which also shows cerebral calcifications and has a specific gene defect test available).

5. Other laboratory studies include CSF immunoglobulin (Ig) G index, NMDA (*N* -methyl-D -aspartate) receptor, and other autoimmune encephalitis–associated antibodies, as well as measles titers in serum and CSF.
6. CSF tests can also confirm, with the appropriate clinical setup, the diagnosis of cerebral folate deficiency, pyridoxine dependency, pyridoxal-5-phosphate dependency, mitochondrial disorders, nonketotic hyperglycinemia, neopterin/biopterin metabolism disorders, adenylosuccinate lyase deficiency, and neurotransmitter deficiencies. In infants who do not respond immediately to antiepileptic therapy, vitamin B_6 (100 mg intravenously) is given as a therapeutic trial to help diagnose pyridoxine-responsive seizures, with precautions to guard against possible apnea. The trial is best done with continuous EEG monitoring, including a preadministration baseline recording period. Prior to the vitamin B_6 trial, a pipecolic acid level and serum, urine, or CSF α-aminoadipic acid semialdehyde levels should be drawn because they are often elevated in this rare syndrome and the therapeutic trial result may not be definitive. Some patients are pyridoxal phosphate, rather than pyridoxine, dependent. Also, patients with cerebral folate deficiency can have intractable seizures. Thus trials of pyridoxal phosphate given orally (up to 50 mg/kg/day given every 6 hr) and folinic acid (2.5-5 mg twice a day, if needed; can titrate up to a maximum dose of 8 mg/kg/day) over several weeks can help diagnose these rare disorders while one is waiting for the definitive diagnosis from CSF or genetic testing. Certain EEG changes such as continuous spike-and–slow-wave seizure activity and burst-suppression patterns may also suggest these vitamin-responsive syndromes.
7. Urine may also need to be tested for urinary sulfites indicating molybdenum cofactor deficiency and for oligosaccharides and mucopolysaccharides. MR spectroscopy can be performed for lactate and creatine peaks to rule out mitochondrial disease and creatine transporter deficiency.
8. Gene testing looks for specific disorders that can manifest with seizures, including *SCN1A* mutations in Dravet syndrome; *ARX* gene for West

syndrome in males; *MECP2*, *CDKL5*, and protocadherin 19 for Rett syndrome and similar presentations; syntaxin-binding protein for Ohtahara syndrome; and polymerase G for West syndrome and other seizures in infants. Gene testing can also be performed for other dysmorphic or metabolic syndromes.

9. Muscle biopsy can be performed for mitochondrial enzymes and coenzyme Q10 levels, and skin biopsy for inclusion bodies seen in neuronal ceroid lipofuscinosis and Lafora body disease is sometimes needed.
10. Genetic panels are available that include multiple genes that can cause epilepsy at specific ages; whole-exome sequencing is also available. These can be helpful in selected patients. The increasing availability of gene panels, particularly ones that can test for amenably treatable conditions such as vitamin B_6 -dependent epilepsy, and the quick turnaround time for these test results are currently starting to replace and obviate the need for many of the tests listed above in points 1-9.
11. MRI should also be performed to identify congenital disorders (cortical dysplasias, lissencephaly, schizencephaly), calcifications, focal lesions (basal ganglia), and myelinization disorders (acute disseminated encephalomyelitis [ADEM], leukodystrophies). MRI may identify specific disorders such as posterior reversible encephalopathy syndrome (PRES), stroke (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), Rasmussen encephalitis, tumors, cerebral edema, hemorrhage, or venous thrombosis. It should also be noted that seizures alone may cause reversible MRI abnormalities; these may include transient gray matter and subcortical white matter signals or transient hippocampal and temporal lobe abnormalities.

Most patients do not require a workup anywhere near the above-described extensive testing. The pace and extent of the workup must depend critically upon the clinical epileptic and nonepileptic features, the family and antecedent personal history of the patient, the medication responsiveness of the seizures, the likelihood of identifying a treatable condition, and the wishes and need of the family to assign a specific diagnosis to the child's illness.

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611.3

Focal Seizures and Related Epilepsy Syndromes

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Keywords

focal seizures with preserved awareness
focal seizures with impaired awareness
secondary generalized seizures
(Todd) paralysis
aura
automatisms
benign childhood epilepsy with centrotemporal spikes (BECTS)
atypical BECTS
benign epilepsy with occipital spikes
Panayiotopoulos type
Gastaut type
infantile familial convulsion syndromes
benign infantile nonfamilial syndromes
autosomal dominant frontal lobe epilepsy
epilepsy of infancy with migrating focal seizures (EIMFS)
malignant migrating partial seizures of infancy
pseudo–Lennox-Gastaut syndrome
mesial or medial temporal sclerosis
Landau-Kleffner epileptic aphasia syndrome
syndrome of continuous spike waves in slow-wave sleep
Rasmussen encephalitis

Focal (previously called *partial*) seizures account for approximately 40% of seizures in children and can be divided into **focal seizures with preserved awareness** (previously called *simple partial seizures*), in which consciousness is not impaired, and **focal seizures with impaired awareness** (previously called *complex partial seizures*), in which consciousness is affected.

Focal seizures with preserved or impaired awareness can each occur in isolation, one can temporally lead to the other (usually from preserved to impaired awareness), and/or each can progress into **secondary generalized seizures,** called focal to bilateral tonic-clonic seizures, although less commonly the secondary generalized seizure may be tonic, clonic, or atonic.

Focal Seizures With Preserved Awareness

These can take the form of sensory seizures (auras, called *focal aware seizures*) or brief motor seizures, the specific nature of which gives clues as to the location of the seizure focus. Brief motor seizures are the most common and include focal tonic, clonic, or atonic seizures. Often there is a motor (Jacksonian) march from face to arm to leg, adversive head and eye movements to the contralateral side, or postictal **(Todd) paralysis** that can last minutes or hours, and sometimes longer. Unlike tics, motor seizures are not under partial voluntary control; seizures are more often stereotyped and are less likely than tics to manifest different types in a given patient.

Focal Seizures With Impaired Awareness

These seizures usually last 1-2 min and are often preceded by an **aura,** such as a rising abdominal feeling, déjà vu or déjà vécu, a sense of fear, complex visual hallucinations, micropsia or macropsia (temporal lobe), generalized difficult-to-characterize sensations (frontal lobe), focal sensations (parietal lobe), or simple visual experiences (occipital lobe). Children younger than 7 yr old are less likely than older children to report auras, but parents might observe unusual preictal behaviors that suggest the experiencing of auras. Subsequent manifestations consist of decreased responsiveness, staring, looking around seemingly purposelessly, and automatisms. **Automatisms** are automatic semipurposeful movements of the mouth (oral, alimentary such as chewing) or of the extremities (manual, such as manipulating the sheets; leg automatisms such as shuffling, walking). Often there is salivation, dilation of the pupils, and flushing or color change. The patient might appear to react to some of the stimulation around him or her but does not later recall the epileptic event. At times, walking and/or marked limb flailing and agitation occur, particularly in patients with frontal lobe seizures. Frontal lobe seizures often occur at night and can be very numerous and brief, but other complex partial seizures from other areas in the brain can also occur at night. There is often contralateral dystonic posturing of the arm and, in some cases, unilateral or bilateral tonic arm stiffening. Some seizures have these manifestations with minimal or no automatisms. Others consist of altered consciousness with contralateral motor, usually clonic, manifestations. After the seizure, the patient can have postictal automatisms, sleepiness, and/or other transient focal deficits such as weakness (Todd paralysis) or aphasia.

Focal to Bilateral Tonic-Clonic Seizures

These can either start with generalized clinical phenomena (from rapid spread of the discharge from the initial focus) or as focal seizures with subsequent clinical generalization. There is often adversive eye and head deviation to the side contralateral to the side of the seizure focus, followed by generalized tonic, clonic, or tonic-clonic activity. Tongue biting, urinary and stool incontinence, vomiting with risk of aspiration, and cyanosis are common. Fractures of the vertebrae or humerus are rare complications. Most such seizures last 1-2 min. Focal tonic or focal to bilateral tonic-clonic seizures often manifest as adversive head deviation to the contralateral side, fencing, hemi- or full figure-of-four arm, and/or Statue of Liberty postures. These postures usually suggest a frontal origin and, when awareness is preserved during them, favor that the seizure originated from the medial frontal supplementary motor area.

EEG in patients with focal/partial seizures usually shows focal spikes or sharp waves in the lobe where the seizure originates. A sleep-deprived EEG with recording during sleep increases the diagnostic yield and is advisable in all patients whenever possible (Fig. 611.3). Despite that, approximately 15% of children with epilepsy initially have normal EEGs because the discharges are relatively infrequent or the focus is deep. If repeating the test does not detect paroxysmal findings, longer recordings in the laboratory or using ambulatory EEG or even inpatient 24-hr video EEG monitoring may be helpful. The latter is particularly helpful if the seizures are frequent enough, because it then can allow visualization of the clinical events and the corresponding EEG tracing.

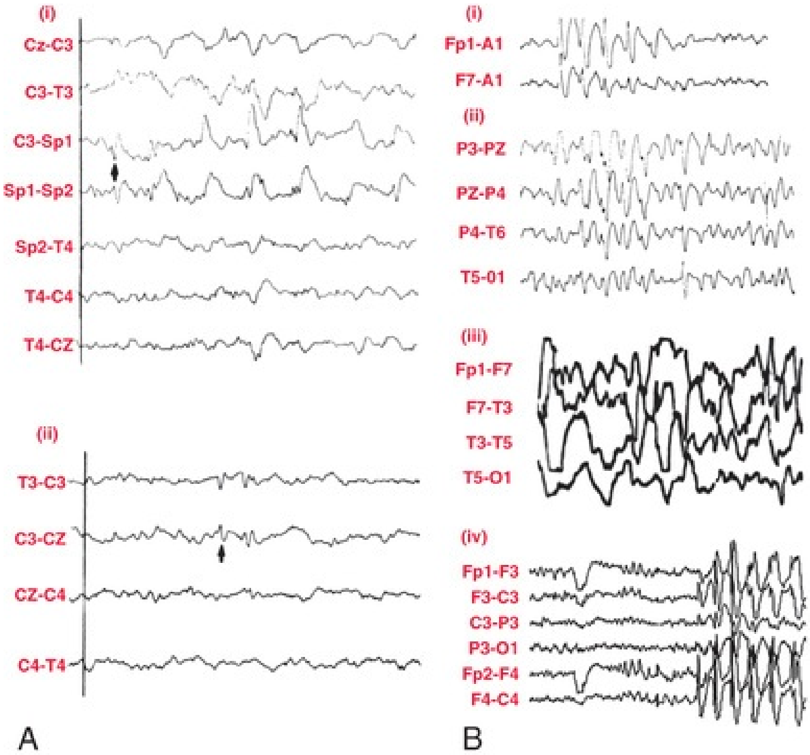
(i)
Cz-C3
C3-T3
C3-Sp1
Sp1-Sp2
Sp2-T4
T4-C4
T4-CZ
(ii)
T3-C3
C3-CZ
CZ-C4
C4-T4
A
(i)
Fp1-A1
F7-A1
(ii)
P3-PZ
PZ-P4
P4-T6
T5-01
(iii)
Fp1-F7
F7-T3
T3-T5
T5-O1
(iv)
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
B

FIG. 611.3 **A,** Representative EEG associated with partial seizures: (i) Spike discharges from the left temporal lobe *(arrow)* in a patient with complex partial seizures caused by mesial temporal sclerosis; (ii) left central-parietal spikes *(arrow)* characteristic of benign partial epilepsy with centrotemporal spikes. **B,** Representative EEGs associated with generalized seizures: (i) 3/sec spike-and-wave discharge of absence seizures with normal background activity; (ii) 1-2/sec interictal slow spike waves in a patient with Lennox-Gastaut syndrome; (iii) hypsarrhythmia with irregular multifocal high-voltage spike-and-wave activity with a chaotic high-voltage slow background; (iv) juvenile myoclonic epilepsy EEG showing 4-6/sec spike and waves enhanced by photic stimulation.

Brain imaging is critical in patients with focal seizures. In general, MRI is preferable to CT, which misses subtle but, occasionally, potentially clinically significant lesions. MRI can show pathologies such as changes as a result of previous strokes or hypoxic injury, malformations, medial temporal sclerosis, arteriovenous malformations, inflammatory pathologies, or tumors (Fig. 611.4).

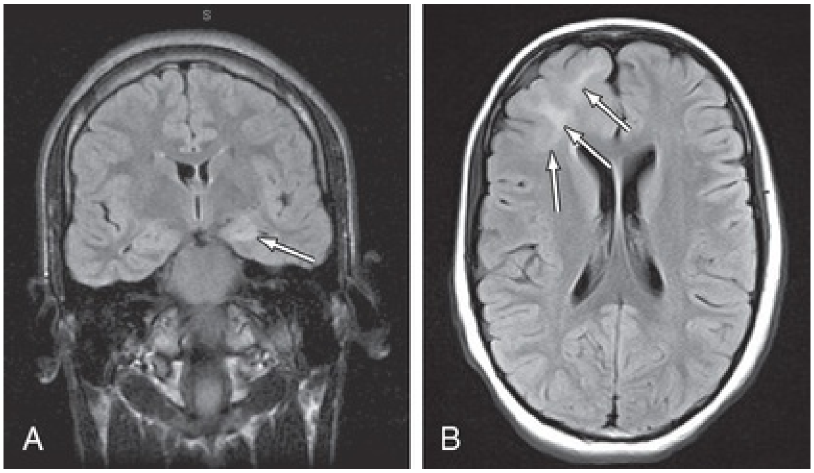

FIG. 611.4 **A,** Coronal fluid-attenuated inversion-recovery (FLAIR) MRI scan of a 13 yr old with intractable seizures and mesial temporal sclerosis (MTS). The *arrow* points at the hippocampus with the high-intensity signal characteristic of MTS. **B,** Axial FLAIR MRI of a 7 yr old with intractable seizures and right frontal cortical dysplasia. The *arrows* point at the high-intensity signal corresponding to the dysplasia. (A, from Lee JYK, Adelson PD: Neurosurgical management of pediatric epilepsy, Pediatr Clin North Am 51:441-456, 2004.)

Benign Epilepsy Syndromes With Focal Seizures

The most common such syndrome is **benign childhood epilepsy with centrotemporal spikes (BECTS),** which typically starts during childhood (ages 3-10 yr) and is outgrown by adolescence. The child typically wakes up at night due to a focal seizure with preserved awareness causing buccal and throat tingling and tonic or clonic contractions of one side of the face, with drooling and inability to speak but with preserved consciousness and comprehension. Focal seizures with impaired awareness and secondary generalized seizures can also occur. EEG shows typical wide-based centrotemporal spikes that are markedly increased in frequency during drowsiness and sleep. MRI is normal. Patients respond very well to antiepileptic drugs (AEDs) such as oxcarbazepine and carbamazepine. In some patients who only have rare and mild seizures, treatment might not be needed. **Atypical BECTS** is a less common variant of the disorder characterized by often a younger age of onset, multiple seizure types including drop attacks, atypical EEG patterns including secondary bilateral synchrony, and/or other comorbidities such as developmental delay.

Benign epilepsy with occipital spikes can occur in early childhood (**Panayiotopoulos type**) and manifests with focal seizures with impaired awareness and with ictal vomiting, or they appear in later childhood (**Gastaut type**) as focal seizures with impaired awareness, visual auras, and migraine headaches that occur independently or postictally (epilepsy–migraine sequence). Both are typically outgrown in a few years.

In infants, several less common **benign infantile familial convulsion syndromes** have been reported. For some of these, the corresponding gene mutation and its function are known (see Tables 611.2 and 611.3). A number of **benign infantile nonfamilial syndromes** have been reported, including focal seizures with impaired awareness with temporal foci, focal to bilateral tonic-clonic seizures with variable foci, tonic seizures with midline foci, and focal seizures in association with mild gastroenteritis. All of these have a good prognosis and respond to treatment promptly; often, only short-term therapy (e.g., 6 mo), if any therapy, is needed. **Nocturnal autosomal dominant frontal lobe epilepsy** has been linked to acetylcholine-receptor and to *KCNT1* gene mutations. It manifests with nocturnal seizures with dystonic posturing, agitation, screaming, and kicking that respond promptly to carbamazepine. Several other less frequent familial benign epilepsy syndromes with different localizations have also been described, some of which occur exclusively or predominantly in adults.

Severe Epilepsy Syndromes With Focal Seizures

Symptomatic structural/metabolic epilepsy secondary to focal brain lesions has a higher chance of being severe and refractory to therapy than genetic (idiopathic) epilepsy. It is important to note that many patients with focal lesions, for example, old strokes or brain tumors, either never have seizures or have well-controlled epilepsy. In infants, *drug-resistant epilepsy* with focal seizures is often caused by severe metabolic problems, hypoxic-ischemic injury, or congenital malformations. In addition, in this age-group, a syndrome of multifocal severe partial seizures with progressive mental regression and cerebral atrophy called **epilepsy of infancy with migrating focal seizures** (EIMFS; previously called malignant migrating partial seizures of infancy) has been described. Some cases of EIMFS are secondary to mutations in the calcium-sensitive potassium channel

KCNT1. Brain malformations causing focal epilepsy include focal cortical dysplasia, hemimegalencephaly, Sturge-Weber cutaneous lesion, tuberous sclerosis, and congenital tumors such as ganglioglioma and dysembryoplastic neuroepithelial tumors, as well as others. The intractable seizures can be focal seizures with or without impaired awareness, focal to bilateral tonic-clonic seizures, or combinations thereof. If secondary generalized seizures predominate and take the form of absence-like seizures and drop attacks, the clinical picture can mimic the generalized epilepsy syndrome of Lennox-Gastaut syndrome and has been termed by some **pseudo–Lennox-Gastaut syndrome.**

Temporal lobe epilepsy can be caused by any temporal lobe lesion. A common cause is **mesial** (also termed **medial**) **temporal sclerosis,** a condition often preceded by febrile seizures and, rarely, genetic in origin. Pathologically, these patients have atrophy, gliosis or cortical dysplasia of the hippocampus, and, in some, these conditions of the amygdala. Some patients have mutations on the *SUCO* gene. Medial temporal lobe epilepsy is the most common cause of surgically remediable partial epilepsy in adolescents and adults. Occasionally, in patients with other structural or genetic focal or generalized epilepsies, the focal discharges are so continuous that they cause an epileptic encephalopathy. Activation of temporal discharges in sleep can lead to loss of speech and verbal auditory agnosia **(Landau-Kleffner epileptic aphasia syndrome).** Activation of secondary generalized and at times focal discharges in sleep leads to more global delay secondary to the **syndrome of continuous spike waves in slow-wave sleep** (>85% of the slow-wave sleep recording is dominated by discharges).

The syndrome of **Rasmussen encephalitis** is a form of chronic encephalitis that manifests with unilateral intractable partial seizures, epilepsia partialis continua, and progressive hemiparesis of the affected side, with progressive atrophy of the contralateral hemisphere. The etiology is usually unknown, although autoimmune etiologies have been hypothesized.

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611.4

Generalized Seizures and Related Epilepsy Syndromes

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Keywords

Jeavons syndrome
myoclonic absences
atypical absence seizures
juvenile absence seizures
genetic generalized tonic-clonic seizures
childhood absence epilepsy
benign myoclonic epilepsy of infancy
febrile seizures plus syndrome
juvenile myoclonic epilepsy (Janz syndrome)
photoparoxysmal epilepsy
reflex
stimulus-provoked epilepsy
early myoclonic infantile encephalopathy
early infantile epileptic encephalopathy (Ohtahara syndrome)
myoclonic epilepsy of infancy (Dravet syndrome)
West syndrome
hypsarrhythmia
Lennox-Gastaut syndrome
myoclonic astatic epilepsy (Doose syndrome)
nodding syndrome

progressive myoclonic epilepsies
type I or Unverricht-Lundborg disease
type II or Lafora body disease
myoclonic epilepsy with ragged red fibers (MERRF)
sialidosis type I
neuronal ceroid lipofuscinoses
type 3 neuronopathic Gaucher disease
dentatorubral-pallidoluysian atrophy
action myoclonus–renal failure syndrome
progressive myoclonus epilepsy–ataxia syndrome
North Sea progressive myoclonic epilepsy
myoclonic encephalopathy in nonprogressive disorders
Landau-Kleffner syndrome
continuous spike waves in slow-wave sleep (CSWS)
electrical status epilepticus in sleep (ESES)
amenably treatable metabolic epilepsies
pyridoxine-dependent epilepsy
pyridoxal phosphate–responsive neonatal epileptic encephalopathy
folinic acid–responsive seizures
cerebral folate deficiency
tetrahydrobiopterin deficiencies
creatine deficiency syndromes
biotinidase deficiency
developmental delay
epilepsy
and neonatal diabetes
hyperinsulinism–hyperammonemia syndrome
GLUT-1 deficiency syndrome
thiamine transporter mutations with acute basal ganglia disease
riboflavin transporter deficiency

Absence Seizures

Typical absence seizures usually start at 5-8 yr of age and are often, due to their brevity, overlooked by parents for many months even though they can occur up to hundreds of times per day. Unlike focal seizures with impaired awareness they do not have an aura, usually last for only a few seconds, and are accompanied by eyelid flutter or upward rolling of the eyes but typically not by the usually more florid automatisms seen in focal seizures with impaired awareness (absence seizures can have simple automatisms such as lip smacking or picking at clothing, and the head can very minimally fall forward). Absence seizures do not have a postictal period and are characterized by immediate resumption of what the patient was doing before the seizure. Hyperventilation for 3-5 min can precipitate the seizures and the accompanying 3-Hz spike-and–slow-wave discharges. The presence of eye closure eyelid myoclonia **(Jeavons syndrome)** and periorbital, perioral, or limb myoclonic jerks (the latter called **myoclonic absences**) with the typical absence seizures usually predicts difficulty in controlling the seizures with medications. Early-onset absence seizures (<4 yr of age) or drug resistance should trigger evaluation for a glucose transporter defect, which is often associated with low CSF glucose levels and an abnormal sequencing test of the transporter gene.

Atypical absence seizures have associated myoclonic components and tone changes of the head (head drop) and body and are also usually more difficult to treat. They are precipitated by drowsiness and are usually accompanied by 1- to 2-Hz spike-and–slow-wave discharges.

Juvenile absence seizures are similar to typical absences but occur at a later age and are accompanied by 4- to 6-Hz spike-and–slow-wave and polyspike-and–slow-wave discharges. These are usually associated with juvenile myoclonic epilepsy (see Benign Generalized Epilepsies).

Generalized Motor Seizures

The most common generalized motor seizures are generalized tonic-clonic seizures that can be either primarily generalized (bilateral) or focal to bilateral tonic-clonic (as described in Chapter 611.3) from a unilateral focus. If there is no partial component, the seizure usually starts with loss of consciousness and, at times, with a sudden cry, upward rolling of the eyes, and a generalized tonic contraction with falling, apnea, and cyanosis. In some, a clonic or myoclonic component precedes the tonic stiffening. The tonic phase is followed by a clonic phase that, as the seizure progresses, shows slowing of the rhythmic contractions until the seizure stops, usually 1-2 min later. Incontinence and a postictal period often follow. The latter usually lasts for a few minutes up to several hours with semicoma or obtundation and postictal sleepiness, weakness, ataxia, hyper- or hyporeflexia, and headaches. There is a risk of aspiration and injury. First aid measures include positioning the patient on his or her side, clearing the mouth if it is open, loosening tight clothes or jewelry, and gently extending the head and, if possible, insertion of an airway by a trained professional. The mouth should not be forced open with a foreign object (this could dislodge teeth, causing aspiration) or with a finger in the mouth (this could result in serious injury to the examiner's finger). Many patients have single **genetic generalized tonic-clonic seizures** that may be associated with intercurrent illness or with a cause that cannot be ascertained (see Chapter 611.2). Generalized tonic, atonic, and astatic seizures often occur in severe generalized pediatric epilepsies. Generalized myoclonic seizures can occur in either benign or difficult-to-control generalized epilepsies (see Benign Generalized Epilepsies and Severe Generalized Epilepsies).

Benign Generalized Epilepsies

Childhood absence epilepsy typically starts in mid-childhood, and most patients outgrow it before adulthood. Approximately 25% of patients also develop generalized tonic-clonic seizures, half before and half after the onset of absences. **Benign myoclonic epilepsy of infancy** consists of the onset of myoclonic and other seizures during the first year of life, with generalized 3-Hz spike-and–slow-wave discharges. Often, it is initially difficult to distinguish this type from more severe syndromes, but follow-up clarifies the diagnosis. **Febrile seizures plus syndrome** manifests febrile seizures and multiple types of generalized seizures in multiple family members, and at times different individuals within the same family manifest different generalized and febrile seizure types (see Chapter 611.1).

Juvenile myoclonic epilepsy (Janz syndrome) is the most common generalized epilepsy in young adults, accounting for 5% of all epilepsies. It has been linked to mutations in many genes, including *CACNB4; CLNC2; EJM2, 3, 4, 5, 6, 7, 9; GABRA1; GABRD;* and *Myoclonin1/EFHC1* (see Table 611.3). Typically, it starts in early adolescence with one or more of the following manifestations: myoclonic jerks in the morning, often causing the patient to drop things; generalized tonic-clonic or clonic-tonic-clonic seizures upon awakening; and juvenile absences. Sleep deprivation, alcohol (in older patients), and photic stimulation, or, rarely, certain cognitive activities can act as precipitants. The EEG usually shows generalized 4- to 5-Hz polyspike-and–slow-wave discharges. There are other forms of generalized epilepsies such as **photoparoxysmal**

epilepsy, in which generalized tonic-clonic, absence, or myoclonic generalized seizures are precipitated by photic stimuli such as strobe lights, flipping through TV channels, and viewing video games. Other forms of **reflex** (i.e., **stimulus-provoked**) **epilepsy** can occur; associated seizures are usually generalized, although some may be focal (see Chapter 611.9).

Severe Generalized Epilepsies

Severe generalized epilepsies are associated with intractable seizures and developmental delay. **Early myoclonic infantile encephalopathy** starts during the first 2 mo of life with severe myoclonic seizures and a burst suppression pattern on EEG. It is usually caused by inborn errors of metabolism such as nonketotic hyperglycinemia. **Early infantile epileptic encephalopathy (Ohtahara syndrome)** has a similar age of onset and EEG but manifests as tonic seizures and is usually caused by brain malformations or syntaxin-binding protein 1 mutations. The term *early infantile epileptic encephalopathy* (EIEE) has also been applied, mostly by genetics experts, to the increasing number of other genetic epileptic encephalopathies and developmental epileptic encephalopathies that are associated with an increasing number of specific genes with pathogenic mutations (see Table 611.3); these may or may not manifest as Ohtahara syndrome, but all share the characteristic of early-onset epileptic encephalopathy. For example, EIEE type 4 is Ohtahara syndrome caused by syntaxin-binding protein 1 mutations. Severe **myoclonic epilepsy of infancy (Dravet syndrome)** starts as focal febrile status epilepticus or focal febrile seizures and later manifests as myoclonic and other seizure types (see Chapter 611.1).

West syndrome starts between the ages of 2 and 12 mo and consists of a triad of infantile epileptic spasms that usually occur in clusters (particularly in drowsiness or upon arousal), developmental regression, and a typical EEG picture called **hypsarrhythmia** (see Fig. 611.3). Hypsarrhythmia is a high-voltage, slow, chaotic background with multifocal spikes. Patients with cryptogenic (sometimes called idiopathic, now referred to as unknown etiology) West syndrome have normal development before onset, whereas patients with symptomatic West syndrome have preceding developmental delay owing to perinatal encephalopathies, malformations, underlying metabolic disorders, or other etiologies (see Chapter 611.2). In males, West syndrome can also be caused by *ARX* gene mutations (often associated with ambiguous genitalia and cortical migration abnormalities). West syndrome, especially in cases of unknown etiology (cryptogenic cases, i.e., cases that are not symptomatic of a metabolic or structural brain disorder), is a medical emergency because a delay in diagnosis of 3 wk or longer can affect the long-term prognosis. The spasms are often overlooked by parents and by physicians, being mistaken for startles caused by colic or other benign paroxysmal syndromes (see Chapter 612).

Lennox-Gastaut syndrome typically starts between the ages of 2 and 10 yr and consists of a triad of developmental delay, multiple seizure types that as a rule include atypical absences, and myoclonic, astatic, and tonic seizures, as well as specific EEG abnormalities. The tonic seizures occur either in wakefulness (causing falls and injuries) or also, typically, in sleep. The third component is the EEG findings (see Fig. 611.3): 1- to 2-Hz spike and slow waves, polyspike bursts in sleep, and a slow background in wakefulness. Patients commonly have tonic, myoclonic, atonic, and other seizure types causing falls and are difficult to control. Most are left with long-term cognitive impairment and intractable seizures despite multiple therapies. Some, but not all, patients start with Ohtahara syndrome, develop West syndrome, and then progress to Lennox-Gastaut syndrome. **Myoclonic astatic epilepsy (Doose syndrome)** is a syndrome similar to, but milder than, Lennox-Gastaut syndrome that usually does not have tonic seizures or polyspike bursts in sleep. The prognosis is more favorable than that for Lennox-Gastaut syndrome. Another syndrome characterized by atonic seizures causing head nodding as well as tonic, clonic, and stimulus-sensitive seizures is the **nodding syndrome,** which is seen in some African countries and is often associated with encephalopathy, stunted growth, and variable degrees of cognitive deficits. The underlying etiology is a likely autoimmune reaction to the parasitic worm *Onchocerca volvulus.*

Progressive myoclonic epilepsies are a group of epilepsies characterized by progressive dementia and worsening myoclonic and other seizures. **Type I,** or **Unverricht-Lundborg disease,** is caused by mutations in the cystatin B *(CSTB)* gene, is more slowly progressive than the other types, and usually starts in adolescence. **Type II,** or **Lafora body disease,** can have an early childhood onset but usually starts in adolescence, is more quickly progressive, and is usually fatal within the 2nd or 3rd decade. It can be associated with photosensitivity, manifests periodic acid–Schiff–positive Lafora inclusions on muscle or skin biopsy (in eccrine sweat gland cells), and has been shown to be caused by laforin *(EPM2A)* or malin *(NHLRC1/EPM2B)* gene mutations. Other causes of progressive myoclonic epilepsy include **myoclonic epilepsy with**

ragged red fibers (**MERRF** , caused by various mutations in mitochondrial DNA), **sialidosis type I** (caused by mutations in the *NEU1* gene), **neuronal ceroid lipofuscinoses** (lysosomal storage disorders caused by mutations in the *CLN1-CLN14* genes), **type 3 neuronopathic Gaucher disease** (caused by lysosomal glucocerebrosidase deficiency), **dentatorubral-pallidoluysian atrophy** (caused by unstable expansion of trinucleotide repeats on the *ATN1* gene), **action myoclonus–renal failure syndrome** (a.k.a. EPM4, caused by mutations in the *SCARB2* gene), **progressive myoclonus epilepsy–ataxia syndrome** (a.k.a. EPM5, caused by mutations in the *PRICKLE1* gene), and **North Sea progressive myoclonic epilepsy** (a.k.a. EPM6, caused by mutations in the *GOSR2* gene).

Myoclonic encephalopathy in nonprogressive disorders is an epileptic encephalopathy that occurs in some congenital disorders affecting the brain, such as Angelman syndrome, and consists of almost continuous and difficult-to-treat myoclonic and, at times, other seizures.

Landau-Kleffner syndrome is a rare condition of presumed autoimmune but sometimes also of genetic (*GRIN2A* mutations) etiology. It is characterized by loss of language skills and by verbal auditory agnosia in a previously normal child. At least 70% have associated clinical seizures, but some do not. The seizures when they occur are of several types, including focal with preserved awareness, focal to bilateral tonic-clonic, atypical absence, focal with impaired awareness, and occasionally myoclonic seizures. High-amplitude spike-and-wave discharges predominate and tend to be bitemporal. In the later evolutionary stages of the condition, the EEG findings may be normal. The spike discharges are always more apparent during non–rapid eye movement sleep; thus, a child in whom Landau-Kleffner syndrome is suspected should have an EEG during sleep. CT and MRI studies typically yield normal results. In the related but clinically distinct epilepsy syndrome with **continuous spike waves in slow-wave sleep (CSWS)** , the discharges occur in > 85% of the slow-wave sleep, a finding termed **electrical status epilepticus in sleep (ESES).** ESES can also occur in Landau-Kleffner syndrome, but in CSWS the discharges are usually frontal or generalized and the delays usually global. The approach to and therapy for the two syndromes are similar. Valproic acid is often the anticonvulsant that is used first to treat the clinical seizures and may help the aphasia. Some children respond to clobazam, to the combination of valproic acid and clobazam, or to levetiracetam. For therapy of the aphasia, nocturnal diazepam (0.2-0.5 mg/kg orally at bedtime for several months) is often used as first- or second-line therapy, as are oral steroids. Oral prednisone is started at 2 mg/kg/day for 1-2 mo, then weaned over a period of 1-3 mo. Alternatively, monthly infusions of high-dose intravenous methylprednisolone have been used instead of oral steroids. Long-term therapy is often needed irrespective of which drug(s) elicit a patient response. If the seizures and aphasia persist after diazepam and steroid trials, then a course of intravenous immunoglobulins should be considered because many patients can respond to that. It is imperative to initiate speech therapy and maintain it for several years, because improvement in language function occurs over a prolonged period.

Amenably treatable metabolic epilepsies are well recognized. **Pyridoxine-dependent epilepsy** typically presents with a neonatal or infantile (and rarely childhood) onset of encephalopathy with, at times, reports of increased fetal movements (seizures) in utero. There are recurrent focal motor seizures, generalized tonic seizures, and myoclonus. Seizures progress to status epilepticus if no pyridoxine is used. Diagnosis is confirmed by the presence of elevated plasma, urine, and CSF α-aminoadipic semialdehyde and elevated plasma and CSF pipecolic acid levels. The presence of either homozygous or compound heterozygous mutations in *ALDH7A1* alleles (which encode the protein antiquitin) confirms the diagnosis. The use of pyridoxine 100 mg daily orally (higher doses, up to 500-600 mg/day, have been used) or intravenously helps stop the seizures. Mutations of the *PROSC* gene can also cause pyridoxine-dependent epilepsy. **Pyridoxal phosphate–responsive neonatal epileptic encephalopathy** (pyridox[am]ine 5′-phosphate oxidase [PNPO] deficiency) may present similarly in the absence of gastrointestinal symptoms. Diagnostically, there are reduced pyridoxal phosphate levels in the CSF with increased levels of CSF levodopa and 3-methoxytyrosine, along with decreased CSF homovanillic acid and 5-hydroxyindoleacetic acid. The EEG may show a burst suppression pattern. Treatment is by enteral administration of pyridoxal phosphate (up to 50 mg/kg/day every 6 hr). **Folinic acid–responsive seizures** may also present with neonatal or infantile epileptic encephalopathy and intractable seizures. Some of these patients have a diagnostic profile similar to that of pyridoxine-dependent epilepsy patients and their disorder is caused by the same gene mutations but responds to folinic acid supplementation in addition to pyridoxine. **Cerebral folate deficiency,** which also responds to high doses of folinic acid (1-3 mg/kg/day), may manifest with epilepsy, intellectual disability, developmental regression, dyskinesias, and autism. CSF 5-methyltetrahydrofolate levels are decreased, with normal plasma and red blood cell folate levels. There are usually mutations in the folate receptor *(FOLR1)* gene or blocking autoantibodies against membrane-associated folate receptors of the choroid plexus. **Tetrahydrobiopterin deficiencies** with or without hyperphenylalaninemia may present with epilepsies and symptoms resulting from deficiencies of dopamine (parkinsonism, dystonia), noradrenaline (axial hypotonia), serotonin (depression, insomnia, temperature changes), and folate (myelin formation, basal ganglia calcifications, and seizures). Treatment is by substitution therapy with tetrahydrobiopterin and neurotransmitter precursors started as early as possible. **Creatine deficiency syndromes** present typically with developmental delay, seizures, autistic features, and movement disorders and are diagnosed by gene sequencing and abnormal levels of urine creatine and guanidinoacetic acid and/or, particularly in the case of creatine transporter deficiency, an absent creatine peak on MR spectroscopy of the brain. Use of creatine monohydrate and dietary restrictions is helpful. **Biotinidase deficiency** presenting as developmental delay, seizures, ataxia, alopecia, and skin rash and often associated with intermittent metabolic acidosis and an organic acid profile of lactic and propionic acidemia, responds to the use of biotin. Serine biosynthesis defects with low serine levels in plasma or CSF amino acids often present with congenital microcephaly, intractable seizures, and psychomotor retardation and respond to supplemental serine and glycine. **Developmental delay, epilepsy, and neonatal diabetes** is caused by activating mutations in the adenosine triphosphate–sensitive potassium channels. Sulfonylurea drugs that block the potassium channel treat the neonatal diabetes and probably also favorably affect the central nervous system (CNS) symptoms and affect seizures. **Hyperinsulinism–hyperammonemia syndrome** is caused by activating mutations of the glutamate dehydrogenase encoded by the *GLUD1* gene. Patients present with hypoglycemic seizures after a protein-rich meal with hyperammonemia (ammonia levels 80-150 µmol/L). They are managed with a combination of protein restriction, AEDs, and diazoxide (a potassium channel agonist that inhibits insulin release). **GLUT-1 deficiency syndrome** classically presents with infantile-onset epilepsy, developmental delay, acquired microcephaly, and complex movement disorders. It causes impaired glucose transport to the brain that is typically diagnosed by genetic testing or a finding of low CSF lactate and CSF glucose, or low CSF-to–serum glucose ratios (<0.4). The manifestations of the disease are usually responsive to the ketogenic diet. **Thiamine transporter mutations with acute basal ganglia disease** often presents with accompanying seizures and is responsive to biotin and thiamine supplementation. **Riboflavin transporter deficiency** can also manifest as a seizure in addition to the usual symptoms of neuromuscular (polyneuropathy) weakness; it is treated with high-dose riboflavin supplementation.

611.5

Mechanisms of Seizures

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Keywords

underlying etiology
epileptogenesis
epileptic state of increased excitability
seizure-related neuronal injury

One can distinguish in the pathophysiology of epilepsy four distinct, often sequential, mechanistic processes. First is the **underlying etiology,** which is any pathology or pathologic process that can disrupt neuronal function and connectivity and that eventually leads to the second process **(epileptogenesis),** which makes the brain epileptic. Sometimes the underlying etiology can directly increase excitability even without the contribution of the downstream effects of epileptogenesis.

In some genetic epilepsies, a disorder in ion channel function and/or structure is the underlying etiology that leads to an aberrant signal transduction, which can cause seizures. These mutations can involve voltage-gated channels (Na^+ , K^+ , Ca^{2+} , Cl^- , and HCN [hydrogen cyanide]), ligand-gated channels (nicotinic acetylcholine and γ-aminobutyric acid A receptors [$GABA_A$]), or other proteins. For example, in Dravet syndrome, the loss-of-function mutation in the *SCN1A* gene, which encodes a voltage-gated sodium channel, causes decreased excitability in inhibitory GABAergic interneurons, leading to increased excitability and epilepsy. In human cortical dysplasia, the expression of the NR2B subunit of the NMDA receptor is increased, leading to excessive depolarizing currents. Gene mutations can also affect neurotransmitter function through other mechanisms. For example, *ARX* gene mutations can lead to dysfunction in GABAergic neurons and can cause X-linked West syndrome, among other epilepsies. In fragile X syndrome, it is hypothesized that mutations in the *FMR* gene cause enhanced glutamatergic signaling via the mGluR5 receptor. In Rett syndrome, mutations in the *MECP2* gene lead to increased NMDA receptor expression, which can cause epilepsy and other symptoms associated with the disorder.

In infantile spasms, animal models suggest that increases in stress-related corticotropin-releasing hormone, sodium channel blockade, and NMDA receptor stimulation are contributing mechanisms.

Autoimmune etiologies for epilepsy are becoming better recognized. Autoantibodies, sometimes generated due to cross-reactivity from a recent infection or secondary to a malignancy, can bind to extracellular receptors or other proteins expressed in neurons. This in turn leads to an inflammatory response and, in some cases, seizures. NMDA-receptor antibody encephalitis is probably the best-characterized autoimmune cause of epilepsy, but other epilepsy syndromes have been associated with autoantibodies targeting the voltage-gated potassium channel complex (anti-LGI2 and anti-CASPR2), GABA receptors (GABA-A and GABA-B), glycine receptors, and glutamic acid decarboxylase (GAD).

Second, **epileptogenesis** is the mechanism through which the brain, or part of it, turns epileptic. Lately, the role of large-scale molecular cell signaling pathways in epileptogenesis has also been implicated in the mechanisms leading to epilepsy, namely, the mammalian target of rapamycin (mTOR), the Ras/ERK, and repressor element 1 (RE1)–silencing transcription factor (REST) pathways. The mTOR pathway is seen in tuberous sclerosis, hemimegalencephaly, and cortical dysplasia–related epilepsies; the Ras/ERK pathway in a number of syndromes; and the REST pathway in epileptogenesis after acute neuronal injury. Repeat seizures lead through the above and other mechanisms to the rewiring of the brain and to long-term epilepsy.

The third process is the resultant **epileptic state of increased excitability** that is present in all patients irrespective of the underlying etiology or mechanism of epileptogenesis. In epileptogenic neurons, a dysregulation of glutamatergic excitation versus GABAergic inhibition occurs, which creates a seizure focus or network.

The fourth process is **seizure-related neuronal injury** as often is demonstrated by MRI in patients after prolonged status epilepticus or those with long-term drug-resistant epilepsy. For example, many patients show acute swelling in the hippocampus or other regions after status epilepticus and long-term hippocampal atrophy with sclerosis on MRI. There is evidence from surgically resected epileptic tissue that apoptotic pathways are activated in foci of drug-resistant epilepsy.

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611.6

Treatment of Seizures and Epilepsy

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Keywords

group 1 sports
group 2 sports
group 3 sports
sudden unexpected death in epilepsy (SUDEP)
drugs of first choice
West syndrome
infantile spasms
Lennox-Gastaut syndrome
Dravet syndrome
absence seizures
benign myoclonic epilepsies
severe myoclonic epilepsies
focal and focal to bilateral tonic-clonic seizures
potential for paradoxical seizure aggravation
drug-resistant epilepsy
vitamin-responsive epilepsies
biotin thiamine–responsive basal ganglia disease
epileptogenic zone
stereo-EEG
Wada test
functional MRI
focal resection
hemispherectomy

multiple subpial transection
corpus callosotomy
vagus nerve stimulation
responsive neurostimulation (RNS)
cardiocerebral channelopathies

Deciding on Long-Term Therapy

After a first seizure, if the risk of recurrence is low, as when the patient has a normal neurodevelopmental status, EEG, and MRI (risk ~ 20%), treatment is usually not started. If the patient has an abnormal EEG, MRI, development status, and/or neurologic exam and/or has a positive family history of epilepsy, the risk is higher, and often treatment is started. Other considerations are also important, such as motor vehicle driving status and type of employment in older patients or the parents' ability to deal with recurrences or AED drug therapy in children. The decision is therefore always individualized. All aspects of this decision-making process should be discussed with the family. Fig. 611.5 presents an overview of the approach to the treatment of seizures and epilepsy.

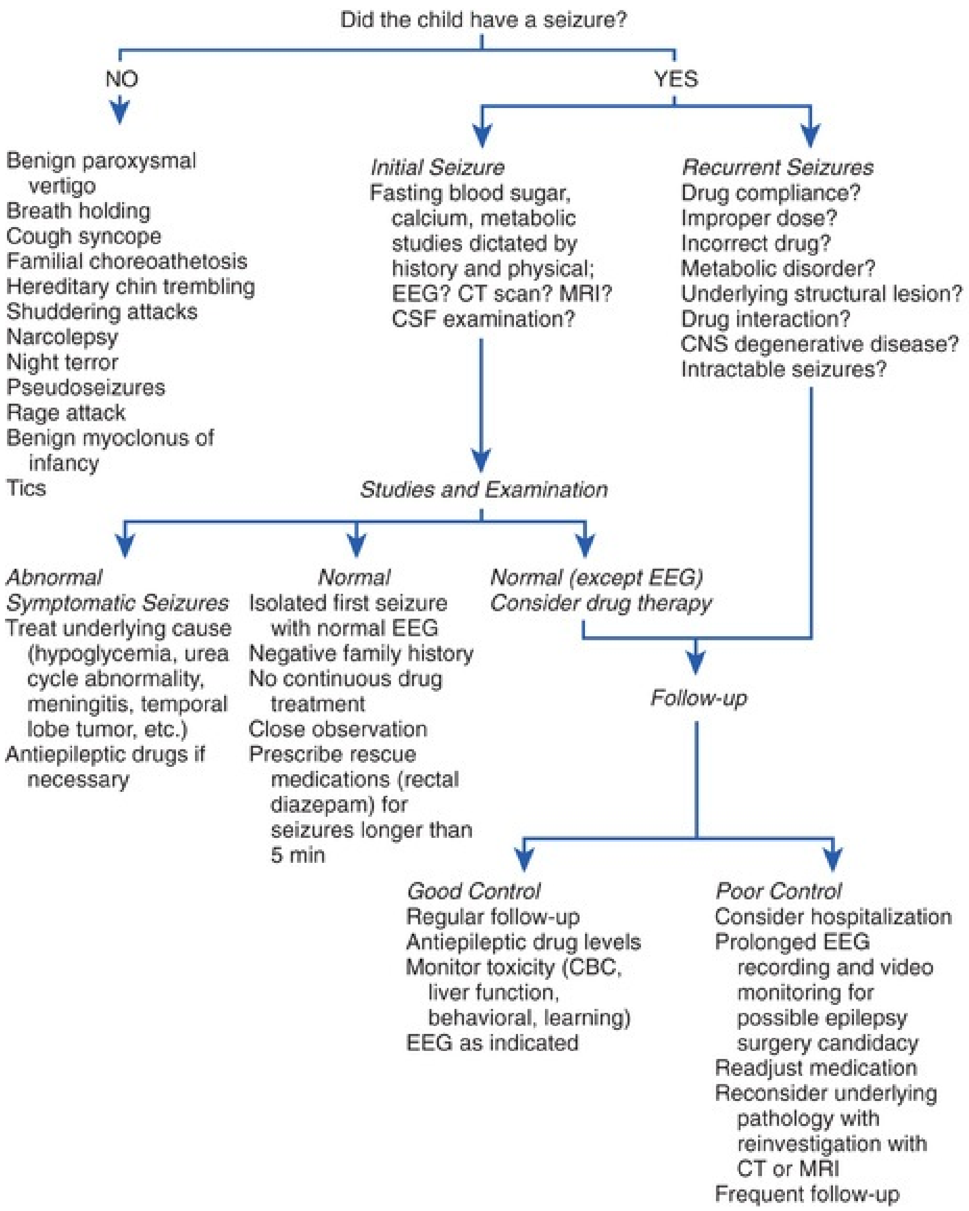
Did the child have a seizure?
NO
YES
Benign paroxysmal vertigo
Breath holding
Cough syncope
Familial choreoathetosis
Hereditary chin trembling
Shuddering attacks
Narcolepsy
Night terror
Pseudoseizures
Rage attack
Benign myoclonus of infancy
Tics
Initial Seizure
Fasting blood sugar, calcium, metabolic studies dictated by history and physical;
EEG? CT scan? MRI?
CSF examination?
Recurrent Seizures
Drug compliance?
Improper dose?
Incorrect drug?
Metabolic disorder?
Underlying structural lesion?
Drug interaction?
CNS degenerative disease?
Intractable seizures?
Studies and Examination
Abnormal
Symptomatic Seizures
Treat underlying cause (hypoglycemia, urea cycle abnormality, meningitis, temporal lobe tumor, etc.)
Antiepileptic drugs if necessary
Normal
Isolated first seizure with normal EEG
Negative family history
No continuous drug treatment
Close observation
Prescribe rescue medications (rectal diazepam) for seizures longer than 5 min
Normal (except EEG)
Consider drug therapy
Follow-up
Good Control
Regular follow-up
Antiepileptic drug levels
Monitor toxicity (CBC, liver function, behavioral, learning)
EEG as indicated
Poor Control
Consider hospitalization
Prolonged EEG recording and video monitoring for possible epilepsy surgery candidacy
Readjust medication
Reconsider underlying pathology with reinvestigation with CT or MRI
Frequent follow-up

FIG. 611.5 Algorithm for the approach to the child with a suspected convulsive disorder.

Counseling

An important part of the management of a patient with epilepsy is educating the family and the child about the disease, its management, and the limitations it might impose and how to deal with them. It is important to establish a successful therapeutic alliance. Restrictions on driving (in adolescents), swimming, and certain sports are usually necessary (Table 611.7). In most states, the physician is not required to report the epileptic patient to the motor vehicle registry; this is the responsibility of the patient. The physician then is requested to complete a specific form for patients who are being cleared to drive. Also in most states, a seizure-free period of 6 mo, and in some states longer, is required before driving is allowed. Often swimming in rivers, lakes, or the sea and underwater diving are prohibited, but swimming in swimming pools may be allowable. When swimming, even patients with epilepsy that is under excellent control should be under the continuous supervision of an observer who is aware of the condition and capable of lifeguard-level rescue.

Table 611.7

Sports and Special Considerations for the Child With Epilepsy*

CLINICAL SITUATION	GROUP 1	GROUP 2	GROUP 3
Acute symptomatic seizures (one or more)	Permitted	Neurologist's discretion	Neurologist's discretion
One unprovoked seizure	Permitted	Permitted if > 12 mo of seizure freedom	Permitted if > 12 mo of seizure freedom
Seizure freedom for > 12 mo	Permitted	Permitted	Permitted
Sleep-related seizures	Permitted	Neurologist's discretion	Neurologist's discretion
Seizures without impaired awareness	Permitted	Neurologist's discretion	Not recommended
Seizures with impaired awareness	Neurologist's discretion	Neurologist's discretion	Not recommended
Resolved epilepsy with no seizures > 10 yr and off AEDs > 5 yr	Permitted	Permitted	Permitted
Medication withdrawal	Neurologist's discretion	Neurologist's discretion	Neurologist's discretion

* Specific advice should be individualized, depending on the patient's clinical condition. Group 1: low-risk sports; Group 2: moderate-risk sports; Group 3: high-risk sports. Refer to Chapter 611.6 for further details about the definition of each group.

Modified from Capovilla G, Kaufman KR, Perucca E, et al: Epilepsy, seizures, physical exercise, and sports: a report from the ILAE Task Force on Sports and Epilepsy, Epilepsia 57:6-12, 2016.

The physician, parents, and child should jointly evaluate the risk of involvement in athletic activities. To participate in athletics, proper medical management, good seizure control, and proper supervision are crucial to avoid significant risks. The ILAE Task Force on Sports and Epilepsy provides general recommendations to assist with making decisions regarding sports participation in patients with epilepsy. Per these recommendations, sports are grouped into categories based on the potential risk of injury or death to the patient and to bystanders. **Group 1 sports** are associated with no significant additional risk to patients with epilepsy and include most athletics (excluding pole vaulting), bowling, most collective contact sports such as judo and wrestling, most ground-based collective sports (e.g., baseball, basketball, cricket, field hockey, football, rugby), cross country skiing, curling, dancing, golf, and racquet sports, including tennis and table tennis. **Group 2 sports** are associated with a moderate risk to patients with epilepsy but not to bystanders; they include alpine skiing, archery, pole vaulting, biathlon/triathlon/modern pentathlon, canoeing, collective sports that can potentially lead to serious injury (boxing, karate, kickboxing, etc.), cycling, fencing, gymnastics, horse riding, ice hockey, shooting, skateboarding, roller and ice skating, skiing and snowboarding, swimming, water skiing, and weightlifting. **Group 3 sports** are considered a high risk for the patient and for bystanders; they include aviation, climbing, platform and springboard diving, horse racing, motor sports, parachuting and other forms of skydiving, rodeo, scuba diving, ski jumping, solitary sailing, as well as surfing and wind surfing. Table 611.7 summarizes the ILAE suggestions and specific situations in which the sport may or may not be permissible. In general, there has been a shift toward encouraging safe sports participation in patients with epilepsy rather than indiscriminately restricting their participation; however, the decision has to be individualized to the patient and his/her family.

Counseling is helpful to support the family and to educate them about the resources available in the community. Educational and, in some cases, psychological evaluation may be necessary to evaluate for possible learning disabilities or abnormal behavioral patterns that might coexist with the epilepsy. Epilepsy does carry a risk of increased mortality rates (two or more times the standardized mortality rates of the general population) and of sudden unexpected death. This is mostly related to the conditions associated with or underlying the epilepsy (e.g., tumor, metabolic diseases), to poor seizure control (e.g., in patients with severe epileptic encephalopathies, or drug-resistant seizures), and to poor compliance with prescribed therapies. Thus, it is recommended that family members be informed about this increased risk without inappropriately increasing their anxiety. Many family members feel they need to observe the patient continuously in wakefulness and sleep and have the patient sleep in the parents' room to detect seizures. There are currently advertised seizure-detection devices that use motion sensors placed under the mattress or worn on the wrist to detect seizures. Some are disappointing and ineffective in detecting seizures, whereas data from other equipment are encouraging in that they were useful in detecting a majority of generalized tonic-clonic seizures during sleep; most have not been rigorously studied. Whether such measures can reduce the risk of **sudden unexpected death in epilepsy (SUDEP)** remains to be seen, and the parents need to guard against being overprotective to avoid adversely affecting the psychology of the child. Education about what to do in case of seizures, the choices of treatment or no treatment and of medications and their side effects, and the potential complications of epilepsy should be provided to the parents and, if the child is old enough, to the child.

Mechanisms of Action of Antiepileptic Drugs

AEDs reduce excitability by interfering with the sodium, potassium, or calcium ion channels, by reducing excitatory neurotransmitter release or function, or by enhancing GABAergic inhibition (Fig. 611.6). Most medications have multiple mechanisms of action, and the exact mechanism responsible for their activity in human epilepsy is usually not fully understood. Often, medications acting on sodium channels are effective against partial seizures, and medications acting on T-type calcium channels are effective against absence seizures. Voltage-gated sodium channels are blocked by felbamate, valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, phenytoin, rufinamide, lacosamide, and zonisamide. T-type calcium channels, found in the thalamus area, are blocked by valproate, zonisamide, and ethosuximide. Voltage-gated calcium channels are inhibited by gabapentin, pregabalin, lamotrigine, and felbamate. N-type calcium channels are inhibited by levetiracetam. Ezogabine/retigabine opens KCNQ/Kv7 voltage-gated potassium channels, but it has been withdrawn from the market.

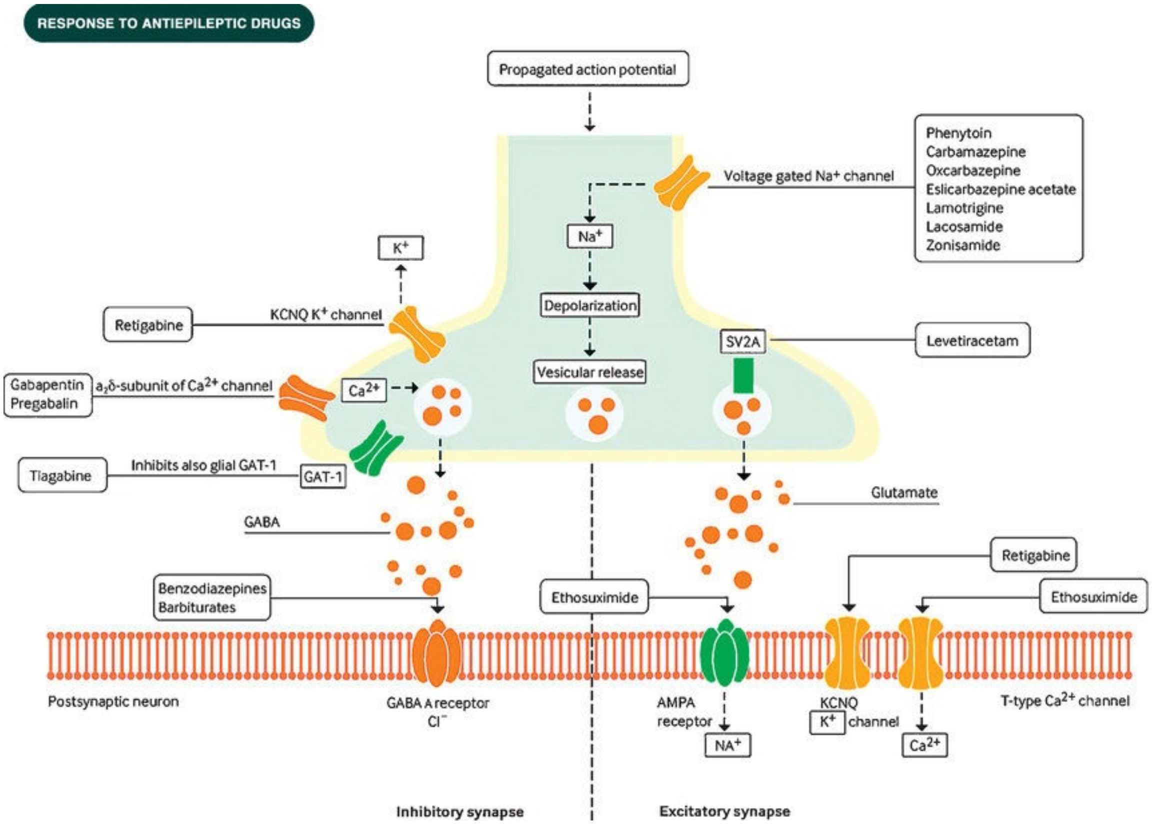
RESPONSE TO ANTIEPILEPTIC DRUGS
Propagated action potential
Voltage gated Na+ channel
Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate
Lamotrigine
Lacosamide
Zonisamide
Na+
Depolarization
Vesicular release
K+
Retigabine
KCNQ K+ channel
SV2A
Levetiracetam
Gabapentin
Pregabalin
a2δ-subunit of Ca2+ channel
Ca2+
Tiagabine
Inhibits also glial GAT-1
GAT-1
Glutamate
GABA
Retigabine
Benzodiazepines
Barbiturates
Ethosuximide
Ethosuximide
Postsynaptic neuron
GABA A receptor
Cl−
AMPA receptor
NA+
KCNQ
K+ channel
T-type Ca2+ channel
Ca2+
Inhibitory synapse
Excitatory synapse

FIG. 611.6 Mechanisms of action of AEDs, which are diverse, mainly involving modulation of voltage-activated ion channels, potentiation of GABA, and inhibition of glutamate. Approved AEDs have effects on inhibitory *(left-hand side)* and excitatory *(right-hand side)* nerve terminals. The antiepileptic efficacy in trials of most of these drugs as initial add-ons does not differ greatly, indicating that seemingly similar antiseizure activity can be obtained by mechanisms aimed at diverse targets. However, putative mechanisms of action were determined only after discovering the antiseizure effects; mechanism-driven drug discovery has played only a minor role. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GAT-1, sodium-dependent and chloride-dependent GABA transporter 1; SV2A, synaptic vesicle glycoprotein 2A. (From Schmidt D, Schachter SC: Drug treatment of epilepsy in adults, BMJ 348:g254, 2014.)

GABA_A receptors are activated by phenobarbital, benzodiazepines, topiramate, felbamate, and levetiracetam. Tiagabine, by virtue of its binding to GABA transporters 1 (GAT-1) and 3 (GAT-3), is a GABA reuptake inhibitor. GABA levels are increased by vigabatrin via its irreversible inhibition of GABA transaminases. Valproate inhibits GABA transaminases, acts on GABA_B presynaptic receptors (also done by gabapentin), and activates glutamic acid decarboxylase (the enzyme that forms GABA).

Glutaminergic transmission is decreased by felbamate that blocks NMDA and

AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid)/kainate receptors. Topiramate also blocks AMPA/kainate receptors. Levetiracetam and brivaracetam bind to the presynaptic vesicle protein SV2A found in all neurotransmitter vesicles and possibly result in inhibition of presynaptic neurotransmitter release in a use-dependent manner. Perampanel blocks glutamate AMPA receptors.

Choice of Drug According to Seizure Type and Epilepsy Syndrome

Drug therapy should be based on the type of seizure and the epilepsy syndrome, as well as on other individual factors. In general, the **drugs of first choice** for focal seizures and epilepsies are oxcarbazepine and levetiracetam; for absence seizures, ethosuximide; for juvenile myoclonic epilepsy, or valproate (less so in women due to its hormonal and fetal side effects); other choices include levetiracetam (which is often the first drug to use in other primary generalized seizures), lamotrigine, zonisamide, topiramate, and perampanel. There is significant controversy about these choices, and therapy should always be individualized (see Choice of Drug: Other Considerations).

West syndrome is best treated with hormonal therapy in the form of either ACTH injections or, possibly, oral steroids. There are several protocols that range in dose from high to intermediate to low. The recommended regimen of ACTH (80 mg/mL) is a daily dose of 150 units/m^2 (divided into twice-daily intramuscular injections of 75 units/m^2) administered over a 2-wk period with a subsequent gradual taper over a 2-wk period (30 units/m^2 in the morning for 3 days; 15 units/m^2 in the morning for 3 days; 10 units/m^2 in the morning for 3 days; and 10 units/m^2 every other morning for 6 days; then stop). Response is usually observed within the first 7 days. During the tapering period of any regimen, spasm relapse can occur. Remediation entails increasing the dose to the previously effective dose for 2 wk and then beginning the taper again. Synthetic ACTH (tetracosactide/cosyntropin) can also be used as long as the long-acting (depot) preparation is chosen. Oral high-dose prednisolone is a lower-cost alternative to ACTH and does not necessitate families learning how to administer intramuscular injections; however, it may be inferior in efficacy to ACTH, particularly in those with cryptogenic (of unknown etiology) West syndrome.

Awake and asleep EEGs are often done 1, 2, and 4 wk after the initiation of hormonal therapy to monitor the patient's response, with the aim of clearing the EEG from hypsarrhythmia and of stopping the seizures. Side effects, more common with the higher doses, include hypertension, electrolyte imbalance, infections, hyperglycemia and/or glycosuria, and gastric ulcers. Prophylactic therapy for ulcers with an H_2 blocker or protein pump inhibitor is desirable while the patient is receiving hormonal therapy. Also, live vaccines are contraindicated and other vaccines are not effective during ACTH and steroid therapy due to the immune-suppressive effects of these hormonal agents. All vaccines are thus not given during hormonal therapy and in the period following it (usually ≤ 3 mo after the last dose).

Vigabatrin can be used as a first-line agent for the treatment of **infantile spasms** in patients with tuberous sclerosis and is the second-line choice if hormonal therapy was unsuccessful in other cases of infantile spasms. Its principal side effect is retinal toxicity that is seen in approximately 30% of patients, most often if the drug is used for longer than 6 mo, with resultant visual field defects that persist despite withdrawal of the drug. The level of evidence for its efficacy is weaker than that for ACTH but stronger than that of other alternative medications. Emerging evidence suggests that dual treatment with vigabatrin and hormonal therapy at the onset of spasms may be superior to hormonal therapy alone. Ketogenic diet is probably the third-line therapy. Subsequent alternative treatment options for spasms include valproate, benzodiazepines such as nitrazepam and clonazepam, topiramate, lamotrigine, zonisamide, pyridoxine, and intravenous gamma globulin (IVIG). None of these alternative drugs offers uniformly satisfactory results. However, they are useful for decreasing the frequency and severity of seizures in patients with symptomatic infantile spasms and as adjunctive therapy in patients with idiopathic infantile spasms who do not respond completely to ACTH or vigabatrin.

Lennox-Gastaut syndrome is another difficult-to-treat epilepsy syndrome. Treatment of seizures in the syndrome varies according to the preponderant seizure type. For drop attacks (tonic, atonic, or myoclonic astatic seizures), clobazam, valproate, lamotrigine, topiramate, felbamate, and rufinamide are considered to be effective. Felbamate is used as a last-resort medication because of its potential toxicity. These drugs might control other types of seizures (partial, generalized tonic-clonic, atypical absence, other tonic, myoclonic), as well. For patients who have a preponderance of atypical absence seizures, valproate, lamotrigine, or ethosuximide are often suitable drugs to try because they are relatively less toxic than many of the alternative drugs. Clonazepam is often helpful but produces significant sedation, hyperactivity, and drooling, and often tolerance to its antiepileptic effects develops in a few months. Consequently, in Lennox-Gastaut or other drug-resistant epilepsy syndromes, clonazepam is often used as a rescue medication for clusters of seizures (disintegrating tablet preparation) or as a bridge over a few days until dose changes of background medications take effect. In resistant cases of Lennox-Gastaut syndrome and related epilepsies, ketogenic diet, zonisamide, levetiracetam, acetazolamide, methsuximide, corticosteroids, or IVIG can be used.

Dravet syndrome is usually treated with benzodiazepines such as clobazam and with valproate. The ketogenic diet can also be useful in patients with this syndrome, including cases with refractory status. Stiripentol, which is available in some countries, is useful, particularly if used in combination with valproate and clobazam, but doses need to be adjusted because stiripentol can increase clobazam levels and valproate can increase stiripentol levels. Other medications include zonisamide and topiramate. Lamotrigine, carbamazepine, oxcarbazepine, and phenytoin are reported to exacerbate seizures in Dravet syndrome. Barbiturate use during status epilepticus in this syndrome is suspected to be associated with adverse outcomes; consequently, alternative acute therapies in such cases need to be considered.

Cannabidiol has recently been approved by the FDA for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients ≥ 2 yr. The starting dose is 2.5 mg/kg taken twice daily (5 mg/kg/day). After 1 week the dose is usually increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). If it is tolerated and needed the dose may be increased up to 10 mg/kg twice daily (20 mg/kg/day). It comes as an oral solution (100 mg/mL).

Absence seizures are most often initially treated with ethosuximide, which is as effective as, but less toxic than, valproate; both are more effective than lamotrigine (which has fewer side effects than valproate). Alternative drugs of first choice are lamotrigine and valproate, especially if generalized tonic-clonic seizures coexist with absence seizures, because these two medications are effective against the latter seizures whereas ethosuximide is not. Patients resistant to ethosuximide might still respond to valproate or to lamotrigine. In absence seizures, the EEG is usually helpful in monitoring the response to therapy and is often more sensitive than the parents' observations in detecting these seizures. The EEG often normalizes when complete seizure control is achieved. This is usually not true for partial epilepsies. Other medications that could be used for absence seizures include acetazolamide, zonisamide, or clonazepam.

Benign myoclonic epilepsies are often best treated with valproate, particularly when patients have associated generalized tonic-clonic and absence seizures. Zonisamide, clonazepam, lamotrigine, and topiramate are alternatives.

Severe myoclonic epilepsies are treated with medications effective for Lennox-Gastaut syndrome, such as topiramate, clobazam, valproate, and zonisamide. Levetiracetam may also have efficacy in myoclonic epilepsies.

Focal and focal to bilateral tonic-clonic seizures can be treated with oxcarbazepine, levetiracetam, carbamazepine, phenobarbital, topiramate, lacosamide, zonisamide, valproic acid, lamotrigine, clobazam, perampanel, or clonazepam (see Table 611.2). Oxcarbazepine and levetiracetam are often being used first.

Choice of Drug: Other Considerations

Because there are many options for each patient, the choice of which drug to use is always an individualized decision based on comparative effectiveness data from randomized controlled trials and on several other considerations delineated below.

◆ **Comparative effectiveness** (Tables 611.8 and 611.9 list dosages) and the **potential for paradoxical seizure aggravation** by some AEDs (e.g., precipitation of myoclonic seizures by lamotrigine in Dravet syndrome and exacerbation of absence seizures by carbamazepine and tiagabine) must be considered. Although many antiseizure medications have not been studied in the pediatric population, off-label use of these medications in children is common, and there are studies that have shown that, in general, their efficacy in adults is predictive of their efficacy in children with the same seizure types.

Table 611.8

Comparison of Recommendations for the Treatment of Pediatric Epilepsy

SEIZURE TYPE OR EPILEPSY SYNDROME	FDA APPROVED [†]	ILAE (2013)[*] [†]
Focal-onset	CBZ, ezogabine, lacosamide, LEV, LTG, OXC, PB, PER, PHT, TPM, VGB	A: OXC B: None C: CBZ, PB, PHT, TPM, VGB, VPA D: CLB, CZP, LTG, ZNS
BCECT	None	A, B: None C: CBZ, VPA D: GBP, LEV, OXC, STM
Childhood absence epilepsy	ESM, VPA	A: ESM, VPA B: None C: LTG D: None
Juvenile myoclonic epilepsy	LEV, LTG, TPM	A, B, C: None D: TPM, VPA
Lennox-Gastaut syndrome	CLB, FLB, LTG, rufinamide (atonic), TPM	Not reviewed
Infantile spasms	ACTH, VGB	Not reviewed
Primary generalized tonic-clonic seizures	LEV, LTG, TPM, PER	A: None B: None C: CBZ, PB, PHT, TPM, VPA D: OXC

[*] ILAE recommendations are listed according to levels of evidence supporting the efficacy of the options. Level A: one or more class I randomized controlled trials (RCTs) or two or more class II RCTs; Level B: one class II RCT or two or more class III RCTs; Level C: two or more class III RCTs; Level D: one class III double-blind or open-label study *or* one class IV clinical study *or* data from expert committee reports, opinions from experienced clinicians.

[†] More recent data are available after FDA approval and ILAE review, and the implications of these data have been incorporated as much as possible into prior Table 611.8 . Together, these two tables aim to provide as complete a picture as possible of the state of the art and the approved indications for the therapy of pediatric epilepsy.

AAN, American Academy of Neurology; ACTH, adrenocorticotropic hormone; BCECT, benign childhood epilepsy with centrotemporal spikes; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FDA, Food and Drug Administration; FLB, felbamate; GBP, gabapentin; ILAE, International League against Epilepsy; LEV, levetiracetam; LTG, lamotrigine; NICE, National Institute for Clinical Excellence; OXC, oxcarbazepine; PB, phenobarbital; PER, perampanel; PHT, phenytoin; STM, sulthiame; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Modified and updated from Perucca E, Tomson T: ILAE Subcommission on AED Guidelines: updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, Epilepsia 54(3):551-563, 2013.

Table 611.9

Dosages of Selected Antiepileptic Drugs

MEDICATION	FDA APPROVAL (AGE APPROVED)	MAINTENANCE ORAL DOSAGE (mg/kg/day) UNLESS OTHERWISE SPECIFIED	USUAL DOSING	THERAPEUTIC LEVELS	PREPARATION
Acetazolamide	Absence seizures (adults)	1-12 mo; 10 > 1 yr: 20-30	bid or tid	10-15 mg/L	125, 250, 500 mg tabs
Brivaracetam	Focal sz (age >16 yr)	50-200 mg/day	bid		10, 25, 50, 75, 100 mg tabs; 10 mg/mL ora and IV solns
Bromide		50-100	bid or qd	10-15 mEq/L, other references 75-352 mg/dL	Supplied as triple bromide soln (240 mg/mL or 500 mg/mL of bromid salt)
Carbamazepine*	Focal and GTC (all ages)	10-20	tid or qid SR usually bid	3-12 mg/L	150, 300 mg ER caps; 100, 200, 400 mg ER tabs 100 mg chewable tabs 200 mg tabs; 100 mg/5 mL susp
Clobazam †	LGS (all ages above 2 yr)	10-40 mg/day	bid	60-200 µg/L	10 mg, 20 mg tabs; 2.5 mg/mL soln
Clonazepam †	Absence sz, LGS, myoclonic sz (all ages)	0.05	bid or tid	25-85 µg/L	0.5, 1, 2 mg tabs; 0.125, 0.25, 0.5 mg orally disintegrating tabs
Diazepam	Focal sz (all ages >6 mo)	0.25-1.5 0.01-0.25 IV 0.2-0.5 mg/kg rectal	bid or tid	100-700 µg/L	2, 5, 10 mg tabs 5 mg/mL, 5 mg/5 mL soln

		(according to age; see Table 611.15)			Rectal gel that can be dialed to dispense 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20 mg
Eslicarbazepine	Focal sz (adult)	800-1600 mg/day	qd		200, 400, 600, 80 mg tabs
Ethosuximide	Absence sz (>3 yr)	20-30	bid or tid	40-100 mg/L	250 mg caps; 250 mg/5 mL soln
Felbamate	LGS (>2 yr) Focal sz (>14 yr)	15-45	bid or tid	50-110 mg/L	400, 600 mg tabs; 600 mg/5 mL susp
Gabapentin ‡	Focal sz (>3 yr)	30-60	tid	2-20 mg/L	100, 300, 400 mg caps; 300, 600, 800 mg tabs; 250 mg/5 mL soln; 25 mg/mL susp
Lacosamide	Focal sz (>17 yr)	4-12	bid	≤ 15 µg/L	50, 100, 150, 200 mg tabs 10 mg/mL ora soln
Lamotrigine	LGS, focal and tonic-clonic sz (age > 2 yr)	5-15 §	tid	1-15 mg/L	25, 100, 150, 200 mg tabs 5, 25 mg chewable dispersible tabs 25, 50, 100, 200 mg ODTs 25, 50, 100, 200, 250, 300 mg ER tabs
		1-5 ¶	bid		
Levetiracetam †	Focal-onset (age ≥ 1 mo), tonic-clonic sz (age ≥ 6 yr), myoclonic (age ≥ 12 yr)	20-60	bid or tid	6-40 mg/L	250, 500, 750 mg tabs 100 mg/mL soln 500, 750 mg SR (ER) tabs
Lorazepam	Status epilepticus (all ages)	0.05-0.1	bid or tid	20-30 µg/L	0.5, 1, 2 mg tabs 2 mg/mL soln
Methsuximide	Absence sz (children and older)	10-30	bid or tid	10-50 mg/L	150, 300 mg caps
Nitrazepam	—	0.25-1	bid or tid	<200 µg/L	5 mg tabs
Oxcarbazepine*	Focal sz (>2 yr)	20-60	bid	13-35 mg/L	150, 300, 600 mg tabs 300 mg/5 mL susp
Perampanel	Focal sz (>12 yr)	2-12 mg per day (>12 yr)	qhs	20-800 ng/mL	2, 4, 6, 8, 10, 12 mg tabs; 0.5

					mg/mL soln
Phenobarbital	Myoclonic, focal and tonic-clonic sz and status (all ages)	<5 yr, 3-5 >5 yr, 2-3	bid or qd	10-40 mg/L	15, 30, 60, 90, 100 mg tabs 4 mg/mL soln
Phenytoin	Focal, tonic-clonic sz and status (all ages)	<3 yr, 8-10 >3 yr, 4-7	tabs, susp: tid caps: qd	5-20 mg/L	50 mg tabs 30,100 mg caps 125 mg/5 mL susp
Pregabalin	Focal sz (adults)	2-14	bid	Up to 10 µg/mL	25, 50, 75, 100, 150, 200, 225, 300 mg caps 20 mg/mL soln
Primidone	Focal and tonic-clonic sz (all ages)	10-20	bid or tid	4-13 mg/L	50, 250 mg tabs, susp
Rufinamide [†]	LGS (age > 4 yr)	30-45	bid	<60 µg/mL	200, 400 mg tabs
Sulthiame [‖]		5-15	bid or tid	1.5-20 µg/mL	50, 200 mg caps
Tiagabine	Focal sz (age > 2 yr)	0.5-2	bid, tid, qid	80-450 µg/L	2, 4, 12, 16 mg tabs
Topiramate [†]	LGS, focal and tonic-clonic sz (all ages)	3-9, slow titration	bid or tid	2-25 mg/L	25, 100, 200 mg tabs 15, 25 mg sprinkle caps
Valproate	Absence, myoclonic, focal and tonic-clonic sz (age > 2 yr)	15-40. Higher doses are used if patient is on enzyme inducers (≤60 mg/kg/day)	Sprinkle caps: bid Soln: tid	50-100 mg/L	250 mg caps 125 mg sprinkle caps 125, 250, 500 mg tabs 250 mg/5 mL soln
Vigabatrin	Infantile spasms and focal sz (age > 1 mo)	50-150	bid	20-160 µg/mL (following levels is not useful for this drug)	500 mg tabs 500 mg powder for soln
Zonisamide	Focal sz (age > 16 yr)	4-8	bid or qd	10-40 mg/L	100 mg caps

[*] Usually start by one-fourth maintenance dose and increase by one fourth every 2-3 days to full dose.

[†] Usually start with one-fourth maintenance dose and increase by one fourth every 7 days to full dose.

[‡] Usually start with one-fourth maintenance dose and increase by one fourth every day to full dose.

[§] Child receiving enzyme inducers.

[‖] Available in some European countries.

¶ Child receiving valproate.

Unless specified otherwise, as above, one would usually target the lower range of the therapeutic dose and then adjust it as needed, depending on the response, side effects, and/or levels. The dosing schedule (e.g., bid or tid) can depend on if a sustained-release preparation is available and if the patient is taking enzyme inducers (e.g., carbamazepine) or inhibitors (e.g., valproic acid) that could affect the drug (as indicated in the dosing schedule in the table and in the text).

cap, capsule; ER, extended release; GTC, generalized tonic-clonic; LGS, Lennox-Gastaut syndrome; ODT, orally disintegrating tablet; soln, solution; SR, sustained release; susp, suspension; sz, seizure(s); tab, tablet.

◆ **Comparative tolerability** (Table 611.10): Adverse effects can vary according to the profile of the patient. The most prominent example is the increased risk of liver toxicity for valproate therapy in children who are younger than 2 yr of age, taking polytherapy, and/or have metabolic disorders. Thus, if metabolic disorders are suspected, other drugs should be considered first and valproate should not be started until the metabolic disorders are ruled out by normal amino acids, organic acids, acylcarnitine profile, lactate, pyruvate, liver function tests, and perhaps gene testing for mitochondrial disorders (see the paragraph on the presence of comorbid conditions later). The choice of an AED can also be influenced by the likelihood of occurrence of nuisance side effects, such as weight gain (valproate, carbamazepine), gingival hyperplasia (phenytoin), alopecia (valproate), hyperactivity (benzodiazepines, barbiturates, levetiracetam, valproate, gabapentin), or irritability/anger (levetiracetam and perampanel). Children with behavior problems and/or with attention-deficit disorder can become particularly hyperactive with the GABAergic drugs mentioned above. This often affects the choice of medications.

Table 611.10

Some Adverse Effects of Antiepileptic Drugs*

ANTIEPILEPTIC DRUG	SIDE EFFECT(S)
Acetazolamide	Nuisance: dizziness, polyuria, electrolyte imbalance Serious: Stevens-Johnson syndrome, renal calculi
Benzodiazepines	Nuisance: dose-related neurotoxicity (drowsiness, sedation, ataxia), hyperactivity, drooling, increased secretions Serious: apnea
Brivaracetam	Dizziness, nausea/vomiting, fatigue, depressed mood
Bromide	Nuisance: irritability, spurious hyperchloremia (falsely high chloride due to bromide) Serious: psychosis, rash, toxicity developing slowly owing to the very long half-life
Carbamazepine	Nuisance: tics, transient leukopenia; hyponatremia, weight gain, nausea; dizziness Serious: Stevens-Johnson syndrome, agranulocytosis, aplastic anemia, liver toxicity
Clobazam	Nuisance: drowsiness, sedation, drooling Serious: Stevens-Johnson syndrome, toxic epidermal necrolysis
Eslicarbazepine	Dizziness, ataxia, nausea/vomiting, diplopia, tremor, somnolence, headache, fatigue
Felbamate	Nuisance: anorexia, vomiting, insomnia, hyperactivity, dizziness Serious: major risks for liver and hematologic toxicity requiring close monitoring (1 in 500 in children > 2 yr with complex neurologic disorders)
Gabapentin	In children: acute onset of aggression, hyperactivity In adults: euphoria and behavioral disinhibition, weight gain
Lacosamide	Nuisance: diplopia, headache, dizziness, nausea Serious: possibly cardiac arrhythmias (if predisposed)
Lamotrigine	Nuisance: CNS side effects: headache, ataxia, dizziness, tremor, but usually less than other AEDs Serious: Stevens-Johnson syndrome, rarely liver toxicity
Levetiracetam	CNS adverse events: somnolence, asthenia, dizziness, but usually less than other AEDs In children: anger, irritability, other behavioral symptoms In adults: depressive mood
Oxcarbazepine	Somnolence, headache, dizziness, nausea, apathy, rash, hypertrichosis, gingival hypertrophy, hyponatremia
Perampanel	Aggression, homicidal ideation, suicidal thoughts/behavior
Phenobarbital and other barbiturates	Nuisance: neurotoxicity, insomnia, hyperactivity, signs of distractibility, fluctuation of mood, aggressive outbursts Serious: liver toxicity, Stevens-Johnson syndrome
Phenytoin and other	Nuisance: gingival hyperplasia, coarsening of the facies, hirsutism,

hydantoins	cerebellovestibular symptoms (nystagmus and ataxia) Serious: Stevens-Johnson syndrome, liver toxicity
Pregabalin	Nuisance: dizziness, peripheral edema, blurred vision, weight gain, thrombocytopenia Serious: hypersensitivity reactions
Primidone	Nuisance: CNS toxicity (dizziness, slurred speech, giddiness, drowsiness, depression) Serious: liver toxicity, Stevens-Johnson syndrome
Rufinamide	Nuisance: somnolence, vomiting Serious: contraindicated in familial short QT interval
Succinimides	Nuisance: nausea, abdominal discomfort, anorexia, hiccups Serious: Stevens-Johnson syndrome, drug-induced lupus
Tiagabine	Nuisance: dizziness, somnolence, asthenia, headache and tremor, precipitation of absence or myoclonic seizures Serious: precipitation of nonconvulsive status epilepticus
Topiramate	Nuisance: cognitive dysfunction, weight loss, hypohidrosis, fever Serious: precipitation of glaucoma, renal calculi
Valproic acid	Nuisance: weight gain; hyperammonemia tremor, alopecia, menstrual irregularities Serious: hepatic and pancreatic toxicity
Vigabatrin	Nuisance: hyperactivity Serious: irreversible visual field deficits, retinopathy that requires frequent ophthalmologic evaluations and follow-up
Zonisamide	Fatigue, dizziness, anorexia, psychomotor slowing, ataxia, rarely hallucinations, hypohidrosis and fever, renal calculi

[*] Essentially all AEDs can cause CNS toxicity and potentially rashes and serious allergic reactions. For a full list of side effects, please review the drug's FDA-approved packet insert.

AED, antiepileptic drug; CNS, central nervous system.

◆ **Cost and availability:** The cost of the newer AEDs often precludes their use, particularly in developing countries where cost is a major issue. Also, many drugs are not available in many countries (1) because they are too expensive; (2) because, paradoxically, they are too inexpensive (lower profit margin); or (3) because of regulatory restrictions. AEDs have a narrow therapeutic range, and thus switching from brand name to generic formulations, or from one generic to another, can result in changes in levels that could result in breakthrough seizures or side effects.

◆ **Ease of initiation** of the AED: Medications that are started very gradually, such as lamotrigine and topiramate, should not be chosen in situations when there is a need to achieve a therapeutic level quickly. In such situations, medications that have intravenous preparations or that can be started and titrated more quickly, such as levetiracetam, phenytoin, lacosamide, or valproate, should be considered instead.

◆ **Drug interactions** and presence of background medications: An example is the potential interference of enzyme-inducing drugs with many chemotherapeutic agents. In those cases, medications such as gabapentin or levetiracetam are used. Also, valproate inhibits the metabolism and increases the levels of lamotrigine, phenobarbital, and felbamate. It also displaces protein-bound phenytoin from protein-binding sites, increasing the free fraction, and, thus, the free and not the total level needs to be checked when both medications are being used together. Enzyme inducers such as phenobarbital, carbamazepine, phenytoin, and primidone reduce levels of lamotrigine, valproate, and, to a lesser extent, topiramate, zonisamide, and perampanel. Medications exclusively excreted by the kidney, such as levetiracetam and gabapentin, are not subject to such interactions.

◆ **The presence of comorbid conditions:** For example, the presence of migraine in a patient with epilepsy can lead to the choice of a medication that is effective against both conditions, such as valproate, topiramate, or zonisamide. In an obese patient, a medication such as valproate might be avoided, and a medication that decreases the appetite, such as topiramate or zonisamide, might be used instead. In adolescent girls of child-bearing potential, enzyme-inducing AEDs are often avoided because they can interfere with birth control pills; other AEDs, particularly valproate, can increase risks for fetal malformations. Valproic acid may unmask or exacerbate certain underlying metabolic disorders; these include nonketotic hyperglycinemia, DNA polymerase γ mutations *(POLG)* with mitochondrial DNA depletion (also known as Alpers-Huttenlocher syndrome), other mitochondrial disorders (Leigh syndrome; mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]; myoclonic epilepsy with ragged red fibers; myoclonic epilepsy–myopathy–sensory ataxia syndrome), and hyperammonemic encephalopathies. Manifestations may include hepatotoxicity or encephalopathy.

◆ **Coexisting seizures:** In a patient with both absence and generalized tonic-clonic seizures, a drug that has a broad spectrum of antiseizure effects, such as lamotrigine or valproate, could be used rather than medications that have a narrow spectrum of efficacy, such as phenytoin and ethosuximide.

◆ **History of prior response** to specific AEDs: For example, if a patient or a family member with the same problem had previously responded to carbamazepine, carbamazepine could be a desirable choice.

◆ **Mechanism of drug actions:** At present, in most patients the current understanding of the pathophysiology of epilepsy does not allow a specific choice of AEDs based on the assumed pathophysiology of the epilepsy. However, in general, it is believed that it is better to avoid combining medications that have similar mechanisms of action, such as phenytoin and carbamazepine (both work on sodium channels). A number of medications, such as lamotrigine and valproate or topiramate and lamotrigine, are reported to have synergistic effects, possibly because they have different mechanisms of action.

◆ **Ease of use:** Medications that are given once or twice a day are easier to use than medications that are given 3 or 4 times a day. Availability of a pediatric liquid preparation, particularly if palatable, also plays a role.

◆ **Ability to monitor the medication** and adjust the dose: Some medications are difficult to adjust and to follow, requiring frequent blood levels. The prototype of such medications is phenytoin, but many of the older medications such as valproate and phenobarbital also require blood level monitoring for optimal titration. However, monitoring in itself can represent a practical or patient satisfaction disadvantage for the older drugs as compared with the newer AEDs, which generally do not require blood level monitoring except to check for compliance.

◆ **Patient's and family's preferences:** All things being equal, the choice between two or more acceptable alternative AEDs might also depend on the patient's or family's preferences. For example, some patients might want to avoid gingival hyperplasia and hirsutism as side effects but might tolerate weight loss, or vice versa.

◆ **Genetics** and genetic testing: A genetic predisposition to developing AED-induced side effects is another factor that may be a consideration. For example, there is a strong association between the human leukocyte antigen HLA-B*1502 allele and severe cutaneous reactions induced by carbamazepine, oxcarbazepine, phenytoin, or lamotrigine in Chinese Han patients and, to a lesser extent, Southeast Asian populations; hence, these AEDs should be avoided in genetically susceptible persons after testing for the allele. Mutations of the

SCN1A sodium channel gene indicating Dravet syndrome could also lead to avoiding lamotrigine, carbamazepine, oxcarbazepine, and phenytoin, and to the use of the more appropriate valproate, clobazam, or stiripentol.

◆ **Teratogenic profiles:** Based on available evidence, levetiracetam and lamotrigine are FDA pregnancy category C drugs and probably the safest AEDs to use during pregnancy. Valproate is a category X drug that is associated with neural tube defects, hypospadias, and cardiovascular malformations. *The use of valproate should thus be avoided if possible during pregnancy.* Topiramate, phenobarbital, and phenytoin are category D drugs with birth defects associated with their use reported in humans. The decision to transition to a less teratogenic AED rather than continuing on an existing regimen must be made on a case-by-case basis and take into account the risk of seizures during pregnancy versus the risk of teratogenicity.

◆ **Underlying etiology:** The cause for the patient's epilepsy must be considered and can lead to more specific therapy choices, such as the use of immune-modulating therapy for autoimmune encephalopathy or personalized and precision therapies for specific epileptic channelopathies or vitamin-responsive epilepsies.

Initiating and Monitoring Therapy

In nonemergency situations, or when loading is not necessary, the **maintenance dose** of the chosen AED is started (see Table 611.9). With some medications (e.g., oxcarbazepine, carbamazepine, topiramate, and perampanel), even smaller doses are initially started and then **gradually increased** up to the maintenance dose to build tolerance to adverse effects such as sedation. For example, the starting dose of oxcarbazepine is usually 8-10 mg/kg/day. Increments of 5 mg/kg/day can be added every 3 days until a therapeutic level is achieved and a therapeutic response is established or until unacceptable adverse effects occur. With other medications such as zonisamide, phenobarbital, phenytoin, or valproate, starting at the maintenance dose is usually tolerated. With some, such as levetiracetam and gabapentin, either approach can be used. Patients should be counseled about potential adverse effects, and these should be monitored during follow-up visits (see Table 611.10).

Titration

Levels of many AEDs should usually be determined after initiation to ensure compliance and therapeutic concentrations. Monitoring is most helpful for the older AEDs, such as phenytoin, carbamazepine, valproate, phenobarbital, and ethosuximide. After starting the maintenance dosage or after any change in the dosage, a steady state is not reached until 5 half-lives have elapsed, which, for most AEDs, is 2-7 days (half-life: 6-24 hr). For phenobarbital, it is 2-4 wk (mean half-life: 69 hr). For zonisamide, it is 14 days during monotherapy and less than that during polytherapy with enzyme inducers (half-life: 63 hr in monotherapy and 27-38 hr during combination therapy with enzyme inducers). If a therapeutic level has to be achieved faster, a loading dose may be used for some drugs, usually with a single dose that is twice the average maintenance dose per half-life. For valproate it is 20 mg/kg, for phenytoin it is 20 mg/kg, and for phenobarbital it is 10-20 mg/kg. A lower loading dosage of phenobarbital is sometimes given in older children (5 mg/kg, which may be repeated once or more in 24 hr) to avoid excessive sedation.

Only one drug should be used initially, and the dose increased until complete control is achieved or until side effects prohibit further increases. Then, and only then, may another drug be added and the initial drug subsequently tapered. Control with one drug **(monotherapy**) should be the goal, although some patients eventually need to take multiple drugs. When appropriate, levels should also be checked upon addition (or discontinuation) of a second drug because of potential drug interactions. During follow-up, repeating the EEG every few months may be helpful to evaluate changes in the predisposition to seizures. This is especially true in situations where tapering off of medication is contemplated in any seizure type and during follow-up to assess the response for absence seizures, because the EEG mirrors the response in such patients.

Monitoring

For the older AEDs, before starting treatment, baseline laboratory studies, including complete blood count, platelets, liver enzymes, and possibly kidney function tests and urinalysis, are often obtained and repeated periodically. Laboratory monitoring is more relevant early on, because idiosyncratic adverse effects such as allergic hepatitis and agranulocytosis are more likely to occur in the first 3-6 mo of therapy. These laboratory studies are usually initially checked once or twice during the 1st mo, then every 3-4 mo thereafter. Serious concerns have been raised about the real usefulness of routine monitoring (in the absence of clinical signs) because the yield of significant adverse effects is low and the costs may be high. There are currently many advocates of less-frequent routine monitoring.

In approximately 10% of patients, a reversible dose-related leukopenia may occur in patients taking carbamazepine or phenytoin. This adverse effect responds to decreasing the dose or to stopping the medication and should be distinguished from the much-less-common idiosyncratic aplastic anemia or agranulocytosis. One exception requiring frequent (even weekly) monitoring of liver function and blood counts throughout the therapy is felbamate, owing to the high incidence of liver and hematologic toxicity (1 in 500 children under 2 yr of age with complex neurologic disorders who are taking the drug). The gum hyperplasia that is seen with phenytoin necessitates good oral hygiene (brushing teeth at least twice per day and rinsing the mouth after taking the phenytoin); in a few cases, it may be severe enough to warrant surgical reduction and/or a change of medication. Allergic rash can occur with any medication, but is probably most common with lamotrigine, carbamazepine, and phenytoin.

Side Effects

During follow-up the patient should be monitored for side effects. Occasionally, a Stevens-Johnson–like syndrome develops, probably most commonly with lamotrigine; it also has been found to be particularly common in Chinese patients who have the allele HLA-B*1502 and are taking oxcarbazepine, carbamazepine, and/or lamotrigine.

Other potential side effects are rickets from phenytoin, phenobarbital, primidone, and carbamazepine (enzyme inducers that reduce the 25-hyrdroxy-vitamin D level by inducing its metabolism) and hyperammonemia from valproate. Skeletal monitoring is warranted in patients taking chronic AED therapy because it is often associated with osteopenia independent of or secondary to vitamin D deficiency (low bone density, rickets, and hypocalcemia), particularly in patients taking enzyme-inducing medications. Thus, counseling the patient about sun exposure and vitamin D intake, monitoring vitamin D levels, and, in most cases, giving vitamin D supplementation is recommended. There is currently no consensus on the dose to be used for supplementation or prophylaxis, but starting doses of 2,000 IU/day with follow-up of the levels are reasonable.

Irreversible hepatic injury and death are particularly feared in young children (<2 yr old) who are receiving valproate in combination with other AEDs, particularly those who might have inborn errors of metabolism such as aminoacidopathies and mitochondrial disease. Virtually all AEDs can produce sleepiness, ataxia, nystagmus, and slurred speech with toxic levels.

The U.S. Food and Drug Administration (FDA) has determined that the use of AEDs may be associated with an increased risk of suicidal ideation and action and has recommended counseling about this side effect before starting these medications. This is obviously more applicable to adolescents and adults.

When adding a new AED, the doses used are often affected by the background medications. For example, if the patient is receiving enzyme inducers, the doses needed of valproate, lamotrigine, topiramate, zonisamide, and perampanel are often higher, sometimes 1.5-2 times, than the usual maintenance doses. On the other hand, if the patient is taking valproate (an enzyme-inhibiting AED), the doses of phenobarbital or lamotrigine are approximately half of what is usually needed. Thus, changes in the dosing of the background medication are often done as the interacting medication is being started or stopped. Genetic variability in enzymes that metabolize AEDs and in the presence of inducible multidrug-resistance genes (pharmacogenomics) might account for some of the variation among individuals in responding to certain AEDs and for the variability in the drug dose necessary for seizure control. However, the use of this new knowledge is currently largely restricted to research investigations, and it has yet to be applied in routine clinical practice.

Additional Treatments

The principles of monotherapy indicate that a second medication needs to be considered after the first either is pushed as high as tolerated and still does not control the seizures or results in intolerable adverse effects. In those cases, a second drug is started and the first is tapered and then discontinued. The second drug is then again pushed to the dose that controls the seizure or that results in intolerable side effects. If the second drug fails, monotherapy with a third drug and **dual (combination) therapy** are considered.

Patients with **drug-resistant** (previously referred to as *intractable* or *refractory*) **epilepsy** (those who have failed at least two fair trials of appropriate medications) warrant a careful diagnostic reevaluation to look for degenerative, metabolic, or inflammatory underlying disorders (e.g., mitochondrial disease, Rasmussen encephalitis; see Chapter 611.2) and to investigate them for candidacy for epilepsy surgery. Treatable metabolic disorders that can manifest as drug-resistant epilepsy include pyridoxine-dependent and pyridoxal-responsive epilepsy; cerebral folate deficiency; other vitamin-responsive conditions (such as biotin/thiamine–responsive basal ganglia disease and riboflavin-responsive epilepsy); neurotransmitter disorders; biotinidase deficiency; glucose transporter 1 deficiency (responds to the ketogenic diet); serine synthesis defects; creatine deficiency syndromes; untreated phenylketonuria; developmental delay, epilepsy, and neonatal diabetes; and hyperinsulinemia–hyperammonemia. Often patients who do not respond to AEDs are candidates for steroids, IVIG, or the ketogenic diet.

Steroids may be a first-line treatment in certain cases (e.g., ACTH use in West syndrome) but may also be used for other drug-resistant epilepsy syndromes such as Lennox-Gastaut, myoclonic astatic, continuous spike waves in slow-wave sleep, and Landau-Kleffner syndromes. In these situations, steroid therapy is typically given as a monthly intravenous infusion (pulse steroids) or as daily oral prednisone 2 mg/kg/day (or equivalent). This dose is maintained for 1-2 mo, then tapered off over 1-3 mo. Pulse steroids are usually better tolerated compared with a daily steroid regime, which can cause more weight gain, hyperglycemia, hypertension, immunosuppression, and other side effects.

Because relapses occur commonly during tapering, and in such syndromes as Landau-Kleffner and continuous spike waves in slow-wave sleep, therapy for longer than 1 yr is often needed.

IVIG has also been reported to be similarly effective in non–immunodeficient patients with West, Lennox-Gastaut, Landau-Kleffner, and continuous spike waves in slow-wave sleep syndromes and may also have efficacy in partial seizures. One should check the IgA levels before starting the infusions (to assess the risk for allergic reactions, because these are increased in patients with complete IgA deficiency) and guard against allergic reactions during the infusion that can occur even in the absence of IgA deficiency. Low IgA, low IgG_2 , and male sex are reported to possibly predict a favorable response. The usual regimen is 2 g/kg divided over 2-4 consecutive days followed by 1 g/kg once a month for 6 mo. The mechanisms of action of steroids and IVIG are not known but are presumed to be antiinflammatory, because it has been demonstrated that seizures increase cytokines and that these, in turn, increase neuronal excitability by several mechanisms, including activation of glutamate receptors. Steroids and ACTH might also stimulate brain neurosteroid receptors that enhance GABA activity and might reduce corticotrophin-releasing hormone, which is known to be epileptogenic.

The ketogenic diet is believed to be effective in glucose transporter protein 1 deficiency, pyruvate dehydrogenase deficiency, myoclonic-astatic epilepsy, tuberous sclerosis complex, Rett syndrome, severe myoclonic epilepsy of infancy (Dravet syndrome), and infantile spasms. There is also a suggestion of possible efficacy in selected mitochondrial disorders—glycogenosis type V, Landau-Kleffner syndrome, Lafora body disease, and subacute sclerosing panencephalitis. The diet is absolutely contraindicated in carnitine deficiency (primary); carnitine palmitoyltransferase I or II deficiency; carnitine translocase deficiency; β-oxidation defects; medium-chain acyl dehydrogenase deficiency; long-chain acyl dehydrogenase deficiency; short-chain acyl dehydrogenase deficiency; long-chain 3-hydroxyacyl-coenzyme A deficiency; medium-chain 3-hydroxyacyl–coenzyme A deficiency; pyruvate carboxylase deficiency; and porphyrias. Thus, an appropriate metabolic workup, depending on the clinical picture, usually needs to be performed before starting the diet (e.g., acyl carnitine profile, total and free carnitine levels). The diet has been used for refractory seizures of various types (partial or generalized) and consists of an initial period of fasting followed by a diet with a 3 : 1 or 4 : 1 fat:nonfat calorie ratio, with fats consisting of animal fat, vegetable oils, or medium-chain triglycerides. Many patients do not tolerate it, owing to diarrhea, vomiting, hypoglycemia, dehydration, or lack of palatability. Diets such as the low-glycemic–index diet and the modified Atkins diet are easier to institute, do not require hospitalization, and may also be effective in treating epilepsy.

Cannabidiol (CBD) is a nonpsychoactive extract of the cannabis plant that has gained prominence as a possible adjunct (add-on) therapy for drug-resistant epilepsies such as Dravet and Lennox-Gastaut syndromes.

Precision therapy, as it applies to pediatric epilepsy, is defined as a patient-specific, or more accurately physiology-specific, selection of therapy as determined by the available information regarding the underlying pathophysiology based on the primary specific genetic, metabolic, and/or other cause of epilepsy in that patient. The use of precision therapies (Table 611.11) has expanded as more epileptogenic gene mutations are identified as part of routine genetic screening for drug-resistant epilepsies. This has allowed for targeted therapy based on the specific gene mutation identified (see Table 611.11). Examples include the use of quinidine for gain-of-function *KCNT1* mutations and retigabine for loss-of-function *KCNQ2* mutations. Gain-of-function *KCNQ2* mutations do not respond to retigabine, a fact that emphasizes the need for careful gene analysis that accounts for the functional outcome of each particular gene mutation.

Table 611.11

Precision Therapy: Treatment Considerations for Genetic Epilepsies and Other Syndromes With a High Prevalence of Epilepsy

GENE MUTATION	EPILEPTIC DISORDER	TREATMENT CONSIDERATIONS
ALDH7A1	Pyridoxine-dependent epilepsy	Pyridoxine
BTD	Biotinidase deficiency–associated epilepsy	Biotin
FOLR1	Cerebral folate deficiency	Folinic acid
GRIN2A	GRIN2A-related epilepsy	Memantine and dextromethorphan for gain-of-function mutation
KCNQ2	Benign familial neonatal or infantile seizures; KCNQ2-related epileptic encephalopathy	Retigabine for loss-of-function mutations*
KCNT1	Migrating focal seizures of infancy	Quinidine for gain-of-function mutations
PNPO	Pyridoxal 5′-phosphate dependent epilepsy	Pyridoxal 5′-phosphate
PRRT2	Benign familial infantile epilepsy; paroxysmal dyskinesias; hemiplegic migraine; episodic ataxia	Oxcarbazepine and carbamazepine
SCN1A	Dravet syndrome; GEFS+; other SCN1A-related epilepsies	Avoid using sodium channel blockers (carbamazepine, oxcarbazepine, lamotrigine, lacosamide, phenytoin) and vigabatrin
SCN2A	Benign neonatal or infantile seizures; Dravet	Phenytoin and carbamazepine

	syndrome; GEFS+; infantile spasms; other early infantile epileptic encephalopathies	
SCN8A	Early infantile epileptic encephalopathies; benign infantile seizures; movement disorders	High-dose phenytoin
SLC2A1	Glucose transporter–deficiency syndrome	Ketogenic diet
SLC19A3	Biotin thiamine–responsive basal ganglia disease	Biotin and thiamine
TSC1; TSC2	Tuberous sclerosis complex	Vigabatrin for infantile spasms; possibly everolimus for drug-resistant seizures

[*] Withdrawn for market.

Adapted from Hani A, Mikati MA: Current and emerging therapies of severe epileptic encephalopathies, Semin Pediatr Neurol 23(2):180-186, 2016; Mudigoudar B, Weatherspoon S, Wheeless JW: Emerging antiepileptic drugs for severe pediatric epilepsies, Semin Pediatr Neurol 23(2):167-179, 2016; Smith LA, Ullman JFP, Olson HE, et al: A model program for translational medicine in epilepsy genetics, J Child Neurol 32(4):429-436. 2017.

Vitamin-responsive epilepsies also warrant special attention because if they are diagnosed early and precision therapy is given for them, the therapy can have a significant impact on seizure control and neurodevelopmental outcomes. Examples include the use of pyridoxine for antiquitin deficiency–associated epilepsies, biotin for biotinidase deficiency, folate for cerebral folate deficiency, and biotin/thiamine for **biotin thiamine–responsive basal ganglia disease,** which can have coexisting epilepsy and is caused by defects in a cerebral thiamine transporter.

Approach to Epilepsy Surgery

If a patient has failed three drugs, the chance of achieving seizure freedom using AEDs is generally < 10%. Therefore, proper evaluation for surgery is necessary as soon as patients fail two or three AEDs, usually within 2 yr of the onset of epilepsy and often sooner than 2 yr. Performing epilepsy surgery in children at an earlier stage (e.g., < 5 yr of age) allows transfer of function in the developing brain. Candidacy for epilepsy surgery requires proof of resistance to AEDs used at maximum, tolerably nontoxic doses; absence of expected unacceptable adverse consequences of surgery; and a properly defined **epileptogenic zone** (area that needs to be resected to achieve seizure freedom). The epileptogenic zone is identified by careful analysis, by an expert team of epilepsy specialists in an epilepsy center, of the following parameters: seizure semiology, interictal EEG, video-EEG long-term monitoring, neuropsychological profile, and MRI. Other techniques, such as invasive EEG (depth electrodes, subdurals), single-photon emission CT, magnetoencephalography, and positron emission tomography are also often needed when the epileptogenic zone is difficult to localize or when it is close to eloquent cortex. **Stereo-EEG** is a newer method of invasive EEG monitoring used to localize epileptic areas of the cortex. It involves the stereotactic implantation of depth electrodes through multiple burr holes in the skull using robot-assisted implantations and computer-based 3-D localization, which allows for the implantation of many more depth electrodes than previously possible. To avoid resection of eloquent cortex, several procedures can be used, including the **Wada test.** In this test, intracarotid infusion of amobarbital is used to anesthetize one hemisphere to lateralize memory and speech by testing them during that unilateral anesthesia. Other tests to localize function include **functional MRI,** magnetoencephalography, and cortical stimulation with subdural and depth electrodes. Developmental delay or psychiatric diseases must be considered in assessing the potential impact of surgery on the patient. The usual minimal presurgical evaluation includes video-EEG monitoring, imaging, and age-specific neuropsychological assessment.

Epilepsy surgery is often used to treat drug-resistant epilepsy of a number of etiologies, including cortical dysplasia, tuberous sclerosis, polymicrogyria, hypothalamic hamartoma, Landau-Kleffner syndrome, and hemispheric syndromes, such as Sturge-Weber syndrome, hemimegalencephaly, and Rasmussen encephalitis. Patients with drug-resistant epilepsy resulting from metabolic or degenerative problems are not candidates for resective epilepsy surgery. **Focal resection** of the epileptogenic zone is the most common procedure. **Hemispherectomy** is used for diffuse hemispheric lesions in cases such as Rasmussen encephalitis; **multiple subpial transection,** a surgical technique in which the horizontal connections of the epileptic focus are partially cut without resecting it, is sometimes used for unresectable foci located in eloquent cortex, as in Landau-Kleffner syndrome. In Lennox-Gastaut syndrome, **corpus callosotomy** is used as a palliative procedure for drop attacks. **Vagus nerve stimulation** is often used for drug-resistant epilepsies of various types and for seizures of diffuse focal or multifocal anatomic origin that do not yield themselves to resective surgery. This technique is considered palliative rather than curative because it most often leads to seizure frequency reduction rather than seizure cessation. By producing low-amplitude current stimulations, usually once every 5 min, this device results in reduction of seizures. Also, caretakers can activate the device by swiping a magnet over it at the time of the seizure, which can shorten seizure duration. More recent vagus nerve stimulators have integrated heart rate monitoring that detects tachycardia patterns typically associated with seizures and then activates the stimulator during these times. **Responsive neurostimulation (RNS)** is a technique that has been used in adults with epilepsy; it requires the implantation of subdural or depth electrodes to directly monitor seizure activity on a long-term basis to detect and abort the seizures. Once a seizure is detected, electrical stimulation is delivered to that area of the brain to stop the seizure. Gamma knife stereotactic radiosurgery is a less invasive surgical technique that uses a gamma radiation beam to ablate epileptic areas in the cortex; it has been used to treat mesial temporal sclerosis and hypothalamic hamartomas and for corpus callosotomies. Other minimally invasive techniques include laser interstitial thermal therapy (LITT) to ablate relatively small (<3x3 cm) epileptogenic zones and CO_2 laser callosotomy. Focal resection and hemispherectomy result in a high rate (50–80%) of seizure freedom. Corpus callosotomy and vagal nerve stimulation result in lower rates of seizure freedom (5–10% for vagal nerve stimulation and lower for callosotomy); however, these procedures do result in significant reductions in the frequency and severity of seizures, decreases in medication requirements, and meaningful improvements in the patient's quality of life in approximately half or more of eligible patients.

Discontinuation of Therapy

Discontinuation of AEDs is usually indicated when children are free of seizures for at least 2 yr. In more severe syndromes, such as temporal lobe epilepsy secondary to mesial temporal sclerosis, Lennox-Gastaut syndrome, or severe myoclonic epilepsy, a prolonged period of seizure freedom with treatment is often warranted before AEDs are withdrawn, if withdrawal is attempted at all. In self-limited (benign) epilepsy syndromes, the duration of therapy can often be as short as 6 mo.

Many factors should be considered before discontinuing medications, including the likelihood of remaining seizure-free after drug withdrawal based on the type of epilepsy syndrome and etiology; the risk of injury in case of seizure recurrence (e.g., if the patient drives); and the adverse effects of AED therapy. Most children who have not had a seizure for 2 yr or longer and who have a normal EEG when AED withdrawal is initiated, remain free of seizures after discontinuing medication, and most relapses occur within the first 6 mo.

Certain risk factors can help clinicians predict the prognosis after AED withdrawal. The most important risk factor for seizure relapse is an abnormal EEG before medication is discontinued. Children who have remote structural (symptomatic) epilepsy are less likely to be able to stop AEDs than are children who have a benign genetic (idiopathic) epilepsy. In patients with absences or in patients treated with valproate or other medications for primary generalized epilepsy, the risk of relapse might still be high despite a normal EEG because valproate (and less so other AEDs for primary generalized epilepsy) can normalize EEGs with generalized spike-wave abnormalities. Thus, in these patients, repeating the EEG during drug tapering may help identify a recurrence of the EEG abnormality and associated seizure risk before clinical seizures recur. Older age of epilepsy onset, longer duration of epilepsy, presence of multiple seizure types, and need to use more than one AED are all factors associated with a higher risk of seizure relapse after AED withdrawal.

AED therapy should be discontinued gradually; often over a period of 3-6 mo. Abrupt discontinuation can result in withdrawal seizures or in status epilepticus. Withdrawal seizures are especially common with phenobarbital and benzodiazepines; consequently, special attention must be given to a prolonged tapering schedule during the withdrawal of these AEDs. Seizures that occur more than 2-3 mo after AEDs are completely discontinued indicate relapse, and resumption of treatment is usually warranted. Seizures that occur before that, such as during or shortly after a medication taper, may be withdrawal seizures or alternatively may indicate a relapse.

The decision to attempt AED withdrawal must be assessed mutually by the clinician, the parents, and the child depending on the child's age. Risk factors should be identified and precautionary measures should be taken. The patient and family should be counseled fully on what to expect, what precautions to take (e.g., cessation of driving for a period of time), and what to do in case of relapse. A prescription for rectal diazepam or intranasal midazolam to be given at the time of seizures that might occur during and after tapering is usually warranted (see Table 611.16 for dosing).

Sudden Unexpected Death in Epilepsy (SUDEP)

SUDEP is the most common epilepsy-related cause of mortality and is responsible for up to 17% of deaths in patients with epilepsy. Risk factors include polytherapy with more than three AEDs, male gender, young age at epilepsy onset, developmental delay, poor AED compliance, nocturnal seizures, poorly controlled convulsive seizures (especially if > 3 per yr), high frequency of seizures (especially if > 50 per yr), and having epilepsy for > 30 yr in adults. Patients are usually found dead in their bed in a prone position with evidence suggesting a recent seizure.

Respiratory, cardiogenic, and mixed respiratory/cardiogenic mechanisms have been hypothesized to cause SUDEP. Respiratory models include seizure-induced central hypoventilation, neurogenic pulmonary edema, and disturbances in the brainstem serotonergic system leading to respiratory arrest. Cardiogenic models include seizure-induced cardiac arrhythmia as well as **cardiocerebral channelopathies** in which ion channels that are expressed in both the brain and heart cause cardiac dysfunction concurrent with the seizures. *SCN1A*, *SNC8A*, *ATP1A3*, and *KCNQ1* are examples of genes that encode for cardiocerebral ion channels known to cause epilepsy and that have also been associated with SUDEP. Mixed respiratory/cardiogenic models include seizure-induced dysautonomia, high levels of adenosine during seizure causing cardiorespiratory collapse, and spreading depression in the brainstem causing dysautonomia. More data are needed to determine if safety pillows, seizure detection devices, or selective serotonin reuptake inhibitors may be of benefit in preventing SUDEP. *It is currently recommended to counsel the patients and family regarding SUDEP, even if the topic is not comfortable to talk about.* In addition to providing them with important information, such counseling may also encourage families to address modifiable risk factors such as AED compliance. Table 611.12 lists other possible preventive measures.

Table 611.12

Measures in Clinical Practice to Reduce the Risk of SUDEP

Counseling: Explaining SUDEP and risk factors is imperative, even if the discussion may be uncomfortable. Emphasize modifiable risk factors, such as compliance with taking medication.

Reduction of tonic-clonic seizures: optimum treatment, good drug compliance, lifestyle advice (e.g., alcohol intake, sleep deprivation)

Treatment changes: change in a gradually staged manner; when switching drugs, introduce the new drug before withdrawing the old drug; the patient should have access to immediate advice in the event of worsening seizures during periods of change

Supervision at night for patients at high risk: attendance, use of alarms (balancing the benefits of independent living and the penalties of intrusive monitoring)

Choice of drugs: caution with AEDs with potential cardiorespiratory adverse effects

Act on ictal warning signs: tonic-clonic seizures that are prolonged, associated with marked cyanosis, severe bradycardia or apnea, and postictal EEG suppression; complex partial seizures with marked atonia (drop attacks); seizure in those with preexisting cardiac or respiratory impairment

Supervision after a tonic-clonic seizure: continuous attendance until full consciousness is restored; call emergency services for high-risk seizures

EEG, electroencephalogram; SUDEP, sudden unexpected death in epilepsy.

From Shorvan S, Tomson T: Sudden unexpected death in epilepsy, Lancet 378:2028-2036, 2011.

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611.7

Neonatal Seizures

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Keywords

subtle seizures
clonic seizures
tonic seizures
spasms
myoclonic seizures
jitteriness
hypoxic-ischemic encephalopathy
vascular events
intracranial infections
brain malformations
hypoglycemia
hypocalcemia
hypomagnesemia
hyponatremia
local anesthetic intoxication
amino acid or organic acid
nonketotic hyperglycinemia
pyridoxine- and pyridoxal-dependency disorders
benign neonatal convulsions (5th-day fits)
benign familial neonatal seizures
early myoclonic encephalopathy and early infantile epileptic encephalopathy (Ohtahara syndrome)
electroclinical dissociation
hypoxic-ischemic injury
Aicardi syndrome
lumbar puncture
inborn errors of metabolism

- organic acidemia
- maple syrup urine disease
- nonketotic hyperglycinemia
- biotinidase deficiency
- benign familial neonatal seizures
- pyridoxine dependency
- cytoarchitectural abnormalities

Seizures are possibly the most important and common indicator of significant neurologic dysfunction in the neonatal period. Seizure incidence is higher during this period than in any other period of life: 57.5 per 1,000 in infants with birth weights < 1,500 g and 2.8 per 1,000 in infants weighing between 2,500 and 3,999 g have seizures.

Pathophysiology

The immature brain has many differences from the mature brain that render it more excitable and more likely to develop seizures. Based predominantly on animal studies, these are delay in Na^+ , K^+ -adenosine triphosphatase maturation and increased NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor density. In addition, the specific types of these receptors that are increased are those that are permeable to calcium (GLUR2 AMPA receptors). This contributes to increased excitability and to the long-term consequences associated with seizures, particularly those resulting from perinatal hypoxia. Medications that block AMPA receptors, such as topiramate, may thus prove useful in this clinical setup.

Another difference is delay in the development of inhibitory GABAergic transmission. In fact, GABA in the immature brain has an excitatory function because the chloride gradient is reversed relative to the mature brain, with higher concentrations of chloride being present intracellularly than extracellularly. Thus, opening of the chloride channels in the immature brain results in depolarizing the cell and not in hyperpolarizing it. This phenomenon appears to be more prominent in male neonates, perhaps explaining their greater predisposition to seizures. This phenomenon is, however, more applicable to newborn animals than to human neonates because the rule is that GABAergic drugs are inhibitory in human newborns, including premature infants.

Types of Neonatal Seizures

There are five main neonatal seizure types: subtle, clonic, tonic, spasms, and myoclonic. Spasms, focal clonic, focal tonic, and generalized myoclonic seizures are, as a rule, associated with electrographic discharges (epileptic seizures), whereas motor automatisms and subtle, generalized tonic, and multifocal myoclonic episodes are frequently not associated with discharges and thus are thought to often represent release phenomena secondary to brain injury rather than true epileptic seizures (Table 611.13). To determine clinically whether such manifestations are seizures or release phenomena is often difficult, but precipitation of such manifestations by stimulation and aborting them by restraint or manipulation would suggest that they are not epileptic seizures. One needs to keep in mind, however, that epileptic seizures can also be induced by stimulation. Thus, in many cases, specifically in sick neonates with history of neurologic insults, continuous bedside EEG is necessary to make this distinction.

Table 611.13

Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures

CLASSIFICATION	CHARACTERIZATION
Focal clonic	Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk
	May be unifocal or multifocal
	May occur synchronously or asynchronously in muscle groups on one side of the body
	May occur simultaneously but asynchronously on both sides
	Cannot be suppressed by restraint
	Pathophysiology: epileptic
Focal tonic	Sustained posturing of single limbs
	Sustained asymmetric posturing of the trunk
	Sustained eye deviation
	Cannot be provoked by stimulation or suppressed by restraint
	Pathophysiology: epileptic
Generalized tonic	Sustained symmetric posturing of limbs, trunk, and neck
	May be flexor, extensor, or mixed extensor/flexor
	May be provoked or intensified by stimulation
	May be suppressed by restraint or repositioning
	Presumed pathophysiology: nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk
	Typically not repetitive or may recur at a slow rate
	May be generalized, focal, or fragmentary
	May be provoked by stimulation
	Presumed pathophysiology: may be epileptic or nonepileptic

Spasms	May be flexor, extensor, or mixed extensor/flexor
	May occur in clusters
	Cannot be provoked by stimulation or suppressed by restraint
	Pathophysiology: epileptic
Motor automatisms	
Ocular signs	Random and roving eye movements or nystagmus (distinct from tonic eye deviation)
	May be provoked or intensified by tactile stimulation
	Presumed pathophysiology: nonepileptic
Oral-buccal-lingual movements	Sucking, chewing, tongue protrusions
	May be provoked or intensified by stimulation
	Presumed pathophysiology: nonepileptic
Progression movements	Rowing or swimming movements
	Pedaling or bicycling movements of the legs
	May be provoked or intensified by stimulation
	May be suppressed by restraint or repositioning
	Presumed pathophysiology: nonepileptic
Complex purposeless movements	Sudden arousal with transient increased random activity of limbs
	May be provoked or intensified by stimulation
	Presumed pathophysiology: nonepileptic

From Mizrahi EM, Kellaway P: Diagnosis and management of neonatal seizures, Philadelphia, 1998, Lippincott-Raven, Table 4, p. 21.

Subtle Seizures

Subtle seizures include transient eye deviations, nystagmus, blinking, mouthing, abnormal extremity movements (rowing, swimming, bicycling, pedaling, and stepping), fluctuations in heart rate, hypertension episodes, and apnea. Subtle seizures occur more commonly in premature than in full-term infants.

Clonic Seizures

Clonic seizures can be focal or multifocal. Multifocal clonic seizures incorporate several body parts and are migratory in nature. The migration follows a non-Jacksonian trend; for example, jerking of the left arm can be associated with jerking of the right leg. Generalized clonic seizures that are bilateral, symmetric, and synchronous are uncommon in the neonatal period, presumably due to decreased connectivity associated with incomplete myelination at this age.

Tonic Seizures

Tonic seizures can be focal or generalized (generalized are more common). Focal tonic seizures include persistent posturing of a limb or posturing of the trunk or neck in an asymmetric way, often with persistent horizontal eye deviation. Generalized tonic seizures are bilateral tonic limb extensions or tonic flexions of the upper extremities often associated with tonic extension of the lower extremities and trunk.

Spasms

Spasms are sudden generalized jerks lasting 1-2 sec that are distinguished from generalized tonic spells by their shorter duration and by the fact that spasms are usually associated with a single, very brief, generalized discharge.

Myoclonic Seizures

Myoclonic seizures are divided into focal, multifocal, and generalized types. Myoclonic seizures can be distinguished from clonic seizures by the rapidity of the jerks (<50 msec) and by their lack of rhythmicity. Focal myoclonic seizures characteristically affect the flexor muscles of the upper extremities and are sometimes associated with seizure activity on EEG. Multifocal myoclonic movements involve asynchronous twitching of several parts of the body and are not commonly associated with seizure discharges on EEG. Generalized myoclonic seizures involve bilateral jerking associated with flexion of the upper and occasionally lower extremities. The latter type of myoclonic jerks is more commonly correlated with EEG abnormalities than the other types.

Seizures Versus Jitteriness

Jitteriness can be defined as rapid motor activities, such as a tremor or shake, that can be ended by flexion or holding the limb. Seizures, on the other hand, generally do not end with tactile or motor suppression. Jitteriness, unlike most seizures, is usually induced by a stimulus. Also unlike jitteriness, seizures often involve eye deviation and autonomic changes.

Etiology

Table 611.14 lists causes of neonatal seizures.

Table 611.14

Causes of Neonatal Seizures According to Common Age of Presentation

AGES 1-4 DAYS

Hypoxic-ischemic encephalopathy
Drug withdrawal, maternal drug use of narcotic or barbiturates
Drug toxicity: lidocaine, penicillin
Intraventricular hemorrhage
Acute metabolic disorders

- Hypocalcemia
- Sepsis
- Maternal hyperthyroidism, or hypoparathyroidism
- Hypoglycemia
- Perinatal insults, prematurity, small for gestational age
- Maternal diabetes
- Hyperinsulinemic hypoglycemia
- Hypomagnesemia
- Hyponatremia or hypernatremia
- Iatrogenic or inappropriate antidiuretic hormone secretion

Inborn errors of metabolism

- Galactosemia
- Hyperglycinemia
- Urea cycle disorders

Pyridoxine dependency and pyridoxal-5-phosphate dependency (must be considered at any age)

AGES 4-14 DAYS

Infection

- Meningitis (bacterial)
- Encephalitis (enteroviral, herpes simplex)

Metabolic disorders

- Hypocalcemia related to diet, milk formula
- Hypoglycemia, persistent
- Inherited disorders of metabolism
- Galactosemia
- Fructosemia
- Leucine sensitivity
- Hyperinsulinemic hypoglycemia, hyperinsulinism, hyperammonemia syndrome
- Anterior pituitary hypoplasia, pancreatic islet cell tumor
- Beckwith syndrome

Drug withdrawal, maternal drug use of narcotics or barbiturates
Benign neonatal convulsions, familial and nonfamilial
Kernicterus, hyperbilirubinemia
Developmental delay, epilepsy, neonatal diabetes syndrome

AGES 2-8 WK

Infection

- Herpes simplex or enteroviral encephalitis
- Bacterial meningitis

Head injury

- Subdural hematoma
- Child abuse

Inherited disorders of metabolism

- Aminoacidurias
- Urea cycle defects
- Organic acidurias

- Neonatal adrenoleukodystrophy

Malformations of cortical development

- Lissencephaly
- Focal cortical dysplasia

Tuberous sclerosis
Sturge-Weber syndrome

Hypoxic-Ischemic Encephalopathy

This is the most common cause of neonatal seizures, accounting for 50–60% of patients. Seizures secondary to this encephalopathy occur within 12 hr of birth.

Vascular Events

These include intracranial bleeds and ischemic strokes and account for 10–20% of patients. Three types of hemorrhage can be distinguished: primary subarachnoid hemorrhage, germinal matrix–intraventricular hemorrhage, and subdural hemorrhage. Patients with arterial strokes or venous sinus thrombosis can present with seizure and these can be diagnosed by neuroimaging. Venous sinus thrombosis could be missed unless MR or CT venography studies are requested.

Intracranial Infections

Bacterial and nonbacterial infections account for 5–10% of the cases of neonatal seizures and include bacterial meningitis, TORCH (*t* oxoplasmosis, *o* ther infections, *r* ubella, *c* ytomegalovirus, *h* erpes simplex virus) infections, and, particularly, herpes simplex encephalitis.

Brain Malformations

Brain malformations account for 5–10% of neonatal seizure cases. An example is **Aicardi syndrome,** which affects girls only and consists of retinal lacunae, agenesis of the corpus callosum, and severe seizures, including subsequent infantile spasms with hypsarrhythmia that is sometimes initially unilateral on EEG.

Metabolic Disturbances

Metabolic disturbances include disturbances in glucose, calcium, magnesium, other electrolytes, amino acids, or organic acids and pyridoxine dependency (Table 611.15).

Table 611.15

Overview of Diagnostic Findings in Inborn Errors of Metabolism Presenting With Isolated Neonatal Seizures

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DISORDER	MRI AND MRS FINDINGS	CSF FINDINGS	FURTHER DIAGNOSTIC TESTING
Pyridoxine-dependent seizures	Normal or hypoplasia of corpus callosum and cerebellum	Increased levels of α-AASA, pipecolic acid, and neurotransmitter markers	Urinary and serum α-AASA or pipecolic acid, *ALDH7A1* gene testing
Pyridoxal-phosphate–dependent seizures	Generalized atrophy	May be normal, or nonspecific changes	Pyridoxamine-5-phosphate oxidase gene testing
Defects of serine biogenesis	Initially normal, progressing to profound hypomyelination	Low levels of serine; may also have low levels of glycine or 5-MTHF	Skin biopsy for 3-phosphoglycerate dehydrogenase activity
GLUT-1 deficiency	Normal or generalized atrophy	CSF glucose < 40 mg/dL or < half of serum glucose	FDG-PET; 3-OMG uptake in red blood cells; gene testing for *SLC2A1*
Nonketotic hyperglycinemia	Normal, or agenesis or thinning of the corpus callosum	Increased levels of glycine, and increased CSF/plasma glycine ratio	Liver glycine cleavage complex enzyme activity; gene testing for nonketotic hyperglycinemia
Sulfite oxidase/molybdenum cofactor deficiency	MRI findings can mimic those of hypoxic-ischemic injury; MRS reveals increased levels of lactate, myoinositol, and choline, with decreased levels of NAA	Normal or nonspecific changes in amino acid profile	Plasma homocysteine and uric acid; urine sulfites, sulfocysteine, and thiosulfates; sulfite oxidase enzyme activity in skin or liver biopsy
Congenital neuronal ceroid-lipofuscinosis	Generalized cerebral hypoplasia	Normal	Cathepsin D gene testing
γ-aminobutyric acid transferase deficiency	MRI indicates leukodystrophy and agenesis of the corpus callosum; MRS indicates elevated levels of γ-aminobutyric acid in the basal ganglia	Increased levels of homocarnosine	Enzyme activity in lymphocytes
Dihydropyrimidine	Diffuse atrophy	Increased levels of	Dihydropyrimidine dehydrogenase

dehydrogenase deficiency		uracil and thymine	gene testing
Creatine deficiency syndromes	MRI indicates delayed myelination MRS reveals absent creatine peak	Normal	Serum creatine and guanidinoacetate; urinary creatine, creatinine, and guanidinoacetate; fibroblast enzyme activity; specific genetic testing

3-OMG, 3-O-methyl-D-glucose;5-MTHF, 5-methyltetrahydrofolate; α-AASA, α-aminoadipic emialdehyde; CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate.

For current information on the best locations to perform biochemical and genetic testing, see genereviews.org .

From Ficicioglu C, Bearden D: Isolated neonatal seizures: when to suspect inborn errors of metabolism, Pediatric Neurol 45:283-291, 2011, Table 2.

Hypoglycemia can cause neurologic disturbances and is very common in small neonates and neonates whose mothers are diabetic or prediabetic. The duration of hypoglycemia is very critical in determining the incidence of neurologic symptoms.

Hypocalcemia occurs with two peaks. The first peak corresponds to low-birthweight infants and is evident in the first 2-3 days of life. The second peak occurs later in neonatal life and often involves large, full-term babies who consume milk that has an unfavorable ratio of phosphorus to calcium and phosphorus to magnesium. **Hypomagnesemia** is often associated with hypocalcemia. **Hyponatremia** can cause seizures and is often secondary to inappropriate antidiuretic hormone secretion or water intoxication.

Local anesthetic intoxication seizures can result from neonatal intoxication with local anesthetics that are inadvertently administered into the infant's scalp.

Neonatal seizures can also result from disturbances in **amino acid or organic acid** metabolism. These are usually associated with acidosis and/or hyperammonemia. However, even in the absence of these findings, if a cause of the seizures is not immediately evident, then ruling out metabolic causes requires a full metabolic workup (see Chapter 611.2), including examination of serum amino acids, acyl carnitine profile, lactate, pyruvate, ammonia, very-long-chain fatty acids (for neonatal adrenoleukodystrophy and Zellweger syndrome), examination of urine for organic acids, α-aminoadipic acid semialdehyde and sulfocysteine, as well as examination of CSF for glucose, protein, cells, amino acids, lactate, pyruvate, α-aminoadipic acid semialdehyde, pyridoxal phosphate, 5-MTHF (5-methyltetrahydrofolate), succinyladenosine, and CSF neurotransmitter metabolites. This is because many inborn errors of metabolism, such as nonketotic hyperglycinemia, can manifest with neonatal seizures (often mistaken initially for hiccups, which these patients also have) and can be detected only by performing these tests. Definitive diagnosis of **nonketotic hyperglycinemia,** for example, requires measuring the ratio of CSF glycine to plasma glycine.

Pyridoxine- and **pyridoxal-dependency disorders** can cause severe seizures. These seizures, which are often multifocal clonic, usually start during the first few hours of life. Cognitive impairment is often associated if therapy is delayed (see Chapter 611.4).

Drug Withdrawal

Seizures can rarely be caused by the neonate's passive addiction and then drug withdrawal after birth. Such drugs include narcotic analgesics, sedative–hypnotics, and others. The associated seizures appear during the first 3 days of life.

Neonatal Seizure Syndromes

Seizure syndromes include **benign neonatal convulsions (5th-day fits),** which are usually apneic, and focal motor seizures that start around the 5th day of life. Interictal EEG shows a distinctive pattern called *theta pointu alternant* (runs of sharp 4- to 7-Hz activity), and ictal EEG shows multifocal electrographic seizures. Patients have a good response to medications and a good prognosis. Autosomal dominant **benign familial neonatal seizures** have an onset at 2-4 days of age and usually remit at 2-15 wk of age. The seizures consist of ocular deviation, tonic posturing, clonic jerks, and, at times, motor automatisms. Interictal EEG is usually normal. These are caused by mutations in the *KCNQ2* and *KCNQ3* genes. Approximately 16% of patients develop later epilepsy. **Early myoclonic encephalopathy** and **early infantile epileptic encephalopathy (Ohtahara syndrome)** are discussed in Chapter 611.4 .

Miscellaneous Conditions

Miscellaneous conditions include benign neonatal sleep myoclonus and hyperekplexia, which are nonepileptic conditions (see Chapter 612).

Diagnosis

Some cases can be correctly diagnosed by simply taking the prenatal and postnatal history and performing an adequate physical examination; however, the *American Clinical Neurophysiology Society Guidelines for Neonatal EEG Monitoring recommend EEG monitoring in cases where there is a clinical concern for seizure and/or when an infant has a condition that predisposes the infant to seizures*. EEG monitoring can show epileptiform activity (e.g., sharp waves) between the seizures (suggesting an increased risk for seizures) and confirm electrographic seizure activity if a clinical seizure is recorded. Additionally, EEG monitoring is often necessary because electrographic seizures can occur without observed clinical signs **(electroclinical dissociation).** This is presumed to be caused by the immaturity of cortical connections, resulting, in many cases, in no or minimal clinical manifestations.

Continuous bedside EEG monitoring in the neonatal intensive care unit is thus now part of routine clinical practice for neonates at risk for neonatal seizures and brain injury. Amplitude-integrated EEG (aEEG) monitoring is becoming increasingly used as an adjunct to conventional EEG monitoring and provides a bedside graphic representation of a neonate's electrocerebral activity, which may aid in earlier seizure identification. Appropriately trained nurses and providers can identify possible seizure activity using aEEG and can then contact the neurophysiologist to confirm the presence or absence of seizures. Examples of situations in which continuous EEG monitoring should be used include cases of **hypoxic-ischemic injury** (particularly if an infant is undergoing therapeutic hypothermia), intracranial infarct or hemorrhage, or CNS infection; for seizure screening in infants receiving paralytics; in infants with congenital cerebral malformations, and/or in infants in whom clinical events suspected to be seizures need to be characterized.

Careful neurologic examination of the infant might uncover the cause of the seizure disorder. Examination of the retina might show the presence of chorioretinitis, suggesting a congenital TORCH infection, in which case titers of mother and infant are indicated. The **Aicardi syndrome** is associated with coloboma of the iris and retinal lacunae. Inspection of the skin might show hypopigmented lesions characteristic of tuberous sclerosis (seen best on ultraviolet light examination) or the typical crusted vesicular lesions of incontinentia pigmenti; both neurocutaneous syndromes are often associated with generalized myoclonic seizures beginning early in life. An unusual body or urine odor suggests an inborn error of metabolism.

Blood should be obtained for determinations of glucose, calcium, magnesium, electrolytes, and blood urea nitrogen. If hypoglycemia is a possibility, bedside serum glucose testing is indicated so that treatment can be initiated immediately. Hypocalcemia can occur in isolation or in association with hypomagnesemia. A lowered serum calcium level is often associated with birth trauma or a CNS insult in the perinatal period. Additional causes include maternal diabetes, prematurity, DiGeorge syndrome, and high-phosphate feedings. Hypomagnesemia (<1.5 mg/dL) is often associated with hypocalcemia and occurs particularly in infants of malnourished mothers. In this situation, the seizures are resistant to calcium therapy but respond to intramuscular magnesium, 0.2 mL/kg of a 50% solution of $MgSO_4$. Serum electrolyte measurement can indicate significant hyponatremia (serum sodium < 115 mEq/L) or hypernatremia (serum sodium > 160 mEq/L) as a cause of the seizure disorder.

A **lumbar puncture** may be indicated in neonates with seizures, unless the cause is obviously related to a metabolic disorder (such as hypoglycemia or hypocalcemia) or attributable to a structural etiology such as hypoxic-ischemic injury or intracranial hemorrhage. The CSF findings can indicate a bacterial meningitis or aseptic encephalitis. Prompt diagnosis and appropriate therapy improve the outcome for these infants. Bloody CSF indicates a traumatic tap or a subarachnoid or intraventricular bleed. Immediate centrifugation of the specimen can assist in differentiating the two disorders. A clear supernatant suggests a traumatic tap, and a xanthochromic color suggests a subarachnoid bleed. Mildly jaundiced normal infants can have a yellowish discoloration of the CSF that makes inspection of the supernatant less reliable in the newborn period.

Many **inborn errors of metabolism** cause generalized convulsions in the newborn period. Because these conditions are often inherited in an autosomal recessive or X-linked recessive fashion, it is imperative that a careful family history be obtained to determine if there is consanguinity or whether siblings or close relatives developed seizures or died at an early age. Serum ammonia determination is useful for screening for the hypoglycemic hyperammonemia syndrome and for suspected urea cycle abnormalities. In addition to having generalized clonic seizures, these latter infants present during the first few days of life with increasing lethargy progressing to coma, anorexia and vomiting, and a bulging fontanel. If the blood gases show an anion gap and a metabolic acidosis with the hyperammonemia, urine organic acids should be immediately determined to investigate the possibility of an **organic acidemia** such as methylmalonic or propionic acidemia.

Maple syrup urine disease should be suspected when a metabolic acidosis occurs in association with generalized clonic seizures, vomiting, a bulging fontanel, and muscle rigidity during the 1st wk of life. The result of a rapid screening test using 2,4-dinitrophenylhydrazine that identifies keto derivatives in the urine is positive in maple syrup urine disease.

Additional metabolic causes of neonatal seizures include **nonketotic hyperglycinemia,** an intractable condition characterized by markedly elevated plasma and CSF glycine levels, prominent hiccups, persistent generalized seizures, and lethargy rapidly leading to coma; ketotic hyperglycinemia in which seizures are associated with vomiting, fluid and electrolyte disturbances, and a metabolic acidosis; and Leigh disease suggested by elevated levels of serum and CSF lactate or an increased lactate:pyruvate ratio. **Biotinidase deficiency** should also be considered. A comprehensive description of the diagnosis and management of these metabolic diseases is discussed in Part X, Metabolic Disorders.

Unintentional **injection of a local anesthetic** into a fetus during labor can produce intense tonic seizures. These infants are often thought to have had a traumatic delivery because they are flaccid at birth, have abnormal brainstem reflexes, and show signs of respiratory depression that sometimes require ventilation. Examination may show a needle puncture of the skin or a perforation or laceration of the scalp. An elevated serum anesthetic level confirms the diagnosis. The treatment consists of supportive measures and promotion of urine output by administering intravenous fluids with appropriate monitoring to prevent fluid overload.

Benign familial neonatal seizures, an autosomal dominant condition, begins on the 2nd to 3rd day of life, with a seizure frequency of 10-20/day. Patients are normal between seizures, which stop in 1-6 mo. These are caused by mutations in the voltage-sensitive potassium channel genes *Kv7.2* and *Kv7.3* (*KCNQ2* and *KCNQ3*). Other mutations in the *Kv7.2* gene cause severe neonatal epileptic encephalopathy. **Fifth-day fits** occur on day 5 of life (4-6 days) in normal-appearing neonates. The seizures are multifocal and are often present for < 24 hr. The diagnosis requires exclusion of other causes of seizures and sequencing of the above genes. The prognosis is good for the benign form.

Pyridoxine dependency, a rare disorder, must be considered when seizures begin shortly after birth with signs of fetal distress in utero and are resistant to conventional anticonvulsants such as phenobarbital or phenytoin even if there is an initial treatment response. The history may suggest that similar seizures occurred in utero. When pyridoxine-dependent seizures are suspected, 100 mg of pyridoxine should be administered intravenously during the EEG, which should be promptly performed once the diagnosis is considered. The seizures abruptly cease, and the EEG often normalizes in the next few hours or longer. Not all cases of pyridoxine dependency respond dramatically to the initial bolus of intravenous pyridoxine. Therefore, a 6-wk trial of oral pyridoxine (100-200 mg/day) or preferably pyridoxal phosphate (because pyridoxine does not help infants with the related but distinct syndrome of pyridoxal dependency) is recommended for infants in whom a high index of suspicion continues after a negative response to intravenous pyridoxine. Measurement of serum pipecolic acid and α-aminoadipic acid semialdehyde (elevated) and CSF pyridoxal-5-phosphate (decreased) needs to be performed before initiation of the trials without delay. These children require lifelong supplementation of oral pyridoxine (100 mg/day at times with folinic acid) or pyridoxal phosphate (up to 50 mg/kg/day given every 6 hr). Cerebral folate deficiency should also be ruled out by a medication trial (folinic acid 1-3 mg/kg/day) and by CSF levels of 5-methyltetrahydrofolate assay. Gene sequencing can confirm the diagnosis (see Chapter 611.4). The earlier the therapy is initiated in these vitamin-responsive disorders, the more favorable the outcome.

Drug-withdrawal seizures can occur in the newborn nursery but can take several weeks to develop because of prolonged excretion of the drug by the neonate. The incriminated drugs include barbiturates, benzodiazepines, heroin, and methadone. The infant may be jittery, irritable, and lethargic and can have myoclonus or frank clonic seizures. The mother might deny the use of drugs; a serum or urine drug screen might identify the responsible agent.

Infants with focal seizures, suspected stroke or intracranial hemorrhage, and severe **cytoarchitectural abnormalities** of the brain (including lissencephaly and schizencephaly) who clinically may appear normal or microcephalic should undergo MRI or CT scan. Indeed, it is appropriate to recommend imaging of all neonates with seizures unexplained by serum glucose, calcium, or electrolyte disorders.

Prognosis

Over the last few decades, the prognosis of neonatal seizures has improved owing to advancements in obstetric and intensive neonatal care. Mortality rates have decreased from 40% to 20%. The correlation between EEG and prognosis is very clear. Although neonatal EEG interpretation is very difficult, EEG was found to be highly associated with the outcome in premature and full-term infants. An abnormal background is a powerful predictor of a less favorable later outcome. In addition, prolonged electrographic seizures (>10 min/hr), multifocal periodic electrographic discharges, and spread of the electrographic seizures to the contralateral hemisphere are also correlated with a poorer outcome. The underlying etiology of the seizures is the main determinant of outcome. For example, patients with seizures secondary to hypoxic-ischemic encephalopathy have a 50% chance of developing normally, whereas those with seizures caused by primary subarachnoid hemorrhage or hypocalcemia have a much better prognosis.

Treatment

A mainstay in the therapy of neonatal seizures is the diagnosis and treatment of the underlying etiology (e.g., hypoglycemia, hypocalcemia, meningitis, drug withdrawal, trauma) whenever one can be identified. There are conflicting approaches regarding the control of neonatal seizures. Most experts advocate complete control of clinical as well as electrographic seizures. Others argue for treating clinical seizures only. An important consideration before starting anticonvulsants is deciding, based on the severity, duration, and frequency of the seizures, if the patient needs to receive intravenous therapy and loading with an initial bolus or can simply be started on maintenance doses of a long-acting drug. Patients often require assisted ventilation after receiving intravenous or oral loading doses of AEDs, and thus precautions for observations and for needed interventions are necessary.

Lorazepam and Other Benzodiazepines

Lorazepam is often used in the acute treatment of neonatal seizures; it is distributed to the brain very quickly and exerts its anticonvulsant effect in less than 5 min. It is not very lipophilic and does not clear out from the brain very rapidly. Its action can last 6-24 hr. Usually, it does not cause hypotension or respiratory depression. The dose is 0.1 mg/kg when used for acute treatment of seizures, and 0.05 mg/kg (range: 0.02-0.10 mg/kg) every 4-8 hr when used as a scheduled medication. Diazepam has also been used, and midazolam is often started as a continuous infusion for refractory cases of neonatal seizures. Midazolam doses used have been in the range of 0.05-0.15 mg/kg as an initial intravenous bolus, with a continuous infusion of 0.5-1 µg/kg/min intravenously that can then be gradually titrated upward, if tolerated, every 5 min or longer, to a maximum of approximately 33 µg/kg/min (2 mg/kg/hr).

Phenobarbital

Phenobarbital is considered by many as the first-choice long-acting drug in neonatal seizures. Whether to use a benzodiazepine first depends on the clinical situation. The usual loading dose is 20 mg/kg. If this dosage is not effective, then additional doses of 5-10 mg/kg can be given until a cumulative dose of 40 mg/kg is reached. Respiratory support may be needed after phenobarbital loading. Twenty-four hours after starting the loading dose, maintenance dosing can be started at 3-6 mg/kg/day, usually administered in two separate doses. Phenobarbital is metabolized in the liver and is excreted through the kidneys. Thus, any abnormality in the function of these organs alters the drug's metabolism and can result in toxicity. In infants with acidosis or critical illness that might alter the serum protein content, free (i.e., not protein bound) levels of the drug should be followed carefully. The use of phenobarbital can be associated with electroclinical dissociation, where electrographic seizures persist despite the resolution of clinical seizures, after the drug is given. Subsequent EEG monitoring is therefore imperative to rule out subclinical seizure activity.

Phenytoin and Fosphenytoin

The only randomized control trial to compare the efficacy of phenobarbital versus phenytoin did not find that one drug was superior to the other for the treatment of neonatal seizures. Fosphenytoin or phenytoin can thus be used as a first-line or second-line agent. Due to its reduced solubility, potentially severe local cutaneous reactions, interaction with other drugs, and possible cardiac toxicity, intravenous phenytoin is not widely used, and fosphenytoin is the preferred agent. Phenytoin is given at a loading dose of 20 mg/kg at a rate not to exceed 0.5-1.0 mg/kg/min, so as to prevent cardiac problems; the medication needs to be avoided in patients with significant heart disease. The heart rate should be monitored while the drug is administered. It is not possible to mix phenytoin or fosphenytoin with dextrose solutions. Additionally, phenytoin and fosphenytoin should not be used in conjunction with intravenous lidocaine owing to the concern that both drugs can increase the risk of cardiac arrhythmias and hypotension.

As stated above, fosphenytoin, which is a phosphate ester prodrug, is preferable to phenytoin. It is highly soluble in water and can be administered very safely intravenously and intramuscularly, without causing injury to tissues. Fosphenytoin is administered in phenytoin equivalents (PE). The usual loading dose of fosphenytoin is 15-20 PE/kg administered over 30 min. Maintenance doses of 4-8 PE/kg/day can be given. As is the case for phenobarbital, free levels of the drug should be monitored in neonates whose serum pH or protein content might not be normal.

Other Medications

Approximately 45% of neonates respond to the first drug used if it is phenobarbital or phenytoin and an additional 15% respond to the second agent. **Levetiracetam** (which can be given intravenously with a later convenient conversion to oral solution) and topiramate (oral) are reported to be the drugs of second and third choice for approximately half of the surveyed pediatric neurologists, and some have used them even before phenobarbital or phenytoin in selected cases. The dosages used are 30-60 mg/kg/day of levetiracetam, at times lower or higher, and 5-10 mg/kg/day of topiramate (sometimes higher). There is growing evidence that lidocaine is an effective second- or third-line agent, and some studies suggest it may be superior to benzodiazepines in treating neonatal seizures. A bolus dose of 2 mg/kg is given, followed by an infusion at a rate of 4-6 mg/kg/hr. Cardiac arrhythmias and hypotension were not reported at this dosing range but are potential side effects at higher doses. Lidocaine should not be used in conjunction with phenytoin or fosphenytoin owing to concern for cardiac side effects. Bumetanide has previously been used as an adjunct drug, particularly with phenobarbital, because of its effect on the chloride gradient; however, the most recent open-label study did not show an added benefit and suggested that bumetanide use is associated with an increased risk of hearing loss. Primidone, carbamazepine, lamotrigine, or valproate use, although reported in some studies, is rarely warranted. Valproate, for example, is more likely to be toxic in children younger than 2 yr of age than in older children.

Duration of Therapy

The duration of therapy is related to the risk of epilepsy developing later in infants suffering from neonatal seizures, a risk that ranges from 10–30% and depends on the individual neurologic examination, the etiology of the seizures, and the EEG at the time of discharge from the hospital. In general, if the EEG before the time of discharge does not show evidence of epileptiform activity, medications are usually tapered at that time. If the EEG remains paroxysmal, the decision is usually delayed until several months after discharge.

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611.8

Status Epilepticus

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Keywords

convulsive status epilepticus
nonconvulsive status
febrile status epilepticus
nonconvulsive status epilepticus
epilepsia partialis continua
refractory status epilepticus
superrefractory status epilepticus (SRSE)
new-onset refractory status epilepticus (NORSE)
devastating epileptic encephalopathy in school-age children (DESC)
fever-induced refractory epileptic encephalopathy in school-age children (FIRES)
hemiconvulsion–hemiplegia–epilepsy syndrome
Rasmussen encephalitis
pseudo–status epilepticus
refractory status epilepticus treatment

ketogenic diet
anti-NMDA receptor encephalitis or CNS vasculitis
inhaled anesthetics
induced hypothermia

Status epilepticus (SE) is a medical emergency that should be anticipated in any patient who presents with an acute seizure. The ILAE has refined the definition of SE to reflect the time at which treatment should be initiated (t_1) and time at which continuous seizure activity leads to long-term sequelae (t_2) such as neuronal injury, depending on the type of SE. In the past, the cutoff time was 30 min based on animal studies that showed evidence of neuronal damage after this time point, but this has been reduced to emphasize the risks involved with the longer durations and the need for early and aggressive pharmacologic intervention. For generalized tonic-clonic seizures, SE is defined as continuous convulsive activity or recurrent generalized convulsive seizure activity without regaining of consciousness (t_1 = 5 min, $t_2 \geq$ 30 min). The definition differs for SE consisting of focal seizures with impaired awareness (t_1 = 10 min, t_2 = 30 min) and absence SE (t_1 = 10-15 min, t_2 = unknown). The most common type of SE is **convulsive status epilepticus** (generalized tonic, clonic, or tonic-clonic), but other types do occur, including **nonconvulsive status** (focal with impaired awareness, absence), myoclonic status, epilepsia partialis continua, and neonatal status epilepticus. The incidence of SE ranges between 10 and 60 per 100,000 population in various studies. SE is most common in children younger than 5 yr of age, with an incidence in this age-group of > 100 per 100,000 children.

Approximately 30% of patients presenting with SE are having their first seizure, and approximately 40% of these later develop epilepsy. **Febrile status epilepticus** is the most common type of SE in children. In the 1950s and 1960s, mortality rates of 6–18% were reported after SE; currently, with the recognition of SE as a medical emergency, a lower mortality rate of 4–5% is observed, most of it secondary to the underlying etiology rather than to the seizures. SE carries an approximately 14% risk of new neurologic deficits, most of them (12.5%) secondary to the underlying pathology.

Nonconvulsive status epilepticus manifests as a confusional state, dementia, hyperactivity with behavioral problems, fluctuating impairment of consciousness with at times unsteady sitting or walking, fluctuating mental status, confusional state, hallucinations, paranoia, aggressiveness catatonia, and or psychotic symptoms. It should be considered in any of these situations, especially in an unresponsive or encephalopathic child. **Epilepsia partialis continua** has been defined previously and can be caused by tumor, vascular etiologies, mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]), and Rasmussen encephalitis.

Refractory status epilepticus is SE that has failed to respond to therapy, usually with at least two medications (such as a benzodiazepine and another medication). Currently, the trend is not to assign a minimum duration, whereas in the past a minimum duration of 30 min, 60 min, or even 2 hr was cited. **Superrefractory status epilepticus** is SE that has failed to resolve, or recurs, within 24 hr or more despite therapy that includes a continuous infusion such as midazolam and/or pentobarbital.

New-onset refractory status epilepticus (NORSE) has been identified as a distinct entity that can be caused by almost any of the causes of SE in a patient without prior epilepsy. It also is often of unknown etiology, presumed to be encephalitic or postencephalitic, can last several weeks or longer, and often, but not always, has a poor prognosis. **Devastating epileptic encephalopathy in school-age children (DESC),** also called **fever-induced refractory epileptic encephalopathy in school age children (FIRES),** is a syndrome of refractory SE that is associated with acute febrile infections, appears to be parainfectious in nature, and appears to be highly drug resistant but is often responsive to the ketogenic diet.

Etiology

Etiologies include new-onset epilepsy of any type; drug intoxication (e.g., tricyclic antidepressants) in children and drug and alcohol abuse in adolescents; drug withdrawal or overdose in patients taking AEDs; hypoglycemia; hypocalcemia; hyponatremia; hypomagnesemia; acute head trauma; encephalitis; meningitis; autoimmune encephalitis (such as anti-NMDA receptor; steroid-responsive encephalopathy associated with autoimmune thyroiditis/SREAT, and anti–voltage-gated potassium channel complex antibody syndromes); ischemic (arterial or venous) stroke; intracranial hemorrhage; folinic acid and pyridoxine- and pyridoxal-phosphate dependency (these usually present in infancy, but childhood onset is also possible); inborn errors of metabolism (see Chapter 611.2) such as nonketotic hyperglycinemia in neonates and mitochondrial encephalopathy with lactic acidosis (MELAS) in infants, children and adolescents; ion channel–related epilepsies (e.g., sodium and potassium channel mutations reviewed in the sections above); hypoxic-ischemic injury (e.g., after cardiac arrest); systemic conditions (such as hypertensive encephalopathy, posterior reversible encephalopathy, renal or hepatic encephalopathy); brain tumors; and any other disorder that can cause epilepsy (such as brain malformations, neurodegenerative disorders, different types of progressive myoclonic epilepsy, storage diseases).

A rare condition called **hemiconvulsion–hemiplegia–epilepsy syndrome** consists of prolonged febrile SE presumably caused by focal acute encephalitis with resultant atrophy in the involved hemisphere, contralateral hemiplegia, and chronic epilepsy. It should be suspected early on to attempt to control the seizures as early as possible. This and the somewhat similar condition mentioned above called FIRES are likely to have a parainfectious-autoimmune etiology. **Rasmussen encephalitis** often causes epilepsia partialis continua (see Chapter 611.3) and sometimes convulsive SE. Several types of infections are more likely to cause encephalitis with SE, such as herpes simplex (complex partial and convulsive status), *Bartonella* (particularly nonconvulsive status), Epstein-Barr virus, and mycoplasma (postinfectious encephalomyelitis with any type of status epilepticus). Postinfectious encephalitis and acute disseminated encephalomyelitis are common causes of SE, including refractory SE. HHV6 can cause a distinct epileptic syndrome with limbic SE in immunosuppressed patients.

Mechanisms

The mechanisms leading to the establishment of sustained seizure activity seen in SE appear to involve (1) failure of desensitization of AMPA glutamate receptors, thus causing the persistence of increased excitability, and (2) reduction of GABA-mediated inhibition as a result of intracellular internalization of $GABA_A$ receptors. This explains the clinical observation that SE is often less likely to stop in the next specific period of time the longer the seizure has lasted and why benzodiazepines appear to be decreasingly effective the longer seizure activity lasts. During SE, there is an increased cerebral metabolic rate and a compensatory increase in cerebral blood flow that, after approximately 30 min, is not able to keep up with the increases in cerebral metabolic rate. This leads to a transition from adequate to inadequate cerebral oxygen tensions and, together with other factors, contributes to neuronal injury resulting from SE.

Therapy

SE is a medical emergency that requires initial and continuous attention to securing the airway, breathing, and circulation (with continuous monitoring of vital signs including ECG) and determination and management of the underlying etiology (e.g., hypoglycemia). Laboratory studies, including glucose, sodium, calcium, magnesium, complete blood count, basic metabolic panel, CT scan, and continuous EEG, are needed for all patients. Blood and spinal fluid cultures, toxic drug screens, and tests for inborn errors of metabolism are often needed. AED levels need to be determined in all patients known already to be taking these drugs. EEG is helpful in ruling out **pseudo–status epilepticus** (psychological conversion reaction mimicking SE) or other movement disorders (chorea, tics), rigors, clonus with stimulation, and decerebrate/decorticate posturing. The EEG can also be helpful in identifying the type of SE (generalized vs focal), which can guide further testing for the underlying etiology and further therapy. EEG can also help distinguish between postictal depression and later stages of SE in which the clinical manifestations are subtle (e.g., minimal myoclonic jerks) or absent (electroclinical dissociation), and can help in monitoring the therapy, particularly in patients who are paralyzed and intubated. Neuroimaging must be considered after the child has been stabilized, especially if it is indicated by the clinical manifestations, by an asymmetric or focal nature of the EEG abnormalities, or by lack of knowledge of the underlying etiology.

The initial emergent therapy should be started for convulsive seizures lasting longer than 5 min and involves the use of a benzodiazepine medication (Fig. 611.7). The American Epilepsy Society SE Guidelines recommend using either intravenous lorazepam, intravenous diazepam, or intramuscular midazolam as a first-line agent. The Neurocritical Care Society SE Guidelines recommend intravenous lorazepam as a first-line agent and, if the patient does not have intravenous access, using intramuscular midazolam. Table 611.16 outlines the drugs and dosages typically used in SE. If intravenous access is not available, other options besides intramuscular midazolam include buccal or intranasal midazolam, intranasal lorazepam, or rectal diazepam. With all options, respiratory depression is a potential side effect for which the patient should be monitored and managed as needed. If seizures persist 5 min after the initial benzodiazepine dose, a second dose of the drug should be given. Less evidence supports the use of phenytoin/fosphenytoin, phenobarbital, valproate, or levetiracetam as alternative first-line agents. Additionally, in some infants, a trial of pyridoxine may be warranted.

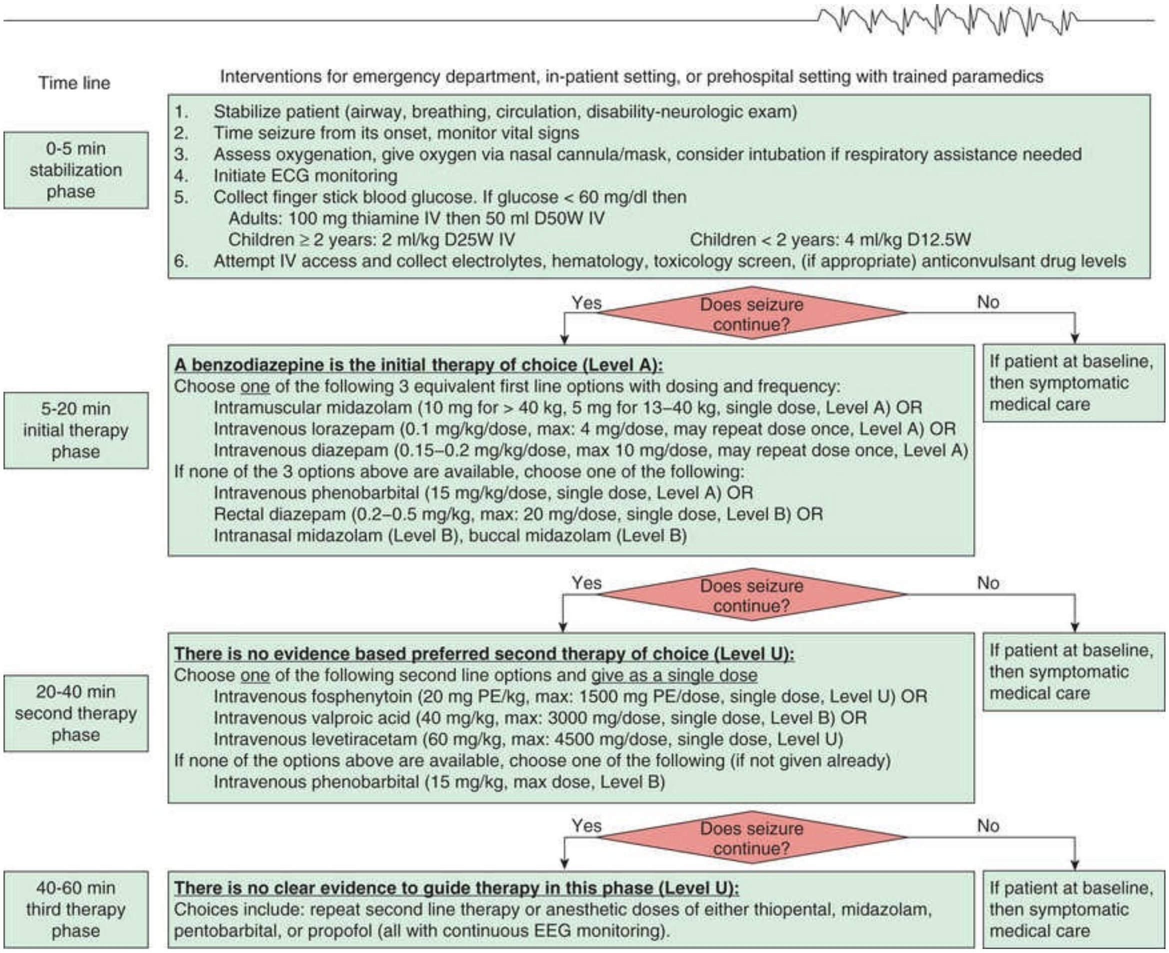
Time line
Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics
0-5 min stabilization phase
5-20 min initial therapy phase
20-40 min second therapy phase
40-60 min third therapy phase
Yes
Does seizure continue?
No
If patient at baseline, then symptomatic medical care

1. Stabilize patient (airway, breathing, circulation, disability-neurologic exam)
2. Time seizure from its onset, monitor vital signs
3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed
4. Initiate ECG monitoring
5. Collect finger stick blood glucose. If glucose < 60 mg/dl then
   Adults: 100 mg thiamine IV then 50 ml D50W IV
   Children ≥ 2 years: 2 ml/kg D25W IV   Children < 2 years: 4 ml/kg D12.5W
6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels

A benzodiazepine is the initial therapy of choice (Level A):
Choose one of the following 3 equivalent first line options with dosing and frequency:
  Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13–40 kg, single dose, Level A) OR
  Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
  Intravenous diazepam (0.15–0.2 mg/kg/dose, max 10 mg/dose, may repeat dose once, Level A)
If none of the 3 options above are available, choose one of the following:
  Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
  Rectal diazepam (0.2–0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
  Intranasal midazolam (Level B), buccal midazolam (Level B)

There is no evidence based preferred second therapy of choice (Level U):
Choose one of the following second line options and give as a single dose
  Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose, Level U) OR
  Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
  Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose, Level U)
If none of the options above are available, choose one of the following (if not given already)
  Intravenous phenobarbital (15 mg/kg, max dose, Level B)

There is no clear evidence to guide therapy in this phase (Level U):
Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).

FIG. 611.7 Proposed treatment algorithm for status epilepticus. Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate. (From Glauser T, Shinnar S, Gloss D, et al: Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society, Epilepsy Currents 16[1]:48-61, 2016, Fig.1.)

Table 611.16

Doses of Commonly Used Antiepileptic Drugs in Status Epilepticus

DRUG*	ROUTE	DOSAGE
Lorazepam	Intravenous	0.1 mg/kg up to maximum of 4 mg, may repeat in 5-10 min
	Intranasal	0.1 mg/kg up to maximum of 5 mg
Midazolam	Intravenous	0.2 mg/kg up to 10 mg total dose, may repeat in 5-10 min Continuous infusion maintenance: 0.05-2 mg/kg/hr
	Intramuscular	0.2 mg/kg
	Intranasal	0.2 mg/kg
	Buccal	0.5 mg/kg
Diazepam	Intravenous	0.15 mg/kg up to a maximum total dose of 10 mg; may repeat in 5-10 min
	Rectal	2-5 yr: 0.5 mg/kg
		6-11 yr: 0.3 mg/kg
		≥12 yr: 0.2 mg/kg
Fosphenytoin	Intravenous	Loading: 20 mg/kg PE, infusion rate maximum 50 mg PE/min Maintenance: 4-8 mg/kg/24 hr divided TID
Ketamine	Intravenous	Loading: 1 mg/kg Maintenance: 0.5-2 mg/kg/hr
Phenobarbital	Intravenous	Loading: 15-20 mg/kg (maximum 1,000 mg) Maintenance: 3-5 mg/kg/24 hr divided bid
Pentobarbital coma	Intravenous	Loading: 5-15 mg/kg Maintenance: 1-5 mg/kg/hr
Propofol	Intravenous	Loading: 1-2 mg/kg Maintenance infusion: 1.2 -3.9 mg/kg/hr
Thiopental	Intravenous	Loading: 2-7 mg/kg, infusion rate maximum 50 mg/min Maintenance infusion: 0.5-5 mg/kg/hr
Valproate	Intravenous	Loading: 20-40 mg/kg Maintenance: 30-60 mg/kg/24 hr divided BID
Lacosamide †	Intravenous	Loading: 4-8 mg/kg (maximum 400 mg) Maintenance: 4-12 mg/kg/day divided BID (maximum 400 mg/day)
Levetiracetam	Intravenous	Loading: 30-60 mg/kg (maximum 4,500 mg) Maintenance: 30-60 mg/kg/24 hr divided BID (maximum 3,000 mg /day)
Topiramate	Enterally	Loading: 5-10 mg/kg Maintenance: 5-12 mg/kg/day divided BID (maximum 400 mg/day)

[*] Reflects current trends in use that may not be FDA approved. For FDA indications, see Table 611.8 .

[†] May cause PR prolongation.

PE, phenytoin sodium equivalents.

If the emergent therapy with a benzodiazepine is unsuccessful (persistent seizures 5 min after the second benzodiazepine dose), fosphenytoin, valproate, or levetiracetam is the recommended option for urgent therapy. Fosphenytoin is given at a loading dose of 20 PE/kg and a level is usually taken 2 hr later to ensure achievement of a therapeutic concentration. Depending on the level and response, a maintenance dose can be started right away or, more commonly, 6 hr following the initial bolus. Valproate is given at a loading dose of 20-40 mg/kg, but its use should be avoided in patients younger than 2 yr of age and in those with hepatic dysfunction or mitochondrial disease. Levetiracetam is given at loading doses of 30-60 mg/kg and is well tolerated, although less data are available regarding its efficacy. Intravenous phenobarbital is an alternative option if valproate, fosphenytoin, or levetiracetam is not available but is not recommended as a first-line urgent therapy due to its side effects. The phenobarbital dose used in neonates is usually 20 mg/kg as a loading dose, but in infants and children the dose is often lower to avoid respiratory depression, with the dose repeated if there is not an adequate response. If seizures persist after administration of the urgent therapy medication, a decision must be made regarding re-dosing with another second-line agent or proceeding to a continuous infusion. This decision is case-dependent. The Neurocritical Care Society Guidelines on SE suggest that definitive seizure control should be achieved within 60 min of seizure onset, which may prompt opting for the more aggressive therapy (i.e., proceeding to continuous infusion and intubation) in a patient who has already had convulsive seizures for more than 30-60 min. Due to the multiple available options in the choice of drugs to abort prolonged seizures, it is important for each institution to develop its own algorithm for managing SE to increase efficacy and to decrease delays to treatment.

After the second or third medication is given, and sometimes before that, the patient might need to be intubated. All patients with SE, even the ones who respond, need to be admitted to the intensive care unit for completion of therapy and monitoring. Ideally, emergent and urgent therapies should have been received within less than 30 min so as to initiate the subsequent therapy soon, thus reducing the chances of sequelae. For **refractory status epilepticus treatment,** an intravenous bolus followed by continuous infusion of midazolam, propofol, pentobarbital, or thiopental is used. Subsequent boluses and adjustment of the rate of the infusion are usually made, depending on clinical and EEG responses. Because most of these patients need to be intubated and paralyzed, the EEG becomes the method of choice by which to follow them. The goal is to stop electrographic seizure activity before reducing the therapy. Usually this implies achievement of complete flattening of the EEG. Some consider that achieving a burst suppression pattern may be enough, and the periods of flattening in such a case need to be 8-20 sec to ensure interruption of electrographic seizure activity. However, this is an area that is in need of further study.

Patients receiving these therapies require careful attention to blood pressure and to systemic complications, and some develop multiorgan failure. It is not unusual for patients put into pentobarbital coma to have to be given multiple vasopressors to maintain their blood pressure during therapy.

The choice among the above options to treat refractory and superrefractory SE often depends on the experience of the specific center. Midazolam probably has fewer side effects but is less effective, and barbiturate coma is more effective but carries a higher risk of side effects. Some patients taking propofol develop a propofol infusion syndrome with lactic acidosis, hemodynamic instability, and rhabdomyolysis with higher infusion rates (>67 µg/kg/min). This limits the use of propofol in the pediatric population. Electrolytes, creatine phosphokinase, and organ function studies need to be monitored if a patient is being given propofol infusion therapy. Often, barbiturate coma and similar therapies are maintained for 1 or more days before it is possible to gradually taper the therapy, usually over a few days. However, in some cases, including cases of NORSE, such therapies need to be maintained for several weeks or even months. Even though the prognosis in NORSE cases is often poor and many patients do not survive, meaningful recovery despite a prolonged course is still possible. This appears to apply to the FIRES syndrome, too.

Patients with **superrefractory status epilepticus (SRSE)** have persistent seizure activity or seizure recurrence despite 24 hr of general anesthesia with medications such as midazolam, pentobarbital, and/or propofol. In addition to these continuous infusions, polytherapy with other AEDs is usually initiated, although data are lacking regarding the optimal treatment strategy. The most commonly used drugs are fosphenytoin, valproate, phenobarbital, levetiracetam, topiramate, and lacosamide. If the addition of such drugs is not successful, other SRSE treatment options are outlined in the next paragraph, although the evidence supporting most of these treatments is limited to case series or case reports. Treatment must be individualized, and identifying the underlying etiology for the SRSE is of the utmost importance because treating the underlying etiology may also treat the seizures (e.g., immunotherapy for anti-NMDA receptor encephalitis).

Ketamine infusion is becoming a better-recognized treatment option. It is an NMDA receptor antagonist and may be of particular benefit because NMDA receptors are upregulated in SE. **Ketogenic diet** has also been found to be effective in children, although the response may take up to a week following diet initiation and ketosis may be more difficult to achieve if the patient is receiving pentobarbital, which has a carbohydrate-rich carrier fluid. Immunotherapy with intravenous steroids, immunoglobulins, and/or plasma exchange is often used in cases of SRSE of unclear etiology. In specific situations such as **anti-NMDA receptor encephalitis** or **CNS vasculitis,** immunotherapy may be the first-line therapy. Because it can take some time to definitively diagnose autoimmune encephalitides, immunotherapy is often initiated empirically if the clinical history is consistent with the diagnosis. **Inhaled anesthetics** such as isoflurane have been used for SRSE but are associated with a number of adverse reactions and require the presence of an anesthesiologist at bedside, which limits their use. **Induced hypothermia** has also been used but further studies are needed to assess its safety and efficacy. In select cases of lesional SRSE, emergent neurosurgery may be an option. Such cases include performing hemispherectomy for **Rasmussen encephalitis** or focal resection if the seizures are secondary to an area of cortical dysplasia. The use of vagal nerve stimulation, electroconvulsive therapy, and transcranial magnetic stimulation (for epilepsia partialis continua) has also been reported. Allopregnanolone, a neurosteroid, has shown promise in the treatment of pediatric and adult SRSE, and clinical trials are currently underway to better determine its efficacy.

For **nonconvulsive status epilepticus** and **epilepsia partialis continua,** therapy needs to be tailored according to the clinical manifestations and often consists of trials of sequential oral or sometimes parenteral AEDs without resorting to barbiturate coma or overmedication that could result in respiratory compromise. The approach to focal status epilepticus with impaired awareness is sometimes similar to the approach to generalized convulsive status epilepticus and sometimes intermediate between the approach for epilepsia partialis and that for convulsive status, depending on severity.

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611.9

Reflex Seizures (Stimulus-Precipitated Seizures)

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Keyword

photic stimulation

Many patients with epilepsy can identify precipitating or provoking events that predispose them to having a seizure. Common precipitants in these patients include stress, lack of sleep, fever, or fatigue.

There is another group of patients who have seizures in response to a specifically identifiable sensory stimulus or activity and are considered to have reflex seizures. Because no known reflex may be involved, more appropriate terms may be sensory-precipitated or stimulus-sensitive seizures. Stimuli may be external (light, patterns, music, brushing teeth) or internal (math, reading, thinking, self-induced). Reflex seizures may be generalized, partial, nonconvulsive, absence, or myoclonic. One pattern is photosensitive seizures in which repetitive **photic stimulation** induces photoparoxysmal epileptogenic discharges on EEG and sometimes seizures.

Photosensitive seizures are a well-recognized disorder stimulated by bright or flashing lights (TV, video games, discotheques, concert light shows) or by patterns (TV, video games, lines on the road while traveling). Visual sensitivity may occur in 0.3–3% of the population, whereas photosensitive or pattern-induced seizures may occur in 1 in 4,000 people in the at-risk age-group of 5-25 yr. When Japanese children were exposed to a Pokémon cartoon that induced seizures in many, only 24% of those had a history of prior spontaneous seizures. Patients tend to outgrow photosensitive or pattern-induced seizures in their 30s. Photoparoxysmal responses, with an abnormal EEG response to photic stimulation, are more common than photic-induced seizures.

For patients with isolated photosensitive or pattern-induced seizures, avoidance or modification of stimuli is the initial approach. Such activities may include wearing blue or polarized sunglasses, avoiding high-contrast flashing-light video games, avoiding discotheques, using a TV remote control or watching TV in a well-lit room at a distance of > 8 feet, and covering one eye when in a provocative situation.

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611.10

Nodding Syndrome

Michael J. Boivin

Keywords

nodding disease
seizures
Onchocerca volvulus
brain atrophy
neurodisability
children
Africa
ivervectin
autoimmune
leiomodin-1
antibodies

Nodding syndrome is an epidemic progressive epilepsy encephalopathy syndrome typified by atonic seizures that affects children between 5 and 15 yr of age in geographically localized regions, including Uganda, Liberia, Tanzania, the Democratic Republic of Congo, and southern Sudan. The prevalence is approximately 6.8 per 1,000 children. Nodding episodes are characterized by at least daily, rapid, paroxysmal, forward head-bobbing spells lasting several minutes; some patients are unresponsive, whereas others may respond to commands or continue what they were doing before the episode. These spells may be indicative of atonic seizures, although there may also be associated definable generalized tonic-clonic or *absence* seizures. The EEG demonstrates a disorganized slow background and interictal generalized 2.5- to 3.0-Hz spike–and–slow waves, with generalized electrodecrement and paraspinal electromyography dropout suggestive of an atonic seizure. Nodding episodes may be triggered during meals while eating hot foods or drinking cold liquids; cold environmental temperatures may also trigger a nodding episode. Treatment of seizures is indicated; however, the response to treatment is poor.

Nodding syndrome is characterized by stunted brain growth, which includes significant brain atrophy near the hippocampal and glial matter of the brain and significant cerebellar involvement. Routine CSF analyses are usually negative, but brain MRI shows cerebral and cerebellar atrophy. An MRI study of Tanzanian nodding disease patients revealed that the most frequent abnormality was generalized atrophy, followed by intraparenchymal pathologies such as changes in the hippocampus, gliotic lesions, and subcortical signal abnormalities. Epidemiologically, there is an association between intraparenchymal cerebral pathologies and skin infection with *Onchocerca volvulus* . This nematode is carried by the blackfly, the bites of which can cause onchocerciasis, a highly prevalent type of blindness caused by infection.

Given the extent of the brain pathogenesis in nodding disease, it is not surprising that it is accompanied by lifelong profound cognitive neurodisability, severe behavior problems, and high mortality rates (Table 611.17 lists case definitions). The origin of these seizures is unknown; They typically arise in previously healthy children, although there may be a family history of seizures.

Table 611.17

Consensus Case Definition and Modified Consensus Case Definition for Nodding Syndrome, Uganda, 2012-2013*

TYPE OF CASE	CONSENSUS CASE DEFINITION	MODIFIED CONSENSUS CASE DEFINITION
Suspected case	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person	Reported head nodding (repetitive involuntary drops of the head toward the chest on 2 or more occasions) in a previously normal person
Probable case	Suspected case of head nodding, with both major criteria: Age of onset of nodding ranging from 3-18 yr Frequency of nodding 5-20 per min	Suspected case of head nodding, with 1 major criterion: Age of onset of nodding ranging from 3-18 yr
	Plus at least 1 of the following minor criteria: Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) Clustering in space or time with similar cases Triggering by food or cold weather Stunting or wasting Delayed sexual or physical development Psychiatric symptoms	Plus at least 1 of the following minor criteria: Other neurologic abnormalities (cognitive decline, school dropout because of cognitive or behavioral problems, other seizures or neurologic abnormalities) Clustering in space or time with similar cases Triggering by food or cold weather Stunting or wasting Psychiatric symptoms
Confirmed case	Probable case, with documented nodding episode Observed and recorded by a trained healthcare worker, *or* Videotaped nodding episode, *or* Video/EEG/EMG documenting head nodding as atonic seizures	Probable case, with documented nodding episode Observed and recorded by a trained healthcare worker, *or* Videotaped nodding episode, *or* Video/EEG/EMG documenting head nodding as atonic seizures

* The consensus case definition was drafted at the first International Scientific Meeting on Nodding Syndrome, held July 30 to August 1, 2012, in Kampala, Uganda. Meeting report available at http://www.who.int/neglected_diseases/diseases/Nodding_syndrom_Kampala_Report_2012.pdf .

The modified consensus case definition was developed during the March 2013 single-stage cluster survey conducted by the Centers for Disease Control and Prevention (CDC) and the Ugandan Ministry of Health to assess the prevalence of nodding syndrome in Uganda.

EEG, electroencephalographic; EMG, electromyographic.

From Iyengar PJ, Wamala J, Ratto J, et al: Prevalence of nodding syndrome–Uganda, 2012-2013, MMWR Morb Mortal Wkly Rep 63:603-606, 2014, Table 1.

Studies in Uganda support the hypothesis that nodding syndrome is an autoimmune epileptic disorder caused by molecular mimicry with *O. volvulus* antigens. Histologic postmortem examination of brains has revealed polarizable material in the majority of specimens, but it has proved difficult to characterize or identify. There is evidence of autoantibodies to leiomodin-1 in both the sera and CSF of Ugandan patients with nodding syndrome. Because leiomodin-1 antibodies cross-react with *O. volvulus* proteins, nodding syndrome may be an autoimmune epilepsy initiated by the infection caused by this parasite. Therefore, it may be preventable by treatment with antiparasitic strategies, such as the drug ivermectin. It may also perhaps be treatable in its early stages with immunomodulatory therapies.

Onchocerciasis tends to have the highest prevalence in rural east and central African areas with poorly developed healthcare and social service infrastructures. Because of this, families with children affected by nodding disease, often existing on the margins of their resources in impoverished areas, have little in the way of caregiving resources needed to cope with the profound disability that results from this disease. This further diminishes the prognosis for these children because of further risk to their health from accidental injury (e.g., burns from cooking fires), malnutrition due to difficulty in feeding, and/or neglect.

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CHAPTER 612

Conditions That Mimic Seizures

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The misdiagnosis of epilepsy is estimated to be as high as 5–40%. Often all that is needed to differentiate nonepileptic paroxysmal disorders from epilepsy is a careful and detailed history in addition to a thorough clinical examination, but sometimes an electroencephalogram (EEG) or more advanced testing may be necessary. The ready availability of video recording on mobile phones can provide invaluable information. Nonepileptic paroxysmal disorders can be classified according to the age at presentation and the clinical manifestations: (1) syncope and other generalized paroxysms, (2) movement disorders and other paroxysmal movements and postures, (3) oculomotor and visual abnormalities and visual hallucinations, and (4) sleep-related disorders (Table 612.1).

Table 612.1

Conditions That Mimic Seizures According to Age of Presentation

AGE	SYNCOPE AND OTHER GENERALIZED PAROXYSMS	MOVEMENT DISORDERS AND OTHER ABNORMAL MOVEMENTS	OCULOMOTOR AND VISUAL ABNORMALITIES	SLEEP DISORDERS
Neonate	Apnea Paroxysmal extreme pain disorder	Jitteriness, tremor, increased startle reflex, hiccups Hyperekplexia, paroxysmal dystonic choreoathetosis	Paroxysmal tonic upgaze Alternating hemiplegia of childhood, staring, daydreaming, and time-out “unresponsiveness”	Benign neonatal sleep myoclonus Sleep transition disorders, REM
Infants	Reflex anoxic seizures Breath-holding spells Benign	Jitteriness Sandifer syndrome Paroxysmal dystonic choreoathetosis Benign myoclonus	Paroxysmal tonic upgaze Oculomotor apraxia Spasmus nutans Opsoclonus–	Non-REM partial arousal disorders REM sleep disorders disorders

	paroxysmal vertigo Paroxysmal extreme pain disorder	of early infancy Pathologic startle Shuddering attacks, infantile head atonic attacks Benign paroxysmal torticollis Psychological disorders Alternating hemiplegia of childhood Jactatio capitis (head banging) Drug reactions	myoclonus syndrome, staring, daydreaming, and time-out “unresponsiveness”	Narcolepsy Sleep transition disorders (somnambulism, somniloquy)
Children and adolescents	Benign paroxysmal vertigo Compulsive Valsalva-like maneuver Familial hemiplegic migraine Syncope (long QT, vasovagal, vagovagal, orthostatic, migraine-induced) Psychogenic seizures Transient global amnesia Hyperventilation spells, factitious disorder	Tics Tremor Pathologic startle Paroxysmal dyskinesias Alternating hemiplegia of childhood Benign paroxysmal torticollis Episodic ataxia Psychological disorders, including factitious disorder imposed on another, malingering Masturbation Psychogenic seizures Cataplexy Jactatio capitis (head banging) Episodic rage, drug reactions, factitious disorder	Staring, daydreaming, and time-out “unresponsiveness” Drug reactions, hallucinations, visual snow Conversion reactions, factitious disorder	Non-REM partial arousal disorders REM sleep disorders Narcolepsy Sleep transition disorders (somnambulism, somniloquy) Sleep myoclonus Restless legs syndrome, conversion reactions, factitious disorder

REM, rapid eye movement.

From Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy, Pediatr Neurol 37(5):309-316, 2007.

Syncope and Other Generalized Paroxysms

Apnea

Apneic episodes (cessation of breathing > 20 sec) in neonates and apnea due to brainstem compression are usually associated with bradycardia. In contrast, apnea associated with seizures is usually accompanied by tachycardia. Of note, exceptions are seen because bradycardia can occur during some epileptic seizures and severe apnea of any cause can be followed by anoxic seizures. The term **brief resolved unexplained event (BRUE)** has replaced the term *apparent life-threatening event (ALTE)* and is defined as an event in an infant reported as a sudden, brief, self-resolving episode consisting of one or more of the following: (1) cyanosis or pallor; (2) absent, decreased, or irregular breathing; (3) a marked change in tone (hyper- or hypotonia); and (4) an altered level of responsiveness (see Chapter 403). A BRUE, which usually lasts less than 1 min, is diagnosed only when no explanation is evident after an appropriate history and physical examination have been conducted. **Sleep apnea** can either be central (most commonly in premature neonates) or obstructive. Apnea can also be secondary to near cerebral herniation and intermittent brainstem compression in the context of increased intracranial pressure or Chiari malformations. **Ondine's curse** (idiopathic congenital central alveolar hypoventilation syndrome) consists of an inadequate respiratory drive in sleep with periods of prolonged apnea requiring tracheostomy and mechanical ventilation (see Chapter 446.2).

Breath-Holding Spells

The term *breath-holding spells* is actually a misnomer, because they are not necessarily self-induced but result from the immaturity of the autonomic system and occur in two different forms. The first type is the **pallid breath-holding spell,** which is caused by reflex vagal-cardiac bradycardia and asystole. The second type is the **cyanotic,** or **blue, breath-holding spell,** which does not occur during inspiration but results from prolonged expiratory apnea and intrapulmonary shunting (see Chapter 43). Episodes usually start with a cry (often, in the case of the pallid type, a silent cry with marked pallor) and progress to apnea and cyanosis. Spells usually begin between 6 and 18 mo of age. Syncope, tonic posturing, and even reflex anoxic seizures may follow the more severe episodes, particularly in breath-holding spells of the pallid type. Injury (such as even a minor bump on the head), pain, and frustration, particularly with surprise, are common triggers. There usually is a family history of vasovagal syncope or breath-holding spells. Education and reassurance of the parents is usually all that is needed because these episodes are, as a rule, self-limited and are outgrown within a few years. However, screening for anemia and for electrical cardiac disturbances with an electrocardiogram is recommended because the spells are worsened by iron-deficiency anemia and can rarely be the presenting sign of long-QT syndromes. Anticholinergic drugs (e.g., atropine sulfate 0.03 mg/kg/day, in 2-3 divided doses with a maximum daily dose of 1.2 mg), or antiseizure drug therapy for coexisting anoxic seizures that are recurrent, prolonged, and not responding to other measures may, rarely, be needed. If antiseizure medications are needed it is ill-advised to use medications that may increase irritability, such as levetiracetam. It is important also to educate parents on how to handle more severe spells with first-aid measures or even basic cardiopulmonary resuscitation when needed. Extremely severe episodes resulting in marked bradycardia and asystole have been reported to respond to a cardiac pacemaker. All parents should be taught not to provide secondary gain when the episodes occur, because this can reinforce them. Also, preparation for unpleasant experiences (such as receiving a shot) rather than surprising the child with them, can help limit the number of spells.

Compulsive Valsalva-Like Maneuver

In children with intellectual disability, including Rett syndrome, syncopal convulsions may be self-induced by maneuvers such as the Valsalva maneuver. In this case, true breath holding occurs, and it usually lasts for approximately 10 sec during inspiration. Some clinicians advocate the use of naloxone in such cases. In the authors’ experience, a compulsive Valsalva-like maneuver can rarely be a feature of a panic attack or conversion disorder. When clinically stereotyped, a prolonged EEG and a careful workup by a pediatric epileptologist is needed in order to rule out epileptic seizures.

Neurally Mediated Syncope

Syncope can present with drop attacks and can also lead to generalized convulsions, termed *anoxic seizures*. These convulsions, triggered by a sudden reduction of oxygen to the brain, are clinically similar to, and can be misdiagnosed as, generalized epileptic seizures. **Vasovagal (neurocardiogenic) syncope** is usually triggered by dehydration, heat, standing for a long time without movement, hot showers, the sight of blood, pain, swallowing, vomiting, sudden exposure to cold as with cold water immersion, and a sudden episode of stress (see Chapter 87). The history is usually the clue to distinguishing syncope from epileptic seizures: there is initially pallor and sweating followed by blurring of vision, dizziness, and nausea and then a gradual collapse with loss of consciousness. Of importance is the fact that such prodromal features have an insidious onset and build up gradually, often arising from a state of malaise when they precede syncope. However, in epilepsy, when auras with similar features precede an epileptic seizure, such features are usually sudden, short in duration, and followed by other manifestations of complex partial seizures such as stereotyped automatisms. Abdominal pain, a common aura in temporal lobe epilepsy, occurs in vasovagal syncope and can be a trigger or a consequence of that process (intestinal vagal hyperactivity). Urinary incontinence and a brief period of convulsive jerks are not uncommon in vasovagal syncope. These occur with a frequency of 10% and 50%, respectively. Postictal confusion only rarely occurs, and the rule is the occurrence of only brief postictal tiredness with a subsequent remarkable ability to resume planned activities. Most children with vasovagal syncope have an affected first-degree relative; reports demonstrate autosomal dominant inheritance at least in some families. The EEG is normal and the tilt test has been used for diagnostic purposes in selected cases. In most cases with a typical history, this test is not needed. In addition, **exercise-induced anaphylaxis** has rarely been reported. In **stretch syncope,** which occurs mostly in adolescents while stretching the neck and the trunk backward and the arms outward, or during flexion of the neck, the presumed mechanism is mechanical disruption of brain perfusion caused by compression of the vertebral arteries. In some other cases, this may be associated with an abnormally prolonged stylomastoid process compressing the carotids. If the latter condition is suspected, neuroimaging with cranial CT or MRI is required for proper diagnosis of the stylomastoid anomaly. **Migraine** can also induce vasovagal syncope. Other causes of syncope include primary autonomic failure, which is rare in children, and familial dysautonomia is the only relatively common form. **Familial dysautonomia,** a disease found in Ashkenazi Jews, is characterized by absence of overflow emotional tears, depressed patellar reflexes, and lack of a flare reaction following intradermal histamine. **Dopamine β-hydroxylase deficiency** is a very rare cause of primary autonomic failure and is characterized by a complicated perinatal course (hypotension, hypotonia, hypothermia), ptosis, highly arched palate, hyperflexible joints, nocturia, and later impaired ejaculation.

Postural Tachycardia Syndrome

See Chapter 87.1 .

Cardiac Syncope

See also Chapters 87 and 463 .

Long QT (LQT) syndromes can cause life-threatening pallid syncope. Accompanying this are ventricular arrhythmias and, usually, torsades de pointes or even ventricular fibrillation. When accompanied by congenital deafness, it is part of the autosomal recessive Jervell and Lange-Nielsen syndrome (type 1, LQT 1, associated with the *KvLQT1* potassium channel mutation). The Romano-Ward syndrome is an autosomal dominant syndrome with incomplete penetrance (LQT 2 associated with an *HERG* potassium channel mutation). LQT 3 is associated with an *SCN1A* sodium channel mutation, LQT 4 with an ankyrin protein mutation, LQT 5 (milder form) with *KCNE1* mutations, LQT 6 with *KCNE2* potassium channel gene mutations, LQT 9 with caveolin sodium channel–related protein mutations, and LQT 10 with *SCN4B* sodium channel mutations. LQT 7 and LQT 8 have associated clinical and neurologic manifestations. LQT 7 (Andersen-Tawil) syndrome is associated with periodic paralysis, skeletal developmental abnormalities, clinodactyly, low-set ears, and micrognathia (mutations in the *KCNJ2* gene). LQT 8, or the Timothy syndrome (mutations in the calcium channel gene *CACNA1C*), manifests with congenital heart disease, autism, syndactyly, and immune deficiency. All family members of an affected child should be investigated. Affected individuals need insertion of cardiac defibrillators, and their families should be taught cardiopulmonary resuscitation. As a rule, children with a new-onset seizure disorder of unclear etiology should get an electrocardiogram to rule out LQT syndrome masquerading as a seizure disorder. Cardiac syncope is usually sudden without the gradual onset and symptoms that accompany vagal syncope. Aortic stenosis can cause sudden syncope at the height of exercise (usually hypertrophic) or directly at the end (usually valvular), and, if suspected, warrants an echocardiogram.

Migraine and Migraine Variants

Familial hemiplegic migraine (FHM) is a rare type of autosomal dominant migraine with the prominent feature of transient motor weakness. Attacks begin as early as 5-7 yr of age. In a genetically susceptible child, attacks may be precipitated by head trauma, exertion, or emotional stress. The three genes commonly identified are *CACNA1* A in FHM1 (neuronal calcium channel subunit), *ATP1A2* in FHM2 (sodium potassium adenosine triphosphatase subunit), and *SCN1A* in FHM3 (neuronal sodium channel subunit). Mutations of other genes such as PRRT2 can also cause FHM. However, at least a quarter of the affected families and most of the sporadic patients do not carry a mutation in these three genes. Headaches occur in all attacks in most patients. The presence of negative phenomena (e.g., numbness, visual scotomas) in addition to positive phenomena (pins and needles, flickering lights) and the progressive and successive occurrence of visual, sensory, motor, aphasic, and basilar signs and symptoms, in that order, help differentiate these attacks from epileptic seizures. Persistent cerebellar deficits (e.g., nystagmus, ataxia) may be present. Verapamil, acetazolamide, and lamotrigine have been successfully used to prevent attacks, and verapamil and ketamine have been used for the acute episode; ergot derivatives, nimodipine, Midrin (isometheptene mucate, dichloralphenazone, and paracetamol), and probably triptans and propranolol are to be avoided because of concerns of exacerbating the attacks. Interestingly, the co-occurrence of epileptic seizures has been reported in a minority of patients with hemiplegic migraine. It is important also to note that recurrent attacks akin to hemiplegic migraine can be symptomatic of Sturge-Weber syndrome or various metabolic diseases (e.g., mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, as well as alternating hemiplegia of childhood).

Benign paroxysmal vertigo of childhood is a common migraine equivalent that consists of brief seconds-to-minutes episodes of vertigo that is often accompanied by postural imbalance and nystagmus. It is important to note that vertigo does not always refer to a spinning motion; it can also refer to a backward or forward motion (vertigo titubans) where children sometimes report that objects seem to be moving toward them. The child appears frightened during the episode. Diaphoresis, nausea, vomiting, and, rarely, tinnitus may be present. Episodes usually remit by 6 yr of age. MRIs and EEGs are normal, but caloric testing, if done, can show abnormal vestibular function. Diphenhydramine, 5 mg/kg/day (maximum of 300 mg/day) may be used for a cluster of attacks. Preventive therapy with cyproheptadine may rarely be needed for frequent attacks.

Cyclic vomiting syndrome (CVS) is another related periodic migraine variant that can respond to antimigraine or antiepileptic drugs. This and other periodic syndromes have been associated with genetic mutations that can cause hemiplegic migraine. Recurrent vomiting can also be caused by neuromyelitis optica, juvenile Alexander disease, brainstem pathology, inborn errors of metabolism with intermittent presentations, and seizures, usually from the nondominant temporal lobe. With the latter, there is as a rule impaired consciousness. Prophylaxis for CVS has included medications such as amitriptyline, propranolol, cyproheptadine, sumatriptan, erythromycin, coenzyme Q, fluoxetine, or antiepileptics. Acute therapy usually consists of 10% dextrose intravenously, with ondansetron and an antihistamine or benzodiazepine.

The Alice in Wonderland syndrome (see Visual Hallucinations , later), confusional migraine, and abdominal migraine are also migraine variants. One should note that many patients with migraine or migraine variants (including FHM) have coexisting epilepsy, and children with epilepsy have a higher incidence of migraine headaches compared with the general population, so providers should be aware that such patients may have symptoms attributable to either.

Psychological Disorders

Psychogenic nonepileptic seizures (pseudoseizures, PNESs) are conversion reactions that can be diagnosed clinically based on the characteristics of the spells (Table 612.2). A video of the event is usually possible because most of the events are witnessed. If needed, a diagnosis can be confirmed by video-EEG with capture of an episode to eliminate any residual doubts about its nature, because these seizures can often occur in patients who also have epileptic seizures. A social history is very important because PNESs are often a reaction to physical or sexual abuse or to the inability to cope with psychosocial tasks. They are best managed acutely by reassurance about their relatively benign nature and by a supportive attitude while at the same time avoiding positive reinforcement of the episodes. The use of terms such as *nonepileptic stress seizures* facilitates communication with families, given the often-perceived negative connotation of the term *psychogenic*. Psychiatric evaluation and follow-up are needed to uncover an underlying psychopathology and to establish continued support because psychogenic seizures can persist over long periods of time. Malingering and factitious disorder imposed on another (formerly called Munchausen syndrome by proxy) are often difficult to diagnose, but an approach similar to that for psychogenic seizures, including video-EEG monitoring, is often helpful. Sad cases of loss of consciousness related to suffocation by caregivers in infants and toddlers have also been reported.

Table 612.2

Comparison of Generalized Seizures and Some Disorders That Can Mimic Them

CONDITION	PRECIPITANTS (MAY NOT APPLY TO ALL PATIENTS)	PRODROME	ICTAL SYMPTOMS	POSTICTAL SYMPTOMS
Generalized seizures	Sleep deprivation, television, video games, visual patterns, and photic stimulation	Rarely irritability or nonspecific behavioral changes	Usually 2-3 min Consciousness might be preserved if atonic or, in some, tonic seizures Synchronous bilateral movements Tongue biting	Delayed recovery with postictal depression, incontinence (may be ictal also)
Syncope: vasovagal	Fatigue, emotional stress, dehydration, vomiting, choking, swallowing	Blurring of vision, tinnitus, dizziness, nausea, sweating, Crying in breath-holding spells	Loss of consciousness for seconds, pallor, and rarely reflex anoxic seizures	Rapid recovery with no postictal depression
Syncope with reflex anoxic seizures	Minor bump to head, upsetting surprises			
Syncope: trigeminal vagal	Cold water on face			
Syncope: orthostatic	Standing up, bathing, awakening			
Hyperekplexia	Auditory and tactile stimuli	None	Tonic stiffening, cyanosis if severe, nonfatigable nose-tap–induced startles	Depending on severity, may have postictal depression
Cardiac	Exercise	None	Loss of consciousness, often only for a few seconds, pallor	Rarely
Psychogenic	Suggestion, stress	None	Eyes closed, with active opposition to attempts to open them Asynchronous flailing limb movements that vary between attacks Motor activity stops and starts	No postictal depression

			during a spell Weeping and crying No injury May respond to suggestion during “loss of consciousness” Usually longer than 2-3 min	

Adapted from Obeid M, Mikati MA: Expanding spectrum of paroxysmal events in children: potential mimickers of epilepsy, Pediatr Neurol 37(5):309-316, 2007.

Paroxysmal Extreme Pain Disorder

Paroxysmal extreme pain disorder, previously called familial rectal pain syndrome, is caused by an autosomal dominant gain-of-function mutation in a sodium channel (Nav1.7) encoded by the *SCN9A* gene. Paroxysmal extreme pain disorder usually starts in infancy and persists throughout life. Autonomic manifestations predominate initially, with skin flushing in all cases and harlequin color change and tonic attacks in most. Dramatic syncope with bradycardia and sometimes asystole occur. Later, the disorder is characterized by attacks of excruciating, deep burning pain often in the rectal, ocular, or jaw areas, but also diffusely in some. Attacks are triggered by defecation, cold, wind, eating, and emotion. Carbamazepine is used, but the response is often incomplete. Neurologically impaired children can often have irritability without clear etiology even after investigations, and this has been reported to respond to gabapentin (for neurologic irritability).

Autonomic Storms

Autonomic storms are also referred to as diencephalic seizures, paroxysmal sympathetic hyperactivity, sympathetic storms, paroxysmal autonomic instability with dystonia, dysautonomia, and central autonomic dysfunction. Spells of hyperhidrosis and changes in blood pressure, temperature, and autonomic instability occur in patients with severe diffuse brain injury or localized hypothalamic injury and have been termed autonomic storms. The term *diencephalic seizures* is discouraged because the episodes are not truly seizures. Therapy is difficult and has included, with mixed results, clonidine, propranolol, baclofen (oral or intrathecal), benzodiazepines (particularly clonazepam), bromocriptine, chlorpromazine, hydralazine, methadone, cyproheptadine, morphine, and sympathectomy.

Serotonin syndrome caused by antidepressants, stimulants, opioids, certain herbs such as St. John's Wart, and some other medications can produce similar symptoms, and if not recognized, can at times be fatal, as can the similar **neuroleptic malignant syndrome** caused by antipsychotic medications.

Movement Disorders and Other Paroxysmal Movements and Postures

Neonatal Jitteriness and Clonus

Jitteriness consists of recurrent tremors. These movements manifest as equal backward-and-forward movements of the limbs, occurring spontaneously, or triggered by touch or loud sounds. Movement suppression by stimulus removal or by relaxing the affected limbs, the lack of autonomic symptoms, and the clear difference from the two-phased (fast contraction, slow relaxation) clonic activity and the very quick myoclonic jerks, point to a nonepileptic event. Hypocalcemia, hypoglycemia, drug withdrawal, and hypoxic-ischemic encephalopathy are possible etiologies, but jitteriness is also often seen in normal neonates. Clonus as a result of corticospinal tract injury usually occurs in later infancy and childhood and can be stopped by a change in position. Two to three beats of clonus can be within normal in some neonates.

Hyperekplexia (Stiff Baby Syndrome) and Pathologic Startles

Hyperekplexia is a rare, sporadic or dominantly inherited disorder with neonatal onset of life-threatening episodes of tonic stiffening that precipitate apnea and convulsive hypoxic seizures. It is characterized by a triad of generalized stiffness, nocturnal myoclonus, and later a pathologic startle reflex. Stiffness may result in difficulty in swallowing, choking spells, hip dislocations, umbilical or inguinal hernias, and delayed motor development. Stiffness in the neonatal form improves by 1 yr of age and may disappear during sleep. The genetic cause is a defect in the α or β subunits of the strychnine-sensitive glycine receptors. However, other less common culprit mutations that disrupt the glycine receptor signaling complex have also been described. A specific diagnostic sign can be elicited by tapping the nose, which produces a nonfatigable startle reflex with head retraction. Bathing, sudden awakening, and auditory or tactile stimuli can induce attacks. The differential diagnosis includes congenital stiff person syndrome, startle epilepsy, myoclonic seizures, neonatal tetany, phenothiazine toxicity, and Schwartz-Jampel syndrome. Making a prompt diagnosis is extremely important so that treatment with clonazepam can be initiated, because hypoxic brain injury can result from a prolonged episode. Other antiepileptics have also been effective. Repeatedly flexing the baby at the neck and hips (the Vigevano maneuver) can abort the episodes. Of note, rare challenging cases of children with hyperekplexia and concomitant epileptic seizures (including myoclonic seizures) have been reported. In other children after brain injury, and in many patients with cerebral palsy, an **exaggerated startle reflex** can occur. This is more common than hyperekplexia. In Tay-Sachs disease and similar gangliosidoses, an exaggerated startle to sound occurs and has been, inappropriately, interpreted as hyperacusis. **Hiccups** can occur normally in newborns but can be a feature of nonketotic hyperglycinemia, citrullinemia, and neuromyelitis optica syndromes, the latter presenting during later childhood and adolescence rather than in neonates. In addition, in children with neurologic diseases, a related limited repertoire of movements and behaviors, startle, arousal, or signs of distress may be clinically expressed with stereotyped movements that can mimic epileptic seizures.

Benign Paroxysmal Torticollis of Infancy

This condition typically presents as morning episodes of painless retrocollis and, later, torticollis, often triggered by changes in posture. Attacks may start with abnormal ocular movements and progress to stillness in an abnormal posture. This usually lasts for minutes (usually termed paroxysmal rather than periodic) or more commonly hours and, at times, days (usually periodic). A neurologic exam between attacks, an EEG, and neuroimaging studies are normal. It affects girls more than boys (3 : 1), often begins before 3 mo of age, and spontaneously remits before the age of 5 yr. Medical therapy is not needed. It is considered to be a migraine equivalent and cosegregates with migraine in families.

Sandifer Syndrome and Rumination

Gastroesophageal reflux in infants may cause paroxysmal episodes of generalized stiffening and opisthotonic posturing that may be accompanied by apnea, staring, and minimal jerking of the extremities. Episodes often occur 30 min after a feed. In older children, this syndrome manifests with episodic dystonic or dyskinetic movements consisting of laterocollis, retrocollis, or torticollis, the exact pathophysiology of which remains elusive. Reflux can also present with rumination consisting of contraction of abdominal muscles followed by mouthing and swallowing movements and at times vomiting.

Alternating Hemiplegia of Childhood

This is a rare, often severe, disorder that consists of attacks of flaccid hemiplegia affecting one or both sides lasting minutes to days, starting in the first 18 mo of life. Earlier manifestations include paroxysmal nystagmus, which is often monocular and ipsilateral to the hemiplegia or dystonia. Dystonic spells are the rule also. Patients can have episodes of reduced consciousness and confusion that are not epileptic. Most affected children also have ataxia and developmental delay, and many have choreoathetosis and behavioral problems. Most of the patients are initially misdiagnosed as having refractory focal epilepsy with Todd's paralysis. About half of them also have epileptic seizures, which makes the differential diagnosis even more difficult. Flunarizine 2.5-20 mg/day reduces the frequency and severity of the attacks. Most cases are caused by mutations in the *ATP1A3* gene; rarely, a similar clinical picture can occur as a result of mutations in *ATP1A2* or the glucose transporter 1 *(GLUT1/SLC2AI)* gene. Of note, the *ATP1A3* gene has also been reported in a syndrome of **relapsing encephalopathy with cerebellar ataxia (RECA)** during febrile illnesses.

Paroxysmal Dyskinesias and Other Movement Disorders

These disorders are characterized by sudden attacks that consist of choreic, dystonic, ballistic, or mixed movements (Table 612.3). A sensation of fatigue or weakness confined to one side may herald an attack. Consciousness is preserved and patients may be able to perform a motor activity, such as walking, despite the attack. The variability in the pattern of severity and localization between different attacks may also help in differentiating them from seizures. The frequency of attacks increases in adolescence and steadily decreases in the 3rd decade. Neurologic examination between attacks, EEG, laboratory investigations, and imaging studies are normal. **Chorea** consists of involuntary rapid fast movements that are slower than myoclonus and not rhythmic. Common causes are poststreptococcal Sydenham chorea, antiphospholipid antibody syndrome, and systemic lupus erythematosus. **Drug reactions** can result in abnormal movements; they include **oculogyric crisis** with many antiemetics and lamotrigine toxicity, choreoathetosis with phenytoin, dystonia and facial dyskinesias with antidopaminergic drugs, and tics with carbamazepine. Strokes, focal brain lesions, connective tissue disorders (e.g., systemic lupus erythematosus), vasculitis, or metabolic and genetic disorders can also cause movement disorders. Mutations of the glucose transporter 1 *(GLUT1/SLC2A1)* gene have been described in patients with **exercise-induced dyskinesia.**

Table 612.3

Differential Diagnoses of Various Types of Paroxysmal Dyskinesia

FEATURES	**PKD**	**PNKD**		**PED**	**PHD (EPI WITH DYSTONI EPILEPT SEIZURE**
		PNKD1 (MR1+VE)	**PNKD2 (MR1-VE)**		
Nomenclature	PKC	PDC, FPC	PDC, FPC	PEDt	ADNFLE
Inheritance	AD–16q	AD–2q35	AD–2q13	AD/AR	AD–20q13 1q21, 8p21
Gene	PRRT2	MR1	Not known	SLC2A1	CHRN CHRN KCNT
Age at onset (yr)	1-20	<1-12	1-23	Usually childhood	Usually ch
Triggers	Sudden whole-body movement	Coffee, alcohol, stress	Exercise	After 10-15 min of exercise	Sleep
Clinical features	Chorea, athetosis, ballismus, dystonia	Chorea, athetosis, dystonia, ballismus	Chorea, athetosis, dystonia, ballismus	Mainly leg dystonia	Wakes up dystonic p
Usual duration	<1-5 min	10 min to 1 hr	10 min to 2-3 hr	10-15 min	<1 min
Frequency	1-20/day	1/wk	1/wk	Daily, weekly, or monthly	Several/nig
Associations	Infantile seizures, migraine, writer's cramp, essential tremor	Migraine	Epilepsy	RE-PED-WC	
Medication	Carbamazepine Phenytoin	Clonazepam Benzodiazepine	Clonazepam Benzodiazepine	Acetazolamide L-DOPA	Carban Oxcarb

	Oxcarbazepine			Antiepileptics Trihexyphenidyl Ketogenic diet in *SLC2A1* mutation cases	
Prognosis	Excellent	Excellent, worse than PKD	Minimally worse than PNKD MR1+	Poor medication response	Excellent

AD, autosomal dominant; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; AR, autosomal recessive; FPC, familial paroxysmal choreoathetosis; MR1, myofibrillogenesis regulator 1–positive; MR1−, myofibrillogenesis regulator 1–negative; PDC, paroxysmal dystonic choreoathetosis; PED, paroxysmal exercise-induced dyskinesia; PEDt, paroxysmal exercise-induced dystonia; PHD, paroxysmal hypnogenic dyskinesia; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal nonkinesigenic dyskinesia; RE-PED-WC, rolandic epilepsy–paroxysmal exercise-induced dystonia–writer's cramp.

From Friedman NR, Ghosh D, Moodley M: Syncope and paroxysmal disorders other than epilepsy. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's Pediatric Neurology, 5th ed., Philadelphia, 2012, WB Saunders, Table 65-1.

Motor Tics

These are movements that are under partial control and are associated with an urge to do them and with subsequent relief. They are usually exacerbated by emotions and often change in character over time. **Simple tics,** which occur at some time in about one in five children, involve one or two muscle groups; **complex tics** involve multiple tics or muscle groups; and **Tourette syndrome** consists of multiple motor tics and vocal tics for more than a year. In patients with tics who have Tourette syndrome, there is often a family history of tics and/or obsessive-compulsive disorder or personality traits. Some rare cases appear to occur after preceding streptococcal infections and have been termed as PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections). PANS, on the other hand, refers to an acute onset of obsessive-compulsive symptoms with other behavioral problems and often with tics but without the association of streptococcal infections (acute-onset neuropsychiatric syndrome).

Episodic Ataxias

Episodic ataxias form a clinically and genetically heterogeneous group of diseases that manifest with recurrent truncal ataxia and incoordination. Of the eight syndromes described so far, only two (types 1 and 2) have been reported in a large number of families from different ethnic groups. **Type 1** is caused by mutations in the voltage-gated potassium channel Kv1.1. It consists of brief episodes (seconds to minutes) of cerebellar ataxia and occasional partial seizures with interictal myokymia as a main diagnostic feature. **Type 2** is characterized by longer attacks (minutes to hours) and interictal cerebellar signs. It is caused by mutations in the voltage-gated calcium channel gene *CACNA1A*. This type is more responsive than type 1 to acetazolamide; the drug can reduce the frequency and severity of attacks but not the interictal signs and symptoms.

Benign Motoric Paroxysms in Infancy

Benign myoclonus of infancy consists of myoclonic jerks of the extremities in wakefulness and sometimes also in sleep with no concurrent epileptic EEG changes in a neurologically normal child. **Shuddering attacks** are characterized by rapid tremors of the head, shoulder, and trunk, lasting a few seconds, often associated with eating, and recurring many times a day. Others have considered shuddering as an early manifestation of essential tremor because a family history of essential tremor is often present. **Infantile head atonic attacks** consist of repeated head drops, hundreds to thousands per day, usually appearing at 3-6 mo of life and spontaneously subsiding by the 1st yr of life, without concurrent EEG epileptic activity. Spontaneous remission occurs in all three syndromes, usually within a few months. Video-EEG is normal ictally and interictally in these syndromes but should be performed to differentiate them from infantile spasms and epileptic myoclonus. **Hereditary chin trembling** at a frequency faster than 3 Hz starting shortly after birth and precipitated by stress has been described in several families.

Brainstem Dysfunction

Decorticate or decerebrate posturing that mimics epileptic tonic seizures may be secondary to decompensated hydrocephalus, intracranial hemorrhage, brainstem tumors, Chiari malformation, or other causes of sudden rises in intracranial pressure that lead to brainstem dysfunction. The term *cerebellar fits* has been used to describe drop attacks, extensor posturing with varying degrees of altered consciousness and respiratory compromise secondary to crowding of the posterior fossa, and near herniation in decompensated cerebellar tumors and certain cases of Chiari malformation.

Psychological Disorders

Many psychological disorders can be mistaken for epileptic seizures. Pleasurable behaviors similar to masturbation may occur from infancy onward, and may consist of rhythmic rocking movements in the sitting or lying position or rhythmic hip flexion and adduction. **Infantile gratification** (masturbation), which is more common in girls, usually occurs at 2-3 yr of age and is often associated with perspiration, irregular breathing, and grunting, but no loss of consciousness. Occasionally this is associated with child abuse or with other psychopathology. **Stereotypies,** or repetitive movements that are more complex than tics and do not change and wax and wane as do tics (e.g., head banging, head rolling, body rocking, and hand flapping), usually occur in neurologically impaired children. **A mannerism** is a pattern of socially acceptable, situational behavior that is seen in particular situations such as gesturing when talking. Mannerisms should not be confused with stereotypies, which are generally pervasive over almost every other activity, such as head shaking or hand flapping in multiple situations. Stereotypies, unlike mannerisms, increase with stress. Unlike tics and mannerisms, stereotypies usually start before the age of 3 yr, involve more body parts, are more rhythmic, and most importantly occur when a child is engrossed with an object or activity of interest; children rarely try to suppress stereotypies. **Panic and anxiety attacks** have been described in children; at times, these may be clinically indistinguishable from actual epileptic seizures and therefore may necessitate video-EEG monitoring. **Rage attacks** usually occur in patients with a personality disorder and are usually not seizures, although rare cases of partial seizures can manifest as rage attacks. **Hyperventilation spells** can be precipitated by anxiety and are associated with dizziness, tingling, and, at times, carpopedal spasm. **Transient global amnesia** consists of isolated short-term memory loss for minutes to hours that occurs mostly in adults but has been reported in children. The etiology can be emotional stress, an epileptic disorder, migraine, a vascular disorder, or a drug-related reaction.

Oculomotor and Visual Abnormalities

Paroxysmal Tonic Upgaze of Childhood

This usually starts before 3 mo of age and consists of protracted attacks (hours to days) of continuous or episodic upward gaze deviation, during which horizontal eye movements are preserved. A downbeating nystagmus occurs on downward gaze. Symptoms are reduced or relieved by sleep, exacerbated by fatigue and infections, and spontaneously remit after a few years. Up to 50% of patients may have psychomotor and language delay. Although imaging and laboratory tests were nonrevealing in the seminal cases, white matter lesions have been later reported in some patients. An association with *CACNA1A* gene mutations in a few patients who also suffered from ataxia has been reported, pointing to etiologic and clinical heterogeneity. The differential diagnosis includes drug reactions, tics, Chediak-Higashi disease, Rett syndrome, and Wilson disease. Most of those, however, occur at a later age. Therapy with low-dose levodopa/carbidopa may be helpful. Of note, concomitant absence epilepsy has been reported in few cases.

Oculomotor Apraxia and Saccadic Intrusions

In oculomotor apraxia, saccadic eye movements are impaired. Sudden head turns compensating for lateral gaze impairment mimic seizures. This disorder may be idiopathic (Cogan congenital oculomotor apraxia) or may occur in the context of Joubert syndrome, ataxia telangiectasia, spinocerebellar ataxias, or lysosomal storage diseases. A selective loss of Purkinje cells required to suppress omnipause neurons and initiate saccadic eye movement is believed to occur in some of the disorders. Saccadic intrusions are involuntary, sudden, conjugate eye movements away from the desired eye position. These are not necessarily pathologic.

Spasmus Nutans

This disorder presents with a triad of nystagmus, head tilt, and head nodding. If diurnal fluctuation occurs, symptoms may look like those of epileptic seizures. A brain MRI should be performed because the triad has been associated with masses in the optic chiasm and third ventricle. Retinal disease should also be ruled out. In the absence of these associations, remission occurs before 5 yr of age.

Opsoclonus–Myoclonus Syndrome

In opsoclonus–myoclonus syndrome, the term *dancing eyes* refers to continuous, random, irregular, and conjugate eye movements that may fluctuate in intensity. The finding usually accompanies myoclonus and ataxia (dancing feet). Neuroblastoma (more commonly), encephalitis, and a presumed postinfectious etiology are possible causes. In addition to treating the underlying etiology, adrenocorticotropic hormone (ACTH), corticosteroids, rituximab, and clonazepam are often needed. Recurrences are not infrequent, and developmental delay is common. The opsoclonus and myoclonus may recur after treatment. The long-term neurologic prognosis remains poor, yet the presence of this syndrome is associated with a favorable treatment response of a coexisting neuroblastoma. Opsoclonus with epileptic myoclonus has also been described in a child with glucose transporter-1 deficiency (GLUT1).

Daydreaming and Behavioral Staring

Staring may be a manifestation of absence seizures, which should be differentiated from daydreaming and from behavioral staring because of fatigue and inattention. This is common in children with **attention deficit disorder** because these patients are often referred to rule out absence seizures. Hyperventilation in the office precipitates absences and is a useful clinical test**.** Episodes of staring only in certain settings (e.g., school) are unlikely to be seizures. In addition, responsiveness to stimulation such as touch and lack of interruption of playing activity characterize nonepileptic staring. **Daydreaming** occurs often in children, and **time-out staring** occurs in children when they are overwhelmed with external stimuli or with demands and shut down, ignoring their surroundings and staring.

Visual Hallucinations

Temporal lobe seizures can be associated with complex visual auras, such as seeing people and places, often with subsequent focal seizure manifestations. **Occipital lobe seizures** usually cause simple visual hallucinations and may occur as isolated auras or may be accompanied by headache and nausea (**Gastaut type** of benign occipital epilepsy), making them difficult to differentiate from **migraine.** Hallucinations in occipital seizures are characterized by colorful shapes, circles, and spots seen for seconds and confined to one hemifield, whereas migrainous auras usually last minutes and consist of black-and-white lines, scotomas, and/or fortification spectra that start in the center of the vision. **Visual snow** is a phenomenon that can be confused with occipital seizures and a migraine aura. It consists of dynamic continuous tiny dots in all of the visual field lasting > 3 mo with at least two to four additional specific visual symptoms (afterimages [i.e., palinopsia], enhanced visual phenomena [i.e., entotopic phenomena such as excessive floaters and photopsias], photophobia, and impaired night vision [i.e., nyctalopia]). Although it can occur in patients with migraine or with psychological stress, the underlying pathology is not clear. Unlike migraine, it is associated with increased, rather than decreased, metabolism on PET scans of the lingual gyrus, which is the visual memory area, and patients usually do not respond to antimigraine therapies. **Alice in Wonderland syndrome** consists of the visual distortion of one's body or surroundings (bigger, smaller, closer, or more distant) and has been associated with migraine, epilepsy, acute infection such as Epstein-Barr virus, or fever. Hallucinations can also be **secondary to other causes:** drug exposure, midbrain lesions, and psychiatric illnesses. In addition, retinal-associated hallucinations can occur in the form of flashes of light in the context of inflammatory etiologies, trauma, or optic nerve edema. **Charles Bonnet syndrome** is the occurrence of visual hallucinations due to ocular origin visual loss or, at times, to intracranial pathology.

Sleep-Related Disorders

Paroxysmal nonepileptic sleep events are more common in epileptic patients than in the general population, which makes their diagnosis difficult. Of note, the EEG pattern of frontal lobe epileptic seizures may be similar to the one seen in normal arousals, making their diagnosis challenging, especially because they have nonspecific hypermotor manifestations such as thrashing, body rocking, kicking, boxing, pedaling, bending, running, and various vocalizations. The diagnosis of such epileptic seizures is made on the basis of highly stereotyped, usually brief (<1 min) events arising several times a night from non-rapid eye movement sleep.

Benign Sleep Myoclonus and Neonatal Sleep Myoclonus

Neonatal sleep myoclonus consists of repetitive, usually bilateral, rhythmic jerks involving the upper and lower limbs during non-rapid eye movement sleep, sometimes mimicking clonic seizures. Although the rule is that it is not stimulus sensitive, a slow (1-Hz) rocking of the infant in a head-to-toe direction is a specific diagnostic test that may sometimes reproduce the neonatal sleep myoclonus. The lack of autonomic changes, occurrence only in sleep, and suppression by awakenings may help in differentiating these events from epileptic seizures. Remission is spontaneous, usually at 2-3 mo of age. In older children and adults, sleep myoclonus consists of random myoclonic jerks of the limbs.

Non-Rapid Eye Movement Partial Arousal Disorders

Brief **nocturnal confusional arousals** occur during slow-wave sleep and are normal in children. Such episodes can vary from chewing, sitting up, and mumbling to agitated sleepwalking, and usually last for 10-15 min. With **somnambulism** , there is often a positive family history, and it usually occurs 1-3 hr after sleep onset. **Night terrors** similarly occur in deep sleep, most often at 2-7 yr of age and more so in males. Stress increases the risk of both. In night terrors, the child screams; appears terrified; has dilated pupils, tachycardia, tachypnea, unresponsiveness, agitation, and thrashing that increase with attempts to be consoled; is difficult to arouse; and may have little or no vocalization. In older children with persistent night terrors, an underlying psychological etiology may be present. The diagnosis is based on the history. However, rarely, video-EEG monitoring may be needed, especially if stereotyped motoric features are suggested by the history. At times, the use of bedtime diazepam (0.2-0.3 mg/kg) or clonazepam (0.125 to 0.5 mg) may help control the problem while psychological factors are being investigated. **Restless leg syndrome** can cause painful leg dysesthesias that cause nocturnal arousals and insomnia. It can be either genetic or associated with iron deficiency, systemic illness, or some drugs such as antidepressants. Therapy depends upon treating the underlying cause and, if needed, on dopaminergic drugs, such as levodopa/carbidopa, or antiepileptics, such as gabapentin.

Rapid Eye Movement Sleep Disorders

Unlike night terrors, **nightmares** tend to occur later during the night and the child has a memory of the event**. Rapid eye movement sleep behavior disorder** consists of loss of atonia during REM sleep, enabling patients to act out their dreams and thus mimicking nocturnal frontal or temporal lobe seizures. It is more common in adults. Children with autism and developmental delay are more likely to have it than other children.

Sleep Transition Disorders

Nocturnal head banging **(jactatio capitis nocturna)** , rolling, repetitive limb movements, or body rocking often occur in infants and toddlers as they are trying to fall asleep and can be mistaken for seizures or spasms. They usually remit spontaneously by 5 yr of age. No specific therapy is needed, but in exceptional cases, clonazepam at bedtime may be used.

Narcolepsy–Cataplexy Syndrome

Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, hypnogogic hallucinations, and disturbed nighttime sleep. The persistence of rapid eye movement sleep atonia upon awakening or its intrusion during wakefulness leads to sleep paralysis or cataplexy, respectively. Loss of tone in cataplexy occurs in response to strong emotions and spreads from the face downward, leading to a fall in a series of stages rather than a sudden one. Consciousness is maintained in cataplexy. A selective loss of hypocretin-secreting neurons in the hypothalamus is at the origin of this disorder. The fact that DQB1*0602 is a predisposing HLA allele identified in 85–95% of patients with narcolepsy–cataplexy suggests an autoimmune-mediated neuronal loss. The diagnosis is based on the multiple sleep latency test. Therapy relies on scheduled naps; medications such as amphetamines, methylphenidate, tricyclic antidepressants, modafinil, or sodium oxybate; and counseling about precautions in work and driving.

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CHAPTER 613

Headaches

Andrew D. Hershey, Marielle A. Kabbouche, Hope L. O'Brien, Joanne Kacperski

Headache is a common complaint in children and adolescents. Headaches can be a primary problem or occur as a symptom of another disorder (a secondary headache). Recognizing this difference is essential for choosing the appropriate evaluation and treatment to ensure successful management of the headache. Primary headaches are most often recurrent, episodic headaches and for most children are sporadic in their presentation.

The most common forms of *primary headache* in childhood are migraine and tension-type headaches (Table 613.1). Other forms of primary headache, including the trigeminal autonomic cephalalgias and cluster headaches, occur much less commonly. Primary headache can progress to very frequent or even daily headaches with chronic migraine and chronic tension-type headaches being increasingly recognized as a problem for children and adolescents. These more frequent headaches can have an enormous impact on the life of the child and adolescent, as reflected in school absences and decreased school performance, social withdrawal, and changes in family interactions. To reduce this impact, a treatment strategy that incorporates acute treatments, preventive treatments, and biobehavioral therapies must be implemented.

Table 613.1

Classification of Headaches (ICHD-3 Beta Code Diagnosis)

MIGRAINE
Migraine with or without aura
Migraine with typical aura (with or without headache)
Migraine with brainstem aura
Hemiplegic migraine (sporadic or familial types 1, 2, 3 or other genetic loci)

Retinal migraine

Chronic migraine

Complications of Migraine

Status migrainosus

Persistent aura without infarction

Migrainous infarction

Migraine aura–triggered seizure

Episodic Syndromes That May Be Associated With Migraine

Recurrent gastrointestinal disturbance

Cyclical vomiting syndrome

Abdominal migraine

Benign paroxysmal vertigo

Benign paroxysmal torticollis

Episodic colic

TENSION-TYPE HEADACHE (TTH)

Infrequent episodic TTH associated with or without pericranial tenderness

Frequent episodic TTH associated with or without pericranial tenderness

Chronic TTH associated with or without pericranial tenderness

Probable TTHs

TRIGEMINAL AUTONOMIC CEPHALALGIAS (TACS)

Cluster headache (episodic or cluster)

Paroxysmal hemicrania (episodic or cluster)

Short-lasting unilateral neuralgiform headache attacks with or without conjunctival injection and tearing (SUNCT)

Episodic SUNCT

Chronic SUNCT

Short-lasting unilateral neuralgiform headache attacks with or without cranial autonomic symptoms (SUNA)

Episodic SUNA

Chronic SUNA

Hemicrania continua

Probable trigeminal autonomic cephalalgias

OTHER PRIMARY HEADACHE DISORDERS

Primary cough headache

Primary exercise headache

Primary headache associated with sexual activity

Primary thunderclap headache

Cold-stimulus headache (external application, ingestion, or inhalation)

External-pressure headache

External-compression headache

External-traction headache

Primary stabbing headache

Nummular headache

Hypnic headache

New daily persistent headache (NDPH)

HEADACHE ATTRIBUTED TO TRAUMA OR INJURY TO THE HEAD AND/OR NECK

Acute headache attributed to traumatic (mild, moderate, or severe) injury to the head

Persistent headache attributed to traumatic (mild, moderate, or severe) injury to the head

Acute or persistent headache attributed to whiplash

Acute or persistent headache attributed to craniotomy

HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDER

Headache attributed to ischemic stroke or transient ischemic attack

Headache attributed to nontraumatic intracerebral hemorrhage

Headache attributed to nontraumatic subarachnoid hemorrhage

    Headache attributed to nontraumatic acute subdural hemorrhage
    Headache attributed to unruptured vascular malformation

Headache attributed to unruptured saccular aneurysm

Headache attributed to arteriovenous malformation

Headache attributed to dural arteriovenous fistula

Headache attributed to cavernous angioma

Headache attributed to encephalotrigeminal or leptomeningeal angiomatosis (Sturge-Weber syndrome)

Headache attributed to arteritis

Headache attributed to giant cell arteritis

Headache attributed to primary angiitis of the central nervous system

Headache attributed to secondary angiitis of the central nervous system

Headache attributed to cervical carotid or vertebral artery disorder

Headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection

Postendarterectomy headache

Headache attributed to carotid or vertebral angioplasty

Headache attributed to cerebral venous thrombosis

Headache attributed to other acute intracranial arterial disorder

Headache attributed to an intracranial endovascular procedure

Angiography headache

Headache attributed to reversible cerebral vasoconstriction syndrome

Headache attributed to intracranial arterial dissection

Headache attributed to genetic vasculopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)

Headache attributed to another genetic vasculopathy

Headache attributed to pituitary apoplexy

HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDER

Headache attributed to increased cerebrospinal fluid pressure

Headache attributed to idiopathic intracranial hypertension

Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes

Headache attributed to intracranial hypertension secondary to hydrocephalus

Headache attributed to low cerebrospinal fluid pressure

Post–dural puncture headache

Cerebrospinal fluid fistula headache

Headache attributed to spontaneous intracranial hypotension

Headache attributed to noninfectious inflammatory disease

Headache attributed to neurosarcoidosis

Headache attributed to aseptic (noninfectious) meningitis

Headache attributed to other noninfectious inflammatory disease

Headache attributed to lymphocytic hypophysitis

Syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL)

Headache attributed to intracranial neoplasm

Headache attributed to colloid cyst of the third ventricle

Headache attributed to carcinomatous meningitis

Headache attributed to hypothalamic or pituitary hypersecretion or hyposecretion

Headache attributed to intrathecal injection

Headache attributed to epileptic seizure

Hemicrania epileptica

Postictal headache

Headache attributed to Chiari malformation type I

Headache attributed to other nonvascular intracranial disorder

HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL

Headache attributed to use of or exposure to a substance

Nitric oxide donor–induced headache

Phosphodiesterase inhibitor–induced headache

Carbon monoxide–induced headache

Alcohol-induced headache

Monosodium glutamate–induced headache

Cocaine-induced headache

Histamine-induced headache

Calcitonin gene-related peptide–induced headache

Headache attributed to exogenous acute pressor agent

Headache attributed to occasional or long-term use of non–headache medication

Headache attributed to exogenous hormone

Medication-Overuse Headache (MOH)

Ergotamine-overuse headache

Triptan-overuse headache

Simple analgesic–overuse headache

Paracetamol (acetaminophen)-overuse headache

Acetylsalicylic acid–overuse headache

Other nonsteroidal antiinflammatory drug–overuse headache

Opioid-overuse headache

Combination analgesic–overuse headache

Headache Attributed to Substance Withdrawal

Caffeine-withdrawal headache

Opioid-withdrawal headache

Estrogen-withdrawal headache

HEADACHE ATTRIBUTED TO INFECTION

Acute or chronic headache attributed to bacterial meningitis or meningoencephalitis

Persistent headache attributed to past bacterial meningitis or meningoencephalitis

Acute or chronic headache attributed to intracranial fungal or other parasitic infection

Headache attributed to brain abscess

Headache attributed to subdural empyema

Headache attributed to systemic infection (acute or chronic)

HEADACHE ATTRIBUTED TO DISORDER OF HOMEOSTASIS

Headache attributed to hypoxia and/or hypercapnia

High-altitude headache

Headache attributed to airplane travel

Diving headache

Sleep apnea headache

Dialysis headache

Headache attributed to arterial hypertension

Headache attributed to pheochromocytoma

Headache attributed to hypertensive crisis with or without hypertensive encephalopathy

Headache attributed to preeclampsia or eclampsia

Headache attributed to autonomic dysreflexia

Headache attributed to hypothyroidism

Headache attributed to fasting

Cardiac cephalalgia

Headache attributed to other disorder of homoeostasis

HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDER OF THE CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CERVICAL STRUCTURE

Headache attributed to disorder of cranial bone

Headache attributed to retropharyngeal tendonitis

Headache attributed to craniocervical dystonia

Headache attributed to acute glaucoma

Headache attributed to refractive error

Headache attributed to heterophoria or heterotropia (latent or persistent squint)

Headache attributed to ocular inflammatory disorder

Headache attributed to tracheitis

Headache attributed to disorder of the ears

Headache attributed to acute or chronic or recurring rhinosinusitis

Headache attributed to temporomandibular disorder

Head or facial pain attributed to inflammation of the stylohyoid ligament

Headache or facial pain attributed to other disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure

HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDER

Headache attributed to somatization disorder

Headache attributed to psychotic disorder

PAINFUL CRANIAL NEUROPATHIES AND OTHER FACIAL PAINS

Classical trigeminal neuralgia

Classical trigeminal neuralgia, purely paroxysmal or with concomitant persistent facial pain

Painful trigeminal neuropathy

Painful trigeminal neuropathy attributed to acute herpes zoster

Postherpetic trigeminal neuropathy

Painful posttraumatic trigeminal neuropathy

Painful trigeminal neuropathy attributed to multiple sclerosis (MS) plaque

Painful trigeminal neuropathy attributed to space-occupying lesion

Painful trigeminal neuropathy attributed to other disorder

Glossopharyngeal neuralgia

Classical nervus intermedius (facial nerve) neuralgia

Nervus intermedius neuropathy attributed to herpes zoster

Occipital neuralgia

Optic neuritis

Headache attributed to ischemic ocular motor nerve palsy

Tolosa-Hunt syndrome
Paratrigeminal oculosympathetic (Raeder) syndrome
Recurrent painful ophthalmoplegic neuropathy
Burning mouth syndrome (BMS)
Persistent idiopathic facial pain (PIFP)
Central neuropathic pain
Central neuropathic pain attributed to multiple sclerosis
Central post-stroke pain (CPSP)

From Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version), Cephalalgia 33(9):629-808, 2013.

Secondary headache is a headache that is a symptom of an underlying illness (see Table 613.1). The underlying illness should be clearly present as a direct cause of the headaches with close association of timing and symptomatology. This is often difficult when two or more common conditions occur in close temporal association. This frequently leads to the misdiagnosis of a primary headache as a secondary headache. This is, for example, the case when migraine is misdiagnosed as a sinus headache. In general, the key components of a secondary headache are the likely direct cause-and-effect relationship between the headache and the precipitating condition. In this regard, when the presumed cause of the secondary headache has been treated (antibiotics) or given adequate time to recover (posttraumatic headache), the headache symptoms should have resolved. If this does not occur, either the diagnosis must be reevaluated or the effectiveness of the treatment reassessed.

In all instances of primary headaches, the neurologic examination should be normal. If it is not normal or a secondary headache is suspected, this raises a red flag. *The presence of an abnormal neurologic examination or unusual neurologic symptoms is a key clue that additional investigation is warranted.*

613.1

Migraine

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Migraine is the most frequent type of recurrent headache that is brought to the attention of parents and primary care providers, but it remains underrecognized and undertreated, particularly in children and adolescents. Migraine is characterized by episodic attacks that may be moderate to severe in intensity, focal in location on the head, have a throbbing quality, and associated with nausea, vomiting, light sensitivity, and/or sound sensitivity. Compared with migraine in adults, pediatric migraine may be shorter in duration and has a bilateral, often bifrontal, location. Migraine can also be associated with an aura that may be typical (visual, sensory, or dysphasic) or atypical (hemiplegic, Alice in Wonderland syndrome) (Tables 613.2 to 613.6). In addition, a number of migraine variants have been described and, in children, include abdominally related symptoms without headache, and components of the periodic syndromes of childhood (see Table 613.1). Treatment of migraine requires the incorporation of an acute treatment plan, a preventive treatment plan if the migraine occurs frequently or is disabling, and a biobehavioral plan to help cope with both the acute attacks and frequent or persistent attacks if present.

Table 613.2

Migraine Without Aura

A. At least 5 attacks fulfilling criteria B to D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least 1 of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version), Cephalalgia 33(9):629-808, 2013, Table 4.

Table 613.3

Migraine With Typical Aura

A. At least 2 attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory, and/or speech/language symptoms, each fully reversible, but no motor, brainstem, or retinal symptoms
C. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 min
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

From Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version), Cephalalgia 33(9):629-808, 2013, Table 6.

Table 613.4

Migraine With Brainstem Aura

A. At least 2 attacks fulfilling criteria B to D
B. Aura consisting of visual, sensory, and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
C. At least 2 of the following brainstem symptoms:
   1. Dysarthria
   2. Vertigo
   3. Tinnitus
   4. Hypacusis
   5. Diplopia
   6. Ataxia
   7. Decreased level of consciousness

D. At least 2 of the following 4 characteristics:
   1. At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
   2. Each individual aura symptom lasts 5-60 min
   3. At least 1 aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 min, by headache

E. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

From Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version), Cephalalgia 33(9):629-808, 2013, Table 7.

Table 613.5

Vestibular Migraine With Vertigo

A. At least 5 episodes fulfilling criteria C and D
B. A current or past history of 1.1 *migraine without aura* or 1.2 *migraine with aura*

C. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 hr
D. At least 50% of episodes are associated with at least 1 of the following 3 migrainous features:
  1. Headache with at least 2 of the following 4 characteristics:
    a. Unilateral location
    b. Pulsating quality
    c. Moderate or severe intensity
    d. Aggravation by routine physical activity
  2. Photophobia and phonophobia
  3. Visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

From Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version), Cephalalgia 33(9):629-808, 2013, Table 8.

Table 613.6

Chronic Migraine

A. Headache (tension-type–like and/or migraine-like) on 15 or more days/mo for more than 3 mo and fulfilling criteria B and C
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B to D for 1.1 *migraine without aura* and/or criteria B and C for 1.2 *migraine with aura*
C. On 8 or more days/mo for more than 3 mo, fulfilling any of the following:
  1. Criteria C and D for 1.1 *migraine without aura*
  2. Criteria B and C for 1.2 *migraine with aura*
  3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis

From Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version), Cephalalgia 33(9):629-808, 2013, Table 9.

Epidemiology

Up to 75% of children report having a significant headache by the time they are 15 yr of age. Recurrent headaches are less common, but remain highly frequent. Migraine has been reported to occur in up to 10.6% of children between the ages of 5 and 15 yr and up to 28% of older adolescents. When headaches are occurring more than 15 days a month they are termed chronic migraine and may occur in up to 1% of children and adolescents. The risk of conversion to a daily headache becomes more likely as the frequency increases or ineffective acute treatments are utilized. This explains the necessity to treat the headaches aggressively or prevent the headaches altogether, trying to block transformation to chronic migraine.

Migraine can impact a patient's life through school absences, limitation of home activities, and restriction of social activities. This can be assessed through simple tools such as PedMIDAS. As headaches become more frequent, their negative impact increases in magnitude. This can lead to further complications, including anxiety and school avoidance, requiring a more extensive treatment plan.

Classification and Clinical Manifestations

Criteria have been established to guide the clinical and scientific study of headaches; these are summarized in *The International Classification of Headache Disorders* , 3rd edition (ICHD-3 beta). Table 613.1 contrasts the different clinical types of migraine; Tables 613.2 to 613.6 list the specific criteria for migraine types.

Migraine Without Aura

Migraine without aura is the most common form of migraine in both children and adults. The ICHD-3 beta (see Table 613.2) requires this to be recurrent (at least five headaches that meet the criteria, typically over the past year, but no firm time period is required). The recurrent episodic nature helps differentiate this from a secondary headache, as well as separates migraine from tension-type headache. Because headaches may first start in young childhood, this may limit the diagnosis in children as they are just be beginning to have headaches.

The duration of the headache is defined as 4-72 hr for adults. It has been recognized that children may have shorter-duration headaches, so an allowance has been made to reduce this duration to 2-72 hr in children and adolescents under the age of 18 yr. Note that this duration is for the untreated or unsuccessfully treated headache. Furthermore, if the child falls asleep with the headache, the entire sleep period is considered part of the duration. These duration limits help differentiate migraine from both short-duration headaches, including the trigeminal autonomic cephalalgias, and prolonged headaches, such as those caused by idiopathic intracranial hypertension (pseudotumor cerebri). Some prolonged headaches may still be migraine, but a migraine that persists beyond 72 hr is classified as a variant termed **status migrainosus.**

The quality of migraine pain is often, but not always, throbbing or pounding. This may be difficult to elicit in young children and drawings or demonstrations may help confirm the throbbing quality.

The location of the pain has classically been described as **unilateral (hemicrania);** in young children it is more commonly bilateral. A more appropriate way to think of the location would therefore be focal, to differentiate it from the diffuse pain of tension-type headaches. Of particular concern is the exclusively occipital headache because although these can be migraines, they are more frequently secondary to another more proximate etiology such as posterior fossa abnormalities.

Migraine, when allowed to fully develop, often worsens in the face of and secondarily results in altered activity level. For example, worsening of the pain occurs classically in adults when going up or down stairs. This history is often not elicited in children. A change in the child's activity pattern can be easily observed as a reduction in play or physical activity. Older children may limit or restrict their sports activity or exercise during a headache attack.

Migraine may have a variety of associated symptoms. In younger children, nausea and vomiting may be the most obvious symptoms and often outweigh the headache itself. This often leads to the overlap with several of the gastrointestinal periodic diseases, including recurrent abdominal pain, recurrent vomiting, cyclic vomiting, and abdominal migraine. The common feature among all of these related conditions is an increased propensity among children with them for the later development of migraine. Oftentimes, early childhood recurrent vomiting may in fact be migraine, but the child is not asked about or is unable to describe headache pain. This may occur as early as infancy because babies with colic have a higher incidence of migraine once they are able to express their symptoms. Once a clear head pain becomes evident, the earlier diagnosis of a gastrointestinal disorder is no longer appropriate.

When headache is present, vomiting raises the concern of a secondary headache, particularly related to increased intracranial pressure. *One of the red flags for this is the daily or near daily early morning vomiting, or headaches waking the child up from sleep.* When the headaches associated with vomiting episodes are sporadic and not worsening, it is more likely that the diagnosis is migraine. Vomiting and headache caused by increased intracranial pressure are frequently present on first awakening and remit with maintenance of upright posture. In contrast, if a migraine is present on first awakening *(a relatively infrequent occurrence in children),* getting up and going about normal, upright activities usually makes the headache and vomiting worse.

As the child matures, light and sound sensitivity **(photophobia** and

phonophobia) may become more apparent. This is either by direct report of the patient or the interpretation by the parents of the child's activity because the parent may become aware of this symptom before the child. These symptoms are likely a component of the hypersensitivity that develops during an acute migraine attack and may also include smell sensitivity **(osmophobia)** and touch sensitivity **(cutaneous allodynia).** Although only the photophobia and phonophobia are components of the ICHD-3 beta criteria, these other symptoms are helpful in confirming the diagnosis and may be helpful in understanding the underlying pathophysiology and determining the response to treatment. The final ICHD-3 beta requirement is the exclusion of causes of secondary headaches, and this should be an integral component of the headache history.

Migraine typically runs in families with reports of up to 90% of children having a first- or second-degree relative with recurrent headaches. Given the underdiagnoses and misdiagnosis in adults, this is often not recognized by the family, and a headache family history is required. When a family history is not identified, this may be the result of either a lack of awareness of migraine within the family or an underlying secondary headache in the child. Any child whose family, upon close and both direct and indirect questioning, does not include individuals with migraine or related syndromes (e.g., motion sickness, cyclic vomiting, menstrual headache) should have an imaging procedure performed to look for anatomic etiologies for headache.

In addition to the classifying features, there may be additional markers of a migraine disorder. These include such things as triggers (skipping meals, inadequate or irregular sleep, dehydration, and weather changes are the most common), pattern recognition (associated with menstrual periods in adolescents or Monday-morning headaches resulting from changes in sleep patterns over the weekend and nonphysiologic early waking on Monday mornings for school), and prodromal symptoms (a feeling of irritability, tiredness, and food cravings prior to the start of the headache) (Fig. 613.1). Although these additional features may not be consistent, they do raise the index of suspicion for migraine and provide a potential mechanism of intervention. In the past, food triggers were considered widely common, but the majority have either been discredited with scientific study or represent such a small number of patients that they only need to be addressed when consistently triggering the headache.

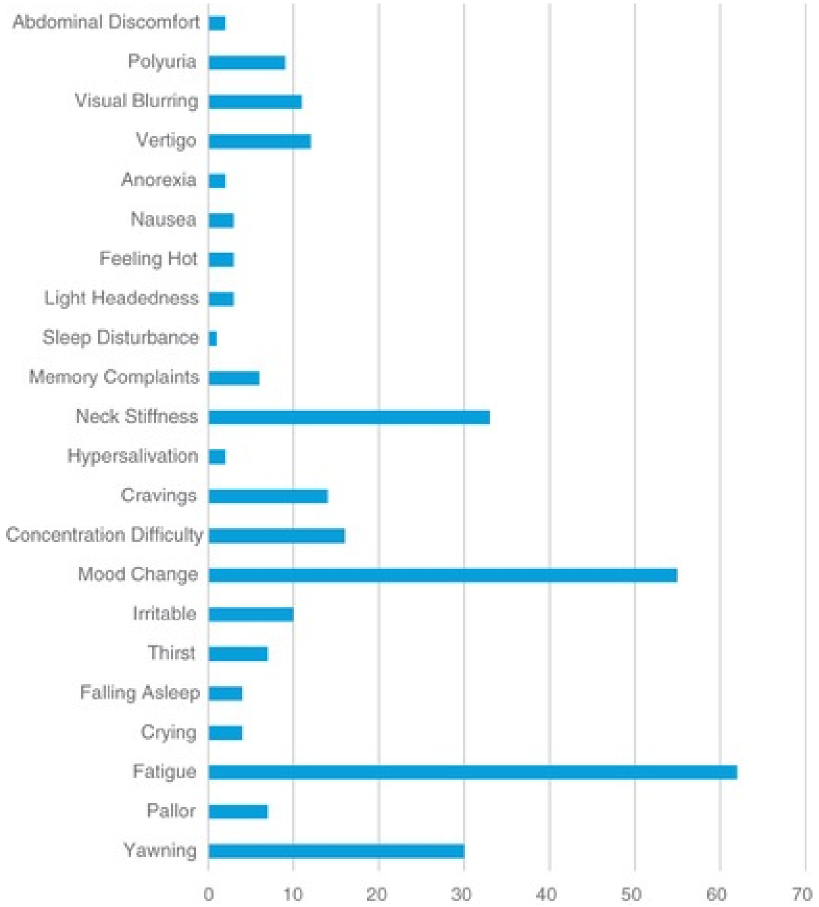

FIG. 613.1 Frequency of different premonitory symptoms reported. (From Karsan N, Prabhakar P, Goadsby PJ: Characterizing the premonitory stage of migraine in children: a clinic-based study of 100 patients in a specialist headache service, J Head Pain 17:94, 2016, Fig. 1.)

Migraine With Aura

The aura associated with migraine is a neurologic warning that a migraine is going to occur. In the common forms this can be the start of a typical migraine or a headache without migraine, or it may even occur in isolation. For a typical aura, the aura needs to be visual, sensory, or dysphasic, lasting longer than 5 min and less than 60 min with the headache starting within 60 min (see Table 613.3). The importance of the aura lasting longer than 5 min is to differentiate the migraine aura from a seizure with a postictal headache, whereas the 60-min maximal duration is to separate migraine aura from the possibility of a more prolonged neurologic event such as a transient ischemic attack. In a revision to the ICHD-3b criteria, it has been suggested that for a diagnosis of aura there needs to be a positive symptom and not just a loss of function (flashing lights, tingling).

The most common type of visual aura in children and adolescents is **photopsia** (flashes of light or light bulbs going off everywhere). These photopsias are often multicolored and when gone, the child may report not being able to see where the flash occurred. Less likely in children are the typical adult auras, including *fortification spectra* (brilliant white zigzag lines resembling a starred pattern castle) or *shimmering scotoma* (sometimes described as a shining spot that grows or a sequined curtain closing). In adults, the auras typically involve only half the visual field, whereas in children they may be randomly dispersed. Blurred vision is often confused as an aura but is difficult to separate from photophobia or difficulty concentrating during the pain of the headache.

Sensory auras are less common. They typically occur unilaterally. Many children describe this sensation as insects or worms crawling from their hand, up their arm, to their face with a numbness following this sensation. Once the numbness occurs, the child may have difficulty using the arm because they have lost sensory input, and a misdiagnosis of hemiplegic migraine may be made.

Dysphasic auras are the least-common type of typical aura and have been described as an inability or difficulty to respond verbally. The patient afterward will describe an ability to understand what is being asked, but cannot answer back. This may be the basis of what in the past has been referred to as confusional migraine, and special attention needs to be paid to asking the child about this possibility and their degree of understanding during the initial phases of the attack. Most of the time, these episodes are described as a motor aphasia, and they are often associated with sensory or motor symptoms.

Much less commonly, *atypical forms of aura can occur,* including hemiplegia (true weakness, not numbness, and may be familial), vertigo or lower cranial nerve symptoms (formerly called basilar-type, formerly thought to be caused by basilar artery dysfunction, now thought to be a more brainstem-based migraine with brainstem aura) (see Table 613.4), and distortion (Alice in Wonderland syndrome). Whenever these rarer forms of aura are present, further investigation is warranted. Not all motor auras can be classified as hemiplegic migraine spectrum, and they should be differentiated from those very specific migrainous events, because the diagnosis of hemiplegic migraine has genetic, pathophysiologic, and therapeutic implications.

Hemiplegic migraine is one of the better-known forms of rare auras. This transient unilateral weakness usually lasts only a few hours but may persist for days. Both familial and sporadic forms have been described. The familial hemiplegic migraine is an autosomal dominant disorder with mutations described in three separate genes: *CACNA1A*, *ATP1A2*, and *SCN1A.* Some patients with familial hemiplegic migraine have other yet-to-be-identified genetic mutations. Multiple polymorphisms have been described for these genes. Hemiplegic migraines may be triggered by minor head trauma, exertion, or emotional stress. The motor weakness is usually associated with another aura symptom and may progress slowly over 20-30 min, first with a visual aura and then, in sequence, with sensory, motor, aphasic, and basilar auras. Headache is present in more than 95% of patients and usually begins during the aura; headache may be unilateral or bilateral and may have no relationship to the motor weakness. Some patients may develop attacks of coma with encephalopathy, cerebrospinal fluid (CSF) pleocytosis, and cerebral edema. Long-term complications may include seizures, repetitive daily episodes of blindness, cerebellar signs with the development of cerebellar atrophy, and mental retardation.

Migraine with brainstem aura (basilar-type migraine) was formerly considered a disease of the basilar artery because many of the unique symptoms were attributed to dysfunction in this area of the brainstem. Some of the symptoms described include vertigo, tinnitus, diplopia, blurred vision, scotoma, ataxia, and an occipital headache. The pupils may be dilated, and ptosis may be evident.

Syndrome of transient headache and neurologic deficits with CSF lymphocytosis (HaNDL) describes transient migraine-like headaches associated with neurologic deficits (motor, sensory, language impairments) and CSF showing pleocytosis. It is considered a self-limited migraine-like syndrome of unknown etiology and is rarely reported in the pediatric population.

Childhood periodic syndromes are a group of potentially related symptoms that occur with increased frequency in children with migraine. The hallmark of these symptoms is the recurrent episodic nature of the events. Some of these have included gastrointestinal-related symptoms (colic, motion sickness, recurrent abdominal pain, recurrent vomiting including cyclic vomiting, and abdominal migraine), sleep disorders (sleepwalking, sleep talking, and night terrors), unexplained recurrent fevers, and even seizures.

The gastrointestinal symptoms span the spectrum from the relatively mild (motion sickness on occasional long car rides) to severe episodes of uncontrollable vomiting that may lead to dehydration and the need for hospital admission to receive fluids. These latter episodes may occur on a predictable time schedule and hence have been called cyclic vomiting. During these attacks, the child may appear pale and frightened but does not lose consciousness. After a period of deep sleep, the child awakens and resumes normal play and eating habits as if the vomiting had not occurred. Many children with cyclic vomiting have a positive family history of migraine and as they grow older have a higher than average likelihood of developing migraine. Cyclic vomiting may be responsive to migraine-specific therapies; careful attention is needed for fluid replacement if the vomiting is excessive. **Cyclic vomiting of migraine** must be differentiated from gastrointestinal disorders, including intestinal obstruction (malrotation, intermittent volvulus, duodenal web, duplication cysts, superior mesenteric artery compression, and internal hernias), peptic ulcer, gastritis, giardiasis, chronic pancreatitis, and Crohn disease. Abnormal gastrointestinal motility and pelviureteric junction obstruction can also cause cyclic vomiting. Metabolic causes include disorders of amino acid metabolism (heterozygote ornithine transcarbamylase deficiency), organic acidurias (propionic acidemia, methylmalonic acidemia), fatty acid oxidation defects (medium-chain acyl-coenzyme A dehydrogenase deficiency), disorders of carbohydrate metabolism (hereditary fructose intolerance), acute intermittent porphyria, and structural central nervous system lesions (posterior fossa brain tumors, subdural hematomas or effusions). The diagnosis is a diagnosis of exclusion, and children will need a full workup to be labeled as having cyclic vomiting syndrome. Cyclic vomiting syndrome is more frequent in younger children and will gradually transform into a typical migraine attack by puberty (see Chapter 369).

The diagnosis of **abdominal migraine** can be confusing but can be thought of as a migraine without the headache. Like a migraine, it is an episodic disorder characterized by midabdominal pain with pain-free periods between attacks. At times this pain is associated with nausea and vomiting (thus crossing into the recurrent abdominal pain or cyclic vomiting spectrum). The pain is usually described as dull and may be moderate to severe. The pain may persist from 1-72 hr and, although it is usually in the midline, it may be periumbilical or poorly localized by the child. To meet the criteria of abdominal migraine, the child must complain at the time of the abdominal pain of at least two of the following: anorexia, nausea, vomiting, or pallor. As with cyclic vomiting, a thorough history and physical examination with appropriate laboratory studies must be completed to rule out an underlying gastrointestinal disorder as a cause of the abdominal pain. Careful questioning about the presence of headache or head pain needs to be addressed directly to the child because many times, this is truly a migraine but in the child's mind (as well as the parents' observation), the abdominal symptoms are paramount.

Diagnosis and Differential Diagnosis

A thorough history and physical examination, including a neurologic examination with special focus on headache, has been shown to be the most sensitive indicator of an underlying etiology. The history needs to include a thorough evaluation of the prodromal symptoms, any potential triggering events or timing of the headaches, associated neurologic symptoms, and a detailed characterization of the headache attacks, including frequency, severity, duration, associated symptoms, use of medication, and disability. The disability assessment should include the impact on school, home, and social activities and can easily be assessed with tools such as PedMIDAS. A family history of headaches and any other neurologic, psychiatric, and general health conditions is also important both for identification of migraine within the family as well as the identification of possible secondary headache disorders. The familial penetrance of migraine is so robust that the absence of a family history of migraine or its equivalent phenomena should raise the concern that the diagnosis may not be migraine and warrants further history taking, referral to a headache specialist, or investigation. The lack of a family history may be due to a lack of awareness of the family of the migraine (“doesn't everybody get headaches?”). When headaches are refractory, a history of potential comorbid conditions, which includes mood disorders and illicit substance use, especially in teenagers, that may influence adherence and acceptability of the treatment plan, may also need to be addressed. Patients with difficult to treat chronic migraines may have raised intracranial pressure; a lumbar puncture with lowering of the pressure may resolve the migraine. These patients may not have papilledema. In addition, disorders such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), Moyamoya disease, and SMART (stoke-like migraine attacks after radiation therapy) may initially present with migraines.

Neuroimaging is warranted when the neurologic examination is abnormal or unusual neurologic features occur during the migraine; when the child has headaches that awaken the child from sleep or that are present on first awakening and remit with upright posture; when the child has brief headaches that only occur with cough or bending over; when the headache is mostly in the occipital area; and when the child has migrainous headache with an absolutely negative family history of migraine or its equivalent (e.g., motion sickness, cyclic vomiting; Table 613.7). In this case, an MRI is the imaging method of choice because it provides the highest sensitivity for detecting posterior fossa lesions and does not expose the child to radiation.

Table 613.7

Indications for Neuroimaging in a Child With Headaches

Abnormal neurologic examination
Abnormal or focal neurologic signs or symptoms
• Focal neurologic symptoms or signs developing during a headache (i.e., complicated migraine) • Focal neurologic symptoms or signs (except classic visual symptoms of migraine) develop during the aura, with fixed laterality; focal signs of the aura persisting or recurring in the headache phase
Seizures or very brief auras (<5 min)
Unusual headaches in children
• Atypical auras, including basilar-type, hemiplegic • Trigeminal autonomic cephalalgia, including cluster headaches in child or adolescent • An acute secondary headache (i.e., headache with known underlying illness or insult)
Headache in children younger than 6 yr old or any child who cannot adequately describe his or her headache
Brief cough headache in a child or adolescent
Headache worst on first awakening or that awakens the child from sleep
Migrainous headache in the child with no family history of migraine or its equivalent

In the child with a headache that is instantaneously at its worst at onset, a CT scan looking for blood is the best initial test; if it is negative, a lumbar puncture should be done looking especially for xanthochromia of the CSF. There is no evidence that laboratory studies or an electroencephalogram is beneficial in a typical migraine without aura or migraine with aura.

Treatment

Table 613.8 outlines the drugs used to manage migraine headaches in children. The American Academy of Neurology established useful practice guidelines for the management of migraine as follows:

Table 613.8

Drugs Used in the Management of Migraine Headaches in Children

DRUG	DOSE	MECHANISM	SIDE EFFECTS	COMMENTS
ACUTE MIGRAINE				
Analgesics				
Acetaminophen	15 mg/kg/dose	Analgesic effects	Overdose, fatal hepatic necrosis	Effectiveness limited in migraine
Ibuprofen	7.5-10 mg/kg/dose	Antiinflammatory and analgesic	GI bleeding stomach upset, kidney injury	Avoid overuse (2-3 times per wk)
Triptans				
Almotriptan* (ages 12-17 yr)	12.5 mg	5-HT$_{1b/1d}$ agonist	Vascular constriction, serotonin symptoms such as flushing, paresthesias, somnolence, GI discomfort	Avoid overuse (>4-6 times per mo)
Eletriptan	40 mg	Same	Same	Avoid overuse (>4-6 times per mo)
Frovatriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (>4-6 times per mo)
Naratriptan	2.5 mg	Same	Same	May be effective for menstrual migraine prevention Avoid overuse (>4-6 times per mo)
Rizatriptan* (ages 6-17 yr)	5 mg for child weighing <40 kg, 10 mg	Same	Same	Available in tablets and melts Avoid overuse (>4-6 times per mo.)
Sumatriptan	Oral: 25, 50, 100 mg Nasal: 10 mg SC: 6 mg	Same	Same	Avoid overuse (>4-6 times per mo)
Zolmitriptan (NS ages 12+)	Oral: 2.5, 5 mg Nasal: 5 mg*	Same	Same	Available in tablets and melts Avoid overuse (>4-6 times per mo)
PROPHYLAXIS (NONE APPROVED BY FDA FOR CHILDREN)				
Calcium Channel Blockers				
Flunarizine †	5 mg HS	Calcium channel blocking agent	Headache, lethargy, dizziness	May ↑ to 10 mg HS
Anticonvulsants				
Valproic acid	20 mg/kg/24 hr (begin 5 mg/kg/24 hr)	↑ Brain GABA	Nausea, pancreatitis, fatal hepatotoxicity	↑ 5 mg/kg every 2 wk
Topiramate* (12-17 yr)	100-200 mg divided bid	↑ Activity of GABA	Fatigue, nervousness	Increase slowly over 12-16 wk
Levetiracetam	20-60 mg/kg divided bid	Unknown	Irritability, fatigue	Increase every 2 wk starting at 20 mg/kg divided bid
Gabapentin	900-1800 mg divided bid	Unknown	Somnolence, fatigue aggression, weight gain	Begin 300 mg, ↑ 300 mg/wk

Antidepressants				
Amitriptyline	1 mg/kg/day	↑ CNS serotonin and norepinephrine	Cardiac conduction, abnormalities and dry mouth, constipation, drowsiness, confusion	Increase by 0.25 mg/kg every 2 wk Morning sleepiness reduced by administration at dinnertime
Antihistamines				
Cyproheptadine	0.2-0.4 mg/kg divided bid; max: 0.5 mg/kg/24 hr	H_1 -receptor and serotonin agonist	Drowsiness, thick bronchial secretions	Preferred in children who cannot swallow pills; not well tolerated in adolescents
Antihypertensive				
Propranolol	10-20 mg tid	Nonselective β-adrenergic blocking agent	Dizziness, lethargy	Begin 10 mg/24 hr ↑ 10 mg/wk (contraindicated in asthma and depression)
Others				
Coenzyme Q10	1-3 mg/kg/day	Increases fatty acid oxidation in mitochondria	No adverse effects reported	Fat soluble; ensure brand contains small amount of vitamin E to help absorption
Riboflavin	50-400 mg daily	Cofactor in energy metabolism	Bright yellow urine, polyuria and diarrhea	
Magnesium	9 mg/kg divided tid	Cofactor in energy metabolism	Diarrhea or soft stool	
Butterbur	50-150 mg daily	May act similar to a calcium channel blocker	Burping	
OnabotulinumtoxinA	100 units (age 11-17 yr)	Inhibits acetylcholine release from nerve endings	Ptosis, blurred vision, hematoma at injection site	Used off label in children
SEVERE INTRACTABLE				
Prochlorperazine	0.15 mg/kg/IV; max dose 10 mg	Dopamine antagonist	Agitation, drowsiness, muscle stiffness, akinesia and akathisia	May have increased effectiveness when combined with ketorolac and fluid hydration
Metoclopramide	0.2 mg/kg IV; 10 mg max dose	Dopamine antagonist	Drowsiness, urticaria, agitation, akinesia and akathisia	Caution in asthma patients
Ketorolac	0.5 mg/kg IV; 15 mg max dose	Antiinflammatory and analgesic	GI upset, bleeding	
Valproate sodium injection	15 mg/kg IV: 1,000 mg max dose	↑ Brain GABA	Nausea, vomiting, somnolence, thrombocytopenia	Would avoid in hepatic disease
Dihydroergotamine IV	0.5 mg/dose every 8 hr (<40 kg) 1.0 mg/dose		Nausea, vomiting, vascular constriction, phlebitis	Dose may need to be adjusted for side effects (decrease) or limited effectiveness (increase)

	every 8 hr (>40 kg)			
Nasal spray	0.5-1.0 mg/dose 0.5 mg/spray			

[*] FDA approved in the pediatric population.

[†] Available in Europe.

↑, Increase; CNS, central nervous system; GABA, γ-aminobutyric acid; GI, gastrointestinal; hs, at night; SC, subcutaneous.

- Reduction of headache frequency, severity, duration, and disability
- Reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
- Improvement in quality of life
- Avoidance of acute headache medication escalation
- Education and enabling of patients to manage their disease to enhance personal control of their migraine
- Reduction of headache-related distress and psychological symptoms

To accomplish these goals, three components need to be incorporated into the treatment plan: (1) An acute treatment strategy should be developed for stopping a headache attack on a consistent basis with return to function as soon as possible, with the goal being 2 hr maximum; (2) a preventive treatment strategy should be considered when the headaches are frequent (one or more per week) and disabling; and (3) biobehavioral therapy should be started, including a discussion of adherence, elimination of barriers to treatment, and healthy habit management.

Acute Treatment

Management of an acute attack is to provide headache freedom as quickly as possible with return to normal function. This mainly includes two groups of medicines: nonsteroidal antiinflammatory drugs (NSAIDs) and triptans. Most migraine headaches in children will respond to appropriate doses of NSAIDs when they are administered at the onset of the headache attack. Ibuprofen has been well documented to be effective at a dose of 7.5-10.0 mg/kg and is often preferred; however, acetaminophen (15 mg/kg) can be effective in those with a contraindication to NSAIDs. Special concern for the use of ibuprofen or other NSAIDs includes ensuring that the children can recognize and respond to onset of the headache. This means discussing with the child the importance of telling the teacher when the headache starts at school and ensuring that proper dosing guidelines and permission have been provided to the school. In addition, overuse needs to be avoided, limiting the NSAID (or any combination of nonprescription analgesics) to not more than 2-3 times per week. The limitation of any analgesic to not more than three headaches a week is necessary to prevent the transformation of the migraines into medication-overuse headaches. If a patient has maximized the weekly allowance of analgesics, the patient's next step is to only use hydrating fluids for the rest of the week as an abortive approach. If ibuprofen is not effective, naproxen sodium also may be tried in similar doses. Aspirin is also a reasonable option but is usually reserved for older children (>16 yr). Use of other NSAIDs has yet to be studied in pediatric migraine. The goal of the primary acute medication should be headache relief within 1 hr with return to function in 10 of 10 headaches.

When a migraine is especially severe, NSAIDs alone may not be sufficient. In this case, a triptan may be considered. Multiple studies have demonstrated their effectiveness and tolerability. There are currently three triptans that are approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of episodic migraine in the pediatric population. Almotriptan is approved for the treatment of acute migraine in adolescents (ages 12-17 yr). Rizatriptan is approved for the treatment of migraine in children as young as age 6 yr. The intranasal formulation of zolmitriptan was recently approved by the FDA in the United States for use in children ages 12 and over. Several studies have shown it to provide rapid and effective relief, and it has been demonstrated to be well tolerated for treatment of acute migraine in patients 12 yr and older. Zolmitriptan nasal spray may be of particular benefit to those with nausea and in patients who have difficulty swallowing tablets.

The combination of naproxen sodium and sumatriptan has been studied and may be effective in children. Controlled clinical trials demonstrate that intranasal sumatriptan is safe and effective in children older than age 8 yr with moderate to severe migraine. At present, pediatric studies showing the effectiveness of oral sumatriptan are lacking, and there is insufficient evidence to support the use of subcutaneous sumatriptan in children. For most adolescents, dosing is the same as for adults; a reduction in dose is made for children weighing less than 40 kg.

The triptans vary by rapidity of onset and biologic half-life. This is related to both their variable lipophilicity and dose. Clinically, 60–70% of patients respond to the first triptan tried, with 60–70% of the patients who did not respond to the first triptan responding to the next triptan. Therefore, in the patient who does not respond to the first triptan in the desired way (rapid reproducible response without relapse or side effects), it is worthwhile to try a different triptan. The most common side effects of the triptans are caused by their mechanism of action—tightness in the jaw, chest, and fingers as a result of vascular constriction and a subsequent feeling of grogginess and fatigue from the central serotonin effect. The vascular constriction symptoms can be alleviated through adequate fluid hydration during an attack.

The most effective way to administer acute treatment is with the recognition that NSAIDs and triptans have different mechanisms of action. NSAIDs are used for all headaches, mild to severe, with their use being restricted to fewer than two to three attacks per week; the triptans are added for moderate to severe headaches, with their use being restricted to not more than four to six attacks per month. For an acute attack, the NSAIDs can be repeated once in 3-4 hr, if needed for that specific attack, and the triptans can be repeated once in 2 hr if needed. It is important to consider the various formulations available, and these options should be discussed with pediatric patients and their parents, especially if a child is unable to swallow pills or take an oral dose because of nausea.

Because vascular dilation is a common feature of migraine that may be responsible for some of the facial flushing, followed by paleness and the lightheaded feeling accompanying the attacks, fluid hydration should be integrated into the acute treatment plan. For oral hydration, this can include the sports drinks that combine electrolytes and sugar to provide the intravascular rehydration.

Antiemetics were used for acute treatment of the nausea and vomiting. Further study has identified that their unique mechanism of effectiveness in headache treatment is related to their antagonism of dopaminergic neurotransmission. Therefore, the antiemetics with the most robust dopamine antagonism (i.e., prochlorperazine and metoclopramide) have the best efficacy. These can be very effective for status migrainosus or a migraine that is unresponsive to the NSAIDs and triptans. They require intravenous administration because other forms of administration of these drugs are less effective than the NSAIDs or triptans. When combined with ketorolac and intravenous fluids in the emergency department or an acute infusion center, intravenous antiemetics can be very effective. When they are not effective, further inpatient treatment may be required using dihydroergotamine (DHE), which will mean an admission to an inpatient unit for more aggressive therapy of an intractable attack.

Emergency Department Treatments for Intractable Headaches

When an acute migraine attack does not respond to the recommended outpatient regimen and the headache is disabling, more aggressive therapeutic approaches are available and may be necessary to prevent further increase in the duration as well as the frequency of headaches. These migraines fall into the classification of status migrainosus and patients may need to be referred to an infusion center, the emergency room, or an inpatient unit.

Available specific treatments for migraine headache in an emergency room setting include the following: antidopaminergic medications such as prochlorperazine and metoclopramide; NSAIDs such as ketorolac; vasoconstrictor medications such as DHE; and antiepileptic drugs such as sodium valproate.

Antidopaminergic Drugs: Prochlorperazine and Metoclopramide

The use of antidopaminergic medications is not limited to controlling the nausea and vomiting often present during a migraine headache. Their potential pharmacologic effect may be a result of their antidopamine property and the underlying pathologic process involving the dopaminergic system during a migraine attack. Prochlorperazine is very effective in aborting an attack in the emergency room when given intravenously with a bolus of intravenous fluid. Results show a 75% improvement with 50% headache freedom at 1 hr and 95% improvement with 60% headache freedom at 3 hr. Prochlorperazine may be more effective than metoclopramide. The average dose of metoclopramide is 0.13-0.15 mg/kg, with a maximum dose of 10 mg given intravenously over 15 min. The average dose of prochlorperazine is 0.15 mg/kg, with a maximum dose of 10 mg. These medications are usually well-tolerated, but *extrapyramidal reactions* are more frequent in children than older persons. An acute extrapyramidal reaction can be controlled in the emergency room with 25-50 mg of diphenhydramine given intravenously. There is no need for premedication with diphenhydramine to prevent side effects. Diphenhydramine should only be used if needed when side effects are present.

Nonsteroidal Antiinflammatory Drugs: Ketorolac

It is known that an aseptic inflammation occurs in the central nervous system as a result of the effect of multiple reactive peptides in patients with migraines. Ketorolac is often used in the emergency department as monotherapy for a migraine attack or in combination with other drugs. In monotherapy, the response to ketorolac is 55.2% improvement. When the ketorolac is combined with prochlorperazine, the response rate jumps to 93%.

Antiepileptic Drugs: Sodium Valproate

Antiepileptic drugs have been used as prophylactic treatment for migraine headache for years with adequate double-blinded, controlled studies on their efficacy in adults. The mechanism in which sodium valproate acutely aborts migraine headaches is not well understood. Sodium valproate is given as a bolus of 15-20 mg/kg push (over 10 min). This intravenous load is followed by an oral dose (15-20 mg/day) in the 4 hr after the injection. Patients may benefit from a short-term preventive treatment with an extended-release form after discharge from the emergency room. Sodium valproate is usually well tolerated. Patients should be receiving a fluid load during the procedure to prevent a possible hypotensive episode.

Triptans

Subcutaneous sumatriptan (0.06 mg/kg) has an overall efficacy of 72% at 30 min and 78% at 2 hr, with a recurrence rate of 6%. Because children tend to have a shorter duration of headache, a recurrence rate of 6% would seem appropriate for this population. DHE, if recommended for the recurrences, should not be given in the 24 hr after triptan use. Triptans are contraindicated in patients treated with ergotamine within 24 hr and within 2 wk of treatment with monoamine oxidase inhibitors. Triptans may rarely produce a serotonin syndrome in patients taking a serotonin receptor reuptake inhibitor. *Both triptans and ergotamine are contraindicated in hemiplegic migraines.*

Dihydroergotamine (DHE)

DHE is an old migraine medication used as a vasoconstrictor to abort the vascular phase of migraine headache. The effectiveness is discussed in detail in the section Inpatient Management of Intractable Migraine and Status Migrainosus, below. One dose of DHE can be effective for abortive treatment in the emergency department. Emergency room treatment of migraine shows a recurrence rate of 29% at 48-72 hr, with 6% of patients needing even more aggressive therapy in an inpatient unit.

Inpatient Management of Intractable Migraine and Status Migrainosus

Six to 7% of patients fail acute treatment in the emergency department. These patients are usually admitted for 3-5 days and receive extensive parenteral treatment. A child should be admitted to the hospital for a primary headache when the child is in status migrainosus, has an exacerbation of a chronic severe headache, or has an analgesic overuse headache with an acute exacerbation. The goal of inpatient treatment is to control a headache that has been unresponsive to other abortive therapy and is disabling to the child. Treatment protocols include the use of DHE, antiemetics, sodium valproate, and other drugs.

Dihydroergotamine

Ergots are one of the oldest treatments for migraine headache. DHE is a parenteral form used for acute exacerbations. Its effect stems from the $5HT_{1A\text{-}1B\text{-}1D\text{-}1F}$ receptor agonist affinity and central vasoconstriction. DHE has a greater α-adrenergic antagonist activity and is less vasoconstrictive peripherally. Before initiation of an intravenous ergot protocol, a full history should be obtained and a neurologic examination performed. Females of childbearing age should be evaluated for pregnancy before ergots are administered.

The DHE protocol consists of the following: Patients are premedicated with 0.13-0.15 mg/kg of prochlorperazine 30 min prior to the DHE dose (maximum of three prochlorperazine doses to prevent extrapyramidal syndrome; after 3 doses of prochlorperazine a non-dopamine antagonist antiemetic should be used, such as ondansetron). A dose of 0.5-1.0 mg of DHE is used (depending on age and tolerability) every 8 hr until headache freedom. The first dose should be divided into two half doses separated by 30 min; they are considered test doses. When the headache ceases, an extra dose is given in an attempt to prevent recurrence after discharge. The response to this protocol is a 97% improvement and 77% headache freedom. The response is noticeable by the fifth dose; the drug can reach its maximum effects after the tenth dose. Side effects of DHE include nausea, vomiting, abdominal discomfort, a flushed face, and increased blood pressure. The maximum dose used in this protocol is 15 mg total of DHE.

Sodium Valproate

Sodium valproate is used when DHE is contraindicated or has been ineffective. One adult study recommends the use of valproate sodium as follows: Bolus with 15 mg/kg (maximum of 1,000 mg), followed by 5 mg/kg every 8 hr until headache freedom or up to a maximum of ten doses. Always give an extra dose after headache ceases. This protocol was studied in adults with chronic daily headaches and showed an 80% improvement. It is well tolerated and is useful in children when DHE is ineffective, contraindicated, or not tolerated.

Other Inpatient Therapies

During an inpatient admission for status migrainosus, we highly recommend that other services, such as behavioral medicine and holistic medicine, become involved if they are available. The behavioral medicine staff can play a major role in talking to patients about their specific triggers and can also evaluate school, as well as home and social, stressors. The staff would also initiate some coping skills during the admission and evaluate the necessity for further outpatient follow-up for cognitive behavioral therapy, biofeedback, or treatment for other comorbidities. The holistic medicine staff, when consulted, can offer holistic approaches to pain control, including relaxation techniques, as well as medical massage and craniosacral therapy.

Preventive Therapy

When the headaches are frequent (more than one headache per week) or disabling (causing the patient to miss school, home, or social activities, or having a PedMIDAS score > 20), preventive or **prophylactic therapy** may be warranted. The goal of this therapy should to be to reduce the frequency (to one to two headaches or fewer per month) and level of disability (PedMIDAS score < 10). Prophylactic agents should be given for at least 4-6 mo at an adequate dose and then weaned over several weeks. Evidence in adult studies has begun to demonstrate that persistent frequent headaches foreshadow an increased risk of progression with decreased responsiveness and increased risk of refractoriness in the future. It is unclear whether this also occurs in children and/or adolescents and whether early treatment of headache in childhood prevents development of refractory headache in adulthood.

Multiple preventive medications have been utilized for migraine prophylaxis in children. When analyzed as part of a practice parameter, only one medication, **flunarizine** (a calcium channel blocking agent), demonstrated a level of effectiveness viewed as substantial; it is not available in the United States. Flunarizine is typically given at 5 mg orally daily and increased after 1 mo to 10 mg orally daily, with a month off of the drug every 4-6 mo.

A commonly used preventive therapy for headache and migraine is amitriptyline. Typically, a dose of 1 mg/kg daily at dinner or in the evening is effective. However, this dose needs to be reached slowly (i.e., over weeks, with an increase every 2 wk until the goal is reached) to minimize side effects and improve tolerability. Side effects include sleepiness and those related to amitriptyline's anticholinergic activity. Weight gain has been observed in adults using amitriptyline but is a less frequent occurrence in children. Amitriptyline does have the potential to exacerbate the prolonged QT syndrome, so it should be avoided in patients with this diagnosis and looked for in patients taking the drug who complain of a rapid or irregular heart rate.

Antiepileptic medications are also used for migraine prophylaxis, with topiramate, valproic acid, and levetiracetam having been demonstrated to be effective in adults. There are limited studies in children for migraine prevention, but all of these medications have been assessed for safety and tolerability in children with epilepsy.

Topiramate has become widely used for migraine prophylaxis in adults. Topiramate was also demonstrated to be effective in an adolescent study. This study demonstrated that a 25-mg dose twice a day was equivalent to placebo, whereas a 50-mg dose twice a day was superior. Thus it appears that the adult dosing schedule is also effective in adolescents with an effective dosage range of 50 mg twice a day to 100 mg twice a day. This dose needs to be reached slowly to minimize the cognitive slowing associated with topiramate use. Side effects include weight loss, paresthesias, kidney stones, lowered bicarbonate levels, decreased sweating, and rarely glaucoma and changes in serum transaminases. In addition, in adolescent females taking birth control pills, the lowering of the effectiveness of the birth control by topiramate needs to be discussed.

A comparative effectiveness study in children (8-17 yr) of the two most common treatments (amitriptyline and topiramate) compared with placebo (the

CHAMP study) demonstrated that all three treatments were effective, but there was not statistical superiority for amitriptyline or topiramate over placebo.

Valproic acid has long been used for epilepsy in children and has been demonstrated to be effective in migraine prophylaxis in adults. The effective dose in children appears to be 10 mg/kg orally twice a day. Side effects of weight gain, ovarian cysts, and changes in serum transaminases and platelet counts need to be monitored. Other antiepileptics, including lamotrigine, levetiracetam, zonisamide, gabapentin, and pregabalin, are also used for migraine prevention.

β-Blockers have long been used for migraine prevention. The studies on β-blockers have a mixed response pattern with variability both between β-blockers and between patients with a given β-blocker. Propranolol is the best studied for pediatric migraine prevention with unequivocally positive results. The contraindication for use of propranolol in children with asthma or allergic disorders or diabetes and the increased incidence of depression in adolescents using propranolol limit its use somewhat. It may be very effective for a mixed subtype of migraine (basilar-type migraine with postural orthostatic tachycardia syndrome). This syndrome has been reported to be responsive to propranolol. α-Blockers and calcium channel blockers, aside from flunarizine, also have been used in pediatric migraine; their effectiveness, however, remains unclear.

In very young children, cyproheptadine may be effective in prevention of migraine or the related variants. Young children tend to tolerate the increased appetite induced by the cyproheptadine and tend not to be subject to the lethargy seen in older children and adults; the weight gain is limiting once children start to enter puberty. Typical dosing is 0.1-0.2 mg/kg orally twice a day.

Nutraceuticals have become increasingly popular over the past few years, especially among families who prefer a more natural approach to headache treatment. Despite studies showing success of these therapies in adults, few studies have shown effectiveness in pediatric headaches. Riboflavin (vitamin B_2), at doses ranging from 25-400 mg, is the most widely studied with good results. Side effects are minimal and include bright yellow urine, diarrhea, and polyuria. Coenzyme Q10 supplementation may be effective in reducing migraine frequency at doses of 1-2 mg/kg/day. Butterbur is also effective in reducing headaches, with minimal side effects, including burping. Use in children has been limited to avoid the potential toxicity of butterbur-containing pyrrolizidine alkaloids, which are naturally contained and are a known carcinogen and toxic to the liver.

OnabotulinumtoxinA is the first medication FDA-approved for chronic migraine in adults. There are studies in children indicating its effectiveness; use in children is considered off-label. The limited available studies revealed the following: The average dose used was 188.5 units ± 32 units with a minimum dose of 75 units and maximum of 200 units. The average age of patients receiving the treatment was 16.8 ± 2.0 yr (minimum 11 yr; maximum 21 yr). OnabotulinumtoxinA injections improved disability scores (PedMIDAS) and headache frequency in pediatric chronic daily headache patients and chronic migraine in this age-group. OnabotulinumtoxinA not only had a positive effect on the disability scoring for these young patients with headache but was also able to transform the headaches from chronic daily to intermittent headaches in more than 50% of the patients.

Eptinezumab, Erenumab, Galcanezumab, and Fremanezumab—humanized monoclonal antibodies against the calcitonin gene-related peptide or its receptor—have demonstrated safety and efficacy in adult patients with migraine. The US Food and Drug Administration has approved these agents for use in adults with migraine, including chronic migraine. As yet, there are no completed studies in children and adolescents.

Biobehavioral Therapy

Biobehavioral evaluation and therapy are essential for effective migraine management. This includes identification of behavioral barriers to treatment, such as a child's shyness or limitation in notifying a teacher of the start of a migraine or a teacher's unwillingness to accept the need for treatment. Additional barriers include a lack of recognition of the significance of the headache problem and reverting to bad habits once the headaches have responded to treatment. Adherence is equally important for acute and preventive treatment. The need to have a sustained response, long enough to prevent relapse (to stay on preventive medication), is often difficult when the child starts to feel better. Establishing a defined treatment goal (one or two or fewer headaches per month for 4-6 mo) helps with acceptance.

Because many of the potential triggers for frequent migraines (skipping meals, dehydration, decreased or altered sleep) are related to a child's daily routine, a discussion of healthy habits is a component of biobehavioral therapy. This should include adequate fluid intake without caffeine, regular exercise, not skipping meals and making healthy food choices, and adequate (8-9 hr) sleep on a regular basis. Sleep is often difficult in adolescents because middle and high schools often have very early start times, and the adolescent's sleep architecture features a shift to later sleep onset and waking. This has been one of the explanations for worsening headaches during the school year in general and at the beginning of the school year and week.

Biofeedback-assisted relaxation and cognitive behavioral therapy (usually in combination with amitriptyline) are effective for both acute and preventive therapy and may be incorporated into this multiple treatment strategy. This provides the child with a degree of self-control over the headaches and may further help the child cope with frequent headaches.

Young Adults and the Transition of Headache Care From a Pediatric to an Adult Provider

Migraine is a chronic condition that begins in childhood. Males are diagnosed at a younger age than females; however, during development, the prevalence becomes highest among women, starting at puberty. Some adolescents and women report migraine associated with menses; the pain symptoms are described as lasting longer and having a higher intensity. The role of oral contraceptive pills (OCPs) is often a topic of discussion among female adolescents and young women. Studies have shown improvement of menstrual migraine in adult patients taking oral estrogens and progesterone; similar studies have not been done in adolescents. OCPs are not approved by the U.S. FDA for treatment of menstrual migraine; they have been associated with an increased risk of stroke among women with migraine aura. Therefore, their use in adolescents as a prophylactic agent is not advised.

Comorbid conditions such as anxiety and depression are seen with a high prevalence among adults with migraine; however, the prevalence among adolescent patients remains unclear. Diagnostic tools capable of differentiating mood disorders from pain symptoms in the pediatric population are limited, which makes identifying those at risk challenging. However, it is important to keep in mind the potential of mood disorders, especially in young adults.

Remission of migraine is seen in up to 34% of adolescents, and almost 50% continue to have migraine persisting into adulthood. Despite the high prevalence, the transition of care in this population has yet to be studied. Successful transition of care from a pediatric to an adult provider has been shown to improve outcomes in patients with chronic disease.

Early diagnosis and treatment of migraine can help minimize the progression of the disease in adults. This, together with careful screening for comorbid conditions, may help identify those at risk for refractory migraine, minimize disability, and improve overall headache outcomes.

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613.2

Secondary Headaches

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Headaches can be a common symptom of other underlying illnesses. In recognition of this, the ICHD-3 beta has classified potential secondary headaches (see Table 613.1). The key to the diagnosis of a secondary headache is to recognize the underlying cause and demonstrate a direct cause and effect. Until this has been done, the diagnosis is speculative. This is especially true when the suspected etiology is common.

Headache is a common occurrence following concussion or mild traumatic brain injury (mTBI), reported in as many as 86% of high school and college athletes who have suffered from head trauma. Although there are no strict criteria for determining who will develop persistent headache following concussion, it is important to gather information to rule out other secondary headaches and significant primary headache disorders and to identify those who may be at risk for persistent headache following concussion.

Chronic or persistent headaches are headaches that last for more than 3 mo following head trauma. This definition is consistent with the classification of persistent posttraumatic headaches in the ICHD-3b. Although concussion and posttraumatic headache are rapidly evolving areas of study, there is an unfortunate lack of definitive scientific evidence at this time on these topics in pediatrics. The ICHD-3 classifies posttraumatic headaches as acute if they last less than 3 mo and persistent if they last more than 3 mo. This time period is consistent with ICHD-II diagnostic criteria, although the term *persistent* has been adopted in place of *chronic.* Although the ICHD-3 criteria state that posttraumatic headaches begin within 7 days after injury to the head or after regaining consciousness, the authors comment that this 7-day cutoff is arbitrary, and some experts believe that headaches may develop after a longer interval. Some studies have shown that about half of children with posttraumatic headache 3 mo after concussion had a history of preexisting headaches, and 31% had a history of migraine or probable migraine before the injury. Furthermore, 56% of patients with headaches at 3 mo following injury had a family history of migraine. Based on our clinical experience and studies of patients with prolonged postconcussion symptoms in general, we have concerns that those with prior concussion and persistent posttraumatic headaches, preexisting anxiety and/or depression, and maladaptive coping styles may also be at higher risk for persistent posttraumatic headache. One study investigating risk factors for prolonged postconcussion syndrome supports these theories; the researchers found that a personal or family history of mood disorders or migraine, as well as prior concussion and delayed symptom onset, were associated with symptoms for ≥ 3 mo following concussion.

Despite being classified as a secondary headache, a posttraumatic headache generally presents with clinical features that are observed in primary headache disorders, including tension-type, migraine, and cervicogenic headaches. The few reports that have thus far assessed the characteristics of posttraumatic headache in the pediatric population have also reported various proportions of migraine or tension-type characteristics, with the reported prevalence of each varying among individual studies.

Although headache is reported to be the most common symptom following concussion, there is a paucity of studies regarding the safety and efficacy of headache treatments for persistent posttraumatic headaches. As most clinicians who manage concussion and posttraumatic headaches can attest, these headaches may be difficult to treat. There are currently no established guidelines for their treatment, especially when persistent, and practices can vary widely. Most treatment algorithms proposed have been extrapolated from the primary headache literature and small noncontrolled trials of posttraumatic headache regimens. When posttraumatic headaches become problematic or persistent, a multidimensional management approach, including pharmacologic intervention, physical rehabilitation, and cognitive-behavioral therapies, are often used. Management should therefore be relevant to the type of headache and also focused on the clinical needs of the child.

Like primary headache disorders, these headaches can have a substantial effect on the child's life, leading to lost school days and withdrawal from social interactions. Referral for biobehavioral therapy and coping strategies may be necessary. Adherence should be promoted and can be optimized by educating both the patient and the family about the proper use of acute and prophylactic medications, establishing realistic expectations including expectations for recovery, and emphasizing compliance at the initiation of treatment.

Children with persistent posttraumatic headaches may require frequent analgesics. Rebound headaches are common and can complicate treatment. The excessive use of symptomatic headache medicines, most commonly simple analgesics, can cause medication-overuse headaches in susceptible patients and has been well-described in patients with primary headache disorders. Medication overuse can be a contributing factor in headache chronicity in 20–30% of children and adolescents, with chronic daily headache unrelated to concussion. Because analgesics are commonly recommended for the treatment of acute headaches following concussion, some susceptible patients with concussion are at risk for developing a medication-overuse pattern that causes a chronic headache syndrome.

There is no clear evidence to help guide the clinician on the timing of initiation of preventive therapy in children to decrease the likelihood of developing persistent posttraumatic headaches. Although many medications are being used to manage persistent posttraumatic headaches, most have supporting data for management of migraine or chronic migraine and few have been studied for the treatment of persistent posttraumatic headaches in a systematic manner.

Sinus headache is the most overdiagnosed form of recurrent headache. Although no studies have evaluated the frequency of misdiagnosis of an underlying migraine as a sinus headache in children, in adults, it has been found that up to 90% of adults diagnosed as having a sinus headache either by themselves or their physician appear to have migraine. When headaches are recurrent and respond within hours to analgesics, migraine should be considered first. In the absence of purulent nasal discharge, fever, or chronic cough, the diagnosis of sinus headache should not be made.

Medication-overuse headaches (MOHs) frequently complicate primary and secondary headaches. An MOH is defined as a headache present for more than 15 days/mo for longer than 3 mo and intake of a simple analgesic on more than 15 days/mo and/or prescription medications, including triptans or combination medications, on more than 10 days/mo. Some of the signs that should raise suspicion of medication overuse are the increasing use of analgesics (nonprescription or prescription) with either decreased effectiveness or frequent wearing off (i.e., analgesic rebound). An MOH can be worsened by ineffective medications or misdiagnosis of the headache. Patients should be cautioned against the frequent use of antimigraine medications, including combination analgesics or triptans.

Serious causes of secondary headaches are likely to be related to **increased intracranial pressure.** This can be caused by a mass (tumor, vascular malformation, cystic structure) or an intrinsic increase in pressure (idiopathic intracranial hypertension, also known as pseudotumor cerebri). In the former case, the headache is caused by the mass effect and local pressure on the dura; in the latter case, the headache is caused by diffuse pressure on the dura. The etiology of idiopathic intracranial hypertension may be the intake of excessive amounts of fat-soluble compounds (e.g., vitamin A, retinoic acid, and minocycline), hormonal changes (increased incidence in females), or blockage of venous drainage (as with inflammation of the transverse venous sinus from mastoiditis). When increased pressure is suspected, either by historical suspicion or the presence of papilledema, an MRI with magnetic resonance angiography and magnetic resonance venography should be performed, followed by a lumbar puncture if no mass or vascular anomaly is noted. The lumbar puncture can be diagnostic and therapeutic of idiopathic intracranial hypertension but must be performed with the patient in a relaxed recumbent position with legs extended, because abdominal pressure can artificially raise intracranial pressure. If headache persists or there are visual field changes, pharmaceutical treatment with a carbonic anhydrase inhibitor, optic nerve fenestration, or a shunt needs to be considered.

Additional causes of secondary headaches in children that may not be associated with increased intracranial pressure include arteriovenous malformations, berry aneurysm, collagen vascular diseases affecting the central nervous system, hypertensive encephalopathy, infectious or autoimmune etiologies, acute subarachnoid hemorrhage, and stroke. The management of secondary headache depends on the cause. Helpful laboratory tests and neuroradiologic procedures depend on the clues provided by the history and physical examination. By definition, a secondary headache has a specific cause and should resolve once this cause is treated. If the headache persists, the diagnosis and treatment should be questioned because either the diagnosis, which may include a primary headache, or the treatment, or both, may be incorrect.

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613.3

Tension-Type Headaches

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Tension-type headaches (TTHs) may be very common in children and adolescents, with a prevalence in some studies as high as 48%, with those having a combination of migraine and TTH being around 20%. Because of their mild to moderate nature, relative lack of associated symptoms, and lower degree of associated disability, they are often ignored or have a minimal impact. The ICHD-3 beta subclassifies TTHs as infrequent (<12 times/yr) (Table 613.9); frequent (1-15 times/mo); and chronic (>15 headaches/mo). They can further be separated into headaches with or without pericranial muscle tenderness. The classification of TTH can be likened to the opposite of migraine. Whereas migraines are typically moderate to severe, are focal in location, are worsened by physical activity or limit physical activity, and have a throbbing quality, TTHs are mild to moderate in severity, are diffuse in location, are not affected by activity (although the patient may not feel like being active), and are nonthrobbing (often described as a constant pressure). TTH is much less frequently associated with nausea, photophobia, or phonophobia and is never associated with more than one of these at a time or with vomiting. TTH must be recurrent, but at least 10 headaches are required and the duration can be 30 min to 7 days. Secondary headaches with other underlying etiologies must be ruled out.

Table 613.9

Infrequent Episodic Tension-Type Headache

A. At least 10 episodes of headache occurring on < 1 day/mo on average (<12 days/yr) and fulfilling criteria B to D
B. Lasting from 30 min to 7 days
C. At least 2 of the following 4 characteristics:
    1. Bilateral location
    2. Pressing or tightening (nonpulsating) quality
    3. Mild or moderate intensity
    4. Not aggravated by routine physical activity, such as walking or climbing stairs
D. Both of the following:
    1. No nausea or vomiting
    2. No more than 1 of photophobia or phonophobia
E. Not better accounted for by another ICHD-3 beta diagnosis

From Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders, ed 3 (beta version), Cephalalgia 33(9):629-808, 2013, Table 10.

Evaluation of patients with suspected TTHs requires a detailed headache history and complete general and neurologic examination. This is to establish the diagnosis and ensure exclusion of secondary etiologies. When secondary headaches are suspected, further, directed evaluation is indicated.

Treatment of TTHs can require acute therapy to stop attacks, preventive therapy when frequent or chronic, and behavioral therapy. It is often suspected that there may be underlying psychological stressors (hence, the misnomer as a stress headache), but this is often difficult to identify in children, and although it may be suspected by the parents, it cannot be confirmed in the child. Studies of and conclusive evidence to guide the treatment of TTH in children are lacking, but the same general principles and medications used in migraine can be applied to children with TTHs (see Chapter 613.1). Oftentimes, simple analgesics (ibuprofen or acetaminophen) can be effective for acute treatment. Flupirtine is a nonopioid analgesic that has been approved in Europe for the treatment of TTH in children as young as age 6 yr but is not available in the United States. Amitriptyline has the most evidence of effective prevention of TTH; biobehavioral intervention, including biofeedback-assisted relaxation training and coping skills, can be useful as well.

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CHAPTER 614

Neurocutaneous Syndromes

Mustafa Sahin, Nicole Ullrich, Siddharth Srivastava, Anna Pinto

The neurocutaneous syndromes include a heterogeneous group of disorders characterized by abnormalities of both the integument and central nervous system (CNS) of variable severity (Table 614.1). Many of the disorders are hereditary and believed to arise from a defect in differentiation of the primitive ectoderm (nervous system, eyeball, retina, and skin). Disorders classified as neurocutaneous syndromes include neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), tuberous sclerosis complex (TSC), Sturge-Weber syndrome (SWS), von Hippel–Lindau disease (VHL), PHACE (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta, cardiac defects, eye abnormalities) syndrome, ataxia-telangiectasia (AT), linear nevus syndrome, hypomelanosis of Ito, and incontinentia pigmenti.

Table 614.1

Genetic and Clinical Features Associated With Neurocutaneous Syndromes

SYNDROME	GENE(S)	INHERITANCE	CLINICAL FEATURES
Tuberous sclerosis complex	*TSC1 (tuberous sclerosis 1; hamartin)* *TSC2 (tuberous sclerosis 2; tuberin)*	Autosomal dominant	Angiofibromas, hypomelanotic macules, shagreen patches, ungual fibromas, cortical dysplasias, subependymal giant cell astrocytomas, subependymal nodules, intellectual disability, epilepsy including infantile spasms, autism spectrum disorder, retinal hamartomas, cardiac rhabdomyomas, lymphangioleiomyomatosis, renal angiomyolipomas
Von Hippel–Lindau	*VHL (von Hippel–Lindau tumor suppressor)*	Autosomal dominant	Cerebellar hemangioblastomas, retinal angiomas, endolymphatic sac tumors, pancreatic neuroendocrine tumors, renal cysts, renal cell carcinomas, pheochromocytomas
Linear nevus sebaceous	*HRAS (HRas proto-*	Somatic mosaicism	Linear sebaceous nevus, hemimegalencephaly, ventriculomegaly, intellectual disability, epilepsy, ocular

	oncogene, GTPase) *KRAS (KRAS proto-oncogene, GTPase)* *NRAS (neuroblastoma RAS viral oncogene homolog)*		defects (e.g., strabismus), cardiac defects (e.g., coarctation of the aorta), urogenital defects (e.g., horseshoe kidney), skeletal defects (e.g., fibrous dysplasia)
PHACE	Unknown		Posterior fossa malformations, hemangiomas, arterial lesions (e.g., dysplasia of cerebral arteries), cardiac defects (e.g., coarctation of the aorta), ocular defects (e.g., microphthalmia), ventral defects (e.g., sternal clefting)
Incontinentia pigmenti	*IKBKG (inhibitor of kappa B kinase gamma)*	X-linked dominant	Distinctive skin lesion appearing in four stages (bullous, verrucous, pigmentary, atretic), alopecia, dental anomalies (e.g., hypodontia), intellectual disability, epilepsy, ocular defects (e.g., retinal neovascularization), nail defects (e.g., dystrophic nails)

614.1

Neurofibromatosis

Nicole Ullrich

The neurofibromatoses are autosomal dominant disorders that cause tumors to grow on nerves and result in other systemic abnormalities. There are three types, neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2), and schwannomatosis, all of which are clinically and genetically distinct diseases and should be considered separate entities.

Clinical Manifestations and Diagnosis

NF1 has an incidence of 1 in 3,000 live births and is caused by autosomal dominant loss-of-function mutations in the *NF1* gene. Approximately 50% are inherited from an affected parent, and the other 50% result from a sporadic gene mutation. The disease is clinically diagnosed when any two of the following seven features are present: (1) six or more café-au-lait macules > 5 mm in greatest diameter in prepubertal individuals and > 15 mm in greatest diameter in postpubertal individuals (Fig. 614.1). Café-au-lait macules (CALMs) are the hallmark of neurofibromatosis and are present in almost 100% of patients. They are present at birth but increase in size, number, and pigmentation, especially during the first few years of life. The CALMs are scattered over the body surface, with predilection for the trunk and extremities. CALMs are not specific for NF1 and may be observed in other disorders (Table 614.2). (2) Axillary or inguinal freckling consisting of multiple hyperpigmented areas 2-3 mm in diameter (Fig. 614.2). Skinfold freckling usually appears between 3 and 5 yr of age. The frequency of axillary and inguinal freckling is reported to be > 80% by 6 yr of age. (3) Two or more iris Lisch nodules, which are hamartomas located within the iris and are best identified by a slit-lamp examination (Fig. 614.3). They are present in more than 74% of patients with NF1. The prevalence of Lisch nodules increases with age, from only 5% of children younger than 3 yr of age, to 42% among children 3-4 yr of age, and virtually 100% of adults older than 21 yr of age. (4) Two or more neurofibromas or one plexiform neurofibroma. Neurofibromas are most visible on the skin, but they may occur on any peripheral nerve in the body, including along peripheral nerves and blood vessels and within viscera, including the gastrointestinal tract. These lesions appear characteristically during adolescence or pregnancy, suggesting a hormonal influence. They are usually small, rubbery lesions with a slight purplish discoloration of the overlying skin. Plexiform neurofibromas are typically congenital and result from diffuse thickening of nerve trunks and surrounding soft tissues. The skin overlying a plexiform neurofibroma may be coarse and associated with hyperpigmentation. Plexiform neurofibromas may produce overgrowth of an extremity and a deformity of the corresponding bone. (5) A distinctive osseous lesion such as sphenoid dysplasia (which may cause pulsating exophthalmos) or cortical thinning of long bones with or without pseudoarthrosis (most often the tibia). (6) Optic gliomas are present in approximately 15–20% of individuals with NF1; however, only ~ 30% of these are clinically symptomatic and require tumor-directed therapy. They are the most frequently observed CNS tumor in NF1. Because of visual acuity compromise, it is recommended that all children with NF1 undergo at least annual ophthalmologic examinations, or more frequent ones if there is a concern. The most common time to develop symptoms is between the ages of 2-6 yr; they manifest as a change in visual acuity, a change in the visual fields, or pallor of the optic nerve. Extension into the hypothalamus can lead to precocious puberty. The brain MRI findings of an optic glioma include diffuse thickening, localized enlargement, or a distinct focal mass originating from the optic nerve or chiasm (Fig. 614.4). (7) A first-degree relative with NF1 whose diagnosis was based on the aforementioned criteria.

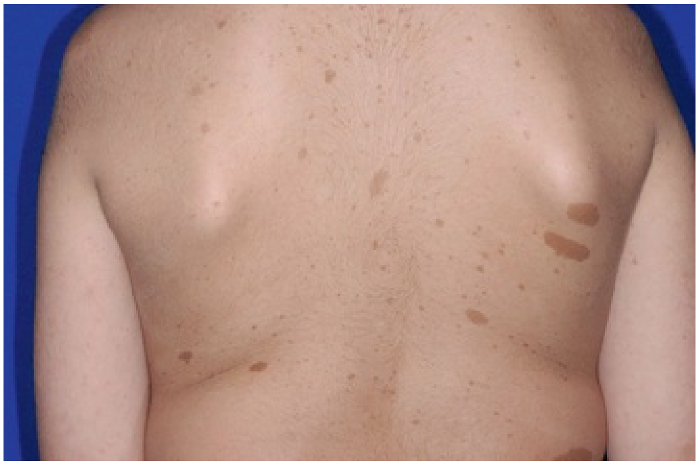

FIG. 614.1 Neurofibromatosis type 1 (NF1). The presence of six or more café-au-lait (CAL) spots larger than 0.5 cm in diameter in children and 1.5 cm in adolescents suggests the possibility of NF1, although having CAL spots alone does not allow for definitive diagnosis. (From Paller AS, Mancini AJ: Hurwitz clinical pediatric dermatology, 5th ed., Philadelphia, 2016, Elsevier, Fig. 11-44.)

Table 614.2

Diseases Associated With Multiple Café-Au-Lait Spots

DISEASE	MAJOR FEATURES
Ataxia telangiectasia	Progressive ataxia, lymphoreticular malignancy
Bannayan-Riley-Ruvalcaba syndrome	Macrosomia, megalencephaly, lipomas, intestinal polyps
Basal cell nevus syndrome	Multiple basal cell epitheliomas, jaw cysts, skeletal anomalies
Bloom syndrome	Short stature, photosensitivity, chromosome breaks, malignancy
Fanconi anemia	Limb anomalies, renal anomalies, pancytopenia
Gaucher disease	Jewish predilection, ataxia, mental retardation
Hunter syndrome	Thickened skin, coarse facies, skin papules, joint contractures
Jaffe-Campanacci syndrome	Fibromas of long bones, hypogonadism, mental retardation, ocular/cardiac anomalies
Legius syndrome	Axillary freckling macrocephaly, a Noonan-like facial dysmorphism, lipomas

Maffucci syndrome	Venous malformations, enchondromas
McCune-Albright syndrome	Polyostotic fibrous dysplasia, precocious puberty
Multiple lentigines syndrome	Multiple lentigines, hypertelorism, pulmonic stenosis
Multiple mucosal neuroma syndrome	Mucosal neuromas, thyroid carcinoma, pheochromocytoma, parathyroid adenoma, dysautonomia
Neurofibromatosis type 1	Neurofibromas, central nervous system tumors, iris hamartomas, axillary freckles, skeletal anomalies
Neurofibromatosis type 2	Vestibular schwannoma, meningioma, subcapsular cataracts, skin plexiform schwannomas
Russell-Silver syndrome	Short stature, asymmetry, limb anomalies
Tuberous sclerosis	White macules, multiple hamartomas, central nervous system anomalies
Watson syndrome	Pulmonic stenosis, axillary freckles, low intelligence

From Marcoux DA, Duran-McKinster C, Baselga E, et al: Pigmentary abnormalities. In Schachner LA, Hansen RC (eds): Pediatric dermatology, 4th ed., Philadelphia, 2011, Mosby, Table 10-2.

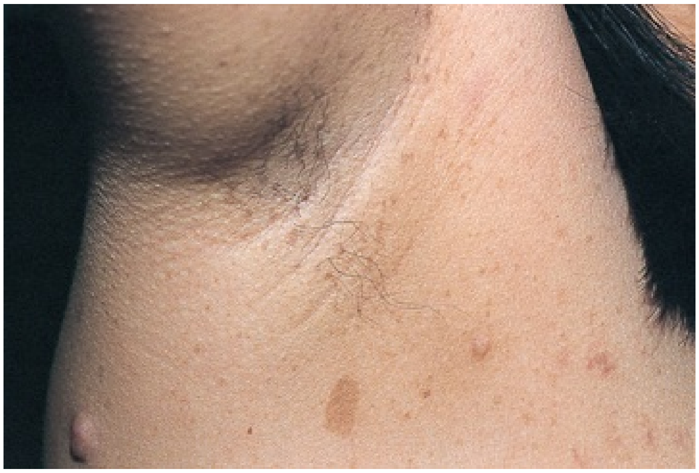

FIG. 614.2 von Recklinghausen neurofibromatosis. Axillary freckling (Crowe's sign) is a pathognomonic sign. (From Habif TP, editor: Clinical dermatology: a color guide to diagnosis and therapy, 4th ed., Philadelphia, 2004, Mosby, Fig. 26-11.)

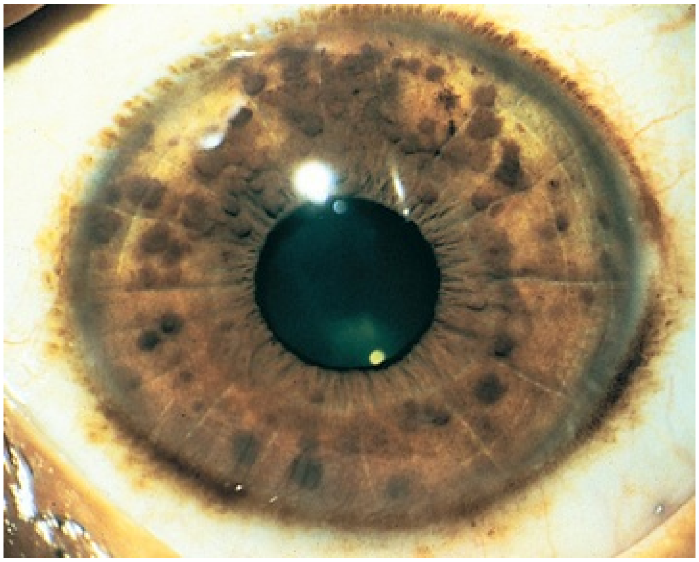

FIG. 614.3 Neurofibromatosis type 1 (NF1). Pigmented hamartomas of the iris (Lisch nodules). (From Zitelli BJ, McIntire S, Nowalk AJ, editors: Zitelli and Davis' atlas of pediatric physical diagnosis, 6th ed., Philadelphia, 2012, Mosby, Fig. 15-9.)

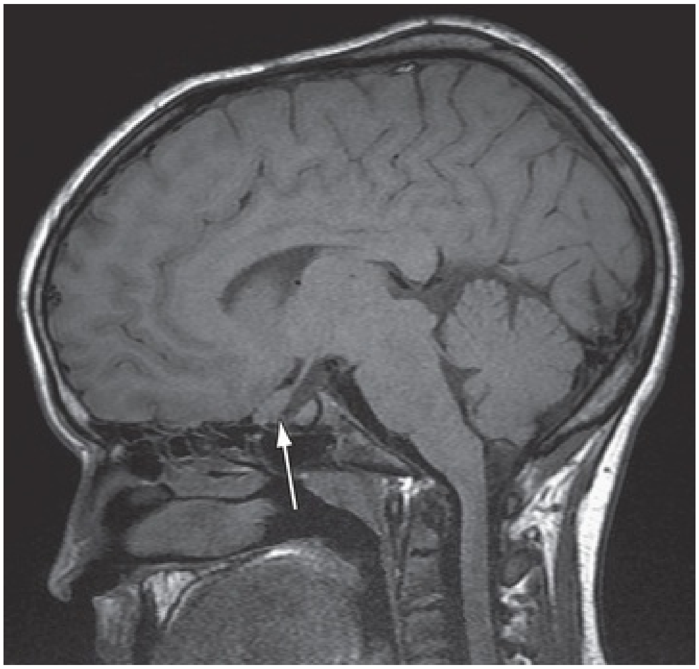

FIG. 614.4 Optic glioma. Sagittal T1-weighted MRI scan of a patient with NF1 shows thickening of the optic nerve *(arrow).*

Children with NF1 are susceptible to **neurologic complications.** MRI studies of selected children have shown abnormal hyperintense T2-weighted signals in the optic tracts, brainstem, globus pallidus, thalamus, internal capsule, and cerebellum (Fig. 614.5). These signals, **unidentified bright objects,** tend to disappear with age; most have disappeared by 30 yr of age. It is unclear what the unidentified bright objects represent pathologically, and there is disagreement as to the relationship between the presence and number of unidentified bright objects and the occurrence of learning disabilities, attention-deficit disorders, behavioral and psychosocial problems, and abnormalities of speech among affected children. Therefore, imaging studies such as brain MRIs should be reserved for patients with clinical symptoms only.

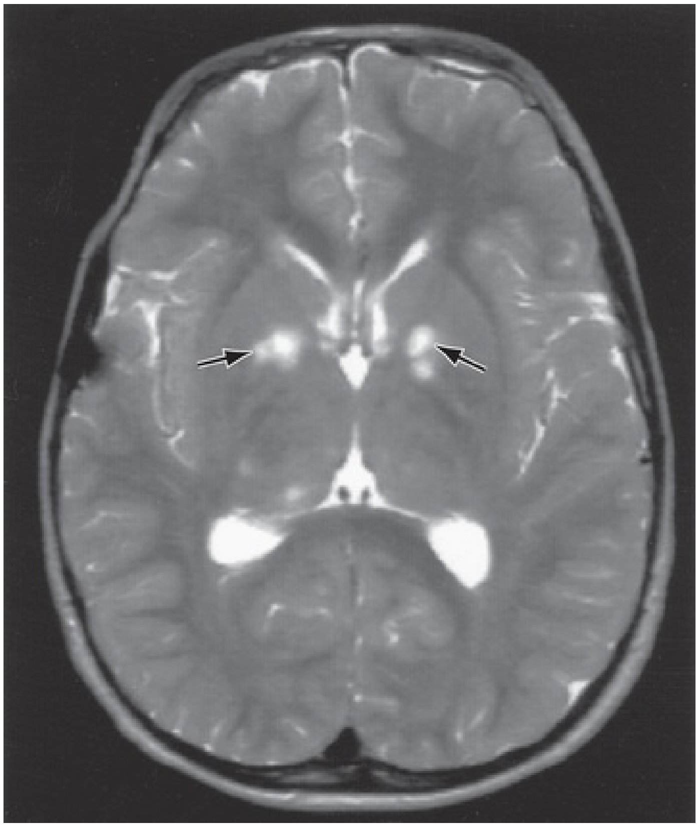

FIG. 614.5 T2-weighted MRI scan of a patient with NF1. Note the high-signal areas (unidentified bright objects) in the basal ganglia *(arrows).*

One of the most common complications is a learning disability affecting more than half of individuals with NF1. Seizures are observed in approximately 8% of NF1 patients. The cerebral vessels may develop aneurysms or stenosis consistent with moyamoya syndrome (see Chapter 619). Neurologic sequelae of these vascular abnormalities include transient cerebrovascular ischemic attacks, hemiparesis, and cognitive defects. Precocious puberty may become evident in the presence or absence of lesions of the optic pathway tumors. Malignant peripheral nerve sheath tumors are in the family of aggressive sarcomas and occur either de novo or as the result of malignant degeneration of an existing plexiform neurofibroma. The lifetime risk is 8–13%. Additionally, the incidence of pheochromocytoma, rhabdomyosarcoma, leukemia, and Wilms tumor is higher than in the general population. Scoliosis is a common complication found in approximately 10% of the patients. Patients with NF1 are at risk for hypertension, which may be present in isolation or result from renal vascular stenosis or a pheochromocytoma.

Mosaic NF1 (also called *segmental NF1*) has manifestations limited to one or more body segments secondary to somatic (or gonadal) mutations expressed in those locations. Lesions may be unilateral or bilateral, asymmetric or symmetric, and confined to a narrow band or a single quadrant. Neurologic manifestations are rare but have been reported.

Management

Because of the diverse and unpredictable complications associated with NF1, close multidisciplinary follow-up is necessary. Patients with NF1 should have regular clinical assessments at least yearly, focusing the history and examination on the potential problems for which they are at increased risk. These assessments include yearly ophthalmologic examination, neurologic assessment, blood pressure monitoring, and scoliosis evaluation. Neuropsychological and educational testing should be considered as needed. The National Institutes of Health (NIH) Consensus Development Conference has advised against routine imaging studies of the brain and optic tracts because treatment in these asymptomatic NF1 children is rarely required. However, all symptomatic cases (i.e., those with visual disturbance, proptosis, increased intracranial pressure) must be studied without delay. Selumetinib, an oral inhibitor of MAPK kinase 1 and 2, has been demonstrated, in preliminary trials in children with NF1-related inoperable plexiform neurofibromas, to be effective in inducing partial responses and reducing tumor progression.

Genetic Counseling

Although NF1 is an autosomal dominant disorder, more than half the cases are sporadic, representing de novo mutations. The *NF1* gene on chromosome region 17q11.2 encodes for a protein also known as neurofibromin. Neurofibromin acts as an inhibitor of the oncogene Ras (Fig. 614.6). The diagnosis of NF1 is based on the clinical features. However, molecular testing for the *NF1* gene mutations is available and can be useful in a number of cases. Some scenarios in which genetic testing is helpful include patients who meet only one of the criteria for clinical diagnosis, those with unusually severe disease, and those seeking prenatal/preimplantation diagnosis.

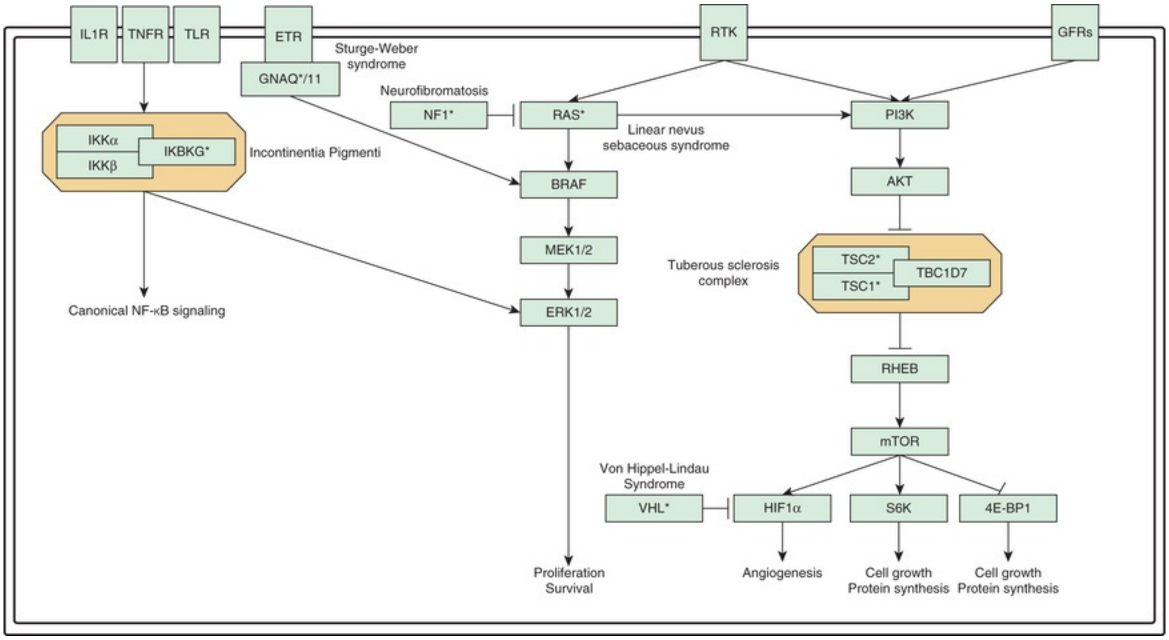
IL1R
TNFR
TLR
ETR
RTK
GFRs
Sturge-Weber syndrome
GNAQ*/11
Neurofibromatosis
NF1*
RAS*
PI3K
IKKα
IKKβ
IKBKG*
Incontinentia Pigmenti
Linear nevus sebaceous syndrome
BRAF
AKT
MEK1/2
Tuberous sclerosis complex
TSC2*
TSC1*
TBC1D7
Canonical NF-κB signaling
ERK1/2
RHEB
mTOR
Von Hippel-Lindau Syndrome
VHL*
HIF1α
S6K
4E-BP1
Proliferation Survival
Angiogenesis
Cell growth Protein synthesis
Cell growth Protein synthesis

FIG. 614.6 Schematic representation of the cellular pathways affected by mutations in the genes associated with neurocutaneous disorders, such as NF1, TSC, and SWS. The *asterisks* denote genes with associated syndromes discussed in the chapter.

NF2 is a less common disorder than NF1; it is also transmitted in an autosomal dominant manner, with an incidence of 1 in 25,000 births. The clinical diagnostic criteria were established by the United States National Institutes of Health consensus conference and modified into the Manchester criteria and the Baser criteria. Diagnosis may also be confirmed by genetic testing from the blood or identical mutation in two separate tumors from the same individual. Typically, NF2 is diagnosed when one of the following four features is present: (1) bilateral vestibular schwannomas; (2) a parent, sibling, or child with NF2 and either unilateral vestibular schwannoma or any two of the following: meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular lenticular opacities; (3) unilateral vestibular schwannoma and any two of the following: meningioma, schwannoma, glioma, neurofibroma, or posterior subcapsular lenticular opacities; or (4) multiple meningiomas (two or more) and unilateral vestibular schwannoma or any two of the following: schwannoma, glioma, neurofibroma, or cataract. Symptoms of tinnitus, hearing loss, facial weakness, headache, or unsteadiness may appear during childhood, although signs of a cerebellopontine angle mass are more commonly present in the 2nd and 3rd decades of life. CALMs and skin plexiform schwannomas are visible in the pediatric age-group. Posterior subcapsular lens opacities are identified in approximately 50% of patients with NF2 using a slit-lamp examination. The *NF2* gene (which codes for a protein known as merlin, or schwannomin) is located on chromosome 22q1.11. Table 614.3 notes the frequency of lesions in NF2.

Table 614.3

Frequency of Lesions Associated With Neurofibromatosis Type 2

	FREQUENCY OF ASSOCIATION WITH NF2
NEUROLOGIC LESIONS	
Bilateral vestibular schwannomas	90–95%
Other cranial nerve schwannomas	24–51%
Intracranial meningiomas	45–58%
Spinal tumors	63–90%
Extramedullary	55–90%
Intramedullary	18–53%
Peripheral neuropathy	Up to 66%
OPHTHALMOLOGIC LESIONS	
Cataracts	60–81%
Epiretinal membranes	12–40%
Retinal hamartomas	6–22%
CUTANEOUS LESIONS	
Skin tumors	59–68%
Skin plaques	41–48%
Subcutaneous tumors	43–48%
Intradermal tumors	Rare

From Asthagiri AR, Parry DM, Butman JA, et al: Neurofibromatosis type 2, Lancet 373:1974-1984, 2009, Table 1.

Ophthalmologic evaluation, MRI of the brain and spine, audiology, and brainstem-evoked potentials are all important components of the ongoing management of individuals with NF2. Because of the frequency of developing multiple concurrent tumors, intracranial lesions are managed conservatively, with the goal of preserving hearing and maximizing the quality of life.

Schwannomatosis is a form of neurofibromatosis that is clinically distinct from NF1 and NF2 and is characterized by multiple schwannomas in the absence of bilateral vestibular schwannomas. Although the overall incidence is much lower, at 0.47 in 1,000,000 persons, individuals with schwannomatosis are thought to account for 2–10% of all individuals who undergo surgical resection for schwannoma. It is estimated that at least 20% are familial in nature. Diagnosis should be considered in an individual who presents with multiple schwannomas, particularly if there is an affected family member. Evaluation also includes brain and spinal MRI to exclude vestibular and other schwannomas. At any time of presentation, the initial workup must distinguish between NF2 and schwannomatosis. Linkage analysis led to the discovery of the tumor suppressor gene *SMARCB1* as the major predisposing gene in schwannomatosis. *SMARCB1* , also known as *INI1* , is involved in the regulation of the cell cycle, growth, and differentiation. The optimal management and frequency of surveillance imaging have not been established; however, MRI is typically performed yearly.

Legius syndrome (caused by *SPRED1* mutations) resembles a mild form of NF1. Patients with Legius syndrome present with multiple CALMs and macrocephaly, with and without skinfold freckling. However, other typical features of NF1, such as Lisch nodules, neurofibromas, optic nerve gliomas, and malignant peripheral nerve sheath tumors, are not seen with *SPRED1* mutations.

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614.2

Tuberous Sclerosis

Siddharth Srivastava, Mustafa Sahin

Tuberous sclerosis complex (TSC) is a multisystem disease characterized by an autosomal dominant mode of inheritance, variable expressivity, and a prevalence of 1 in 6,000 to 10,000 newborns. Spontaneous genetic mutations occur in 65% of the cases. Molecular genetic studies have identified two foci for TSC: the *TSC1* gene is located on chromosome 9q34, and the *TSC2* gene is on chromosome 16p13. The *TSC1* gene encodes a protein called hamartin, while the *TSC2* gene encodes a protein called tuberin. Within a cell, these two molecules form a complex along with a third protein, TBC1D7 (Tre2-Bub2-Cdc16 1 domain family, member 7). Consequently, a mutation in either the *TSC1* gene or the *TSC2* gene results in a similar disease in patients, though individuals with *TSC2* mutations tend to be more severely affected.

Tuberin and hamartin are involved in a key pathway in the cell that regulates protein synthesis and cell size (see Fig. 614.6). One of the ways cells regulate their growth is by controlling the rate of protein synthesis. A protein called mTOR (mechanistic target of rapamycin) is one of the master regulators of cell growth (mTOR has additional roles in the CNS, where it helps regulate neuronal development and synaptic plasticity). mTOR, in turn, is controlled by RHEB (Ras homolog enriched in brain), a small cytoplasmic guanosine triphosphatase.

When RHEB is activated, the protein synthesis machinery is turned on, most likely via mTOR signaling, and the cell grows. Under normal conditions, the tuberin/hamartin complex keeps RHEB in an inactive state. However, in TSC, there is disinhibition of RHEB and subsequent overactivation of the mTOR pathway. Accordingly, the *TSC1* and *TSC2* genes can be considered tumor-suppressor genes. The loss of either tuberin or hamartin protein results in the formation of numerous benign tumors (hamartomas).

TSC is an extremely heterogeneous disease with a wide clinical spectrum varying from severe intellectual disability and intractable epilepsy to normal intelligence and a lack of seizures. This variation is often seen within the same family, that is, with individuals carrying the same mutation. The disease affects many organ systems other than the skin and brain, including the heart, kidney, eyes, lungs, and bone (Fig. 614.7).

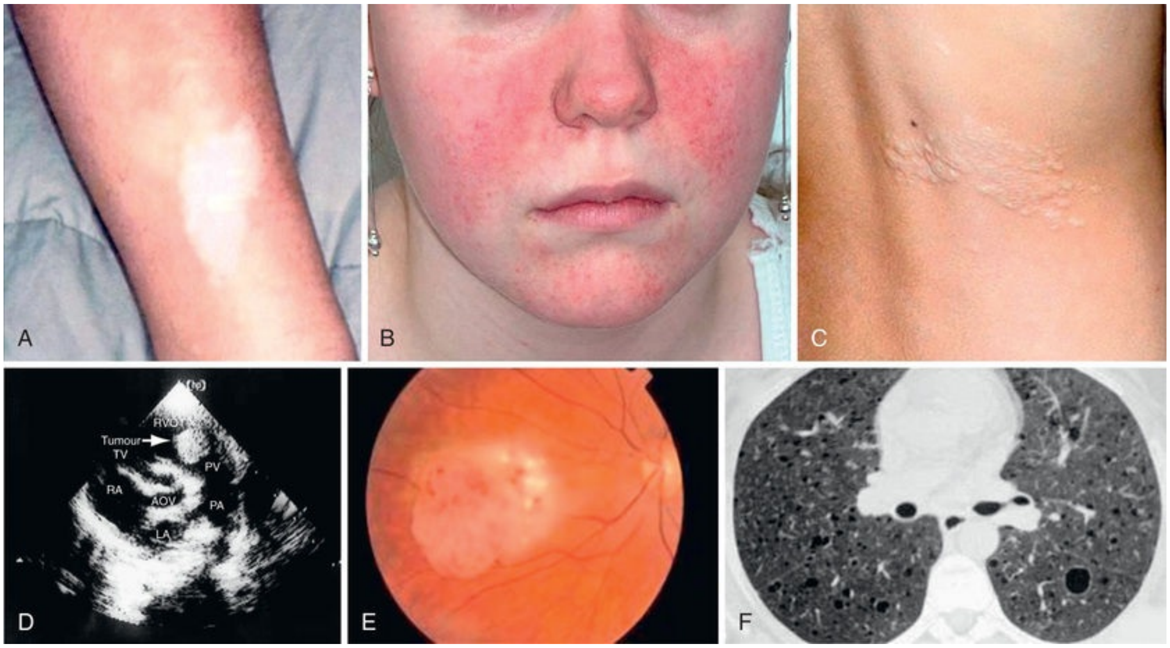

FIG. 614.7 Dermatologic, cardiac, and pulmonary manifestations of tuberous sclerosis. **A,** Hypomelanotic macules. **B,** Facial angiofibromas. **C,** Shagreen patch. **D,** Hyperechoic rhabdomyoma detected by echocardiography. **E,** Retinal hamartoma. **F,** Lymphangioleiomyomatosis. (From Curatolo P, Bombardieri R, Jozwiak S: Tuberous sclerosis, Lancet 372:657-668, 2008, Fig. 7.)

Clinical Manifestations and Diagnosis

Definite TSC is diagnosed when at least two major or one major plus two minor features are present (Tables 614.4 and 614.5 list the major and minor features). In addition, carrying a pathogenic mutation in *TSC1* or *TSC2* is sufficient for the diagnosis of TSC.

Table 614.4

Major Features of Tuberous Sclerosis Complex

Cortical dysplasias (including tubers and cerebral white matter migration lines)
Subependymal nodules
Subependymal giant cell astrocytoma
Facial angiofibromas (≥3) or forehead plaque
Ungual fibromas (≥2)
Hypomelanotic macules (≥3, ≥ 5 mm in diameter)
Shagreen patch
Multiple retinal nodular hamartomas
Cardiac rhabdomyoma
Renal angiomyolipoma
Pulmonary lymphangioleiomyomatosis

Table 614.5

Minor Features of Tuberous Sclerosis Complex

Dental enamel pits (>3)
Intraoral fibromas (≥2)
Retinal achromic patch
Confetti skin lesions
Nonrenal hamartomas
Multiple renal cysts

The hallmark of TSC is the involvement of the CNS. Retinal lesions consist of two types: hamartomas (elevated mulberry lesions or plaque-like lesions (Fig. 614.8) and white depigmented patches (similar to the hypopigmented skin lesions). The characteristic brain lesion is a cortical tuber (Fig. 614.9). Brain

MRI is the best way of identifying cortical tubers, which can form before birth.

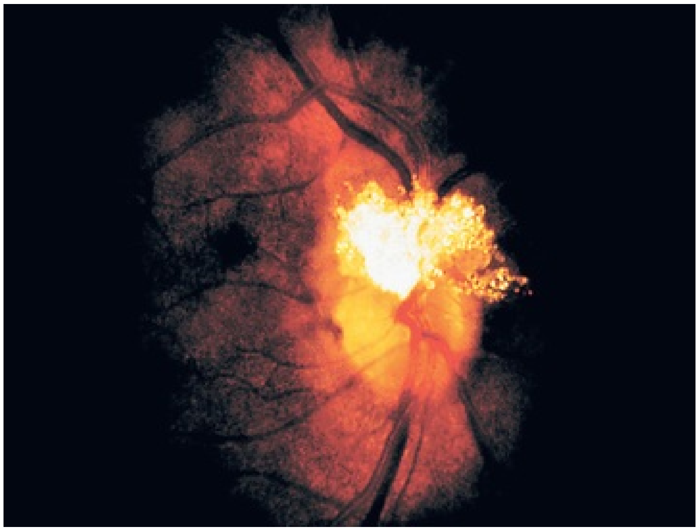

FIG. 614.8 A mulberry lesion involving the superior part of the optic nerve in a patient with tuberous sclerosis. (From Yanoff M, Sassani JW: Ocular pathology, 7th ed., Philadelphia, 2015, WB Saunders, Fig. 2-7.)

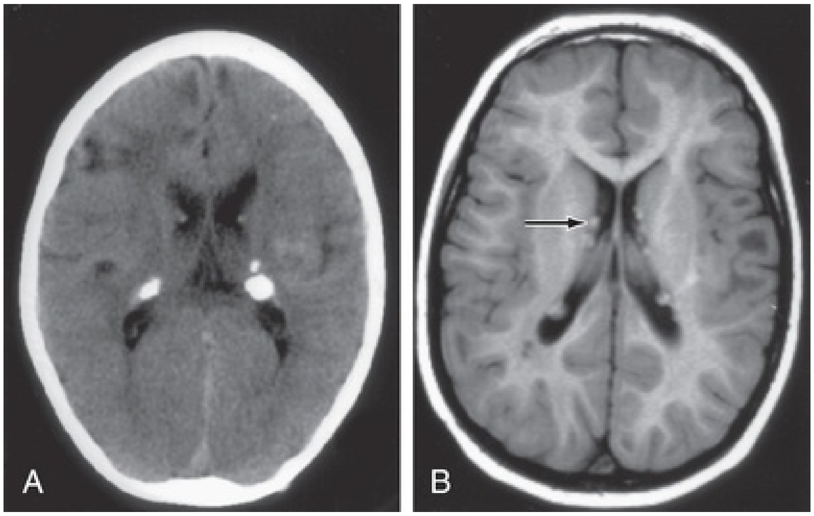

FIG. 614.9 Tuberous sclerosis. **A,** CT scan with subependymal calcifications characteristic of tuberous sclerosis. **B,** The MRI demonstrates multiple subependymal nodules in the same patient *(arrow).* Parenchymal tubers are also visible on both the CT and the MRI scan as low-density areas in the brain parenchyma.

Subependymal nodules are lesions found along the wall of the lateral ventricles, where they undergo calcification and project into the ventricular cavity, producing a candle-dripping appearance. These lesions do not cause any problems; however, in 5–10% of cases, these benign lesions can grow into **subependymal giant cell astrocytomas (SEGAs).** These tumors can grow and block the circulation of cerebrospinal fluid around the brain and cause hydrocephalus, which requires immediate neurosurgical intervention. Thus, it is recommended that all asymptomatic TSC patients undergo brain MRI every 1-3 yr to monitor for new occurrences of SEGA. Patients with large or growing SEGAs, or with SEGAs causing ventricular enlargement without other manifestations, should undergo MRI scans more frequently, and the patients and their families should be educated regarding the potential of new symptoms due to increased intracranial pressure. Surgical resection should be performed for acutely symptomatic SEGA. For growing but otherwise asymptomatic SEGAs, either surgical resection or medical treatment with an mTOR inhibitor (everolimus) may be used. Treatment with everolimus can be effective in slowing the growth or even reducing the size of SEGAs. Everolimus is also effective in treating renal angiomyolipomas, and sirolimus, another mTOR inhibitor, is approved for lymphangioleiomyomatosis.

The most common neurologic manifestations of TSC consist of epilepsy, cognitive impairment, and autism spectrum disorder. TSC may present during infancy with infantile spasms and a hypsarrhythmic electroencephalogram pattern. However, it is important to remember that TSC patients can have infantile spasms without hypsarrhythmia. The seizures may be difficult to control, and at a later age, they may develop into focal-onset seizures or generalized myoclonic seizures (see Chapter 611). Vigabatrin is the first-line therapy for infantile spasms. Adrenocorticotropic hormone (ACTH) can be used if treatment with vigabatrin fails. Anticonvulsant therapy for other seizure types in TSC should generally follow that of other epilepsies, and epilepsy surgery should be considered for medically refractory TSC patients. Everolimus (adjunctive) has been effective therapy for reducing the number of seizures in patients with treatment-refractory seizures. In addition to epilepsy, about 90% of individuals with TSC have a spectrum of cognitive, behavioral, psychiatric, and academic impairments termed tuberous sclerosis–associated neuropsychiatric disorders (TAND), which include intellectual disability, autism spectrum disorder, attention deficit hyperactivity disorder, anxiety, and depression. About 45% of individuals with TSC have intellectual disability, and up to 50% have autism spectrum disorder.

Skin Lesions

More than 90% of patients show the typical hypomelanotic macules that have been likened to an ash leaf on the trunk and extremities. Visualization of the hypomelanotic macule is enhanced by the use of a Wood ultraviolet lamp (see Chapter 672). To count as a major feature, at least three hypomelanotic macules must be present (see Fig. 614.7). Facial angiofibromas develop between 4 and 6 yr of age; they appear as tiny red nodules over the nose and cheeks and are sometimes confused with acne (see Fig. 614.7). Later, they enlarge, coalesce, and assume a fleshy appearance. A shagreen patch is also characteristic of TSC and consists of a roughened, raised lesion with an orange-peel consistency located primarily in the lumbosacral region (see Fig. 614.7). Forehead fibrous plaques usually occur on one side of the forehead. They are characteristically raised, yellow-brown or flesh-colored, and soft-to-hard in consistency. Forehead plaques are histologically similar to facial angiofibromas, though the former can appear at any time point. During adolescence or later, small fibromas or nodules of skin may form around fingernails or toenails in 15–20% of TSC patients (Fig. 614.10).

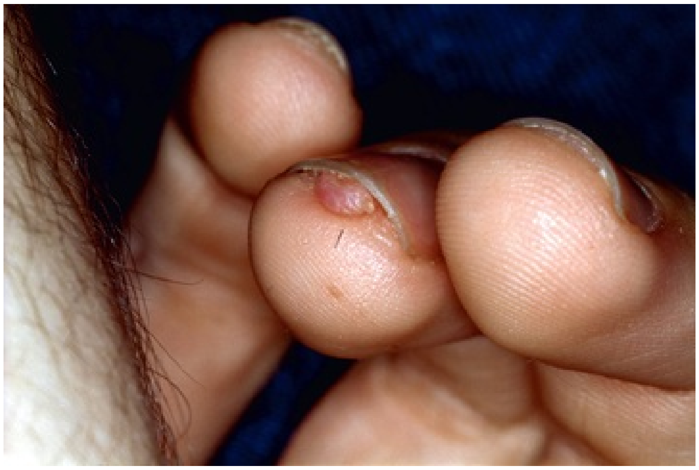

FIG. 614.10 Periungual fibroma in a patient with tuberous sclerosis complex (TSC).

Other Organ Involvement

Approximately 50% of children with TSC have cardiac rhabdomyomas, which may be detected in the fetus by an echocardiogram, usually by 20-30 wk gestation. The rhabdomyomas may be numerous and located throughout the ventricular myocardium, and although they can cause congestive heart failure and arrhythmias in a minority of patients, they tend to slowly resolve spontaneously. In 75–80% of patients older than 10 yr of age, the kidneys display angiomyolipomas that are usually benign tumors. Angiomyolipomas begin in childhood in many individuals with TSC, but they may not be problematic until young adulthood. By the 3rd decade of life, they may cause lumbar pain and hematuria from slow bleeding, and rarely they may result in sudden retroperitoneal bleeding. Embolization followed by corticosteroids to alleviate postembolization syndrome is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy should be avoided as a way of maintaining renal function, because lesions can be numerous and bilateral. For asymptomatic, growing angiomyolipomas measuring larger than 3 cm in diameter, an mTOR inhibitor, everolimus, is approved for treatment by the U.S. Food and Drug Administration (FDA). Selective embolization or kidney-sparing resection is an alternative therapy for asymptomatic angiomyolipoma. Single or multiple renal cysts are also commonly present in TSC; renal cell carcinoma, on the other hand, is rare. Lymphangioleiomyomatosis is the classic pulmonary lesion in TSC and only affects women, beginning in late adolescence (≥15 yr). Rapamycin is approved by the U.S. FDA for lymphangioleiomyomatosis.

Diagnosis of TSC relies on a high index of suspicion when assessing a child with infantile spasms. A careful evaluation for the typical skin and retinal lesions should be completed in all patients with a seizure disorder or autism spectrum disorder. Brain MRI confirms the clinical diagnosis in most cases. Genetic testing for *TSC1* and *TSC2* mutations is available and should be considered when the individual patient does not meet all the clinical criteria, or in order to provide molecular confirmation of a clinical diagnosis. Prenatal testing may be offered when a known *TSC1/2* mutation exists in that family.

Management

As for routine follow-up of individuals with TSC, the following are recommended in addition to physical examination: brain MRI every 1-3 yr, renal imaging using ultrasound, CT or MRI every 1-3 yr; echocardiogram every 1-3 yr in patients with cardiac rhabdomyomas; electrocardiogram every 3-5 yr; high-resolution chest CT every 5-10 yr in females older than 18 yr; dental examination twice a year; skin examinations once a year; detailed ophthalmic examination once a year in patients with vision concerns or retinal lesions (sooner if they are receiving treatment with vigabatrin); neurodevelopmental testing at the time of beginning 1st grade; and screening for TAND at each clinic visit. Based on the complications of the disease, additional follow-up testing may be required for each individual. Symptoms and signs of increased intracranial pressure suggest obstruction of the foramen of Monro by a SEGA and warrant immediate investigation and surgical intervention.

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614.3

Sturge-Weber Syndrome

Anna Pinto

Sturge-Weber syndrome (SWS) is a segmental vascular neurocutaneous disorder with a constellation of symptoms and signs characterized by capillary malformation in the face (port-wine birthmark) and brain (leptomeninges), as well as abnormal blood vessels of the eye leading to glaucoma. Patients present with seizures, hemiparesis, stroke-like episodes, headaches, and developmental delay. Approximately 1 in 20,000 to 50,000 live births are affected with SWS.

Etiology

The sporadic incidence and focal nature of SWS suggests the presence of somatic mutations. Whole-genome sequencing from affected and unaffected skin of three patients with SWS identified a single-nucleotide variant (c.548G→A, p.Arg183Gln) in the *GNAQ* gene (see Fig. 614.6). Others have confirmed this mutation in samples of affected tissue from 88% of SWS patients (23 of 26) from a larger cohort, as well as from 92% of participants (12 of 13) with apparently nonsyndromic port-wine birthmarks (PWBs). Brain tissue from SWS patients also demonstrates the same change in the *GNAQ* gene. These results strongly suggest that SWS occurs as a result of *mosaic mutations* in *GNAQ* .

The *GNAQ* p.R183Q mutation is enriched in endothelial cells in SWS brain lesions, thereby revealing endothelial cells as a source of aberrant Gαq signaling. The timing of the somatic mutation in *GNAQ* during development likely affects the clinical phenotype. Low flow of the leptomeningeal capillary malformation appears to result in a chronic hypoxic state leading to cortical atrophy and calcifications.

Clinical Manifestations

Facial PWBs are present at birth, but not all are associated with SWS (Table 614.6). In fact, the overall incidence of SWS has been reported to be 20–50% in those with a PWB involving the forehead and upper eyelid. The PWB tends to be unilateral, and ipsilateral to the brain involvement (Fig. 614.11). The capillary malformation may also be evident over the lower face and trunk and in the mucosa of the mouth and pharynx. Buphthalmos and glaucoma of the ipsilateral eye are common complications. Seizures occur in 75–80% of all SWS patients and in over 90% of those with bilateral brain involvement. Early onset of seizures will likely occur during the 1st yr of life but rarely during the 1st mo of life, and they are typically focal clonic and contralateral to the side of the facial capillary malformation. They may become refractory to anticonvulsants, and status epilepticus is often associated. One third of children with intractable epilepsy associated with SWS experience episodes of *prolonged postictal deficits*, which would last from 1 day to a few years, until recovering back to baseline. Some patients also develop slowly progressive hemiparesis. Transient stroke-like episodes or visual defects persisting for several days and unrelated to seizure activity are common and probably result from thrombosis of cortical veins in the affected region. Although neurodevelopment appears to be normal in the first year of life, intellectual disability or severe learning disabilities are present in at least 50% of patients in later childhood, probably the result of intractable epilepsy and increasing cerebral atrophy. The degree of visual field, hemiparesis, seizure frequency, and cognitive function (based on age-group: infant/preschooler, child, and adult) can be rated using a validated SWS neurologic rating system.

Table 614.6

Port Wine Stain–Associated Syndromes

Sturge-Weber syndrome
Klippel-Trénaunay syndrome
Parkes Weber syndrome
Phakomatosis pigmentovascularis
Proteus syndrome
CLOVES syndrome
Macrocephaly–capillary malformation (M-CM) syndrome
Capillary malformation–arteriovenous malformation (CM-AVM) syndrome
Cobb syndrome

Bannayan-Riley-Ruvalcaba syndrome
Beckwith-Wiedemann syndrome
Von Hippel–Lindau disease
Rubinstein-Taybi syndrome
Wyburn-Mason syndrome
Roberts syndrome
Coat disease

CLOVES, Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies.

From Paller AS, Mancini (eds): Hurwitz clinical pediatric dermatology, 5th ed., Philadelphia, 2016, Elsevier, Box 12-2.

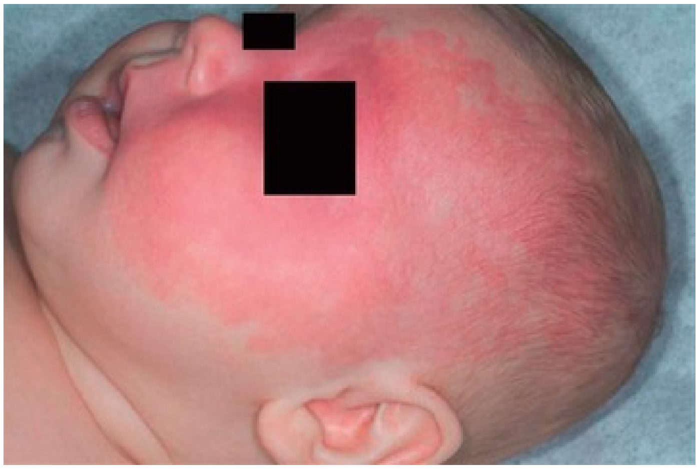
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FIG. 614.11 Port-wine stain involving both the V1 and V2 dermatomes. (Courtesy Dr. Anne W. Lucky, Cincinnati Children's Hospital.)

Diagnosis

Brain MRI with contrast is the imaging modality of choice for demonstrating the extension of pial capillary malformation in SWS (Fig. 614.12). White matter abnormalities are common and are thought to be a result of chronic hypoxia. Often, atrophy is noted ipsilateral to the leptomeningeal capillary malformation. Calcifications can be seen best with a head CT (Fig. 614.13). The choroid plexus is frequently enlarged, and the degree of plexal enlargement shows a positive correlation with the extent of the leptomeningeal capillary malformation. Positron emission tomography using 18 F-deoxyglucose has been used to study cerebral metabolism in patients with SWS, and it has been useful for the surgical planning and prognosis. Ophthalmologic evaluation examining for glaucoma is also necessary and is a lifelong concern because ocular complications can occur at any moment during a lifetime. Based on the involvement of the brain and the face, there are three types of SWS in the Roach Scale:

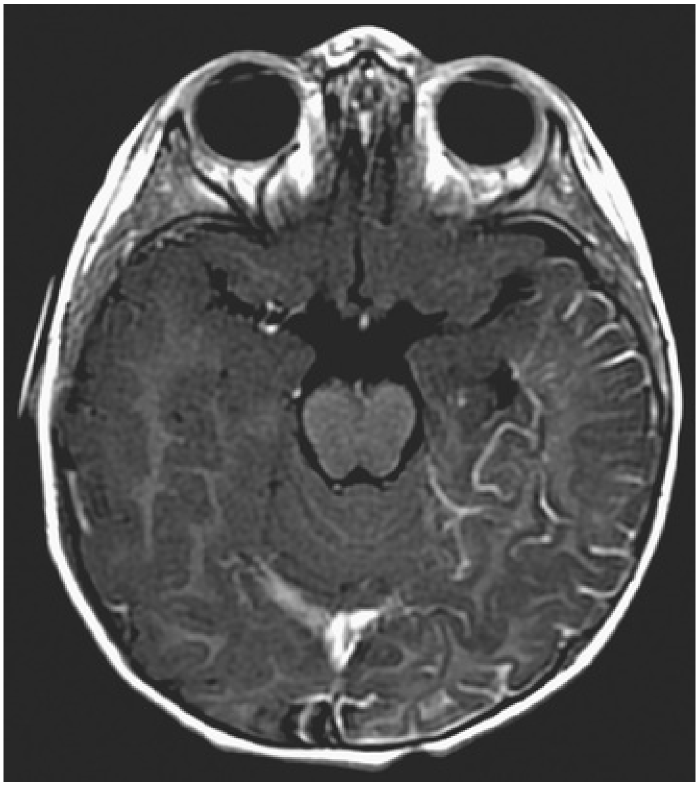

FIG. 614.12 Gadolinium-enhanced axial T1 fluid-attenuated inversion recovery (FLAIR) images of a 15 mo old with Sturge-Weber syndrome shows leptomeningeal enhancement in left hemisphere.

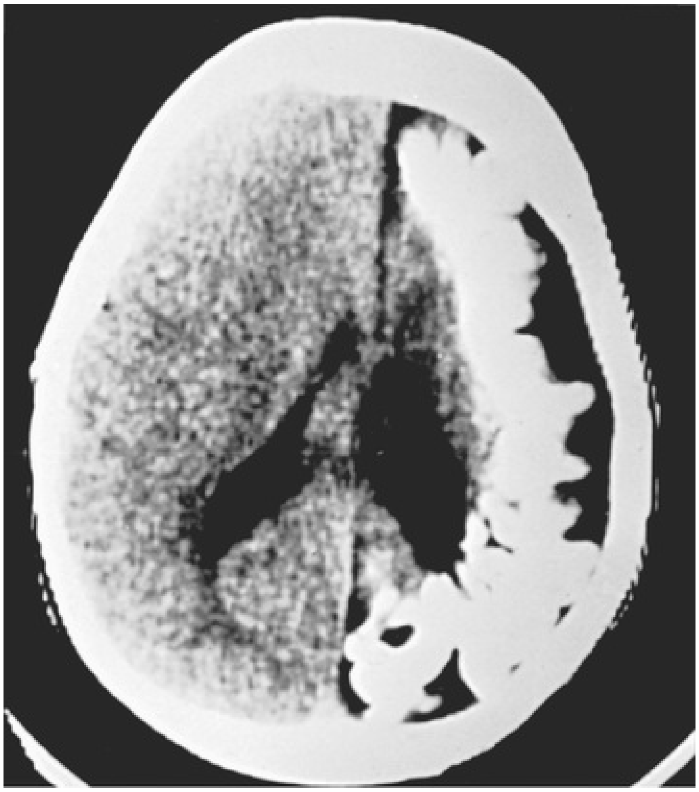

FIG. 614.13 CT scan of a patient with Sturge-Weber syndrome showing unilateral calcification and underlying atrophy of a cerebral hemisphere.

Type I—Both facial and leptomeningeal angiomas present; may have glaucoma.
Type II—Facial angioma alone (no CNS involvement); may have glaucoma.
Type III—Isolated leptomeningeal angiomas; usually no glaucoma.

In addition, there is an overlap syndrome between SWS and **Klippel-Trenaunay syndrome** (mixed capillary, venous, or lymphatic malformations involving bone and muscle in one limb).

Management

The management of SWS is symptomatic and multidisciplinary but not well studied by prospective studies. Discovery of the causative somatic mosaic mutation suggests new insights into the pathophysiology of this vascular malformation disorder and potential novel treatment strategies for future study. Treatment is aimed at seizure control, relief of headaches, and prevention of stroke-like episodes, as well as monitoring of glaucoma and laser therapy for the cutaneous capillary malformations. Seizures beginning in infancy are not always associated with a poor neurodevelopmental outcome. For patients with well-controlled seizures and normal or near-normal development, management consists of anticonvulsants and surveillance for complications, including glaucoma, buphthalmos, and behavioral abnormalities. If the seizures are refractory to anticonvulsant therapy, especially in infancy and the first 1 to 2 yr, and arise from primarily one hemisphere, most medical centers advise a hemispherectomy. The use of low-dose aspirin is still controversial. The medication is not used routinely, but patients with stroke-like events and frequent refractory seizures may benefit from this form of treatment. Because of the risk of glaucoma, regular measurement of intraocular pressure is indicated. The facial PWB is often a target of ridicule by classmates, leading to psychological trauma. Pulsed-dye laser therapy often provides excellent clearing of the PWB, particularly if it is located on the forehead.

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614.4

Von Hippel-Lindau Disease

Siddharth Srivastava, Mustafa Sahin

von Hippel–Lindau disease affects many organs, including the cerebellum, spinal cord, retina, kidney, pancreas, and epididymis. Its incidence is around 1 in 36,000 newborns. It results from an autosomal dominant mutation affecting a tumor suppressor gene, *VHL.* Approximately 80% of individuals with von Hippel–Lindau syndrome have an affected parent, and approximately 20% have a *de novo* gene mutation. Molecular testing is available and detects mutations in almost 100% of probands.

The major neurologic features of the condition include cerebellar hemangioblastomas and retinal angiomas (also known as retinal capillary hemangioblastomas). Patients with cerebellar hemangioblastoma present in early adult life with symptoms and signs of increased intracranial pressure. A smaller number of patients have hemangioblastoma of the spinal cord, producing abnormalities of proprioception and disturbances of gait and bladder function. A brain CT or MRI scan typically shows a cystic cerebellar lesion with a vascular mural nodule. Total surgical removal of the tumor is curative.

Approximately 25% of patients with cerebellar hemangioblastoma have retinal angiomas. Retinal angiomas are characterized by small masses of thin-walled capillaries that are fed by large and tortuous arterioles and venules. They are usually located in the peripheral retina so that vision is unaffected. Exudation in the region of the angiomas may lead to retinal detachment and visual loss. Retinal angiomas are treated with photocoagulation and cryocoagulation, and both have produced good results, though complications such as retinal edema can occur.

Cystic lesions of the kidneys, pancreas, liver, and epididymis, as well as pheochromocytoma, are frequently associated with von Hippel–Lindau disease. Renal carcinoma is the most common cause of death, and CNS hemangioblastomas also contribute to morbidity. Regular follow-up and appropriate imaging studies are necessary to identify lesions that may be treated at an early stage. In affected individuals 1 yr and older, there should be a yearly assessment of neurologic status, vision/ophthalmologic status, hearing, and blood pressure. After age 5 yr, there should be laboratory screening for pheochromocytoma every year, hearing evaluation every 2-3 yr, and contrast-enhanced MRI with thin cuts of the internal auditory canal to evaluate for endolymphatic sac tumors in those who are symptomatic. After age 16 yr, there should be abdominal ultrasound yearly to identify visceral lesions, and MRI of the abdomen and entire neural axis every 2 yr.

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614.5

Linear Nevus Sebaceous Syndrome

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This sporadic condition is characterized by a large facial nevus, neurodevelopmental abnormalities, and systemic defects. The nevus is usually located on the forehead and nose and tends to be midline in its distribution. It may be quite faint during infancy but later becomes hyperkeratotic, with a yellow-brown appearance. Two thirds of the patients with linear nevus syndrome demonstrate associated neurologic findings, including cortical dysplasia, glial hamartomas, and low-grade gliomas. Cerebral and cranial anomalies, predominantly hemimegalencephaly and enlargement of the lateral ventricles, are reported in 72% of cases. The incidence of epilepsy and intellectual disability is as high as 75% and 60%, respectively. Focal neurologic signs, including hemiparesis and homonymous hemianopia, may occur. Other organ systems may be involved, including the eyes (strabismus, retinal abnormalities, coloboma, cataracts, corneal revascularization, and ocular hemangiomas), heart (aortic coarctation), kidneys (horseshoe kidney), and skeleton (fibrous dysplasia, skeletal hypoplasia, and scoliosis/kyphoscoliosis). The syndrome is associated with somatic mutations in members of the Ras family of oncogenes, including *HRAS* (HRas proto-oncogene, GTPase), *KRAS* (KRAS proto-oncogene, GTPase), and *NRAS* (neuroblastoma RAS viral oncogene homolog) (see Fig. 614.6).

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614.6

PHACE Syndrome

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See also Chapter 669 .

The syndrome denotes *p* osterior fossa malformations, *h* emangiomas, *a* rterial anomalies, *c* oarctation of the aorta and other cardiac defects, and *e* ye abnormalities. It is also referred to as *PHACES syndrome* when ventral developmental defects, including *s* ternal clefting and/or a *s* upraumbilical raphe, are present. Large facial hemangiomas may be associated with a Dandy-Walker malformation, vascular anomalies (such as coarctation of aorta, aplasia or hypoplastic carotid arteries, aneurysmal carotid dilation, and aberrant left subclavian artery), persistent fetal vasculature, morning glory disc anomaly, glaucoma, cataracts, microphthalmia, optic nerve hypoplasia, and ventral defects (sternal clefts). Endocrinopathies (such as hypopituitarism, hypothyroidism, growth hormone deficiency, and diabetes insipidus) can also occur. The facial hemangioma is typically ipsilateral to the aortic arch. The Dandy-Walker malformation is the most common developmental abnormality of the brain. Other anomalies include hypoplasia or agenesis of the cerebellum, cerebellar vermis, corpus callosum, cerebrum, and septum pellucidum. Cerebrovascular anomalies can result in acquired, progressive vessel stenosis and acute ischemic stroke. According to a case series of 29 children with PHACE syndrome, 69% had abnormal neurodevelopment, including 44% with language delay, 36% with gross motor delay, and 8% with fine motor delay. Over half (52%) had neurologic exam abnormalities, the most common of which was abnormal speech (such as dysarthria or aphasia). Overall, there is a female predominance. The underlying pathogenesis of PHACE syndrome remains unknown, though evidence that infantile hemangiomas may result from abnormal growth and differentiation of hemogenic endothelium highlights some avenues for further investigation. Due to the involvement of multiple organ systems in PHACE syndrome, clinical care should require multidisciplinary input. The beta-blocker propranolol is emerging as a treatment for infantile hemangiomas associated with PHACE syndrome.

LUMBAR syndrome (*l* ower-segment hemangioma, *u* rogenital defects, *m* yelopathy of spinal cord, *b* ony deformities, *a* rterial and anorectal defects, *r* enal anomalies), also called **SACRAL syndrome** (*s* pinal dysraphism, *a* nogenital anomalies, *c* utaneous anomalies, *r* enal-urologic anomalies, *a* ngioma of *l* umbosacral localization), is a possible variant of PHACES syndrome in the lumbosacral region.

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614.7

Incontinentia Pigmenti

Siddharth Srivastava, Mustafa Sahin

Incontinentia pigmenti (IP) is a rare, heritable, multisystem ectodermal disorder that features dermatologic, dental, ocular, and CNS abnormalities. The phenotype is produced by defects in the X-linked dominant gene *IKBKG (inhibitor of kappa B kinase gamma,* previously *NEMO)* , which plays a role in activating the anti-apoptotic signaling molecule NF-kappaB (NF-κB). In the majority of males, IP causes embryonic lethality owing to increased vulnerability to cell death, so those who survive may have *somatic mosaicism* for a pathogenic *IKBKG* variant or a 47,XXY karyotype. Among affected females, an abnormal gene product causes apoptosis in cells; therefore, highly skewed X-inactivation can be a result. The paucity of affected males, the occurrence of female-to-female transmission, and an increased frequency of spontaneous abortions in carrier females support this supposition.

Clinical Manifestations and Diagnosis

This disease has four stages, not all of which may occur in a given patient. The **1st (bullous) stage** is evident at birth or in the first few weeks of life and consists of erythematous linear streaks and plaques of vesicles (Fig. 614.14) that are most pronounced on the limbs and circumferentially on the trunk. The lesions may be confused with those of herpes simplex, bullous impetigo, or mastocytosis, but the linear configuration is unique. Histopathologically, epidermal edema and eosinophil-filled intraepidermal vesicles are present. Eosinophils also infiltrate the adjacent epidermis and dermis. Blood eosinophilia as high as 65% of the white blood cell count is common. The **1st stage** generally resolves by 4 mo of age, but mild, short-lived recurrences of blisters may develop during febrile illnesses. In the **2nd (verrucous) stage,** as blisters on the distal limbs resolve, they become dry and hyperkeratotic, forming verrucous plaques. The verrucous plaques rarely affect the trunk or face and generally involute within 6 mo. Epidermal hyperplasia, hyperkeratosis, dyskeratosis, and papillomatosis are characteristic. The **3rd (pigmentary) stage** is the hallmark of incontinentia pigmenti. It generally develops over weeks to months and may overlap the earlier phases or, more commonly, begin to appear in the 1st few mo of life. Hyperpigmentation is more often apparent on the trunk than the limbs and is distributed in macular whorls, reticulated patches, flecks, and linear streaks that follow Blaschko lines. The axillae and groin are characteristically affected. The sites of involvement are not necessarily those of the preceding vesicular and warty lesions. The pigmented lesions, once present, persist throughout childhood. They generally begin to fade by early adolescence and often disappear by age 16 yr. Occasionally, the pigmentation remains permanently, particularly in the groin. The lesion, histopathologically, shows vacuolar degeneration of the epidermal basal cells and melanin in melanophages of the upper dermis as a result of incontinence of pigment. In the **4th (atretic) stage,** hairless, anhidrotic, hypopigmented patches or streaks occur as a late manifestation of incontinentia pigmenti; they may develop, however, before the hyperpigmentation of stage 3 has resolved. The lesions develop mainly on the flexor aspect of the lower legs and less often on the arms and trunk. On histology, there are decreased rete ridges (epidermal protrusions) and sweat gland secretory coils during this stage.

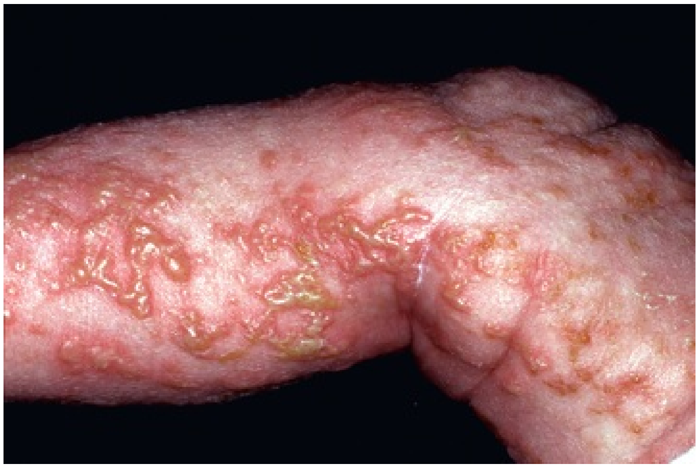

FIG. 614.14 Whorled vesicular phase of incontinentia pigmenti.

Approximately 80% of affected children have other defects. Alopecia, which may be scarring and patchy or diffuse, is most common on the vertex and occurs in up to 40% of patients. Hair may be lusterless, wiry, and coarse. Dental anomalies, which are present in up to 80% of patients and are persistent throughout life, consist of late dentition, hypodontia, conical teeth, malocclusion, and impaction. CNS manifestations, including seizures, intellectual disability, hemiplegia, hemiparesis, spasticity, microcephaly, and cerebellar ataxia, are found in up to 30% of affected children. Ocular anomalies, such as retinal neovascularization, microphthalmos, strabismus, optic nerve atrophy, cataracts, and retrolenticular masses, occur in > 30% of children. Nonetheless, > 90% of patients have normal vision. Notably, retinal neovascularization could herald abnormalities in the CNS vasculature that predispose the patient to ischemic or hemorrhagic stroke. Less common abnormalities include dystrophy of nails (ridging, pitting), subungual and periungual keratotic tumors, and skeletal defects.

Diagnosis of incontinentia pigmenti is made on clinical grounds, although major and minor criteria have been established to aid in the diagnosis. Satisfaction of at least one of the major criteria is needed for a clinical diagnosis; lack of fulfillment of any of the minor criteria should direct the clinician toward the possibility of another diagnosis. Wood's lamp examination may be useful in older children and adolescents to highlight pigmentary abnormalities. Clinical molecular testing is available, and around 65% of affected females and 16% of affected males have an 11.7-kb common deletion in *IKBKG* that removes exons 4 through 10. Skin biopsy may be helpful if the patient has unclear clinical findings and negative genetic testing. For male patients with negative genetic testing from blood, a mutation may be detectable in skin cells from an affected region, increasing the utility of a skin biopsy. The differential diagnosis includes hypomelanosis of Ito, which presents with similar skin manifestations and is often associated with chromosomal mosaicism.

Management

The choice of investigative studies and the plan of management depend on the occurrence of particular noncutaneous abnormalities because the skin lesions are benign. Dermatology may be involved to characterize the nature of skin lesions, as well as to manage skin manifestations that are extensive. Medical genetics and genetic counseling can help establish a molecular diagnosis in addition to providing family counseling. Ophthalmology is important for delineating the presence and extent of retinal neovascularization (which can be treated with cryotherapy and laser photocoagulation) and other ocular abnormalities. Neurology can help evaluate and treat relevant concerns such as microcephaly, seizures, and motor abnormalities. A brain MRI is useful if there is a neurologic deficit or retinal neovascularization. Dentistry can provide teeth implants along with routine care. If dental abnormalities affect speech or feeding, then input from speech pathologists and nutritionists may be necessary. Finally, developmental medicine can formulate recommendations regarding developmental and behavioral concerns.

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CHAPTER 615

Movement Disorders

Jonathan W. Mink

Movement disorders are characterized by impaired voluntary movements or excessive involuntary movements that may result in abnormalities in posture, tone, balance, or fine motor control. Most movement disorders in children are characterized by involuntary movements. These involuntary movements can represent the sole disease manifestation, or they may be one of many signs and symptoms.

Evaluation of movement disorders begins with a comprehensive history and careful neurologic examination. It is often difficult for children and caregivers to describe abnormal movements, which makes observation of the movements by the clinician an essential component of the evaluation. If the movements are not apparent at the time of the examination, video examples from home or school can be invaluable. With the increasing availability of high-quality video capability on cellular phones, obtaining a short video is feasible for most families. Resources are available to guide families in gathering useful video data.

There is no specific diagnostic test to differentiate among movement disorders. The category of movement assists in localizing the pathologic process, whereas the onset of the disorder, age of the patient, and degree of abnormal motor activity and associated neurologic findings help organize the investigation.

When considering the type of movement disorder, the following questions concerning the history and examination of the movement are helpful.

◆ What is the distribution of the movements across body parts?

- Are the movements symmetric?
- What is the speed of the involuntary movements? Are they rapid and fast or slow and sustained?
- When do the movements occur? Are they present at rest? Are they present with maintained posture or with voluntary actions?
- Are the movements seen in relation to certain postures or body positions?
- Do the abnormal movements occur only with specific tasks?
- Can the child voluntarily suppress the movements, even for a short time?
- Are the movements stereotyped?
- Are the movements rhythmic?
- What is the temporal pattern of the movements? Are they continuous or intermittent? Do they occur in discrete episodes?
- Are the involuntary movements preceded by an urge to make the movement?
- Do the movements persist during sleep?
- Are the movements associated with impairment of motor function?
- What factors aggravate or alleviate the movements?

The first decision to be made is whether the movement disorder is **hyperkinetic** (characterized by excessive and involuntary movements) or **hypokinetic** (characterized by slow voluntary movements and a general paucity of movement). Hyperkinetic movement disorders are much more common than hypokinetic disorders in children. Once the category of movement disorder is recognized, the etiology can be considered. The clinical history, including the birth history, medication/toxin exposure, trauma, infections, family history, progression of the involuntary movements, developmental progress, and behavior should be explored as the underlying cause is established. Table 615.1 lists the types and clinical characteristics of selected hyperkinetic movement disorders.

Table 615.1

Selected Types of Involuntary Movement in Childhood

TYPE	CHARACTERISTICS
Stereotypies (see Chapter 37)	Involuntary, patterned, coordinated, repetitive, rhythmic movements that occur in the same fashion with each repetition
Tics (see Chapter 37)	Involuntary, sudden, rapid, abrupt, repetitive, nonrhythmic, simple or complex motor movements or vocalizations (phonic productions). Tics are usually preceded by an urge that is relieved by carrying out the movement
Tremor	Oscillating, rhythmic movements about a fixed point, axis, or plane
Dystonia (see Chapter 615.4)	Intermittent and sustained involuntary muscle contractions that produce abnormal postures and movements of different parts of the body, often with a twisting quality
Chorea (see Chapter 615.2)	Involuntary, continual, irregular movements or movement fragments with variable rate and direction that occur unpredictably and randomly
Ballism	Involuntary, high-amplitude, flinging movements typically occurring proximally. Ballism is essentially a large amplitude chorea
Athetosis	Slow, writhing, continuous, involuntary movements
Myoclonus	Sudden, quick, involuntary muscle jerks

615.1

Ataxias

Peter E. Morrison, Jonathan W. Mink

Ataxia is the inability to make smooth, accurate, and coordinated movements. It occurs because of a dysfunction of the cerebellum, its inputs or outputs, its sensory pathways in the posterior columns of the spinal cord, or a combination of these. Ataxias may be generalized but can also primarily affect the gait, the hands and arms, or the trunk; they may be acute or chronic, or acquired or genetic (Tables 615.2 to 615.6).

Table 615.2

Selected Causes of Ataxia in Childhood

CONGENITAL CAUSES
Agenesis of vermis of the cerebellum
Aplasia or dysplasia of the cerebellum
Basilar impression
Cerebellar dysplasia with microgyria, macrogyria, or agyria
Cervical spinal bifida with herniation of the cerebellum (Chiari malformation type 3)
Chiari malformation
Dandy-Walker syndrome
Encephalocele
Hydrocephalus (progressive)
Hypoplasia of the cerebellum
DEGENERATIVE AND/OR GENETIC CAUSES
Acute intermittent cerebellar ataxia
Ataxia, retinitis pigmentosa, deafness, vestibular abnormality, and intellectual deterioration
Ataxia-telangiectasia
Biemond posterior column ataxia
Cerebellar ataxia with deafness, anosmia, absent caloric responses, nonreactive pupils, and hyporeflexia
Cockayne syndrome
Dentate cerebellar ataxia (dyssynergia cerebellaris progressiva)
Familial ataxia with macular degeneration
Friedreich ataxia
Hereditary cerebellar ataxia, intellectual retardation, choreoathetosis, and eunuchoidism
Hereditary cerebellar ataxia with myotonia and cataracts
Hypertrophic interstitial neuritis
Marie ataxia
Marinesco-Sjögren syndrome
Multiple-system atrophy
Pelizaeus-Merzbacher disease
Periodic attacks of vertigo, diplopia, and ataxia–autosomal-dominant inheritance
Posterior and lateral column difficulties, nystagmus, and muscle atrophy
Progressive cerebellar ataxia and epilepsy
Ramsay Hunt syndrome (myoclonic seizures and ataxia)
Roussy-Lévy disease
Spinocerebellar ataxia (SCA); olivopontocerebellar ataxias
Vanishing white matter syndrome
ENDOCRINOLOGIC CAUSES
Acquired hypothyroidism
Cretinism

INFECTIOUS, POSTINFECTIOUS, AND INFLAMMATORY CAUSES

Acute cerebellar ataxia
Acute disseminated encephalomyelitis
Autoimmune (anti–glutamic acid decarboxylase, anti–γ-aminobutyric acid_B receptor antibodies)
Cerebellar abscess
Cerebellitis
Coxsackievirus
Diphtheria
Echovirus
Fisher syndrome
Infectious mononucleosis (Epstein-Barr virus infection)
Infectious polyneuropathy
Japanese B encephalitis
Mumps encephalitis
Mycoplasma pneumonia
Paraneoplastic (opsoclonus-myoclonus-ataxia syndrome)
Pertussis
Polio
Postbacterial meningitis
Rubeola
Tuberculosis
Typhoid
Varicella

METABOLIC CAUSES

Abetalipoproteinemia
Argininosuccinic aciduria
Ataxia with vitamin E deficiency (AVED)
Congenital disorders of glycosylation
GM_2 gangliosidosis (late)
Hartnup disease
Hyperalaninemia
Hyperammonemia I and II (urea cycle defects)
Hypoglycemia
Kearns-Sayre syndrome
Leigh disease
Maple syrup urine disease (intermittent)
Myoclonic epilepsy with ragged red fibers (MERRF)
Metachromatic leukodystrophy
Mitochondrial complex defects (I, III, IV)
Multiple carboxylase deficiency (biotinidase deficiency)
Neuronal ceroid-lipofuscinosis
Neuropathy, ataxia, retinitis pigmentosa (NARP)
Niemann-Pick disease (late infantile)
5-Oxoprolinuria
Pyruvate decarboxylase deficiency
Refsum disease
Sialidosis
Triose-phosphate isomerase deficiency
Tryptophanuria
Wernicke encephalopathy

NEOPLASTIC CAUSES

Frontal lobe tumors
Hemispheric cerebellar tumors

- Midline cerebellar tumors
- Neuroblastoma
- Pontine tumors (primarily gliomas)
- Spinal cord tumors

PRIMARY PSYCHOGENIC CAUSES

Conversion reaction

TOXIC CAUSES

- Alcohol
- Benzodiazepines
- Carbamazepine
- Clonazepam
- Dextromethorphan
- Lead encephalopathy
- Neuroblastoma
- Phenobarbital
- Phenytoin
- Primidone
- Tic paralysis poisoning

TRAUMATIC CAUSES

- Acute cerebellar edema
- Acute frontal lobe edema

VASCULAR CAUSES

- Angioblastoma of cerebellum
- Basilar migraine
- Cerebellar embolism
- Cerebellar hemorrhage
- Cerebellar thrombosis
- Posterior cerebellar artery disease
- Vasculitis
- von Hippel-Lindau disease

Modified from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF (eds): *Swaiman's pediatric neurology* , 5e, Philadelphia, 2012, WB Saunders, Box 67-1.

Table 615.3

Treatable Causes of Inherited Ataxia

DISORDER	METABOLIC ABNORMALITY	DISTINGUISHING CLINICAL FEATURES	TREATMENT
Acute disseminated encephalomyelitis	Demyelination	Positive MRI findings	Steroids, IVIG, rituximab

Ataxia with vitamin E deficiency	Mutation in α-tocopherol transfer protein	Ataxia, areflexia, retinopathy	Vitamin E
Bassen-Kornzweig syndrome	Abetalipoproteinemia	Acanthocytosis, retinitis pigmentosa, fat malabsorption	Vitamin E
Hartnup disease	Tryptophan malabsorption	Pellagra rash, intermittent ataxia	Niacin
Familial episodic ataxia type 1 and type 2	Mutations in potassium channel (KCNA1) and α_{1A} voltage-gated calcium channel, respectively	Episodic attacks, worse with pregnancy or birth control pills	Acetazolamide
Multiple carboxylase deficiency	Biotinidase deficiency	Alopecia, recurrent infections, variable organic aciduria	Biotin
Mitochondrial complex defects	Complexes I, III, IV	Encephalomyelopathy	Possibly riboflavin, CoQ10, dichloroacetate
Opsoclonus-myoclonus-ataxia syndrome	Paraneoplastic or spontaneous autoimmune	Underlying neuroblastoma or autoantibodies	Steroids, IVIG, rituximab
Pyruvate dehydrogenase deficiency	Block in E-M and Krebs cycle interface	Lactic acidosis, ataxia	Ketogenic diet, possibly dichloroacetate
Refsum disease	Phytanic acid, α-hydroxylase	Retinitis pigmentosa, cardiomyopathy, hypertrophic neuropathy, ichthyosis	Dietary restriction of phytanic acid
Urea cycle defects	Urea cycle enzymes	Hyperammonemia	Protein restriction, arginine, benzoate, α-ketoacids

CoQ10, Coenzyme Q10; E-M, mitochondrial electron transport; IVIG, intravenous immunoglobulin.

Modified from Stumpf DA: The inherited ataxias, *Pediatr Neurol* 1:129-133, 1985, Table 1; and from Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF (eds): *Swaiman's pediatric neurology* , 5e, Philadelphia, 2912, WB Saunders, 2012, Table 67-1.

Table 615.4

Autosomal-Recessive Cerebellar Ataxias

ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (yr)
Friedreich ataxia	9q13	*X25*	Frataxin	GAA repeat	2-51
Friedreich ataxia 2	9p23–p11	Unknown	Unknown	Unknown	5-20
AVED	8q13	*TTP1*	TTPA	Missense mutation, deletion, insertion	2-52
Ataxia-telangiectasia	11q22.3	*ATM*	ATM	Missense and deletion mutations	Infancy
ATLD	11q21	*hMRE11*	MRE11A	Missense and deletion	9-48 mo

				mutations	
Ataxia-ocular apraxia 1	9p13.3	*APTX*	Aprataxin	Frameshift, missense, nonsense mutations	2-18
SCAR1	9q34	*SETX*	Senataxin	Frameshift, missense, nonsense mutations	9-22
SCAR2	9q34–qter	Unknown	Unknown	Unknown	Congenital
SCAR3	6p23–p21	Unknown	Unknown	Unknown	3-52
SCAR4	1p36	Unknown	Unknown	Unknown	23-39
SCAR5	15q24–q26	Unknown	Unknown	Unknown	1-10
SCAR6	20q11–q13	Unknown	Unknown	Unknown	Infancy
SCAR7	11p15	Unknown	Unknown	Unknown	Childhood
SCAR8	11p15	*SYNE1*	SYNE1	Splice site mutation, nonsense mutations	17-46
SCAR9	1q41	*ADCK3*	ADCK3	Splice site mutation, missense, nonsense mutations	3-11
Ataxia, Cayman type	19q13.3	*ATCAY*	Caytaxin	Missense mutation	Birth
IOSCA	10q24	*C10orf2*	Twinkle	Missense, silent mutations	9-24 mo
Progressive myoclonic epilepsy	21q22.3	*CST6*	Cystatin B	5′ dodecamer repeat	6–13
ARSACS	13q12	*SACS*	Sacsin	Frameshift and nonsense mutations	1–20
Congenital disorders of glycosylation	Multiple	Multiple	Multiple		Birth

ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; ATLD, ataxia-telangiectasia-like disorder; AVED, ataxia with vitamin E deficiency; IOSCA, infantile-onset spinocerebellar ataxia; SCAR, spinocerebellar ataxia, autosomal recessive.

From Jafar-Nejad P, Maricich SM, Zoghbi HY: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF (eds): *Swaiman's pediatric neurology* , 5e, Philadelphia, 2012, WB Saunders, Table 67-2.

Table 615.5

The Episodic Ataxias

EPISODIC ATAXIA	CHROMOSOME	GENE	GENE PRODUCT	MECHANISM	AGE OF ONSET (YEARS)	DURATION OF EPISODES, FREQUENCY	FEATU
EA1	12p13	*EA1*	KCNA1	Channelopathy	Early childhood	Seconds to minutes can be several per day	Ataxia, by exer stress, s motion
EA2/FHM	19p13	*CACNA1A*	Cav2.1	Channelopathy: missense and nonsense mutations, deletion	4–30	Minutes to days	Ata mig ocu feat inte nys atax

							epil Res ace
EA3	1q42	Unknown	Unknown	Unknown	1–42	1 min to 6 hours	Ver imb tinn dipl Res ace
EA4	Unknown	Unknown	Unknown	Unknown	23–42	Short, can evolve to constant	Vertigo tinnitus nystag oscillo trigger of visu
EA5	2q22-q23	*CACNB4*	CACNB4	Channelopathy: missense and nonsense mutations	Juvenile	Hours	Ataxia; mutati Germa produc epileps ataxia
EA6	5p13	*SLC1A3*	EAAT1	Missense mutation	5	Hours to days	Progres seizure hemipl
EA7	19q13	Unknown	Unknown	Unknown	<20	Hours to days; once a month to once a year	Weakn dysarth
EA8	1p36-p34	Unknown	Unknown	Unknown	2	Minutes to hours; twice a day to twice a month	Ataxia, dysarth persist intenti

From Jafar-Nejad P, Maricich SM, Zoghbi H: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, et al (eds): *Swaiman's pediatric neurology* , 6e, Philadelphia, 2018, WB Saunders, Table 91-4.

Table 615.6

The Hereditary Spastic Ataxias

SPASTIC ATAXIA (MIM#)	GENE	MODE OF INHERITANCE	AGE OF ONSET (YEARS)	FEATURES
SPAX1 (108600)	*VAMP1*		10-20 yr	Progressive leg spasticity, dysarthria, ocular movement abnormalities
SPAX2 (611302)	*KIF1C*		1-16 yr	Frequent falls, ataxia, head tremor, hyperreflexia, fasciculations
SPAX3/ARSAL (611390)	*MARS2*	AR	2-59 yr; mean 15 yr	Ataxia and spasticity
SPAX4 (613672)	*MTPAP*	AR	Early childhood	Ataxia, spastic paraparesis, dysarthria, optic atrophy, upper limb hypertonia
SPAX5 (614487)	*AFG3L2*	AR	Childhood	Spasticity, ataxia, oculomotor apraxia, dystonia, myoclonic epilepsy

SPAX6/SACS/ARCSACS (270660)	*SACS*	AR	Childhood	Spasticity and ataxia, very slow course, stops progressing after age 20
SPAX7	Unknown	AD	Infancy to 20 yr	Symmetric ataxia, dysarthria, pyramidal signs, optic atrophy
SPAR (607565)	Unknown	—	15-35 yr	Later onset: spastic paraplegia Early onset: + ataxia, mental retardation

From Jafar-Nejad P, Maricich SM, Zoghbi H: The cerebellum and the hereditary ataxias. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, et al (eds): *Swaiman's pediatric neurology* , 6e, Philadelphia, 2018, WB Saunders, Table 91-5.

Signs and symptoms of ataxia include clumsiness, difficulty walking or sitting, falling to one side, slurred speech, low muscle tone, intention tremor, dizziness, delayed motor development, or a combination of these. Genetic or chronic causes of cerebellar ataxia are often characterized by a long duration of symptoms, a positive family history, muscle weakness and abnormal gait, abnormal tone and strength, abnormal deep tendon reflexes, pes cavus, and sensory defects. Distinguishing ataxia from vestibular dysfunction may be difficult; however, labyrinth disorders are often characterized by severe vertigo, nausea and vomiting, position-induced vertigo, and a severe sense of unsteadiness.

Congenital anomalies of the posterior fossa, including the Dandy-Walker malformation, Chiari malformation, and encephalocele, are prominently associated with ataxia because of their destruction or abnormal development of the cerebellum (see Chapter 609.09). *MRI is the method of choice for investigating congenital abnormalities of the cerebellum, vermis, and related structures.* **Agenesis of the cerebellar vermis** presents in infancy with generalized hypotonia and decreased deep tendon reflexes. Delayed motor milestones and truncal ataxia are typical. **Joubert syndrome and related disorders** are autosomal recessive disorders marked by developmental delay, hypotonia, abnormal eye movements, abnormal respirations, and a distinctive malformation of the cerebellum and brainstem that manifests as the “molar tooth sign” on axial MRI. Mutations in more than 21 different genes are associated with Joubert syndrome, but only approximately 50% of cases have a demonstrated causal mutation.

The major **infectious or postinfectious causes of ataxia** include acute cerebellar ataxia, infectious cerebellitis, and acute labyrinthitis. **Acute cerebellar ataxia** occurs primarily in children 1-3 yr of age and is a diagnosis of exclusion. The condition often follows a viral illness, such as varicella virus, coxsackievirus, or echovirus infection, by 2-3 wk. It is thought to represent an autoimmune response to the viral agent affecting the cerebellum (see Chapter 621). The onset is typically sudden, and the truncal ataxia can be so severe that the child is unable to stand or sit. Vomiting may occur initially, but fever and nuchal rigidity are absent due to the lack of meningeal involvement. Horizontal nystagmus is evident in approximately 50% of cases, and, if the child is able to speak, dysarthria may be impressive. Examination of the cerebrospinal fluid is typically normal at the onset of ataxia, but a mild lymphocytic pleocytosis (10-30/mm^3) is not unusual. Later in the course, the cerebrospinal fluid protein undergoes a moderate elevation. The ataxia begins to improve in a few weeks but may persist for as long as 3 mo and rarely longer than that. The incidence of acute cerebellar ataxia appears to have declined with increased rates of vaccination against varicella. **The prognosis for complete recovery is excellent.** A small number of patients have long-term sequelae, including behavioral and speech disorders, as well as ataxia and incoordination. **Acute cerebellitis,** in contrast, is a more severe form of cerebellar ataxia characterized by abnormalities on MRI scans, more severe symptoms, and a worse long-term prognosis. Infectious agents include Epstein-Barr virus, mycoplasma, mumps, and influenza virus. Cerebellar abscesses can also occur with bacterial infections. In many, the etiology is unknown, but autoimmune cerebellitis may represent some of these unknown cases. Clinically, patients may present with ataxia, increased intracranial pressure from obstructive hydrocephalus, headache, and fever. **Acute labyrinthitis** may be difficult to differentiate from acute cerebellar ataxia in a toddler. The condition is associated with middle ear infections and presents with intense vertigo, vomiting, and abnormalities in labyrinthine function.

Toxic causes of ataxia include alcohol, thallium (which is used occasionally in homes as a pesticide), dextromethorphan, and the anticonvulsants, particularly phenytoin and carbamazepine when serum levels exceed the usual therapeutic range.

Brain tumors (see Chapter 524), including tumors of the cerebellum and frontal lobe, may present with ataxia. Cerebellar tumors cause ataxia because of direct disruption of cerebellar function or indirectly because of increased intracranial pressure from compression of the fourth ventricle. Frontal lobe tumors may cause ataxia as a consequence of destruction or interruption of the association fibers connecting the frontal lobe with the cerebellum, or because of increased intracranial pressure. Neuroblastoma (see Chapter 525) may be associated with a paraneoplastic encephalopathy characterized by progressive ataxia, myoclonic jerks, and opsoclonus (nonrhythmic, conjugate horizontal and vertical oscillations of the eyes).

Several **metabolic disorders** are characterized by ataxia, including abetalipoproteinemia, arginosuccinic aciduria, and Hartnup disease (Table 615.7). **Abetalipoproteinemia** (Bassen-Kornzweig disease) is an autosomal recessive disorder caused by a mutation in the microsomal triglyceride transfer protein (MTP). This disorder begins in childhood with steatorrhea and failure to thrive. A blood smear shows acanthocytosis, which consists of spiculated red blood cells. Serum chemistries reveal decreased levels of cholesterol and triglycerides and absent serum β-lipoproteins. Neurologic signs become evident by late childhood and consist of ataxia, retinitis pigmentosa, peripheral neuritis, abnormalities of position and vibration sense, muscle weakness, and intellectual disability. Vitamin E is undetectable in the serum of patients with neurologic symptoms. In addition, ataxia may be one manifestation of a **mitochondrial disorder;** these include MERFF (myoclonic epilepsy with ragged red fibers), Kearns-Sayre syndrome, *POLG1* mutations, and Charlevoix-Saguenay syndrome.

Table 615.7

Genetic and Metabolic Disorders That Can Cause a Spastic-Ataxic Syndrome

	AGE AT ONSET	TREATMENT AVAILABLE	DIAGNOSTIC TESTS, IN ADDITION TO METABOLIC TESTS	MODE OF INHERITANCE	GENES
Abetalipoproteinemia (MIM # 200100)	C	Yes	Blood lipid profile, vitamin E	AR	*MTP*
Adrenomyeloneuropathy (MIM # 300100)	A	Yes	MRI spinal cord, blood VLCFA	X-linked	*ABCD1*
Ataxia with (primary) vitamin E deficiency (MIM # 277460)	C	Yes	Blood vitamin E	AR	*TTPA*
CAMOS (also SCAR5; MIM # 606937)*	C	No	—	AR	*ZNF592*
CARASIL (MIM # 600142)	A	No	MRI	AR	*HTRA1*
Cerebral amyloid angiopathy: presenile dementia with spastic ataxia (MIM # 176500)*	A	No	MRI	AD	*ITM2B*
Cerebral folate deficiency (MIM # 613068)	C	Yes	CSF folates	AR	*FOLR1*
Childhood-onset spastic ataxia with optic atrophy and mental	C	No	—	AR	Unknown

retardation (MIM %270500)*					
Coenzyme Q10 deficiency (MIM # 607426)	C	Yes	—	AR	>3 different genes
Female carriers of EIEE1 (MIM # 308350)*	A	No	—	X-linked	*ARX*
Gaucher disease type III (MIM # 231000)	C-A	Yes	—	AR	*GBA*
Glutaric acidemia II (MIM # 231680)	C	Yes	MRI	AR	*ETFA*, *ETFB*, *ETFDH*
GM2 gangliosidosis (MIM # 272800)	A	No	MRI	AR	*HEXA*, *HEXB*, *GM2A*
Hereditary spastic ataxia with congenital miosis (MIM %108650)(SPAX7)*	C	No	—	AD	Unknown
Krabbe disease (MIM # 245200)	C-A	No	MRI	AR	*GALC*
LBSL (MIM # 611105)*	C-A	No	MRI	AR	*DARS2*
Megaloencephalic leukoencephalopathy with subcortical cysts (MIM # 604004)*	C	No	MRI	AR	*MLC1*
Metachromatic leukodystrophy (MIM # 250100)	C-A	Yes	MRI	AR	*ARSA*
Nonketotic hyperglycinemia (MIM # 605899)	C-A	Yes	CSF amino acids	AR	>3 different genes
Optic atrophy ± deafness, ophthalmoplegia, myopathy, ataxia, neuropathy (MIM * 605290)*	C	No	—	AD	*OPA1*
PHARC (MIM # 612674)*	C	No	—	AR	*ABHD12*
Triple H syndrome (MIM # 238970)*	C-A	Yes	Blood ammonia, amino acids	AR	*SLC25A15*
Type III 3-methylglutaconic aciduria (MIM # 258501)*	C	No	Urine organic acids	AR	*OPA3*
Vanishing whiter matter leukodystrophy (#603896)*	C	No	MRI	AR	>3 different genes

* OMIM.

A, adult onset; C, childhood onset; C-A, all ages possible, predominantly onset in adolescence; CAMOS, cerebellar ataxia with mental retardation, optic atrophy, and skin abnormalities; CARASIL, cerebral arteriopathy with subcortical infarcts and leukoencephalopathy; E1EE1, early infantile epileptic encephalopathy 1; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MIM%, phenotype description or locus, molecular basis unknown; MIM#, phenotype description, molecular basis known; MRI, brain MRI unless otherwise stated; when MRI is indicated, a typical or pathognomonic pattern can be recognized; PHARC, polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract; triple H, hyperornithinemia-hyperammonemia-homocitrullinuria; VLCFA, very-long-chain fatty acids.

Modified from deBot ST, Willemsen MAAP, Vermeer S, et al: Reviewing the genetic causes of spastic-ataxias, *Neurology* 79:1507-1514, 2012, Table 2.

Degenerative diseases of the central nervous system represent an important group of ataxic disorders of childhood because of the genetic consequences and poor prognosis. **Ataxia-telangiectasia,** an autosomal recessive condition, is the most common of the degenerative ataxias and is heralded by ataxia beginning at approximately age 2 yr and progressing to loss of ambulation by adolescence. Ataxia-telangiectasia is caused by mutations in the *ATM* gene located at 11q22-q23. ATM is a phosphytidylinositol-3 kinase that phosphorylates proteins involved in DNA repair and cell-cycle control. Oculomotor apraxia of horizontal gaze, defined as difficulty shifting the gaze from one object to another and overshooting the target with lateral movement of the head, followed by refixating the eyes, is a frequent finding. In addition, strabismus, hypometric saccade pursuit abnormalities, and nystagmus are often seen. Ataxia-telangiectasia may present with chorea (see Chapter 615.2) rather than ataxia. The telangiectasia becomes evident by mid-childhood and is found on the bulbar conjunctiva, over the bridge of the nose, and on the ears and exposed surfaces of the extremities. Examination of the skin shows a loss of elasticity. Abnormalities of immunologic function that lead to frequent sinopulmonary infections include decreased serum and secretory immunoglobulin (Ig) A, as well as diminished IgG_2 , IgG_4 , and IgE levels in more than 50% of patients. Children with ataxia-telangiectasia have a 50- to 100-fold increased risk of developing lymphoreticular tumors (lymphoma, leukemia, and Hodgkin disease), as well as brain tumors. Additional laboratory abnormalities include an increased incidence of chromosome breaks, particularly of chromosome 14, and elevated levels of α-fetoprotein. Death typically results from infection or tumor dissemination.

Friedreich ataxia is inherited as an autosomal recessive disorder involving the spinocerebellar tracts, dorsal columns in the spinal cord, pyramidal tracts, and cerebellum and medulla. Most patients are homozygous for a GAA trinucleotide repeat expansion in the noncoding region of the gene coding for the mitochondrial protein frataxin. Mutations cause oxidative injury associated with excessive iron deposits in mitochondria. The onset of ataxia is somewhat later than in ataxia-telangiectasia but usually occurs before the age of 10. The ataxia is slowly progressive and involves the lower extremities to a greater degree than the upper extremities. Examination will demonstrate a positive Romberg test and absent deep tendon reflexes (particularly at the ankle); the plantar response is typically extensor (Babinski sign). Patients develop a characteristic explosive, dysarthric speech, and nystagmus is present in most children. Although patients may appear apathetic, their intelligence is preserved. They may have significant weakness of the distal musculature of the hands and feet. Marked loss of vibration and joint position sense is common and is caused by degeneration of the posterior columns. Friedreich ataxia is also characterized by skeletal abnormalities, including high-arched feet (pes cavus) and hammertoes, as well as progressive kyphoscoliosis. Results of electrophysiologic studies, including visual, auditory brainstem, and somatosensory-evoked potentials, are often abnormal. Hypertrophic cardiomyopathy with progression to intractable congestive heart failure is the cause of death for most patients.

Several forms of **spinocerebellar ataxia** are similar to Friedreich ataxia but are less common (Fig. 615.1). **Roussy-Levy disease** has, in addition to ataxia, atrophy of the muscles of the lower extremity with a pattern of wasting similar to that observed in Charcot-Marie-Tooth disease. **Ramsay Hunt syndrome** has an associated myoclonic epilepsy.

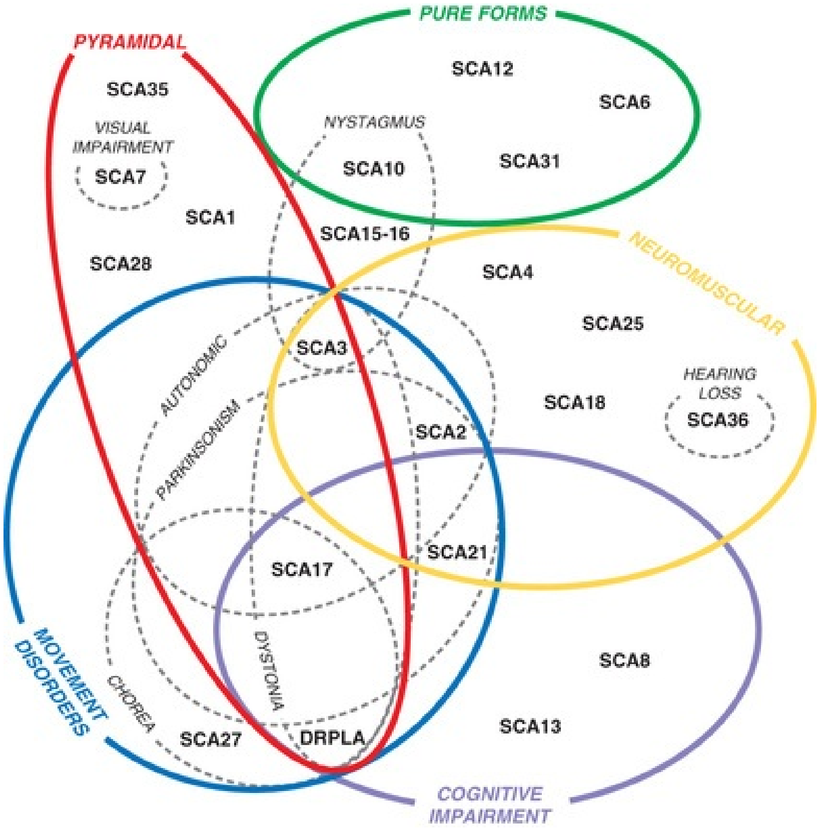
PURE FORMS
PYRAMIDAL
SCA12
SCA6
SCA35
VISUAL IMPAIRMENT
SCA7
NYSTAGMUS
SCA10
SCA31
SCA1
SCA15-16
NEUROMUSCULAR
SCA28
SCA4
SCA25
SCA3
AUTONOMIC
HEARING LOSS
SCA36
SCA18
PARKINSONISM
SCA2
SCA21
SCA17
DYSTONIA
SCA8
MOVEMENT DISORDERS
CHOREA
SCA27
DRPLA
SCA13
COGNITIVE IMPAIRMENT

FIG. 615.1 Organization of SCAs according to main clinical features. (From Rossi M, Perez-Lloret S, Doldan L, et al: Autosomal dominant cerebellar ataxias: a systematic review of clinical features, *Eur J Neurol* 21:607-615,

2014, Fig. 2.)

There are more than 20 dominantly inherited spinocerebellar ataxias, some of which present in childhood. These include those associated with CAG (polyglutamine) trinucleotide repeats and noncoding microsatellite expansions. Dominantly inherited episodic ataxias caused by potassium or calcium channel dysfunction present as episodes of ataxia and muscle weakness. Some of these disorders may respond to acetazolamide. The dominantly inherited **olivopontocerebellar atrophies** include ataxia, cranial nerve palsies, and abnormal sensory findings in the second or third decade, but can present in children with rapidly progressive ataxia, nystagmus, dysarthria, and seizures.

Additional degenerative ataxias include **Pelizaeus-Merzbacher disease, neuronal ceroid lipofuscinoses,** and late-onset **GM_2 gangliosidosis** (see Chapter 617). Rare forms of progressive cerebellar ataxia have been described in association with **vitamin E deficiency.** A number of autosomal dominant progressive spinocerebellar ataxias have been defined at the molecular level, including those caused by unstable trinucleotide repeat expansions.

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615.2

Chorea, Athetosis, Tremor

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Chorea, meaning “dance-like” in Greek, refers to rapid, chaotic movements that seem to flow from one body part to another. Affected individuals often appear restless and movements exhibit randomness. They often demonstrate motor impersistence on neurologic examination, showing classic signs such as “darting tongue” (difficulty maintaining tongue protrusion) or “milkmaid grip” (difficulty maintaining grip). Chorea tends to occur both at rest and with action, although certain actions or postures can exacerbate chorea. Patients often attempt to incorporate the involuntary movements into more purposeful movements, making them appear fidgety. *Chorea increases with stress and disappears in sleep*. Chorea has traditionally been divided into primary and secondary forms; however, this classification scheme in movement disorders can cause confusion given the recent explosion of genetic discoveries in the field. Rather, it may be more helpful to classify chorea causes by etiology: acquired or inherited (Tables 615.8 and 615.9).

Table 615.8

Acquired Causes of Chorea

STRUCTURAL-BASAL GANGLIA LESIONS
Stroke Moyamoya disease Vascular malformations Hemorrhage Choreoathetoid cerebral palsy Postcardiac transplant (postpump chorea) Mass lesions (CNS lymphoma, metastatic brain tumors) Multiple sclerosis plaque Extrapontine myelinolysis Trauma
PARAINFECTIOUS AND AUTOIMMUNE DISORDERS
Poststreptococcal Sydenham chorea Chorea secondary to systemic lupus erythematosus Chorea secondary to antiphospholipid antibody syndrome Acute disseminated encephalomyelitis Anti-NMDA receptor encephalitis Rasmussen encephalitis Chorea gravidarum Postinfectious or postvaccinal encephalitis Paraneoplastic choreas
INFECTIOUS DISORDERS
HIV encephalopathy Toxoplasmosis Cysticercosis Diphtheria Bacterial endocarditis Neurosyphilis Scarlet fever Viral encephalitis (mumps, measles, varicella)
METABOLIC OR TOXIC DISORDERS
Acute intermittent porphyria Hyponatremia/hypernatremia Hypocalcemia Hyperthyroidism Hypoparathyroidism Hepatic/renal failure Carbon monoxide poisoning Methyl alcohol Toluene Manganese poisoning Mercury poisoning Organophosphate poisoning Pheochromocytoma

PSYCHOGENIC DISORDERS	
DRUG-INDUCED DISORDERS	
Dopamine-Blocking Agents (upon withdrawal or as a tardive syndrome)	Phenothiazines Butyrophenones Benzamides
Antiparkinsonian Drugs	L-DOPA Dopamine agonists Anticholinergics
Antiepileptic Drugs	Phenytoin Carbamazepine Valproic acid
Psychostimulants	Amphetamines Methylphenidate Cocaine
Calcium Channel Blockers	Cinnarizine Flunarizine Verapamil
Others	Lithium Baclofen Digoxin Tricyclic antidepressants Cyclosporine Steroids/oral contraceptives Theophylline Propofol

Table 615.9

Inherited Causes of Childhood-onset Chorea

DISEASE NAME	INHERITANCE	ASSOCIATED GENE	AGE OF ONSET	NEUROLOGIC OR PSYCHIATRIC MANIFESTATIONS	SYSTE SYMPT
CHOREA PROMINENT FEATURE					
Ataxia- telangiectasia	AR	*ATM*	18 mo-3 yr	Chorea often initial symptom; also have oculomotor apraxia, ataxia, and dystonia	Telangie increase sinopul infectio increase incidenc cancer
Ataxia with oculomotor apraxia 1 and 2 (especially type 1)	AR	*APTX*	Onset later than ataxia-telangiectasia	Chorea, dystonia, oculomotor apraxia, ataxia, distal sensory axonal neuropathy	
Friedreich ataxia	AR	GAAn in *FRDA*	Over 2 yr, usually teenagers	Gait ataxia, axonal neuropathy, areflexia, extensor plantar response. Can have various movements (tremor, dystonia, chorea, myoclonus).	Cardiom diabetes

				Cases of chorea without cerebellar signs described	
GNAO1- related dyskinesias	AR	*GNAO1*	Infancy	Ballismus, chorea, orofacial dyskinesias; can alternatively cause Ohtahara syndrome	
Benign hereditary chorea	AD	*NKX2-1*	Prior to age 5 yr	Chorea; can have myoclonus, learning disability	Thyroid lung dis
Benign hereditary chorea with or without facial "myokymia"	AD	ADCY5	Infancy to late adolescence	Chorea, choreic facial twitches (previously called myokymia); can have myoclonus or dystonia	Some re congesti failure
PDE10A- associated chorea	AD or AR	*PDE10A*	AD: childhood AR: infancy	Chorea, MRI striatal changes in AD form	
Paroxysmal nonkinesigenic dyskinesias	AD	*MR1*	Infancy to 10 yr	Dystonia, chorea, or a combination	
3-methylglutaconic aciduria type III (Costeff syndrome)	AR	*OPA3*	Infancy	Bilateral optic atrophy and chorea early; spasticity, ataxia, and dementia later	
Congenital cataracts, facial dysmorphism, and neuropathy	AR	*CTDP1*	Infancy or childhood	Progressive neuropathy, delayed psychomotor development, mild chorea, hypomyelination, hearing loss	Skeletal abnorma dysmorp congeni cataracts microco hypogo
Dentatorubral-pallidoluysian atrophy	AD	CAGn in *atrophin-1*	Mostly adults but seen in a few children	Neurodegeneration, chorea, tics, dementia, seizures, ataxia, psychiatric symptoms	
Huntington chorea/disease	AD	CAGn in *HTT*	Adolescence to 40s	Younger onset *without* chorea and with parkinsonism, but later, teenagers can manifest chorea, emotional disturbances similar to adult form	
Huntington disease-like-3 (HDL3)	AR	Linked to chromosome 4p15.3	Childhood	Neurodegeneration, chorea, dystonia, ataxia, dementia, seizures	
Idiopathic basal ganglia calcification (IBGC), childhood onset (bilateral striopallidodentate calcinosis)	AR or AD	*SLC20A2* or *PDGFRB*	Infancy to second decade of life	Tetraplegia, chorea, severe cognitive impairment, microcephaly, basal ganglia calcifications	Early de
Choreoacanthocytosis	AR	*VPS13A*	Mean age 20 yr but described in childhood	Psychiatric symptoms (ex: obsessive-	Acantho increase and/or li

				compulsive disorder) can precede neurologic symptoms Neurodegeneration, progressive hyperkinetic movements (limb chorea, orofacial dyskinesias, tics, dystonia), dementia, seizures, cognitive decline, sensorimotor polyneuropathy	transam
Spinocerebellar ataxia 1	AD	CAGn in *ATXN1*	Childhood	Neurodegeneration, progressive ataxia, mild cognitive impairment, dysarthria, ophthalmoplegia, optic atrophy, spasticity, dystonia or chorea	
Spinocerebellar ataxia 17	AD	CAGn or CAAn in *TBP*	Mostly early adulthood but some teenagers reported	Neurodegeneration, psychiatric symptoms (depression, hallucinations), frontal release signs, chorea, dystonia, and parkinsonism; may have ocular movement abnormalities	
Leigh syndrome	X-linked	*PDHA1*	Infancy or childhood	Neurodegeneration, psychomotor delay, hypotonia and chorea and other hyperkinetic movements can be prominent, progresses to feeding and swallowing defects, nystagmus, ophthalmoplegia, optic atrophy, seizures Lesions in basal ganglia, cerebrum, cerebellum, spinal cord	Lactic a respirato failure
Nonketotic hyperglycemia (glycine encephalopathy)	AR	*GLDC*, *GCST*, or *GCSH*	Neonates/infancy	Hypotonia, severe myoclonic epilepsy, profound cognitive impairment, restlessness	Hypergl
Infantile bilateral striatal necrosis	AR	*NUP62*	Infancy	Developmental regression, intellectual	

				disability, pendular nystagmus, optic atrophy, dysphagia, dystonia, choreoathetosis, spasticity, and severe bilateral striatal atrophy	
CHOREA SOMETIMES PRESENT					
Spinocerebellar ataxia 7	AD	CAGn in *ATXN7*	Childhood	Neurodegenerative mitochondrial disorder, progressive ataxia, dysarthria, dysphagia, optic atrophy, ophthalmoplegia, spasticity, dystonia or chorea may occur	Retinal degener
Wilson disease	AR	*ATP7B*	12 yr to early 20s	Dysarthria, drooling, pharyngeal dysmotility, clumsiness, tremor (“wing-beating”), psychiatric symptoms (decline in school, anxiety, depression, psychosis); chorea and dystonia variable	Hepatic dysfunc (asymm hepatom acute tra fulminar hepatitis Kayser- rings of
Lesch-Nyhan disease	X-linked	*HPRT*	Early childhood	Self-injurious behaviors, intellectual disability, motor disability, pyramidal signs, dystonia superimposed on hypotonia, may have chorea or ballismus, abnormal ocular motility	Hyperur nephroli gout
Pantothenate kinase–associated neurodegeneration (PKAN), classic form	AR	*PANK2*	Prior to 6 yr old (in classic onset)	Progressive motor difficulties, personality changes, cognitive decline, dysarthria, spasticity; later onset of movements (dystonia most common, chorea or tremor may also be present); “eye of the tiger” sign on MRI of brain	Pigment retinal degener acanthoc
Paroxysmal kinesigenic dyskinesia (PKD)	AD	*PRRT2*	1-20 yr	Short episodes triggered by sudden movement; dystonia is most common movement but can have chorea	
Biopterin-dependent hyperphenylalaninemia (group of disorders)	Usually AR	Multiple genetic causes	Neonate	Initially hypotonic with poor suck, decreased movements, and microcephaly; months	Elevate phenyla level at Autonor

				later, oculogyric crises, swallowing difficulties, variable hypo- and hyperkinetic movements, seizures, cognitive impairment	symptor several later
Glutaric aciduria	AR	*GCDH*	First 6 mo	Hypotonia and jitteriness at birth; at 6-18 mo, progressive hyperkinetic movements (dystonia, choreoathetosis); may have seizures	
Alternating hemiplegia of childhood	AR	*ATP1A-3*	Neonate to < 18 mo	Transient episodes of alternating hemiplegia/hemiparesis, dystonic attacks, paroxysmal abnormal ocular movements, seizures, episodes of autonomic dysfunction; between attacks, may have ataxia, dystonia, and/or choreoathetosis; most have intellectual disability	
Succinate semialdehyde dehydrogenase deficiency	AR	*ALDH5A*	Infancy to early childhood	Intellectual disability, pronounced language dysfunction, autistic traits, hypotonia, aggression, ataxia, anxiety, hallucinations, can have choreoathetosis	

Sydenham chorea (St. Vitus dance) is the most common acquired chorea of childhood. It occurs in 10–20% of patients with **acute rheumatic fever,** typically weeks to months after a group A β-hemolytic streptococcal infection (see Chapter 178). Peak incidence is at age 8-9 yr, with a female predominance of 2 : 1. There is evidence that group A β-hemolytic streptococci promote the generation of cross-reactive or polyreactive antibodies through molecular mimicry between streptococcal and host antigens. Specifically, antibodies against the *N* -acetyl-β-D -glucosamine epitope (GlcNAc) of streptococcal group A carbohydrate target intracellular β-tubulin and extracellular lysoganglioside GM$_1$ in human caudate-putamen preparations. These antibodies are also capable of directing calcium/calmodulin–dependent protein kinase II activation, which may cause the neurologic manifestations of Sydenham chorea by increasing dopamine release into the synapse.

The clinical hallmarks of Sydenham chorea are chorea, hypotonia, and emotional lability. Onset of the chorea is typically over hours to days but it may be more abrupt. Chorea is typically generalized although often asymmetric; however, up to 20% have hemichorea. Parents often describe the child as seeming clumsy and dropping items while awake with cessation of movement with sleep. Hypotonia manifests with the *pronator sign* (arms and palms turn outward when held overhead) and the *choreic hand* (spooning of the extended hand by flexion of the wrist and extension of the fingers). When chorea and hypotonia are severe, the child may be incapable of feeding, dressing, or walking without assistance. Speech is often involved, sometimes to the point of being unintelligible. Periods of uncontrollable crying and extreme mood swings are characteristic and may precede the onset of the movement disorder. Patients may also demonstrate inattention, anxiety, obsessive-compulsive symptoms, paranoia, and a reluctance to speak.

Sydenham chorea is a clinical diagnosis; a combination of acute *and* convalescent serum antistreptolysin O titers may help to confirm an acute streptococcal infection. Negative titers do not exclude the diagnosis. All patients with Sydenham chorea should be evaluated for carditis and started on long-term antibiotic prophylaxis (e.g., penicillin G benzathine 0.6 to 1.2 million units intramuscularly every 4 wk or penicillin V 250 mg orally twice daily) to decrease the risk of rheumatic heart disease with recurrence; this should be continued until the patient is 21 yr old. For patients with chorea that is impairing, treatment options include valproate, carbamazepine, and dopamine receptor antagonists. Historically, there have been conflicting data regarding the efficacy of prednisone, intravenous immunoglobulin (IVIG), and other immunomodulatory agents in Sydenham chorea, making it difficult to recommend their routine use. A randomized, double-blinded study of 37 children with Sydenham chorea compared high-dose prednisone (2 mg/kg/day, max: 60 mg) for 4 wk versus placebo and found that steroids significantly reduced the time to remission (54.3 days vs 119.9 days in controls). A randomized-entry controlled trial of IVIG, plasma exchange, and low-dose prednisone demonstrated an overall decreased severity of chorea in the IVIG and plasma exchange groups at a 1-mo follow-up. An unblended study in South Africa compared IVIG with standard treatment (penicillin and haloperidol) and found improvement in outcome scores at up to 6 mo. However, there is no evidence that prednisone, IVIG, or plasma exchange alters the recurrence rate or long-term outcome.

Sydenham chorea usually resolves spontaneously within 1 yr, but symptoms can recur in about 20% of patients despite penicillin prophylaxis. Remote recurrence of chorea is rare, but may be provoked by streptococcal infections, pregnancy **(chorea gravidarum),** or oral contraceptive use.

Although less commonly seen than Sydenham chorea, **systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome (APS)** (see Chapter 183) are well-known causes of chorea in children. In some cases, chorea may be the presenting sign of these disorders and clinically may be indistinguishable from Sydenham chorea. A retrospective study of a large pediatric lupus cohort examined the prevalence of antiphospholipid antibodies and evaluated their association with neuropsychiatric symptoms. There was a significant association between a persistently positive lupus anticoagulant and chorea; however, only 2 of the 137 patients in the cohort had chorea. Regardless, a child with chorea of unknown cause should be investigated for the presence of antiphospholipid antibodies.

Additional causes of acquired chorea include metabolic (hyperthyroidism, hypoparathyroidism), infectious (Lyme disease), immune-mediated (anti–*N* -methyl-ᴅ -aspartate receptor antibody syndrome), vascular (stroke, moyamoya disease, post-pump chorea), heredodegenerative disorders (Wilson disease), and drugs (see Table 615.8). Although chorea is a hallmark of Huntington disease in adults, children who develop Huntington disease tend to present with rigidity and bradykinesia **(Westphal variant)** or dystonia rather than chorea.

There have been remarkable advances made in the recognition of the genetic underpinnings of various diseases that manifest with chorea. Although some entities present with predominantly chorea, others have different multiple neurologic, psychiatric, and systemic manifestations that accompany the movement disorder (see Table 615.9). For example, **benign hereditary chorea** is a relatively rare cause of chorea in childhood. It typically presents prior to age 5 yr; the chorea is either stable or slowly progressive early on. Chorea tends to improve in the late teen to young adult years and often remits by mid-adulthood. It is most commonly secondary to a mutation in the gene *NKX2-1,* which encodes for the protein thyroid transcription factor-1 (TTF1). The majority of patients (80%) also have involvement of the thyroid or lungs, or both. Although children are considered cognitively normal, there are reports of an increased incidence of learning disabilities and ADHD in this population. The gene *ADCY5*, which encodes for an adenylyl cyclase, has been associated with a form of familial benign chorea with onset of paroxysmal movements starting anywhere from infancy to late adolescence. Chorea is the most commonly described movement, although there are reports of myoclonic or dystonic movements, as well. It has commonly been associated with choreic facial twitches that were previously considered facial myokymia (known as **familial dyskinesia with facial myokymia**). Interestingly, movements in this form can persist in sleep. Symptoms can fluctuate such that chorea may be paroxysmal; they tend to be worsened by specific actions and anxiety. These patients also tend to have a stable or very slowly progressive course that tends to stabilize and even improve in middle age. It has not been associated with thyroid or lung disease; however, congestive heart failure has been reported in five patients. Although these conditions are called benign, these movements can be disabling and progressive in some patients. Therefore, some patients may warrant symptomatic treatment. Although there is no proven symptomatic treatment for these conditions, there have been reports of benefit with dopamine-receptor blocking or depleting agents. In a few cases, low-dose levodopa has provided benefit. A pure, benign, and nonprogressive childhood-onset chorea has been described in a few patients with associated mutations in the gene *PDE10A,* which encodes for a phosphodiesterase. Children with de novo dominant mutations characteristically have symmetric T2-hyperintensities in the bilateral striatum on brain MRI brains. Children with recessive homozygous mutations have been described with an earlier age of onset and a more severe clinical course.

Paroxysmal dyskinesias can present with chorea or dystonia, or both; however, chorea is most commonly associated with **paroxysmal nonkinesigenic dyskinesia (PNKD).** This disorder presents in the 1st decade of life, with about one third of patients manifesting symptoms in the 1st yr of life. Patients often have both chorea and dystonia, although some patients manifest only dystonia. Episodes can last minutes to hours, and children are normal between episodes. The episodes are not triggered by sudden movement but can be precipitated by alcohol, caffeine, or emotional stress. About half of patients report a premonitory sensation or a sense of anxiety prior to an episode. Although various genes have been implicated in this disorder, the gene *MR-1* is most commonly associated with PNKD. Patients often respond to benzodiazepines.

Some inherited disorders classified as ataxia syndromes also manifest with significant chorea. For example, **ataxia-telangiectasia** typically presents as a mixed movement disorder with ataxia, dystonia, and chorea in early childhood (18 mo to 3 yr). These symptoms present prior to the appearance of telangiectasias. Over time, children have progression of limb and gait involvement and typically become nonambulatory in childhood. Children also present with oculomotor apraxia (difficulty in initiating horizontal and vertical saccades). Ataxia- telangiectasia is an autosomal recessive disorder secondary to mutations in the *ATM* gene. Because this gene encodes for a protein involved in DNA repair mechanisms, affected children are at increased risk of sinopulmonary infectious and lymphoreticular neoplasms. When this disease is suspected, the initial workup involves testing the alpha-fetoprotein (AFP) level, which is abnormally increased in this population. **Ataxia with oculomotor apraxia type 1 (AOA1)** is also associated with a mixed movement disorder and is due to mutations in the gene *APTX,* which encodes for the aprataxin protein. Up to 80% of children have chorea and dystonia as their initial symptom. Other neurologic symptoms include oculomotor apraxia, ataxia, and a distal sensory axonal neuropathy. The movement disorder tends to be most severe early in the disease and improves as the disease progresses. Unlike ataxia-telangiectasia, this disorder is not associated with skin findings or an increased incidence of cancer.

Chorea can also be a major manifestation in children with inherited conditions that have a progressive, severe course. For example, **pontocerebellar hypoplasia type 2A (PCH-2A)** is associated with chorea present from a young age. In a natural history of 33 children with this disorder, the majority had chorea within the first 6 mo of life. PCH-2A is associated with an acquired microcephaly, extrapyramidal dyskinesias, and spasticity. These children have significant psychomotor retardation with early death. Although various genes have been implicated in the different forms of pontocerebellar hypoplasia, PCH-2A is associated with mutations in the gene *TSEN54,* which encodes for a protein involved in tRNA splicing. Mutations in the gene *GNAO1,* which encodes for the alpha subunit of G proteins, have been described as causing a particular movement disorder in affected children. This gene has previously been described as a cause of early infantile epileptic encephalopathy **(Ohtahara syndrome).** However, affected children may instead manifest with hypotonia, developmental delay without epilepsy, and a movement disorder characterized by chorea and ballismus in the first decade of life. Chorea tends to start acutely during an illness. Some children with *GNAO1* mutations have a severe movement disorder without seizures. Orofacial dyskinesias are common. Children often have periods of movement exacerbations that can be accompanied by autonomic changes. These movements can be refractory to treatment and led to death in two of the children described in this study. Deep brain stimulation has been proposed as a potential treatment for these medically refractory children.

Athetosis is characterized by slow, continuous, writhing movements that repeatedly involve the same body part(s), usually the distal extremities, face, neck, or trunk. Like chorea, athetosis may occur at rest and is often worsened by voluntary movement. Because athetosis tends to occur with other movement disorders, such as chorea **(choreoathetosis)** and dystonia, it is often difficult to distinguish as a discrete entity. Choreoathetosis is associated with cerebral palsy, kernicterus, and other forms of basal ganglia injury; therefore, it is often seen in conjunction with **rigidity** —increased muscle tone that is equal in the flexors and extensors in all directions of passive movement regardless of the velocity of the movement. This is to be differentiated from **spasticity,** a velocity-dependent (clasp-knife) form of hypertonia that is seen with upper motor neuron dysfunction. As with chorea, athetosis/choreoathetosis can also be seen with hypoxic-ischemic injury and dopamine-blocking drugs.

Tremor is a rhythmic, oscillatory movement around a central point or plane that results from the action of antagonist muscles. Tremor can affect the extremities, head, trunk, or voice and can be classified by both its frequency (slow [4 Hz], intermediate [4-7 Hz], and fast [>7 Hz]) and by the context in which it is most pronounced. **Rest tremor** is maximal when the affected body part is inactive and supported against gravity, whereas **postural tremor** is most notable when the patient sustains a position against gravity. **Action tremor** occurs with performance of a voluntary activity and can be subclassified into **simple kinetic tremor,** which occurs with limb movement, and **intention tremor,** which occurs as the patient's limb approaches a target and is a feature of cerebellar disease.

Essential tremor (ET) is the most common movement disorder in adults, and 50% of persons diagnosed with ET report an onset in childhood; thus ET may be the most common tremor disorder in children as well. Clinical experience in a pediatric movement disorders clinic suggests that ET is more common in the pediatric population than the literature would suggest. ET is an autosomal dominant condition with variable expressivity but complete penetrance by the age of 60 yr. Although the genetics of ET are not fully understood, at least three different genes (*EMT1* on chromosome 3q13, *EMT2* on chromosome 2p22-25, *EMT3* on chromosome 6p23, *EMT4* on chromosome 16p11.2, and EMT5 on chromosome 11q14.1) have been linked to this condition. In addition, polymorphisms in the gene *LINGO1* (also known as *LRRN6A)* on chromosome 15q24 have been associated with ET. Based on functional imaging studies, the defect is thought to localize to cerebellar circuits.

ET is characterized by a slowly progressive, bilateral, 4- to 9-Hz postural tremor that involves the upper extremities and occurs in the absence of other known causes of tremor. Mild asymmetry is common, but ET is rarely unilateral. ET may be worsened by actions, such as trying to pour water from cup to cup. Affected adults may report a history of ethanol responsiveness. In the adult literature, there is a consensus on diagnostic criteria; however, there are no specific criteria in children. Unlike adults, children do not require a 5-yr duration of symptoms to make the diagnosis of ET. Most young children come to medical attention once a parent, teacher, or therapist notices the tremor, rather than because the tremor causes impairment. Most children with ET do not require pharmacologic intervention. If they are having difficulty with their handwriting or self-feeding, an occupational therapy evaluation and/or assistive devices, such as wrist weights and weighted silverware, may be helpful. Teenagers tend to report more impairment from ET. Teenagers who do require pharmacotherapy usually respond to the same medications that are used in adults—propranolol and primidone. Propranolol, which is generally considered the first-line treatment, can be started at 10-40 mg daily and titrated to effect, with most patients responding to doses of 60-80 mg/day. Propranolol should not be used in patients with reactive airway disease. Primidone can be started at 12.5-25 mg at bedtime and increased gradually in a twice-daily schedule. Most patients respond to doses of 50-200 mg/day. Other treatment options for ET reported in the adult literature include atenolol, gabapentin, pregabalin, topiramate, and alprazolam. Surgical treatments, which include deep brain stimulation of the thalamus and unilateral thalamotomy, are generally reserved for adults with medically refractory disabling tremor.

Enhanced physiologic tremor is one of the most common etiologies of tremor in adolescents. This tremor occurs in healthy people and is characterized by a symmetric hand tremor that is often of faster frequency and lower amplitude than an ET. Triggers include increased emotions, fatigue, fever, hunger, and waking from sleep. Substances such as caffeine may enhance a tremor. Weighted objects may decrease tremor frequency.

In children 3-7 yr old, coordination difficulties due to **developmental delay** can present with nonprogressive tremor. Many children with motor delays will have a hand and possibly truncal tremor that is most apparent with fine motor tasks, such as drawing, using scissors, or playing with small toys. The history often shows that these children are behind typically developing children in terms of fine and/or gross motor skills and speech articulation. Examination shows that the movement tends to be a small-amplitude, regular or irregular postural or intention tremor. Walking and running may be clumsy. Evidence-based treatment has not been established for tremor related to developmental delay; however, referral to occupational therapy may help to identify strategies to improve coordination in these children.

Infantile tremor syndrome is a disorder of unknown etiology that presents at age 6-18 mo with regression or plateaued development, coarse tremor, and anemia. Potential etiologies include deficiencies in vitamin B_{12} , iron, zinc, or magnesium.

There are numerous secondary etiologies of tremor in children (Table 615.10). **Holmes tremor,** previously referred to as midbrain or rubral tremor, is characterized by a slow-frequency, high-amplitude tremor that is present at rest and with intention. It is a symptomatic tremor, which usually results from lesions of the brainstem, cerebellum, or thalamus. **Psychogenic tremor** is distinguished by its variable appearance, abrupt onset and remission, nonprogressive course, and association with selective but not task-specific disabilities. In some cases, tremor may even occur as a manifestation of another movement disorder, as is seen with position- or task-specific tremor (e.g., writing tremor), dystonic tremor, and myoclonic tremor.

Table 615.10

Selected Causes of Tremor in Children

BENIGN TREMORS
Enhanced physiologic tremor
Developmental delay
Shuddering attacks
Jitteriness
Spasmus nutans
STATIC INJURY/STRUCTURAL TREMORS
Cerebellar malformation
Stroke (particularly in the midbrain or cerebellum)
Multiple sclerosis
HEREDITARY/DEGENERATIVE TREMORS
Familial essential tremor
Fragile X premutation
Wilson disease
Huntington disease
Juvenile parkinsonism (tremor is rare)
Pallidonigral degeneration

METABOLIC TREMORS

- Hyperthyroidism
- Hyperadrenergic state (including pheochromocytoma and neuroblastoma)
- Hypomagnesemia
- Hypocalcemia
- Hypoglycemia
- Hepatic encephalopathy
- Vitamin B_{12} deficiency
- Inborn errors of metabolism
- Mitochondrial disorders

DRUGS/TOXINS

Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, bronchodilators), neuroleptics, cyclosporine, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors

PERIPHERAL NEUROPATHIES

FUNCTIONAL (PSYCHOGENIC) TREMORS

When evaluating a child with tremor, it is important to screen for common metabolic disturbances, including electrolyte abnormalities and thyroid disease, assess the child's caffeine intake, and review the child's medication list for known tremor-inducing agents. It is also critical to exclude Wilson disease in teenagers with characteristic “wing-beating” tremor, because this is a treatable condition.

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615.3

Myoclonus

Jonathan W. Mink

Myoclonus refers to very brief, abrupt, involuntary, nonsuppressible, jerky contractions (or interruption of contractions) involving a single muscle or muscle group. The rapidity of these movements is often described as *shock-like*. In some cases, myoclonus can be elicited by a sensory stimulus (reflex myoclonus; the most common example is the acoustic startle response in infancy) or volitional movement (action myoclonus). It is present in normal and pathologic situations, both epileptic and nonepileptic. Epileptic myoclonus is discussed in Chapter 611

. Etiologic classification of myoclonus is summarized in Table 615.11 .

Table 615.11

Selected Causes of Myoclonus in Children

PHYSIOLOGIC CAUSES
Hiccups
Hypnic jerks (sleep starts)
Nocturnal (sleep) myoclonus
DEVELOPMENTAL CAUSES
Benign neonatal sleep myoclonus
Benign myoclonus of early infancy
Myoclonus with fever
STORAGE DISEASES
Juvenile Gaucher disease (type III)
Sialidosis type 1 (cherry-red spot–myoclonus)
GM$_1$ gangliosidosis
Neuronal ceroid-lipofuscinosis (late infantile)
INHERITED DEGENERATIVE DISEASES
Dentatorubral-pallidoluysian atrophy (DRPLA)
Huntington disease
Progressive myoclonus ataxia
Ramsay Hunt syndrome
Early myoclonic encephalopathy
Rasmussen encephalitis
INFECTIOUS AND POSTINFECTIOUS DISEASES
Meningitis (viral or bacterial)
Encephalitis
Epstein-Barr virus (EBV)
Coxsackievirus
Influenza
Human immunodeficiency virus (HIV)
Acute disseminated encephalomyelitis (ADEM)
METABOLIC CAUSES
Uremia
Hepatic failure
Electrolyte disturbances
Hypoglycemia or hyperglycemia
Aminoacidurias
Organic acidurias
Urea cycle disorders
POLG1 mutations
Myoclonic epilepsy with ragged red fibers (MERRF)
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
Biotinidase deficiency (usually epileptic)
Cobalamin deficiency (infantile)
Leigh syndrome

TOXIC CAUSES

Psychotropic medications (tricyclic antidepressants, lithium, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, neuroleptics)
Antibiotics (penicillin, cephalosporins, quinolones)
Antiepileptics (phenytoin, carbamazepine, lamotrigine, gabapentin, benzodiazepines [in infants], vigabatrin)
Opioids
General anesthetics
Antineoplastic drugs
Strychnine, toluene, lead, carbon monoxide, mercury

HYPOXIA
Lance-Adams Syndrome

FUNCTIONAL (PSYCHOGENIC) CAUSES

Physiologic myoclonus occurs in healthy individuals in specific settings. It includes such entities as hiccups, sleep starts, and sleep myoclonus. Sleep starts, also known as hypnic or hypnagogic myoclonus, occur with sleep initiation. They are often accompanied by a sense of falling. Sleep starts are normal physiologic phenomena and no treatment is required. Sleep myoclonus (nocturnal myoclonus) is also a part of normal sleep physiology. It typically occurs during rapid eye movement (REM) sleep owing to transient failure of brainstem inhibition. Sleep myoclonus tends to persist throughout life. No treatment is required.

Benign myoclonus may occur in association with specific developmental stages. Benign neonatal sleep myoclonus is characterized by repetitive myoclonic jerks occurring during sleep. The myoclonus is typically more distal than proximal and is more prominent in the upper than the lower extremities. The myoclonus can be focal, multifocal, unilateral, or bilateral. Typically, the movements occur in clusters of jerks at 1-5 Hz over a period of several seconds. Benign neonatal sleep myoclonus begins during the 1st wk of life, diminishes in the 2nd mo, and is usually gone before 6 mo of age. The movements are most likely to occur during quiet (non-REM) sleep, but have been described in all sleep stages. Waking the baby causes the movements to abruptly cease. Neurologic examination and outcome are normal.

Myoclonus also can occur with fever in otherwise normal children. The myoclonic jerks may be quite frequent, but they are self-limited, ceasing when the fever resolves. Febrile myoclonus may be more common in younger children. No treatment is required.

Opsoclonus myoclonus (ataxia) syndrome (OMS/OMAS) is characterized by a combination of rapid, chaotic involuntary eye movements (opsoclonus), multifocal myoclonus, and ataxia. Irritability is a common feature. It typically begins abruptly in early childhood, most often before age 5 yr. A common misdiagnosis is acute cerebellar ataxia (ACA) because both ACA and OMAS have subacute, progressive disturbances in gait, truncal instability, and behavioral irritability. Irritable toddlers are difficult to examine thoroughly, adding to the challenge of discerning the presence of multifocal mini-myoclonus and action myoclonus plus ataxia in a toddler with OMAS versus titubation, gait, and limb ataxia in ACA. At its peak, OMAS can cause marked disability for the child.

OMAS is an autoimmune condition in which there is abnormal B-cell trafficking in the central nervous system. It may follow a viral infection in many cases. A large proportion of children (40% by one estimate) with OMAS have a neuroblastoma, a potentially fatal neural crest tumor (see Chapter 525). Conversely, only a small proportion of children with neuroblastoma (probably < 5%) have OMAS. The subacute onset of OMAS and the association with neural crest tumors support an autoimmune paraneoplastic etiology. Intensive research into multiple circulating autoantibodies, including antibodies to Purkinje cell targets, has not, to date, identified any unique, consistently present, disease-associated antibody.

OMAS is a clinical diagnosis. In the presence of subacute irritability, tremor, and ataxia, a diagnosis of OMAS must be considered, and children diagnosed with ACA should continue to be monitored for the emergence of symptoms characteristic of OMAS. The presence of opsoclonus has a high positive predictive value for OMAS, but its absence does not have a high negative predictive value. That is, because opsoclonus can be subtle, intermittent, or late, clinicians and parents need to continue to watch for it. Brain MRI should be normal, and cerebrospinal fluid unremarkable. No immune studies are clinically established for this diagnosis. The search for a neuroblastoma should be thorough and persistent in this clinical setting. MRI with gadolinium or CT with contrast of the chest and abdomen has the highest yield. Nuclear medicine ^{131} I-MIBG (metaiodobenzylguanidine) or ^{111} In-penetreotide (somatostatin receptor ligand) PET scans and urine collection for elevated 24-hr urine catecholamines and serum neuron-specific enolase may be considered but have a lower yield.

Multimodal treatment is required for OMAS. If related to neuroblastoma, the child will likely need immune-modulating treatments even if a tumor is identified and resected. Adrenocorticotrophin (ACTH) protocols are recommended based on expert consensus and clinical experience. In addition to ACTH, combination treatment with IVIG, plasmapheresis, rituximab, or other immune-modulating therapies may be needed. Symptomatic pharmacologic and behavioral therapy for myoclonus, behavioral problems, aggression, and insomnia may also be beneficial. Physical therapy, occupational therapy, and speech therapy may be beneficial. Suboptimal cognitive outcomes occur in most cases.

Cause of other types of myoclonus are listed in Table 615.11 .

Treatment of myoclonus is symptomatic and may be ineffective in many cases. Cortical myoclonus may respond to benzodiazepines and is commonly treated with clonazepam (although sleep myoclonus may worsen). Valproic acid is sometimes helpful, but it must be used with caution due to its ability to cause tremor as a side effect, with consequent confusion of symptoms. Other epilepsy medications, including levetiracetam and zonisamide, may be effective in some forms of myoclonus. Carbamazepine can worsen myoclonus.

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615.4

Dystonia

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Keywords

dystonia, movement disorder
dopa-responsive dystonia
paroxysmal dyskinesia
tardive dyskinesia
metabolic disorder

Dystonia is a disorder of movement characterized by sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. Major causes of dystonia include primary generalized dystonia, medications, metabolic disorders, and perinatal asphyxia (Tables 615.12 and 615.13).

Table 615.12

Causes of Dystonia in Childhood

STATIC INJURY/STRUCTURAL DISORDERS
Cerebral palsy
Hypoxic-ischemic injury
Kernicterus
Head trauma
Encephalitis
Tumors
Stroke in the basal ganglia (which may be a result of vascular abnormalities or varicella)
Congenital malformations
HEREDITARY/DEGENERATIVE DISORDERS
DYT1 (early-onset primary torsion dystonia, *TOR1A*)
DYT2 (early-onset dystonia with craniocervical involvement, autosomal recessive)

DYT3 (adult-onset dystonia-parkinsonism, X-linked *TAF1*)
DYT4 (adult-onset spasmodic dysphonia, *TUBB4A*)
DYT5 (dopa-responsive dystonia, *GCH1*)
DYT6 (adult-onset torsion dystonia with craniocervical and laryngeal involvement, *THAP1*)
DYT7 (adult-onset cervical dystonia)
DYT8 (paroxysmal nonkinesigenic dyskinesia, *MR1*)
DYT10 (paroxysmal kinesigenic dyskinesia, *PRRT2*)
DYT11 (myoclonus dystonia, *SGCE*)
DYT12 (rapid-onset dystonia-parkinsonism, *ATP1A3*)
DYT18 (paroxysmal exercise-induced dyskinesia, *SLC2A1*)
DYT23 (craniocervical dystonia with limb tremor, *ANO3*)
Fahr disease (often caused by hypoparathyroid disease)
Neurodegeneration with brain iron accumulation
Huntington disease (particularly the Westphal variant, IT15-4p16.3)
Spinocerebellar ataxias (SCAs, including SCA3/Machado-Joseph disease)
Neuronal ceroid-lipofuscinoses (NCLs)
Rett syndrome
Striatal necrosis
Leigh disease
Leber hereditary ocular neuropathy (LHON)
Neuroacanthocytosis
HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration)
Ataxia-telangiectasia
POLG1 mutations
Tay-Sachs disease
Sandhoff disease
Niemann-Pick type C
GM_1 gangliosidosis
Mitochondrial membrane protein–associated neurodegeneration (MPAN)
Metachromatic leukodystrophy (MLD)
Lesch-Nyhan disease
Pantothenate kinase–associated neurodegeneration (PKAN)

METABOLIC DISEASE

Glutaric aciduria types 1 and 2
Acyl-coenzyme A (CoA) dehydrogenase deficiencies
Dopa-responsive dystonia
Aromatic l-amino acid decarboxylase deficiency
Aminolevulinic acid dehydrase
Biotin-responsive basal ganglia disease
Mitochondrial disorders
Wilson disease
Vitamin E deficiency
Homocystinuria
Methylmalonic aciduria
Tyrosinemia

DRUGS/TOXINS

Neuroleptic and antiemetic medications (haloperidol, chlorpromazine, olanzapine, risperidone, prochlorperazine)
Calcium channel blockers
Stimulants (amphetamine, cocaine, ergot alkaloids)
Anticonvulsants (carbamazepine, phenytoin)
Thallium
Manganese

Carbon monoxide
Ethylene glycol
Cyanide
Methanol
Wasp sting

PAROXYSMAL DISORDERS

Paroxysmal kinesigenic choreoathetosis (PKD)
Paroxysmal nonkinesigenic choreoathetosis (PNKD)
Paroxysmal exercise-induced dystonia (PED)
Complex migraine
Alternating hemiplegia of childhood (AHC)
Paroxysmal torticollis of infancy

DISORDERS THAT MIMIC DYSTONIA

Tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures)
Arnold-Chiari malformation type II
Atlantoaxial subluxation
Syringomyelia
Posterior fossa mass
Cervical spine malformation (including Klippel-Feil syndrome)
Skew deviation with vertical diplopia causing neck twisting
Juvenile rheumatoid arthritis
Sandifer syndrome (associated with hiatal hernia in infants)
Spasmus nutans
Tics
Infant masturbation
Spasticity
Myotonia
Rigidity
Stiff-person syndrome
Isaac syndrome (neuromyotonia)
Startle disease (hyperekplexia)
Neuroleptic malignant syndrome
Central herniation with posturing
Psychogenic dystonia

From Sanger TD, Mink JW: Movement disorders. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF (eds): *Swaiman's pediatric neurology: principles and practice* , 5e, Philadelphia, 2012, WB Saunders, Box 68-2.

Table 615.13

Examples of Primary and Secondary Dystonia in Childhood

DIAGNOSIS	ADDITIONAL CLINICAL FEATURES
Aicardi-Goutières syndrome	Encephalopathy, developmental regression Acquired microcephaly Sterile pyrexias

	Lesions on the digits, ears (chilblain) Epilepsy CT: calcification of the basal ganglia
Alternating hemiplegia of childhood	Episodic hemiplegia/quadriplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia
ARX gene mutation (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine
Complex regional pain syndrome	Lower limb involvement Prominent pain
Dopa-responsive dystonia (DRD)	Diurnal variation
Drug-induced dystonia	
Dystonia-deafness optic neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence
DYT1 dystonia	Lower limb onset followed by generalization
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: striatal necrosis
GM_1 gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: putaminal hyperintensity
Huntington disease	Parkinsonism Epilepsy Family history of Huntington disease
Kernicterus	Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia MRI: hyperintense lesions in the globus pallidus
Leigh syndrome	Motor delays, weakness, hypotonia Ataxia, tremor Elevated lactate MRI: bilateral symmetric hyperintense lesions in the basal ganglia or thalamus
Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment

	Elevated uric acid
Myoclonus dystonia	Myoclonus Head, upper limb involvement
Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Neuroacanthocytosis	Oromandibular and lingual dystonia
Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Rapid-onset dystonia parkinsonism (DYT12)	Acute onset Distribution face > arm > leg Prominent bulbar signs
Rett syndrome	Female Developmental regression following a period of normal development Stereotypic hand movements Acquired microcephaly Epilepsy
Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
Tics	Stereotyped movements Premonitory urge, suppressible
Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD

Inherited Primary Dystonias

Primary generalized dystonia, also referred to as primary torsion dystonia or *dystonia musculorum deformans,* is caused by a group of genetic disorders with onset in childhood (Fig. 615.2). One form, which occurs more commonly in the Ashkenazi Jewish population, is caused by a dominant mutation in the *DYT1* gene coding for the adenosine triphosphate (ATP)–binding protein torsinA. The initial manifestation of *DYT1* dystonia is often intermittent unilateral posturing of a lower extremity, which assumes an extended and rotated position. Ultimately, all four extremities and the axial musculature can be affected, but the dystonia may also remain localized to one limb. Cranial involvement can occur in *DYT1* dystonia, but it is uncommon compared with non-*DYT1* dystonias. There is a wide clinical spectrum, varying even within families. If a family history of dystonia is absent, the diagnosis should still be considered, given the intrafamilial variability in clinical expression.

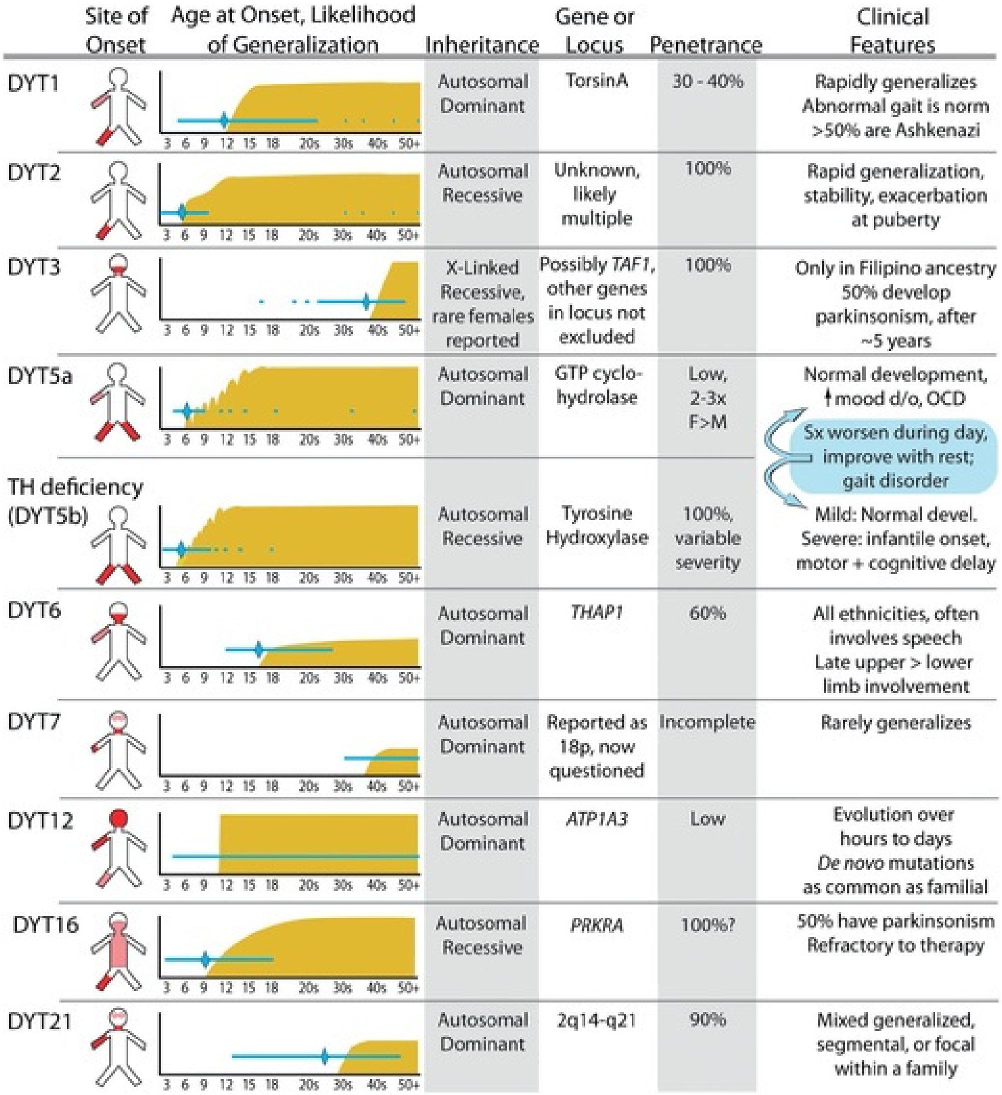

	Site of Onset	Age at Onset, Likelihood of Generalization	Inheritance	Gene or Locus	Penetrance	Clinical Features
DYT1			Autosomal Dominant	TorsinA	30 - 40%	Rapidly generalizes Abnormal gait is norm >50% are Ashkenazi
DYT2			Autosomal Recessive	Unknown, likely multiple	100%	Rapid generalization, stability, exacerbation at puberty
DYT3			X-Linked Recessive, rare females reported	Possibly *TAF1*, other genes in locus not excluded	100%	Only in Filipino ancestry 50% develop parkinsonism, after ~5 years
DYT5a			Autosomal Dominant	GTP cyclo-hydrolase	Low, 2-3x F>M	Normal development, ↑mood d/o, OCD Sx worsen during day, improve with rest; gait disorder
TH deficiency (DYT5b)			Autosomal Recessive	Tyrosine Hydroxylase	100%, variable severity	Mild: Normal devel. Severe: infantile onset, motor + cognitive delay
DYT6			Autosomal Dominant	*THAP1*	60%	All ethnicities, often involves speech Late upper > lower limb involvement
DYT7			Autosomal Dominant	Reported as 18p, now questioned	Incomplete	Rarely generalizes
DYT12			Autosomal Dominant	*ATP1A3*	Low	Evolution over hours to days *De novo* mutations as common as familial
DYT16			Autosomal Recessive	*PRKRA*	100%?	50% have parkinsonism Refractory to therapy
DYT21			Autosomal Dominant	2q14-q21	90%	Mixed generalized, segmental, or focal within a family

FIG. 615.2 Syndromes with dystonia as the presenting or a predominant feature; primary dystonias or dystonia-plus syndromes that commonly begin with dystonia are listed. The most common sites of dystonia onset are indicated on the homunculus in *red,* with less common sites of onset in *pink.* The distribution in age of onset is indicated by a *blue bar,* with the mean age indicated by a *blue diamond,* and rare but reported outliers indicated by *extralinear blue dashes.* Typical rates of progression and the likelihood of generalization are indicated by *yellow plots.* Note that homunculi and plots represent the most common clinical presentations, but variations on these axes are not uncommon. (From Waugh JL, Sharma N: Clinical neurogenetics: dystonia from phenotype to genotype, *Neurol Clin* 31:969-986, 2013, Fig. 1.)

More than a dozen loci for genes for torsion dystonia have been identified *(DYT1-DYT24)*. One is the autosomal dominant disorder **dopa-responsive dystonia (DRD, *DYT5a*),** also called Segawa syndrome. The gene for DRD codes for guanosine triphosphate cyclohydrolase 1, the rate-limiting enzyme for tetrahydrobiopterin synthesis, which is a cofactor for synthesis of the neurotransmitters dopamine and serotonin. Thus, the genetic mutation results in dopamine deficiency. The hallmark of the disorder, particularly in adolescents and adults, is diurnal variation: Symptoms worsen as the day progresses and may transiently improve with sleep. Early-onset patients, who tend to present with delayed or abnormal gait from dystonia of a lower extremity, can easily be confused with patients with dystonic cerebral palsy. It should be noted that in the presence of a progressive dystonia, diurnal fluctuation, or loss of previously achieved motor skills, a prior diagnosis of cerebral palsy should be reexamined. **DRD responds dramatically to small daily doses of levodopa.** The responsiveness to levodopa is a sustained benefit, even if the diagnosis is delayed several years, as long as contractures have not developed. More rarely, an autosomal recessive form of this disorder is caused by mutations in the tyrosine hydroxylase *(TH)* gene.

Myoclonus dystonia (DYT11), caused by mutations in the epsilon-sarcoglycan *(SCGE)* gene, is characterized by dystonia involving the upper extremities, head, and/or neck, as well as myoclonic movements in these regions. Although a combination of myoclonus and dystonia typically occurs, each manifestation can present in isolation. When repetitive, the myoclonus may take on a tremor-like appearance, termed *dystonic tremor.* Improvement in symptoms following alcohol ingestion, reported by affected adult family members, may be a helpful clue to this diagnosis.

Common to the inherited dystonias, there is considerable intrafamilial variability in clinical manifestations, distribution, and severity of dystonia. In primary dystonias, although the main clinical features are motor, there may be an increased risk for major depression. Anxiety, obsessive-compulsive disorder, and depression have all been reported in the myoclonus–dystonia syndrome. Screening for psychiatric comorbidities should not be overlooked in this population.

Drug-Induced Dystonias

A number of medications are capable of inducing involuntary movements, or drug-induced movement disorders, in children and adults. Dopamine-blocking agents, including antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide, prochlorperazine), as well as atypical antipsychotics (e.g., risperidone, ariprazole) can produce acute dystonic reactions or delayed (tardive) drug-induced movement disorders. **Acute dystonic reactions,** occurring in the first days of exposure, typically involve the face and neck, and manifest as torticollis, retrocollis, oculogyric crisis, or tongue protrusion. Life-threatening presentations with laryngospasm and airway compromise can also occur, requiring prompt recognition and treatment of this entity. Intravenous diphenhydramine, 1-2 mg/kg/dose (maximum dose 50 mg), may rapidly reverse the drug-related dystonia. The degree of potency of the dopamine blocker, young age, and prior dystonic reactions may be predisposing factors. Acute dystonic reactions have also been described with cetirizine.

Severe rigidity combined with high fever, autonomic symptoms (tachycardia, diaphoresis), delirium, and dystonia are signs of **neuroleptic malignant syndrome,** which typically occurs a few days after starting or increasing the dose of a neuroleptic drug, or in the setting of withdrawal from a dopaminergic agent. In contrast to acute dystonic reactions, which take place within days, neuroleptic malignant syndrome typically occurs within a month of medication initiation or dose increase.

Delayed-onset involuntary movements, **tardive dyskinesias,** develop in the setting of chronic neuroleptic use, usually longer than 3 mo. Involvement of the face, particularly the mouth, lips, and/or jaw with chewing or tongue thrusting, is characteristic. The risk of tardive dyskinesia, which is much less frequent in children compared with adults, increases as the medication dose, duration of treatment, and polypharmacy increase. There are data to suggest that children with autism spectrum disorders may also be at increased risk for this drug-induced movement disorder. Unlike acute dystonic reactions and neuroleptic malignant syndrome, discontinuation of the offending agent may not result in clinical improvement. In these patients, use of dopamine-depletors, such as reserpine or tetrabenazine, may prove helpful.

Therapeutic doses of phenytoin, carbamazepine, or valproate rarely cause progressive dystonia in children with epilepsy, particularly in those who have an underlying structural abnormality of the brain.

During evaluation of new-onset dystonia, a careful history of prescriptions and potential medication exposures is critical.

Cerebral Palsy

See Chapter 616.1 .

Metabolic Disorders

Disorders of monoamine neurotransmitter metabolism, of which DRD is one, present in infancy and early childhood with dystonia, hypotonia, oculogyric crises, and/or autonomic symptoms. Common comorbidities such as epilepsy, developmental delay, and microcephaly, which are also found in cerebral palsy and other more common disorders, likely contribute to underdiagnosis of this group of rare diseases. The more common disorders in this group include DRD, tyrosine hydroxylase deficiency, and aromatic amino acid decarboxylase deficiency. Abnormalities of the dopamine transporter (DAT) can also present in infancy with dystonia.

Wilson disease is an autosomal recessive inborn error of copper transport characterized by cirrhosis of the liver and degenerative changes in the central nervous system, particularly the basal ganglia (see Chapter 384.2). It has been determined that there are multiple mutations in the Wilson disease gene *(WND),* accounting for the variability in presentation of the condition. The neurologic manifestations of Wilson disease rarely appear before age 10 yr, and the initial sign is often progressive dystonia. Tremors of the extremities develop, unilaterally at first, but they eventually become coarse, generalized, and incapacitating. Other neurologic signs of Wilson disease relate to a progressive basal ganglia disease, such as parkinsonism, dysarthria, dysphonia, and choreoathetosis. Less frequent are ataxia and pyramidal signs. The MRI or CT scan shows ventricular dilation in advanced cases, with atrophy of the cerebrum, cerebellum, and/or brainstem, along with signal intensity change in the basal ganglia, thalamus, and/or brainstem, particularly the midbrain.

Pantothenate kinase–associated neurodegeneration is a rare autosomal recessive neurodegenerative disorder. Many patients have mutations in pantothenate kinase 2 *(PANK2)* localized to mitochondria in neurons. The condition usually begins before 6 yr of age and is characterized by rapidly progressive dystonia, rigidity, and choreoathetosis. Spasticity, extensor plantar responses, dysarthria, and intellectual deterioration become evident during adolescence, and death usually occurs by early adulthood. MRI shows lesions of the globus pallidus, including low signal intensity in T2-weighted images (corresponding to iron pigments) and an anteromedial area of high signal intensity (tissue necrosis and edema), or *eye-of-the-tiger* sign (Fig. 615.3). Neuropathologic examination indicates excessive accumulation of iron-containing pigments in the globus pallidus and substantia nigra. Similar disorders of high brain iron content without *PANK2* mutations, including phospholipase A2–associated neurodegeneration (PLAN), mitochondrial membrane protein–associated neurodegeneration (MPAN), beta-propeller protein–associated neurodegeneration (BPAN), neuroferritinopathy, aceruloplasminemia, and others, have been grouped as disorders of neurodegeneration with brain iron accumulation. Patterns of iron deposition visualized by brain MRI have shown utility in differentiating these disorders.

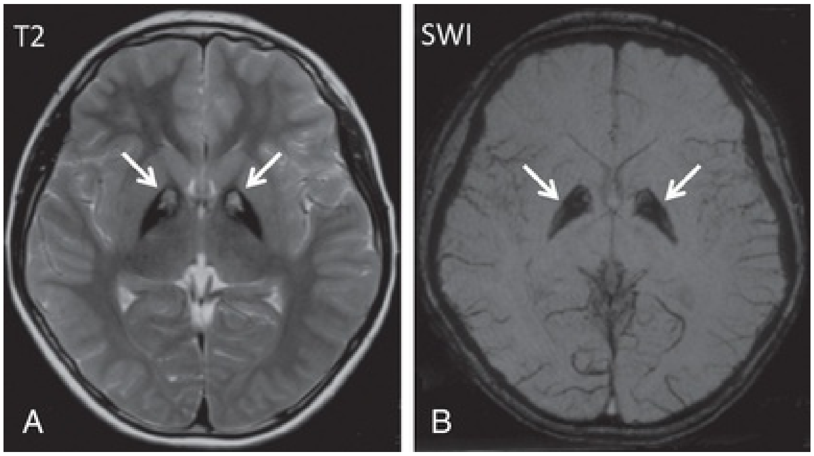

FIG. 615.3 Pantothenate kinase–associated neurodegeneration (PKAN). **A,** Axial T2-weighted image showing symmetric hypointensity in the bilateral globi pallidi with central hyperintensity (eye-of-the-tiger sign, *arrows*). **B,** Axial susceptibility-weighted image (SWI) image showing hypointensity in the globi pallidi representing increased iron accumulation *(arrows).* (From Bosemani T, Meoded A, Poretti A: Susceptibility-weighted imaging in pantothenate kinase-associated neurodegeneration, *J Pediatr* 164:212, 2014.)

Biotin-responsive basal ganglia disease manifests with episodes of acute dystonia, external ophthalmoplegia, and encephalopathy. *SLC19A3* is the responsible mutated gene. MRI demonstrates involvement of the basal ganglia, with vasogenic edema and the *bat-wing* sign (Fig. 615.4). **Treatment with biotin and thiamine results in improvement in 2-4 days.**

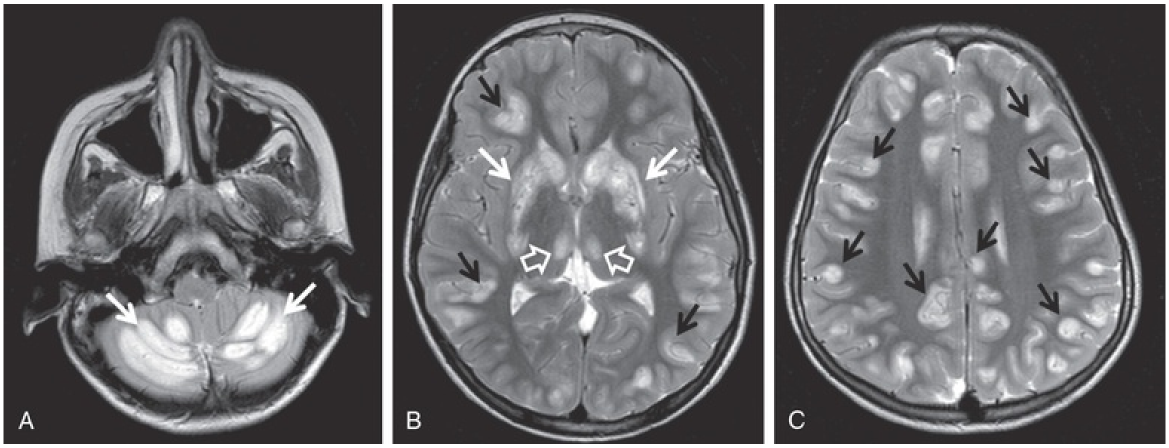

FIG. 615.4 Biotin-responsive basal ganglia disease. An initial brain MRI showed high signal intensity alterations on T2-weighted images bilaterally involving the **(A)** cerebellum *(arrows),* **(B)** basal ganglia *(white arrows),* and medial nucleus of the thalamus *(open arrows),* and **(B, C)** cerebral cortex *(black arrows)* . (Modified from Tabarki B, Al-Sheikh F, Al-Shahwan S, Zuccoli G: Bilateral external ophthalmoplegia in biotin-responsive basal ganglia disease, *J Pediatr* 162:1291-1292, 2013.)

Although dystonia may present in isolation as the first sign of a metabolic or neurodegenerative disorder, this group of diseases should be considered mainly in those who demonstrate signs of systemic disease (e.g., organomegaly, short stature, hearing loss, vision impairment, epilepsy) and those with episodes of severe illness, evidence of regression, or cognitive impairment. Table 615.12 outlines additional features suggestive of specific disorders.

Other Disorders

Although uncommon, movement disorders, including dystonia, may be part of the presenting symptoms of **complex regional pain syndrome.** Onset of involuntary movements within 1 yr of the traumatic event, an affected lower limb, pain disproportionate to the inciting event, and changes in the overlying skin and blood flow to the affected area suggest complex regional pain syndrome. Although sustained dystonia can produce pain or discomfort, complex regional pain syndrome should be considered in those who have a prominent component of pain and a recent history of trauma to the affected limb.

Paroxysmal dyskinesias can cause a combination of dystonic posturing and choreoathetoid movements. By far the most common is **paroxysmal kinesigenic dyskinesia** (PKD), which most commonly presents around the age of 10 yr with attacks of chorea or dystonic posturing lasting seconds to minutes. The movements are most commonly precipitated by voluntary movements and are often easily controlled by low doses of carbamazepine or other antiepileptic medications. Many patients have a mutation in *PRRT2,* a transmembrane protein that interacts with SNAP 25. **Paroxysmal nonkinesigenic dyskinesia** (PNKD) is characterized by prolonged attacks precipitated by emotional stress or alcohol rather than voluntary movement. The attacks are less frequent, perhaps a few times per year or less, but they may last hours. PNKD is less responsive to treatment than PKD. Finally, the rarest form of paroxysmal dyskinesia is **exercise-induced dystonia.** Dystonia in this disorder occurs after periods of prolonged exercise and tends to last between 10 and 30 min. Patients may also suffer from migraines and epilepsy. This disorder is caused by mutations in *SLC2A1,* which encodes the glucose transporter type 1 protein, and is part of GLUT-1 deficiency syndrome. Case reports indicate some patients may have improvement with the ketogenic diet.

There are disorders unique to childhood that warrant exploration in this section as well. **Benign paroxysmal torticollis of infancy** is characterized by recurrent episodes of cervical dystonia beginning in the first few months of life. The torticollis may alternate sides from one episode to the next and may also persist during sleep. Associated signs and symptoms include irritability, pallor, vomiting, vertigo, ataxia, and occasionally limb dystonia. The family history is often notable for migraine and/or motion sickness in first-degree relatives. Despite the high frequency of spells, imaging studies are normal, and the outcome is uniformly benign with resolution by 3 yr of age.

In **alternating hemiplegia of childhood (AHC),** episodic hemiplegia affecting either side of the body is the hallmark of the disorder. However, patients are also affected by episodes of dystonia, ranging from minutes to days in duration. On average, both features of the disorder commence at approximately 6 mo of age. Episodic abnormal eye movements are observed in a large proportion of patients (93%) with onset as early as the first week of life. AHC is associated with mutations in the *ATP1A2* and *ATP1A3* genes. The disorder can be triggered by fluctuations in temperature, certain foods, or water exposure. Over time, epilepsy and cognitive impairment emerge, and the involuntary movements change from episodic to constant. Infantile onset and the paroxysmal nature of symptoms early in the disease course are key features to this diagnosis. Another disorder linked to mutations in *ATP1A3,* **rapid-onset dystonia parkinsonism (RODP),** often presents in adolescents with acute to subacute progressive dystonia and bradykinesia, often after a stressor such as recent illness. Although the classic forms of these two disorders, AHC and RODP, are generally caused by nonoverlapping mutations, molecular genetics has allowed the identification of patients with intermediate phenotypes.

Finally, although it is a diagnosis of exclusion, the presence of odd movements or selective disability may indicate a psychogenic dystonia in older children. There is considerable overlap in features of organic and **psychogenic movement disorders,** making the diagnosis difficult to establish. For instance, both organic and psychogenic movement disorders have the potential to worsen in the setting of stress and may dissipate with relaxation or sleep. The history should include a review of recent stressors, psychiatric symptoms, and exposure to others with similar disorders. On examination, a changing movement disorder, inconsistent motor or sensory exam, or response to suggestion, are supportive of a possible psychogenic movement disorder. Early recognition of this disorder may lessen morbidity caused by unnecessary diagnostic and interventional procedures.

An approach to diagnostic testing is noted in Table 615.14 and Fig. 615.5 .

Table 615.14

Clinical Scenarios That Should Prompt Genetic Testing

Limb-onset dystonia in early adolescence: test torsinA (DYT1), especially with Ashkenazi ancestry
Cervical/cranial onset in mid-adolescence: test THAP1 (DYT6), especially with strained speech (spasmodic dysphonia)
Normal gait in the morning, disabled by the evening: give levodopa; if symptoms improve, test guanosine triphosphate (GTP) cyclohydrolase 1 (DYT5a); if negative, test tyrosine hydroxylase (DYT5b)
Mixed myoclonus and dystonia with onset throughout childhood: test ε-sarcoglycan (DYT11), especially if symptoms are alcohol responsive in family members
Onset of dystonia ± parkinsonism over hours to days: test ATP1A3 (DYT12), especially if symptoms progress in a rostral to caudal fashion
Paroxysmal dystonia ± chorea triggered by:
Sudden movement: test PRRT2 (DYT10), especially if there is a family history of complex migraines or benign seizures/chorea in infancy
Caffeine or alcohol: test PNKD (DYT8), especially if symptoms are rare but last many minutes to hours
Exertion or if the ratio of cerebrospinal fluid/serum glucose is less than 0.5, test SLC2A1 (DYT18), especially in families with unexplained cognitive delay or seizure disorder

From Waugh JL, Sharma N: Clinical neurogenetics: dystonia from phenotype to genotype, *Neurol Clin* 31:969-986, 2013, Box, p. 975.

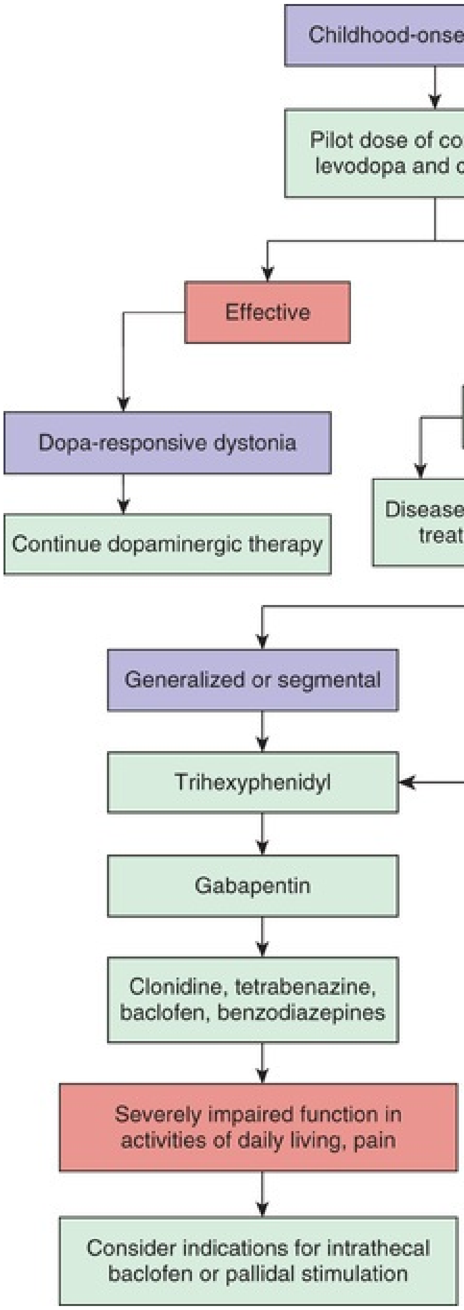
Childhood-onset dystonia
Pilot dose of combination levodopa and carbidopa
Effective
Not effective
Dopa-responsive dystonia
Continue dopaminergic therapy
Further investigation
Disease-specific treatment
Generalized or segmental
Focal
Trihexyphenidyl
Botulinum toxin
Gabapentin
Clonidine, tetrabenazine, baclofen, benzodiazepines
Severely impaired function in activities of daily living, pain
Consider indications for intrathecal baclofen or pallidal stimulation

FIG. 615.5 Therapeutic approaches to the management of childhood-onset dystonia. Pharmacologic agents should be used sparingly where possible. High doses and polypharmacy inevitably arise when dystonia is severe enough to cause pain and interferes with daily cares, sitting comfort, and sleep. As with intractable epilepsy, consideration for functional neurosurgery should be considered when two or more drugs have failed to control dystonia. (From Lin JP: Advances in pharmacotherapies for movement disorders in children: current limitations and future progress, *Curr Opin Pediatr* 29:652-664, 2017, Fig. 6.)

Treatment

Children with generalized dystonia, including those with involvement of the muscles of swallowing, may respond to the anticholinergic agent trihexyphenidyl. Titration occurs slowly over the course of months in an effort to limit untoward side effects, such as urinary retention, mental confusion, or blurred vision. Additional drugs that have been effective include levodopa and diazepam. Segmental dystonia, such as torticollis, often responds well to botulinum toxin injections. Intrathecal baclofen delivered through an implantable constant infusion pump may be helpful in some patients. Deep brain stimulation with leads implanted in the globus pallidus is most helpful for children with severe primary generalized dystonia. Deep brain stimulation may also be of benefit in children with secondary dystonias, such as cerebral palsy.

In the case of drug-induced dystonias, removal of the offending agent and treatment with intravenous diphenhydramine typically suffices. For neuroleptic malignant syndrome, dantrolene may be indicated.

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CHAPTER 616

Encephalopathies

Michael V. Johnston

Encephalopathy is a generalized disorder of cerebral function that may be acute or chronic, progressive, or static. The etiologies of the encephalopathies in children include infectious, toxic (carbon monoxide, drugs, lead), metabolic, genetic, and ischemic causes. Hypoxic-ischemic encephalopathy is discussed in Chapter 120.4 .

616.1

Cerebral Palsy

Michael V. Johnston

See also Chapters 53 , 117.2 , and 615.4 .

Cerebral palsy (CP) is a diagnostic term used to describe a group of permanent disorders of movement and posture causing activity limitation that are attributed to nonprogressive disturbances in the developing fetal or infant brain. The motor disorders are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior as well as by epilepsy and secondary musculoskeletal problems. CP is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious, and other acquired etiologies that produce a common group of neurologic phenotypes. CP has historically been considered a static encephalopathy, but some of the neurologic features of CP, such as movement disorders and orthopedic complications, including scoliosis and hip dislocation, can change or progress over time. Many children and adults with CP function at a high educational and vocational level, without any sign of cognitive dysfunction.

Epidemiology and Etiology

CP is the most common and costly form of chronic motor disability that begins in childhood; data from the Centers for Disease Control and Prevention indicate that the incidence is 3.6 per 1,000 children with a male:female ratio of 1.4 : 1. The Collaborative Perinatal Project, in which approximately 45,000 children were regularly monitored from in utero to the age of 7 yr, found that most children with CP had been born at term with uncomplicated labors and deliveries. In 80% of cases, features were identified pointing to antenatal factors causing abnormal brain development. A substantial number of children with CP had congenital anomalies external to the central nervous system (CNS). Fewer than 10% of children with CP had evidence of intrapartum asphyxia. Intrauterine exposure to maternal infection (chorioamnionitis, inflammation of placental membranes, umbilical cord inflammation, foul-smelling amniotic fluid, maternal sepsis, temperature > 38°C during labor, urinary tract infection) was associated with a significant increase in the risk of CP in normal birthweight infants. Elevated levels of inflammatory cytokines have been reported in heelstick blood collected at birth from children who later were identified with CP. Genetic factors may contribute to the inflammatory cytokine response, and a functional polymorphism in the interleukin-6 gene is associated with a higher rate of CP in term infants.

The prevalence of CP has increased somewhat as a result of the enhanced survival of very premature infants weighing < 1,000 g, who go on to develop CP at a rate of approximately 15 per 100. However, the gestational age at birth-adjusted prevalence of CP among 2 yr old former premature infants born at 20-27 wk of gestation has decreased over the past decade. The major lesions that contribute to CP in preterm infants are **intracerebral hemorrhage** and **periventricular leukomalacia** (PVL). Although the incidence of intracerebral hemorrhage has declined significantly, PVL remains a major problem. PVL reflects the enhanced vulnerability of immature oligodendroglia in premature infants to oxidative stress caused by ischemia or infectious/inflammatory insults. White matter abnormalities (loss of volume of periventricular white matter, extent of cystic changes, ventricular dilation, thinning of the corpus callosum) present on MRI at 40 wk of gestational age in former preterm infants are a predictor of later CP.

In 2006, the European Cerebral Palsy Study examined prenatal and perinatal factors as well as clinical findings and results of MRI in a contemporary cohort of more than 400 children with CP. In agreement with the Collaborative Perinatal Project study, more than half the children with CP in this study were born at term, and less than 20% had clinical or brain imaging indicators of possible intrapartum factors such as asphyxia. The contribution of intrapartum factors to CP is higher in some underdeveloped regions of the world. Also in agreement with earlier data, antenatal infection was strongly associated with CP and 39.5% of mothers of children with CP reported having an infection during the pregnancy, with 19% having evidence of a urinary tract infection and 11.5% reporting taking antibiotics. Multiple pregnancy was also associated with a higher incidence of CP and 12% of the cases in the European CP study resulted from a multiple pregnancy, in contrast to a 1.5% incidence of multiple pregnancy in the study. Other studies have also documented a relationship between multiple births and CP, with a rate in twins that is 5-8 times greater than in singleton pregnancies and a rate in triplets that is 20-47 times greater. Death of a twin in utero carries an even greater risk of CP; it is 8 times that of a pregnancy in which both twins survive and approximately 60 times the risk in a singleton pregnancy. Infertility treatments are also associated with a higher rate of CP, probably because these treatments are often associated with multiple pregnancies. Among children from multiple pregnancies, 24% were from pregnancies after infertility treatment compared with 3.4% of the singleton pregnancies in the study. CP is more common and more severe in boys than girls, and this effect is enhanced at the extremes of body weight. Male infants with intrauterine growth retardation and a birthweight less than the 3rd percentile are 16 times more likely to have CP than males with optimal growth, and infants with weights above the 97th percentile are 4 times more likely to have CP.

Clinical Manifestations

CP is generally divided into several major motor syndromes that differ according to the pattern of neurologic involvement, neuropathology, and etiology (Table 616.1). The physiologic classification identifies the major motor abnormality, whereas the topographic taxonomy indicates the involved extremities. CP is also commonly associated with a spectrum of developmental disabilities, including intellectual impairment, epilepsy, and visual, hearing, speech, cognitive, and behavioral abnormalities. The motor handicap may be the least of the child's problems.

Table 616.1

Classification of Cerebral Palsy and Major Causes

MOTOR SYNDROME (APPROX. % OF CP)	NEUROPATHOLOGY/MRI	MAJOR CAUSES
Spastic diplegia (35%)	Periventricular leukomalacia Periventricular cysts or scars in white matter, enlargement of ventricles, squared-off posterior ventricles	Prematurity
		Ischemia
		Infection
		Endocrine/metabolic (e.g., thyroid)
Spastic quadriplegia (20%)	Periventricular leukomalacia	Ischemia, infection
	Multicystic encephalomalacia Cortical malformations	Endocrine/metabolic, genetic/developmental
Hemiplegia (25%)	Stroke: in utero or neonatal Focal infarct or cortical, subcortical damage Cortical malformations	Thrombophilic disorders
		Infection
		Genetic/developmental
		Periventricular hemorrhagic infarction
Extrapyramidal (athetoid, dyskinetic) (15%)	Asphyxia: symmetric scars in putamen and thalamus Kernicterus: scars in globus pallidus, hippocampus Mitochondrial: scarring of globus pallidus, caudate, putamen, brainstem No lesions: ? dopa-responsive dystonia	Asphyxia
		Kernicterus
		Mitochondrial
		Genetic/metabolic

Infants with **spastic hemiplegia** have decreased spontaneous movements on the affected side and show hand preference at a very early age. The arm is often more involved than the leg and difficulty in hand manipulation is obvious by 1 yr of age. Walking is usually delayed until 18-24 mo, and a circumductive gait is apparent. Examination of the extremities may show growth arrest, particularly in the hand and thumbnail, especially if the contralateral parietal lobe is abnormal, because extremity growth is influenced by this area of the brain. Spasticity refers to the quality of increased muscle tone, which increases with the speed of passive muscle stretching and is greatest in antigravity muscles. It is apparent in the affected extremities, particularly at the ankle, causing an equinovarus deformity of the foot. An affected child often walks on tiptoe because of the increased tone in the antigravity gastrocnemius muscles, and the affected upper extremity assumes a flexed posture when the child runs. Ankle clonus and a

Babinski sign may be present, the deep tendon reflexes are increased, and weakness of the hand and foot dorsiflexors is evident. Difficulty in selective motor control is also present. About one third of patients with spastic hemiplegia have a seizure disorder that usually develops in the first year or two; approximately 25% have cognitive abnormalities including mental retardation. MRI is far more sensitive than cranial CT scan for most lesions seen with CP, although a CT scan may be useful for detecting calcifications associated with congenital infections. In the European CP study, 34% of children with hemiplegia had injury to the white matter that probably dated to the in utero period and 27% had a focal lesion that may have resulted from a stroke. Other children with hemiplegic CP had malformations from multiple causes including infections (e.g., cytomegalovirus), lissencephaly, polymicrogyria, schizencephaly, or cortical dysplasia. Focal cerebral infarction (stroke) secondary to intrauterine or perinatal thromboembolism related to thrombophilic disorders, such as the presence of anticardiolipin antibodies, is an important cause of hemiplegic CP (see Chapter 619). Family histories suggestive of thrombosis and inherited clotting disorders, such as factor V Leiden mutation, may be present and evaluation of the mother may provide information valuable for future pregnancies and other family members.

Spastic diplegia is bilateral spasticity of the legs that is greater than in the arms. Spastic diplegia is strongly associated with damage to the immature white matter during the vulnerable period of immature oligodendroglia between 20-34 wk of gestation. However, approximately 15% of cases of spastic diplegia result from in utero lesions in infants who go on to delivery at term. The first clinical indication of spastic diplegia is often noted when an affected infant begins to crawl. The child uses the arms in a normal reciprocal fashion but tends to drag the legs behind more as a rudder (commando crawl) rather than using the normal 4-limbed crawling movement. If the spasticity is severe, application of a diaper is difficult because of the excessive adduction of the hips. If there is paraspinal muscle involvement, the child may be unable to sit. Examination of the child reveals spasticity in the legs with brisk reflexes, ankle clonus, and a bilateral Babinski sign. When the child is suspended by the axillae, a scissoring posture of the lower extremities is maintained. Walking is significantly delayed, the feet are held in a position of equinovarus, and the child walks on tiptoe. Severe spastic diplegia is characterized by disuse atrophy and impaired growth of the lower extremities and by disproportionate growth with normal development of the upper torso. The prognosis for normal intellectual development for these patients is good, and the likelihood of seizures is minimal. Such children often have learning disabilities and deficits in other abilities, such as vision, because of disruption of multiple white matter pathways that carry sensory as well as motor information.

The most common neuropathologic finding in children with spastic diplegia is periventricular leukomalacia (PVL), which is visualized on MRI in more than 70% of cases. MRI typically shows scarring and shrinkage in the periventricular white matter with compensatory enlargement of the cerebral ventricles. However, neuropathology has also demonstrated a reduction in oligodendroglia in more widespread subcortical regions beyond the periventricular zones, and these subcortical lesions may contribute to the learning problems these patients can have. MRI with diffusion tensor imaging is being used to map white matter tracks more precisely in patients with spastic diplegia, and this technique has shown that thalamocortical sensory pathways are often injured as severely as motor corticospinal pathways (Fig. 616.1). These observations have led to greater interest in the importance of sensory deficits in these patients, which may be important for designing rehabilitative techniques.

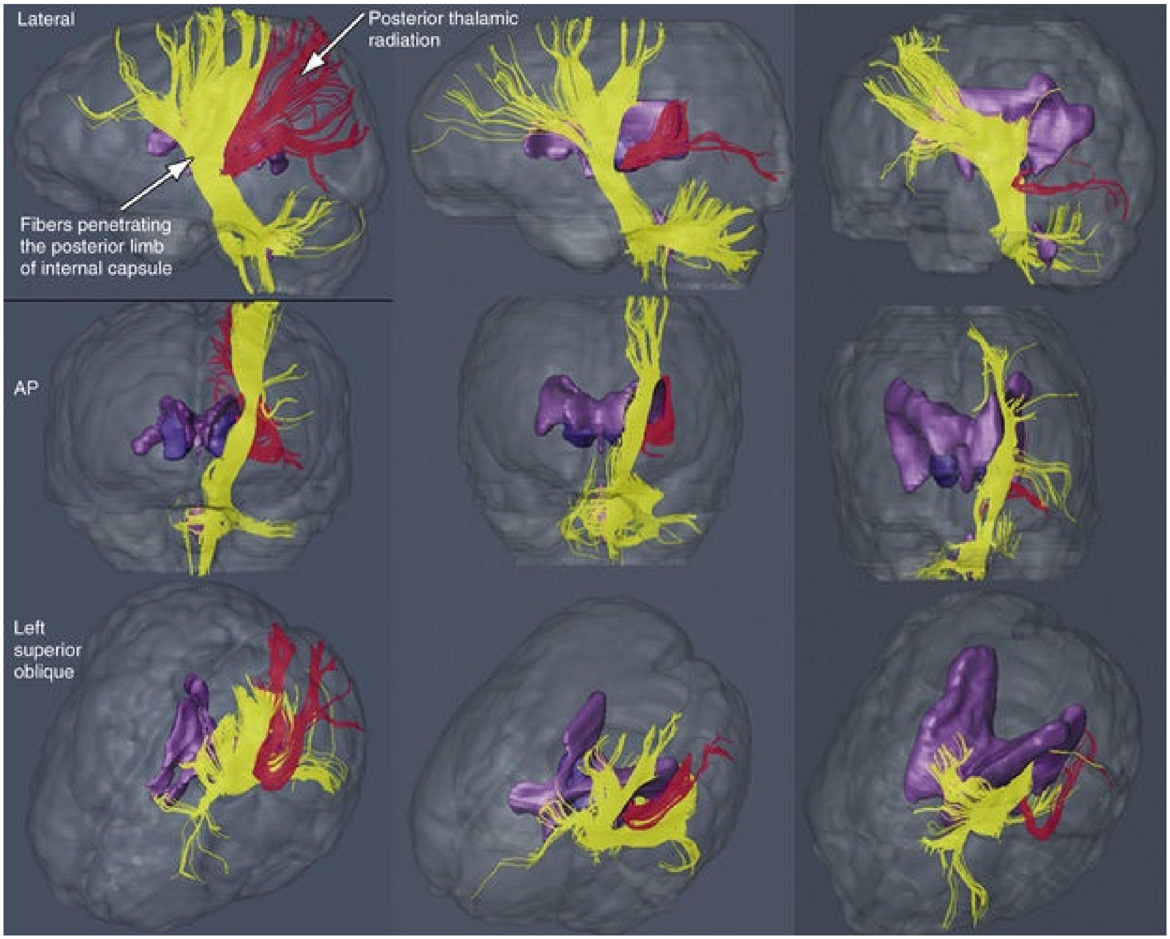
Lateral
Posterior thalamic radiation
Fibers penetrating the posterior limb of internal capsule
AP
Left superior oblique

FIG. 616.1 Diffusion tensor image of white matter pathways in the brains of two patients with spastic diplegia on the right compared with a normal child on the far left. Yellow fibers are corticospinal pathways projected from the motor cerebral cortex at the top downward into the brainstem, whereas red fibers are thalamocortical sensory fibers projected from the thalamus upward to the cortex. In the children with spastic diplegia, both the corticospinal and thalamocortical pathways are reduced in size but the ascending thalamocortical pathways are more affected. (From Nagae LM, Hoon AH Jr, Stashinko E, et al: Diffusion tensor imaging in children with periventricular leukomalacia: variability of injuries to white matter tracts, AJNR Am J Neuroradiol 28:1213-1222, 2007.)

Spastic quadriplegia is the most severe form of CP because of marked motor impairment of all extremities and the high association with intellectual disability and seizures. Swallowing difficulties are common as a result of supranuclear bulbar palsies, often leading to aspiration pneumonia and growth failure. The most common lesions seen on pathologic examination or on MRI scanning are severe PVL and multicystic cortical encephalomalacia. Neurologic examination shows increased tone and spasticity in all extremities, decreased spontaneous movements, brisk reflexes, and plantar extensor responses. Flexion contractures of the knees, elbows, and wrists are often present by late childhood. Associated developmental disabilities, including speech and visual abnormalities, are particularly prevalent in this group of children. Children with spastic quadriparesis often have evidence of athetosis and may be classified as having mixed CP.

Athetoid CP, also called **choreoathetoid, extrapyramidal,** or **dyskinetic CP,** is less common than spastic CP and makes up approximately 15–20% of patients with CP. Affected infants are characteristically hypotonic with poor head control and marked head lag and develop variably increased tone with rigidity and dystonia over several years. The term *dystonia* refers to the abnormality in tone in which muscles are rigid throughout their range of motion and involuntary contractions can occur in both flexors and extensors leading to limb positioning in fixed postures. Unlike spastic diplegia, the upper extremities are generally more affected than the lower extremities in extrapyramidal CP. Feeding may be difficult, and tongue thrust and drooling may be prominent. Speech is typically affected because the oropharyngeal muscles are involved. Speech may be absent or sentences are slurred, and voice modulation is impaired. Generally, upper motor neuron signs are not present, seizures are uncommon, and intellect is preserved in many patients. This form of CP is also referred to in Europe as dyskinetic CP and is the type most likely to be associated with **birth asphyxia.** In the European CP study, 76% of patients with this form of CP had lesions in the basal ganglia and thalamus. Extrapyramidal CP secondary to acute intrapartum near-total asphyxia is associated with bilaterally symmetric lesions in the posterior putamen and ventrolateral thalamus. These lesions appear to be the correlate of the neuropathologic lesion called *status marmoratus* in the basal ganglia. Athetoid CP can also be caused by **kernicterus** secondary to high levels of bilirubin, and in this case the MRI scan shows lesions in the globus pallidus bilaterally. Extrapyramidal CP can also be associated with lesions in the basal ganglia and thalamus caused by metabolic genetic disorders such as mitochondrial disorders and glutaric aciduria. MRI scanning and possibly metabolic testing are important in the evaluation of children with extrapyramidal CP to make a correct etiologic diagnosis. In patients with dystonia who have a normal MRI, it is important to have a high level of suspicion for dihydroxyphenylalanine (DOPA)-responsive dystonia **(Segawa disease),** which causes prominent dystonia that can resemble CP. These patients typically have diurnal variation in their signs with worsening dystonia in the legs during the day; however, this may not be prominent. These patients can be tested for a response to small doses of L-dopa and/or cerebrospinal fluid can be sent for neurotransmitter analysis.

Associated comorbidities are common and include pain (in 75%), cognitive disability (50%), hip displacement (30%), seizures (25%), behavioral disorders (25%), sleep disturbances (20%), visual impairment (19%), and hearing impairment (4%).

Diagnosis

A thorough history and physical examination should preclude a **progressive disorder** of the CNS, including degenerative diseases, metabolic disorders, spinal cord tumor, or muscular dystrophy. The possibility of anomalies at the base of the skull or other disorders affecting the cervical spinal cord needs to be considered in patients with little involvement of the arms or cranial nerves. An MRI scan of the brain is indicated to determine the location and extent of structural lesions or associated congenital malformations; an MRI scan of the spinal cord is indicated if there is any question about spinal cord pathology. Additional studies may include tests of hearing and visual function. Genetic evaluation should be considered in patients with congenital malformations (chromosomes) or evidence of metabolic disorders (e.g., amino acids, organic acids, MR spectroscopy). In addition to the genetic disorders mentioned earlier that can present as CP, the urea cycle disorder arginase deficiency is a rare cause of spastic diplegia and a deficiency of sulfite oxidase or molybdenum cofactor can present as CP caused by perinatal asphyxia. Tests to detect inherited thrombophilic disorders may be indicated in patients in whom an in utero or neonatal stroke is suspected as the cause of CP. Because CP is usually associated with a wide spectrum of developmental disorders, a multidisciplinary approach is most helpful in the assessment and treatment of such children. The differential diagnosis must include disorders that may mimic the various types of CP. These may include the hereditary spastic diplegias (Table 616.2), monoamine transmitter disorders (Table 616.3 and Fig. 616.2), and many treatable inborn errors of metabolism, including disorders of amino acids, creatine, fatty acid oxidation, lysosomes, mitochondria, organic acids, and vitamin cofactors.

Table 616.2

Clinical and Neuroimaging Findings in Hereditary Spastic

Paraplegias (HSP) with Pediatric Onset[*]

HSP FORM	HSP TYPE	INHERITANCE	GENE	CHILDHOOD ONSET	DISEASE CHARACTERISTICS[†]	NEUROIMAGI FINDINGS (BR
Pure	SPG3A	Aut. dom	*ATL1*	+++	None	Normal
Pure	SPG4	Aut. dom	*SPAST*	++	None	Leukoencephalo thin corpus callo
Pure	SPG6	Aut. dom	*NIPA1*	+	None	Normal
Pure	SPG10	Aut. dom	*KIF5A*	+++	Neuropathy	Normal
Pure	SPG12	Aut. dom	*RTN2*	+++	None	Normal
Pure	SPG31	Aut. dom	*REEP1*	++	None	Normal
Complicated	SPG1	X-linked	*L1CAM*	++	Intellectual disability, adducted thumb	Thin corpus callo
Complicated	SPG2	X-linked	*PLP1*	+++	Intellectual disability, epilepsy	Normal
Complicated	SPG7	Aut. rec.	*SPG7*	+	Optic atrophy, neuropathy, cerebellar ataxia	Cerebellar atropl
Complicated	SPG11	Aut. rec.	*KIAA1840*	+++	Intellectual disability, neuropathy	Leukoencephalo thin corpus callo
Complicated	SPG15	Aut. rec.	*ZFYVE26*	+++	Intellectual disability, retinopathy, cerebellar ataxia	Leukoencephalo thin corpus callo
Complicated	SPG17	Aut. rec.	*BSCL2*	+	Neuropathy	Normal

[*] Onset before 18 yr of age.

[†] Other than the classic HSP symptoms, including spastic paraparesis, atrophy of the distal lower extremities, and neurogenic bladder dysfunction.

Aut. dom., autosomal dominant; aut. rec., autosomal recessive; +, occasional; ++, common; +++, characteristic.

From Lee RW, Poretti A, Cohen JS, et al: A diagnostic approach for cerebral palsy in the genomic era, Neurol Med 16:821-844, 2014, Table 5, p. 832.

Table 616.3

Clinical Features of the Monoamine Neurotransmitter Disorders

	AGE AT PRESENTATION	MOTOR AND COGNITIVE DELAY	EXTRAPYRAMIDAL HYPERKINETIC FEATURES	EXTRAPYRAMIDAL HYPOKINETIC FEATURES	PYRAMIDAL TRACT FEATURES
AD GTPCH-D	Childhood (but can occur at any age)	Not common	Yes	Yes	No
SR-D	Infancy	In most	Yes	Yes	Yes

AR GTPCH-D	Infancy	Yes	Yes	Yes	Yes
PTPS-D	Infancy to childhood	In most	Yes	Yes	Yes
DHPR-D	Infancy to childhood	Yes	Yes	Yes	Yes
PCD-D	Infancy	No	No	No	No
TH-D	Infancy to early childhood	In most	Yes	Yes	Yes
AADC-D	Mainly infancy (but can occur at any age)	Yes	Yes	Yes	Yes
PLP-DE	Infancy to early childhood	In most	Yes	Yes	Yes
DTDS	Infancy	Yes	Yes	Yes	Yes in older children

From Kurian MA, Gissen P, Smith M, et al: The monoamine neurotransmitter disorders: an expanding range of neurological syndromes, Lancet Neurol 10:721-731, 2011, Table, p. 722.

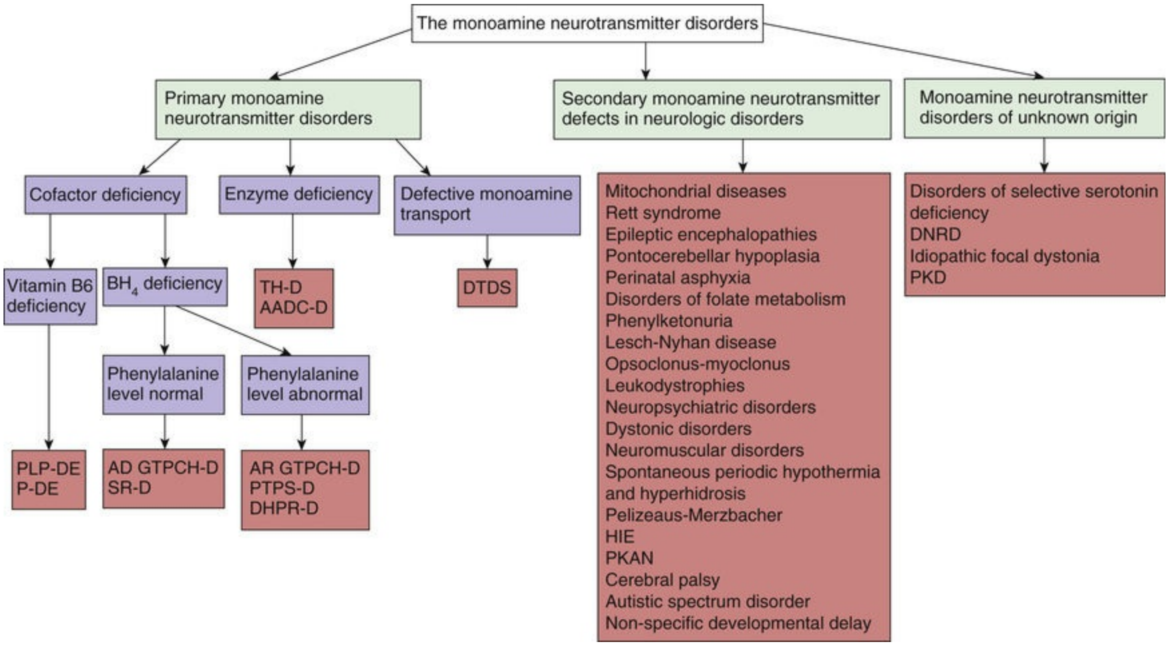
The monoamine neurotransmitter disorders
Primary monoamine neurotransmitter disorders
Secondary monoamine neurotransmitter defects in neurologic disorders
Monoamine neurotransmitter disorders of unknown origin
Cofactor deficiency
Enzyme deficiency
Defective monoamine transport
Vitamin B6 deficiency
BH4 deficiency
TH-D AADC-D
DTDS
Phenylalanine level normal
Phenylalanine level abnormal
PLP-DE P-DE
AD GTPCH-D SR-D
AR GTPCH-D PTPS-D DHPR-D
Mitochondrial diseases
Rett syndrome
Epileptic encephalopathies
Pontocerebellar hypoplasia
Perinatal asphyxia
Disorders of folate metabolism
Phenylketonuria
Lesch-Nyhan disease
Opsoclonus-myoclonus
Leukodystrophies
Neuropsychiatric disorders
Dystonic disorders
Neuromuscular disorders
Spontaneous periodic hypothermia and hyperhidrosis
Pelizeaus-Merzbacher
HIE
PKAN
Cerebral palsy
Autistic spectrum disorder
Non-specific developmental delay
Disorders of selective serotonin deficiency
DNRD
Idiopathic focal dystonia
PKD

FIG. 616.2 Classification of the monoamine neurotransmitter disorders. BH_4, tetrahydrobiopterin; TH-D, tyrosine hydroxylase deficiency; AADC-D, aromatic L-amino acid decarboxylase deficiency; DTDS, dopamine transporter deficiency syndrome; PLP-DE, pyridoxal-phosphate–dependent epilepsy, P-DE, pyridoxine-dependent epilepsy; AD GTPCH-D, autosomal dominant GTP cyclohydrolase 1 deficiency; SR-D, sepiapterin reductase deficiency; AR GTPCH-D, autosomal recessive GTP cyclohydrolase 1 deficiency; PTPS-D, 6-pyruvoyltetrahydropterin synthase deficiency; DHPR-D, dihydropteridine reductase deficiency; HIE, hypoxic ischemic

encephalopathy; PKAN, pantothenate kinase associated neurodegeneration; DNRD, dopa nonresponsive dystonia; PKD, paroxysmal kinesigenic dyskinesia. (From Kurian MA, Gissen P, Smith M, et al: The monoamine neurotransmitter disorders: an expanding range of neurological syndromes, Lancet Neurol 10:721-731, 2011, Fig. 1.)

Treatment

Some progress has been made in both prevention of CP before it occurs and treatment of children with the disorder. Preliminary results from controlled trials of magnesium sulfate, given intravenously to mothers in premature labor with birth imminent before 32 wk gestation, showed a significant reduction in the risk of CP at 2 yr of age. Nonetheless, one study that followed preterm infants whose mothers received magnesium sulfate demonstrated no benefit in terms of the incidence of CP and abnormal motor, cognitive, or behavioral function at school age. Furthermore, several large trials have shown that cooling term infants with hypoxic-ischemic encephalopathy to 33.3°C for 3 days, starting within 6 hr of birth, reduces the risk of the dyskinetic or spastic quadriplegia form of CP.

For children who have a diagnosis of CP, a team of physicians, including neurodevelopmental pediatricians, pediatric neurologists, and physical medicine and rehabilitation specialists, as well as occupational and physical therapists, speech pathologists, social workers, educators, and developmental psychologists, is important to reduce abnormalities of movement and tone and to optimize normal psychomotor development. Parents should be taught how to work with their child in daily activities such as feeding, carrying, dressing, bathing, and playing in ways that limit the effects of abnormal muscle tone. Families and children also need to be instructed in the supervision of a series of exercises designed to prevent the development of contractures, especially a tight Achilles tendon. Physical and occupational therapies are useful for promoting mobility and the use of the upper extremities for activities of daily living. Speech language pathologists promote acquisition of a functional means of communication and work on swallowing issues. These therapists help children to achieve their potential and often recommend further evaluations and adaptive equipment.

Children with spastic diplegia are treated initially with the assistance of adaptive equipment, such as orthoses, walkers, poles, and standing frames. If a patient has marked spasticity of the lower extremities or evidence of hip dislocation, consideration should be given to performing surgical soft-tissue procedures that reduce muscle spasm around the hip girdle, including an adductor tenotomy or psoas transfer and release. A rhizotomy procedure in which the roots of the spinal nerves are divided produces considerable improvement in selected patients with severe spastic diplegia and little or no basal ganglia involvement (Fig. 616.3). A tight heel cord in a child with spastic hemiplegia may be treated surgically by tenotomy of the Achilles tendon or sometimes with serial botulinum toxin injections. Quadriplegia is managed with motorized wheelchairs, special feeding devices, modified typewriters, and customized seating arrangements. The function of the affected extremities in children with **hemiplegic CP** can often be improved by therapy in which movement of the good side is constrained with casts while the impaired extremities perform exercises that induce improved hand and arm functioning. This constraint-induced movement therapy is effective in patients of all ages.

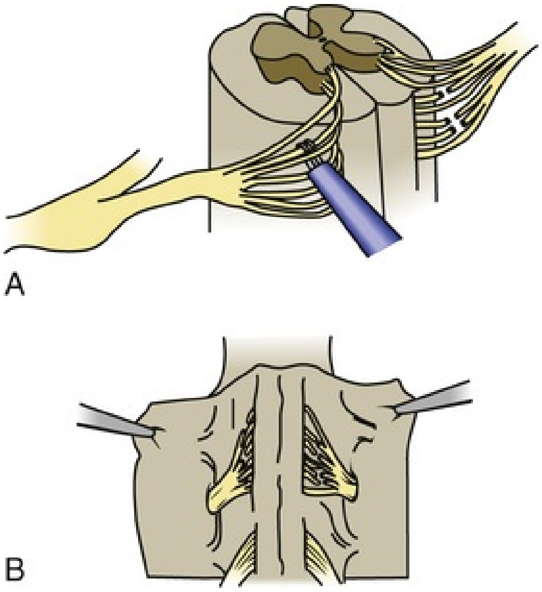

FIG. 616.3 Schematic of the technique of selective dorsal rhizotomy. **A,** After laminectomy, the dura is opened and the dorsal spinal rootlets are exposed. The rootlets are stimulated so that abnormal rootlet activity can be identified. **B,** A proportion of rootlets are transected. (From Koman LA, Smith BP, Shilt JS: Cerebral palsy, Lancet 363:1619-1631, 2004. Reproduced with permission from Wake Forest University Orthopaedic Press.)

Several drugs have been used to treat spasticity, including the benzodiazepines and baclofen. These medications have beneficial effects in some patients but can also cause side effects such as sedation for benzodiazepines and lowered seizure threshold for baclofen. Several drugs can be used to treat spasticity, including oral diazepam (0.01-0.3 mg/kg/day, divided bid or qid), baclofen (0.2-2 mg/kg/day, divided bid or tid), or dantrolene (0.5-10 mg/kg/day, bid). Small doses of levodopa (0.5-2 mg/kg/day) can be used to treat dystonia or DOPA-responsive dystonia. Artane (trihexyphenidyl, 0.25 mg/day, divided bid or tid and titrated upward) is sometimes useful for treating dystonia and can increase the use of the upper extremities and vocalizations. Reserpine (0.01-0.02 mg/kg/day, divided bid to a maximum of 0.25 mg daily) or tetrabenazine (12.5-25.0 mg, divided bid or tid) can be useful for hyperkinetic movement disorders, including athetosis or chorea.

Intrathecal baclofen delivered with an implanted pump has been used successfully in many children with severe spasticity, and can be useful because it delivers the drug directly around the spinal cord where it reduces neurotransmission of afferent nerve fibers. Direct delivery to the spinal cord overcomes the problem of CNS side effects caused by the large oral doses needed to penetrate the blood–brain barrier. This therapy requires a team approach and constant follow-up for complications of the infusion pumping mechanism and infection.

Botulinum toxin injected into specific muscle groups for the management of spasticity shows a very positive response in many patients. Botulinum toxin injected into salivary glands may also help reduce the severity of drooling, which is seen in 10–30% of patients with CP and has been traditionally treated with anticholinergic agents. Patients with rigidity, dystonia, and spastic quadriparesis sometimes respond to levodopa, and children with dystonia may benefit from carbamazepine or trihexyphenidyl. **Deep brain stimulation** has been used in selected refractory patients. Hyperbaric oxygen has not been shown to improve the condition of children with CP.

Communication skills may be enhanced by the use of Bliss symbols, talking typewriters, electronic speech–generating devices, and specially adapted computers, including artificial intelligence computers to augment motor and language function. Significant behavior problems may substantially interfere with the development of a child with CP; their early identification and management are important, and the assistance of a psychologist or psychiatrist may be necessary. Learning and attention deficit disorders and mental retardation are assessed and managed by a psychologist and educator. Strabismus, nystagmus, and optic atrophy are common in children with CP; an ophthalmologist should be included in the initial assessment and ongoing treatment. Lower urinary tract dysfunction should receive prompt assessment and treatment.

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616.2

Mitochondrial Encephalomyopathies

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See Chapters 105.4 and 629.4 .

Mitochondrial encephalomyopathies are a heterogeneous group of clinical syndromes caused by genetic lesions that impair energy production through oxidative phosphorylation and mitochondrial function. The signs and symptoms of these disorders reflect the vulnerability of the nervous system, muscles, and other organs to energy deficiency. Signs of brain and muscle dysfunction (seizures, weakness, ptosis, external ophthalmoplegia, psychomotor regression, hearing loss, movement disorders, and ataxia) in association with lactic acidosis are prominent features of mitochondrial disorders. Cardiomyopathy and diabetes mellitus can also result from mitochondrial disorders.

Children with mitochondrial disorders often have multifocal signs that are intermittent or relapsing–remitting, often in association with intercurrent illness. Many of these disorders were described as clinical syndromes before their genetics were understood. Children with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) present with developmental delay, weakness, and headaches, as well as focal signs that suggest a stroke. Brain imaging indicates that injury does not fit within the usual vascular territories. Children with myoclonic epilepsy with ragged red fibers (MERRF) present with myoclonus and myoclonic seizures as well as intermittent muscle weakness. The ragged red fibers referred to in the name of this disorder are clumps of abnormal mitochondria seen within muscle fibers in sections from a muscle biopsy stained with Gomori trichrome stain. NARP syndrome (neuropathy, ataxia, and retinitis pigmentosa), Kearns-Sayre syndrome (KSS; ptosis, ophthalmoplegia, heart block), Leigh disease (subacute necrotizing encephalomyelopathy), and Leber hereditary optic neuropathy (LHON) are also defined as relatively homogeneous clinical subgroups, although the age of presentation/diagnosis can vary (Table 616.4). It is important to keep in mind that mitochondrial disorders can be difficult to diagnose. They often present with novel combinations of signs and symptoms as a consequence of high mutation rates for mitochondrial DNA (mtDNA), and the severity of disease varies from person to person. Nuclear gene mutations (over 400 possible genes) are more common in the childhood disorders, but mitochondrial gene abnormalities are also seen.

Table 616.4

Clinical Manifestations of Mitochondrial Encephalomyopathies

TISSUE	SYMPTOMS/SIGNS	MELAS	MERRF	NARP	KSS	LEIGH	LHON
CNS	Regression	+	+		+	+	
	Seizures	+	+				

	Ataxia	+	+	+	+		
	Cortical blindness	+					
	Deafness	+		+			
	Migraine	+					
	Hemiparesis	+					
	Myoclonus	+	+				
	Movement disorder	+					+
Nerve	Peripheral neuropathy	+	+	+	+		
Muscle	Ophthalmoplegia				+		
	Weakness	+	+	+	+	+	
	RRF on muscle biopsy	+	+		+		
	Ptosis				+		
Eye	Pigmentary retinopathy			+	+		
	Optic atrophy				+	+	+
	Cataracts						
Heart	Conduction block				+		+
	Cardiomyopathy				+		
Blood	Anemia	+					
	Lactic acidosis		+		+	+	
Endocrine	Diabetes mellitus				+		
	Short stature	+	+		+		
Kidney	Fanconi syndrome	+	+		+		

KSS, Kearns-Sayre syndrome; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NARP, neuropathy, ataxia, and retinitis pigmentosa; RRF, ragged red fibers.

Mitochondrial diseases can be caused by mutations of nuclear DNA (nDNA) or mtDNA (see Chapters 97 , 104 , and 105). Oxidative phosphorylation in the respiratory chain is mediated by four intramitochondrial enzyme complexes (complexes I-IV) and two mobile electron carriers (coenzyme Q and cytochrome c) that create an electrochemical proton gradient utilized by complex V (adenosine triphosphate [ATP] synthase) to create the ATP required for normal cellular function. The maintenance of oxidative phosphorylation requires coordinated regulation of nuclear DNA and mtDNA genes. Human mtDNA is a small (16.6 kb), circular, double-stranded molecule that has been completely sequenced and encodes 37 genes including 13 structural proteins, all of which are subunits of the respiratory chain complexes, as well as 2 ribosomal RNAs and 22 transfer RNAs (tRNAs) needed for translation. The nuclear DNA is responsible for synthesizing approximately 70 subunits, transporting them to the mitochondria via chaperone proteins, ensuring their passage across the inner mitochondrial membrane, and coordinating their correct processing and assembly. Diseases of mitochondrial oxidative phosphorylation can be divided into three groups: (1) defects of mtDNA, (2) defects of nDNA, and (3) defects of communication between the nuclear and mitochondrial genome. mtDNA is distinct from nDNA for the following five reasons: (1) its genetic code differs from nDNA, (2) it is tightly packed with information because it contains no introns, (3) it is subject to spontaneous mutations at a higher rate than nDNA, (4) it has less efficient repair mechanisms, (5) it is maternally inherited.

Inheritance of mutations present on mtDNA is nonmendelian and can be complex. At fertilization, mtDNA is present in hundreds or thousands of copies per cell and is transmitted by maternal inheritance from her oocyte to all her children, but only her daughters can pass it on to their children. Through the process called heteroplasmy or threshold effect, mtDNA-containing mutations can be distributed unequally between cells in specific tissues. Some cells receive few or no mutant genomes **(normal** or **wild-type homoplasmy),** whereas others receive a mixed population of **mutant** and **wild-type** mtDNAs **(heteroplasmy),** and still others receive primarily or exclusively **mutant** genomes **(mutant homoplasmy).** The important implications of maternal inheritance and heteroplasmy are as follows: (1) inheritance of the disease is maternal, but both sexes are equally affected; (2) phenotypic expression of an mtDNA mutation depends on the relative proportions of mutant and wild-type genomes, with a minimum critical number of mutant genomes being necessary for disease expression **(threshold effect);** (3) at cell division, the proportional distribution may shift between daughter cells (mitotic segregation), leading to a corresponding phenotypic change; and (4) subsequent generations are affected at a higher rate than in autosomal dominant diseases. The critical number of mutant mtDNAs required for the threshold effect may vary, depending on the vulnerability of the tissue to impairments of oxidative metabolism as well as on the vulnerability of the same tissue over time that may increase with aging. In contrast to maternally inherited disorders caused by mutations in mtDNA, diseases resulting from defects in nDNA follow mendelian inheritance. Mitochondrial diseases caused by defects in nDNA include defects in substrate transport (plasmalemmal carnitine transporter, carnitine palmitoyltransferases I and II, carnitine acylcarnitine translocase defects), defects in substrate oxidation (pyruvate dehydrogenase complex, pyruvate carboxylase, intramitochondrial fatty acid oxidation defects), defects in the Krebs cycle (α-ketoglutarate dehydrogenase, fumarase, aconitase defects), and defects in the respiratory chain (complexes I-V), including defects of oxidation/phosphorylation coupling (Luft syndrome) and defects in mitochondrial protein transport.

Diseases caused by defects in mtDNA can be divided into those associated with point mutations that are maternally inherited (e.g., LHON, MELAS, MERRF, and NARP/mtLeigh syndromes) and those caused by deletions or duplications of mtDNA that reflect altered communication between the nucleus and the mitochondria (KSS; Pearson syndrome, a rare severe encephalopathy with anemia and pancreatic dysfunction; and progressive external ophthalmoplegia). These disorders can be inherited by sporadic, autosomal dominant or recessive mechanisms, and mutations in multiple genes, including mitochondrial mtDNA polymerase γ catalytic subunit (POLG), have been identified. **POLG mutations** have also been identified in patients with Alpers-Huttenlocher syndrome, which causes a refractory seizure disorder and hepatic failure as well as autosomal dominant and recessive progressive external ophthalmoplegia, childhood myocerebrohepatopathy spectrum disorders, myoclonic epilepsy myopathy sensory ataxia syndrome, and *POLG* -related ataxia neuropathy spectrum disorders. Other genes that regulate the supply of nucleotides for mtDNA synthesis are associated with severe encephalopathy and liver disease, and new disorders are being identified that result from defects in the interactions between mitochondria and their milieu in the cell.

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-Like Episodes

Children with MELAS may be normal for the first several years, but they gradually display delayed motor and cognitive development and short stature. The clinical syndrome is characterized by (1) recurrent stroke-like episodes of hemiparesis or other focal neurologic signs with lesions most commonly seen in the posterior temporal, parietal, and occipital lobes based on cranial CT or MRI evidence of focal brain abnormalities); (2) lactic acidosis or ragged red fibers (RRF), or both; and (3) at least two of the following: focal or generalized seizures, dementia, recurrent migraine headaches, and vomiting. In one series, the onset was before age 15 yr in 62% of patients, and hemianopia or cortical blindness was the most common manifestation. Cerebrospinal fluid protein is often increased. The MELAS 3243 mutation on mtDNA is the most common mutation to produce MELAS and can also be associated with different combinations of exercise intolerance, myopathy, ophthalmoplegia, pigmentary retinopathy, hypertrophic or dilated cardiomyopathy, cardiac conduction defects, deafness, endocrinopathy (diabetes mellitus), and proximal renal tubular dysfunction. A number of other mutations have been reported, and two patients have been described with bilateral rolandic lesions and epilepsia partialis continua associated with mtDNA mutations at 10158T>C and 10191T>C. MELAS is a progressive disorder that has been reported in siblings. However, most maternal relatives of MELAS patients are mildly affected or unaffected. MELAS is punctuated with episodes of stroke leading to dementia (see Chapter 629.4).

Regional cerebral hypoperfusion can be detected by single-photon emission CT studies and MR spectroscopy can detect focal areas of lactic acidosis in the brain. Neuropathology may show cortical atrophy with infarct-like lesions in both cortical and subcortical structures, basal ganglia calcifications, and ventricular dilation. Muscle biopsy specimens usually show ragged red fibers (RRFs). Mitochondrial accumulations and abnormalities have been shown in smooth muscle cells of intramuscular vessels and of brain arterioles and in the epithelial cells and blood vessels of the choroid plexus, producing a mitochondrial angiopathy. Muscle biochemistry shows complex I deficiency in many cases; however, multiple defects have also been documented involving complexes I, III, and IV. Targeted molecular testing for specific mutations or sequence analysis and mutation scanning are generally used to make a diagnosis of MELAS when clinical evaluation suggests the diagnosis. Because the number of mutant genomes is lower in blood than in muscle, muscle is the preferable tissue for examination. Inheritance is maternal, and there is a highly specific, although not exclusive, point mutation at nt 3243 in the $tRNA^{Leu(UUR)}$ gene of mtDNA in approximately 80% of patients. An additional 7.5% have a point mutation at nt 3271 in the $tRNA^{Leu(UUR)}$ gene. A third mutation has been identified at nt 3252 in the $tRNA^{Leu(UUR)}$ gene. The prognosis in patients with the full syndrome is poor. Therapeutic trials reporting some benefit have included corticosteroids, coenzyme Q10, nicotinamide, carnitine, creatine, riboflavin, and various combinations of these; L -arginine and preclinical studies reported some success with resveratrol and also with a new agent, EPI-743, a coenzyme Q10 analogue compound.

Myoclonic Epilepsy and Ragged Red Fibers

MERRF syndrome is characterized by progressive myoclonic epilepsy, mitochondrial myopathy, and cerebellar ataxia with dysarthria and nystagmus. Onset may be in childhood or in adult life, and the course may be slowly progressive or rapidly downhill. Other features include dementia, sensorineural hearing loss, optic atrophy, peripheral neuropathy, and spasticity. Because some patients have abnormalities of deep sensation and pes cavus, the condition may be confused with Friedreich ataxia. A significant number of patients have a positive family history and short stature. This condition is maternally inherited.

Pathologic findings include elevated serum lactate concentrations, RRF on muscle biopsy, and marked neuronal loss and gliosis affecting, in particular, the dentate nucleus and inferior olivary complex with some dropout of Purkinje cells and neurons of the red nucleus. Pallor of the posterior columns of the spinal cord and degeneration of the gracile and cuneate nuclei occur. Muscle biochemistry has shown variable defects of complex III, complexes II and IV, complexes I and IV, or complex IV alone. More than 80% of cases are caused by a heteroplasmic G to A point mutation at nt 8344 of the $tRNA^{Lys}$ gene of mtDNA. Additional patients have been reported with a T to C mutation at nt 8356 in the $tRNA^{Lys}$ gene. Targeted mutation analysis or mutation analysis after sequencing of the mitochondrial genome is used to diagnose MERRF.

There is no specific therapy, although coenzyme Q10 appeared to be beneficial in a mother and daughter with the MERRF mutation. The anticonvulsant levetiracetam is reported to help reduce myoclonus and myoclonic seizures in this disorder.

Neuropathy, Ataxia, and Retinitis Pigmentosa (NARP) Syndrome

This maternally inherited disorder presents with either Leigh syndrome or with neurogenic weakness and NARP syndrome, as well as seizures. It is caused by a point mutation at nt 8993 within the ATPase subunit 6 gene. The severity of the disease presentation appears to have close correlation with the percentage of mutant mtDNA in leukocytes. Two clinical patterns are seen in patients with NARP syndrome: (1) neuropathy, ataxia, retinitis pigmentosa, dementia, and ataxia, and (2) severe infantile encephalopathy resembling Leigh syndrome with lesions in the basal ganglia on MRI.

Leber Hereditary Optic Neuropathy (LHON)

LHON is characterized by onset usually between the ages of 18 and 30 yr of acute or subacute visual loss caused by severe bilateral optic atrophy, although children as young as 5 yr have been reported to have LHON. Three mtDNA mutations account for most cases of LHON and at least 85% of patients are young men. An X-linked factor may modulate the expression of the mtDNA point mutation. The classic ophthalmologic features include circumpapillary telangiectatic microangiopathy and pseudoedema of the optic disc. Variable features may include cerebellar ataxia, hyperreflexia, Babinski sign, psychiatric symptoms, peripheral neuropathy, or cardiac conduction abnormalities (preexcitation syndrome). Some cases are associated with widespread white matter lesions as seen with multiple sclerosis. Lactic acidosis and RRF tend to be conspicuously absent in LHON. More than 11 mtDNA point mutations have been described, including a usually homoplasmic G to A transition at nt 11,778 of the ND4 subunit gene of complex I. The latter mutation leads to replacement of a highly conserved arginine residue by histidine at the 340th amino acid and accounts for 50–70% of cases in Europe and more than 90% of cases in Japan. Certain LHON pedigrees with other point mutations are associated with complex neurologic disorders and may have features in common with MELAS syndrome and with infantile bilateral striatal necrosis. One family has been reported with pediatric onset of progressive generalized dystonia with bilateral striatal necrosis associated with a homoplasmic G14459A mutation in the mtDNA *ND6* gene, which is also associated with LHON alone and LHON with dystonia. Idebenone and EPI-743 have been studied for treatment of this disorder.

Kearns-Sayre Syndrome (KSS)

KSS is a characteristic multiorgan disorder involving external ophthalmoplegia, heart block, and retinitis pigmentosa with onset before age 20 yr caused by single deletions in mtDNA. There must also be at least one of the following: heart block, cerebellar syndrome, or cerebrospinal fluid protein > 100 mg/dL. Other nonspecific but common features include dementia, sensorineural hearing loss, and multiple endocrine abnormalities, including short stature, diabetes mellitus, and hypoparathyroidism. The prognosis is guarded, despite placement of a pacemaker, and progressively downhill, with death resulting by the 3rd or 4th decade. Unusual clinical presentations can include renal tubular acidosis and Lowe syndrome. There are also a few overlap cases of children with KSS and stroke-like episodes. Muscle biopsy shows RRF and variable cytochrome c oxidase (COX)-negative fibers. Most patients have mtDNA deletions, and some have duplications. These may be new mutations accounting for the generally sporadic nature of KSS. A few pedigrees have shown autosomal dominant transmission. Patients should be monitored closely for endocrine abnormalities, which can be treated. Coenzyme Q10 is reported anecdotally to have some beneficial effect; a positive effect of folinic acid for low folate levels has been reported. A report of positive effects of a cochlear implant for deafness is also reported.

Sporadic progressive external ophthalmoplegia with ragged red fibers is a clinically benign condition characterized by adolescent or young adult–onset ophthalmoplegia, ptosis, and proximal limb girdle weakness. It is slowly progressive and compatible with a relatively normal life. The muscle biopsy material demonstrates RRF and COX-negative fibers. Approximately 50% of patients with progressive external ophthalmoplegia have mtDNA deletions, and there is no family history.

Reversible Infantile Cytochrome C Oxidase Deficiency Myopathy

Mutations in mtDNA are also responsible for a reversible form of severe neuromuscular weakness and hypotonia in infants that is the result of a maternally inherited homoplasmic m.14674T>C mt-tRNA^{Glu} mutation associated with a deficiency of COX. Affected children present within the first few weeks of life with hypotonia, severe muscle weakness, and very elevated serum lactate levels, and they often require mechanical ventilation. However, feeding and psychomotor development are not affected. Muscle biopsies taken from these children in the neonatal period show RRF and deficient COX activity, but these findings disappeared within 5-20 mo when the infants recovered spontaneously. It is difficult to distinguish these infants from those with lethal mitochondrial disorders without waiting for them to improve. The mechanism for this recovery is not established, but it may reflect a developmental switch in mitochondrial RNAs later in infancy. This reversible disorder is observed only in

COX deficiency associated with the 14674T>C mt-tRNA^{Glu} mutation, so it is suggested that infants with this type of severe weakness in the neonatal period be tested for this mutation to help with prognosis.

Leigh Disease (Subacute Necrotizing Encephalomyopathy)

Leigh disease is a progressive degenerative disorder presenting in infancy with feeding and swallowing problems, vomiting, and failure to thrive associated with lactic acidosis and lesions seen in the brainstem and/or basal ganglia on MRI (Table 616.5). There are several genetically determined causes of Leigh disease that result from nuclear DNA mutations in genes that code for components of the respiratory chain: pyruvate dehydrogenase complex deficiency, complex I or II deficiency, complex IV (COX) deficiency, complex V (ATPase) deficiency, and deficiency of coenzyme Q10. These defects may occur sporadically or be inherited by autosomal recessive transmission, as in the case of COX deficiency; by X-linked transmission, as in the case of pyruvate dehydrogenase E_1 α deficiency; or by maternal transmission, as in complex V (ATPase 6 nt 8993 mutation) deficiency. Approximately 30% of cases are caused by mutations in mtDNA. Delayed motor and language milestones may be evident, and generalized seizures, weakness, hypotonia, ataxia, tremor, pyramidal signs, and nystagmus are prominent findings. Intermittent respirations with associated sighing or sobbing are characteristic and suggest brainstem dysfunction. Some patients have external ophthalmoplegia, ptosis, retinitis pigmentosa, optic atrophy, and decreased visual acuity. Abnormal results on CT or MRI scan consist of bilaterally symmetric areas of low attenuation in the basal ganglia and brainstem as well as elevated lactic acid on MR spectroscopy (Fig. 616.4). Pathologic changes consist of focal symmetric areas of necrosis in the thalamus, basal ganglia, tegmental gray matter, periventricular and periaqueductal regions of the brainstem, and posterior columns of the spinal cord. Microscopically, these spongiform lesions show cystic cavitation with neuronal loss, demyelination, and vascular proliferation. Elevations in serum and CSF lactate levels are characteristic, and hypertrophic cardiomyopathy, hepatic failure, and rental tubular dysfunction can occur. The overall outlook is poor, but a few patients experience prolonged periods of remission. There is no definitive treatment for the underlying disorder, but a range of vitamins, including riboflavin, thiamine, and coenzyme Q10, are often given to try to improve mitochondrial function. Biotin, creatine, succinate, idebenone, and EPI-743, as well as a high-fat diet, have also been used. Phenobarbital and valproic acid should be avoided because of their inhibitory effect on the mitochondrial respiratory chain.

Table 616.5

Clinical Features of Congenital Leigh Syndrome or Leigh-like Syndrome

NEUROLOGIC MANIFESTATIONS
Brainstem
Bradypnea, hypopnea, episodes of apnea Bradycardia Tetraparesis Hypotonia (floppy infant) Failure to thrive, poor sucking Swallowing difficulties, dysphagia, poor feeding, poor sucking Vomiting Spasticity, brisk tendon reflexes Dysphasia, dysarthria Squint Absence of optic or acoustic blink
Other Cerebral Manifestations
Stroke-like episodes Delay of developmental milestones Paralysis of vertical gaze Myoclonic jerks of limbs or eyelids Hypothermia Drowsiness, dizziness Psychomotor (mental) retardation Ataxia, tremor Seizures, convulsions Growth retardation Dystonia Clumsiness, dullness Nystagmus, uncoordinated eye movement, slow saccades Optic atrophy Visual loss Facial dyskinesia Ocular apraxia Drooling Gaze fixation difficulty
Peripheral Nervous System Manifestations
Cranial nerve palsies Generalized wasting Bilateral ptosis Chronic progressive external ophthalmoplegia, strabismus

Reduced tendon reflexes
Polyneuropathy
Muscle weakness
Myopathy
NONNEUROLOGIC MANIFESTATIONS
Dysmorphic Features
Lip cleft
Short distal phalanges
Single palmar crease
Rostral vertebrae
Round face
Frontal bossing
Flat nasal root
Microcephaly
Thin lips
Small chin
Long, featureless philtrum
Hypospadia
Others
Inguinal hernia
Stiff neck
Retinal dystrophy, retinopathy
Deafness, hypoacusis
Hypertrophic, dilated cardiomyopathy
Pancreatitis
Diarrhea
Urinary excretion of Krebs-cycle intermediates
Intrauterine growth restriction
Hypertrichosis
Villous atrophy
Nephrotic syndrome
Nephropathy
Hyperhidrosis
Scoliosis

From Finsterer J: Leigh and Leigh-like syndrome in children and adults, Pediatr Neurol 39:223-235, 2008, Table 1.

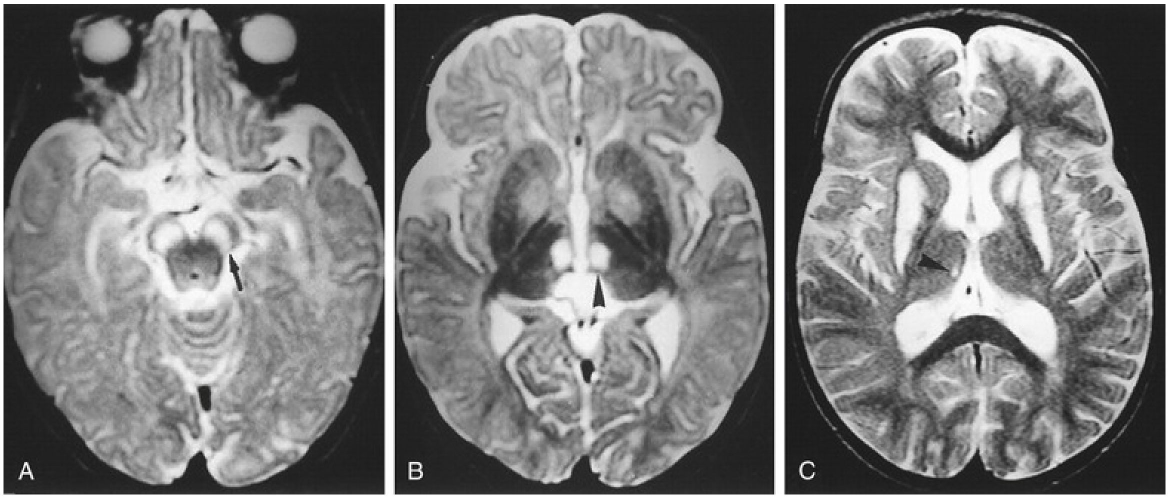

FIG. 616.4 Leigh syndrome. Axial T2-weighted MRIs (TR/TE/NEX = 3,000/120/1 msec) of 8 mo old girl with Leigh syndrome because of a *SURF1* mutation indicate hyperintense lesions in the substantia nigra and medial thalamic nuclei **(A, B).** Follow-up images (TR/TE/NEX = 2,028/120/2 msec) at age 26 mo **(C)** indicate hyperintense putamina and hyperintense left caudate nucleus. (From Farina L, Chiapparini L, Uziel G, et al: MR findings in Leigh syndrome with COX deficiency and SURF-1 mutations, AJNR Am J Neuroradiol 23:1095-1100, 2002, Fig. 2.)

Mitochondrial DNA Depletion Syndrome

Mitochondrial DNA depletion syndrome is a group of autosomal recessive disorders that cause a significant drop in mitochondrial DNA in muscle, the liver, and the brain (Table 616.6). The condition is usually fatal in infancy, although some children have survived into the teenage years.

Table 616.6

Manifestations of Mitochondrial DNA Depletion Syndrome

MUTATED GENE	SYNDROME	CLINICAL MANIFESTATIONS	mtDNA DEPLETION	MULTIPLE DELETIONS
POLG1	HC, AHS	Brain, liver	x	x
DGUOK	HC	Brain, liver	x	x
TK2	M	Muscle	x	x
MPV17	HC	Cerebrum, liver	x	x
TYMP	MNGIE	Nerve, muscle, GI, brain	x	x
SUCLA2	EM	Brain, muscle	x	
SUCLG1	EM	Brain, muscle	x	
RRM2B	M	Muscle	x	x

PEO1 /twinkle	HC, IOSCA, MIRAS	Brain, liver	x	x

AHS, Alpers-Huttenlocher syndrome; EM, encephalomyopathic form; GI, gastrointestinal; HC, hepatocerebral form; IOSCA, infantile-onset spinocerebellar ataxia; M, myopathic form; MIRAS, mitochondrial recessive ataxia syndrome; MNGIE, mitochondrial neurogastrointestinal encephalopathy.

From Finsterer J, Ahting U: Mitochondrial depletion syndromes in children and adults, Can J Neurol Sci 40:635-644, 2013, Table 2.

Reye Syndrome

This encephalopathy, which has become uncommon, is associated with pathologic features characterized by fatty degeneration of the viscera (microvesicular steatosis) and mitochondrial abnormalities and biochemical features consistent with a disturbance of mitochondrial metabolism (see Chapter 388).

Recurrent Reye-like syndrome is encountered in children with genetic defects of fatty acid oxidation, such as deficiencies of the plasmalemmal carnitine transporter, carnitine palmitoyltransferases I and II, carnitine acylcarnitine translocase, medium- and long-chain acyl-coenzyme A dehydrogenase, multiple acyl-coenzyme A dehydrogenase, and long-chain L-3 hydroxyacyl-coenzyme A dehydrogenase or trifunctional protein. These disorders are manifested by recurrent hypoglycemic and hypoketotic encephalopathy, and they are inherited in an autosomal recessive pattern. Other potential inborn errors of metabolism presenting with Reye syndrome include urea cycle defects (ornithine transcarbamylase, carbamyl phosphate synthetase) and certain of the organic acidurias (glutaric aciduria type I), respiratory chain defects, and defects of carbohydrate metabolism (fructose intolerance).

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616.3

Other Encephalopathies

Michael V. Johnston

Human Immunodeficiency Virus (HIV) Encephalopathy

Encephalopathy is an unfortunate and common manifestation in infants and children with HIV infection (see Chapter 302).

Lead Encephalopathy

See Chapter 739 .

Burn Encephalopathy

An encephalopathy develops in approximately 5% of children with significant burns in the first several weeks of hospitalization (see Chapter 92). There is no single cause of burn encephalopathy, but rather it is caused by a combination of factors that include anoxia (smoke inhalation, carbon monoxide poisoning, laryngospasm), electrolyte abnormalities, bacteremia and sepsis, cortical vein thrombosis, a concomitant head injury, cerebral edema, drug reactions, and emotional distress. Seizures are the most common clinical manifestation of burn encephalopathy, but altered states of consciousness, hallucinations, and coma may also occur. Management of burn encephalopathy is directed to a search for the underlying cause and treatment of hypoxemia, seizures, specific electrolyte abnormalities, or cerebral edema. The prognosis for complete neurologic recovery is generally excellent, particularly if seizures are the primary abnormality.

Hypertensive Encephalopathy

Hypertensive encephalopathy is most commonly associated with renal disease in children; including acute glomerulonephritis, chronic pyelonephritis, and end-stage renal disease (see Chapters 472 and 550). In some cases, hypertensive encephalopathy is the initial manifestation of underlying renal disease. Marked systemic hypertension produces vasoconstriction of the cerebral vessels, which leads to vascular permeability, causing areas of focal cerebral edema and hemorrhage. The onset may be acute, with seizures and coma, or more indolent, with headache, drowsiness and lethargy, nausea and vomiting, blurred vision, transient cortical blindness, and hemiparesis. Examination of the eyegrounds may be nondiagnostic in children, but papilledema and retinal hemorrhages may occur. MRI often shows increased signal intensity in the occipital lobes on T2-weighted images, which is known as **posterior reversible leukoencephalopathy (PRES)** and may be confused with cerebral infarctions. These high-signal areas may appear in other regions of the brain as well. PRES may also be seen in children without hypertension. In all circumstances, PRES manifests with generalized motor seizures, headache, mental status changes, and visual disturbances. CT may be normal in PRES; MRI is the study of choice. Treatment is directed at restoration of a normotensive state and control of seizures with appropriate anticonvulsants.

Radiation Encephalopathy

Acute radiation encephalopathy is most likely to develop in young patients who have received large daily doses of radiation. Excessive radiation injures vessel endothelium, resulting in enhanced vascular permeability, cerebral edema, and numerous hemorrhages. The child may suddenly become irritable and lethargic, complain of headache, or present with focal neurologic signs and seizures. Patients occasionally develop hemiparesis as the result of an infarct secondary to vascular occlusion of the cerebral vessels. Steroids are often beneficial in reducing the cerebral edema and reversing the neurologic signs. Late-radiation encephalopathy is characterized by headaches and slowly progressive focal neurologic signs, including hemiparesis and seizures. Exposure of the brain to radiation for treatment of childhood cancer increases the risk of later cerebrovascular disease, including stroke, moyamoya disease, aneurysm, vascular malformations, mineralizing microangiopathy, and stroke-like migraines. Some children with acute lymphocytic leukemia treated with a combination of intrathecal methotrexate and cranial irradiation develop neurologic signs months or years later; signs consist of increasing lethargy, loss of cognitive abilities, dementia, and focal neurologic signs and seizures (see Chapter 521). The CT scan shows calcifications in the white matter, and the postmortem examination demonstrates a necrotizing encephalopathy. This devastating complication of the treatment of leukemia has prompted reevaluation and reduction in the use of cranial radiation in the treatment of these children.

Acute Necrotizing Encephalopathy

Acute necrotizing encephalopathy (ANE) is a rare, severe encephalopathy seen more commonly in Asian countries. It is thought to be triggered by a viral infection (influenza, HHV-6) in a genetically susceptible host. Table 616.7 lists the diagnostic criteria. The elevation of hepatic enzymes without hyperammonemia is a unique feature. A familial or recurrent form is associated with mutations in the *RANBP2* gene and is designated ANE1. MRI findings are characterized by symmetric lesions that must be present in the thalami (Fig. 616.5). The prognosis is usually poor; however, some patients have responded to steroids and intravenous immunoglobulin (IVIG).

Table 616.7

Diagnostic Criteria for Acute Necrotizing Encephalopathy of Childhood

1. Acute encephalopathy following (1-3 days) a febrile disease. Rapid deterioration in the level of consciousness. Seizures.
2. No cerebrospinal fluid pleocytosis. Increase in cerebrospinal fluid protein
3. CT or MRI evidence of symmetric, multifocal brain lesions. Involvement of the bilateral thalami. Lesions also common in the cerebral periventricular white matter, internal capsule, putamen, upper brainstem tegmentum, and cerebellar medulla. No involvement of other central nervous system regions
4. Elevation of serum aminotransferases of variable degrees. No increase in blood ammonia
5. Exclusion of resembling diseases
    A. Differential diagnosis from clinical viewpoints.
    Overwhelming bacterial and viral infections, and fulminant hepatitis; toxic shock, hemolytic-uremic syndrome, and other toxin-induced diseases; Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke
    B. Differential diagnosis from radiologic viewpoints.
    Leigh encephalopathy and related mitochondrial cytopathies; glutaric acidemia, methylmalonic acidemia, and infantile bilateral striatal necrosis; Wernicke encephalopathy and carbon monoxide poisoning; acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, other types of encephalitis, and vasculitis; arterial or venous infection, and the effects of severe hypoxia or head trauma

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Modified from Hoshino A, Saitoh M, Oka, et al: Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes, Brain Dev 34:337-343, 2012, Table 1.

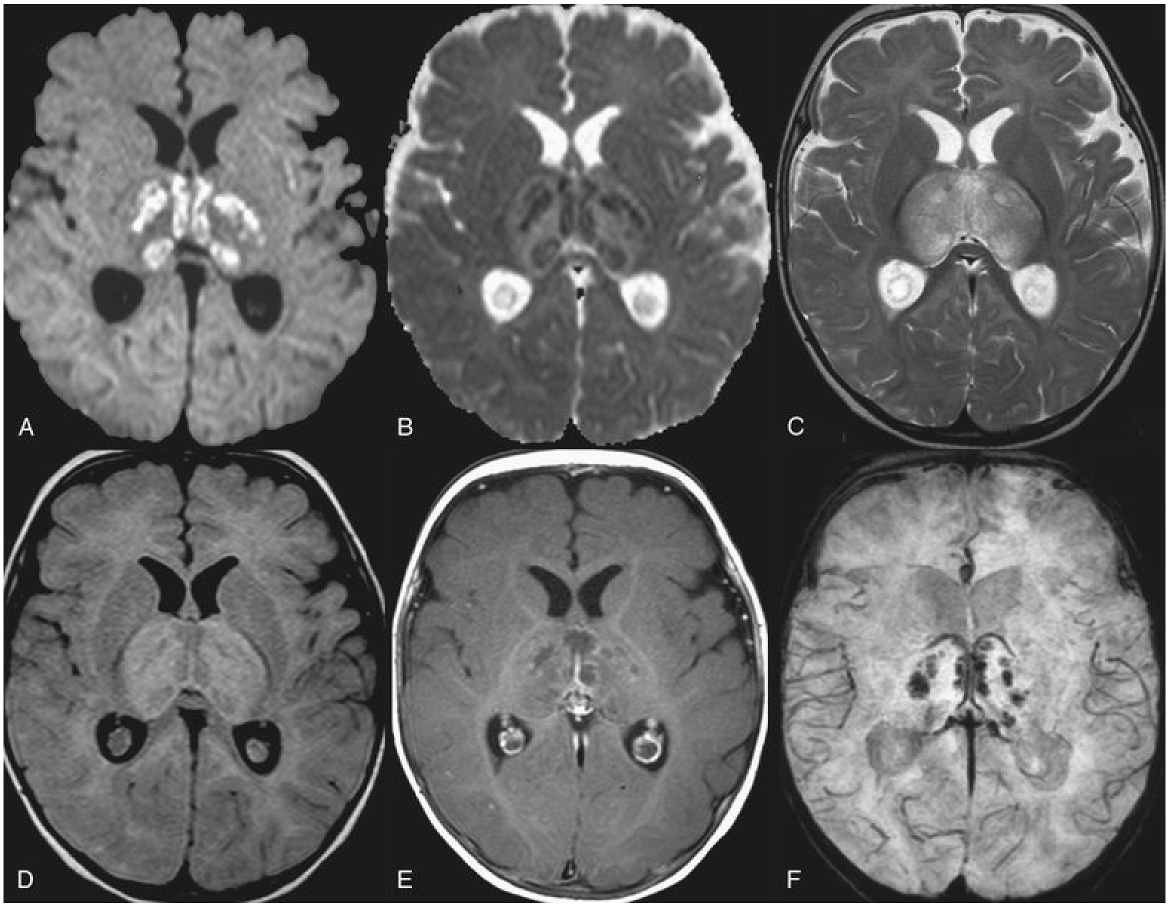

FIG. 616.5 Acute necrotizing encephalopathy. MRI at presentation. **A,** Axial diffusion-weighted image; **B,** axial apparent diffusion coefficient (ADC) map; **C,** axial T2-weighted image; **D,** axial fluid-attenuated inversion recovery (FLAIR) image; **E,** contrast-enhanced axial T1-weighted image; **F,** axial susceptibility weighted image. Diffusion-weighted images **(A)** and corresponding ADC map **(B)** clearly show multiple areas of restricted diffusion against a background of increased diffusion involving both thalami, which are swollen. On T2-weighted **(C)** and FLAIR **(D)** images, the thalami are markedly swollen and hyperintense. On T1-weighted images obtained after intravenous gadolinium chelate injection **(E),** multiple necrotic portions are well delineated by peripheral faint, linear enhancement. Incidental choroid plexus cysts are detected. Susceptibility weighted image **(F)** shows multiple hypointense spots, consistent with petechial hemorrhage. (From Bergamino L, Capra V, Biancheri R, et al: Immunomodulatory therapy in recurrent acute necrotizing encephalopathy ANE1: is it useful? Brain Dev 34:384-391, 2012, Fig. 1.)

Cystic Leukoencephalopathy

An autosomal recessive disorder caused by mutations of RNASET2 proteins produces a brain MRI study that closely resembles congenital cytomegalovirus infection. Cystic leukoencephalopathy is manifest as a static encephalopathy without megalencephaly.

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616.4

Autoimmune Encephalitis

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Keywords

autoimmune
antibodies
encephalitis
NMDA receptor
GABAAR receptor
glutamic acid decarboxylase 65 (GAD65)
VGKC-complex
anti-NMDA receptor encephalitis
limbic encephalitis
acute disseminated encephalomyelitis (ADEM)
neuromyelitis optica spectrum disorder (NMOSD)
aquaporin 4
myelin oligodendrocyte glycoprotein (MOG)
Hashimoto encephalopathy
opsoclonus–myoclonus
Bickerstaff encephalitis

chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)
Rasmussen encephalitis
fever-induced refractory epileptic encephalopathy syndrome (FIRES)
rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD)
basal ganglia encephalitis
pseudomigraine syndrome with CSF pleocytosis
headache with neurologic deficits and CSF lymphocytosis (HaNDL)
ophthalmoplegic migraine
recurrent cranial neuralgia
progressive encephalomyelitis with rigidity and myoclonus (PERM)

Autoimmune encephalitis comprises an expanding group of clinical syndromes that can occur at all ages (<1 yr to adult) but preferentially affect younger adults and children (Table 616.8). Some of these disorders are associated with antibodies against neuronal cell surface proteins and synaptic receptors involved in synaptic transmission, plasticity, or neuronal excitability. The syndromes vary according to the associated antibody, with phenotypes that resemble those in which the function of the target antigen is pharmacologically or genetically modified.

Table 616.8

Autoimmune Encephalitis in Children

DISEASE	ANTIBODIES AND/OR MECHANISMS	SYNDROME	ANCILLARY TEST	TREATMENT/PROGNOSIS
Anti-NMDAR encephalitis	Antibodies against the GluN1 subunit of the NMDAR. In children, most cases are idiopathic. In a subgroup of patients, the disease is triggered by the presence of a tumor. In another subgroup, the disease is triggered by HSV	Psychiatric symptoms, decreased verbal output, sleep disorder (mainly insomnia), seizures, dyskinesias (orofacial, limbs), dystonia, rigidity and other abnormal movements, autonomic dysfunction, hypoventilation	EEG: almost always abnormal (epileptic and/or slow activity). In some patients it shows the pattern of extreme delta brush. Brain MRI: nonspecific abnormal findings in ~ 35% CSF: pleocytosis and/or increased	80% substantial or complete recovery after immunotherapy and tumor removal (if appropriate). About 50% of patients need second-line immunotherapies.* Relapses in ~ 15% of patients. Worse outcome when post-HSE

	encephalitis.		proteins in ~ 80%	
Encephalitis associated with GABA$_A$ R antibodies	Antibodies against α1, β3, or γ2 subunits of the GABA$_A$ R. ~40% of adults have an underlying tumor (thymoma). Children usually do not have tumor association.	Refractory seizures, epilepsia partialis continua. Patients may develop limb or orofacial dyskinesias.	EEG: almost always abnormal; frequent epileptic activity MRI: multifocal corticosubcortical FLAIR/T2 hyperintensities in 77% of patients CSF: pleocytosis and/or increased proteins	80% show moderate or good recovery after immunotherapy.
Encephalitis with mGluR5 antibodies (Ophelia syndrome)	Antibodies against mGluR5 Frequent association with Hodgkin lymphoma	Abnormal behavior, seizures, memory deficits	EEG: frequently abnormal with nonspecific findings MRI: normal or nonspecific findings CSF: frequent pleocytosis and/or increased proteins	Good recovery after tumor treatment and immunotherapy
Other autoimmune encephalitis (very infrequent in children)	Antibodies against neuronal cell surface (GABA$_B$ R, DPPX, GlyR) or intraneuronal antigens (Hu, Ma2, GAD65 amphiphysin) All these antibodies rarely associate with tumors in children.	The syndrome varies depending on the autoantibody, and the phenotypes are often different from those reported in adults. GABA$_B$ R: encephalitis, seizures, cerebellar ataxia DPPX: CNS hyperexcitability, PERM GlyR: PERM or stiff person syndrome Hu: brainstem or limbic encephalitis Ma2: encephalitis, diencephalic encephalitis (only in adults) GAD65: limbic encephalitis,	MRI: variable changes depending on the syndrome CSF: frequent pleocytosis and/or increased proteins	Disorders with antibodies against cell surface antigens are substantially more responsive to immunotherapy than those with antibodies against intracellular antigens.

		epilepsy		
ADEM	50–60% of patients with ADEM harbor MOG antibodies.	Seizures, motor deficits, ataxia, or visual dysfunction accompanied by encephalopathy	MRI with T2/FLAIR large, hazy abnormalities, with or without involvement of the deep gray matter CSF: frequent pleocytosis and/or increased proteins	In ~ 90% of patients, the disease is monophasic and shows good response to steroids. Some patients develop relapsing disease (with prolonged detection of MOG antibodies).
NMOSD	Patients can have AQP4 or MOG antibodies; some patients are seronegative.	Typical involvement of optic nerves and spinal cord Encephalopathy in the context of diencephalic or area postrema syndromes	Characteristic involvement of brain areas rich in AQP4 (periaqueductal gray matter, hypothalamus, optic nerve and central involvement of the spinal cord)	High risk of relapses and long-term disability. Requires chronic immunotherapy. Patients with MOG antibodies have better long-term outcome than those with AQP4 antibodies or seronegative cases.
Opsoclonus–myoclonus and other cerebellar–brainstem encephalitis	Most patients do not have detectable autoantibodies (a few patients have Hu antibodies). Neuroblastoma occurs in 50% of children < 2 yr old; teratoma in teenagers and young adults.	Opsoclonus often accompanied by irritability, ataxia, falling, myoclonus, tremor, and drooling	MRI: usually normal; it may show cerebellar atrophy over time. EEG: Normal CSF: may be normal or show abnormalities suggesting B-cell activation	Neuroblastoma treatment (if it applies) Partial neurologic response to immunotherapy in many young children regardless of presence or absence of neuroblastoma. (Better outcomes if aggressive immunotherapy is used.) Good response to treatment in teenagers with teratoma-associated opsoclonus
Bickerstaff encephalitis	GQ1b antibodies (~65%, nonspecific for this disorder)	Ophthalmoplegia, ataxia, and decreased level of consciousness. Frequent hyperreflexia. Patients may develop hyporeflexia and overlap with Miller-Fisher syndrome.	MRI: abnormal in ~30% (T2-signal abnormalities in the brainstem, thalamus, and cerebellum) Nerve conduction studies: abnormal in ~ 45% (predominant axonal degeneration, and less often demyelination)	Good response to steroids, IVIG, or plasma exchange
Hashimoto encephalitis	TPO antibodies[†] (nonspecific	Stroke-like symptoms, tremor, myoclonus, aphasia, seizures, ataxia, sleep	48% hypothyroidism, MRI often normal	Steroid-responsive. Partial responses are frequent.

	for this disorder)	and behavioral problems	EEG: slow activity CSF: elevated protein	
Rasmussen encephalitis	Most likely immune mediated (unclear mechanism)	Progressive refractory partial seizures, cognitive decline, focal deficits, and brain hemiatrophy	MRI: progressive unilateral hemispheric atrophy	Limited response to immunotherapy. Patients may need functional hemispherectomy
Basal ganglia encephalitis	Infrequent antibodies against D2R	Lethargy, abnormal movements, behavioral change, agitation, psychosis	MRI: Basal ganglia T2/FLAIR abnormalities, but may be normal in up to 50% CSF: frequently, elevated protein	Mostly monophasic, variable outcome. 40% complete recovery with immunotherapy.
CLIPPERS	No specific autoantibody association	Episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and occasionally spinal cord dysfunction	MRI: symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, midbrain, and, occasionally, spinal cord	Steroid-responsive but patients may require chronic steroid or other immunosuppressive therapy.
ROHHAD	Cause unknown, postulated autoimmune or genetic Frequently associated with neural crest tumors	Rapid-onset obesity, hyperphagia, abnormal behavior, autonomic dysfunction, and central hypoventilation	Brain MRI, usually normal	Symptomatic treatment. In some patients, limited response to immunotherapy

[*] Includes rituximab and cyclophosphamide.

[†] Diagnosis of exclusion, after ruling out relevant autoantibodies (e.g., NMDAR, AMPAR, among others).

AQP4, aquaporin 4; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CSF, cerebrospinal fluid; D2R, dopamine 2 receptor; DPPX, dipeptidyl-peptidase-like protein-6; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; GABAAR, γ-aminobutyric acid-A receptor; GABABR, γ-aminobutyric acid-B receptor; GAD65, glutamic acid decarboxylase 65; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; mGluR5, metabotropic glutamate receptor 5; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDAR, N-methyl-d-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorder; PERM, progressive encephalomyelitis with rigidity and myoclonus; ROHHAD, rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation; TPO, thyroid peroxidase.

Most of these disorders are severe and potentially fatal, but patients frequently respond to immunotherapy with good outcomes. Moreover, because of the broad spectrum of symptoms—including alterations of behavior, psychosis, catatonia, insomnia, memory deficits, seizures, abnormal movements, and autonomic dysregulation—patients usually require a multidisciplinary treatment approach, often in an intensive care unit.

The identification of these disorders provides a definitive diagnosis for many cases of encephalitis previously considered idiopathic, infectious, or postinfectious even though no causative agents were found. Because the etiology and pathogenic mechanisms were unknown, some of these disorders were previously defined with descriptive terms. More than half of cases under the ill-defined term encephalitis lethargica and some cases of choreoathetosis post–herpes simplex encephalitis are known to be anti–*N* -methyl-D -aspartate receptor **(NMDAR) encephalitis.**

The mechanisms that trigger the production of the antibodies are unknown. In a small subgroup of adolescent or young adult patients, the presence of a tumor that expresses the target neuronal antigen likely contributes to the triggering of the immune response. In addition, the high prevalence of prodromal viral-like symptoms has suggested that nonspecific viral infections may contribute to breaking the immune tolerance for neuronal proteins and increasing the permeability of the blood–brain barrier to antibodies. Nonetheless, in many of these diseases the blood–brain barrier appears intact, and there is evidence that the autoantibodies are synthesized within the CNS by plasma cells that form part of the local brain and meningeal inflammatory infiltrates.

Anti-*N* -Methyl-D-Aspartate Receptor Encephalitis

In this disease, the immunoglobulin G antibodies target the GluN1 subunit of the NMDA receptor. The exact frequency of this disorder is unknown, but it is considered the second most common cause of autoimmune encephalitis after acute disseminated encephalomyelitis in children and adolescents. Overall, the disease predominates in females (80%), although in patients younger than 12 yr the frequency of males is higher (40%). The resulting syndrome is highly predictable and usually evolves in stages. In teenagers and young adults, the disorder usually presents with prominent psychiatric manifestations that may include rapidly progressive anxiety, agitation, delusional thoughts, bizarre behavior, labile affect, mood disturbances (mania), catatonic features, memory deficit, language disintegration, aggression, and insomnia or other sleep disturbances. In many cases, these symptoms had been preceded by a few days of prodromal headache, fever, or viral infection–like symptoms. Patients are often misdiagnosed with new-onset psychosis or a primary psychiatric disorder. However, in a few days or weeks, additional symptoms occur, including a decreased level of consciousness, seizures (including status epilepticus), limb or oral dyskinesias, choreoathetoid movements, and autonomic instability that usually includes tachycardia, bradycardia, fluctuation of blood pressure, hypoventilation, hyperthermia, and sialorrhea. In rare instances, bradycardia and cardiac pauses occur, at times requiring the transient use of a pacemaker. The disorder also occurs in toddlers and infants (the youngest patient identified to date was 2 mo old), and although the evolution of the syndrome is similar to that of adults, young patients more frequently present with seizures and movement disorders. Because of the age of patients, the psychiatric-behavioral features may be missed. In this young age-group, behavior changes include irritability, new-onset temper tantrums, agitation, aggression, reduced speech, mutism, and autistic-like regression. Moreover, compared with adults, some children also develop cerebellar ataxia and hemiparesis; in contrast, autonomic dysfunction is usually milder and less severe in children.

Brain MRI studies are abnormal in approximately 35% of patients, usually showing nonspecific cortical and subcortical T2–fluid-attenuated inversion recovery (FLAIR) signal abnormalities, sometimes with transient cortical or meningeal enhancement; nonspecific white matter abnormalities can occur. However, if white matter changes are predominant, an overlapping syndrome should be suspected (Figs. 616.6 and 616.7). The cerebrospinal fluid (CSF) is initially abnormal in approximately 80% of patients, showing moderate lymphocytic pleocytosis and, less frequently, increased protein synthesis and oligoclonal bands. The electroencephalogram (EEG) is abnormal in virtually all patients, and it usually shows focal or diffuse slow activity in the delta and theta ranges, which does not correlate with abnormal movements. In addition, many patients develop epileptic activity, requiring video monitoring for adequate clinical management. A characteristic EEG pattern called extreme delta brush, characterized by beta–delta complexes, occurs in 30% of adults and has been described in children (Fig. 616.8).

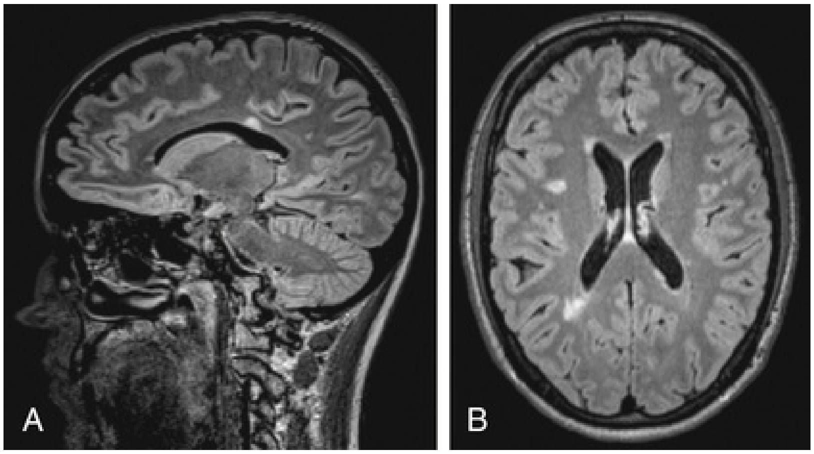

FIG. 616.6 Overlapping demyelinating syndrome in two patients with NMDAR encephalitis. **A,** FLAIR-hyperintense lesions in the corpus callosum of a 20 yr old female patient with NMDAR encephalitis, one lesion with a “Dawson finger” aspect typical of multiple sclerosis. Further demyelinating lesions were observed in the periventricular white matter, with two of the lesions showing contrast enhancement. Lesions were detected on a routine follow-up MRI; however, the patient had suffered from fatigue during the last 6 mo before the MRI. Shortly after the MRI, she developed hypoesthesia of both lower legs and bladder dysfunction. A treatment with intravenous steroids was initiated, and symptoms partially remitted. **B,** FLAIR-hyperintense lesions in the periventricular white matter of a 26 yr old female patient with NMDAR encephalitis. In total, 14 supratentorial lesions were detected, and two lesions showed contrast enhancement. MRI was performed because the patient had reported intermittent double vision. The patient was treated with intravenous steroids, and the double vision remitted. (From Heine J, Pruss H, Bartsch T, et al: Imaging of autoimmune encephalitis: relevance for clinical practice and hippocampal function. Neuroscience 309:68-83, 2015, Fig. 3.)

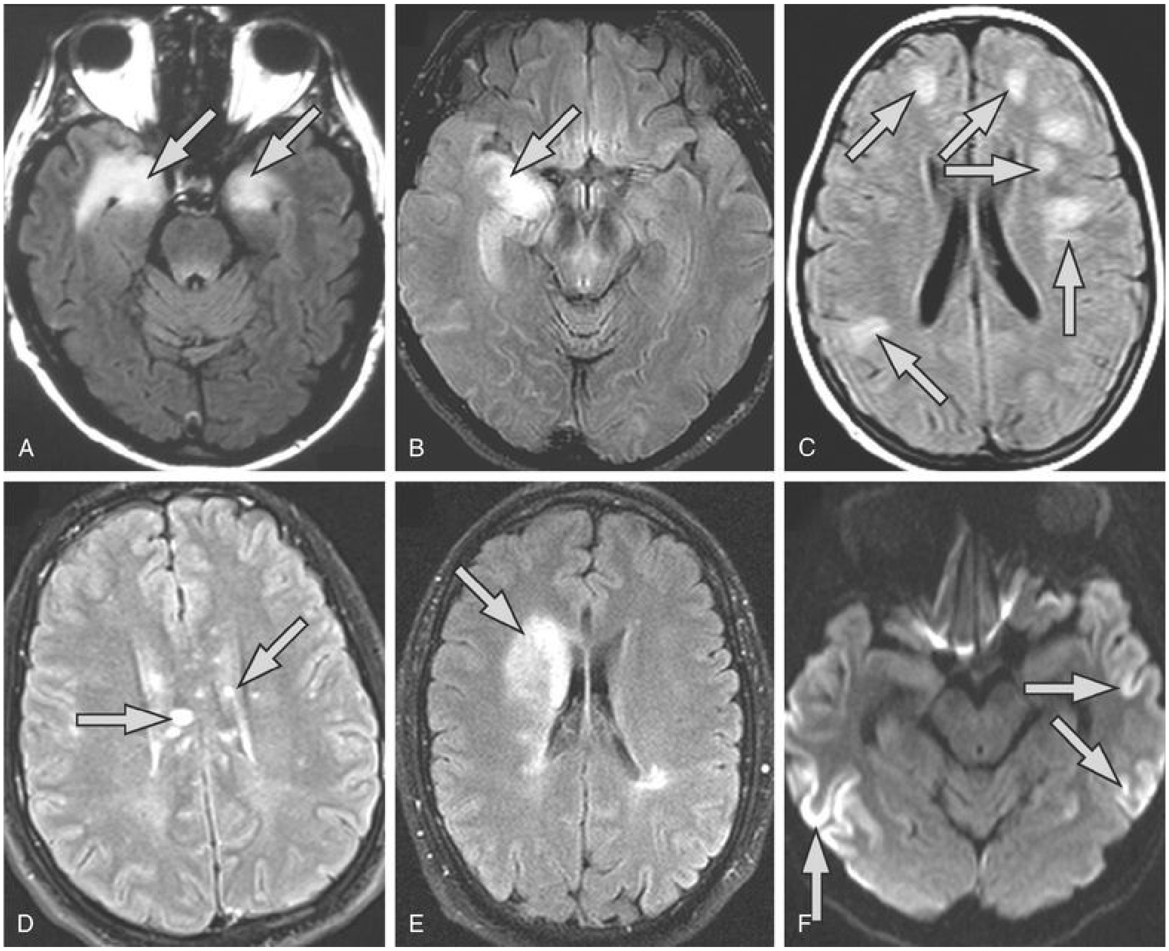

FIG. 616.7 MRI patterns in autoimmune encephalitis and its mimics. Typical MRI of limbic encephalitis **(A)** with bilateral abnormalities in the medial temporal lobe on T2-weighted fluid-attenuated inversion recovery imaging; this patient with autopsy-proven limbic encephalitis did not have serum or CSF antineuronal antibodies. Patient with final diagnosis of glioma **(B)** who presented with unilateral right hippocampal involvement mimicking limbic encephalitis. Typical MRI of acute disseminated encephalomyelitis **(C)** with bilateral large lesions in the white matter. Multiple lesions involving the corpus callosum in a patient with Susac syndrome **(D).** MRI of a patient with overlapping syndrome (NMDA receptor and myelin oligodendrocyte glycoprotein antibodies **(E)** showing a right frontal abnormality compatible with demyelination. Diffusion MRI sequence in a patient with AMPA receptor antibody-associated encephalitis **(F)** mimicking MRI changes seen in patients with Creutzfeldt-Jakob disease. Left side of images = right side of brain. (From Graus F, Titulaer MJ, Balu R, et al: A clinical approach to diagnosis of autoimmune encephalitis, Lancet Neurol 15:391-404, 2016, Fig. 2.)

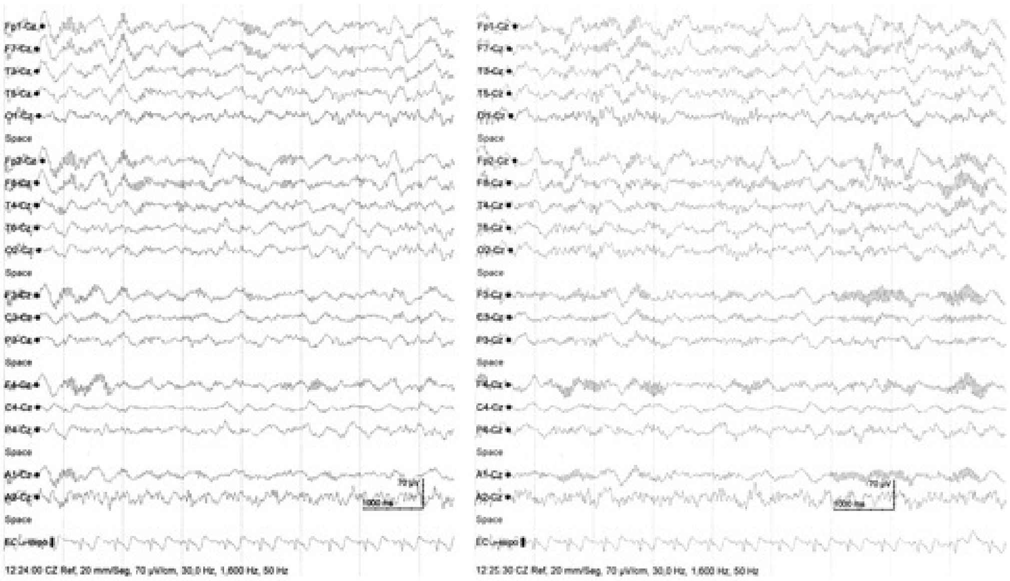

FIG. 616.8 Electroencephalogram showing a pattern called extreme delta brush in a 14 yr old girl with anti–*N* -methyl-D -aspartate receptor (NMDAR) encephalitis. This pattern has been found to be characteristic of anti-NMDAR encephalitis. It consists of a nearly continuous combination of delta activity with superimposed fast activity, usually in the beta range, symmetrically involving all regions, with a frontal preference in patients who are not under sedation or anesthesia. (From Armangue T, Titulaer MJ, Málaga I, et al: Pediatric anti-N-methyl-D-aspartate receptor encephalitis: clinical analysis and novel findings in a series of 20 patients, J Pediatr 162:850-856, 2012, Fig. 2.)

The diagnosis of the disorder is established by demonstrating NMDAR antibodies in CSF and serum. The sensitivity is higher in CSF compared with serum (100% vs 85%), and the levels of antibodies in CSF appear to correlate better with the outcome. Antibodies may remain detectable, albeit at lower titers, after patients recover.

The presence of an underlying tumor, usually a teratoma, is age and sex dependent. Whereas 40% of females older than 12 yr have an underlying teratoma of the ovary, the presence of a tumor is exceptional in young males and females or young adult male patients. In children, an MRI of the abdomen and pelvis and abdominal and testicular ultrasound are the preferred tumor screening tests.

In a small number of patients, anti-NMDAR encephalitis occurs simultaneously with or after infections with a variety of pathogens, including *Mycoplasma pneumoniae,* herpes simplex virus 1 (HSV1), human herpes virus 6, enterovirus, and influenza virus. With the exception of HSV1, a pathogenic link with most of these infections has not been established. There is evidence that some patients with HSV encephalitis develop antibodies against the GluN1 subunit of the NMDAR and other neuronal cell surface proteins and receptors, which leads to the presentation of new or relapsing neurologic symptoms 2-12 wk after completing treatment for HSV encephalitis. In children younger than 4 yr, this type of autoimmune encephalitis usually manifests with choreoathetosis and dyskinesias (known as choreoathetosis post-HSV encephalitis; see **Videos 616.1 ▶ , 616.2 ▶ , and 616.3 ▶**). In contrast, older children and adults more ofte develop predominantly behavioral symptoms.

Although no prospective clinical trials have been done, there is evidence that tumor removal, when appropriate, and prompt immunotherapy improve the outcome. Most children receive first-line immunotherapies, including corticosteroids, IVIG, or plasma exchange. However, because these treatments fail in almost 50% of patients, and with an increasing number of reports showing that rituximab can be effective, this treatment is increasingly being used in combination with IVIG and steroids or after first-line immunotherapies. Cyclophosphamide can be effective when there has been no response to these treatments.

Although anti-NMDAR encephalitis has a mortality rate of 7%, approximately 80% of patients recover substantially or fully. Recovery is usually slow and can take as long as 2 yr after symptom onset. The last symptoms to improve are problems in social interactions and language and executive functions. Relapses occur in approximately 15% of patients; they can develop as partial syndromes, are usually milder than the initial episode, and respond equally well to immunotherapy. Initial comprehensive immunotherapy appears to prevent or reduce the number of relapses. The efficacy of chronic immunosuppression with drugs such as azathioprine or mycophenolate mofetil in preventing relapses is unknown.

The differential diagnosis of anti-NMDAR encephalitis is extensive and varies according to the stage of the disease (Table 616.9). The most frequently considered disorders are viral encephalitis, neuroleptic malignant syndrome, acute psychosis, and drug abuse.

Table 616.9

Differential Diagnosis of Anti-NMDAR and Other Types of Autoimmune Encephalitis in Children

DISORDER	COMMENTS

Viral encephalitis	Viral encephalitis is often suggested by the acute onset of symptoms, CSF pleocytosis, and hyperthermia. Most viral encephalitides (except rabies) occur with higher levels of CSF pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent in viral encephalitis than in anti-NMDAR encephalitis.
Relapsing post–herpes simplex virus encephalitis	Occurs ~ 2-12 wk after successful treatment of herpes simplex encephalitis. This may represent a true viral relapse of encephalitis (CSF PCR-positive, progression of necrotic MRI changes, response to acyclovir) or an autoimmune disorder (CSF PCR-negative, no new necrotic lesions on MRI, lack of response to acyclovir). In a proportion of the latter patients, the disorder is anti-NMDAR encephalitis.
New-onset psychosis	Because most patients with anti-NMDAR encephalitis present with psychosis, a psychiatric disorder is frequently considered. As the disease evolves, the development of neurologic symptoms usually reveals the diagnosis.
Drugs/toxins	The acute development of personality and behavioral changes and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually leads to a suspicion of drug abuse (e.g., ketamine, phencyclidine, among others).
Neuroleptic malignant syndrome	The occurrence of an altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest NMS. In addition, some patients with anti-NMDAR encephalitis have elevated serum creatine kinase and rhabdomyolysis (in the absence of antipsychotic medication). The frequent use of neuroleptics to control the abnormal behavior adds further confusion between both syndromes. The presence of dyskinesias and catatonia suggest anti-NMDAR encephalitis.
Limbic encephalitis	Criteria of LE are well defined. Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are largely restricted to the temporal lobes.
Encephalitis lethargica	This is an ill-defined entity, likely representing multiple disorders. Criteria include acute or subacute encephalitis with at least three of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive–compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Many patients categorized as encephalitis lethargica hyperkinetica have anti-NMDAR encephalitis.
Childhood disintegrative disorder/late-onset autism	Children with anti-NMDAR encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder. Although the prognosis of CDD is poor, most patients with anti-NMDAR encephalitis respond to immunotherapy and have a substantial clinical recovery.
Kleine-Levin syndrome	Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and child-like behavior, which are typical components of Kleine-Levin syndrome, may occur transiently during the process of recovery of anti-NMDAR encephalitis, or as permanent sequelae.
Inborn errors of metabolism	Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process. Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including 3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome), Wilson syndrome, and Lesch-Nyhan syndrome. Pantothenate kinase–associated neurodegeneration, porphyria, and urea cycle defects should also be considered.
Genetic disorders that can manifest as autoimmune encephalitis	HLH, RANBP2 mutations, interferonopathies, autoinflammatory syndromes including cryopyrin-associated periodic syndromes, and CTLA4 deficiency can present with clinical features mimicking ADEM or autoimmune or infectious encephalitis. MRI often shows hyperintense T2/FLAIR abnormalities involving white matter with contrast enhancement in HLH and CTLA4 deficiency; both thalami in *RANBP2* mutations; and may show striatal necrosis with or without associated hypomyelination in ADAR1 interferonopathy. CSF is abnormal in most patients. Some patients develop systemic symptoms (e.g., fever, arthralgias or rash in autoinflammatory syndromes, or autoimmune cytopenias or hypogammaglobulinemia in CTLA4 deficiency) that can help to make the diagnosis, which is confirmed by genetic testing.
Monoamine	Deficiency of dopamine or serotonin, or both, can result in encephalopathy, epilepsy, and

neurotransmitter disorders	pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the CSF for levels of these neurotransmitters.
Acquired demyelinating disorders	ADEM and NMOSD are immune-mediated inflammatory and demyelinating disorders of the central nervous system. These disorders should be considered in the differential diagnosis of multifocal neurologic abnormalities and encephalopathy in children. As with anti-NMDAR encephalitis, these disorders may be preceded by an infection and can show pleocytosis. The diagnosis is suggested by the MRI findings. In NMOSD, the presence of AQP4 antibodies in serum or CSF is associated with relapses and poor prognosis. MOG antibodies occur in ≈ 50% of children with ADEM and some patients with NMOSD.
CNS vasculitis	CNS vasculitis results in neurologic deficits and psychiatric manifestations. The diagnosis is established by angiography in large-vessel angiitis and brain biopsy in small-vessel angiitis. In the latter, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, Complement 3, von Willebrand factor antigen) are usually elevated, and the MRI shows FLAIR/T2 abnormalities in the white and/or gray matter suggesting ischemia and microhemorrhages, but are not restricted to vascular territories and frequent leptomeningeal and/or local enhancement.
Systemic rheumatic disorders	Systemic lupus erythematosus and other rheumatic disorders can result in encephalopathy and multifocal neurologic and psychiatric manifestations. These disorders are usually suggested by the presence of signs and symptoms of involvement of systemic organs: skin, joints, kidneys, blood-forming cells, and blood vessels.

ADEM, acute disseminated encephalomyelitis; AQP4, aquaporin 4; CDD, childhood disintegrative disorder; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; HLH, hemophagocytic lymphohistiocytosis; LE, limbic encephalitis; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMDAR, *N* -methyl-D -aspartate receptor; NMOSD, neuromyelitis optica spectrum disorders; NMS, neuroleptic malignant syndrome; PCR, polymerase chain reaction; RANBP2, Ras-related nuclear protein-binding protein 2; CTLA4, cytotoxic T-lymphocyte-associated protein 4; ADAR1, adenosine deaminase acting on RNA 1.

Other Types of Encephalitis Associated With Antibodies Against Neuronal Cell Surface Antigens

Encephalitis with antibodies against the γ-aminobutyric acid A receptor (GABA$_A$ R) is a rare autoimmune encephalitis that can affect children (40% of patients < 18 yr) and develops with status epilepticus, refractory seizures, or epilepsia partialis continua in association with antibodies against the α1, β3, or γ2 subunits of the GABA$_A$ R. Young children can develop abnormal movements suggesting anti-NMDAR encephalitis but with studies negative for NMDAR antibodies. Unlike other types of autoimmune encephalitis in which the brain MRI is usually normal or shows nonspecific findings, adult and pediatric patients with this disorder frequently develop multifocal hyperintense cortical-subcortical FLAIR/T2 abnormalities. In adults, this encephalitis may occur with thymoma, but children rarely have an underlying tumor.

The **Ophelia syndrome** is a form of encephalitis that occurs in association with Hodgkin lymphoma and predominantly affects young adults, teenagers, or children. Some patients develop antibodies against mGluR5, a receptor involved in learning and memory. Neurologic symptoms are highly responsive to treatment of the tumor and immunotherapy.

Autoimmune limbic encephalitis refers to an inflammatory process of the limbic system, including the medial temporal lobes, amygdala, and cingulate gyri. In adults, the most frequent immune-mediated limbic encephalitis occurs in association with antibodies against proteins that were once thought to be voltage-gated potassium channels (VGKCs) but which, in fact, target a secreted neuronal protein called leucine-rich glioma-inactivated 1 (LGI1) and a protein called Caspr2 expressed in the brain and the juxtaparanodal regions of myelinated nerves. Patients with LGI1 antibody–associated limbic encephalitis often develop *hyponatremia;* in some patients, the disorder is preceded by dystonic or myoclonic-like movements, described as *faciobrachial dystonic seizures.* Patients with Caspr2 antibodies can develop limbic encephalitis, neuromyotonia, or **Morvan syndrome,** which includes encephalopathy, seizures, a sleep disorder, autonomic dysfunction, and neuromyotonia. Studies have demonstrated that in patients without LGI1 or Caspr2 antibodies, the detection of VGKC-complex antibodies has very limited clinical significance. In children, the identification of LGI1 or Caspr2 antibodies is unusual; therefore, a positive test for VGKC-complex antibodies should be interpreted with caution because it does not necessarily indicate autoimmune encephalitis. In children, autoimmune or paraneoplastic limbic encephalitis is exceptional. Unfortunately, any type of encephalopathy resulting in seizures and alteration of memory and behavior is often labeled as limbic encephalitis, making data based on literature searches using the term *limbic encephalitis* unreliable. Excluding patients with NMDAR or GABAAR antibody–associated encephalitis, fewer than 30 children with limbic and other types of antibody-associated encephalitis have been reported in the English literature, some of them with antibodies against neuronal cell surface receptors or proteins ($GABA_B$ R, DPPX, GlyR), intracellular proteins (Hu, Ma2, GAD65, amphiphysin), or intracellular proteins of unknown identity (VGKC-complex proteins). In some patients, an underlying tumor was identified, including leukemia, ganglioneuroblastoma, neuroblastoma, or small-cell carcinoma of the ovary.

In practice, determination of the type of autoantibodies and location of the target antigens is important because an encephalitis in which the antigens are on the cell surface (e.g., NMDAR or GABAAR) responds better to immunotherapy than one in which the antigens are intracellular (e.g., GAD65).

Acquired Demyelinating Syndromes With Encephalopathy

Acute disseminated encephalomyelitis (ADEM) is the most frequent autoimmune encephalitis in children (see Chapter 618.4). Symptoms may include seizures, motor deficits, ataxia, and visual dysfunction, among others. Antibodies against myelin oligodendrocyte glycoprotein (MOG) occur in 50–60% of patients with ADEM and have a negative predictive value for evolution to multiple sclerosis in children with a first demyelinating event (see Chapter 618.4). MOG antibodies have also been described in patients with autoimmune encephalitis and MRI findings showing predominant gray matter involvement (cortex and deep gray matter structures).

Neuromyelitis optica spectrum disorder (NMOSD) can present as an encephalopathy with predominant involvement of diencephalic and area postrema regions. These patients often harbor aquaporin 4 (AQP4) antibodies or MOG antibodies. Determination of these antibodies should be considered in patients with encephalopathy and MRI findings showing involvement of AQP4-rich regions, such as the periaqueductal gray matter, hypothalamus, optic nerves, and central region of the spinal cord (see Chapter 618.2).

Hashimoto Encephalopathy

Hashimoto encephalopathy, or more appropriately, steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT), is defined by the detection of thyroid peroxidase (TPO) antibodies in patients with acute or subacute encephalitis that responds to corticosteroids. Clinical features are not specific and may include stroke-like episodes, tremor, myoclonus, transient aphasia, sleep and behavior abnormalities, hallucinations, seizures, and ataxia. The CSF usually shows an elevated protein level with less frequent pleocytosis. EEG studies almost always are abnormal, frequently showing generalized slowing. A brain MRI is usually normal, although it may show diffuse white matter abnormalities and meningeal enhancement that can resolve with steroid therapy. Because TPO antibodies occur in approximately 10% of asymptomatic children (i.e., those who are nonencephalopathic and, in most cases, euthyroid) and can also be found in some patients who have more relevant antibody-associated diseases, the detection of TPO antibodies should be viewed as a marker of autoimmunity rather than a disease-specific or pathogenic antibody. Therefore, the presence of TPO antibodies should not prevent testing for more relevant antibodies, such as NMDAR antibodies.

Opsoclonus–Myoclonus and Other Types of Brainstem–Cerebellar Encephalitis

Opsoclonus–myoclonus occurs in infants, teenagers, and adults, although it probably represents different diseases and pathogenic mechanisms. In infants, the syndrome usually develops in the first 2 yr of life (mean: 20 mo), and at least 50% of patients have an underlying neuroblastoma. The child often presents with irritability, ataxia, falling, myoclonus, tremor, and drooling. Additional symptoms may include a refusal to walk or sit, speech problems, hypotonia, and the typical features of opsoclonus characterized by rapid, chaotic, multidirectional eye movements without saccadic intervals. Because opsoclonus may be absent at symptom presentation, patients may initially be diagnosed with acute cerebellitis or labyrinthitis. Typically, CSF abnormalities suggest B-cell activation, and the presence of antibodies against neuronal proteins has been demonstrated in some patients, although the identification of a specific autoantigen has been elusive.

Immunotherapy, including corticosteroids and IVIG, often improves the abnormal eye movements, but residual behavioral, language, and cognitive problems persist in the majority of patients, often requiring special education. In addition, insomnia and an abnormal response to pain are common. Relapses occur in 50% of patients, usually as a result of an intercurrent infection or drug tapering. Patients treated with more aggressive immunosuppression (often including rituximab) have better outcomes compared with historic control series or patients who did not receive these treatments. Delay in treatment appears to be associated with a poorer neurologic outcome; therefore, in cases with neuroblastoma, removal of the tumor should not delay the start of immunotherapy.

In teenagers and young adults, opsoclonus–myoclonus and brainstem–

cerebellar encephalitis without opsoclonus are often considered idiopathic or postinfectious; however, there is evidence that some of these patients have an underlying **teratoma,** usually in the ovaries. These patients do not harbor NMDAR antibodies, and compared with those with anti-NMDAR encephalitis, they are less likely to present with psychosis and behavioral changes and rarely develop dyskinesias. Although these patients do not appear to have neuronal antibodies, the CSF often shows pleocytosis and an elevated protein concentration. Identification of this subphenotype of opsoclonus–myoclonus is important because patients usually have full recovery after treatment with immunotherapy (corticosteroids, IVIG, and/or plasma exchange) and removal of the ovarian teratoma if it is present. The prognosis of opsoclonus–myoclonus in teenagers and young adults seems better than that of young children (with or without neuroblastoma) or of the paraneoplastic opsoclonus of older patients, usually related to breast, ovarian, or lung cancer.

Bickerstaff Encephalitis

This term is used to describe patients with rapid progression (<4 wk) of bilateral external ophthalmoplegia, ataxia, and decreased level of consciousness. Although this entity has been described more frequently in adults, children as young as 3 yr old have been identified. Most patients are treated with steroids, IVIG, or plasma exchange, and they often have a good outcome. Serum GQ1b immunoglobulin G antibodies are found in 66% of patients. Brain MRI abnormalities occur in 30% of patients and usually include increased T2-signal abnormalities in the brainstem, thalamus, and cerebellum and sometimes in the cerebral white matter. Some patients develop hyporeflexia and limb weakness, with predominant axonal involvement, overlapping with symptoms of the Miller–Fisher syndrome and the axonal subtype of the Guillain–Barré syndrome.

Chronic Lymphocytic Inflammation With Pontine Perivascular Enhancement Responsive to Steroids

CLIPPERS is a clinically and radiologically distinct pontine-predominant encephalomyelitis. Patients usually present with episodic diplopia or facial paresthesias with subsequent development of symptoms of brainstem and, occasionally, spinal cord dysfunction. A brain MRI shows symmetric curvilinear gadolinium enhancement peppering the pons and extending variably into the medulla, brachium pontis, cerebellum, and midbrain and occasionally into the spinal cord. The clinical and radiologic findings usually respond to high-dose steroids but may worsen after steroid tapering, requiring chronic steroid or other immunosuppressive therapy. The differential diagnosis is extensive and includes infections, acquired demyelinating syndromes, granulomatous disease, lymphoma, or vasculitis. Biopsy studies may be needed to exclude these and other conditions.

Autoimmune Encephalopathies Associated With Epilepsy and Status Epilepticus

Rasmussen encephalitis is an inflammatory encephalopathy characterized by progressive refractory focal seizures, cognitive deterioration, and focal neurologic deficits that occur with gradual atrophy of one brain hemisphere. The disorder frequently presents in children 6-8 yr old, although adolescents and adults can be affected. The etiology is unknown, and, therefore, multiple theories are proposed, including the presence of neuronal antibodies and T-cell–mediated mechanisms triggered by a viral infection. None of these mechanisms satisfactorily explain the unilateral brain involvement characteristic of the disorder. Treatment with high-dose steroids, plasma exchange, or IVIG can ameliorate symptoms in early stages of the disease. Rituximab and intraventricular γ-interferon have been effective in a few isolated cases. In a small series, patients treated with tacrolimus showed better outcomes of neurologic function and slower progression of cerebral hemiatrophy but did not have improved seizure control. An open-label study using a monoclonal antibody against tumor necrosis factor (TNF)-α (adalimumab) led to seizure control and preservation of cognitive function in approximately 50% of patients. The most effective treatment for control of the seizures is functional hemispherectomy, which consists of surgical disconnection of the affected hemisphere.

The discovery of treatment-responsive encephalitis associated with antibodies against cell surface or synaptic proteins has suggested that there may be an autoimmune basis for several devastating encephalopathies with refractory seizures. Some well-defined types of autoimmune encephalitis, such as anti-NMDAR or $GABA_A$ R encephalitis, can present with refractory seizures or status epilepticus. Most of these patients develop other clinical features that suggest the diagnosis of the disease, and testing for the corresponding antibodies leads to the correct diagnosis and initiation of immunotherapy.

A devastating epileptic encephalopathy associated with fever named **fever-induced refractory epileptic encephalopathy syndrome (FIRES),** among other terms, is suspected to be an infection-triggered autoimmune process because of its biphasic clinical course and the occasional finding of neuronal antibodies in a few patients. However, the lack of response to most treatments, including immunotherapy, and the rare and inconsistent association with different types of antibodies have cast doubts on an autoimmune pathogenesis. Some investigators suggest a genetic error in metabolism.

Antibodies to VGKC-complex proteins different from LGI1 and Caspr2 have been described in some children with encephalitis with or without status epilepticus. Given that the target antigens are most likely intracellular and the response to immunotherapy is unpredictable, the significance of these antibodies is unclear.

Other Suspected Types of Autoimmune Encephalitis

Vasculitis of the CNS and rheumatic diseases associated with autoimmune mechanisms that can result in encephalitis are discussed in Chapter 620 .

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (**ROHHAD;** see also Chapter 60.1) usually affects children who had normal development until 2-4 yr of age and then developed a rapid onset of hyperphagia, weight gain, and abnormal behavior (social disinhibition, irascibility, impulsivity, lethargy, outburst of euphoria and laughing, impaired concentration), followed by autonomic dysfunction (abnormal pupillary responses, thermal dysregulation, gastrointestinal dysmotility) and central hypoventilation. An autoimmune or paraneoplastic etiology of ROHHAD syndrome is supported by the frequent association with neural crest tumors, the identification in some patients of genetic factors predisposing them to autoimmunity, and the finding in some patients of intrathecal oligoclonal bands and infiltrates of lymphocytes and histiocytes in the hypothalamus. Furthermore, responses to immunotherapy have been described in a few patients. A possible genetic origin is suggested because of the similarities of this syndrome with the congenital central hypoventilation syndrome (Ondine curse) related to a *PHOX2B* mutation, which presents in the neonatal period and is also associated with autonomic problems (Hirschsprung disease) and neural crest tumors (see Chapter 446.2). However, no mutations in *PHOX2B* and other candidate genes have been found in patients with ROHHAD.

The term **basal ganglia encephalitis** is used to describe patients with predominant or isolated involvement of the basal ganglia. These patients typically have abnormal movements and neuropsychiatric disease. Although these clinical manifestations may have multiple etiologies, including metabolic, toxic, genetic, and infectious processes, an immune-mediated etiology has been postulated in some patients. There have been no clinical trials, but case reports and small noncontrolled case series describe the potential benefit of immunotherapy. Antibodies against the dopamine-2 receptor have been infrequently identified in these patients, as well as in patients with Sydenham chorea and Tourette syndrome.

Pseudomigraine syndrome with CSF pleocytosis (PMP) or **headache with neurologic deficits and CSF lymphocytosis (HaNDL)** is an ill-defined entity that predominantly affects young male adults with a family history of migraine, although adolescents can be affected. This syndrome is characterized by repeat episodes of severe headache with transient neurologic deficits, accompanied by aseptic CSF lymphocytosis and a normal brain MRI. Patients frequently show a high CSF opening pressure, an elevated CSF protein concentration, and focal EEG slowing, which normalize after the episodes of headache. Because of the inflammatory characteristics of the CSF and the high prevalence of prodromal viral-like symptoms, an infectious–autoimmune-mediated mechanism has been proposed. Other theories include spreading cortical depression and trigeminal-vascular activation.

An immune-mediated mechanism and trigeminal-vascular activation are also considered as possible mechanisms of **ophthalmoplegic migraine,** also named **recurrent cranial neuralgia.** This disorder predominantly affects young children and is characterized by recurrent bouts of headache in addition to palsy of cranial nerves III, IV, and/or VI. In contrast to PMP/HaNDL, CSF studies do not show pleocytosis, and in approximately 75% of patients, the MRI shows focal nerve thickening and contrast enhancement. Observational data suggest that treatment with steroids may be beneficial. In this syndrome, as well as in PMP/HaNDL, the differential diagnosis includes structural, neoplastic, traumatic, metabolic, and infectious disorders.

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CHAPTER 617

Neurodegenerative Disorders of Childhood

Jennifer M. Kwon

Neurodegenerative disorders of childhood encompass a large, heterogeneous group of diseases from specific genetic and biochemical defects. Children with suspected neurodegenerative disorders were once subjected to brain and rectal (neural) biopsies, but with modern neuroimaging techniques and specific biochemical and molecular diagnostic tests, these invasive procedures are rarely necessary. The most important component of the diagnostic investigation continues to be a thorough history and physical examination. The hallmark of a neurodegenerative disease is **regression and progressive deterioration** of neurologic function with loss of speech, vision, hearing, or locomotion, often associated with seizures, feeding difficulties, and impairment of intellect. The age of onset, rate of progression, and principal neurologic findings determine whether the disease affects primarily the white or the gray matter. Upper motor neuron signs and progressive spasticity are the hallmarks of white matter disorders; convulsions and intellectual and visual impairments that occur early in the disease course are the hallmarks of gray matter disorders. A precise history confirms regression of developmental milestones, and the neurologic examination localizes the process within the nervous system. Although the outcome of a neurodegenerative condition is usually fatal and available therapies are often limited in effect, it is important to make the correct diagnosis so that genetic counseling may be offered and prevention strategies can be implemented. Bone marrow transplantation and other novel therapies may prevent the progression of disease in certain individuals who are either presymptomatic or very early in their disease course. For all conditions in which the specific genetic defect is known, prevention by prenatal diagnosis (chorionic villus sampling or amniocentesis) is possible as is carrier detection. Table 617.1

summarizes selected inherited neurodegenerative and metabolic disorders by their usual age of onset.

Table 617.1

Selected Metabolic Conditions Associated With Developmental Regression

AGE AT ONSET (yr)	CONDITIONS	COMMENTS
<2, often with hepatomegaly or hepatic effects	Fructose intolerance	Vomiting, hypoglycemia, poor feeding, failure to thrive (when given fructose)
	Galactosemia	Lethargy, hypotonia, icterus, cataract, hypoglycemia (when given lactose)
	Glycogenosis (glycogen storage disease) types I-IV	Hypoglycemia, cardiomegaly (type II)
	Mucopolysaccharidosis types I and II	Coarse facies, stiff joints
	GM_1 gangliosidosis	Coarse facies, macroglossia, cherry- red spot in macula
	Niemann-Pick disease, infantile type	Gray matter disease, failure to thrive
	Zellweger syndrome	Hypotonia, high forehead, flat facies
	Gaucher disease (neuronopathic form)	Extensor posturing, irritability
	Carbohydrate-deficient glycoprotein syndromes	Dysmyelination, cerebellar hypoplasia
<2, without hepatomegaly	Krabbe disease	Irritability, extensor posturing, optic atrophy, and blindness
	Rett syndrome	Girls with deceleration of head growth, loss of hand skills, hand wringing, impaired language skills, gait apraxia
	Maple syrup urine disease	Poor feeding, tremors, myoclonus, opisthotonos
	Phenylketonuria	Light pigmentation, microcephaly
	Menkes kinky hair disease	Hypertonia, irritability, seizures, abnormal hair
	Tay-Sachs disease, GM_2 gangliosidoses	Seizures, cherry-red spot of macula, increased startle response
	Subacute necrotizing encephalopathy of Leigh disease	White matter disease, basal ganglia, brainstem lesions
	Canavan disease	White matter disease, macrocephaly
	Neurodegeneration with brain iron accumulation disease (see Table 617.4)	Cerebellar atrophy, optic atrophy, iron accumulation in basal ganglia, movement disorder
2-5	Niemann-Pick disease types III and IV	Hepatosplenomegaly, gait difficulty
	Wilson disease	Liver disease, Kayser-Fleischer ring; deterioration of cognition is late
	Neuronal ceroid lipofuscinosis	Gray matter disease
	Mitochondrial encephalopathies (e.g., myoclonic epilepsy with ragged red fibers [MERRF])	Gray matter disease
	Ataxia–telangiectasia	Basal ganglia disease
	Neurodegeneration with brain iron accumulation syndrome	Basal ganglia disease
	Metachromatic leukodystrophy	White matter disease

	Adrenoleukodystrophy	White matter disease, behavior problems, deteriorating school performance, vision loss
5-15	Adrenoleukodystrophy	Same as for adrenoleukodystrophy in 2 to 5 yr olds
	Neuronal ceroid lipofuscinosis, juvenile and adult forms	Gray matter disease
	Refsum disease	Peripheral neuropathy, ataxia, retinitis pigmentosa
	Sialidosis II, juvenile form	Cherry-red macula, myoclonus, ataxia, coarse facies

Adapted from Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, 2e, Philadelphia, 2004, WB Saunders, p. 542.

617.1

Sphingolipidoses

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Keywords

sphingolipidosis
sphingolipid disorder
GM_1 gangliosidosis
GM_2 gangliosidosis
Tay-Sachs disease
Sandhoff disease
Krabbe disease
metachromatic leukodystrophy
cherry-red spot

The sphingolipidoses are characterized by intracellular storage of lipid substrates resulting from defective catabolism of the sphingolipids comprising cellular membranes (Fig. 617.1). The sphingolipidoses are subclassified into six categories: Niemann-Pick disease, Gaucher disease, GM_1 gangliosidosis, GM_2

gangliosidosis, Krabbe disease, and metachromatic leukodystrophy. Niemann-Pick disease and Gaucher disease are discussed in Chapter 104.4 .

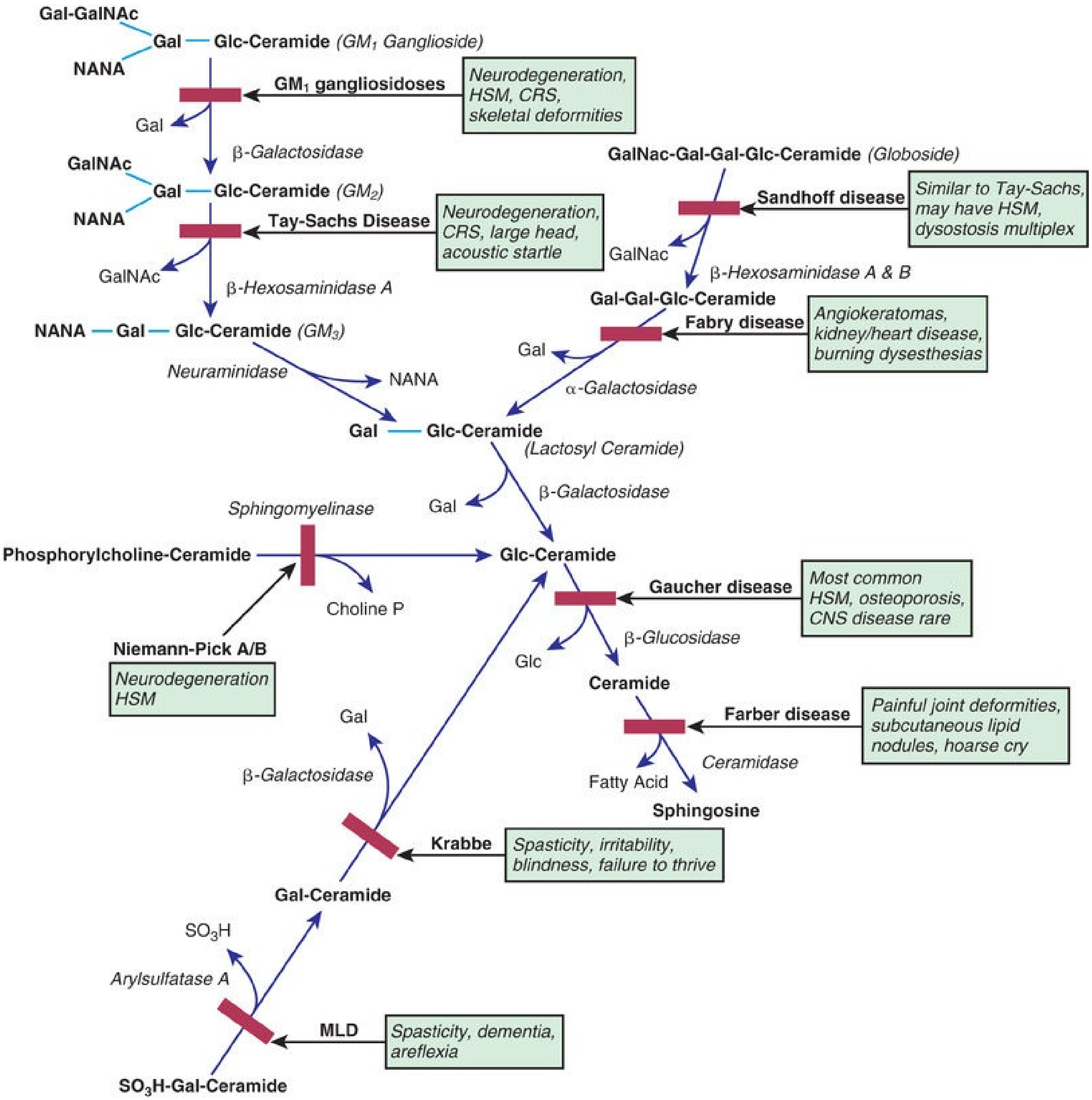
Gal-GalNAc
Gal — Glc-Ceramide (GM₁ Ganglioside)
NANA
GM₁ gangliosidoses
Neurodegeneration, HSM, CRS, skeletal deformities
Gal
β-Galactosidase
GalNAc
Gal — Glc-Ceramide (GM₂)
NANA
Tay-Sachs Disease
Neurodegeneration, CRS, large head, acoustic startle
GalNAc
β-Hexosaminidase A
NANA — Gal — Glc-Ceramide (GM₃)
Neuraminidase
NANA
GalNac-Gal-Gal-Glc-Ceramide (Globoside)
Sandhoff disease
Similar to Tay-Sachs, may have HSM, dysostosis multiplex
GalNac
β-Hexosaminidase A & B
Gal-Gal-Glc-Ceramide
Fabry disease
Angiokeratomas, kidney/heart disease, burning dysesthesias
Gal
α-Galactosidase
Gal — Glc-Ceramide
(Lactosyl Ceramide)
Gal
β-Galactosidase
Sphingomyelinase
Phosphorylcholine-Ceramide
Glc-Ceramide
Choline P
Niemann-Pick A/B
Neurodegeneration HSM
Gaucher disease
Most common HSM, osteoporosis, CNS disease rare
Glc
β-Glucosidase
Ceramide
Farber disease
Painful joint deformities, subcutaneous lipid nodules, hoarse cry
Fatty Acid
Ceramidase
Sphingosine
Gal
β-Galactosidase
Krabbe
Spasticity, irritability, blindness, failure to thrive
Gal-Ceramide
SO₃H
Arylsulfatase A
MLD
Spasticity, dementia, areflexia
SO₃H-Gal-Ceramide

FIG. 617.1 Sphingolipid degradation pathway showing the sites of enzyme deficiencies and their associated disorders. Sphingolipids are composed of a ceramide backbone with oligosaccharide side chains. CRS, cherry-red spot (retinal); Gal-, galactosyl-; GalNAc, N-acetyl-galactose; Glc-, glucosyl-; HSM, hepatosplenomegaly; MLD, metachromatic leukodystrophy; NANA, N-acetyl-neuraminic acid.

Gangliosidoses

See also Chapter 104.4 .

Gangliosides are glycosphingolipids, normal constituents of the neuronal and synaptic membranes. The basic structure of a GM_1 ganglioside consists of an oligosaccharide chain attached to a hydroxyl group of ceramide and sialic acid bound to galactose. The gangliosides are catabolized by sequential cleavage of the sugar molecules by specific exoglycosidases. Abnormalities in catabolism result in an accumulation of the ganglioside within the cell. Defects in ganglioside degradation can be classified into two groups: the GM_1 gangliosidoses and GM_2 gangliosidoses.

GM_1 Gangliosidoses

The three subtypes of GM_1 gangliosidoses are classified according to age at presentation: infantile (type 1), juvenile (type 2), and adult (type 3). The condition is inherited as an autosomal recessive trait and results from a marked deficiency of acid β-galactosidase. This enzyme may be assayed in leukocytes and cultured fibroblasts. The acid β-galactosidase gene has been mapped to chromosome 3p22.3. Prenatal diagnosis is possible by measurement of acid β-galactosidase in or direct molecular testing of cultured amniotic cells.

Infantile GM_1 gangliosidosis presents at birth or during the neonatal period with anorexia, poor sucking, and inadequate weight gain. Development is globally delayed, and generalized seizures are prominent. The phenotype is striking and shares many characteristics with Hurler syndrome. The facial features are coarse, the forehead is prominent, the nasal bridge is depressed, the tongue is large (macroglossia), and the gums are hypertrophied. Hepatosplenomegaly is present early in the course as a result of accumulation of foamy histiocytes, and kyphoscoliosis is evident because of anterior beaking of the vertebral bodies. The neurologic examination is dominated by apathy, progressive blindness, deafness, spastic quadriplegia, and decerebrate rigidity. A cherry-red spot in the macular region is visualized in approximately 50% of cases. The **cherry-red spot** is characterized by an opaque ring (sphingolipid-laden retinal ganglion cells) encircling the normal red fovea (Fig. 617.2). Children rarely survive beyond age 2-3 yr, and death may be from aspiration pneumonia.

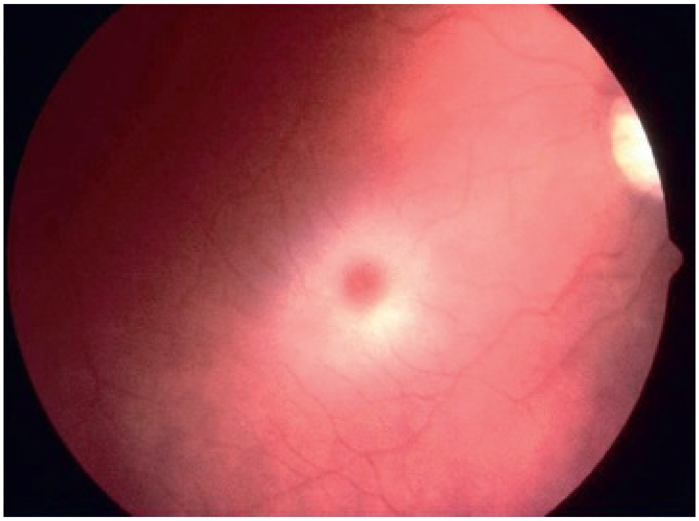

FIG. 617.2 A cherry-red spot in a patient with GM_1 gangliosidosis. Note the whitish ring of sphingolipid-laden ganglion cells surrounding the fovea. (From Leavitt JA, Kotagal S: The “cherry red” spot. Pediatr Neurol 37(1):74–75, 2007, Fig. 1.)

Juvenile GM_1 gangliosidosis has a delayed onset beginning about 1 yr of age. The initial symptoms consist of incoordination, weakness, ataxia, and regression of language. Thereafter, convulsions, spasticity, decerebrate rigidity, and blindness are the major findings. Unlike the infantile type, this type is not usually marked by coarse facial features and hepatosplenomegaly. Radiographic examination of the lumbar vertebrae may show minor beaking. Children rarely survive beyond 10 yr of age. **Adult GM_1 gangliosidosis** is a slowly progressive disease consisting of spasticity, ataxia, dysarthria, and a gradual loss of cognitive function.

GM_2 Gangliosidoses

The GM_2 gangliosidoses are a heterogeneous group of autosomal recessive inherited disorders that consist of several subtypes, including Tay-Sachs disease (TSD), Sandhoff disease, juvenile GM_2 gangliosidosis, and adult GM_2 gangliosidosis. **TSD** is most prevalent in the Ashkenazi Jewish population and has an approximate carrier rate of 1 in 30 Jews in the United States. TSD is caused by mutations in the *HEXA* gene located on chromosome 15q23. Affected infants appear normal until approximately 6 mo of age, except for a marked startle reaction to noise that is evident soon after birth. Affected children then begin to lag in developmental milestones, and by 1 yr of age, they lose the ability to stand, sit, and vocalize. Early hypotonia develops into progressive spasticity, and relentless deterioration follows, with convulsions, blindness, deafness, and cherry-red spots in almost all patients (see Fig. 617.2). Macrocephaly becomes apparent by 1 yr of age and results from the 200- to 300–fold normal content of GM_2 ganglioside deposited in the brain. Few children live beyond 3-4 yr of age, and death is usually associated with aspiration or bronchopneumonia. A deficiency of the isoenzyme hexosaminidase A is found in tissues of patients with TSD. An accurate and inexpensive carrier detection test is available (serum or leukocyte hexosaminidase A), and this has been an effective tool in the defined population of Ashkenazi Jews. Targeted screening is responsible for the fact that currently, the rare children with TSD born in the United States are most commonly born to non-Jewish parents who are not routinely screened.

Sandhoff disease is very similar to TSD in the mode of presentation, including progressive loss of motor and language milestones beginning at 6 mo of age. Seizures, cherry-red spots, macrocephaly, and doll-like facies are present in most patients; however, children with Sandhoff disease may also have splenomegaly. The visual evoked potentials (VEPs) are normal early in the course of Sandhoff disease and TSD but become abnormal or absent as the disease progresses. The auditory brainstem responses show prolonged latencies. The diagnosis of Sandhoff disease is established by finding deficient levels of hexosaminidases A and B in serum and leukocytes. Children usually die by 3 yr of age. Sandhoff disease is caused by mutations in the *HEXB* gene located on chromosome 5q13.

Juvenile GM_2 gangliosidosis develops in mid-childhood, initially with clumsiness followed by ataxia. Signs of spasticity, athetosis, loss of language, and seizures gradually develop. Progressive visual loss is associated with optic atrophy, but cherry-red spots rarely occur in juvenile GM_2 gangliosidosis. A deficiency of hexosaminidase is variable (total deficiency to near normal) in these patients. Death occurs around 15 yr of age.

Adult GM_2 gangliosidosis is characterized by a myriad of neurologic signs, including slowly progressive gait ataxia, spasticity, dystonia, proximal muscle atrophy, and dysarthria. Generally, visual acuity and intellectual function are unimpaired. Hexosaminidase A activity alone or hexosaminidases A and B activity is reduced significantly in the serum and leukocytes.

Krabbe Disease (Globoid Cell Leukodystrophy)

Krabbe disease (KD) is a rare autosomal recessive neurodegenerative disorder characterized by severe myelin loss and the presence of globoid bodies in the white matter. The gene for KD *(GALC)* is located on chromosome 14q24.3-q32.1. The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside β-galactosidase (GALC). KD is a disorder of myelin destruction rather than abnormal myelin formation. Normally, myelination begins in the 3rd trimester, corresponding with a rapid increase of GALC activity in the brain. In patients with KD, galactocerebroside cannot be metabolized during the normal turnover of myelin because of deficiency of GALC. When galactocerebroside is injected into the brains of experimental animals, a globoid cell reaction ensues. It is postulated that a similar phenomenon occurs in humans; nonmetabolized galactocerebroside stimulates the formation of globoid cells that reflect the destruction of oligodendroglial cells. Because oligodendroglial cells are responsible for the elaboration of myelin, their loss results in myelin breakdown, thus producing additional galactocerebroside and causing a vicious circle of myelin destruction.

The symptoms of KD become evident in the first few months of life and include excessive irritability and crying, unexplained episodes of hyperpyrexia, vomiting, and difficulty feeding. In the initial stage of KD, children are often treated for colic or milk allergy with frequent formula changes. Generalized seizures may appear early in the course of the disease. Alterations in body tone with rigidity and opisthotonos and visual inattentiveness as a result of optic atrophy become apparent as the disease progresses. In the later stages of the illness, blindness, deafness, absent deep-tendon reflexes, and decerebrate rigidity constitute the major physical findings. Most patients die by 2 yr of age. MRI and magnetic resonance spectroscopy are useful for evaluating the extent of demyelination in KD. Umbilical cord blood (stem cell) transplantation from unrelated donors in asymptomatic babies may favorably alter the natural history but will not help patients who already have neurologic symptoms.

Late-onset KD has been described beginning in childhood or adolescence. Patients present with optic atrophy and cortical blindness, and their condition may be confused with adrenoleukodystrophy. Slowly progressive gait disturbances, including spasticity and ataxia, are prominent. As with classic KD, globoid cells are abundant in the white matter, and leukocytes are deficient in GALC. An examination of the cerebrospinal fluid shows an elevated protein content, and the nerve conduction velocities are markedly delayed as a result of segmental demyelination of the peripheral nerves.

Metachromatic Leukodystrophy

This disorder of myelin metabolism is inherited as an autosomal recessive trait and is characterized by a deficiency of arylsulfatase A activity. The *ARSA* gene is located on chromosome 22q13.33. The absence or deficiency of arylsulfatase A leads to accumulation of cerebroside sulfate within the myelin in both the central and peripheral nervous systems because of the inability to cleave sulfate from galactosyl-3-sulfate ceramide. The excessive cerebroside sulfate is thought to cause myelin breakdown. Prenatal diagnosis of metachromatic leukodystrophy (MLD) is made by assaying of arylsulfatase A activity in chorionic villi or cultured amniotic fluid cells. Cresyl violet applied to tissue specimens produces metachromatic staining of the sulfatide granules, giving the disease its name. Some individuals with low arylsulfatase A enzyme activity are clinically normal and have a pseudodeficiency state that can only be confirmed by additional genetic or biochemical tests. Those affected with MLD are generally classified according to age of onset: late infantile, juvenile, and adult.

Late infantile MLD begins with insidious onset of gait disturbances between 1 and 2 yr of age. The child initially appears awkward and frequently falls, but locomotion is gradually impaired significantly and support is required to walk. The extremities are hypotonic, and the deep-tendon reflexes are absent or diminished. Within the next several months, the child can no longer stand, and deterioration in intellectual function becomes apparent. The speech is slurred and dysarthric, and the child appears dull and apathetic. Visual fixation is diminished, nystagmus is present, and examination of the retina shows optic atrophy. Within 1 yr from the onset of the disease, the child is unable to sit unsupported, and progressive decorticate postures develop. Feeding and swallowing are impaired because of pseudobulbar palsies, and a feeding gastrostomy is required. Patients ultimately become stuporous and die of aspiration or bronchopneumonia by age 5-6 yr. Neurophysiologic evaluation shows slowing of peripheral nerve conduction velocities and progressive changes in the VEPs, auditory brainstem responses, and somatosensory evoked potentials. CT and MRI images of the brain indicate diffuse symmetric attenuation of the cerebellar and cerebral white matter, and examination of the cerebrospinal fluid shows an elevated protein content. Bone marrow transplant or lentiviral hematopoietic stem cell gene therapy is a promising experimental therapy for the management of late infantile MLD patients identified very early in the course of their disease.

Juvenile MLD has many features in common with late infantile MLD, but the onset of symptoms is delayed to 5-10 yr of age. Deterioration in school performance and alterations in personality may herald the onset of the disease. This is followed by incoordination of gait, urinary incontinence, and dysarthria. Muscle tone becomes increased, and ataxia, dystonia, or tremor may be present. In the terminal stages, generalized tonic-clonic convulsions are prominent and are difficult to control. Patients rarely live beyond mid-adolescence.

Adult MLD occurs from the 2nd to 6th decades. Abnormalities in memory, psychiatric disturbances, and personality changes are prominent features. Slowly progressive neurologic signs, including spasticity, dystonia, optic atrophy, and generalized convulsions, lead eventually to a bedridden state characterized by decorticate postures and unresponsiveness.

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617.2

Neuronal Ceroid Lipofuscinoses

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Keywords

neuronal ceroid lipofuscinosis
NCL
CLN

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, lysosomal storage disorders characterized by visual loss, progressive dementia, seizures, motor deterioration, and early death. The NCLs are so named because of the intracellular accumulation of fluorescent lipopigments ceroid and lipofuscin. They comprise a genetically and phenotypically heterogeneous group of disorders (currently there are at least nine NCL types) that have traditionally been subclassified by age of onset, among other clinical features. They differ from one another in the associated ultrastructural patterns of the inclusions as seen by electron microscopy. Evaluation of neuronal biopsies (either brain, rectal, conjunctival, or skin) was once required for diagnosis. With the advent of enzymatic and molecular testing methods, clinicians can make specific NCL diagnoses using less-invasive methods (Table 617.2).

Table 617.2

Clinical and Genetic Characteristics of the Neuronal Ceroid Lipofuscinoses

NCL TYPE	GENE[*]	PROTEIN	AGE OF ONSET	CLINICAL PRESENTATION
Congenital	*CLN10*	Cathepsin [‡]	Birth (but can	Severe seizures, blindness, rigidity, early

			present later, even in adults)	death Can also present similar to late-infantile forms
Infantile	*CLN1*	Palmitoyl-protein thioesterase-1 (PPT1)[‡]	6-24 mo	Early onset, often rapid progression of seizures; cognitive and motor decline with visual loss
Variant infantile	*CLN1*		3 yr to adulthood	Chronic course Initial visual loss followed then by slow mental and motor decline and seizures
Late infantile	*CLN2*	Tripeptidyl peptidase-1 (TPP1)[‡]	2-8 yr	Seizures, often severe and intractable; cognitive and motor decline; and visual loss
	CLN5	Partially soluble protein		
	CLN6	Membrane protein		
	CLN7	Membrane protein		
	CLN8	Membrane protein	5-10 yr	Severe epilepsy, progressive with mental retardation
Juvenile	*CLN3*	Membrane protein	4-10 yr	Visual loss is usually the initial presenting complaint Also have mental and motor disorders and seizures

[*] Note that all of the NCL genes have the prefix CLN. The adult form (also called Kufs disease, with locus CLN4, caused by mutations in *DNAJC5*) is not well characterized and is not included in the table. Genetic testing is available for all listed genes.

[‡] Enzyme testing is available.

Infantile-type neuronal ceroid lipofuscinosis (INCL, Haltia-Santavuori) begins in the 1st yr of life with myoclonic seizures, intellectual deterioration, and blindness. Optic atrophy and brownish discoloration of the macula are evident on examination of the retina, and cerebellar ataxia is prominent. The electroretinogram typically shows small-amplitude or absent waveforms. Death occurs during childhood. The infantile form is caused by recessive mutations of the gene for the lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1) on chromosome 1p32. A number of cell types in INCL patients show characteristic intracellular fine granular osmiophilic deposits discernible by electron microscopy.

A subset of children with PPT1 enzyme deficiency has a much less severe course with clinical features resembling those of the juvenile-onset NCL patients. Clinically, these variant INCL patients have a course that is often quite distinct from the typical, classic rapidly degenerating infantile form, yet they have PPT1 deficiency and granular osmiophilic deposits on pathology. There is no clear *CLN1* genotype that predicts severity of phenotype.

Late infantile-type neuronal ceroid lipofuscinosis (LINCL, Jansky-

Bielschowsky) generally presents with myoclonic seizures beginning between 2 and 4 yr of age in a previously normal child. Dementia and ataxia are combined with a progressive loss of visual acuity and microcephaly. Examination of the retina shows marked attenuation of vessels, peripheral black bone spicule pigmentary abnormalities, optic atrophy, and a subtle brown pigment in the macular region. The electroretinogram and VEP are abnormal early in the course of disease. The autofluorescent material is deposited in neurons, fibroblasts, and secretory cells. Electron microscopic examination of the storage material in skin or conjunctival biopsy material typically shows curvilinear profiles. LINCL can be caused by autosomal recessive mutations of several different genes: *CLN2* gene, which codes for a tripeptidyl peptidase-1 (TPP1) that is essential for the degradation of cholecystokinin-8, as well as the *CLN5*, *CLN6*, and *CLN8* genes, which code for membrane proteins that have not been completely characterized. *CLN8* is also known as the locus of northern epilepsy syndrome, which is often called progressive epilepsy with cognitive impairment. *CLN2* has been treated with intraventricular cerliponase alfa with less decline in language and motor function but serious side effects.

Juvenile-type neuronal ceroid lipofuscinosis (JNCL, Spielmeyer-Vogt or **Batten disease)** is the most common form of NCL disease and is generally caused by autosomal-recessive mutations in *CLN3* . (Patients who present clinically with JNCL but have PPT1 or TPP1 deficiency are said to have variant INCL or LINCL, respectively.) Children affected with JNCL tend to develop normally for the 1st 5 yr of life. Their initial symptom is usually progressive visual loss and their retinal pigmentary changes often result in an initial diagnosis of retinitis pigmentosa. The funduscopic changes are similar to those for the late infantile type. After disease onset, there may be a rapid decline with changes in cognition and personality, motor incoordination, and seizures. Myoclonic seizures are not as prominent as in LINCL, but parkinsonism can develop and impair ambulation. Patients die in their late twenties to early thirties. In JNCL caused by *CLN3*, the electron microscopy of tissues show deposits called fingerprint profiles, and routine light microscopy of a peripheral blood smear may show lymphocyte vacuoles.

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617.3

Adrenoleukodystrophy

See Chapter 104.2 .

617.4

Sialidosis

Jennifer M. Kwon

Keywords

sialidosis
myoclonus
myoclonus epilepsy

Sialidosis is the result of lysosomal sialidase deficiency, secondary to autosomal recessive mutations in the sialidase (α-neuraminidase, *NEU1*) gene on chromosome 6p21.3. The accumulation of sialic acid–oligosaccharides with markedly increased urinary excretion of sialic acid–containing oligosaccharides is associated with clinical presentations that range from the milder sialidosis type I to the more severe sialidosis type II associated with both neurologic and somatic features.

Sialidosis type I, the **cherry-red spot myoclonus syndrome,** usually presents in the 2nd decade of life, when a patient complains of visual deterioration. Inspection of the retina shows a cherry-red spot, but, unlike patients with TSD, visual acuity declines slowly in individuals with cherry-red spot myoclonus syndrome. Myoclonus of the extremities is gradually progressive and often debilitating and eventually renders patients nonambulatory. The myoclonus is triggered by voluntary movement, touch, and sound and is not controlled with anticonvulsants. Generalized convulsions responsive to antiepileptic drugs occur in most patients.

Sialidosis type II patients present at a younger age and have cherry-red spots and myoclonus, as well as somatic involvement, including coarse facial features, corneal clouding (rarely), and dysostosis multiplex, producing anterior beaking of the lumbar vertebrae. Type II patients may be further subclassified into congenital and infantile (childhood) forms, depending on the age at presentation. Examination of lymphocytes shows vacuoles in the cytoplasm, biopsy of the liver demonstrates cytoplasmic vacuoles in Kupffer cells, and membrane-bound vacuoles are found in Schwann cell cytoplasm, all attesting to the multiorgan nature of sialidosis type II. No distinctive neuroimaging findings or abnormalities in electrophysiologic studies are noted in this group of disorders. Patients with sialidosis have been reported to live beyond the 5th decade.

Some cases of what appears to be sialidosis type II are the result of combined deficiencies of β-galactosidase and α-neuraminidase resulting from deficiency of protective protein/cathepsin A that prevents premature intracellular degradation of these two enzymes. These patients have galactosialidosis and they are clinically indistinguishable from those with sialidosis type II. Consequently, patients who have features of sialidosis type II with marked urinary excretion of oligosaccharides should be tested for protective protein/cathepsin A deficiency as well as sialidase deficiency.

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617.5

Miscellaneous Neurodegenerative Disorders

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Keywords

Pelizaeus-Merzbacher disease

hypomyelinating
leukodystrophy
Menkes disease
Alexander disease
Rett syndrome
brain iron

Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is an X-linked recessive disorder characterized by nystagmus and abnormalities of myelin. PMD is caused by mutations in the proteolipid protein *(PLP1)* gene, on chromosome Xq22, which is essential for CNS myelin formation and oligodendrocyte differentiation. Mutations in the same gene can cause familial spastic paraparesis (progressive spastic paraparesis type 2, SPG2). *PLP1* mutations causing disease include point mutations, deletions, gene duplications, and other gene dosage changes.

Clinically, classic PMD is recognized by nystagmus and roving eye movements, along with head nodding during infancy. Developmental milestones are delayed; ataxia, choreoathetosis, and spasticity ultimately develop. Optic atrophy and dysarthria are associated findings, and death occurs in the 2nd or 3rd decade. The major pathologic finding is a loss of myelin with intact axons, suggesting a defect in the function of oligodendroglia. An MRI scan shows a symmetric pattern of delayed myelination. It is now recognized that a broad spectrum of phenotypes, including SPG2 and peripheral nerve abnormalities, can also result from mutations in the *PLP1* gene.

Other PMD-like, hypomyelinating leukodystrophies continue to be identified and should be considered in the differential diagnosis of PMD. These include Allan-Herndon-Dudley syndrome and the TUBB4A related disorders

Alexander Disease

This is a rare disorder that causes progressive macrocephaly and leukodystrophy. Alexander disease is caused by dominant mutations in the glial fibrillary acidic protein *(GFAP)* gene, on chromosome 17q21, and cases are usually sporadic in families. Pathologic examination of the brain discloses deposition of eosinophilic hyaline bodies called Rosenthal fibers in astrocyte processes. These accumulate in a perivascular distribution throughout the brain. In the classic infantile form of Alexander disease, degeneration of white matter is most prominent frontally. The diagnosis may be suggested by MRI (Fig. 617.3) and MR spectroscopy demonstrating abnormal metabolic substrates. Affected children develop progressive loss of intellect, spasticity, and unresponsive seizures causing death by 5 yr of age. However, there are milder forms that present later in life and may not have the characteristic frontal predominance or megalencephaly.

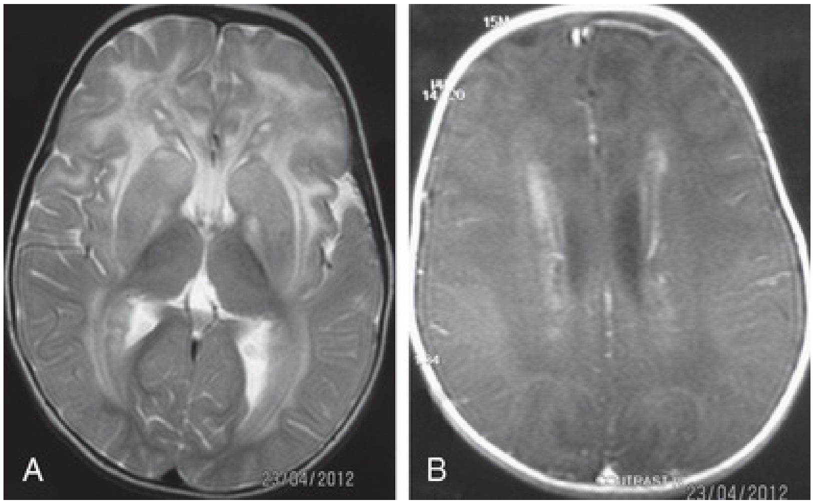

FIG. 617.3 Alexander disease. MRI of the index patient at the age of 15 mo. **A,** Axial T2-weighted sequences (TR/TE: 4000/99) at the basal ganglia and thalamus level demonstrating diffuse bilateral, symmetric increased signal predominantly of the frontal periventricular, but also of the subcortical, white matter and the basal ganglia. **B,** Significant periventricular rim after intravenous gadolinium infusion (T1-weighted sequences; TR/TE: 400/88). (From Zafeiriou DI, Dragoumi P, Vargiami E: Alexander disease. J Pediatr 162:648, 2013.)

Canavan Spongy Degeneration

See Chapter 103.15 .

Other Leukodystrophies

Metabolic and degenerative disorders can present with significant cerebral white matter changes, such as some mitochondrial disorders (see Chapters 104.1 and 616.2) and glutaric aciduria type 1 (see Chapter 103.14). In addition, the broader use of brain MRI has brought to light new leukodystrophies.

One example is vanishing white matter disease or childhood ataxia with central nervous system (CNS) hypomyelination characterized by ataxia and spasticity (Fig. 617.4). Some patients also have optic atrophy, seizures, and cognitive deterioration. The age of presentation and the rapidity of decline in leukodystrophies can be quite variable. In the early-onset forms, decline is usually rapid and followed quickly by death; in the later-onset forms, mental decline is usually slower and milder. Interestingly, acute demyelination in these disorders can be triggered by fever or fright. The diagnosis of vanishing white matter disease or childhood ataxia with CNS hypomyelination is based on clinical findings, characteristic abnormalities on cranial MRI, and autosomal recessive mutations in one of five causative genes *(EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5)* encoding the five subunits of the eucaryotic translation initiation factor, eIF2B. An approach to leukodystrophies based on MRI findings is noted in Fig. 617.5 , and the diagnostic evaluation is noted in Table 617.3 .

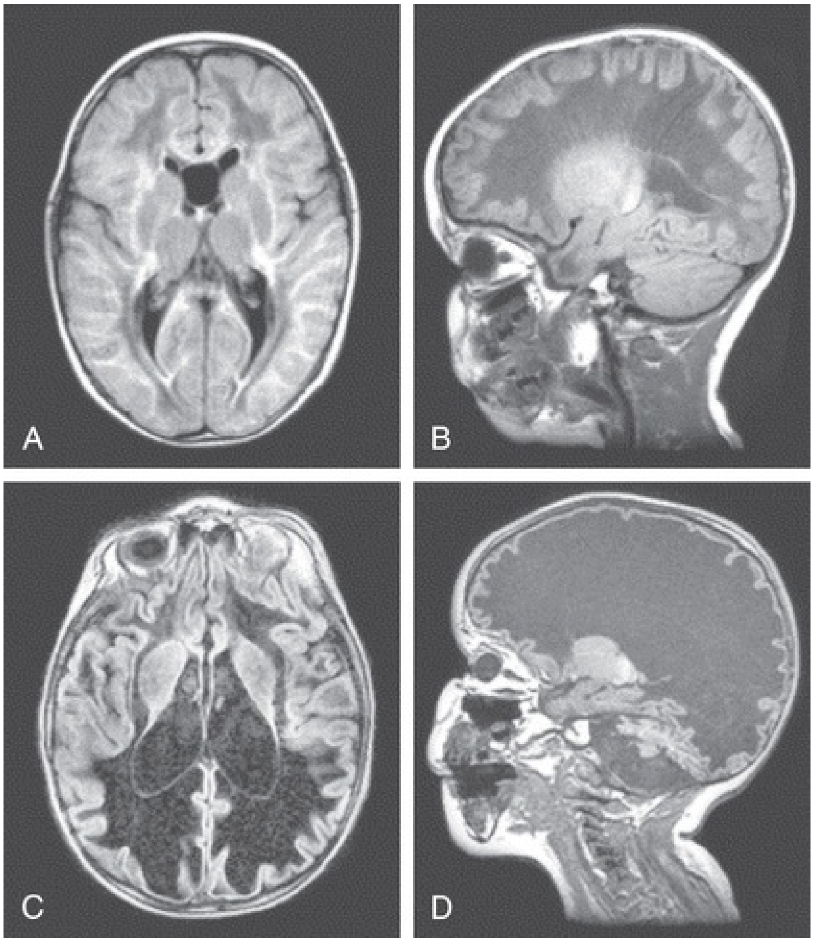

FIG. 617.4 T1-weighted and FLAIR images of a patient with vanishing white matter disease. Axial FLAIR **(A, C)** and sagittal T1-weighted **(B, D)** images of a patient at ages 1½ and 2½ yr. The first MRI **(A, B)** was obtained soon after the onset of symptoms. The initial FLAIR image **(A)** shows diffuse abnormality and partial cystic degeneration of the cerebral white matter, whereas the follow-up FLAIR image **(C)** shows that all of the cerebral white matter has been replaced by fluid. The initial T1-weighted sagittal image **(B)** shows the typical stripe-like pattern within the abnormal white matter, whereas the follow-up image **(D)** shows that all of the cerebral white matter has disappeared and that only the cerebral cortex and ependymal lining are preserved. Surprisingly, the absent white matter looks swollen with stretching of the overlying cortex in the broad gyri. The cerebellum has become highly atrophic. (From Van der Knaap MS, Valk J: Magnetic resonance of myelination and myelin disorders, 3e. Heidelberg, 2004, Springer.)

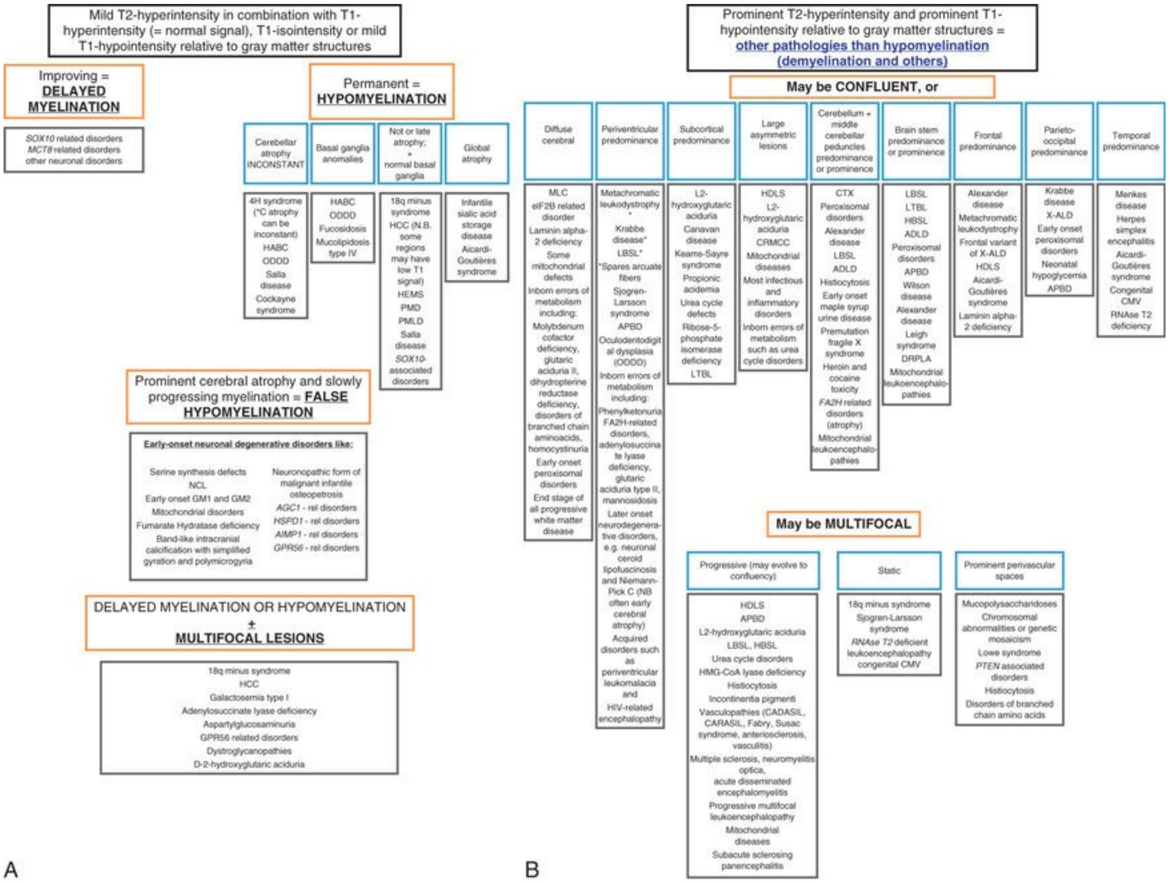
A
Mild T2-hyperintensity in combination with T1-hyperintensity (= normal signal), T1-isointensity or mild T1-hypointensity relative to gray matter structures
Improving = DELAYED MYELINATION
SOX10 related disorders
MCT8 related disorders
other neuronal disorders
Permanent = HYPOMYELINATION
Cerebellar atrophy INCONSTANT
Basal ganglia anomalies
Not or late atrophy; + normal basal ganglia
Global atrophy
4H syndrome (*C atrophy can be inconstant)
HABC
ODDD
Salla disease
Cockayne syndrome
HABC
ODDD
Fucosidosis
Mucolipidosis type IV
18q minus syndrome
HCC (N.B. some regions may have low T1 signal)
HEMS
PMD
PMLD
Salla disease
SOX10-associated disorders
Infantile sialic acid storage disease
Aicardi-Goutières syndrome
Prominent cerebral atrophy and slowly progressing myelination = FALSE HYPOMYELINATION
Early-onset neuronal degenerative disorders like:
Serine synthesis defects
NCL
Early onset GM1 and GM2
Mitochondrial disorders
Fumarate Hydratase deficiency
Band-like intracranial calcification with simplified gyration and polymicrogyria
Neuronopathic form of malignant infantile osteopetrosis
AGC1 - rel disorders
HSPD1 - rel disorders
AIMP1 - rel disorders
GPR56 - rel disorders
DELAYED MYELINATION OR HYPOMYELINATION ± MULTIFOCAL LESIONS
18q minus syndrome
HCC
Galactosemia type I
Adenylosuccinate lyase deficiency
Aspartylglucosaminuria
GPR56 related disorders
Dystroglycanopathies
D-2-hydroxyglutaric aciduria
B
Prominent T2-hyperintensity and prominent T1-hypointensity relative to gray matter structures = other pathologies than hypomyelination (demyelination and others)
May be CONFLUENT, or
Diffuse cerebral
Periventricular predominance
Subcortical predominance
Large asymmetric lesions
Cerebellum + middle cerebellar peduncles predominance or prominence
Brain stem predominance or prominence
Frontal predominance
Parieto-occipital predominance
Temporal predominance
MLC
eIF2B related disorder
Laminin alpha-2 deficiency
Some mitochondrial defects
Inborn errors of metabolism including: Molybdenum cofactor deficiency, glutaric aciduria II, dihydropterine reductase deficiency, disorders of branched chain aminoacids, homocystinuria
Early onset peroxisomal disorders
End stage of all progressive white matter disease
Metachromatic leukodystrophy*
Krabbe disease*
LBSL*
*Spares arcuate fibers
Sjogren-Larsson syndrome
APBD
Oculodentodigital dysplasia (ODDD)
Inborn errors of metabolism including: Phenylketonuria FA2H-related disorders, adenylosuccinate lyase deficiency, glutaric aciduria type II, mannosidosis
Later onset neurodegenerative disorders, e.g. neuronal ceroid lipofuscinosis and Niemann-Pick C (NB often early cerebral atrophy)
Acquired disorders such as periventricular leukomalacia and HIV-related encephalopathy
L2-hydroxyglutaric aciduria
Canavan disease
Kearns-Sayre syndrome
Propionic acidemia
Urea cycle defects
Ribose-5-phosphate isomerase deficiency
LTBL
HDLS
L2-hydroxyglutaric aciduria
CRMCC
Mitochondrial diseases
Most infectious and inflammatory disorders
Inborn errors of metabolism such as urea cycle disorders
CTX
Peroxisomal disorders
Alexander disease
LBSL
ADLD
Histiocytosis
Early onset maple syrup urine disease
Premutation fragile X syndrome
Heroin and cocaine toxicity
FA2H related disorders (atrophy)
Mitochondrial leukoencephalopathies
LBSL
LTBL
HBSL
ADLD
Peroxisomal disorders
APBD
Wilson disease
Alexander disease
Leigh syndrome
DRPLA
Mitochondrial leukoencephalopathies
Alexander disease
Metachromatic leukodystrophy
Frontal variant of X-ALD
HDLS
Aicardi-Goutières syndrome
Laminin alpha-2 deficiency
Krabbe disease
X-ALD
Early onset peroxisomal disorders
Neonatal hypoglycemia
APBD
Menkes disease
Herpes simplex encephalitis
Aicardi-Goutières syndrome
Congenital CMV
RNAse T2 deficiency
May be MULTIFOCAL
Progressive (may evolve to confluency)
Static
Prominent perivascular spaces
HDLS
APBD
L2-hydroxyglutaric aciduria
LBSL, HBSL
Urea cycle disorders
HMG-CoA lyase deficiency
Histiocytosis
Incontinentia pigmenti
Vasculopathies (CADASIL, CARASIL, Fabry, Susac syndrome, anteriosclerosis, vasculitis)
Multiple sclerosis, neuromyelitis optica, acute disseminated encephalomyelitis
Progressive multifocal leukoencephalopathy
Mitochondrial diseases
Subacute sclerosing panencephalitis
18q minus syndrome
Sjogren-Larsson syndrome
RNAse T2 deficient leukoencephalopathy
congenital CMV
Mucopolysaccharidoses
Chromosomal abnormalities or genetic mosaicism
Lowe syndrome
PTEN associated disorders
Histiocytosis
Disorders of branched chain amino acids

FIG. 617.5 MRI pattern recognition in the leukodystrophies and genetic leukoencephalopathies (gLEs). Three major MRI characteristics help to discriminate between the different types of leukodystrophy and gLE. The first discriminator is the presence or absence of *hypomyelination* **(A).** Within this subset, the presence of improvement of myelination or atrophy directs the clinician toward a series of gLEs. Within the true hypomyelinating leukodystrophies, the presence of basal ganglia and cerebellar involvement further helps refine the diagnosis. If the pattern is not one of hypomyelination, then the second discriminator is whether the white matter abnormalities are *confluent or isolated and multifocal* **(B).** If the white matter abnormalities are confluent, then the third discriminator is the *predominant localization of the abnormalities* **(B).** 4H, hypomyelination, hypodontia, and hypogonadotropic hypogonadism; HACB, hypomyelination with atrophy of the basal ganglia and cerebellum; HEMS, hypomyelination of early myelinating structures; ODDD, oculodentodigital dysplasia; HCC, hypomyelination with congenital cataract; PMD, Pelizaeus-Merzbacher disease; PMLD, Pelizaeus-Merzbacher–like disease; NCL, neuronal ceroid lipofuscinosis; APDB, adult polyglucosan body disease; ADLD, autosomal dominant leukodystrophy with autonomic symptoms; CRMCC, cerebroretinal microangiopathy with calcifications and cysts; CTX, cerebrotendinous xanthomatosis; DRPLA, dentatorubral pallidoluysian atrophy; *E1F2B*- related disorder (vanishing white matter disease or CACH; HDLS, hereditary diffuse leukoencephalopathy with spheroids/neuroaxonal leukodystrophy with spheroids; HBSL, hypomyelination with brainstem and spinal cord and leg involvement; LTBL, leukoencephalopathy with thalamic

and brainstem involvement and high lactate; LBSL, leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MLC, megalencephalic leukodystrophy with subcortical cysts; X-ALD, X-linked adrenoleukodystrophy. (Pattern recognition reprinted with permission from Genereviews; from Parikh S, Bernard G, Leventer RJ, et al: A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies, Mol Gen Metab 114:501-515, 2018, Fig. 2, pp. 508-509.)

Table 617.3

Clinical and Laboratory Tests That Aid in the Diagnosis of Leukodystrophies and Genetic Leukoencephalopathies

CLINICAL/LABORATORY TEST *	DIAGNOSTIC TARGET
Brain and spinal MRI (± gadolinium, ± MRS)	Establish white matter disease; ± evidence of leaky blood brain–barrier and metabolite accumulation (mitochondrial disorders, Canavan disease, Sjögren-Larson syndrome, peroxisomal biogenesis disorders)
Ophthalmologic exam	Document ophthalmologic signs in several leukodystrophies
Head CT	Assess for calcifications
Plasma very-long-chain fatty acids	X-linked adrenoleukodystrophy and adrenomyeloneuropathy and peroxisomal biogenesis disorders
Lysosomal enzymes (leukocytes)	Metachromatic leukodystrophy, Krabbe disease, multiple sulfatase deficiency, galactosialidosis, sialidosis
Blood lactate, pyruvate, amino acids	Mitochondrial disorders
Lumbar puncture (cell count, protein, ± CSF neopterin, ± interferon-alpha)	Nonspecific marker of demyelination; ± pleocytosis and markers for Aicardi-Goutières syndrome
Urine sulfatides	Metachromatic leukodystrophy, multiple sulfatase deficiency
Urine organic acids	L-2-hydroxyglutarate; N-acetyl aspartic acid for Canavan disease; Krebs cycle intermediates (mitochondrial disorders)
Neurophysiologic studies (BAER EMG/NCV, VEP, SSEP)	Characterize involvement of cranial and peripheral nerves, optic tracts, and spinal tracts
Genetic analyses	As indicated for each leukodystrophy or genetic leukoencephalopathy

[*] Additional tests may be indicated for patients with certain distinctive clinical presentations or extraneurologic features suggestive of one or more specific leukodystrophies.

BAER, brainstem auditory evoked response test; CSF, cerebrospinal fluid; CT, computed tomography; EMG, electromyogram; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NCV, nerve conduction velocity test; SSEP, somatosensory evoked potential test; VEP, visual evoked potential test.

From Parikh S, Bernard G, Leventer RJ, et al: A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies, Mol Gen Metab 114:501-515, 2018, Table 6.

Menkes Disease

Menkes disease (kinky hair disease) is a progressive neurodegenerative condition inherited as an X-linked recessive trait. The Menkes gene, *ATP7A,* on Xq21.1, codes for a copper-transporting, P-type adenosine triphosphatase, and mutations in the protein are associated with low serum copper and ceruloplasmin levels, as well as a defect in intestinal copper absorption and transport. Symptoms begin in the first few months of life and include hypothermia, hypotonia, and generalized myoclonic seizures. The facies are distinctive, with chubby, rosy cheeks and kinky, colorless, friable hair. Microscopic examination of the hair shows several abnormalities, including trichorrhexis nodosa (fractures along the hair shaft) and pili torti (twisted hair). Feeding difficulties are prominent and lead to failure to thrive. Severe cognitive impairment and optic atrophy are constant features of the disease. Neuropathologic changes include tortuous degeneration of the gray matter and marked changes in the cerebellum with loss of the internal granule cell layer and necrosis of the Purkinje cells. Death can occur by 3 yr of age in untreated patients. Very rarely does Menkes disease manifest in females, and when it does, symptoms are milder.

Copper histidine therapy may be effective in preventing neurologic deterioration in some patients with Menkes disease, particularly when treatment is begun in the neonatal period or, preferably, with the fetus. These presymptomatic children are currently identified because of a family history of an affected brother. Copper is essential in the early stages of CNS development, and its absence probably accounts for the neuropathologic changes. Infants diagnosed presymptomatically in the 1st 10 days of life can be started on an experimental protocol of daily copper–histidine subcutaneous injections (as of 2017, only available at NIH under a program supervised by Dr. Stephen Kaler). Optimal response to copper–histidine injection treatment appears to occur only in patients who are identified in the newborn period and whose mutations permit residual copper-transport activity.

The **occipital horn syndrome,** a skeletal dysplasia caused by different mutations in the same gene as that involved in Menkes disease, is a relatively mild disease. The two diseases are often confused, because the biochemical abnormalities are identical. Resolution of the uncertainty about treatment of patients with Menkes disease will require careful genotype–phenotype correlation, along with further clinical trials of copper therapy.

Rett Syndrome

This syndrome is not strictly speaking a degenerative disease but is a disorder of early brain development marked by a period of developmental regression and deceleration of brain growth after a relatively normal neonatal course. It is an X-linked disease that occurs predominantly in females. The frequency is approximately 1 in 15,000-22,000 children. Rett syndrome is caused by mutations in the *MeCP2* gene on Xq28, which codes for a transcription factor that binds to methylated CpG islands and silences transcription. Development may proceed normally until 1 yr of age, when regression of language and motor milestones and acquired microcephaly become apparent. An ataxic gait or fine tremor of hand movements is an early neurologic finding. Most children develop peculiar sighing respirations with intermittent periods of apnea that may be associated with cyanosis. The hallmark of Rett syndrome is repetitive hand-wringing movements and a loss of purposeful and spontaneous use of the hands; these features may not appear until 2-3 yr of age. Autistic behavior is a typical finding in all patients. Generalized tonic-clonic convulsions occur in the majority but may be well controlled by anticonvulsants. Feeding disorders and poor weight gain are common. After the initial period of neurologic regression, the disease process appears to plateau, with persistence of the autistic behavior. Cardiac arrhythmias may result in sudden, unexpected death at a rate that is higher than the general population. Generally, females survive into adulthood.

Postmortem studies show significantly reduced brain weight (60–80% of normal) with a decrease in the number of synapses, associated with a decrease in dendritic length and branching. The phenotype may be related to failure to suppress expression of genes that are normally silent in the early phases of postnatal development. Although very few males survive with the classic Rett syndrome phenotype, genotyping of boys without the classic Rett syndrome phenotype but with intellectual disability and other atypical neurologic features has detected a significant number with mutations in *MeCP2.* Mutations in *MeCP2* have been demonstrated in normal female carriers, females with Angelman syndrome, and males with fatal encephalopathy, Klinefelter (47 XXY) syndrome, and familial X-linked cognitive impairment. Males may present with a Rett-like syndrome if they have an *MECP2* duplication.

Some females have an atypical Rett phenotype associated with severe myoclonic seizures in infancy, slowing of head growth, and developmental arrest and have mutations in another X-linked gene encoding for cyclin-dependent kinase–like 5 (CDKL5), which may interact with MeCP2 and other proteins regulating gene expression.

Neurodegeneration With Brain Iron Accumulation

Neurodegeneration with brain iron accumulation represents multiple, age-of-onset–dependent disorders characterized by extrapyramidal symptoms and intellectual deterioration and regression, with iron deposition in the basal ganglia. There is significant phenotypic variability of these disorders; however, a characteristic finding on MRI demonstrates symmetric T2-signal homogeneous *hypointensity*. Common neurodegeneration with brain iron accumulation disorders are distinguished in Table 617.4 and an approach to their diagnosis is noted in Fig. 617.6 . Clinical features, which are highly variable, may include dystonia, parkinsonism, ataxia, spasticity, psychiatric symptoms, and intellectual impairment. Treatment should focus on the specific disorder and is usually symptomatic relief rather than curative. Iron chelation has been attempted without major long-term benefit.

Table 617.4

Overview of Neurodegeneration With Brain Iron Accumulation Conditions and Genes (if Known)

CONDITION (ACRONYM)	SYNONYM	GENE	CHROMOSOMAL POSITION	LB PATHOLOGY	CHILDHOOD-ONS VARIANT	
					AGE OF ONSET	CLINICA PRESEN
PKAN	NBIA1	*PANK2*	20p13	No	Early childhood, around age 3	Typical P
PLAN	NBIA2, PARK14	*PLA2G6*	22q12	√	Infancy	Infantile neuroaxo dystrophy
FAHN	SPG35	*FA2H*	16q23	Not known	Childhood	Leukodys hereditary paraplegi
MPAN	—	*C19orf12*	19q12	√	—	Pyramida extrapyra syndrome

Kufor-Rakeb disease	PARK9	*ATP13A2*	1p36	√	Childhood-teens	Parkinsor pyramida signs, eye movemer
BPAN	SENDA syndrome	*WDR45*	Xp11.23	Not known	Childhood	Encephal with psyc regressio static
Aceruloplasminemia	—	*CP*	3q23	No	—	—
Neuroferritinopathy	—	*FTL*	19q13	No	—	—
Idiopathic late-onset cases	—	Probably heterogeneous	Probably heterogeneous	Heterogeneous	—	—

√, Present; BPAN, beta-propeller–associated neurodegeneration; CP, ceruloplasmin; FA2H, fatty acid 2-hydroxylase; FAHN, fatty acid 2-hydroxylase–associated neurodegeneration; FTL, ferritin light chain; MPAN, mitochondrial membrane–associated neurodegeneration; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase 2; PKAN, pantothenate kinase–associated neurodegeneration; PLA2G6, phospholipase A2; PLAN, PLA2G6-associated neurodegeneration; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood; SPG, spastic paraplegia.

From Schneider SA, Zorzi G, Nardocci N: Pathophysiology and treatment of neurodegeneration with brain iron accumulation in the pediatric population, Curr Treat Option Neurol 15:652-667, 2013, Table 1.

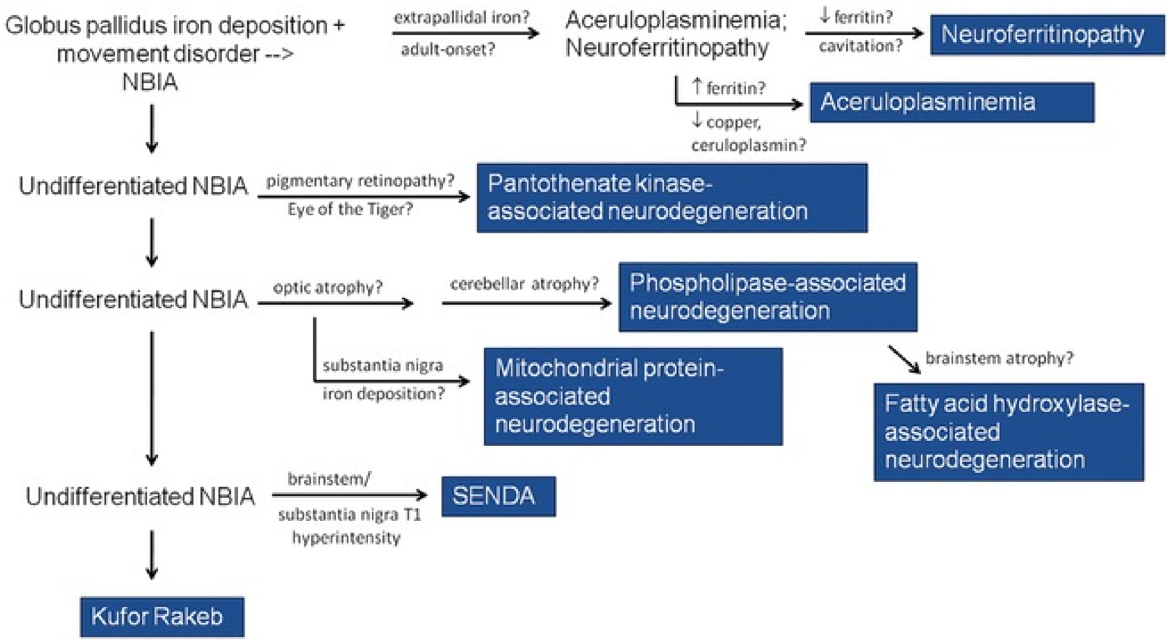
Globus pallidus iron deposition + movement disorder --> NBIA
extrapallidal iron?
adult-onset?
Aceruloplasminemia; Neuroferritinopathy
↓ferritin?
cavitation?
Neuroferritinopathy
↑ferritin?
↓copper, ceruloplasmin?
Aceruloplasminemia
Undifferentiated NBIA
pigmentary retinopathy?
Eye of the Tiger?
Pantothenate kinase-associated neurodegeneration
Undifferentiated NBIA
optic atrophy?
cerebellar atrophy?
Phospholipase-associated neurodegeneration
substantia nigra iron deposition?
Mitochondrial protein-associated neurodegeneration
brainstem atrophy?
Fatty acid hydroxylase-associated neurodegeneration
Undifferentiated NBIA
brainstem/ substantia nigra T1 hyperintensity
SENDA
Kufor Rakeb

FIG. 617.6 Clinical and radiographic approach to neurodegeneration with brain iron accumulation. NBIA, neurodegeneration with brain iron

accumulation; SENDA, static encephalopathy of childhood with neurodegeneration in adulthood. (From Kruer MC, Boddaert N: Neurodegeneration with brain iron accumulation: a diagnostic algorithm, Semin Pediatr Neurol 19:67-74, 2012, Fig. 1.)

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CHAPTER 618

Demyelinating Disorders of the Central Nervous System

Cheryl Hemingway

Acquired demyelinating disorders of the central nervous system (CNS) collectively are rare disorders occurring with an annual incidence of 0.5-1.66 per 100,000 children. They present with neurologic dysfunction caused by immune-mediated attacks on the white matter insulating the brain, optic nerves, and spinal cord. The white matter insulation is formed by myelin contained within oligodendrocytes wrapping around nerve axons. In contrast to genetically determined leukodystrophies (sometimes called dysmyelinating disorders) that produce disrupted white matter, acquired demyelinating disorders generally target normally formed white matter.

There have been significant advances in our understanding of the pathogenesis of demyelination together with a growing interest in the role of B cells and CNS antibodies in demyelination. There are two IgG antibodies recognized as playing an important role in demyelination, aquaporin 4-antibody (AQP4-Ab) and myelin oligodendrocyte glycoprotein antibody (MOG-Ab). The aquaporins, plasma membrane water-transporting proteins, are expressed in astrocytes and involved in water movement, cell migration, and neuroexcitation. Myelin oligodendrocyte glycoprotein is exclusively expressed in the CNS, and although it is only a minor component of the myelin sheath, its location on the outermost lamellae and on the cell surface of oligodendrocytes makes it available for antibody binding. Increased awareness of the importance of these antibodies, together with available disease-modifying treatments (DMTs) has made accurate diagnosis in demyelinating disorders crucial.

Pediatric demyelinating syndromes are characterized clinically by (1) localization of neurologic deficits (i.e., a single site, such as the spinal cord [transverse myelitis, TM], optic nerves [optic neuritis, ON], or brainstem versus a polyregional demyelination); (2) the presence or absence of encephalopathy; (3) the disease course (i.e., monophasic versus repeated attacks involving either the same region or new CNS regions); and (4) the presence or absence of specific antibodies.

MRI of the brain and spine is useful to characterize both symptomatic and clinically silent demyelinating lesions, aid in the diagnosis of demyelinating syndrome, and predict the likelihood of further recurrence. Serial MRIs may be needed to confirm the diagnosis and can be used to monitor the treatment response and guide the escalation of a DMT. The presence of oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) analysis is used to confirm the diagnosis of multiple sclerosis (MS) (Table 618.1); their absence may suggest an alternative diagnosis. However, OCBs are seen in other inflammatory CNS diseases. Additional studies, including an autoimmune profile, antibody testing, metabolic testing, genetic testing, catheter angiography, and sometimes even brain biopsy, may be required to evaluate for mimics of demyelination, such as systemic rheumatologic disorders, mitochondrial disorders, primary CNS angiitis, infection, neoplasm, and genetic conditions such as leukodystrophies (Tables 618.2 and 618.3).

Table 618.1

Acute Demyelinating Disorders of the Central Nervous System

DISORDER	DEFINITION
Acute disseminated encephalomyelitis (ADEM)	A first polyfocal CNS event with presumed inflammatory cause Encephalopathy present that cannot be explained by fever MRI often showing diffuse, poorly demarcated T2 lesions No new symptoms, signs, or MRI findings after initial 3 mo
Multiphasic ADEM	New event of ADEM 3 mo or more after the initial event that can be associated with new or reemerging prior clinical and MRI findings Frequently associated with the presence of MOG-Ab
Clinically isolated syndrome (CIS)	A first monofocal or multifocal CNS demyelinating event Encephalopathy is absent, unless caused by fever
Multiple sclerosis (MS)	MS can be diagnosed in those for whom there is **no better explanation** if dissemination in time (DIT) and dissemination in space (DIS) can be demonstrated. **DIS is met when** there are neurologic lesions affecting separate sites (periventricular, juxtacortical, infratentorial, or spinal regions) within the CNS **DIT is met when** MRI demonstrates the simultaneous presence of a gadolinium-enhancing lesion and nonenhancing lesion OCBs are positive in the CSF or follow-up MRI after at least 30 days shows accumulation of a new T2 lesion

Primary progressive MS	PPMS is very rare in childhood but can be diagnosed after 1 yr of a progressive deficit and 2 of the following: (1) a positive brain MRI, (2) a positive spinal cord MRI, and (3) positive OCB
MOG-Ab–associated demyelination	MDEM: recurrent ADEM (see above) ADEM-ON: ADEM or MDEM followed by optic neuritis (ON) NMOSD: ON and acute transverse myelitis (ATM), either sequentially or simultaneously Relapsing inflammatory ON (RION) Brainstem demyelination: recurrent episodes of demyelination often involving in particular the posterior fossa and brainstem
Neuromyelitis optica spectrum disorders (NMOSDs)	Provided there is no better explanation, if AQP4–positive, then only one of the following core criteria is needed: optic neuritis acute myelitis area postrema syndrome (nausea, vomiting, hiccups) acute brainstem syndrome narcolepsy, acute diencephalic syndrome with MRI lesions symptomatic cerebral syndrome with MRI lesions If AQP4-negative or unavailable need 2 core criteria (one of which needs to be ON with compatible brain MRI or longitudinally extensive optic nerve changes, longitudinally extensive TM, or area postrema syndrome with MRI-compatible lesion) dissemination in space (2 or more different core criteria)

Table 618.2

Differential Diagnosis of Demyelinating Disorders

Multifocal white matter lesions	Demyelination (e.g., ADEM, MS, CIS, NMOSD, AHL) Primary and secondary vasculitides (e.g., primary angiitis of the CNS, neurosarcoid, SLE, Bechet syndrome, scleroderma) Autoantibody (e.g., NMDAR-Ab, Hashimoto encephalopathy) Mitochondrial (e.g., POLG) Leukoencephalopathy (e.g., DARS) X-linked Charcot-Marie-Tooth disease Migraine Normal variant Prior insult and residual gliosis (e.g., congenital infections or hypoxic damage)
Bilateral or diffuse white matter lesions	Leukodystrophy (e.g., adrenal LD, Alexander disease, metachromatic LD, Krabbe disease) Leukoencephalopathy (e.g., Aicardi-Goutières syndrome) Mitochondrial (e.g., Leber hereditary optic neuropathy, Leigh disease, MELAS, MERFF) Tumor (e.g., gliomatosis cerebri, astrocytoma, lymphoma) Hemophagocytic lymphohistiocytosis (HLH) Tumor Infection
Deep gray, thalamic, and striatal lesions	Infection (e.g., mycoplasma, Epstein-Barr virus, West Nile virus, Japanese B encephalitis, enterovirus) Biotin-responsive basal ganglia disease (e.g., SLC19A3) Acute necrotizing encephalopathy (ANE) and *RANBP2* gene mutation

Table 618.3

MR Imaging Red Flags for the Diagnosis of Children with Acquired Demyelinating Syndromes

MR imaging	Leptomeningeal enhancement	SVcPACNS Infection Tumor HLH	Leptomeningeal enhancement is not a feature of MS in adults; it has emerged as a red flag for vasculitic or malignant processes in the pediatric cohort.
	Lesion expansion	Tumor Lymphoma PML Sarcoidosis	Increased size of T2 lesions on serial imaging is well recognized in MS, although this should always prompt consideration of malignancy. Increasing size of a white matter–predominant lesion without lesion enhancement in a patient treated with immunosuppressant therapy (or a patient with known HIV) should prompt consideration of PML. PML is a risk for MS patients exposed to more intense immunosuppressive therapies.
	Hemorrhage	ANE Stroke Cerebellitis AHLE Large-vessel CNS vasculitis SVcPACNS	Although susceptibility-weighted imaging reveals tiny microfoci of hemosiderin in MS patients, hemorrhage large enough to be visible on conventional MRI sequences is not a feature of ADS or MS, and should prompt consideration of disorders in which the cerebral vasculature is specifically involved.

ADS, acquired demyelinating syndrome; AHLE, acute hemorrhagic leukoencephalitis; CNS, central nervous system; HIV, human immunodeficiency virus; HLH, hemophagocytic lymphohistiocytosis; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; SVcPACNS, small-vessel childhood primary angiitis of the central nervous system.

From O'Mahony J, Shroff M, Banwell B: Mimics and rare presentations of pediatric demyelination, Neuroimaging Clin North Am 23:321-336, 2013, Table 2.

The majority of children presenting with an episode of demyelination are monophasic; they do not relapse. Monophasic demyelinating disorders of childhood include acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis (TM); relapsing forms of demyelination include MS and neuromyelitis optica spectrum disorder (NMOSD).

618.1

Acute Disseminated Encephalomyelitis

Cheryl Hemingway

ADEM is an inflammatory, demyelinating event of early childhood presenting with an acute onset of *polyfocal* neurologic deficits, accompanied by *encephalopathy* and changes compatible with demyelination on brain MRI (see Table 618.1).

Epidemiology

Although ADEM can occur at any age, most series report a mean age of between 5 and 8 yr with a slight male predominance. The reported incidence ranges from 0.1-0.6 per 100,000 per year in the pediatric population. ADEM is usually monophasic, but recurrence can occur; if the recurrence is 3 mo or longer after the first episode, the condition is termed *multiphasic disseminated encephalomyelitis (MDEM)*. Up to 50% of cases of ADEM have been found to be associated with MOG-Ab positivity in the serum (see Chapter 618.6), and almost all cases of MDEM are MOG-Ab positive; there is thus a strong likelihood that as MOG-Ab testing becomes more available, cases of non-MOG-Ab–positive MDEM will become exceptionally rare. An episode of ADEM can also be followed by non-ADEM demyelination in a new location. In this scenario, if the MOG-Ab is negative, MS may be diagnosed. If ADEM is followed by a relapse in a specific location, such as the optic nerve (ON), then ADEM-ON is diagnosed. If the ON and spinal cord are involved, then NMOSD (see Table 618.1); the latter two are frequently associated with MOG-Ab positivity.

Pathogenesis

Molecular mimicry induced by infectious exposure or vaccine has been thought to trigger production of CNS autoantigens, although causality has never been proven. Many patients experience a transient febrile illness in the month prior to ADEM onset. Preceding infections associated with ADEM include influenza, Epstein-Barr virus, cytomegalovirus, varicella, enterovirus, measles, mumps, rubella, herpes simplex, and *Mycoplasma pneumoniae*. Postvaccination ADEM has been reported following immunizations for rabies, smallpox, measles, mumps, rubella, Japanese encephalitis B, pertussis, diphtheria–polio–tetanus, and influenza, although the risk of ADEM postvaccination is significantly lower than following the infection itself.

Clinical Manifestations

Initial symptoms of ADEM may include lethargy, fever, headache, vomiting, meningeal signs, and seizures, including status epilepticus. *Encephalopathy* is the hallmark of ADEM, ranging from changes in behavior and persistent irritability to coma. Focal neurologic deficits can be difficult to ascertain in the obtunded or very young child, but common neurologic signs in ADEM include visual loss, cranial neuropathies, ataxia, and motor and sensory deficits, plus bladder/bowel dysfunction with concurrent spinal cord demyelination. The clinical course is usually rapidly progressive over days. Intensive care unit admission may be required, particularly for patients with brainstem dysfunction or raised intracranial pressure.

Neuroimaging

Head CT scanning may be normal or show hypodense regions. Cranial MRI, the imaging study of choice, typically exhibits bilateral, large, multifocal, and sometimes confluent, edematous mass-like T2 lesions with variable enhancement within white and gray matter of the cerebral hemispheres, cerebellum, and brainstem. Deep gray matter structures (e.g., thalami, basal ganglia) are often involved, although this may not be specific to ADEM (Figs. 618.1 and 618.2). The spinal cord may have an abnormal T2 signal or enhancement, with or without clinical signs of myelitis. MRI lesions of ADEM typically appear to be of similar age, but their evolution may lag behind the clinical presentation. Serial MRI imaging 3-12 mo following ADEM shows improvement and often complete resolution of T2 abnormalities, although residual gliosis may remain.

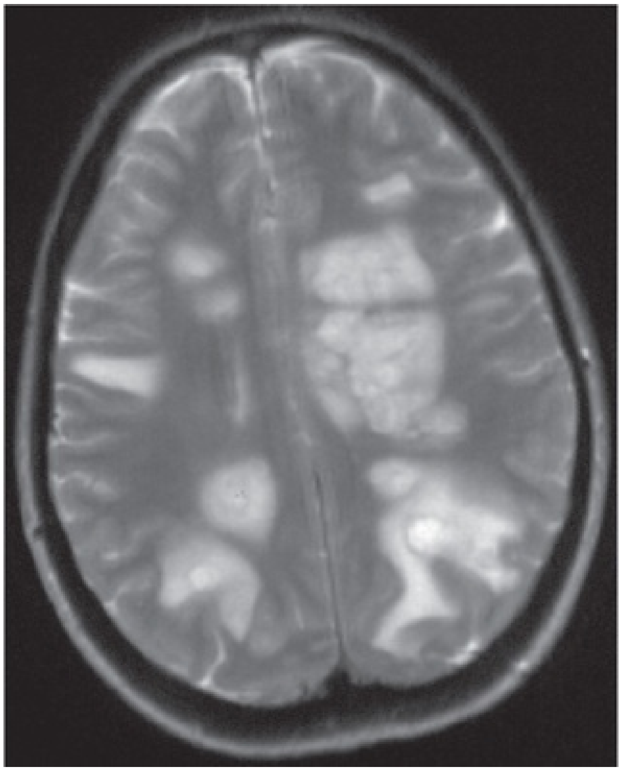

FIG. 618.1 Girl 6 yr of age diagnosed with ADEM presenting with encephalopathy, ataxia, and motor deficits following mild viral infection. MRI T2-weighted axial image shows bilateral, diffuse, poorly demarcated lesions. Gray matter involvement, including thalamus and basal ganglia, is commonly seen.

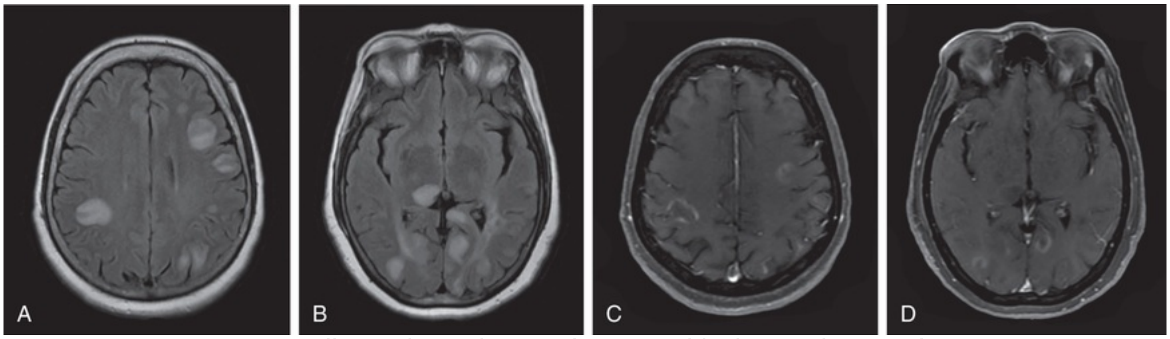

FIG. 618.2 Acute disseminated encephalomyelitis (ADEM). **A** and **B,** T2-FLAIR images show numerous asymmetric rounded hyperintense, predominantly subcortical, white matter lesions. Some lesions involve the cortex. A right pulvinar lesion is also seen. **C** and **D,** Postcontrast T1 image demonstrates incomplete ring enhancement associated with these lesions. All the lesions show similar imaging features. Marked improvement was seen after steroid therapy. (From Haaga JR, Boll DT (eds): CT and MRI of the whole body, 6th ed, vol 1, Philadelphia, 2017, Elsevier, Fig 10-15, p.

280.)

Severe involvement may progress to an **acute hemorrhagic leukoencephalopathy** (Weston-Hurst disease) with large lesions, edema, mass affect, and a polymorphonucleated cell pleocytosis (in contrast to lymphocytic pleocytosis in the CSF noted in typical ADEM).

Laboratory Findings

There is no biologic marker for ADEM, and laboratory findings can vary widely. CSF studies are often normal or can exhibit pleocytosis with lymphocytic or monocytic predominance. CSF protein can be elevated, especially on repeat studies. Elevated CSF immune globulin production can be present, but true OCB positivity is rare. Electroencephalograms often show generalized slowing, consistent with *encephalopathy*, although polyregional demyelination of ADEM can also cause focal slowing or epileptiform discharges.

Differential Diagnosis

ADEM is a clinical diagnosis supported by MRI, CSF, and serum findings. The differential diagnosis for ADEM is broad, and empirical antibiotic and antiviral treatment should be considered while infectious evaluations are pending. Follow-up MRI examinations 3-12 mo after ADEM should show improvement; new or enlarging T2 lesions should prompt reevaluation for other etiologies, such as MS, antibody-associated disorders, leukodystrophies, tumor, vasculitis, or mitochondrial, metabolic, or rheumatologic disorders (Table 618.4 and see Tables 618.1 to 618.3).

Table 618.4

Features That May Distinguish ADEM from a First Attack of MS

	ADEM WITH OR WITHOUT MOG-AB	MS
Age and sex	<10 yr Boys and girls equal	>10 yr Female preponderance
Seizures	+	−
Encephalopathy	+	−
Fever/vomiting	+	−
Family history	No	20%

Optic neuritis	Bilateral	Unilateral
Manifestations	Polysymptomatic	Monosymptomatic
CSF	Pleocytosis (lymphocytosis) OCBs negative	Acellular OCBs positive
MRI	Large, fluffy, poorly demarcated T2 lesions involving white and gray matter	Ovoid T2 lesions involving juxtacortical, periventricular, or infratentorial areas or spinal lesions; T1 hypointense lesions
MRI follow-up after 30 days	No new lesions	New lesions seen

+ , More likely to be present; −, less likely to be present; ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis, MOG-Ab, myelin oligodendrocyte glycoprotein antibody; OCBs, oligoclonal bands.

Treatment

Although there are no randomized controlled trials to compare acute treatments for ADEM or other demyelinating disorders of childhood, high-dose intravenous steroids are commonly employed (typically, methylprednisolone 20-30 mg/kg per day for 5 days with a maximum dose of 1000 mg per day) followed by an oral prednisolone taper of 1-2 mg/kg/day (maximum 40-60 mg/day) over 4-6 wk. Other treatment options include intravenous immunoglobulin (usually 2 g/kg administered over 2-5 days) or plasmapheresis (typically 5-7 exchanges administered every other day) for refractory or severe cases. There is no consensus about the timing of these treatments for ADEM.

Prognosis

Most children experience full motor recovery after ADEM, but residual defects can be seen, and cognitive deficits or behavioral changes are not uncommon. Recovery starts within days to weeks, but symptoms can fluctuate.

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618.2

Optic Neuritis

Cheryl Hemingway

Optic neuritis (ON) is defined as inflammation of one or both optic nerves. It presents with visual dysfunction. It can be idiopathic and can occur together with other systemic inflammatory conditions or inflammatory conditions of the CNS, such as ADEM, MS, or NMOSD.

Epidemiology and Clinical Presentation

ON is one of the most common of the acquired demyelinating syndromes and accounts for a quarter of all demyelinating presentations in childhood. The typical presentation is unilateral or bilateral visual loss over hours to days, abnormal color vision, visual field loss, and sometimes a relative afferent pupillary defect. The visual loss can be quite severe, with the majority of children at 20/200VA or worse. Periocular pain or pain with eye movement and, at times, a headache are common features. Bilateral ON is more common in younger children and is often associated with a preceding viral infection. Unilateral ON can also be followed in time by bilateral involvement. Funduscopic examination in some patients reveals optic nerve head swelling (papillitis), but in others inflammation occurs in the retrobulbar optic nerve portion and thus the appearance of the optic nerve is normal. Optic nerve pallor is often noted following an initial episode or in those with relapsing ON.

Diagnostic Evaluation

Electrodiagnostics, in particular visual evoked potentials (VEPs), may be helpful, with the VEPs often detecting prolonged latency. In the younger child, VEPs may also detect clinically silent episodes of ON in the opposite eye. Optical coherence tomography (OCT) can detect structural retinal change, such as retinal nerve fiber layer (RNFL) thinning, and may be helpful in monitoring the young child.

MRI of the orbits may be normal but usually shows, on T1-weighted images, thickened optic nerves, with an increased signal on T2-weighted scans (Fig. 618.3F and G). Longitudinally extensive ON involving the chiasm is thought to be more commonly associated with antibody-mediated demyelination (see Fig. 618.3C).

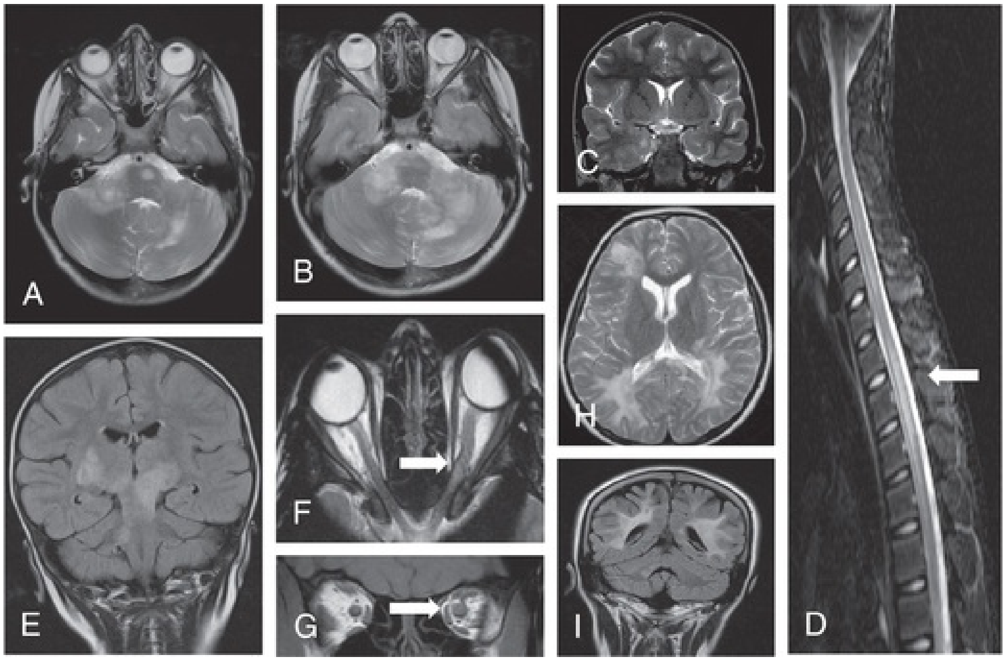

FIG. 618.3 MRI images highlighting the spectrum of possible phenotypes in relapsing myelin oligodendrocyte glycoprotein (MOG) antibody–associated disorders. **A,** Axial T2 flair weighted MRI brain from a 6 yr old girl with bilateral ON, ataxia, and lethargy, initially diagnosed with ADEM until her relapse **(B)** with further multiple brainstem lesions associated with MOG-Ab positivity. **C,** T2-weighted coronal MRI with longitudinally extensive ON with both pre- and postchiasm involvement and **(D)** sagittal

spine MRI with longitudinally extensive TM from a 9 yr old girl diagnosed with MOG-Ab–associated NMOSD following simultaneous presentation of bilateral visual impairment and paraparesis requiring ventilatory support. **E,** MRI brain T2 flair demonstrating asymmetric, bilateral, poorly defined lesion involving the brainstem and extending into the middle cerebellar peduncle. **F** and **G,** Orbital MRI shows a thickened left optic nerve in a 13 yr old girl with recurrent left ON associated with positive MOG-Ab. **H,** Axial T2 diffuse, bilateral, asymmetric leukodystrophy-like phenotype associated with MOG-Ab. **I,** Coronal T2 flair brain MRI similarly showing the leukodystrophy-like appearance seen over time in those with young-onset relapsing MOG-Ab–associated demyelination.

CSF analysis for OCBs is not always indicated, but this together with an MRI of the brain is very useful for predicting the risk of MS. In the face of a normal MRI brain scan and negative OCBs, the risk of developing MS is extremely low.

There are a number of conditions that can both mimic and be associated with ON. A detailed ophthalmologic review is essential, and depending on the history and clinical findings, investigations may be needed to exclude systemic rheumatologic disorders (e.g., systemic lupus erythematosus [SLE], sarcoidosis, Behçet disease), infectious diseases (viral disease, Lyme disease, syphilis, tuberculosis), mitochondrial disorders (e.g., Leber hereditary optic neuropathy), vascular events, or toxic, nutritional, or metabolic disorders. Antibody testing in serum for both AQP4-Ab and MOG-Ab is recommended to ensure that prophylactic treatment can be provided if indicated (e.g., AQP4-Ab positive) or to provide counseling on the risk of recurrence (MOG-Ab positivity).

Treatment

No randomized controlled trials have been conducted for pediatric ON, but the standard of care, based on clinical experience and adult trials, is high-dose intravenous steroids (typically methylprednisolone 20-30 mg/kg per day for 3-5 days, with a maximum dose of 1000 mg per day). In adults, the Optic Neuritis Treatment Trial (ONTT) showed that steroid administration led to a faster recovery, but no differences were seen in the long-term visual outcome. As with other severe episodes of demyelination, further treatment options include intravenous immunoglobulin (usually 2 g/kg administered over 2-5 days) or plasmapheresis (typically 5-7 exchanges administered every other day); there is no clear evidence of their benefit and no consensus about when to use them in isolated ON. Trials in adults have concentrated on neuroprotection; phenytoin has a beneficial effect on RNFL thinning in acute ON.

Prognosis

Reassuringly, full recovery of high-contrast visual acuity (HCVA) usually occurs in children, although irreversible damage is often detected in the structural integrity and may be evidenced by RNFL thinning on OCT, defective color vision, and impairments in low-contrast visual acuity (LCVA). Pediatric patients with AQP4-antibody–associated optic nerve demyelination are thought to more commonly be left with long-term visual disability than patients with other causes of ON.

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618.3

Transverse Myelitis

Cheryl Hemingway

Transverse myelitis (TM) is a condition characterized by rapid development of both motor and sensory deficits at any level of the spinal cord. TM presents acutely as either partial or complete cord involvement with bilateral signs and in adults and older children with a clear sensory level. TM has multiple causes and can be idiopathic or secondary to either an immune-mediated condition (postinfectious or antibody driven) or as a result of direct infection (infectious myelitis). In TM, evidence of spinal cord inflammation can be demonstrated by an MRI-documented–enhancing lesion, CSF pleocytosis (>10 cells), or an increased immunoglobulin G (IgG) index. The progression is rapid, and the time to maximal disability is more than 4 hr and sooner than 21 days.

Epidemiology

TM is more common in adults but is estimated to affect around 2 per million children per year. A bimodal age distribution is observed in those younger than 5 yr and older than 10 yr. Although they represent a small subset, children 5 yr of age and younger develop spinal cord dysfunction over hours to a few days. They often have a history of an infectious disease, possibly of viral or mycoplasmal origin, or of an immunization within the few weeks preceding the development of their neurologic difficulties. The clinical loss of function is often severe and may seem complete. Although a slow recovery (weeks to months) is common in these cases, it is likely to be incomplete. The likelihood of independent ambulation in young children is approximately 40%. The pathologic findings of perivascular infiltration with mononuclear cells imply an infectious or inflammatory basis. Overt necrosis of the spinal cord may be seen and may be tied to specific etiologies, including infectious etiologies such as enterovirus infection.

In older children, the syndrome may be different, and outcomes may vary by etiology. Although the onset is also rapid, with a nadir in neurologic function occurring between 2 days and 2 wk, recovery is more rapid and more likely to be complete. In a small but important number of cases, necrosis and irreversible injury may occur. The condition can be associated with underlying etiologies, including systemic vasculitic entities (e.g., SLE), antibody-mediated CNS disorders (e.g., AQP4-Ab or MOG-Ab-associated NMOSD), infectious etiologies (e.g., mycoplasma, enterovirus), or idiopathic disease. Pathologic or imaging examinations show acute inflammation with demyelination in some cases. There is no sex or familial predisposition in those with idiopathic TM.

Acute flaccid myelitis is an idiopathic (probably caused by enterovirus D68 or D71) disorder presenting with paralysis or weakness, CSF pleocytosis, and MRI demonstrating myelitis with abnormalities often of the anterior horn gray matter. Paralysis may be asymmetric and is not usually accompanied by a sensory deficit; cranial nerve involvement may include facial weakness, dysarthria, and dysphagia.

Clinical Manifestations

TM is often preceded within the previous 1-3 wk by a mild nonspecific illness, minimal trauma, or perhaps an immunization. Discomfort or overt pain in the neck or back, depending on the level of the lesion, is common. Depending on its severity, the condition progresses to numbness, anesthesia, ataxia, areflexia, and motor weakness in the truncal and appendicular musculature at or distal to the lesion. Paralysis begins as flaccidity (paraparesis, tetraparesis), but over a few weeks, spasticity develops and is evidenced by hyperreflexia and clonus. Rarely is the weakness unilateral. Unilaterality suggests the presence of a hemicord lesion, associated most commonly with MS, and, as such, should raise suspicion for this disorder, particularly in adolescents with this presentation. Urinary retention is a common and early finding; incontinence occurs later in the course. Although most have sensory loss manifesting as anesthesia, paresthesia, or allodynia, early sensory findings may be isolated to the posterior column, emphasizing the importance of the evaluation of vibratory sensation. Other findings may include priapism or respiratory compromise, as well as spinal shock and subsequent autonomic dysreflexia.

Diagnostic Evaluation

Because acute TM is a diagnosis of exclusion, a thorough evaluation should be completed in all cases. The differential diagnosis includes, amongst other conditions, Guillain-Barré syndrome, demyelinating disorders, systemic rheumatologic conditions, meningitis and infectious myelitis, spinal cord infarction, arteriovenous malformations, trauma, mass lesions, bony and intervertebral disc distortion, abscess, and spine and spinal cord tumors (Table 618.5).

Table 618.5

Clinical and Radiologic Mimics of Transverse Myelitis

EXTRAAXIAL COMPRESSION DISEASE

1. Vertebral spine disorders
    a. Trauma (e.g., blunt, penetrating)
    b. Atlantoaxial subluxation (e.g., trisomy 21, mucopolysaccharidosis type IV, Grisel syndrome)
    c. Destructive lesions (e.g., tuberculosis, lymphoma, Langerhans cell histiocytosis)
    d. Scheuermann disease
2. Epidural disease
    a. Tumor (e.g., neuroblastoma, Wilms tumor, Ewing sarcoma)
    b. Abscess (e.g., associated dermal sinus, vertebral body infection)
    c. Hematoma
3. Arachnoiditis (e.g., tuberculosis, cryptococcosis, carcinomatous infiltration)
4. Spinal nerve root inflammation (e.g., Guillain-Barré syndrome)

SPINAL CORD DISORDERS

1. Congenital malformation (e.g., neurenteric cysts, spinal cord tethering)
2. Infection (e.g., non-polio enteroviruses, West Nile virus, human T-lymphocyte virus 1, Zika virus, neurocysticercosis)
3. Vascular disorders (e.g., arteriovenous malformation, cavernomas, Cobb syndrome, spinal cord infarction)
4. Vasculitis (e.g., SLE, Behçet disease)
5. Nutritional disorders (e.g., vitamin B_{12} deficiency)
6. Toxic injury (e.g., chemotherapy, radiation)
7. Immune mediated (e.g., ADEM, NMOSD, MS), anti-NMDA receptor antibodies

Modified from Thomas T, Branson HM: Childhood transverse myelitis and its mimics, Neuroimaging Clin North Am 23:267–278, 2013, Box 11.

MRI with and without contrast enhancement is essential to rule out a mass lesion requiring neurosurgical intervention. In both conditions, T1-weighted images of the spine at the anatomic level of involvement may be normal or may show distention of the spinal cord. In the infantile form, T2-weighted images show high signal intensity that extends over multiple segments. In the adolescent form, the high signal is often centrally located, involving the gray matter and the neighboring white matter. It may be limited to one or two segments but frequently extends over multiple segments. A limited degree of contrast enhancement after the administration of gadolinium is expected, especially in the infantile form, and denotes an inflammatory condition. Cervical and cervicothoracic lesions represent the majority of acute TM lesions. Axial cuts of the spinal cord are invaluable and can help to establish potential etiologies. Hemicord involvement may indicate MS. Holocord involvement with typical brain and optic nerve involvement may indicate NMOSD. If the involvement is predominantly of the gray matter, it may indicate a vasculitic or infectious process, including SLE or enterovirus infection. Nerve root enhancement is occasionally seen and should raise suspicion for a mixed picture (central and peripheral demyelination) or anterior horn cell involvement (Fig. 618.4). In up to 6% of presentations, MRI with 1.5T and 3T may not show spinal cord lesions. Repeat imaging at 7 days may show atrophy in these cases. *MRI of the brain is also indicated.* Evidence of other foci of demyelination is seen in at least 40% of patients, and depending on the lesion localization, MS, NMOSD, SLE, and enterovirus-associated acute flaccid myelitis should be considered. In patients with *encephalopathy,* ADEM must be considered.

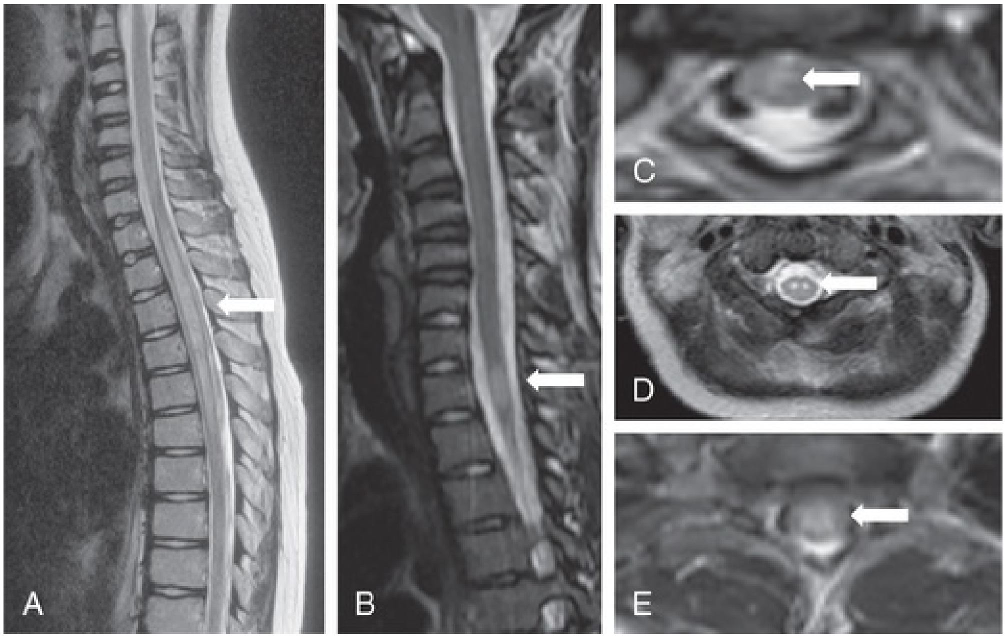

FIG. 618.4 Transverse myelitis. **A,** Sagittal T2-weighted image demonstrates a longitudinal hyperintense spinal cord lesion in a 12 yr old girl with first presentation of AQP4-Ab–positive NMOSD *(arrow).* **B,** Sagittal T1-weighted image shows a short segment at T1 *(arrow)* in a 14 yr old girl with ON and MS. Axial T2-weighted images of the spine with different etiologies showing typical hemicord appearance in MS **(C),** anterior horn cell involvement in polio **(D),** and holocord involvement in NMOSD **(E).** (**C, D,** and **E,** Courtesy Dr. Felice D'Arco, Great Ormond Street Hospital, London.)

After exclusion of a mass lesion on MRI, a lumbar puncture is indicated. The number of mononuclear cells is usually elevated. The level of CSF protein may be elevated or normal. CSF should be analyzed for cells, protein, immunoglobulin index, OCBs, and infectious etiologies. The presence of inflammatory cells is essential for the diagnosis of TM.

Because one of the most important possibilities for this condition is neuromyelitis optica spectrum disorder (NMOSD), the serum of all patients should be analyzed for both AQP-4 and MOG antibodies. Older children with the condition should also have serum studies sent for other autoimmune disorders, especially SLE.

Treatment

There are no standards for the treatment of TM. Available evidence suggests that modulation of the immune response may be effective in decreasing the severity and duration of the condition. The use of high-dose steroids, particularly methylprednisolone, is the initial approach to treatment of the childhood forms of TM. If there is a poor response to high-dose steroids, other therapeutic approaches for acute intervention include intravenous immunoglobulin and plasma exchange. If the TM is secondary to an underlying antibody-driven disorder, treatments such as rituximab or cyclophosphamide can be considered. Long-term prophylactic therapy is recommended for children with recurrent forms of the disease (Table 618.6).

Table 618.6

The 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis in Patients with an Attack at Onset

	NUMBER OF LESIONS WITH OBJECTIVE CLINICAL EVIDENCE	ADDITIONAL DATA NEEDED FOR A DIAGNOSIS OF MULTIPLE SCLEROSIS
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomic location †)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI ‡
1	≥2	Dissemination in time demonstrated by an additional

clinical attack		clinical attack or by MRI OR demonstration of CSF-specific OCBs [‡]
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI AND Dissemination in time demonstrated by an additional clinical attack or by MRI OR demonstration of CSF-specific OCBs [‡]

[*] No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of MS is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting MS, with a presentation other than a typical clinically isolated syndrome or with atypical features. If imaging or other tests (e.g., CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of MS, and alternative diagnoses should be considered.

[†] Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurologic findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed.

[‡] The presence of CSF-specific OCBs does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

If the 2017 McDonald criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS. If MS is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald criteria are not completely met, the diagnosis is possible MS. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not MS.

From Thompson AJ, Banwell BL, Barkhof F, et al: Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet 17:162-173, 2018.

Prognosis

Older children with acute TM have a better outcome than adults, with nearly 50% making a good recovery by 2 yr. This may reflect the higher likelihood of MOG-Ab–associated disorders in the older child. The most common sequelae in the remaining 50% are sensory problems and bladder dysfunction.

The treatment of acute flaccid myelitis has included steroids and IVIG; despite these therapies, patients often have an incomplete recovery.

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618.4

Multiple Sclerosis

Cheryl Hemingway

Multiple sclerosis (MS) is a chronic demyelinating autoimmune disorder of the brain, spinal cord, and optic nerves characterized by a relapsing–remitting course of neurologic events without encephalopathy separated in time (i.e., more than one episode of at least 24 hr at least 30 days apart) and space (i.e., in more than one CNS region) (Table 618.6). When presenting for the first time in those under 18 yr, it is known as pediatric-onset MS (POMS). Recurrent events lead to progressive accumulation of both physical and cognitive disability and brain atrophy.

Epidemiology and Risk Factors

POMS is rare, with an estimated incidence in northern countries such as the United Kingdom and Canada of 1-2 per million under 16 yr of age. Around 10% of MS patients report in retrospect that they experienced their first symptoms before the age of 18 yr. Before puberty, the condition appears to affect males and females equally, but after puberty there is almost a 2 : 1 female predominance. Almost always, POMS presents as the relapsing-remitting form, and features suggestive of primary progressive MS should prompt careful evaluation for alternative conditions (Table 618.7).

Table 618.7

Differential Diagnosis of Multiple Sclerosis: Selected Disorders with a Progressive Course

	CLINICAL FEATURES	MRI FINDINGS	CSF FINDINGS	OTHER INVESTIGATIO
HTLV1-associated myelopathy	Progressive myelopathy; residence or travel to an	Spinal cord atrophy (thoracic more than	OCBs sometimes	CSF HTLV1 antibo testing

	endemic area (especially West Indies or Japan)	cervical); T2-hyperintense brain lesions in some patients	present	
Dural arteriovenous fistula	Subacute, progressive myelopathy	Extensive spinal cord T2 hyperintensity often extending to conus, with or without gadolinium enhancement; dilated veins over dorsal surface of cord (often subtle); brain MRI normal	OCBs absent	Spinal angiography
Nutritional myelopathy (vitamin B_{12} or copper deficiency)	Subacute progressive myelopathy or myeloneuropathy; optic atrophy (severe vitamin B_{12} deficiency); anemia or pancytopenia	T2 hyperintensity of upper cervical cord classically affecting posterior columns; brain MRI normal	OCBs absent	Serum B_{12} , methylmalonic acic serum copper level ceruloplasmin
Primary lateral sclerosis (or upper motor neuron predominant ALS)	Spastic quadriparesis or hemiparesis; with or without bulbar involvement; with or without development of lower motor neuron signs	MRI normal or showing T2 hyperintensity in corticospinal tracts	OCBs absent	Electromyography looking for lower n neuron involvemen
Leukodystrophies: adrenomyeloneuropathy; Krabbe disease; Alexander disease; hereditary diffuse leukoencephalopathy with axonal spheroids	Progressive myelopathy (adrenomyeloneuropathy, Krabbe disease); bulbar symptoms, ataxia (Alexander disease); early cognitive impairment (hereditary diffuse leukoencephalopathy with axonal spheroids)	Highly variable; diffuse, symmetric T2 hyperintensity sparing subcortical U fibers; with posterior hemispheric predominance (adrenomyeloneuropathy); spinal cord MRI normal or showing atrophy	OCBs absent	Very-long-chain fat acids (adrenomyeloneurc genetic testing avai for some leukodyst
Hereditary spastic paraplegia (especially *SPG5*)	Slowly progressive myelopathy (spasticity greater than weakness) with or without other neurologic symptoms and family history	Spinal cord atrophy; supratentorial and infratentorial white matter lesions *(SPG5);* atrophy of corpus callosum	OCBs absent	Genetic testing
Spinocerebellar ataxias	Progressive cerebellar ataxia, with or without other neurologic symptoms and family history	Early, prominent cerebellar findings, with or without spinal cord, atrophy	OCBs absent	Genetic testing

CSF, cerebrospinal fluid; HTLV1, human T-lymphotropic virus type 1; OCB, oligoclonal band; ALS, amyotrophic lateral sclerosis.

From Brownlee WJ, Hardy TA, Fazekas F, Miller DH: Multiple sclerosis 1: diagnosis of multiple sclerosis: progress and challenges. Lancet 389:1336-1346, 2017, Table 2, p. 1341.

In adults, a possible complex interplay of environmental (e.g., sunlight, low vitamin D status, obesity, and toxins), infectious (e.g., Epstein-Barr virus exposure), and genetic factors (e.g., HLADRB1*15:01, obesity) are thought to influence MS *susceptibility.* Studies in pediatrics have so far confirmed the role of some but not all of the above factors, and it may be that environmental factors in pediatric MS are more important than genetic factors.

Pathogenesis

Immune system dysregulation involving T and B lymphocytes triggers inflammation, axonal demyelination, axonal loss, and regeneration within both white and gray matter. Inflammatory infiltrates within actively demyelinating lesions of relapsing-remitting MS are targets for DMTs.

Clinical Manifestations

Presenting symptoms in pediatric MS are polyregional in more than half of patients and include focal sensory loss or other paresthesia (39–63%); cerebellar symptoms such as ataxia or dysarthria (44–55%); unilateral or, less often, bilateral pain on eye movements and reduced visual acuity (ON) (36–38%); brainstem symptoms in 30–31%, and in 29–50%, motor deficits, including focal deficits, hemiparesis, paraparesis, and bowel/bladder dysfunction (from TM or other spinal lesions). Encephalopathy is not seen apart from when there is significant brainstem involvement.

Imaging and Laboratory Findings

Brain MRI exhibits typically discrete, ovoid, asymmetric T2 lesions in cerebral white matter, particularly in the periventricular regions, as well as juxtacortical, cortical, brainstem, cerebellar, and, less commonly, the deep gray matter (Fig. 618.5). Spine MRI typically, when involved, shows partial-width cord lesions restricted to 1-2 spine segments. *Longitudinally extensive lesions* are more likely to occur in NMOSD (associated with MOG-Ab and AQP4-Ab) than in MS. CSF may be normal or exhibit mild lymphocytosis, particularly in younger children. CSF OCBs are positive in CSF but not in serum *(type 2 pattern)* in more than 90% of pediatric MS patients, but are usually negative *(type 1 pattern)* or present in both CSF and serum *(type 4 pattern)* in NMOSD. Abnormal evoked potential studies can localize disruptions in visual, auditory, or somatosensory pathways.

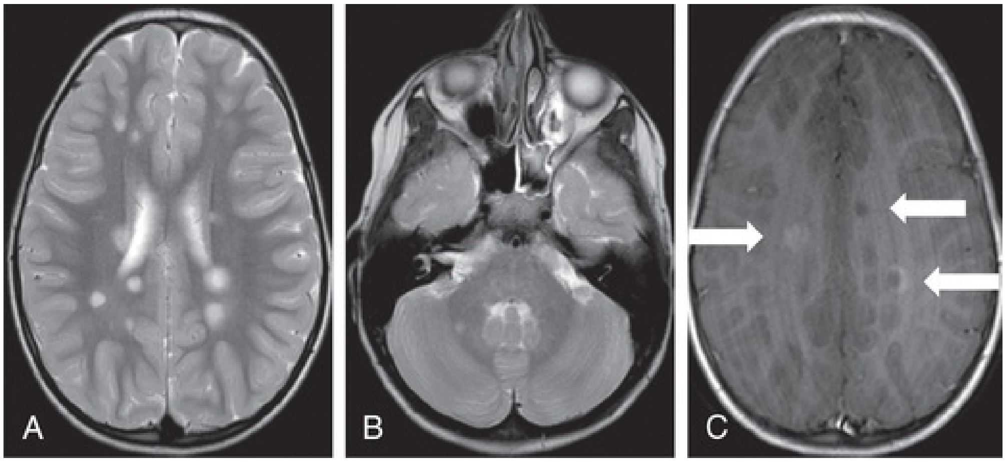

FIG. 618.5 Girl 5 yr old diagnosed on imaging with MS following presentation with left-sided weakness. **A,** Axial MRI T2-weighted brain MRI shows multiple, discrete, ovoid white matter lesions in periventricular region and cortical, juxtacortical, and infratentorial lesions **(B). C,** Axial T1 area of hypointensity and two contrast-enhancing lesions (*arrows).*

Diagnosis and Differential Diagnosis

Pediatric MS can usually be diagnosed following two demyelinating episodes *without* encephalopathy localizing to distinct CNS regions, lasting longer than 24 hr and separated by more than 30 days, provided no other plausible explanation exists. MS diagnostic criteria use an MRI to serve as a surrogate for recurrent demyelination, enabling MS diagnosis after the first event. For adults and children the initial MRI may be sufficient to diagnose MS if it demonstrates dissemination in space (≥2 T2 lesions involving juxtacortical, periventricular, infratentorial, or spine regions) and time (presence of gadolinium-enhancing lesion and nonenhancing T2 lesion in same scan). Alternatively, MS can be diagnosed with a follow-up MRI at any time interval exhibiting accumulation of T2 or gadolinium-enhancing lesions in the brain or spine. The 2017 McDonald diagnostic criteria allow the presence of intrathecal OCBs to substitute for dissemination in time (see Table 618.1). Challenges may arise in distinguishing a first attack of pediatric MS from other acquired demyelinating syndromes, in particular those associated with known antibodies (e.g., AQP4-Ab or MOG-Ab) or ADEM (Table 618.8 and see Table 618.4).

Table 618.8

Differential Diagnosis of Multiple Sclerosis: Clinical, MRI, and Serologic Findings of the Main Disorders That Can Resemble Relapsing-Remitting Disease

	NEUROLOGIC FEATURES	MRI FEATURES	BLOOD TEST AND CSF FINDINGS
Acute disseminated encephalomyelitis (typically found in children)	Similar to MS symptoms but encephalopathy is typical; also multifocal symptoms	Large spectrum from small punctate lesions to tumefactive lesions with mass effect, in the supratentorial or infratentorial white matter, bilateral, and asymmetric; involvement of cerebral cortex, deep gray matter, brainstem, and spinal cord; enhancement	CSF pleocytosis; serum antibody to MOG
Neuromyelitis optica spectrum disorders	Concomitant or concurrent (severe) ON and TM; nausea and vomiting; paroxysmal tonic spasms	Longitudinally extensive spinal cord lesion (>3 vertebral segments); optic chiasmal involvement; pencil-thin ependymal enhancement and cloud-like enhancement	Serum antibody to AQP4 and to MOG; sometimes, mild pleocytosis; CSF OCBs infrequent
Neurosarcoidosis	Cranial nerve involvement (primarily facial and optic nerve); headache; raised intracranial pressure; meningitis; seizures; myelopathy	Meningeal enhancement with pituitary, hypothalamic, and cranial nerve involvement; brain white matter lesions; simultaneous enhancement of all lesions	Raised serum and CSF ACE (not sensitive or specific for sarcoidosis); CSF OCBs sometimes present
CNS vasculitis	Confusion, headache, personality change; seizures; stroke-like symptoms	Ischemic, multiple lesions; predominance of lesions at corticosubcortical junction; intracranial hemorrhage; meningeal enhancement; simultaneous enhancement of all lesions; microbleeds	Serum antineutrophil cytoplasmic antibodies; CSF OCBs sometimes present
Susac syndrome	Visual loss; sensorineural hearing loss; encephalopathy; headache; memory loss; behavioral disturbances	Focal and small lesions in supratentorial and infratentorial regions (both white matter and gray matter); involvement of corpus callosum (snowball lesions); leptomeningeal enhancement	CSF OCBs usually absent
Hypoxic-ischemic vasculopathies (in particular small-vessel disorder)	Stroke events; cognitive decline; focal neurologic signs; gait disturbance	Punctate and peripheral white matter lesions, sparing U fibers; symmetric and confluent periventricular lesions; lacunar infarcts; involvement of central transverse fibers in pons; microbleeds	Serum testing for vascular risk factors (diabetes, hypercholesterolemia); CSF OCBs absent
Cerebral autosomal dominant arteriopathy with subcortical infarcts and	Migraine; stroke events; psychiatric problems and dementia	Temporal pole lesions; external capsule and U-fiber lesions; microbleeds	CSF OCBs absent; testing for *NOTCH3* gene mutation

leukoencephalopathy (CADASIL)			
Connective tissue disorders (SLE, Sjögren syndrome, antiphospholipid antibodies syndrome)	Optic nerve, brain, and spinal cord involvement; neuropsychiatric symptoms; seizures; ischemic episodes	Brain infarcts and hemorrhage; basal ganglia lesions; punctate (subcortical) lesions; spinal cord lesions; cerebral venous sinus thrombosis; parotid gland involvement in Sjögren syndrome	Serum antinuclear antibody; extractable nuclear antigens (in particular, anti SS-A(Ro) and SS-B(La) antibodies for Sjögren syndrome, and anti-Sm for SLE); CSF OCBs usually absent
Neuro-Behçet disease	Brainstem syndrome; myelopathy; meningoencephalitis	Large brainstem lesions; basal ganglia, subcortical white matter, and spinal cord lesions; gadolinium enhancement; cerebral venous sinus thrombosis	HLA-B5; CSF pleocytosis; CSF OCBs usually absent
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)	Cranial nerve dysfunction and long-tract signs; symptoms referable to brainstem or cerebellar dysfunction; spinal cord syndrome; cognitive dysfunction	Multiple punctate, patchy, and linear regions of gadolinium enhancement relatively confined to pons; lesions also involving cerebellum, basal ganglia, supratentorial white matter, brainstem, and spinal cord	CSF OCBs sometimes present
Fabry disease	Stroke events; vertigo	Posterior infarcts; multiple white matter lesions with pulvinar involvement (T1 hypointense lesions)	Reduced activity of GLA enzyme; analysis of *GLA* gene
Leber hereditary optic neuropathy	Bilateral sequential optic neuropathies with poor visual recovery; more common in men than women	Normal or might show white matter lesions (Harding disease)	OCBs absent; genetic testing

Infectious diseases are not included in this table but should be considered, especially in cases of atypical demyelinating lesions. CSF, cerebrospinal fluid; ACE, angiotensin-converting enzyme; GLA, α galactosidase A; OCB, oligoclonal band.

Modified from Thompson AJ, Baranzini SE, Geurts J, et al: Multiple sclerosis, Lancet 391:1622-1636, 2018, Table 3, pp. 1628-1629.

Treatment

Relapses causing functional disability may be treated with, 20-30 mg/kg/day (maximum 1000 mg/day) for 3-5 days, with or without prednisolone taper. DMTs reduce the relapse frequency and T2 lesion load, mainly by targeting the inflammatory response that predominates during the relapsing-remitting phase of MS. There are now a large number of available treatment options, including injectable treatments, oral medications, and infusions. They range from immunomodulating to immunosuppressing options, and the choice and sequencing are becoming highly specialized (Table 618.9). Almost all DMT use in pediatrics is off label, and a number of randomized controlled trials are currently in progress. The only medication with U.S. FDA approval at the present time is fingolimod, following completion of a 2 yr randomized, double-blind, controlled trial between oral fingolimod and intramuscular interferon-beta-1α. This trial demonstrated that in those between 10 and 18 yr of age with POMS, fingolimod reduced the annualized relapse rate by 82% when compared with interferon-beta-1α. This efficacy is greater than that seen in adults, possibly due to the greater inflammatory nature of POMS. This is one of the reasons that prompt initiation of treatment is recommended for all those diagnosed with POMS.

Table 618.9

Overview of Available and Emerging Therapies Used in Pediatric Multiple Sclerosis and Other Relapsing Demyelinating Disorders

MEDICATION AND ROUTE OF ADMINISTRATION	MEDICATION CLASS	MECHANISM IN MS	COMMONLY REPORTED OR SERIOUS SIDE EFFECTS	EFFICACY
FIRST-LINE THERAPIES APPROVED FOR MS IN ADULTS				
Interferon-β-1a and β-1b (subcutaneous or intramuscular injection on alternate days, 3 times weekly, weekly or bimonthly depending on preparation)	Immunomodulator	Modulates T cells and cytokine production	Injection site reaction; flu-like symptoms; headache, muscle aches, transaminitis; leukopenia; tissue necrosis at injection site (rare)	~33% decrease in ARR and slows progression of disability
Glatiramer acetate (daily or 3 times weekly, subcutaneous injection)	Immunomodulator	Modulates T-cell response by altering antigen presentation	Injection site reactions; transient flushing, chest tightness and shortness of breath. Lipodystrophy at injection sites	~33% decrease in ARR and slows progression of disability
Dimethyl fumarate (DMF) (oral medication 12 hourly with food i.e, twice a day)	Immunomodulator	Unclear mechanism but modulates cytokine production and decreases lymphocyte count. Neuroprotectant;	Flushing reaction; GI upset; headache; proteinuria, leukopenia. Rare reports of PML in those with severe prolonged lymphopenia	Reduces number of relapses by ~ 50% compared with placebo in adults. Pediatric trials ongoing

		antioxidant		
SECOND-LINE THERAPIES APPROVED FOR MS IN ADULTS				
Teriflunomide	Immunomodulator	Impairs DNA proliferation via pyrimidine synthesis inhibition and decreases T and B cells	Infections; headaches; diarrhea; transaminitis; alopecia; teratogenicity	Pediatric trials ongoing
Natalizumab (infusion over 2-3 hr every 4 wk)	Monoclonal antibody	Targets α_4 -integrin on vascular endothelium and prevents T- and B-cell migration into CNS and other tissues	Infusion reactions with headache, dizziness, rash; rare anaphylaxis. May affect liver function. Risk of PML able to be stratified by JC virus status, length of treatment, and previous treatments. Immune reconstitution syndrome after discontinuation; melanoma	Reduces number of relapses by ~,70% in adults
Fingolimod (daily oral medication: first dose, cardiac monitoring required and need to ensure good compliance because of risks of first-dose bradycardia and heart block)	Immunomodulator	Modulates sphingosine-1-phosphate receptors; causes T-cell sequestration in lymphoid compartments	First-dose bradycardia; cardiac arrhythmia; systemic viral infection; persistent lymphopenia with risk of severe herpetic and varicella infection; macular edema; transaminitis; basal cell carcinoma. Rare cases of PML	FDA approved for pediatrics May 2018 following trial showing 82% decrease in ARR compared with interferon β
Alemtuzumab (infusions 2 courses: first for 5 consecutive days; second 12 mo later for 3 consecutive days)	Monoclonal antibody	Anti-CD52 antibody target; depletes mature T cells	Infusion reactions; opportunistic infection, secondary autoimmune disorders, including thyroiditis (50% risk), immune thrombocytopenia (1%), Goodpasture syndrome. Need monthly blood tests for 4 yr after last course.	Highly effective in adults; ~ 55% decrease in ARR compared with interferons. Pediatric trial ongoing
Cladribine (oral tablets 2 courses: first for 4-5 consecutive days during mo 1 and 2; second as before 12 mo later)	Immunomodulator	Selective activity against CD4 and CD8 T cells and CD19 B cells via adenosine deaminase activity	Neutropenia, lymphopenia, infection, oral herpes, GI disorders, and rash	Reduced relapses by ~ 58% vs placebo in adults and delay in disability progression. No evidence as yet in pediatrics.
Rituximab (infusions given 2	Monoclonal antibody	Targets CD20, a marker of	Infusion-related side effects; hepatitis, PML (rate	Used off label for adult MS; no

wk apart ~ every 6 mo)		immature B cells; depletes B-cell populations	undefined).	efficacy assessments available in pediatric MS
Ocrelizumab (infusions given 2 wk apart ~ every 6 mo)	Monoclonal antibody	Targets CD20, a marker of immature B cells; depletes B-cell populations	Headache; infusion-related side effects; theoretic risk of PML (undefined) and, possibly, malignancy	In adult MS showed decrease in ARR of 50% compared with interferons; no evidence in pediatric MS to date
Laquinimod (daily oral medication)	Immunomodulator	Modulates T-cell and cytokine production; antiinflammatory; possibly neuroprotective	Transaminitis, back pain, headache	In adult MS ARR of 20–25% compared with placebo; no data in pediatric use to date
OTHER MEDICATIONS USED FOR DEMYELINATING DISORDERS				
Azathioprine (intravenous infusion or oral tablets daily)	Chemotherapeutic	Disrupts purine metabolism; effects include cytotoxic immune cell depletion	GI side effects, alopecia, bone marrow suppression, and blood dyscrasias, transaminitis, infections, secondary malignancy, alopecia. Increased side effects with low TPMT enzyme activity	No efficacy assessments available in pediatric MS, small retrospective studies for NMOSD
Cyclophosphamide (intravenous infusion or oral tablets daily)	Chemotherapeutic	DNA alkylation; effects include cytotoxic immune cell depletion	Hemorrhagic cystitis; bladder cancer; late-onset malignancy; infection; infertility	No efficacy assessments available in pediatric demyelination
Mycophenolate mofetil (MMF) (intravenous infusion or oral tablets twice daily)	Immunosuppressant	Disrupts purine synthesis and impairs B- and T-lymphocyte proliferation	GI side effects, alopecia, bone marrow suppression and blood dyscrasias, transaminitis, infections, secondary malignancy, alopecia. Teratogenic.	
Vitamin D	Vitamin/hormone	Modulates immune cell expression	Hypercalcemia and kidney stones at serum 25(OH) vitamin D level > 100 ng/mL	Prospective trials in pediatric and adult MS are currently underway

CNS, central nervous system; ARR, annualized relapse rate; MS, multiple sclerosis; JC virus, John Cunningham virus; PML, progressive multifocal leukoencephalopathy; TPMT, thiopurine methyltransferase; GI, gastrointestinal.

The debate about DMT use for both adult and pediatric patients concerns whether one should start with the safer, less efficacious first-line agents and escalate if treatment fails, or whether remission should first be induced with the more effective treatments and then the patient maintained on safer medications. Adult trials to answer this question are underway. Currently, the more efficacious treatments are generally used only for those with highly active MS, although one could argue that with the increased inflammatory activity, higher relapse rate, and young age at which disability occurs, pediatric-onset MS in particular may benefit from high-efficacy early treatment (HEET).

Prognosis

Studies of pediatric MS prior to widespread DMT use suggested a higher relapse rate but slower rate of disease progression compared with adults. Despite this longer time to irreversible disability (20-30 yr), pediatric MS patients acquire disability at a younger age than adults owing to the earlier age of onset of disease. Similar to adults with MS, pediatric MS patients can acquire fixed neurologic deficits affecting the visual and other cranial nerves, motor and sensory function, balance, and bowel/bladder function. Children with MS have also been shown to have an overall smaller head size, brain volume, and thalamic volume in particular. This can be attributed to gray matter degeneration, and cognitive disability can be demonstrated in 30–50% of young people with pediatric-onset MS, more than that seen in adult-onset MS.

Fatigue is a major symptom in pediatric MS that can lead to a poor quality of life. It is important to address this together with other factors, such as mood, sleep quality, and sleep hygiene. Pharmacologic management of fatigue is challenging, but psychology-based therapy with cognitive behavioral therapy and pacing has been shown to be effective.

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618.5

Neuromyelitis Optica Spectrum Disorders

Cheryl Hemingway

Neuromyelitis optica spectrum disorders (NMOSDs) classically present with episodes of ON and/or longitudinally extensive TM. The discovery of pathogenic antibodies to the astrocyte water channel protein aquaporin-4 (AQP4) and the incorporation of these antibodies into the 2015 revised diagnostic criteria for NMOSDs have not only enabled clinicians to clearly distinguish AQP4-Ab–related disorders from other demyelinating conditions but has also widened the spectrum of the group of disorders to include brainstem syndromes (e.g., area postrema syndrome) and recurrent forms of ON and TM (see Table 618.1). MOG-Ab has recently been identified in many of the antibody-negative presentations, with no reports of both antibodies being present in a single individual.

Epidemiology

AQP4-Ab–positive NMOSD presents usually in the older adult, with MOG-Ab NMOSD much more common in children and young people, but both can occur across a wide age spectrum. Population studies vary significantly but suggest a pediatric incidence for NMOSDs of 0.5–4.5%. AQP4-Ab–driven NMOSD is significantly more common in females than in males, with MOG-Ab–associated disorders having only a slight female preponderance. NMOSD is also more common in Asians than in blacks or whites and appears to have a higher mortality rate in individuals of African descent than in others. Although most cases of NMO are idiopathic and only occasional familial cases have been reported, there are a few known genetic risk factors, including the HLA-DRB1*0301 allele and a single-nucleotide polymorphism in CD58, which have been associated with NMOSDs in specific population groups.

Pathogenesis

The water channels, against which the AQP4-IgG antibody is directed, are most abundant on the astrocyte foot processes within the periventricular regions, brainstem, optic nerves, and spinal cord. Antibody, mainly of the IgG1 subtype, binds to the extracellular loops of the AQP4 protein activating the classical complement pathway with C5b-C9 components, leading to leukocyte attraction and degranulation and causing astrocyte death. Chemokines from dying astrocytes and activated leukocytes attract macrophages, leading to death of oligodendrocytes and neurons, with subsequent necrosis or even cavitation in affected tissues.

Clinical Manifestations

NMOSD presents most commonly with ON, TM, or an area postrema syndrome such as intractable vomiting or hiccups. The symptoms and signs of TM depend on the spinal level and completeness of the inflammatory changes. ON or TM may occur simultaneously or may be separated in time by weeks or even years. Some patients present with seizures and encephalopathy mimicking ADEM. Others exhibit endocrinopathies such as the syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus or hyperinsulinemia, disrupted puberty, or obesity. NMOSD has also been associated with other autoimmune conditions, such as SLE, Sjögren syndrome, diabetes, and thyroiditis.

Imaging and Laboratory Findings

Neuroimaging studies should include the entire spine, optic nerves if visual symptoms are present, and brain. Brain imaging can be normal, may have subtle changes in the white matter tracts, or can demonstrate large, hazy, ill-defined white matter lesions and/or gray matter involvement, such as thalamic lesions. Brain lesions frequently localize to areas of high AQP4-ab expression, such as the periaqueductal gray matter, dorsal brainstem, and diencephalon (Fig. 618.6). Spinal imaging may reveal short or longitudinally extensive TM; longitudinally extensive ON involving the chiasm is more common in MOG-Ab disease but can occur in both. Imaging can usually be distinguished from MS by the absence of discrete, well-defined oval lesions in the periventricular white matter, but AQP4-Ab and MOG-Ab disease are often not able to be reliably differentiated on imaging.

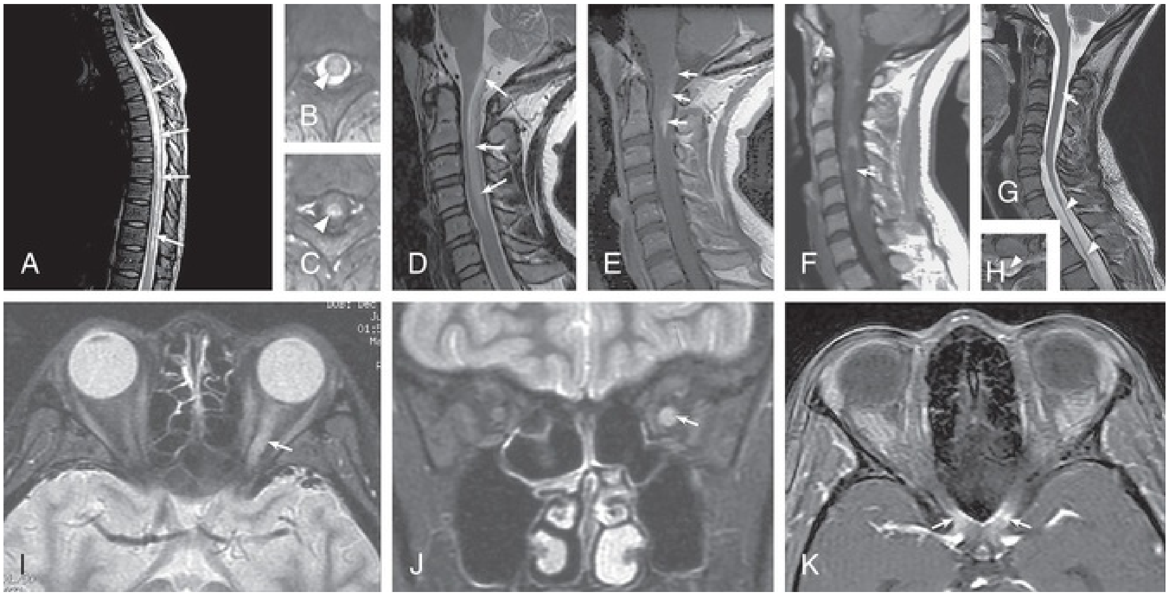

FIG. 618.6 Spinal cord and optic nerve MRI patterns in NMOSD. Spinal cord imaging in the context of acute myelitis in NMOSDs usually reveals a longitudinally extensive transverse myelitis (LETM) lesion extending over three or more vertebral segments. Sagittal T2-weighted MRI of the thoracic spinal cord **(A)** demonstrates a typical LETM lesion involving most of the thoracic spinal cord *(arrows).* LETM lesions have a predilection for the central cord, as shown by axial T2-weighted (**B;** *arrowhead*) and T1-weighted MRIs with gadolinium (**C;** *arrowhead*). Cervical LETM may extend into the medulla, a characteristic NMOSD pattern demonstrated in **D** (*arrows;* sagittal T2-weighted MRI) and **E** (*arrows;* sagittal T1-weighted MRI with gadolinium). Acute LETM lesions can be associated with intralesional hypointensity, as shown by sagittal T1-weighted MRI (**F;** *arrow*); in this example, a rim of gadolinium enhancement surrounds the hypointense region. Chronic sequelae of LETM may include longitudinally extensive segments of spinal cord atrophy, as shown by T2-weighted MRI using the sagittal plane (**G;** the two *arrowheads* indicate the atrophic segment and the top *arrow* indicates the normal diameter of unaffected cervical spinal cord) and axial plane (**H;** *arrowhead* shows an atrophic spinal cord). Fast spin echo fat-suppressed T2-weighted MRI in the axial **(I)** and coronal **(J)** planes shows increased signal throughout most of the length of the left optic nerve, especially its posterior portion *(arrows).* Axial T1-weighted MRI with gadolinium shows enhancement of the optic chiasm (**K;** *arrows*). These images are from two different patients experiencing acute ON in the setting of NMOSD. (From Wingerchuk DM, Banwell B, Bennett JL, et al: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders, Neurology 85:177-189, 2015, Fig. 1.)

AQP4-Ab can be found in both the serum and CSF, with the serum being more sensitive. MOG-Ab also is more commonly positive in serum, implying extrathecal production of antibody. If there is a high clinical suspicion of an antibody-driven disorder and a negative test, it is important to recognize that there are a number of different methods of antibody testing and the sensitivity of the assays varies, so repeat testing may be indicated. CSF in patients with NMOSD often has a number of white blood cells, with a higher cell count seen in MOG-Ab. Unlike MS, CSF in NMOSD is usually negative for OCBs.

Diagnosis and Differential Diagnosis

The International Panel for NMO Diagnosis (IPND) published new criteria for NMOSD in 2015. They placed a high emphasis on the presence or absence of AQP4 antibody (see Table 618.1). In seropositive patients, once alternative diagnoses have been excluded, only one core clinical criterion is required: ON, TM, area postrema syndrome, narcolepsy, or diencephalic syndrome with compatible MRI lesions. If AQP4-ab negative, the diagnosis is more stringent, with two core clinical criteria required.

The differential diagnosis includes other demyelinating disorders, such as MS or ADEM; vasculitis and rheumatologic disorders including SLE, Behçet disease, and neurosarcoidosis (usually accompanied by other nonneurologic manifestations); idiopathic TM, tropical spastic paraparesis, and viral encephalomyelitis (none of which have NMO antibodies in the serum or CSF); genetic disorders such as hemophagocytic lymphohistiocytosis (HLH) or mutation in the DARS gene; metabolic causes such as biotinidase deficiency and riboflavin-responsive conditions; idiopathic causes of isolated ON, or other acute forms of monocular or binocular visual loss (Table 618.10 ; see also Chapter 649). Additional considerations, depending on the location of the lesions, include lymphoma, Langerhans cell histiocytosis, tuberculosis, and vitamin B_{12} or E deficiencies.

Table 618.10

Red Flags: Findings Atypical for NMOSD*

RED FLAGS (CLINICAL AND LABORATORY)
1. Clinical features and laboratory findings
Progressive overall clinical course (neurologic deterioration unrelated to attacks; consider MS)
Atypical time to attack nadir: less than 4 hr (consider cord ischemia/infarction); continual worsening for more than 4 wk from attack onset (consider sarcoidosis or neoplasm)
Partial TM, especially when not associated with LETM MRI lesion (consider MS)
Presence of CSF OCBs (OCBs occur in < 20% of NMO cases vs > 80% of MS cases)
2. Comorbidities associated with neurologic syndromes that mimic NMOSD
Sarcoidosis, established or suggestive clinical, radiologic, or laboratory findings thereof (e.g., mediastinal

adenopathy, fever and night sweats, elevated serum angiotensin-converting enzyme or interleukin-2 receptor levels) Cancer, established or with suggestive clinical, radiologic, or laboratory findings thereof; consider lymphoma or paraneoplastic disease (e.g., collapsin response mediator protein-5–associated optic neuropathy and myelopathy or anti-Ma–associated diencephalic syndrome) Chronic infection, established or with suggestive clinical, radiologic, or laboratory findings thereof (e.g., HIV, syphilis)
RED FLAGS (CONVENTIONAL NEUROIMAGING)
1. Brain a. Imaging features (T2-weighted MRI) suggestive of MS (MS-typical) Lesions with orientation perpendicular to a lateral ventricular surface (Dawson fingers) Lesions adjacent to lateral ventricle in the inferior temporal lobe Juxtacortical lesions involving subcortical U-fibers Cortical lesions b. Imaging characteristics suggestive of diseases other than MS and NMOSD Lesions with persistent (>3 mo) gadolinium enhancement 2. Spinal cord Characteristics more suggestive of MS than NMOSD Lesions in < 3 complete vertebral segments on sagittal T2-weighted sequences Lesions located predominantly (>70%) in the peripheral cord on axial T2-weighted sequences Diffuse, indistinct signal change on T2-weighted sequences (as sometimes seen with long-standing or progressive MS)

[*] These are some common or key findings that should prompt a thorough investigation for competing differential diagnoses before making a diagnosis of NMOSD.

LETM, longitudinally extensive transverse myelitis lesions; MS, multiple sclerosis; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorders.

From Wingerchuk DM, Banwell B, Bennett JL, et al: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders, Neurology 85:177-189, 2015, Table 2, p. 180.

Treatment

Treatment involves (1) acute and longer-term removal of the antibody, (2) minimizing CNS injury, and (3) treating symptoms. Initial episodes and relapses may be treated acutely with methylprednisolone, 20-30 mg/kg/day (maximum 1000 mg/day) usually for 5 days, but for a severe attack, this can be extended. An oral taper is recommended, especially if antibody results are not available at the time of discharge. If there is minimal improvement acutely, plasma exchange (PLEX) can be considered either before or after IVIG (2 g/kg over 2-5 days) and a repeat course of steroids. Rituximab can be used both acutely and to prevent further relapses.

In adult AQP4-Ab–positive NMOSD, effective DMT options include azathioprine, mycophenolate mofetil (MMF), or rituximab. Small retrospective studies in AQP4-Ab–positive pediatric NMOSD have confirmed benefit in reducing the relapse rate with both MMF and rituximab. Preliminary evidence in adults suggests that eculizumab, a monoclonal antibody against the C5 complement protein, reduces recurrences and may improve disability in patients with severe NMOSD. A pilot study of tocilizumab, an anti-IL-6 monoclonal antibody, demonstrated efficacy in AQP4-NMOSD in adults. Trials are currently ongoing with satralizumab, a humanized IL-6 monoclonal antibody, in both adults and children. Medications used for treatment of MS are either ineffective or can exacerbate relapses, again highlighting the importance of an accurate diagnosis.

Prognosis

The majority of AQP4-positive patients have a relapsing phenotype with progressive accrual of disability, whereas those with MOG-Ab-positive NMOSD can be monophasic. In the relapsing phenotypes, the relapse rate is higher in those with AQP4-Ab disorders than MOG-Ab, and some studies show a better recovery and long-term prognosis for MOG-Ab–associated disorders. Similar to adults with NMOSD, pediatric patients are often left with fixed neurologic deficits affecting the visual acuity, visual fields, color vision, motor and sensory function, balance, and bowel/bladder function, and the best outcomes are achieved with a multidisciplinary team.

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618.6

Myelin Oligodendrocyte Glycoprotein–Associated Disorders

Cheryl Hemingway

There is an increasing awareness of a group of demyelinating disorders that are associated with an IgG antibody to a glycoprotein in the outer layer of the myelin sheath, myelin oligodendrocyte glycoprotein (MOG).

Clinical Presentation

The clinical phenotype appears to be distinct from MS but overlaps with patients with ADEM and AQP4-Ab–positive NMOSD. MOG-Ab is present in more than one third of children who present with an initial episode of demyelination, in more than half of those presenting with ADEM, and in almost all of those with relapsing ADEM (MDEM). MOG autoimmunity is not only more common in the young, but it also appears to demonstrate age-dependent phenotypes, with presentation in the pediatric population more heterogeneous than that seen in adults. In adults, the majority of cases present with ON or NMOSD, whereas in pediatric patients, MOG-Abs are also detected in a range of other relapsing phenotypes, including relapsing inflammatory optic neuritis (RION), ADEM followed by optic neuritis (ADEM-ON), brainstem demyelination, and AQP4-Ab–negative NMOSD (see Table 618.1).

Imaging and Laboratory Findings

MRI findings are atypical for MS and can show widespread white matter involvement and increased frequency of longitudinally extensive TM, and over time they can develop into a leukodystrophy-like pattern (see Fig. 618.3). These findings, previously thought to be attributed to early-onset MS, are now being recognized as hallmarks of MOG-Ab–associated disease. Intrathecal OCBs are not normally present, again something previously thought attributable to early-onset MS.

Treatment

Treatment of acute attacks is similar to other demyelinating disorders and includes high-dose methylprednisolone, plasma exchange, and IVIG, depending on the severity of the presentation and the response. There is currently no clarity about DMTs that may be helpful over the long term. A complicating factor is the potentially long interval between relapses, making it difficult to determine the true efficacy of DMTs and guide early decisions as to whether or not to treat. Some studies have also demonstrated a potential worsening when MOG-Ab disorders are treated with MS medications, highlighting again the importance of an accurate clinical diagnosis.

In those who are assessed as likely to benefit from DMTs, medications such as mycophenolate mofetil and azathioprine are frequently offered, either with or without steroids. Rituximab has been used, and although there are some reports of benefit, there are also reports of severe exacerbations, particularly in those with relapsing brainstem demyelination. It is important to remember that although both AQP4 and MOG disorders are antibody driven, the former is an astrocytopathy whereas the latter is an oligodendrocytopathy, making extrapolation of treatment effects from one condition to the other unwise. In a recent large study, the only treatment consistently to have shown benefit in high-risk individuals was monthly IVIG.

Although the full spectrum of phenotypes and best treatment options are currently still being determined, it is important to consider MOG-Ab–associated disorders in the differential diagnosis and to seek expert advice on treatment when possible.

Prognosis

Although some phenotypes appear to be associated with a more benign course than, for example, AQP4-Ab demyelination, other phenotypes such as brainstem demyelination can have a very high relapse rate and be quite debilitating. Relapses can also occur many years after the first event, with intervals of more than 10 yr having been reported. Cognitive deficits are seen frequently in those with young onset and frequent relapses.

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CHAPTER 619

Pediatric Stroke

Nomazulu Dlamini, Gabrielle A. deVeber

Stroke is an important cause of acquired brain injury in newborns, children, and adolescents. The ischemic varieties of arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are, together, more common than brain malignancy (incidence ~ 5 in 100,000 children per year). Perinatal stroke is more common (1 in 2,500-4,000 live births) and is the leading cause of hemiparetic cerebral palsy. A similar number of children have hemorrhagic stroke (HS) and other forms of cerebrovascular disease. Acute stroke is a neurologic emergency; however, delays in recognition are common and delayed treatment worsens outcomes. In comparison with stroke in adults, there is a more diverse group of disorders producing stroke in neonates and children.

619.1

Arterial Ischemic Stroke

Nomazulu Dlamini, Gabrielle A. deVeber

Arterial blood reaches the brain via the anterior (internal carotid) and posterior (vertebrobasilar) circulations, converging at the circle of Willis. Strokes most often involve the middle cerebral artery territory but can occur in any cerebral artery of any size. AIS is the focal brain infarction that results from occlusion of these arteries.

The diagnosis of stroke in children is frequently delayed. This is a consequence of subtle and nonspecific clinical presentations, poor awareness by primary care pediatric physicians, a complicated differential diagnosis (see Chapter 619.5), and a high frequency (>50%) of negative initial brain CT scans in true AIS. *The acute onset of a focal neurologic deficit in a child is stroke until proven otherwise.* The most common focal presentation is hemiparesis, but acute visual, speech, sensory, or balance deficits also occur. Importantly, new-onset seizures, especially focal motor seizures, frequently herald stroke in children. Children with these presentations require urgent neuroimaging and consultation with a child neurologist, because emergency interventions may be indicated. AIS is a clinical and radiographic diagnosis. Although CT imaging can demonstrate mature AIS and exclude hemorrhage, cerebral MRI is required to identify early and small infarcts. **Diffusion-weighted MRI** demonstrates AIS from minutes to 7 days following the onset; MR angiography can confirm vascular occlusion and suggest possible arteriopathy (Fig. 619.1). Diffusion-weighted MRI can also demonstrate wallerian degeneration in the descending corticospinal tract, which correlates with chronic hemiparesis.

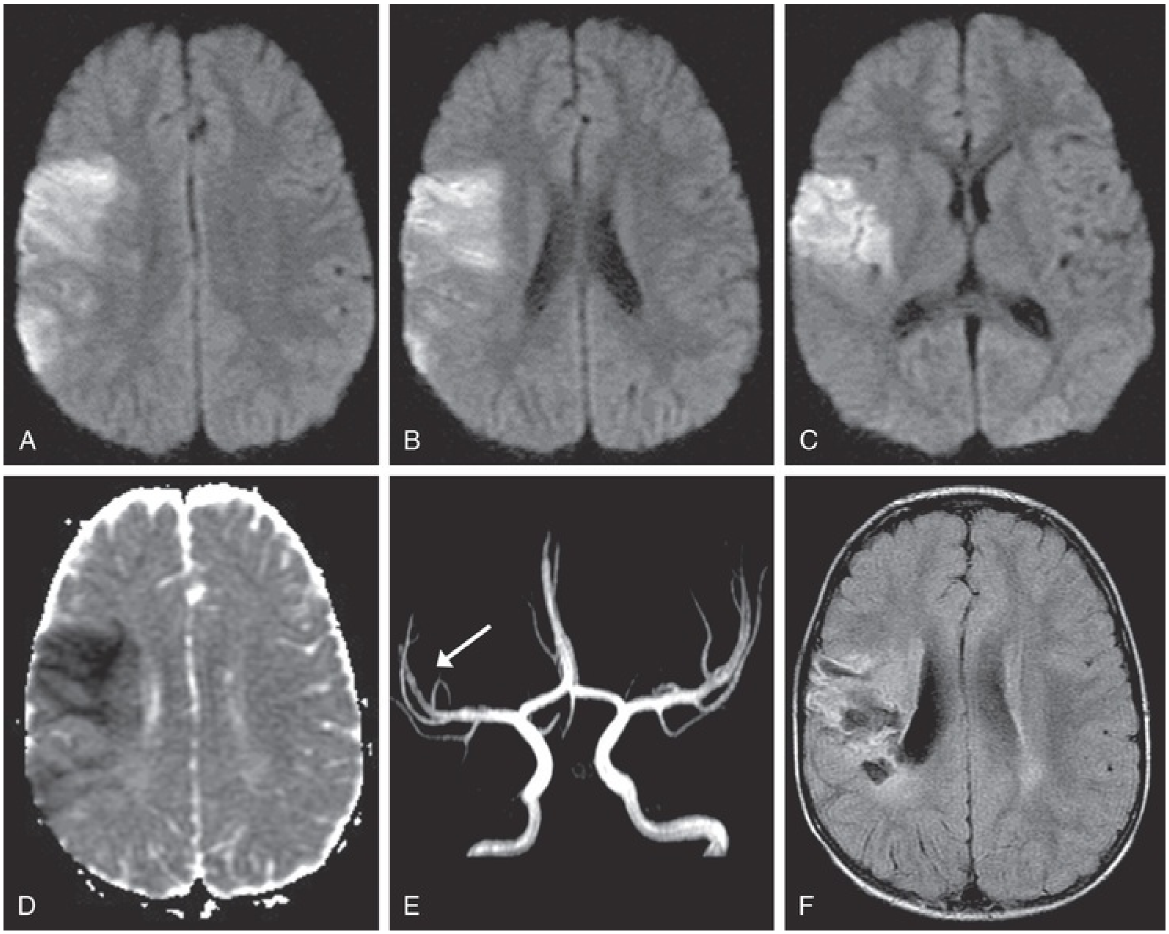

FIG. 619.1 Arterial ischemic stroke. A healthy 3 yr old boy had sudden onset of left-sided weakness. Examination also demonstrated left-sided hemisensory loss and neglect. **A** to **C,** Diffusion-weighted MRI shows focal increased signal in the right temporal-parietal region in the territory of the middle cerebral artery (MCA). **D,** Apparent diffusion coefficient map confirms restricted diffusion consistent with infarction (ischemic stroke). **E,** MR angiogram shows decreased flow in the corresponding branch of the MCA. **F,** Follow-up MRI at 3 mo shows atrophy and gliosis in the same region.

Many possible risk factors for childhood AIS are recognized (Table 619.1), although their specific pathophysiologic mechanisms remain poorly understood. Half of children with AIS are healthy before stroke onset. Three main categories of etiology should be considered: **arteriopathy, cardiac disease,** and **hematologic disease.** Hence, in addition to a careful history taking and physician examination, a full investigation (including vascular imaging, echocardiography, and blood tests for inflammatory, infectious, and prothrombotic disorders) are important because these tests often reveal multiple predispositions and triggering risk factors.

Table 619.1

Risk Factors for Arterial Ischemic Stroke in Children

MAJOR CATEGORY	EXAMPLES
Arteriopathy	Transient cerebral arteriopathy (TCA) (synonyms: childhood primary angiitis of the central nervous system [cPACNS]; focal cerebral arteriopathy [FCA]) Postvaricella and other viruses angiopathy (PVA) Systemic/secondary vasculitis (e.g., Takayasu arteritis) Moyamoya disease/syndrome Arterial infection (e.g., bacterial meningitis, tuberculosis; see Table 691.2) Fibromuscular dysplasia Traumatic or spontaneous carotid or vertebral artery dissection Vasospasm in reversible cerebral vasoconstriction syndrome (RCVS) (e.g., Call-Fleming syndrome) Migraine Congenital/genetic arteriopathies (e.g., PHACES syndrome, Alagille syndrome, CADASIL; mutations in ACTA2, COL4A1, COL4A2, and ADA2)
Cardiac	Complex congenital heart diseases (cyanotic ≫ acyanotic) Cardiac catheterization/procedure (e.g., balloon atrial septostomy) Ventricular assistive device use Cardiac surgery Extracorporeal membrane oxygenation (ECMO) Arrhythmia Valvular heart disease Endocarditis Cardiomyopathy, severe ventricular dysfunction Intracardiac lesions (e.g., atrial myxoma) Septal defects (atrial septal defect, ventricular septal defect, patent foramen ovale [possible paradoxical emboli])
Hematologic	Sickle cell anemia Iron-deficiency anemia Inherited prothrombotic (e.g., factor V Leiden, prothrombin gene mutation 20210A) Acquired prothrombotic (e.g., protein C/S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies, oral contraceptives, pregnancy)
Other including metabolic/genetic etiologies	Acute systemic illness (e.g., dehydration, sepsis, diabetic ketoacidosis) Chronic systemic illness (e.g., systemic lupus erythematosus, leukemia) Illicit drugs and toxins (e.g., cocaine) Hereditary dyslipoproteinemia Familial hypoalphalipoproteinemia Familial hypercholesterolemia Type IV, type III hyperlipoproteinemia Tangier disease Progeria Fabry disease (α-galactosidase A deficiency) Neurofibromatosis type 1 Heritable disorders of connective tissue Ehlers-Danlos syndrome (type IV) Marfan syndrome Pseudoxanthoma elasticum Homocystinuria (cystathionine β-synthase deficiency, or 5,20-methylenetetrahydrofolate reductase), hyperhomocysteinemia Menkes syndrome

	Congenital disorders of glycosylation See also: stroke mimics (see Chapter 619.5)

CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; PHACES, posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities.

Modified from Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children, Stroke 39:2644–2691, 2008, Table 2.

Arteriopathy, a disorder of the cerebral arteries, is a leading cause of childhood AIS, present in more than 50% of children. One common arteriopathy that affects healthy school-age children features unilateral irregular stenosis of the proximal middle cerebral artery and neighboring arteries with associated basal ganglia infarction. This entity has been published under multiple names —**transient cerebral arteriopathy,** post–varicella angiopathy, nonprogressive childhood primary angiitis of the central nervous system (CNS), and focal cerebral arteriopathy—reflecting uncertainty regarding the pathogenesis.

Transient cerebral arteriopathy is nearly always self-limited and may be the result of focal inflammation. However, at the time of AIS diagnosis it may be indistinguishable from intracranial dissection or early moyamoya disease. Diffuse, bilateral, progressive **vasculitis** is rare and can represent progressive childhood primary angiitis of the CNS or occur associated with systemic vasculitides (Table 619.2). Cranial infections (e.g., bacterial or tuberculous meningitis) also produce **infectious arteritis** and thrombophlebitis of surface vessels. A**rterial dissection** can be spontaneous or posttraumatic and involves extracranial arteries more frequently than intracranial arteries. **Moyamoya** demonstrates progressive occlusion of the distal internal carotid arteries. It may be idiopathic **(moyamoya disease)** or associated with other conditions **(moyamoya syndrome)** such as sickle cell anemia, neurofibromatosis type 1, trisomy 21, William syndrome, Alagille syndrome, chromosomal microdeletions/microduplications and disorders following irradiation. **Congenital/genetic disorders** of craniocervical arteries include PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities) syndrome, fibromuscular dysplasia, or CADASIL (cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy). *ACTA2*, *COL41A*, and *ADA2* mutations may be associated with AIS, and new genetic arteriopathic conditions are steadily being added to this list. Hence, targeted genetic testing and whole-exome sequencing is recommended. Vasospasm as occurs in migraine, subarachnoid hemorrhage, or reversible cerebral vasoconstriction syndrome (sometimes called Call-Fleming syndrome) can cause AIS. Metabolic strokes are seen in organic acidemia, methylmalonic acidemia, propionic acidemia, isovaleric acidemia, glutaric aciduria type II, mitochondrial encephalomyopathies, MELAS, MERRF, MERRF/MELAS overlap syndrome, and Kearns-Sayre syndrome.

Table 619.2

Classification of Cerebral Vasculitis

Infectious vasculitides
Bacterial, fungal, parasitic
Spirochetal (syphilis, Lyme disease, leptospirosis)
Viral, rickettsial, mycobacterial, free-living amebae, cysticercosis, other helminths
Necrotizing vasculitides
Classic polyarteritis nodosa
Wegener granulomatosis
Allergic angiitis and granulomatosis (Churg-Strauss syndrome)
Necrotizing systemic vasculitis overlap syndrome
Lymphomatoid granulomatosis
Vasculitis associated with collagen vascular disease
Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Sjögren syndrome
Vasculitis associated with other systemic diseases
Behçet disease
Ulcerative colitis
Sarcoidosis
Relapsing polychondritis
Kohlmeier-Degos disease
Takayasu arteritis
Hypersensitivity vasculitides
Henoch-Schönlein purpura
Drug-induced vasculitides
Chemical vasculitides
Essential mixed cryoglobulinemia
Miscellaneous vasculitides
Vasculitis associated with neoplasia
Vasculitis associated with radiation
Cogan syndrome
Dermatomyositis–polymyositis
X-linked lymphoproliferative syndrome
Kawasaki disease
Primary central nervous system vasculitis

Modified from Roach ES, Golomb MR, Adams R, et al: Management of stroke in infants and children, Stroke 39:2644-2691, 2008, Table 5.

Cardioembolic stroke makes up approximately 25% of childhood AIS cases, with the maximal embolic risk concurrent with catheterization, surgical repair, or ventricular assist device use. AIS complicates approximately 0.5% of pediatric cardiac surgeries, and reoperation increases the risk. Although **complex congenital heart diseases** are most frequently associated with AIS, acquired conditions, including arrhythmia, cardiomyopathy, and infective endocarditis, should also be considered. A **patent foramen ovale** provides a possible conduit for paradoxical venous thromboembolism to the brain. All children with suspected AIS require a thorough cardiovascular examination, an electrocardiogram, and an echocardiogram. Prothrombotic coagulation disorders and infection identified at the time of the index cardiogenic stroke increase the stroke recurrence risk.

Hematologic disorders associated with AIS include **sickle cell anemia,** in which the stroke risk is increased 400-fold, although effective screening (using transcranial Doppler) and transfusion therapy have reduced the incidence. Iron-deficiency anemia also increases the risk and is easily treatable. **Coagulation disorders** are associated with childhood AIS. They include hereditary (e.g., factor V Leiden) and acquired (e.g., antiphospholipid antibodies, lipoprotein-a elevation) **prothrombotic states** and **prothrombotic medications,** including oral contraceptives and asparaginase chemotherapy. Additional AIS risk factors include migraine, acute childhood illnesses, chronic systemic illnesses, illicit drugs and toxins, and rare inborn errors of metabolism.

Treatment of childhood AIS is multifaceted and multiple consensus-based guidelines are available. In general, emergency thrombolysis is not recommended for young children and mechanical thrombectomy for young children is also not recommended given the absence of safety and efficacy data.

Nonetheless, some pediatric stroke centers offer thrombolysis with or without thrombectomy for pediatric patients with AIS. Most candidates are preteen or adolescent patients with AIS; younger children may also be candidates for thrombolysis but often have mimics of stroke and must be evaluated carefully for other diagnoses. The safety and efficacy of thrombolysis and/or thrombectomy in children with AIS has only been reported anecdotally but has not been tested with randomized trials.

Early initiation of antithrombotic strategies is paramount to prevent early reinfarction. Depending on the suspected cause, this includes anticoagulation with heparin or antiplatelet strategies, usually aspirin. Hyperacute neuroprotective strategies are essential to initiate within minutes in suspected stroke because they prevent progressive ischemic brain injury. These include control of blood glucose (avoid hypo- and hyperglycemia), temperature (avoid hyperthermia, maintain normal temperature), and maintenance of adequate cerebral perfusion (avoid hypo- and hypertension) and oxygenation. Urgent treatment of seizures is an important neuroprotective strategy, including possible monitoring with continuous electroencephalography (EEG). Early malignant infarct edema is life-threatening, more common in children, and predictable, and emergency surgical decompression can be life-saving. Disease-specific treatments include transfusion therapy in sickle cell disease, immunosuppression in vasculitis, and revascularization surgery in moyamoya. Long-term treatment goals include **secondary stroke prevention,** including antiplatelet therapy in arteriopathy and anticoagulation in cardiogenic causes. Multimodal, family-centered **rehabilitation** programs are required for most survivors, targeting motor deficits, language and intellectual impairments, behavioral and social disabilities, and epilepsy. Long-term attention to arterial health lifestyle factors may also be important. Outcomes after childhood AIS include: recurrent stroke in 10–50%, depending on the cause and preventive treatment, death in 2–6%; neurologic deficits in 60–70%; and seizure disorders in ≤ 30%.

Adolescents and young adults with idiopathic (cryptogenic) AIS and a patent foramen ovale (PFO) may benefit from percutaneous PFO closure to prevent a recurrent stroke.

Perinatal Arterial Ischemic Stroke

Perinatal stroke is very common. It differs from childhood stroke, and it has two distinct clinical presentations. Acute symptomatic neonatal AIS presents with focal seizures within 24-28 hr of birth (Fig. 619.2). MRI diffusion abnormalities in an arterial territory confirm recent infarction. Alternatively, some affected neonates are asymptomatic at birth and present in later infancy with signs of early hand preference and congenital hemiparesis. Hand dominance within the first year of life is abnormal and may be the result of perinatal stroke. Imaging reveals focal encephalomalacia in an arterial territory, typically as lesions in the large middle cerebral artery.

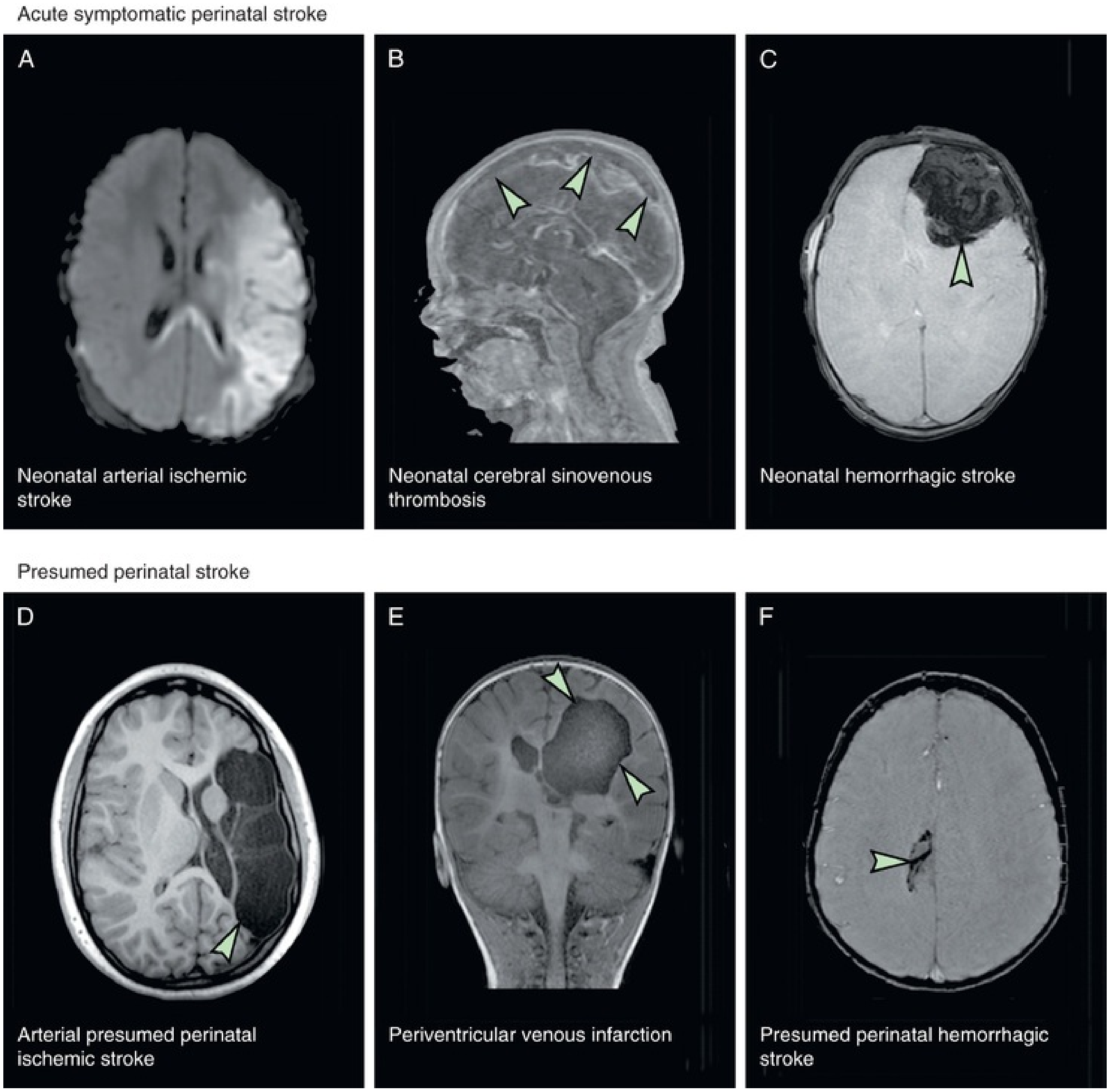
Acute symptomatic perinatal stroke
A
Neonatal arterial ischemic stroke
B
Neonatal cerebral sinovenous thrombosis
C
Neonatal hemorrhagic stroke
Presumed perinatal stroke
D
Arterial presumed perinatal ischemic stroke
E
Periventricular venous infarction
F
Presumed perinatal hemorrhagic stroke

FIG. 619.2 Perinatal stroke diseases by MRI. **A,** Neonatal arterial ischemic stroke features acute restriction on axial diffusion-weighted MRI in an arterial territory; diaschisis of the splenium of the corpus callosum is also evident. **B,** Neonatal cerebral sinovenous thrombosis is evident as a filling defect on sagittal MR venogram (shown), in this case, in the superior sagittal sinus *(arrows).* **C,** Neonatal hemorrhagic stroke detectable on gradient echo or susceptibility-weighted MRI *(arrow).* **D,** Arterial presumed perinatal ischemic stroke in a child with hemiparesis is diagnosed by focal encephalomalacia on CT or MRI (axial T1-weighted MRI shown) in an arterial territory *(arrow).* **E,** Periventricular venous infarction presents with congenital hemiparesis with a focal lesion affecting the periventricular white matter with sparing of the cortex and basal ganglia, shown on coronal T1-weighted MRI (porencephaly indicated with *arrows*). **F,** Presumed perinatal hemorrhagic stroke with a focal area of remote parenchymal injury showing hemorrhage (gradient echo, *arrow*). (From Dunbar M, Kirton A: Perinatal stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury, Lancet 2:666-676, 2018, Fig. 2, p. 668.)

In acute neonatal AIS, seizure control is important, but antithrombotic agents are rarely required because recurrent stroke is rare; the exceptions are neonates with congenital heart disease and cardiac embolism, prothrombotic disorders, and, perhaps, those with congenital arterial anomalies (stenosis, hypoplasia). The pathophysiology is complex and poorly understood. Most are idiopathic, although established causes include congenital heart disease, thrombotic placentopathy, arterial anomalies, and hereditary or other prothrombotic disorders and meningitis. Many other maternal, prenatal, perinatal, obstetric, and neonatal factors have been investigated with several strong associations found (e.g., infertility, primiparity, multiple gestation). Although outcomes can be favorable, most children incur lifelong disability. Perinatal stroke accounts for most cases of hemiparetic cerebral palsy (congenital hemiplegia, see Chapter 616.1). Additional morbidity, seen in approximately 25%, includes disorders of language, learning, cognition, and behavior and longer-term epilepsy. Stroke recurrence rates in subsequent pregnancies are extremely low in the absence of a familial prothrombotic disorder.

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619.2

Cerebral Sinovenous Thrombosis

Nomazulu Dlamini, Gabrielle A. deVeber

Keywords

pediatric sinovenous thrombosis
venous stroke
treatment

Cerebral venous drainage occurs via the cerebral sinovenous system. The superficial system (i.e., cortical veins, superior sagittal sinus) and deep system (i.e., internal cerebral veins, straight sinus) converge at the torcula to exit the cranial vault via the paired transverse and sigmoid sinuses and jugular veins. In cerebral sinovenous thrombosis (CSVT), thrombotic occlusion of these venous structures can create regional or diffuse increased intracranial pressure, cerebral edema, and, in 50% of cases, venous infarction or hemorrhage (venous stroke). CSVT may be more common in children than in adults, and risk is greatest in the neonatal period.

Clinical presentations are typically gradual, variable, and nonspecific compared with AIS. Neonates often present with encephalopathy and seizures. Children may present with symptoms mimicking idiopathic intracranial hypertension, including progressive headache, papilledema, diplopia secondary to 6th cranial nerve palsy, or with acute focal deficits. Seizures, lethargy, and confusion are common. Diagnosis requires high clinical suspicion and specifically requested imaging of the cerebral venous system. Nonenhanced CT is insensitive in detecting CSVT, and so either contrast **CT venography** or MR venography is necessary to demonstrate filling defects in the cerebral venous system (Fig. 619.3). MRI offers superior parenchymal imaging compared with CT.

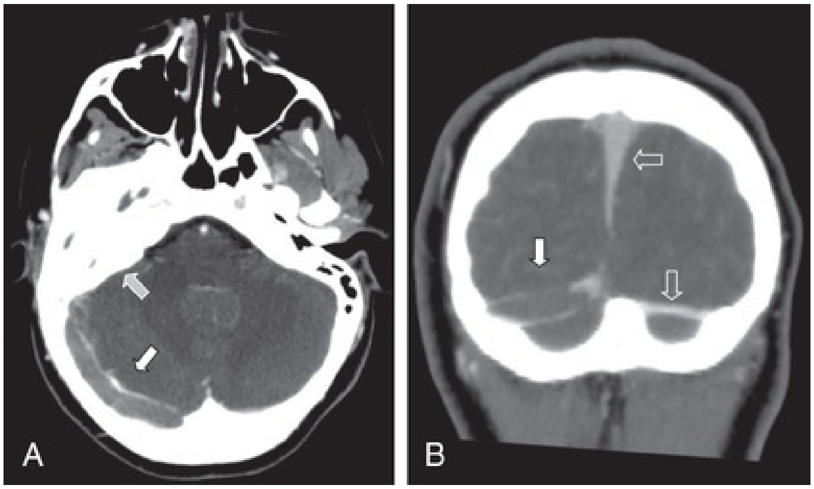

FIG. 619.3 Cerebral sinovenous thrombosis. A 9 yr old girl presented with fever and progressive right-sided headache. She complained of double vision and had papilledema on examination. Axial **(A)** and coronal **(B)** CT venography demonstrates a large thrombus in the right transverse sinus that fails to opacify with contrast *(full arrows).* Note normal filling in superior sagittal sinus and smaller left transverse sinuses *(empty arrows, right)* and opacification of the mastoid air cells *(hatched arrow, left).* Cause was otitis

media/mastoiditis with septic thrombophlebitis of transverse sinus.

Table 619.3 lists the risk factors for CSVT. **Prothrombotic states** associated with childhood CSVT include inherited conditions (e.g., prothrombin gene mutation of 20210A) and acquired conditions (e.g., antiphospholipid antibodies), prothrombotic medications (e.g., asparaginase, oral contraceptives), and common childhood illnesses (e.g., otitis media, iron-deficiency anemia, and dehydration). **Systemic diseases** associated with increased risk of CSVT include leukemia, inflammatory bowel disease, and nephrotic syndrome.

Table 619.3

Common Risk Factors for CSVT in Children

MAJOR CATEGORIES	EXAMPLES
Blood coagulation	Prothrombotic conditions Factor V Leiden, prothrombin gene mutation 20210A, protein C deficiency, protein S deficiency, antithrombin III deficiency, lipoprotein a, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies), pregnancy/puerperium Dehydration (e.g., gastroenteritis, neonatal failure to thrive) Iron-deficiency anemia Drugs and toxins (e.g., L -asparaginase, oral contraceptives) Acute systemic illness (e.g., sepsis, disseminated intravascular coagulation) Chronic systemic illness (e.g., inflammatory bowel disease, systemic lupus erythematosus, leukemia) Nephrotic syndrome Inborn errors of metabolism (e.g., homocystinuria)
Blood vessel	Infection/thrombophlebitis Otitis media, mastoiditis, bacterial meningitis, sinusitis, dental abscess, pharyngitis Lemierre syndrome Sepsis Trauma: skull fractures, closed head trauma Compression: birth, occipital bone compression in neonates in supine lying Iatrogenic: neurosurgery, jugular lines, extracorporeal membrane oxygenation Venous malformations (e.g., dural arteriovenous fistulas)

Head and neck disorders can directly involve cerebral veins and sinuses thereby causing CSVT. Common infections, including meningitis, otitis media, and mastoiditis, can cause **septic thrombophlebitis** of venous channels. CSVT can complicate head trauma especially in veins adjacent to skull fractures. Neurosurgical procedures in proximity to cerebral venous structures may also lead to injury and CSVT. Finally, obstruction of the jugular veins and proximal stasis may result in CSVT. In neonates, because the cranial sutures are unfused, mechanical distortion of the underlying venous sinuses may occur and predispose to CSVT either during labor and delivery or with supine lying due to occipital bone compression of the posterior sagittal sinus.

Anticoagulation therapy plays an important role in childhood CSVT treatment. Substantial indirect evidence has led to a consensus recommendation for anticoagulation with unfractionated or low-molecular-weight heparins in most children. The presence of hemorrhagic venous infarcts is not an absolute contraindication. Treatment is usually planned for 6 mo, although if reimaging at 3 mo confirms recanalization, treatment is usually discontinued. However, anticoagulation of neonates is more controversial and guidelines differ. Evidence suggests that 30% of untreated neonates and children will extend their thrombosis in the 1st week following diagnosis, and additional venous infarction can result. Therefore, if anticoagulation is withheld, early (e.g., 5-7 days) repeat venous imaging is paramount. Protocols supporting initial anticoagulation recommend shorter treatment durations (i.e., 6 wk to 3 mo) in neonates. Children with persistent risk factors may require prophylactic long-term anticoagulation. At initial diagnosis, supportive interventions include management of infection, detection and treatment of seizures, and neuroprotective measures (e.g., normothermia, normotension, normovolemia, normoglycemia). **Compressive optic neuropathy** secondary to prolonged increased intracranial pressure after CSVT is an important and easily missed complication that can lead to permanent visual loss. Regular funduscopic examination by an ophthalmologist and treatment directed at reducing intracranial pressure (e.g., acetazolamide, serial lumbar puncture) may be required. Most neurologic morbidity is suffered by those incurring venous infarction. Consistent with other forms of childhood stroke, a comprehensive neurorehabilitation program is required.

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619.3

Spinal Cord Lesions Associated With Vascular Processes

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Keywords

transverse myelitis
spinal cord
infarction
vasculitis

vertebral artery dissection
vascular disease
pediatric

Most cases of **transverse myelitis** (TM) in childhood are postinfectious or, if recurrent, are associated with underlying demyelinating processes, such as multiple sclerosis (see Chapter 618.4) or neuromyelitis optica (see Chapter 618.2). However, in a small proportion of children presenting with acute spinal cord symptoms, infarction and necrosis may occur. This pathology may be associated with disease of the vessels, such as systemic lupus erythematosus (SLE)–associated **vasculitis** (see Chapter 183) or other vascular events such as **embolism** (including nucleus propulsus embolism–fibrocartilaginous embolism). Rarely, **arteriovenous malformations** of the spinal cord may exist, and may cause myelopathy and infarction with hemorrhage in the spinal cord. An acute onset and a peak of symptoms over minutes to hours may suggest a vascular process.

Vasculitic Processes: Systemic Lupus Erythematosus

Most cases of SLE-associated myelitis are longitudinally extensive, and although reports in pediatric populations are rare, the disorder can occur. In 23–60% of cases, myelitis may be the first clinical manifestation of lupus and may in many cases occur at times of low systemic SLE disease activity. Poor recovery is frequent in these cases, with only 14% of patients experiencing complete recovery. In children, other vasculitic etiologies of cord disease, such as Bechet disease, exist.

Spinal Cord Embolism

Other rare etiologies of an acute increased T2 signal on a spinal cord MRI presenting clinically as transverse myelitis (TM) include cord infarction due to thromboembolism, such as that due to fibrocartilaginous embolism or originating from a vertebral artery dissection. Although ischemic myelopathy due to a **vertebral artery dissection** will occur in the cervical spine, fibrocartilaginous embolism may occur anywhere in the spinal cord. A hyperacute onset and lesion appearance (wedge-shaped distribution) together with MRI diffusion-weighted imaging showing diffusion restriction may be helpful in distinguishing ischemic thromboembolic abnormalities from inflammatory TM.

Clinical Manifestations

As with inflammatory TM, patients will present with acute onset of motor weakness accompanied by sensory abnormalities. The weakness may progress over minutes to hours. Pain or discomfort localized to the back or neck, depending on lesion localization, is frequently reported, with rapid progression of motor weakness and early areflexia reflecting spinal shock. Spasticity, hyperreflexia, and clonus will occur in the ensuing weeks. A sensory level and motor weakness are present, distal to the lesion, with urinary symptoms, including urinary retention, a frequent occurrence.

Investigations

MRI of the spinal cord, including T1- and T2-weighted axial as well as sagittal cuts with gadolinium, are necessary to evaluate for the presence of a focal spinal cord lesion. Given the frequency of longitudinally extensive lesions in myelopathy in pediatric populations, both cervical and thoracic spine imaging should be included in all patients presenting with acute TM. Inclusion of imaging sequences sensitive for hemorrhage (gradient echo sequences) may help, as will diffusion sequences. Finally, the inclusion of brain MRI scans, including associated vascular imaging of head and neck vessels, will help to evaluate for the possibility of large-vessel disease. Particular attention should be paid to the possibility of vertebral artery dissection in the event of a cervical spine lesion and ischemic brain lesions in the distribution of the posterior circulation.

Lumbar puncture can be performed once MRI evaluation has ruled out a severe cord expansion or mass leading to complete spinal column block. Although inflammatory TM may be associated with elevations in the CSF white blood cells (WBCs) and protein, ischemic myelopathy due to embolism will not show an acute pleocytosis. However, in a vasculitic event such as myelopathy associated with SLE, increased CSF protein and WBCs may be present.

Serum testing for the presence of underlying rheumatologic disorders should be performed in patients presenting with TM. A workup for hypercoagulable states should be performed in the event that a high suspicion for ischemic myelopathy is present.

Treatment

In addition to supportive care, treatment is directed at the suspected underlying disease process. Given the low likelihood of complete recovery in ischemic lesions of the spinal cord and the significant disability associated with spinal cord injury, when underlying etiologies such as SLE are found, prophylactic treatment is recommended. Supportive care, including pain control for neuropathic pain, spasticity management, and management of urinary symptoms, is frequently required in this population. When vascular abnormalities are identified or if ischemic myelitis is the clear cause, low-dose aspirin (2-4 mg/kg/day) for prevention of recurrence may be indicated.

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619.4

Hemorrhagic Stroke

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Keywords

hemorrhage
vascular malformations
treatment

Hemorrhagic stroke (HS) includes nontraumatic intracranial hemorrhage and is classified by the intracranial compartment containing the hemorrhage. Intraparenchymal bleeds may occur in any location, whereas intraventricular hemorrhage may be isolated or an extension of intraparenchymal hemorrhage. Bleeding outside the brain may occur in the subarachnoid, subdural, or epidural spaces.

Clinical presentations vary according to location, cause, and rate of bleeding. Acute hemorrhages may feature instantaneous or **thunderclap headache,** loss of consciousness, and nuchal rigidity in addition to focal neurologic deficits and seizures. HS can be rapidly fatal. In bleeds associated with vascular malformations, pulsatile tinnitus, cranial bruit, macrocephaly, and high-output heart failure may be present. The diagnosis relies on imaging, and CT scanning is highly sensitive to acute HS. However, lumbar puncture may be required to exclude subarachnoid hemorrhage. MRI is highly sensitive to even small amounts of both acute and chronic hemorrhage and offers improved diagnostic accuracy (Fig. 619.4). Angiography by CT, MR, or conventional catheterization means is often required to exclude underlying vascular abnormalities (e.g., vascular malformations, aneurysms).

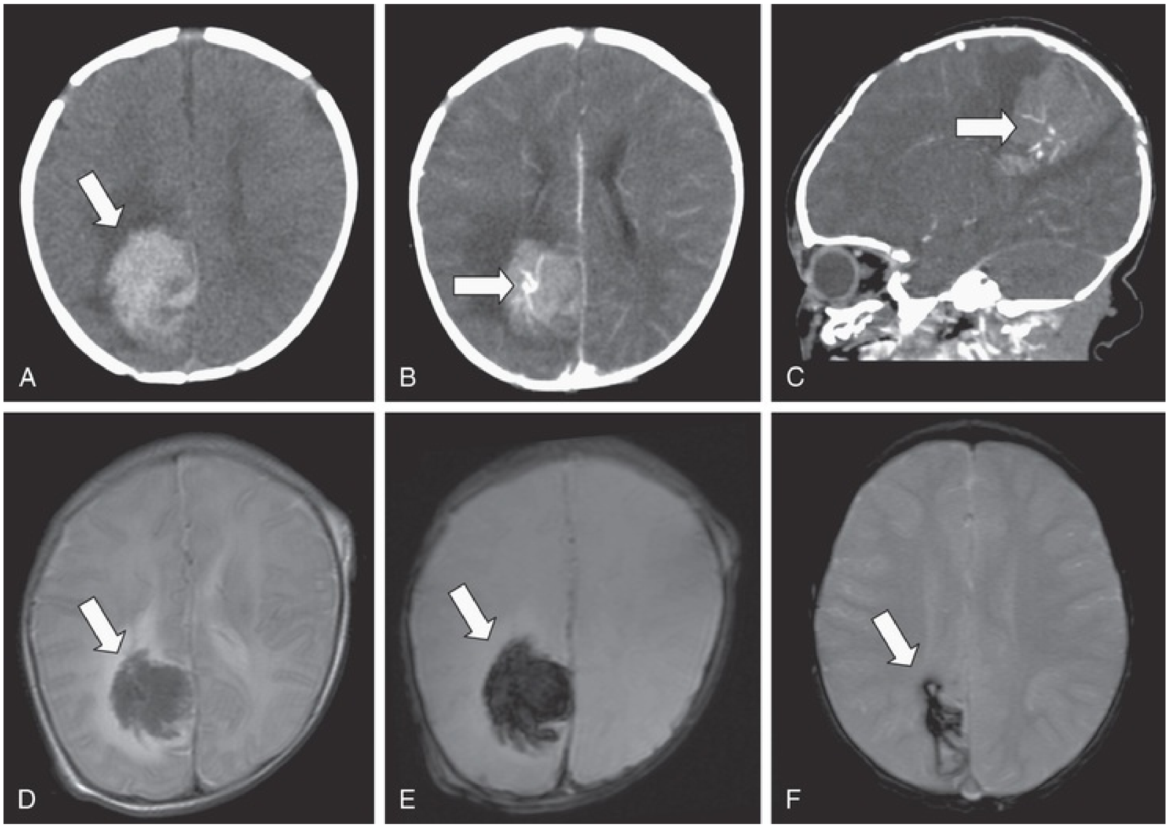

FIG. 619.4 Hemorrhagic stroke. A healthy 1 mo old presented with sudden-onset irritability followed by focal left body seizures. Plain CT scan of head demonstrates a large hyperdense lesion in the right parietal region with surrounding edema, consistent with acute hemorrhage **(A).** Axial **(B)** and sagittal **(C)** contrast CT scans suggest an abnormal cluster of vessels

in the center of the hemorrhage, consistent with an arteriovenous malformation. T2-weighted MRI differentiates the acute hemorrhage from surrounding edema **(D).** Gradient echo MRI, both acutely **(E)** and at 3 mo **(F),** demonstrates the presence of blood product.

Abusive head trauma with intracranial bleeding in children may present as primary subdural or parenchymal hemorrhage with no apparent history of trauma. Clinicians should search for the following: subtle scalp, suborbital or ear bruising; retinal hemorrhages in multiple layers; and chronic failure to thrive. In infants with subdural bleeds, x-rays should be performed to rule out fractures. Epidural hematoma is nearly always caused by trauma, including middle meningeal artery injury typically associated with skull fracture. Subdural hematoma can occur spontaneously or with trivial trauma in children with brain atrophy because of stretching of bridging veins.

Causes of and risk factors for HS (Table 619.4) include vascular malformations and systemic disorders. **Arteriovenous malformations** are the most common cause of childhood subarachnoid and intraparenchymal HS and may occur anywhere. Neonates with vein of Galen malformations may present with heart failure, progressive macrocephaly, or, rarely, hemorrhage. In older children with arteriovenous malformations, the risk of bleeding is approximately 2–4% per year throughout life. Somatic mutations in *KRAS* have been noted in some patients with arteriovenous malformations of the brain. Other vascular malformations leading to HS include cavernous angiomas **(cavernomas),** dural arteriovenous fistulas, and vein of Galen malformations. Cerebral cavernous malformations may be sporadic or familial (autosomal dominant) and associated with mutations in the *CCM1* , *CCM2* , or *CCM3* genes. Cerebral aneurysms are a less common cause of subarachnoid hemorrhage in children and may suggest an underlying disorder (e.g., polycystic kidney disease, infective endocarditis) (Fig. 619.5). A common cause for HS is bleeding from a preexisting brain tumor. Arterial diseases that usually cause ischemic stroke, including fibromuscular dysplasia, vasculitis, intracranial dissection, and moyamoya, can also predispose to HS. Additional causes of parenchymal HS include hypertensive hemorrhage and hematologic disorders such as thrombocytopenic purpura, hemophilia, acquired coagulopathies (e.g., disseminated intravascular coagulopathy, liver failure), anticoagulant therapy (e.g., warfarin), or illicit drug use. Ischemic infarcts may undergo hemorrhagic transformation, particularly in CSVT, and may be difficult to differentiate from primary HS.

Table 619.4

Potential Risk Factors for Hemorrhagic Stroke in Children

MAJOR CATEGORIES	EXAMPLES
Vascular disorder	Arteriovenous malformations Cavernous malformations (“cavernomas”) Venous angiomas and other venous anomalies Hereditary hemorrhagic telangiectasia Intracranial aneurysm Choroid plexus angiomas (pure intraventricular hemorrhage) Moyamoya disease/syndrome Inflammatory vasculitis (see Chapter 619.1) Genetic lesions arteriopathy (see Chapter 619.1) Neoplastic with unstable vasculature Drugs/toxins (cocaine, amphetamine) Cerebral sinovenous thrombosis
Blood disorder	Idiopathic thrombocytopenic purpura Hemolytic-uremic syndrome Hepatic disease/failure coagulopathy Vitamin K deficiency (hemorrhagic disease of the newborn) Disseminated intravascular coagulopathy
Trauma	Middle meningeal artery injury (epidural hematoma) Bridging vein injury (subdural hematoma) Subarachnoid hemorrhage Hemorrhagic contusions (coup and contrecoup) Nonaccidental trauma (subdural hematomas of different ages) Iatrogenic (neurosurgical procedures, angiography) Rupture of arachnoid cyst

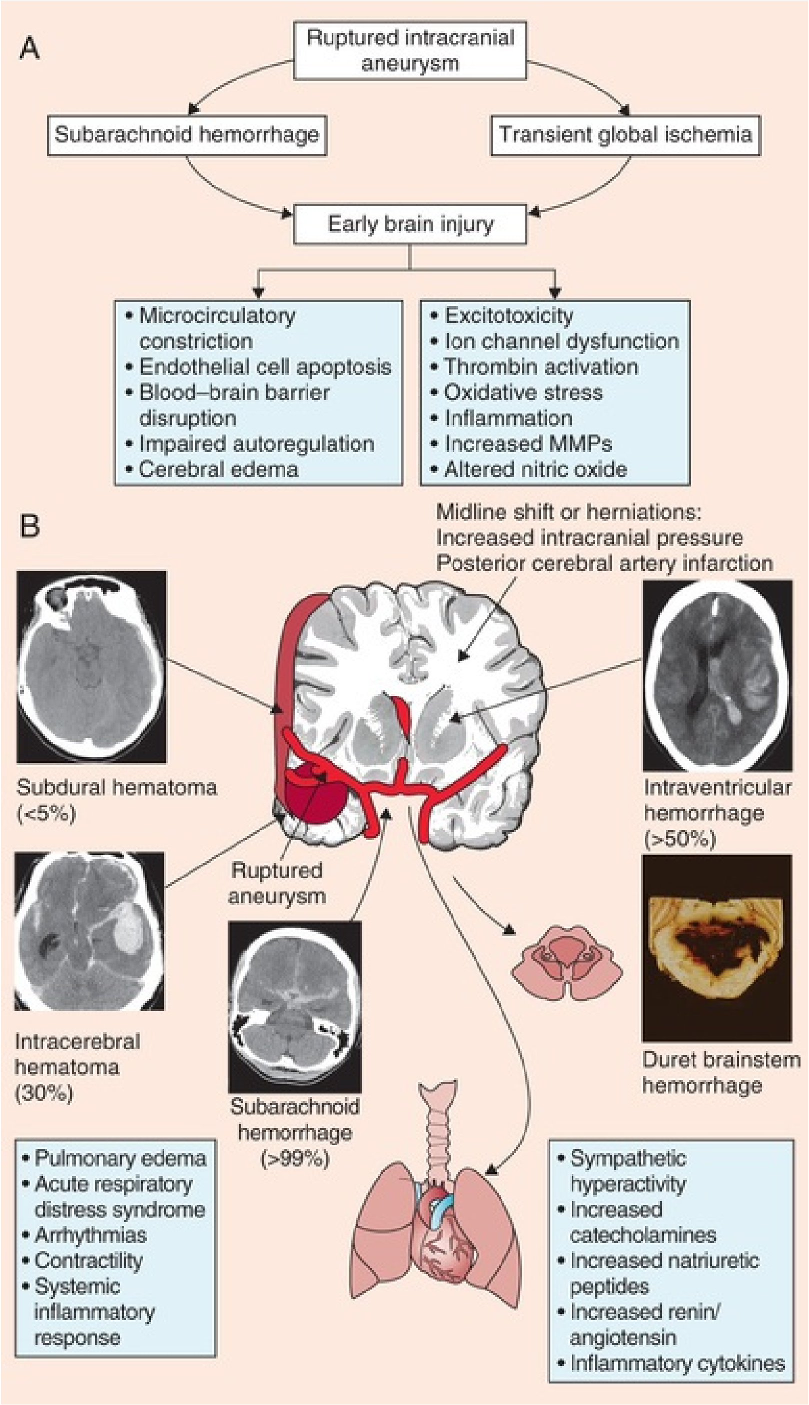
A
Ruptured intracranial aneurysm
Subarachnoid hemorrhage
Transient global ischemia
Early brain injury
• Microcirculatory constriction
• Endothelial cell apoptosis
• Blood–brain barrier disruption
• Impaired autoregulation
• Cerebral edema
• Excitotoxicity
• Ion channel dysfunction
• Thrombin activation
• Oxidative stress
• Inflammation
• Increased MMPs
• Altered nitric oxide
B
Midline shift or herniations:
Increased intracranial pressure
Posterior cerebral artery infarction
Subdural hematoma (<5%)
Intraventricular hemorrhage (>50%)
Ruptured aneurysm
Intracerebral hematoma (30%)
Subarachnoid hemorrhage (>99%)
Duret brainstem hemorrhage
• Pulmonary edema
• Acute respiratory distress syndrome
• Arrhythmias
• Contractility
• Systemic inflammatory response
• Sympathetic hyperactivity
• Increased catecholamines
• Increased natriuretic peptides
• Increased renin/ angiotensin
• Inflammatory cytokines

FIG. 619.5 Pathophysiology of subarachnoid hemorrhage. Hemorrhage into various compartments (subarachnoid, intraventricular, intracerebral, subdural) can cause brain shift, increased intracranial pressure, herniation, Duret brainstem hemorrhages, and death. Systemic effects of subarachnoid hemorrhage include cardiac and pulmonary complications. Brain injury from this condition initially is due to transient global ischemia and effects of the hemorrhage. Delayed neurologic complications can ensue. MMPs, matrix metalloproteinases. (From Macdonald RL, Schweizer TA: Spontaneous subarachnoid haemorrhage, Lancet 389:655-666, 2017,

Fig. 2.)

Management of acute childhood HS requires emergency neurosurgical intervention for a large or rapidly expanding hemorrhage. The same principles of neuroprotection for vulnerable brain suggested in the AIS sections also apply to HS. Reversal of anticoagulant therapy (with, for example, vitamin K, fresh-frozen plasma) may be required, but the role of other medical interventions, such as factor VII, are unstudied in children. The recurrence risk for those with structural lesions is significant, and serial imaging may be required. Definitive repair or removal of the vascular malformation may require a combined approach with interventional endovascular methods and neurosurgery. Outcomes from childhood HS are not well studied but likely depend on lesion size, location, and etiology. Compared with AIS, the HS mortality rate is higher, but long-term deficits are less common.

Neonatal HS has unique features. Cranial ultrasound can detect many neonatal parenchymal bleeds, especially in the preterm infant, where bleeds are located centrally within the cranium including germinal matrix bleeding and intraventricular hemorrhage and in the cerebellum (see Chapter 120.3). Germinal matrix injury or bleeding may also occur in utero, resulting in periventricular venous infarction that becomes symptomatic in later infancy as congenital hemiparesis. Subarachnoid and subdural blood may be detected by imaging in up to 25% of normal term newborns. Term HS is poorly studied and includes the etiologies listed above, although HS may be idiopathic in more than 50% of cases. Term intraventricular bleeding is often secondary to deep CSVT with specific management implications.

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619.5

Differential Diagnosis of Stroke-Like Events

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The diagnosis of stroke in childhood requires a high index of suspicion balanced with awareness of the differential diagnosis for stroke-like events (Table 619.5). An acute onset of a focal neurologic deficit should be considered a stroke until proven otherwise and assessed with neuroimaging. However, pediatric stroke must be differentiated from other stroke-like disorders that may require their own urgent specific treatment.

Table 619.5

Differential Diagnosis of Stroke-Like Episodes in Children

DISORDER	CLINICAL DISTINCTION FROM STROKE	IMAGING DISTINCTION FROM STROKE
Migraine	Evolving or “marching” symptoms, short duration, complete resolution, headache, personal or family history of migraine	Typically normal Migrainous infarction is rare
Seizure*	Positive symptoms, Todd	Normal or may identify source of seizures (e.g.,

	paralysis is postseizure and limited	malformation, old injury)
Infection	Fever, encephalopathy, gradual onset, meningismus	Normal or signs of encephalitis/cerebritis, which are typically diffuse and bilateral. Arterial ischemic stroke and cerebral sinovenous thrombosis can occur in bacterial meningitis
Demyelination	Gradual onset, multifocal symptoms, encephalopathy Accompanying optic neuritis or transverse myelitis	Multifocal lesions, characteristic appearance (e.g., patchy in acute disseminated encephalomyelitis, ovoid in multiple sclerosis), typical locations (e.g., pericallosal in multiple sclerosis), less likely to show restricted diffusion
Hypoglycemia	Risk factor (e.g., insulin therapy), related to meals, additional systemic symptoms	Bilateral, symmetric May see restricted diffusion Posterior dominant pattern
Watershed infarction caused by global hypoxic-ischemic encephalopathy	Risk factor (e.g., hypotension, sepsis, heart disease), bilateral deficits	Bilateral, symmetric restricted diffusion in border zones between major arteries (watershed zones)
Hypertensive encephalopathy (posterior reversible leukoencephalopathy)	Documented hypertension, bilateral visual symptoms, encephalopathy	Posterior dominant, bilateral, patchy lesions involving gray and white matter; usually no restricted diffusion
Inborn errors of metabolism	Preexisting delays/regression, multisystem disease, abnormal biochemical profiles	May have restricted diffusion lesions but bilateral, symmetric, not conforming to established vascular territories. MR spectroscopy changes (e.g., high lactate in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes)
Vestibulopathy	Symptoms limited to vertigo, imbalance (i.e., no weakness). Gradual onset	Normal
Acute cerebellar ataxia	Sudden-onset bilaterally symmetric ataxia; postviral	Normal
Channelopathy	Syndromic cluster of symptoms not localizing to single lesion. Gradual onset, progressive evolution	Normal
Alternating hemiplegia	History of contralateral events Choreoathetosis/dystonia	Normal

* Seizures, however, can also herald the onset of true stroke.

Migraine

A careful history and examination can often suggest migraine as the cause of acute focal deficits. Migraine auras should last between 5 and 60 min and resolve completely. Neurologic deficits associated with migraine typically evolve slowly compared with stroke, with sensory disturbance or weakness marching across body areas over minutes. Although evolution into a migrainous headache is expected, headache may also accompany acute infarction. Furthermore, a group of uncommon migraine subtypes can occur without headache and can more closely mimic stroke in children. These entities include familial hemiplegic migraine, basilar migraine, and migraine aura without headache. Migraine can also (rarely) cause a stroke, referred to as migrainous infarction.

Seizure

Prolonged focal seizure activity is frequently followed by a period of focal neurologic deficit (so called **Todd paresis**), which typically resolves rapidly over hours after the seizure. Very rarely, focal seizures can manifest with only “negative” symptoms producing only hemiparesis or other acute-onset focal neurologic deficits. A known past history of seizures, and EEG findings may be helpful. Urgent brain imaging should be considered in new cases of prolonged or recurrent focal seizure with persisting Todd paresis because stroke in children is often associated with seizures at onset.

Infection

Life-threatening and treatable brain infections, including bacterial meningitis and herpes encephalitis, can be mistaken for stroke. However, symptom onset in primary CNS infection is typically more gradual and less focal with fever as a consistent feature. Children with bacterial meningitis are at risk for both venous and arterial stroke.

Demyelination

Acute disseminated encephalomyelitis, clinically isolated syndrome, multiple sclerosis, and other demyelinating conditions can present with acute focal neurologic deficits. The symptom onset and initial progression are more gradual compared with stroke onset (i.e., typically hours or days versus minutes). Multifocal deficits, or concurrent encephalopathy in the case of acute disseminated encephalomyelitis, would decrease the probability of stroke.

Hypoglycemia

Acute lowering of blood glucose levels can produce focal deficits mimicking stroke. New-onset hypoglycemia in otherwise healthy children is rare, but predisposing conditions include insulin-dependent diabetes, adrenal insufficiency, steroid withdrawal, and ketogenic diet.

Global Hypoxic-Ischemic Encephalopathy

Generalized decreases in cerebral perfusion can produce focal areas of watershed brain infarction, which, when asymmetric, can mimic vasoocclusive forms of stroke. Watershed ischemic injury should be accompanied by recognized hypotension or conditions predisposing to low cerebral perfusion, such as sepsis, dehydration, or cardiac dysfunction. Clinical presentations would involve more generalized and bilateral cerebral dysfunction compared with stroke, and the anatomic location of the infarct is in typical bilateral watershed zones rather than conforming to an established arterial territory.

Hypertensive Encephalopathy

The posterior reversible leukoencephalopathy syndrome is seen in children with hypertension, often in the context of an acute rise in blood pressure. Posterior regions are selectively involved, possibly resulting in symptoms of bilateral cortical visual dysfunction in addition to encephalopathy and seizures.

Inborn Errors of Metabolism

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS; see Chapter 616.2) are the classic examples, though other mitochondrial diseases can mimic stroke. Features favoring MELAS include a history of developmental regression, posterior (and often bilateral) lesions not respecting vascular territories on MRI, and elevated serum or cerebrospinal fluid lactate (on MR spectroscopy). In contrast to these types of metabolic infarction, children with Fabry disease (see Chapter 631.6), hyperhomocysteinemia, and homocystinuria (see Chapter 103.4) are at risk of true ischemic stroke.

Vestibulopathy and Ataxia

Acute-onset vertigo and/or ataxia can be confused with brainstem or cerebellar stroke. Simple bedside tests of vestibular function with otherwise intact brainstem functions are reassuring. This differential diagnosis includes acute vestibular neuronopathy, viral labyrinthitis, and the benign paroxysmal vertigos, as well as acute cerebellar ataxia and episodic ataxias.

Channelopathies

An increasing number of nervous system ion channel mutations are described that feature sudden focal neurologic deficits, thereby mimicking stroke. These include the migraine syndromes mentioned above, as well as a growing list of episodic ataxias. A strong family history raises suspicion, but most require additional investigation.

Alternating Hemiplegia of Childhood

Alternating hemiplegia of childhood typically presents in late infancy with acute intermittent episodes of hemiplegia that alternate from one side of the body to the other. The hemiplegia persists for minutes to weeks and then resolves spontaneously. Choreoathetosis and dystonic movements are commonly observed in the hemiparetic extremity. Signs spontaneously regress with sleep but recur with awakening. Affected children may also experience sudden attacks of redness and warmth (i.e., flushing) or unusual paleness (i.e., pallor) of the skin occurring during or separately from episodes of hemiplegia. Almost all affected individuals have some level of developmental delay and intellectual disability that typically progresses over time. Neuroimaging including MRA should be completed to exclude moyamoya disease. Alternating hemiplegia of childhood is linked to mutations in the *ATP1A3* gene.

CHAPTER 620

Central Nervous System Vasculitis

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Autoimmune-mediated inflammatory brain diseases are recognized as an etiology for neurologic and neuropsychiatric symptoms in children and adults and include primary central nervous system (CNS) vasculitis, secondary CNS vasculitis, and autoimmune encephalitis (Fig. 620.1 ; see Chapter 616.4).

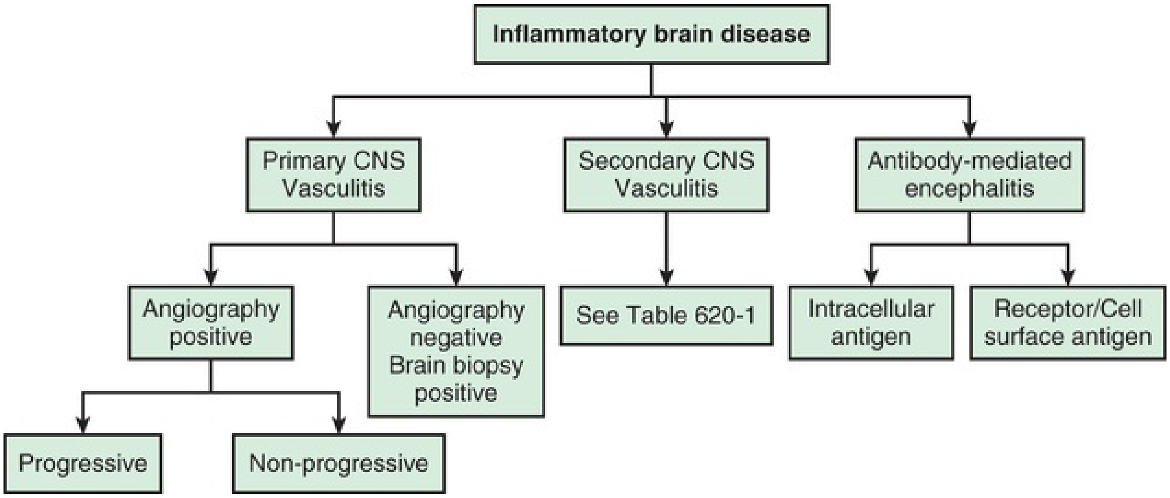
Inflammatory brain disease
Primary CNS Vasculitis
Secondary CNS Vasculitis
Antibody-mediated encephalitis
Angiography positive
Angiography negative Brain biopsy positive
See Table 620-1
Intracellular antigen
Receptor/Cell surface antigen
Progressive
Non-progressive

FIG. 620.1 Classification algorithm for CNS vasculitis within the spectrum of immune-mediated inflammatory brain diseases.

Primary angiitis of the CNS (PACNS) is recognized as the underlying etiology of a broad spectrum of neurologic and psychiatric symptoms in children. Criteria characteristic of childhood CNS vasculitis (cPACNS) include (1) newly acquired focal and/or diffuse neurologic deficits and/or psychiatric symptoms in a child 18 yr of age or younger, **plus** (2) angiographic and/or histologic evidence of vasculitis **in the absence of** (3) a systemic underlying condition known to cause or mimic the findings. Two broad categories of cPACNS are recognized based on the predominant vessel size affected: large/medium-vessel cPACNS and small-vessel cPACNS. Large/medium-vessel cPACNS is diagnosed by angiography demonstrating features of vessel wall inflammation, wall swelling and edema, and resulting luminal stenosis. Based on the clinical course and the corresponding distribution of vessel stenosis within the vascular tree of the CNS, children with large/medium-vessel cPACNS are classified as having a monophasic, nonprogressive subtype (NPcPACNS) or a progressive subtype (PcPACNS). The latter is characterized by chronic, progressive vessel wall inflammation affecting both proximal and distal vessel segments in one or both hemispheres. In contrast, NPcPACNS is a monophasic illness; vessel inflammation occurs in a characteristic distribution and is limited to the proximal vessel segments of the anterior and/or middle cerebral artery and/or distal internal carotid artery of one hemisphere. Small-vessel cPACNS (SVcPACNS) is considered a progressive illness; the diagnosis is confirmed on brain biopsies because angiography is normal.

Secondary childhood CNS vasculitis can affect all cerebral vessel segments and can occur in the context of infections or rheumatic or other inflammatory conditions or as a result of systemic or local vascular irritation (Table 620.1). The neuropsychiatric manifestations of secondary CNS vasculitis are the same as those of primary CNS vasculitis. Secondary CNS vasculitis is distinguished from primary CNS vasculitis largely by the non-CNS manifestations of the underlying systemic vasculitic disease.

Table 620.1

Causes of Secondary CNS Vasculitis

VIRAL INFECTIONS
Varicella-zoster virus, HIV, hepatitis C virus, cytomegalovirus, parvovirus B19
BACTERIAL INFECTIONS
Treponema pallidum, Borrelia burgdorferi, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Bartonella henselae, Rickettsia spp.
FUNGAL INFECTIONS
Aspergillosis, mucormycosis, coccidioidomycosis, candidosis
PARASITIC INFECTIONS
Cysticercosis
SYSTEMIC VASCULITIDES
Wegener granulomatosis, Churg-Strauss syndrome, Behçet disease, polyarteritis nodosa, Henoch-Schönlein

purpura, Kawasaki disease, giant-cell arteritis, Takayasu arteritis, Degos disease

CONNECTIVE TISSUE DISEASES

Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis, mixed connective tissue disease

MISCELLANEOUS

Antiphospholipid antibodies syndrome, Hodgkin and non-Hodgkin lymphomas, neurosarcoidosis, inflammatory bowel disease, graft-versus-host disease, bacterial endocarditis, acute bacterial meningitis, drug-induced CNS vasculitis (cocaine, amphetamine, ephedrine, phenylpropanolamine)

From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis, Lancet 380:767-776, 2012.

Epidemiology

The incidence and prevalence of primary CNS vasculitis is undetermined. In the past, the majority of children have been diagnosed at autopsy. Increased physician awareness, improved diagnostic markers, sensitive neuroimaging techniques, and brain biopsies have led to dramatically increased recognition and decreased mortality rates. Exploring the epidemiology of primary CNS vasculitis remains a challenge: The disease has many names, including isolated angiitis of the CNS, transient cerebral angiitis, postvaricella angiopathy, and focal cerebral arteriopathy. Furthermore, children are frequently diagnosed with their presenting clinical phenotype, such as stroke, movement disorder, psychosis, or cognitive decline. Within clinical phenotypes, such as arterial ischemic stroke or status epilepticus in children without preexisting epilepsy, cPACNS should be considered an important etiology.

Clinical Manifestations

Recognition of childhood CNS vasculitis requires a very high level of suspicion because any neurologic or psychiatric presentation can be the result of an underlying CNS vasculitis. The clinical phenotype may provide clues to the size of the primarily affected vessel segments and resulting cPACNS subtype: the majority of children with large/medium cPACNS present with arterial ischemic stroke features. Focal neurologic deficits, such as hemiparesis, facial droop, aphasia, or any other distinct gross or fine motor deficits, may be the result of large-vessel inflammation causing stenosis and a decreased blood supply to the specific functional areas of the brain. Initially, these focal deficits wax and wane; they may even briefly resolve without therapeutic intervention and can therefore be easily overlooked. Headaches can be a symptom of vascular disease and are commonly reported in cPACNS. New-onset headaches in children without any family history of migraine can serve as a diagnostic clue. Cognitive dysfunction in cPACNS often includes loss of higher executive function, concentration difficulties, learning and memory problems, atypical behavior or personality changes, and loss of social and emotional control. Seizures are a hallmark of SVcPACNS, as more than 80% of children with SVcPACNS present with seizures. Often there is a disconnection between the clinical presentation and the child's electroencephalogram findings. In many centers, refractory status epilepticus is increasingly recognized as the presenting phenotype of SVcPACNS. Optic neuritis and spinal cord disease are also recognized in SVcPACNS.

Constitutional features of fever or fatigue may point toward an underlying systemic illness causing a secondary CNS vasculitis. All children with suspected or confirmed CNS vasculitis require a careful assessment for associated systemic illness.

Diagnosis

The first step is considering vasculitis as a possible underlying etiology of newly acquired neurologic deficits and/or psychiatric symptoms (Table 620.2). The likelihood of CNS vasculitis in general and a specific subtype of CNS vasculitis in particular depends on the demographic characteristics of the patient, the CNS and non-CNS features of the clinical presentation, the preceding symptoms, and the mode of onset of the disease. SVcPACNS is more commonly seen in girls of all ages, whereas large/medium cPACNS has a clear male preponderance. Seizures are a hallmark of SVcPACNS, whereas strokes often reflect large/medium-vessel inflammation. Laboratory markers of vasculitis typically include C-reactive protein, erythrocyte sedimentation rate, and complete blood counts. But inflammatory markers lack sensitivity and specificity in cPACNS, particularly when the CNS is involved in isolation. More than 50% of children with large/medium-vessel cPACNS have normal inflammatory markers at diagnosis. In contrast, the majority of children with SVcPACNS present with mild to moderately raised markers. Von Willebrand factor antigen, an endothelial cell–derived protein, is a proposed biomarker of vasculitis correlating closely with disease activity in cPACNS. It may be of particular importance for distinguishing SVcPACNS from demyelinating diseases. Cerebrospinal fluid (CSF) analysis is abnormal in up to 90% of SVcPACNS patients and less than half of large/medium-vessel cPACNS patients. Within the latter group, children with the progressive subtype have a higher likelihood of presenting with abnormal CSF findings, including high opening pressure, raised CSF cell count, typically with lymphocyte predominance, and raised CSF protein. Oligoclonal bands are seen in 20% of children with SVcPACNS. They are rarely seen in other subtypes. Autoimmune encephalitis (see Chapter 616.4) is one of the key differential diagnoses of SVcPACNS.

Table 620.2

Proposed Diagnostic Evaluation of Suspected Childhood Primary CNS Vasculitis

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1. Clinical evaluation: Newly acquired symptom or deficit in a previously healthy child
    - Focal neurologic deficit: hemiparesis, hemisensory loss, aphasia, ataxia, movement abnormality, paresthesia, facial droop, ataxia, vision loss, spinal cord symptoms, others
    - Seizures or (refractory) seizure status
    - Diffuse neurologic deficit, including cognitive decline with loss of higher executive function, concentration difficulties, learning or memory problems, behavior or personality changes, loss of social skills or emotional/impulse control, others
    - Headaches
    - Meningitis symptoms, abnormal level of consciousness
    - Psychiatric symptoms, including hallucinations

    Differential diagnosis approach:
    - Underlying illness known to cause, be associated or mimic CNS vasculitis: check all potential clinical features
2. Laboratory tests
    - Blood inflammatory markers: C-reactive protein, erythrocyte sedimentation rate and complete blood counts
    - Endothelial markers: von Willebrand factor (vWF) antigen
    - Cerebrospinal fluid (CSF) inflammatory markers: opening pressure, cell count, protein, oligoclonal bands

    Differential diagnosis approach:
    - Infections/postinfectious inflammation: cultures, serologies, Gram stain
    - Autoimmune encephalitis: check neuronal antibodies in CSF and blood
    - Systemic inflammation/rheumatic disease: characteristic laboratory markers such as complement, autoantibodies
    - Thromboembolic conditions: procoagulatory profile
3. Neuroimaging
    - Parenchymal imaging on MRI:
    - Inflammatory lesions: T2/fluid attenuated inversion recovery sequences plus gadolinium contrast (lesion enhancement)
    - Ischemic lesions: diffusion-weighted images/apparent diffusion coefficient mapping

  - Vessel imaging
4. Brain biopsy

Neuroimaging is a valuable diagnostic modality for cPACNS. Parenchymal lesions may be inflammatory or ischemic in nature and are best viewed on MRI, including T2/fluid-attenuated inversion recovery (FLAIR) sequences and diffusion-weighted images (DWI) (Fig. 620.2). CNS lesions in children with large/medium-vessel cPACNS are predominantly ischemic in nature and restricted to large vascular territories. In contrast, MRI lesions in children with SVcPACNS are not restricted to major vascular territories; lesions are primarily inflammatory and may enhance with contrast. In this subtype, focal or generalized meningeal enhancement is commonly seen if children are imaged prior to immunosuppressive therapy.

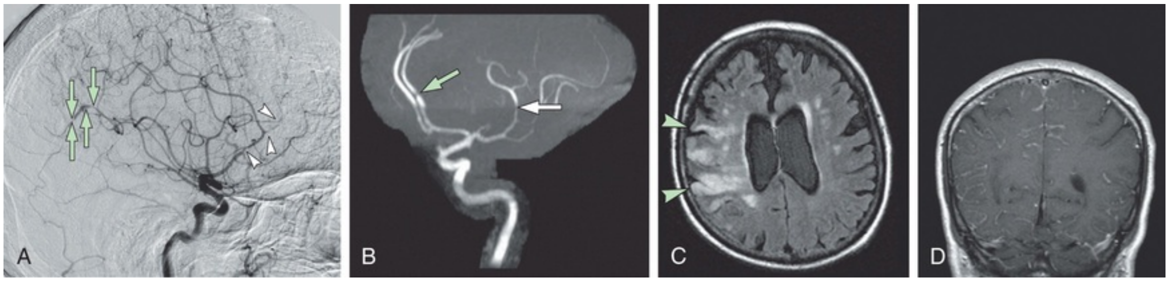

FIG. 620.2 Imaging of patients with primary CNS vasculitis. **A,** Cerebral angiogram shows alternating stenosis and dilation of the distal middle cerebral artery *(arrows)* and the anterior cerebral artery *(arrowheads).* **B,** MR angiography of the brain shows a short-segment stenosis of the anterior cerebral artery *(green arrow)* and stenosis of the distal middle cerebral artery *(white arrow).* **C,** Fluid attenuation inversion recovery–weighted MRI shows a large abnormality within the right cerebral hemisphere consistent with ischemia *(arrowheads).* **D,** MRI shows diffuse, asymmetric, nodular, and linear leptomeningeal enhancement, with dura only slightly affected. (From Salvarani C, Brown Jr RD, Hunder GG: Adult primary central nervous system vasculitis, Lancet 380:767-776, 2012, Fig. 2.)

Evidence of vessel stenosis confirms the diagnosis in large/medium-vessel cPACNS subtypes; brain biopsies are not required. Important information about the disease activity can be obtained from post–gadolinium contrast studies of the vascular wall. The vessel wall of an inflamed cerebral vessel in active large/medium-vessel cPACNS subtypes is thickened and enhances contrast. Vessel wall enhancement may also be useful for the assessment of ongoing disease activity. Conventional angiography, when compared with MR angiography, has a higher sensitivity in detecting vessel stenosis in the distal vessel segments, the posterior circulation, and in very young children. Vessel wall imaging is often normal in children with SVcPACNS, sometimes mandating a brain biopsy to definitively make the diagnosis. Studies of regional blood flow or therapeutic trials of antiinflammatory or immunosuppressive agents are nonsurgical alternatives that do not afford specific diagnostic information. Biopsies should target low-risk, nonfunctional areas identified on MRI. In the appropriate clinical context, nonlesional biopsies have a high yield for confirming the diagnosis of SVcPACNS. Characteristic findings in SVcPACNS include an intramural and/or perivascular mononuclear infiltrate, evidence of endothelial activation, and reactive astrocyte activation. Gliosis and perivascular demyelination are hallmarks of long-standing disease. Hemorrhagic lesions have also been reported. Findings typically seen in adult PACNS, including granulomas or vessel wall necrosis, are rarely seen in children with SVcPACNS. In children, the diagnostic yield of brain biopsies has been reported to be up to 70%. Diagnostic yield may be improved if the biopsy includes the meninges and gray and white matter and if it is done prior to initiation of immunosuppression. In adults, a recent study reported the diagnostic yield of biopsies for PACNS to be 11%, with an identified alternate diagnosis reported in about 30% of cases. In this study, smaller biopsies and closed procedures were less likely to be diagnostic, and biopsy-related complications occurred in 16% of patients.

Disorders that may be seen in adolescents and young adults that produce the reversible vasoconstriction syndrome must also be considered. These include migraine, drug-induced vasospasm, and postpartum angiopathy. Differentiating vasculitis is important for therapy and prognosis (Table 620.3).

Table 620.3

Characteristics of Primary CNS Vasculitis and Reversible Cerebral Vasoconstriction Syndrome

	PCNSV	**RCVS**
Precipitating factor	None	Postpartum onset or onset after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal (leukocytosis and high total protein concentration)	Normal to near normal

MRI	Abnormal in almost all patients	Normal in 70% of patients
Angiography	Possibly normal; otherwise, diffuse abnormalities are often indistinguishable from RCVS; irregular and asymmetric arterial stenoses or multiple occlusions are more suggestive of PCNSV; abnormalities might be irreversible	Always abnormal, strings-of-beads appearance of cerebral arteries; abnormalities reversible within 6-12 wk
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with or without cytotoxic agents	Nimodipine

CSF, cerebrospinal fluid; PCNSV, primary CNS vasculitis; RCVS, reversible cerebral vasoconstriction syndrome.

From Salvarani C, Brown Jr. RD, Hunder GG: Adult primary central nervous system vasculitis, Lancet 380:767-776, 2012, Table 2.

Treatment

Corticosteroids are the mainstay of acute immunosuppressive management of cPACNS. Usually pulse therapy is initially given. Antithrombotic therapy is equally important, particularly in large/medium-vessel cPACNS subtypes, because children are at high risk for recurrent ischemic events. For the distinct cPACNS subtypes, different treatment regimens should be considered. Nonprogressive cPACNS is a monophasic inflammatory illness with the highest risk of poor neurologic outcome. Vessel wall inflammation causes severe proximal stenosis and a high risk of stroke recurrence. High-dose corticosteroid pulses are commonly given, followed by a 6- to 12-wk course of oral steroids at tapering doses. Second-line immunosuppressive agents are used uncommonly. All children require antithrombotic therapy, though no unifying regimen exists. Many centers initially use low-molecular-weight heparin followed by long-term antiplatelet therapy. When reimaged at 3 mo, children should have stable or improved vessel disease, no newly affected vessel segments, and no evidence of contrast wall enhancement. At this point, the immunosuppressive therapy is commonly discontinued, and children are only kept on antiplatelet agents.

Progressive cPACNS and SVcPACNS are considered chronic progressive vasculitis subtypes requiring a prolonged course of combination immunosuppression. High-dose corticosteroids are initially used, followed by long-term oral corticosteroids with a slow taper. Many centers use an induction-maintenance protocol, adding cyclophosphamide to corticosteroids (for 6 mo), followed by mycophenolate mofetil or other oral second-line agents during maintenance therapy (usually 18 mo). Additionally, there are emerging observational studies suggesting the efficacy of rituximab as an initial induction treatment. Symptomatic therapy is essential, including anticonvulsants or psychotropic medication if required. Supportive therapy includes bone protection with calcium and vitamin D, prophylaxis against *Pneumocystis* pneumonia, and gastric mucosal protection as required.

Prognosis

The mortality rate of cPACNS has significantly improved. In large-vessel cPACNS, the risk of stroke recurrence is thought to be high in patients who are found to have progression on vascular imaging at 12 mo (especially if there was simultaneous progression and improvement occurring across multiple vessels).

Some treatment protocols for SVcPACNS report a good outcome, defined as no functional neurologic deficits, in two thirds of children. Children presenting with status epilepticus and SVcPACNS have the poorest cognitive outcome. Multidisciplinary care involving neurology, rheumatology, hematology, and rehabilitation is ideal and may potentially improve outcomes.

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CHAPTER 621

Central Nervous System Infections

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Infection of the central nervous system (CNS) is a significant cause of morbidity and mortality in children. Identification of CNS infections can be problematic for clinicians because symptoms can be nonspecific in younger infants, and a delayed or missed diagnosis contributes to the morbidity and mortality rates associated with these diseases. Over the past 3 decades, implementation of multiple conjugate vaccines has greatly reduced the incidence of bacterial infection of the CNS. Nonetheless, viral infections remain a significant cause of CNS disease, with atypical bacterial, fungal, and parasitic pathogens also contributing to a smaller number of pediatric CNS infections.

Regardless of the etiology, many patients with CNS infection have similar clinical manifestations. **Common symptoms** include headache, nausea, vomiting, anorexia, photophobia, restlessness, altered state of consciousness, and irritability. **Common signs** of CNS infection include fever, neck pain and rigidity, focal neurologic deficits, seizures, obtundation, and coma. The severity and constellation of signs are determined by host–pathogen interactions and the affected region of the CNS.

Historically, infection of the CNS has been classified according to the affected tissue. Meningitis describes primary involvement of the meninges, whereas encephalitis indicates brain parenchymal involvement. However, these anatomic boundaries may be indistinct during infection, and patients may have evidence of both meningeal and parenchymal involvement. Terms such as meningoencephalitis may better describe diffuse infections of the CNS by pathogens such as viruses. Brain abscess is the most common example of a focal infection of the CNS (see Chapter 622).

The diagnosis of CNS infection depends on a combination of imaging of the brain and testing the cerebrospinal fluid (CSF) by culture, PCR, and serologic methods. Pending many of these tests, standard CSF studies provide initial data to help differentiate bacterial from viral infections. Table 621.1 provides an overview of the typical CSF abnormalities with various CNS disorders.

Table 621.1

Cerebrospinal Fluid Findings in Central Nervous System Disorders

CONDITION	**PRESSURE (cm H_2O)**	**LEUKOCYTES (mm^3)**	**PROTEIN (mg/dL)**	**GLUCOSE (mg/dL)**	**COMMENTS**
Normal	<28	<5, ≥75% Lymphocytes In neonates: <20	20-45	>50 (or 75% serum glucose)	
COMMON FORMS OF MENINGITIS					
Acute bacterial meningitis	Usually elevated	100-10,000 or more; usually 300-2,000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <50% of serum glucose)	Organisms usually seen on Gram stain and isolated by culture
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period of time	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain. Pretreatment may render CSF sterile. PCR-based assays may detect bacterial DNA
Viral meningitis or meningoencephalitis	Normal or slightly elevated	Rarely > 1,000 cells. Eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand. PMNs early but mononuclear cells predominate through most of the course	Usually 50-200	Generally normal; may be decreased to < 40 in some viral diseases, particularly mumps (15–20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on MRI or CT scans or EEG. Most arboviruses detected by serology. Most other viruses detected by PCR of CSF
UNCOMMON FORMS OF MENINGITIS					
Tuberculous meningitis	Usually elevated	10-500; PMNs early, but lymphocytes predominate through most of the course	100-3,000; may be higher in presence of block	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms rarely seen on smear. Large volumes of CSF required for recovery of organisms. *Mycobacterium tuberculosis* can be detected by PCR of CSF

Fungal meningitis	Usually elevated	5-500; PMNs early, but mononuclear cells predominate for most of the course. Cryptococcal meningitis may lack pleocytosis. Coccidioidal meningitis may have eosinophilia	25-500	<50; decreases with time if treatment is not provided	Budding yeast may be seen. Organisms may be recovered by culture. Cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection
Syphilis (acute) and leptospirosis	Usually elevated	50-500; lymphocytes predominate	50-200	Usually normal	Positive CSF serology. Spirochetes not demonstrable by smear or culture; dark-field examination may be positive
Amebic *(Naegleria)* meningoencephalitis	Elevated	1,000-10,000 or more; PMNs predominate	50-500	Normal or slightly decreased	Mobile amebas may be seen by wet-mount microscopy of CSF
BRAIN ABSCESSES AND PARAMENINGEAL FOCUS					
Brain abscess	Usually elevated	5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach > 100,000	75-500	Normal unless abscess ruptures into ventricular system	CSF cultures are only positive in 24% of cases unless abscess ruptures into ventricular system
Subdural empyema	Usually elevated	100-5,000; PMNs predominate	100-500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10-500; lymphocytes predominate	50-200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with spinal block	10-100; lymphocytes predominate	50-400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100-1,000 or more; PMNs predominate	50-100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with ruptured dermoids
NONINFECTIOUS CAUSES					
Sarcoidosis	Normal to elevated slightly	0-100; mononuclear	40-100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0-500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture. Positive neuronal and ribosomal P

					protein antibodies in CSF
Tumor, leukemia	Slightly elevated to very high	0-100 or more; mononuclear or blast cells	50-1,000	Normal to decreased (20-40)	Cytology may be positive
Acute disseminated encephalomyelitis	Normal or elevated	~100 lymphocytes	Normal to elevated	Normal	MRI adds to diagnosis
Autoimmune encephalitis	Normal	~100 lymphocytes	Normal to elevated	Normal	Anti-NMDAR antibody–positive (CSF is more sensitive than serum)

CSF, cerebrospinal fluid; EEG, electroencephalogram; HSV, herpes simplex virus; NMDAR, *N* -methyl-D -aspartate receptor; PCR, polymerase chain reaction; PMN, polymorphonuclear neutrophils.

621.1

Acute Bacterial Meningitis Beyond the Neonatal Period

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Bacterial meningitis is one of the most serious pediatric infections, as it is associated with a high rate of acute complications and a risk of long-term morbidity and mortality. However, the deployment of antibiotics and vaccines against the most common causes of meningitis has significantly altered the spectrum of disease that clinicians observe today. In the 1980s, the most common causes of bacterial meningitis in children older than 1 mo of age in the United States were *Haemophilus influenzae* type b, *Streptococcus pneumoniae,* and *Neisseria meningitidis.* The incidence of meningitis caused by all three organisms has been significantly reduced in countries that have introduced universal immunization against these pathogens, and *S. pneumoniae* is now the most common cause of bacterial meningitis in the United States. Demonstrating the impact of vaccination in the United States, invasive *H. influenzae* disease occurred in 67-129 cases per 100,000 children under the age of 5 yr in the 1980s.

By 2014, *H. influenzae* –associated diseases were exceptionally rare; there were only a total of 40 invasive cases in the United States (0.19 cases per 100,000 children < age 5 yr).

Epidemiology

A major risk factor for bacterial meningitis is the lack of preexisting immunity to specific pathogens and serotypes, reflected by the higher incidence of meningitis in young infants. Additional risk factors include recent colonization with pathogenic bacteria, close contact (household, daycare centers, college dormitories, military barracks) with individuals having invasive disease caused by *N. meningitidis* or *H. influenzae* type b, crowding, poverty, black or Native American race, and male sex. The mode of transmission of these pathogens is through contact with respiratory tract secretions or droplets. The risk of meningitis is increased among infants and young children with occult bacteremia; the odds ratio is greater for meningococcus (85 times) and *H. influenzae* type b (12 times) relative to that for pneumococcus.

Native American and Eskimo populations exhibit a higher incidence of bacterial meningitis because these populations have altered immunoglobulin production in response to encapsulated pathogens. Defects of the complement system (C5-C8) are associated with recurrent meningococcal infection, and defects of the properdin system are associated with a significant risk of lethal meningococcal disease. Splenic dysfunction (e.g., in sickle cell anemia) or asplenia (caused by trauma or a congenital defect) is associated with an increased risk of pneumococcal, *H. influenzae* type b, and meningococcal sepsis and meningitis. T-lymphocyte defects (congenital or acquired by chemotherapy, AIDS, or malignancy) are associated with an increased risk of *Listeria monocytogenes* infections of the CNS.

The risk of pneumococcal meningitis is increased in children with congenital or acquired CSF leak across a mucocutaneous barrier, such as a lumbar dural sinus, cranial or midline facial defects (cribriform plate), fistulas of the middle ear (stapedial foot plate) or inner ear (oval window, internal auditory canal, cochlear aqueduct), or CSF leakage as a result of basilar or other skull fracture. The risk of pneumococcal bacterial meningitis was historically increased by more than 30-fold in children with cochlear implants, though advances in implant design have reduced this risk. Lumbosacral dermal sinus and myelomeningocele are associated with staphylococcal, anaerobic, and Gram-negative enteric bacterial meningitis. CSF shunt infections increase the risk of meningitis caused by *Pseudomonas aeruginosa, Staphylococcus* spp. (*Staphylococcus aureus* and coagulase-negative species), *Propionibacterium* spp., and other lower-virulence bacteria that typically colonize the skin.

Streptococcus pneumoniae

See also Chapter 209 .

Although the incidence of pneumococcal meningitis has been reduced, *S. pneumoniae* remains the most frequently identified pathogen of bacterial meningitis in the United States and in other countries that have adopted similar vaccination strategies. The 7-valent pneumococcal conjugate vaccine (PCV7) was included in the routine U.S. vaccination schedule in 2000 and contained serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, responsible for ~ 85% of invasive pneumococcal infections in the country. A dramatic decrease in the rate of pneumococcal meningitis followed, from 8.2 cases per 100,000 in 1998-1999 to 0.59 cases per 100,000 in 2004-2005. Similar reductions were also identified in other nations that introduced this vaccine. However, an increased incidence of invasive disease caused by serotypes not contained in the original vaccine was observed, known as serotype replacement. As a result, a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States in 2010, containing the serotypes in PCV7 plus serotypes 1, 3, 5, 6A, 7F, and 19A. Postmarketing surveillance data suggest the rate of invasive pneumococcal infections has decreased further, though there are conflicting data as to whether the rate of pneumococcal meningitis has decreased. Based on data from the CDC Active Bacterial Surveillance system, the incidence of invasive pneumococcal infections has fallen from 142.9 per 100,000 children under age 1 in 1977 to 15.9 per 100,000 children under age 1 in 2014. Children with anatomic or functional asplenia secondary to sickle cell disease and those infected with HIV have infection rates that are 20- to 100-fold higher than those of healthy children in the 1st 5 yr of life. Additional risk factors for contracting pneumococcal meningitis include otitis media, mastoiditis, sinusitis, pneumonia, CSF otorrhea or rhinorrhea, the presence of a cochlear implant, and immunosuppression.

Neisseria meningitidis

See also Chapter 218 .

Six serogroups of meningococcus, A, B, C, X, Y, and W-135, are responsible for invasive disease in humans. Meningococcal meningitis may be sporadic or may occur in major epidemics, particularly in the African meningitis belt, where serogroup A accounts for 80–85% of outbreaks. In the United States, serogroup B is the most common cause of meningitis in infants and is also a cause of outbreaks on college campuses. Meningococcal cases are more common in the winter and spring, likely due to associations with viral infections including influenza. Nasopharyngeal carriage of *N. meningitidis* occurs in 1–15% of adults. Most infections of children are acquired from a contact in a daycare facility, a colonized adult family member, or an ill patient with meningococcal disease. Colonization may last weeks to months; recent colonization places nonimmune younger children at greatest risk for meningitis. The incidence of disease occurring in association with an index case in the family is 1%, a rate that is 1,000-fold the risk in the general population. The risk of secondary cases occurring in contacts at daycare centers is approximately 1 in 1,000. Children younger than 5 yr of age have the highest rates of meningococcal infection, and a second peak in incidence occurs in persons between 15 and 24 yr of age. College freshmen living in dormitories have an increased incidence of infection compared with non–college-attending, age-matched controls.

Haemophilus influenzae Type b

See also Chapter 221 .

Before universal *H. influenzae* type b vaccination in the United States, approximately 70% of cases of bacterial meningitis occurring in the 1st 5 yr of life were caused by this pathogen. Invasive infections occurred primarily in infants 2 mo to 2 yr of age, the peak incidence was at 6-9 mo of age, and 50% of cases occurred in the 1st yr of life. The risk to children was markedly increased among family or daycare center contacts of patients with *H. influenzae* type b disease. Currently, many U.S. medical trainees in pediatrics will likely never treat a patient with invasive *H. influenzae* type b disease because of the success of vaccination efforts. Likewise, global vaccination efforts have also lead to remarkable declines in the incidence of this disease. Incompletely vaccinated individuals, those in underdeveloped countries who are not vaccinated, and those with blunted immunologic responses to vaccine (such as children with HIV infection) remain at risk for *H. influenzae* type b meningitis.

Pathology and Pathophysiology

Several gross pathologic changes can be identified in cases of meningitis. A purulent exudate of varying thickness may be distributed around the cerebral veins, venous sinuses, convexity of the brain, and cerebellum, and in the sulci, sylvian fissures, basal cisterns, and spinal cord. Ventriculitis with bacteria and inflammatory cells in ventricular fluid may be present (more often in neonates), in addition to subdural effusions and empyema. Perivascular inflammatory infiltrates may also be present, and the ependymal membrane may be disrupted. Vascular and parenchymal cerebral changes have been described at autopsy, including polymorphonuclear infiltrates extending to the subintimal region of the small arteries and veins, vasculitis, thrombosis of small cortical veins, occlusion of major venous sinuses, necrotizing arteritis producing subarachnoid hemorrhage, and cerebral cortical necrosis in the absence of identifiable thrombosis. Cerebral infarction is a frequent sequela that is caused by vascular occlusion from inflammation, vasospasm, and thrombosis. The extent of the infarct may range from microscopic to an entire hemisphere.

Inflammation of spinal nerves and roots produces meningeal signs, and inflammation of the cranial nerves produces cranial neuropathies of optic, oculomotor, facial, and auditory nerves. Increased intracranial pressure (ICP) also produces oculomotor nerve palsy because of the presence of temporal lobe compression of the nerve during tentorial herniation. Abducens nerve palsy may be a nonlocalizing sign of elevated ICP.

Increased ICP is a result of cell death (cytotoxic cerebral edema), cytokine-induced increased capillary vascular permeability (vasogenic cerebral edema), and increased hydrostatic pressure (interstitial cerebral edema) after obstructed reabsorption of CSF in the arachnoid villus or obstruction of the flow of fluid from the ventricles. ICP may exceed 30 cm H_2O and cerebral perfusion may be further compromised if the cerebral perfusion pressure (mean arterial pressure minus mean ICP) is < 50 mm Hg as a result of systemic hypotension. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may produce excessive water retention and potentially increase the risk of elevated ICP (see Chapter 575). Hypotonicity of brain extracellular spaces may cause cytotoxic edema with cell swelling and lysis. Tentorial, falx, or cerebellar herniation does not usually occur, because the increased ICP is transmitted to the entire subarachnoid space and there is little structural displacement. Furthermore, if the fontanels are still patent, increased ICP is not always dissipated.

Hydrocephalus can occur as an acute complication of bacterial meningitis because it is often caused by adhesive thickening of the arachnoid villi around the cisterns at the base of the brain. Thus, this thickening leads to interference with the normal resorption of CSF and development of hydrocephalus. Less often, obstructive hydrocephalus develops after fibrosis and gliosis of the cerebral aqueduct or the foramina of Magendie and Luschka.

Elevated CSF protein levels are partly a result of increased vascular permeability of the blood–brain barrier and the loss of albumin-rich fluid from the capillaries and veins traversing the subdural space. Continued transudation may result in subdural effusions, usually found in the later phase of acute bacterial meningitis. **Hypoglycorrhachia** (reduced CSF glucose levels) is attributable to altered glucose transport by the cerebral tissue.

Damage to the cerebral cortex may be a result of the focal or diffuse effects of vascular occlusion (infarction, necrosis, lactic acidosis), hypoxia, bacterial invasion (cerebritis), toxic encephalopathy (bacterial toxins), elevated ICP, ventriculitis, and transudation (subdural effusions). These pathologic factors result in the clinical manifestations of impaired consciousness, seizures, cranial nerve deficits, motor and sensory deficits, and later psychomotor retardation.

Pathogenesis

Bacterial meningitis outside the neonatal period is typically due to bacterial colonization of the nasopharynx with subsequent invasion into the bloodstream, causing bacteremia. The bacterial organisms then breech the blood–brain barrier (BBB) and enter the CNS to cause infection and inflammation. These steps involve complex interactions between the host and pathogen, and many of the mechanisms still require further research.

Meningitic pathogens frequently colonize the nasopharynx of children, but rapid invasion after recent colonization may also occur. The microbiome of the nasopharynx is a complex community of bacteria that may enhance or inhibit colonization of other bacteria. *S. pneumoniae* can synthesize hydrogen peroxide, which can inhibit growth of *H. influenzae* type b. Conversely, *H. influenzae* type B can invoke a specific immune response that targets clearance of *S. pneumoniae*. Other bacteria may alter the microbiome of the nasopharynx, and studies after the implementation of pneumococcal vaccines have identified alterations to the composition of nasopharyngeal bacterial populations. Bacterial proteins act to enhance colonization because *N. meningitidis* and *H. influenzae* type b express pili that attach to mucosal epithelial cell receptors. Viruses can also enhance bacterial adherence by a combination of expression of viral factors that interact with host adhesion proteins.

After attachment to epithelial cells, bacteria breach the mucosa and enter the bloodstream. Various models of invasion have been developed; for example, *N. meningitidis* can be transported across the mucosal surface within a phagocytic vacuole after ingestion by the epithelial cell. Expression of the bacterial polysaccharide capsule also appears to be tightly regulated as it can enhance or inhibit the efficiency of bacterial translocation of the mucosal barrier. Viruses can disrupt the mucosal barrier, thereby contributing to bacterial invasion. In particular, there is a significant association between recent influenza infection and development of meningococcemia. Once bacteria reach the bloodstream, the capsule is a critical component for survival because it interferes with opsonic phagocytosis. Host-related developmental defects in bacterial opsonic phagocytosis also contribute to the bacteremia. In nonimmune hosts, the defect may be from an absence of preformed IgM or IgG anticapsular antibodies, whereas in immunodeficient patients, various deficiencies of components of the complement or properdin system may interfere with effective opsonic phagocytosis. Asplenia may also reduce opsonic phagocytosis by the reticuloendothelial system.

A higher quantity of bacteria is associated with meningitis, suggesting that a critical threshold may be necessary for breaching the BBB. Bacterial factors including the capsid play a role in crossing the BBB through transcellular, paracellular, and Trojan-horse (within infected phagocytes) mechanisms of traversal. Bacteria gain entry to the CSF through the choroid plexus of the lateral ventricles and the meninges and then circulate to the extracerebral CSF and subarachnoid space. Bacteria rapidly multiply because the CSF concentrations of complement and antibodies are inadequate to contain bacterial proliferation. Chemotactic factors then incite a local inflammatory response characterized by polymorphonuclear cell infiltration. The presence of bacterial cell wall lipopolysaccharide (endotoxin) of Gram-negative bacteria (*H. influenzae* type b, *N. meningitidis*) and of pneumococcal cell wall components (teichoic acid, peptidoglycan) stimulates a marked inflammatory response, with local production of tumor necrosis factor, interleukin 1, prostaglandin E, and other inflammatory mediators. The subsequent inflammatory response is characterized by neutrophilic infiltration, increased vascular permeability, alterations of the blood–brain barrier, and vascular thrombosis. Meningitis-associated brain injury is not simply caused by viable bacteria but occurs as a consequence of the host reaction to the inflammatory cascade initiated by bacterial components.

Rarely, meningitis may follow bacterial invasion from a contiguous focus of infection such as paranasal sinusitis, otitis media, mastoiditis, orbital cellulitis, or cranial or vertebral osteomyelitis or may occur after introduction of bacteria via penetrating cranial trauma, dermal sinus tracts, or meningomyelocele.

Clinical Manifestations

The onset of acute meningitis has two predominant patterns. Most often, meningitis is preceded by several days of fever accompanied by upper respiratory tract or gastrointestinal symptoms, followed by nonspecific signs of CNS infection, such as increasing lethargy and irritability. Fortunately, the more dramatic presentation is less common and presents with sudden and progressive shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness often resulting in progression to coma or death within 24 hr.

The signs and symptoms of meningitis are related to the nonspecific findings associated with a systemic infection and the manifestations of meningeal irritation. Nonspecific findings include fever, anorexia and poor feeding, headache, upper respiratory symptoms, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs, such as petechiae, purpura, or an erythematous macular rash. The rash of meningococcemia is typified by an initial petechial rash that evolves into ecchymotic and purpuric lesions. Meningeal irritation is manifested as nuchal rigidity, back pain, **Kernig sign** (flexion of the hip 90 degrees with subsequent pain with extension of the leg), and **Brudzinski sign** (involuntary flexion of the knees and hips after passive flexion of the neck while supine). In children, particularly in those younger than 12-18 mo, the Kernig and Brudzinski signs are not consistently present. In adults, fever, headache, and nuchal rigidity are present in only 40% of cases of bacterial meningitis. Increased ICP is suggested by headache, emesis, bulging fontanel or diastasis (widening) of the sutures, oculomotor (anisocoria, ptosis) or abducens nerve paralysis, hypertension with bradycardia, apnea or hyperventilation, decorticate or decerebrate posturing, stupor, coma, or signs of herniation. Papilledema is more common in complicated meningitis and is suggestive of a more chronic process, such as the presence of an intracranial abscess, subdural empyema, or occlusion of a dural venous sinus. Focal neurologic signs usually are a result of vascular occlusion. Cranial neuropathies of the ocular, oculomotor, abducens, facial, and auditory nerves may also be the result of focal inflammation. Overall, approximately 10–20% of children with bacterial meningitis have focal neurologic signs.

Seizures (focal or generalized) related to cerebritis, infarction, or electrolyte disturbances occur in 20–30% of patients with meningitis. Seizures that occur on presentation or within the first 4 days of onset are usually of little prognostic significance. Poor prognosis is suggested when seizures persist after the fourth day of illness, which can be refractory to treatment.

Alteration in mental status is common among patients with meningitis and may be the consequence of increased ICP, cerebritis, or hypotension; manifestations include irritability, lethargy, stupor, obtundation, and coma. Comatose patients have a poor prognosis. Additional manifestations of meningitis include photophobia and tache cérébrale, which is elicited by stroking the skin with a blunt object and observing a raised red streak within 30-60 sec.

Diagnosis

Lumbar puncture (LP), in order to obtain CSF for Gram stain and culture, is the most important step in the diagnosis of meningitis. In addition, testing the CSF for neutrophilic pleocytosis, elevated protein, and reduced glucose concentrations can provide results within a few hours and could be suggestive of a diagnosis of bacterial meningitis (see Table 621.1). **Contraindications** to an immediate LP include (1) evidence of increased ICP (other than a bulging fontanel) such as 3rd or 6th cranial nerve palsy with a depressed level of consciousness, or the Cushing reflex (hypertension and bradycardia associated with respiratory abnormalities; see Chapter 608); (2) severe cardiopulmonary compromise requiring prompt resuscitative measures for shock or in patients in whom positioning for the LP would further compromise cardiopulmonary function; or (3) infection of the skin overlying the site of the LP. Thrombocytopenia is a relative contraindication for LP. *If an LP is delayed, empirical antibiotic therapy should be initiated.*

Some clinicians obtain a head CT scan prior to LP to evaluate for evidence of increased ICP, as an LP in the setting of elevated ICP could cause brain herniation. However, a head CT scan may delay diagnosis of meningitis and initiation of antimicrobials, and it does not always rule out increased ICP. Therefore, routine head CT scans prior to LP are not recommended unless the patient has clinical signs or is at risk for elevated ICP, including papilledema, focal neurologic findings, coma, history of hydrocephalus, or history of a previous neurosurgical procedure including CSF shunt placement. However, if the decision is made to obtain a CT scan prior to LP, antimicrobial therapy should not be delayed. LP may be performed after increased ICP has been appropriately treated.

Blood cultures should be performed in all patients with suspected meningitis. Blood cultures reveal the responsible bacteria in up to 80–90% of cases of meningitis. Elevations of the C-reactive protein, erythrocyte sedimentation rate, and procalcitonin can be seen in both bacterial and viral meningitis and should not be used to routinely determine which patients should receive antimicrobials.

Lumbar Puncture

See also Chapter 608 .

The CSF leukocyte count in bacterial meningitis often is elevated to > 1,000/mm^3 and, typically, there is a neutrophilic predominance (75–95%). Turbid CSF is present when the leukocyte count exceeds 200-400/mm^3 . Normal healthy neonates may have as many as 20 leukocytes/mm^3 , but older children without viral or bacterial meningitis have < 8 leukocytes/mm^3 in the CSF; in the healthy state, these cells are mostly lymphocytes or monocytes.

A CSF leukocyte count < 250/mm^3 may be present in as many as 20% of patients with acute bacterial meningitis. Pleocytosis may be absent in patients with severe overwhelming sepsis associated with meningitis; this is a poor prognostic sign. Pleocytosis with a lymphocytic predominance may be present during the early stage of acute bacterial meningitis; conversely, neutrophilic pleocytosis may be present in patients in the early stages of acute viral meningitis. The shift to lymphocytic-monocytic predominance in viral meningitis invariably occurs within 8-24 hr of the initial LP. The Gram stain is positive in > 70% of patients with untreated bacterial meningitis. In the absence of CNS infection or inflammatory disease, children with seizure, particularly those with fever-associated status epilepticus, *do not* exhibit CSF pleocytosis.

A diagnostic conundrum in the evaluation of children with suspected bacterial meningitis is the analysis of CSF obtained from children already receiving antibiotic therapy. This is a common clinical scenario, as 25–50% of children being evaluated for bacterial meningitis have received antibiotics before a CSF sample is obtained. CSF obtained from children with bacterial meningitis can be negative on Gram stain and culture as early as 2-4 hr after administration of antibiotics, especially in situations of *N. meningitidis* and sensitive *S. pneumoniae* meningitis. However, pleocytosis with a predominance of neutrophils, an elevated protein level, and a reduced concentration of CSF glucose will usually persist for several days after the administration of appropriate parenteral antibiotics. Therefore, despite negative cultures, the presumptive diagnosis of bacterial meningitis can be made on the basis of an abnormal CSF cell count, protein, and glucose. Rapid antigen tests for use on CSF have been developed, but these tests have technical limitations and a high false positivity rate in children and are therefore not recommended. PCR using broad-based bacterial 16S ribosomal RNA gene patterns may be useful in diagnosing the cause of culture-negative meningitis because of prior antibiotic therapy or the presence of a nonculturable or fastidious pathogen.

A traumatic LP may also complicate the interpretation of CSF tests, as CSF leukocytes and protein concentration are significantly affected by traumatic LPs. Typically, the Gram stain, culture, and glucose level are unlikely to be influenced by blood in a CSF sample. Repeat LP at a higher interspace may produce fluid that is less hemorrhagic, but this fluid usually contains red blood cells. Although methods for correcting for the presence of red blood cells have been proposed for red blood cell counts < 10,000 cells/mm^3 , these corrections can be imprecise, and it is prudent to rely on the bacteriologic results rather than attempt to interpret the CSF leukocyte and protein results after a traumatic LP.

Differential Diagnosis

Currently, the vast majority of cases of meningitis are caused by *S. pneumoniae* and *N. meningitidis*, whereas *H. influenzae* type b is relatively rare in nations with a high immunization rate against this pathogen. However, other pathogens that are less frequently identified in meningitis can cause similar clinical manifestations. These organisms include other bacteria, including other types of *H. influenzae* , *Mycobacterium tuberculosis*, *Nocardia* spp., *Treponema pallidum* (syphilis), and *Borrelia burgdorferi* (Lyme disease); fungi, such as those endemic to specific geographic areas *(Coccidioides*, *Histoplasma*, and *Blastomyces)* and those responsible for infections in compromised hosts *(Candida*, *Cryptococcus*, and *Aspergillus);* parasites, such as *Toxoplasma gondii* and *Taenia solium*, and most frequently, viruses (Table 621.2 and see Chapter 621.2). Focal infections of the CNS, including brain abscess and parameningeal abscess (subdural empyema, cranial and spinal epidural abscess), may also be confused with meningitis. In addition, noninfectious illnesses (autoimmune, rheumatologic) can cause generalized inflammation of the CNS. Relative to infections, these disorders are very uncommon and include malignancy, collagen vascular syndromes, and exposure to toxins (see Table 621.2).

Table 621.2

Clinical Conditions and Infectious Agents Associated With Aseptic Meningitis

VIRUSES

Arboviruses: La Crosse, eastern equine, western equine, Venezuelan equine, St. Louis encephalitis, Powassan and California encephalitis, chikungunya, Colorado tick fever, dengue, Jamestown Canyon, Japanese encephalitis, Rift Valley fever, tick-borne encephalitis, West Nile, Zika

Enteroviruses (coxsackievirus, echovirus, enterovirus, poliovirus)

Parechovirus

Herpes simplex (types 1 and 2)

Varicella-zoster virus

Epstein-Barr virus

Cytomegalovirus

Human herpesvirus types 6 and 7

Parvovirus B19

Adenovirus

Variola (smallpox)

Measles

Mumps

Rubella

Influenza A and B

Parainfluenza

Rhinovirus

Rabies virus

Lymphocytic choriomeningitis

Rotaviruses

Cardiovirus A

Hendra and Nipah viruses

Astroviruses

Coronaviruses

Human T-cell lymphotrophic virus (HTLV-1)

Human immunodeficiency virus

BACTERIA

Mycobacterium tuberculosis (early and late)

Leptospira spp. (leptospirosis)

Treponema pallidum (syphilis)

Borrelia spp. (relapsing fever)

Borrelia burgdorferi (Lyme disease)

Nocardia spp. (nocardiosis)

Brucella spp.

Bartonella spp. (cat-scratch disease)

Rickettsia rickettsii (Rocky Mountain spotted fever)

Rickettsia prowazekii (typhus)

Ehrlichia spp.

Anaplasma spp.

Coxiella burnetii

Mycoplasma pneumonia

Mycoplasma hominis

Chlamydia trachomatis

Chlamydia psittaci

Chlamydia pneumoniae

Ureaplasma spp.

Partially treated bacterial meningitis

BACTERIAL PARAMENINGEAL FOCUS

Sinusitis

Mastoiditis

Brain abscess

Subdural-epidural empyema

Cranial osteomyelitis

FUNGI

Coccidioides immitis (coccidioidomycosis)

Blastomyces dermatitidis (blastomycosis)

Cryptococcus neoformans (cryptococcosis)

Histoplasma capsulatum (histoplasmosis)

Candida species

Other fungi *(Alternaria, Aspergillus, Cephalosporium, Cladosporium, Drechslera hawaiiensis, Paracoccidioides brasiliensis, Petriellidium boydii, Sporotrichum schenckii, Ustilago* spp.*, Zygomycetes)*

PARASITES (EOSINOPHILIC)

Angiostrongylus cantonensis

Gnathostoma spinigerum

Baylisascaris procyonis

Strongyloides stercoralis
Trichinella spiralis
Toxocara canis
Taenia solium (cysticercosis)
Paragonimus spp.
Schistosoma spp.
Fasciola spp.
PARASITES (NONEOSINOPHILIC)
Toxoplasma gondii (toxoplasmosis)
Acanthamoeba spp.
Naegleria fowleri
Balamuthia mandrillaris
Malaria
POSTINFECTIOUS
Vaccines: rabies, influenza, measles, poliovirus
Demyelinating or allergic encephalitis
SYSTEMIC OR IMMUNOLOGICALLY MEDIATED
Acute disseminated encephalomyelitis (ADEM)
Autoimmune encephalitis
Bacterial endocarditis
Kawasaki disease
Systemic lupus erythematosus
Vasculitis, including polyarteritis nodosa
Sjögren syndrome
Mixed connective tissue disease
Rheumatoid arthritis
Behçet disease
Granulomatosis with polyangiitis
Lymphomatoid granulomatosis
Granulomatous arteritis
Sarcoidosis
Familial Mediterranean fever
Vogt-Koyanagi-Harada syndrome
MALIGNANCY
Leukemia
Lymphoma

Metastatic carcinoma

Central nervous system tumor (e.g., craniopharyngioma, glioma, ependymoma, astrocytoma, medulloblastoma, teratoma)

DRUGS

Intrathecal injections (contrast media, serum, antibiotics, antineoplastic agents)

Nonsteroidal antiinflammatory agents

OKT3 monoclonal antibodies

Carbamazepine

Azathioprine

Intravenous immune globulins

Antibiotics (trimethoprim–sulfamethoxazole, sulfasalazine, ciprofloxacin, isoniazid)

MISCELLANEOUS

Heavy metal poisoning (lead, arsenic)

Foreign materials (shunt, reservoir)

Subarachnoid hemorrhage

Postictal state

Mollaret syndrome (recurrent)

Intraventricular hemorrhage (neonate)

Familial hemophagocytic syndrome

Postneurosurgical procedure

Dermoid–epidermoid cyst

Syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (HaNDL)

Compiled from Bronstein DE, Glaser CA: Aseptic meningitis and viral meningitis. In Cherry J, Demmler-Harrison GJ, Kaplan SL, et al (eds): Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 7e, Philadelphia, 2014, WB Saunders, pp. 484-492; Romero JR: Aseptic and viral meningitis. In Long SS, Pickering LK, Prober CG (eds): Principles and Practice of Pediatric Infectious Diseases, 4e, Philadelphia, 2012, Saunders, pp. 292-297.

Determining the specific cause of CNS infection is facilitated by careful examination of the CSF with specific stains (Kinyoun carbol fuchsin for mycobacteria, India ink for fungi), cytology, antigen detection *(Cryptococcus),* CSF serology (syphilis, West Nile virus, arboviruses), and PCR (herpes simplex virus, enterovirus, and others). Other potentially valuable diagnostic tests include blood cultures, CT or MRI of the brain, serum serologic tests, and, rarely, meningeal or brain biopsy. The differential diagnosis also includes immune or inflammatory diseases such as Sweet syndrome, CNS vasculitis, sarcoidosis, lymphoma, autoimmune encephalitis, acute disseminated encephalomyelitis, and neonatal-onset multisystem inflammatory disease.

Acute viral meningoencephalitis is the most likely infection to be confused with bacterial meningitis (Table 621.3 and see Table 621.2). Although children with viral meningoencephalitis typically appear less ill than those with bacterial meningitis, both types of infection have a spectrum of severity. Some children with bacterial meningitis may have relatively mild signs and symptoms, whereas some with viral meningoencephalitis may be critically ill. Although classic CSF profiles associated with bacterial versus viral infection tend to be distinct (see Table 621.1), these cases can overlap in the number of CSF leukocytes and glucose and protein levels. Quite often, children are empirically treated with antibiotics for > 48 hr to await CSF culture and PCR data to delineate between these two groups of pathogens.

Table 621.3

Etiologies and Epidemiology of Meningoencephalitis

PATHOGEN	EPIDEMIOLOGY
VIRAL MENINGOENCEPHALITIS	
Mosquito-Borne Arboviruses	
West Nile virus	Common in North America, Europe, Africa, Middle East, and Asia. In temperate regions, peaks in summer/fall months
Japanese encephalitis virus	Endemic to Asia. Vaccine available for prevention.
La Crosse encephalitis virus and California encephalitis virus	After West Nile virus, La Crosse is the second most common arbovirus in the United States. Peak in summer/fall
St. Louis encephalitis virus	Endemic to western United States. Peak summer/fall
Jamestown Canyon virus	Present in the eastern United States
Eastern equine encephalitis virus	Affects U.S. states adjacent to and east of the Mississippi River; also present in South America
Western equine encephalitis virus	Cases identified in North and South America. Now rare cause of encephalitis in the United States; typically identified west of the Mississippi River
Venezuelan equine encephalitis virus	Endemic to central and South America; rare outbreaks in the United States
Zika virus	Africa, Asia, and recent epidemic in Caribbean countries and North, Central, and South America. Congenital infection associated with microcephaly and other brain malformations. In adults, also associated with Guillain-Barré syndrome
Chikungunya virus	Africa, Asia, and recently introduced to the Western Hemisphere. Rarely associated with CNS infection
Dengue virus	Present in equatorial regions; rare cause of CNS disease
Murray Valley	Present in northern Australia, Indonesia, and Papua New Guinea

encephalitis virus	
Kunjin virus	Present in Oceania
Rochio virus	Outbreak identified in Brazil
Semliki Forest virus	Rare cause of human disease in Africa
Usutu virus	Identified in cases from Africa and Europe
Rift Valley fever virus	Present in Africa and the Middle East
Tick-Borne Arboviruses	
Powassan virus	Endemic to northeastern regions of the United States
Tick-borne encephalitis virus	Present in a band stretching across Europe, Russia, and northern Asia
Severe fever with thrombocytopenia syndrome virus	Primary vector hypothesized to be ticks. Present in East Asia
Colorado tick encephalitis virus	Cases present in western United States and Canada
Thogotoviruses	Thogoto virus and Dhori virus implicated in CNS infection
Sandfly-borne arboviruses	
Toscana virus	Common cause of viral meningoencephalitis in Mediterranean countries
Chandipura virus	Identified in sandflies in western Africa and India
Viruses Transmitted by Animals	
Rabies virus	Globally widespread. Associated with bites with saliva exposure by infected bats, dogs, cats, raccoons, skunks, foxes, and other medium- to large-sized animals. Small rodents are not known to transmit rabies to humans. Vaccine and immunoglobulin available for prevention and postexposure prophylaxis
Lymphocytic choriomeningitis virus	Virus is present in rodents worldwide. Transmitted by contact or aerosolization of rodent urine, feces, saliva, or bedding material
Hendra virus	Present in Australia. Spread by contact with horse tissues
Nipah virus	Cases identified in Asia. Transmitted by contact with infected pigs or bats and infected humans
Herpes B virus	Transmitted to humans through bites of macaques or by contamination of a wound with infected monkey tissue or fluids
Viruses Spread Through Human-to-Human Contact	
Enteroviruses (coxsackievirus, echovirus, enterovirus, poliovirus)	Fecal-oral transmission. Prevalent worldwide. In temperate regions, peak incidence in summer/fall. Poliovirus nearly eradicated owing to global vaccination efforts
Parechoviruses	Fecal-oral transmission. Infection typically occurs early in infancy. Cause of CNS disease and sepsis-like syndrome in neonates/infants
Mumps	Approximately 1 : 1,000 cases of mumps are associated with encephalitis. Remains endemic in Africa and Asia, where vaccination rates are low
Measles	Encephalitis typically occurs in association with classic symptoms of measles. Measles remains endemic in Asia, Africa, and parts of Europe. Also associated with postinfectious autoimmune diseases such as acute disseminated encephalomyelitis and subacute sclerosing panencephalitis
Rubella	Most often associated with postinfectious encephalitis. Many countries in Africa and Asia do not routinely vaccinate against rubella. In rare cases, can cause progressive rubella panencephalitis
Influenza A and B virus	Most common in winter and early spring months
Coronaviruses	Infect neuronal cells in vitro; rarely associated with CNS diseases in humans. Most prevalent in winter months
Vaccinia and variola	Variola infection has been eradicated
Parvovirus B19	Rarely associated with encephalitis

Rotavirus	Virus has been isolated from the CSF of patients with encephalitis and gastroenteritis
Astroviruses	Emerging cause of meningoencephalitis
Human immunodeficiency virus	Meningoencephalitis can develop during acute retroviral syndrome. Chronic infection may cause encephalopathy.
JC virus	Most commonly associated with progressive multifocal leukoencephalopathy in immunocompromised hosts
Other rare viral causes (adenoviruses, respiratory syncytial virus, parainfluenza, rhinovirus, reoviruses)	Many other viruses are infrequently detected in the CSF or other body sites of patients with meningoencephalitis, but the significance of identifying these viruses is unclear
Members of Herpesviridae Viral Family	
Herpes simplex virus (HSV) types 1 and 2	HSV1 can cause severe encephalitis associated with involvement of the temporal lobes. HSV2 may cause severe infection in neonates. Primary HSV2 infection with genital lesions is associated with mild meningoencephalitis
Varicella-zoster virus (VZV)	Occurs about 1 wk into symptoms; typically presents as cerebellar ataxia or diffuse encephalitis
Epstein-Barr virus (EBV)	Rare cause of meningoencephalitis. Detection of EBV DNA in the CSF can also be indicative of integrated genomes in leukocytes that are not actively replicating.
Cytomegalovirus (CMV)	Occurs almost exclusively in immunocompromised patients, including patients with AIDS
Roseolovirus (HHV-6 and HHV-7)	Associated with CNS diseases, but in some cases, the significance of detection of HHV-6/7 is unclear because inflammation may cause reactivation of virus
Nonviral Infectious Meningoencephalitis	
Rickettsia	Rocky Mountain spotted fever and typhus associated with cerebral vasculitis causing encephalitis
Ehrlichia /*Anaplasma*	Endemic to the Midwest and Eastern portions of the United States
Borrelia burgdorferi	Encephalitic symptoms early after infection; meningitis typically presents 4 wk after infection. Endemic to the northeastern and midwestern portions of the United States
Bartonella spp.	Classic presentation of recent cat exposure, papule at the site of inoculation, regional lymphadenopathy, and seizures. CSF may lack pleocytosis
Leptospira spp.	Fresh-water exposure; may present with conjunctivitis, hepatitis, and acute kidney injury
Treponema pallidum	Present in sexually active persons
Mycoplasma pneumoniae	Organism has been detected in the CSF by PCR. However, association between CNS diseases and detection of *Mycoplasma* is controversial
Other bacterial spp.	Tuberculous and other bacteria may have an encephalitic component
Fungal	Immunologically compromised patients at special risk: cryptococcosis, histoplasmosis, aspergillosis, mucormycosis, candidiasis, coccidioidomycosis
Protozoal	*Plasmodium* , *Trypanosoma* , *Naegleria fowleri* , *Balamuthia mandrillaris* , *Acanthamoeba* spp., and *Toxoplasma gondii*
Metazoal	Trichinosis; echinococcosis; cysticercosis; schistosomiasis, *Baylisascaris procyonis* , *Paragonimus* spp., *Gnathostoma* spp., and *Angiostrongylus cantonensis*
Transmissible spongiform encephalopathy	Prion diseases, including Creutzfeldt-Jakob disease, Kuru, and other rare syndromes
Parainfectious or postinfectious encephalitis	It is postulated that viral infection outside of the CNS triggers development of cell-mediated antigen–antibody complexes plus complement that leads to CNS tissue damage. The following pathogens have been proposed to mediate disease in this manner: measles, mumps, rubella, varicella-zoster, influenza A and B, herpesviruses, enteroviruses, rickettsial infections, and *M. pneumoniae.*
Vaccine-associated encephalitis	Similar to parainfectious or postinfectious meningoencephalitis, the following vaccines have been very rarely associated with encephalitis: rabies, measles, vaccinia, and yellow fever

Toxin-mediated encephalitis	Various toxins have been implicated, including lead intoxication, bacterial toxins, Reye syndrome, and ingestion of toxins
Inborn error of metabolism	Various disorders of metabolic pathways have been associated with meningoencephalitis
AUTOIMMUNE ENCEPHALITIS	
N-methyl D-aspartate (NMDA) receptor–associated encephalitis	In teenagers and young adults, it may be the most common cause of meningoencephalitis. In childhood, boys and girls are affected equally; by young adulthood, most cases are seen in women. Frequently occurs in conjunction with teratomas. Recent cases associated with recent HSV encephalitis
Acute disseminated encephalomyelitis	Often preceded by a viral prodrome, proposed to be triggered by viral infection
Neuromyelitis optica (Devic disease)	Typically presents with optic neuritis and/or myelitis, associated with other autoimmune disorders. More frequent in females
Paraneoplastic	Various tumors associated with generation of antibodies that react to CNS epitopes
Rheumatologic	Systemic lupus erythematosus, Sjögren syndrome, Kikuchi-Fujimoto disease, Behçet disease, Hashimoto thyroiditis all associated with encephalitic symptoms
Other	Many other conditions can mimic meningoencephalitis, including acquired metabolic disorders, stroke, migraine, epilepsy, venous sinus thrombosis, and subdural/epidural hematomas

CNS, central nervous system; CSF, cerebrospinal fluid.

Adapted from Glaser C, Long SS: Encephalitis. In Long SS, Pickering LK, Prober CG (eds): Principles and Practice of Pediatric Infectious Diseases, 4e, Philadelphia, 2012, Saunders, pp. 297-314.

Treatment

Essential to improving clinical outcomes in patients with bacterial meningitis is prompt recognition, diagnostic testing, and initiation of appropriate antimicrobial therapy. Several studies have demonstrated that delays in initiating antimicrobial therapy, even at the level of a few hours, are significantly associated with adverse clinical outcomes and death. If there are signs of focal neurologic findings, papilledema, or increased ICP, antibiotics should be given prior to obtaining a head CT scan and LP, and the increased ICP should be treated simultaneously (see Chapter 85). A CT scan then should be performed prior to LP to determine the safety of the procedure. Some patients with meningitis will develop multiple organ system failure, shock (see Chapter 88), and acute respiratory distress syndrome (see Chapter 89), requiring further management in an intensive care unit.

Initial Antibiotic Therapy

The initial (empirical) choice of antibiotic therapy for meningitis in immunocompetent infants and children should achieve bactericidal levels in the

CSF and have excellent activity against the typical bacterial causes of meningitis (Table 621.4). Although there are substantial geographic differences in the frequency of resistance of *S. pneumoniae* to β-lactam antibiotics, rates are increasing throughout the world. In the United States, 25–50% of strains of *S. pneumoniae* are currently resistant to penicillin; relative resistance (minimal inhibitory concentration = 0.1-1.0 µg/mL) is more common than high-level resistance (minimal inhibitory concentration = 2.0 µg/mL). Resistance to cefepime, cefotaxime and ceftriaxone is also evident in up to 25% of isolates. In contrast, most strains of *N. meningitidis* are sensitive to penicillin and cephalosporins, although rare resistant isolates have been reported. Approximately 30–40% of isolates of *H. influenzae* type b produce β-lactamases and, therefore, are resistant to ampicillin. These β-lactamase–producing strains remain sensitive to third- and fourth-generation cephalosporins.

Table 621.4

Antibiotics Used for the Treatment of Bacterial Meningitis[*]

DRUGS	NEONATES		INFANTS AND CHILDREN
	0-7 DAYS	**8-28 DAYS**	
Amikacin [†][‡]	15-20 divided q12h	30 divided q8h	20-30 divided q8h
Ampicillin	200-300 divided q8h	300 divided q6h	300 divided q6h
Cefepime	150 divided q8h	150 divided q8h	150 divided q8h
Cefotaxime[**]	100-150 divided q8h or q12h	150-200 divided q6h or q8h	225-300 divided q6h or q8h
Ceftriaxone [§]	—	—	100 divided q12h or q24h
Ceftazidime	100-150 divided q8h or q12h	150 divided q8h	150-200 divided q8h
Gentamicin [†][‡]	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Meropenem	—	—	120 divided q8h
Nafcillin	75 divided q8h or q12h	100-150 divided q6h or q8h	200 divided q6h
Penicillin G	150,000 divided q8h or q12h	200,000 divided q6h or q8h	300,000-400,000 divided q4h or q6h
Rifampin	—	10-20 divided q12h	10-20 divided q12h or q24h
Tobramycin [†][‡]	5 divided q12h	7.5 divided q8h	7.5 divided q8h
Vancomycin [†][‡][‖]	20-30 divided q8h or q12h	30-45 divided q6h or q8h	60 divided q6h

[*] Dosages in mg/kg (units/kg for penicillin G) per day.

[†] Smaller doses and longer dosing intervals, especially of aminoglycosides and vancomycin for very-low-birthweight neonates, may be advisable.

[‡] Monitoring of serum levels is recommended to ensure safe and therapeutic values.

[§] Use in neonates is not recommended, because of inadequate experience in neonatal meningitis and concerns of displacement of bilirubin from albumin, leading to worsening of hyperbilirubinemia.

[‖] Goal vancomycin trough of 15-20 µg/mL. An alternative dosing regimen outside the neonatal period includes: < 3 mo 15 mg/kg/dose q8h, 3-11 mo 15 mg/kg/dose q6h, 1-8 yr 20 mg/kg/dose q6h, 9-13 yr 20 mg/kg/dose q8h, ≥14 yr 15 mg/kg/dose q8h.

[**] Cefotaxime is no longer available.

Adapted from Tunkel AR, Hartman BJ, Kaplan SL, et al: Practice guidelines for the management of bacterial meningitis, Clin Infect Dis 39:1267-1284, 2004, Table 6.

The recommended empirical antibiotic regimen in a suspected case of meningitis outside the neonatal period is vancomycin combined with a third-generation cephalosporin (ceftriaxone). Because of the efficacy of third-generation cephalosporins in the therapy of meningitis caused by sensitive *S. pneumoniae, N. meningitidis,* and *H. influenzae* type b, ceftriaxone (50 mg/kg/dose given every 12 hr) should be part of the initial empirical therapy. Based on the substantial rate of resistance of *S. pneumoniae* to β-lactam drugs, vancomycin (60 mg/kg/day given every 6-8 hr; some experts would start as high as 80 mg/kg/day; goal trough 15-20 µg/mL) is also recommended as part of initial empirical therapy. Patients allergic to penicillin or cephalosporin antibiotics can be treated with meropenem (40 mg/kg/dose every 8 hr); other alternative drugs include fluoroquinolones or chloramphenicol, if available. Alternatively, allergic patients can be desensitized to the antibiotic (see Chapter 177).

If *L. monocytogenes* infection is suspected, as in young infants or those with a T-lymphocyte deficiency, ampicillin (300 mg/kg/day, divided every 6 hr) also should be given because cephalosporins are inactive against *L. monocytogenes.* Intravenous trimethoprim-sulfamethoxazole is an alternative treatment for *L. monocytogenes* and has documented clinical efficacy.

If a patient is immunocompromised and Gram-negative bacterial meningitis is suspected, initial therapy might include cefepime or meropenem.

Duration of Antibiotic Therapy

Historically, the duration of antibiotic therapy for meningitis has been based on long-standing experience and expert opinion rather than randomized clinical trials. In the 1960s and 1970s, the standard of care for treatment of meningitis was repeating an LP prior to the end of antimicrobial therapy. The total length of therapy would be determined according to whether the CSF parameters (white blood cell count, protein, and glucose) had normalized or not. However, studies in the 1980s showed that CSF parameters did not predict which patients would develop relapsed infection after stopping antibiotics, because abnormal CSF values were not associated with future development of relapsed infection. Therefore, a repeat LP prior to discontinuation of antibiotics for typical bacterial meningitis is not recommended. Currently, the recommended treatment duration for uncomplicated *S. pneumoniae* meningitis is 10-14 days with a 3rd-generation cephalosporin or intravenous penicillin (300,000-400,000 units/kg/day, divided every 4-6 hr) used for penicillin-sensitive isolates, or vancomycin if the isolate is resistant to penicillins and cephalosporins. For *N. meningitidis* meningitis, the recommended treatment duration is 5-7 days with intravenous penicillin (300,000 units/kg/day) for strains with a minimum inhibitory concentration (MIC) of penicillin < 0.1 µg/mL, or ceftriaxone for strains with an MIC of 0.1-1 µg/mL. Uncomplicated *H. influenzae* type b meningitis should be treated for 7-10 days with ampicillin for β-lactamase–negative strains, or a 3rd-generation cephalosporin for β-lactamase–positive isolates. Patients who receive intravenous or oral antibiotics prior to LP and do not have an identifiable pathogen, but do have evidence of bacterial meningitis based on their CSF profile, should receive therapy with ceftriaxone or cefotaxime for 7-10 days. Shorter durations of antibiotics for meningitis might be effective; a double-blinded, randomized study of African children with meningitis demonstrated equivalent outcomes when treating with ceftriaxone for 5 versus 10 days. In addition, during epidemics of meningitis in Africa, single intramuscular dosages of ceftriaxone or chloramphenicol can be used. Further data are necessary to determine the full efficacy of shorter treatment durations for meningitis.

Meningitis caused by *Escherichia coli* or *P. aeruginosa* may require therapy with a 3rd- or 4th-generation cephalosporin or carbapenem active against the isolate in vitro. Most isolates of *E. coli* are sensitive to ceftriaxone, and most isolates of *P. aeruginosa* are sensitive to ceftazidime. Repeat examination of CSF is indicated in some neonates, in all patients with meningitis from Gram-negative bacilli, and in patients with infection caused by a β-lactam–resistant *S. pneumoniae*. The CSF should be sterile within 24-48 hr of initiation of appropriate antibiotic therapy. Gram-negative bacillary meningitis should be treated for 3 wk or at least 2 wk after CSF sterilization, which may occur after 2-10 days of treatment. If focal signs are present or the child does not respond to treatment, a parameningeal focus may be present, and a CT or MRI scan should be performed.

Side effects of antibiotic therapy of meningitis include phlebitis, drug fever, rash, emesis, oral candidiasis, and diarrhea. Ceftriaxone may cause reversible gallbladder pseudolithiasis, detectable by abdominal ultrasonography. This is usually asymptomatic but may be associated with emesis and upper right quadrant pain.

Corticosteroids

Rapid killing of bacteria in the CSF effectively sterilizes the meningeal infection but releases toxic cell products after cell lysis (e.g., endotoxin) that precipitate the cytokine-mediated inflammatory cascade. The resultant edema formation and neutrophilic infiltration may produce additional neurologic injury with worsening of CNS signs and symptoms. Therefore, agents that limit production of inflammatory mediators could be of benefit in bacterial meningitis.

In a Cochrane review of using steroids in meningitis treatment, steroids reduced hearing loss in children with meningitis due to *H. influenzae* type b but not due to other pathogens. The use of steroids in children did not reduce mortality rates; however, steroids did improve survival rates in adults with pneumococcal meningitis. These data support the use of intravenous dexamethasone, 0.15 mg/kg/dose given every 6 hr for 2 days, in the treatment of *H. influenzae* type b meningitis in children older than 6 wk of age. Corticosteroids appear to have maximum benefit if given 1-2 hr before antibiotics are initiated. They also may be effective if given concurrently with or soon after the first dose of antibiotics. Pediatric data regarding benefits, if any, of corticosteroids in the treatment of meningitis caused by other bacteria remain inconclusive.

Complications

During the treatment of meningitis, acute CNS complications can include seizures, increased ICP, cranial nerve palsies, stroke, cerebral or cerebellar herniation, and thrombosis of the dural venous sinuses.

Collections of fluid in the subdural space develop in 10–30% of patients with meningitis and are asymptomatic in 85–90% of patients. Subdural effusions are especially common in infants. Symptomatic subdural effusions may result in a bulging fontanel, diastasis of sutures, enlarging head circumference, emesis, seizures, fever, and abnormal results of cranial transillumination. CT or MRI scanning confirms the presence of a subdural effusion. In the presence of an increased ICP or a depressed level of consciousness, symptomatic subdural effusion should be treated by aspiration through the open fontanel (see Chapters 85 and 608). Fever alone is not an indication for aspiration.

SIADH occurs in some patients with meningitis, resulting in hyponatremia and reduced serum osmolality. This may exacerbate cerebral edema or result in hyponatremic seizures (see Chapter 85).

Fever associated with bacterial meningitis usually resolves within 5-7 days of the onset of therapy. Prolonged fever (>10 days) is noted in approximately 10% of patients. Prolonged fever is usually caused by intercurrent viral infection, nosocomial or secondary bacterial infection, thrombophlebitis, or drug reaction. Nosocomial infections are especially important to consider in the evaluation of these patients. In meningitis caused by *N. meningitidis*, pericarditis or arthritis may occur during treatment and is caused by either bacterial dissemination or immune complex deposition. In general, infectious pericarditis or arthritis occurs earlier in the course of treatment than immune-mediated disease.

Thrombocytosis, eosinophilia, and anemia may develop during therapy for meningitis. Anemia may be a result of hemolysis or bone marrow suppression. Disseminated intravascular coagulation is most often associated with the rapidly progressive pattern of presentation and is noted most commonly in patients with shock and purpura. The combination of endotoxemia and severe hypotension initiates the coagulation cascade; the coexistence of ongoing thrombosis may produce symmetric peripheral gangrene.

Prognosis

Appropriate antibiotic therapy and supportive care have reduced the mortality rate of bacterial meningitis beyond the neonatal period to < 10%. The highest mortality rates are observed with pneumococcal meningitis. Severe neurodevelopmental sequelae may occur in 10–20% of patients recovering from bacterial meningitis, and as many as 50% have some neurologic sequelae. The prognosis is worse among infants younger than 6 mo and in those with a high bacterial burden in their CSF. Those with seizures occurring more than 4 days into therapy or with coma or focal neurologic signs on presentation also have an increased risk of long-term sequelae. There does not appear to be a correlation between the duration of symptoms before a diagnosis of meningitis and outcomes.

The most common neurologic sequelae from meningitis include hearing loss, cognitive impairment, recurrent seizures, delay in acquisition of language, visual impairment, and behavioral problems. Sensorineural hearing loss is the most common sequela of bacterial meningitis and, usually, is already present at the time of initial presentation. It is a result of cochlear or auditory nerve inflammation and occurs in as many as 30% of patients with pneumococcal meningitis, 10% with meningococcal meningitis, and 5–20% of those with *H. influenzae* type b meningitis. All patients with bacterial meningitis should undergo careful audiologic assessment before or soon after discharge from the hospital. Frequent reassessment on an outpatient basis is indicated for patients who develop a hearing deficit.

Prevention

Vaccination and antibiotic prophylaxis of susceptible at-risk contacts represent two opportunities to reduce the transmission and development of secondary cases of bacterial meningitis. The availability and application of each of these approaches depend on the specific organism.

Neisseria meningitidis

See also Chapter 218 .

Chemoprophylaxis is recommended for all close contacts of patients with meningococcal meningitis, regardless of age or immunization status. Close contacts should be treated with rifampin 10 mg/kg/dose every 12 hr (maximum dose of 600 mg) for 2 days as soon as possible after identification of a case of suspected meningococcal meningitis or sepsis. Alternative options include ceftriaxone 125 mg intramuscularly once for children under age 15 yr, or 250 mg intramuscularly once for persons older than 15 yr, or ciprofloxacin 500 mg orally once. Close contacts include household, daycare center, and nursery school contacts and healthcare workers who have direct exposure to oral secretions (mouth-to-mouth resuscitation, suctioning, intubation). If there is a high suspicion of meningococcemia in the index patient, exposed contacts should be treated immediately. In addition, all contacts should be educated about the early signs of meningococcal disease and the need to seek prompt medical attention if these signs develop.

Many countries have included a quadrivalent conjugate meningococcal vaccine (types A, C, Y, and W-135; Menactra and Menveo) as part of routine immunization schedules. In the United States, the Advisory Committee on Immunization Practices (ACIP) of the CDC recommends a two-dose vaccine series for all children, with the first dose administered at the age of 11-12 yr and a second dose at age 16-18 yr. Vaccination is also recommended for persons 2 mo to 18 yr of age who are at increased risk for meningococcal disease, including those with asplenia, functional asplenia, or complement deficiencies or who are receiving a terminal complement inhibitor (eculizumab). Two meningococcal vaccines against serogroup B have been developed. In the United Kingdom, meningococcal B vaccine is administered to all infants at 2, 4, and 12 mo of age. This differs from the United States, where currently the vaccine is recommended for children 10 yr and older at increased risk for invasive disease and is optional for persons 16-23 yr of age.

Haemophilus influenzae Type B

See also Chapter 221 .

Rifampin prophylaxis should be given to all household contacts of patients with invasive disease caused by *H. influenzae* type b, *if* any close family member younger than 48 mo has not been fully immunized or if an immunocompromised child of any age resides in the household. A household contact is one who lives in the residence of the index case or who has spent a minimum of 4 hr with the index case for at least 5 of the 7 days preceding the patient's hospitalization. Family members should receive rifampin prophylaxis immediately after the diagnosis is suspected in the index case because > 50% of secondary family cases occur in the first week after the index patient has been hospitalized. The dose of rifampin is 20 mg/kg/day (maximum dose of 600 mg) given once each day for 4 days.

Three conjugate vaccines for *H. influenzae* type b are licensed in the United States. Although each vaccine elicits different profiles of antibody response in infants immunized at 2-6 mo of age, all result in protective levels of antibody with a 93% efficacy rate against invasive infections after the primary series. Efficacy is not as consistent in Native American populations, a group recognized as having a higher incidence of disease. All children should be immunized with *H. influenzae* type b conjugate vaccine beginning at 2 mo of age.

Streptococcus pneumoniae

See also Chapter 209 .

Antibiotic prophylaxis should not be administered to contacts of children diagnosed with pneumococcal meningitis. Routine administration of PCV13 conjugate vaccine against *S. pneumoniae* is recommended for children younger than 5 yr of age. The initial dose of the series is given at 2 mo of age. Children who are at high risk of invasive pneumococcal infections, including those with functional or anatomic asplenia and those with underlying immunodeficiency (such as infection with HIV, primary immunodeficiency, and those receiving immunosuppressive therapy) should receive PCV13 and the 23-valent pneumococcal polysaccharide vaccine (PPSV23).

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621.2

Viral Meningoencephalitis

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Viral meningoencephalitis is an acute inflammatory process involving the meninges and/or brain parenchymal tissue. These infections are caused by a number of different pathogens, and quite often, no pathogen can be identified from the CSF and brain tissue specimens. The CSF is characterized by pleocytosis and the absence of microorganisms on Gram stain and routine bacterial culture. Outcomes are quite variable because cases of meningoencephalitis caused by some pathogens are self-limited whereas others cause significant long-term neurologic sequelae.

Etiology

Among the most common causes of viral meningoencephalitis are viruses of the family *Picornaviridae,* including the **enteroviruses** (poliovirus, coxsackievirus, enterovirus, and echovirus) and **parechoviruses** (see Chapters 276 and 277). Meningoencephalitis caused by these viruses is often self-limited but can be severe in neonates or chronic in immunocompromised hosts (particularly X-linked agammaglobulinemia; see Chapter 150). Human coxsackievirus A7 and enteroviruses D68 and 71 have been associated with neurologic symptoms, including acute flaccid paralysis. Parechoviruses are an important cause of meningoencephalitis in infants and rarely cause disease in older children. The clinical manifestations are similar to those of the enteroviruses, but infants with parechovirus infection may exhibit abdominal signs or a sepsis-like syndrome. In addition, parechovirus infection is associated with more severe MRI lesions of the cerebral cortex, and CSF pleocytosis may be minimal or absent.

The term **arbovirus** refers to a broad range of viruses from multiple viral families that are transmitted by arthropod vectors, typically mosquitoes or ticks (see Chapters 294 and 295). Most of these viral infections are considered zoonotic, as their primary reservoir is in birds or small animals. Humans are often dead-end hosts because a sufficient viremia does not develop to enable transmission back to arthropod vectors. However, humans are the primary reservoir for viruses such as Zika, chikungunya, and dengue. The most common arboviruses that cause meningoencephalitis include West Nile virus (WNV), Japanese encephalitis virus, and La Crosse virus, with other arboviruses described in Table 621.3 . WNV made its appearance in the Western Hemisphere in 1999 and is now the most common arbovirus causing meningoencephalitis. WNV may also be transmitted by blood transfusion, organ transplantation, or vertically across the placenta. Most children with WNV are either asymptomatic or have a nonspecific viral-like illness. Approximately 1% of infected humans develop CNS disease; adults are more severely affected than children.

Several members of the viral family Herpesviridae can cause meningoencephalitis (see Chapters 279-284). Herpes simplex virus (HSV) type 1 is an important cause of severe, sporadic encephalitis in children and adults, with progression to coma and death in 70% of cases without antiviral therapy. In neonates, severe encephalitis with diffuse brain involvement can be caused by HSV type 2, transmitted vertically at delivery. A mild transient (and sometimes recurrent) form of meningoencephalitis with HSV type 2 may accompany genital herpes infection in sexually active adolescents and adults. Varicella-zoster virus may cause CNS infection in a close temporal relationship with clinical manifestations of chickenpox. The most common manifestation of CNS involvement is cerebellar ataxia and the most severe is acute encephalitis. After primary infection, varicella-zoster virus becomes latent in spinal and cranial nerve roots and ganglia, and reactivation occurs as herpes zoster that can be accompanied by mild meningoencephalitis. Epstein-Barr virus is associated with various CNS syndromes (see Chapter 281). Cytomegalovirus infection of the CNS can occur with congenital infection or disseminated disease in immunocompromised hosts, but it is an exceptionally rare cause of meningoencephalitis in immunocompetent infants and children (see Chapter 282). Human herpesvirus 6 is associated with encephalitis, but detection of the virus can also be reflective of latency in lymphocytes with reactivation due to inflammation (see Chapter 283).

Mumps can cause meningoencephalitis and has a higher incidence in regions where the mumps vaccine is not distributed (see Chapter 275). Mumps meningoencephalitis is typically mild, but deafness from damage of the 8th cranial nerve can occur. Meningoencephalitis is also associated with acute infection with measles, rubella, respiratory viruses (adenovirus, coronaviruses, influenza virus, parainfluenza virus, respiratory syncytial virus), rotavirus, lymphocytic choriomeningitis virus, or rabies. HIV is associated with acute meningoencephalitis and can cause chronic encephalopathy leading to neurocognitive decline (see Chapter 302). In exceptionally rare situations, meningoencephalitis may follow live virus vaccination against polio, measles, mumps, or rubella.

Epidemiology

Most cases of meningoencephalitis occur in the summer and late fall because these times are associated with a higher incidence of circulating enteroviruses and arboviruses. In 2016, the most common arbovirus responsible for meningoencephalitis in the United States was West Nile virus (WNV), with a total of 2,039 cases; fewer than 100 cases were caused by the La Crosse, Jamestown Canyon, St. Louis, Powassan, and eastern equine encephalitis viruses combined (see Chapter 294). In Asia, the most common cause is Japanese encephalitis virus. Epidemiologic considerations in aseptic meningitis due to agents other than enteroviruses also include the season of the year, location and travel, climatic conditions, animal exposures, mosquito or tick bites, and factors related to the specific pathogen.

Several studies have attempted to describe the causative pathogens associated with meningoencephalitis, including the California Encephalitis Project. Despite extensive testing, however, no pathogen can be identified in up to 63% of cases of meningoencephalitis. Newer assays such as next-generation sequencing have the potential to identify novel or previously unrecognized pathogens in causing meningoencephalitis. Occult meningoencephalitis cases caused by pathogens such as *Leptospira,* astroviruses, and *Propionibacterium acnes* have been identified through this methodology. In addition to infectious agents, autoimmune encephalitis is a common cause of an encephalitis-like illness.

Pathogenesis and Pathology

Neurologic damage is caused by direct invasion and destruction of neural tissues by actively multiplying viruses or by a host reaction to viral antigens. Tissue sections of the brain generally are characterized by meningeal congestion and mononuclear infiltration, perivascular cuffs of lymphocytes and plasma cells, some perivascular tissue necrosis with myelin breakdown, and neuronal disruption in various stages, including, ultimately, neuronophagia and endothelial proliferation or necrosis. A marked degree of demyelination with preservation of neurons and their axons is considered to represent predominantly “postinfectious” or an autoimmune encephalitis. In HSV encephalitis, the cerebral cortex (classically the temporal lobes in HSV-1 encephalitis) is often severely affected. Arboviruses tend to affect the entire brain, while rabies has a predilection for the basal structures. Involvement of the spinal cord, nerve roots, and peripheral nerves is variable.

Clinical Manifestations

The progression and severity of disease are related to the relative degree of meningeal and parenchymal involvement, which, in part, is determined by the specific etiology. The clinical course of infection varies from case to case, even with the same causative pathogen. Some children may have mild symptoms at onset, only to lapse into a coma and rapidly die. In others, the illness may be ushered in by high fever, violent convulsions interspersed with bizarre movements, and hallucinations, followed by complete recovery.

The onset of meningoencephalitis is generally acute, although CNS signs and symptoms are often preceded by a nonspecific febrile illness of a few days' duration. The presenting manifestations in older children include headache and hyperesthesia, and in infants, irritability and lethargy. Headache is most often frontal or generalized; adolescents frequently complain of retrobulbar pain. Fever, nausea and vomiting, photophobia, and pain in the neck, back, and legs are common. With high fevers, patients may develop altered mental status that progresses to encephalopathy in combination with uncontrolled body movements and seizures. Focal neurologic signs may be persistent, fluctuating, or migratory. WNV and nonpolio enteroviruses may cause anterior horn cell injury and acute flaccid paralysis. Encephalitis is more common than aseptic meningitis in WNV infection, while acute flaccid paralysis may be noted in approximately 5% of patients. Loss of bowel and bladder control and unprovoked emotional outbursts may also occur. Nonetheless, many patients have a nonspecific febrile illness in association with WNV infection and may never seek medical attention.

Exanthems can precede or accompany CNS signs, especially with enteroviruses, varicella-zoster virus, measles, rubella, and WNV. Examination often reveals nuchal rigidity without significant localizing neurologic changes at the onset of symptoms. Specific conditions associated with CNS viral infection include Guillain-Barré syndrome, transverse myelitis, hemiplegia, and cerebellar ataxia.

A mild encephalopathy with a reversible splenial lesion (of the corpus callosum) **(MERS)** has been associated with various pathogens, including rotavirus, salmonella virus, CMV, adenovirus, and influenza virus.

Diagnosis

Diagnosis of meningoencephalitis relies on a combination of analyzing the CSF by PCR, serology, and in rare situations, brain biopsy. The diagnosis is supported by associated symptoms and examination of the CSF, which usually shows a mild mononuclear predominance (see Table 621.1). Other tests of potential value in the evaluation of patients with suspected viral meningoencephalitis include an electroencephalogram (EEG) and MRI. EEG typically shows diffuse slow-wave activity, although focal changes in temporal regions can be observed in HSV meningoencephalitis. MRI of the brain may demonstrate focal brain lesions that correlate with clinical disease, including temporal lobe involvement to suggest HSV-1 disease. Hyperdense lesions may also be identified on T2 and FLAIR imaging.

Differential Diagnosis

Meningoencephalitis is not exclusively caused by viruses, as other pathogens are also associated with this condition (see Table 621.3). The most important diagnosis to differentiate from meningoencephalitis is bacterial meningitis, given the consequences if that disease is untreated. Most children with acute bacterial meningitis are more critically ill than those with CNS viral infection. Parameningeal bacterial infections, such as brain abscess or subdural or epidural empyema, may have features similar to viral CNS infections. Infections caused by *M. tuberculosis* (see Chapter 242), *T. pallidum* (syphilis, see Chapter 245), and *B. burgdorferi* (Lyme disease, see Chapter 249) may exhibit more indolent clinical courses. *Bartonella henselae* is associated with cat exposure, a papule at the site of inoculation, regional lymphadenopathy, and new-onset seizures (see Chapter 236). *Mycoplasma pneumoniae* has been implicated as a causative pathogen in meningoencephalitis as a direct pathogen or postinfectious disorder (see Chapter 250). Serologic testing for *Mycoplasma* can be nonspecific, and IgM titers can be elevated for several months after infection; PCR may be more specific but is not sensitive.

Infections caused by fungi, rickettsias, protozoa, and other parasites may also need to be included in the differential diagnosis. Consideration of these agents usually arises as a result of accompanying symptoms, local geographic epidemiology, and host immune factors.

Various noninfectious disorders may be associated with CNS inflammation and have manifestations overlapping with those associated with viral meningoencephalitis. Some of these disorders include malignancy, autoimmune diseases, intracranial hemorrhage, and exposure to certain drugs or toxins.

Attention to the history and other organ involvement usually allows elimination of these diagnostic possibilities. Autoimmune encephalitis due to anti–*N* -methyl-D -aspartate (anti-NMDA) receptor antibodies is an important cause of noninfectious encephalitis in children (see Chapter 616.4). In teenagers and young adults with meningoencephalitis, anti-NMDA receptor encephalitis can occur more frequently than enteroviruses or HSV meningoencephalitis. Detection of these antibodies in the serum and CSF confirms this diagnosis. Anti-NMDA receptor encephalitis has also been associated with recent HSV encephalitis, but this etiology of this association is unknown. Acute disseminated encephalomyelitis (ADEM) may also initially be confused with encephalitis (see Chapter 618).

Laboratory Findings

The CSF findings in meningoencephalitis are characterized by a pleocytosis of leukocytes with counts typically < 1,000/mm^3 . Very early in the disease, the cells are often polymorphonuclear, whereas mononuclear cells predominate for the remainder of the duration of the illness. This change in cell type often occurs over 8-12 hr. The protein concentration in CSF tends to be elevated, and concentrations may be very high if brain destruction is extensive, as with HSV encephalitis. The glucose level is typically normal, although hypoglycorrhachia can occur with certain viruses. For example, a substantial depression of CSF glucose concentrations may be observed with mumps encephalitis. With parechoviruses, the CSF glucose, protein, and cell counts may be normal.

The primary means of detection of nonbacterial pathogens causing meningoencephalitis is nucleic acid amplification. Obtaining a CSF sample early in the course of disease is important for detection of viruses. By the time patients with WNV meningoencephalitis present for medical care, viral nucleic acid may be absent in the CSF. Therefore, the test of choice for detection of WNV and other arboviruses is serology (on both blood and CSF). Viruses detected in blood, nasopharyngeal, stool, and urine specimens can be used to suggest a potential viral etiology. However, caution must be practiced when viruses are detected in locations outside the CSF, because these viruses may not explain the patient's CNS symptoms. Viral culture, once routine, has been largely phased out of routine testing due to its low sensitivity, requirement for skilled laboratory technicians, and relative delay in testing results (several days to weeks).

A serum specimen should be obtained early in the course of illness for testing for serology. If initial CSF PCRs and serology are not diagnostic, serologic testing should be repeated 2-3 wk later. A four-fold increase in titers for a specific virus would be suggestive of the etiology of the patient's presentation.

Treatment

For most causes of viral meningoencephalitis, no effective antiviral agents exist; therefore, treatment is primarily supportive care. Intravenous fluids are typically administered because of poor oral intake. NSAIDs are often used for symptomatic relief of headache. It is important to monitor patients with severe encephalitis closely for seizures, cerebral edema, disturbed fluid and electrolyte balance, aspiration, respiratory failure, and cardiac arrest.

Members of the herpesvirus family can be treated with antivirals, with acyclovir, ganciclovir, cidofovir, and foscarnet having variable activities against each virus (see Chapters 279-284). Parenteral acyclovir has been specifically shown to dramatically reduce morbidity and mortality rates in HSV-associated meningoencephalitis. Various other antivirals are currently in development, but clinical efficacy of these drugs is largely unknown. Often when no pathogens are identified and a postinfectious or autoimmune etiology is suspected, patients are treated with a combination of steroids, intravenous immunoglobulin, and plasmapheresis (see Chapters 616 and 618).

Prognosis

Supportive and rehabilitative efforts are very important after patients recover from the acute phase of illness. Motor incoordination, seizures, total or partial deafness, and behavioral disturbances may follow viral meningoencephalitis. Visual disturbances from chorioretinopathy and perceptual amblyopia may also occur. Some sequelae of infection may be very subtle. Therefore, neurologic, developmental, and audiologic evaluations should be part of the routine follow-up of children who have recovered from viral meningoencephalitis.

Recovery from viral infections of the CNS depends on the severity of the clinical illness, the specific causative agent, and the age of the child. If the clinical illness is severe and substantial parenchymal involvement is evident, the prognosis is poor, with potential deficits being intellectual, motor, psychiatric, epileptic, visual, or auditory in nature. Severe sequelae should also be anticipated in those with infection caused by HSV if it was not diagnosed and treated early in the disease. Overall, several studies have found that most children will have persistent symptoms years after the diagnosis of meningoencephalitis. These poor outcomes are likely reflective of a combination of poor diagnostics for identifying pathogens that cause meningoencephalitis and a lack of specific therapies for most viral pathogens.

Prevention

For some viruses that cause meningoencephalitis, vaccines are available for prevention. Widespread use of effective viral vaccines for polio, measles, mumps, rubella, and varicella has almost eliminated CNS complications from these diseases in the United States. Vaccination against Japanese encephalitis virus is also available, but because of high costs, this vaccine has not been widely distributed in Asia. The availability of domestic animal vaccine programs against rabies has reduced the frequency of rabies encephalitis.

Control of encephalitis caused by arboviruses has been less successful because specific vaccines are only in various stages of development for clinical trials. The primary method for reducing arbovirus infections is vector control, through methods that include insecticides and eradicating insect breeding sites. Furthermore, minimizing mosquito and tick bites through the application of *N,N* -diethyl-3-methylbenzamide (DEET)–containing insect repellents on exposed skin and wearing long-sleeved shirts, long pants, and socks when outdoors, especially at dawn and dusk, reduces the risk of arboviral infection.

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621.3

Eosinophilic Meningitis

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Eosinophilic meningitis is defined as > 10 eosinophils/mm^3 of CSF or a finding that at least 10% of leukocytes in the CSF are eosinophils. The most common cause worldwide of eosinophilic CSF pleocytosis is CNS infection with helminthic parasites. Nonetheless, the differential diagnosis of CSF eosinophilic pleocytosis is broad, especially in countries where helminthic infestation is uncommon, such as the United States.

Etiology

Although any tissue-migrating helminth may cause eosinophilic meningitis, the most common worldwide cause is human infection with the rat lungworm, *Angiostrongylus cantonensis* (see Chapter 323). Other parasites that can cause eosinophilic meningitis include *Gnathostoma spinigerum* (dog and cat roundworm; see Chapter 323), *Baylisascaris procyonis* (raccoon roundworm), *Ascaris lumbricoides* (human roundworm, see Chapter 317), *Toxocara canis* (see Chapter 324), *Trichinella spiralis* (see Chapter 325), *Toxoplasma gondii* (see Chapter 316), *Paragonimus westermani*, *Echinococcus granulosus* (see Chapter 330), *Schistosoma japonicum* (see Chapter 326), *Onchocerca volvulus*, and *Taenia solium* (see Chapter 329). Eosinophilic meningitis may also occur as an unusual manifestation of more common viral, bacterial, or fungal infections of the CNS; for example, coccidioidomycosis has been particularly associated with eosinophilic meningitis. Noninfectious causes of eosinophilic meningitis include multiple sclerosis, malignancy, hypereosinophilic syndrome, or a reaction to medications or ventriculoperitoneal shunt materials.

Epidemiology

A. cantonensis is found in Southeast Asia, the South Pacific, Japan, Taiwan, Egypt, Ivory Coast, and Cuba. Infection is acquired by eating raw or undercooked freshwater snails, slugs, prawns, or crabs containing infectious 3rd-stage larvae. *Gnathostoma* infections are found in Japan, China, India, Bangladesh, and Southeast Asia. Gnathostomiasis is acquired by eating undercooked or raw fish, frog, bird, or snake meat. *B. procyonis* (raccoon roundworm) is endemic in the United States and acquired by children playing outdoors where raccoons may deposit the organisms (raccoon latrines).

Clinical Manifestations

Patients with eosinophilic meningitis from helminthic infestation typically become ill 1-3 wk after exposure, as this reflects the transit time for parasites to migrate from the gastrointestinal tract to the CNS. Concomitant findings include fever, vomiting, abdominal pain, creeping skin eruptions, pleurisy, or peripheral eosinophilia. Neurologic symptoms may include headache, meningismus, ataxia, cranial nerve palsies, and paresthesias. Paraparesis or incontinence can result from radiculitis or myelitis.

Diagnosis

The presumptive diagnosis of helminth-induced eosinophilic meningitis is most often based on the travel and exposure history in the presence of typical clinical and laboratory findings. Direct visualization of helminths in CSF is difficult because there typically is a low burden of organisms. Serologic assays for helminthic infections are also of limited utility because they are not readily available commercially and there is substantial cross-reactivity between different helminth species.

Treatment

Treatment is supportive, because infection is self-limited and anthelmintic drugs do not appear to influence the outcome of infection. Analgesics should be given for headache and radiculitis, and CSF removal or shunting should be performed to relieve hydrocephalus, if present. Steroids may decrease the duration of headaches in adults with eosinophilic meningitis. Treatment of *B. procyonis* should be initiated empirically with albendazole and corticosteroids.

Prognosis

Overall, up to 70% of patients improve significantly within 4 wk after the onset of symptoms. The mortality rate associated with eosinophilic meningitis is < 5%; untreated raccoon roundworm infection may be fatal or associated with severe sequalae.

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CHAPTER 622

Brain Abscess

Andrew B. Janowski, David A. Hunstad

The incidence of brain abscess is between 0.3 and 1.3 cases per 100,000 people per year. Development of brain abscess is most often associated with an underlying etiology, including: contiguous spread from an associated infection (meningitis, otitis media, mastoiditis, sinusitis, soft tissue infection of the face or scalp, orbital cellulitis, or dental infections); direct compromise of the blood–brain barrier due to penetrating head injuries or surgical procedures; embolic phenomena (endocarditis); right-to-left shunts (congenital heart disease or pulmonary arteriovenous malformation); immunodeficiency; or infection of foreign material inserted into the central nervous system (CNS), including ventriculoperitoneal shunts.

Pathology

Cerebral abscesses occur in both hemispheres in children, but in adults, left-sided abscesses are more common, likely due to penetrating injuries from right-handed assailants. Nearly 80% of abscesses occur in the frontal, parietal, and temporal lobes, while abscesses in the occipital lobe, cerebellum, and brainstem account for the remainder of cases. In 18% of cases, multiple brain abscesses are present, and in nearly 20% of cases, no predisposing risk factor can be identified. Abscesses in the frontal lobe are often caused by extension from sinusitis or orbital cellulitis, whereas abscesses located in the temporal lobe or cerebellum are frequently associated with otitis media and mastoiditis.

Etiology

The predominant organisms that cause brain abscesses are streptococci, which account for one third of all cases in children, with members of the *Streptococcus anginosus* group *(S. anginosus, Streptococcus constellatus,* and *Streptococcus intermedius)* being the most common streptococci. Other important streptococci include *Streptococcus pneumoniae, Enterococcus* spp., and other viridans streptococci. *Staphylococcus aureus* is the second most common organism in pediatric brain abscesses, accounting for 11% of cases, and is most often associated with penetrating injuries. Other bacteria isolated from brain abscesses include Gram-negative aerobic organisms (*Haemophilus* spp., *Escherichia coli, Klebsiella pneumoniae, Proteus* spp., and other Enterobacteriaceae) and anaerobic bacteria (Gram-positive spp., *Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., and *Actinomyces* spp.). In neonates with meningitis, abscess formation is a complication in 13% of cases, with *Citrobacter koseri, Cronobacter sakazakii, Serratia marcescens,* and *Proteus mirabilis* being special considerations in this age-group. In up to 27% of cases, more than one organism is cultured. Abscesses associated with mucosal infections (sinusitis or dental infections) frequently are polymicrobial and include anaerobic organisms. Atypical bacteria, including *Nocardia, Mycobacterium,* and *Listeria* spp., and fungi *(Aspergillus, Candida, Cryptococcus)* are more common in children with impaired host defenses.

Clinical Manifestations

Often the early stages of cerebritis and abscess formation are asymptomatic or associated with nonspecific symptoms, including low-grade fever, headache, and lethargy. As the inflammatory process proceeds, vomiting, severe headache, seizures, papilledema, focal neurologic signs (hemiparesis), and coma may develop. A cerebellar abscess is characterized by nystagmus, ipsilateral ataxia and dysmetria, vomiting, and headache. If the abscess ruptures into the ventricular cavity, overwhelming shock and death occur in 27–85% of cases.

Diagnosis

The key to diagnosis of brain abscesses is prompt imaging of the CNS. Brain MRI with contrast is the diagnostic test of choice because it can aid in differentiating abscesses from cysts and necrotic tumors (Fig. 622.1). As an alternative, cranial CT can provide more rapid imaging results but cannot provide the fine tissue detail offered by MRI (Fig. 622.2). Both MRI and CT scans with contrast can demonstrate a ring-enhancing abscess cavity. The CT findings of cerebritis are characterized by a parenchymal low-density lesion, whereas T2-weighted MRI images feature increased signal intensity. Other abnormalities in common laboratory tests can be observed in children with brain abscesses. The peripheral white blood cell count is elevated in 60% of cases, and blood cultures are positive in 28% of cases. Lumbar puncture is not routinely recommended in cases of brain abscesses, because the procedure could cause brain herniation from elevated intracranial pressure. When tested, the cerebrospinal fluid (CSF) is normal in 16% of cases, 71% of cases exhibit CSF pleocytosis, and 58% will have an elevated CSF protein level. CSF cultures are positive in only 24% of cases; therefore, a culture obtained from the abscess fluid is essential for identifying bacterial pathogens. In some cases, culture of the abscess fluid can be sterile, and alternative testing including 16S ribosomal RNA sequencing may be used to identify organisms. An electroencephalogram (EEG) may identify corresponding focal slowing.

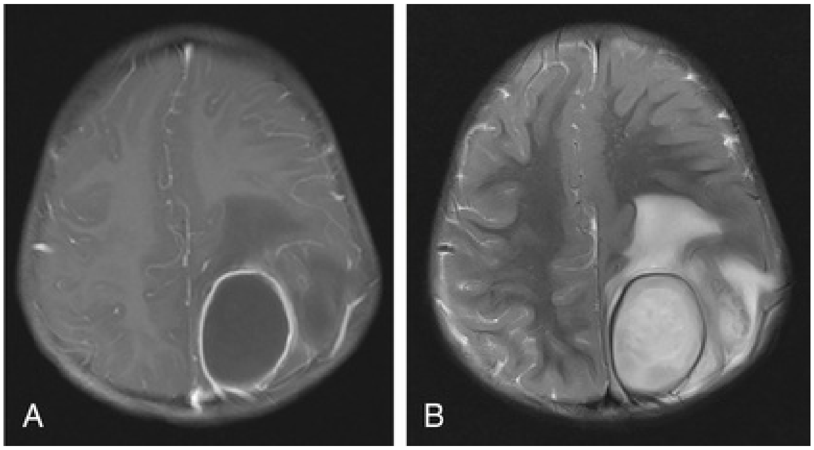

FIG. 622.1 MRI of the brain of a 2 yr old boy with an atrial septal defect and a brain abscess caused by MRSA. **A,** T1 fl2D postcontrast axial image demonstrating the enhancement of the rim of the abscess. **B,** T2 TSE axial image showing a large fluid-filled lesion with surrounding edema.

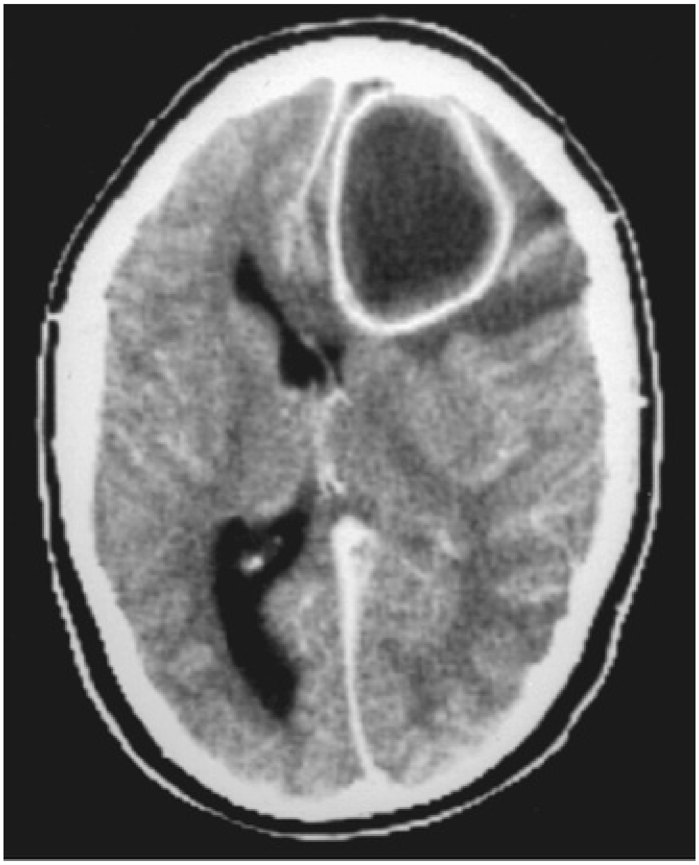

FIG. 622.2 Brain abscess shown on CT with contrast. Note the large, wall-enhancing abscess in the left frontal lobe causing a shift of the brain to the right. The patient had no neurologic signs until just before the CT scan because the abscess is located in the frontal lobe, a "silent" area of the brain.

Treatment

The initial management of a brain abscess includes prompt diagnosis and initiation of an antibiotic regimen that is based on the most likely pathogens. Empiric therapy consists of a combination of a 3rd-generation cephalosporin and metronidazole, often with vancomycin to provide coverage of methicillin-resistant *S. aureus* and cephalosporin-resistant strains of *S. pneumoniae*. If resistant Gram-negative organisms are suspected, as in cases of infected ventriculoperitoneal shunts, cefepime or meropenem may be used as the β-lactam in the initial regimen. *Listeria monocytogenes* may cause a brain abscess in the neonate and if suspected, penicillin G or ampicillin with gentamicin is recommended. In immunocompromised patients, broad-spectrum antibiotic coverage is used, and amphotericin B therapy should be considered for activity against fungi.

Neurosurgical procedures for brain abscess have been greatly enhanced by stereotactic MRI or CT systems, allowing for optimized approaches to minimize morbidity. Aspiration of the abscess is recommended for diagnostic cultures and decompression unless contraindicated based on the location or the patient's condition. There are limited data regarding injection of antibiotics into the abscess cavity, and this technique is not routinely recommended. Small abscesses under 2.5 cm in diameter or multiple abscesses may be treated with antibiotics in the absence of drainage, with follow-up neuroimaging studies to ensure a decrease in abscess size. Surgical excision of an abscess is rarely required, because such a procedure may be associated with greater morbidity compared with aspiration of a cavity. Administration of glucocorticoids can reduce edema, though evidence for improved outcomes with steroids is lacking.

The antibiotic regimen may be narrowed or made more specific once abscess culture data are available, though most abscesses are polymicrobial and not all organisms present may be isolated in culture. *The duration of parenteral antibiotic therapy depends on the organism and response to treatment but is most typically 6 wk.*

Prognosis

Mortality rates prior to the 1980s ranged from 11–53%. More recent mortality rates accompanying wider use of CT and MRI, improved microbiologic techniques, and prompt antibiotic and surgical management, range from 5–10%. Factors associated with high mortality rates at the time of admission include delayed administration of antimicrobials, age < 1 yr, multiple abscesses, and coma. Long-term sequelae occur in about one third of the survivors and include hemiparesis, seizures, hydrocephalus, cranial nerve abnormalities, and behavioral and learning difficulties.

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CHAPTER 623

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Alasdair P.J. Parker

Idiopathic intracranial hypertension (IIH), or pseudotumor cerebri, is frequently considered a potential cause of headache with papilledema in children with normal standard findings on brain MRI. A false-positive diagnosis is common, and outlined below are strategies to avoid it. The pathophysiology is poorly understood, and no randomized controlled trial exists regarding treatment strategies in children.

IIH is rare, but an accurate diagnosis is essential because of the risk of visual failure. There has been an evolution in the investigation of this condition. Previously, normal levels of intracranial pressure (ICP) were unclear, leading to overdiagnosis of IIH. Now, studies in children with ICP monitoring show an upper limit of normal as 10 mm Hg (13.5 cm H_2O) between the ages of 2 and 5 yr, with the adult level of cerebrospinal fluid (CSF) pressure being reached by 8 yr of age. Currently, the 90th percentile of CSF pressure on lumbar puncture has been reported to be 28 cm CSF (22 mm Hg) in children age 1 to 18 yr, without a significant age effect. Other normal parameters include CSF cell count, protein content, and ventricular size, although the ventricular size on brain MRI could be slightly decreased. Papilledema is almost universally present, and in rare cases where it is not, great care should be taken before the diagnosis, as there is a high rate of misdiagnosis (Fig. 623.1).

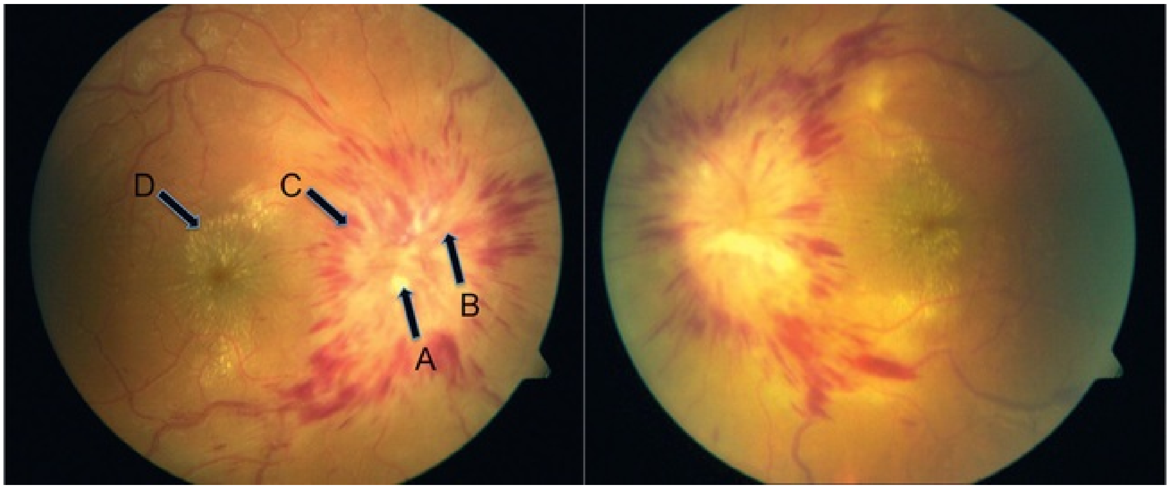

FIG. 623.1 Optic nerve photos of the right and left eyes, respectively, demonstrating grade 5 optic nerve head edema with characteristics, including *(A)* total obscuration of the optic cup; *(B)* total obscuration of a segment of a major blood vessel; *(C)* total obscuration of the disc margin; and *(D)* macular star. (From Vickers AL, El-Dairi MA: Subacute vision loss in young, obese female, J Pediatr 163:1518-1519, 2013, Fig. 1.)

Etiology

IIH, by definition, will not have an identifiable cause, despite typical findings. A large proportion of children referred to the pediatrician with possible/probable IIH after a thorough history, examination, and careful investigation will have *secondary IH* with an underlying cause identified. Table 623.1 lists some of the many disorders that cause IH with no obstructive lesion on MRI, including venous obstruction; metabolic disorders such as galactosemia, hypoparathyroidism, pseudohypoparathyroidism, hypophosphatasia, prolonged corticosteroid therapy or rapid corticosteroid withdrawal, possibly growth hormone treatment, refeeding of a significantly malnourished child, hypervitaminosis A, severe vitamin A deficiency, Addison disease, obesity, menarche, oral contraceptives, and pregnancy; infections such as roseola infantum, sinusitis, chronic otitis media and mastoiditis, and Guillain-Barré syndrome; drugs such as nalidixic acid, doxycycline, minocycline, tetracycline, nitrofurantoin, isotretinoin used for acne therapy especially when combined with tetracycline, and sodium valproate; hematologic disorders such as polycythemia, various anemias, and Wiskott-Aldrich syndrome; and, importantly, obstruction of intracranial drainage by cerebral venous thrombosis.

Table 623.1

Secondary Intracranial Hypertension Without an Obstructive Lesion on MRI

HEMATOLOGIC DISORDERS
Wiskott-Aldrich syndrome
Iron-deficiency anemia
Aplastic anemia
Sickle cell disease
Polycythemia
Bone marrow transplantation and associated treatments
Prothrombotic states
Fanconi anemia
INFECTIONS
Acute sinusitis
Otitis media (lateral sinus thrombosis)
Mastoiditis
Tonsillitis
Measles
Roseola
Varicella, recurrent varicella-zoster virus infection
Lyme disease
HIV or associated treatment complications
DRUG-RELATED CONDITIONS
Tetracyclines
Sulfonamides
Nalidixic acid
Fluoroquinolones
Corticosteroid therapy and withdrawal
Nitrofurantoin
Cytarabine
Cyclosporine
Phenytoin
Mesalamine
Isotretinoin
Amiodarone
Oral contraceptive pills/implants
RENAL DISORDERS

Nephrotic syndrome

Chronic renal insufficiency

Post–renal transplantation

Peritoneal dialysis

NUTRITIONAL DISORDERS

Hypovitaminosis A

Vitamin A intoxication

Hyperalimentation in malnourished patient

Vitamin D–dependent rickets

CONNECTIVE TISSUE DISORDERS

Antiphospholipid antibody syndrome

Systemic lupus erythematosus

Behçet disease

ENDOCRINE DISORDERS

Polycystic ovarian syndrome

Hypothyroidism

Hypoparathyroidism/hyperparathyroidism

Congenital adrenal hyperplasia

Addison disease

Recombinant growth hormone

OTHER CONDITIONS

Dural sinus thrombosis

Obesity (in pubertal patients)

Superior vena cava syndrome

Sleep apnea

Guillain-Barré syndrome

Crohn disease

Ulcerative colitis

Turner syndrome

Galactosemia

Atrial septal defect repair

Moebius syndrome

Sarcoidosis

Clinical Manifestations

IIH is rare under the age of 10 yr, with a female sex preponderance and for reasons that are poorly understood, patients are much more likely to be obese. The most frequent symptom is chronic (weeks-to-months), progressive, frontal headache that may worsen with postural changes or a Valsalva maneuver. Although vomiting may occur, it is rarely as persistent and insidious as that associated with a posterior fossa tumor. **Transient visual obscuration (TVO)** lasting seconds and diplopia (secondary to dysfunction of the abducens nerve) may also occur, as may pulsatile tinnitus. TVO is a transient graying out or vision loss often associated with postural changes or Valsalva maneuvers. Children are alert and lack constitutional symptoms. **Papilledema** with an enlarged blind spot is the most consistent sign. It is frequently misdiagnosed. The optic nerve head drusen and/or optic neuritis may be mistaken for papilledema. Hence, optical coherence tomography (Fig. 623.2) and *B* -ultrasound are strongly advised in all cases. Inferior nasal or peripheral visual field defects may be detected. The presence of other focal neurologic signs should prompt an investigation to uncover a process other than IIH. All children should undergo cranial MRI, which may show papilledema or enlargement of the optic nerve sheaths/pituitary fossa, but nothing else. MR venography is essential, both to exclude a venous thrombosis and to identify the tapering of the lateral sinuses that is commonly seen in intracranial hypertension.

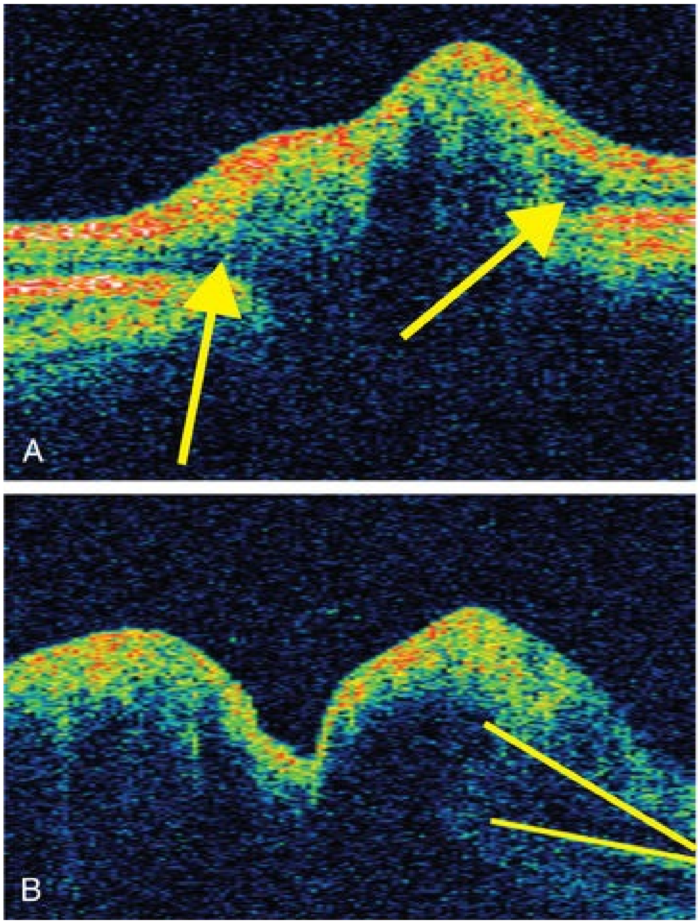

FIG. 623.2 **A,** Optical coherence tomogram (cross-sectional image) through an optic disc with drusen showing the typically irregular tissue underlying the elevated surface of the disc with no extension of the subretinal hyporeflective layer *(arrows)* beyond the optic nerve head. **B,** Optical coherence tomogram (cross-sectional image) of a papilledematous optic disc showing a smoothly elevated disc with underlying hyporeflective fluid extending beyond the disc into the subretinal space in a lazy-V pattern (illustrated by *yellow lines*). (Courtesy Louise Allen, MD, FRCOphth, Cambridge, United Kingdom.)

All children will require measurement of their CSF pressure. Standard opening pressures in cm H_2 O using a manometer can be falsely raised. More accurate recording will be achieved using an electronic transducer (similar equipment routinely attaches onto an arterial line), which will give a computer-aided recording with waveform analysis, both on opening and in steady state for 20 min (when relaxed, happy, in the lateral decubitus position, and not held tightly or in the overflexed position). Cooperation of the child is required and is helped by the presence of a play specialist or use of nitrous oxide during needle insertion thereby avoiding pain, crying, Valsalva maneuver, or abnormal respiration. When lumbar puncture opening pressure is measured under general anesthesia, it is important to record a normal end-tidal partial pressure of carbon dioxide (ET-pCO_2). Because secondary IH is more common, renal, liver, thyroid, hematologic, inflammatory, and autoimmune profiles should be obtained on venous blood testing. The tests are likely to help reduce the false-positive rate. CSF infusion studies can also be helpful, particularly in borderline cases. A summary of diagnostic criteria is noted in Table 623.2 .

Table 623.2

Diagnostic Criteria for Idiopathic Intracranial Hypertension (IIH)

DIAGNOSIS OF IIH	DIAGNOSIS OF IIH WITHOUT PAPILLOEDEMA
Diagnosis of IIH is definite if the patient fulfils A–E A. Papilledema B. Normal neurologic examination except for sixth cranial nerve abnormalities C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion, and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used D. Normal CSF composition E. Elevated lumbar puncture opening pressure (≥250 mm CSF in adults; ≥280 in children or obese adults) in a properly performed lumbar puncture.	In the absence of papilledema, a diagnosis of IIH can be made if B–E are satisfied, and in addition the patient has unilateral or bilateral abducens nerve palsy. In the absence of papilledema or sixth nerve palsy, a diagnosis of IIH can be suggested but not made if B–E are satisfied, and in addition at least three of the following are present on neuroimaging: 1. Empty sella. 2. Flattening of the posterior aspect of the globe. 3. Distention of the perioptic subarachnoid space with or without a tortuous optic nerve. 4. Transverse venous sinus stenosis.

The diagnosis of IIH is considered probable if A–D are met but the CSF pressure is below 250 mm.

From Mollan SP, Ali F, Hassan-Smith G, et al: Evolving evidence in adult idiopathic intracranial hypertension: pathophysiology and management, J Neurol Neurosurg Psychiatry 87(9):982-992, 2016, Table 1.

Treatment

There are no randomized clinical trials to guide the treatment of IIH. Optic atrophy and visual impairment are the most significant complications. Any causes of secondary IH should be treated (e.g., withdrawal of a drug). Obese children with IIH need a weight-loss regimen. Acetazolamide (10-30 mg/kg/24 hr) probably is an effective regimen, and, more recently, some authors have recommended using topiramate or furosemide. Corticosteroids are not routinely administered, although they may be used in a patient with severe intracranial hypertension who is at risk of losing visual function and awaiting surgical intervention; rarely, a ventriculoperitoneal or lumboperitoneal shunt is necessary.

Optic nerve sheath fenestration may also be attempted in refractory situations of IIH, but its value is debated. Any child whose intracranial pressure proves to be refractory to treatment warrants repeat full investigation. Serial monitoring of visual function (i.e., visual acuity, color vision, and visual fields) is required in children old enough to participate. Serial optic nerve examination is also essential. Optical coherence tomography is useful to serially follow changes in papilledema. Serial visual-evoked potentials are useful if the visual acuity cannot be reliably documented. The initial diagnostic lumbar puncture may be therapeutic. The spinal needle produces a small rent in the dura that allows CSF to escape the subarachnoid space, thus reducing intracranial pressure. Several additional lumbar taps and the removal of sufficient CSF to reduce the opening pressure by 50% occasionally lead to resolution of the process.

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CHAPTER 624

Spinal Cord Disorders

Mark R. Proctor

624.1

Tethered Cord

Mark R. Proctor

Normally, as the spine flexes and extends, the spinal cord is free to move up and down within the spinal canal. If the spinal cord is fixed at any point, its movement is restricted and the spinal cord and nerve roots can become stretched. This fixing of the spinal cord, regardless of the underlying cause, is called a tethered cord. When pain, neurologic deterioration, or bladder and bowel dysfunction occurs in response to the fixation, it is called the **tethered cord syndrome.**

By full gestational age, the spinal cord ends on average at the lumbar L1-2 disc space, although there is a normal bell-shaped distribution from thoracic T12-L3. Spinal cord tethering cannot be determined by position of the conus medullaris alone, but a position below L3 is concerning for tethering, especially when associated with an abnormality that connects the cord to the bones or soft tissues around the spine. Similarly, the spinal cord can be tethered even if it terminates in a normal position if a tethering lesion is present. This can occur from a variety of causes.

In its simplest form, the tethered cord syndrome results from a thickened filum terminale, which normally extends as a thin, very mobile structure from the tip of the conus to the sacrococcygeal region, where it attaches. When this structure is thickened and/or shortened, the cord can become tethered. This stretching between two points can cause symptoms later in life. Fatty infiltration is often seen in the thickened filum (Fig. 624.1).

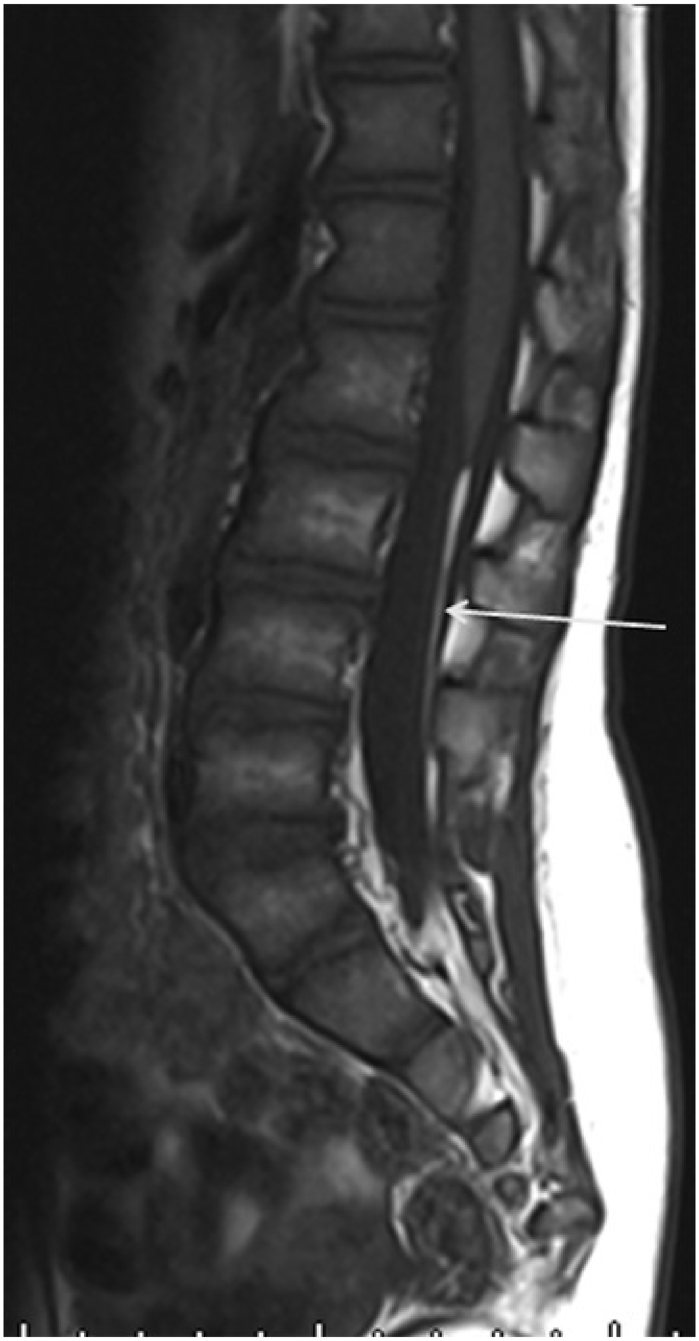

FIG. 624.1 Sagittal T1 MRI showing thickening and fatty infiltration of the filum terminale *(arrow)* in a patient with a symptomatic tethered spinal cord.

Other conditions that are well-established as causes of symptomatic tethering include various forms of occult dysraphism, such as lipomyelomeningocele, myelocystocele, and diastematomyelia. These conditions can be associated with cutaneous manifestations such as midline lipomas, asymmetry of the gluteal fold (Fig. 624.2), dimples, and hairy patches called hypertrichosis (Fig. 624.3). Probably the most commonly known type of symptomatic tethered cord involves patients who had previously undergone closure of an open myelomeningocele and later become symptomatic with pain or neurologic deterioration. Tethered cord syndrome can also be iatrogenic and associated with scarring of the spinal cord in patients who have undergone surgical procedures that disrupt the pial surface of the spinal cord.

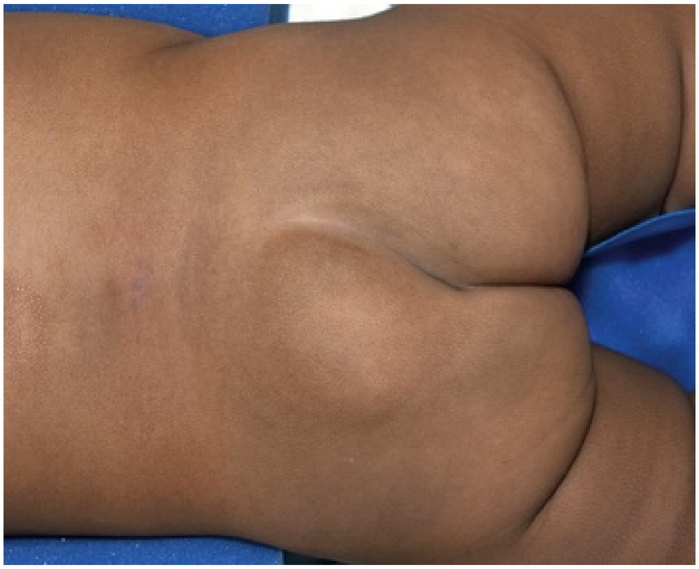

FIG. 624.2 Child with a lipomyelomeningocele demonstrating an extraspinal mass and an asymmetry of the gluteal fold indicative of underlying occult dysraphism. (Used with permission from Barrow Neurological Institute.)

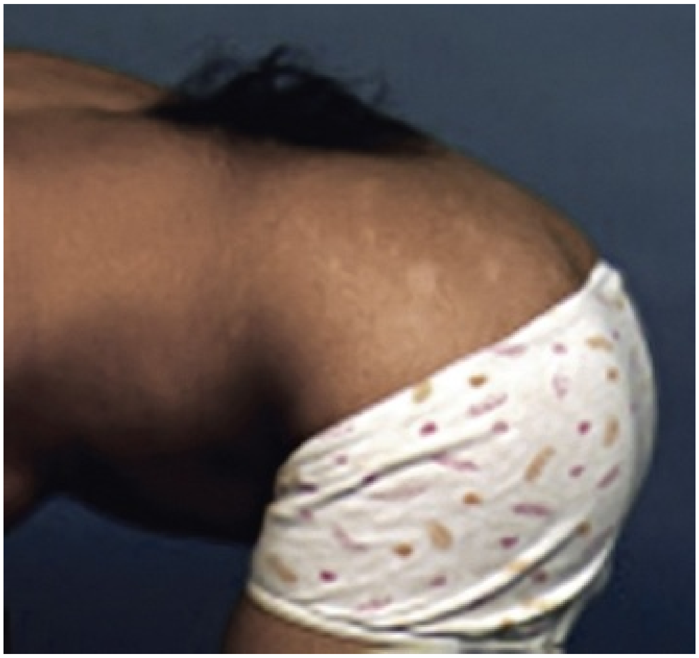

FIG. 624.3 Hairy patch or hypertrichosis usually associated with diastematomyelia. (Used with permission from Barrow Neurological Institute.)

Clinical Manifestations

Patients at risk for the subsequent development of the tethered cord syndrome can often be identified at birth by the presence of an open myelomeningocele or by cutaneous manifestations of dysraphism (see Chapter 609). It is important to examine the back of the newborn for cutaneous midline lesions (lipoma, dermal sinus, tail, or hairy patch) that may signal an underlying form of occult dysraphism. Dermal sinuses are almost always located *above* the gluteal fold, and dimples in the gluteal cleft directly overlying the coccyx are generally benign fibrous tracts called coccygeal pits that are not associated with spinal tethering. However, cutaneous abnormalities may be absent in patients with tethered spinal cord, and these patients present later in life with clinical manifestations.

Patients who become symptomatic later in life generally present with one of four clinical manifestations, including neurologic, orthopedic, bowel/bladder, and/or pain symptoms. One orthopedic presentation is asymmetry of the feet, with a smaller, high-arch foot with clawing of the toes (Fig. 624.4), sometimes referred to as the neuroorthopedic syndrome. Characteristically, there is no ankle jerk on the involved side and the calf is atrophied. Scoliosis can also be a presenting sign. Another clinical presentation is increasing urinary urgency, which may progress to incontinence. Constipation progressing to incontinence can affect the gastrointestinal system as well. Finally, severe generalized back pain, often radiating into the lower extremities, can occur, particularly in older adolescents and adults.

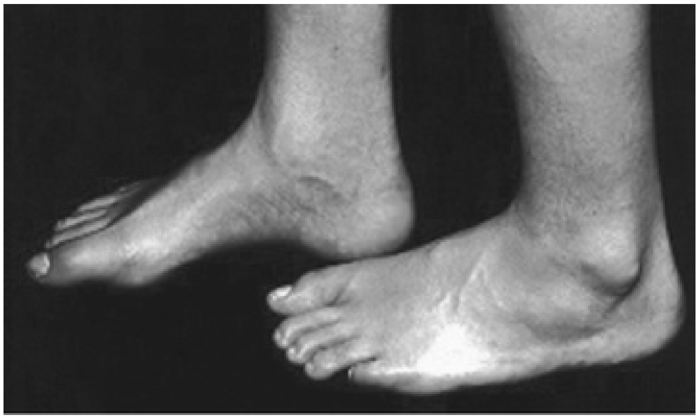

FIG. 624.4 Example of neuropathic changes to the right foot as a result of spinal cord tethering, with a smaller high-arched foot and absent ankle jerk on exam. (Used with permission from Barrow Neurological Institute.)

Diagnostic Evaluation

When patients present with symptoms related to the tethered cord syndrome, a thorough motor and sensory examination of the patient must be documented. Assessment of bladder function with an ultrasound of the bladder and urodynamic studies is useful in analyzing bladder innervation. Magnetic resonance imaging (MRI) is the diagnostic study of choice for the anatomy of the tethering lesion and to provide information about the risks of surgical intervention.

Treatment

There are no nonsurgical options for the management of tethered cord syndrome. Because the presence of asymptomatic tethering is most likely to be at least suspected in the newborn, prophylactic surgery to prevent late deterioration has been advocated by some neurosurgeons. This strategy remains controversial and depends to some extent on a careful assessment of the risks compared with the benefits. If surgical intervention is chosen, microsurgical dissection with release of the spinal cord attachment to the overlying dura and soft tissues is the goal of treatment.

Outcome

The outcome of surgery depends on the complexity of the underlying lesion and the presenting condition of the child because existing deficits are generally not reversed. Releasing a thickened filum terminale or detethering of patients with diastematomyelia generally yields a good outcome, and the chance of recurrent symptoms is very low. Patients with symptomatic tethered cord who undergo repair of a myelomeningocele or a lipomyelomeningocele have a significant possibility of recurrent tethering and recurrent symptoms.

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624.2

Diastematomyelia (Split-Cord Malformation)

Diastematomyelia is a relatively rare form of occult dysraphism in which the spinal cord is divided into two halves and can present as tethered spinal cord. In **type 1** split-cord malformation, there are two spinal cords, each in its own dural tube and separated by a spicule of bone and cartilage (Fig. 624.5). In a **type 2** split-cord malformation, the two spinal cords are enclosed in a single dural sac with a fibrous septum between the two spinal segments (Fig. 624.6). In both cases, the anatomy of the outer half of the spinal cord is essentially normal but the medial half is extremely underdeveloped. Undeveloped nerve roots and dentate ligaments terminate medially into the medial dural tube in type 1 cases and terminate in the membranous septum in type 2 cases. Both types have an associated defect in the bony spinal segment. In the case of type 2 lesions, this defect can be quite subtle.

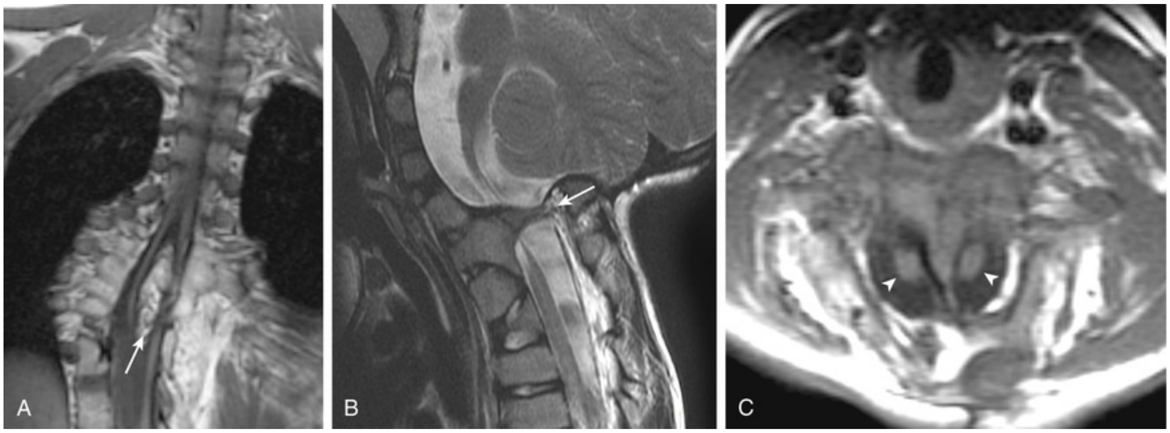

FIG. 624.5 Diastematomyelia type 1. Coronal **(A)** T1-weighted MRI in a patient with type 1 DSM shows a large ossified spur *(arrow)* that splits the thoracic spinal cord. Numerous vertebral segmentation anomalies with posterior rib fusions are present. Sagittal T2-weighted **(B)** and axial T1-weighted **(C)** MRI of a different patient shows a type 1 cervical DSM with ossified spur (*arrow* in **B**) and two hemicords (*arrowheads* in **C**). (From Moore KR: Congenital abnormalities of the spine. In Coley BD (ed): Caffey's pediatric diagnostic imaging, 13e, Philadelphia, 2019, Elsevier, Fig. 43-12.)

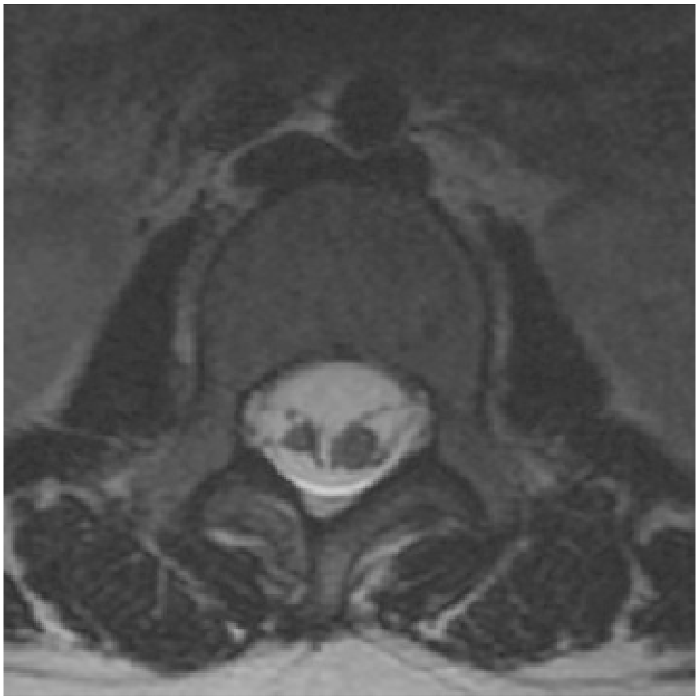

FIG. 624.6 Diastematomyelia type 2. Axial T2-weighted MRI in a patient with type 2 DSM shows the spinal cord split into two hemicords within a single dural tube. No fibrous or osseous septum was identified. (From Moore KR: Congenital abnormalities of the spine. In Coley BD (ed): Caffey's pediatric diagnostic imaging, 13e, Philadelphia, 2019, Elsevier, 2019, Fig. 43-13.)

Clinical Manifestations

Patients with both type 1 and type 2 split-cord malformations will have presentations similar to other types of spinal tethering lesions. This may include subtle signs of neurologic involvement, such as unilateral calf atrophy and a high arch in one or both feet early in life, but they are more likely to be neurologically normal. These patients are tethered by the adherence of the spinal cord so they may develop progressive loss of bowel and bladder function and sensory and motor difficulties in the lower extremities. Back pain is a common symptom in adolescents and adults with split-cord malformation but is uncommon in small children.

Cutaneous manifestations of dysraphism are present in 90% of patients with split-cord malformations. Large, hairy, midline patches called hypertrichosis, the most common cutaneous manifestations, are present in approximately 60% of the cases.

Diagnostic Evaluation

MRI, the study of choice, shows the two spinal cords. The frequent association of bony abnormalities in this condition may require further evaluation with computed tomography (CT).

Treatment

The treatment of split-cord malformations is surgical. This abnormality is a form of tethered cord syndrome, and its treatment is to release the spinal cord to move freely with movement of the spine. In type 1 split-cord malformations, the two half cords are in separate dural sacs with medial attachment to the dura and bony septum. In this case, the dura needs to be opened, the bony septum removed, the medial attachments to the dura lysed, and a single dural tube created. For type 2 lesions, the membranous septum should be lysed. An attachment of this membrane to the anterior dura should be explored and lysed as well. Retethering of this type is rare as there is no reason to disrupt the pial layer of the spinal cord.

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624.3

Syringomyelia

Mark R. Proctor

Syringomyelia is a cystic distention of the spinal cord caused by obstruction of the flow of spinal fluid from within the spinal cord to its point of absorption. There are three recognized forms of syringomyelia, depending on the underlying cause. Communicating syringomyelia implies that cerebrospinal fluid (CSF) from within the ventricles communicates with the fluid within the spinal cord and is assumed to be the source of the CSF that distends the spinal cord. Noncommunicating syringomyelia implies that ventricular CSF does not communicate with the fluid within the spinal cord. It primarily occurs in the context of intramedullary tumors and obstructive lesions. In the final form of syringomyelia, that is, posttraumatic syringomyelia, spinal cord injury results in damage and subsequent softening of the spinal cord. This softening, combined with the scarring of the surrounding spinal cord tissue, results in progressive distention of the cyst. Syringomyelia is highly associated with Chiari malformation, and can also be seen after infection or trauma, but many cases seen on imaging are normal anatomic variants unassociated with syndromes or any symptoms. It is also associated with connective tissue disorders (Ehlers-Danlos syndrome).

Clinical Manifestations

Signs and symptoms of syringomyelia develop insidiously over years or decades. The classic presentation is the **central cord syndrome.** Syringomyelia affects the spinal cord beginning from the central region, where the cervical and thoracic nerve fibers are located, so it less commonly affects the lumbar and sacral fibers, which are more laterally located in the spinal cord. Therefore, in syringomyelia the patient develops numbness beginning in the shoulder in a cape-like distribution followed by the development of atrophy and weakness in the upper extremities. Trophic ulcers of the hands are characteristic of advanced cases.

Other forms of presentation include scoliosis that may be rapidly progressive and often can be presumed from the absence of superficial abdominal reflexes. Urgency and bladder dysfunction as well as lower extremity spasticity also may be part of the presentation.

In patients with syringomyelia related to significant prior spinal cord injury, the presentation is usually severe pain in the area of the spinal cord distention above the level of the initial injury. There is also an ascending level of motor and sensory dysfunction.

Diagnostic Evaluation

MRI is the radiologic study of choice (Figs. 624.7 and 624.8). The study should include the entire spine, and gadolinium-enhanced sequences should be a part of it if there is a suspicion for tumor. Specific attention should be paid to the craniovertebral junction because of the frequent association of syringomyelia with Chiari malformations. Obstruction to the flow of CSF from the fourth ventricle can cause syringomyelia; therefore, most patients also should undergo imaging of the brain if a Chiari malformation is seen on the cervical imaging.

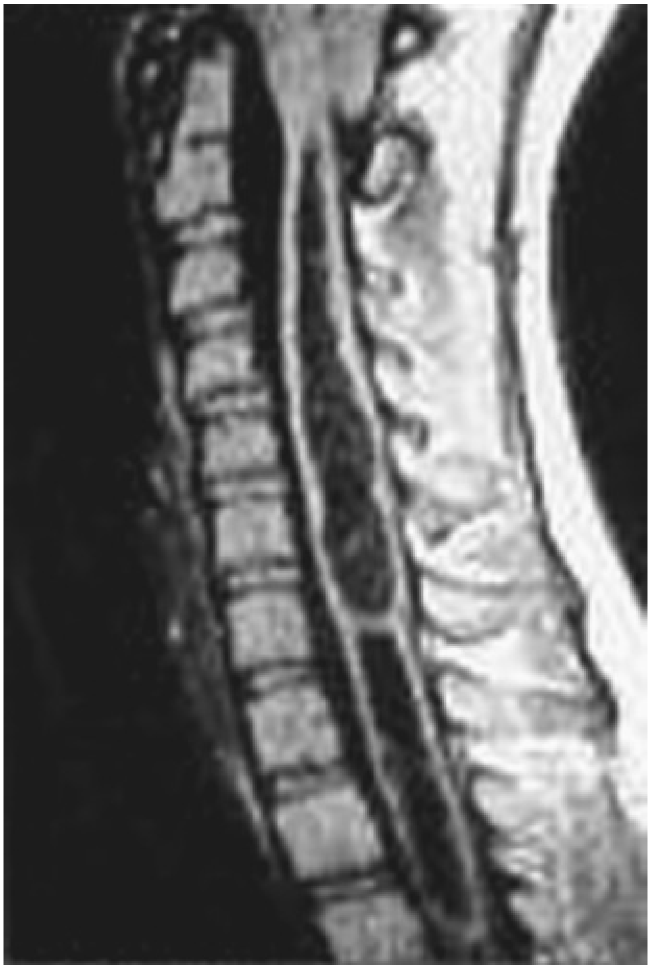

FIG. 624.7 Sagittal MRI of patient with a Chiari I malformation and a holocord syrinx. (Used with permission from Barrow Neurological Institute.)

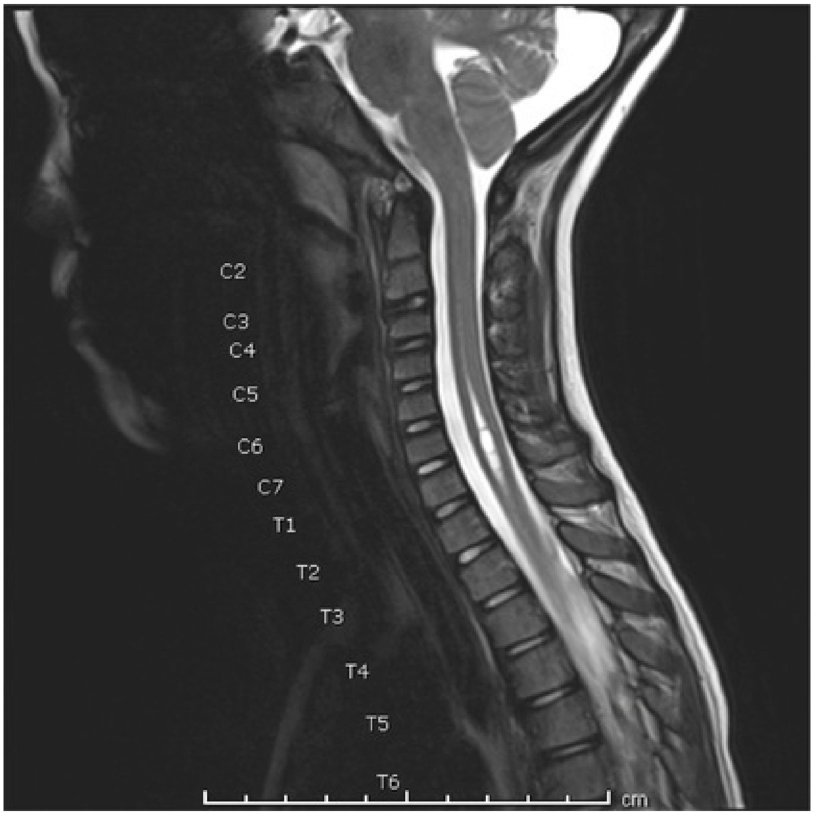

FIG. 624.8 T2 MRI scan of the cervical and thoracic spinal cord showing dilation of the central canal (C5-T1) in the absence of a Chiari malformation or other pathology.

Treatment

The treatment of syringomyelia should be tailored to the underlying cause, and rarely is the syringomyelia addressed directly. If that cause can be removed or ameliorated, the syrinx should improve. Direct surgery on the syrinx is associated with a much higher surgical risk profile.

Communicating syringomyelia is most frequently seen in the context of abnormalities at the craniovertebral junction, often associated with Chiari malformations (see Fig. 624.7). In such cases, decompression of the craniovertebral junction is usually effective in the management of the syringomyelia. In the context of the Chiari II malformation associated with spina bifida, syringomyelia usually results from an insidious failure of the shunt used to treat the hydrocephalus. This distention of the spinal cord results in a rapid development of scoliosis and occasionally spasticity in the lower extremities. Repair of the shunt is often effective treatment, and only rarely is surgical decompression at the craniovertebral junction necessary. Other conditions that can cause obstruction at the craniocervical junction include inflammatory conditions such as chronic meningitis, as seen in tuberculosis or meningeal carcinomatosis.

Noncommunicating syringomyelia results from blocking the flow of spinal cord extracellular fluid or CSF within the central canal by an intramedullary spinal cord tumor or severe external compression of the spinal cord. In such cases, management should be directed to tumor resection or to decompression of constricting elements.

Traumatic syrinxes result from hematomyelia in the substance of the spinal cord coupled with severe arachnoidal scarring around the circumference of the spinal cord. When progressive, this form of syringomyelia is treated by exploration and lysis of the adhesions that fix the spinal cord to the overlying dura. Microscopic lysis of the scar surrounding the spinal cord at the point of injury allows the spinal cord to collapse and prevents it from being distorted by a hydrostatic column of spinal fluid pulsations.

In rare cases, direct drainage procedures must be employed, and can result in symptomatic and radiographic improvement. Syrinx-to-subarachnoid or pleural shunting with a small piece of silicone tubing is the treatment option. These procedures often have short-lived success because the tubing tends to become obstructed, so they should be reserved for cases with obstructive symptoms.

In the current era, where many children are undergoing spinal MR imaging, some children who demonstrate no neurologic deficits are being referred to pediatric neurosurgeons with the diagnosis of syringomyelia. Many of these children were scanned because of back pain or as part of a screening for scoliosis. They are found on MRI to have a **persistent central canal** and the diagnosis of syringomyelia is made. These syrinxes are 1-3 mm in diameter and may extend over several segments (see Fig. 624.8). There is no distortion of the spinal cord in the region and no change in signal of the surrounding spinal cord. These syrinxes have been called “idiopathic” syrinxes. Follow-up of significant numbers of such children has shown them to be benign in nature and probably represent a normal variant. There does not seem to be a need for routine follow-up imaging without new symptoms. They need no treatment and do not require limitations of activity.

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624.4

Spinal Cord Tumors

Mark R. Proctor

Tumors of the spine and spinal cord are rare in children. Different types of tumors have different relationships with the spinal cord, meninges, and bony elements of the spine (Fig. 624.9). Intramedullary spinal cord tumors arise within the substance of the spinal cord itself (Fig. 624.10). They represent between 5% and 15% of primary central nervous system tumors. This percentage may well reflect the relative volume of spinal cord compared with brain. Approximately 10% of intramedullary spinal cord tumors are malignant astrocytic tumors, but most are World Health Organization grade I or II tumors of glial or ependymal origin. In children, low-grade astrocytomas and gangliogliomas represent the most common tumor types, with ependymomas being less common than in adults.

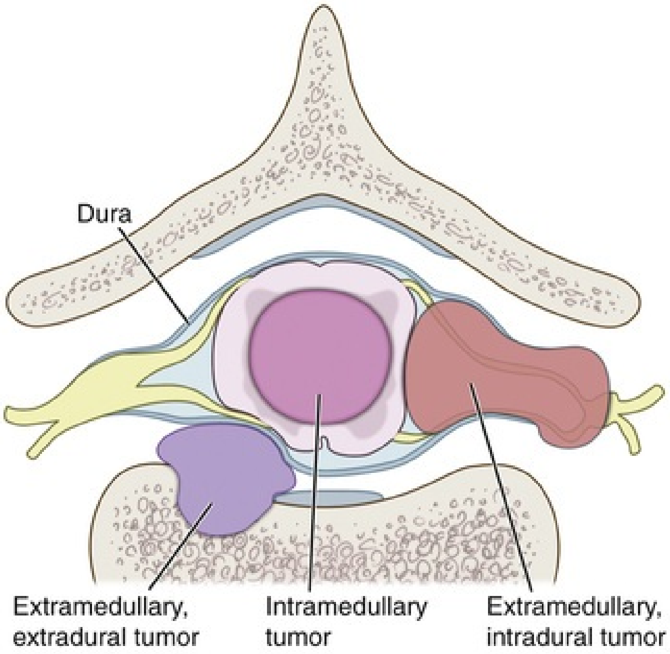
Dura
Extramedullary, extradural tumor
Intramedullary tumor
Extramedullary, intradural tumor

FIG. 624.9 Diagram of the relationship of various tumors to the spine, nerve roots, and spinal cord. (Used with permission from Barrow Neurological Institute.)

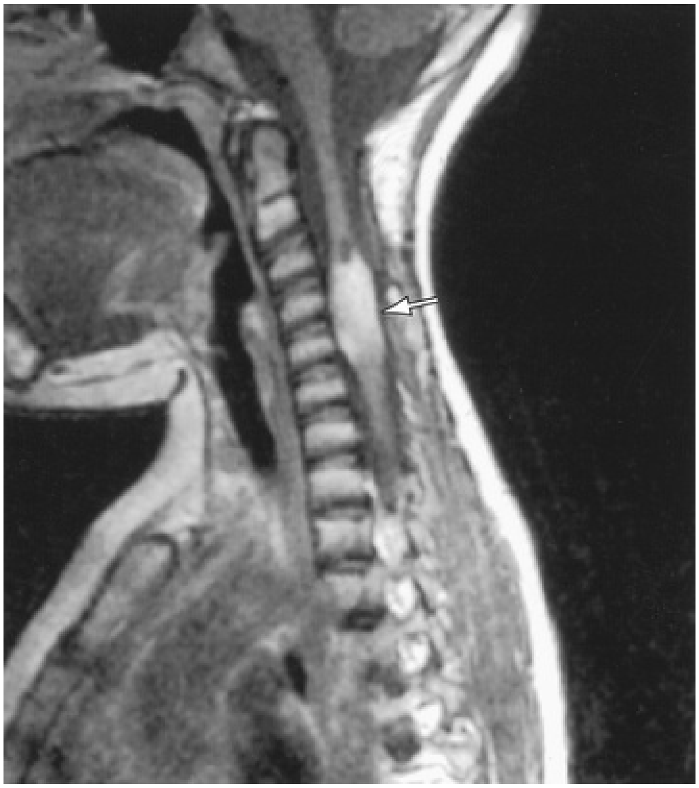

FIG. 624.10 T1-weighted MRI scan of a spinal cord tumor *(arrow).* The fusiform expansion of the cervical cord enhances after intravenous gadolinium injection.

Except in the context of neurofibromatosis (NF-1 and NF-2; see Chapter 614.1), intradural extramedullary tumors are extremely rare in children. Most are nerve sheath tumors, either schwannomas or, in the case of NF-2, neurofibromas. Intraspinal meningiomas in children are essentially found only in patients with NF-2, or those who have undergone prior irradiation for some reason. The intradural extramedullary compartment is also a site for metastatic tumors from primary cancers such as leukemia or primitive neuroectodermal tumors. Myxopapillary ependymoma, a benign subtype found in the filum terminale, is another extramedullary tumor seen in children.

Extradural spinal tumors characteristically begin in the bones of the spine. Primary tumors in this location include aneurysmal bone cysts, Langerhans cell histiocytosis (formerly called eosinophilic granuloma), osteoid osteoma, and giant cell tumors. In infants, the extradural space is often the site of neuroblastomas or ganglioneuroblastomas, which tend to extend from a paraspinal location into the epidural space through the intervertebral foramen. In older patients, the bones of the spine may be the site of multiple myeloma and metastases from common malignant tumors, such as chordoma and sarcomas.

Clinical Manifestations

With the exception of the uncommon malignant glial tumors of the spinal cord, which tend to present precipitously, intramedullary spinal cord tumors present in a very insidious manner. Back pain related to the level of the tumor is a common presenting complaint. It is likely that this pain will awaken the child from sleep and improve as the day progresses. Before the use of MRI became routine, the time from the first onset of symptoms to diagnosis of the tumor could be very prolonged, extending years. Weakness, gait disturbance, and sensory deficits are usually subtle but detectable on formal neurologic examination. Scoliosis, limb asymmetry, and bowel or bladder disturbance may be the presenting complaints associated with intramedullary spinal cord tumors.

Nerve sheath tumors primarily arise from the sensory rootlet of the exiting spinal nerve. They are very slow-growing tumors and present with symptoms and signs relative to the nerve root involved. Pain in a band-like distribution around the chest or into an extremity is the most common presenting complaint. Tumor growth eventually leads to spinal cord compression and involvement of adjacent nerve roots, but pain is the more likely presenting symptom.

Extramedullary extradural tumors have a tendency to present more acutely owing to rapid growth within a confined space. Such children may present with acute paresis and urinary retention. They can also present abruptly with severe pain and neurologic deficit at the time of pathologic fracture of the vertebral body. Benign tumors such as giant cell tumors and aneurysmal bone cysts present more insidiously as the tumor slowly grows and begins to compress neural structures. Osteoid osteomas present with severe pain relieved by nonsteroidal antiinflammatory drugs.

Diagnostic Evaluation

MRI with and without gadolinium enhancement of the spinal cord is the diagnostic study of choice and is essential in the diagnosis of spinal cord tumors, especially intramedullary spinal cord tumors. Most astrocytic tumors of the spinal cord and most ependymomas show diffuse enhancement and will distend the spinal cord focally. These tumors may involve the entire length of the spinal cord (holocord astrocytomas), although much of the change might be due to the associated syrinx. Nerve sheath tumors characteristically enhance and are focal. They may exit through the neural foramen and distend the canal, as can be seen on MRI. They also may be visualized on plain radiographs of the affected area of the spine due to their chronic effect on the bones.

Plain radiographs of the spine are helpful in defining the relationship of extradural tumors to the bony spine and in documenting evidence of instability in the case of pathologic compression fractures. When a pathologic fracture occurs, CT is essential to determine the effect of the tumor on the bone. Because many of these tumors occur as metastatic lesions, a general staging of the extent of disease is essential. In the case of Langerhans cell histiocytosis, a thorough bone survey should be conducted to look for other lesions. Radionucleotide bone scanning is also useful in determining the extent of the disease.

Treatment

The primary treatment of both intramedullary and extramedullary intradural tumors is surgical removal. For both low-grade astrocytomas and ependymomas, microsurgical removal with the intent of total removal is the treatment of choice. This goal should be attainable in most patients with ependymomas and in many patients with low-grade astrocytomas and gangliogliomas. Adjunctive treatment of these tumors is often unnecessary in patients treated with adequate surgical resection. Likewise, schwannomas should be resectable. Occasionally, however, the nerve root must be resected. Doing so may be of no consequence in the thoracic spinal cord, but an attempt to remove the tumor while salvaging the motor root in the cervical and lumbosacral region is critical to preserve movement. Malignant astrocytic tumors cannot be resected without major morbidity and, in any case, carry an extremely poor prognosis. In the case of grades III and IV astrocytomas of the spinal cord, decompression and biopsy followed by radiation therapy and possibly chemotherapy are utilized.

The diagnosis and treatment of extramedullary spinal cord tumors must be individualized. Patients with bony involvement may be at risk of instability, and treatment will therefore involve both tumor resection and stabilization of the spine. For extramedullary tumors with soft-tissue components such as neuroblastomas, treatment is determined by the nature of the tumor and degree of spinal cord compression, and may require needle biopsy of the lesion to direct treatment. In the absence of significant neurologic compression, surgical intervention may not be indicated if adjuvant therapies might be effective.

Outcome

The prognosis for patients with benign intramedullary spinal cord tumors depends, to some extent, on the patient's condition at the time of surgical intervention. It is very unlikely that nonambulatory patients will improve after surgery, and most patients will have at least transient worsening with surgery. If, however, patients are ambulatory at the time of surgery, they are likely to recover at least to their preoperative level of function. The majority of intramedullary tumors in children are benign and behave like tumors with the same histologic findings in the brain. The evidence would point to the fact that intramedullary ependymomas act in a more benign fashion than they do in the fourth ventricle. Gross total removal without adjuvant treatment is the preferred method of treatment and carries not only a much longer progression-free survival time but an improved quality of life as well.

Malignant spinal cord tumors are usually lethal, with death resulting from diffuse metastases via the CSF pathways. Successful resection of nerve sheath tumors should be curative. In the context of neurofibromatosis, however, many more tumors can be found at other levels or can be expected to develop later in life. Surgical intervention in the context of neurofibromatoses should be performed only for clearly symptomatic lesions.

The outcome of treatment of extramedullary tumors depends on the cell type and, in most cases, on the efficacy of nonsurgical, adjunctive therapies. For aneurysmal bone cysts and giant cell tumors, resection of the tumor and fusion of the spine are the treatments of choice.

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624.5

Spinal Arteriovenous Malformations

Mark R. Proctor

Arteriovenous malformations of the spinal cord are rare lesions in children. Only about 60 patients younger than age 18 yr are treated in the United States each year. These lesions are complex, and despite their rarity there are multiple subtypes, which require different treatment strategies. Patients commonly present with back or neck pain, depending on the segments of the spinal cord involved, and they may experience the insidious onset of motor and sensory disturbances. Sudden onset of paraplegia secondary to hemorrhage has been reported. Occasionally, patients present with subarachnoid hemorrhage without overt neurologic deficits, similar to the presentation associated with cerebral aneurysms. In some cases, bruits are audible upon auscultation over the bony spine.

Diagnostic Evaluation

When a spinal arteriovenous malformation is suspected, MRI of the spinal cord is first needed to make the diagnosis and to obtain a general idea of the location of the lesion (Fig. 624.11). MR angiography or CT angiography may provide further information, but formal catheter angiography of the spinal cord is needed to obtain an adequate understanding of the complex anatomy of the lesion and to plan the intervention.

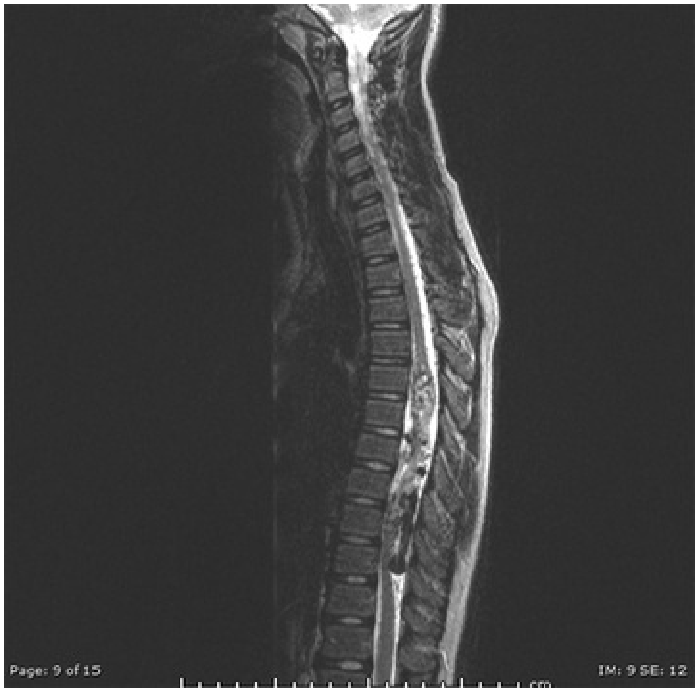

FIG. 624.11 T-2 weighted MRI showing an extensive thoracic spinal arteriovenous malformation.

Treatment

Open microsurgery had been the mainstay of treatment for spinal cord arteriovenous fistulas and arteriovenous malformations. With the rapid development of interventional techniques, the percentage of patients undergoing microsurgery has decreased from 70% to approximately 30%. Stereotactic radiosurgery may be used adjunctively. Treatment of these complex lesions requires the commitment of an organized neurovascular treatment program.

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PART XXVII

Neuromuscular Disorders

OUTLINE

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Chapter 628 Endocrine and Toxic Myopathies
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CHAPTER 625

Evaluation and Investigation of Neuromuscular Disorders

Harvey B. Sarnat

The term *neuromuscular disease* defines disorders of the motor unit and excludes influences on muscular function from the brain, such as spasticity. The motor unit has four components: a motor neuron in the brainstem or ventral horn of the spinal cord; its axon, which together with other axons forms the peripheral nerve; the neuromuscular junction; and all muscle fibers innervated by a single motor neuron. The size of the motor unit varies among different muscles and with the precision of muscular function required. In large muscles, such as the glutei and quadriceps femoris, hundreds of muscle fibers are innervated by a single motor neuron; in small, finely tuned muscles, such as the stapedius or the extraocular muscles, a 1 : 1 ratio can prevail. The motor unit is influenced by suprasegmental or upper motor neuron control that alters properties of muscle tone, precision of movement, reciprocal inhibition of antagonistic muscles during movement, and sequencing of muscle contractions to achieve smooth, coordinated movements. Suprasegmental impulses also augment or inhibit the monosynaptic stretch reflex; the corticospinal tract is inhibitory upon this reflex.

Diseases of the motor unit are common in children. These neuromuscular diseases may be genetically determined, congenital or acquired, acute or chronic, and progressive or static. Because specific therapy is available for many diseases and because of genetic and prognostic implications, a precise diagnosis is important; laboratory confirmation is required for most diseases because of overlapping clinical manifestations.

Genetic Testing

Many chromosomal loci are identified with specific neuromuscular diseases as a result of genetic linkage studies and the isolation and cloning of specific genes. In some cases, such as Duchenne muscular dystrophy, the genetic defect is a deletion of nucleotide sequences and is associated with a defective protein product, dystrophin. In other cases, such as myotonic muscular dystrophy, the genetic defect is an expansion or repetition, rather than a deletion, in a codon (a set of three consecutive nucleotide repeats that encodes for a single amino acid), with many copies of a particular codon (in this example they are also associated with abnormal messenger RNA). Some diseases manifest as autosomal dominant and autosomal recessive traits in different pedigrees; these distinct mendelian genotypes can result from different genetic mutations on different chromosomes (nemaline myopathy) or from small differences in the same gene at the same chromosomal locus (myotonia congenita), despite many common phenotypic features and shared histopathologic findings in a muscle biopsy specimen. Among the several clinically defined mitochondrial myopathies, specific mitochondrial DNA deletions and transfer RNA point mutations are recognized. The inheritance patterns and chromosomal and mitochondrial loci of common neuromuscular diseases affecting infants and children are summarized in Table 626.1 in Chapter 626 .

Genotype:phenotype correlations are not always as precise as one would like for diagnosis; many genetic mutations, even on different chromosomes, cause the same phenotype, and the converse is also true in that the same genetic mutation may yield many clinical variations of the phenotype in different patients. Even a disease as stereotyped and predictable as Duchenne muscular dystrophy is now known to be associated with dozens of different genotype variations in out-of-frame deletions and mutations of the large dystrophin gene. This explains why specific therapies might be beneficial for some patients and not alter the natural course of the disease in others.

Clinical Manifestations

Examination of the neuromuscular system includes an assessment of muscle bulk, tone, and strength. Tone and strength should not be confused: **Passive tone** is range of motion around a joint; a**ctive tone** is physiologic resistance to movement. Head lag when an infant is pulled to a sitting position from supine is a sign of weakness, not of low tone. Hypotonia may be associated with normal strength or with weakness; enlarged muscles may be weak or strong; thin, wasted muscles may be weak or have unexpectedly normal strength. The distribution of these components is of diagnostic importance. In general, myopathies follow a proximal distribution of weakness and muscle wasting (with the notable exception of myotonic muscular dystrophy); neuropathies are generally distal in distribution (with the notable exception of juvenile spinal muscular atrophy; Table 625.1). Involvement of the face, tongue, palate, and extraocular muscles provides an important distinction in the differential diagnosis. **Tendon stretch reflexes** are generally lost in neuropathies and in motor neuron diseases and are diminished but preserved in myopathies (see Table 625.1). A few specific clinical features are important in the diagnosis of some neuromuscular diseases. **Fasciculations** of muscle, which are often best seen in the tongue, are a sign of denervation. Sensory abnormalities indicate neuropathy. Fatigable weakness is characteristic of neuromuscular junctional disorders. Myotonia is specific for a few myopathies.

Table 625.1

Distinguishing Features of Disorders of the Motor System (Except Genetic)

LOCUS OF LESION	WEAKNESS				DEEP TENDON REFLEXES	ELECTRO-MYOGRAPHY	MUSCLE BIOPSY	OTHER
	Face	Arms	Legs	Proximal-Distal				
Central	0	+	+	≥	Normal or ↑	Normal	Normal	Seizures, hemiparesis, and delayed development
Ventral horn cell	Late	++++	++++	≥	0	Fasciculations and fibrillations	Denervation pattern	Fasciculations (tongue)
Peripheral nerve	0	+++	+++	<	↓	Fibrillations	Denervation pattern	Sensory deficit, elevated cerebrospinal fluid protein, depressed nerve biopsy
Neuromuscular junction	+++	+++	+++	=	Normal	Decremental response (myasthenia); incremental response and BSAP (botulism)	Normal	Response to neostigmine or edrophonium (myasthenia); constipation and fixed pupils (botulism)
Muscle	Variable	++	+	>	↓	Short duration,	Myopathic	Elevated

	(+ to ++++)					small-amplitude motor unit potentials and myopathic polyphasic potentials	pattern[*]	muscle enzyme levels (variable)

[*] Can also show unique features, as in central core disease, nemaline myopathy, myotubular myopathy, and congenital fiber type disproportion.

+ to ++++, varying degrees of severity; BSAP, brief-duration, small-amplitude, overly abundant motor unit potentials.

From Volpe J: Neurology of the newborn, ed 4, Philadelphia, 2001, WB Saunders, p. 706.

Some features do not distinguish myopathy from neuropathy. Muscle pain or **myalgias** are associated with acute disease of either myopathic or neurogenic origin. Acute dermatomyositis and acute polyneuropathy (Guillain-Barré syndrome) are characterized by myalgias. Muscular dystrophies and spinal muscular atrophies are not associated with muscle pain. Myalgias also occur in several metabolic diseases of muscle and in ischemic myopathy, including vascular diseases such as dermatomyositis. Myalgias denote the acuity, rather than the nature, of the process, so that progressive but chronic diseases, such as muscular dystrophy and spinal muscular atrophy, are not painful, but acute stages of inflammatory myopathies and acute denervation of muscle often do present with muscular pain and tenderness to palpation. **Contractures** of muscles, whether present at birth or developing later in the course of an illness, occur in both myopathic and neurogenic diseases.

Infant boys who are weak in late fetal life and in the neonatal period often have **undescended testes.** The testes are actively pulled into the scrotum from the anterior abdominal wall by a pair of cords that consist of smooth and striated muscle called the gubernacula. The gubernacula are weakened in many congenital neuromuscular diseases, including spinal muscular atrophy, myotonic muscular dystrophy, and many congenital myopathies.

The thorax of infants with congenital neuromuscular disease often has a funnel shape, and the ribs are thin and radiolucent as a result of intercostal muscle weakness during intrauterine growth. This phenomenon is characteristically found in infantile spinal muscular atrophy but also occurs in myotubular myopathy, neonatal myotonic dystrophy, and other disorders (Fig. 625.1). Because of the small muscle mass, the birthweight may be low for gestational age.

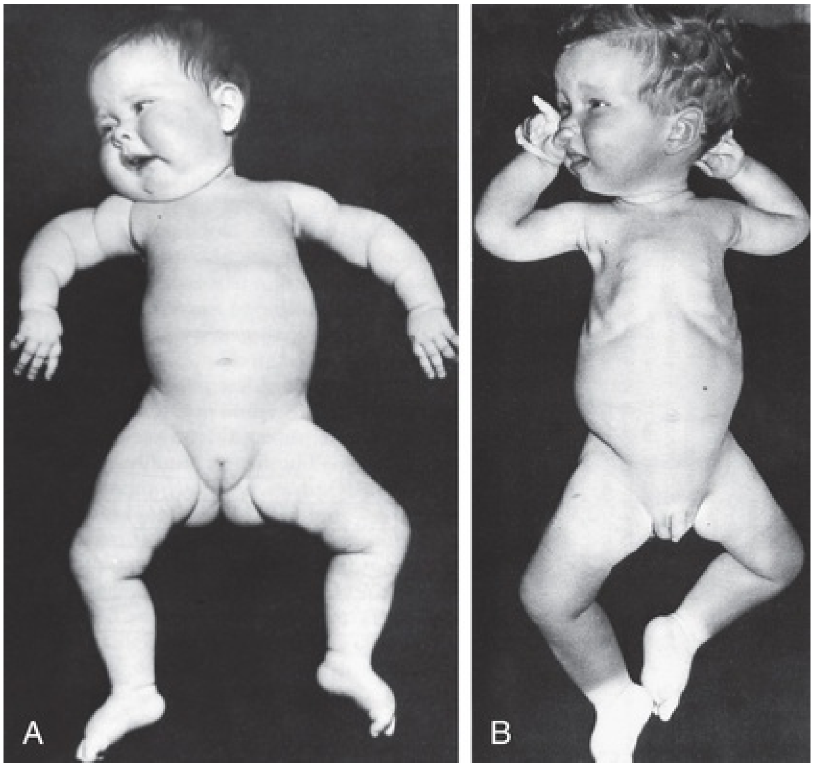

FIG. 625.1 Type 1 spinal muscular atrophy (Werdnig-Hoffmann disease). Characteristic postures in 6 wk old **(A)** and 1 yr old **(B)** infants with severe weakness and hypotonia from birth. Note the frog-leg posture of the lower limbs and internal rotation ("jug handle") **(A)** or external rotation **(B)** at the shoulders. Note also intercostal recession, especially evident in **B,** and normal facial expressions. (From Volpe J: Neurology of the newborn, ed 4, Philadelphia, 2001, WB Saunders, p. 645.)

Generalized hypotonia and motor developmental delay are the most common presenting manifestations of neuromuscular disease in infants and young children (Table 625.2 and Figs. 625.2 to 625.4). These features can also be expressions of neurologic disease, endocrine and systemic metabolic diseases, and Down syndrome, or they may be nonspecific neuromuscular expressions of malnutrition or chronic systemic illness (Table 625.3). A prenatal history of decreased fetal movements and intrauterine growth retardation is often found in patients who are symptomatic at birth. Developmental disorders tend to be of slow onset and are progressive. Acute flaccid paralysis in older infants and children has a different differential diagnosis (Table 625.4).

Table 625.2

Pattern of Weakness and Localization in the Floppy Infant

ANATOMIC REGION OF HYPOTONIA	CORRESPONDING DISORDERS	PATTERN OF WEAKNESS AND INVOLVEMENT
Central nervous system	Chromosomal disorders Inborn errors of metabolism Cerebral dysgenesis Cerebral, spinal cord trauma	Central hypotonia Axial hypotonia more prominent Hyperactive reflexes
Motor neuron	Spinal muscular atrophy	Generalized weakness; often spares the diaphragm, facial muscles, pelvis, and sphincters
Nerve	Peripheral neuropathies	Distal muscle groups involved Weakness with wasting
Neuromuscular junction	Myasthenia syndromes Infantile botulism	Bulbar, oculomotor muscles exhibit greater degree of involvement
Muscle	Congenital myopathies Metabolic myopathies Congenital muscular dystrophy Congenital myotonic dystrophy	Weakness is prominent Proximal musculature Hypoactive reflexes Joint contractures

From Prasad AN, Prasad C: The floppy infant: contribution of genetic and metabolic disorders, Brain Dev 27:457-476, 2003.

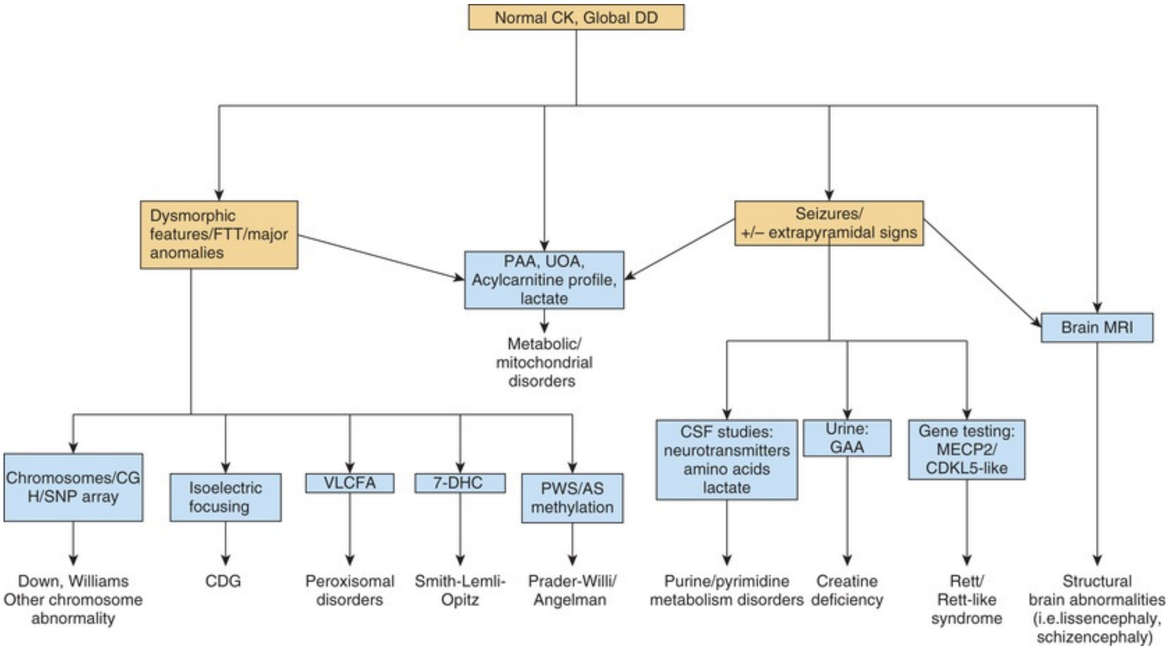
Normal CK, Global DD
Dysmorphic features/FTT/major anomalies
Seizures/ +/– extrapyramidal signs
PAA, UOA, Acylcarnitine profile, lactate
Metabolic/ mitochondrial disorders
Brain MRI
Chromosomes/CGH/SNP array
Isoelectric focusing
VLCFA
7-DHC
PWS/AS methylation
CSF studies: neurotransmitters amino acids lactate
Urine: GAA
Gene testing: MECP2/ CDKL5-like
Down, Williams Other chromosome abnormality
CDG
Peroxisomal disorders
Smith-Lemli-Opitz
Prader-Willi/ Angelman
Purine/pyrimidine metabolism disorders
Creatine deficiency
Rett/ Rett-like syndrome
Structural brain abnormalities (i.e.lissencephaly, schizencephaly)

FIG. 625.2 **Central hypotonia. CK, creatine kinase; PAA, plasma amino acids; UOA, urine organic acids; CDG, congenital disorders of glycosylation; DD, developmental delay; VLCFA, very-long-chain fatty acids; GAA, guanidinoacetate. (From Lisi EC, Cohn RD: Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature, Dev Med Child Neurol 53:586-599, 2011, Fig. 1.)**

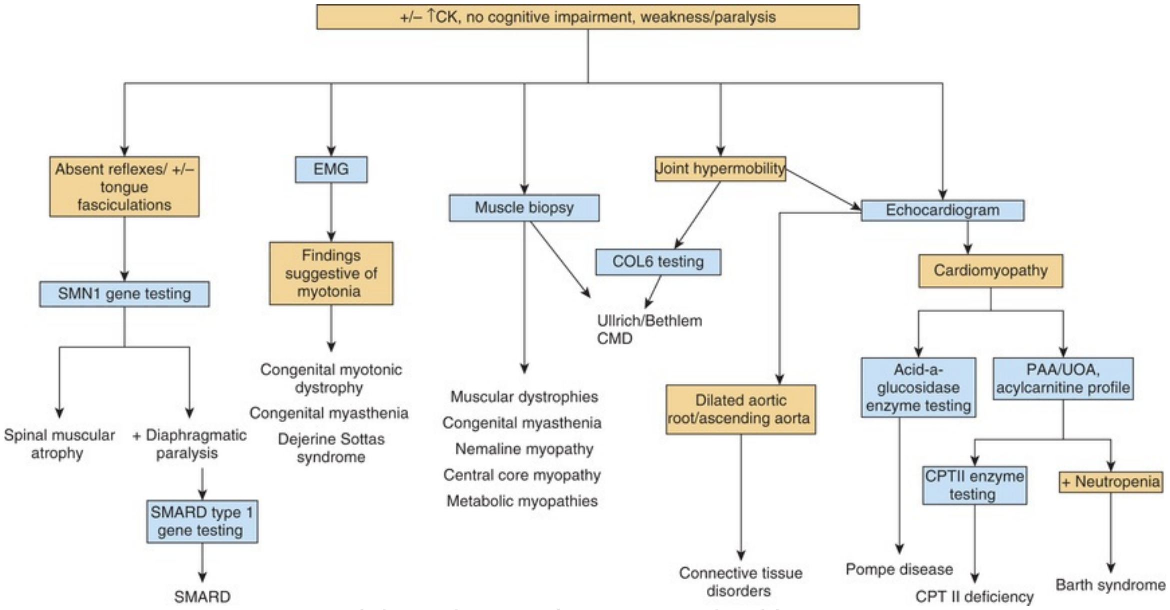
+/– ↑CK, no cognitive impairment, weakness/paralysis
Absent reflexes/ +/– tongue fasciculations
SMN1 gene testing
Spinal muscular atrophy
+ Diaphragmatic paralysis
SMARD type 1 gene testing
SMARD
EMG
Findings suggestive of myotonia
Congenital myotonic dystrophy
Congenital myasthenia
Dejerine Sottas syndrome
Muscle biopsy
Muscular dystrophies
Congenital myasthenia
Nemaline myopathy
Central core myopathy
Metabolic myopathies
Joint hypermobility
COL6 testing
Ullrich/Bethlem CMD
Dilated aortic root/ascending aorta
Connective tissue disorders
Echocardiogram
Cardiomyopathy
Acid-a-glucosidase enzyme testing
Pompe disease
PAA/UOA, acylcarnitine profile
CPTII enzyme testing
CPT II deficiency
+ Neutropenia
Barth syndrome

FIG. 625.3 Peripheral hypotonia. CK, creatine kinase; EMG, electromyography; +/–, with or without; PAA, plasma amino acids; UOA, urine organic acids; SMARD, spinomuscular atrophy with respiratory distress. (From Lisi EC, Cohn RD: Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature, Dev Med Child Neurol 53:586-599, 2011, Fig. 2.)

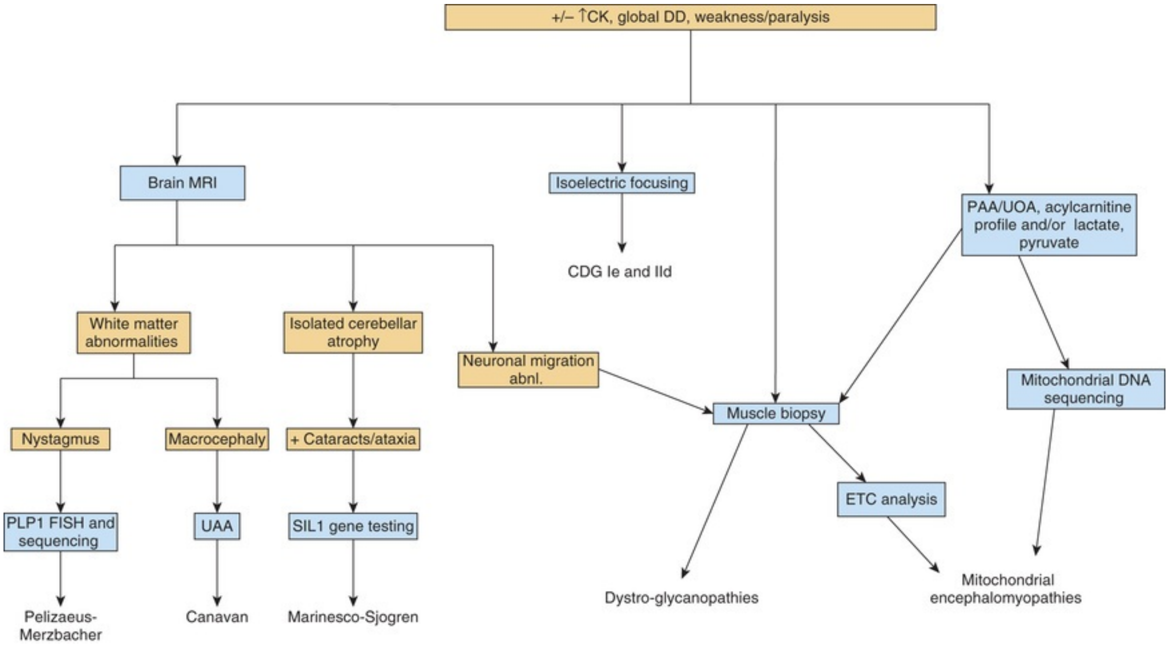
+/– ↑CK, global DD, weakness/paralysis
Brain MRI
Isoelectric focusing
CDG Ie and IId
PAA/UOA, acylcarnitine profile and/or lactate, pyruvate
White matter abnormalities
Isolated cerebellar atrophy
Neuronal migration abnl.
Muscle biopsy
Mitochondrial DNA sequencing
Nystagmus
Macrocephaly
+ Cataracts/ataxia
ETC analysis
PLP1 FISH and sequencing
UAA
SIL1 gene testing
Pelizaeus-Merzbacher
Canavan
Marinesco-Sjogren
Dystro-glycanopathies
Mitochondrial encephalomyopathies

FIG. 625.4 Combined hypotonia. DD, developmental delay; CDG, congenital disorders of glycosylation; PAA, plasma amino acids; UOA, urine organic acids; UAA, urine amino acids; +/–, with or without. (From Lisi EC, Cohn RD: Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature, Dev Med Child Neurol 53:586-599, 2011, Fig. 3.)

Table 625.3

Differential Diagnosis of Infantile Hypotonia

CEREBRAL HYPOTONIA
Benign congenital hypotonia*
CHROMOSOME DISORDERS
Prader-Willi syndrome
Trisomy
CHRONIC NONPROGRESSIVE ENCEPHALOPATHY
CEREBRAL MALFORMATION
Perinatal distress*
Postnatal disorders*
Peroxisomal disorders
Cerebrohepatorenal syndrome (Zellweger syndrome)
Neonatal adrenoleukodystrophy
OTHER GENETIC DEFECTS

Familial dysautonomia

Oculocerebrorenal syndrome (Lowe syndrome)

OTHER METABOLIC DEFECTS

Acid maltase deficiency* (see Pompe disease)

Infantile GM_1 gangliosidosis

Pyruvate carboxylase deficiency

SPINAL CORD DISORDERS

Spinal muscular atrophies

Acute infantile

Autosomal dominant

Autosomal recessive

Cytochrome c oxidase deficiency

X-linked

Chronic infantile

Autosomal dominant

Autosomal recessive

Congenital cervical spinal muscular atrophy

Infantile neuronal degeneration

Neurogenic arthrogryposis

Polyneuropathies

Congenital hypomyelinating neuropathy

Giant axonal neuropathy

Hereditary motor–sensory neuropathies

DISORDERS OF NEUROMUSCULAR TRANSMISSION

Familial infantile myasthenia

Infantile botulism

Transitory myasthenia gravis

Fiber-type disproportion myopathies

Central core disease

Congenital fiber-type disproportion myopathy

Myotubular (centronuclear) myopathy

Acute

Chronic

Nemaline (rod) myopathy

Autosomal dominant

Autosomal recessive

Metabolic myopathies

Acid maltase deficiency (Pompe disease)
Cytochrome c oxidase deficiency

MUSCULAR DYSTROPHIES

Bethlem myopathy
Congenital dystrophinopathy
Congenital muscular dystrophy
Merosin deficiency primary
Merosin deficiency secondary
Merosin positive
Congenital myotonic dystrophy

[*] Denotes the most common conditions and the ones with disease-modifying treatments.

Modified from Fenichel's clinical pediatric neurology, 7th ed, Philadelphia, 2013, Elsevier, Box 6.1.)

Table 625.4

Differential Diagnosis of Acute Flaccid Paralysis

Brainstem stroke

Brainstem encephalitis

Acute anterior poliomyelitis

- Caused by poliovirus
- Caused by other neurotropic viruses
- Unknown cause of acute flaccid myelitis

Acute myelopathy

- Space-occupying lesions
- Acute transverse myelitis

Peripheral neuropathy

- Guillain-Barré syndrome
- Post–rabies vaccine neuropathy
- Diphtheritic neuropathy
- Heavy metals, biologic toxins, or drug intoxication
- Acute intermittent porphyria
- Vasculitic neuropathy
- Critical illness neuropathy
- Lymphomatous neuropathy

Disorders of neuromuscular transmission

- Myasthenia gravis
- Biologic or industrial toxins
- Tic paralysis

Disorders of muscle

- Hypokalemia
- Hypophosphatemia

- Inflammatory myopathy
- Acute rhabdomyolysis
- Trichinosis
- Familial periodic paralyses (normokalemic, hypokalemic, hyperkalemic)

From Hughes RAC, Camblath DR: Guillain-Barré syndrome, Lancet 366:1653-1666, 2005.

Laboratory Findings

Serum Enzymes

Several lysosomal enzymes are released by damaged or degenerating muscle fibers and may be measured in serum. The most useful of these enzymes is **creatine kinase (CK),** which is found in only three organs and may be separated into corresponding isozymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. Serum CK determination is not a universal screening test for neuromuscular disease because many diseases of the motor unit are not associated with elevated enzymes. The CK level is characteristically elevated in certain diseases, such as Duchenne muscular dystrophy, and the magnitude of increase is characteristic for particular diseases. CK may also be elevated in certain nonneuromuscular disorders (Table 625.5).

Table 625.5

Nonneuromuscular Disorders That Can Cause Elevated Creatine Kinase Levels

ENDOCRINE DISORDERS
Hyperthyroidism (rare)
Hypothyroidism
Hyperparathyroidism
Acromegaly
Cushing syndrome

METABOLIC DISTURBANCES
Hyponatremia
Hypokalemia
Hypophosphatemia

MUSCLE TRAUMA
Strenuous exercise
Intramuscular injections
Needle electromyography
Seizures

MEDICATIONS
Statins
Fibrates

Antiretrovirals
Beta-blockers
Clozapine
Angiotensin II receptor blockers
Hydroxychloroquine
Isotretinoin
Colchicine

OTHERS
Celiac disease
Malignancy
Macro creatine kinase
Surgery
Pregnancy
Cardiac disease
Acute kidney disease
Viral illness
Predisposition to malignant hyperthermia

(From Moghadam-Kia S, Oddis CV, Aggarwal R: Approach to asymptomatic creatine kinase elevation, Cleveland Clin J Med 83(1):37-42, 2016, Table 1.)

Rhabdomyolysis is often a dramatic event associated with high plasma CK levels, myoglobinuria, and muscle pain or tenderness. It may be acquired (Table 625.6 and Fig. 625.5), due to metabolic diseases (Table 625.7), or occur spontaneously or secondary to various triggers (Fig. 625.6).

Table 625.6

Causes of Rhabdomyolysis

NONTRAUMATIC CAUSES

Nonexertional Causes

Alcohol/drug abuse:
Ethanol, methanol, ethylene glycol, heroin, methadone, barbiturates, cocaine, caffeine, amphetamine, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), phencyclidine, benzodiazepines, toluene (from glue sniffing), gasoline/paint sniffing

Medication:
Salicylates, fibric acid derivatives (bezafibrate, clofibrate, fenofibrate, gemfibrozil), neuroleptics, antipsychotics (haloperidol, fluphenazine, perphenazine, chlorpromazine), quinine, corticosteroids, statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, cerivastatin), theophylline, cyclic antidepressants, selective serotonin reuptake inhibitors, antibiotics (fluoroquinolones, pyrazinamide, trimethoprim/ sulphonamide, amphotericin B, itraconazole, levofloxacin), zidovudine, benzodiazepines, antihistamines, aminocaproic acid, phenylpropanolamine

Toxic agents:
Carbon monoxide (CO), hemlock herbs from quail, snake bites, spider venom, massive honey bee envenomations, *Tricholoma equestre* (mushroom), buffalo fish

Anesthetics and neuromuscular blocking agents:
Barbiturates, benzodiazepines, propofol, succinylcholine in patients with Duchenne/Becker muscular dystrophy

Infections:
Viral: influenza A and B, HIV, enterovirus, adenovirus, Coxsackievirus, Epstein-Barr virus, echovirus, cytomegalovirus, herpes simplex virus, varicella-zoster virus, West Nile virus. *Bacterial: Legionella* species, *Salmonella* species, *Francisella* species, *Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus, Pseudomonas aeruginosa, Neisseria meningitidis, Haemophilus influenzae, Coxiella burnetii, Leptospira* species, *Mycoplasma* species, *Escherichia coli,* fungal and malarial infections

Electrolyte disturbances:
Hyponatremia, hypernatremia, hypokalemia, hypophosphatemia, hypocalcinemia, hyperosmotic conditions

Endocrine disorders:
Hypothyroidism, hyperthyroidism, diabetic ketoacidosis, nonketotic hyperosmolar diabetic coma, hyperaldosteronism

Idiopathic inflammatory myopathies:
Polymyositis, dermatomyositis, necrotizing myositis

Temperature extremes:
Heatstroke, malignant hyperthermia, exposure to cold

Muscle ischemia:
Thrombosis, embolism

Neuroleptic malignant syndrome

Exertional Causes

Extreme physical exertion

Sickle cell disease (crisis)

Status epilepticus

Hyperkinetic syndrome

Severe dystonia

Status asthmaticus

TRAUMATIC CAUSES

Multiple injury

Crush injury:
Bombings, earthquakes, building collapse, mine accidents, train or motor vehicle accidents

High-voltage electrical injury

Extensive third-degree burns

Vascular/orthopedic surgery:
Intraoperative use of tourniquets, tight dressings or casts, prolonged application of air splints or pneumatic antishock garments, and clamping of vessels during surgery

Prolonged immobility:
Immobilization after trauma, anesthesia, coma, drug- or alcohol-induced unconsciousness

(Modified from Zutt R, van der Kooi AJ, Linthorst GE, et al: Rhabdomyolysis: review of the literature, Neuromusc Dis 24:651-659, 2014, Table 2.)

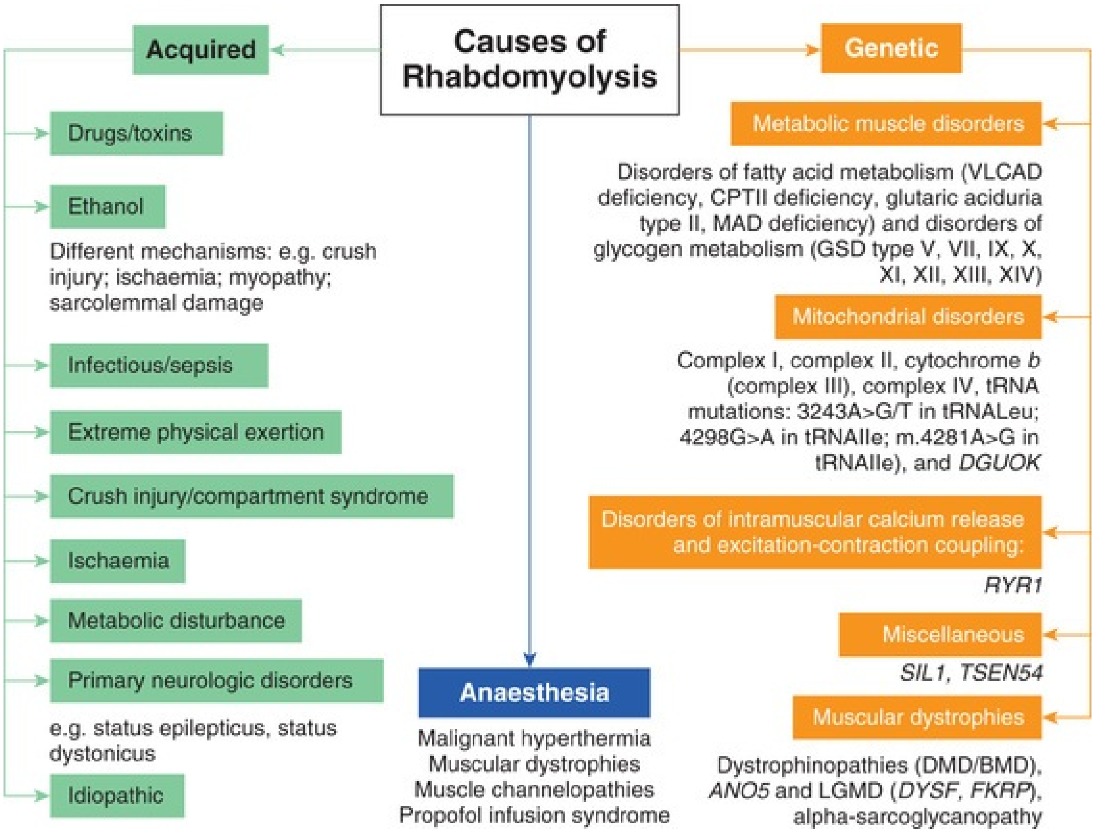
Causes of Rhabdomyolysis
Acquired
Drugs/toxins
Ethanol
Different mechanisms: e.g. crush injury; ischaemia; myopathy; sarcolemmal damage
Infectious/sepsis
Extreme physical exertion
Crush injury/compartment syndrome
Ischaemia
Metabolic disturbance
Primary neurologic disorders
e.g. status epilepticus, status dystonicus
Idiopathic
Anaesthesia
Malignant hyperthermia
Muscular dystrophies
Muscle channelopathies
Propofol infusion syndrome
Genetic
Metabolic muscle disorders
Disorders of fatty acid metabolism (VLCAD deficiency, CPTII deficiency, glutaric aciduria type II, MAD deficiency) and disorders of glycogen metabolism (GSD type V, VII, IX, X, XI, XII, XIII, XIV)
Mitochondrial disorders
Complex I, complex II, cytochrome b (complex III), complex IV, tRNA mutations: 3243A>G/T in tRNALeu; 4298G>A in tRNAIle; m.4281A>G in tRNAIle), and DGUOK
Disorders of intramuscular calcium release and excitation-contraction coupling:
RYR1
Miscellaneous
SIL1, TSEN54
Muscular dystrophies
Dystrophinopathies (DMD/BMD), ANO5 and LGMD (DYSF, FKRP), alpha-sarcoglycanopathy

FIG. 625.5 Examples of conditions associated with rhabdomyolysis. In individual cases, both genetic and environmental factors may combine to trigger a rhabdomyolysis event; anesthesia-induced rhabdomyolysis is the best-characterized example. VLCAD, very-long-chain acyl-CoA dehydrogenase; CPTII, carnitine palmitoyl-transferase-II; MAD, multiple acyl-CoA dehydrogenase; GSD, glycogen storage disease; tRNA, transfer ribonucleic acid; *DGUOK,* deoxyguanosine kinase gene; *RYR1,* ryanodine receptor 1 gene; *SIL1,* SIL1, *Saccharomyces cerevisiae,* homolog of; *TSEN54:* tRNA splicing endonuclease 54 gene, *S. cerevisiae,* homolog of; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; *ANO5,* anoctamin 5 gene; LGMD, limb-girdle muscular dystrophy; *DYSF,* dysferlin gene; *FKRP,* fukutin-related protein gene. (From Scalco RS, Gardiner AR, Pitceathly RDS, et al: Rhabdomyolysis: a genetic perspective, Orphanet J Rare Dis 10:51, 2015, Fig. 1.)

Table 625.7

Inherited Neuromuscular Disorders Associated With Episodes of Rhabdomyolysis*

GENE	**DISEASE NAME**	**BASELINE CREATINE KINASE LEVELS**	**PATTERN OF INHERITANCE**	**TRIGGER FOR RHABDOMYOLYSIS**
DISORDERS OF GLYCOGEN METABOLISM				
PYGM	Glycogen storage disease type V, McArdle disease	High	AR	Aerobic and anaerobic exercise, symptom onset within minutes
PFKM	Glycogen storage disease type VII, Tarui disease	High	AR	Aerobic and anaerobic exercise, symptom onset within minutes
ALDOA	Glycogen storage disease type XII	Normal Mild elevation, high	AR	Febrile illness, infection
ENO3	Glycogen storage disease type XIII	Normal High	AR	Aerobic and anaerobic exercise, symptom onset within minutes
PGAM2	Glycogen storage disease type X	High	AR	Aerobic and anaerobic exercise, symptom onset within minutes
PGK1	Phosphoglycerate kinase 1 deficiency	Normal High	X-linked	Aerobic and anaerobic exercise, symptom onset within minutes
PGM1	Glycogen storage disease type XIV	High	AR	Aerobic and anaerobic exercise, symptom onset within minutes, general anesthesia
PHKA1	Glycogen storage disease type IX	?	X-linked	Aerobic and anaerobic exercise, symptom onset within minutes
PHKB			AR	
DISORDERS OF FATTY ACID METABOLISM:				
ACADVL	Deficiency of very-long-chain acyl-CoA dehydrogenase	Normal High	AR	Fasting, prolonged exercise, cold, infections, fever
CPT2	Carnitine palmitoyl-transferase deficiency	Normal	AR	Prolonged exercise, fasting, fever, infection, high fat intake, cold exposure, heat, emotional stress, drugs
ETFA	Glutaric aciduria type II	Normal	AR	Physical exercise, fasting, irregular diet or infection
ETFB	Multiple acyl-coenzyme A dehydrogenase deficiency	Mildly to moderately elevated		
ETFDH				
MITOCHONDRIAL DISORDERS				
COI (MTCO1)	Mitochondrial disorder	Normal	Maternal inheritance	Prolonged or repetitive exercise
COII (MTCO2)	Mitochondrial disorder	Normal	Maternal inheritance	Exercise
COIII (MTCO3)	Mitochondrial disorder	Normal	Maternal inheritance	Prolonged exercise, viral illness, unknown cause
DGUOK	Mitochondrial disorder	?	AR	Viral illness
FDX1L	Mitochondrial disorder	Normal High	AR	?After exercise
HADHA	Mitochondrial trifunctional protein deficiency	Normal	AR	Strenuous physical activity
HADHB				
ISCU	Iron–sulphur cluster deficiency myopathy (mitochondrial disorder)	?	AR	Exercise

MTCYB	Mitochondrial disorder	Normal	?Sporadic mutations	Exercise
POLG1	One case report of rhabdomyolysis in association with propofol infusion syndrome		AD, AR	Propofol infusion syndrome
DISORDERS OF INTRAMUSCULAR CALCIUM RELEASE AND EXCITATION–-CONTRACTION COUPLING				
RYR1	Malignant hyperthermia susceptibility, exertional rhabdomyolysis, congenital myopathy	Normal or mildly to moderately elevated (usually < 1000 IU/L)	AD, AR	Heat, infection, alcohol, drugs, anesthetic (malignant hyperthermia susceptibility), and exercise
MUSCULAR DYSTROPHIES				
ANO5	Anoctaminopathy-5	High	AR	Unprovoked; no trigger has been identified
DMD	Duchenne muscular dystrophy, Becker muscular dystrophy	High	X-linked	Exercise, anesthetic drugs
DYSF	Limb–girdle muscular dystrophy 2B, Miyoshi myopathy	High	AR	Exercise
FKTN	Fukuyama congenital muscular dystrophy	High	AR	One case following the use of halothane and succinylcholine
FKRP	Limb–girdle muscular dystrophy 2I	High	AR	Exercise
MISCELLANEOUS				
LPIN1	Phosphatidic acid phosphatase deficiency	Normal, high	AR	Febrile illness, anesthesia, and fasting
SIL1	Marinesco-Sjögren syndrome	Normal, high	AR	Febrile infection
TSEN54	Pontocerebellar hypoplasia type 2	Normal, high	AR	Hyperthermia
TANGO2	Encephalocardiomyopathy	High	AR	Encephalocardiomyopathy crisis

[*] The table summarizes genes, disease names, baseline serum CK levels (between acute episodes of rhabdomyolysis), patterns of inheritance, and triggers for rhabdomyolysis. Genes commonly associated with rhabdomyolysis episodes are indicated in bold.

AD, autosomal dominant; AR, autosomal recessive.

(From Scalco RS, Gardiner AR, Pitceathly RDS, et al: Rhabdomyolysis: a genetic perspective, Orphanet J Rare Dis 10:51, 2015, Table 1.)

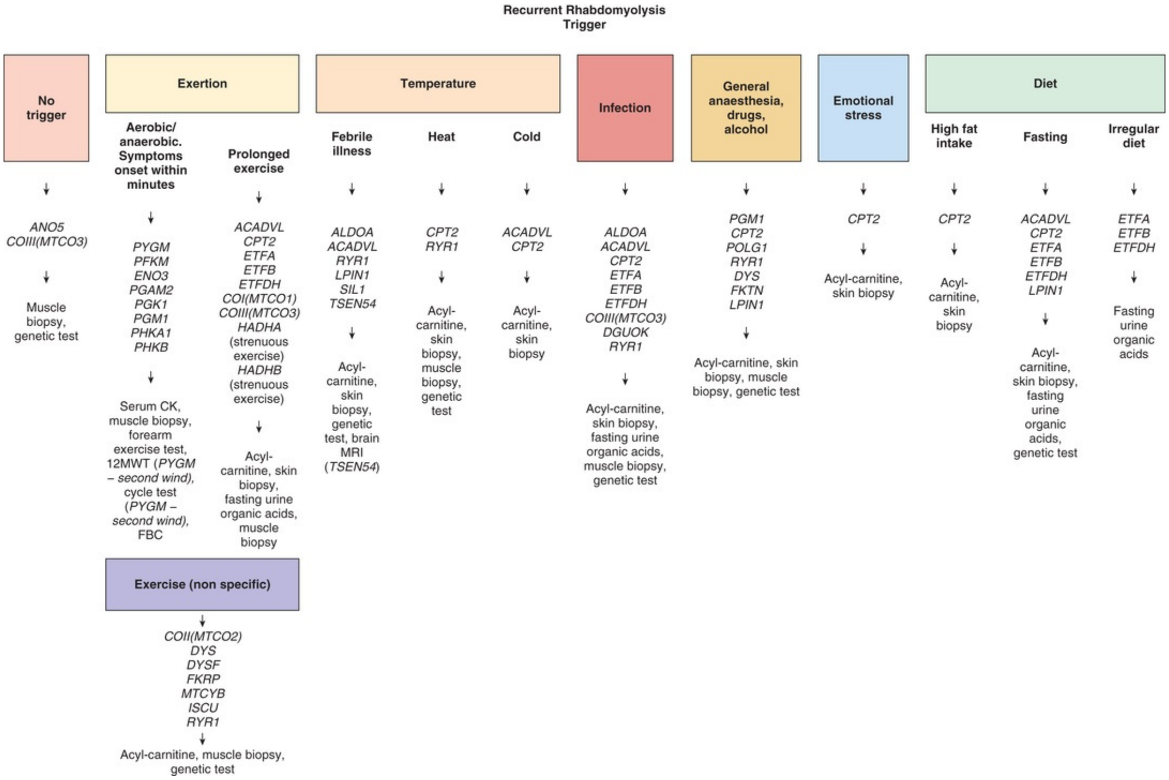
Recurrent Rhabdomyolysis Trigger
No trigger
ANO5
COIII(MTCO3)
Muscle biopsy, genetic test
Exertion
Aerobic/ anaerobic. Symptoms onset within minutes
PYGM
PFKM
ENO3
PGAM2
PGK1
PGM1
PHKA1
PHKB
Serum CK, muscle biopsy, forearm exercise test, 12MWT (PYGM – second wind), cycle test (PYGM – second wind), FBC
Prolonged exercise
ACADVL
CPT2
ETFA
ETFB
ETFDH
COI(MTCO1)
COIII(MTCO3)
HADHA (strenuous exercise)
HADHB (strenuous exercise)
Acyl-carnitine, skin biopsy, fasting urine organic acids, muscle biopsy
Exercise (non specific)
COII(MTCO2)
DYS
DYSF
FKRP
MTCYB
ISCU
RYR1
Acyl-carnitine, muscle biopsy, genetic test
Temperature
Febrile illness
ALDOA
ACADVL
RYR1
LPIN1
SIL1
TSEN54
Acyl-carnitine, skin biopsy, genetic test, brain MRI (TSEN54)
Heat
CPT2
RYR1
Acyl-carnitine, skin biopsy, muscle biopsy, genetic test
Cold
ACADVL
CPT2
Acyl-carnitine, skin biopsy
Infection
ALDOA
ACADVL
CPT2
ETFA
ETFB
ETFDH
COIII(MTCO3)
DGUOK
RYR1
Acyl-carnitine, skin biopsy, fasting urine organic acids, muscle biopsy, genetic test
General anaesthesia, drugs, alcohol
PGM1
CPT2
POLG1
RYR1
DYS
FKTN
LPIN1
Acyl-carnitine, skin biopsy, muscle biopsy, genetic test
Emotional stress
CPT2
Acyl-carnitine, skin biopsy
Diet
High fat intake
CPT2
Acyl-carnitine, skin biopsy
Fasting
ACADVL
CPT2
ETFA
ETFB
ETFDH
LPIN1
Acyl-carnitine, skin biopsy, fasting urine organic acids, genetic test
Irregular diet
ETFA
ETFB
ETFDH
Fasting urine organic acids

FIG. 625.6 Examples of different triggers of rhabdomyolysis. The identification of triggers may help in guiding genetic testing and may also aid in the interpretation of variants of uncertain significance identified on next-generation sequencing in patients presenting with RM. CK, creatine kinase; 12MWT, 12-minute walk test; FBC, full blood count. (From Scalco RS, Gardiner AR, Pitceathly RDS, et al: Rhabdomyolysis: a genetic perspective, Orphanet J Rare Dis 10:51, 2015, Fig. 2.)

Molecular Genetic Markers

Many DNA markers of hereditary myopathies, including the muscular dystrophies, and neuropathies are available from leukocytes in blood samples. If the clinical manifestations suggest a particular disease, these tests can provide a definitive diagnosis and not subject the child to more-invasive procedures, such as muscle biopsy. Other molecular markers are available only in muscle biopsy tissue.

Nerve Conduction Velocity

Motor and sensory nerve conduction velocity may be measured electrophysiologically by using surface electrodes. Neuropathies of various types are detected by decreased conduction. The site of a traumatic nerve injury may also be localized. The nerve conduction value at birth is about half of the mature value achieved by age 2 yr. Tables are available for normal values at various ages in infancy, including for preterm infants. Because the nerve conduction velocity study measures only the fastest conducting fibers in a nerve, 80% of the total nerve fibers must be involved before slowing in conduction is detected.

Electromyography

Electromyography (EMG) requires insertion of a needle into the belly of a muscle and recording of the electrical potentials in various states of contraction. It is less useful in pediatrics than in adult medicine, in part because of technical difficulties in recording these potentials in young children and in part because the best results require the patient's cooperation for full relaxation and maximal voluntary contraction of a muscle. Many children are too frightened to provide such cooperation. Characteristic EMG patterns distinguish denervation from myopathic involvement. The specific type of myopathy is not usually definitively diagnosed, but certain specialized myopathic conditions, such as myotonia, may be demonstrated. An EMG can transiently raise the serum CK level.

EMG combined with repetitive electrical stimulation of a motor nerve supplying a muscle to produce tetany is useful in demonstrating myasthenic decremental responses. Small muscles, such as the abductor digiti quinti of the hypothenar eminence, are used for such studies. Additional specialized tests, such as single myofiber EMG, may provide supplementary evidence in selected cases, but are performed only in large neuromuscular centers.

Imaging of Muscles and the Central Nervous System

Ultrasonography, computed tomography (CT) scans, and, more often, magnetic resonance imaging (MRI) are used to image muscle in many neuromuscular diseases. Although these methods are not always definitively diagnostic, in experienced hands, they provide a supplementary means of following the progression of disease over time. MRI is quite useful in identifying inflammatory myopathies of immune (dermatomyositis) or infectious (viral, bacterial, parasitic) origin. MRI is the study of choice to image the spinal cord, if a tumor or other structural lesion of the spinal cord is suspected as the cause of muscular dysfunction, and the nerve roots and plexus (e.g., brachial plexus). Brain MRI is indicated in some myopathies, such as the congenital muscular dystrophies, in which cerebral malformations often accompany the myopathy because the mutated gene responsible is expressed in both muscle and the developing brain.

Muscle Biopsy

The muscle biopsy is traditionally the most important and specific diagnostic study of most neuromuscular disorders. Molecular genetic diagnosis supersedes the muscle biopsy or renders it as secondary in diagnostic importance, to be used if a definitive diagnosis of a hereditary disease is not provided by molecular genetic testing in blood. Thus, the muscle biopsy is no longer essential for spinal muscular atrophy, most muscular dystrophies, and most congenital myopathies. Muscle biopsy remains useful in select cases, however, to provide morphologic details and metabolic profiles not revealed by genetic testing alone or as a primary diagnostic procedure if the genetics is equivocal or negative. Not only are neurogenic and myopathic processes distinguished by muscle biopsy, but also the type of myopathy and specific enzymatic deficiencies may be determined. *In addition, there are conditions that may have associated identifiable disease-causing genes in most but not all patients.*

The vastus lateralis (quadriceps femoris) is most frequently sampled. The deltoid should be avoided in most cases because it normally exhibits a 60–80% predominance of type I fibers, so that the distribution patterns of fiber types are difficult to recognize. Muscle biopsy is a simple outpatient procedure that may be performed under local anesthesia with or without femoral nerve block. Needle biopsies are preferred in some centers but are not percutaneous and require an incision in the skin similar to open biopsy; numerous samples must be taken to conduct an adequate examination of the tissue, and they provide inferior specimens. The volume of tissue from a needle biopsy is usually not adequate for all required studies, including supplementary biochemical studies, such as mitochondrial respiratory chain enzymes; a small, clean, open biopsy is therefore advantageous.

Histochemical studies of frozen sections of the muscle are obligatory in all pediatric muscle biopsies because many congenital and metabolic myopathies cannot be diagnosed from paraffin sections using conventional histologic stains. Immunohistochemistry is a useful supplement in some cases, such as for demonstrating dystrophin in suspected Duchenne muscular dystrophy or merosin in congenital muscular dystrophy. A portion of the biopsy specimen should be fixed for potential electron microscopy, but the ultrastructure has additional diagnostic value only in selected cases. Interpretation of muscle biopsy samples is complex and should be performed by an experienced pathologist. A portion of frozen muscle tissue should also be routinely saved for possible biochemical analysis (mitochondrial cytopathies, carnitine palmitoyltransferase, acid maltase).

Immunocytochemical reactivities can be applied to formalin-fixed, paraffin-embedded sections and do not require frozen sections. Some reactivities, such as slow and fast myosin, can distinguish fiber types and hence substitute for myofibrillar adenosine triphosphatase histochemical stains in frozen sections. An increasing number of sarcolemmal regional proteins can be demonstrated that are specific for each of the various muscular dystrophies and include the dystrophins, merosin, sarcoglycans, and dystroglycans. Ryanodine receptors, important in myasthenia gravis and in malignant hyperthermia, also can be demonstrated. In addition, immunocytochemical reactivities can distinguish the various types of inflammatory cells in autoimmune myopathies, including T and B lymphocytes and macrophages.

Nerve Biopsy

Nerve biopsy is applied less frequently because of the precision diagnosis of many hereditary peripheral neuropathies by less invasive and more specific genetic diagnosis. In some cases not definitively diagnosed by genetic testing, the nerve biopsy still provides valuable diagnostic information. The most commonly sampled nerve is the sural nerve, a pure sensory nerve that supplies a small area of skin on the lateral surface of the foot. Whole or fascicular biopsy specimens of this nerve may be taken. When the sural nerve is severed behind the lateral malleolus of the ankle, regeneration of the nerve occurs in more than 90% of cases, so that permanent sensory loss is not experienced. The sural nerve is often involved in many neuropathies in which the clinical manifestations are predominantly motor.

Electron microscopy is performed on most nerve biopsy specimens because many morphologic alterations cannot be appreciated at the resolution of a light microscope. Teased fiber preparations are sometimes useful in demonstrating segmental demyelination, axonal swellings, and other specific abnormalities, but these time-consuming procedures are not done routinely. Special stains may be applied to ordinary frozen or paraffin sections of nerve biopsy material to demonstrate myelin, axoplasm, and metabolic products.

Cardiac Assessment

Cardiac evaluation is important if myopathy is suspected because of involvement of the heart in muscular dystrophies and in inflammatory and metabolic myopathies (Table 625.8). Electrocardiography often detects early cardiomyopathy or conduction defects that are clinically asymptomatic. At times, a more complete cardiac workup, including echocardiography and consultation with a pediatric cardiologist, is indicated. Serial pulmonary function tests also should be performed in muscular dystrophies and in other chronic or progressive diseases of the motor unit.

Table 625.8

Gene Mutations and Cardiac Manifestations of the Neuromuscular Disorders

NEUROMUSCULAR DISORDER	GENE MUTATION	CARDIOMYOPATHY	ECG	ARRHYTHMIA
Duchenne muscular dystrophy	Dystrophin	Dilated	Short PR interval, prolonged QT interval, increased QT:PT ratio, right ventricular hypertrophy, deep Q waves II, III, aVF, %, v6	Increased baseline HR, decreased rate variability, premature ventricular beats (58% of patients by 24 yr of age)
Duchenne muscular dystrophy, female carrier	Dystrophin	Dilated	None	Uncommon
Becker muscular dystrophy	Dystrophin	Dilated	Conduction system disease	Similar to DMD
Emery Dreifuss autosomal dominant or proximal dominant limb–girdle muscular dystrophy IB	Lamin A/C	Dilated	Conduction abnormalities: prolonged PR interval and sinus bradycardia	Atrial fibrillation or flutter and atrial standstill. Ventricular dysrhythmias
Limb–girdle muscular dystrophy	α, β, γ, δ sarcoglycans	Dilated	Incomplete right bundle branch block, tall R waves in VI and	Uncommon

			V2 or left anterior hemiblock	
Congenital muscular dystrophy	Laminin alpha 2	Dilated	None	None
Limb–girdle muscular dystrophy 21	Fukutin	Dilated	AV node and bundle branch block, age at onset late teens and early 20s	Atrial arrhythmias and/or ventricular arrhythmias
Emery Dreifuss X-linked	Emerin	Rare	Conduction abnormalities: prolonged PR interval and sinus bradycardia	Atrial fibrillation or flutter and atrial standstill
Friedreich ataxia	Frataxin gene	Hypertrophic	T-wave inversion, left axis deviation and repolarization abnormalities	Ventricular arrhythmias
Myotonic dystrophy type 1, infantile	Myotonic dystrophy protein kinase gene	Hypertrophic	Conduction disease, prolonged PR interval, widening of the QRS complex	Atrial fibrillation and flutter, complete heart block
Myotonic dystrophy type 1	Myotonic dystrophy protein kinase gene	LV noncompaction	Conduction disease, prolonged PR interval, widening of the QRS complex	Atrial fibrillation and flutter, complete heart block

From Hsu DT: Cardiac manifestations of neuromuscular disorders in children, Paediatr Respir Rev 11:35-38, 2010, Table 1.

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CHAPTER 626

Developmental Disorders of Muscle

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A heterogeneous group of congenital neuromuscular disorders is known as the **congenital myopathies** (Tables 626.1 and 626.2). Most of these disorders have subcellular abnormalities that can be demonstrated only by muscle biopsy, by means of histochemistry, immunocytochemistry, and electron microscopy. In others, the muscle biopsy abnormality is not a subcellular anatomic defect but an aberration in the ratio and sizes of specific myofiber types. A genetic etiology is demonstrated in many of the congenital myopathies, and molecular genetic testing from blood samples may confirm the diagnosis without muscle biopsy in several of the congenital myopathies, muscular dystrophies, and spinal muscular atrophy.

Table 626.1

Classification of Muscular Dystrophies

MUSCULAR DYSTROPHY	INHERITANCE	OMIM NUMBER	LOCUS	GENE SYMBOL	PROTEIN	MAIN LOCALIZAT
Duchenne or Becker muscular dystrophy	X-R	310200 (Duchenne); 300376 (Becker)	Xq21·2	*DMD*	Dystrophin	Sarcolemma-associated pro
LIMB–GIRDLE MUSCULAR DYSTROPHY						
Type 1A	AD	159000	5q31	*MYOT*	Myotilin	Sarcomere-associated pro (Z-disc)
Type 1B	AD	159001	1q21·2	*LMNA*	Lamin A/C	Nuclear lamin associated pro
Type 1C	AD	607780	3p25	*CAV3*	Caveolin-3	Sarcolemma-associated pro
Type 1D	AD	603511	7q	*DNAJB6*	Co-chaperone DNAJB6	Sarcomere-associated pro (Z-disc)

Type 1E	AD	602067	6q23	*DES*	Desmin	Intermediate filament prote
Type 1F	AD	608423	7q32	Unknown	Unknown	Unknown
Type 1G	AD	609115	4p21	Unknown	Unknown	Unknown
Type 1H	AD	613530	3p23–p25	Unknown	Unknown	Unknown
Type 2A	AR	253600	15q15·1	*CAPN3*	Calpain-3	Myofibril-associated pro
Type 2B	AR	253601	2p13	*DYSF*	Dysferlin	Sarcolemma-associated pro
Type 2C	AR	253700	13q12	*SGCG*	γ-Sarcoglycan	Sarcolemma-associated pro
Type 2D	AR	608099	17q12–q21·33	*SGCA*	α-Sarcoglycan	Sarcolemma-associated pro
Type 2E	AR	604286	4q12	*SGCB*	β-Sarcoglycan	Sarcolemma-associated pro
Type 2F	AR	601287	5q33	*SGCD*	δ-Sarcoglycan	Sarcolemma-associated pro
Type 2G	AR	601954	17q12	*TCAP*	Titin cap (telethonin)	Sarcomere-associated pro (Z-disc)
Type 2H	AR	254110	9q31–q34	*TRIM32*	Tripartite motif-containing 32 (ubiquitin ligase)	Sarcomeric-associated pro (Z-disc)
Type 2I	AR	607155	19q13·3	*FKRP*	Fukutin-related protein	Putative glycosyltransf enzymes
Type 2J	AR	608807	2q31	*TTN*	Titin	Sarcomeric pr
Type 2K	AR	609308	9q34	*POMT1*	Protein-1-O-mannosyltransferase 1	Glycosyltransf enzymes
Type 2L	AR	611307	11p14·3	*ANO5*	Anoctamin 5	Transmembran protein, possib sarcoplasmic reticulum
Type 2M	AR	611588	9q31	*FKTN*	Fukutin	Putative glycosyltransf enzymes
Type 2N	AR	613158	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltransf enzymes
Type 2O	AR	613157	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransf enzymes
Type 2P	AR	613818	3p21	*DAG1*	Dystrophin-associated glycoprotein 1	Sarcomeric-associated pro
Type 2Q	AR	613723	8q24	*PLEC1*	Plectin 1	Sarcolemma-associated pro (Z-disc)
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY						
Type 1	AD	158900	4q35	Unknown	DUX4 and chromatin rearrangement	Nuclear

Type 2	AD	158901	18	Unknown	SMCHD1	Structural maintenance o chromosome's flexible hinge domain contai 1
EMERY-DREIFUSS MUSCULAR DYSTROPHY						
X-linked type 1	X-R	310300	Xq28	*EMD*	Emerin	Nuclear memb protein
X-linked type 2	X-R	300696	Xq27·2	*FHL1*	Four and a half LIM domain 1	Sarcomere an sarcolemma
Autosomal dominant	AD	2181350	1q21·2	*LMNA*	Lamin A/C	Nuclear memb protein
Autosomal recessive	AR	604929	1q21·2	*LMNA*	Lamin A/C	Nuclear memb protein
With nesprin-1 defect	AD	612998	6q25	*SYNE1*	Spectrin repeat containing, nuclear envelope 1 (nesprin-1)	Nuclear memb protein
With nesprin-2 defect	AD	5612999	4q23	*SYNE2*	Spectrin repeat containing, nuclear envelope 2 (nesprin-2)	Nuclear memb protein
Congenital muscular dystrophy with merosin deficiency (MDC1A)	AR	607855	6q2	*LAMA2*	Laminin α_2 chain of merosin	Extracellular matrix protein
Congenital muscular dystrophy	AR	604801	1q42	Unknown	Unknown	Unknown
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1C)	AR	606612	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransf enzymes
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (MDC1D)	AR	608840	22q12	*LARGE*	Like-glycosyl transferase	Putative glycosyltransf enzymes
Fukuyama congenital muscular dystrophy	AR	253800	9q31–q33	*FCMD*	Fukutin	Putative glycosyltransf enzymes
WALKER–WARBURG SYNDROME						
With fukutin defect	AR	236670	9q31–q33	*FCMD*	Fukutin	Putative glycosyltransf enzymes
With protein-O-mannosyltransferase 1 defect	AR	236670	9q34	*POMT1*	Protein-1-O-mannosyltransferase 1	Glycosyltrans enzymes
With protein-O-mannosyltransferase 2 defect	AR	236670	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltrans enzymes

With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect	AR	236670	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransf enzymes
With fukutin-related protein defect	AR	236670	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransf enzymes
MUSCLE–EYE–BRAIN DISEASE						
With protein-O-linked mannose β 1,2-N-aminyltransferase 1 defect	AR	253280	1p34	*POMGNT1*	Protein-O-linked mannose β 1,2-N-aminyltransferase 1	Glycosyltransf enzymes
With fukutin-related protein defect	AR	253280	19q13	*FKRP*	Fukutin-related protein	Putative glycosyltransf enzymes
With protein-O-mannosyltransferase 2 defect	AR	253280	14q24	*POMT2*	Protein-O-mannosyltransferase 2	Glycosyltransf enzymes
Congenital muscular dystrophy caused by glycosylation disorder	AR	NA	9q34·1	*DPM2*	Dolichyl-phosphate mannosyltransferase polypeptide 2	Glycosyltransf enzymes
Congenital muscular dystrophy caused by glycosylation disorder	AR	NA	1q21·3	*DPM3*	Dolichyl-phosphate mannosyltransferase polypeptide 3	Glycosyltransf enzymes
Congenital muscular dystrophy with mitochondrial structural abnormalities	mtDNA	602541	22q13	*CHKB*	Choline kinase	Sarcolemmal a mitochondrial membrane
Congenital muscular dystrophy with rigid spine syndrome	AR	602771	1p36	*SEPN1*	Selenoprotein N1	Endoplasmic reticulum prot
ULLRICH SYNDROME						
With collagen type VI subunit α_1 defect	AR	254090	21q22·3	*COL6A1*	Collagen type VI, subunit α_1	Extracellular matrix protein
With collagen type VI subunit α_2 defect	AR	254090	21q22·3	*COL6A2*	Collagen type VI, subunit α_2	Extracellular matrix protein
With collagen type VI subunit α_3 defect	AR	254090	2q37	*COL6A3*	Collagen type VI, subunit α_3	Extracellular matrix protein
Congenital muscular dystrophy with integrin α_7 defect	AR	613204	12q13	*ITGA7*	Integrin α_7	External sarcolemmal protein
Congenital muscular dystrophy with integrin α_9 defect	AR	NA	3p21·3	*ITGA9*	Integrin α_9	External sarcolemmal protein

Muscular dystrophy with generalized lipodystrophy	AR	NA	17q21–q23	*PTRF*	Polymerase I and transcript release factor (cavin-1)	T tubules and sarcolemma
Oculopharyngeal muscular dystrophy	AD or AR	164300	14q11·2	*PABPN1*	Polyadenylate-binding protein nuclear 1	Unknown

AD, autosomal dominant; AR, autosomal recessive; NA, not assigned; OMIM, Online Mendelian Inheritance in Man; X-R, X-linked recessive.

From Mercuri E, Muntoni F: Muscular dystrophies, Lancet 381:845-858, 2013, Table 1.

Table 626.2

Clinical Signs of Muscular Dystrophy

MUSCULAR DYSTROPHY	MOTOR FUNCTION	DISTRIBUTION OF WEAKNESS	RIGID SPINE	CARDIOMYOPATHY	RESPIRATORY IMPAIRMENT	DISEA COURS
CONGENITAL-ONSET MUSCULAR DYSTROPHY						
Congenital muscular dystrophy with merosin deficiency	Independent ambulation generally not achieved in patients with absent merosin	Upper limbs > lower limbs	–	Not frequent	++	Slowly progres
Congenital muscular dystrophy and abnormal glycosylation of dystroglycan (Walker-Warburg syndrome, muscle–eye–brain disease, congenital muscular dystrophy type 1C, etc.)	Independent ambulation generally not achieved	Upper limbs > lower limbs	–	Not frequent	+	Slowly progres
Congenital muscular dystrophy with rigid spine syndrome type 1 (SEPN1)	Ambulation achieved	Axial muscles > limbs	++	–	Early respiratory failure	Progres of respirat signs > motor s
Ullrich syndrome	Ambulation achieved in ~50% but lost by middle teens	Proximal and axial	++	–	Early respiratory failure	Progres of respirat and mo signs
FROM EARLY-ONSET TO CHILDHOOD-ONSET MUSCULAR DYSTROPHY						
Duchenne muscular dystrophy	Independent ambulation achieved,	Proximal > distal (pattern A)	–	++	++	Progres of moto cardiac,

	but lost before age of 13 yr					respirat signs
Emery-Dreifuss muscular dystrophy with lamin AC deficiency (type 2)	Ambulation achieved in all cases except for rare cases with congenital onset	Scapuloperoneal (pattern B)	++	++	In adulthood in the typical form, but also in childhood (congenital variants)	Slowly progres
Limb–girdle muscular dystrophy with lamin AC deficiency (type 1B)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	+	++	In adulthood	Progres of cardi signs > motor s
Limb–girdle muscular dystrophy with calpain deficiency (type 2A)	Ambulation achieved	Proximal > distal (pattern A)	+	–	Not frequent	Slow progres
CHILDHOOD-ONSET AND ADULTHOOD-ONSET MUSCULAR DYSTROPHY						
Becker muscular dystrophy	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	–	++	Not frequent	Progres with substan variabil
Limb–girdle muscular dystrophy with sarcoglycan deficiency (types 2C, 2D, 2E, 2F)	Independent ambulation achieved, generally lost in the 2nd decade	Proximal > distal (pattern A)	–	++	++	Progres of moto cardiac, respirat signs
Limb–girdle muscular dystrophy with abnormal glycosylation of dystroglycan (types 2I, 2K, 2L, 2M, 2N, 2O)	Independent ambulation achieved, variable progression	Proximal > distal (pattern A)	–	++	+(+)	Progres
Limb–girdle muscular dystrophy with dysferlin deficiency (type 2B)	Independent ambulation always achieved	Both pattern A and pattern E	–	–	–	Progres in adultho
Limb–girdle muscular dystrophy with telethonin deficiency (type 2G)	Independent ambulation achieved, generally lost in the 4th decade	Proximal > distal (pattern A); in some pattern B	–	+	+	Progres in adultho
Limb–girdle muscular dystrophy with titin deficiency (type 2J)	Independent ambulation achieved	Proximal > distal (pattern A) but also pattern E	–	–	–	Roughl half los ambula in adultho
Facioscapulohumeral	Independent	Pattern D	–	–	Uncommon and	Slowly

dystrophy	ambulation achieved, variable progression				mild	progres
Emery-Dreifuss muscular dystrophy with merin deficiency (type 1)	Independent ambulation achieved, variable progression	Scapuloperoneal (pattern B)	+	++	Not frequent	Progres of cardi signs > motor s
ADULT-ONSET MUSCULAR DYSTROPHY						
Limb–girdle muscular dystrophy with anoctamin deficiency (type 2L)	Onset in adulthood, 8 : 1 ratio of men to women	Mainly lower limbs pattern A, rarely pattern E	–	–	–	Slowly progres in adultho
Limb–girdle muscular dystrophy type 1A (myotilin)	Independent ambulation achieved	Proximal > distal (pattern A)	–	–	–	General slowly progres in adultho
Limb–girdle muscular dystrophy with caveolin deficiency (type 1C)	Independent ambulation achieved; rippling might be seen before weakness	Proximal and distal	–	+	–	Slowly progres variable

–, Absent; +, mild; ++, severe; +(+), variable; CK, creatine kinase; N, normal.

From Mercuri E, Muntoni F: Muscular dystrophies, Lancet 381:845-858, 2013, Table 2.

Most congenital myopathies are *nonprogressive conditions*, but some patients show slow clinical deterioration accompanied by additional changes in their muscle histology. In some congenital myopathies, such as severe neonatal nemaline myopathy, the clinical expression can be life-threatening because of dysphagia and respiratory and/or cardiac insufficiency. Cardiomyopathy develops in some patients with congenital myopathies (Tables 626.3 and 626.4). Most of the diseases in the category of congenital myopathies are hereditary, some as classical mendelian traits and others as sporadic or novel point mutations. Though clinical features, including phenotype, can raise a strong suspicion of a congenital myopathy, the definitive diagnosis is determined by the histopathologic findings in the muscle biopsy specimen or by genetic testing in lymphocytes if a specific known mutation is suspected. The morphologic and histochemical abnormalities differ considerably from those of the muscular dystrophies, spinal muscular atrophies, and neuropathies, but there may be co-expression, exemplified by congenital muscle fiber–type disproportion in infantile myotonic dystrophy. Many are reminiscent of the embryologic development of muscle, thus suggesting possible defects in the genetic regulation of muscle development.

Table 626.3

Cardiac Involvement in Muscular Dystrophies

MUSCULAR DYSTROPHY	ONSET AND FIRST SIGNS	PROGRESSION	CARDIAC DEATH	SURVEILLANCE
Duchenne muscular dystrophy	Dilated cardiomyopathy with reduced left-ventricular ejection fraction after 10 yr of age	Dilated cardiomyopathy in almost all patients by 18 yr of age. Ventricular dysrhythmias occur in older patients	Congestive heart failure or sudden death in 20% of patients, although the contribution of heart to death of ventilated patients is now well established	Echocardiography every 2 yr in the 1st decade of life and annually after 10 yr of age (or more frequently if abnormalities are identified)
Becker muscular dystrophy	Dilated cardiomyopathy, generally after 10 yr of age	Present in 40% of patients older than 18 yr and more than 80% of those older than 40 yr. Most patients develop dilated cardiomyopathy followed by ventricular arrhythmias	Death from congestive heart failure and arrhythmias is estimated to occur in up to 50% of cases. Cardiac transplants reported	Echocardiography at least every 5 yr
Myotonic dystrophy	Cardiac abnormalities can occur as early as the 2nd decade of life	Conduction deficits occur in about 65% of adult patients	20–30% of patients; mean 54 yr of age. Sudden death is mainly caused by conduction blocks, but ventricular tachyarrhythmias are also a possible cause of death	ECG yearly. Holter monitoring is recommended in patients with ECG abnormalities to detect asymptomatic conduction blocks and arrhythmias
EMERY-DREIFUSS MUSCULAR DYSTROPHY				
X-linked recessive Emery-Dreifuss muscular dystrophy (type 1)	Conduction disturbances generally in the 2nd decade	Ventricular myocardium might become involved, leading to mild ventricular dilation and low-to-normal systolic function	Sudden death is by far the most common cause of death and can be very unpredictable	ECG and yearly Holter monitoring are indicated. Pacemaker implantation should be considered if sinus node or atrioventricular node disease develops. Defibrillator might be needed in some patients
Emery-Dreifuss muscular dystrophy 2 and limb–girdle muscular dystrophy 1B	Conduction disease and cardiac failure	Dysrhythmias (sinus bradycardia, atrioventricular conduction block, or atrial arrhythmias)	Sudden death reported also in patients with pacemaker. Rare death with	ECG and yearly Holter monitoring are indicated. Defibrillator implantation should be considered because

		present in 92% of patients older than 30 yr	defibrillator also reported. Cardiac failure. Cardiac transplants reported	pacemaker does not have a substantial effect on mortality rates
LIMB–GIRDLE MUSCULAR DYSTROPHY				
Sarcoglycanopathies	ECG and/or echocardiographic abnormalities reported in 20–30% of patients (especially β and δ variants; less common in α variant)	Severe dilated cardiomyopathy and lethal ventricular arrhythmias might occur in patients with Duchenne muscular dystrophy–like dystrophy	Typically by cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb–girdle muscular dystrophy 2I	Cardiac involvement reported in 29–62% of limb–girdle muscular dystrophy 2I patients. Dilated cardiomyopathy may start in teenage years	Symptomatic cardiac failure over time, at a mean age of 38 yr (range: 18-58 yr)	Cardiac failure. Cardiac transplants reported	No evidence-based standards of care exist, but experts have made recommendations
Limb–girdle muscular dystrophy 1E	Dilated, restrictive, hypertrophic cardiomyopathies and arrhythmias. Cardiac involvement can precede muscle weakness in some patients	Major cardiac signs, such as atrioventricular block, can be the presenting symptom or occur within a decade of onset of muscle weakness	Life-threatening cardiac complications in roughly 50% of patients, at a mean age of 40 yr, including sudden death, end-stage heart failure, atrioventricular block, and syncope	No evidence-based standards of care exist, but experts have made recommendations
CONGENITAL MUSCULAR DYSTROPHY				
Congenital muscular dystrophy merosin muscular dystrophy type C1A	Occasional reports of reduced left ventricular systolic function	Not well characterized	Rare by cardiac failure	No evidence-based standards of care exist, but experts have made recommendations
Fukuyama congenital muscular dystrophy	Systolic left-ventricular dysfunction may develop in the 2nd decade	Symptomatic cardiac failure over time	Death from congestive heart failure might occur by the age of 20 yr	No evidence-based standards of care exist, but experts have made recommendations
Muscular dystrophy type C1C	Dilated cardiomyopathy reported in young children	Not well characterized	Not reported	No evidence-based standards of care exist, but experts have made recommendations
Facioscapulohumeral muscular dystrophy	Uncommon	Not well characterized	Not reported	No evidence-based standards of care exist, but experts have made recommendations

ECG, electrocardiogram.

From Mercuri E, Muntoni F: Muscular dystrophies, Lancet 381:845-858, 2013, Table 3.

Table 626.4

Myopathies Developing Ventricular Arrhythmias or Sudden Cardiac Death

MYOPATHIES	ARRHYTHMIAS	SUDDEN CARDIAC DEATH
DMD, XL-EDMD, MD1, MD2, RyR-channelopathy, mitochondrial MP, FAODs, VLCAD, Danon disease	VTs	r
BMD	Reentry VT	r
Laminopathy	VT, ventricular fibrillation	r
FSH, hypokalemic periodic paralysis	VTs	nr
MFM	Nonsustained VT	r
Desminopathy, MELAS	Sustained VT	r
NARP, PEO	Nonsustained VTs	nr
KSS	Torsade de pointes	r
CPT-II deficiency	Cardiac arrest	r
Barth syndrome	Ventricular arrhythmia	r

BMD, Becker muscular dystrophy; CPT, carnitine palmityl transferase; DMD, Duchenne muscular dystrophy; FSH, facioscapulohumeral muscular dystrophy; MD1 MD2, myotonic dystrophy; MELAS, mitochondrial encephalomyelopathy with lactic acidosis and stroke; MFM, myofibrillar myopathy; MP, myopathy; NARP, neuropathy, ataxia, and retinitis pigmentosa; nr, not reported; PEO, progressive external ophthalmoplegia; r, reported; XL-EDMD, Emery-Dreifuss muscular dystrophy.

Modified from Finsterer J, Stollberger C, Keller H: Arrhythmia-related workup in hereditary myopathies, J Electrocardiol 45:376-384, 2012, Table 5.

Congenital myopathies often show closer genetic relationships than previously appreciated between entities that have quite distinct pathologic phenotypes in the muscle biopsy and distinctiveness in clinical expression with a degree of overlap. Mutation of the *tropomyosin-3* (*TPM3*) gene is one of the well-documented etiologies of nemaline myopathy, but identical genetic mutations of this gene are also shown to be capable of causing isolated congenital fiber–type disproportion without nemaline rods, cap myopathy, centronuclear (“myotubular”) myopathy, and central core/minicore disease.

Myogenic Regulatory Genes and Genetic Loci of Inherited Diseases of Muscle

A family of four myogenic regulatory genes shares encoding transcription factors of basic helix–loop–helix proteins associated with common DNA nucleotide sequences. These genes direct the differentiation of striated muscle from any undifferentiated mesodermal cell. The earliest basic helix-loop-helix gene to program the differentiation of myoblasts is myogenic factor 5 *(MYF5).* The second gene, *myogenin,* promotes fusion of myoblasts to form myotubes. *Herculin* (also known as *MYF6*) and *MYOD1* are the other two myogenic genes. *Myf5* cannot support myogenic differentiation without *myogenin, MyoD,* and *MYF6.* Each of these four genes can activate the expression of at least one other and, under certain circumstances, can autoactivate as well. Another gene known as **myomaker** also facilitates myoblast fusion. The expression of *MYF5* and of *herculin* is transient in early ontogenesis but returns later in fetal life and persists into adult life.

The human locus of the *MYOD1* gene is on chromosome 11, very near to the domain associated with embryonal rhabdomyosarcoma. The genes *Myf5* and *herculin* are on chromosome 12, and *myogenin* is on chromosome 1.

The myogenic genes are activated during muscle regeneration, recapitulating the developmental process; *MyoD* in particular is required for myogenic stem cell (progenitor satellite cell) activation in adult muscle. The *PAX3, PAX7,* and *WNT3a* genes also play important roles in myogenesis and interact with each of the four basic genes mentioned above. Another gene, *myostatin,* is a negative regulator of muscle development by preventing myocytes from differentiating. The precise integrative roles of the myogenic genes in developmental myopathies are not yet fully defined.

The myogenic genes are important not only for fetal myogenesis but also for regeneration of muscle at any age, particularly in degenerative diseases such as muscular dystrophies and autoimmune inflammatory myopathies and in injuries of muscle secondary to trauma or to toxins. Satellite cells in mature muscle that mediate regeneration have the same somitic origin as embryonic muscle progenitor cells, but the genes that regulate them differ. *Pax3* and *Pax7* mediate the migration of primitive myoblast progenitors from the myotomes of the somites to their peripheral muscle sites in the embryo, but only one of two *Pax7* genes continues to act postnatally for satellite cell survival. Then it, too, no longer is required after the juvenile period for muscle satellite (i.e., stem) cells to become activated for muscle regeneration.

Treatment of Congenital Myopathies

Treatment remains largely supportive care for respiratory insufficiency and feeding and swallowing difficulties in particular, but genetic approaches specific for identified mutations are being investigated and may eventually reverse some of the most disabling clinical deficits. Administration of steroids, as well as other antiinflammatory agents, which is useful in many patients with Duchenne muscular dystrophy, is not effective for the congenital myopathies. Long-term outcomes for some congenital myopathies are noted in Figs. 626.1 and 626.2 .

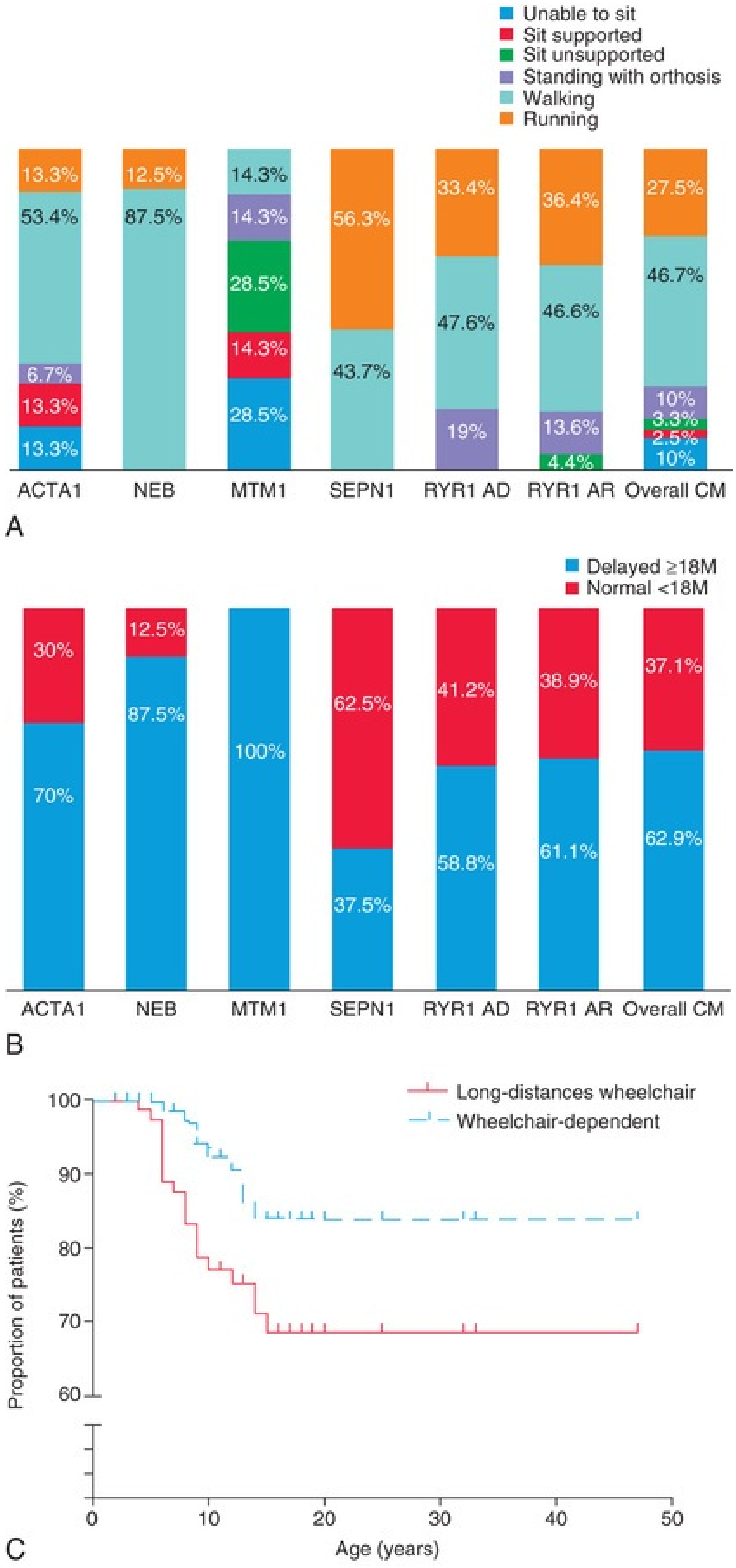
Unable to sit
Sit supported
Sit unsupported
Standing with orthosis
Walking
Running
13.3%
53.4%
6.7%
13.3%
13.3%
12.5%
87.5%
14.3%
14.3%
28.5%
14.3%
28.5%
56.3%
43.7%
33.4%
47.6%
19%
36.4%
46.6%
13.6%
4.4%
27.5%
46.7%
10%
3.3%
2.5%
10%
ACTA1
NEB
MTM1
SEPN1
RYR1 AD
RYR1 AR
Overall CM
A
Delayed ≥18M
Normal <18M
30%
70%
12.5%
87.5%
100%
62.5%
37.5%
41.2%
58.8%
38.9%
61.1%
37.1%
62.9%
ACTA1
NEB
MTM1
SEPN1
RYR1 AD
RYR1 AR
Overall CM
B
Long-distances wheelchair
Wheelchair-dependent
Proportion of patients (%)
100
90
80
70
60
0
10
20
30
40
50
Age (years)
C

FIG. 626.1 Motor abilities. **A,** Maximal motor ability: all patients with *SEPN1* and *NEB* mutations walked independently, whereas motor ability was more variable with other genetic backgrounds. **B,** Walking age: the majority of ambulant patients walked late (39.3%) or at the upper limit of normal at 18 mo (23.6%). At last follow-up, 3.2% were younger than 18 mo. **C,** Kaplan-Meier curve showing wheelchair use in patients who achieved independent ambulation: 20 of 89 (22.5%) started with a manual wheelchair for long distances, whereas a further deterioration of motor performance was observed in 8 of 20, who became wheelchair-bound. *ACTA1* , skeletal muscle α-actin; AD, autosomal dominant; AR, autosomal recessive; CM, congenital myopathy; *MTM1* , myotubularin; *NEB* , nebulin; *RYR1* , ryanodine receptor type 1; *SEPN1* , selenoprotein N. (From Colombo I, Scoto M, Manzur AY, et al: Congenital myopathies, Neurology 84:28-35, 2015. Fig. 3.)

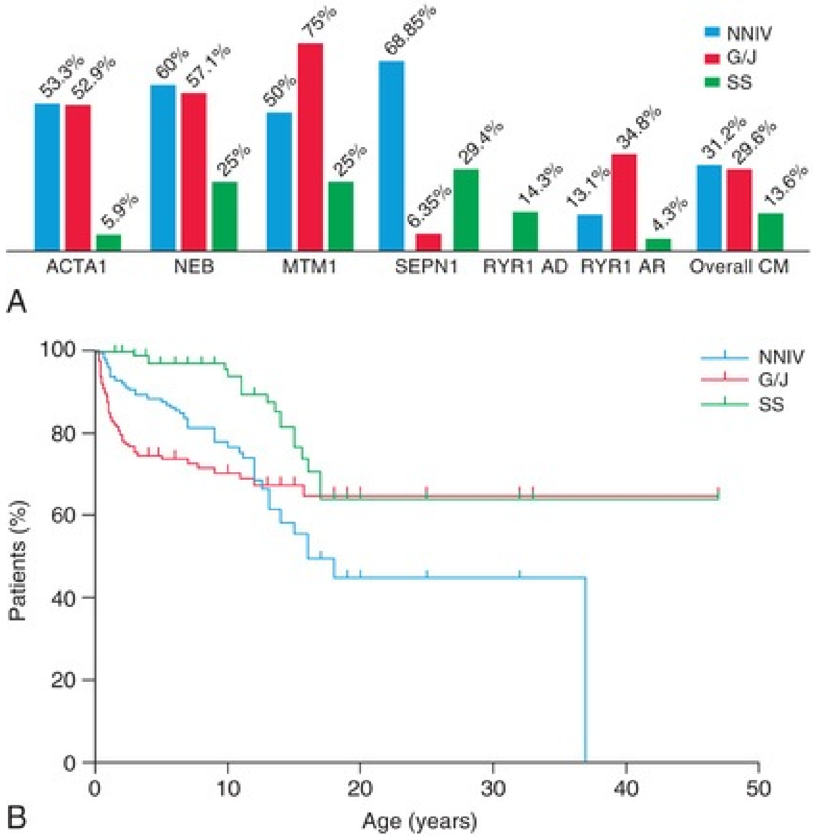

FIG. 626.2 Respiratory, feeding, and orthopedic procedures. **A,** Prevalence of NNIV, G/J, and SS according to genetic background: overall about one third of cases required NNIV and G/J insertion. Only a minority of cases required scoliosis surgery. **B,** Kaplan-Meier curves showing ventilation, G/J, and SS-free patients: NNIV was started at a mean age of 8.53 yr,

whereas G/J was placed earlier, at a mean age of 2.74 yr, usually within the first year. SS was performed at a mean age of 12.0 yr. AD, autosomal dominant; AR, autosomal recessive; CM, congenital myopathy; G/J, gastrostomy/jejunostomy; NNIV, nocturnal noninvasive ventilation; SS, scoliosis surgery. (From Colombo I, Scoto M, Manzur AY, et al: Congenital myopathies, Neurology 84:28-35, 2015, Fig. 4.)

626.1

Myotubular Myopathy (Centronuclear Myopathy)

Harvey B. Sarnat

The term **myotubular myopathy** is a misnomer because it implies maturational arrest of fetal muscle during the myotubular stage of development at 8-15 wk of gestation. It was based on the morphologic appearance of myofibers as a row of central nuclei and mitochondria within a core of cytoplasm, with contractile myofibrils forming a cylinder around this core (Fig. 626.3). These morphologically abnormal myofibers are not true fetal myotubes; hence, the more neutral and descriptive term **centronuclear myopathy** is preferred.

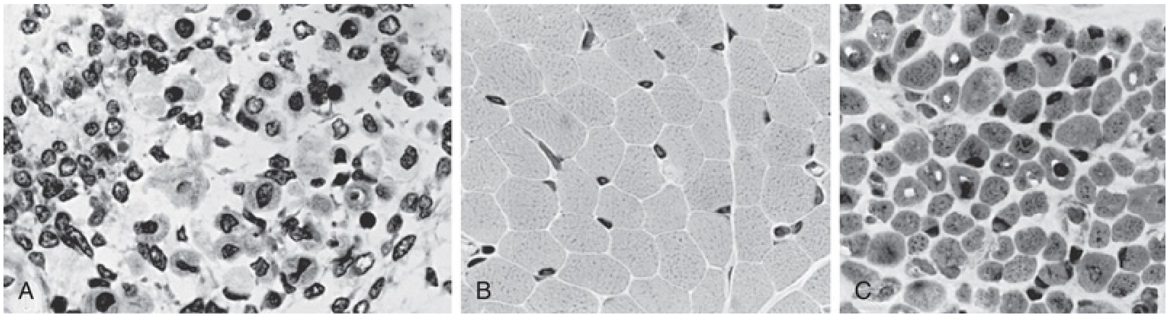

FIG. 626.3 Cross section of muscle from a 14 wk old human fetus **(A),** a normal full-term neonate **(B),** and a term neonate with X-linked recessive myotubular myopathy **(C).** Myofibers have large central nuclei in the fetus

and in the myotubular myopathy patient, and nuclei are at the periphery of the muscle fiber in the term neonate as in the adult (hematoxylin and eosin, ×500).

Pathogenesis

The common pathogenesis involves loss of myotubularin protein, leading to structural and functional abnormalities in the organization of T-tubules and sarcoplasmic reticulum and defective excitation-contraction coupling. Though animal models knocked out for *Mtm1* show severe reduction of ryanodine receptor 1–mediated calcium release, human *MTM1* mutations do not affect calcium homeostasis and calcium release mediated through the ryanodine receptor 1, though they do affect myotube size and nuclear content. In true fetal myotubes, the peripheral migration of central nuclei and the core of internuclear mitochondria is initiated by the regression of fetal vimentin intermediate filaments at 15-20 wk gestation that hold these structures in the center of the myotube, but this is not the mechanism of centronuclear myopathies, except perhaps in *neonatal myotonic dystrophy,* which does involve maturational arrest of some myofibers.

Clinical Manifestations

Fetal movements can decrease in late gestation. Polyhydramnios is a common complication because of pharyngeal weakness of the fetus and inability to swallow amniotic fluid.

At birth, affected infants have a thin muscle mass involving axial, limb girdle, and distal muscles; severe generalized hypotonia; and diffuse weakness. Respiratory efforts may be ineffective, requiring ventilatory support. Gavage feeding may be required because of weakness of the muscles of sucking and deglutition. The testes are often undescended. Facial muscles may be weak, but infants *do not* have the characteristic facies of myotonic dystrophy. Ptosis may be a prominent feature. Ophthalmoplegia is observed in a few cases. The palate may be high. The tongue is thin, but fasciculations *are not* seen. Tendon stretch reflexes are weak or absent.

Myotubular myopathy is not associated with cardiomyopathy (mature cardiac muscle fibers normally have central nuclei), but one report describes complete atrioventricular block without cardiomyopathy in a patient with confirmed X-linked myotubular myopathy. Congenital anomalies of the central nervous system (CNS) or of other systems are not associated. A single patient with progressive dementia was reported, who had a mutation removing the start signal of exon 2. Patients with much milder symptoms or a much later age of onset with mutations in the same gene are also known. Some of these are *manifesting* carriers.

Laboratory Findings

Serum levels of creatine kinase (CK) are normal. Electromyography does not show evidence of denervation; results are usually normal or show minimal nonspecific myopathic features in early infancy. Nerve conduction velocity may be slow but is usually normal. The electrocardiogram appears normal. Chest radiographs show no cardiomegaly; the ribs may be thin.

Diagnosis

If the diagnosis is strongly suspected from the clinical presentation, especially if this diagnosis was confirmed in a sibling, genetic tests can be performed in the neonatal period. In most cases the diagnosis is not so evident, but the muscle biopsy findings are diagnostic at birth, even in premature infants. More than 90% of muscle fibers are small and have centrally placed, large vesicular nuclei in a single row. Spaces between nuclei are filled with sarcoplasm containing mitochondria. Histochemical stains for oxidative enzymatic activity and glycogen reveal a central distribution as in fetal myotubes. The cylinder of myofibrils shows mature histochemical differentiation with adenosine triphosphatase stains. The connective tissue of muscle spindles, blood vessels, intramuscular nerves, and motor end plates is mature. Ultrastructural features other than those that define the disease are also mature. Electron microscopy shows disorganized triads and focal loss of myofilaments. Vimentin and desmin show strong immunoreactivity in muscle fibers in congenital centronuclear myopathy and no demonstrable activity in normal term neonatal muscle. Several myotubularins are present in circulating platelets and may prove to be a simple noninvasive screening test in patients suspected of having this disease. The molecular genetic marker in blood is available also for early prenatal diagnosis if suspicion is strong because of a family history. Prenatal diagnosis by amniocentesis is feasible in strongly suspected involved fetuses. Table 626.5 distinguishes centronuclear myopathy from other congenital myopathies.

Table 626.5

Specific Congenital Myopathies: Distinguishing Clinical Features

MYOPATHY	NEONATAL HYPOTONIA AND WEAKNESS	SEVERE FORM WITH NEONATAL DEATH	FACIAL WEAKNESS	PTOSIS	EXTRAOCULAR MUSCULAR WEAKNESS
Central core disease	+	0	±	0	0
Nemaline myopathy	+	+	+	0	0
Myotubular myopathy (centronuclear myopathy)	+	+	+	+	+
Congenital fiber-type disproportion	+	±	±	0	+

+ , Often a prominent feature; ±, variably a prominent feature; 0, not a prominent feature.

From Volpe JJ: Neurology of the newborn, ed 5, Philadelphia, 2008, Elsevier Saunders, p. 820.

Genetics

At least five genes are involved in this disorder and account for approximately 80% of patients. These include mutations in myotubularin (*MTM1* gene) with X-linked severe manifestations; dynamin 2 *(DNM2)* with autosomal dominant or sporadic occurrence; amphiphysin 2 *(BIN1)* and titin *(TTN)* mutations with autosomal recessive inheritance and ryanodine receptor 1 *(RYR1),* with autosomal recessive or sporadic occurrence.

X-linked recessive inheritance is the most common trait in this disease affecting males. The mothers of affected infants are clinically asymptomatic, but their muscle biopsy specimens show minor alterations. Genetic linkage on the X chromosome has been localized to the Xq28 site, a locus different from the Xp21 gene of Duchenne and Becker muscular dystrophies. A deletion in the responsible *MTM1* gene has been identified. It encodes a protein called myotubularin. This gene belongs to a family of similar genes encoding enzymatically active and inactive forms of phosphatidylinositol-3-phosphatases that form dimers. *MTM1* , dynamin-2, and amphiphysin all are localized to the T-tubule wall in triads. This crucial region is where the action potential releases a signal to the ryanodine receptor to release calcium. The pathogenesis is in the regulation of enzymatic activity and binding to other proteins induced by dimer interactions. Although only a single *MTM1* gene is involved, five distinct point mutations and many different alleles, as well as large duplications, can produce the same clinical disease. Mutations in the dynamin-2 protein result in an autosomal dominant form of centronuclear myopathy and may account for up to half of all patients with centronuclear myopathy, but these cases usually are mild and might not manifest clinically until adult life as diffuse, slowly progressive weakness and generalized muscular pseudohypertrophy.

Other rarer centronuclear myopathies also are known; some are autosomal recessive and affect both sexes and others are sporadic and of unknown genetic origin. The recessive forms are sometimes divided into an early-onset form with or without ophthalmoplegia and a late-onset form without ophthalmoplegia.

Treatment

Only supportive and palliative treatment is presently available. Progressive scoliosis may be treated by long posterior fusion. Genetic and neuropathologic studies of X-linked centronuclear (myotubular) myopathy have led to effective gene therapy in mice and in dogs, so that the animals are more ambulatory and have improved weakness; the therapy results in long-term expression of the myotubularin transgene with normal muscular performance and neurologic function in the absence of muscle pathology. Human trials of gene therapy for X-linked centronuclear myopathy are in progress.

Prognosis

Approximately 75% of severely affected neonates with the X-linked disease die within the first few weeks or months of life. Survivors do not experience a progressive course but have major physical handicaps, rarely walk, and remain severely hypotonic. Late-onset and especially autosomal dominant forms have a much better prognosis, often with mild static weakness. Treatment by gene therapy may dramatically change this prognosis.

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626.2

Congenital Muscle Fiber–Type Disproportion

Harvey B. Sarnat

Congenital muscle fiber–type disproportion (CMFTD) occurs as an isolated congenital myopathy but also develops in association with various unrelated disorders, which include nemaline rod disease and Krabbe disease (globoid cell leukodystrophy), early in the course before the expression of the neuropathy; congenital muscular dystrophy with merosin deficiency (occasionally); cerebellar hypoplasia and certain other brain malformations; fetal alcohol syndrome; some glycogenoses; multiple sulfatase deficiency; Lowe syndrome; rigid spine myopathy; and some infantile cases of myotonic muscular dystrophy. *CMFTD is, therefore, a syndrome.* Several specific genetic mutations are confirmed, including *TPM2*, *TPM3*, *MYH7*, *ACTA1*, and *LMNA*.

Pathogenesis

The association of CMFTD with *cerebellar hypoplasia* suggests that the pathogenesis may be an abnormal suprasegmental influence on the developing motor unit during the stage of histochemical differentiation of muscle between 20 and 28 wk of gestation. Muscle fiber types and growth are determined by innervation and are mutable even in adults. Although CMFTD does not actually correspond with any normal stage of development, it appears to be an embryologic disturbance of fiber-type differentiation and growth.

Clinical Manifestations

As an isolated condition not associated with other diseases, CMFTD is usually a *nonprogressive* disorder present at birth. Patients have generalized hypotonia and weakness, but the weakness is usually not severe. *Contractures* are present at birth in 25% of patients. Poor head control and developmental delay for gross motor skills are common in infancy. Walking is usually delayed until 18-24 mo but is eventually achieved. Because of the hypotonia, subluxation of the hips can occur. Muscle bulk is reduced. The muscle wasting and hypotonia are proportionately greater than the weakness, and the child may be stronger than expected during examination. Cardiomyopathy is a rare complication. Respiratory weakness usually is mild but can be demonstrated in 30% of neonates and young infants. Dysphagia is infrequent except if CMFTD is secondary to myotonic dystrophy, nemaline myopathy, or a systemic metabolic disease with additional encephalopathy.

The facies of children with CMFTD often raise suspicion, especially if the child is referred for assessment of developmental delay and hypotonia. The head is dolichocephalic, and facial weakness is present. The palate is usually high arched. Thin muscles of the trunk and extremities give a thin, wasted appearance. The phenotype is very similar to that of nemaline myopathy, which also includes CMFTD as part of the pathologic phenotype. Patients do not complain of myalgias. The clinical course generally is nonprogressive or only slowly progressive unless it is associated with other congenital myopathies.

Laboratory Findings

The serum CK, electrocardiogram, electromyography studies, and nerve conduction velocity results are normal in isolated CMFTD. If other diseases are associated, laboratory investigation of those conditions discloses the specific features. Specific genetic studies are indicated if there is a family history.

Diagnosis

CMFTD is diagnosed by muscle biopsy that shows a disproportion in the size and relative ratios of the histochemical fiber types: Type I fibers are uniformly small, and type II fibers are hypertrophic; type I fibers are more numerous than type II fibers. Degeneration of myofibers and other primary myopathic features are absent. The biopsy is diagnostic at birth. Table 626.5 lists the features that distinguish CMFTD from other congenital myopathies. Selective atrophy or even hypoplasia of type II myofibers is not CMFTD, though it has sometimes been labeled as *reverse CMFTD.*

Genetics

Many cases of simple CMFTD are sporadic, although an autosomal recessive inheritance is well documented in some families and an autosomal dominant trait is suspected in others. The genetic basis is heterogeneous in hereditary forms; a mutation in the insulin receptor gene at 19p13.2 is reported. Translocation t(10;17) was seen in one family. X-linked transmission with linkage to Xp23.12-p11.4 and Xq13.1-q22.1 also is described. *LMNA* gene mutations produce familial CMFTD, clearly a germline mutation with mendelian autosomal transmission. In three unrelated families with CMFTD, a heterozygous missense mutation of the skeletal muscle α-actin gene *(ACTA1)* was demonstrated, but this genetic defect represents a minority; mutations in *TPM3* or *TPM2* are the more common genetic findings. Large duplications in the *TPM3* gene can cause CMFTD. *MYH7* de novo mutations lead to exon skipping. In CMFTD associated with cerebellar hypoplasia, the epigenetic effect is on cerebellar development and the muscular expression is secondary.

Treatment

No drug therapy is available. Physiotherapy may be helpful for some patients in strengthening muscles that do not receive sufficient exercise in daily activities. Mild congenital contractures often respond well to gentle range-of-motion exercises and rarely require plaster casting or surgery. The relative rarity of early-onset congenital myopathies such as CMFTD and the diversity of the genotype make focused gene therapies difficult, but the identification of specific molecular mechanisms and novel gene editing strategies are a basis for future therapy.

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626.3

Nemaline Rod Myopathy

Goknur Haliloglu

Nemaline rods (derived from the Greek *nema*, meaning “thread”) are rod-shaped, inclusion-like abnormal structures within muscle fibers. They are difficult to demonstrate histologically with conventional hematoxylin-and-eosin stain but are easily seen with special stains. They are not foreign inclusion bodies but rather consist of excessive Z-band material with a similar ultrastructure (Fig. 626.4). Chemically, the rods are composed of actin, α-actinin, tropomyosin-3, and the protein nebulin. Nemaline rod formation may be an unusual reaction of muscle fibers to injury because these rod structures have rarely been found in other diseases. They are most abundant in the congenital myopathy known as *nemaline rod disease*. Most rods are within the myofibrils, but intranuclear rods are occasionally demonstrated by electron microscopy. Intranuclear rods occur mainly in neonates with severe weakness; they usually indicate *ACTA1* mutations and may coexist with the more usual cytoplasmic rods. Nemaline myopathy caused by an *ACTA1* mutation is one of a spectrum of *actinopathies.*

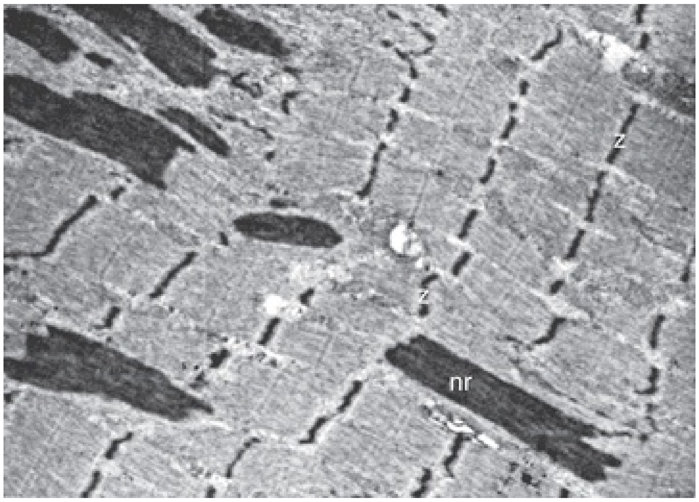

FIG. 626.4 Electron micrograph of the muscle from a patient shown in Fig. 626.6 . Nemaline rods (nr) are seen within many myofibrils. They are identical in composition to the normal Z-bands (z) (×6,000).

Mutations in tropomyosin-2 *(TPM2)* can cause a congenital myopathy *related* to nemaline rod myopathy, designated cap myopathy, in which accumulations of distorted myofilaments are focally present on the periphery of fibers. They may coexist with myofibrillar nemaline rods. Somatic mosaicism is demonstrated in *TPM2* -related nemaline myopathy with cap structures.

Mutations in muscle-specific Kelch BTB genes *(KBTBD13, KLHL40, KLHL41)* cause nemaline myopathy with potential signatures on muscle biopsy. Autosomal dominant *KBTBD13* mutations are identified in families with nemaline myopathy and cores. Autosomal recessive *KLHL40* and *KLHL41* mutations are described in severe early-onset nemaline myopathy with fetal akinesia phenotypes and congenital fractures (see Chapter 626.10).

Clinical Manifestations

Prenatal, neonatal, infantile, juvenile, and adult-onset forms of the disease are known. There is a highly variable degree of muscle weakness, ranging from presentations within the *fetal akinesia* spectrum to only mildly affected adults. All defining features of congenital myopathies can occur in different contexts; although there is not a clear genotype-phenotype correlation, there may be clinical clues for specific mutations. Prenatal and neonatal forms are severe and usually fatal because of respiratory failure since birth. In the infantile form, generalized hypotonia and weakness, which can include bulbar-innervated and respiratory muscles, and a very thin muscle mass are characteristic (Fig. 626.5). The head is dolichocephalic, and the palate high arched or even cleft. Muscles of the jaw may be too weak to hold it closed (Fig. 626.6). Decreased fetal movements are reported by the mother, and neonates suffer from hypoxia and dysphagia; arthrogryposis may be present (see Chapter 626.10). Infants with severe neonatal and infantile nemaline myopathy have facies and a phenotype that are nearly indistinguishable from those of *neonatal myotonic dystrophy*, but their mothers have normal facies.

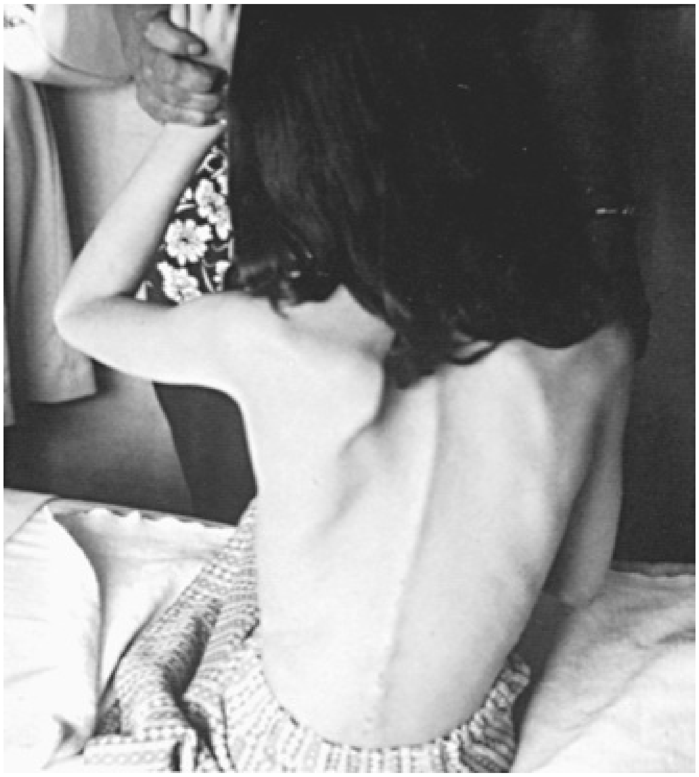

FIG. 626.5 Back of a 13 yr old girl with the juvenile form of nemaline rod disease. The paraspinal muscles are very thin, and winging of the scapulas is evident. The muscle mass of the extremities is also greatly reduced proximally and distally.

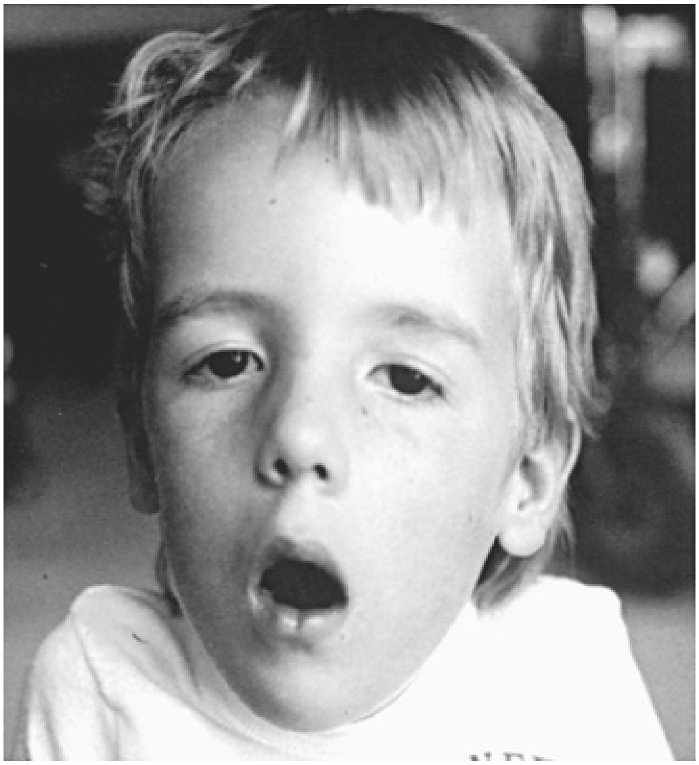

FIG. 626.6 Infantile form of nemaline rod disease in a 6 yr old boy. Facial weakness and generalized muscle wasting are severe. The head is dolichocephalic. The mouth is usually open because the masseters are too weak to lift the mandible against gravity for more than a few seconds.

In *NEB* -related nemaline myopathy, which is the most common form, patients usually present in infancy or childhood, and there is a disproportional axial and bulbar involvement compared with limb weakness. In spite of preserved ambulation, scoliosis and respiratory involvement are universal. Distal muscle involvement may be a presenting feature in some patients. *ACTA1* -related nemaline myopathy is typically severe, and additional phenotypes include (1) progressive scapuloperoneal and distal weakness in a large single family with autosomal dominant inheritance, demonstrating muscle atrophy without nemaline rods; (2) a severe congenital presentation with myofibrillar features on muscle biopsy; (3) LGMD phenotype; (4) autosomal recessive congenital muscular dystrophy with a rigid spine; and (5) zebra body myopathy. Cardiomyopathy is not a feature of *NEB* -related nemaline myopathy; however, it has been rarely reported in patients with *ACTA1* mutations.

The *juvenile form* is the mildest and is not associated with respiratory failure, but the phenotype, including facial involvement, is similar. *Adult-onset* presentations are in the form of slowly progressive proximal weakness with axial involvement, and although not symptomatic in childhood and adolescence, these patients retrospectively report difficulties with sportive activities in childhood.

Laboratory Findings

The serum CK level is normal or mildly elevated. The muscle biopsy is diagnostic. In addition to the characteristic nemaline rods, it also shows CMFTD or, at least, fiber-type I predominance. In some patients, uniform type I fibers are seen with few or no type II fibers. Focal myofibrillar degeneration and an increase in lysosomal enzymes have been found in a few severe cases associated with progressive symptoms. Intranuclear nemaline rods, demonstrated by electron microscopy, are correlated with the most severe neonatal manifestations. Potential pathologic hallmarks of *KLHL40* mutations are miliary bodies and leimodin-3 (*LMOD3*) mutations; the latter are a fringe of thin filaments radiating from the nemaline bodies and paired nemaline bodies interconnected by thin filaments. Because nemaline bodies can occur in other myopathies, their presence in the muscle biopsy is not pathognomonic in the absence of the supportive clinical manifestations. **Sporadic late-onset nemaline myopathy (SLONM)** may be associated with monoclonal gammopathy, HIV infection, and various autoimmune disorders, and should be differentiated from genetic causes because it is a potentially treatable condition.

Genetics

Autosomal dominant, autosomal recessive, and X-linked dominant forms in females can occur. Nemaline myopathy can be caused by mutations in at least 10 genes, including *ACTA1* (skeletal muscle α-actin), *NEB* (nebulin), *TPM3* (slow muscle α-tropomyosin), *TPM2* (β-tropomyosin), *CFL2* (skeletal muscle cofilin), *TNNT1* (slow muscle troponin-T), *LMOD3* (leiomodin 3), *KBTBD13* (Kelch-repeat and BTB domain containing 13), *KLHL40,* and *KLHL41* (Kelch-like 40 and 41). All of the genes implicated in nemaline myopathy encode proteins constituting the thin filaments of myofibrils or regulate thin-filament organization and stability. Overall, recessive mutations in *NEB* and de novo dominant mutations in *ACTA1* are most common, and represent approximately 50% and 25% of cases, respectively. *TNNT1* nemaline myopathy known to be specific for Old Order Amish populations is also identified in other populations.

Mutations in muscle-specific Kelch proteins are increasingly recognized. *KBTBD13* nemaline myopathy is characterized by autosomal dominant inheritance and phenotypic variability. *KLHL40* and *KLHL41* nemaline myopathies represent the severest end of the spectrum, with in utero presentations, fetal akinesia, arthrogryposis, congenital fractures, and specific signatures on muscle biopsy samples (see Chapter 626.10). Kelch-BTB proteins act as E3-ubiquitin ligases and mediate protein turnover. In animal and cell culture studies, *KLHL40* was shown to stabilize leiomodin-3 (Lmod3) and the absence of *KLHL40* was shown to reduce Lmod3 and Neb, which was further confirmed in muscle biopsy samples of some patients with *KLHL40.* This led to identification of mutations in the gene encoding leiomodin-3, a protein especially present at the pointed end of muscle thin filaments. *LMOD3* nemaline myopathy is characterized by a severe phenotype with, again, potential hallmarks on muscle biopsy.

Treatment and Prognosis

There is no cure, and management is mainly supportive and symptomatic. Survivors are usually wheelchair-dependent and unable to overcome gravity. Both proximal and distal muscles are involved. Congenital *arthrogryposis* and *fractures* can occur and predict a poor prognosis. Gastrostomy may be needed for chronic dysphagia. Special attention to respiratory function in patients presenting with scoliosis and axial involvement is important to recognize early signs and symptoms of **nocturnal hypoventilation syndrome.** In the juvenile form, patients are ambulatory and are able to perform most tasks of daily living. Weakness is not usually progressive, but some patients have more difficulty over time or enter a phase of progressive weakness. Cardiomyopathy is an uncommon complication. Death usually results from respiratory insufficiency, with or without superimposed pneumonia.

Based on preclinical data in a mouse model of *ACTA1* -related nemaline myopathy, a variety of pharmacologic compounds and supplements, including L-thyrosine, have been tested in five patients with nemaline myopathy; a beneficial effect has been suggested, with reduced fatigue and improvement of drooling. Treatments targeting the neuromuscular junction are another option; a single patient with *KLHL40* -related nemaline myopathy had a sustained beneficial response to the acetylcholinesterase inhibitor pyridostigmine, a result that corresponds to experiences in other congenital myopathies, mainly centronuclear myopathies. Drugs targeting thin filaments and their interactions, myostatin inhibitors to promote muscle growth, and cardiac α-actin upregulation in *ACTA1* -related nemaline myopathy are being investigated in animal models.

Despite recent advances in our understanding of pathophysiologic concepts and efforts for therapy, genetic counseling and prenatal diagnosis should be considered in families with an index patient and a precise genetic diagnosis.

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626.4

Core Myopathies

Goknur Haliloglu

The core myopathies are the most common form of congenital myopathy, consisting of *central core diseases* (CCDs), *multiminicore disease* (MmD), and *atypical cores*. Cores are regions within muscle fibers in which only amorphous, granular cytoplasm is found, with an absence of myofibrils and organelles. Cores are devoid of mitochondria that contain disordered sarcomeric proteins. Histochemical stains show a lack of enzymatic activities of all types within these cores, as well as an absence of contractile proteins (actin and myosin) that form the thin and thick myofilaments. Longitudinally extensive areas in the central area of myofiber devoid of oxidative enzyme activity represent central cores, and multiple smaller areas of reduced activity affecting shorter segments of the myofiber are characteristic of multicores and minicores. On electron microscopy, cores are characterized by an abnormal sarcomeric structure, including Z-band streaming, complete myofibrillary disorganization, and accumulation of Z-band material. Although variants of central cores, called minicores and multicores, are described in some families, they are believed to represent the same basic disease process. Pathologic features may evolve, with changes and abnormalities becoming more evident over time.

Clinical Manifestations

The phenotypical spectrum of core myopathies ranges from mild to severe. Hypotonia, joint laxity, motor developmental delay, hip girdle or axial muscle weakness, orthopedic complications such as recurrent shoulder or patellar dislocations, congenital hip dislocation or dysplasia, or foot deformities may be presenting features. In older children, CCD is an important differential diagnosis of progressive thoracolumbar scoliosis. There is also an intrafamilial variability, with some individuals presenting only with muscle stiffness, exertional myalgia, or rhabdomyolysis.

Genetic resolution of core myopathies has led to mutation-specific clinical presentations and phenotype–genotype correlations.

Central Core Disease

Central core disease (CCD) is most commonly associated with ryanodine 1 gene *(RYR1)* mutations, which are described as the predominant genetic causes of nondystrophic neuromuscular disorders. These disorders range from dominantly inherited CCD, subgroups of recessively inherited multiminicore disease (MmD), centronuclear myopathy (CNM) (see Chapter 626.1), and CFTD (see Chapter 626.2) to **malignant hyperthermia susceptibility (MHS)** trait. MHS is a dominantly inherited allelic trait, described as a pharmacogenetic predisposition to a severe and potentially life-threatening reaction in response to halogenated anesthetic agents and depolarizing muscle relaxants. MHS is suspected in an individual with congenital myopathy when (1) there is a positive family history of MHS, (2) there have been previous difficulties with anesthesia, and (3) the patient has a documented *RYR1* mutation.

Dominantly inherited *RYR1* -related CCD is characterized by mild to moderate muscle weakness presenting from infancy to childhood (Fig. 626.7). The clinical spectrum ranges from fetal akinesia deformation sequence to milder adult forms. The distribution of weakness is typically proximal, with prominent hip girdle and axial muscle involvement. Congenital hip dislocation, scoliosis, and generalized joint laxity are common. In contrast to the recessive forms with a more severe clinical phenotype, there is no extraocular muscle involvement. Bulbar, respiratory, and cardiac involvement is uncommon. Myalgia may be prominent. Except for patients with a severe neonatal onset, most patients with CCD achieve independent ambulation. CCD tends to be stable over long periods, with a possible slowly progressive course in adulthood. *RYR1* -related MHS is allelic to CCD, and some patients with CCD may also be malignant hyperthermia susceptible. Fig. 626.8 shows a family with a recessive *RYR1* mutation in the index patient and his asymptomatic father who is carrying a dominant *RYR1* -MHS gene. Characteristics and recently identified phenotypes due to *RYR1* mutations are summarized in Table 626.6 .

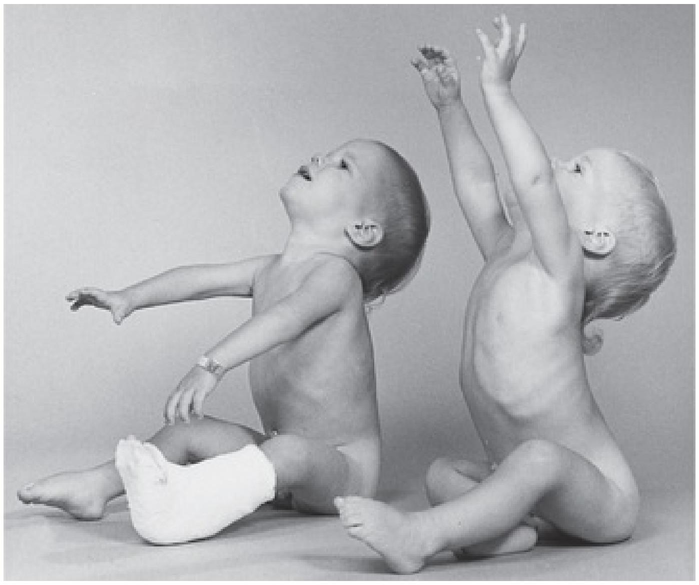

FIG. 626.7 Central core disease. Photograph of twins, one of whom has the disease. Note the weakness of the proximal upper extremities. (From Cohen ME, Duffner PK, Heffner R: Central core disease in one of identical twins, J Neurol Neurosurg Psychiatry 41:659-663, 1978.)

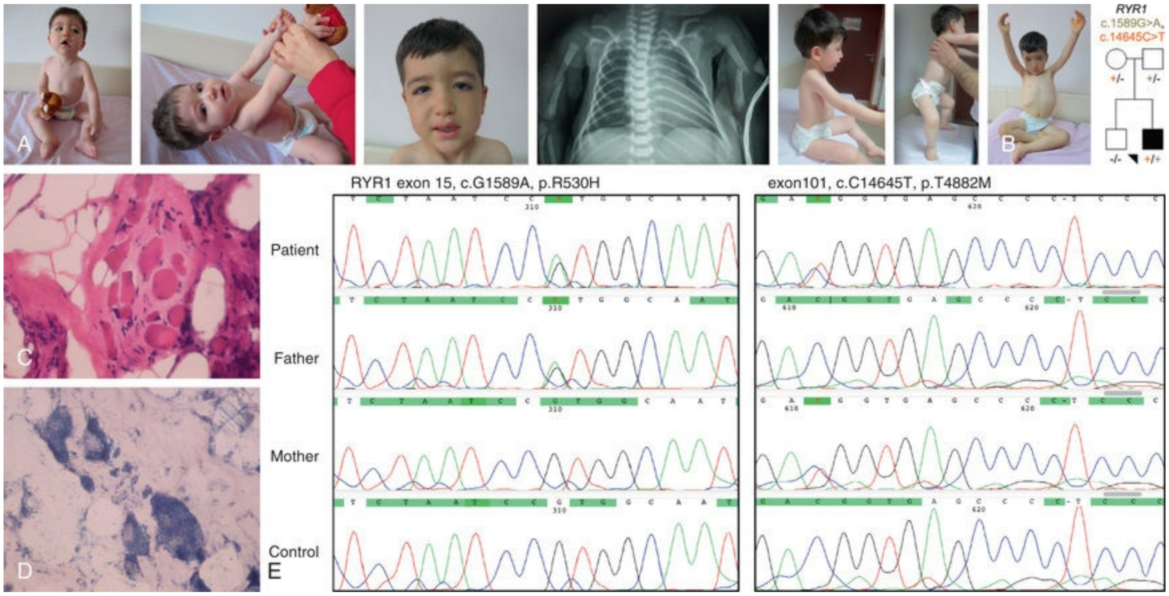
A
B
RYR1
c.1589G>A,
c.14645C>T
+/-
+/-
-/-
+/+
C
D
E
RYR1 exon 15, c.G1589A, p.R530H
exon101, c.C14645T, p.T4882M
Patient
Father
Mother
Control

FIG. 626.8 Index patient presenting with developmental delay and hypotonia at the age of 19 mo. Note the bilateral humerus fractures at birth. He had a previous diagnosis of osteogenesis imperfecta. He has facial weakness, a myopathic face, and involvement of the neck flexor muscles with head-lag; his maximum motor capacity is to sit without support. **A,** He is unable to stand on his feet. **B,** At 4 yr of age, the patient is unable to walk. Muscle biopsy at the age of 19 mo, demonstrating myopathic

changes with increased fatty and fibrous tissue infiltration (HE) **(C)** and central cores (NADH) **(D).** The index patient is carrying a recessive *RYR1* mutation, and his father is carrying a dominant *RYR1* -malignant hyperthermia susceptibility mutation **(E).**

Table 626.6

Characteristics and Clinical Phenotypes Related to Ryanodine 1 *(RYR1)* Mutation-related Central Core Disease (CCD)

EARLY-ONSET *RYR1* -RELATED PHENOTYPES	**LATE-ONSET *RYR1* - RELATED PHENOTYPES**
Dominant mutations typically present with congenital hypotonia, weakness, hip dislocation at birth. Motor milestones are delayed; independent ambulation is eventually achieved. Weakness tends to involve hip girdle and quadriceps with sparing of facial and extraocular muscles.	Malignant hyperthermia susceptibility (MHS)
Recessive mutations have a tendency of earlier and more severe presentation compared with most patients with dominant mutations; however, they are also associated with a wide range of clinical phenotypes and pathologic features.	King-Denborough syndrome
Recessive phenotypes can be further grouped as clinical groups with and without ophthalmoparesis.	Exertional rhabdomyolysis
Dominant and recessive mutations with a severe neonatal presentation leading to death are described.	Periodic paralysis
RYR1- related centronuclear myopathy (CNM) presents with a variable degree of external ophthalmoparesis, frequently associated with facial weakness.	Late-onset axial myopathy
Histopathologic features may resemble congenital fibre-type disproportion (CFTD) congenital muscular dystrophy (CMD).	

MHS-related *RYR1* mutations have also been described as a common cause of induced and episodic phenotypes such as *exertional rhabdomyolysis*, which account for up to 30% of presentations in otherwise healthy individuals throughout life (see Chapter 625). Late-onset presentations in adulthood highlight the relevance of the congenital myopathies for adult neuromuscular practice. A predisposing genetic background should be considered if episodes are familial, recurrent, out of context to the exercise performed, or preceded by other symptoms, such as cramps, myalgia, and weakness. *RYR1* -related rhabdomyolysis may occur up to 72 hr after exercise and may mimic viral myositis; in contrast to other metabolic myopathies, fasting *does not* appear to be a triggering factor.

Due to expression of ryanodine receptors other than striated skeletal muscle, *non*$^{-}$ *skeletal muscle presentations of RYR1-related myopathies* are recognized. *Mild bleeding abnormalities* are described in patients with malignant hyperthermia carrying gain-of-function *RYR1* mutations by altering vascular smooth muscle cell function. A bleeding defect in the animal model and one patient was reversed by treatment with the RyR1 antagonist dantrolene, suggesting a therapeutic role for *RYR1* -related bleeding disorders and, potentially, other bleeding disorders, as well. Another observed phenotype is severe CNS involvement in an adolescent suffering a malignant hyperthermia episode. Striking similarities in terms of cerebellar involvement seen in this patient and *heat stroke victims* indicated a potential link between *RYR1* -related exertional rhabdomyolysis and neuroleptic malignant syndrome. Some of the psychopharmacologic drugs, such as olanzapine, should be considered as triggering agents in patients with *RYR1* mutations and exertional rhabdomyolysis. An emerging question is *cardiac involvement* in *RYR1* -related myopathies. Sudden unexplained death, dilated cardiomyopathy presumed to be due to a viral infection, bicuspid aortic valve, and sinus bradycardia are described; cardiologic assessment should be considered to define a cardiac phenotype associated with *RYR1* -related myopathies.

Multiminicore Disease

Multiminicore disease (MmD) is typically recessively inherited, and the clinical phenotype depends on the underlying genetic background. Presentations may vary and overlap between the most common and recognizable classic form, a severe neonatal form, a form with external ophthalmoplegia, and a moderate form with hand involvement. The *classic phenotype* due to recessive selenoprotein N1 *(SEPN1)* mutations can be summarized as axial weakness, early spinal rigidity, scoliosis, and respiratory impairment (Fig. 626.9). The onset is early, with predominant involvement of the neck muscles. Infants unable to hold up their heads, despite being able to walk independently, can present as having an *isolated neck myopathy* or *dropped-head syndrome.* A myopathic face, high-arched or cleft palate, high-pitched voice, feeding difficulties, and failure to thrive can be accompanying features. These patients may look very similar to each other, with an asthenic and atrophic muscle phenotype and growth retardation, who are mainly investigated and referred with a preliminary diagnosis of celiac disease. The proximal shoulder girdle muscles and inner thigh are affected more. Axial weakness is replaced with contractures of the spinal extensor muscles in time, leading to a *rigid spine deformity.* Usually by the second decade, there is a progressive scoliosis, lateral deviation of the trunk, and respiratory impairment that is overall in disproportion to the skeletal muscle weakness. MmD should be considered in the differential diagnosis of diseases presenting with *early neuromuscular chronic respiratory failure* (i.e., chronic-onset respiratory muscle weakness whilst the patient is still ambulant). Respiratory involvement may lead to secondary cardiac failure. Ophthalmoplegia is not a feature of this classic form, but it has exceptionally been recognized in the last stages of disease in patients with a severe course.

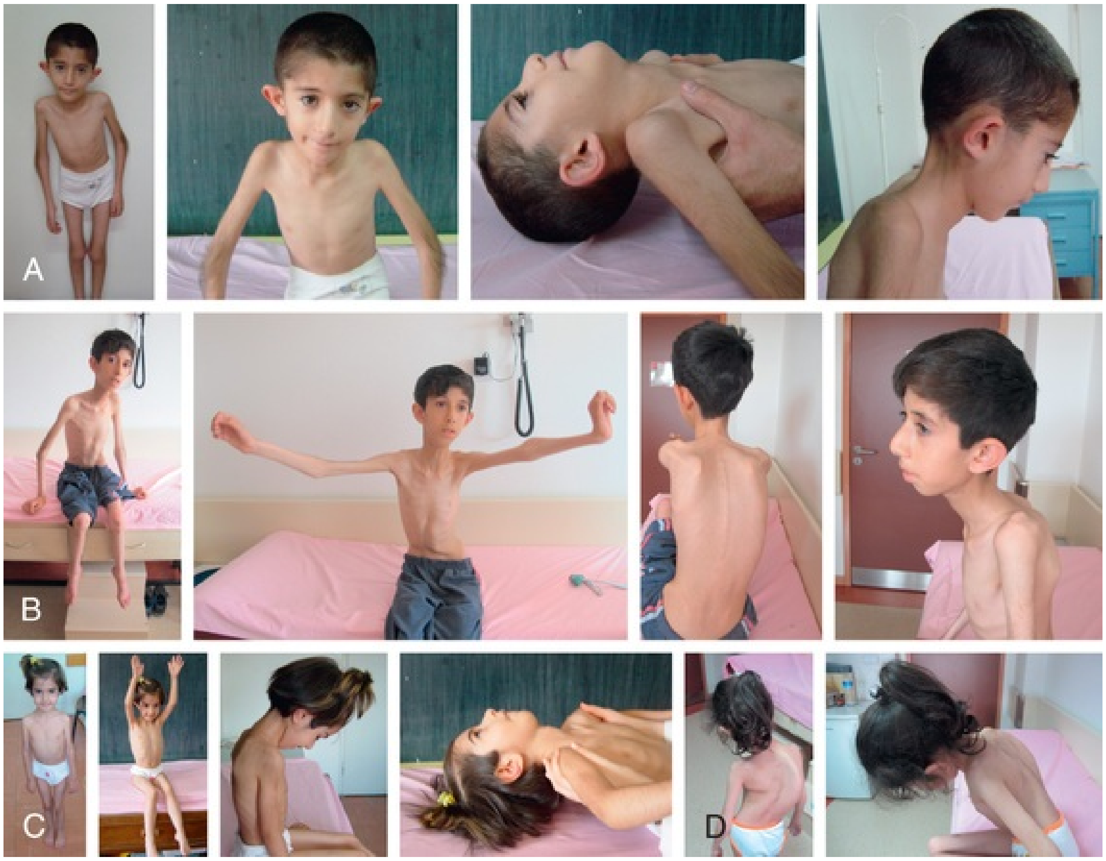

FIG. 626.9 Patients with a typical *SEPN1* -related multiminicore disease (MmD) phenotype at the ages of 10 yr **(A),** 12 yr **(B),** 7 yr **(C),** and 8 yr **(D).** Note asthenic, atrophic phenotype, with rigid spine syndrome, weakness in neck flexor muscles, and varying degrees of scoliosis.

MmD phenotypes due to *recessive RYR1 mutations* are characterized by a milder respiratory but prominent bulbar impairment compared with those with the classic form. External ophthalmoplegia, recurrent episodes of periodic paralysis, distal weakness and wasting mainly affecting the hands, arthrogryposis, cryptorchidism, and dysmorphic features have also been described in the *RYR1* -related MmD spectrum. Hypertrophic cardiomyopathy associated with short-chain acyl-coenzyme A dehydrogenase deficiency, and primary cardiomyopathies due to mutations in myosin heavy chain 7 *(MYH7)* or titin *(TTN)* genes, have been described in MmD. Although not reported in *SEPN1* -related MmD, there is a potential risk for MHS in *RYR1* -related MmD.

Laboratory Findings

The diagnosis of core myopathies may be challenging and requires a combination of a detailed clinical (phenotype recognition) and laboratory (histopathologic, muscle imaging, genetic) evaluation and interpretation. The serum CK value is normal, except during crises of malignant hyperthermia, which can result in rhabdomyolysis or extensive acute myofiber necrosis (see Chapter 629.2). Muscle imaging (ultrasonography and MRI) may serve as a noninvasive tool to describe characteristic selective muscle involvement. Recognition of these patterns may help to distinguish typical dominantly inherited CCD forms and *SEPN1* -related MmD from a variety of neuromuscular diseases. The diagnosis of a core myopathy based on pathologic findings may be straightforward; however, the typical picture may evolve over time, with early muscle biopsies showing almost no or minimal changes. Core formation is a nonspecific finding and may be observed in the denervation process, tenotomy, metabolic conditions, or even healthy probands after eccentric exercise. *Moth-eaten fibers* described in muscular dystrophies may resemble minicores in MmD. The presence of cores without associated weakness, as reported in some MHS individuals, is not sufficient to give a diagnosis of core myopathy. Cores and other structural abnormalities specific for other structural myopathies, such as nemaline rods or centralized nuclei, can coexist. Muscular dystrophies due to lamin A/C *(LMNA)* mutations, collagen VI—related myopathies, metabolic myopathies (Pompe disease), myofibrillary myopathies in patients with cardiomyopathy, and congenital myasthenic syndromes may mimic core myopathies based on clinical and/or pathologic features and should be considered in the differential diagnosis.

Due to the extreme clinical and pathologic overlaps among the early-onset muscle diseases, there has been a shift in the traditional diagnostic pathways. Taking all of these issues into account, the diagnosis of core myopathies, like other congenital myopathies, requires a combined effort on the part of the clinician, pathologist, and molecular geneticist.

Genetics

Central core myopathies are transmitted as either an autosomal dominant or autosomal recessive trait, or *de novo* dominant mutations. They are caused by the same abnormal gene at the 19q13.1 locus. This gene programs the ryanodine receptor *(RYR1),* a tetrameric receptor that contains a non–voltage-gated calcium channel; it is prevalent in the sarcoplasmic reticulum and especially at the junction of the T-tubule with the cisternae of the sarcoplasmic reticulum. It contains the channel by which calcium is released among the myofilaments. Mutations in the *RYR1* gene are also the cause of **malignant hyperthermia (MH)** . In centronuclear myopathies, autosomal recessive mutations of *RYR1* are known to be a frequent cause, and recently a patient with a dominant de novo mutation of *RYR1* was also described (see Chapter 629.2). Patients presenting with congenital myopathy, ptosis, external ophthalmoplegia, and prominent internal nuclei in addition to other structural findings are highly likely candidates for *RYR1* mutations. Of note, recessive core disease may be associated with tissue-specific silencing of the normal allele, an epigenetic phenomenon. Certain missense mutations can be associated with autosomal dominant MH, and management of the asymptomatic carrier of the MH-susceptibility allele should be treated accordingly.

Mutations in the slow β-myosin gene *(MYH7),* autosomal recessive titin *(TTN)* mutations, and recessive mutations of the satellite cell gene *(MEGF10)* are other identified causes of core myopathy. The latter is characterized by *early-onset myopathy, areflexia, respiratory distress, and dysphagia* (EMARRD). A single patient has been described who presented with severe congenital myopathy and ophthalmoplegia and recessive variants in the gene encoding the alpha-1 subunit of the dihydropyridine receptor *(CACNA1S),* a gene in which dominant mutations are known to be associated with **hypokalemic periodic paralysis** and **MH.** Functional studies are required to link *CACNA1S* mutations to congenital myopathies.

MmD is caused mainly by recessive mutations in *SEPN1* and *RYR1* . Selenoprotein N is an integral membrane protein localized in the endoplasmic reticulum, which is expressed in several tissues, including the skeletal muscle, heart, lung, and placenta. It is also highly expressed in the diaphragm; this could explain the finding of early restrictive respiratory insufficiency in patients. *SEPN1* mutations also cause CFTD (see Chapter 626.2) and rigid spine muscular dystrophy (see Chapter 627).

Treatment and Prognosis

The treatment for core myopathies is symptomatic and should be, in general, parallel to consensus standard care guidelines in congenital myopathies. Orthopedic complications, rehabilitation, and feeding problems should be managed accordingly. Scoliosis and other skeletal deformities require special attention because they may develop quickly and progress in severity disproportionately to the limb weakness. Compared with other congenital myopathies, there are a higher number of treatment failures in congenital hip dislocation and dysplasia in CCD.

CCD is consistently associated with **malignant hyperthermia (MH),** which can precede the diagnosis of CCD. All patients and asymptomatic carriers should be counseled in terms of a potentially fatal adverse reaction to volatile anesthetics and muscle relaxants. **Preoperative anesthetic consultation** in patients known to be subject to general anesthesia should be considered. **Wearing a medical alert bracelet** should be advised in terms of any emergency. Treatment of MH requires dantrolene and additional supportive care measures. Of note, prophylactic dantrolene is not recommended prior to anesthesia even in cases where MHS has been established.

There may be an insidious onset of respiratory muscle involvement, particularly in patients with MmD and *SEPN1* mutations. Patients may be symptomatic after an intercurrent illness or anesthesia or even sedation at the time of a muscle biopsy procedure. Multidisciplinary care requires input from pulmonologists. Signs and symptoms of **sleep-disordered breathing, nocturnal hypoventilation syndrome** should be questioned. Respiratory function tests in sitting and supine positions and polysomnography are necessary to introduce noninvasive positive-pressure ventilation in a timely manner. Patients with severe early-onset disease may require invasive mechanical ventilation. Cardiac complications are uncommon in CCD, but baseline electrocardiography and echocardiography studies are appropriate in most cases. Secondary right ventricular dysfunction and cardiac failure may complicate the situation in patients with respiratory impairment.

A subjective improvement in muscle strength and functional test results has been reported in patients with CCD who are taking β-2 agonists (salbutamol, albuterol). Current and future therapeutic approaches include (1) modification of *RYR1* function, (2) correction of associated oxidative abnormalities, (3) use of pharmacologic compounds enhancing muscle contractility and/or neuromuscular transmission, and (4) correction of a specific gene defect. N-acetylcysteine (NAC), as an antioxidant, may serve as a potential treatment option for *RYR1* - and *SEPN1* -related myopathies, and the first clinical trials in humans are currently under way.

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626.5

Myofibrillar Myopathies

Goknur Haliloglu, Harvey B. Sarnat

Myofibrillar myopathies (MFMs) are rare, inherited or sporadic, *progressive* neuromuscular disorders, diagnosed based on distinct morphologic features. There is a wide range of clinical and genetic heterogeneity within MFMs, which are also subgrouped as *protein aggregate myopathies.* A variety of phenotypic presentations are described due to cardiac, skeletal, and smooth muscle involvement. Core histopathologic findings can be defined as focal disintegration of myofibrils predominantly at the Z-disc level, accumulation of myofibrillar degradation products, and ectopic expression of a large number of proteins. Myofibril dissolution begins at the Z-disc, and some sarcomeres of myofibers have disorganization or dissolution of myofibrils adjacent to other areas of normal sarcomeres within the same fiber. Abnormal protein aggregations, intense congophilia of many hyaline structures, internalized nuclei, fiber splitting, vacuoles, *core-like* lesions, a mild to severe increase in endomysial collagen, and increased fiber size variability ranging from very hypotrophic to hypertrophic fibers are among the common features. These zones are associated with streaming of the Z-discs, and there is an expression of a large number of proteins in the aggregates, including dystrophin, sarcoglycans, ubiquitin, desmin intermediate filaments, αB-crystallin, and several Z-disc proteins such as myotilin and filamin-C. *Mitochondrial dysfunction* in the form of abnormal mitochondrial distribution is a frequent finding. Although a detailed immunocytochemical and ultrastructural study of the muscle biopsy tissue is required for the diagnosis and can provide clues about the underlying causative gene, the final diagnosis of the MFM subtype depends on molecular genetic testing. Overexpression or upregulation of normal proteins, such as desmin or αB-crystallin in myofibers, may be an additional feature in many other neuromuscular conditions, so MFM should be used when these accumulations are due to a mutation in the respective protein. The MFM subtypes are classified according to the affected protein, such as desminopathy, αB-crystallinopathy, or

Bag3opathy.

Clinical Manifestations and MFM Subtypes According to Genetic Background

Most MFMs are not symptomatic in childhood, but occasionally older children and adolescents show early symptoms of nonspecific proximal and distal weakness. MFMs usually present in mid-adulthood, with a slowly progressive weakness involving proximal and distal muscles. The distal presentation is usually more pronounced than the proximal weakness. Sensory symptoms, muscle stiffness, aching, and cramps may be additional symptoms. Affected individuals may show signs of *peripheral neuropathy* and overt *cardiomyopathy.* Autosomal recessive forms present with an early and more severe course compared with autosomal dominant forms. There is also a large interfamilial and intrafamilial variability in the clinical expression of the disease. The degree of involvement and pattern of progression vary between affected individuals.

MFM subtypes with main clinical features are summarized in Table 626.7 . Cardiac involvement can sometimes be the initial and only symptom, especially in desminopathies. Syncopal episodes, conduction defects (complete atrioventricular block, right bundle branch block, left anterior hemiblock), rhythm problems (ventricular arrhythmia), cardiomyopathy (dilated, restrictive, hypertrophic), persistent ductus arteriosus, and congestive heart failure are among the cardiac presentations. Facial, axial, and neck muscle involvement, bulbar signs, swallowing and feeding difficulties, rigid spine deformity, early respiratory insufficiency, and early-onset cataracts can be additional clues for the diagnosis. Smooth muscle involvement can present in the form of intestinal malabsorption and pseudo-obstruction.

Table 626.7

Subtypes of Myofibrillar Myopathies (MYMs)

GENE/PROTEIN	DISEASE	INHERITANCE PATTERN	AGE OF ONSET	MAIN CLINICAL FEATURES
DES /desmin	Desminopathy Desminopathy	Dominant, de novo	Early/middle adulthood	Distal > proximal weakness, cardiopathy,

		Recessive	Infancy/childhood	respiratory insufficiency
CRYAB /αB-crystallin	αB-crystallinopathy αB-crystallinopathy	Dominant Recessive	Middle adulthood Infancy	Distal > proximal weakness, cardiopathy, respiratory insufficiency, cataracts Limb and axial stiffness and weakness, respiratory failure
MYOT /myotilin	Myotilinopathy Myotilinopathy	Dominant Recessive	Middle/late adulthood Early/middle adulthood	Distal and proximal weakness, cardiopathy, and respiratory insufficiency in a minority of patients Distal and proximal weakness, arrhythmia
ZASP /ZASP	ZASPopathy	Dominant	Middle/late adulthood	Distal > proximal weakness, cardiopathy, and neuropathy in a minority of patients
FLNC /filamin C	MFM-filaminopathy	Dominant	Middle adulthood	Proximal > distal weakness, respiratory failure, and cardiopathy in a subset of patients
BAG3 /BAG3	BAG3 myopathy	De novo	Childhood	Proximal and distal weakness, respiratory insufficiency, hypertrophic cardiomyopathy, peripheral neuropathy
FHL1 /FHL1	Reducing body myopathy, FHL1 myopathy	X-linked	Infancy/childhood, adulthood (rare)	Delayed motor milestones, proximal > distal weakness, scoliosis, contractures, rapid loss of ambulation, respiratory insufficiency; milder course in adult-onset patients
TTN /titin	Hereditary myopathy with early respiratory failure (HMERF)	Dominant	Early-late adulthood	Distal, proximal, and neck weakness, early respiratory insufficiency
PLEC /plectin	Epidermolysis bullosa simplex with muscular	Recessive	Skin blistering since birth, myopathy in infancy/childhood,	Proximal and distal weakness, cardiomyopathy,

	dystrophy (EBS-MD)		adulthood	cataracts, epidermolysis, nail and tooth abnormalities, brain abnormalities
ACTA1 /α-actin	MFM-actinopathy	De novo	Infancy	Upper limb > lower limb weakness, respiratory insufficiency, contractures
HSPB8 /HSPB8	HSPB8 myopathy	Dominant	Early/middle adulthood	Distal > proximal weakness, peripheral motor neuropathy
DNAJB6 /DNAJB6	Limb–girdle muscular dystrophy 1D	Dominant	Middle adulthood	Distal and proximal weakness
PYROXD1 /PYROXD1*	PYROXD1 myopathy	Recessive	Infancy/early childhood	Slowly progressive symmetric proximal and distal weakness, generalized reduction in muscle bulk, neck weakness, scapular winging, mild to moderate facial weakness, mild ptosis, high-arched palate, nasal speech, swallowing difficulties, mild restrictive lung disease, mild length-dependent axonal neuropathy and evidence of cardiac involvement in the 3rd decade

* PYROXD1 is a nuclear-cytoplasmic oxidoreductase localized to the nucleus and to the striated sarcomeric components.

Adapted from Kley RA, Olive M, Schroder R: New aspects of myofibrillar myopathies, Curr Opin Neurol 29:628-634, 2016.

Some MFM subtypes may be associated with early-infantile onset. An example is a unique autosomal recessive myopathy in *Cree native infants* characterized by severe generalized muscular hypertonia that is not relieved by neuromuscular blockade and hence is myopathic in origin. Most die in infancy of respiratory insufficiency because of diaphragmatic involvement. The muscle biopsy shows similar findings to many other MFMs (Fig. 626.10); a novel αB-crystallin gene mutation is the cause. An early disease onset may also be seen in desminopathy; Bag3opathy; autosomal recessive epidermolysis bullosa simplex with muscular dystrophy (EBS-MD) within the group of *plectinopathies;*

hereditary myopathy with early respiratory failure (HMERF) within the group of *titinopathies;* actin-related MFM; and PYROXD1-myopathy.

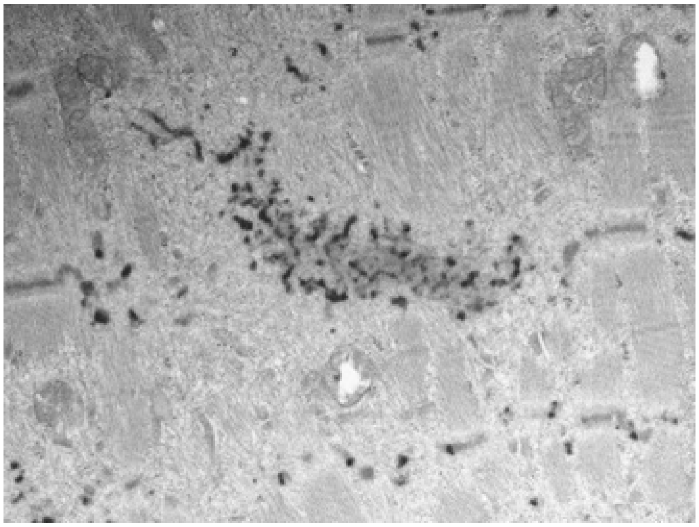

FIG. 626.10 Electron micrograph of quadriceps femoris muscle biopsy of a 1 mo old native girl with Cree myofibrillar myopathy. Within the same myofiber, some sarcomeres are well formed and others exhibit disarray of the thick and thin myofilaments and fragmentation of Z-bands. Mitochondria appear normal (×21,400).

MFM disease genes encode proteins that are structural and functional components of the sarcomere, extrasarcomeric cytoskeleton, or protein quality control systems. PYROXD1 is classified as a class I pyridine nucleotide-disulphide oxidoreductase, which belongs to an ancient family of enzymes that regulate the redox state of other proteins. An early-onset PYROXD1-myopathy is described, characterized histologically by multiple internalized nuclei, large zones of sarcomeric disorganization, accumulation of thin filaments, thickened Z-bands, and desmin-positive inclusions. There is a distinctive histopathology that combines features of central and minicore disease and the centronuclear, myofibrillar, and nemaline myopathies in patients described so far, which clearly indicates the overlap between congenital myopathies and MFMs.

In about half of the affected individuals with MFMs, the genetic defect remains unknown.

Laboratory Findings

The diagnosis of MFMs rests on common morphologic features observed in muscle histologic studies. Immunocytochemical studies and electron microscopy of muscle can provide clues about the causative gene. Peripheral nerve and myocardial pathologic findings have been described briefly in a small number of patients with MFMs; testing is not routinely performed on clinical grounds. The serum CK level can be normal or mildly elevated. Electromyography reveals myopathic or both myopathic and neuropathic features, abnormal nerve conduction studies, and electrical irritability (fibrillation potentials, positive sharp waves, complex repetitive discharges, and myotonic discharges). Muscle MRI can demonstrate different patterns of involvement according to MFM subtypes. The final diagnosis is based on the combination of clinical features, muscle biopsy features, and molecular genetic test results.

Proteomic analysis of protein aggregates yields to identification of diagnostic biomarkers in different MFM subtypes. The ratio of filamin C to myotilin in aggregates is described as a highly sensitive and specific diagnostic marker for myotilinopathy. The combination of immunofluorescence studies with proteomic findings will further facilitate identification of several proteins involved in protein quality control and degradation, which may also act as therapeutic targets.

The differential diagnosis includes congenital myopathies, myotonic dystrophy, mitochondrial diseases, and peripheral neuropathies in childhood.

Treatment

There is no curative treatment available for MFMs. Treatment is supportive and symptomatic. Cardiac screening (electrocardiography, echocardiography, and 24-hr Holter monitoring) should be performed at least once a year. In the case of cardiac abnormalities or in patients with desminopathies, pediatric cardiology follow-up is recommended twice a year. A pacemaker and an implantable cardioverter defibrillator (ICD), cardiac transplantation, respiratory support, range-of-motion physical therapy, and assisted devices can be introduced accordingly. Slit-lamp examination for the detection of lens opacities should be considered. There is no known increased risk for malignant hyperthermia; however, the possibility cannot yet be completely excluded. Genetic counseling and prenatal diagnosis should be offered according to the inheritance pattern and underlying gene defect.

The generation of patient-mimicking cell and animal models provides a basis for preclinical and clinical evaluation of novel therapeutic strategies. Initial animal studies are based on avoiding strenuous exercise, treatment with an antioxidant-N-acetyl-L-cysteine, modulation of autophagic activity, and use of antiaggregation drugs such as doxycycline and 4-phenylbutyrate (a chemical chaperone approved for urea cycle disorders).

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626.6

Brain Malformations and Muscle Development

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Infants with **cerebellar hypoplasia** are hypotonic and developmentally delayed, especially in gross motor skills. Muscle biopsy is sometimes performed to exclude a congenital myopathy. A biopsy specimen can show delayed maturation of muscle, fiber-type predominance, or CMFTD. Other malformations of the brain may also be associated with abnormal histochemical patterns, but supratentorial lesions are less likely than brainstem or cerebellar lesions to alter muscle development. Abnormal descending impulses along bulbospinal pathways probably alter discharge patterns of lower motor neurons that determine the histochemical differentiation of muscle at 20-28 wk of gestation. The corticospinal tract does not participate because it is not yet functional during this period of fetal life.

There are a variety of muscular dystrophies associated with cerebral and ocular phenotypes, suggesting common mechanisms affecting development of the muscle, the brain, and the eye. It is clear that in at least some of these cases, the abnormal protein implicated in pathogenesis is expressed in the muscle, brain, and eye, and is important for the stabilization of muscle, migration of central neurons, and normal tissue development in the eye.

Alpha dystroglycan–related dystrophies (αDG-RD) are a group of muscle diseases with a broad phenotypic and genetic spectrum, including several congenital muscular dystrophies (see Chapter 627.6), with severe brain involvement in the form of cobblestone lissencephaly (Walker-Warburg syndrome, Fukuyama disease, and muscle–eye–brain disease of Santavuori) to the limb–girdle muscular dystrophy (LGMD) spectrum (see Chapter 627.4).

Dystrophin–glycoprotein complex forms a critical link between the extracellular matrix and cytoskeleton, and in the muscle tissue, stabilizes the muscle membrane. Dystroglycan simply interacts with proteins in the extracellular matrix and cytoskeleton via dystrophin (Fig. 626.11). αDG is a transmembrane glycoprotein, and extensive posttranslational glycosylation (O-linked mannosylation) is required for its proper function, to mediate binding to basement membrane proteins (laminin alpha-2 chain, perlecan, agrin), neurexin in the brain, pikachurin in the eye, and Slit (by interaction with laminin globular [G] domains).

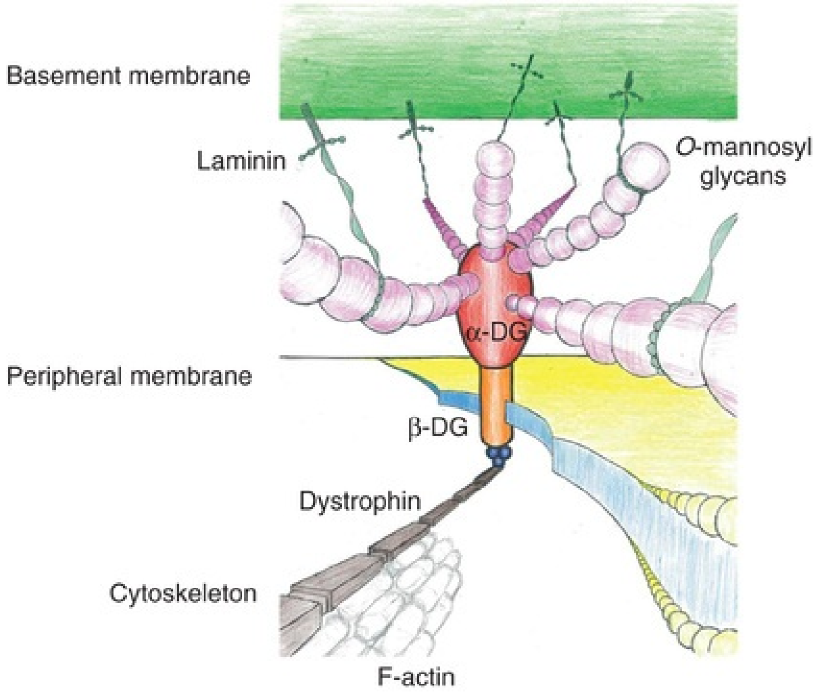

FIG. 626.11 Schematic drawing of dystrophin–-glycoprotein complex (DGC) and glycosylated α-dystroglycan (DG). α-DG links extracellular components such as laminin, and links β-DG, a transmembrane glycoprotein. Via dystrophin it binds to actin cytoskeleton. α-DG is heavily glycosylated, and its glycans play a role in binding to laminin. (From Taniguchi-Ikeda M, Morioka I, Iijima K, Toda T: Mechanistic aspects of the formation of α-dystroglycan and therapeutic research for the treatment of α-dystroglycanopathy: a review, Mol Aspects Med 51:115-124, 2016.)

Defects of O-glycosylation of αDG are considered to be central to the pathogenesis of αDG-RD. Deletion of dystroglycan or its glycosyltransferases results in migration defects in the form of type II cobblestone lissencephaly and a variety of eye malformations affecting both the retina and anterior chamber, such as glaucoma and cataracts.

Animal studies show that glycosylated dystroglycan is required for proper guidance and development of several axonal tracts. Dystroglycan is required not only for the integrity of basement membranes along which developing axonal pathways extend, but also because it directly binds to the laminin G domain of Slit, organizing Slit distribution in vivo. It maintains a growth environment and functions as an extracellular scaffold that controls axon guidance events by organizing the availability of axonal growth and guidance cues at critical intermediate targets. Misregulation of Slit-Robo signaling involved in axonal guidance and neuronal connectivity is reflected to patients with αDG-RD.

On clinical grounds, classification is difficult because there are patients with milder abnormalities, such as microcephaly, cerebellar hypoplasia with or without cysts, learning disabilities with normal neuroimaging features and CMD or LGMD phenotype, and with normal cognitive function. Neuroimaging signatures on brain MRI can be summarized as cobblestone complex (type II cobblestone lissencephaly to focal pachygyria or polymicrogyria), midbrain hypoplasia, relatively thick tectum, fused colliculi, ventral pontine cleft, pontomesencephalic kink, abnormalities of cerebellar foliation, cerebellar cysts, hydrocephalus, occipital encephalocele, and patchy and confluent involvement of white matter with a high signal intensity on T2-weighted and FLAIR images (Fig. 626.12). A **high serum CK level** in the presence of the aforementioned imaging features simply differentiates a muscle disorder from other genetic causes of cortical malformations of development. A reduction or absence of immunolabeling with antibodies, which recognize glycosylated epitopes of αDG in muscle biopsy, is a pathologic signature for αDG-RD.

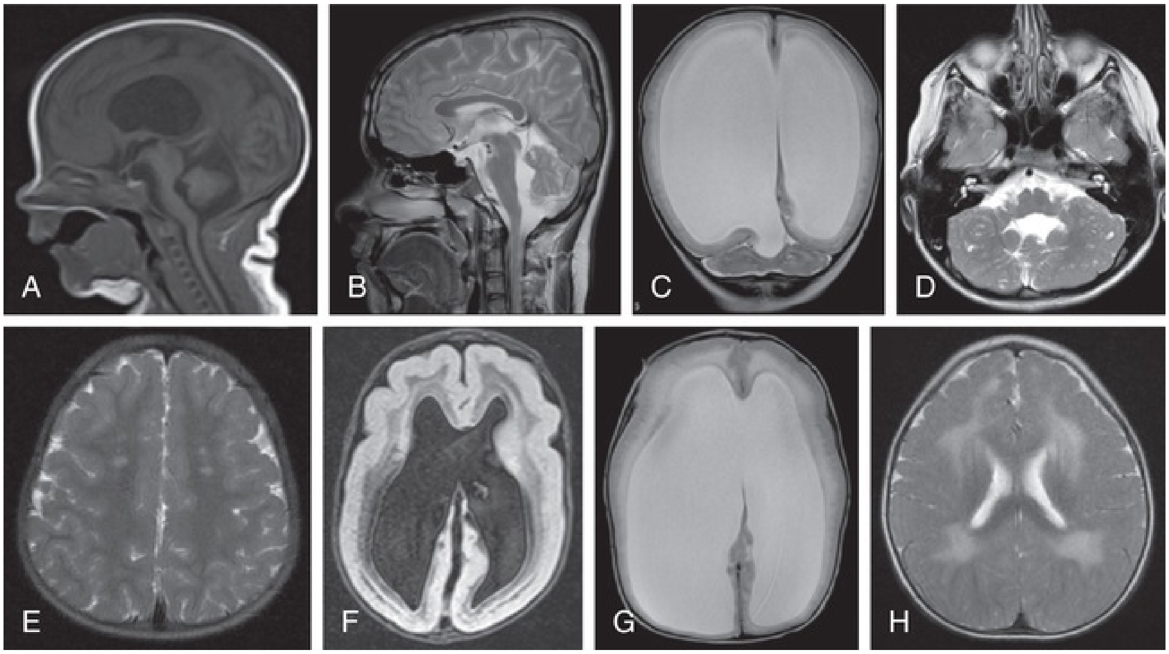

FIG. 626.12 Sagittal T1W image shows hypoplastic and "kinked" brainstem, and cerebellar hypoplasia *(POMGnt1)* **(A).** Sagittal T2W image revealing dorsal pontine flattening **(B)** *(POMK).* Coronal T2W image demonstrates huge ventriculomegaly, cerebellar hypoplasia, and cortical cobblestone lissencephaly *(ISPD)* **(C).** Axial T2W image showing cerebellar microcysts *(FKRP)* **(D).** Axial T2W image reveals bilateral frontal polymicrogyria **(E).** Axial FLAIR image shows lissencephaly *(POMGnt1)* **(F).** Axial T2W image reveals cobblestone lissencephaly **(G).** Axial T2W image shows cerebral periventricular white matter lesions **(H).**

There is an ever-expanding list of genes involved in αDG-RD. To date, mutations in up to 19 glycosyltransferases and accessory proteins have been found to be involved in the glycosylation of αDG (*DAG1*, *POMT1*, *POMT2*, *POMGnT1*, *POMGnT2*, *LARGE*, *FKRP*, *FKTN*, *ISPD*, *GTDC2*, *B3GNT1*, *B3GALNT2*, *GMPPB*, *TMEM5*, *SGK196*, *DPM1*, *DPM2*, *DPM3*, *DOLK*); the availability of targeted gene panels and next-generation sequencing (NGS) techniques will further increase the diagnostic yield in this spectrum.

Congenital disorders of glycosylation, involving both N- and O-glycosylation (mutations in *DPM1* , *DPM2* , and *DPM3*), overlap with αDG-RD, and may present with high serum CK levels, cognitive impairment, microcephaly, feeding difficulties, myoclonic epilepsy, and cerebellar hypoplasia.

Another example is a **CMD form overlapping with Marinesco-Sjögren syndrome (MSS) and dystroglycanopathy** due to *INPP5K* mutations, in patients with short stature, intellectual disability, and cataracts, described as a continuum of αDG-RD. *INPP5K* encodes inositol polyphosphate-5-phosphatase K, which has been shown to regulate myoblast differentiation and protein processing through its interaction with the endoplasmic reticulum chaperones.

Genes identified so far, functioning in the endoplasmic reticulum and/or Golgi apparatus, point to a common mechanism involving an interaction between the cells and the surrounding extracellular matrix in terms of brain malformations and muscle development.

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626.7

Amyoplasia

Harvey B. Sarnat

Congenital absence of individual muscles is common and is often asymmetric. A common aplasia is the *palmaris longus muscle* of the ventral forearm, which is absent in 30% of normal subjects and is fully compensated for by other flexors of the wrist. Unilateral absence of a *sternocleidomastoid muscle* is one cause of congenital torticollis. Absence of one *pectoralis major muscle* is part of the **Poland anomalad.**

When innervation does not develop, as in the lower limbs in severe cases of *myelomeningocele,* muscles can fail to develop. In *sacral agenesis,* the abnormal somites that fail to form bony vertebrae can also fail to form muscles from the same defective mesodermal plate, a disorder of induction resulting in segmental amyoplasia. Skeletal muscles of the extremities fail to differentiate from embryonic myomeres if the long bones do not form. The absence of one long bone, such as the radius, is associated with variable aplasia or hypoplasia of associated muscles, such as the flexor carpi radialis. End-stage neurogenic atrophy of muscle is sometimes called **amyoplasia,** but this use is semantically incorrect.

Generalized amyoplasia usually results in fetal death, and live-born neonates rarely survive. A mutation in one of the myogenic genes is the suspected etiology because of genetic knockout studies in mice, but it has not been proven in humans. An estimated 400 discrete diagnoses can lead to congenital arthrogryposis. The two largest categories are amyoplasia and distal arthrogryposis, which combined make up 50– 65% of all diagnoses within the arthrogryposis subset. Amyoplasia, the most common, is not clearly an inherited genetic syndrome of characteristic upper and lower limb contractures. Distal arthrogryposes, by contrast, have an underlying genetic abnormality, which in many cases seems to target the fast-twitch muscles of the developing fetus.

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626.8

Muscular Dysgenesis (Proteus Syndrome Myopathy)

Harvey B. Sarnat

Proteus syndrome is a disturbance of cellular growth involving ectodermal and mesodermal tissues, representing a cellular mosaicism. The genetic defect is a mutation in the *AKT1* gene, of the same genetic family as *AKT3*, which causes hemimegalencephaly; indeed, many children with Proteus syndrome also have hemimegalencephaly as another tissue overgrowth, not a separate association. These genes participate in the mammalian target of rapamycin (mTOR) pathway. Proteus syndrome also manifests as asymmetric overgrowth of the extremities, verrucous cutaneous lesions, angiomas of various types, thickening of bones, and excessive growth of muscles without weakness. Severe seizures, beginning in neonates, are uncommon. Histologically, the muscle demonstrates a unique *muscular dysgenesis.* Abnormal zones are adjacent to zones of normal muscle formation and do not follow anatomic boundaries.

Proteus syndrome is recognized as a phenotypical variety of the *epidermal nevus syndrome*, together with linear sebaceous nevus of Jadassohn, CLOVES syndrome, and others, as a postzygotic somatic mosaicism.

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626.9

Benign Congenital Hypotonia

Harvey B. Sarnat

Benign congenital hypotonia is not a disease, but it is a descriptive term for infants or children with nonprogressive hypotonia of unknown origin. The hypotonia is not usually associated with weakness or developmental delay, although some children acquire gross motor skills more slowly than normal. Tendon stretch reflexes are normal or hypoactive. There are no cranial nerve abnormalities, and intelligence is normal.

The **diagnosis** is one of exclusion (see Table 625.2 in Chapter 625) after results of laboratory studies, including muscle biopsy and imaging of the brain with special attention to the cerebellum, are normal. Muscle biopsy is deferred in some mild cases to follow the clinical evolution over time, but the diagnosis in these infants is more provisional. No known molecular genetic basis for this syndrome has been identified in the majority, but a rare form with an *RYR1* mutation and malignant hyperthermia is recognized. Table 625.3 in Chapter 625 lists the differential diagnoses.

The prognosis is generally good; no specific therapy is required. Contractures do not develop. Physical therapy might help achieve motor milestones (walking) sooner than expected. Hypotonia persists into adult life. The disorder is not always as *benign* as its name implies because a common complication is recurrent dislocation of joints, especially the shoulders. Excessive motility of the spine can result in stretch injury, compression, or vascular compromise of nerve roots or of the spinal cord. These are particular hazards for patients who perform gymnastics or who become circus performers because of agility of joints without weakness or pain.

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626.10

Arthrogryposis

Goknur Haliloglu

See also Chapter 702 .

Arthrogryposis (arthro, joint; gryp, curved), arthrogryposis multiplex congenita (multiplex, multiple; congenita, present at birth), and multiple congenital contractures are descriptive terms, used interchangeably to define contractures in two or more different body parts. Arthrogryposis is a sign rather than a diagnosis; anything that interferes or limits normal fetal movement can lead to congenital contractures. The contractures usually (1) involve the limbs, but also may include the jaw, neck, and spine; (2) are nonprogressive in nature; and (3) improve over time with early physiotherapy and orthopedic interventions.

Although each specific type is rare, the incidence of arthrogryposis is described as 1 in 3,000-5,000 live births, according to population-based studies.

Fetal Movement and the Link to Arthrogryposis

The main background factor in all forms of arthrogryposis is decreased or lack of fetal movement *(fetal akinesia/hypokinesia),* and the clinical severity is directly correlated with the onset. An early onset and long duration of decreased movements lead to a more severe phenotype at birth. The first trimester is a critical period in terms of progressive motor development. There is an evolution of the movement pattern; early fetal activity is believed to be generated by central pattern networks in the spinal cord and mediated by feedback from the immature muscle fibers of myotomes, shifting to a more specific pattern owing to the development of the supraspinal parts of the brain. The development of joints, joint spaces, and movements start at 5½ , 7, and 8 embryonic wk, respectively. Therefore, decreased fetal movement beyond 10 wk is a sign of maldevelopment and/or dysfunction of the early fetal central or peripheral nervous system. General movements with relatively simple and stereotypical sideways bending of the head and trunk can be noticed as early as 7 wk of pregnancy (embryonal, 5 wk). They develop in a craniocaudal and proximal-to-distal direction, with a propagation from the shoulders and hips first, to the upper and, then, lower limbs (7-9 wk). At this time point, jaw opening also begins. Isolated arm and leg movements can be visible from 8-9 wk to 10 wk, respectively. By 11 wk of pregnancy, a full range of limb movements (extension, flexion, rotation, abduction, and adduction of each limb) develop. Developmentally, fetal sucking and swallowing are described in the early second trimester. Fetal breathing movements begin around 12-14 wk, and by 20 wk become more regular. Facial movements are recognized in the late second trimester, and between 24 and 35 wk show a developmental progression from unrelated facial movements toward fetal facial gestalts.

Animal models demonstrated the link between embryonic movement and muscle contraction to joint formation. Contracting musculature is the main role player in maintaining joint progenitor cells committed to their fate, and for correct joint cavitation and formation. A key modulator of joint formation, beta-catenin, is activated in a contraction-dependent manner. Further, a reduced muscle phenotype also has a differential effect on ossification centers, with significant decreases in bone formation. Muscle development, early spontaneous contraction, innervation, and joint and bone formation seem to be complex interdependent developmental processes that finally allow normal limb movement and maintenance. Although not investigated in detail, normal fetal breathing and/or swallowing and lung and gastrointestinal maturation may be affected through the same developmental processes.

Decreased movement is associated with a compensatory connective tissue response, *collagenosis* (an increase of connective tissue around the joints), which limits the joint movements and increases contractures. Any effort to mobilize the joints may lead to minor fractures of abnormal joint surfaces. Diaphragmatic and intercostal muscle dysfunction further results in loss of rhythmic thoracic movements and leads to a small thoracic cage and failure of maturation of the alveoli and surfactant, leading to pulmonary hypoplasia. By 15 wk of gestation, development of the lung is arrested at the canalicular phase, which is also a critical point for joint development. Lack of muscle pull at sites of normal attachment may lead to craniofacial abnormalities, with facial weakness leading to a tented upper lip appearance.

Pathologic changes with an onset during intrauterine development are confined to primary alterations in anterior horn cells, roots, peripheral nerves, motor endplates, or muscles. Spinal cord involvement, with abnormal histology and unequal distribution of alpha motor neurons in anterior horn cells, is described in infants with the neurogenic forms of arthrogryposis.

Basic Categories, Etiologies, and Classifications

Decreased or lack of in utero movements are all reflected in the clinical features of the **lethal forms of lower motor neuron diseases** and the **fetal akinesia/hypokinesia deformation sequence (FADS), Pena-Shokeir phenotype,** which represents the severe end of the arthrogryposis spectrum. This phenotype can be described as intrauterine growth restriction, multiple joint contractures, shortened limbs, craniofacial changes (micrognathia, cleft palate, high nasal root, ocular hypertelorism), pulmonary hypoplasia, polyhydramnios, decreased gut motility, a shortened gut, a short umbilical cord, skin changes, and short limbs. Iatrogenic fractures due to osteoporosis of long bones in the prenatal period can be an additional feature. They may be isolated or associated with additional organ system abnormalities.

Lower motor neuron diseases, characterized by degeneration of anterior horn cells of the spinal cord and descending tracts, may overlap with arthrogryposis and FADS. The prototype in childhood is **spinal muscular atrophy (SMA)** (see Chapters 630.2 and 630.3).

Lethal congenital contracture syndrome (LCCS) and **lethal arthrogryposis with anterior horn cell disease (LAAHD)** are two independent neurogenic arthrogryposis subtypes, with a remarkable phenotypic overlap and ever-expanding heterogeneity at the phenotypic and molecular genetic levels.

Amyoplasia and **distal arthrogryposis (DA)** are the two most common categories of conditions, accounting for up to 50–65% of the patients presenting with arthrogryposis.

The most common type is Amyoplasia, which stands for A, no; myo, muscle; and plasia, growth; it is also called classic arthrogryposis. It is a sporadic condition in which limb muscle tissue is replaced by fatty tissue. Despite extensive genetic studies, no chromosomal or single gene etiology has been identified to date. Amyoplasia (with a capital A), is a diagnosis of exclusion, so it should be distinguished from other genetic forms of arthrogryposis presenting with decreased or absent muscle mass. The natural course, management, and genetic counseling depend on a correct diagnosis. The incidence of Amyoplasia is 1/10,000 live births. Discordant monozygotic twinning is described, that is, at least 6.6% of the affected individuals are described to have an unaffected monozygotic twin.

The diagnosis should be considered in the presence of symmetric congenital, rigid contractures with a characteristic position of limbs in the newborn period (internal rotation of the shoulders, fixed extension of the elbows, pronation of the forearm, flexion of the wrist, camptodactyly, and severe equinovarus deformity of the feet; Fig. 626.13), accompanied by shortness of the affected limbs; a marked decrease in limb muscle mass; lack of flexion creases on limbs, fingers, and hands; mild intrauterine growth retardation; dimples overlying affected joints; spared trunk; nevus flammeus over the craniofacial midline; bone fractures; osteoporosis of the long bones; normal CNS function; and a negative family history. There may be spinal involvement. Muscle defects in the abdominal wall, inguinal hernias, bowel atresia, absence of trunk muscles, digit compromise, or constriction bands of the limbs or digits can accompany the clinical picture owing to vascular compromise. There is a range of severity, from very mild to severe involvement, with almost 15% of patients presenting with a pure, isolated upper extremity or lower extremity involvement. The diagnosis of these forms requires experience and evaluation of a differential diagnostic list. Contractures usually improve over time with early physiotherapy and orthopedic care (see Chapter 702), with almost 85% of affected individuals being ambulatory by age 5 yr and two thirds being able to live independent lives.

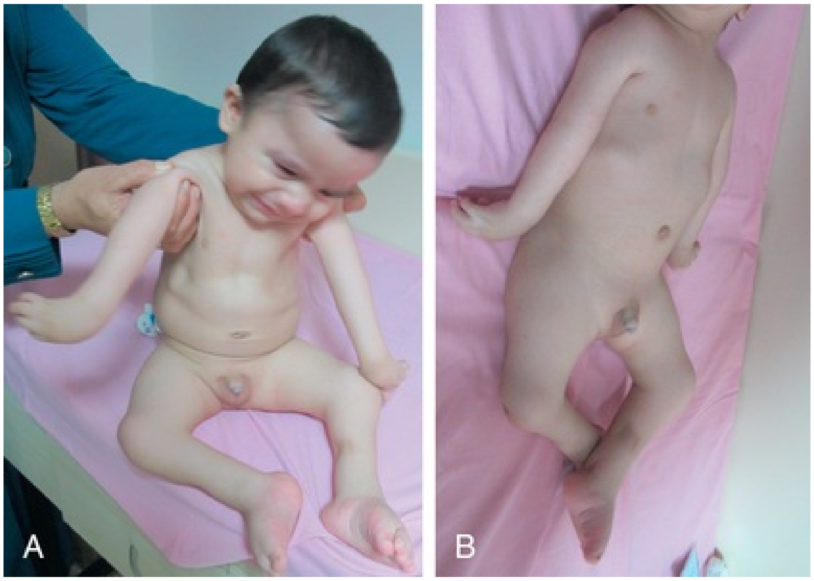

FIG. 626.13 Typical appearance of a patient with amyoplasia with internal rotation of the shoulders, fixed extension of the elbows, clenched wrist **(A),** hip dysplasia, and equinovarus deformity **(B).**

Distal arthrogryposis (DA) is a heterogeneous group with a wide phenotypic variability, primarily involving the hands and feet, with sparing of the proximal joints. The prevalence is not known. It is often associated with abnormal facies and autosomal dominant inheritance, but autosomal recessive and sporadic patients are also described. Patients usually present in an orthopedic environment. There is an expanded classification with 11 different syndromes (see Chapter 702 , Table 702.2). Abnormalities of fast-twitch muscles are identified in a majority of patients with DA. Mutations in sarcomeric muscle proteins (troponin, tropomyosin, and myosin) can cause DA or congenital myopathies. Other than this clinical overlap due to a particular gene mutation, a particular phenotype may be associated with mutations in different genes. Some of the DA forms prove that embryonic expression of some of the genes during fetal life, such as myosin heavy chain *(MYH3)*, affects sarcomeric proteins and the force generation in muscle cells. Dominant and recessive gene mutations related to mechanotransduction are identified in the DA group.

Among over 400 conditions described within this complex category (including gene mutations, chromosomal abnormalities, deletions, and duplications), over 320 genes have been implicated, and a responsible gene has been identified in more than 150 of the conditions. Considering this extreme clinical and genetic heterogeneity, it is suggested that classifications can be done at different levels, depending on the *area of involvement* , *overall cause of fetal akinesia/hypokinesia* , and *etiologic process underlying the developmental dysfunction* , or taking into consideration the *cardinal features*, as in the case of amyoplasia and DA (Table 626.8). With the utility of next-generation sequencing technologies and recent advances in our molecular diagnostic pathway, the field of arthrogryposis is moving to *gene-based classification* systems and grouping conditions according to affected or associated gene products and involved developmental pathways.

Table 626.8

Major Causes of Arthrogryposis Multiplex Congenita

SITE OF MAJOR PATHOLOGIC FINDINGS	DISORDER
Cerebrum–brain stem	Microcephaly; migrational disorders: lissencephaly-pachygyria (e.g., Zellweger syndrome), schizencephaly, polymicrogyria, agenesis of corpus callosum; fetal alcohol syndrome; cytomegalovirus infection; pontocerebellar hypoplasia (type I); dentato-olivary dysplasia; leptomeningeal angiomatosis; encephaloclastic processes: neuronal destruction, porencephalies, hydranencephaly, multicystic encephalomalacia; hydrocephalus
Anterior horn cell	Developmental agenesis–hypoplasia–dysgenesis (amyoplasia congenita); destructive disorders (apparent intrauterine ischemic events); degenerative disorders (severe Werdnig-Hoffmann disease [SMA type 0 or IA], lethal congenital contracture syndrome, spinal muscular atrophy with pontocerebellar hypoplasia, spinal muscular atrophy with respiratory distress, X-linked infantile spinal muscular atrophy, early-onset non-5q spinal muscular atrophy); Möbius

	syndrome; cervical spinal atrophy; lumbar spinal atrophy; lumbosacral meningomyelocele; sacral agenesis; other
Peripheral nerve or root	Hypomyelinative polyneuropathy; axonal polyneuropathy; neurofibromatosis
Neuromuscular junction	Infant of myasthenic mother; congenital myasthenic syndromes; multiple pterygium syndrome (Escobar type); infant of mother with multiple sclerosis (?)
Muscle	Congenital muscular dystrophy (merosin-positive and merosin-negative); congenital myotonic dystrophy; myotubular myopathy; central core disease; nemaline myopathy; congenital myopathy due to sodium channel mutation; congenital polymyositis; congenital fiber-type disproportion; glycogen storage myopathy (muscle phosphorylase deficiency, phosphofructokinase deficiency); mitochondrial myopathy; Freeman-Sheldon syndrome
Primary disorder of joint or connective tissue	Marfan syndrome; contractural arachnodactyly; other disorders of connective tissue; intrauterine periarticular inflammation
Intrauterine mechanical obstruction	Uterine abnormality; amniotic bands; oligohydramnios; twin pregnancy; extrauterine pregnancy

From Ghosh PS, Volpe JJ: Arthrogryposis multiplex congenita. In Volpe JJ, editor: Volpe's neurology of the newborn, ed 6, Philadelphia, 2018, Elsevier, Table 31-3.

The etiology can be based on abnormalities of the CNS, nerve, muscle, and connective tissue; lack of space; maternal illness; environmental agents; or vascular compromise; they may result in decreased intrauterine movements. As an alternative approach, genetic, sporadic (amyoplasia), and environmental backgrounds or neurogenic, myopathic, syndromic, and metabolic categories can be used to review possible etiologies.

For practical purposes, the clinical classification is often based on the presence and absence of additional organ system abnormalities or malformations and the presence or absence of CNS involvement, including intellectual disability, and lethality. Of the children with arthrogryposis, ~ 30% will primarily have limb involvement, ~ 30% will have affected limbs plus other body areas but normal cognitive function, and ~ 30% will have CNS dysfunction.

Diagnostic Approach and Laboratory Evaluation

In such a diverse group of disorders with extreme heterogeneity at the etiologic, phenotypic, and molecular genetic levels, establishing a specific diagnosis is important. The natural history, evolution, prognosis, therapeutic interventions, and genetic counseling/prenatal diagnosis depend on a precise diagnosis.

The first step in the diagnostic approach is detailed history taking, including information about the pregnancy, delivery, and family history, with at least a three-generation pedigree analysis (Table 626.9). The maternal perception of intrauterine movements, any difference compared with previous pregnancies, polyhydramnios, oligohydramnios, intrauterine infections, toxic exposures, maternal illness, maternal and paternal age, breech presentation, type of delivery, and any event complicating the delivery should be reviewed. Newborns with arthrogryposis are prone to hypoxic-ischemic insults.

Table 626.9

Clinical Evaluation of Arthrogryposis: Clues for a Detailed History

PREGNANCY	• Maternal illness, acute or chronic (diabetes, myasthenia gravis, myotonic dystrophy, etc.) • Infections (rubella, rubeola, zika virus, coxsackievirus, enterovirus, Akabane virus, etc.) • Fever (>39°C, determine timing in gestation) • Nausea (viral encephalitis, position of baby, etc.) • Drugs (curare, robaxin, alcohol, phenytoin, addictive drugs, misoprostol, etc.) • Fetal movement (polyhydramnios, fetal kicking in one place, rolling decreased) • Oligohydramnios, chronic leakage of amniotic fluid • Polyhydramnios, hydrops • Trauma during pregnancy (blow to the abdomen, attempted termination, car accident, etc.) • Other complications during pregnancy, such as bleeding, abnormal lie, threatened abortion • Prenatal diagnosis (early amniocentesis, ultrasound studies, etc.)
DELIVERY HISTORY	• Presentation (breech, transverse, etc.) • Length of gestation • Traumatic delivery (limb, CNS, fracture, etc.) • Intrauterine mass (twin, fibroid, etc.) • Abnormal uterine structure or shape • Abnormal placenta, membranes, or cord length or position • Time of year, geographic location
FAMILY HISTORY	• Marked variability within family • Change with time (degeneration vs improvement) • Increased incidence of congenital contractures in 2nd- and 3rd-degree relatives • Hyperextensibility or hypotonia present in family member • Rule out myotonic dystrophy, myasthenia gravis in parents (particularly mother) • Consanguinity • Advanced parental (mother or father) age • Increased stillbirths or miscarriages • If more than one consecutively affected child, consider maternal antibodies to fetal neurotransmitter
NEWBORN EVALUATION	Description of contractures • Which limbs and joints • Proximal vs distal • Flexion vs extension

	• Amount of limitation (fixed vs passive vs active movement) • Characteristic position at rest • Severity • Complete fusion or ankylosis vs soft tissue contracture Other anomalies (contractures are most obvious, look for other anomalies) Deformities Genitalia (cryptorchid, lack of labia, microphallus, etc.) Limbs (pterygium, shortening, webs, cord wrapping, absent patella, dislocated radial heads, dimples, etc.) Jaw (micrognathia, trismus, etc.) Facies (asymmetry, flat bridge of nose, hemangioma, movement, etc.) Scoliosis and kyphosis (fixed or flexible) Dimple (over specific joints or bones) Skin (hemangioma, defects, hirsutism) Dermatoglyphics Hernias, inguinal and umbilical, abdominal wall defect Other features of fetal akinesia sequence • Intrauterine growth retardation • Pulmonary hypoplasia • Craniofacial anomalies (hypertelorism, cleft palate, depressed tip of nose, high-bridged nose) • Functional short gut with feeding problem • Short umbilical cord
MALFORMATIONS	Eyes (small, corneal opacities, malformed, ptosis, strabismus, etc.) CNS (structural malformation, seizures, ID, etc.) Palate (high, cleft, submucous, etc.) Limb (deletion anomalies, radioulnar synostosis, etc.) GU (structural anomalies of kidneys, ureters, and bladder) Skull (craniosynostosis, asymmetry, microcephaly, etc.) Heart (congenital structural anomalies vs cardiomyopathy) Lungs (hypoplasia vs weak muscles or hypoplastic diaphragm) Tracheal and laryngeal clefts and stenosis Changes in vasculature (hemangiomas, cutis marmoratus, blue cold distal limbs, etc.) Other visceral anomalies
OTHER FEATURES	Neurologic examination (detailed) • Vigorous vs lethargic • Deep tendon reflexes (present vs absent, slow vs fast) • Sensory intact or not Muscle • Mass (normal or decreased) • Texture (soft vs firm) • Fibrous bands • Normal tendon attachments or not • Changes with time
COURSE	***Changes with time*** Developmental landmarks (motor vs social and language) Growth of affected limbs Progression of contractures Lethal vs CNS damage vs stable vs improvement Asymmetry Trunk vs limb changes Intellectual abilities Socialization Feeding problems ***Response to therapy*** Spontaneous improvement

	Response to physical therapy Response to casting Which surgery at which time Development of motor strength proportionate to limb size Abnormal reaction to drugs

CNS, central nervous system; ID, intellectual disability; GU, genitourinary.

From Hall JG: Arthrogryposis (multiple congenital contractures): Diagnostic approach to etiology, classification, genetics, and general principles, Eur J Med Genet 57:464-472, 2014.

There is not a standard set of laboratory investigations that can serve as a diagnostic tool (Table 626.10). Radiologic tests (radiographs, brain and muscle MRIs), electrophysiologic tests (electromyography, nerve conduction velocities), muscle biopsy, chromosomal microarray analysis (array comparative genomic hybridization [CGH]), and molecular genetic tests must be individualized for each patient. Input from a clinical geneticist and experienced multidisciplinary team is invaluable. Documentation of the range of motion, distribution of contractures, muscle tone and strength, and facial involvement with serial photographs and/or videos should be a part of follow-up visits. There is no laboratory test that can substitute for experience in making the clinical judgment.

Table 626.10

Laboratory Evaluation

Documentation of range of motion and position with photographs
Radiographs if • Bony anomalies (gracile, fusions, extra or missing carpals and tarsals, etc.) • Disproportionate • Scoliosis • Ankylosis • Dislocation (hips, radial head, patella, etc.)
MRI to evaluate CNS (brain and spinal cord) and muscle mass obscured by contractures
Ultrasonographic evaluation of CNS (brain and spinal cord) or other anomalies, and to establish potential muscle tissue
Chromosome studies/CGH array if • Multiple system involvement • CNS abnormality (eye, microcephaly, ID, lethargy, degenerative course) • Streaky or segmental involvement • Consider fibroblast studies if lymphocytes were normal and patient has ID with no diagnosis • DNA gene testing if condition fits a known disorder for which gene testing is available • Consider next-generation sequencing technologies (targeted gene panels, whole-exome sequencing, whole-genome sequencing) if family available
Video of movement, including facial, range of movement, strength-repeat at regular intervals
Viral culture as appropriate and specific antibodies or IgM levels in newborn
Muscle biopsy in normal and affected areas at time of surgery to distinguish myopathic forms from neuropathic forms (do special histopathology and electron microscopic studies) If elevated creatine kinase or unusual muscle response, consider muscle biopsy earlier, examine mitochondria

EMG in normal and affected area
Nerve conduction in normal and affected area
Creatine kinase if • Generalized weakness • Doughy or decreased muscle mass • Progressive course
Eye examination (opacities, retinal degeneration, etc.)
Maternal antibodies to neurotransmitters, if myasthenia gravis or recurrent affected pregnancies without diagnosis
Spinal muscular atrophy (SMN) DNA testing according to clinical features
Mitochondrial DNA analysis
Metabolic screening

CGH, comparative genomic hybridization; CNS, central nervous system; EMG, electromyography; ID, intellectual disability; IgM, immunoglobulin M; MRI, magnetic resonance imaging.

From Hall JG: Arthrogryposis (multiple congenital contractures): diagnostic approach to etiology, classification, genetics, and general principles, Eur J Med Genet 57:464-472, 2014.

In the case of a recognized phenotype, molecular tests can be directed toward the working diagnosis. Depending on the availability of next-generation sequencing technologies, the traditional diagnostic trend has shifted to a diagnosis by genetic sequencing. Disease-specific targeted gene panels can serve a diagnostic purpose, because other than a variety of early-onset muscle diseases, mitochondrial and metabolic diseases are covered, as well. In a large cohort of patients presenting with fetal akinesia/hypokinesia, arthrogryposis, or severe congenital myopathies, the use of next-generation sequencing provided a conclusive diagnosis in 18 out of 38 families (47%). Diagnostic yields range between 20% and 60%, depending on the homogeneity of the patient population; however, despite all efforts, nearly 50% of patients with arthrogryposis of a genetic origin do not have a precise molecular diagnosis.

Autopsy evaluation is extremely valuable. It should include an extensive workup for visceral anomalies, malformations of cortical development, and the number of anterior horn cells and their size in the spinal cord, with special attention paid to patchy involvement and the presence or absence of tracts at various levels in the spinal cord. Evaluation of the peripheral nerve, eye, and muscle tissue from different muscle groups and the diaphragm is also needed. Tendon attachments, fibrous bands replacing muscle, and cartilaginous or bony fusions can be evaluated, in addition to the presence of other malformations, deformations, or disruptions. Microarray analysis from different tissues and DNA extraction and molecular testing are also possible.

Differential Diagnosis

There is an ever-expanding list of disorders presenting with arthrogryposis. Almost 50% of fetal akinesia/hypokinesia presentations are neuromuscular in origin, involving all points along the neuromuscular axis (motor neurons, peripheral nerves, neuromuscular junctions, and the skeletal muscle regulatory and contractile apparatus). Mechanosensitive ion channels are another area of interest.

On clinical grounds, from a neuromuscular standpoint, one can recognize severe spinal muscular atrophies (SMA type 0), atypical SMA forms with arthrogryposis and bone fractures (see Chapter 630.2), lower motor neuron diseases (see Chapter 630.3), congenital muscular dystrophies (CMDs) with specific attempts to recognize early sclerotic forms of the Ullrich CMD phenotype (Fig. 626.14) (see Chapter 627.6), and CMD with CNS involvement–alpha dystroglycan–related CMD (Fig. 626.15) (see Chapter 626.06). In any infant with contractures and/or facial weakness with a tented upper lip, examination of the mother should be routinely performed for myotonic reactions as a first step for CMD (Fig. 626.16 and **Video 626.1** ▶) (see also Chapter 627.3). With the same clinical presentation, if the myotonic reaction of the mother is negative, congenital myopathies (Fig. 626.17 and **Video 626.2** ▶) (see also Chapter 626.03) should be included in the differential diagnosis. Fetal acetylcholine receptor inactivation syndrome is characterized by clinical features ranging from mild facial and bulbar myopathy to arthrogryposis, and *maternal treatment* can improve the outcome (see Chapter 630.1). Some pterygium syndromes may respond to *acetylcholine treatment.*

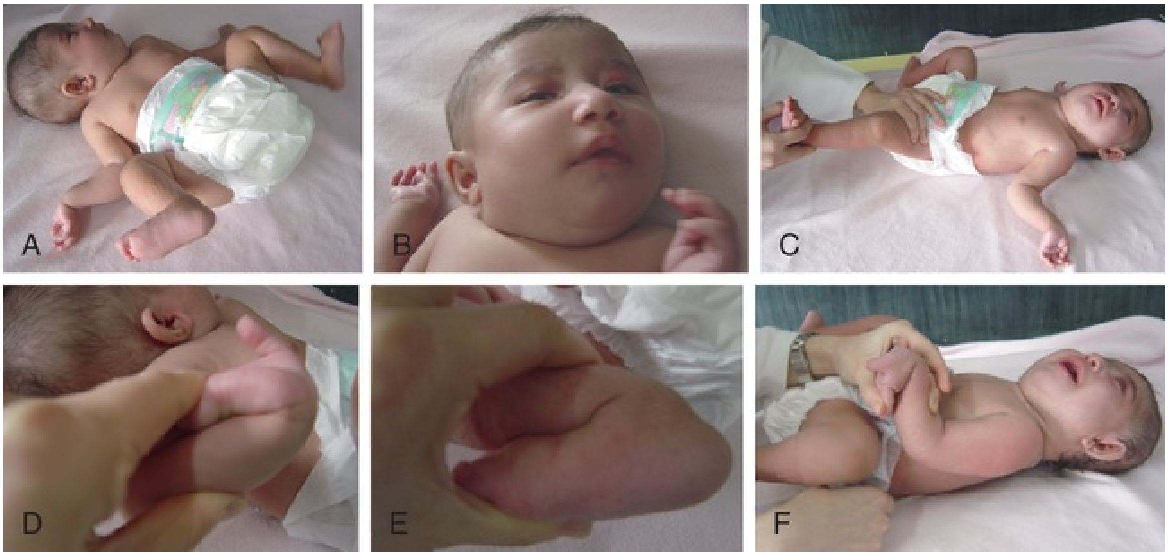

FIG. 626.14 A 3 mo old male infant, born with arthrogryposis **(A),** congenital torticollis **(B),** proximal knee contractures **(C),** and distal laxity **(D-F),** a clinical phenotype consistent with Ullrich congenital muscular dystrophy.

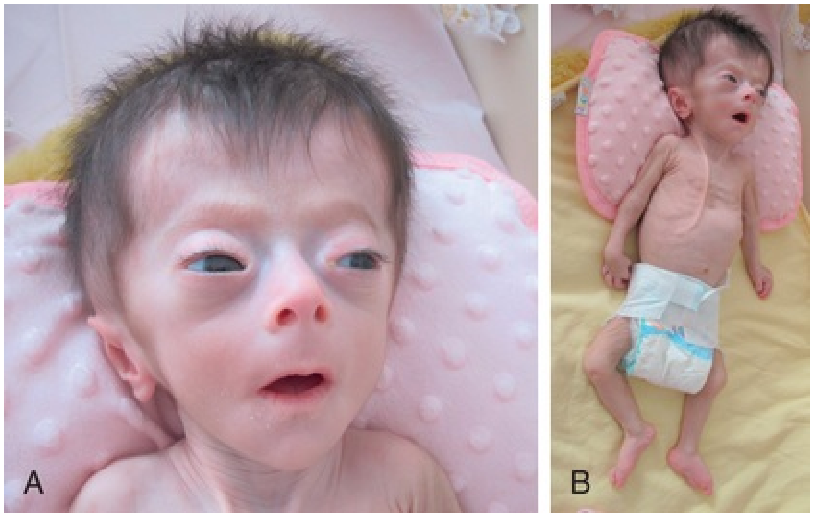

FIG. 626.15 A 3 mo old female infant with an intrauterine diagnosis of hydrocephalus and arthrogryposis. Ventriculoperitoneal shunt replacement at birth. Note dysmorphic facial features, megalocornea **(A),** failure to thrive, decrease in muscle mass, and generalized weakness **(B).** A high serum CK level with CNS malformation on brain MRI led to diagnosis of Walker-Warburg syndrome with *POMT1* mutation.

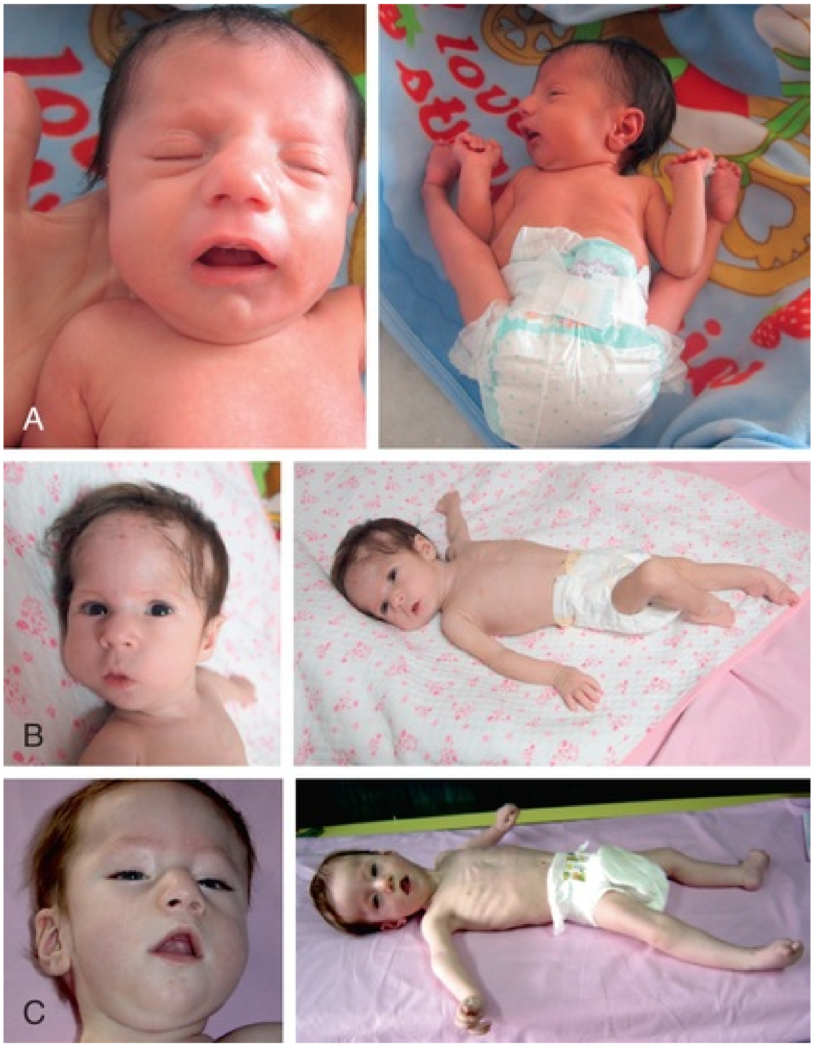

FIG. 626.16 Arthrogryposis due to congenital myotonic dystrophy in the newborn period **(A),** at age 3 mo **(B),** and at 1 yr **(C).** Note severe hyperextension of the limbs at birth (A) and facial weakness characterized by tented upper lip **(B** and **C),** signs that should lead to physical examination of the mother. See also Video 626.1 ▶ .

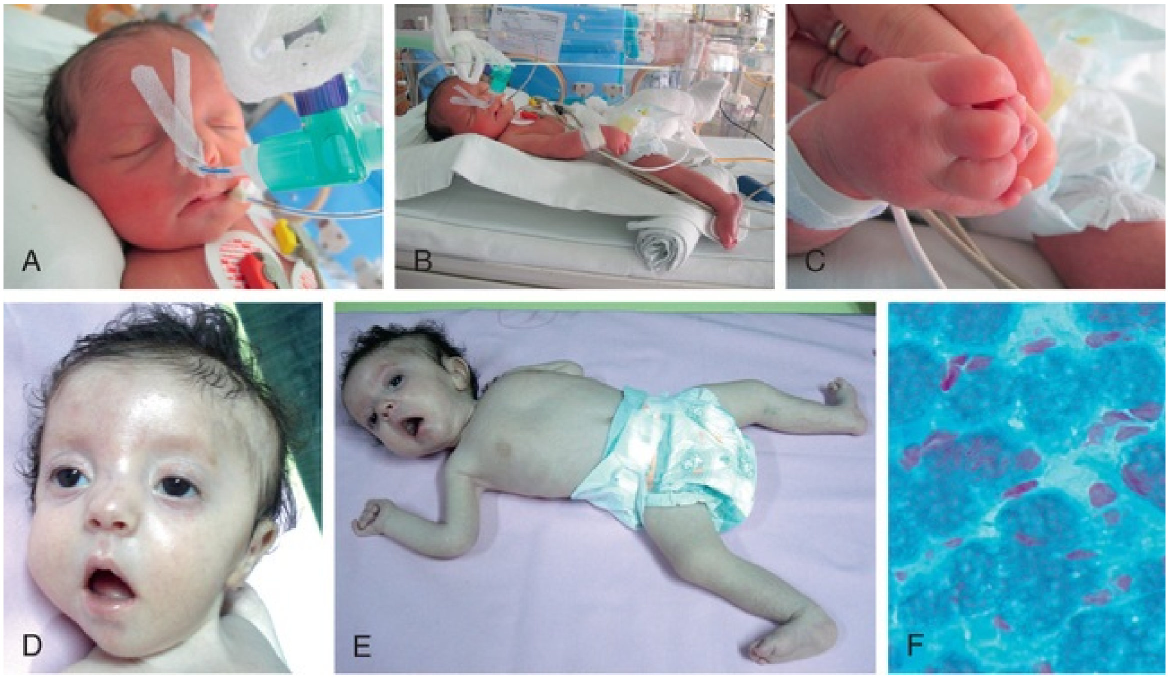

FIG. 626.17 Arthrogryposis, respiratory insufficiency, and fractures at birth **(A-C),** with a family history of consanguinity and similarly affected infant at the age of 3 mo with dysmorphic features, severe facial involvement (tented upper lip), frontal bossing, epicanthus **(D),** pectus excavatum deformity, and severe generalized weakness **(E).** Muscle biopsy revealed intracytoplasmic nemaline rods **(F),** leading to a diagnosis of *KHL40* -nemaline myopathy. See also Video 626.2 .

Prevention or treatment of metabolic disturbances (metabolic acidosis) or treating an inherited metabolic disease may also have a positive impact on the outcome. Carbohydrate-deficient glycoprotein syndrome (CDG), perinatal lethal forms of Gaucher disease, glycogen storage disease types IV and VII (phosphofructokinase deficiency), Zellweger syndrome spectrum, adenylosuccinate lyase deficiency, and ARC (arthrogryposis, renal dysfunction, cholestasis) syndrome are among the diseases in this group with an autosomal recessive inheritance.

Genetic Counseling and Prenatal Diagnosis

Establishing a molecular diagnosis in an index patient with a genetic form of arthrogryposis is required for appropriate genetic counseling and prenatal diagnosis. Despite maternal care and the availability of prenatal ultrasonography

(US), which can confirm abnormal movements and postural findings as early as 11 wk, 75% of affected individuals with arthrogryposis were reported to be not diagnosed before birth. Real-time US can visualize contractures, the quality of in utero movements, the joint positioning, lung hypoplasia, nuchal edema, the muscle mass, and the bone growth in the first or early second trimester. Prenatal or postnatal MR findings can be used as a complementary adjunct to US, especially for the evaluation of accompanying CNA malformations. The maternal perception of decreased intrauterine movements and high-risk pregnancies should be carefully evaluated. In an effort to improve the detection rate and guide the diagnostic strategy, an algorithm can be applied as early as the first prenatal US at 12 wk, in the first trimester (Fig. 626.18).

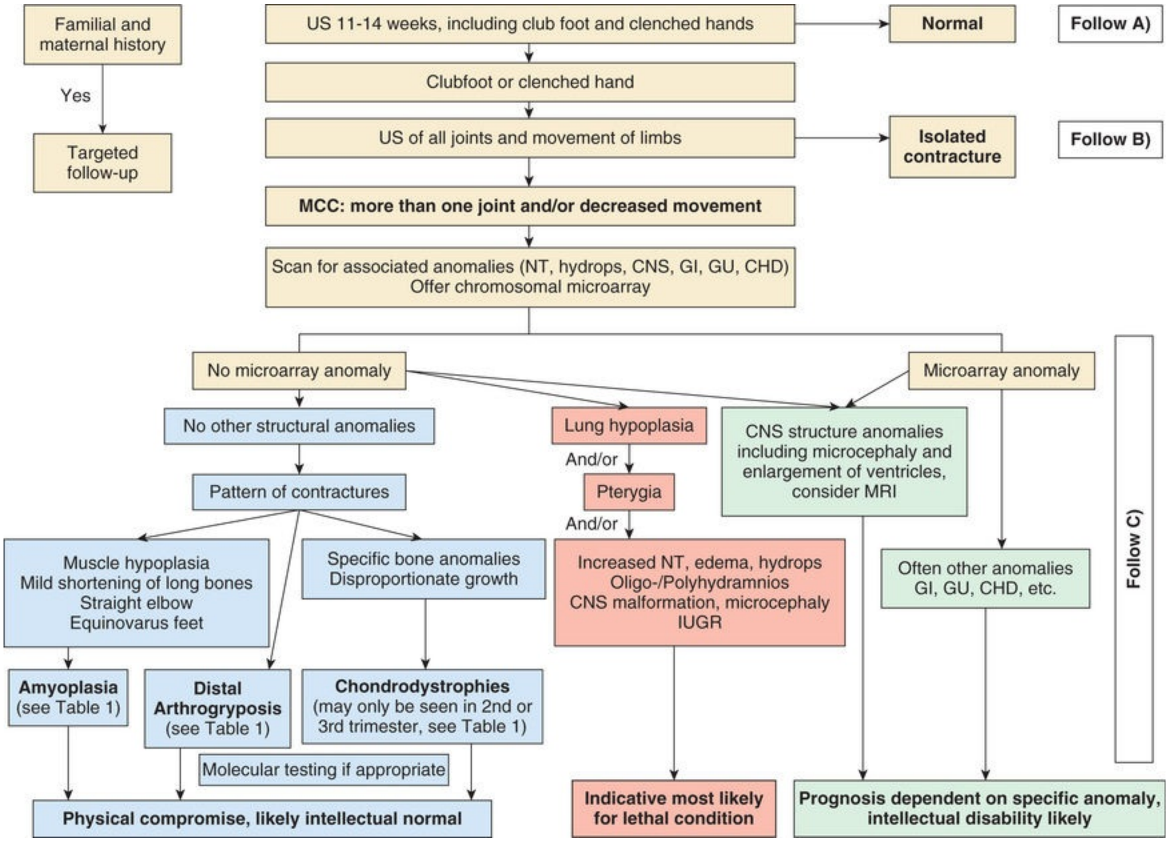
Familial and maternal history
Yes
Targeted follow-up
US 11-14 weeks, including club foot and clenched hands
Normal
Follow A)
Clubfoot or clenched hand
US of all joints and movement of limbs
Isolated contracture
Follow B)
MCC: more than one joint and/or decreased movement
Scan for associated anomalies (NT, hydrops, CNS, GI, GU, CHD)
Offer chromosomal microarray
No microarray anomaly
Microarray anomaly
Follow C)
No other structural anomalies
Lung hypoplasia
And/or
Pterygia
And/or
CNS structure anomalies including microcephaly and enlargement of ventricles, consider MRI
Pattern of contractures
Muscle hypoplasia
Mild shortening of long bones
Straight elbow
Equinovarus feet
Specific bone anomalies
Disproportionate growth
Increased NT, edema, hydrops
Oligo-/Polyhydramnios
CNS malformation, microcephaly
IUGR
Often other anomalies
GI, GU, CHD, etc.
Amyoplasia (see Table 1)
Distal Arthrogryposis (see Table 1)
Chondrodystrophies (may only be seen in 2nd or 3rd trimester, see Table 1)
Molecular testing if appropriate
Physical compromise, likely intellectual normal
Indicative most likely for lethal condition
Prognosis dependent on specific anomaly, intellectual disability likely

FIG. 626.18 Proposed diagnostic algorithm for the detection and differential diagnosis of multiple congenital contractures (MCCs): the algorithm should be applied as early as the first trimester (first ultrasound at 12 wk), the earliest detectable onset of MCC and fetal akinesia, and is valid for all three trimesters. If the first trimester scan is missed, an early second-trimester scan (14-16 wk) is provided instead. In case of a normal ultrasound in the first trimester, ultrasound assessment for MCC and fetal akinesia should be repeated at 18-20 wk following the given algorithm. In

case of an apparently isolated contracture in the first trimester, assessment for MCC and fetal akinesia should be repeated at 18-20 wk following the given algorithm. Differential prenatal onset of conditions leading to MCC and fetal akinesia has to be accounted for. In case of MCC, further exams should be provided at 14, 18, 20, 23, 28, and 32 wk, each time following the algorithm until the most probable diagnosis and outcome can be provided. Fetal autopsy is considered as a standard of care. Differential prenatal onset of conditions leading to MCC and fetal akinesia has to be accounted for. (From Filges I, Hall JG: Failure to identify antenatal multiple contractures and fetal akinesia: proposal of guidelines to improve diagnosis, Prenat Diagn 33:61-74, 2013.)

Timely recognition leads to a further etiologic and diagnostic workup and pregnancy management and creates time for informed choices, in utero stimulation, or early delivery according to the degree of lung maturation. In a case of detection of contractures in a prenatal US study, physicians involved in the care of a pregnant woman should examine her to rule out myotonic dystrophy, in order to prevent serious complications. Due to high rates of infertility, before introducing artificial reproductive techniques, myotonic dystrophy should be considered. As a result of genetic anticipation, the diagnosis of the mother may be delayed to the time of giving birth to a severely affected infant with arthrogryposis (see Chapter 627.3). Arthrogryposis with a history of myasthenia gravis in the mother should be evaluated accordingly, because miscarriage, stillbirth, or neonatal death can complicate the picture (see Chapter 630.1).

Chromosomal abnormalities and autosomal recessive, autosomal dominant, X-linked, and mitochondrial inheritance have been all described in the disorders related to arthrogryposis, and genetic counseling should be provided accordingly. If a specific diagnosis is not made, the empirical recurrence risk is defined as 3%, and it is slightly higher (7%) for arthrogryposis plus CNS involvement.

Management

Each affected individual with arthrogryposis is unique, and the natural course of the condition depends on the underlying etiology and management. A multidisciplinary team approach (pediatricians, pediatric orthopedic specialists, plastic or hand surgeons, rehabilitation physicians, occupational therapists, physical therapists, medical geneticists, neurologists) is essential in standard care (see Chapter 702). Management is shifting to a multidisciplinary clinic that provides patient-centered, comprehensive care in a coordinated manner.

In terms of amyoplasia, follow-up is required to identify treatment outcomes such as the development of degenerative arthritis, the need for orthotics for ambulation, or the possibility of becoming overweight in adulthood. Cytokines and other factors released in response to early therapeutic interventions are suggested to facilitate the elongation of pathologic periarticular soft tissues and increase joint motion. The core principle of management in DA is to preserve muscle function. Anesthesia-related complications due to limited jaw opening, restrictive pulmonary function, and the risk of malignant hyperthermia should be considered in the setting of multiple surgeries.

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CHAPTER 627

Muscular Dystrophies

Diana X. Bharucha-Goebel

The term *dystrophy* means abnormal growth, derived from the Greek *trophe,* meaning nourishment. A muscular dystrophy is distinguished from all other neuromuscular diseases by four obligatory criteria: *It is a primary myopathy, it has a genetic basis, the course is progressive, and degeneration and death of muscle fibers occur at some stage in the disease.* This definition excludes neurogenic diseases such as spinal muscular atrophy, nonhereditary myopathies such as dermatomyositis, nonprogressive and nonnecrotizing congenital myopathies such as congenital muscle fiber–type disproportion, and nonprogressive inherited metabolic myopathies. Some metabolic myopathies can fulfill the definition of a progressive muscular dystrophy but are not traditionally classified as dystrophies (muscle carnitine deficiency).

Many muscular dystrophies might eventually be reclassified as metabolic myopathies once the biochemical defects are better defined. Muscular dystrophies are a group of unrelated diseases, each transmitted by a different genetic trait and each differing in its clinical course and expression. Identifiable mutations in some genes may lead to a spectrum of clinical phenotypes, ranging in age of onset, severity, and presence of comorbidities. Some muscular dystrophies are more severe and/or may be present at birth or soon after birth, typically defined as *congenital muscular dystrophies,* whereas others may have an onset in childhood or even in adulthood. There is a range of severity from those that lead to death in the neonatal period to those that progress gradually over decades, generally with a normal lifespan. Some categories of dystrophies, such as limb–girdle muscular dystrophy (LGMD), are not homogeneous diseases but rather syndromes encompassing several distinct clinical entities and a number of putative genes.

627.1

Duchenne and Becker Muscular Dystrophies

Diana X. Bharucha-Goebel

Duchenne muscular dystrophy (DMD) is the most common hereditary neuromuscular disease affecting all races and ethnic groups. Its characteristic clinical features are progressive weakness, intellectual impairment, and hypertrophy of the calves, with proliferation of connective tissue and progressive fibrosis in muscle. The incidence is 1 in 3,600 liveborn infant boys. This disease is inherited as an X-linked recessive trait. The abnormal gene is at the Xp21 locus and is one of the largest genes. **Becker muscular dystrophy** (BMD) is a disease that is fundamentally similar to DMD, with a genetic defect at the same locus, but clinically it follows a milder and more protracted course.

Clinical Manifestations

Infant boys with DMD are rarely symptomatic at birth or in early infancy, although some are mildly hypotonic. Early gross motor skills, such as rolling over, sitting, and standing, are usually achieved at the appropriate ages or may be mildly delayed. Distinctive facies are not an early feature because facial muscle weakness is a late event; in later childhood, a “transverse” or horizontal smile may be seen. Walking is often accomplished at the normal age of approximately 12 mo, but hip girdle weakness may be seen in a subtle form as early as the 2nd yr. Toddlers might assume a lordotic posture when standing to compensate for gluteal weakness. An early Gowers’ sign may be seen by age 3 yr, but nearly always is evident by age 5 or 6 yr (see Fig. 608.5 in Chapter 608). A Trendelenburg (waddling) gait frequently appears at this time as well. Common presentations in toddlers include delayed walking, frequent falling, toe walking, and trouble running or walking upstairs, developmental delay, and, less often, malignant hyperthermia after anesthesia.

The length of time a patient with DMD remains ambulatory varies greatly. Patients may demonstrate increased difficulties with ambulation, due to the proximal lower extremity weakness, and further confounded by progressive ankle contractures and toe walking. The age of complete loss of ambulation ranges typically from about 10-14 yr. The age at which loss of independent ambulation occurs has increased over time with the advent of clinical care guidelines recommending the use of corticosteroids (e.g., prednisone or deflazacort) in boys with DMD (see section on treatment below). With orthotic bracing, physiotherapy, and sometimes minor surgery (Achilles tendon lengthening), most are able to walk until age 12 yr. Maintenance of ambulation is not only important for preservation of autonomy in activities of daily living (which has psychosocial benefits for the patient and his family), but also provides additional benefits in slowing the progression of scoliosis (that typically worsens after loss of ambulation) and in maintenance of pulmonary health.

The relentless progression of weakness continues into the second decade. The function of distal muscles is usually relatively well enough preserved, allowing the child to continue to use eating utensils, a pencil, and a computer keyboard. As the disease progresses in the teenage years, the upper extremity strength declines further, and patients may have increased difficulties bringing hands to mouth independently, fatigue with writing, and worsening contractures, including in the hands and fingers. Respiratory muscle involvement frequently manifests as a weak and ineffective cough, frequent pulmonary infections, and decreasing respiratory reserve. Early pulmonary symptoms often include snoring and sleep apnea. Parents or patients may report an increased frequency of headaches, difficulty awakening in the mornings, and increased daytime fatigue as signs of sleep-disordered breathing. Pharyngeal weakness can lead to episodes of aspiration, nasal regurgitation of liquids, and an airy or nasal voice quality. The function of the extraocular muscles remains well preserved. Incontinence due to anal and urethral sphincter weakness is an uncommon and very late event.

Contractures most often involve the ankles, knees, hips, and elbows. As upper extremity weakness progresses, contractures are also seen in neck lateral rotation, shoulders, and fingers. **Scoliosis** is common in patients with DMD. The thoracic deformity further compromises the pulmonary capacity and compresses the heart. It may also lead to more discomfort, and if severe enough, risk for hip dislocation. Scoliosis usually progresses more rapidly after the child becomes nonambulatory. However, in the era of corticosteroid use, there may be a further protective effect on the development of and rate of progression of scoliosis. Enlargement of the calves (pseudohypertrophy) and wasting of thigh muscles are classic features. The enlargement is caused by hypertrophy of some muscle fibers, infiltration of muscle by fat, and proliferation of collagen. After the calves, the next most common site of muscular hypertrophy is the tongue, followed by muscles of the forearm. Abnormalities of the muscle are demonstrated using muscle MRI techniques to assess signal, water content, fat fractions, and even MR spectroscopy profiles (Fig. 627.1). Fasciculations of the tongue do not occur. The voluntary sphincter muscles rarely become involved.

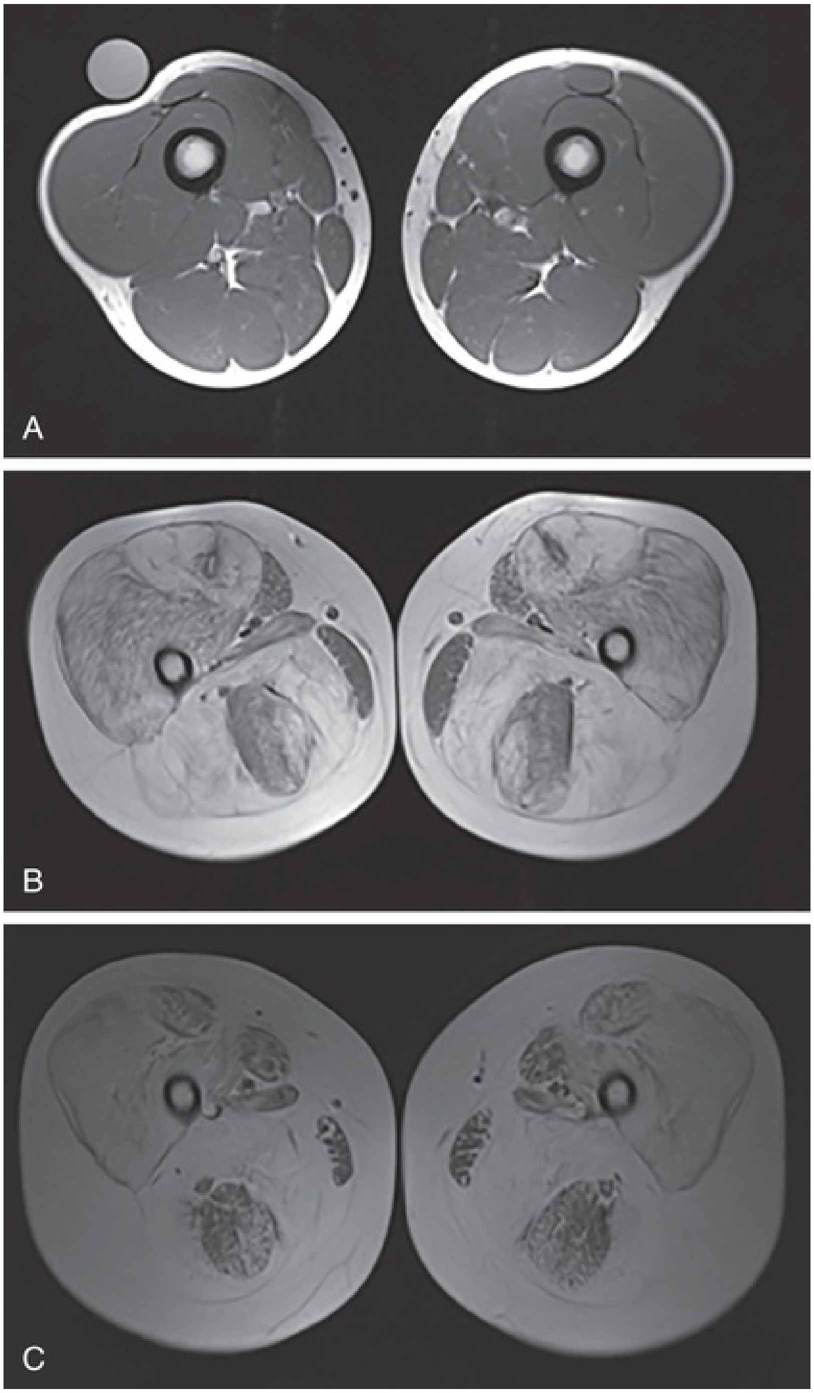

FIG. 627.1 Axial T1 MRI images of the thigh in a healthy 14 yr old male **(A),** 9 yr old ambulant male with DMD **(B),** and 14 yr old ambulant male with DMD **(C),** showing the increased fatty infiltration and muscle atrophy in the boys with DMD. (Courtesy Dr. Ami Mankodi, Neurogenetics Branch, NINDS/NIH.)

Unless ankle contractures are severe, ankle deep tendon reflexes remain well preserved until terminal stages. The knee-deep tendon reflexes may be present until about 6 yr of age but are less brisk than the ankle jerks and are eventually lost with the progression of weakness. In the upper extremities, the brachioradialis reflex is usually stronger than the biceps or triceps brachii reflexes.

Cardiomyopathy, including persistent tachycardia, myocardial fibrosis, and cardiomyopathy, occurs in a majority of patients with DMD. The severity of cardiac involvement does not necessarily correlate with the degree of skeletal muscle weakness. In patients with DMD, the progression of cardiomyopathy typically occurs after loss of independent ambulation. However, in patients with BMD, patients may develop worsening of cardiomyopathy and even develop severe heart failure despite still being ambulant. Smooth muscle dysfunction, particularly of the gastrointestinal tract, is a minor, but often overlooked, feature.

Intellectual impairment occurs in a majority of patients, although only 20–30% have an IQ < 70. There is a range in the extent of intellectual disability, with some patients requiring specialized education and having difficulty with reading and writing, to those less severely affected who may only require some additional tutoring or assistance. The extent of severity of the intellectual disability does not appear to correlate with the severity of the myopathy but may be related to the location of the mutations in the dystrophin gene. Epilepsy is slightly more common than in the general pediatric population, although it is not a salient feature of DMD. Autism-like behavior may develop in some patients. Dystrophin is expressed in brain and retina, as well as in striated and cardiac muscle, though the level is lower in brain than in muscle. This distribution might explain some of the central nervous system manifestations. Abnormalities in cortical architecture and of dendritic arborization may be detected neuropathologically; cerebral atrophy is demonstrated by MRI late in the clinical course. Patients with DMD and BMD may occasionally report myalgias that are often exercise or exertion induced. Calcinosis of muscle is rare.

Death in boys with DMD occurs in the late teens to 20s.The causes of death are respiratory failure during sleep, intractable heart failure, pneumonia, or, occasionally, aspiration and airway obstruction.

In **BMD,** the onset is often after 5 or 7 yr of age, and boys remain ambulatory until late adolescence or even well into adulthood. Calf pseudohypertrophy, cardiomyopathy, and elevated serum levels of creatine kinase (CK) are similar to those of patients with DMD. Given the increased level of activity in BMD patients, the cardiac manifestations, including tachycardia, shortness of breath, or fatigue, may be evident earlier in patients with BMD and even in the setting of independent ambulation. Learning disabilities are less common. The onset of weakness is later in BMD than in DMD. The lifespan in patients with BMD is typically into the 40s and 50s, with cardiac complications as well as pulmonary complications frequently leading to morbidity.

Laboratory Findings

The serum CK level is consistently greatly elevated in DMD, even in presymptomatic stages, including at birth. The usual serum concentration is 15,000-35,000 IU/L (normal < 160 IU/L). A normal serum CK level is incompatible with the diagnosis of DMD, although in terminal stages of the disease, the serum CK value may be considerably lower than it was a few years earlier because there is less muscle to degenerate. Other lysosomal enzymes present in muscle, such as aldolase and aspartate aminotransferase, are also increased but are less specific.

Cardiac assessment by echocardiography and electrocardiography (ECG) are essential and should be monitored. The recommendation is for cardiac surveillance every other year starting at the time of diagnosis, and then yearly when the child demonstrates cardiac manifestations or reaches the age of 10 yr old. After the diagnosis of DMD is established, patients should be referred to a pediatric cardiologist who is familiar with the care of DMD patients for long-term cardiac care. Cardiac MRI may detect changes such as muscle fibrosis in the heart evident even earlier than the changes seen by echocardiography.

Electromyography (EMG) shows characteristic myopathic features but is not specific for DMD. No evidence of denervation is found. Motor and sensory nerve conduction velocities are normal.

Diagnosis

Genetic evaluation for DMD typically begins with deletion/duplication analysis of the dystrophin gene, using dosage analysis. If negative, then sequencing of the dystrophin gene by next-generation sequencing is performed. If genetic analysis is still negative for a mutation in the dystrophin gene, but if the suspicion is high based on clinical features and serum CK levels, then muscle biopsy with dystrophin immunohistochemistry may be useful. Immunohistochemical staining of frozen sections of muscle biopsy tissue detects differences in the rod domain, the carboxyl-terminus (that attaches to the sarcolemma), and the N terminus or amino terminus (that attaches to the actin myofilaments) of the large dystrophin molecule, and may be prognostic of the clinical course as Duchenne or Becker disease. More-severe weakness occurs with truncation of the dystrophin molecule at the carboxyl-terminus than at the amino terminus. Dystroglycans and other sarcolemmal regional proteins, such as merosin and sarcoglycans, also can be measured because they may be secondarily decreased. Further genetic testing could be done, which may include RNA sequencing from muscle to attempt to identify a mutation altering splicing (e.g., one that may not be identified on next-generation sequencing).

The **muscle biopsy** is diagnostic and shows characteristic changes (Figs. 627.2 and 627.3). Myopathic changes include endomysial connective tissue proliferation, scattered degenerating and regenerating myofibers, foci of mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis, mild architectural changes in still-functional muscle fibers, and many dense fibers. These hypercontracted fibers probably result from segmental necrosis at another level, allowing calcium to enter the site of breakdown of the sarcolemmal membrane and trigger a contraction of the whole length of the muscle fiber. Calcifications within myofibers are correlated with secondary β-dystroglycan deficiency.

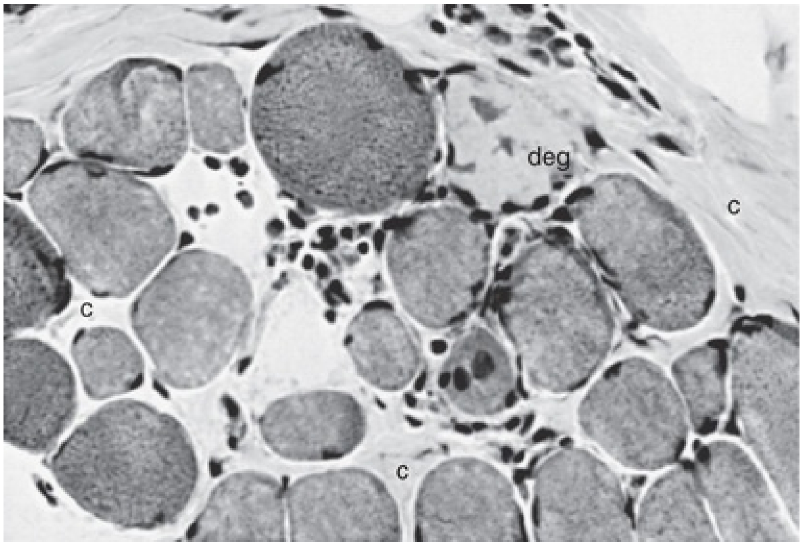

FIG. 627.2 Muscle biopsy of a 4 yr old boy with Duchenne muscular dystrophy. Both atrophic and hypertrophic muscle fibers are seen, and some fibers are degenerating *(deg).* Connective tissue *(c)* between muscle fibers is increased (hematoxylin and eosin, ×400).

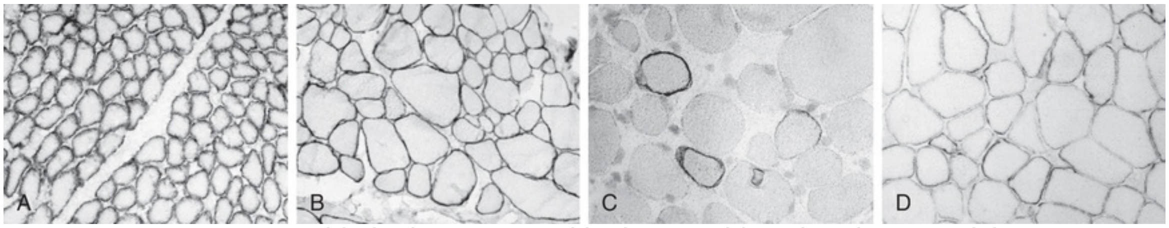

FIG. 627.3 Dystrophin is demonstrated by immunohistochemical reactivity in the muscle biopsies of a normal term male neonate **(A),** a 10 yr old boy with limb–girdle muscular dystrophy **(B),** a 6 yr old boy with Duchenne muscular dystrophy **(C),** and a 10 yr old boy with Becker muscular dystrophy **(D).** In the normal condition, and also in non–X-linked muscular dystrophies in which dystrophin is not affected, the sarcolemmal membrane of every fiber is strongly stained, including atrophic and hypertrophic fibers. In Duchenne dystrophy, most myofibers express no detectable dystrophin, but a few scattered fibers known as revertant fibers show near-normal immunoreactivity. In Becker muscular dystrophy, the abnormal dystrophin molecule is thin, with pale staining of the sarcolemma, in which reactivity varies not only between myofibers but also along the circumference of individual fibers (×250).

The decision about whether muscle biopsy should be performed to establish the diagnosis sometimes presents problems. If there is a family history of the disease, particularly in the case of an involved brother whose diagnosis has been confirmed, a patient with typical clinical features of DMD and high concentrations of serum CK probably does not need to undergo biopsy. The result of the genetic testing (dystrophin deletion/duplication analysis and sequencing) might also influence whether to perform a muscle biopsy. A first case in a family, even if the clinical features are typical, should have the diagnosis confirmed to ensure that another myopathy is not masquerading as DMD. The most common muscles sampled are the vastus lateralis and the gastrocnemius.

Genetic Etiology and Pathogenesis

Despite the X-linked recessive inheritance in DMD, approximately 30% of cases are new or de novo mutations, and the mother is not a carrier. The female carrier state usually shows no muscle weakness, but due to skewed X-inactivation, about 8% of carrier females are *manifesting* carriers with some weakness, although typically milder than is seen in affected males. These symptomatic females are explained by the Lyon hypothesis, in which the normal X chromosome becomes inactivated and the one with the gene deletion is active (see Chapter 97). The full clinical picture of DMD has occurred in several females with Turner syndrome in whom the single X chromosome must have had the Xp21 gene deletion.

The asymptomatic carrier state of DMD is associated with elevated serum CK values in about 50% of cases. The level of increase is usually in the magnitude of hundreds or a few thousand but does not have the extreme values noted in affected males. Prepubertal females who are carriers of the dystrophy also have increased serum CK values, with highest levels at 8-12 yr of age. If the mother of an affected male has normal CK levels, it is unlikely that her daughter can be identified as a carrier by measuring CK. Muscle biopsy of suspected female carriers can detect an additional 10% in whom serum CK is not elevated; a specific genetic diagnosis using polymerase chain reaction (PCR) on peripheral blood is definitive. Approximately 40% of female carriers may be at risk of developing cardiomyopathy or fibrosis (as has been seen by cardiac imaging of carrier females), even in the absence of skeletal muscle weakness.

A 427-kDa cytoskeletal protein known as *dystrophin* is encoded by the gene at the Xp21.2 locus. This gene contains 79 exons of coding sequence and 2.5 Mb of DNA. This subsarcolemmal protein attaches to the sarcolemmal membrane overlying the A and M bands of the myofibrils and consists of four distinct regions or domains: the amino terminus contains 250 amino acids and is related to the *N* -actin binding site of α-actinin; the second domain is the largest, with 2,800 amino acids, and contains many repeats, giving it a characteristic rod shape; a third, cysteine-rich domain is related to the carboxyl-terminus of α-actinin; and the final carboxyl-terminal domain of 400 amino acids is unique to dystrophin and to a dystrophin-related protein encoded by chromosome 6. The absence of dystrophin at the sarcolemma disrupts the membrane cytoskeleton and leads to loss secondarily of other components of the cytoskeleton.

The molecular defects in the dystrophinopathies vary and include intragenic deletions, duplications, or point mutations of nucleotides. Approximately 65% of patients have deletions; approximately 10% exhibit duplications, and approximately 10% have point mutations or smaller rearrangements. In less than 1% of cases, a deep intronic mutation may lead to an alteration of splicing and thereby may impact the reading frame. The site or size of the intragenic abnormality does not always correlate well with the phenotypic severity; in both the Duchenne and Becker forms the mutations are mainly near the middle of the gene, involving deletions in regions between exons 45-55. Phenotypic or clinical variations are explained by the alteration of the translational reading frame of messenger RNA (mRNA), which results in unstable, truncated dystrophin molecules and severe, classic DMD; mutations that preserve the reading frame still permit translation of coding sequences further downstream on the gene and produce a semifunctional dystrophin, expressed clinically as BMD. An even milder form of adult-onset disease, formerly known as **quadriceps myopathy,** is also caused by an abnormal dystrophin molecule. The clinical spectrum of the dystrophinopathies not only includes the classic Duchenne and Becker forms but also ranges from a severe neonatal muscular dystrophy to asymptomatic children with persistent elevation of serum CK levels > 1,000 IU/L.

Analysis of the dystrophin protein requires a muscle biopsy and is demonstrated by Western blot analysis or in tissue sections by immunohistochemical methods using either fluorescence or light microscopy of antidystrophin antisera (see Fig. 627.3). In classic DMD, levels of < 3% of normal are found; in BMD, the molecular weight of dystrophin is reduced to 20–90% of normal in 80% of patients, but in 15% of patients the dystrophin is of normal size but reduced in quantity, and 5% of patients have an abnormally large protein caused by excessive duplications or repeats of codons. Selective immunoreactivity of different parts of the dystrophin molecule in sections of muscle biopsy material distinguishes the Duchenne and Becker forms (Fig. 627.4). The demonstration of deletions and duplications also can be made from blood samples by the more rapid PCR, which identifies as many as 98% of deletions by amplifying 18 exons but cannot detect duplications. The diagnosis can thus be confirmed at the molecular genetic level from either the muscle biopsy material or from peripheral blood, although as many as 30% of males with DMD or BMD have a false-normal blood PCR; all cases of dystrophinopathy are detected by muscle biopsy.

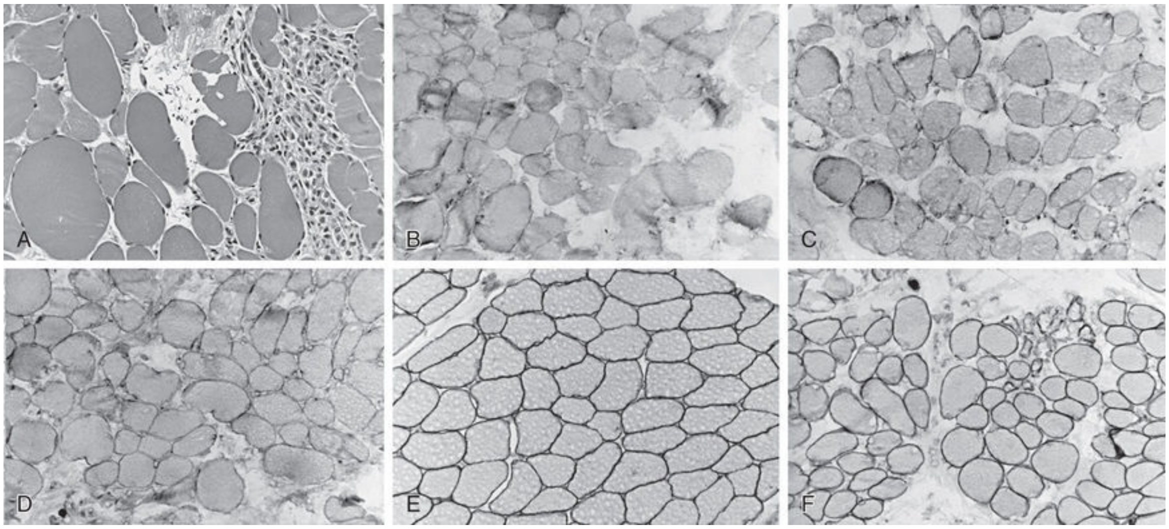

FIG. 627.4 Quadriceps femoris muscle biopsy specimens from a 4 yr old boy with Becker muscular dystrophy. **A,** Myofibers vary greatly in size, with both atrophic and hypertrophic forms; at the right is a zone of degeneration and necrosis infiltrated by macrophages, similar to Duchenne muscular dystrophy (hematoxylin and eosin, ×250). Immunoreactivity using antibodies against the dystrophin molecule in the rod domain **(B),** carboxyl-terminus **(C),** and amino terminus **(D)** all show deficient but not totally absent dystrophin expression; most fibers of all sizes retain some dystrophin in parts of the sarcolemma but not around the entire circumference in cross section. Alternatively, the prominence of dystrophin is less, appearing weak, when compared with the simultaneously incubated normal control from another child of similar age **(E). F,** Merosin expression is normal in this patient with Becker dystrophy, in both large and small myofibers, and is lacking only in frankly necrotic fibers. Compare with classic Duchenne muscular dystrophy illustrated in Figs. 627.3**C** and 627.8 .

The same methods of DNA analysis from blood samples may be applied for carrier detection in female relatives at risk, such as sisters and cousins, and to determine whether the mother is a carrier or whether a new mutation occurred in the embryo. Prenatal diagnosis is possible as early as the 12th wk of gestation by sampling chorionic villi for DNA analysis by Southern blot or PCR, and in cases of aborted fetuses with DMD, muscle demonstrates abnormal dystrophin staining by immunohistochemistry.

Treatment

There is no medical cure for this disease at this time. The mainstay of management for DMD has been supportive care and preventive care thus far. Much can be done to treat complications and to improve the quality of life of affected children.

Glucocorticoids (prednisone or deflazacort) have been shown to slow the decline in muscle strength and increase the time a patient maintains independent ambulation, and it may have additional benefits on scoliosis progression. Initiation of steroids is indicated when a child shows a plateau in development and/or a regression in motor development as compared with peers. This typically occurs by 4-6 yr old. Recommended doses are prednisone 0.75 mg/kg/day or deflazacort 0.9 mg/kg/day. Alternative protocols for steroid administration include weekend-only dosing, alternate-day regimens, or 10-day-on/10-day-off regimens; the daily regimen has been the preferred regimen based upon comparative studies. Long-term complications include weight gain, osteoporosis, delayed puberty, growth retardation, acne, glucose intolerance, and cataracts. Given the improvements with steroids in motor abilities, as well as potentially in pulmonary, orthopedic, and cardiac health, they are recommended for children with DMD.

Exondys51 (eteplirsen) is an exon 51 skipping antisense oligonucleotide approach that binds RNA and skips over the defective exon, restoring the reading frame, thereby producing a shorter but potentially functional dystrophin protein. This only applies to patients with mutations amenable to this repair (~13% of patients). It is given as a weekly IV infusion. Ataluren permits readthrough of premature stop codons (10–15% of patients) from a nonsense mutation, resulting in production of a functional dystrophin. It may have benefits in patients at a certain level of disease progression. Additional exon skipping approaches and gene replacement strategies are currently in clinical trials.

Cardiac care initially includes ACE inhibitors, angiotensin receptor blockers, or beta blockers. Other agents used include aldosterone antagonists (e.g., aldactone or eplerenone). The optimal time to initiation of cardiac medications is under an ongoing review; although most providers classically initiated cardiac treatment at the time of a drop in the left ventricular ejection fraction to < 55%, some centers advocate for initiation of treatment before the echocardiogram abnormalities are detected. This is based on more recent data showing MRI changes in the heart preceding the echocardiogram abnormalities, and a potentially cardioprotective effect with agents such as ACE inhibitors. Due to potential risks for hyperkalemic or malignant hyperthermia reactions to anesthesia, it is recommended to avoid agents such as inhaled anesthetics or muscle relaxants.

Pulmonary infections should be promptly treated. Patients should avoid contact with children who have obvious respiratory or other contagious illnesses. Immunizations for influenza virus and other routine vaccinations are indicated. When sleep-disordered breathing is suspected, children should undergo sleep studies and the use of BiPAP should be considered. Additional devices such as a cough assist device, proper suctioning, and nebulized therapies may assist with airway clearance as children develop weakness in coughing.

Preservation of a good **nutritional state** is important. DMD is not a vitamin-deficiency disease, and excessive doses of vitamins should be avoided. Adequate calcium intake is important to minimize osteoporosis in boys confined to a wheelchair. However, due to chronic corticosteroid use combined with the loss of ambulation, boys with DMD are at higher risk for osteopenia and osteoporosis, putting them at higher risk for fractures in the setting of even minor injuries or falls. DEXA scans should be done in boys with DMD and vitamin D levels should be optimized. Some patients with low bone density may require additional therapies such as pamidronate. Because of the decreased caloric expenditure in nonambulant children and the use of corticosteroids, these children tend to eat excessively and gain weight. Obesity makes a patient with myopathy even less functional because part of the limited reserve muscle strength is dissipated in lifting the weight of excess subcutaneous adipose tissue. Dietary restrictions with supervision may be needed.

Physiotherapy delays but does not always prevent contractures. At times, contractures are actually useful in functional rehabilitation. If contractures prevent extension of the elbow beyond 90 degrees and the muscles of the upper limb no longer are strong enough to overcome gravity, the elbow contractures are functionally beneficial in fixing an otherwise flail arm and in allowing the patient to eat and write. Surgical correction of the elbow contracture may be technically feasible, but the result may be deleterious. Stretching and bracing methods may be useful depending on the location of the contracture and level of severity of the contracture. Surgical interventions should be considered with caution and with input from the neurologist, physical therapist, and/or physical medicine and rehabilitation specialists involved in the child's care. Physiotherapy contributes little to muscle strengthening because patients usually are already using their entire reserve for daily functioning, and exercise cannot further strengthen involved muscles. Excessive exercise can actually accelerate the process of muscle fiber degeneration.

Special vigilance should be maintained in watching for progressive scoliosis, which should be treated early by orthopedists using external braces or corsets and occasionally by surgeons. Scoliosis often progresses more rapidly once the patient loses independent ambulation.

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627.2

Emery-Dreifuss Muscular Dystrophy/Laminopathies

Diana X. Bharucha-Goebel

Emery-Dreifuss muscular dystrophy is a form of muscular dystrophy caused by mutations involving nuclear envelope proteins. It was first described as a rare X-linked recessive disorder caused by mutations in the *EMD* gene encoding emerin. The usual locus of its associated genetic abnormality is on the long arm within the large Xq28 region that includes other mutations that cause myotubular myopathy, neonatal adrenoleukodystrophy, and the Bloch-Sulzberger type of incontinentia pigmenti; it is far from the gene for DMD on the short arm of the X chromosome. Subsequently, *dominant mutations* in the *LMNA* gene located on chromosome 1q21 that encodes for nuclear envelope protein lamins A/C was found to be mutated in male and female affected patients. This form can manifest both as a congenital muscular dystrophy or one with an onset later in adolescence or adulthood, and it represents a broad phenotypic spectrum. In addition to the motor manifestations, which are variable, there is also a risk of sudden death from ventricular fibrillation, which can occur as early as in childhood in some cases.

Clinical manifestations range from a congenital muscular dystrophy with severe weakness, respiratory insufficiency, and contractures from infancy or children with weakness and a *dropped head syndrome* to the more classic EDMD forms. In the childhood-onset EDMD forms, symptoms may begin between 5 and 15 yr of age, but many patients survive to late adult life because of the slow progression of the disease's course. Muscles *do not* exhibit pseudohypertrophy. Contractures of the elbows, ankles, and neck extensor muscles develop early, and muscle becomes wasted in a scapulohumeroperoneal distribution. Facial weakness *does not* typically occur; this disease is thus distinguished clinically from autosomal dominant scapulohumeral and scapuloperoneal syndromes of *neurogenic* origin. Myotonia is absent. Intellectual function is normal. *Dilated cardiomyopathy* is severe and is often the cause of death, more commonly from conduction defects such as atrial fibrillation/flutter and sudden ventricular fibrillation than from intractable myocardial failure. Stroke is another complication, secondary to the cardiac arrhythmia. Respiratory insufficiency is more prominent in the early and severe forms and may require mechanical ventilation, especially in the severe congenital-onset patients. The serum CK value is only mildly to moderately elevated, further distinguishing this disease from other X-linked recessive muscular dystrophies.

Nonspecific myofiber necrosis and endomysial fibrosis are seen in the muscle biopsy. Many centronuclear fibers and a selective histochemical type I muscle fiber atrophy can cause confusion with myotonic dystrophy.

Genetics

The defective gene in the X-linked form is called *EMD* or *EDMD* and encodes a protein, emerin. Unlike other dystrophies in which the defective gene is expressed at the sarcolemmal membrane, emerin is expressed at the inner nuclear membrane; this protein stabilizes the nuclear membrane against the mechanical stresses that occur during muscular contraction. It interacts with *Nesprin-1* and *Nesprin-2* genes, also critical for nuclear membrane integrity. Complete deletion of *EDMD* occurs in approximately 25% of cases and results from an inversion in the Xq28 region; total absence of emerin is demonstrated by both Western blotting and immunoreactivity in tissue sections. Another gene, *LMNA*, at the 1q21 locus, is linked to the nuclear envelope and encodes lamins A and C, sometimes termed *laminopathy.* This genetic mutation causes a similar clinical phenotype to EMD defects, except that both sexes are affected and it is transmitted as either an autosomal dominant or recessive trait. Most *EMD* deletions are null mutations, whereas more than 80% of *LMNA* alterations are caused by missense mutations, and with a minority of mutations being nonsense or out-of-frame mutations. Desmin protein also may be mutated and seen to be abnormally expressed in the muscle biopsy. Homozygous nonsense mutations in these *lamin A/C* genes are lethal due to cardiomyopathy and conduction disturbances. There are still many patients with an EDMD phenotype clinically, where the underlying genetic defect remains unknown.

Diagnostics

In suspected cases, emerin deficiency may be demonstrated not only in the muscle biopsy by immunoreactivity and Western blotting techniques but also in a variety of other tissues, including circulating lymphocytes in peripheral blood, exfoliative buccal mucosal cells, and skin fibroblasts. Emerin is absent in varying proportions in female carriers. Muscle histology in *LMNA* patients is typically *nonspecific* with myopathic or mild dystrophic changes, with variability in fiber size, increase in connective tissue, and necrotic fibers. Genetic testing of the specific genes also is available. Patients should have careful cardiac evaluation, including an electrocardiogram, echocardiogram, and at least 24-hr Holter monitoring. Serum CK levels should be measured because they may be moderately elevated; though nonspecific, this provides a baseline for comparison with future measurements. Muscle MRI of the glutei and lower extremities may be helpful, particularly in *LMNA* mutations. EMG is not definitively diagnostic, but it provides a serial means of following the progression of the myopathy. Muscle biopsy is diagnostic from the onset of symptoms. In the differential diagnosis, an Emery-Dreifuss–like syndrome with joint contractures, mild weakness, and later-onset cardiac symptoms is caused by *FHL1* mutations of *myofibrillar myopathy,* but reducing bodies are absent.

Treatment should be supportive, with special attention to cardiac conduction defects, and can require medications or a pacemaker. Implantable cardioverter-defibrillators are now available and have prevented sudden death in some patients with Emery-Dreifuss muscular dystrophy. In patients with cardiac arrhythmias or a severe decrease in left ventricular function, there may be an increased risk of thromboembolic events, and antithrombotic drugs may be considered. Pulmonary care should include monitoring with pulmonary function tests (PFTs) as well as surveillance for sleep-disordered breathing if clinically indicated. Orthopedic management, use of orthotic devices, or physical therapy to try to minimize or slow down the rate of progression of contractures may be beneficial.

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627.3

Myotonic Muscular Dystrophy

Diana X. Bharucha-Goebel

Myotonic dystrophy is the second most common muscular dystrophy in North America, Europe, and Australia, having an incidence varying from 1 in 20,000 to 1 in 100,000 in the general population. It is inherited as an autosomal dominant trait. **Classic myotonic dystrophy (type 1)** (DM1, or Steinert disease) is caused by a CTG trinucleotide expansion on chromosome 19q13.3 in the 3′ untranslated region of *DMPK*, the gene that encodes a serine–threonine protein kinase. **Type 2 (DM2)** is associated with an unstable CCTG tetranucleotide repeat expansion on chromosome 3q21 of an intron of the zinc finger 9 protein gene. A third **late form (DM3)** is identified at locus 15q21-q24.

Myotonic dystrophy is an example of a genetic defect causing dysfunction in multiple organ systems. Not only is striated muscle severely affected, but smooth muscle of the alimentary tract and uterus is also involved, cardiac function is altered, and patients have multiple and variable endocrinopathies, immunologic deficiencies, cataracts, dysmorphic facies, an increased risk for malignancies, intellectual impairment, and other neurologic abnormalities.

Clinical Manifestations

DM1 becomes symptomatic at any age, but DM2 is rarely expressed in infancy or early childhood. In the usual clinical course, *excluding the severe neonatal form*, DM1 infants can appear almost normal at birth, or facial wasting and hypotonia can already be early expressions of the disease. The facial appearance is characteristic, consisting of an inverted-V–shaped upper lip, thin cheeks, and scalloped, concave temporalis muscles (Fig. 627.5). The head may be narrow, and the palate is high and arched because the weak temporal and pterygoid muscles in late fetal life do not exert sufficient lateral forces on the developing head and face.

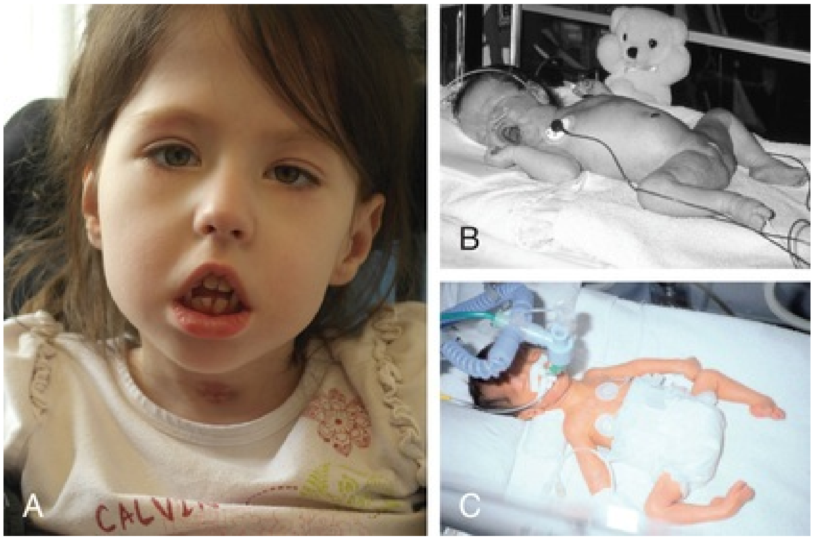

FIG. 627.5 A 6 yr old with congenital myotonic dystrophy with 1975 cytosine-thymine-guanine (CTG) repeats in the *DMPK* gene showing the characteristic elongated facies, left ptosis, and an open, down-turned (tented) mouth with dental malocclusion. **(A),** The tracheostomy scar is evidence of the severe respiratory distress requiring intubation at the time of birth. Neonate with congenital myotonic dystrophy **(B)** also with an open, down-turned mouth and frog-leg position of lower extremities. A neonate with congenital myotonic dystrophy with severe respiratory distress and arthrogryposis **(C).** (**A,** From Konersman C: Hypotonia, weakness, stroke. In Kliegman RM, Lye PS, Bordini BJ, et al. (eds): Nelson symptom-based diagnosis, Philadelphia, 2018, Elsevier, 2018, Fig. 29.16. **B,** From Johnston H: The floppy weak infant revisited, Brain Dev 25:155-158, 2003; **C,** from Echenne B, Bassez G: Congenital and infantile myotonic dystrophy, Handbook Clin Neurol 113:1387-1393, 2013.)

In DM1, weakness is often mild in the first few years (childhood-onset form), or may not even become evident until adolescence or early adulthood (classic/adult-onset form). Progressive wasting of distal muscles becomes increasingly evident, particularly in the intrinsic muscles of the hands. The thenar and hypothenar eminences are flattened, and the atrophic dorsal interossei leave deep grooves between the fingers. The dorsal forearm muscles and anterior compartment muscles of the lower legs also become wasted. The tongue is thin and atrophic. Wasting of the sternocleidomastoids gives the neck a long, thin, cylindrical contour. Proximal muscles also eventually undergo atrophy, and scapular winging appears. Difficulty with climbing stairs and the Gowers' sign are progressive. Tendon stretch reflexes are usually preserved.

The distal distribution of muscle wasting in myotonic dystrophy is an *exception* to the general rule of myopathies having proximal and neuropathies having distal distribution patterns. The muscular atrophy and weakness in myotonic dystrophy are slowly progressive throughout childhood and adolescence and continue into adulthood. It is rare for patients with myotonic dystrophy to lose the ability to walk even in late adult life, although splints or bracing may be required to stabilize the ankles.

Myotonia, a characteristic feature shared by few other myopathies, does not occur in infancy and is usually not clinically or even electromyographically evident until about age 5 yr. Exceptional patients develop it as early as age 3 yr. Myotonia is a very slow relaxation of muscle after contraction, regardless of whether that contraction was voluntary or was induced by a stretch reflex or electrical stimulation. During physical examination, myotonia may be demonstrated by asking the patient to make tight fists and then to quickly open the hands (grip myotonia; Fig. 627.6). It may be induced by striking the thenar eminence with a rubber percussion hammer (percussion myotonia), and it may be detected by watching the involuntary drawing of the thumb across the palm. Myotonia can also be demonstrated in the tongue by pressing the edge of a wooden tongue blade against its dorsal surface and by observing a deep furrow that disappears slowly. The severity of myotonia does not necessarily parallel the degree of weakness, and the weakest muscles often have only minimal myotonia. *Myotonia is not a painful muscle spasm.* Musculoskeletal pain and fatigue are fairly commonly reported in patients with myotonic dystrophy.

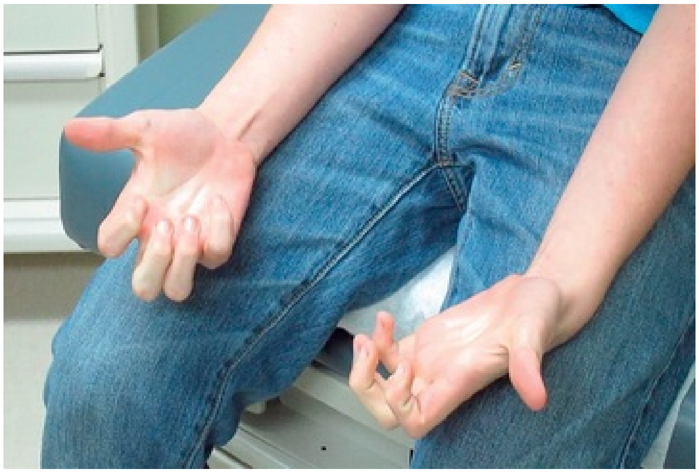

FIG. 627.6 The patient was asked to squeeze with both of his hands for several seconds and then suddenly release his grasp, and several seconds passed before full relaxation was achieved, an exam finding known as grip myotonia. (From Hughes BN, Hogue JS, Hsieh DT: Grip and percussion myotonia in myotonic dystrophy type 1, J Pediatr 164:1234, 2014.)

The **speech** of patients with myotonic dystrophy is often articulated poorly and is slurred because of the involvement of the muscles of the face, tongue, and pharynx. Both myotonia and weakness can drive the difficulties in patients' speech and swallowing. Difficulties with swallowing sometimes occur, and more severely involved patients may be at risk for aspiration pneumonia. Incomplete external ophthalmoplegia sometimes results from extraocular muscle weakness.

Smooth muscle involvement of the **gastrointestinal tract** results in slow gastric emptying, poor peristalsis, and constipation. Some patients have encopresis associated with anal sphincter weakness. Women with myotonic dystrophy can have ineffective or abnormal uterine contractions during labor and delivery.

Cardiac involvement is usually manifested as heart block in the Purkinje conduction system and arrhythmias (and sudden death) rather than as cardiomyopathy, unlike most other muscular dystrophies. Atrial or ventricular tachyarrhythmias have also resulted in sudden death in adults and older children.

Endocrine abnormalities involve many glands and appear at any time during the course of the disease so that the endocrine status must be reevaluated annually. Hypothyroidism is common; hyperthyroidism occurs rarely. Adrenocortical insufficiency can lead to an addisonian crisis even in infancy. Diabetes mellitus is common in patients with myotonic dystrophy; some children have a disorder of insulin release rather than defective insulin production. The onset of puberty may be precocious or, more often, delayed. Testicular atrophy and testosterone deficiency are common in adults and are responsible for a high incidence of male infertility. Ovarian atrophy is rare. Frontal baldness is also characteristic in male patients and often begins in adolescence.

Immunologic deficiencies are common in myotonic dystrophy. The plasma immunoglobulin G level is often low.

Cataracts often occur in myotonic dystrophy. They may be congenital, or they can begin at any time during childhood or adult life. Early cataracts are detected only by slit-lamp examination; periodic examination by an ophthalmologist is recommended. Visual evoked potentials are often abnormal in children with myotonic dystrophy and are unrelated to cataracts. They are not usually accompanied by visual impairment.

About half of the patients with myotonic dystrophy are **intellectually impaired,** but severe intellectual impairment is unusual. The remainder are of average or occasionally above-average intelligence. Epilepsy is not common. Cognitive impairment might result from accumulations of mutant *DMPK* mRNA and aberrant alternative splicing in cerebral cortical neurons. A higher-than-expected incidence of autism occurs in children with DM1.

A severe **congenital form** of myotonic dystrophy appears in a minority of involved infants born to mothers with symptomatic myotonic dystrophy (see Fig. 627.5). All patients with this severe congenital disease to date have had the DM1 form. Symptoms may present prenatally with polyhydramnios and decreased fetal movements. At birth, patients typically have marked hypotonia, respiratory difficulties or respiratory failure, and feeding difficulties, and they may have additional orthopedic manifestations, such as clubfoot deformities or more extensive congenital contractures (arthrogryposis multiplex congenita). Facial wasting is prominent. Infants can require gavage feeding or ventilator support for respiratory muscle weakness or apnea. Those requiring ventilation for < 30 days often survive, and those with prolonged ventilation have an infant mortality rate of 25% and a lower likelihood of ventilator-free survival. Children ventilated for < 30 days have better motor, language, and daily activity skills than those requiring prolonged ventilation. One or both leaves of the diaphragm may be nonfunctional. The abdomen becomes distended with gas in the stomach and intestine because of poor peristalsis from smooth muscle weakness. The distention further compromises respiration. Inability to empty the rectum can compound the problem. Myotonia is typically not present in the congenital form during the neonatal period but may be present in childhood (typically after 5 yr old).

Laboratory Findings

The classic myotonic electromyogram is not found in infants but can appear in children in the early school years. The levels of serum CK and other serum enzymes from muscle may be normal or only mildly elevated in the hundreds (never the thousands).

ECG should be performed annually in early childhood. Ultrasound imaging of the abdomen may be indicated in affected infants to determine diaphragmatic function. Radiographs of the chest and abdomen and additional studies of gastrointestinal motility or swallowing studies may be needed.

Endocrine assessment should be undertaken to determine thyroid and adrenal cortical function and to verify carbohydrate metabolism (glucose tolerance test). Immunoglobulins should be examined, and, if needed, more extensive immunologic studies should be performed.

Diagnosis

The primary diagnostic test is a DNA analysis of blood to demonstrate the abnormal expansion of the CTG or CCTG repeat. Prenatal diagnosis also is feasible. The muscle biopsy specimen in older children shows many muscle fibers with central nuclei and selective atrophy of histochemical type I fibers, but degenerating fibers are usually few and widely scattered, and there is little or no fibrosis of muscle. Intrafusal fibers of muscle spindles are also abnormal. In young children with the common form of the disease, the biopsy specimen can even appear normal or at least not show myofiber necroses, which is a striking contrast with DMD. In the severe neonatal form of myotonic dystrophy, the muscle biopsy reveals maturational arrest in various stages of development in some and congenital muscle fiber–type disproportion in others. It is likely that the sarcolemmal membrane of muscle fibers not only has abnormal properties of electrical polarization but is also incapable of responding to trophic influences of the motor neuron. Muscle biopsy is not usually required for diagnosis, which in typical cases can be based on the clinical manifestations, including the family history. **Neonatal myotonic dystrophy** causing arthrogryposis multiplex and/or severe neonatal hypotonia must be distinguished from amyoplasia, congenital muscular dystrophy with or without merosin expression, congenital myasthenia gravis, spinal muscular atrophy, and arthrogryposis secondary to oligohydramnios.

Genetics

The genetic defect in myotonic muscular dystrophy is on chromosome 19 at the 19q13 locus. It consists of an expansion of the *DM* gene that encodes a serine–threonine kinase *(DMPK),* with numerous repeats of the CTG codon. Expansions range from 50 to > 2,000, with the normal alleles of this gene ranging in size from 5-37; the larger the expansion, the more severe the clinical expression, with the largest expansions seen in the severe neonatal form. Rarely, the disease is associated with no detectable repeats, perhaps a spontaneous correction of a previous expansion but a phenomenon still incompletely understood. Another myotonic dystrophy (proximal myotonic myopathy) is a clinical entity linked to at least two different chromosomal loci than classic myotonic dystrophy but to one locus that shares a common unique pathogenesis in being mediated by a mutant mRNA. Defects in RNA splicing explain the insulin resistance in myotonic dystrophies as well as the myotonia.

Clinical and genetic expression can vary between siblings or between an affected parent and child. In the severe neonatal form of the disease, the mother is the transmitting parent in 94% of cases, a fact not explained by increased male infertility alone. Several cases of paternal transmission have been reported. Genetic analysis reveals that symptomatic neonates usually have many more repeats of the CTG codon than do patients with the more classic form of the disease, regardless of which parent is affected. Myotonic dystrophy often exhibits a pattern of **anticipation** in which each successive generation has a tendency to be more severely involved than the previous generation. Prenatal genetic diagnosis of myotonic dystrophy is available.

Treatment

There is no specific medical treatment, but the cardiac, endocrine, gastrointestinal, and ocular complications can often be treated. Physiotherapy and orthopedic treatment of contractures in the neonatal form of the disease may be beneficial. Myotonia may improve with exercise (warm-up phenomenon), and avoidance of extreme cold temperatures may be helpful. Cardiac surveillance with an annual EKG as well as Holter studies and an echocardiogram about every 2 yr should be pursued. Cardiac pacemaker implantation might be considered for heart block, and antiarrhythmic drugs might be indicated but are needed only rarely in children. Respiratory issues should be addressed; management strategies may include BiPAP, cough assist, and incentive spirometry.

Myotonia may be diminished, and function may be restored by drugs that raise the depolarization threshold of muscle membranes, such as mexiletine, phenytoin, carbamazepine, procainamide, and quinidine sulfate. These drugs also have cardiotropic effects; thus, cardiac evaluation is important before prescribing them. Phenytoin and carbamazepine are used in doses similar to those when used as antiepileptics (see Chapter 611.6); serum concentrations of 10-20 µg/mL for phenytoin and 5-12 µg/mL for carbamazepine should be maintained. If a patient's disability is caused mainly by weakness rather than by myotonia, these drugs will be of no value. Excess sleepiness is sometimes managed with methylphenidate or modafinil. Low-impact to moderate exercise maybe beneficial for myalgias.

Anesthesia precautions should be considered given the higher rates of complications with anesthesia in patients with myotonia. Succinylcholine should be avoided owing to the risk of myotonia, and, instead, short-acting nondepolarizing muscle relaxants should be used that are modified in terms of dosing for the extent of muscle wasting. For induction, a modified rapid-sequence induction for intubation should be used. During recovery, neostigmine should be used with caution, and extubation should occur when a patient is more fully awake. Following sedation, patients should be monitored closely because of the risk of aspiration.

Other Myotonic Syndromes

Most patients with myotonia have myotonic dystrophy. However, myotonia is not specific for this disease and occurs in several rarer conditions.

Myotonic chondrodystrophy (Schwartz-Jampel disease) is a rare congenital disease characterized by generalized muscle hypertrophy and weakness. Dysmorphic phenotypic features and the radiographic appearance of long bones are reminiscent of Morquio disease (see Chapter 107), but abnormal mucopolysaccharides are not found. Dwarfism, joint abnormalities, and blepharophimosis are present. Several patients have been the products of consanguinity, suggesting autosomal recessive inheritance. The muscle protein perlecan, encoded by the *SJS1* gene, a large heparan sulfate proteoglycan of basement membranes and cartilage, is defective in some cases of Schwartz-Jampel disease and explains both the muscular hyperexcitability and the chondrodysplasia.

EMG reveals continuous electrical activity in muscle fibers, closely resembling or identical to myotonia. Muscle biopsy reveals nonspecific myopathic features, which are minimal in some cases and pronounced in others. The sarcotubular system is dilated.

Myotonia congenita (Thomsen disease), a type of channelopathy, is the most common of the nondystrophic myotonia syndromes (Tables 627.1 to 627.4) and is characterized by weakness and generalized muscular hypertrophy so that affected children resemble bodybuilders (Herculean appearance). Myotonia is prominent and can develop at age 2-3 yr, earlier than in myotonic dystrophy. The disease is clinically stable and is apparently not progressive for many years. Muscle biopsy specimens show minimal pathologic changes, and the EMG demonstrates myotonia. Various families are described as showing either autosomal dominant (Thomsen disease) or recessive (Becker disease, not to be confused with BMD or DMD) inheritance. Mutations may be nonsense, missense, or frameshift. However, specifically, missense mutations that alter the activation of the CLC-1 dimer lead to the dominantly inherited forms of the disease. Patients with the recessive form (Becker disease) tend to be have more severe disease. The autosomal dominant and autosomal recessive forms of myotonia congenita have been mapped to the same 7q35 locus. This gene is important for the integrity of chloride channels of the sarcolemmal and T-tubular membranes.

Table 627.1

Chloride Channel Myopathies

CLINICAL FEATURES	AUTOSOMAL-DOMINANT MYOTONIA CONGENITA OF THOMSEN	AUTOSOMAL-RECESSIVE GENERALIZED MYOTONIA OF BECKER
Inheritance	Dominant	Recessive
Gene defect	Chromosome 7; mutation in skeletal muscle chloride channel	Chromosome 7; mutation in skeletal muscle chloride channel
Age of onset	Infancy to early childhood	Late childhood; occasionally starts earlier or begins in teens
Myopathy	Muscle hypertrophy frequent; no myopathy, although variants uncommonly develop weakness	Occasional muscle wasting and weakness can occur late; hypertrophy of muscles frequently occurs in legs
Myotonia	Generalized stiffness, especially after rest; improves with exercise; prominent myotonia of eye closure, but not paradoxical myotonia	Generalized stiffness, especially after rest; transient weakness is prominent after complete relaxation for several minutes; myotonia occurs in eyes; no paradoxical myotonia
Provocative stimuli	Prolonged rest or maintenance of the posture	Prolonged rest or maintenance of the same posture
Therapy for symptoms	Exercise; antimyotonia therapy (e.g., mexiletine); Achilles' tendon stretching helps prevent need for heel cord–lengthening surgery	Exercise; especially avoiding prolonged rest; antimyotonia therapy (e.g., mexiletine); transient weakness does not improve after mexiletine

From Moxley III RT, Heatwole C: Channelopathies: myotonic disorders and periodic paralysis, In Swaiman KF, Ashwal S, Ferriero DM, et al. (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, Table 151-3.

Table 627.2

Sodium Channel Myotonias Without Periodic Paralysis

CLINICAL FEATURES	ACETAZOLAMIDE-RESPONSIVE SODIUM CHANNEL MYOTONIA	MYOTONIA FLUCTUANS
Inheritance	Dominant	Dominant
Gene defect	Chromosome 17; mutation in skeletal muscle sodium	Chromosome 17; mutation in skeletal

	channel	muscle sodium channel
Age of onset	First decade	First or second decade
Myopathy	Rare	Rare, muscle hypertrophy common
Myotonia	Face, paraspinal muscles, paradoxical myotonia of eyelids, grip limbs; varies in severity and often there is pain with myotonia	Face, limbs, eyelids; frequently fluctuates in severity; especially after exercise
Provocative stimuli	Fasting, cold, oral potassium, infection	Exercise–rest–exercise, oral potassium
Therapy for symptoms	Acetazolamide, mexiletine; avoid high-potassium diet; monitor during and after surgery for rigidity and rhabdomyolysis	Mexiletine; avoid high-potassium diet; monitor during and after surgery for rigidity and rhabdomyolysis

From Moxley III RT, Heatwole C: Channelopathies: myotonic disorders and periodic paralysis, In Swaiman KF, Ashwal S, Ferriero DM, et al. (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, 2018, Table 151-4.

Table 627.3

Sodium Channel Myopathies With Periodic Paralysis

CLINICAL FEATURES	**PARAMYOTONIA CONGENITA**	**PARAMYOTONIA CONGENITA WITH HYPERKALEMIC PERIODIC PARALYSIS**	**HYPERKALEMIC PERIODIC PARALYSIS WITH MYOTONIA**
Inheritance	Dominant	Dominant	Dominant
Gene defect	Chromosome 17; mutation in skeletal muscle sodium channel	Chromosome 17; mutation in skeletal muscle sodium channel	Chromosome 17; mutation in skeletal muscle sodium channel
Age of onset	First decade	First decade	First decade
Myopathy	Very rare	Rare	Infrequent
Myotonia	Especially paradoxical myotonia of the eyelids and grip	Especially paradoxical myotonia of the eyelids and grip	Especially paradoxical myotonia of the eyelids
Provocative stimuli	Cold exposure followed by exercise leads to focal paralysis; occasionally exercise provokes stiffness	Oral potassium load, rest after exercise mainly in morning (hyperkalemic weakness), cold exposure followed by exercise (focal paralysis)	Rest after exercise, cold, oral potassium
Therapy for symptoms	Mexiletine, mild exercise, keep patient warm	Mild exercise, thiazides, mexiletine	Thiazides, acetazolamide, sodium restriction

From Moxley III RT, Heatwole C: Channelopathies: myotonic disorders and periodic paralysis. In Swaiman KF, Ashwal S, Ferriero DM, et al. (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia Table 151-5.

Table 627.4

Channelopathies with Hypokalemic Periodic Paralysis

CLINICAL FEATURES	**ANDERSEN SYNDROME: PERIODIC PARALYSIS WITH CARDIAC DYSRHYTHMIA**	**CALCIUM CHANNEL PERIODIC PARALYSIS**	**SODIUM CHANNEL PERIODIC PARALYSIS**	**POTASSIUM CHANNEL PERIODIC PARALYSIS**	**PERIODIC PARALYSIS WITH THYROID DISEASE**
Inheritance	Dominant	Dominant	Dominant	Dominant	Sporadic; occasionally dominant
Age of onset	First or second decade	First to third decade	First to third decade	Not yet determined	Third decade (males 20 : 1)
Myopathy	Typical; also short stature; dysmorphic features; prolonged QT interval on electrocardiogram; ventricular dysrhythmias	Moderately common late; vacuoles frequently seen on biopsy	Not yet determined	Not yet determined	Infrequent
Myotonia	No	No	No	No	No
Provocative stimuli	Rest after exercise, oral glucose	High-carbohydrate meals, rest after exercise, cold, emotional stress/excitement	High-carbohydrate meals, rest after exercise, cold, emotional stress/excitement	Usually by strenuous exercise followed by rest; less consistent provocation after high carbohydrate intake	High-carbohydrate meals, rest after exercise, acetazolamide
Therapy for symptoms	Mild exercise, glucose, high sodium intake, acetazolamide, dichlorphenamide	Acetazolamide, dichlorphenamide, potassium, spironolactone	Acetazolamide, dichlorphenamide, potassium, spironolactone	Acetazolamide	Propranolol, restoration of euthyroid state, oral potassium, spironolactone

From Moxley III RT, Heatwole C: Channelopathies: myotonic disorders and periodic paralysis. In Swaiman KF, Ashwal S, Ferriero DM, et al. (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, Table 151-6.

Paramyotonia is a temperature-related myotonia that is aggravated by cold and alleviated by warm external temperatures. Patients have difficulty when swimming in cold water or if they are dressed inadequately in cold weather. *Paramyotonia congenita* (Eulenburg disease) is a defect in a gene at the 17q13.1-13.3 locus, the identical locus identified in hyperkalemic periodic paralysis. By contrast with myotonia congenita, paramyotonia is a disorder of the voltage-gated sodium channel caused by a mutation in the α subunit. Myotonic dystrophy also is a sodium channelopathy (see Table 627.3).

In sodium channelopathies, exercise produces increasing myotonia, whereas in chloride channelopathies, exercise reduces the myotonia. This is easily tested during examination by asking patients to close the eyes forcefully and open them repeatedly; it becomes progressively more difficult in sodium channel disorders and progressively easier in chloride channel disorders.

Treatments for the nondystrophic myotonias include mexiletine as the first line (both for sodium channel and chloride channel myotonias). Mexiletine has been shown to improve stiffness as well as decrease handgrip myotonia. Other treatment options include carbamazepine, phenytoin, and gabapentin.

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627.4

Limb–Girdle Muscular Dystrophies

Diana X. Bharucha-Goebel

Limb–girdle muscular dystrophies (LGMDs) encompass a heterogeneous group of progressive hereditary muscular dystrophies that mainly affect muscles of the hip and shoulder girdles (Table 627.5). Distal muscles also eventually become atrophic and weak, and in a few subtypes, distal muscles such as calves may have weakness earlier in disease. Hypertrophy of the calves and ankle contractures develop in some forms, causing potential confusion with BMD. Over 30 genetic forms of LGMD are described, each at a different chromosomal locus and expressing different protein defects. Some include diseases classified with other traditional groups, such as the lamin-A/C defects of the nuclear membrane (see Emery-Dreifuss muscular dystrophy), and some forms of congenital muscular dystrophy. **LGMD1** denotes autosomal dominant inheritance and **LGMD2** implies an autosomal recessive trait, but neither term defines the genetic etiology. LGMD2 is mainly a group of several *sarcoglycanopathies* , calpainopathy resulting from a mutation in the *calpain-3* gene (*CAPN3*), alpha-dystroglycanopathies, or dysferlinopathies that include Miyoshi myopathy (which usually does not become symptomatic until late adolescent into adult life).

Table 627.5

Limb–Girdle Muscular Dystrophies

TYPE	INHERITANCE	GENE	PROTEIN	CLINICAL FEATURES
LGMD1A	AD	*TTID*	Myotilin	Adult-onset myofibrillar myopathy; mildly elevated CK; muscle biopsy: rimmed vacuoles, rod-like inclusions, and Z-band streaming
LGMD1B	AD	*LMNA*	Lamin A/C	Onset 1st-4th decade of life; Contractures, +/– axial weakness, cardiac arrhythmia and/or cardiomyopathy (potentially life-threatening); CK normal or mildly elevated
LGMD1C	AD	*CAV3*	Caveolin	Onset variable: 1st decade to adulthood; presents with myalgias +/– rippling muscles and proximal weakness; CK 4-25x elevated
LGMD1D	AD	*DNAJB6*	HSP40	Onset classically adulthood; proximal weakness;

				CK normal to 5x elevated; gradually progressive
LGMD1E	AD	*DES*	Desmin	Myofibrillar myopathy; cardiomyopathy and cardiac arrhythmias; CK normal or mildly elevated; muscle biopsy: inclusions and desmin accumulation
LGMD1F	AD	*TNPO3*	Transportin	Onset variable: 1st decade to adulthood; proximal weakness +/– scapular winging; +/– respiratory involvement
LGMD2A	AR	*CAPN3*	Calpain 3	Onset at 8-15 yr, progression variable (variable loss of ambulation in 2nd or 3rd decade); scapular winging common; cardiac spared; CK very high
LGMD2B	AR	*DYSF*	Dysferlin	Onset in adolescence or early adulthood; mild weakness initially; limb–girdle pattern weakness or Miyoshi myopathy (calf weakness) at onset; gradually progressive; cardiac spared; gastric atrophy earlier in disease
LGMD2C	AR	*SGCG*	**γ -**Sarcoglycan	Duchenne-like, onset 4-7 yr; CK very high; respiratory failure often in 3rd decade; + cardiac involvement; loss of ambulation by teenage years
LGMD2D	AR	*SGCA*	α-Sarcoglycan (adhalin)	Duchenne-like, onset 2-15 yr; frequent loss of ambulation; quadriceps weakness; rare cardiomyopathy; CK very high
LGMD2E	AR	*SGCB*	β-Sarcoglycan	Phenotype between Duchenne and Becker muscular dystrophies; onset 1st decade; loss of ambulation 10-25 yr old; occasional cardiomyopathy
LGMD2F	AR	*SGCD*	**δ -**Sarcoglycan	Onset 2-10 yr old; loss of ambulation by 1st or 2nd decade; dilated cardiomyopathy; also a milder phenotype described
LGMD2G	AR	*TCAP*	Telethonin	Rare disease; onset in adolescence; CK up to 10x normal
LGMD2H	AR	*TRIM32*	Tripartite motif containing 32	Seen in Hutterite population; onset childhood to young adulthood; proximal weakness; slowly progressive; ambulatory into adulthood
LGMD2I	AR	*FKRP*	Fukutin-related protein	Dystroglycanopathy; variable phenotype: early onset never ambulate to milder and later onset with muscle cramps; cardiomyopathy common; +/– respiratory failure
LGMD2J	AR	*TTN*	Titin	Onset 3-10 yr; variable severity; +/– respiratory insufficiency; progressive with loss of ambulation (some patients with the severe congenital myopathy phenotype may never ambulate); muscle biopsy: variable fiber size; rods; internal nuclei
LGMD2K	AR	*POMT1*	Protein O-mannosyl transferase 1	Onset 1st decade; mild weakness and fatigue; slow progression; intellectual disability
LGMD2L	AR	*ANO5*	Anoctamin	More common in Northern Europe and Canada; Onset 2nd to 3rd decade; no cardiomyopathy; report of patients with premature ventricular contractions. Limb–girdle or Miyoshi myopathy phenotypes
LGMD2M	AR	*FKTN*	Fukutin	Early onset, high CK, progression over

				time; variable intellectual disability; vermis hypoplasia and polymicrogyria; some patients develop dilated cardiomyopathy
LNGD2N	AR	*POMT2*	Protein O-mannosyl transferase 2	LGMD phenotype with or without intellectual disability
LGMD2O	AR	*POMGnT1*	**	More likely a congenital muscle disease/Walker-Warburg syndrome or muscle–eye–brain presentation (possible childhood LGMD phenotype)
LGMD2P	AR	*DAG1*	Dystroglycan	Childhood onset (1st decade); very high CK; fatigue and proximal weakness; +/– CNS (intellectual disability), respiratory and eye (cataracts) involvement
LGMD2Q	AR	*PLEC1*	Plectin	Childhood onset, loss of ambulation in adulthood
LGMD2R	AR	*DES*	Desmin	Adult-onset weakness; proximal and distal weakness; cardiac: atrioventricular block (may require early pacemaker by 20s); cardiomyopathy (onset in childhood or 20s); with respiratory involvement
LGMD2S	AR	*TRAPPC11*	Transport protein particle complex 11	Onset infancy or childhood; high CK; proximal weakness; fatigue; +/– seizures, spasticity, hyperkinetic movements, intellectual disability
LGMD2T	AR	*GMPPB*	GDP-mannose pyrophosphorylase B	Can manifest as congenital onset or childhood onset LGMD with or without intellectual disability; seizures; cataracts
LGMD2U	AR	*ISPD*	Isoprenoid synthase domain	Can manifest as congenital muscular dystrophy or childhood-onset LGMD with or without intellectual disability; Some patients lose independent ambulation; +/– cardiomyopathy; +/– respiratory insufficiency
LGMD2V	AR	*GAA*	Alpha-1,4 glucosidase	Pompe disease (infantile, juvenile, or adult-onset forms): cardiomyopathy (more in infantile form), respiratory insufficiency, weakness. EMG: irritative myopathy (can see myotonia/cone–rod dystrophies and myopathic recruitment)

** *POMGnT1* – encodes for protein: Protein-O-linked mannose beta 1,2 N-acetylglucosaminyl transferase

LGMD, limb–girdle muscular dystrophy.

The onset of disease is variable, with some patients manifesting by 4-5 years of age (e.g., sarcoglycanopathies), to others presenting in late adolescence to adulthood (e.g., dysferlinopathy or anoctaminopathy). For many LGMDs, the initial clinical manifestations rarely appear before middle or late childhood or may be delayed until early adult life. Low back pain may be a presenting complaint because of the lordotic posture resulting from gluteal muscle weakness. In many of these disorders, loss of independent ambulation may occur, ranging from within the first decade of life to loss of ambulation in early adulthood, highlighting the variability in rate of progression (even for the same disease). Although weakness of neck flexors and extensors is common, weakness of facial, lingual, and other bulbar-innervated muscles are rarely involved. As weakness and muscle wasting progress, tendon stretch reflexes become diminished. Cardiac involvement can occur in some of the subtypes. Intellectual function is generally normal in most, but can be involved to varying degrees, especially in some of the alpha-dystroglycanopathies (e.g., LGMDs due to mutations in *POMT2* , *POMGnT1* , *GMPPB* , and *ISPD*). The clinical differential diagnosis of LGMD includes juvenile/ Type 3 spinal muscular atrophy (Kugelberg-Welander disease), myasthenia gravis, and metabolic myopathies.

The EMG and muscle biopsy frequently show confirmatory evidence of muscular dystrophy, but none of the findings are specific enough to make the definitive diagnosis without additional clinical or immunohistochemical criteria. In some cases, α-sarcoglycan (formerly known as *adhalin*), a dystrophin-related glycoprotein of the sarcolemma, is deficient; this specific defect may be demonstrated in the muscle biopsy by immunocytochemistry, as may deficiency of three other forms of sarcoglycan as well. Increased serum CK level is typical, but the magnitude of elevation varies among families. The ECG is usually unaltered.

A mutated dystrophin-associated protein in the sarcoglycan complex (**sarcoglycanopathy** ; **LGMD types 2C, 2E, and 2F**) is responsible for some cases of autosomal recessive LGMD. Most sarcoglycanopathies result from a mutation in α-sarcoglycan; other LGMDs resulting from deficiencies in β-, γ-, and δ-sarcoglycan also occur. In normal smooth muscle, α-sarcoglycan is replaced by ε-sarcoglycan, and the others are the same. *Dystroglycanopathies* are caused by mutations leading to the abnormal glycosylation of alpha-dystroglycan, and regardless of the gene, all mutations seem to be implicated in a common pathway that impacts dystroglycan function. Histochemically, dystroglycanopathies often show defects (loss or reduction) of immunoreactivity to one of two antibodies: VIA41 or IIH6, which recognize carbohydrate moieties of alpha-dystroglycan. The extent of reduction can vary from subtle to severe.

Another group of LGMDs (**type 2B**) are caused by allelic mutations of the dysferlin *(DYSF)* gene, another gene expressing a protein essential to structural integrity of the sarcolemma, though not associated with the dystrophin-glycoprotein complex. *DYSF* interacts with caveolin-3 or calpain-3, and *DYSF* deficiency may be secondary to defects in these other gene products. Dysferlinopathies can present with the classic LGMD pattern of proximal weakness, or may present with early weakness in the lower legs, specifically calf weakness, known as Miyoshi myopathy. Primary calpain-3 defect (type 2A) has wide clinical variability, with age of onset ranging from 2-40 years old, and age at loss of independent ambulation ranging from 5 years old to the late 30s. Respiratory compromise can be seen later in the disease, but is less severe than in some other LGMDs. Both are slowly progressive myopathies with onset in adolescence or young adult life and can affect distal as well as proximal muscles. Cardiomyopathy is rare. Chronically elevated serum CK in the thousands is found in dysferlinopathies. Ultrastructure shows a thickened basal lamina over defects in the sarcolemma and replacement of the sarcolemma by multiple layers of small vesicles. Regenerating myofibers outnumber degenerating myofibers. Mutations in *CAV3* can also have a variable neuromuscular phenotype ranging from: limb girdle phenotype (LGMD1C) to distal myopathy to rippling muscle disease to hyperCKemia and exercise intolerance. There are also reports of patients with rhabdomyolysis with caveolinopathies. These disorders were formerly called *hyperCKemia* and *rippling muscle disease*, the latter sometimes confused with myotonia. An autosomal recessive mutation in the calcium-activated chloride channel anoctamin-5 can causes one of the following phenotypes: a proximal LGMD2L; a distal Miyoshi myopathy phenotype; or hyperCKemia. It typically presents in adulthood, and is more commonly seen in Northern Europe and Canada. There does not seem to be any associated cardiomyopathy, although there are reports of early premature ventricular contractions (PVCs).

There is genetic overlap of the group of LGMDs with the congenital muscular dystrophies, such as Walker-Warburg syndrome with *POMT* , Fukuyama muscular dystrophy with *FKRP* genetic defects, and *GMPPB* . Patients with mutations in these genes can present with an early CMD like phenotype to a childhood or later onset LGMD phenotype, and in both motor phenotypes may or may not have varying degrees of intellectual disability.

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627.5

Facioscapulohumeral Muscular Dystrophy

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Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy (after Duchenne muscular dystrophy and myotonic dystrophy). Autosomal dominant inheritance is generally the mode of inheritance, and genetic anticipation is often found within several generations of a family, the succeeding more severely involved at an earlier age than the preceding. The genetic mechanism in autosomal dominant **FSHD1** involves integral deletions of a 3.3-kb tandem repeat (D4Z4) in the subtelomeric region at the 4q35 locus. D4Z4 acts as a lamins-dependent insulator, exhibiting both enhancer-blocking and barrier activities, and displaces the telomere toward the nuclear periphery. Normally, there are 11-100 tandem copies or D4Z4 repeats. When there are fewer repeats (<10 repeat units), this enables chromatin remodeling and leads to decreased methylation, thus turning on DUX4 expression (which is normally dormant). In addition, the disease will only manifest in chromosomes that carry a pLAM1 polyadenylate site distal to the last D4Z4 repeat. When these factors all exist, this creates a “permissive” haplotype or state that allows for the expression of DUX4, which is normally repressed. Approximately 5–10% of families with this phenotype do not map to the 4q35 locus. **FSHD2,** although clinically overlapping with FSHD1, is not caused by the contraction in D4Z4 repeats. However, instead, it is caused by mutations of the *SMCHD1* gene (on chromosome 18p) that can lead to hypomethylation of D4Z4. When these mutations exist in the setting of a “permissive” haplotype and the polyadenylation signal, DUX4 is expressed, again sharing a final common pathway in leading to the same clinical disease. The prevalence varies geographically but ranges from 1 : 8,000-20,000. Though the clinical onset is generally in later childhood or adult life, early molecular defects arising during myogenesis are demonstrated in the human fetus, and patients can present as early as in the infantile period.

Clinical Manifestations

Facioscapulohumeral dystrophy shows the earliest and most severe weakness in facial and shoulder girdle muscles. Asymmetric weakness or patchy weakness, when present, should raise suspicion for FSHD. The facial weakness in FSHD differs from that of myotonic dystrophy; rather than an inverted V–shaped upper lip, the mouth in facioscapulohumeral dystrophy is rounded and appears puckered because the lips protrude. Inability to close the eyes completely in sleep is a common expression of upper facial weakness; some patients have extraocular muscle weakness, although ophthalmoplegia is rarely complete. Facioscapulohumeral dystrophy has been associated with Möbius syndrome on rare occasions. Pharyngeal and tongue weakness may be absent and is never as severe as the facial involvement. Hearing loss, which may be subclinical, and retinal vasculopathy (indistinguishable from Coats disease) are associated features, particularly in severe cases of facioscapulohumeral dystrophy with early-childhood onset.

Scapular winging is prominent, often even in infants. Flattening or even concavity of the deltoid contour is seen, and the biceps and triceps brachii muscles are wasted and weak. Muscles of the hip girdle and thighs also eventually lose strength and undergo atrophy, and the Gowers sign and a Trendelenburg gait appear. Contractures of the extremities are rare. Finger and wrist weakness occasionally is the first symptom. Weakness of the anterior tibial and peroneal muscles can lead to footdrop; this complication usually occurs only in advanced cases with severe weakness. Lumbar lordosis and kyphoscoliosis are common complications of axial muscle involvement. Calf pseudohypertrophy is not a usual feature but is described rarely.

There is a great deal of clinical variability, including within families. Facioscapulohumeral muscular dystrophy can be a mild disease causing minimal disability. Clinical manifestations might not be expressed in childhood and are delayed into middle adult life. In more severe cases, patients may present early in life. About 20% of patients will lose independent ambulation, and about 10–15% of patients may require noninvasive or invasive respiratory support. Unlike most other muscular dystrophies, asymmetry of weakness is common. About 30% of affected patients are asymptomatic or show only mild scapular winging and decreased tendon stretch reflexes, of which they were unaware until formal neurologic examination was performed.

Laboratory Findings

Serum levels of CK and other enzymes vary greatly, ranging from normal or near-normal to elevations of several thousand. An ECG should be performed, although the anticipated findings are usually normal. EMG reveals nonspecific myopathic muscle potentials. Diagnostic molecular testing in individual cases and within families is indicated for prediction.

Diagnosis and Differential Diagnosis

Molecular genetic diagnosis is the most specific confirmation if clinical suspicion is high, with or without a family history of the disease. Muscle biopsy distinguishes more than one form of facioscapulohumeral dystrophy, consistent with clinical evidence that several distinct diseases are embraced by the term *facioscapulohumeral dystrophy.* Muscle biopsy and EMG also distinguish the primary myopathy from a neurogenic disease with a similar distribution of muscular involvement. The general histopathologic findings in the muscle biopsy material are extensive proliferation of connective tissue between muscle fibers, extreme variation in fiber size with many hypertrophic as well as atrophic myofibers, and scattered degenerating and regenerating fibers. An *inflammatory* type of facioscapulohumeral muscular dystrophy is also distinguished, characterized by extensive lymphocytic infiltrates within muscle fascicles. Despite the resemblance of this form to inflammatory myopathies such as polymyositis, there is no evidence of autoimmune disease, and steroids and immunosuppressive drugs do not alter the clinical course. A precise histopathologic diagnosis has important therapeutic implications. Mononuclear cell *inflammation* in a muscle biopsy sample of infants younger than 2 yr old is usually facioscapulohumeral dystrophy or, less often, a congenital muscular dystrophy.

Treatment

Pulmonary function should be followed routinely, and if there are concerns for daytime headaches or increased fatigue, a sleep study should be performed to assess for any sleep-disordered breathing or sleep apnea. Light aerobic exercise and stretching regimens may help to prevent deconditioning or disuse atrophy over time. High-intensity training and strength training or weight lifting are not recommended, because they will not help in regaining strength or in retarding the progression of weakness or muscle wasting. Footdrop and scoliosis may be treated by orthopedic measures. In selected cases, surgical wiring of the scapulas (scapular fixation surgery) to the thoracic wall provides improved shoulder stability and abduction of the arm, but brachial plexopathy, frozen shoulder, and scapular fractures are reported complications. Additional rehabilitation options for scapular support include kinesiotaping. Chronic pain can be seen commonly in patients with FSHD, and may require further management, including gabapentin, tricyclic antidepressants, or exercise and cognitive behavioral therapy. Cosmetic improvement of the facial muscles of expression may be achieved by reconstructive surgery, which grafts a fascia lata to the zygomatic muscle and to the zygomatic head of the quadratus labii superioris muscle. Exercise of facial muscles can help minimize secondary disuse atrophy. Routine eye exams should be performed (testing for Coats' disease), and in young affected children, audiograms should be performed. No effective pharmacologic or genetic treatment is presently clinically available.

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627.6

Congenital Muscular Dystrophies

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The term *congenital muscular dystrophies (CMDs)* refers to a group of hereditary disorders with early (prenatal, neonatal, or early-childhood) onset and histologic features suggestive of a dystrophic process. It is used to encompass several distinct diseases that have a common characteristic of severe involvement at birth or in early childhood but that, ironically, often follow a more benign clinical course than the early onset and histopathologic changes in the muscle biopsy would suggest. A distinguishing feature of the congenital dystrophies, by contrast with other muscular dystrophies, is a high association with brain malformations, particularly disorders of cortical development such as lissencephaly/pachygyria and polymicrogyria, often complicated by severe epilepsy (Fig. 627.7). Most of the CMDs are inherited in an autosomal recessive manner.

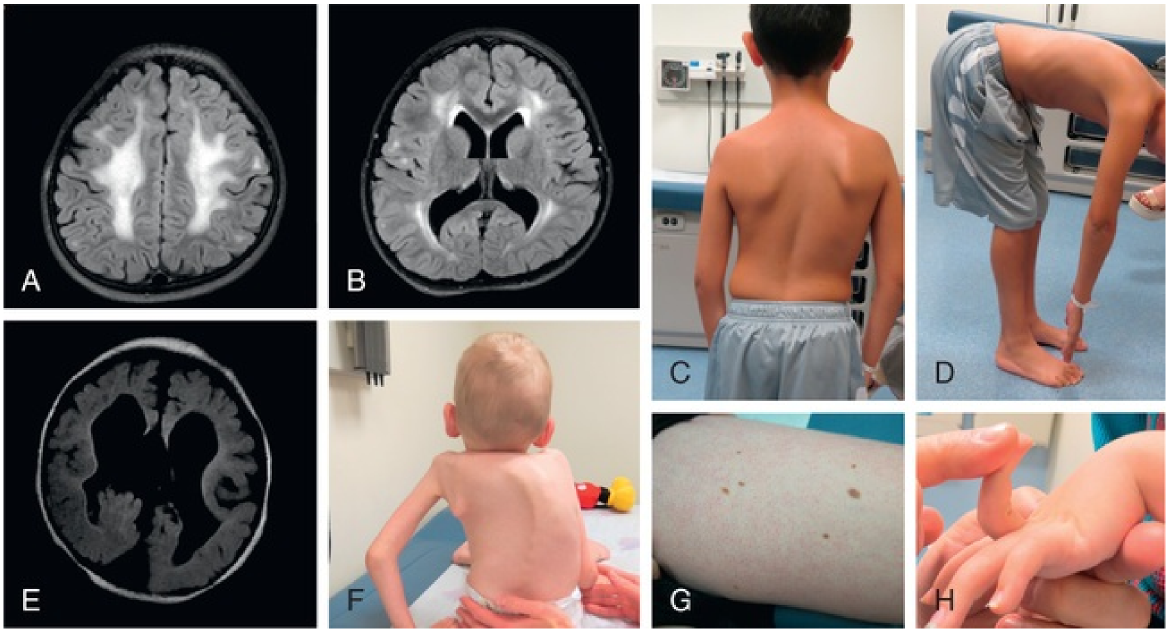

FIG. 627.7 Findings in congenital muscular dystrophies. **A** and **B,** Axial FLAIR brain MRI images showing the increased T2 hyperintensity seen within the white matter in patients with LAMA2 CMD. **C,** Scapular winging and scoliosis in patient with SEPN1 muscular dystrophy. **D,** Rigid spine noted in forward flexion in patient with SEPN1 muscular dystrophy. **E,** Brain MRI in patient with muscle–eye–brain disease with absent corpus callosum, Dandy-Walker malformation, subependymal cysts. **F,** Early and severe kyphoscoliosis in a child with Ullrich congenital muscular dystrophy. **G,** Keratosis pilaris, a common skin finding in patients with collagen VI–related CMDs. **H,** Distal hyperlaxity seen in patients with collagen VI–related CMDs. (Courtesy Drs. Carsten Bönnemann and Reghan Foley, Neuromuscular and Neurogenetics Disorders of Childhood Section, NINDS/NIH.)

Clinical Manifestations

In several distinct clinical and genetic diseases grouped under the umbrella term *congenital muscular dystrophies,* infants often have contractures or arthrogryposis at birth and are diffusely hypotonic. In some cases, weakness in infancy may be less significant and initial motor milestones may even be normal. The muscle mass is thin in the trunk and extremities. Head control is often poor due to neck weakness and marked axial hypotonia. Facial muscles may be mildly involved, but ophthalmoplegia, pharyngeal weakness, and weak sucking are not common. A minority has severe dysphagia and requires gavage or gastrostomy. Tendon stretch reflexes may be hypoactive or absent. Distal arthrogryposis is common in all forms of congenital muscular dystrophy (see

Chapter 626.10). Congenital contractures involving axial or proximal joints (including, for example, of the elbows) are often suggestive of **Ullrich congenital muscular dystrophy** due to mutation(s) in one of the three collagen VI genes *(COL6A1, COL6A2, COL6A3).*

The congenital muscular dystrophies can be classified according to the type of protein altered by the specific genetic mutations. Diseases of extracellular matrix proteins include LAMA2-related CMD (merosin deficiency, *LAMA2* mutation at locus 6q22-q23) and COL6-related CMD (Ullrich congenital muscular dystrophy in the more severe form, to Bethlem myopathy in the milder form of the disease) (*COL6A1*, -*A2*, and -*A3* mutations at 21q22 and 2q37 loci). A protein of the endoplasmic reticulum (*SEPN1* mutation at 1p35) is the basis of rigid spine syndrome. Abnormal glycosylation of α-dystroglycan causes Walker-Warburg syndrome (*POMT1* mutation at 9q34), muscle–eye–brain disease of Santavuori (*POMGnT1* mutation at 1p32), Fukuyama muscular dystrophy (*FCMD* mutation at 8q31-q33 and 9q31), and congenital muscular dystrophy with secondary merosin deficiency (*FKRP* mutation at 19q13). Mutations in genes that affect the glycosylation of α-dystroglycan can also lead to milder or later-onset limb–girdle muscular dystrophy phenotypes (with or without intellectual involvement; see Chapter 627.4). Glycosylation defects (dystroglycanopathies) result in defective neuroblast migration in the fetal brain and also can cause dilated cardiomyopathy. The dystroglycan molecule interacts with both proteins of the plasma (sarcolemmal) membrane and those of the extracellular matrix and basal lamina not only in muscle but also in brain, where defective dystroglycan and poor glycosylation result in gaps in the pial limiting membrane, a discontinuous glia limitans, causing cobblestone lissencephaly and glioneuronal heterotopia of overmigrated neural cells during formation of the cerebral cortex.

The **Fukuyama type** of congenital muscular dystrophy is the second most common muscular dystrophy in Japan (after DMD); it has also been reported in children of Dutch, German, Scandinavian, and Turkish ethnic backgrounds. In the Fukuyama variety, severe cardiomyopathy and malformations of the brain usually accompany the skeletal muscle involvement. Signs and symptoms related to these organs are prominent: cardiomegaly and heart failure, intellectual disability, seizures, microcephaly, and failure to thrive.

Central neurologic disease can accompany forms of congenital muscular dystrophy other than Fukuyama disease. The mental and neurologic status is the most variable feature; an apparently normal brain and normal intelligence do not preclude the diagnosis if other manifestations indicate this myopathy. The cerebral malformations that occur are not consistently of one type and vary from severe dysplasias (holoprosencephaly, lissencephaly) to milder conditions (agenesis of the corpus callosum, focal heterotopia of the cerebral cortex and subcortical white matter, cerebellar hypoplasia). Seizures are a frequent complication, as early as the neonatal period, and may include infantile spasms and other severe infantile epilepsies.

Congenital muscular dystrophy is a constant association with cerebral dysgenesis in the **Walker-Warburg syndrome** and in **muscle–eye–brain disease.** The neuropathologic findings are those of neuroblast migratory abnormalities in the cerebral cortex, cerebellum, and brainstem. Studies indicate considerably more genetic overlap between Walker-Warburg, Fukuyama, and muscle–eye–brain forms of congenital muscular dystrophy that explain mixed and transitional phenotypes, so that, for example, a *Fukutin* -related *(FKRP)* gene can cause a Walker-Warburg or muscle–eye–brain presentation, or *POMGnT1* also can produce phenotypes other than classic Walker-Warburg disease.

Laboratory Findings

The serum CK level is usually moderately elevated from several hundred to many thousand IU/L; only marginal increases are sometimes found. EMG shows nonspecific myopathic features. Investigation of all forms of congenital muscular dystrophy should include cardiac assessment and an imaging study of the brain. Muscle biopsy is essential for the diagnosis, but if there is a high degree of suspicion (e.g., a confirmed genetic defect in a sibling or clear phenotype), specific genetic testing might avoid the muscle biopsy.

Diagnosis

Muscle biopsy is diagnostic in the neonatal period or thereafter. An extensive proliferation of endomysial collagen envelops individual muscle fibers even at birth, also causing them to be rounded in cross-sectional contour by acting as a rigid sleeve, especially during contraction. The perimysial connective tissue and fat are also increased, and the fascicular organization of the muscle may be disrupted by the fibrosis. Tissue cultures of intramuscular fibroblasts exhibit increased collagen synthesis, but the structure of the collagen is normal. Muscle fibers vary in diameter, and many show central nuclei, myofibrillar splitting, and other cytoarchitectural alterations. Scattered degenerating and regenerating fibers are seen. No inflammation or abnormal inclusions are found.

Immunocytochemical reactivity for merosin (α_2 chain of laminin) at the sarcolemmal region is absent in approximately 40% of cases and normally expressed in the others (Figs. 627.8 and 627.9). Merosin is a protein that binds the sarcolemmal membrane of the myofiber to the basal lamina or basement membrane. Merosin also is expressed in brain and in Schwann cells. The presence or absence of merosin does not always correlate with the severity of the myopathy or predict its course. Adhalin (α-dystroglycan) may be reduced to varying degrees in the alpha-dystroglycanopathies, and there can be secondary reduction of merosin (laminin 211). Collagen VI is selectively reduced, absent, or mislocalized in COL6-related CMDs. Mitochondrial dysfunction may be another secondary defect.

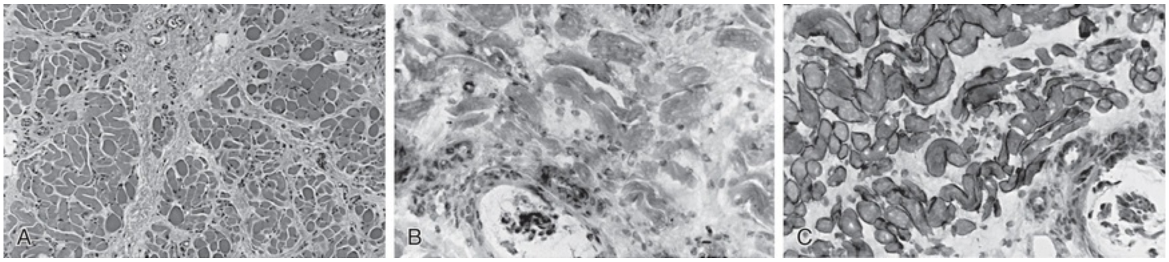

FIG. 627.8 Quadriceps femoris muscle biopsy of a 6 mo old girl with congenital muscular dystrophy associated with merosin (α_2 -laminin) deficiency. **A,** Histologically, the muscle is infiltrated by a great proliferation of collagenous connective tissue; myofibers vary in diameter, but necrotic fibers are rare. **B,** Immunocytochemical reactivity for merosin (α_2 -laminin) is absent in all fibers, including the intrafusal myofibers of a muscle spindle seen at bottom. **C,** Dystrophin expression (rod domain) is normal. Compare with Figs. 627.3 , 627.4 , and 627.9 .

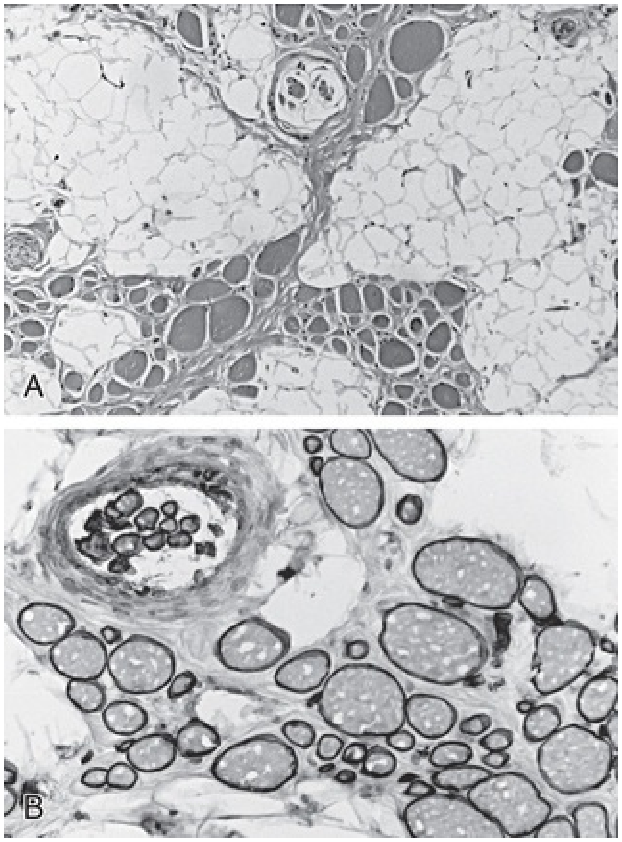

FIG. 627.9 Quadriceps femoris muscle biopsy specimen of a 2 yr old girl with congenital muscular dystrophy. **A,** The fascicular architecture of the muscle is severely disrupted, and muscle is replaced by fat and connective tissue; the remaining small groups of myofibers of variable size are seen, including a muscle spindle at top. **B,** Merosin expression is normal in both extrafusal fibers of all sizes and in intrafusal spindle fibers. The severity of the myopathy does not relate to the presence or absence of merosin in congenital muscular dystrophy. Compare with Fig. 627.8 .

Treatment

Supportive care at this time is the mainstay of therapy. A consensus statement on the management of patients with congenital muscular dystrophies was published in 2010 (Wang et al). Given the high prevalence of respiratory insufficiency in this population, it is important at every visit to screen for respiratory function with pulmonary function testing and eliciting information on the frequency and duration of respiratory illnesses, the frequency of lower respiratory infections, abnormal breathing in sleep, increased daytime fatigue, or headaches. Sleep studies should be performed early (especially in collagen VI CMD and SEPN1 muscular dystrophy), where the respiratory compromise can occur even in ambulant patients because of increased diaphragmatic weakness. Additional respiratory supports may include chest PT, cough assist with suctioning, BiPAP, and, in more advanced stages, invasive ventilation or sip/puff ventilation options for continuous ventilator supports. Weight gain should be optimized to make sure the patient is not losing weight or gaining excess weight. Swallowing should be assessed to screen for dysphagia. Some children will require G-tube feeds owing to insufficient oral intake to meet caloric needs, whereas others may require nearly full G-tube feeds owing to swallowing difficulties. Speech therapy may be needed for assessment for dysphagia but also because some of these children will have some difficulty with articulation because of oromotor weakness that can affect communication early in life. Constipation occurs frequently and should be medically managed through diet or stool softeners. Physical therapists and physiatrists should be involved in working with the patients on assistive devices and stretching and bracing regimens to try to slow down the progression of or manage contractures. Children may develop scoliosis (or in collagen VI–related CMD, kyphoscoliosis deformities), and should be followed regularly by orthopedic specialists to determine when bracing or surgical interventions are needed. Children with alpha-dystroglycanopathies with CNS involvement may require additional supports, including speech therapies, individualized education plans for learning and intellectual disabilities, seizure management, and spasticity management.

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CHAPTER 628

Endocrine and Toxic Myopathies

Harvey B. Sarnat

Thyroid Myopathies

See also Chapters 579-584 .

Thyrotoxicosis causes proximal weakness and wasting accompanied by myopathic electromyographic changes. Rarely the myopathy may be limited to painless external ophthalmoplegia and proptosis, at least initially. Thyroxine binds to myofibrils and, if in excess, impairs contractile function. Hyperthyroidism can also induce myasthenia gravis and hypokalemic periodic paralysis, the latter mainly affecting East Asian males who have a genetic predisposition. A mutation in the gene *KCNJ18* may be responsible for altering the potassium channel Kir2.6 in up to one third of cases. Potassium supplementation and propranolol are useful in treating thyrotoxic periodic paralysis.

Hypothyroidism, whether congenital or acquired, consistently produces hypotonia and a proximal distribution of weakness. Although muscle wasting is most characteristic, one form of cretinism, the Kocher-Debré-Sémélaigne syndrome, is characterized by generalized pseudohypertrophy of weak muscles. Infants can have a Herculean appearance reminiscent of myotonia congenita. The serum creatine kinase (CK) level is elevated in hypothyroid myopathy and returns to normal after thyroid replacement therapy.

Results of muscle biopsy in hypothyroidism reveal acute myopathic changes, including myofiber necrosis and sometimes central cores. In hyperthyroidism, the muscle biopsy specimen shows only mild, nonspecific myopathic changes without necrosis of myofibers. The clinical and pathologic features of hyperthyroid myopathy and hypothyroid myopathy resolve after appropriate treatment of the thyroid disorder. Many of the systemic symptoms of hyperthyroidism, including myopathic weakness and ophthalmoparesis, improve with the administration of β-blockers.

Most patients with primary **hyperparathyroidism** (see Chapter 591) develop weakness, fatigability, fasciculations, and muscle wasting that is reversible after removal of the parathyroid adenoma. The serum CK and muscle biopsy remain normal, but electromyography can show nonspecific myopathic features. A minority of patients develop myotonia that could be confused with myotonic dystrophy.

Steroid-Hormone Induced Myopathy

Natural Cushing disease and iatrogenic Cushing syndrome from exogenous corticosteroid administration can cause painless, symmetric, progressive proximal weakness, increased serum CK levels, and a myopathic electromyogram and muscle biopsy specimen (see Chapter 595). Myosin filaments may be selectively lost. The 9α-fluorinated steroids, such as dexamethasone, betamethasone, and triamcinolone, are the most likely to produce *steroid myopathy.* Dexamethasone alters the abundance of ceramides in myotubes in developing muscle. In patients with dermatomyositis or other myopathies treated with steroids, it is sometimes difficult to distinguish refractoriness of the disease from steroid-induced weakness, especially after long-term steroid administration. Vitamin D is another factor altering muscle metabolism and particularly its sensitivity to insulin; vitamin D deficiency may be accentuated and contribute to steroid myopathy, especially in type 2 diabetic patients and insulin resistance.

All patients who have been taking steroids for long periods develop reversible type II myofiber atrophy; this is a *steroid effect* but is not steroid myopathy unless it progresses to become a necrotizing myopathy. At greatest risk in the pediatric age-group are children requiring long-term steroid therapy for asthma, rheumatoid arthritis, dermatomyositis, lupus, and other autoimmune or inflammatory diseases or who are being treated for leukemia or other hematologic diseases. In addition to steroids, the drugs listed in Table 628.1 can cause acute or chronic toxic myopathies. An incompletely understood entity known as critical illness myopathy is a progressive weakness of patients with extended illnesses who remain in the intensive care unit; it is associated pathologically with selective loss of thick (myosin) myofilaments; immobility and excessive steroid treatment are believed to be important factors. Various steroids are sometimes used chronically in the treatment of Duchenne muscular dystrophy; they may actually exaggerate the weakness because of steroid myopathy superimposed on the dystrophic process (see Chapter 627).

Table 628.1

Toxic Myopathies

INFLAMMATORY CAUSES

- Cimetidine
- D -Penicillamine
- Procainamide
- L -Tryptophan
- L-dopa

NONINFLAMMATORY NECROTIZING OR VACUOLAR CAUSES

- Cholesterol-lowering agents
- Chloroquine
- Colchicine
- Emetine
- ε-Aminocaproic acid
- Labetalol
- Cyclosporine and tacrolimus
- Isotretinoic acid (vitamin A analog)
- Vincristine
- Statins
- Alcohol

RHABDOMYOLYSIS AND MYOGLOBINURIA

- Cholesterol-lowering drugs (especially statins)
- Alcohol
- Heroin
- Amphetamine
- Toluene
- Cocaine
- ε-Aminocaproic acid
- Pentazocine
- Phencyclidine

MALIGNANT HYPERTHERMIA

- Halothane
- Ethylene
- Diethyl ether
- Methoxyflurane
- Ethyl chloride
- Trichloroethylene
- Gallamine
- Succinylcholine

MITOCHONDRIAL CAUSES

Zidovudine

MYOTONIA

- 2,4-*d* -Chlorophenoxyacetic acid
- Anthracene-9-carboxycyclic acid
- Cholesterol-lowering drugs
- Chloroquine
- Cyclosporine

MYOSIN LOSS

- Nondepolarizing neuromuscular blocking agents
- Intravenous glucocorticoids

Modified from Goldman L, Ausiello D: Cecil textbook of medicine, ed 22, Philadelphia, 2004, WB Saunders, p. 2399.

Hyperaldosteronism is accompanied by episodic and reversible weakness similar to that of periodic paralysis. Another clinical presentation is muscle cramps at rest. The proximal myopathy can become irreversible in chronic cases. Elevated CK levels and even myoglobinuria sometimes occur during acute attacks. Arterial hypertension is a frequent manifestation, and in children, aldosterone-secreting adenomas up to 6 mm in diameter or multiple adrenocortical micronodules of 0.5 mm should be considered in the differential diagnosis of idiopathic hypertension and muscle weakness or cramps. Hereditary primary aldosteronism is due to a mutation in one of the potassium channel genes *KCNJ5* and *GIRK4* .

Chronic growth hormone excess (sometimes illicitly acquired by adolescent athletes or seen in acromegaly) produces atrophy of some myofibers and hypertrophy of others, and scattered myofiber degeneration. Despite the augmented protein synthesis induced by growth hormone, it impairs myofibrillar adenosine triphosphatase activity and reduces sarcolemmal excitability, with resultant diminished, rather than increased, strength corresponding to the larger muscle mass. It has been used therapeutically in muscular dystrophy with both a positive effect and complications. *Ghrelin* is an intestinal hormone that activates a growth hormone secretagogue receptor and stimulates growth hormone release. In addition to its effect as a “hunger hormone” that involves food intake and fat deposition, it also prevents muscular atrophy by inducing myodifferentiation and myoblast fusion.

Statin-Induced Rhabdomyolysis With

Myoglobinuria

Myalgias that may progress to acute or subacute myofiber necrosis can be induced in 10–15% of patients taking statin drugs (HMG-CoA reductase inhibitors). These widely prescribed drugs are mainly used in adults to lower plasma cholesterol levels but also are sometimes administered to adolescents, particularly in familial cases of hypercholesterolemia. Statins lower the patient's levels of coenzyme-Q10, which is needed for mitochondrial electron transport. Exercise does not exacerbate statin myopathy.

Mitochondrial Dysfunction in Toxic Myopathies

Impaired mitochondrial function, enzymatic activity in the five respiratory chain complexes, and alterations in the mitochondrial ultrastructure are a common basis for the clinical effects of many toxic organic compounds and heavy metals that affect both muscle and peripheral nerves. Statin toxicity is mentioned above. Another example is excessive zinc intake as a dietary supplement (see Chapter 632). These acquired, induced mitochondrial cytopathies can produce weakness and resemble the clinical progression of genetic mitochondrial myopathies plus neuropathy.

Critical Illness Myopathy

Patients who are in the intensive care unit for extended periods sometimes develop progressive weakness and myalgias that cannot be attributed simply to disuse atrophy. The pathogenesis remains uncertain, but some factors may include inhibition of protein synthesis, mitochondrial dysfunction, oxidative stress, and disruption of intramuscular calcium homeostasis. Patients with severe disease may even develop rhabdomyolysis, with elevated serum CK and myoglobinuria leading to renal damage.

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CHAPTER 629

Metabolic Myopathies and Channelopathies

Harvey B. Sarnat

Table 629.1 describes the differential diagnosis of metabolic myopathies.

Table 629.1

Muscle Channelopathies

	MYOTONIA CONGENITA	PARAMYOTONIA CONGENITA	OTHER SODIUM CHANNEL MYOTONIAS	HYPERKALEMIC PERIODIC PARALYSIS	HYPOKALEMIC PERIODIC PARALYSIS
Gene	*CLCN1*	*SCN4A*	*SCN4A*	*SCN4A*	*CACNA1S, SCN4A*
Chromosome	7q35	17q23	17q23	17q23	1q32, 17q23*
Clinical features	Myotonia	Myotonia, episodic weakness	Myotonia	Episodic weakness, myotonia	Episodic weakness
Triggers	Cold (some patients)	Cold	Potassium (some patients)	Potassium, rest after exercise	Carbohydrates, rest after exercise
Acute treatment	n/a	n/a	n/a	Carbohydrate/glucose	Potassium oral, rarely IV
Chronic treatment	Mexiletine, phenytoin, procainamide	Mexiletine, phenytoin, procainamide	Mexiletine, phenytoin, procainamide, acetazolamide	Acetazolamide, dichlorphenamide	Potassium, acetazolamide, dichlorphenamide, potassium-sparing diuretic

Exercise testing	Short exercise test (SET): Postexercise decrement, rapid return to baseline	SET: Postexercise decrement, facilitated by repetition or cold	SET: Often nondiagnostic	Long exercise test (LET): Postexercise decrement	LET: Postexercise decrement
Laboratory features	n/a	n/a	n/a	Ictal high potassium[‡]	Ictal low potassium
Commercially available genetic testing	Yes	Yes	Yes	Yes	Yes

[*] Calcium channel gene chromosome 1, sodium channel gene chromosome 17.

[†] Exact location not determined.

[‡] Case reports of families with mutations associated with hyperkalemic periodic paralysis and normal potassium.

From Statland JM, Barohn RJ: Muscle channelopathies: the nondystrophic myotonias and periodic paralyses, *Continuum* 19(6):1598-1614, 2013, Table 4.1 .

629.1

Periodic Paralyses and Other Muscle Channelopathies

Harvey B. Sarnat

Episodic, reversible weakness or paralysis, known as **periodic paralysis,** is associated with transient alterations in serum potassium levels, usually hypokalemia but occasionally hyperkalemia. All familial forms of periodic paralysis are caused by mutations in genes encoding voltage-gated ion channels in muscle: sodium, calcium, and potassium (see Table 629.1). Nonhereditary causes of periodic paralysis are caused by a diverse group of disorders that affect potassium balance (Table 629.2).

Table 629.2

Secondary Causes of Periodic Paralysis

HYPOKALEMIC

- Thyrotoxic
- Primary hyperaldosteronism (Conn syndrome)
- Renal tubular acidosis (e.g., Fanconi syndrome)
- Juxtaglomerular apparatus hyperplasia (Bartter syndrome)
- Gastrointestinal potassium wastage
- Villous adenoma
- Laxative abuse
- Pancreatic non–insulin-secreting tumors with diarrhea
- Nontropical sprue
- Barium intoxication
- Potassium-depleting diuretics
- Amphotericin B
- Licorice
- Corticosteroids
- Toluene toxicity
- *p* -Aminosalicylic acid
- Carbenoxolone

HYPERKALEMIC

- Addison disease
- Hypoaldosteronism
- Excessive potassium supplementation
- Potassium-sparing diuretics
- Chronic renal failure

From Chinnery PF: Muscle diseases. In Goldman L, Schafer AI, editors: *Goldman's Cecil medicine* , ed 24, Philadelphia, 2012, Elsevier, Table 429-8, p. 2415.

During attacks of **hypokalemic paralysis,** myofibers are electrically unexcitable, although the contractile apparatus can respond normally to calcium. The genetic disorder is inherited as an autosomal dominant trait. It is precipitated in some patients by a heavy carbohydrate meal, insulin, epinephrine including that induced by emotional stress, hyperaldosteronism or hyperthyroidism, administration of amphotericin B, or ingestion of licorice.

Attacks of hypokalemic paralysis often begin in infancy, particularly in the hyperkalemic form, and the disease is nearly always symptomatic by 10 yr of age, affecting both sexes equally. Late childhood or adolescence is the more typical age of onset of the hypokalemic form, Andersen-Tawil syndrome, and paramyotonia congenita. Periodic paralysis is an episodic event; patients are unable to move after awakening and gradually recover muscle strength during the next few minutes or hours. All four extremities are involved. Muscles that remain active in sleep, such as the diaphragm, extraocular muscles (rapid eye movements), and cardiac muscle, are not affected. Patients are normal between attacks, but in adult life the attacks become more frequent, and the disorder causes progressive myopathy with permanent weakness even between attacks. The usual frequency of attacks in childhood is once a week. The differential diagnosis includes thyrotoxic periodic paralysis, myotonia congenita, and paramyotonia congenita. A triad of periodic paralysis, potentially fatal cardiac ventricular ectopy (caused by a defect in Kir2.1 channels for terminal repolarization), and characteristic physical features is known as **Andersen-Tawil syndrome.**

Alterations in serum potassium levels occur only during acute episodes and are accompanied by T-wave changes in the electrocardiogram. Hypokalemia may be caused by alterations in calcium gradients. The creatine kinase (CK) level may be mildly elevated at those times. Plasma phosphate levels often decrease during symptomatic periods. Muscle biopsy findings are often normal between attacks, but during an attack a vacuolar myopathy is demonstrated. Pathologic changes in the periodic paralyses are similar, whether the disease is the result of a sodium or a potassium channel defect, suggesting that the changes might result from the recurrent paralytic state rather than the specific channelopathy. The vacuoles are dilated sarcoplasmic reticulum and invaginations of the extracellular space into the cytoplasm, and they may be filled with glycogen. Muscle biopsy is not essential to diagnose periodic paralysis, however. Hypoglycemia does not occur. Loci for the majority of periodic paralyses have been demonstrated and the genes at least partially characterized, but many patients with the same clinical phenotype exhibit no mutations in the identified genes.

Treatment

Paralytic attacks of hypokalemic periodic paralysis are best treated by the oral administration of potassium or even fruit juices that contain potassium. A low sodium intake and the administration of acetazolamide, 5 mg/kg/day bid or tid as a starting dose, often is effective in abolishing attacks or at least reducing their frequency and severity. Dichlorphenamide, a carbonic anhydrase inhibitor, is approved for the treatment of primary hypokalemic and hyperkalemic periodic paralysis syndromes in adults. The drug reduced the frequency, with few side effects (paresthesias, confusion, dysgeusia). Acetazolamide has also been used off label for these conditions.

Other Muscle Channelopathies

Disorders of ion channels other than the well-documented potassium channelopathies also are recognized (see Table 629.1). A rare, severe **neonatal myotonia** is secondary to a mutation of the voltage-gated sodium-channel *SCN4A* gene; it is unrelated to neonatal myotonic dystrophy, myotonia congenita, or infantile myofibrillar myopathies. This same gene also is responsible for severe neonatal **episodic laryngospasm.** Mexiletine is effective treatment of the myotonia, but the long-term prognosis remains poor, with death by 2 yr of age. Sodium channel blockers, such as carbamazepine, phenytoin, and procainamide, are alternatives.

Neuromyotonia, a continuous muscle activity of neurogenic origin, may be caused by mutations in genes encoding or antibodies against potassium channels, but is rare in childhood. **Schwartz-Jampel disease,** resulting from an autosomal recessive trait, involves severe muscle stiffness, myotonia, blepharospasm, and chondroplasia. It becomes symptomatic in the first year of life and is slowly progressive until midadolescence, after which it is stable. It is no longer considered a variant of myotonic dystrophy and is caused by a mutation in the *HSPG2* gene that encodes perlecan, the major heparin sulphate proteoglycan of basement membranes. Sodium channel blockers may be useful.

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629.2

Malignant Hyperthermia

Harvey B. Sarnat

See also Chapters 74 and 626.4 .

This syndrome is usually inherited as an autosomal dominant trait. It occurs in all patients with central core disease but is not limited to that particular myopathy. The gene is at the 19q13.1 locus in both central core disease and malignant hyperthermia without this specific myopathy. At least 15 separate mutations in this gene are associated with malignant hyperthermia. The gene programs the ryanodine receptor, a tetrameric calcium-release channel in the sarcoplasmic reticulum, in apposition to the voltage-gated calcium channel of the transverse tubule (see Table 629.1). It occurs rarely in Duchenne and other muscular dystrophies, in various other myopathies, in some children with scoliosis, and in an isolated syndrome not associated with other muscle disease. Affected children sometimes have peculiar facies. All ages are affected, including premature infants whose mothers underwent general anesthesia for cesarean section. The disorder affects 1-in-10,000 to 1-in-250,000 anesthetics, but prevalence of genetic abnormalities may be as high as 1 : 400.

Acute episodes are precipitated by exposure to general anesthetics and occasionally to local anesthetic drugs. Patients suddenly develop extreme fever, rigidity of muscles, and metabolic and respiratory acidosis; the serum CK level rises to as high as 35,000 IU/L. Myoglobinuria can result in tubular necrosis and acute renal failure.

The muscle biopsy specimen obtained during an episode of malignant hyperthermia or shortly afterward is not indicated but shows widely scattered necrosis of muscle fibers known as rhabdomyolysis. Between attacks, the muscle biopsy specimen is normal unless there is an underlying chronic myopathy.

It is important to recognize patients at risk of malignant hyperthermia because the attacks may be prevented by administering dantrolene sodium before an anesthetic is given. Patients at risk, such as siblings, are identified by the caffeine contracture test: a portion of fresh muscle biopsy tissue in a saline bath is attached to a strain gauge and exposed to caffeine and other drugs; an abnormal spasm is diagnostic. The syndrome-associated receptor also may be demonstrated by immunochemistry in frozen sections of the muscle biopsy. The gene defect of the ryanodine receptor is present in 50% of patients; gene testing is available only for this genetic group. This receptor also may be seen in the muscle biopsy by immunoreactivity. Another candidate gene is at the 1q31 locus.

Apart from the genetic disorder of malignant hyperthermia, some drugs can induce acute rhabdomyolysis with myoglobinuria and potential renal failure, but this usually occurs in patients who are predisposed by some other metabolic disease (mitochondrial myopathies). Valproic acid can induce this process in children with mitochondrial cytopathies or with carnitine palmitoyltransferase deficiency.

Guidelines for DNA screening include patient referral criteria and clinical interpretation of laboratory findings. Dantrolene sodium is specific treatment or preventive if administered to patients at risk before an anesthetic.

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629.3

Glycogenoses

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See also Chapter 105.1 and Table 629.3 .

Table 629.3

Metabolic Diseases That Affect Muscle

NAME(S)	ENZYME DEFICIENCY	CLINICAL FEATURES	DIAGNOSTIC TESTING
Glycogen storage disease type II (Pompe disease)	α-1,4-Glucosidase (GAA enzyme)	• Infantile-onset Pompe: poor feeding, motor delay and hypotonia with weakness, respiratory difficulties, cardiac issues (short P-R interval with wide QRS complex, cardiomegaly, LV outflow obstruction, cardiomyopathy) • Late-onset Pompe: limb–girdle	• Measure α-glucosidase (GAA) enzyme activity on dried blood spot to screen • Confirm via *GAA* gene sequencing demonstrating biallelic mutations for definitive diagnosis • Baseline elevated CK (~10× normal) in infantile-onset

		pattern of weakness, respiratory insufficiency without clinical heart disease • GAA enzyme replacement therapy available	form; baseline CK may be normal in adult-onset form • Muscle biopsy may show vacuoles (lysosomes) and glycogen accumulation with positively staining PAS; 20–30% of patients with adult-onset form may not show specific changes on biopsy
Glycogen storage disease type IIIa (Debrancher deficiency, Cori disease, Forbes disease)	Amylo-1,6-glucosidase	• Ketotic hypoglycemia, hepatomegaly, hyperlipidemia, elevated liver enzymes, cardiomyopathy in childhood, limb–girdle pattern of weakness in 20s–30s	• Baseline elevated CK (2-20× normal) • Triglycerides, cholesterol, and liver enzymes are elevated • *AGL* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease type IV (Brancher deficiency, Andersen disease)	Glycogen branching enzyme (GBE)	• Fatal perinatal neuromuscular subtype: fetal akinesia, polyhydramnios, fetal hydrops • Congenital neuromuscular subtype: hypotonic newborn, respiratory distress, dilated cardiomyopathy, death in infancy • Childhood neuromuscular subtype: chronic progressive myopathy, dilated cardiomyopathy	• Demonstrate deficiency of GBE in the liver, muscle, or skin fibroblasts • *GBE1* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease type V (McArdle disease)	Myophosphorylase	• Exercise-induced muscle cramps and pain, especially early in exercise, that improve with rest or lower intensity (2nd-wind phenomenon) • Recurrent myoglobinuria +/− rhabdomyolysis	• Baseline elevated CK (>5× normal) • *PYGM* gene sequencing demonstrating biallelic mutations for definitive diagnosis • Quantitative or qualitative (stain) on muscle biopsy shows virtual absence of enzyme activity • Subsarcolemmal glycogen accumulation on muscle biopsy on LM (either PAS-positive or vacuoles on H&E) and EM
Glycogen storage disease type VII (Tarui disease)	Phosphofructokinase	• Classical form: muscle aching, cramping, exercise intolerance, myoglobinuria, nausea/vomiting after intense exercise, starting in childhood; hemolytic anemia • Late-onset form: cramps, myalgia, mild proximal weakness in adulthood • Infantile form: hypotonia, arthrogryposis, intellectual disability, fatal in infancy	• Baseline elevated CK • *PFK* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease VIII	Phosphorylase b kinase	• Exercise intolerance, cramps, myoglobinuria, progressive	• Baseline elevated CK • PhK enzyme activity reduced

(phosphorylase kinase [PhK] deficiency)		muscle weakness in childhood to adulthood • Hepatomegaly, growth retardation, fasting ketosis and hypoglycemia	in muscle • *PHKA1* gene sequencing or/and *PHKB* gene sequencing demonstrating biallelic mutations for definitive diagnosis
	Phosphorylase a1 kinase	• Same as above but X-linked and very rare	
Glycogen storage disease IX (phosphoglycerate kinase deficiency)	Phosphoglycerate kinase	• Myopathic form: muscle weakness, pain, cramping, especially with exercise with myoglobinuria +/− rhabdomyolysis	• Baseline mildly elevated CK • *PGK1* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease X (Phosphoglycerate mutase deficiency)	Phosphoglycerate mutase	• Strenuous exercise intolerance, cramps, myoglobinuria	• Baseline mildly elevated CK • *PGAM2* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Glycogen storage disease XI (lactate dehydrogenase deficiency)	Lactate dehydrogenase	• Exercise intolerance, cramping, recurrent myoglobinuria	• Normal CK between attacks • *LDHA* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Systemic primary carnitine deficiency	Solute carrier family 22 (sodium-dependent carnitine transporter)	• Childhood myopathic form: hypotonia, dilated cardiomyopathy that could result in death, proximal muscle weakness in early childhood (2–4 yr) • Adult form: fatigability	• Baseline CK elevated • Reduced plasma carnitine levels • Increased lipid deposition on muscle biopsy • *SLC22A5* gene sequencing demonstrating biallelic mutations for definitive diagnosis
Carnitine palmitoyltransferase II deficiency	Carnitine palmitoyltransferase II (CPT II)	• Myopathic form: recurrent myalgia and myoglobinuria after prolonged exercise, cold, or fasting; weakness during attacks; onset from childhood to adulthood • Severe infantile form: liver failure, cardiomyopathy, seizures, hypoketotic hypoglycemia, myopathy before 1 yr of age (rare)	• Normal CK between attacks • CPT II gene sequencing demonstrating biallelic mutations for definitive diagnosis • Muscle biopsy can be normal

CK, creatine kinase; EM, electron microscopy; H&E, hematoxylin and eosin; LM, light microscopy; LV, left ventricular; PAS, periodic acid–Schiff.

From Konersman C: Hypotonia, weakness, and stroke. In Kliegman RM, Lye PS, Bordini BJ, et al (eds): *Nelson symptom-based diagnosis* , Philadelphia, 2018, Elsevier, Table 29.12.

Glycogenosis I (von Gierke disease) is not a true myopathy because the deficient liver enzyme glucose-6-phosphatase is not normally present in muscle. Nevertheless, children with this disease are hypotonic and mildly weak for unknown reasons.

Glycogenosis II (Pompe disease) is an autosomal recessively inherited deficiency of the glycolytic lysosomal enzyme α-glucosidase (formerly known as acid maltase) that cleaves the α-1,4 and α-1,6 glycosidic linkages. Of the 12 known glycogenoses, type II is the only one with a defective lysosomal enzyme. The defective gene is at locus 17q23, with more than 200 distinct mutations identified. Two clinical forms are described. The **infantile** form is a severe generalized myopathy and cardiomyopathy. Patients have cardiomegaly and hepatomegaly and are diffusely hypotonic and weak. The serum CK level is greatly elevated. A muscle biopsy specimen reveals a vacuolar myopathy with abnormal lysosomal enzymatic activities such as acid and alkaline phosphatases. Evidence of a secondary mitochondrial cytopathy is often demonstrated; it includes electron microscopic demonstration of paracrystallin structures within muscle mitochondria and low concentrations of respiratory chain enzymes. Death in infancy or early childhood is usual; however, enzyme replacement therapy has improved the outcome.

The **late childhood** or **adult** form is a much milder myopathy without cardiac or hepatic enlargement. It might not become clinically expressed until later childhood or early adult life but may be symptomatic as myopathic weakness and hypotonia even in early infancy. Even in late adult-onset acid maltase deficiency, > 50% of the patients report difficulties with muscle strength dating from childhood. Ultrastructural evidence of secondary mitochondrial cytopathy also occurs, as with infantile Pompe disease. MRI of muscle may show distinctive changes that differ from other myopathies.

The serum CK level is greatly elevated, and the muscle biopsy findings are diagnostic even in the presymptomatic stage. The diagnosis of glycogenosis II is confirmed by quantitative assay of acid maltase activity in muscle or liver biopsy specimens. An evidence-based review and Canadian guidelines for diagnosis and management were recently published.

A rare variant of the milder form of acid maltase deficiency can show muscle acid maltase activity in the low normal range with only intermittent decreases to subnormal values; the muscle biopsy findings are similar although milder. In another form, **Danon disease,** transmitted as an X-linked recessive trait at the Xq24 locus, the primary deficiency is lysosomal membrane protein-2 (LAMP2) and results in hypertrophic cardiomyopathy, proximal myopathy, and intellectual disability.

Glycogenosis III (Cori-Forbes disease), a deficiency of debrancher enzyme (amylo-1,6-glucosidase), is more common than is usually diagnosed, and it is generally the least severe. Hypotonia, weakness, hepatomegaly, and fasting hypoglycemia in infancy are common, but these features often resolve spontaneously, and patients become asymptomatic in childhood and adult life.

Others experience slowly progressive distal muscle wasting, hepatic cirrhosis, recurrent hypoglycemia, and heart failure. This more serious chronic course is particularly seen in the Inuit population. Minor myopathic findings including vacuolation of muscle fibers are found in the muscle biopsy specimen.

Glycogenosis IV (Andersen disease) is a deficiency of brancher enzyme, resulting in the formation of an abnormal glycogen molecule, amylopectin, in the liver, reticuloendothelial cells, and skeletal and cardiac muscle. Hypotonia, generalized weakness, muscle wasting, and contractures are the usual signs of myopathic involvement. Most patients die before age 4 yr because of hepatic or cardiac failure. A few children without neuromuscular manifestations have been described.

Glycogenosis V (McArdle disease) is caused by muscle glycogen phosphorylase deficiency inherited as an autosomal recessive trait at locus 11q13, encoded by the *PMGM* gene. Exercise intolerance is the cardinal clinical feature. Physical exertion results in cramps, weakness, and myoglobinuria, but strength is normal between attacks. The serum CK level is elevated only during exercise. A characteristic clinical feature is lack of the normal rise in serum lactate levels during ischemic exercise because of inability to convert pyruvate to lactate under anaerobic conditions in vivo. Myophosphorylase deficiency may be demonstrated histochemically and biochemically in the muscle biopsy tissue. Some patients have a defect in adenosine monophosphate–dependent muscle phosphorylase β-kinase, a phosphorylase enzyme activator. Muscle phosphorylase deficiency was the first neuromuscular disease to be diagnosed by MR spectroscopy, which shows that the intramuscular pH does not decrease with exercise and there is no depletion of adenosine triphosphatase but that the phosphocreatine concentration falls excessively. This noninvasive technique may be useful in some patients if the radiologist is experienced with the disease.

A rare **neonatal form of myophosphorylase deficiency** causes feeding difficulties in early infancy, may be severe enough to result in neonatal death, or can follow a course of slowly progressive weakness resembling a muscular dystrophy. The long-term prognosis is good. Patients must learn to moderate their physical activities, but they do not develop severe chronic myopathic handicaps or cardiac involvement.

Glycogenosis VII (Tarui disease) is muscle phosphofructokinase deficiency. Although this disease is rarer than glycogenosis V, the symptoms of exercise intolerance, clinical course, and inability to convert pyruvate to lactate are identical. The distinction is made by biochemical study of the muscle biopsy specimen. It is transmitted as an autosomal recessive trait at the 1cenq32 locus, and some mutations are particularly prevalent in the Ashkenazi Jewish population.

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629.4

Mitochondrial Myopathies

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See also Chapters 105.4 and 616.2 and Table 629.4 .

Table 629.4

Select Mitochondrial Disorders with Hypotonia Classified by Clinical Phenotypes

CLINICAL PHENOTYPE	ASSOCIATED MUTATIONS	MODE OF INHERITANCE	COMMON CLINICAL FEATURES
MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and strokelike episodes)	tRNA point mutations: • m.3243A>G in tRNA $^{\text{Leu}}$ (~80% of cases) • m.3217T>C in tRNA $^{\text{Leu}}$ (~7.5% of cases) • m.13513G>A encoding NADH-ubiquinone (<15% of cases) • m.3252A>G in tRNA $^{\text{Leu}}$ (<5% of cases) • Multiple other mtDNA point mutations	Maternal	• Cardinal: strokelike episodes, intermittent encephalopathy, T2/FLAIR abnormalities on brain MRI that do not respect vascular territory, lactic acidosis • Other: hearing loss, diabetes, short stature, gastrointestinal issues
MERRF syndrome (myoclonic epilepsy with ragged red fibers)	tRNA point mutations: • m.8344A>G in tRNA $^{\text{Lys}}$ (>80% of cases) • m.8356T>C in tRNA $^{\text{Lys}}$ • m.8363G>A in tRNA $^{\text{Lys}}$ • m.8361G>A in tRNA $^{\text{Lys}}$ • Multiple other mtDNA point mutations	Maternal	• Cardinal: myoclonus, proximal weakness, generalized epilepsy, ataxia • Other: multiple lipomatosis, hearing loss, cognitive impairment, neuropathy
KSS (Kearns–Sayre syndrome)	Single large mtDNA deletion (1.1-10-kb) • m.8470_13446del4977 (deletion of 4977 base pairs; most common) • Multiple other mtDNA deletions	Sporadic	• Cardinal: multisystemic disease with progressive external ophthalmoplegia, pigmentary retinopathy, cardiomyopathy before age 20 yr • Other: short stature, proximal muscle weakness, hearing loss, dementia, ataxia, multiple endocrinopathies (diabetes, hypothyroidism, hypoparathyroidism, hypogonadism)
CPEO (chronic progressive external ophthalmoplegia)	Single large mtDNA deletion (1.1-10 kb)	Sporadic	• Cardinal: skeletal muscle disorder with ptosis, ophthalmoparesis, +/− proximal muscle weakness
	• m.3243A>G in tRNA $^{\text{Leu}}$ (most common; same as MELAS) • Multiple other mtDNA point mutations	Maternal	
	• Multiple mtDNA deletions caused by mutations in the following nuclear genes: *SLC25A4* encoding ANT1, *C10orf2* encoding twinkle,	Autosomal dominant	

	POLG1 encoding mtDNA polymerase, *POLG2, OPA1*		
Leigh syndrome (subacute necrotizing encephalomyelopathy)	mtDNA mutations: • m.8993T>G or m.8993T>C in *MT-ATP6* (~10% of cases) • Multiple other mtDNA point mutations	Maternal	• Hypotonia, spasticity, movement disorders (chorea), cerebellar ataxia, neuropathy, bilateral basal ganglia lesions, seizures, lactic acidosis, psychomotor retardation/regression especially with illness between 3-12 mo of age • Hypertrophic cardiomyopathy
	• m.8470_13446del4977 (deletion of 4977 base pairs; also seen in KSS)	Sporadic	
	Nuclear gene mutations resulting in respiratory chain complex deficiencies: • Complex I: *NDUFV1*, *NDUFS1, NDUFS2, NDUFS3*, *NDUFS4, NDUFS7, NDUFS8, NDUFA1, NDUFA2, NDUFA10*, *NDUFA9, NDUFA12*, *NDUFAF2*, *NDUFAF5, NDUFAF6*, *FOXRED1* • Complex II: *SDHA, SDHAF1* • Complex III: *BCS1L, UQCRQ, TTC19* • Complex IV: *SURF1*, *COX10, COX15, SCO2, NDUFA4, PET100, LRPPRC*	Autosomal recessive	
NARP (neurogenic muscle weakness, ataxia, retinitis pigmentosa)	• m.8993T>G or m.8993T>C in *MT-ATP6* (50% of cases)	Maternal	• Proximal neurogenic muscle weakness, sensory neuropathy, seizures, ataxia, pigmentary retinopathy, learning difficulties, dementia with onset usually in childhood
Mitochondrial DNA depletion syndrome	• Homozygous or compound heterozygous mutations in *TK2* (thymidine kinase 2), a mitochondrial deoxyribonuclease, resulting in mitochondrial depletion	Autosomal recessive	• Hypotonia, proximal muscle weakness, axial weakness, respiratory insufficiency, marked clinical variability with death in infancy to early adulthood due to respiratory insufficiency

FLAIR, fluid-attenuated inversion recovery; GI, gastrointestinal; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide, reduced form; tRNA, transfer RNA.

Data from DiMauro S, Hirano M: MERRF, *GeneReviews* [Internet], June 3, 2003, Seattle: University of Washington; DiMauro S, Hirano M: MELAS, *GeneReviews* [Internet] February 27, 2001, Seattle: University of Washington; Thorburn DR, Rahman S: Mitochondrial DNA-associated Leigh syndrome and NARP, *GeneReviews* [Internet], October 30, 2003, Seattle: University of Washington; Liang C, Ahmad K, Sue CM: The broadening spectrum of mitochondrial disease: shifts in the diagnostic paradigm, *Biochim Biophys Acta* 1840:1360-1367, 2014; Konersman C: Hypotonia, weakness, and stroke. In Kliegman RM, Lye PS, Bordini BJ, et al (eds): *Nelson symptom-based diagnosis* , Philadelphia, 2018, Elsevier, Table 29.11.

Several diseases involving muscle, brain, and other organs are associated with structural and functional abnormalities of mitochondria, producing defects in aerobic cellular metabolism, the electron transport chain, and the Krebs cycle (Table 629.5 and see Table 629.4). Because mitochondria are found in all cells except mature erythrocytes, the term **mitochondrial cytopathy** is used preferentially to emphasize the multisystemic nature of these diseases. The structural aberrations are best demonstrated by electron microscopy of the muscle biopsy sample, revealing a proliferation of abnormally shaped cristae, including stacked or whorled cristae and paracrystallin structures that occupy the space between cristae and are formed from CK. Muscle biopsies of neonates, infants, and toddlers show more severe involvement of endothelial cells of intramuscular capillaries than of myofibers, unlike the reverse in adults, but endothelial paracrystallin structures are globular rather than brick shaped as in myofibers. The endoplasmic reticulum becomes abnormally adherent to mitochondria. Similar endothelial mitochondrial alterations are seen in the brain in Leigh and other infantile mitochondrial encephalopathies. Histochemical study of the muscle biopsy specimen reveals abnormal clumping of oxidative enzymatic activity and scattered myofibers, with loss of cytochrome-c oxidase activity and with increased neutral lipids within myofibers. Ragged red muscle fibers occur in some mitochondrial myopathies, particularly those with a combination of respiratory chain complexes I and IV deficiencies. Accumulations of this membranous material beneath the muscle fiber membrane are best demonstrated by special stains, such as modified Gomori trichrome.

Table 629.5

Clinical Spectrum of Mitochondrial Disease

NERVOUS SYSTEM
• Hypotonia • Failure to thrive • Motor regression • Stroke (nonvascular) • Dementia • Episodic encephalopathy (elevated cerebrospinal fluid lactate) • Intellectual disability • Neuropathy (axonal, demyelinating, or sensory ganglionopathy) • Ophthalmoparesis (slowly progressive) • Ptosis (slowly progressive; little diurnal variation; asymmetric at onset) • Optic atrophy • Retinitis pigmentosa (perimacular; vision usually spared) • Ataxia • Central apnea • Epilepsy (focal or multifocal myoclonus; status epilepticus; triggered by sodium valproate) • Migraines

• Sensorineural hearing loss (asymmetric; young onset; partial recovery possible)
HEART
• Cardiomyopathy • Conduction block or arrhythmia
SKELETAL MUSCLE
• Myopathy (proximal, symmetric weakness; myalgia) • Exercise intolerance • Episodic rhabdomyolysis
OTHER
• Lactic acidosis • Recurrent bowel obstruction (pseudoobstruction) • Short stature • Diabetes (young onset; nonobese)

Data from Amato A, Russell J: *Neuromuscular disorders* , 1st ed, New York, 2008, McGraw-Hill; Liang C, Ahmad K, Sue CM: The broadening spectrum of mitochondrial disease: shifts in the diagnostic paradigm, *Biochim Biophys Acta* 1840:1360-1367, 2014.

These characteristic histochemical and ultrastructural changes are most consistently seen with point mutations in mitochondrial transfer RNA. The large mitochondrial DNA (mtDNA) deletions of 5 or 7.4 kb (the single mitochondrial chromosome has 16.5 kb) are associated with defects in mitochondrial respiratory oxidative enzyme complexes, if as few as 2% of the mitochondria are affected, but minimal or no morphologic or histochemical changes may be noted in the muscle biopsy specimen, even by electron microscopy; hence, quantitative biochemical studies of the muscle tissue are needed to confirm the diagnosis. Because most of the subunits of the respiratory chain complexes are encoded by nuclear DNA (nDNA) rather than mtDNA, mendelian autosomal inheritance is possible, rather than maternal transmission as with pure mtDNA point mutations. Complex II (succinate dehydrogenase) is the only enzyme complex in which all of its subunits are encoded by nDNA; hence, it is histochemically reactive in all mitochondrial diseases with mtDNA point mutations. Serum lactate is elevated in some diseases, and cerebrospinal fluid lactate is more consistently elevated, even if serum concentrations are normal.

Several distinct mitochondrial diseases that primarily affect striated muscle or muscle and brain are identified. These can be divided into the ragged red fiber diseases and non–ragged fiber diseases. The ragged red fiber diseases include Kearns-Sayre, MELAS (*m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*troke-like episodes) syndrome, MERRF (*m*yoclonic *e*pilepsy with *r*agged *r*ed *f*ibers) syndrome, and progressive external ophthalmoplegia syndromes, which are associated with a combined defect in respiratory chain complexes I and IV. The non–ragged fiber diseases include Leigh encephalopathy and Leber hereditary optic atrophy; they involve complex I or IV alone or, in children, the common combination of defective complexes III and V. **Kearns-Sayre syndrome** is characterized by the triad of progressive external ophthalmoplegia, pigmentary degeneration of the retina, and onset before age 20 yr. Heart block, cerebellar deficits, and a high cerebrospinal fluid protein content are often associated. Visual evoked potentials are abnormal. Patients usually do not experience weakness of the trunk or extremities or dysphagia. Most cases are sporadic.

Chronic progressive external ophthalmoplegia may be isolated or accompanied by limb muscle weakness, dysphagia, and dysarthria. A few patients described as having *ophthalmoplegia plus* have additional central nervous system involvement. Autosomal dominant inheritance is found in some pedigrees, but most cases are sporadic.

MERRF and **MELAS syndromes** are other mitochondrial disorders affecting children. The latter is characterized by stunted growth, episodic vomiting, seizures, and recurring cerebral insults causing hemiparesis, hemianopia, or even cortical blindness, and dementia. The disease behaves as a degenerative disorder, and children die within a few years.

Other “degenerative” diseases of the central nervous system that also involve myopathy with mitochondrial abnormalities include **Leigh subacute necrotizing encephalopathy** (see Chapter 105.4) and **cerebrohepatorenal (Zellweger) disease, primarily a peroxisomal disease with secondary mitochondrial alterations** (see Chapter 104.2). Another recognized mitochondrial myopathy is **cytochrome-c oxidase deficiency. Oculopharyngeal muscular dystrophy** is also fundamentally a mitochondrial myopathy.

Mitochondrial depletion syndrome of early infancy is characterized by severely decreased oxidative enzymatic activities in most or all five of the complexes; in addition to diffuse muscle weakness, neonates and young infants can show multisystemic involvement, and the syndrome occurs in several forms: myopathic; encephalomyopathic; hepatoencephalopathic; and intestinal encephalopathic. Cardiomyopathy and sometimes bullous skin lesions or generalized edema also can occur. **Alpers syndrome** is genetically homogeneous and is caused by mtDNA depletion and mutations in the *POLG1* gene. Several other genes are identified, mostly in later-onset forms; hence, mitochondrial depletion is a syndrome and not a single disease. **Barth syndrome** is an X-linked recessive mitochondrial disorder characterized by cardiomyopathy, myopathy of striated muscle, growth retardation, neutropenia, and high serum and urinary concentrations of 3-methyl-glutaconic acid.

Many rare diseases with only a few case reports are suspected of being mitochondrial disorders. It is also now recognized that secondary mitochondrial defects occur in a wide range of nonmitochondrial diseases, including inflammatory autoimmune myopathies, Pompe disease, and some cerebral malformations, and also may be induced by certain drugs and toxins, so that interpretation of mitochondrial abnormalities as primary defects must be approached with caution.

mtDNA is distinct from the DNA of the cell nucleus and is inherited exclusively from the mother; mitochondria are present in the cytoplasm of the ovum but not in the head of the sperm, the only part that enters the ovum at fertilization. The rate of mutation of mtDNA is 10 times higher than that of nDNA. The mitochondrial respiratory enzyme complexes each have subunits encoded either in mtDNA or nDNA. Complex II (succinate dehydrogenase, a Krebs cycle enzyme) has four subunits, all encoded in nDNA; complex III (ubiquinol or cytochrome-b oxidase) has nine subunits, only one of which is encoded by mtDNA and eight of which are programmed by nDNA; complex IV (cytochrome-c oxidase) has thirteen subunits, only three of which are encoded by mtDNA. For this reason, mitochondrial diseases of muscle may be transmitted as autosomal recessive traits rather than by strict maternal transmission, even though all mitochondria are inherited from the mother.

In Kearns-Sayre syndrome, a single large mtDNA deletion has been identified, but other genetic variants are known; in MERRF and MELAS syndromes of mitochondrial myopathy, point mutations occur in transfer RNA.

Investigations

Investigation for mitochondrial cytopathies begins with serum lactate. Lactic acid is not increased in all mitochondrial cytopathies, so that a normal result is not necessarily reassuring; cerebrospinal fluid lactate is increased in some cases in which serum lactate is normal, particularly if there are clinical signs of encephalopathy. Serum 3-methyl-glutaconic acid often is increased in mitochondrial cytopathies in general, demonstrated in more than 50 different genetic mutations, and hence is a good screening measurement; it rarely is increased in other metabolic diseases. This product also may be increased in urine. Hepatic enzymes (transaminases) should be measured in blood. Cardiac evaluation often is warranted. Molecular markers in blood for the common diseases with known mtDNA point mutations identify many of the mitochondrial cytopathies presenting in adult life or adolescence, but less frequently in children and least in young infants. MRI of the brain may reveal hyperintense lesions of the basal ganglia and MR spectroscopy can demonstrate an increased lactate peak. The muscle biopsy provides the best evidence of all mitochondrial myopathies and should include histochemistry for oxidative enzymes, electron microscopy, and quantitative biochemical assay of respiratory chain enzyme complexes and coenzyme-Q10; muscle tissue also can be analyzed for mtDNA. Many mitochondrial disorders also can affect the Schwann cells and axons of peripheral nerves and present clinically with neuropathy; hence, motor and sensory nerve conduction velocities can be measured in selected patients; sural nerve biopsy is required only rarely if neuropathy is the predominant finding and the diagnosis is not evident from other studies.

A diagnostic approach is noted in Fig. 629.1 .

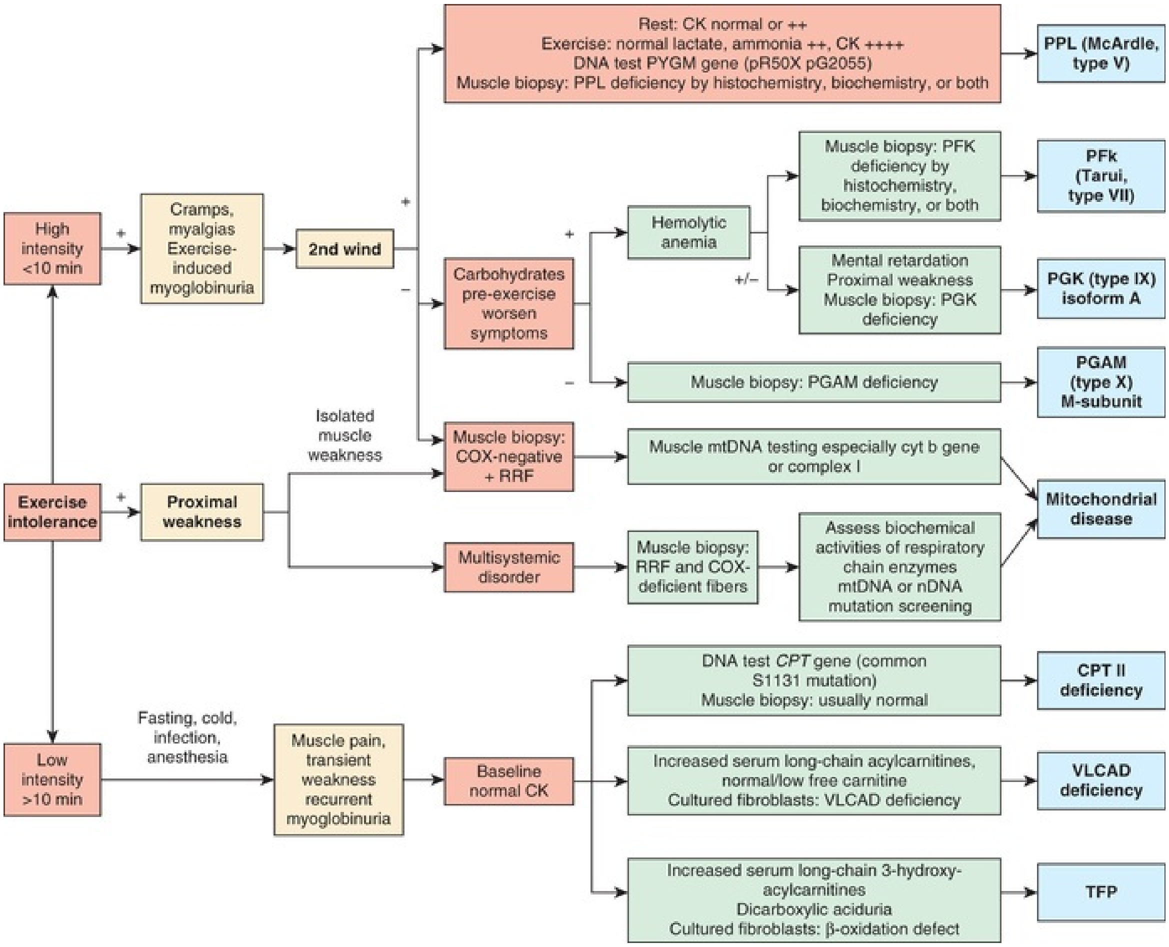
High intensity <10 min
+
Cramps, myalgias Exercise-induced myoglobinuria
2nd wind
+
Rest: CK normal or ++
Exercise: normal lactate, ammonia ++, CK ++++
DNA test PYGM gene (pR50X pG2055)
Muscle biopsy: PPL deficiency by histochemistry, biochemistry, or both
PPL (McArdle, type V)
−
Carbohydrates pre-exercise worsen symptoms
+
Hemolytic anemia
Muscle biopsy: PFK deficiency by histochemistry, biochemistry, or both
PFk (Tarui, type VII)
+/−
Mental retardation Proximal weakness Muscle biopsy: PGK deficiency
PGK (type IX) isoform A
−
Muscle biopsy: PGAM deficiency
PGAM (type X) M-subunit
Isolated muscle weakness
Muscle biopsy: COX-negative + RRF
Muscle mtDNA testing especially cyt b gene or complex I
Mitochondrial disease
Exercise intolerance
+
Proximal weakness
Multisystemic disorder
Muscle biopsy: RRF and COX-deficient fibers
Assess biochemical activities of respiratory chain enzymes mtDNA or nDNA mutation screening
DNA test CPT gene (common S1131 mutation)
Muscle biopsy: usually normal
CPT II deficiency
Low intensity >10 min
Fasting, cold, infection, anesthesia
Muscle pain, transient weakness recurrent myoglobinuria
Baseline normal CK
Increased serum long-chain acylcarnitines, normal/low free carnitine
Cultured fibroblasts: VLCAD deficiency
VLCAD deficiency
Increased serum long-chain 3-hydroxy-acylcarnitines
Dicarboxylic aciduria
Cultured fibroblasts: β-oxidation defect
TFP

FIG. 629.1 Clinical diagnostic algorithm for patients with exercise intolerance in whom a metabolic myopathy is suspected. CK, creatine

kinase; COX, cytochrome-c oxidase; CPT, carnitine palmitoyl transferase; cyt *b,* cytochrome *b* ; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; PFK, phosphofructokinase; PGAM, phosphoglycerate mutase; PGK, phosphoglycerate kinase; PPL, myophosphorylase; RRF, ragged red fibers; TFP, trifunctional protein deficiency; VLCAD, very-long-chain acyl-coenzyme A dehydrogenase. (From Berardo A, Di Mauro S, Hirano M: A diagnostic algorithm for metabolic myopathies, *Curr Neurol Neurosci Rep* 10:118-126, 2010, Fig. 1.)

Treatment

There is no effective treatment of mitochondrial cytopathies, but various *cocktails* are often used empirically to try to overcome the metabolic deficits. These include oral carnitine supplements, riboflavin, coenzyme-Q10, ascorbic acid (vitamin C), vitamin E, and other antioxidants. Although some anecdotal reports are encouraging, no controlled studies that prove efficacy have been published.

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629.5

Lipid Myopathies

Harvey B. Sarnat

See Chapter 104.4 .

Considered as metabolic organs, skeletal muscles are the most important sites in the body for long-chain fatty acid metabolism because of their large mass and their rich density of mitochondria where fatty acids are metabolized. They are the major source of energy for skeletal muscle during sustained exercise or fasting. Hereditary disorders of lipid metabolism that cause progressive myopathy are an important, relatively common, and often treatable group of muscle diseases (Table 629.6). Increased lipid within myofibers is seen in the muscle biopsy of some mitochondrial myopathies and is a constant, rather than an unpredictable, feature of specific diseases. Among the ragged red fiber diseases, Kearns-Sayre syndrome always shows increased neutral lipid, whereas MERRF and MELAS syndromes do not, a useful diagnostic marker for the pathologist. Free fatty acids are converted to acyl-coenzyme A by fatty acyl-coenzyme A synthetases; the resulting long-chain fatty acids bind to carnitine and are transported into mitochondria where β-oxidation is carried out. Disorders of lipid fuel utilization and lipid storage disorders can be divided into defects of transport and oxidation of exogenous fatty acids within mitochondria and defects of endogenous triglyceride catabolism.

Table 629.6

Lipid Metabolism Deficiencies

Carnitine palmitoyltransferase*
Primary systemic/muscle carnitine deficiency
Secondary carnitine deficiency
β-Oxidation defects
Medications (valproic acid)

* Deficiency can produce exercise intolerance and myoglobinuria.

From Chinnery PF: Muscle diseases. In Goldman L, Schafer AI, editors: *Goldman's Cecil medicine* , ed 24, Philadelphia, 2012, Elsevier, Table 429-7, p.

2413.

Muscle carnitine deficiency is an autosomal recessive disease caused by mutations in the *SLC22A5* gene, involving deficient transport of dietary carnitine across the intestinal mucosa. Carnitine is acquired from dietary sources but is also synthesized in the liver and kidneys from lysine and methionine; it is the obligatory carrier of long- and medium-chain fatty acids into muscle mitochondria.

The clinical course may be one of sudden exacerbations of weakness or can resemble a progressive muscular dystrophy with generalized proximal myopathy and sometimes facial, pharyngeal, and cardiac involvement. Symptoms usually begin in late childhood or adolescence or may be delayed until adult life. Progression is slow but can end in death.

The serum CK level is mildly elevated. Muscle biopsy material shows vacuoles filled with lipid within muscle fibers in addition to nonspecific changes suggestive of a muscular dystrophy. Mitochondria can appear normal or abnormal. Carnitine measured in muscle biopsy tissue is reduced, but the serum carnitine level is normal.

Treatment stops the progression of the disease and can even restore lost strength if the disease is not too advanced. It consists of special diets low in long-chain fatty acids. Steroids can enhance fatty acid transport. Specific therapy with L -carnitine taken orally in large doses overcomes the intestinal barrier in some patients. Some patients also improve when given supplementary riboflavin, and other patients seem to improve with propranolol.

Systemic carnitine deficiency is a disease of impaired renal and hepatic synthesis of carnitine rather than a primary myopathy. Patients with this autosomal recessive disease experience progressive proximal myopathy and show muscle biopsy changes similar to those of muscle carnitine deficiency; however, the onset of weakness is earlier and may be evident at birth. Endocardial fibroelastosis also can occur. Episodes of acute hepatic encephalopathy resembling Reye syndrome can occur. Hypoglycemia and metabolic acidosis complicate acute episodes. Cardiomyopathy may be the predominating feature in some cases and result in death.

Cerebral infarctions and myopathy occur in children, particularly when accompanied by hypoglycemia. The mean age at presentation is approximately 9 yr. A brain MRI shows distinctive changes related to multiple infarcts of various sizes.

The concentration of carnitine is reduced in serum as well as in muscle and liver. L -Carnitine deficiency can be corrected by oral administration of carnitine on a daily basis.

A similar clinical syndrome may be a complication of renal Fanconi syndrome because of excessive urinary loss of carnitine or loss during chronic hemodialysis.

Treatment with L -carnitine improves the maintenance of blood glucose and serum carnitine levels but does not reverse the ketosis or acidosis or improve the exercise capacity.

Muscle carnitine palmitoyltransferase (CPT) deficiency manifests as episodes of rhabdomyolysis, coma, and elevated serum CK levels. It is the most common identified cause of recurrent myoglobinuria in adults, but myoglobinuria is not a constant feature in all. CPT transfers long-chain fatty acid acyl-coenzyme A residues to carnitine on the outer mitochondrial membrane for transport into the mitochondria. Exercise intolerance and myoglobinuria resemble glycogenoses V and VII. The degree of exercise that triggers an attack varies among individuals, ranging from casual walking to strenuous exercise. Fasting hypoglycemia can occur. Some patients present only in late adolescence or adult life with myalgias. Genetic transmission is autosomal recessive and is caused by a defect on chromosome 1 at the 1p32 locus. Administration of valproic acid can precipitate acute rhabdomyolysis with myoglobinuria in patients with CPT deficiency; it should be avoided in the treatment of seizures or migraine if they occur. *Very long-chain acyl-coenzyme A dehydrogenase deficiency* has a similar clinical presentation but mainly with adult onset.

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629.6

Vitamin E Deficiency Myopathy

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In experimental animals, deficiency of vitamin E (α-tocopherol, an antioxidant also important in mitochondrial superoxide generation) produces a progressive myopathy closely resembling a muscular dystrophy. Myopathy and neuropathy are recognized in humans who lack adequate intake of this antioxidant. Patients with chronic malabsorption, those undergoing long-term dialysis, and premature infants who do not receive vitamin E supplements are particularly vulnerable. Treatment with high doses of vitamin E can reverse the deficiency. Myopathy caused by chronic hypervitaminosis E also occurs.

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CHAPTER 630

Disorders of Neuromuscular Transmission and of Motor Neurons

630.1

Myasthenia Gravis

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Autoimmune Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disease of the postsynaptic endplate leading to abnormal neuromuscular transmission or blockade, characterized clinically by rapid fatigability of striated muscle, particularly extraocular and palpebral muscles and those of swallowing. It must be distinguished from congenital myasthenic syndrome, a genetic disorder of receptors on the presynaptic and postsynaptic membranes, as well as the synapse of the neuromuscular junction and toxin-induced disorders of neurotransmission, such as botulism (see below). In MG, the release of acetylcholine (ACh) into the synaptic cleft by the axonal terminal is normal, but the postsynaptic muscle membrane (i.e., *sarcolemma*) or *motor endplate* is less responsive than normal. This is due to antibodies against the postsynaptic acetylcholine receptor (AChR), leading to an abnormal architecture/folding pattern of the postsynaptic membrane, as well as a decreased number of receptors to which acetylcholine can bind.

Infants born to *myasthenic mothers* can have a **transient neonatal myasthenic syndrome** secondary to placentally transferred anti-AChR antibodies, distinct from congenital myasthenic syndromes (Tables 630.1 to 630.3).

Table 630.1

Classification of the Congenital Myasthenia Syndromes*

SYNDROME	PERCENTAGE
PRESYNAPTIC	
Choline acetyltransferase deficiency	5
SNAP25 deficiency	0.3
Synaptotagmin 2 deficiency†	0
SYNAPTIC BASAL LAMINA–ASSOCIATED	
Endplate AChE deficiency	12.6
Laminin β2 deficiency	0.3
POSTSYNAPTIC	
Primary AChR deficiency ± minor kinetic abnormality	33
Primary kinetic defect ± minor AChR deficiency	17.5
Na channel myasthenia	0.3
Plectin deficiency	0.6
DEFECTS IN EP DEVELOPMENT AND MAINTENANCE	
Agrin deficiency	0.3
LRP4 deficiency	0.6
MuSK deficiency	0.3
Dok-7 deficiency	9.8
Rapsyn deficiency	14
CONGENITAL DEFECT OF GLYCOSYLATION	
GFPT1 deficiency	3
DPAGT1 deficiency	0.6
ALG2† deficiency	0
ALG14† deficiency	0
OTHER MYASTHENIC SYNDROMES	
PREPL deletion syndrome	0.3
Defects in the mitochondrial citrate synthase carrier†	0
CMS associated with centronuclear myopathies	0.3
TOTAL	**100%**

* Classification based on cohort of 353 congenital myasthenic syndrome patients investigated at the Mayo Clinic between 1988 and 2014.

† Defects in ALG2 and ALG14, synaptotagmin 2, and the mitochondrial citrate synthesis carrier were identified at other medical centers.

Modified from Darras BT, Monani UR, De Vivo DC: Genetic disorders affecting the motor neuron: spinal muscular atrophy. In Swaiman KF, Ashwal S, Ferriero DM, et al (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, Table 144-1.

Table 630.2

Distinctive Clinical and Electrodiagnostic Features of Congenital Myasthenic Syndrome

	PRESYNAPTIC		**SYNAPTIC**	**POSTSYNAPTIC**		
	CHOLINE ACETYLTRANSFERASE DEFICIENCY	**LMS-LIKE FORM**	**ACHE DEFICIENCY**	**PRIMARY ACHR DEFICIENCY**	**SLOW-CHANNEL CMS**	**FAST-CHANNEL CMS**
Autosomal dominant inheritance					X (most mutations)	
Episodic apnea triggered by stressors	X					
Neonatal hypotonia and respiratory insufficiency	X	X	X (in severe cases)	X (in severe cases)		
Skeletal deformities			X	X		X (in severe cases)
Delayed pupillary light responses			X			
Prominent neck, wrist, and finger extensor weakness					X	
Repetitive CMAPs after single stimulus			X		X	
Progressive decrement with prolonged exercise or repetitive stimulation	X			X		
Marked increment (>200%) with high-frequency repetitive stimulation		X				
Decrement repairs with AChE inhibitors				X		X
Clinical						X

improvement with AChE inhibitors						
Clinical worsening with AChE inhibitors			X		X	

AChE, acetylcholinesterase; AChR, acetylcholine receptor; CMAPs, compound muscle action potentials; CMS, congenital myasthenic syndrome; LEMS, Lambert-Eaton myasthenic syndrome.

From Muppidi S, Wolfe GI, Barhon RJ: Diseases of the neuromuscular junction. In Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors: Swaiman's pediatric neurology, ed 5, Philadelphia, 2012, Elsevier, Table 91-3.

Table 630.3

Differential Diagnosis of Congenital Myasthenic Syndromes

NEONATAL PERIOD, INFANCY, CHILDHOOD
• Spinal muscular atrophy
• Morphologically distinct congenital myopathies (central core disease, nemaline myopathy, myotubular myopathy)
• Congenital muscular dystrophies
• Limb–girdle or facioscapulohumeral muscular dystrophy
• Infantile myotonic dystrophy
• Mitochondrial myopathy
• Brainstem anomaly
• Möbius syndrome
• Congenital fibrosis of the external ocular muscles
• Infantile botulism
• Seropositive and seronegative forms of autoimmune myasthenia gravis
• Neonatal autoimmune myasthenia gravis via passive transfer of mother's antibodies, with or without arthrogryposis multiplex
ADULT
• Motor neuron disease
• Peripheral neuropathy*
• Limb–girdle or facioscapulohumeral dystrophy
• Mitochondrial myopathy
• Chronic fatigue syndrome
• Seropositive and seronegative forms of autoimmune myasthenia gravis

* This diagnosis was suspected in some cases of the slow-channel CMS.

From Darras BT, Monani UR, De Vivo DC: Genetic disorders affecting the motor neuron: spinal muscular atrophy. In Swaiman KF, Ashwal S, Ferriero DM, et al. (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, 2018, Box 144-2.

Clinical Manifestations

The age of onset for immune-mediated MG ranges anywhere from 11 mo to 17 yr of age. In the prepubertal age-groups, the female:male ratio is about 1.5 : 1, and in the postpubertal age-groups, the female:male ratio is about 1 : 1. In juvenile autoimmune MG, unilateral or bilateral but usually *asymmetric ptosis* and some degree of extraocular muscle weakness are the earliest and most constant signs. Extraocular weakness is not confined to muscles innervated by just one or two of the three corresponding brainstem nuclei; it is progressive. Older children might complain of diplopia, and young children might hold open their eyes with their fingers or thumbs if the ptosis is severe enough to obstruct vision. Pupillary responses to light are preserved. Dysphagia and facial weakness also are common and, in early infancy, feeding difficulties are frequent as the cardinal sign of myasthenia; in severe cases, aspiration and airway obstruction may occur. Poor head control because of weakness of the neck flexors may be prominent. Involvement initially may appear to be limited to bulbar-innervated muscles, but the disease can be systemic and progressive weakness eventually involves limb–girdle muscles and distal muscles of the hands in many cases. Fasciculations of muscle, myalgias, and sensory symptoms do not occur. Tendon stretch reflexes may be diminished but rarely are lost. *Ocular myasthenia gravis may prove to be transitory over time, but in some patients, weakness never progresses to involve the axial or appendicular muscles.* This disorder accounts for approximately 25% of all juvenile MG patients and is most frequent in children of Chinese and southeastern Asian descent, suggesting an ethnic genetic predisposition. In addition, prepubertal patients are more likely to have *ocular only* myasthenia, whereas a majority of postpubertal patients with myasthenia will have generalized symptoms.

Rapid fatigue of muscles is a characteristic feature of MG that distinguishes it from most other neuromuscular diseases. Ptosis increases progressively as patients are asked to sustain an upward gaze for 30-90 sec. Holding the head up from the surface of the examining table while lying supine is very difficult (indicative of neck flexion weakness), and gravity cannot be overcome for more than a few seconds. Repetitive opening and closing of the fists produces rapid fatigue of hand muscles, and patients cannot elevate their arms for more than 1-2 min because of fatigue of the deltoids. Patients are more symptomatic late in the day or when tired. Dysphagia can interfere with eating, and the muscles of the jaw soon tire when an affected child chews. Reviewing activities of daily living helps determine the severity of symptoms (Table 630.4). Additional triggers for exacerbation of weakness may include heat and intercurrent illness.

Table 630.4

Myasthenia Gravis Activities of Daily Living Scale (MG-ADL)

GRADE	0	1	2	3
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Difficult to understand speech
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube
Swallowing	Normal	Rare episode of choking	Frequent choking, modifications in diet	Gastric tube
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do 1 of these functions
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant
TOTAL MG-ADL SCORE				

From Wolfe GI, Herbelin L, Nations SP, et al: Myasthenia gravis activities of daily living profile, Neurology 52:1487-1489, 1999.

Left untreated, MG is usually progressive and can become life-threatening because of respiratory muscle involvement and the risk of aspiration, particularly at times when the child is otherwise unwell, as during an upper respiratory tract infection. Familial myasthenia (congenital myasthenic syndrome) usually is not progressive, but may vary in severity from milder forms, limb–girdle forms, to more severe forms, including those with respiratory failure.

Myasthenic crisis is an acute or subacute severe increase in weakness in patients with MG, usually precipitated by an intercurrent infection, surgery, or even emotional stress. It may require intravenous cholinesterase inhibitors, immunoglobulin, plasma exchange, gavage feeding, and even transient ventilator support. It must be distinguished from **cholinergic crisis** secondary to overdosing with anticholinesterase medications. The muscarinic effects include abdominal cramps, diarrhea, profuse sweating, salivation, bradycardia, increased weakness, and miosis. Cholinergic crisis requires only supportive care and withholding of further doses of cholinergic drugs, and it passes within a few hours; the dose of medication to be restarted should be reconsidered, unless the patient had taken an overdose that was not prescribed.

Approximately 70–80% of younger children and adolescents with immune-mediated MG will have elevated AChR antibodies. Approximately 30% of affected adolescents show elevations, but anti-AChR antibodies are only occasionally demonstrated in the plasma of prepubertal children. Some with negative titers of anticholinesterase exhibit anti–muscle-specific tyrosine kinase (MuSK) circulating antibodies. MuSK is localized at the neuromuscular junction and appears essential to fetal development of this junction. Additional autoantibodies related to immune MG include LRP4, titin, and ryanodine receptor (RyR) antibodies.

Infants born to myasthenic mothers can have respiratory insufficiency, inability to suck or swallow, and generalized hypotonia and weakness, a syndrome typically referred to as transient neonatal myasthenia. They might show little spontaneous motor activity for several days to weeks. The onset of symptoms typically occurs within the first 1-3 days of life. Some require ventilatory support and feeding by gavage during this period. Some patients may also require pyridostigmine (acetylcholinesterase inhibitor) management transiently. After the abnormal antibodies disappear from the blood and muscle tissue, these infants regain normal strength and are not at increased risk of developing MG in later childhood. Patients usually show full recovery by about 2 mo of age. A small minority develops *fetal akinesia sequence* with multiple joint contractures *(arthrogryposis)* that develop in utero from lack of fetal movement. AChR antibodies can usually be demonstrated in maternal blood, but at times maternal antibodies may not be detected. Rates of transient neonatal myasthenia are estimated to be as high as 10–20% of infants born to mothers with MG.

Congenital Myasthenic Syndromes

A heterogeneous group of genetic diseases of neuromuscular transmission is collectively called **congenital myasthenic syndromes** (CMSs)**.** The etiology and pathogenesis of these syndromes are unrelated to either transitory neonatal myasthenia caused by placental transfer of maternal antibodies or to autoimmune MG, despite overlap of clinical symptoms. CMSs are nearly always *permanent static* disorders without spontaneous remission (see Tables 630.1 and 630.2). Several distinct genetic forms are recognized, nearly all with onset at birth or in early infancy with symptoms that may include hypotonia, external ophthalmoplegia, ptosis, dysphagia, weak cry, facial weakness, easy muscle fatigue generally, and sometimes respiratory insufficiency or failure, the last often precipitated by a minor respiratory infection. In the childhood-onset forms, findings such as fatigability, delayed motor milestones, and fluctuating ocular symptoms (ptosis and extraocular muscle weakness) are common. Cholinesterase inhibitors have a favorable effect in most, but in some forms the symptoms and signs are actually worsened. Children with most types of congenital MG do not experience myasthenic crises and rarely exhibit elevations of anti-ACh antibodies in plasma.

Mutations responsible for CMS have been identified in 24 different genes. The genetic mutations are known in *less than half* of children with CMS. The most common genes associated with CMS include *CHAT, CHRNE, DOK7, COLQ, GFPT,* and *RAPSN.* CMS can be caused by mutations affecting proteins involved in ACh synthesis, vesicle fusion into the synaptic cleft, ACh breakdown in the synaptic cleft, and reuptake of choline, within subunits of the postsynaptic acetylcholine receptor, as well as in postsynaptic glycosylation pathways. Basal lamina-associated proteins can lead to synaptic cleft abnormalities due to mutations in the *COLQ, COL13A1,* and *LAMB2* genes. These pathways emphasize the role of the integrity of the extracellular matrix proteins in the formation and maintenance of the synapse. Anti-AChR and anti-MuSK antibodies are usually, but not always, absent in serum, unlike in autoimmune forms of MG affecting older children and adults.

There may be clinical clues that aid in the diagnosis (Table 630.5). In patients with apneic episodes, consider *RAPSN, CHAT,* and *COLQ.* Apneic episodes in patients with choline acyltransferase (CHAT) mutations can be episodic but can also be life-threatening. Although most CMS syndromes are inherited in a recessive fashion, there are several where an autosomal dominant pattern of inheritance or de novo dominant pattern of inheritance can be seen, including *CHRNA1, CHRNB1, CHRND, CHRNE,* and *SYT2.* Mutations in the *RAPSN* gene can lead to an early-onset hypotonia with respiratory failure and episodic apnea, but can also present in milder limb–girdle patterns of weakness with an onset in childhood or adolescence. Genes associated with a more limb–girdle myasthenic syndrome phenotype include *GFPT1, DPAGT1, ALG2, ALG14, GMPPB,* and *PREPL.* Genes affecting the postsynaptic AChR subunits may be associated with a slow-channel CMS in which patients may have variable weakness, typically with worsening with AChE inhibitors, as well as a fast-channel CMS syndrome;

they can show improvement in symptoms in response to AChE inhibitors.

Table 630.5

Clinical Clues Pointing to a Specific Congenital Myasthenic Syndrome or Disease Protein

• Dominant inheritance: slow-channel CMS, SNAP25, and synaptotagmin
• Refractory or worsened by AChE inhibitors: ColQ, Dok-7, MuSK, Agrin, LRP4, plectin, and laminin-β2
• Repetitive compound muscle action potential (CMAP) evoked by single nerve stimuli: slow-channel CMS and ColQ deficiency
• Delayed pupillary light response: some patients with ColQ deficiency
• Congenital contractures: rapsyn, AChR δ or γ subunit, ChAT, SNAP 25
• Greater than 50% decrease of CMAP amplitude after subtetanic stimulation at 10 Hz for 5 min followed by slow recovery over 5-10 min: ChAT deficiency
• Sudden apneic episodes provoked by fever or stress: ChAT, rapsyn, sodium channel myasthenia
• Limb–girdle and axial distribution of weakness: Dok7, GFPT1, DPAGT1, ALG2, ALG14, LRP4, and occasionally rapsyn and ColQ
• Selectively severe weakness and atrophy of distal limb muscle: slow-channel syndrome and in some patients with agrin deficiency
• Tubular aggregates of the sarcoplasmic reticulum in muscle fibers: GFPT1, DPAGT1, ALG2
• Autophagic myopathy: GFPT1 and DPAGT1
• Stridor and vocal cord paralysis in neonates or infants: Dok-7
• Nephrotic syndrome and ocular malformations (Pierson syndrome): laminin-β2
• Association with seizures or intellectual disability: DPAGT1
• Intellectual disability and cerebellar ataxia: SNAP25
• Developmental anomalies of eye, brain, and heart: mitochondrial citrate carrier deficiency
• Association with epidermolysis bullosa simplex: plectin deficiency

From Selcen D, Engel AG: Congenital myasthenic syndrome. In Swaiman KF, Ashwal S, Ferriero DM, et al (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, Box 144-3.

Rare Other Causes of Myasthenia

MG is occasionally associated with hypothyroidism, usually **Hashimoto thyroiditis.** Other collagen vascular diseases and also some centronuclear myopathies may be associated with defects in neuromuscular transmission. Thymomas, noted in some adults, rarely coexist with MG in children. Likewise, lung carcinomas that occur in adults associated with Lambert-Eaton myasthenic syndrome are not seen in children. Lambert-Eaton syndrome in children is rare but has been reported with lymphoproliferative disorders and with neuroblastoma. Postinfectious MG in children is transitory and usually follows a varicella-zoster infection by 2-5 wk as an immune response.

Laboratory Findings and Diagnosis

MG is one of the few neuromuscular diseases in which electromyography (EMG) is more specifically diagnostic than a muscle or nerve biopsy. A *decremental response* is seen to repetitive nerve stimulation; the muscle potentials diminish rapidly in amplitude until the muscle becomes refractory to further stimulation. Electrophysiologically, this response is due to endplate potentials decreasing with subsequent repetitive stimulations, such that stimuli are no longer resulting in endplate potentials that achieve a threshold to result in a propagating motor action potential. This results in a cumulative lowering of the compound muscle action potential (CMAP) amplitude with the repeated stimuli. A decline of greater than 10% between waves 1 : 4 on repetitive stimulation is diagnostic for a decremental response, and suggestive of a disorder of neuromuscular transmission. The motor nerve conduction velocity remains normal. This unique EMG pattern is the electrophysiologic correlate of the fatigable weakness observed clinically and is reversed after a cholinesterase inhibitor is administered. A myasthenic decrement may be absent or difficult to demonstrate in muscles that are not involved clinically. This feature may be confusing in early cases or in patients showing only weakness of extraocular muscles. Special electrophysiologic studies are required in the classification of CMS and involve estimating the number of AChRs per endplate and in vitro study of endplate function. These special studies and patch-clamp recordings of kinetic properties of channels are performed on special biopsy samples of intercostal muscle strips that include both the origin and insertion of the muscle but are only performed in specialized centers. If myasthenia is limited to the extraocular, levator palpebrae, and pharyngeal muscles, repetitive nerve stimulation of the distal and proximal muscles (e.g., abductor pollicis brevis muscle or trapezius muscle, respectively), although diagnostic in the generalized disease, is usually normal.

Anti-AChR antibodies should be assayed in the plasma but are inconsistently demonstrated. Antibodies against the MuSK receptor should be sought in children without circulating AChR antibodies, a diagnostic finding when elevated, which further delineates the etiology. Many cases of congenital MG result from failure to synthesize or release ACh at the presynaptic membrane. In some cases, the gene that mediates the enzyme choline acetyltransferase for the synthesis of ACh is mutated. In others, there is a defect in the quantal release of vesicles containing ACh. The treatment of such patients with cholinesterase inhibitors is futile. In some patients such as those with *COLQ* and *DOK7* mutations as well as slow-channel myasthenia, acetylcholinesterase inhibitors (e.g., pyridostigmine) can lead to no response or even worsening of symptoms. Clinical genetic testing for congenital myasthenic syndrome can be done by panels that are commercially available and can test anywhere from 14-21 CMS-associated genes.

Other serologic tests of autoimmune disease, such as antinuclear antibodies and abnormal immune complexes, should also be sought. If these are positive, more extensive autoimmune disease involving vasculitis or tissues other than muscle is likely. A thyroid profile should always be examined. The serum creatine kinase level is normal in MG.

The heart is not involved, and electrocardiographic findings remain normal. Radiographs of the chest often reveal an enlarged thymus, but the hypertrophy is not a thymoma. It may be further defined by tomography or by CT or MRI of the anterior mediastinum if the radiographic findings are uncertain, but caution should be used when selecting the optimal imaging modalities because of radiation exposure for CT and anesthetic risk in a myasthenic patient if sedated MRI is needed for a younger myasthenic child.

The role of conventional muscle biopsy in MG is limited. It is not required in most cases, but approximately 17% of patients show inflammatory changes, sometimes called *lymphorrhages*, that are interpreted by some physicians as a mixed myasthenia–polymyositis immune disorder. Muscle biopsy tissue in MG shows a nonspecific type II muscle fiber atrophy, similar to that seen with disuse atrophy, steroid effects on muscle, polymyalgia rheumatica, and many other conditions. The ultrastructure of motor endplates shows simplification of the membrane folds; the AChRs are located in these postsynaptic folds, as shown by bungarotoxin (snake venom), which binds specifically to the AChRs.

A clinical test for MG is administration of a short-acting cholinesterase inhibitor, usually edrophonium chloride. Ptosis and ophthalmoplegia improve within a few seconds, and the fatigability of other muscles decreases.

Recommendations on the Use of Cholinesterase Inhibitors as a Diagnostic Test for MG in Infants and Children

Children Two Years of Age and Older

◆ The child should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, or inability of the cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits is not a criterion.

◆ An intravenous infusion should be started to enable the administration of medications in the event of an adverse reaction.

◆ Electrocardiographic monitoring is recommended during the test.

◆ A dose of atropine sulfate (0.01 mg/kg) should be available in a syringe, ready for intravenous administration at the bedside during the edrophonium test, to block acute muscarinic effects of the cholinesterase inhibitor, mainly abdominal cramps and/or sudden diarrhea from increased peristalsis, profuse bronchotracheal secretions that can obstruct the airway, or, rarely, cardiac arrhythmias. Some physicians pretreat all patients with atropine before administering edrophonium, but this is not recommended unless there is a history of a reaction to tests. Atropine can cause the pupils to be dilated for as long as 14 days after a single dose, and the pupillary effects of homatropine can last 4-7 days.

◆ Edrophonium chloride (Tensilon) is administered intravenously. The initial test dose is 0.01 mg/kg (no more than 1 mg [for children <30 kg], and no more than 2 mg initial dose [for children >30 kg]). After the initial dose, repeat doses may be given intravenously. For children <30 kg, repeat at a rate of 1 mg every 30-45 seconds to a maximum cumulative dose of 5 mg. For children >30 kg, repeat doses of 1 mg every 30-45 seconds to a maximum cumulative dose of 10 mg. In adults, the average edrophonium dose to show positive responses is approximately 3.3 mg for ptosis and approximately 2.6 mg for oculomotor symptoms. Side effects include nausea and emesis; light-headedness from bradycardia (atropine is the antidote) and bronchospasm are less common side effects. The edrophonium test may be done by intramuscular or subcutaneous injection but may require modification of dosing.

◆ Effects should be seen within 10 sec and disappear within 120 sec. Weakness is measured as, for example, the distance between the upper and lower eyelids before and after administration, degree of external ophthalmoplegia, or ability to swallow a sip of water.

◆ Long-acting cholinesterase inhibitors, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness. The neostigmine (Prostigmin) test may be used (as outlined later) but might not be as definitively diagnostic as the edrophonium test.

Children Younger Than Two Years of Age

◆ Infants ideally should have a specific fatigable weakness that can be measured, such as ptosis of the eyelids, dysphagia, and inability of the cervical muscles to support the head. Nonspecific generalized weakness without cranial nerve motor deficits makes it less easy to assess results but may be a criterion at times.

◆ An intravenous line should be started as a rapid route for medications in the event of an adverse effect of the test medication.

◆ Electrocardiographic monitoring is recommended during the test.

◆ Pretreatment with atropine sulfate to block the muscarinic effects of the test medication is not recommended, but atropine sulfate should be available at the bedside in a prepared syringe. If needed, it should be administered intravenously in a dose of 0.01 mg/kg.

◆ Edrophonium is not recommended for use in infants; its effect is too brief for objective assessment, and an increased incidence of acute cardiac arrhythmias is reported in infants, especially neonates, with this drug.

◆ Prostigmin methyl sulfate (neostigmine) is administered intramuscularly at a dose of 0.04 mg/kg.

If the result is negative or equivocal, another dose of 0.04 mg/kg may be administered 4 hr after the first dose (a typical dose is 0.5-1.5 mg). The peak effect is seen in 20-40 min. Intravenous Prostigmin is **contraindicated** because of the risk of cardiac arrhythmias, including fatal ventricular fibrillation, especially in young infants.

◆ Long-acting cholinesterase inhibitors administered orally, such as pyridostigmine (Mestinon), are generally not as useful for the acute assessment of myasthenic weakness because the onset and duration are less predictable.

The test should be performed in the emergency department, hospital ward, or intensive care unit; the important issue is preparation for potential complications such as cardiac arrhythmia or cholinergic crisis, as outlined.

Treatment

Some patients with mild MG require no treatment. Cholinesterase-inhibiting drugs are the primary therapeutic agents. Pyridostigmine bromide (Mestinon) may be given orally starting at 0.5-1 mg/kg per dose every 4-6 hr while the patient is awake, to a maximum of 60 mg per dose. The maximum daily recommended dose is 7 mg/kg/day, with most adults achieving effect with total daily doses of <960 mg per day, divided in 4-8 doses. Pyridostigmine is given in short-acting forms, and can also be used in a long-acting form at bedtime for patients with more weakness upon awakening in the morning. Overdoses of cholinesterase inhibitors produce cholinergic crises with symptoms such as increased secretions, diarrhea, and cramping; atropine blocks the muscarinic effects but does not block the nicotinic effects that produce additional skeletal muscle weakness. In the rare familial MG caused by the absence of endplate acetylcholinesterase, cholinesterase inhibitors are not helpful and often cause increased weakness; these patients can be treated with ephedrine or diaminopyridine, both of which increase ACh release from terminal axons.

Because of the autoimmune basis of the disease, long-term steroid treatment with prednisone may be effective. Thymectomy should be considered and might provide a cure. Thymectomy is most effective in patients who have high titers of anti-AChR antibodies in the plasma and who have been symptomatic for < 2 yr. Thymectomy is ineffective in congenital and familial forms of MG. Treatment of hypothyroidism usually abolishes an associated myasthenia without the use of cholinesterase inhibitors or steroids.

If the specific genetic mutation can be identified in a patient with one of the CMSs, specific therapeutic approaches are available for some that differ from the treatments listed above.

Plasmapheresis is effective treatment in some children, particularly those who do not respond to steroids, but plasma exchange therapy provides only temporary remission. Intravenous immunoglobulin is beneficial and should be tried before plasmapheresis because it is less invasive. Plasmapheresis and intravenous immunoglobulin appear to be most effective in patients with high circulating levels of anti-AChR antibodies. Refractory patients, as well as patients with MuSK-related MG, might respond more effectively to rituximab, a monoclonal antibody to the B-cell CD20 antigen.

Neonates with transient maternally transmitted MG require cholinesterase inhibitors for only a few days or occasionally for a few weeks, especially to allow feeding. No other treatment is usually necessary. In non–maternally transmitted congenital MG, identification of the specific molecular defect is important for treatment; Table 630.6 summarizes specific therapies for each type.

Table 630.6

Potential Therapies in Congenital Myasthenic Syndromes

SYNDROME	THERAPY
AChE	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
AChR deficiency	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR fast	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses

channel	If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
AChR slow channel	Quinidine sulfate • Adults: Begin for 1 wk with 200 mg tid; gradual increase to maintain a serum level of 1-25 µg/mL • Children: 15-60 mg/kg/day in 4-6 divided doses; not available in several countries If quinidine sulfate is not available, fluoxetine 80-100 mg/day in adults Avoid AChE inhibitors
ChAT	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
DOK7	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries If ephedrine is not obtainable, 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults Avoid AChE inhibitors
Laminin β_2	Ephedrine 3 mg/kg/day in 3 divided doses; begin with 1 mg/kg; not obtainable in several countries Avoid AChE inhibitors
MuSK	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses 3,4-Diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults
Rapsyn	AChE inhibitors: pyridostigmine bromide (Mestinon) 4-5 mg/kg/day in 4-6 divided doses If necessary add 3,4-diaminopyridine 1 mg/kg/day in 4 divided doses, up to 60 mg/day in adults

Modified from Eyemard B, Hantaï D, Estounet B: Congenital myasthenic syndromes, Handb Clin Neurol 113:1469-1480, 2013.

Complications

Children with MG do not tolerate neuromuscular-blocking drugs, such as succinylcholine and pancuronium, and may be paralyzed for weeks after a single dose. An anesthesiologist should carefully review myasthenic patients who require a surgical anesthetic, and such anesthetics should be administered only by an experienced physician/anesthesiologist. Also, certain antibiotics can potentiate myasthenia and should be avoided; these include the aminoglycosides, beta blocking agents, procainamide, chloroquine, and fluoroquinolones.

Prognosis

Some patients with autoimmune MG experience spontaneous remission after a period of months or years; others have a permanent disease extending into adult life. Immunosuppression, thymectomy, and treatment of associated hypothyroidism might provide a cure. Genetically determined congenital myasthenic syndromes may show initial worsening in infancy but then remain static throughout childhood and into adult life.

Other Causes of Neuromuscular Blockade

Organophosphate chemicals, commonly used as insecticides, can cause a myasthenia-like syndrome in children exposed to these toxins (see Chapter 77).

Botulism results from ingestion of food containing the toxin of *Clostridium botulinum*, a Gram-positive, spore-bearing, anaerobic bacillus (see Chapter 237). The incubation period is short, only a few hours, and symptoms begin with nausea, vomiting, and diarrhea. Cranial nerve involvement soon follows, with diplopia, dysphagia, weak suck, facial weakness, and absent gag reflex. The mechanism is cleavage by the botulinum toxin of several of the structural glycoproteins of the wall (i.e., membrane) of synaptic vesicles within axonal terminals. These glycoproteins include synaptobrevin and synaptotagmin, but synaptophysin is resistant.

In **infantile botulism,** which classically presents between the ages of 4 and 7 mo, honey as well as spores from dirt (e.g., near construction sites) are common sources of contamination. The earliest signs are usually constipation, poor feeding, and then a weak cry. On evaluation, patients appear hypotonic, with facial weakness, dysphagia, and a poor gag. Generalized weakness with a risk of respiratory failure can occur. Generalized hypotonia and weakness then develop and can progress to respiratory failure. Neuromuscular blockade is documented by electromyography (EMG) with repetitive nerve stimulation. Slow repetitive nerve stimulation may show a decremental response, and baseline CMAP amplitudes may be low. With rapid repetitive nerve stimulation, there is an incremental response. EMG/repetitive nerve stimulation studies may help in confirming a diagnosis if the clinical presentation is not straightforward. However, when suspected, botulinum toxin studies should be sent preferentially from stool samples from the patient, and then treatment should be initiated as soon as possible with Botulinum Immune Globulin IV (Baby-BIG or BIG-IV). BIG-IV, which is human-derived antibotulism toxin antibodies, is approved by the United States Food and Drug Administration for the treatment of infant botulism types A and B. Early use of BIG-IV has shortened the overall length of hospitalization and improved the time to recovery. Respiratory and feeding/gavage support may be required for days or weeks until the toxin is cleared from the body.

Tick paralysis is a disorder of ACh release from axonal terminals due to a neurotoxin that blocks depolarization. It also affects large myelinated motor and sensory nerve fibers. This toxin is produced by the wood tick or dog tick, insects common in the Appalachian and Rocky Mountains of North America. The tick embeds its head into the skin, usually the scalp, and neurotoxin production is maximal about 5-6 days later. Motor symptoms include weakness, loss of coordination, and sometimes an ascending paralysis resembling Guillain-Barré syndrome. Tendon reflexes are lost. Sensory symptoms of tingling paresthesias can occur in the face and extremities. The diagnosis is confirmed by identification of the tick, and treatment involves the prompt removal of the entire tick. It is important to monitor patients closely, because some patients may show worsened respiratory symptoms for the first day after tick removal. Most patients will show rapid improvement within a few hours to a few days from the time of tick removal.

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630.2

Spinal Muscular Atrophies

Goknur Haliloglu

Spinal muscular atrophy (SMA) is a degenerative disease of motor neurons that begins in fetal life and continues to be progressive in infancy and childhood. Among the autosomal recessive disorders in childhood, SMA is the most common cause of infant mortality, and is second in birth prevalence only to cystic fibrosis. The incidence of SMA is estimated to be 1 in 6,000-10,000 newborns, with a carrier frequency of approximately 1/40-1/60. It is a clinically heterogeneous, panethnic disorder. SMA is caused by a homozygous deletion in the survival motor neuron 1 *(SMN1)* gene on chromosome 5q13. Infrequent families with autosomal dominant inheritance are described, and a rare X-linked recessive form also occurs. There is also a separate group of clinically and genetically heterogeneous non-5q SMA forms (see Chapter 630.3).

The pathologic hallmark of SMA is the progressive denervation of muscle. This is compensated for in part by reinnervation from an adjacent motor unit, but giant motor units are thus created, with subsequent atrophy of muscle fibers when the reinnervating motor neuron eventually becomes involved. Motor neurons of cranial nerves III, IV, and VI to the extraocular muscles, as well as those of the sacral spinal cord innervating striated muscle of the urethral and anal sphincters, are selectively spared. The upper motor neurons (layer 5 pyramidal neurons in the cerebral cortex) also remain normal.

SMA is classified clinically into a severe infantile form, also known as **Werdnig-Hoffmann disease** or SMA type I; a late infantile and more slowly progressive form, SMA type II; a more chronic or juvenile form, **Kugelberg-Welander disease,** or SMA type III; and an **adult-onset form** (SMA type IV). A severe fetal form that is usually fatal in the perinatal period has been described as SMA type 0, with motor neuron degeneration demonstrated in the spinal cord as early as midgestation. These distinctions of types are based upon the age at onset, severity of weakness, maximum motor milestone achieved, and clinical course (Table 630.7). Some patients are transitional between types I and II or between types II and III in terms of clinical function. Of note, the *SMN* gene region comprises a centromeric copy containing the *SMN2* gene. Although there is a correlation between the severity of disease, age at onset, and *SMN2* copy number to an extent, it is believed that the phenotype of SMA spans a broad continuum without a clear delineation of subtypes.

Table 630.7

Clinical Classification of Spinal Muscular Atrophy

SPINAL MUSCULAR ATROPHY TYPE	**OTHER NAMES**	**AGE AT ONSET**	**LIFE EXPECTANCY WITH A NATURAL COURSE OF DISEASE**	**HIGHEST MOTOR MILESTONE ACHIEVED**	**OTHER FEATURES**	***SMN2* COPY NUMBER**
Type 0 (<1%)	Very severe	Neonatal with prenatal signs	No survival beyond the first months after birth	Never sits	• Reduced intrauterine movements • Arthrogryposis • Respiratory distress • Feeding problems • Cranial nerve involvement • Facial diplegia • Autonomic dysfunction • Cardiac abnormalities, thin ribs, fractures	1
Type IA * **(50–60%)**	Prenatal, congenital SMA, Werdnig-Hoffmann disease	Prenatal	<6 mo	Mostly unable to achieve motor milestones	• Severe weakness at birth • Profound hypotonia • Areflexia • Early respiratory failure • Joint contractures	1-2 copies in 80% of the patients
Type IB * **Type IC (50–60%)**	Werdnig-Hoffman disease, severe SMA (nonsitters)	Type IB (0-3 mo) Type IC (3-6 mo)	<2 yr without respiratory support	Never sits unsupported	• Weakness • Frog-leg posture, hypotonia • Tongue fasciculations • Hyporeflexia, areflexia • Sucking and swallowing difficulties • Respiratory failure	1-2 copies in 80% of the patients
Type II (30%)	Intermediate SMA (sitters)	6-18 mo	>2 yr ~ 70% alive at 25 yr of age	Sits independently, never stands or walks	• Proximal weakness, hypotonia • Postural hand tremor • Hyporeflexia • Average or above-average	3 copies in >80% of patients

					intellectual skills by adolescence • Scoliosis	
Type III (10%)	Kugelberg-Welander disease, mild SMA (walkers)	>18 mo Type IIIA (prior to 3 yr) Type IIIB (after 3 yr)	Almost normal	Stands and walks	• May have hand tremor • Resembles muscular dystrophy	3-4 copies in 96% of patients
Type IV (Adult SMA) (1%)	Adult SMA	>21 yr	Normal	Normal		≥4 copies

[*] SMA types I, IA, IB, and IC all have a 60% proportion of total SMA.

Modified from Darras BT: Spinal muscular atrophies, Pediatr Clin North Am 62:743-766, 2015; Mercuri E, Bertini E, Iannaccone ST: Spinal muscular atrophy: controversies and challenges, Lancet Neurol 11:443-452, 2012.

Muscle biopsy does not distinguish types I and II, though type III shows a more adult than perinatal pattern of denervation and reinnervation. Type 0 can show biopsy features more similar to those of myotubular myopathy because of maturational arrest; scattered myotubes and other immature fetal fibers also are demonstrated in the muscle biopsies of patients with types I and II, but they do not predominate. Autonomic motor neurons of both the sympathetic and parasympathetic systems are not spared, but usually do not show clinical manifestations until late stages. Autonomic deficits may involve the detrusor muscle of the urinary bladder or the smooth muscle urethral and anal sphincters, in all three forms of SMA. In some patients with type I SMA and respiratory distress, there may be severe autonomic dysregulation with dysautonomia and cardiovascular collapse leading to death or to severe ischemic brain damage. The differential diagnosis is noted in Table 630.8 .

Table 630.8

Differential Diagnosis of 5q Spinal Muscular Atrophy

SPINAL CORD DISORDERS
Neoplasms (SMA types I, II, III)
Other myelopathies (SMA types I, II, III)

OTHER MOTOR NEURON DISORDERS

SMARD1 (SMA type I)

Juvenile muscular atrophy of distal upper extremity (Hirayama disease)

Fazio-Londe disease, Brown-Vialetto-van Laere syndrome

Other non-5q SMAs (SMA types I, II, III)

Juvenile ALS (SMA types I, II, III)

NEUROPATHIES

Congenital hypomyelinating or axonal neuropathies (SMA types I, II)

Hereditary motor and sensory neuropathies (SMA types I, II, III)

CIDP (SMA types II, III)

NEUROMUSCULAR JUNCTION DISORDERS

Botulism (SMA type I)

Congenital myasthenic syndromes (SMA types I, II, III)

Lambert-Eaton myasthenic syndrome (SMA type III)

Autoimmune myasthenia gravis (SMA types II, III)

MYOPATHIES

Congenital myopathies (SMA types I, II, III)

Congenital myotonic dystrophy (SMA type I)

Congenital muscular dystrophies (SMA types I, II)

Muscular dystrophies (DMD/BMD, LGMD) (SMA type III)

Mitochondrial myopathies (SMA types I, II, III)

Acid maltase/Pompe disease (SMA types I, II, III)

Other metabolic myopathies (SMA types I, II, III)

Inflammatory myopathies (SMA type III)

Channelopathies (SMA type III)

OTHER DISORDERS

Chromosomal abnormalities (SMA types I, II, III)

Prader-Willi syndrome (SMA type III)

Central nervous system abnormalities (SMA types I, II, III)

Hexosaminidase A deficiency (SMA types III, IV)

ALS, amyotrophic lateral sclerosis; BMD, Becker muscular dystrophy; CIDP, chronic inflammatory polyneuropathy; DMD, Duchenne muscular dystrophy; LGMD, limb–girdle muscular dystrophy; SMARD1, spinal muscular atrophy with respiratory distress 1.

From Darras BT, Monani UR, De Vivo DC: Genetic disorders affecting the motor neuron: spinal muscular atrophy. In Swaiman KF, Ashwal S, Ferriero DM, et al (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, Box 139-1.

Etiology

The cause of SMA is genetic as an autosomal recessive mendelian trait. It appears to be a pathologic continuation of a process of programmed cell death (apoptosis) that is normal in embryonic life. A surplus of motor neuroblasts and other neurons is generated from primitive neuroectoderm, but only about half survive and mature to become neurons; the excess cells have a limited life cycle and degenerate. If the process that arrests physiologic cell death fails to intervene by a certain stage, neuronal death can continue in late fetal life and postnatally. The survivor motor neuron gene *(SMN)* arrests apoptosis of motor neuroblasts. Unlike most genes that are highly conserved in evolution, *SMN* is a uniquely mammalian gene. An additional function of *SMN*, both centrally and peripherally, is to transport RNA-binding proteins to the axonal growth cone to ensure an adequate amount of protein-encoding transcripts essential for growth cone mobility, both during fetal development and in postnatal synaptic remodeling.

Clinical Manifestations and Course

The cardinal features of the classic, most common phenotype, **SMA type I,** can be summarized as a presentation before the age of 6 mo with severe hypotonia (Fig. 630.1); symmetric generalized muscle weakness affecting the lower limbs more than the upper limbs, proximal more than distal; frog-leg posture; absence of deep tendon reflexes; tongue fasciculations; and selective involvement of the axial and intercostal muscles but sparing of diaphragm. SMA is in the differential diagnosis list of floppy infant syndrome (see Chapter 628). Due to the involvement of the intercostal respiratory muscles, there is a typical paradoxical abdominal breathing pattern, bell-shaped chest, and weak cough (Video 630.1 ▶). Infants lie flaccid with little movement, unable to overcome gravity, and lack head control. These infants rarely achieve improvements of motor function and acquire motor developmental milestones (see Fig. 626.1 in Chapter 626). In contrast to their severe weakness and floppiness, infants with

SMA type I have an alert and bright expression with preserved cognitive functions. There is no involvement of the facial and extraocular muscles at presentation, although facial weakness does occur at later stages of the disease.

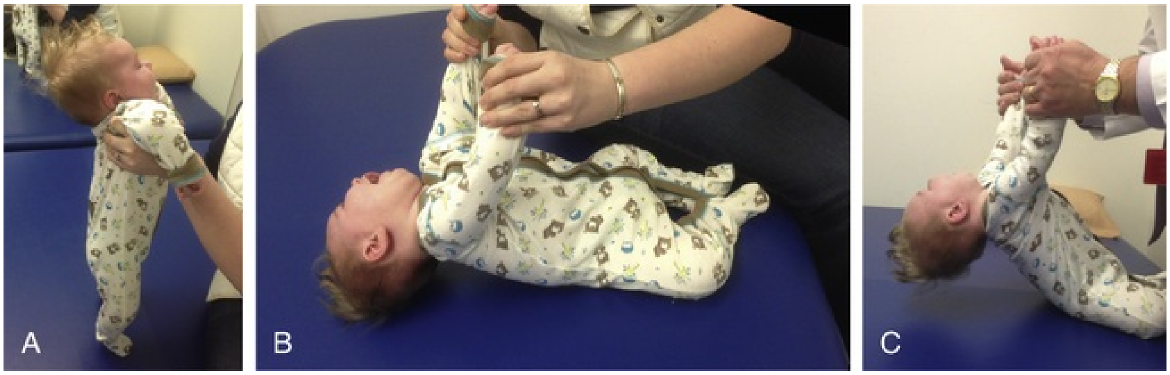

FIG. 630.1 Type I spinal muscular atrophy (Werdnig-Hoffmann disease): clinical manifestations of weakness of limb and axial musculature in a 4–mo old infant with severe weakness and hypotonia. With vertical suspension **(A),** note the dangling lower limbs with lack of hip flexion, tendency of the upper limbs to slip through the examiner's hands, and lack of neck flexion with resulting head lag. When subject is supine, note the *frog-leg* positioning of the legs and the lack of traction response **(B)** and the lag of head **(C),** with attempts by the examiner to pull the infant to a sitting position. (From Oskoui M, Darras BT, De Vivo DC: Spinal muscular atrophy: 125 years later and on the verge of a cure. In Sumner CJ, Paushkin S, Ko C-P, eds: Spinal muscular atrophy: disease mechanisms and therapy. San Diego, 2017, Academic Press, Chapters 1 and 3–19.)

SMA type I is not homogeneous within itself. At least three clinical subgroups can be defined as (1) severe weakness from birth or the neonatal period; head control is never achieved; (2) presentation after the neonatal period, within the first 2 mo; head control is never achieved; and (3) onset after the neonatal period but head control is achieved, and some of the infants may gain the ability to sit with support. There may be a range of clinical presentations and courses of respiratory involvement and swallowing and sucking difficulties in this fragile group of SMA type I patients.

Infants with SMA type I develop respiratory failure within the first 2 yr of life, and without respiratory and nutritional support, they usually do not survive beyond their second birthday. A multidisciplinary approach (respiratory, gastrointestinal, and orthopedic interventions) combined with noninvasive ventilatory support (NIV) and enteral feeding have changed the natural course of the disease over the years. To date, the median time to either death or full-time noninvasive ventilation (NIV > 16 hr/day) is 13.5 mo with improved supportive respiratory and nutritional care. Infants who are symptomatic prenatally or at birth are classified as having a rare phenotype, **SMA type 0** (<1%); they can present with severe muscle weakness, respiratory distress, feeding problems, and cranial nerve involvement. Congenital contractures, ranging from simple clubfoot to generalized arthrogryposis, occur in approximately 10% of severely involved neonates (see Chapter 626.10). There is a perception of decreased intrauterine movements by the mother, and these infants usually die within the first months of life. Although motor neurons are primarily affected tissue in SMA, other tissues, including those of the brain, cardiac system, vascular system, and even sensory nerves, may also contribute to the overall phenotype, especially in the most severe forms of the disease. Early-stage developmental congenital heart defects described in severe SMA patients, generally carrying one copy of *SMN2,* include atrial septal defects, a dilated right ventricle, ventricular septal defects, and hypoplastic left heart syndrome. These patients are also prone to possible involvement of the autonomic nervous system, which may result in arrhythmia and sudden death. Vasculopathy can be another rare presentation, and ulceration and necrosis of the fingers and toes have also been described in two severe type I SMA patients.

In **type II SMA,** affected infants are usually able to suck and swallow, and respiration is adequate in early infancy. Developmental delay in gross motor milestones or stagnation of motor development between the ages of 6 and 18 mo is rather typical for this form. Proximal muscle weakness is again more prominent in the lower extremities compared with the upper extremities. Patients can sit without support but are unable to walk independently. These children show progressive weakness, but many survive into the school years or beyond, although they are confined to an electric wheelchair and severely handicapped. Nasal speech and problems with deglutition develop later. Respiratory complications are less severe and develop later during the course of the disease. Scoliosis becomes a major complication in many patients with long survival times. Gastroesophageal reflux may lead to malnutrition or to aspiration with acute airway obstruction or pneumonia.

Kugelberg-Welander disease is the mildest **SMA (type III),** and patients can appear normal in infancy. The progressive weakness is proximal in distribution, particularly involving the shoulder girdle muscles. Patients are ambulatory and develop a variable course of proximal muscle weakness after the age of 18 mo. There may be a transition to SMA type II, and loss of ambulation can occur at some point during the course of the disease. Symptoms of bulbar muscle weakness are rare. Patients with this form of SMA may have muscular hypertrophy rather than atrophy, and it may easily be confused with a muscular dystrophy (Video 630.2). Longevity can extend well into adult life. Fasciculations are a specific clinical sign of the denervation of muscle. In thin children, they may be seen in the deltoid and biceps brachii muscles and occasionally the quadriceps femoris muscles, but the continuous, involuntary, worm-like movements may be masked by a thick pad of subcutaneous fat. Fasciculations are best observed in the tongue, where almost no subcutaneous connective tissue separates the muscular layer from the epithelium. If the intrinsic lingual muscles are contracted, as in crying or when the tongue protrudes, fasciculations are more difficult to see than when the tongue is relaxed. Cramps and myalgias of appendicular and axial muscles are common, especially in later stages, and problems of micturition may be present, though adolescent patients may be too embarrassed to state them unless the physician directly inquires.

The outstretched fingers of children with SMA often show a characteristic tremor *(polyminimyoclonus)* owing to fasciculations and weakness (Video 630.3). It should not be confused with a cerebellar tremor.

The adult phenotype of the disease is **SMA type IV,** which is characterized by a mild muscle weakness with an onset usually in the second or third decade of life.

There may be an intrafamilial variability in the clinical expression of the disease.

The intelligence is normal, and children often appear brighter than their normal peers because the effort they cannot put into physical activities is redirected to intellectual development, and they are often exposed to adult speech more than to juvenile language because of the social repercussions of the disease. Progressive deterioration of ambulation and the high risk of falling and fracturing long bones or the pelvis eventually require use of a wheelchair; an electric wheelchair often is needed because weakness of the upper extremities does not allow the patient to manually push the wheels. Progressive scoliosis is another serious complication and may have a further adverse effect on respiration.

Laboratory Findings

The serum creatine kinase (CK) level may be normal, but more commonly is mildly elevated (up to 2- to 4-fold), but usually not more than 10 times the normal upper limit. The chest x-ray in early-onset disease may demonstrate thin ribs. Electrocardiography (EKG) may serve as a simple and practical tool in patients with SMA to demonstrate a baseline tremor as an artefact representing muscle fibrillations more prominent on lead II (Fig. 630.2). Although seen in mainly lower motor neuron diseases, including poliomyelitis, recognition of this EKG pattern may prevent further electrophysiologic tests (electromyography [EMG] and nerve conduction studies [NCSs]) in SMA patients. Electrophysiologic studies (EMG-NCS) should be reserved for selected atypical patients. The results of motor nerve conduction studies are normal, except for mild slowing in terminal stages of the disease, an important feature distinguishing SMA from peripheral neuropathy. EMG shows fibrillation potentials and other signs of the denervation of muscle. There is no need for a muscle biopsy, which demonstrates a neurogenic pattern with group atrophy in all forms of SMA.

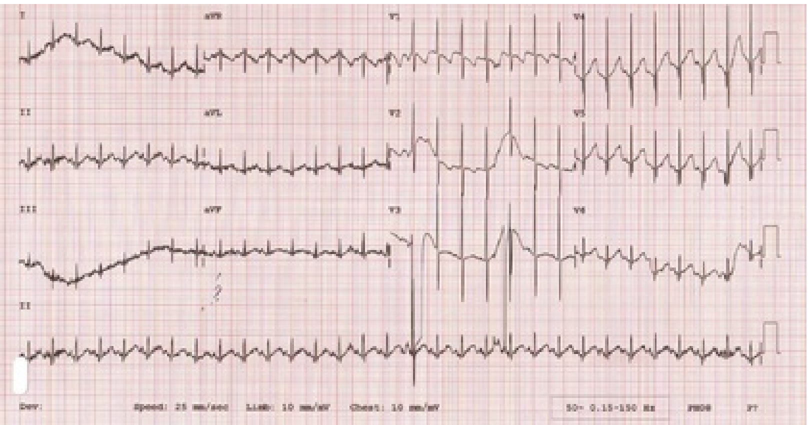

FIG. 630.2 Standard 12-lead EKG (25 mm/s, 10 mV/mm, diagnostic filter 0.05-150 Hz) showed diffuse somatic muscle fibrillations, baseline tremor, more prominent on lead II.

Diagnosis

The simplest, most definitive first-step diagnostic test in a patient with a clinical suspicion of SMA and normal and/or mildly elevated serum CK levels, is a molecular genetic marker in the blood for the homozygous deletion in *SMN1*

(Table 630.9). The current gold standard is *SMN1* deletion/mutation and *SMN2* copy number testing, with a minimal standard of *SMN1* deletion testing. The absence of *SMN1* exon 7 (with or without deletion of exon 8) confirms the diagnosis of SMA. The genetic test for SMA has a 95% sensitivity and nearly 100% specificity (see Table 630.9). Real-time polymerase chain reaction (PCR) or multiplex ligation-dependent probe amplification (MLPA) tests give quick and reliable *SMN1* gene copy numbers. Semiquantitative assays improve the diagnostic sensitivity up to 98%. According to different scenarios, for example, if the patient has a single *SMN1* copy, the coding region of the second undeleted allele should be sequenced to identify the second causative mutation, including point mutations, insertions, and deletions. Of note, in ~ 30% of patients with a clinical picture, mutations are not detected in the *SMN1/SMN2* coding region, which is more common for type III SMA patients. Direct sequencing of the gene is also recommended in patients with a clinical diagnosis, two *SMN1* copies, and a consanguineous background.

Table 630.9

Molecular Genetic Tests in Spinal Muscular Atrophy

TYPE OF MUTATION	TEST APPLIED	MUTATION DETECTION RATE
Homozygous deletion of exon 7 *	*SMN1* Targeted mutation analysis Polymerase chain reaction/restriction enzyme analysis or multiplex ligation probe amplification methodologies	Approximately 95–98%
Compound heterozygosity (deletion of SMN1 exon 7 [allele 1] and an intragenic mutation of SMN1 † **[allele 2])**	Targeted mutation analysis combined with *SMN1* sequence analysis ‡	2–5%
***SMN2* copy number** ‖	Quantitative polymerase chain reaction analysis and other methodologies ¶	Not available

* Testing for exon 8 deletion is not necessary.

† Small intragenic deletions/insertions and nonsense, missense, and splice site mutations.

‡ Whole-gene deletions/duplications are not detected.

‖ SMN2 copy number ranges from 0 to 5.

¶ MLPA, long-range PCR, CMA that includes the *SMN1* , *SMN2* chromosomal segment.

From Darras BT: Spinal muscular atrophies, Pediatr Clin North Am 62: 743-766, 2015; Adapted from Markowitz JA, Singh P, Darras BT: Spinal muscular atrophy: a clinical and research update, Pediatr Neurol 46:1-12, 2012.

Muscle biopsy used to be the diagnostic test before the genetic marker from blood samples became available, and muscle biopsy now is used more selectively in patients showing equivocal or negative genetic findings. The muscle biopsy in infancy reveals a characteristic pattern of perinatal denervation that is unlike that of mature muscle. Groups of giant type I fibers are mixed with fascicles of severely atrophic fibers of both histochemical types (Fig. 630.3). Scattered immature myofibers resembling myotubes also are demonstrated. In juvenile SMA, the pattern may be more similar to adult muscle that has undergone many cycles of denervation and reinnervation. Neurogenic changes in muscle also may be demonstrated by EMG, but the results are less definitive than by muscle biopsy in infancy. Sural nerve biopsy is now performed only occasionally, but shows mild sensory neuropathic changes, and the sensory nerve conduction velocity may be slowed; hypertrophy of unmyelinated axons also is seen. At autopsy, mild degenerative changes are seen in sensory neurons of dorsal root ganglia and in somatosensory nuclei of the thalamus, but these alterations are not perceived clinically as a sensory loss or paresthesias. The most pronounced neuropathologic lesions are the extensive neuronal degeneration and gliosis in the ventral horns of the spinal cord and brainstem motor nuclei, especially the hypoglossal nucleus. On rare instances, the clinical features of an SMA-like presentation may be a feature of mitochondrial diseases (*SCO2, DGUOK, and* TK2 mutations). *SCO2* encodes one of the COX assembly proteins, and the latter two gene mutations are associated with mitochondrial DNA depletion syndromes. Unexpectedly elevated serum CK levels at some point in the clinical course of these patients can be a clue to considering a mitochondrial disease in the differential diagnosis. Depending on the stage and progression of the disease, a muscle biopsy demonstrating ragged red fibers and COX-deficient fibers, may help in the differential diagnosis.

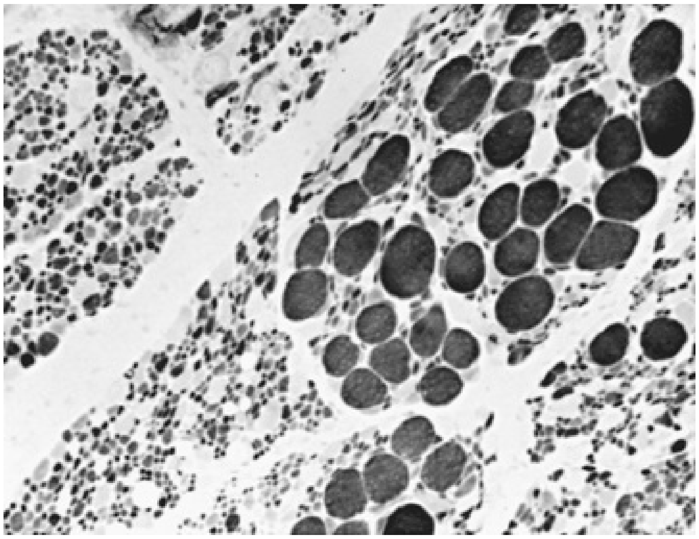

FIG. 630.3 Muscle biopsy of neonate with infantile spinal muscular atrophy. Groups of giant type I (darkly stained) fibers are seen within muscle fascicles of severely atrophic fibers of both histochemical types. This is the characteristic pattern of perinatal denervation of muscle. Myofibrillar adenosine triphosphatase, preincubated at pH 4.6 (×400).

Genetics

Molecular genetic diagnosis by DNA probes in blood samples or in muscle biopsy or chorionic villi tissues is available for the diagnosis of suspected cases and for prenatal diagnosis. Most cases are inherited as an autosomal recessive trait.

The genetic locus for all three of the common forms of SMA is on chromosome 5, a deletion at the 5q11-q13 locus, indicating that they are variants of the same disease rather than different diseases. The affected *SMN1* gene has a molecular weight of 38 kDa and contains 8 exons that span 20 kb and telomeric and centromeric exons that differ only by 5 bp and produce a transcript encoding 294 amino acids. *SMN1* is duplicated in a highly homologous gene called *SMN2,* and both genes are transcribed. *SMN2* remains present in all patients with SMA, but cannot fully compensate the *SMN1* defect. However, a molecular basis for correlation between the *SMN2* copy number and clinical severity of the SMA is the capability of *SMN2* to encode a small amount of an identical *SMN* protein. The critical difference between *SMN1* and *SMN2* is a cytosine (C) to thymine (T) transition in exon 7 of *SMN2* (Fig. 630.4).

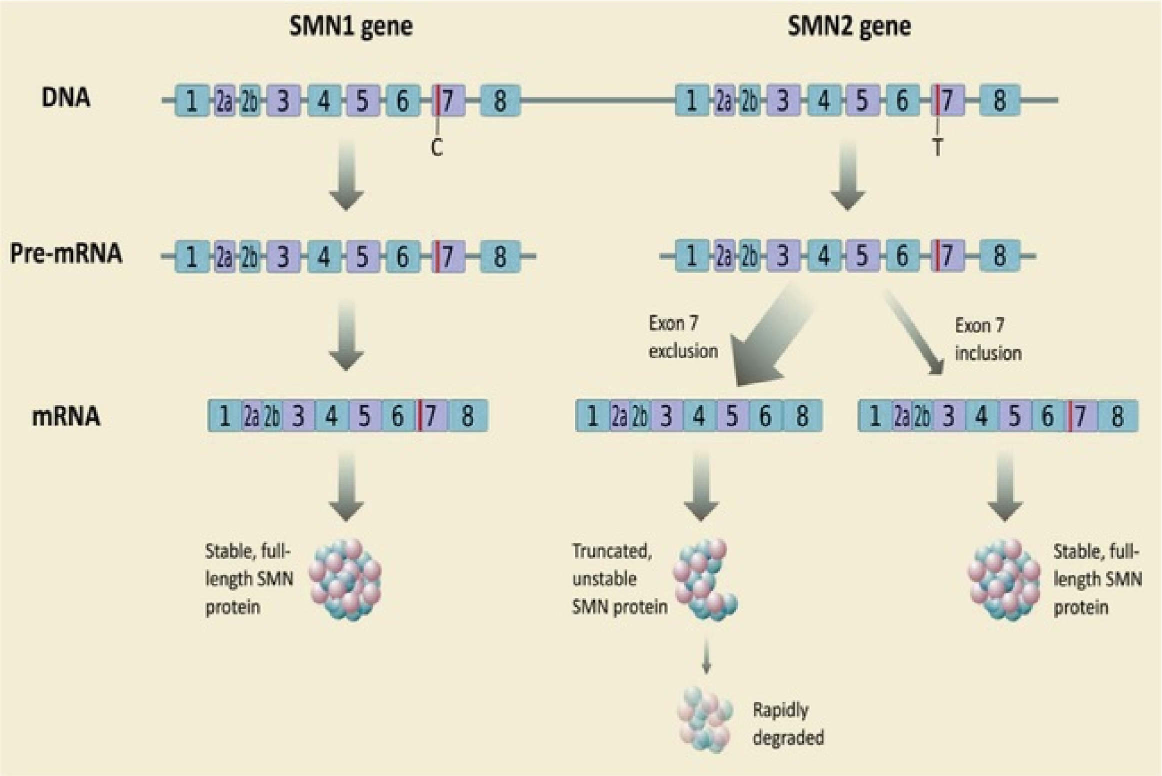
SMN1 gene
SMN2 gene
DNA
1
2a
2b
3
4
5
6
7
8
C
T
Pre-mRNA
Exon 7 exclusion
Exon 7 inclusion
mRNA
Stable, full-length SMN protein
Truncated, unstable SMN protein
Rapidly degraded
Stable, full-length SMN protein

FIG. 630.4 Genetics of spinal muscular atrophy. In humans, the SMN protein is encoded by the *SMN1* and *SMN2* genes. The C to T substitution in exon 7 of *SMN2* is translationally silent, but alters splicing such that the majority of *SMN2* transcripts lack exon 7 and the truncated protein is unstable. Normally, *SMN1* produces abundant SMN protein. In SMA, homozygous mutation of *SMN1* results in only a small amount of functional SMN protein contributed by the varying copy numbers of *SMN2.* mRNA 5, messenger RNA; SMN 5, survival motor neuron. (From Farrar MA, Park SB, Vucic S, et al: Emerging therapies and challenges in spinal muscular atrophy, Ann Neurol 81:355-368, 2017.)

The SMN complex has a role in the formation of small nuclear ribonucleoproteins (snRNPs), through assembly of Sm-proteins (a distinctive family of RNA-associated small proteins) onto small nuclear RNAs (SnRNAs). SMN deficiency and reduced snRNP assembly capacity are hypothesized to cause aberrant splicing or transport of RNPs to motor neurons. Dysregulation of genes involved in synaptogenesis and the maintenance of neuromuscular junctions in animal studies possibly explains the special vulnerability of motor neurons. A second view is that, independent from snRNPs assembly, SMN may have a motor neuron–specific role such as mRNA transport along the axon. Considering the length of axons, integrity of neuromuscular junctions, and interactions with skeletal muscle, SMN protein deficiency may be detrimental for motor neurons. SMN is localized in bright-dot–like structures, called gems (gemini of Cajal bodies) in the nucleus. It is also present in other cellular structures such as Golgi bodies, cell membranes, and especially the axon and growth cone compartments of motor neurons. Owing to its localization in ribonucleoprotein granules in neurites and growth cones in neurons, SMN modulates axonal growth and localization of β-actin messenger ribonucleic acid (mRNA) in growth cones of motor neurons. Early functional impairment of sensory-motor connectivity in animal models showed that motor neuron loss follows afferent synapse loss with the same temporal and topographic pattern, with changes occurring first in motor neurons innervating the proximal muscles and axial muscles, and then the distal muscles. The third view connects SMN function, in a direct or indirect manner, to actin dynamics and actin-dependent processes. There is an expansion in the spectrum of SMN function, including actin dynamics, vesicular transport, protein translation and trafficking, mRNA transport, apoptosis, and many others, which are reflected to widespread pathophysiologic findings described in humans and animal models (Fig. 630.5).

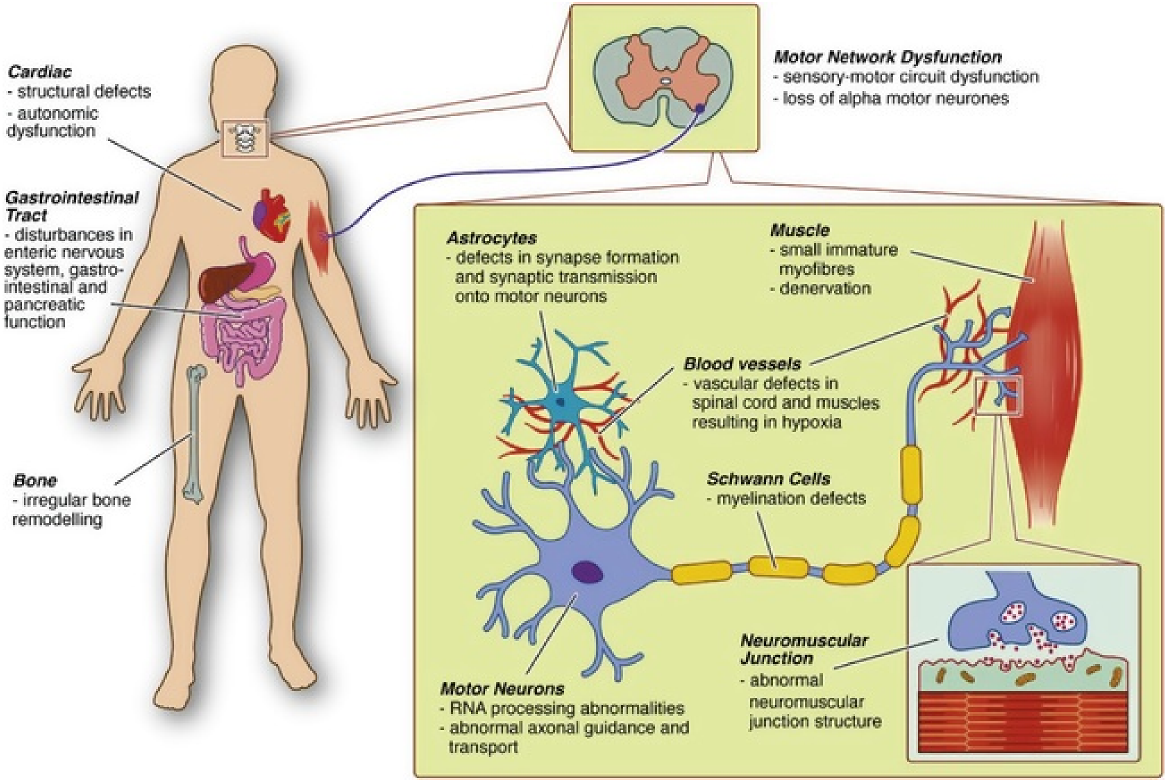
Cardiac
- structural defects
- autonomic dysfunction
Gastrointestinal Tract
- disturbances in enteric nervous system, gastro-intestinal and pancreatic function
Bone
- irregular bone remodelling
Motor Network Dysfunction
- sensory-motor circuit dysfunction
- loss of alpha motor neurones
Astrocytes
- defects in synapse formation and synaptic transmission onto motor neurons
Muscle
- small immature myofibres
- denervation
Blood vessels
- vascular defects in spinal cord and muscles resulting in hypoxia
Schwann Cells
- myelination defects
Neuromuscular Junction
- abnormal neuromuscular junction structure
Motor Neurons
- RNA processing abnormalities
- abnormal axonal guidance and transport

FIG. 630.5 Pathophysiologic findings in SMA. Multiple functional abnormalities in motor networks have been identified in SMA mice and humans, including defects in astrocytes, Schwann cells, motor neurons, and skeletal muscle. Disease-associated phenotypes have also been

reported across a range of other organs in SMA mice (in some cases supported by data from human patients), including cardiac structural and functional abnormalities, gastrointestinal tract dysfunction, and irregular bone remodeling. One potential unifying factor may be a deficiency in the development of the vasculature in SMA, with the resulting hypoxia likely impacting a range of cell types. SMA, spinal muscular atrophy. (From Farrar MA, Park SB, Vucic S, et al: Emerging therapies and challenges in spinal muscular atrophy, Ann Neurol 81:355-368, 2017.)

The severity of the disease is inversely correlated with the amount of functional SMN protein. In that sense, other than the *SMN2* copy number, which is the major protective modifier, the severity of the phenotype can be also influenced by other genetic modifiers, including plastin 3 and neurocalcin. Nutritional deficiency, oxidative stress, and hypoxia may contribute to widespread splicing alterations, including *SMN2*, and affect the disease progression.

Carrier testing by dose analysis is available and is based on semiquantitative real-time PCR or MLPA. In this context, limitations of the molecular testing, difficulties in predicting the offspring's phenotype based solely on the *SMN2* copy number, and the effect on reproductive planning should be considered.

Newborn screening is aimed at identifying presymptomatic SMA patients. Deoxyribonucleic acid (DNA) extraction from newborn blood spots, followed by either liquid microbead array or real-time PCR techniques, have been developed, which helps to identify *SMN1* homozygous deletions. Challenges in newborn screening include the inability to detect carriers of heterozygous deletions of *SMN1* , and *SMN2* copy numbers.

Management

A multidisciplinary and supportive approach is the key in the management of a patient with SMA. Follow-up coordination should be managed by an expert in neuromuscular disorders, and the team ideally should include a pediatric and an adult neurologist, respiratory physicians, geneticists, gastroenterologists, palliative care physicians, rehabilitation specialists, orthopedic surgeons, and allied healthcare professionals. The consensus statement for the standard of care in SMA includes ethical and palliative care sections. Despite increased standards and technologic advances, there is a high variability in terms of ventilatory support, nutritional support, and scoliosis surgery. In terms of advances in disease-modifying treatments that will change the natural course of the disease, care and treatment options should be discussed clearly with the family and/or patients to define expectations, the quality of life, and palliative care issues. Because SMA is a dynamic disease by nature, a proactive plan should be introduced in almost every care subtopic (Table 630.10). Overall, supportive therapy should aim to help the patient to be as functionally independent as possible.

Table 630.10

Management of Spinal Muscular Atrophy

	PROBLEMS	ASSESSMENTS	INTERVENTIONS
Respiratory	Respiratory muscle weakness Paradoxical breathing, bell-shaped chest Weak cough Difficulties in mobilization of mucus Recurrent pulmonary infections Mucus plugs Atelectasis Respiratory failure	Cough effectiveness Respiratory muscle function tests Overnight oximetry Forced vital capacity (>6 yr) Overnight polysomnography if disordered breathing suspected Acute respiratory infections	Referral to respiratory specialist Routine immunizations Annual influenza vaccination Airway clearance techniques and cough assistance (chest physiotherapy, postural drainage, mechanical or manual cough assistance) Respiratory devices–noninvasive ventilation (nocturnal and/or daytime if indicated)* Antibiotics intensified airway clearance Increased ventilation support*
Nutritional	Swallowing dysfunction Failure to thrive Prolonged feeding times Gastroesophageal reflux High risk for aspiration pneumonia Constipation Delayed gastric emptying Increased fat mass and particular risk for becoming overweight (nonambulatory SMA type II patients) Decreased bone mineral intensity	Feeding and swallowing assessment Assess caloric intake Assess for signs of reflux or aspiration Assess for constipation Assess calcium and vitamin D status	Nutritional supplementation Modifying food consistency Optimizing oral intake Positioning and seating alterations Nasogastric, nasojejunal, or percutaneous gastrostomy (as soon as reduced oral intake is recognized) Nissen fundoplication (if indicated) Hydration, regular oral aperients Calcium and vitamin D supplementation (if indicated)
Orthopedic physiotherapy	Scoliosis, hip subluxation, joint contractures (nonambulatory SMA type II patients) Pain Limited mobility	Posture, mobility, function Contractures Scoliosis Hip subluxation/dislocation	Equipment to assist with mobility, self-care, and function Physiotherapy, standing frames, orthoses Spinal surgery [†] Stretching, adequate positioning Exercises with low resistance or

			high repetition Evaluation with functional motor scales developed for SMA patients
Other organ involvement	Reduced muscle mass Higher risk of hypoglycemia during fasting Congenital heart failure (SMA type 0) Obesity, hyperinsulinemia with insulin resistance, and/or impaired glucose metabolism (nonambulatory type II SMA patients)	Consider hypoglycemia during surgery and febrile episodes Assess glucose metabolism if indicated	Appropriate treatment if indicated Referral to cardiologist Referral to endocrinologist
Psychological	Issues related to quality of life index Evaluation of family matrix	Assess for depression/anxiety	Counseling, pharmacotherapy Appropriate referrals

[*] The appropriate level of interventional support to prolong life, particularly in SMA type I, is controversial, and the consensus statement recognizes the importance of discussions with the family to explore and define the potential quality of life and palliative care issues. The philosophy and introduction of proactive respiratory support in patients with SMA type I varies considerably and practice varies internationally.

[†] There is no consensus on management of scoliosis or hip subluxation/dislocation in nonambulant patients. If there is no fast progression of scoliosis, surgery should be delayed until at least 10-12 yr of age to allow for optimum growth. Otherwise, growing rods and vertical expandable prosthetic titanium ribs should be considered. Possibility of intrathecal administration of drugs should be taken into account.

The management of SMA incorporates a multidisciplinary and supportive approach, including neurologists (adult and pediatric), respiratory physicians, geneticists, gastroenterologists, palliative care physicians, rehabilitation specialists, orthopedic surgeons, and allied health care professionals.

Modified from Farrar MA, Park SB, Vucic S, et al: Emerging therapies and challenges in spinal muscular atrophy, Ann Neurol, 81:355-368, 2017; and from Pechman A, Kirschner J: Diagnosis and new treatment avenues in spinal muscular atrophy, Neuropediatrics 48(4):273-281, 2017.

Therapeutic Advances

SMN-antisense oligonucleotide (ASO), nusinersen, administered intrathecally is approved by the U.S. FDA and by the European Medicines Agency for all types of SMA patients. It modifies the splicing of *SMN2* by inducing an increase in exon 7 retention in *SMN2* pre-mRNA, which finally allows a protein product similar to *SMN1* . Phase 1 to phase 3 studies in SMA type I (0-6 mo) and SMA type II/III patients (2-14 yr), showed favorable safety, tolerability, and encouraging clinical efficacy. The primary endpoint was met in each study at interim analysis with statistically significant improvement in motor milestones. In an ongoing, open-label clinical trial, the effect has also been tested in presymptomatic patients with SMA, with favorable results so far. Long-term follow-up is necessary to evaluate the effect of this treatment at different stages of the disease. Scoliosis, surgical interventions, and severe respiratory disease may complicate the lumbar puncture procedure.

Orally administered small molecules (RG7916 and LMI070) are also able to promote exon 7 inclusion and are currently under investigation.

Another therapeutic approach is gene therapy (AVXS-101), to replace *SMN1* and thus increase the production of the full-length SMN protein. Adeno-associated viral vector (AAV-9) is able to transport a functional copy of *SMN1* crossing the blood–brain barrier. An interim analysis of a phase I clinical trial of intravenously administered AVXS-101 in SMA type I patients revealed a safety profile and efficacy with achievement of motor milestones.

In terms of neuroprotective strategies, phase 2 studies with oral *olesoxime (TRO19622)* in the SMA type II or nonambulant type III patient population showed stabilization or improvement compared with placebo. Although the primary endpoint was not met, olesoxime was safe and might be used in combination with other drugs targeting other mechanisms of the disease. The role of exercise as a neuroprotective measure is also under investigation. Current clinical trials also include fast skeletal troponin activator (CK2127107), pyridostigmine, and 4-aminopyridine to enhance nerve or muscle function.

Genetic counseling, depending on carrier screening tests, or in the presence of a previously affected child with SMA, may help with reproductive planning (prenatal diagnosis or preimplantation diagnosis). **Prenatal diagnosis** should be offered to families with an index patient in the family (recurrence risk is 25%), and antenatal screening by chorionic villus sampling between the 10th and 12th gestational week of pregnancy may serve for *SMN1* deletion/mutation analysis.

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630.3

Other Motor Neuron Diseases

Goknur Haliloglu

Motor neuron diseases (MNDs) are a heterogeneous group of progressive neurodegenerative disorders characterized by upper and lower neuron dysfunction, with an onset from birth to adulthood. A variety of causes, including hereditary, immune-mediated, infectious, paraneoplastic, and sporadic diseases, should be considered.

Acute flaccid paralysis is the most common presentation of MND in children; it may occur in outbreaks. *Poliomyelitis* used to be a major cause of chronic disability, but with the routine use of polio vaccine, this viral infection is rare (see Chapter 276). Other enteroviruses, such as coxsackievirus and echovirus, or the live polio vaccine virus can also cause an acute infection of motor neurons, with symptoms and signs similar to poliomyelitis, although usually milder. Specific PCR tests and viral cultures of cerebrospinal fluid are diagnostic. A clustering of cases of acute flaccid paralysis has been reported during outbreaks of enterovirus D68 in multiple states in children (mean age 7-11 yr). Limb weakness is often asymmetric and includes bulbar weakness, as well as cranial nerve VI and VII involvement. MRI may demonstrate longitudinal spinal cord lesions with dominant anterior horn cell involvement (Fig. 630.6). Cerebrospinal fluid pleocytosis and elevated protein are common. Treatments have included steroids and intravenous immunoglobulin; persistent paresis is a common sequelae. Motor neuron infection with the West Nile virus also occurs.

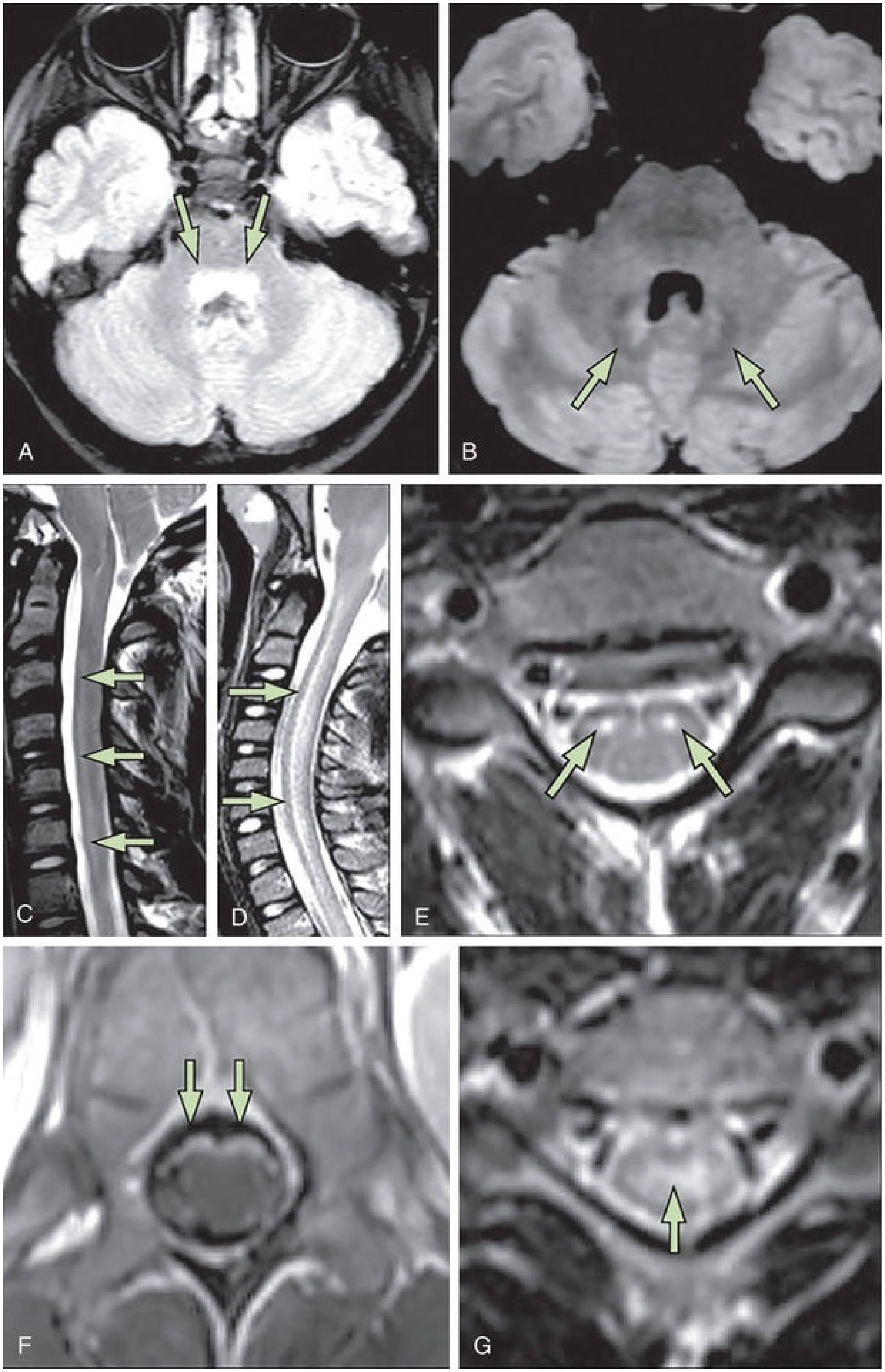
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FIG. 630.6 Brain and spinal cord MRI. Axial FLAIR image at the level of the pons showing increased signal in the tegmentum (A; case 2). Axial FLAIR image at the level of the pons showing increased signal in the dentate nuclei, right greater than left, and sagittal T2-weighted image of the cervical spine shows long segment hyperintensity in the ventral cord (B, C; case 5). Sagittal T2-weighted image shows extensive increased signal in the central cord and cord swelling (D) at presentation (D to F; case 1). Five weeks after presentation, axial T2-weighted imaging of the cervical spine shows residual increased signal in the anterior horns (E) and an axial T1-weighted postcontrast image shows ventral nerve root enhancement at the level of the conus medullaris (F). Axial T2-weighted image of the cervical spine showing increased signal in the central grey matter (G; case 6). Cases 2, 5, and 6 were children with enterovirus D68 identified in the nasopharynx. (From Messacar K, Schreiner TL, Maloney JA, et al: A cluster of acute flaccid paralysis and cranial nerve dysfunction temporally associated with an outbreak of enterovirus D68 in children in Colorado, USA, Lancet 385:1662-1671, 2015, Fig. 3.)

In children, an insidious onset, slow progression, and family history can be clues for a genetic basis. Although the most common MND in children is 5q13-associated SMA, with a typical or predominant lower motor neuron phenotype, there is a clinically and genetically heterogeneous group of MNDs that overlap with **hereditary spastic paraplegias (HSPs), hereditary sensory-motor neuropathies (HSMN),** and **juvenile forms of amyotrophic lateral sclerosis (ALS).**

A less common group of MNDs, not associated with *SMN1,* are called **non-5q13-associated SMAs;** this heterogeneous group can be associated with X-linked, autosomal dominant or autosomal recessive SMAs, **distal SMAs, segmental SMAs,** or **distal hereditary motor neuropathies** or **neuronopathies.** Additional features, such as deafness; epilepsy; encephalopathy; spasticity; visual impairment; or brainstem, cerebellar, gastrointestinal, or rheumatologic disorders may be indicative of a widespread involvement. These **atypical SMA** phenotypes can also be called **SMA-plus syndromes,** and they show extensive phenotypic overlap and molecular genetic heterogeneity (Table 630.11). Primary involvement of the upper motor neuron, with a progressive upper and lower motor neuron loss, characterize **juvenile amyotrophic lateral sclerosis,** which is rare and ultimately fatal.

Table 630.11

Main Forms of SMA Not Linked to *SMN1* (non-5q SMA, SMA-plus Syndromes, Atypical SMAs)

SMA VARIANT	AGE OF ONSET	CHARACTERISTIC KEY FEATURES	INHERITANCE/GENE/GENE FUNCTION

SMA with pontocerebellar hypoplasia (PCH1)	Early infancy	Severe hypotonia, areflexia, muscle weakness, central visual impairment, dysphagia, respiratory insufficiency, acquired microcephaly, and cranial MRI shows cerebellar hypoplasia with variable involvement of pons	AR *VRK1* *EXOSC3* *EXOSC8* *TSEN54* *SLC254A6* RNA processing *MORC2* Mitochondrial DNA repair, RNA processing, lipid metabolism
SMA with progressive myoclonic epilepsy (SMAPME)	Childhood with normal initial development	Proximal muscle weakness, hypotonia, areflexia, muscle wasting. Tongue fasciculation and may have sensorineural hearing loss, polyarticular arthritis, and facial weakness. Later drug-resistant myoclonic epilepsy	AR *ASAH1* Cytoskeletal architecture–axonal branching, autophagy (lysosomes)
SMA with skeletal abnormalities SMA with congenital arthrogryposis and fractures SMA, X-linked (SMAX2) Lethal arthrogryposis with anterior horn cell degeneration (LAAHD) (Finnish) Lethal congenital contracture syndrome 1 (LCCS1) (Finnish) Lethal congenital contracture syndrome 2 (LCCS2) (Israeli-Bedouin)	Antenatal	Arthrogryposis, fractures, cardiac defects, severe hypotonia, weakness, areflexia with tongue fasciculations, and respiratory insufficiency. Early death Congenital fractures, arthrogryposis, and tongue fasciculation Fetal akinesia deformation sequence. Death in utero or within days of delivery. Normal spinal cord Lethal in the fetal period, most severe form of arthrogryposis, abnormal spinal cord with marked thinning Congenital contractures, dysmorphism, and urinary bladder involvement. Majority early death.	AR *SMN1* *TRIP4* *ASCC1* *UBA1* RNA processing X-linked *UBE1* Protein degradation via proteasomes AR *GLE1* RNA processing-mRNA export mediator AR GLE1 RNA processing-mRNA export mediator AR *ERBB3* RNA processing-modulator of phosphatidylinositol-3-kinase/Akt pathway
SMA-plus disorders, mitochondrial diseases related Cardioencephalomyopathy with cytochtome C oxidase deficiency (CEMCOX1) Mitochondrial depletion syndrome 2 (MTDP2) Mitochondrial depletion syndrome 3 (MTDP3)	Infancy Infancy/childhood Infancy	SMA phenotype with hypertrophic cardiomyopathy, seizures, psychomotor retardation, ophthalmoplegia, cranial MRI showing white matter and basal ganglia abnormalities Hypotonia, muscle weakness, respiratory failure, psychomotor	AR *SCO2* Mitochondrial structure and function AR *TK2* Mitochondrial function, depletion of mitochondrial DNA AR *DGUOK*

		retardation with seizures and ophthalmic involvement. Progressive and wide variability SMA with infantile onset liver dysfunction, nystagmus, cerebral atrophy and death	Mitochondrial function, depletion of mitochondrial DNA
SMA-plus disorders with distinctive patterns of weakness SMA, lower extremity predominant 1 (SMALED1) SMA, lower extremity predominant 2 (SMALED2) Scapuloperoneal SMA (SPSMA) Congenital distal SMA (CDSMA) SMA with respiratory distress (SMARD) SMA with respiratory distress 2 (SMARD2) Brown-Vialetto-Van Laere (BVVL) syndrome	Congenital to adulthood Congenital to adulthood Early adulthood Congenital Infancy Early childhood to adulthood	Nonprogressive, proximal leg dominant weakness, specific limb MRI pattern (sparing of thigh adductors and semitendinosus) Slow progression muscle weakness (proximal > distal leg > arms), some contractures Progressive weakness of face and pectoral muscles with laryngeal palsy. May have sensorineural deafness, skeletal abnormalities, specific limb MRI pattern (sparing of biceps femoris and medial gastrocnemius) Nonprogressive proximal and distal legs only weakness and contractures Distal > proximal lower limb > upper limb weakness with early diaphragm weakness and respiratory insufficiency Progressive pontobulbar palsy with weakness of the arms, hands, and face; ataxia; dysphagia; tongue wasting and fasciculations; sensorineural deafness; early respiratory failure	AD *DYNC1H1* Cytoskeletal dynamics, dynein complex for axonal transport AD *BICD2* Cytoskeletal dynamics, dynein-dynactin complex AD *TRPV4* Calcium channel AD *TRPV4* Calcium channel AR *IGHMBP2* Ribosomal biogenesis in RNA processing X-linked *LASIL* AR *SLC52A3* *SLC52A2* *UBQLN1* Vitamin transport, protein degradation through proteasome

AD, autosomal dominant; AR, autosomal recessive; RNA, ribonucleic acid.

Modified from Teoh HL, Carey K, Sampaio H, et al: inherited pediatric motor neuron disorders: beyond spinal muscular atrophy, Neural Plast 2017:6509493, 2017.

Parallel to advances in next-generation techniques, there has been an increase in the molecular diagnostic yield and expansion of clinical phenotypes. This further helps not only to understand the natural course and common pathophysiologic mechanisms involved, but also indicates the appropriate genetic counseling and prenatal diagnosis.

A pattern of weakness, amyotrophy, and progression (proximal or distal, bulbar or respiratory involvement), the presence of spasticity, deep tendon reflexes, and the family history should be evaluated. In contrast to typical SMA, electrophysiologic studies and electromyography (EMG) may serve as important tools to demonstrate a neurogenic basis. Multisystem assessment, including vision, hearing, and cognitive development, is required. Clinical evaluation and recognition of distinctive features will help to classify MND and consider **treatable MND** forms in the differential diagnosis.

SMA with respiratory distress (SMARD) is a rare autosomal recessive disease due to mutations in the gene encoding IGHMBP2 on chromosome 11q13. In contrast to classical SMA type I, *predominant distal weakness* with *diaphragmatic palsy* results in severe respiratory failure. There is usually an early presentation between 6 wk and 6 mo of age, with intrauterine growth retardation, a weak cry and suck, and congenital foot deformities. Routine chest X-ray may reveal *diaphragmatic eventration,* which causes early respiratory failure. Atypical patients with peripheral neuropathy and no respiratory involvement have also been described. Beyond the core symptoms, sensory and autonomic dysfunction (excessive sweating, urinary retention, constipation, and cardiac arrhythmia), seizures, and progressive cranial nerve involvement can be additional features.

Brown-Vialetto-Van Laere (BVVL) syndrome is a rare heterogeneous neurodegenerative disorder characterized by involvement of cranial nerves VII to XII, progressive facial weakness, sensorineural deafness, dysphagia, tongue amyotrophy, fasciculations, bulbar palsy, and respiratory insufficiency. It may present at all ages. Weakness of the arms and hands, optic atrophy, and ataxia may be additional presentations. The clinical presentation of **Fazio-Londe syndrome** is the same, and characterized by progressive bulbar palsy resulting from motor neuron degeneration more in the brainstem than the spinal cord, *without sensorineural deafness.*

Identification of mutations in the riboflavin transporter genes (Table 630.11) provided a targeted therapeutic strategy with oral or intravenous *high-dose riboflavin supplementation* with the customary dose being 10 mg/kg/day. The clinical response in this group may be variable, ranging from a rapid response to gradual improvement over 12 mo, clinical stabilization, or rarely no response. Recognition of *abnormal acylcarnitine profiles* mimicking *multiple acyl-CoA dehydrogenase deficiency* in BVVL should also be taken into account. A biochemical response to treatment is also evident. The common core phenotype of this treatable MND includes progressive axonal sensorimotor neuropathy (manifesting with sensory ataxia and severe weakness of the upper limbs and axial muscles with distinctly preserved muscle power of the lower limbs), hearing loss, optic atrophy, and respiratory insufficiency.

The classic form of **pontocerebellar hypoplasia with SMA (PCH1)** is characterized by severe hypotonia, areflexia, muscle weakness, central visual impairment, dysphagia, respiratory insufficiency, and acquired microcephaly, with a presentation in the first months of life and death in infancy. There is a wide clinical spectrum, with a severe antenatal onset representing the severe end of the spectrum with arthrogryposis and polyhydramnios.

SMA with progressive myoclonic epilepsy (SMAPME) is characterized by treatment-resistant progressive myoclonic epilepsy combined with proximal muscle weakness, areflexia, atrophy, progressive weakness, and dysphagia, followed by normal developmental milestones. Mild facial weakness, tongue fasciculations, sensorineural hearing loss, and tremor may be additional features. Rare variants include the recently described *polyarticular arthritis with SMA, mild SMA without seizures*, *eyelid myoclonic status epilepticus*, and *absence and atonic seizures* in adolescence.

Lethal arthrogryposis with anterior horn cell disease (LAAHD) and **SMA with congenital arthrogryposis and fractures** are atypical SMA forms within the fetal akinesia/hypokinesia spectrum (see Chapter 626.10).

A variety of **mitochondrial diseases** may present with an SMA-like clinical phenotype. In addition to hypotonia, weakness, and respiratory failure, there is a more extensive spectrum of multisystem involvement, such as infantile hypertrophic cardiomyopathy, hepatic failure, spasticity, Leigh-like syndrome, encephalopathy, seizures, brainstem dysfunction, global developmental delay, ptosis, and ophthalmoplegia. Lactic acidosis and increased serum CK levels may further help to include genes involved in *COX assembly proteins* and *mitochondrial depletion syndromes* in the molecular genetic workup.

SMA with lower extremity predominance (SMALED) is characterized by congenital or early-onset, proximal lower limb–predominant muscle weakness and atrophy. There is again a wide range of clinical presentations from the antenatal to adulthood periods. Spasticity and cognitive impairment can be a part of the clinical picture in some patients.

Scapuloperoneal SMA is an autosomal dominant condition defined by its selective muscle involvement, progressive distal weakness, and atrophy.

Laryngeal palsy, sensorineural deafness, short stature, scoliosis, and mild limb and skeletal dysplasia may accompany the picture.

Motor neurons become involved in several metabolic diseases of the nervous system, such as gangliosidosis (Tay-Sachs disease), ceroid lipofuscinosis (Batten disease), and glycogenosis II (Pompe disease), but the signs of denervation may be minor or obscured by the more prominent involvement of other parts of the central nervous system or of muscle. Amyotrophy related to lower motor neuron degeneration is a prominent future of some multisystem disorders, such as infantile neuroaxonal dystrophy (INAD), achalasia–addisonianism–alacrima (AAA, triple A, or Allgrove syndrome), and Chédiak-Higashi syndrome (CHS).

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CHAPTER 631

Hereditary Motor-Sensory Neuropathies

Harvey B. Sarnat

The hereditary motor-sensory neuropathies (HMSNs) are a group of progressive diseases of peripheral nerves (Table 631.1). Motor components generally dominate the clinical picture, but sensory and autonomic involvement is expressed later. Sural nerve biopsy used to be the most definitive means of diagnosis, but with the expanded knowledge of the molecular genetics of this group of diseases, the diagnosis of most can be confirmed by less invasive genetic testing. Electromyography (EMG) remains a useful adjunct to clinical diagnosis and helps distinguish between **demyelinating** or **hypo myelinating** and **axonal** forms. Clinical clues are noted in Tables 631.2 and 631.3 .

Table 631.1

Hereditary Peripheral Neuropathies

DISORDER (OMIM NO.)	CLINICAL FEATURES	NERVE CONDUCTION STUDIES	GENE OR LOCUS
CMT1 (DEMYELINATING)			
CMT1 A-F (HMSN type I)	Autosomal dominant. Onset 1st-4th decade. Predominant distal weakness, decreased DTRs, mild distal sensory loss, hypertrophy of nerves common	Delayed motor and sensory conduction studies. Motor studies typically < 38 m/s	
1A (118220)	Commonest form recognized, seen in all ages (but more adults)		*PMP22* duplication or point mutation
1B (118200)	Approximately 5% of CMT1 group		*MPZ*
1C (601098)	Childhood onset, starts with abnormal gait, then distal weakness and wasting, occasional nerve hypertrophy. Rarely, early-onset hearing loss		*LITAF*

1D (607678)	Possible cranial nerve involvement. Late onset in childhood or early adulthood		*EGR2*
1E (118300)	Associated with deafness (29–45%)		*PMP22*
1F (607734)			*NEFL*
Hereditary neuropathy with liability to pressure palsies (tomaculous neuropathy) (162500)	Autosomal dominant. Recurrent mononeuropathy simplex or multiplex frequently related to trauma	Significant slowing of motor and sensory conduction velocities in clinically affected nerves but also in unaffected nerves	*PMP 22* deletion
Slowed NCVs Asymptomatic	Often a miscellaneous group. Incidentally detected with no clinical symptoms. Autosomal dominant	Moderately slowed conduction velocities	*ARHGEF10*
CMT2 (AXONAL)			
CMT2 A-L (HMSN type II)	Autosomal dominant (A, B, D, E, F, G, I) Autosomal recessive (BI, B2, H, K) Clinically similar to CMT type 1, except for later onset, absence of peripheral nerve enlargement, and less marked weakness	Nerve conduction velocities greater than HMSN type I (>38 m/s) but below normal range occasionally	
2A1 (118210) 2A2 (609260)	CMT2A: prominent distal weakness, proximal weakness also present in 60%. Optic atrophy and central involvement reported. Main form related to *MFN2* mutations		2A1: *KIF1B* (one family) 2A2: *MFN2*
2B (600882) 2B1 (605588)	CMT2B: severe sensory loss: often complications with infections, arthropathy, amputations, foot ulcers, distal weakness		2B: *RAB7* 2B1: *LMNA*
2B2 (605589)	Average onset 34 yr (Costa Rican family)		*?MED25*
2C (606071)	Vocal cord, diaphragm, and respiratory involvement, decreased longevity. Allelic with congenital dSMA (600175) and scapuloperoneal muscular atrophy (181405)		*TRP4* 12q23–q24 *TRP4*
2D (601472) (allelic to dSMA)	Upper limb predominance		*GARS*
2E (607684) (1F dominant is allelic to CMT2E)	30% associated with deafness, early childhood onset with gait abnormalities, occasional hyperkeratosis, increased sensory involvement	Intermediate/slow nerve conduction studies	*NEFL*
2F (606595)	Trophic changes in feet and knees		*HSPB1* (*HSP27*)
2G (608591)	Onset age 9-76 yr, average age 20 yr, large Spanish family. Also severe form with early onset		12q12–q13
2H (607731) 2H (allelic to CMT4A–CMT4C2 in original publication)	Pyramidal involvement, vocal cord involvement	Intermediate/slow nerve conduction studies	*GDAP1*
2I (607677)	CMT I and J: possible late onset, pupillary anomalies, pain, hearing loss, dysphagia		*MPZ*
2J (607736)	Vocal cord paralysis, more severe early-onset form		*MPZ*
2K (607831)	Occasional proximal leg weakness (like dHMN		*GDAP1*

	II), large Chinese family, with onset at age 15-33 yr. Scoliosis		
2L (608673)			*HSPB8* 12q24
HMSN II with onset in early childhood (EOHMSN) Severe early-onset axonal neuropathy (SEOAN)	Autosomal dominant or recessive. Weakness within first 5 yr, rapid progression of weakness, usually complete paralysis below elbows and knees by teens, absent DTRs, moderate sensory changes in most cases. Normal CSF protein. Occasional optic atrophy or spasticity	Axonal pattern with axonal-degenerative polyneuropathy. Absent SNAPs, no response to stimulation in cerebral palsy nerve, upper limb nerves normal or mildly slowed. EMG: denervation	*MFN2* ; *GDAP1* Heterogeneous
Spinal muscular atrophy with respiratory distress type 1 (SMARD1)/severe infantile axonal neuropathy with respiratory failure (SIANR) Allelic to dHMN6 dSMA1 (604320)	Autosomal recessive. Onset in infancy (3-6 mo), respiratory failure, progressive distal weakness, eventual plateau. No recovery	Absent conduction in most cases	*IGHMBP2*
Hereditary motor and sensory neuropathy (HMSN-P) (Okinawa type)	Adult onset (after 30 yr). Autosomal dominant. Slowly progressive proximal dominant area of weakness. Fasciculations of extremities and trunk. Raised creatine kinase, hyperlipidemia, diabetes mellitus, eventual loss of ambulation, absent DTRs, sensory disturbances. Most patients described from Japan	Motor and sensory axonal neuropathy. SNAPs, CMAPs, MNCVs, and SNCVs reduced or absent EMG: fasciculations, fibrillations, and neuromyotonic picture early on	3q13
CMT3 * AND 4			
CMT3 (Déjèrine-Sottas syndrome) (145900)	Onset first 2 yr, overall disability ?less severe than CMT4. Hypotonia, motor delay by first yr, poor coordination, ataxia, distal weakness (max. lower limbs), short stature. By 2nd decade, proximal weakness, hand and foot deformities. Nerve hypertrophy. Moderate to severe sensory loss. Scoliosis. Common cranial nerve involvement, nystagmus, deafness, and mild bifacial weakness. Raised CSF protein	Motor conduction velocities usually < 10 m/s. SAPs absent. EMG: chronic denervation	*PMP22* , *MPZ* , *PRX* , *EGR2* , *FIG4*
CMT4 (A-J) Autosomal recessive	Clinical picture similar to or slightly more severe than in CMT1 form, increased ataxia, areflexia, scoliosis. Nerve hypertrophy rare	Moderate slowing of nerve conduction studies	
4A (214400)	Onset < 2 yr, Tunisian and Moroccan families. Severe progressive. Less-severe European phenotypes	25-35 m/s	*GDAP1*
4B1 (601382)	Ophthalmoplegia, vocal cord paralysis, facial, bulbar weakness (all infrequent). Weakness below 5 yr, proximal and distal weakness,	9-20 m/s	*MTMR2* , *(MPZ)*

	absent DTRs		
4B2 (604563)	Early onset: 1st decade; glaucoma and deafness sometimes. Recorded in Tunisia, Japan, and Turkey	15-30 m/s	*SBF2* , *MTMR13*
4C (601596)	Early-onset scoliosis, commoner in Algerians, glaucoma and neutropenia. 1st and 2nd decades	4-37 m/s	*SH3TC2* (*KIAA1985*)
4D (601455) (HMSN-Lom)	Closed gypsy pedigree; onset < 10 yr. Deafness (by 2nd-3rd decade). Tongue atrophy	10-20 m/s	*NDRG1*
4E (605253)	Congenital hypomyelinating neuropathy	5-20 m/s	*ERG2/KROX 20, MPZ*
4F (145900)	Severely affected at birth or by 7 yr; arthrogryposis multiplex congenita common; respiratory and feeding difficulties; often die young	<5 m/s	*PRX*
4G (605285)	Type Russe. Onset 8-16 yr. Origin Bulgaria	30-35 m/s	10q22
4H (609311)	Increased in Lebanese/Turkish. Onset infancy to childhood (1-2 yr). Delayed motor milestones. Occasional scoliosis, increased distal weakness, usually absent DTRs	<10 m/s or absent	*FDG4*
4J (611228)	Onset by 5 yr. Severe disorder. Similarities to motor neuron disease	2-7 m/s; some cases higher	*FIG4*
CCFDN (604168)	Congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy	19-33 m/s	*CTDP1*
MIXED PATHOLOGY (AXONAL AND DEMYELINATING)			
CMT X X-linked CMT X1 (302800)	X-linked dominant. Onset 1st-2nd decade. Progressive wasting and weakness of distal limb musculature, especially hands, more marked in affected males than carrier females	Median nerve motor conduction studies < 40 m/s (but faster than in CMT1A). Intermediate slowing less uniform along nerves with dispersion more pronounced	*GJB1*
X2 (302801)	X-linked recessive. Rare infantile onset, intellectual disability, females very mildly affected	Mixed demyelinating/axonal	Xp22.2
X3 (302802)	X-linked recessive. ± Spasticity. Females unaffected	Mixed demyelinating/axonal	Xq26
X4 (310490)	X-linked (Cowchock syndrome). Severe neuropathy, females very mildly affected. Isolated case reports. Onset birth to early childhood. Slowly progressive. Many develop deafness by 5 yr. Mental retardation commonly seen. Occasional optic atrophy	Axonal neuropathy. Motor conduction velocities: mild delay (33-56 m/s). Sensory very abnormal. EMG: denervation, large motor unit potential, and fasciculation	Xq24–26.1
X5 (311070)	X-linked. Mild to moderate neuropathy, deafness, optic atrophy. Allelic with Rosenberg-Chutorian (opticoacoustic neuropathy) and Arts syndromes	Axonal neuropathy: mild demyelinating changes	Xq21.32–q24 *PRPS1*
Intermediate forms of CMT	Patients have neurophysiologic results that fall between axonal and demyelinating ranges	“Intermediate values” 30-40 m/s: most accurate from median motor nerves. Some forms have normal	

		nerve conduction studies (DI-CMTB)	
DI-CMTA	Italian family		10q24.1–q25.1
DI-CMTB (606482)	American family		*DNM2*
DI-CMTC (608323)			*YARS*
DI-CMTD (607791)	Myelin protein zero		*MPZ*
A–autosomal recessive form (608340)	Overlap conditions: Recessive CMT with *GADP1* mutations: (CMT2K and 4A) Spanish and Tunisian family: severe childhood forms reported. Also called DI-CMTA autosomal recessive form CMT with NF-L: (CMT1F and 2E)		Overlap: *GJB1* *NF-L* *GDAP1*
OTHER HMSN AND HMN SYNDROMES			
HMSN V/spastic paraplegia with HMSN type V/CMT5 (CMT with pyramidal signs) (600631)	Variable inheritance. Spasticity in lower limbs causing difficulty walking and toe walking. Autosomal recessive form associated with mental retardation. Lower limb marked spasticity with little weakness, increased DTRs, extensor plantars, pes cavus, often distal amyotrophy. Expanding field with multiple subforms, n = 37. Not all associated with peripheral neuropathy CMT with pyramidal signs: part of HMSN V but described without spasticity	Small/absent SNAPs. Motor studies axonal in type	*SPG3A, SPAST, NIPA1, BSCL2, SPG4, SPG7, SPG20, SPG21, SPG30, PLP1* CMT with pyramidal signs: *MFN2*
HMSN VI (allelic CMT2A)	Visual impairment due to optic atrophy. Dominant and recessive forms. Onset in 1st decade. Distal weakness, often proximal involvement too. Less sensory involvement. Scoliosis	No response or motor conduction around 45 m/s. Sensory nerves often cannot be stimulated	*MFN2*
HMSN VII	HMSN with retinitis pigmentosa. CSF protein raised. Usually adult onset. Rare entity described in a few families, mainly of adult onset		
DISTAL HEREDITARY MOTOR NEURONOPATHIES (dHMN)			
dHMNI (182960)	Autosomal dominant. Juvenile onset. Distal weakness and wasting	Normal nerve conduction studies, occasional mild slowing. EMG neurogenic	*HSPB1* 7q34–q36
dHMNII (608634)	Autosomal dominant. Adult onset, distal weakness and wasting		*HSPB8, HSPB3*
dHMNIIjuv (158590)	(Allelic CMT2F, CMT2L)		*HSPB1*
dHMNIII	Autosomal recessive. Infantile to adult onset. Slow, progressive muscle wasting and weakness, variable diaphragmatic paralysis		11q13.3
dHMNIV (607088) Distal SMA type 3	Autosomal recessive. Juvenile onset. Severe muscle wasting and weakness and diaphragmatic paralysis		11q13
dHMNV (600794)	(Allelic CMT2D) Autosomal dominant. Upper limb		*GARS*

	predominance, occasional pyramidal features		
dHMN type V (Silver syndrome) (270685)	Autosomal dominant. Prominent hand muscle weakness and wasting, mild to severe spasticity of lower limbs		*BSCL2*
dHMNVI (604320)	(Allelic SMARD1) Autosomal recessive. Severe infantile form with respiratory distress		*IGHMBP2*
dHMNVIIA (158580)	Autosomal dominant. Onset with vocal cord paralysis		*DCTN1*
dHMNVIIB (607641)	Autosomal dominant. Onset with vocal cord paralysis and facial weakness		2q14 Xq13–q21
X-linked dHMN			
dHMN/ALS4 (602433)	X-linked recessive. Juvenile onset with distal wasting and weakness		*SETX*
dHMN-J (Jerash)	Autosomal dominant. Early onset symptomatic in 2nd decade with pyramidal tract signs		9p21.1–p12
Congenital distal SMA (600175)	Autosomal recessive. Onset from 6-10 yr with pyramidal features in one Jordanian family		12q23–q24
	Autosomal dominant congenital nonprogressive distal HMN with contractures		
Peripheral neuropathy with agenesis of corpus callosum (Charlevoix disease or Andermann syndrome) (218000)	Autosomal recessive. Increased in French Canadian populations. Progressive axonal neuropathy. CNS malformations: absence/hypoplasia of corpus callosum in most, early onset, developmental delay, areflexia, dysmorphology. Later, increased motor disability, hallucinatory psychosis. Death by 3rd decade	EMG: denervation. Axonal neuropathy	*SLC12A6 (KCC3)*
Hereditary neuralgic amyotrophy (brachial plexus neuropathy) (162100)	Autosomal dominant. Episodes of paralysis and muscle weakness initiated by severe pain. Onset can be from birth or later childhood but usually adult onset. Outcome usually good but some left with residual dysfunction. Episodes often triggered by infections, immunizations, and stress. Some pedigrees dysmorphic with hypotelorism	Normal or mildly prolonged MNCVs distal to affected brachial plexus	*SEPT9*
HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES			
HSN (HSAN) 1 (162400)	Type 1: Autosomal dominant. Onset 2nd-5th decade. Predominant loss of pain and temperature sensation, preservation of vibration sense, lancinating pain, variable distal motor involvement	Normal to low-normal MNCVs, disturbance of sensory conduction of variable severity Type 1B: Autosomal dominant. Predominantly sensory neuropathy with cough and gastroesophageal reflux, rarely foot ulcers. More often	*SPTLC1* *RAB7* 3p24–p22

		adult onset. Hearing often abnormal	
HSN (HSAN) 2(A) (201300)	Autosomal recessive. Onset in infancy/early childhood to first 2 decades. Mutilating acropathy. Often unrecognized fractures. Marked sensory loss affecting all cutaneous modalities, most marked distally in all limbs. Autonomic dysfunction less marked. Absent or decreased DTRs	Normal MNCVs; SNAPs are absent	*WNK1*
HSN (HSAN) 2B (223900)	Autosomal recessive. Impaired sensation, ulcers, and arthropathy develop in childhood		*FAM134B*
HSN (HSAN) 3 (Riley-Day syndrome, familial dysautonomia) (223900)	Autosomal recessive. History of neurologic abnormality and of difficult feeding from birth. Failure to produce tears regularly. Absent or reduced DTRs. Absent corneal reflexes, postural hypotension, emotional lability. Relative indifference to pain, absence of fungiform papillae on tongue, absence of flare with intradermal histamine. Normal intelligence	Motor conduction velocities usually slightly below control values. Sensory conduction normal or decreased	*IKBAP*
HSN (HSAN) 4 (congenital insensitivity to pain with anhidrosis, CIPA) (256800)	Autosomal recessive. Onset from infancy, often high fevers due to truncal anhidrosis during hot weather. Painless injuries of extremities and oral structures, often self-mutilation. Lack of pain sensation, both peripheral and visceral, inability to distinguish hot and cold. Preservation of DTRs. Mild mental retardation. Hyperactivity and emotional lability common	Nerve conduction studies normal. Sympathetic skin responses are absent (histamine test)	*NTRK1*
HSN (HSAN) 5 (608654)	Autosomal recessive. Onset in early life. Rare disorder. Painless injuries of the extremities. Lack of pain and thermal sensitivity in the limbs but preservation of response to tactile and mechanical stimuli. Preservation of muscle strength and DTRs. Distal anhidrosis. Bone and joint fractures; arthropathy. Normal intelligence	Normal motor and sensory nerve conduction studies	*NGFβ*

[*] The term CMT3 should be reserved for hereditary neuropathies in which hypomyelination is the dominant feature. This would include congenital hypomyelinating neuropathy, Déjèrine-Sottas disease, and congenital amyelinating neuropathy.

CCFDN, congenital cataract, microcornea, facial dysmorphism, mental retardation, distal motor peripheral neuropathy; CIPA, congenital insensitivity to pain with anhidrosis; CMAP, compound motor unit action potential; CMT, Charcot-Marie-Tooth disease; CP, common peroneal; CSF, cerebrospinal fluid; dHMN, distal hereditary motor neuronopathy; DI, dominant intermediate; dSMA, distal spinal muscular atrophy; DTR, deep tendon reflex; EMG, electromyography; EOHMSN, early-onset HMSN; HMN, hereditary motor neuropathy; HMSN, hereditary motor and sensory neuropathy; HSAN, hereditary sensory and autonomic neuropathy; HSN, hereditary sensory neuropathy; MNCV, motor nerve conduction velocity; OMIM, Online Mendelian Inheritance in Man; SAP, sensory action potential; SEOAN, severe early-onset axonal neuropathy; SMA, spinal muscular atrophy; SNAP, sensory nerve action potential.

From Wilmshurst JM, Ouvrier R: Hereditary peripheral neuropathies of childhood: an overview for clinicians, Neuromuscul Disord 21(11):763-775, 2011.

Table 631.2

Polyneuropathies With Onset in Infancy

SALIENT CLINICAL FEATURE	CLINICAL PHENOTYPE	GENE	MODE OF INHERITANCE
AXONAL NEUROPATHIES			
Pes cavus with footdrop	CMT2E	*NEFL*	AD, AR
Optic atrophy	CMT2A	*MFN2*	AD, AR
	CMT4A	*GDAP1*	AR
	IOSCA	*C10orf2*	AR
	Infantile neuroaxonal dystrophy	*PLA2G6*	AR
Ophthalmoparesis	Mitochondrial disorders	*SCO2* *C10orf2* *TK2*	AR
Skeletal abnormalities	CMT2C, SPSMA, congenital dSMA	*TRPV4*	AD
Arthrogryposis	Congenital dSMA	*TRPV4*	AD
	SMARD1	*IGHMBP2*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital fractures	Unknown	Unknown, presumed AR
Congenital fractures	X-linked SMA	*UBE1*	X-linked
	SMA with congenital fractures	Unknown	Unknown, presumed AR
Vocal cord paresis	CMT2A	*MFN2*	AD, AR
	CMT2C, SPSMA, congenital dSMA	*TRPV4*	AD
	CMT4A	*GDAP1*	AR
	BVVL/Fazio-Londe disease	*SLC52A3*	AR
Early infantile respiratory failure	SMA1	*SMN1*	AR
	SMARD1	*IGHMBP2*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital fractures	Unknown	Unknown, presumed AR
	Lethal neonatal AR axonal sensorimotor polyneuropathy	Unknown	AR
	Congenital axonal neuropathy with encephalopathy	Unknown	Unknown, presumed AR
Predominant motor involvement	Congenital dSMA, SPSMA	*TRPV4*	AD
	SMA1	*SMN1*	AR
	X-linked SMA	*UBE1*	X-linked
	Pontocerebellar hypoplasia type 1	*EXOSC3, VRK1, TSEN54, RARS2*	AR
	SMA with congenital	Unknown	Unknown,

	fractures		presumed AR
	Mitochondrial disorders	*SCO2*, *TK2*	AR
Kinky hair hepatopathy	Giant axonal neuropathy	*GAN*	AR
	Mitochondrial disorders	*DGUOK* *C10orf2*	AR
	MTP/LCHAD deficiency	*HADHA/HADHB*	AR
Cardiomyopathy	Mitochondrial disorders	*SCO2*	AR
		TK2	AR
		DGUOK	AR
	MTP/LCHAD deficiency	*HADHA/HADHB*	AR
CNS involvement	Pontocerebellar hypoplasia type 1	*EXOSC3*, *VRK1*, *TSEN54*, *RARS2*	AR
	Giant axonal neuropathy	*GAN*	AR
	Infantile neuroaxonal dystrophy	*PLA2G6*	AR
	HMSN/ACC	*KCC3*	AR
	IOSCA	*C10orf2*	AR
	CMTX1	*GJB1*	X-linked
	Mitochondrial disorders	*SCO2*	AR
		TK2	AR
		DGUOK	AR
	Adrenoleukodystrophy	*ABCD1*	X-linked
Developmental regression	Adrenoleukodystrophy	*ABCD1*	X-linked
Dysautonomia, chronic skin ulceration	HSAN III (Riley-Day syndrome)	*IKBKAP*	AR
DEMYELINATING NEUROPATHIES			
Acute sensory ataxia, walking difficulties in a previously well child	GBS		
Slowly progressive weakness, ataxia in a previously well child; responsive to steroids	CIDP		
Developmental regression	MLD	*ARSA*	AR
	Krabbe disease	*GALC*	AR
Irritable, stiff, crying infant; occasional unexplained fevers	Krabbe disease	*GALC*	AR
Pes cavus with footdrop, marked difficulties walking	CMT1A	*PMP22* point mutations or duplication	De novo (AD), AR
	CMT1B	*MPZ*	De novo (AD)
	CMT1F	*NEFL*	AD, AR
	CMT4C	*SH3TC2*	AR
	CMT4E	*EGR2*	AR, AD
	CMT4F	*PRX*	AR
	CMT4H	*FGD4*	AR
Early respiratory insufficiency	CMT1A	*PMP22* point mutations or duplication	De novo (AD), AR
	CMT1B	*MPZ*	De novo (AD)
	CMT4C	*SH3TC2*	AR
	CMT4E	*EGR2*	AR, AD
Severe scoliosis requiring surgery in infancy	CMT1B	*MPZ*	De novo (AD)
	CMT4C	*SH3TC2*	AR
Facial weakness	CMT4B1	*MTMR2*	AR

	CMT4B2	*SBF2*	AR
	CMT4C	*SH3TC2*	AR
Sensorineural hearing loss	CMT1A	*PMP22* point mutations or duplication	De novo (AD), AR
	CMT4C	*SH3TC2*	AR
	CMT4F	*PRX*	AR
Congenital nystagmus	CMT1B	*MPZ*	De novo (AD)
	CMT4C	*SH3TC2*	AR

AD, autosomal dominant; AR, autosomal recessive; BVVL, Brown-Vialetto-Van Laere syndrome; CMT, Charcot-Marie-Tooth disease; CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; dSMA, distal spinal muscular atrophy; GBS, Guillain-Barré syndrome; HMSN/ACC, hereditary motor and sensory neuropathy with agenesis of the corpus callosum; HSAN, hereditary sensory and autonomic neuropathy; IOSCA, infantile-onset spinocerebellar ataxia; MLD, metachromatic leukodystrophy; MTP/LCHAD, mitochondrial trifunctional protein/long-chain 3-hydroxyacyl-CoA dehydrogenase; SMA, spinal muscular atrophy; SMARD, spinal muscular atrophy with respiratory distress type 1; SPSMA, scapuloperoneal spinal muscular atrophy.

From Konersman C: Hypotonia, weakness, and stroke. In Kliegman RM, Lye PS, Bordini BJ, et al (eds): Nelson symptom-based diagnosis, Philadelphia, 2018, Elsevier, Table 29.19.

Table 631.3

Infantile Demyelinating Neuropathies With CNS Involvement

	INHERITANCE	GENE	OTHER FEATURES
ASSOCIATED WITH CNS HYPOMYELINATION			
Hypomyelination with congenital cataracts (HCC)	AR	*DRCTNNBIA*	Congenital cataracts, pyramidal signs, cerebellar signs, intellectual disability
Peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome and Hirschsprung disease (PCWH)	AD	*SOX10*	Waardenburg syndrome, Hirschsprung disease, spasticity, ataxia, dysautonomia, intellectual disability
Pelizaeus-Merzbacher disease	X-linked	*PLP1* *	Early nystagmus and titubation, ataxia, spasticity, movement disorder, intellectual disability
Pelizaeus-Merzbacher–like disease	AR	*GJA12*	Nystagmus, ataxia, delayed development
Cockayne syndrome	AR	*ERCC6*, *ERCC8*	Growth failure, photosensitivity, retinopathy, progressive neurologic impairment
ASSOCIATED WITH ABNORMAL CNS WHITE MATTER			

Metachromatic leukodystrophy	AR	*ARSA*	Psychomotor regression, spasticity, seizures
Krabbe disease	AR	*GALC*	Extreme irritability, spasticity, psychomotor regression
Niemann-Pick disease type C [†]	AR	*NPC1*, *NPC2*	Hepatomegaly, vertical gaze palsy, progressive ataxia, dystonia, cataplexy
Merosin-deficient congenital muscular dystrophy	AR	*LAMA2*	Proximal weakness, raised creatine kinase, muscular dystrophy
Navajo neurohepatopathy	AR	*MPV17*	Liver disease, corneal scarring, recurrent metabolic acidosis, recurrent infections, failure to thrive
ASSOCIATED WITH OTHER CNS INVOLVEMENT			
Congenital disorders of glycosylation	AR	*Multiple genes*	Variable features
Congenital cataracts, facial dysmorphism and neuropathy (CCFDN)	AR	*CTDP1*	Congenital cataracts, microretina, intellectual disability, facial dysmorphism, short stature, hypogonadism
POLG-related hepatocerebral mtDNA deletion syndromes	AR	*POLG1*	Encephalopathy, refractory seizures, liver dysfunction
Leigh syndrome	AR, X-linked, mitochondrial	*Multiple genes*	Psychomotor regression, brainstem and basal ganglia signs, raised lactate levels

[*] Peripheral neuropathy associated with *PLP1* null mutations only.

[†] Peripheral neuropathy rarely seen in Niemann-Pick disease type.

AD, autosomal dominant; AR, autosomal recessive.

From Yiu EM, Ryan MM: Demyelinating prenatal and infantile developmental neuropathies, J Peripher Nerve Syst 17:32-52, 2012, Table 4.

Classification of HMSNs is difficult because no simple unifying scheme is capable of incorporating all the clinical presentations and overlapping genetics (see Table 631.1). In some neuropathies, a diverse genotype of mutations of different genes at different chromosomal loci may produce a similar phenotype. One classification identifies

I. Hereditary neuropathies secondary to general diseases;

- II. Primary neuropathies as:
  - IIa. Hereditary motor sensory neuropathies;
  - IIb. Distal hereditary motor neuropathies;
  - IIc. Hereditary sensory ± autonomic neuropathies;
- III. Syndromic neuropathies, including congenital hypomyelinating neuropathies; and
- IV. Hereditary sensory neuropathy (Refsum disease).

631.1

Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease, HMSN Type IIa)

Harvey B. Sarnat

Charcot-Marie-Tooth disease is the most common genetically determined neuropathy and has an overall prevalence of 3.8/100,000 population. It is transmitted as an autosomal dominant trait with 83% expressivity; the 17p11.2 locus is the site of the abnormal gene. Autosomal recessive transmission also is described but is rarer. The gene product is peripheral myelin protein 22 (PMP22). A much rarer X-linked HMSN type I results from a defect at the Xq13.l locus, causing mutations in the gap junction protein connexin-32. Other forms have been reported (see Table 631.1). Both fatty acid binding by PMP22 and the kinetics of its membrane interactions are affected by mutations.

Clinical Manifestations

Most patients are asymptomatic until late childhood or early adolescence, but young children sometimes manifest gait disturbance as early as the second year of life. The peroneal and tibial nerves are the earliest and most severely affected. Children with the disorder are often described as being clumsy, falling easily, or tripping over their own feet. Application of the Cumberland Ankle Instability Tool for Youth is a means of objectively documenting and following this manifestation. The onset of symptoms may be delayed until after the fifth decade.

Muscles of the anterior compartment of the lower legs become wasted, and the legs have a characteristic stork-like contour. The muscular atrophy is accompanied by progressive weakness of dorsiflexion of the ankle and eventual footdrop. The process is bilateral but may be slightly asymmetric. Pes cavus deformities invariably develop as a result of denervation of intrinsic foot muscles, further destabilizing the gait. Atrophy of muscles of the forearms and hands is usually not as severe as that of the lower extremities, but in advanced cases contractures of the wrists and fingers produce a claw hand. Proximal muscle weakness is a late manifestation and is usually mild. Axial muscles are not involved.

The disease is slowly progressive throughout life, but patients occasionally show accelerated deterioration of function over a few years. Most patients remain ambulatory and have normal longevity, although orthotic appliances are required to stabilize the ankles.

Sensory involvement mainly affects large myelinated nerve fibers that convey proprioceptive information and vibratory sense, but the threshold for pain and temperature can also increase. Some children complain of tingling or burning sensations of the feet, but pain is rare. Because the muscle mass is reduced, the nerves are more vulnerable to trauma or compression. Autonomic manifestations may be expressed as poor vasomotor control with blotching or pallor of the skin of the feet and inappropriately cold feet.

Nerves often become palpably enlarged. Tendon stretch reflexes are lost distally. Cranial nerves are not affected. Sphincter control remains well preserved. Autonomic neuropathy does not affect the heart, gastrointestinal tract, or bladder. Intelligence is normal. A unique point mutation in *PMP22* causes progressive auditory nerve deafness in addition, but this is usually later in onset than the peripheral neuropathy.

Davidenkow syndrome is a variant of HMSN type I with a scapuloperoneal distribution.

Laboratory Findings and Diagnosis

Motor and sensory nerve conduction velocities are greatly reduced, sometimes as slow as 20% of the normal conduction time. In new cases without a family history, both parents should be examined and nerve conduction studies should be performed.

Electromyography (EMG) and muscle biopsy are not usually required for diagnosis, but they show evidence of many cycles of denervation and reinnervation. The serum creatine kinase level is normal. The cerebrospinal fluid (CSF) protein may be elevated, but no cells appear in the CSF.

Sural nerve biopsy is diagnostic. Large- and medium-size myelinated fibers are reduced in number, collagen is increased, and characteristic **onion bulb formations** of proliferated Schwann cell cytoplasm surround axons. This pathologic finding is called **interstitial hypertrophic neuropathy.** Extensive segmental demyelination and remyelination also occur. The definitive molecular genetic diagnosis may be made in blood.

Treatment

Stabilization of the ankles is a primary concern. In early stages, stiff boots that extend to the midcalf often suffice, particularly when patients walk on uneven surfaces such as ice and snow or stones. As the dorsiflexors of the ankles weaken further, lightweight plastic splints may be custom-made to extend beneath the foot and around the back of the ankle. They are worn inside the socks and are not visible, reducing self-consciousness. External short-leg braces may be required when footdrop becomes complete. Surgical fusion of the ankle may be considered in some cases.

The leg should be protected from traumatic injury. In advanced cases, compression neuropathy during sleep may be prevented by placing soft pillows beneath or between the lower legs. Burning paresthesias of the feet are not common but are often abolished by phenytoin, carbamazepine, or gabapentin. Progressive resistance exercise for foot dorsiflexion may attenuate the progression of weakness.

Hereditary sensory autonomic neuropathy 1 has, in preliminary studies, been treated with oral L-serine, with biochemical improvements (lowering of toxic metabolites).

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631.2

Peroneal Muscular Atrophy (Axonal Type)

Harvey B. Sarnat

Peroneal muscular atrophy is clinically similar to HMSN type I, but the rate of progression is slower and the disability is less. EMG shows denervation of muscle. Sural nerve biopsy reveals axonal degeneration rather than the demyelination and whorls of Schwann cell processes typical in type I. The locus is on chromosome 1 at 1p35-p36; this is a different disease than HMSN type I, although both diseases are transmitted as autosomal dominant traits. An autosomal recessive infantile motor axonal neuropathy can closely mimic infantile spinal muscular atrophy.

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631.3

Congenital Hypomyelinating Neuropathy and Déjèrine-Sottas Disease (HMSN Type III)

Harvey B. Sarnat

Congenital hypomyelinating neuropathy is an interstitial hypertrophic neuropathy of autosomal dominant transmission, clinically similar to HMSN type I but more severe. Symptoms develop in early infancy and are rapidly progressive, with hypotonia and breathing and feeding difficulties. Pupillary abnormalities, such as lack of reaction to light and *Argyll Robertson pupil,* are common. Kyphoscoliosis and pes cavus deformities complicate approximately 35% of cases. Nerves become palpably enlarged at an early age. Déjèrine-Sottas disease is a more slowly progressive variant with onset usually before age 5 yr.

An autosomal recessive form of congenital hypomyelinating neuropathy also is known and may be caused by various genetic mutations, including *MTMR2, PMP22, EGR2,* and *MPZ.* A secondary mutation in the *EGR2* gene may intensify the clinical manifestation of Déjèrine disease. Neonatal hypotonia and developmental delay in infancy are hallmark clinical features. Many patients exhibit congenital insensitivity to pain. Cranial nerves are inconsistently involved, and respiratory distress and dysphagia are rare complications. Tendon reflexes are absent. **Arthrogryposis** is present at birth in at least half of the cases.

The onion bulb formations seen in the sural nerve biopsy specimen are pronounced. Hypomyelination also occurs. In the recessive form, hypomyelination may not be accompanied by interstitial hypertrophy in all cases.

The genetic locus of 17p11.2 is identical to that of HMSN type I or Charcot-Marie-Tooth disease. Monoallelic mutations in *MPZ* (myelin protein zero), *PMP22*, or *EGR2* (early grow response 2) are the most frequent genetic causes. The clinical and pathologic differences may be phenotypic variants of the same disease, analogous to the situation in Duchenne and Becker muscular dystrophies. An autosomal recessive form of Déjèrine-Sottas disease is incompletely documented.

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631.4

Roussy-Lévy Syndrome

Harvey B. Sarnat

Roussy-Lévy syndrome is defined as a combination of HMSN type II and cerebellar deficit resembling Friedreich ataxia, but it does not have cardiomyopathy.

631.5

Refsum Disease (HMSN Type IV) and Infantile Refsum Disease

Harvey B. Sarnat

See also Chapter 104.2 .

Refsum disease is a rare autosomal recessive disease caused by an enzymatic block in β-oxidation of phytanic acid to pristanic acid. Phytanic acid is a branched-chain fatty acid that is derived mainly from dietary sources: spinach, nuts, and coffee. Levels of phytanic acid are greatly elevated in plasma, CSF, and brain tissue. Phytanic and very-long-chain fatty acids may be lipotoxic by impairing mitochondrial function in the central and peripheral nervous systems. The CSF shows an albuminocytologic dissociation, with a protein concentration of 100-600 mg/dL. Genetic linkage studies identify two distinct loci at 10p13 and 6q22-q24 with *PHYH* and *PEX7* genetic mutations, respectively. The infantile form also can be caused by the *PEX1*, *PEX2*, or *PEX26* genes, which produce both clinical and biochemical differences from the classic form, and include minor facial dysmorphism, retinitis pigmentosa, sensorineural hearing loss, hypercholesterolemia, hepatomegaly, and failure to thrive. Phytanic acid accumulation in infantile Refsum disease is secondary to a primary peroxisomal disorder; hence, autosomal recessive Refsum disease is really a different disease.

The clinical onset of classic Refsum disease is usually between 4 and 7 yr of age, with intermittent motor and sensory neuropathy. Ataxia, progressive neurosensory hearing loss, retinitis pigmentosa with loss of night vision, ichthyosis, and liver dysfunction also develop in various degrees. Skeletal malformations from birth and cardiac findings of conduction disturbances and cardiomyopathy appear in the majority. Motor and sensory nerve conduction velocities are delayed. Sural nerve biopsy shows loss of myelinated axons. Treatment is by dietary management and periodic plasma exchange. With careful management, life expectancy can be normal. Hearing loss due to acoustic nerve involvement may sometimes be improved with cochlear implantation.

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631.6

Fabry Disease

Harvey B. Sarnat

See also Chapter 104.4 .

Fabry disease, a rare X-linked recessive trait, results in storage of ceramide trihexoside because of deficiency of the enzyme ceramide trihexosidase, which cleaves the terminal galactose from ceramide trihexoside (ceramide-glucose-galactose-galactose), resulting in tissue accumulation of this trihexoside lipid in central nervous system neurons, Schwann cells and perineurial cells, ganglion cells of the myenteric plexus, skin, kidneys, blood vessel endothelial and smooth muscle cells, heart, sweat glands, cornea, and bone marrow. It results from a missense mutation disrupting the crystallographic structure of α-galactosidase A.

Clinical Manifestations

The presentation is in late childhood or adolescence, with recurrent episodes of burning pain and paresthesias of the feet and lower legs so severe that patients are unable to walk. These episodes are often precipitated by fever or by physical activity. Objective sensory and motor deficits are not demonstrated on neurologic examination, and reflexes are preserved. Autonomic nerve involvement is almost universal and may cause cardiac rhythm abnormalities, cutaneous mottling, and gastrointestinal peristaltic abnormalities, but autonomic expression is variable between patients. Cardiac involvement is not limited to autonomic abnormalities of arrhythmias and conduction defects, but may also include left ventricular hypertrophy, coronary artery disease, and valvular infiltrative myopathy. Characteristic skin lesions are seen in the perineal region, scrotum, buttocks, and periumbilical zone as flat or raised red-black telangiectasias known as **angiokeratoma corporis diffusum.** Hypohidrosis may be present. Corneal opacities, cataracts, and necrosis of the femoral heads are inconstant features. Tortuosity of retinal vessels and of the vertebral and basilar arteries can occur. The disease is progressive. Hypertension and renal failure are usually delayed until early adult life. Recurrent strokes result from vascular wall involvement. Death often occurs in the 5th decade owing to cerebral infarction or renal insufficiency, but a significant morbidity already occurs in childhood despite the absence of major organ failure. Heterozygous female carriers may be asymptomatic or less severely affected than symptomatic males; corneal opacities involve 70–80%, though cataracts are rare.

Laboratory Findings

Motor and sensory nerve conduction velocities are normal to only mildly slow, showing preservation of large myelinated nerve fibers. CSF protein is normal. Proteinuria is present early in the course. An electrochemical skin conductance test is abnormal in the majority of Fabry patients as an indication of small sensory nerve and autonomic nerve involvement. Cardiac evaluation should include ECG, echocardiography, and coronary artery assessment in selected cases.

Calcifications often are seen in the pulvinar of the thalamus, as demonstrated by computed tomography (CT) or magnetic resonance imaging (MRI), and are specific imaging findings, believed caused by cerebral hyperperfusion. Positron tomography, by contrast, shows reduced cerebral blood flow velocity and impaired autoregulation because of the glycosphingolipid storage in vascular endothelial cells.

Pathologic features are usually first detected in skin or sural nerve biopsy specimens. Electron microscopy demonstrates crystalline glycosphingolipids, appearing as *zebra bodies*, in lysosomes of endothelial cells, in smooth myocytes of arterioles, and in Schwann cells. Nerves show a selective loss of small myelinated fibers and relative preservation of large- and medium-sized axons, in contrast to most axonal neuropathies, in which large myelinated fibers are most involved.

An assay for the deficient enzyme, α-galactosidase-A, may be performed from blood leukocytes, skin fibroblasts, and other tissues. This test may permit detection of the female carrier state; for females, gene sequencing is preferred.

Treatment

See Chapter 104.4 for the specific therapy of Fabry disease, including enzyme replacement.

Medical therapy of painful neuropathies includes management of the initiating disease and therapy directed to the neuropathic pain independent of the etiology. Pain may be burning or associated with paresthesia, hyperalgesia (abnormal response to noxious stimuli), or allodynia (induced by nonnoxious stimuli; see Chapter 76). Neuropathic pain is often successfully managed by tricyclic antidepressants; selective serotonin reuptake inhibitors are less effective. Anticonvulsants (carbamazepine, phenytoin, gabapentin, lamotrigine) are effective, as are narcotic and nonnarcotic analgesics. **Enzyme replacement therapy** has improved the short- and long-term prognosis of the clinical neuropathy and also reverses the increased blood flow velocity in the brain.

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631.7

Giant Axonal Neuropathy

Diana X. Bharucha-Goebel

Giant axonal neuropathy is a rare autosomal recessive disease with onset in early childhood. It is a progressive mixed peripheral neuropathy and degeneration of central white matter, similar to the leukodystrophies. Ataxia and nystagmus are accompanied by signs of progressive peripheral neuropathy. A large majority of affected children have frizzy or kinky hair, which microscopically shows variation in the diameter of the shaft and twisting, similar to that in Menkes disease; hence, microscopic examination of a few scalp hairs provides a simple screening tool in suspected cases. Focal axonal enlargements are seen in both the peripheral nervous system and the central nervous system, but the myelin sheath is intact. The disease is a general proliferation of intermediate filaments, including neurofilaments in axons, glial filaments (i.e., Rosenthal fibers) in brain, cytokeratin in hair, and vimentin in Schwann cells and fibroblasts.

Nonsense, missense mutations, splice site mutations, or deletions occur in the *GAN* gene, with allelic heterogeneity at 16q24. These mutations are responsible for defective synthesis of the protein gigaxonin, a member of the cytoskeletal BTB/kelch superfamily, crucial to linkage between intermediate proteins and the cell membrane. MRI shows white matter lesions of the brain similar to leukodystrophies (Fig. 631.1A and B), and MR spectroscopy demonstrates increased ratios of choline:creatine and myoinositol:creatine, with decreased *N* -acetyl aspartate, indicating demyelination and glial proliferation, as well as axonal loss. Gigaxonin is expressed in a wide variety of neuronal cell types and is localized to the Golgi apparatus and endoplasmic reticulum. *GAN* mutations have been demonstrated in human cell lines of neoplastic cells and also in a variety of tumors.

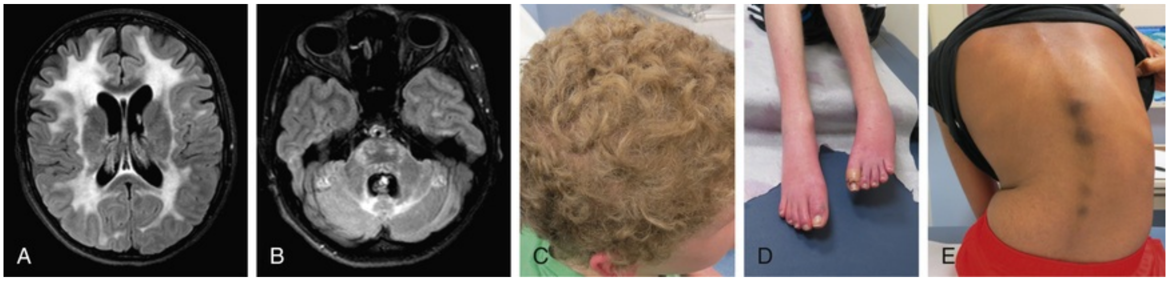

FIG. 631.1 Giant axonal neuropathy. **A** and **B,** White matter abnormalities on T2/FLAIR sequences seen diffusely and including the brainstem and cerebellum in a more advanced patient with GAN. There is also mild ex vacuo dilatation of the ventricles due to progressive atrophy. **C,** Typical kinky hair in GAN (i.e., dry and tight curly hair) often evident in patients from birth or early childhood. **D,** Patients with GAN develop distal atrophy and contractures and may have pedal erythema. **E,** Children with GAN often develop scoliosis by 8-10 yr of age.

The diagnosis is suspected clinically based upon a childhood onset of ataxic gait, findings of neuropathy, and kinky or curly hair (see Fig. 631.1C); it is genetically confirmed by testing of the *GAN* gene. Pathology findings of enlarged or swollen axons from peripheral nerve biopsy are characteristic. Clinically, the onset of symptoms occurs within the first 5 yr of life, and there is progressive ataxia and weakness. As the disease progresses, patients also develop dysphagia, dysarthria, optic neuropathy, respiratory insufficiency, scoliosis (see Fig. 631.1E), and some in later stages they will develop seizures. A mutation of *BAG3,* one of several genes associated with myofibrillar myopathy (see Chapter 626.5), also can cause the finding of giant axons histologically, but clinically is distinguished from giant axonal neuropathy caused by mutations in the *GAN* gene.

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631.8

Hypermyelinating (Tomaculous) Neuropathy; Hereditary Neuropathy With Liability to Pressure Palsies

Harvey B. Sarnat

This hereditary neuropathy is characterized by redundant overproduction of myelin around each axon in an irregular segmental fashion so that tomaculous (sausage-shaped) bulges occur in the individual myelinated nerve fibers. Other sections of the same nerve can show loss of myelin. Such nerves are particularly prone to pressure palsies, and patients, usually beginning in adolescence, present with recurrent or intermittent mononeuropathies secondary to minor trauma or entrapment neuropathies, such as carpal tunnel syndrome, peroneal palsies, and even writer's cramp. Phenotype expression is somewhat variable. It is transmitted as an autosomal dominant trait, with loci identified at 17p11.2 and 17p12, and deletion of exons in the *PMP22* gene (in some patients, only microdeletions). Duplication of the same 17p12 locus leads to Charcot-Marie-Tooth disease type 1A, myelin protein zero *(MPZ)* gene mutation. Sural nerve biopsy is diagnostic, but special teased fiber preparations should be made to demonstrate the myelin abnormalities most clearly. Skin or conjunctival biopsies also may be diagnostic. Electrophysiologic nerve conduction studies are abnormal but nonspecific. Genetic studies are definitive.

Treatment is supportive and includes avoiding trauma and prolonged nerve compression, including postures when sitting or lying. Surgical release of entrapped nerves is indicated at times, particularly of the ulnar nerve.

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631.9

Leukodystrophies

Harvey B. Sarnat

Several hereditary degenerative diseases of white matter of the central nervous system also cause peripheral neuropathy. The most important are Krabbe disease (globoid cell leukodystrophy), metachromatic leukodystrophy, and adrenoleukodystrophy (see Chapters 104 and 617). Within the brain, they produce progressive but selective demyelination, affecting the deep white matter of the centrum semiovale with relative sparing of U-fibers around each gyrus. Additional metabolic disorders associated with peripheral neuropathy are noted in Table 631.4 .

Table 631.4

Inherited Metabolic Disorders Associated With Neuropathy

CATEGORY	DISEASE	STORED MATERIAL	AGE OF ONSET	NE FE
1. Lysosomal				
Mucopolysaccharidoses	Hurler Hunter Sanfilippo A-D	Dermatan/heparan sulfate Dermatan/heparan sulfate Heparan sulfate	Infantile Infantile Infantile	
Sphingolipidoses	Krabbe disease Fabry disease Metachromatic leukodystrophy	Galactosylceramide Trihexosylceramide Sulfatide	Infantile to adult Adolescence Late infancy > adolescence	NC Sm abı
Glycoproteinoses	Fucosidosis α and β mannosidosis Sialidosis I and II Schindler disease	Oligosaccharides Oligosaccharides Oligosaccharides Oligosaccharides	Infantile Infantile to adolescence I = juvenile	

			II = infantile Infantile	
2. Peroxisomal	Adrenomyeloneuropathy Refsum disease Hyperoxaluria	VLCFA Phytanic acid Calcium oxalate	Variable: childhood to adult Childhood/adolescence < 5 yr	
3. Lipid disorders	Cerebrotendinous xanthomatosis Tangier disease Abetalipoproteinemia	Cholestanol Cholesterol esters	Late childhood/adolescence Childhood/adolescence Birth but neuropathy develops in childhood	
4. Mitochondrial	LCHAD Leigh NARP	3-Hydroxy dicarboxylic aciduria Lactate/pyruvate Lactate/pyruvate	Early infancy Early infancy/childhood Usually adolescence	
5. Other	Acute intermittent porphyria	δ = aminolevulinic acid	Usually after puberty	Ca ax

LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; NARP, neuropathy, ataxia, and retinitis pigmentosa; NCVs, nerve conduction velocities; VLCFA, very-long-chain fatty acids.

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CHAPTER 632

Toxic Neuropathies

Harvey B. Sarnat

Many chemicals (organophosphates), toxins, and drugs can cause peripheral neuropathy (Table 632.1). **Heavy metals** are well-known neurotoxins. Lead poisoning, especially if chronic, causes mainly a motor neuropathy selectively involving large nerves, such as the common peroneal, radial, and median nerves, a condition known as mononeuritis multiplex (see Chapter 739). Arsenic produces painful burning paresthesias and motor polyneuropathy. Exposure to industrial and agricultural chemicals is a less-common cause of toxic neuropathy in children than in adults, but insecticides are neurotoxins for both insects and humans, and if they are used as sprays in closed spaces, they may be inhaled and induce lethargy, vomiting, seizures, and neuropathy, particularly with recurrent or long-term exposure. Working adolescents and children in developing countries are also at risk. Lithium is widely used in batteries, as well as in medication for the treatment of psychosis and other psychiatric conditions, but can be neurotoxic, especially cumulatively over time. **Puffer fish poisoning,** which can be acquired even when fish contaminated with the venom has been cooked, produces a Guillain-Barré–like syndrome. Ethanol abuse can be neurotoxic and particularly affects the optic nerves, but optic neuritis is not a peripheral neuropathy.

Table 632.1

Toxic and Metabolic Neuropathies

METALS
Arsenic (insecticide, herbicide) Gold Lead (paint, batteries, pottery) Lithium (batteries) Mercury (metallic, vaporized)

Thallium (rodenticides) Zinc (chronic excessive intake)
DRUGS
Amiodarone Chloramphenicol Chloroquine Cisplatin Colchicine Dapsone Ethambutol Ethanol Fluoroquinolones Gold Hydralazine Isoniazid Metronidazole Nitrofurantoin Nitrous oxide Nucleosides (antiretroviral agents dideoxycytidine [ddC], didanosine [ddI], d4T, others) Penicillamine Pentamidine Phenytoin Pyridoxine (excessive) Statins Stilbamidine Suramin Tacrolimus Taxanes (paclitaxel, docetaxel) Thalidomide Tryptophan (eosinophilia–myalgia syndrome) Vincristine
OCCUPATIONAL OR INDUSTRIAL CHEMICALS
Acrylamide (grouting, flocculation) Carbon disulfide (solvent) Cyanide Dichlorophenoxyacetate Dimethylaminopropionitrite Ethylene oxide (gas sterilization) Hexacarbons (glue, solvents) Organophosphates (insecticides, petroleum additive) Polychlorinated biphenyls Tetrachlorobiphenyl Trichloroethylene
METABOLIC DISORDERS
Fabry disease Krabbe disease Leukodystrophies Porphyria Tangier disease Tyrosinemia Uremia
BIOLOGIC AND INFECTIOUS NEUROPATHIES
Diphtheria Herpesviruses HIV

Leprosy
Lyme disease
Rabies
Serum sickness
West Nile virus
Zika virus

The most frequent cause of toxic neuropathies in children is **prescribed medications,** though street drugs and even some legal over-the-counter products also can be neurotoxic. Antimetabolic and immunosuppressive drugs, such as vincristine, cisplatin, and paclitaxel, produce polyneuropathies as complications of chemotherapy for neoplasms and immunologic disorders, such as juvenile idiopathic arthritis. This *iatrogenic* cause is usually an axonal degeneration rather than primary demyelination, unlike primary autoimmune neuropathies. Excessive vitamin intake of *megavitamins* can be neurotoxic. Zinc compounds are widely sold without prescription as dietary supplements and promoted for treatment of a variety of disorders, both neurologic (e.g., hyposmia) and immunologic, and for various visceral organ systems; most claims are not evidence-based. Zinc ions are essential for the conservation of postsynaptic membranes and mitochondria. Chronic excessive zinc intake is cumulative and becomes toxic by impairing synaptic activity and mitochondrial respiratory chain enzymes, especially complex I enzymes, resulting in polyneuropathy, myopathy, and encephalopathy. Mitochondrial dysfunction also is a frequent basis of neuropathy in many other toxic neuropathies.

Chronic uremia is associated with toxic neuropathy and myopathy. The neuropathy is caused by excessive levels of circulating parathyroid hormone (see Chapter 628). Reduction in serum parathyroid hormone levels is accompanied by clinical improvement and a return to normal of nerve conduction velocity. Peripheral nerve axonal damage, particularly of small fibers, can be secondary to mitochondrial loss or dysfunction in toxic neuropathies. Abnormal toxic complex lipids, generated in Schwann cells by deficient mitochondrial respiration, are capable of damaging or destroying neighboring axons, a secondary mitochondrial toxic neuropathy. Small heat-shock proteins can be provoked that also may contribute to toxic neuropathy.

Biologic neurotoxins associated with diphtheria, Lyme disease, West Nile virus disease, leprosy, herpesviruses (Bell palsy), and rabies also produce peripheral nerve– or ventral horn cell–induced weakness or paralysis. Human immunodeficiency virus (HIV) infections also produce neuropathy, and this infection is particularly prevalent in children in several African countries, including those who emigrate to western countries as refugees. Tick paralysis, botulism, and paralytic shellfish poisoning cause neuromuscular junction blockade rather than true neuropathy. Various inborn errors of metabolism are also associated with peripheral neuropathy from metabolite toxicity or deficiencies (see Part XI and Table 632.1).

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CHAPTER 633

Autonomic Neuropathies

Monique M. Ryan

Involvement of small, lightly or unmyelinated autonomic nerve fibers is seen in many peripheral neuropathies; the autonomic manifestations are usually mild or subclinical. Some autonomic neuropathies are more symptomatic, causing variable disturbances of autonomic regulation of the cardiovascular, gastrointestinal, genitourinary, thermoregulatory, sudomotor, and pupillomotor systems.

The differential diagnosis is noted in Table 631.1 (in Chapter 631) and Tables 633.1 , 633.2 , and 633.3 . Table 633.4 lists the tests useful in assessing autonomic nervous system function. The treatment of acquired autonomic dysfunction includes both management of the primary disorder (Guillain-Barré syndrome, diabetes) and symptomatic management of organ-specific manifestations (Table 633.5).

Table 633.1

Classifications of Pediatric Autonomic Disorders

ETIOLOGY	TOPOGRAPHY	FREQUENCY	NEUROTRANSMISSION
Functional Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia	**Generalized** Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia Hereditary sensory autonomic neuropathies Other rare genetic disorders Reflex (vasovagal)	**Common** Reflex (vasovagal) syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia Obesity Diabetes Anorexia nervosa Other metabolic disorders	**Pandysautonomia (adrenergic and cholinergic failure)** Autoimmune autonomic ganglionopathy Acute autonomic and sensory neuropathy Guillain-Barré syndrome Paraneoplastic neuropathies Porphyria

	syncope Postural tachycardia syndrome Orthostatic intolerance without tachycardia Immune-mediated		
Inherited Hereditary sensory autonomic neuropathies Other rare genetic disorders	**Pupil** Argyll Robertson pupil Adie pupil Horner syndrome Pourfour du Petit syndrome	**Rare** Immune-mediated Traumatic Hereditary sensory autonomic neuropathies Other rare genetic disorders	**Pure adrenergic failure** Dopamine-beta hydroxylase deficiency Pure adrenergic neuropathy
Metabolic Obesity Diabetes Anorexia Other metabolic disorders	**Face** Cluster headache Harlequin syndrome Gustatory sweating		**Pure cholinergic failure** Botulism Lambert-Eaton syndrome Adie pupil Chagas disease Acute cholinergic neuropathy
Immune-mediated Autoimmune autonomic ganglionopathy Guillain-Barré syndrome Anti-NMDA receptor encephalitis Paraneoplastic autonomic neuropathy Sjögren disease	**Limbs** Raynaud phenomenon Acrocyanosis Primary idiopathic hyperhidrosis		
Infectious Chagas disease HIV Tetanus			
Neoplasia Catecholamine-secreting tumors Brainstem and posterior fossa tumors			
Trauma and malformations Spinal cord injury Traumatic brain injury Syringomyelia Arnold-Chiari malformation			
Drugs			
Postsurgical or postradiotherapy			

usages Acquired baroreflex failure			

From Palma JA, Norcliffe-Kaufmann, Fuente-Mora C, et al: Disorders of the autonomic nervous system: autonomic dysfunction in pediatric practice. In Swaiman KF, Ashwal S, Ferriero DM, et al (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, Table 154-1.

Table 633.2

Hereditary Sensory and Autonomic Neuropathies

TYPE	GENE	INHERITANCE	ONSET	AUTONOMIC FEATURES	SENSORY FEATURES	OTHER FEATURES
HSAN 1A	*SPTLC1*	AD	Adult	Varying degrees of distal anhidrosis	Progressive loss of pain, temperature, and fine-touch sensation. Varying degrees of sensorineural hearing loss Episodes of lancinating limb pain	One case with congenital presentation reported with severe growth and mental retardation, microcephaly, hypotonia, and respiratory insufficiency
HSAN 1B	3p24-p22 locus					Cough and gastroesophageal reflux
HSAN 1C	*SPTLC2*					Varying degrees of distal muscle weakness
HSAN 1D	*ALT1*			None		—
HSAN 1E	*DMNT1*			None		Early-onset dementia
HSAN 1F	*ATL3*			None		—
HSAN 2A	*WNK1*	AR	Childhood or adolescence	None	Varying degrees of progressive loss of pain, temperature, and fine-touch sensation	
HSAN 2B	*FAM134B*			Varying degrees of hyperhidrosis, urinary incontinence, and pupillary abnormalities		—
HSAN 2C	*KIF1A*			None		—
HSAN 2D	*SCN9A*			Urinary and fecal incontinence, reduced sweating		Lack of fungiform lingual papillae, hyposmia, hearing loss, hypogeusia, and bone dysplasia
HSAN 3	*IKAP (ELP-1)*	AR	Newborn	Impaired lacrimation	Impaired pain and temperature	Described in Ashkenazi

				Orthostatic hypotension Paroxysmal hypertension and vomiting episodes with skin blotching Normal or increased sweating	sensation with preserved fine-touch sensation	Jewish ancestry Neonatal hypotonia Respiratory and feeding difficulties Neuropathic joints Optic neuropathy, chronic lung disease, scoliosis, rhabdomyolysis Renal failure Varying degrees of cognitive and behavioral problems
HSAN 4	*NTRK (TRKA)*	AR	Newborn	Anhidrosis Episodic hyperthermia Undetectable plasma norepinephrine	Loss of pain and temperature sensation Preserved fine-touch and vibration sensation	Frequent fractures Neuropathic joints Slow-healing wounds Varying degrees of cognitive and behavioral problems
HSAN 5	*NGFβ*	AR	Newborn	Variable degree of anhidrosis	Loss of pain and temperature sensation Preserved fine-touch and vibration sensation	Frequent fractures Neuropathic joints Tooth loss from gingival disease
HSAN 6	*DST*	AR	Newborn	Impaired lacrimation Labile blood pressure and heart rate Hyperthermia and skin-blotching episodes	Loss of pain and temperature sensation	Described in Ashkenazi Jewish ancestry Neonatal hypotonia Respiratory and feeding difficulties, delayed psychomotor development, neuropathic joints All described patients died before age 3
HSAN 7	*SCN11A*	AD (only a heterozygous de	Newborn	Hyperhidrosis and gastrointestinal	Loss of pain and temperature	Frequent fractures

		novo mutation described)		dysfunction	sensation	Neuropathic joints Slow-healing wounds

From Palma JA, Norcliffe-Kaufmann, Fuente-Mora C, et al: Disorders of the autonomic nervous system: autonomic dysfunction in pediatric practice. In Swaiman KF, Ashwal S, Ferriero DM, et al (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, Table 154-2.

Table 633.3

Other Genetic and Metabolic Disorders Causing Autonomic Dysfunction

DISEASE	AUTONOMIC FEATURES
Dopamine beta-hydroxylase deficiency	Ptosis, hypotension, hypothermia; treatment with droxidopa
Aromatic L-amino acid decarboxylase deficiency	Ptosis, poor feeding, hypotension, hypotonia; treatment with agents to increase neurotransmitter levels
Menkes disease	Orthostatic hypotension; uncertain treatment
Fabry disease	Hypohidrosis or hyperhidrosis, decreased salivation; treatment enzyme replacement
Acute intermittent porphyria (AIP)	Tachycardia, hypotension or hypertension; treatment as for AIP
Porphyria variegata	As for AIP
Hirschsprung disease	Tachycardia, hypertension, hyperthermia; treatment symptomatic (see Table 633.5)
Congenital central hypoventilation syndrome (CCHS)	Constipation, pupillary abnormalities, hypothermia; treatment as per CCHS
Pitt-Hopkins syndrome	As for CCHS
Rett syndrome	Irregular breathing, abnormal heart rate variability, sudden death; treatment as per Rett syndrome
Alexander disease	Constipation, hypothermia, sleep-disordered breathing; treatment as per Alexander disease
Hyperbradykinism	Orthostatic hypotension, purple legs; treatment symptomatic (see Table 633.5)
Panayiotopoulos syndrome	Hypertension, tachycardia, cardiac arrest; treatment symptomatic (see Table 633.5)
Cold-induced sweating syndrome	Unexplained fevers, impaired thermoregulation; treatment symptomatic (see Table 633.5)

Table 633.4

Autonomic Function Testing

The sympathetic and parasympathetic divisions of the autonomic nervous system are involved in all tests of autonomic function

CARDIAC PARASYMPATHETIC NERVOUS SYSTEM FUNCTION

Heart rate variability with deep respiration (respiratory sinus arrhythmia); time-domain and frequency-domain assessments
Heart rate response to the Valsalva maneuver

Heart rate response to standing

SYMPATHETIC ADRENERGIC FUNCTION

Blood pressure response to upright posture (standing or tilt table)
Blood pressure response to Valsalva maneuver
Microneurography

SYMPATHETIC CHOLINERGIC FUNCTION

Thermoregulatory sweat testing
Quantitative sudomotor-axon reflex test
Sweat imprint methods
Sympathetic skin response

From Freeman R: Autonomic peripheral neuropathy, Lancet 365:1259-1270, 2005.

Table 633.5

Symptomatic Management of Autonomic Dysfunction

PROBLEM	TREATMENT
Orthostatic hypotension	Volume and salt supplements Adequate hydration Pressure garments Fluorohydrocortisone (mineralocorticoid) Midodrine (α agonist)
Aspiration pneumonitis	Gastrostomy with/without fundoplication
Dysautonomic crises	Clonidine, diazepam, carbidopa
Gastroparesis	Prokinetic agents (metoclopramide, domperidone, erythromycin)
Hypomotility	Fiber, laxatives
Urinary dysfunction	Timed voiding; bladder catheterization
Hyperhidrosis	Anticholinergic agents (glycopyrrolate, propantheline) Intracutaneous botulism toxin
Anhidrosis	Cool baths, cooling vests

633.1

Familial Dysautonomia

Monique M. Ryan

Familial **dysautonomia** (Riley-Day syndrome) is an autosomal recessive disorder most commonly seen in Eastern European Jews, in whom its incidence is 1 in 10,000-20,000. It is very rare in other ethnic groups but is, overall, the most common HSAN. The defective gene, *IKBKAP* (IκB kinase–associated protein), is at the 9q31-q33 locus. This and other autonomic neuropathies are often regarded as **neurocristopathies** because the abnormal tissues are largely derived from the neural crest. Mutations in *IKBKAP* affect the development and maturation of peripheral nerves.

Pathology

This disease of the peripheral nerves is characterized pathologically by a reduced number of the small unmyelinated nerve fibers that carry pain, temperature, and taste sensation and mediate autonomic functions, including baroreceptors. There is also the loss of small and large myelinated fibers from peripheral nerves. The dorsal root ganglia are small, with reduced neurons. The number of parasympathetic ganglion cells in the myenteric plexuses is reduced. Optic nerve involvement, with predominant loss of papillomacular nerve fibers, may impair visual acuity. Fungiform and circumvallate papillae (taste buds) are absent or reduced in the tongue (Fig. 633.1).

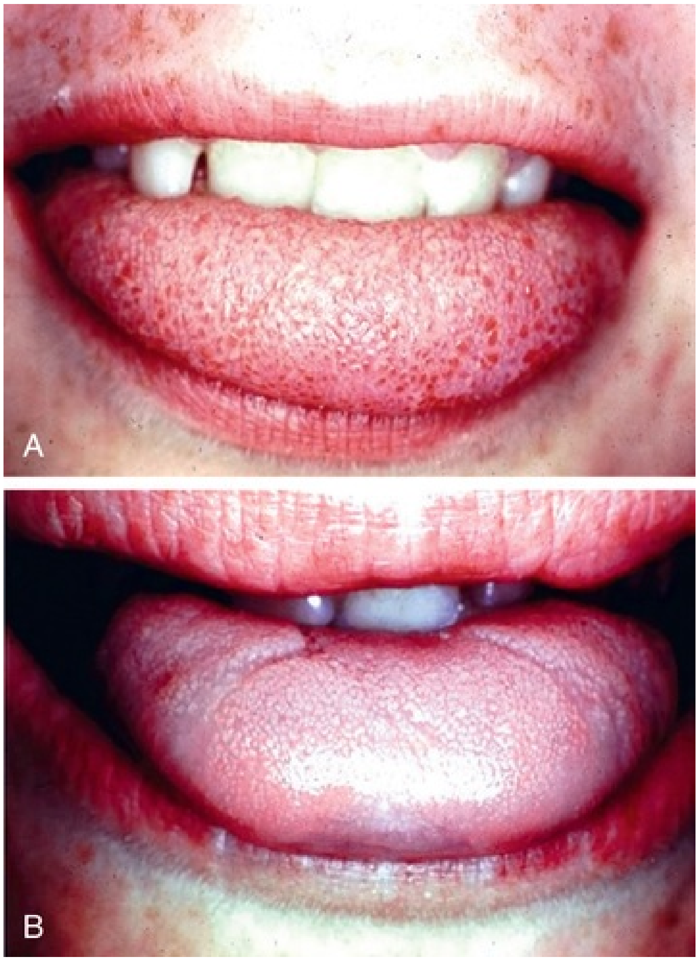

FIG. 633.1 **A,** Normal tongue with fungiform papillae present on the tip. **B,** Dysautonomic tongue. Note the absence of the highly vascularized fungiform papillae from the tongue tip, which gives the appearance of a smooth tongue. (From Axelrod FB, Gold-von Simson G: Hereditary sensory and autonomic neuropathies: types II, III, and IV, Orphanet J Rare Dis 2:39, 2007, Fig. 4.)

Clinical Manifestations

Clinical manifestations are highly variable. Affected infants and children may be hypotonic, with motor delay and feeding difficulties. Breath-holding spells, followed by syncope, are common in the first 5 yr of life. Responses to hypoxia and hypercapnia are reduced. Recurrent pneumonia often leads to chronic lung disease. Affected persons may experience profound postural hypotension without compensatory tachycardia but they can also develop extreme hypertension and tachycardia when under emotional and/or physical stress.

Temperature dysregulation is reflected by the development of hyperthermia or hypothermia with infections and environmental stressors.

As affected children become older, insensitivity to pain becomes evident and traumatic injuries are frequent. Pain and temperature sensation is reduced, although to a lesser degree than in other HSANs (see Table 633.2). **Alacrima** (absence of tears with emotional crying) is a universal finding. Corneal ulcerations result from decreased corneal sensation and xerophthalmia. Newly erupting teeth cause tongue ulcerations and, in older children, dental trauma; soft tissue mutilation may be prominent. Walking is delayed and appears ataxic, probably as a result of a combination of poor sensory feedback from muscle spindles, vestibular nerve dysfunction, and cerebellar involvement. The deep tendon reflexes are absent. Scoliosis or kyphosis, or both, is a serious complication in most patients and is usually progressive. There is an increased incidence of urinary incontinence. Bradycardia and other cardiac arrhythmias can occur; some patients require a cardiac pacemaker.

Approximately 40% of patients experience seizures; some are associated with hypoxia during breath-holding and some with fever, but some have no obvious precipitants. Emotional lability and learning disabilities are common in school-age children with familial dysautonomia. Puberty is often delayed, especially in girls. Short stature can occur, but growth velocity can be accelerated by treatment with growth hormone.

After 3 yr of age, **dysautonomic crises** begin, usually with attacks of cyclic vomiting lasting 24-72 hr or even longer. These repeated episodes of retching and vomiting are associated with tachycardia, hypertension, profuse sweating, blotching of the skin, apprehension, and irritability. Prominent gastric distention can occur, causing abdominal pain and even respiratory distress. Hematemesis can complicate pernicious vomiting.

Laboratory Findings

Electrocardiography discloses prolonged corrected QT intervals with lack of appropriate shortening with exercise, reflecting aberrant autonomic regulation of cardiac conduction. Chest radiographs may show atelectasis and pulmonary changes resembling cystic fibrosis. The urinary vanillylmandelic acid level is decreased, and the homovanillic acid level is increased. The plasma level of dopamine β-hydroxylase (the enzyme that converts dopamine to epinephrine) is diminished. Sural nerve biopsy shows loss of unmyelinated fibers, but nerve conduction studies and electromyography are often normal, because they reflect only the function of large myelinated fibers. Electroencephalography is useful for evaluating seizures.

Diagnosis

All HSANs are characterized by failure of the intradermal injection of histamine phosphate to elicit a normal axon flare response. Because the skin of a normal infant reacts more intensely to histamine, a 1 : 10,000 dilution should be used. Instillation of 2.5% methacholine into the conjunctival sac produces miosis in patients with familial dysautonomia but no detectable effect on a normal pupil; this is a nonspecific sign of parasympathetic denervation from any cause. Methacholine is applied to only one eye in this test, with the other eye serving as a control; the pupils are compared at 5-min intervals for 20 min. The combination of alacrima, absent fungiform papillae, decreased patellar reflexes, and an abnormal histamine test with Ashkenazi Jewish lineage is diagnostic. Because of variable expression and potential overlap with other HSANs, genetic testing should be used to confirm the diagnosis.

Treatment

Symptomatic treatment includes special attention to the respiratory and gastrointestinal systems to prevent aspiration and malnutrition, methylcellulose eye drops or topical ocular lubricants to replace tears and prevent corneal ulceration, orthopedic management of scoliosis and joint problems, and anticonvulsants where required. Gastrostomy, with or without fundoplication, should be considered in those with recurrent aspiration. Hyperpyrexia from anhidrosis can be life-threatening and should be treated aggressively. Chronic lung disease should be treated symptomatically. Patients should be warned that their insensitivity to hypoxia may place them at risk of complications with underwater swimming, air travel, and travel to high altitudes. Protection from injuries is important because of the lack of pain as a protective mechanism. Some children may require a cardiac pacemaker.

Dysautonomic crises respond poorly to standard antiemetics and are usually treated with centrally acting medications such as diazepam and clonidine. Carbidopa, a DOPA decarboxylase inhibitor, is also effective in dysautonomic crises.

Prognosis

Sixty percent of patients die in childhood before the age of 20 yr, usually of chronic pulmonary failure or aspiration. Older patients often develop chronic renal disease related to vasomotor instability and hypertension. The prognosis is improved by treatment in a center familiar with this disease. Newer measures to better control vasomotor stability and vomiting improve the quality of life, but their effect on longevity is not yet known.

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633.2

Other Autonomic Neuropathies

Monique M. Ryan

Congenital Insensitivity to Pain and Anhidrosis

Congenital insensitivity to **pain** and **anhidrosis,** or HSAN type IV, is an autosomal recessive disorder with an onset in infancy (see Table 633.2). Affected children usually present with episodes of overheating related to warm environmental temperatures, because they have absent or reduced sweating. Infantile hypotonia improves with growth. Frequent burns and traumatic injuries result from the lack of pain perception, which also causes poor healing of fractures and a tendency for development of chronic osteomyelitis and Charcot joints. Temperature sensation is also markedly impaired. Anhidrosis causes a thick, calloused appearance of the skin, with lichenification of the palms and chronic dystrophic changes in the nails. There is no alacrima, but corneal ulceration may result from hypoesthesia. Almost all patients have behavioral and cognitive deficits. Nerve biopsy reveals an almost total absence of unmyelinated nerve fibers, which usually convey pain, temperature, and autonomic sensation. The diagnosis is confirmed by targeted genetic testing.

Allgrove Syndrome (Triple a Syndrome)

Allgrove syndrome is a rare autonomic neuropathy characterized by early-onset alacrima, feeding difficulties and achalasia, autonomic dysfunction with orthostatic hypotension, altered heart rate variability, hyperreflexia, ataxia, muscle weakness, sensorimotor polyneuropathy, and adrenocorticotropic hormone–resistant adrenal insufficiency, which develops in the first decade. The gene *AAAS* (alacrima-achalasia-adrenal insufficiency neurologic disorder) is located on chromosome 12q13.

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CHAPTER 634

Guillain-Barré Syndrome

Monique M. Ryan

Guillain-Barré syndrome (GBS) is an autoimmune disorder that is thought to be a **postinfectious polyneuropathy,** involving mainly motor but also sensory and sometimes autonomic nerves. This syndrome affects people of all ages and is not hereditary. Most patients in the United States and Europe have a demyelinating neuropathy, but primarily axonal degeneration is apparent in some forms of GBS, seen mainly in China, Mexico, Bangladesh, and Japan.

Clinical Manifestations

The onset of weakness usually follows a nonspecific gastrointestinal or respiratory infection by approximately 10 days. The original infection might have caused only gastrointestinal (especially *Campylobacter jejuni,* but also *Helicobacter pylori*), respiratory tract (especially *Mycoplasma pneumoniae*), or systemic (Zika virus) symptoms. Consumption of undercooked poultry, unpasteurized milk, and contaminated water are the main sources of gastrointestinal infections. West Nile virus also can mimic Guillain-Barré–like syndrome, but more often causes a motor neuron disease similar to poliomyelitis. GBS may follow administration of vaccines against rabies, influenza, and conjugated meningococcal vaccine, particularly serogroup C. Other infectious precursors of GBS include mononucleosis, Lyme disease, cytomegalovirus, and the Zika virus.

Initial symptoms include numbness and paresthesia, followed by weakness (Fig. 634.1). Radicular back pain and myalgia are common in the initial stages; affected children can be very irritable. Weakness usually begins in the lower extremities and progressively involves the trunk, the upper limbs, and finally the bulbar muscles, but weakness is sometimes proximally prominent. Extraocular muscle involvement is rare, but many patients develop facial weakness. In most patients, weakness is essentially symmetric. Weakness progresses over days or weeks, the clinical nadir occurring in less than 4 wk. Approximately 60% of children lose the ability to walk at some point in their illness; a small proportion progress to flaccid tetraplegia. The maximal severity of weakness is reached by 4 wk after onset. The differential diagnosis of GBS is shown in Table 634.1 .

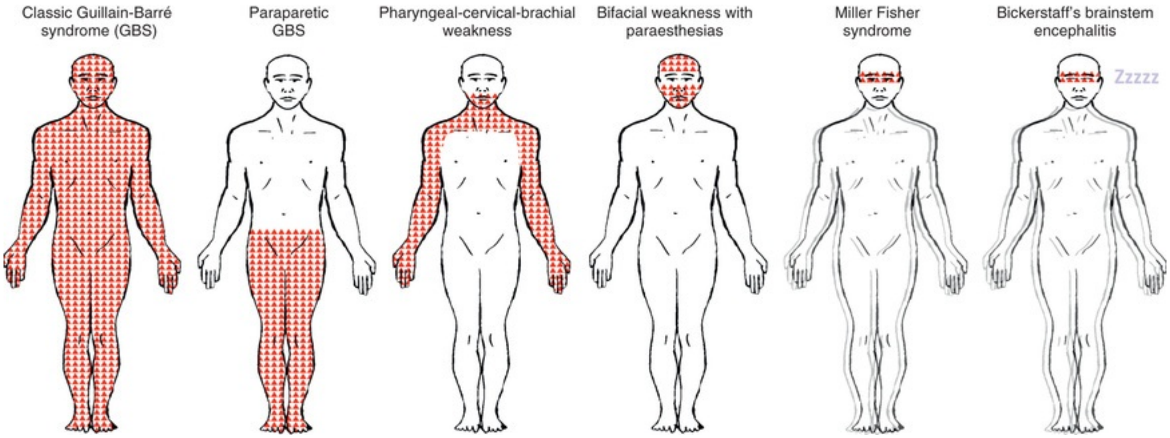
Classic Guillain-Barré syndrome (GBS)
Paraparetic GBS
Pharyngeal-cervical-brachial weakness
Bifacial weakness with paraesthesias
Miller Fisher syndrome
Bickerstaff's brainstem encephalitis
Zzzzz

FIG. 634.1 Patterns of weakness in Guillain-Barré syndrome (GBS) and Miller Fisher syndrome and their subtypes. GBS and Miller Fisher syndrome and their subtypes form a continuum of discrete and overlapping syndromes. Shaded areas indicate patterns of weakness. The *double outline (blurring the figures)* indicates the presence of ataxia. *Zzzzz* indicates hypersomnolence. The pattern of weakness for each subtype is as follows: Classic GBS, tetraparesis with or without motor cranial nerve involvement; paraparetic GBS, lower limbs; pharyngeal-cervical-brachial weakness, bulbar, neck, and upper limbs; bifacial weakness with paresthesias, facial; Miller Fisher syndrome, external ophthalmoplegia; Bickerstaff brainstem encephalitis, external ophthalmoplegia. Facial weakness and motor cranial nerve involvement are more frequent in demyelinating-type classic GBS (acute inflammatory demyelinating polyradiculoneuropathy) than in axonal-type GBS (acute motor axonal neuropathy). In Miller Fisher syndrome, there is ataxia, and in its central nervous system subtype, Bickerstaff brainstem encephalitis, there is additional hypersomnolence. (From Wakerley BR, Yuki N: Mimics and chameleons in Guillain-Barré and Miller Fisher syndromes, Pract Neurol 15:90-99, 2015, Fig. 1.)

Table 634.1

Differential Diagnosis of Childhood Guillain-Barré Syndrome

SPINAL CORD LESIONS
Acute transverse myelitis
Epidural abscess
Tumors
Poliomyelitis
Enteroviruses
Acute flaccid myelitis
Hopkins syndrome
Vascular malformations
Cord infarction
Fibrocartilaginous embolism
Cord compression from tumors
Acute disseminated encephalomyelitis
Bickerstaff brainstem encephalitis
Anterior spinal artery syndrome
PERIPHERAL NEUROPATHIES
Toxic
• Vincristine
• Thalidomide
• Glue sniffing
• Heavy metal: gold, arsenic, lead, thallium, mercury
• Organophosphate pesticides
• Fluoroquinolones
• Isoniazid
• Dapsone
• Nitrous oxide
• Snake venom
• Puffer fish
• Buckthorn toxin
• Carbon monoxide
Infections
• HIV
• Diphtheria
• West Nile virus
• Cytomegalovirus (radiculitis)
• Leprosy
• Lyme disease
• Zika virus
Inborn errors of metabolism/hereditary
• Leigh disease
• Tangier disease
• Porphyria
• Fabry disease
• Tyrosinemia
• Mitochondrial neuropathies
Critical illness: polyneuropathy/myopathy
Eosinophilic granulomatosis with polyangiitis
Granulomatosis with polyangiitis
Sarcoidosis
Systemic lupus erythematosus
Microscopic polyangiitis
Other vasculitides

Nutritional deficiencies
• Vitamin B_1 , B_6 , B_{12} , E
• Riboflavin
NEUROMUSCULAR JUNCTION DISORDERS
Tick paralysis
Myasthenia gravis
Acute flaccid myeltis
Botulism
Hypercalcemia
MYOPATHIES
Periodic paralyses (hypokalemic or hyperkalemic)
Dermatomyositis
Critical illness myopathy/polyneuropathy
OTHER
Conversion disorder
Chronic inflammatory demyelinating polyneuritis (acute onset)

Bulbar involvement occurs in about 50% of cases and can result in respiratory insufficiency (see Fig. 634.1). Dysphagia and facial weakness can be signs of impending respiratory failure, interfere with saliva control and swallowing, and increase the risk of aspiration. Vocal cord paralysis may cause dyspnea or a hoarse voice. Severe bulbar and respiratory muscle involvement can lead to death if GBS is not recognized and treated.

The **autonomic nervous system** is also involved in some cases. Lability of blood pressure and heart rate, postural hypotension, episodes of profound bradycardia or tachycardia, and occasional asystole occur, more commonly in younger patients or those with severe weakness. Cardiovascular monitoring is important, especially early in the disease course, when rapid progression of weakness, respiratory insufficiency, and autonomic instability can be life-threatening. The tendon reflexes are lost in GBS, usually early in the course, but are sometimes preserved until later; areflexia is more common but hyporeflexia may be seen. Of affected children, 10% retain their reflexes throughout. This variability can cause diagnostic confusion.

Subtypes of GBS include an acute inflammatory demyelinating polyneuropathy and an acute motor axonal neuropathy; these are distinguished by findings on nerve conduction studies and an associated pattern of antiganglioside antibodies (Table 634.2). Localized forms of GBS also occur and include a pattern of facial diplegia with paresthesias and a pattern of pharyngeal-cervical-brachial weakness. **Miller-Fisher syndrome (MFS)** is an uncommon GBS variant associated with acute external (and occasionally internal) ophthalmoplegia, ataxia, and areflexia. The 6th cranial nerve is most often involved in MFS. Although areflexia is seen in MFS, patients have no or only very mild lower extremity weakness, compared with GBS. Distal paresthesias are common in MFS. Urinary incontinence or retention is a complication in approximately 20% of cases but is usually transient. MFS overlaps clinically with Bickerstaff brainstem encephalitis.

Table 634.2

Guillain-Barré Syndrome Subtypes and Rare Variants Described in Childhood

	RELATIVE FREQUENCY	ASSOCIATED IGG-ANTIGANGLIOSIDE ANTIBODIES
SUBTYPES		
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Common (more in Western world)	None/GM1 (~10%)
Acute motor axonal neuropathy (AMAN)	Common (more in developing countries)	GM1, GD1a
Acute motor and sensory axonal neuropathy (AMSAN)	Rare	GM1, GM1b, GD1a
Miller Fisher syndrome (MFS/FS)	Uncommon	GQ1b, GT1a
VARIANTS		
Bickerstaff brainstem encephalitis (BBE)	Rare	GQ1b, GT1a
Polyneuritis cranialis (PC)	Rare	GQ1b, GT1a
Pharyngeal-cervical-brachial variant (PCB)	Rare	GT1a > GQ1b ≫ GD1a
Acute sensory neuropathy	Very rare	GQ1b, GT1a
Acute pandysautonomia	Very rare	
Acute ophthalmoparesis	Very rare	GQ1b, GT1a
Paraparesis	Very rare	

From Rabie M, Ashwal S, Nevo Y: Inflammatory neuropathies. In Swaiman KF, Ashwal S, Ferriero DM, et al (eds): Swaiman's pediatric neurology, 6/e, Elsevier, 2018, Philadelphia, Table 143-3.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP, sometimes called *chronic inflammatory relapsing polyneuritis*) is a more chronic, slowly progressive, acquired inflammatory neuropathy with some clinical overlap with GBS. Symptoms such as weakness and paresthesias develop over more than 4-6 wk, recur intermittently (relapsing), or progress slowly over periods of months to years. Weakness is generally both proximal and distal, and variably severe. Hyporeflexia or areflexia is almost universal. Motor deficits occur in 94% of cases and sensory paresthesias in 64%, but cranial nerve and autonomic involvement is uncommon. The cerebrospinal fluid (CSF) shows no pleocytosis, but the CSF protein is almost always elevated. Nerve conduction studies show variable slowing of nerve conduction; where required, sural nerve biopsy shows patchy myelin loss and focal inflammatory changes. Acute-onset

CIDP may be difficult to distinguish from GBS; CIDP may also be difficult to distinguish from GBS with treatment-related symptom fluctuations.

Congenital GBS is very rare, manifesting as generalized hypotonia, weakness, and areflexia in an affected neonate, fulfilling all electrophysiologic and CSF criteria and in the absence of maternal neuromuscular disease. Treatment is not always required.

Laboratory Findings and Diagnosis

CSF studies are helpful in diagnosing GBS. The CSF protein is usually elevated to more than twice the upper limit of normal, the glucose level is normal, and there is no pleocytosis; there should be fewer than 10 white blood cells/mm^3 . Bacterial cultures are negative, whereas viral studies rarely isolate specific viruses. The dissociation between high CSF protein and a lack of cellular response (cytoalbuminologic dissociation) in a patient with an acute or subacute polyneuropathy is essentially diagnostic of GBS. These findings may not be apparent in the first week after the onset of symptoms (Table 634.3).

Table 634.3

Diagnostic Criteria for Guillain-Barré Syndrome*

FEATURES NEEDED FOR DIAGNOSIS OF GUILLAIN-BARRÉ SYNDROME IN CLINICAL PRACTICE
• Progressive weakness in legs and arms (sometimes initially only in legs).
• Areflexia (or decreased tendon reflexes) in weak limbs.
ADDITIONAL SYMPTOMS
• Progressive phase lasts days to 4 wk (often 2 wk).
• Relative symmetry.
• Mild sensory symptoms or signs (not present in acute motor axonal neuropathy).
• Cranial nerve involvement, especially bilateral weakness of facial muscles.
• Autonomic dysfunction.
• Pain (common).
FEATURES THAT SHOULD RAISE DOUBT ABOUT THE DIAGNOSIS OF GUILLAIN-BARRÉ SYNDROME
• CSF: increased number of mononuclear cells or polymorphonuclear cells (>50 cells/µL).
• Severe pulmonary dysfunction with little or no limb weakness at onset.
• Severe sensory signs with little or no weakness at onset.
• Bladder or bowel dysfunction at onset.
• Fever at onset.
• Sharp spinal cord sensory level.
• Marked, persistent asymmetry of weakness.
• Persistent bladder or bowel dysfunction.

• Slow progression of weakness and without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or acute-onset chronic inflammatory demyelinating polyneuropathy).
NERVE CONDUCTION STUDIES
• Can be helpful in clinical practice but are generally not required to diagnose Guillain-Barré syndrome.
• Essential for classification of Guillain-Barré syndrome as acute inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy.
• Acute inflammatory demyelinating polyneuropathy: features of demyelination (decreased motor nerve conduction velocity, prolonged distal motor latency, increased F-wave latency, conduction blocks, and temporal dispersion).
• Acute motor axonal neuropathy: no features of demyelination (one demyelinating feature in one nerve, if distal CMAP amplitude is less than 10% LLN, can be found; distal CMAP amplitude less than 80% LLN in at least two nerves. Transient motor nerve conduction block might be present.

[*] Classification of Guillain-Barré syndrome as either acute inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy is not required for the diagnosis of Guillain-Barré syndrome. Whether acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy require different treatments is unknown. The amount of conduction slowing required to define demyelination differs between classification systems.

CSF, cerebrospinal fluid; CMAP, compound muscle action potential; LLN, lower limit of normal.

From Willison HJ, Jacobs BC, van Doorn PA: Guillain-Barré syndrome, Lancet 388:717-727, 2016, Panel 1.

On magnetic resonance imaging (MRI) of the spinal cord in GBS, typical findings include thickening of the cauda equina and intrathecal nerve roots with gadolinium enhancement (Fig. 634.2). Atypical findings should prompt consideration of the alternative diagnoses listed in Table 634.1 . Imaging in CIDP is similar but demonstrates greater enhancement of spinal nerve roots (Fig. 634.3).

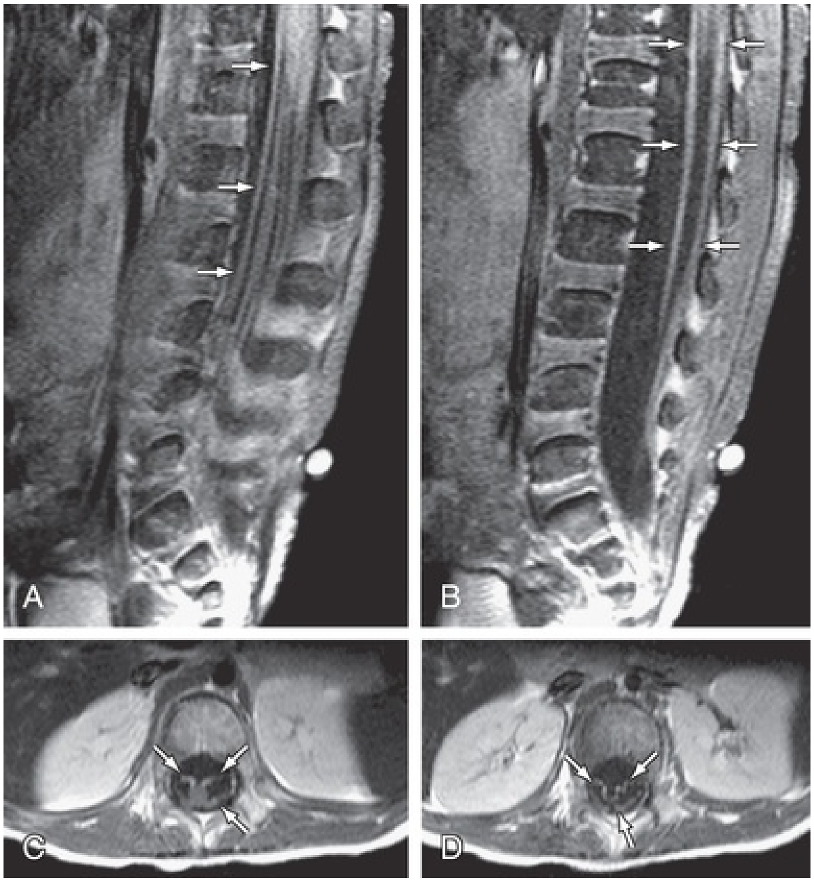

FIG. 634.2 Guillain-Barré syndrome. Sagittal off-midline **(A)** and midline **(B)** postgadolinium T1-weighted fat-saturated images through the lumbar spine of a patient who could not ambulate. **C** and **D,** Axial postcontrast T1-weighted images through the conus medullaris and proximal lumbar nerve roots, respectively. The images show extensive contrast enhancement of nerve roots (*arrows* in **A-D**), in keeping with changes of Guillain-Barré syndrome. (From Slovis TL, editor: Caffey's pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 65-6.)

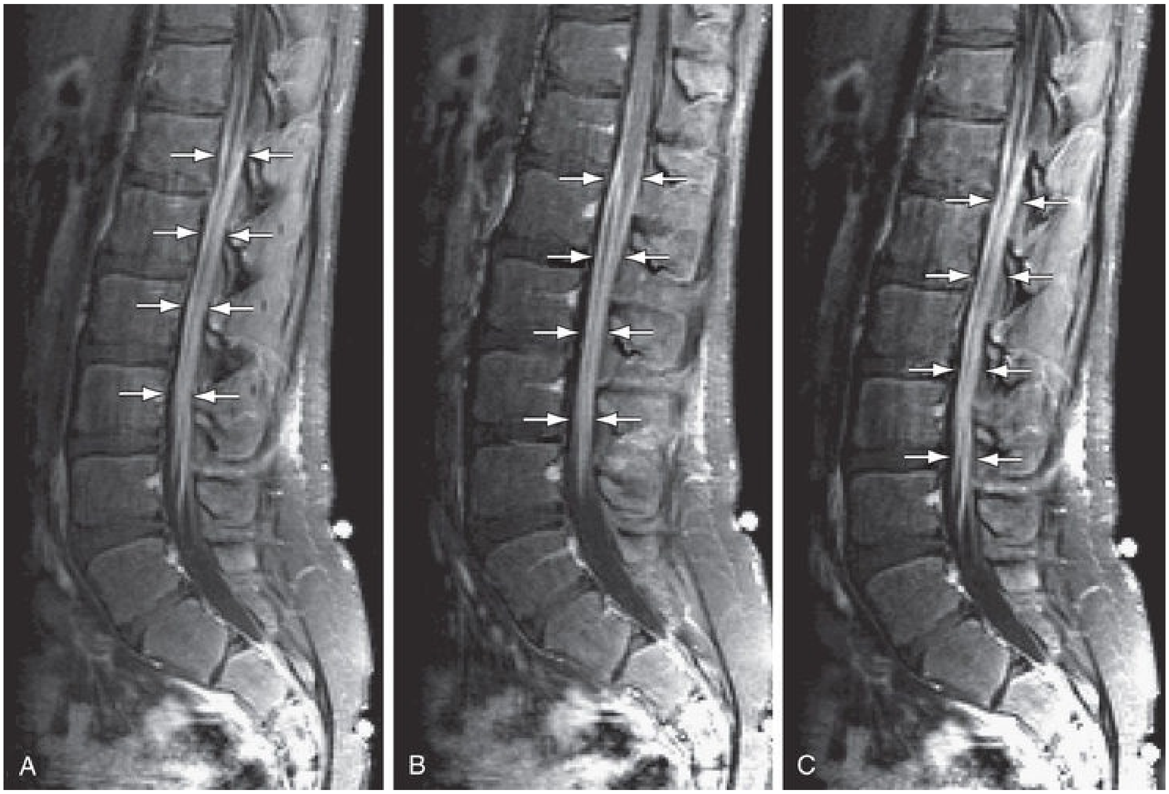

FIG. 634.3 Chronic inflammatory demyelinating polyneuropathy (CIDP) in a 13 yr old boy with peripheral neuropathy and gait disturbance. Sagittal fat-saturated T1-weighted images off the midline to the right **(A),** at the midline **(B),** and off the midline to the left **(C).** (From Slovis TL, editor: Caffey's pediatric diagnostic imaging, ed 11, Philadelphia, 2008, Mosby, Fig. 65-7.)

Nerve conduction studies and electromyography are sensitive to early signs of peripheral nerve inflammation in GBS. Motor and sensory nerve conduction velocities are reduced to a variable extent, reflecting the patchy nature of nerve involvement in this disorder, which is also reflected in the presence of focal conduction block and dispersed responses. Electromyography may show acute denervation of muscle. Serum creatine kinase levels may be mildly elevated or normal. Serum antiganglioside antibodies against GM_1 and GD_1 are sometimes elevated in GBS, particularly in cases with primarily axonal rather than demyelinating neuropathy, suggesting that they might play a role in disease propagation and/or recovery in some cases (see Table 634.1). Sural nerve biopsy shows segmental demyelination, focal inflammation, and Wallerian degeneration, but is almost never required for diagnosis.

Serologic testing for *Campylobacter* and *Helicobacter* infections helps establish causation if results are positive but does not alter treatment. Stool cultures are rarely positive because the infection is self-limited and only occurs for about 3 days, and the neuropathy follows the acute gastroenteritis.

Treatment

Patients in early stages of this acute disease should be admitted to the hospital for observation because the ascending paralysis can rapidly involve respiratory muscles and cause respiratory failure and autonomic instability (Fig. 634.4). The respiratory effort (measured by bedside testing or spirometry) *must* be monitored for changes predicting an onset of hypoventilation and respiratory failure. Patients with milder weakness and slow progression may be treated expectantly, with observation for stabilization and spontaneous remission. Severe or rapidly progressive muscle weakness is treated with intravenous immunoglobulin (IVIG); common protocols include IVIG 0.4 g/kg/day for 5 consecutive days or 1g/kg/day for 2 days. Plasmapheresis and/or immunosuppressive drugs are alternatives if IVIG is ineffective. Steroids are not effective for weakness but may help with pain. Supportive care, such as respiratory support, prevention of pressure sores, nutritional support, pain management, prevention of deep vein thrombosis, and treatment of secondary bacterial infections is important.

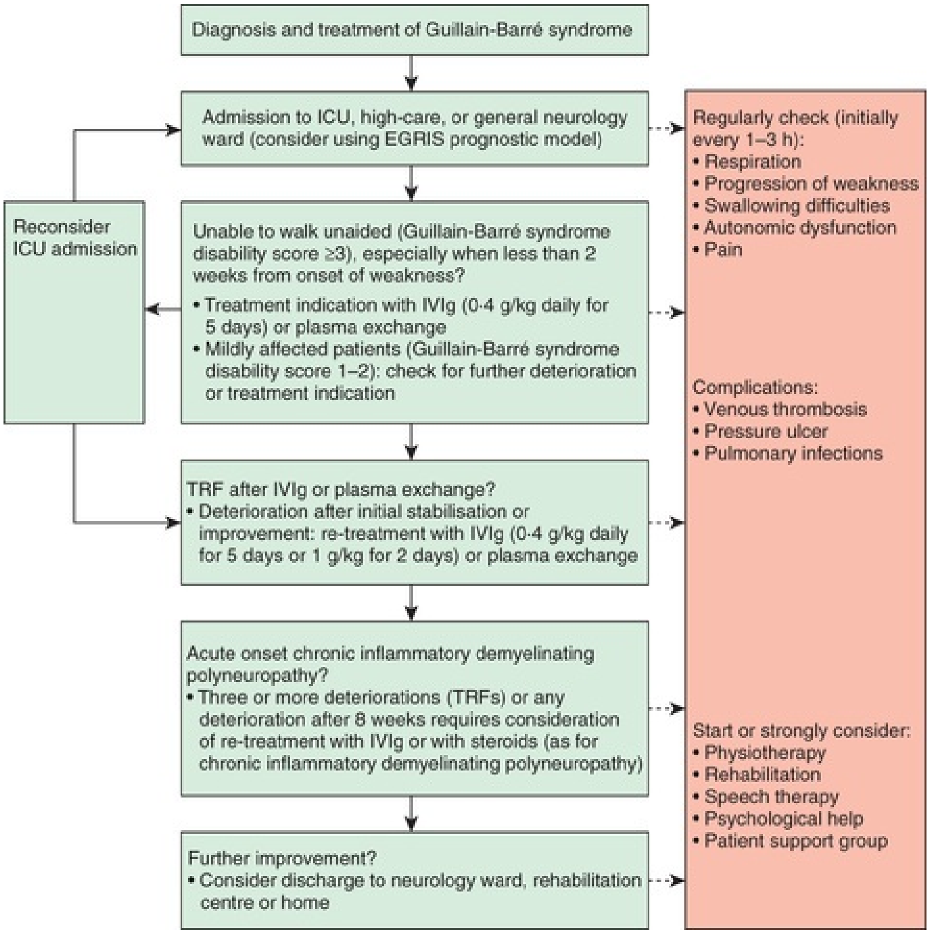
Diagnosis and treatment of Guillain-Barré syndrome
Admission to ICU, high-care, or general neurology ward (consider using EGRIS prognostic model)
Reconsider ICU admission
Unable to walk unaided (Guillain-Barré syndrome disability score ≥3), especially when less than 2 weeks from onset of weakness?
• Treatment indication with IVIg (0·4 g/kg daily for 5 days) or plasma exchange
• Mildly affected patients (Guillain-Barré syndrome disability score 1–2): check for further deterioration or treatment indication
TRF after IVIg or plasma exchange?
• Deterioration after initial stabilisation or improvement: re-treatment with IVIg (0·4 g/kg daily for 5 days or 1 g/kg for 2 days) or plasma exchange
Acute onset chronic inflammatory demyelinating polyneuropathy?
• Three or more deteriorations (TRFs) or any deterioration after 8 weeks requires consideration of re-treatment with IVIg or with steroids (as for chronic inflammatory demyelinating polyneuropathy)
Further improvement?
• Consider discharge to neurology ward, rehabilitation centre or home
Regularly check (initially every 1–3 h):
• Respiration
• Progression of weakness
• Swallowing difficulties
• Autonomic dysfunction
• Pain
Complications:
• Venous thrombosis
• Pressure ulcer
• Pulmonary infections
Start or strongly consider:
• Physiotherapy
• Rehabilitation
• Speech therapy
• Psychological help
• Patient support group

FIG. 634.4 Treatment algorithm for Guillain-Barré syndrome. *Solid lines* are treatment flow; *dashed lines* are issues that need to be considered. ICU, intensive care unit; EGRIS, Erasmus GBS Respiratory Insufficiency Score; IVIG, intravenous immunoglobulin; TRF, treatment-related fluctuation. (From Willison HJ, Jacobs BC, van Doorn PA: Guillain-Barré syndrome, Lancet 388:717-727, 2016, Fig. 3.)

Neuropathic pain in GBS should be treated aggressively, with narcotic analgesics where necessary, and with medications such as gabapentin.

CIDP can be treated with either oral or pulsed steroids or IVIG, with refractory cases often requiring use of other immunosuppressive medications. Children with relapsing or slowly progressive weakness often need months to years of therapy, but most eventually achieve a sustained remission. The outcome is generally good, but some children have permanent deficits.

Prognosis

GBS is usually a monophasic illness; spontaneous recovery begins within 2-3 wk but can take months. Therapy with IVIG hastens recovery but not does alter the long-term outcome. As many as 60% become nonambulant during their illness, but most eventually regain full strength. A minority has some residual weakness, most often of the ankle dorsiflexors. Clinical features predicting a severe course and slow (possibly incomplete) recovery include cranial nerve involvement, the need for ventilatory support, and maximum disability at the time of presentation. Neurophysiologic studies do not necessarily predict the long-term outcome, but children with demyelinating forms of GBS generally recover more quickly than those with axonal forms. The tendon reflexes are usually the last function to recover. Improvement usually follows a gradient opposite the direction of involvement, with bulbar function recovering first and lower extremity weakness resolving last. Bulbar and respiratory muscle involvement can lead to death if the syndrome is not recognized and treated. Fatigue is the most common long-term residuum of GBS. Relapses occur in about 4% of children with GBS and are generally responsive to immunomodulatory treatment.

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CHAPTER 635

Bell Palsy

Monique M. Ryan

Bell palsy is an *acute-onset* peripheral facial nerve palsy that is not associated with any other cranial nerve neuropathies or brainstem dysfunction. It is a common disorder at all ages from infancy through adolescence, usually developing suddenly about 2 wk after a viral infection. Numerous viruses have been linked with Bell palsy (Table 635.1). Active or reactivation of herpes simplex or varicella-zoster virus are probably the most common causes of Bell palsy (Fig. 635.1). In **Ramsay Hunt syndrome** (herpes zoster oticus), an acute facial nerve palsy is associated with painful vesicles in the external auditory canal or auricle. Hereditary forms of Bell palsy are rare. Rarely, Bell palsy occurs in the context of systemic hypertension or type 1 diabetes mellitus. *Unilateral or bilateral facial nerve palsy is often a sign of Lyme disease.*

Table 635.1

Etiologies of Acute Peripheral Facial Palsy

COMMON
Idiopathic
Herpes simplex virus type 1*
Varicella-zoster virus*
Lyme disease
LESS COMMON INFECTIOUS CAUSES
Otitis media ± cholesteatoma
Epstein-Barr virus
Cytomegalovirus
Mumps
Human herpesvirus 6
Intranasal influenza vaccine
Mycoplasma
Toxocara
Rickettsia

AIDS/HIV

OTHER LESS COMMON ASSOCIATIONS

Trauma
Schwannoma of facial nerve
Infiltrative tumor
Aneurysm or vascular malformation
Anomalous narrowing of facial nerve canal
Hypertension
Sjögren syndrome
Diabetes mellitus, type 1
Guillain-Barré syndrome
Sarcoidosis
Kawasaki syndrome
Melkersson-Rosenthal syndrome[†]
Treatment with ribavirin or interferon

[*] Implicated in idiopathic Bell palsy.

[†] Noncaseating granulomas with facial (lips, eyelids) edema, recurrent alternating facial paralysis, family history, migraines, or headaches.

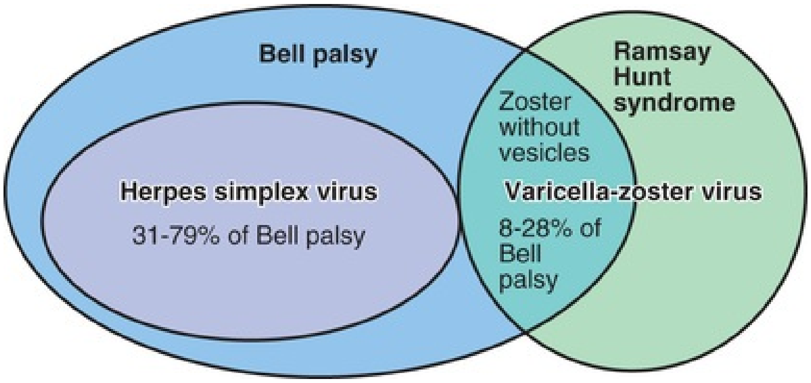
Bell palsy
Ramsay Hunt syndrome
Zoster without vesicles
Herpes simplex virus
31-79% of Bell palsy
Varicella-zoster virus
8-28% of Bell palsy

FIG. 635.1 Involvement of herpes simplex and varicella-zoster viruses in acute facial palsy. (Modified from Hato N, Murakami S, Gyo K: Steroid and antiviral treatment for Bell's palsy, Lancet 371:1818–1820, 2008.)

Clinical Manifestations

Pain behind the ear may precede weakness, which develops acutely. Both the upper and lower portions of the face are paretic, and the corner of the mouth droops. Patients are unable to close the eye on the affected side and are hence at risk of exposure keratitis. Taste on the anterior two thirds of the tongue is lost on the involved side in approximately 50% of cases; this finding helps establish the anatomic limits of the lesion as being proximal or distal to the chorda tympani branch of the facial nerve. Lacrimation is spared. Facial numbness and paresthesias are rare, but when present suggest concomitant involvement of the trigeminal nerve.

Imaging is not required for typical Bell palsy. In children less than 2 yr of age or those in whom there is a suspicion of other pathologies because of atypical findings or chronic or recurrent weakness, magnetic resonance imaging (MRI) of the facial nerve excludes structural lesions causing facial nerve dysfunction. Serology and other viral studies are generally noncontributory. A full blood count should be considered to exclude leukemia in younger patients or those with atypical findings. Lyme antibody testing is indicated in children from endemic areas.

In patients who do not recover within a few weeks, neurophysiologic examination of the facial nerve helps to determine the severity of the facial neuropathy and the likely speed of recovery. In chronic cases, other causes of facial neuropathy should be considered, including hypertension, diabetes, facial nerve tumors such as schwannomas and neurofibromas, infiltration of the facial nerve by leukemic cells or by a rhabdomyosarcoma of the middle ear, brainstem infarcts or tumors, and traumatic injury of the facial nerve.

Treatment

In contrast to adults, the outcome of pediatric Bell palsy is so good that a benefit from treatment with corticosteroids, with or without acyclovir, has not been established, although many centers recommend oral prednisone (1 mg/kg/day for 5-7 days, followed by a 1 wk taper) started within the first 3 days after onset. In adults, treatment often includes steroids *plus* an antiviral agent (valacyclovir, famciclovir). Protection of the cornea with methylcellulose eye drops or an ocular lubricant is especially important at night.

Prognosis

Most children experience a complete spontaneous recovery from Bell palsy within a few weeks from onset. A small proportion (<10%) has some residual facial weakness. Bilateral Bell palsy is rare, but as many as 15% of children experience recurrent episodes of facial weakness.

Nerve regrowth is occasionally misdirected, resulting in **synkinesis,** where activation of one muscle group may produce activation of another inappropriate muscle group; blinking may result in mouth twitching, smiling may cause eye blinking, and lacrimation (crocodile tears) may occur while eating. This complication is much less common in children than adults.

Facial Palsy at Birth

Facial palsy at birth is usually a compression neuropathy from forceps application during delivery and recovers spontaneously in a few days or weeks in most cases. **Congenital absence of the depressor angularis oris muscle** causes facial asymmetry, especially when an infant who is affected cries, and is often associated with other congenital anomalies, especially of the heart. It is not a facial nerve lesion but is a cosmetic defect that does not interfere with feeding. Infants with **Möbius syndrome** can have bilateral or, less commonly, unilateral facial palsy, often with hypoglossal palsies and other neurologic deficits; this syndrome can be genetic or may reflect a developmental anomaly of the brainstem.

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PART XXVIII

Disorders of the Eye

OUTLINE

Chapter 636 Growth and Development of the Eye

Chapter 637 Examination of the Eye

Chapter 638 Abnormalities of Refraction and Accommodation

Chapter 639 Disorders of Vision

Chapter 640 Abnormalities of Pupil and Iris

Chapter 641 Disorders of Eye Movement and Alignment

Chapter 642 Abnormalities of the Lids

Chapter 643 Disorders of the Lacrimal System

Chapter 644 Disorders of the Conjunctiva

Chapter 645 Abnormalities of the Cornea

Chapter 646 Abnormalities of the Lens

Chapter 647 Disorders of the Uveal Tract

Chapter 648 Disorders of the Retina and Vitreous

Chapter 649 Abnormalities of the Optic Nerve

Chapter 650 Childhood Glaucoma

Chapter 651 Orbital Abnormalities

Chapter 652 Orbital Infections

Chapter 653 Injuries to the Eye

CHAPTER 636

Growth and Development of the Eye

Scott E. Olitsky, Justin D. Marsh

The eye of a normal full-term infant at birth is approximately 65% of adult size. Postnatal growth is maximal during the 1st yr, proceeds at a rapid but decelerating rate until the 3rd yr, and continues at a slower rate thereafter until puberty, after which little change occurs. The anterior structures of the eye are relatively large at birth but thereafter grow proportionately less than the posterior structures. This results in a progressive change in the shape of the globe such that it becomes more spherical.

In an infant, the sclera is thin and translucent, with a bluish tinge. The cornea is relatively large in newborns (averaging 10 mm) and attains adult size (nearly 12 mm) by the age of 2 yr or earlier. Its curvature tends to flatten with age, resulting in a progressive change in the refractive properties of the eye. A normal cornea is perfectly clear. In infants born prematurely, however, the cornea may have a transient opalescent haze. The anterior chamber in a newborn appears shallow, and the angle structures, important in the maintenance of normal intraocular pressure, must undergo further differentiation after birth. The iris, typically light blue or gray at birth in white individuals, undergoes progressive change of color as the pigmentation of the stroma increases in the 1st 6 mo of life. The pupils of a newborn infant tend to be small and are often difficult to dilate. This is the result of an immature iris dilator muscle. Remnants of the **pupillary membrane** (anterior vascular capsule) are often evident on ophthalmoscopic examination, appearing as cobweb-like lines crossing the pupillary aperture, especially in preterm infants.

The lens of a newborn infant is more spherical than that of an adult; its greater refractive power helps to compensate for the relative shortness of the young eye. The lens continues to grow throughout life, as new peripheral fibers continually push older fibers toward the center of the lens. With age, the lens becomes progressively denser and more resistant to the change of shape that occurs during accommodation.

The fundus of a newborn's eye is less pigmented than that of an adult; the choroidal vascular pattern is highly visible, and the retinal pigment pattern often has a fine peppery or mottled appearance. In some darkly pigmented infants, the fundus has a gray or opalescent sheen. In a newborn, the macular landmarks, particularly the foveal light reflex, are less-well defined due to incomplete maturation of the retinal layers. The peripheral retina appears pale or grayish, and the peripheral retinal vasculature is immature, especially in premature infants. The optic nerve head color varies from pink to slightly pale, sometimes grayish. Within 4-6 mo, the appearance of the fundus approximates that of the mature eye.

Superficial retinal hemorrhages may be observed in many newborn infants. These are usually absorbed promptly and rarely leave any permanent effect. The majority of birth-related retinal hemorrhages resolve within 2 wk, with complete resolution of all such hemorrhages within 4-6 wk of birth. Conjunctival hemorrhages also may occur at birth and are resorbed spontaneously without consequence.

Remnants of the primitive **hyaloid vascular system** may appear as small tufts or wormlike structures projecting from the disc (Bergmeister papilla) or as a fine strand traversing the vitreous; in some cases, only a small dot (Mittendorf dot) remains on the posterior aspect of the lens capsule.

An infant's eye is somewhat **hyperopic** (farsighted). The general trend is for hyperopia to increase from birth until age 7 yr. Thereafter, the level of hyperopia tends to decrease rapidly until age 14 yr. Elimination of the hyperopic state may occur during this time. If the process continues, a child may become **myopic** (nearsighted). A slower continuation of the decrease in hyperopia, or increase in myopia, continues into the 3rd decade of life. The refractive state at any time in life depends on the net effect of many factors: the size of the eye, the state of the lens, and the curvature of the cornea.

Newborn infants tend to keep their eyes closed much of the time, but normal newborns can see, respond to changes in illumination, and fixate points of contrast. The visual acuity in newborns is estimated to be approximately 20/400. This poor vision is a result of the immature, multilayered foveal anatomy. Retinal development continues postnatally, maturing completely during the 1st few yr of life. One of the earliest responses to a formed visual stimulus is an infant's regard for the mother's face, evident especially during feeding. By 2 wk of age, an infant shows more sustained interest in large objects, and by 8-10 wk of age, a normal infant can follow an object through an arc of 180 degrees. The acuity improves rapidly and may reach 20/30-20/20 by the age of 2-3 yr.

Many normal infants may have imperfect coordination of the eye movements and alignment during the early days and weeks, but proper coordination should be achieved by 3-6 mo, usually sooner. Persistent deviation of an eye in an infant at 6 mo of age requires evaluation.

Tears often are not present with crying until after 1-3 mo. Preterm infants have reduced reflex and basal tear secretion, which may allow topically applied medications to become concentrated and lead to rapid drying of their corneas.

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CHAPTER 637

Examination of the Eye

Scott E. Olitsky, Justin D. Marsh

The eye exam is a routine part of pediatric well child care, which begins in the newborn period. The primary care physician plays a critical role in the detection of both obvious and insidious, asymptomatic eye diseases. School and community screening programs can also be effective in identifying problems at an early age. The American Academy of Ophthalmology recommends preschool vision screening during well child visits as a means of reducing preventable visual loss (Table 637.1). Referrals to an ophthalmologist should be made when a significant ocular abnormality or visual acuity deficit is suspected. An ophthalmologist should also examine high-risk children, such as those with a family history of eye disease, or various systemic or genetic disorders, such as Down syndrome or juvenile idiopathic arthritis.

Table 637.1

Vision Screening Guidelines

FUNCTION	RECOMMENDED TESTS	REFERRAL CRITERIA	COMMENTS
AGES 3-5 YR			
Distance visual acuity	Snellen letters Snellen numbers Tumbling E test HOTV test (contains only these 4 letters)	<4 of 6 correct on 20-ft line with either eye tested at 10 ft monocularly (i.e., <10/20 or 20/40), or Two-line difference between eyes, even within the passing range (i.e., 10/12.5 and	Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages 6 yr and older

		10/20 or 20/25 and 20/40)	
	Picture tests		Testing distance of 3 m (10 ft) is recommended for all visual acuity tests
	-Allen figures		
	-Lea symbols		A line of figures is preferred over a single figure.
			The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to eye; the examiner must ensure that it is not possible to peek with the nontested eye
Ocular alignment	Cross cover test at 3 m (10 ft)	Any eye movement	
	or		
	Random dot E stereo test at 40 cm (630 sec of arc)	<4 of 6 correct	
	Simultaneous red reflex test (Bruckner test)	Any asymmetry of pupil color, size, brightness	Direct ophthalmoscope used to view both red reflexes simultaneously in a darkened room from 2-3 ft away; detects asymmetric refractive errors as well
Ocular media clarity (cataracts, tumors, etc.)	Red reflex	White pupil, dark spots, absent reflex	Direct ophthalmoscope, darkened room. View eyes separately at 12-18 inches; white reflex indicates possible retinoblastoma
AGES 6 YR AND OLDER			
Distance visual acuity	Snellen letters Snellen numbers Tumbling E test HOTV test	<4 of 6 correct on 4.5 m (15 ft) line with either eye tested at 3 m (10 ft) monocularly (i.e., <10/15 or 20/30)	Tests are listed in decreasing order of cognitive difficulty; the highest test that the child is capable of performing should be used; in general, the tumbling E or the HOTV test should be used for ages 3-5 yr and Snellen letters or numbers for ages 6 yr and older
	Picture tests	Two-line difference between eyes, even within the passing range (i.e., 10/10 and 10/15 or 20/20 and 20/30)	Testing distance of 3 m (10 ft) is recommended for all visual acuity tests
	-Allen figures		
	-Lea symbols		A line of figures is preferred over a single figure
			The nontested eye should be covered by an occluder held by the examiner or by an adhesive occluder patch applied to the eye; the examiner must ensure that it is not possible to peek with the nontested eye
Ocular alignment	Cross cover test at 3 m (10 ft)	Any eye movement	
	or		
	Random dot E stereo test at 40 cm (630 sec of arc)	<4 of 6 correct	

The basic eye exam, whether performed by a pediatrician or an ophthalmologist, must include visual acuity and visual field testing, assessment of pupils, ocular motility and alignment, a general external/facial examination, and finally, examination of the media and fundus via ophthalmoscopy.

The periodicity for visual assessment should occur beginning in the newborn to 6 mo age group and continue at ages 6-12 mo, 1-3 yr, 4-5 yr, and 6 yr and older. The assessments include an ocular history, inspection of the lids and eyes, red reflex testing, pupil examination, ocular motility testing, and assessment of visual acuity.

When indicated, biomicroscopy (slit-lamp examination), cycloplegic refraction, and tonometry are performed by an ophthalmologist. Special diagnostic procedures, such as ultrasound, fluorescein angiography, electroretinography, or visual evoked response testing, are also indicated for specific conditions.

Visual Acuity

There are various means of assessing visual acuity in the pediatric population. A child's age and ability to cooperate, as well as clinician preference, all factor in deciding which test to use. The most common visual acuity test in infants is an assessment of their ability to fixate and follow a target. If appropriate targets are used, this response can be demonstrated by approximately 6 wk of age.

The test begins by seating the child comfortably in the caretaker's lap. The object of visual interest, usually a bright-colored toy or target with lights, is slowly moved to the right and to the left. The examiner observes whether the infant's eyes turn toward the object and follow its movements. The examiner can use a thumb or palm of the hand to occlude one of the infant's eyes in order to test each eye separately. Although a sound-producing object might compromise the purity of the visual stimulus, in practice, toys that squeak or rattle heighten an infant's awareness and interest in the test.

The human face is a better target than test objects. The examiner can exploit this by moving his or her face slowly in front of the infant's face. If the appropriate following movements are not elicited, the test should be repeated with the caretaker's face as the test stimulus. It should be remembered that even children with poor vision can follow a large object without apparent difficulty, especially if only 1 eye is affected.

An objective measurement of visual acuity is usually possible when children reach the age of 2.5-3 yr. Children this age are tested using a schematic picture or other illiterate eye chart. Examples include Allen or Lea symbols and tumbling E. Each eye should be tested separately. It is essential to prevent peeking. The examiner should hold the occluder in place and observe the child throughout the test. The child should be reassured and encouraged throughout the test, as many children are intimidated by the process and fear a “bad grade” or punishment for errors. In addition, many children may be too timid to verbally identify figures being tested and may be more willing to participate if given the opportunity to match the presented symbols to identical symbols provided on a handout during the exam.

The tumbling E test, in which the child indicates which direction the E is facing, is the most widely used visual acuity test for preschool children. Right–left presentations are more confusing than up–down presentations. With pretest practice, the test can be performed by most children ages 3-4 yr.

An adult-type **Snellen acuity chart** can be used at 5-6 yr of age if the child knows letters. A visual acuity of 20/40 is generally accepted as normal for 3 yr old children. At 4 yr of age, 20/30 is acceptable. By 5 or 6 yr of age, most children attain 20/20 vision.

Optokinetic nystagmus (the response to a sequence of moving targets; “railroad” nystagmus) can also be used to assess vision; this can be calibrated by targets of various sizes (stripes or dots) or by a rotating drum (known as an OKN drum) at specified distances.

The visual evoked response, an electrophysiologic method of evaluating the response to light and special visual stimuli, such as calibrated stripes or a checkerboard pattern, can also be used to study visual function in selected cases.

Preferential looking tests are used for evaluating vision in infants and children who cannot respond verbally to standard acuity tests. This is a behavioral technique based on the observation that, given a choice, an infant prefers to look at patterned rather than unpatterned stimuli. Because these tests require the presence of a skilled examiner, their use is often limited to research protocols involving preverbal children.

Visual Field Assessment

Like visual acuity testing, visual field assessment must be geared to a child's age and abilities. Formal visual field examination (perimetry and scotometry) can often be accomplished in school-age children. In younger children and in the pediatrician's office, the examiner must often rely on confrontation techniques and finger counting in quadrants of the visual field. In many such children, only testing by attraction can be accomplished; the examiner observes a child's response to familiar objects brought into each of the 4 quadrants of the visual field of each eye in turn. The child's bottle, a favorite toy, and lollipops are particularly effective attention-getting items. These gross methods can often detect diagnostically significant field changes such as the bitemporal hemianopia of a chiasmal lesion or the homonymous hemianopia of a cerebral lesion.

Color Vision Testing

Color vision testing can be accomplished when a child is able to name or trace the test figures, which include numbers, shapes, or other symbols. The common color vision testing tools include Ishihara color plates or Hardy Rand Littler. Color vision testing is not frequently necessary in young children; however, parents may request testing, particularly if their child seems to be slow in learning colors or if there is a family history of color vision deficiency. It is important to keep in mind and reassure parents that “color-deficient” children do not misname colors, and that true “color blindness” is very rare and not compatible with normal vision. **Color deficiency** is common in male patients but rare in females, as the gene is transmitted in an X-linked manner. **Achromatopsia** , which may be encountered occasionally, is a condition of complete color blindness associated with subnormal visual acuity, nystagmus, and photophobia.

Color discrimination is a means of assessing the intensity of a hue, typically red. Patients describe the intensity of red depicted from the test object. A change in color discrimination (often referred to as color “desaturation”) can be a sign of optic nerve or retinal disease.

Pupillary Examination

The pupil exam includes evaluations of both the direct and consensual responses to light, accommodation (a near target), and reduced illumination, noting the size and symmetry of the pupils under each testing condition. Special care must be taken to differentiate the reaction to light from the reaction to near gaze. A child's natural tendency is to look directly at the approaching light, inducing the near gaze reflex when one is attempting to test only the reaction to light; accordingly, every effort must be made to control fixation on a distance target. The swinging flashlight test is especially useful for detecting unilateral or asymmetric prechiasmatic afferent defects in children (see “Marcus Gunn Pupil

” in Chapter 640).

Ocular Motility

Ocular motility testing assesses alignment and extraocular muscle function. This is tested by having a child follow an object in various positions of gaze, known as the cardinal positions. The cardinal positions are those in which one extraocular muscle predominantly functions and a deficit can be identified if present. Movements of each eye individually (**ductions**) and of the 2 eyes together (**versions** , conjugate movements, and convergence) are assessed.

Alignment can be assessed in 2 ways. The first is symmetry of the corneal light reflexes. The second method is to occlude each eye in an alternating fashion and observe for a change in fixation of the viewing eye (see discussion on cover testing for strabismus in Chapter 641).

Binocular Vision

Attaining binocular visual function is one of the primary goals of amblyopia therapy and ocular realignment surgery. Just as there are multiple methods for assessing visual acuity, there are various means of testing the level of binocular vision. The Titmus test is probably the most frequently used test; a series of three-dimensional images are shown to the child while he or she wears a set of polarized glasses. The level of difficulty with which these images can be detected correlates with the degree of binocular vision present.

External Examination

The external examination begins with general inspection, paying close attention to size, shape, and symmetry of the orbits, in addition to the position and movement of the lids and position and symmetry of the globes. Viewing the eyes and lids in such a manner aids in detecting orbital asymmetry, lid masses, proptosis (exophthalmos), and abnormal pulsations. Palpation is also important in detecting orbital and lid masses. Orbital dermoids and capillary hemangiomas are frequently evaluated during the external examination.

The lacrimal system is assessed by looking for evidence of tear deficiency, overflow of tears (epiphora), erythema, and swelling in the region of the tear sac or gland. The lacrimal gland is located in the superotemporal orbit, beneath the eyebrow. The tear drainage system, which includes the lacrimal sac, is located within the medial wall of the orbit, where the eyelids meet the bridge of the nose. The sac is massaged to check for reflux when obstruction is suspected. The presence and position of the puncta are also checked.

The lids and conjunctivae are specifically examined for focal lesions, foreign bodies, and inflammatory signs; loss and misdirection of lashes should also be noted. When necessary, the lids can be everted in the following manner: (1) instruct the patient to look down; (2) grasp the lashes of the patient's upper lid between the thumb and index finger of 1 hand; (3) place a probe, a cotton-tipped applicator, or the thumb of the other hand at the upper margin of the tarsal plate; and (4) pull the lid down and outward and evert it over the probe, using the instrument as a fulcrum. Foreign bodies commonly lodge in the concavity just above the lid margin and are exposed only by fully everting the lid.

The anterior segment of the eye is then evaluated with oblique focal illumination, noting the luster and clarity of the cornea, the depth and clarity of the anterior chamber, and the features of the iris. Transillumination of the anterior segment aids in detecting opacities and in demonstrating atrophy or hypopigmentation of the iris; these latter signs are important when ocular albinism is suspected. When necessary, fluorescein dye can be used to aid in diagnosing abrasions, ulcerations, and foreign bodies.

Biomicroscopy (Slit-Lamp Examination)

The slit-lamp exam provides a highly magnified view of the various structures of the eye and an optical section through the media of the eye—the cornea, aqueous humor, lens, and vitreous. Lesions can be identified and localized according to their depth within the eye; the resolution is sufficient to detect individual inflammatory cells in the aqueous and anterior vitreous. With the addition of special lenses and prisms, the angle of the anterior chamber and components of the fundus also can be examined with a slit lamp. Biomicroscopy is often crucial in trauma and in examining for iritis. It is also helpful in diagnosing many metabolic and genetic diseases of childhood.

Fundus Examination (Ophthalmoscopy)

The ideal setting for ophthalmoscopy is with a well-dilated pupil, unless there are neurologic or other contraindications. Tropicamide (Mydriacyl) 0.5–1% and phenylephrine (Neo-Synephrine) 2.5% are recommended as mydriatics of short duration. These are safe for most children, but the possibility of adverse systemic effects must be recognized. For very small infants, especially 6 mo or younger, more dilute preparations may be advisable. Beginning with posterior landmarks, the disc and the macula, the 4 quadrants are systematically examined by following each of the major vessel groups to the periphery. Retinal hemorrhages, vascular anomalies, and posterior uveitis are often appreciated during this segment of the examination. Color, cup, and contour of the optic nerve should be noted as well. Abnormalities are frequently followed with further imaging studies such as a CT or MRI or diagnostic testing such as automated perimetry (see “Visual Field Assessment ” above). The midperipheral retina can be seen if a child is directed to look up and down and to the right and left. Even with care, only a limited fraction of the fundus can be seen with a direct or handheld ophthalmoscope. For examination of the far periphery, an indirect ophthalmoscope is used, and full dilation of the pupil is essential.

Refraction

Refraction determines the focusing power of the eye: the degree of nearsightedness (myopia), farsightedness (hypermetropia), or astigmatism. Retinoscopy provides an objective determination of the amount of correction needed and can be performed at any age, including the newborn period. In young children, it is best done with cycloplegia using cyclopentolate 1% eye drops in an ophthalmologist's office. Subjective refinement of refraction involves asking patients for preferences in the strength and axis of corrective lenses; it can be accomplished in many school-age children. Refraction and determination of visual acuity with appropriate corrective lenses in place are essential steps in deciding whether a patient has a visual defect or amblyopia. Photoscreening cameras aid ancillary medical personnel in screening for refractive errors in preverbal children. The accuracy and practical usefulness of these devices are still being investigated.

Tonometry

Tonometry is the method of assessing intraocular pressure. It may be performed with a portable, stand-alone instrument or by the applanation method during slit-lamp examination. Alternative methods are pneumatic, electronic, or rebound tonometry. When accurate measurement of the pressure is necessary in a child who cannot cooperate, it may be performed with sedation or general anesthesia. A gross estimate of pressure can be made by palpating the globe with the index fingers placed side by side on the upper lid above the tarsal plate.

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CHAPTER 638

Abnormalities of Refraction and Accommodation

Scott E. Olitsky, Justin D. Marsh

Emmetropia is the state in which parallel rays of light come to focus on the retina with the eye at rest (nonaccommodating). Even though such an ideal optical state is common, the opposite condition, ametropia, often occurs. Three principal types of **ametropia** exist: **hyperopia** (farsightedness), **myopia** (nearsightedness), and **astigmatism** (Fig. 638.1). The majority of children are physiologically hyperopic at birth. Yet a significant number, especially those born prematurely, are myopic and often have some degree of astigmatism. With growth, the refractive state tends to change and should be evaluated periodically.

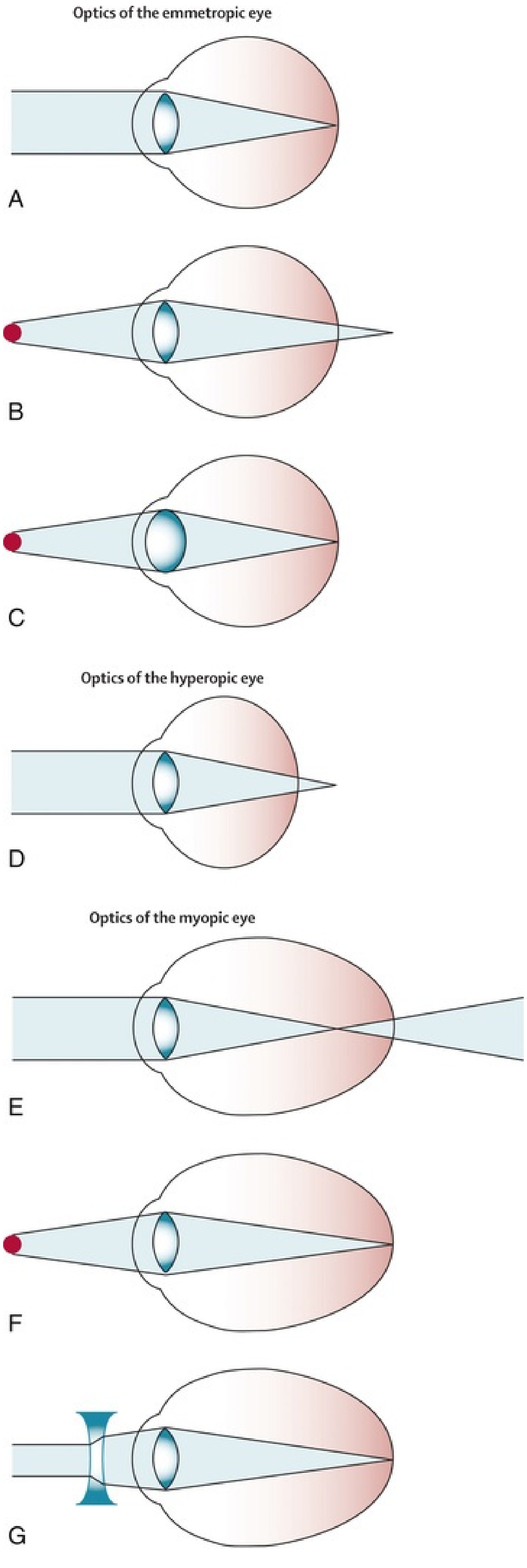
Optics of the emmetropic eye
A
B
C
Optics of the hyperopic eye
D
Optics of the myopic eye
E
F
G

FIG. 638.1 Schematic optics of the eye. **A-C,** Emmetropic eyes. **D,** Hyperopic eyes. **E-G,** Myopic eyes. **A,** In emmetropic eyes, the parallel rays of a distant object are focused on the photoreceptors. **B,** When a closer object is viewed, the image is in focus behind the photoreceptors. The image can be brought forward into focus on the photoreceptors by the process of accommodation—increasing the optical power of the lens **(C)** . In hyperopic eyes **(D)** , the eye is too short, and the image of a distant object is focused behind the photoreceptors, and can be brought into focus by accommodation. Myopic eyes are eyes that have grown too long **(E)** , and the image of a distant object falls in front of the photoreceptors, and cannot be brought into focus by accommodation. When closer objects are viewed, the image moves back toward the photoreceptors, and at a certain distance (the far point), which is related inverse to the severity of the myopia, it comes into focus **(F)** . Closer objects can then be brought into focus using accommodation. Optical correction for myopia is achieved with concave (diverging) lenses, which move the image into focus on the photoreceptors **(G)** *.* Contact lenses work in a similar way, whereas refractive surgery reduces the power of the cornea to bring the image of distant objects into focus. For equal corneal power, myopic eyes have longer axial lengths than emmetropic eyes, with deeper anterior and vitreal chambers. Their lenses tend to be thinner and of lower power than those of emmetropic eyes. (From Morgan IG, Ohno-Matusi K, Saw SM: Myopia. *Lancet* 379:1739–1746, 2012, Fig. 1, p. 1740.)

Measurement of the refractive state of the eye (refraction) can be accomplished both objectively and subjectively. The objective method involves directing a beam of light from a retinoscope onto a patient's retina. Using loose lenses of various strengths held in front of the eye, the retinal light reflex (viewed through the pupil) can be neutralized, yielding a precise refraction. An objective refraction is obtainable at any age because it requires no response from the patient. In infants and children, it is generally more accurate to perform a refraction after instillation of eye drops that produce **mydriasis** (dilation of the pupil) and **cycloplegia** (paralysis of accommodation); those used most commonly are tropicamide (Mydriacyl), cyclopentolate (Cyclogyl), and atropine sulfate. A subjective refraction involves placing lenses in front of the eye and having the patient report which lenses provide the clearest image of the letters on a chart. This method is dependent on a patient's ability to discriminate and communicate but can be used for some children and can be helpful in determining the best refractive correction for children who are developmentally capable.

Hyperopia

If parallel rays of light come to focus posterior to the retina with the eye in a neutral state, hyperopia or farsightedness exists. This may result from a shorter anteroposterior diameter of the eye or a lower refractive power of the cornea or lens.

In hyperopia, the additional refracting power needed to bring objects into focus at distance and near is generated through the accommodative mechanism. If the accommodative effort required for focus is within that child's accommodative amplitude, the vision is clear. In high degrees of hyperopia requiring greater accommodative effort, vision may be blurred, and the child may complain of eyestrain, headaches, or fatigue. Squinting, eye rubbing, and lack of interest in reading are frequent manifestations. If the induced discomfort is great enough, a child may not make the effort to focus and may develop bilateral amblyopia (ametropic amblyopia). Esotropia may also be associated (see discussion on convergent strabismus, accommodative esotropia in Chapter 641). Convex lenses (spectacles or contact lenses) of sufficient strength to provide clear vision and comfort are prescribed when indicated. Even children who have high degrees of hyperopia but who have good vision will happily wear glasses because they provide comfort by eliminating the excessive accommodation required to see well. Preverbal children should also be given glasses for high levels of hyperopia to prevent the development of esotropia or amblyopia. Children with normal levels of hyperopia do not require correction in the majority of cases.

Myopia

In myopia, parallel rays of light come to focus anterior to the retina. This is a result of either a long anteroposterior diameter of the eye or a higher refractive power of the cornea or lens. The principal symptom is blurred vision for distant objects. The far point of clear vision varies inversely with the degree of myopia; as the myopia increases, the far point of clear vision moves closer to the eye. With myopia of 1 diopter, for example, the far point of clear focus is 1 m from the eye; with myopia of 3 diopters, the far point of clear vision is only $\frac{1}{3}$ m from the eye. Thus myopic children tend to hold objects and reading material closer, prefer to be close to the blackboard, and may be uninterested in distant activities. Squinting is common because the visual acuity is improved when the lid aperture is reduced, also known as the pinhole effect.

Myopia is infrequent in infants and preschool-age children. It is more common in infants with a history of **retinopathy of prematurity.** A hereditary tendency to myopia is also observed, and children of myopic parents should be examined at an early age. Nonsyndromic myopia is associated in some families with variants in the high-grade myopia-1 locus (*MYP1*) as well as in *SLITRK6* and *RASGRF1* genes. The incidence of myopia increases during the school years, especially during the preteen and teen years. The degree of myopia also increases with age during the growing years.

Concave lenses (spectacles or contact lenses) of appropriate strength to provide clear vision and comfort are prescribed. Changes are usually needed periodically, from every few months to every 1-2 yr. Globally the prevalence of myopia appears to be increasing, leading to heightened interest in myopia prevention treatment. Numerous therapies, including cycloplegic agents (topical atropine sulfate), peripheral defocus contact lenses, and reading addition spectacle lenses (bifocal lenses) are under investigation in attempt to prevent or slow the progression of myopia.

Excimer laser correction for myopia has been approved for adults since 1995. The laser is applied to the corneal stroma to reshape the cornea, changing its refractive power. Laser-assisted in situ keratomileusis (LASIK) uses either a microkeratome or a femtosecond laser to produce an epithelial-stromal flap permitting the underlying corneal tissue to be ablated. The flap is then reseated and assumes the altered corneal shape. Photorefractive keratectomy (PRK) uses manual removal of the epithelium following treatment with alcohol to expose the Bowman layer and stroma, which is then treated by the excimer laser. The epithelium regenerates to cover the defect over a period of 4-10 days. Visual improvement is usually significant and remains stable over time. Risks are greatest with high degrees of myopia (>10 diopters) and include starbursts, halos, and distorted images or multiple images (usually at night). Refractive surgery is not approved for pediatric patients but is being used off-label to treat of some forms of amblyopia and certain circumstances of myopia and astigmatism, usually by PRK.

In most cases, myopia is not a result of pathologic alteration of the eye and is referred to as simple or physiologic myopia. Some children may have **pathologic myopia** , a rare condition caused by a pathologically abnormal axial length of the eye; this is usually associated with thinning of the sclera, choroid, and retina and often with some degree of uncorrectable visual impairment. Tears or breaks in the retina may occur as it becomes increasingly thin, leading to the development of retinal detachments. Myopia may also occur as a result of other ocular abnormalities, such as keratoconus, ectopia lentis, congenital stationary night blindness, and glaucoma. Myopia is also a major feature of Stickler syndrome, a genetic disorder of connective tissue involving problems with vision, hearing, and facial and skeletal development; it is also common in Marfan syndrome, homocystinuria, and Marchesani syndrome.

Astigmatism

In astigmatism, the refractive powers of the various meridians of the eye differ. Most cases are caused by irregularity in the curvature of the cornea, although some astigmatism results from changes in the lens. Mild degrees of astigmatism are common and may produce no symptoms. With greater degrees, distortion of vision can occur. To achieve a clearer image, a person with astigmatism uses accommodation or squints to obtain a pinhole effect. Symptoms include eyestrain, headache, and fatigue. Cylindrical or spherocylindrical lenses are used to provide optical correction when indicated. Glasses may be needed constantly or only part time, depending on the degree of astigmatism and the severity of the attendant symptoms. In some cases, contact lenses are used.

Infants and children with corneal irregularity resulting from injury, ptosis, or hemangiomas of the periorbita or eyelid are at increased risk of astigmatism and associated amblyopia.

Anisometropia

When the refractive state of one eye is significantly different from the refractive state of the other eye, **anisometropia** exists. If uncorrected, 1 eye may always be out of focus, leading to the development of amblyopia. Early detection and correction are essential if normal visual development in both eyes is to be achieved.

Accommodation

During accommodation, the ciliary muscle contracts, the suspensory fibers of the lens relax, and the lens assumes a more rounded shape, adding power to the lens.

The amplitude of accommodation is greatest during childhood and gradually diminishes with age. The physiologic decrease in accommodative ability that occurs with age is called **presbyopia** .

Disorders of accommodation in children are relatively rare. Premature presbyopia is occasionally encountered in young children. The most common cause of paralysis of accommodation in children is intentional or inadvertent use of cycloplegic substances, topically or systemically; included are all the anticholinergic drugs and poisons, as well as plants and plant substances having these effects. Neurogenic causes of accommodative paralysis include lesions affecting the oculomotor nerve (3rd cranial nerve) in any part of its course. Differential diagnoses include tumors, degenerative diseases, vascular lesions, trauma, and infectious etiologies. Systemic disorders that may cause impairment of accommodation include botulism, diphtheria, Wilson disease, diabetes mellitus, and syphilis. Adie tonic pupil may also lead to a deficiency of accommodation after some viral illnesses (see Chapter 640). An apparent defect in accommodation may be psychogenic in origin; it is common for a child to feign inability to read when it can be demonstrated that visual acuity and ability to focus are normal.

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CHAPTER 639

Disorders of Vision

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Severe visual impairment (corrected vision poorer than **6/60**) and blindness in children have many etiologies and may be caused by multiple defects affecting any structure or function along the visual pathways (Table 639.1). The overall incidence is approximately 2.5 per 100,000 children; the incidence is higher in developing countries, in low birthweight infants, and in the 1st yr of life. The most common causes occur during the prenatal and perinatal time periods; the cerebral-visual pathways, optic nerve, and retinal sites are most often affected. Important prenatal causes include autosomal recessive (most common), autosomal dominant, and X-linked genetic disorders as well as hypoxia and chromosomal syndromes. Perinatal/neonatal causes include retinopathy of prematurity, hypoxia–ischemia, and infection. Severe visual impairment starting in older children may be due to central nervous system or retinal tumors, infections, hypoxia–ischemia, injuries, neurodegenerative disorders, or juvenile idiopathic arthritis.

Table 639.1

Causes of Childhood Severe Visual Impairment or Blindness

Congenital

Optic nerve hypoplasia or aplasia
Septo-optic dysplasia
Optic coloboma
Congenital hydrocephalus
Hydranencephaly

Porencephaly
Micrencephaly
Encephalocele, particularly occipital
Morning glory disc
Aniridia
Microphthalmia/anophthalmia
Peters anomaly
Rieger anomaly
Persistent pupillary membrane
Glaucoma
Cataracts
Persistent hyperplastic primary vitreous

Phakomatoses

Tuberous sclerosis
Neurofibromatosis (special association with optic glioma)
Sturge-Weber syndrome
von Hippel-Lindau disease

Tumors

Retinoblastoma
Optic glioma
Perioptic meningioma
Craniopharyngioma
Cerebral glioma
Astrocytoma
Posterior and intraventricular tumors when complicated by hydrocephalus
Pseudotumor cerebri

Neurodegenerative Diseases

Cerebral storage disease
Gangliosidoses, particularly Tay-Sachs disease, Sandhoff variant, generalized gangliosidosis

Other lipidoses and ceroid lipofuscinoses, particularly the late-onset disorders such as those of Jansky-Bielschowsky and of Batten-Mayou-Spielmeyer-Vogt
Mucopolysaccharidoses, particularly Hurler syndrome and Hunter syndrome
Leukodystrophies (dysmyelination disorders), particularly metachromatic leukodystrophy and Canavan disease
Demyelinating sclerosis (myelinoclastic diseases), especially Schilder disease and Devic neuromyelitis optica
Special types: Dawson disease, Leigh disease, the Bassen-Kornzweig syndrome, Refsum disease
Retinal degenerations: retinitis pigmentosa and its variants and Leber congenital type
Optic atrophies: congenital autosomal recessive type, infantile and congenital autosomal dominant types, Leber disease, and atrophies associated with hereditary ataxias—the types of Behr, of Marie, and of Sanger-Brown

Infectious/Inflammatory Processes

Encephalitis, especially in the prenatal infection syndromes caused by *Toxoplasma gondii* , cytomegalovirus, rubella virus, *Treponema pallidum* , herpes simplex virus, Zika virus
Meningitis; arachnoiditis
Chorioretinitis
Endophthalmitis
Trachoma
Keratitis
Uveitis
Optic neuritis

Hematologic Disorders

Leukemia with central nervous system involvement

Vascular and Circulatory Disorders

Collagen vascular diseases
Arteriovenous malformations—intracerebral hemorrhage, subarachnoid hemorrhage
Central retinal occlusion
Retinal vasculitis

Trauma

Contusion or avulsion of optic nerves, chiasm, globe, cornea
Cerebral contusion or laceration
Intracerebral, subarachnoid, or subdural hemorrhage
Retinal detachment
Laser injury

Drugs and Toxins

Quinine
Ethambutol
Methanol
Many others

Other

Retinopathy of prematurity
Sclerocornea
Conversion reaction
Osteopetrosis

Modified from Kliegman R: *Practical strategies in pediatric diagnosis and therapy.* Philadelphia, 1996, WB Saunders.

Amblyopia

This is a decrease in visual acuity, unilateral or bilateral, that occurs in visually immature children as a result of a lack of a clear image projecting onto the retina. The unformed retinal image may occur secondary to a deviated eye **(strabismic amblyopia),** an unequal need for vision correction between the eyes **(anisometropic amblyopia),** a high refractive error in both eyes **(ametropic amblyopia),** or a media opacity within the visual axis **(deprivation amblyopia).**

The development of visual acuity normally proceeds rapidly in infancy and early childhood. Anything that interferes with the formation of a clear retinal image during this early developmental period can produce amblyopia. Amblyopia occurs only during the critical period of development before the cortex has become visually mature, within the 1st decade of life. The younger the child, the more susceptible he or she is to the development of amblyopia.

The **diagnosis** of amblyopia is confirmed when a complete ophthalmologic examination reveals reduced acuity that is unexplained by an organic abnormality. If the history and ophthalmologic examination do not support the diagnosis of amblyopia in a child with poor vision, consideration must be given to other causes (neurologic, psychologic). *Amblyopia is usually asymptomatic and can avoid detection until vision screening, which may delay diagnosis as screening programs often target school-age children.* This is problematic, as amblyopia is more resistant to treatment at an older age, being reversed more rapidly in younger children whose visual system is less mature. Thus 1 key to the successful treatment of amblyopia is early detection and prompt intervention.

Most often **treatment** first consists of removing any media opacity or prescribing appropriate glasses, if needed, so that a well-focused retinal image can be produced in each eye. The sound eye is then covered (occlusion therapy) or blurred with glasses (fogging) or drops (penalization therapy) to stimulate proper visual development of the more severely affected eye. Occlusion therapy may provide a more rapid improvement in vision, but some children may better tolerate atropine penalization. The best treatment for any 1 patient should be selected on an individual basis. The goals of treatment should be thoroughly understood, and the treatment carefully supervised. Close monitoring of amblyopia therapy by an ophthalmologist is essential, especially in the very young, to avoid deprivation amblyopia in the good eye. Many families need reassurance and support throughout the trying course of treatment. Although full-time occlusion has historically been considered the best way to treat children with amblyopia, a series of prospective studies has shown that some children can achieve similar results with part-time patching or the use of atropine drops. Historical thought was that older children would not respond to amblyopia therapy. Studies suggest children and adolescents deemed visually mature who demonstrate amblyopia, particularly refractive or anisometropic in etiology, can demonstrate improvement in vision with appropriate therapy.

Diplopia

Diplopia, or double vision, is generally a result of a misalignment of the visual axes. Occluding either eye relieves the diplopia if it is binocular in origin. Affected children commonly squint, cover 1 eye with a hand, or assume an abnormal head posture (a face turn or head tilt) to alleviate the bothersome sensation. These behaviors, especially in preverbal children, are important clues to diplopia. *The onset of diplopia in any child warrants prompt evaluation; it may signal the onset of a serious problem such as increased intracranial pressure, a brain tumor, infection (Lyme disease), migraine, Guillain-Barré syndrome, or an orbital mass* (Fig. 639.1).

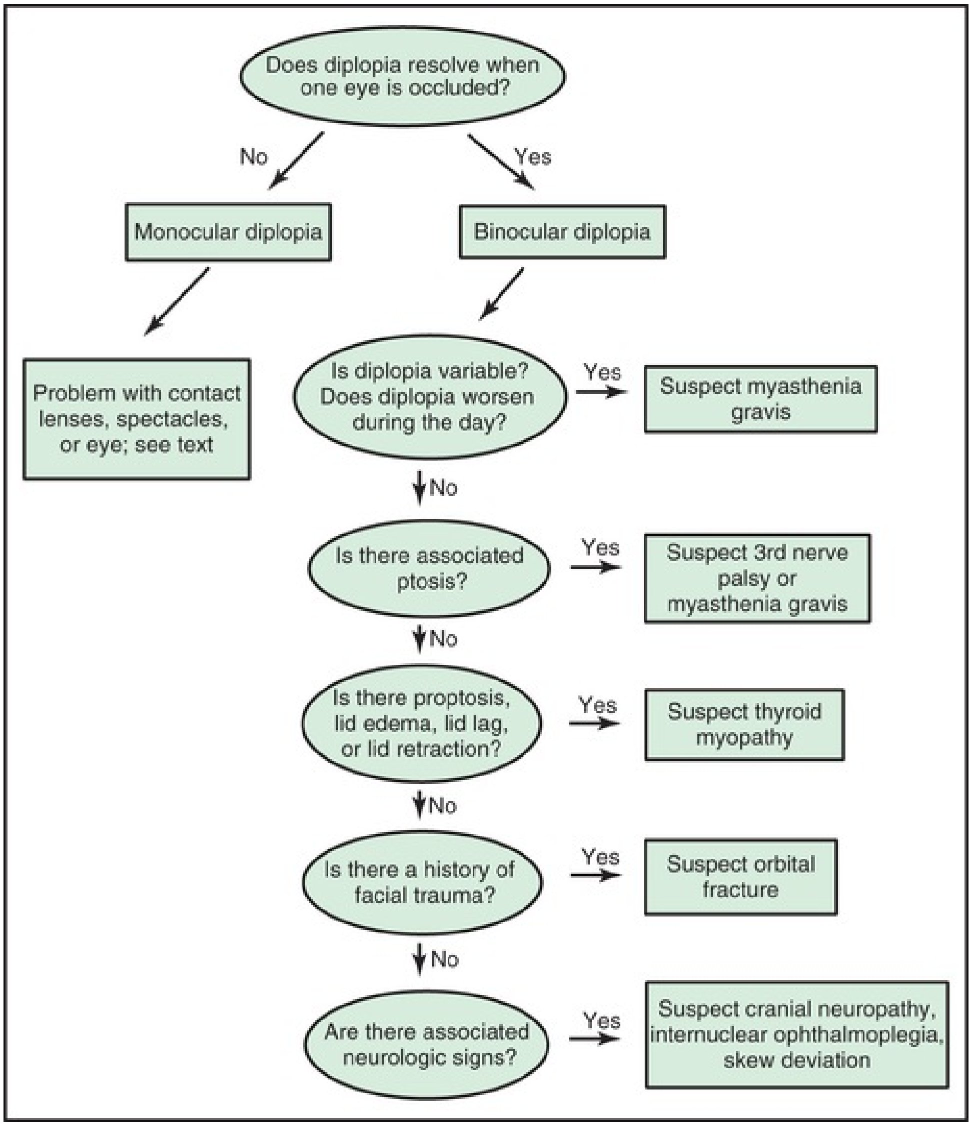
Does diplopia resolve when one eye is occluded?
No
Yes
Monocular diplopia
Binocular diplopia
Problem with contact lenses, spectacles, or eye; see text
Is diplopia variable? Does diplopia worsen during the day?
Yes
Suspect myasthenia gravis
No
Is there associated ptosis?
Yes
Suspect 3rd nerve palsy or myasthenia gravis
No
Is there proptosis, lid edema, lid lag, or lid retraction?
Yes
Suspect thyroid myopathy
No
Is there a history of facial trauma?
Yes
Suspect orbital fracture
No
Are there associated neurologic signs?
Yes
Suspect cranial neuropathy, internuclear ophthalmoplegia, skew deviation

FIG. 639.1 General approach to diplopia. The clinician should first distinguish monocular from binocular diplopia and, in patients with binocular diplopia, address the 5 questions on the right side of the figure. Only then should the clinician identify which muscle is weak, although this is unnecessary if the clinician already suspects myasthenia (from fatigability) or full third nerve palsy (from weakness of the medial rectus, superior rectus, inferior rectus, and inferior oblique muscles, with or without a dilated pupil). Uncommon causes of diplopia and associated ptosis, not presented in the figure, are botulism, the Fisher variant of Guillain-Barre syndrome, and aberrant regeneration of the third nerve. Uncommon causes of diplopia and associated orbital findings (e.g., proptosis) are carotid-cavernous fistula (which causes and orbital bruit), orbital tumor, and pseudotumor. (From McGee S: *Evidence-based physical diagnosis* , ed 3, Philadelphia, 2012, Elsevier, Fig. 57.1, p. 522.)

Monocular diplopia results from refractive error, dislocation of the lens, cataract, dry eyes, or some defect in the media or macula. With this type of diplopia, occluding the nondiplopic eye will not relieve the symptoms. Monocular diplopia may often have psychological causes.

Suppression

In the presence of strabismus, diplopia occurs secondary to the same image falling on different regions of the retina in each eye. In a visually immature child, a process may occur in the cortex that eliminates the disability of seeing double. This is an active process and is termed **suppression** . It develops only in children. Although suppression eliminates the annoying symptom of diplopia, it is the potential awareness of a second image that tends to keep our eyes properly aligned. Once suppression develops, it may allow an intermittent strabismus to become constant or strabismus to redevelop later in life, even after successful treatment during childhood.

Amaurosis

Amaurosis is partial or total loss of vision; the term is usually reserved for profound impairment, blindness, or near blindness. When amaurosis exists from birth, primary consideration in the differential diagnosis must be given to developmental malformations, damage consequent to gestational or perinatal infection, anoxia or hypoxia, perinatal trauma, and the genetically determined diseases that can affect the eye itself or the visual pathways. Often the reason for amaurosis can be readily determined by objective ophthalmic examination; examples are severe microphthalmia, corneal opacification, dense cataracts, chorioretinal scars, macular defects, retinal dysplasia, and severe optic nerve hypoplasia. In other cases, an intrinsic retinal disease may not be apparent on initial ophthalmoscopic examination or the defect may involve the brain and not the eye. Neuroradiologic (MRI or CT) and electrophysiologic (electroretinography) evaluation are helpful in these cases.

Amaurosis that develops in a child who once had useful vision has different implications. In the absence of obvious ocular disease (cataract, chorioretinitis, retinoblastoma, retinitis pigmentosa), consideration must be given to many neurologic and systemic disorders that can affect the visual pathways (see Table 639.1). Amaurosis of rather rapid onset may indicate an encephalopathy (hypertension), infectious or inflammatory (optic neuritis) processes, vasculitis, migraine, leukemia, drugs or toxins, eclampsia, or trauma. It may be caused by acute demyelinating disease affecting the optic nerves, chiasm, or cerebrum. In some cases, precipitous loss of vision is a result of increased intracranial pressure, rapidly progressive hydrocephalus, or dysfunction of a ventricular shunt. More slowly progressive visual loss suggests tumor or neurodegenerative disease. Gliomas of the optic nerve and chiasm and craniopharyngiomas are primary diagnostic considerations in children who show progressive loss of vision.

Clinical manifestations of impairment of vision vary with the age and abilities of a child, the mode of onset, and the laterality and severity of the deficit. The first clue to amaurosis in an infant may be **nystagmus** or **strabismus,** with the vision deficit itself passing undetected for some time. Timidity, clumsiness, or behavioral change may be the initial clues in the very young. Deterioration in school progress and indifference to school activities are common signs in an older child. School-age children often try to hide their disability and, in the case of very slowly progressive disorders, may not themselves realize the severity of the problem; some detect and promptly report small changes in their vision.

Any evidence of loss of vision requires prompt and thorough ophthalmic evaluation. Complete delineation of childhood amaurosis and its cause may require extensive investigation involving neurologic evaluation, electrophysiologic tests, neuroradiologic procedures, and sometimes metabolic and genetic studies. Furthermore, attendant special educational, social, and emotional needs must be met.

Nyctalopia

Nyctalopia, or night blindness, is vision that is defective in reduced illumination. It generally implies impairment in function of the rods, particularly in dark adaptation time and perceptual threshold. Stationary congenital night blindness may occur as an autosomal dominant, autosomal recessive, or X-linked recessive condition. It may be associated with myopia and nystagmus. Children may have excessive problems going to sleep in a dark room, which may be mistaken for a behavioral problem. Progressive night blindness usually indicates primary or secondary retinal, choroidal, or vitreoretinal degeneration (see Chapter 648); it occurs also in vitamin A deficiency or as a result of retinotoxic drugs such as quinine.

Psychogenic Disturbances

Vision problems of psychogenic origin are common in school-age children. Both conversion reactions and willful feigning are encountered. The usual manifestation is a report of reduced visual acuity in 1 or both eyes. Another common manifestation is constriction of the visual field. In some cases, the symptom is diplopia or polyopia (see Chapters 35 and 38).

Important clues to the diagnosis are inappropriate affect, excessive grimacing, inconsistency in performance, and suggestibility. A thorough ophthalmologic examination is essential to differentiate organic from functional visual disorders.

Affected children usually fare well with reassurance and positive suggestions. In some cases, mental health care is indicated. In all cases, the approach must be supportive and nonpunitive.

Dyslexia

This is the inability to develop the capability to read at an expected level despite an otherwise normal intellect (Chapter 50). The terms *reading disability* and *dyslexia* are often used interchangeably. Most dyslexic individuals also display poor writing ability. Dyslexia is a primary reading disorder and should be differentiated from secondary reading difficulties caused by intellectual disability, environmental or educational deprivation, and systemic physical or other organic brain or eye diseases. Because there is not 1 standard test for dyslexia, the diagnosis is usually made by comparing reading ability with intelligence and standard reading expectations. Dyslexia is a language-based disorder and is not caused by any defect in the eye or visual acuity per se, nor is it attributable to a defect in ocular motility or binocular alignment. Although ophthalmologic evaluation of children with a reading problem is recommended to diagnose and correct any concurrent ocular problems such as a refractive error, amblyopia, or strabismus, treatment directed to the eyes themselves cannot be expected to correct developmental dyslexia (see Chapter 50).

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CHAPTER 640

Abnormalities of Pupil and Iris

Scott E. Olitsky, Justin D. Marsh

Aniridia

The term *aniridia* is a misnomer because iris tissue is usually present, although it is hypoplastic (Fig. 640.1). Two thirds of the cases are dominantly transmitted with a high degree of penetrance. The other third of cases are sporadic and are considered new mutations. The condition is bilateral in 98% of all patients, regardless of the means of transmission, and is found in approximately 1/50,000 persons. *PAX6* is the mutated gene at the chromosome 11p3 region.

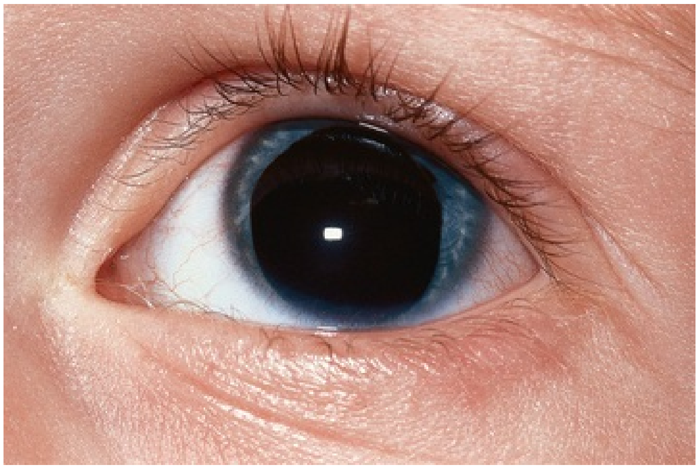

FIG. 640.1 Partial aniridia in a member of an autosomal dominant pedigree. (From Hoyt CS, Taylor D, editors: Pediatric ophthalmology and strabismus, ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 32.22, p. 304.)

Aniridia is a panocular disorder and should not be thought of as an isolated iris defect. Macular and optic nerve hypoplasia are commonly present, and lead to decreased vision and sensory nystagmus. The visual acuity is approximately 20/200 in most patients, although the vision may occasionally be better. Other ocular deformities are common and may involve the lens and cornea. The cornea may be small, and a cellular infiltrate (pannus) occasionally develops in the superficial layers of the peripheral cornea. Clinically this appears as a gray opacification. Lens abnormalities include cataract formation and partial or total lens dislocation. **Glaucoma** develops in as many as 75% of individuals with aniridia.

One fifth of sporadic aniridic patients may develop **Wilms tumor** (see Chapter 526.1). The gene for aniridia is very close to the Wilms tumor gene; deletions in this area cause the association. Of particular interest is the association of aniridia, genitourinary anomalies, intellectual disability, and a partial deletion of the short arm of chromosome 11. Among individuals thus affected, the appearance of Wilms tumor is more common. It is thought that only patients with sporadic aniridia are at risk for developing Wilms tumor, although Wilms tumor has occurred in a patient with familial aniridia. Wilms tumor usually presents before the 5th yr, and these children should be screened using renal ultrasonography every 3-6 mo until approximately 5 yr of age if there is an 11p13 region deletion placing the child at risk for Wilms tumor.

Coloboma of the Iris

A **coloboma** is the defect formed when the embryonic fissure fails to close completely. This developmental defect may present as a defect in a sector of the iris, a hole in the substance of the iris, or a notch in the pupillary margin (Fig. 640.2). Simple colobomas are frequently transmitted as an autosomal dominant trait and may occur alone or in association with other anomalies and syndromes; these include CHARGE, Cat eye, Glotz, Walker Warburg, trisomy 13, trisomy 18, Rieger, congenital colobomatous microphthalmia iris coloboma, and anal atresia syndromes, as well as various deletion syndromes (4p, 13q, 2q31.1, 15q24). Because of the anatomic location of the embryonic fissure, an iris coloboma is always located inferiorly, giving the iris a keyhole appearance. An iris coloboma may be the only externally visible part of a more extensive coloboma that also involves the fundus and optic nerve. When this occurs, vision is likely to be severely affected. Therefore all children with an iris coloboma should undergo a full ophthalmologic examination.

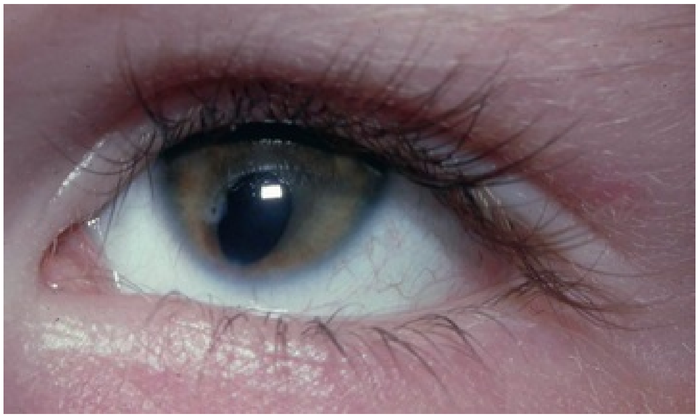

FIG. 640.2 Coloboma (“keyhole pupil”). (From Hoyt CS, Taylor D, editors: Pediatric ophthalmology and strabismus, ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 38.11, p. 372.)

Microcoria

Microcoria (congenital miosis) appears as a small pupil that does not react to light or accommodation and that dilates poorly, if at all, with medication. The condition may be unilateral or bilateral. In bilateral cases, the degree of miosis may be different in each eye. The eye may be otherwise normal or may demonstrate other abnormalities of the anterior segment. Congenital microcoria is usually transmitted as an autosomal dominant trait, although it may occur sporadically.

Congenital Mydriasis

In this disorder, the pupils appear dilated, do not constrict significantly to light or near gaze, and respond minimally to miotic agents. The iris is otherwise normal, and affected children are usually healthy. Trauma, pharmacologic mydriasis, and neurologic disorders should be considered. Many apparent cases of congenital mydriasis show abnormalities of the central iris structures and may be considered a form of aniridia.

Dyscoria and Corectopia

Dyscoria is abnormal shape of the pupil, and corectopia is abnormal pupillary position. They may occur together or independently as congenital or acquired anomalies.

Congenital corectopia is usually bilateral and symmetric and rarely occurs as an isolated anomaly; it is usually accompanied by dislocation of the lens (ectopia lentis et pupillae), and the lens and pupil are commonly dislocated in opposite directions. **Ectopia lentis et pupillae** is transmitted as an autosomal recessive disorder; consanguinity is common. It is associated with mutations in *ADAMTSL4* , a secreted glycoprotein widely distributed in the eye, which binds fibrillin-1 microfibrils and accelerates microfibril biogenesis.

When acquired, distortion and displacement of the pupil are frequently a result of trauma or intraocular inflammation. Prolapse of the iris after perforating injuries of the eye leads to peaking of the pupil in the direction of the perforation. Posterior synechiae (adhesions of the iris to the lens) are commonly seen when inflammation due to any cause occurs in the anterior segment.

Anisocoria

Anisocoria occurs when the pupils are of different sizes. This may be a result of local or neurologic disorders. As a rule, if the inequality is more pronounced in the *presence of bright focal illumination* or on near gaze, there is a defect in pupillary constriction and the larger pupil is abnormal. If the anisocoria is worse in *reduced illumination* , a defect in dilation exists and the smaller pupil is abnormal (Figs. 640.3 and 640.4). Neurologic causes of anisocoria (parasympathetic or sympathetic lesions) must be differentiated from local causes such as synechiae (adhesions), congenital iris defects (colobomas, aniridia), and pharmacologic effects. **Horner syndrome** is an important cause of anisocoria (see below). Simple central anisocoria may occur in otherwise healthy individuals.

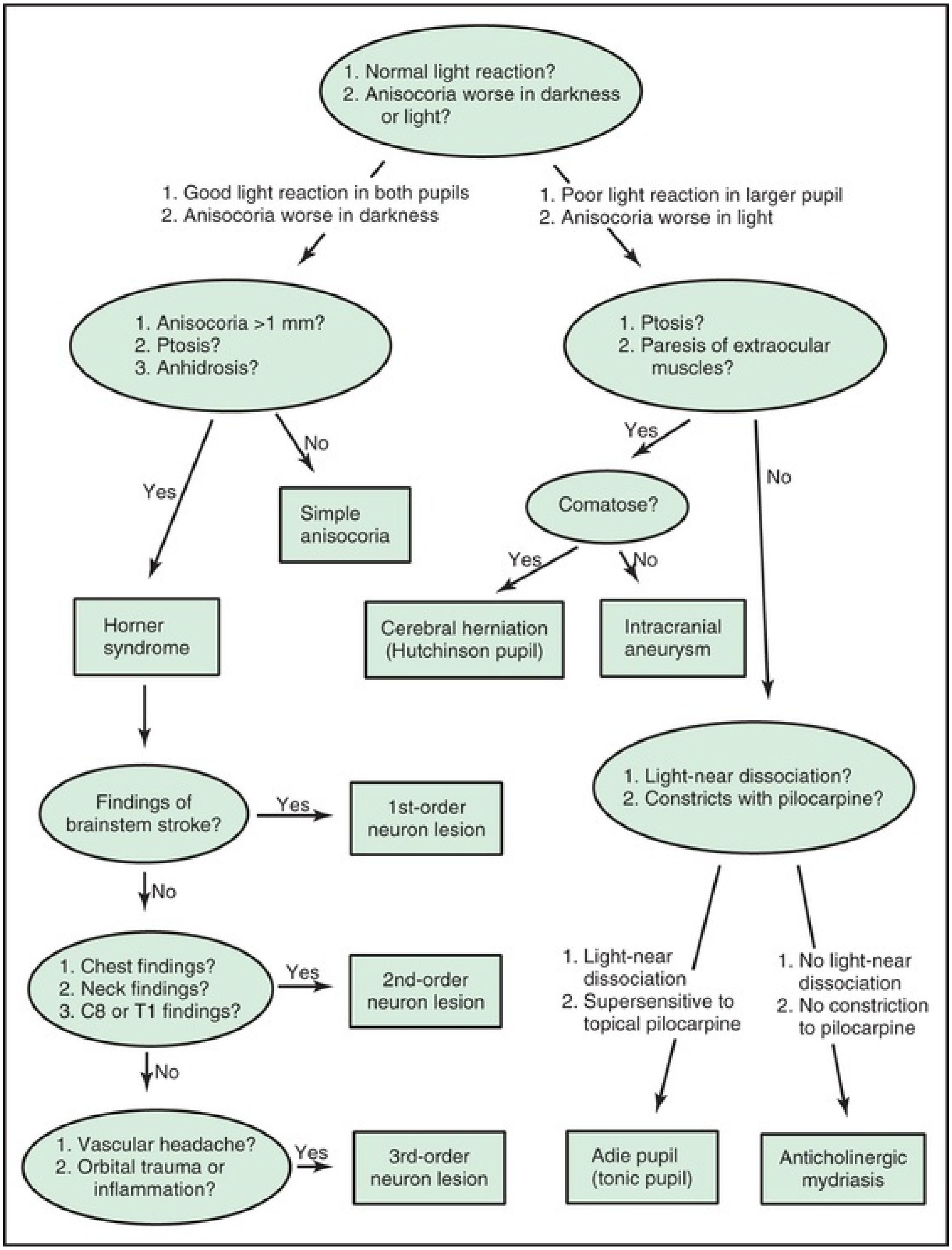
1. Normal light reaction?
2. Anisocoria worse in darkness or light?
1. Good light reaction in both pupils
2. Anisocoria worse in darkness
1. Poor light reaction in larger pupil
2. Anisocoria worse in light
1. Anisocoria >1 mm?
2. Ptosis?
3. Anhidrosis?
1. Ptosis?
2. Paresis of extraocular muscles?
Yes
No
Simple anisocoria
Yes
Comatose?
No
Yes
No
Horner syndrome
Cerebral herniation (Hutchinson pupil)
Intracranial aneurysm
1. Light-near dissociation?
2. Constricts with pilocarpine?
Findings of brainstem stroke?
Yes
1st-order neuron lesion
No
1. Light-near dissociation
2. Supersensitive to topical pilocarpine
1. No light-near dissociation
2. No constriction to pilocarpine
1. Chest findings?
2. Neck findings?
3. C8 or T1 findings?
Yes
2nd-order neuron lesion
No
1. Vascular headache?
2. Orbital trauma or inflammation?
Yes
3rd-order neuron lesion
Adie pupil (tonic pupil)
Anticholinergic mydriasis

FIG. 640.3 **Approach to anisocoria. The first 2 questions (Is there normal light reaction? And Is anisocoria worse in darkness or light?) distinguish problems with the pupillary dilator muscle (i.e., Horner syndrome, simple anisocoria; *left side of figure*) from problems with the pupillary constrictor muscle (i.e., third cranial nerve, iris; *right side of figure*). Two other tests distinguish Horner syndrome from simple anisocoria: the cocaine test and pupillary dilator lag (i.e., the pupil dilates slowly in darkness, as documented in photographs). (From Czarnecki JSC, Pilley SFJ, Thompson HS: The analysis of anisocoria: the use of photography in the clinical evaluation of unequal pupils. Can J Ophthalmol 14:297–302, 1979; and Thompson HS, Pilley SFJ: Unequal pupils: a flow chart for sorting out the anisocorias. Surv Ophthalmol 21(1):45–48, 1976.)**

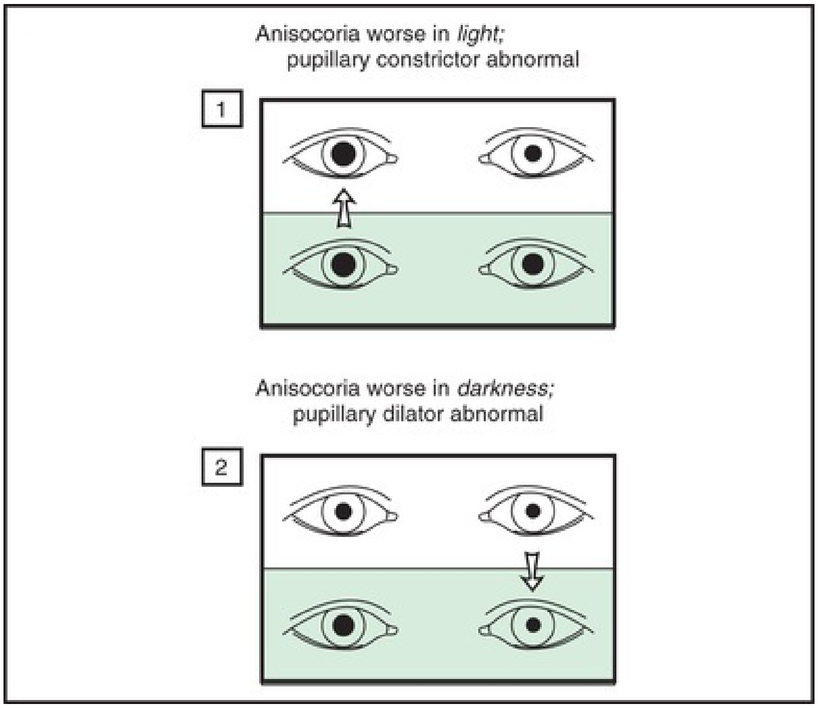
Anisocoria worse in *light;*
pupillary constrictor abnormal
1
Anisocoria worse in *darkness;*
pupillary dilator abnormal
2

FIG. 640.4 Patient 1 *(top)* has more prominent anisocoria in light than darkness, indicating that the pupillary constrictor of the larger pupil is abnormal (i.e., it fails to constrict in light, *arrow*). Patient 2 has more prominent anisocoria in darkness than light, indicating that the pupillary dilator of the smaller pupil is abnormal (i.e., it fails to dilate in darkness, *arrow*). The diagnosis in patient 1 (abnormal pupillary constrictor) could be a third nerve palsy, tonic pupil, pharmacologic mydriasis, or a disorder of the iris. The diagnosis in patient 2 (abnormal pupillary dilator) could be Horner syndrome or simple anisocoria. In patient 2, both pupils will react to light, whereas the larger pupil of patient 1 does not react well to light. (From McGee S: Evidence-based physical diagnosis, ed 3, Philadelphia, 2012, Elsevier/Saunders, Fig. 20.4, p. 170.)

Dilated Fixed Pupil

Differential diagnosis of a dilated unreactive pupil includes internal ophthalmoplegia caused by a central or peripheral lesion, Hutchinson pupil of transtentorial herniation, tonic pupil, pharmacologic blockade, and iridoplegia secondary to ocular trauma (see Fig. 640.3).

The most common cause of a dilated unreactive pupil is purposeful or accidental instillation of a cycloplegic agent, particularly atropine and related substances. Central nervous system lesions, such as a pinealoma, may cause internal ophthalmoplegia in children. Because the external surface of the oculomotor nerve carries the fibers responsible for pupillary constriction, compression of the nerve along its intracranial course may be associated with internal ophthalmoplegia, even before the development of ptosis or an ocular motility deficit. Although ophthalmoplegic migraine is a common cause of a third nerve palsy with pupillary involvement in children, an intracranial aneurysm must also be considered in the differential diagnosis. The blown pupil of transtentorial herniation, occurring with increasing intracranial pressure, is generally unilateral, and patients usually are obviously ill. The **pilocarpine test** can help differentiate neurologic iridoplegia from pharmacologic blockade. In the case of neurologic iridoplegia, the dilated pupil constricts within minutes after instillation of 1 or 2 drops of 0.5–1% pilocarpine; if the pupil has been dilated with atropine, pilocarpine has no effect. Because pilocarpine is a long-acting drug, this test is not to be used in acute situations in which pupillary signs must be carefully monitored. Because of the consensual pupil response to light, even complete uniocular blindness does not cause a unilaterally dilated pupil.

Tonic Pupil

This is typically a large pupil that reacts poorly to light (the reaction may be very slow or essentially nil), reacts poorly and slowly to accommodation, and redilates in a slow, tonic manner. The features of tonic pupil are explained by cholinergic supersensitivity of the sphincter after peripheral (postganglionic) denervation and imperfect reinnervation. A distinctive feature of a tonic pupil is its sensitivity to dilute cholinergic agents. Instillation of 0.125% pilocarpine causes significant constriction of the involved pupil and has little or no effect on the unaffected side. The condition is usually unilateral.

Tonic pupil may develop after the acute stage of a partial or complete iridoplegia. It can be seen after trauma to the eye or orbit and may occur in association with toxic or infectious conditions. For those in the pediatric age group, tonic pupil is uncommon. Infectious processes (primarily viral syndromes) and trauma are the primary causes. Features of tonic pupil may also be seen in infants and children with familial dysautonomia (Riley-Day syndrome), although the significance of these findings has been questioned. Tonic pupil has also been reported in young children with Charcot-Marie-Tooth disease. The occurrence of tonic pupil in association with decreased deep tendon reflexes in young women is referred to as **Adie syndrome.**

Ross syndrome is similar to Adie syndrome and includes decreased deep tendon reflexes and hypohidrosis.

Marcus Gunn Pupil

A **relative afferent pupillary defect** (Marcus Gunn pupil) indicates an asymmetric, *prechiasmatic* , afferent conduction defect. It is best demonstrated by the swinging flashlight test, which allows comparison of the direct and consensual pupillary responses in both eyes (Fig. 640.5). With patients fixing on a distant target (to control accommodation), a bright focal light is directed alternately into each eye in turn. In the presence of an afferent lesion, both the direct response to light in the affected eye and the consensual response in the other eye are subnormal. Swinging the light to the better or normal eye causes both pupils to react (constrict) normally. Swinging the light back to the affected eye causes both pupils to redilate to some degree, reflecting the defective conduction. This is a very sensitive and useful test for detecting and confirming optic nerve and retinal disease. This test is only abnormal if there is a “relative” difference in the conduction properties of the optic nerves. Therefore patients with bilateral and symmetric optic nerve disease will not demonstrate an afferent pupillary defect. A subtle relative afferent defect may be found in some children with amblyopia.

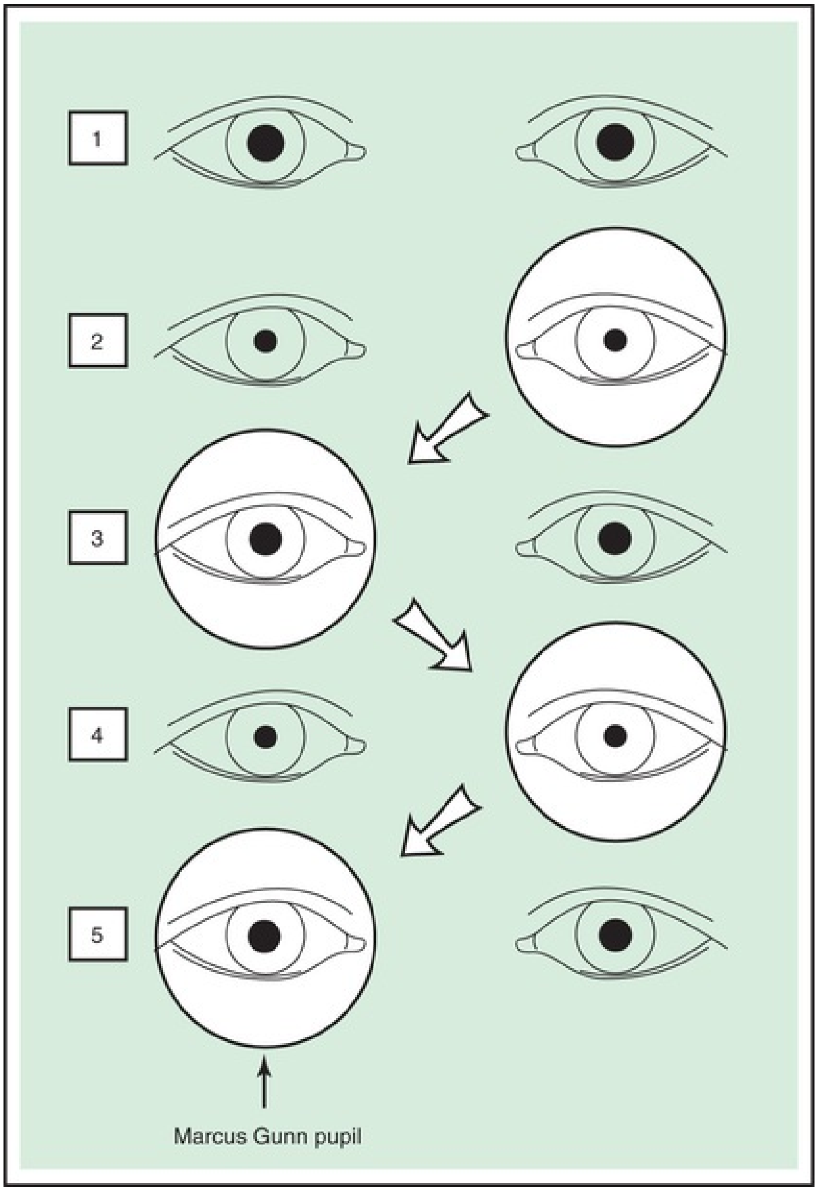

FIG. 640.5 The relative afferent pupillary defect (Marcus Gunn pupil). The figure depicts a patient with an abnormal right optic nerve. Under normal room light illumination (row 1), the pupils are symmetrical. During the swinging flashlight test, the pupils constrict when the normal eye is illuminated (rows 2 and 4) but dilate when the abnormal eye is illuminated (rows 3 and 5). Although both pupils constrict or dilate simultaneously, the clinician is usually focused on just the illuminated pupil. The pupil that dilates during the swinging flashlight test has the “relative afferent pupillary defect” and is labeled the Marcus Gunn pupil. (From McGee S: Evidence-based physical diagnosis, ed 3, Philadelphia, 2012, Elsevier/Saunders, Fig. 20.2, p. 165.)

Horner Syndrome

The principal signs of oculosympathetic paresis (Horner syndrome) are homolateral miosis, mild ptosis, and apparent enophthalmos with slight elevation of the lower lid as a result of the ptosis. Patients may also have decreased facial sweating, increased amplitude of accommodation, and transient decrease in intraocular pressure. If paralysis of the ocular sympathetic fibers occurs before the age of 2 yr, heterochromia iridis with hypopigmentation of the iris may occur on the affected side (Fig. 640.6).

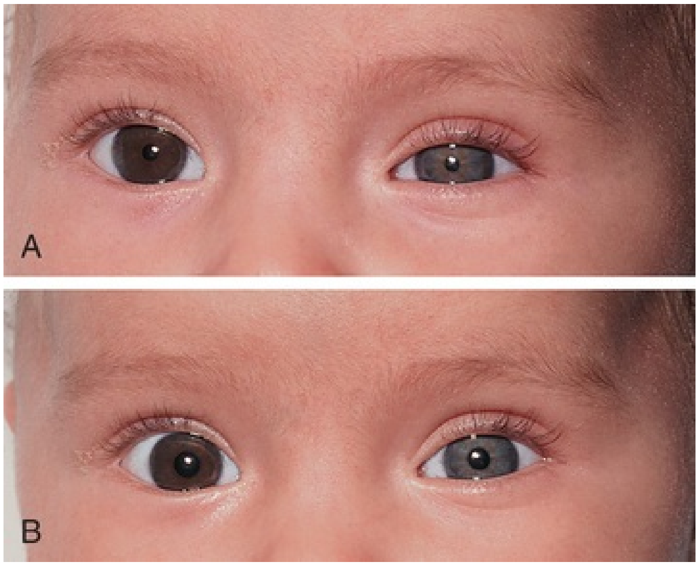

FIG. 640.6 Left congenital Horner syndrome showing upper- and lower-lid ptosis and an iris heterochromia, with the lighter eye being the affected eye. In bright light **(A)** and in the dark **(B)** . (From Hoyt CS, Taylor D, editors: Pediatric ophthalmology and strabismus, ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 63.9, p. 661.)

Oculosympathetic paralysis may be caused by a lesion (tumor, trauma, infarction) in the midbrain, brainstem, upper spinal cord, neck, middle fossa, or orbit. Congenital oculosympathetic paresis, often as part of **Klumpke brachial palsy** , is common, although the ocular signs, particularly the anisocoria, may pass undetected for years. Horner syndrome is also seen in some children after thoracic surgery. *Congenital* Horner syndrome may occur in association with vertebral anomalies and with enterogenous cysts. In some infants and children, Horner syndrome is the presenting sign of tumor in the mediastinal or cervical region—particularly neuroblastoma. Rare causes of Horner syndrome, such as vascular lesions, also occur in the pediatric age group. In many cases, no cause of congenital Horner syndrome can be identified. Occasionally the condition is familial.

When the cause of Horner syndrome is in question, investigative procedures should be implemented and may include imaging of the head, neck, and chest, as well as 24-hr urinary catecholamine assay. Examining old photographs and old records can sometimes be helpful in establishing the age at onset of Horner syndrome.

The cocaine test is useful in diagnosing oculosympathetic paralysis; a normal pupil dilates within 20–45 min after instillation of 1 or 2 drops of 4% cocaine, whereas the miotic pupil of an oculosympathetic paresis dilates poorly, if at all, with cocaine. In some cases, there is denervation supersensitivity to dilute phenylephrine; 1 or 2 drops of a 1% solution dilates the affected pupil but not the normal one. Furthermore instillation of 1% hydroxyamphetamine hydrobromide dilates the pupil only if the postganglionic sympathetic neuron is intact.

Paradoxical Pupil Reaction

Some children exhibit paradoxical constriction of the pupils to darkness. An initial brisk constriction of the pupils occurs when the light is turned off, followed by slow redilation of the pupils. The response to direct light stimulation and the near response are normal. The mechanism is not clear, but paradoxical constriction of the pupils in reduced light can be a sign of retinal or optic nerve abnormalities. The phenomenon has been observed in children with congenital stationary night blindness, albinism, retinitis pigmentosa, Leber congenital retinal amaurosis, and Best disease. It has also been observed in those with optic nerve anomalies, optic neuritis, optic atrophy, and possibly amblyopia. Thus children with paradoxical pupillary constriction to darkness should have a thorough ophthalmologic examination.

Persistent Pupillary Membrane

Involution of the pupillary membrane and anterior vascular capsule of the lens is usually completed during the 5th-6th mo of fetal development. It is common to see some remnants of the pupillary membrane in newborns, particularly in premature infants. These membranes are nonpigmented strands of obliterated vessels that cross the pupil and may secondarily attach to the lens or cornea. The remnants tend to atrophy in time and usually present no problem. In some cases, however, significant remnants that remain obscure the pupil and interfere with vision. In rare cases, there is patency of the vascular elements; hyphema may result from rupture of persistent vessels.

Intervention must be considered to minimize amblyopia in infants with extensive persistent pupillary membrane of sufficient degree to interfere with vision in the early months of life. In some cases, mydriatics and occlusion therapy may be effective, but in others, surgery may be needed to provide an adequate pupillary aperture.

Heterochromia

In heterochromia, the 2 irides are of different color (heterochromia iridium) or a portion of an iris differs in color from the remainder (heterochromia iridis). Simple heterochromia may occur as an autosomal dominant characteristic. Congenital heterochromia is also a feature of Waardenburg syndrome, an autosomal dominant condition characterized principally by lateral displacement of the inner canthi and puncta, pigmentary disturbances (usually a median white forelock and patches of hypopigmentation of the skin), and defective hearing. Change in the color of the iris may occur as a result of trauma, hemorrhage, intraocular inflammation (iridocyclitis, uveitis), intraocular tumor (especially retinoblastoma), intraocular foreign body, glaucoma, iris atrophy, oculosympathetic palsy (Horner syndrome), melanosis oculi, previous intraocular surgery, and some glaucoma medications.

Other Iris Lesions

Discrete nodules of the iris, referred to as **Lisch nodules** , are commonly seen in patients with neurofibromatosis (see Chapter 614.1). Lisch nodules represent melanocytic hamartomas of the iris and vary from slightly elevated pigmented areas to distinct ball-like excrescences. The nodules cause no visual disturbance. Lisch nodules are found in 92–100% of individuals older than 5 yr of age who have neurofibromatosis. Slit-lamp identification of these nodules may help fulfill the criteria required to confirm the diagnosis of neurofibromatosis.

In leukemia (see Chapter 522), there may be infiltration of the iris, sometimes with **hypopyon** , an accumulation of white blood cells in the anterior chamber, which may herald relapse or involvement of the central nervous system.

The lesion of **juvenile xanthogranuloma** (nevoxanthoendothelioma; see Chapter 690) may occur in the eye as a yellowish fleshy mass or plaque of the iris. Spontaneous **hyphema** (blood in the anterior chamber), glaucoma, or a red eye with signs of uveitis may be associated. A search for the skin lesions of xanthogranuloma should be made in any infant or young child with spontaneous hyphema. In many cases, the ocular lesion responds to topical corticosteroid therapy.

Leukocoria

This includes any white pupillary reflex, or so-called cat's-eye reflex. Primary diagnostic considerations in any child with leukocoria are cataract, persistent hyperplastic primary vitreous, cicatricial retinopathy of prematurity, retinal detachment, retinoschisis, larval granulomatosis, and retinoblastoma (Fig. 640.7). Also to be considered are endophthalmitis, organized vitreous hemorrhage, leukemic ophthalmopathy, exudative retinopathy (as in Coats disease), and less-common conditions such as medulloepithelioma, massive retinal gliosis, the retinal pseudotumor of Norrie disease, the so-called pseudoglioma of the Bloch-Sulzberger syndrome, retinal dysplasia, and the retinal lesions of the phakomatoses. A white reflex may also be seen with fundus coloboma, large atrophic chorioretinal scars, and ectopic medullation of retinal nerve fibers. *Leukocoria is an indication for prompt and thorough evaluation* .

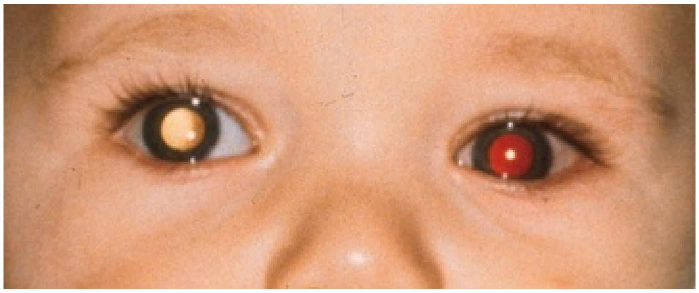

FIG. 640.7 **Red reflex. Normal red reflex in the left eye and white reflex in the right eye. This patient was later diagnosed with retinoblastoma in the right eye. (From Martin RJ, Fanaroff AA, Walsch MC editors: Fanaroff & Martin's neonatal-perinatal medicine, ed 10, Vol 2, Philadelphia, 2015, Elsevier/Saunders, Fig. 103.7, p. 1739.)**

The diagnosis can often be made by direct examination of the eye by ophthalmoscopy and biomicroscopy. Ultrasonographic and radiologic examinations are often helpful. In some cases, the final diagnosis rests with a pathologist.

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CHAPTER 641

Disorders of Eye Movement and Alignment

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Strabismus

Strabismus, or misalignment of the eyes, is one of the most common eye problems encountered in children, affecting approximately 4% of children younger than 6 yr of age. Strabismus can result in vision loss (amblyopia) and can have significant psychological effects. Early detection and treatment of strabismus are essential to prevent permanent visual impairment. Of children with strabismus, 30–50% develop amblyopia. Restoration of proper alignment of the visual axis must occur at an early stage of visual development to allow these children a chance to develop normal binocular vision. The word strabismus means "to squint or to look obliquely." Many terms are used in discussing and characterizing strabismus.

Orthophoria is the ideal condition of exact ocular balance. It implies that the oculomotor apparatus is in perfect equilibrium so that the eyes remain coordinated and aligned in all positions of gaze and at all distances. Even when binocular vision is interrupted, as by occlusion of 1 eye, truly orthophoric individuals maintain perfect alignment. Orthophoria is seldom encountered because the majority of individuals have a small latent deviation (heterophoria).

Heterophoria is a latent tendency for the eyes to deviate. This latent deviation is normally controlled by fusional mechanisms that provide binocular vision or avoid diplopia (double vision). The eye deviates only under certain conditions, such as fatigue, illness, or stress, or during tests that interfere with maintenance of these normal fusional abilities (such as covering 1 eye). If the amount of heterophoria is large, it may give rise to bothersome symptoms, such as transient diplopia (double vision), headaches, or asthenopia (eyestrain). Some degree of heterophoria is found in normal individuals; it is usually asymptomatic.

Heterotropia is a misalignment of the eyes that is constant. It occurs because of an inability of the fusional mechanism to control the deviation. Tropias may be unilateral or may alternate between either eye, depending on the patient. In an alternating tropia, there is no preference for fixation of either eye, and both eyes drift with equal frequency. Because each eye is used periodically, vision usually develops normally. A unilateral tropia is a more serious situation because only 1 eye is constantly misaligned. The undeviated eye becomes the preferred eye, resulting in loss of vision or amblyopia of the deviated eye.

It is common in ocular misalignments to describe the type of deviation. This helps to make decisions on the cause and treatment of the strabismus. The prefixes *eso-*, *exo-*, *hyper-*, and *hypo-* are added to the terms *phoria* and *tropia* to further delineate the type of strabismus. Esophorias and esotropias are inward or convergent deviations of the eyes, commonly known as crossed eyes. Exophorias and exotropias are divergent or outward-facing eye deviations, walleyed being the lay term. Hyperdeviations and hypodeviations designate upward or downward, respectively, deviations of an eye. In cases of unilateral strabismus, the deviating eye is often part of the description of the misalignment (left esotropia).

Diagnosis

Many techniques are used to assess ocular alignment and movement of the eyes to aid in diagnosing strabismic disorders. In a child with strabismus or any other ocular disorder, assessment of visual acuity is mandatory. Decreased vision in 1 eye requires evaluation for a strabismus or other ocular abnormalities, which may be difficult to discern on a brief screening evaluation. Even strabismic deviations of only a few degrees in magnitude, too small to be evident by gross inspection, may lead to amblyopia and significant vision loss.

Corneal light reflex tests are perhaps the most rapid and easily performed diagnostic tests for strabismus. They are particularly useful in children who are uncooperative and in those who have poor ocular fixation. To perform the **Hirschberg corneal reflex test,** the examiner projects a light source onto the cornea of both eyes simultaneously as a child looks directly at the light. Comparison should then be made of the placement of the corneal light reflex in each eye. In straight eyes, the light reflection appears symmetric and, because of the relationship between the cornea and the macula, slightly nasal to the center of each pupil. If strabismus is present, the reflected light is asymmetric and appears displaced in 1 eye. The Krimsky method of the corneal reflex test uses prisms placed over 1 or both eyes to align the light reflections. The amount of prism needed to align the reflections is used to measure the degree of deviation. Although it is a useful screening test, corneal light reflex testing may not detect a small angle or an intermittent strabismus.

Cover tests for strabismus require a child's attention and cooperation, good eye movement capability, and reasonably good vision in each eye (Fig. 641.1). If any of these are lacking, the results of these tests may not be valid. These tests consist of the cover–uncover test and the alternate cover test. In the cover–uncover test, a child looks at an object in the distance, preferably 6 m away. An eye chart is commonly used for fixation in children older than 3 yr of age. For younger children, a noise-making toy or movie helps hold their attention for the test. As the child looks at the distant object, the examiner covers 1 eye and watches for movement of the uncovered eye. If no movement occurs, there is no apparent misalignment of that eye. After 1 eye is tested, the same procedure is repeated on the other eye. When performing the alternate cover test, the examiner rapidly covers and uncovers each eye, shifting back and forth from one eye to the other. If the child has an ocular deviation, the eye rapidly moves as the cover is shifted to the other eye. Both the cover–uncover test and the alternate cover test should be performed at both distance and near fixation. The cover–uncover test differentiates tropias, or manifest deviations, from latent deviations, called **phorias** .

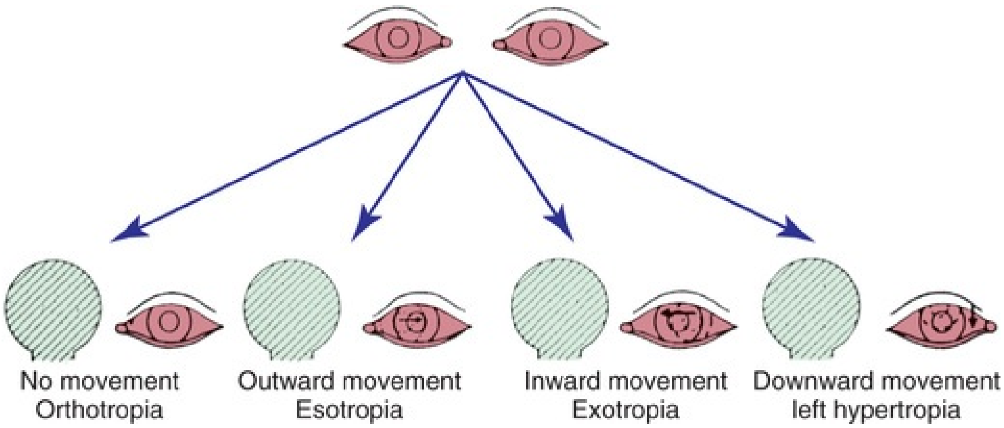

FIG. 641.1 The cover test. In each instance, the occluder is placed over the right eye while the patient is viewing a fixation target and the examiner is watching for movement of the patient's left eye. If the left eye is not aligned, it will need to move to look at the fixation target. If there is no movement of the left eye, the test needs to be

repeated by occluding the left eye and watching for movement of the right eye. (From Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, editors: Nelson pediatric symptom-based diagnosis, Philadelphia, 2018, Elsevier, Fig. 32.6, p. 567.)

Clinical Manifestations and Treatment

The etiologic classification of strabismus is complex, and the causative types must be distinguished; there are comitant and noncomitant forms of strabismus.

Comitant Strabismus

Comitant strabismus is the most common type of strabismus. The individual extraocular muscles usually have no defect. The amount of deviation is constant, or relatively constant, in the various directions of gaze.

Pseudostrabismus (pseudoesotropia) is one of the most common reasons a pediatric ophthalmologist is asked to evaluate an infant. This condition is characterized by the false appearance of strabismus when the visual axes are aligned accurately. This appearance may be caused by a flat, broad nasal bridge, prominent epicanthal folds, or a narrow interpupillary distance. The observer may see less white sclera nasally than would be expected, and the impression is that the eye is turned in toward the nose, especially when the child gazes to either side. Parents frequently comment that when their child looks to the side, the eye almost disappears from view. Pseudoesotropia can be differentiated from a true misalignment of the eyes when the corneal light reflex is centered in both eyes and when the cover–uncover test shows no refixation movement. Once pseudoesotropia has been confirmed, parents can be reassured that the child will outgrow the appearance of esotropia. As the child grows, the bridge of the nose becomes more prominent and displaces the epicanthal folds, and the medial sclera becomes proportional to the amount visible on the lateral aspect. It is the appearance of crossing that the child will outgrow. Some parents of children with pseudoesotropia erroneously believe that their child has an actual esotropia that will resolve on its own. Because true esotropia can develop later in children with pseudoesotropia, parents and pediatricians should be cautioned that reassessment is required if the apparent deviation does not improve.

Esodeviations are the most common type of ocular misalignment in children and represent >50% of all ocular deviations. *Congenital esotropia* is a confusing term. Few children who are diagnosed with this disorder are actually born with an esotropia. For this reason, infants with confirmed onset earlier than 6 mo are typically considered to have what was previously classified as congenital esotropia, though the term **infantile esotropia** is perhaps a more accurate description.

Between 2 and 4 mo of age, many infants have infantile esotropia (neonatal misalignments), which in most resolve spontaneously. Those that resolve without treatment do so before 10-12 wk of age and have intermittent or variable deviations. Those most likely to benefit from active treatment have persistent esotropia (10 wk-6 mo of age) and constant esotropia (40 PD), in combination with a refractive error ≤ +3.00 D, and the absence of prematurity, developmental delay, meningitis, nystagmus, eye anomalies, and incomitant or paralytic strabismus. The evaluation is noted in Figure 641.2 .

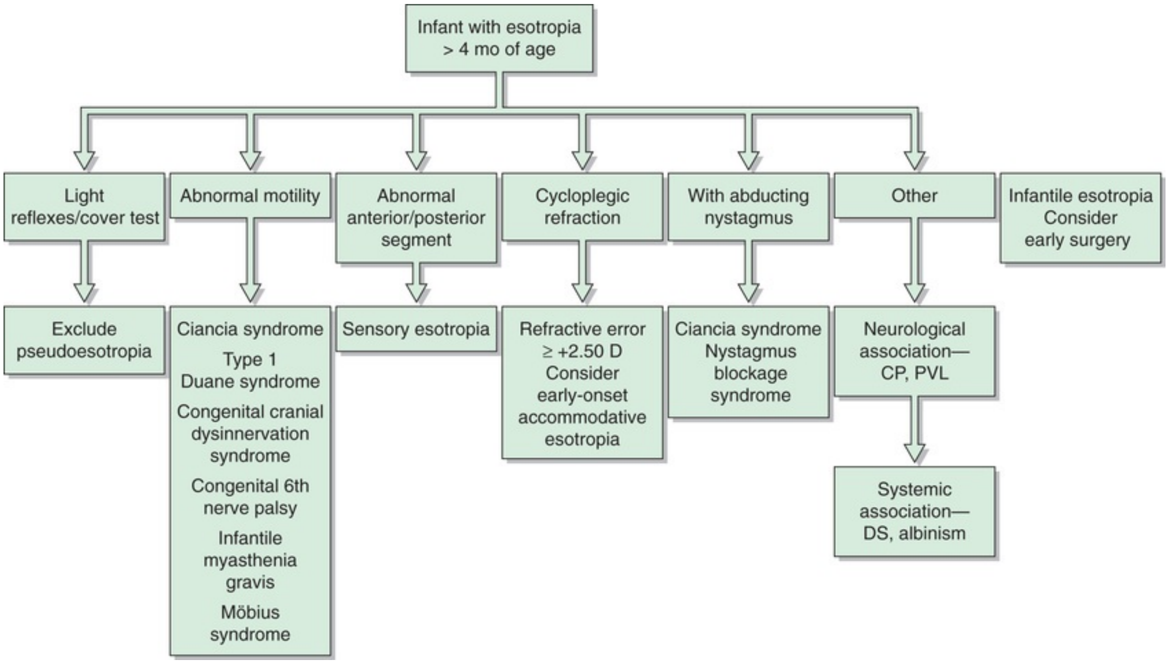
Infant with esotropia > 4 mo of age
Light reflexes/cover test
Abnormal motility
Abnormal anterior/posterior segment
Cycloplegic refraction
With abducting nystagmus
Other
Infantile esotropia Consider early surgery
Exclude pseudoesotropia
Ciancia syndrome
Type 1 Duane syndrome
Congenital cranial dysinnervation syndrome
Congenital 6th nerve palsy
Infantile myasthenia gravis
Möbius syndrome
Sensory esotropia
Refractive error ≥ +2.50 D Consider early-onset accommodative esotropia
Ciancia syndrome Nystagmus blockage syndrome
Neurological association— CP, PVL
Systemic association— DS, albinism

FIG. 641.2 Work-up of infant ≥4 mo of age with esotropia. *CP* , Cerebral palsy; *DS* , Down syndrome; *PVL* , periventricular leukomalacia. (From Hoyt CS, Taylor D, editors: Pediatric ophthalmology and strabismus, ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 74.4, p. 767.)

The characteristic angle of infantile esodeviations is large and constant (Fig. 641.3). Because of the large deviation, cross-fixation is frequently encountered. This is a condition in which the child looks to the right with the left eye and to the left with the right eye. With cross-fixation, there is no need for the eye to turn away from the nose (abduction) as the adducting eye is used in side gaze; this condition simulates a 6th nerve palsy. Abduction can be demonstrated by the doll's-head maneuver or by patching 1 eye for a short time. Children with infantile esotropia tend to have refractive errors similar to those of normal children of the same age. This contrasts with the characteristic high level of farsightedness associated with accommodative esotropia. **Amblyopia** is common in children with infantile esotropia.

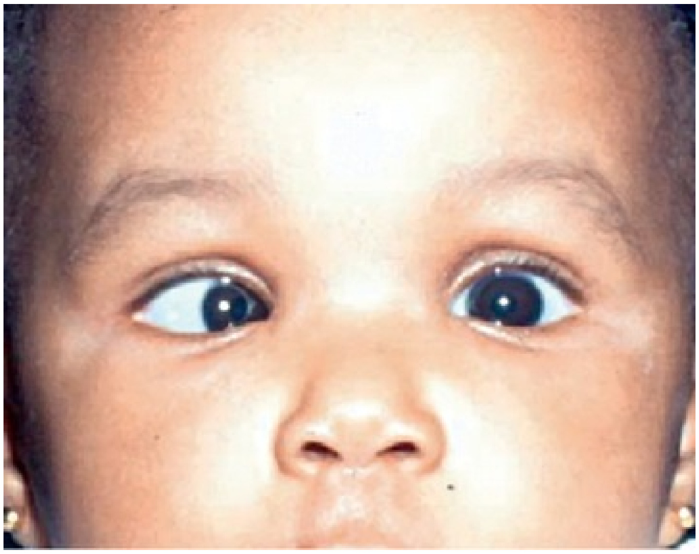

FIG. 641.3 **Congenital esotropia. Note the large angle of crossing.**

The primary goal of **treatment** in infantile esotropia is to eliminate or reduce the deviation as much as possible. Ideally this results in normal sight in each eye, in straight-looking eyes, and in the development of binocular vision. Early treatment is more likely to lead to the development of binocular vision, which helps maintain long-term ocular alignment. Once any associated amblyopia is treated, surgery is performed to align the eyes. Even with successful surgical alignment, it is common for vertical deviations to develop in children with a history of infantile esotropia. The 2 most common forms of vertical deviations to develop are inferior oblique muscle overaction and dissociated vertical deviation. In inferior oblique muscle overaction, the overactive inferior oblique muscle produces an upshoot of the eye closest to the nose when the patient looks to the side (Fig. 641.4). In dissociated vertical deviation, 1 eye drifts up slowly with no movement of the other eye. Surgery may be necessary to treat either or both of these conditions.

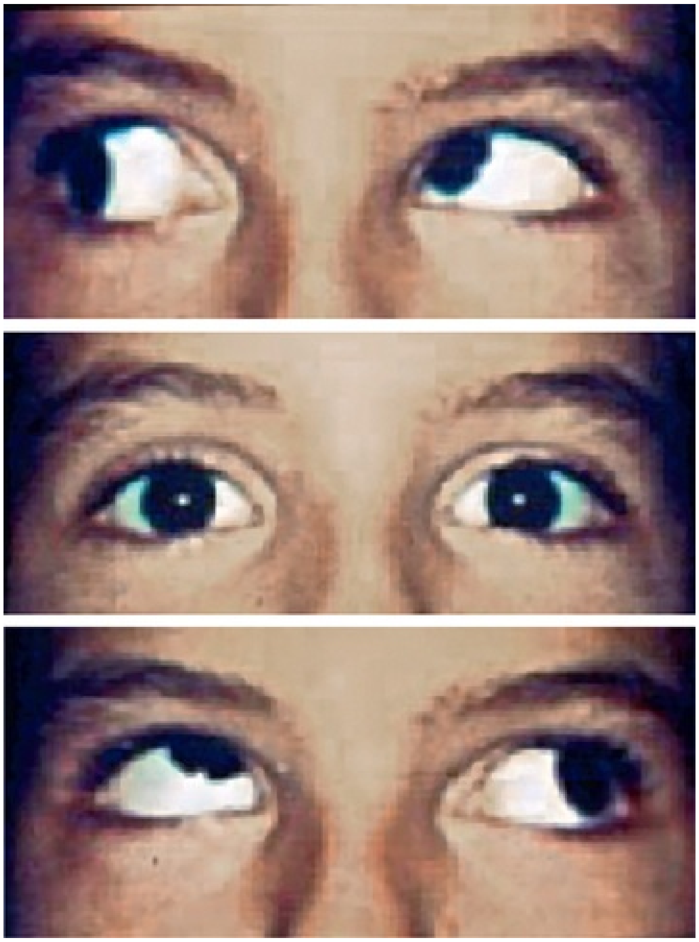

FIG. 641.4 Inferior oblique muscle overaction.

It is important that parents realize that early successful surgical alignment is only the beginning of the treatment process. Because many children may redevelop strabismus or amblyopia, they need to be monitored closely during the visually immature period of life.

Accommodative esotropia is defined as a “convergent deviation of the eyes associated with activation of the accommodative (focusing) reflex.” It usually occurs in a child who is between 2 and 3 yr of age and who has a history of acquired intermittent or constant crossing. Amblyopia occurs in the majority of cases.

The mechanism of accommodative esotropia involves uncorrected hyperopia, accommodation, and accommodative convergence. The image entering a hyperopic (farsighted) eye is blurred. If the amount of hyperopia is not significant, the blurred image can be sharpened by accommodating (focusing of the lens of the eye). Accommodation is closely linked with convergence (eyes turning inward), as both are required to view an object at near. If a child's hyperopic refractive error is large or if the amount of convergence that occurs in response to each unit of accommodative effort is great, esotropia may develop.

The **treatment** for accommodative esotropia is to prescribe the full hyperopic (farsighted) correction. These glasses eliminate a child's need to accommodate and therefore correct the esotropia (Fig. 641.5). Although many parents are initially concerned that their child will not want to wear glasses, the benefits of binocular vision and the decrease in the focusing effort required to see clearly provide a strong stimulus to wear glasses, and they are generally accepted well. The full hyperopic correction sometimes straightens the eye position at distance fixation but leaves a residual deviation at near fixation. This may be observed, treated with bifocal lenses, or treated with surgery.

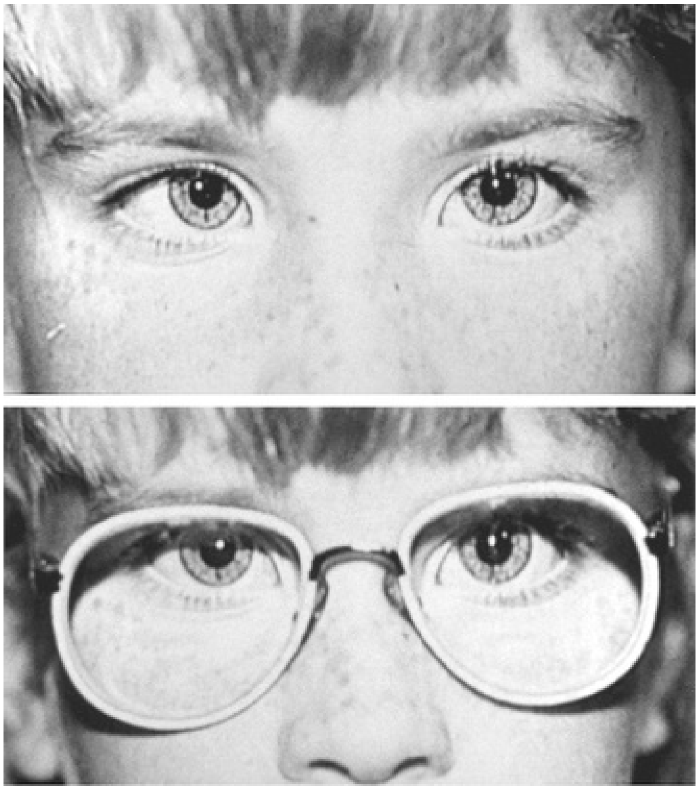

FIG. 641.5 **Accommodative esotropia. Control of deviation with corrective lenses.**

It is important to warn parents of children with accommodative esotropia that the esodeviation may appear to increase without glasses after the initial correction is worn. Parents frequently state that before wearing glasses, their child had a small esodeviation, whereas after removal of the glasses, the esodeviation becomes quite large. Parents often blame the increased esodeviation on the glasses. This apparent increase is a result of a child's using the appropriate amount of accommodative effort after the glasses have been worn. When these children remove their glasses, they continue to use an accommodative effort to bring objects into proper focus and increase the esodeviation.

Most children maintain straight eyes once initially treated. Because hyperopia generally decreases with age, patients may outgrow the need to wear glasses to maintain alignment. In some patients, a residual esodeviation persists even when wearing their glasses. This condition commonly occurs when there is a delay between the onset of accommodative esotropia and treatment. In others, the esotropia may initially be eliminated with glasses, but crossing redevelops and is not correctable with glasses. The crossing that is no longer correctable with glasses is the deteriorated or nonaccommodative portion. Surgery for this portion of the crossing may be indicated to restore binocular vision.

Exodeviations are the second most common type of misalignment. The divergent deviation may be intermittent or constant. Intermittent exotropia is the most common exodeviation in childhood. It is characterized by outward drifting of 1 eye, which usually occurs when a child is fixating at distance. The deviation is generally more frequent with fatigue or illness. Exposure to bright light may cause reflex closure of the exotropic eye. Because the eyes initially can be kept straight most of the time, visual acuity tends to be good in both eyes and binocular vision is initially normal.

The age at onset of intermittent exotropia varies but is often between age 6 mo and 4 yr. The decision to perform eye muscle surgery is based on the amount and frequency of the deviation. If the deviation is small and infrequent, it is reasonable to observe the child. If the exotropia is large or increasing in frequency, surgery is indicated to maintain normal binocular vision.

Constant exotropia may rarely be congenital. Congenital exotropia may be associated with neurologic disease or abnormalities of the bony orbit, as in Crouzon syndrome. Exotropia that occurs later in life may represent a deterioration of an intermittent exotropia that was present in childhood. Surgery can restore binocular vision even in long-standing cases.

Noncomitant Strabismus

When an eye muscle is paretic, palsied, or restricted, a muscle imbalance occurs in which the deviation of the eye varies according to the direction of gaze. Recent onset of a paretic muscle can be suggested by the symptom of double vision that increases in one direction, the findings of an ocular deviation that increases in the field of action of the paretic muscle, and an increase in the deviation when the child fixates with the paretic eye. It is important to differentiate a noncomitant strabismus from a comitant deviation because noncomitant forms of strabismus are often associated with trauma, systemic disorders, or neurologic abnormalities.

3rd Nerve Palsy

In the pediatric population, 3rd nerve palsies are usually congenital. The congenital form is often associated with a developmental anomaly or birth trauma. Acquired 3rd nerve palsies in children can be an ominous sign and may indicate a neurologic abnormality such as an intracranial neoplasm or an aneurysm. Other less-serious causes include an inflammatory or infectious lesion, head trauma, postviral syndromes, and migraines.

A 3rd nerve palsy, whether congenital or acquired, usually results in an exotropia and a hypotropia, or downward deviation of the affected eye, as well as complete or partial ptosis of the upper lid. This characteristic strabismus results from the action of the normal, unopposed muscles, the lateral rectus muscle, and the superior oblique muscle. If the internal branch of the 3rd nerve is involved, pupillary dilation may be noted as well. Eye movements are usually limited nasally, in elevation, and in depression. In addition, clinical findings and treatment may be complicated in congenital and traumatic cases of 3rd nerve palsy, owing to misdirection of regenerating nerve fibers, referred to as *aberrant regeneration* . This results in anomalous and paradoxical eyelid, eye, and pupil movement such as elevation of the eyelid, constriction of the pupil, or depression of the globe on attempted medial gaze.

4th Nerve Palsy

These palsies can be congenital or acquired. Because the 4th nerve has a long intracranial course, it is susceptible to damage resulting from head trauma. In children, however, 4th nerve palsies are more frequently congenital than traumatic. A palsied 4th nerve results in weakness in the superior oblique muscle, which causes an upward deviation of the eye, a hypertropia. Because the antagonist muscle, the inferior oblique, is relatively unopposed, the affected eye demonstrates an upshoot when looking toward the nose. Children typically present with a head tilt to the shoulder opposite the affected eye, their chin down, and their face turned away from the affected side. This head position places the eye away from the area of greatest action of the affected muscle and therefore minimizes the deviation and the associated double vision. Because the abnormal head posture maintains the child's ocular alignment, amblyopia is uncommon. Because no abnormality exists in the neck muscles, attempts to correct the head tilt by exercises and neck muscle surgery are ineffective. Recognition of a superior oblique paresis can be difficult because deviation of the head and the eye may be minimal. **Treatment** may include eye muscle surgery to improve the ocular alignment and eliminate the abnormal head posture.

6th Nerve Palsy

These palsies produce markedly crossed eyes with limited ability to move the afflicted eye laterally. Children frequently present with their head turned toward the palsied muscle, a position that helps preserve binocular vision. The esotropia is largest when the eye is moved toward the affected muscle.

Congenital 6th nerve palsies are rare. Decreased lateral gaze in infants is often associated with other disorders, such as infantile esotropia or Duane retraction syndrome. In neonates, a transient 6th nerve paresis can occur; it usually clears spontaneously by 6 wk. It is believed that increased intracranial pressure associated with labor and delivery is the contributing factor.

Acquired 6th nerve palsies in childhood are often an ominous sign because the 6th nerve is susceptible to increased intracranial pressure associated with hydrocephalous and intracranial tumors. Other causes of 6th nerve defects in children include trauma, vascular malformations, meningitis, and Gradenigo syndrome. A benign 6th nerve palsy, which is painless and acquired, can be noted in infants and older children. This is frequently preceded by a febrile illness or upper respiratory tract infection and may be recurrent. Complete resolution of the palsy is common in this scenario, though other causes of an acute 6th nerve palsy should be eliminated before this diagnosis is made.

Strabismus Syndromes

Special types of strabismus have unusual clinical features. Most of these disorders are caused by structural anomalies of the extraocular muscles or adjacent tissues. Most strabismus syndromes produce noncomitant misalignments.

Monocular Elevation Deficiency

A monocular elevation deficit in both abduction and adduction is referred to as monocular elevation deficiency (previously called double-elevator palsy). It may represent a paresis of both elevators, the superior rectus and inferior oblique muscles, or a possible restriction to elevation from a fibrotic inferior rectus muscle. When an affected child fixates with the nonparetic eye, the paretic eye is hypotropic and the ipsilateral upper eyelid may appear ptotic. Fixation with the paretic eye causes a hypertropia of the nonparetic eye and a disappearance of the ptosis (Fig. 641.6). Because the apparent ptosis is actually secondary to the strabismus, correction of the hypotropia treats the pseudoptosis.

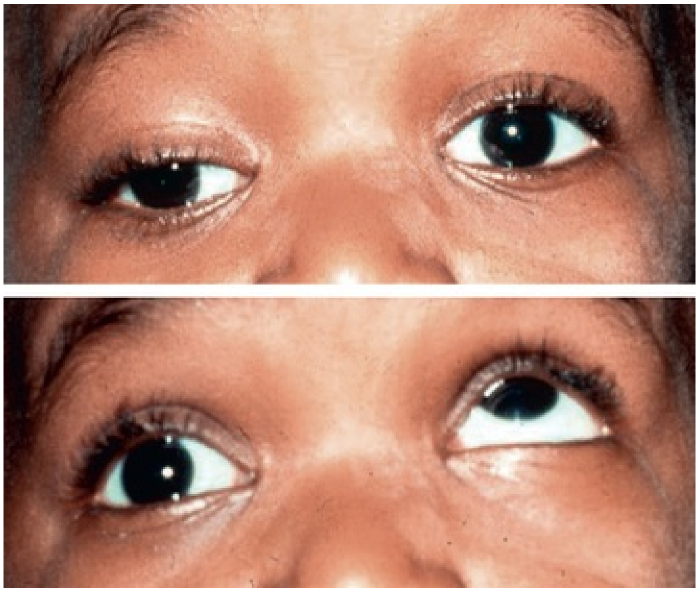

FIG. 641.6 Double-elevator palsy of the right eye. Note the disappearance of the apparent ptosis when fixating with the involved eye.

Duane Syndrome

This congenital disorder of ocular motility is characterized by retraction of the globe on adduction. This is attributed to the absence of the 6th nerve nucleus and anomalous innervation of the lateral rectus muscle, which results in co-contraction of the medial and lateral rectus muscles on attempted adduction of the affected eye. Within the spectrum of Duane syndrome, patients may exhibit impairment of abduction, impairment of adduction, or upshoot or downshoot of the involved eye on adduction. They may have esotropia, exotropia, or relatively straight eyes. Many exhibit a compensatory head posture to maintain single vision. Some develop amblyopia. Surgery to improve alignment or to reduce a noticeable face turn can be helpful in selected cases. Duane syndrome usually occurs sporadically. It is sometimes inherited as an autosomal dominant trait. It usually occurs as an isolated condition but may occur in association with various other ocular and systemic anomalies.

Möbius Syndrome

The distinctive features of Möbius syndrome are congenital facial paresis and abduction weakness. The facial palsy is commonly bilateral, frequently asymmetric, and often incomplete, tending to spare the lower face and platysma. Ectropion, epiphora, and exposure keratopathy may develop. The abduction defect may be unilateral or bilateral. Esotropia is common. The cause is unknown. Whether the primary defect is maldevelopment of cranial nerve nuclei, hypoplasia of the muscles, or a combination of central and peripheral factors is unclear. Some familial cases have been reported. Associated developmental defects may include ptosis, palatal and lingual palsy, hearing loss, pectoral and lingual muscle defects, micrognathia, syndactyly, supernumerary digits, and the absence of hands, feet, fingers, or toes. Surgical correction of the esotropia is indicated and any attendant amblyopia should be treated.

Brown Syndrome

In this syndrome, elevation of the eye in the adducted position is restricted (Fig. 641.7). An associated downward deviation of the affected eye in adduction may also occur. A compensatory head posture may be evident. Brown syndrome occurs as a result of restriction of the superior oblique tendon as it moves through the trochlea. Cases may be congenital or acquired. Acquired Brown syndrome may follow trauma to the orbit involving the region of the trochlea or sinus surgery. It may also occur with inflammatory processes, particularly sinusitis and juvenile idiopathic arthritis.

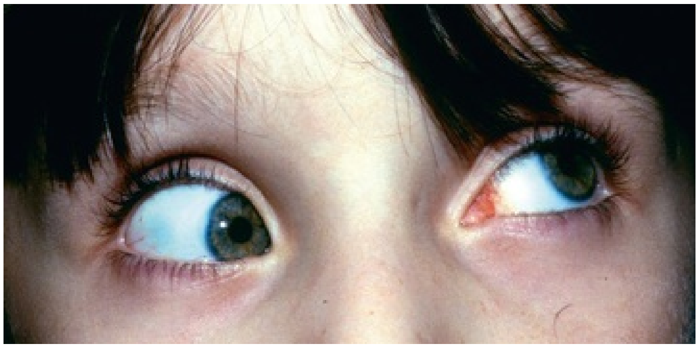

FIG. 641.7 Brown syndrome of the right eye.

Acquired inflammatory Brown syndrome may respond to treatment with either nonsteroidal medications or corticosteroids. Surgery may be helpful for selected cases of Brown syndrome.

Parinaud Syndrome

This eponym designates a palsy of vertical gaze, isolated or associated with pupillary or nuclear oculomotor (3rd cranial nerve) paresis. It indicates a lesion affecting the mesencephalic tegmentum. The ophthalmic signs of midbrain disease include vertical gaze palsy, dissociation of the pupillary responses to light and to near focus, general pupillomotor paralysis, corectopia, dyscoria, accommodative disturbances, pathologic lid retraction, ptosis, extraocular muscle paresis, and convergence paralysis. Some cases have associated spasms of convergence, convergent retraction nystagmus, and vertical nystagmus, particularly on attempted vertical gaze. Combinations of these signs are referred to as the **sylvian aqueduct syndrome** .

A principal cause of vertical gaze palsy and associated mesencephalic signs in children is tumor of the pineal gland or third ventricle. Differential diagnosis includes trauma and demyelinating disease. In children with hydrocephalus, impairment of vertical gaze and pathologic lid retraction are referred to as the setting-sun sign. A transient supranuclear disorder of gaze is sometimes seen in healthy neonates.

Congenital Ocular Motor Apraxia

This congenital disorder of conjugate gaze is characterized by a defect in voluntary horizontal gaze, compensatory jerking movement of the head, and retention of slow pursuit and reflexive eye movements. Additional features are absence of the fast (refixation) phase of optokinetic nystagmus and obligate contraversive deviation of the eyes on rotation of the body. Affected children typically are unable to look quickly to either side voluntarily in response to a command or in response to an eccentrically presented object but may be able to follow a slowly moving target to either side. To compensate for the defect in purposive lateral eye movements, children jerk their head to bring the eyes into the desired position and may also blink repetitively in an attempt to change fixation. The signs tend to become less conspicuous with age.

The pathogenesis of congenital ocular motor apraxia is unknown. It may be a result of delayed myelination of the ocular motor pathways. Structural abnormalities of the central nervous system have been found in a few patients, including agenesis of the corpus callosum and cerebellar vermis, porencephaly, hamartoma of the foramen of Monro, and macrocephaly. Many children with congenital ocular motor apraxia show delayed motor and cognitive development.

Nystagmus

Nystagmus (rhythmic oscillations of 1 or both eyes) may be caused by an abnormality in any 1 of the 3 basic mechanisms that regulate position and movement of the eyes: the fixation, conjugate gaze, or vestibular mechanism. In addition, physiologic nystagmus may be elicited by appropriate stimuli (Table 641.1).

Table 641.1

Specific Patterns of Nystagmus

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Latent nystagmus	Conjugate jerk nystagmus toward viewing eye	Congenital vision defects, occurs with occlusion of eye
Manifest latent nystagmus	Fast jerk to viewing eye	Strabismus, congenital idiopathic nystagmus
Periodic alternating	Cycles of horizontal or horizontal-rotary that change direction	Caused by both visual and neurologic conditions
Seesaw nystagmus	One eye rises and intorts as other eye falls and extorts	Usually associated with optic chiasm defects
Nystagmus retractorius	Eyes jerk back into orbit or toward each other	Caused by pressure on mesencephalic tegmentum (Parinaud syndrome)
Gaze-evoked nystagmus	Jerk nystagmus in direction of gaze	Caused by medications, brainstem lesion, or labyrinthine dysfunction
Gaze-paretic nystagmus	Eyes jerk back to maintain eccentric gaze	Cerebellar disease

Downbeat nystagmus	Fast phase beating downward	Posterior fossa disease, drugs
Upbeat nystagmus	Fast phase beating upward	Brainstem and cerebellar disease; some visual conditions
Vestibular nystagmus	Horizontal-torsional or horizontal jerks	Vestibular system dysfunction
Asymmetric or monocular nystagmus	Pendular vertical nystagmus	Disease of retina and visual pathways
Spasmus nutans	Fine, rapid, pendular nystagmus	Torticollis, head nodding; idiopathic or gliomas of visual pathways

From Kliegman R: Practical strategies in pediatric diagnosis and therapy, Philadelphia, 1996, WB Saunders.

Congenital sensory nystagmus is generally associated with ocular abnormalities that lead to decreased visual acuity; common disorders that lead to early-onset nystagmus include albinism, aniridia, achromatopsia, congenital cataracts, congenital macular lesions, and congenital optic atrophy. In some instances, nystagmus occurs as a dominant or X-linked characteristic without obvious ocular abnormalities.

Congenital idiopathic motor nystagmus is characterized by horizontal jerky oscillations with gaze preponderance; the nystagmus is coarser in one direction of gaze than in the other, with the jerk toward the direction of gaze. There are no ocular anatomic defects that cause the nystagmus, and the visual acuity is generally near normal. There may be a null point in which the nystagmus damps and the vision improves; a compensatory head posture will develop that places the eyes into the position of least nystagmus. The cause of congenital idiopathic motor nystagmus is unknown; in some instances, this is familial. Eye muscle surgery may be performed to eliminate an abnormal head posture by bringing the point of best vision into straight-ahead gaze.

Acquired nystagmus requires prompt and thorough evaluation. Worrisome pathologic types are the gaze-paretic or gaze-evoked oscillations of cerebellar, brainstem, or cerebral disease.

Nystagmus retractorius or **convergent nystagmus** is repetitive jerking of the eyes into the orbit or toward each other. It is usually seen with vertical gaze palsy as a feature of Parinaud (sylvian aqueduct) syndrome. The causal condition may be neoplastic, vascular, or inflammatory. In children, nystagmus retractorius suggests particularly the presence of pinealoma or hydrocephalus.

A diagnostic approach to nystagmus is noted in Figs. 641.8 and 641.9 , and Table 641.2 .

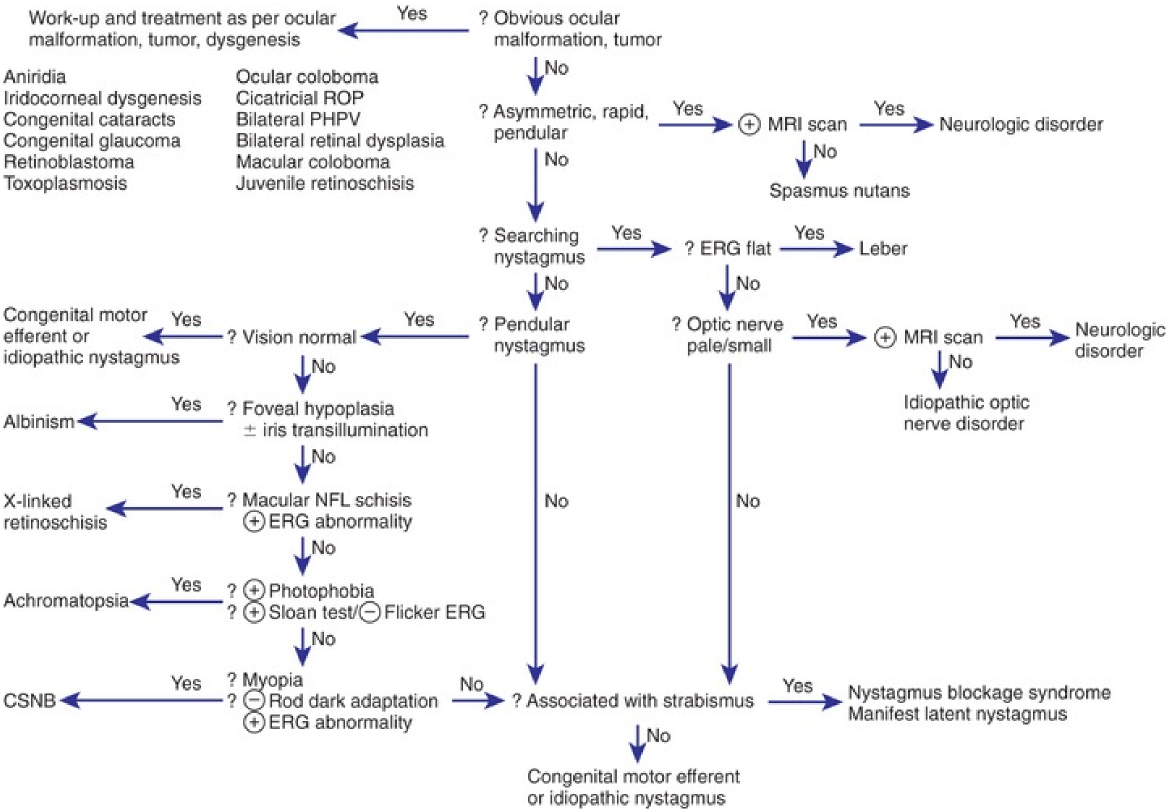
Work-up and treatment as per ocular malformation, tumor, dysgenesis
Yes
? Obvious ocular malformation, tumor
Aniridia
Iridocorneal dysgenesis
Congenital cataracts
Congenital glaucoma
Retinoblastoma
Toxoplasmosis
Ocular coloboma
Cicatricial ROP
Bilateral PHPV
Bilateral retinal dysplasia
Macular coloboma
Juvenile retinoschisis
No
? Asymmetric, rapid, pendular
Yes
⊕ MRI scan
Yes
Neurologic disorder
No
Spasmus nutans
No
? Searching nystagmus
Yes
? ERG flat
Yes
Leber
No
No
Congenital motor efferent or idiopathic nystagmus
Yes
? Vision normal
Yes
? Pendular nystagmus
? Optic nerve pale/small
Yes
⊕ MRI scan
Yes
Neurologic disorder
No
Idiopathic optic nerve disorder
No
Albinism
Yes
? Foveal hypoplasia ± iris transillumination
No
X-linked retinoschisis
Yes
? Macular NFL schisis ⊕ ERG abnormality
No
No
No
Achromatopsia
Yes
? ⊕ Photophobia
? ⊕ Sloan test/⊖ Flicker ERG
No
CSNB
Yes
? Myopia
? ⊖ Rod dark adaptation
⊕ ERG abnormality
No
? Associated with strabismus
Yes
Nystagmus blockage syndrome
Manifest latent nystagmus
No
Congenital motor efferent or idiopathic nystagmus

FIG. 641.8 Algorithm for the work-up of an infant with nystagmus. ⊕ , Positive; ⊖ , negative; *CSNB* , congenital stationary night blindness; *ERG* , electroretinogram; *NFL* , nerve fiber layer; *PHPV* , persistent hyperplastic primary vitreous; *ROP* , retinopathy of prematurity. (From Nelson LB: Harley's pediatric ophthalmology, ed 4, Philadelphia, 1998, WB Saunders, p. 470.)

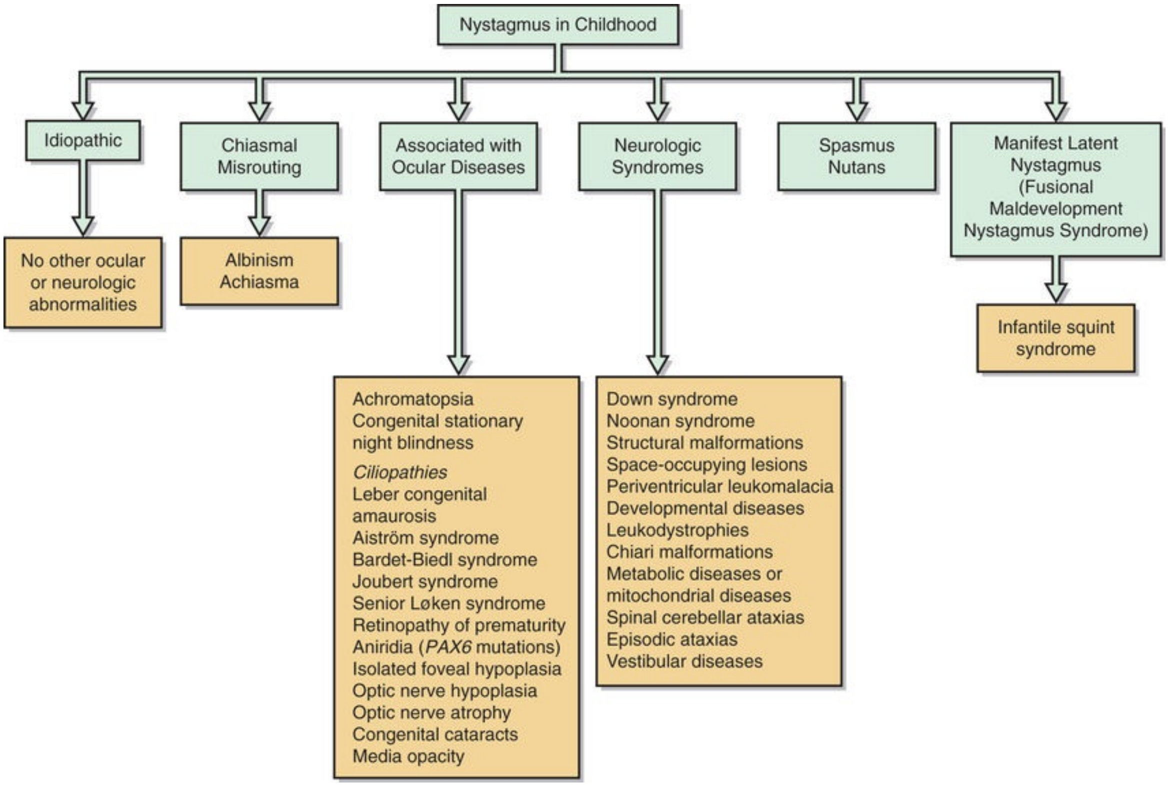
Nystagmus in Childhood
Idiopathic
Chiasmal Misrouting
Associated with Ocular Diseases
Neurologic Syndromes
Spasmus Nutans
Manifest Latent Nystagmus (Fusional Maldevelopment Nystagmus Syndrome)
No other ocular or neurologic abnormalities
Albinism
Achiasma
Infantile squint syndrome
Achromatopsia
Congenital stationary night blindness
Ciliopathies
Leber congenital amaurosis
Aiström syndrome
Bardet-Biedl syndrome
Joubert syndrome
Senior Løken syndrome
Retinopathy of prematurity
Aniridia (*PAX6* mutations)
Isolated foveal hypoplasia
Optic nerve hypoplasia
Optic nerve atrophy
Congenital cataracts
Media opacity
Down syndrome
Noonan syndrome
Structural malformations
Space-occupying lesions
Periventricular leukomalacia
Developmental diseases
Leukodystrophies
Chiari malformations
Metabolic diseases or mitochondrial diseases
Spinal cerebellar ataxias
Episodic ataxias
Vestibular diseases

FIG. 641.9 Classification of nystagmus based on associated diseases. (From Hoyt CS, Taylor D, editors: Pediatric ophthalmology and strabismus, ed 4, Philadelphia, 2013, Elsevier Saunders, Fig. 89.2, p. 910.)

Table 641.2

Key Distinguishing Features of Peripheral and Central Types of Spontaneous and Positional Nystagmus

TYPE OF NYSTAGMUS	PERIPHERAL (END ORGAN AND NERVE)	CENTRAL (BRAIN STEM AND CEREBELLUM)
Spontaneous	Unidirectional, fast phase away from the lesion, combined horizontal torsional, inhibited with fixation	Bidirectional or unidirectional; often pure horizontal, vertical, or torsional; *not* inhibited with fixation
Static positional	Fixed or changing direction, inhibited with fixation	Fixed or changing direction, *not* inhibited with fixation
Paroxysmal positional	Vertical-torsional, occasionally horizontal-torsional, vertigo prominent, fatigability, latency	Often pure vertical, vertigo less prominent, no latency, nonfatigable

From Goldman L, Schafer AI, editors: Goldman-Cecil medicine, ed 25, Philadelphia, 2016, Elsevier Table 424.5, p. 2579.

Spasmus nutans is a special type of acquired nystagmus in childhood (see also Chapter 615). In its complete form, it is characterized by the **triad** of pendular nystagmus, head nodding, and torticollis. The nystagmus is characteristically very fine, very rapid, horizontal, and pendular; it is often asymmetric, sometimes unilateral. Signs usually develop within the first year or two of life. Components of the triad may develop at various times. In many cases, the condition is benign and self-limited, usually lasting a few months, sometimes years. The cause of this classic type of spasmus nutans, which usually resolves spontaneously, is unknown. Some children exhibiting signs resembling those of spasmus nutans have underlying brain tumors, particularly hypothalamic and chiasmal optic gliomas. Appropriate neurologic and neuroradiologic evaluation and careful monitoring of infants and children with nystagmus are therefore recommended.

Other Abnormal Eye Movements

To be differentiated from true nystagmus are certain special types of abnormal eye movements, particularly opsoclonus, ocular dysmetria, and flutter (Table 641.3).

Table 641.3

Specific Patterns of Nonnystagmus Eye Movements

PATTERN	DESCRIPTION	ASSOCIATED CONDITIONS
Opsoclonus	Multidirectional conjugate movements of varying rate and amplitude	Hydrocephalus, diseases of brainstem and cerebellum, neuroblastoma, paraneoplasia syndrome
Ocular dysmetria	Overshoot of eyes on rapid fixation	Cerebellar dysfunction
Ocular flutter	Horizontal oscillations with forward gaze and sometimes with blinking	Cerebellar disease, hydrocephalus, or central nervous system neoplasm
Ocular bobbing	Downward jerk from primary gaze, remains for a few sec, then drifts back	Pontine disease
Ocular myoclonus	Rhythmic to-and-fro pendular oscillations of the eyes, with synchronous nonocular muscle movement	Damage to red nucleus, inferior olivary nucleus, and ipsilateral dentate nucleus

From Kliegman R: Practical strategies in pediatric diagnosis and therapy, Philadelphia, 1996, WB Saunders.

Opsoclonus

Opsoclonus and ataxic conjugate movements are spontaneous, nonrhythmic, multidirectional, chaotic movements of the eyes. The eyes appear to be in agitation, with bursts of conjugate movement of varying amplitude in varying directions. Opsoclonus is most often associated with infectious or autoimmune encephalitis. It may be the first sign of neuroblastoma or other tumors producing a paraneoplastic syndrome.

Ocular Motor Dysmetria

This is analogous to dysmetria of the limbs. Affected individuals show a lack of precision in performing movements of refixation, characterized by an overshoot (or undershoot) of the eyes with several corrective to-and-fro oscillations on looking from one point to another. Ocular motor dysmetria is a sign of cerebellar or cerebellar pathway disease.

Flutter-Like Oscillations

These intermittent to-and-fro horizontal oscillations of the eyes may occur spontaneously or on change of fixation. They are characteristic of cerebellar disease.

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CHAPTER 642

Abnormalities of the Lids

Scott E. Olitsky, Justin D. Marsh

Ptosis

In blepharoptosis, the upper eyelid droops below its normal level. Congenital ptosis is usually a result of a localized dystrophy of the levator muscle in which the striated muscle fibers are replaced with fibrous tissue. The condition may be unilateral or bilateral, and can be familial, transmitted as a dominant trait.

Parents often comment that the eye looks smaller because of the drooping eyelid. The lid crease is decreased or absent where the levator muscle would normally insert below the skin surface. Because the levator is replaced by fibrous tissue, the lid does not move downward fully in downgaze (lid lag). If the ptosis is severe, affected children often attempt to raise the lid by lifting their brow or adapting a chin-up head posture to maintain binocular vision.

Marcus Gunn jaw-winking ptosis (maxillopalpebral synkinesis) accounts for 5% of ptosis in children. In this syndrome, an abnormal synkinesis exists between the 5th and 3rd cranial nerves; this causes the eyelid to elevate with movement of the jaw. The wink is produced by chewing or sucking and may be more noticeable than the ptosis itself (Fig. 642.1).

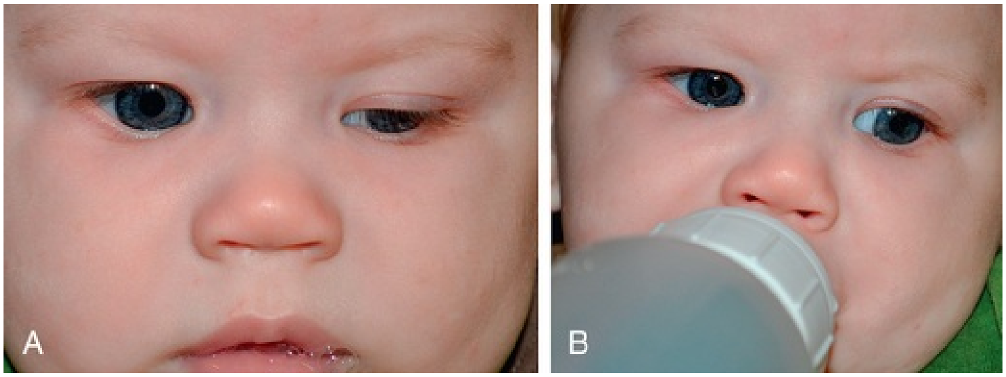

FIG. 642.1 **Marcus Gunn jaw-winking phenomenon. A, Left upper lid ptosis. B, The left lid raises up while the patient sucks from the bottle. (From Martin RJ, Fanaroff AA, Walsch MC, editors: Fanaroff & Martin's neonatal-perinatal medicine, ed 10, Philadelphia, 2015, Elsevier, Fig. 103.2.)**

Although ptosis in children is often an isolated finding, it may occur in association with other ocular or systemic disorders. Systemic disorders include myasthenia gravis, muscular dystrophy, and botulism. Ocular disorders include mechanical ptosis secondary to lid tumors, blepharophimosis syndrome, congenital fibrosis syndrome, combined levator/superior rectus maldevelopment, and congenital or acquired 3rd nerve palsy. A small degree of ptosis is seen in Horner syndrome (see Chapter 640). A complete ophthalmic and systemic examination is therefore important in the evaluation of a child with ptosis.

Amblyopia may occur in children with ptosis. The amblyopia may be secondary to the lid's covering the visual axis (deprivation) or induced astigmatism (anisometropia). When amblyopia occurs, it should generally be treated before treating the ptosis.

Treatment of ptosis in a child is indicated for elimination of an abnormal head posture, improvement in the visual field, prevention of amblyopia, and restoration of a normal eyelid appearance. The timing of surgery depends on the degree of ptosis, its cosmetic and functional severity, the presence or absence of compensatory posturing, the wishes of the parents, and the discretion of the surgeon. Surgical treatment is determined by the amount of levator function that is present. A levator resection may be used in children with moderate to good function. In patients with poor or absent function, a frontalis suspension procedure may be necessary. This technique requires that a suspension material be placed between the frontalis muscle and the tarsus of the eyelid. It allows patients to use their brow and frontalis muscle more effectively to raise their eyelid. Amblyopia may still exist even after surgical correction and should be treated if present.

Epicanthal Folds

These vertical or oblique folds of skin extend on either side of the bridge of the nose from the brow or lid area, covering the inner canthal region. They are present to some degree in most young children and become less apparent with age. The folds may be sufficiently broad to cover the medial aspect of the eye, making the eyes appear crossed (pseudoesotropia). Epicanthal folds are a common feature of many syndromes, including chromosomal aberrations (trisomies) and disorders of single genes.

Lagophthalmos

This is a condition in which complete closure of the lids over the globe is difficult or impossible. It may be paralytic because of a facial palsy involving the orbicularis muscle, or spastic, as in thyrotoxicosis. It may be structural when retraction or shortening of the lids results from scarring or atrophy consequent to injury (burns) or disease. Children with various craniosynostosis syndromes can have problematic lagophthalmos. Infants with collodion membrane may have temporary lagophthalmos caused by the restrictive effect of the membrane on the lids. Lagophthalmos may accompany proptosis or **buphthalmos** (enlarged cornea because of elevated intraocular pressure) when the lids, although normal, cannot effectively cover the enlarged or protuberant eye. A degree of physiologic lagophthalmos may occur normally during sleep, but functional lagophthalmos in an unconscious or debilitated patient can be a problem.

In patients with lagophthalmos, exposure of the eye may lead to drying, infection, corneal ulceration, or perforation of the cornea; the result may be loss of vision, even loss of the eye. In lagophthalmos, protection of the eye by artificial tear preparations, ophthalmic ointment, or moisture chambers is essential. Gauze pads are to be avoided because the gauze may abrade the cornea. In some cases, surgical closure of the lids (tarsorrhaphy) may be necessary for long-term protection of the eye.

Lid Retraction

Pathologic retraction of the lid may be myogenic or neurogenic. Myogenic retraction of the upper lid occurs in **thyrotoxicosis** , in which it is associated with 3 classic signs: a staring appearance (Dalrymple sign), infrequent blinking (Stellwag sign), and lag of the upper lid on downward gaze (von Graefe sign).

Neurogenic retraction of the lids may occur in conditions affecting the anterior mesencephalon. Lid retraction is a feature of the **syndrome of the sylvian aqueduct** . In children, it is commonly a sign of hydrocephalus. It may occur with meningitis. Paradoxical retraction of the lid is seen in the Marcus Gunn jaw-winking syndrome. It may also be seen with attempted eye movement after recovery from a 3rd nerve palsy, if aberrant regeneration of the oculomotor nerve fibers has occurred.

Simple staring and the physiologic or reflexive lid retraction (“eye popping”), in contrast to pathologic lid retractions, occur in infants in response to a sudden reduction in illumination or as a startle reaction.

Ectropion, Entropion, and Epiblepharon

Ectropion is eversion of the lid margin; it may lead to overflow of tears (epiphora) and subsequent maceration of the skin of the lid, inflammation of exposed conjunctiva, or superficial exposure keratopathy. Common causes are scarring consequent to inflammation, burns, or trauma and weakness of the orbicularis muscle as a result of facial palsy; these forms may be corrected surgically. Protection of the cornea is essential. Ectropion is also seen in certain children who have faulty development of the lateral canthal ligament; this may occur in Down syndrome.

Entropion is inversion of the lid margin, which may cause discomfort and corneal damage because of the inward turning of the lashes (trichiasis). A principal cause is scarring secondary to inflammation such as occurs in trachoma or as a sequela of Stevens-Johnson syndrome. There is also a rare congenital form. Surgical correction is effective in many cases.

Epiblepharon is commonly seen in childhood and may be confused with entropion. In epiblepharon, a roll of skin beneath the lower eyelid lashes causes the lashes to be directed vertically and to touch the cornea (Fig. 642.2). Unlike entropion, the eyelid margin itself is not rotated toward the cornea. Epiblepharon usually resolves spontaneously. If corneal scarring begins to occur, surgical correction may be necessary.

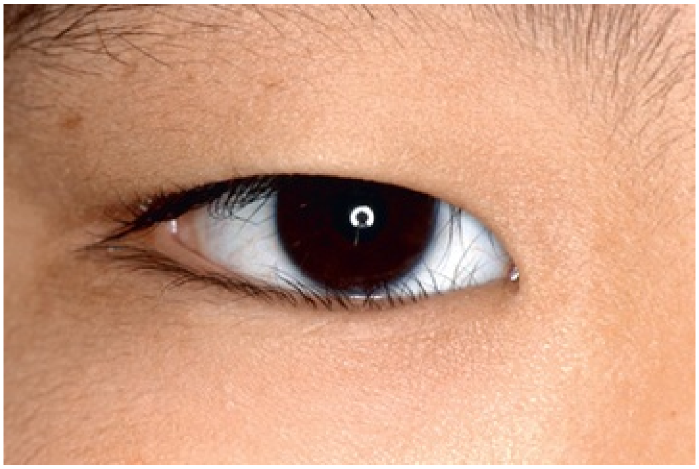

FIG. 642.2 Epiblepharon.

Blepharospasm

This spastic or repetitive closure of the lids may be caused by irritative disease of the cornea, conjunctiva, or facial nerve; fatigue or uncorrected refractive error; or common tic. Thorough ophthalmic examination for pathologic causes, such as trichiasis, keratitis, conjunctivitis, or foreign body, is indicated. Local injection of botulinum toxin may give relief, but frequently must be repeated.

Blepharitis

This inflammation of the lid margins is characterized by erythema and crusting or scaling; the usual symptoms are irritation, burning, and itching. The condition is commonly bilateral and chronic or recurrent. The 2 main types are **staphylococcal** and **seborrheic.** In staphylococcal blepharitis, ulceration of the lid margin is common, the lashes tend to fall out, and conjunctivitis and superficial keratitis are often associated. In seborrheic blepharitis, the scales tend to be greasy, the lid margins are less red, and ulceration usually does not occur. Commonly blepharitis presents as a combination of the 2.

Thorough daily cleansing of the lid margins with a cloth or moistened cotton applicator to remove scales and crusts is important in the **treatment** of both forms. Staphylococcal blepharitis is treated with an antistaphylococcal antibiotic applied directly to the lid margins. When a child also has seborrhea, concurrent treatment of the scalp is important.

Pediculosis of the eyelashes may produce a clinical picture of blepharitis. The lice can be smothered with ophthalmic-grade petrolatum ointment applied to the lid margin and lashes. Nits should be mechanically removed from the lashes. It should be remembered that pediculosis can represent a sexually transmitted disease. Molluscum virus involvement of the lids can also cause blepharitis.

Hordeolum (Stye)

Infection of the glands of the lid may be acute or subacute; tender focal swelling and redness are noted. The usual agent is *Staphylococcus aureus.* When the meibomian glands are involved, the lesion is referred to as an internal hordeolum; the abscess tends to be large and may point through either the skin or the conjunctival surface. When the infection involves the glands of Zeis or Moll, the abscess tends to be smaller and more superficial and points at the lid margin; it is then referred to as an external hordeolum or stye.

Treatment is frequent warm compresses and, if necessary, surgical incision and drainage. In addition, topical antibiotic preparations are often used. Untreated, the infection may progress to cellulitis of the lid or orbit, requiring the use of systemic antibiotics.

Chalazion

A chalazion is a granulomatous inflammation of a meibomian gland characterized by a firm, nontender nodule in the upper or lower lid. This lesion tends to be chronic and differs from internal hordeolum in the absence of acute inflammatory signs. Although many chalazia subside spontaneously, excision may be necessary if they become large enough to distort vision (by inducing astigmatism by exerting pressure on the globe) or become cosmetically unacceptable. Patients who experience frequent chalazia formation, or those who have significant corneal changes secondary to the underlying blepharitis, may benefit from systemic, low-dose erythromycin or azithromycin treatment.

Coloboma of the Eyelid

This cleft-like deformity may vary from a small indentation or notch of the free margin of the lid to a large defect involving almost the entire lid. If the gap is extensive, ulceration and corneal opacities may result from exposure. Early surgical correction of the lid defect is recommended. Other deformities frequently associated with lid colobomas include dermoid cysts or dermolipomas on the globe; they often occur in a position corresponding to the site of the lid defect. Lid colobomas may also be associated with extensive facial malformation, as in mandibulofacial dysostosis (Franceschetti or Treacher Collins syndrome).

Tumors of the Lid

A number of lid tumors arise from surface structures (the epithelium and sebaceous glands). Nevi may appear in early childhood; most are junctional. Compound nevi tend to develop in the prepubertal years and dermal nevi at puberty. Malignant epithelial tumors (basal cell carcinoma, squamous cell carcinoma) are rare in children, but the basal cell nevus syndrome and the malignant lesions of xeroderma pigmentosum and of Rothmund-Thomson syndrome may develop in childhood.

Other lid tumors arise from deeper structures (the neural, vascular, and connective tissues). **Capillary hemangiomas** are especially common in children (Fig. 642.3). Many tend to regress spontaneously, although they may show alarmingly rapid growth in infancy. In many cases, the best management of such hemangiomas is patient observation, allowing spontaneous regression to occur (see Chapter 669). In the case of a rapidly expanding lesion, which may cause amblyopia by obstructing the visual axis or inducing astigmatism, **treatment** should be considered. Systemic propranolol has been shown to be an effective treatment without the risks associated with corticosteroid use. Other treatment options include topical timolol, corticosteroids (systemically or by direct injection), and surgical excision. Nevus flammeus (port-wine stain), a noninvoluting hemangioma, occurs as an isolated lesion or in association with other signs of Sturge-Weber syndrome. Affected patients should be monitored for the development of glaucoma. **Lymphangiomas** of the lid appear as firm masses at or soon after birth and tend to enlarge slowly during the growing years. Associated conjunctival involvement, appearing as a clear, cystic, sinuous conjunctival mass, may provide a clue to the diagnosis. In some cases, there is also orbital involvement. The **treatment** may include sclerosant therapy, percutaneous drainage, or surgical excision.

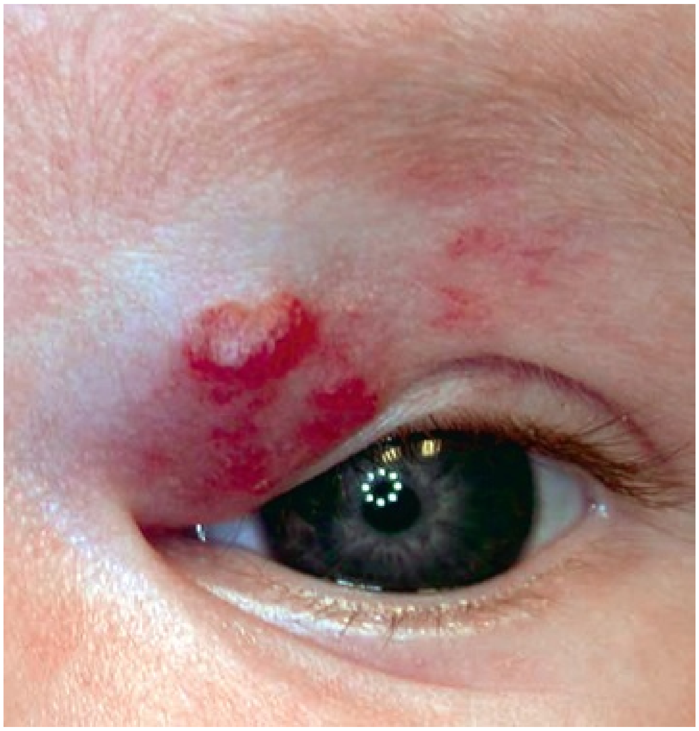

FIG. 642.3 Capillary hemangioma of the eyelid. (Courtesy of Amy Nopper, MD, and Brandon Newell, MD.)

Plexiform neuromas of the lids occur in children with neurofibromatosis, often with ptosis as the first sign. The lid may take on an S-shaped configuration. The lids may also be involved by other tumors, such as retinoblastoma, neuroblastoma, and rhabdomyosarcoma of the orbit; these conditions are discussed elsewhere.

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CHAPTER 643

Disorders of the Lacrimal System

Scott E. Olitsky, Justin D. Marsh

The Tear Film

The tear film, which bathes the eye, is actually a complex structure composed of 3 layers. The innermost mucin layer is secreted by the goblet and epithelial cells of the conjunctiva, and the acinar cells of the lacrimal gland. It adds stability and provides an attachment for the tear film to the conjunctiva and cornea. The middle aqueous layer constitutes 98% of the tear film and is produced by the main lacrimal gland and accessory lacrimal glands. It contains various electrolytes and proteins as well as antibodies. The outermost lipid layer is produced largely from the sebaceous meibomian glands of the eyelid and retards evaporation of the tear film. Tears drain medially into the punctal openings of the lid margin and flow through the canaliculi into the lacrimal sac and then through the nasolacrimal duct into the nose (Fig. 643.1). Preterm infants have reduced tear secretion. This may mask the diagnosis of a nasolacrimal duct obstruction and concentrate topically applied medications. Tear production reaches adult levels near term.

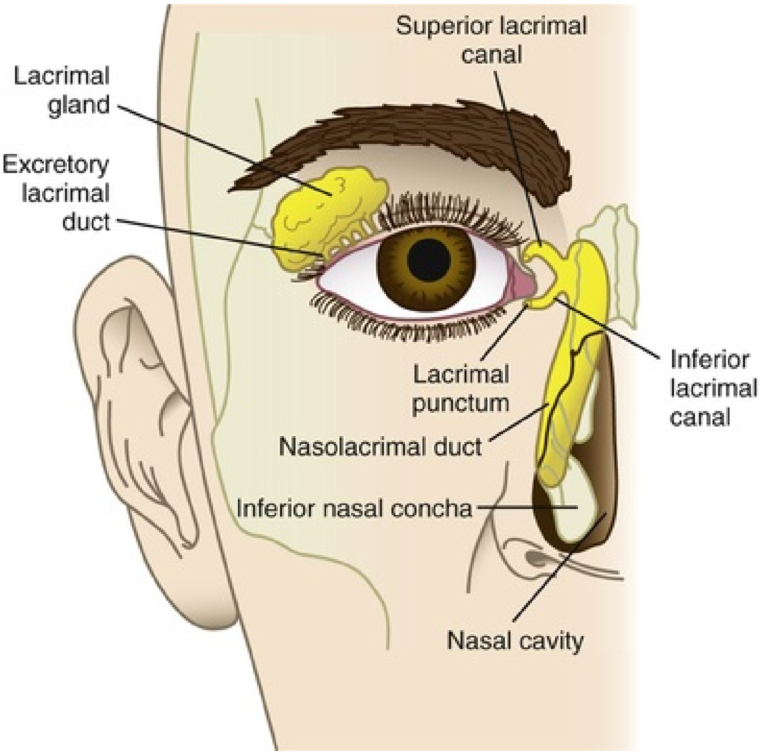
Superior lacrimal canal
Lacrimal gland
Excretory lacrimal duct
Inferior lacrimal canal
Lacrimal punctum
Nasolacrimal duct
Inferior nasal concha
Nasal cavity

FIG. 643.1 The lacrimal apparatus.

Dacryostenosis

Congenital nasolacrimal duct obstruction (CNLDO), or dacryostenosis, is the most common disorder of the lacrimal system, occurring in up to 20% of newborn infants. It is usually caused by a failure of canalization of the epithelial cells that form the nasolacrimal duct as it enters the nose beneath the inferior turbinate (valve of Hasner). Signs of CNLDO may be present at the time of birth, although the condition may not become evident until normal tear production develops. Signs of CNLDO include an excessive tear lake, overflow of tears onto the lid and cheek, and reflux of mucoid material that is produced in the lacrimal sac. Erythema or maceration of the skin may result from irritation and rubbing produced by dripping of tears and discharge. If the blockage is complete, these signs may be severe and continuous. If obstruction is only partial, the nasolacrimal duct may be capable of draining the basal tear film that is produced. However, under periods of increased tear production (exposure to cold, wind, sunlight) or increased closure of the distal end of the nasolacrimal duct (nasal mucosal edema), tear overflow may become evident or may increase.

Infants at increased risk for CNLDO include those with trisomy 21, EEC (ectrodactyly, ectodermal dysplasia, clefting) syndrome, branchiooculofacial syndrome, craniometaphyseal or craniodiaphyseal dysplasias, LADD (lacrimo-auriculo-dento-digital) syndrome, CHARGE (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies) syndrome, and Goldenhar syndrome.

Infants with CNLDO may develop acute infection and inflammation of the nasolacrimal sac (**dacryocystitis**), inflammation of the surrounding tissues (**pericystitis**), or rarely periorbital cellulitis. With dacryocystitis, the sac area is swollen, red, and tender, and patients may have systemic signs of infection such as fever and irritability.

The primary **treatment** of uncomplicated nasolacrimal duct obstruction is a regimen of nasolacrimal massage, usually 2-3 times daily, accompanied by cleansing of the lids with warm water. Topical antibiotics are used for control of mucopurulent drainage. A bland ophthalmic ointment may be used on eyelids if the skin is macerated. Most cases of CNLDO resolve spontaneously; 96% before 1 yr of age. For cases that do not resolve by 1 yr, the nasolacrimal duct may be probed in the office with topical anesthesia, with a cure rate of approximately 80%. Some ophthalmologists intubate the nasolacrimal system at the same time, as this may improve the outcome of the procedure.

Acute dacryocystitis or cellulitis requires prompt treatment with systemic antibiotics. In such cases, some form of definitive surgical intervention is usually indicated.

A **dacryocystocele** (mucocele) is an unusual presentation of a nonpatent nasolacrimal sac that is obstructed both proximally and distally. Dacryocystoceles can be seen at birth or shortly after birth as a bluish subcutaneous mass just below the medial canthal tendon (Fig. 643.2). Initial **treatment** of dacryocystocele is usually conservative, involving massage/digital decompression of the lacrimal sac. If resolution of the dacryocystocele is not achieved with conservative management, the surgical probing may be beneficial. At times, the intranasal portion of the nasolacrimal duct becomes distended, causing respiratory compromise. In one study, 9.5% of infants with dacryocystocele had related respiratory compromise. These infants benefit from early probing. Another associated complication of dacryocystocele is that of dacryocystitis/cellulitis. This requires systemic antibiotics, often with hospitalization. In the aforementioned study, 65% of infants with dacryocystocele developed dacryocystitis/cellulitis. Once the cellulitis has improved, the nasolacrimal system should be probed if spontaneous resolution has not occurred.

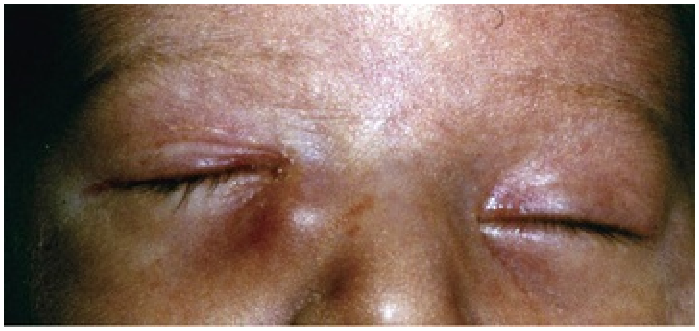

FIG. 643.2 Dacryocystocele below inner canthus of the right eye.

Not all tearing in infants and children is caused by nasolacrimal obstruction. Tearing may also be a sign of glaucoma, intraocular inflammation, or external irritation, such as that from a corneal abrasion or foreign body.

Alacrima and “Dry Eye”

Alacrima refers to a wide spectrum of disorders with reduced or absent tear secretion. Occasionally normal basal tearing occurs with an absence of emotional tearing. Etiologies can be divided into syndromes that have a pathologic association or are inherited. Associated syndromes include familial dysautonomia (Riley-Day syndrome), anhidrotic ectodermal dysplasia, and triple-A syndrome (Allgrove syndrome). Examples of pathologic association include aplasia of cranial nerve nuclei and lacrimal gland aplasia/hypoplasia. Both autosomal recessive and autosomal dominant inheritance have been reported in isolated congenital alacrima. In addition, medications with anticholinergic side effects can decrease tear production. The patients with alacrima have variable presentation, including no symptoms, photophobia, foreign body sensation, eye pain, and decreased vision. The symptoms, if present, often occur early in life. Because the dryness can be severe, damage to the cornea and subsequent loss of vision may occur. The goal of treatment is to minimize corneal irritation, corneal scarring, and loss of vision. Aggressive ocular lubrication is used to prevent these sequelae.

An **acquired abnormality** of any layer of the tear film may produce a dry eye. Commonly acquired disorders that may lead to a decreased or unstable tear film include Sjögren syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, vitamin A deficiency, viral infections of the lacrimal gland, ocular pemphigoid, trachoma, chemical burns, irradiation, isotretinoin treatment of acne, graft-versus-host disease, and meibomian gland dysfunction. Corneal exposure as a consequence of poor lid closure or other pathologic states can quickly lead to pathologically dry eyes. Examples of conditions leading to such exposure include ichthyosis, xeroderma pigmentosum, and certain craniosynostoses syndromes, such as Crouzon, Apert, or Pfeiffer. Any tear deficiency can lead to corneal ulceration, scarring, or infection. **Treatment** includes correction of the underlying disorder when possible and frequent instillation of an ocular lubricant. In some cases, occlusion of the lacrimal puncta is helpful. In severe cases, tarsorrhaphy may be necessary to protect the cornea.

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CHAPTER 644

Disorders of the Conjunctiva

Scott E. Olitsky, Justin D. Marsh

Conjunctivitis

The conjunctiva reacts to a wide range of bacterial and viral agents, allergens, irritants, toxins, and systemic diseases. Conjunctivitis is common in childhood and may be infectious or noninfectious. The differential diagnosis of a red-appearing eye includes conjunctival disease, as well as other ocular sites (Table 644.1).

Table 644.1

The Red Eye

CONDITION	**ETIOLOGY**	**SIGNS AND SYMPTOMS**	**TREATMENT**
Bacterial conjunctivitis	*Haemophilus influenzae, Haemophilus aegyptius, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis*	Mucopurulent unilateral or bilateral discharge, normal vision, photophobia	Topical antibiotics, parenteral ceftriaxone for gonococcus, *H. influenzae*
Hyperacute bacterial conjunctivitis	*Neisseria gonorrhoeae, Neisseria meningitides*	Conjunctival injection and edema (chemosis); gritty sensation	
Viral conjunctivitis	Adenovirus, ECHO virus, coxsackievirus, herpes simplex virus	As above; may be hemorrhagic, unilateral	Self-limited
Neonatal conjunctivitis	*Chlamydia trachomatis* , gonococcus, chemical (silver nitrate), *S. aureus*	Palpebral conjunctival follicle or papillae; as above	Ceftriaxone for gonococcus and erythromycin for *C. trachomatis*
Allergic conjunctivitis	Seasonal pollens or allergen exposure	Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae	Antihistamines, topical mast cell stabilizers or prostaglandin inhibitors, steroids
Keratitis	Herpes simplex virus, adenovirus,	Severe pain, corneal swelling,	Specific antibiotics

	S. pneumoniae, S. aureus, Pseudomonas, Acanthamoeba , chemicals	clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection	for bacterial/fungal infections; keratoplasty, acyclovir for herpes
Endophthalmitis	*S. aureus, S. pneumoniae, Candida albicans* , associated surgery or trauma	Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze	Antibiotics
Anterior uveitis (iridocyclitis)	JIA, postinfectious with arthritis and rash, sarcoidosis, Behçet disease, Kawasaki disease, inflammatory bowel disease	Unilateral/bilateral; erythema, ciliary flush, irregular pupil, iris adhesions; pain, photophobia, small pupil, poor vision	Topical steroids, plus therapy for primary disease
Posterior uveitis (choroiditis)	Toxoplasmosis, histoplasmosis, *Toxocara canis*	No signs of erythema, decreased vision	Specific therapy for pathogen
Episcleritis/scleritis	Idiopathic autoimmune disease (e.g., SLE, Henoch-Schönlein purpura)	Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation	Episcleritis is self-limiting; topical steroids for fast relief
Foreign body	Occupational exposure	Unilateral, red, gritty feeling; visible or microscopic size	Irrigation, removal; check for ulceration
Blepharitis	*S. aureus, Staphylococcus epidermidis* , seborrheic, blocked lacrimal duct; rarely molluscum contagiosum, *Phthirus pubis, Pediculus capitis*	Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins	Topical antibiotics, warm compresses, lid hygiene
Dacryocystitis	Obstructed lacrimal sac: *S. aureus, H. influenzae*, pneumococcus	Pain, tenderness, erythema, and exudates in area of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis	Systemic, topical antibiotics; surgical drainage
Dacryoadenitis	*S. aureus, Streptococcus* , CMV, measles, EBV, enteroviruses; trauma, sarcoidosis, leukemia	Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis	Systemic antibiotics; drainage of orbital abscesses
Orbital cellulitis (postseptal cellulitis)	Paranasal sinusitis: *H. influenzae, S. aureus, S. pneumoniae* , streptococci Trauma: *S. aureus* Fungi: *Aspergillus, Mucor* spp. if immunodeficient	Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, ophthalmoplegia, fever, lid edema, leukocytosis	Systemic antibiotics, drainage of orbital abscesses
Periorbital cellulitis (preseptal cellulitis)	Trauma: *S. aureus,* streptococci Bacteremia: pneumococcus, streptococci, *H. influenzae, S. aureus*	Cutaneous erythema, warmth, normal vision, minimal involvement of orbit; fever, leukocytosis, toxic appearance	Systemic antibiotics

CMV, cytomegalovirus; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.

From Behrman R, Kliegman R: *Nelson's essentials of pediatrics,* ed 3, Philadelphia, 1998, WB Saunders.

Ophthalmia Neonatorum

This form of conjunctivitis, occurring in infants younger than 4 wk of age, is the most common eye disease of newborns. Its many different causal agents vary greatly in their virulence and outcome. Silver nitrate instillation may result in a mild self-limited chemical conjunctivitis, whereas *Neisseria gonorrhoeae* and *Pseudomonas* are capable of causing corneal perforation, blindness, and death. The risk of conjunctivitis in newborns depends on frequencies of maternal infections, prophylactic measures, circumstances during labor and delivery, and postdelivery exposure to microorganisms.

Epidemiology

Conjunctivitis during the neonatal period is usually acquired during vaginal delivery and reflects the sexually transmitted infections prevalent in the community. The incidence of gonococcal ophthalmia neonatorum can be reduced by widespread use of silver nitrate prophylaxis, prenatal screening, and treatment of maternal gonorrhea. Gonococcal ophthalmia neonatorum has an incidence of 0.3/1,000 live births in the United States. In comparison, *Chlamydia trachomatis* is the most common organism causing ophthalmia neonatorum in the United States, with an incidence of 8.2/1,000 births.

Clinical Manifestations

The clinical manifestations of the various forms of ophthalmia neonatorum are not specific enough to allow an accurate diagnosis. Although the timing and character of the signs are somewhat typical for each cause of this condition, there is considerable overlap, and physicians should not rely solely on clinical findings. Regardless of its cause, ophthalmia neonatorum is characterized by redness and chemosis (swelling) of the conjunctiva, edema of the eyelids, and discharge, which may be purulent.

Neonatal conjunctivitis is a potentially blinding condition. The infection may also have associated systemic manifestations that require treatment. Therefore any newborn infant who develops signs of conjunctivitis needs a prompt and comprehensive systemic and ocular evaluation to determine the agent causing the infection and the appropriate treatment.

The onset of inflammation caused by silver nitrate drops usually occurs within 6-12 hr after birth, with clearing by 24-48 hr. The usual incubation period for conjunctivitis caused by *N. gonorrhoeae* is 2-5 days, and for that caused by *C. trachomatis* , 5-14 days. Gonococcal infection may be present at birth owing to prolonged rupture of amniotic membranes or be delayed beyond 5 days of life due to partial suppression by ocular prophylaxis. Gonococcal conjunctivitis may also begin in infancy after inoculation by the contaminated fingers of adults. The time of onset of disease with other bacteria is highly variable.

Gonococcal conjunctivitis begins with mild inflammation and a serosanguineous discharge. Within 24 hr, the discharge becomes thick and purulent, and tense edema of the eyelids with marked chemosis occurs. If proper treatment is delayed, the infection may spread to involve the deeper layers of the conjunctivae and the cornea. Complications include corneal ulceration and perforation, iridocyclitis, anterior synechiae, and rarely panophthalmitis. Conjunctivitis caused by *C. trachomatis* (inclusion blennorrhea) may vary from mild inflammation to severe swelling of the eyelids with copious purulent discharge. The process involves mainly the tarsal conjunctivae; the corneas are rarely affected. Conjunctivitis caused by *Staphylococcus aureus* or other organisms is similar to that produced by *C. trachomatis.* Conjunctivitis caused by *Pseudomonas aeruginosa* is uncommon, acquired in the nursery, and a potentially serious process. It is characterized by the appearance on days 5-18 of edema, erythema of the lids, purulent discharge, pannus formation, endophthalmitis, sepsis, shock, and death.

Diagnosis

Conjunctivitis appearing after 48 hr should be evaluated for a possibly infectious cause. Gram stain of the purulent discharge should be performed and the material cultured. If a viral cause is suspected, a swab should be submitted in tissue culture media for virus isolation. In chlamydial conjunctivitis, the diagnosis is made by examining Giemsa-stained epithelial cells scraped from the tarsal conjunctivae for the characteristic intracytoplasmic inclusions, by isolating the organisms from a conjunctival swab using special tissue culture techniques, by immunofluorescent staining of conjunctival scrapings for chlamydial inclusions, or by tests for chlamydial antigen or DNA. The differential diagnosis of ophthalmia neonatorum includes dacryocystitis caused by congenital nasolacrimal duct obstruction with lacrimal sac distention (dacryocystocele; see Chapter 643).

Treatment

Treatment of infants in whom gonococcal ophthalmia is suspected where the Gram stain shows the characteristic intracellular Gram-negative diplococci should be initiated immediately with ceftriaxone, 25-50 mg/kg/24 hr for one dose IV or IM, not to exceed 125 mg. The eye should also be irrigated initially with saline every 10-30 min, gradually increasing to 2-hr intervals until the purulent discharge has cleared. Treatment (ceftriaxone 25-50 mg/kg/day, IM or IV in a single daily dose for 7 days, with cefotaxime 25 mg/kg q 12 hr substituted if the patient has hyperbilirubinemia) is extended if sepsis or other extraocular sites are involved. Associated meningitis is treated for 10-14 days. Neonatal conjunctivitis secondary to chlamydial infections is treated with oral erythromycin (50 mg/kg/24 hr in 4 divided doses) for 2 wk. This cures conjunctivitis and may prevent subsequent chlamydial pneumonia. *Pseudomonas* neonatal conjunctivitis is treated with systemic antibiotics, including an aminoglycoside, plus local saline irrigation and gentamicin ophthalmic ointment. Staphylococcal conjunctivitis is treated with parenteral methicillin and local saline irrigation.

Prognosis and Prevention

Before the institution of topical ophthalmic prophylaxis at birth, gonococcal ophthalmia was a common cause of blindness or permanent eye damage. If properly applied, this form of prophylaxis is highly effective unless infection is present at birth. Drops of 0.5% erythromycin or 1% silver nitrate are instilled directly into the open eyes at birth using wax or plastic single-dose containers. Saline irrigation after silver nitrate application is unnecessary. Silver nitrate is ineffective against active infection and may have limited use against *Chlamydia* . Povidone-iodine (2% solution) may also be an effective prophylactic agent, especially in developing countries.

Identification of maternal gonococcal infection and appropriate treatment has become a standard element of routine prenatal care. An infant born to a woman who has untreated gonococcal infection should receive a single dose of ceftriaxone, 50 mg/kg (maximum 125 mg) IV or IM, in addition to topical prophylaxis. The dose should be reduced for premature infants. Penicillin (50,000 units) should be used if the mother's gonococcal isolate is known to be penicillin sensitive.

Neither topical prophylaxis nor topical treatment prevents the afebrile pneumonia that occurs in 10–20% of infants exposed to *C. trachomatis.* Although chlamydial conjunctivitis is often a self-limiting disease, chlamydial pneumonia may have serious consequences. It is important that infants with chlamydial disease receive systemic treatment. Treatment of colonized pregnant women with erythromycin may prevent neonatal disease.

Acute Purulent Conjunctivitis

This is characterized by more or less generalized (bilateral in 50–75%) conjunctival hyperemia, edema, mucopurulent exudate, glued eyes (lids stuck together after sleeping), and various degrees of ocular pain and discomfort. It is usually a result of bacterial infection. In addition, there is usually little or no pruritus or periauricular lymph node enlargement; the peak season is between December and April. Bacterial conjunctivitis is more common in young children (<5 yr), whereas viral conjunctivitis is more common among adolescents and adults. The most frequent causes are nontypable *Haemophilus influenzae* (60–80%; associated with ipsilateral otitis media), pneumococci (20%), and staphylococci (5–10%). Bacterial purulent conjunctivitis, especially that caused by pneumococcus or *H. influenzae,* may occur in epidemics. Conjunctival smear and culture are helpful in differentiating specific types. These common forms of acute purulent conjunctivitis usually respond well to warm compresses and topical instillation of antibiotic drops, which shortens the duration of illness and hastens return to school. Topical antibiotics include aminoglycosides (gentamicin, tobramycin), quinolones (ciprofloxacin, ofloxacin, moxifloxacin), and combinations of antibiotics and chloramphenicol (Table 644.2). Brazilian purpuric fever caused by *Haemophilus aegyptius* manifests as conjunctivitis and sepsis. **Hyperacute bacterial conjunctivitis** is caused by gonococcal or meningococcal infection and requires systemic, not topical, antimicrobial therapies. Concerning symptoms that should require an ophthalmology referral include vision loss, severe purulent discharge, corneal involvement, conjunctival scarring, cutaneous-conjunctival involvement (Stevens-Johnson syndrome), recurrent symptoms, severe pain, herpes simplex virus infection, severe photophobia, and involvement with a contact (cosmetic or prescription) lens.

Table 644.2

Topical Antibiotics Used to Treat Bacterial Conjunctivitis: Adult Dosages

DRUG	DOSAGE
Bacitracin (AK-Tracin, Bacticin) ointment	Apply 0.5 inch in eye q3-4h
Ciprofloxacin (Ciloxan) 0.3% ophthalmic solution	1-2 gtt in eye q15min × 6h, then q30min × 18h, then q1h × 1 day, then q4h × 12 days*

Gatifloxacin (Zymar) 0.3% ophthalmic solution	1 gt in eye q2h up to 8 × per day × 2 days, then 1 gt qid × 5 days
Gentamicin (Gentak, Gentasol) 0.3% ophthalmic solution or ointment	Ointment: 0.5 inch applied to eye 2-3 × per day Solution: 1-2 gtt in eye q4h
Levofloxacin (Quixin) 0.5% ophthalmic solution	1-2 gtt in eye q2h × 2 days while awake, then q4h × 5 days while awake
Moxifloxacin (Vigamox) 0.5% ophthalmic solution	1 gt in eye tid × 7 days
Neomycin/polymyxin B/gramicidin (Neosporin) ophthalmic solution	1-2 gtt in eye q4h × 7-10 days
Ofloxacin (Ocuflox) 0.3% ophthalmic solution	1-2 gtt in eye q2-4h × 2 days, then 1-2 gtt in eye qid × 5 days
Polymyxin B and trimethoprim (Polytrim) ophthalmic solution	1 gt in eye q3h × 7-10 days
Sulfacetamide (Isopto Cetamide, Ocusulf-10, Sodium Sulamyd, Sulf-10, AK-Sulf) 10% ophthalmic solution, ointment	Ointment: 0.5-inch ribbon in eye q3-4h and qhs × 7 days Solution: 1-2 gtt in eye q2-3h × 7-10 days
Tobramycin (AK-Tob, Tobrex) 0.3% ophthalmic solution	1-2 gtt in eye q4h

[*] Exceeds dosage recommended by the manufacturer.

From Bope ET, Kellerman RD, editors: *Conn's current therapy* , Philadelphia, 2014, Elsevier/Saunders, Table 2, p. 321.

Viral Conjunctivitis

This is generally characterized by a watery discharge. Follicular changes (small aggregates of lymphocytes) are often found in the palpebral conjunctiva. Involvement is often unilateral and associated with periauricular nodes. Viral conjunctivitis occurs more often in the summer and in older children (>5 yr). Conjunctivitis resulting from adenovirus infection is relatively common, sometimes with corneal involvement as well as pharyngitis or pneumonia. Outbreaks of conjunctivitis caused by enterovirus are also encountered; this type may be hemorrhagic (Fig. 644.1). Acute hemorrhagic conjunctivitis may be epidemic because of enterovirus CA24 or 70 and is characterized by red, swollen, and painful eyes with a hemorrhagic watery discharge. Conjunctivitis is commonly associated with such systemic viral infections as childhood exanthems, particularly measles. Viral conjunctivitis is usually self-limited.

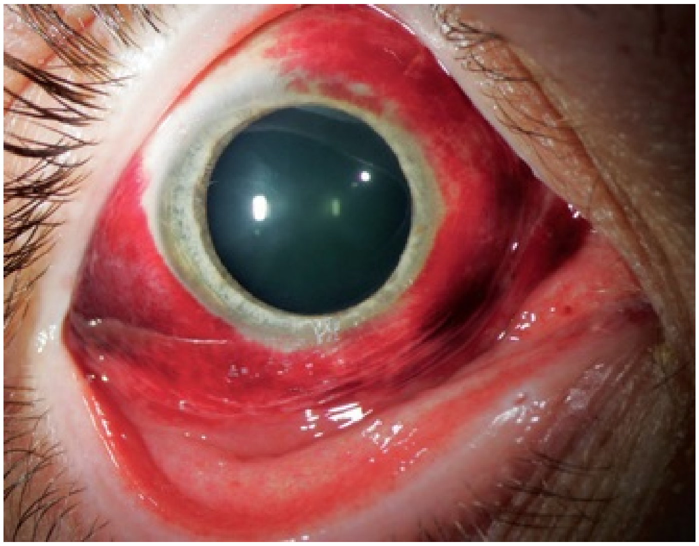

FIG. 644.1 Acute hemorrhagic conjunctivitis (AHC) is a highly contagious conjunctivitis that presents with symptoms of pain, redness, and tearing. Ocular findings include extensive subconjunctival hemorrhages, follicles, and chemosis. Causative agents include coxsackie group A24 (CA24) and enterovirus E70 (EV70). (From Krachmer JH, Palay DA: *Cornea atlas* , ed 3, London: Elsevier, 2014. Fig 7-23.)

Epidemic Keratoconjunctivitis

This is caused by adenovirus serotypes 8, 19, or 37, and is transmitted by direct contact. It initially presents as a sensation of a foreign body beneath the lids, with itching and burning. Edema (chemosis) and photophobia develop rapidly, and large oval follicles appear within the conjunctiva. Preauricular adenopathy and a pseudomembrane on the conjunctival surface occur frequently. Subepithelial corneal infiltrates may develop and may cause blurring of vision; these usually disappear but may permanently reduce visual acuity. Corneal complications are less common in children than in adults. Children may have associated upper respiratory tract infection and pharyngitis. No specific medical therapy is available to decrease the symptoms or shorten the course of the disease. Emphasis must be placed on prevention of spread of the disease. A replicating virus is present in 95% of patients 10 days after the appearance of symptoms.

Pharyngoconjunctival fever presents with high fever, pharyngitis, bilateral conjunctivitis, and periauricular lymphadenopathy. It is highly contagious.

Membranous and Pseudomembranous Conjunctivitis

These types of conjunctivitis can be encountered in a number of diseases. The classic membranous conjunctivitis is that of diphtheria, accompanied by a fibrin-rich exudate that forms on the conjunctival surface and permeates the epithelium; the membrane is removed with difficulty and leaves raw bleeding areas. In pseudomembranous conjunctivitis, the layer of fibrin-rich exudate is superficial and can often be stripped easily, leaving the surface smooth. This type occurs with many bacterial and viral infections, including staphylococcal, pneumococcal, streptococcal, or chlamydial conjunctivitis, and in epidemic keratoconjunctivitis. It is also found in vernal conjunctivitis and in Stevens-Johnson disease.

Allergic Conjunctivitis

This is usually accompanied by intense itching, clear watery discharge, and conjunctival edema (chemosis). It is commonly seasonal (spring-summer). Cold compresses and topical antihistamine drops give symptomatic relief. Topical mast cell stabilizers or prostaglandin inhibitors may also help. In selected cases, topical corticosteroids are used under an ophthalmologist's supervision but should not be used routinely or for a long time.

Vernal Conjunctivitis

This usually begins in the prepubertal years and may recur for many years. Atopy appears to have a role in its origin, but the pathogenesis is uncertain. Extreme itching and tearing are the usual complaints. Large, flattened, cobblestone-like papillary lesions of the palpebral conjunctivae are characteristic (Fig. 644.2). A stringy exudate and a milky conjunctival pseudomembrane are frequently present. Small elevated lesions of the bulbar conjunctiva adjacent to the limbus (Horner-Trantas dots) may be found. Smear of the conjunctival exudate reveals many eosinophils. Topical corticosteroid therapy and cold compresses afford some relief. Topical mast cell stabilizers or prostaglandin inhibitors are useful when long-term control is needed. The long-term use of corticosteroids should be avoided.

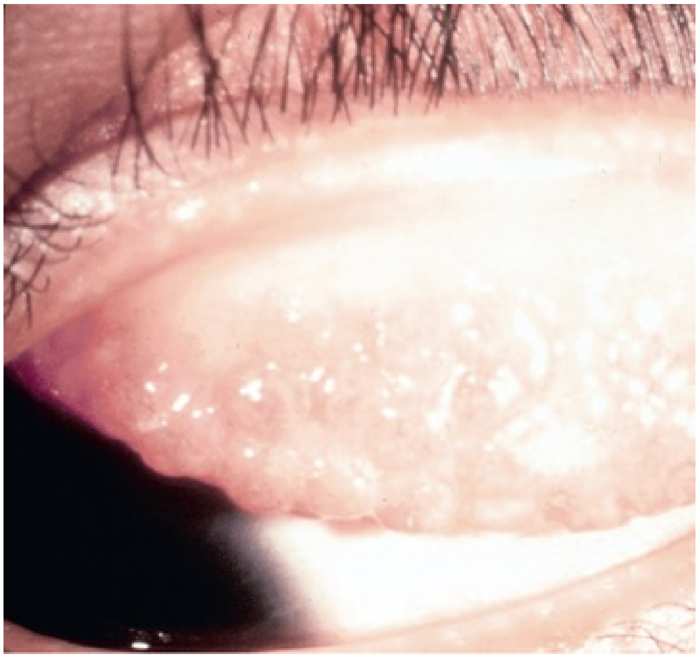

FIG. 644.2 **Vernal conjunctivitis.**

Parinaud Oculoglandular Syndrome

This represents a form of cat-scratch disease and is caused by *Bartonella henselae,* which is transmitted from cat to cat by fleas (see Chapter 236). Kittens are more likely than adult cats to be infected. Humans can become infected when they are scratched by a cat. In addition, bacteria may pass from a cat's saliva to its fur during grooming. The bacteria can then be deposited on the conjunctiva after rubbing one's eyes after handling the cat. Lymphadenopathy and conjunctivitis are hallmarks of the disease. Conjunctival granulomas may develop (Fig. 644.3). The course is generally self-limited, but antibiotics may be used in some cases.

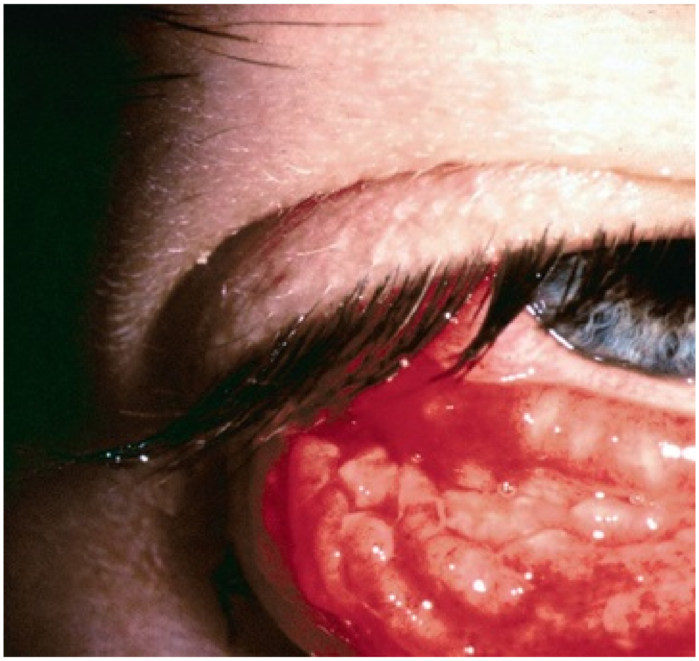

FIG. 644.3 Conjunctival granulomas in Parinaud oculoglandular syndrome.

Chemical Conjunctivitis

This can result when an irritating substance enters the conjunctival sac (as in the acute but benign conjunctivitis caused by silver nitrate in newborns). Other common offenders are household cleaning substances (including detergent pods), sprays, smoke, smog, metal halide bulbs, and industrial pollutants. Alkalis tend to linger in the conjunctival tissues and continue to inflict damage for hours or days. Acids precipitate the proteins in tissues and so produce their effect immediately. In either case, prompt, thorough, and copious irrigation is crucial. Extensive tissue damage, even loss of the eye, can result, especially if the offending agent is an alkali.

Other Conjunctival Disorders

Subconjunctival hemorrhage is manifested by bright or dark red patches in the bulbar conjunctiva and may result from injury or inflammation. It commonly occurs spontaneously. It may occasionally result from severe sneezing or coughing. Rarely, it may be a manifestation of a blood dyscrasia. Subconjunctival hemorrhages are self-limiting and require no treatment.

Pinguecula is a yellowish-white, slightly elevated mass on the bulbar conjunctiva, usually in the interpalpebral region (Fig. 644.4). It represents elastic and hyaline degenerative changes of the conjunctiva. No treatment is required except for cosmetic reasons, in which case simple excision suffices.

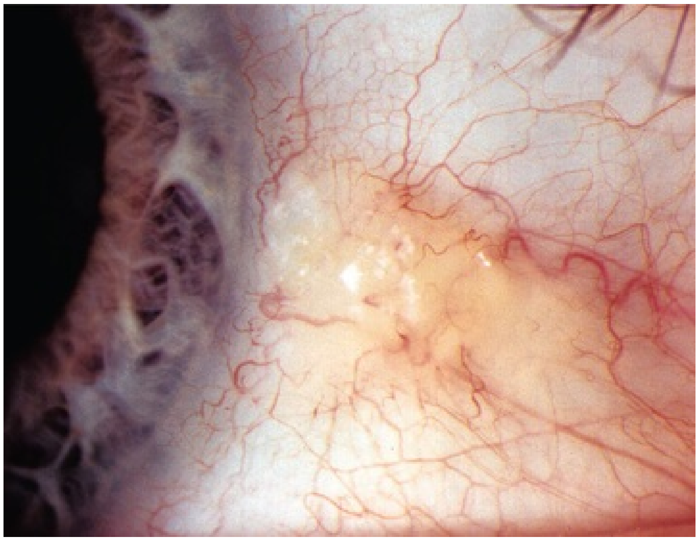

FIG. 644.4 Pinguecula. These lesions are found at the 3-o'clock and 9-o'clock positions and are extremely common, especially in older patients. (From Palay DA, Krachmer JH: *Primary care ophthalmology* , ed 2, Philadelphia, 2005, Elsevier Mosby. Fig. 3.49, p 62.)

Pterygium is a fleshy triangular conjunctival lesion that may encroach on the cornea. It typically occurs in the nasal interpalpebral region (Fig. 644.5). The pathologic findings are similar to those of a pinguecula. The development of pterygia is related to exposure to ultraviolet light, and it therefore is more commonly found among people who live near the equator. Removal is suggested when the lesion encroaches far onto the cornea. Recurrence after removal is common.

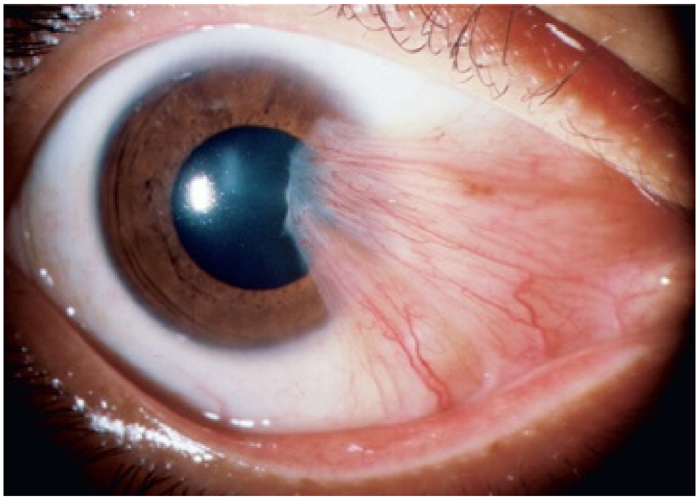

FIG. 644.5 Pterygium. These lesions are found in the horizontal meridian, most common nasally. (From Palay DA, Krachmer JH: Primary care ophthalmology, ed 2, Philadelphia, 2005, Elsevier Mosby. Fig. 3.50, p 62.)

Dermoid cyst and **dermolipoma** are benign lesions, clinically similar in appearance. They are smooth, elevated, round to oval lesions of various sizes. The color varies from yellowish white to fleshy pink. The most frequent site is the upper outer quadrant of the globe; they also commonly occur near or straddling the limbus. Dermolipoma is composed of adipose and connective tissue. Dermoid cysts may also contain glandular tissue, hair follicles, and hair shafts. Excision for cosmetic reasons is feasible. Dermolipomas are often connected to the extraocular muscles, making their complete removal impossible without sacrificing ocular motility.

Conjunctival nevus is a small, slightly elevated lesion that may vary in pigmentation from pale salmon to dark brown. It is usually benign, but careful observation for progressive growth or changes suggestive of malignancy is advised.

Symblepharon is a cicatricial adhesion between the conjunctiva of the lid and the globe; the lower lid is usually affected. It follows operation or injuries, especially burns from lye, acids, or molten metals. It is a serious complication of Stevens-Johnson syndrome. It may interfere with motion of the eyeball and may cause diplopia. The adhesions should be separated and the raw surfaces kept from uniting during healing. Grafts of oral mucous membrane may be necessary.

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CHAPTER 645

Abnormalities of the Cornea

Scott E. Olitsky, Justin D. Marsh

Megalocornea

This is a nonprogressive symmetric condition characterized by an enlarged cornea (>12 mm in diameter) and an anterior segment in which there is no evidence of previous or concurrent ocular hypertension. High myopia is frequently present and may lead to reduced vision. A frequent complication is the development of lens opacities in adult life. All modes of inheritance have been described, although X-linked recessive is the most common; therefore this disorder more commonly affects males. Systemic abnormalities that may be associated with megalocornea include Marfan syndrome, craniosynostosis, and Alport syndrome. The cause of the enlargement of the cornea and the anterior segment is unknown, but possible explanations include a defect in the growth of the optic cup and an arrest of congenital glaucoma.

Pathologic corneal enlargement caused by glaucoma is to be differentiated from this anomaly. Any progressive increase in the size of the cornea, especially when accompanied by photophobia, lacrimation, or haziness of the cornea, requires prompt ophthalmologic evaluation.

Microcornea

Microcornea, or anterior microphthalmia, is an abnormally small cornea in an otherwise relatively normal eye. It may be familial, with transmission being dominant more often than recessive. More commonly, a small cornea is just one feature of an otherwise developmentally abnormal or microphthalmic eye; associated defects include colobomas, microphakia, congenital cataract, glaucoma, and aniridia.

Keratoconus

This is a disease of unclear pathogenesis characterized by progressive thinning and bulging of the central cornea, which becomes cone shaped. Although familial cases are known, most cases are sporadic. It is a common ocular condition with an incidence of 1 in 2,000 adults. Eye rubbing and contact lens wear have been implicated as pathogenic, but the evidence to support this is equivocal. The incidence is increased in individuals with atopy, Down syndrome, Marfan syndrome, and retinitis pigmentosa.

Most cases are bilateral, but involvement may be asymmetric. The disorder usually presents and progresses rapidly during adolescence; progression slows and stabilizes when patients reach full growth. Descemet membrane may occasionally be stretched beyond its elastic breaking point, causing an acute rupture in the membrane with resultant sudden and marked corneal edema (acute hydrops, Fig. 645.1) and decrease in vision. The corneal edema resolves as endothelial cells cover the defective area. Some degree of corneal scarring occurs, but the visual acuity is often better than before the initial incident. Signs of keratoconus include Munson sign (bulging of the lower eyelid on looking downward) and the presence of a Fleischer ring (a deposit of iron in the epithelium at the base of the cone). Glasses and contact lenses are the first step in treating the visual distortion caused by keratoconus. Corneal cross linking is a relatively new procedure using riboflavin and UV light, and may arrest the progression of keratoconus. If the cornea vaults too severely for the vision to be corrected with contact lenses then a corneal transplant must be performed to restore vision.

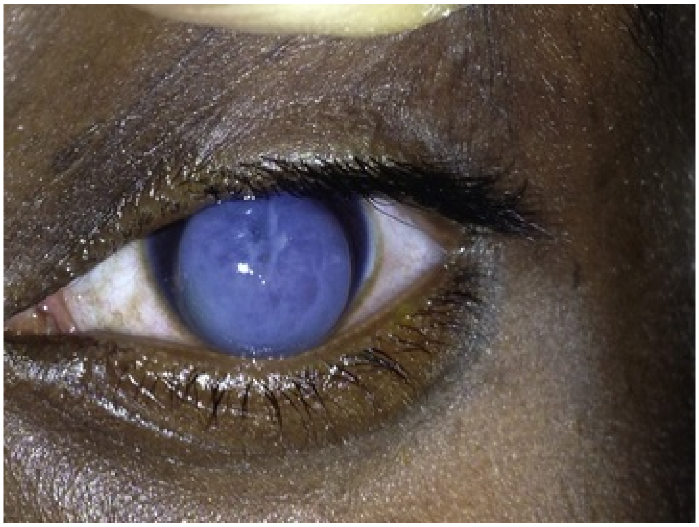

FIG. 645.1 Acute hydrops from keratoconus with significant corneal edema.

Neonatal Corneal Opacities

Loss of the normal transparency of the cornea in neonates may occur secondary to either intrinsic hereditary or extrinsic environmental causes (Table 645.1).

Table 645.1

Stumped: Differential Diagnosis of Neonatal Corneal Opacities

DIAGNOSIS	LATERALITY	OPACITY	OCULAR PRESSURE	OTHER OCULAR ABNORMALITIES	NATURAL HISTORY	I
S—Sclerocornea	Unilateral or bilateral	Vascularized, blends with sclera, clearer centrally	Normal (or elevated)	Cornea plana	Nonprogressive	S
T—Tears in endothelium and Descemet membrane						
Birth trauma	Unilateral	Diffuse edema	Normal	Possible hyphema, periorbital ecchymoses	Spontaneous improvement in 1 mo	S
Infantile glaucoma	Bilateral	Diffuse edema	Elevated	Megalocornea, photophobia and tearing, abnormal angle	Progressive unless treated	A r

U—Ulcers						
Herpes simplex keratitis	Unilateral	Diffuse with geographic epithelial defect	Normal	None	Progressive	S
Congenital rubella	Bilateral	Disciform or diffuse edema, no frank ulceration	Normal or elevated	Microphthalmos, cataract, pigment epithelial mottling	Stable, may clear	S
Neurotrophic exposure	Unilateral or bilateral	Central ulcer	Normal	Lid anomalies, congenital sensory neuropathy	Progressive	S
M—Metabolic (rarely present at birth) (mucopolysaccharidoses IH, IS; mucolipidosis type IV)*	Bilateral	Diffuse haze, denser peripherally	Normal	Few	Progressive	A d
P—Posterior corneal defect	Unilateral or bilateral	Central, diffuse haze or vascularized leukoma	Normal or elevated	Anterior chamber cleavage syndrome	Stable, sometimes early clearing or vascularization	S a r
E—Endothelial dystrophy						
Congenital hereditary endothelial dystrophy	Bilateral	Diffuse corneal edema, marked corneal thickening	Normal	None	Stable	A d r
Posterior polymorphous dystrophy	Bilateral	Diffuse haze, normal corneal thickness	Normal	Occasional peripheral anterior synechiae	Slowly progressive	A d
Congenital hereditary stromal dystrophy	Bilateral	Flaky, feathery stromal opacities; normal corneal thickness	Normal	None	Stable	A d
D—Dermoid	Unilateral or bilateral	White vascularized mass, hair, lipid arc	Normal	None	Stable	S

* Mucopolysaccharidosis IH (Hurler syndrome); mucopolysaccharidosis IS (Scheie syndrome).

From Nelson LB, Calhoun JH, Harley RD: *Pediatric ophthalmology,* ed 3, Philadelphia, 1991, WB Saunders, p. 210.

Sclerocornea

In sclerocornea, the normally translucent cornea is replaced by sclera-like tissue. Instead of a clearly demarcated cornea, white, feathery, often ill-defined and vascularized tissue develops in the peripheral cornea, appearing to blend with and extend from the sclera. The central cornea is usually clearer, but total replacement of the cornea with sclera may occur. The curvature of the cornea is often flatter, similar to the sclera. Potentially coexisting abnormalities include a shallow anterior chamber, iris abnormalities, and microphthalmos. This condition is usually bilateral. In approximately 50% of cases, a dominant or recessive inheritance has been described. Sclerocornea has been reported in association with numerous systemic abnormalities including limb deformities, craniofacial defects, and genitourinary disorders. In generalized sclerocornea, especially if bilateral, early corneal transplantation should be considered in an effort to provide vision.

Sclerocornea is classified into one of the congenital corneal opacity disorders with cornea plana if it involves peripheral scleralization or total sclerocornea disorders such as Peters anomaly.

Peters Anomaly

Peters anomaly is a central corneal opacity (leukoma) that is present at birth (Fig. 645.2). It is often associated with iridocorneal adhesions that extend from the iris collarette to the border of the corneal opacity. Approximately 50% of patients have other ocular abnormalities, which may include cataracts, glaucoma, and microcornea. As many as 80% of cases may be bilateral, and 60% are associated with systemic malformations (**Peters plus syndrome**) that may include short stature, developmental delay, dysmorphic facial features, and cardiac, genitourinary, and central nervous system malformations. Some investigators have divided Peters anomaly into two types: a mesodermal or neuroectodermal form (type 1), which does not show associated lens changes, and a surface ectodermal form (type 2), which does. Histologic findings include a focal absence of Descemet membrane and corneal endothelium in the region of the opacity. Peters anomaly may be caused by incomplete migration and differentiation of the precursor cells of the central corneal endothelium and Descemet membrane, or a defective separation between the primitive lens and cornea during embryogenesis.

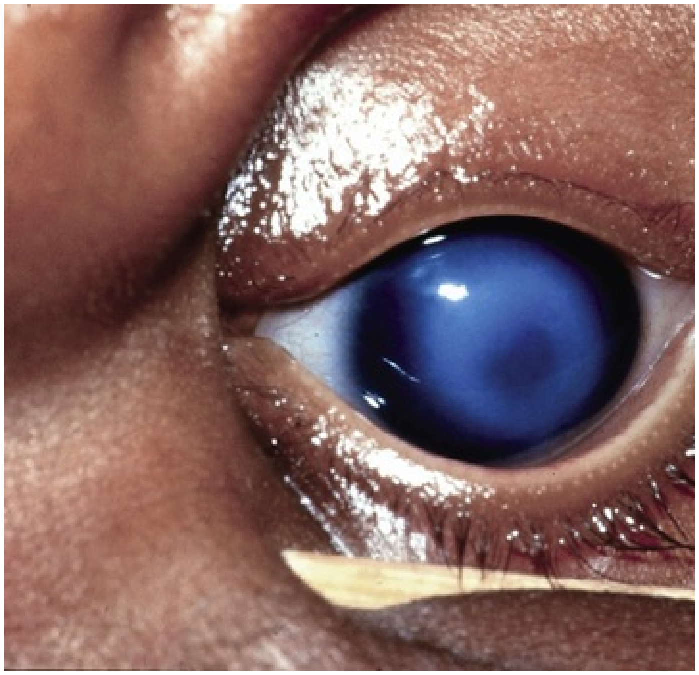

FIG. 645.2 **Peters anomaly. Central opacity in a patient with Peters anomaly.**

Corneal Dystrophies

These are rare inherited disorders that may present during childhood or early adulthood with bilateral involvement (although severity may be asymmetric) that progresses with time. In most, inheritance is autosomal dominant with variable expression; the most common mutation is in *TGFB1* , which is associated with the granular corneal dystrophy types 1 and 2, as well as lattice corneal dystrophy. Congenital hereditary endothelial dystrophy is both an autosomal recessive *(SLC4A11)* and dominant (unknown gene) disorder; the recessive form presents at birth and is more severe.

Dermoids

Epibulbar dermoids are choristomas. They are often present at birth and may increase in size with age. They occur most frequently in the lower temporal quadrant. They most commonly straddle the limbus and extend into the peripheral cornea (Fig. 645.3). Rarely, they may be confined entirely to the cornea or conjunctiva. Epibulbar (or limbal) dermoids may cause visual disturbance by encroaching on the visual axis or by contributing to the development of astigmatism, which may lead to amblyopia.

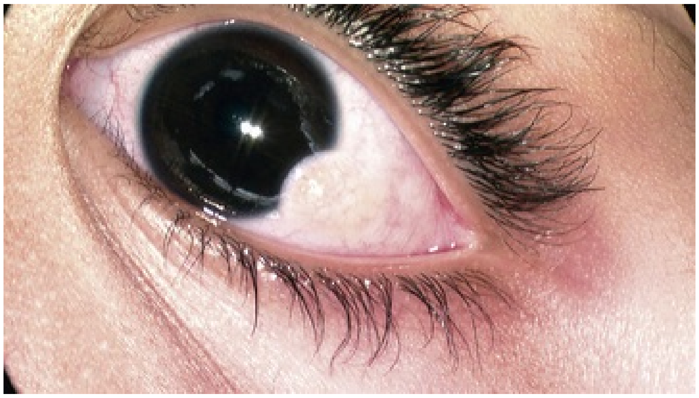

FIG. 645.3 **Limbal dermoid. Inferotemporal lesion in a patient with Goldenhar syndrome.**

A dermoid usually appears as a well-circumscribed rounded or oval, gray or pinkish-yellow mass with a dry surface from which short hairs may protrude. It may affect only the superficial layers of the cornea, although full-thickness involvement is common. Associated ocular anomalies include eyelid and iris colobomas, microphthalmos, and retinal and choroidal defects. A total of 30% of dermoids are associated with systemic abnormalities. Many of the associated anomalies involve developmental defects of the first branchial arch (vertebral anomalies, dysostosis of the facial bones, ear anomalies and dental anomalies, and Goldenhar syndrome). Epibulbar dermoids are found in 75% of cases of Goldenhar syndrome.

Dendritic Keratitis

Infection of the cornea with the herpes simplex virus produces a characteristic lesion of the corneal epithelium, referred to as a dendrite; it has a branching tree-like pattern that can be demonstrated by fluorescein staining (Fig. 645.4). The acute episode is accompanied by pain, photophobia, tearing, blepharospasm, and conjunctival injection. Specific treatment may include mechanical debridement of the involved corneal epithelium to remove the source of infection and eliminate an antigenic stimulus to inflammation in the adjacent stroma. Medical treatment involves the use of trifluridine, topical ganciclovir, or systemic acyclovir. In addition, a cycloplegic agent is useful to relieve pain from spasm of the ciliary muscle. Overly aggressive topical antiviral treatment itself can be toxic to the cornea and should be avoided. Recurrent infection and deep stromal involvement can lead to corneal scarring and loss of vision.

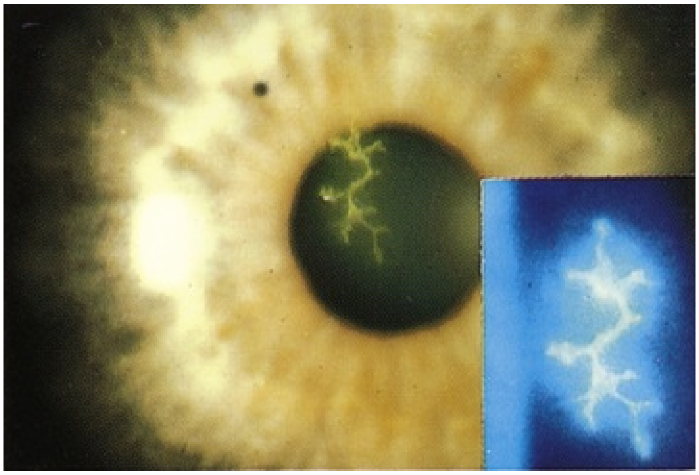

FIG. 645.4 Herpes simplex corneal epithelial keratitis in diffuse light and in light passed through a cobalt blue filter after fluorescein staining (inset). Note the dendritic staining pattern characteristic of herpes simplex. (From Goldman L, Schafer AI, editors: *Goldman-Cecil medicine* , ed 25, Philadelphia, 2016, Elsevier/Saunders. Fig. 423.19.)

Topical use of corticosteroids causes exacerbation of superficial herpetic disease of the eye and may lead to corneal perforation; eye drops combining steroids and antibiotics are therefore to be avoided in treatment of red eye, unless there are clear-cut indications for their use and close supervision during therapy.

Infants born to mothers infected with herpes simplex virus should be examined carefully for signs of ocular involvement. Intravenous acyclovir is required for treatment of ocular herpes in newborns.

Corneal Ulcers

The usual signs and symptoms are focal or diffuse corneal haze, hyperemia, lid edema, pain, photophobia, tearing, and blepharospasm. **Hypopyon** (pus in the anterior chamber) is common. Corneal ulcers require prompt treatment. They result most frequently from contact lens wear and traumatic lesions that become secondarily infected. Many organisms are capable of infecting the cornea. One of the most serious is *Pseudomonas aeruginosa* ; it can rapidly destroy stromal tissue and lead to corneal perforation. *Neisseria gonorrhoeae* also is particularly damaging to the cornea. Indolent ulcers may be caused by fungi, often in association with the use of contact lenses. In each case, scrapings of the cornea must be studied in an effort to identify the infectious agent and to determine the best therapy. Although aggressive local treatment is generally needed to save the eye, systemic treatment may be necessary in some cases as well. Perforation or scarring resulting from corneal ulceration is an important cause of blindness throughout the world and is estimated to be responsible for 10% of blindness in the United States.

Unexplained corneal ulcers in infants and young children should raise the question of a sensory defect, as in Riley-Day or Goldenhar-Gorlin syndrome, or of a metabolic disorder such as tyrosinemia (Fig. 645.5). Corneal ulceration can also occur as a consequence of severe vitamin deficiencies, such as those seen with cystic fibrosis.

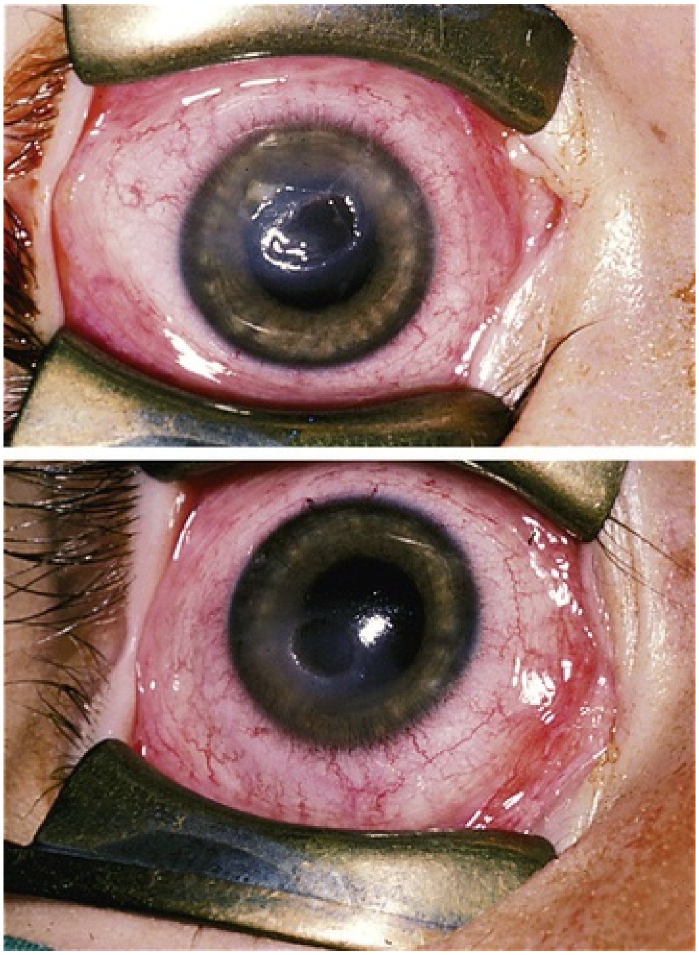

FIG. 645.5 Riley-Day syndrome. This child had a combination of anesthetic corneas and dry eyes that had been treated for several months by topical wetting agents without success. He responded well to a bilateral tarsorrhaphy and lubricant ointment. Later, punctal occlusion allowed enough wetting of his eyes to allow the tarsorrhaphies to be undone. (From Hoyt CS, Taylor D, editors: *Pediatric ophthalmology and strabismus* , ed 4, Philadelphia, 2013, Elsevier Saunders. Fig. 33.9, p. 315.)

Phlyctenules

These are small, yellowish, slightly elevated lesions usually located at the corneal limbus; they may encroach on the cornea and extend centrally. A small corneal ulcer is often found at the head of the advancing lesion, with a fascicle of blood vessels behind the head of the lesion. Although once thought to represent a sign of systemic tuberculin infection, phlyctenular keratoconjunctivitis is now accepted as a morphologic expression of delayed hypersensitivity to diverse antigens. In children, it commonly occurs as a result of a hypersensitivity reaction to nonpathogenic staphylococcal strains at the eyelid margin. Treatment usually consists of eliminating the underlying disorder, usually staphylococcal blepharitis or meibomianitis, and suppressing the immune response with the use of topical corticosteroid therapy. A superficial stromal pannus and scarring sometimes remain after treatment.

Interstitial Keratitis

This denotes nonulcerative inflammation of the corneal stroma. There is a diverse list of causes of interstitial keratitis (IK), including bacterial, viral, parasitic, and inflammatory etiologies. In the United States, herpesvirus infections and congenital syphilis account for the majority of cases of IK. Although the corneal findings may regress with time, “ghost vessels,” which represent the previous vascular changes, and patchy corneal scarring remain and serve as permanent stigmata of the disease.

Cogan syndrome is IK associated with hearing loss and vestibular symptoms. Although its cause is unknown, a systemic vasculitis is suspected. Prompt treatment is required to avoid permanent hearing loss. Both the corneal changes and the auditory involvement may respond to the use of immunosuppressive agents.

Corneal Manifestations of Systemic Disease

Several metabolic diseases produce distinctive corneal changes in childhood. Refractile polychromatic crystals are deposited throughout the cornea in cystinosis (see Chapter 103.4). Corneal deposits producing various degrees of corneal haze also occur in certain types of mucopolysaccharidosis (MPS; see Chapter 107), particularly MPS IH (Hurler), MPS IS (Scheie), MPS I H/S (Hurler-Scheie compound), MPS IV (Morquio), MPS VI (Maroteaux-Lamy), and sometimes MPS VII (Sly). Corneal deposits may develop in patients with GM_1 (generalized) gangliosidosis (see Chapter 104.4). In Fabry disease, fine opacities radiating in a whorl or fan-like pattern occur, and corneal changes can be important in identifying the carrier state (see Chapter 104.4). A spray-like pattern of corneal opacities may also be seen in the Bloch-Sulzberger syndrome (incontinentia pigmenti; see Chapter 614.7). In Wilson disease (see Chapter 384.2), the distinctive corneal sign is the Kayser-Fleischer ring, a golden brown ring in the peripheral cornea resulting from changes in Descemet's membrane. Pigmented corneal rings may develop in neonates with cholestatic liver disease. Corneal changes may occur in autoimmune hypoparathyroidism and band keratopathy in patients with hypercalcemia (see Chapter 588). Transient keratitis may occur with rubeola and sometimes with rubella (see Chapter 274).

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CHAPTER 646

Abnormalities of the Lens

Scott E. Olitsky, Justin D. Marsh

Cataracts

A cataract is any opacity of the lens (Fig. 646.1). Some are clinically unimportant; others significantly affect visual function. The incidence of infantile cataracts is approximately 2-13/10,000 live births. Approximately 60% of cataracts are an isolated defect, 22% are part of a syndrome, and the remaining cases are associated with other unrelated major birth defects. Cataracts are more common in low birthweight infants. Infants who weigh at or below 2,500 g have three- to fourfold increased odds of developing infantile cataracts. Some cataracts are associated with other ocular or systemic diseases.

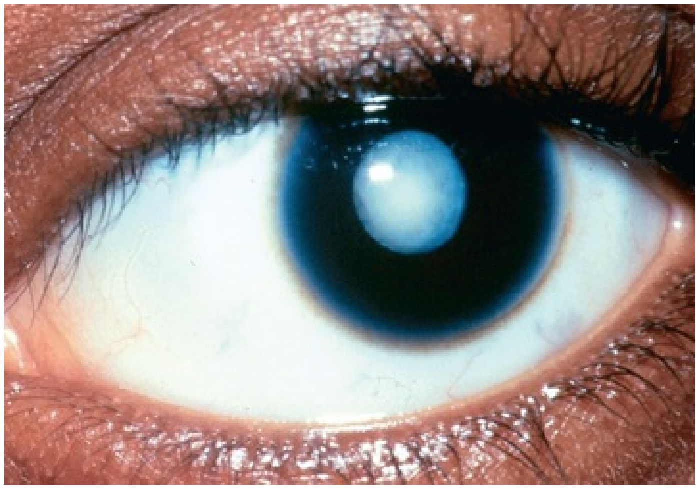

FIG. 646.1 **Leukocoria secondary to cataract.**

Differential Diagnosis

The differential diagnosis of cataracts in infants and children includes a wide range of developmental disorders, infectious and inflammatory processes, metabolic diseases, and toxic and traumatic insults (Table 646.1). Cataracts may also develop secondary to intraocular processes, such as retinopathy of prematurity, persistent hyperplastic primary vitreous, retinal detachment, retinitis pigmentosa, and uveitis. Finally, a fraction of cataracts in children are inherited (Fig. 646.2).

Table 646.1

Differential Diagnosis of Cataracts

Developmental Variants

Prematurity (Y-suture vacuoles) with or without retinopathy of prematurity
Mittendorf dot (remnant of hyaloid artery)
Persistent pupillary membrane (remnant of embryonic lens vasculature)

Genetic Disorders

Simple Mendelian Inheritance
Autosomal dominant (most common)
Autosomal recessive
X-linked
Major Chromosomal Defects
Trisomy disorders (13, 15, 18, 21)
Turner syndrome (45X)
Deletion syndromes (11p13, 18p, 18q)
Duplication syndromes (3q, 20p, 10q)
Multisystem Genetic Disorders
Alport syndrome (hearing loss, renal disease)
Alström syndrome (nerve deafness, diabetes mellitus)
Apert disease (craniosynostosis, syndactyly)
Cerebrooculofacial syndrome
Cockayne syndrome (premature senility, skin photosensitivity)
Conradi disease (chondrodysplasia punctata)

Crouzon disease (dysostosis craniofacialis)
Ectodermal dysplasia
Hallermann-Streiff syndrome (microphthalmia, small pinched nose, skin atrophy, and hypotrichosis)
Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis)
Ichthyosis (keratinizing disorder with thick, scaly skin)
Incontinentia pigmenti (dental anomalies, mental retardation, cutaneous lesions)
Laurence Moon Bardet Biedl Syndrome
Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal disease)
Marfan syndrome
Meckel-Gruber syndrome (renal dysplasia, encephalocele)
Myotonic dystrophy
Nail–patella syndrome (renal dysfunction, dysplastic nails, hypoplastic patella)
Marinesco-Sjögren syndrome (cerebellar ataxia, hypotonia)
Nevoid basal cell carcinoma syndrome (autosomal dominant, basal cell carcinoma erupts in childhood)
Progeria
Rothmund-Thomson syndrome (poikiloderma: skin atrophy)
Rubinstein-Taybi syndrome (broad great toe, mental retardation)
Smith-Lemli-Opitz syndrome (toe syndactyly, hypospadias, mental retardation)
Sotos syndrome (cerebral gigantism)
Spondyloepiphyseal dysplasia (dwarfism, short trunk)
Werner syndrome (premature aging in 2nd decade of life)
Inborn Errors of Metabolism
Abetalipoproteinemia (absent chylomicrons, retinal degeneration)
Fabry disease (α-galactosidase A deficiency)
Galactokinase deficiency
Galactosemia (galactose-1-phosphate uridyltransferase deficiency)
Homocystinemia (subluxation of lens, mental retardation)
Infantile neuronal ceroid lipofuscinosis
Mannosidosis (acid α-mannosidase deficiency)
Niemann-Pick disease (sphingomyelinase deficiency)
Refsum disease (phytanic acid α-hydrolase deficiency)

Wilson disease (accumulation of copper leads to cirrhosis and neurologic symptoms)
Zellweger syndrome

Endocrinopathies

Albright hereditary osteodystrophy
Hypocalcemia (hypoparathyroidism)
Hypoglycemia
Diabetes mellitus

Congenital Infections

Toxoplasmosis
Cytomegalovirus infection
Syphilis
Rubella
Perinatal herpes simplex infection
Measles (rubeola)
Poliomyelitis
Influenza
Varicella-zoster

Ocular Anomalies

Peters anomaly (corneal opacifications with iris-corneal dysgenesis)
Rieger syndrome (iris dysplasia, myotonic dystrophy)
Microphthalmia
Coloboma
Aniridia
Mesodermal dysgenesis
Norrie disease
Persistent pupillary membrane
Posterior lenticonus
Persistent fetal vasculature
Primitive hyaloid vascular system

Retinitis pigmentosa

Miscellaneous Disorders

Atopic dermatitis
Drugs (corticosteroids)
Radiation
Trauma
Juvenile idiopathic arthritis
Retinopathy of prematurity
Spherocytosis
IDIOPATHIC

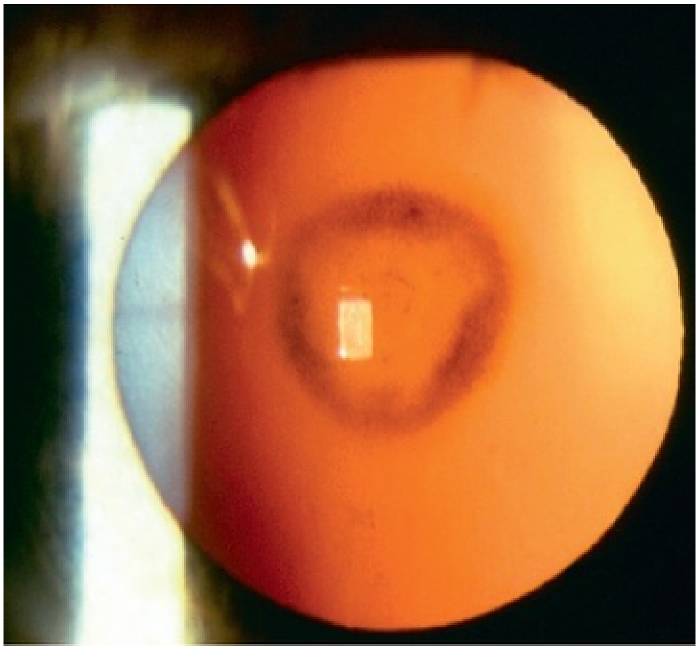

FIG. 646.2 **Central lamellar cataract.**

Developmental Variants

Early developmental processes may lead to various congenital lens opacities. Discrete dots or white plaque-like opacities of the lens capsule are common and sometimes involve the contiguous subcapsular region. Small opacities of the posterior capsule may be associated with persistent remnants of the primitive hyaloid vascular system (the common Mittendorf dot), whereas those of the anterior capsule may be associated with persistent strands of the pupillary membrane or vascular sheath of the lens. Congenital cataracts of this type are usually stationary and rarely interfere with vision, but in some cases, progression occurs.

Prematurity

A special type of lens change seen in some preterm newborn infants is the so-called cataract of prematurity. The appearance is of a cluster of tiny vacuoles in the distribution of the Y sutures of the lens. They can be visualized with an ophthalmoscope and are best seen with the pupil well dilated. The pathogenesis is unclear. In most cases, the opacities disappear spontaneously, often within a few weeks.

Mendelian Inheritance

Many cataracts unassociated with other diseases are hereditary. The most common mode of inheritance is autosomal dominant. Penetrance and expressivity vary. Autosomal recessive inheritance occurs less frequently; it is sometimes found in populations with high rates of consanguinity. X-linked inheritance of cataracts unassociated with disease is relatively rare.

Congenital Infection Syndrome

Cataracts in infants and children can be a result of prenatal infection. Lens opacity may occur in any of the major congenital infection syndromes (e.g., toxoplasmosis, cytomegalovirus, syphilis, rubella, herpes simplex virus). Cataracts may also occur secondary to other perinatal infections, including measles, poliomyelitis, influenza, varicella-zoster, and vaccinia.

Metabolic Disorders

Cataracts are a prominent manifestation of many metabolic diseases, particularly certain disorders of carbohydrate, amino acid, calcium, and copper metabolism. A primary consideration in any infant with cataracts is the possibility of **galactosemia** (see Chapter 105.2). In classic infantile galactosemia, galactose-

1-phosphate uridyl transferase deficiency, the cataract is typically of the zonular type, with haziness or opacification of 1 or more of the perinuclear layers of the lens. Haziness or clouding of the nucleus also often occurs. In its early stages, the cataract generally has a distinctive oil droplet appearance and is best detected with the pupil fully dilated. Progression to complete opacification of the lens may occur within weeks. With early treatment (galactose-free diet), the lens changes may be reversible.

In **galactokinase deficiency** , cataracts are the sole clinical manifestation. The cataracts are usually zonular and may appear in the 1st few mo of life, 1st few yr of life, or later in childhood.

In children with juvenile-onset diabetes mellitus, lens changes are uncommon. Some develop snowflake-like white opacities and vacuoles of the lens. Others develop cataracts that may progress and mature rapidly, sometimes in a matter of days, especially during adolescence. An antecedent event may be the sudden development of myopia caused by changes in the optical density of the lens. Congenital lens opacities may be seen in children of diabetic and prediabetic mothers (see Chapter 127.1).

Hypoglycemia in neonates can also be associated with early development of cataracts. Ketotic hypoglycemia is also associated with cataracts.

An association between cataracts and hypocalcemia is well established. Various lens opacities may be seen in patients with hypoparathyroidism (see Chapter 589).

The **oculocerebral renal syndrome of Lowe** is associated with cataracts in infants. Affected male children frequently have dense bilateral cataracts at birth, often in association with glaucoma and miotic pupils. Punctate lens opacities are frequently present in heterozygous females.

The distinctive sunflower cataract of **Wilson disease** is not commonly seen in children. Various lens opacities may be seen in children with certain of the sphingolipidoses, mucopolysaccharidoses, and mucolipidoses, particularly Niemann-Pick disease, mucosulfatidosis, Fabry disease, and aspartylglycosaminuria.

Chromosomal Defects

Lens opacities of various types may occur in association with chromosomal defects, including trisomies 13, 18, and 21; Turner syndrome; and a number of deletion (11p13, 18p, 18q) and duplication (3q, 20p, 10q) syndromes.

Drugs, Toxic Agents, and Trauma

Of the various drugs and toxic agents that may produce cataracts, corticosteroids are of major importance in the pediatric age group. Steroid-related cataracts characteristically are posterior subcapsular lens opacities. The incidence and severity vary. The relative significance of dose, mode of administration, duration of treatment, and individual susceptibility is controversial, and the pathogenesis of steroid-induced cataracts is unclear. The effect on vision depends on the extent and density of the opacity. In many cases, the acuity is only minimally or moderately impaired. Reversibility of steroid-induced cataracts may occur in some cases. All children receiving long-term steroid treatment should have periodic eye examinations.

Trauma to the eye is a major cause of cataracts in children (Fig. 646.3). Opacification of the lens may result from blunt or penetrating injury. Cataracts can be an important manifestation of child abuse.

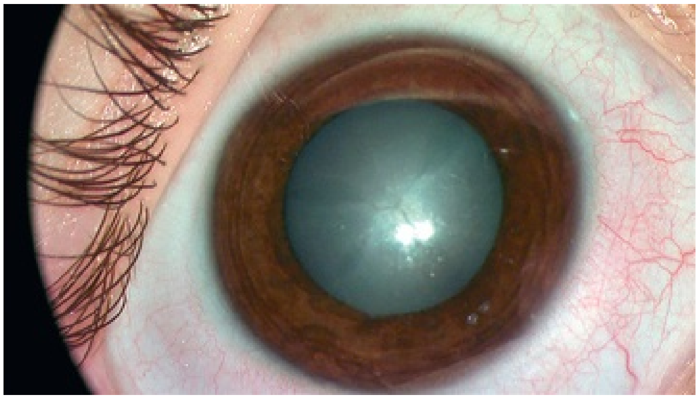

FIG. 646.3 **Diffuse cataract related to blunt trauma.**

Cataract formation after exposure to therapeutic radiation is dose and duration dependent. Adult research shows 50% occurrence in lens dose of 15 Gy. Delayed onset is the rule.

Miscellaneous Disorders

The list of multisystem syndromes and diseases associated with lens opacities and other eye anomalies is extensive (see Table 646.1).

Treatment

The treatment of cataracts that significantly interfere with vision includes the following: (1) surgical removal of lens material to provide an optically clear visual axis; (2) correction of the resultant aphakic refractive error with spectacles, contact lenses, or intraocular lens implantation; and (3) correction of any associated sensory deprivation amblyopia. Because the use of spectacles may not be possible in children after cataract removal, the use of contact lenses for visual rehabilitation is sometimes a medical necessity. Intraocular lens implantation has become a mainstay for visual rehabilitation in children 2 yr or older. A multicenter trial studied the visual outcomes in very young children treated with a contact lens versus an intraocular lens implant. One yr after treatment, the children randomized into the intraocular lens implant group had more intraoperative complications, adverse events, and need for additional intraocular surgery. Although the median visual acuity was better in the contact lens group, the difference did not reach statistical significance. Treatment of the amblyopia may be the most demanding and difficult step in the visual rehabilitation of infants or children with cataracts. Not all cataracts require surgical intervention. Cataracts that are not visually significant should be monitored for change, and the child should be monitored for the development of amblyopia.

Prognosis

Prognosis depends on many factors, including the nature of the cataract, the underlying disease, age at onset, age at intervention, duration and severity of any attendant amblyopia, and presence of any associated ocular abnormalities (e.g., microphthalmia, retinal lesions, optic atrophy, glaucoma, nystagmus, and strabismus). Persistent amblyopia is the most common cause of poor visual recovery after cataract surgery in children. Secondary conditions and complications may develop in children who have had cataract surgery, including inflammatory sequelae, secondary membranes, glaucoma, retinal detachment, and changes in the axial length of the eye. All of these should be considered in planning treatment.

Ectopia Lentis

Normally the lens is suspended in place behind the iris diaphragm by the zonular fibers of the ciliary body. Abnormalities of the suspensory system resulting from a developmental defect, disease, or trauma may result in instability or displacement of the lens. Displacement of the lens is classified as luxation, which is complete displacement of the lens (also known as dislocation) (Fig. 646.4), or as subluxation, which is a partial displacement (Fig. 646.5). Symptoms include blurring of vision, which is often the result of refractive changes such as myopia, astigmatism, or aphakic hyperopia. Some patients experience diplopia (double vision). An important sign of displacement is **iridodonesis** , a tremulousness of the iris caused by the loss of its usual support. Also, the anterior chamber may appear deeper than normal. Sometimes the equatorial region ("edge") of the displaced lens may be visible in the pupillary aperture. On ophthalmoscopy, this may appear as a black crescent. Also, the difference between the phakic and aphakic portions can be appreciated when focusing on the fundus.

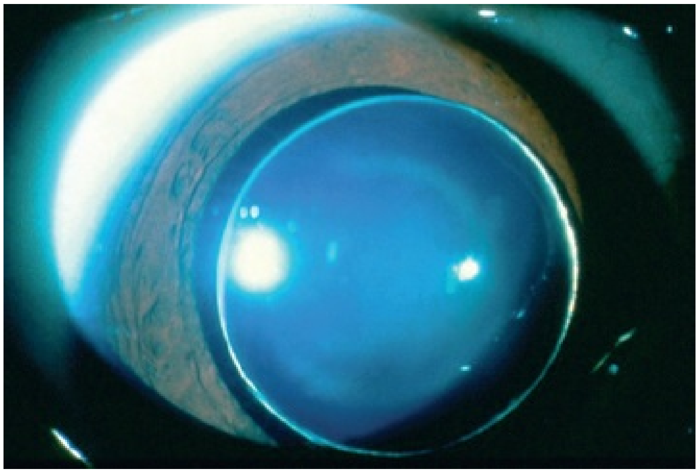

FIG. 646.4 Complete dislocation of lens into the anterior chamber seen in Weill-Marchesani syndrome.

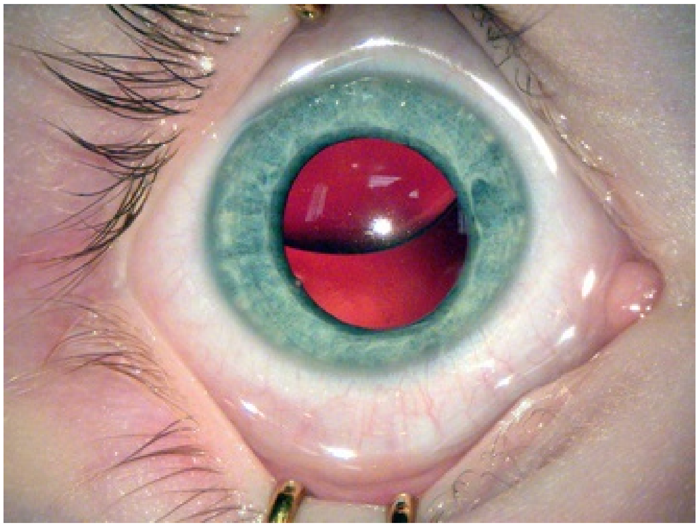

FIG. 646.5 Marfan syndrome. Upward lens subluxation. (From Hoyt CS, Taylor D: *Pediatric ophthalmology and strabismus,* ed 4, Philadelphia, 2013, Elsevier Saunders. Fig. 35.9A, p. 333.)

Differential Diagnosis

A major cause of lens displacement is trauma. Displacement may also occur as a result of ocular disease such as uveitis, intraocular tumor, congenital glaucoma, high myopia, megalocornea, or aniridia or in association with cataract. Ectopia lentis may also be inherited or associated with systemic disease.

Displacement of the lens occurring as a heritable ocular condition unassociated with systemic abnormalities is referred to as *simple ectopia lentis* . Simple ectopia lentis is usually transmitted as an autosomal dominant condition. The lens is generally displaced upward and temporally. The ectopia may be present at birth or may appear later in life. Another form of heritable dislocation is **ectopia lentis et pupillae** (see Chapter 640). In this condition, both the lens and pupil are displaced, usually in opposite directions. This condition is generally bilateral, with 1 eye being almost a mirror image of the other. Ectopia lentis et pupillae is an autosomal recessive condition, although variable expression with some intermingling with simple ectopia lentis has been reported.

Systemic disorders associated with displacement of the lens include Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, and sulfite oxidase deficiency. Ectopia lentis occurs in approximately 80% of patients with Marfan syndrome. In approximately 50% of patients with Marfan syndrome, the ectopia is evident by 5 yr of age. In most cases, the lens is displaced superiorly and temporally; it is almost always bilateral and relatively symmetric. In homocystinuria, the lens is usually displaced inferiorly and somewhat nasally. The subluxation of the lens occurs early in life and is often evident by 5 yr of age. In Weill-Marchesani syndrome, the displacement of the lens is often downward and forward, and the lens tends to be small and round.

Ectopia lentis is also associated occasionally with other conditions, including Ehlers-Danlos, Sturge-Weber, Crouzon, and Klippel-Feil syndromes; oxycephaly; and mandibulofacial dysostosis. A syndrome of dominantly inherited blepharoptosis, high myopia, and ectopia lentis has also been described.

Treatment and Prognosis

Displacement of the lens often results only in optical problems. In some cases, however, more serious complications may develop, such as glaucoma, uveitis, retinal detachment, or cataract. Management must be individualized according to the type of displacement, its cause, and the presence of any complicating ocular or systemic conditions. For many patients, optical correction by spectacles or contact lenses can be provided. Manipulation of the iris diaphragm with mydriatic or miotic drops may sometimes help improve vision. In selected cases, the best treatment is surgical removal of the lens. In many children, treatment of any associated amblyopia must be instituted early. In addition, for children with ectopia lentis, safety precautions should be taken to prevent injury to the eye.

Other Disorders of the Lens

Microspherophakia

The term *microspherophakia* refers to a small, round lens that may occur as an isolated anomaly (probably autosomal recessive) or in association with other ocular abnormalities, such as ectopia lentis, myopia, or retinal detachment (possibly autosomal dominant). Microspherophakia may also occur in association with various systemic disorders, including Marfan syndrome, Weill-Marchesani syndrome, Alport syndrome, mandibulofacial dysostosis, and Klinefelter syndrome.

Anterior Lenticonus

Anterior lenticonus is a rare bilateral condition in which the anterior capsule of the lens thins, allowing the lens to bulge forward centrally. It may be accompanied by lens opacities or other eye anomalies and is a prominent feature of Alport syndrome. The increased curvature of the central area may cause high myopia. Spontaneous rupture of the anterior capsule may occur, requiring prompt surgical intervention.

Posterior Lenticonus

Posterior lenticonus, which occurs more commonly than anterior lenticonus, is characterized by a circumscribed round or oval bulge of the posterior lens capsule and cortex, involving the central region of the lens. In the early stages, by the red reflex test, this may look like an oil droplet. It occurs in infants and young children and tends to increase with age. Usually the lens material within and surrounding the capsular bulge eventually becomes opacified. Posterior lenticonus usually occurs as an isolated ocular anomaly. It is generally unilateral but may be bilateral. It is believed to be sporadic, although autosomal dominant and X-linked inheritance has been suggested in some cases. Infants or children with posterior lenticonus may require optical correction, amblyopia treatment, and surgery for progressive cataract.

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CHAPTER 647

Disorders of the Uveal Tract

Scott E. Olitsky, Justin D. Marsh

Uveitis (Iritis, Cyclitis, Chorioretinitis)

The uveal tract (the inner vascular coat of the eye, consisting of the iris, ciliary body, and choroid) is subject to inflammatory involvement in numerous systemic diseases, both infectious and noninfectious, and in response to exogenous factors, including trauma and toxic agents (Table 647.1). Inflammation may affect any one portion of the uveal tract preferentially or all parts together.

Table 647.1

Uveitis in Childhood

Anterior Uveitis

Juvenile idiopathic arthritis (pauciarticular)
Sarcoidosis
Trauma
Tuberculosis
Kawasaki disease
Ulcerative colitis
Crohn syndrome
Reactive postinfectious (enteric or genital) with arthritis and rash
Spirochetal (syphilis, leptospiral)
Brucellosis
Heterochromic iridocyclitis (Fuchs)
Viral (herpes simplex, herpes zoster)
Ankylosing spondylitis
Stevens-Johnson syndrome

Chronic infantile neurologic cutaneous arthritis syndrome (CINCA)
Familial Mediterranean fever
Hyperimmunoglobulin D syndrome
Tumor necrosis factor receptor–associated periodic syndrome
Muckle-Wells syndrome
Blau syndrome
Psoriasis
Multiple sclerosis
Cyclic neutropenia
Chronic granulomatous disease
X-linked lymphoproliferative disease
Hypocomplementemic vasculitis
Idiopathic
Drugs

Posterior Uveitis (Choroiditis—May Involve Retina)

Toxoplasmosis
Toxocariasis
Parasites (toxocariasis)
Sarcoidosis
Cat-scratch disease
Tuberculosis
Viral (rubella, herpes simplex, HIV, cytomegalovirus, West Nile)
Subacute sclerosing panencephalitis
Tubulointestinal nephritis and uveitis syndrome
Idiopathic

Anterior and/or Posterior Uveitis

Sympathetic ophthalmia (trauma to other eye)
Vogt-Koyanagi-Harada syndrome (uveootocutaneous syndrome: poliosis, vitiligo, alopecia, deafness, tinnitus, uveitis, aseptic meningitis, retinitis)
Behçet syndrome
Lyme disease

Iritis may occur alone or in conjunction with inflammation of the ciliary body as iridocyclitis or in association with pars planitis. Pain, photophobia, and lacrimation are the characteristic symptoms of acute anterior uveitis, but the inflammation may develop insidiously without disturbing symptoms. Signs of anterior uveitis include conjunctival hyperemia, particularly in the perilimbal region (ciliary flush), and cells and protein ("flare") in the aqueous humor (Fig. 647.1). Inflammatory deposits on the posterior surface of the cornea (keratic precipitates) and congestion of the iris may also be seen. More chronic cases may show degenerative changes of the cornea (band keratopathy), lenticular opacities (cataract), development of glaucoma, and impairment of vision. The cause of anterior uveitis is often obscure; primary considerations in children are rheumatoid disease, particularly pauciarticular arthritis, Kawasaki disease, Reiter syndrome, and sarcoidosis. Iritis may be secondary to corneal disease, such as herpetic keratitis or a bacterial or fungal corneal ulcer, or to a corneal abrasion or foreign body. Traumatic iritis and iridocyclitis are especially common in children.

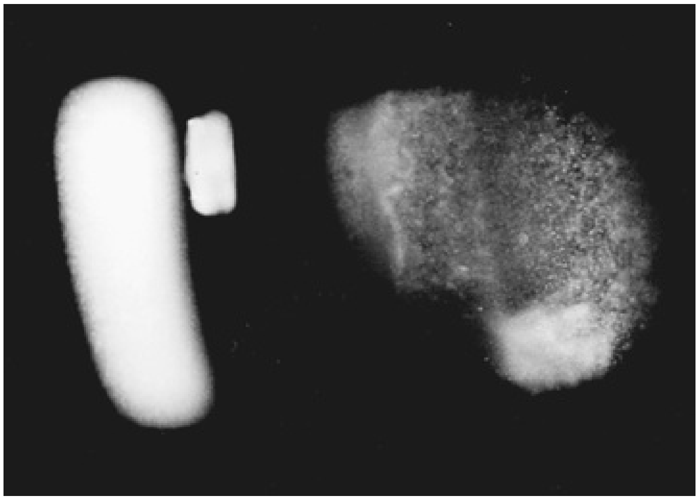

FIG. 647.1 **Cell and flare in the anterior chamber. The flare represents protein leakage. (Courtesy of Peter Buch, CRA.)**

Iridocyclitis that occurs in children with juvenile idiopathic arthritis deserves special mention. Unlike most forms of anterior uveitis, it rarely creates pain, photophobia, or conjunctival hyperemia. Loss of vision may not be noticed until severe and irreversible damage has occurred. Because of the lack of symptoms and the high incidence of uveitis in these children, routine periodic screening is necessary. Ophthalmic screening guidelines are based on 3 factors that predispose children with arthritis to uveitis:

1. Type of arthritis
2. Age of onset of arthritis
3. Antinuclear antibody (ANA) status

Table 647.2 has been developed by the American Academy of Pediatrics for children with juvenile idiopathic arthritis without known iridocyclitis.

Table 647.2

Examination Schedule for Children With Juvenile Idiopathic Arthritis Without Known Iridocyclitis

JIA SUBTYPE	**AGE OF ONSET**	
	≤6 YR	**>6 YR**
OLIGOARTHRITIS OR POLYARTHRITIS		
Positive ANA		
Less than 4 yr duration	Every 3 mo	Every 6 mo
4-7 yr duration	Every 6 mo	Annually
More than 7 yr duration	Annually	Annually
Negative ANA		
Less than 4 yr duration	Every 6 mo	Annually
4-7 yr duration	Annually	Annually
More than 7 yr duration	Annually	Annually
Systemic	Annually regardless of duration	Annually regardless of duration

ANA, antinuclear antibody; JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis.

Choroiditis, inflammation of the posterior portion of the uveal tract, invariably also involves the retina; when both are obviously affected, the condition is termed *chorioretinitis* . The causes of posterior uveitis are numerous; the more common are toxoplasmosis, histoplasmosis, cytomegalic inclusion disease, sarcoidosis, syphilis, tuberculosis, and toxocariasis (Fig. 647.2). Depending on the etiology, the inflammatory signs may be diffuse or focal. Vitreous reaction often occurs as well. With many types, the result is atrophic chorioretinal scarring demarcated by pigmentation, often with visual impairment. Secondary complications include retinal detachment, glaucoma, and phthisis.

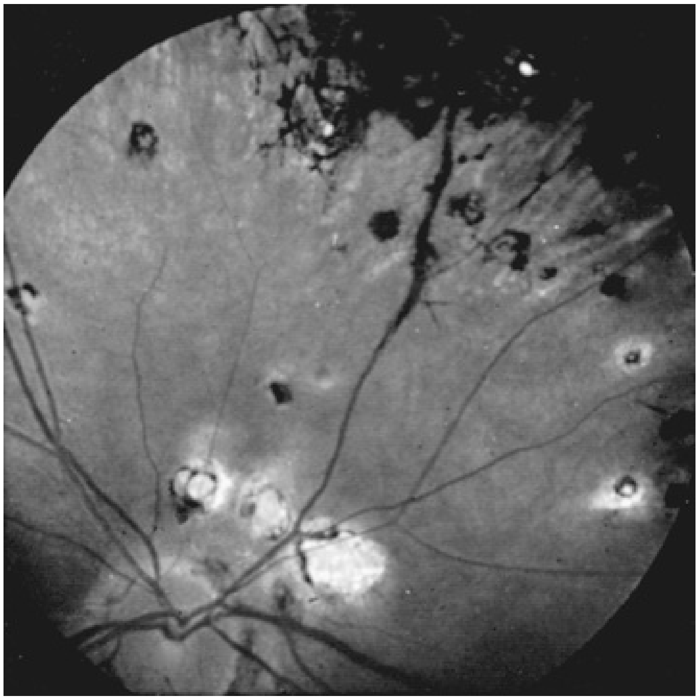

FIG. 647.2 Focal atrophic and pigmented scars of chorioretinitis.

Panophthalmitis is inflammation involving all parts of the eye. It is frequently suppurative, most often as a result of a perforating injury or of septicemia. It produces severe pain, marked congestion of the eye, inflammation of the adjacent orbital tissues and eyelids, and loss of vision. In many cases, the eye is lost despite intensive treatment of the infection and inflammation. Enucleation of the eye or evisceration of the orbit may be necessary.

Sympathetic ophthalmia is a rare type of inflammatory response that affects the uninjured eye after a perforating injury. It may occur weeks, months, or even years after the injury. A hypersensitivity phenomenon is the most probable cause. Loss of vision in the uninjured (sympathizing) eye may result. Removal of the injured eye prevents the development of sympathetic ophthalmia but does not stop the progression of the disease once it has occurred. Therefore early enucleation should be considered if there is no hope of visual recovery after a severe injury.

Treatment

The various forms of intraocular inflammation are treated according to their underlying systemic causal factors. When infection is proved or suspected, appropriate systemic antimicrobial or antiviral therapy is used. In some cases, intravitreal injection is indicated.

Elimination of the intraocular inflammation is important to reduce the risk of severe, and often permanent, vision loss. Untreated, the inflammatory process may lead to the development of band keratopathy (calcium deposition in the cornea), cataracts, glaucoma, and irreversible retinal damage. Anterior inflammation may respond well to topical corticosteroid treatment. Posterior cases often require systemic therapy. The use of topical and systemic corticosteroids can lead to the development of glaucoma and cataracts. To reduce the need for topical and systemic corticosteroids, systemic immunosuppression is often used in patients requiring long-term treatment. Immunosuppressive agents include methotrexate, cyclosporine, and tumor necrosis factor inhibitors. Multiple agents may be needed in recalcitrant cases. Noninfectious inflammatory uveitis in adolescents has been treated with adalimumab, a human antitumor necrosis factor-α monoclonal antibody resulting in improved vision, lack of disease progression, and an ability to wean steroids. Cycloplegic agents, particularly atropine, are also used to reduce inflammation and to prevent adhesion of the iris to the lens (posterior synechiae), especially in anterior uveitis. Extensive posterior synechiae formation can lead to acute angle closure glaucoma.

Surgery may be required for patients who develop glaucoma because of the underlying disease process or the need for corticosteroid treatment. Cataract surgery should be delayed until the inflammation has been under control for a period of time. Cataract surgery in children with a history of prolonged uveitis can carry significant risk. There is no universal agreement concerning the use of intraocular lenses in these patients.

Pars planitis is an uncommon idiopathic form of intermediate uveitis characterized by anterior chamber involvement, anterior vitreous cells and condensations, and peripheral retinal vasculitis. The average age of onset is 9 yr. It is predominately bilateral and seen more frequently in males. Painless decreased vision is the usual presenting sign. The prognosis is good when adequate medical treatment is sought early in the course of the disease.

Masquerade syndromes can sometimes mimic intraocular inflammation. Retinoblastoma, leukemia, retained intraocular foreign body, juvenile xanthogranuloma, and peripheral retinal detachments may produce signs similar to those seen in uveitis. These syndromes should be kept in mind when evaluating a patient with suspected uveitis or if a patient does not respond as anticipated to antiinflammatory treatment.

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CHAPTER 648

Disorders of the Retina and Vitreous

Scott E. Olitsky, Justin D. Marsh

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a complex disease of the developing retinal vasculature in infants born prematurely. It may be acute (early stages) or chronic (late stages). Clinical manifestations range from mild, usually transient changes of the peripheral retina to severe progressive vasoproliferation, scarring, and potentially blinding retinal detachment. ROP includes all stages of the disease and its sequelae.

Pathogenesis

Beginning at 16 wk of gestation, retinal angiogenesis normally proceeds from the optic disc to the periphery, reaching the outer rim of the retina (ora serrata) nasally at about 36 wk and extending temporally by approximately 40 wk. Injury to this process results in various pathologic and clinical changes. The first observation in the acute phase is cessation of vasculogenesis. Rather than a gradual transition from a vascularized to avascular retina, there is an abrupt termination of the vessels marked by a line in the retina. The line may then grow into a ridge composed of mesenchymal and endothelial cells. Cell division and differentiation may later resume, and vascularization of the retina may proceed. Alternatively, there may be progression to an abnormal proliferation of vessels out of the plane of the retina, into the vitreous, and over the surface of the retina. Cicatrization and traction on the retina may follow, leading to retinal detachment.

The risk factors associated with ROP are not fully known, but prematurity and the associated retinal immaturity at birth represent the major factors.

Oxygenation, respiratory distress, apnea, bradycardia, heart disease, infection, hypercarbia, acidosis, anemia, and the need for transfusion are thought by some to be contributory factors. Generally the lower the gestational age, the lower the birthweight, and the sicker the infant, the greater the risk for ROP.

The basic pathogenesis of ROP is still unknown. Exposure to the extrauterine environment, including the necessarily high inspired oxygen concentrations, produces cellular damage, perhaps mediated by free radicals. Later in the course of the disease, peripheral hypoxia develops and vascular endothelial growth factors (VEGFs) are produced in the nonvascularized retina. These growth factors stimulate abnormal vasculogenesis, causing neovascularization to occur. Because of poor pulmonary function, a state of relative retinal hypoxia occurs. This causes upregulation of VEGF, which, in susceptible infants, can cause abnormal fibrovascular growth. This neovascularization may then lead to scarring and loss of vision.

Classification

The currently used international classification of ROP describes the location, extent, and severity of the disease. To delineate location, the retina is divided into 3 concentric zones centered on the optic disc (Fig. 648.1). Zone I, the posterior or inner zone, extends twice the disc-macular distance, or 30 degrees in all directions from the optic disc. Zone II, the middle zone, extends from the outer edge of zone I to the ora serrata nasally and to the anatomic equator temporally. Zone III, the outer zone, is the residual crescent that extends from the outer border of zone II to the ora serrata temporally. The extent of involvement is described by the number of circumferential clock hours involved.

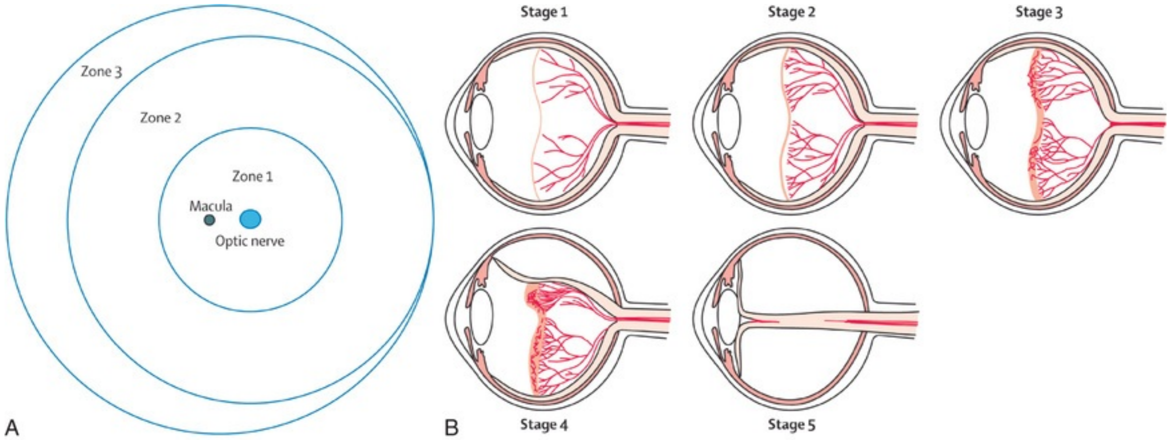

FIG. 648.1 The retina is divided into 3 zones and the extent or severity of retinopathy in these zones is classified in terms of 5 stages. **A,** Diagram of right eye. **B,** Stage 1 is characterized by a thin demarcation line between vascularized and nonvascularized retina, stage 2 by a ridge, stage 3 by extraretinal fibrovascular proliferation, stage 4 by partial retinal detachment, and stage 5 by total retinal detachment. In stage 3, extraretinal neovascularization can become severe enough to cause retinal detachment (stages 4-5), which usually leads to blindness. (**A,** From Hellström A, Smith LEH, Dammann O: Retinopathy of prematurity. Lancet 382:1445–1454, 2013, Fig. 3, p. 1450; **B,** courtesy Lisa Hård.)

The phases and severity of the disease process are classified into 5 stages. Stage 1 is characterized by a demarcation line that separates vascularized from avascular retina. This line lies within the plane of the retina and appears relatively flat and white. Often noted is abnormal branching or arcading of the retinal vessels leading into the line. Stage 2 is characterized by a ridge; the demarcation line has grown, acquiring height, width, and volume and extending up and out of the plane of the retina. Stage 3 is characterized by the presence of a ridge and the development of extraretinal fibrovascular tissue (Fig. 648.2*A*). Stage 4 is characterized by subtotal retinal detachment caused by traction from the proliferating tissue in the vitreous or on the retina. Stage 4 is subdivided into 2 phases: (a) subtotal retinal detachment not involving the macula and (b) subtotal retinal detachment involving the macula. Stage 5 is total retinal detachment.

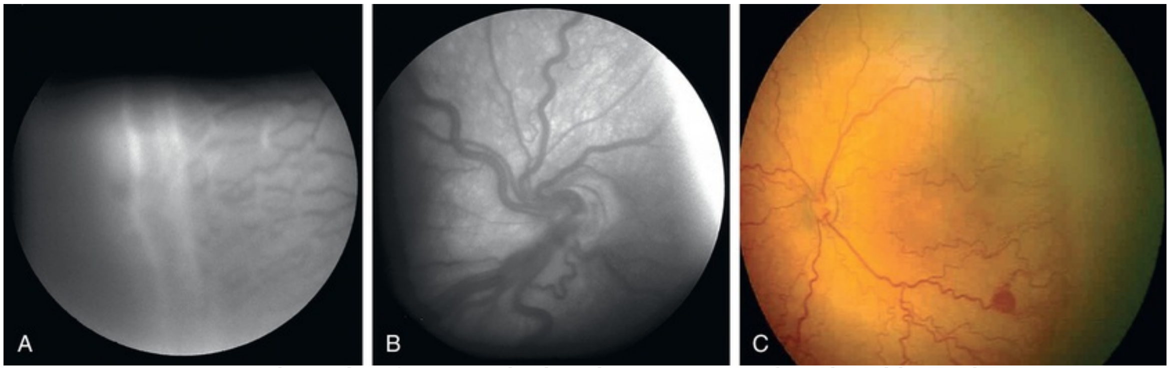

FIG. 648.2 **Retinopathy of prematurity (ROP). A, In stage 3, there is a ridge and extraretinal vascular tissue. B, Retinal vessels are dilated and tortuous in active zone 1 ROP with plus disease. C, Zone 1 ROP with plus disease.**

When signs of posterior retinal vascular changes accompany the active stages of ROP, the term *plus disease* is used (see Fig. 648.2*B* and *C*). Patients reaching the point of dilation and tortuosity of the retinal vessels also frequently demonstrate the associated findings of engorgement of the iris, pupillary rigidity, and vitreous haze.

The Early Treatment for Retinopathy of Prematurity Cooperative has described types 1 and 2 ROP as follows:

Type 1 ROP

- Zone I, any stage with plus
- Zone I, stage 3 without plus
- Zone II, stage 2 to 3 with plus

Type 2 ROP

- Zone I, stage 1 to 2 without plus
- Zone II, stage 3 without plus

Clinical Manifestations and Prognosis

In more than 90% of at-risk infants, the course is one of spontaneous arrest and regression, with little or no residual effects or visual disability. Fewer than 10% of infants have progression toward severe disease, with significant extraretinal vasoproliferation, cicatrization, detachment of the retina, and impairment of vision.

Some children with arrested or regressed ROP are left with demarcation lines, undervascularization of the peripheral retina, or abnormal branching, tortuosity, or straightening of the retinal vessels. Some are left with retinal pigmentary changes, dragging of the retina (so-called dragged disc), ectopia of the macula, retinal folds, or retinal breaks. Others proceed to total retinal detachment, which commonly assumes a funnel-like configuration. The clinical picture is often that of a retrolental membrane, producing leukokoria (a white reflex in the pupil). Some patients develop cataract, glaucoma, and signs of inflammation. The end stage is often a painful blind eye or a degenerated phthisical eye. The spectrum of ROP also includes myopia, which is often progressive and of significant degree in infancy. The incidence of anisometropia, strabismus, amblyopia, and nystagmus may also be increased.

Diagnosis

Systematic serial screening ophthalmologic examinations of infants at risk are recommended. Infants with a birthweight of less than 1,500 g or gestational age of 32 wk or less and selected infants with a birthweight between 1,500 and 2,000 g or gestational age of more than 32 wk with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their pediatrician or neonatologist to be at high risk, should have retinal screening examinations. The timing of the initial screening exam is based on the infant's age. Table 648.1 was developed from an evidence-based analysis of the Multicenter Trial of Cryotherapy for ROP. The examination can be stressful to fragile preterm infants, and the dilating drops can have untoward side effects. Infants must be carefully monitored during and after the examination. Some neonatologists and ophthalmologists advocate the use of topical tetracaine and/or oral sucrose to reduce the discomfort and stress to the infant. Follow-up is based on the initial findings and risk factors but is usually 2 wk or less.

Table 648.1

Timing of First Eye Examination Based on Gestational Age at Birth

GESTATIONAL AGE AT BIRTH	AGE AT INITIAL EXAMINATION IN WEEKS	
	Postmenstrual	**Chronologic**

22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

Treatment

In selected cases, laser photocoagulation of the avascular retina reduces the more severe complications of progressive ROP (Table 648.2). Advances in vitreoretinal surgical techniques have had limited success in reattaching the retina in infants with total retinal detachment (stage 5 ROP), but the visual results are often disappointing. The Early Treatment for Retinopathy of Prematurity Cooperative study did find improved structural and visual outcomes with a redefined threshold for treatment. It demonstrated the importance of plus disease and the presence of posterior retinal involvement in the determination of when to treat ROP. Treatment should be considered for any eye with type 1 ROP. Serial examinations are indicated for any eye with type 2 ROP; treatment is considered if type 2 progresses to type 1 or if threshold ROP develops.

Table 648.2

Criteria for Peripheral Ablative Therapy for Retinopathy of Prematurity

1. Zone II: Plus disease with stage 2 or 3 ROP
2. Zone I: Plus disease with stage 1 or 2 ROP
3. Zone I: Stage 3 ROP

ROP, retinopathy of prematurity.

Data from Early Treatment for Retinopathy of Prematurity Cooperative Group: Revised indications for the treatment of retinopathy of prematurity: results of the Early Treatment for Retinopathy of Prematurity Randomized Trial. *Arch*

Ophthalmol 121:1684, 2003.

Intravitreal injections of VEGF antagonists are being used for zone 1 ROP treatment but continue to be debated for use in less severe forms of the disease.

Prevention

Prevention of ROP ultimately depends on the prevention of premature birth and its attendant problems (see Chapters 114 and 117.2). However, a number of other potential factors have been studied in order to decrease the occurrence of ROP in these premature infants. Ambient light had been considered by some to be a potential agent that could hopefully be manipulated. The LIGHT-ROP study definitively found that ambient light reduction had no impact on ROP. The association between ROP and oxygen saturation has been studied for decades. Recent research has focused on maintaining oxygen saturation levels for severely premature infants at levels sufficiently low to minimize the risk of ROP and sufficiently high to optimize survival.

Persistent Fetal Vasculature

Persistent fetal vasculature (PFV; formerly called persistent hyperplastic primary vitreous) includes a spectrum of manifestations caused by the persistence of various portions of the fetal hyaloid vascular system and associated fibrovascular tissue.

Pathogenesis

During development of the eye, the hyaloid artery extends from the optic disc to the posterior aspect of the lens; it sends branches into the vitreous and ramifies to form the posterior portion of the vascular capsule of the lens. The posterior portion of the hyaloid system normally regresses by the 7th fetal mo and the anterior portion by the 8th fetal mo. Small remnants of the system, such as a tuft of tissue at the disc (Bergmeister papilla) or a tag of tissue on the posterior capsule of the lens (Mittendorf dot), are common findings in healthy persons. More extensive remnants and associated complications constitute PFV. Two major forms are described, anterior PFV and posterior PFV. Variability is great, and mixed or intermediate forms occur.

Clinical Manifestations

The usual clinical feature of anterior PFV is the presence of a vascularized plaque of tissue on the back surface of the lens in an eye that is microphthalmic or slightly smaller than normal. The condition is usually unilateral and may occur in infants with no other abnormalities and no history of prematurity. The fibrovascular tissue tends to undergo gradual contracture. The ciliary processes become elongated, and the anterior chamber may become shallow. The lens is usually smaller than normal and may be clear, but it often becomes cataractous and may swell or absorb fluid. Large or anomalous vessels of the iris may be present. The anterior chamber angle may have abnormalities. In time, the cornea may become cloudy.

Anterior PFV is usually noted in the 1st wk or mo of life. The most frequent presenting signs are leukocoria (white pupillary reflex), strabismus, and nystagmus. The course is usually progressive and the outcome poor. Major complications are spontaneous intraocular hemorrhage, swelling of the lens caused by rupture of the posterior capsule, and glaucoma. The eye may eventually deteriorate. The spectrum of posterior PFV includes fibroglial veils around the disc and macula, vitreous membranes and stalks containing hyaloid artery remnants projecting from the disc, and meridional retinal folds. Traction detachment of the retina may occur. Vision may be impaired, but the eye is usually retained.

Treatment

Surgery is performed in an effort to prevent complications, to preserve the eye and a reasonably good cosmetic appearance, and, in some cases, to salvage vision. Surgical treatment usually involves aspirating the lens and excising the abnormal tissue. If useful vision is to be attained, refractive correction and aggressive amblyopia therapy are required. In some cases, the affected eye is enucleated because distinguishing between this white mass and retinoblastoma can be difficult. Ultrasonography and CT are valuable diagnostic aids.

Retinoblastoma

Also see Chapter 529 .

Retinoblastoma (Fig. 648.3) is the most common primary malignant intraocular tumor of childhood. It occurs in approximately 1/15,000 live births; 250-300 new cases are diagnosed in the United States annually. Hereditary and nonhereditary patterns of transmission occur; there is no predilection for gender or race. The hereditary form occurs earlier and is usually bilateral and multifocal, whereas the nonhereditary form is generally unilateral and unifocal. Fifteen percent of unilateral cases are hereditary. Bilateral cases often present earlier than unilateral cases. Unilateral tumors are often large by the time they are discovered. The average age at diagnosis is 15 mo for bilateral cases compared with 27 mo for unilateral cases. It is unusual for a child to present with a retinoblastoma after 3 yr of age. Rarely, the tumor is discovered at birth, during adolescence, or even in early adulthood.

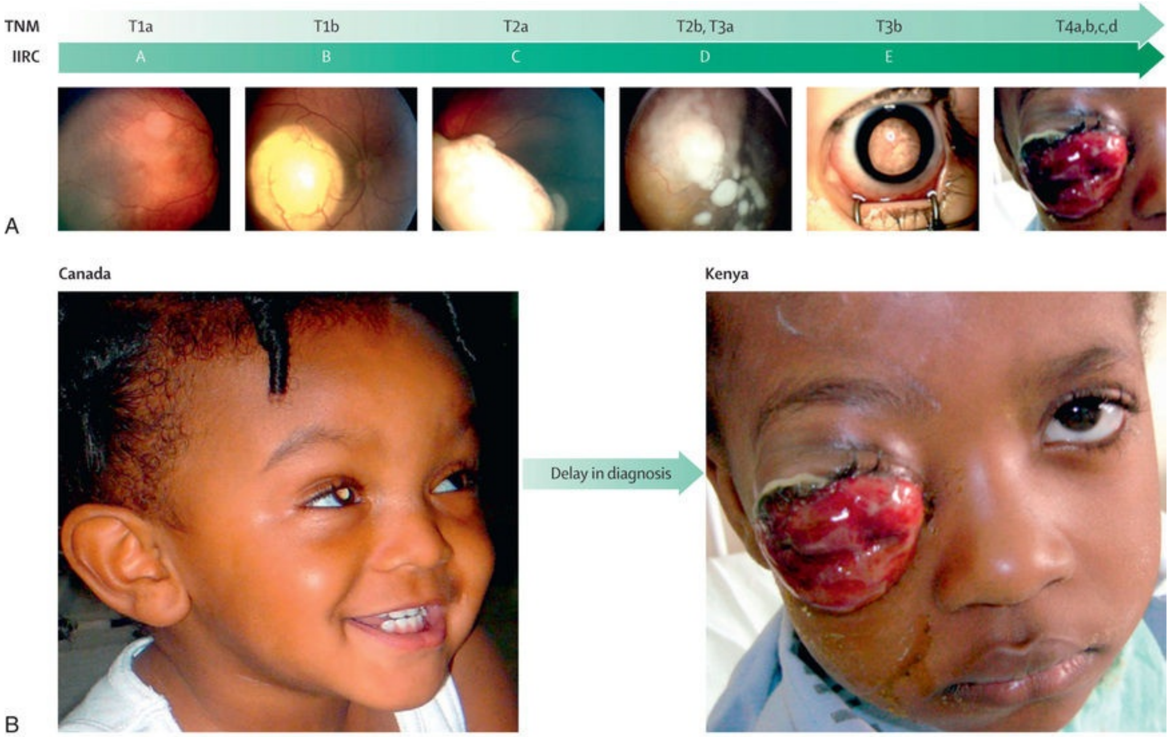

FIG. 648.3 Progression of retinoblastoma from small intraretinal tumors to a massive orbital retinoblastoma probably extending into the brain. A, Progression of retinoblastoma from small intraretinal tumors that can be cured by laser treatment and cryotherapy (TNM T1a, IIRC A) to massive orbital retinoblastoma probably extending into the brain (TNM T4a-b). B, A difference in age at diagnosis recorded between Canada and Kenya could mean the difference between possible cure and certain death The Canadian child with leukocoria was diagnosed because of the left-hand image, which was taken by his sister with his mother's mobile phone. *IIRC,* International Intraocular Retinoblastoma Classification; *TNM,* tumor node metastasis cancer staging. (From Dimaras H, Kimani K, Dimba EAO, et al: Retinoblastoma. Lancet 379:1436–1444, 2012, Fig. 1, p. 1438.)

Clinical Manifestations

The clinical manifestations of retinoblastoma vary depending on the stage at which the tumor is detected. The initial sign in the majority of patients is a white pupillary reflex (leukocoria). Leukocoria results because of the reflection of light off the white tumor. The second most frequent initial sign of retinoblastoma is strabismus. Less frequent presenting signs include pseudohypopyon (tumor cells layered inferiorly in front of the iris) caused by tumor seeding in the anterior chamber of the eye, hyphema (blood layered in front of the iris) secondary to iris neovascularization, vitreous hemorrhage, and signs of orbital cellulitis. On examination, the tumor appears as a white mass, sometimes small and relatively flat, sometimes large and protuberant. It may appear nodular. Vitreous haze or tumor seeding may be evident.

The retinoblastoma gene is a recessive suppressor gene located on chromosome 13 at the 13q14 region. Because of the hereditary nature of retinoblastoma, family members of affected children should undergo a complete ophthalmologic examination and genetic counseling. Newborn siblings and children of affected patients should be referred to an ophthalmologist shortly after birth, when the peripheral retina can be evaluated without the need for an examination under anesthesia.

Diagnosis

Retinoblastoma is diagnosed by direct observation by an experienced ophthalmologist. Ancillary testing such as CT or ultrasonography may help to confirm the diagnosis and demonstrate calcification within the mass. MRI may better detect the presence of an associated pineoblastoma (trilateral retinoblastoma). A definitive diagnosis occasionally cannot be made, and removal of the eye must be considered to avoid the possibility of lethal metastasis of the tumor. Because a biopsy can lead to spread of the tumor, histologic confirmation before enucleation is not possible in most cases. Therefore removal of a blind eye in which the diagnosis of retinoblastoma is likely may be appropriate.

Treatment

Therapy varies, depending on the size and location of the tumor as well as whether it is unilateral or bilateral. Advanced tumors may be treated by enucleation. Other treatment modalities include the use of external beam irradiation, radiation plaque therapy, laser or cryotherapy, and chemoreduction (systemic chemotherapy) followed by local therapies (i.e., laser therapy, cryotherapy, and brachytherapy). During the last decade there has been a dramatic shift in the treatment of retinoblastomas. Intraarterial chemotherapy involves delivery of chemotherapeutic agents via the ophthalmic artery and has dramatically reduced the need for enucleation in many cases of retinoblastoma.

Nonocular secondary tumors are common in patients with germinal mutations; they are estimated to occur with an incidence of 1% per yr of life. The most common secondary tumor is osteogenic sarcoma of the skull and long bones; the risk is higher in patients treated with radiation. Other malignancies include lung, brain, soft tissue, and skin.

The prognosis for children with retinoblastoma depends on the size and extension of the tumor. When confined to the eye, most tumors can be cured. The prognosis for long-term survival is poor when the tumor has extended into the orbit or along the optic nerve.

Retinitis Pigmentosa

This progressive retinal degeneration is characterized by pigmentary changes, arteriolar attenuation, usually some degree of optic atrophy, and progressive impairment of visual function. Dispersion and aggregation of the retinal pigment produce various ophthalmoscopically visible changes ranging from granularity or mottling of the retinal pigment pattern to distinctive focal pigment aggregates with the configuration of bone spicules (Fig. 648.4). Other ocular findings include subcapsular cataract, glaucoma, and keratoconus.

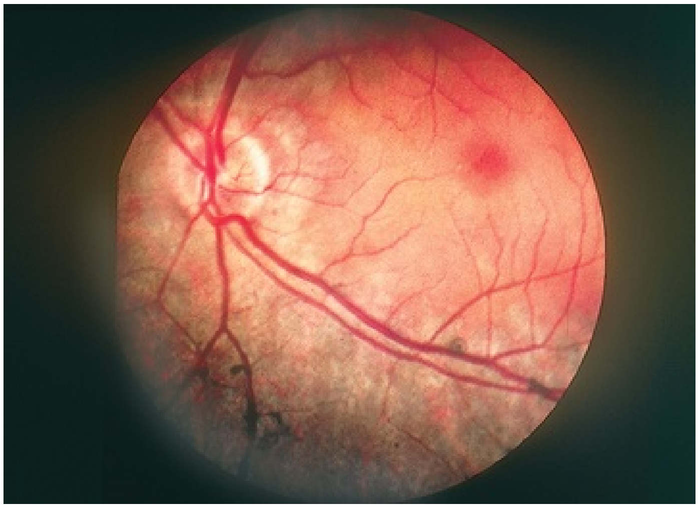

FIG. 648.4 Retinitis pigmentosa. Fundus photograph shows "bone spicule" pigmentation of the midperipheral fundus, waxy pallor of the optic disc, and attenuated retinal vessels, the most consistent finding in retinitis pigmentosa. (Courtesy of Dr. John I. Loewenstein.)

Impairment of night vision or dark adaptation is often the first clinical manifestation. Progressive loss of peripheral vision, often in the form of an expanding ring scotoma or concentric contraction of the field, is usual. There may be loss of central vision. Retinal function, as measured by electroretinography (ERG), is characteristically reduced. The disorder may be autosomal recessive, autosomal dominant, or X-linked. Children with autosomal recessive retinitis pigmentosa are more likely to become symptomatic at an earlier age (median age 10.7 yr). Those with autosomal dominant retinitis pigmentosa are more likely to present in their 20s. Only supportive treatment is available.

A special form of retinitis pigmentosa is **Leber congenital retinal amaurosis,** in which the retinal changes tend to be pleomorphic, with various degrees of pigment disorder, arteriolar attenuation, and optic atrophy. The incidence is approximately 1 in 81,000 births. There are mutations in at least 19 different genes producing this early (infancy) onset autosomal recessive severe retinal degenerative disease. Ten percent have mutations in the *LRAT* or *RPE65* genes, involved in retinoid metabolism. The retina may initially appear normal during infancy. Visual impairment, nystagmus, and poor pupillary reaction are usually evident soon after birth; the ERG findings are abnormal early and confirm the diagnosis. Retinal pigment epithelium (RPE)–specific 65-kDa deficiency is the cause of autosomal recessive disease. Gene replacement therapy (subretinal injection) shows early promise for people affected with Leber congenital retinal amaurosis; however, improvement in vision is not consistently sustained. Some patients may benefit from oral 9-cis retinoid therapy.

Usher syndrome , an autosomal recessive disorder, is the most common cause of retinitis pigmentosa *and* sensorineural deafness (incidence, 1 : 25,000). Type 1 Usher syndrome presents at birth with profound hearing loss and poor balance; vision loss progresses more slowly and begins during adolescence. Patients with type 3 disease have normal hearing at birth but develop hearing loss and night blindness around puberty. To date, 11 genetic loci have been located (5 for type 1; 3 for type 2; 1 for type 3).

Clinically similar, secondary pigmentary retinal degenerations, which must be differentiated from retinitis pigmentosa, occur in a wide variety of metabolic diseases, neurodegenerative processes, and multifaceted syndromes. Examples include the progressive retinal changes of the mucopolysaccharidoses (particularly Hurler, Hunter, Scheie, and Sanfilippo syndromes; see Chapter 107) and certain of the late-onset gangliosidoses (Batten-Mayou, Spielmeyer-Vogt, and Jansky-Bielschowsky diseases; see Chapters 104.4 and 617.2), the progressive retinal degeneration associated with progressive external ophthalmoplegia (Kearns-Sayre syndrome; see Chapter 616.2), and the retinitis pigmentosa–like changes in the Laurence-Moon and Bardet-Biedl syndromes. The retinal manifestations of abetalipoproteinemia (Bassen-Kornzweig syndrome; see Chapter 104) and Refsum disease (see Chapter 104.2) are also similar to those found in retinitis pigmentosa. The diagnosis of the latter 2 disorders in a patient with presumed retinitis pigmentosa is important because treatment is possible. There is also an association of retinitis pigmentosa and congenital hearing loss, as in Usher syndrome.

Stargardt Disease (Fundus Flavimaculatus)

This autosomal recessive retinal disorder is characterized by slowly progressive bilateral macular degeneration and impairment of vision. It usually appears at 8 to 14 years of age, and affected children are often initially misdiagnosed as having functional visual loss. The foveal reflex becomes obtunded or appears grayish, pigment spots develop in the macular area, and macular depigmentation and chorioretinal atrophy eventually occur. Macular hemorrhages may also develop. Some patients also have white or yellow spots beyond the macula or pigmentary changes in the periphery; the term *fundus flavimaculatus* is commonly used for this condition. It is now recognized that Stargardt disease and fundus flavimaculatus represent different entities on the spectrum of the same disease. Central visual acuity is reduced, often to 20/200, but total loss of vision does not occur. ERG findings vary. The condition is not associated with central nervous system abnormalities and is to be differentiated from the macular changes of many progressive metabolic neurodegenerative diseases. The most common (95%) genetic mutation responsible for Stargardt macular dystrophy involves the *ABCA4* gene.

Best Vitelliform Degeneration

This macular dystrophy is characterized by a distinctive yellow or orange discoid subretinal lesion in the macula, resembling the intact yolk of a fried egg. Diagnosis is usually made at 3-15 yr of age, with a mean age of presentation of 6 yr. Vision is usually normal at this stage. The condition may be progressive; the yolk-like lesion may eventually degenerate (“scramble”) and result in pigmentation, chorioretinal atrophy, and vision impairment. The condition is usually bilateral. There is no association with systemic abnormalities. Inheritance is usually autosomal dominant. The vitelliform macular dystrophy gene *(VMD2)* has been identified and DNA testing is available. In vitelliform macular degeneration, the ERG response is normal. Electro-oculographic findings are abnormal in affected patients and carriers, and this test is useful in diagnosis and genetic counseling.

Cherry-Red Spot

Because of the special histologic features of the macula, certain pathologic processes affecting the retina produce an ophthalmoscopically visible sign referred to as a cherry-red spot, a bright to dull red spot at the center of the macula surrounded and accentuated by a grayish-white or yellowish halo (Fig. 648.5). The halo is a result of a loss of transparency of the retinal ganglion cell layer secondary to edema, lipid accumulation, or both. Because ganglion cells are not present in the fovea, the retina surrounding the fovea is opacified but the fovea transmits the normal underlying choroidal color (red), accounting for the presence of the cherry-red spot. A cherry-red spot typically occurs in certain sphingolipidoses, principally in Tay-Sachs disease (GM_2 type 1), in the Sandhoff variant (GM_2 type 2), and in generalized gangliosidosis (GM_1 type 1). Similar but less distinctive macular changes occur in some cases of metachromatic leukodystrophy (sulfatide lipidosis), in some forms of neuronopathic Niemann-Pick disease, in galactosialidosis, and in certain mucolipidoses. The cherry-red spot that characteristically occurs as a result of retinal ischemia secondary to vasospasm, ocular contusion, or occlusion of the central retinal artery must be differentiated from the cherry-red spot of neurodegenerative disease (see Chapters 104.4 and 617).

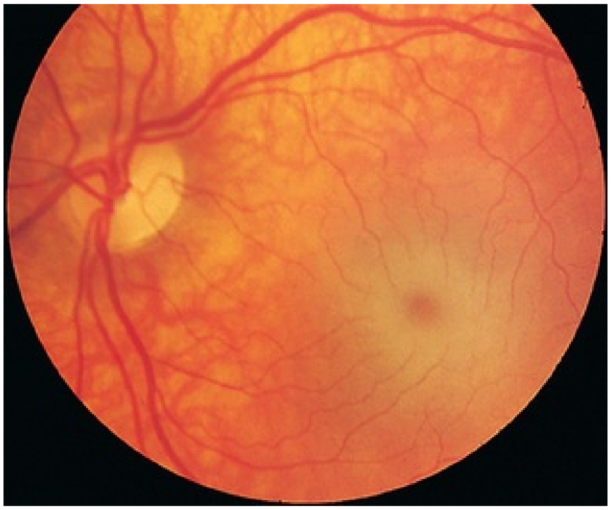

FIG. 648.5 Cherry-red spot seen in a case of Tay-Sachs disease. Because the parafoveal area has many retinal ganglion cells and the fovea has none, the fovea retains its orange-red color but is surrounded by a retina that is whitish. This produces the cherry-red spot in the macula. (From Cheng KP, Biglan AW: Ophthalmology. In Zitelli BJ, McIntire S, Nowalk AJ, editors: Zitelli and Davis' atlas of pediatric physical diagnosis, ed 6, Philadelphia, 2012, Saunders. Fig. 19.102.)

Phakomas

See also Chapter 614 .

These are the herald lesions of the hamartomatous disorders. In Bourneville disease (tuberous sclerosis), the distinctive ocular lesion is a refractile, yellowish, multinodular cystic lesion arising from the disc or retina; the appearance of this typical lesion is often compared with that of an unripe mulberry (Fig. 648.6). Equally characteristic and more common in tuberous sclerosis are flatter, yellow to whitish retinal lesions that vary in size from minute dots to large lesions approaching the size of the disc. These lesions are benign astrocytic proliferations. Rarely, similar retinal phakomas occur in von Recklinghausen disease (neurofibromatosis). In von Hippel-Lindau disease (angiomatosis of the retina and cerebellum), the distinctive fundus lesion is a hemangioblastoma; this vascular lesion usually appears as a reddish globular mass with large paired arteries and veins passing to and from the lesion. In Sturge-Weber syndrome (encephalofacial angiomatosis), the fundus abnormality is a choroidal hemangioma; the hemangioma may impart a dark color to the affected area of the fundus, but the lesion is best seen with fluorescein angiography.

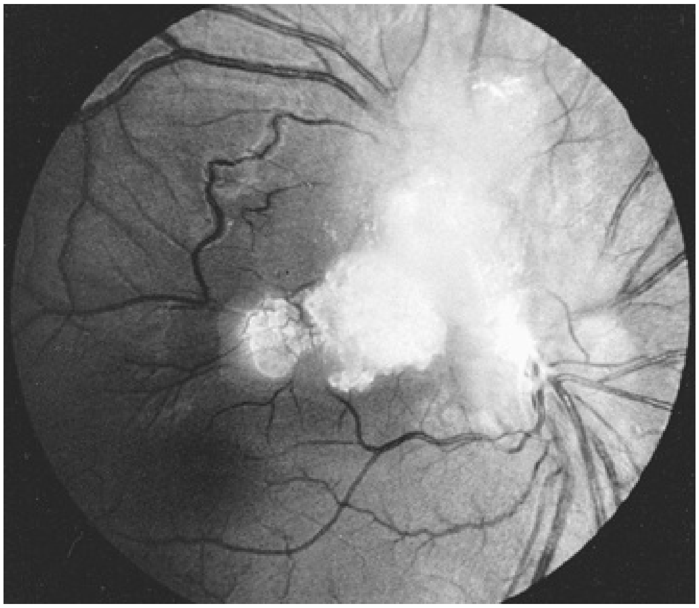

FIG. 648.6 Retinal phakoma of tuberous sclerosis.

Retinoschisis

Congenital hereditary retinoschisis, also referred to as juvenile X-linked retinoschisis, is a bilateral vitreoretinal dystrophy that has a bimodal age of presentation. The first group presents with strabismus and nystagmus at a mean age of 1.5-2 yr and is the most severely affected. The second group presents at 6-

7 yr with poor vision. Retinoschisis is characterized by splitting of the retina into inner and outer layers. The usual ophthalmoscopic finding in affected males is an elevation of the inner layer of the retina, most commonly in the inferotemporal quadrant of the fundus, often with round or oval holes visible in the inner layer. Schisis of the fovea is virtually pathognomonic and is found in almost 100% of patients. Ophthalmoscopically, this appears in early stages as small, fine striae in the internal limiting membrane. These striae radiate outward in a petaloid or spoke-wheel configuration. In some cases frank retinal detachment or vitreous hemorrhage occurs.

Vision impairment varies from mild to severe; visual acuity may worsen with age, but good vision is often retained. Carrier females are asymptomatic, but linkage studies may be useful to help detect carriers.

Retinal Detachment

A retinal detachment is a separation of the outer layers of the retina from the underlying RPE. During embryogenesis, the retina and RPE are initially separated. During ocular development, they join together and are held in apposition to each other by various physiologic mechanisms. Pathologic events leading to a retinal detachment return the retina–RPE to its former separated state. The detachment can occur as a congenital anomaly but more commonly arises secondary to other ocular abnormalities or trauma. Three types of detachment are described, and each may occur in children. Rhegmatogenous detachments result from a break in the retina that allows fluid to enter the subretinal space. In children, these are usually a result of trauma (such as child abuse) but may occur secondary to myopia or ROP or after surgery for congenital cataract. Tractional retinal detachments result when vitreoretinal membranes pull on the retina. They can occur in diabetes, sickle cell disease, and ROP. Exudative retinal detachments result when exudation exceeds absorption. This can be seen in Coats disease, retinoblastoma, and ocular inflammation.

The presenting sign of retinal detachment in an infant or child may be loss of vision, secondary strabismus or nystagmus, or leukocoria (white pupillary reflex). In addition to direct examination of the eye, special diagnostic studies such as ultrasonography and neuroimaging (CT, MRI) may be necessary to establish the cause of the detachment and the appropriate treatment. Prompt treatment is essential if vision is to be salvaged.

Coats Disease

This exudative retinopathy of unknown nonhereditary cause is characterized by telangiectasia of retinal vessels with leakage of plasma to form intraretinal and subretinal exudates and by retinal hemorrhages and detachment (Fig. 648.7). The condition is usually unilateral. It predominantly affects boys, usually appearing in the 1st decade. The condition is nonfamilial and, for the most part, occurs in otherwise healthy children. The most frequent presenting signs are blurring of vision, leukocoria, and strabismus. Rubeosis of the iris, glaucoma, and cataract may develop. **Treatment** with photocoagulation or cryotherapy may be helpful.

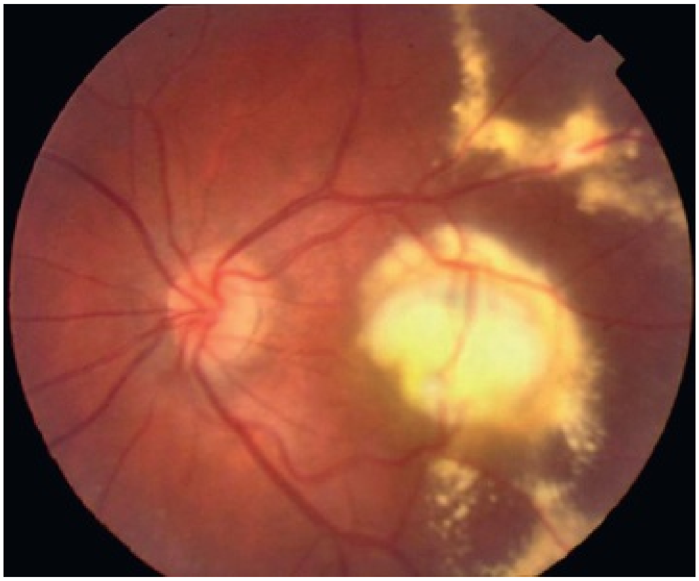

FIG. 648.7 Coats disease with massive retinal exudation.

Familial Exudative Vitreoretinopathy

This progressive retinal vascular disorder is of unknown cause, but clinical and angiographic findings suggest an aberration of vascular development. Avascularity of the peripheral temporal retina is a significant finding in most cases, with abrupt cessation of the retinal capillary network in the region of the equator. The avascular zone often has a wedge- or V -shaped pattern in the temporal meridian. Glial proliferation or well-marked retinochoroidal atrophy may be found in the avascular zone. Excessive branching of retinal arteries and veins, dilation of the capillaries, arteriovenous shunt formation, neovascularization, and leakage from retinal vessels of the farthest vascularized retina occur. Vitreoretinal adhesions are usually present at the peripheral margin of the vascularized retina. Traction, retinal dragging and temporal displacement of the macula, falciform retinal folds, and retinal detachment are common. Intraretinal or subretinal exudation, retinal hemorrhage, and recurrent vitreous hemorrhages may develop. Patients may also develop cataracts and glaucoma. Vision impairment of varying severity occurs. The condition is usually bilateral. Familial exudative vitreoretinopathy (FEVR) is usually an autosomal dominant condition with incomplete penetrance. Asymptomatic family members often display a zone of avascular peripheral retina.

The findings in FEVR may resemble those of ROP in the cicatricial stages, but unlike ROP, the neovascularization of FEVR seems to develop years after birth, and most patients with FEVR have no history of prematurity, oxygen therapy, prenatal or postnatal injury or infection, or developmental abnormalities. FEVR is also to be differentiated from Coats disease, angiomatosis of the retina, peripheral uveitis, and other disorders of the posterior segment.

Hypertensive Retinopathy

In the early stages of hypertension, no retinal changes may be observable. Generalized constriction and irregular narrowing of the arterioles are usually the first signs in the fundus. Other alterations include retinal edema, flame-shaped hemorrhages, cotton-wool spots (retinal nerve fiber layer infarcts), and papilledema (Fig. 648.8). These changes are reversible if the hypertension can be controlled in the early stages, but in long-standing hypertension, irreversible changes may occur. Thickening of the vessel wall may produce a silver- or copper-wire appearance. Hypertensive retinal changes in a child should alert the physician to renal disease, pheochromocytoma, collagen disease, and cardiovascular disorders, particularly coarctation of the aorta.

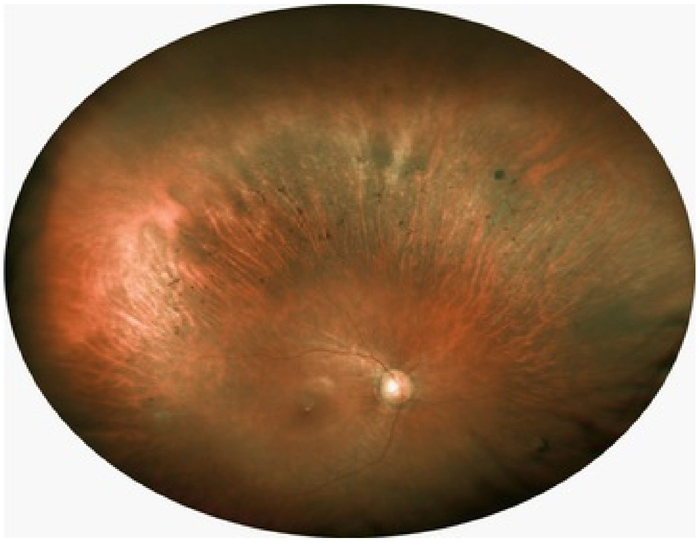

FIG. 648.8 Hypertension retinopathy with narrowed arterioles whose sclerosed walls create the appearance of "nicking" when the arterioles cross venules. (From Yanoff M, Duker JS, editors: Ophthalmology. Philadelphia, 2009, Mosby Elsevier.)

Diabetic Retinopathy

The retinal changes of diabetes mellitus are classified as nonproliferative or proliferative. Nonproliferative diabetic retinopathy is characterized by retinal microaneurysms, venous dilation, retinal hemorrhages, and exudates. The microaneurysms appear as tiny red dots. The hemorrhages may be of both the dot and blot type, representing deep intraretinal bleeding, and the splinter or flame-shaped type, involving the superficial nerve fiber layer. The exudates tend to be deep and to appear waxy. There may also be superficial nerve fiber infarcts called cytoid bodies or cotton-wool spots, as well as retinal edema. These signs may wax and wane. They are seen primarily in the posterior pole, around the disc and macula, or well within the range of direct ophthalmoscopy. Involvement of the macula may lead to decreased vision.

Proliferative retinopathy, the more serious form, is characterized by neovascularization and proliferation of fibrovascular tissue on the retina, extending into the vitreous. Neovascularization may occur on the optic disc, elsewhere on the retina, or on the iris and in the anterior chamber angle (or rubeosis irides) (Fig. 648.9). Traction on these new vessels leads to hemorrhage and, eventually, scarring. The vision-threatening complications of proliferative diabetic retinopathy are retinal and vitreous hemorrhages, cicatrization, traction, and retinal detachment. Neovascularization of the iris may lead to secondary glaucoma if not treated promptly.

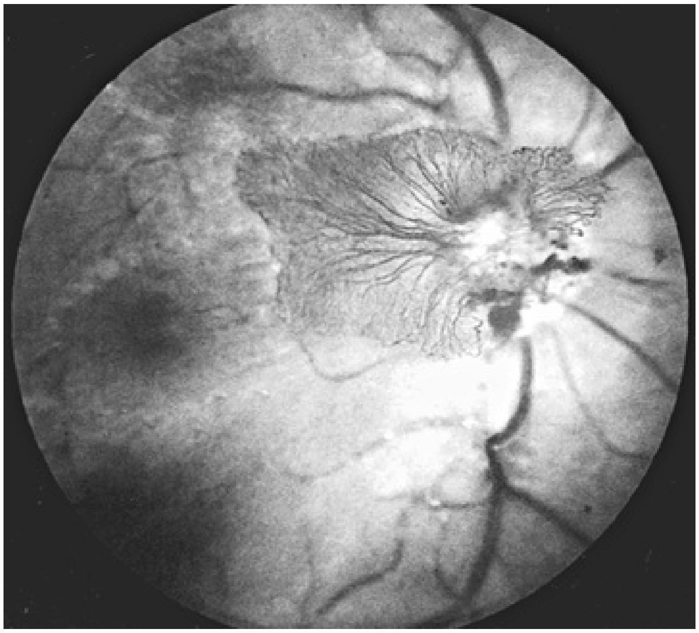

FIG. 648.9 Proliferative diabetic retinopathy with neovascularization of the disc.

Diabetic retinopathy involves the alteration and nonperfusion of retinal capillaries, retinal ischemia, and neovascularization, but its pathogenesis is not yet completely understood, either in terms of location of the primary pathogenetic mechanism (retinal vessels vs. surrounding neuronal or glial tissue) or the specific biochemical factors involved. The better the degree of long-term metabolic control, the lower the risk of diabetic retinopathy.

Clinically, the prevalence and course of retinopathy relate to a patient's age and to disease duration. Detectable microvascular changes are rare in prepubertal children, with the prevalence of retinopathy increasing significantly after puberty, especially after the age of 15 yr. The incidence of retinopathy is low during the 1st 5 yr of disease and increases progressively thereafter, with the incidence of proliferative retinopathy becoming substantial after 10 yr and with increased risk of visual impairment after 15 yr or more.

Ophthalmic examination guidelines have been proposed by the American Academy of Pediatrics. An initial exam is recommended at age 9 yr if the diabetes is poorly controlled. If the diabetes is well controlled, an initial exam 3 yr after puberty with annual follow-up is recommended.

In addition to retinopathy, patients with juvenile-onset diabetes may develop optic neuropathy, characterized by swelling of the disc and blurring of vision. Patients with diabetes may also develop cataracts, even at an early age, sometimes with rapid progression.

Treatment

Macular edema is the leading cause of visual loss in diabetic persons. Photocoagulation may be used to decrease the risk of continued vision loss in patients with macular edema.

Proliferative retinopathy causes the most severe vision loss and can lead to total loss of vision and even loss of the eye. Patients who have proliferative disease and who display certain high-risk characteristics should undergo panretinal photocoagulation to preserve their central vision. Neovascularization of the iris is also treated with panretinal photocoagulation to stop the development of neovascular glaucoma.

Vitrectomy and other intraocular surgery may be necessary in patients with nonresolving vitreous hemorrhage or traction retinal detachment. The value of technologic advances, such as insulin infusion pumps and pancreatic transplants, in preventing ocular complications is under investigation (see Chapter 607).

Subacute Bacterial Endocarditis

At some time during the disease, retinopathy is present in approximately 40% of cases of subacute bacterial endocarditis. The lesions include hemorrhages, hemorrhages with white centers (Roth spots), papilledema, and, rarely, embolic occlusion of the central retinal artery (Fig. 648.10).

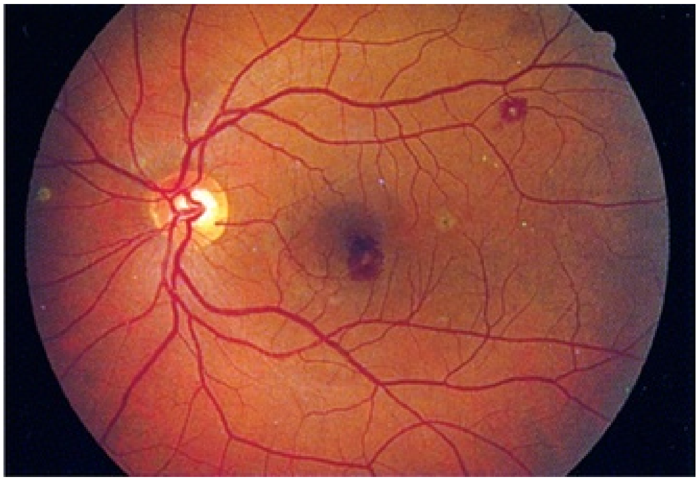

FIG. 648.10 Roth's spots. Multiple white-centered hemorrhages in a man with recurrent subacute bacterial endocarditis. White-centered hemorrhages are also seen with leukemia and diabetes. The small white scars are probably the residua of previous episodes. (From Goldman L, Schafer AI, editors: Goldman-Cecil Medicine, ed 25, Philadelphia, 2016, Elsevier/Saunders. Fig. 423.28, p. 2569.)

Blood Disorders

In primary and secondary anemias, retinopathy in the form of hemorrhages and cotton-wool patches may occur. Vision can be affected if hemorrhage occurs in the macular area. The hemorrhages may be light and feathery or dense and preretinal. In polycythemia vera, the retinal veins are dark, dilated, and tortuous. Retinal hemorrhages, retinal edema, and papilledema may be observed. In leukemia, the veins are characteristically dilated, with sausage-shaped constrictions; hemorrhages, particularly white-centered hemorrhages and exudates, are common during the acute stage. In the sickling disorders, fundus changes include vascular tortuosity, arterial and venous occlusions, “salmon patches,” refractile deposits, pigmented lesions, arteriolar-venous anastomoses, and neovascularization (with “sea-fan” formations), sometimes leading to vitreous hemorrhage and retinal detachment. Individuals with sickle cell hemoglobin C and sickle cell hemoglobin β-thalassemia, hemoglobinopathies are at a higher risk of the development of retinopathy than are those with homozygous hemoglobin S disease. It is thought that the more anemic state of those patients with homozygous hemoglobin S disease offers protection from vascular occlusions in the retina.

Trauma-Related Retinopathy

Retinal changes may occur in patients who suffer trauma to other parts of the body. The occurrence of retinal hemorrhages in infants who have been physically abused is well documented (Fig. 648.11 ; see Chapter 16). Retinal, subretinal, subhyaloid, and vitreous hemorrhages have been described in infants and young children with inflicted neurotrauma. Often there are no signs of direct trauma to the eye, periocular region, or head. Such cases may result from violent shaking of an infant, and permanent retinal damage may result.

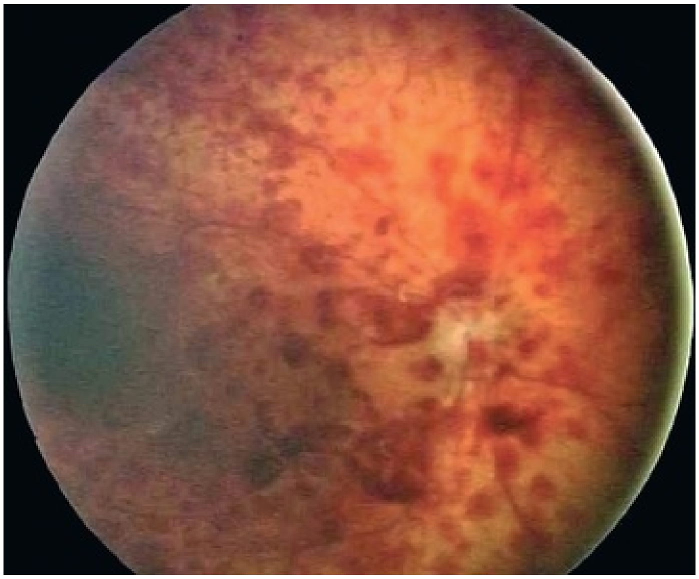

FIG. 648.11 Shaken baby syndrome (inflicted neurotrauma). Retinal hemorrhages in multiple layers too numerous to count into the far periphery.

In patients with severe head or chest compressive trauma, a traumatic retinal angiopathy known as **Purtscher retinopathy** may occur. This is characterized by retinal hemorrhage, cotton-wool spots, possible disc swelling, and decreased vision. The pathogenesis is unclear, but there is evidence of arteriolar obstruction in this condition. A Purtscher-like fundus picture may also occur in several nontraumatic settings, such as acute pancreatitis, lupus erythematosus, and childbirth. **Laser pointers** may produce vision loss with varying findings depending on the retinal area exposed to the nonionizing radiation.

Myelinated Nerve Fibers

Myelination of the optic nerve fibers normally terminates at the level of the disc, but in some individuals, ectopic myelination extends to nerve fibers of the retina. The condition is most commonly seen adjacent to the disc, although more peripheral areas of the retina may be involved. The characteristic ophthalmoscopic picture is a focal white patch with a feathered edge or brushstroke appearance. Because the macula is generally unaffected, the visual prognosis is good. A relative or absolute visual field defect corresponding to areas of ectopic myelination is usually the only associated ocular abnormality. Extensive unilateral involvement, however, is associated with ipsilateral myopia, amblyopia, and strabismus. If unilateral high myopia and amblyopia are present, appropriate optical correction and occlusion therapy should be instituted. For unknown reasons, the disorder is more commonly encountered in patients with craniofacial dysostosis, oxycephaly, neurofibromatosis, and Down syndrome.

Coloboma of the Fundus

The term *coloboma* describes a defect such as a gap, notch, fissure, or hole. The typical fundus coloboma is a result of malclosure of the embryonic fissure, which leaves a gap in the retina, RPE, and choroid, thus baring the underlying sclera. The defect may be extensive, involving the optic nerve, ciliary body, and iris and even the lens, or it may be localized to 1 or more portions of the fissure. The usual appearance is of a well-circumscribed, wedge-shaped white area extending inferonasally below the disc, sometimes involving or engulfing the disc. In some cases, there is ectasia or cyst formation in the area of the defect. Less extensive colobomatous defects may appear as only single or multiple focal punched-out chorioretinal defects or anomalous pigmentation of the fundus in the line of the embryonic fissure. Colobomas may occur in 1 or both eyes. A visual field defect usually corresponds to the chorioretinal defect. Visual acuity may be impaired, particularly if the defect involves the disc or macula.

Fundus colobomas may occur in isolation as sporadic defects or as an inherited condition. Isolated colobomatous anomalies are commonly inherited in an autosomal dominant manner with highly variable penetrance and expressivity. Family members of affected patients should receive appropriate genetic counseling. Colobomas may also be associated with such abnormalities as microphthalmia, glioneuroma of the eye, cyclopia, or encephalocele. They occur in children with various chromosomal disorders, including trisomies 13 and 18, triploidy, cat's-eye syndrome, and 4p−. Ocular colobomas also occur in many multisystem disorders, including the CHARGE (*C,* coloboma; *H,* heart disease; *A,* atresia choanae; *R,* retarded growth and development and/or central nervous system anomalies; *G,* genetic anomalies and/or hypogonadism; *E,* ear anomalies and/or deafness) association; Joubert, Aicardi, Meckel, Warburg, and Rubinstein-Taybi syndromes; linear sebaceous nevus; Goldenhar and Lenz microphthalmia syndromes; and Goltz focal dermal hypoplasia.

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CHAPTER 649

Abnormalities of the Optic Nerve

Scott E. Olitsky, Justin D. Marsh

Optic Nerve Aplasia

This rare congenital anomaly is typically unilateral. The optic nerve, retinal ganglion cells, and retinal blood vessels are absent. A vestigial dural sheath usually connects with the sclera in a normal position, but no neural tissue is present within this sheath. Optic nerve aplasia typically occurs sporadically in an otherwise healthy person.

Optic Nerve Hypoplasia

Hypoplasia of the optic nerve is a nonprogressive condition characterized by a subnormal number of optic nerve axons with normal mesodermal elements and glial supporting tissue. In typical cases, the nerve head is small and pale, with a pale or pigmented peripapillary halo or double ring sign (Fig. 649.1).

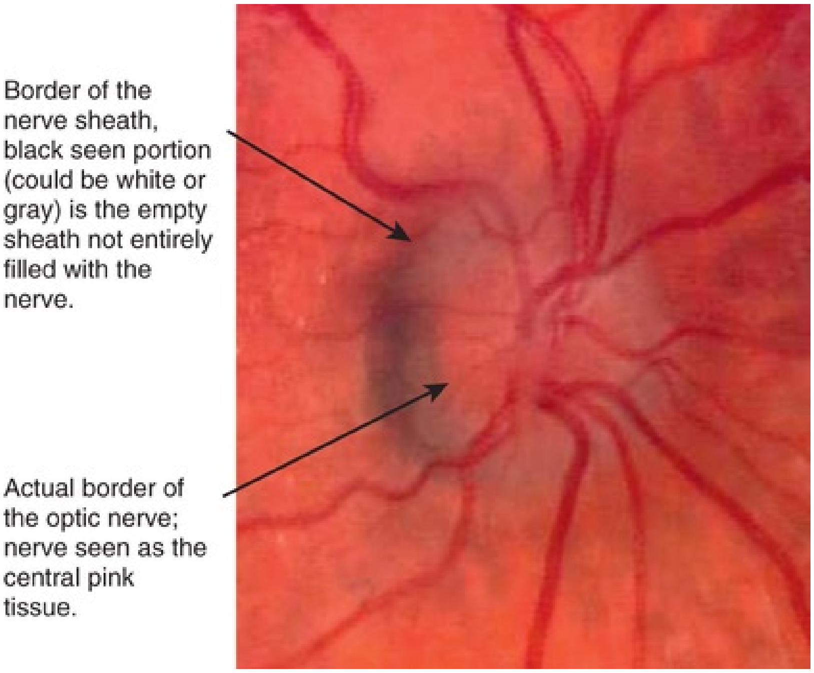
Border of the nerve sheath, black seen portion (could be white or gray) is the empty sheath not entirely filled with the nerve.
Actual border of the optic nerve; nerve seen as the central pink tissue.

FIG. 649.1 Optic nerve hypoplasia: the "double ring sign." The first ring shows the border of the nerve sheath, and the second ring is formed by the actual border of the optic nerve tissue edge. (From Martin RJ, Fanaroff AA, Walsh MC, editors: *Fanaroff & Martin's neonatal-perinatal medicine* , ed 10, Philadelphia, 2015, Elsevier. Fig. 103.24, p. 1753.)

This anomaly is associated with defects of vision and of visual fields of varying severity, ranging from blindness to normal or near-normal vision. It may be associated with systemic anomalies that most commonly involve the central nervous system (CNS). Protean CNS defects such as hydranencephaly or anencephaly or more focal lesions compatible with continued development may accompany optic nerve hypoplasia, but unilateral or bilateral optic nerve hypoplasia may be found without any concomitant defects.

Optic nerve hypoplasia is a principal feature of **septo-optic dysplasia of de Morsier,** a developmental disorder characterized by the association of anomalies of the midline structures of the brain with hypoplasia of the optic nerves, optic chiasm, and optic tracts; typically noted are agenesis of the septum pellucidum, partial or complete agenesis of the corpus callosum, and malformation of the fornix, with a large chiasmatic cistern. Patients may have hypothalamic abnormalities and endocrine defects ranging from panhypopituitarism to isolated deficiency of growth hormone, hypothyroidism, or diabetes insipidus. Neonatal hypoglycemia and seizures are important presenting signs in affected infants.

MRI is preferred for evaluating CNS abnormalities in patients with optic nerve hypoplasia. During MRI, special attention should be directed to the pituitary infundibulum, where ectopia of the posterior pituitary may be found. Posterior pituitary ectopia appears on MRI as an absence of the pituitary infundibulum with an abnormal bright spot at the upper infundibulum area. This abnormality is present in approximately 15% of patients and suggests a posterior pituitary hormone deficiency, requiring further endocrinologic workup. Endocrine function should be watched closely in patients with optic nerve hypoplasia. The cause of optic nerve hypoplasia remains unclear.

Children with **periventricular leukomalacia** display an unusual form of optic nerve hypoplasia. The optic nerve demonstrates a large cup within a normal-size optic disc. This form of optic nerve hypoplasia occurs secondary to transsynaptic degeneration of optic axons caused by the primary bilateral lesion in the optic radiation (periventricular leukomalacia).

Optic Nerve Coloboma

Optic nerve colobomas can be unilateral or bilateral. The visual acuity can range from normal to complete blindness. The coloboma develops secondary to incomplete closure of the embryonic fissure. The defect may produce a partial or total excavation of the optic disc (Fig. 649.2). Chorioretinal and iris colobomas may also occur. Optic nerve colobomas may be seen in a multitude of ocular and systemic abnormalities, including the CHARGE (*C,* coloboma; *H,* heart disease; *A,* atresia choanae; *R,* retarded growth and development and/or CNS anomalies; *G,* genetic anomalies and/or hypogonadism; *E,* ear anomalies and/or deafness) association.

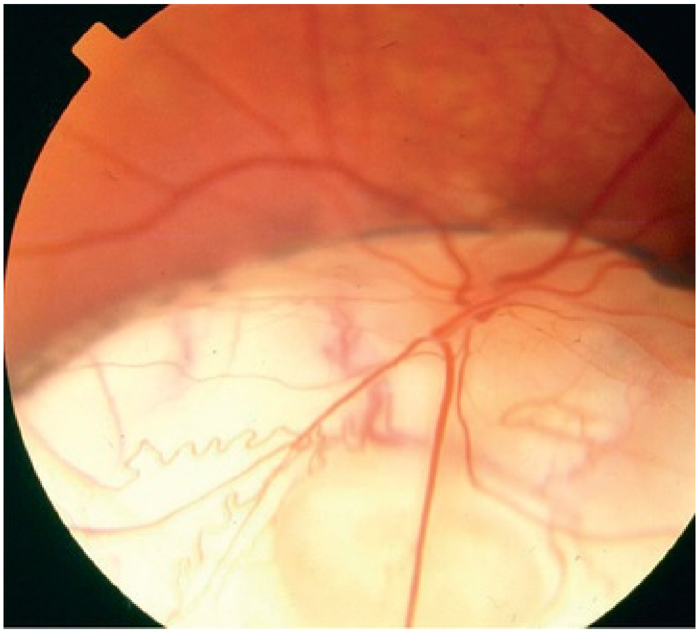

FIG. 649.2 Optic nerve coloboma.

Morning Glory Disc Anomaly

This term describes a congenital malformation of the optic nerve characterized by an enlarged, excavated, funnel-shaped disc with an elevated rim resembling a morning glory flower. White glial tissue is present in the central part of the disc (Fig. 649.3). The retinal vessels are abnormal and appear at the peripheral disc, coursing over the elevated pink rim in a radial fashion. Pigmentary mottling of the peripapillary region is usually seen. Most cases are unilateral. Females are affected twice as often as males. Visual acuity is usually severely reduced. Morning glory disc anomaly has been associated with basal encephalocele in patients with midfacial anomalies. Abnormalities of the carotid circulation can also be seen in patients with morning glory anomaly. Moyamoya disease is a well-described associated finding.

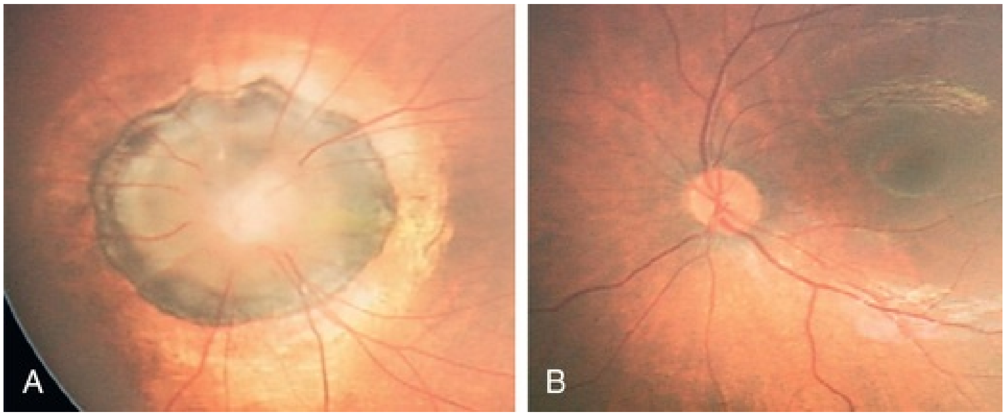

FIG. 649.3 **A,** Morning glory disc anomaly. The defect looks like a fully opened morning glory flower. **B,** Normal appearance of scaled fundus photography. (From Martin RJ, Fanaroff AA, Walsh MC, editors: *Fanaroff & Martin's neonatal-perinatal medicine* , ed 10, Philadelphia, 2015, Elsevier. Fig. 103.25, p. 1754.)

Tilted Disc

In this congenital anomaly, the vertical axis of the optic disc is directed obliquely, so that the upper temporal portion of the nerve head is more prominent and anterior to the lower nasal portion of the disc. The retinal vessels emerge from the upper temporal portion of the disc rather than from the nasal side. Often noted is a peripapillary crescent or conus. Associated visual field defects and myopic astigmatism may be found. Clinical recognition of the tilted disc syndrome is important to avoid confusion of its disc and visual field signs with those of papilledema and intracranial tumor.

Drusen of the Optic Nerve

These globular, acellular bodies are thought to arise from axoplasmic derivatives of disintegrating nerve fibers. Drusen may be buried within the optic nerve, producing elevation of the optic nerve head (which can be confused with papilledema), or they may be partially or completely exposed, appearing as refractile bodies at the surface of the disc. Visual field defects and spontaneous hemorrhages of the peripapillary nerve fiber layer may occur in association with drusen. Drusen may occur as an autosomal dominant condition. B-scan ultrasonography can help to positively identify drusen suspected on clinical ophthalmic exam (Fig. 649.4).

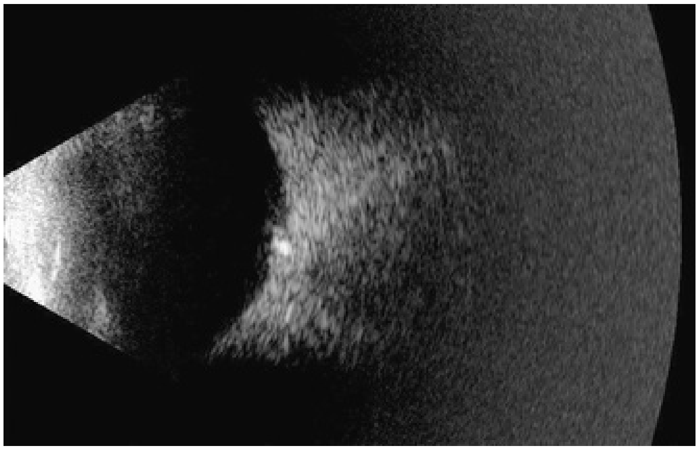

FIG. 649.4 Optic nerve drusen seen on B-scan ultrasonography.

Papilledema

The term *papilledema* is reserved to describe swelling of the nerve head secondary to increased intracranial pressure (ICP). Clinical manifestations of papilledema include edematous blurring of the disc margins, fullness or elevation of the nerve head, partial or complete obliteration of the disc cup, capillary congestion and hyperemia of the nerve head, generalized engorgement of the veins, loss of spontaneous venous pulsation, hemorrhages in the nerve fiber layer around the disc, and peripapillary exudates (see Fig. 608.2). In some cases edema extending into the macula may produce a fan- or star-shaped figure. In addition, concentric peripapillary retinal wrinkling (Paton lines) may be noted. Transient obscuration of vision may occur, lasting seconds and associated with postural changes. Vision, however, is usually normal in acute papilledema. Normally, when the ICP is relieved, the papilledema resolves and the disc returns to a normal or nearly normal appearance within 6-8 wk. Sustained chronic papilledema or long-standing unrelieved increased ICP may, however, lead to permanent nerve fiber damage, atrophic changes of the disc, macular scarring, and impairment of vision.

The *pathophysiology* of papilledema is probably as follows: elevation of intracranial subarachnoid cerebrospinal fluid (CSF) pressure, elevation of CSF pressure in the sheath of the optic nerve, elevation of tissue pressure in the optic nerve, stasis of axoplasmic flow and swelling of the nerve fibers in the optic nerve head, and secondary vascular changes and the characteristic ophthalmoscopic signs of venous stasis. Associated neuro-ophthalmic signs of increased ICP in infants and children include 6th cranial nerve palsy and attendant esotropia, lid retraction, paresis of upward gaze, tonic downward deviation of the eyes, and convergent nystagmus.

The common **etiologies** of papilledema in childhood are intracranial tumors and obstructive hydrocephalus, intracranial hemorrhage, the cerebral edema of trauma, meningoencephalitis, toxic encephalopathy, and certain metabolic diseases. Regardless of the cause, the optic disc signs of increased ICP in early childhood may occasionally be modified by the distensibility of the young skull. In the absence of conditions associated with early closure of sutures and early obliteration of the fontanel (craniosynostosis, Crouzon disease, and Apert syndrome), infants with increased ICP may not develop papilledema.

The **differential diagnosis** of papilledema includes structural changes of the disc (pseudopapilledema, pseudoneuritis, drusen, and myelinated nerve fibers), with which it may be confused, and the disc swelling of papillitis associated with optic neuritis in addition to the disc changes of hypertension and diabetes mellitus. Unless retinal hemorrhage or edema involves the macular area, the preservation of good central vision and the absence of an afferent pupillary defect (Marcus Gunn pupil) help to differentiate acute papilledema from the edema of the optic nerve head found in acute optic neuritis.

Papilledema is a neurologic emergency. It can be accompanied by other signs of increased ICP, including headaches, nausea, and vomiting. Neuroimaging should be performed; if no intracranial masses are detected; a lumbar puncture and determination of CSF pressure should follow.

Optic Neuritis

This is any inflammation or demyelinization of the optic nerve with attendant impairment of function. The process is usually acute, with rapidly progressive loss of vision. It may be unilateral or bilateral. Pain on movement or palpation of the globe may precede or accompany the onset of visual symptoms. There is decreased visual activity, decreased color vision and contrast sensitivity, a relative afferent pupillary defect, and a normal macula and peripheral retina.

When the retrobulbar portion of the nerve is affected without ophthalmoscopically visible signs of inflammation at the disc, the term *retrobulbar optic neuritis* is applied. When there is ophthalmoscopically visible evidence of inflammation of the nerve head, the term *papillitis* or *intraocular optic neuritis* is used. When there is involvement of both the retina and the papilla, the term *optic neuroretinitis* is used.

In childhood, optic neuritis may occur as an isolated condition or as a manifestation of a neurologic or systemic disease. Optic neuritis may be secondary to inflammatory diseases (systemic lupus erythematosus, sarcoidosis, Behçet disease, autoimmune optic neuritis); infections (tuberculosis, syphilis, Lyme disease, meningitis, viral encephalitis, HIV, or postinfectious disease); and toxic or nutritional disorders (methanol, ethambutol, vitamin B_{12} deficiency). It may signify one of the many demyelinating diseases of childhood (see Chapter 618). Although a significant percentage of adults who experience an episode of optic neuritis eventually develop other symptoms associated with multiple sclerosis (MS), young children with optic neuritis are seemingly at less risk (risk of MS is 19% within 20 yr). High-risk features suggestive of MS include visual acuity better than no light perception, periocular pain, acutely normal-appearing optic nerve, no retinal abnormalities, and abnormal MRI suggesting a demyelinating disease. Bilateral optic neuritis in children may be associated with acute disseminated encephalomyelitis or **neuromyelitis optica (NMO or Devic disease).** NMO is characterized by rapid and severe bilateral visual loss accompanied by transverse myelitis and paraplegia. Involvement of the brain stem and occasionally the cortex may be seen on MRI. NMO-specific immunoglobulin G (directed to the aquaporin 4 water channel) is the diagnostic test of choice for Devic syndrome. Optic neuritis may also be secondary to an exogenous toxin or drug, as with lead poisoning or as a complication of long-term high-dose treatment with chloramphenicol or vincristine. Extensive pediatric neurologic and ophthalmic investigation, including MRI and lumbar puncture, is usually required. Idiopathic NMO is associated with anti–aquaporin 4 antibodies, otherwise known as NMO antibodies.

In most cases of acute optic neuritis, some improvement in vision begins within 1-4 wk after onset, and vision may improve to normal or near normal within weeks or months. The course varies with cause. Although central vision may recover fully, it is common to find permanent defects in other areas of visual function (contrast sensitivity, color, brightness sense, and motion perception). Recurrences may occur especially, but not universally, in patients who go on to develop MS.

A **treatment** trial has demonstrated that high-dose intravenous methylprednisolone may help to speed the visual recovery in young adults, and it may prevent the development of MS in those at risk. It is unknown to what degree the results of the aforementioned trial may be extrapolated to optic neuritis in childhood.

Leber Optic Neuropathy

This entity is characterized by a sudden loss of central vision occurring in the 2nd and 3rd decades of life and primarily affects young males. A characteristic peripapillary telangiectatic microangiopathy occurs not only in the presymptomatic phase of involved eyes but also in a high number of asymptomatic offspring in the female line. Disc hyperemia and edema mark the acute phase of visual loss. One eye is usually affected before the other. Visual field loss and impaired color vision are also present. In time, progressive optic atrophy and vision loss usually ensue. The tortuous angiopathy becomes less obvious. Although visual function after the initial loss generally remains stable, a significant and sometimes complete recovery may occur in as many as 30% of affected individuals. This recovery may take place years or decades after the initial episode of acute vision loss. The peripapillary angiopathy, the lack of short-term remission, and the degree of symmetry serve to distinguish most cases of Leber disease from the optic neuritis of MS.

Leber optic neuropathy is maternally inherited and is caused by defective cytoplasmic mitochondrial DNA. Multiple point mutations in the mitochondrial DNA that lead to the development of the disorder have been found. Because of the mitochondrial nature of the disorder, skeletal and cardiac muscle disorders, including electrocardiographic abnormalities, may also be encountered in affected individuals.

Optic Atrophy

This term denotes degeneration of optic nerve axons, with attendant loss of function. The ophthalmoscopic signs of optic atrophy are pallor of the disc and loss of substance of the nerve head, sometimes with enlargement of the disc cup. The associated vision defect varies with the nature and site of the primary disease or lesion.

Optic atrophy is the common expression of a wide variety of congenital or acquired pathologic processes (Table 649.1). The cause may be traumatic, inflammatory, degenerative, neoplastic, or vascular; intracranial tumors and hydrocephalus are principal causes of optic atrophy in children. In some cases progressive optic atrophy is hereditary. **Dominantly inherited infantile optic atrophy** is a relatively mild heredodegenerative type that tends to progress through childhood and adolescence. **Autosomal recessively inherited congenital optic atrophy** is a rare condition that is evident at birth or develops at a very early age; the visual defect is usually profound. **Behr optic atrophy** is a hereditary type associated with hypertonia of the extremities, increased deep tendon reflexes, mild cerebellar ataxia, some degree of mental deficiency, and possibly external ophthalmoplegia. This disorder principally afflicts boys 3-11 yr of age. Some forms of heredodegenerative optic atrophy are associated with sensorineural hearing loss, as may occur in some children with juvenile-onset (insulin-dependent) diabetes mellitus. In the absence of an obvious cause, optic atrophy in an infant or child warrants extensive etiologic investigation.

Table 649.1

Causes of Childhood Optic Atrophy

- Compressive intracranial lesions
- Compressive bony disorders
- Craniosynostosis
- Fibrous dysplasia
- Hydrocephalus
- Postpapilledema optic atrophy
- Infectious
- Hereditary
- Leber hereditary optic neuropathy
- Dominant optic atrophy (Kjer)
- Recessive optic atrophy
- Behr optic atrophy
- DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness) (Wolfram) optic atrophy
- Toxic or nutritional optic neuropathy

- Hypoxia
- Trauma
- Postoptic neuritis
- Radiation optic neuropathy
- Paraneoplastic syndromes
- Neurodegenerative disorders with optic atrophy
- Krabbe disease
- Canavan disease
- Leigh disease
- Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like (MELAS) episodes
- Neonatal adrenoleukodystrophy
- Metachromic leukodystrophy
- Riley-Day syndrome
- Lactic acidosis
- Spinocerebellar degeneration
- Mucopolysaccharidosis
- Ocular disorders
- Glaucoma
- Retinal disease
- Vascular disease
- Uveitis
- Optic nerve hypoplasia

From Martin RJ, Fanaroff AA, Walsh MC, editors: *Fanaroff & Martin's neonatal-perinatal medicine* , ed 10, Philadelphia, 2015, Elsevier. Box 103.5.

Optic Nerve Glioma

Optic nerve glioma, more properly referred to as **juvenile pilocytic astrocytoma,** is the most frequent tumor of the optic nerve in childhood. This neuroglial tumor may develop in the intraorbital, intracanalicular, or intracranial portion of the nerve; the chiasm is often involved.

The tumor is a cytologically benign hamartoma that is generally stationary or only slowly progressive. The principal *clinical manifestations* when the tumor occurs in the intraorbital portion of the nerve are unilateral loss of vision, proptosis, and deviation of the eye; optic atrophy or congestion of the optic nerve head may occur. Chiasmal involvement may be attended by defects of vision and visual fields (often bitemporal hemianopia), increased ICP, papilledema or optic atrophy, hypothalamic dysfunction, pituitary dysfunction, and sometimes nystagmus or strabismus. Juvenile pilocytic astrocytomas occur with increased frequency in patients with neurofibromatosis (see Chapter 614.1).

Treatment of optic pathway gliomas is controversial. The best management is usually periodic observation with serial radiography (preferably MRI). Only symptomatic and radiographically progressing optic nerve gliomas require strong consideration for treatment. If a patient has unsightly proptosis with complete or nearly complete loss of vision of the affected eye, surgical removal may be appropriate when the tumor is confined to the intraorbital, intracanalicular, or prechiasmal portion of the nerve. When the chiasm is involved, resection is not usually indicated and radiation and chemotherapy may be necessary.

Traumatic Optic Neuropathies

Injury to the optic nerve may result from both direct and indirect trauma. Direct trauma to the optic nerve is a result of a penetrating injury to the orbit with transection or contusion of the nerve. Blunt trauma to the orbit may also lead to severe visual loss if the traumatic force is transmitted to the optic canal and causes disruption of the blood supply to the intracanalicular portion of the nerve. Treatment with high-dose corticosteroids has not proved to be effective; it has been shown that similar regimens involve an increased relative risk of death when they are given to patients who have experienced significant head injuries.

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CHAPTER 650

Childhood Glaucoma

Scott E. Olitsky, Justin D. Marsh

Glaucoma is a general term used to indicate damage to the optic nerve with visual field loss that is caused by or related to elevated pressure within the eye. It is classified according to the age of the affected individual at presentation and the association of other ocular or systemic conditions. Glaucoma that begins within the 1st 3 yr of life is called infantile (congenital); that which begins between the ages of 3 and 30 yr is called juvenile.

Primary glaucoma indicates that the cause is an isolated anomaly of the drainage apparatus of the eye (trabecular meshwork). More than 50% of infantile cases are primary glaucoma. In secondary glaucoma, other ocular or systemic abnormalities are associated, even if a similar developmental defect of the trabecular meshwork is also present. Primary infantile glaucoma occurs with an incidence of 0.03% (Table 650.1).

Table 650.1

Primary and Secondary Childhood Glaucomas

Primary Glaucomas

A. Congenital open-angle glaucoma
    1. Congenital
    2. Infantile
    3. Late recognized
B. Autosomal dominant juvenile glaucoma
C. Primary angle-closure glaucoma
D. Associated with systemic abnormalities
    1. Sturge-Weber syndrome

2. Neurofibromatosis type 1 (NF-1)
3. Stickler syndrome
4. Oculocerebrorenal (Lowe) syndrome
5. Rieger syndrome
6. Hepatocerebrorenal syndrome
7. Marfan syndrome
8. Rubinstein-Taybi syndrome
9. Infantile glaucoma associated with mental retardation and paralysis
10. Oculodentodigital dysplasia
11. Open-angle glaucoma associated with microcornea and absence of frontal sinuses
12. Mucopolysaccharidosis
13. Trisomy 13
14. Cutis marmorata telangiectasia congenita
15. Warburg syndrome
16. Kniest syndrome (skeletal dysplasia)
17. Michel syndrome
18. Nonprogressive hemiatrophy

E. Associated with ocular abnormalities

1. Congenital glaucoma with iris and pupillary abnormalities
2. Aniridia
    a. Congenital glaucoma
    b. Acquired glaucoma
3. Congenital ocular melanosis
4. Sclerocornea
5. Iridotrabecular dysgenesis
6. Peters syndrome
7. Iridotrabecular dysgenesis and ectropion uveae
8. Posterior polymorphous dystrophy
9. Idiopathic or familial elevated episcleral venous pressure
10. Anterior corneal staphyloma
11. Congenital microcornea with myopia
12. Congenital hereditary endothelial dystrophy
13. Congenital hereditary iris stromal hypoplasia

Secondary Glaucomas

A. Traumatic glaucoma
  1. Acute glaucoma
    a. Angle concussion
    b. Hyphema
    c. Ghost cell glaucoma
  2. Late-onset glaucoma with angle recession
  3. Arteriovenous fistula

B. Secondary to intraocular neoplasm
  1. Retinoblastoma
  2. Juvenile xanthogranuloma
  3. Leukemia
  4. Melanoma
  5. Melanocytoma
  6. Iris rhabdomyosarcoma
  7. Aggressive nevi of the iris

C. Secondary to uveitis
  1. Open-angle glaucoma
  2. Angle-blockage glaucoma
    a. Synechial angle closure
    b. Iris bombé with pupillary block

D. Lens-induced glaucoma
  1. Subluxation-dislocation and pupillary block
    a. Marfan syndrome
    b. Homocystinuria
  2. Spherophakia and pupillary block
  3. Phacolytic glaucoma

E. Secondary to surgery for congenital cataract
  1. Lens material blockage of the trabecular meshwork (acute or subacute)
  2. Pupillary block
  3. Chronic open-angle glaucoma associated with angle defects

F. Steroid-induced glaucoma

G. Secondary to rubeosis
  1. Retinoblastoma
  2. Coats disease
  3. Medulloepithelioma

    4. Familial exudative vitreoretinopathy

H. Secondary angle-closure glaucoma
    1. Retinopathy of prematurity
    2. Microphthalmos
    3. Nanophthalmos
    4. Retinoblastoma
    5. Persistent hyperplastic primary vitreous
    6. Congenital pupillary iris-lens membrane

I. Glaucoma associated with increased venous pressure
    1. Carotid or dural-venous fistula
    2. Orbital disease

J. Secondary to maternal rubella

K. Secondary to intraocular infection
    1. Acute recurrent toxoplasmosis
    2. Acute herpetic iritis

From Nelson LB: *Harley's pediatric ophthalmology,* ed 4, Philadelphia, 1998, WB Saunders, p. 294.

Clinical Manifestations

The symptoms of infantile glaucoma include the classic triad of epiphora (tearing), photophobia (sensitivity to light), and blepharospasm (eyelid squeezing; Fig. 650.1). Each can be attributed to corneal irritation. Only approximately 30% of affected infants demonstrate the classic symptom complex. Signs of glaucoma include corneal edema, corneal and ocular enlargement, and conjunctival injection (Fig. 650.2).

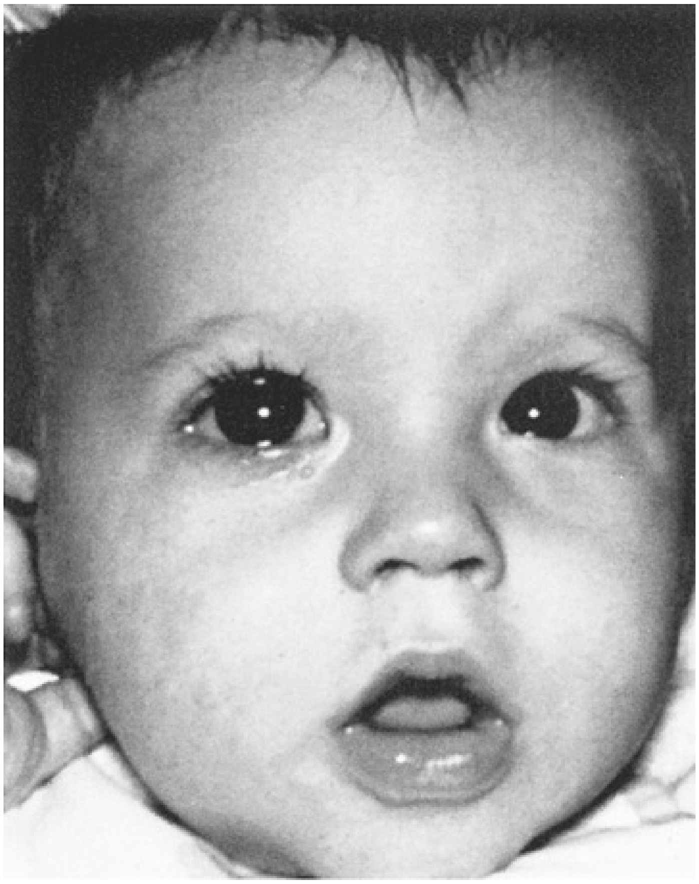

FIG. 650.1 Tearing of the right eye caused by glaucoma. Note the increased corneal diameter of the right eye. (From Nelson LB: *Harley's pediatric ophthalmology* , ed 4, Philadelphia, 1998, WB Saunders, p. 285.)

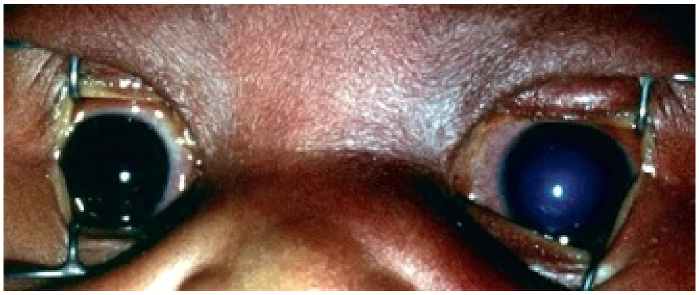

FIG. 650.2 Infantile glaucoma. The left cornea is enlarged and edematous.

The sclera and cornea are more elastic in early childhood than later in life. An increase in intraocular pressure (IOP), therefore, leads to an expansion of the globe, including the cornea, and the development of buphthalmos (“ox eye”). If the cornea continues to enlarge, breaks occur in the endothelial basement membrane (the Descemet membrane) and may lead to permanent corneal scarring. These breaks in the Descemet membrane (Haab striae) are visible as horizontal edematous lines that cross or curve around the central cornea. They rarely occur beyond 3 yr of age or in corneas <12 mm in diameter. The cornea also becomes edematous and cloudy, with increased IOP. The corneal edema leads to tearing and photophobia. If any of these other signs or symptoms are present, glaucoma should be considered in a child suspected of having a nasolacrimal duct obstruction.

Children with unilateral glaucoma generally present early because the difference in the corneal size between the eyes can be noticed. When the disease is bilateral, parents may not recognize the increased corneal size. Many parents view the large eyes as attractive and do not seek help until other symptoms develop.

Cupping of the optic nerve head is detected by ocular examination. The optic nerve of an infant is easily distended by excessive pressure. Deep central cupping readily occurs and may regress with normalization of pressure.

Some infants and children with early-onset glaucoma have more extensive maldevelopment of the anterior segment of the eye. The neurocristopathies comprise a spectrum of conditions relating to abnormal embryologic development of the anterior segment. They are usually bilateral and may include abnormalities of the iris, cornea, and lens. Other ocular anomalies that may be associated with glaucoma in infants and children are aniridia, cataract, spherophakia, and ectopia lentis. Glaucoma may also develop secondary to persistent hyperplastic primary vitreous or retinopathy of prematurity.

Trauma, intraocular hemorrhage, ocular inflammatory disease, and intraocular tumor are also important causes of glaucoma in the pediatric population. Systemic disorders associated with glaucoma in infants and children are Sturge-Weber syndrome (see Chapter 614.3), neurofibromatosis (see Chapter 614.1), Lowe syndrome, Marfan syndrome (see Chapter 722), congenital rubella (see Chapters 131 and 274), and a number of chromosomal syndromes (see Chapter 98).

Glaucoma occurs frequently in children with a history of congenital cataracts. Glaucoma may develop in up to 25% of children who have undergone cataract surgery early in life. The cause of aphakic glaucoma is not known but is thought to be the result of a coexistent anterior chamber deformity. Children treated for cataracts must be monitored closely for this complication, which may threaten vision.

Diagnosis and Treatment

The diagnosis of infantile glaucoma is made on recognition of the signs and symptoms. Once the diagnosis is established, treatment is started promptly. Unlike adult glaucoma, in which medication is often the first line of therapy, for infantile glaucoma the treatment is primarily surgical. Procedures used to treat glaucoma in children include surgery to establish a more normal anterior chamber angle (goniotomy and trabeculotomy), to create a site for aqueous fluid to exit the eye (trabeculectomy and Seton surgery), or to reduce aqueous fluid production (cyclocryotherapy and cyclophotocoagulation). Many children frequently require several operations to lower and maintain their IOP adequately, and long-term medical therapy may be necessary as well. Patients with multiple ocular abnormalities and those with aphakic glaucoma generally require more surgeries to achieve and maintain adequate IOP control. Although vision may be reduced secondary to glaucomatous optic nerve damage or corneal scarring, amblyopia is the most common cause of loss of vision in these children.

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CHAPTER 651

Orbital Abnormalities

Scott E. Olitsky, Justin D. Marsh

Hypertelorism and Hypotelorism

Hypertelorism is wide separation of the eyes or an increased interorbital distance, which may occur as a morphogenetic variant, a primary deformity, or a secondary phenomenon in association with developmental abnormalities, such as frontal meningocele or encephalocele or the persistence of a facial cleft. Often associated are strabismus, generally exotropia, and sometimes optic atrophy.

Hypotelorism refers to narrowness of the interorbital distance, which may occur as a morphogenetic variant alone or in association with other anomalies, such as epicanthus or holoprosencephaly, or secondary to a cranial dystrophy, such as scaphocephaly.

Exophthalmos and Enophthalmos

Protrusion of the eye is referred to as *exophthalmos* or *proptosis* and is a common indicator of orbital disease. It may be caused by shallowness of the orbits, as in many craniofacial malformations, or by increased tissue mass within the orbit, as with neoplastic, vascular, and inflammatory disorders. Ocular complications include exposure keratopathy, ocular motor disturbances, and optic atrophy with loss of vision.

Posterior displacement or sinking of the eye back into the orbit is referred to as *enophthalmos* . This may occur with orbital fracture or with atrophy of orbital tissue.

Orbital Inflammation

Inflammatory disease involving the orbit may be primary or secondary to systemic disease. **Idiopathic orbital inflammatory disease (formerly called orbital pseudotumor)** represents a wide spectrum of clinical entities. Symptoms at the time of presentation may include pain, eyelid swelling, proptosis, red eye, and fever. The inflammation may involve a single extraocular muscle (myositis) or the entire orbit. Orbital apex syndrome is a serious condition that may also involve the cavernous sinus and may compress or displace the optic nerve. Confusion with orbital cellulitis is common but can be differentiated by the lack of associated sinus disease, its appearance on CT scan, and lack of improvement with systemic antibiotics. Orbital inflammatory disease is often idiopathic but may be associated with systemic lupus erythematosus, Crohn disease, myasthenia gravis, sarcoidosis, thyroid associated orbitopathy, lymphoproliferative disorders, polyangiitis with granulomatosis, and lymphoma. **Treatment** includes the use of high-dose systemic corticosteroids. Often the symptoms improve dramatically shortly after treatment is initiated. Bilateral involvement, associated uveitis, disc edema, and recurrence of inflammation are not uncommon in the pediatric population. Immunotherapy or radiation treatment may be necessary for resistant or recurrent cases.

Thyroid-related ophthalmopathy (see also Chapter 579) is believed to be secondary to an immune mechanism, leading to inflammation and deposition of mucopolysaccharides and collagen in the extraocular muscles and orbital fat. Involvement of the extraocular muscles may lead to a restrictive strabismus. Lid retraction and exophthalmos may cause corneal exposure and infection or perforation. Involvement of the posterior orbit can compress the optic nerve. Treatment of thyroid-related ophthalmopathy may include the use of systemic corticosteroids, radiation of the orbit, eyelid surgery, strabismus surgery, or orbital decompression to eliminate symptoms and protect vision. The degree of orbital involvement is often independent of the status of the systemic disease.

Other systemic disorders that may cause inflammatory disease within the orbit include lymphoma (see Chapter 523), sarcoidosis (see Chapter 190), amyloidosis (see Chapter 189), polyarteritis nodosa (see Chapter 192.3), systemic lupus erythematosus (see Chapter 183), dermatomyositis (see Chapter 184), granulomatosis with polyangiitis (see Chapter 192), and juvenile xanthogranuloma (see Chapter 534).

Tumors of the Orbit

Various tumors occur in and about the orbit in childhood. Among benign tumors, the most common are vascular lesions (principally hemangiomas; Fig. 651.1) and dermoids. Among malignant neoplasms, rhabdomyosarcoma, lymphosarcoma, and metastatic neuroblastoma are the most frequent. Optic nerve gliomas (see Chapter 649) are most commonly seen in patients with neurofibromatosis and may present with poor vision or proptosis. Retinoblastoma (see Chapter 529) may extend into the orbit if it is discovered late or goes untreated. Teratomas are rare tumors that typically grow rapidly after birth and exhibit explosive proptosis.

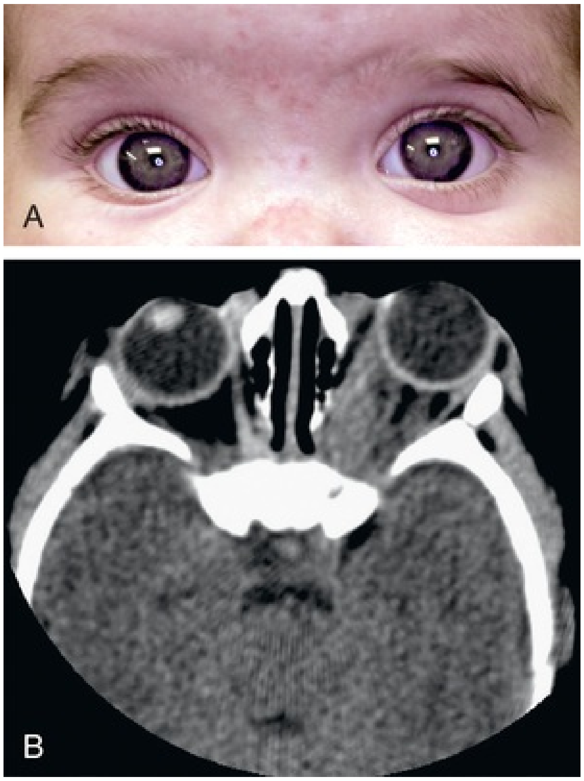

FIG. 651.1 **Orbital hemangioma. A, Note the proptosis. B, CT scan. (Courtesy of Amy Nopper, MD, and Brandon Newell, MD.)**

The effects of orbital tumors vary with their locations and growth patterns. The principal signs are proptosis, resistance to retroplacement of the eye, and impairment of eye movement. A palpable mass may be found. Other significant signs are ptosis, optic nerve head congestion, optic atrophy, and loss of vision. Bruit and visible pulsation of the globe are important clues to vascular lesions.

Evaluation of orbital tumors includes ultrasonography, MRI, and CT.

Pseudotumor of the orbit also must be considered in children with signs of a mass lesion. In selected cases, an incisional or excisional biopsy of the lesion may be warranted.

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CHAPTER 652

Orbital Infections

Scott E. Olitsky, Justin D. Marsh, Mary Anne Jackson

Orbital infections are common in children. It is important to be able to distinguish the different forms of infection that occur in the orbital region, to allow rapid diagnosis and treatment to prevent loss of vision or spread of the infection to the nearby intracranial structures (Table 652.1).

Table 652.1

Manifestations of Orbital Cellulitis Associated With Ethmoid Sinusitis

MANIFESTATIONS	CLINICAL AND CT IMAGING DESCRIPTION
Inflammatory edema	Eyelid edema and erythema; eye may be swollen shut
	Fever
	Painless extraocular muscle movement; full range of motion
	Visual acuity normal
	Edema of orbit without abscess formation
Orbital cellulitis	Inflammation of orbital contents without discrete abscess formation
	Fever, malaise
Subperiosteal abscess	Purulent exudate beneath medial orbital periosteum of lamina papyracea
	Pain on extraocular muscle movement
	Fever, malaise
	Displacement of globe (down and out)
Orbital abscess/orbital apex syndrome	Purulent collection within orbit
	Proptosis, chemosis
	Ophthalmoplegia; pain on extraocular muscle movement
	Decreased vision
	Fever, malaise
Septic cavernous sinus thrombophlebitis	Bilateral (contralateral) eye findings; ptosis, proptosis, swelling, ophthalmoplegia
	Severe headaches
	Meningismus, fever, severe malaise
	Decreased vision

Dacryoadenitis

Dacryoadenitis is inflammation of the lacrimal gland; it most commonly occurs in the pediatric population and in some young adults and is related to a variety of infectious pathogens. Pain, redness, swelling, increase in tearing, and discharge over the lacrimal gland are noted and usually visible at the lateral one third of the upper eyelid; concurrent preauricular lymphadenopathy may be noted (Fig. 652.1). It may occur with mumps (in which case it is usually acute and bilateral, subsiding in a few days or weeks), with influenza, infectious mononucleosis, and herpes zoster. *Staphylococcus aureus* may produce a suppurative dacryoadenitis, and other bacterial causes include streptococci and *Neisseria gonorrhoeae* . Chronic dacryoadenitis is associated with certain systemic diseases, particularly sarcoidosis, tuberculosis, and syphilis. Some systemic diseases may produce enlargement of the lacrimal and salivary glands (Mikulicz syndrome).

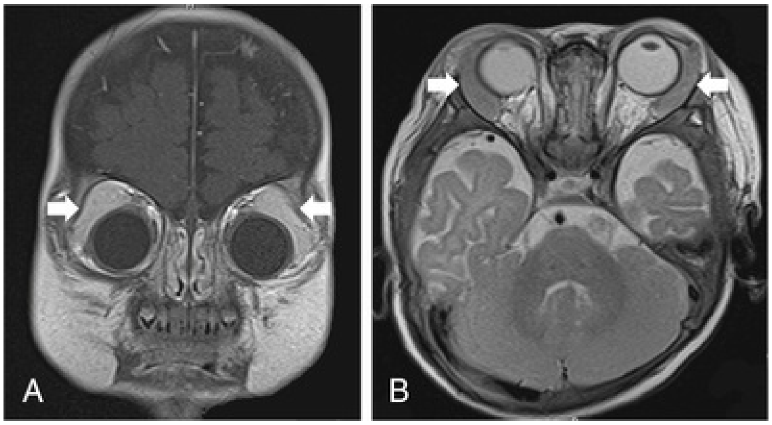

FIG. 652.1 **MRI of the bilateral lacrimal glands. A, Coronal T1-weighted image. B, Axial T2-weighted image. The bilateral lacrimal glands are markedly enlarged *(arrows)* . (From Hoshino A, Fujii T, Hibino S, Abe Y: Acute infantile dacryoadenitis. *J Pediatr* 164:425, 2014. Fig. 2).**

Dacryocystitis

Dacryocystitis is an infection of the lacrimal sac and generally requires obstruction of the nasolacrimal system to allow its development. Acute, subacute, and chronic forms are described. Most patients with dacryocystitis present with redness and swelling over the region of the lacrimal sac (Fig. 652.2

). It is treated with warm compresses and systemic antibiotics. This helps control the infection, but the obstruction usually requires definitive treatment to reduce the risk of recurrence.

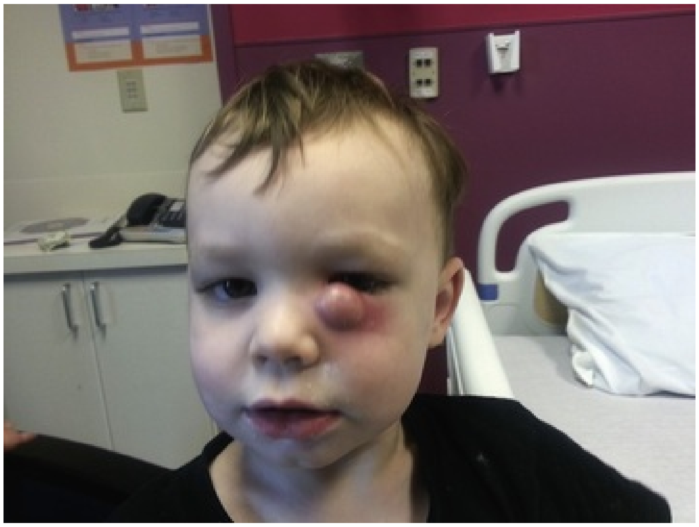

FIG. 652.2 Dacrycystitis in a child previously treated for nasolacrimal duct obstruction.

Dacryocystitis may occur in newborns as a complication of a congenital dacryocystocele (see Chapter 643). If present, systemic antibiotics and digital pressure for decompression are recommended. The obstruction of the nasolacrimal system may resolve once the infection clears. If spontaneous resolution does not occur, probing should be considered within a short time frame. An intranasal cyst may be present in conjunction with the dacryocystocele. If this occurs, marsupialization of the cyst may be needed at the time of the probing.

Preseptal Cellulitis

Inflammation of the lids and periorbital tissues without signs of true orbital involvement (such as proptosis or limitation of eye movement) is generally referred to as *periorbital* or *preseptal cellulitis* and is a form of facial cellulitis. This is a common entity in young children, usually under age 5 yr, and may be caused by direct seeding related to bacteremia (usually seen in those <3 yr), sinusitis, trauma, or other infected wound in the periorbital region, or an abscess of the lid or periorbital region (pyoderma, hordeolum, conjunctivitis, dacryocystitis, insect bite). Brown recluse spider bites are often associated with considerable local swelling, and in the first 24 hr, the bite itself may not be obvious to the parent or the examiner.

Patients present with eyelid swelling; the edema may be so intense as to make it difficult to evaluate the globe. Prior to the *Haemophilus influenzae* type B (Hib) vaccine, the most common cause of pediatric preseptal (facial) cellulitis was bacteremia caused by Hib. Group A streptococcus, pneumococcus, and *S. aureus* (especially if related to an infected wound or bite) are now the most common etiologic agents. Occasionally young children with herpes simplex virus infection of the periorbital tissues will present first with swelling and redness, followed by the appearance of discrete tiny ulcers.

Clinical examination will show **lack of** proptosis, normal ocular movement, and normal pupil function. CT imaging can demonstrate edema of the lids and subcutaneous tissues anterior to the orbital septum (Fig. 652.3); however, imaging is not necessary in those without signs of an orbital process. Antibiotic therapy and careful clinical monitoring and evaluation to identify signs of local progression are essential. In well-appearing children with infected traumatic wounds or insect bites associated with periorbital cellulitis, oral antibiotics that target *S. aureus* and GAS may be considered. For young children in whom a hematogenous process is suspected, or in any toxic, ill appearing child, blood cultures should be obtained, and hospitalization and intravenous antibiotics are required. Most recommend intravenous ampicillin with sulbactam or intravenous clindamycin plus cefotaxime (or ceftriaxone) for hospitalized patients.

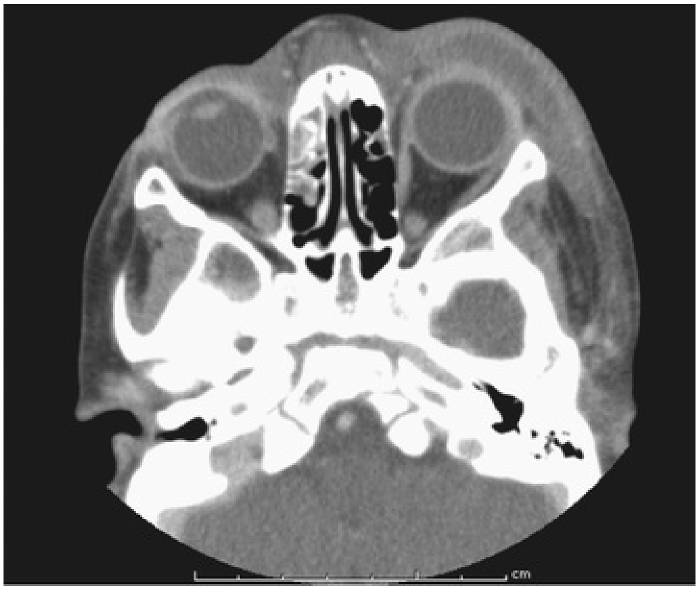

FIG. 652.3 CT scan of a patient with preseptal cellulitis.

Periorbital necrotizing fasciitis is a severe, rapidly spreading form of periorbital bacterial infection, involving both superficial and deep fascial planes. The disease may have no preceding events or may follow trauma to the periorbital skin. Initial symptoms resemble periorbital/facial cellulitis but rapidly progress to tissue necrosis, blistering, and significant systemic toxicity. Streptococci and *S. aureus* are the most common pathogens. Treatment includes broad spectrum antibiotics, surgical debridement, and when available, hyperbaric oxygen therapy.

Orbital Cellulitis

Inflammation of the tissues of the orbit, characterized by the triad of proptosis, painful limitation of movement of the eye, and potentially decreased visual acuity, is termed *orbital cellulitis* (see Table 652.1). Edema of the conjunctiva (chemosis) and inflammation and swelling of the eyelids may be seen. The mean age is 6.8 yr, ranges from 1 wk to 16 yr, and a 2 : 1 predilection in boys is reported. An increased risk is seen in the winter, as complicated sinusitis often follows respiratory viral infection (e.g., influenza). Patients often feel ill, are febrile, and appear toxic, and leukocytosis sometimes but not always may be appreciated (also see Chapter 221). Practitioners should have an increased clinical suspicion for intracranial extension in those with headache, vomiting, and always if any focal neurologic findings are present.

Orbital cellulitis may follow direct infection of the orbit from a wound, hematogenous seeding of organisms during bacteremia, or *more often* direct extension or venous spread of infection from contiguous sites such as the lids, conjunctiva, globe, lacrimal gland, nasolacrimal sac, or *more commonly* from the paranasal (ethmoid) sinuses. The **differential diagnosis** includes idiopathic orbital inflammation, myositis, sarcoidosis, granulomatous vasculitis, leukemia, lymphoma, histiocytic disorders, rhabdomyosarcoma, ruptured dermoid cyst, orbital trauma, and orbital foreign body. In some cases, primary or metastatic tumor in the orbit can produce the clinical picture of orbital cellulitis.

While the most common cause of orbital cellulitis in children is direct extension or venous spread from infected paranasal sinuses, an antecedent history of sinusitis requiring antibiotic therapy is generally not reported. The spread of infection to the orbit from the sinuses is more prevalent in children because of their thinner bony septa and sinus wall, greater porosity of bones, open suture lines, and larger vascular foramina. The spread of infection is also facilitated by the venous and lymphatic communication between the sinuses and surrounding structures, which allow flow in either direction, facilitating retrograde thrombophlebitis. Frequently noted pathogenic organisms include group A streptococcus, streptococcus species (especially *Streptococcus anginosus* also known as the *Streptococcus milleri* group), and anaerobes (e.g., *Bacteroides* spp., *Prevotella* spp.). *S. aureus* , including methicillin-resistant *S. aureus* , may be seen, most often in older patients. Occasionally group C streptococci are implicated in orbital infections. *Streptococcus pneumoniae* , group A streptococcus, and less commonly *Haemophilus* species may be identified in bacteremic cases.

The potential for complications is great. Visual loss can occur secondary to an increase in orbital pressure that causes retinal artery occlusion or optic neuritis. This is more likely to occur in the presence of an orbital abscess. Extension of infection from the orbit into the cranial cavity may lead to cavernous sinus thrombosis or meningitis, epidural or subdural empyema, or brain abscesses. Additional complications include optic atrophy, exposure keratitis, and retinal or choroidal ischemia. Therefore an interdisciplinary team involving an infectious disease specialist, ophthalmologist, otolaryngologist, and where indicated, a pediatric neurosurgeon should be involved in the care of the patient with orbital infection.

Orbital cellulitis must be recognized promptly and treated aggressively. Hospitalization and systemic antibiotic therapy are indicated. All patients should undergo CT imaging of the orbit, paranasal sinuses, and imaging should be performed with intravenous contrast. Additional brain imaging should be performed to evaluate for intracranial extension. Lumbar puncture should be considered only in those with a meningitis presentation, assuming there are no signs of elevated intracranial pressure or focal neurologic findings on examination. Parenteral antibiotics should be initiated immediately. Antimicrobial agents should begin with intravenous ampicillin with sulbactam OR intravenous clindamycin plus ceftriaxone, cefepime (or cefotaxime when available); in cases where there is suspicion for intracranial extension, vancomycin plus cefotaxime (or ceftriaxone) plus metronidazole should be given.

If the patient does not show evidence of improvement or if there are signs of progression, sinus drainage should be considered. The presence of an orbital or subperiosteal abscess (Figs. 652.4 and 652.5) may require urgent drainage of the orbit. The clinical presentation and course of each individual patient should dictate the need and timing of abscess drainage.

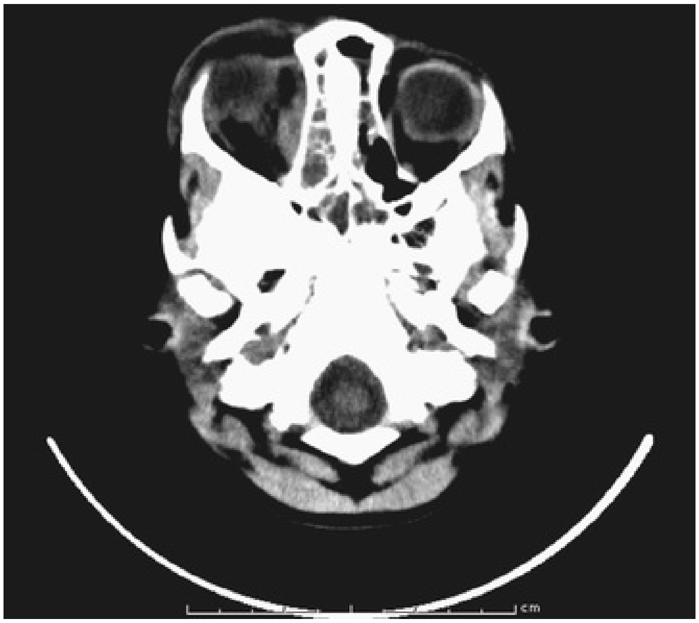

FIG. 652.4 CT scan demonstrating a subperiosteal abscess along the medial wall of the orbit.

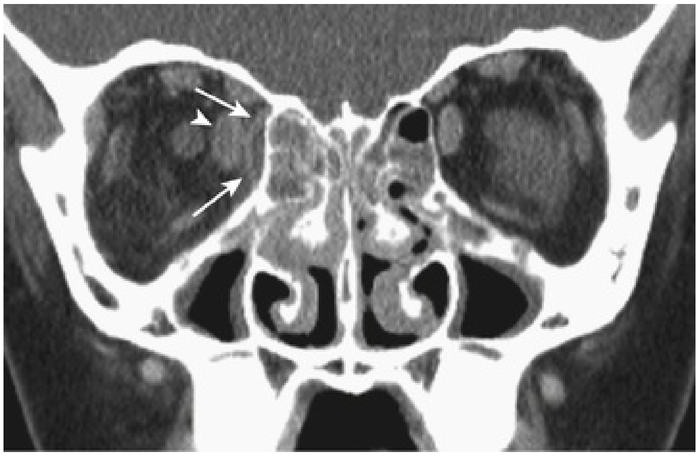

FIG. 652.5 An orbital subperiosteal abscess in a 9 yr old girl. A coronal contrast-enhanced computed tomography image shows a small, low-attenuation, rim-enhancing fluid collection consistent with an abscess *(arrows)* in the medial aspect of the orbit with mass effect on the medial rectus muscle *(arrowhead),* which is thickened. Bilateral ethmoid sinus disease with infiltration of the right retroorbital fat is demonstrated. (From Coley BD, editor: *Caffey's pediatric diagnostic imaging,* ed 12, Vol 1, Philadelphia, 2013, Elsevier Saunders. Fig. 8.17, p. 80.)

Children <9 yr of age with a medial **subperiosteal abscess** can initially be managed with intravenous antibiotics, which usually are sufficient for resolution of the abscess. Patients should be examined frequently (every 6 hr until improvement) for signs of visual deterioration or pupillary abnormalities. Most will become afebrile within 48 hr and have examination improvement by 72 hr. If there are pupillary abnormalities, decreased vision, or failure to improve, the subperiosteal abscess should be drained. Many recommend routine drainage for a subperiosteal abscess in children >9 yr of age. Operative procedures should be coordinated with the otolaryngologist to allow for sinus drainage at the same time that the subperiosteal abscess is drained, and cultures should be obtained from the sinus and the abscess.

If there is an **orbital abscess** , drainage should be performed of the orbit and cultures should similarly be obtained from sinuses and the orbital abscess. Coordinated procedures with the ophthalmologist and otolaryngologist should be undertaken so that sinus drainage can be provided under the same anesthesia. Similarly, if neurosurgical intervention is required, operative coordination should occur with ophthalmology and otolaryngology; cultures should be obtained. The use of adjunctive corticosteroids, sinus rinses, and anticoagulation for cavernous venous thrombosis and or superior ophthalmic vein thrombosis is controversial.

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CHAPTER 653

Injuries to the Eye

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Approximately 30% of all blindness in children results from trauma. Children and adolescents account for a disproportionate number of episodes of ocular trauma. Boys ages 11-15 yr are the most vulnerable; their injuries outnumber those in girls by a ratio of about 4 : 1. The majority of injuries are related to sports, sticks, stones, fireworks, paint balls, air-powered BB guns, and other projectiles. High-velocity projectiles and fireworks cause particularly devastating ocular and orbital injuries. Much of the trauma is avoidable (see Chapter 13). Any part of the orbit or globe may be affected (Fig. 653.1).

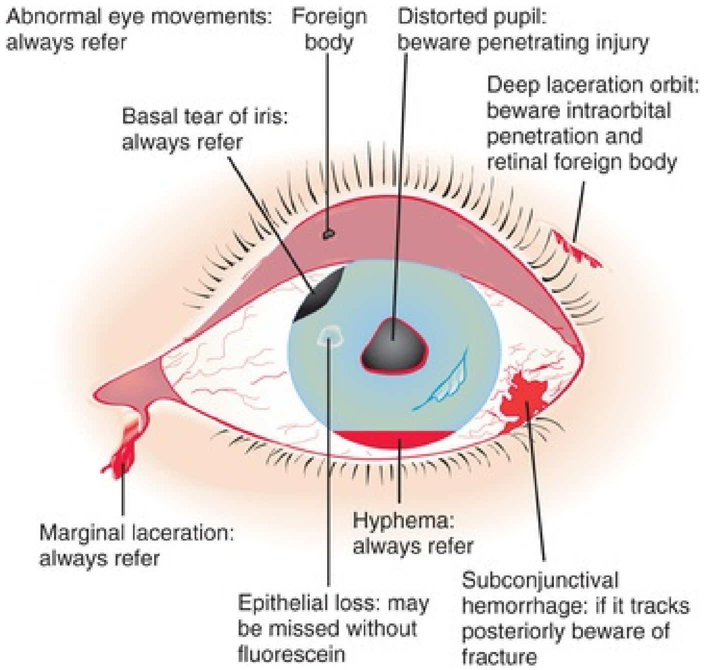
Abnormal eye movements: always refer
Foreign body
Distorted pupil: beware penetrating injury
Deep laceration orbit: beware intraorbital penetration and retinal foreign body
Basal tear of iris: always refer
Marginal laceration: always refer
Hyphema: always refer
Subconjunctival hemorrhage: if it tracks posteriorly beware of fracture
Epithelial loss: may be missed without fluorescein

FIG. 653.1 The injured eye. (From Khaw PT, Shah P, Elkington AR: Injury to the eye. *BMJ* 328:36–38, 2004.)

Ecchymosis and Swelling of the Eyelids

Ecchymosis and edema of the eyelids are common after blunt trauma (Fig. 653.2). These disorders are self-limiting, absorb spontaneously, and can be treated with iced compresses and analgesics. Periorbital ecchymosis should prompt careful examination of the eye and surrounding structures for more serious injuries such as orbital bone fracture, intraocular hemorrhage, or rupture of the globe.

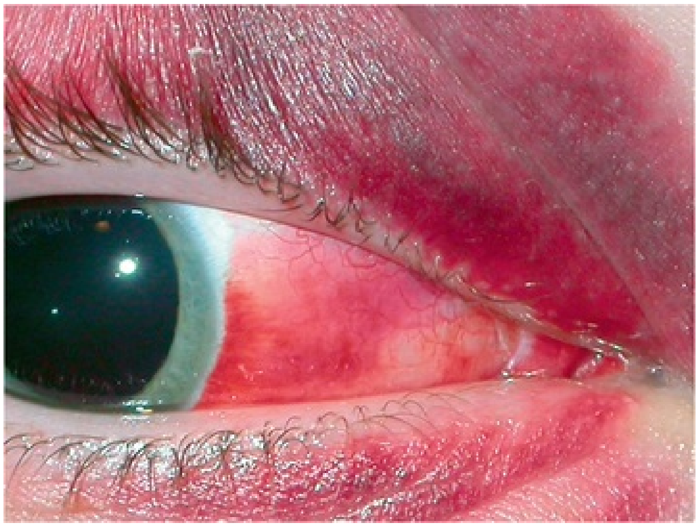

FIG. 653.2 Eyelid ecchymosis and subconjunctival hemorrhage.

Lacerations of the Eyelids

Eyelid lacerations may vary from simple to complex. When evaluating an eyelid laceration, key findings include depth of the laceration, its location, and whether there is involvement of the canaliculus (lacrimal ducts). Most superficial eyelid lacerations may be closed by the primary caregiver, but if a laceration is deep, involves the lid margin, or involves the canaliculus, it should be evaluated by an ophthalmologist. The levator muscle is responsible for elevation of the upper eyelid and runs deep to the skin and orbicularis oculi muscle. If the levator muscle is compromised and not recognized at initial repair, ptosis will occur. Therefore if orbital fat is visible in the laceration, the laceration has compromised the skin, orbicularis oculi, and levator muscles, and orbital septum and must be meticulously repaired to avoid ptosis. Eyelid margin involvement (Fig. 653.3) also requires careful repair to avoid lid malposition and notch formation. These can lead to ocular surface problems in the future, resulting in corneal scarring and loss of vision. Lacerations involving the canaliculus require intubation of the nasolacrimal system, in addition to repair of the laceration of the eyelid to avoid future tearing problems. Proper primary repair of eyelid lacerations often achieves a superior outcome to secondary repair at a later date. As with any eyelid injury, careful examination of the eye and surrounding tissue is required.

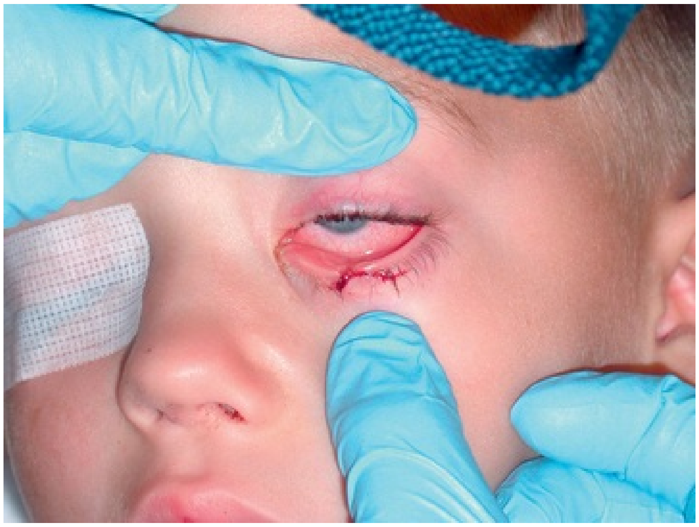

FIG. 653.3 Eyelid margin laceration.

Superficial Abrasions of the Cornea

When the corneal epithelium is scratched, abraded, or denuded, it exposes the underlying epithelial basement layer and superficial corneal nerves. This is accompanied by pain, tearing, photophobia, and decreased vision. Corneal abrasions are detected by instilling fluorescein dye and inspecting the cornea using a blue-filtered light (Fig. 653.4). A slit lamp is ideal for this examination, but a direct ophthalmoscope with a blue filter or a handheld Wood lamp is adequate for young children.

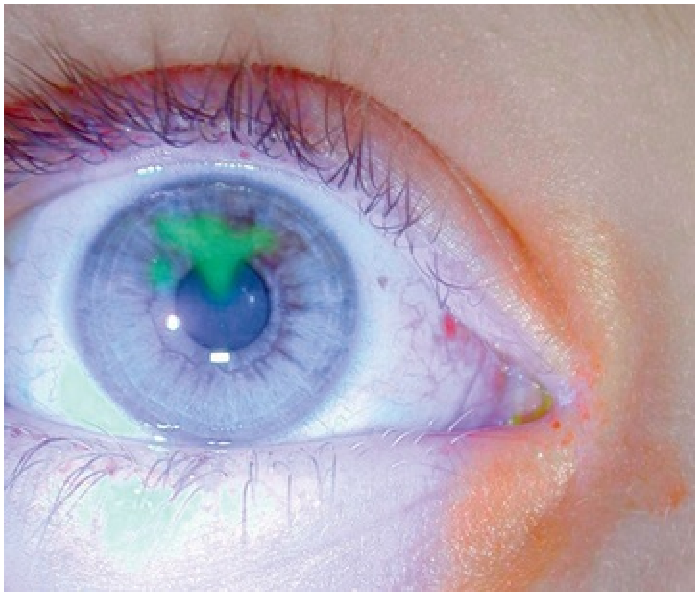

FIG. 653.4 Corneal abrasion with fluorescein staining.

Treatment of a corneal abrasion is directed at promoting healing and relieving pain. Abrasions are treated with frequent applications of a topical antibiotic ointment until the epithelium is completely healed. The use of a semipressure patch does not improve healing time or decrease pain. An improperly applied patch may itself abrade the cornea. A topical cycloplegic agent (cyclopentolate hydrochloride 1%) can relieve the pain from ciliary spasm in patients with large abrasions. Topical anesthetics should not be given at home, because they retard epithelial healing and inhibit the natural blinking reflex.

Foreign Body Involving the Ocular Surface

This usually produces acute discomfort, tearing, and inflammation. Most foreign bodies can be detected by examination in good light with the aid of magnification (Fig. 653.5) or a direct ophthalmoscope set on a high plus lens (+10 or +12). In many cases, slit-lamp examination is necessary, especially if the particle is deep or metallic. Some conjunctival foreign bodies tend to lodge under the upper eyelid, causing the sensation of corneal foreign body, as they make contact with the globe on eyelid movement; they may also produce vertically oriented linear corneal abrasions (Fig. 653.6). Finding these abrasions should lead to a suspicion of such a foreign body, and eversion of the lid may be necessary (see Chapter 637). If a foreign body is suspected but not found, further examination is indicated. If the history suggests injury with a high-velocity particle, radiologic examination of the eye may be needed to explore the possibility of an intraocular foreign body.

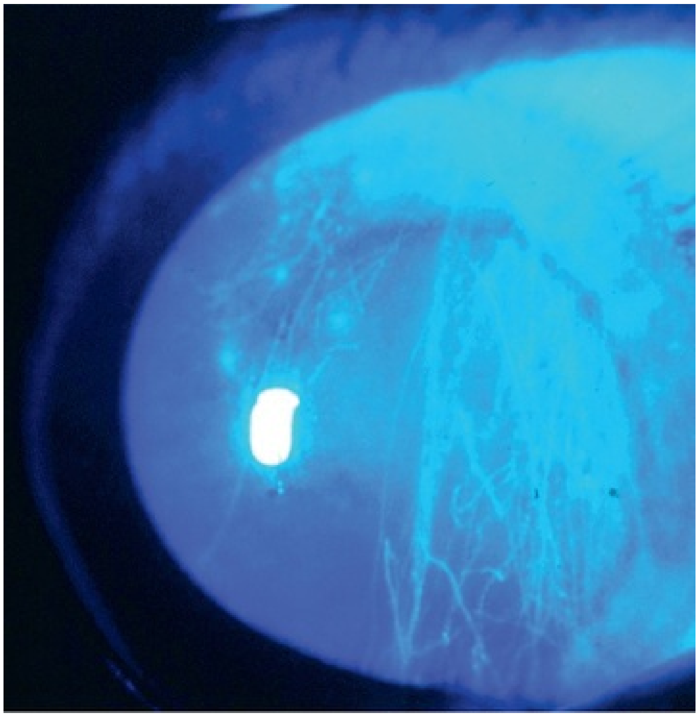

FIG. 653.5 Vertically oriented linear corneal abrasions secondary to a foreign body underneath the upper eyelid.

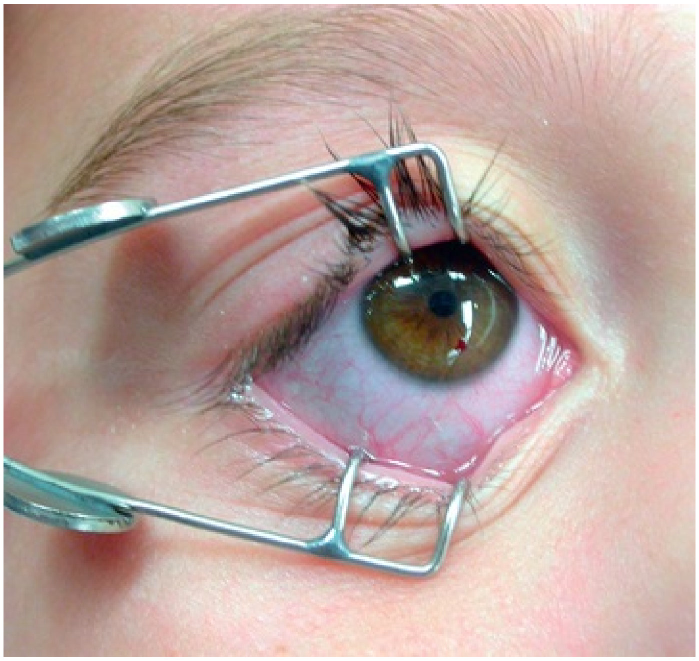

FIG. 653.6 Superficial corneal foreign body.

Removal of a foreign body can be facilitated by instillation of a drop of topical anesthetic. Many foreign bodies can be removed by irrigation or by gently wiping them away with a moistened cotton-tipped applicator. Embedded foreign bodies or foreign bodies in the central cornea should be treated by an ophthalmologist. Removal of corneal foreign bodies may leave epithelial defects, which are treated as corneal abrasions. Metallic foreign bodies may cause rust to form in the corneal tissues; examination by an ophthalmologist 1 or 2 days after removal of a foreign body is recommended because a rust ring might require further treatment.

Hyphema

This is the presence of blood in the anterior chamber of the eye. It may occur with either a blunt or perforating injury and represents a situation that may threaten vision. Hyphema appears as a bright or dark red fluid level between the cornea and iris, or as a diffuse murkiness of the aqueous humor. Children with hyphema present with acute loss of vision, with or without pain. The treatment of hyphema involves efforts to minimize the vision-threatening sequelae, such as rebleeding, glaucoma, and corneal blood staining. Bedrest is necessary, with elevation of the head of the bed to 30 degrees. A shield (without underlying patch) is placed on the affected eye, and a cycloplegic agent is used to immobilize the iris. In addition, topical or systemic steroids are used to minimize intraocular inflammation. Antiemetics should be considered if the patient is experiencing nausea. All nonsteroidal anti-inflammatories and aspirin must be avoided. Rarely, hospitalization and sedation may be necessary to ensure compliance in some children. If the intraocular pressure is elevated, topical and systemic pressure-lowering medications are used. If the pressure is not controllable by such measures, then surgical evacuation of the clot may be required to minimize the risk of permanent vision loss. Patients with sickle cell disease or trait are at higher risk of acute loss of vision secondary to elevated intraocular pressure or optic nerve infarction and may require more aggressive intervention. Individuals with a history of traumatic hyphema have an increased incidence of glaucoma later in life and should be monitored on a regular basis throughout their lives.

Open Globe

A penetrating, perforating, or blunt injury resulting in compromise of the cornea or sclera of the eye is one of the most sight-threatening injuries that can be sustained (Fig. 653.7). An open globe is a true ophthalmologic emergency that requires prompt, careful evaluation and immediate repair to minimize vision loss. Permanent vision loss can result from corneal scarring, loss of intraocular contents, or infection. Evaluation involves careful history including time and mechanism of the injury, as well as visual acuity and inspection of the eye. A full-thickness corneal wound will often present with prolapsed iris tissue through the wound. If this is not immediately evident, a peaked or irregular pupil may be a sign of full-thickness laceration. Scleral compromise may be more difficult to identify because of overlying structures. The thinnest part of the sclera is at the corneoscleral junction (the limbus) and just posterior to the insertion of the rectus muscles. When an open globe is caused by blunt force injury, these are the 2 areas most likely involved. A ruptured globe occurs when the compressive traumatic force is high enough to lead to a rupture of the globe itself. Although the term *ruptured globe* is frequently used to describe any open eye, the term should be reserved for this specific form of trauma. The force required to rupture the globe often is severe enough to lead to other permanent injuries to the eye with a resultant poor prognosis even when the rupture itself can be repaired. Therefore the specific term denotes a poorer prognosis than many other forms of open globe injuries.

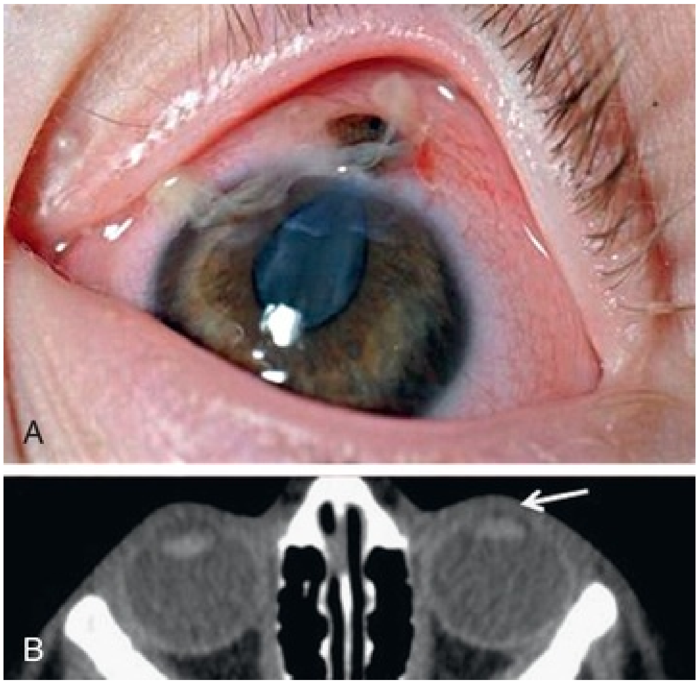

FIG. 653.7 **A,** External photograph of an open globe injury with a peaked pupil because of iris prolapse through the sclera, a shallow anterior chamber, and a traumatic cataract. **B,** CT imaging demonstrating a shallow left anterior chamber when compared with the right *(arrow)* but without evidence of an intraocular foreign body. (From Hwang RY, Schoenberger SD: Imaging a peaked pupil in a traumatic open globe injury. *J Pediatr* 163:1517, 2013. Figs. A and B, p. 1517.)

The overlying conjunctiva may not be compromised but a subconjunctival hemorrhage may be present, obscuring the view. In these cases, look for a shallow anterior chamber, low intraocular pressure, or pigment within the involved area. If the patient has been diagnosed with an open globe, the examination should be stopped, an eye shield placed immediately, and the ophthalmologist contacted to minimize further ocular compromise.

Optic Nerve Trauma

The optic nerve may be injured in both penetrating and blunt trauma. The injury may occur at any point between the globe and the chiasm. Traumatic injury to the optic nerve, regardless of cause or location, results in reduced vision and a pupillary defect. Direct trauma to the intraorbital optic nerve may cause transection, partial transection, or optic sheath hemorrhage. Fractures involving the skull base may cause injury to the intracranial portions of the optic nerve. Treatment decisions are difficult because there are no universally accepted guidelines, and the prognosis for good visual outcome is often poor. Medical management involves observation and the use of high-dose corticosteroids, although the use of corticosteroids has not been proven to improve visual outcomes and has been shown to increase the risk of death in patients with significant head injury. Surgical intervention involves optic nerve sheath decompression for nerve sheath hemorrhages. If compression of the optic nerve is secondary to orbital hemorrhage, prompt lateral canthotomy and cantholysis should be performed to relieve intraorbital pressure. Decompression of the optic canal may be performed if there is compression of the optic nerve by a bone fragment. Optic canal decompression is controversial in the absence of direct bone compression.

Chemical Injuries

Chemical burns of the cornea and adnexal tissue are among the most urgent of ocular emergencies, and they are most common in toddler and preschool age children and men. Laundry detergent pods have become an increasingly common source of ocular injury to young children over the last decade. Alkali burns are usually more destructive than acid burns because they react with fats to form soaps, which damage cell membranes, allowing further penetration of the alkali into the eye. Acids generally cause less severe, more localized tissue damage. The corneal epithelium offers moderate protection against weak acids, and little damage occurs unless the pH is 2.5 or less. Most stronger acids precipitate tissue proteins, creating a physical barrier against their further penetration.

Mild acid or alkali burns are characterized by conjunctival injection and swelling and mild corneal epithelial erosions. The corneal stroma may be mildly edematous, and the anterior chamber may have mild to moderate cell and flare reactions. With strong acids, the cornea and conjunctiva rapidly become white and opaque. The corneal epithelium may slough, leaving a relatively clear stroma; this appearance may initially mask the severity of the burn. Severe alkali burns are characterized by corneal opacification.

Emergency treatment of a chemical burn begins with immediate, copious irrigation with water or saline. Local debridement and removal of foreign particles should be performed as irrigation continues. If the nature of the chemical injury is unknown, the use of pH test paper is helpful in determining whether the agent was basic or acidic. Irrigation should continue for at least 30 min or until 2 L of irrigant has been instilled in mild cases and for 2-4 hr or until 10 L of irrigant has been instilled in severe cases. At the end of irrigation, the pH should be within a normal range (7.3-7.7). The pH should be checked again approximately 30 min after irrigation to ensure that it has not changed. The goal of treatment is to minimize sequelae that may threaten vision, such as conjunctival scarring, corneal scarring/opacification, glaucoma, cataract, and phthisis.

Orbital Fractures

The orbit is the bony structure surrounding the eye. Any of these bones may fracture in a traumatic incident. Superior and lateral wall fractures are the least common of the fracture sites, but superior orbital fracture is the most significant because of the potential of intracranial injury. The medial wall of the orbit is very susceptible to fracture because of the thin nature of the lamina papyracea. Perhaps the most common site of fracture from blunt trauma is the orbital floor. This is often referred to as blowout fracture. At times, the fracture may act as a trapdoor, entrapping orbital contents within the fracture site. In some cases, there may be very little external evidence of trauma, the so called “white-eyed blow-out fracture.”

The patient often presents with a recent history of periorbital trauma and pain. Diplopia, eyelid swelling, eye movement restriction, or hypesthesia may or may not be present. Eye symptoms may be associated with nausea and bradycardia if the inferior rectus is entrapped in the fracture site. A complete ophthalmic examination, including, visual acuity, examination of the pupil for ocular alignment, ocular motility, anterior segment, and fundus status, as well as the history of the injury, is required because there are often accompanying ocular injuries. The diagnosis of fracture is suspected if eye misalignment, eye movement restriction, or enophthalmos (sunken eye) are present. The diagnosis is verified by orbital CT scan.

Medical management includes iced compresses to the orbit and elevation of the head of the bed for the 1st 24-48 hr. Broad-spectrum antibiotics are sometimes recommended for 14 days because of the exposure of the orbital contents to the sinus cavity. In medial wall fractures, instructions not to blow one's nose should be given to the patient to avoid orbital emphysema and subsequent optic nerve compression. Consider neurosurgical consultation in orbital roof fractures. Indications for surgical repair of orbital fractures are diplopia in primary gaze or downgaze that persists for 2 wk, enophthalmos, or fracture of the orbital floor involving more than half of the floor. Extraocular muscle entrapment often requires prompt surgical repair because affected patients have significant pain, nausea, and vomiting that are difficult to control. Rarely, extraocular muscle entrapment can cause activation of the oculocardiac reflex, requiring urgent fracture repair.

Penetrating Wounds of the Orbit

These demand careful evaluation for possible damage to the eye, optic nerve, orbital contents, or brain. Examination should include investigation for a retained foreign body. Orbital hemorrhage and infection are common with penetrating wounds of the orbit; such injuries must be treated as emergencies.

Child Abuse

See Chapter 16 .

This is a major cause of injuries to the eye and orbital region. The possibility of nonaccidental trauma must be considered in any child with ecchymosis or laceration of the lids, hemorrhage in or about the eye, cataract or dislocated lens, retinal detachment, or fracture of the orbit. Inflicted childhood neurotrauma (shaken baby syndrome) occurs secondary to violent, nonaccidental, repetitive, unrestrained acceleration-deceleration head and neck movements, with or without blunt head trauma in children typically younger than 3 yr of age. Inflicted childhood neurotrauma accounts for approximately 10% of all cases of child abuse and carries a mortality rate of up to 25%. Detection of abuse is not only important in order to treat the pathology that is discovered but also to prevent further abuse or even death. The ocular manifestations are numerous and may have a prominent role in recognition of this syndrome. Retinal hemorrhage is the most common ophthalmic finding and occurs at all levels of the retina. The pattern of hemorrhage helps distinguish this disorder from other causes of retinal hemorrhage or from accidental injuries (Fig. 653.8). Retinal hemorrhages can occur without associated intracranial pathology.

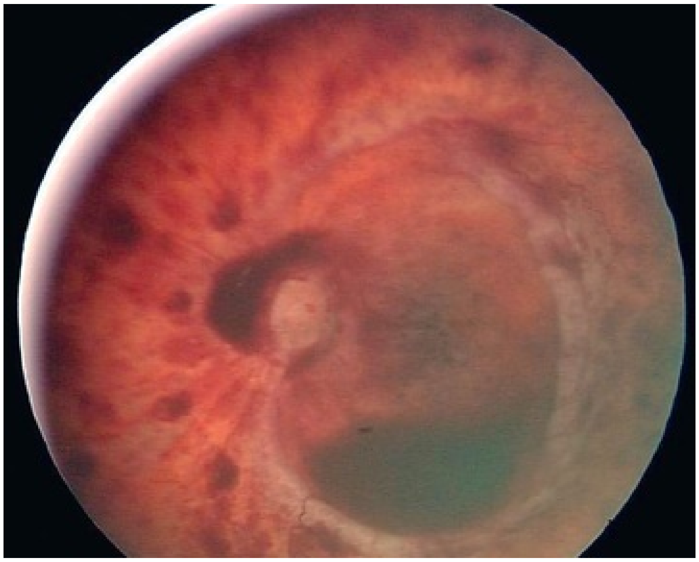

FIG. 653.8 Retinal hemorrhages in an abused child.

Fireworks-Related Injuries

Injuries related to the use of fireworks can be the most devastating of all ocular traumas that occur in children. At least 20% of emergency department visits for fireworks-related injuries are for ocular trauma. In the United States, a majority of these injuries take place around Independence Day, and most occur despite adult supervision.

Sports-Related Ocular Injuries and Their Prevention

Although sports injuries occur in all age groups, far more children and adolescents participate in high-risk sports than do adults. The greater number of participating children, their athletic immaturity, and the increased likelihood of their using inadequate or improper eye protection account for their disproportionate share of sports-related eye injuries (see Chapter 713).

The sports with the highest risk of eye injury are those in which no eye protection can be worn, including boxing, wrestling, and martial arts. Other high-risk sports include those that use a rapidly moving ball or puck, bat, stick, racquet, or arrow (baseball, hockey, lacrosse, racquet sports, and archery) or involve aggressive body contact (football and basketball). Related to both risk and frequency of participation, the highest percentage of eye injuries are in basketball and baseball.

Protective eyewear, designed for a specific activity, is available for most sports. For basketball, racquet sports, and other recreational activities that do not require a helmet or face mask, molded polycarbonate sports goggles that are secured to the head by an elastic strap are suggested. For hockey, football, lacrosse, and baseball (batter), specific helmets with polycarbonate face shields and guards are available. Children should also wear sports goggles under their helmets. For baseball, goggles and helmets should be worn for batting, catching, and base running; goggles alone are usually sufficient for other positions.

Handheld Laser Retinal Injury

Handheld laser pointers, often purchased to light cigarettes or for other purposes, may produce significant retinal damage if the power output is ≥150 mW. If a person looks directly at the light, direct foveal injury may occur before he or she has time to blink. Central (foveal) blurring and decreased visual activity are the chief complaints. Retinal injuries include retinal disruption, subretinal edema, and macular holes (Fig. 653.9), which usually require surgical repair.

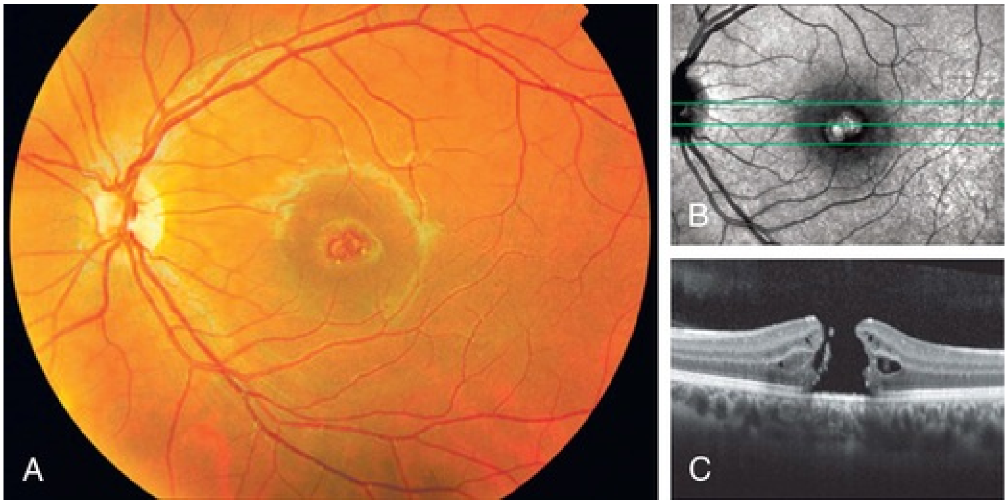

FIG. 653.9 **Laser damage to the left eye. A, Color photo of the fundus of the left eye showing a macular hole. Note the changes at the retinal pigment epithelium. B, Infrared photo of the left fundus. C, Optical coherence tomography of the left eye showing the macular hole. (From Petrou P, Patwary S, Banerjee PJ, et al: Bilateral macular hole from a handheld laser pointer. *Lancet* 383:1780, 2014.)**

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PART XXIX

The Ear

OUTLINE

Chapter 654 General Considerations and Evaluation of the Ear
Chapter 655 Hearing Loss
Chapter 656 Congenital Malformations of the Ear
Chapter 657 External Otitis (Otitis Externa)
Chapter 658 Otitis Media
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CHAPTER 654

General Considerations and Evaluation of the Ear

Joseph Haddad Jr, Sonam N. Dodhia

Clinical Manifestations

Diseases of the ear and temporal bone typically manifest with 1 or more of 8 clinical signs and symptoms.

Otalgia usually is associated with inflammation of the middle ear (about 50% of cases) or external ear, but it can represent pain referred from involvement of the teeth, temporomandibular joint, or pharynx (Table 654.1). In young infants, pulling or rubbing the ear along with general irritability or poor sleep, especially when associated with fever, may be the only signs of ear pain. Ear pulling alone is not diagnostic of ear pathology.

Table 654.1

Causes of Otalgia and Sources for Referred Pain

Intrinsic

External Ear

A. External otitis
B. Cerumen impaction
C. Foreign body
D. Perichondritis
E. Preauricular cyst or sinus

F. Insects
G. Myringitis
H. Trauma
I. Tumor

Middle Ear, Eustachian Tube, and Mastoid

A. Barotrauma
B. Middle ear effusion
C. Negative intratympanic pressure (eustachian tube dysfunction)
D. Acute otitis media
E. Mastoiditis
F. Aditus block
G. Complication of otitis media
H. Tumor
I. Eosinophilic granuloma
J. Granulomatosis with polyangiitis

Extrinsic

Trigeminal Nerve

A. Dental
B. Jaw
C. Temporomandibular joint
D. Oral cavity (tongue)
E. Infratemporal fossa tumors

Facial Nerve

A. Bell palsy
B. Tumors
C. Herpes zoster

Glossopharyngeal Nerve

A. Tonsil
B. Oropharynx
C. Nasopharynx

Vagus Nerve

A. Laryngopharynx
B. Esophagus
C. Gastroesophageal reflux
D. Thyroid

Cervical Nerves

A. Lymph nodes
E. Cysts
C. Cervical spine
D. Neck infections

Miscellaneous

A. Migraine
B. Neuralgias
C. Paranasal sinuses
D. Central nervous system
E. Drug induced (mesalazine, sulfasalazine)
F. Factitious disorder by proxy

From Bluestone CD, Stool SE, Alper CM, et al: *Pediatric otolaryngology* , ed 4, Vol 1, Philadelphia, 2003, Saunders, p. 288.

Purulent otorrhea is a sign of otitis externa, otitis media (OM) with perforation of the tympanic membrane (TM), drainage from the middle ear through a patent tympanostomy tube, or, rarely, drainage from a first branchial cleft sinus. Bloody drainage may be associated with acute or chronic inflammation (often with granulation tissue and/or an ear tube), trauma, neoplasm, foreign body, or blood dyscrasia. Clear drainage suggests a perforation of the TM with a serous middle-ear effusion or, rarely, a cerebrospinal fluid leak draining through defects (congenital or traumatic) in the external auditory canal or from the middle ear.

Hearing loss results either from disease of the external or middle ear (conductive hearing loss) or from pathology in the inner ear, retrocochlear structures, or central auditory pathways (sensorineural hearing loss [SNHL]); the underlying etiology can be genetic or nongenetic and syndromic or nonsyndromic. The most common cause of hearing loss in children is OM.

Swelling around the ear most commonly is a result of inflammation (e.g., external otitis, perichondritis, mastoiditis), trauma (e.g., hematoma), benign cystic masses, or neoplasm.

Vertigo is a specific type of dizziness that is defined as any illusion or sensation of motion. **Dizziness** is less specific than vertigo and refers to a sensation of altered orientation in space. Vertigo is an uncommon complaint in children; the child or parent might not volunteer information about balance unless asked specifically. The most common cause of dizziness in young children is eustachian tube–middle-ear disease, but true vertigo also may be caused by labyrinthitis, perilymphatic fistula between the inner and middle ear as a result of trauma or a congenital inner ear defect, cholesteatoma in the mastoid or middle ear, vestibular neuronitis, benign paroxysmal vertigo, Meniere disease, or disease of the central nervous system. Older children might describe a feeling of the room spinning or turning; younger children might express the dysequilibrium only by falling, stumbling, or clumsiness.

Nystagmus may be unidirectional, horizontal, or jerk nystagmus. It is vestibular in origin and usually is associated with vertigo.

Tinnitus rarely is described spontaneously by children, but it is common, especially in patients with eustachian tube–middle-ear disease or SNHL. Children can describe tinnitus if asked directly about it, including laterality and the quality of the sound.

Facial Paralysis

The facial nerve may be dehiscent in its course through the middle ear as a normal variant in as many as 50% of people. Infection with local inflammation, most commonly in acute OM, can lead to a temporary paralysis of the facial nerve. It also can result from Lyme disease, cholesteatoma, Bell palsy, Ramsay Hunt syndrome (herpes zoster oticus), fracture, neoplasm, or infection of the temporal bone. Congenital facial paralysis can result from birth trauma or congenital abnormality of the 7th nerve or from a syndrome such as Möbius or CHARGE (coloboma, heart defects, atresia choanae, retarded growth, genital hypoplasia, and ear anomalies), or it may be associated with other cranial nerve abnormalities and craniofacial anomalies.

Physical Examination

Complete examination with special attention to the head and neck can reveal a condition that can predispose to or be associated with ear disease in children. The facial appearance and the character of speech can give clues to an abnormality of the ear or hearing. Many craniofacial anomalies, such as cleft palate, mandibulofacial dysostosis (Treacher Collins syndrome), and trisomy 21 (Down syndrome), are associated with disorders of the ear and eustachian tube. Mouth breathing and hyponasality can indicate intranasal or postnasal obstruction. **Hypernasality** is a sign of velopharyngeal insufficiency. Examining the oropharyngeal cavity might uncover an overt cleft palate or a submucous cleft (usually associated with a bifid uvula), both of which predispose to OM with effusion. A nasopharyngeal tumor with nasal and eustachian tube blockage may be associated with OM.

The position of the patient for examination of the ear, nose, and throat depends on the patient's age and ability to cooperate, the clinical setting, and the examiner's preference. The child can be examined on an examination table or in the parent's lap. The presence of a parent or assistant usually is necessary to minimize movement and provide better examination results (Fig. 654.1). An examining table may be desirable for uncooperative older infants or when a procedure, such as microscopic evaluation or tympanocentesis, is performed. Wrapping the child in a sheet or using a papoose board can help to minimize movement. Lap examination is adequate and preferable in most infants and young children; the parent may assist in restraining the child by folding the child's wrists and arms over the child's own abdomen with one hand and holding the child's head against the parent's chest with the other hand. If necessary, the child's legs can be held between the parent's knees. To avoid ear trauma with movement, the examiner should hold the otoscope with the hand placed firmly against the child's head or face, so that the otoscope moves with the head. Pulling up and out on the pinna straightens the ear canal and allows better exposure of the TM.

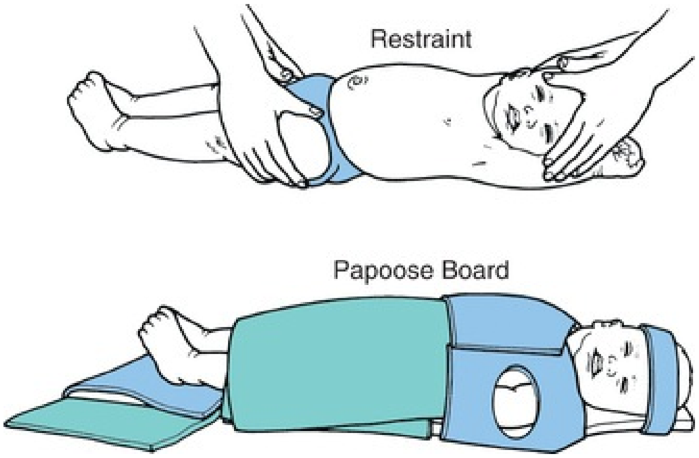

FIG. 654.1 Methods of restraining an infant for examination and for procedures such as tympanocentesis or myringotomy. (From Bluestone CD, Klein JO: Otitis media in infants and children, ed 2, Philadelphia, 1995, WB Saunders, p. 91.)

When examining the ear, inspecting the auricle and external auditory meatus for infection can aid in evaluating complications of OM. External otitis can result from acute OM with discharge, or inflammation of the posterior auricular area can indicate a periostitis or subperiosteal abscess extending from the mastoid air cells. The presence of preauricular pits or skin tags also should be noted because affected children have a slightly higher incidence of SNHL; ear pits can develop chronic infection.

Cerumen is a protective, waxy, water-repellent coating in the ear canal that can interfere with examination. Cerumen usually is removed using the surgical head of the otoscope, which allows passage of a wire loop or a blunt curette under direct visualization. Other methods include gentle irrigation of the ear canal with warm water, which should be performed only if the TM is intact, or instillation of a solution such as diluted hydrogen peroxide in the ear canal (with intact TM only) for a few minutes to soften the wax for suction removal or irrigation. Some commercial preparations such as trolamine polypeptide oleate–condensate (Cerumenex) can cause dermatitis of the external canal with chronic use and should be used only under a physician's supervision.

Inflammation of the ear canal with associated pain often indicates external otitis. Abnormalities of the external auditory canal include stenosis (common in children with trisomy 21), bony exostoses, otorrhea, and the presence of foreign bodies. Cholesteatoma of the middle ear can manifest in the canal as intermittent foul-smelling drainage, sometimes associated with white debris; cholesteatoma of the external canal can appear as a white, pearl-like mass in the canal skin. White or gray debris of the canal suggests fungal external otitis. Newborn ear canals are filled with vernix caseosa, which is soft and pale yellow and should disappear shortly after birth.

The TM and its mobility are best assessed with a pneumatic otoscope. The normal TM is in a neutral position; a bulging TM may be caused by increased middle-ear air pressure, with or without pus or effusion in the middle ear; a bulging drum can obscure visualization of the malleus and annulus. Retraction of the TM usually indicates negative middle-ear pressure, but it also can result from previous middle-ear disease with fixation of the ossicles, ossicular ligaments, or TM. When retraction is present, the bony malleus appears more prominent, and the incus may be more visible posterior to the malleus.

The normal TM has a silvery-gray, “waxed paper” appearance (Fig. 654.2). A white or yellow TM can indicate a middle-ear effusion. A red TM alone might not indicate pathology, because the blood vessels of the membrane may be engorged as a result of crying, sneezing, or nose blowing, though hemorrhagic redness is associated with acute OM. A normal TM is translucent, allowing the observer to visualize the middle-ear landmarks: incus, promontory, round window niche, and often the chorda tympani nerve. If a middle-ear effusion is present, an air–fluid level or bubbles may be visible (see Fig. 654.2). Inability to visualize the middle-ear structures indicates opacification of the drum, usually caused by thickening of the TM or a middle-ear effusion, or both. Assessment of the light reflex often is not helpful, because a middle ear with effusion reflects light as well as a normal ear. Bullae (blister of the TM) formation is associated with acute OM.

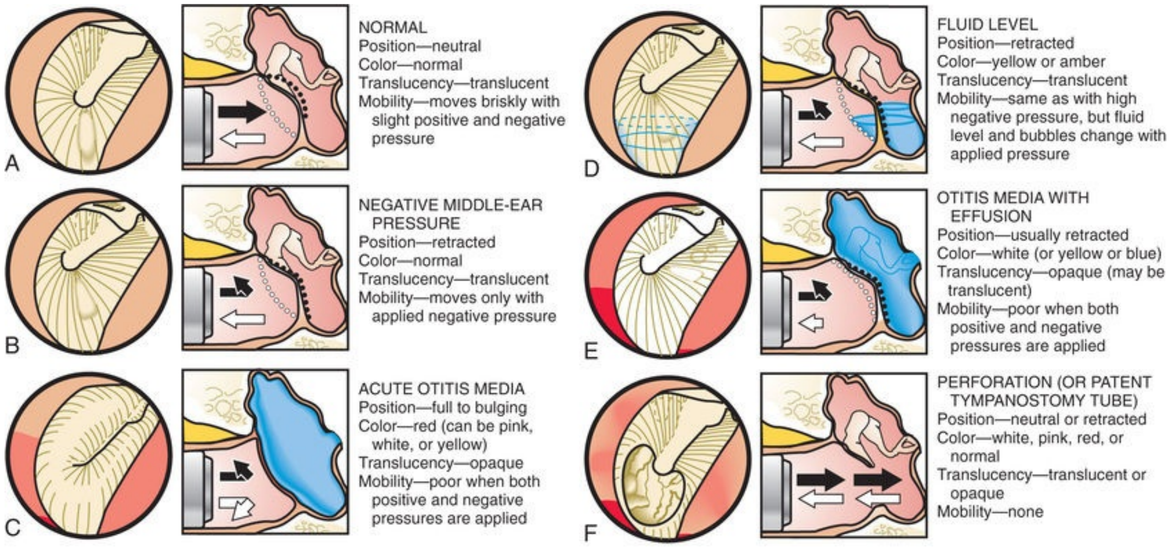
A
NORMAL
Position—neutral
Color—normal
Translucency—translucent
Mobility—moves briskly with slight positive and negative pressure
B
NEGATIVE MIDDLE-EAR PRESSURE
Position—retracted
Color—normal
Translucency—translucent
Mobility—moves only with applied negative pressure
C
ACUTE OTITIS MEDIA
Position—full to bulging
Color—red (can be pink, white, or yellow)
Translucency—opaque
Mobility—poor when both positive and negative pressures are applied
D
FLUID LEVEL
Position—retracted
Color—yellow or amber
Translucency—translucent
Mobility—same as with high negative pressure, but fluid level and bubbles change with applied pressure
E
OTITIS MEDIA WITH EFFUSION
Position—usually retracted
Color—white (or yellow or blue)
Translucency—opaque (may be translucent)
Mobility—poor when both positive and negative pressures are applied
F
PERFORATION (OR PATENT TYMPANOSTOMY TUBE)
Position—neutral or retracted
Color—white, pink, red, or normal
Translucency—translucent or opaque
Mobility—none

FIG. 654.2 **A–F,** Common conditions of the middle ear, as assessed with the otoscope. (From Bluestone CD, Klein JO: Otitis media in infants and children, ed 3, Philadelphia, 2001, WB Saunders, p. 131.)

TM mobility is helpful in assessing middle-ear pressures and the presence or absence of fluid (see Fig. 654.2). To best perform pneumatic otoscopy, a speculum of adequate size is used to obtain a good seal and allow air movement in the canal. A rubber ring around the tip of the speculum can help obtain a better canal seal. Normal middle-ear pressure is characterized by a neutral TM position and brisk TM movement to both positive and negative pressures.

Eardrum retraction is most common when negative middle-ear pressure is present; with even moderate negative middle-ear pressure, there is no visible inward movement with applied positive pressure in the ear canal (see Fig. 654.2). However, negative canal pressure, which is produced by releasing the rubber bulb of the pneumatic otoscope, can cause the TM to bounce out toward the neutral position. The TM can retract in both the presence and absence of middle-ear fluid, and if the middle-ear fluid is mixed with air, the TM might still have some mobility. Outward eardrum movement is less likely in the presence of severe negative middle-ear pressure or middle-ear effusion.

The TM that exhibits fullness (bulging) moves to applied positive pressure but not to applied negative pressure if the pressure within the middle ear is positive. A full TM and positive middle-ear pressure without an effusion may be seen in young infants who are crying during the otoscopic examination, in older infants and children with nasal obstruction, and in the early stage of acute OM. When the middle-ear–mastoid air cell system is filled with an effusion and little or no air is present, the mobility of the TM is severely decreased or absent in response to both applied positive and negative pressures.

Tympanocentesis , or aspiration of the middle ear, is the definitive method of verifying the presence and type of a middle-ear effusion and is performed by inserting, through the inferior portion of the TM, an 18-gauge spinal needle attached to a syringe or a collection trap (Fig. 654.3). Culturing of the ear canal and alcohol cleansing should precede tympanocentesis and culture of the middle-ear aspirate; a canal culture is taken first to help determine whether organisms cultured from the middle ear are contaminants from the external canal or true middle-ear pathogens.

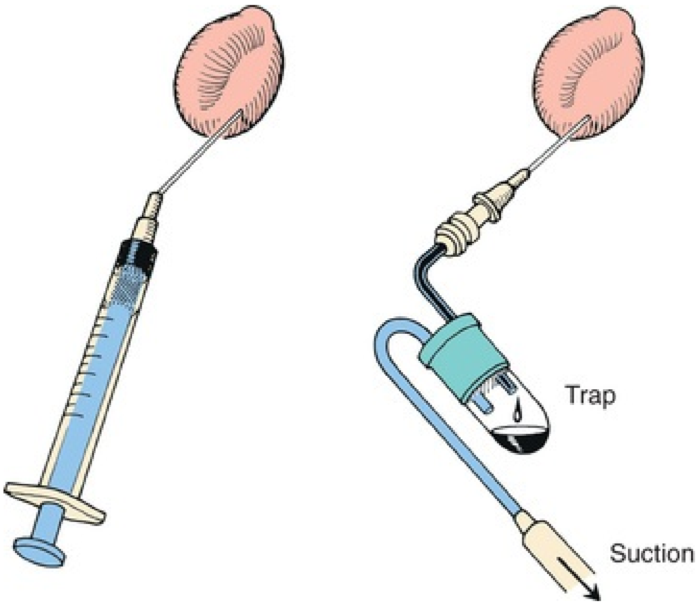

FIG. 654.3 Tympanocentesis can be performed with a needle attached to a tuberculin syringe *(left)* or by using an Alden-Senturia collection trap (Storz Instrument Co, St. Louis). (From Bluestone CD, Klein JO: Otitis media in infants and children, ed 2, Philadelphia, 1995, WB Saunders, p. 127.)

Further diagnostic studies of the ear and hearing include audiometric evaluation, impedance audiometry (tympanometry), acoustic reflectometry, and specialized eustachian tube function studies. Diagnostic imaging studies, including CT and MRI, often provide further information about anatomic abnormalities and the extent of inflammatory processes or neoplasms. Specialized assessment of labyrinthine function should be considered in the evaluation of a child with a suspected vestibular disorder (see Chapter 660).

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CHAPTER 655

Hearing Loss

Joseph Haddad Jr, Sonam N. Dodhia, Jaclyn B. Spitzer

Incidence and Prevalence

Bilateral neural hearing loss is categorized as **mild** (20-30 dB hearing level, HL), **moderate** (30-50 dB HL), **moderately severe** (50-70 dB HL), **severe** (75-85 dB HL), or **profound** (>85 dB). The World Health Organization estimates that approximately 360 million people (5% of the world's population, including 32 million children) have disabling hearing loss. An additional 364 million people have mild hearing loss. Half of these cases could have been prevented. In the United States, the average incidence of neonatal hearing loss is 1.6 per 1,000 infants; the rate by state varies from 0.22 to 3.61 per 1,000. Among children and adolescents, the prevalence of mild or greater hearing loss is 3.1% and is higher among Latin Americans, African Americans, and persons from lower-income families.

Onset of hearing loss in children can occur at any time in childhood. When less-severe hearing loss or the transient hearing loss that commonly accompanies middle-ear disease in young children is considered, the number of affected children increases substantially.

Types of Hearing Loss

Hearing loss can be peripheral or central in origin. Peripheral hearing loss can be conductive, sensorineural, or mixed. **Conductive hearing loss (CHL)** commonly is caused by dysfunction in the transmission of sound through the external or middle ear. CHL is the most common type of hearing loss in children and occurs when sound transmission is physically impeded in the external and/or middle ear. Common causes of CHL in the *ear canal* include aural atresia or stenosis, impacted cerumen, or foreign bodies. In the *middle ear* , perforation of the tympanic membrane (TM), discontinuity or fixation of the ossicular chain, otitis media (OM) with effusion, otosclerosis, and cholesteatoma can cause CHL.

Damage to or maldevelopment of structures in the inner ear can cause **sensorineural hearing loss (SNHL)** . Causes include hair cell destruction from noise, disease, or ototoxic agents; cochlear malformation; perilymphatic fistula of the round or oval window membrane; and failure in development or lesions of the acoustic division of the 8th nerve. Coexistent CHL and SNHL is considered a **mixed hearing loss** .

An auditory deficit originating along the central auditory nervous system pathways from the proximal 8th nerve to the cerebral cortex usually is considered **central** (or **retrocochlear**) **hearing loss.** Tumors or demyelinating disease of the 8th nerve and cerebellopontine angle can cause hearing deficits but spare the outer, middle, and inner ear. These causes of hearing loss are rare in children. Functional disorders of the eighth nerve and/or brainstem pathways may manifest in a variety of clinical defects known collectively as auditory neuropathy spectrum disorder (ANSD) or auditory dyssynchrony, without abnormalities demonstrable on imaging. Other forms of central auditory deficits, known as **central auditory processing disorders** , include those that make it difficult even for children with normal hearing sensitivity to listen selectively in the presence of noise, to combine information from the 2 ears properly, to process speech when it is slightly degraded, and to integrate auditory information when it is delivered faster although they can process it when delivered at a slow rate. These deficits can manifest as specific language disorders or poor attention, or as academic or behavior problems in school. Strategies for coping with such disorders are available for older children, and identification and documentation of the central auditory processing disorder allow parents and teachers to make appropriate accommodations to enhance learning.

Etiology

Most CHL is acquired, with middle-ear fluid the most common cause. Congenital causes include anomalies of the pinna, external ear canal, TM, and ossicles. Rarely congenital cholesteatoma or other masses in the middle ear manifest as CHL. TM perforation (e.g., trauma, OM), ossicular discontinuity (e.g., infection, cholesteatoma, trauma), tympanosclerosis, acquired cholesteatoma, or masses in the ear canal or middle ear (Langerhans cell histiocytosis, salivary gland tumors, glomus tumors, rhabdomyosarcoma) also can manifest as CHL. Uncommon diseases that affect the middle ear and temporal bone and can manifest with CHL include otosclerosis, osteopetrosis, fibrous dysplasia, and osteogenesis imperfecta.

SNHL may be congenital or acquired. Acquired SNHL may be caused by genetic, infectious, autoimmune, anatomic, traumatic, ototoxic, and idiopathic factors (Tables 655.1 to 655.4). The recognized risk factors account for approximately 50% of cases of moderate to profound SNHL.

Table 655.2

Infectious Pathogens Implicated in Sensorineural Hearing Loss in Children

Congenital Infections

- Cytomegalovirus
- Lymphocytic choriomeningitis virus
- Rubella virus
- *Toxoplasma gondii*
- *Treponema pallidum*

Acquired Infections

- *Borrelia burgdorferi*
- Epstein-Barr virus
- *Haemophilus influenzae*
- Lassa virus
- Measles virus
- Mumps virus
- *Neisseria meningitidis*
- Nonpolio enteroviruses
- *Plasmodium falciparum*
- *Streptococcus pneumoniae*
- Varicella-zoster virus

From Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children. *Lancet* 365:879–890, 2005.

Table 655.1

Indicators Associated With Hearing Loss

Indicators Associated With Sensorineural and/or Conductive Hearing Loss

Neonates (Birth to 28 Days) When Universal Screening Is Not Available

Family history of hereditary childhood sensorineural hearing loss
In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis
Craniofacial anomalies, including those with morphologic abnormalities of the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
Birthweight <1500 g (3.3 lb)
Hyperbilirubinemia at a serum level requiring exchange transfusion
Ototoxic medications, including but not limited to the aminoglycosides, used in multiple courses or in combination with loop diuretics
Bacterial meningitis
Apgar scores of 0-4 at 1 min or 0-6 at 5 min
Mechanical ventilation lasting ≥5 days; extracorporeal membrane oxygenation
Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; white forelock

Infants and Toddlers (Age 29 Days to 2 Yr) When Certain Health Conditions Develop That Require Rescreening

Parent or caregiver concern regarding hearing, speech, language, and/or developmental delay
Bacterial meningitis and other infections associated with sensorineural hearing loss
Head trauma associated with loss of consciousness or skull fracture
Stigmata or other findings associated with a syndrome known to include a sensorineural and/or conductive hearing loss; neurofibromatosis, osteopetrosis, and Usher Hunter, Waardenburg, Alport, Pendred, or

Jervell and Lange-Nielsen syndrome
Ototoxic medications, including but not limited to chemotherapeutic agents or aminoglycosides used in multiple courses or in combination with loop diuretics
Recurrent or persistent otitis media with effusion for 3 mo or longer
Skeletal dysplasia

Infants and Toddlers (Age 29 Days to 3 Yr) Who Require Periodic Monitoring of Hearing

Some newborns and infants pass initial hearing screening but require periodic monitoring of hearing to detect delayed-onset sensorineural and/or conductive hearing loss. Infants with these indicators require hearing evaluation at least every 6 mo until age 3 yr, and at appropriate intervals thereafter

Indicators Associated With Delayed-Onset Sensorineural Hearing Loss

Family history of hereditary childhood hearing loss
In utero infection, such as cytomegalovirus, rubella, syphilis, herpes simplex, or toxoplasmosis
Neurofibromatosis type 2 and neurodegenerative disorders
Cogan syndrome (vasculitis: keratitis, uveitis, vertigo, arthritis, dermatitis)

Indicators Associated With Conductive Hearing Loss

Recurrent or persistent otitis media with effusion
Anatomic deformities and other disorders that affect eustachian tube function
Neurodegenerative disorders

Note: At all ages, parents’ concern about hearing loss must be taken seriously even in the absence of risk factors.

Adapted from American Academy of Pediatrics, Joint Committee on Infant Hearing: Joint Committee on Infant Hearing 1994 position statement. *Pediatrics* 95:152, 1995.

Table 655.3

Common Types of Early-Onset Hereditary Nonsyndromic Sensorineural Hearing Loss

LOCUS	GENE	AUDIO PHENOTYPE
DFN3	*POU3F4*	Conductive hearing loss as a result of stapes fixation mimicking otosclerosis; superimposed progressive SNHL
DFNA1	*DIAPH1*	Low-frequency loss beginning in the 1st decade and progressing to all frequencies to produce a flat audio profile with profound losses throughout the auditory range
DFNA2	*KCNQ4*	Symmetric high-frequency sensorineural loss beginning in the 1st decade and progressing over all frequencies
	GJB3	Symmetric high-frequency sensorineural loss beginning in the 3rd decade
DFNA3	*GJB2*	Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment
	GJB6	Childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing impairment
DFNA6, 14, and 38	*WFS1*	Early-onset low-frequency sensorineural loss; approximately 75% of families dominantly segregating this audio profile carry missense mutations in the C-terminal domain of wolframin
DFNA8, and 12	*TECTA*	Early-onset stable bilateral hearing loss, affecting mainly mid to high frequencies
DFNA10	*EYA4*	Progressive loss beginning in the 2nd decade as a flat to gently sloping audio profile that becomes steeply sloping with age
DFNA11	*MYO7A*	Ascending audiogram affecting low and middle frequencies at young ages and then affecting all frequencies with increasing age
DFNA13	*COL11A2*	Congenital midfrequency sensorineural loss that shows age-related progression across the auditory range
DFNA15	*POU4F3*	Bilateral progressive sensorineural loss beginning in the 2nd decade
DFNA20, and 26	*ACTG1*	Bilateral progressive sensorineural loss beginning in the 2nd decade; with age, the loss increases with threshold shifts in all frequencies, although a sloping configuration is maintained in most cases
DFNA22	*MYO6*	Postlingual, slowly progressive, moderate to severe hearing loss
DFNB1	*GJB2*, *GJB6*	Hearing loss varies from mild to profound. The most common genotype, 35delG/35delG, is associated with severe to profound SNHL in about 90% of affected children; severe to profound deafness is observed in only 60% of children who are compound heterozygotes carrying 1 35delG allele and any other *GJB2* SNHL-causing allele variant; in children carrying 2 *GJB2* SNHL-causing missense mutations, severe to profound deafness is not observed
DFNB3	*MYO7A*	Severe to profound sensorineural hearing loss
DFNB4	*SLC26A4*	DFNB4 and Pendred syndrome (see Table 655.5) are allelic. DFNB4 hearing loss is associated with dilation of the vestibular aqueduct and can be unilateral or bilateral. In the high frequencies, the loss is severe to profound; in the low frequencies, the degree of loss varies widely. Onset can be congenital (prelingual), but progressive postlingual loss also is common
DFNB7,	*TMC1*	Severe-to-profound prelingual hearing impairment

and 11		
DFNB9	*OTOF*	*OTOF* -related deafness is characterized by two phenotypes: prelingual nonsyndromic hearing loss and, less frequently, temperature-sensitive nonsyndromic auditory neuropathy spectrum disorder. The nonsyndromic hearing loss is bilateral severe-to-profound congenital deafness
DFNB12	*CDH23*	Depending on the type of mutation, recessive mutations of *CDH23* can cause nonsyndromic deafness or type 1 Usher syndrome (USH1), which is characterized by deafness, vestibular areflexia, and vision loss as a result of retinitis pigmentosa
DFNB16	*STRC*	Early-onset nonsyndromic autosomal recessive sensorineural hearing loss
mtDNA 1555A > G	*12S rRNA*	Degree of hearing loss varies from mild to profound but usually is symmetric; high frequencies are preferentially affected; precipitous loss in hearing can occur after aminoglycoside therapy

SNHL , Sensorineural hearing loss.

Adapted from Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children. *Lancet* 365:879–890, 2005.

Table 655.4

Common Types of Syndromic Sensorineural Hearing Loss

SYNDROME	GENE	PHENOTYPE
DOMINANT		
Waardenburg (WS1)	*PAX3*	Major diagnostic criteria include dystopia canthorum, congenital hearing loss, heterochromic irises, white forelock, and an affected 1st-degree relative. Approximately 60% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Waardenburg (WS2)	*MITF* , others	Major diagnostic criteria are as for WS1 but without dystopia canthorum. Approximately 80% of affected children have congenital hearing loss; in 90%, the loss is bilateral.
Branchiootorenal	*EYA1*	Diagnostic criteria include hearing loss (98%), preauricular pits (85%), and branchial (70%), renal (40%), and external-ear (30%) abnormalities. The hearing loss can be conductive, sensorineural, or mixed, and mild to profound in degree.
CHARGE syndrome	*CHD7*	Choanal atresia, colobomas, heart defect, retardation, genital hypoplasia, ear anomalies, deafness. Can lead to sensorineural or mixed hearing loss. Can be autosomal dominant or isolated cases.
Goldenhar syndrome	Unknown	Part of the hemifacial microsomia spectrum. Facial hypoplasia, ear anomalies, hemivertebrae, parotid gland dysfunction. Can cause conductive or mixed hearing loss. Can be autosomal dominant or sporadic.
RECESSIVE		
Pendred syndrome	*SLC26A4*	Diagnostic criteria include sensorineural hearing loss that is congenital, nonprogressive, and severe to profound in many cases, but can be late-onset and progressive; bilateral dilation of the vestibular aqueduct with or without cochlear hypoplasia; and an abnormal perchlorate discharge test or goiter.
Alport syndrome	*COL4A3*, *COL4A4*, and *COL4A5*	Nephritis, deafness, lens defects, retinitis. Can lead to bilateral sensorineural hearing loss in the 2,000-8,000 Hz range. The hearing loss develops gradually and is not generally present in early infancy.
Usher syndrome type 1 (USH1)	*USH1A*, *MYO7A*, *USH1C*, *CDH23*,	Diagnostic criteria include congenital, bilateral, and profound hearing loss, vestibular areflexia, and retinitis pigmentosa (commonly not diagnosed until tunnel vision and nyctalopia become severe enough to be noticeable).

	USH1E, PCDH15, USH1G	
Usher syndrome type 2 (USH2)	*USH2A, USH2B, USH2C*, others	Diagnostic criteria include mild to severe, congenital, bilateral hearing loss and retinitis pigmentosa; hearing loss may be perceived as progressing over time because speech perception decreases as diminishing vision interferes with subconscious lip reading.
Usher syndrome type 3 (USH3)	*USH3*	Diagnostic criteria include postlingual, progressive sensorineural hearing loss, late-onset retinitis pigmentosa, and variable impairment of vestibular function.

Adapted from Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children. *Lancet* 365:879–890, 2005.

Sudden SNHL in a previously healthy child is uncommon but may be from OM or other cochlear pathologies such as autoimmunity. Usually these causes are obvious from the history and physical examination. Sudden loss of hearing in the absence of obvious causes often is the result of a vascular event affecting the cochlear apparatus or nerve, such as embolism or thrombosis (secondary to prothrombotic conditions), or an autoimmune process. Additional causes include perilymph fistula, drugs, trauma, and the first episode of Meniere syndrome. In adults, sudden SNHL is often idiopathic and unilateral; it may be associated with tinnitus and vertigo. Identifiable causes of sudden SNHL include infections (Epstein-Barr virus, varicella-zoster virus, herpes simplex virus), vascular injury to the cochlea, enlarged vestibular aqueduct, endolymphatic hydrops, and autoimmune inflammatory diseases. In most patients with sudden SNHL, no etiology is discovered, and it is termed **idiopathic sudden SNHL** .

Infectious Causes

The most common infectious cause of congenital SNHL is **cytomegalovirus (CMV)** , which infects 1 in 100 newborns in the United States (see Chapters 131 and 282). Of these, 6,000-8,000 infants each year have clinical manifestations, including approximately 75% with SNHL. Congenital CMV warrants special attention because it is associated with hearing loss in its symptomatic and asymptomatic forms with bilateral and unilateral hearing loss, respectively; the hearing loss may be progressive. Some children with congenital CMV have suddenly lost residual hearing at 4-5 yr of age. Much less common congenital infectious causes of SNHL include toxoplasmosis and syphilis. Congenital CMV, toxoplasmosis, and syphilis also can manifest with delayed onset of SNHL months to years after birth. Rubella, once the most common viral cause of congenital SNHL, is very uncommon because of effective vaccination programs.

In utero infection with herpes simplex virus is rare, and hearing loss is not an isolated manifestation.

Other postnatal infectious causes of SNHL include neonatal group B streptococcal sepsis and bacterial meningitis at any age. *Streptococcus pneumoniae* is the most common cause of bacterial meningitis that results in SNHL after the neonatal period and has become less common with the routine administration of pneumococcal conjugate vaccine. *Haemophilus influenzae* type b, once the most common cause of meningitis resulting in SNHL, is rare owing to the *H. influenzae* type b conjugate vaccine. Uncommon infectious causes of SNHL include Lyme disease, parvovirus B19, and varicella. Mumps, rubella, and measles, all once common causes of SNHL in children, are rare owing to vaccination programs. When these infectious etiologies occur, the resulting hearing loss is frequently bilateral and severe.

Genetic Causes

Genetic causes of SNHL probably are responsible for as many as 50% of SNHL cases (see Tables 655.3 and 655.4). These disorders may be associated with other abnormalities, may be part of a named syndrome, or can exist in isolation. SNHL often occurs with abnormalities of the ear and eye and with disorders of the metabolic, musculoskeletal, integumentary, renal, and nervous systems.

Autosomal dominant hearing losses account for approximately 10% of all cases of childhood SNHL. Waardenburg (types I and II) and branchiootorenal syndromes represent two of the most common autosomal dominant syndromic types of SNHL. Types of SNHL are coded with a 4-letter code and a number, as follows: **DFN** = deafness, A = dominant, B = recessive, and number = order of discovery (e.g., DFNA 13). Autosomal dominant conditions in addition to those just discussed include DFNA 1-18, 20-25, 30, 36, 38, and mutations in the crystallin gene *(CRYM).*

Autosomal recessive genetic SNHL, both syndromic and nonsyndromic, accounts for approximately 80% of all childhood cases of SNHL. Usher syndrome (types 1, 2, and 3: all associated with blindness, retinitis pigmentosa), Pendred syndrome, and the Jervell and Lange-Nielsen syndrome (one form of the long Q-T syndrome) are three of the most common syndromic recessive types of SNHL. Other autosomal recessive conditions include Alström syndrome, type 4 Bartter syndrome, biotinidase deficiency, and DFNB 1-18, 20-23, 26-27, 29-33, 35-40, 42, 44, 46, 48, 49, 53, and 55.

Unlike children with an easily identified syndrome or with anomalies of the outer ear, who may be identified as being at risk for hearing loss and consequently monitored, children with nonsyndromic hearing loss present greater diagnostic difficulty. Mutations of the connexin-26 and -30 genes are identified in autosomal recessive (DNFB 1) and autosomal dominant (DNFA 3) SNHL and in sporadic patients with nonsyndromic SNHL; up to 50% of nonsyndromic SNHLs may be related to a mutation of connexin-26. Mutations of the *GJB2* gene colocalize with DFNA 3 and DFNB 1 loci on chromosome 13, are associated with autosomal nonsyndromic susceptibility to deafness, and are associated with as many as 30% of cases of sporadic severe to profound congenital deafness and 50% of cases of autosomal recessive nonsyndromic deafness. In addition, mutations in *GJB6* are associated with approximately 5% of recessive nonsyndromic deafness. Sex-linked disorders associated with SNHL, thought to account for 1–2% of SNHLs, include Norrie disease, the otopalatal digital syndrome, Nance deafness, and Alport syndrome. Chromosomal abnormalities such as trisomy 13-15, trisomy 18, and trisomy 21 also can be accompanied by hearing impairment. Patients with Turner syndrome have monosomy for all or part of one X chromosome and can have CHL, SNHL, or mixed hearing loss. The hearing loss may be progressive. Mitochondrial genetic abnormalities also can result in SNHL (see Table 655.3).

Many genetically determined causes of hearing impairment, both syndromic and nonsyndromic, do not express themselves until sometime after birth. Alport, Alström, Down, and Hunter-Hurler syndromes and von Recklinghausen disease are genetic diseases that can have SNHL as a late manifestation.

Physical Causes

Agenesis or malformation of cochlear structures may be genetic; these include the Scheibe, Mondini (Fig. 655.1), Alexander, and Michel anomalies, enlarged vestibular aqueducts (in isolation or associated with Pendred syndrome), and semicircular canal anomalies. These anomalies most likely develop before the 8th wk of gestation and result from arrest in normal development, aberrant development, or both. Many of these anomalies also have been described in association with other congenital conditions such as intrauterine CMV and rubella infections. These abnormalities are quite common; in as many as 20% of children with SNHL, obvious or subtle temporal bone abnormalities are seen on high-resolution CT scanning or MRI.

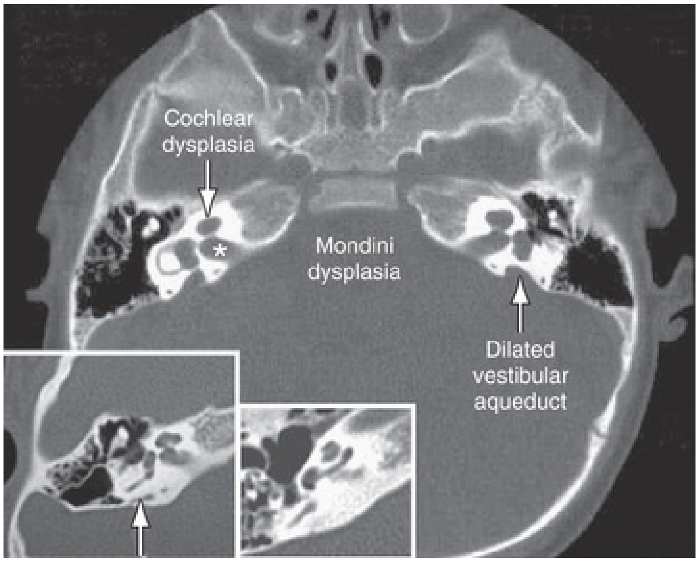

FIG. 655.1 **Mondini dysplasia shown by CT of the temporal bone in a child with Pendred syndrome. Both dilation of the vestibular aqueduct and cochlear dysplasia are present in this section. In the larger of the 2 inset images of a normal temporal bone, the vestibular aqueduct is visible but much smaller *(arrow).* The cochlea appears normal, and in the smaller inset image of a more inferior axial section, the expected number of cochlear turns can be clearly counted. *Internal auditory canal. (From Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children. *Lancet* 365:879–890, 2005.)**

Conditions, diseases, or syndromes that include craniofacial abnormalities may be associated with CHL and possibly with SNHL. Pierre Robin Sequence and Treacher Collins, Klippel-Feil, Crouzon, and branchiootorenal syndromes and osteogenesis imperfecta often are associated with hearing loss. Congenital anomalies causing CHL include malformations of the ossicles and middle-ear structures and atresia of the external auditory canal.

SNHL also can occur secondary to exposure to toxins, chemicals, antimicrobials, and noise exposure. Early in pregnancy, the embryo is particularly vulnerable to the effects of toxic substances. Ototoxic drugs, including aminoglycosides, loop diuretics, and chemotherapeutic agents (cisplatin) also can cause SNHL. Congenital SNHL can occur secondary to exposure to these drugs as well as to thalidomide and retinoids. Certain chemicals, such as quinine, lead, and arsenic, can cause hearing loss both prenatally and postnatally. Among adolescents, the use of personal listening devices at high volume settings has been found to be correlated to hearing loss.

Trauma, including temporal bone fractures, inner ear concussion, head trauma, iatrogenic trauma (e.g., surgery, extracorporeal membrane oxygenation), radiation exposure, and noise, also can cause SNHL. Other uncommon causes of SNHL in children include autoimmune disease (systemic or limited to the inner ear), metabolic abnormalities, and neoplasms of the temporal bone.

Effects of Hearing Impairment

The effects of hearing impairment depend on the nature and degree of the hearing loss and on the individual characteristics of the child. Hearing loss may be unilateral or bilateral, conductive, sensorineural, or mixed; mild, moderate, severe, or profound; of sudden or gradual onset; stable, progressive, or fluctuating; and affecting a part or all of the audible spectrum. Other factors, such as intelligence, medical or physical condition (including accompanying syndromes), family support, age at onset, age at time of identification, and promptness of intervention, also affect the impact of hearing loss on a child.

Most hearing-impaired children have some usable hearing. Only 6% of those in the hearing-impaired population have bilateral profound hearing loss. Hearing loss very early in life can affect the development of speech and language, social and emotional development, behavior, attention, and academic achievement. Some cases of hearing impairment are misdiagnosed because affected children have sufficient hearing to respond to environmental sounds and can learn some speech and language but when challenged in the classroom cannot perform to full potential.

Even mild or unilateral hearing loss can have a detrimental effect on the development of a young child and on school performance. Children with such hearing impairments have greater difficulty when listening conditions are unfavorable (e.g., background noise and poor acoustics), as can occur in a classroom. The fact that schools are auditory-verbal environments is unappreciated by those who minimize the impact of hearing impairment on learning. Hearing loss should be considered in any child with speech and language difficulties or below-par performance, poor behavior, or inattention in school (Table 655.5).

Table 655.5

Hearing Handicap as a Function of Average Hearing Threshold Level of the Better Ear

AVERAGE THRESHOLD	COMMON	WHAT CAN BE HEARD	DEGREE OF HANDICAP (IF NOT	PROBABLE

LEVEL (dB) AT 500-2,000 Hz (ANSI)	**DESCRIPTION**	**CAUSES**	**WITHOUT AMPLIFICATION**	**TREATED IN 1ST YR OF LIFE)**	**NEEDS**
0-15	Normal range	Conductive hearing loss	All speech sounds	None	None
16-25	Slight hearing loss	Otitis media, TM perforation, tympanosclerosis; eustachian tube dysfunction; some SNHL	Vowel sounds heard clearly, may miss unvoiced consonant sounds	Mild auditory dysfunction in language learning Difficulty in perceiving some speech sounds	Consideration of need for hearing aid, speech reading, auditory training, speech therapy, appropriate surgery, preferential seating
26-30	Mild	Otitis media, TM perforation, tympanosclerosis, severe eustachian dysfunction, SNHL	Hears only some speech sounds, the louder voiced sounds	Auditory learning dysfunction Mild language retardation Mild speech problems Inattention	Hearing aid Lip reading Auditory training Speech therapy Appropriate surgery
31-50	Moderate hearing loss	Chronic otitis, ear canal/middle ear anomaly, SNHL	Misses most speech sounds at normal conversational level	Speech problems Language retardation Learning dysfunction Inattention	All of the above, plus consideration of special classroom situation
51-70	Severe hearing loss	SNHL or mixed loss due to a combination of middle-ear disease and sensorineural involvement	Hears no speech sound of normal conversations	Severe speech problems Language retardation Learning dysfunction Inattention	All of the above; probable assignment to special classes
71+	Profound hearing loss	SNHL or mixed	Hears no speech or other sounds	Severe speech problems Language retardation Learning dysfunction Inattention	All of the above; probable assignment to special classes or schools

ANSI , American National Standards Institute; *SNHL* , sensorineural hearing loss; *TM* , tympanic membrane.

Modified from Northern JL, Downs MP: *Hearing in children,* ed 4, Baltimore, 1991, Williams & Wilkins.

Children with moderate, severe, or profound hearing impairment, and those with other handicapping conditions, often are educated in classes or schools for children with special needs. There is a strong trend toward integrating a child with hearing loss into the least restrictive learning environment; this approach can only be successful if there are sufficient supportive services available to support auditory and other learning needs. The auditory management and choices regarding modes of communication and education for children with hearing handicaps must be individualized, because these children are not a homogeneous group. A team approach to individual case management is essential, because each child and family unit has unique needs and abilities.

Hearing Screening

Hearing impairment can have a major impact on a child's development, and because early identification improves prognosis, screening programs have been widely and strongly advocated. The National Center for Hearing Assessment and Management estimates that the detection and treatment at birth of hearing loss saves $400,000 per child in special education costs; screening costs approximately $8-$50/child. Data from the Colorado newborn screening program suggest that if hearing-impaired infants are identified and treated by age 6 mo, these children (with the exception of those with bilateral profound impairment) should develop the same level of language as their age-matched peers who are not hearing impaired. These data provide compelling support for establishing mandated newborn hearing screening programs for all children. The American Academy of Pediatrics endorses the goal of universal detection of hearing loss in infants before 3 mo of age, with appropriate intervention no later than 6 mo of age. The Centers for Disease Control and Prevention estimates that of the approximately 4 million infants born in the United States in 2014, 97.9% were screened for hearing loss.

Until mandated screening programs are established universally, many hospitals will continue to use other criteria to screen for hearing loss. Some use the high-risk criteria (see Table 655.1) to decide which infants to screen; some screen all infants who require intensive care; and some do both. The problem with using high-risk criteria to screen is that 50% of cases of hearing impairment will be missed, either because the infants are hearing impaired but do not meet any of the high-risk criteria or because they develop hearing loss after the neonatal period.

The recommended hearing screening techniques are either otoacoustic emissions (OAE) testing or auditory brainstem evoked responses (ABRs). The ABR test, an auditory evoked electrophysiologic response that correlates highly with hearing, has been used successfully and cost-effectively to screen newborns and to identify further the degree and type of hearing loss. OAE tests, used successfully in most universal newborn screening programs, are quick, easy to administer, and inexpensive, and they provide a sensitive indication of the presence of hearing loss. Results are relatively easy to interpret. OAE tests elicit no response if hearing is worse than 30-40 dB, no matter what the cause; children who fail OAE tests undergo an ABR for a more definitive evaluation as meta-analyses have demonstrated that ABR has a higher sensitivity and specificity. It is recommended that both OAE measurement and ABR screening be used in the intensive care unit setting. Screening methods such as observing behavioral responses to uncalibrated noisemakers or using automated systems such as the Crib-o-gram (Canon) or the auditory response cradle (in which movement of the infant in response to sound is recorded by motion sensors) *are not recommended.*

Many children become hearing impaired after the neonatal period and therefore are not identified by newborn screening programs. Often it is not until children are in preschool or kindergarten that further hearing screening takes place; an evidence-based systematic review has identified pure-tone and OAE screening to be effective, with pure-tone screening having higher sensitivity. Among adolescents, high frequency hearing loss is associated with exposure to loud noises, so attention should be paid to those frequencies on a hearing screen; most noise-induced hearing loss is around 4 kHz. Fig. 655.2 provides recommendations for postneonatal screening.

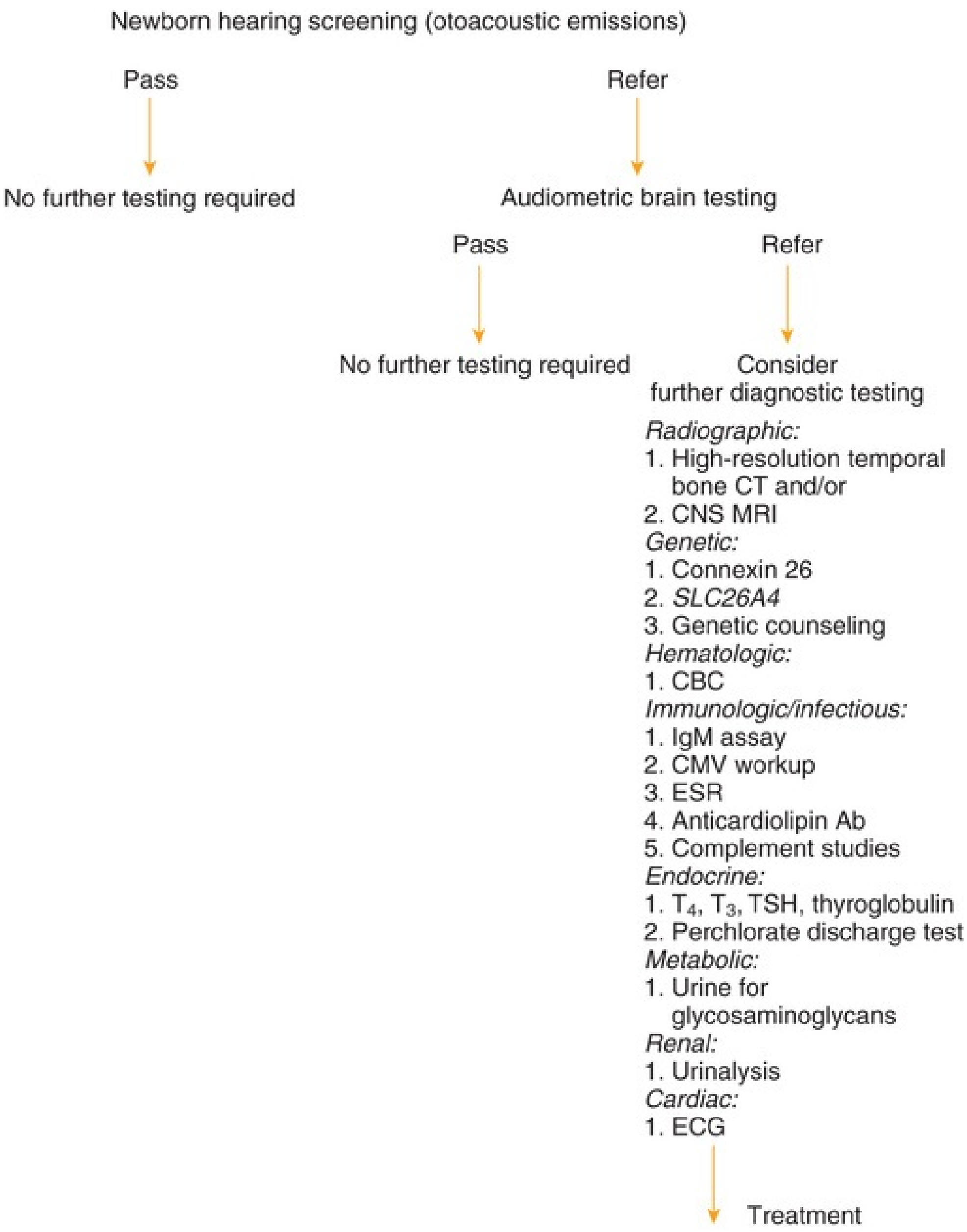
Newborn hearing screening (otoacoustic emissions)
Pass
Refer
No further testing required
Audiometric brain testing
Pass
Refer
No further testing required
Consider further diagnostic testing
Radiographic:
1. High-resolution temporal bone CT and/or
2. CNS MRI
Genetic:
1. Connexin 26
2. SLC26A4
3. Genetic counseling
Hematologic:
1. CBC
Immunologic/infectious:
1. IgM assay
2. CMV workup
3. ESR
4. Anticardiolipin Ab
5. Complement studies
Endocrine:
1. T4, T3, TSH, thyroglobulin
2. Perchlorate discharge test
Metabolic:
1. Urine for glycosaminoglycans
Renal:
1. Urinalysis
Cardiac:
1. ECG
Treatment

FIG. 655.2 **Algorithm for newborn hearing screening. Ab, antibody; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M; MRI, magnetic resonance imaging; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone. (From Norton SJ, Bhama PK, Perkins JA: Early detection and diagnosis of infant hearing impairment. In Flint PW, Haughey BH, Lund VJ, et al, editors: Cummings otolaryngology head and neck surgery, ed 5, Philadelphia, 2010, Mosby, Fig 190.1.)**

Identification of Hearing Impairment

The impact of hearing impairment is greatest on an infant who has yet to develop language; consequently, identification, diagnosis, description, and treatment should begin as soon as possible. Infants with a prenatal or perinatal history that puts them at risk (see Table 655.3) or those who have failed a formal hearing screening should be evaluated by an experienced clinical audiologist until a reliable assessment of auditory sensitivity has been obtained. Pediatricians should encourage families to cooperate with the follow-up plan. Infants who are born at risk but who were not screened as neonates (e.g., because of transfer from one hospital to another) should have a hearing screening by age 3 mo.

Hearing-impaired infants, who are born at risk or are screened for hearing loss in a neonatal hearing screening program, account for only a portion of hearing-impaired children. Children who are congenitally deaf because of autosomal recessive inheritance or subclinical congenital infection often are not identified until 1-3 yr of age. Usually those with more-severe hearing loss are identified at an earlier age, but identification often occurs later than the age at which intervention can provide an optimal outcome, especially in countries lacking technologic resources. Children who hear normally develop extensive receptive and expressive language by 3-4 yr of age (Table 655.6) and exhibit behavior reflecting normal auditory function (Table 655.7). Failure to fulfill these criteria should be the reason for an audiologic evaluation. Parents' concern about hearing and any delayed development of speech and language should alert the pediatrician, because parents' concern usually precedes formal identification and diagnosis of hearing impairment by 6 mo to 1 yr of age.

Table 655.6

Criteria for Referral for Audiologic Assessment

AGE (mo)	REFERRAL GUIDELINES FOR CHILDREN WITH "SPEECH" DELAY
12	No differentiated babbling or vocal imitation
18	No use of single words
24	Single-word vocabulary of ≤10 words
30	<100 words; no evidence of 2 word combinations; unintelligible
36	<200 words; no use of telegraphic sentences; clarity <50%
48	<600 words; no use of simple sentences; clarity ≤80%

From Matkin ND: Early recognition and referral of hearing-impaired children. *Pediatr Rev* 6:151–156, 1984. Reproduced by permission of Pediatrics.

Table 655.7

Guidelines for Referral of Children With Suspected Hearing Loss

AGE (mo)	NORMAL DEVELOPMENT
0-4	Should startle to loud sounds, quiet to mother's voice, momentarily cease activity when sound is presented at a conversational level
5-6	Should correctly localize to sound presented in a horizontal plane, begin to imitate sounds in own speech repertoire or at least reciprocally vocalize with an adult
7-12	Should correctly localize to sound presented in any plane Should respond to name, even when spoken quietly
13-15	Should point toward an unexpected sound or to familiar objects or persons when asked
16-18	Should follow simple directions without gestural or other visual cues; can be trained to reach toward an interesting toy at midline when a sound is presented
19-24	Should point to body parts when asked; by 21-24 mo, can be trained to perform play audiometry

From Matkin ND: Early recognition and referral of hearing-impaired children. *Pediatr Rev* 6:151–156, 1984.

Clinical Audiologic Evaluation

When hearing impairment is suspected in a young child, reliable and valid estimates of auditory function can be obtained using electrophysiologic and age-appropriate behavioral measurement. Successful treatment strategies for hearing-impaired children rely on prompt identification and ongoing assessment to define the dimensions of auditory function. Cooperation among the pediatrician and specialists in areas such as audiology, speech and language pathology, education, and child development is necessary to optimize auditory-verbal development. Therapy for hearing-impaired children may include an amplification device, a **frequency modulation** (FM) system in the classroom, close monitoring of hearing and auditory skills, speech and language therapy, counseling of parents and families, advising teachers, and dealing with public agencies.

Audiometry

Audiologic evaluation technique varies as a function of the age and developmental level of the child, the reason for the evaluation, and the child's otologic condition or history. An audiogram provides the fundamental description of hearing sensitivity (Fig. 655.3). Hearing thresholds are assessed as a function of frequency using pure tones (single frequency stimuli) at octave intervals from 250 to 8,000 Hz. When the child is old enough to accept their placement, earphones typically are used to assess each ear independently. Prior to this stage, testing may be performed in a sound treated environment with stimuli delivered via speakers; this approach permits description only of the better hearing ear.

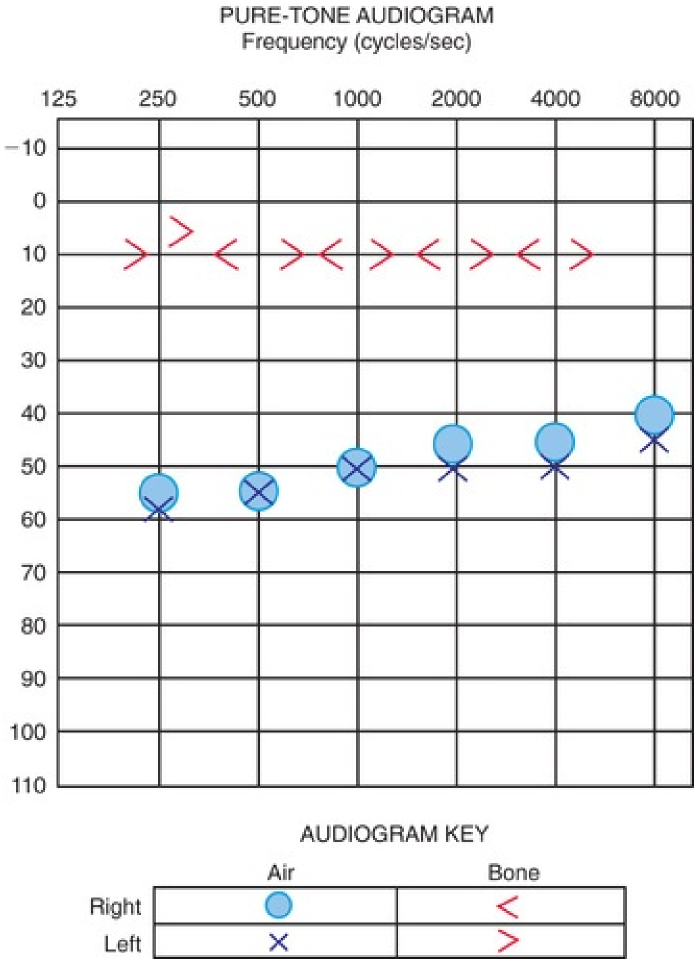

FIG. 655.3 **Audiogram showing bilateral conductive hearing loss.**

Air-conducted signals are presented through earphones (or loudspeakers) and are used to provide information about the sensitivity of the entire auditory system. These same test sounds can be delivered to the ear through an oscillator that is placed on the head, usually on the mastoid. Such signals are considered bone-conducted because the bones of the skull transmit vibrations as sound energy directly to the inner ear, essentially bypassing the outer and middle ears. In a normal ear, and also in children with SNHL, the air- and bone-conduction thresholds are equivalent. In those with CHL, bone-conduction thresholds are more sensitive than air- conducted responses; this is called the **air–bone gap** , which indicates the amount of hearing loss attributable to dysfunction in the outer and/or middle ear. In mixed hearing loss, both the bone- and air-conduction thresholds are abnormal, and there is additionally an air–bone gap.

Speech-Recognition Threshold

Another measure useful for describing auditory function is the **speech-recognition threshold (SRT)** , which is the lowest intensity level at which a score of approximately 50% correct is obtained on a task of recognizing spondee words. Spondee words are 2-syllable words or phrases that have equal stress on each syllable, such as *baseball* , *hotdog* , and *pancake* . Listeners must be familiar with all the words for a valid test result to be obtained. The SRT should correspond to the average of pure-tone thresholds at 500, 1,000, and 2,000 Hz, the pure-tone average. The SRT is relevant as an indicator of a child's potential for development and use of speech and language; it also serves as a check of the validity of a test because children with nonorganic hearing loss (malingerers) might show a discrepancy between the pure-tone average and SRT. An SRT may be obtained in a child with expressive speech or language limitations using modified techniques, such a picture-pointing responses.

The basic battery of hearing tests concludes with an assessment of a child's ability to understand monosyllabic words when presented at a comfortable listening level. Performance on such word recognition tests assists in the differential diagnosis of hearing impairment and provides a measure of how well a child performs when speech is presented at loudness levels similar to those encountered in conversation. For speech recognition as well, a picture pointing response may be obtained with standardized tests.

Play Audiometry

Hearing testing technique is age dependent. For children at or above the developmental level of a 5-6 yr old, conventional test methods can be used. For children 30 mo to 5 yr of age, play audiometry can be used. Responses in play audiometry usually are conditioned motor activities associated with a game, such as dropping blocks in a bucket, placing rings on a peg, or completing a puzzle. The technique can be used to obtain a reliable audiogram for a preschool child.

Visual Reinforcement Audiometry

For children between the ages of about 6 and 30 mo, **visual reinforcement audiometry (VRA)** is commonly used. In this technique, the child is conditioned to turn his/her head in response to a tonal signal from a speaker in the same location as an animated (mechanical) toy or video reinforcer. If infants are properly conditioned, by presenting sounds associated with the reinforcer, VRA can provide reliable estimates of hearing sensitivity for tonal signals and speech sounds. In most applications of VRA, sounds are presented by loudspeakers in a sound field, so *ear-specific* information is not obtained. Assessment of an infant often is designed to rule out hearing loss that would be sufficient to affect the development of speech and language. Normal sound-field response levels of infants indicate sufficient hearing for this purpose despite the possibility of different HLs in the 2 ears. When ear-specific information is needed in this age group, the ABR is conducted under sleep deprived or sedated conditions.

Behavioral Observation Audiometry

Used as a screening device for infants <5 mo of age, **behavioral observation audiometry** is limited to unconditioned, reflexive responses to complex (not frequency-specific) test sounds such as warble tones, narrow band noise, speech, or music presented using calibrated signals from a loudspeaker. Response levels can vary widely within and among infants and usually do not provide a reliable estimate of sensitivity. The types of responses observed during this testing may include alterations in sucking behavior, initiation or cessation in crying, pupillary dilatation, and alterations in respiration.

Assessment of a child with suspected hearing loss is not complete until pure-tone hearing thresholds and SRTs (a reliable audiogram) have been obtained in each ear. Behavioral observation audiometry and VRA in sound-field testing give estimates of hearing responsivity in the *better-hearing ear* . When significant hearing loss is suspected in infants, electrophysiologic assessments must be conducted to permit early intervention.

Acoustic Immittance Testing

Acoustic immittance testing is a standard part of the clinical audiologic test battery and includes tympanometry, acoustic reflex threshold measurement, and acoustic reflex decay testing. It is a useful objective assessment technique that provides information about the status of the TM, middle ear and acoustic reflex arc. Tympanometry can be performed in a physician's office and is helpful in the diagnosis and management of OM with effusion, a common cause of mild to moderate hearing loss in young children.

Tympanometry

Tympanometry provides a graph (tympanogram) of the middle ear's ability to transmit sound energy (admittance or compliance) or impede sound energy (impedance) as a function of air pressure in the external ear canal. Because most immittance test instruments measure acoustic admittance, the term *admittance* is used here. The principles apply to whatever units of measurement are used.

A probe is inserted into the entrance of the external ear canal so that an airtight seal is obtained. A manometer in the probe varies air pressure, while a sound generator presents a tone, and a microphone measures the sound pressure level reflected back. The sound pressure measured in the ear canal relative to the known intensity of the probe signal is used to estimate the acoustic admittance of the ear canal and middle-ear system. Admittance can be expressed in a unit called a millimho (mmho) or as a volume of air (mL) with equivalent acoustic admittance. Additionally, an estimate can be made of the volume of air enclosed between the probe tip and TM. The acoustic admittance of this volume of air is deducted from the overall admittance measure to obtain a measure of the admittance of the middle-ear system alone. Estimating ear canal volume also has a diagnostic benefit, because an abnormally large value is consistent with the presence of an opening in the TM (perforation, pressure equalization tube, or surgical defect).

Once the admittance of the air mass in the external auditory canal has been eliminated, it is assumed that the remaining admittance measure accurately reflects the admittance of the entire middle-ear system. Its value is controlled largely by the dynamics of the TM. Abnormalities of the TM can dictate the shape of tympanograms, thus obscuring abnormalities medial to the TM. In addition, the frequency of the probe tone, the speed and direction of the air pressure change, and the air pressure at which the tympanogram is initiated can all influence the outcome. The effect of the probe tone frequency is well documented, and in young children (<4-6 mo) with small ear canals, use of a high frequency probe tone, either 678 or 1,000 Hz, is recommended.

When air pressure in the ear canal is equal to that in the middle ear, the middle-ear system is functioning optimally. That is, the pressure equalization function of the eustachian tube permits the middle ear to rest at atmospheric pressure, equivalent to the condition in the ear canal. Therefore the ear canal pressure at which there is the greatest flow of energy (admittance) should be a reasonable estimate of the air pressure in the middle-ear space. This pressure is determined by finding the maximum or **peak admittance** on the tympanogram and obtaining its value on the x -axis. The value on the y -axis at the tympanogram peak is an estimate of peak admittance based on admittance tympanometry (Table 655.8). This peak measure sometimes is referred to as **static acoustic admittance** , even though it is estimated from a dynamic measure. Normative values for peak admittance as a function of air pressure are well established.

Table 655.8

Norms for Peak (Static) Admittance Using a 226-Hz Probe Tone for Children and Adults

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AGE GROUP	ADMITTANCE (mL)	SPEED OF AIR PRESSURE SWEEP	
		≤50 daPa/sec*	**200 daPa/sec †**
Children (3-5 yr)	Lower limit	0.30	0.36
	Median	0.55	0.61
	Upper limit	0.90	1.06
Adults	Lower limit	0.56	0.27
	Median	0.85	0.72
	Upper limit	1.36	1.38

* Ear canal volume measurement based on admittance at lowest tail of tympanogram.

† Ear canal measurement based on admittance at lowest tail of tympanogram for children and at +200 daPa for adults.

daPa , decaPascals.

Adapted from Margolis RH, Shanks JE: Tympanometry: basic principles of clinical application. In Rintelman WS, editor: *Hearing assessment* , ed 2, Austin, 1991, PRODED, pp. 179–245.

Tympanometry in Otitis Media With Effusion

Children who have OM with effusion often have reduced peak admittance or high negative tympanometric peak pressures (see Fig. 658.5*C* in Chapter 658). However, in the diagnosis of effusion, the tympanometric measure with the greatest sensitivity and specificity is the shape of the tympanogram rather than its peak pressure or admittance. The tympanogram is classified based on shape and peak admittance location. The greater the stiffening of the TM and ME, the lower the peak. As negative pressure within the middle ear increases, the peak becomes more negatively displaced. The more rounded the peak (or, in an absent peak, a flat tympanogram), the higher is the probability that an effusion is present (see Fig. 658.5*B* in Chapter 658). The stage of OM may affect the tympanometric findings. An immobile TM/ME system based on significant effusion, as reflected in flat tympanogram, may evolve into findings of negative ME pressure and later positive pressure as the OM resolves, returning to a normal tympanogram.

Acoustic Reflex Threshold Test

The **acoustic reflex threshold test** also is part of the immittance test battery. With a properly functioning middle-ear system, admittance at the TM decreases due to the stiffening action of the middle ear muscles (stapedius and, to a lesser extent, tensor tympani). In healthy ears, the stapedial reflex occurs after exposure to loud sounds as a protective mechanism. Admittance instruments are designed to present reflex activating signals (pure tones of various frequencies or noise), either to the same ear or the contralateral ear, while measuring the concomitant changes in admittance. Very small admittance changes that are time locked to presentations of the signal are considered to be a result of middle-ear muscle reflexes. Admittance changes may be absent when the hearing loss is sufficient to prevent the signal from reaching the loudness level necessary to elicit the reflex or when a middle-ear condition affects HLs or introduces sufficient stiffening to obscure reading the reflex activity. The acoustic reflex test also is used in the assessment of SNHL and the integrity of the neurologic components of the reflex arc, including crossed and uncrossed activity of cranial nerves VII and VIII.

Auditory Brainstem Response

The auditory brainstem response (ABR) test is used to screen newborn hearing, confirm hearing loss in young children, obtain ear-specific information in young children, and test children who cannot, for whatever reason, cooperate with behavioral test methods. It also is important in the diagnosis of auditory dysfunction (i.e., estimation of hearing thresholds) and of disorders of the auditory nervous system. The ABR test is a far-field recording of minute electrical discharges from numerous neurons. The stimulus, therefore, must be able to cause synchronous discharge of the large numbers of neurons involved.

Stimuli with very rapid onset, such as clicks or tone bursts, must be used. Unfortunately, the rapid onset required to create a measurable ABR also causes energy to be spread in the frequency domain, reducing the frequency-specificity of the response.

The ABR result is not affected by sedation or general anesthesia. Infants and children from about 4 mo to 4 yr of age routinely are sedated to minimize electrical interference caused by muscle activity during testing. The ABR also can be performed in the operating room when a child is anesthetized for another procedure. Children younger than 4 mo of age might sleep for a long enough period of time after feeding to allow an ABR to be done.

The ABR is recorded as 5-7 waves. Waves I, III, and V can be obtained consistently in all age groups; waves II and IV appear less consistently. The latency of each wave (time of occurrence of the wave peak after stimulus onset) increases, and the amplitude decreases with reductions in stimulus intensity; latency also decreases with increasing age, with the earliest waves reaching mature latency values earlier in life than the later waves. Age-specific normative data have been obtained in several studies.

The ABR test has 2 major uses in a pediatric setting. As an audiometric test, it provides information on the ability of the peripheral auditory system to transmit information to the auditory nerve and beyond. It also is used in the differential diagnosis or monitoring of central nervous system pathology. For hearing threshold estimation, the goal is to find the minimum stimulus intensity that yields an observable ABR, generally relying on wave V, the most robust aspect of morphology. Plotting latency versus intensity for various waves also aids in the differential diagnosis of hearing impairment. A major advantage of auditory assessment using the ABR test is that ear-specific threshold estimates can be obtained on infants or patients who are difficult to test. ABR thresholds using click stimuli correlate best with behavioral hearing thresholds in the higher frequencies (1,000-4,000 Hz); responsivity in the low frequencies requires different stimuli (tone bursts/pips or filtered clicks) or the use of masking, neither of which isolates the low-frequency region of the cochlea in all cases, and this can affect interpretation.

The ABR test does not assess “hearing.” It reflects auditory neuronal electrical responses that can be correlated to behavioral hearing thresholds, but a normal ABR result only suggests that the auditory system, up to the level of the midbrain, is responsive to the stimulus used. Conversely, a failure to elicit an ABR indicates an impairment of the system's synchronous response but does not necessarily mean that there is no “hearing.” The behavioral response to sound sometimes is normal when no ABR can be elicited, such as in neurologic demyelinating disease.

Hearing losses that are sudden, progressive, or unilateral are indications for ABR testing. Although it is believed that the different waves of the ABR reflect activity in increasingly rostral levels of the auditory system, the neural generators of the response have not been precisely determined. Each ABR wave beyond the earliest waves probably is the result of neural firing at many levels of the system, and each level of the system probably contributes to several ABR waves. High-intensity click stimuli are used for the neurologic application. The morphology of the response and wave, interwave latencies, and interaural latency differences are examined in respect to age-appropriate forms. Delayed or missing waves in the ABR result often have diagnostic significance.

The ABR and other electrical responses are extremely complex and difficult to interpret. A number of factors, including instrumentation design and settings, environment, degree and configuration of hearing loss, and patients’ characteristics, can influence the quality of the recording. Therefore testing and interpretation of electrophysiologic activity as it possibly relates to hearing should be carried out by trained audiologists to avoid the risk that unreliable or erroneous conclusions will affect a patient's care.

Otoacoustic Emissions

During normal hearing, OAEs originate from the outer hair cells in the cochlea and are detected by sensitive amplifying processes. They travel from the cochlea through the middle ear to the external auditory canal, where they can be detected using miniature microphones. Transient evoked OAEs (TEOAEs) may be used to check the integrity of the cochlea. In the neonatal period, detection of OAEs can be accomplished during natural sleep, and TEOAEs can be used as screening tests in infants and children for hearing down to the 30 dB level of hearing loss. They are less time consuming and elaborate than ABRs, and may be used when behavioral tests cannot be accomplished. TEOAEs are reduced or absent owing to various dysfunctions in the middle and inner ears. They are absent in patients with >30 dB of hearing loss and are not used to determine the hearing threshold; rather, they provide a screen for whether hearing is present at >30-40 dB. CHL, such as OM or congenitally abnormal middle-ear structures, reduce the transfer of TEOAEs and may be incorrectly interpreted as a cochlear hearing disorder. If a hearing loss is suspected based on the absence of OAEs, the ears should be examined for the evidence of pathology, tympanometry should be conducted, and then ABR testing should be used for confirmation and identification of the type, degree, and laterality of hearing loss.

Treatment

With the use of universal hearing screening within the United States, the early diagnosis and treatment of children with hearing loss is common. Testing for hearing loss is possible even in very young children, and it should be done if parents suspect a problem. Any child with a known risk factor for hearing loss should be evaluated in the first 6 mo of life.

Once a hearing loss is identified, a full developmental and speech and language evaluation is needed. Counseling and involvement of parents are required in all stages of the evaluation and treatment or rehabilitation. A CHL often can be corrected through treatment of a middle-ear effusion (i.e., ear tube placement) or surgical correction of the abnormal sound-conducting mechanism. Dependent on the level of hearing loss, children with SNHL should be evaluated for possible hearing aid use by a pediatric audiologist. Current guidelines indicate that within 1 mo of diagnosis of SNHL, children should be fitted with **hearing aids** , and hearing aids may be fitted for children as young as 1 mo of age. Compelling evidence from the hearing screening program in Colorado shows that identification and amplification before age 6 mo makes a very significant difference in the speech and language abilities of affected children, compared with cases identified and amplified after the age of 6 mo. In these children, repeat audiologic testing is needed to reliably identify the degree of hearing loss and to fine-tune the use of hearing aids. Hearing aids remain the rehabilitative device of choice, in the context of an individually designed treatment plan, for children with mild, moderate, or moderately severe CHL, mixed HL, or SNHL. For children with severe or profound SNHL, a trial with hearing aids is needed to determine if this approach is sufficient for the development of language; other options may need to be explored if there are indications that speech and language are delayed with a hearing aid in this HL group. Importantly, efficacy of hearing aids depends on their consistent use. There is great variability in how often children wear their hearing aids. Though there is no specific recommendation regarding the minimal number of hours per day that the hearing aids should be worn, parents should be encouraged to have their child use hearing aids full-time in order to facilitate speech and language development.

When it is clear that hearing aids are not providing the auditory stimulation needed to support language development, the parents require counseling to consider alternative treatments. A **cochlear implant** may be necessary to facilitate intelligible oral communication (i.e., oralism). This approach requires years of intensive speech and language training and is dependent on providing the best possible auditory stimulation possible. This option is very attractive to parents with hearing because it is the most familiar form of communication to them. While there is a heavy emphasis in the medical world valuing the development of oral language (speech production), parents should also be provided with information about alternatives such as sign language, total communication, and cued speech. Each of these communication modalities has advantages and disadvantages. **Sign language** allows the child to develop a language system early and can support academic training. The consequence of this option is that the dominant hearing world does not interact easily with users of sign language and the child is likely to become part of the deaf community and may face significant challenges integrating into hearing society. Such possibilities as academic success and college/graduate school training are not excluded by the use of sign language, but a narrower set of venues may be available to accommodate the child's learning needs. While this option is acceptable to deaf parents already in the deaf culture, many hearing parents are uncomfortable with this path for their child. This option also requires that the parents become fluent in sign language.

Total communication is an educational philosophy in which both sign and oral language are encouraged. In theory, the two systems support and clarify information transfer and enhance academic progress. Depending on the particular school and/or teachers, one system may be emphasized over the other. **Cued speech** is an approach in which the development of oral language is supported by a system of hand gestures near the mouth and throat to disambiguate confusions that result from lip reading alone. This system can be highly successful in supporting spoken language, and requires that parents become fluent in the use of the cues. Other factors should be taken into account in making the choice of communication modality. Significant comorbidities, such as visual impairment or other developmental delays, may limit the ability of a child to derive benefit from some choices. Support for the parents in making this decision may require counseling from an audiologist, social worker, deaf educator, and/or psychologist. Organizations of parents of deaf children, such as the A.G. Bell Association and the John Tracy Clinic, can provide a wealth of support and information to parents in this process.

Infants and young children with profound congenital or prelingual onset of deafness have benefited from **multichannel cochlear implants** (Fig. 655.4). Cochlear implants are systems which combine internal (surgically implanted) and externally worn components. These implants consist of four main components: the externals, which include a microphone, a minicomputer sound (speech) processor, a transmitter; and the internal, an electrode array. These implants bypass injury to the organ of Corti and provide neural stimulation through the digitization of auditory stimuli into digital radiofrequency impulses. Specifically, sound is initially detected by the microphone and then is processed by the speech processor. The speech processor is programmed by an audiologist to implement (the manufacturer's) proprietary speech processing strategies that are highly sophisticated manipulations of the input signal. Signals from the speech processor are transmitted across the skin by an FM signal to the internal receiver, which converts these signals to electrical impulses. Finally, these electrical impulses are sent to the electrode array located in the cochlea, where electrical fields are created that act on the cochlear nerve. This is in contrast to the transmission of sound in a healthy ear, which involves the transmission of sound vibrations to the hair cells of the cochlea, the release of ions and neurotransmitters in the cochlea, and the transmission of neural impulses to the cochlear nerve and then the brain.

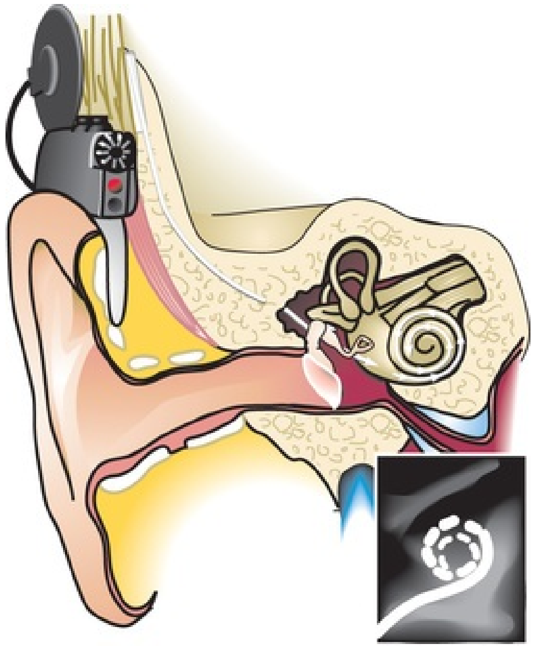

FIG. 655.4 All cochlear implants share key components, including a microphone, speech processor, and transmitter coil, shown in a behind-the-ear position in this diagram. The microphone and speech processor pick up environmental sounds and digitize them into coded signals. The signals are sent to the transmitter coil and relayed through the skin to the internal device imbedded in the skull. The internal device converts the code to electronic signals, which are transmitted to the electrode array wrapping around the cochlea. The inset shows the radiographic appearance of the stimulating electrode array. (Reproduced with permission from MED-EL Corporation, Innsbruck, Austria. From Smith RJH, Bale JF Jr, White KR: Sensorineural hearing loss in children. *Lancet* 365:879–890, 2005.)

Surgical implantation is done under general anesthesia and involves mastoidectomy and widening of the facial recess. The approach to the cochlea is through the facial recess. After fastening the internal stimulator package in the mastoid process, the cochlea must be opened in order to insert the electrode array, which is most commonly done through an opening made in the round window. Care is taken to avoid contamination of the cochlear fluids by bone dust or blood. After the cochlea is closed, generally with fascia, the wound is closed. An audiologist performs testing in the operating room to verify the functional integrity of the implanted device. These electrophysiologic responses from the VIII nerve are critical to determining a starting point for programming the external device after the wound has healed. A plain x-ray is often performed in the operating room as well to document placement of the array in the scala tympani.

The healing process following surgery is approximately 3-4 wk for a child.

During this time, the child cannot hear. When the child is brought in for the first stimulation using the external equipment, programs are developed that provide first access to sound. The methods to create the programs entail a combination of electrophysiologic measures and behavioral testing that is similar to the pediatric audiologic assessments described above. The initial programs are a starting point, followed by modifications and enhancements that are based on the parents’ and audiologist's observations of changing auditory awareness and vocalization.

When parents elect to pursue cochlear implantation for their child, a long-term commitment is necessary to ongoing engagement with a team of rehabilitation specialists. Audiologic management entails consistent monitoring of the child's response to the implant and impact on emerging language skills. Speech and language therapy is necessary to stimulate language and to teach parents skills to support speech development. The child should be in a preschool setting in which speech, language, social, and academic precursor skills are fostered. For some parents, this engagement is very challenging, not only in terms of time required but also in terms of the emotional consequences of attempting to minimize the impact of hearing loss on their child's future; support for the parents is often needed in this process from the team.

A serious possible complication of cochlear implantation is pneumococcal meningitis. All children receiving a cochlear implant must be vaccinated with the pneumococcal polyvalent vaccine PCV13 (Table 655.9), and rates of pneumococcal meningitis have declined considerably since implementation of the vaccine.

Table 655.9

Recommended Pneumococcal Vaccination Schedule for Persons With Cochlear Implants

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AGE AT FIRST PCV13 DOSE (mo)[*]	PCV12 PRIMARY SERIES	PCV13 ADDITIONAL DOSE	PPV23 DOSE
2-6	3 doses, 2 mo apart [†]	1 dose at 12-15 mo of age [‡]	Indicated at ≥24 mo of age [§]
7-11	2 doses, 2 mo apart [†]	1 dose at 12-15 mo of age [‡]	Indicated at ≥24 mo of age [§]
12-23	2 doses, 2 mo apart [¶]	Not indicated	Indicated at ≥24 mo of age [§]
24-59	2 doses, 2 mo apart [¶]	Not indicated	Indicated [§]
≥60	Not indicated [|]	Not indicated [|]	Indicated

[*] A schedule with a reduced number of total 13-valent pneumococcal conjugate vaccine (PCV13) doses is indicated if children start late or are incompletely vaccinated. Children with a lapse in vaccination should be vaccinated according to the catch-up schedule (see Chapter 209).

[†] For children vaccinated at younger than age 1 yr, minimum interval between doses is 4 wk.

[‡] The additional dose should be administered 8 wk or more after the primary series has been completed.

[§] Children younger than age 5 yr should complete the PCV13 series first; 23-valent pneumococcal polysaccharide vaccine (PPV23) should be administered to children 24 mo of age or older 8 wk or more after the last dose of PCV13 (see Chapter 182). (Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR Recomm Rep* 49[RR-9]:1–35, 2000, and Licensure of a 13-valent pneumococcal conjugate vaccine [PCV13] and recommendations for use among children—Advisory Committee on Immunization Practices [ACIP]. *MMWR Morb Mortal Wkly Rep* 59(9):258–261, 2010.)

[¶] Minimum interval between doses is 8 wk.

[|] PCV13 is not recommended generally for children age 5 yr or older.

PCV , Pneumococcal conjugate vaccine; *PPV* , pneumococcal polysaccharide vaccine.

From Centers for Disease Control and Prevention Advisory Committee on Immunization Practices: Pneumococcal vaccination for cochlear implant candidates and recipients: Updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 52(31):739–740, 2003.

The Food and Drug Administration (FDA) has approved cochlear implantation in patients over 12 mo of age with severe to profound bilateral hearing loss not benefitting from hearing aids; however, off-label use of cochlear implants has demonstrated efficacy in those younger than 12 mo and in children with residual hearing. Cochlear implantation before age 2 yr improves hearing and speech, enabling more than 90% of children to be in mainstream education. Most develop age-appropriate auditory perception and oral language skills. There is increasing evidence to support expansion of the candidacy for cochlear implantation in children to be based on outcomes of advanced testing using speech stimuli, especially in noise. To date, implantation of children with devices that combine acoustic input (similar to a hearing aid) with electric stimulation from a cochlear implant has not been approved by the FDA. These devices, called electroacoustic cochlear implants, or hybrids, may offer hope for children using hearing aids but struggling with noise in the classroom or social contexts.

Management of **idiopathic sudden SNHL** is controversial and has included oral prednisone, intratympanic (also called transtympanic) dexamethasone perfusion, or a combination of both; the latter combination may be the most useful.

Genetic Counseling

Families of children with the diagnosis of SNHL or a syndrome associated with SNHL and/or CHL should be referred for genetic counseling. This will give the parents an idea of the likelihood of similar diagnoses in future pregnancies, and the geneticist can assist in the evaluation and testing of the patient to establish a diagnosis.

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CHAPTER 656

Congenital Malformations of the Ear

Joseph Haddad Jr, Sonam N. Dodhia

The external and middle ears, derived from the first and second branchial arches and grooves, grow throughout puberty, but the inner ear, which develops from the otocyst, reaches adult size and shape by midfetal development. The ossicles are derived from the first and second arches (malleus and incus), and the stapes arises from the second arch and the otic capsule. The malleus and incus achieve adult size and shape by the 15th wk of gestation, and the stapes achieves adult size and shape by the 18th wk of gestation. Although the pinna, ear canal, and tympanic membrane (TM) continue to grow after birth, congenital abnormalities of these structures develop during the first half of gestation. Malformed external and middle ears may be associated with serious renal anomalies, mandibulofacial dysostosis, hemifacial microsomia, and other craniofacial malformations. Facial nerve abnormalities may be associated with any of the congenital abnormalities of the ear and temporal bone. Malformations of the external and middle ears also may be associated with abnormalities of the inner ear and both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL).

Congenital ear problems may be minor and mainly cosmetic, or major, affecting both appearance and function. Any child born with an abnormality of the pinna, external auditory canal, or TM should have a complete audiologic evaluation in the neonatal period. Imaging studies are necessary for evaluation and treatment; in the patient with other craniofacial abnormalities, a team approach with other specialists can assist in guiding therapy.

Pinna Malformations

Severe malformations of the external ear are rare, but minor deformities are common. Isolated abnormalities of the external ear occur in approximately 1% of children (Fig. 656.1). A **pit-like** depression just in front of the helix and above the tragus may represent a cyst or an epidermis-lined fistulous tract (Fig. 656.2). These are common, with an incidence of approximately 8 in 1,000 children, and may be unilateral or bilateral and familial. The pits require surgical removal only if there is recurrent infection. Accessory **skin tags** , with an incidence of 1-2/1,000 live births, can be removed for cosmetic reasons by simple ligation if they are attached by a narrow pedicle (see Fig. 656.1). If the pedicle is broad based or contains cartilage, the defect should be corrected surgically. An unusually prominent or "lop" ear results from lack of bending of the cartilage that creates the antihelix. It may be improved cosmetically in the neonatal period by applying a firm framework (sometimes soldering wire is used) attached by Steri-Strips to the pinna and worn continuously for weeks to months. Otoplasty for cosmetic correction can be considered in children older than 5 yr of age, when the pinna has reached approximately 80% of its adult size.

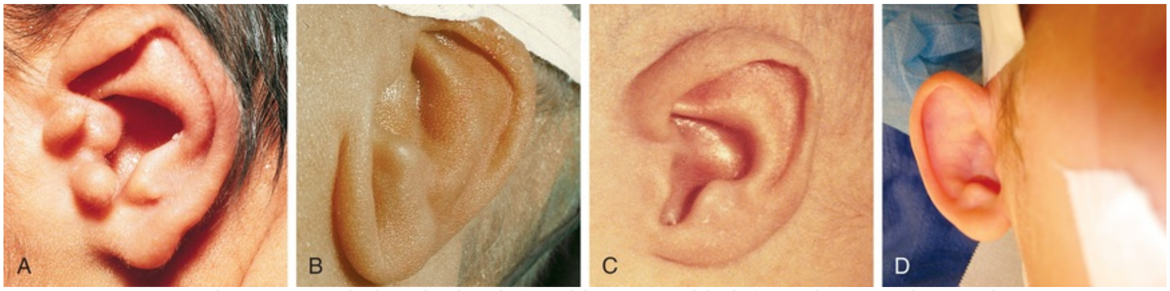

FIG. 656.1 Minor congenital auricular deformities. A, In this infant, the superior portion of the helix is folded over, obscuring the triangular fossa; the antihelix is sharply angulated; and there are three preauricular skin tags. B, This neonate with orofaciodigital and Turner syndromes has a simple helix and a redundant folded lobule. The ear is low set and posteriorly rotated, and the antitragus is anteriorly displaced. C, This infant with Rubinstein-Taybi syndrome has an exaggerated elongated intertragal notch. D, Prominent ear in an otherwise normal child. The auricular cartilage is abnormally contoured, making the ear protrude forward. (C, Courtesy Dr. Michael E. Sherlock, Lutherville, Maryland). (From Zitelli BJ, McIntire SC, Nowalk AJ, editors: *Zitelli and Davis' atlas of pediatric physical diagnosis* , ed 7, Philadelphia, 2018, Elsevier, fig. 24.17, p. 875.)

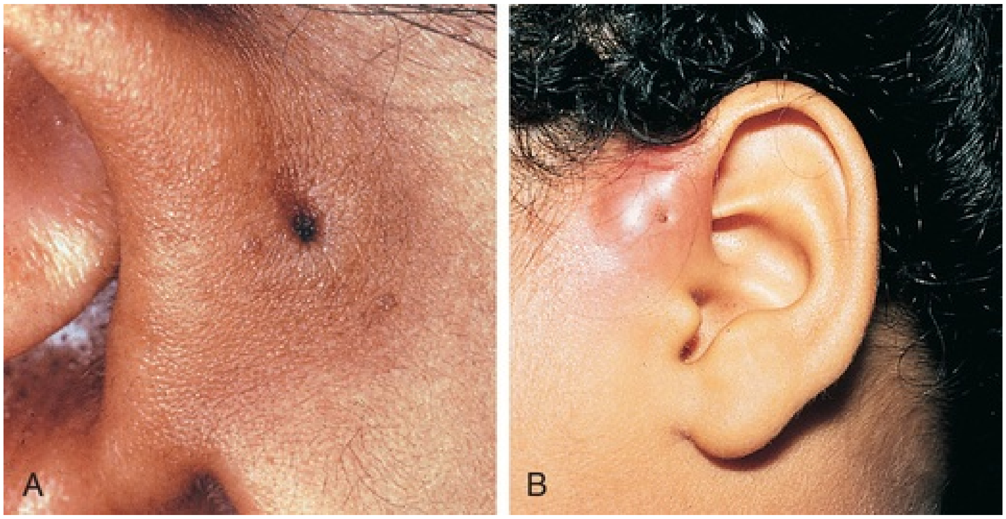

FIG. 656.2 **Preauricular sinuses. A, These congenital remnants are located anterior to the pinna and have an overlying surface dimple. B, In this child, the sinus has become infected, forming an abscess. (A, Courtesy Michael Hawke, MD.) (From Zitelli BJ, McIntire SC, Nowalk AJ, editors: *Zitelli and Davis' atlas of pediatric physical diagnosis* , ed 7, Philadelphia, 2018, Elsevier, fig. 24.18, p. 876.)**

The term **microtia** may indicate subtle abnormalities of the size, shape, and location of the pinna and ear canal, or major abnormalities with only small nubbins of skin and cartilage and the absence of the ear canal opening; **anotia** indicates complete absence of the pinna and ear canal (Fig. 656.3). Microtia can have a genetic or environmental predisposition. Several hereditary forms of microtia have been identified that exhibit either autosomal dominant or recessive mendelian inheritance. In addition, some forms due to chromosomal aberrations have been reported. Most of the responsible genes that have been identified are homeobox genes, which are involved in the development of pharyngeal arches. Microtic ears often are more anterior and inferior in placement than normal auricles, and the location and function of the facial nerve may be abnormal. Surgery to correct microtia is considered for both cosmetic and functional reasons; children who have some pinna can wear regular glasses, a hearing aid, and earrings, and feel more normal in appearance. If the microtia is severe, some patients may opt for creation and attachment of a prosthetic ear, which cosmetically closely resembles a real ear. Surgery to correct severe microtia may involve a multistage procedure, including carving and transplantation of autogenous cartilage rib grafts and local soft tissue flaps. Cosmetic reconstruction of the auricle usually is performed between 5 and 7 yr of age and is performed before canal atresia repair in children deemed appropriate for this surgery.

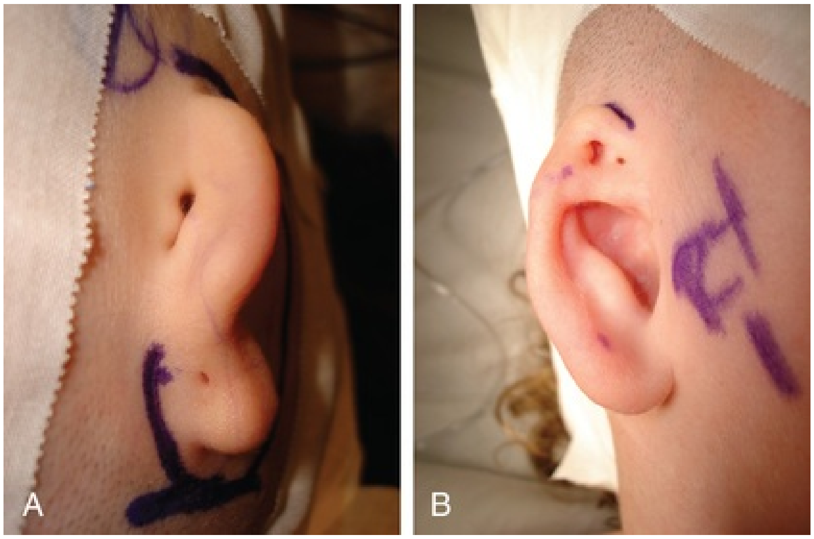

FIG. 656.3 **A,** Grade 3 microtia and congenital aural atresia of the right external ear. In this otherwise normal child, the pinna failed to develop properly and the external canal was atretic. Audiometric testing revealed a 60-dB hearing loss. **B,** Grade 2 microtia. Note deficiency of superior portion of auricle. Such isolated deformities stem from abnormal development of the first and second branchial arches. (From Zitelli BJ, McIntire SC, Nowalk AJ, editors: *Zitelli and Davis' atlas of pediatric physical diagnosis* , ed 7, Philadelphia, 2018, Elsevier, fig. 24.16, p. 875.)

Congenital Stenosis or Atresia of the External Auditory Canal

Stenosis or atresia of the ear canal often occurs in association with malformation of the auricle and middle ear. Malformations can occur in isolation or as part of a genetic syndrome. For example, the ear canal is narrow in trisomy 21, and external canal stenosis or atresia is common in branchiooculofacial syndrome, leading to CHL. Audiometric evaluation of these children should be undertaken as early in life as possible. Most children with significant CHL secondary to bilateral atresia wear bone conduction hearing aids for the 1st several years of life. Diagnosis, evaluation, and surgical planning often are aided by CT, and sometimes MRI, of the temporal bone. Mild cases of ear canal stenosis do not require surgical enlargement unless the patient develops chronic external otitis or severe cerumen impaction that affects hearing.

Reconstructive ear canal and middle-ear surgery for atresia usually is considered for children older than 5 yr of age who have bilateral deformities resulting in a significant CHL. The aim of reconstructive surgery is to improve hearing to a point where the child may not need a hearing aid or to provide an ear canal and pinna so that the child can derive improved benefit from an air-conduction hearing aid. Hearing results for atresiaplasty range from fair to excellent. CT evidence of an adequate middle-ear cleft, ossicles, and mastoid is required to perform the surgery; the position of the facial nerve, which often is in an abnormal location in these children, also must be considered (Fig. 656.4). The use of bone-anchored hearing aids is a safe, reliable, and low-risk alternative to atresiaplasty and hearing results are generally excellent. Bone-anchored hearing aids may also be useful for rehabilitation of nonoptimal atresiaplasty hearing results. These devices are approved by the US Food and Drug Administration for surgical placement in children age 5 yr and older; prior to age 5 yr, they can be worn with a soft band around the head. Disadvantages include the fact that cosmesis is not very good (a bone-anchored hearing aid has a visible titanium abutment and snap-on hearing aid) and frequent wound care is required. Middle ear implants are effective alternatives for those who cannot tolerate foreign bodies in the ear for medical reasons or rely on good perception of high-frequency sounds.

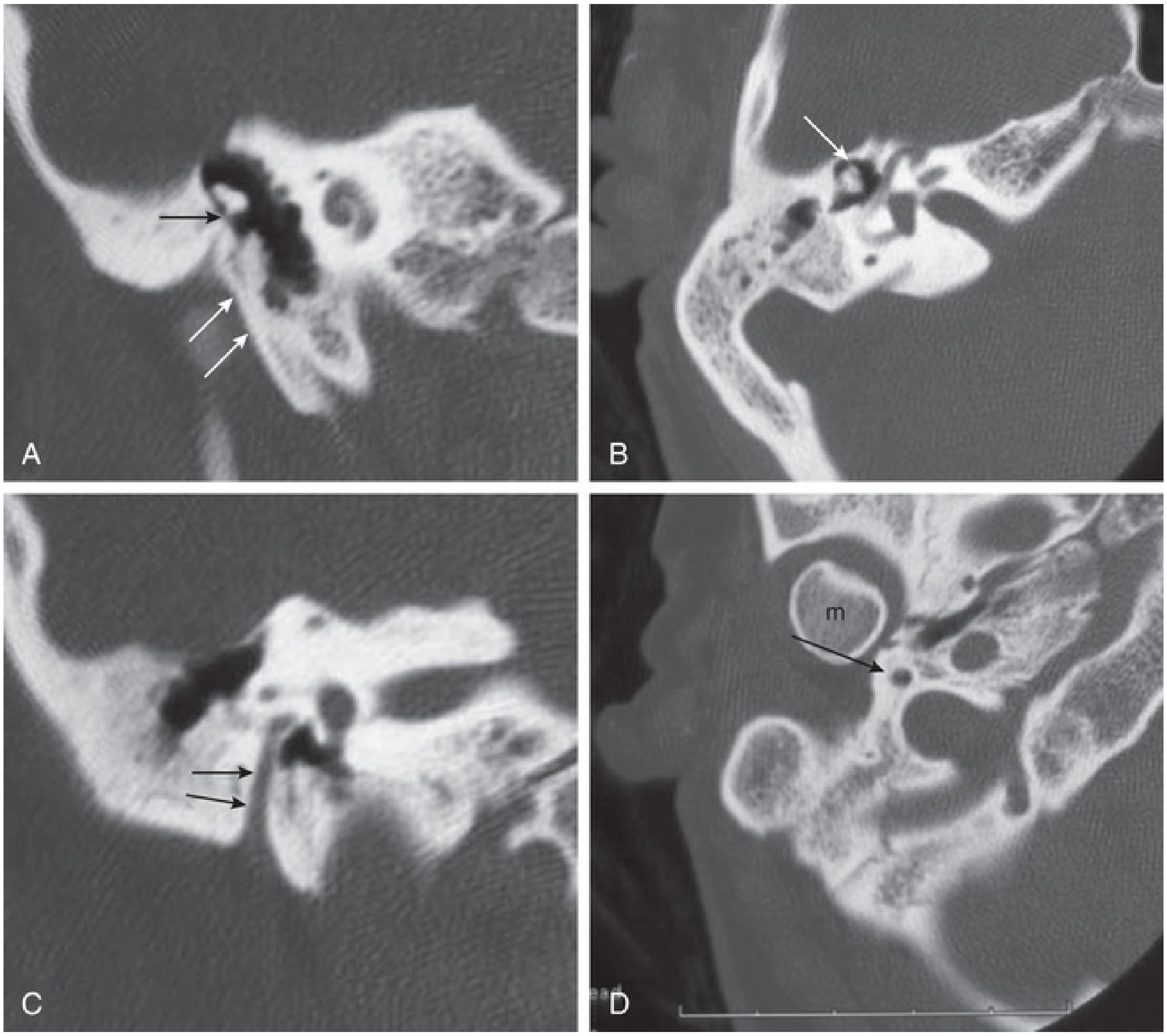

FIG. 656.4 External auditory canal atresia on CT scans. A, Coronal scan of right ear shows absent external auditory canal with thick bony atresia plate *(white arrows).* Malleus neck is rotated and fused to superior portion of atresia plate *(black arrow).* B, Axial scan through attic shows fused ossicular mass *(arrow).* C, Coronal scan more posterior to A shows mastoid segment of facial nerve canal positioned more anteriorly than normal *(arrows).* D, Axial scan more inferior to B shows anterior-posterior mastoid segment of the facial nerve en face *(arrow).* Note abnormally close relationship to mandibular condoyle. (From Faerber EN, Booth TN, Swartz JD: Temporal bone and ear. In Slovis TL editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, fig. 44.7, p. 584.)

Congenital Middle-Ear Malformations

Children may have congenital abnormalities of the middle ear as an isolated defect or in association with other abnormalities of the temporal bone, especially the ear canal and pinna, or as part of a syndrome. Affected children usually have CHL but may have mixed CHL and SNHL. Most malformations involve the ossicles, with the incus most commonly affected. Other less-common abnormalities of the middle ear include persistent stapedial artery, high-riding jugular bulb, and abnormalities of the shape and volume of the aerated portion of the middle ear and mastoid; all present problems for a surgeon. Depending on the type of abnormality and the presence of other anomalies, surgery may be considered to improve hearing.

Congenital Inner Ear Malformations

Congenital inner ear malformations have been identified and classified as a result of improvements in imaging modalities, especially CT and MRI. As many as 20% of children with SNHL may have anatomic abnormalities identified on CT or MRI. Congenital malformations of the inner ear usually are associated with SNHL of various degrees, from mild to profound. These malformations are most commonly found in infants and may occur as isolated anomalies or in association with other syndromes, genetic abnormalities, or structural abnormalities of the head and neck. High-resolution temporal bone CT can identify enlarged vestibular aqueducts and cochlear nerve canal stenosis in association with SNHL. Although no therapy exists for this condition, it may be associated with progressive SNHL in some children; therefore diagnosis may have some prognostic value.

Congenital perilymphatic fistula of the oval or round window membrane may present as a rapid-onset, fluctuating, or progressive SNHL with or without vertigo, and often is associated with congenital inner ear abnormalities. Middle-ear exploration may be required to confirm this diagnosis, because no reliable nonoperative diagnostic test exists. It may be necessary to repair a perilymphatic fistula to prevent possible spread of infection from the middle ear to the labyrinth or meninges, to stabilize hearing loss, and to improve vertigo when present.

Congenital Cholesteatoma

A congenital cholesteatoma (approximately 2–5% of all cholesteatomas) is a nonneoplastic, destructive, cystic lesion that usually appears as a white, round, cyst-like structure medial to an intact TM. Cysts are seen most commonly in boys and in the anterior-superior portion of the middle ear, although they can present in other locations and within the TM or in the skin of the ear canal. They can be classified as "open," meaning in direct continuity with mucosa of the middle ear, or "closed." Affected children often have no prior history of otitis media. One theory for the pathogenesis is that the cyst derives from a congenital rest of epithelial tissue that persists beyond 33 wk of gestation, when it ordinarily would disappear. Other theories include squamous metaplasia of the middle ear, entrance of squamous epithelium through a nonintact eardrum into the middle ear, ectodermal implants between the first and second branchial arch remnants, and residual amniotic fluid squamous debris. Congenital or acquired cholesteatoma should be suspected when deep retraction pockets, keratin debris, chronic drainage, aural granulation tissue, or a mass behind or involving the TM is present. Congenital cholesteatoma is often asymptomatic whereas acquired cholesteatoma commonly presents with otorrhea. Besides acting as a benign tumor causing local bone destruction, the keratinaceous debris of a cholesteatoma serves as a culture medium, leading to chronic otitis media. Complications include ossicular erosion with hearing loss, bone erosion into the inner ear with dizziness, or exposure of the dura, with consequent meningitis or a brain abscess. Evaluation includes a CT scan (Fig. 656.5) to detect bone erosion, and audiometry to assess air and bone conduction and speech reception and discrimination. Treatment includes cholesteatoma removal, repair of damaged small middle ear bones, and mastoidectomy in 50% of congenital and >90% of acquired cholesteatoma cases. A second-look procedure 6-9 mo after primary surgery is usually recommended to detect and remove small amounts of residual disease prior to more extensive recurrence or development of complications. Higher initial stage of disease, erosion of ossicles, cholesteatoma abutting or enveloping the incus or stapes, and need for removal of the ossicles are associated with increased likelihood of residual cholesteatoma, which occurs in ~10% of congenital and ~25% of acquired cases. More extensive disease at initial surgery is associated with poorer hearing outcomes. Children with significant inflammation or extensive scarring may require a 2-stage procedure with initial removal of the cholesteatoma and subsequent repair of damaged middle ear structures.

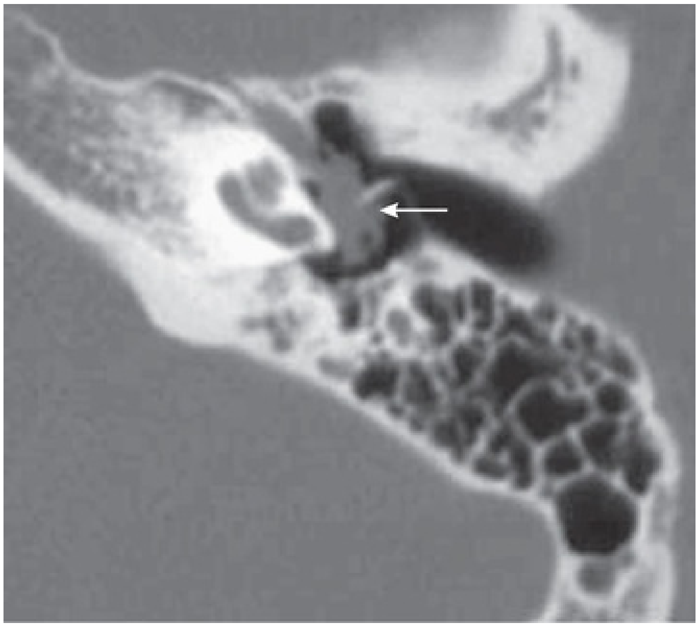

FIG. 656.5 Congenital cholesteatoma. Axial CT of left ear shows soft tissue mass *(arrow)* in the middle ear. This mass was noted otoscopically behind an intact membrane. (From Faerber EN, Booth TN, Swartz JD. Temporal bone and ear. In Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, fig. 44.31, p. 598.)

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CHAPTER 657

External Otitis (Otitis Externa)

Joseph Haddad Jr, Sonam N. Dodhia

In an infant, the outer two thirds of the ear canal is cartilaginous and the inner one third is bony. In an older child and adult, the outer one third is cartilaginous and the inner two thirds is bony. The epithelium is thinner in the bony portion than in the cartilaginous portion, there is no subcutaneous tissue, and epithelium is tightly applied to the underlying periosteum; hair follicles, sebaceous glands, and apocrine glands are scarce or absent. The skin in the cartilaginous area has well-developed dermis and subcutaneous tissue and contains hair follicles, sebaceous glands, and apocrine glands. The highly viscid secretions of the sebaceous glands and the watery, pigmented secretions of the apocrine glands in the outer portion of the canal combine with exfoliated surface cells of the skin to form **cerumen** , a protective, waxy, water-repellent coating.

The normal flora of the external canal consists mainly of aerobic bacteria and includes coagulase-negative staphylococci (see Chapter 208.3), *Corynebacterium* (diphtheroids; see Chapter 214), *Micrococcus* , and occasionally *Staphylococcus aureus* (see Chapter 208.1), viridans streptococci (see Chapter 212), and *Pseudomonas aeruginosa* (see Chapter 232.1). **Excessive wetness** (swimming, bathing, increased environmental humidity), **dryness** (dry canal skin and lack of cerumen), the presence of other skin pathologic conditions (previous infection, eczema, or other forms of dermatitis), and trauma (due to digital or foreign body, use of cotton-tipped swabs) make the skin of the canal vulnerable to infection by the normal flora or exogenous bacteria, and predispose to colonization with gram-negative bacteria.

Etiology

External otitis (**swimmer's ear** , although it can occur without swimming) is caused most commonly by *P. aeruginosa* (up to 60%), but *S. aureus* , *Enterobacter aerogenes* , *Proteus mirabilis* , *Klebsiella pneumoniae* , streptococci, coagulase-negative staphylococci, diphtheroids, and fungi such as *Candida* and *Aspergillus* also may be isolated. External otitis results from chronic irritation and maceration from excessive moisture in the canal. The loss of protective cerumen may play a role, as may trauma, but cerumen impaction with trapping of water also can cause infection. Inflammation of the ear canal due to herpesvirus, varicella-zoster virus, other skin exanthems, and eczema also may predispose to external otitis.

Clinical Manifestations

The predominant symptom is acute rapid onset (typically within 48 hr) of ear pain (otalgia), often severe, accentuated by manipulation of the pinna or by pressure on the tragus and by jaw motion. The severity of the pain and tenderness (tragus or pinna, or both) may be disproportionate to the degree of inflammation, because the skin of the external ear canal is tightly adhered to the underlying perichondrium and periosteum. Itching often is a precursor of pain and usually is characteristic of chronic inflammation of the canal or resolving acute otitis externa. Conductive hearing loss (CHL) may result from edema of the skin and tympanic membrane (TM), serous or purulent secretions, or the canal skin thickening associated with chronic external otitis.

Edema of the ear canal, erythema, and thick, clumpy otorrhea are prominent signs of the acute disease. The cerumen usually is white and soft in consistency, as opposed to its usual yellow color and firmer consistency (Fig. 657.1). The canal often is so tender and swollen that the entire ear canal and TM cannot be adequately visualized, and complete otoscopic examination may be delayed until the acute swelling subsides. If the TM can be visualized, it may appear either normal or opaque. TM mobility may be normal or, if the TM is thickened, mobility may be reduced in response to positive and negative pressure.

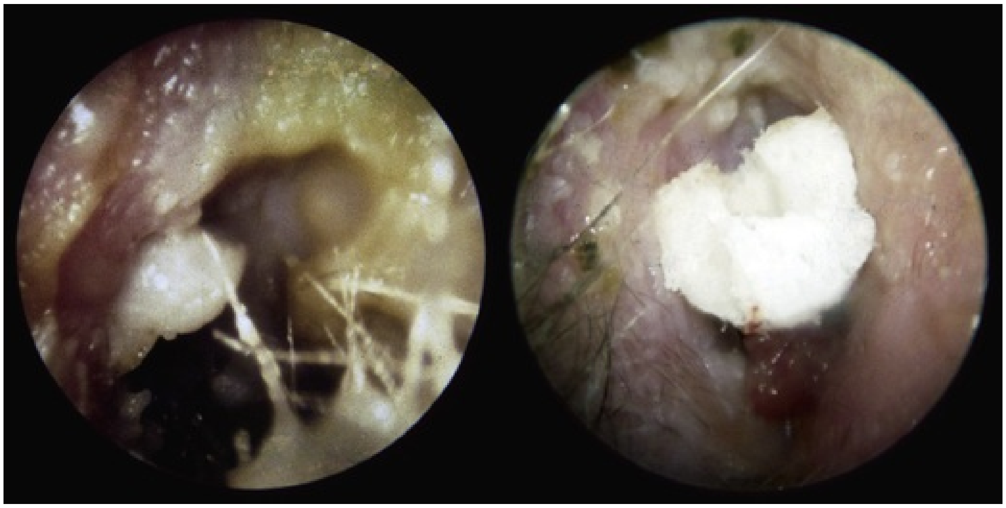

FIG. 657.1 **Acute otitis externa. Erythema, edema, and copious purulent debris are seen in the *left image* . In some cases, an edematous canal with granulation tissue *(right image)* necessitates the placement of an ear wick to assist topical drug delivery in the acute setting. (Courtesy of Dr. John W. House, Los Angeles, CA.)**

Other physical findings may include palpable and tender lymph nodes in the periauricular region, and erythema and swelling of the pinna and periauricular skin. Rarely, facial paralysis, other cranial nerve abnormalities, vertigo, and/or sensorineural hearing loss are present. If these occur, **necrotizing (malignant) otitis externa** , an invasive infection of the temporal bone and skull base, is probable. Fortunately, this disease is rare in children and is seen only in association with immunocompromise or severe malnourishment. In adults, it is associated with diabetes mellitus.

Diagnosis

Diffuse external otitis may be confused with **furunculosis** , **otitis media (OM)** , and **mastoiditis** (Table 657.1). Furuncles occur in the lateral hair-bearing part of the ear canal; furunculosis usually causes a localized swelling of the canal limited to one quadrant, whereas external otitis is associated with concentric swelling and involves the entire ear canal. In OM, the TM may be perforated, severely retracted, or bulging and immobile; hearing usually is impaired. If the middle ear is draining through a perforated TM or tympanostomy tube, secondary external otitis may occur; if the TM is not visible owing to drainage or ear canal swelling, it may be difficult to distinguish acute OM with drainage from an acute external otitis. Pain on manipulation of the auricle and significant lymphadenitis are not common features of OM, and these findings assist in the differential diagnosis. In some patients with external otitis, the periauricular edema is so extensive that the auricle is pushed forward, creating a condition that may be confused with acute mastoiditis and a subperiosteal abscess. In mastoiditis, the postauricular fold is obliterated, whereas in external otitis, the fold is usually better preserved. In acute mastoiditis, a history of OM and hearing loss is usual; tenderness is noted over the mastoid and not on movement of the auricle; and otoscopic examination may show sagging of the posterior canal wall.

Table 657.1

Differential Diagnosis of Painful External Ear and Auditory Canal Disorders

DISORDER	CLINICAL FEATURES
Acute otitis externa	Diffuse redness, swelling, and pain of the canal with greenish to whitish exudate; often very tender pinna
Malignant otitis externa	Rapidly progressive, severe swelling and redness of pinna: pinna may be laterally displaced
Dermatitis	
Eczema	History of atopy, presence of lesions elsewhere; lesions are scaly, red, pruritic, and weeping
Contact	History of cosmetic use or irritant exposure; lesions are scaly, red, pruritic, and weeping
Seborrhea	Scaly, red, papular dermatitis; scalp may have thick, yellow scales
Psoriasis	History or presence of psoriasis elsewhere; erythematous papules that coalesce into thick, white plaques
Cellulitis	Diffuse redness, tenderness, and swelling of the pinna
Furuncles	Red, tender papules in areas with hair follicles (distal third of the ear canal)
Infected periauricular cyst	Discrete, palpable lesions; history of previous swelling at same site; cellulitis may develop, obscuring cystic structure
Insect bites	History of exposure; lesions are red, tender papules
Herpes zoster	Painful, vesicular lesions in the ear canal and tympanic membrane in the distribution of cranial nerves V and VII
Perichondritis	Inflammation of the cartilage, usually secondary to cellulitis
Tumors	Palpable mass, destruction of surrounding structures
Foreign body	Foreign body may cause secondary trauma to the ear canal or become a nidus for an infection of the ear canal
Trauma	Bruising and swelling of external ear; there may be signs of basilar skull fracture (cerebrospinal fluid otorrhea, hemotympanum)

From Kliegman RM, Lye PS, Bordini BJ, et al, editors: *Nelson pediatric symptom-based diagnosis* , Philadelphia, 2018, Elsevier, table 4.1, p. 62.

Referred otalgia may come from disease in the paranasal sinuses, teeth, pharynx, parotid gland, neck and thyroid, and cranial nerves (trigeminal neuralgia; herpes simplex virus, varicella-zoster virus; Table 654.1).

Treatment

Topical otic preparations containing acetic acid with or without hydrocortisone, or neomycin (active against Gram-positive organisms and some Gram-negative organisms, notably *Proteus* spp.), polymyxin (active against Gram-negative bacilli, notably *Pseudomonas* spp.), or a quinolone (ciprofloxacin), with or without hydrocortisone, are all highly effective in treating most forms of acute external otitis. A non-ototoxic (quinolone) antibiotic should be chosen in the setting of known TM perforation or tympanostomy tube. If canal edema is marked, the patient may need referral to a specialist for cleaning and possible wick placement. An otic antibiotic and corticosteroid eardrop is often recommended. A wick can be inserted into the ear canal and topical antibiotics applied to the wick 3 times a day for 24-48 hr. The wick can be removed after 2-3 days, at which time the edema of the ear canal usually is markedly improved, and the ear canal and TM are better seen. Topical antibiotics are then continued by direct instillation. When the pain is severe, oral analgesics (e.g., ibuprofen, acetaminophen) may be necessary for a few days.

Someone other than the patient should place the drops in the ear canal while the patient is recumbent with the affected ear facing up. The drops should fill the canal, and the patient should remain in place for 3-5 min. Moving the ear to and fro, gently, may enhance the drops to fill the ear canal. Patients should respond to initial therapeutics in 48-72 hr. Failure to improve in this time frame should prompt assessment of drug delivery and adherence to therapy, consideration for change in therapy, and consideration of alternate diagnoses. Careful evaluation for underlying conditions should also be undertaken in patients with severe or recurrent otitis externa. Figure 657.2 outlines an approach to managing acute external otitis.

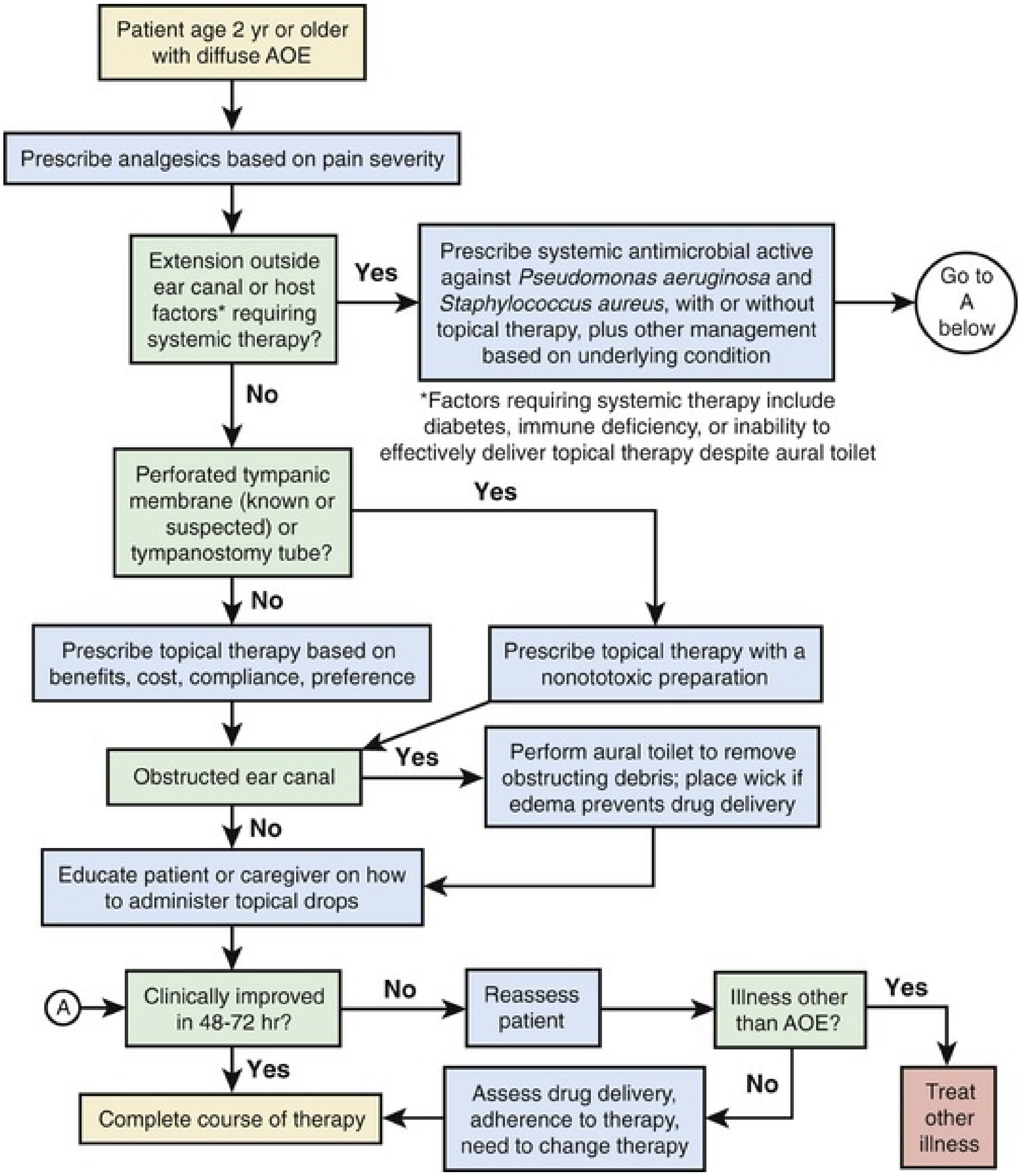
Patient age 2 yr or older with diffuse AOE
Prescribe analgesics based on pain severity
Extension outside ear canal or host factors* requiring systemic therapy?
Yes
Prescribe systemic antimicrobial active against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, with or without topical therapy, plus other management based on underlying condition
Go to A below
No
*Factors requiring systemic therapy include diabetes, immune deficiency, or inability to effectively deliver topical therapy despite aural toilet
Perforated tympanic membrane (known or suspected) or tympanostomy tube?
Yes
No
Prescribe topical therapy based on benefits, cost, compliance, preference
Prescribe topical therapy with a nonototoxic preparation
Obstructed ear canal
Yes
Perform aural toilet to remove obstructing debris; place wick if edema prevents drug delivery
No
Educate patient or caregiver on how to administer topical drops
A
Clinically improved in 48-72 hr?
No
Reassess patient
Illness other than AOE?
Yes
Treat other illness
Yes
Complete course of therapy
No
Assess drug delivery, adherence to therapy, need to change therapy

FIG. 657.2 **Flow chart for managing acute otitis externa *(AOE)* . (From Rosenfeld RM, Brown L, Cannon CR, et al.: Clinical practice guideline: acute otitis externa. *Otolaryngol Head Neck Surg* 134:S4–S23, 2006. Copyright 2006 American Academy of Otolaryngology—Head and Neck Surgery Foundation, Inc.)**

As the inflammatory process subsides, cleaning the canal with a suction or cotton-tipped applicator to remove the debris enhances the effectiveness of the topical medications. In subacute and chronic infections, periodic cleansing of the canal is essential. In severe, acute external otitis associated with fever and lymphadenitis, oral or parenteral antibiotics may be indicated; an ear canal culture should be done, and empirical antibiotic treatment can then be modified if necessary, based on susceptibility of the organism cultured. A fungal infection of the external auditory canal, or **otomycosis** , is characterized by fluffy white debris, sometimes with black spores seen; treatment includes cleaning and application of antifungal solutions such as clotrimazole or nystatin; other antifungal agents include m-cresyl acetate 25%, gentian violet 2%, and thimerosal 1 : 1,000.

Necrotizing otitis externa , commonly caused by *P. aeruginosa* (see Chapter 232.1), requires immediate culture, intravenous antibiotics, and imaging studies to evaluate the extent of the disease. Surgical intervention to obtain cultures or debride devitalized tissue may be necessary.

Prevention

Preventing external otitis may be necessary for individuals susceptible to recurrences, especially children who swim. The most effective prophylaxis is instillation of dilute alcohol or acetic acid (2%) immediately after swimming or bathing. During an acute episode of otitis externa, patients should not swim and the ears should be protected from excessive water during bathing. A hair dryer may be used to clear moisture from the ear after swimming as a method of prevention. Cotton (or other material) tipped swabs may cause trauma in an attempt to clean a normal ear and should be avoided.

Other Diseases of the External Ear

Furunculosis

Furunculosis, caused by *S. aureus* , affects only the hair-containing outer third of the ear canal, and typically occurs at the inferior entrance to the meatus. Mild forms are treated with oral antibiotics active against *S. aureus.* If an abscess develops, incision and drainage may be necessary.

Acute Cellulitis

Acute cellulitis of the auricle and external auditory canal usually is caused by group A streptococcus and occasionally by *S. aureus.* The skin is red, hot, and indurated, without a sharply defined border. Fever may be present with little or no exudate in the canal. Parenteral administration of penicillin G or a penicillinase-resistant penicillin is the therapy of choice.

Perichondritis and Chondritis

Perichondritis is an infection involving the skin and perichondrium of the auricular cartilage; extension of infection to the cartilage is termed **chondritis** . The ear canal, especially the lateral aspect, also may be involved. Early perichondritis may be difficult to differentiate from cellulitis because both are characterized by skin that is red, edematous, and tender. The main cause of perichondritis/chondritis and cellulitis is trauma (accidental or iatrogenic, laceration or contusion), including ear piercing, especially when done through the cartilage. The most commonly isolated organism in perichondritis and chondritis is *P. aeruginosa*, although other Gram-negative and, occasionally, Gram-positive organisms may be found. Treatment involves systemic, often parenteral, antibiotics; surgery to drain an abscess or remove nonviable skin or cartilage may also be needed. Removal of all ear jewelry is mandatory in the presence of infection.

Dermatoses

Various dermatoses (seborrheic, contact, infectious eczematoid, or neurodermatoid) are common causes of inflammation of the external canal; scratching and the introduction of infecting organisms cause acute external otitis in these conditions.

Seborrheic dermatitis is characterized by greasy scales that flake and crumble as they are detached from the epidermis; associated changes in the scalp, forehead, cheeks, brow, postauricular areas, and concha are usual.

Contact dermatitis of the auricle or canal may be caused by earrings or by topical otic medications such as neomycin, which may produce erythema, vesiculation, edema, and weeping. Poison ivy, oak, and sumac also may produce contact dermatitis. Hair care products have been implicated in sensitive individuals.

Infectious eczematoid dermatitis is caused by a purulent infection of the external canal, middle ear, or mastoid; the purulent drainage infects the skin of the canal or auricle, or both. The lesion is weeping, erythematous, or crusted.

Atopic dermatitis occurs in children with a familial or personal history of allergy; the auricle, particularly the postauricular fold, becomes thickened, scaly, and excoriated.

Neurodermatitis is recognized by intense itching and erythematous, thickened epidermis localized to the concha and orifice of the meatus.

Treatment of these dermatoses depends on the type but should include application of an appropriate topical medication, elimination of the source of infection or contact when identified, and management of any underlying dermatologic problem. In addition to topical antibiotics (or antifungals), topical steroids are helpful if contact dermatitis (see Chapter 674.1), atopic dermatitis (see Chapter 674), or eczematoid dermatitis is suspected.

Herpes Simplex Virus

See Chapter 279 .

Herpes simplex virus may appear as vesicles on the auricle and lips. The lesions eventually become encrusted and dry and may be confused with impetigo. Topical application of a 10% solution of carbamide peroxide in anhydrous glycerol is symptomatically helpful. The **Ramsay Hunt syndrome** (herpes zoster oticus with facial paralysis) may present initially with otalgia, with subsequent appearance of vesicles in the ear canal and on the pinna and with facial paralysis and pain. Other cranial nerves may be affected as well, especially the 8th nerve. Treatment of herpes zoster oticus includes systemic antiviral agents, such as acyclovir, and systemic corticosteroids. As many as 50% of patients with Ramsay Hunt syndrome do not completely recover their facial nerve function.

Bullous Myringitis

Commonly associated with an acute upper respiratory tract infection, bullous myringitis presents as an ear infection with more severe pain than usual. On examination, hemorrhagic or serous blisters (bullae) may be seen on the TM. The disease sometimes is difficult to differentiate from acute OM, because a large bulla may be confused with a bulging TM. The organisms involved are the same as those that cause acute OM, including both bacteria and viruses. Treatment consists of empiric antibiotic therapy and pain medications. In addition to ibuprofen or codeine for severe pain, a topical anesthetic eardrop may also provide some relief. Incision of the bullae, although not necessary, promptly relieves the pain.

Exostoses and Osteomas

Exostoses represent benign hyperplasia of the perichondrium and underlying bone. Those involving the auditory canal tend to be found in people who swim often in cold water. Exostoses are broad based, often multiple, and bilateral. Osteomas are benign bony growths in the ear canal of uncertain cause (see Chapter 528.2). They usually are solitary and attached by a narrow pedicle to the tympanosquamous or tympanomastoid suture line. Both are more common in males; exostoses are more common than osteomas. Surgical treatment is recommended when large masses cause cerumen impaction, ear canal obstruction, or hearing loss.

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CHAPTER 658

Otitis Media

Joseph E. Kerschner, Diego Preciado

The term **otitis media (OM)** has 2 main categories: acute infection, which is termed suppurative or **acute otitis media (AOM),** and inflammation accompanied by **middle-ear effusion (MEE),** termed nonsuppurative or **secretory OM,** or **otitis media with effusion (OME).** These 2 main types of OM are interrelated: acute infection usually is succeeded by residual inflammation and effusion that, in turn, predispose children to recurrent infection. MEE is a feature of both AOM and of OME and is an expression of the underlying middle-ear mucosal inflammation. MEE results in the conductive hearing loss (CHL) associated with OM, ranging from none to as much as 50 dB of hearing loss.

The peak incidence and prevalence of OM is during the 1st 2 yr of life. More than 80% of children experience at least one episode of OM by the age of 3 yr. OM is a leading reason for physician visits and for use of antibiotics and figures importantly in the differential diagnosis of fever. Recurrent OM often serves as the sole or the main basis for myringotomy with insertion of tympanostomy tubes and adenoidectomy, the most frequently performed operations in infants and young children. OM is also the most common cause of acquired hearing loss in children. OM has a propensity to become chronic and recur. The earlier in life a child experiences the 1st episode, the greater the frequency of recurrence, severity, and persistence of MEE.

Accurate diagnosis of AOM in infants and young children may be difficult (Figs. 658.1 to 658.3). Symptoms may not be apparent, especially in early infancy and in chronic stages of the disease. Accurate visualization of the tympanic membrane (TM) and middle-ear space may be difficult because of anatomy, patient cooperation, or blockage by cerumen, removal of which may be arduous and time consuming. Abnormalities of the eardrum may be subtle and difficult to appreciate. In the face of these difficulties, both underdiagnosis and overdiagnosis occur.

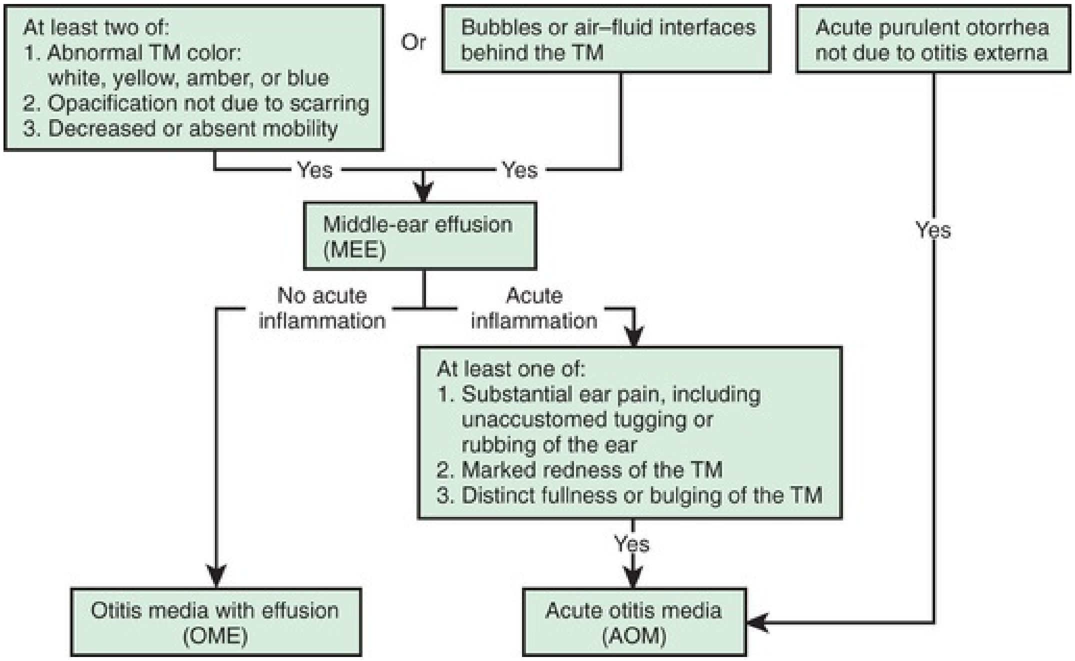
At least two of:
1. Abnormal TM color: white, yellow, amber, or blue
2. Opacification not due to scarring
3. Decreased or absent mobility
Or
Bubbles or air–fluid interfaces behind the TM
Acute purulent otorrhea not due to otitis externa
Yes
Yes
Middle-ear effusion (MEE)
Yes
No acute inflammation
Acute inflammation
At least one of:
1. Substantial ear pain, including unaccustomed tugging or rubbing of the ear
2. Marked redness of the TM
3. Distinct fullness or bulging of the TM
Yes
Otitis media with effusion (OME)
Acute otitis media (AOM)

FIG. 658.1 Algorithm for distinguishing between acute otitis media and otitis media with effusion. *TM,* tympanic membrane.

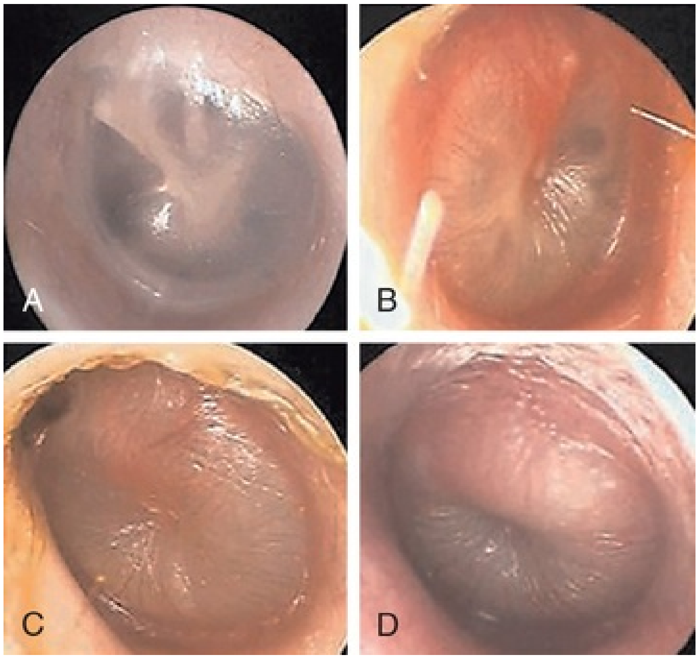

FIG. 658.2 Examples of normal tympanic membrane **(A)** and of mild bulging **(B),** moderate bulging **(C),** and severe bulging **(D)** of the tympanic membrane from middle-ear effusion. (Courtesy of Alejandro Hoberman, MD.)

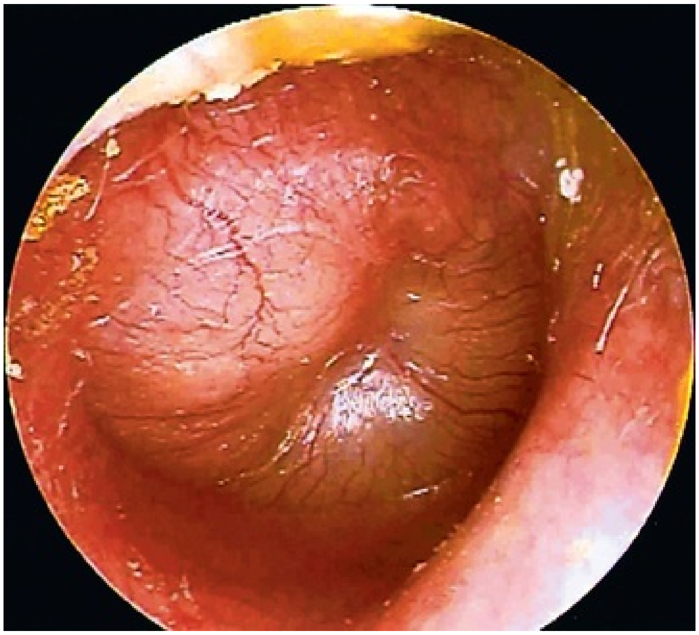

FIG. 658.3 Tympanic membrane in acute otitis media.

Epidemiology

Several factors affect the occurrence of OM, including age, gender, race, genetic background, socioeconomic status, breast milk feeding, degree of exposure to tobacco smoke, degree of exposure to other children, presence or absence of respiratory allergy, season of the year, and pneumococcal vaccination status. Children with certain types of immune deficiencies and congenital craniofacial anomalies (cleft palate) are particularly prone to OM.

Age

The age of onset of OM is an important predictor of the development of recurrent and chronic OM, with earlier age of onset having an increased risk for exhibiting these difficulties later in life. The development of at least one episode of OM is reported as 63–85% by 12 mo and 66–99% by 24 mo of age. The percentage of days with MEE is reported as 5–27% during the 1st yr of life and 6–18% during the 2nd yr of life. Across groups, rates are highest at 6-20 mo of age. After the age of 2nd yr, the incidence and prevalence of OM decline progressively, although the disease remains relatively common into the early school-age years. The most likely reasons for the higher rates in infants and younger children include less-well–developed immunologic defenses and less-favorable eustachian tubal factors involving both the structure and function of the tube.

Gender

Epidemiologic data suggest an incidence of OM greater in boys than in girls, although some studies have found no gender-related differences in the occurrence of OM.

Race

OM is especially prevalent and severe among Native American, Inuit, and indigenous Australian children. Studies comparing the occurrence of OM in white children and black children have given conflicting results.

Genetic Background

That middle-ear disease tends to run in families is a commonplace observation, suggesting that OM has a heritable component. The degree of concordance for the occurrence of OM is much greater among monozygotic than among dizygotic twins.

Socioeconomic Status

Elements contributing to the association of poverty with OM include crowding, limited hygienic facilities, suboptimal nutritional status, limited access to medical care, and limited resources for complying with prescribed medical regimens.

Breast Milk Compared With Formula Feeding

Most studies have found a protective effect of breast milk feeding against OM. This protective effect may be greater in socioeconomically disadvantaged than in more advantaged children. The protective effect is attributable to the milk itself rather than to the mechanics of breastfeeding.

Exposure to Tobacco Smoke

Tobacco smoke exposure is an important preventable risk factor in the development of OM. Studies that have used objective measures to determine infant exposure to second-hand tobacco smoke, such as cotinine levels, have consistently identified a significant linkage between tobacco smoke and OM.

Exposure to Other Children

OM is more common with repeated exposure to other children, whether at home or in out-of-home group daycare. Together, but independently, family socioeconomic status and the extent of exposure to other children appear to constitute 2 of the most important identifiable risk factors for developing OM.

Season

In keeping with the pattern of occurrence of upper respiratory tract infections in general, highest rates of occurrence of OM are observed during cold weather months and lowest rates during warm weather months. In OM, it is likely that these findings strongly depend on the significant association of OM with viral respiratory illnesses.

Congenital Anomalies

OM is universal among infants with unrepaired palatal clefts and is also highly prevalent among children with submucous cleft palate, other craniofacial anomalies, and Down syndrome (see Chapter 98.2). The common feature in these congenital anomalies is a deficiency in eustachian tube function, which predisposes these children to middle-ear disease.

Other Factors

Pacifier use is linked with an increased incidence of OM and recurrence of OM, although the effect is small. Neither maternal age nor birthweight nor season of birth appears to influence the occurrence of OM once other demographic factors are accounted. Some suggest an association of OM with bottle feeding in the recumbent position (propped bottle). Children with HIV infection have a high risk for recurrent OM.

Etiology

Acute Otitis Media

Pathogenic bacteria can be isolated by standard culture techniques from middle-ear fluid in most documented AOM cases. Three pathogens predominate in AOM: *Streptococcus pneumoniae* (see Chapter 209), nontypeable *Haemophilus influenzae* (see Chapter 221), and *Moraxella catarrhalis* (see Chapter 223). The overall incidence of these organisms has changed with the use of the conjugate pneumococcal vaccine. Widespread use of the expanded serotype coverage 13-valent as compared with the 7-valent pneumococcal conjugate vaccine has further reduced the prevalence of *S. pneumoniae* as a cause of AOM, particularly the virulent 19A serotype. Less common pathogens include group A streptococcus (see Chapter 210), *Staphylococcus aureus* (see Chapter 208.1), and Gram-negative organisms. Gram-negative organisms and *S. aureus* are found most commonly in neonates and very young infants who are hospitalized; in outpatient settings, the distribution of pathogens in these young infants is similar to that in older infants. Molecular techniques to identify nonculturable bacterial pathogens have suggested the importance of other bacterial species such as *Alloiococcus otitidis*.

Evidence of respiratory viruses also may be found in middle-ear exudates of children with AOM, either alone or, more commonly, in association with pathogenic bacteria. Of these viruses, rhinovirus and respiratory syncytial virus are found most often. AOM is a known complication of bronchiolitis; middle-ear aspirates in children with bronchiolitis regularly contain bacterial pathogens, suggesting that respiratory syncytial virus is rarely, if ever, the sole cause of their AOM. Using more precise measures of viable bacteria than standard culture techniques, such as polymerase chain reaction assays, a much higher rate of bacterial pathogens can be demonstrated. It remains uncertain whether viruses alone can cause AOM, or whether their role is limited to setting the stage for bacterial invasion, and perhaps also to amplifying the inflammatory process and interfering with resolution of the bacterial infection. Viral pathogens have a negative impact on eustachian tube function, can impair local immune function and increase bacterial adherence, and can change the pharmacokinetic dynamics, reducing the efficacy of antimicrobial medications.

Otitis Media With Effusion

Using standard culture techniques, the pathogens typically found in AOM are recoverable in only 30% of children with OME. However, using polymerase chain reaction assays, MEEs contain evidence of bacterial DNA and viral RNA in much larger proportions of these children. These patients do not have sterile effusions as previously thought. Biofilms of pathogenic bacteria are present on the middle-ear mucosa and adenoid pad in most children with chronic OM. Biofilms consist of aggregated and adherent bacteria, embedded in an extracellular matrix and in neutrophil extracellular traps, allowing for protection against antimicrobials, and their presence may contribute to the persistence of pathogens and the recalcitrance of chronic OM to antibiotic treatment (see Chapter 223).

Pathogenesis

A multifactorial disease process, risk profile, and host-pathogen interactions play important roles in the pathogenesis of OM. Such events as alterations in mucociliary clearance through repeated viral exposure experienced in daycare settings or through exposure to tobacco smoke may tip the balance of pathogenesis in less-virulent OM pathogens in their favor, especially in children with a unique host predisposition.

Anatomic Factors

Patients with significant craniofacial abnormalities affecting the eustachian tube function have an increased incidence of OM. During the pathogenesis of OM the eustachian tube demonstrates decreased effectiveness in ventilating the middle-ear space.

Under usual circumstances the eustachian tube is passively closed and is opened by contraction of the tensor veli palatini muscle. In relation to the middle ear, the tube has three main functions: ventilation, protection, and clearance. The middle-ear mucosa depends on a continuing supply of air from the nasopharynx delivered by way of the eustachian tube. Interruption of this ventilatory process by tubal obstruction initiates an inflammatory response that includes secretory metaplasia, compromise of the mucociliary transport system, and effusion of liquid into the tympanic cavity. Measurements of eustachian tube function have demonstrated that the tubal function is suboptimal during the events of OM with increased opening pressures.

Eustachian tube obstruction may result from extraluminal blockage via hypertrophied nasopharyngeal adenoid tissue or tumor or may result from intraluminal obstruction via inflammatory edema of the tubal mucosa, most commonly as a consequence of a viral upper respiratory tract infection. Progressive reduction in tubal wall compliance with increasing age may explain the progressive decline in the occurrence of OM as children grow older. The protection and clearance functions of the eustachian tube may also be involved in the pathogenesis of OM. Thus, if the eustachian tube is patulous or excessively compliant, it may fail to protect the middle ear from reflux of infective nasopharyngeal secretions, whereas impairment of the mucociliary clearance function of the tube might contribute to both the establishment and persistence of infection. The shorter and more horizontal orientation of the tube in infants and young children may increase the likelihood of reflux from the nasopharynx and impair passive gravitational drainage through the eustachian tube.

Children with **craniofacial abnormalities** experience an increased incidence of OM associated with the abnormal eustachian tube function. In children with cleft palate, where OM is a universal finding, a main factor underlying the chronic middle-ear inflammation appears to be impairment of the opening mechanism of the eustachian tube. Possible factors include muscular changes, tubal compliance factors, and defective velopharyngeal valving, which may result in disturbed aerodynamic and hydrodynamic relationships in the nasopharynx and proximal portions of the eustachian tubes. In children with other craniofacial anomalies and with Down syndrome, the high prevalence of OM has also been attributed to structural and/or functional eustachian tubal abnormalities.

Host Factors

The effectiveness of a child's immune system in response to the bacterial and viral insults of the upper airway and middle ear during early childhood probably is the most important factor in determining which children are otitis prone. The maturation of this immune system during early childhood is most likely the primary event leading to the decrease in incidence of OM with increased age. Immunoglobulin (Ig) A deficiency is found in some children with recurrent AOM, but the significance is questionable; many children with IgA deficiency do not experience recurrent episodes of AOM. Selective IgG subclass deficiencies (despite normal total serum IgG) may be found in children with recurrent AOM in association with recurrent sinopulmonary infection, and these deficiencies probably underlie the susceptibility to infection. Children with HIV infection have recurrent and difficult to treat episodes of AOM in the 1st and 2nd year of life. Children with recurrent OM that is not associated with recurrent infection at other sites rarely have a readily identifiable immunologic deficiency. Evidence that subtle immune deficits play a role in the pathogenesis of recurrent AOM is provided by studies involving antibody responses to various types of infection and immunization; by the observation that breast milk feeding, as opposed to formula feeding, confers some protection against the occurrence of OM in infants with cleft palate; and by studies in which young children with recurrent AOM achieved a measure of protection from intramuscularly administered bacterial polysaccharide Ig or intravenously administered polyclonal Ig. This evidence, along with the documented decrease in incidence of upper respiratory tract infections and OM as children's immune systems develop and mature, is indicative of the importance of a child's innate immune system in the pathogenesis of OM (see Chapter 150).

Viral Pathogens

Although OM may develop and persist in the absence of apparent respiratory tract infection, many, if not most, episodes are initiated by viral or bacterial upper respiratory tract infection. Among children in group daycare, AOM was observed in approximately 30–40% of children with respiratory illness caused by respiratory syncytial virus (see Chapter 287), influenza viruses (see Chapter 285), or adenoviruses (see Chapter 289), and in approximately 10–15% of children with respiratory illness caused by parainfluenza viruses (see Chapter 286), rhinoviruses (see Chapter 290), or enteroviruses (see Chapter 277). Viral infection of the upper respiratory tract results in release of cytokines and inflammatory mediators, some of which may cause eustachian tube dysfunction.

Respiratory viruses also may enhance nasopharyngeal bacterial colonization and adherence and impair host immune defenses against bacterial infection.

Allergy

Evidence that respiratory allergy is a primary etiologic agent in OM is not convincing; however, in children with both conditions it is possible that the otitis is aggravated by the allergy.

Clinical Manifestations

Symptoms of AOM are variable, especially in infants and young children. In young children, evidence of ear pain may be manifested by irritability or a change in sleeping or eating habits and occasionally, holding or tugging at the ear. *Pulling at the ear alone has a low sensitivity and specificity.* Fever may also be present and may occasionally be the only sign. Rupture of the TM with purulent otorrhea is uncommon. Systemic symptoms and symptoms associated with upper respiratory tract infections also occur; occasionally there may be no symptoms, the disease having been discovered at a routine health examination. The Acute Otitis Media Severity of Symptom (AOM-SOS) scale is a 5-item validated symptom score which has proven beneficial as a tool to monitor AOM symptoms in patients and studies of antimicrobial effectiveness in OM. OME often is not accompanied by overt complaints of the child but can be accompanied by hearing loss. This hearing loss may manifest as changes in speech patterns but often goes undetected if unilateral or mild in nature, especially in younger children. Balance difficulties or disequilibrium can also be associated with OME, and older children may complain of mild discomfort or a sense of fullness in the ear.

Examination of the Tympanic Membrane

Otoscopy

Two types of otoscope heads are available: **surgical** or **operating** , and **diagnostic** or **pneumatic** . The surgical head embodies a lens that can swivel over a wide arc and an unenclosed light source, thus providing ready access of the examiner's instruments to the external auditory canal and TM. Use of the surgical head is optimal for removing cerumen or debris from the canal under direct observation and is necessary for satisfactorily performing tympanocentesis or myringotomy. The diagnostic head incorporates a larger lens, an enclosed light source, and a nipple for the attachment of a rubber bulb and tubing. When an attached speculum is fitted snugly into the external auditory canal, an airtight chamber is created comprising the vault of the otoscope head, the bulb and tubing, the speculum, and the proximal portion of the external canal. Although examination of the ear in young children is a relatively invasive procedure that is often met with lack of cooperation by the patient, this task can be enhanced if done with as little pain as possible. The outer portion of the ear canal contains hair-bearing skin and subcutaneous fat and cartilage that allow a speculum to be placed with relatively little discomfort. Closer to the TM the ear canal is made of bone and is lined only with skin and no adnexal structures or subcutaneous fat; a speculum pushed too far forward and placed in this area often causes skin abrasion and pain. Using a rubber-tipped speculum or adding a small sleeve of rubber tubing to the tip of the plastic speculum may serve to minimize patient discomfort and enhance the ability to achieve a proper fit and an airtight seal, facilitating pneumatic otoscopy.

Learning to perform **pneumatic otoscopy** is a critical skill in being able to assess a child's ear and in making an accurate diagnosis of AOM. By observing as the bulb is alternately squeezed gently and released, the degree of TM mobility in response to both positive and negative pressure can be estimated, providing a critical assessment of middle-ear fluid, which is a hallmark sign of both AOM and OME (see Fig. 658.1). With both types of otoscope heads, bright illumination is also critical for adequate visualization of the TM.

Clearing the External Auditory Canal

Children's ears are “self-cleaning” because of squamous migration of ear canal skin. Parental cleaning of cerumen with cotton-tipped swabs often worsens cerumen impaction by pushing cerumen deeper into the canal, compacting it. If the TM is obscured by cerumen, the cerumen should be removed. This can be accomplished through direct visualization using a headlight or through the surgical head of the otoscope by using an ear curette or gentle suction with a No. 5 or 7 French ear suction tube. During this procedure, it may be most advantageous to restrain the infant or young child in the prone position, turning the child's head to the left or right as each ear is cleared. In children old enough to cooperate, usually beginning at approximately 5 yr of age, clearing of the external canal may be achieved more easily and less traumatically by lavage than by mechanical removal, provided one can be certain that a TM perforation is not present.

Tympanic Membrane Findings

Important characteristics of the TM consist of contour, color, translucence, structural changes, if any, and mobility. The TM is anatomically divided into the pars tensa and pars flaccida. The pars tensa comprises the lower two thirds of the drum inferior to the lateral process of the malleus. Its contour is normally **slightly concave;** abnormalities consist of fullness or bulging or, conversely, extreme retraction. The normal color of the pars tensa is **pearly gray** , with the pars flaccida being slightly more vascular in nature. Erythema may be a sign of inflammation or infection, but unless intense, erythema alone may result from crying or vascular flushing. Abnormal whiteness of the membrane may result from either scarring or the presence of effusion in the middle-ear cavity; this effusion also may impart an amber, pale yellow, or, rarely, bluish color. Rarely a persistent focal white area may be indicative of a congenital cholesteatoma in the middle-ear space. Normally, the membrane is translucent, although some degree of opacity may be normal in the 1st few mo of life; later, opacification denotes either scarring or, more commonly, underlying effusion. Structural changes include scars, perforations, and retraction pockets. Retractions or perforations, especially in the posterior-superior quadrant, or pars flaccida, of the TM may be a sign of cholesteatoma formation. Of all the visible characteristics of the TM, mobility is the most sensitive and specific in determining the presence or absence of MEE. Mobility is generally not an all-or-none phenomenon. A total absence of mobility does exist with a TM perforation that can develop following a substantial increase in middle-ear pressure associated with effusion. When a perforation is not present, substantial impairment of mobility is the more common finding with MEE. Bulging of the TM is the most specific finding of AOM (97%) but has lower sensitivity (51%) (see Fig. 658.2).

Diagnosis

A diagnosis of AOM according to the 2013 American Academy of Pediatrics guidelines should be made in children who present with:

◆ moderate to severe bulging of the TM or new-onset otorrhea not caused by otitis externa
◆ mild bulging of the TM and recent (<48 hr) onset of ear pain or intense TM erythema

A **diagnosis of AOM should *not*** be made in children without MEE.

AOM and OME may evolve into the other without any clearly differentiating physical findings; any schema for distinguishing between them is to some extent arbitrary. In an era of increasing bacterial resistance, distinguishing between AOM and OME is important in determining treatment, because OME in the absence of acute infection does not require antimicrobial therapy. Purulent otorrhea of recent onset is indicative of AOM; thus difficulty in distinguishing clinically between AOM and OME is limited to circumstances in which purulent otorrhea is not present. Both AOM without otorrhea and OME are accompanied by physical signs of MEE, namely, the presence of at least 2 of 3 TM abnormalities: white, yellow, amber, or (rarely) blue discoloration; opacification other than that caused by scarring; and decreased or absent mobility. Alternatively, in OME, either air-fluid levels or air bubbles outlined by small amounts of fluid may be visible behind the TM, a condition often indicative of impending resolution (see Fig. 658.3).

To support a diagnosis of AOM instead of OME in a child with MEE, distinct fullness or bulging of the TM may be present, with or without accompanying erythema, or, at a minimum, MEE should be accompanied by ear pain that appears clinically important. Unless intense, erythema alone is insufficient because erythema, without other abnormalities, may result from crying or vascular flushing. In AOM, the malleus may be obscured and the TM may resemble a bagel without a hole but with a central depression (see Fig. 658.3). Rarely, the TM may be obscured by surface bullae or may have a cobblestone appearance. Bullous myringitis is a physical manifestation of AOM and not an etiologically discrete entity. Within days after onset, fullness of the membrane may diminish, even though infection may still be present.

In OME, bulging of the TM is absent or slight or the membrane may be retracted (Fig. 658.4); erythema also is absent or slight but may increase with crying or with superficial trauma to the external auditory canal incurred in clearing the canal of cerumen.

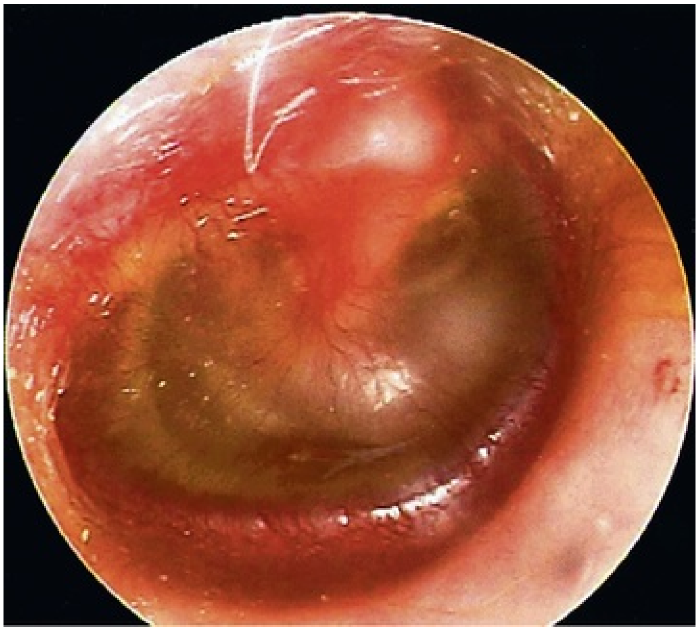

FIG. 658.4 Tympanic membrane in otitis media with effusion.

Both before and after episodes of OM and also in the absence of OM, the TM may be retracted as a consequence of negative middle-ear air pressure. The presumed cause is diffusion of air from the middle-ear cavity more rapidly than it is replaced via the eustachian tube. Mild retraction is generally self-limited, although in some children it is accompanied by mild CHL. More extreme retraction is of concern, as discussed later in the section on sequelae of OM.

Conjunctivitis-Associated Otitis Media

Simultaneous appearance of purulent and erythematous conjunctivitis with an ipsilateral OM is a well-recognized presentation, caused by nontypeable *H. influenzae* in most children. The disease often is present in multiple family members and affects young children and infants. Topical ocular antibiotics are ineffective. In an era of resistant organisms, this clinical association can be important in antibiotic selection, with oral antibiotics (see later) effective against resistant forms of nontypeable *H. influenzae.*

Asymptomatic Purulent Otitis Media

Rarely, a child will present during a routine exam without fever, irritability, or other overt signs of infection, but on exam, the patient will demonstrate an obvious purulent MEE and bulging TM. Although an uncommon presentation of "acute" OM, the bulging nature of the TM and the obvious purulence of the effusion do warrant antimicrobial therapy.

Tympanometry

Tympanometry, or **acoustic immittance testing,** is a simple, rapid, atraumatic test that, when performed correctly, offers objective evidence of the presence or absence of MEE. The tympanogram provides information about **TM compliance** in electroacoustic terms that can be thought of as approximately equivalent to TM mobility as perceived visually during pneumatic otoscopy. The absorption of sound by the TM varies inversely with its stiffness. The stiffness of the membrane is least, and accordingly its compliance is greatest, when the air pressures impinging on each of its surfaces—middle-ear air pressure and external canal air pressure—are equal. In simple terms, anything tending to stiffen the TM, such as TM scarring or middle-ear fluid, reduces the TM compliance, which is recorded as a flattening of the curve of the tympanogram. An ear filled with middle-ear fluid generally has a very noncompliant TM and therefore a flattened tympanogram tracing.

Tympanograms may be grouped into 1 of 3 categories (Fig. 658.5). Tracings characterized by a relatively steep gradient, sharp-angled peak, and middle-ear air pressure (location of the peak in terms of air pressure) that approximates atmospheric pressure (see Fig. 658.5*A*) (type A curve) are assumed to indicate normal middle-ear status. Tracings characterized by a shallow peak or no peak are often termed “flat” or type B (see Fig. 658.5*B*) and usually are assumed to indicate the presence of a middle-ear abnormality that is causing decreased TM compliance. The most common such abnormality in infants and children is MEE. Tracings characterized by intermediate findings—somewhat shallow peak, often in association with a gradual gradient (obtuse-angled peak) or negative middle-ear air pressure peak (often termed type “C”), or combinations of these features (see Fig. 658.5*C*)—may or may not be associated with MEE and must be considered nondiagnostic or equivocal with respect to OM. However, type C tympanograms do suggest eustachian tube dysfunction and some ongoing pathology in the middle ear and warrant follow-up.

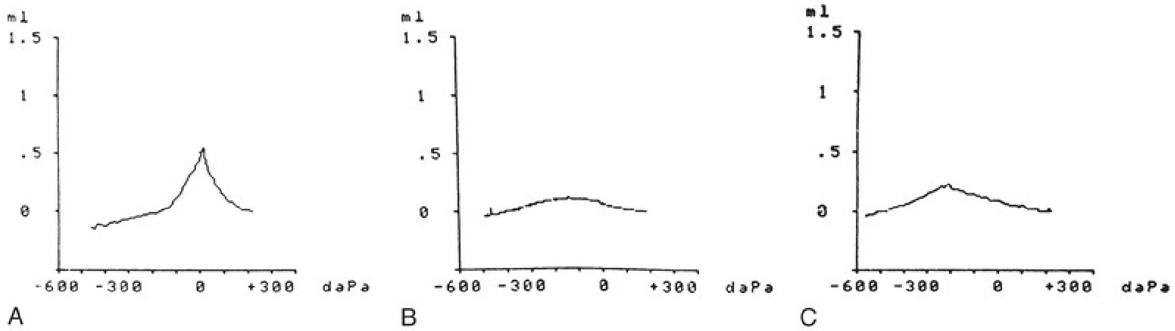

FIG. 658.5 Tympanograms obtained with a Grason-Stadler GSI 33 Middle Ear Analyzer, exhibiting **(A)** high admittance, steep gradient (i.e., sharp-angled peak), and middle-ear air pressure approximating atmospheric pressure (0 decaPascals [daPa]); **(B)** low admittance and indeterminate middle-ear air pressure; and **(C)** somewhat low admittance, gradual gradient, and markedly negative middle-ear air pressure.

When reading a tympanogram, it is important to look at the volume measurement. The type B tympanometric response is analyzed within the context of the recorded volume. A flat, “low”-volume (≤1 mL) tracing typically reflects the volume of the ear canal only, representing MEE, which impedes the movement of an intact ear drum. A flat, high-volume (>1 mL) tracing typically reflects the volume of the ear canal and middle-ear space, representing a perforation (or patent tympanostomy tube) in the TM. In a child with a tympanostomy tube present, a flat tympanogram with a volume <1 mL would suggest a plugged or nonfunctioning tube and middle-ear fluid, whereas a flat tympanogram with a volume >1 mL would suggest a patent tympanostomy tube.

Although tympanometry is quite sensitive in detecting MEE, it can be limited by patient cooperation, the skill of the individual administering the test, and the age of the child, with less-reliable results in very young children. Use of tympanometry may be helpful in office screening, may supplement the examination of difficult to examine patients, and may help to identify patients who require further attention because their tympanograms are abnormal. Tympanometry also may be used to help confirm, refine, or clarify questionable otoscopic findings; to objectify the follow-up evaluation of patients with known middle-ear disease; and to validate otoscopic diagnoses of MEE. Even though tympanometry can predict the probability of MEE, it cannot distinguish the effusion of OME from that of AOM.

Prevention

General measures to prevent OM that have been supported by numerous investigations include avoiding exposure to individuals with respiratory infection; appropriate vaccination strategies against pneumococci and influenzae; avoiding environmental tobacco smoke; and breast milk feeding.

Immunoprophylaxis and Vaccination Status

Heptavalent pneumococcal conjugate vaccine (PCV7) reduced the overall number of episodes of AOM by only 6–8% but with a 57% reduction in serotype-specific episodes. Reductions of 9–23% are seen in children with histories of frequent episodes, and a 20% reduction is seen in the number of children undergoing tympanostomy tube insertion. The 13-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV13) contains the 7 serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and 6 additional serotypes (serotypes 1, 3, 5, 6A, 7F, and 19A). Early data indicate a significant reduction in the number of invasive pneumococcal mastoiditis cases since the introduction of PCV13. With the widespread use of PCV13, continued surveillance will be necessary to detect other emerging serotypes, which are also demonstrating increasing resistance. Although the influenza vaccine also provides a measure of protection against OM, the relatively limited time during which individuals and even communities are exposed to influenza viruses limits the vaccine's effectiveness in broadly reducing the incidence of OM. Limitation of OM disease is only a portion of the benefit realized from the vaccinations for pneumococci and influenza viruses.

Treatment

Management of Acute Otitis Media

AOM can be very painful. Whether or not antibiotics are used for treatment, pain should be assessed and, if present, treated (Table 658.1). Individual episodes of AOM have traditionally been treated with antimicrobial drugs. Concern about increasing bacterial resistance has prompted some clinicians to recommend withholding antimicrobial treatment in some cases unless symptoms persist for 2 or 3 days or worsen (Table 658.2). Three factors argue in favor of routinely prescribing antimicrobial therapy for children who have documented AOM using the diagnostic criteria outlined previously. First, pathogenic bacteria cause a majority of cases. Second, symptomatic improvement and resolution of infection occur more promptly and more consistently with antimicrobial treatment than without, even though most untreated cases eventually resolve. Third, prompt and adequate antimicrobial treatment may prevent the development of suppurative complications. The sharp decline in such complications during the last half-century seems likely attributable, at least in part, to the widespread routine use of antimicrobials for AOM. In the Netherlands, where initial antibiotic treatment is routinely withheld from most children older than 6 mo of age, and where only approximately 30% of children with AOM receive antibiotics at all, the incidence of acute mastoiditis, although low (in children younger than age 14 yr, 3.8 per 100,000 person-yr), appears slightly higher than rates in other countries with higher antibiotic prescription rates by approximately 1-2 episodes per 100,000 person-yr. Groups in other countries where initial conservative management of AOM is the standard in children older than 6 mo, such as Denmark, report acute mastoiditis rates similar to those of the Netherlands (4.8 per 100,000 person-yr).

Table 658.1

Therapy for Otalgia in Acute Otitis Media

Therapy for Otalgia in Acute Otitis Media

APPROACH	RECOMMENDATIONS
Acetaminophen, ibuprofen	Preferred therapy
Benzocaine, antipyrine (topical)	Brief, benefit over acetaminophen in patients older than 5 yr
Topical antibiotics (fluoroquinolones) with or without steroids for chronic suppurative otitis (perforated tympanic membrane)	Preferred treatment with ear canal cleaning; must culture
Homeopathic agents	Not recommended
Narcotic analgesia with codeine or analogs	Not recommended
Tympanostomy/myringotomy	Not recommended for initial approach; an option for otitis media unresponsive to antibiotic therapy

Table 658.2

Recommendations for Initial Management for Uncomplicated Acute Otitis Media[*]

AGE	OTORRHEA WITH AOM[*]	UNILATERAL OR BILATERAL AOM[*] WITH SEVERE SYMPTOMS[†]	BILATERAL AOM[*] WITHOUT OTORRHEA	UNILATERAL AOM[*] WITHOUT OTORRHEA
6 mo to 2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 yr	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation[‡]

[*] Applies only to children with well-documented AOM with high certainty of diagnosis.

[†] A toxic-appearing child, persistent otalgia more than 48 hr, temperature ≥39°C (102.2°F) in the past 48 hr, or if there is uncertain access to follow-up after the visit.

[‡] This plan of initial management provides an opportunity for shared decision making with the child's family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48-72 hr of AOM onset.

NOTE: For infants younger than age 6 mo, a suspicion of AOM should result in antibiotic therapy.

AOM, acute otitis media.

From Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media, *Pediatrics* 131:e964–e999, 2013, Table 4.

Given that most episodes of OM will spontaneously resolve, consensus guidelines have been published by the American Academy of Pediatrics to assist clinicians who wish to consider a period of "watchful waiting" or observation prior to treating AOM with antibiotics (see Tables 658.2 and 658.3 ; Fig. 658.6). The most important aspect of these guidelines is that close follow-up of the patient must be ensured to assess for lack of spontaneous resolution or worsening of symptoms and that patients should be provided with adequate analgesic medications (acetaminophen, ibuprofen) during the period of observation. When pursuing the practice of watchful waiting in patients with AOM, the certainty of the diagnosis, the patient's age, and the severity of the disease should be considered. For younger patients, <2 yr of age, it is recommended to treat all confirmed diagnoses of AOM. In very young patients, <6 mo of age, even presumed episodes of AOM should be treated because of the increased potential of significant morbidity from infectious complications. In children between 6 and 24 mo of age who have a questionable diagnosis of OM but severe disease, defined as temperature of >39°C (102°F), significant otalgia, or toxic appearance, antibiotic therapy is also recommended. Children in this age group with a questionable diagnosis and nonsevere disease can be observed for a period of 2-3 days with close follow-up. In children older than 2 yr of age, observation might be considered in all episodes of nonsevere OM or episodes of questionable diagnosis, while antibiotic therapy is reserved for confirmed, severe episodes of AOM. Information from Finland suggests that the "watchful waiting" or delayed treatment approach does not worsen the recovery from AOM, or increase the complication rates.

Table 658.3

Suggested Antibiotics for Treatment of Otitis Media and for Patients Who Have Failed First-Line Antibiotic Treatment

Initial Immediate or Delayed Antibiotic Treatment		**Antibiotic Treatment After 48-72 hr of Failure of Initial Antibiotic Treatment**	
RECOMMENDED FIRST-LINE TREATMENT	**ALTERNATIVE TREATMENT (IF PENICILLIN ALLERGY OR SUSPICION OF BETA LACTAMASE-PRODUCING ORGANISMS)**	**RECOMMENDED TREATMENT**	**ALTERNATIVE TREATMENT**
Amoxicillin (Pathogens include *Pneumococcus* , *H. influenzae* non-type B, *Moraxella)*	Cefdinir	Amoxicillin-clavulanate	Ceftriaxone
or	*or*	*or*	Faliure of second antibiotic
Amoxicillin-clavulanate Ceftriaxone IM/IV for 1-3 days	Cefpodoxime Ceftriaxone Levofloxacin	Ceftriaxone	Azithromycin Tympanocentesis*
ANTIBIOTIC DOSAGE			

- Amoxicillin 90 mg/kg/day bid for 10 days
- Amoxicillin-clavulanate (ratio 14 : 1) 90 mg/kg/day of amoxicillin component bid for 10 days
- Ceftriaxone 50 mg/kg/day qd IM, IV for 1-3 days
- Cefdinir 14 mg/kg/day qd for 10 days
- Cefpodoxime 10 mg/kg/day bid for 10 days
- Levofloxacin 20 mg/kg/day bid if ≤ 5 yr for 10 days; 10 mg/kg/day bid if > 5 yr for 10 days
- Azithromycin 10 mg/kg/day on day 1 QD then 5 mg/kg/day days 2-5 qd or 10 mg/kg/day for 3 days QD or 20 mg/kg once

[*] Tympanocentesis for those who fail second-line therapy.

IM, intramuscular; IV intravenous; bid, twice daily; qd, once daily.

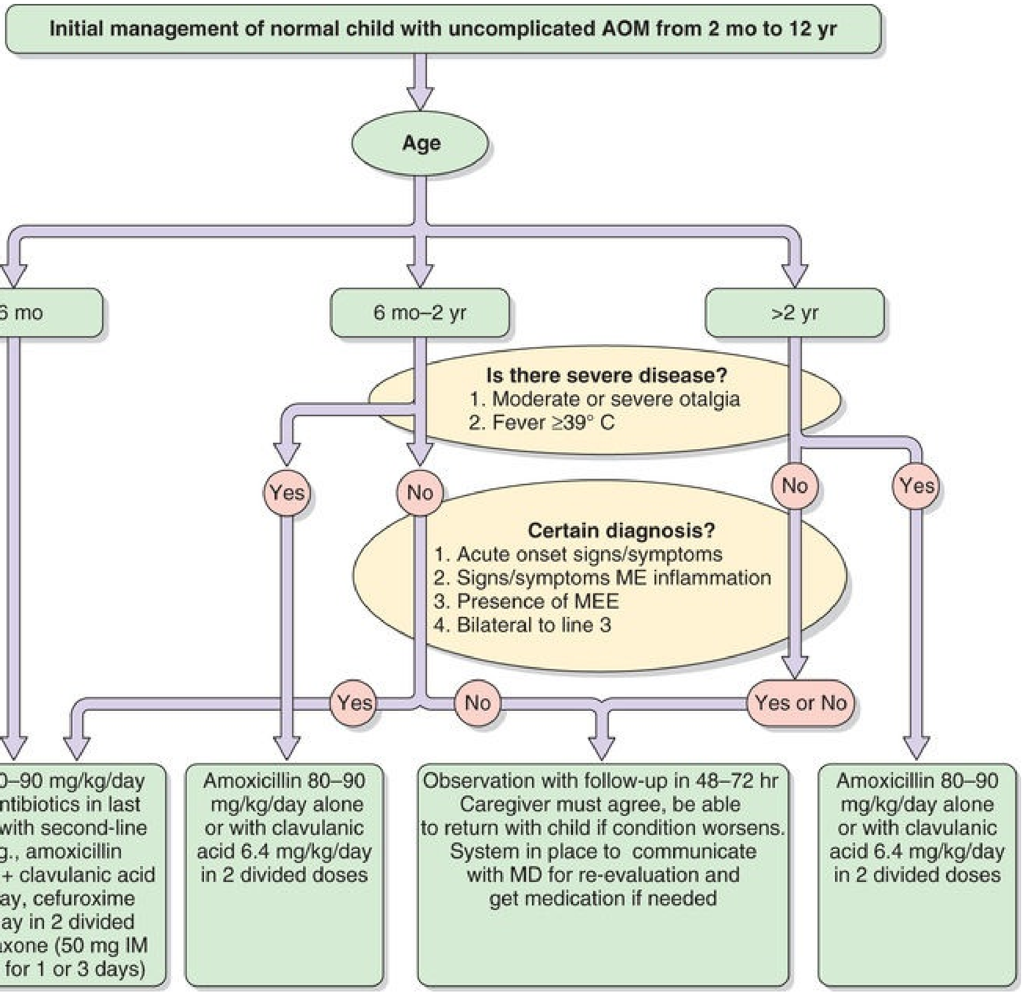
Initial management of normal child with uncomplicated AOM from 2 mo to 12 yr
Age
<6 mo
6 mo–2 yr
>2 yr
Is there severe disease?
1. Moderate or severe otalgia
2. Fever ≥39° C
Yes
No
No
Yes
Certain diagnosis?
1. Acute onset signs/symptoms
2. Signs/symptoms ME inflammation
3. Presence of MEE
4. Bilateral to line 3
Yes
No
Yes or No
Amoxicillin 80–90 mg/kg/day If received antibiotics in last 30 days start with second-line therapy e.g., amoxicillin 90 mg/kg/day + clavulanic acid 6.4 mg/kg/day, cefuroxime (30 mg/kg/day in 2 divided doses), ceftriaxone (50 mg IM or IV per day for 1 or 3 days)
Amoxicillin 80–90 mg/kg/day alone or with clavulanic acid 6.4 mg/kg/day in 2 divided doses
Observation with follow-up in 48–72 hr Caregiver must agree, be able to return with child if condition worsens. System in place to communicate with MD for re-evaluation and get medication if needed
Amoxicillin 80–90 mg/kg/day alone or with clavulanic acid 6.4 mg/kg/day in 2 divided doses

FIG. 658.6 Algorithm for management of acute otitis media. (From Mazer BD: Otitis media. In Leung DYM, Szefler SJ, Bonilla FA, et al. editors: Pediatric allergy: principles and practices, ed 3, Philadelphia, 2016, Elsevier, Fig 25-3.)

Accurate diagnosis is the most crucial aspect of the treatment of OM. In studies using stringent criteria for diagnosis of AOM, the benefit of antimicrobial treatment is enhanced. In addition, subpopulations of patients clearly receive more benefit from oral antimicrobial therapy than others. *Younger children, children with otorrhea, and children with bilateral AOM have a significantly enhanced benefit from antimicrobial therapy in comparison with older children, children without otorrhea, or children with unilateral AOM.*

Bacterial Resistance

Persons at greatest risk of harboring resistant bacteria are those who are younger than 2 yr of age, who are in regular contact with large groups of other children, especially in daycare settings, or who recently have received antimicrobial treatment. The development of resistant bacterial strains and their rapid spread have been fostered and facilitated by selective pressure resulting from extensive use of antimicrobial drugs, the most common target of which, in children, is OM. Many strains of each of the pathogenic bacteria that commonly cause AOM are resistant to commonly used antimicrobial drugs.

Although antimicrobial resistance rates vary between countries, in the United States approximately 40% of strains of nontypeable *H. influenzae* and almost all strains of *M. catarrhalis* are resistant to aminopenicillins (e.g., ampicillin and amoxicillin). In most cases the resistance is attributable to production of β-lactamase and can be overcome by combining amoxicillin with a β-lactamase inhibitor (clavulanate) or by using a β-lactamase–stable antibiotic. Occasional strains of nontypeable *H. influenzae* that do not produce β-lactamase are resistant to aminopenicillins and other β-lactam antibiotics by virtue of alterations in their penicillin-binding proteins. It is worth noting that bacterial resistance rates in northern European countries where antibiotic use is less are comparatively exceedingly lower (β-lactamase resistance in 6–10% of isolates) than in the United States.

In the United States, approximately 50% of strains of *S. pneumoniae* are penicillin-nonsusceptible, divided approximately equally between penicillin-intermediate and, even more difficult to treat, penicillin-resistant strains. A much higher incidence of resistance is seen in children attending daycare. Resistance by *S. pneumoniae* to the penicillins and other β-lactam antibiotics is mediated not by β-lactamase production but by alterations in penicillin-binding proteins. This mechanism of resistance can be overcome if higher concentrations of β-lactam antibiotics at the site of infection can be achieved for a sufficient time interval. Many penicillin-resistant strains of *S. pneumoniae* are also resistant to other antimicrobial drugs, including sulfonamides, macrolides, and cephalosporins. In general, as penicillin resistance increases, so also does resistance to other antimicrobial classes. Resistance to macrolides, including azithromycin and clarithromycin, by *S. pneumoniae* has increased rapidly, rendering these antimicrobials far less effective in treating AOM. One mechanism of resistance to macrolides also results in resistance to clindamycin, which otherwise is generally effective against resistant strains of *S. pneumoniae*. Unlike resistance to β-lactam antibiotics, macrolide resistance cannot be overcome by increasing the dose.

First-Line Antimicrobial Treatment

Amoxicillin remains the drug of 1st choice for uncomplicated AOM under many circumstances because of its excellent record of safety, relative efficacy, palatability, and low cost. Amoxicillin is the most efficacious of available oral antimicrobial drugs against both penicillin-susceptible and penicillin-nonsusceptible strains of *S. pneumoniae* . Increasing the dose from the traditional 40-45 mg/kg/24 hr to 80-90 mg/kg/24 hr will generally provide efficacy against penicillin-intermediate and some penicillin-resistant strains. This higher dose should be used particularly in children younger than 2 yr of age, in children who have recently received treatment with β-lactam drugs, and in children who are exposed to large numbers of other children because of their increased likelihood of an infection with a nonsusceptible strain of *S. pneumoniae* . A limitation of amoxicillin is that it may be inactivated by the β-lactamases produced by many strains of nontypeable *H. influenzae* and most strains of *M. catarrhalis* . Episodes of AOM caused by these pathogens often resolve spontaneously. Allergies to penicillin antibiotics should be categorized into type I hypersensitivity, consisting of urticaria or anaphylaxis, and those that fall short of type I reactions, such as rash formation. For children with a non–type I reaction in which cross reactivity with cephalosporins is less of a concern, first-line therapy with cefdinir would be an appropriate choice. In children with a type I reaction or known sensitivity to cephalosporin antibiotics, there are far fewer choices. Resistance to trimethoprim-sulfamethoxazole by many strains of both nontypeable *H. influenzae* and *S. pneumoniae* and a reported high clinical failure rate in children with AOM treated initially with this antimicrobial argue against its use. Similarly, increasing rates of macrolide resistance argue against the efficacy of azithromycin. Although not approved by the FDA for use in children, many clinicians have used quinolones in this patient population. Early alternative management in these allergic patients with tympanostomy tubes can allow for lessening of the severity of their disease and the utilization of topical antimicrobials.

Duration of Treatment

The duration of treatment of AOM has historically been set at 10 days, and most efficacy studies examining antimicrobial treatment in AOM have used this duration as a benchmark. Studies comparing shorter with longer durations of treatment suggest that short-course treatment will often prove inadequate in children younger than 6 yr of age and particularly in children younger than 2 yr of age. For most episodes in most children, treatment that provides tissue concentrations of an antimicrobial for at least 10 days is advisable. Treatment for longer than 10 days may be required for children who are very young or are having severe episodes or whose previous experience with OM has been problematic.

Follow-Up

The principal goals of follow-up are to assess the outcome of treatment and to differentiate between inadequate response to treatment and early recurrence. The appropriate interval for follow-up should be individualized. Follow-up within days is advisable in the young infant with a severe episode or in a child of any age with continuing pain. Follow-up within 2 wk is appropriate for the infant or young child who has been having frequent recurrences. At that point, the TM is not likely to have returned to normal, but substantial improvement in its appearance should be evident. In the child with only a sporadic episode of AOM and prompt symptomatic improvement, follow-up 1 mo after initial examination is early enough, or in older children, no follow-up may be necessary. The continuing presence of MEE alone following an episode of AOM is not an indication for additional or second-line antimicrobial treatment. However, persisting MEE does warrant additional follow-up to ensure that this resolves and does not lead to persisting hearing loss or other complications.

Unsatisfactory Response to First-Line Treatment

AOM is essentially a closed-space infection and its resolution depends both on eradication of the offending organism and restoration of middle-ear ventilation. Factors contributing to unsatisfactory response to first-line treatment, in addition to inadequate antimicrobial efficacy, include poor compliance with treatment regimens; concurrent or intercurrent viral infection; persistent eustachian tube dysfunction and middle-ear under-aeration; reinfection from other sites or from incompletely eradicated middle-ear pathogens; and immature or impaired host defenses. The identification of biofilm formation in the middle ear of children with chronic OM also indicates that, in some children, eradication with standard antimicrobial therapy is likely to be unsuccessful. Despite these many potential factors, switching to an alternative or second-line drug is reasonable when there has been inadequate improvement in symptoms or in middle-ear status as reflected in the appearance of the TM, or when the persistence of purulent nasal discharge suggests that the antimicrobial drug being used has less-than-optimal efficacy. Second-line drugs may also appropriately be used when AOM develops in a child already receiving antimicrobial therapy, or in an immunocompromised child, or in a child with severe symptoms whose previous experience with OM has been problematic.

Second-Line Treatment

When treatment of AOM with a first-line antimicrobial drug has proven inadequate, numerous second-line alternatives are available (see Table 658.3). Drugs chosen for second-line treatment should be effective against β-lactamase–producing strains of nontypeable *H. influenzae* and *M. catarrhalis* and against susceptible and most nonsusceptible strains of *S. pneumoniae.* Only four antimicrobial agents meet these requirements: amoxicillin-clavulanate, cefdinir, cefuroxime axetil, and intramuscular ceftriaxone. Because high-dose amoxicillin (80-90 mg/kg/24 hr) is effective against most strains of *S. pneumoniae* and because the addition of clavulanate extends the effective antibacterial spectrum of amoxicillin to include β-lactamase–producing bacteria, high-dose amoxicillin-clavulanate is particularly well-suited as a second-line drug for treating AOM. The 14 : 1 amoxicillin-clavulanate formulation contains twice as much amoxicillin as the previously available 7 : 1 formulation. Diarrhea, especially in infants and young children, is a common adverse effect but may be ameliorated in some cases by feeding active culture yogurt and usually is not severe enough to require cessation of treatment. Cefdinir has demonstrated broad efficacy in treatment, is generally well tolerated with respect to taste, and can be given as a once-daily regimen. The ability to also use cefdinir in most children with mild type 1 hypersensitivity reactions has further added to its favorable selection as a second-line agent. Both cefuroxime axetil and intramuscular ceftriaxone have important limitations for use in young children. The currently available suspension of cefuroxime axetil is not palatable and its acceptance is low. Ceftriaxone treatment entails both the pain of intramuscular injection and substantial cost, and the injection may need to be repeated once or twice at 2-day intervals to achieve the desired degree of effectiveness. Nonetheless, use of ceftriaxone is appropriate in severe cases of AOM when oral treatment is not feasible, or in highly selected cases after treatment failure using orally administered second-line antimicrobials (i.e., amoxicillin-clavulanate or cefuroxime axetil), or when highly resistant *S. pneumoniae* is found in aspirates obtained from diagnostic tympanocentesis.

Clarithromycin and azithromycin have only limited activity against nonsusceptible strains of *S. pneumoniae* and against β-lactamase–producing strains of nontypeable *H. influenzae.* Macrolide use also appears to be a major factor in causing increases in rates of resistance to macrolides by group A streptococcus and *S. pneumoniae* . Clindamycin is active against most strains of *S. pneumoniae*, including resistant strains, but is not active against nontypeable *H. influenzae* or *M. catarrhalis.*

Other antimicrobial agents that have been traditionally used in the management of AOM have such significant lack of effectiveness against resistant organisms that use seldom outweighs the potential side effects or complications possible from the medications. This includes cefprozil, cefaclor, loracarbef, cefixime, trimethoprim-sulfamethoxazole, and erythromycin-sulfisoxazole. Cefpodoxime has demonstrated reasonable effectiveness in some investigations but is generally poorly tolerated because of its taste.

Antimicrobial Prophylaxis

In children who have developed frequent episodes of AOM, antimicrobial prophylaxis with subtherapeutic doses of an aminopenicillin or a sulfonamide has been used in the past to provide protection against recurrences of AOM (although not of OME). However, because of the increased incidence of resistant organisms and the contribution of antimicrobial usage to bacterial resistance, the risks of sustained antimicrobial prophylaxis clearly outweigh potential benefits.

Myringotomy and Tympanocentesis

Myringotomy is a long-standing treatment for AOM but is not commonly needed in children receiving antimicrobials. **Indications for myringotomy** in children with AOM include severe, refractory pain; hyperpyrexia; complications of AOM such as facial paralysis, mastoiditis, labyrinthitis, or central nervous system infection; and immunologic compromise from any source. Myringotomy should be considered as third-line therapy in patients that have failed two courses of antibiotics for an episode of AOM. In children with AOM in whom clinical response to vigorous, second-line treatment has been unsatisfactory, either diagnostic tympanocentesis or myringotomy is indicated to enable identification of the offending organism and its sensitivity profile. Either procedure may be helpful in effecting relief of pain. Tympanocentesis with culture of the middle-ear aspirate may also be indicated as part of the sepsis work-up in very young infants with AOM who show systemic signs of illness such as fever, vomiting, or lethargy, and whose illness accordingly cannot be presumed to be limited to infection of the middle ear. Performing tympanocentesis can be facilitated by use of a specially designed tympanocentesis aspirator. Studies reporting the use of strict, individualized criteria for the diagnosis of AOM that include office tympanocentesis with bacterial culture followed by culture-guided antimicrobial therapy demonstrate significant reduction in the frequency of recurrent AOM episodes and tympanostomy tube surgery. However, many primary care physicians do not feel comfortable performing this procedure, there is the potential for complications, and parents may view this procedure as traumatic. Often, children requiring this intervention have a strong enough history of recurrent OM to warrant the consideration of tympanostomy tube placement, so that the procedure can be performed under general anesthesia.

Early Recurrence After Treatment

Recurrence of AOM after apparent resolution may be caused by either incomplete eradication of infection in the middle ear or upper respiratory tract reinfection by the same or a different bacteria or bacterial strain. Recent antibiotic therapy predisposes patients to an increased incidence of resistant organisms, which should also be considered in choosing therapy, and, generally, initiating therapy with a second-line agent is advisable (see Table 658.3).

Myringotomy and Insertion of Tympanostomy Tubes

When AOM is recurrent, despite appropriate medical therapy, consideration of surgical management of AOM with tympanostomy tube insertion is warranted. This procedure is effective in reducing the rate of AOM in patients with recurrent OM and in significantly improving the quality of life in patients with recurrent AOM. Individual patient factors, including the risk profile, severity of AOM episodes, child's development and age, presence of a history of adverse drug reactions, concurrent medical problems, and parental wishes, will affect the timing of a decision to consider referral for this procedure. When a patient experiences three episodes of AOM in a 6-mo period, or four episodes in a 12-mo period with one episode in the preceding 6 mo, potential surgical management of the child's AOM should be discussed with the parents. In this scenario, 2013 guidelines on tympanostomy tube placement indicate that if MEE if persistent in one or two ears and present at the time of evaluation by the otolaryngologist, then myringotomy is indicated. However, if MEE has cleared, the guidelines recommend holding off on myringotomy and offering observation unless there are additional considerations such as difficulty with tolerating antibiotic therapy (allergic concerns or other tolerance difficulties), severe episodes of acute OM, or other developmental considerations. Not infrequently, one or more of these additional considerations do impact a child's care.

Tube Otorrhea

Although tympanostomy tubes often reduce the incidence of AOM in most children, patients with tympanostomy tubes may still develop AOM. One advantage of tympanostomy tubes in children with recurrent AOM is that if patients do develop an episode of AOM with a functioning tube in place, these patients will manifest purulent drainage from the tube. By definition, children with functioning tympanostomy tubes without otorrhea do not have bacterial AOM as a cause for a presentation of fever or behavioral changes and should not be treated with oral antibiotics. If tympanostomy tube otorrhea develops, ototopical treatment, and not oral antibiotics, should be considered as first-line therapy, as recommended by the 2013 tympanostomy tube guidelines. With a functioning tube in place, the infection is able to drain, there is usually negligible pain associated with the infection, and the possibility of developing a serious complication from an episode of AOM is extremely remote. Importantly, strict water precautions after tympanostomy tube placement do not appear to impact the occurrence of posttympanostomy otorrhea, and as such water precautions are no longer recommended in children with myringotomy tubes, per the 2013 guidelines. However, when otorrhea does occur, it is important to maintain the ear canal dry while ototopical treatment is administered. The current quinolone otic drops approved by the U.S. Food and Drug Administration for use in the middle-ear space in children are formulated with ciprofloxacin/dexamethasone (Ciprodex) and ofloxacin (Floxin). The topical delivery of these otic drops allows them to use a higher antibiotic concentration than can be tolerated by administering oral antibiotics, and they have excellent coverage of even the most resistant strains of common middle-ear pathogens, as well as coverage of *S. aureus* and *Pseudomonas aeruginosa* . The high rate of success of these topical preparations, their broad coverage, the lower likelihood of their contributing to the development of resistant organisms, the relative ease of administration, the lack of significant side effects, and the lack of ototoxicity make them the 1st choice for tube otorrhea. Oral antibiotic therapy should generally be reserved for cases of tube otorrhea that have other associated systemic symptoms, patients who have difficulty in tolerating the use of topical preparations, or, possibly, patients who have failed an attempt at topical otic drops. Despite these advantages of ototopical therapy, survey data have indicated that, compared with otolaryngologists, primary care practitioners are less likely to prescribe ototopicals as 1st-line therapy in tympanostomy tube otorrhea. As a result of the relative ease in obtaining fluid for culture and the possibility of the development of fungal otitis, which has shown an increase with the utilization of broad-spectrum quinolone ototopicals, patients who fail topical therapy should also have culture performed to rule out the development of fungal otitis. Other otic preparations are available; although these either have some risk of ototoxicity or have not received approval for use in the middle ear, many of these preparations were widely used prior to the development of the current quinolone drops and were generally considered reasonably safe and effective. In all cases of tube otorrhea, attention to aural toilet (e.g., cleansing the external auditory canal of secretions, and avoidance of external ear water contamination) is important. In some cases with very thick, tenacious discharge, topical therapy may be inhibited due to lack of delivery of the medication to the site of infection. Suctioning and removal of the secretions, often done through referral to an otolaryngologist, may be quite helpful. When children with tube otorrhea fail to improve satisfactorily with conventional outpatient management, they may require tube removal, hospitalization to receive parenteral antibiotic treatment, or both.

Management of Otitis Media With Effusion

Management of OME depends on an understanding of its natural history and its possible complications and sequelae. Children with OME should be should be assessed for any baseline sensory, physical, cognitive, or behavioral factors risk which may portend risk of learning problems from middle ear effusion. Moreover, clinicians should evaluate developmentally at-risk children for OME at the time of diagnosis of an at-risk condition such as Down syndrome, autism, speech and language delay, permanent hearing loss, craniofacial syndromes, blindness, or global developmental delay; and at 12-18 mo of age (if diagnosed as being at risk prior to this time). However, children not at developmental risk and who do not have symptoms that may be attributable to OME, such as hearing difficulties, balance (vestibular) problems, poor school performance, behavioral problems, or ear discomfort should not be routinely screen children for OME. When MEE persists for longer than 3 mo, an age-appropriate hearing test and consideration of referral to an otolaryngologist are appropriate. In older children (generally older than age 4 yr), and depending upon the expertise in the primary care physician's office, hearing screening may be achieved by the primary care physician. For any child who fails a hearing screening in the primary care physician's office, referral to an otolaryngologist is warranted. In considering the decision to refer the patient for consultation, the clinician should attempt to determine the impact of the OME on the child and educate the family in this regard. Most cases of OME resolve without treatment within 3 mo. For children with OME being managed expectantly, the 2016 guidelines for management of OME recommend examination should be performed at 3- to 6-mo intervals, until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected. Although hearing loss may be of primary concern, OME causes a number of other difficulties in children that should also be considered. These include predisposition to recurring AOM, pain, disturbance of balance, and tinnitus. In addition, long-term sequelae that have been demonstrated to be associated with

OME include pathologic middle-ear changes; atelectasis of the TM and retraction pocket formation; adhesive OM; cholesteatoma formation and ossicular discontinuity; and conductive and sensorineural hearing loss. Long-term adverse effects on speech, language, cognitive, and psychosocial development have also been demonstrated. This impact is related to the duration of effusion present, whether the effusion is unilateral or bilateral, the degree of underlying hearing loss, and other developmental and social factors affecting the child. In considering the impact of OME on development, it is especially important to take into consideration the overall presentation of the child. Although it is unlikely that OME causing unilateral hearing loss in the mild range will have long-term negative effects on an otherwise healthy and developmentally normal child, even a mild hearing loss in a child with other developmental or speech delays certainly has the potential to compound this child's difficulties (Table 658.4). At a minimum, children with OME persisting longer than 3 mo deserve close monitoring of their hearing levels with skilled audiologic evaluation; frequent assessment of developmental milestones, including speech and language assessment; and attention paid to their rate of recurrent AOM.

Table 658.4

Sensory, Physical, Cognitive, or Behavioral Factors That Place Children Who Have Otitis Media With Effusion at an Increased Risk for Developmental Difficulties (Delay or Disorder)

Permanent hearing loss independent of otitis media with effusion
Suspected or diagnosed speech and language delay or disorder
Autism-spectrum disorder and other pervasive developmental disorders
Syndromes (e.g., Down) or craniofacial disorders that include cognitive, speech, and language delays
Blindness or uncorrectable visual impairment
Cleft palate with or without associated syndrome
Developmental delay

From American Academy of Family Physicians; American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Pediatrics Subcommittee on Otitis Media with Effusion: Otitis media with effusion, *Pediatrics* 113(5):1412–1429, 2004, Table 3, p. 1416.

Variables Influencing Otitis Media With Effusion Management Decisions

Patient-related variables that affect decisions on how to manage OME include the child's age; the frequency and severity of previous episodes of AOM and the interval since the last episode; the child's current speech and language development; the presence of a history of adverse drug reactions, concurrent medical problems, or risk factors such as daycare attendance; and the parental wishes. In considering surgical management of OME with tympanostomy tubes, particular benefit is seen in patients with persisting OME punctuated by episodes of AOM, because the tubes generally provide resolution of both conditions. Persistence of MEE after recurrent AOM (three episodes in 6 mo or four in 12 mo) indicate tympanostomy tube placement. Disease-related variables that most otolaryngologists consider in the treatment of OME include whether the effusion is unilateral or bilateral; the apparent quantity of effusion; the duration, if known; the degree of hearing impairment; the presence or absence of other possibly related symptoms, such as tinnitus, vertigo, or disturbance of balance; and the presence or absence of mucopurulent or purulent rhinorrhea, which, if sustained for longer than 2 wk, would suggest that concurrent nasopharyngeal or paranasal sinus infection is contributing to continuing compromise of middle-ear ventilation.

Medical Treatment

In some studies, antimicrobials have demonstrated some efficacy in resolving OME, presumably because they help to eradicate nasopharyngeal infection, unapparent middle-ear infection, or both. The most significant effects of antibiotics for OME have been shown with treatment durations of 4 wk and 3 mo. However, in the current era of bacterial antimicrobial resistance, the small potential benefit of antimicrobial therapy is outweighed by the negative potential of treatment and is not recommended. Instead, treatment should be limited to cases in which there is evidence of associated bacterial upper respiratory tract infection or untreated middle-ear infection. For this purpose, the most broadly effective drug available should be used as recommended for AOM.

The efficacy of corticosteroids in the treatment of OME has been demonstrated to be short term. Therefore the risk-to-benefit ratio for steroids is such that they are no longer recommended for treatment of OME. Antihistamine-decongestant combinations are not effective in treating children with OME and are not indicated in management of OME. Antihistamines alone, decongestants alone, and mucolytic agents are also ineffective and not recommended for treating patients with OME. The risk profile for decongestants and antihistamines in children are such that, unless there is some other medical condition such as documented allergic disease for antihistamine therapy, these medications are contraindicated for OME treatment. Randomized controlled trials do not support the use of topical intranasal steroid sprays to treat the manifestations of eustachian tube dysfunction and their use for OME resolution is also not recommended. Inflation of the eustachian tube by the Valsalva maneuver or other means has not demonstrated long-term efficacy but is unlikely to lead to significant harm. Other “alternative” therapies, including spinal manipulation, currently have no demonstrated efficacy or role in children with OME.

Myringotomy and Insertion of Tympanostomy Tubes

When OME persists despite an ample period of watchful waiting, generally 3-6 mo or perhaps longer in children with unilateral effusion, consideration of surgical intervention with tympanostomy tubes is appropriate. Myringotomy alone, without tympanostomy tube insertion, permits evacuation of MEE and may sometimes be effective, but often the incision heals before the middle-ear mucosa returns to normal and the effusion soon reaccumulates. Inserting a tympanostomy tube offers the likelihood that middle-ear ventilation will be sustained for at least as long as the tube remains in place and functional. Tympanostomy tubes have a variable duration of efficacy based on design. Tubes that are designed for a shorter duration, 6-12 mo, have a lesser impact on disease-free middle-ear spaces in children. Some studies comparing the efficacy of tympanostomy tube types, including shorter-acting tubes, with watchful waiting provide a less helpful assessment of the differences between these approaches. Tubes that are somewhat longer acting, effective for 12-18 mo, are generally more appropriate for most children undergoing tube placement. Regardless of type, tympanostomy tube placement nearly uniformly reverses the CHL associated with OME. Occasional episodes of obstruction of the tube lumen and premature tube extrusion may limit the effectiveness of tympanostomy tubes, and tubes can also be associated with otorrhea. However, placement of tympanostomy tubes is generally quite effective in providing resolution of OME in children. Tympanostomy tubes generally extrude on their own but rarely require surgical removal after several years in place. Sequelae following tube extrusion include residual perforation of the eardrum, tympanosclerosis, localized or diffuse atrophic scarring of the eardrum (which may predispose to the development of a retraction pocket), residual CHL, and cholesteatoma. The more serious of these sequelae are quite infrequent. Recurrence of MEE following the extrusion of tubes does develop, especially in younger children. However, most children without underlying craniofacial abnormalities require only 1 set of tympanostomy tubes. In developed countries, immunologic maturity and other developmental changes provide improved middle-ear health and resolution of chronic OME by the time of tube extrusion. However, in some populations and specifically First Peoples (includes Australian Aborigines, American Indians, Alaskan Eskimos, as well as other populations), even with an absence of craniofacial abnormalities, there is a preponderance of chronic OME, and these patients should have increased follow-up after tube extrusion. Because even previously persistent OME may clear spontaneously during the summer months, watchful waiting through the summer season may be advisable in children with OME who are otherwise well and without developmental or speech concerns. In considering surgical management of OME in children, primarily in those with bilateral disease and hearing loss, it has been demonstrated that placement of tympanostomy tubes results in a significant improvement in their quality of life.

Adenoidectomy

Adenoidectomy may reduce the risk of subsequent recurrences of both AOM and OME in older children who have undergone tube insertion and in whom, after extrusion of tubes, OM continues to be a problem. Efficacy appears to be independent of adenoid size and probably derives from removal of the focus of infection in the nasopharynx as a site of biofilm formation, chronic inflammation impacting eustachian tube function, and recurrent seeding of the middle ear via the eustachian tube. The 2016 guidelines state that adenoidectomy should not be performed at the time of tympanostomy tube insertion in children younger than 4 yr of age, unless a distinct indication exists (nasal obstruction, chronic adenoiditis). However, in children older than 4 yr of age, one should recommend tympanostomy tubes, adenoidectomy, or both when surgery is performed for OME.

Complications of Acute Otitis Media

Most complications of AOM consist of the spread of infection to adjoining or nearby structures, the development of chronicity, or both. Suppurative complications are relatively uncommon in children in developed countries but occur not infrequently in disadvantaged children whose medical care is limited. The complications of AOM may be classified as either intratemporal or intracranial (Table 658.5).

Table 658.5

Manifestations of the Sequelae and Complications of Otitis Media

COMPLICATION	CLINICAL FEATURES
ACUTE	
Perforation with otorrhea	Immobile tympanic membrane secondary to visible perforation, exudate in ear canal
Acute mastoiditis with periostitis	Tenderness and erythema over mastoid process, no destruction of bony trabeculae
Acute mastoid osteitis	Destruction of bony trabeculae; tenderness and erythema over mastoid process coupled with outward displacement of pinna
Petrositis	Infection of perilabyrinthine cells; may present with otitis, paralysis of lateral rectus, and ipsilateral orbital or facial pain (Gradenigo syndrome)
Facial nerve palsy	Peripheral cranial nerve VII paralysis
Labyrinthitis	Vertigo, fever, ear pain, nystagmus, hearing loss, tinnitus, nausea and vomiting
Lateral sinus thrombosis	Headache, fever, seizures, altered states of consciousness, septic emboli
Meningitis	Fever, headache, nuchal rigidity, seizures, altered states of consciousness
Extradural empyema	Fever, headache, seizures, altered states of consciousness
Subdural empyema	Fever, headache, seizures, altered states of consciousness
Brain abscess	Fever, headache, seizures, altered states of consciousness, focal neurologic examination
NONACUTE	
Chronic perforation	Immobile tympanic membrane secondary to perforation
Otitis media with effusion (OME)	Immobile, opaque tympanic membrane
Adhesive otitis	Irreversible conductive hearing loss secondary to chronic OME

Tympanosclerosis	Thickened white plaques may cause conductive hearing loss
Chronic suppurative otitis media	Following acute otitis media with perforation, secondary infection with *Staphylococcus aureus, Pseudomonas aeruginosa* , or anaerobes develops, causing chronic otorrhea
Cholesteatoma	White, pearl-like destructive tumor with otorrhea arising near or within tympanic membrane; may be secondary to chronic negative middle ear pressure
Otitic hydrocephalus	Increased intracranial pressure secondary to AOM; signs and symptoms include severe headaches, blurred vision, nausea, vomiting, papilledema, diplopia (abducens paralysis)

AOM, acute otitis media.

From Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, editors: *Nelson Pediatric Symptom-Based Diagnosis* , Philadelphia, 2018, Elsevier, Table 4.6, p 67.

Intratemporal Complications

Direct but limited extension of AOM leads to complications within the local region of the ear and temporal bone. These complications include dermatitis, TM perforation, chronic suppurative OM (CSOM), mastoiditis, hearing loss, facial nerve paralysis, cholesteatoma formation, and labyrinthitis.

Infectious Dermatitis

This is an infection of the skin of the external auditory canal resulting from contamination by purulent discharge from the middle ear. The skin is often erythematous, edematous, and tender. Management consists of proper hygiene combined with systemic antimicrobials and ototopical drops as appropriate for treating AOM and tube otorrhea.

Tympanic Membrane Perforation

Rupture of the TM can occur with episodes of either AOM or OME. Although damage to the TM from these episodes generally heals spontaneously, chronic perforations can develop in a small number of cases and require further surgical intervention in the future.

Chronic Suppurative Otitis Media

CSOM consists of persistent middle-ear infection with discharge through a TM perforation. The disease is initiated by an episode of AOM with rupture of the membrane. The mastoid air cells are invariably involved. The most common etiologic organisms are *P. aeruginosa* and *S. aureus;* however, the typical AOM bacterial pathogens may also be the cause, especially in younger children or in the winter months. Treatment is guided by the results of microbiologic investigation. If an associated cholesteatoma is not present, parenteral antimicrobial treatment combined with assiduous aural cleansing is likely to be successful in clearing the infection, but in refractory cases, tympanomastoidectomy can be required. Similar to chronic OME, this is much more commonly found in children with First Peoples ancestry.

Mastoiditis

Mastoiditis is an important complication associated with OM (see Chapter 659).

Facial Paralysis

The facial nerve, as it traverses the middle ear and mastoid bone, may be affected by adjacent infection. Facial paralysis occurring as a complication of AOM is uncommon and often resolves after myringotomy and parenteral antibiotic treatment. Facial paralysis in the presence of AOM requires urgent attention because prolonged infection can result in the development of permanent facial paralysis, which can have a devastating effect on a child. Facial paralysis in an infant or child requires complete and unequivocal examination of the TM and middle-ear space. Any difficulty in examination requires urgent consultation with an otolaryngologist. Any examination that demonstrates an ear abnormality also requires urgent referral to an otolaryngologist. If facial paralysis develops in a child with mastoid osteitis or with CSOM, mastoidectomy should be undertaken urgently.

Cholesteatoma

Cholesteatoma is a cystlike growth originating in the middle ear, lined by keratinized, stratified squamous epithelium and containing desquamated epithelium and/or keratin (see Chapter 656 ; Fig. 658.7).

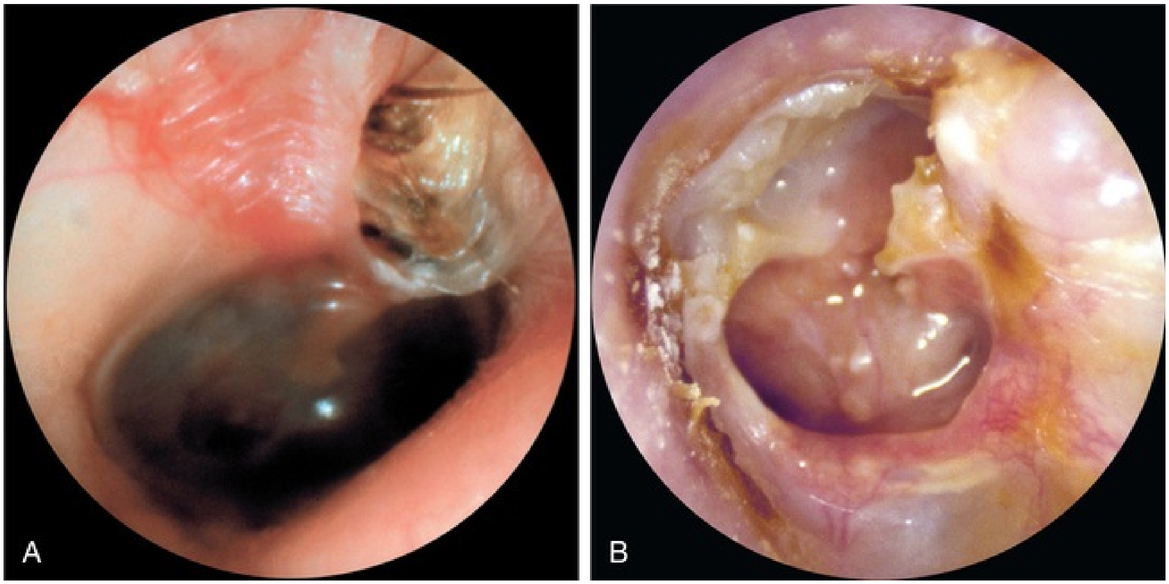

FIG. 658.7 **A,** Primary acquired cholesteatoma in the region of the pars flaccida with scutum erosion. **B,** Cholesteatoma developing at the margin of perforation (secondary acquired cholesteatoma) with secondary infection. (From Chole RA, Sudhoff HH: Chronic otitis media, mastoiditis, and petrositis. In Flint PW, Haughey BH, Lund VJ, et al, editors: Cummings otolaryngology—head and neck surgery, ed 5, Philadelphia, 2010, Elsevier, Figs 139-4, 139-5.)

Acquired cholesteatoma develops most often as a complication of long-standing chronic OM. The condition also may develop from a deep retraction pocket of the TM or as a consequence of epithelial implantation in the middle-ear cavity from traumatic perforation of the TM or insertion of a tympanostomy tube. Cholesteatomas tend to expand progressively, causing bony resorption, often extend into the mastoid cavity, and may extend intracranially with potentially life-threatening consequences. Acquired cholesteatoma commonly presents as a chronically draining ear in a patient with a history of previous ear disease. Cholesteatoma should be suspected if otoscopy demonstrates an area of TM retraction or perforation with white, caseous debris persistently overlying this area. Along with otorrhea from this area, granulation tissue or polyp formation identified in conjunction with this history and presentation should prompt suspicion of cholesteatoma. The most common location for cholesteatoma development is in the superior portion of the TM *(pars flaccida)*. Most patients also present with CHL on audiologic evaluation. When cholesteatoma is suspected, otolaryngology consultation should be sought immediately. Delay in recognition and treatment can have significant long-term consequences, including the need for more extensive surgical treatment, permanent hearing loss, facial nerve injury, labyrinthine damage with loss of balance function, and intracranial extension. The required treatment for cholesteatoma is tympanomastoid surgery.

Congenital cholesteatoma is an uncommon condition generally identified in younger patients (Fig. 658.8). The etiology of congenital cholesteatoma is thought to be a result of epithelial implantation in the middle-ear space during otologic development in utero. Congenital cholesteatoma most commonly presents in the anterior-superior quadrant of the TM but can be found elsewhere. Congenital cholesteatoma appears as a discrete, white opacity in the middle-ear space on otoscopy. Unlike patients with acquired cholesteatoma, there is generally not a strong history of OM or chronic ear disease, history of otorrhea, or changes in the TM anatomy such as perforation or retraction. Similar to acquired cholesteatoma many patients do have some degree of abnormal findings on audiologic evaluation, unless identified very early. Congenital cholesteatoma also requires surgical resection.

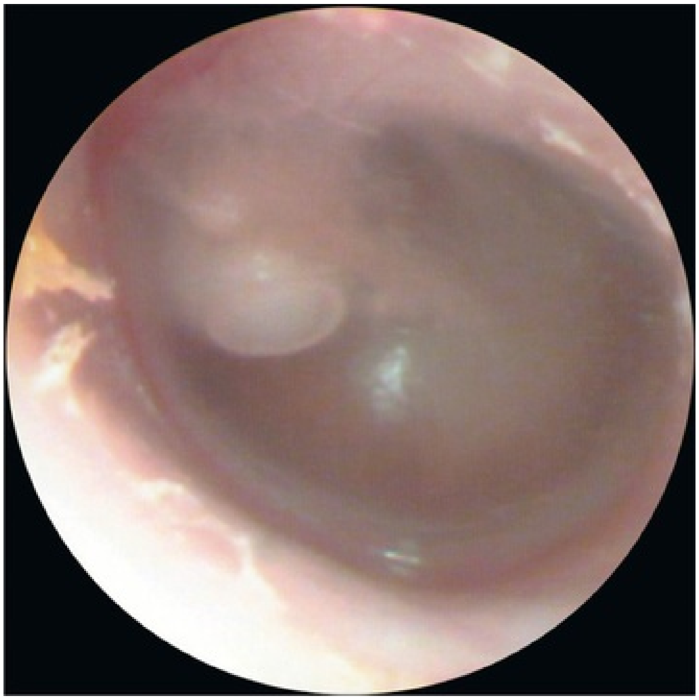

FIG. 658.8 Congenital chronic otitis media with cholesteatoma. (From Chole RA, Sudhoff HH: Chronic otitis media, mastoiditis, and petrositis. In Flint PW, Haughey BH, Lund VJ, et al. (eds): Cummings otolaryngology—head and neck surgery, ed 5, Philadelphia, 2010, Elsevier, Fig 139-6.)

Labyrinthitis

This occurs uncommonly as a result of the spread of infection from the middle ear and/or mastoid to the inner ear (see Chapter 660). Cholesteatoma or CSOM is the usual source. Symptoms and signs include vertigo, tinnitus, nausea, vomiting, hearing loss, nystagmus, and clumsiness. Treatment is directed at the underlying condition and must be undertaken promptly to preserve inner-ear function and prevent the spread of infection.

Intracranial Complications

Meningitis, epidural abscess, subdural abscess, focal encephalitis, brain abscess (see Chapters 621 and 622), sigmoid sinus thrombosis (also called *lateral sinus thrombosis*), and otitic hydrocephalus each may develop as a complication of acute or chronic middle-ear or mastoid infection, through direct extension, hematogenous spread, or thrombophlebitis. Bony destruction adjacent to the dura is often involved, and a cholesteatoma may be present. In a child with middle-ear or mastoid infection, the presence of any systemic symptom, such as high spiking fevers, headache, or lethargy of extreme degree, or a finding of meningismus or of any central nervous system sign on physical examination should prompt suspicion of an intracranial complication.

When an intracranial complication is suspected, lumbar puncture should be performed only after imaging studies establish that there is no evidence of mass effect or hydrocephalus. In addition to examination of the cerebrospinal fluid, culture of middle-ear exudate obtained via tympanocentesis may identify the causative organism, thereby helping to guide the choice of antimicrobial medications. Myringotomy should be performed to permit middle-ear drainage. Concurrent tympanostomy tube placement is preferable to allow for continued decompression of the “infection under pressure” that is the causative event leading to intracranial spread of the infection.

Treatment of intracranial complications of OM requires urgent, otolaryngologic, and, often, neurosurgical consultation, intravenous antibiotic therapy, drainage of any abscess formation, and tympanomastoidectomy in patients with coalescent mastoiditis.

Sigmoid sinus thrombosis may be complicated by dissemination of infected thrombi with resultant development of septic infarcts in various organs. With prompt recognition and wide availability of MRI, which facilitates diagnosis, this complication is exceedingly rare. Mastoidectomy may be required even in the absence of osteitis or coalescent mastoiditis, especially in the case of propagation or embolization of infected thrombi. In the absence of coalescent mastoiditis, sinus thrombosis can often be treated with tympanostomy tube placement and intravenous antibiotics. Anticoagulation therapy may also be considered in the treatment of sigmoid sinus thrombosis; however, otolaryngology consultation should be obtained before initiating this therapy to coordinate the possible need for surgical intervention prior to anticoagulation.

Otitic hydrocephalus, a form of **idiopathic intracranial hypertension,** or **pseudotumor cerebri** (see Chapter 623), is an uncommon condition that consists of increased intracranial pressure without dilation of the cerebral ventricles, occurring in association with acute or chronic OM or mastoiditis. The condition is commonly also associated with lateral sinus thrombosis, and the pathophysiology is thought to involve obstruction by thrombus of intracranial venous drainage into the neck, producing a rise in cerebral venous pressure and a consequent increase in cerebrospinal fluid pressure. Symptoms are those of increased intracranial pressure. Signs may include, in addition to evidence of OM, paralysis of 1 or both lateral rectus muscles and papilledema with or without visual acuity loss. MRI can confirm the diagnosis. Treatment measures include the use of antimicrobials and medications such as acetazolamide or furosemide to reduce intracranial pressure, mastoidectomy, repeated lumbar puncture, lumboperitoneal shunt, and ventriculoperitoneal shunt. If left untreated, otitic hydrocephalus may result in loss of vision secondary to optic atrophy.

Physical Sequelae

The physical sequelae of OM consist of structural middle-ear abnormalities resulting from long-standing middle-ear inflammation. In most instances, these sequelae are consequences of severe and/or chronic infection, but some may also result from the noninfective inflammation of long-standing OME. The various sequelae may occur singly, or interrelatedly in various combinations.

Tympanosclerosis consists of whitish plaques in the TM and nodular deposits in the submucosal layers of the middle ear. The changes involve hyalinization with deposition of calcium and phosphate crystals. Uncommonly, there may be associated CHL. In developed countries, probably the most common cause of tympanosclerosis is tympanostomy tube insertion.

Atelectasis of the TM is a descriptive term applied to either severe retraction of the TM caused by high negative middle-ear pressure or loss of stiffness and medial prolapse of the membrane from long-standing retraction or severe or chronic inflammation. A **retraction pocket** is a localized area of atelectasis. Atelectasis is often transient and usually unaccompanied by symptoms, but a deep retraction pocket may lead to erosion of the ossicles and adhesive otitis and may serve as the nidus of a cholesteatoma. For a deep retraction pocket, and for the unusual instance in which atelectasis is accompanied by symptoms such as otalgia, tinnitus, or CHL, the required treatment is tympanostomy tube insertion and, at times, tympanoplasty. Patients with persisting atelectasis and retraction pockets should have referral to an otolaryngologist.

Adhesive OM consists of proliferation of fibrous tissue in the middle-ear mucosa, which may, in turn, result in severe TM retraction, CHL, impaired movement of the ossicles, ossicular discontinuity, and cholesteatoma. The hearing loss may be amenable to surgical correction.

Cholesterol granuloma is an uncommon condition in which the TM may appear to be dark blue secondary to middle-ear fluid of this color. Cholesterol granulomas are rare, benign cysts that occur in the temporal bone. They are expanding masses that contain fluids, lipids, and cholesterol crystals surrounded by a fibrous lining and generally require surgical removal. Tympanostomy tube placement will not provide satisfactory relief. This lesion requires differentiation from bluish middle-ear fluid, which can also rarely develop in patients with the more common OME.

Chronic perforation may rarely develop after spontaneous rupture of the TM during an episode of AOM or from acute trauma but more commonly results as a sequela of CSOM or as a result of failure of closure of the TM following extrusion of a tympanostomy tube. Chronic perforations are generally accompanied by CHL. Surgical repair of a TM perforation is recommended to restore hearing, prevent infection from water contamination in the middle-ear space, and prevent cholesteatoma formation. Chronic perforations are almost always amenable to surgical repair, usually after the child has been free of OM for an extended period.

Permanent **CHL** (see Chapter 655) may result from any of the conditions just described. Rarely, permanent sensorineural hearing loss may occur in association with acute or chronic OM, secondary to spread of infection or products of inflammation through the round window membrane, or as a consequence of suppurative labyrinthitis.

Possible Developmental Sequelae

Permanent hearing loss in children has a significant negative impact on development, particularly in speech and language. The degree to which OM impacts long-term development in children is difficult to assess, and there have been conflicting studies examining this question. Developmental impact is most likely to be significant in children that have greater levels of hearing loss, hearing loss that is sustained for longer periods of time, or hearing loss that is bilateral and in children who have other developmental difficulties or risk factors for developmental delay (Table 658.4).

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CHAPTER 659

Acute Mastoiditis

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Mastoiditis, a suppurative infection of the mastoid air cell system, is one of the most common infectious complications of acute otitis media. Coalescent mastoiditis occurs when the suppurative infection leads to bony breakdown of the fine bony septa separating individual mastoid air cells.

Anatomy

The temporal bone forms a portion of the skull base and has multiple complex anatomic functions. The mastoid process is a pyramid-shaped outgrowth of the temporal bone. The inferior extent is attached to the sternocleidomastoid muscle. The mastoid process borders the middle cranial fossa, posterior cranial fossa, and sigmoid sinus. It is composed of a system of interlinked mucosa-lined air cells that communicate with the middle ear space and contains the fallopian canal, which includes the facial nerve, the chorda tympani supplying taste to the anterior two third of the tongue, and the semicircular canal system. Because the mastoid cavity is anatomically adjacent to the meninges, brain, venous sinuses of the brain, facial nerve, and cervical lymph nodes, mastoiditis often accompanies or precedes intracranial complications of acute otitis media.

Epidemiology

In the preantibiotic era, acute mastoiditis was much more common than nowadays and a feared complication of acute otitis media (AOM) with high rates of intracranial infectious complications, morbidity, and mortality. Mastoiditis currently occurs in approximately 1-4 cases per 100,000 population <2 yr and less commonly among older children. A multicenter study with 223 consecutive cases of acute mastoiditis reported 28% of patients were younger than 1 yr of age, 38% of patients were between 1 and 4 yr of age, 22% of patients were between 4 and 8 yr of age, and 8% of patients were between 8 and 18 yr of age. Some studies reported decreased incidence of acute mastoiditis following introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) while others reported no change or nominal increases. One study reported a sharp decrease in acute mastoiditis beginning in 2010, which coincided with licensure and widespread use of the 13-valent pneumococcal conjugate vaccine (PCV13). Another study, which included data from 8 hospitals, found that the proportion of PCV13 serotypes isolated from cases of mastoiditis decreased from 50% in 2011 to 29% in 2013, with most of the decrease attributable to decreases in serotype 19A. Changes in rates of mastoiditis are likely related to changing incidence of acute otitis media in response to pneumococcal conjugate vaccines. Other factors influencing the occurrence of mastoiditis include rate of antibiotic prescription for AOM, access to healthcare, and rates of antimicrobial resistance. In countries such as the Netherlands and Iceland that adhere to a watchful waiting strategy for treatment of AOM, rates of acute mastoiditis have increased slightly compared with countries where antibiotics are routinely used to treat AOM, although the causal nature of this relationship is unclear. Despite large differences in antibiotic prescription rates in different countries, due to the overall low incidence of acute mastoiditis, the number of children needed to be treated with antibiotics to prevent one case of acute mastoiditis ranges from 2,500 to 4,800. Some studies have reported a recent increase in incidence, which has correlated with an increase in infections with drug resistant bacteria. All-cause mortality among children with mastoiditis is 0.03%.

Microbiology

Streptococcus pneumoniae remains the most common pathogen cultured from cases of acute mastoiditis (Table 659.1). Following introduction of PCV7, pneumococcal serotype 19A was commonly associated with acute mastoiditis. This serotype is frequently resistant to penicillin and macrolide antibiotics. PCV13 use has been associated with fewer serotype 19A infections overall; its impact on the etiology of mastoiditis is less clear. Other bacteria commonly cultured include *Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa*, and *Haemophilus influenzae* . *P. aeruginosa* is more likely in patients with chronic otitis media and/or cholesteatoma, older children, and those with previous tympanostomy tubes.

Table 659.1

Etiology of Acute Mastoiditis

Bacteria	**Frequency**
Streptococcus pneumoniae	10–51%
Streptococcus pyogenes	0–12%
Staphylococcus aureus	2–10%
Pseudomonas aeruginosa	10%
Haemophilus influenzae	2–3%
No growth	20–40%

Clinical Manifestations

Acute mastoiditis and AOM present similarly in children. Ninety-seven percent of children with an acute mastoiditis have a coexisting acute otitis media on the affected side. The remaining 3% of children with acute mastoiditis either had a serous middle ear effusion at the time of presentation or had a history of AOM within the past 2 wk. Other clinical manifestations include protrusion of the ear (87%), retroauricular swelling and tenderness (67%), retroauricular erythema (87%), fever (60%), otalgia, and hearing loss (Table 659.2). Children with acute mastoiditis were less likely to have bilateral infection. Some children do not have external signs of infection.

Table 659.2

Differential Diagnosis of Postauricular Involvement of Acute Mastoiditis With Periosteitis/Abscess

Disease	**POSTAURICULAR SIGNS AND SYMPTOMS**				**External Canal Infection**	**Middle-Ear Effusion**
	Crease*	**Erythema**	**Mass**	**Tenderness**		
Acute mastoiditis with periosteitis	May be absent	Yes	No	Usually	No	Usually
Acute mastoiditis with subperiosteal abscess	Absent	Maybe	Yes	Yes	No	Usually
Periosteitis of pinna with postauricular extension	Intact	Yes	No	Usually	No	No
External otitis with postauricular	Intact	Yes	No	Usually	Yes	No

extension						
Postauricular lymphadenitis	Intact	No	Yes[†]	Maybe	No	No

[*] Postauricular crease (fold) between pinna and postauricular area.

[†] Circumscribed.

From Bluestone CD, Klein JO, editors: *Otitis media in infants and children* , ed 3, Philadelphia, 2001, WB Saunders, p 333.

Imaging

Acute mastoiditis is usually diagnosed based on history and clinical findings. CT scan of the temporal bone can confirm the diagnosis, whereas head CT can identify intracranial complications (see Chapter 658), including epidural abscess or subdural empyema. Findings of acute mastoiditis include bony demineralization, loss of bony septations in the mastoid cavity (Fig. 659.1), and, occasionally, subperiosteal abscess (Fig. 659.2). CT scans have the advantage of being readily available in most emergency rooms, can quickly evaluate for intracranial complications, and can identify whether there is bony destruction or a drainable fluid collection. Contrast administration is necessary as part of the CT scan to allow evaluation for sigmoid sinus thrombosis (Fig. 659.3) and to evaluate for abscess formation. Magnetic resonance imaging is generally reserved for patients in whom there is a suspected intracranial complication. Incidental detection of mastoid air cell opacification occurs in more than 20% of children (and in 40% of children younger than 2 yr) undergoing MRI for other reasons, so imaging findings must be interpreted in the appropriate clinical context.

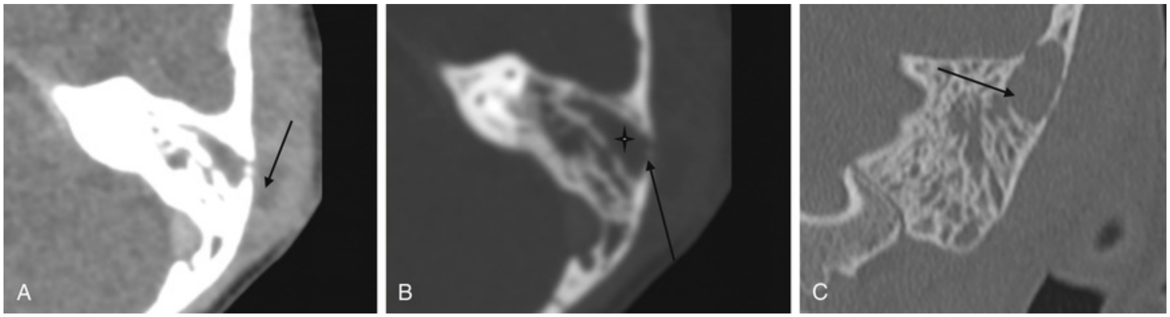

FIG. 659.1 This contrasted CT scan shows coalescent mastoiditis with subperiosteal abscess formation. Panel A and B contain axial images with soft tissue windows and bone windows, respectively. In panel A, the *arrow*

points to the subperiosteal abscess. The *star* in panel B shows the loss of bony septations in the mastoid cavity and the *arrow* points to the erosion of the bony cortex. Panel C is a coronal image showing demineralization of the mastoid tegmen abutting the middle cranial fossa. The image in panel C is a precursor to epidural abscess formation.

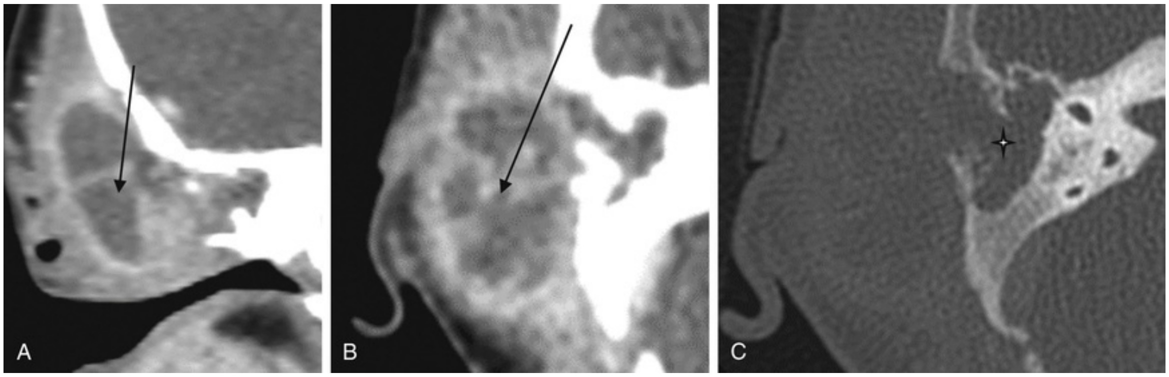

FIG. 659.2 This contrasted CT scan shows an advanced case of coalescent mastoiditis with subperiosteal abscess formation. Panel A and B contain axial and coronal images, respectively. In panel A and B the *arrow* points to the subperiosteal abscess. In panel C, there is extensive loss of bony septations in the mastoid cavity in the area noted with the *star.*

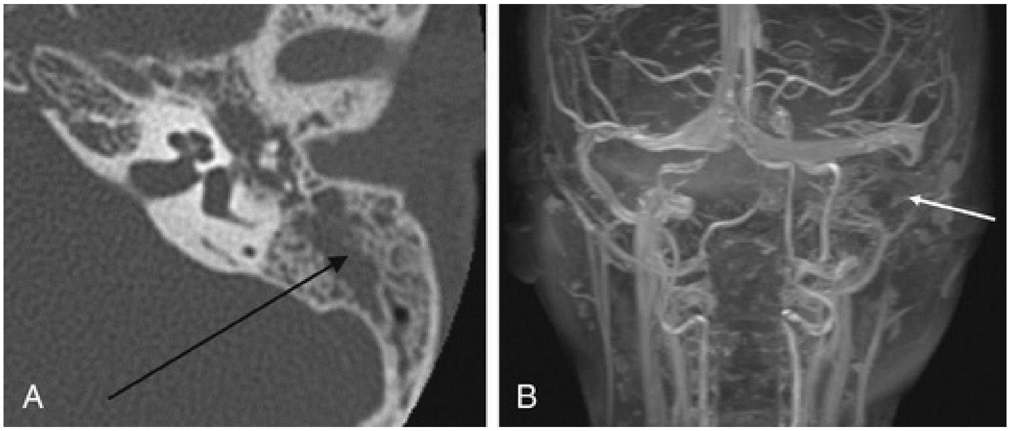

FIG. 659.3 Panel A contains an axial CT scan with bone windows. There is opacification of the mastoid air cells, a small region of coalescence as indicated by the *arrow,* and opacification of the middle ear space. Panel B shows a CT venogram with a sigmoid sinus thrombosis. The *arrow* points to the area where a patent sigmoid sinus should be present.

There is a limited role for ultrasound in diagnosis of acute mastoiditis.

Ultrasound can be used as a screening test when a postauricular subperiosteal abscess is suspected due to clinical findings such as protrusion of the pinna and retroauricular erythema. If there is a fluid collection on ultrasound or concern for a defect in the cranial vault, further imaging with a CT and/or MRI would be recommended. Because ultrasound cannot identify intracranial complications, its use must be limited to a highly selected patient population.

Management

Managing acute mastoiditis first requires diagnosing it, and in many ways that is the most difficult part of the process. Acute mastoiditis is a rare complication of AOM, and there is a large degree of overlap between the presentations of children with both disease processes. For the pediatrician confronted with a majority of uncomplicated acute otitis media, it is difficult to decide when to initiate a more extensive evaluation. Any time there is a purulent middle ear effusion along with postauricular findings, acute mastoiditis needs to be in the differential diagnosis. In general, children with acute mastoiditis will appear sicker than children with uncomplicated acute otitis media and many of them have already failed to respond to appropriate antibiotic therapy for acute otitis media. Focal neurologic deficits in a child with acute otitis media or mastoiditis suggest intracranial spread of infection or facial paresis as an additional complication. In a child with suspected mastoiditis, it is critical to document normal facial nerve function at the time of the initial exam so that if this complication does develop during the hospital course, the surgical team can be sure of the time course of the complication.

Complete blood count typically reveals leukocytosis with neutrophil predominance. C-reactive protein is often highly elevated. If otorrhea is present, implying a perforated tympanic membrane, the fluid should be sent for gram stain and culture. Blood culture should be considered in any child appearing toxic. For children with postauricular findings consistent with acute mastoiditis, admission to the hospital for intravenous antibiotic therapy and serial exams is recommended.

Deciding whether to obtain imaging is a decision made on an individual patient basis. In highly selected cases, ultrasound can be helpful to differentiate postauricular erythema from a postauricular abscess and avoids the risk of ionizing radiation exposure. However, ultrasound is not as sensitive as CT scanning and will underdiagnose postauricular abscess formation and will provide no information as to whether there is an intracranial complication present such as a brain abscess. Some authors advocate deferring CT scanning in patients with clinically suspected acute mastoiditis and without focal neurologic findings to allow for an initial 24-48 hr period of intravenous antibiotic therapy as an inpatient. If there is any concern about the possibility of an intracranial complication, a contrasted CT scan is the most sensitive test readily available and should be ordered upon presentation.

Antibiotic therapy should initially be administered intravenously. Empiric antibiotic selection may include a β-lactam/β-lactamase inhibitor combination (e.g., ampicillin-sulbactam) or third-generation cephalosporin (e.g., cefotaxime, ceftriaxone). In children with chronically draining ears or concern for cholesteatoma, there is an increased incidence of gram-negative infection and coverage should include antibiotics with activity against *Pseudomonas* spp. (e.g., ceftazidime, cefepime). If intracranial infection is suspected, broader spectrum antimicrobial coverage (e.g., vancomycin plus a 3rd-generation cephalosporin) should be initiated. In cases of uncomplicated acute mastoiditis (e.g., absence of intracranial complications or localized abscess formation), a 24-48 hr trial of intravenous antibiotics may yield clinical improvement without surgical intervention. The total duration of therapy is 3-4 wk, with transition from intravenous to oral therapy at discharge for those without intracranial complications. The optimal duration of intravenous therapy is unknown, but some experts recommend a minimum of 7 days of intravenous therapy prior to oral transition, whereas others transition once the patient demonstrates clinical improvement and surgical intervention is no longer required.

Otolaryngology consultation can be helpful to assist with management and to determine whether surgical intervention would be beneficial. Many patients will benefit from tympanostomy tube placement at the time of the acute infection to allow localized ototopical antibiotic treatment and aspiration of middle ear fluid for culture and sensitivity. In a patient with an additional extracranial complication such as facial paresis, drainage of the middle ear space with placement of a tympanostomy tube is required and should take place urgently. A small group of patients may necessitate mastoidectomy, surgical removal of diseased bone and granulation tissue in the mastoid cavity. At the time of surgery, a drain is often placed to allow purulent secretions an egress. Indications for mastoidectomy include coalescent mastoiditis, postauricular abscess formation, infectious intracranial complication, and failure to respond to appropriate IV antibiotics. When intracranial complications occur or there are mental status changes, evaluation by otolaryngology and neurosurgery and emergent mastoidectomy are indicated. Most children with mastoiditis make a full recovery. Long-term otologic complications like sensorineural or conductive hearing loss are uncommon. A posttreatment audiogram is often obtained to evaluate the hearing status after an infection.

Special Situations

When treating acute mastoiditis, several uncommon situations require particular attention. Selecting empiric antibiotics for unvaccinated and undervaccinated children is challenging and in this patient population, it is especially important to obtain a sample of middle ear fluid for Gram stain and culture to guide antibiotic therapy. There is an increased incidence in acute mastoiditis in children with autism spectrum disorder. Immunocompromised patients should be treated more aggressive medically with prolonged courses of antibiotic and may benefit from more aggressive surgical treatment to remove infected tissue. Sigmoid sinus thrombosis can occur secondary to acute mastoiditis. If this does occur, in addition to the standard treatment for acute mastoiditis, consideration should be given to involving hematology and for administering systemic anticoagulation. Otitic hydrocephalus, which is elevated intracranial pressure following middle ear infection, is associated with sigmoid sinus thrombosis, and management requires consultation with neurology and/or neurosurgery.

More children with profound sensorineural hearing loss are undergoing cochlear implantation in one or both ears at an early age. One study reported a 3.5% rate of acute mastoiditis in children with a cochlear implant. Despite having a foreign body present in the middle ear and inner ear space, the majority of cases of acute mastoiditis can be managed with tympanostomy tube placement, intravenous antibiotic therapy, and incision and drainage of an abscess without explantation of the device.

Benign and malignant tumors can affect the temporal bone of children, although these tumors are very rare. The presentation mimics that of chronic otitis media and chronic mastoiditis and this often leads to a delay in diagnosis. Hearing loss, otalgia, and otorrhea are common symptoms. The main differentiating factor is the protracted course of otorrhea and refractory nature of symptoms despite appropriate medical therapy. Aural polyps or a mass lesion may be present on physical exam. Potential causes include rhabdomyosarcoma, nonrhabdomyosarcomatous sarcoma (including chondrosarcoma, chordoma, osteosarcoma, Ewing sarcoma, fibrosarcoma, angiosarcoma, and chloroma), Langerhans cell histiocytosis (formerly histiocytosis X) (Fig. 659.4), lymphoma, and metastasis, as well as multiple other rare tumors.

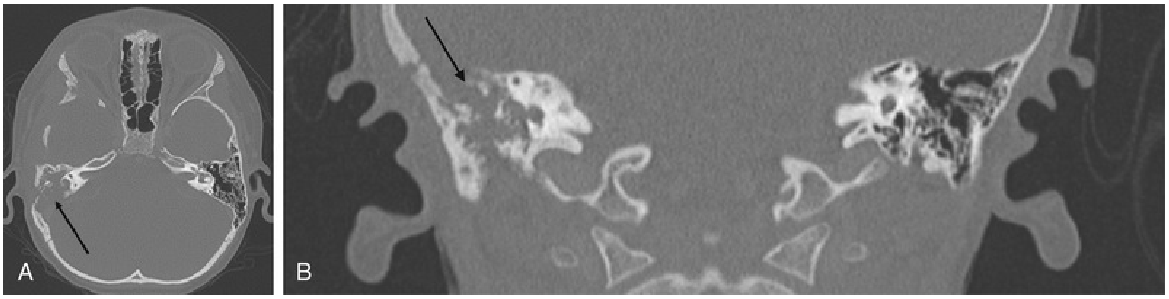

FIG. 659.4 Panel A and B contain an axial and coronal CT scan, respectively, of a patient with Langerhans cell histiocytosis of the right temporal bone. In panel A there is opacification of the mastoid with loss of bony septations. There is erosion of the bone separating the cranial fossa from the mastoid cavity *(arrow)* . Panel B shows the bony erosion caused by the tumor and the erosion of the mastoid tegmen *(arrow)* .

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CHAPTER 660

The Inner Ear and Diseases of the Bony Labyrinth

Joseph Haddad Jr, Sonam N. Dodhia

Genetic factors can impact the anatomy and function of the inner ear. Infectious agents, including viruses, bacteria, and protozoa, also can cause abnormal function, most commonly as sequelae of congenital infection (see Table 655.2) or bacterial meningitis (see Chapter 621.1). Other acquired diseases of the labyrinthine capsule include otosclerosis, osteopetrosis, Langerhans cell histiocytosis (see Chapter 534.1), fibrous dysplasia, and other types of bony dysplasia. All of these can cause both conductive hearing loss (CHL) and sensorineural hearing loss (SNHL), as well as vestibular dysfunction.

Other Diseases of the Inner Ear

Labyrinthitis (also called **vestibular neuritis**) may be a complication of direct spread of infection from acute or chronic otitis media or mastoiditis and also can complicate bacterial meningitis as a result of organisms entering the labyrinth through the internal auditory meatus, endolymphatic duct, perilymphatic duct, vascular channels, or hematogenous spread. Clinical manifestations of vestibular neuritis can include a sudden onset of rotatory vertigo, dysequilibrium, postural imbalance (furniture walking) with falls to the affected side, deep-seated ear pain, nausea, vomiting, and spontaneous horizontal (occasionally rotary) nystagmus.

The dizziness may last a few days, but balance issues, particularly following rapid head movements toward the affected ear, may last for months. Vestibular neuritis is usually unilateral and is not associated with other neurologic defects; subjective hearing loss is unusual in vestibular neuritis. If hearing loss is present, idiopathic SNHL should be considered, as well as classical labyrinthitis (vestibular and cochlear nerves). Treatment of vestibular neuritis may include prednisone and vestibular rehabilitative exercises. Recurrent episodes should suggest another diagnosis such as vestibular migraine or benign paroxysmal positional vertigo.

In children, viral labyrinthitis is often associated with hearing loss. **Acute serous labyrinthitis** , characterized by mild symptoms of vertigo and hearing loss, most commonly develops secondary to middle-ear infection without direct invasion. **Acute suppurative labyrinthitis** , characterized by abrupt, severe onset of these symptoms, may be caused by bacterial meningitis, or acute middle ear or mastoid infection via a dehiscent horizontal semicircular canal. In these latter cases, a cholesteatoma is almost always present. Treatment of acute infectious labyrinthitis includes antimicrobial agents in cases of bacterial infection or antiviral agents (acyclovir, valacyclovir) in cases of herpes zoster oticus. Oral corticosteroids reduce labyrinthine inflammation and may prevent sequelae. A short course (≤3 days) of vestibular suppressants (dimenhydrinate 1-2 mg/kg) alleviates acute symptoms such as nausea. If it is secondary to otitis media, otologic surgery may be required to remove underlying cholesteatoma or drain the middle ear and mastoid. **Chronic labyrinthitis** , most commonly associated with cholesteatoma, manifests with SNHL and vestibular dysfunction that develops over time; surgery is required to remove the cholesteatoma. Chronic labyrinthitis also occurs uncommonly secondary to long-standing otitis media, with the slow development of SNHL, usually starting in the higher frequencies, and possibly with vestibular dysfunction. In addition, and more commonly, children with chronic middle-ear fluid often are unsteady or off balance, a situation that improves immediately when the fluid resolves.

Vertigo and dizziness are common among older children and adolescents. Benign **paroxysmal vertigo,** the most common cause of vertigo in pediatric patients, is characterized by short periods of vertigo or dizziness lasting seconds to a few minutes and associated with imbalance and nystagmus; tinnitus or hearing loss is unusual. **Basilar/vestibular migraine** is a common cause of episodic vertigo or dizziness and is associated with headache (50–70% of patients), rotary or to-and-fro nystagmus, and sensitivity to noise and bright light (see Chapter 613.1). **Benign paroxysmal positional vertigo** is less common in young children and more common with increasing age into adulthood. Particles form in the semicircular canals (canalolithiasis), most often the posterior canal; symptoms occur with position changes of the head and may last sec to min.

Vertigo and nystagmus may be demonstrated by changing position (sitting to lying down on the right or left). Treatment involves canalith repositioning maneuvers to shift the debris from the canals into the utricle.

Otosclerosis, an autosomal dominant disease that affects only the temporal bones, causes abnormal bone growth that can result in fixation of the stapes in the oval window, leading to progressive hearing loss. In one series in North America, otosclerosis was found in 0.6% of temporal bones of children younger than 5 yr of age and 4% of those ages 5-18 yr. The hearing loss is usually conductive at first, but SNHL can develop. White girls and women are affected most commonly, with onset of otosclerosis in teenagers or young adults, often associated with pregnancy. Corrective surgery to replace the stapes with a mobile prosthesis often is successful.

Osteogenesis imperfecta is a systemic disease that can involve both the middle and inner ears (see Chapter 721). Hearing loss occurs in approximately 20% of young children and as many as 50% of adults by the age of 50 with this disease. The hearing loss most commonly is conductive but can be sensorineural or mixed. Etiologies of hearing loss include otosclerosis, ossicle fractures, or neural degeneration. If the hearing loss is severe enough, a hearing aid may be a preferable alternative to surgical correction of the fixed stapes, because stapedectomy in children with osteogenesis imperfecta can be technically very difficult, and the disease and the hearing loss may be progressive.

Osteopetrosis, a very uncommon skeletal dysplasia, can involve the temporal bone, including the middle ear and ossicles, resulting in a moderate to severe, usually CHL. Recurrent facial nerve paralysis also can occur as a result of excess bone deposition; with each recurrence, less facial function might return (see Chapter 719).

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CHAPTER 661

Traumatic Injuries of the Ear and Temporal Bone

Joseph Haddad Jr, Sonam N. Dodhia

Auricle and External Auditory Canal

Auricle trauma is common in certain sports. Hematoma, with accumulation of blood between the perichondrium and the cartilage, can follow trauma to the pinna and is especially common in teenagers involved in wrestling or boxing. Prompt drainage of a hematoma can prevent irreversible damage. Immediate needle aspiration or, when the hematoma is extensive or recurrent, incision and drainage and a pressure dressing are necessary to prevent perichondritis, which can result in cartilage loss and a “cauliflower ear deformity.” Sports helmets should be worn when appropriate during activities when head trauma is possible.

Frostbite of the auricle should be managed by rapidly rewarming the exposed pinna with warm irrigation or warm compresses.

Foreign bodies in the external canal are common in childhood. Often these can be removed in the office setting without general anesthesia if the child is mature enough to understand and cooperate and is properly restrained; if an adequate headlight, surgical head otoscope, or otomicroscope is used for visualizing the object; and if appropriate instruments such as alligator forceps, wire loops or a blunt cerumen curette, or suction are used, depending on the shape of the object. Gentle irrigation of the ear canal with body temperature water or saline may be used to remove very small objects, but only if the tympanic membrane (TM) is intact. Attempts to remove an object from a struggling child or with poor visualization and inadequate tools result in a terrified child with a swollen and bleeding ear canal and can then mandate general anesthesia to remove the object. Difficult foreign bodies, especially those that are large, deeply embedded, or associated with canal swelling, are best removed by an otolaryngologist and/or under general anesthesia. Disk batteries are removed emergently because they leach a basic fluid that can cause severe tissue destruction. Insects in the canal are first killed with mineral oil or lidocaine and are then removed under otomicroscopic examination. Objects retained in the external auditory canal can lead to complications such as otalgia, conductive hearing loss, infection, and aural drainage.

After a foreign body is removed from the external canal, the TM should be inspected carefully for traumatic perforation, middle-ear effusion, abrasions, and bleeding. If a foreign body has resulted in acute inflammation of the canal, topical otic medications as described for acute external otitis should be instituted (see Chapter 657).

Tympanic Membrane and Middle Ear

Traumatic perforation of the TM usually results from sudden external compression, such as a slap, or penetration by a foreign object such as a stick or cotton-tipped swab. The perforation may be linear or stellate. It is most commonly in the anterior portion of the pars tensa when it is caused by compression, and it may be in any quadrant of the TM when caused by a foreign object. Systemic antibiotics and topical otic medications are not required unless suppurative otorrhea is present. Small traumatic TM perforations often heal spontaneously, but it is important to evaluate and monitor the patient's hearing to ensure that spontaneous healing occurs. If the TM does not heal within several months, surgical graft repair should be considered. As long as the perforation is present, otorrhea can occur from water entering the middle ear from the ear canal, which can occur during swimming or bathing; appropriate precautions should be taken. Perforations resulting from penetrating foreign bodies are less likely to heal than those caused by compression. Audiometric examination reveals a conductive hearing loss, with larger air-bone gaps seen in larger perforations. Immediate surgical exploration may be indicated if the injury is accompanied by 1 or more of the following: vertigo, nystagmus, severe tinnitus, moderate to severe hearing loss, or cerebrospinal fluid (CSF) otorrhea. At the time of exploration, it is necessary to inspect the ossicles, especially the stapes, for possible dislocation or fracture and to clear sharp objects that might have penetrated the oval or round windows. Sensorineural hearing loss results if the stapes subluxates or dislocates into the oval window or if either the oval or round window is penetrated. Children should not be given access to cotton-tipped applicators, because the applicators commonly cause ear trauma. Contact with small objects should be limited to times of parental supervision.

Perilymphatic fistula can occur after barotrauma or an increase in CSF pressure. It should be suspected in a child who develops a sudden SNHL or vertigo after physical exertion, deep water diving, air travel, playing a wind instrument, or significant head trauma. The leak characteristically is at the oval (Fig. 661.1) or the round window and may be associated with congenital abnormalities of these structures or an anatomic abnormality of the cochlea or semicircular canals. Perilymphatic fistulas occasionally close spontaneously, but immediate surgical repair of the fistula is recommended to control vertigo and to stop any progression of the SNHL; even timely surgery does not usually restore the SNHL. No reliable test is known for perilymphatic fistula, so middle-ear exploration is required for diagnosis and treatment.

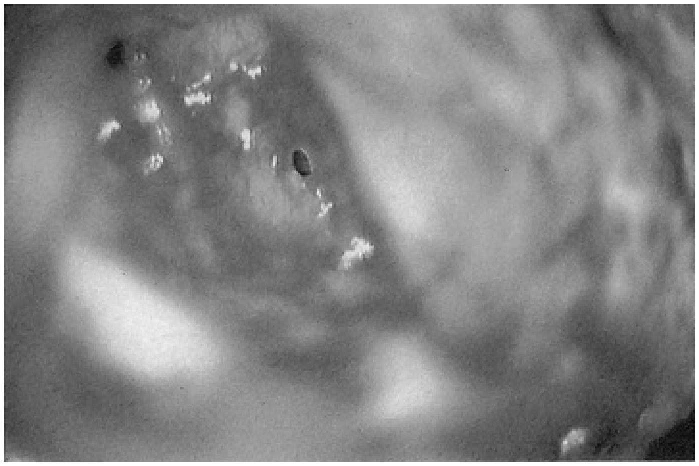

FIG. 661.1 Intraoperative view of traumatic oval window perilymphatic fistula. (From Kim SH, Kazahaya K, Handler SD: Traumatic perilymphatic fistulas in children: etiology, diagnosis and management, *Int J Pediatr Otorhinolaryngol* 60(2):147–153, 2001, Fig. 2.)

Temporal Bone Fractures

Children are particularly prone to basilar skull fractures, which usually involve the temporal bone. Temporal bone trauma should be considered in head injuries, and the status of the ear and hearing should be evaluated. Temporal bone fractures are divided into longitudinal (70–80%), transverse (10–20%), and mixed. Longitudinal fractures (Fig. 661.2) are commonly manifested by bleeding from a laceration of the external canal or TM; postauricular ecchymosis **(Battle sign); hemotympanum** (blood behind an intact TM); conductive hearing loss resulting from TM perforation, hemotympanum, or ossicular injury; delayed onset of facial paralysis (which usually improves spontaneously); and temporary CSF otorrhea or rhinorrhea (from CSF running down the eustachian tube) (Fig. 661.3). Transverse fractures of the temporal bone have a graver prognosis than longitudinal fractures and are often associated with immediate facial paralysis and damage to the labyrinth or internal auditory canal. Facial paralysis might improve if caused by edema, but surgical decompression of the nerve is often recommended if there is no evidence of clinical recovery and facial nerve studies are unfavorable. If the facial nerve has been transected, surgical decompression and anastomosis offer the possibility of some functional recovery. Transverse fractures are also associated with severe SNHL, vertigo, nystagmus, tinnitus, nausea, and vomiting associated with loss of cochlear and vestibular function; hemotympanum; rarely, external canal bleeding; and CSF otorrhea, either in the external auditory canal or behind the TM, which can exit the nose via the eustachian tube.

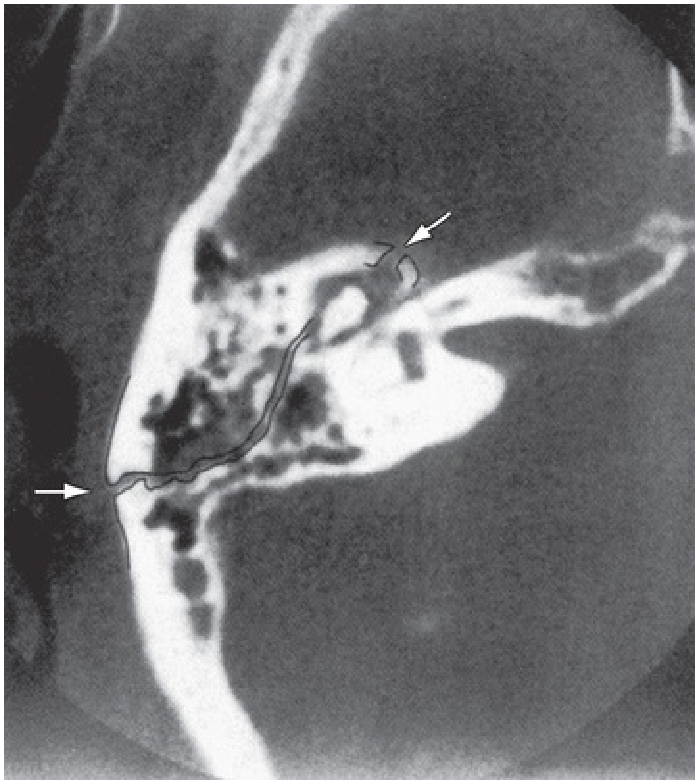

FIG. 661.2 High-resolution axial CT of uncomplicated longitudinal fracture *(arrows).* A hematoma is present. The course of the fracture has been touched. (From Schubiger O, Valavanis A, Stuckman G, et al: Temporal bone fractures and their complications: examination with high resolution CT, *Neuroradiology* 28:93–99, 1986.)

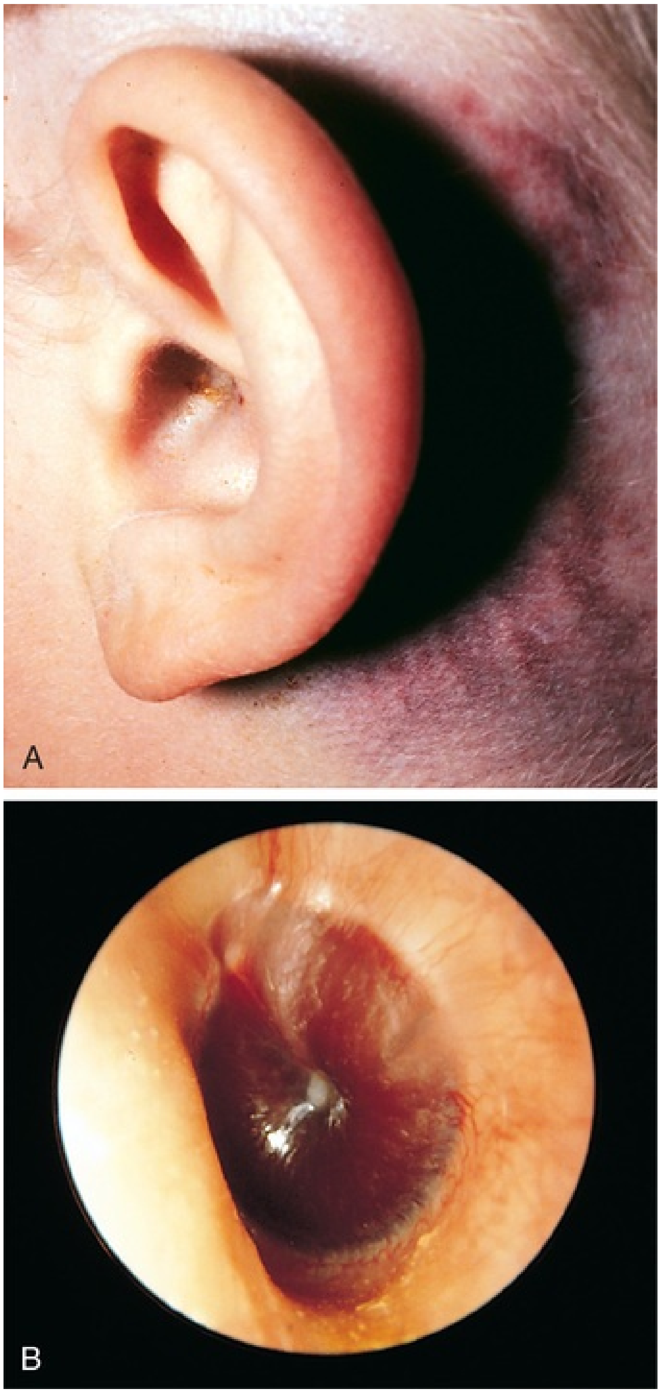

FIG. 661.3 Basilar skull fracture. **A,** The presence of a basilar skull fracture involving the temporal bone is often signaled by postauricular ecchymotic discoloration, termed the Battle sign. **B,** The force of the blow may also cause tearing of the ear canal or, as shown here, middle ear hemorrhage with hemotympanum. Depending on the timing of examination, this may appear red or blue. (***B,*** Courtesy Michael Hawke, MD; From Zitelli BJ, McIntire SC, Nowalk AJ, editors: *Zitelli and Davis' Atlas of Pediatric Physical Diagnosis* , ed 7, Philadelphia, 2018, Elsevier, Fig. 24-15, p 874.)

If temporal bone fracture is suspected or seen on radiographs, gentle examination of the pinna and ear canal is indicated; lacerations or avulsion of soft tissue is common with temporal bone fractures. Vigorous removal of external auditory canal blood clots or tympanocentesis is not indicated, because removing the clot can further dislodge the ossicles or reopen CSF leaks. The effectiveness of prophylactic antibiotics to prevent meningitis in patients with basilar skull fractures and CSF otorrhea or rhinorrhea cannot be determined because studies to date are flawed by biases. If a patient is afebrile and the drainage is not cloudy, watchful waiting without antibiotics is indicated. Surgical intervention is reserved for children who require repair of a nonhealing TM perforation, who have suffered dislocation of the ossicular chain, or who need decompression of the facial nerve. SNHL can also follow a blow to the head without an obvious fracture of the temporal bone (labyrinthine concussion).

Acoustic Trauma

Acoustic trauma results from exposure to high-intensity sound (fireworks, gunfire, loud music, heavy machinery) and is initially manifested by a temporary decrease in the hearing threshold, most commonly at 4,000 Hz on an audiometric examination, and tinnitus. If the sound is between 85 and 140 dB, the loss is usually temporary (after a rock concert), but both the hearing loss and the tinnitus can become permanent with chronic noise exposure; the frequencies from 3,000 to 6,000 Hz are most often involved. Sudden, extremely loud (>140 dB), short-duration noises with loud peak components (gunfire, bombs) can cause permanent hearing loss after a single exposure. Noise-induced hearing loss results from interactions between genes and the environment. A meta-analysis demonstrated that loud music exposure resulted in increased hearing thresholds and decreased otoacoustic emissions in children and adolescents. Ear protection and avoidance of chronic exposure to loud noise are preventive measures. Hearing loss from chronic noise exposure should be entirely preventable. Parents should be made aware of the dangers of acoustic trauma, from the environment and from the use of headphones, and should take measures to minimize exposure. Treatment with high-dose steroids for 1-2 wk should be considered to treat acute hearing loss related to noise trauma.

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CHAPTER 662

Tumors of the Ear and Temporal Bone

Joseph Haddad Jr, Sonam N. Dodhia

Benign tumors of the external canal include osteomas and monostotic and polyostotic fibrous dysplasia. Osteomas are usually unilateral and located lateral in the bony canal; they require removal only if hearing is impaired or external otitis results. Exostoses (see Chapter 528.2), or localized bony hyperplasias, may be confused with osteomas; however, exostoses are usually bilateral and located in the region of the annulus of the tympanic membrane. Masses occurring over the mastoid bone, such as first branchial cysts, dermoid cysts, and lipomas, may be confused with primary mastoid tumors; imaging can help with the diagnosis and treatment plan.

Eosinophilic granuloma , which can occur in isolation or as part of the systemic Langerhans cell histiocytosis (see Chapter 534.1), should be suspected in patients with otalgia, otorrhea (sometimes bloody), hearing loss, abnormal tissue within the middle ear or ear canal, and roentgenographic findings of a sharply delineated destructive lesion of the temporal bone. Definitive diagnosis is made by biopsy. Treatment depends on the site of the lesion and histology. Depending on the site, it may be treated by surgical excision, curettage, or local radiation. If the lesion is part of a systemic presentation of Langerhans cell histiocytosis, chemotherapy in addition to local therapy (surgery with or without radiation) is indicated. Long-term follow-up is necessary whether the temporal bone lesion is a single isolated lesion or part of a multisystem disease.

Rhabdomyosarcoma is the most common malignancy of the temporal bone in children. Symptoms and signs of rhabdomyosarcoma (see Chapter 527) originating in the middle ear or ear canal include a mass or polyp in the middle ear or ear canal, bleeding from the ear, otorrhea, otalgia, facial paralysis, and hearing loss. Other cranial nerves also may be involved. Diagnosis is based on biopsy, but the extent of disease is determined by both CT and MRI of the temporal and facial bones, skull base, and brain (Fig. 662.1). Management usually involves a combination of chemotherapy, radiation, and surgery.

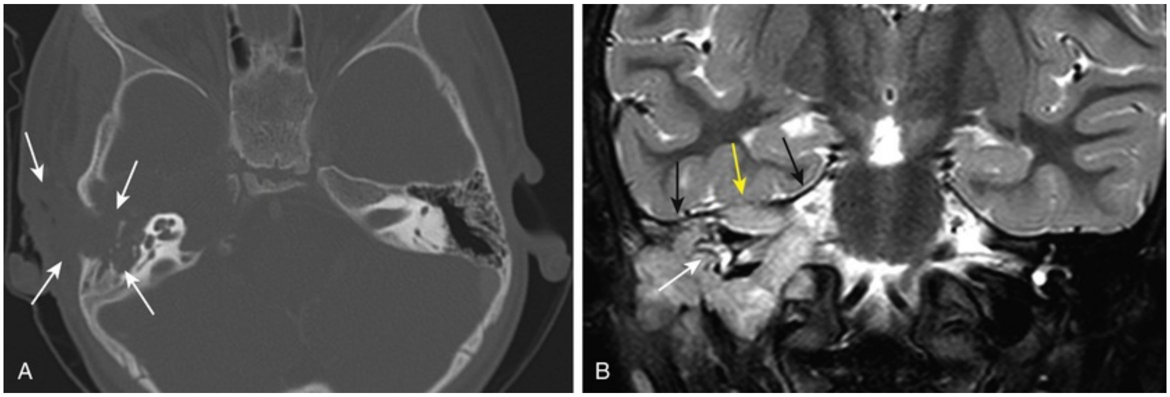

FIG. 662.1 Rhabdomyosarcoma in a 2 yr old boy with hearing loss and right periauricular swelling. **A,** Axial CT shows a large soft tissue mass of the right temporal bone *(arrows)* with extensive osseous destruction. **B,** Coronal STIR MR image shows hyperintense mass of the right temporal bone. Focal loss of integrity of the floor of right middle cranial fossa *(yellow arrow)* and intact dura *(black arrows)* are shown. Destruction of the bony labyrinth *(white arrow)* by the mass. (Modified from Koral K: Neoplasia. In Coley BD (ed): Caffey's pediatric diagnostic imaging, ed 13, Philadelphia, 2019, Elsevier, Fig. 12.1.)

Non-Hodgkin lymphoma (see Chapter 523.2) and leukemia (see Chapter 522) also occur rarely in the temporal bone. Although primary neoplasms of the middle ear are very uncommon in children, they include adenoid cystic carcinoma, adenocarcinoma, and squamous cell carcinoma. Benign tumors of the temporal bone include glomus tumors. The initial signs and symptoms of the more common nasopharyngeal neoplasms (angiofibroma, rhabdomyosarcoma, epidermoid carcinoma) may be associated with insidious onset of chronic otitis media with effusion (often unilateral). A high index of suspicion is needed for diagnosing these tumors early.

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PART XXX

The Skin

OUTLINE

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CHAPTER 663

Morphology of the Skin

Nicole R. Bender, Yvonne E. Chiu

Epidermis

The mature epidermis is a stratified epithelial tissue composed predominantly of keratinocytes (Fig. 663.1). The epidermis protects the organism from the external environment through physical, chemical, and immunologic barrier functions, and prevents water loss. Epidermal differentiation results in the formation of a functional barrier to the external world. The epidermis comprises four histologically recognizable layers, described here from deepest to most superficial. The first or basal layer consists of columnar cells that rest on the dermal-epidermal junction. Basal keratinocytes are connected to the dermal-epidermal junction by hemidesmosomes. Basal keratinocytes are attached to themselves and to the cells in the spinous layer by desmosomal, tight, gap, and adherens junctions. The role of the basal keratinocyte is to serve as a continuing supply of keratinocytes for the normally differentiating epidermis as well as a reservoir of cells to repair epidermal damage. The second layer is the spinous layer, composed of 3-4 layers of spinous cells. Their role is to synthesize keratin, which makes up the keratin intermediate filament network. The third layer is the granular layer, which consists of 2-3 layers of granular cells. Granular cells contain keratohyalin and lamellar granules, containing the protein and lipid components that make up the cornified layer. The fourth layer, or cornified layer, is composed of multiple layers of dead, highly compacted cells. The dead cells are composed mainly of disulfide-bonded keratins cross-linked by filaggrins. The intercellular spaces are composed of hydrophobic lipids, predominantly ceramides, cholesterol, and fatty acids, serving as an effective barrier against water and salt loss as well as permeation of water-soluble substances. As the cornified layer is replenished, the oldest or most superficial layer is shed in a highly regulated process. The normal process of epidermal differentiation from basal cell to shedding of the cornified layer takes 28 days.

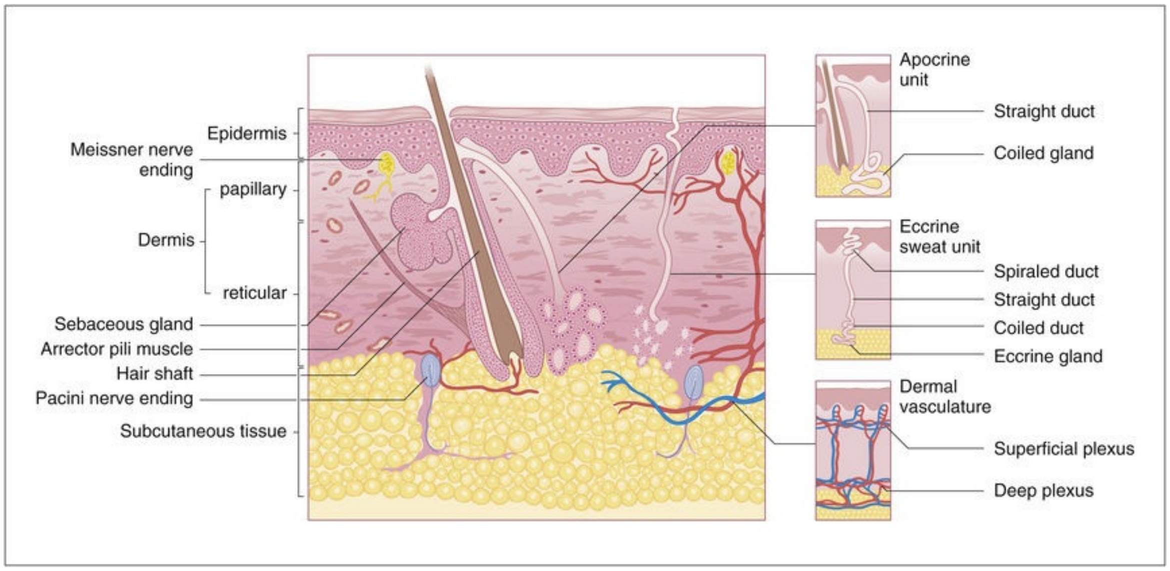
Epidermis
Meissner nerve ending
papillary
Dermis
reticular
Sebaceous gland
Arrector pili muscle
Hair shaft
Pacini nerve ending
Subcutaneous tissue
Apocrine unit
Straight duct
Coiled gland
Eccrine sweat unit
Spiraled duct
Straight duct
Coiled duct
Eccrine gland
Dermal vasculature
Superficial plexus
Deep plexus

FIG. 663.1 Schematic of skin structure. (From James WD, Berger T, Elston D: *Andrews' diseases of the skin: clinical dermatology* , ed 12, Philadelphia, 2016, Elsevier, Fig. 1.1.)

The epidermis also contains 3 other cell types. The **melanocytes** are pigment-forming cells, which are responsible for skin color and protection from ultraviolet radiation. Epidermal melanocytes are derived from the neural crest and migrate to the skin during embryonic life. They reside in the interfollicular epidermis and in the hair follicles. Melanocytes produce intracellular organelles (melanosomes) containing melanin, which they transfer via dendrites to the keratinocytes to protect the keratinocyte nucleus from ultraviolet damage. **Merkel** cells are type I slow-adapting mechanosensory receptors for touch that differentiate within the epidermis from epidermal progenitor cells. **Langerhans** cells are dendritic cells of the mononuclear phagocyte system. They are recognized electron microscopically by a specific organelle, the Birbeck granule, which resembles a tennis racket on electron microscopy. These cells are derived from bone marrow and participate in immune reactions in the skin, playing an active part in antigen presentation and processing.

The junction of the epidermis and dermis is the basement membrane zone. This complex structure is a result of contributions from both epidermal and mesenchymal cells. The dermal-epidermal junction extends from the basal cell plasma membrane to the uppermost region of the dermis. Ultrastructurally, the basement membrane appears as a trilaminar structure, consisting of a lamina lucida immediately adjacent to the basal cell plasma membrane, a central lamina densa, and the subbasal lamina on the dermal side of the lamina densa. Several structures within this zone act to anchor the epidermis to the dermis. The plasma membrane of basal cells contains electron-dense plates known as hemidesmosomes; tonofilaments course within basal cells to insert at these sites. The **hemidesmosomes** are composed of 180- and 230-kDa bullous pemphigoid antigens (BP180 [BPAG2, type XVII collagen] and BP230 [BPAG1], respectively), $\alpha_6 \beta_4$ and $\alpha_3 \beta_1$ integrins, and plectin. Anchoring filaments originate in the plasma membrane, primarily near the hemidesmosomes, and insert into the lamina densa. Anchoring fibrils, composed predominantly of type VII collagen, extend from the lamina densa into the uppermost dermis, where they loop through collagen fibrils before reinserting into the lamina densa.

Dermis

The dermis provides the skin with most of its mechanical properties (see Fig. 663.1). The dermis forms a tough, pliable, fibrous supporting structure between the epidermis and the subcutaneous fat. The predominant dermal cell is a spindle-shaped fibroblast that is responsible for the synthesis of collagen, elastic fibers, and mucopolysaccharides. Phagocytic histiocytes, mast cells, and motile leukocytes are also present. Within the dermis are blood vessels, lymphatics, neural structures, eccrine and apocrine sweat glands, hair follicles, sebaceous glands, and smooth muscle. Morphologically, the dermis can be divided into 2 layers: the superficial papillary layer that interdigitates with the rete ridges of the epidermis and the deeper reticular layer that lies beneath the papillary dermis. The papillary layer is less dense and more cellular, whereas the reticular layer appears more compact because of the coarse network of interlaced collagen and elastic fibers.

The extracellular matrix of the dermis consists of collagen and elastic fibers embedded in an amorphous ground substance. Collagen provides strength and stability to the dermis, while elastic fibers allow for elasticity. The gelatinous ground substance serves as a supporting medium for the fibrillar and cellular components and as a storage place for a substantial portion of body water.

Subcutaneous Tissue

The **panniculus,** or subcutaneous tissue, consists of fat cells and fibrous septa that divide it into lobules and anchor it to the underlying fascia and periosteum (see Fig. 663.1). Blood vessels and nerves are also present in this layer, which serves as a storage depot for lipid, an insulator to conserve body heat, and a protective cushion against trauma.

Appendageal Structures

Appendageal structures are derived from aggregates of epidermal cells that become specialized during early embryonic development. Small buds (primary epithelial germs) appear in the 3rd fetal mo and give rise to hair follicles, sebaceous and apocrine glands, and the attachment bulges for the arrector pili muscles. Eccrine sweat glands are derived from separate epidermal downgrowths that arise in the 2nd fetal mo and are completely formed by the 5th mo. Formation of nails is initiated in the 3rd intrauterine mo.

Hair Follicles

The pilosebaceous unit includes the hair follicle, sebaceous gland, arrector pili muscle, and, in areas such as the axillae, an apocrine gland. Hair follicles are distributed throughout the skin, except in the palms, soles, lips, and glans penis. Individual follicles extend from the surface of the epidermis to the deep dermis (see Fig. 663.1). The hair follicle is divided into 4 segments: the infundibulum, which extends from the skin surface to the opening of the sebaceous duct; the isthmus, extending from the sebaceous duct opening to the bulge; the lower follicle between the bulge and the hair bulb; and the hair bulb. The bulge is at the insertion of the arrector pili muscle and is a focus of epidermal stem cells. The bulb is where the matrix cells and the dermal papilla are involved in formation and maintenance of the hair. The growing hair consists of the hair shaft, made of dead keratinocytes, and its supporting inner and outer root sheaths.

Human hair growth is cyclic, with alternate periods of growth (anagen), transition (catagen), and rest (telogen). The length of the anagen phase varies from months to years, while catagen and telogen last approximately 3 wk and 3 mo, respectively. At birth, all hairs are in the anagen phase. Subsequent generative activity lacks synchrony, so an overall random pattern of growth and shedding prevails. At any time, approximately 85% of hairs are in the anagen phase. Scalp hair usually grows about 1 cm per month.

The types of hair are lanugo, terminal, and vellus hairs. Lanugo hair is thin and short; this hair is shed in utero and is replaced by vellus hair by 36-40 wk of gestation. Vellus hair is short, soft, and frequently unpigmented and is distributed over the rest of the body. Terminal hair is long and coarse and is found on the scalp, beard, eyebrows, eyelashes, and axillary and pubic areas. During puberty, androgenic hormone stimulation causes pubic, axillary, and beard hair to change from vellus hair to terminal hair.

Sebaceous Glands

Sebaceous glands occur in all areas except the palms, soles, and dorsal feet and are most numerous on the face, upper chest, and back (see Fig. 663.1). Their ducts open into the hair follicles except on the eyelids, lips, nipples, prepuce, and labia minora, where they emerge directly onto the skin surface. These holocrine glands are saccular structures that are often branched and lobulated and consist of a proliferative basal layer of small flat cells peripheral to the central mass of lipidized cells. The latter cells disintegrate as they move toward the duct and form the lipid secretion known as sebum, which consists of triglycerides, wax esters, squalene, and cholesterol esters. The purpose of sebum production likely relates to hydrophobic skin barrier function. Sebaceous glands depend on hormonal stimulation and are activated by androgens at puberty. Fetal sebaceous glands are stimulated by maternal androgens, and their lipid secretion, together with desquamated stratum corneum cells, constitutes the vernix caseosa.

Apocrine Glands

The apocrine glands are located in the axillae, areolae, perianal and genital areas, and the periumbilical region (see Fig. 663.1). These large, coiled, tubular structures continuously secrete an odorless milky fluid that is discharged in response to adrenergic stimuli, usually because of emotional stress. Bacterial biotransformation of apocrine sweat components (fatty acids, thioalcohols, and steroids) accounts for the unpleasant odor associated with perspiration. Apocrine glands remain dormant until puberty, when they enlarge and secretion begins in response to androgenic activity. The secretory coil of the gland consists of a single layer of cells enclosed by a layer of contractile myoepithelial cells. The duct is lined with a double layer of cuboidal cells and opens into the pilosebaceous complex.

Eccrine Sweat Glands

Eccrine sweat glands are distributed over the entire body surface and are most abundant on the palms and soles (see Fig. 663.1). Those on the hairy skin respond to thermal stimuli and serve to regulate body temperature by delivering water to the skin surface for evaporation; in contrast, sweat glands on the palms and soles respond mainly to psychophysiologic stimuli.

Each eccrine gland consists of a secretory coil located in the reticular dermis or subcutaneous fat and a secretory duct that opens onto the skin surface. Sweat pores can be identified on the epidermal ridges of the palm and fingers with a magnifying lens but are not readily visualized elsewhere. Two types of cells constitute the single-layered secretory coil: small dark cells and large clear cells. These rest on a layer of contractile myoepithelial cells and a basement membrane. The glands are supplied by sympathetic nerve fibers, but the pharmacologic mediator of sweating is acetylcholine rather than epinephrine. Sweat from these glands consists of water, sodium, potassium, calcium, chloride, phosphorus, lactate, and small quantities of iron, glucose, and protein. The composition varies with the rate of sweating but is always hypotonic in normal children.

Nails

Nails are specialized protective epidermal structures that form convex, translucent, tight-fitting plates on the distal dorsal surfaces of the fingers and toes. The nail plate, which is derived from a metabolically active matrix of multiplying cells situated beneath the posterior nail fold, is composed of anucleate keratinocytes. Nail growth is relatively slow; complete fingernail regrowth takes 6 mo, while complete toenail regrowth requires 12-18 mo. The nail plate is bounded by the lateral and posterior nail folds; a thin eponychium (the cuticle) protrudes from the posterior fold over a crescent-shaped white area called the lunula. The eponychium serves as a sealant barrier to protect the germinal matrix of the nail plate. The hyponychium refers to the volar surface epithelium of the distal digit, and seals the nail bed distally. The pink color beneath the nail reflects the underlying vascular bed. Nail health relies on several factors, including nutrition, hydration, local infection/irritation, and systemic disease.

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CHAPTER 664

Dermatologic Evaluation of the Patient

Nicole R. Bender, Yvonne E. Chiu

History and Physical Examination

Although many skin disorders are easily recognized by simple inspection, the history and physical examination are often necessary for accurate assessment. The skin examination should be performed under adequate illumination. In addition to the skin covering the entire body surface, mucous membranes (conjunctiva, oropharynx, nasal mucosa, and anogenital mucosa), hair, and nails should be examined when appropriate. The color, turgor, texture, temperature, and moisture of the skin and the growth, texture, caliber, and luster of the hair and nails should be noted. Skin lesions should be palpated, inspected, and classified on the bases of morphology, size, color, texture, firmness, configuration, location, and distribution. One must also decide whether the changes are those of the *primary* lesion itself or whether the clinical pattern has been altered by a *secondary* factor such as infection, trauma, or therapy.

Primary lesions are classified as macules, papules, patches, plaques, nodules, tumors, vesicles, bullae, pustules, wheals, and cysts. A **macule** represents an alteration in skin color but cannot be felt. When the lesion is >1 cm, the term **patch** is used. **Papules** are palpable solid lesions <1 cm. **Plaques** are palpable lesions >1 cm in size and have a flat surface. **Nodules** are palpable lesions >1 cm with a rounded surface. The word **tumor** may be used for a large nodule that is suspected to be neoplastic in origin. Vesicles are raised, fluid-filled lesions <1 cm in diameter; when larger, they are called **bullae. Pustules** contain purulent material. **Wheals** are flat-topped, palpable lesions of variable size, duration, and configuration that represent dermal collections of edema fluid. **Cysts** are circumscribed, thick-walled lesions; they are covered by a normal epidermis and contain fluid or semisolid material.

Primary lesions may change into secondary lesions, or secondary lesions may develop over time where no primary lesion existed. Primary lesions are usually more helpful for diagnostic purposes than secondary lesions. Secondary lesions include scales, purpura, petechiae, ulcers, erosions, excoriations, fissures, crusts, and scars. **Scales** consist of compressed layers of stratum corneum cells that are retained on the skin surface. **Purpura** are the result of bleeding into the skin and have a red-purple color; they may be flat or palpable. **Petechiae** are small purpura <2–3 mm. **Erosions** involve focal loss of the epidermis, and they heal without scarring. **Ulcers** extend into the dermis and tend to heal with scarring. Ulcerated lesions inflicted by scratching are often linear or angular in configuration and are called **excoriations. Fissures** are caused by splitting or cracking. **Crusts** consist of matted, retained accumulations of blood, serum, pus, and epithelial debris on the surface of a weeping lesion. **Scars** are end-stage lesions that can be thin, depressed, and atrophic; raised and hypertrophic; or flat and pliable. **Lichenification** is a thickening of skin with accentuation of normal skin lines that is caused by chronic irritation (rubbing, scratching) or inflammation.

If the diagnosis is not clear after a thorough examination, one or more diagnostic procedures may be indicated.

Biopsy of Skin

Biopsy of skin is occasionally required for diagnosis. Punch biopsy is a simple, relatively painless procedure and usually provides adequate tissue for examination if the appropriate lesion is sampled. The selection of a fresh, well-developed primary lesion is extremely important to obtain an accurate diagnosis. The site of the biopsy should have relatively low risk for damage to underlying dermal structures. After cleansing of the site, the skin is anesthetized by intradermal injection of 1–2% lidocaine, with or without epinephrine, with a 27- or 30-gauge needle. A punch, 3 or 4 mm in diameter, is pressed firmly against the skin and rotated until it sinks to the proper depth. All 3 layers (epidermis, dermis, and subcutis) should be contained in the plug. The plug should be lifted gently with forceps or extracted with a needle and separated from the underlying tissue with iris scissors. Bleeding abates with firm pressure and with suturing. The biopsy specimen should be placed in 10% formaldehyde solution (Formalin) for appropriate processing.

Wood Lamp

A Wood lamp emits ultraviolet light mainly at a wavelength of 365 nm. The examination, which is performed in a darkened room, is useful in accentuating changes in pigmentation and detecting fluorescence in certain infectious disorders. Discrete areas of altered pigment can often be visualized more clearly by using a Wood lamp, particularly if the pigmentary change is epidermal. Hyperpigmented lesions appear darker, and hypopigmented lesions (e.g., those seen in **tuberous sclerosis**) lighter than the surrounding skin. Blue-green fluorescence is detectable at the base of each infected hair shaft in ectothrix infections, such as tinea capitis caused by *Microsporum* species. Scales and crusts may appear pale yellow, but this color is not evidence of a fungal infection. Dermatophyte lesions of the skin (tinea corporis) do not fluoresce; macules of tinea versicolor have a golden fluorescence under a Wood lamp. **Erythrasma** , an intertriginous infection caused by *Corynebacterium minutissimum*, may fluoresce pink-orange, whereas *Pseudomonas aeruginosa* is yellow-green under a Wood lamp.

Potassium Hydroxide Preparation

Potassium hydroxide (KOH) preparation is a rapid and reliable method for detecting fungal elements of both yeasts and dermatophytes. Scaly lesions should be scraped at the active border for optimal recovery of mycelia and spores. Vesicles should be unroofed, and the blister roof should be clipped and placed on a slide for examination. In tinea capitis, infected hairs must be plucked from the follicle; scales from the scalp do not usually contain mycelia. A few drops of 20% KOH are added to the specimen. Dimethyl sulfoxide is usually in solution with the KOH, negating the need to heat the specimen. If using KOH without dimethyl sulfoxide, the specimen is gently heated over an alcohol lamp or on a hot plate until the KOH begins to bubble. Alternatively, sufficient time (10-20 min) can be allowed for dissolution of the keratin at room temperature. The preparation is examined under low-intensity light microscopy for fungal elements.

Tzanck Smear

Tzanck smear had been useful in the diagnosis of infections caused by herpes simplex virus or varicella zoster virus and for the detection of acantholytic cells in pemphigus. An intact, fresh vesicle is ruptured and drained of fluid. The roof and base of the blister are then carefully scraped with a no. 15 scalpel blade, with care taken to avoid drawing a significant amount of blood; the material is smeared on a clear glass slide and air dried. Staining with Giemsa stain is preferable, but Wright stain is acceptable. Balloon cells and multinucleated giant cells are diagnostic of herpes virus infection; acantholytic epidermal cells, large round epidermal cells with hypertrophic nuclei, are characteristic of pemphigus.

Direct fluorescent assay and polymerase chain reaction tests have largely replaced Tzanck smears in the diagnosis of herpes simplex and varicella zoster infections. Both of these are rapid, sensitive, and specific, with the polymerase chain reaction even more so. When obtaining specimens for these tests, the vesicles should be ruptured prior to sample collection with the swab.

Immunofluorescence Studies

Immunofluorescence studies of skin can be used to detect tissue-fixed antibodies to skin components and complement; characteristic staining patterns are specific for certain skin disorders (Table 664.1). Direct immunofluorescence detects autoantibodies bound to cutaneous antigens in the skin, while indirect immunofluorescence detects circulating autoantibodies present in the serum.

Table 664.1

Immunofluorescence Findings in Immune-Mediated Cutaneous Diseases

DISEASE	INVOLVED SKIN	UNINVOLVED SKIN	DIRECT IF FINDINGS	INDIRECT IF FINDINGS	CIRCULATING ANTIBODIES
Dermatitis herpetiformis	Negative	Positive	Granular IgA ± C in papillary dermis	None	IgA antiendomysial and transglutaminase antibodies
Bullous pemphigoid	Positive	Positive	Linear IgG and C band in BMZ, occasionally IgM, IgA, IgE	IgG to BMZ	IgG anti-BP180 and anti-BP230
Pemphigus (all	Positive	Positive	IgG in	IgG to	IgG antidesmoglein 1 and

variants)			intercellular spaces of epidermis between keratinocytes	intercellular spaces of epidermis between keratinocytes	3 (pemphigus vulgaris and foliaceus). IgA antidesmocollin 1 (IgA pemphigus).
Linear IgA bullous dermatosis (chronic bullous dermatosis of childhood)	Positive	Positive	Linear IgA at BMZ, occasionally C	Low titer, rare IgA, anti-BP180	None
Discoid lupus erythematosus	Positive	Negative	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	Usually ANA-negative
Systemic lupus erythematosus	Positive	Variable; 30–50% of sun-exposed skin; 10–30% of photoprotected skin	Linear IgG, IgM, IgA, and C3 at BMZ (lupus band)	None	ANA Anti-Ro (SSA), anti-La (SSB) Anti-RNP Anti-dsDNA Anti-Sm
Henoch-Schönlein purpura	Positive	Positive	IgA around vessel walls	None	None

ANA , Antinuclear antibody; *BMZ* , basement membrane zone at the dermal-epidermal junction; *BP* , bullous pemphigoid; *C* , complement; *dsDNA* , double-stranded deoxyribonucleic acid; *IF* , immunofluorescence; *Ig* , immunoglobulin; *Sm* , Smith; *SSA/SSB* , Sjögren syndrome A/B; *RNP* , ribonucleoprotein.

Skin biopsy specimens for direct immunofluorescence should be obtained from involved sites except in those diseases for which perilesional skin or uninvolved skin is required. A punch biopsy sample is obtained, and the tissue is placed in a special transport medium or immediately frozen in liquid nitrogen for transport or storage. Thin cryostat sections of the specimen are incubated with fluorescein-conjugated antibodies to the specific antigens.

Serum of patients can be examined by indirect immunofluorescence techniques using sections of normal human skin, guinea pig lip, or monkey esophagus as substrate. The substrate is incubated with fresh or thawed frozen serum and then with fluorescein-conjugated antihuman globulin. If the serum contains antibody to epithelial components, its specific staining pattern can be seen on fluorescence microscopy. By serial dilution, the titer of circulating antibody can be estimated.

664.1

Cutaneous Manifestations of Systemic

Diseases

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Selected diseases have signature skin findings, often as the presenting signs of illness, which can facilitate the assessment of patients with complex medical states (Table 664.2).

Table 664.2

Characteristics of Cutaneous Signs of Systemic Diseases

DISEASE	AGE OF ONSET	SKIN LESIONS	DISTRIBUTION	DIAGNOSTIC EVALUATION(S) AND FINDINGS	ASSOCIA SYMPTO
Systemic lupus erythematosus	Any	Erythematous patches and plaques; palpable purpura; livedo reticularis; Raynaud phenomenon; urticaria	Photodistribution; “malar” face	ANA panel Anti-dsDNA Leukopenia/lymphopenia Thrombocytopenia Complement levels Urinalysis	Arthriti Nephri Cerebri Serosit
Discoid lupus erythematosus	Any	Annular, scaly plaques; atrophy; dyspigmentation	Photodistribution	ANA	Scarring
Neonatal lupus erythematosus	Newborn	Annular, erythematous, scaly plaques	Head/neck	ANA Anti-Ro (SSA), anti-La (SSB)	Heart b Throm
Juvenile dermatomyositis	Any	Erythematous to violaceous scaly macules; discrete papules overlying joints	Periocular face; shoulder girdle; extensor extremities	ANA AST ALT Aldolase Creatine kinase Lactate dehydrogenase	Fatigue Proxim weakne Calcifi Vascul
Morphea	Any	Sclerotic plaques; resolve with hyperpigmentation and atrophy	Variable	Skin biopsy MRI brain	Neurol (seizur headac neurolo deficits asympt MRI abnorm Muscul (joint c

					limb le discrep arthritis arthralg
Henoch-Schönlein purpura	Childhood and adolescence	Purpuric papules and plaques	Buttocks; lower extremities	Urinalysis Blood urea nitrogen/creatinine ratio Skin biopsy	Abdom Arthriti
Kawasaki disease	Infancy, childhood	Erythematous maculopapular to urticarial plaques; acral and groin erythema, edema, desquamation	Diffuse	Leukocytosis ESR C-reactive protein Thrombocytosis	Strawb Conjun Lymph Cardiov compli
Inflammatory bowel disease	Childhood and adolescence	Aphthae; erythema nodosum; pyoderma gangrenosum; lip swelling	Oral and perianal predominate	Skin biopsy	Abdom Diarrhe Crampi Arthriti Conjun
Sweet syndrome	Any	Infiltrated erythematous, edematous plaques	Head and neck predominate	Skin biopsy Leukocytosis ESR	Fever Flu-like Conjun
Graft versus host disease	Any	Acute: erythema, papules, vesicles, bullae	Diffuse with predilection for head/neck and palms/soles	Skin biopsy Liver function	Fever Mucosi Hepatit
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Any	Erythema; urticarial macules and plaques	Diffuse	Liver function Eosinophilia Atypical lymphocytosis	Facial e Lymph Fever Hepatit
Serum sickness-like reaction (SSLR)	Any	Edematous, urticarial plaques	Diffuse	None	Fever Lymph Arthriti

[*] NOMID, Neonatal onset multisystem inflammatory disease and other recurrent fever syndromes.

ALT , Alanine aminotransferase; *ANA* , antinuclear antibodies; *AST* , aspartate aminotransferase; *dsDNA* , double-stranded deoxyribonucleic acid; *ESR* , erythrocyte sedimentation rate; *SSA/SSB* , Sjögren syndrome A/B.

Connective Tissue Diseases

Lupus Erythematosus

Lupus erythematosus (LE; see Chapter 183) is an idiopathic autoimmune inflammatory disease that may be multisystemic (i.e., systemic LE or SLE) or confined to the skin. Distinct cutaneous lupus subtypes seen in children include acute cutaneous LE, subacute cutaneous LE, chronic cutaneous LE (including discoid LE, discussed under “Discoid Lupus Erythematosus”), and neonatal LE (discussed under “Neonatal Lupus Erythematosus”).

Systemic Lupus Erythematosus

SLE is a chronic inflammatory multisystem disease with approximately 15–20% of cases diagnosed in childhood. It is diagnosed when 4 of 11 well-defined clinical and 6 immunologic criteria are present (see Chapter 183), where you must meet one clinical and one immunologic criteria each. Four of the clinical criteria are skin findings. **Criterion 1** is acute cutaneous lupus, which may involve the classic malar or “butterfly” rash (Fig. 664.1), bullous lupus lesions, psoriasiform and/or annular polycyclic lupus lesions that resolve without scarring, and photosensitive erythematous macular or papular eruption (Fig. 664.2). The malar rash must be distinguished from other causes of a “red face,” most notably seborrheic dermatitis, atopic dermatitis, and rosacea. **Criterion 2** is chronic cutaneous lupus, which includes discoid lupus lesions, hypertrophic (verrucous) lupus lesions and lupus panniculitis, among others. **Criterion 3** is oral or nasal ulcers in the absence of other causes such as vasculitis, Behcet's, infection (HSV), or inflammatory bowel disease. **Criterion 4** is nonscarring alopecia which may include diffuse thinning or hair fragility in the absence of other causes such as alopecia areata, drugs, or iron deficiency. Patients may meet full SLE criteria based on skin findings alone with one immunologic criterion (such as positive ANA or anti-dsDNA). Other associated but not diagnostic cutaneous findings include purpuric lesions, livedo reticularis, Raynaud phenomenon, and urticaria.

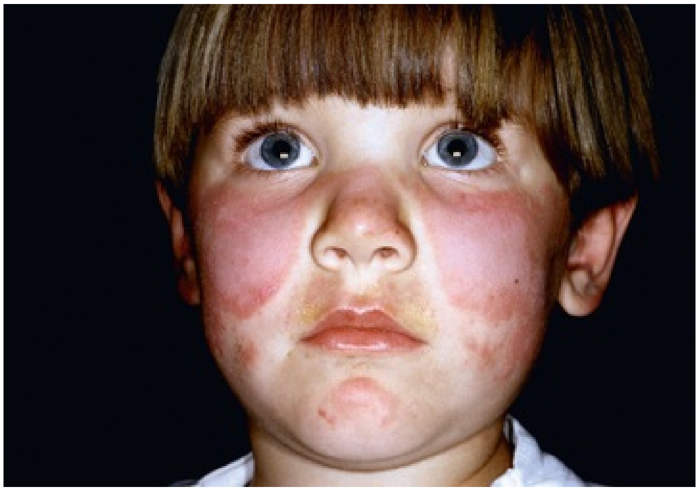

FIG. 664.1 Malar rash of systemic lupus erythematosus.

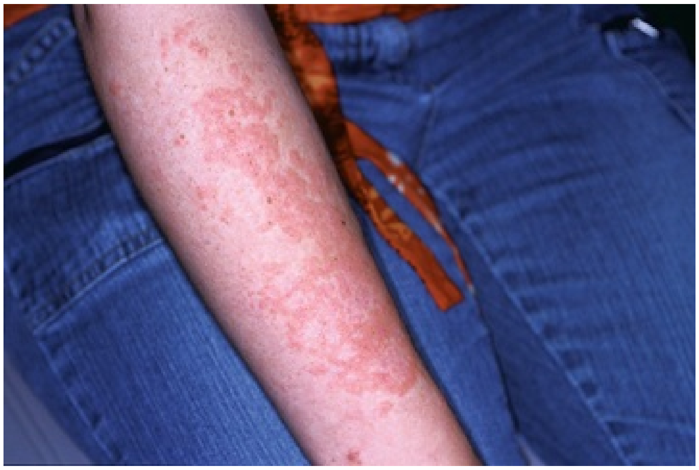

FIG. 664.2 Photosensitive rash of systemic lupus erythematosus.

On histology, cutaneous LE demonstrates varying degrees of epidermal atrophy, plugging of hair follicles, and a vacuolar alteration at an inflamed dermal-epidermal junction. Deposition of immunoglobulins (IgM, IgG) and complement in lesional skin may help confirm the diagnosis. Immune deposits in nonlesional sun-exposed skin are found in the majority of patients with SLE (lupus band test), although clinical use of this test has been mostly abandoned in favor of serologic testing.

The skin lesions often respond to treatment of the SLE with systemic agents. Oral hydroxychloroquine is used most commonly, but many other systemic therapies are effective, including both classic and biologic immunosuppressants.

Low- to mid-potency topical corticosteroids, topical calcineurin inhibitors, and intralesional corticosteroid injection may be considered for adjunctive therapy for skin lesions. A multispecialty approach is recommended, as pediatric patients are at significantly higher risk for long-term morbidity than adults.

Neonatal Lupus Erythematosus

Neonatal LE (see Chapter 183.1) manifests at birth or during the 1st few wk of life as annular, erythematous, scaly plaques, typically on the head, neck, and upper trunk (Fig. 664.3). Telangiectasias are also common. Ultraviolet light may exacerbate or initiate cutaneous lesions. Passive transplacental transfer of maternal anti-Ro/SSA and anti-La/SSB antibodies causes the transient skin lesions, though most infants are born to mothers without a known rheumatologic diagnosis. Antibody levels wane by 6 mo, generally resulting in clearance of the rash. Congenital heart block occurs in 30% of affected infants, but only 10% of affected infants have both skin and cardiac abnormalities. Noncardiac extracutaneous manifestations, such as anemia, thrombocytopenia, and cholestatic liver disease, are less common. Neonatal LE is often misdiagnosed as infantile eczema, seborrheic dermatitis, or tinea corporis. Skin lesions are typically managed conservatively, given the transient nature of neonatal LE, and strict sun avoidance and protection are important. If necessary, low- to mid-potency topical corticosteroids may be used. Systemic agents should be avoided. Maternal antinuclear antibody testing is indicated.

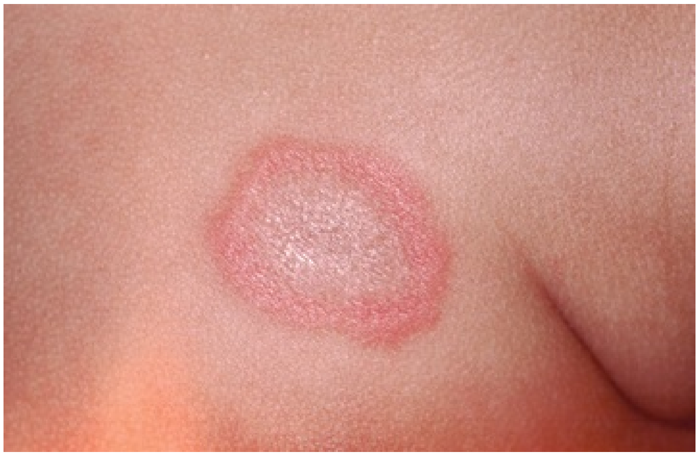

FIG. 664.3 Annular plaque in neonatal lupus erythematosus.

Discoid Lupus Erythematosus

Discoid LE (DLE) is uncommon in early childhood and manifests in late adolescence. The signature skin findings in DLE are chronic, erythematous, scaly, atrophic plaques (Fig. 664.4) on sun-exposed skin that frequently heal with scarring and dyspigmentation. Extracutaneous features may include involvement of the nasal and oral mucosa, eyes, and nails. The differential diagnosis includes other photodermatoses, such as polymorphous light eruption, juvenile springtime eruption, and juvenile dermatomyositis (JDM). There is a distinct overlap between SLE and DLE, with common histopathologic features and photoexacerbation; most patients with DLE have normal laboratory results and do not progress to systemic disease.

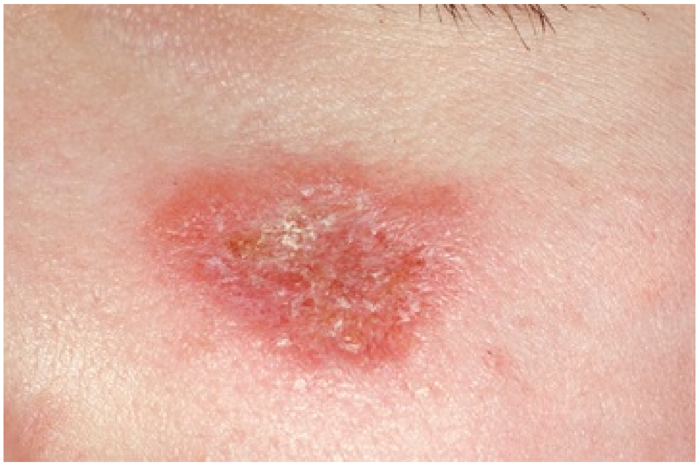

FIG. 664.4 Erythematous scaly plaque of discoid lupus erythematosus.

First-line treatment of DLE consists of low- to mid-potency topical corticosteroids. Other topical options include calcineurin inhibitors and retinoids. Intralesional corticosteroid injection is also effective for severe localized lesions. Oral hydroxychloroquine is used first-line for severe skin disease or as a second-line agent when lesions are not controlled with topical or local agents. Strict ultraviolet light avoidance is important.

Juvenile Dermatomyositis

Characteristic skin findings are often the presenting sign of JDM (see Chapter 184). An ill-defined, erythematous to violaceous, scaly, minimally pruritic eruption occurs in photodistributed areas such as the face, upper trunk, and extensor extremities. Circumscribed periocular involvement of this **heliotrope** rash involving the eyelids may take the appearance of “raccoon eyes,” particularly in young children. Distinctive erythematous, scaly papules overlying the knuckles and other joints **(Gottron papules)** are helpful in suggesting the diagnosis in the absence of associated muscle weakness (Fig. 664.5). Other cutaneous features include nail fold and gingival margin telangiectasia, palmar hyperkeratosis (“mechanic's hands”), ulceration resulting from vasculopathy or underlying calcinosis, lipodystrophy, and a poikilodermatous (dyspigmentation and telangiectasia) eruption over the shoulder girdle (“shawl sign”). Cutaneous features may precede the systemic illness, which is primarily characterized by muscle weakness and pain. The differential diagnosis includes atopic dermatitis, other connective tissue diseases, lichen planus, medication reactions, and infectious exanthems. Lesional skin demonstrates epidermal atrophy and vacuolar degeneration at the dermal-epidermal junction, often similar to LE. JDM is distinct from adult dermatomyositis in both presentation and prognosis. Pediatric patients have more difficulty with gastrointestinal vasculopathy and cutaneous calcifications, and JDM is not a paraneoplastic phenomenon as in adults. A rare clinical variant known as **amyopathic dermatomyositis** occurs when only skin, and not muscle, is involved.

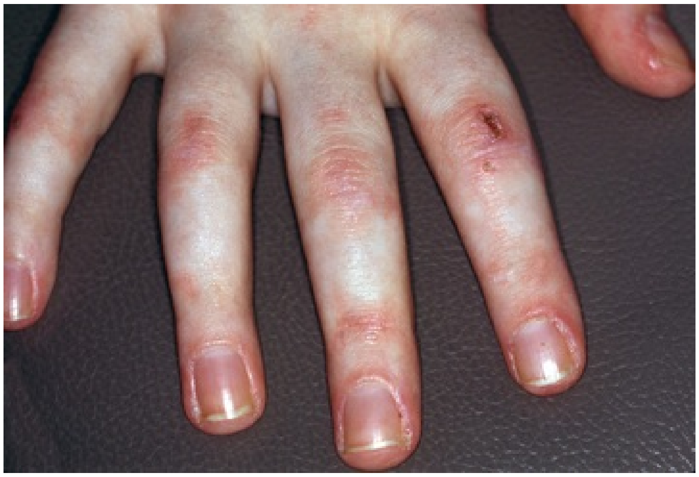

FIG. 664.5 Gottron papules in juvenile dermatomyositis.

Skin lesions benefit from systemic immunosuppressive therapy as discussed in detail in Chapter 184 . Adjunctive treatment options for skin disease include topical corticosteroids and calcineurin inhibitors. The cutaneous calcinosis of JDM is difficult to manage, with a variety of agents showing limited benefit, and no treatment consensus exists. Strict photoprotection and sunlight avoidance are vital to prevent cutaneous exacerbations.

Systemic Sclerosis

Systemic sclerosis is characterized by skin hardening and thickening, along with systemic features. It frequently manifests as acral (sclerodactyly, ulceration, nail fold telangiectasia, or Raynaud phenomenon) and facial changes (pinched nose, furrowed perioral skin, or “scleroderma facies”) (see Chapter 185). Overlap syndromes such as **mixed connective tissue disease** may include some physical and laboratory features of scleroderma.

Morphea

Morphea, also called localized scleroderma (see Chapter 185), is another autoimmune connective tissue disease characterized by skin hardening and thickening. The lesions of morphea are generally more localized and it is thought to be a distinct disorder from systemic sclerosis. There are five subtypes of morphea, including circumscribed (plaque), linear, generalized, pansclerotic, and mixed. Though morphea is not characterized by the degree of systemic involvement that systemic sclerosis has, it can have extracutaneous manifestations. Neurologic findings such as seizures, migraine headaches, focal neurologic deficits, and asymptomatic MRI abnormalities are seen in some patients, predominately those with linear morphea of the head and neck. Musculoskeletal complications can include joint contractures, limb length and girth discrepancies, arthritis, and arthralgias, and these are most common in children with linear morphea of a limb.

Vasculitides

The vasculitides (see Chapter 192) encompass a broad group of disorders having considerable overlap with connective tissue diseases. Immune-mediated inflammation of blood vessels of varying size may be caused by an underlying inflammatory state, infection, medication, or malignancy. Common clinical features include **palpable nonthrombocytopenic purpuric** skin lesions, arthritis, fever, myalgia, fatigue, and weight loss as well as an elevated erythrocyte sedimentation rate. Extracutaneous organs that may be involved include the joints, lungs, kidneys, and central nervous system.

Henoch-Schönlein Purpura (Immunoglobulin A Vasculitis)

Henoch-Schönlein purpura (see Chapter 192.1) is a vasculitis that manifests in school-age children as palpable purpuric lesions in gravity dependent areas, predominantly the buttocks and lower extremities (Fig. 664.6). **Infantile hemorrhagic edema (IHE;** also called acute hemorrhagic edema of infancy) shares some clinical features with Henoch-Schönlein purpura but appears in infants and toddlers. IHE is characterized by the sudden onset of circumscribed edema with purpuric papules and plaques on the trunk and extremities but, unlike Henoch-Schönlein purpura, commonly affects the face and lacks other organ involvement. Henoch-Schönlein purpura must also be differentiated from infectious causes of purpuric skin lesions, such as meningococcemia, Rocky Mountain spotted fever, and purpuric viral exanthems such as those caused by enteroviruses, as well as from juvenile rheumatoid arthritis and other vasculitides. Diagnosis is confirmed by histologic confirmation of a small vessel vasculitis with the immunofluorescence finding of IgA in blood vessel walls. Skin lesions are generally managed conservatively and self-resolve in 3–4 wk. Systemic treatment is discussed in detail in Chapter 192.1 .

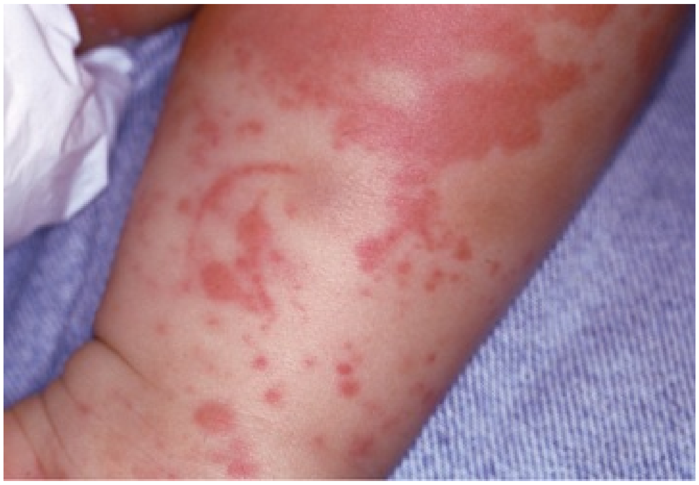

FIG. 664.6 Purpura of the lower leg in Henoch-Schönlein purpura.

Kawasaki Disease

Kawasaki disease (see Chapter 191) is a common vasculitis usually seen in children younger than age 5 yr. The skin eruption of Kawasaki disease is polymorphic, manifesting variously as maculopapular or morbilliform eruptions, urticaria, targetoid lesions, or psoriasiform lesions on the trunk and extremities. Early involvement with erythema and peeling in the perineum/inguinal region may be an initial clue to the diagnosis. Acral edema and desquamation are also prominent features but typically occur later. Classic mucocutaneous features include erythematous cracked lips, nonpurulent conjunctivitis with sparing of the limbus, and lingual plaques (“white strawberry tongue”) that shed to produce denuded, erythematous patches with prominent papilla (“strawberry tongue”). Extracutaneous features include high fever, cervical lymphadenopathy, arthritis, and occasionally cardiac or gastrointestinal disease. First-line treatment is with aspirin and intravenous immunoglobulin, as discussed in Chapter 191 .

Behçet Disease

Behçet disease (see Chapter 186) is a multisystem disease that includes oral and genital ulceration and ocular disease (uveitis, relapsing iridocyclitis) in older children and adults. Recurrent aphthous stomatitis is present in almost all patients and is commonly the presenting symptom. Genital ulcerations may resemble aphthae; can occur on the penis, scrotum, or vulva; and may be particularly painful in females. Perianal ulceration is more common in children than adults. Additional skin findings may include folliculitis, purpuric lesions, erythema nodosum, and pustule formation after venipuncture or skin trauma **(pathergy)** . Differential diagnosis of oral lesions includes recurrent aphthous stomatitis, herpes simplex, and rare oculocutaneous syndromes (e.g., MAGIC [mouth and genital ulcers with inflamed cartilage] syndrome). Skin biopsy demonstrates nongranulomatous vasculitis in all vessel sizes. Oral lesions may respond to swish and spit/swallow preparations variably including corticosteroids, antihistamines, antibiotics, and analgesics. Skin lesions are managed with topical corticosteroids, topical anesthetics such as sucralfate, and systemic agents as outlined in Chapter 186 .

Gastrointestinal Diseases

Inflammatory Bowel Disease

Inflammatory bowel disease includes ulcerative colitis (see Chapter 362.1) and Crohn's disease (see Chapter 362.2). Skin lesions of inflammatory bowel disease are classified as specific or reactive. Specific cutaneous manifestations have the same histologic features and pathologic mechanism as the underlying inflammatory bowel disease lesions and include aphthous ulcers, granulomatous cheilitis, perianal fistulas and fissures, and metastatic Crohn's disease (discussed below). Reactive cutaneous manifestations occur secondary to immune-mediated antigen cross-reactivity between gut and skin components; examples include erythema nodosum and pyoderma gangrenosum.

Up to 30% of patients with **ulcerative colitis** present with cutaneous manifestations. Aphthous ulcers are common and may worsen with gastrointestinal exacerbations. Erythema nodosum, occurring in up to 10% of patients, manifests as warm, erythematous nodules, often on the distal lower extremities. Pyoderma gangrenosum is a focal, ulcerative process that has distinctive, inflamed, undermined borders and a purulent, boggy center. Thrombophlebitis also occurs at an increased rate in patients with ulcerative colitis.

Crohn disease classically manifests as perianal fissures and skin tags, abscesses, sinuses, and fistulas; these may be presenting signs. Enlargement of the lips and a cobblestone appearance of oral mucosa may also be present. As in ulcerative colitis, aphthae, erythema nodosum, and pyoderma gangrenosum occur at increased frequency and may improve with treatment of the underlying disease. Noncaseating granulomatous inflammation is seen on routine histopathology, and when found in skin not contiguous with the intestinal tract, is labeled **metastatic Crohn disease.** Metastatic lesions may appear as solitary or multiple, localized plaques or nodules and may be located on perianal, perioral, or other cutaneous surfaces, including scars and ileostomy sites. In most cases of inflammatory bowel disease-associated skin disease, treatment of the underlying condition improves the cutaneous sequelae.

Rarely, these associated skin findings may be seen without the classic GI manifestations, warranting continued GI surveillance for subsequent disease development. Isolated cutaneous involvement is treated similarly with systemic steroid-sparing and biologic agents with or without topical or intralesional corticosteroids. Azathioprine, a common treatment, causes increased risk for nonmelanoma skin cancers.

Cutaneous Manifestations of Malignancy

Skin disease associated with malignancy has a wide variety of presentations, including both metastatic lesions and nonmalignant paraneoplastic conditions. Cutaneous metastases manifest as firm nodules and occur at any cutaneous site. Paraneoplastic reaction patterns are often distinctive and can aid in the diagnosis of the underlying malignancy. Some genetic syndromes have an increased malignancy risk that may be suggested initially by cutaneous signs. Other cutaneous findings that may signal an underlying malignancy include pruritus, ichthyosis, acanthosis nigricans, urticaria, pemphigus, and erythroderma.

Sweet Syndrome

Also known as **acute febrile neutrophilic dermatosis** , Sweet syndrome (see Chapter 194) occurs in several forms, including classical (usually idiopathic or infection-related, Fig. 664.7), malignancy-associated, immunodeficiency-related, autoinflammatory (recurrent fever) syndromes, and drug-induced. Pathogenesis for all 4 forms remains unclear; however, new data is emerging implicating a potential IL-1-mediated pathway. Malignancy-associated Sweet syndrome is most commonly associated with hematologic malignancies, especially **acute myelogenous leukemia** . It manifests abruptly before, during, or after the malignancy course and is characterized by tender, erythematous, edematous plaques or nodules that may be pustular or targetoid, often accompanied by fever, anemia, and leukocytosis. Oral ulcers are more common in malignancy-associated Sweet syndrome than in other forms of the disease, and extracutaneous manifestations involving various organ systems may also occur. Diagnosis is confirmed by the presence of a dense neutrophilic infiltrate without evidence of vasculitis. The differential diagnosis includes other neutrophilic dermatoses-like pyoderma gangrenosum as well as cellulitis, erythema multiforme, Behçet disease, and erythema nodosum. First-line treatment for both malignancy-associated and nonmalignancy-associated Sweet syndrome is oral glucocorticoids (prednisone 1-2 mg/kg/day for 2-4 wk) in combination with high-potency topical or intralesional corticosteroids. Systemic steroid-sparing agents include colchicine and dapsone.

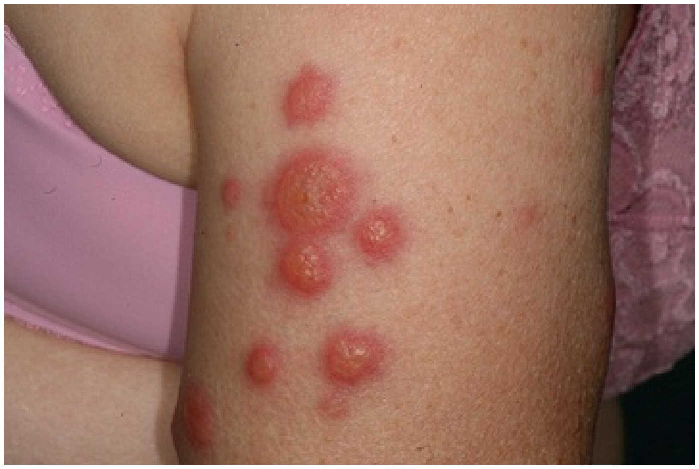

FIG. 664.7 Clinical picture of idiopathic Sweet syndrome. (From Prat L, Bouaziz JD, Wallach D, et al: Neutrophilic dermatoses as systemic diseases. *Clin Dermatol* 32:376–388, 2014, Fig. 1.)

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH, see Chapter 534.1) is a neoplastic disorder characterized by proliferation of myeloid dendritic cells. Once thought to be Langerhans cells, which are skin-resident dendritic cells, the cells of LCH are now understood to represent a distinct cell type. LCH can be a single-system or multisystem disease, with the neoplastic infiltrate in organs such as skin, bone, central nervous system, lung, hematopoietic system, liver, and spleen. When present on the skin, the lesions of LCH can be crusted erosions, scaly papules, or purpura. There is a predilection for the scalp, palms, soles, and intertriginous areas such as axillae and groin. Prognosis and treatment is variable depending on the organ systems involved.

Necrolytic Migratory Erythema (Glucagonoma Syndrome)

Necrolytic migratory erythema is a distinctive migratory erythema that often signals an underlying neoplasm, usually an α-cell pancreatic tumor. Polycyclic, weeping, erythematous patches and plaques on the face, extremities, and groin occur in association with glossitis and cheilitis. The lesions are painful or pruritic, enlarge and coalesce over time, and may develop central clearing with vesicles, crusts, and scales peripherally. Skin biopsy reveals superficial necrolysis with perivascular infiltrate. Elevated glucagon levels, hyperglycemia, and hypoaminoacidemia confirm the diagnosis, and tumor resection leads to resolution of the rash. Other treatments for necrolytic migratory erythema include somatostatin analogs (octreotide) and nutritional support; however, these measures do not affect the underlying tumor burden.

Erythromelalgia

This disorder may be primary (*SCN9A* mutations) or secondary (myeloproliferative disorders, paraneoplastic, autoimmune) and is characterized by the triad of recurrent extremity pain, warmth, and redness. Warmth, exercise, sitting, or wearing shoes or gloves may initiate the episode. Cooling and elevation may relieve symptoms (see Chapter 193.5).

Cutaneous Reactions in the Setting of Immunosuppression

Medication reactions, infectious etiologies, and graft versus host disease (GVHD) are included in the differential diagnosis in immunosuppressed patients; cutaneous and histologic similarities can be confounding.

Medication Reactions

The majority of medication reactions are mild morbilliform or exanthematous eruptions of little clinical consequence. Identifying the suspect medication may be difficult owing to the many medications used in immunosuppressed patients. Features that may help identify suspect medications include rash onset relative to exposure, character of distribution and spread, associated symptoms, and laboratory data. Medication eruptions begin on the trunk **7-10 days after exposure** ; they spread peripherally and are associated with pruritus and, less commonly, with fever, arthralgia, and lymphadenopathy. Eosinophilia may support a diagnosis of drug eruption but may be absent in the setting of bone marrow suppression. Penicillins, sulfa drugs, cephalosporins, nonsteroidal antiinflammatory drugs, anticonvulsants, and aminoglycosides are common offenders. Medication eruptions may resolve despite continued use of the offending agent, or they may progress to more severe involvement. A careful drug history, elimination of all nonessential, suspect medications or change to medications of dissimilar class, and treatment of pruritus with emollients, topical steroids, antihistamines, and antipruritics are indicated. Skin biopsies are rarely useful in distinguishing medication eruptions from viral exanthems, although GVHD, if sufficiently advanced, may have signature histopathologic findings.

Graft Versus Host Disease

GVHD (see Chapter 163) may have florid cutaneous expression in addition to characteristic extracutaneous features such as fever, mucositis, diarrhea, and hepatitis. It may be either acute or chronic. **Acute GVHD** occurs in 20–70% of hematopoietic stem cell transplants, depending on histocompatibility differences. It may be mistaken for a medication reaction or infectious exanthem because of the nonspecific erythematous maculopapular (morbilliform) eruption that often starts focally and then generalizes. Features that suggest acute GVHD include timing of eruption (typically 1-3 wk after transplantation, at the time of hematopoietic reconstitution), initial involvement of the head and neck including the ears, and subsequent spread to the trunk, extremities, palms, and soles. In severe cases of acute GVHD, blistering, necrolysis, and erythroderma occur. **Chronic GVHD** occurs in approximately 65% of long-term transplant survivors who may or may not have experienced prior acute GVHD. Cutaneous manifestations of chronic GVHD are distinctive, with sclerotic, poikilodermic scaly plaques and lichen planus-like papules predominating on the trunk and distal extremities (Fig. 664.8). Sclerotic areas are prone to contracture and chronic wound development. Involvement of the hair, nails, and oral mucosa is also common in chronic GVHD. First-line treatment for GVHD includes systemic glucocorticoids and other immunosuppressants supplemented by mid- to high-potency topical corticosteroids. In mild disease, topical corticosteroids or topical calcineurin inhibitors alone may be effective. Second-line treatment approaches include phototherapy (narrow band UVB or UVA1) and extracorporeal photopheresis. All patients with GVHD benefit from sunlight protection, emollient use, and topical or oral antipruritics.

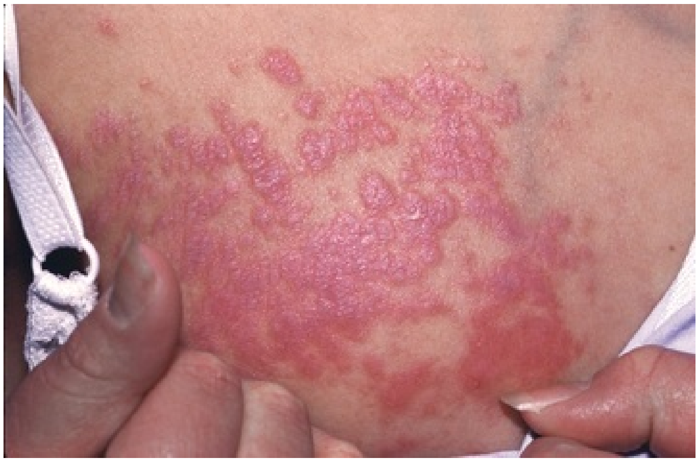

FIG. 664.8 Lichenoid eruption in chronic graft versus host disease.

664.2

Multisystem Medication Reactions

Nicole R. Bender, Yvonne E. Chiu

See also Chapter 177 .

Most cutaneous reactions that result from the use of systemic medications are confined to the skin and resolve without sequelae after discontinuation of the offending agent (Table 664.3). More severe drug eruptions may be life-threatening, making rapid recognition vital (see Chapter 673). Genetics and, particularly, ethnicity appear to play a major role in determination of the occurrence of multisystem medication reactions, particularly to anticonvulsants.

Table 664.3

Drug Eruptions in Pediatric Patients

ERUPTION	KEY DRUGS	LESIONAL PATTERN	MUCOSAL CHANGES
Urticaria	Penicillins, cephalosporins, sulfonamides,	Pruritic erythematous wheals	None

	aspirin/NSAIDs, radiocontrast media, TNF inhibitors	(Fig. 664.12)	
Angioedema	Aspirin/NSAIDs, ACE inhibitors	Swelling of subcutaneous and deep dermal tissues	May be present
Serum sickness–like reaction	Cephalosporins, penicillins, minocycline, bupropion, sulfonamides	Annular urticarial plaques (Fig. 664.11)	None
Exanthematous	Any drug	Erythematous macules and/or papules	None
Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)	Phenytoin, phenobarbital, carbamazepine, lamotrigine, allopurinol, sulfonamides, dapsone, minocycline	Edema; erythematous macules and/or papules; sometimes vesicles or bullae (Fig. 664.10)	May be present
Lichenoid	ACE inhibitors, β-blockers, gold salts, hydrochlorothiazide, hydroxychloroquine, penicillamine, griseofulvin, tetracycline, carbamazepine, phenytoin, NSAIDs	Discrete flat-topped, reddish purple papules and plaques	May be present
Fixed drug	Sulfonamides, ibuprofen, acetaminophen, tetracyclines, pseudoephedrine, barbiturates, lamotrigine, metronidazole, penicillin	Solitary to few erythematous, hyperpigmented plaques (Fig. 664.13)	Unusual
Pustular (acute generalized exanthematous pustulosis)	β-Lactam antibiotics, macrolides, clindamycin, terbinafine, calcium channel blockers, antimalarials	Generalized small pustules and papules (Fig. 664.14)	Unusual
Acneiform	Corticosteroids, androgens, lithium, iodides, phenytoin, isoniazid, tetracycline, B vitamins, azathioprine	Follicle-based inflammatory papules and pustules predominate	None
Pseudoporphyria	NSAIDs, cyclooxygenase-2 inhibitors, tetracyclines, furosemide	Photodistributed blistering and skin fragility	None
Vasculitis	Penicillins, NSAIDs, sulfonamides, cephalosporins	Purpuric papules, especially on the lower extremities; urticaria, hemorrhagic bullae, digital necrosis, pustules, ulcers	Rarely
Stevens-Johnson/toxic epidermal necrolysis	Sulfonamides, anticonvulsants, NSAIDs, allopurinol, dapsone	Target lesions, bullae, epidermal necrosis with detachment (see Figs. 673.3 and 673.4)	Present
Drug-induced lupus	Minocycline, procainamide, hydralazine, isoniazid, penicillamine, carbamazepine, chlorpromazine, infliximab	Rarely has skin manifestations but may be urticarial, vasculitic, erythematous	Rare

ACE , Angiotensin converting enzyme; *NSAIDs* , Nonsteroidal antiinflammatory drugs; *TNF* , tumor necrosis factor.

Adapted from Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology,* ed 3, Philadelphia, 2006, Elsevier/Saunders, p. 526.

Drug Rash With Eosinophilia and Systemic Symptoms (DRESS Syndrome)

Drug rash with eosinophilia and systemic symptoms (DRESS syndrome), or drug rash with eosinophilia and systemic symptoms, is also called drug hypersensitivity syndrome or anticonvulsant hypersensitivity syndrome. It is classically seen **2-6 wk after initial exposure** to an anticonvulsant (carbamazepine, phenobarbital, phenytoin, lamotrigine) or other drugs (allopurinol, minocycline, sulfonamides [dapsone, sulfasalazine], other antibiotics) and often manifests as the triad of **fever, rash,** and **hepatitis** (Fig. 664.9). The skin rash is initially located on the head, upper trunk, and arms. A diffuse exanthem of pruritic, morbilliform papules is most common, though any morphology may be present (Fig. 664.10). Exfoliation early in the course, as seen in toxic epidermal necrolysis, is uncommon. If mucous membrane involvement occurs, it is usually mild. Prominent periocular or facial edema, cervical lymphadenopathy, pharyngitis, and malaise accompany this dramatic cutaneous eruption. *Eosinophilia (≥500/µL) and atypical lymphocytosis are common but not always present.* Hepatitis ranging from mild elevation of liver transaminase values to frank hepatic failure may also be accompanied by interstitial nephritis, pneumonitis, myocarditis, shock, and encephalitis; mortality rate from these complications approaches 10%. Late-onset thyroiditis and hypothyroidism may occur months later as a result of antimicrosomal antibodies directed against thyroid peroxidases involved in drug metabolism.

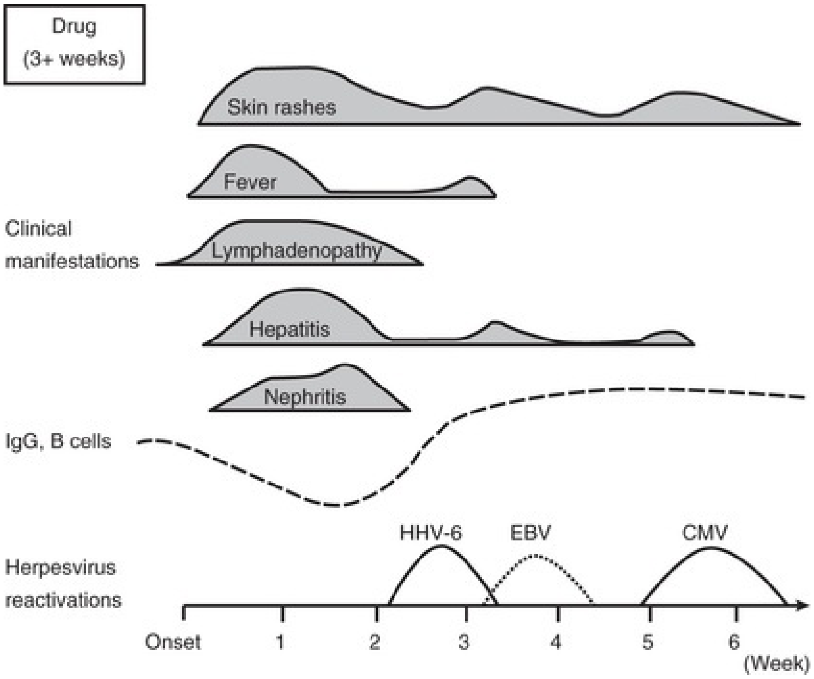
Drug
(3+ weeks)
Skin rashes
Fever
Clinical manifestations
Lymphadenopathy
Hepatitis
Nephritis
IgG, B cells
HHV-6
EBV
CMV
Herpesvirus reactivations
Onset
1
2
3
4
5
6
(Week)

FIG. 664.9 Clinical symptoms and laboratory findings of drug-induced

hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms. *CMV,* cytomegalovirus; *EBV,* Epstein-Barr virus; *HHV* , Human herpes virus. (From Kano Y, Ishida T, Hirahara K, Shiohara T: Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. *Med Clin N Am* 94:743–759, 2010 [Fig. 1, p. 745]).

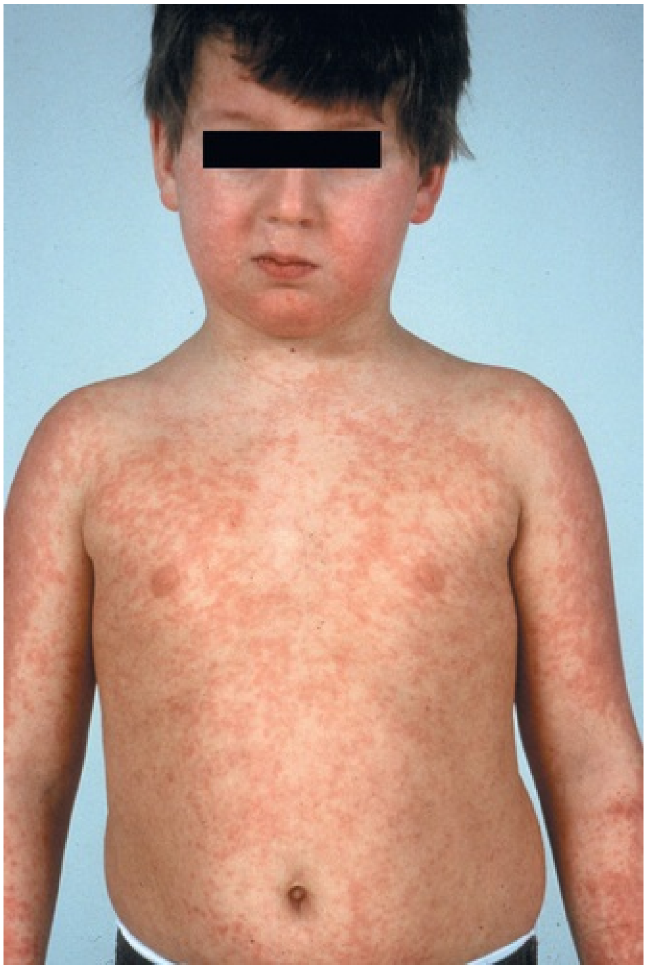

FIG. 664.10 A 9 yr old boy with cerebral palsy and seizures treated with carbamazepine. Seventeen days after start of therapy he demonstrated fever, rash (exanthematous), lymphadenopathy, and nephritis, all part of a drug-induced hypersensitivity syndrome. (From Schachner LA, Hansen RC, editors: *Pediatric dermatology* , ed 3, Philadelphia, 2003, Mosby, p. 1269.)

DRESS syndrome is caused by a T-cell response specific to the drug. Reactivation of herpesviruses, especially human herpesvirus 6, also contributes to DRESS syndrome via an unknown pathogenic mechanism. Genetic predisposition with particular HLA allele types has also been implicated with specific ethnic groups and drugs, such as HLA-A*3101 with carbamazepine. The differential diagnosis includes Stevens-Johnson syndrome, viral exanthem, macrophage activation, and hemophagocytic syndromes, and GVHD in the appropriate clinical setting. DRESS syndrome is often distinguished from other medication reactions by its later onset following drug exposure and more persistent course.

Withdrawal of the medication is the primary therapeutic intervention. Lymphocyte transformation tests and patch testing are helpful for identifying the offending drug when multiple suspect agents are present, but drug discontinuation should not be delayed while awaiting results. Symptomatic treatment of pruritus and pain can be accomplished with emollients and mid- to high-potency topical corticosteroids (twice daily for 1 wk). Oral corticosteroid therapy is necessary in the setting of rapidly evolving or severe hepatic or renal involvement. Counseling about increased risk with similar medications and in family members is important. DRESS syndrome can have a relapsing course, both in the skin and other organ systems, well after the medication has been withdrawn and initial improvement achieved, necessitating close follow-up for several months.

Serum Sickness–Like Reaction

Serum sickness–like reaction (SSLR) manifests as annular, urticarial, sharply marginated, coalescing plaques, often with a lavender hue to the center (Fig. 664.11). In addition, acral erythema/edema, arthritis/arthralgia, lymphadenopathy, and fever are often present. Unlike with true serum sickness (see Chapter 175), laboratory evidence of circulating immune complexes and multisystem involvement of vasculitis are typically absent. The differential diagnosis includes Kawasaki disease, connective tissue diseases, acute annular urticaria, and DRESS syndrome. SSLR is most commonly seen after 10-14 days after exposure to various drugs (especially cephalosporins, penicillins, minocycline, and other antibiotics), as well as after certain infections and vaccinations. The cause of drug-related SSLR is unknown, but a toxic metabolite is suspected. In contrast to DRESS syndrome, SSLR typically occurs after repeated drug exposures. Medication withdrawal and symptomatic treatment with oral antihistamines and analgesics are recommended. Systemic glucocorticoids are indicated for severe joint involvement or extensive rashes.

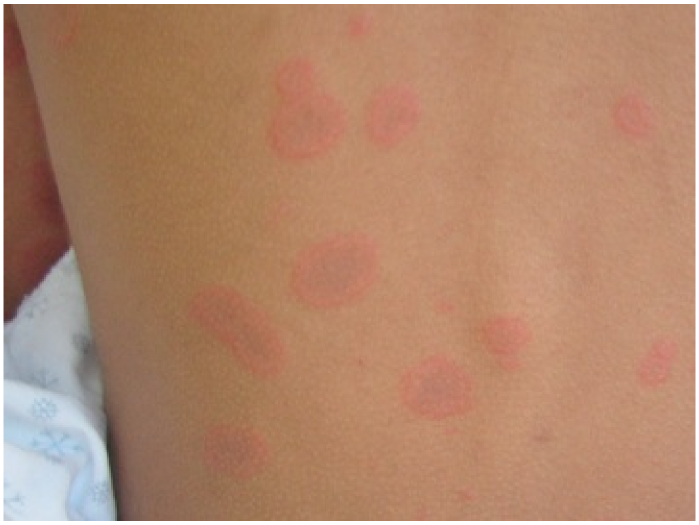

FIG. 664.11 Serum sickness-like reaction is composed of urticarial plaques with an erythematous border and violaceous centers.

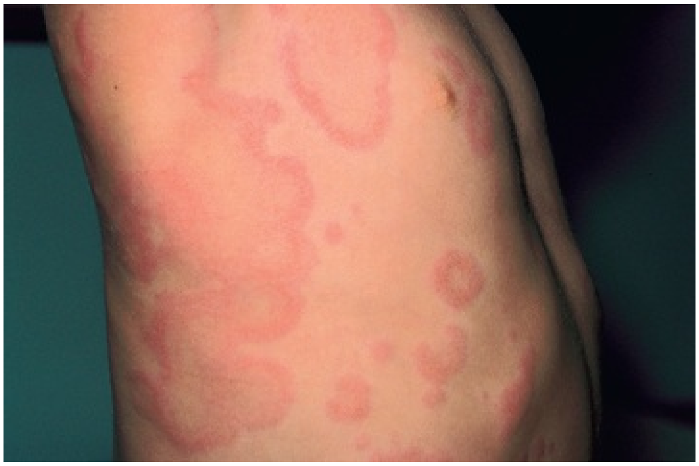

FIG. 664.12 Urticaria. Transient well-circumscribed erythematous wheals occurred in this girl as a reaction to administration of cefixime. Note the edematous center and halo of erythema. Circling a lesion and noting whether it is clear 24 hours later facilitates diagnosis. (From Paller AS, Mancini AJ (eds): *Hurwitz Clinical Pediatric Dermatology,* 5th ed, 2016, Elsevier, Philadelphia, Fig. 20-2, p. 469.)

Fixed-Drug Eruption

Fixed-drug eruption (FDE) occurs minutes to hours after exposure to a drug and is characterized by mild pruritus or burning, of a well circumscribed dusty red, brown, gray or, if severe, violaceous patch appearing on the extremities, trunk, lips, or genitals (Fig. 664.13). There is usually one lesion that on reexposure to the drug appears in the same (fixed) location as the previous episode (often appearing more rapidly). On occasion, there may be 2 or more lesions. Stopping the offending agent is required; the FDE will then resolve within 10-14 days, often with residual hyperpigmentation. Offending medications include sulfonamides, tetracyclines, nonsteroidal antiinflammatory drugs (NSAIDs), and acetaminophen.

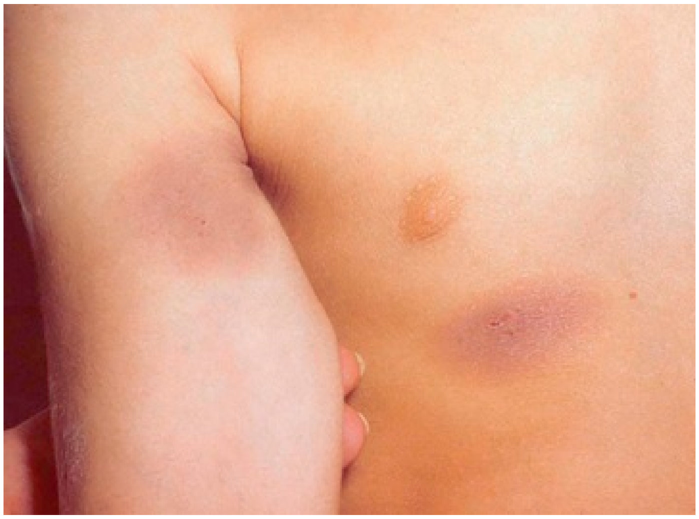

FIG. 664.13 Multiple fixed-drug eruption.

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis is often drug-related (most commonly aminopenicillins, macrolides, sulfonamides), occurring **within hours to days after drug exposure** . It is characterized by many nonfollicular sterile pustules with underlying edema and erythema, typically beginning on the face and intertriginous regions (Fig. 664.14). Neutrophilia and fever are common, whereas eosinophilia is less common than in DRESS syndrome. The rash may burn or itch; mucous membrane involvement is rare and often mild. Internal organ involvement is not common and often is asymptomatic. A pustular smear is always indicated to rule out infection in the setting of leukocytosis, fever, and a pustular rash. Differential diagnosis includes generalized pustular psoriasis, bullous impetigo, IgA pemphigus, and subcorneal pustular dermatosis. Therapy consists of stopping the causative drug and offering symptomatic relief with moist dressings, emollients, and mid-potency topical corticosteroids (applied twice daily for 1 wk).

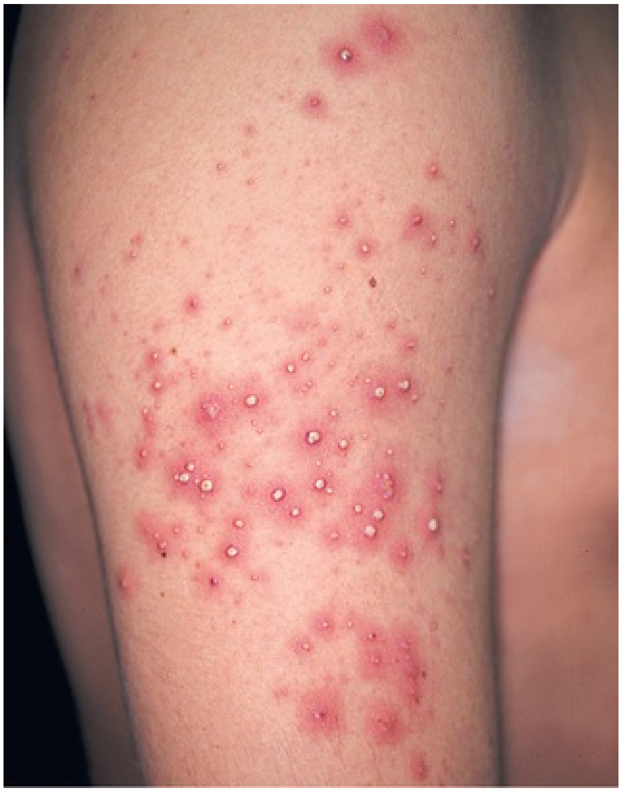

FIG. 664.14 Acute generalized exanthematous pustulosis is characterized by the acute onset of fever and generalized erythema with numerous, small, discrete, sterile, nonfollicular pustules. Pustules may appear in a few days after the drug therapy is started. Pustules resolve in <15 days, followed by desquamation. (From Habif TP, editor: *Clinical dermatology* , ed 4, Philadelphia, 2004, Mosby, p. 490.)

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CHAPTER 665

Principles of Dermatologic Therapy

Daren A. Diiorio, Stephen R. Humphrey

Competent skin care requires an appreciation of primary versus secondary lesions, a specific diagnosis, and knowledge of the natural course of the disease. If the diagnosis is uncertain, it is better to err on the side of less-aggressive rather than more-aggressive treatment.

In the use of topical medication, consideration of vehicle is as important as the specific therapeutic agent. Acute **weeping lesions** respond best to wet compresses, followed by lotions or creams. For **dry, thickened,** scaly skin, or for treatment of a contact allergic reaction possibly the consequence of a component of a topical medication, an ointment base is preferable, as it helps to occlude and moisten the affected area. Gels and solutions are most useful for the scalp and other hairy areas because of their faster absorption. The site of involvement is of considerable importance because the most desirable vehicle may not be cosmetically or functionally appropriate, such as an ointment on the face or hands. A patient's preference should also play a part in the choice of vehicle because compliance is poor if a medication is not acceptable to a patient. Ointments tend to sting less and are the least irritating. Cosmetically acceptable foam delivery systems have been developed, and the number of products and formulations available is increasing.

Most **lotions** are mixtures of water and oil that can be poured. After the water evaporates, the small amount of remaining oil covers the skin. Some shake lotions are a suspension of water and insoluble powder; as the water evaporates, cooling the skin, a thin film of powder covers the skin. **Creams** are emulsions of oil and water that are viscous and do not pour (more oil than in lotions). **Ointments** have oils and a small amount of water or no water at all; they feel greasy, lubricate dry skin, trap water, and aid in occlusion. Ointments without water usually require no preservatives because microorganisms require water to survive. Because of this, ointments often have the lowest number and concentration of ingredients, decreasing the risk of sensitizing the skin.

Therapy should be kept as simple as possible, and specific written instructions about the frequency and duration of application should be provided. Physicians should become familiar with one or two preparations in each category and should learn to use them appropriately. Prescribing nonspecific proprietary medications that may contain sensitizing agents should be avoided. Certain preparations, such as topical antihistamines and sensitizing anesthetics, are never indicated.

Wet Dressings

Wet dressings cool and dry the skin by evaporation and cleanse it by removing crusts and exudate, which would cause further irritation if permitted to remain. The dressings decrease pruritus, burning, and stinging sensations and are indicated for acutely inflamed moist or oozing dermatitis. Although various astringent and antiseptic substances may be added to the solution, cool or tepid tap water compresses are just as effective. Dressings of multiple layers of Kerlix, gauze, or soft cotton material may be saturated with water and remoistened as often as necessary. Compresses should be applied for 10-20 min at least every 4 hr and should usually be continued for 24-48 hr.

Alternatively, cotton long johns can be soaked in water and then wrung as dry as possible. These are placed on the child and covered with dry pajamas, preferably sleeper pajamas with feet. The child should sleep in these overnight. This type of dressing can be used nightly for up to 1 wk.

Wet dressings or wet wraps in conjunction with topical steroids may also be used in more severe cases of dermatitis (e.g., atopic dermatitis). In this method, a thin layer of the topical steroid is applied to the affected areas, which are then covered with warm, wet wraps for approximately 30 min to 1 hr 2-3 times daily. This method is especially effective in children with extensive and severe dermatitis.

Bath Oils, Colloids, Soaps

Bath oil has little benefit in the treatment of children. It offers little moisturizing effect but increases the risk of injury during a bath. Bath oil may lubricate the surface of the bathtub, causing an adult or child to fall when stepping into the tub. Tar bath solutions can be prescribed and may be helpful for psoriasis and atopic dermatitis. Colloids such as starch powder and colloidal oatmeal are soothing and antipruritic for some patients when added to the bathwater. Oilated colloidal oatmeal contains mineral oil and lanolin derivatives for lubrication if the skin is dry. These can also lubricate the bathtub surface. Ordinary bath soaps may be irritating and drying if patients have dry skin or dermatitis. Synthetic soaps are much less irritating. Fragrance-free soaps and cleansers are often better tolerated and less likely to irritate skin. When skin is acutely inflamed, avoidance of soap is advised.

Lubricants

Lubricants, such as lotions, creams, and ointments, can be used as moisturizers for dry skin and as vehicles for topical agents such as corticosteroids and keratolytics. In general, ointments are the most effective emollients. Numerous commercial preparations are available. Some patients do not tolerate ointments, and some may be sensitized to a component of the lubricant; some preservatives in creams are also sensitizers. These preparations can be applied several times a day if necessary and tolerated. Maximal effect is achieved when they are applied to dry skin 2 or 3 times daily. Lotions containing menthol and camphor in an emollient vehicle can help control pruritus and dryness, but the use of moisturizers in addition to these products is best to decrease skin dryness.

Shampoos

Special shampoos containing sulfur, salicylic acid, zinc, and selenium sulfide are useful for conditions in which there is scaling of the scalp, such as seborrheic dermatitis or psoriasis. Tar-containing shampoos are useful in these conditions. Most shampoos also contain surfactants and detergents. They should be used as frequently as necessary to control scaling. Patients should be instructed to leave the lathered shampoo in contact with the scalp for 5-10 min before thorough rinsing.

Shake Lotions

Shake lotions are useful antipruritic agents; they consist of a suspension of powder in a liquid vehicle. Water-dispersible oil may be added for lubrication. These preparations can be used effectively in combination with wet dressings for exudative dermatitis. Cooling occurs as the lotion evaporates and the powder deposited on the skin absorbs moisture.

Powders

Powders are hygroscopic and serve as absorptive agents in areas of excessive moisture. When dry, powders decrease friction between 2 surfaces. They are most useful in the intertriginous areas and between the toes, where maceration and abrasion may result from friction on movement. Coarse powders may cake; therefore, they should be of fine particle size and inert, unless medication has been incorporated in the formulation. The use of cornstarch-based powders in inflamed or broken skin may serve as a good growth environment for microorganisms and should be avoided.

Pastes

Pastes contain fine powder in ointment vehicles and are not often prescribed in current dermatologic therapy; in certain situations, however, they can be used effectively to protect vulnerable or damaged skin. A stiff zinc oxide paste is bland and inert and can be applied to the diaper area to prevent further irritation due to diaper dermatitis. Zinc oxide paste should be applied in a thick layer completely obscuring the skin and is removed more easily with mineral oil than with soap and water.

Keratolytic Agents

Urea-containing agents are hydrophilic; they hydrate the stratum corneum and make the skin more pliable. In addition, because urea dissolves hydrogen bonds and epidermal keratin, it is effective in treating scaling disorders. Concentrations of 10–40% are available in several commercial lotions and creams, which can be applied once or twice daily as tolerated. Salicylic acid is an effective keratolytic agent and can be incorporated into various vehicles in concentrations up to 6% to be applied 2 or 3 times daily. Salicylic acid preparations should not be used in treating small infants or on large surface areas or denuded skin; percutaneous absorption may result in salicylism. The α-hydroxy acids, particularly lactic acid and glycolic acid, are available in commercial preparations or can be incorporated in an ointment vehicle in concentrations up to 12%. Some creams contain both urea and lactic acid. The α-hydroxy acid preparations are useful for the treatment of keratinizing disorders and may be applied once or twice daily. Some patients complain of burning with the use of these agents; in such cases, the frequency of application should be decreased.

Tar Compounds

Tars are obtained from bituminous coal, shale, petrolatum (coal tars), and wood. They are antipruritic and astringent and appear to promote normal keratinization. They may be useful for chronic eczema and psoriasis, and their efficacy may be increased if the affected area is exposed to UV light after the tar has been removed. Tars should not be used for acute inflammatory lesions. Tars are often messy and unacceptable because they may stain and they have an odor. They may be incorporated into shampoos, bath oils, lotions, and ointments. A useful preparation for pediatric patients is liquor carbonis detergens 2–5% in a cream or ointment vehicle. Tar gel and tar in light body oil are relatively pleasant cosmetic preparations that cause minimal staining of skin and fabrics. Tars can also be incorporated into a vehicle with a topical corticosteroid. The frequency of application varies from 1 to 3 times daily, according to tolerance. Many children refuse to use tar preparations because of their odor and staining characteristics.

Antifungal Agents

Antifungal agents are available as powders, lotions, creams, ointments, and solutions for the treatment of dermatophyte and yeast infections. Nystatin, naftifine, and amphotericin B are specific for *Candida albicans* and are ineffective in other fungal disorders. Tolnaftate is effective against dermatophytes but not against yeast. The spectrum for ciclopirox olamine includes the dermatophytes, *Malassezia furfur,* and *C. albicans.* The azoles clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, and sulconazole have a similar broad spectrum. Butenafine has a similar broad spectrum and also has antiinflammatory properties. Terbinafine has greater activity against dermatophytes but poorer activity against yeasts than the azoles. The topical antifungal agents should be applied 1-2 times a day for most fungal infections. All have low sensitizing potential; additives such as preservatives and stabilizers in the vehicles may cause allergic contact dermatitis. Ointments containing 6% benzoic acid and 3% salicylic acid are potent keratolytic agents that have also been used for the treatment of dermatophyte infections. Irritant reactions are common.

Topical Antibiotics

Topical antibiotics have been used for many years to treat local cutaneous infections, although their efficacy, with the exception of mupirocin, fusidic acid, and retapamulin, has been questioned. Ointments are the preferred vehicles (except in the treatment of acne vulgaris; see Chapter 689) and combinations with other topical agents such as corticosteroids are, in general, inadvisable. Whenever possible, the etiologic agent should be identified and treated specifically. Antibiotics in wide use as systemic preparations should be avoided because of the risk of bacterial resistance. The sensitizing potential of certain topical antibiotics, such as neomycin and nitrofurazone, should be kept in mind and avoided when possible. Mupirocin, fusidic acid, and retapamulin are the most effective topical agents currently available and are as effective as oral erythromycin in treatment of mild to moderate impetigo. Polysporin and bacitracin are not as effective.

Topical Corticosteroids

Topical corticosteroids are potent antiinflammatory agents and effective antipruritic agents. Successful therapeutic results are achieved in a wide variety of skin conditions. Corticosteroids can be divided into 7 different categories on the basis of strength (Table 665.1), but for practical purposes, 4 categories can be used: low, moderate, high, and super. Low-potency preparations include hydrocortisone, desonide, and hydrocortisone butyrate. Medium-potency compounds include amcinonide, betamethasone, flurandrenolide, fluocinolone, mometasone furoate, and triamcinolone. High-potency topical steroids include fluocinonide and halcinonide. Betamethasone dipropionate and clobetasol propionate are superpotent preparations and should be prescribed with care.

Some of these compounds are formulated in several strengths according to clinical efficacy and degree of vasoconstriction. Physicians using topical steroids should become familiar with preparations within each class.

Table 665.1

Potency of Topical Glucocorticosteroids

Class 1—Superpotent

Betamethasone dipropionate, 0.05% gel, ointment
Clobetasol propionate cream, ointment, 0.05%
Halobetasol propionate cream, ointment, 0.05%

Class 2—Potent

Betamethasone dipropionate cream 0.05%
Desoximetasone cream, ointment, gel 0.05% and 0.25%
Fluocinonide cream, ointment, gel, 0.05%

Class 3—Upper Mid-Strength

Betamethasone dipropionate cream, 0.05%
Betamethasone valerate ointment, 0.1%
Fluticasone propionate ointment, 0.005%
Mometasone furoate ointment, 0.1%
Triamcinolone acetonide cream, 0.5%

Class 4—Mid-Strength

Desoximetasone cream, 0.05%
Fluocinolone acetonide ointment, 0.025%
Triamcinolone acetonide ointment, 0.1%

Class 5—Lower Mid-Strength

Betamethasone valerate cream/lotion, 0.1%
Fluocinolone acetonide cream, 0.025%
Fluticasone propionate cream, 0.05%
Triamcinolone acetonide cream/lotion, 0.1%

Class 6—Mild Strength

Desonide cream, 0.05%

Class 7—Least Potent

Topicals with hydrocortisone, dexamethasone, flumethasone, methylprednisolone, and prednisolone

From Weston WL, Lane AT, Morelli JG: *Color textbook of pediatric dermatology* , ed 4, St. Louis, 2007, Mosby, p. 418.

All corticosteroids can be obtained in various vehicles, including creams, ointments, solutions, gels, and aerosols. Some are available in a foam vehicle. Absorption is enhanced by an ointment or gel vehicle, but the vehicle should be selected on the basis of the type of disorder and the site of involvement. Frequency of application should be determined by the potency of the preparation, the location on the body, and the severity of the eruption. Applying a thin film 2 times daily usually suffices. Adverse local effects include cutaneous atrophy, striae, telangiectasia, acneiform eruptions, purpura, hypopigmentation, and increased hair growth. Systemic adverse effects of high-potency and superpotent topical steroids occur with long-term use and include poor growth, cataracts, and suppression of adrenal function.

The relative skin thickness should be considered in regard to the selection of class of steroid (see Table 665.1). Thin skin such as the eyelids, face, groin, and genitalia will absorb a substantial amount of medication compared to the thickest skin on the palms and soles. One adult fingertip's worth of medication is enough to cover an area the size of an adult palm and is approximately half a gram of medication. Knowing the area being treated and which medication class to prescribe can decrease potential for side effects.

In selected circumstances, corticosteroids may be administered by intralesional injection (acne cysts, keloids, psoriatic plaques, alopecia areata, persistent insect bite reactions). Only experienced physicians should use this method of administration.

Topical Nonsteroidal Antiinflammatory Agents

Calcineurin-inhibiting antiinflammatory agents that inhibit T-cell activation may be used instead of topical steroids for the treatment of atopic dermatitis and other inflammatory conditions. These agents are pimecrolimus and tacrolimus. They do not have the adverse local effects seen with topical steroids. Stinging with application is the most common complaint and may be lessened by mixing the medication with an ointment such as petrolatum jelly for the initial applications. These agents are only as strong as medium-potency topical steroids. In 2006, the FDA issued a boxed warning for topical calcineurin inhibitors because data from animal experiments and case reports suggested potential for an increased risk of lymphoma with systemic use. There has been no clear link between topical calcineurin inhibitor use and lymphoma risk established despite multiple epidemiological and clinical studies.

Sunscreens

Sunscreens are of 2 general types: (1) those, such as zinc oxide and titanium dioxide, that absorb all wavelengths of the UV and visible spectrums; and (2) a heterogeneous group of chemicals that selectively absorb energy of various wavelengths within the UV spectrum. In addition to the spectrum of light that is blocked, other factors to be considered include cosmetic acceptance, sensitizing potential, retention on skin while swimming or sweating, required frequency of application, and cost. Sunscreen ingredients include para-aminobenzoic acid (PABA) with ethanol, PABA esters, cinnamates, and benzophenone. These block transmission of the majority of solar UVB and some UVA wavelengths. Avobenzone and ecamsule are more effective in blocking UVA. Antioxidants may also be found in some sunscreens. Lip protectants that absorb in the UVB range are also available. Sunscreens are designated by sun protection factor (SPF). The SPF is defined as the amount of time to develop a mild sunburn with the sunscreen compared with the amount of time without the sunscreen. A minimum SPF factor of 15 is required for most fair-skinned individuals to prevent sunburn; however, an SPF of 30 should be recommended most often. The higher the SPF, the better the protection is against UVB rays. Sunscreens do not include any measurement of the efficacy in blocking UVA. The efficacy of these agents depends on careful attention to instructions for use. Chemical sunscreens should be applied at least 30 min before sun exposure to permit penetration into the epidermis, again on arrival at the destination, and every subsequent hour when exposed to direct sunlight. Most patients with photosensitivity eruptions require protection by agents that absorb both UVB and UVA wavelengths (see Chapter 675).

Although sunscreens do confer photoprotection and may decrease the development of nevi, protection is incomplete against all harmful UV light. Midday (10 AM to 4 PM) sun avoidance is the primary method of photoprotection. Clothing, hats, and staying in the shade offer additional sun protection.

Laser Therapy

The vascular-specific pulsed dye laser therapy is used mainly for the treatment of capillary malformations (port-wine stains). Spider telangiectasia, small facial pyogenic granulomas, superficial and ulcerated hemangioma, and warts may also be treated. Vascular-specific pulsed dye lasers produce light that is readily absorbed by oxyhemoglobin, producing selective photothermolysis of vascular lesions.

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CHAPTER 666

Dermatologic Diseases of the Neonate

Kathleen A. Long, Kari L. Martin

Minor evanescent lesions of newborn infants, particularly when florid, may cause undue concern. Most of these entities are relatively common, benign, and transient and do not require therapy.

Sebaceous Hyperplasia

Minute, profuse, yellow-white papules are frequently found on the forehead, nose, upper lip, and cheeks of a term infant; they represent hyperplastic sebaceous glands (Fig. 666.1). These tiny papules diminish gradually in size and disappear entirely within the first few weeks of life; no treatment is required.

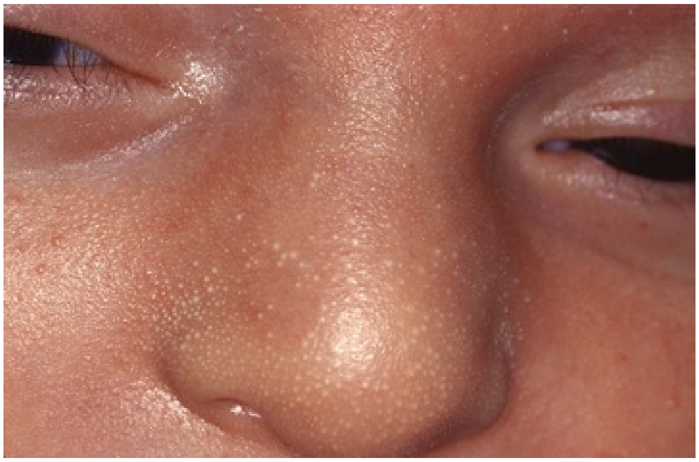

FIG. 666.1 Sebaceous hyperplasia. Minute white-yellow papules on the nose of a newborn.

Milia

Milia are superficial epidermal inclusion cysts that contain laminated keratinized material. The lesion is a firm cyst, 1-2 mm in diameter, and pearly, opalescent white. Milia may occur at any age but in neonates are most frequently scattered over the face and gingivae and on the midline of the palate, where they are called Epstein pearls. Milia exfoliate spontaneously in most infants and may be ignored; those that appear in scars or sites of trauma in older children may be gently unroofed and the contents extracted with a fine-gauge needle.

Sucking Blisters

Solitary or scattered superficial bullae present at birth on the upper limbs of infants are presumably induced by vigorous sucking on the affected part in utero. Common sites are the radial aspect of the forearm, thumb, and index finger. These bullae resolve rapidly without sequelae. They may occur in conjunction with sucking pads (calluses), which are found on the lips and are a result of combined intracellular edema and hyperkeratosis.

Cutis Marmorata

When a newborn infant is exposed to low environmental temperatures, an evanescent, lacy, reticulated red and/or blue cutaneous vascular pattern appears over most of the body surface. This vascular change represents an accentuated physiologic vasomotor response that disappears with increasing age, although it is sometimes discernible even in older children. No treatment is needed. Cutis marmorata telangiectatica congenita presents in a similar fashion, but is a vascular anomaly in which the lesions are more intense, may be segmental, and are persistent despite warming of the infant. They may be associated with loss of dermal tissue, epidermal atrophy, and ulceration (Fig. 666.2). The lower extremities are usually affected with limb atrophy noted on the affected side. Gradual fading of the livid erythema occurs over 3-5 yr, but limb asymmetry is permanent. Extracutaneous findings such as ocular and neurological abnormalities may be associated in 20–80% of cases. There is no specific treatment.

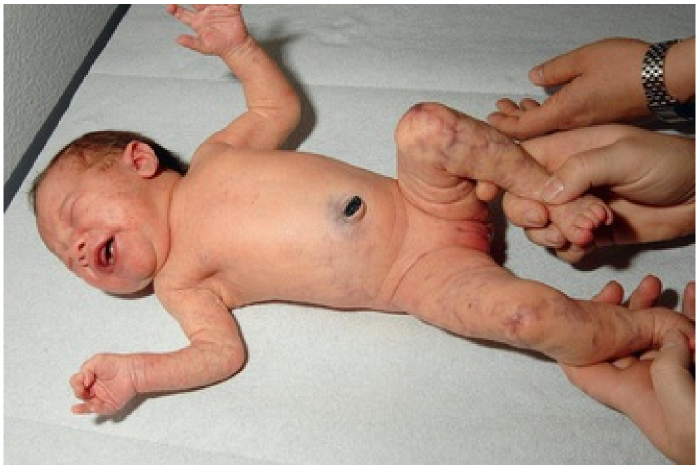

FIG. 666.2 Newborn girl with reticulate erythema/livedo on legs, right arm, and cheeks. (From Pleimes M, Gottler S, Weibel L: Characteristic congenital reticular erythema: cutis marmorata telangiectatica congenital. *J Pediatr* 163:604, 2013, Fig. 1.)

Harlequin Color Change

A dramatic vascular event, harlequin color change occurs transiently in up to 10% of newborns, most commonly on the days 2-52 of life. It probably reflects an imbalance in the autonomic vascular regulatory mechanism. When the infant is placed on one side, the body is bisected longitudinally into a pale upper half and a deep red dependent half. The color change lasts only for a few minutes and occasionally affects only a portion of the trunk or face. Changing the infant's position may reverse the pattern. Muscular activity causes generalized flushing and obliterates the color differential. Repeated episodes may occur but do not indicate permanent autonomic imbalance. There is generally no need for treatment. This disorder should be readily distinguishable from **Harlequin syndrome** , which is associated with paroxysmal hemifacial flushing and sweating with or without a Horner syndrome. Symptoms are induced by heat, stress, or exercise. Some cases are secondary to trauma, cervical cord syrinx, or neuroblastoma. Although rarely congenital, most cases occur in older children.

Nevus Simplex (Salmon Patch)

Nevus simplex is a small, pale pink, ill-defined, vascular macule that occurs most commonly on the glabella, eyelids, upper lip, and nuchal area of 30–40%

of normal newborn infants. These lesions persist for several months and may become more visible during crying or changes in environmental temperature. Most lesions on the face eventually fade and disappear completely, although lesions occupying the entire central forehead often do not. Those on the posterior neck and occipital areas usually persist. Treatment is not usually indicated, though pulsed dye laser treatment can be helpful in lightening lesions that are persistent and cosmetically bothersome. Nevus simplex should not be confused with a port-wine stain (capillary malformation), which is a permanent lesion and may be associated with Sturge-Weber syndrome. Nevus simplex is usually symmetric, with lesions on both eyelids or on both sides of midline. Port-wine stains are often larger and unilateral, and they usually end along the midline (see Chapter 669).

Dermal Melanocytosis (Mongolian Spots)

Dermal melanocytosis, which appears as blue or slate-gray macular lesions, has variably defined margins. It occurs most commonly in the sacral area but may be found over the posterior thighs, legs, back, and shoulders (Fig. 666.3). The spots may be solitary or numerous and often involve large areas. The incidence of these lesions varies widely across ethnicities, being most common in African American, Asian, and Hispanic infants (25–80% depending on the study) and less common in Caucasian infants (around 6%). The peculiar hue of these macules is a result of the dermal location of melanin-containing melanocytes (mid-dermal melanocytosis) that are presumably arrested in their migration from neural crest to epidermis. They usually fade during the first few years of life as a result of darkening of the overlying skin. If lesions persist, they may be treated with lasers, if desired. Malignant degeneration does not occur. The characteristic appearance and congenital onset distinguish these spots from the bruises of child abuse. Rarely Mongolian spots are associated with Hurler or Hunter syndromes, GM1 gangliosidosis, Niemann-Pick disease, mucolipidosis, and mannosidosis.

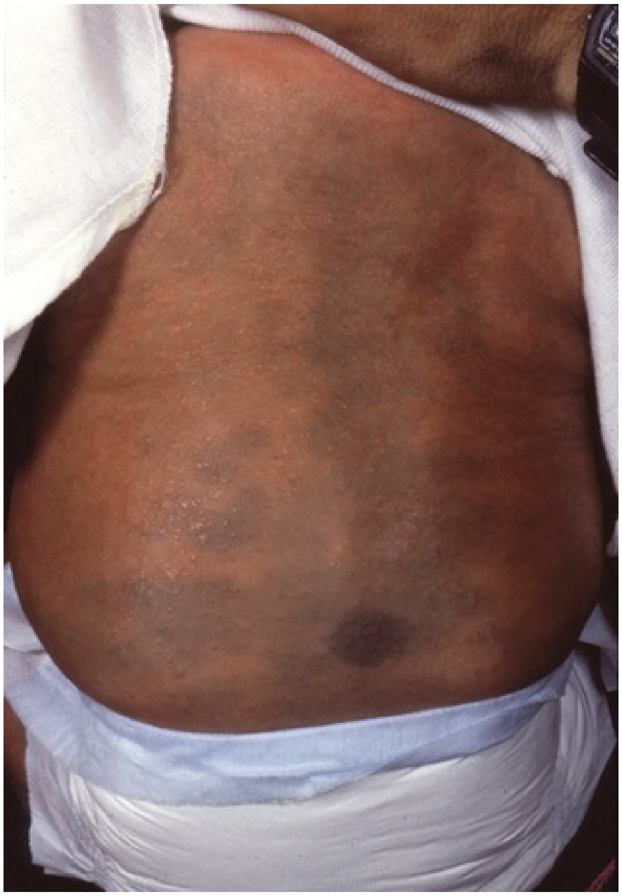

FIG. 666.3 Extensive Mongolian spot on the back of a newborn. (Courtesy of Fitzsimons Army Medical Center teaching file.)

Erythema Toxicum

A benign, self-limited, evanescent eruption, erythema toxicum occurs in approximately 50% of full-term infants; preterm infants are affected less commonly. The lesions are firm, yellow-white, 1-2 mm papules or pustules with a surrounding erythematous flare (Fig. 666.4). At times, splotchy erythema is the only manifestation. Lesions may be sparse or numerous and either clustered in several sites or widely dispersed over much of the body surface. The palms and soles are usually spared. Peak incidence occurs on the 2nd day of life, but new lesions may erupt during the first few days as the rash waxes and wanes. Onset may occasionally be delayed for a few days to weeks in premature infants. Eosinophils can be demonstrated in Wright-stained smears of the intralesional contents. Cultures are sterile.

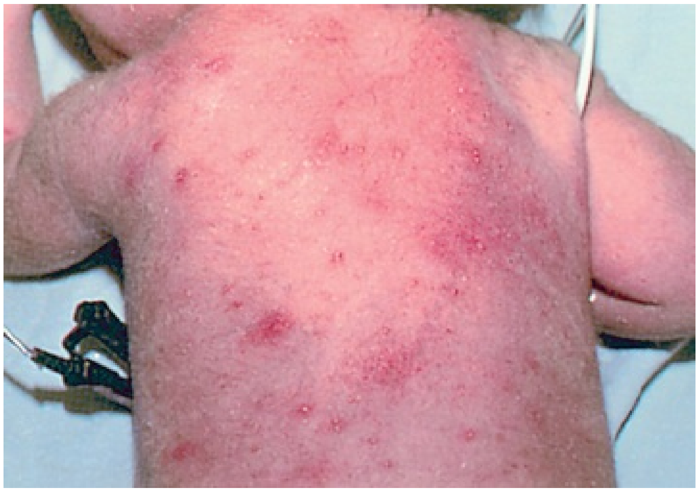

FIG. 666.4 Erythema toxicum on the trunk of a newborn infant.

The cause of erythema toxicum is unknown. The lesions can mimic pyoderma, candidiasis, herpes simplex, transient neonatal pustular melanosis, and miliaria but can be differentiated by the characteristic infiltrate of eosinophils and the absence of organisms on a stained smear. The course is brief (3-7 days), and lesions generally resolve without pigmentation. No therapy is required. Incontinentia pigmenti and eosinophilic pustular folliculitis also have eosinophilic infiltration but can be distinguished by their distribution, histologic type, and chronicity.

Transient Neonatal Pustular Melanosis

Pustular melanosis, which is more common among African American than Caucasian infants, is a transient, benign, self-limited dermatosis of unknown etiology that is characterized by 3 types of lesions: (1) evanescent superficial pustules, (2) ruptured pustules with a collarette of fine scale, at times with a central hyperpigmented macule, and (3) hyperpigmented macules (Fig. 666.5). Lesions are present at birth, and one or all types of lesions may be found in a profuse or sparse distribution. Pustules represent the early phase of the disorder, and macules, the late phase. The pustular phase rarely lasts more than 2-3 days; hyperpigmented macules may persist for as long as 3 mo. Sites of predilection are the anterior neck, forehead, and lower back, although the scalp, trunk, limbs, palms, and soles may be affected.

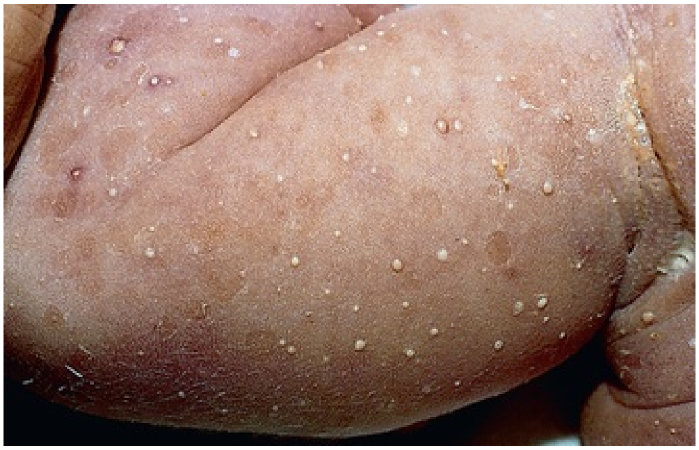

FIG. 666.5 Transient neonatal pustular melanosis. Multiple papules present at birth on the arm of an infant. (From Weston WL, Lane AT, Morelli JG, editors: *Color textbook of pediatric dermatology* , ed 3, Philadelphia, 2002, Mosby, p 331.)

The active phase shows an intracorneal or subcorneal pustule filled with polymorphonuclear leukocytes, debris, and an occasional eosinophil. The macules are characterized only by increased melanization of epidermal cells. Cultures and smears can be used to distinguish these pustules from those of pyoderma and erythema toxicum, because the lesions of pustular melanosis do not contain bacteria or dense aggregates of eosinophils. **No therapy is required.**

Infantile Acropustulosis

Onset of infantile acropustulosis generally occurs at 2-10 mo of age; lesions are occasionally noted at birth (Fig. 666.6). Darkly pigmented males have a predisposition, but infants of both sexes and all races may be affected. The cause is unknown.

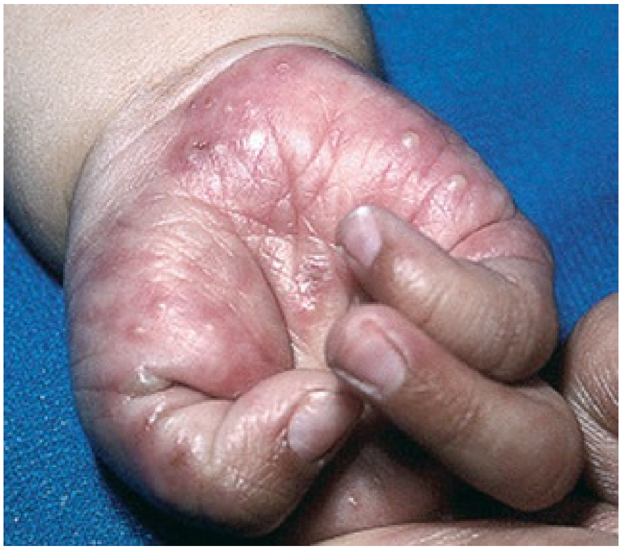

FIG. 666.6 Acropustulosis of infancy. Multiple tense erythematous papules and pustules on the palm of this 4 mo old girl. (From Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, editors: *Nelson Pediatric Symptom-Based Diagnosis* , Philadelphia, 2017, Elsevier, Fig. 47.3, p 854.)

The lesions are initially discrete erythematous papules that become vesiculopustular within 24 hr and subsequently crust before healing. They are intensely pruritic. Preferred sites are the palms of the hands and the soles and sides of the feet, where the lesions may be extensive. A less dense eruption may be found on the dorsum of the hands and feet, ankles, and wrists. Pustules occasionally occur elsewhere on the body. Each episode lasts 7-14 days, during which time pustules continue to appear in crops. After a 2-4 wk remission, a new outbreak follows. This cyclic pattern continues for approximately 2 yr; permanent resolution is often preceded by longer intervals of remission between periods of activity. Infants with acropustulosis are otherwise well.

Wright-stained smears of intralesional contents show abundant neutrophils or, occasionally, a predominance of eosinophils. Histologically, well-circumscribed, subcorneal, neutrophilic pustules, with or without eosinophils, are noted.

The differential diagnosis in neonates includes transient neonatal pustular melanosis, erythema toxicum, milia, cutaneous candidiasis, and staphylococcal pustulosis. In older infants and toddlers, additional diagnostic considerations include scabies, dyshidrotic eczema, pustular psoriasis, subcorneal pustular dermatosis, and hand-foot-and-mouth disease. A therapeutic trial of a scabicide is warranted in equivocal cases.

Therapy is directed at minimizing discomfort for infants. Topical corticosteroids and/or oral antihistamines decrease the severity of the pruritus and an infant's irritability. Dapsone (1 to 2 mg/kg/day by mouth, divided in 1 to 2 doses) is effective but has potentially serious side effects, notably, hemolytic anemia and methemoglobinemia; its use should be limited to particularly severe cases.

Eosinophilic Pustular Folliculitis

Eosinophilic pustular folliculitis is defined as recurrent crops of pruritic, coalescing, follicular papulopustules on the face, trunk, and extremities. Fifty percent of patients have peripheral eosinophilia with eosinophil counts exceeding 5%, and approximately 30% have leukocytosis (>10,000 leukocytes/mm^3).

Infants account for <10% of all cases of eosinophilic pustular folliculitis. The clinical and histologic appearances of this disorder in infants closely resemble those in immunocompetent adults, with minor exceptions. In infants, the lesions are most prominent on the scalp, although they also occur on the trunk and extremities and occasionally are found on the palms and soles. The classic annular and polycyclic appearance with centrifugal enlargement is not seen in infants. The differential diagnosis includes erythema toxicum neonatorum, infantile acropustulosis, localized pustular psoriasis, pustular folliculitis, and transient neonatal pustular melanosis. High-potency topical corticosteroids are the most effective treatment (see Table 665.1 in Chapter 665).

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CHAPTER 667

Cutaneous Defects

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Skin Dimples

Cutaneous depressions over bony prominences and in the acral area, at times associated with pits and creases, may occur in normal children and in association with dysmorphologic syndromes. Skin dimples may develop in utero as a result of interposition of tissue between a sharp bony point and the uterine wall, which leads to decreased subcutaneous tissue formation.

Dimples may also be present overlying an area of bone hypoplasia. Bilateral acromial skin dimples are usually an isolated finding, but they are also seen in association with deletion of the long arm of chromosome 18. Dimples tend to occur over the patella in congenital rubella, over the lateral aspects of the knees and elbows in prune-belly syndrome, on the pretibial surface in campomelic dwarfs, and in the shape of an H on the chin in whistling face syndrome.

Sacral dimples are common and usually are isolated findings. They may be seen in multiple syndromes or in association with spina bifida occulta and diastomyelia. Association with a mass or other cutaneous stigma (hair, aplasia cutis, lipoma, hemangioma) should increase concern for underlying spinal dysraphism (see Chapter 609). Simple sacral dimples do not predict underlying spinal cord malformations, and spinal ultrasounds should not be performed in these cases because most of the abnormal findings reported in them are of no clinical significance. In infants younger than 3 months who warrant imaging, ultrasound is a cost-effective, noninvasive method. *MRI of the spine is the imaging modality of choice for patients are older than 3 months if there is a strong suspicion of a spinal dysraphism.*

Redundant Skin

Loose folds of skin must be differentiated from a congenital defect of elastic tissue or collagen such as cutis laxa, Ehlers-Danlos syndrome, or pseudoxanthoma elasticum. Redundant skin over the posterior part of the neck is common in the Turner, Noonan, Down, and Klippel-Feil syndromes and monosomy 1p36; more generalized folds of skin occur in infants with trisomy 18 and short-limbed dwarfism.

Amniotic Constriction Bands

Partial or complete constriction bands that produce defects in extremities and digits are found in 1 in 10,000–45,000 otherwise normal infants. Constrictive tissue bands are caused by primary amniotic rupture, with subsequent entanglement of fetal parts, particularly limbs, in shriveled fibrotic amniotic strands. This event is probably sporadic, with negligible risk of recurrence. Formation of constrictive tissue bands is associated with maternal history of abdominal trauma, amniocentesis, and hereditary defects of collagen such as Ehlers-Danlos syndrome and osteogenesis imperfecta. Treatment traditionally involves multiple surgical elongating procedures such as Z- and W-plasties. A surgical alternative uses lipoinjection and multiple internal incisions on the deep surface of the band.

Adhesive bands involve the craniofacial area and are associated with severe defects such as encephalocele and facial clefts. Adhesive bands result from broad fusion between disrupted fetal tissue and an intact amniotic membrane. The craniofacial defects appear not to be caused by constrictive amniotic bands but to result from a vascular disruption sequence with or without cephaloamniotic adhesion (see Chapter 128).

The limb–body wall complex involves vascular disruption early in development, affecting several embryonic structures; it includes at least 2 of the following 3 characteristics: exencephaly or encephalocele with facial clefts, thoracoschisis and/or abdominoschisis, and limb defects.

Preauricular Sinuses and Pits

Pits and sinus tracts anterior to the pinna may be a result of imperfect fusion of the tubercles of the 1st and 2nd branchial arches. These anomalies may be unilateral or bilateral, may be familial, are more common among females and African Americans, and at times are associated with other anomalies of the ears and face. Preauricular pits are present in branchiootorenal dysplasia 1 syndrome (*EYA-1* gene), an autosomal dominant disorder that consists of external ear malformations, branchial fistulas, hearing loss, and renal anomalies. When the tracts become chronically infected, retention cysts may form and drain intermittently; such lesions may require excision.

Accessory Tragi

An accessory tragus typically appears as a single pedunculated, flesh-colored papule in the preauricular region anterior to the tragus. Less commonly, accessory tragi are multiple or bilateral and may be located in the preauricular area, on the cheek along the line of the mandible (Fig. 667.1), or on the lateral aspect of the neck anterior to the sternocleidomastoid muscle. In contrast to the rest of the pinna, which develops from the 2nd branchial arch, the tragus and accessory tragi derive from the 1st branchial arch. Accessory tragi may occur as isolated defects or in chromosomal 1st branchial arch syndromes that include anomalies of the ears and face, such as cleft lip, cleft palate, and mandibular hypoplasia. An accessory tragus is consistently found in oculoauriculovertebral syndrome (Goldenhar syndrome). Other associated syndromes include mandibulofacial dysostosis (Treacher Collins syndrome), Townes-Brocks, VACTERL, and Wolf-Hirschhorn syndrome. Surgical excision is appropriate.

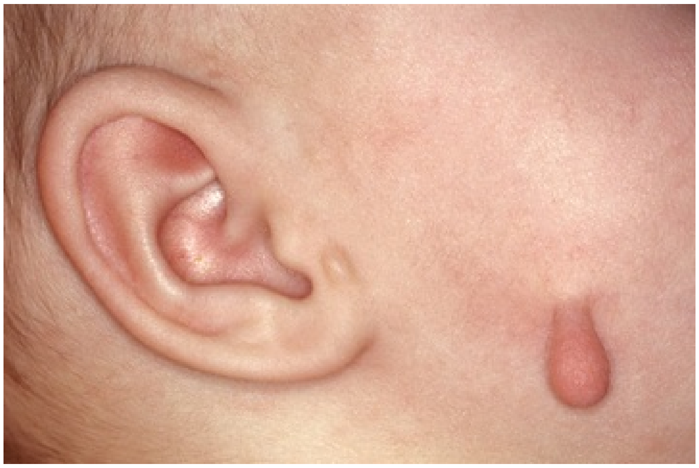

FIG. 667.1 Accessory tragus on cheek along jaw line.

Studies are controversial on whether patients with accessory tragi and preauricular pits have a higher prevalence of hearing loss and urinary tract anomalies. *Renal ultrasound should be performed when found with at least one of the following: family history of deafness, auricular and/or renal malformation, or a maternal history of gestational diabetes.*

Branchial Cleft and Thyroglossal Cysts and Sinuses

Cysts and sinuses in the neck may be formed along the course of the 1st, 2nd, 3rd, or 4th branchial clefts as a result of improper closure during embryonic life. Second branchial cleft cysts are the most common. The lesions may be unilateral or bilateral (2–3%) and may open onto the cutaneous surface or drain into the pharynx. Secondary infection is an indication for systemic antibiotic therapy**.** These anomalies may be inherited as autosomal dominant traits.

Thyroglossal cysts and fistulas are similar defects located in or near the midline of the neck; they may extend to the base of the tongue. **A pathognomonic sign** is vertical motion of the mass with swallowing and tongue protrusion. In nearly 50% of affected children, the cyst or fistula manifests as an infected midline upper neck mass. Cysts in the tongue base may be differentiated from an undescended lingual thyroid by radionuclide scanning. Unlike branchial cysts, a thyroglossal duct cyst often appears after an upper respiratory infection (see Chapter 579).

Supernumerary Nipples

Solitary or multiple accessory nipples may occur in a unilateral or bilateral distribution along a line from the anterior axillary fold to the inguinal area. They are more common among African-American (3.5%) than white (0.6%) children. Prevalence ranges from 0.1% to 0.99% in the literature. Accessory nipples may or may not have areolae and may be mistaken for congenital nevi. They may be excised for cosmetic reasons, but otherwise, treatment is not necessary. Renal or urinary tract anomalies, malignancies—especially genitourinary cancers—and hematologic abnormalities may rarely occur in children with this finding (see

Chapter 566).

Aplasia Cutis Congenita (Congenital Absence of Skin)

Developmental absence of skin is usually noted on the scalp as multiple or solitary (70%), noninflammatory, well-demarcated, oval or circular 1–2 cm ulcers (Table 667.1). The appearance of lesions varies, depending on when they occurred during intrauterine development. Those that form early in gestation may heal before delivery and appear as atrophic, fibrotic scars with associated alopecia, whereas more recent defects may manifest as ulcerations. Most occur at the vertex of the scalp just lateral to the midline, but similar defects may also occur on the face, trunk, and limbs, where they are often symmetric and usually associated with an intrauterine fetal demise of a twin (fetus papyraceus). The depth and size of the ulcer varies. Only the epidermis and upper dermis may be involved, resulting in minimal scarring or hair loss, or less often the defect may extend to the deep dermis, to the subcutaneous tissue, and, rarely, to the periosteum, skull, and dura. Lesions may be surrounded by a ring of hair known as the hair collar sign (Fig. 667.2).

Table 667.1

Freiden's Classification of Aplasia Cutis Congenita

GROUP	DEFINITION	INHERITANCE
1	Isolated scalp involvement; may be associated with single defects	AD
2	Scalp ACC with limb reduction defects (Adams-Oliver syndrome); may be associated with encephalocele	AD
3	Scalp ACC with epidermal nevus	Sporadic
4	ACC overlying occult spinal dysraphism, spina bifida, or meningoencephalocele	Sporadic
5	ACC with placental infarcts, and/or fetus papyraceus	Sporadic
6	ACC with epidermolysis bullosa	AD or AR
7	ACC localized to extremities without blistering; usually affecting pretibial areas and dorsum of hands and feet	AD or AR
8	ACC caused by teratogens (e.g., varicella, herpes, methimazole)	Sporadic
9	ACC associated with malformation syndromes (e.g., trisomy 13, deletion 4p−, deletion Xp22.1, ectodermal dysplasia, Johanson-Blizzard syndrome, Adams-Oliver syndrome)	Variable

ACC , aplasia cutis congenital; *AD* , autosomal dominant; *AR* , autosomal recessive.

Modified from Frieden IJ: Aplasia cutis congenital: a clinical review and proposal for classification. *J Am Acad Dermatol* 14:646–660, 1986.

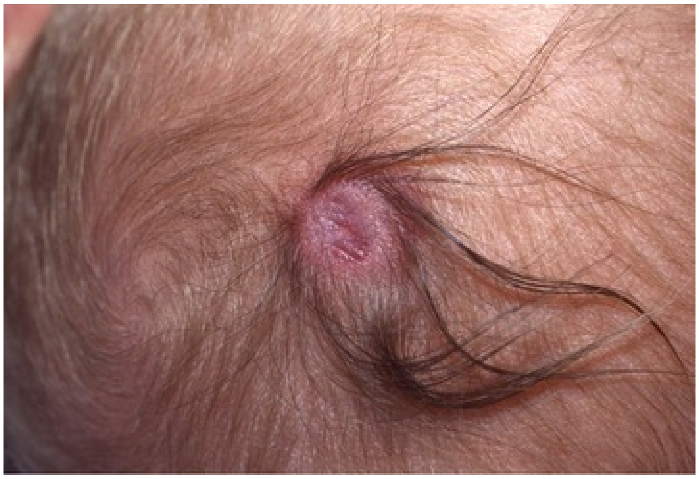

FIG. 667.2 Solitary scalp vertex lesion of aplasia cutis congenita with hair collar.

Diagnosis is made on the basis of physical findings indicative of in utero disruption of skin development. Lesions are sometimes mistakenly attributed to scalp electrodes or obstetric trauma. Most are sporadic, but autosomal dominant and recessive cases also occur; some are due to mutations in *BMS1* , a ribosomal guanosine triphosphatase.

Although most individuals with aplasia cutis congenita have no other abnormalities, these lesions may be associated with isolated physical anomalies or with malformation syndromes, including Opitz, Adams-Oliver, oculocerebrocutaneous, Johanson-Blizzard, and 4p(−), X-p22 microdeletion syndromes, trisomy 13–15, and chromosome 16–18 defects (see Table 667.1). Aplasia cutis congenita may also be found in association with an overt or underlying embryologic malformation, such as congenital pulmonary malformations, meningomyelocele, gastroschisis, omphalocele, or spinal dysraphism. Aplasia cutis congenita in association with the **vanishing twin syndrome** (fetus papyraceus) is apparently caused by ischemic or thrombotic events in the placenta and fetus such as the hypovolemia that occurs with acute transfusion from a surviving to a dying twin. Blistering or skin fragility and/or absence or deformity of nails in association with aplasia cutis congenita is a well-recognized manifestation of epidermolysis bullosa.

Major complications are rare and more often associated with large, stellate lesions of the midline parietal scalp. Hemorrhage, secondary local infection, and meningitis have been reported. If the defect is small, recovery is uneventful, with gradual epithelialization and formation of a hairless atrophic scar over a period of several weeks. Small bony defects usually close spontaneously in the 1st yr of life. Large or numerous scalp defects may require repair, but care must be taken as abnormal underlying venous structures have complicated surgical repair. Truncal and limb defects, despite being large, usually epithelialize and form atrophic scars, which can later be revised.

Although the **hair collar sign** is often associated with aplasia cutis, it may also be seen with encephaloceles, meningoceles, heterotopic glial elements, or hamartoma. Brain MRI is often indicated to evaluate for these lesions in patients with the hair collar sign without aplasia cutis (Fig. 667.3).

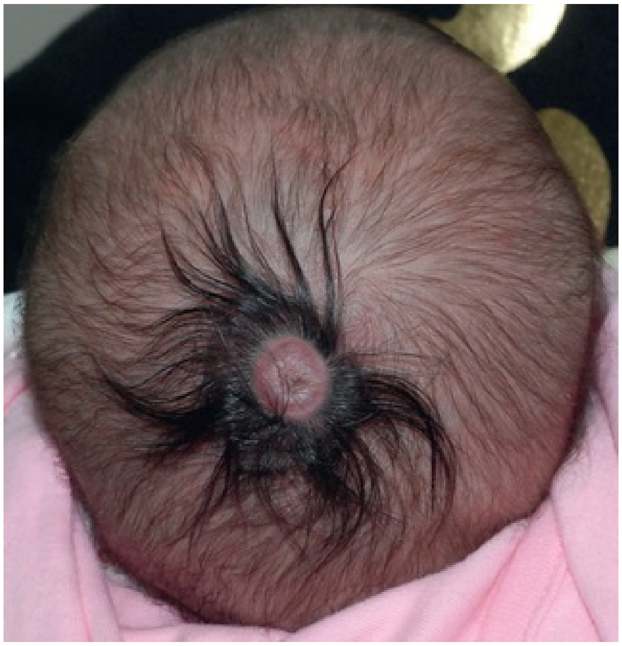

FIG. 667.3 An elastic protruding hairless nodule measuring up to 1.5 cm in diameter, with a ring of dark, coarse, long hairs surrounding the nodule forming a “hair collar.” (From Chien MM, Chen KL, Chiu HC: The “hair collar” sign. *J Pediatr* 168:246, 2016.)

Focal Facial Dermal Dysplasias

The focal facial dermal dysplasias (FFDDs) are a rare group of conditions sharing bitemporal or preauricular lesions resembling scars or aplasia cutis congenita. FFDD1 (Brauer syndrome) is inherited in an autosomal dominant fashion and typically has mild associated facial features. FFDD2 (Brauer-Setleis syndrome) and FFDD3 (Setleis syndrome) are associated with thin, puckered periorbital skin, distichiasis and/or absent eyelashes, upslanting palpebral fissures, flat nasal bridge, large lips, and redundant facial skin. FFDD2 is inherited in an autosomal dominant fashion, whereas FFDD3 is autosomal recessive and caused by mutations in *TWIST2;* autosomally dominant cases of FFDD3 have been reported and are caused by chromosome duplication/triplication of the 1p36.22p36.21 region. FFDD4 has no other related skin findings; it is inherited both in autosomal dominant and recessive manners and is caused by mutations in *CYP26C1* .

Focal Dermal Hypoplasia (Goltz-Gorlin Syndrome)

A rare congenital mesoectodermal and ectodermal disorder, focal dermal hypoplasia is characterized by dysplasia of connective tissue in the skin and skeleton. This disorder is an X-linked dominant disorder caused by mutations in the *PORCN* gene. It manifests as numerous soft tan papillomas. Other cutaneous findings include linear atrophic lesions; reticulated hypopigmentation and hyperpigmentation; telangiectasias; congenital absence of skin; angiofibromas presenting as verrucous excrescences; and papillomas of the lips, tongue, circumoral region, vulva, anus, and the inguinal, axillary, and periumbilical areas. Partial alopecia, sweating disorders, and dystrophic nails are additional, less common ectodermal anomalies. The most frequent skeletal defects are syndactyly, clinodactyly, polydactyly, and scoliosis. Osteopathia striata are fine parallel vertical stripes noted on radiographs in the metaphyses of long bones of patients with this disorder; these are highly characteristic of focal dermal hypoplasia but are not pathognomonic. Many ocular abnormalities, the most common of which are colobomas, strabismus, nystagmus, and microphthalmia, are also characteristic. Small stature, enamel hypoplasia, soft tissue anomalies, and peculiar dermatoglyphic patterns are also common. Cognitive impairment occurs occasionally. There is no specific treatment.

Dyskeratosis Congenita (Zinsser-Engman-Cole Syndrome)

Dyskeratosis congenita (DKC), a rare familial syndrome, consists classically of the triad of reticulated hyperpigmentation of the skin (Fig. 667.4), dystrophic nails, and mucous membrane leukoplakia in association with immunologic and hematologic abnormalities. Patients with DKC also show signs of premature aging and increased occurrence of cancer, especially squamous cell carcinoma. DKC may be X-linked recessive (*DKC-1* gene), autosomal dominant (*hTERC* and *TINF2* genes), or autosomal recessive (*NOLA3* gene). Onset occurs in childhood, most commonly as nail dystrophy**.** The nails become atrophic and ridged longitudinally with progression to pterygia and complete nail loss. Skin changes usually appear after onset of nail changes and consist of reticulated gray-brown pigmentation, atrophy, and telangiectasia, especially on the neck, face, and chest. Hyperhidrosis and hyperkeratosis of the palms and soles, sparse scalp hair, and easy blistering of the hands and feet are also characteristic. Blepharitis, ectropion, and excessive tearing because of atresia of the lacrimal ducts are occasional manifestations. Oral leukokeratosis may give rise to squamous cell carcinoma. Other mucous membranes, including conjunctival, urethral, and genital, may be involved. Infection, malignancy, pulmonary fibrosis, and bone marrow failure are common, and death before age 40 yr is typical. No effective treatment exists. Allogenic hemopoietic stem cell transplantation is curative treatment when bone marrow failure occurs.

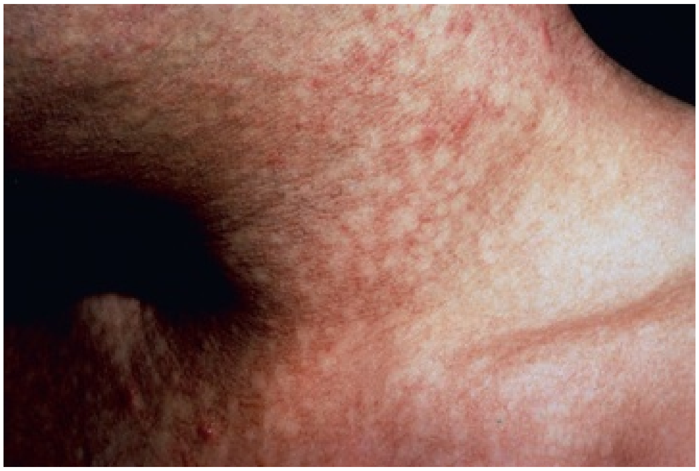

FIG. 667.4 Reticulated dyspigmentation on neck of patient with dyskeratosis congenita.

Cutis Verticis Gyrata

Cutis verticis gyrata, an unusual alteration of the scalp that is more common in males, may be present from birth or may develop during adolescence. The scalp is characterized by convoluted elevated folds, 1-2 cm in thickness, usually in the fronto-occipital axis. Unlike the lax skin of other disorders, the convolutions cannot generally be flattened by traction. Primary cutis gyrata may be associated with intellectual disability, retinitis pigmentosa, sensorineural deafness, and thyroid aplasia. Secondary cutis gyrata may be due to chronic inflammatory diseases, tumors, nevi, and acromegaly.

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CHAPTER 668

Ectodermal Dysplasias

Nadia Y. Abidi, Kari L. Martin

Ectodermal dysplasia (ED) is a heterogeneous group of disorders characterized by a constellation of findings involving defects of two or more of the following: teeth, skin, and appendageal structures, including hair, nails, and eccrine and sebaceous glands. Although more than 150 EDs have been described, the majority are rare, with an estimated incidence of 3.5 in 10,000 individuals.

Individuals presenting with a constellation of abnormalities involving the teeth, skin, and nails should raise suspicion for a diagnosis of ED. Table 668.1 provides a general list of abnormalities that may be seen in patients with EDs. Further specifying the specific type of ED can be challenging because there are a large number of subtypes and most are extremely rare.

Table 668.1

Clinical Abnormalities in Ectodermal Dysplasia

	CLINICAL FEATURES
Teeth	Small primary teeth, anodontia or hypodontia of secondary teeth, conical or peg teeth, premature loss of teeth, delayed eruption of teeth, defective enamel, small widely spaced teeth, elongated pulp chamber in teeth
Skin	Atopic dermatitis, xerosis, photosensitivity, palmoplantar keratoderma, facial telangiectasias
Hair	Abnormal quantity, structure and quality: thin, brittle, slow growing, kinky or wooly, fragile, dry and lusterless hair. Often involves scalp, eyebrows and eyelashes.
Nails	Brittle, dystrophic, absent, ridging, pitting
Sweat	Hypohidrosis, hyperhidrosis of palms and soles
Other	Recurrent sinus infection, nasal congestion, hoarse voice, wheezing

[a] Normal phenotype is also possible for any of these categories.

ED , Ectodermal dysplasia.

Hypohidrotic Ectodermal Dysplasia

The syndrome known as hypohidrotic ectodermal dysplasia (HED) manifests as a triad of defects: partial or complete absence of sweat glands, anomalous dentition, and hypotrichosis. There are 4 recognized types of HED (Table 668.2); HED-1 (X-linked recessive) is most common, with a frequency in 1 per 17,000 live births.

Table 668.2

Four Recognized Types of Anhidrotic Ectodermal Dysplasia (ED)

TYPE	INHERITANCE	GENE DEFECT
ED-1	X-linked recessive	Ectodysplasin A1 *(EDA1)*
ED-2	Autosomal recessive	Ectodysplasin A anhidrotic receptor *(EDAR)*
		EDA-A1 receptor death domain *(EDARADD)*
		WNT10A
ED-3	Autosomal dominant	*EDAR*
		EDARADD
ED-anhidrotic with immune deficiency	X-linked recessive Autosomal dominant	*IκK-γ (NEMO)* *NFκB-IA*

In HED, affected patients are unable to sweat and may experience episodes of high fever in warm environments, which may be mistakenly considered to be fevers of unknown origin. This error is particularly common in infancy, when the facial changes are not easily appreciated. Diagnosis at this time may be made using the starch-iodine test or palmar or scalp biopsy. Scalp biopsy is the most sensitive and is 100% specific. It shows a complete lack of eccrine structures. Aside from patients with *WNT10A* mutations—who do not have facial dysmorphism—the typical facies are characterized by frontal bossing; malar hypoplasia; a flattened nasal bridge; recessed columella; thick, everted lips; wrinkled, hyperpigmented periorbital skin; and prominent, low-set ears (Fig. 668.1). The skin over the entire body is dry, finely wrinkled, and hypopigmented, often with a prominent venous pattern. Extensive peeling of the skin is a clinical clue to diagnosis in the newborn period. The paucity of sebaceous glands may account for the dry skin. The scalp hair is sparse, fine, and lightly pigmented, and eyebrows and lashes are sparse or absent. Other body hair is also sparse or absent. Sexual hair growth is normal. Anodontia or hypodontia with widely spaced, conical teeth is a consistent feature (see Fig. 668.1).

Otolaryngic and ophthalmologic abnormalities secondary to decreased saliva and tear production are seen. The incidence of atopic diseases in children with HED is high. Gastroesophageal reflux is common and may play a role in failure to thrive, which is seen in 20% of cases. Sexual development is usually normal. Historically, the infant mortality rate has been 30%. Carrier females of X-linked HED may have no or less severe clinical manifestations.

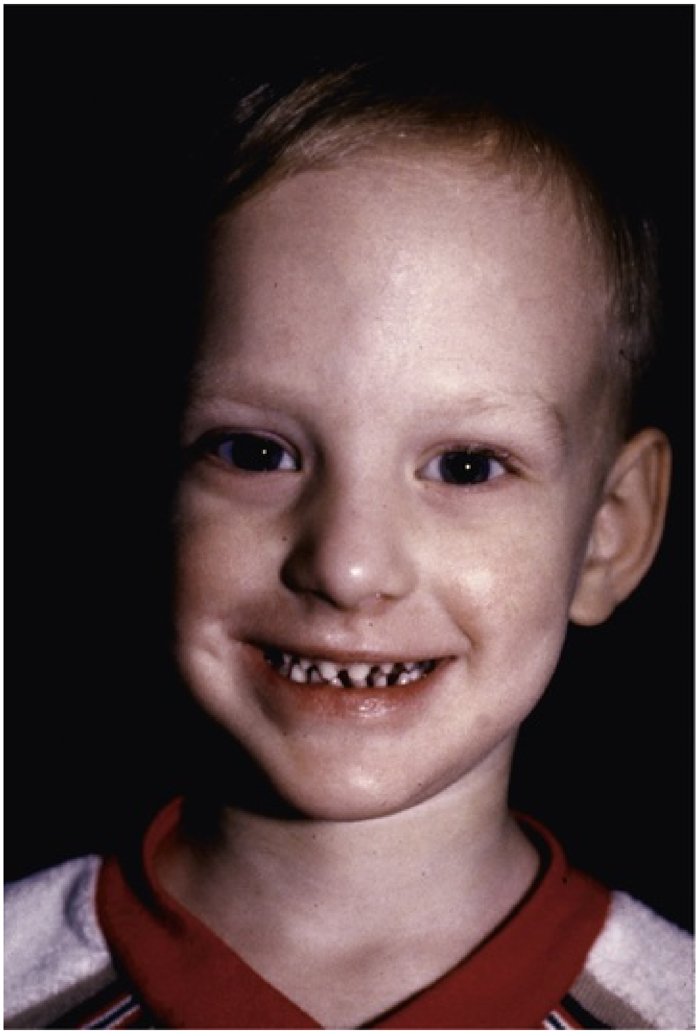

FIG. 668.1 Hypohidrotic ectodermal dysplasia is characterized by pointed ears, fine hair, periorbital hyperpigmentation, midfacial hypoplasia, and pegged teeth. (Courtesy of the Fitzsimons Army Medical Center teaching file.)

Hypohidrotic ED with immune deficiencies causes similar findings in sweating and hair and nail development, in association with a dysgammaglobulinemia. Significant mortality is seen from recurrent infections. A variety of mutations of the genes encoding the tumor necrosis factor α (TNFα)-related signaling pathway proteins—key in signal transduction from ectoderm to mesoderm during development—are the molecular basis for this disorder (see Table 668.2).

Treatment of children with HED includes protecting them from exposure to high ambient temperatures. Early dental evaluation is necessary so that prostheses can be provided for cosmetic reasons and for adequate nutrition. The use of artificial tears prevents damage to the cornea in patients with defective lacrimation. Alopecia may necessitate the wearing of a wig to improve appearance.

Hidrotic Ectodermal Dysplasia (Clouston Syndrome)

The salient features of the autosomal dominant disorder hidrotic ED are dystrophic, hypoplastic, or absent nails; sparse hair; and hyperkeratosis of the palms and soles (Table 668.3). Conjunctivitis and blepharitis are common. The dentition and sweating are always normal. Absence of eyebrows and eyelashes, clubbing of the fingers, and hyperpigmentation over the knees, elbows, and knuckles have been noted in some affected individuals. Mutations in the *GJB6* gene encoding the gap junction protein connexin 30 are responsible for this disorder. A similar disorder associated with deafness has been described with mutations in the *GJB2* gene encoding the connexin 26 protein. Mutations in *GJB1* have also been implicated.

Table 668.3

Common Ectodermal Dysplasias—Inheritance and Characteristic Clinical Findings

TYPE	INHERITANCE(S)	CHARACTERISTIC CLINICAL FINDINGS
Hypohidrotic ED	XLR, AD, AR	Distinctive facies: prominent forehead, thick lips and flattened nasal bridge. Collodion-like membrane. Eczema. Hypotrichosis of scalp and trunk, light/brittle/slow growing hair Hypodontia, conical teeth Hypohidrosis
Hypohidrotic ED-immune deficiency (EDA-ID)	XLR, AD	Seborrheic dermatitis-like rash, intertrigo Hypotrichosis

		Hypodontia, pointed teeth Hypohidrosis/Anhidrosis Recurrent infections Decreased immunoglobulin levels
Hidrotic ED (Clouston)	AD	Hyperpigmented skin over joints. Palmoplantar keratoderma, conjunctivitis, blepharitis Milky-white nails in early childhood, nail dystrophy, clubbing Sparse, wiry, brittle, pale scalp hair to total alopecia Normal sweating
Witkop tooth and nail syndrome	AD	Usually normal hair, rarely sparse or fine Normal sweating Small primary teeth, hypodontia causing lower lip eversion (“pouting lower lip”) Thin, slow growing hypoplastic nails (toes > fingers), Koilonychia
EEC	AD	Dry skin, aplasia or hypoplasia of skin Normal sweating Coarse lightly pigmented hair, thick eyebrows Hypodontia (reduced number), taurodontia, premature loss of teeth, dental enamel abnormalities Ectrodactyly more common than syndactyly Nail dystrophy, transverse ridging and pitting Corneal erosion, lacrimal duct abnormality, blepharitis, GU defects, cleft lip or palate
AEC (Hay-Wells syndrome) and RHS	AD	Erosive dermatitis, neonatal erythroderma (scalp, hands, etc.), dyspigmentation of skin Coarse, wiry, lightly pigmented hair, patchy alopecia ± Hypohidrosis Hypodontia, conical teeth Nail absence or dystrophy with thickened nails Ectrodactyly more common than syndactyly Lacrimal duct abnormality, hearing loss, cleft lip/palate, ankyloblepharon, reflux
Limb-mammary	AD	Normal hair Hypodontia ± Hypohidrosis Nail dystrophy Ectrodactyly more common than syndactyly Bifid uvula, hypoplastic nipples, joint contracture of hand, lacrimal duct atresia, cleft palate
ADULT	AD	Dry skin, photosensitivity, lentigines Hypodontia, premature loss of teeth Normal sweating Pitting and longitudinal ridging of nails Ectrodactyly and syndactyly No cleft palate or lip Hypoplastic nipples, lacrimal duct atresia,

AD , Autosomal dominant; *ADULT* , acro-dermato-ungal-lacrimal-tooth; *AEC* , Ankyloblepharon-ectodermal dysplasia-clefting; *AR* , autosomal recessive; *ED* , ectodermal dysplasia; *EEC* , ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome; *RHS* , Rapp-Hodgkin syndrome; *XLR* , X-linked recessive.

In addition to the EDs, there are other disorders associated with absent or decreased sweat production (Table 668.4).

Table 668.4

Disorders Associated With Decreased Sweat Production

Cutaneous Lesions

Congenital absence of sweat glands without ectodermal dysplasia
Incontinentia pigmenti
Burns

Multisystem Disorders

Fabry disease
Crisponi syndrome
Chronic graft vs. host disease
Sjögren syndrome

Neurologic Disorders

Spinal cord injury
Guillain-Barré syndrome
Hereditary sensory autonomic neuropathy type I, II, IV
Complex regional pain syndrome
Multiple sclerosis
Multiple system atrophy
Ross syndrome
Shy-Drager syndrome

Medications

Anticholinergic drugs
Opioids
Botulism toxin

Clonidine
Barbiturate overdose
Alpha-2 receptor antagonists

Other

Idiopathic acquired generalized anhidrosis
Hypothyroidism
Conversion disorder
Heat shock
Sympathectomy

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CHAPTER 669

Vascular Disorders

Kari L. Martin

Nearly all vascular lesions of childhood may be divided into vascular malformations and vascular tumors (Table 669.1). Vascular malformations are developmental disorders of blood vessel formation. Malformations do not regress but slowly enlarge. They should be named after the predominant vessel(s) forming the lesion: arterial, capillary, lymph, or venous or combinations of these. Vascular tumors exhibit endothelial cell hyperplasia and proliferation. The International Society for the Study of Vascular Anomalies (ISSVA) continues to update the classification structure for vascular disorders as new disorders are identified and as the biology and genetic causes for established disorders are found. The complete classification, associated syndromes, and causative genetic mutations can be found at www.issva.org .

Table 669.1

International Society for the Study of Vascular Anomalies Classification System

VASCULAR MALFORMATION	VASCULAR TUMOR
Simple	Benign
Capillary malformation (CM)	Infantile hemangioma
Venous malformation (VM)	Congenital hemangioma
Lymphatic malformation (LM)	Rapidly involuting congenital hemangioma (RICH)
Arteriovenous malformation (AVM)	Noninvoluting congenital hemangioma (NICH)
Arteriovenous fistula	Partially involuting congenital hemangioma (PICH)
Combined	Tufted angioma
CVM, CLM, LVM, CLVM,	Pyogenic granuloma
CAVM, CLAVM, others	Locally Aggressive or Borderline
Of Major Vessels	Kaposiform hemangioendothelioma
Associated with other anomalies	Malignant
	Epithelioid hemangioendothelioma
	Angiosarcoma

Modified from the full ISSVA classification documentation found at www.issva.org . This table highlights the most common vascular disorders.

Vascular Malformations

Capillary Malformation (Port-Wine Stain)

Capillary malformations (CMs) are present at birth. These vascular malformations consist of mature dilated dermal capillaries. The lesions are macular, sharply circumscribed, pink to purple, and tremendously varied in size (Fig. 669.1). The head and neck region is the most common site of predilection; most lesions are unilateral. The mucous membranes can be involved. As a child matures into adulthood, the CM may become darker in color and pebbly in consistency; it may occasionally develop elevated areas that bleed spontaneously.

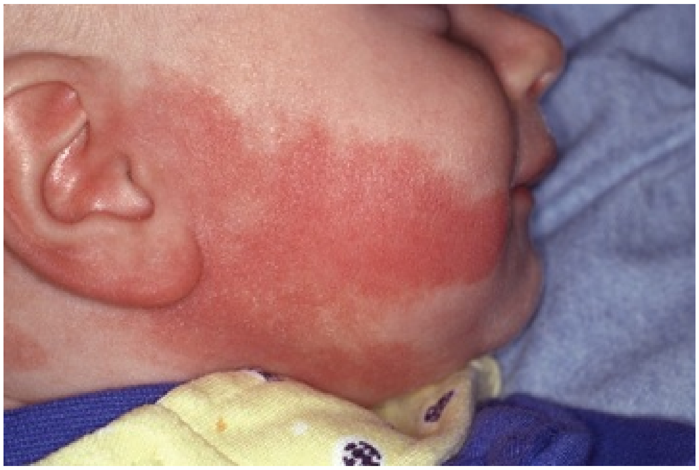

FIG. 669.1 **Capillary malformation. Pink macule on the cheek of an infant.**

True CM should be distinguished from nevus simplex, which, in contrast, is a relatively transient lesion often located in the midline (see Chapter 666). When a CM is lateral and localized to the forehead and upper eyelid, the diagnosis of Sturge-Weber syndrome (glaucoma, leptomeningeal venous angioma, seizures, hemiparesis contralateral to the facial lesion, intracranial calcification) must be considered (see Chapter 614.3). Early screening for glaucoma is important to prevent additional damage to the eye. CMs also occur as a component of Klippel-Trenaunay syndrome and with moderate frequency in other syndromes, including MCAP (megalencephaly, capillary malformation, polymicrogyria), Cobb (spinal arteriovenous malformation [AVM], port-wine stain), CLOVES (congenital lipomatous, overgrowth, vascular malformations, epidermal nevi, skeletal anomalies), Proteus, Beckwith-Wiedemann, and Bonnet-Dechaume-Blanc syndromes. In the absence of associated anomalies, morbidity from these lesions may include a poor self-image, hypertrophy of underlying structures, and traumatic bleeding.

The most effective treatment for CM is with the pulsed-dye laser. This therapy is targeted to hemoglobin within the lesion and avoids thermal injury to the surrounding normal tissue. After such treatment, the texture and pigmentation of the skin are generally normal without scarring. Therapy can begin in infancy, when the surface area of involvement is smaller. There may be advantages to treating within the 1st year of life. Although this approach is quite effective, redarkening of the stain may occur over time, making ongoing treatments useful. Masking cosmetics may also be used.

Venous Malformation

Venous malformations include vein-only malformations and combination malformations. Malformations consisting of veins only range from nodules containing a mass of venules (Fig. 669.2) to diffuse large vein abnormalities that may consist of either a superficial component resembling varicose veins, deeper venous malformations, or both. Most venous malformations are sporadic, although inherited forms exist as well. Inherited forms and up to 40% of sporadic venous malformations are caused by *TIE2* mutations. Treatment is reserved for painful or symptomatic lesions. Surgical excision is best for small or superficial nodular lesions and sclerotherapy or laser ablation is used for larger, diffuse lesions. Localized intravascular coagulopathy can be problematic in these lesions because of the chronic slow flow. This leads to both painful thrombotic episodes and the risk of progression to systemic disseminated intravascular coagulopathy. Pulmonary embolus has been reported in patients with large venous malformations.

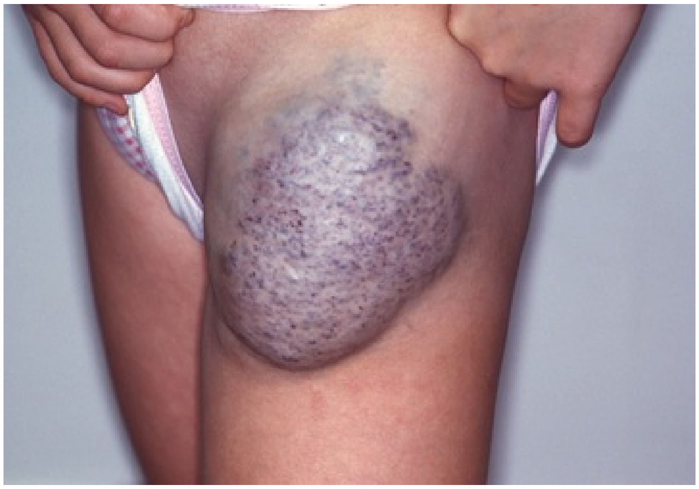

FIG. 669.2 Nodular venous malformation on the leg of an adolescent.

Lymphatic Malformations

See Chapter 516 .

Arteriovenous Malformation

AVMs are direct connections of artery to vein that bypass the capillary bed (Fig. 669.3). AVMs of the skin are very rare. Skin changes are often noted at birth, but they tend to be very subtle presenting as a red-pink patch. Over time the lesions deepen in color and often result in thickening of the skin and surrounding tissue. They are diagnosed from their obvious arterial palpation. Some AVMs are progressive and can lead to significant morbidity and even mortality, so early diagnosis and evaluation by an experienced multidisciplinary team is essential.

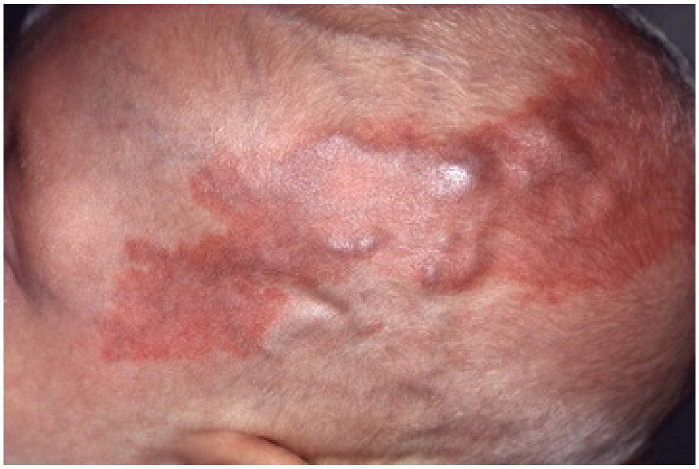

FIG. 669.3 **Arteriovenous malformation in conjunction with a port-wine stain of the scalp of a newborn.**

Klippel-Trenaunay and Parkes-Weber Syndromes

Klippel-Trenaunay syndrome is a term historically used to describe complex, mixed vascular malformation with overgrowth of bone and soft tissue (Fig. 669.4). The anomaly is present at birth and usually involves a lower limb but may involve more than 1 limb, as well as portions of the trunk or face. Enlargement of the soft tissues may be gradual and may involve the entire extremity, a portion of it, or selected digits. The vascular lesion most often is a capillary malformation, generally localized to the hypertrophied area. The deep venous system may be absent or hypoplastic. Venous blebs and/or vesicular lymphatic lesions may be present on the malformation's surface. Thick-walled venous varicosities typically become apparent ipsilateral to the vascular malformation after the child begins to ambulate. If there is an associated AVM, the disorder is called **Parkes-Weber syndrome** .

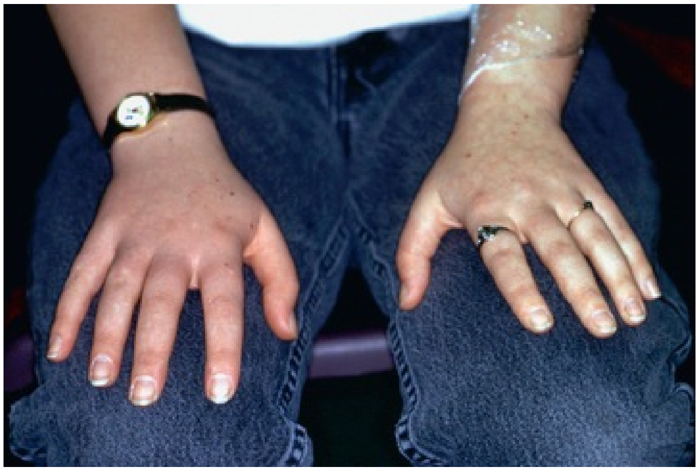

FIG. 669.4 Overgrowth of the right arm and hand in and adolescent with Klippel-Trenaunay syndrome.

These disorders can be confused with Maffucci syndrome or, if the surface vascular lesion is minimal, with Milroy disease. Pain, limb swelling, and cellulitis may occur. Thrombophlebitis, dislocations of joints, hematuria secondary to angiomatous involvement of the urinary tract, rectal bleeding from lesions of the gastrointestinal tract, pulmonary lesions, and malformations of the lymphatic vessels are infrequent complications. MRI may delineate the extent of the anomaly, but surgical correction or palliation is often difficult. Sclerotherapy or endovenous laser ablation may be of benefit when a venous component is the dominant vessel in the malformation. The indications for radiologic studies of viscera and bones are best determined by clinical evaluation. Supportive care includes compression bandages for varicosities; surgical treatment may help carefully selected patients. Leg-length differences should be treated with orthotic devices to prevent the development of spinal deformities. Corrective bone surgery may eventually be needed to treat significant leg-length discrepancy.

Angiokeratoma Circumscriptum

Several forms of angiokeratoma have been described. Angiokeratomas are characterized by ectasia of superficial lymphatic vessels and capillaries with hyperkeratosis of the overlying epidermis. Angiokeratoma circumscriptum is a rare disorder consisting of a solitary lesion or multiple lesions that manifest as a plaque or plaques of blue-red crusted papules or nodules. The limbs are the sites of predilection. **If therapy is desired, surgical excision is the treatment of choice.**

Cutis Marmorata Telangiectatica Congenita

Cutis marmorata telangiectatica congenita, a benign vascular anomaly apparent at birth, is composed of dilated superficial capillaries and veins. Involved areas of skin have a reticulated red or purple hue that resembles physiologic cutis marmorata but is more pronounced and relatively unvarying (Fig. 669.5). The lesions may be restricted to a single limb and a portion of the trunk or may be more widespread. The lesions become more pronounced during changes in environmental temperature, physical activity, or crying. In some cases, the underlying subcutaneous tissue is atrophic, and ulceration may occur within the reticulated bands. Rarely, defective growth of bone and other congenital abnormalities may be present. No specific therapy is indicated. Mild vascular-only cases may show gradual improvement. Cutis marmorata telangiectatica congenita may be associated with CM, Adams-Oliver syndrome, patent ductus arteriosus, and a variety of other anomalies. It must be differentiated from reticulate CM and physiologic cutis marmorata.

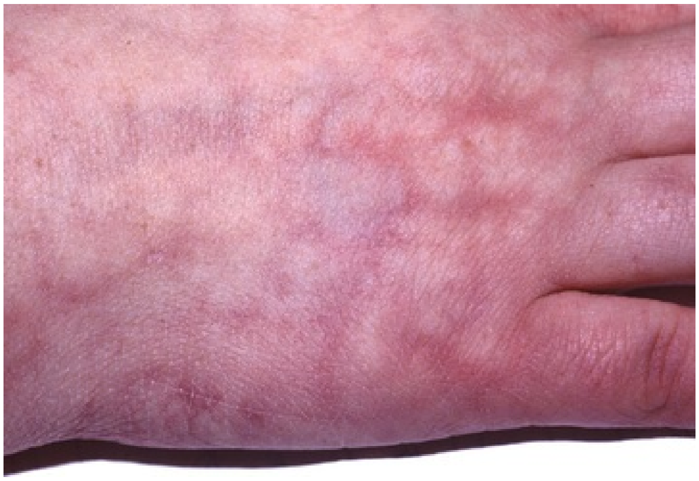

FIG. 669.5 **Mottled pattern of cutis marmorata telangiectatica congenita on the right hand.**

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus is a rare syndrome consisting of numerous venous malformations of the skin, mucous membranes, and gastrointestinal tract. Typical lesions are blue-purple and rubbery in consistency; they vary in size from a few millimeters to a few centimeters in diameter. They are sometimes painful or tender. The nodules occasionally are present at birth but usually are progressive during childhood. New lesions may continue to develop throughout life. Large disfiguring and irregular blue marks may also occur. The lesions, which can rarely be located in the liver, spleen, and central nervous system in addition to the skin and gastrointestinal tract, do not involute spontaneously. Recurrent gastrointestinal hemorrhage due to lesions in the gastrointestinal tract may lead to severe anemia. Palliation can be achieved by excision of involved bowel.

Phakomatosis Pigmentovascularis

Phakomatosis pigmentovascularis is a rare disorder characterized by the association of a capillary malformation and melanocytic lesions. Typically, the capillary malformation is extensive, and associated pigmentary lesions may include dermal melanocytosis (mongolian spots), café-au-lait macules, or a nevus spilus (speckled nevus). Nonpigmented skin lesions that may occur in this setting include nevus anemicus and epidermal nevi. Systemic anomalies are seen in rare cases.

Nevus Anemicus

Although present at birth, nevus anemicus may not be detectable until early childhood. The nevus consists of solitary or numerous, sharply delineated pale macules or patches that are most often on the trunk but may also occur on the neck or limbs. These nevi may simulate plaques of vitiligo, leukoderma, or nevoid pigmentary defects, but they can be readily distinguished because of their response to firm stroking. Stroking evokes an erythematous line and flare in normal surrounding skin, but the skin of a nevus anemicus does not redden. They can also be diagnosed by diascopy, in which pressure of the skin with a glass slide will obscure the borders of a nevus anemicus. Although the cutaneous vasculature appears normal histologically, the blood vessels within the nevus do not respond to injection of vasodilators. It has been postulated that the persistent pallor may represent a sustained localized adrenergic vasoconstriction.

Vascular Tumors

Vascular tumors include infantile hemangiomas (IHs), tufted angiomas, kaposiform hemangioendotheliomas, rapidly involuting congenital hemangiomas, and noninvoluting congenital hemangiomas, as well as additional more rare entities.

Infantile Hemangioma

IHs are proliferative, benign vascular tumors of vascular endothelium that may be present at birth or, more commonly, may become apparent in the 1st or 2nd week of life, predictably enlarge, and then spontaneously involute. IHs are the most common tumor of infancy, occurring in 5% of newborns. Risk factors include prematurity, low birthweight, female sex, and white race. IHs should be classified as superficial, deep, or mixed (Fig. 669.6). The terms *strawberry* and *cavernous* should not be used to describe hemangiomas. The immunohistochemical marker GLUT-1 is specifically expressed in an IH, which helps distinguish it histologically from other vascular anomalies. Superficial IHs are bright red, protuberant, compressible, sharply demarcated lesions that may occur on any area of the body (Fig. 669.7 , see also Fig. 669.6). Although sometimes present at birth, they more often appear in the 1st or 2nd month of life and are heralded by an erythematous or blue mark or an area of pallor, which subsequently develops a fine telangiectatic pattern before the growth phase (see Fig. 669.7). The presenting sign may occasionally be an ulceration of the perineum or lip. Favored sites are the face, scalp, back, and anterior chest; lesions may be solitary or multiple. Patterns of facial involvement include frontotemporal, maxillary, mandibular, and frontonasal regions. IHs that are more deeply situated are more diffuse and are less defined than superficial IHs. The lesions are cystic, firm, or compressible, and the overlying skin may appear normal in color or may have a bluish hue (Fig. 669.8).

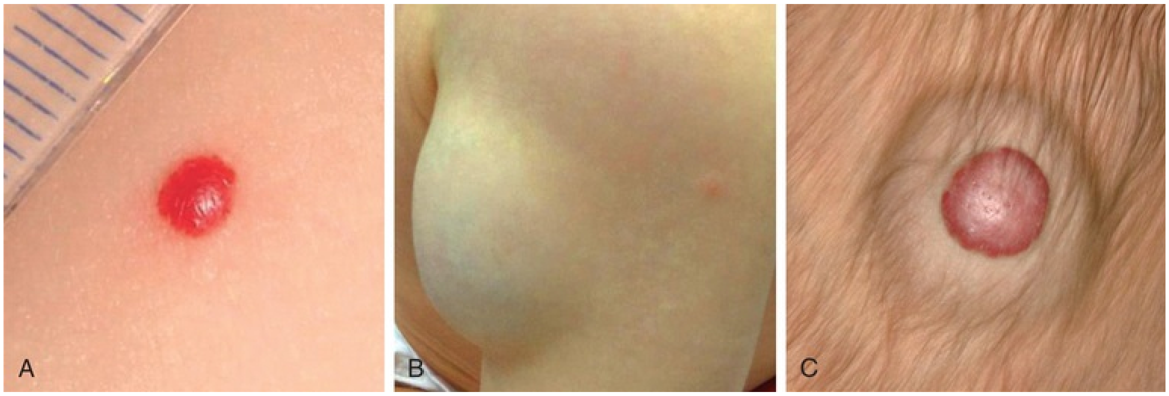

FIG. 669.6 Types of infantile hemangiomas according to anatomical location. A, *Bright red* , intracutaneous hemangioma. B, *Bluish* , deep hemangioma. C, Mixed type. (From Léaute-Labréze C, Harper JI, Hieger PH: Infantile haemangioma. *Lancet* 390:85–94, 2017, Fig. 4, p. 88.)

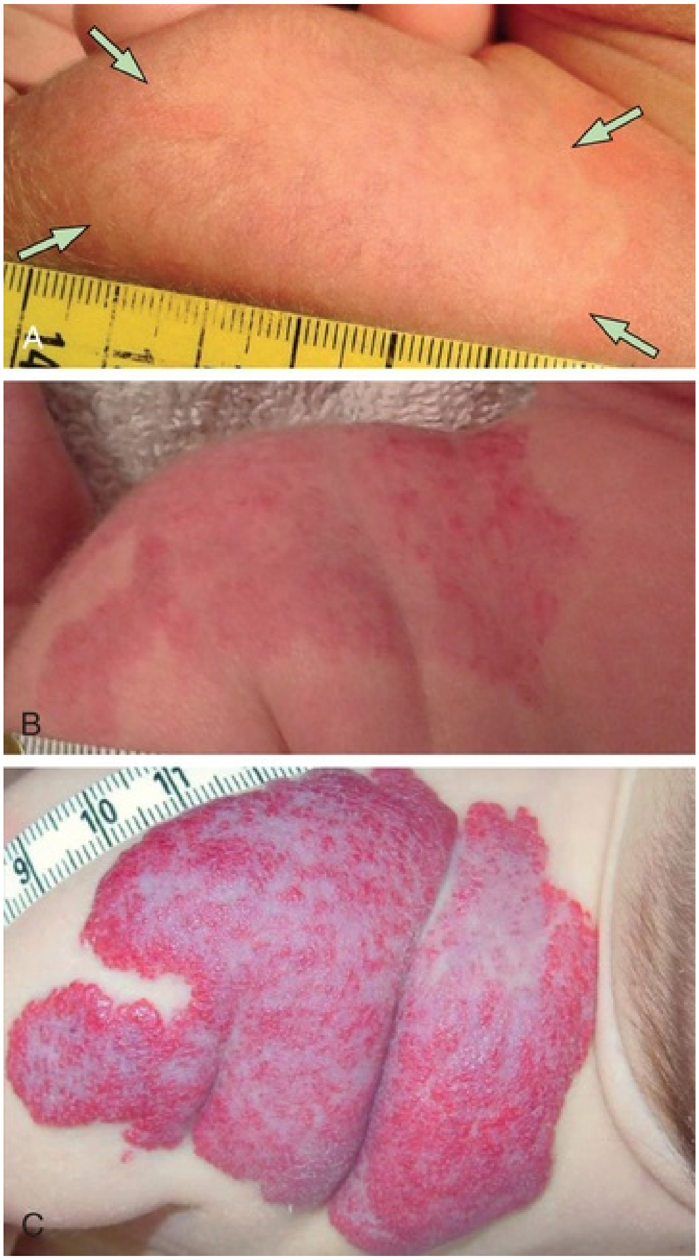

FIG. 669.7 Precursor lesions of infantile hemangioma. Figure shows a sharply demarcated, so-called anemic spot on the left shoulder. A, Day 3. B, Day 21. C, Day 90. (From Léaute-Labréze C, Harper JI, Hieger PH: Infantile haemangioma. *Lancet* 390:85–94, 2017, Fig. 3, p. 87.)

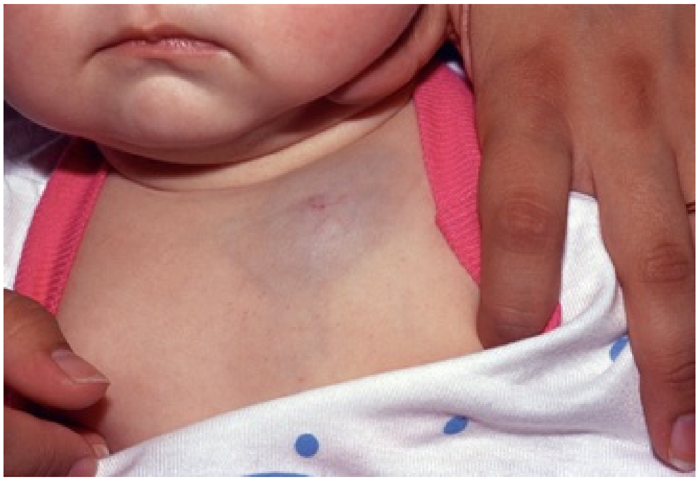

FIG. 669.8 Deep hemangioma of the chest.

Most IHs are mixed, having both superficial and deep components. IHs undergo a phase of rapid expansion, followed by a stationary period and finally by spontaneous involution (Fig. 669.9). Regression may be anticipated when the lesion develops pale gray areas centrally. The course of a particular lesion is unpredictable, but approximately 60% of these lesions reach maximal involution by 5 yr of age, and 90–95% by 9 yr. Spontaneous involution cannot be correlated with size or site of involvement, but lip lesions seem to persist most often. Complications include impairment of a vital function, ulceration, secondary infection, and permanent disfigurement. The location of a lesion may interfere with a vital function (e.g., on eyelid interfering with vision, on urethra with urination, on airway with respiration). IHs in a “beard” distribution may be associated with upper airway or subglottic involvement. Stridor should suggest a tracheobronchial lesion. Large visceral IHs may be complicated by coexistent hypothyroidism because of type 3 iodothyronine deiodinase, and symptoms may be difficult to detect in this age group. Table 669.2 lists other concerning features.

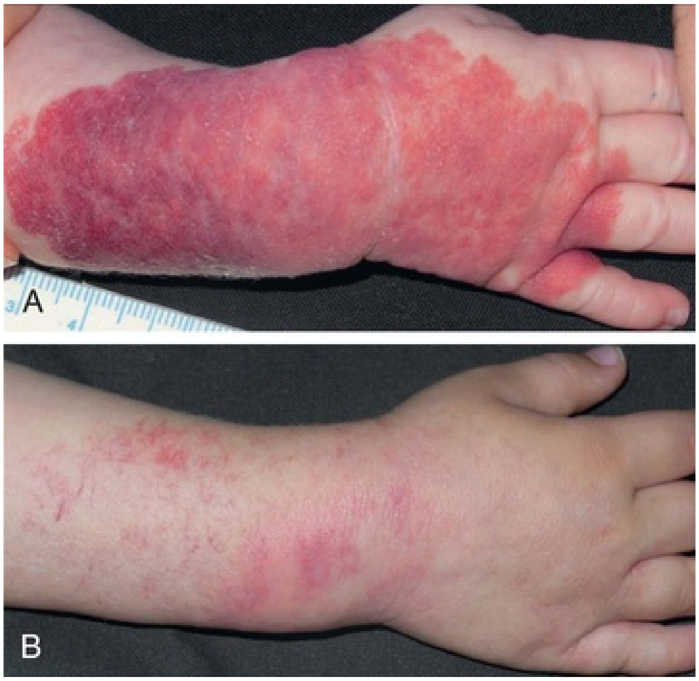

FIG. 669.9 **Spontaneous regression of infantile hemangioma. A, Hemangioma on right lower arm, age 14 wk. B, Residual telangiectasia at age 23 mo. (From Léaute-Labréze C, Harper JI, Hieger PH: Infantile haemangioma. *Lancet* 390:85–94, 2017, Fig. 5, p. 88.)**

Table 669.2

Clinical "Red Flags" Associated With Hemangiomas

CLINICAL FINDING	RECOMMENDED EVALUATION
Facial hemangioma involving significant area of face	Evaluate for PHACES (posterior fossa abnormalities, hemangioma, and arterial, cardiac, eye, and sternal abnormalities): MRI for orbital hemangioma ± posterior fossa malformation
	Cardiac, ophthalmologic evaluation
	Evaluate for midline abnormality: supraumbilical raphe, sternal atresia, cleft palate, thyroid abnormality
Cutaneous hemangiomas in beard distribution	Evaluate for airway hemangioma, especially if manifesting with stridor
Periocular hemangioma	MRI of orbit Ophthalmologic evaluation
Paraspinal midline vascular lesion	Ultrasonography or MRI to evaluate for occult spinal dysraphism
Multifocal infantile hemangiomas	Evaluate for parenchymal hemangiomas, especially hepatic/central nervous system Guaiac stool test, liver ultrasound
Large hemangioma, especially hepatic	Ultrasonography with Doppler flow study
	MRI
	Thyroid function studies
Thrill and/or bruit associated with hemangioma	Consider cardiac evaluation and echocardiography to rule out diastolic reversal of flow in aorta

	MRI to evaluate extent and flow characteristics
LUMBAR syndrome	MRI of spine, kidneys

LUMBAR , Lower body infantile hemangiomas and other skin defects, urogenital anomalies and ulceration, myelopathy, boney deformities, anorectal malformations and arterial anomalies, renal anomalies.

From Blei F: Vascular anomalies: from bedside to bench and back again. *Curr Probl Pediatr Adolesc Health* 32:67–102, 2002.

In the usual patient with an IH who has no serious complications or extensive growth resulting in tissue destruction and severe disfigurement, treatment consists of expectant observation. Because almost all lesions regress spontaneously, therapy is rarely indicated. Parents require repeated reassurance and support. After spontaneous involution, many patients are left with small cosmetic defects, such as telangiectasia, hypopigmentation, fibrofatty deposits, and scars if the lesion has ulcerated. Residual telangiectasias may be treated with pulsed-dye laser therapy. Other defects can be treated or minimized by judicious surgical repair if desired.

In the rare case in which intervention is required, topical timolol solution (1 drop of 0.5% gel-forming solution applied twice each day) is effective, especially in small, superficial, nonulcerating and nonmucosal IH. Topical timolol treatment is a very safe alternative to observation alone for a superficial IH. Timolol solution may also be used with caution in the treatment of an ulcerated IH, with or without occlusion.

In a disfiguring, life- or vision-threatening, or ulcerated IH that is not responding to other treatment, oral propranolol is the first-line treatment. IHs typically respond with growth arrest and often early signs of involution within a couple weeks of treatment initiation. Dosing varies ranging from 1 to 3 mg/kg/day, though best outcomes occur at 3 mg/kg/d with no increase in side effects. Some recommend inpatient initiation of propranolol for infants younger than 8 wk gestational age or those with comorbid conditions. The dose is initiated at 1 mg/kg/day divided into 3 doses with heart rate and blood pressure monitoring at 1 and 2 hr after each dose. If that dose is tolerated, the dose is increased to 2 mg/kg/day divided into 3 doses. The outpatient initiation assumes good social support and access to the hospital. The initial dose and monitoring is similar to the inpatient plan; if the dose is tolerated for 3-7 days, the dose is increased to 1.5 mg/kg/day. If the latter dose is tolerated after 3-7 days, the dose is increased to 2 mg/kg/day. In all situations, propranolol must be given a minimum of 6 hr after the last dose. Risks of propranolol treatment include hypoglycemia, bradycardia, hypotension, gastroesophageal reflux disease or worsening of existing disease, hyperkalemia, and bronchospasm/wheezing. Nonetheless, reports of side effects of propranolol used for IH treatment are rare. Increased propranolol levels occur with inhibitors of CYP2D6 (cimetidine, amiodarone, fluoxetine, quinidine, ritonavir) and CPY1A2 (cimetidine, ciprofloxacin, isoniazid, ritonavir, theophylline); decreased blood levels occur with inducers of hepatic drug metabolism (rifampin, phenytoin, phenobarbital).

In patients unable to tolerate propranolol, or if the IH has not responded after a couple of weeks of treatment, systemic oral corticosteroids may be used. Termination of growth and sometimes regression may be evident after 2-4 wk of therapy. When a response is obtained, the dose should be decreased gradually, though most patients will require treatment until about 1 yr of age.

Intralesional corticosteroid injection in the hands of an experienced physician can also induce rapid involution of a localized IH, but has risks of ulceration, tissue atrophy, and blindness if used near the orbit. Vincristine is used by some oncologists to treat significant IH. Interferon-α therapy may also be effective, but spastic diplegia is seen in 10% of cases. Use of these therapies has become less necessary since the introduction of propranolol.

In patients with large segmental IH of the face, **PHACES** syndrome should be considered (Fig. 669.10 , Table 669.3). PHACES stands for **p** osterior fossa brain defects such as Dandy-Walker malformation or cerebellar hypoplasia, large segmental facial infantile **h** emangioma, **a** rterial cerebrovascular abnormalities such as aneurysms and stroke, **c** oarctation of the aorta, **e** ye abnormalities. **S** ternal raphe defects such as pits, scars, or **s** upraumbilical raphe are infrequently observed. Evaluation of children at risk for PHACES is important both to detect any underlying abnormalities and also before starting systemic therapy, which may be indicated given the size and location of the IH typically associated with this syndrome. PHACES children with cervical and intracranial arterial abnormalities are at increased risk of cerebrovascular accidents and specialized care by an experienced multidisciplinary team is essential.

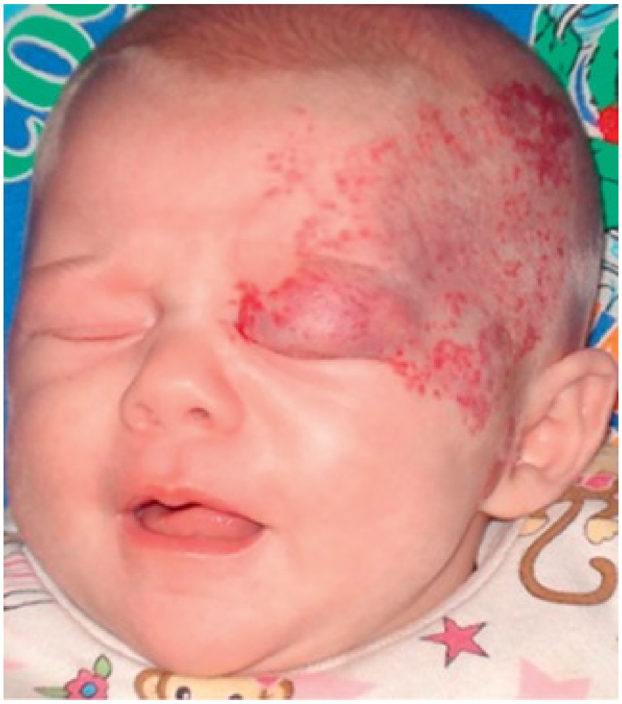

FIG. 669.10 Large segmental infantile hemangioma of the face in a 2-mo-old girl with definite PHACE. (From Garzon MC, Epstein LG, Heyer GL, et al: PHACE syndrome: consensus-derived diagnosis and care recommendations. *J Pediatr* 178:24–33, 2016, Fig 1, p. 25.)

Table 669.3

Diagnostic Criteria—Revised

ORGAN SYSTEMS	MAJOR CRITERIA	MINOR CRITERIA
Arterial anomalies	Anomaly of major cerebral or cervical arteries* Dysplasia[†] of the large cerebral arteries Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate-severe hypoplasia of the large cerebral and cervical arteries Aberrant origin or course of the large cerebral or cervical arteries except common arch variants such as bovine arch. Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic, and/or trigeminal arteries)	Aneurysm of any of the cerebral arteries
Structural brain	Posterior fossa brain anomalies Dandy-Walker complex Other hypoplasia/dysplasia of the mid and/or hind brain	Midline brain anomalies Malformation of cortical development

Cardiovascular	Aortic arch anomalies Coarctation of the aorta Dysplasia* Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch/double aortic arch Systemic venous anomalies
Ocular	Posterior segment abnormalities Persistent hyperplastic primary vitreous Persistent fetal vasculature Retinal vascular anomalies Morning glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma	Anterior segment abnormalities Microphthalmia Sclerocornea Coloboma Cataracts
Ventral/midline	Anomaly of the midline chest and abdomen • Sternal defect • Sternal pit • Sternal cleft • Supraumbilical raphe	Ectopic thyroid hypopituitarism Midline sternal papule/hamartoma
Definite PHACE		
Hemangioma >5 cm in diameter of the head including scalp PLUS 1 major criteria or 2 minor criteria	Hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 2 major criteria	
Possible PHACE		
Hemangioma >5 cm in diameter of the head including scalp PLUS 1 minor criteria	Hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 1 major or 2 minor	No hemangioma PLUS 2 major criteria

[*] Internal carotid artery middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.

[†] Includes kinking, looping, tortuosity, and/or dolichoectasia.

From Garzon MC, Epstein LG, Heyer GL, et al: PHACE syndrome: consensus-derived diagnosis and care recommendations. *J Pediatr* 178:24–33, 2016, Table II, p. 27.

Multifocal Infantile Hemangioma

Diffuse neonatal hemangiomatosis (or benign neonatal hemangiomatosis) is a historical term to describe a condition in which numerous or multifocal vascular lesions are widely distributed (Fig. 669.11). In the past, several distinct diagnoses have been lumped together under this clinical phenotype with mortality cited as high as 60–80%. Upon further analysis, this group of disorders has been found to comprise several distinct entities which are important to distinguish from one another given their varying prognoses and management strategies. Therefore the term *multifocal IH* is more accurate and leads to correct treatments and prognosis for these patients with more than 1 cutaneous (and/or visceral) IH.

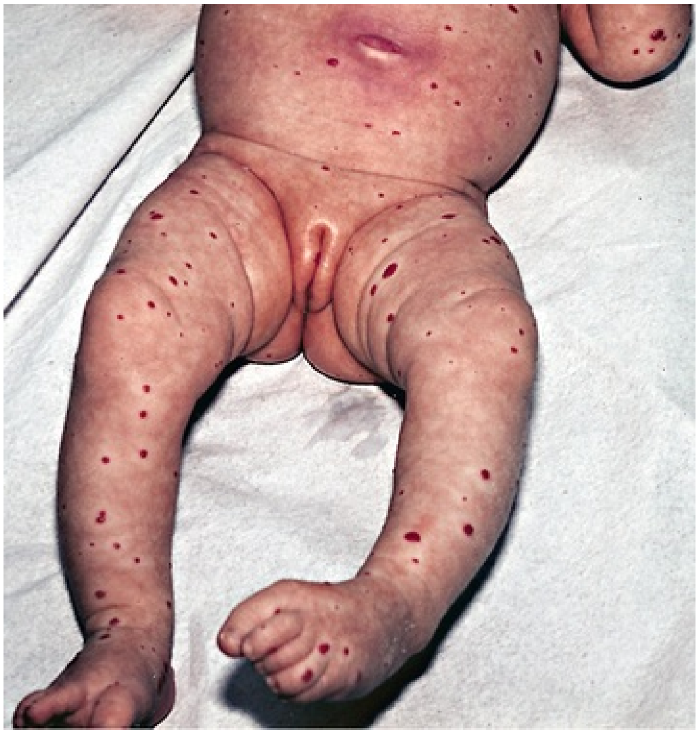

FIG. 669.11 Disseminated cutaneous (and liver) neonatal hemangiomatosis. (From Eichenfield LF, Frieden IJ, Esterly NB: *Textbook of neonatal dermatology,* ed 2, Philadelphia, 2008, WB Saunders, p. 359.)

Multifocal IHs may occur in the skin as well as visceral organs, but remain GLUT-1–positive when biopsied, have a relatively good prognosis with low morbidity, and respond to systemic propranolol just as solitary cutaneous IH. *Patients with more than 5 cutaneous IH should undergo an abdominal physical exam and possibly liver ultrasound to detect liver IH, which can grow quite large.*

Multifocal lymphangioendotheliomatosis (also known as cutaneovisceral angiomatosis) also presents with many vascular tumors in the skin and visceral organs, but is GLUT-1–negative and complicated by severe thrombocytopenia and gastrointestinal bleeding with high mortality. Therefore accurate diagnosis in patients who present with multifocal vascular tumors is critical so early, appropriate management may be initiated.

Congenital Hemangioma

Congenital hemangiomas are benign vascular tumors that are present typically at birth. They are most often red or blue hued with telangiectasia and may have a ring of pallor. They do not undergo further growth after delivery as IHs do, but instead either stay stable **(non-involuting congenital hemangiomas—NICH)** or decrease rapidly in size, leaving fibrofatty residual tissue behind **(rapidly involuting congenital hemangiomas—RICH)** . There are also cases where congenital hemangiomas will decrease in size to a certain point and then remain stable instead of resolving completely; these are known as **partially involuting congenital hemangiomas (PICH)** . They are distinguishable from IH because of their clinical course as well as negative GLUT-1 markers on histopathology.

Kaposiform Hemangioendothelioma

Kaposiform hemangioendothelioma (KHE) is a rare and potentially life-threatening vascular tumor. Initial cases described IHs with purpura and coagulopathy, but these are now known to have been KHE. KHE classically presents as a red to purple firm plaque on the lateral neck, axilla, trunk, or extremities. Visceral tumors occur as well. Lesions may occasionally get smaller over time but rarely resolve completely. Tufted angioma, once thought to be a separate tumor on the same clinical spectrum as KHE, is considered under the umbrella term of KHE (Fig. 669.12). The main complication of these tumors is the development of **Kasabach-Merritt phenomenon (KMP)** , which may be fatal; therefore early diagnosis and treatment is important. Retroperitoneal or intrathoracic lesions in the absence of cutaneous lesions are uncommon but are often associated with KMP.

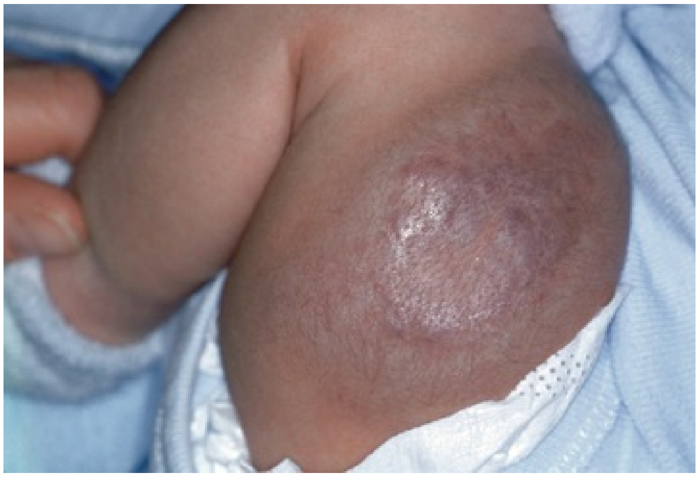

FIG. 669.12 Nodular tufted angioma on the left thigh.

Kasabach-Merritt Phenomenon

KMP is a life-threatening combination of a rapidly enlarging KHE, thrombocytopenia, microangiopathic hemolytic anemia, and an acute or chronic consumption coagulopathy. The clinical manifestations are usually evident during early infancy. The vascular lesion is usually cutaneous and is only rarely located in viscera. The associated thrombocytopenia may lead to precipitous hemorrhage accompanied by ecchymoses, petechiae, and a rapid increase in the size of the vascular lesion. Severe anemia from hemorrhage or microangiopathic hemolysis may ensue. The platelet count is depressed, but the bone marrow contains increased numbers of normal or immature megakaryocytes. The thrombocytopenia has been attributed to sequestration or increased destruction of platelets within the lesion. Hypofibrinogenemia and decreased levels of consumable clotting factors are relatively common (see Chapter 511.06).

Treatment includes surgical excision of small lesions, although this is often difficult because of coagulopathy. Additional pharmacologic treatments include systemic steroids with or without vincristine as first-line therapy in most cases. Antiplatelet, antifibrinolytic, and other chemotherapeutic agents have been used with mixed results. Ongoing studies of sirolimus use in KHE patients are underway; initial case reports have been promising. The mortality rate overall once patients have KMP is significant.

Pyogenic Granuloma (Lobular Capillary Hemangioma)

A pyogenic granuloma (PG) is a small red, glistening, sessile, or pedunculated papule that often has a discernible epithelial collarette (Fig. 669.13). The surface may be weeping and crusted or completely epithelialized. PGs initially grow rapidly, may ulcerate, and bleed easily when traumatized because they consist of exuberant granulation tissue. They are relatively common in children, particularly on the face, arms, and hands. Such a lesion located on a finger or hand may appear as a subcutaneous nodule. PGs may arise at sites of injury, but a history of trauma often cannot be elicited.

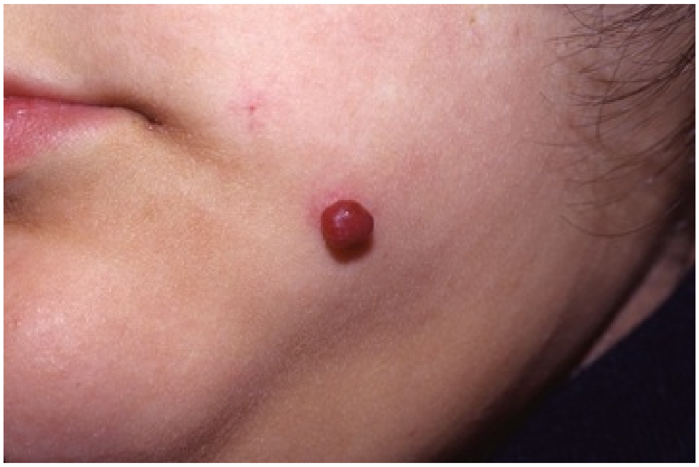

FIG. 669.13 **Pyogenic granuloma on the left cheek.**

PGs are benign but a nuisance because they bleed easily with trauma and may recur if incompletely removed. Numerous satellite papules have developed after surgical excision of PGs from the back, particularly in the interscapular region. Small lesions may regress after cauterization with silver nitrate; larger lesions require excision and electrodesiccation of the base of the granuloma. Small (<5 mm) lesions may be treated successfully with pulsed-dye laser therapy.

Angiokeratoma of Mibelli

Angiokeratoma of Mibelli is characterized by 1-8 mm red, purple, or black scaly, verrucous, occasionally crusted papules and nodules that appear on the dorsum of the fingers and toes and on the knees and the elbows. Less commonly, palms, soles, and ears may be affected. In many patients, onset has followed frostbite or chilblains. These nodules bleed freely after injury and may involute in response to trauma. **They may be effectively eradicated by cryotherapy, electrofulguration, excision, or laser ablation.**

Spider Angioma

A vascular spider (nevus araneus) consists of a central feeder artery with many dilated radiating vessels and a surrounding erythematous flush, varying from a few millimeters to several centimeters in diameter (Fig. 669.14). Pressure over the central vessel causes blanching; pulsations visible in larger nevi are evidence for the arterial source of the lesion. Spider angiomas are associated with conditions in which there are increased levels of circulating estrogens, such as cirrhosis and pregnancy, but they also occur in up to 15% of normal preschool-age children and 45% of school-age children. Sites of predilection in children are the dorsum of the hand, forearm, nose, infraocular region, lips, and ears. Lesions often regress spontaneously after puberty. If removal is desired, pulsed dye laser therapy is the mode of choice; resolution is achieved in 90% of cases with a single treatment.

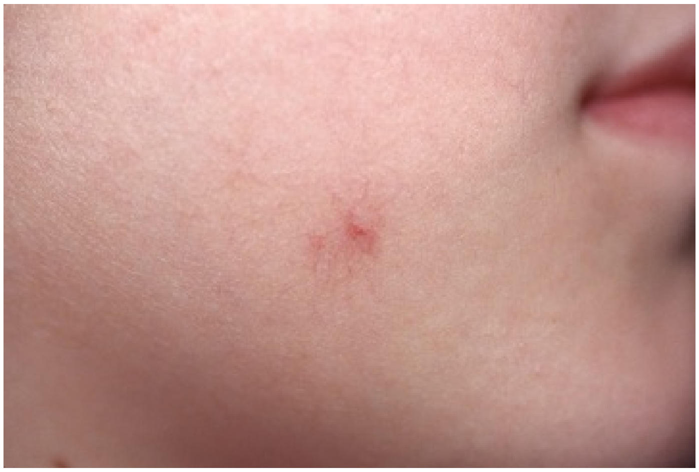

FIG. 669.14 **Spider telangiectasia with visible central arteriole component.**

Maffucci Syndrome

The association of spindle cell hemangiomas with nodular enchondromas in the metaphyseal or diaphyseal cartilaginous portion of long bones is known as Maffucci syndrome. Maffucci syndrome is caused by somatic mosaic mutations in the *IDH1* and *IDH2* genes. Vascular lesions are typically soft, compressible, asymptomatic blue to purple subcutaneous masses that grow in proportion to a child's growth and stabilize by adulthood. Mucous membranes or viscera may also be involved. Onset occurs during childhood. Bone lesions may produce limb deformities and pathologic fractures. Malignant transformation of enchondromas (chondrosarcoma, angiosarcoma) or primary malignancies (ovarian, fibrosarcoma, glioma, pancreatic) may be a complication (see Chapter 528).

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Hereditary hemorrhagic telangiectasia (HHT), which is inherited as an autosomal dominant trait, occurs in 2 types. The gene in **HHT-1** encodes endoglin (*ENG*), a membrane glycoprotein on endothelial cells that binds transforming growth factor-β. **HHT-2** is caused by mutations in the *ACVRL1* gene (activin A receptor type 2-like kinase 1) and is associated with increased risk for hepatic involvement and pulmonary hypertension. Affected children may experience recurrent epistaxis before detection of the characteristic skin and mucous membrane lesions. The mucocutaneous lesions, which usually develop at puberty, are 1-4 mm, sharply demarcated red to purple macules, papules, or spider-like projections, each composed of a tightly woven mat of tortuous telangiectatic vessels (Fig. 669.15). The nasal mucosa, lips, and tongue are usually involved; less commonly, cutaneous lesions occur on the face, ears, palms, and nail beds. Vascular ectasias may also arise in the conjunctivae, larynx, pharynx, gastrointestinal tract, bladder, vagina, bronchi, brain, and liver.

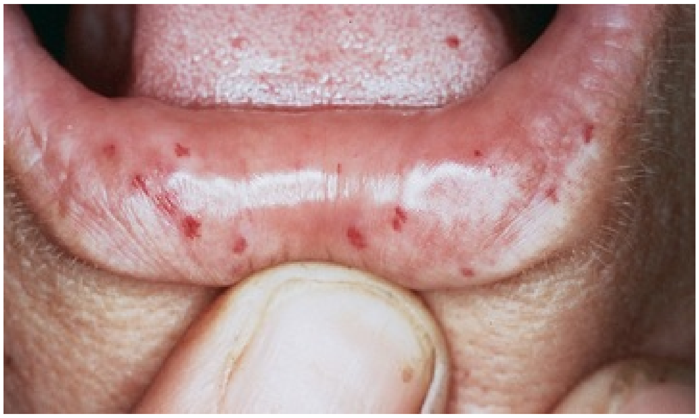

FIG. 669.15 Hereditary hemorrhagic telangiectasia. Telangiectases are found on the lips, oral mucosa, nasal mucosa, skin, and conjunctiva. Epistaxis is the most common manifestation of the disease. Blood transfusions may be required. (From Habif TP: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 4, Philadelphia, 2004, Mosby, Fig. 23.22, p. 831.)

Massive hemorrhage is the most serious complication of HHT and may result in severe anemia. Bleeding may occur from the nose, mouth, gastrointestinal tract, genitourinary tract, or lungs; epistaxis is often the only complaint occurring in 80% of patients. Approximately 15–20% of patients with AVMs in the lungs present with stroke due to embolic abscesses (Fig. 669.16). Persons with HHT have normal levels of clotting factors and an intact clotting mechanism. In the absence of serious complications, the life span of a person with HHT is normal. Local lesions may be ablated temporarily with chemical cautery or electrocoagulation. More drastic surgical measures may be required for lesions in critical sites, such as the lung or gastrointestinal tract. Bevacizumab, an antivascular endothelial growth factor agent, has been effective in treating affected patients with HHT, who have high cardiac output secondary to hepatic AVMs.

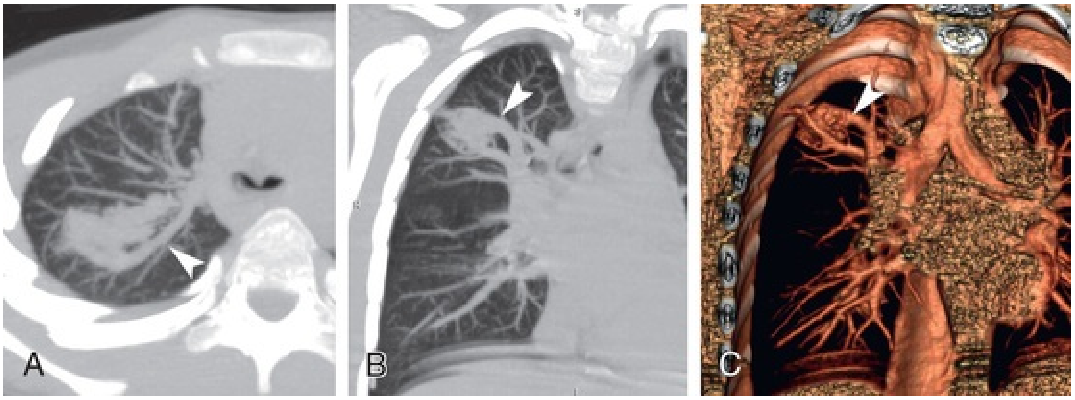

FIG. 669.16 **Chest multislice spiral CT in a patient showing a large pulmonary arteriovenous malformation in the posterior segment of right upper lobe *(arrowhead).* A, Axial maximum intensity projection image. B, Coronal maximum intensity projection image. C, Three-dimensional volume rendering. (From Giordano P, Lenato GM, Suppressa P, et al: Hereditary hemorrhagic telangiectasia: arteriovenous malformations in children. *J Pediatr* 163:179–186, 2013, Fig. 1, p. 182.)**

Ataxia-Telangiectasia

See Chapter 615.1 .

Ataxia-telangiectasia is transmitted as an autosomal recessive trait because of a mutation in the *ATM* gene. The characteristic telangiectasias develop at approximately 3 yr of age, first on the bulbar conjunctivae and later on the nasal bridge, malar areas, external ears, hard palate, upper anterior chest, and antecubital and popliteal fossae. Additional cutaneous stigmata include café-au-lait spots, premature graying of the hair, and sclerodermatous changes. Progressive cerebellar ataxia, neurologic deterioration, sinopulmonary infections, and malignancies are also seen.

Angiokeratoma Corporis Diffusum (Fabry Disease)

See Chapter 104.4 .

An inborn error of glycolipid metabolism (α-galactosidase), angiokeratoma corporis diffusum is an X-linked recessive disorder that is fully penetrant in males and is of variable penetrance in carrier females. Angiokeratomas appear before puberty and occur in profusion over the genitalia, hips, buttocks, and thighs and in the umbilical and inguinal regions. They consist of 0.1-3.0 mm red to blue-black papules that may have a hyperkeratotic surface. Telangiectasias are seen in the mucosa and conjunctiva. On light microscopy, these angiokeratomas appear as blood-filled, dilated, endothelium-lined vascular spaces. Granular lipid deposits are demonstrable in dermal macrophages, fibrocytes, and endothelial cells.

Additional clinical manifestations include recurrent episodes of fever and agonizing pain, cyanosis and flushing of the acral limb areas, paresthesias of the hands and feet, corneal opacities detectable on slit-lamp examination, and hypohidrosis. Renal involvement and cardiac involvement are the usual causes of death. The biochemical defect is a deficiency of the lysosomal enzyme α-galactosidase, with accumulation of ceramide trihexoside in tissues, particularly vascular endothelium, and excretion in urine (see Chapter 104.4 for therapy). Similar cutaneous lesions have also been described in another lysosomal enzyme disorder, α-L -fucosidase deficiency, and in sialidosis, a storage disease with neuraminidase deficiency.

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CHAPTER 670

Cutaneous Nevi

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Nevus skin lesions are characterized histopathologically by collections of well-differentiated cell types normally found in the skin. Vascular nevi are described in Chapter 669 . Melanocytic nevi are subdivided into 2 broad categories: those that appear after birth (acquired nevi) and those that are present at birth (congenital nevi).

Acquired Melanocytic Nevus

Melanocytic nevi are benign clusters of melanocytic nevus cells that arise as a result of alteration and proliferation of melanocytes at the epidermal–dermal junction.

Epidemiology

The number of acquired melanocytic nevi increases gradually during childhood and more slowly in early adulthood. The number reaches a plateau in the 3rd or 4th decade and then slowly decreases thereafter. The mean number of melanocytic nevi in an adult varies depending on genetics, skin color, and sun exposure. The greater the number of nevi present, the greater is the risk for development of melanoma, though the majority of melanomas arise de novo. Sun exposure during childhood, particularly intermittent, intense exposure of an individual with light skin, and a propensity to burn and freckle rather than tan are important determinants of the number of melanocytic nevi that develop. Red-haired children, despite their light skin and propensity to freckle and sunburn, have fewer nevi than other children. Increased numbers of nevi are also associated with immunosuppression and administration of chemotherapy.

Clinical Manifestations

Melanocytic nevi have a well-defined life history and are classified as junctional, compound, or dermal in accordance with the location of the nevus cells in the skin. In childhood, >90% of nevi are junctional; melanocyte proliferation occurs at the junction of the epidermis and dermis to form nests of cells. Junctional nevi appear anywhere on the body in various shades of brown; they are relatively small, discrete, flat, and variable in shape. Although some nevi, particularly those on the palms, soles, and genitalia, remain junctional throughout life, most become compound as melanocytes migrate into the papillary dermis to form nests at both the epidermal–dermal junction and within the dermis. If the junctional melanocytes stop proliferating, nests of melanocytes remain only within the dermis, forming an intradermal nevus. With maturation, compound and intradermal nevi may become raised, dome-shaped, verrucous, or pedunculated. Slightly elevated lesions are usually compound. Distinctly elevated lesions are usually intradermal. With age, the dermal melanocytic nests regress and nevi gradually disappear.

Prognosis and Treatment

Acquired pigmented nevi are benign, but a very small percentage undergo malignant transformation. Suspicious changes are indications for excision and histopathologic evaluation. This includes rapid increase in size; unusual colors such as red, black, varying shades of brown, gray, and white; bleeding; textures such as scaling, erosion, ulceration, and induration; and regional lymphadenopathy. Most of these changes are from irritation, infection, or maturation; darkening and gradual increase in size and elevation normally occur during adolescence and should not be cause for concern. Two common benign changes are clonal nevi (fried-egg moles) and eclipse nevi. A **clonal nevus** is light brown with a dark raised center representing a clonal change of a subset of nevus cells within the lesion. **Eclipse nevi** are flat and light brown with dark brown rims. They are seen primarily in the scalp (Fig. 670.1). Consideration should be given to the presence of risk factors for development of melanoma and the patient's parents’ wishes about removal of the nevus. If doubt remains about the benign nature of a nevus, excision is a safe and simple outpatient procedure that may be justified to allay anxiety.

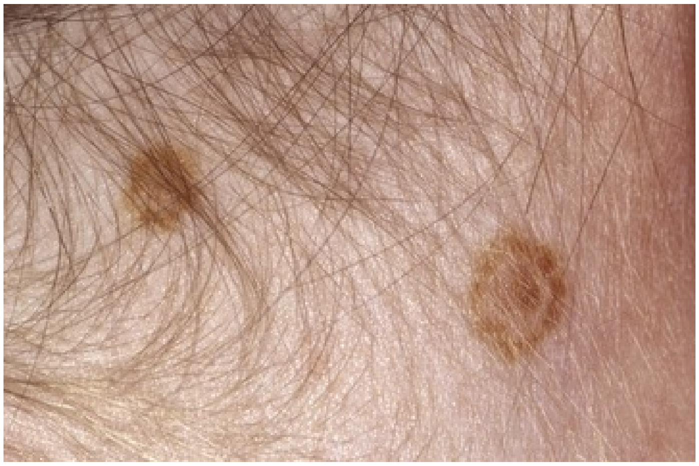

FIG. 670.1 Eclipse nevi (rim moles) in the scalp.

Atypical Melanocytic Nevus

Atypical melanocytic nevi occur both in an autosomal dominant familial melanoma-prone setting (familial mole–melanoma syndrome, dysplastic nevus syndrome, BK mole syndrome) and as a sporadic event. Only 2% of all pediatric melanomas occur in individuals with this familial syndrome; melanoma develops before age 20 yr in 10% of individuals with the syndrome. Malignant melanoma has been reported in children with dysplastic nevus syndrome as young as 10 yr old. Risk for development of melanoma is essentially 100% in individuals with dysplastic nevus syndrome who have 2 family members who have had melanomas. The term *atypical mole syndrome* describes lesions in those individuals without an autosomal dominant familial history of melanoma but with more than 50 nevi, some of which are atypical. The lifetime risk of melanoma associated with dysplastic nevi in this context is estimated to be 5–10%.

Atypical nevi tend to be large (5-15 mm) and round to oval. They have irregular margins and variegated color, and portions of them are elevated. These nevi are most common on the posterior trunk, suggesting that intermittent, intense sun exposure has a role in their genesis. They may also occur in sun-protected areas such as the breasts, buttocks, and scalp. Atypical nevi do not usually develop until puberty, although scalp lesions may be present earlier. Atypical nevi demonstrate disordered proliferation of atypical intraepidermal melanocytes, lymphocytic infiltration, fibroplasia, and angiogenesis. It may be helpful to obtain histopathologic documentation of dysplastic change by biopsy to identify these individuals. It is prudent to excise borderline atypical nevi in immunocompromised children or in those treated with irradiation or chemotherapeutic agents. Although chemotherapy is associated with the development of a greater number of melanocytic nevi, it has not been directly linked to increased risk for development of melanoma. The threshold for removal of clinically atypical nevi is also lower at sites that are difficult to observe, such as the scalp. Children with atypical nevi should undergo a complete skin examination every 6-12 mo. In these children, photographic mole mapping serves as a useful adjunct in following nevus change. Parents must be counseled about the importance of sun protection and avoidance and should be instructed to look for early signs of melanoma on a regular basis, approximately every 3-4 mo.

Congenital Melanocytic Nevus

Congenital melanocytic nevi are present in 2–3% of newborn infants. These nevi have been categorized by size: giant congenital nevi are >40 cm in diameter (adult size) or >5% of the body surface; large nevi are 20-40 cm, medium nevi are 1.5-20 cm, and small nevi are <1.5 cm in diameter. Congenital nevi are characterized by the presence of nevus cells in the lower reticular dermis; between collagen bundles; surrounding cutaneous appendages, nerves, and vessels in the lower dermis; and occasionally extending to the subcuticular fat. Large and giant congenital nevi often harbor *NRAS* mutations, while *BRAF* mutations typically seen in regular melanocytic nevi are most common in small or medium congenital nevi. Identification is often uncertain, however, because they may have the histologic features of ordinary junctional, compound, or intradermal nevi. Some nevi that were not present at birth display histopathologic features of congenital nevi; these should not be considered congenital, but may be called congenital nevus-like nevi (CNLN). Furthermore, congenital nevi may be difficult to distinguish clinically from other types of pigmented lesions, adding to the difficulty that parents may have in identifying nevi that were present at birth. The clinical differential diagnosis includes dermal melanocytosis, café-au-lait macules, and smooth muscle hamartomas.

Sites of predilection for small congenital nevi are the lower trunk, upper back, shoulders, chest, and proximal limbs. The lesions may be flat, elevated, verrucous, or nodular and may be various shades of brown, blue, or black. Given the difficulty in identifying small congenital nevi with certainty, data regarding their malignant potential are controversial and likely overstated. The true incidence of melanoma in congenital nevi, especially small and medium-sized lesions, is unknown. Removal of all small congenital nevi is not warranted because the development of melanoma in a small congenital nevus is an exceedingly rare event before puberty. A number of factors must be weighed in the decision about whether or not to remove a nevus, including its location, the ability to monitor it clinically, the potential for scarring, the presence of other risk factors for melanoma, and the presence of atypical clinical features.

Giant congenital pigmented nevi (<1 in 20,000 births) occur most commonly on the posterior trunk (Fig. 670.2) but may also appear on the head or extremities. These nevi are of special significance because of their association with leptomeningeal melanocytosis (neurocutaneous melanocytosis) and their predisposition for development of malignant melanoma.

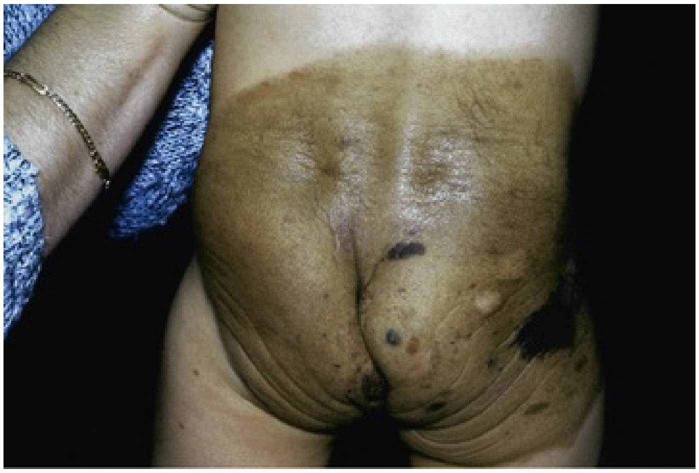

FIG. 670.2 “Bathing suit” large congenital melanocytic nevus.

Leptomeningeal involvement occurs most often when the nevus is located on the head or midline on the trunk, particularly when associated with multiple “satellite” melanocytic nevi (>20 lesions). Nevus cells within the leptomeninges and brain parenchyma may cause increased intracranial pressure, hydrocephalus, seizures, intellectual disability, and motor deficits and may result in melanoma. Malignancy can be identified by careful cytologic examination of the cerebrospinal fluid for melanin-containing cells. MRI demonstrates asymptomatic leptomeningeal melanosis in 30% of individuals with giant congenital nevus of the type described above. The overall incidence of malignant melanoma arising in a giant congenital nevus is 1–2%. The median age at diagnosis of the melanomas that arise within a giant congenital nevus is 7 yr. The mortality rate approaches 100%. The risk of melanoma is greater in patients in whom the predicted adult size of the nevus is >40 cm, lesions on trunk, and presence of satellite lesions. Management of giant congenital nevi remains controversial and should involve the parents, pediatrician, dermatologist, and plastic surgeon. If the nevus lies over the head or spine, MRI may allow detection of neural melanosis**,** the presence of which makes gross removal of a nevus from the skin a futile effort. In the absence of neural melanosis, early excision and repair aided by tissue expanders or grafting may reduce the burden of nevus cells and thus the potential for development of melanoma, but at the cost of many potentially disfiguring operations. Nevus cells deep within subcutaneous tissues may evade excision. Random biopsies of the nevus are not helpful, but biopsy of newly expanding nodules is indicated. Follow-up every 6 mo for 5 yr and every 12 mo thereafter is recommended. Serial photographs of the nevus may aid in detecting changes.

Melanoma

Malignant melanoma is the most common skin cancer in children, and approximately 1% of all melanomas occur before 20 yr of age. An estimated 400 cases of pediatric melanoma are diagnosed each year. The incidence of melanoma in the pediatric population increases with age, from 1-2 cases per 1 million in children under age 10 to 16.9 cases in children aged 15-19 yr. The incidence of pediatric melanoma has increased by an average of 2% per yr between 1973 and 2009. This increase was especially notable in females between the ages of 15-19. In this age group, melanoma accounts for 6% of all childhood cancers. Melanoma develops primarily in white individuals, on the head and trunk in males, and on the extremities in females. In preadolescent patients, melanoma is more likely to present on the head and neck than in other locations. Risk factors for development of melanoma include the presence of the familial atypical mole–melanoma syndrome or xeroderma pigmentosum; an increased number of acquired melanocytic nevi, or atypical nevi; fair complexion; excessive sun exposure, especially intermittent exposure to intense sunlight; a personal or family (first-degree relative) history of a previous melanoma; giant congenital nevus; and immunosuppression. In previously well children, UV radiation is responsible for most melanomas. Fewer than 5% of childhood melanomas develop within giant congenital nevi or in individuals with the familial atypical mole–melanoma syndrome. Approximately 40–50% of the time, melanoma develops at a site where there was no apparent nevus. The mortality rate from melanoma is related primarily to tumor thickness and the level of invasion into the skin. About 75% of pediatric cases are localized, and have an excellent outcome. Ninety percent of pediatric patients diagnosed with melanoma are expected to be alive in 5 yr. In patients with nodal disease, the outcomes are intermediate with about 60% expected to survive long term.

There is variability in prognosis depending on the age of diagnosis in pediatric patients. Children younger than 10 with melanoma often have poor prognostic features. They are more often non-white, have head and neck primary tumors, thicker primary lesions, a higher incidence of spitzoid morphology, vascular invasion and nodal metastases, and more often have syndromes that predispose them to melanoma. The treatment of melanomas, as in adult patients, is surgical excision with 1 cm margins for tumors <1 mm deep, 1-2 cm margins for tumors >1 mm and <2 mm deep, and 2 cm margins for tumors >2 mm deep. Sentinel lymph node biopsy has become a widespread practice in pediatric melanoma. It should be considered in lesions >1 mm and in thin lesions with ulceration, mitotic rate greater than 1 mm^2 , and young age. Though pediatric patients are more likely to have nodal metastases than their adolescent counterparts, this has not been associated with a decrease in overall survival. Alternatively, in adolescents, nodal disease is a significant negative prognostic factor. Increased tumor thickness and ulceration are associated with lymph node positivity. If the sentinel node is positive, a lymph node dissection can be considered. Patients with regional lymph node involvement can be offered treatment with interferon alfa-2b. *BRAF* and *MEK* inhibitors are not currently available for pediatric patients; however phase 1 and 2 clinical trials are currently ongoing for adolescent patients.

Given the lack of effective therapy for melanoma, prevention and early detection are the most effective measures. Emphasis should be given to avoidance of intense midday sun exposure between 10 AM and 3 PM ; wearing of protective clothing such as a hat, long sleeves, and pants; and use of sunscreen. Early detection includes frequent clinical and photographic examinations of patients at risk (dysplastic nevus syndrome) and prompt response to rapid changes in nevi (size, shape, color, inflammation, bleeding or crusting, and sensation). The ABCDE rule (asymmetry, border irregularities, color variability, diameter >6 mm, evolving), which is a useful screening tool for adults, may not be as effective for children. Unlike adult melanomas, which are usually pigmented, pediatric melanomas are often amelanotic and can mimic benign lesions such as warts and pyogenic granulomas. They are also more likely to have regular borders and to be less than 6 mm in diameter. They often present as papules or papulonodules. To highlight these differences from adult melanomas, an **ABCDE rule for pediatric melanoma** has been proposed: **A** melanotic, **B** leeding, **B** umps, uniform **C** olor, small **D** iameter, **D** e novo and in **E** volution.

Halo Nevus

Halo nevi occur primarily in children and young adults, most commonly on the back (Fig. 670.3). Development of the lesion may coincide with puberty or pregnancy. Several pigmented nevi frequently develop halos simultaneously. Subsequent disappearance of the central nevus over several months is the usual outcome, and the depigmented area usually repigments. Excision and histopathologic examination of the lesion is indicated only when the nature of the central lesion is in question. An acquired melanocytic nevus occasionally develops a peripheral zone of depigmentation over a period of days to weeks. There is a dense inflammatory infiltrate of lymphocytes and histiocytes in addition to the nevus cells. The pale halo reflects disappearance of the melanocytes. This phenomenon is associated with congenital nevi, blue nevi, Spitz nevi, dysplastic nevi, neurofibromas, and primary and secondary malignant melanoma, and occasionally with poliosis, Vogt-Koyanagi-Harada syndrome, and pernicious anemia. Patients with vitiligo have an increased incidence of halo nevi. Individuals with halo nevi have circulating antibodies against the cytoplasm of melanocytes and nevus cells.

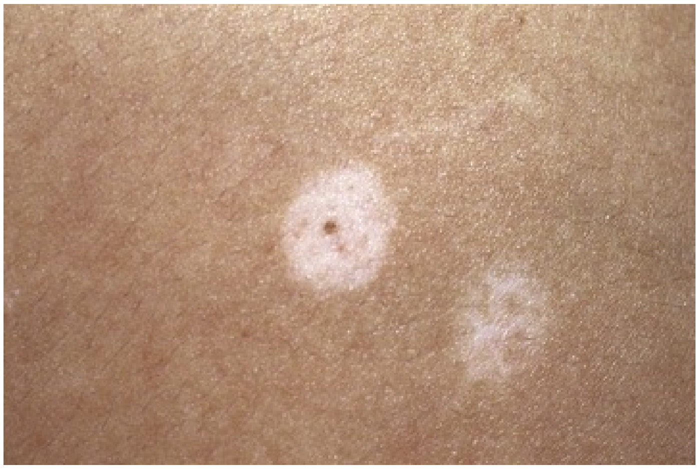

FIG. 670.3 **Well-developed halo nevus.**

Spitz Nevus (Spindle and Epithelioid Cell Nevus)

Spitz nevus manifests most commonly in the 1st 2 decades of life as a pink to red, smooth, dome-shaped, firm, hairless papule on the face, shoulder, or upper limb (Fig. 670.4). Most are <1 cm in diameter, but they can achieve a size of 3 cm. Rarely, they occur as numerous grouped lesions. Visually similar lesions include pyogenic granuloma, hemangioma, nevocellular nevus, juvenile xanthogranuloma, and basal cell carcinoma, but these entities are histologically distinguishable. Classic appearing Spitz nevi can be monitored with regular clinical and dermoscopic examination, and multiple dermoscopy studies have demonstrated a tendency for these benign lesions to develop a reticular or homogeneous pattern and/or regress over time. Guidelines recommend excision be reserved for suspicious lesions (>8-10 mm, with excessive growth, asymmetry, or ulceration) in children over 12 yr of age and for suspicious lesions in all ages when melanoma cannot be excluded. If a nevus arouses clinical suspicion that it may be a melanoma, an excisional biopsy of the entire lesion is recommended. If the margins of excision of a Spitz nevus are positive but the biopsy sample suggested a typical Spitz nevus, reexcision of the site is no longer routinely recommended. Because Spitz nevi may be difficult to distinguish histopathologically from malignant melanoma, immunohistochemistry and genomic alteration studies can be useful adjunct tools. Atypical Spitz tumors are Spitz nevi with atypical histologic features or unknown malignant potential.

Management for these tumors is not clearly defined, and may range from clinical monitoring to yearly nodal ultrasonography to potentially sentinel lymph node biopsy and lymphadenectomy. However a prognostic implication of positive sentinel lymph node biopsy has not been established and given the potential morbidity of the procedure, it is often avoided.

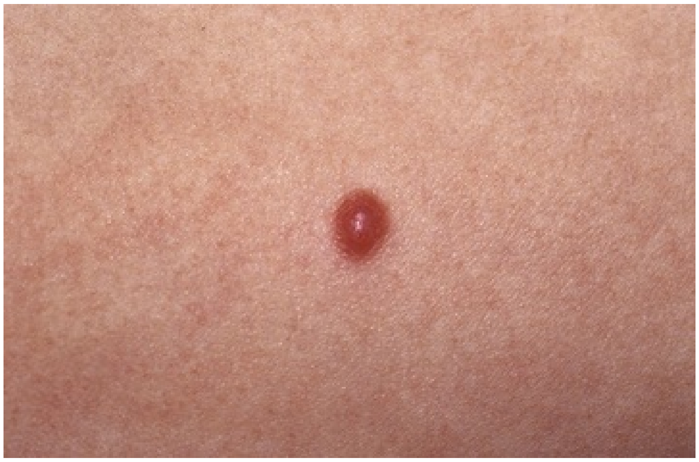

FIG. 670.4 **Dome-shaped red Spitz nevus.**

Zosteriform Lentiginous Nevus (Agminated Lentigines)

Zosteriform lentiginous nevus is a unilateral, linear, band-like collection of numerous 2-10 mm brown or black macules on the face, trunk, or limbs. The nevus may be present at birth or may develop during childhood. There are higher numbers of melanocytes in elongated rete ridges of the epidermis.

Nevus Spilus (Speckled Lentiginous Nevus)

Nevus spilus is a flat brown patch within which are darker flat or raised brown melanocytic elements with a prevalence of 2–3% (Fig. 670.5). It varies considerably in size and can occur anywhere on the body. The color of the macular component may vary from light to dark brown, and the number of darker lesions may be low or high. Nevus spilus is rare at birth and is commonly acquired in late infancy or early childhood. Dark elements within the nevus are usually present initially and tend to increase in number gradually over time. The darker macules represent nevus cells in a junctional or dermal location; the patch has increased numbers of melanocytes in a lentiginous epidermal pattern. The malignant potential of these nevi is uncertain; nevus spilus is found more commonly in individuals with melanoma than in matched control subjects. Like congenital melanocytic nevi, the risk of melanoma developing within a nevus spilus is thought to be proportionate to the size of the lesion as a whole. The nevi need not be excised, unless atypical features or recent clinical changes are noted.

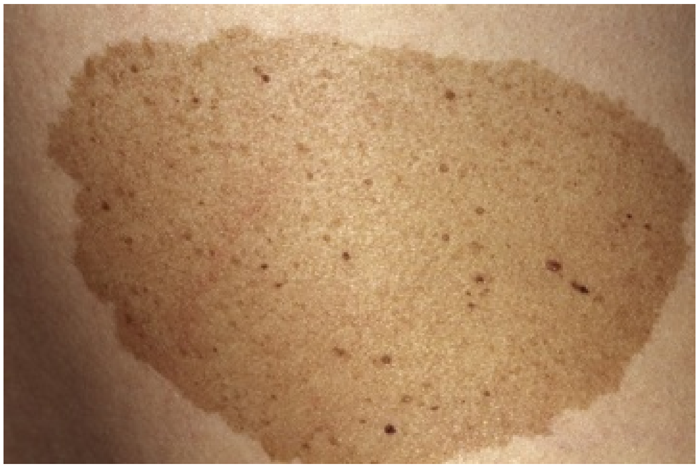

FIG. 670.5 **Nevus spilus.**

Nevus of Ota and Nevus of Ito

Nevus of Ota is more common among females and Asian and African-American patients. This nevus consists of a permanent patch composed of partially confluent blue, black, and brown macules. Enlargement and darkening may occur with time. Occasionally, some areas of the nevus are raised. The macular nevi resemble the more common dermal melanocytosis of the lower back and buttocks in color and occur unilaterally in the areas supplied by the 1st and 2nd divisions of the trigeminal nerve. Nevus of Ota differs from a more common dermal melanocytosis patch, not only by its distribution but also by having a speckled rather than a uniform appearance. Both are forms of mid-dermal melanocytosis. Nevus of Ota also has a greater concentration of elongated, dendritic dermal melanocytes located in the upper rather than the lower portion of the dermis. This nevus is sometimes present at birth; in other cases, it may arise during the 1st or 2nd decade of life. Patchy involvement of the conjunctiva, hard palate, pharynx, nasal mucosa, buccal mucosa, or tympanic membrane occurs in some patients. Malignant change is exceedingly rare. Laser therapy may effectively decrease the pigmentation but can be unpredictable.

Nevus of Ito is localized to the supraclavicular, scapular, and deltoid regions. This nevus tends to be more diffuse in its distribution and less mottled than nevus of Ota. It is also a form of mid-dermal melanocytosis. The only available treatments are masking with cosmetics and laser therapy.

Blue Nevi

The common blue nevus is a solitary, asymptomatic, smooth, dome-shaped, blue to blue-gray papule <10 mm in diameter on the dorsal aspect of the hands and feet. Rarely, common blue nevi form large plaques. Blue nevus is nearly always acquired, often during childhood and more commonly in females. Microscopically, it is characterized by groups of intensely pigmented spindle-shaped melanocytes in the dermis. This nevus is benign.

The cellular blue nevus is typically 1-3 cm in diameter and occurs most frequently on the buttocks and in the sacrococcygeal area. In addition to collections of deeply pigmented dermal dendritic melanocytes, cellular islands composed of large spindle-shaped cells are noted in the dermis and may extend into the subcutaneous fat. A histologic continuum may be seen from blue nevi to cellular blue nevi. A combined nevus is the association of a blue nevus with an overlying melanocytic nevus.

The blue-gray that is characteristic of these nevi is an optical effect caused by dermal melanin. Longer wavelengths of visible light penetrate to the deep dermis and are absorbed there by melanin; shorter-wavelength blue light cannot penetrate deeply but instead is reflected back to the observer.

Nevus Depigmentosus (Achromic Nevus)

Nevi depigmentosi are usually present at birth; they are localized macular hypopigmented patches or streaks, often with bizarre, irregular borders (Fig.

670.6). They can resemble hypomelanosis of Ito clinically, except that they are more localized and often unilateral. Small lesions may also resemble the ash leaf macules of tuberous sclerosis. Nevi depigmentosi appear to represent a focal defect in transfer of melanosomes to keratinocytes.

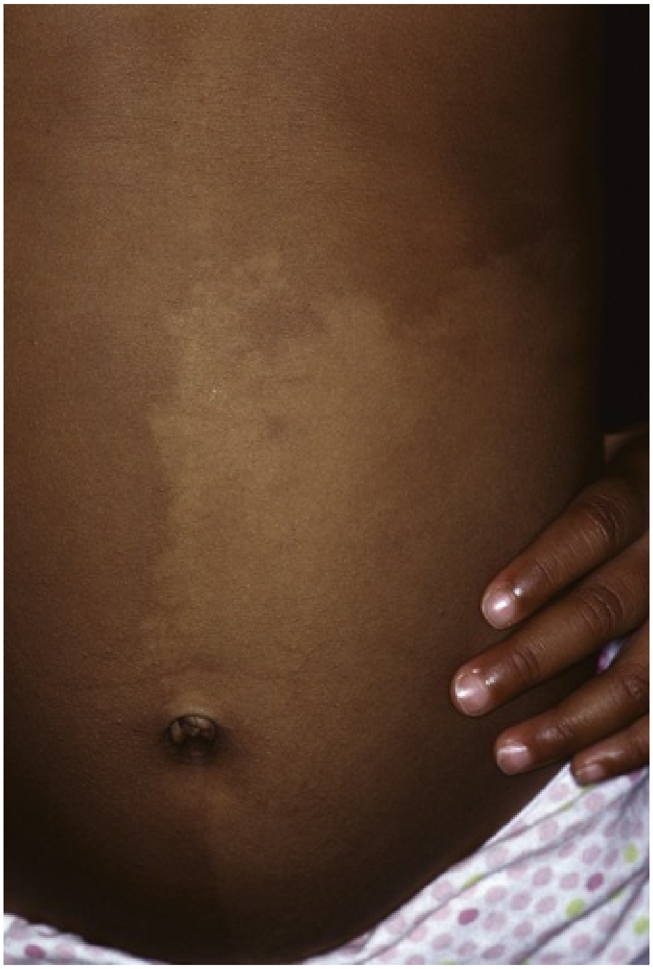

FIG. 670.6 **Large nevus depigmentosus of the abdomen.**

Epidermal Nevi

Epidermal nevi may be visible at birth or may develop in the first few months or years of life. They affect both sexes equally and usually occur sporadically. Epidermal nevi are hamartomatous lesions characterized by hyperplasia of the epidermis and/or adnexal structures in a focal area of the skin.

Epidermal nevi are classified into a number of variants, depending on the morphology and extent of the individual nevus and the predominant epidermal structure. An epidermal nevus may appear initially as a discolored, slightly scaly patch that, with maturation, becomes more linear, thickened, verrucous, and hyperpigmented. *Systematized* refers to a diffuse or extensive distribution of lesions, and *ichthyosis hystrix* indicates that the distribution is extensive and bilateral (Fig. 670.7). Morphologic types include pigmented papillomas, often in a linear distribution; unilateral hyperkeratotic streaks involving a limb and perhaps a portion of the trunk; velvety hyperpigmented plaques; and whorled or marbled hyperkeratotic lesions in localized plaques or over extensive areas of the body along Blaschko lines. An inflammatory linear verrucous variant is markedly pruritic and tends to become erythematous, scaling, and crusted. Many have *RAS* mutations.

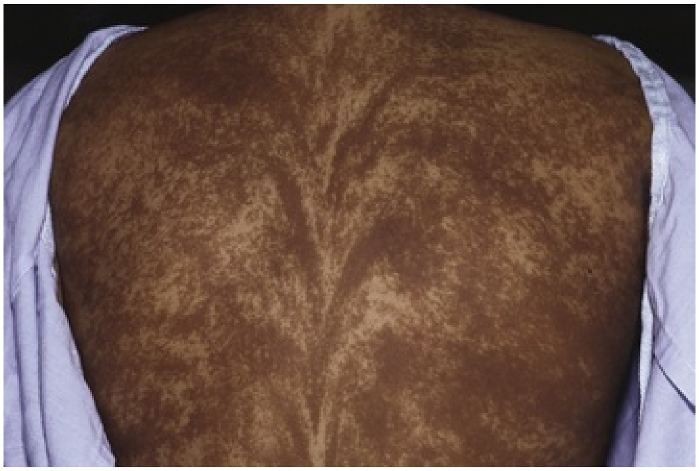

FIG. 670.7 **Epidermal nevus (ichthyosis hystrix type).**

The histologic pattern evolves as an epidermal nevus matures, but epidermal hyperplasia of some degree is apparent in all stages of development. One or another dermal appendage may predominate in a particular lesion. These nevi must be distinguished from lichen striatus, lymphangioma circumscriptum, shagreen patch of tuberous sclerosis, congenital hairy nevi, linear porokeratosis, linear lichen planus, linear psoriasis, the verrucous stage of incontinentia pigmenti, and nevus sebaceus (Jadassohn). Keratolytic agents such as retinoic acid and salicylic acid may be moderately effective in reducing scaling and controlling pruritus, but definitive treatment requires full-thickness excision; recurrence is usual if more superficial removal is attempted. Alternatively, the nevus may be left intact. Epidermal nevi are occasionally associated with other abnormalities of the skin and soft tissues, eyes, and nervous, cardiovascular, musculoskeletal, and urogenital systems. In these instances, the disorder is referred to as epidermal nevus syndrome. This syndrome, however, is not a distinct clinical entity.

Nevus Sebaceus (Jadassohn)

A relatively small, sharply demarcated, oval or linear, elevated yellow-orange plaque that is usually devoid of hair, nevus sebaceus occurs on the head and neck of infants (Fig. 670.8). Although the lesion is characterized histopathologically by an abundance of sebaceous glands, all elements of the skin are represented. It is frequently flat and inconspicuous in early childhood. With maturity, usually during adolescence, the lesions become verrucous and studded with large rubbery nodules. The changing clinical appearance reflects the histologic pattern, which is characterized by a variable degree of hyperkeratosis, hyperplasia of the epidermis, malformed hair follicles, and often a profusion of sebaceous glands and the presence of ectopic apocrine glands. Sebaceous nevi are caused by somatic mosaic mutations in *HRAS* and *KRAS*. The disruption of these oncogenes helps explain the 14% incidence of these lesions developing tumors throughout a patient's lifetime. Most tumors are benign (trichoblastomas, syringocystadenoma papilliferum, trichilemmomas), but basal cell carcinoma can occur as well. The treatment of choice is total excision before adolescence. Sebaceous nevi associated with central nervous system, skeletal, and ocular defects represent a variant of the epidermal nevus syndrome.

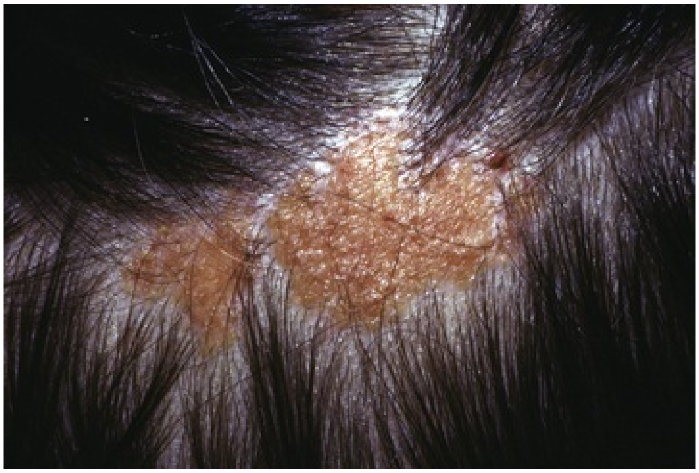

FIG. 670.8 Orange-yellow nevus sebaceus of the scalp.

Becker Nevus (Becker Melanosis)

Becker nevus develops predominantly in males, during childhood or adolescence, initially as a hyperpigmented patch. The lesion commonly develops hypertrichosis, limited to the area of hyperpigmentation, and evolves into a unilateral, slightly thickened, irregular, hyperpigmented plaque. The most common sites are the upper torso and upper arm (Fig. 670.9). The nevus shows an increased number of basal melanocytes and variable epidermal hyperplasia. Becker melanosis is commonly associated with a smooth muscle hamartoma, which may appear as slight perifollicular papular elevations or slight induration. Stroking of such a lesion may induce smooth muscle contraction and make the hairs stand up (pseudo-Darier sign). The nevus is benign, has no risk for malignant change, and is rarely associated with other anomalies.

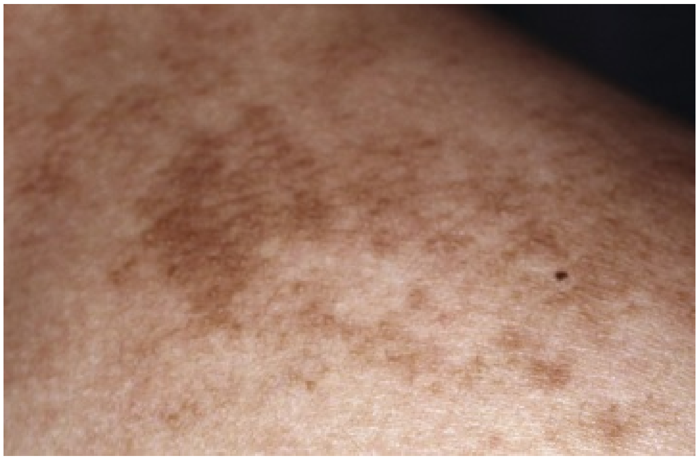

FIG. 670.9 Becker nevus on the shoulder of an adolescent male.

Nevus Comedonicus

An uncommon organoid nevus of epithelial origin, nevus comedonicus consists of linear plaques of plugged follicles that simulate comedones; they may be present at birth or may appear during childhood. The horny plugs represent keratinous debris within dilated, malformed pilosebaceous follicles. The lesions are most often unilateral and may develop at any site. Rarely, they are associated with other congenital malformations, including skeletal defects, cerebral anomalies, and cataracts. Although these lesions are often asymptomatic, some affected individuals experience recurrent inflammation, resulting in cyst formation, fistulas, and scarring. There is no effective treatment except full-thickness excision; palliation of larger lesions may be achieved by regular applications of a retinoic acid preparation.

Connective Tissue Nevus

Connective tissue nevus is a hamartoma of collagen, elastin, and/or glycosaminoglycans of the dermal extracellular matrix. It may occur as a solitary defect or as a manifestation of an associated disorder. These nevi may occur at any site but are most common on the back, buttocks, arms, and thighs. They are skin-colored, ivory, or yellow plaques, 2-15 cm in diameter, composed of many tiny papules or grouped nodules that are frequently difficult to appreciate visually because of the subtle color changes. The plaques have a rubbery or cobblestone consistency on palpation. Biopsy findings are variable and include increased amounts and/or degeneration or fragmentation of dermal collagen, elastic tissue, or ground substance. Similar lesions occurring with tuberous sclerosis are called shagreen patches; however, shagreen patches consist only of excessive amounts of collagen. The association of many small papular connective tissue nevi with osteopoikilosis is called dermatofibrosis lenticularis disseminata (Buschke-Ollendorff syndrome).

Smooth Muscle Hamartoma

Smooth muscle hamartoma is a developmental anomaly resulting from hyperplasia of the smooth muscle (arrector pili) associated with hair follicles. It is usually evident at birth or shortly thereafter as a flesh-colored or lightly pigmented plaque with overlying hypertrichosis on the trunk or limbs (Fig. 670.10). Transient elevation or a rippling movement of the lesion, caused by contraction of the muscle bundles, can sometimes be elicited by stroking of the surface (pseudo-Darier sign). Smooth muscle hamartoma can be mistaken for congenital pigmented nevus, but the distinction is important because the former has no risk for malignant melanoma and need not be removed.

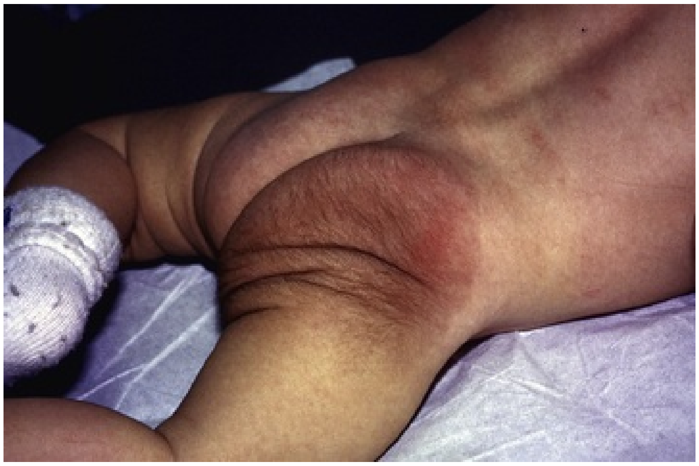

FIG. 670.10 **Large smooth muscle hamartoma of the buttock.**

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CHAPTER 671

Hyperpigmented Lesions

Joel C. Joyce

Disorders of Pigment

Normal pigmentation requires migration of melanoblasts from the neural crest to the dermal-epidermal junction, enzymatic processes to form pigment, structural components to contain the pigment (melanosomes), and transfer of pigment to the surrounding keratinocytes. Increased skin color may be generalized or localized and may result from various defects in any of these requirements. Some of these aberrations are a manifestation of systemic disease, others represent generalized or focal developmental or genetic defects, and still others may be nonspecific and the result of cutaneous inflammation.

Ephelides (Freckles)

Ephelides are well-demarcated macules—light or dark brown, round, oval, or irregularly shaped—that occur in sun-exposed areas such as the face, upper back, arms, and hands. They are usually less than 3 mm in diameter and induced by exposure to sun, particularly during the summer, and may fade or disappear during the winter. They are a result of increased sun-induced melanogenesis and melanosome transport from melanocytes to keratinocytes and not from increased numbers of melanocytes. They are more common in redheads and fair-haired individuals and first appear in the preschool years. Histologically, they are marked by increased melanin pigment in epidermal basal cells, which have more numerous and larger dendritic processes than the melanocytes of the surrounding paler skin. The lack of melanocytic proliferation or elongation of epidermal rete ridges distinguishes them from lentigines. Freckles have been identified as a marker for increased risk for ultraviolet (UV)-induced neoplasia and hence melanoma independent of melanocytic nevi.

Lentigines

Lentigines, often mistaken for freckles or junctional nevi, are small (usually <5 mm but occasionally 1-2 cm), round, dark-brown macules that can appear anywhere on the body with an early age of onset. They are more common in darkly pigmented than in lightly pigmented individuals. They are unrelated to sun exposure and remain permanently. Histologically they have elongated, club-shaped epidermal rete ridges with increased numbers of melanocytes and dense epidermal deposits of melanin. No nests of melanocytes are found. The lesions are benign and, when few, may be viewed as a normal occurrence. They are seen most commonly on the lower lip.

Eruptive/generalized lentiginosis (lentiginosis profusa) involves innumerable small pigmented macules that are present at birth or appear during childhood. There are no associated abnormalities, and mucous membranes are spared. **Carney complex** is an autosomal dominant syndrome characterized by multiple lentigines and neoplasias, including: myxomas of the skin, heart (atrial), and breast; psammomatous melanotic schwannomas; epithelioid blue nevi of skin and mucosae; growth hormone–producing pituitary adenomas; and testicular Sertoli cell tumors. Components of the Carney complex have been described previously as the NAME (nevi, atrial myxoma, myxoid neurofibroma, ephelides) and LAMB (lentigines, atrial myxoma, mucocutaneous myxoma, blue nevi) syndromes. The complex is inherited in an autosomal dominant pattern and caused by an inactivating mutation of the *PRKAR1* gene.

The **multiple lentigines syndrome** (formerly LEOPARD) is an autosomal dominant entity consisting of a generalized, symmetric distribution of *l* entigines (Fig. 671.1) in association with *e* lectrocardiographic *a* bnormalities, *o* cular hypertelorism, *p* ulmonary stenosis, *a* bnormal genitals (cryptorchidism, hypogonadism, hypospadias), growth *r* etardation, and sensorineural *d* eafness (type 1, *PTPN11* gene; type 2, *RAF1* gene). Other features include hypertrophic obstructive cardiomyopathy and pectus excavatum or carinatum.

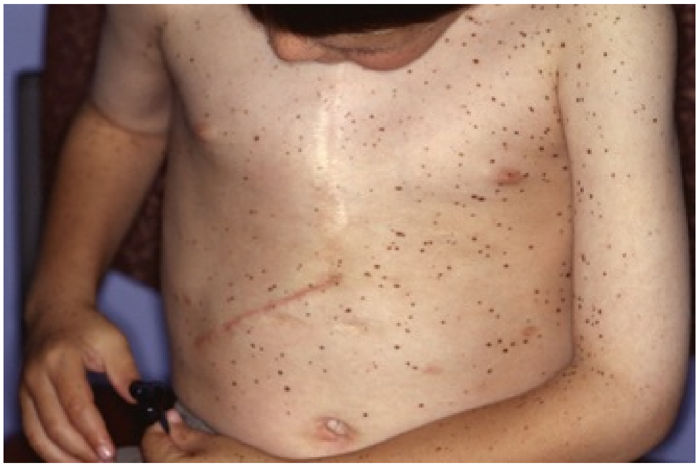

FIG. 671.1 Multiple lentigines in LEOPARD (*l* entigines in association with *e* lectrocardiographic *a* bnormalities, *o* cular hypertelorism, *p* ulmonary stenosis, *a* bnormal genitals [cryptorchidism, hypogonadism, hypospadias], growth *r* etardation, and sensorineural *d* eafness) syndrome.

The **Peutz-Jeghers syndrome** is characterized by melanotic macules on the lips and mucous membranes and by gastrointestinal (GI) polyposis. It is inherited as an autosomal dominant trait (*STK11* gene). Onset is noted in infancy and early childhood when pigmented macules appear on the lips and buccal mucosa. The macules are usually a few millimeters in size but may be as large as 1-2 cm. Macules also occasionally appear on the palate, gums, tongue, and vaginal mucosa. Cutaneous lesions may develop on the nose, hands, and feet; around the mouth, eyes, and umbilicus; and as longitudinal bands or diffuse hyperpigmentation of the nails. Pigmented macules often fade from the lips and skin during puberty and adulthood but generally do not disappear from mucosal surfaces. Buccal mucosal macules are the most constant feature of the disorder; in some families, occasional members may be affected only with the pigmentary changes. Indistinguishable pigmentary changes beginning in adult life, without intestinal involvement, also occur sporadically in individuals.

Polyposis usually involves the jejunum and ileum but may also occur in the stomach, duodenum, colon, and rectum (see Chapter 372). Episodic abdominal pain, diarrhea, melena, and intussusception are frequent complications. Patients have a significantly increased risk of GI tract and non–GI tract tumors at a young age. GI cancer has been reported in 2–3% of patients; the lifetime relative risk for GI malignancy is 13. The relative risk of non–GI tract malignancies, including ovarian, cervical, and testicular tumors, is 9. Peutz-Jeghers syndrome must be differentiated from other syndromes associated with multiple lentigines (Laugier-Hunziker syndrome), from ordinary freckling, from Gardner syndrome, and from Cronkhite-Canada syndrome, a disorder characterized by GI polyposis, alopecia, onychodystrophy, and diffuse pigmentation of the palms, volar aspects of the fingers, and dorsal hands. Treatment of Peutz-Jeghers melanotic macules is not required, but various lasers have been effective for cosmesis in some cases.

Café-Au-Lait Spots

Café-au-lait spots are uniformly hyperpigmented, sharply demarcated macular lesions, the hues of which vary with the normal degree of pigmentation of the individual: they are tan or light brown in white individuals and may be dark brown in black children (Figs. 671.2 and 671.3). Café-au-lait spots vary tremendously in size and may be large, covering a significant portion of the trunk or limb. The borders are usually smooth, but some have exceedingly irregular borders. The lesions are characterized by increased numbers of melanocytes and melanin in the epidermis but lack the clubbed rete ridges that typify lentigines. One to three café-au-lait spots are common in normal children; 10% of normal children have café-au-lait macules. The spots may be present at birth or may develop during childhood.

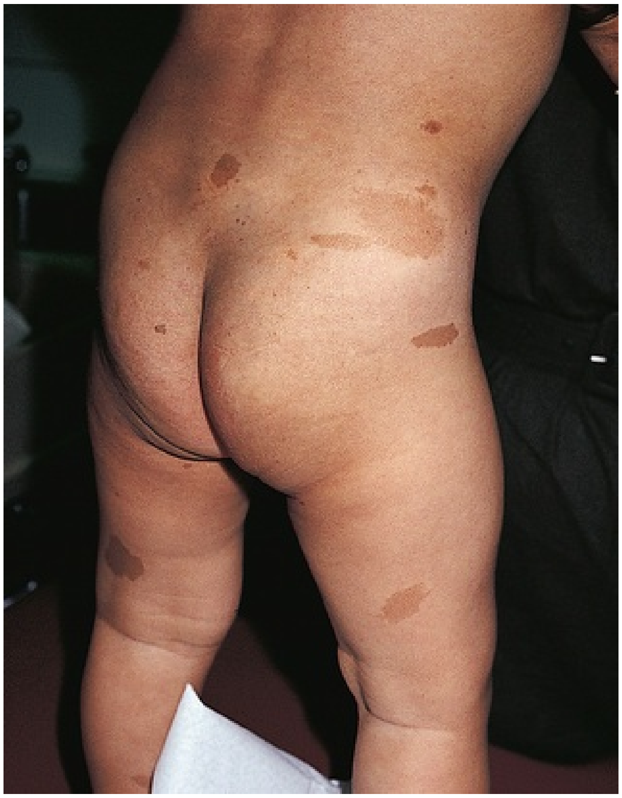

FIG. 671.2 Multiple café-au-lait macules on a child with neurofibromatosis type 1. (From Eichenfield LF, Frieden IJ, Esterly NB: *Textbook of neonatal dermatology* , Philadelphia, 2001, WB Saunders, p. 372.)

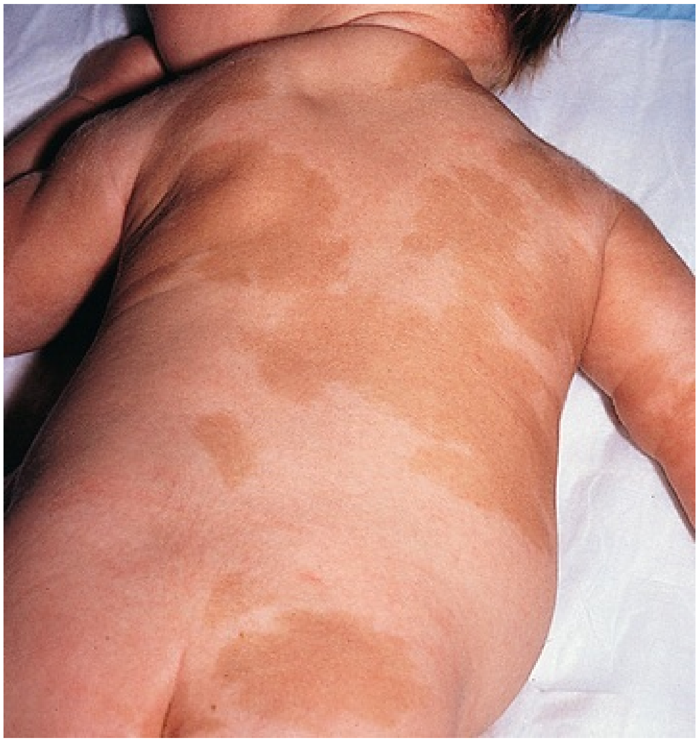

FIG. 671.3 Multiple patterned café-au-lait spots in a child with McCune-Albright syndrome. (From Eichenfield LF, Frieden IJ, Esterly NB: *Textbook of neonatal dermatology* , Philadelphia, 2001, WB Saunders, p. 373.)

Large, often asymmetric café-au-lait spots with irregular borders are characteristic of patients with Albright **(McCune-Albright)** syndrome (*GNAS1* gene; see Chapter 578.6). This disorder includes polyostotic fibrous dysplasia of bone, leading to pathologic fractures; precocious puberty; and numerous hyperfunctional endocrinopathies. The macular hyperpigmentation may be present at birth or may develop late in childhood (see Fig. 671.3). Cutaneous pigmentation is typically most extensive on the side showing the most severe bone involvement.

Neurofibromatosis Type 1 (Von Recklinghausen Disease)

The café-au-lait spot (macule) is the most familiar cutaneous hallmark of the autosomal dominant neurocutaneous syndrome known as neurofibromatosis type 1 (*NF1* , neurofibromin gene; see Figure 671.2 and Chapter 614.1). Included in the criteria for this diagnosis is the presence of 6 or more café-au-lait spots >5 mm in diameter in prepubertal patients or 6 or more café-au-lait spots >15 mm in diameter in postpubertal patients. Multiple café-au-lait macules commonly produce a freckled appearance of non–sun-exposed areas such as the axillae (Crowe sign), the inguinal and inframammary regions, and under the chin. Café-au-lait macules can also be seen in segmental NF-1,which results from somatic mosaicism arising from postzygotic mutations in the *NF1* gene such that the clinical manifestations of NF-1 are present only in a localized body segment. Another variant of NF-1 is hereditary spinal neurofibromatosis, which is a rare disorder that generally presents with multiple café-au-lait macules and multiple symmetric spinal root neurofibromas, but other stigmata of NF-1 are typically absent. The lesions also occur with certain other disorders, including other types of neurofibromatosis, but in many of these disorders the café-au-lait spots are not a major feature of the disorder (Table 671.1).

Table 671.1

Other Syndromes Associated With Café-Au-Lait Macules

STRENGTH OF ASSOCIATION	SYNDROME	CLINICAL FEATURES	GENE OR LOCUS
Strong	Neurofibromatosis type 2	Acoustic neuromas, schwannomas, neurofibromas, meningiomas, juvenile posterior subcapsular lenticular opacity; café-au-lait seen but not a criterion for diagnosis	*NF2*
	Multiple familial café-au-lait	Multiple café-au-lait without other stigmata of NF-1	?
	Legius (NF-1–like) syndrome	Multiple café-au-lait and skinfold freckling without other stigmata of NF-1	*SPRED1*
	McCune-Albright syndrome	Segmental café-au-lait, precocious puberty, other endocrinopathies, polyostotic fibrous dysplasia	*GNAS1*
	Mismatch repair cancer syndrome (constitutional mismatch repair deficiency syndrome)	Multiple café-au-lait, adenomatous colonic polyps, multiple malignancies, including colonic adenocarcinoma, glioblastoma, medulloblastoma, and lymphoma	*MLH1*, *MSH2*, *MSH6*, *PMS2*
	Ring chromosome syndromes	Multiple café-au-lait, microcephaly, mental retardation, short stature, skeletal anomalies	Chromosomes 7, 11, 12, 15, 17
	LEOPARD/multiple lentigines syndrome	Café-au-lait, café-noir, lentigines, cardiac conduction defects, ocular hypertelorism, pulmonary stenosis, genitourinary anomalies, growth retardation, hearing loss	*PTPN11*
	Cowden syndrome (multiple hamartoma syndrome)	Facial trichilemmomas, cobblestoning of the oral mucosa, predisposition to soft tissue tumors (lipomas, neuromas), GI polyps, fibrocystic breast disease and breast carcinoma, thyroid adenoma, and thyroid cancer	*PTEN*

	Bannayan-Riley-Ruvalcaba syndrome	Facial trichilemmomas, oral papillomas, pigmented genital macules, GI polyps, macrocephaly, vascular anomalies, mental retardation	*PTEN*
Weak	Ataxia-telangiectasia	Cerebellar ataxia, cutaneous and ocular telangiectasias, immunodeficiency, hypogonadism, predisposition to lymphoreticular malignancy	*ATM*
	Bloom syndrome	Photosensitivity, immunodeficiency, chronic lung disease, cryptorchidism, syndactyly, short stature, susceptibility to malignancy	*RECQL3*
	Fanconi anemia	Bone marrow failure, multiple congenital anomalies, predisposition to malignancy, mental retardation, microcephaly	*FANCA*, *FANCB* (putative), *FANCC*, *FANCD* locus on chromosome 3, *FANCE* locus on chromosome 6, *FANCF*, *FANCG*, *FANCH* (putative)
	Russell-Silver syndrome and Russell-Silver syndrome, X-linked	Short stature, craniofacial and body asymmetry, low birthweight, microcephaly, triangular facies, 5th finger clinodactyly, congenital cardiac defects	Multiple genes on chromosomes 7 and 11, particularly *H19* and *IGF2* located on 11p15
	Tuberous sclerosis	Facial angiofibromas, cutaneous collagenomas, seizures, mental retardation, hypomelanotic macules, periungual fibromas, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, pulmonary lymphangiomyomatosis renal angiomyolipoma, retinal hamartomas	*TSC1*, *TSC2*
	Turner syndrome	Short stature, lymphedema, congenital heart disease, valgus deformity	X-chromosomal anomalies (XO karyotype or Xp deletion)
	Noonan syndrome	Facial dysmorphism, pulmonary valve stenosis, webbed neck, pectus excavatum, mental retardation, short stature, cryptorchidism, hematologic malignancies	*PTPN11*, *SOS1*, *RAF1*, *KRAS*
	Multiple mucosal neuroma (MEN) syndrome 1	Parathyroid adenoma, pituitary adenoma, pancreatic islet adenoma, lipoma, gingival papules, facial angiofibromas, collagenomas	*MENIN*
	MEN syndrome 2B	Mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma, parathyroid adenoma, marfanoid habitus	*RET*
	Johanson-Blizzard syndrome	Short stature, failure to thrive, microcephaly, sensorineural hearing loss, dental anomalies, congenital heart disease, exocrine pancreatic insufficiency, imperforate anus, genitourinary anomalies, mental retardation, hypothyroidism	*UBR1*
	Microcephalic osteodysplastic primordial dwarfism type II	Short stature, microcephaly, intrauterine growth retardation, dysmorphic facies, skeletal anomalies, developmental delay, premature puberty	*PCNT2*
	Nijmegen breakage	Short stature, growth retardation, microcephaly,	*NBS1*

	syndrome	cleft lip/palate, dysmorphic facies, bronchiectasis, sinusitis, dysgammaglobulinemia with recurrent urinary tract and GI infections, mental retardation, spontaneous chromosomal instability, predisposition to malignancy	
	Rubinstein-Taybi syndrome	Short stature, microcephaly, dysmorphic facies, congenital cardiac disease, sternal anomalies, skeletal anomalies, mental retardation	*CREBBP, EP300*
	Kabuki syndrome I	Postnatal growth retardation, microcephaly, dysmorphic facies, congenital cardiac defects, malabsorption, anal stenosis, genitourinary anomalies, congenital hip dysplasia, hirsutism, mental retardation	*KMT2D*

GI , Gastrointestinal.

From Shah KN: The diagnostic and clinical significance of café-au-lait macules. *Pediatr Clin North Am* 57(5):1131–1153, 2010, Table 2. Updates from OMIM (Online Mendelian Inheritance in Man. https://www.omim.org).

Incontinentia Pigmenti (Bloch-Sulzberger Disease)

See Chapter 614.7 .

PostInflammatory Pigmentary Changes

Either hyperpigmentation or hypopigmentation can occur as a result of cutaneous inflammation. Alteration in pigmentation usually follows a severe inflammatory reaction but may result from mild dermatitis. Dark-skinned are more likely than fair-skinned children to show these changes. Although altered pigmentation may persist for weeks to months, patients can be reassured that these lesions are usually temporary. **Sun protection and treatment of the underlying dermatitis can shorten duration.**

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CHAPTER 672

Hypopigmented Lesions

Joel C. Joyce

Albinism

Congenital oculocutaneous albinism (OCA) consists of partial or complete failure of melanin production in the skin, hair, and eyes despite the presence of normal number, structure, and distribution of melanocytes. These disorders may be divided into two major classes: those with abnormal protein function involved in the formation and transfer of melanin and those with defects in melanosomes (Table 672.1). Tyrosinase is the copper-containing enzyme that catalyzes at multiple steps in melanin biosynthesis (see Chapter 103.2). Tyrosinase-positive variants are characterized by darkening of the hair bulb on incubation with tyrosine.

Table 672.1

Genes Associated With Hypopigmentation

DISORDER	GENE DEFECT
OCULOCUTANEOUS ALBINISM	
OCA1	*TYR*
OCA2	*OCA2*
OCA3	*TRP-1*
OCA4	*MATP*
HERMANSKY-PUDLAK	
Type 1	*HPS1*
Type 2	*AP3B1* (HPS-2)
Type 3	*HPS3*
Type 4	*HPS4*
Type 5	*HPS5*
Type 6	*HPS6*
Type 7	*DTNBP1* (HPS-7)
Type 8	*BLOC1S3* (HPS-8)

Type 9	*BLOC1S6* (HPS-9)
Type 10	*AP3D1* (HPS-10)
CHÉDIAK-HIGASHI	*CHS1/LYST*
PIEBALDISM	*KIT* (C-KIT receptor)
	Heterozygous *SLUG*
WAARDENBURG	
Type 1	Heterozygous *PAX3*
Type 2a	*MITF*
Type 2b	*WS2B*
Type 2c	*WS2C*
Type 2d	*SNAIL*
Type 2e	*SOX10*
Type 3	Homozygous *PAX3*
Type 4	*SOX10*
	EDNRB
	EDN3

Data from OMIM (Online Mendelian Inheritance in Man. https://www.omim.org).

Oculocutaneous albinism type 1 (OCA1) is characterized by great reduction in or absence of tyrosinase activity. OCA1A, the most severe form, is characterized by a lack of visible pigment in hair, skin, and eyes (Fig. 672.1). This manifests as photophobia, nystagmus, defective visual acuity, white hair, and white skin. The irises are blue-gray in oblique light and prominent pink in reflected light. OCA1B, or yellow mutant albinism, manifests at birth as white hair, pink skin, and gray eyes. This type is particularly prevalent in Amish communities. Progressively the hair becomes yellow-red, the skin tans lightly on exposure to the sun, and the irises may accumulate some brown pigment, with a resultant improvement in visual acuity. Photophobia and nystagmus are present but mild. OCATS is a temperature-sensitive type of albinism. The abnormal tyrosinase has decreased activity at 35–37°C (95–98.6°F). Therefore cooler regions of the body such as the limbs and head pigment to some degree, whereas other areas remain depigmented.

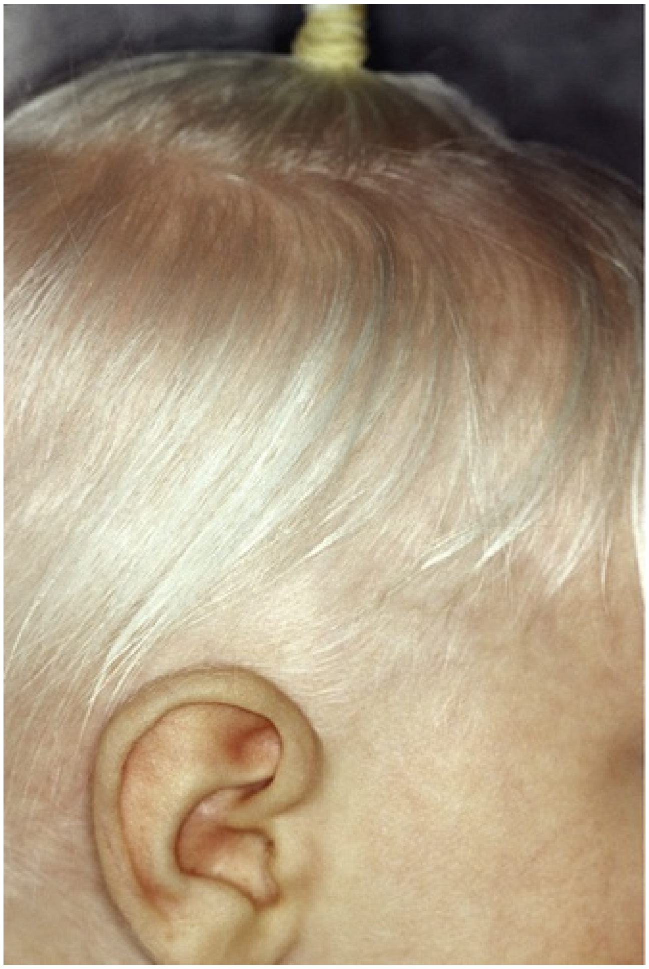

FIG. 672.1 White hair and skin in oculocutaneous albinism type 1 (OCA1).

OCA2 ranges from nearly normal to closely resembling type 1 albinism. This is the most common form of albinism seen worldwide. Little or no melanin is present at birth, but pigment, particularly red-yellow pigment, may accumulate during childhood to produce straw-colored or light brown skin in white individuals. Pigmented nevi may develop. Progressive improvement in visual acuity and nystagmus occurs with aging. Black individuals may have yellow-brown skin, dark-brown freckles in sun-exposed areas, and brown coloration of the irises. **Brown OCA** is an allelic variant of OCA2. Prader-Willi and Angelman syndromes, which include hypopigmentation, have deletions that include the gene *(OCA2)* involved in OCA2.

OCA3 (rufous albinism) is seen predominantly in patients of African descent. It is characterized by red hair, reddish brown skin, pigmented nevi, freckles, reddish brown to brown eyes, nystagmus, photophobia, and decreased visual acuity.

OCA4 is a rare OCA with clinical findings similar to those in OCA2.

The **Cross-McKusick-Breen syndrome** consists of tyrosinase-positive albinism with ocular abnormalities, cognitive impairment, spasticity, and athetosis. The genetic defect is unidentified.

Because of the absence of normal protection by adequate amounts of epidermal melanin, persons with albinism are predisposed to development of actinic keratoses and cutaneous carcinoma secondary to skin damage by ultraviolet light. Protective clothing and a broad-spectrum sunscreen (see Chapter 675) should be worn during exposure to sunlight.

Oculocutaneous Albinism With Melanosomal Abnormalities

See Table 672.1 .

Hermansky-Pudlak syndrome is a collection of autosomal recessive genetic disorders characterized by OCA, ceroid accumulation in lysosomes, and prolonged bleeding time. In mice, 16 distinct genetic loci that produce coat color mutant phenotypes associated with platelet deficiencies are recognized; 10 have been identified in humans.

Chédiak-Higashi syndrome (see Chapter 156) is another genetic abnormality associated with dysfunction of lysosome-related organelles. Patients with Chédiak-Higashi syndrome have hypopigmentation of the skin, eyes, and hair; prolonged bleeding times and easy bruising; recurrent infections; abnormal natural killer cell function; and peripheral neuropathy. Chédiak-Higashi syndrome is caused by mutations in the *CHS1/LYST* gene, which is a lysosomal trafficking regulatory gene.

Melanoblast Migration Abnormalities

See Table 672.1 .

Piebaldism

A congenital autosomal dominant disorder, **piebaldism** is characterized by sharply demarcated amelanotic patches that occur most frequently on the forehead, anterior scalp (producing a white forelock), ventral trunk, elbows, and knees. Islands of normal or darker-than-normal pigmentation may be present within the amelanotic areas (Fig. 672.2). The plaques are a result of a permanent localized absence of melanocytes as a result of a defect in the *KIT* protooncogene, which encodes the cell surface receptor transmembrane tyrosine kinase. The pattern of depigmentation arises from defective melanoblast migration from the neural crest during development. The reason that piebaldism is a localized and not a generalized process remains unknown. Piebaldism must be differentiated from vitiligo, which may be progressive and is not usually congenital, nevus depigmentosus, and Waardenburg syndrome.

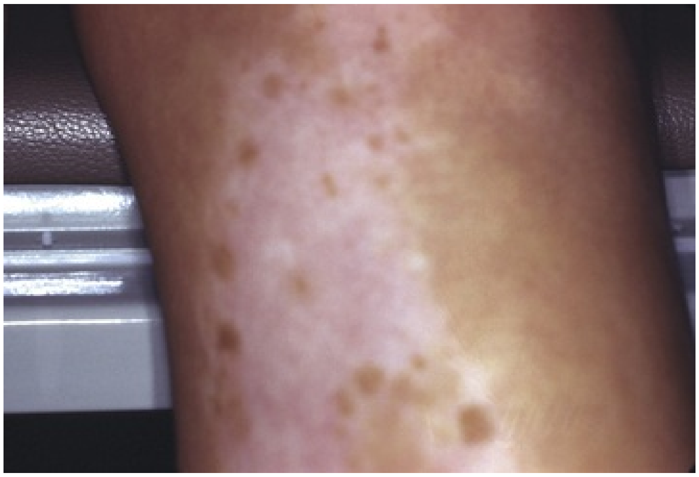

FIG. 672.2 Depigmented macule with islands of hyperpigmentation in piebaldism.

Waardenburg Syndrome

Waardenburg syndrome also manifests at birth as localized areas of depigmented skin and hair. There are four types of Waardenburg syndrome. The hallmark of **Waardenburg type 1** is the white forelock, which is seen in 20–60% of patients. Only 15% of patients have areas of depigmented skin. Deafness occurs in 9–37%, heterochromia irides in 20%, and unibrow (**synophrys**) in 17–69% of those affected. Dystopia canthorum (i.e., telecanthus) is seen in all patients with Waardenburg type 1. **Waardenburg type 2** is similar to type 1, except that patients with type 2 lack dystopia canthorum, but they also have a higher incidence of deafness. **Waardenburg type 3** is similar to Waardenburg type 1, except that patients also have limb abnormalities. It is also called the Klein-Waardenburg syndrome. **Waardenburg type 4** is also called the Shah-

Waardenburg syndrome. Patients with this type all have Hirschsprung disease. Dystopia canthorum is seldom seen in these patients.

Tuberous Sclerosis Complex (*TSC1, TSC2* Genes)

See Chapter 614.2 for a discussion of this complex.

Hypomelanosis of Ito

Hypomelanosis of Ito is a rare congenital skin disorder affecting children of both sexes that can have associated defects in several organ systems. There is no evidence for genetic transmission; chromosomal mosaicism and chromosomal translocations have been reported. Hypomelanosis of Ito is currently a descriptive rather than definitive diagnosis. Blaschkoid or mosaic hypomelanosis is a better descriptive term.

The skin lesions of hypomelanosis of Ito are generally present at birth but may be acquired in the first 2 yr of life. The lesions are similar to a negative image of those present in incontinentia pigmenti, consisting of bizarre, patterned, hypopigmented macules arranged over the body surface in sharply demarcated whorls, streaks, and patches that follow the lines of Blaschko (Fig. 672.3). The palms, soles, and mucous membranes are spared. The **hypopigmentation** remains unchanged throughout childhood but fades during adulthood. The degree of depigmentation varies from hypopigmented to achromic. Neither inflammatory nor vesicular lesions precede the development of the pigmentary changes as in incontinentia pigmenti. The hypopigmented areas demonstrate fewer and smaller melanocytes and a decreased number of melanin granules in the basal cell layer than normal. Inflammatory cells and pigment incontinence are lacking.

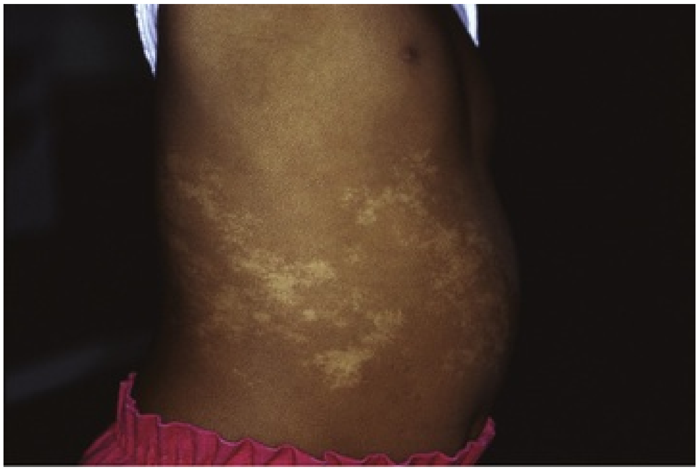

FIG. 672.3 Marbled hypopigmented streaks on the abdomen in hypomelanosis of Ito.

The majority of patients with mosaic hypomelanosis have no associated abnormalities, but involvement of other organ systems can rarely occur. The most commonly associated abnormalities involve the nervous system, including intellectual disability (70%), seizures (40%), microcephaly (25%), and muscular hypotonia (15%). The musculoskeletal system is the second most frequently involved system, affected by scoliosis and thoracic and limb deformities. Minor ophthalmologic defects (strabismus, nystagmus) are present in 25% of patients, and 10% have cardiac defects. These frequencies are likely to be overestimated because patients with isolated skin disease often do not seek further evaluation. The differential diagnosis includes systematized nevus depigmentosus, which is a stable leukoderma not associated with systemic manifestations. Differentiation from incontinentia pigmenti, particularly the hypopigmented 4th stage, is critical for genetic counseling because incontinentia pigmenti, unlike hypomelanosis of Ito, is inherited.

Vitiligo

Epidemiology and Etiology

Vitiligo is an acquired macular depigmentation disorder associated with the destruction of melanocytes. The disorder represents a clinical end-point resulting from a complex interaction of environmental, genetic, and immunologic factors. Autoimmune, genetic, autocytotoxic, and neural theories have been postulated. The prevalence is 0.5–2.0% of most populations.

There is definitely an autoimmune component to vitiligo. Eighty percent of patients with active disease have an antibody to a surface antigen on pigmented melanocytes. These antibodies appear to be cytotoxic for melanocytes. There is also a correlation between disease activity and the titer of serum antimelanocyte antibody. Melanocyte-specific $CD8^+$ T lymphocytes are also involved in the pathogenesis of vitiligo. These antibodies and T cells recognize a variety of melanocyte enzymatic and structural proteins.

The genetic epidemiology of vitiligo is part of a broader genetically determined autoimmune and autoinflammatory diathesis. Fifteen to 20% of patients with generalized vitiligo have one or more affected first-degree relatives. In these families the genetic pattern is suggestive of polygenic, multifactorial inheritance. In the other patients, the disease occurs sporadically. Genome-wide association studies in patients with vitiligo have identified a substantial number of associated genes, of which consistent association is seen with *DDR1, XBP1, NLRP1, PTPN22,* and *COMT* , although many other genes have been implicated.

Many authorities believe that the cause of melanocyte destruction in vitiligo is an endogenous cellular abnormality. It has been suggested that melanocytes are destroyed because of the accumulation of a toxic melanin synthesis intermediate and/or lack of protection from hydrogen peroxide and other oxygen radicals. There is in vitro evidence that some of these metabolites may be lethal to melanocytes. Others believe that neurochemical factors damage melanocytes and cause **depigmentation** . This possibility would explain the pattern of involvement in segmental vitiligo that runs roughly along the course of a dermatome.

Clinical Manifestations

There are two subtypes of vitiligo, generalized (nonsegmental) and segmental, which probably are distinctly different diseases (Table 672.2). Generalized vitiligo (85–90% of cases) may be divided into widespread (type A) and localized (type B). Approximately 50% of all patients with vitiligo have onset before 18 yr of age, and 25% demonstrate depigmentation before age 8 yr. Most children have the generalized form, but the segmental type is more common among children than among adults. Patients with the generalized form usually present with a remarkably symmetric pattern of white macules and patches (Fig. 672.4); the margins may be somewhat hyperpigmented. The patches tend to be acral and/or periorificial. Occasionally, almost the entire skin surface becomes depigmented. Vitiligo lesions may develop in areas of traumatized skin (Koebner phenomenon) (Fig. 672.5).

Table 672.2

Vitiligo Subgroups

DERMATOMAL OR SEGMENTAL	NONDERMATOMAL OR NONSEGMENTAL
Onset in childhood	Can begin in childhood; 50% before 20 yr
Less common	More common
Rapid onset; stabilizes in ~ 1 yr	Progressive, with flare-ups; life long
Involves hair following onset	Involves hair in later stages
Autoimmune diseases uncommon	Personal or family history of autoimmunity* common
Often occurs in the face	Occurs at sites sensitive to pressure, friction or trauma; Koebner phenomenon
Responsive to autologous grafting, with repigmentation	Relapses after autologous grafting
Difficult to distinguish from nevus depigmentosus	Associated halo nervus

* Autoimmune thyroid diseases, type 1 diabetes, psoriasis, pernicious anemia, systemic lupus erythematosus, Addison disease, alopecia areata.

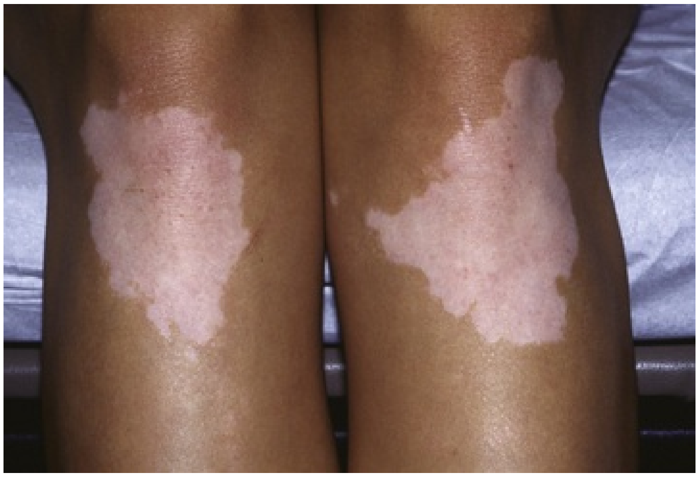

FIG. 672.4 Sharply demarcated, symmetric, depigmented areas of vitiligo.

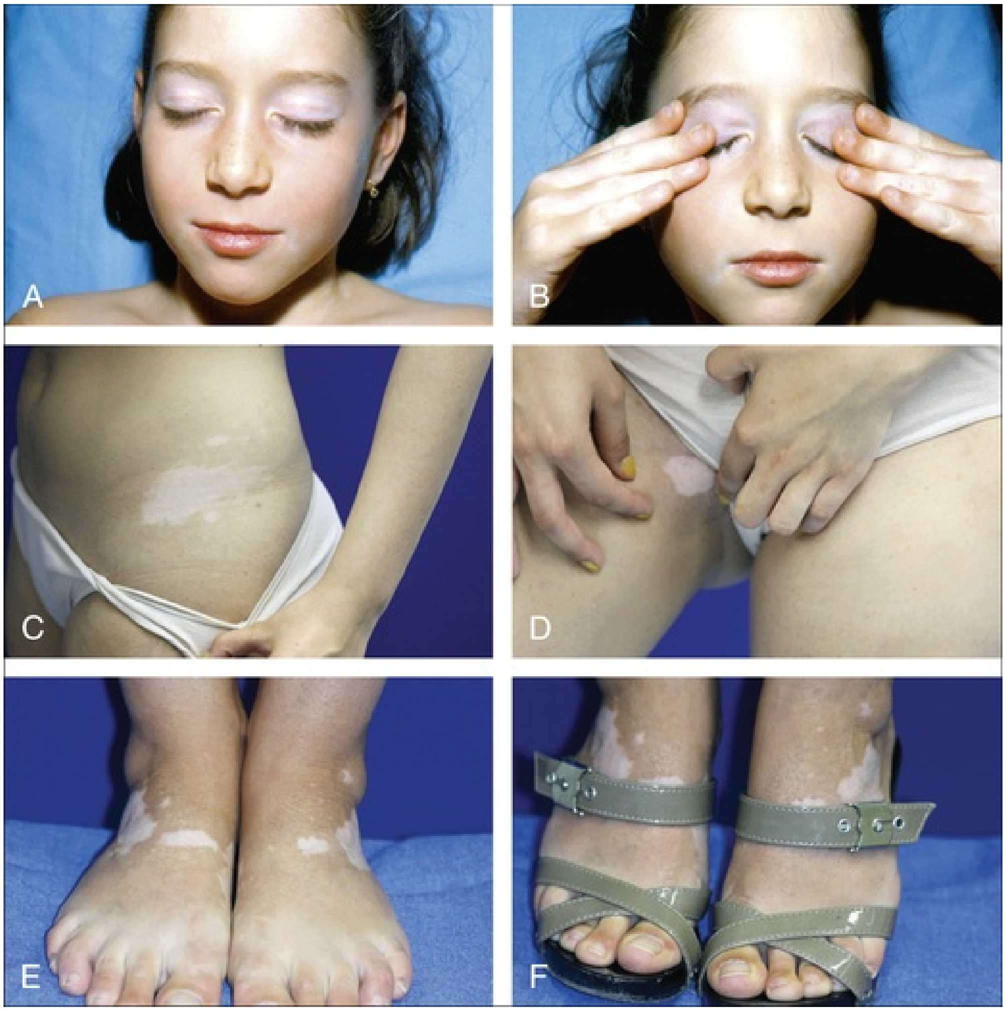

FIG. 672.5 Koebner phenomenon in relation to daily living activities **A** and **B,** Eye rubbing. **C** and **D,** Underwear print. **E** and **F,** Shoe print. (From Ezzedine K, Eleftheriadou V, Whitton M, van Geel N: Vitilgo. *Lancet* 386:74–82, 2015. Fig. 5, p. 79).

There are several varieties of localized vitiligo. A form of localized vitiligo is the halo nevus phenomenon, whereby benign moles develop depigmented rings at the periphery. Premature graying of scalp hair (canities) has also been considered a form of localized vitiligo. In segmental vitiligo, depigmented areas are limited to a quasidermatomal distribution. This type of vitiligo has a rapid onset and progression in a localized area without the development of depigmentation in other areas.

A number of **autoimmune diseases** occur in up to 20% of patients with vitiligo, including Addison disease, Hashimoto thyroiditis, pernicious anemia, diabetes mellitus, hypoparathyroidism, and polyglandular autoimmune syndrome with selective immunoglobulin A deficiency. In addition, other diseases with possible immune defects, such as alopecia areata and morphea, have been seen in patients with vitiligo.

Vogt-Koyanagi-Harada syndrome is vitiligo associated with uveitis, dysacusia, meningoencephalitis, and depigmentation of the skin, scalp hair, eyebrows, and eyelashes. In **Alezzandrini syndrome** , vitiligo is associated with tapetoretinal degeneration and deafness.

Light microscopic examination of early lesions shows mild inflammatory change. Over time, degenerative changes occur in melanocytes, leading to their complete disappearance.

The differential diagnosis of vitiligo includes other causes of widespread acquired leukoderma. The two most common problem diagnoses are tinea versicolor and postinflammatory hypopigmentation.

Treatment

Localized areas of vitiligo may respond to potent topical steroid, topical tacrolimus, or topical pimecrolimus. In patients with more extensive involvement, narrow-band ultraviolet light B (UVB) [UVB311] is the treatment of choice. Systemic therapy and whole body depigmentation is rarely used in children. In all forms of vitiligo, response to therapy is slow, taking many months to years. For those not interested in treatment, cover-up cosmetics may be used. All areas of vitiligo are susceptible to sun damage, and care should be taken to minimize sun exposure of affected areas. Spontaneous remission may be seen in a small percentage of cases.

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CHAPTER 673

Vesiculobullous Disorders

Joel C. Joyce

Many diseases are characterized by vesiculobullous lesions; they vary considerably in cause, age of onset, and pattern. The morphology and distribution of the blister often provides a visual clue to the location of the lesion within the skin. Blisters localized to the **epidermal layers** are thin-walled, relatively flaccid, and easily ruptured. **Subepidermal blisters** are tense, thick-walled, and more durable. Biopsies of blisters can be diagnostic because the level of cleavage within the skin and associated findings, such as the nature of the inflammatory infiltrate, are characteristic for a particular disorder. Other diagnostic procedures, such as immunofluorescence and electron microscopy, can often help to distinguish vesiculobullous disorders that have nearly identical histopathologic findings (Table 673.1).

Table 673.1

Sites of Blister Formation and Diagnostic Studies for the Vesiculobullous Disorders

DISORDER	BLISTER CLEAVAGE SITE	DIAGNOSTIC STUDIES
Acrodermatitis enteropathica	IE	Zn level
Bullous impetigo	GL	Smear, culture
Bullous pemphigoid	SE (junctional)	Direct and indirect immunofluorescence studies
Candidosis	SC	KOH preparation, culture
Dermatitis herpetiformis	SE	Direct immunofluorescence studies
Dermatophytosis	IE	KOH preparation, culture
Dyshidrotic eczema	IE	Routine histopathology
EB—simplex	IE	Electron microscopy; immunofluorescence mapping; genetic testing
EB of the hands and feet	IE	Electron microscopy; immunofluorescence mapping; genetic testing

Junctional EB (lethalis)	SE (junctional)	Electron microscopy; immunofluorescence mapping; genetic testing
Recessive dystrophic EB	SE	Electron microscopy; immunofluorescence mapping; genetic testing
Dominant dystrophic EB	SE	Electron microscopy; immunofluorescence mapping; genetic testing
Epidermolytic hyperkeratosis	IE	Routine histopathology
Erythema multiforme	SE	Routine histopathology
Erythema toxicum	SC, IE	Smear for eosinophils
Incontinentia pigmenti	IE	Smear for eosinophils Routine histopathology
Insect bites	IE	Routine histopathology
Kindler syndrome	IE, SE	Electron microscopy; immunostaining; genetic testing
Linear immunoglobulin A dermatosis	SE	Direct immunofluorescence studies
Mastocytosis	SE	Routine histopathology
Miliaria crystallina	IC	Routine histopathology
Neonatal pustular melanosis	SC, IE	Smear for cells
Pemphigus foliaceus	GL	Viral PCR or direct and indirect immunofluorescence studies
		Tzanck smear
Pemphigus vulgaris	Suprabasal	Viral PCR or direct and indirect immunofluorescence studies
		Tzanck smear
Scabies	IE	Scraping
Staphylococcal scalded skin syndrome	GL	Routine histopathology
Toxic epidermal necrolysis	SE	Routine histopathology
Viral blisters	IE	Viral PCR (preferred) or direct immunofluorescence testing for HSV and VZV Culture Routine histopathology

EB , Epidermolysis bullosa; *GL* , granular layer; *HSV* , herpes simplex virus; *IC* , intracorneal; *IE* , intraepidermal; *KOH* , potassium hydroxide; *PCR* , polymerase chain reaction; *SC* , subcorneal; *SE* , subepidermal; *VZV* , varicella-zoster virus.

673.1

Erythema Multiforme

Joel C. Joyce

Keywords

erythema multiforme
herpes simplex
Mycoplasma pneumoniae
targetoid

Etiology

Among the numerous factors implicated in the etiology of erythema multiforme (EM), infection with herpes simplex virus (HSV) is the most common. Infection with *Mycoplasma pneumoniae* is implicated, particularly in children and young adults, but differentiation from Stevens-Johnson syndrome and the *M. pneumoniae* –associated mucositis (see later) can be confusing. HSV labialis and, less commonly, HSV genitalis are implicated in 60–70% of episodes of EM and are believed to trigger nearly all episodes of recurrent (>6 episodes/yr) EM, frequently in association with sun exposure. HSV antigens and DNA are present in skin lesions of EM but are absent in nonlesional skin. The presence of the human leukocyte antigens A33, B62, B35, DQw3 (DQB1*0301 split), and DR53 is associated with an increased risk of HSV-induced EM, particularly the recurrent form. Most patients experience a single self-limited episode of EM. Lesions of HSV-induced recurrent EM typically develop 10-14 days after onset of recurrent HSV eruptions, have a similar appearance from episode to episode, but may vary in frequency and duration in a given patient. Not all episodes of recurrent HSV evolve into EM in susceptible patients.

Drug-related EM is less common (<10% of patients) and may be associated with nonsteroidal antiinflammatory agents, including acetaminophen, sulfonamides, and other antibiotics. The differential diagnosis in drug-related EM should include toxic epidermal necrolysis and drug hypersensitivity syndrome.

Clinical Manifestations

EM has numerous morphologic manifestations on the skin, varying from erythematous macules, papules, vesicles, bullae, or urticaria-appearing plaques to patches of confluent erythema. The eruption appears most commonly in patients between the ages of 10 and 40 yr (with highest incidence in males in the 2nd decade) and usually is asymptomatic, although a burning sensation or pruritus may be present. The diagnosis of EM is established by finding the classic lesion: doughnut-shaped, target-like (iris or bull's-eye) papules with an erythematous outer border, an inner pale ring, and a dusky purple to necrotic center (which sometimes blisters and erodes; Figs. 673.1 and 673.2).

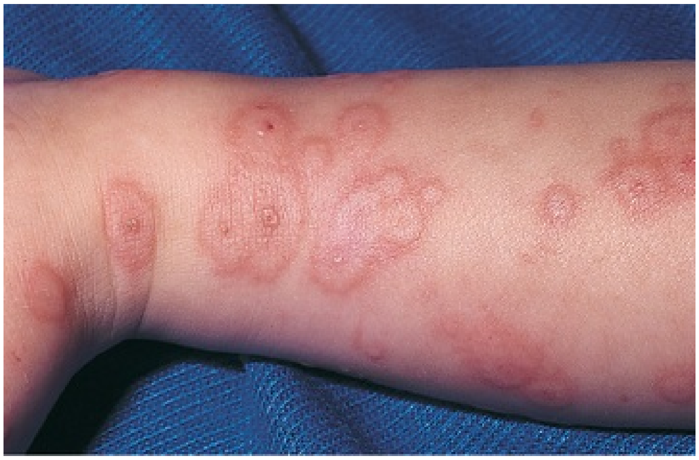

FIG. 673.1 Early fixed papules with a central dusky zone on the dorsum of the hand of a child with erythema multiforme caused by herpes simplex virus. (From Weston WL, Lane AT, Morelli J: Color textbook of pediatric dermatology, ed 3, St. Louis, 2002, Mosby, p. 156.)

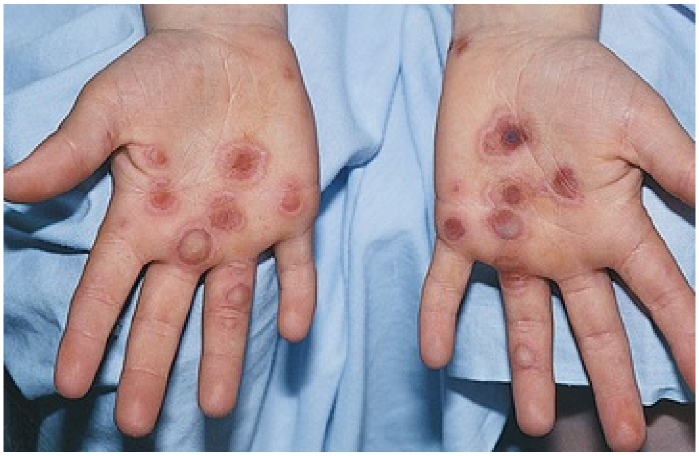

FIG. 673.2 “Target” or “iris” lesions with characteristic central dusky zone on palms of a child with erythema multiforme caused by herpes simplex

virus. (From Weston WL, Lane AT, Morelli J: Color textbook of pediatric dermatology, ed 3, St. Louis, 2002, Mosby, p. 156.)

EM is characterized by an abrupt, symmetric cutaneous eruption, most commonly on the extensor upper extremities; lesions are relatively sparse on the face, trunk, and legs. Lesions can be seen on the palms and soles. The eruption often appears initially as red macules or urticarial plaques that expand centrifugally to form lesions up to 2 cm in diameter with a dusky to necrotic center. Lesions of a particular episode typically appear within 72 hr and remain fixed in place (average duration: 7 days). Oral lesions may occur with a predilection for the vermilion border of the lips and the buccal mucosa, but other mucosal surfaces are spared. EM may manifest initially as urticarial-like lesions, but in distinction to urticaria, a given lesion of EM does not fade within 24 hr. Prodromal symptoms are generally absent. Prognosis is favorable with limited long-term morbidity. Lesions typically resolve without sequelae in approximately 2 wk, but in darker pigmented individuals, pigmentary alterations at the site of lesions can be long-standing. *Progression to Stevens-Johnson syndrome does not occur.* Many authors distinguish between **EM minor** (mainly cutaneous typical or atypical targetoid lesions affecting <10% body surface area plus no or limited mucosal involvement, often limited to 1 site, such as the mouth) from **EM major** (same cutaneous involvement pattern as EM minor plus 2 or more mucosal sites with more-severe oral involvement). EM major and Stevens-Johnson syndrome are separate entities.

Pathogenesis

The pathogenesis of EM is unclear, but it may be a host-specific, cell-mediated immune response to an antigenic stimulus, resulting in damage to keratinocytes. HSV *Pol1* gene expressed in HSV-induced recurrent EM lesions upregulates/activates the transcription factor SP1 and inflammatory cytokines. These cytokines, released by activated mononuclear cells and keratinocytes, may contribute to epidermal cell death and constitutional symptoms.

Pathology

Microscopic findings in EM are variable but may aid in diagnosis. Early lesions typically show slight intercellular edema, rare dyskeratotic keratinocytes, and basal vacuolation in the epidermis and a perivascular lymphohistiocytic infiltrate with edema in the upper dermis. More mature lesions show an accentuation of these characteristics and the development of lymphocytic exocytosis and an intense, perivascular, and interstitial mononuclear infiltrate in the upper third of the dermis. In severe cases, the entire epidermis becomes necrotic.

Differential Diagnosis

The differential diagnosis of EM also includes bullous pemphigoid (BP), pemphigus, linear immunoglobulin (Ig) A dermatosis, graft-versus-host disease, fixed-drug eruption, bullous-drug eruption, urticaria, viral infections such as HSV, reactive arthritis syndromes, Kawasaki disease, Sweet syndrome, Behçet disease, allergic vasculitis, erythema annulare centrifugum, polymorphous-drug eruption, and periarteritis nodosa. EM that primarily involves the oral mucosa may be confused with Stevens-Johnson syndrome, BP, pemphigus vulgaris (PV), vesiculobullous or erosive lichen planus, Behçet syndrome, recurrent aphthous stomatitis, and primary herpetic gingivostomatitis. In contrast to EM, Stevens-Johnson syndrome manifests with erythematous or purpuric macules (no papules) and usually begins on the trunk. Serum sickness–like reaction to cefaclor (or other antibiotics) may also manifest as EM-like lesions; the lesions may develop a dusky to purple center, but in most cases, the eruption of cefaclor-induced serum sickness–like reaction is pruritic, transient, and migratory and is probably urticarial rather than true EM.

Treatment

Treatment of EM is supportive. Topical emollients, systemic antihistamines, and nonsteroidal antiinflammatory agents do not alter the course of the disease but may provide symptomatic relief. For individuals with severe mucosal disease, opioids can be used to control pain and diligent oral hygiene is essential. No controlled, prospective studies support the use of corticosteroids in the management of EM. Prophylactic oral acyclovir given for 6 mo may be effective in controlling *recurrent episodes of HSV-associated EM* . On discontinuation of acyclovir, both HSV and EM may recur, although episodes may be less frequent and milder. For recurrent cases not responsive to antiviral therapy, steroid-sparing agents used to decrease frequency of recurrence include azathioprine, mycophenolate mofetil, and dapsone. Appropriate laboratory monitoring is recommended.

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673.2

Stevens-Johnson Syndrome

Joel C. Joyce

Keywords

Stevens-Johnson syndrome
blistering disorder
drug rash

Etiology

Drugs, particularly sulfonamides, nonsteroidal antiinflammatory agents, antibiotics, and anticonvulsants, are the most common precipitants of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS and TEN exist along a spectrum: SJS is defined as affected body surface area <10%, SJS-TEN overlap syndrome is affected body surface area between 10% and 30%, and TEN is affected body surface area >30%. **TEN** is the most severe disorder in the clinical spectrum of the disease, involving considerable constitutional toxicity and extensive necrolysis of the mucous membranes and >30% of the body surface area. Approximately 80% of cases are classified as SJS. In children in the United States, the risk of death is 0.3–1.5%. Human leukocyte antigen (HLA)-B*1502 and HLA-B*5801 are implicated in the development of these two disorders in Han Chinese patients receiving carbamazepine and in Japanese patients receiving allopurinol, respectively.

Infections, particularly in children, are also associated with SJS, although current thinking defines most cases of classic SJS as secondary to medications. Terms such as " ***M. pneumoniae* –associated mucositis** " or "**atypical SJS** " have caused difficulty with diagnosis and classification. Individuals, typically children or young adults, often with upper respiratory symptoms from *M. pneumoniae* infection, suffer from variable degrees of mucosal ulceration and erosion (typically mouth but including other mucosae), but lack other cutaneous involvement (unlike traditional SJS-TEN) and are found to have evidence of infection with *M. pneumoniae* , typically by polymerase chain reaction evaluation. In addition to the following supportive treatment, affected individuals benefit from antimicrobial treatment for *M. pneumoniae.* Morbidity is typically less severe than for SJS-TEN spectrum disease.

Clinical Manifestations

Cutaneous lesions in SJS generally consist initially of erythematous macules that rapidly and variably develop central necrosis to form vesicles, bullae, and areas of denudation on the face, trunk, and extremities. The skin lesions are typically more widespread than in EM and are accompanied by involvement of 2 **or more mucosal surfaces,** namely the eyes, oral cavity, upper airway or esophagus, gastrointestinal tract, or anogenital mucosa (Fig. 673.3). A burning sensation, edema, and erythema of the lips and buccal mucosa are often the presenting signs, followed by development of bullae, ulceration, and hemorrhagic crusting. Lesions may be preceded by a flulike upper respiratory illness. Pain from mucosal ulceration is often severe, but skin tenderness is minimal to absent in SJS, in contrast to pain in TEN. Corneal ulceration, anterior uveitis, panophthalmitis, bronchitis, pneumonitis, myocarditis, hepatitis, enterocolitis, polyarthritis, hematuria, and acute tubular necrosis leading to renal failure may occur. Disseminated cutaneous bullae and erosions may result in increased insensible fluid loss and a high risk of bacterial superinfection and sepsis. New lesions occur in crops, and complete healing may take 4-6 wk; ocular scarring, visual impairment, and strictures of the esophagus, bronchi, vagina, urethra, or anus may remain. Nonspecific laboratory abnormalities in SJS include leukocytosis, elevated erythrocyte sedimentation rate, and, occasionally, increased liver transaminase levels and decreased serum albumin values.

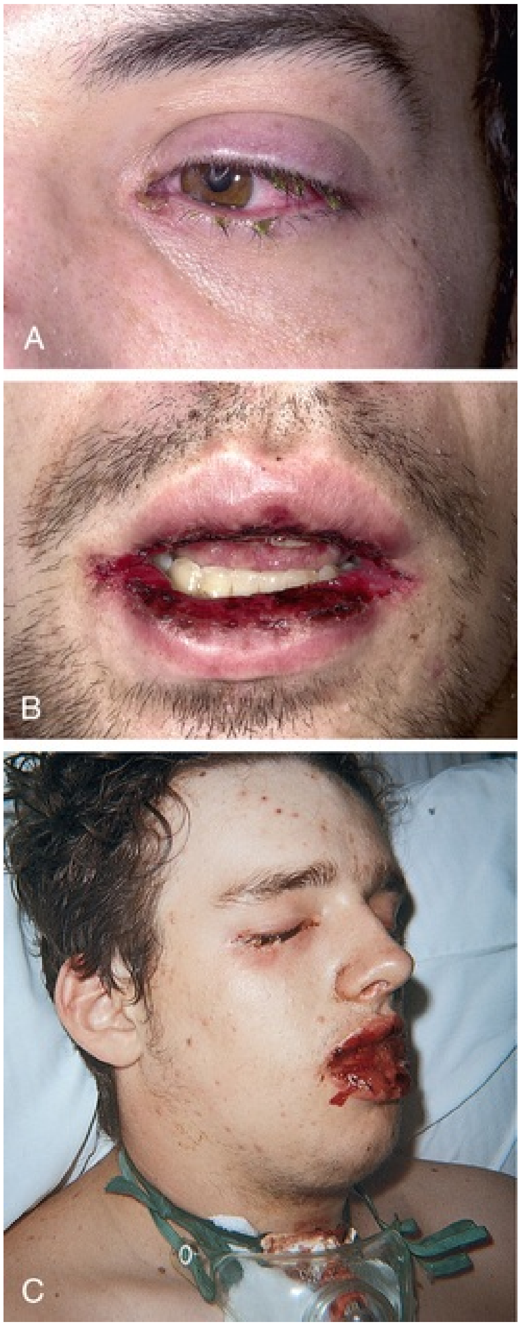

FIG. 673.3 Bullae are present on the conjunctivae (**A**) and in the mouth (**B**) with Stevens-Johnson syndrome. **C,** Sloughing, ulceration, and necrosis in the oral cavity interfere with eating. Genital lesions cause dysuria and interfere with voiding. (From Habif TP, editor: Clinical dermatology, ed 4, Philadelphia, 2004, Mosby, p. 631.)

Pathogenesis

Pathogenesis is related to drug-specific $CD8^+$ cytotoxic T cells, with perforin/granzyme B and granulysin triggering keratinocyte apoptosis. This process is followed by expanded enactment of apoptosis involving the interaction of soluble Fas ligand with Fas receptor. Consideration has been given to the role that macrophages/monocytes play in development of SJS/TEN via tumor necrosis factor-α, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), and tumor necrosis factor–inducer of apoptosis weak (TWEAK) signaling pathways. It is likely that many affected individuals have yet unrecognized underlying genetic predispositions.

Differential Diagnosis

The differential diagnosis of SJS includes TEN, urticaria, *M. pneumoniae*–associated mucositis, drug rash (or reaction) with eosinophilia and systemic symptoms (DRESS) syndrome (see Chapter 664.2) and other drug eruptions and viral exanthems, including Kawasaki disease. SJS has rarely been reported in patients with systemic lupus erythematosus.

Treatment

Management of SJS is supportive and symptomatic. Potentially offending drugs must be discontinued as soon as possible. Ophthalmologic consultation is mandatory because ocular sequelae such as corneal scarring can lead to vision loss. Application of cryopreserved amniotic membrane to the ocular surface during the acute phase of the disease limits the destructive and long-term sequelae. Early topical steroid treatment may also reduce ocular sequelae. Oral lesions should be managed with mouthwashes and glycerin swabs. Vaginal lesions should be observed closely and treated to prevent vaginal stricture or fusion. Topical (oral) anesthetics (diphenhydramine, dyclonine, viscous lidocaine) may provide relief from pain, particularly when applied before eating. Denuded skin lesions can be cleansed with saline or Burrow solution compresses. Treatment may require admission to an intensive care unit; IV fluids; nutritional support; sheepskin or air-fluid bedding; daily saline or Burrow solution compresses; paraffin gauze or colloidal gel (Hydrogel) dressing of denuded areas; saline compresses on the eyelids, lips, or nose; analgesics; and urinary catheterization (when needed). A daily examination for infection and ocular lesions, which constitute the major cause of long-term morbidity, is essential. Systemic antibiotics are indicated for documented urinary or cutaneous infections and for suspected bacteremia (*Staphylococcus aureus* or *Pseudomonas aeruginosa*) because infection is the leading cause of death. Prophylactic systemic antibiotics are not necessary. Although corticosteroids are sometimes advocated in early, severe cases of SJS, no prospective double-blind studies evaluating their efficacy have been reported. Most authorities discourage their use because of reports of increased morbidity and mortality (sepsis) with their administration, although definitive trials in children are lacking. IV immunoglobulin (IVIG; 1.5-2.0 g/kg/day × 3 days) should be considered in early disease. Total dose >2 g/kg has shown improved but not statistically significant outcomes in children compared with adults. Other immunosuppressive treatment regimens have not demonstrated clear benefit or repeated success in multiple controlled studies.

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673.3

Toxic Epidermal Necrolysis

Joel C. Joyce

Keywords

Toxic epidermal necrolysis
blistering disorder
drug reaction

Epidemiology and Etiology

The pathogenesis of TEN is not proved but may involve a hypersensitivity phenomenon that results in damage primarily to the basal cell layer of the epidermis. Epidermal damage appears to result from keratinocyte apoptosis. This condition is triggered by many of the same factors that are thought to be responsible for SJS (see Chapter 673.2), principally drugs such as the sulfonamides, amoxicillin, phenobarbital, hydantoin, and allopurinol. TEN is defined by (1) widespread blister formation and morbilliform or confluent erythema, associated with skin tenderness; (2) absence of target lesions; (3) sudden onset and generalization within 24-48 hr; (4) histologic findings of full-thickness epidermal necrosis and a minimal-to-absent dermal infiltrate. These criteria categorize TEN as a separate entity from EM.

Clinical Manifestations

The prodrome consists of fever, malaise, localized skin tenderness, and diffuse erythema. Inflammation of the eyelids, conjunctivae, mouth, and genitals may precede skin lesions. Flaccid bullae may develop, although this is not a prominent feature. Characteristically, full-thickness epidermis is lost in large sheets (Fig. 673.4). The **Nikolsky sign** (denudation of the skin with gentle tangential pressure) is present but only in the areas of erythema (see Fig. 673.4). Healing takes place over 14 or more days. Scarring, particularly of the eyes, may result in corneal opacity. The course may be relentlessly progressive, complicated by severe dehydration, electrolyte imbalance, shock, and secondary localized infection and septicemia. Loss of nails and hair may also occur. Long-term morbidity includes alterations in skin pigmentation, eye problems (lack of tears, conjunctival scarring, loss of lashes), and strictures of mucosal surfaces. The differential diagnosis includes staphylococcal scalded skin syndrome, in which the blister cleavage plane is intraepidermal; graft-versus-host disease; chemical burns; drug eruptions; toxic shock syndrome; and pemphigus. The use of skin histopathology to differentiate SJS-TEN from other similar blistering disorders can be difficult, but early full-thickness epidermal necrosis tends to portend a worse clinical prognosis.

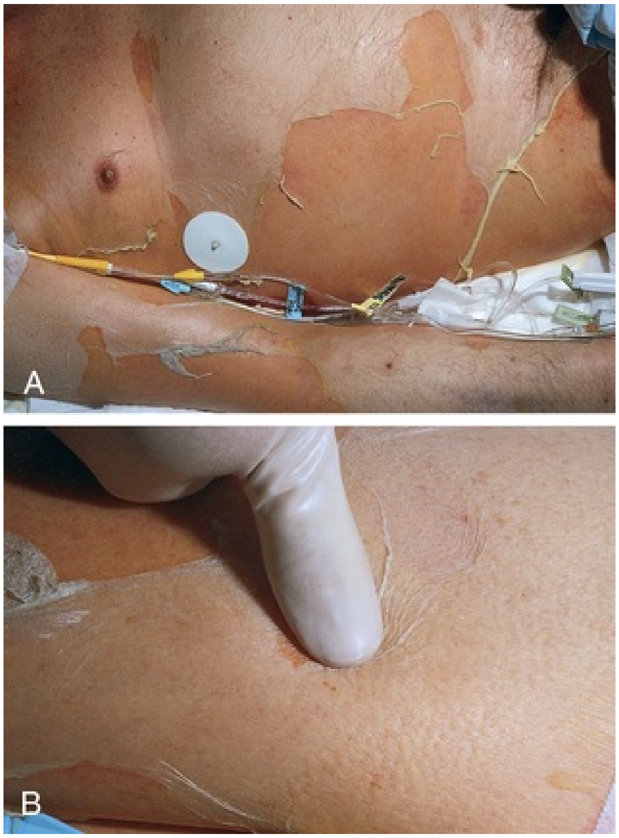

FIG. 673.4 **A,** Large sheets of full-thickness epidermis are shed. **B,** Toxic epidermal necrolysis begins with diffuse, hot erythema. In hours the skin becomes painful, and with slight thumb pressure, the skin wrinkles, slides laterally, and separates from the dermis (Nikolsky sign). (From Habif TP, editor: Clinical dermatology, ed 4, Philadelphia, 2004, Mosby, p. 633.)

Anticonvulsant hypersensitivity syndrome (DRESS syndrome; see Chapter 664.2) is a multisystem reaction that appears approximately 3 wk to 3 mo after the start of therapy with the offending agent. The skin eruption is red-pink morbilliform eruption often associated with facial swelling, lymphadenopathy, fever, hepatic, renal and pulmonary disease, eosinophilia, atypical lymphocytosis, and leukocytosis.

Treatment

Appreciation of the specific etiologic factor is crucial. Because most cases are drug-induced, cessation of the offending agent is critical as soon as possible. Management is similar to that for severe burns and may be best accomplished in a burn unit (see Chapter 92). It may include strict reverse isolation, meticulous fluid and electrolyte therapy, use of an air-fluid bed, and daily cultures. Systemic antibiotic therapy is indicated when secondary infection is evident or suspected. Skin care consists of cleansing with isotonic saline or Burrow solution. Biologic or colloid gel (Hydrogel) dressings alleviate pain and reduce fluid loss. Narcotics are often required for pain relief. Mouth and eye care, as for EM major and SJS, may be necessary. Because of an immune mechanism, systemic glucocorticosteroids and IVIG have been used with apparent success. Nonetheless, this treatment remains controversial although trends toward decreased morbidity and mortality in children receiving high-dose IVIG have been demonstrated (see Chapter 673.2). Case reports have shown efficacy of anti-TNF-α inhibitors in treating TEN in adults and effective use has been shown in children on a limited basis (infliximab 5 mg/kg IV dosed once, maximum 300 mg).

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673.4

Mechanobullous Disorders

Joel C. Joyce

Keywords

epidermolysis bullosa
epidermolysis bullosa simplex
junctional epidermolysis bullosa
dystrophic epidermolysis bullosa
Kindler syndrome
genetic disorder

Epidermolysis Bullosa

Diseases categorized under the general term epidermolysis bullosa (EB) are a heterogeneous group of congenital, genetic blistering disorders. They differ in severity and prognosis, clinical and histologic features, and inheritance patterns but are all characterized by induction of blisters by trauma and exacerbation of blistering in warm weather. The disorders can be categorized under three major headings with multiple subgroupings: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), and dystrophic epidermolysis bullosa (DEB) (Tables 673.2 –673.7). Recently, the decreasing cost and increasing availability of genetic testing has made prompt and accurate diagnosis of EB available to those beyond specialized centers that offer blister mapping and electron microscopy. **Kindler syndrome** , which includes poikiloderma and photosensitivity, as well as easy blistering, is also considered a separate form of EB. **Epidermolysis bullosa acquisita** is an autoimmune disorder producing antibodies to the α chain of type VII collagen. It is rare in children. It is often acquired secondary to other autoimmune diseases or malignancy but has rare congenital forms. Affected mothers may pass the autoantibody to the fetus resulting in similar but transient lesions in the newborn.

Table 673.2

Classification and Affected Genes in Epidermolysis Bullosa Simplex

TYPE	INHERITANCE	AFFECTED GENE
EBS, suprabasal, acantholytic	AR	*DSP* /desmoplakin
EBS, suprabasal, acantholytic	AR	*JUP* /plakoglobin

EBS, suprabasal, skin fragility—plakoglobin deficiency	AR	*JUP* /plakoglobin
EBS, suprabasal, skin fragility—woolly hair	AR	*DSP* /desmoplakin
EBS, suprabasal, skin fragility—ectodermal dysplasia	AR	*PKP1* /plakophilin-1
EBS, suprabasal, acral peeling skin syndrome	AR	*TGM5*
		Transglutaminase 5
EBS, suprabasal; EBS superficialis	AD or AR	?
EBS, basal, generalized severe (formerly Dowling-Meara)	Usually AD	*KRT5, KRT14* /keratins 5, 14
EBS, basal, generalized intermediate (formerly Koebner)	Usually AD	*KRT5, KRT14* /keratins 5, 14
EBS, basal, localized (formerly Weber-Cockayne)	Usually AD	*KRT5, KRT14* /keratins 5, 14
EBS, basal, with mottled pigmentation	AD	*KRT5* > *KRT14*
EBS, basal, migratory circinate	AD	*KRT5* , C-terminal
EBS, basal, Ogna type	AD	*PLEC1* /plectin
EBS, basal, with muscular dystrophy	AR	*PLEC1* /plectin
EBS, basal, with pyloric atresia	AR	*PLEC1* /plectin
EBS, basal, BP230	AR	*DST-e* /dystonin-e
EBS, basal, exophilin 5	AR	*EXPH5* /exophilin

AD, Autosomal dominant; *AR,* autosomal recessive; *EBS,* epidermolysis bullosa simplex.

From Paller AS, Mancini AJ, editors: Hurwitz clinical pediatric dermatology, ed 5, Philadelphia, 2016, Elsevier, Table 13.1, p. 318.

Epidermolysis Bullosa Simplex

EBS is a nonscarring, autosomal dominant or recessive disorder. The defect in *most common* types of EBS is in keratin 5 or 14, which makes up intermediate filaments of the basal keratinocytes (Table 673.3). The intraepidermal bullae result from cytolysis of the basal cells. There are multiple other rare variants with defects that also result in intraepidermal blistering (see Table 673.2).

Table 673.3

Characteristics of Major Forms of Epidermolysis Bullosa Simplex, Basal

TYPE	CLINICAL MANIFESTATIONS
EBS, localized (formerly Weber-Cockayne)	Easy blistering on palms and soles
	May be focal keratoderma of palms and soles in adults
	25% show oral mucosal erosions
	Rarely show reticulated pigmentation, especially on arms and trunk and punctate keratoderma (EBS with mottled pigmentation)
EBS, generalized, intermediate (formerly Koebner)	Generalized blistering
	Variable mucosal involvement
	Focal keratoderma of palms and soles
	Nail involvement in 20%
	Improves with advancing age
EBS, generalized, severe	Most severe in neonate, infant; improves beyond childhood

(formerly Dowling-Meara)	Large, generalized blisters; later, smaller (herpetiform) blisters
	Mucosal blistering, including esophageal
	Nails thickened, shed but regrow
	May have natal teeth
EBS with mottled pigmentation	Reticulated hyperpigmentation, especially on arms and trunk
	Punctate keratoses and keratoderma

EBS, Epidermolysis bullosa simplex.

From Paller AS, Mancini AJ, editors: Hurwitz clinical pediatric dermatology, ed 5, Philadelphia, 2016, Elsevier, Table 13.2, p. 319.

In **EBS–generalized other (formerly Koebner)** , blisters are usually present at birth or during the neonatal period. Sites of predilection are the hands, feet, elbows, knees, legs, and scalp. Intraoral lesions are minimal, nails rarely become dystrophic and usually regrow even when they are shed, and dentition is normal. Bullae heal with minimal to no scar or milia formation. Secondary infection is the primary complication. The propensity to blister decreases with age, and the long-term prognosis is good. Blisters should be drained by puncturing, but the blister top should be left intact to protect the underlying skin. Erosions may be covered with a semipermeable dressing. Diligent wound care and protection of areas subject to pressure is beneficial. Observation for infection is important and should be treated promptly.

EBS–localized (**formerly Weber-Cockayne**) predominantly affects the hands and feet and often manifests when a child begins to walk; onset may be delayed until puberty or early adulthood, when heavy shoes are worn or the feet are subjected to increased trauma. Bullae are usually restricted to the hands and feet (Fig. 673.5); rarely, they occur elsewhere, such as the dorsal aspect of the arms and the shins. The disorder ranges from mildly incapacitating to crippling at times of severe exacerbations. Treatment is similar to that described previously.

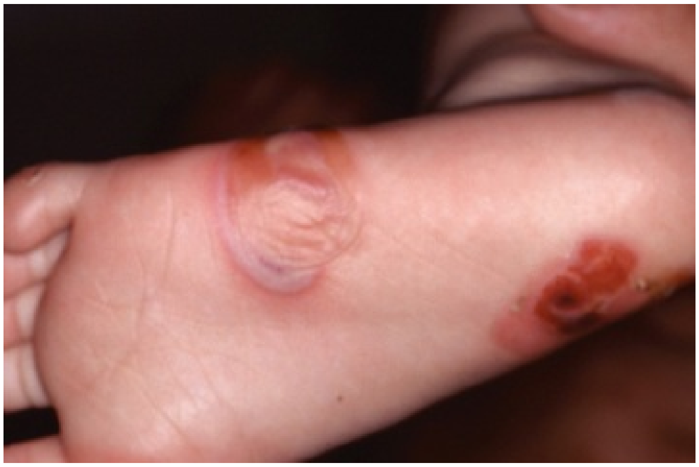

FIG. 673.5 Bullae of the feet in epidermolysis bullosa simplex–localized (Weber-Cockayne).

EBS–Dowling-Meara (herpetiformis) is characterized by grouped blisters resembling those of herpes simplex (Fig. 673.6). During infancy, blistering may be severe and extensive, may involve mucous membranes, and may result in shedding of nails, formation of milia, and mild pigmentary changes, without scarring. After the 1st few months of life, warm temperatures do not appear to exacerbate blistering. Hyperkeratosis and hyperhidrosis of the palms and soles may develop, but generally, the condition improves with age. Maintenance of nutritional status and treatment of infections is important, particularly in infancy. Day-to-day management may involve wound care techniques as described later.

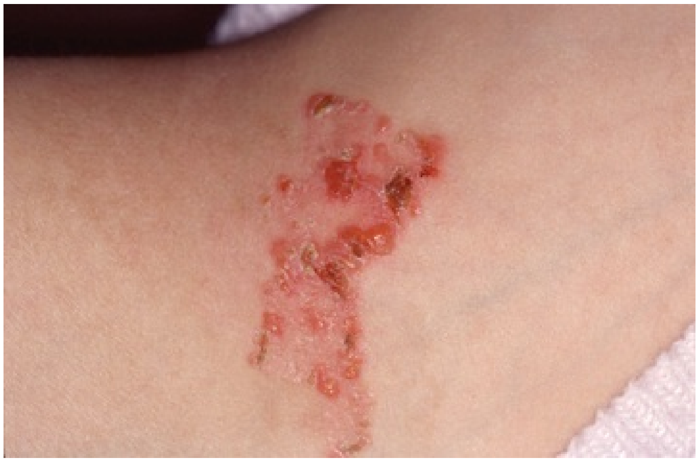

FIG. 673.6 Grouped vesicle on an erythematous base in epidermolysis bullosa simplex–Dowling-Meara.

Junctional Epidermolysis Bullosa

JEB–Herlitz is an autosomal recessive condition that is life threatening (Tables 673.4 and 673.5). Blisters appear at birth or develop during the neonatal period, particularly on the perioral area, scalp, legs, diaper area, and thorax. Nails eventually become dystrophic and then often permanently lost. Mucous membrane involvement may be severe, and ulceration of the respiratory, gastrointestinal, and genitourinary epithelium has been documented in many affected children, although less frequently than in severe recessive DEB. Healing is delayed, and vegetating granulomas may persist for a long time. Large, moist, erosive plaques (Fig. 673.7) may provide a portal of entry for bacteria, and septicemia is a frequent cause of death. Mild atrophy may be seen in areas of recurrent blistering. Defective dentition with early loss of teeth as a result of rampant caries is characteristic. Growth retardation and recalcitrant anemia are almost invariable. In addition to infection, cachexia and circulatory failure are common causes of death. Most patients die within the first 2-3 yr of life.

Table 673.4

Classification and Causes of Major Forms of Junctional Epidermolysis Bullosa

TYPE	INHERITANCE	GENE DEFECT
JEB, generalized severe (formerly Herlitz)	AR	*LAMA3, LAMB3, LAMC2/* laminin 332
JEB, generalized, intermediate (formerly non-Herlitz)	AR	Mild mutation: laminin 332
JEB, generalized, intermediate (formerly non-Herlitz)	AR	*COL17A1* /type XVII collagen
JEB, generalized with pyloric atresia	AR	*ITGA6, ITGB4* /integrin α6 or β4
JEB, generalized, late onset	AR	*COL17A1* /type XVII collagen
JEB, generalized, with respiratory and renal involvement	AR	*ITGA3/* integrin α3
JEB, localized	AR	*COL17A1* /type XVII collagen
		ITGA6, ITGB4 /integrin α6β4
		laminin 332
JEB with pyloric atresia	AR	*ITGA6, ITGB4* /integrin α6 or β4
JEB, localized, inversa	AR	*COL17A1* /type XVII collagen
LOC syndrome	AR	Laminin 332, α3 chain

AR, Autosomal recessive; *JEB,* junctional epidermolysis bullosa; *LOC,* laryngoonychocutaneous syndrome.

From Paller AS, Mancini AJ, editors: Hurwitz clinical pediatric dermatology, ed 5, Philadelphia, 2016, Elsevier, Table 13.3, p. 321.

Table 673.5

Characteristics of Major Forms of Junctional Epidermolysis Bullosa

TYPE	CLINICAL MANIFESTATIONS
JEB, generalized severe (formerly Herlitz)	50% of patients die by 2 yr old
	Blisters heal with atrophic scarring but no milia
	Periungual and fingerpad blistering, erythema
	Blistering of oral and esophageal mucosae
	Laryngeal and airway involvement with early hoarseness
	Later, perioral granulation tissue with sparing of lips
	Anonychia
	Dental enamel hypoplasia, excessive caries
	Growth retardation
	Anemia
JEB, generalized, intermediate (formerly non-Herlitz)	Less severe, but similar manifestations to Herlitz type, including dental, nail and laryngeal involvement
	Granulation tissue is rare
	Perinasal cicatrization
	Less mucosal involvement
	Alopecia
	Anemia but not as severe as JEB, generalized severe
JEB, localized	Localized blisters without residual scarring or granulation tissue
	Minimal mucosal involvement
	Dental and nail abnormalities as in JEB, generalized severe
JEB, generalized with pyloric atresia	Usually lethal in neonatal period
	Generalized blistering, leading to atrophic scarring
	May be born with large areas of cutis aplasia
	No granulation tissue
	Nail dystrophy or anonychia
	Pyloric atresia, genitourinary malformations
	Rudimentary ears
	Dental enamel hypoplasia (survivors)
	Variable anemia, growth retardation, mucosal blistering

JEB, Junctional epidermolysis bullosa.

From Paller AS, Mancini AJ, editors: Hurwitz clinical pediatric dermatology, ed 5, Philadelphia, 2016, Elsevier, Table 13.4, p. 321.

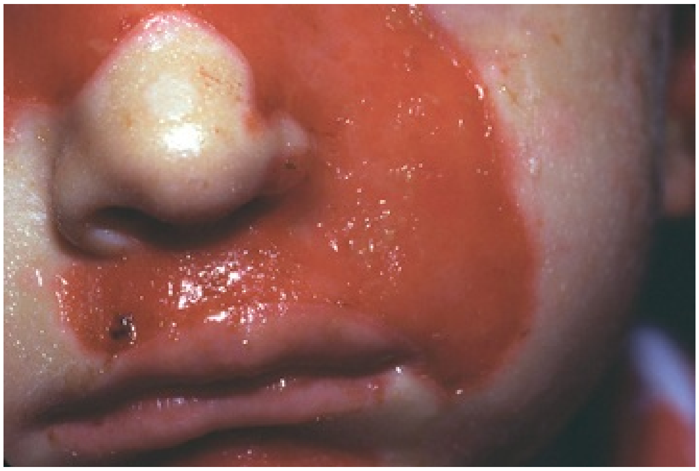

FIG. 673.7 Nonhealing granulation tissue in junctional epidermolysis bullosa.

JEB–non-Herlitz is a heterogeneous group of disorders. Blistering may be severe in the neonatal period, making differentiation from the Herlitz type difficult. All conditions associated with the Herlitz type may be seen but are usually milder. **JEB–non-Herlitz generalized (formerly generalized atrophic benign EB)** is included as a variant of non-Herlitz JEB. Another variant of non-Herlitz JEB is associated with pyloric atresia.

In all types of JEB, a subepidermal blister is found on light microscopic examination, and electron microscopy demonstrates a cleavage plane in the lamina lucida, between the plasma membranes of the basal cells and the basal lamina. Absence or a great reduction of hemidesmosomes is seen on electron micrographs in **JEB–Herlitz** and some cases of **JEB–non-Herlitz** . The defect is in laminin 332 (formerly laminin 5 or epiligrin), a glycoprotein associated with anchoring filaments beneath the hemidesmosomes. In JEB– non-Herlitz, defects have also been described in other hemidesmosomal components, such as type XVII collagen (BP180). In **JEB–pyloric atresia** , the defect is in the $\alpha_6 \beta_4$ integrin.

Treatment for JEB is supportive. The diet should provide adequate calories and *supplemental iron* . Infections should be treated promptly. Transfusions of packed red blood cells may be required if the patient shows no response to iron and erythropoietin therapy. Strict adherence to wound care regimens is essential. Current wound care regimens include highly specialized nonadherent bandages designed specifically for children with chronic skin fragility. Tissue-engineered skin grafts (artificial skin derived from human keratinocytes and fibroblasts) may be beneficial.

Dystrophic Epidermolysis Bullosa

All forms of DEB result from mutations in collagen VII, a major component of anchoring fibrils that tether the basement membrane and overlying epidermis to its dermal foundation (Tables 673.6 and 673.7). The blister is subepidermal in all types of DEB. The type and location of the mutation dictate the severity of the phenotype.

Table 673.6

Classification and Cause of Major Forms of Dystrophic Epidermolysis Bullosa

TYPE	**INHERITANCE**	**GENE DEFECT**
Dominant		
DDEB, generalized	AD	*COL7A1* /collagen VII
DDEB, rare types: acral, pretibial, pruriginosa, nails only, bullous dermolysis of newborn	AD	*COL7A1* /collagen VII
RDEB, generalized severe	AR	*COL7A1* /collagen VII
RDEB, generalized intermediate	AR	*COL7A1* /collagen VII
RDEB, inversa	AR	*COL7A1* /collagen VII
RDEB, rare types: localized, pretibial, pruriginosa, centripetalis, bullous dermolysis of the newborn	AR	*COL7A1* /collagen VII

AD, Autosomal dominant; *AR,* autosomal recessive; *DDEB* , dominant dystrophic epidermolysis bullosa; *RDEB,* recessive dystrophic epidermolysis bullosa.

From Paller AS, Mancini AJ, editors: Hurwitz clinical pediatric dermatology, ed 5, Philadelphia, 2016, Elsevier, Table 13.5, p. 323.

Table 673.7

Characteristics of Major Forms of Dystrophic Epidermolysis Bullosa

TYPE	**CLINICAL MANIFESTATIONS**
Dominant dystrophic	Onset at birth to early infancy
	Blistering predominates on dorsum of hands, elbows, knees, and lower legs
	Milia associated with scarring
	Some patients develop scarlike lesions, especially on the trunk
	80% have nail dystrophy
Recessive dystrophic, severe generalized	Present at birth
	Widespread blistering, scarring, milia

	Deformities: pseudosyndactyly, joint contractures
	Severe involvement of mucous membranes, nails; alopecia
	Growth retardation, poor nutrition
	Anemia
	Mottled, carious teeth
	Osteoporosis, delayed puberty, cardiomyopathy, glomerulonephritis, renal amyloidosis, IgA nephropathy
	Predisposition to squamous cell carcinoma in heavily scarred areas
Recessive dystrophic, generalized intermediate	Generalized blisters from birth with milia, scarring
	Less anemia, growth retardation, mucosal but more esophageal issues with advancing age

IgA, immunoglobulin A.

From Paller AS, Mancini AJ, editors: Hurwitz clinical pediatric dermatology, ed 5, Philadelphia, 2016, Elsevier, Table 13.6, p. 323.

Dominant DEB is the most common type of DEB. The spectrum of dominant DEB is varied. Blisters may be manifest at birth and are often limited and characteristically form over acral bony prominences. The lesions heal promptly, with the formation of soft, wrinkled scars, milia, and alterations in pigmentation (Fig. 673.8). Abnormal nails and nail loss are common. In many cases, the blistering process is mild, causing little restriction of activity and not impairing growth and development. Mucous membrane involvement tends to be minimal.

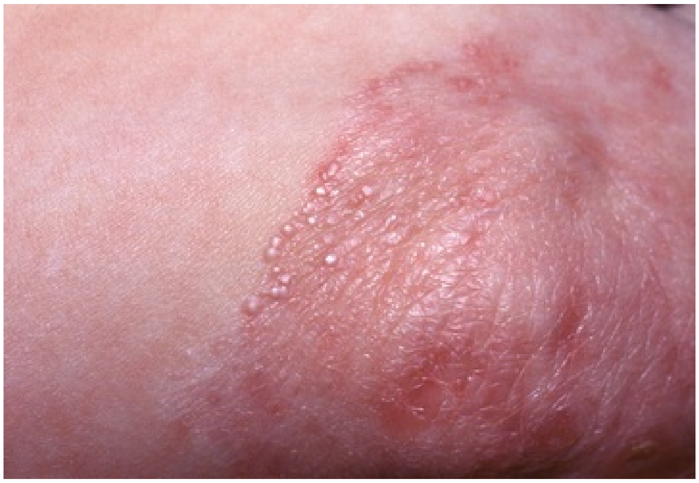

FIG. 673.8 Scarring with milia formation over the knee in dominant dystrophic epidermolysis bullosa.

Recessive DEB–severe generalized (formerly recessive DEB–Hallopeau-Siemens) is the most incapacitating form of EB, although the clinical spectrum is wide. Some patients have blisters, scarring, and milia formation primarily on the hands, feet, elbows, and knees (Fig. 673.9). Others have extensive erosions and blister formation at birth that seriously impede their care and feeding. Mucous membrane lesions are common and may cause severe nutritional deprivation, even in older children, whose growth may be retarded. During childhood, esophageal erosions and strictures, scarring of the buccal mucosa, flexion contractures of joints secondary to scarring of the integument, development of cutaneous squamous cell carcinomas, and the development of digital fusion may significantly limit the quality of life (Fig. 673.10). Squamous cell carcinomas and infection are major causes of morbidity and mortality.

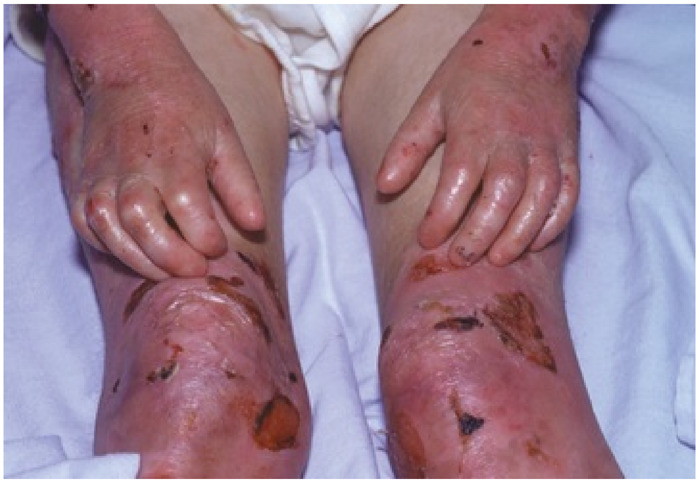

FIG. 673.9 Severe scarring of the hands and knees in recessive dystrophic epidermolysis bullosa.

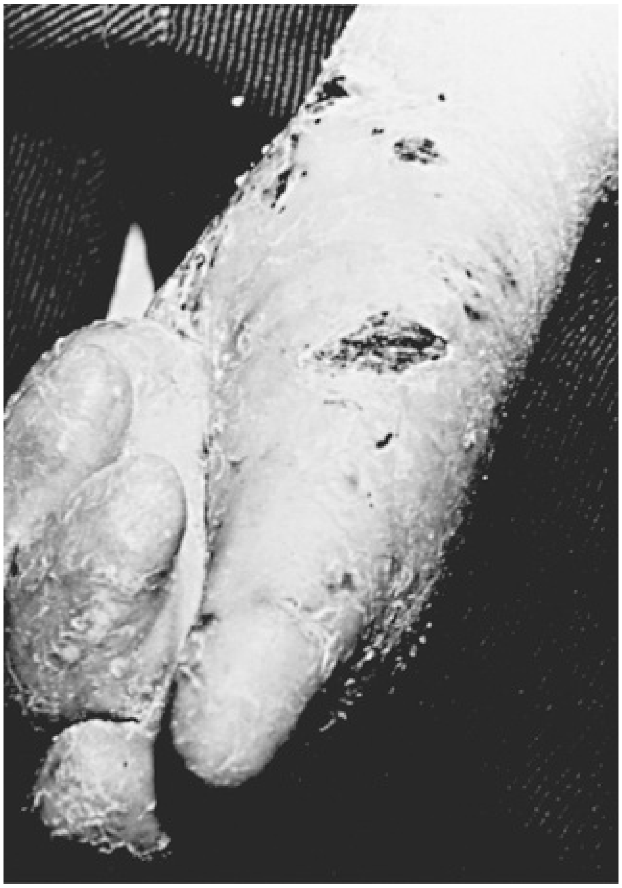

FIG. 673.10 Mitten-hand deformity of recessive dystrophic epidermolysis bullosa.

Although the skin becomes less sensitive to trauma with aging in patients with recessive DEB, the progressive and permanent deformities complicate management, and the overall prognosis is poor. *Foods that traumatize the buccal or esophageal mucosa should be avoided.* If esophageal scarring develops, a semiliquid diet and esophageal dilatations may be required. Stricture excision or colonic interposition may be needed to relieve esophageal obstruction. In infants, severe oropharyngeal involvement may necessitate the use of special feeding devices such as a gastrostomy tube. Iron therapy for anemia, intermittent antibiotic therapy for secondary infections, and periodic surgery for release of digits may reduce morbidity. Newer-generation wound care dressings, including nonstick dressings made from silicone, are a mainstay of treatment and the daily maintenance of the skin barrier to reduce new skin trauma and promote healing. Newer compounds for treating itch, reducing inflammation, and fighting infection, particularly with antimicrobial peptides, aid in promoting more effective wound healing when dressings are used, therefore reducing morbidity.

Beyond wound care and care of comorbid conditions in EB, a number of new technologies offer a wider array of practical and hypothetical treatment options for EB patients. Tissue-engineered skin grafts containing keratinocytes and fibroblasts are of some benefit. Skin grafts which have undergone gene-editing may show promise. Pluripotent stem cells, taken from areas of revertant mosaicism of a patient's own skin, provide personalized options for treatments for affected patients. Transdermal gene therapy with allogeneic fibroblasts and the delivery of functional collagens is being pursued, as are other forms of protein replacement therapy. Allogeneic bone marrow transplantation may also be beneficial as may the induction of pluripotent stem cells.

Kindler Syndrome

Kindler syndrome, often considered a distant subtype of EB, contains features of both EB, such as congenital blistering, and congenital poikilodermas, such as Rothmund-Thomson syndrome and Bloom syndrome (see Chapter 675), which include photosensitivity, congenital poikiloderma, and progressive cutaneous atrophy. Blisters tend to appear on acral sites in infancy or early childhood and are provoked by trauma. Photosensitivity can appear as increased susceptibility to sunburn. Both blistering and photosensitivity can improve greatly with advancing age, but poikilodermatous changes can be progressive. Sclerodermoid-like changes and nail abnormalities of the hands and feet, as well as dental abnormalities, have been reported.

Kindler syndrome is an autosomal recessive disorder caused by mutations in *KIND1* (also known as *FERMT1*), which encodes kindlin-1, a protein thought to regulate interactions between the extracellular matrix and actin filaments. Blister formation has been shown to occur within the epidermis, within the basement membrane zone, and below the basement membrane. Because Kindler syndrome is often confused with EB, at least initially, it can be confirmed by electron microscopy, immunostaining for anti-kindlin-1 antibodies within the skin, or mutation analysis of the *KIND1* gene.

Treatment is similar to that for EB, with efforts to reduce trauma to the skin, meticulous wound care, and treatment of skin infections. In addition, sun avoidance measures are beneficial because they can slow the rate of the development of poikiloderma.

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673.5

Pemphigus

Joel C. Joyce

Keywords

pemphigus
bullous pemphigoid
Nikolsky sign

Pemphigus Vulgaris

Etiology/Pathogenesis

PV is a rare autoimmune blistering disorder caused by circulating antibodies to desmoglein III that result in suprabasal cleaving with consequent blister formation. Desmoglein III is a 30-kDa glycoprotein that is complexed with plakoglobin, a plaque protein of desmosomes. The desmogleins are a subfamily of the cadherin family of cell adhesion molecules.

Clinical Manifestations

PV usually first appears as painful oral ulcers, which may be the only evidence of the disease for weeks or months. Subsequently, large, flaccid bullae emerge on nonerythematous skin, most commonly on the face, trunk, pressure points, groin, and axillae. The **Nikolsky sign** is present. The lesions rupture and enlarge peripherally, producing painful, raw, denuded areas that have little tendency to heal. When healing occurs, it is without scarring, but hyperpigmentation is common. Malodorous, verrucous, and granulomatous lesions may develop at sites of ruptured bullae, particularly in the skinfolds; as this pattern becomes more pronounced, the condition may be more properly referred to as *pemphigus vegetans* . Because the course may rapidly lead to debility, malnutrition, and death, prompt diagnosis is essential. **Neonatal PV** develops in utero as a result of placental transfer of maternal antidesmoglein antibodies from women who have active PV, although it may occur when the mother is in remission. High antepartum maternal titers of PV antibodies and increased maternal disease activity correlate with a poor fetal outcome, including demise.

Pathology

Biopsy of a fresh small blister reveals a suprabasal (intraepidermal) blister containing loose, acantholytic epidermal cells that have lost their intercellular bridges and thus their contact with one another. Immunofluorescence staining with an IgG antibody produces a characteristic pattern (“chicken wire”) on direct immunofluorescence preparations of both involved and uninvolved skin of essentially all patients. Serum IgG antibody titers to desmoglein correlate with the clinical course in many patients; thus serial determinations may have predictive value.

Differential Diagnosis

PV must be differentiated from EM, BP, SJS, and TEN.

Treatment

The disease is best treated initially with systemic methylprednisolone 1-2 mg/kg/day. Azathioprine, cyclophosphamide, mycophenolate mofetil, and methotrexate therapy all have been useful in maintenance regimens. IVIG given in cycles may be beneficial to patients whose disease does not respond to steroids. Rituximab with IVIG replacement has been effective in the management of severe pemphigus. Excellent control of the disease may be obtained, but relapse is common. It has been successfully used in children.

Pemphigus Foliaceus

Etiology/Pathogenesis

Pemphigus foliaceus is caused by circulating antibodies to a 50-kDa portion of the 160-kDa desmosomal glycoprotein desmoglein I, which result in subcorneal cleavage leading to superficial erosions. This extremely rare disorder is characterized by subcorneal blistering; the site of cleavage is high in the epidermis rather than suprabasal as in PV.

Clinical Manifestations

The superficial blisters rupture quickly, leaving erosions surrounded by erythema that heal with crusting and scaling (Fig. 673.11). The **Nikolsky sign** is present. Focal lesions are usually localized to the scalp, face, neck, and upper trunk. Mucous membrane lesions are minimal or absent. Pruritus, pain, and a burning sensation are frequent complaints. The clinical course varies but is generally more benign than that of PV. **Fogo selvagem (endemic pemphigus foliaceus),** which is endemic in certain areas of Brazil, is identical clinically, histopathologically, and immunologically to pemphigus foliaceus. Recently, it was shown that anti–desmoglein-1 antibodies in individuals with fogo selvagem cross react with sand fly (*Lutzomyia* sp.) salivary proteins, suggesting an environmental trigger for this autoimmune disease.

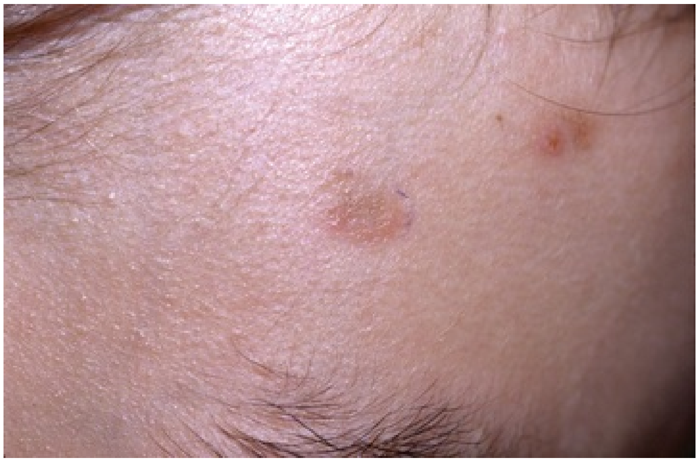

FIG. 673.11 Superficial erosions in pemphigus foliaceus.

Pathology

An intraepidermal acantholytic bulla high in the epidermis is diagnostic. It is imperative to select an early lesion for biopsy. Immunofluorescent staining with an IgG antibody reveals a characteristic intercellular staining pattern similar to that of PV but higher in the epidermis.

Differential Diagnosis

When generalized, the eruption may resemble exfoliative dermatitis or any of the chronic blistering disorders; localized erythematous plaques simulate seborrheic dermatitis, psoriasis, impetigo, eczema, and systemic lupus erythematosus.

For localized disease, superpotent topical corticosteroids used twice a day may be all that is needed for control until remission. For more generalized disease, long-term remission is usual after suppression of the disease by systemic methylprednisolone (1 mg/kg/day) therapy. Dapsone (25-100 mg/day) also may be used.

Bullous Pemphigoid

Etiology/Pathogenesis

BP is caused by circulating antigens to either the 180-kDa or 230-kDa BP antigen that result in a subepidermal blister. The 230-kDa protein (BP230) is part of the hemidesmosome, whereas the 180-kDa protein (BP180, now known as type XVII collagen) localizes to both the hemidesmosome and the upper lamina lucida and is a transmembrane collagenous protein.

Clinical Manifestations

The blisters of BP typically arise in crops on a normal, erythematous, eczematous, or urticarial base. Bullae appear predominantly on the flexural aspects of the extremities, in the axillae, and on the groin and central abdomen. Infants have involvement of the palms, soles, and face more frequently than older children do. Individual lesions vary greatly in size, are tense, and are filled with serous fluid that may become hemorrhagic or turbid. Oral lesions occur less frequently and are less severe than in PV. Pruritus, a burning sensation, and subcutaneous edema may accompany the eruption, but constitutional symptoms are not prominent.

Pathology

Biopsy material should be taken from an early bulla arising on an erythematous base. A subepidermal bulla and a dermal inflammatory infiltrate, predominantly of eosinophils, can be identified histopathologically. In sections of a blister or perilesional skin, a band of Ig (usually IgG) and C3 can be demonstrated in the basement membrane zone by direct immunofluorescence. Indirect immunofluorescence studies of serum have positive results in ≈70% of cases for IgG antibodies to the basement membrane zone; however, the titers do not correlate well with the clinical course.

Diagnosis and Differential Diagnoses

BP rarely occurs in children but must be considered in the differential diagnosis of any chronic blistering disorder. The differential diagnosis includes bullous EM, pemphigus, linear IgA dermatosis, bullous drug eruption, dermatitis herpetiformis (DH), herpes simplex infection, and bullous impetigo, which can be differentiated by histologic examination, immunofluorescence studies, and cultures. The large, tense bullae of BP can generally be distinguished from the smaller, flaccid bullae of PV.

Treatment

Localized BP can be successfully suppressed with superpotent topical corticosteroids twice a day. Generalized disease usually requires systemic methylprednisolone (1 mg/kg/day) therapy. Doxycycline has some benefits but is not as effective as prednisone. Rarely are other immunosuppressive treatments necessary, such as azathioprine or mycophenolate mofetil. Refractory cases have been treated with rituximab, but the condition usually remits within a year in most children.

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673.6

Dermatitis Herpetiformis

Joel C. Joyce

Keywords

dermatitis herpetiformis
celiac disease
gluten

Etiology/Pathogenesis

In DH, IgA antibodies are directed at epidermal transglutaminase (transglutaminase 3). **Gluten-sensitive enteropathy (celiac disease)** is found in all patients with DH, although the majority are asymptomatic or have minimal gastrointestinal symptoms (see Chapter 364.2). The severity of the skin disease and the responsiveness to gluten restriction do not correlate with the severity of the intestinal inflammation. An antibody to smooth muscle endomysium is found in 70–90% of patients with DH. Ninety percent of patients with the disease express HLA-DQ2. HLA-DQ2–negative patients with DH usually express HLA-DQ8.

Clinical Manifestations

DH is characterized by symmetric, grouped, small, tense, erythematous, stinging, intensely pruritic papules and vesicles. The eruption is pleomorphic, including erythematous, urticarial, papular, vesicular, and bullous lesions. Sites of predilection are the knees, elbows, shoulders, buttocks, forehead, and scalp; mucous membranes are usually spared. Hemorrhagic lesions may develop on the palms and soles. When pruritus is severe, excoriations may be the only visible sign (Fig. 673.12).

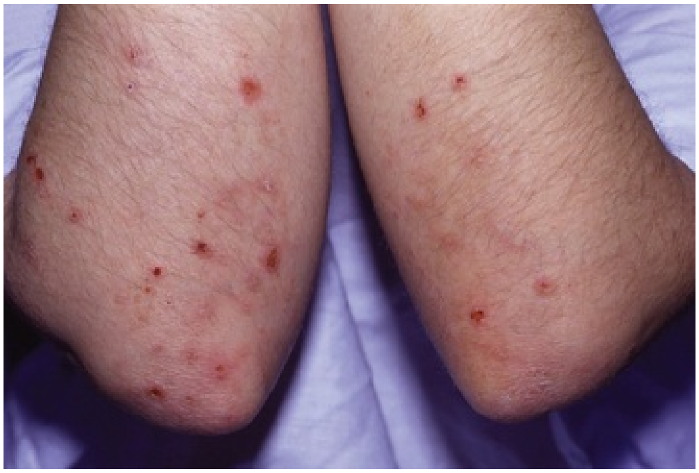

FIG. 673.12 Multiple excoriations around the elbows in dermatitis herpetiformis.

Pathology

Subepidermal blisters composed predominantly of neutrophils are found in dermal papillae. The presence of granular IgA on direct immunofluorescence in the dermal papillary tips is diagnostic.

Differential Diagnosis

DH may mimic other chronic blistering diseases and may also resemble scabies, papular urticaria, insect bites, contact dermatitis, and papular eczema.

Treatment

Patients with DH show response within weeks to months to a gluten-free diet. Oral administration of dapsone (0.5-2.0 mg/kg/day divided qd or bid, maximum initial dose in adults is 50 mg/day with increased doses to achieve control up to 300 mg/dose) provides immediate relief from the intense pruritus but must be used with caution because of possible serious side effects (methemoglobinemia, hemolysis, and hypersensitivity syndrome [sulfone syndrome]). Dapsone alone may not relieve the intestinal inflammation of celiac disease. Local antipruritic measures may also be useful. Jejunal biopsy is indicated to diagnose gluten-sensitive enteropathy because cutaneous manifestations may precede malabsorption. The disease is chronic and either a gluten-free diet or dapsone must be continued indefinitely to prevent relapse.

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673.7

Linear Immunoglobulin A Dermatosis (Chronic Bullous Dermatosis of Childhood)

Joel C. Joyce

Keywords

linear IgA dermatosis
chronic bullous dermatosis of childhood

Etiology/Pathogenesis

Linear IgA dermatosis is a heterogeneous autoimmune disorder with antibodies targeting multiple antigens. It has been reported to be the most common autoimmune blistering disorder in children. It is caused by circulating IgA antibodies, most commonly to LABD97 and LAD-1, which are degradation proteins of BP180 (type XVII collagen). Linear IgA dermatosis may also be seen as a drug eruption. Most cases of drug-induced linear IgA dermatosis are related to vancomycin, although anticonvulsants, ampicillin, cyclosporine, and captopril are implicated.

Clinical Manifestations

This rare dermatosis is most common in the 1st decade of life, with a peak incidence during the preschool years. The eruption consists of many large symmetrically located, tense bullae filled with clear or hemorrhagic fluid. The bullae are often clustered together and develop on a normal or erythematous, urticarial base. Areas of predilection are the genitals and buttocks (Fig. 673.13), the perioral region, and the scalp. Sausage-shaped bullae may be arranged in an annular or rosette-like fashion around a central crust (Fig. 673.14). Erythematous plaques with gyrate margins bordered by intact bullae may develop over larger areas. Pruritus may be absent or very intense, and systemic signs or symptoms are absent.

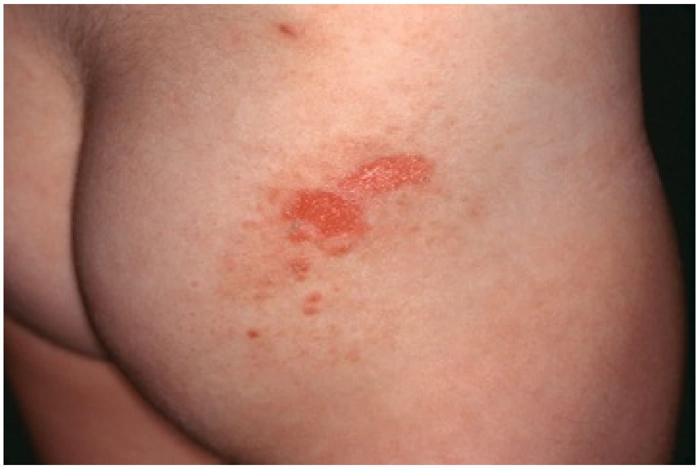

FIG. 673.13 Erosion on an erythematous base after loss of blister roof in linear immunoglobulin A dermatosis.

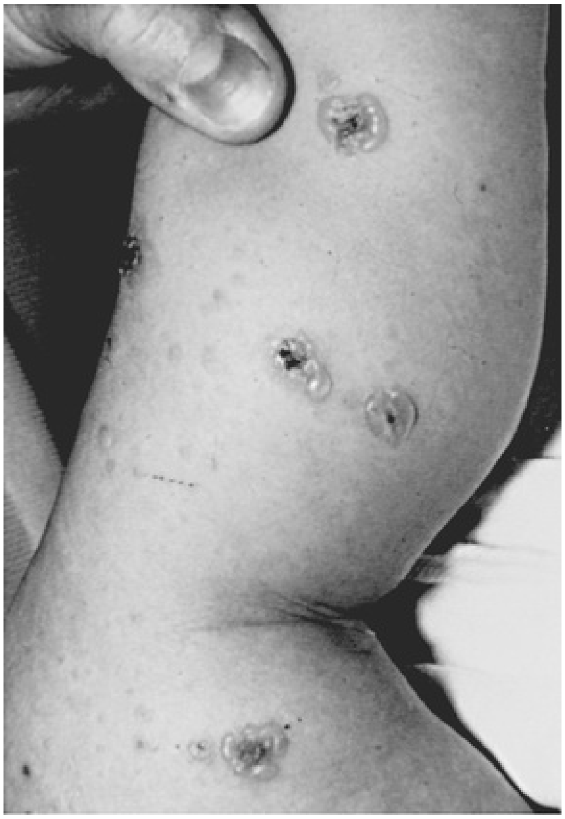

FIG. 673.14 Rosette-like blisters around a central crust typical of linear immunoglobulin A dermatosis (chronic bullous dermatosis of childhood).

Pathology

The subepidermal bullae are infiltrated with a mixture of inflammatory cells. Neutrophilic abscesses may be noted in the dermal papillary tips, indistinguishable from those of DH. The infiltrate may also be largely eosinophilic, resembling that in BP. Therefore direct immunofluorescence studies are required for a definitive diagnosis of linear IgA dermatosis; perilesional skin demonstrates linear deposition of IgA and sometimes IgG and C3 at the dermal-epidermal junction. Immunoelectron microscopy has localized the immunoreactants to the sublamina densa, although a combined sublamina densa and lamina lucida pattern has also been seen.

Differential Diagnosis

The eruption can be distinguished by histopathologic and immunofluorescence studies from pemphigus, BP, DH, and EM. Gram stain and culture preclude the diagnosis of bullous impetigo.

Treatment

Many cases of linear IgA dermatosis respond favorably to oral dapsone (see treatment of DH) or sulfapyridine. Other antibiotics, including erythromycin and dicloxacillin have been used, but the response is often transient. Children who show no response to dapsone may benefit from oral therapy with methylprednisolone (1 mg/kg/day) or a combination of these drugs. The usual course is 2-4 yr, although some children have persistent or recurrent disease; there are typically no long-term sequelae. IgA nephropathy is a rare complication.

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CHAPTER 674

Eczematous Disorders

Nicole R. Bender, Yvonne E. Chiu

Skin disorders are a broad group of cutaneous eruptions characterized by erythema, edema, and pruritus. Acute eczematous lesions demonstrate erythema, weeping, oozing, and the formation of microvesicles within the epidermis. Chronic lesions are generally thickened, dry, and scaly, with coarse skin markings (lichenification) and altered pigmentation. Many types of eczema occur in children; the most common is **atopic dermatitis** (see Chapter 170), although seborrheic dermatitis, allergic and irritant contact dermatitis, nummular eczema, and acute palmoplantar eczema (dyshidrosis) are also relatively common in childhood.

Once the diagnosis of eczema has been established, it is important to further classify the eruption more specifically for proper management. Pertinent historical data often provide the clue. In some instances, the subsequent course and character of the eruption permit classification. Histologic changes are relatively nonspecific, but all types of eczematous dermatitis are characterized by intraepidermal edema known as spongiosis.

674.1

Contact Dermatitis

Nicole R. Bender, Yvonne E. Chiu

The form of eczema known as contact dermatitis can be subdivided into irritant dermatitis, in which nonspecific injury to the skin causes immediate inflammation, and allergic contact dermatitis, resulting from a delayed hypersensitivity reaction. Irritant dermatitis is more frequent in children, particularly during the early years of life. Allergic reactions increase in frequency upon maturation of the immune system.

Irritant Contact Dermatitis

Irritant contact dermatitis can result from prolonged or repetitive contact with physical, chemical, or mechanical irritants, including saliva, urine, feces, fragrance, detergents, dyes, henna, plants, caterpillars, abrasive materials, and chafing.

Irritant contact dermatitis may be difficult to distinguish from atopic dermatitis or allergic contact dermatitis. A detailed history and consideration of the sites of involvement, the age of the child, and contactants usually provide clues to the etiologic agent. The propensity for development of irritant dermatitis varies considerably among children; some may respond to minimal injury, making it difficult to identify the offending agent through history. Children with atopic dermatitis are more prone to irritant contact dermatitis as an exacerbating factor. Irritant contact dermatitis usually clears after removal of the stimulus and temporary treatment with a topical corticosteroid preparation (see Chapter 665). Education of patients and parents about the causes of contact dermatitis is crucial to successful therapy.

Dry skin dermatitis results from repetitive wet-to-dry behaviors such as lip licking (Fig. 674.1), thumb sucking, frequent handwashing, or excessive sweating. Involved skin is erythematous and fissured, localized to the area of exposure. Treatment of dry skin dermatitis begins with eliminating the offending wet-to-dry behavior. Moisturizer cream applied twice daily decreases transepidermal water loss and replenishes skin lipids to improve hydration. A topical steroid is usually necessary to treat the inflammation.

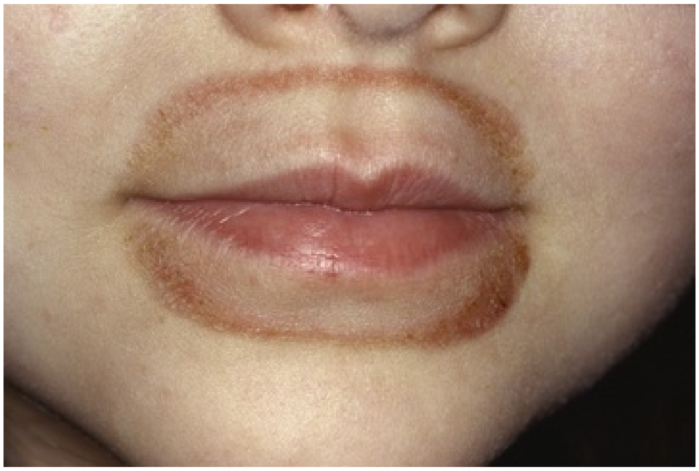

FIG. 674.1 Perioral irritant contact dermatitis from lip licking.

Juvenile plantar dermatosis occurs mainly in prepubertal children with hyperhidrosis who wear occlusive synthetic footwear. Weight-bearing surfaces of the foot may be pruritic or painful and develop a fissured or glazed appearance (Fig. 674.2). Immediate application of a thick emollient when socks and shoes are removed or immediately after swimming usually minimizes juvenile plantar dermatosis. Severe inflammatory cases may require short-term (1-2 wk) application of a medium- to high-potency topical steroid.

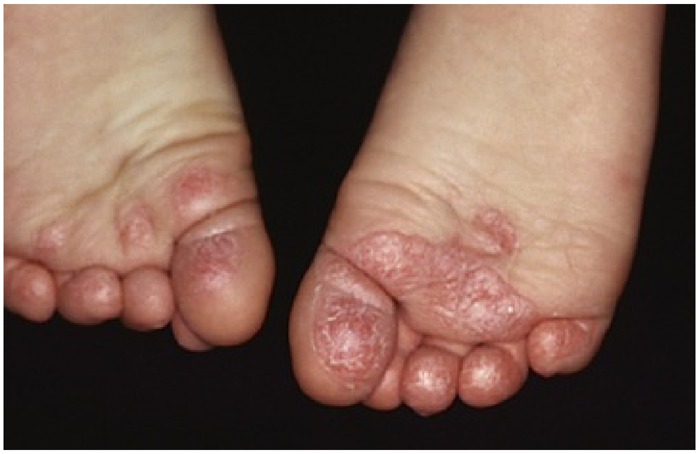

FIG. 674.2 Red, scaly juvenile plantar dermatosis.

Diaper Dermatitis

Diaper dermatitis refers to any rash in the diaper region; the most common of these is irritant diaper dermatitis. Elevated pH in the diaper area and synergistic activity of urinary and fecal enzymes lead to inflammation, which disrupts the normal skin barrier and increases susceptibility to other irritants and organisms. Additional factors are occlusion, friction, and use of diaper wipes and topical preparations. Loose or frequent stooling predisposes an infant to diaper dermatitis. Diaper dermatitis presents with erythema and scaling, often with papulovesicular or bullous lesions, fissures, and erosions in a patchy or confluent pattern (Fig. 674.3). The genitocrural folds are often spared because concave areas are relatively protected. Chronic hypertrophic, flat-topped papules and infiltrative nodules may occur. **Candidal infection** typically represents a secondary process. It is characterized by "beefy" red-pink, tender skin that has numerous 1-2 mm pustules and satellite papules and involves both concave and convex areas. Discomfort may be marked because of intense inflammation. Allergic contact dermatitis, seborrheic dermatitis, psoriasis, candidiasis, atopic dermatitis, child abuse, and rare disorders such as Langerhans cell histiocytosis, nutritional deficiencies, and acrodermatitis enteropathica should be considered when the eruption is persistent or is recalcitrant to simple therapeutic measures.

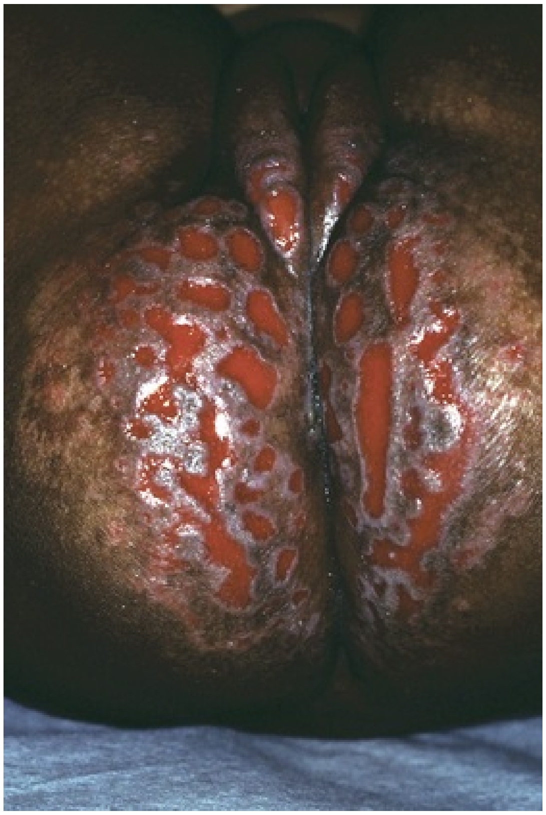

FIG. 674.3 Severe, erosive diaper dermatitis.

Diaper dermatitis often responds to simple measures; some infants are predisposed to diaper dermatitis, and management may be difficult. The damaging effects of overhydration of the skin and prolonged contact with feces and urine can be obviated by frequent changing of the diapers and periods of "rest" free of diaper use. Cleansing of affected skin is best accomplished with a soft cloth and lukewarm water, patted dry. Overwashing should be avoided because it leads to chapping and may worsen the dermatitis. Disposable diapers containing a superabsorbent material may help to maintain a relatively dry environment. First-line therapy for diaper dermatitis is application of a protective barrier agent (ointment or paste) containing petroleum or zinc oxide at every diaper change. Topical sucralfate is an effective barrier with some antibacterial activity, useful for recalcitrant cases. Low-potency nonhalogenated topical corticosteroids, such as 2.5% hydrocortisone, may be used for short time periods (3-5 days). Treatment with a topical anticandidal agent is indicated for secondary candidal infection. Topical preparations containing triamcinolone-nystatin and betamethasone dipropionate-clotrimazole are generally inappropriate for diaper dermatitis in infants because of the higher potency of the corticosteroid component. If using multiple topical agents, the protective barrier should be applied last. When diaper dermatitis does not respond to typical prevention and treatment strategies, non–diaper-associated causes must be considered.

Allergic Contact Dermatitis

Allergic contact dermatitis is common in childhood and should be considered in any child with recalcitrant eczema. Allergic contact dermatitis is underestimated in children with atopic dermatitis, and it has been reported to affect up to 41–77% of all children in the United States. This is a T-cell–mediated hypersensitivity reaction that is provoked by application of an antigen to the skin surface. The antigen penetrates the skin, where it is conjugated with a cutaneous protein, and the hapten-protein complex is transported to the regional lymph nodes by antigen-presenting Langerhans cells. A primary immunologic response occurs locally in the nodes and becomes generalized, presumably because of dissemination of sensitized T cells. Sensitization requires several days and, when followed by a fresh antigenic challenge, manifests as allergic contact dermatitis. Generalized distribution may also occur if enough antigen finds its way into the circulation, such as by consumption. Once sensitization has occurred, each new antigenic challenge may provoke an inflammatory reaction within 8-12 hr; sensitization to a particular antigen usually persists for many years.

Acute allergic contact dermatitis is an erythematous, intensely pruritic, eczematous dermatitis. Acute cases may be edematous and vesiculobullous. The chronic condition has the features of long-standing eczema: lichenification, scaling, fissuring, and pigmentary change. Distinguishing allergic contact dermatitis from other eczematous disorders can be challenging, especially with irritant contact dermatitis which can be clinically identical. The distribution of the eruption often provides a clue to the diagnosis. Airborne sensitizers usually affect exposed areas, such as the face and arms. Jewelry, topical agents, shoes, clothing, henna tattoo dyes, plants, and even toilet seats cause dermatitis at points of contact. Careful evaluation of environmental exposures, cultural customs, daily activity, animal exposures, ear piercing, tattooing, and personal product usage in the patient and all caregivers is essential. Other potential diagnoses to consider include herpes simplex virus, impetigo, cellulitis, and dermatophytoses.

Rhus dermatitis (poison ivy, poison sumac, poison oak), a response to the plant allergen urushiol, is the most common allergic contact dermatitis. It is often vesiculobullous and may be distinguished by linear streaks of vesicles where the plant leaves have brushed against the skin (Fig. 674.4). Fluid from ruptured cutaneous vesicles does not spread the eruption; antigen retained on skin, clothing, or under fingernails initiates new plaques of dermatitis if not removed by washing with soap and water. Antigen may also be carried by animals on their fur. “Black spot” poison ivy dermatitis is a rare variant that results from oxidation of concentrated urushiol left on the skin and manifests as small discrete black lacquer–like glossy papules with surrounding erythema and edema. Sensitization to one plant produces cross reactions with the others. Spontaneous resolution occurs in 1-3 wk, with the most common complication being secondary bacterial infection with normal skin flora. Exposure avoidance and thorough washing after exposure are the mainstays for prevention. Barrier creams or organoclay compounds such as bentoquatam may be effective if applied prior to expected exposure.

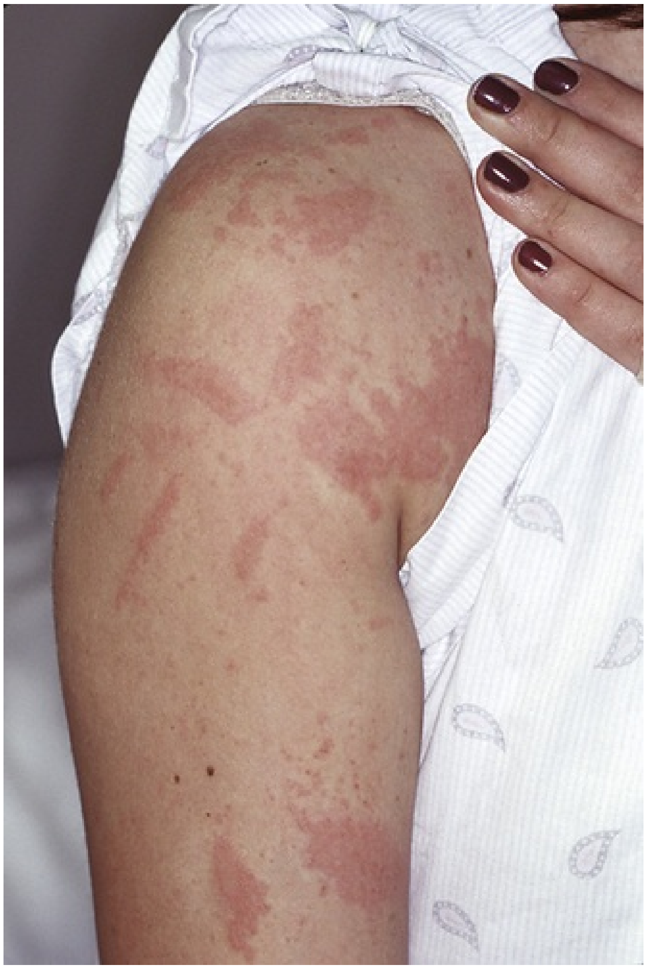

FIG. 674.4 Linear lesions in poison ivy.

Nickel dermatitis develops from contact with jewelry, metal closures on clothing, or even cell phones. Metal closures on pants frequently cause periumbilical dermatitis (Fig. 674.5). Some children are exquisitely sensitive to nickel, with even the trace amounts found in gold jewelry provoking eruptions. The most frequently involved sites from jewelry are the earlobes from nickel-containing earrings. Early ear piercing increases risk of sensitization, and it is recommended to delay piercing until after 10 yr of age. Patch testing for nickel sensitivity is unreliable in infants and toddlers and should only be performed if there is high clinical suspicion.

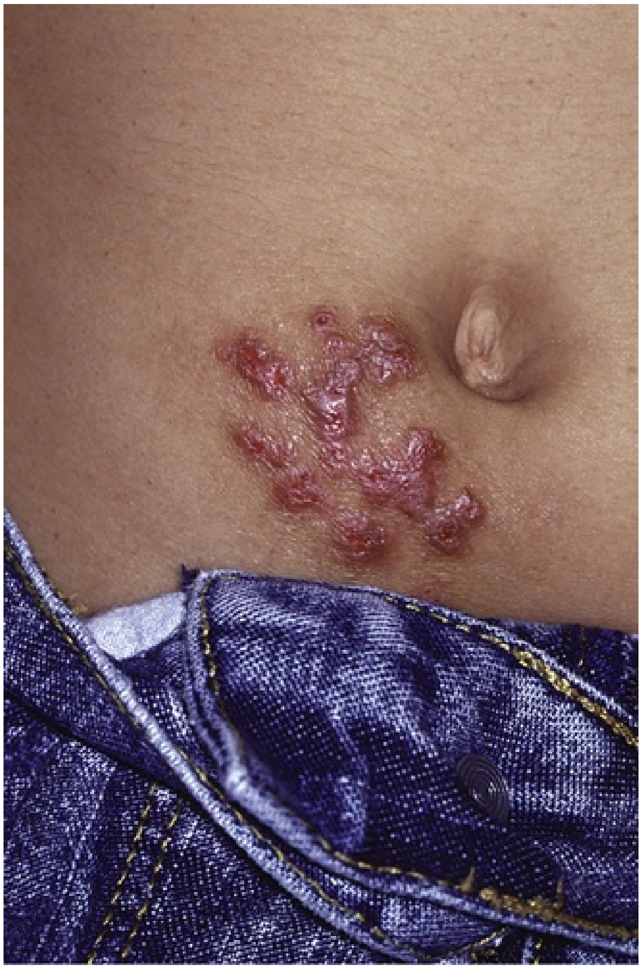

FIG. 674.5 Chronic periumbilical nickel dermatitis.

Shoe dermatitis typically affects the dorsum or soles of the feet and toes, sparing the interdigital spaces; it is usually symmetric. Other forms of allergic contact dermatitis, in contrast to irritant dermatitis, rarely involve the palms and soles. Common allergens are the antioxidants and accelerators in shoe rubber, adhesives, and the chromium salts in tanned leather or shoe dyes. Excessive sweating often leaches these substances from their source.

Apparel contains a number of sensitizers, including dyes, dye fixative, fabric finishes, fibers, resins, and cleaning solutions. Dye may be poorly fixed to clothing and so may be leached out with sweating, as can partially cured formaldehyde resins. The elastic in garments is a frequent cause of clothing dermatitis, and contact allergy to the ink “tag” of tagless baby clothing has been reported. Exposure to other items with fabric, such as infant car seats, may induce reactions similar to clothing.

Topical medications and cosmetics may be unsuspected as allergens, particularly if a medication is being used for a preexisting dermatitis. The most common offenders are neomycin, topical antihistamines, topical anesthetics, fragrances, topical corticosteroids, oxybenzone, and octocrylene in chemical sunscreens, preservatives, dye in temporary tattoos, and ethylenediamine, a stabilizer present in many medications. All types of cosmetics can cause facial dermatitis; involvement of the eyelids is characteristic for nail polish sensitivity.

Neomycin sulfate is present in many nonprescription topical antibiotic preparations, and thus children are frequently exposed at an early age. It is one of the most common causes of allergic contact dermatitis, and use of combination products of neomycin with other antibiotics, antifungals, or corticosteroids may induce co-reactivity with these chemically unrelated substances.

As mentioned previously, diagnosis of allergic contact dermatitis is usually based on history; however, patch testing may be helpful, especially in older children. Identification and avoidance of the offending agent is the mainstay of managing allergic contact dermatitis. First-line treatment for acute eruption is mid-potency topical corticosteroid ointment for 2-3 wk, as well as symptom management with nonsensitizing and fragrance-free emollients/moisturizers, wet dressings, and sedating antihistamines to allow for sleep. Systemic corticosteroids are used when >10% of skin is involved (0.5-1.0 mg/kg prednisone for 7-10 days, followed by a 7-10 day taper). More chronic allergic contact dermatitis is treated with low- to mid-potency topical corticosteroids. Desensitization therapy is rarely indicated. Topical calcineurin inhibitors, such as tacrolimus, may be a potential steroid-sparing alternative agent in select patients.[1]

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674.2

Nummular Eczema

Nicole R. Bender, Yvonne E. Chiu

Nummular eczema is characterized by coin-shaped, severely pruritic, eczematous plaques, commonly involving the extensor surfaces of the extremities (Fig. 674.6), buttocks, and shoulders with facial sparing. The plaques are relatively discrete, boggy, vesicular, slightly scaly, and exudative; when chronic, they often become thickened and lichenified and may develop central clearing. The etiology remains unclear, although nummular eczema possibly represents an atypical morphology of atopic dermatitis. Flares are generally sporadic but may be precipitated by xerosis, irritants, allergens, or occult staphylococcal infection. Most frequently, these lesions are mistaken for tinea corporis, but plaques of nummular eczema are distinguished by the lack of a raised, sharply circumscribed border, the lack of fungal organisms on a potassium hydroxide (KOH) preparation, and frequent weeping or bleeding when scraped. First-line treatment is with emollients, wet dressings, and potent topical corticosteroids. Steroid-impregnated tapes may simultaneously treat and provide barrier protection to these circumscribed eczematous plaques. An oral antihistamine may be helpful, particularly a sedating antihistamine at night. Antibiotics are indicated for secondary infection.

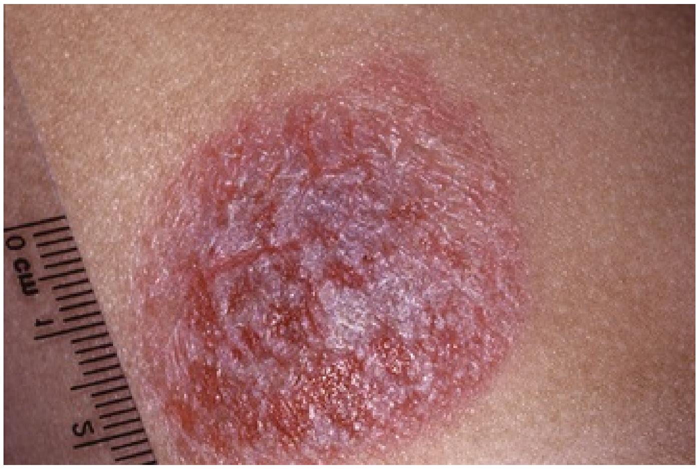

FIG. 674.6 Discrete, boggy plaque of nummular dermatitis.

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674.3

Pityriasis Alba

Nicole R. Bender, Yvonne E. Chiu

Pityriasis alba occurs mainly in children and causes lesions that are hypopigmented, ill-defined, round or oval patches (Fig. 674.7). They may be mildly erythematous and finely scaly. Lesions occur on the face, neck, upper trunk, and proximal portions of the arms and are most pronounced on darker skin tones or after tanning of surrounding skin. Itching is minimal or absent. The cause is unknown, but the eruption appears to be exacerbated by dryness and is often regarded as a mild form of atopic dermatitis. Pityriasis alba is frequently misdiagnosed as vitiligo, tinea versicolor, or tinea corporis. The lesions wax and wane but eventually disappear, and normal pigmentation often takes months to return. Application of a lubricant or emollient may ameliorate the condition, and avoidance of sun exposure and daily sunscreen use can help reduce the appearance of existing lesions by allowing for natural lightening of adjacent unaffected skin. If pruritus is troublesome, or if the lesions are active with erythema and fine scale, a low-potency topical steroid or calcineurin inhibitor may be used.

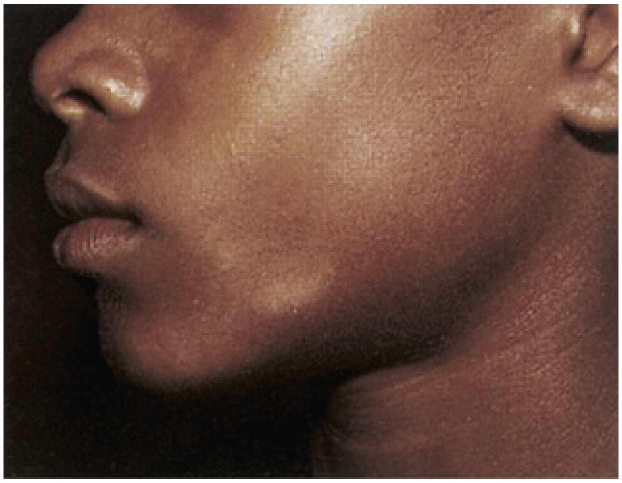

FIG. 674.7 Patchy hypopigmented lesions with diffuse borders characteristic of pityriasis alba.

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674.4

Lichen Simplex Chronicus

Nicole R. Bender, Yvonne E. Chiu

Lichen simplex chronicus is a secondary skin disorder resulting from excessive scratching or rubbing. It is characterized by a chronic pruritic, eczematous, circumscribed plaque that is usually lichenified and hyperpigmented (Fig. 674.8). All affected areas must be accessible to scratching, with the most common sites being the posterior neck, genitalia, wrists, ankles, and dorsal feet. Although the initiating event may be a transient lesion such as an insect bite, trauma from rubbing and scratching accounts for persistence of the plaque. Lichen simplex chronicus may also be seen in other chronic eczematous dermatoses such as atopic dermatitis, typically when poorly controlled. Pruritus must be controlled to permit healing, thus a covering to prevent scratching may be necessary. A high-potency topical corticosteroid under occlusion is often helpful and hastens resolution. Second-line therapy includes adding 6% salicylic acid gel to the topical corticosteroid preparation.

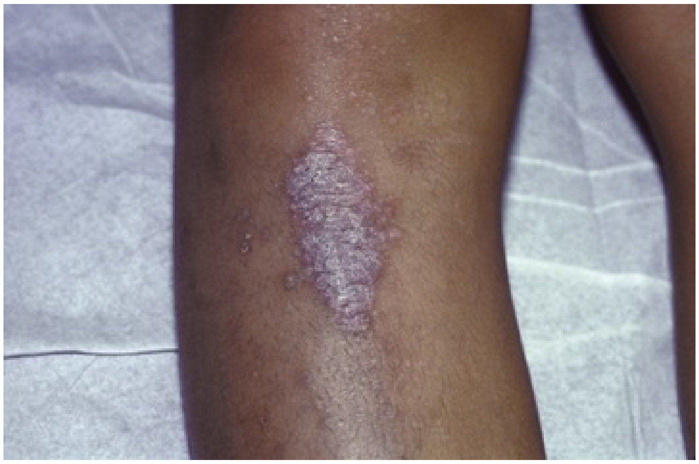

FIG. 674.8 Thickened plaque of lichen simplex chronicus.

674.5

Acute Palmoplantar Eczema

(Dyshidrotic Eczema, Dyshidrosis, Pompholyx)

Nicole R. Bender, Yvonne E. Chiu

A recurrent, sometimes seasonal, blistering disorder of the hands and feet, acute palmoplantar eczema occurs in all age groups but is uncommon in infancy. The pathogenesis is unknown, although possible predisposing factors include a history of atopy, exposure to contact allergens (especially metals) or irritants, or IV immunoglobulin therapy. The disease is characterized by recurrent crops of small, deep-seated “tapioca-like” vesicles, which are intensely pruritic and may coalesce into tense bullae (Fig. 674.9). Sites of predilection are the palms, soles, and lateral aspects of the fingers and toes. Primary lesions are noninflammatory and are filled with clear fluid, which, unlike sweat, has a physiologic pH and contains protein. Maceration and secondary infection are frequent because of scratching. The chronic phase is characterized by thickened, fissured plaques that may cause considerable discomfort, as well as dystrophic nails. Although acute palmoplantar eczema is frequently seen in patients with hyperhidrosis, histologic examination reveals an eczematous reaction around sweat ducts, without any structural or functional abnormalities of the sweat ducts themselves. The diagnosis is made clinically. The disorder may be confused with allergic contact dermatitis, which usually affects the dorsal rather than the volar surfaces, and with dermatophytosis, which can be distinguished by a KOH preparation of the roof of a vesicle and by appropriate cultures.

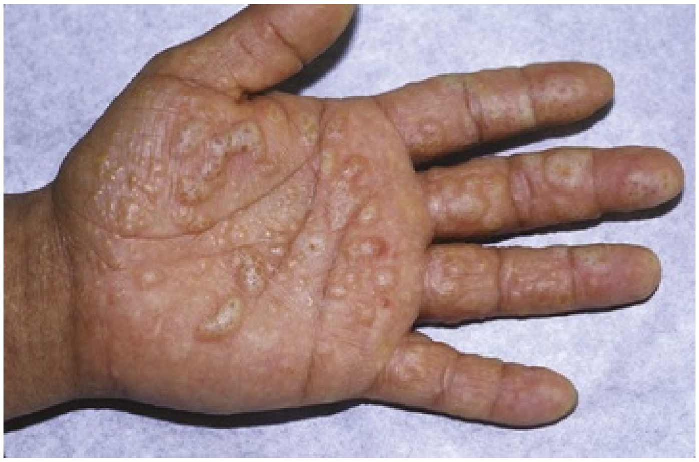

FIG. 674.9 Vesicular palmar lesions of dyshidrotic eczema with large bullae.

Acute palmoplantar eczema responds to wet dressings, liberal emollient use, and potent topical corticosteroid ointment applied twice daily for 2-4 wk. Weeping skin benefits from twice daily soaking in an astringent solution, such as aluminum subacetate. Second-line treatment is topical tacrolimus 0.1% ointment. Severe disease may require oral corticosteroids with 2 wk taper, or even phototherapy such as psoralen UVA and high-dose UVA1. Control of the chronic stage is difficult; lubricants containing mild keratolytic agents in conjunction with a potent topical fluorinated corticosteroid preparation may be indicated. Secondary bacterial infection should be treated systemically with an appropriate antibiotic. Patients should be told to expect recurrence and should protect their hands and feet from the damaging effects of excessive sweating, chemicals, harsh soaps, and adverse weather. Unfortunately, it is impossible to prevent recurrence or to predict its frequency.

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674.6

Seborrheic Dermatitis

Nicole R. Bender, Yvonne E. Chiu

Etiology

Seborrheic dermatitis is a chronic inflammatory disease most common in infancy and adolescence that parallels the distribution, size, and activity of the sebaceous glands. The cause is unknown, as is the role of the sebaceous glands in the disease. *Malassezia furfur* is implicated as a causative agent, although it remains unclear whether dermatitis results from the action of the fungus, its byproducts, or an exaggerated response of the host. In adolescence, seborrheic dermatitis typically occurs after puberty, indicating a possible role for sex hormones.

It is also unknown whether infantile seborrheic dermatitis and adolescent seborrheic dermatitis are the same or different entities. There is no evidence that children with infantile seborrheic dermatitis will experience seborrheic dermatitis as adolescents.

Clinical Manifestations

The disorder may begin in the 1st month of life and typically self-resolves by 1 yr. Diffuse or focal scaling and crusting of the scalp, sometimes called cradle cap (Fig. 674.10), may be the initial and, at times, the only manifestation. A greasy, scaly, erythematous papular dermatitis, which is usually nonpruritic in infants, may involve the face, neck, retroauricular areas, axillae, umbilicus, and diaper area. The dermatitis may be patchy and focal or may spread to involve almost the entire body (Fig. 674.11). Postinflammatory pigmentary changes are common, particularly in black infants. When the scaling becomes pronounced, the condition may resemble psoriasis and, at times, can be distinguished only with difficulty. The possibility of coexistent atopic dermatitis must be considered when there is an acute weeping dermatitis with pruritus, and the two are often clinically inseparable at an early age. An intractable seborrhea-like dermatitis with chronic diarrhea and failure to thrive may reflect systemic dysfunction of the immune system. A chronic seborrhea-like pattern, which responds poorly to treatment, may also result from cutaneous histiocytic infiltrates in infants with Langerhans cell histiocytosis. Seborrheic dermatitis is a common cutaneous manifestation of AIDS in young adults and is characterized by thick, greasy scales on the scalp and large hyperkeratotic erythematous plaques on the face, chest, and genitals.

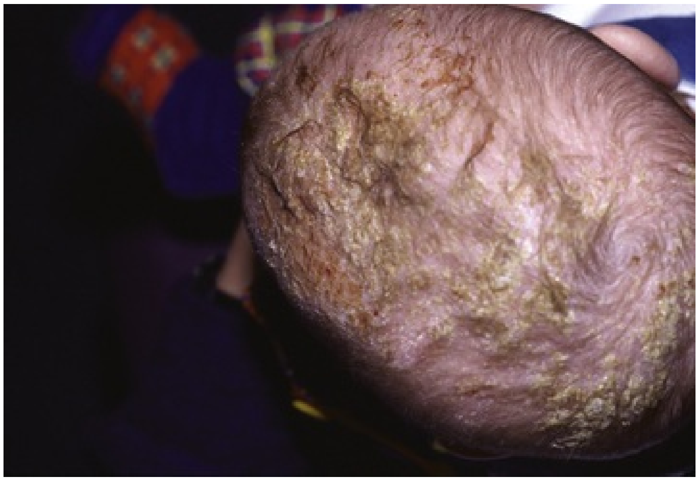

FIG. 674.10 Cradle cap in an infant.

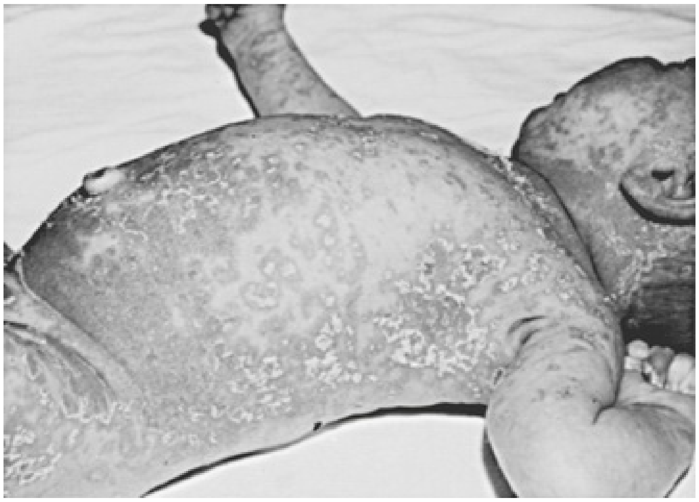

FIG. 674.11 Widespread seborrheic dermatitis.

During adolescence, seborrheic dermatitis is more localized and may be confined to the scalp and intertriginous areas. Also noted may be marginal blepharitis and involvement of the external auditory canal. Scalp changes vary from diffuse, brawny scaling to focal areas of thick, oily, yellow crusts with underlying erythema. Loss of hair is common, and pruritus may be absent to marked. When the dermatitis is severe, erythema and scaling occur at the frontal hairline, the medial aspects of the eyebrows, and in the nasolabial and retroauricular folds. Red, scaly plaques may appear in the axillae, inguinal region, gluteal cleft, and umbilicus. On the extremities, seborrheic plaques may be more eczematous and less erythematous and demarcated. Unlike infantile seborrheic dermatitis, adolescent seborrheic dermatitis generally does not self-resolve and has a chronic relapsing course.

Differential Diagnosis

The differential diagnosis of seborrheic dermatitis includes psoriasis, atopic dermatitis, dermatophytosis, Langerhans cell histiocytosis, and candidiasis. Secondary bacterial infections and superimposed candidiasis are common.

Treatment

Initial management for infantile seborrheic dermatitis is generally conservative given the self-limited nature of this condition. Emollients, baby oil, gentle shampooing with nonmedicated baby shampoo, and gentle use of a soft brush to remove scales are usually effective measures. Persistent lesions may be treated with low-potency topical corticosteroids if inflamed (applied once daily for 1 wk) and a topical antifungal (e.g., ketoconazole 2% cream twice daily). Antifungal shampoos such as ketoconazole 2% shampoo should be used cautiously because they are not tear-free.

First-line therapy for children and adolescents with scalp seborrheic dermatitis is antifungal shampoo used several times weekly to daily (selenium sulfide, ketoconazole, ciclopirox, zinc pyrithione, salicylic acid, or tar). Mid-potency topical corticosteroids such as fluocinolone 0.01% shampoo may also be used for inflamed lesions, applied once daily for 2-4 wk. Nonscalp lesions are treated with topical corticosteroid cream (low-potency for facial lesions, mid-potency elsewhere), as well as topical antifungals such as ketoconazole 2% cream or ketoconazole 2% shampoo used as a body or face wash. Second-line therapy for seborrheic dermatitis includes topical calcineurin inhibitors and keratolytic agents such as urea. Severe adult cases improve with oral antifungal agents; however, pediatric studies are lacking. Once acute disease is controlled, antifungal shampoo used on a weekly basis is effective maintenance to reduce risk of relapse.

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CHAPTER 675

Photosensitivity

Nicole R. Bender, Yvonne E. Chiu

Photosensitivity denotes an abnormal cutaneous reaction to UV radiation, either in sunlight or artificial light. The UV light spectrum contains UVA (320-400 nm wavelength), UVB (290-320 nm wavelength), and UVC (100-290 nm wavelength) subtypes. Transmitted radiation <300 nm is largely absorbed in the epidermis, whereas >300 nm is mostly transmitted to the dermis after variable epidermal melanin absorption. Children vary in susceptibility to UV radiation, depending on their skin type (i.e., its amount of pigment; Table 675.1).

Table 675.1

Sun-Reactive Skin Types

FITZPATRICK SKIN TYPE	SUNBURN, TANNING HISTORY
I	Always burns easily, no tanning
II	Usually burns, minimal tanning
III	Sometimes burns, gradual light brown tan
IV	Minimal to no burning, always tans
V	Rarely burns, tans profusely dark brown
VI	Never burns, pigmented black

Acute Sunburn Reaction

The most common photosensitive reaction seen in children is acute sunburn, which is caused mainly by UVB radiation. Sunlight contains many times more UVA than UVB radiation, but UVA must be encountered in much larger quantities than UVB radiation to produce sunburn. Immediate pigment darkening is caused by UVA radiation–induced photo-oxidative darkening of existing melanin and its transfer from melanocytes to keratinocytes. This effect generally lasts for a few hours and is not photoprotective. UVB-induced effects appear 6-12 hr after initial exposure and reach a peak in 24 hr. Effects include redness, tenderness, edema, and blistering (Fig. 675.1). Severe sunburn induces systemic symptoms of fever, nausea, and headache. Reactive oxidation species generated by UVB induce keratinocyte membrane damage and are involved in the pathogenesis of sunburn. A portion of the vasodilation seen in UVB-induced erythema is mediated by prostaglandins E_2 , E_3 , and F_{2A} . Other inflammatory cytokines induced by UVB include interleukins 1, 6, and 8, and tumor necrosis factor-α. Acute sunburn is a self-limited condition that resolves within 1 wk with desquamation and without scarring. Delayed melanogenesis as a result of UVB radiation begins in 2-3 days and lasts several days to a few weeks. Manufacture of new melanin in melanocytes, transfer of melanin from melanocytes to keratinocytes, increase in size and arborization of melanocytes, and activation of quiescent melanocytes produce delayed melanogenesis and pigment darkening (tanning). This effect reduces skin sensitivity to future UV-induced erythema. The amount of protection afforded depends on the skin type of the patient. Additional effects and possible complications of sun exposure include increased thickness of the stratum corneum, recurrence or exacerbation of herpes simplex labialis, lupus erythematosus, and many other conditions (Table 675.2).

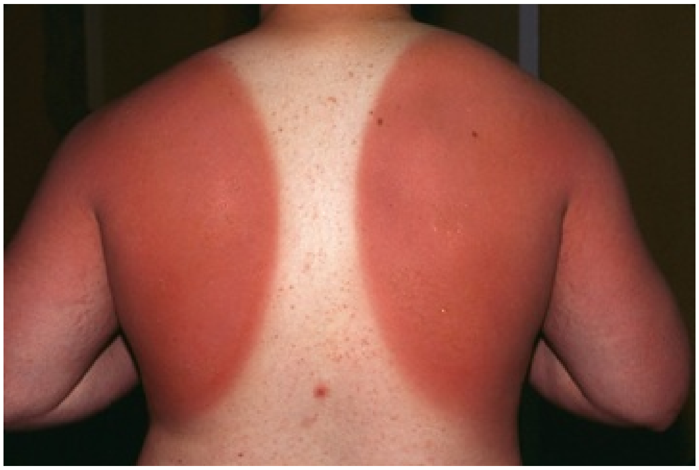

FIG. 675.1 **Sunburn. Well-demarcated, severe erythema.**

Table 675.2

Cutaneous Reactions to Sunlight

Sunburn

Photoallergic drug eruptions:

- Systemic drugs include tetracyclines, psoralens, chlorothiazides, sulfonamides, barbiturates, griseofulvin, thiazides, quinidine, phenothiazines
- Topical agents include coal tar derivatives, psoralens, halogenated salicylanilides (soaps), perfume oils (e.g., oil of bergamot), sunscreens (e.g., PABA, cinnamates, benzophenones)

Phototoxic drug eruptions:

- Systemic agents include nalidixic acid, furosemide, nonsteroidal antiinflammatory agents (naproxen, piroxicam), and high doses of agents causing photoallergic eruptions
- Topical agents include 5-fluorouracial, furocoumarins (e.g., lime, lemon, carrot, celery, dill, parsnip, parsley), and high doses of agents causing photoallergic eruptions

Genetic disorders with photosensitivity:

- Xeroderma pigmentosum
- Bloom syndrome
- Cockayne syndrome
- Rothmund-Thomson syndrome
- Trichothiodystrophy
- Smith-Lemli-Opitz syndrome
- Kindler syndrome

Inborn errors of metabolism:

- Porphyrias
- Hartnup disease and pellagra

Infectious diseases associated with photosensitivity:

- Recurrent herpes simplex infection
- Viral exanthems (accentuated photodistribution; e.g., varicella)

Skin disease exacerbated or precipitated by light:

- Lichen planus
- Darier disease
- Lupus erythematosus including neonatal
- Dermatomyositis
- Psoriasis
- Erythema multiforme
- Atopic dermatitis
- Hailey-Hailey disease

Deficient protection because of a lack of pigment:

- Vitiligo
- Oculocutaneous albinism
- Phenylketonuria
- Chédiak-Higashi syndrome
- Hermansky-Pudlak syndrome
- Waardenburg syndrome
- Piebaldism

PABA, para-aminobenzoic acid.

Acute sunburn should be managed conservatively with cool compresses, aloe vera products, and calamine lotion. Oral analgesics such as ibuprofen and acetaminophen may decrease pain. Topical corticosteroids are only helpful in the acute phase and generally should not be used to treat sunburn once peak erythema has been reached (~24 hr). Topical anesthetics are relatively ineffective and potentially hazardous because of their propensity to cause contact dermatitis. A bland emollient, such as plain petrolatum, is effective in the desquamative phase.

The long-term sequelae of chronic and intense sun exposure are not often seen in children, but most individuals receive >50% of their lifetime UV dose by age 20 yr; therefore pediatricians have a pivotal role in educating patients and their parents about the harmful effects, potential malignancy risks, and irreversible skin damage that result from prolonged exposure to the sun and tanning lights. Premature aging, senile elastosis, actinic keratoses, squamous and basal cell carcinomas, and melanomas all occur with greater frequency in sun-damaged skin. In particular, blistering sunburns in childhood and adolescence significantly increase the risk for development of malignant melanoma.

Sun protection is best achieved by sun avoidance, which includes minimizing time in the midday sun (10 AM to 4 PM), staying in the shade, and wearing protective clothing including wide-brimmed hats. Protection is enhanced by a wide variety of sunscreen agents. Physical sunscreens (zinc oxide, titanium dioxide) block UV light, whereas chemical sunscreens (para-aminobenzoic acid [PABA], PABA esters, salicylates, benzophenones, avobenzone, cinnamates, and ecamsule) absorb damaging radiation. Most chemical sunscreens are effective for only UVB wavelengths but benzophenones and avobenzone provide protection in both the UVA and UVB ranges; ecamsule is a UVA sunscreen. Stabilizers such as octocrylene and diethyl 2,6-naphthalate increase the time of function of the chemical sunscreens. “Broad-spectrum” sunscreens are combination products that absorb both UVA and UVB, and families should be advised to use products labeled as “broad spectrum” with a sun protective factor (SPF) of at least 30, reapply liberally at least every 2 hr while outdoors, and reapply after swimming. Infants younger than 6 mo of age should not be exposed to direct sunlight but may have SPF 15 physical sunscreens applied to small areas of skin if sunlight avoidance is not possible. SPF is defined as the minimal dose of sunlight required to produce cutaneous erythema after application of a sunscreen, divided by the dose required with no use of sunscreen. SPF applies only to UVB protection; there is no associated rating for UVA protection in the United States aside from the “broad spectrum” designation.

Photosensitive Reactions

Photosensitizers in combination with a particular wavelength of light (typically

UVA) cause dermatitis that can be classified as phototoxic or photoallergic reactions. Contact with the photosensitizer may occur externally on the skin, internally by enteral or parenteral administration, or through host synthesis of photosensitizers in response to an administered drug.

Photoallergic reactions occur in only a small percentage of persons exposed to photosensitizers and light and require a time interval for sensitization to take place. Thereafter, dermatitis appears within 24 hr of reexposure to the photosensitizer and light. Typically patients present with an eczematous eruption in sun-exposed areas with sparing behind the ear, under the chin, and under clothing. Photoallergic dermatitis is a T-cell–mediated delayed hypersensitivity reaction in which the drug, acting as a hapten, may combine with a skin protein to form the antigenic substance. Table 675.2 lists some of the important classes of drugs and chemicals responsible for photosensitivity reactions. The most common photoallergens are chemicals present in sunscreens.

Phototoxic reactions occur in all individuals who accumulate adequate amounts of a photosensitizing drug or chemical within the skin. UV radiation excites the agent to a state capable of causing cell or tissue damage through reactive oxygen species formation. Prior sensitization is not required. Dermatitis develops within hours after exposure to radiation in the range of 285-450 nm. The eruption is confined to light-exposed areas and often resembles exaggerated sunburn, but it may be urticarial or bullous. It results in postinflammatory hyperpigmentation. All the drugs that cause photoallergic reactions may also cause a phototoxic dermatitis if given in sufficiently high doses. Several additional drugs and contactants cause phototoxic reactions (see Table 675.2). Postinflammatory hyperpigmentation develops rapidly and can be the presenting sign. Contact with furocoumarin-containing plants causes a disorder called **phytophotodermatitis** . The most common phytophotodermatitis seen in children is caused by lime juice, which presents as hyperpigmentation in streaky patterns on sun-exposed skin consistent with dripping juice or handprints.

Diagnosis of photosensitive reactions caused by drugs or chemicals relies on a high index of suspicion, an appreciation of the distribution pattern of the eruption, and a history of application or ingestion of a known photosensitizing agent. Phototesting and photopatch testing are also helpful when available. First-line treatment for both photoallergy and phototoxicity consists of discontinuation of the offending agent and good sun protection practices, including avoidance of sun exposure. Photoallergic reactions are treated similarly to contact dermatitis, with a topical corticosteroid to alleviate pruritus when necessary. Severe reactions may necessitate a 2-3 wk course of systemic corticosteroid therapy. Phototoxic reactions are treated similarly to sunburn, with comfort measures such as cool compresses, emollients, and oral analgesics.

Porphyrias

See Chapter 110 .

Porphyrias are acquired or inborn disorders due to abnormalities of specific enzyme mutations in the heme biosynthetic pathway. Some have childhood photosensitivity as a consistent feature. The pathogenesis of photosensitivity in porphyria relates to deposition of excess porphyrins in the skin; UV radiation excites these molecules, causing cell and tissue damage via generation of reactive oxygen species. Signs and symptoms may be negligible during the winter, when sun exposure is minimal.

Congenital erythropoietic porphyria (Günther disease) is a rare autosomal recessive disorder affecting the enzyme uroporphyrinogen III synthase. It may cause hydrops fetalis, but more typically manifests in the 1st few months of life as hemolytic anemia and exquisite sensitivity to light, which may induce repeated severe bullous eruptions that result in mutilating scars (Fig. 675.2). **Hyperpigmentation** , hyperkeratosis, vesiculation, and fragility of skin as well as various nail changes develop in light-exposed areas. Light therapy for an affected neonate presenting with jaundice may inadvertently induce skin manifestations. **Hirsutism** in areas of mild involvement, scarring **alopecia** in severely affected areas, pink to red urine, brown teeth (erythrodontia), splenomegaly, and corneal ulceration are additional characteristic manifestations. Laboratory findings include uroporphyrin I and coproporphyrin I in urine, plasma, and erythrocytes, and coproporphyrin I in feces. Teeth and urine from affected patients fluoresce reddish pink under a Wood lamp as a result of the presence of porphyrins. **Hepatoerythropoietic porphyria** , a separate entity, has skin findings that closely resemble those seen in congenital erythropoietic porphyria; this extremely rare disorder presents in early childhood and is discussed in greater depth in Chapter 110 .

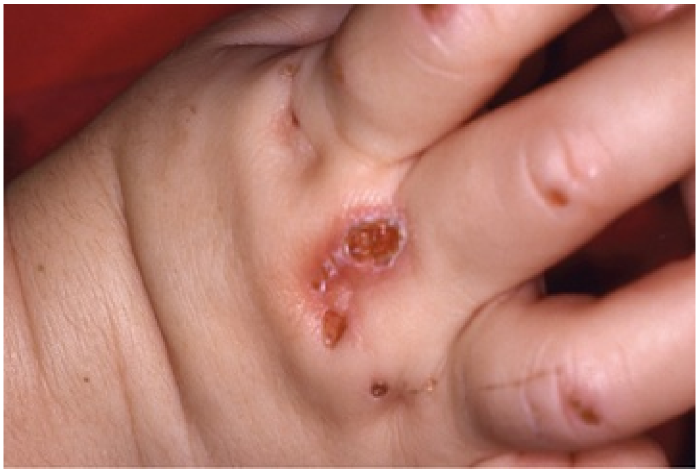

FIG. 675.2 Crusted ulcerations in an infant with congenital erythropoietic porphyria.

Erythropoietic protoporphyria may be autosomal dominant, autosomal recessive, or X-linked and most commonly involves the enzyme ferrochelatase (FECH), the final enzyme in the heme synthetic pathway. Symptoms develop in early childhood and manifest as intense pain, tingling, or pruritus within 30 min of sun exposure, followed by erythema, edema, urticaria, or mild systemic symptoms; these acute manifestations resolve completely within days. The absence of blistering distinguishes erythropoietic protoporphyria from the other cutaneous porphyrias. Nail changes consist of opacification of the nail plate, onycholysis, pain, and tenderness. Recurrent sun exposure produces a subtle chronic eczematous dermatitis with thickened, lichenified skin, especially over the finger joints (Fig. 675.3*A*), as well as mild facial scarring (see Fig. 675.3*B*). Pigmentation, hypertrichosis, skin fragility, and mutilation are not seen. Gallstones develop frequently; however, severe liver disease occurs in <5% of patients. Protoporphyrin is detected in plasma, erythrocytes, and feces. **X-linked protoporphyria** is a similar disorder to erythropoietic protoporphyria but is due to a mutation in 5-aminolevulinic acid synthetase (the 1st and rate-controlling enzyme of heme synthesis) and therefore does not have iron overload or associated anemia.

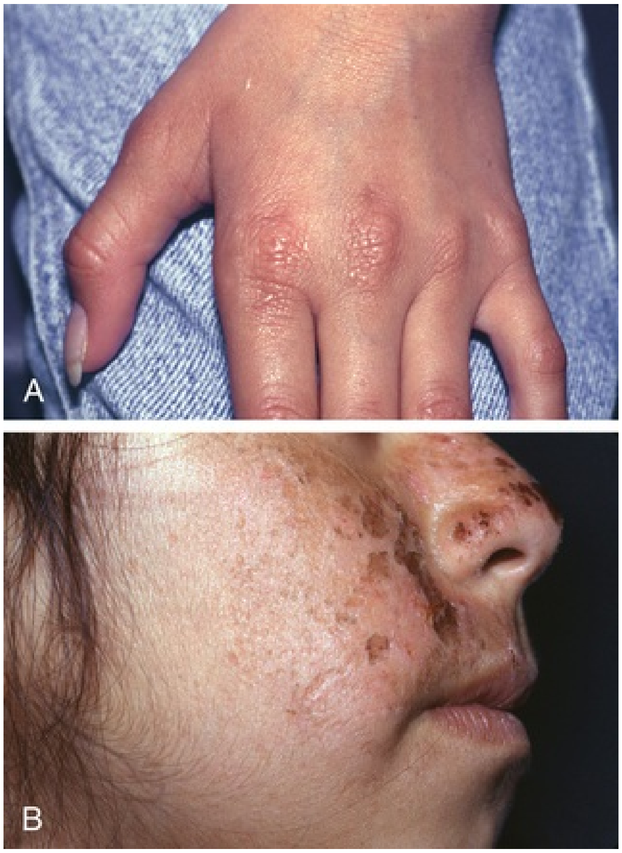

FIG. 675.3 **Erythropoietic protoporphyria. A, Erythematous thickening over the metacarpal phalangeal joints. B, Linear crusts and scarring.**

The wavelengths of light mainly responsible for eliciting cutaneous reactions in porphyria are in the region of 400 nm (UVA light). Window glass, including that in automobiles, transmits wavelengths >320 nm and is not protective, and fluorescent indoor lights may be pathogenic. Patients must avoid direct sunlight, wear protective clothing, and use a sunscreen agent that effectively blocks UVA light. Oral beta-carotene also provides some photoprotective benefit. Afamelanotide, an alpha-melanocyte stimulating hormone (α-MSH) analog, has been gaining use for treatment of erythropoietic protoporphyria and X-linked protoporphyria, and is currently under investigation by the FDA. This drug serves to increase skin pigmentation by increasing melanin production by melanocytes, resulting in increased UV tolerance.

Cutaneous porphyria symptoms are typically constant throughout life, and secondary bacterial infections commonly complicate disease course. Cutaneous porphyrias do not appear to increase risk for skin malignancies. Additional diagnostic and treatment recommendations for the porphyrias are outlined in Chapter 110 .

Pseudoporphyria is a porphyria-like reaction characterized by erythema, blistering, and scarring on sun-exposed skin seen occasionally in patients with juvenile idiopathic arthritis taking nonsteroidal antiinflammatory agents.

Colloid Milium

Colloid milium is a rare, asymptomatic disorder that occurs on the face (nose, upper lip, and upper cheeks) and may extend to the dorsum of the hands and the neck as a profuse eruption of tiny, ivory to yellow, firm, grouped papules. Lesions appear before puberty on otherwise normal skin, unlike the adult variant that develops on sun-damaged skin. Onset may follow an acute sunburn or long-term sun exposure. Most cases reach maximal severity within 3 yr and remain unchanged thereafter, although the condition may remit spontaneously after puberty. Treatment is usually not necessary.

Hydroa Vacciniforme

Hydroa vacciniforme is a vesiculobullous disorder with unclear etiology, although chronic or latent Epstein-Barr virus infections or lymphoproliferative disorders have been implicated. It begins in early childhood and may remit at puberty, with peak incidence in the spring and summer. Erythematous, pruritic macules develop symmetrically within hours of sun exposure over the ears, nose, lips, cheeks, and dorsal surfaces of the hands and forearms. Lesions progress to stinging tender papules and hemorrhagic vesicles and bullae, resembling chickenpox. They become umbilicated, ulcerated, and crusted, eventually healing with pitted scars and telangiectasias. Associated features are rare but include fever, malaise, hypersensitivity to mosquito bites, conjunctivitis, and other ocular symptoms. This eruption should be distinguished from erythropoietic protoporphyria, which rarely shows vesicles. Typical lesions have been reproduced with repeated doses of UVA or UVB light. First-line treatment includes sun avoidance, broad-spectrum sunscreens, and other sun-protective habits. Other potential therapies include mid-potency topical corticosteroids for inflamed lesions, low-dose courses of narrow-band UVB (NB-UVB) therapy, beta-carotene, hydroxychloroquine, or antiviral agents such as acyclovir.

Solar Urticaria

Solar urticaria is a rare disorder induced by UV or visible irradiation. The disorder is mediated by immunoglobulin E antibodies to either an abnormal photoallergen present only in affected patients (type I) or a normal photoallergen ordinarily present in skin (type II), leading to mast cell degranulation and histamine release. Classic urticarial lesions consisting of erythematous pruritic wheals develop on sun-exposed skin (Fig. 675.4) within 5-10 min of sun exposure and fade within 24 hr. Severe reactions involving large areas of skin may lead to systemic symptoms or anaphylaxis. Diagnosis is achieved by history alone or with phototesting. First-line treatment is an oral H_1 antihistamine, plus sun avoidance and protection. Second-line therapy possibilities include oral or topical corticosteroids, photodesensitization using NB-UVB, omalizumab, or intravenous immunoglobulin.

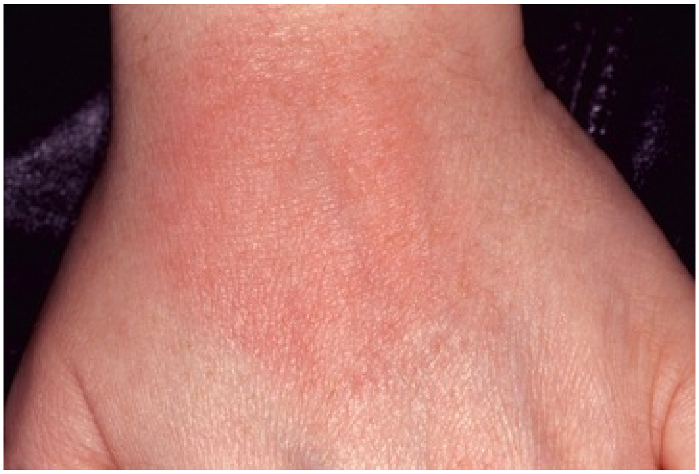

FIG. 675.4 Urticaria after 5 minutes of exposure to artificial ultraviolet A radiation.

Polymorphous Light Eruption

Polymorphous light eruption (PMLE) is a common photosensitivity reaction that develops most commonly in females. The first eruption typically appears in the spring after the first episode of prolonged sun exposure of the season. Onset of the eruption is delayed by hours to days after sun exposure and lasts for days to sometimes weeks. PMLE usually resolves with increased sun exposure throughout the spring and summer. Areas of involvement tend to be symmetric and are characteristic for a given patient, including some but not all of the exposed or lightly covered skin on the face, neck, upper chest, and distal extremities. Lesions have various morphologies but most commonly are pruritic, 2-5 mm, grouped, erythematous papules or papulovesicles or >5 cm, edematous plaques; lesions are nonscarring. A PMLE variant known as **juvenile spring eruption** characteristically occurs on affected boys' ears each spring, while **pinpoint papular PMLE** is a variant characterized by pinpoint-sized lesions occurring in darker-skinned individuals. Most PMLE cases involve sensitivity to UVA radiation, although some are UVB induced. PMLE most likely results from a delayed-type hypersensitivity reaction to a photo-induced antigen within the skin, with individuals having a genetic predisposition. Provocative phototesting, as well as skin biopsy (showing epidermal spongiosis and superficial and deep lymphocytic infiltrate), aid in diagnosis. Treatment is aimed at prevention with sun avoidance, protective clothing, and broad-spectrum sunscreens. Topical corticosteroids (low-potency for facial lesions, high-potency for lesions elsewhere) can be used for mild eruptions. Second-line approaches include prophylactic NB-UVB phototherapy or hydroxychloroquine in early spring and short course systemic glucocorticoids for severe flares.

Actinic Prurigo

Actinic prurigo, often classified as a variant of PMLE, is a chronic familial photodermatitis inherited as an autosomal-dominant trait seen most commonly in Native Americans of North and South America. Human leukocyte antigen (HLA) DRB1*0407 (60–70%) and HLA DRB1*0401 (20%) are strongly associated with actinic prurigo. Most patients are female and are sensitive to UVA radiation. The first episode generally occurs in early childhood, several hr to 2 days after intense sun exposure. The papulonodular lesions are intensely pruritic, erythematous, and crusted. Areas of predilection include the face (Fig. 675.5), lower lip, distal extremities, and, in severe cases, buttocks. Facial lesions may heal with minute pitted or linear scarring. Lesions often become chronic, without periods of total clearing, merging into eczematous plaques that become lichenified and occasionally secondarily infected. Associated features that distinguish this disorder from other photoeruptions and atopic dermatitis include cheilitis, conjunctivitis, and traumatic alopecia of the outer half of the eyebrows. Actinic prurigo is a chronic condition that generally persists into adult life, although it may improve spontaneously in the late teenage years. Sun avoidance, protective clothing, and broad-spectrum sunscreens may be helpful in preventing the eruption. Mid- to high-potency topical corticosteroids and antihistamines palliate the pruritus and inflammation. Severe acute eruptions may require oral glucocorticoids. Treatment with NB-UVB beginning in springtime has shown improved tolerance of sunlight during summer months; however, it may induce symptoms in some patients. Thalidomide 50-100 mg/day is very effective, but its use is limited by toxicity, especially severe birth defects when taken by pregnant females.

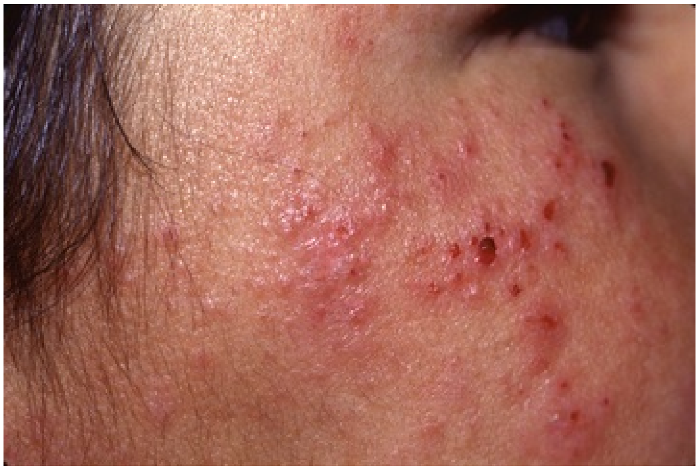

FIG. 675.5 Erythematous, excoriated papules in actinic prurigo.

Cockayne Syndrome

Cockayne syndrome is a rare autosomal recessive disorder. Onset occurs at 1 yr of age and is characterized by facial erythema in a butterfly distribution after sun exposure. Later characteristics include loss of adipose tissue and development of thin, atrophic, hyperpigmented skin, particularly over the face. Associated features include stunted growth, dwarfism; microcephaly; progressive neurologic dysfunction (caused by leukodystrophy); mental retardation; progressive dementia; distinct facies (aged look, pinched nose, sunken eyes, large protuberant ears); long limbs; disproportionately large hands and feet; cool and cyanotic extremities; carious teeth; unsteady gait with tremor; limitation of joint mobility; progressive deafness; cataracts; retinal degeneration; optic atrophy; decreased sweating and tearing; and premature graying of the hair. Complications include diabetes and hepatic or renal impairment. Diffuse extensive demyelination of the peripheral and central nervous systems ensues, and patients generally die of atheromatous vascular disease or infections (especially pneumonia) before the 3rd decade. There are 2 types of Cockayne syndrome. **Type I (*CSA* gene)** is less severe than **type II (*CSB* gene)** . Patients may have xeroderma pigmentosum–Cockayne syndrome overlap, which is phenotypically more like Cockayne syndrome, and is due to mutations in *XPB* , *XPD* , or *XPG* genes. Photosensitivity in Cockayne syndrome is a result of deficient nucleotide excision repair of UV-induced damage, specifically within actively transcribing regions of DNA (transcription-coupled DNA repair). The etiology of neurologic and other associated features remains unclear; however, evidence points toward a mitochondriopathy. The syndrome is distinguished from progeria (see Chapter 109) by the presence of photosensitivity and ocular abnormalities and from xeroderma pigmentosum by the fact that patients with Cockayne syndrome do not develop sun-induced pigmentation or increased risk of skin cancers. Diagnosis is accomplished by genetic testing and performing various tests on cultured fibroblasts. The mainstay of treatment for the photosensitivity of Cockayne syndrome is strict sunlight avoidance and protective measures.

Xeroderma Pigmentosum

Xeroderma pigmentosum is a rare autosomal recessive disorder that results from a defect in nucleotide excision repair. Eight genetic groups have been recognized on the basis of each group's separate defect in ability to repair (xeroderma pigmentosum A through G) or replicate (xeroderma pigmentosum V [variant]) damaged DNA. The wavelength of light that induces the DNA damage ranges from 280 to 340 nm. Skin changes are first noted during infancy or early childhood in sun-exposed areas though lesions may occur at other sites, including the scalp. The skin lesions consist of erythema, scaling, bullae, crusting, ephelides (freckles), telangiectasia, keratoses (Fig. 675.6), basal and squamous cell carcinomas, and malignant melanomas. Interestingly, although most patients experience exaggerated acute sunburn reactions following minimal UV exposure, up to half of affected patients do not and instead develop progressive freckling. This difference in presentation depends on genetic subtype. Ocular manifestations include photophobia, lacrimation, blepharitis, symblepharon, keratitis, corneal opacities, tumors of the lids, and possible eventual blindness. Neurologic abnormalities such as cognitive deterioration and sensorineural deafness develop in approximately 20% of patients.

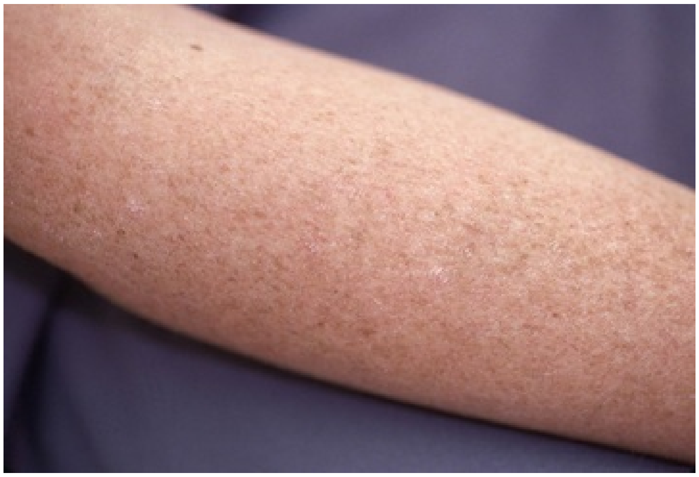

FIG. 675.6 Dyspigmentation and actinic keratoses in child with xeroderma pigmentosum.

This disease is a serious mutilating disorder, and the life span of an affected patient is often brief. Affected families should have genetic counseling. Xeroderma pigmentosum is detectable in cells cultured from amniotic fluid or DNA analysis of chorionic villous samples. Cultured skin fibroblast tests and genetic testing after birth also confirm diagnosis. Affected children should be totally protected from sun exposure; protective clothing, sunglasses, and opaque broad-spectrum sunscreens should be used even for mildly affected children. Light from unshielded fluorescent bulbs and sunlight passing through glass windows (including vehicle windows) are also harmful, thus applied window films are recommended. Early detection and removal of malignancies is mandatory, and oral isotretinoin may be used to prevent nonmelanoma skin cancers. Average age of death of these patients is 32 yr. There is crossover between several subtypes of xeroderma pigmentosum and both Cockayne syndrome and trichothiodystrophy.

Rothmund-Thomson Syndrome

Rothmund-Thomson syndrome is also known as **poikiloderma congenitale** because of the striking skin changes (Fig. 675.7). It is inherited as an autosomal recessive trait. Mutations in the *RECQL4* gene, which encodes a DNA helicase involved in repair and replication of DNA and telomeres, are found in approximately 65% of patients. The other mutations causing Rothmund-Thomson syndrome are unknown. Skin changes are noted as early as 3 mo of age and begin on the face. Plaques of erythema and edema appear in a butterfly distribution, as well as on the forehead, ears, neck, dorsal portions of the hands, extensor surfaces of the arms, and buttocks. These are replaced gradually by **poikiloderma** (reticulated, atrophic, hyperpigmented and hypopigmented telangiectatic patches or plaques). Palmoplantar hyperkeratosis develops in ⅓ of patients. Light sensitivity is present in many cases, and exposure to the sun may provoke formation of bullae. Areas of involvement, however, are not strictly photodistributed. Short stature; small hands and feet; sparse eyebrows, eyelashes, and pubic and axillary hair, and sparse, fine, prematurely gray scalp hair or alopecia; dystrophic nails; various tooth and skeletal abnormalities; and hypogonadism are common. One of the more distinguishing features is an increased incidence of juvenile subcapsular bilateral cataracts. Most patients have normal mental development. Keratoses and later squamous cell carcinomas may develop on exposed skin. The most worrisome association is that with **osteosarcoma** , which occurs in 30% of those patients with Rothmund-Thomson syndrome and *RECQL4* mutations. Genetic testing aids diagnosis. Management of dermatologic findings begins with sun avoidance and protection behaviors, and telangiectatic lesions have been shown to respond to pulsed dye laser therapy. In the absence of malignancy, life expectancy is normal.

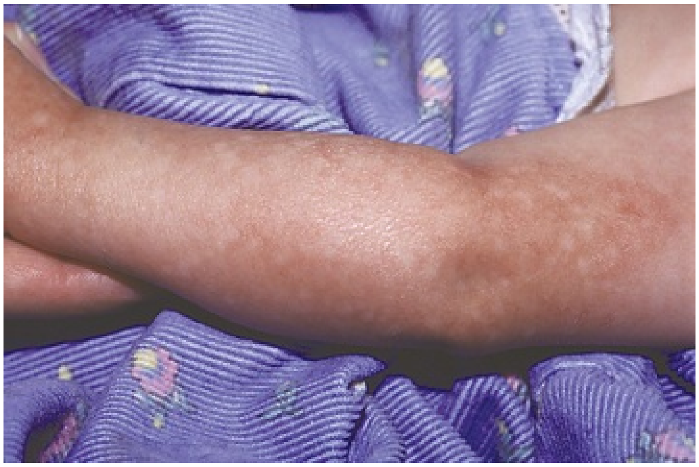

FIG. 675.7 Poikiloderma on the arm of an infant with Rothmund-Thomson syndrome.

Bloom Syndrome

Bloom syndrome is inherited in an autosomal recessive manner, most commonly in the Ashkenazi Jewish population. It is caused by a mutation in the *BLM/RECQL3* gene, encoding a DNA helicase. Patients are sensitive to UV radiation, with increased rates of chromosomal breaks and sister chromatid exchanges. Erythema and telangiectasia develop during infancy in a butterfly distribution on the face after exposure to sunlight. A bullous eruption on the lips and telangiectatic erythema on the cheeks, hands, and forearms may develop. Café-au-lait spots and hypopigmented macules may be present. Intrauterine growth deficiency developing into short stature, referred to as "proportionate dwarfism," and a distinctive facies consisting of a prominent nose and ears and a small, narrow face are generally found. Intellect is average to low average. Immunodeficiency is seen in all patients, manifesting as recurrent ear and pulmonary infections. Gastrointestinal malabsorption, gastroesophageal reflux, and hypogonadism are common. Affected children have an unusual tendency to develop both solid tumors (especially of the skin) and lymphoreticular malignancies, which often result in death during childhood or early adulthood. Sister chromatid exchange analysis is generally performed to confirm diagnosis. The only effective measures to reduce skin disease are sun protection and avoidance.

Hartnup Disease

See Chapter 103.05 .

Hartnup disease is a rare inborn error of metabolism with autosomal recessive inheritance. Neutral amino acids, including tryptophan, are not transported across the brush border epithelium of the intestine and kidneys due to mutation of the *SLC6A19* gene encoding the transporter. This results in deficiency of nicotinamide synthesis and causes a photo-induced **pellagra-like syndrome.** The urine contains increased amounts of monoamine monocarboxylic amino acids, distinguishing Hartnup disease from dietary pellagra. Cutaneous signs, which precede neurologic manifestations, initially develop during the early months of life. An eczematous, occasionally vesiculobullous, eruption occurs on the face and extremities in a glove-and-stocking photodistribution. Hyperpigmentation and hyperkeratosis may supervene and are intensified by further exposure to sunlight. Episodic flares may be precipitated by febrile illness, sun exposure, emotional stress, and poor nutrition. In most cases, mental development is normal, but some patients display emotional instability and episodic cerebellar ataxia. Neurologic symptoms are fully reversible. Administration of nicotinamide and protection from sunlight results in improvement of both cutaneous and neurologic manifestations.

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CHAPTER 676

Diseases of the Epidermis

676.1

Psoriasis

Nicole R. Bender, Yvonne E. Chiu

Psoriasis affects 2–4% of the US population, and pediatric psoriasis accounts for approximately one third of all cases.

Etiology/Pathogenesis

Psoriasis is an inflammatory autoimmune-related disease characterized by inflammation and keratinocyte proliferation. Within the dermis, dendritic cells are activated by self-antigens and release cytokines such as interferon-γ, tumor necrosis factor, and interleukin (IL)-12, IL-17, IL-22, and IL-23, which recruit T cells. Once activated, the T cells release cytokines that induce proliferation and abnormal differentiation of epidermal keratinocytes; in turn, more cytokines are produced to perpetuate the cycle. Psoriasis has a complex multifactorial genetic basis. Family history of psoriasis is present in ~50% of patients, typically a first-degree relative. The major psoriasis-susceptibility gene *(PSORS1)* is human leukocyte antigen (HLA)-CW*0602, encoding a class I major histocompatibility complex protein involved in recognition of self-antigens. Numerous other psoriasis susceptibility genes have been identified.

Factors contributing to disease onset/flares in some patients include bacterial and viral infections, trauma, physical or emotional stress, tobacco use/secondhand exposure, and certain medications.

Clinical Manifestations

This common, chronic skin disorder is first evident within the first 2 decades of life for approximately 30% of affected individuals. **Plaque psoriasis** , the most common (>80%) subtype, is characterized by erythematous papules that coalesce to form plaques with sharply demarcated, irregular borders (Fig. 676.1*A-D*). If they are unaltered by treatment, a thick silvery or yellow-white scale (resembling mica) develops (see Fig. 676.1*A*). Removal of the scale may result in pinpoint bleeding **(Auspitz sign)** . The **Koebner phenomenon** , in which new lesions appear at sites of trauma, is a valuable diagnostic feature. Lesions may occur anywhere, but preferred sites are the scalp, knees, elbows, umbilicus, superior intergluteal fold, genitalia, and ear canal. Nail involvement, a valuable diagnostic sign, is characterized by pitting of the nail plate, detachment of the plate (onycholysis), yellowish-brown subungual discoloration, and accumulation of subungual debris (see Fig. 676.1*G, H,* and *M*). Plaques are generally asymptomatic; however, pruritus is more common in children than adults.

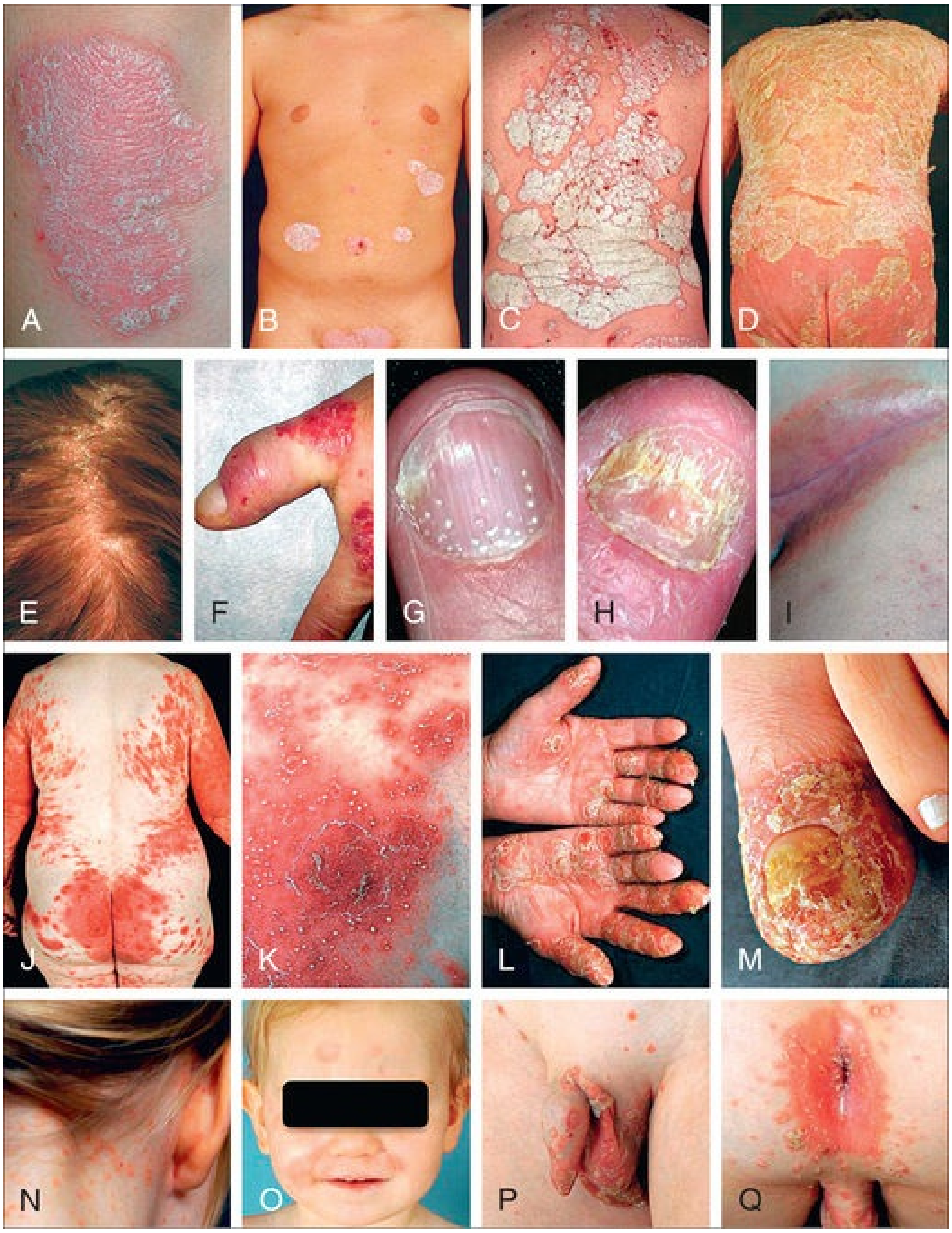

FIG. 676.1 Clinical manifestations of psoriasis. Typical erythematous plaques with silvery scales (A) can be scattered (B, psoriasis nummularis), cover larger areas of the skin (C, psoriasis geographica) or affect the entire body surface (D, erythrodermic psoriasis). Scalp involvement might be accompanied by non-scarring alopecia (E). Psoriatic arthritis affects up to 30% of all patients (F, thumb interphalangeal joint). Nail changes are frequent and range from pitting and yellow or brown discoloration (G) to complete dystrophy (H). Psoriasis inversa occurs in intertriginous areas and is usually devoid of scales (I). Pustular psoriasis might occur in a generalized form (J and K) or localized (L, palmoplantar type and M, acrodermatitis continua suppurativa type). In children, the onset as guttate psoriasis might follow streptococcal infection of the upper respiratory tract (N) and affect any site of the body (O-Q). (From Boehncke WH, Schön MP: Psoriasis. *Lancet* 386:983–992, 2015. Fig. 1, p. 984).

Guttate psoriasis , a variant that occurs predominantly in children, is characterized by an acute eruption of many oval or round papules smaller than 1.5 cm that are morphologically identical to the larger plaques of psoriasis (see Fig. 676.1*N-Q*). Sites of predilection are the trunk, face, and proximal portions of the limbs. The onset usually follows a few weeks after a **streptococcal** infection such as pharyngitis; thus, throat culture and serologic titers should be obtained. Guttate psoriasis has also been observed after perianal streptococcal infection, viral infections, sunburn, and withdrawal of systemic corticosteroid therapy or tumor necrosis factor (TNF)-α inhibitors. Clinical course ranges from spontaneous resolution to chronic disease.

Pustular psoriasis is a multisystem autoinflammatory disease characterized by recurrent episodes with the sudden onset of fever, malaise, extracutaneous organ involvement, and a diffuse erythematous-pustular exanthema. It may be associated with plaque psoriasis in some patients; unregulated cytokine production as a result of mutations in the *IL36RN* , *AP1S3* , and *CARD14* genes are implicated in a subset of patients.

Psoriasis is rare in infants but may be severe and recalcitrant and may pose a diagnostic problem. Psoriatic diaper rash is a common presentation in children younger than 2 yr old. Other rare forms include psoriatic erythroderma (>90% body surface area involvement), linear psoriasis, palmoplantar psoriasis, and inverse psoriasis (occurring in intertriginous areas). Children may also develop juvenile psoriatic arthritis, with or without skin lesions.

Psoriasis may be triggered by mild trauma (piercing, tattoos), sun or chemical burns, medications (beta blockers, NSAIDs), or HIV infection. Comorbid conditions include arthritis, Crohn disease, depression, and nonalcoholic fatty liver disease.

Differential Diagnosis

Psoriasis is a clinical diagnosis. The differential diagnosis of plaque-type psoriasis includes nummular dermatitis, tinea corporis, seborrheic dermatitis, postinfectious arthritis syndromes, and pityriasis rubra pilaris. Scalp lesions may be confused with seborrheic dermatitis, atopic dermatitis, or tinea capitis. Diaper area psoriasis may mimic seborrheic dermatitis, eczematous diaper dermatitis, perianal streptococcal disease, candidiasis, or allergic contact dermatitis. Guttate psoriasis can be confused with viral exanthems, secondary syphilis, pityriasis rosea, and pityriasis lichenoides chronica (PLC). Nail psoriasis must be differentiated from onychomycosis, lichen planus, and other causes of onychodystrophy.

Pathology

When the diagnosis is in doubt, histopathologic examination of an untreated lesion can be helpful. Characteristic changes of psoriasis include parakeratosis, acanthosis, elongated rete ridges, neutrophilic infiltrate in the epidermis sometimes forming microabscesses, dilated dermal blood vessels, and lymphocytic infiltrate in the dermis.

Treatment

The therapeutic approach varies with the age of the child, type of psoriasis, sites of involvement, and extent of the disease. Physical and chemical trauma to the skin should be avoided as much as possible to prevent Koebner response lesions. The treatment of psoriasis should be viewed as a 4-tier process. Efficacy varies with each therapy (Table 676.1).

Table 676.1

Antipsoriatic Therapies

	EFFICACY (%)*	LEVEL OF EVIDENCE	COMMENT
Glucocorticosteroids †	60	1	Skin atrophy if used long-term
Vitamin D derivatives †	45	1	Safest long-term topical treatment
Calcineurin inhibitors †	30	2/3	Reserved for localized sites such as face and intertriginous areas
Ultraviolet B exposure	70	2	Time consuming; cumulative dose might cause adverse effects
Psoralen plus ultraviolet A exposure	90	2	Time consuming; cumulative dose might cause adverse effects (including malignancies)
Acitretin	15	2	Avoid in young women; not recommended as low-dose monotherapy
Cyclosporine	45	1	Often used for a few months only (nephrotoxicity)
Methotrexate	50	2	Effective also in psoriatic arthritis
Fumaric acid esters	50	2	Oral drug, available only in Germany
Apremilast	30	1	Innovative oral drug, effective also in psoriatic arthritis
Adalimumab	70	1	Most widely used biological for this indication
Etanercept	50	1	Regarded as suitable also for intermittent use
Infliximab	80	1	Very fast onset of action; recommended for generalized

			pustular psoriasis (off-label)
Ustekinumab	70	1	Only 4 injections per year during long-term treatment
Secukinumab	80	1	Patients often achieve complete clearance of skin symptoms

[*] Estimated proportion of patients who achieved at least a 75% reduction in their Psoriasis Area and Severity Index score from baseline to end of short-term therapy.

[†] Topical therapeutic, which as monotherapy is shown to treat mild psoriasis only.

From Boehncke WH, Schön MP: Psoriasis. *Lancet* 386:983–992, 2015 (Table. 1, p. 989).

The first tier is topical therapy . The first-line topical agents for lesions on the body are emollients, vitamin D analogs (calcipotriene or calcitriol, although calcitriol is less irritating for children), and mid- to high-potency corticosteroids (see Chapter 665). A proprietary formulation containing both calcipotriene and betamethasone dipropionate (a high-potency topical corticosteroid) exists in ointment and solution forms. The preparation that is least potent but effective should be applied twice a day. Second-line topical options for lesions on the body include retinoids (tazarotene), tar preparations, anthralin, and keratolytics (salicylic acid or urea). Facial or intertriginous lesions may be treated with low-potency topical corticosteroids, and/or topical vitamin D analogs or calcineurin inhibitors as corticosteroid-sparing agents. For scalp lesions, applications of a phenol and saline solution (e.g., Baker Cummins P & S liquid) followed by a tar shampoo are effective in the removal of scales. A high- to superpotency corticosteroid in a foam, solution, or lotion base may be applied when the scaling is diminished. Nail lesions are difficult to treat topically; the first-line approach is a high-potency topical corticosteroid to the proximal nail fold.

The second tier of therapy is phototherapy. Narrow-band ultraviolet B (311 nm; NB-UVB) is an effective and well-tolerated alternative in pediatric patients with plaque and guttate psoriasis poorly controlled with topical treatments. Excimer (308 nm) laser UVB irradiation may be used for localized treatment-resistant plaques. Exposure to natural sunlight is often effective for less-severe psoriasis.

The third tier is systemic therapy , required rarely for children with moderate to severe, recalcitrant or generalized psoriasis. Methotrexate (0.2-0.7 mg/kg/wk) is the first-line systemic agent for children; other options include oral retinoids (0.5-1.0 mg/kg/day) and cyclosporine (3-5 mg/kg/day). Oral retinoids may be cautiously combined with phototherapy, although doses may need to be decreased because of the photosensitizing effects of the medication. Oral retinoids are also considered for generalized pustular and diffuse guttate psoriasis.

The fourth tier of therapy is the biologic response modifiers. TNF-α inhibitors such as etanercept, infliximab, and adalimumab have all been used for pediatric psoriasis, though etanercept is the only one with FDA approval. One study reported a significant improvement in psoriatic lesions at 12 wk with 57% versus 11% of patients receiving etanercept or placebo, respectively, achieving a 75% improvement in Psoriasis Area and Severity Index-75 (PASI-75, a metric to evaluate psoriasis severity). Other potential biologic agents with utility in pediatric psoriasis include ustekinumab, a human monoclonal antibody that blocks IL-12 and IL-23 and their cell-surface receptors. Another study enrolled 110 adolescent patients to determine efficacy and safety of treatment with ustekinumab. Respectively, 78.4% and 80.6% of adolescents receiving half-standard dosage and standard dosage achieved PASI-75 at 12 wk, compared to 10.8% of patients receiving placebo. Biologic IL-17 inhibitors such as secukinumab and ixekizumab and small molecule inhibitor apremilast are also used for pediatric psoriasis. Interleukin-23 inhibitors may also have a role in treatment of severe disease.

Prognosis

Prognosis is best for children with limited disease. Psoriasis is a lifelong disease characterized by remissions and exacerbations. Arthritis or various eye diseases may be extracutaneous complications. Metabolic and cardiovascular disorders also occur with increased frequency in patients with psoriasis. For example, increasing degree of obesity and the associated metabolic syndrome (hyperglycemia, hyperlipidemia, and hypertension) correlates with psoriasis severity. Patients with psoriasis also have increased rates of stroke, myocardial infarction, and other vascular diseases later in adult life. A proposed mechanism involves the systemic proinflammatory state induced by both psoriasis and these associated conditions, although the direction of causality remains unclear. Furthermore, children suffering from psoriasis have a greater risk of taking psychotropic medications for anxiety or depression, and are more likely to report impairment in quality of life due to their chronic disease.

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676.2

Pityriasis Lichenoides

Nicole R. Bender, Yvonne E. Chiu

Pityriasis lichenoides encompasses a disease spectrum ranging from PLC to pityriasis lichenoides et varioliformis acuta (PLEVA; Mucha-Habermann disease). The designation of pityriasis lichenoides as acute or chronic refers to the morphologic appearance of the lesions rather than to the duration of the disease. No correlation is found between the type of lesion at the onset of the eruption and the duration of the disease. Many patients have both acute and chronic lesions simultaneously, and transition of lesions from one form into another occurs occasionally. As a result, some authors advocate using pityriasis lichenoides as the general diagnosis rather than differentiating between PLC and PLEVA. Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) is a rare subtype of PLEVA that is more severe and potentially life-threatening.

Etiology/Pathogenesis

Two main theories exist for the etiology of pityriasis lichenoides. The first is that it arises in a genetically susceptible individual as a hypersensitivity reaction to an infection. The second is that it represents a monoclonal T-cell lymphocytic proliferation on the pathway to cutaneous T-cell dyscrasia.

Clinical Manifestations

Pityriasis lichenoides most commonly manifests in the 2nd and 3rd decades of life; 30% of cases manifest before age 20 yr with peaks of incidence at 5 and 10 yr of age. The overall eruption persists for months to years with a tendency to eventually remit.

PLC manifests gradually as generalized, multiple, 3-5 mm, brown-red papules that are covered by a fine grayish scale (Fig. 676.2). Lesions may be asymptomatic or may cause minimal pruritus and occasionally become vesicular, hemorrhagic, crusted, or superinfected. Individual papules become flat and brownish in 2-6 wk, ultimately leaving a hyperpigmented or hypopigmented macule. Scarring is unusual. Various stages of lesions are present most commonly on the trunk and extremities and generally spare the face, palmoplantar surfaces, scalp, and mucous membranes.

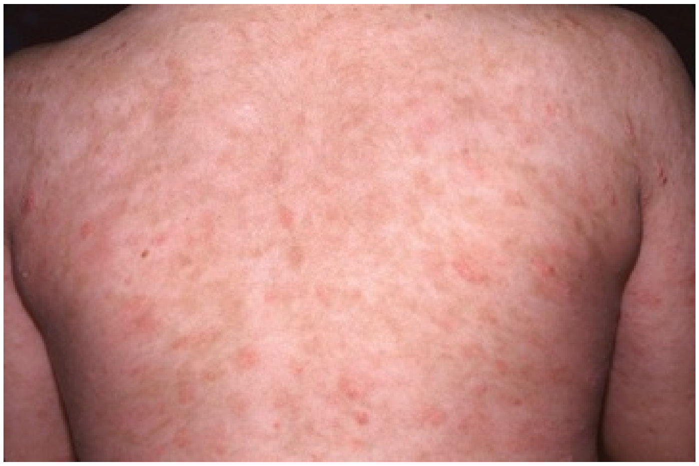

FIG. 676.2 **Widespread plaques with fine scale in pityriasis lichenoides chronica.**

PLEVA manifests as an abrupt eruption of numerous 2- to 3-mm papules that have a vesiculopustular and then a purpuric center, are covered by a dark adherent hemorrhagic or necrotic crust, and are surrounded by an erythematous halo (Fig. 676.3). Constitutional symptoms, such as fever, malaise, headache, and arthralgias, may be present for 2-3 days after the initial outbreak. Lesions are distributed diffusely on the trunk and extremities, as in PLC. Individual lesions heal within a few weeks, sometimes leaving a varioliform scar, and successive crops of papules produce the characteristic polymorphous appearance of the eruption, with lesions in various stages of evolution.

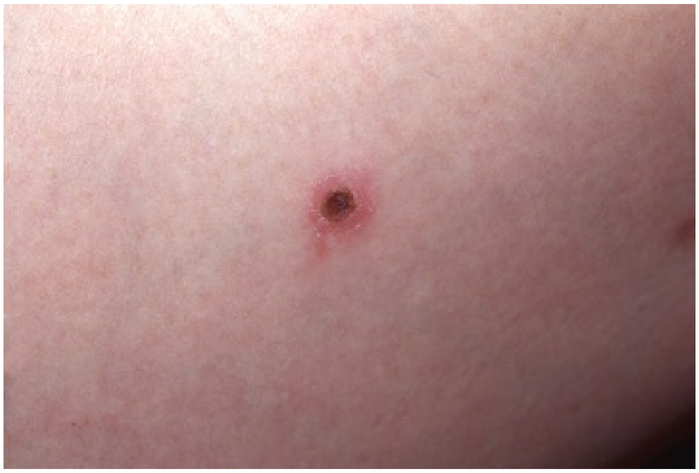

FIG. 676.3 Necrotic lesion with erythematous halo in pityriasis lichenoides et varioliformis acuta.

FUMHD manifests as high fever and ulceronecrotic nodules up to a few centimeters in diameter, which are most common on the anterior trunk and flexor surfaces of the proximal upper extremities. Histopathology of lesions is consistent with PLEVA. Hemorrhagic bullae, mucosal ulcers, arthritis, cardiomyopathy, vasculitis, abdominal complaints, hematologic abnormalities (megaloblastic anemia, pancytopenia, and diffuse intravascular coagulation) and superinfection of cutaneous lesions with *Staphylococcus aureus* may also develop. These patients may have a history of previous PLEVA diagnosis. While there is no reported standardized treatment and there have been reports of fatalities, typically the ulceronecrotic lesions heal with hypopigmented scarring in a few weeks.

Pathology

PLC histologically shows a parakeratotic, thickened corneal layer; epidermal spongiosis; a superficial perivascular infiltrate of macrophages and predominantly CD8 lymphocytes that may extend into the epidermis; and small numbers of extravasated erythrocytes in the papillary dermis.

The histopathologic changes of PLEVA and FUMHD reflect their more severe nature. Intercellular and intracellular edema in the epidermis may lead to degeneration of keratinocytes. A dense perivascular mononuclear cell infiltrate, endothelial cell swelling, and extravasation of erythrocytes into the epidermis and dermis are additional characteristic features.

Differential Diagnosis

The differential diagnosis of pityriasis lichenoides includes guttate psoriasis, pityriasis rosea, drug eruptions, secondary syphilis, viral exanthems, lymphomatoid papulosis, and lichen planus. The chronicity of pityriasis lichenoides helps preclude pityriasis rosea, viral exanthems, and some drug eruptions. A skin biopsy helps distinguish pityriasis lichenoides from other entities in the differential diagnosis.

Treatment

In general, pityriasis lichenoides should be considered a benign condition that does not alter the health of the child. A lubricant to remove excessive scaling may be all that is necessary if the patient is asymptomatic. If treatment is required, first-line agents are oral antiinflammatory antibiotics such as erythromycin (30-50 mg/kg/day for 2-3 mo). Topical corticosteroids (mid-potency, applied twice daily) and topical calcineurin inhibitors may help the pruritus and inflammation, but do not alter the course of the disease. Phototherapy (NB-UVB) is the second-line treatment option. Methotrexate should be reserved for severely symptomatic cases. The rare FUMHD usually requires inpatient treatment; initially, systemic corticosteroids, methotrexate, intravenous immunoglobulin, or cyclosporine may be necessary, with eventual transition to another form of treatment, as mentioned above, once the disease improves and stabilizes.

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676.3

Keratosis Pilaris

Nicole R. Bender, Yvonne E. Chiu

Keratosis pilaris is a common papular eruption resulting from keratin plugging of hair follicles. It displays an autosomal dominant transmission with variable penetrance. Typical areas of involvement include the upper extensor surfaces of the arms and thighs, cheeks, and buttocks. The lesions may resemble gooseflesh; they are noninflammatory, scaly, follicular papules that do not coalesce. They are generally asymptomatic but may be pruritic. Irritation of the follicular plugs occasionally causes erythema surrounding the keratotic papules (Fig. 676.4). A subset of patients have keratosis pilaris associated with facial telangiectasia and ulerythema ophryogenes, a rare cutaneous disorder characterized by inflammatory keratotic facial papules that may result in scars, atrophy, and alopecia. Because the lesions of keratosis pilaris are associated with and accentuated by dry skin, they are often more prominent during the winter. Keratosis pilaris is more frequent in patients with atopic dermatitis and is most common during childhood and early adulthood, tending to subside in the 3rd decade of life. Treatment of keratosis pilaris is optional. Measures to decrease pruritus include moisturization with a bland emollient. Regular applications of a

10–40% urea cream or an alpha-hydroxy acid preparation such as 12% lactic acid cream or lotion can improve the appearance of keratosis pilaris but may further contribute to pruritus and irritation. Therapy may improve the condition but does not cure it.

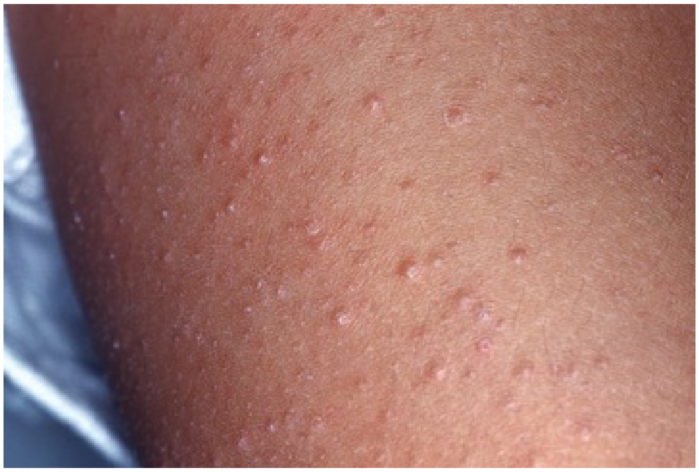

FIG. 676.4 **Keratotic follicular plugs with surrounding erythema in keratosis pilaris.**

676.4

Lichen Spinulosus

Nicole R. Bender, Yvonne E. Chiu

Lichen spinulosus is an uncommon disorder that occurs principally in children and more frequently in boys. The cause is unknown. The lesions consist of sharply circumscribed irregular plaques of spiny, keratotic, follicular plugs. Plaques may occur anywhere on the body and are often distributed symmetrically on the trunk, elbows, knees, and extensor surfaces of the limbs. Although sometimes erythematous or pruritic, the lesions are usually skin colored and asymptomatic.

Treatment is usually unnecessary. For patients who regard the eruption as a cosmetic defect, urea-containing lubricants (10–40%) are often effective in flattening the projections. The plaques usually disappear spontaneously after several months or years.

676.5

Pityriasis Rosea

Nicole R. Bender, Yvonne E. Chiu

Pityriasis rosea is a common benign papulosquamous disorder typically affecting adolescents and young adults 15-30 yr of age. The disease is more commonly seen in the winter, and is usually self-limited.

Etiology/Pathogenesis

The cause of pityriasis rosea is unknown; a viral agent is suspected, with a current focus on human herpesviruses 6 and 7. Supporting evidence for an infectious etiology includes the tendency for it to occur in (familial) case clusters, presence of a prodrome and seasonal variation, and infrequent recurrences; although the rash itself does not appear to be contagious.

Clinical Manifestations

This benign, common eruption occurs most frequently in children and young adults. Although a prodrome of fever, malaise, arthralgia, and pharyngitis may precede the eruption, children rarely complain of such symptoms. A **herald patch** classically precedes the generalized eruption and may occur anywhere on the body. Herald patches are generally larger than other lesions and vary from 1 to 10 cm in diameter; they are annular in configuration and have a raised border with fine, adherent scales. Approximately 5-10 days after the appearance of the herald patch, a widespread, symmetric eruption involving mainly the trunk and proximal limbs becomes evident (Fig. 676.5). In the inverse form of pityriasis rosea, the face, scalp, and distal limbs may be preferentially involved. Lesions may appear in crops for several days. Typical lesions are oval or round, <1 cm in diameter, slightly raised, and pink to brown. The developed lesion is covered by a fine scale, which gives the skin a crinkly appearance. Some lesions clear centrally and produce a collarette of scale that is attached only at the periphery. Papular (more common in black children), vesicular, urticarial, hemorrhagic, large annular, and mucosal lesions are unusual variants. The long axis of each lesion is usually aligned with the cutaneous cleavage lines, a feature that creates the so-called **Christmas tree pattern** on the back. Conformation to skin lines is often more discernible in the anterior and posterior axillary folds and supraclavicular areas. The lesions most commonly are asymptomatic but may be mildly to severely pruritic. Duration of the eruption varies from 2 to 12 wk, with self-resolution. After the eruption has resolved, postinflammatory hypopigmentation or hyperpigmentation may be pronounced, particularly in dark-skinned patients. These changes disappear in subsequent weeks to months.

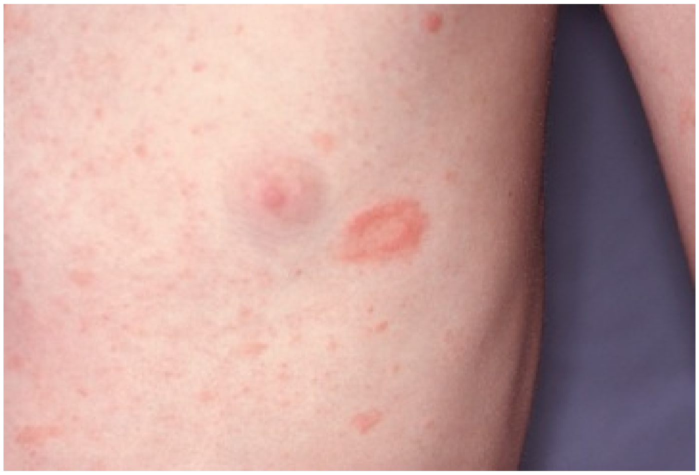

FIG. 676.5 **Herald patch and surrounding pityriasis rosea.**

Differential Diagnosis

The herald patch may be mistaken for tinea corporis, a pitfall that can be avoided if microscopic evaluation of a potassium hydroxide preparation of scrapings of the lesion is performed. The generalized eruption resembles a number of other diseases; secondary syphilis is the most important. Drug eruptions, viral exanthems, guttate psoriasis, PLC, and nummular dermatitis can also be confused with pityriasis rosea.

Treatment

Therapy is unnecessary for asymptomatic patients with pityriasis rosea. If scaling is prominent, a bland emollient may suffice. Pruritus may be suppressed by a lubricating lotion containing menthol and camphor or by an oral antihistamine for sedation, particularly at night, when itching may be troublesome. Occasionally, a mid-potency topical corticosteroid preparation may be necessary to alleviate pruritus. Exposure to natural sunlight and NB-UVB phototherapy may reduce disease duration and severity.

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676.6

Pityriasis Rubra Pilaris

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Etiology/Pathogenesis

The cause of pityriasis rubra pilaris is unknown. Although genetic forms with autosomal dominant or recessive transmission may account for some cases in childhood, most cases are sporadic. Some studies have indicated a role for TNF-α in disease development, while other hypotheses for causal factors include abnormal vitamin A metabolism, trauma, infections, immunosuppression, and UV light exposure.

Clinical Manifestations

This rare inflammatory dermatosis is known for its variability in clinical presentation and course of disease. It often has an insidious onset with diffuse scaling and erythema of the scalp, which is indistinguishable from the findings in seborrheic dermatitis, and with thick hyperkeratosis of the palms and soles (Fig. 676.6*A*). Lesions over the elbows and knees are also common (see Fig. 676.6*B*), and generalized erythroderma develops in some patients. The characteristic primary lesion is a firm, dome-shaped, tiny, acuminate, pink to red papule, which has a central keratotic plug pierced by a vellus hair. Masses of these papules coalesce to form large, erythematous, sharply demarcated orange-pink plaques with overlying scale, within which islands of normal skin can be distinguished. Typical papules on the dorsum of the proximal phalanges are readily palpated. Gray plaques or papules resembling lichen planus may be found in the oral cavity. Dystrophic changes in the nails may occur and mimic those of psoriasis. Lesions are commonly pruritic. In childhood, the prognosis for eventual resolution is relatively good.

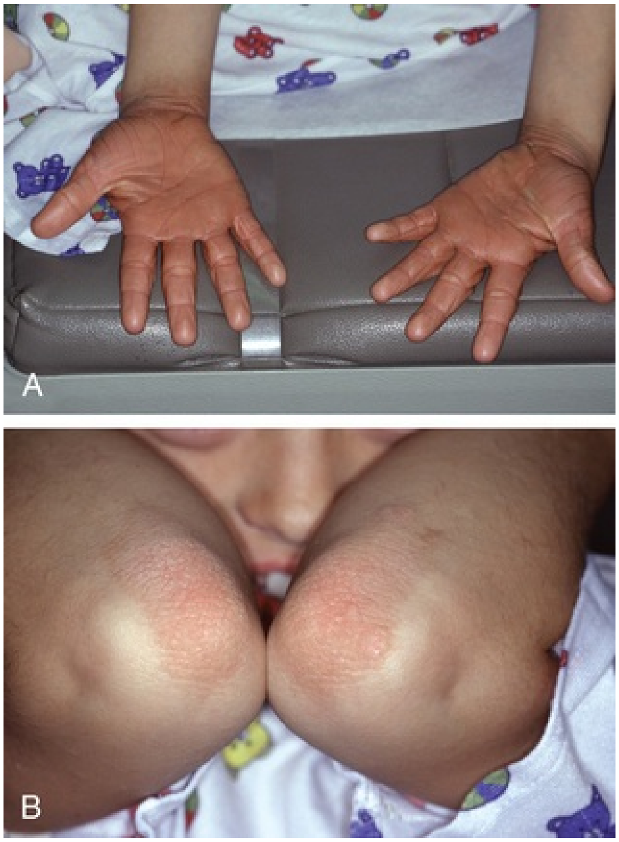

FIG. 676.6 **Pityriasis rubra pilaris. A, Orange palmar hyperkeratosis. B, Elbow lesions.**

Differential Diagnosis

Differential diagnosis includes ichthyosis, seborrheic dermatitis, keratoderma of the palms and soles, and psoriasis.

Histology

Skin biopsy revealing follicular plugging, epidermal acanthosis, perivascular infiltrate, checkerboard pattern of orthokeratosis and parakeratosis, and an intact granular layer may differentiate this condition from psoriasis and seborrheic dermatitis.

Treatment

The numerous therapeutic regimens recommended are difficult to evaluate because pityriasis rubra pilaris has a capricious course with exacerbations and remissions. Moisturization alone is useful in mild cases. Topical agents, such as mid- to high-potency corticosteroids, keratolytics (urea, salicylic acid), vitamin D analogs (calcipotriene), retinoids (tazarotene, tretinoin), and tar, are used in combination with systemic agents for widespread disease and as monotherapy for localized disease. When further treatment is necessary, oral retinoids (isotretinoin or acitretin 0.5-1 mg/kg/day) are used as 1st-line agents, while methotrexate is used as a 2nd-line agent. Third-line treatment options include biologic TNF-α inhibitors, cyclosporine, azathioprine, and NB-UVB phototherapy.

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676.7

Darier Disease (Keratosis Follicularis)

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Etiology/Pathogenesis

A rare genetic disorder, Darier disease is inherited as an autosomal dominant trait and is caused by mutations in the *ATP2A2* gene. This gene encodes a cellular calcium pump, SERCA2, and dysfunction results in loss of adhesion between epidermal cells and abnormal keratinization.

Clinical Manifestations

Onset usually occurs in late childhood and persists throughout life. Typical lesions are small, firm, skin-colored, warty papules that are not always follicular in location. The lesions eventually acquire yellow, malodorous, greasy crusts and coalesce to form large, gray-brown, vegetative plaques (Fig. 676.7). The scalp, face, neck, shoulders, chest, back, axillae, limb flexures, and groin are symmetrically involved. Papules, fissures, crusts, and ulcers may appear on the mucous membranes of the lips, tongue, buccal mucosa, pharynx, larynx, and vulva. Hyperkeratosis of the palms and soles and nail dystrophy with subungual hyperkeratosis and longitudinal red and white banding are variable features. Severe pruritus, secondary infection, offensive odor, and pain may occur. Several exacerbating triggers have been identified: sweating, UV light exposure, heat, friction, surgery, and infections; thus, Darier disease has a chronic relapsing course that usually worsens in summertime.

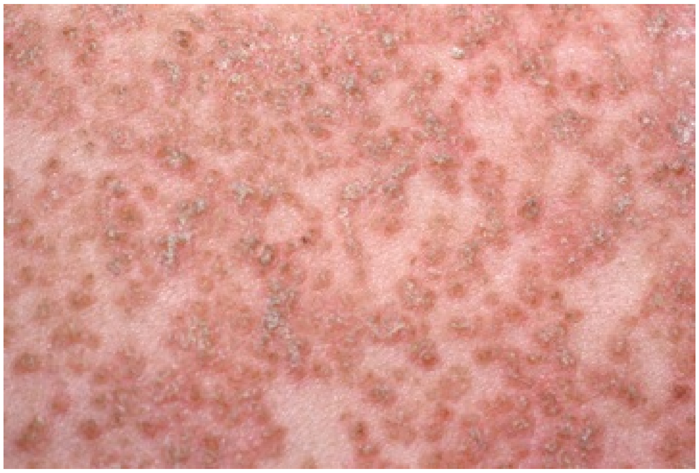

FIG. 676.7 Papules coalescing into large plaque on the back of a patient with Darier disease.

Histology

Histologic changes seen in Darier disease are diagnostic. Hyperkeratosis with keratin plugging, intraepidermal separation (acantholysis) with formation of suprabasal clefts, and dyskeratotic epidermal cells are characteristic features.

Differential Diagnosis

Darier disease is most likely to be confused with seborrheic dermatitis, acanthosis nigricans, flat warts, or Hailey-Hailey disease.

Treatment

Treatment is nonspecific and begins with emollients and avoidance of triggers. First-line treatment for mild/localized disease is low- to mid-potency corticosteroids; second-line treatment is topical retinoids. Further treatment options include topical keratolytic agents (urea, lactic acid), antiseptic washes (triclosan, chlorhexidine gluconate, or bleach), or calcineurin inhibitors. More severe/generalized disease is treated with oral isotretinoin or acitretin (0.5-1.0 mg/kg/day for 3-4 mo). Secondary infections are common and must be treated appropriately. Novel treatments currently being investigated include anti-IL 6 antibodies, cyclooxygenase-2 (COX2) inhibitors and miglustat (a glucosylceramide synthase inhibitor).

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676.8

Lichen Nitidus

Nicole R. Bender, Yvonne E. Chiu

Etiology/Pathogenesis

The etiology of lichen nitidus is unknown but has been linked to immune alteration.

Clinical Manifestations

This uncommon, chronic, benign, papular eruption is characterized by minute (1-2 mm), flat-topped, shiny, firm papules of uniform size. The papules are most often skin-colored but may be pink or red. In black individuals, they are usually hypopigmented (Fig. 676.8). Sites of predilection are the genitals, abdomen, chest, forearms, wrists, and inner aspects of the thighs. The lesions may be sparse or numerous and may form large plaques; careful examination usually discloses linear papules in a line of a scratch (Koebner phenomenon), a valuable clue to the diagnosis because it occurs in only a few diseases. Lichen nitidus occurs in all age groups but is most prevalent in school-age children and young adults. Patients with lichen nitidus are usually asymptomatic and constitutionally well, although pruritus may be severe. The lesions may be confused with those of lichen planus, and lichen nitidus can rarely occur concurrently with lichen planus.

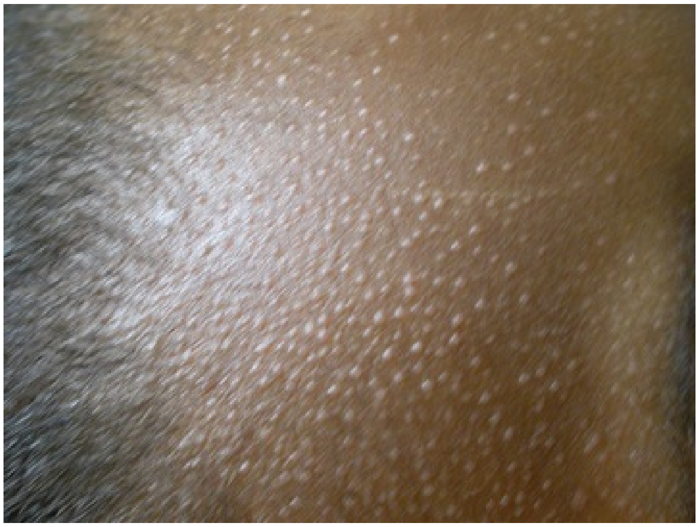

FIG. 676.8 **Slightly hypopigmented, uniform papules of lichen nitidus.**

Differential Diagnosis

Widespread keratosis pilaris can also be confused with lichen nitidus, but the follicular localization of the papules and the absence of Koebner phenomenon in the former distinguish them. Verruca plana (flat warts), if small and uniform in size, may occasionally resemble lichen nitidus.

Histology

Although the diagnosis can be made clinically, a biopsy is occasionally indicated. The lichen nitidus papule consists of sharply circumscribed nests of lymphocytes and histiocytes in the upper dermis enclosed by claw-like epidermal rete ridges.

Treatment

The course of lichen nitidus spans months to years, but the lesions eventually involute completely. No treatment is necessary, but mid- to high-potency topical steroids may be used for pruritus.

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676.9

Lichen Striatus

Nicole R. Bender, Yvonne E. Chiu

Etiology/Pathogenesis

Lichen striatus is hypothesized to be caused by a combination of genetic predisposition present in a mosaic manner in the skin (following the lines of Blaschko) and an infectious trigger.

Clinical Manifestations

A benign, self-limited eruption, lichen striatus consists of a continuous or discontinuous linear band of papules in a Blaschkoid distribution. The primary lesion is a flat-topped, hypopigmented or pink papule covered with fine scale. Aggregates of these papules form multiple bands or plaques. The papules are gradually replaced by hypopigmented macules, which may be the presenting lesion in some cases. The eruption evolves over a period of days or weeks in an otherwise healthy child, remains stationary for weeks to months, and finally remits without sequelae usually within 2 yr. Symptoms are usually absent, although some children complain of itching. Nail dystrophy may occur when the eruption involves the proximal nail fold and matrix (Fig. 676.9).

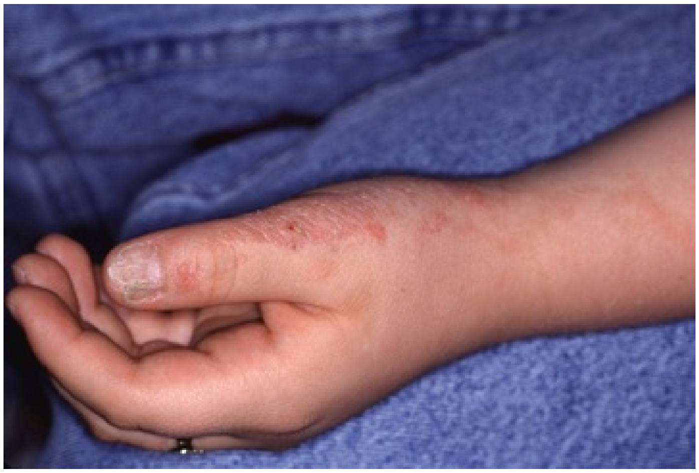

FIG. 676.9 **Lichen striatus with nail dystrophy.**

Differential Diagnosis

Lichen striatus is occasionally confused with other disorders. The initial plaque may resemble papular eczema or lichen nitidus until the linear configuration becomes apparent. Linear lichen planus and linear psoriasis are usually associated with typical individual lesions elsewhere on the body. Linear epidermal nevi are permanent lesions that often become more hyperkeratotic and hyperpigmented than those of lichen striatus.

Treatment

Treatment is not necessary and generally not very effective. A low-potency topical corticosteroid preparation or topical calcineurin inhibitor can be used when pruritus is a problem in a patient with lichen striatus.

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676.10

Lichen Planus

Nicole R. Bender, Yvonne E. Chiu

Etiology/Pathogenesis

The cause of lichen planus is unknown but an immune attack on the skin by cytotoxic T cells is postulated. A genetic predisposition may exist, and other proposed triggers include metal exposure, certain medications, liver disease, vaccinations (especially hepatitis B vaccination), and infections (especially hepatitis C virus).

Clinical Manifestations

This is a rare disorder in young children and uncommon in older ones. It is more often seen in children from the Indian subcontinent and of African-American background. The classic form of lichen planus is the most common subtype in children, often exhibiting an acute eruptive onset. The lesions erupt in an explosive fashion, much like a viral exanthem, and spread to involve most of the body surface. The primary lesion is a violaceous, sharply demarcated, polygonal papule with fine white lines (Wickham's striae) or scale on the surface. Papules may coalesce to form large plaques (Fig. 676.10). The papules are intensely pruritic, and additional papules are often induced by scratching (Koebner phenomenon) so that lines of them are detected. Sites of predilection are the flexor surfaces of the wrists, the forearms, the inner aspects of the thighs, and the ankles.

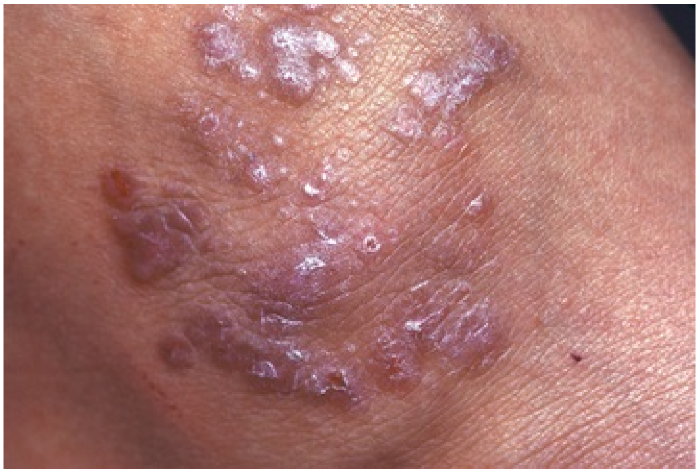

FIG. 676.10 **Flat-topped, purple polygonal papules of lichen planus.**

Hypertrophic, linear, bullous, atrophic, annular, follicular, erosive, ulcerative, and actinic forms of lichen planus may also occur in children. Characteristic lesions of mucous membranes consist of pinhead-size white papules that coalesce to form reticulated and lacy patterns on the buccal mucosa. Erosive ulcers are also common in the oral mucosa, and may also involve the gastrointestinal tract. Nail involvement causes nail dystrophy. The disorder may persist for months to years, but self-resolution eventually occurs in most cases. Intense hyperpigmentation frequently persists for a long time after the resolution of lesions.

Histology

The histopathologic findings in lichen planus are specific, consisting of hyperkeratosis, irregular acanthosis, wedge-shaped hypergranulosis, apoptotic keratinocytes in the lower epidermis and upper dermis, and basal cell degeneration with a band-like lymphocytic infiltrate at the epidermal-dermal junction. Pigment incontinence is frequently seen. Biopsy is indicated if the diagnosis is unclear.

Treatment

Treatment is directed at alleviation of the intense pruritus and amelioration of the skin lesions. First-line treatment with a high-potency topical corticosteroid applied twice daily is effective for localized disease on the trunk or extremities; lesions on the face and genitals may be treated with low- to mid-potency corticosteroids. Alternatives to topical steroids include topical calcineurin inhibitors or vitamin D analogs. Thick lesions may require intralesional corticosteroid injection. Oral antihistamines (hydroxyzine) are often added for the pruritus. Short courses of systemic glucocorticoids or phototherapy (NB-UVB) are used as second-line approaches for rare cases of widespread, intractable lesions. Other medications with reported efficacy include oral retinoids (acitretin), dapsone, metronidazole, griseofulvin, and methotrexate.

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676.11

Porokeratosis

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Etiology/Pathogenesis

Porokeratoses are a group of uncommon dermatoses due to abnormal epidermal keratinization. The etiology is unknown except for the disseminated actinic form, which is secondary to chronic sun exposure. The classic hypothesis proposes peripheral expansion of a clone of mutant epidermal keratinocytes localized to the site of pathology. Genetic susceptibility, with autosomal dominant transmission, and immunosuppression (particularly organ transplantation) may also be involved.

Clinical Manifestations

Porokeratosis is a rare, chronic, progressive disease of keratinization. The prototypical lesion is an atrophic papule or plaque with a surrounding ridge of hyperkeratosis, called cornoid lamella. Several forms have been delineated: solitary plaques, linear porokeratosis, hyperkeratotic lesions of the palms and soles, disseminated eruptive lesions, and superficial actinic porokeratosis. **Classic porokeratosis of Mibelli** begins in childhood and is more common in males. Sites of predilection are the limbs, face, genitals, mucous membranes, palms, and soles. The primary lesion is a small, keratotic papule that slowly enlarges peripherally so that the center becomes depressed, with the edge forming an elevated wall or collar (Fig. 676.11). The configuration of the plaque may be round, oval, or gyrate. The elevated border is split by a thin groove from which minute cornified projections protrude. The central atrophic area is yellow, gray, or tan, and sclerotic, smooth, and dry, whereas the hyperkeratotic border is a darker gray, brown, or black. **Linear porokeratosis** is also more common in childhood and typically follows the lines of Blaschko. The disease is slowly progressive but relatively asymptomatic; some patients experience pruritus or pain.

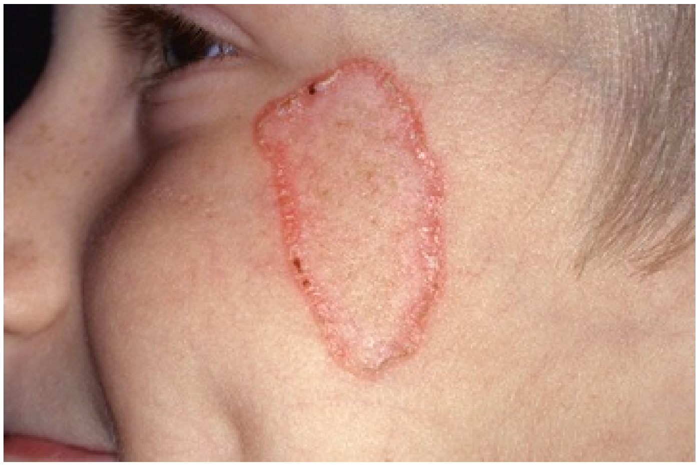

FIG. 676.11 **Large plaque of porokeratosis of Mibelli with raised border and depressed center.**

Histology

A skin biopsy is usually unnecessary but will disclose the characteristic cornoid lamella (plug of stratum corneum cells with retained nuclei), which is responsible for the invariable linear ridge of the lesion. The granular layer is absent beneath the cornoid lamella.

Differential Diagnosis

The differential diagnosis of porokeratosis includes warts, epidermal nevi, lichen planus, granuloma annulare, tinea corporis, nummular eczema, pityriasis rosea, and elastosis perforans serpiginosa.

Treatment

No treatment is uniformly successful, thus therapeutic decisions depend largely on lesion size, location, symptoms, and patient preference. Most lesions are asymptomatic and do not require any intervention; however, when treatment is necessary, options include pharmacologic management (topical vitamin D analogs, topical retinoids, topical 5-fluorouracil, topical imiquimod, or oral retinoids [severe cases only]), destructive therapy (liquid nitrogen cryotherapy, electrodessication and curettage, or various lasers), and surgical removal. In general, the less-invasive topical agents should be attempted first. Good sunlight protection should also be encouraged to decrease risk of malignant transformation.

Prognosis

Typically the course of porokeratosis is slowly progressive, with an increase in size and number of individual lesions. Some cases undergo spontaneous resolution, while infrequently porokeratosis lesions may undergo malignant transformation into squamous cell carcinoma. At-risk lesions appear to be long-standing (average 33.5 year-duration), large size, and location on limbs.

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676.12

Gianotti-Crosti Syndrome (Papular Acrodermatitis)

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Etiology/Pathogenesis

The pathogenesis of Gianotti-Crosti syndrome, also known as papular acrodermatitis, is unclear, but an immunologic reaction to viral infections and immunizations has been postulated. Historically, the most common associations are with Epstein-Barr virus, hepatitis B virus (primarily in countries without routine childhood vaccination programs), coxsackievirus A16, and parainfluenza virus, as well as with many childhood immunizations.

Clinical Manifestations

This distinctive eruption is benign and predominantly occurs in children younger than 5 yr old about 1 wk after a viral illness. Cases are usually sporadic, but epidemics have been recorded. Skin lesions are monomorphic, firm, dusky or coppery red papules ranging in size from 1 to 10 mm (Fig. 676.12), although there is considerable variation in lesion appearance between patients. The papules often have the appearance of vesicles; however, when opened no fluid is obtained. The papules sometimes become hemorrhagic. Lines of papules **(Koebner phenomenon)** may be noted on the extremities following minor local trauma. The papules occur in crops and may become profuse and coalesce into plaques, forming a symmetric eruption on the face, ears, buttocks, and limbs, including the palms and soles. The trunk is relatively spared, as are the scalp and mucous membranes. The eruption is occasionally associated with malaise and low-grade fever but few other constitutional symptoms. The underlying viral infection may cause signs and symptoms, such as lymphadenopathy and hepatomegaly in patients with hepatitis B viremia. The eruption resolves spontaneously but may take up to 2 mo. Some residual pigment change may occur but not scarring.

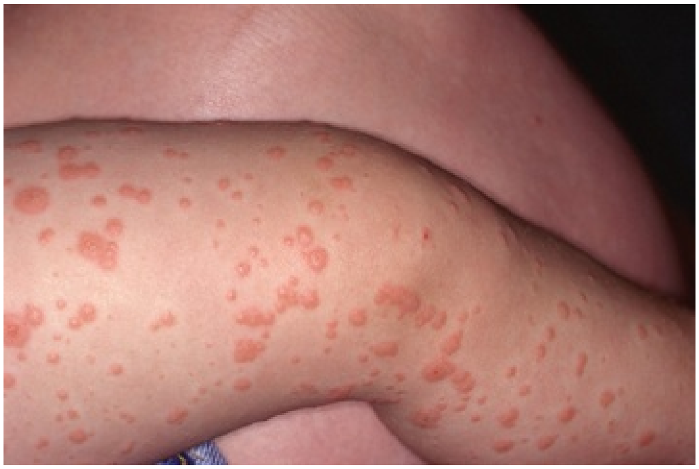

FIG. 676.12 **Numerous, flat-topped, red papules in Gianotti-Crosti syndrome.**

Histology

Skin biopsy in Gianotti-Crosti syndrome is not specific, being characterized by a dermal perivascular mononuclear cell infiltrate, capillary endothelial swelling, and epidermal spongiosis and parakeratosis.

Differential Diagnosis

Gianotti-Crosti syndrome can be confused with other viral exanthems, erythema infectiosum, lichen planus, erythema multiforme, and Henoch-Schönlein purpura.

Treatment

The lesions are typically asymptomatic and resolve spontaneously, thus requiring no treatment. If present, pruritus may be relieved by emollients or calamine lotion. Mid-potency topical steroids may relieve pruritus but do not alter disease course. Sedating antihistamines at bedtime are also helpful.

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676.13

Acanthosis Nigricans

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See also Chapter 60 .

Etiology/Pathogenesis

The skin lesions of acanthosis nigricans may be genetic due to mutations in the fibroblast growth factor receptor gene, or acquired as a manifestation of insulin resistance. In familial cases, acanthosis nigricans is inherited as an autosomal dominant trait and develops in infancy. Insulin resistance with compensatory hyperinsulinism may lead to insulin binding to and activation of insulin-like growth factor receptors, promoting epidermal and fibroblast growth. Common causes of insulin resistance in children are obesity and diabetes mellitus, with acanthosis nigricans seen in >60% of children with a body mass index >98%. Other endocrinopathies such as pituitary hypogonadism, Cushing syndrome, polycystic ovarian syndromes, thyroid disease, and acromegaly, as well as certain drugs (insulin, oral contraceptives and other sex hormones, nicotinic acid, corticosteroids, and heroin) are also implicated as potential underlying causes. In the paraneoplastic form (rare in children), tumor-secreted growth factors induce acanthosis nigricans.

Clinical Manifestations

Acanthosis nigricans is characterized by symmetric, hyperpigmented, velvety, hyperkeratotic plaques with exaggerated skin lines in intertriginous areas. The most common locations are the posterior neck and axillae (Fig. 676.13), but it is also seen in the inframammary areas, groin, inner thighs, and anogenital region. Prior to plaque development, patients notice a “dirty” appearance of affected skin that does not wash clean. Skin lesions remain asymptomatic unless maceration or secondary infection occurs. Acanthosis nigricans is found more commonly in African-American, Hispanic, and Native American children. The clinical severity and histopathologic features of acanthosis nigricans correlate positively with the degree of hyperinsulinism and with the degree of obesity. The **differential diagnosis** includes confluent and reticulated papillomatosis (CARP), Addison disease, pellagra, and erythrasma.

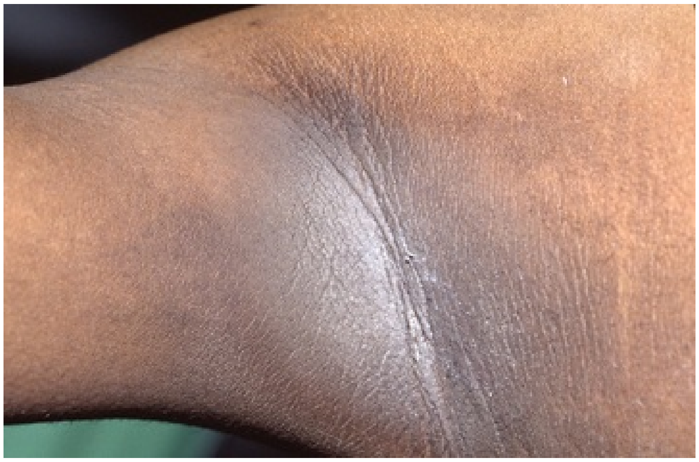

FIG. 676.13 **Velvety hyperpigmentation of the axilla in acanthosis nigricans.**

Histology

The histologic changes are those of papillomatosis and hyperkeratosis rather than acanthosis or excessive pigment formation. A mild dermal inflammatory infiltrate may be present.

Treatment

Treatment is aimed at treatment of the underlying disorder. Acanthosis nigricans in the obese child is associated with risk factors for glucose homeostasis abnormalities, and counseling families on its causes and consequences may motivate them to make healthy lifestyle changes that can decrease the risk for development of cardiac disease and diabetes mellitus. In children with obesity-related acanthosis nigricans, weight loss should be the primary goal. If a drug or malignancy is suspected, removal of that agent or treatment of cancer typically results in resolution. Appearance of skin lesions responds poorly to local medical management; some patients benefit from topical keratolytic agents (40% urea cream or 12% ammonium lactate cream) and agents that inhibit keratinocyte proliferation (topical retinoids and vitamin D analogs).

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CHAPTER 677

Disorders of Keratinization

Kari L. Martin

Disorders of Cornification

Mendelian disorders of cornification (ichthyoses) are a primary group of inherited conditions characterized clinically by patterns of scaling and histopathologically by hyperkeratosis. They are usually distinguishable on the basis of inheritance patterns, clinical features, associated defects, and histopathologic changes (Tables 677.1 and 677.2). Much work is currently underway to better categorize the genotype-phenotype correlation of these diseases. The two main categories of ichthyotic diseases are whether they are limited to the skin or have syndromic associations.

Table 677.1

Disorders of Cornification That Usually Manifest in the First Weeks of Life

DISORDER	INHERITANCE	CLINICAL FEATURES	MUTATION	VISUAL METHOD OF DIAGNOSIS
Harlequin ichthyosis	AR	Thick, armor-like scale with fissuring	*ABCA12*	Clinical
Collodion baby	Usually AR	Shiny collodion membrane	Various	Clinical
Recessive X-linked ichthyosis	Recessive X-linked	Collodion membrane May have genital anomalies	Steroid sulfatase	Plasma cholesterol sulfate
Lamellar ichthyosis	Usually AR	Collodion membrane	Transglutaminase I *ABCA12* *CYP4F22*	Clinical
Congenital ichthyosiform	AR	Collodion membrane	Transglutaminase 1	Clinical

erythroderma			*ALOX12B*	
			ALOXE3	
Epidermolytic ichthyosis	AD	Scaling and blistering	Keratins 1, 10, 2e	Clinical and histologic
Ichthyosis hystrix	AD	Plaques of hyperkeratosis	Keratin 1, *GJB2*	Clinical
Familial peeling skin	AR	Superficial peeling	Type A- *CHST8* Type B loss of corneodesmin	Clinical and histologic
Sjögren-Larsson syndrome	AR	Variable skin thickening	*FAD*	Clinical and fibroblast cultures for FAD
		Mental, developmental retardation		
		Spastic diplegia		
		Seizures		
		“Glistening dots”		
Neutral lipid storage disease	AR	Collodion membrane or ichthyosiform erythroderma	*CGI58*	Blood smear for vacuolated polymorphonuclear leukocytes
Netherton syndrome (see also Table 677.2)	AR	Ichthyosiform erythroderma	*SPINK 5*	Clinical; hair exam later in infancy
		Scant hair, often failure to thrive	Unknown	Clinical and hair microscopy; hair sulfur content
KID (keratitis with ichthyosis and deafness) syndrome	May be AD, AR	Erythrokeratodermatous or thick, leathery skin with stippled papules	*GJB2*	Clinical; auditory evoked potentials
CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome	X-linked dominant	Alopecia	*NSDHL*	Clinical
		Unilateral waxy yellow, scaling		
		Hemidysplasia		
		Limb defects		
Conradi-Hünermann syndrome	X-linked dominant	Thick, psoriasiform scale over erythroderma, patterned along Blaschko lines	*ARSE*	Clinical
		Proximal limb shortening		
Ichthyosis follicularis	Usually X-linked recessive	Prominent follicular hyperkeratoses	*MBTPS2*	Clinical
		Alopecia		
		Photophobia		
CHIME (colobomas of the eyes, heart defects, ichthyosiform dermatosis, mental retardation, and ear abnormalities) syndrome	AR	Ichthyotic erythematous plaques	*PIGL*	Clinical
		Cardiac defects; typical facies		
		Retinal colobomas		
Gaucher disease	AR	Collodion membrane	β-Glucocerebrosidase	Clinical; fibroblast cultures
		Hepatosplenomegaly		

AD, autosomal dominant; AR, autosomal recessive; FAD, fatty aldehyde.

From Eichenfield LF, Frieden IJ, Esterly NB: *Textbook of neonatal dermatology* , Philadelphia, 2001, WB Saunders, p 277.

Table 677.2

Differential Diagnosis of Netherton Syndrome: Disorders With Ichthyosis and Alopecia (Hereditary Disorders Only)*

DISORDER	INHERITANCE	GENE	FEATURES RESEMBLING NETHERTON SYNDROME	DIFFERENTIATION FROM NETHERTON SYNDROME
SAM syndrome	AR Loss-of-function mutations	*DSG1*	CIE with PPK, no collodion membrane; failure to thrive; hypernatremia; barrier defect; dermatitis; high IgE; malabsorption; eosinophilic esophagitis; multiple food allergies; recurrent infections; hypotrichosis; hypoalbuminemia	May have microcephaly, growth hormone deficiency, developmental delay, cardiac defects; psoriasiform dermatitis with acantholysis in skin sections; absence of desmoglein
ADAM17 deficiency	AR Loss-of-function mutations	*ADAM17*	Psoriasiform erythroderma/widespread pustules; failure to thrive; malabsorption; short, broken hair; recurrent infections	Bloody diarrhea; cardiomyopathy/cardiomyositis
EGFR deficiency	AR Loss-of-function mutations	*EGFR*	Erythema, scaling, and widespread pustules; alopecia; failure to thrive, watery diarrhea, high IgE and eosinophils, hypernatremia, hypoalbuminemia; recurrent bronchiolitis	Cardiovascular issues
Trichothiodystrophy	AR Loss-of-function mutations	*ERCC2*, *ERCC3*, *GTF2H5*, *C7Orf11*	CIE-like ichthyosis; short, brittle hair; “tiger tail” hair shaft defect under polarized microscopy	May have impaired intelligence, decreased fertility, short stature, and photosensitivity
IHS (also called autosomal recessive ichthyosis with hypotrichosis [ARIH] syndrome)	AR Loss-of-function mutations	*ST14* (encodes matriptase); abnormal filaggrin processing	Generalized, congenital ichthyosis with sparing of face, palms, and soles; diffuse nonscarring alopecia of scalp, eyelashes, and eyebrows from birth, but improves to sparse, unruly hair during adolescence and merely recession of the frontal hair line by adulthood	May have patchy follicular atrophoderma and hypohidrosis; photophobia from corneal abnormalities; blepharitis; dental abnormalities; hair microscopy may show pili torti or pili bifurcati
IHSC (or NISCH)	AR	*CLDN1*	Congenital generalized	Congenital paucity of bile

syndrome	Loss-of-function mutations	(encodes claudin 1, structural protein of tight junctions)	scaling, predominantly on the limbs and abdomen and sparing skinfolds, palms and soles; coarse, curly hair with frontotemporal cicatricial alopecia	ducts or sclerosing cholangitis leads to neonatal jaundice with hepatomegaly; oligodontia, and enamel dysplasia; blood smears show small eosinophils and keratinocyte vacuoles without lipid contents

[*] Netherton syndrome must also be distinguished from severe atopic dermatitis and immunodeficiency disorders.

AR, autosomal recessive; CIE, congenital ichthyosiform erythroderma; Ig, immunoglobulin; IHS, ichthyosis hypotrichosis syndrome; IHSC, ichthyosis-hypotrichosis-sclerosing cholangitis; NISCH, neonatal ichthyosis sclerosing cholangitis; PPK, palmoplantar keratoderma; SAM, severe dermatitis, multiple allergies, and metabolic wasting.

Collodion Baby

Collodion baby is not a single entity but a newborn phenotype that is most often seen in babies who eventually demonstrate lamellar ichthyosis or congenital ichthyosiform erythroderma (CIE). Less commonly, collodion babies evolve into babies with other forms of ichthyosis or Gaucher disease. A small subset become otherwise healthy babies without chronic skin disease.

Collodion babies are covered at birth by a thick, taut membrane resembling oiled parchment or collodion (Fig. 677.1), which is subsequently shed. Affected neonates have ectropion (eversion of the eyelid away from the globe), flattening of the ears and nose, and fixation of the lips in an O-shaped configuration. Hair may be absent or may perforate the abnormal covering. The membrane cracks with initial respiratory efforts and, shortly after birth, begins to desquamate in large sheets. Admission to a neonatal intensive care unit and a high-humidity environment and application of nonocclusive lubricants facilitates shedding of the membrane. Complete shedding may take several weeks, and a new membrane may occasionally form in localized areas.

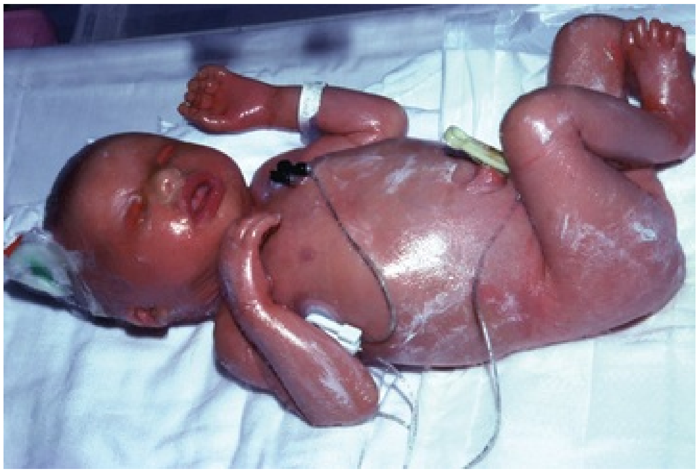

FIG. 677.1 **Typical appearance of a collodion baby.**

Neonatal morbidity and mortality may be due to cutaneous infection, aspiration pneumonia (squamous material), hypothermia, or hypernatremic dehydration from excessive transcutaneous fluid losses as a result of increased skin permeability. The outcome is uncertain, and accurate prognosis depends on identification of the underlying ichthyosis.

Nonsyndromic Ichthyoses

Ichthyosis Vulgaris

Etiology/Pathogenesis

Autosomal dominant or recessive mutations in the filaggrin gene cause ichthyosis vulgaris. Filaggrin is a filament-aggregating protein that assembles the keratin filament cytoskeleton, causing collapse of the granular cells into classic flattened squamous cell shape. Mutations in filaggrin lead to absence or marked reductions in keratohyalin granules.

Clinical Manifestations

Ichthyosis vulgaris is *the most common* of the disorders of keratinization, with an incidence of 1/250 live births. Onset generally occurs in the 1st yr of life. In most cases, it is trivial, consisting only of slight roughening of the skin surface. Scaling is most prominent on the extensor aspects of the extremities, particularly the legs (Fig. 677.2). Flexural surfaces are spared, and the abdomen, neck, and face are relatively uninvolved. Keratosis pilaris, particularly on the upper arms and thighs, accentuated markings, and hyperkeratosis on the palms and soles, and atopy are relatively common. Scaling is most pronounced during the winter months and may abate completely during warm weather. There is no accompanying disorder of hair, teeth, mucosal surfaces, or other organ systems.

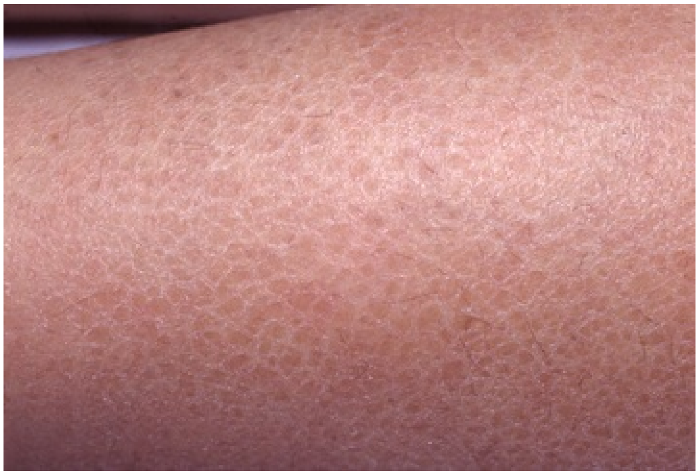

FIG. 677.2 Scale over the shin in ichthyosis vulgaris.

Treatment

Scaling may be diminished by daily applications of an emollient or a lubricant containing urea (10–40%), salicylic acid, or an alpha-hydroxy acid such as lactic acid (5–12%).

X-Linked Ichthyosis

Etiology/Pathogenesis

X-linked ichthyosis involves a deficiency of steroid sulfatase, which hydrolyzes cholesterol sulfate and other sulfated steroids to cholesterol. Cholesterol sulfate accumulates in the stratum corneum and plasma. In the epidermis this accumulation causes malformation of intercellular lipid layers, leading to barrier defects and delay of corneodesmosome degradation, resulting in corneocyte retention.

Clinical Manifestations

Skin peeling may be present at birth but typically begins at 3-6 mo of life.

Scaling is most pronounced on the sides of the neck, lower face, preauricular areas, anterior trunk, and the limbs, particularly the legs. The elbow (Fig. 677.3) and knee flexures are generally spared but may be mildly involved. The palms and soles may be slightly thickened but are also usually spared. The condition gradually worsens in severity and extent. Keratosis pilaris is not present, and there is no increased incidence of atopy. Deep corneal opacities that do not interfere with vision develop in late childhood or adolescence and are a useful marker for the disease because they may also be present in carrier females. Some patients have larger deletions on the X chromosome that encompass neighboring genes, generating *contiguous gene deletion syndromes* . These include Kallmann syndrome (*KAL1* gene), which consists of hypogonadotrophic hypogonadism and anosmia, X-linked chondroplasia punctata (*ARSE* gene), short stature, and ocular albinism. The rate of testicular cancer may be increased in patients with coexistent Kallmann syndrome. There is also an increased risk of attention deficit hyperactivity disorder and autism owing to a contiguous gene defect in neuroligin 4.

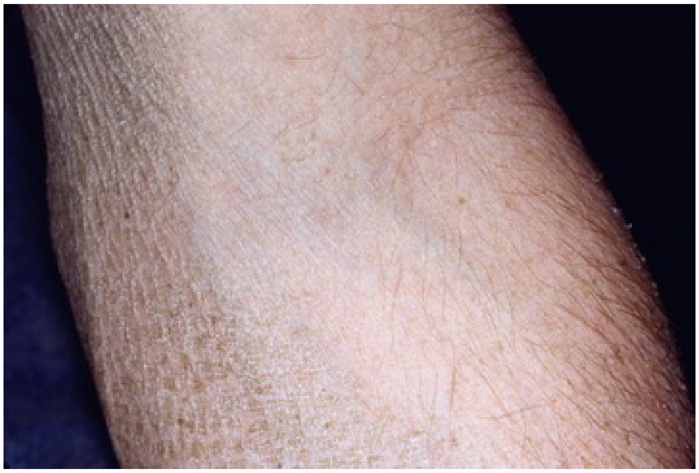

FIG. 677.3 **Sparing of the antecubital fossa in X-linked ichthyosis.**

Reduced steroid sulfatase enzyme activity can be detected in fibroblasts, keratinocytes, and leukocytes and, prenatally, in amniocytes or chorionic villus cells. In affected families, an affected male can be detected by restriction enzyme analysis of cultured chorionic villus cell DNA or amniocytes or by in situ hybridization, which identifies steroid sulfatase gene deletions prenatally in chorionic villus cells. A placental steroid sulfatase deficiency in carrier mothers may result in low urinary and serum estriol values, prolonged labor, and insensitivity of the uterus to oxytocin and prostaglandins.

Treatment

Daily application of emollients and a urea-containing lubricant (10–40%) is usually effective. Glycolic or lactic acid (5–12%) in an emollient base and propylene glycol (40–60%) in water with occlusion overnight are alternative forms of therapy.

Autosomal Recessive Congenital Ichthyoses

Harlequin Ichthyosis

Etiology/Pathogenesis

Harlequin ichthyosis is caused by mutations in the *ABCA12* gene. Mutation in the gene leads to defective lipid transport and *ABCA12* activity is required for the generation of long-chain ceramides that are essential for the development of the normal skin barrier.

Clinical Manifestations

At birth, markedly thickened, ridged, and cracked skin forms horny plates over the entire body, disfiguring the facial features and constricting the digits. Severe ectropion and chemosis obscure the orbits, the nose and ears are flattened, and the lips are everted and gaping. Nails and hair may be absent. Joint mobility is restricted, and the hands and feet appear fixed and ischemic. Affected neonates have respiratory difficulty, suck poorly, and are subject to severe cutaneous infection. Harlequin ichthyosis used to be uniformly fatal in the neonatal period, but with the use of oral retinoids, more patients survive (~80%) beyond infancy and have severe ichthyosis usually resembling lamellar ichthyosis or nonbullous CIE as adolescents and adults. Those with a compound heterozygous genotype have a better prognosis.

Treatment

Initial treatment includes high fluid intake to avoid dehydration from transepidermal water loss and use of a humidified heated incubator, emulsifying ointments, careful attention to hygiene, and oral retinoids. Prenatal diagnosis has been accomplished by fetoscopy, fetal skin biopsy, and microscopic examination of cells from amniotic fluid.

Lamellar Ichthyosis and Congenital Ichthyosiform Erythroderma (Nonbullous Congenital Ichthyosiform Erythroderma)

Lamellar ichthyosis and CIE (nonbullous congenital ichthyosiform erythroderma; non-Harlequin ichthyosis autosomal recessive congenital ichthyoses [ARCI]) are the most common types of autosomal recessively inherited ichthyosis. Both forms are present at or shortly after birth. Most infants with these forms of ichthyosis present with erythroderma and scaling; but among collodion babies, most turn out to have one of these ichthyosis variants.

Etiology/Pathogenesis

Six genes have been identified that cause non-Harlequin ichthyosis ARCI: *TGM* (the gene encoding transglutaminase), *ABCA12* , *NIPAL4* (also known as *ICHTHYIN*), *CYP4F22* , and the lipoxygenase genes *ALOX12B* and *ALOXE3* . Transglutaminase mutations lead to abnormalities in the cornified envelope, whereas defects in *ABCA12* cause abnormal lipid transport and those in *CYP4F22* produce abnormal lamellar granules. The lipoxygenases are likely to play a role in epidermal barrier formation by affecting lipid metabolism.

Clinical Manifestations

After shedding of the collodion membrane, if present, lamellar ichthyosis evolves into large, quadrilateral, dark scales that are free at the edges and adherent at the center. Scaling is often pronounced and involves the entire body surface, including flexural surfaces (Fig. 677.4). The face is often markedly involved, including ectropion and small, crumpled ears. The palms and soles are generally hyperkeratotic. The hair may be sparse and fine, but the teeth and mucosal surfaces are normal. Unlike in CIE, there is little erythema.

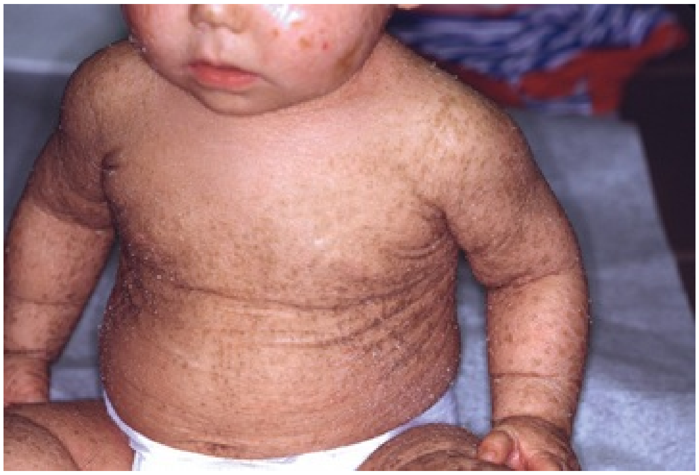

FIG. 677.4 Generalized scaling of lamellar ichthyosis.

In CIE, erythroderma tends to be persistent, and scales, although they are generalized, are finer and whiter than in lamellar ichthyosis (Fig. 677.5). Hyperkeratosis is particularly noticeable around the knees, elbows, and ankles. Palms and soles are uniformly hyperkeratotic. Patients have sparse hair, cicatricial alopecia, and nail dystrophy. Neither form includes blistering.

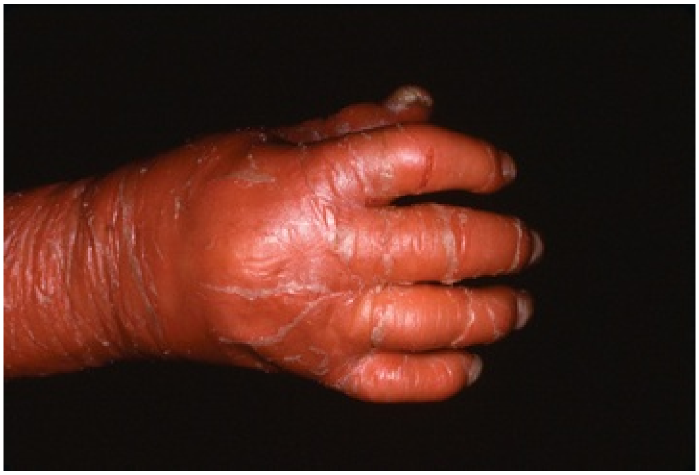

FIG. 677.5 Prominent erythema and scale in congenital ichthyosiform erythroderma.

Treatment

Pruritus may be severe and responds minimally to antipruritic therapy. The unattractive appearance of the child and the bad odor from bacterial colonization of macerated scales may create serious psychologic problems. A high-humidity environment in winter and air conditioning in summer reduce discomfort. Generous and frequent applications of emollients and keratolytic agents such as lactic or glycolic acid (5–12%), urea (10–40%), tazarotene (0.1% gel), and retinoic acid (0.1% cream) may lessen the scaling to some extent, although these agents produce stinging if applied to fissured skin. Oral retinoids have a beneficial effect in these conditions but do not alter the underlying defect and, therefore, must be administered indefinitely. The long-term risks of these compounds (teratogenic effects and toxicity to bone) may limit their usefulness. Ectropion requires ophthalmologic care and, at times, plastic surgical procedures.

Keratinopathic Ichthyoses

Epidermolytic Ichthyosis (Bullous Congenital Ichthyosiform Erythroderma; Epidermolytic Hyperkeratosis)

Etiology/Pathogenesis

Epidermolytic ichthyosis is an autosomal dominant trait that has been shown to be due to defects in either keratin 1 or keratin 10. These keratins are required to form the keratin-intermediate filaments in cells of the suprabasilar layers of the epidermis.

Clinical Manifestations

The clinical manifestations are initially characterized by the onset at birth of widespread blisters and erosions on a background of generalized erythroderma (Fig. 677.6). Recurrent blistering may be widespread in neonates and may cause diagnostic confusion with other blistering disorders. With time, the blister formation ceases, erythema decreases, and generalized hyperkeratosis develops. The scales are small, hard, and verrucous. Distinctive, parallel hyperkeratotic ridges develop over the joint flexures, including the axillary, popliteal, and antecubital fossae, and on the neck and hips. Palmoplantar keratoderma (PPK) is associated with keratin 1 defects. The hair, nails, mucosa, and sweat glands are normal. Malodorous secondary bacterial infection is common and requires appropriate antibiotic therapy.

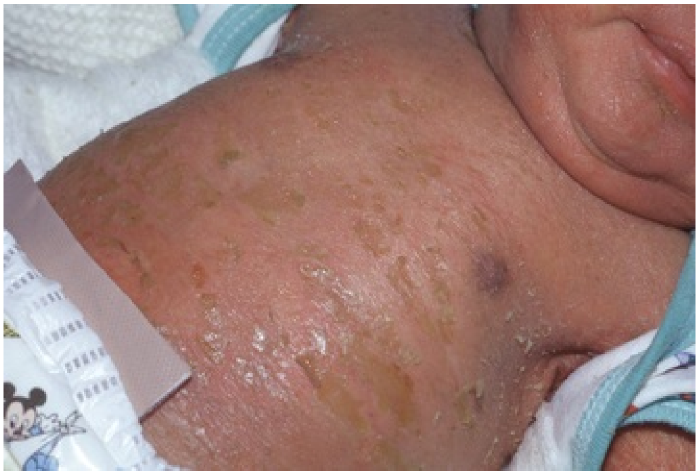

FIG. 677.6 Superficial erosions and hyperkeratosis in epidermolytic hyperkeratosis.

Histopathology

The histopathology is diagnostic of epidermolytic ichthyosis, consisting of hyperkeratosis, degeneration of the epidermal granular layer with an increased number of keratohyalin granules, clear spaces around nuclei, and indistinct cellular boundaries of cells in the upper epidermis. On electron microscopic examination, keratin-intermediate filaments are clumped, and many desmosomes are attached to only one keratinocyte instead of connecting neighboring keratinocytes. Localized forms of the disease may resemble epidermal nevi or keratoderma of the palms and soles but share the distinctive histopathologic changes of epidermolytic ichthyosis.

Treatment

Treatment of epidermolytic ichthyosis is difficult. Morbidity is increased in the neonatal period as a result of prematurity, sepsis, and fluid and electrolyte imbalance. Bacterial colonization of macerated scales produces a distinctive bad odor that can be controlled somewhat by use of an antibacterial cleanser. Intermittent oral antibiotics are generally necessary. Keratolytic agents are often poorly tolerated. Oral retinoids may produce significant improvement. Prenatal diagnosis for affected families is possible by examination of DNA extracts from chorionic villus cells or amniocytes, provided that the specific mutation in the affected parent is known.

Other Nonsyndromic Ichthyoses

Erythrokeratoderma Variabilis

Etiology/Pathogenesis

An autosomal dominant disorder, erythrokeratoderma variabilis (EKV) is caused by mutations in connexins 31 and 30.3. Connexins are proteins that form gap junctions between cells that allow for transport and signaling between neighboring epidermal cells.

Clinical Manifestations

EKV usually manifests in the early months of life, progresses in childhood, and stabilizes in adolescence. It is characterized by two distinctive manifestations: sharply demarcated, hyperkeratotic plaques (Fig. 677.7*A*) and transient figurate erythema (see Fig. 677.7*B*). The distribution is generalized but sparse; sites of predilection are the face, buttocks, axillae, and extensor surfaces of the limbs. The palms and soles may be thickened, but hair, teeth, and nails are normal.

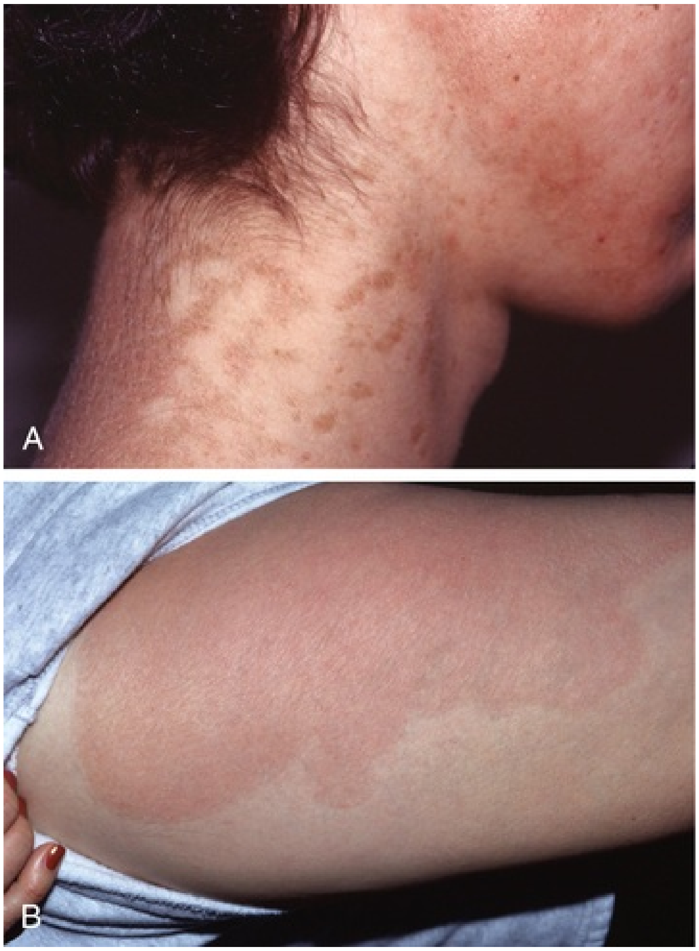

FIG. 677.7 **Erythrokeratoderma variabilis. A, Fixed, hyperkeratotic plaques, B, Migratory, erythematous lesion.**

Treatment

There are case reports that topical tazarotene gel 0.1% and oral retinoids are effective for treatment of EKV.

Symmetric Progressive Erythrokeratoderma

Etiology/Pathogenesis

Symmetric progressive erythrokeratoderma is an autosomal dominant disorder caused by mutations in the gene encoding loricrin. Loricrin is a major component of the epidermal cornified cell envelope.

Clinical Manifestations

The disorder manifests in childhood as large, fixed, geographic and symmetric, fine, scaling, hyperkeratotic, erythematous plaques primarily on the extremities, buttocks, face, ankles, and wrists. The primary feature distinguishing this disorder from EKV is the lack of variable erythema seen in the latter condition.

Treatment

Symmetric progressive erythrokeratoderma is a very rare disorder, but reports of response to topical and oral retinoids exist.

Syndromic Ichthyoses

Sjögren-Larsson Syndrome

Etiology/Pathogenesis

The autosomal recessive inborn error of metabolism known as Sjögren-Larsson syndrome is an abnormality of fatty alcohol oxidation that results from a deficiency of fatty aldehyde dehydrogenase (*FALDH3A2*), a component of the fatty alcohol–nicotinamide adenine dinucleotide oxidoreductase enzyme complex (see Table 677.1).

Clinical Manifestations

The clinical picture of Sjögren-Larsson syndrome consists of ichthyosis, cognitive impairment, and spasticity. The ichthyosis is generalized but is accentuated on the flexures and the lower abdomen and consists of erythroderma, fine scaling, larger platelike scales, and dark hyperkeratosis. The degree of scale varies markedly from patient to patient. Most individuals have palmoplantar hyperkeratosis. The skin changes may be identical to the other forms of ichthyosis, and diagnosis is often delayed until the onset of neurologic symptoms. Pruritus is severe and hypohidrosis is common. Glistening dots in the foveal area are a cardinal ophthalmologic sign. About half the patients have primary retinal degeneration. Motor and speech developmental delays are usually noted before 1 yr of age, and spastic diplegia or tetraplegia, epilepsy, and intellectual disability generally become evident in the 1st-3rd yr of life. Some patients may walk with the aid of braces, but most are confined to wheelchairs. This deficiency can be demonstrated in cultured skin fibroblasts of affected patients and carriers and, prenatally, in cultured chorionic villus cells and amniocytes from affected fetuses. Elevation of urinary leukotriene B4 (LTB4) may provide an easier approach to diagnosis.

Treatment

Treatment is similar to the other forms of ichthyosis; 5-lipoxygenase inhibitors have been used to decrease pruritus.

Netherton Syndrome

Etiology/Pathogenesis

A rare autosomal recessive disorder, Netherton syndrome is caused by mutations in the *SPINK 5* gene, which encodes a serine protease inhibitor (*LEKT1*).

Clinical Manifestations

Netherton syndrome is characterized by ichthyosis (usually ichthyosis linearis circumflexa but occasionally the lamellar or congenital types of ichthyosiform erythroderma), trichorrhexis invaginata and other hair shaft anomalies, and atopic diathesis. The disorder manifests at birth or in the 1st few months of life as generalized erythema and scaling. The trunk and limbs have diffuse erythema and superimposed migratory, polycyclic, and serpiginous hyperkeratotic lesions (Fig. 677.8), some with a distinctive double-edged margin of scale. Lichenification or hyperkeratosis tends to persist in the antecubital and popliteal fossae. The face and scalp may remain erythematous and scaling. Many hair shaft deformities, most notably, trichorrhexis invaginata, have been described in most patients with Netherton syndrome.

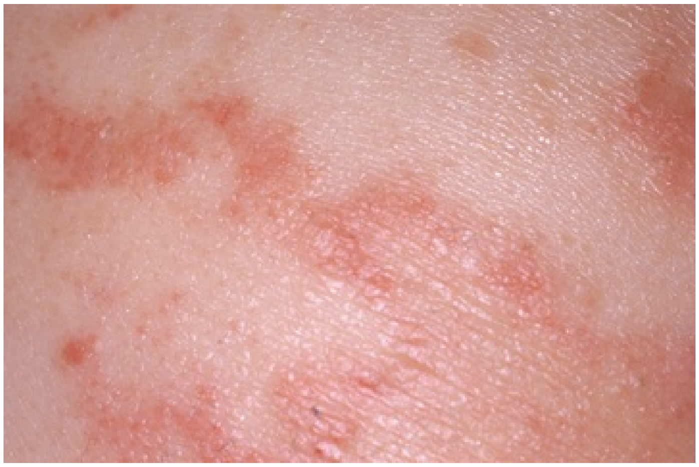

FIG. 677.8 **Serpiginous, erythematous, hyperkeratotic lesions of ichthyosis linearis circumflexa.**

The ichthyosis is present in the 1st 10 days of life and may be especially marked around the eyes, mouth, and perineal area. The erythroderma is often intensified after infection. Infants may suffer from failure to thrive, recurrent bacterial and candidal infections, elevated serum immunoglobulin IgE values, and marked hypernatremic dehydration. The most frequent allergic manifestations are urticaria, angioedema, atopic dermatitis, and asthma. Scalp hair is sparse and short and fractures easily (Fig. 677.9); eyebrows, eyelashes, and body hair are also abnormal. The characteristic hair abnormality can be identified with light microscopy; in the newborn, it may best be identified in eyebrow hair. The differential diagnosis is noted in Table 677.2 .

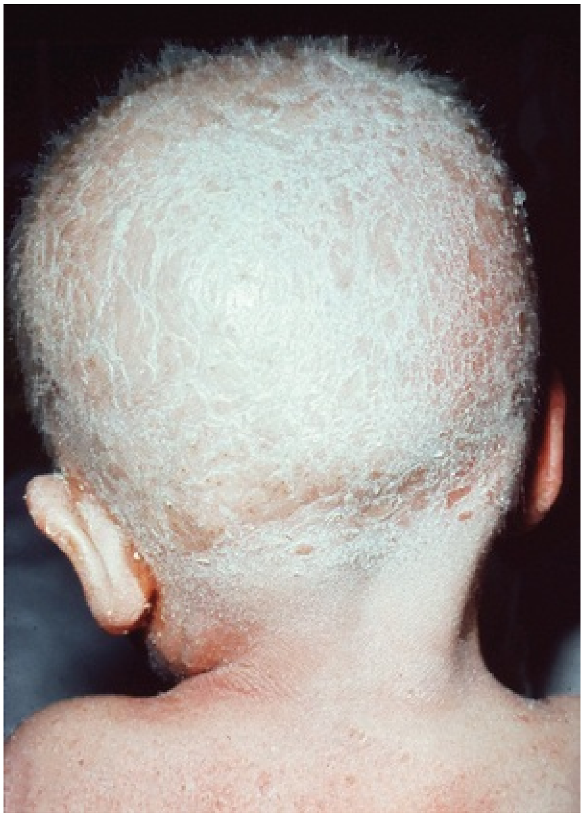

FIG. 677.9 Very short scalp hair and thick scale in Netherton syndrome.

Treatment

Owing to the inflammatory nature of the skin disease, oral antihistamines and topical steroids, as used in the treatment of atopic dermatitis, are helpful for Netherton syndrome.

Refsum Syndrome

See Chapters 104.2 and 631.5 .

Etiology/Pathogenesis

There are two types of Refsum syndrome. The classic form is autosomal recessive and caused by mutations in the *PAHX* gene that result in an increase in phytanic acid. The infantile forms of Refsum syndrome are also autosomal recessive and caused by mutations in the *PEX1* , *PEX2* , or *PEX26* genes. These are peroxisomal abnormalities that lead to an increase in very long-chain fatty acids, di- and tri-hydroxycholestanoic acid, and pipecolic acid as well as phytanic acid.

Clinical Manifestations

Refsum syndrome is a multisystem disorder that becomes symptomatic in the 2nd or 3rd decade of life. The ichthyosis may be generalized, is relatively mild, and resembles ichthyosis vulgaris. The ichthyosis may also be localized to the palms and soles. Chronic polyneuritis with progressive paralysis and ataxia, retinitis pigmentosa, anosmia, deafness, bony abnormalities, and electrocardiographic changes are the most characteristic features. The condition is diagnosed through lipid analysis of the blood or skin, which shows elevated phytanic acid values.

The infantile form begins, as suggested by the name, early in life, and in addition to the changes seen in the classic form, affected patients have hepatomegaly, abnormal bile acid profiles, developmental delay, and cognitive impairment.

Treatment

Phytanic acid is exclusively derived from dietary chlorophyll. Lifelong dietary avoidance of phytanic acid–containing produces clinical improvement in classic Refsum syndrome.

Chondrodysplasia Punctata

See Chapter 104.2 .

Etiology/Pathogenesis

Chondrodysplasia punctata (CPD) is a clinically and genetically heterogeneous condition. X-linked dominant CPD, also known as Conradi-Hünermann syndrome, is the best-characterized form. There is also an X-linked recessive form caused by mutation in the *ARSE* gene. Rhizomelic CPD type 1 is an autosomal recessive disorder caused by mutations in the *PEX7* gene, which encodes the peroxisomal type 2 targeting signal (*PTS2*) receptor. CPD can also be caused by maternal vitamin K deficiency or warfarin teratogenicity.

Clinical Manifestations

These heterogeneous disorders are marked by ichthyosis and bone changes.

Nearly all patients with the X-linked dominant form and approximately 25% of those with the recessive type have cutaneous lesions, ranging from severe, generalized erythema and scaling to mild hyperkeratosis. Rhizomelic CPD is associated with cataracts, hypertelorism, optic nerve atrophy, disproportionate shortening of the proximal extremities, psychomotor retardation, failure to thrive, and spasticity; most affected patients die in infancy. Patients with the X-linked dominant form have asymmetric, variable shortening of the limbs and a distinctive ichthyosiform eruption at birth. Thick, yellow, tightly adherent, keratinized plaques are distributed in a whorled pattern over the entire body. The eruption typically resolves in infancy and may be superseded by a follicular atrophoderma and patchy alopecia.

Additional features in all variants include cataracts and abnormal facies with saddle nose and frontal bossing. The pathognomonic defect, termed CPD, is stippled epiphyses in the cartilaginous skeleton. This defect, which is seen in various settings and inherited disorders, often in association with peroxisomal deficiency and disturbance of cholesterol biosynthesis, disappears by 3-4 yr of age.

Other Syndromes With Ichthyosis

A number of other rare syndromes with ichthyosis as a consistent feature include the following: keratitis with ichthyosis and deafness (KID syndrome, connexin 26 gene), ichthyosis with defective hair having a banded pattern under polarized light and a low sulfur content (trichothiodystrophy), multiple sulfatase deficiency, neutral lipid storage disease with ichthyosis (Chanarin-Dorfman syndrome; *CGI58* gene), and CHILD syndrome (Fig. 677.10 ; congenital hemidysplasia with ichthyosiform erythroderma and limb defects; *NSDHL* gene) (see Table 667.2).

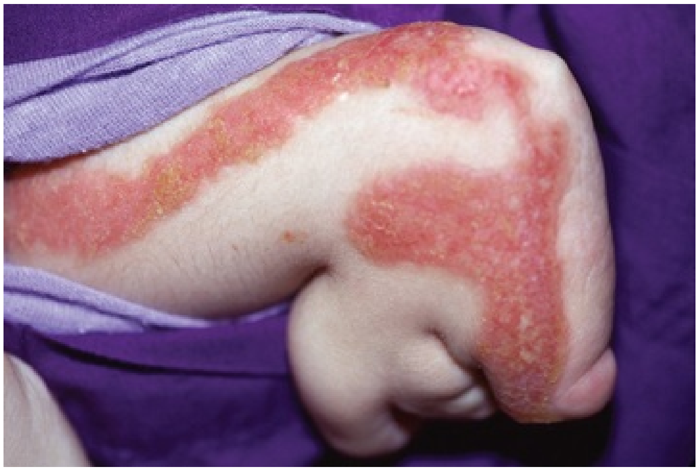

FIG. 677.10 Limb dysplasia and ichthyosiform eruption in CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome.

Palmoplantar Keratodermas

Excessive hyperkeratosis of the palms and soles may occur as a manifestation of a focal or generalized congenital hereditary skin disorder or may result from such chronic skin diseases as psoriasis, eczema, pityriasis rubra pilaris, lupus erythematosus, or postinfectious arthritis syndrome.

Diffuse Hyperkeratosis of Palms and Soles (Unna-Thost, Vorner)

Unna-Thost and Vorner type PPKs, although clinically inseparable, were thought to be separate entities. They were separated histologically by the presence (Vorner) or absence (Unna-Thost) of epidermolytic hyperkeratosis. They represent the clinical spectrum of the same disease caused by mutations in keratin (*KRT1* and *KRT9* genes). This autosomal dominant disorder manifests in the 1st few months of life as erythema that gradually progresses to sharply demarcated, hyperkeratotic, scaling plaques over the palms (Fig. 677.11) and soles. The margins of the plaques often remain red; plaques may extend along the lateral aspects of the hands and feet and onto the volar wrists and the heels. Hyperhidrosis is usually present, but hair, teeth, and nails are usually normal. Striate (*DSG1* , *DSP* , *KRT1* genes) and punctate forms of palmar and plantar hyperkeratosis represent distinct entities.

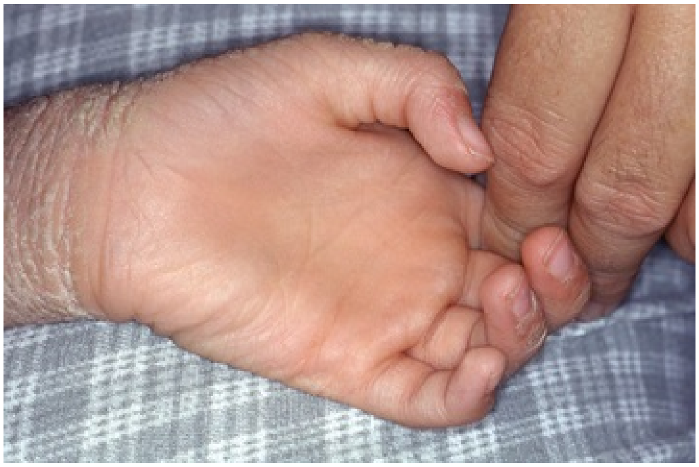

FIG. 677.11 **Palmar keratoderma with epidermolytic changes seen on biopsy.**

Mal De Meleda (*SLURP-1* Gene)

A rare, progressive autosomal recessive condition, mal de Meleda is characterized by erythema and thick scales on the palms, fingers, soles, and flexor aspects of the wrists, knees, and elbows. Hyperhidrosis, nail thickening or koilonychia, and eczema may also occur.

Vohwinkel Palmoplantar Keratoderma (Mutilating Keratoderma)

Vohwinkel PPK is a progressive autosomal dominant disease consisting of honeycombed hyperkeratosis of palms and soles, sparing the arches; starfish-like and linear keratoses on the dorsum of the hands, fingers, feet, and knees; and ainhum-like constriction of the digits that sometimes leads to autoamputation. Varying degrees of alopecia may be seen. Two forms have been identified. Vohwinkel PPK with ichthyosis is caused by mutations in the loricrin gene, and Vohwinkel PPK with deafness by mutations in connexin 26.

Papillon-Lefèvre Syndrome (Cathepsin C Gene)

An autosomal recessive erythematous hyperkeratosis of the palms and soles, Papillon-Lefèvre syndrome sometimes extends to the dorsal hands and feet, elbows, and knees later in childhood. The PPK may be either diffuse, striate, or punctuate. This syndrome is characterized by periodontal inflammation, leading to loss of teeth by age 4-5 yr if untreated.

Other Syndromes

Keratoderma of palms and soles also occurs as a feature of some forms of ichthyosis and ectodermal dysplasia. **Richner-Hanhart syndrome** is an autosomal recessive focal PPK with corneal ulcers, progressive mental impairment, and a deficiency of tyrosine aminotransferase, which leads to tyrosinemia. **Pachyonychia congenita** is transmitted as an autosomal dominant trait with variable expressivity. The classic type I form (Jadassohn-Lewandowski syndrome) is due to mutations in the gene for keratin 16. Major features of the syndrome are onychogryposis; PPK; follicular hyperkeratosis, especially of the elbows and knees; and oral leukokeratosis. The nail dystrophy is the most striking feature and may be present at birth or develop early in life. The nails are thickened and tubular, projecting upward at the free edge to form a conical roof over a mass of subungual keratotic debris. Repeated paronychial inflammation may result in shedding of the nails. The feature seen most consistently among patients with this condition is keratoderma of the palms and soles. Additional associated features include hyperhidrosis of the palms and soles, and bullae and erosions on the palms and soles. Some patients have shown a selective cell-mediated defect in recognition and processing of *Candida*. Surgical removal of the nails and excision of the nail matrix have been helpful in some patients.

Treatment

Treatment for PPK is the same no matter what its cause. In mild cases, emollient therapy may suffice. Keratolytic agents such as salicylic acid, lactic acid, and urea creams may be required. Oral retinoids are the treatment of choice for severe cases unresponsive to topical therapy.

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CHAPTER 678

Diseases of the Dermis

Wendy E. Kim

Keloid

Etiology and Pathogenesis

Keloids are usually induced by trauma and commonly follow ear piercing, burns, scalds, and surgical procedures. The resulting keloid is larger than the initial area of trauma to the skin. Certain individuals are predisposed to keloid formation; a familial tendency (recessive or dominant inheritance) or the presence of foreign material in the wound may have a pathogenic role. *Keloids are a rare feature of Ehlers-Danlos syndrome* , *Rubinstein-Taybi syndrome* , and pachydermoperiostosis. Keloids result from an abnormal fibrous wound healing response in which tissue repair and regeneration–regulation control mechanisms are lost. Collagen production is 20 times that seen in normal scars and the type I:type III collagen ratio is abnormally high. In keloids, tissue values of tumor growth factor-β and platelet-derived growth factor are elevated; fibroblasts are more sensitive to their effects, and their degradation rate is decreased.

Clinical Manifestations

A *keloid* is a sharply demarcated, benign, dense growth of connective tissue that forms in the dermis after trauma. The lesions are firm, raised, pink to hyperpigmented, and rubbery; they may be tender or pruritic. Sites of predilection are the face, earlobes (Fig. 678.1), neck, shoulders, upper trunk, sternum, and lower legs. In both keloids and hypertrophic scars, new collagen forms over a much longer period than in wounds that heal normally.

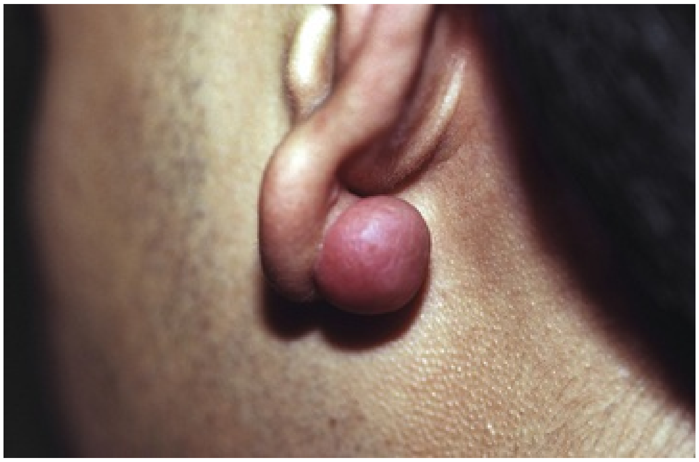

FIG. 678.1 **Keloid of earlobe after piercing.**

Histology

A keloid consists of whorled and interlaced hyalinized collagen fibers.

Differential Diagnosis

Keloids should be differentiated from *hypertrophic scars* , which remain confined to the site of injury and gradually involute over time.

Treatment

Young keloids may diminish in size if injected intralesionally at 4 wk intervals with triamcinolone suspension (10-40 mg/mL). At times, a more concentrated suspension is required. Large or old keloids may require surgical excision followed by intralesional injections of corticosteroid. The risk of recurrence at the same site argues against surgical excision alone, although earlobe keloids respond well to surgical excision, pressure dressings, and intralesional steroids. Placement of topical silicone gel sheeting over the keloid for several hours per day for several weeks may help in some patients.

Striae Cutis Distensae (Stretch Marks)

Etiology and Pathogenesis

Striae formation is common in adolescence. The most frequent causes are rapid growth, pregnancy, obesity, Cushing disease, and prolonged corticosteroid therapy. They may also be seen in patients with Ehlers-Danlos syndrome (Chapter 679). The pathogenesis is unknown, but the occurrence of alterations in elastic fibers is thought to be the primary process.

Clinical Manifestations

These thinned, depressed, erythematous bands of atrophic skin eventually become silvery, opalescent, and smooth. They occur most frequently in areas that have been subject to distention, such as the lower back (Fig. 678.2), buttocks, thighs, breasts, abdomen, and shoulders.

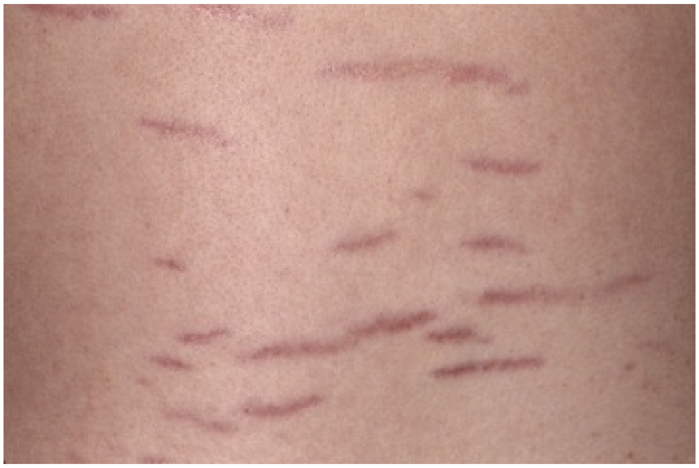

FIG. 678.2 **Striae on the back of an adolescent.**

Differential Diagnosis

Striae distensae resemble atrophic scars.

Treatment

Controlled trials of treatments for striae are lacking; however, striae tend to spontaneously become less conspicuous as the color fades with time.

Corticosteroid-Induced Atrophy

Etiology and Pathogenesis

Both topical and systemic corticosteroid treatment can result in cutaneous atrophy. This is particularly common when a potent or superpotent topical corticosteroid is applied under occlusion or to an intertriginous area for a prolonged period. Keratinocyte growth is decreased, but epidermal maturation is accelerated, resulting in a thinning of the epidermis and stratum corneum. Fibroblast growth and function are also decreased, leading to the dermal changes. The mechanism involves inhibition of synthesis of collagen type I, noncollagenous proteins, and total protein content of the skin, along with progressive reduction of dermal proteoglycans and glycosaminoglycans.

Clinical Manifestations

Affected skin is thin, fragile, smooth, and semitransparent, with telangiectasias, prominent veins, and loss of normal skin markings.

Histology

Histopathologically, there is thinning of the epidermis. Spaces between dermal collagen and elastic fibers are small, producing a more compact but thin dermis.

Treatment

Optimal treatment is prevention by proper use of topical steroids to avoid side effects.

Granuloma Annulare

Etiology and Pathogenesis

The cause of granuloma annulare is unknown. Some cases of granuloma annulare, particularly the generalized form, may be associated with diabetes mellitus or with anterior uveitis. However, most cases are seen in healthy children.

Clinical Manifestations

This common dermatosis occurs predominantly in children and young adults. Affected children are usually healthy. Typical lesions begin as firm, smooth, erythematous papules. They gradually enlarge to form annular plaques with a papular border and a normal, slightly atrophic or discolored central area up to several centimeters in size. Lesions may occur anywhere on the body, but mucous membranes are spared. Favored sites include the dorsum of the hands (Fig. 678.3) and feet. The disseminated papular form is rare in children. Subcutaneous granuloma annulare tends to develop on the scalp and limbs, particularly in the pretibial area. These lesions are firm, usually nontender, skin-colored nodules. Perforating granuloma annulare is characterized by the development of a yellowish center in some of the superficial papular lesions as a result of transepidermal elimination of altered collagen.

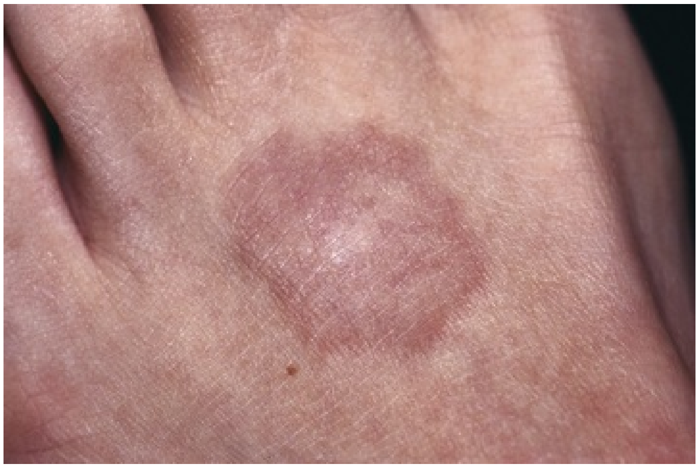

FIG. 678.3 **Annular lesion with a raised papular border and depressed center, characteristic of granuloma annulare.**

Differential Diagnosis

Annular lesions are often mistaken for tinea corporis because of the elevated advancing border. They differ in that they are not scaly. Papular lesions, another variant, may simulate rheumatoid nodules, particularly when grouped on the fingers and elbows.

Histology

The lesion of granuloma annulare consists of a granuloma with a central area of necrotic collagen; mucin deposition; and a peripheral palisading infiltrate of lymphocytes, histiocytes, and foreign body giant cells. The pattern resembles that of necrobiosis lipoidica and rheumatoid nodule, but subtle histologic differences usually permit differentiation.

Treatment

The eruption persists for months to years, but spontaneous resolution without residual change is usual; 50% of lesions clear within 2 yr. Application of a potent or superpotent topical corticosteroid preparation or intralesional injections (5-10 mg/mL) of corticosteroid may hasten involution, but nonintervention is usual.

Necrobiosis Lipoidica

Etiology and Pathogenesis

The cause of necrobiosis lipoidica is unknown, but 50–75% of patients have diabetes mellitus; necrobiosis lipoidica occurs in 0.3% of all diabetic patients. It is also noted in patients with obesity, hypertension, and dyslipidemias.

Clinical Manifestations

This disorder manifests as erythematous papules that evolve into irregularly shaped, sharply demarcated, yellow, sclerotic plaques with central telangiectasia and a violaceous border. Scaling, crusting, and ulceration are frequent. Lesions develop most commonly on the shins (Fig. 678.4). Slow extension of a given lesion over the years is usual, but long periods of quiescence or complete healing with scarring may occur.

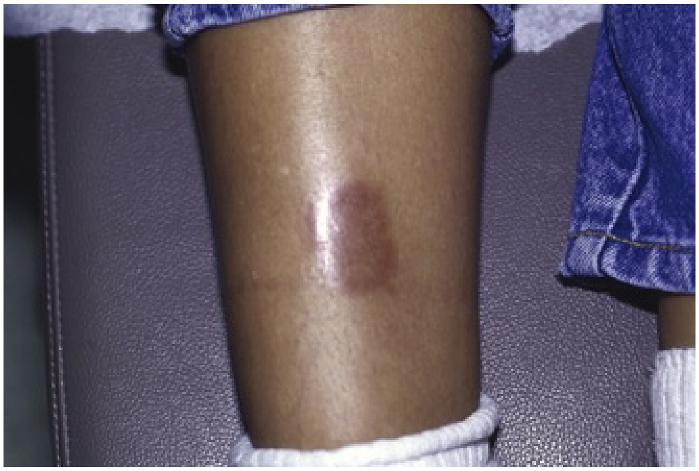

FIG. 678.4 **Yellow sclerotic plaque of necrobiosis lipoidica on the shin.**

Histology

Poorly defined areas of necrobiotic collagen are seen throughout, but primarily low in the dermis, associated with mucin deposition. Surrounding the necrobiotic, disordered areas of collagen is a palisading lymphohistiocytic granulomatous infiltrate. Some lesions are more characteristically granulomatous, with limited necrobiosis of collagen.

Differential Diagnosis

Necrobiosis lipoidica must be differentiated clinically from xanthomas, morphea, granuloma annulare, erythema nodosum, and pretibial myxedema.

Treatment

The lesions persist despite good control of the diabetes but may improve minimally after applications of high-potency topical steroids or local injection of a corticosteroid. Pentoxifylline has also been used.

Lichen Sclerosus

Etiology and Pathogenesis

The cause of lichen sclerosus, a chronic inflammatory dermatosis, is unknown.

Several studies have identified the presence of autoantibodies to the glycoprotein extracellular matrix protein 1 (ECM-1). The exact role of these antibodies is currently under investigation, however.

Clinical Manifestations

Lichen sclerosus manifests initially as shiny, indurated, ivory-colored papules, often with a violaceous halo. The surface shows prominent dilated pilosebaceous or sweat duct orifices that often contain yellow or brown plugs. The papules coalesce to form irregular plaques of variable size, which may develop hemorrhagic bullae in their margins. In the later stages, atrophy results in a depressed plaque with a wrinkled surface. This disorder occurs more commonly in girls than in boys. Sites of predilection in girls are the vulvar (Fig. 678.5), perianal, and perineal skin. Extensive involvement may produce a sclerotic, atrophic plaque of hourglass configuration; shrinkage of the labia and stenosis of the introitus may result. Vaginal discharge precedes vulvar lesions in approximately 20% of patients. In boys, the prepuce and glans penis are often involved, usually in association with phimosis; most boys with the disorder were not circumcised early in life. Sites elsewhere on the body that are most commonly involved include the upper trunk, the neck, the axillae, the flexor surfaces of wrists, and the areas around the umbilicus and the eyes. Pruritus may be severe.

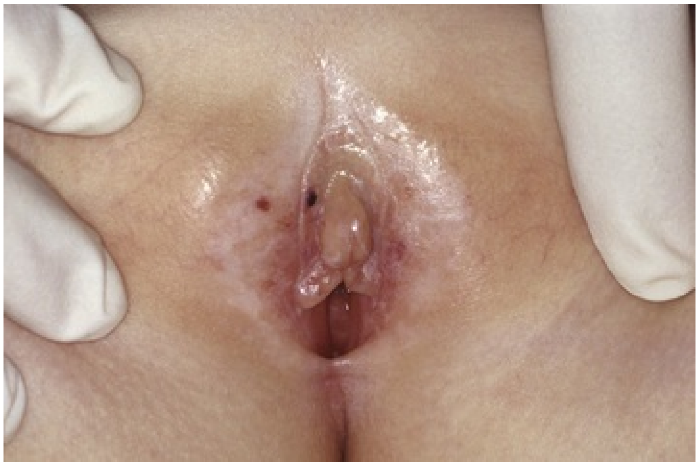

FIG. 678.5 **Ivory-colored perivaginal plaque with hemorrhage.**

Differential Diagnosis

In children, lichen sclerosus is most frequently confused with focal morphea (see Chapter 185), with which it may coexist. In the genital area, it may be mistakenly attributed to sexual abuse.

Histology

Biopsy is diagnostic, revealing hyperkeratosis with follicular plugging, hydropic degeneration of basal cells, a bandlike dermal lymphocytic infiltrate, homogenized collagen, and thinned elastic fibers in the upper dermis.

Treatment

Vulvar lichen sclerosus in childhood usually improves with puberty but does not always resolve completely, and symptoms can recur throughout life. Long-term observation for the development of squamous cell carcinoma is necessary. Superpotent topical corticosteroids provide relief from pruritus and produce clearing of lesions, including those in the genital area. Topical tacrolimus and pimecrolimus have also been used. It is not known how response to treatment affects long-term cancer risk.

Morphea

Etiology and Pathogenesis

Morphea is a sclerosing condition of the dermis and subcutaneous tissue of unknown etiology.

Clinical Manifestations

Morphea is characterized by solitary, multiple, or linear circumscribed areas of erythema that evolve into indurated, sclerotic, atrophic plaques (Fig. 678.6), later healing, or “burning out” with pigment change. It is seen more commonly in females. The most common types of morphea are plaque and linear. Morphea can affect any area of skin. When confined to the frontal scalp, forehead, and midface in a linear band, it is referred to as **en coup de sabre** . When located on one side of the face, it is called **progressive hemifacial atrophy, also known as**

Parry-Romberg Syndrome . These forms of morphea carry a poorer prognosis because of the associated underlying central nervous system involvement or musculoskeletal atrophy that can be cosmetically disfiguring. Linear morphea over a joint may lead to restriction of mobility (Fig. 678.7). Pansclerotic morphea is a rare, severe, disabling variant.

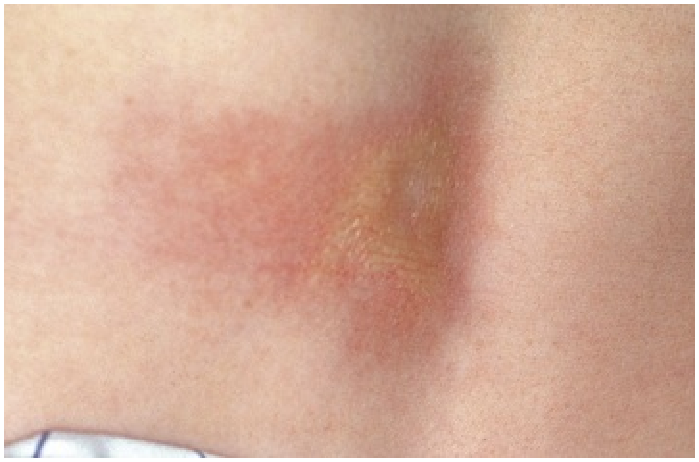

FIG. 678.6 **Erythematous, hyperpigmented plaque of early morphea.**

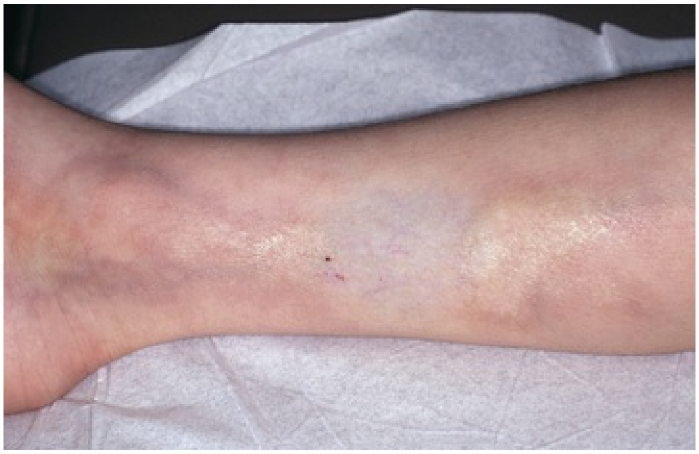

FIG. 678.7 **Linear morphea with involvement over the ankle.**

Differential Diagnosis

The differential diagnosis of morphea includes granuloma annulare, necrobiosis lipoidica, lichen sclerosus, and late-stage European Lyme borreliosis (acrodermatitis chronica atrophicans).

Histology

Thickening or sclerosus of the dermis with collagen degeneration is seen in morphea.

Treatment

Morphea tends to persist, with gradual outward expansion on the skin for 3-5 yr until spontaneous cessation of the inflammatory phase occurs. Topical calcipotriene alone or in combination with high- to superpotency topical steroids or topical tacrolimus have been used for less-severe disease. For the various forms of linear morphea and for severe plaque morphea, ultraviolet A-1 (UVA-1) phototherapy, or methotrexate with or without pulsed intravenous or oral glucocorticosteroids may halt progression and help shorten the disease course. There are no good comparison studies to suggest which therapy is optimal. Physical therapy is needed in linear morphea over a joint to maintain mobility. Significant postinflammatory pigment alteration may persist for years.

Scleredema (Scleredema Adultorum, Scleredema of Buschke)

Etiology and Pathogenesis

The cause of scleredema is unknown. There are 3 types. **Type 1** (55% of cases) is preceded by a febrile illness, often related to an upper or lower respiratory infection (streptococcal most commonly). **Type 2** (25%) is associated with paraproteinemias, including multiple myeloma. **Type 3** (20%) is seen in diabetes mellitus.

Clinical Manifestations

Fifty percent of patients with scleredema are younger than 20 yr old and almost always have type 1. Onset of type 1 is sudden, with brawny edema of the face and neck that spreads rapidly to involve the thorax and arms in a sweater distribution; the abdomen and legs are usually spared. The face acquires a waxy, mask-like appearance. The involved areas feel indurated and woody, are nonpitting, and are not sharply demarcated from normal skin. The overlying skin is normal in color and is not atrophic.

Onset in patients with type 2 and type 3 scleredema may occur insidiously. Systemic involvement, which is uncommon and usually associated with types 2 and 3, is marked by thickening of the tongue; dysarthria; dysphagia; restriction of eye and joint movements; and pleural, pericardial, and peritoneal effusions. Electrocardiographic changes may also be observed. Laboratory data are not helpful.

Differential Diagnosis

Scleredema must be differentiated from scleroderma (see Chapter 185), morphea, myxedema, trichinosis, dermatomyositis, sclerema neonatorum, and subcutaneous fat necrosis.

Histology

Skin biopsy demonstrates an increase in dermal thickness as a result of swelling and homogenization of the collagen bundles, which are separated by large interfibrous spaces. Special stains can identify increased amounts of mucopolysaccharides in the dermis of patients with scleredema.

Treatment

In type 1 scleredema, the active phase of the disease persists for 2-8 wk; spontaneous and complete resolution usually occurs in 6 mo to 2 yr. Recurrent attacks are unusual. In type 2 and 3, disease is slowly progressive. There is no specific therapy.

Lipoid Proteinosis (Urbach-Wiethe Disease, Hyalinosis Cutis Et Mucosae)

Etiology and Pathogenesis

Lipoid proteinosis, an autosomal recessive disorder, is caused by mutations in the *ECM-1* gene, which encodes the ECM-1 protein. ECM-1 has a functional role in the structural organization of the dermis by binding to perlecan, matrix metalloproteinase 9, and fibulin. Pathogenesis involves infiltration of hyaline material into the skin, oral cavity, larynx, and internal organs.

Clinical Manifestations

Lipoid proteinosis may be noted initially in early infancy as hoarseness. Skin lesions appear during childhood and consist of yellowish papules and nodules that may coalesce to form plaques. The classic sign is beaded papules on the eyelids. Lesions also occur on the face, forearms, neck, genitals, dorsum of the fingers, and scalp, where they result in patchy alopecia. Similar deposits are found on the lips, undersurface of the tongue, fauces, uvula, epiglottis, and vocal cords. The tongue becomes enlarged and feels firm on palpation. The patient may be unable to protrude the tongue. Pock-like atrophic scars may develop on the face. Hypertrophic, hyperkeratotic nodules occur at sites of friction, such as the elbows and knees; the palms may be diffusely thickened. The disease progresses until early adult life, but the prognosis is good. Symmetric ossification lateral to the sella turcica in the medial temporal region, identifiable roentgenographically, is pathognomonic but is not always present. Involvement of the larynx can lead to respiratory compromise, particularly in infancy, necessitating tracheostomy. Associated anomalies include dental abnormalities, epilepsy, and recurrent parotitis as a result of infiltrates in the Stensen duct. Virtually any organ can be involved.

Histology

The distinctive histologic pattern in lipoid proteinosis includes dilation of dermal blood vessels and infiltration of homogeneous eosinophilic extracellular hyaline material along capillary walls and around sweat glands. Hyaline material in homogeneous bundles, diffusely arranged in the upper dermis, produces a thickened dermis. The infiltrates appear to contain both lipid and mucopolysaccharide substances.

Treatment

There is no specific treatment for lipoid proteinosis.

Macular Atrophy (Anetoderma)

Etiology and Pathogenesis

Anetoderma is characterized by circumscribed areas of slack skin associated with loss of dermal substance. This disorder may have no associated underlying disease (primary macular atrophy) or may develop after an inflammatory skin condition. Secondary macular atrophy may be a result of direct destruction of dermal elastin or elastolysis on an immunologic basis, especially the presence of antiphospholipid antibodies, which are related to autoimmune disorders. The elastolysis may then be a result of release of elastase from inflammatory cells.

Clinical Manifestations

Lesions vary from 0.5 to 1.0 cm in diameter and, if inflammatory, may initially be erythematous. They subsequently become thin, wrinkled, and blue-white or hypopigmented. The lesions often protrude as small outpouchings that, on palpation, may be readily indented into the subcutaneous tissue because of the dermal atrophy. Sites of predilection include the trunk, thighs, upper arms, and, less commonly, the neck and face. Lesions remain unchanged for life; new lesions often continue to develop for years.

Histology

All types of macular atrophy show focal loss of elastic tissue on histopathologic examination, a change that may not be recognized unless special stains are used.

Differential Diagnosis

Lesions of anetoderma occasionally resemble morphea, lichen sclerosus, focal dermal hypoplasia, atrophic scars, or end-stage lesions of chronic bullous dermatoses.

Treatment

There is no effective therapy for macular atrophy.

Cutis Laxa (Dermatomegaly, Generalized Elastolysis)

Etiology and Pathogenesis

Cutis laxa is a heterogenous group of disorders related to abnormalities in elastic tissue. It may be **autosomal recessive** (type I: *fibulin* 5 and *fibulin* 4 genes; type II: *ATP6V0A2* gene), **autosomal dominant** (*elastin* and *fibulin* 5 genes), **X-linked** (*Cu^{2+} -transporting adenosine triphosphatase, α-polypeptide*), or acquired. Acquired cutis laxa has developed after a febrile illness, inflammatory skin diseases such as lupus erythematosus or erythema multiforme, amyloidosis, urticaria, angioedema, and hypersensitivity reactions to penicillin, and in neonates born to women who were taking penicillamine.

Clinical Manifestations

There may be widespread folds of lax skin, or changes may be mild and limited in extent, resembling anetoderma. Patients with severe cutis laxa have characteristic facial features, including an aged appearance with sagging jowls (bloodhound appearance; Fig. 678.8), a hooked nose with everted nostrils, a short columella, a long upper lip, and everted lower eyelids. The skin is also lax elsewhere on the body and may resemble an ill-fitting suit. Hyperelasticity and hypermobility of the joints are not present as they are in the Ehlers-Danlos syndrome. Many infants have a hoarse cry, probably as a result of laxity of the vocal cords. Tensile strength of the skin is normal.

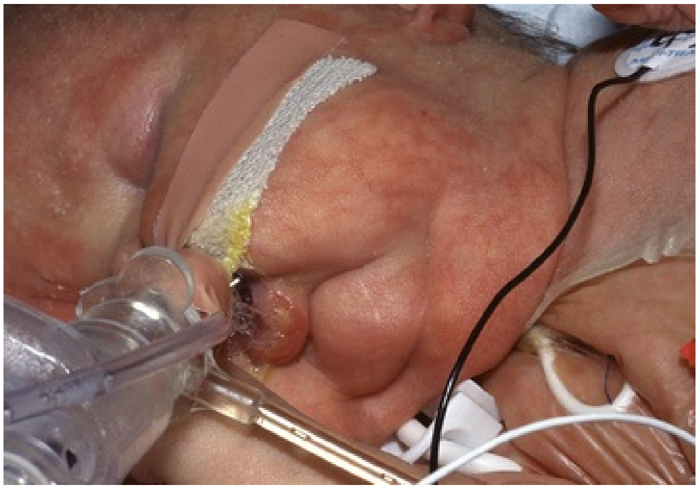

FIG. 678.8 **Pendulous folds of skin of an infant with cutis laxa.**

The dominant form of cutis laxa may develop at any age and is generally benign. When it manifests in infancy, it may be associated with intrauterine growth restriction, ligamentous laxity, and delayed closure of the fontanels. Pulmonary emphysema and mild cardiovascular manifestations may also occur. Patients with the more *common recessive* form of the disease are susceptible to severe complications, such as multiple hernias, rectal prolapse, diaphragmatic atony, diverticula of the gastrointestinal and genitourinary tracts, cor pulmonale, emphysema, pneumothoraces, peripheral pulmonary artery stenosis, and aortic dilation. Characteristic facial features include downward-slanting palpebral fissures, a broad, flat nose, and large ears. Skeletal anomalies, dental caries, growth retardation, and developmental delay also occur. Such patients often have a shortened life span.

Cutis laxa–like skin changes may also be seen in association with multiple other syndromes, including De Barsy syndrome, Lenz-Majewski syndrome, hyperostotic dwarfism, SCARF (**s** keletal abnormalities, **c** utis laxa, craniostenosis, **a** mbiguous genitalia, **r** etardation, **f** acial abnormalities) syndrome, wrinkling skin syndrome, arterial tortuosity syndrome, gerodermia osteodysplasia, macrocephaly alopecia cutis laxa scoliosis syndrome, Urban-Rifkin-Davis syndrome, and Costello syndrome.

Histology

Histologically, elastic tissue is reduced throughout the dermis, with fragmentation, distention, and clumping of the elastic fibers.

Treatment

Treatment for cutis laxa is supportive.

Pseudoxanthoma Elasticum

Etiology and Pathogenesis

Pseudoxanthoma elasticum (PXE) is a primary disorder of elastic tissue. The overwhelming majority of cases are caused by mutations in the *ABCC6* gene. The primary abnormality seen in PXE is an accumulation of mineralized tissue in the skin, Bruch membrane in the retina, and vessel walls. Cutaneous manifestations of PXE may be the present in generalized arterial calcification of infancy.

Clinical Manifestations

Onset of skin manifestations often occurs during childhood, but the changes produced by early lesions are subtle and may not be recognized. The characteristic pebbly, “plucked chicken skin” cutaneous lesions are 1-2 mm, asymptomatic, yellow papules that are arranged in a linear or reticulated pattern or in confluent plaques. Preferred sites are the flexural neck (Fig. 678.9), axillary and inguinal folds, umbilicus, thighs, and antecubital and popliteal fossae. As the lesions become more pronounced, the skin acquires a velvety texture and droops in lax, inelastic folds. The face is usually spared. Mucous membrane lesions may involve the lips, buccal cavity, rectum, and vagina. There is involvement of the connective tissue of the media, and intima of blood vessels, Bruch membrane of the eye, and endocardium or pericardium may result in visual disturbances, angioid streaks in Bruch membrane, intermittent claudication, cerebral and coronary occlusion, hypertension, and hemorrhage from the gastrointestinal tract, uterus, or mucosal surfaces. Women with PXE have an increased risk of miscarriage in the 1st trimester. Arterial involvement generally manifests in adulthood, but claudication and angina have occurred in early childhood.

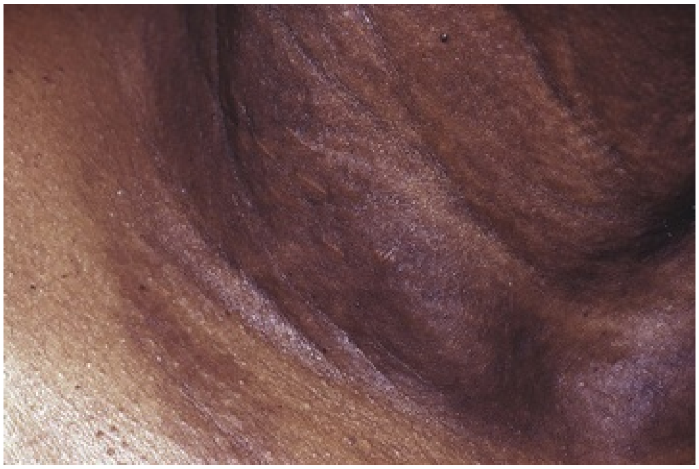

FIG. 678.9 Confluent plaque of pebbly skin in pseudoxanthoma elasticum.

Pathology

Histopathologic examination shows fragmented, swollen, and clumped elastic fibers in the middle and lower 3rd of the dermis. The fibers stain positively for calcium. Collagen near the altered elastic fibers is reduced in amount and is split into small fibers. Aberrant calcification of the elastic fibers of the internal elastic lamina of arteries in PXE leads to narrowing of vessel lumina.

Treatment

There is no effective treatment for PXE, although laser therapy may help prevent retinal hemorrhage. The use of oral phosphate binders has shown promise in decreasing calcification of elastic fibers.

Elastosis Perforans Serpiginosa

Etiology and Pathogenesis

Elastosis perforans serpiginosa (EPS) is characterized by the extrusion of altered elastic fibers through the epidermis. The primary abnormality is probably in the dermal elastin, which provokes a cellular response that ultimately leads to extrusion of the abnormal elastic tissue.

Clinical Manifestations

This is an unusual skin disorder in which 1-3 mm, firm, skin-colored, keratotic papules tend to cluster in arcuate and annular patterns on the posterolateral neck and limbs (Fig. 678.10) and occasionally on the face and trunk. Onset usually occurs in childhood or adolescence. A papule consists of a circumscribed area of epidermal hyperplasia that communicates with the underlying dermis by a narrow channel. There is a great increase in the amount and size of elastic fibers in the upper dermis, particularly in the dermal papillae. Approximately 30% occur in association with osteogenesis imperfecta, Marfan syndrome, PXE, EDS, Rothmund-Thomson syndrome, scleroderma, acrogeria, and Down syndrome. EPS has also occurred in association with penicillamine therapy.

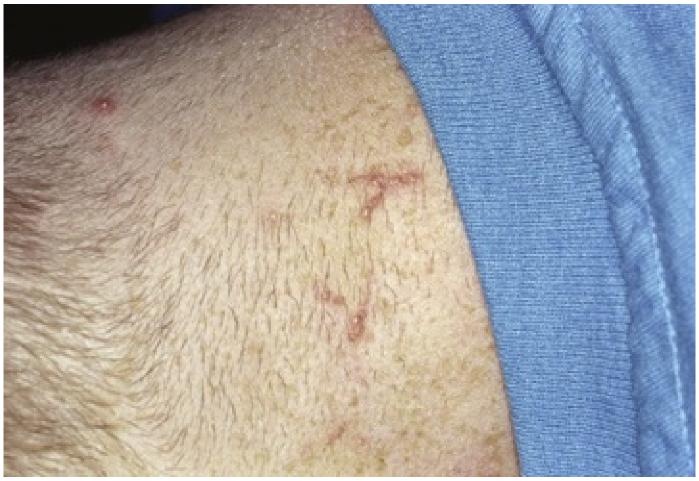

FIG. 678.10 **Arcuate keratotic papule of elastosis perforans serpiginosa.**

Histology

Histopathology reveals a hyperplastic epidermis with extrusion of abnormal elastic fibers and a lymphocytic superficial infiltrate.

Differential Diagnosis

Differential diagnosis of EPS includes tinea corporis, perforating granuloma annulare, reactive perforating collagenosis, lichen planus, creeping eruption, and porokeratosis of Mibelli.

Treatment

Treatment of EPS is ineffective; however, the lesions are asymptomatic and may disappear spontaneously.

Reactive Perforating Collagenosis

Etiology and Pathogenesis

The primary process in reactive perforating collagenosis represents transepidermal elimination of altered collagen. A familial autosomal recessive form has been described.

Clinical Manifestations

Reactive perforating collagenosis usually manifests in early childhood as small papules on the dorsal areas of the hands and forearms, elbows, knees, and, sometimes, face and trunk. Over a period of several weeks, the papules enlarge to 5-10 mm, become umbilicated, and develop keratotic plugs in their centers (Fig. 678.11). Individual lesions resolve spontaneously in 2-4 mo, leaving hypopigmented macules or scars. Lesions may recur in crops; may undergo a linear Koebner phenomenon; and may form in response to cold temperatures or superficial trauma such as abrasions, insect bites, and acne lesions.

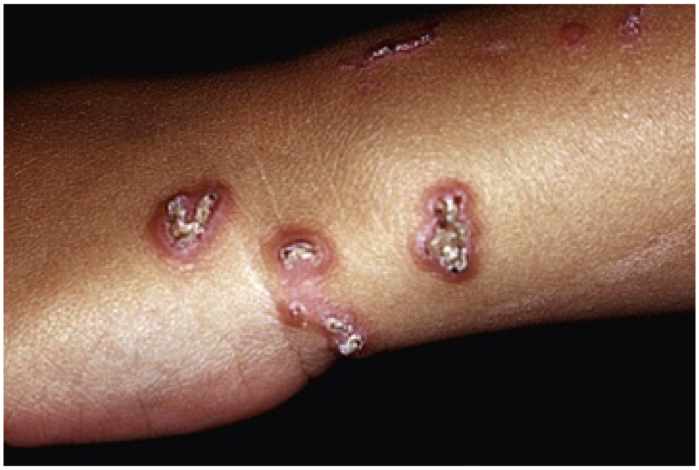

FIG. 678.11 **Hyperkeratotic papules in reactive perforating collagenosis.**

Histology

Collagen in the papillary dermis is engulfed within a cup-shaped perforation in the epidermis. The central crater contains pyknotic inflammatory cells and keratinous debris.

Differential Diagnosis

EPS and Kyrle disease may mimic reactive perforating collagenosis.

Treatment

Reactive perforating collagenosis resolves spontaneously in 6-8 wk. Topical retinoic acid enhances the resolution.

Xanthomas

See Chapter 103 .

Fabry Disease

See Chapter 631.6 .

Mucopolysaccharidoses

See Chapter 107 .

In several of the mucopolysaccharidoses, thick, rough, inelastic skin, particularly on the extremities, and generalized hirsutism are characteristic but nonspecific features. Telangiectasias on the face, forearms, trunk, and legs have been observed in Scheie and Morquio syndromes. In some patients with Hunter syndrome, ivory-colored, distinctive firm papulonodules with a corrugated surface texture are grouped into symmetric plaques on the upper trunk (Fig. 678.12), arms, and thighs. Onset of these unusual lesions occurs in the 1st decade of life, and spontaneous disappearance has been noted.

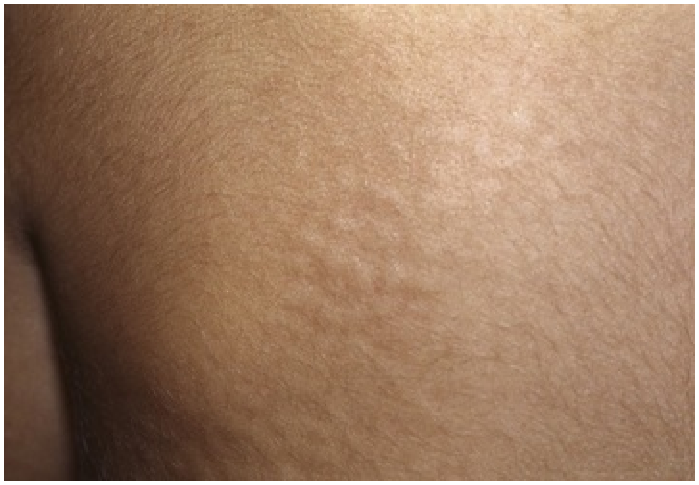

FIG. 678.12 Ivory-colored papules on the upper back in Hunter syndrome.

Mastocytosis

Etiology and Pathogenesis

Mastocytosis encompasses a spectrum of disorders that range from solitary cutaneous nodules to diffuse infiltration of skin associated with involvement of other organs (Table 678.1). All of the disorders are characterized by aggregates of mast cells in the dermis. There are 4 types of mastocytoses: solitary mastocytoma, urticaria pigmentosa (2 forms), diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans. The 2 forms of urticaria pigmentosa are the childhood variant, which resolves without sequelae, and the form that may start in either childhood or adult life and is associated with a mutation (most commonly the *D816V* mutation) in the stem cell factor gene. Stem cell factor (mast cell growth factor), which can be secreted by keratinocytes, stimulates the proliferation of mast cells and increases the production of melanin by melanocytes. The local and systemic manifestations of the disease are at least partly a result of the release of histamine and heparin from mast cell granules; although heparin is present in significant amounts in mast cells, coagulation disturbances occur only rarely. The vasodilator prostaglandin D_2 or its metabolite appears to exacerbate the flushing response. Serum tryptase values can be elevated but not consistently.

Table 678.1

Mastocytosis Classification

Cutaneous Mastocytosis

Urticaria pigmentosa/maculopapular mastocytosis
Diffuse cutaneous mastocytosis
Solitary mastocytoma

Systemic Mastocytosis

Indolent mastocytosis
Smoldering mastocytosis
Aggressive mastocytosis
Systemic mastocytosis with associated hematologic non–mast cell lineage (AHN) disease
Mast cell leukemia

Mast Cell Sarcoma

Modified from Valent P, Akin C, Metcalfe D: Mastocytosis: 2016 Updated WHO classification and novel emerging treatment concepts, *Blood* 129:1420-1427, 2017, Table 2.

Clinical Manifestations

Solitary mastocytomas are usually 1-5 cm in diameter. Lesions may be present at birth or may arise in early infancy at any site. The lesions may manifest as recurrent, evanescent wheals or bullae; in time, an infiltrated, pink, yellow, or tan, rubbery plaque develops at the site of whealing or blistering (Fig. 678.13). The surface acquires a pebbly, orange peel–like texture, and hyperpigmentation may become prominent. Stroking or trauma to the nodule may lead to urtication (Darier sign) due to local histamine release; rarely, systemic signs of histamine release become apparent.

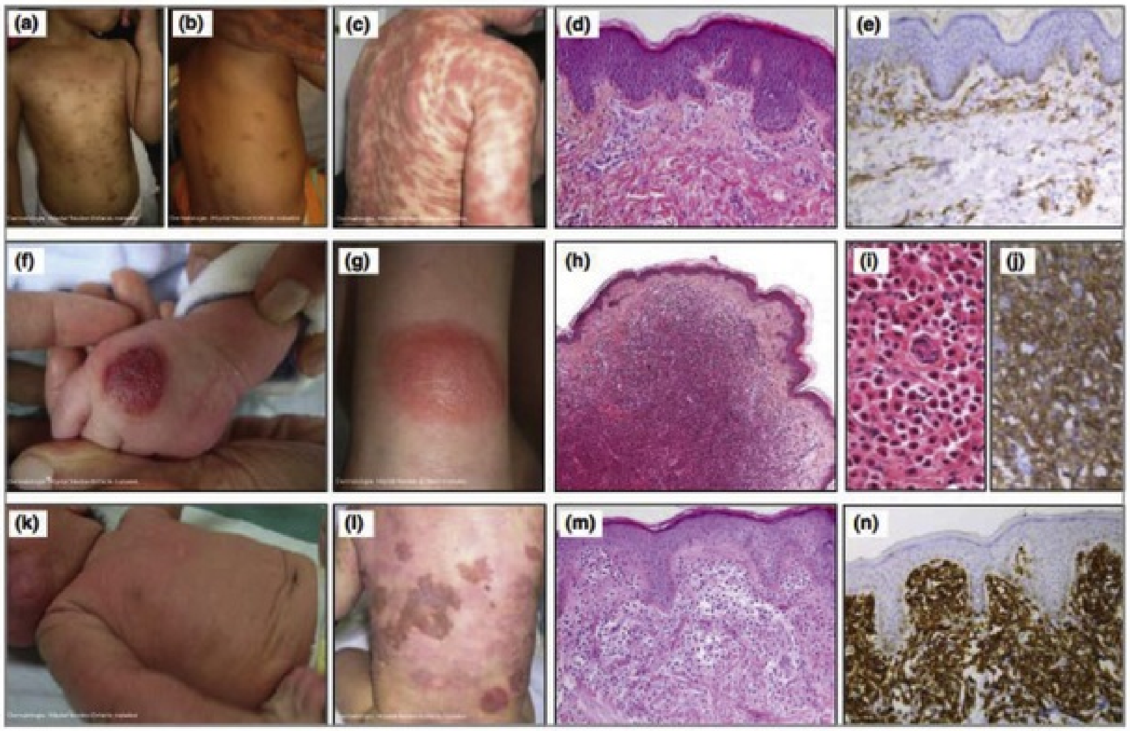

FIG. 678.13 Clinical features and histological findings in childhood mastocytosis. Diagnosis of mastocytosis in children is often obvious and skin biopsy is rarely performed. The histological diagnosis of cutaneous mastocytosis must consider the increased number and proportion of mast cells compared with other inflammatory cells. Mast cells can be rounded, cuboidal, fusiform, or histiocytic-like. Eosinophils may be observed in all mastocytosis subtypes. The epidermis may be hyperpigmented in urticaria pigmentosa (UP) and diffuse cutaneous mastocytosis (DCM), while it is normal in mastocytoma. a–e, UP: a, maculopapular UP; b, plaque-type UP; c, extensive UP with plaques and macules; d, skin biopsy: increased number and proportion of mast cells around the vessels or scattered into the dermis, dilatation of the capillaries of the superficial dermis; e, c-Kit staining. f–j, Mastocytoma: f, mastocytoma localized on the hand; g, mastocytoma localized on the forearm; h, i, skin biopsy: abundant and diffuse infiltration of mast cells throughout the dermis. Mast cells are always recognizable, with a large, pink and granular cytoplasm and a round, dense, central nucleus; j, c-Kit staining. k–n, DCM: k, diffuse infiltration of skin; l, extensive bullous lesions associated with infiltration on the back; m, skin biopsy: diffuse dermal infiltration of mast cells associated with some fibrosis and dilated capillaries; n, c-Kit staining. (From Méni C, Bruneau J, Georgin-Lavialle S, et al: Paediatric mastocytosis: a systematic review of 1747 cases. *Br J Dermatol* 172:642–651, 2015. Fig. 1, p. 643.)

Urticaria pigmentosa is the most common form of mastocytosis in children. In the first type of urticaria pigmentosa, the **classic infantile type** , lesions may be present at birth but more often erupt in crops in the 1st several mo to 2 yr of age. New lesions seldom arise after age 3-4 yr. In some cases, early bullous or urticarial lesions fade, only to recur at the same site, ultimately becoming fixed and hyperpigmented. In others, the initial lesions are hyperpigmented. Vesiculation usually abates by 2 yr of age. Individual lesions range in size from a few millimeters to several centimeters and may be macular, papular, or nodular.

They range in color from yellow-tan to chocolate brown and often have ill-defined borders (see Fig. 678.13). Larger nodular lesions, like solitary mastocytomas, may have a characteristic orange peel texture. Lesions of urticaria pigmentosa may be sparse or numerous and are often symmetrically distributed. Palms, soles, and face are sometimes spared, as are the mucous membranes. The rapid appearance of erythema and whealing in response to vigorous stroking of a lesion can usually be elicited; dermographism of intervening normal skin is also common. Affected children can have intense pruritus. Systemic signs of histamine release, such as anaphylaxis-like episodes, hypotension, syncope, headache, episodic flushing, tachycardia, wheezing, colic, and diarrhea, are uncommon and occur most frequently in the more severe types of mastocytosis. Flushing is by far the most common symptom seen.

The **second type** of urticaria pigmentosa may begin in infancy but typically develops in adulthood. This type does not resolve, and new lesions continue to develop throughout life. It is associated with mutations in the stem cell factor gene. Patients with this type of mastocytosis are the population in whom systemic involvement may develop.

Systemic mastocytosis is marked by an abnormal increase in the number of mast cells in other than cutaneous tissues. It occurs in approximately 5–10% of patients with mutant stem cell factor–related mastocytosis and is uncommon in children. Bone lesions are often silent (but may be painful) and are detectable radiologically as osteoporotic or osteosclerotic areas, principally in the axial skeleton. Gastrointestinal tract involvement may produce complaints of abdominal pain, nausea, vomiting, diarrhea, steatorrhea, and bloating. Mucosal infiltrates may be detectable by barium studies or by small bowel biopsy. Peptic ulcers also occur. Hepatosplenomegaly due to mast cell infiltrates and fibrosis has been described, as has mast cell proliferation in lymph nodes, kidneys, periadrenal fat, and bone marrow. Abnormalities in the peripheral blood, such as anemia, leukocytosis, and eosinophilia, are noted in approximately 30% of patients. Mast cell leukemia may occur.

Diffuse cutaneous mastocytosis is characterized by diffuse involvement of the skin rather than discrete hyperpigmented lesions. Affected patients are usually normal at birth and demonstrate features of the disorder after the 1st few months of life. Rarely, the condition may present with intense generalized pruritus in the absence of visible skin changes. The skin usually appears thickened and pink to yellow and may have a doughy feel and a texture resembling an orange peel. Surface changes are accentuated in flexural areas.

Recurrent bullae (see Fig. 678.13), intractable pruritus, and flushing attacks are common, as is systemic involvement.

Telangiectasia macularis eruptiva perstans is another variant that consists of telangiectatic hyperpigmented macules that are usually localized to the trunk. These lesions do not urticate when stroked. This form of the disease is seen primarily in adolescents and adults.

Differential Diagnosis

The differential diagnosis of solitary mastocytomas includes recurrent bullous impetigo, herpes simplex, congenital melanocytic nevi, and juvenile xanthogranuloma.

Urticaria pigmentosa can be confused with drug eruptions, postinflammatory pigmentary change, juvenile xanthogranuloma, pigmented nevi, ephelides, xanthomas, chronic urticaria, insect bites, and bullous impetigo. Diffuse cutaneous mastocytoma may be confused with epidermolytic hyperkeratosis.

Telangiectasia macularis eruptiva perstans must be differentiated from other causes of telangiectasia. The systemic manifestations of mastocytosis may mimic pheochromocytoma, carcinoid syndrome, vasoactive intestinal peptide secreting tumors, vasculitis, autoinflammatory diseases, hyper-IgE syndrome, somatization disorder, autonomic dysfunction, angioedema, chronic urticaria, and anaphylaxis.

Prognosis

Spontaneous involution occurs in all patients with solitary mastocytomas and classic infantile urticaria pigmentosa. The incidence of systemic manifestations in these patients is very low. The mean duration of urticaria pigmentosa is around 10 yr. A larger number of lesions early in life may lead to later resolution.

Treatment

Solitary mastocytomas usually do not require treatment. Lesions that blister may be treated with topical steroids following each blistering episode.

In urticaria pigmentosa, flushing can be precipitated by excessively hot baths, vigorous rubbing of the skin, and certain drugs, such as codeine, aspirin, morphine, atropine, ketorolac, alcohol, tubocurarine, iodine-containing radiographic dyes, and polymyxin B (Table 678.2). Avoidance of these triggering factors is advisable; it is notable that general anesthesia may be safely performed with appropriate precautions.

Table 678.2

Pharmacologic Agents and Physical Stimuli That May Exacerbate Mast Cell Mediator Release in Patients With Mastocytosis

Immunologic Stimuli

Venoms (immunoglobulin E–mediated bee venom)
Complement-derived anaphylatoxins
Biologic peptides (substance P, somatostatin)
Polymers (dextran)

Nonimmunologic Stimuli

Physical stimuli (heat, cold, rubbing, trauma, sunlight)
Drugs
Acetylsalicylic acid and related nonsteroidal analgesics*
Thiamine
Ketorolac tromethamine
Alcohol
Vancomycin
Dextromethorphan
Narcotics (codeine, morphine)*
Radiographic dyes (iodine containing)

Emotional Issues

Anxiety
Sleep deprivation
Stress

[*] Appears to be a problem in <10% of patients.

From Carter MC, Metcalfe DD: Paediatric mastocytosis. *Arch Dis Child* 86:315–319, 2002, Table 4.

For patients who are symptomatic, oral antihistamines may be palliative. H_1 receptor antagonists (hydroxyzine) are the initial drugs of choice for systemic signs of histamine release. If H_1 antagonists are unsuccessful, H_2 receptor antagonists may be helpful in controlling pruritus or gastric hypersecretion. Topical steroids are of benefit in controlling skin urtication and blistering. Oral mast cell–stabilizing agents, such as cromolyn sodium or ketotifen, may also be effective for diarrhea or abdominal cramping and some systemic symptoms such as headache or muscle pain. Midostaurin, an inhibitor of KIT, may be effected in patients with systemic mastocytosis.

For patients with diffuse cutaneous mastocytosis, the treatment is the same as for urticaria pigmentosa, although in early life. Phototherapy with narrow-band UV (UVB or UVA-1) or psoralen with UVA treatment may be required to control symptoms.

Lesions of telangiectasia macularis eruptiva perstans may be cautiously treated with vascular pulsed-dye lasers.

678.1

Mast Cell Activation Syndrome

James J. Nocton

Keywords

mast cell
mastocytosis

degranulation

The term mast cell activation syndrome (MCAS) has been used to identify a constellation of symptoms, signs, and laboratory abnormalities affecting multiple organ symptoms, which are suggestive of a **mast cell disorder** , but are insufficient to meet criteria for an alternative diagnosis such as **cutaneous mastocytosis** , **systemic mastocytosis** , or allergies. This term and the recognition of MCAS as a distinct entity has yet to be universally accepted, and although criteria for the diagnosis have been proposed (Table 678.3), the definition of the syndrome, its distinction from other mast cell disorders and unrelated conditions, and the means of establishing the diagnosis will likely continue to evolve. The incidence and prevalence of this syndrome in the pediatric population are unknown.

Table 678.3

Proposed Criteria for the Diagnosis of Mast Cell Activation Syndrome*

1. Episodic symptoms consistent with mast cell mediator release affecting ≥2 organ systems evidenced as follows:
    a. Skin: urticaria, angioedema, flushing
    b. Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramping
    c. Cardiovascular: hypotensive syncope or near syncope, tachycardia
    d. Respiratory: wheezing
    e. Naso-ocular: conjunctival injection, pruritus, nasal stuffiness
2. A decrease in the frequency or severity or resolution of symptoms with antimediator therapy: H_1 - and H_2 -histamine receptor inverse agonists, antileukotriene medications (cysteinyl leukotriene receptor blockers or 5-lipoxygenase inhibitor), or mast cell stabilizers (cromolyn sodium)
3. Evidence of an increase in a validated urinary or serum marker of mast cell activation: documentation of an increase of the marker to greater than the patient's baseline value during a symptomatic period on ≥2 occasions or, if baseline tryptase levels are persistently >15 ng, documentation of an increase of the tryptase level above baseline value on 1 occasion. Total serum tryptase level is recommended as the marker of choice; less specific (also from basophils) are 24-hr urine histamine

metabolites or PGD_2 or its metabolite 11-β-prostaglandin F_2 .
4. Rule out primary and secondary causes of mast cell activation and well-defined clinical idiopathic entities.

PGD_2 , prostaglandin D_2 .

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[*] Mast cell activation syndrome for now remains an idiopathic disorder; however, in some cases it could be an early reflection of a monoclonal population of mast cells, in which case with time it could meet the criteria for monoclonal mast cell activation syndrome (MMAS) as 1 or 2 minor criteria for mastocytosis are fulfilled.

From Akin C, Valent P, Metcalfe DD: Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol* 126:1099-104.e4, 2010, p. Table II, p. 1102.

Patients who have been given this diagnosis have had *recurrent* clinical manifestations **consistent with mast cell activation** . Cutaneous symptoms have included urticaria, angioedema, itching, and frequent skin flushing. Gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea are relatively common. Tachycardia, sometimes with hypotension and syncope, may be frequent, and some patients have wheezing episodes and rhinitis. Nonspecific and constitutional symptoms have also been described in patients given this diagnosis, including headache, fatigue, chronic pain, paresthesias, and anxiety and depression. Symptoms may be intermittent over many years and may vary in severity; some patients have developed chronic symptoms over time. The clinical features overlap with those with cutaneous or systemic mastocytosis, however individuals diagnosed with MCAS *do not* have cutaneous mastocytosis and, unlike systemic mastocytosis, they have not had evidence of clonal expansion of mast cells in bone marrow or other tissues. Limited investigations in small numbers of patients have not discovered large increases in the numbers of mast cells in intestinal mucosa tissue in patients with suspected MCAS; conclusive comparison data defining normal numbers of mast cells in these tissues is lacking. It has been hypothesized that those with MCAS have an unknown intrinsic mast cell defect, an abnormal and excessive response to stimulation, or both. This potentially leads to abnormal degranulation and release of mediators including histamine, heparin, and cytokines and increased production of inflammatory prostaglandins and leukotrienes.

The **differential diagnosis** of MCAS is broad, reflecting the protean symptoms and signs that have been proposed to be associated with the syndrome. Pheochromocytoma, the carcinoid syndrome, fibromyalgia and chronic pain syndromes, somatization secondary to primary anxiety or depression, hypereosinophilic syndromes, hereditary angioedema, and dysautonomias should all be considered in patients with symptoms that appear to be potentially related to mast cell activation. In addition, primary clonal mast cell disorders including cutaneous and systemic mastocytosis need to be excluded.

Laboratory abnormalities that might indicate mast cell activation include elevated serum tryptase and increases in 24-hr urinary histamine metabolites (N-methyl histamine, 1-methyl-4-imidazole acetic acid), prostaglandin D_2 , leukotriene E_4 , and 11-β-prostaglandin F_2 . Serum chromogranin A and plasma heparin have also been proposed as potentially useful markers of mast cell activation. No single laboratory test has been shown to be adequately sensitive as a diagnostic test for MCAS.

Proposed **diagnostic criteria** for MCAS require symptoms affecting more than one organ system that are consistent with mast cell mediator release, laboratory evidence of increased markers of mast cell activation on two occasions associated with symptoms, a decrease in severity or frequency of symptoms with antihistamine, antileukotriene, or mast cell stabilizing therapy, and the exclusion of primary clonal mast cell disorders and secondary causes of mast cell activation (allergies, malignancy, autoimmunity) (see Table 678.3). An alternative set of criteria proposes that the diagnosis can be made in patients with symptoms consistent with mast cell mediator release and any of the following: dense infiltrates of mast cells in bone marrow or other tissues, abnormal morphology of mast cells from tissue, mast cells in bone marrow expressing CD2 or CD25, genetic changes in mast cells known to result in increased mast cell activity, or laboratory evidence demonstrating increased markers of mast cell activation. This alternative set of criteria does not require a decrease in severity or frequency of symptoms with treatment. Dense infiltrates of mast cells in bone marrow, abnormal morphology of mast cells, and the expression of CD2 or CD25 are findings that are also associated with systemic mastocytosis; therefore this alternative set of criteria overlaps considerably with the criteria established to diagnose systemic mastocytosis. This has led to speculation that MCAS is part of a spectrum of mast cell dysfunctional disorders that includes systemic mastocytosis, cutaneous mastocytosis, and mast cell leukemia, all of which may potentially share common underlying genetic and other pathogenic factors.

Treatment of MCAS includes medications that interfere with the effects of mast cell mediators, such as the antihistamines and antileukotrienes, as well as medications that interfere with degranulation such as mast cell stabilizers. Prognosis appears to be favorable once the condition is identified, although considerable comorbidities have been identified in patients reported to date.

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CHAPTER 679

Ehlers-Danlos Syndrome

Donald Basel

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of heritable connective tissue disorders that are grouped into seven pathoetiological categories and more broadly divided into multiple subtypes (Table 679.1). Affected individuals are considered to have an overlapping phenotype of abnormally soft, extensible skin, which often heals poorly, in association with joint hypermobility and occasional instability believed to be rooted in a disruption of normal collagen function (Tables 679.2 and 679.3). The variable expression, modes of inheritance and unique phenotypic elements distinguish the subtypes from one another. The hypermobility type is the most common form and is the subject of significant clinical and research interest, given its myriad medical associations and the high population frequency of hypermobility—an estimated 3% of the general population.

Table 679.1

Classification of Ehlers-Danlos Syndrome

TYPE	GENE	SKIN FINDINGS	JOINT CHANGES	INHERITANCE	OT
Classic	*COL5A1*, *COL5A2* (usually haploinsufficiency)	Hyperextensibility, bruising, velvety skin, widened atrophic scars, molluscoid pseudotumors, spheroids	Hypermobility and its complications, joint dislocations	AD	Mit her
	COL1A1 Specific pathogenic variant; c.934C>T			AD	Blu statu oste may rupt

CLASSIC VARIANTS					
Cardiac valvular	Biallelic loss of function for *COL1A2*	Classic EDS features		AR	Sev issu
Periodontal	*C1R* *C1S*	Can have classic EDS features	Can have hypermobility	AD	Peri habi sho
Classic-like	*TNXB*	Hyperextensibility, marked hypermobility, severe bruising, velvety skin, no scarring tendency	Hypermobility	AR	Par mot mut hyp
Hypermobility	Unknown	Mild hyperextensibility, scarring, textural change	Hypermobility, chronic joint pain, recurrent dislocations	AD	Som wit syn
Vascular	*COL3A1* Rare variants in *COL1A1*	Thin, translucent skin, bruising, early varicosities, acrogeria	Small joint hypermobility	AD	Abr coll rupt arte pne
Kyphoscoliosis	*PLOD* (deficient lysyl hydroxylase) *FKBP14*	Soft, hyperextensible skin, bruising, atrophic scars	Hypermobility	AR	Sev mus imp chil kyp frag mar oste sens loss
VARIANTS WITH KYPHOSCOLIOSIS					
Spondylocheirodysplastic form	*SLC39A13*, which encodes the ZIP13 zinc transporter *β4GALT7* or *β3GalT6*, encoding galactosyltransferase I or II, key enzymes in GAG synthesis	Similar to kyphoscoliotic form		AR	Spo dys frag prog kyp con mod loos wri the atro curl
Brittle cornea syndrome	*ZNF469* or *PRDM5*	Skin hyperextensibility	Joint hypermobility	AR	Ky cha corr blue
Musculocontractural	*CHST14* (encoding dermatan 4-O-sulfotransferase) *DSE* (encoding dermatan sulfate epimerase)	Fragile, hyperextensible skin with atrophic scars and delayed wound healing	Hypermobility	AR	Prog kyp thu club arac con cha

					feat diat
Myopathic	*COL12A1*	Soft, hyperextensible	Hypermobile small joints, large joint contractures (hip, knees, elbows)	AD or AR	Cha hyp
Arthrochalasis	Exon 6 deletion of *COL1A1* or *COL1A2*	Hyperextensible, soft skin with or without abnormal scarring	Marked hypermobility with recurrent subluxations	AD	Con disl arth cong
Dermatosparaxis	Type I collagen N-peptidase *ADAMTS-2*	Severe fragility, sagging, redundant skin		AR	Als

AD, Autosomal dominant; *AR,* autosomal recessive; *EDS,* Ehlers–Danlos syndrome; *GAG,* glycosaminoglycan.

From Malfait F, Francomano, Byers P, et al: The 2017 International Classification of the Ehlers–Danlos syndromes. *Am J Med Genet C Semin Med Genet* 175(1):8-26, 2017.

Table 679.2

Common and Uncommon Features of Classic Ehlers-Danlos Syndrome

Skin

Hyperextensible
Velvety
Fragile, thin, poor tensile strength
Atopic scarring (“cigarette-paper” scars)
Striae
Bruising and bleeding (hemosiderin staining of skin)
Piezogenic papules, subcutaneous sphenoids
Wound dehiscence/incisional hernia

Musculoskeletal/Joints

Hypermobile ± joint dislocations
Pes planus
Chronic musculoskeletal pain, sprains
Late walking, hypotonia

Other Organ Involvement

Chiari type I malformation
Gastrointestinal (nausea, reflux, constipation)
Umbilical hernia
Hiatal hernia
Mitral valve prolapse
Aortic root dilation
CSF leak/headache
Pelvic organ prolapse
Premature rupture of fetal membranes
Cervical incompetence
Stress incontinence
Hyperkyphosis
Scoliosis
High arched palate
Femur anteversion (“W” sitting position)
Hollow organ rupture, diverticula
Occipitoatlantoaxial hypermobility

Table 679.3

Associated Features in Ehlers-Danlos/Hypermobility Spectrum Disorders

Autonomic and Neurologic Dysfunction

Postural orthostatic tachycardia syndrome (POTS)
Dizziness
Palpitations
Gastroparesis
Diarrhea
Constipation
Sleep dysfunction
Chronic fatigue
Headache (migraine, new daily headache)
Urinary stress incontinence
Somatosensory amplification

Irritable bowel syndrome
Neuropathic pain

Musculoskeletal Pain

Chronic regional pain syndrome
Fibromyalgia

The connective tissue matrix is complex (Fig. 679.1) and the interplay of cells, collagen and elastin fibers, proteins, and cell signaling molecules remains poorly understood. However, dysfunction at a structural and functional level more than likely explain the complex medical associations typically encountered in this population, with complaints ranging from joint instability and tissue fragility to chronic pain, autonomic dysfunction, and chronic fatigue (see Table 679.3).

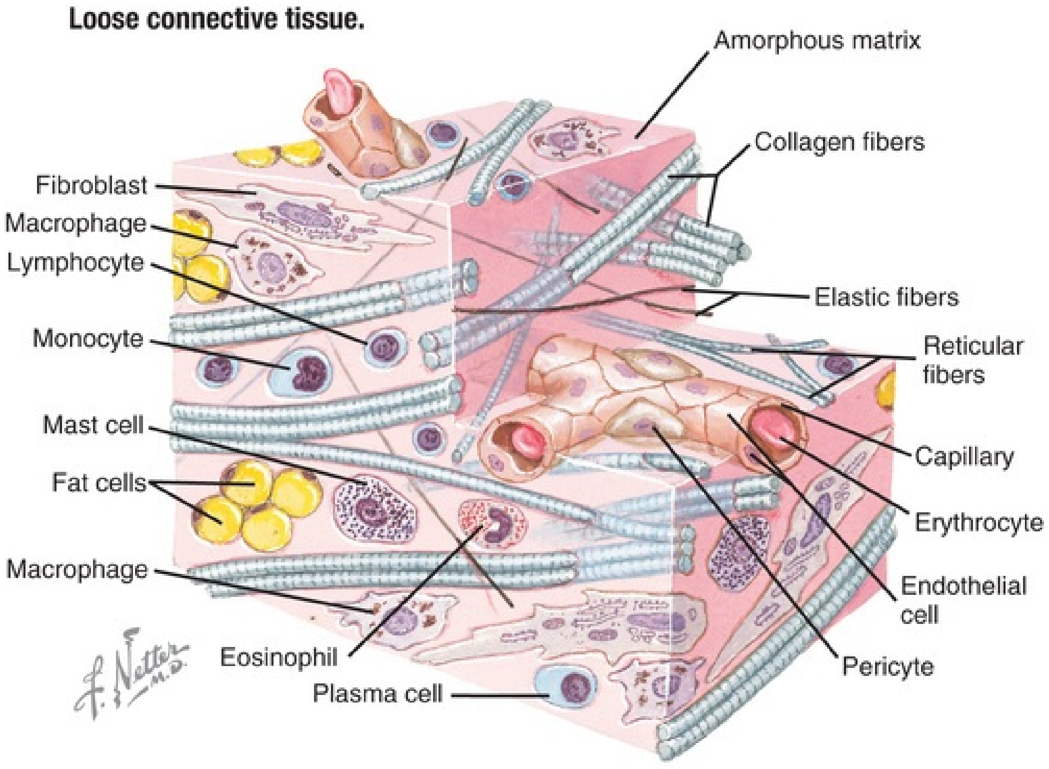
Loose connective tissue.
Amorphous matrix
Collagen fibers
Fibroblast
Macrophage
Lymphocyte
Monocyte
Elastic fibers
Reticular fibers
Mast cell
Capillary
Fat cells
Erythrocyte
Macrophage
Endothelial cell
F. Netter M.D.
Eosinophil
Pericyte
Plasma cell

FIG. 679.1 Complex connective tissue macroenvironment illustrated by intermingled collagen and elastin fibers, nerves, mast cells, and capillaries. Both structure and function can be impacted by an abnormal connective

tissue matrix. (Courtesy Netter Images, Image ID 13192. https://netterimages.com/loose-connective-tissue-ovalle-histology-figure-31-labeled-ovalle-histology-frank-h-netter-13192.html)

Classification of the 6 Most Common Subtypes of Ehlers-Danlos Syndrome

Classic (Genes: *COL5a1* , *COL5a2* , *COL1a1* ; Previously EDS Type I—Gravis, EDS Type II—Mitis)

Classic EDS is the 2nd most common form of EDS and is an autosomal dominant connective tissue disorder characterized by skin hyperelasticity (Fig. 679.2), widened atrophic scars (skin fragility) and joint hypermobility. Other features include easy bruising, which is often associated with hemosiderin staining of the tissues (particularly over regions exposed to frequent trauma, like the shins). The skin is "velvet" to the touch and is particularly fragile, with minor lacerations forming gaping wounds that leave broad, atrophic, papyraceous ("cigarette paper") scars (see Table 679.2 and Fig. 679.3). Additional cutaneous manifestations include molluscoid pseudotumors over pressure points from accumulations of connective tissue and piezogenic papules (Fig. 679.4). Joints are hypermobile, often with joint instability (Fig. 679.5). Scoliosis frequently presents in adolescence and mitral valve prolapse is common. Life expectancy is generally not reduced, although rare rupture of large arteries has been reported. Similar noncutaneous nonarticular comorbidities as seen in hypermobile EDS are found, in particular pain and gastrointestinal dysfunction (see Table 679.3). Premature birth caused by rupture of membranes of an affected offspring is not uncommon. The diagnosis is made by clinical findings and sequencing of *COL5a1* and *COL5a2* genes.

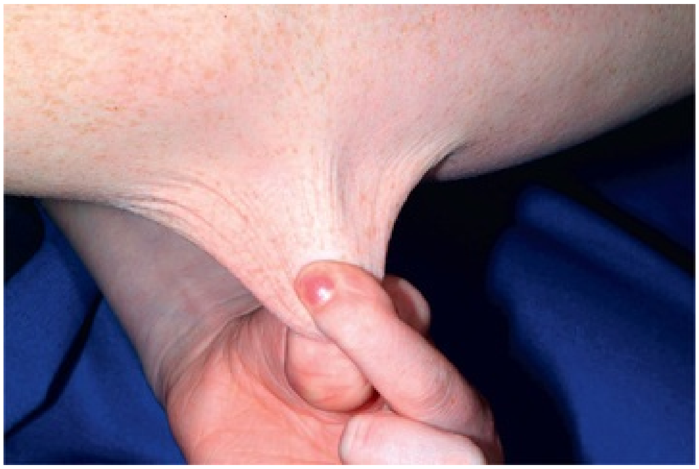

FIG. 679.2 Ehlers–Danlos syndrome (EDS). Skin hyperextensibility on the arm. (From Paller AS, Mancini AJ (eds): Hurwitz Clinical Pediatric Dermatology, ed 5, Philadelphia, 2016, Elsevier, Fig. 6.1, p. 121).

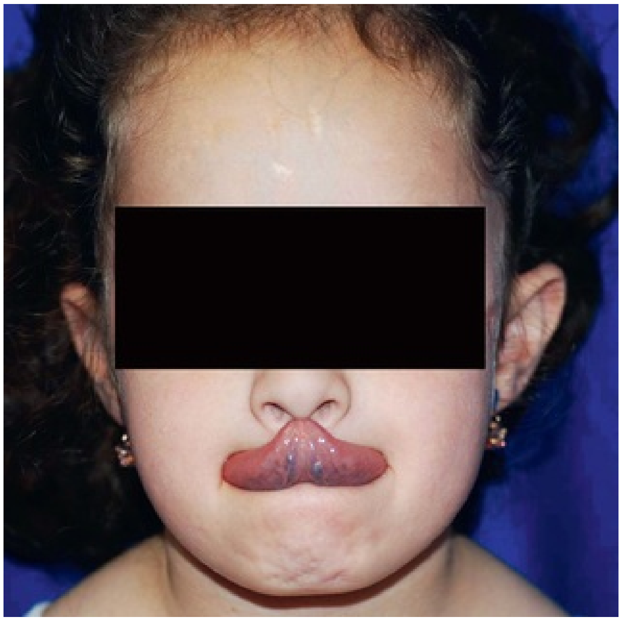

FIG. 679.3 Ehlers–Danlos syndrome (EDS). The Gorlin sign is 5 times more common in EDS than in normal individuals. Note the scars on the forehead. (From Paller AS, Mancini AJ (eds): Hurwitz Clinical Pediatric Dermatology, ed 5, Philadelphia, 2016, Elsevier, Fig. 6.2, p. 121).

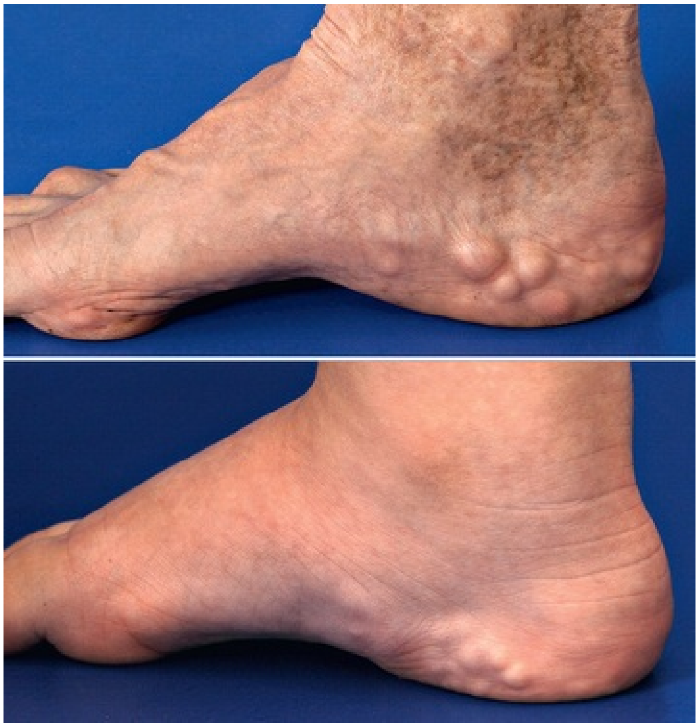

FIG. 679.4 Piezogenic papules on the medial aspects of the heels in a 41-year-old patient with Ehlers-Danlos syndrome *(top)* and his 2-year-old daughter *(bottom).* (From Poppe H, Hamm H: Piezogenic papules in Ehlers-Danlos syndrome. *J Pediatr* 163:1788, 2013.)

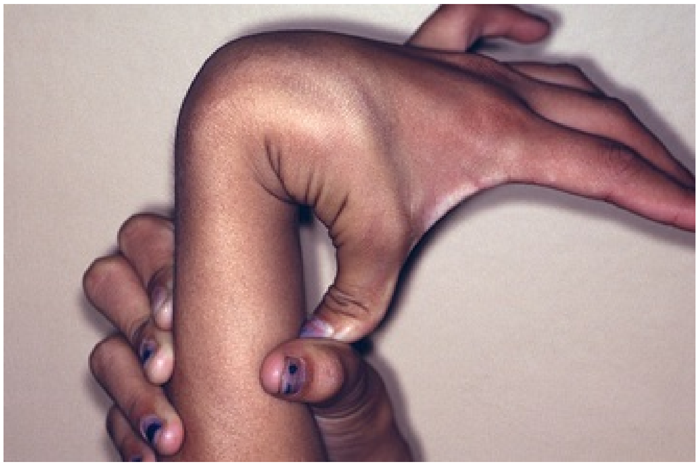

FIG. 679.5 Despite joint hyperextensibility, this patient does not meet Beighton score criteria for the extreme hypermobility seen with hypermobile Ehlers-Danlos syndrome.

Hypermobile (Cause Unknown, Previously EDS Type III)

Hypermobile EDS (hEDS) is the most prevalent form of EDS with an estimated population frequency of between 0.75% and 2%. It is an autosomal dominant disorder, but the causative molecular pathoetiology remains elusive in the majority of affected individuals. Fewer than 3% of patients with a hEDS phenotype are associated with heterozygous tenascin X gene loss of function, whereas a minority of cases are linked to other findings, such as the association with mosaic type 1 collagen defects. Tenascin X was originally identified to cause a recessive form of EDS with characteristics similar to those of classic EDS.

The primary clinical finding in hEDS is generalized joint hypermobility with less prominent skin manifestations. There is inconsistency in the literature as to what defines hypermobility, but generally a score of ≥6 on the Beighton hypermobility scale (Fig. 679.6 , Table 679.4) would qualify as hypermobility in an individual between the ages of 6 and 35 years. Children <6 years of age generally tend toward a hypermobile state. However, joints begin to stiffen in the 4th decade, at which time a score of 3+ is considered significant in the context of a history of joint hypermobility (Table 679.5). Joint instability with frequent dislocations is common but not universal; joints are predisposed to osteoarthritis in adults.

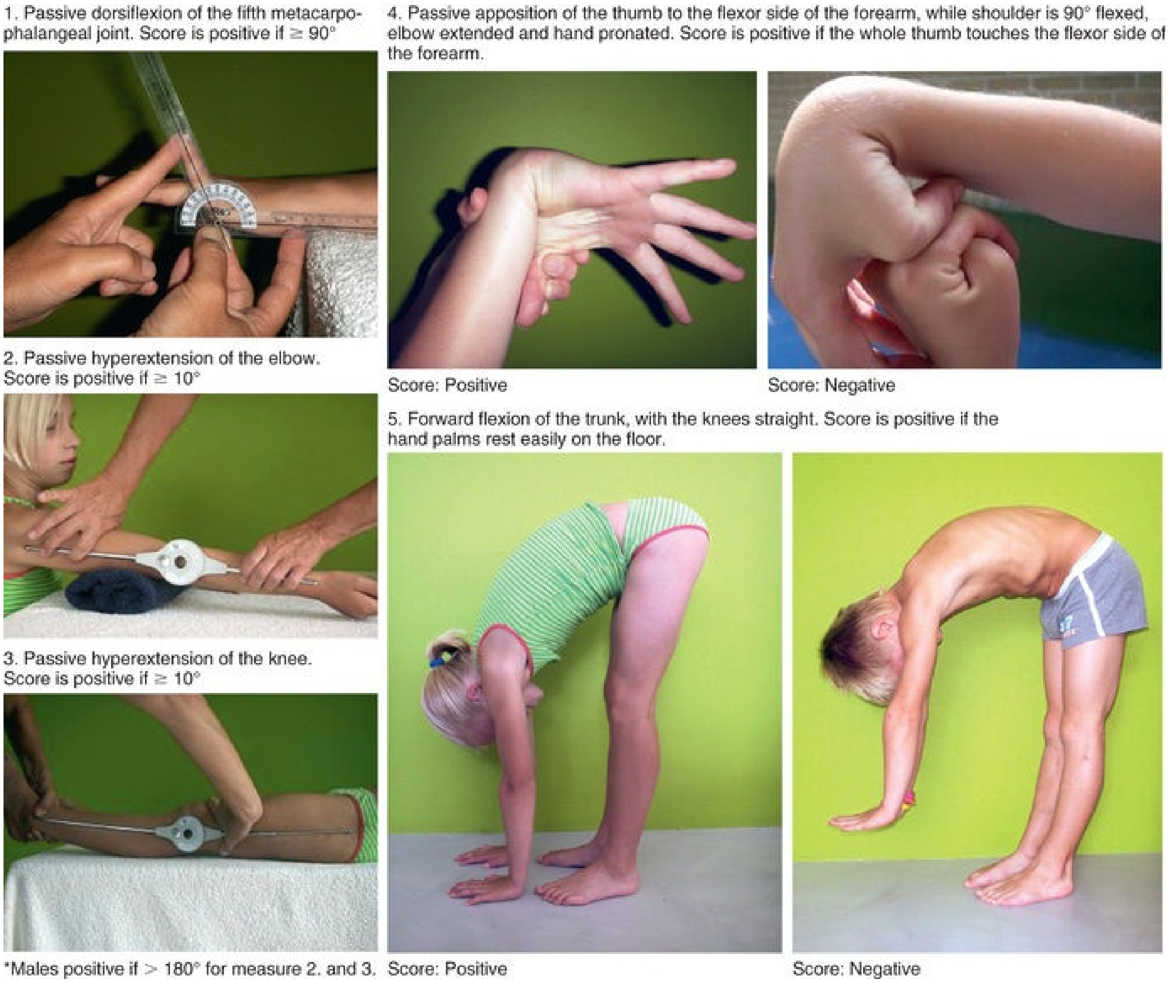

1. Passive dorsiflexion of the fifth metacarpo-phalangeal joint. Score is positive if ≥ 90°

2. Passive hyperextension of the elbow. Score is positive if ≥ 10°

3. Passive hyperextension of the knee. Score is positive if ≥ 10°

*Males positive if > 180° for measure 2. and 3.

4. Passive apposition of the thumb to the flexor side of the forearm, while shoulder is 90° flexed, elbow extended and hand pronated. Score is positive if the whole thumb touches the flexor side of the forearm.

Score: Positive

Score: Negative

5. Forward flexion of the trunk, with the knees straight. Score is positive if the hand palms rest easily on the floor.

Score: Positive

Score: Negative

FIG. 679.6 Beighton score. The range of motion of several key small and large joints is measured to provide an overview of joint hypermobility. Instability is not assessed. Scoring: 2 points for each bilateral measure in Nos. ***1*** to ***4*** and 1 point for No. ***5*** , equaling a total possible score of 9. Hypermobility is considered significant with a score of ≥6 between the ages of 6 and 35. (Modified from Smits-Engelsman B, Klerks M, Kirby A. Beighton Score: A Valid Measure for Generalized Hypermobility in Children. *J Peds* 158(1):119–123.e4, 2011.)

Table 679.4

The Nine-Point Beighton Hypermobility Score

THE ABILITY TO:	RIGHT	LEFT
1. Passively dorsiflex the 5th metacarpophalangeal joint to ≥90°	1	1
2. Oppose the thenar aspect of the thumb to the volar aspect of the ipsilateral forearm	1	1
3. Hyperextend the elbow to ≥10 degrees	1	1
4. Hyperextend the knee to ≥10 degrees	1	1
5. Place hands flat on the floor without bending the knees	1	

	Total 9	

One point may be gained for each side for maneuvers 1-4, so the hypermobility score will have a maximum of 9 points if all are positive.

From Hakim A, Grahame R: Joint hypermobility. *Best Pract Res Clin Rheumatol* 17:989–1004, 2003, Table 1.

Table 679.5

A Five-Part Questionnaire for Identifying Hypermobility

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child did you amuse your friends by contorting your body into strange shapes *or* could you do the splits?
4. As a child or teenager did your shoulder or kneecap dislocate on more than 1 occasion?
5. Do you consider yourself double-jointed?

Answers in the affirmative to 2 or more questions suggest hypermobility with sensitivity 80–85% and specificity 80–90%.

From Hakim A, Grahame R: Joint hypermobility. *Best Pract Res Clin Rheumatol* 17:989–1004, 2003, Table 3.

Patients with hEDS have significant nonarticular comorbidities associated with functional disorders; these present as complex pain, dysautonomia, chronic fatigue, anxiety, and sleep dysfunction (see Table 679.3). The complexity of hEDS most likely originates from the fact that it is genetically heterogeneous and represents an overlapping spectrum of disorders. Although joint hypermobility is the common denominator, symptoms may range from isolated familial joint hypermobility to the extreme multisystem disorder, which significantly impacts daily quality of life. Life expectancy is not reduced. Mild aortic root dilatation has been reported in up to 20% of affected adults. However, this mild dilatation is nonprogressive and not associated with aortic root dissection.

Vascular (vEDS) (Gene: *COL3a1* ; Previously EDS Type IV)

vEDS is an autosomal dominant disorder that shows the most pronounced dermal thinning of all types of EDS. Consequently the skin is translucent and the underlying venous network is prominent, most notably over the chest region. The skin has minimal hyperextensibility but has a “velvet” texture and is often described as “doughy.” The joints show increased mobility, often with instability. Congenital club foot and hip dislocation are frequently associated. Tissue fragility and arterial rupture cause significant morbidity and mortality. The majority of affected individuals experience a major vascular event before 20 years of age. Premature birth, extensive ecchymoses from trauma, a high incidence of bowel rupture (especially the colon), uterine rupture during pregnancy (~5% risk), rupture of the great vessels (80% by 40 years of age), dissecting aortic aneurysm, and stroke all contribute to the increased morbidity and shortened life span associated with this condition. The median age of death is estimated at 50 years. Patients are generally counseled regarding the risks associated with pregnancy and advised to avoid activities that raise intracranial or intrathoracic pressure as a result of a Valsalva maneuver (such as weight training or trumpet playing). Skin protection in childhood is important to minimize trauma (shin guards). Celiprolol, a β1 antagonist and a β2 agonist (vasodilator), may reduce vascular events but is not approved by the US Food and Drug Administration (FDA) for use in the United States. The diagnosis is clinical and confirmed by gene sequencing of *COL3a1*.

Kyphoscoliosis (Gene: *PLOD* [Lysyl Hydroxylase Deficiency]; Previously EDS Type VI)

The kyphoscoliotic form of EDS is distinguished by the severe kyphoscoliosis that develops early in childhood. It is an autosomal recessive disorder with phenotypic overlap with the classical type of EDS in that the skin is soft and fragile, joints are hyperextensible, and easy bruising is notable from a young age. Unique characteristics include marked hypotonia and keratoconus with corneal fragility; globe rupture has been reported. In addition, there is a higher risk for rupture of medium-sized arteries. The severity of the kyphoscoliosis may lead to restrictive lung disease with secondary pulmonary hypertension and reduced life expectancy. The diagnosis is clinical and confirmed by urine screening for an increased ratio of deoxypyridinoline to pyridinoline cross linking as well as gene sequencing of *PLOD*.

Arthrochalasia (Gene: *COL1a1* , *COL1a2* ; Previously EDS Types VIIA and B)

This type of EDS is inherited as an autosomal dominant disorder and characterized by severe joint instability in infancy. Joints show marked hyperextensibility with painless dislocation; the skin bruises easily and is soft and hyperextensible. Congenital hypotonia with gross motor delay is common, and kyphoscoliosis can develop in childhood. The diagnosis is clinical and confirmed by gene sequencing of *COL1a1* and *COL1a2*.

Dermatosparaxis (Type 1 Collagen N-Peptidase; Previously EDS Type VIIC)

This type of EDS is a rare autosomal recessive condition characterized by redundant skin that is soft, fragile, and bruises easily. Affected children often have a characteristic facial appearance, with skin sagging into jowls and fullness around the eyes (“puffy”). Premature rupture of membranes is common; closure of fontanels is delayed. Additional unique features reported in this group include short limbs with brachydactyly (short fingers), frequent hernias (umbilical, inguinal), blue sclerae, and bladder rupture. Joints are hypermobile. The diagnosis is confirmed by gene sequencing of *ADAMTS2*.

Differential Diagnosis

EDS represents a portion of the hereditary connective tissue disorders, many of which have unique features that enable clinical differentiation. The primary differential diagnosis would include Loeys-Dietz syndrome, which has features of both vEDS and Marfan syndrome. EDS has also been confused with MASS syndrome (mitral valve prolapse, aortic root dilation, skeletal changes, skin changes), cutis laxa, and pseudoxanthoma elasticum. In general the skin of patients with cutis laxa hangs in redundant folds, whereas the skin of those with

EDS is hyperextensible and snaps back into place when stretched. Other disorders that impact the integrity of the connective tissues—such as exposure to corticosteroids and osteogenesis imperfecta or mild myopathic disorders (Bethlem myopathy, Ullrich congenital muscular dystrophy)—can be indistinguishable in the early stages of disease.

General Approach to Management

In addition to the EDS type-specific therapies discussed under each disease, there are general approaches to help improve symptoms and avoid complications.

Musculoskeletal pain, which initially involves the joints, eventually may become generalized and requires a combination of physical therapy and nonpharmacologic approaches. Physical therapy should focus on enhancing the strength of the muscles supporting the affected joints. With severe recurrent sprains or dislocations, bracing may be necessary. Pain medication for low- to moderate-intensity pain could include nonsteroidal antiinflammatory drugs (however, their platelet-inhibiting action may increase the risk of cutaneous bleeding). Higher-intensity pain may require other agents, such as selective serotonin receptor inhibitors or low-dose tricyclic antidepressants. Muscle relaxants or antiepileptic agents should be avoided because they may increase fatigue. Surgery for joint dislocations should be avoided if possible, as should prolonged periods of inactivity (which result in rapid muscle deconditioning) (Table 679.6). If surgery is needed for any complication, the sutures should approximate the margins, suture tension should be avoided, and the sutures should be retained longer than usual. Other approaches to pain include cognitive behavioral therapy, acupuncture, and transepidermal electrical nerve stimulation (TENS).

Table 679.6

Lifestyle Recommendations for Hypermobile Ehlers-Danlos Syndrome

Promote regular aerobic fitness

Promote fitness support with strengthening, gentle stretching, and proprioception exercise

Promote postural and ergonomic hygiene, especially during sleep, at school, and in the workplace
Promote weight control (BMI < 25)
Promote daily relaxation activities
Promote lubrication during sexual intercourse (women)
Promote early treatment of malocclusion
Avoid high-impact sports/activities
Avoid low environmental temperatures
Avoid prolonged sitting positions and prolonged recumbency
Avoid sudden head-up postural change
Avoid excessive weight lifting/carrying
Avoid large meals (especially of refined carbohydrates)
Avoid hard foods intake and excessive jaw movements (ice, gums, etc.)
Avoid bladder irritant foods (e.g., coffee and citrus products)
Avoid nicotine and alcohol intake

Note: these recommendations are intended as flexible indications for ameliorating quality of life and do not represent lifesaving solutions.

Adapted from Castori M, Morlino S, Celletti C, et al. Management of pain and fatigue in the joint hypermobility syndrome (aka Ehlers-Danlos syndrome, hypermobility type): principles and proposal for a multidisciplinary approach. *Am J Med Genet* 158:2055–2070, 2012.

Chronic fatigue should be approached by supporting good sleep hygiene and avoiding sedating medications (see Table 679.6). Patients at risk for arterial bowel or uterine rupture should be counseled about preventive measures, appropriate medications (see specific subtype), and early warning signs of organ rupture.

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CHAPTER 680

Diseases of Subcutaneous Tissue

Wendy E. Kim

Diseases involving the subcutis are usually characterized by necrosis and/or inflammation; they may occur either as a primary event or as a secondary response to various stimuli or disease processes. The principal diagnostic criteria relate to the appearance and distribution of the lesions, associated symptoms, results of laboratory studies, histopathology, and natural history and exogenous provocative factors of these conditions.

Corticosteroid-Induced Atrophy

Intradermal or subcutaneous injection of a corticosteroid can produce deep atrophy accompanied by surface pigmentary changes and telangiectasia (Fig. 680.1). These changes occur approximately 2-8 wk after injection and may last for months.

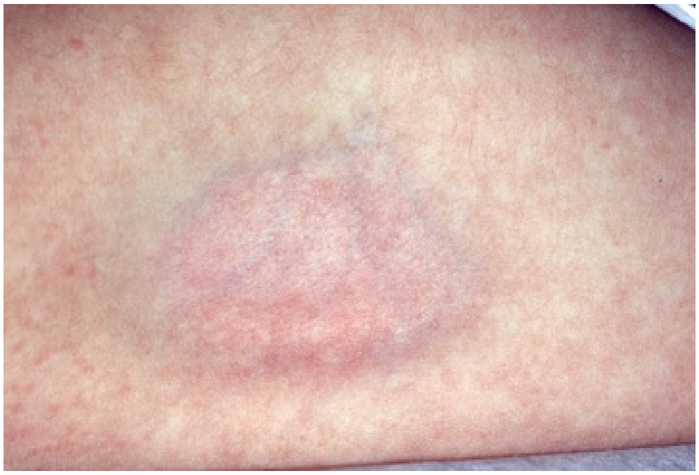

FIG. 680.1 Localized fat atrophy with overlying erythema after steroid injection.

680.1

Panniculitis and Erythema Nodosum

Wendy E. Kim

Inflammation of fibrofatty subcutaneous tissue may primarily involve the fat lobule or, alternatively, the fibrous septum that compartmentalizes the fatty lobules. Lobular panniculitis that spares the subcutaneous vasculature includes poststeroid panniculitis, lupus erythematosus profundus, pancreatic panniculitis, α_1 -antitrypsin deficiency, subcutaneous fat necrosis of the newborn, sclerema neonatorum, cold panniculitis, subcutaneous sarcoidosis, and factitial panniculitis. Lobar panniculitis with vasculitis occurs in erythema induratum and, occasionally, as a feature of Crohn disease (see Chapter 362.2). Inflammation predominantly within the septum, sparing the vasculature, may be seen in erythema nodosum (Table 680.1 and Fig. 680.2), necrobiosis lipoidica, progressive systemic sclerosis (see Chapter 185), and subcutaneous granuloma annulare (see Chapter 678). Septal panniculitis that includes inflammation of the vessels is found primarily in leukocytoclastic vasculitis and polyarteritis nodosa (see Chapter 192).

Table 680.1

Etiology of Erythema Nodosum

Viruses

Epstein-Barr, hepatitis B, mumps

Fungi

Coccidioidomycosis, histoplasmosis, blastomycosis, sporotrichosis

Bacteria and Other Infectious Agents

Group A streptococcus,* tuberculosis,* *Yersinia*, cat-scratch disease, leprosy, leptospirosis, tularemia, mycoplasma, Whipple disease, lymphogranuloma venereum, psittacosis, brucellosis

Other

Sarcoidosis, inflammatory bowel disease,* estrogen-containing oral contraceptives,* systemic lupus erythematosus, Behçet syndrome, severe acne, Hodgkin disease, lymphoma, sulfonamides, bromides, echinacea, Sweet syndrome, pregnancy, idiopathic*

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[*] Common.

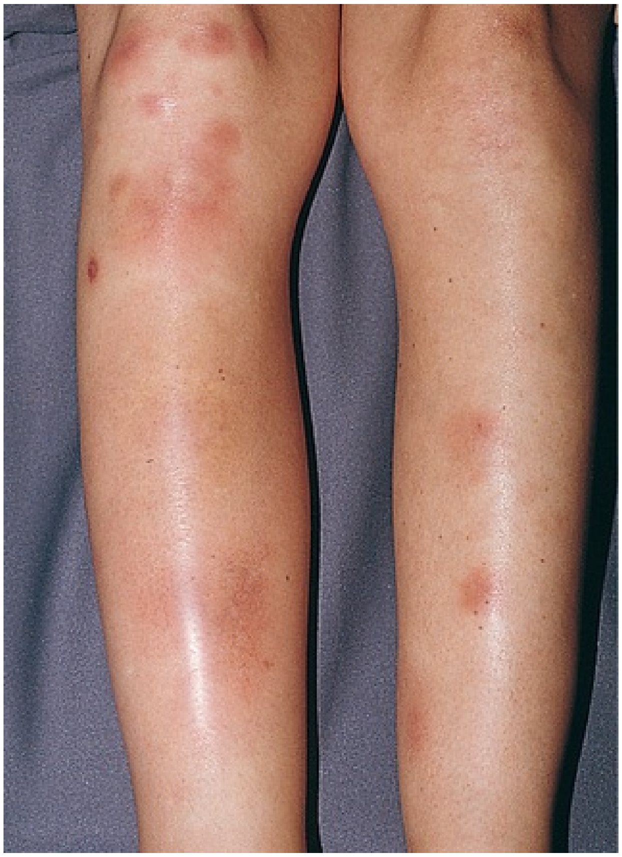

FIG. 680.2 Tender red nodules with indistinct borders in a teenage girl with erythema nodosum. (From Weston AL, Lane AT, Morelli JG: *Color textbook of pediatric dermatology* , ed 3, St. Louis, 2002, Mosby, p. 212.)

Erythema Nodosum

Etiology and Pathogenesis

The etiology is unknown in 30–50% of pediatric cases of erythema nodosum; Table 680.1 lists potential etiologies. The most common etiologies in children include group A streptococcal infection, *Yersinia enterocolitica* gastroenteritis, medications (cephalosporins, penicillins, macrolides), and inflammatory disorders (inflammatory bowel disease); sarcoidosis should be considered in young adults.

Clinical Manifestations

Erythema nodosum is a nodular erythematous hypersensitivity reaction that typically appears with multiple lesions on the lower legs (pretibial area) and less often in other areas, including the extensor surfaces of the arms and thighs. The lesions vary in size from 1 to 6 cm, are symmetric, and are oval with the longer axis parallel to the extremity. They initially appear bright or dull red but progress to a brown or purple; they are painful and usually do not ulcerate (see Fig. 680.2). Initial lesions may resolve in 1-2 wk, but new lesions may continue to appear for 2-6 wk. Repeat episodes may occur weeks to months later. Prior to or immediately at the onset of lesions, there may be systemic manifestations including fever, malaise, arthralgias (50–90%) and rheumatoid factor–negative arthritis.

Histology

A septal panniculitis with thickening of the septa and an inflammatory cell infiltrate comprising of neutrophils occurs acutely. Monocytes and histiocytes predominate in chronic erythema nodosum.

Treatment

Treatment includes that of the underlying disease as well as symptomatic relief with nonsteroidal antiinflammatory agents (ibuprofen, naproxen, salicylates); supersaturated solution of potassium iodide (oral), colchicine, or intralesional corticosteroids are used for persistent lesion tenderness. Oral steroids have been employed in the treatment of severe, persistent, or recurrent lesions. The idiopathic form is a self-limited disorder. Protracted or recurrent cases may warrant further workup, including antistreptolysin O/deoxyribonuclease B, complete blood count, throat culture, purified protein derivative, QuantiFERON-TB gold assay, chest radiograph, erythrocyte sedimentation rate, and C-reactive protein.

Post-Steroid Panniculitis

Etiology and Pathogenesis

The mechanism of the inflammatory reaction in the fat in poststeroid panniculitis is unknown.

Clinical Manifestations

Most cases of poststeroid panniculitis have been reported in children. The disorder occurs in children who have received high-dose corticosteroids. Within 1-2 wk after discontinuation of the drug, multiple subcutaneous nodules usually appear on the cheeks, although other areas may be involved. Nodules range in size from 0.5 to 4.0 cm, are erythematous or skin-colored, and may be pruritic or painful.

Histology

A lobular panniculitis with a mixed infiltrate of lymphocytes, histiocytes, and neutrophils is seen. Scattered swollen adipocytes with eosinophilic, needle-shaped crystals are also seen. The epidermis, dermis, and fibrous septa of the fat are normal. Vasculitis is not seen.

Treatment

Treatment of poststeroid panniculitis is unnecessary because the lesions remit spontaneously over a period of months without scarring.

Lupus Erythematosus Profundus (Lupus Erythematosus Panniculitis)

Etiology and Pathogenesis

It is unknown what separates those patients in whom lupus erythematosus profundus develops from other patients with systemic lupus erythematosus. This variant of chronic cutaneous lupus erythematosus is rare in childhood. Only 2–5% of patients with lupus erythematosus profundus have associated systemic lupus erythematosus. The mean age of onset in reported pediatric cases is 9.8 yr.

Clinical Manifestations

Lupus erythematosus profundus manifests as 1 to several firm, tender, well-defined, purple plaques or nodules 1-3 cm in diameter. A majority of pediatric cases involve the face and proximal upper extremities. This condition may occur in patients with systemic or discoid lupus erythematosus and may precede or follow the development of other cutaneous lesions and/or systemic lupus erythematosus. The overlying skin is usually normal but may be erythematous, atrophic, poikilodermatous, or hyperkeratotic (Fig. 680.3). On healing, a shallow depression generally remains or, rarely, soft pink areas of anetoderma result.

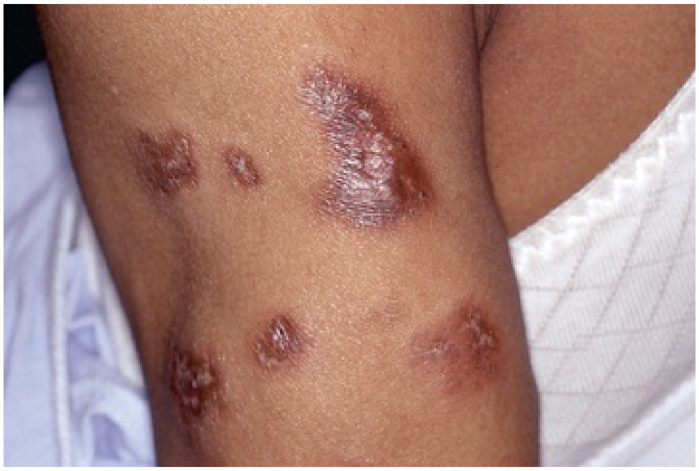

FIG. 680.3 **Deep nodule of lupus profundus with overlying hyperkeratotic lesion of discoid lupus erythematosus.**

Histology

The histopathologic changes in lupus erythematosus profundus are distinctive and may allow the clinician to make the diagnosis in the absence of other cutaneous lesions of lupus erythematosus. The panniculitis is characterized by a mostly nodular dense infiltrate of lymphocytes and plasma cells. Necrosis of the fat lobule is characteristic. A dense perivascular and periappendiceal lymphocytic infiltrate is seen in the dermis. Lichenoid changes may be identified at the epidermal-dermal junction. Histopathologic differentiation from subcutaneous panniculitis–like T-cell lymphoma may be difficult. Results of lupus band and antinuclear antibody tests are usually positive.

Treatment

Nodules tend to be persistent and frequently ulcerate. Long-term follow-up for possible systemic involvement is warranted. There is no consensus on the utility of laboratory testing. Antinuclear antibody is positive in only a small subset of patients. A few case reports show slight neutropenia, leukopenia, and mildly elevated liver function tests. Hydroxychloroquine (2-5 mg/kg/day) is the treatment of choice for lupus erythematosus profundus. Systemic corticosteroids may be helpful, but topical corticosteroids are ineffective. Intralesional corticosteroids may worsen the residual lipoatrophy and lead to ulceration. Immunosuppressive agents are indicated only for the treatment of other severe manifestations of systemic lupus erythematosus. Avoidance of sun exposure and trauma is also important.

Alpha$_1$ -Antitrypsin Deficiency

Etiology and Pathogenesis

Individuals with α_1 -antitrypsin deficiency have severe homozygous deficiency or, rarely, a partial deficiency of the protease inhibitor α_1 -antitrypsin, which inhibits trypsin activity and the activity of elastase, serine proteases, collagenase, factor VIII, and kallikrein (see Chapter 421). Panniculitis occurs with severe α_1 -antitrypsin deficiency or the Z subtype.

Clinical Manifestations

Cellulitis-like areas or tender, red nodules occur on the trunk or proximal extremities. Nodules tend to ulcerate spontaneously and discharge an oily yellow fluid. Panniculitis may be associated with other manifestations of the disease, such as panacinar emphysema, noninfectious hepatitis, cirrhosis, persistent cutaneous vasculitis, cold contact urticaria, and acquired angioedema. Diagnosis can be substantiated by a decreased level of serum α_1 -antitrypsin activity.

Histology

Extensive septal and lobular neutrophilic infiltrate with necrosis of the fat is observed.

Treatment

Panniculitis associated with α_1 -antitrypsin deficiency typically resolves over several weeks following treatment exogenous enzyme replacement therapy.

Pancreatic Panniculitis

Etiology and Pathogenesis

The pathogenesis of pancreatic panniculitis appears to be multifactorial, involving liberation of the lipolytic enzymes lipase, trypsin, and amylase into the circulation and causing adipocyte membrane damage and intracellular lipolysis. There is no correlation, however, between the occurrence of panniculitis and the serum concentration of pancreatic enzymes.

Clinical Manifestations

Pancreatic panniculitis manifests most commonly on the pretibial regions, thighs, or buttocks as tender, erythematous nodules that may be fluctuant and occasionally discharge an oily yellowish substance. It appears most often in males with alcoholism but may also occur in patients with pancreatitis as a result of cholelithiasis or abdominal trauma, with rupture of a pancreatic pseudocyst, with pancreatic ductal adenocarcinoma, or with pancreatic acinar cell carcinoma. Associated features may include polyarthritis (**pancreatitis-panniculitis-polyarthritis syndrome**). In almost 65% of patients, abdominal signs are absent or mild, making the diagnosis difficult.

Histology

Microscopic changes consist of multiple foci of fat necrosis that contain ghost cells with thick, shadowy walls and no nuclei. A polymorphous inflammatory infiltrate surrounds the areas of fat necrosis.

Treatment

The primary pancreatic disorder must be treated. The arthritis may be chronic and responds poorly to treatment with nonsteroidal anti-inflammatory drugs and oral corticosteroids.

Subcutaneous Fat Necrosis

Etiology and Pathogenesis

The cause of subcutaneous fat necrosis (SCFN) is unknown. The disease in infants may be a result of ischemic injury from various perinatal complications, such as maternal preeclampsia, birth trauma, asphyxia, and prolonged hypothermia. Whole-body cooling for neonatal encephalopathy is increasingly associated with SCFN. Susceptibility is attributed to differences in composition between the subcutaneous tissue of young infants and that of older infants, children, and adults. Neonatal fat solidifies at a relatively high temperature because of its relatively greater concentration of high-melting-point saturated fatty acids, such as palmitic and stearic acids.

Clinical Manifestations

This inflammatory disorder of adipose tissue occurs primarily in the 1st 4 wk of life in full-term or postterm infants. Some lesions may be present at birth. Typical lesions are asymptomatic, indurated, erythematous to violaceous sharply demarcated plaques or nodules on the cheeks, buttocks, back, thighs, or upper arms (Fig. 680.4). Lesions may be focal or extensive and are generally asymptomatic, although they may be tender during the acute phase. Uncomplicated lesions involute spontaneously within weeks to months, usually without scarring or atrophy. Calcium deposition may occasionally occur within areas of fat necrosis, which may sometimes result in rupture and drainage of liquid material. These areas may heal with atrophy. A rare but potentially serious complication is **hypercalcemia** . It manifests at 1-6 mo of age (in a review of 20 cases, average age at onset was 6-7 wk) as lethargy, poor feeding, vomiting, failure to thrive, irritability, seizures, shortening of the QT interval on electrocardiography, or renal failure. The origin of the hypercalcemia is unknown, but an accepted hypothesis is that the macrophages present produce 1,25-dihydroxyvitamin D_3 which, in turn, increases calcium uptake. Infants with SCFN should be followed for several months to monitor for delayed hypercalcemia.

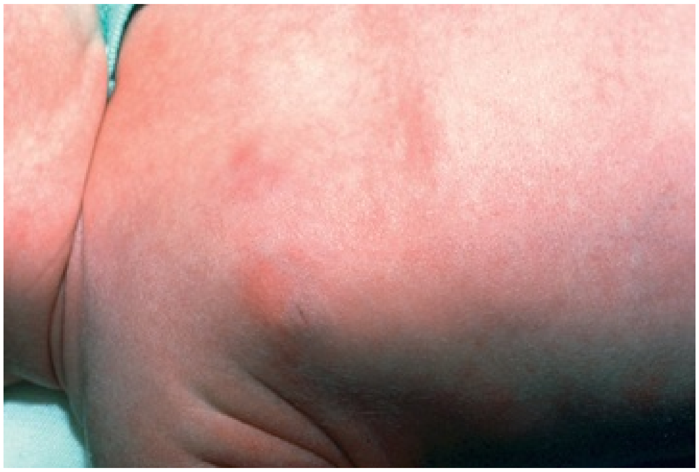

FIG. 680.4 **Red-purple nodular infiltration of the skin of the chest caused by subcutaneous fat necrosis.**

Histology

Histopathologic changes in SCFN are diagnostic, consisting of necrosis of fat; a granulomatous cellular infiltrate composed of lymphocytes, histiocytes, multinucleated giant cells, and fibroblasts; and radially arranged clefts of crystalline triglyceride within fat cells and multinucleated giant cells. Calcium deposits are commonly found in areas of fat necrosis.

Differential Diagnosis

SCFN can be confused with sclerema neonatorum, panniculitis, cellulitis, and hematoma.

Treatment

Because the lesions are self-limited, therapy is not required for uncomplicated cases of SCFN. Needle aspiration of fluctuant lesions may prevent rupture and subsequent scarring but is rarely needed. Treatment of hypercalcemia is aimed at enhancing renal calcium excretion with hydration and furosemide (1-2 mg/kg/dose) and at limiting dietary calcium and vitamin D intake. Reduction of intestinal calcium absorption and alteration of vitamin D metabolism may be accomplished by administering corticosteroids (0.5-1.0 mg/kg/day). Pamidronate (0.25-0.5 mg/kg/day) has been used in severe cases.

Sclerema Neonatorum

Etiology and Pathogenesis

Although the cause remains unknown, 4 theories regarding the pathogenesis of sclerema neonatorum have been proposed. Theoretically it can result from hardening of the subcutaneous fat because of a decrease in body temperature as a consequence of circulatory shock, a defect in lipolytic enzymes or in lipid transport, association with an underlying severe disease, or a special form of edema affecting the connective tissue supporting the adipocytes.

Clinical Manifestations

This uncommon disorder of adipose tissue manifests abruptly in preterm, gravely ill infants as diffuse, yellowish white woody indurations of the skin. It begins on the legs and buttocks and then quickly progresses to other areas, sparing palms and soles. Affected skin becomes stony in consistency, cold, and nonpitting. The face assumes a mask-like expression, and joint mobility may be compromised because of inflexibility of the skin.

Histology

Histopathologic changes in sclerema neonatorum consist of increases in the size of fat cells and the width of the fibrous connective tissue septa. In contrast to SCFN, with which this disorder is most apt to be confused, fat necrosis, inflammation, giant cells, and calcium crystals are generally absent.

Treatment

Sclerema neonatorum is almost always associated with serious illness, such as sepsis, congenital heart disease, multiple congenital anomalies, or hypothermia. The appearance of sclerema in a sick infant should be regarded as an ominous prognostic sign. The outcome depends on the response of the underlying disorder to treatment.

Cold Panniculitis

Etiology and Pathogenesis

The pathogenic mechanism of cold panniculitis may be similar to that of SCFN, involving a greater propensity of fat to solidify in infants than in older children and adults as a result of the higher percentage of saturated fatty acids in the subcutaneous fat of infants. Lesions occur in infants after prolonged cold exposure, especially on the cheeks, or after prolonged application of a cold object such as an ice cube, ice bag, or fruit ice pop to any area of the skin.

Clinical Manifestations

Ill-defined, erythematous to bluish, indurated plaques or nodules arise within hours to a couple days of exposure on exposed surfaces (face, arms, legs); they persist for 2-3 wk and heal without residua.

Histology

Histopathologic examination reveals an infiltrate of lymphoid and histiocytic cells around blood vessels at the dermal-subdermal junction and in the fat lobules; by the 3rd day, some of the fat cells in the subcutis may have ruptured and coalesced into cystic structures.

Differential Diagnosis

Cold panniculitis may be confused with facial cellulitis caused by *Haemophilus influenzae* type b. Unlike the case in buccal cellulitis, the area may be cold to the touch, and the patient is afebrile and appears well. **Familial cold autoinflammatory syndrome** is manifest with urticaria on exposure to cold environments; associated features include conjunctivitis, myalgias, fatigue, and elevated inflammatory markers. **Cold urticaria** , in contrast, occurs on direct contact with cold objects, resulting in urticaria at the site, which can be reproduced with the ice cube test.

Treatment

Treatment is unnecessary because cold panniculitis resolves spontaneously. Recurrence of the lesions is common, emphasizing the importance of parental education in treating affected patients.

Chilblains (Pernio)

Etiology and Pathogenesis

Vasospasm of arterioles from damp cold exposure with resultant hypoxemia and localized perivascular mononuclear inflammation appears to be responsible for chilblains. The disease may be associated with cryoglobulins, lupus erythematosus with antiphospholipid antibodies, anorexia nervosa, or a thin body habitus, or it may be idiopathic.

Clinical Manifestations

The condition is characterized by localized symmetric erythematous to purplish edematous plaques and nodules in areas exposed to cold, typically acral areas (distal hands and feet, ears, face). Lesions develop 12-24 hr after cold exposure and may be associated with itching, burning, or pain. Blister formation and ulceration are rare (see Chapter 93).

Histology

Histopathologic examination reveals marked dermal edema and a perivascular and periappendiceal, predominantly T-cell lymphocytic infiltrate in the papillary and reticular dermis.

Differential Diagnosis

Raynaud phenomenon is a more acute condition than chilblains, with characteristic color changes and no chronic lesions. Frostbite due to extreme cold exposure is painful and involves freezing of the tissue, with resultant tissue necrosis.

Treatment

Most cases of chilblains resolve spontaneously, but the condition can last as long as 2-3 wk. Prevention is the treatment of choice. Nifedipine (0.25-0.5 mg/kg 3 times a day, maximum 10 mg/dose) may be used in severe cases. Unusual or persistent cases of perniosis in children may warrant further workup, including antinuclear antibody titer, cryoglobulins, complete blood count with differential, and cold agglutinins.

Factitial Panniculitis

Etiology and Pathogenesis

Factitial panniculitis results from subcutaneous injection by the patient or a proxy of a foreign substance, the most common types of which are organic materials such as milk and feces; drugs, such as the opiates and pentazocine; oily materials, such as mineral oil and paraffin; and the synthetic polymer povidone.

Clinical Manifestations

Indurated plaques, ulcers, or nodules that liquefy and drain may be noted clinically in factitial panniculitis.

Histology

The histopathology is variable, depending on the injected substance, but may include the presence of birefringent crystals, oil cysts surrounded by fibrosis and inflammation, and an acute inflammatory reaction with fat necrosis. Vessels are characteristically spared.

Treatment

Treatment of factitial panniculitis must address the primary reason for the performance of this self-destructive act. Munchausen syndrome by proxy should be considered in young children.

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680.2

Lipodystrophy

Wendy E. Kim

Several rare conditions are associated with loss of fatty tissue in a partial or generalized distribution; they can be familial or acquired. Loss of adipose tissue at certain sites is often accompanied by the redistribution of fat and consequent hypertrophy of adipose tissue at other sites. The extent of fatty tissue loss or expansion correlates with the degree of clinical and metabolic abnormality.

Partial Lipodystrophy

Partial lipodystrophy may be familial or acquired. Loss of adipose tissue is not preceded by an inflammatory phase, and histopathologic examination reveals only absence of subcutaneous fat.

There are 5 forms of familial partial lipodystrophy (FPLD):

◆ **Type I (FPLD1–Kobberling)** is characterized by loss of adipose tissue confined to the extremities and gluteal region. Fat distribution of the face, neck, and trunk may be normal or increased. Hyperlipidemia, insulin-resistant diabetes mellitus, and eruptive xanthomas may be seen. The gene is unknown, but only females are affected.

◆ **Type 2 (FPLD2–Dunnigan),** the most common form of FPLD, is caused by mutations in the *laminin A/C* gene, leading to the premature death of adipocytes. Fat distribution is normal in childhood but atrophy commences with puberty. Lipodystrophy is seen in the trunk, gluteal region, and extremities. Adipose tissue accumulates in the face and neck and may also be seen in the axillae, back, labia majora, and infra-abdominal region. Insulin-resistant diabetes mellitus and hypertriglyceridemia develop, but high-density lipoprotein and cholesterol levels are low. Both males and females are affected, but the diagnosis may be more difficult in males owing to body habitus.

◆ **Type 3 (FPLD3)** is caused by mutations in the peroxisome proliferation–activated receptor γ *(PPARG)* gene, inhibiting adipocyte differentiation. Lipodystrophy is seen in the distal limbs and gluteal region. Insulin-resistant diabetes mellitus, primary amenorrhea, acanthosis nigricans, hypertension, and fatty infiltration of the liver are present.

◆ **Type 4 (FPLD4)** and **type 5 (FPLD5)** are caused by mutations in *AKT2* and *Perilipin-1 (PLIN1)* , respectively. Both types are also characterized by loss of subcutaneous fat primarily from the extremities.

Acquired partial lipodystrophy (Barraquer-Simons syndrome) is caused by mutations in the *LMNB2* gene. Females are more commonly affected. Fat loss begins in childhood or adolescence and progresses in a cephalotruncal direction, beginning on the face and sparing the lower extremities. Excess fat deposition is seen in the hips and legs, especially in females. Low levels of complement C3 are almost universally seen because of the presence of C3 nephritic factor, which stabilizes C3 convertase, allowing for unopposed activation of the alternate complement pathway leading to decreased level of C3. Membranous proliferative glomerulonephritis and other autoimmune diseases may develop. Insulin-resistant diabetes mellitus is rare.

Generalized Lipodystrophy

Generalized lipodystrophy may also be congenital or acquired.

Congenital generalized lipodystrophy is seen in 4 forms:

◆ **Type 1 (Berardinelli-Seip congenital lipodystrophy type 1 [BSCL1])** is an autosomal recessive disorder caused by mutations in the 1-

acylglycerol-3-phosphate-*O* -acyltransferase *(AGPAT2)* gene.

- **Type 2 (Berardinelli-Seip congenital lipodystrophy type 2 [BSCL2])** is also autosomal recessive and caused by mutations in the seipin gene.
- **Type 3 *(CAV1)*** is autosomal recessive and caused by mutations in the caveolin 1 gene.
- **Type 4 (*PTRF)*** is autosomal recessive and caused by mutations in the polymerase I and transcript release factor gene. In addition to the classic phenotype of congenital generalized lipodystrophy, these patients also have muscular dystrophy and cardiac conduction abnormalities (QT prolongation).

Marked lipodystrophy occurs at birth or in early infancy with prominent muscularity. Diabetes mellitus, hypertriglyceridemia, hepatic steatosis, acanthosis nigricans, and muscular hypertrophy occur. Congenital generalized lipodystrophy types 1 and 2 are the most common, with the latter having a more severe phenotype characterized by extensive fat loss, cardiomyopathy, intellectual impairment, and premature death in approximately 15% of cases.

Acquired generalized lipodystrophy is seen more often in females. The most common associated disorder is juvenile dermatomyositis (78%). Panniculitis preceding the loss of fat is seen in 17% of affected individuals. More than half of these children may have other complications, including acanthosis nigricans, hyperpigmentation, hepatomegaly, hypertension, protuberant abdomen, and hyperlipidemia.

Localized lipoatrophy can be idiopathic or secondary to subcutaneous medication injections, pressure, and panniculitis. Unlike generalized or partial lipodystrophy, localized lipoatrophy involves a small part of the body and has no accompanying metabolic derangements. Idiopathic localized lipoatrophy manifests as annular atrophy at the ankles; a band-like semicircular depression 2-4 cm in diameter is seen on the thighs, abdomen, and/or upper groin or a centrifugally spreading, depressed, bluish plaque with an erythematous margin. **Insulin lipoatrophy** usually occurs approximately 6 mo to 2 yr after the initiation of relatively high doses of insulin. A dimple or well-circumscribed depression at or surrounding the site of injection is typically seen. Biopsy reveals a marked decrease in or absence of subcutaneous tissue without inflammation or fibrosis. In some patients hypertrophy occurs clinically. In these cases, the middermal collagen is replaced by hypertrophic fat cells on histopathologic sections. Adipocytes chronically exposed to high insulin concentrations become insulin-resistant, leading to lipolysis and atrophy. Lesions may also be prevented by frequent alteration of injection sites.

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CHAPTER 681

Disorders of the Sweat Glands

Kari L. Martin, Kimberly M. Ken

Eccrine glands are found over nearly the entire skin surface and provide the primary means, through evaporation of the water in sweat, of cooling the body. These glands, which have no anatomic relationship to hair follicles, secrete a relatively large amount of odorless aqueous sweat. In contrast, apocrine sweat glands are limited in distribution to the axillae, anogenital skin, mammary glands, ceruminous glands of the ear, Moll glands in the eyelid, and selected areas of the face and scalp. Each apocrine gland duct enters the pilosebaceous follicle at the level of the infundibulum and secretes a small amount of a complex, viscous fluid that, on alteration by microorganisms, produces a distinctive body odor. Some disorders of these two types of sweat glands are similar pathogenetically, whereas others are unique to a given gland.

Anhidrosis

Neuropathic anhidrosis results from a disturbance in the neural pathway from the control center in the brain to the peripheral efferent nerve fibers that activate sweating. Disorders in this category, which are characterized by generalized anhidrosis, include congenital insensitivity to pain with anhidrosis (CIPA), tumors of the hypothalamus, and damage to the floor of the third ventricle. Pontine or medullary lesions may produce anhidrosis of the ipsilateral face or neck and ipsilateral or contralateral anhidrosis of the rest of the body. Peripheral or segmental neuropathies, caused by leprosy, amyloidosis, diabetes mellitus, alcoholic neuritis, or syringomyelia, may be associated with anhidrosis of the innervated skin. Various autonomic disorders are also associated with altered eccrine sweat gland function.

At the level of the sweat gland, anticholinergics (drugs such as atropine and scopolamine) may paralyze the sweat glands. Acute intoxication with barbiturates or diazepam has produced necrosis of sweat glands, resulting in anhidrosis with or without erythema and bullae. Eccrine glands are largely absent throughout the skin or are present in a localized area among patients with hypohidrotic ectodermal dysplasia (HED) or localized congenital absence of sweat glands, respectively. Infiltrative or destructive disorders that may produce atrophy of sweat glands by pressure or scarring include scleroderma, acrodermatitis chronica atrophicans, radiodermatitis, burns, Sjögren syndrome, multiple myeloma, and lymphoma. Obstruction of sweat glands may occur in miliaria and in a number of inflammatory and hyperkeratotic disorders, such as the ichthyoses, psoriasis, lichen planus, pemphigus, porokeratosis, atopic dermatitis, and seborrheic dermatitis. Occlusion of the sweat pore may also occur with the topical agents aluminum and zirconium salts, formaldehyde, or glutaraldehyde.

Diverse disorders that are associated with anhidrosis by unknown mechanisms include dehydration; toxic overdose with lead, arsenic, thallium, fluorine, or morphine; uremia; cirrhosis; endocrine disorders such as Addison disease, diabetes mellitus, diabetes insipidus, and hyperthyroidism; and inherited conditions such as autonomic neuropathies, Fabry disease, Franceschetti-Jadassohn syndrome, which combines features of incontinentia pigmenti and HED, CIPA, and familial anhidrosis with neurolabyrinthitis.

Anhidrosis may be complete, but in many cases, what appears clinically to be anhidrosis is actually hypohidrosis caused by anhidrosis of many, but not all, eccrine glands. Compensatory, localized hyperhidrosis of the remaining functional sweat glands may occur, particularly in diabetes mellitus and miliaria. The primary complication of anhidrosis is hyperthermia, seen primarily in anhidrotic ectodermal dysplasia or in otherwise normal preterm or full-term neonates who have immature eccrine glands.

Hyperhidrosis

Etiology and Pathogenesis

Hyperhidrosis is excessive sweating beyond what is physiologically necessary for temperature control and occurs in 3% of the population, with about half having axillary hyperhidrosis. The numerous disorders that can be associated with increased production of eccrine sweat may also be classified into those with neural mechanisms involving an abnormality in the pathway from the neural regulatory centers to the sweat gland and those that are nonneurally mediated and occur by direct effects on the sweat glands (Table 681.1).

Table 681.1

Causes of Hyperhidrosis

Cortical

- Emotional
- Familial dysautonomia
- Congenital ichthyosiform erythroderma
- Epidermolysis bullosa
- Nail-patella syndrome
- Jadassohn-Lewandowsky syndrome
- Pachyonychia congenita
- Palmoplantar keratoderma
- Stroke

Hypothalamic

- Drugs:
    - Alcohol
    - Antipyretics
    - Cocaine
    - Emetics
    - Insulin
    - Opiates (including withdrawal)
    - Ciprofloxacin
    - Exercise
- Infection:
    - Defervescence
    - Chronic illness
- Metabolic:
    - Carcinoid syndrome
    - Debility
    - Diabetes mellitus

- Hyperpituitarism
- Hyperthyroidism
- Hypoglycemia
- Obesity
- Pheochromocytoma
- Porphyria
- Pregnancy
- Rickets
- Infantile scurvy

Cardiovascular:

- Heart failure
- Shock
- Vasomotor
- Cold injury
- Raynaud phenomenon
- Rheumatoid arthritis

Neurologic:

- Abscess
- Familial dysautonomia
- Postencephalitic
- Tumor

Miscellaneous:

- Chédiak-Higashi syndrome
- Compensatory
- Lymphoma
- Phenylketonuria
- Vitiligo
- Frey syndrome

Medullary

- Physiologic gustatory sweating
- Encephalitis
- Granulosis rubra nasi
- Syringomyelia
- Thoracic sympathetic trunk injury

Spinal

- Cord transection
- Syringomyelia

Changes in Blood Flow

- Maffucci syndrome
- Arteriovenous fistula
- Klippel-Trénaunay syndrome
- Glomus tumor
- Blue rubber-bleb nevus syndrome

Clinical Manifestations

The average age at onset of hyperhidrosis is 14-25 yr. The excess sweating may be continuous or may occur in response to emotional stimuli. In severe cases, sweat may be seen to drip constantly from the hands.

Treatment

Excessive sweating of the palms and soles (volar hyperhidrosis) and axillary sweating may respond to 20% aluminum chloride in anhydrous ethanol applied under occlusion for several hours, iontophoresis, injection with botulinum toxin, therapy with oral anticholinergics and antimuscarinic drugs (oxybutynin), or in severe, refractory cases, cervicothoracic or lumbar sympathectomy. Reports of successful treatment of hyperhidrosis with ultrasound and microwave technology are available, but studies are faulted with small sample size and/or lack of controls.

Miliaria

Etiology and Pathogenesis

Miliaria results from retention of sweat in occluded eccrine sweat ducts. The keratinous plug does not form until the later stages of the disease and therefore does not appear to be the primary cause of the sweat duct obstruction. The initial obstruction is postulated to be caused by swelling of the ductal epidermal cells, perhaps from imbibition of water. Retrograde pressure may result in rupture of the duct and leakage of sweat into the epidermis and/or the dermis. The eruption is most often induced by hot, humid weather, but it may also be caused by high fever. Infants who are dressed too warmly may demonstrate this eruption indoors, even during the winter.

Clinical Manifestations

In miliaria crystallina, asymptomatic, noninflammatory, pinpoint, clear vesicles may suddenly erupt in profusion over large areas of the body surface, leaving brawny desquamation on healing (Fig. 681.1). This type of miliaria occurs most frequently in newborn infants because of the relative immaturity and delayed patency of the sweat duct and the tendency for infants to be nursed in relatively warm, humid conditions. It may also occur in older patients with hyperpyrexia or hypernatremia.

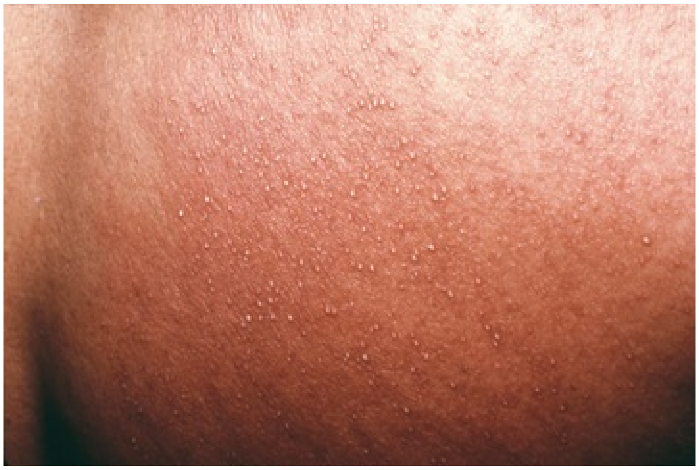

FIG. 681.1 **Superficial clear vesicles of miliaria crystallina.**

Miliaria rubra is a less superficial eruption characterized by erythematous, minute papulovesicles that may impart a prickling sensation. The lesions are usually localized to sites of occlusion or to flexural areas, such as the neck, groin, and axillae, where friction may have a role in their pathogenesis. Involved skin may become macerated and eroded. However, lesions of miliaria rubra are extrafollicular.

Repeated attacks of miliaria rubra may lead to miliaria profunda, which is caused by rupture of the sweat duct deeper in the skin, at the level of the dermal-epidermal junction. Severe, extensive miliaria rubra or miliaria profunda may result in disturbance of heat regulation. Lesions of miliaria rubra may become infected, particularly in malnourished or debilitated infants, leading to development of periporitis staphylogenes, which involves extension of the process from the sweat duct into the sweat gland.

Histology

Histologically, miliaria crystallina reveals an intracorneal or subcorneal vesicle in communication with the sweat duct, whereas in miliaria rubra, one sees focal areas of spongiosis and spongiotic vesicle formation in close proximity to sweat ducts that generally contain a keratinous plug.

Differential Diagnosis

The clarity of the fluid, superficiality of the vesicles, and absence of inflammation permit differentiation of miliaria crystalline from other blistering disorders. Miliaria rubra may be confused with or superimposed on other diaper area eruptions, including candidosis and folliculitis.

Treatment

All forms of miliaria respond dramatically to cooling of the patient by regulation of environmental temperatures and by removal of excessive clothing; administration of antipyretics is also beneficial to patients with fever. Topical agents are usually ineffective and may exacerbate the eruption.

Bromhidrosis

Bromhidrosis, characterized by excessive odor, may result from alteration of either apocrine or eccrine sweat. Apocrine bromhidrosis develops after puberty as a result of the formation of short-chain fatty acids and ammonia by the action of anaerobic diphtheroids on axillary apocrine sweat. Eccrine bromhidrosis is caused by microbiologic degradation of stratum corneum that has become softened by excessive eccrine sweat. The soles of the feet and the intertriginous areas are the primary affected sites. Hyperhidrosis, warm weather, obesity, intertrigo, and diabetes mellitus are predisposing factors. Treatments that may be helpful include cleansing with germicidal soaps, topical clindamycin or erythromycin, or topical application of aluminum or zirconium. In addition, more invasive surgical and laser treatments have been used. Treatment of any associated hyperhidrosis is mandatory.

Hidradenitis Suppurativa

Etiology and Pathogenesis

Hidradenitis suppurativa is a disease of the apocrine gland–bearing areas of the skin. The pathogenesis of hidradenitis suppurativa is controversial. It is believed that it is a primary inflammatory disorder of the hair follicle and not solely an alteration of apocrine glands. It is considered a part of the follicular occlusion tetrad, along with acne conglobata, dissecting cellulitis of the scalp, and pilonidal sinus. The natural history of the disease involves progressive dilation below the follicular obstruction, leading to rupture of the duct, inflammation, sinus tract formation, and destructive scarring.

Clinical Manifestations

Hidradenitis suppurativa is a chronic, inflammatory, suppurative disorder of the follicular units in the axillae, anogenital area, and, occasionally, the scalp, posterior aspect of the ears, female breasts, and periumbilical area. Onset of clinical manifestations is sometimes preceded by pruritus or discomfort and usually occurs during puberty or early adulthood. Solitary or multiple painful erythematous nodules, deep abscesses, and contracted scars are sharply confined to areas of skin containing apocrine glands. When the disease is severe and chronic, sinus tracts, ulcers, and thick, linear fibrotic bands develop. Hidradenitis suppurativa tends to persist for many years, punctuated by relapses and partial remissions. Complications include cellulitis, ulceration, and burrowing abscesses that may perforate adjacent structures, forming fistulas to the urethra, bladder, rectum, or peritoneum. Episodic inflammatory arthritis develops in some patients. Obesity and smoking may worsen or trigger symptoms. Patients with hidradenitis suppurativa have an increased risk of adverse cardiovascular outcomes and a long-term risk of squamous cell carcinoma.

Histology

Early lesions are characterized by a keratinous plug in the apocrine duct or hair follicle orifice and by cystic distention of the follicle. The process generally but not necessarily extends into the apocrine gland. Later changes include inflammation within and around apocrine glands. Scarring may obliterate skin appendages.

Differential Diagnosis

Early lesions of hidradenitis suppurativa are often mistaken for infected epidermal cysts, furuncles, scrofuloderma, actinomycosis, cat-scratch disease, granuloma inguinale, or lymphogranuloma venereum. However, sharp localization to areas of the body that bear apocrine glands should suggest hidradenitis. When involvement is limited to the anogenital region, the condition may be difficult to distinguish from Crohn's disease.

Treatment

Conservative management includes cessation of smoking, weight loss, and avoidance of irritation of the affected area. Warm compresses and topical antiseptic or antibacterial soaps may also be helpful. For mild, early disease, topical clindamycin 1% may be helpful. For more severe disease, therapy may be initiated with doxycycline (100 mg bid) or minocycline (100 mg bid) in adolescents and young adults. Some patients require intermittent or long-term antibiotic treatment. Combination therapy with clindamycin and rifampin is helpful in some patients. Oral retinoids for 5-6 mo may also be effective, although disease may recur. Oral contraceptive agents, which contain a high estrogen:progesterone ratio and low androgenicity of the progesterone, are another alternative. Laser hair ablation has proven helpful in some studies as well. Systemic immunosuppressants (infliximab, adalimumab, cyclosporine, anakinra) and medications targeted at glucose metabolism and the metabolic syndrome (metformin) have been helpful in patients resistant to more traditional measures. Adalimumab, a TNFα inhibitor, is the only FDA-approved medication for the treatment of moderate-to-severe hidradenitis suppurativa. Surgical measures may be required for control or cure, especially in localized, recalcitrant cases.

Fox-Fordyce Disease

Etiology and Pathogenesis

The cause of Fox-Fordyce disease is unknown, but it is related to blockage of apocrine sweat glands.

Clinical Manifestations

This disease is most common in females and manifests during puberty to the 3rd decade of life as pruritus primarily in the axillae, although the areolae, pubic, and perineal regions can also be affected. Pruritus is exacerbated by emotional stress and stimuli that induce apocrine sweating. Dome-shaped, skin-colored to slightly hyperpigmented, follicular papules develop in the pruritic areas.

Histology

Histopathologically, one sees keratinous plugging of the distal apocrine duct, rupture of the intraepidermal portion of the apocrine duct, periductal microvesicle formation, and periductal acanthosis.

Treatment

Fox-Fordyce disease is difficult to treat. Oral contraceptive pills and topical treatments including corticosteroids, antibiotics, or retinoids may help some patients. Systemic isotretinoin and ablative lasers have shown varying efficacy. Mechanical destruction and removal of apocrine glands have been used in recalcitrant cases. Partial response has been seen in one study using botulinum toxin type A.

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CHAPTER 682

Disorders of Hair

Kimberly M. Ken, Kari L. Martin

Disorders of hair in infants and children may be a result of intrinsic disturbances of hair growth, underlying biochemical or metabolic defects, inflammatory dermatoses, or structural anomalies of the hair shaft. Excessive and abnormal hair growth is referred to as hypertrichosis or hirsutism. **Hypertrichosis** is excessive hair growth at inappropriate locations; **hirsutism** is an androgen-dependent male pattern of hair growth in women (see Chapter 567). Hypotrichosis is deficient hair growth. Hair loss, partial or complete, is called alopecia. Alopecia may be classified as nonscarring or scarring; the latter type is rare in children and, if present, is most often caused by prolonged or untreated inflammatory conditions such as pyoderma and tinea capitis.

Hypertrichosis

Hypertrichosis is rare in children and may be localized or generalized and permanent or transient. Table 682.1 lists some of the many causes of hypertrichosis.

Table 682.1

Causes of Hypertrichosis and Associated Conditions

Intrinsic Factors

Racial and familial forms such as hairy ears, hairy elbows, intraphalangeal hair, or generalized hirsutism

Extrinsic Factors

Local trauma

Malnutrition

Anorexia nervosa

Long-standing inflammatory dermatoses

Drugs: Diazoxide, phenytoin, corticosteroids, Cortisporin, cyclosporine, androgens, anabolic agents, hexachlorobenzene, minoxidil, psoralens, penicillamine, streptomycin

Hamartomas or Nevi

Congenital pigmented nevocytic nevus, hair follicle nevus, Becker nevus, congenital smooth muscle hamartoma, fawn-tail nevus associated with diastematomyelia

Endocrine Disorders

Virilizing ovarian tumors, Cushing syndrome, acromegaly, hyperthyroidism, hypothyroidism, congenital adrenal hyperplasia, adrenal tumors, gonadal dysgenesis, male pseudohermaphroditism, nonendocrine hormone–secreting tumors, polycystic ovary syndrome

Congenital and Genetic Disorders

Hypertrichosis lanuginosa, mucopolysaccharidosis, leprechaunism, congenital generalized lipodystrophy, de Lange syndrome, trisomy 18, Rubinstein-Taybi syndrome, Bloom syndrome, congenital hemihypertrophy, gingival fibromatosis with hypertrichosis, Winchester syndrome, lipoatrophic diabetes (Lawrence-Seip syndrome), fetal hydantoin syndrome, fetal alcohol syndrome, congenital erythropoietic or variegate porphyria (sun-exposed areas), porphyria cutanea tarda (sun-exposed areas), Cowden syndrome, Seckel syndrome, Gorlin syndrome, partial trisomy 3q, Ambras syndrome

Hypotrichosis and Alopecia

Table 682.2 lists some of the disorders associated with hypotrichosis and alopecia. True alopecia is rarely congenital; it is more often related to an inflammatory dermatosis, mechanical factors, drug ingestion, infection, endocrinopathy, nutritional disturbance, or disturbance of the hair cycle. Any inflammatory condition of the scalp, such as atopic dermatitis or seborrheic dermatitis, if severe enough, may result in partial alopecia. Unless the hair follicle has been permanently damaged, hair growth returns to normal if the underlying condition is treated successfully.

Table 682.2

Disorders Associated With Alopecia and Hypotrichosis

Congenital total alopecia: Atrichia with papules, Moynahan alopecia syndrome

Congenital localized alopecia: Aplasia cutis, triangular alopecia, sebaceous nevus

Hereditary hypotrichosis: Marie-Unna syndrome, hypotrichosis with juvenile macular dystrophy, hypotrichosis–Mari type, ichthyosis with hypotrichosis, cartilage-hair hypoplasia, Hallermann-Streiff syndrome, trichorhinophalangeal syndrome, ectodermal dysplasia “pure” hair and nail and other ectodermal dysplasias

Diffuse alopecia of endocrine origin: Hypopituitarism, hypothyroidism, hypoparathyroidism, hyperthyroidism

Alopecia of nutritional origin: Marasmus, kwashiorkor, iron deficiency, zinc deficiency (acrodermatitis enteropathica), gluten-sensitive enteropathy, essential fatty acid deficiency, biotinidase deficiency

Disturbances of the hair cycle: Telogen effluvium

Toxic alopecia: Anagen effluvium

Autoimmune alopecia: Alopecia areata

Traumatic alopecia: Traction alopecia, trichotillomania

Cicatricial alopecia: Lupus erythematosus, lichen planopilaris, pseudopelade, morphea (*en coup de sabre*) dermatomyositis, infection (kerion, favus, tuberculosis, syphilis, folliculitis, leishmaniasis, herpes zoster, varicella), acne keloidalis, follicular mucinosis, sarcoidosis

Hair shaft abnormalities: Monilethrix, pili annulati, pili torti, trichorrhexis invaginata, trichorrhexis nodosa, woolly hair syndrome, Menkes disease, trichothiodystrophy, trichodento-osseous syndrome, uncombable hair syndrome (spun-glass hair, pili trianguli et canaliculi)

Hair loss in childhood should be divided into the following 4 categories: congenital diffuse, congenital localized, acquired diffuse, and acquired localized.

Acquired localized hair loss is the most common type of hair loss in childhood. Three conditions—traumatic alopecia, alopecia areata, and tinea capitis—are predominantly seen (Tables 682.3 and 682.4).

Table 682.3

Helpful Historical Clues in the Diagnosis of Hair Disorders

HISTORICAL CONSIDERATIONS	TELOGEN EFFLUVIUM	TRICHOTILLOMANIA	TINEA CAPITIS	ALOPECIA AREATA
Are the spots itchy?	Negative	Negative	Positive	Usually negative
Do the spots come and go?	Negative	Sometimes positive	Negative	Sometimes positive
Is the hair falling out in clumps?	Positive	Negative	Negative	Usually negative
Are there any anxiety disorders or obsessive–compulsive tendencies?	Negative	Positive	Negative	Negative

From Lio PA: What's missing from this picture? An approach to alopecia in children, *Arch Dis Child Educ Pract Ed* 92:193–198, 2007.

Table 682.4

Helpful Physical Examination Clues in the Diagnosis of Hair Disorders

PHYSICAL FINDINGS	TELOGEN EFFLUVIUM	TRICHOTILLOMANIA	TINEA CAPITIS	ALOPECIA AREATA
Scarring?	Negative	Negative	Usually negative	Negative
Exclamation-point hairs?	Negative	Negative	Negative	Positive
Irregular pattern with mixed length and stubbly hairs?	Negative	Positive	Negative	Negative
Scaling, pustules or kerion?	Negative	Negative	Positive	Negative
Positive hair-pull test result?	Positive	Negative	Negative	Usually negative
Nail pitting or grooves?	Negative	Negative	Negative	Positive

From Lio PA: What's missing from this picture? An approach to alopecia in children, *Arch Dis Child Educ Pract Ed* 92:193–198, 2007.

Traumatic Alopecia (Traction Alopecia, Hair Pulling, Trichotillomania)

Traction Alopecia

Traction alopecia is common and is seen in almost 20% of African American schoolgirls. It is caused by trauma to the hair follicles from tight braids or ponytails, headbands, rubber bands, curlers, weaves, or rollers (Fig. 682.1). There is a greater risk of traction alopecia if hair trauma is combined with chemically relaxed hair. Broken hairs and inflammatory follicular papules in circumscribed patches at the scalp margins are characteristic and may be accompanied by regional lymphadenopathy. Children and parents must be encouraged to avoid devices that cause trauma to the hair and, if necessary, to alter the hairstyle. Otherwise scarring of hair follicles may occur. Treatment with topical phenylephrine, an α-1 adrenergic receptor agonist, facilitates contraction of arrector pili smooth muscle and shows promise in decreasing hair loss and increasing the force needed for epilation.

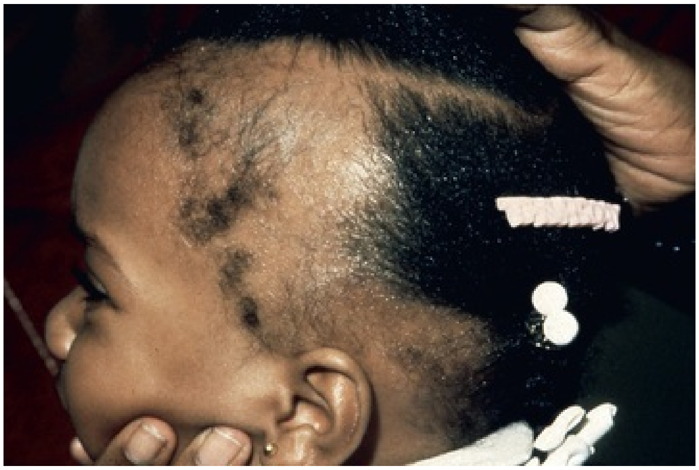

FIG. 682.1 **Traction alopecia.**

Hair Pulling

Hair pulling in childhood is usually an acute reactional process related to emotional stress, or it may be a habit (especially in young children). It may also be seen in trichotillomania (obsessive–compulsive disorder) and as part of more severe psychiatric disorders, usually in adolescents.

Trichotillomania

Etiology and Pathogenesis.

The *Diagnostic and Statistical Manual of Mental Disorders* , 5th edition (DSM-5), classifies trichotillomania in the category of obsessive-compulsive and related disorders. The diagnostic criteria for trichotillomania include visible hair loss attributable to pulling; mounting tension preceding or during hair pulling; gratification or release of tension after hair pulling; and absence of hair pulling attributable to hallucinations, delusions, or an inflammatory skin condition.

Clinical Manifestations.

Compulsive pulling, twisting, and breaking of hair produces irregular areas of incomplete hair loss, most often on the crown and in the occipital and parietal areas of the scalp. Occasionally eyebrows, eyelashes, and body hair are traumatized. Trichotillomania often begins during periods of inactivity (going to bed, watching TV) and is frequently unobserved by the parents. Some plaques of alopecia may have a linear outline. The hairs remaining within the areas of loss are of various lengths (Fig. 682.2) and are typically blunt-tipped because of breakage. The scalp usually appears normal, although hemorrhage, crusting (Fig. 682.3), and chronic folliculitis may also occur. Trichophagy, resulting in trichobezoars, may complicate this disorder.

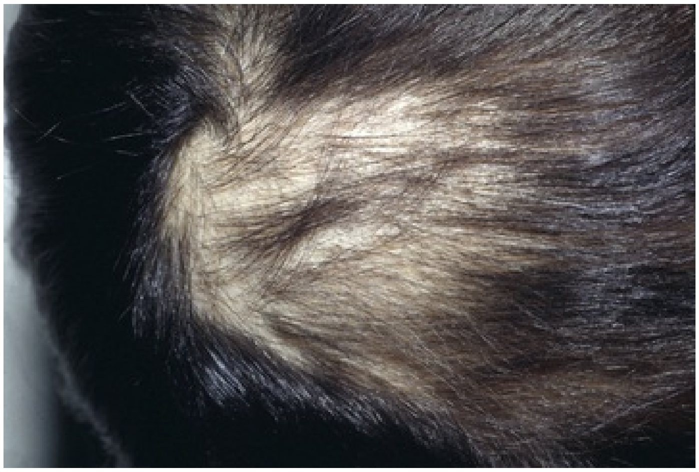

FIG. 682.2 **Hair pulling. Hairs are broken off at various lengths.**

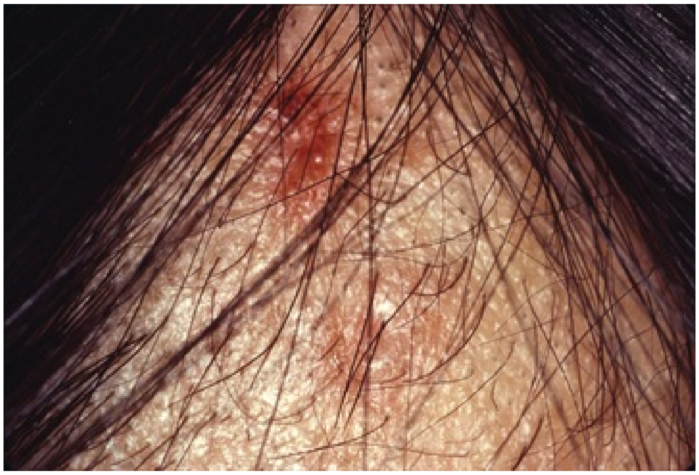

FIG. 682.3 **Hemorrhage and crusting secondary to hair pulling.**

Differential Diagnosis.

Acute reactional hair pulling, tinea capitis, and alopecia areata must be considered in the differential diagnosis of trichotillomania (see Tables 682.3 and 682.4).

Histology.

Histologic changes include coexistent normal and damaged follicles (pigmented hair casts, trichomalacia, and empty follicles), perifollicular hemorrhage, atrophy of some follicles, and catagen transformation of hair. In late stages, perifollicular fibrosis may occur. Long-term repeated trauma may result in irreversible damage and permanent alopecia.

Treatment.

Trichotillomania is closely related to obsessive-compulsive disorder and may be an expression of it for some children. When trichotillomania occurs secondary to obsessive–compulsive disorder, clomipramine 50-150 mg/day or a selective serotonin reuptake inhibitor (SSRI) such as fluoxetine may be helpful, particularly when combined with behavioral interventions (see Chapter 37). *N* - Acetylcysteine may also be helpful.

Alopecia Areata

Etiology and Pathogenesis

Alopecia areata is a T-cell-driven autoimmune disorder producing nonscarring alopecia. The cause is unknown. It is hypothesized that in genetically susceptible individuals, loss of immune privilege of the hair follicle allows for T-cell inflammation against anagen hairs and follicles, leading to stoppage of hair growth.

Clinical Manifestations

Alopecia areata is characterized by rapid and complete loss of hair in round or oval patches on the scalp (Fig. 682.4), eyebrows, eyelashes, and on other body sites. In alopecia totalis, all the scalp hair is lost (Fig. 682.5); alopecia universalis involves all body and scalp hair. The lifetime incidence of alopecia areata is 0.1–0.2% of the population. More than half of affected patients are younger than 20 yr of age.

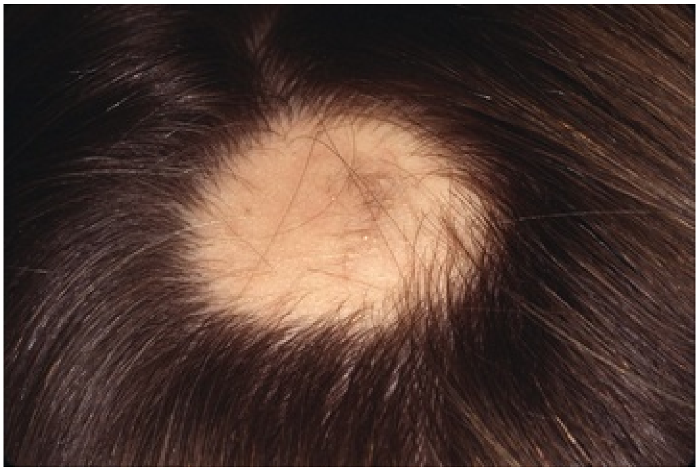

FIG. 682.4 **Circular patch of alopecia areata with normal-appearing scalp.**

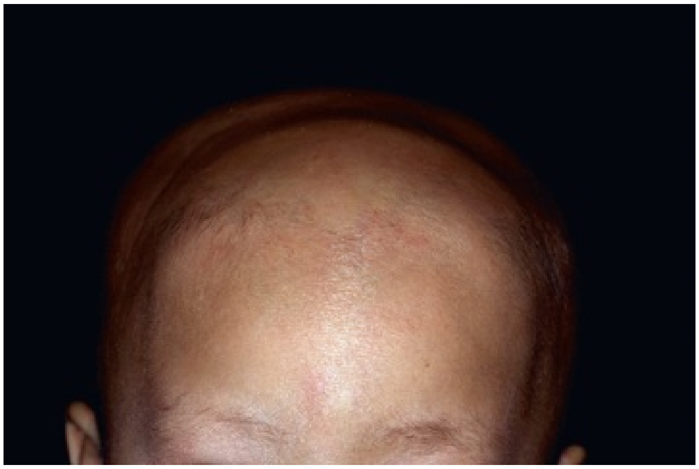

FIG. 682.5 Alopecia totalis: total loss of scalp hair.

The skin within the plaques of hair loss appears normal. Alopecia areata is associated with atopy and with nail changes such as pits (Fig. 682.6), longitudinal striations, and leukonychia. Autoimmune diseases such as Hashimoto thyroiditis, Addison disease, pernicious anemia, ulcerative colitis, myasthenia gravis, collagen vascular diseases, and vitiligo may also be seen. An increased incidence of alopecia areata has been reported in patients with Down syndrome (5–10%).

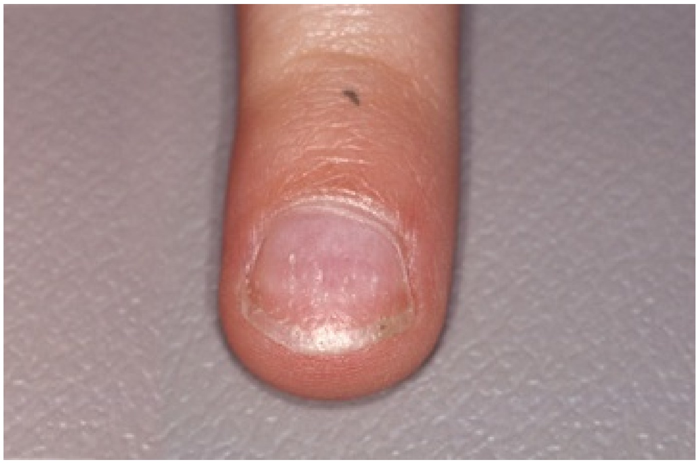

FIG. 682.6 Multiple nail pits in alopecia areata.

Differential Diagnosis

Tinea capitis, seborrheic dermatitis, trichotillomania, traumatic alopecia, and lupus erythematosus should be considered in the differential diagnosis of alopecia areata (see Tables 682.3 and 682.4).

Histology

A perifollicular infiltrate of inflammatory cells is found in biopsy specimens from active areas of alopecia areata.

Treatment

The course is unpredictable, but spontaneous resolution in 6-12 mo is usual, particularly when relatively small, stable patches of alopecia are present. Recurrences are common. Onset at a young age, extensive or prolonged hair loss, and numerous episodes are usually poor prognostic signs. Alopecia universalis, alopecia totalis, and alopecia ophiasis (Fig. 682.7)—a type of alopecia areata in which hair loss is circumferential—are also less likely to resolve. Therapy is difficult to evaluate because the course is erratic and unpredictable. The use of highly potent or superpotent topical corticosteroids is effective in some patients. Intradermal injections of steroid (triamcinolone 5 mg/mL) every 4-6 wk may also stimulate hair growth locally, but this mode of treatment is impractical in young children or in patients with extensive hair loss. Systemic corticosteroid therapy (prednisone 1 mg/kg/day) is associated with good results; the permanence of cure is questionable, however, and the side effects of chronic oral corticosteroids are a serious deterrent. Some patients may maintain hair growth by switching to a more appropriate long-term immunosuppressant such as methotrexate. Additional therapies that are sometimes effective include short-contact anthralin, topical minoxidil, and contact sensitization with squaric acid dibutylester or diphenylcyclopropenone. Janus kinase inhibitors, both oral and topical, are being investigated for treatment and showing promising results. In general parents and patients can be reassured that spontaneous remission of alopecia areata usually occurs. New hair growth may initially be of finer caliber and lighter color, but replacement by normal terminal hair can be expected.

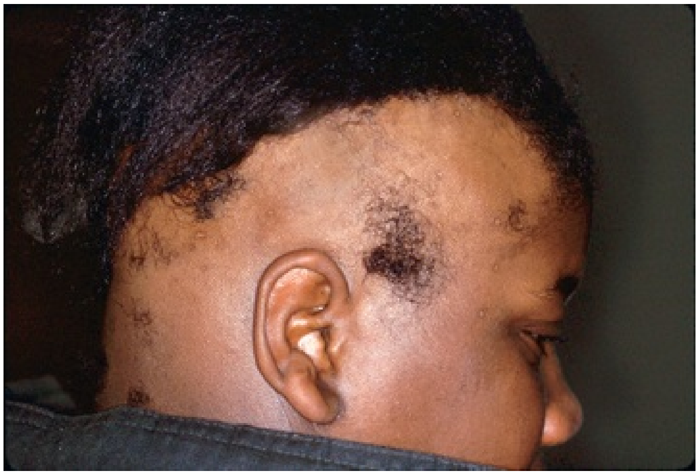

FIG. 682.7 Ophiasis pattern of alopecia areata.

Acquired Diffuse Hair Loss

Telogen Effluvium

Telogen effluvium manifests as sudden loss of large amounts of hair, often with brushing, combing, and washing of hair. Diffuse loss of scalp hair occurs from premature conversion of growing, or anagen, hairs, which normally constitute 80–90% of hairs, to resting, or telogen, hairs. Hair loss is noted 6 wk to 3 mo after the precipitating cause, which may include childbirth; a febrile episode; surgery; acute blood loss, including blood donation; sudden severe weight loss; discontinuation of high-dose corticosteroids or oral contraceptives; hypo- or hyperthyroidism; and psychiatric stress. Telogen effluvium also accounts for the loss of hair by infants in the 1st few months of life; friction from bed sheets, particularly in infants with pruritic, atopic skin, may exacerbate the problem. There is no inflammatory reaction; the hair follicles remain intact, and telogen bulbs can be demonstrated microscopically on shed hairs. Because >50% of the scalp hair is rarely involved, alopecia is usually not severe. Parents should be reassured that normal hair growth will return within approximately 3-6 mo.

Toxic Alopecia (Anagen Effluvium)

Anagen effluvium is an acute, severe, diffuse inhibition of growth of anagen follicles, resulting in the loss of >80–90% of scalp hair. Hairs become dystrophic, and the hair shaft breaks at the narrowed segment. Loss is diffuse, rapid (1-3 wk after treatment), and temporary, as regrowth occurs after the offending agent is discontinued. Causes of anagen effluvium include radiation; cancer chemotherapeutic agents such as antimetabolites, alkylating agents, and mitotic inhibitors; thallium; thiouracil; heparin; the coumarins; boric acid; and hypervitaminosis A (Table 682.5).

Table 682.5

Possible Etiology of Anagen Effluvin

CANCER THERAPY
Chemotherapy
Radiation therapy
TOXIC METAL (see Chapter 738)
Lead (see Chapter 739)
Mercury
Arsenic (rat, insect poison)
Thallium (rat poison)
Bismuth
TOXIC CHEMICALS
Boric acid (pesticide, cleaning agent)
Warfarin
Colchicine

Congenital Diffuse Hair Loss

Congenital diffuse hair loss is defined as congenitally thin hair diffusely related to either hypoplasia of hair follicles or to structural defects in hair shafts.

Structural Defects of Hair

Structural defects of the hair shaft may be congenital, reflect known biochemical aberrations, or be related to damaging grooming practices. All the defects can be demonstrated by microscopic examination of affected hairs, particularly with scanning and transmission electron microscopy, although many can even be seen by simple trichography done in the office.

Trichorrhexis Nodosa

Congenital trichorrhexis nodosa is an autosomal dominant condition. The hair is dry, brittle, and lusterless, with irregularly spaced grayish white nodes on the hair shaft. Microscopically, the nodes have the appearance of two interlocking brushes (Fig. 682.8*A*). The defect results from a fracture of the hair shaft at the nodal points caused by disruption of the cells in the hair cortex. Trichorrhexis nodosa has also been observed in some infants with Menkes syndrome, trichothiodystrophy, citrullinemia, and argininosuccinic aciduria.

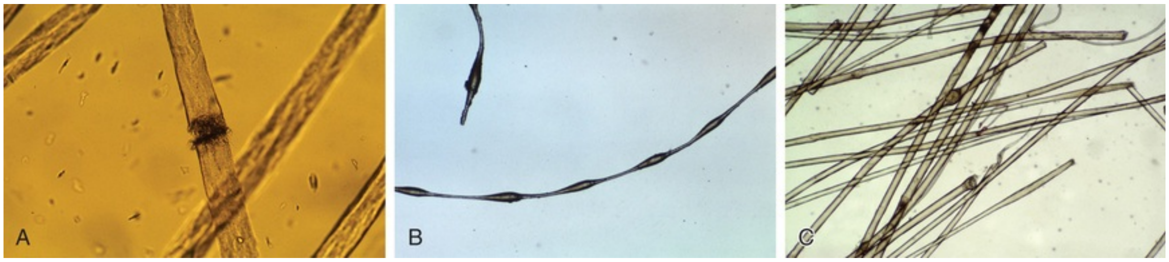

FIG. 682.8 (A) Microscopic hair fracture in trichorrhexis nodosa. (B) Beading of hair in monilethrix. (C) Cup-like abnormality of hair in Netherton syndrome.

Acquired Trichorrhexis Nodosa

Acquired trichorrhexis nodosa, the most common cause of hair breakage, occurs in two forms. Proximal defects are found most frequently in African American children, whose complaint is not of alopecia but of failure of the hair to grow. The hair is short, and longitudinal splits, knots, and whitish nodules can be demonstrated in hair mounts. Easy breakage is demonstrated by gentle traction on the hair shafts. A history of other affected family members may be obtained. The problem may be caused by a combination of genetic predisposition and the cumulative mechanical trauma of rough combing and brushing, hair-straightening procedures, and “permanents.” Patients must be cautioned to avoid damaging grooming techniques. A soft, natural-bristle brush and a wide-toothed comb should be used. The condition is self-limited, with resolution in 2-4 yr, if patients avoid damaging practices. Distal trichorrhexis nodosa is seen more frequently in white and Asian children. The distal portion of the hair shaft is thinned, ragged, and faded; white specks, sometimes mistaken for nits, may be noted along the shaft. Hair mounts reveal the paintbrush defect and the sites of excessive fragility and breakage. Localized areas of the moustache or beard may also be affected. Avoidance of traumatic grooming, regular trimming of affected ends, and the use of cream rinses to lessen tangling ameliorate this condition.

Pili Torti

Patients with pili torti present with spangled, brittle, coarse hair of different lengths over the entire scalp. There is a structural defect in which the hair shaft is grooved and flattened at irregular intervals and is twisted on its axis to various degrees. Minor twists that occur in normal hair should not be misconstrued as pili torti. Curvature of the hair follicle apparently leads to the flattening and rotation of the hair shaft. The genetic defect in isolated pili torti is unknown, and both autosomal dominant and recessive forms have been described. Syndromes in which the hair shaft abnormalities of pili torti are seen in association with other cutaneous and systemic abnormalities include Menkes kinky hair syndrome, Björnstad syndrome (pili torti with deafness; *BCS1L* gene), and multiple ectodermal dysplasia syndromes.

Menkes Kinky Hair Syndrome (Trichopoliodystrophy)

Males with Menkes kinky hair syndrome, an X-linked recessive trait, are born to an unaffected mother after a normal pregnancy. Neonatal problems include hypothermia, hypotonia, poor feeding, seizures, and failure to thrive. Hair is normal to sparse at birth but is replaced by short, fine, brittle, light-colored hair that may have features of trichorrhexis nodosa, pili torti, or monilethrix. The skin is hypopigmented and thin, cheeks typically appear plump, and the nasal bridge is depressed. Progressive psychomotor retardation is noted in early infancy. Mutations in the *ATP7A* gene, encoding a copper-transporting adenosine triphosphatase protein, cause Menkes kinky hair syndrome. It is a result of maldistribution of the copper in the body. Copper uptake across the brush border of the small intestine is increased, but copper transport from these cells into the plasma is defective, resulting in low total body copper stores. Parenteral administration of copper-histidine is helpful if begun in the 1st 2 mo of life.

Monilethrix

The hair shaft defect known as monilethrix is inherited as an autosomal dominant trait with variable age of onset, severity, and course. Mutations in the hair keratins KRT81(hHb1), KRT83 (hHb3), and KRT86 (hHb6) have been identified in autosomal dominant cases, and mutations in desmoglein 4 are found in autosomal recessive cases. The hair appears dry, lusterless, and brittle, and it fractures spontaneously or with mild trauma. Eyebrows, lashes, body and pubic hair, and scalp hair may be affected. Monilethrix may be present at birth, but the hair is usually normal at birth and is replaced in the 1st few months of life by abnormal hairs; the condition is sometimes first apparent in childhood. Follicular papules may appear on the nape of the neck and the occiput and, occasionally, over the entire scalp. Short, fragile beaded hairs that emerge from the horny follicular plugs give a distinctive appearance. Keratosis pilaris and koilonychia of fingernails and toenails may also be present. Microscopically a distinctive, regular beading pattern of the hair shaft is evident, characterized by elliptic nodes that are separated by narrower internodes (see Fig. 682.8B). Not all hairs have nodes, and both normal and beaded hairs may break. Patients should be advised to handle the hair gently to minimize breakage. Treatment is generally ineffective, although oral retinoids and topical minoxidil have produced some improvement.

Trichothiodystrophy

Hair in trichothiodystrophy is sparse, short, brittle, and uneven; the scalp hair, eyebrows, or eyelashes may be affected. Microscopically, the hair is flattened, folded, and variable in diameter; it has longitudinal grooving and nodal swellings that resemble those seen in trichorrhexis nodosa. Under a polarizing microscope, distinctive alternating dark and light bands are seen. The abnormal hair has a cystine content that is <50% of normal because of a major reduction in and altered composition of constituent high-sulfur matrix proteins. Trichothiodystrophy is caused by mutations in DNA repair/transcription genes (*XPD, XPB, TTDN1*, and *TTDA*) and may occur as an isolated finding or in association with various syndrome complexes that include intellectual impairment, short stature, ichthyosis, nail dystrophy, dental caries, cataracts, decreased fertility, neurologic abnormalities, bony abnormalities, and immunodeficiency. Some patients are photosensitive and have impaired DNA repair mechanisms, similar to that seen in groups B and D xeroderma pigmentosum; the incidence of skin cancers, however, is not increased. Patients with trichothiodystrophy tend to resemble one another, with a receding chin, protruding ears, raspy voice, and sociable, outgoing personality. Trichoschisis, a fracture perpendicular to the hair shaft, is characteristic of the many syndromes that are associated with trichothiodystrophy. Perpendicular breakage of the hair shaft has also been described in association with other hair abnormalities, particularly monilethrix.

Trichorrhexis Invaginata (Bamboo Hair)

Short, sparse, fragile hair without apparent growth is characteristic of trichorrhexis invaginata, which is found primarily in association with Netherton syndrome (see Chapter 677). It has also been reported in other ichthyosiform dermatoses. The distal portion of the hair is invaginated into the cup-like proximal portion, forming a fragile nodal swelling (see Fig. 682.8*C*).

Pili Annulati

Alternate light and dark bands of the hair shaft characterize pili annulati. When viewed under the light microscope, the region of the hair shaft that appeared bright in reflected light instead appears dark in the transmitted light as a result of focal aggregates of abnormal air-filled cavities within the shaft. The hair is not fragile. The defect may be autosomal dominant or sporadic in inheritance and usually begins after age 2. Pseudopili annulati is a variant of normal blond hair; an optical effect caused by the refraction and reflection of light from the partially twisted and flattened shaft creates the impression of banding.

Woolly Hair Disease

Woolly hair diseases manifest at birth as peculiarly tight, curly, abnormal hair in a person who is not black. Autosomal dominant and recessive (*PKRY5* gene) types have been described along with the genodermatoses Naxos disease and Carvajal syndrome, which are associated with cardiomyopathy. Woolly hair nevus, a sporadic form, involves only a circumscribed portion of the scalp hair. The affected hair is fine, tightly curled, and light-colored, and it grows poorly. Microscopically, an affected hair is oval and shows twisting of 180 degrees on its axis.

Uncombable Hair Syndrome (Spun-Glass Hair)

The hair of patients with uncombable hair syndrome appears disorderly, is often silvery blond (Fig. 682.9), and may break because of repeated, futile efforts to control it. The condition is probably autosomal dominant in inheritance. Eyebrows and eyelashes are normal. A longitudinal depression along the hair shaft is a constant feature, and most hair follicles and shafts are triangular (pili trianguli et canaliculi). The shape of the hair varies along its length, however, preventing the hairs from lying flat.

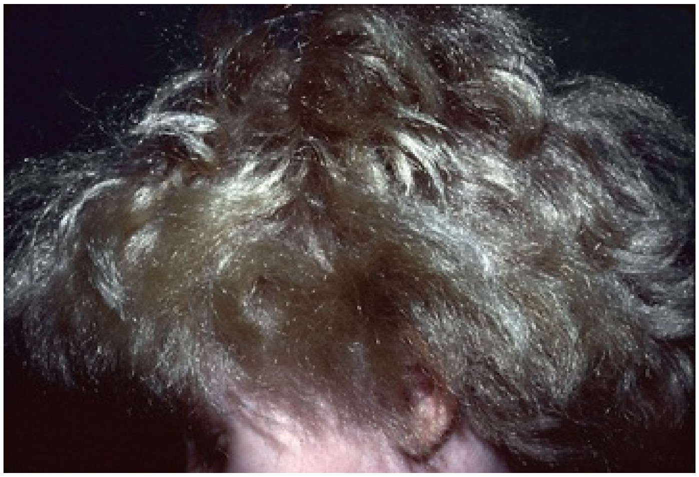

FIG. 682.9 Disorderly silvery-blond hair in uncombable hair syndrome.

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CHAPTER 683

Disorders of the Nails

Kimberly M. Ken, Kari L. Martin

Nail abnormalities in children may be manifestations of generalized skin disease, skin disease localized to the periungual region, systemic disease, drugs, trauma, or localized bacterial and fungal infections (Table 683.1). Nail anomalies are also common in certain congenital disorders (Table 683.2).

Table 683.1

White Nail or Nail Bed Changes

DISEASE	CLINICAL APPEARANCE
Anemia	Diffuse white
Arsenic	Mees lines: transverse white lines
Cirrhosis	Terry nails: most of nail, zone of pink at distal end (see Fig. 663.5)
Congenital leukonychia (autosomal dominant; variety of patterns)	Syndrome of leukonychia, knuckle pads, deafness; isolated finding; partial white
Darier disease	Longitudinal white streaks
Half-and-half nail	Proximal white, distal pink azotemia
High fevers (some diseases)	Transverse white lines
Hypoalbuminemia	Muehrcke lines: stationary paired transverse bands
Hypocalcemia	Variable white
Malnutrition	Diffuse white
Pellagra	Diffuse milky white
Punctate leukonychia	Common white spots
Tinea and yeast	Variable patterns
Thallium toxicity (rat poison)	Variable white
Trauma	Repeated manicure: transverse striations
Zinc deficiency	Diffuse white

From Habif TP, editor: *Clinical dermatology* , ed 4, Philadelphia, 2004, Mosby, p 887.

Table 683.2

Congenital Diseases With Nail Defects

Congenital Diseases With Nail Defects

Large nails	Pachyonychia congenita, Rubinstein-Taybi syndrome, hemihypertrophy
Smallness or absence of nails	Ectodermal dysplasias, nail-patella, dyskeratosis congenita, focal dermal hypoplasia, cartilage-hair hypoplasia, COIF, Ellis–van Creveld, Larsen, epidermolysis bullosa, incontinentia pigmenti, Rothmund-Thomson, Turner, Coffin-Siris, popliteal web, trisomies (8, 13, 18), Apert, Gorlin-Pindborg, long arm 21 deletion, otopalatodigital, elfin facies, anonychia, Noonan, acrodermatitis enteropathica, teratogens (alcohol, warfarin, hydantoin)
Other	Congenital malalignment of the great toenails, familial dystrophic shedding of the nails

COIF , congenital onychodysplasia of index fingers

Abnormalities in Nail Shape or Size

Anonychia is absence of the nail plate, usually a result of a congenital disorder or trauma. It may be an isolated finding or may be associated with malformations of the digits. **Koilonychia** is flattening and concavity of the nail plate with loss of normal contour, producing a spoon-shaped nail (Fig. 683.1). Koilonychia occurs as an autosomal dominant trait or in association with iron-deficiency anemia, Plummer-Vinson syndrome, hemochromatosis, various genodermatoses, and occupational trauma. The nail plate is relatively thin for the 1st year or 2 of life and, consequently, may be spoon-shaped in otherwise normal children.

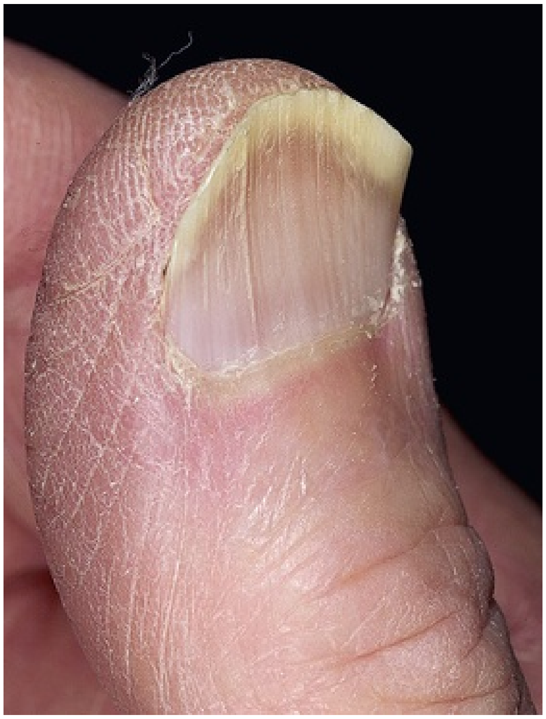

FIG. 683.1 **Spoon nails (koilonychia). Most cases are a variant of normal. (From Habif TP, editor: *Clinical dermatology* , ed 4, Philadelphia, 2004, Mosby, p. 885.)**

Congenital nail dysplasia, an autosomal dominant disorder, manifests at birth as longitudinal streaks and thinning of the nail plate. There is platyonychia and koilonychia, which may overgrow the lateral folds and involve all nails of the toes and fingers.

Nail-patella syndrome is an autosomal dominant disorder in which the nails are 30–50% of their normal size and often have triangular or pyramidal lunulae. The thumbnails are always involved, although in some cases only the ulnar half of the nail may be affected or may be missing. Nail involvement is symmetric and the nails from the index finger to the little finger are progressively less damaged. The patella is also smaller than usual or absent, and this anomaly may lead to knee instability. Iliac horns, bony spines arising from the posterior aspect of the iliac bones; overextension of joints; skin laxity; ocular anomalies; and nephropathy, the most serious feature, may also be present. Nail-patella syndrome is caused by mutations in the transcription factor *LMX1B* gene.

For a discussion of pachyonychia congenita, see Chapter 677 .

Habit tic deformity consists of a depression down the center of the nail with numerous horizontal ridges extending across the nail from it. One or both thumbs are usually involved as a result of chronic rubbing and picking at the nail with an adjacent finger. Treatment aims at cessation of trauma to the nail via massaging with bland ointments, physical barriers, or cyanoacrylate adhesive.

Clubbing of the nails (Hippocratic nails) is characterized by swelling of each distal digit, an increase in the angle between the nail plate and the proximal nail fold (Lovibond angle) to >180 degrees, and a spongy feeling when one pushes down and away from the interphalangeal joint, because of an increase in fibrovascular tissue between the matrix and the phalanx (Fig. 683.2). The pathogenesis is not known. Nail clubbing is seen in association with diseases of numerous organ systems, including pulmonary, cardiovascular (cyanotic heart disease), gastrointestinal (celiac disease, inflammatory bowel disease), and hepatic (chronic hepatitis) systems as well as in healthy individuals as an idiopathic or familial finding (Table 683.3).

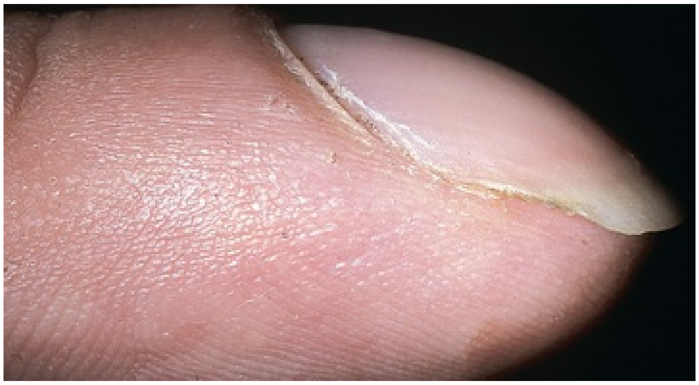

FIG. 683.2 Finger clubbing. The distal phalanges are enlarged to a rounded bulbous shape. The nail enlarges and becomes curved, hard, and thickened. (From Habif TP, editor: *Clinical dermatology* , ed 4, Philadelphia, 2004, Mosby, p 885.)

Table 683.3

Clubbing in Children*

HISTORY	SYMPTOM	DISEASE
Acquired		
Generalized	Pulmonary	Cystic fibrosis
		Bronchiectasis
		Tuberculosis, aspergillosis
		Asthma complicated by lung infections
		Sarcoidosis
		Pulmonary fibrosis
		Tumors
	Cardiovascular	Cyanotic congenital heart disease
		Subacute bacterial endocarditis

		Myxomas
	Gastrointestinal	Inflammatory bowel disease
		Gardner's syndrome
		Parasitosis
		Cirrhosis
		Chronic active hepatitis
	Endocrine	Diamond's syndrome (myxedema, exophthalmos and clubbing)
		Hypervitaminosis A
		Malnutrition
Limited to one or more digits		Aortic/subclavian artery aneurysm
		Brachial plexus injury
		Trauma
		Maffucci's syndrome
		Gout
		Sarcoidosis
		Severe herpetic whitlow
Hereditary		Pachydermoperiostosis
		Familial, isolated
Pseudoclubbing[*]		Apert's syndrome
		Pfeiffer's syndrome
		Rubinstein-Taybi syndrome

[*] Broad distal phalanges with normally shaped nails.

Modified from Baran R, Dawber RPR: *Diseases of the nails and their management* . Oxford, 1984, Blackwell Science, p 29.

Changes in Nail Color

Leukonychia is a white opacity of the nail plate that may involve the entire plate or may be punctate or striate (see Table 683.1). The nail plate itself remains smooth and undamaged. Leukonychia can be traumatic or associated with infections such as leprosy and tuberculosis, dermatoses such as lichen planus and Darier disease, malignancies such as Hodgkin disease, anemia, and arsenic poisoning (Mees lines). Leukonychia of all nail surfaces is an uncommon hereditary autosomal dominant trait that may be associated with congenital epidermal cysts and renal calculi. Paired parallel white bands that do not change position with growth of the nail, fade with pressure, and thus reflect a change in the nail bed are associated with hypoalbuminemia and are called Muehrcke lines. When the proximal portion of the nail is white and the distal 20–50% of the nail is red, pink, or brown, the condition is called half-and-half nails or Lindsay nails; this is seen most commonly in patients with renal disease but may occur as a normal variant. White nails of cirrhosis, or Terry nails (Fig. 683.3), are characterized by a white ground-glass appearance of the entire or the proximal end of the nail and a normal pink distal 1-2 mm of the nail; this finding can also be associated with congestive heart failure, adult onset diabetes, and can be normal in children less than 4 yr old.

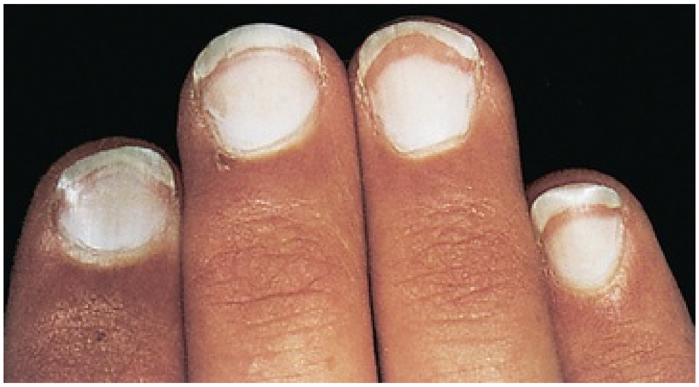

FIG. 683.3 **Terry nails. The nail bed is white with only a narrow zone of pink at the distal end. (From Habif TP, editor: *Clinical dermatology* , ed 4, Philadelphia, 2004, Mosby, p 885.)**

Black pigmentation of an entire nail plate or linear bands of pigmentation (melanonychia striata) is common in African American (90%) and Asian (10–20%) individuals, but is unusual in white individuals (<1%). Most often, the pigment is melanin, which is produced by melanocytes of a junctional nevus in the nail matrix and nail bed and is of no consequence. Extension or alteration in the pigment should be evaluated by biopsy because of the possibility of malignant change.

Bluish black to greenish nails may be caused by *Pseudomonas* infection (Fig. 683.4), particularly in association with onycholysis or chronic paronychia. The coloration is caused by subungual debris and pyocyanin pigment from the bacterial organisms.

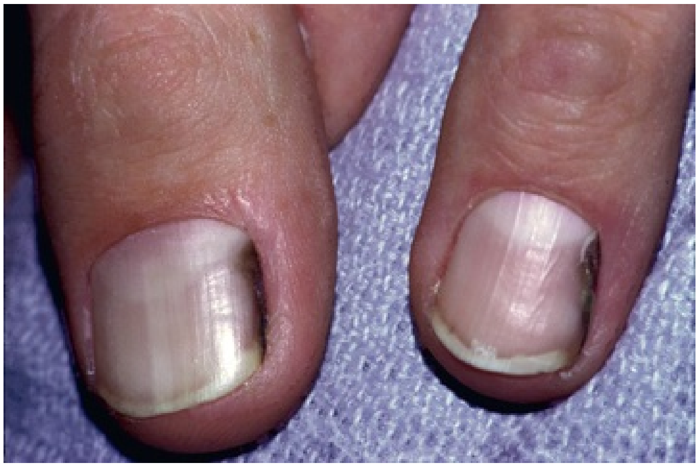

FIG. 683.4 **Green/black discoloration at the edge of the nails secondary to *Pseudomonas* infection.**

Yellow nail syndrome manifests as thickened, excessively curved, slow-growing yellow nails without lunulae. All nails are affected in most cases. Associated systemic diseases include bronchiectasis, recurrent bronchitis, chylothorax, and focal edema of the limbs and face. Deficient lymphatic drainage, caused by hypoplastic lymphatic vessels, is believed to lead to the manifestations of this syndrome.

Splinter hemorrhages most often result from minor trauma but may also be associated with subacute bacterial endocarditis, vasculitis, Langerhans cell histiocytosis, severe rheumatoid arthritis, peptic ulcer disease, hypertension, chronic glomerulonephritis, cirrhosis, scurvy, trichinosis, malignant neoplasms, and psoriasis (Fig. 683.5 and Table 683.4).

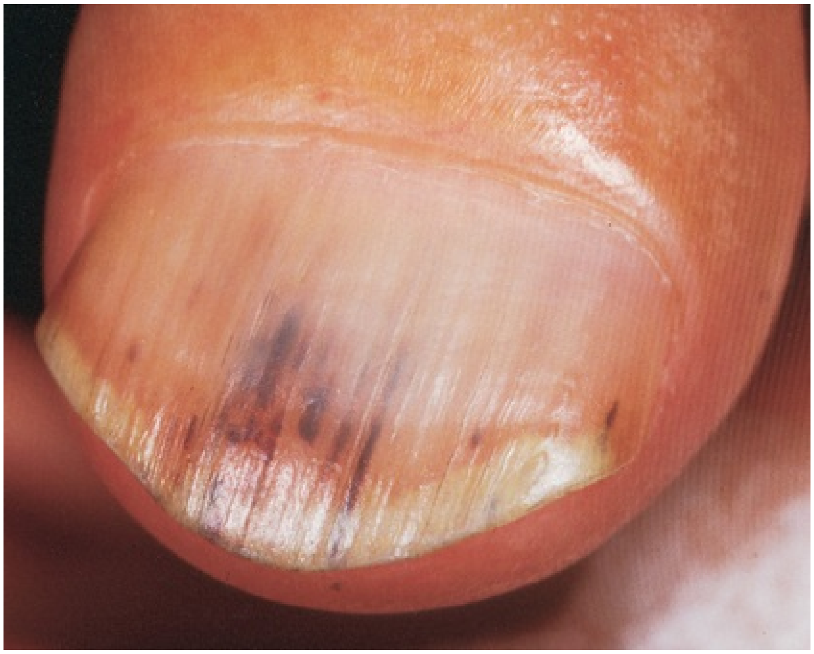

FIG. 683.5 **Splinter hemorrhage of the distal nail bed due to trauma. (From Hordinsky M, Sawaya ME, Scher RK: *Atlas of hair and nails.* London, 1999, Churchill Livingstone.)**

Table 683.4

Disorders Associated With Subungual Hemorrhage

	SPLINTER-SHAPED	HEMATOMAS
Normal variant	+	−
Blood dyscrasias	+	+
Collagen diseases (lupus erythematosus)	+	+
Trichinosis	+	−
Trauma	+	+
Child abuse	+	+
Cryoglobulinemia	+	−
Drug eruptions	+	−
Dialysis	+	−
Endocarditis (SBE)	+	−
Emboli	+	+
Langerhans cells histiocytosis	+	−
Arterial lines or punctures	+	−
Sarcoidosis	+	−
Sepsis	+	−
Thyroid disease	+	−
Vasculitis	+	−
Phototoxicity (tetracyclines)	+	−

From Schachner LA, Hansen RC, editors: *Pediatric dermatology* , ed 4, Philadelphia, 2011, Elsevier, p 813, Table 12.9.

Nail Separation

Onycholysis indicates separation of the nail plate from the distal nail bed. Common causes are trauma, long-term exposure to moisture, hyperhidrosis, cosmetics, psoriasis, fungal infection (distal onycholysis), atopic or contact dermatitis, porphyria, drugs (bleomycin, vincristine, retinoid agents, indomethacin, chlorpromazine [Thorazine]), and drug-induced phototoxicity from tetracyclines (Fig. 683.6) or chloramphenicol.

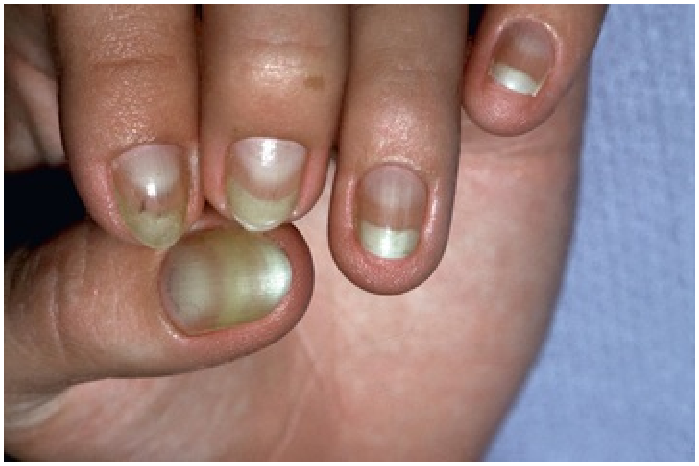

FIG. 683.6 **Distal onycholysis secondary to oral tetracycline usage and ultraviolet light exposure.**

Beau lines are transverse grooves in the nail plate (Fig. 683.7) that represent a temporary disruption of formation of the nail plate. The lines first appear a few weeks after the event that caused the disruption in nail growth. A single transverse ridge appears at the proximal nail fold in most 4-6 wk old infants and works its way distally as the nail grows; this line may reflect metabolic changes after delivery. At other ages, Beau lines are usually indicative of periodic trauma or episodic shutdown of the nail matrix secondary to a systemic disease such as hand-foot-and-mouth disease, measles, mumps, pneumonia, or zinc deficiency. Onychomadesis is an exaggeration of Beau lines leading to proximal separation of the nail bed (Fig. 683.8).

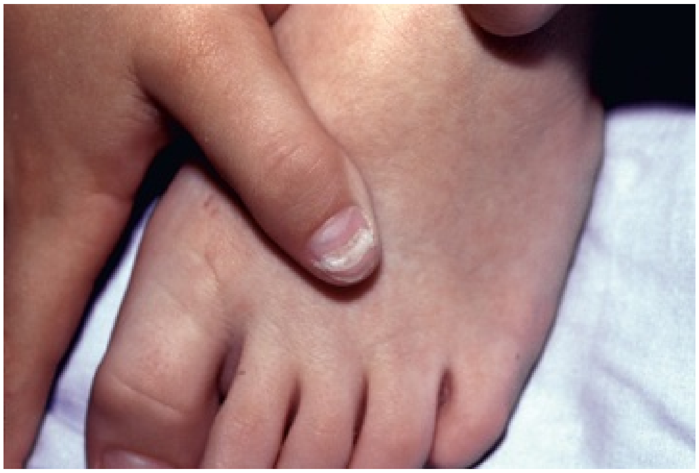

FIG. 683.7 Beau lines. Longitudinal disruption of nail..

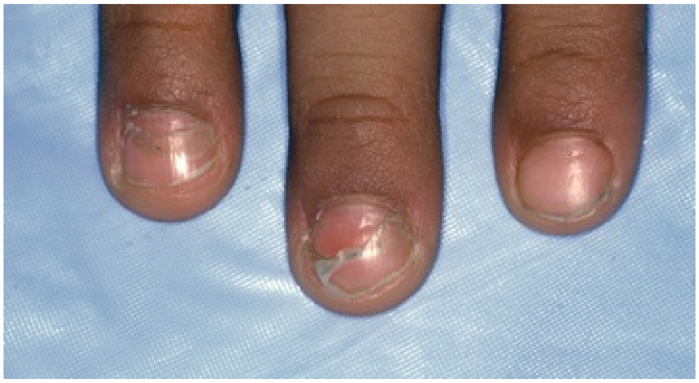

FIG. 683.8 Onychomadesis. Proximal nail bed separation.

Nail Changes Associated With Skin Disease

Nail changes may be particularly associated with various other diseases. Nail changes of psoriasis most characteristically include pitting, onycholysis, yellow-brown discoloration, and thickening. Nail changes in lichen planus include violaceous papules in the proximal nail fold and nail bed, leukonychia, longitudinal ridging, thinning of the entire nail plate, and pterygium formation, which is abnormal adherence of the cuticle to the nail plate or, if the plate is destroyed focally, to the nail bed. Postinfectious reactive arthritis syndromes may include painless erythematous induration of the base of the nail fold; subungual parakeratotic scaling; and thickening, opacification, or ridging of the nail plate. Dermatitis that involves the nail folds may produce dystrophy, roughening, and coarse pitting of the nails. Nail changes are more common in atopic dermatitis than in other forms of dermatitis that affect the hands. Darier disease is characterized by red or white streaks that extend longitudinally and cross the lunula. Where the streak meets the distal end of the nail, a V -shaped notch may be present. Total leukonychia may also occur. Transverse rows of fine pits are characteristic of alopecia areata. In severe cases, the entire nail surface may be rough. Patients with acrodermatitis enteropathica may have transverse grooves (Beau lines) and nail dystrophy as a result of periungual dermatitis.

Trachyonychia (20-Nail Dystrophy)

Trachyonychia is characterized by longitudinal ridging, pitting, fragility, thinning, distal notching, and opalescent discoloration of all the nails (Fig. 683.9). Patients can have no associated skin or systemic diseases and no other ectodermal defects. Its occasional association with alopecia areata has led some authorities to suggest that trachyonychia may reflect an abnormal immunologic response to the nail matrix, whereas histopathologic studies have suggested that it may be a manifestation of lichen planus, psoriasis, or spongiotic (eczematous) inflammation of the nail matrix. The disorder must be differentiated from fungal infections, psoriasis, nail changes of alopecia areata, and nail dystrophy secondary to eczema. Eczema and fungal infections rarely produce changes in all the nails simultaneously. The disorder is self-limited, can be treated with potent topical steroids or topical retinoids, and eventually remits by adulthood.

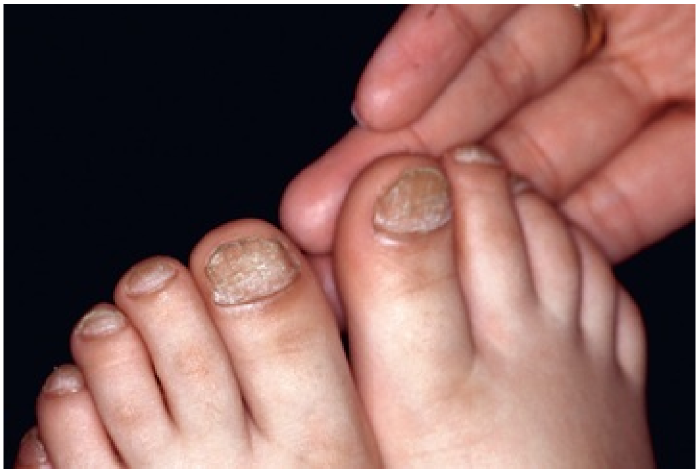

FIG. 683.9 Dystrophy of all nails in trachyonychia.

Nail Infection

Fungal infection (onychomycosis) of the nails has been classified into 4 types. White superficial onychomycosis manifests as diffuse or speckled white discoloration of the surface of the toenails. It is caused primarily by *Trichophyton mentagrophytes,* which invades the nail plate. The organism may be scraped off the nail plate with a blade, but treatment is best accomplished by the addition of a topical azole antifungal agent. Distal subungual onychomycosis, the most common type, involves foci of onycholysis under the distal nail plate or along the lateral nail groove, followed by development of hyperkeratosis and yellow-brown discoloration. The process extends proximally, resulting in nail plate thickening, crumbling (Fig. 683.10), and separation from the nail bed. *Trichophyton rubrum* and, occasionally, *T. mentagrophytes* infect the toenails; fingernail disease is almost exclusively caused by *T. rubrum,* which may be associated with superficial scaling of the plantar surface of the feet and often of one hand. The dermatophytes are found most readily at the most proximal area of the nail bed or adjacent ventral portion of the involved nail plates. Topical therapies such as ciclopirox 8% lacquer, amorolfine 5% lacquer, or bifonazole-urea 1%/40% ointment may be effective for solitary nail infection. Topical efinaconazole 10% and topical tavaborole 5% solution may also be effective; laser treatment is an expensive but safe alternative to oral therapy. Because of its long half-life in the nail, oral itraconazole may be effective when given as pulse therapy (1 wk of each month for 3-4 mo). Dosage is weight-dependent. Oral daily terbinafine is also quite effective. Either agent is superior to griseofulvin, fluconazole, or ketoconazole. The risks, the most concerning of which is hepatic toxicity, and costs of oral therapy are minimized with the use of pulsed dosing.

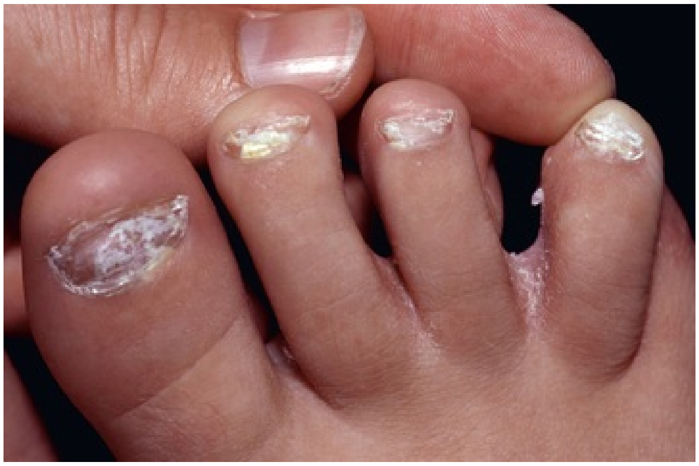

FIG. 683.10 **Discoloration, hyperkeratosis, and crumbling of nail secondary to dermatophyte infection.**

Proximal white subungual onychomycosis occurs when the organism, generally *T. rubrum*, enters the nail through the proximal nail fold, producing yellow-white discoloration of portions of the undersurface of the nail plate. The surface of the nail is unaffected. This occurs almost exclusively in immunocompromised patients and is a well-recognized manifestation of AIDS. Treatment includes oral terbinafine or itraconazole.

Candidal onychomycosis involves the entire nail plate in patients with chronic mucocutaneous candidiasis. It is also commonly seen in patients with AIDS. The organism, generally *Candida albicans*, enters distally or along the lateral nail folds, rapidly involves the entire thickness of the nail plate, and produces thickening, crumbling, and deformity of the plate. Topical azole antifungal agents may be sufficient for treatment of candidal onychomycosis in an immunocompetent host, but oral antifungal agents are necessary for treatment of patients with immune deficiencies. Table 683.5 outlines the differential diagnosis of onychomycosis.

Table 683.5

Differential Diagnosis of Onychomycosis

Psoriasis

- As in onychomycosis: onycholysis, subungual hyperkeratosis, splinter hemorrhages, leuconychia, dystrophy
- Pitting
- Oil drop sign (a translucent yellow-red discoloration seen in the nail bed)
- Other cutaneous features of psoriasis, family history of psoriasis

Lichen planus

- Cutaneous disease at other sites
- Thin nail plate and ridging
- Dorsal pterygium—scarring at proximal aspect of nail

Trauma

- Nail plate can appear abnormal
- Nail bed should be normal
- Distal onycholysis with repeated trauma
- Single nail affected, shape of nail changed, homogenous alteration of nail color

Eczema

- Irregular buckled nails with ridging
- Cutaneous signs of eczema

Yellow nail syndrome

- Nail plate is discolored green-yellow
- Nails are hard with elevated longitudinal curvature
- Nails may be shed, painful
- Associations with bronchiectasis, lymphoedema, and chronic sinusitis

Lamellar onychoschizia (lamellar splitting)

- History of repeated soaking in water
- Usually distal portion of nail

Periungual squamous cell carcinoma/Bowens disease

- Single nail, warty changes of nail fold, ooze from edge of nail

Malignant melanoma

- Black discoloration of nail plate or nail bed
- Pigment can extend onto nail fold
- Can get associated bleeding

Myxoid (mucous) cyst

- Cyst at base of nail, groove in nail extending length of nail

Alopecia areata

- Pits, longitudinal ridging, brittleness
- Hair loss

From Eisman S, Sinclair R: Fungal nail infection: diagnosis and management. *BMJ* 348:g1800, 2014.

Paronychial Inflammation

Paronychial inflammation may be acute or chronic and generally involves one or two nail folds on the fingers. Acute paronychia manifests as erythema, warmth, edema, and tenderness of the proximal nail fold, most commonly as a result of pathogenic staphylococci, streptococci, or *Candida* (Fig. 683.11). Warm soaks and oral agents are generally effective; incision and drainage may occasionally be necessary. Development of chronic paronychia follows prolonged immersion in water (Fig. 683.12), such as occurs in finger or thumb sucking, exposure to irritating solutions, nail fold trauma, or diseases including Raynaud phenomenon, collagen vascular diseases, and diabetes. Swelling of the proximal nail fold is followed by separation of the nail fold from the underlying nail plate and suppuration. Foreign material, embedded in the dermis of the nail fold, becomes a nidus for inflammation and secondary infection with *Candida* species and mixed bacterial flora. A combination of attention to predisposing factors, meticulous drying of the hands, and long-term topical antifungal agents and potent topical corticosteroids may be required for successful treatment of chronic paronychia.

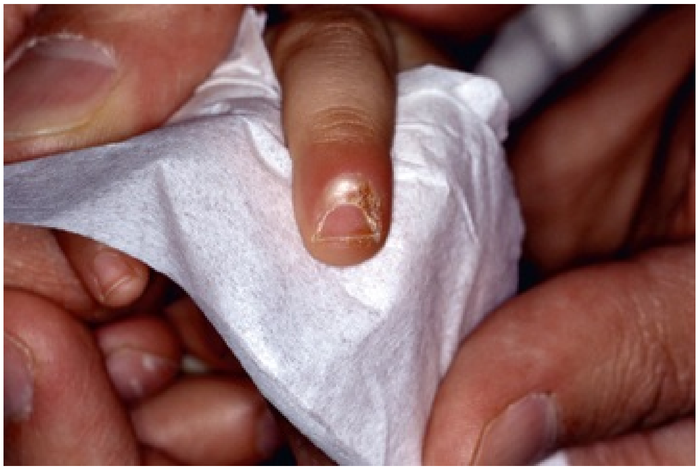

FIG. 683.11 **Acute paronychia secondary to *Staphylococcus aureus.***

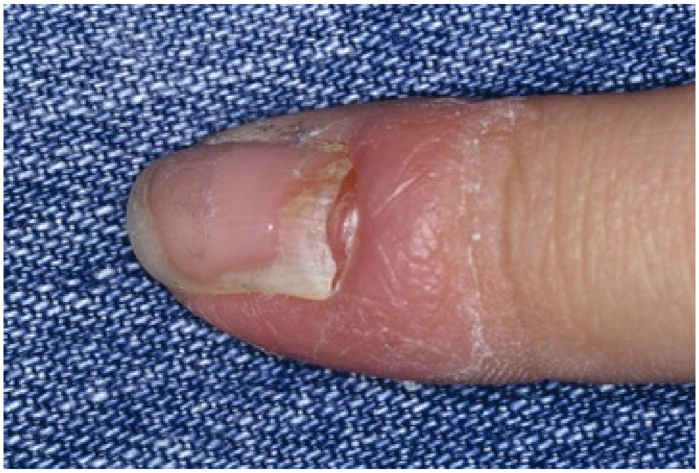

FIG. 683.12 **Chronic paronychia with erythema and lateral nail fold separation.**

Ingrown nail occurs when the lateral edge of the nail, including spicules that have separated from the nail plate, penetrates the soft tissue of the lateral nail fold. Erythema, edema, and pain, most often involving the lateral great toes, are noted acutely; recurrent episodes may lead to formation of granulation tissue. Predisposing factors include (1) congenital malalignment (especially of the great toes); (2) compression of the side of the toe from poorly fitting shoes, particularly if the great toes are abnormally long and the lateral nail folds are prominent; and (3) improper cutting of the nail in a curvilinear manner rather than straight across. Management includes proper fitting of shoes; allowing the nail to grow out beyond the free edge before cutting it straight across; warm water soaks; oral antibiotics if cellulitis affects the lateral nail fold; and, in severe, recurrent cases, application of silver nitrate to granulation tissue, nail avulsion, or excision of the lateral aspect of the nail followed by matricectomy.

Paronychial Tumors

Tumors in the paronychial area include pyogenic granulomas, mucous cysts, subungual exostoses, and junctional nevi. Periungual fibromas that appear in late childhood should suggest a diagnosis of tuberous sclerosis.

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CHAPTER 684

Disorders of the Mucous Membranes

Wendy E. Kim

The mucous membranes may be involved in developmental disorders, genodermatoses, infections, acute and chronic skin diseases, or benign and malignant tumors.

Angular Cheilitis

Angular cheilitis (perlèche) is characterized by inflammation and fissuring at the corners of the mouth, often with associated erosion, maceration, and crusting (Fig. 684.1). Chapping or moisture collection at the angles of the mouth predispose children to developing angular cheilitis. Children who are chronic lip lickers or who have excessive salivation or drooling related to neurologic deficits, orthodontic appliances, or mouth breathing are at increased risk. Atopic dermatitis or contact dermatitis related to toothpaste, chewing gum, mouthwash, or cosmetics are also common causes. Nutritional deficiencies are a less-frequent etiology. Protection can be provided by frequent application of a bland ointment such as petrolatum. Candidiasis should be treated with an appropriate antifungal agent, and contact dermatitis of the perioral skin should be treated with a low-potency topical corticosteroid ointment preparation and frequent use of petrolatum or a similar emollient. Correction of the underlying predisposing factors (if possible) will prevent recurrence.

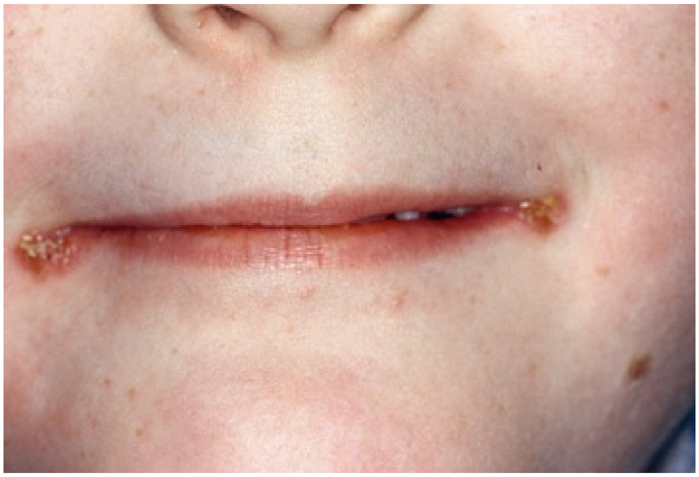

FIG. 684.1 **Angular cheilitis.**

Aphthous Stomatitis (Canker Sores)

Aphthous stomatitis consists of solitary or multiple painful ulcerations occur on the labial (Fig. 684.2), buccal, lingual, sublingual, palatal, or gingival mucosa (see Chapter 341). Lesions may manifest initially as erythematous, indurated papules that erode rapidly to form sharply circumscribed, necrotic ulcers with a gray fibrinous exudate and an erythematous halo. Minor aphthous ulcers are 2-10 mm in diameter and heal spontaneously in 7-10 days. Major aphthous ulcers are >10 mm in diameter, take from 10 to 30 days to heal, and may heal with scarring. A 3rd type of aphthous ulceration is herpetiform in appearance, manifesting as a few to numerous grouped 1-2 mm lesions which tend to coalesce into plaques and heal over 7-10 days. Approximately 30% of patients with recurrent lesions have a family history of the disorder (see Chapter 341 for the differential diagnosis).

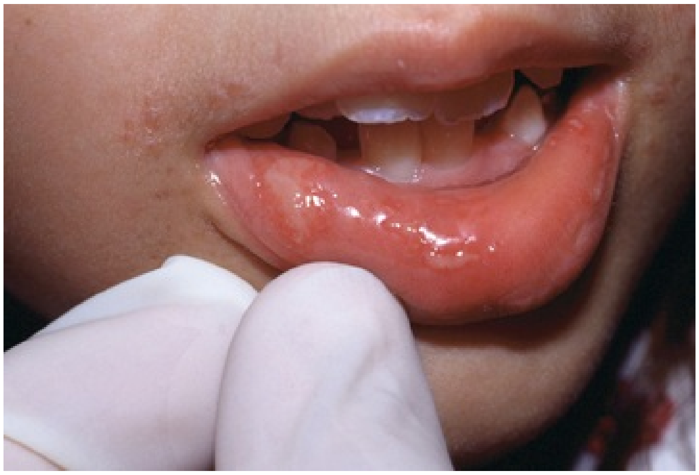

FIG. 684.2 Aphthous ulceration on lower lip.

The etiology of aphthous stomatitis is multifactorial; the condition probably represents an oral manifestation of a number of conditions. Altered local regulation of the cell-mediated immune system, after activation and accumulation of cytotoxic T cells, may contribute to the localized mucosal breakdown. It is a common misconception that aphthous stomatitis is a manifestation of herpes simplex virus infection. Recurrent herpes infections remain localized to the lips and rarely cross the mucocutaneous junction; involvement of the oral mucosa occurs only in primary infections.

Treatment of aphthous stomatitis is supportive. The majority of mild cases do not require therapy. Relief of pain, particularly before eating, may be achieved with the use of a topical anesthetic such as viscous lidocaine or an oral rinse with a combined solution of elixir of diphenhydramine, viscous lidocaine, and an oral antacid. Caution must be taken to avoid hot food and drink after topical anesthetic use. A superpotent topical corticosteroid in a mucosa-adhering agent may help to reduce inflammation, and topical tetracycline mouthwash may also hasten healing. In severe, debilitating cases, systemic therapy with corticosteroids, colchicine, dapsone, or thalidomide may be helpful.

Fordyce Spots

Fordyce spots (Fordyce granules) are asymptomatic, 1-3 mm, yellow-white macules and papules on the vermilion lips and buccal mucosa. They are a common clinical finding and represent a normal anatomic variant of sebaceous glands. They can present in either sex from infancy to adulthood and may become more prominent during puberty due to the influence of androgens. No therapy is required.

Epstein Pearls (Gingival Cysts of the Newborn)

Epstein pearls are white, keratin-containing cysts on the palatal or alveolar mucosa of approximately 80% of neonates. They are epidermal inclusion cysts that form when the soft and hard palates fuse and are analogous to facial milia. They cause no symptoms and are generally shed within a few weeks; no therapy is necessary.

Mucocele

Mucus retention cysts are painless, fluctuant, tense, 2-10 mm, bluish papules on the lips (Fig. 684.3), tongue, palate, or buccal mucosa. Traumatic severance of the duct of a minor salivary gland leads to submucosal retention of mucus secretion. Lesions on the floor of the mouth are known as ranulas when the sublingual or submandibular salivary gland ducts are involved. Fluctuations in size are typical, and the lesions may disappear temporarily after traumatic rupture. Recurrence is prevented by surgical excision of the mucus deposit and associated salivary gland(s).

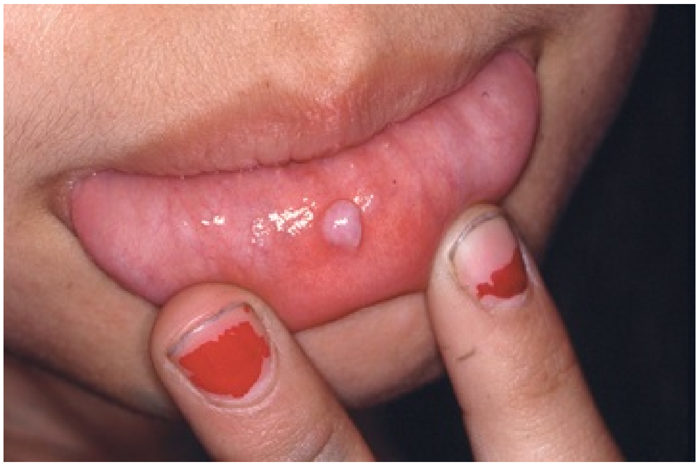

FIG. 684.3 Mucocele on lower lip.

Fissured Tongue

Fissured tongue (scrotal tongue, or lingua plicata) is a common benign developmental anomaly of the tongue. The dorsal tongue has many folds with deep grooves and a pebbled appearance. Fissured tongue can be seen in individuals with Melkersson-Rosenthal syndrome and Down syndrome, and it is often seen in association with geographic tongue. Food particles and debris may become trapped in the fissures, resulting in irritation, inflammation, and halitosis. Careful cleansing with a mouth rinse and soft-bristled toothbrush is recommended.

Geographic Tongue (Benign Migratory Glossitis)

Geographic tongue consists of single or multiple sharply demarcated, irregular, smooth red patches surrounded by an elevated yellowish-white serpiginous border on the dorsum of the tongue. Onset is rapid, and the pattern may change over hours to days. The smooth patches correspond to atrophic filiform papillae, and the elevated margins represent hypertrophic papillae (Fig. 684.4). The etiology of this condition remains unclear. Lesions are typically asymptomatic, but some patients may experience a burning sensation or sensitivity to spicy, hot, or cold foods. No therapy other than reassurance is necessary.

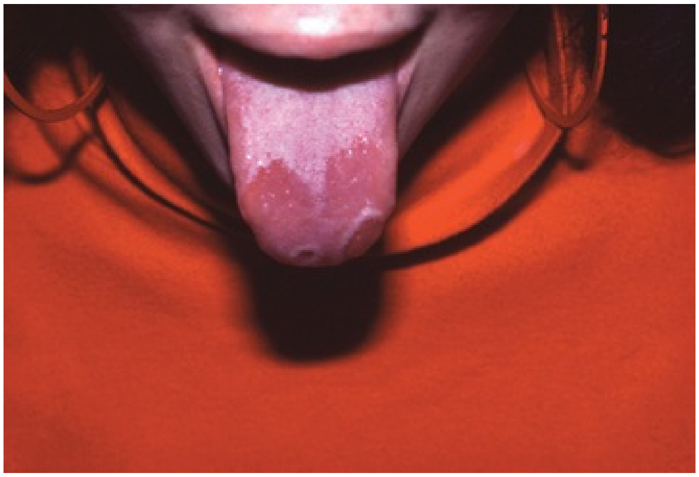

FIG. 684.4 Geographic tongue.

Black Hairy Tongue

Black hairy tongue is a dark coating on the dorsum of the tongue caused by hyperplasia and elongation of the filiform papillae; overgrowth of chromogenic bacteria and fungi and entrapped pigmented residues that adsorb to microbial plaque and desquamating keratin may contribute to the dark coloration. Changes often begin posteriorly and extend anteriorly on the dorsum of the tongue. The condition is most common in adults but may also manifest during adolescence. Poor oral hygiene, lack of oral feeding, treatment with systemic antibiotics such as tetracycline (which promote the growth of *Candida* spp.), and smoking are predisposing factors. Improved oral hygiene and brushing with a soft-bristled toothbrush may be all that is necessary for treatment.

Oral Hairy Leukoplakia

Oral hair leukoplakia occurs in approximately 25% of patients with AIDS but is rare in the pediatric population. It manifests as corrugated and shaggy white plaques on the lateral margins of the tongue which cannot be removed by rubbing. The lesions occasionally may spread to the ventral tongue surface, floor of the mouth, tonsillar pillars, and pharynx. The condition is caused by Epstein-Barr virus, which is present in the upper layer of the affected epithelium. The plaques have no malignant potential. The disorder occurs predominantly in HIV-infected patients but may also be found in individuals who are immunosuppressed for other reasons, such as organ transplantation, leukemia, chemotherapy, and long-term use of inhaled steroids. The condition is generally asymptomatic and does not require therapy.

Acute Necrotizing Ulcerative Gingivitis (Vincent Stomatitis, Fusospirochetal Gingivitis, Trench Mouth)

Acute necrotizing ulcerative gingivitis manifests as painful punched-out ulceration, necrosis, and bleeding of the interdental papillae. A grayish white pseudomembrane may cover the ulcerations. Lesions may spread to involve the buccal mucosa, lips, tongue, tonsils, and pharynx and may be associated with dental pain, a bad taste, low-grade fever, and lymphadenopathy. It occurs most commonly in the 2nd or 3rd decade, particularly in the context of poor dental hygiene, poor nutrition, smoking, and stress.

Noma

Noma is a severe form of fusospirillary gangrenous stomatitis that occurs primarily in malnourished, impoverished children 2-5 yr of age who have had a preceding illness such as measles, scarlet fever, tuberculosis, malignancy, or immunodeficiency. The disease is most prevalent in Africa but also occurs in Asia and Latin America. Sporadic cases associated with immunodeficiency have been reported in developed countries. It manifests as a painful, red, indurated papule on the alveolar margin, followed by ulceration and mutilating gangrenous destruction of tissue in the oronasal region. The process may also involve the scalp, neck, shoulders, perineum, and vulva. Noma neonatorum manifests in the 1st mo of life as gangrenous lesions of the lips, nose, mouth, and anal regions. Affected infants are usually small for gestational age, malnourished, premature, and frequently ill (particularly with *Pseudomonas aeruginosa* sepsis). Care consists of nutritional support, conservative debridement of necrotic soft tissues, empirical broad-spectrum antibiotics such as penicillin and metronidazole, and, in the case of noma neonatorum, antipseudomonal antibiotics (see Chapter 57).

Cowden Syndrome (Multiple Hamartoma Syndrome)

Cowden syndrome is an autosomal dominant condition caused by loss-of-function mutations in the *PTEN* tumor-suppressor gene. Mucocutaneous lesions typically appear in the 2nd or 3rd decade. Oral papillomas are 1-3 mm smooth, pink or whitish papules on the palatal, gingival, buccal, and labial mucosae and may coalesce into a cobblestone appearance. Numerous flesh-colored papules also develop on the face, particularly around the mouth, nose, and ears. These papules are most commonly trichilemmomas, a benign neoplasm of the hair follicle. Associated findings may include acral keratoses, thyroid adenoma, goiter, gastrointestinal polyps, fibrocystic breast nodules, and carcinoma of the breast or thyroid.

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CHAPTER 685

Cutaneous Bacterial Infections

685.1

Impetigo

Daren A. Diiorio, Stephen R. Humphrey

Etiology/Pathogenesis

Impetigo is the most common skin infection in children throughout the world. There are 2 classic forms of impetigo: nonbullous and bullous.

Staphylococcus aureus is the predominant organism of **nonbullous impetigo** in the United States (see Chapter 208); group A β-hemolytic streptococci (GABHS) are implicated in the development of some lesions (see Chapter 210). The staphylococcal types that cause nonbullous impetigo are variable but are not generally from phage group 2, the group that is associated with scalded skin and toxic shock syndromes. Staphylococci generally spread from the nose to normal skin and then infect the skin. In contrast, the skin becomes colonized with GABHS an average of 10 days before development of impetigo. The skin serves as the source for acquisition of GABHS and is the probable primary source for spread of impetigo. Lesions of nonbullous impetigo that grow staphylococci in culture cannot be distinguished clinically from those that grow pure cultures of GABHS.

Bullous impetigo is always caused by *S. aureus* strains that produce exfoliative toxins. The staphylococcal exfoliative toxins (ETA, ETB, ETD) blister the superficial epidermis by hydrolyzing human desmoglein 1, resulting in a subcorneal vesicle. This is also the target antigen of the autoantibodies in pemphigus foliaceus.

Clinical Manifestations

Nonbullous Impetigo

Nonbullous impetigo accounts for more than 70% of cases. Lesions typically begin on the skin of the face or on extremities that have been traumatized. The most common lesions that precede nonbullous impetigo are insect bites, abrasions, lacerations, chickenpox, scabies pediculosis, and burns. A tiny vesicle or pustule forms initially and rapidly develops into a honey-colored crusted plaque that is generally <2 cm in diameter (Fig. 685.1). The infection may be spread to other parts of the body by the fingers, clothing, and towels. Lesions are associated with little to no pain or surrounding erythema, and constitutional symptoms are generally absent. Pruritus occurs occasionally, regional adenopathy is found in up to 90% of cases, and leukocytosis is present in approximately 50%.

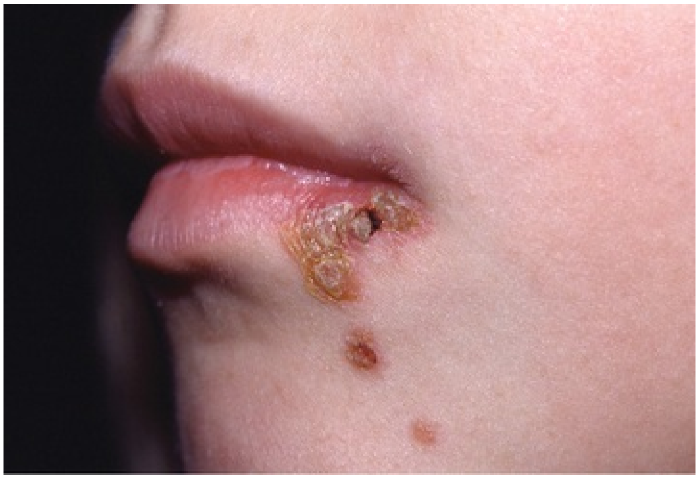

FIG. 685.1 Multiple crusted and oozing lesions of impetigo.

Bullous Impetigo

Bullous impetigo is mainly an infection of infants and young children. Flaccid, transparent bullae develop most commonly on skin of the face, buttocks, trunk, perineum, and extremities. **Neonatal bullous impetigo** can begin in the diaper area. Rupture of a bulla occurs easily, leaving a narrow rim of scale at the edge of shallow, moist erosion. Surrounding erythema and regional adenopathy are generally absent. Unlike those of nonbullous impetigo, lesions of bullous impetigo are a manifestation of localized staphylococcal scalded skin syndrome and develop on intact skin.

Differential Diagnosis

The differential diagnosis of **nonbullous impetigo** includes viruses (herpes simplex, varicella-zoster), fungi (tinea corporis, kerion), arthropod bites, and parasitic infestations (scabies, pediculosis capitis), all of which may become impetiginized.

The differential diagnosis of **bullous impetigo** in neonates includes epidermolysis bullosa, bullous mastocytosis, herpetic infection, and early staphylococcal scalded skin syndrome. In older children, allergic contact dermatitis, burns, erythema multiforme, linear immunoglobulin A dermatosis, pemphigus, and bullous pemphigoid must be considered, particularly if the lesions do not respond to therapy.

Complications

Potential but *very rare* complications of either nonbullous or bullous impetigo include bacteremia with subsequent osteomyelitis, septic arthritis, pneumonia, and septicemia. Positive blood culture results are *very rare* in otherwise healthy children with localized lesions. Cellulitis has been reported in up to 10% of patients with nonbullous impetigo and rarely follows the bullous form. Lymphangitis, suppurative lymphadenitis, guttate psoriasis, and scarlet fever occasionally follow streptococcal disease. There is no correlation between number of lesions and clinical involvement of the lymphatics or development of cellulitis in association with streptococcal impetigo.

Infection with nephritogenic strains of GABHS may result in **acute poststreptococcal glomerulonephritis** (see Chapter 537.4). The clinical character of impetigo lesions does not predict the development of poststreptococcal glomerulonephritis. Children 3-7 yr of age are most commonly affected. The latent period from onset of impetigo to development of poststreptococcal glomerulonephritis averages 18-21 days, which is longer than the 10-day latency period after pharyngitis. Poststreptococcal glomerulonephritis occurs epidemically after either pharyngeal or skin infection. Impetigo-associated epidemics have been caused by M groups 2, 49, 53, 55, 56, 57, and 60. Strains of GABHS that are associated with endemic impetigo in the United States have little or no nephritogenic potential. Acute rheumatic fever does not occur as a result of impetigo.

Treatment

The decision on how to treat impetigo depends on the number of lesions and their locations. Topical therapy with mupirocin 2%, and retapamulin 1% 2-3 times a day for 10-14 days is acceptable for localized disease caused by *S. aureus*.

Systemic therapy with oral antibiotics should be prescribed for patients with streptococcal or widespread involvement of staphylococcal infections; when lesions are near the mouth, where topical medication may be licked off; or in cases with evidence of deep involvement, including cellulitis, furunculosis, abscess formation, or suppurative lymphadenitis. Cephalexin, 25-50 mg/kg/day in 3-4 divided doses for 7 days, is an excellent choice for initial therapy. A culture should be performed, as the emergence of methicillin-resistant *S. aureus* (MRSA) typically requires a different antibiotic choice based on antibiotic susceptibility patterns. If MRSA is suspected, clindamycin, doxycycline or sulfamethoxazole-trimethoprim is indicated. No evidence suggests that a 10-day course of therapy is superior to a 7-day course; twice daily sulfamethoxazole trimethoprim for 3 days has been comparable to once daily for 5 days. Benzathine benzylpenicillin IM has been used when compliance with multiple dose and day oral antibiotics may be poor.

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685.2

Subcutaneous Tissue Infections

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The principal determinations for soft-tissue infections is whether it is *nonnecrotizing* or *necrotizing,* as well as *purulent* or *nonpurulent* (see Fig. 685.2). The former responds to antibiotic therapy alone, whereas the latter requires prompt surgical removal of all devitalized tissue in addition to antimicrobial therapy. Necrotizing soft-tissue infections are life-threatening conditions that are characterized by rapidly advancing local tissue destruction and systemic toxicity including shock. Tissue necrosis distinguishes them from cellulitis. In cellulitis, an inflammatory infectious process involves subcutaneous tissue but does not destroy it. Necrotizing soft-tissue infections may initially manifest with a paucity of early cutaneous signs relative to the rapidity and degree of destruction of the subcutaneous tissues.

Cellulitis

Etiology

Cellulitis is characterized by infection and inflammation of loose connective tissue, with limited involvement of the dermis and relative sparing of the epidermis. A break in the skin from previous trauma, surgery, or an underlying skin lesion predisposes to cellulitis. Cellulitis is also more common in individuals with lymphatic stasis, diabetes mellitus, or immunosuppression.

S. aureus and *Streptococcus pyogenes* (group A streptococcus) are the most common etiologic agents. In patients who are immunocompromised or have diabetes mellitus, other bacterial or fungal agents may be involved, notably *Pseudomonas aeruginosa; Aeromonas hydrophila* and, occasionally, other Enterobacteriaceae; *Legionella* spp.; the Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp.; and *Cryptococcus neoformans.* Children with relapsed nephrotic syndrome may experience cellulitis caused by *Escherichia coli.* In children 3 mo to 5 yr of age, *Haemophilus influenzae* type b was once an important cause of facial cellulitis, but its incidence has declined significantly since the institution of immunization against this organism.

Clinical Manifestations

Cellulitis manifests clinically as a localized area of edema, warmth, erythema, and tenderness. The lateral margins tend to be indistinct because the process is deep in the skin, primarily involving the subcutaneous tissues in addition to the dermis. Application of pressure may produce pitting. Although distinction cannot be made with certainty in any particular patient, cellulitis due to *S. aureus* tends to be more localized and may suppurate, whereas infections caused by *S. pyogenes* (group A streptococci) tend to spread more rapidly and may be associated with lymphangitis. Regional adenopathy and constitutional signs and symptoms such as fever, chills, and malaise are common. Complications of cellulitis are uncommon but include subcutaneous abscess, bacteremia, osteomyelitis, septic arthritis, thrombophlebitis, endocarditis, and necrotizing fasciitis. Lymphangitis or glomerulonephritis can also follow infection with *S. pyogenes.*

Diagnosis

Cellulitis in a neonate should prompt assessment for invasive bacterial infection, including blood culture; lumbar puncture is also usually performed though its necessity for mild cases of cellulitis is controversial in this age group. In older children, cultures of blood or cutaneous aspirates, biopsies or swabs are not routinely recommended. However, blood cultures should be considered if the patient is younger than 1 yr of age, if signs of systemic toxicity are present, if an adequate examination cannot be carried out, or if an immunocompromising condition (e.g., malignancy, neutropenia) is present. Aspirates from the site of inflammation, skin biopsy, and blood cultures allow identification of the causal organism in approximately 25% of cases of cellulitis. Yield of the causative organism is approximately 30% when the site of origin of the cellulitis is apparent, such as an abrasion or ulcer. An aspirate taken from the point of maximum inflammation yields the causal organism more often than a leading-edge aspirate. Lack of success in isolating an organism stems primarily from the low number of organisms present within the lesion. Ultrasonography can be performed if an associated subcutaneous abscess is suspected.

The differential diagnosis includes an exuberant immune-allergic reaction to insect bites particularly mosquito bites (Skeeter syndromes) (see Chapter 171). The **Skeeter syndrome** is characterized by swelling disproportionate to erythema; there is pruritus but usually no tenderness. In addition, **cold panniculitis** may appear as an erythematous but usually nontender swelling after exposure to cold, such as sledding or eating a cold Popsicle (see Chapter 680.1).

Treatment

Empirical antibiotic therapy for cellulitis and the initial route of administration should be guided by the age and immune status of the patient, history of the illness, and location and severity of the cellulitis (Fig. 685.2).

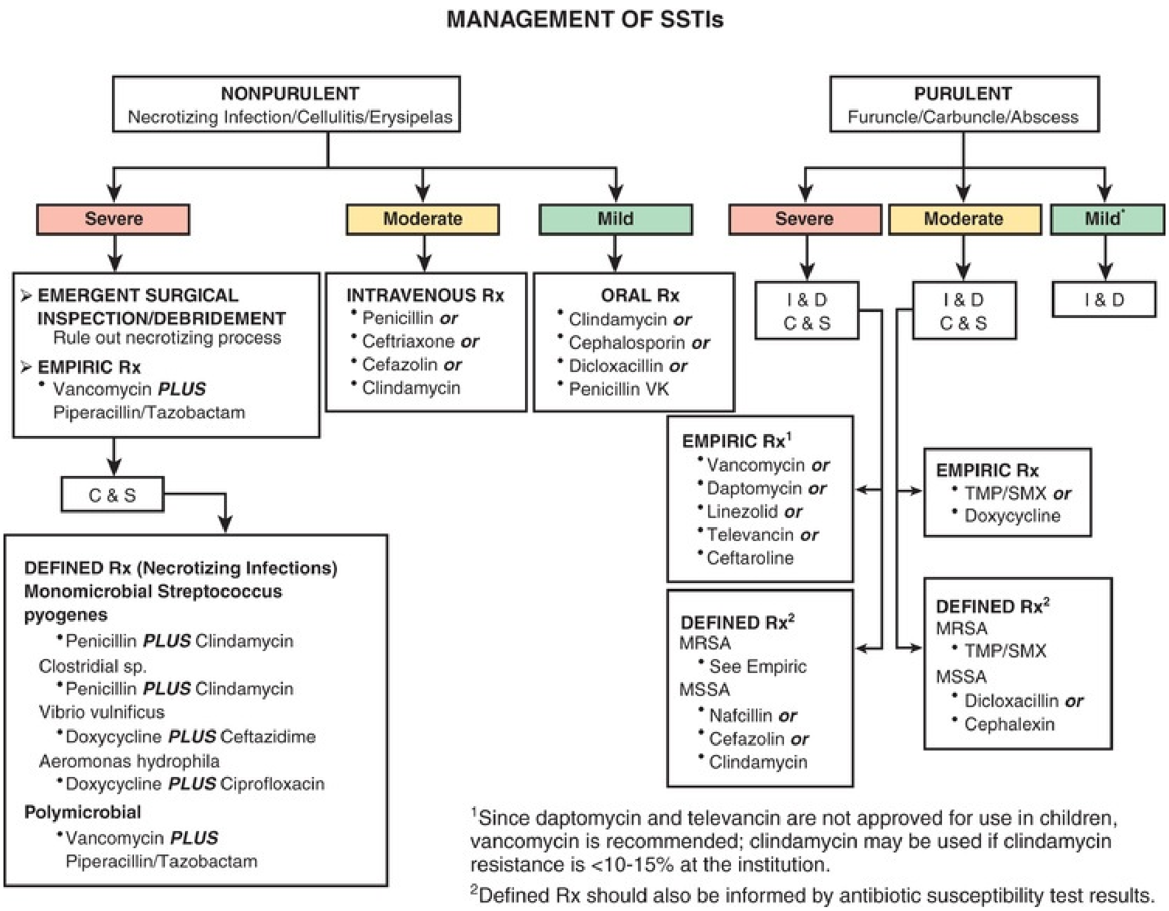
MANAGEMENT OF SSTIs
NONPURULENT
Necrotizing Infection/Cellulitis/Erysipelas
PURULENT
Furuncle/Carbuncle/Abscess
Severe
Moderate
Mild
Severe
Moderate
Mild*
EMERGENT SURGICAL INSPECTION/DEBRIDEMENT
Rule out necrotizing process
EMPIRIC Rx
Vancomycin PLUS Piperacillin/Tazobactam
INTRAVENOUS Rx
Penicillin or
Ceftriaxone or
Cefazolin or
Clindamycin
ORAL Rx
Clindamycin or
Cephalosporin or
Dicloxacillin or
Penicillin VK
I & D
C & S
I & D
C & S
I & D
C & S
DEFINED Rx (Necrotizing Infections)
Monomicrobial Streptococcus pyogenes
Penicillin PLUS Clindamycin
Clostridial sp.
Penicillin PLUS Clindamycin
Vibrio vulnificus
Doxycycline PLUS Ceftazidime
Aeromonas hydrophila
Doxycycline PLUS Ciprofloxacin
Polymicrobial
Vancomycin PLUS Piperacillin/Tazobactam
EMPIRIC Rx1
Vancomycin or
Daptomycin or
Linezolid or
Televancin or
Ceftaroline
DEFINED Rx2
MRSA
See Empiric
MSSA
Nafcillin or
Cefazolin or
Clindamycin
EMPIRIC Rx
TMP/SMX or
Doxycycline
DEFINED Rx2
MRSA
TMP/SMX
MSSA
Dicloxacillin or
Cephalexin
1Since daptomycin and televancin are not approved for use in children, vancomycin is recommended; clindamycin may be used if clindamycin resistance is <10-15% at the institution.
2Defined Rx should also be informed by antibiotic susceptibility test results.

FIG. 685.2 **Purulent skin and soft-tissue infections (SSTIs)** —*Mild infection:* For purulent SSTI, incision and drainage is indicated. *Moderate infection:* Patients with purulent infection with systemic signs of infection. *Severe infection:* Patients who have failed incision and drainage plus oral antibiotics or those with systemic signs of infection such as temperature >38°C (100.4°F), tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >24 breaths/min), or abnormal white blood cell count (<12,000 or <400 cells/µL), or immunocompromised patients. **Nonpurulent SSTIs** —*Mild infection:* Typical cellulitis/erysipelas with no focus of purulence. *Moderate infection:* Typical cellulitis/erysipelas with systemic signs of infection. *Severe infection:* Patients who have failed oral antibiotic treatment or those with systemic signs of infection (as defined above under purulent infection), or those who are immunocompromised, or those with clinical signs of deeper infection such as bullae, skin sloughing, hypotension, or evidence of organ dysfunction. Three newer agents, oritavancin, tedizolid, and dalbavancin, are also effective agents in SSTIs, including those caused by methicillin-resistant *Staphylococcus aureus* . C & S, culture and sensitivity; I & D, incision and drainage; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *Staphylococcus aureus;* Rx, treatment; TMP/SMX, trimethoprim-sulfamethoxazole. (Modified from Stevens DL, Bisno AL, Chambers HF, et al: Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 59:147–159, 2014, Fig. 1.)

Neonates should receive an intravenous antibiotic with a β-lactamase–stable antistaphylococcal antibiotic such as nafcillin, cefazolin, or vancomycin, and an aminoglycoside such as gentamicin or a 3rd-generation cephalosporin such as cefotaxime.

In infants and children older than 2 mo with mild to moderate infections, particularly if fever, lymphadenopathy, and other constitutional signs are absent, treatment of cellulitis may be initiated orally on an outpatient basis with a penicillinase-resistant penicillin such as dicloxacillin or a 1st-generation cephalosporin such as cephalexin or, if MRSA is suspected, with clindamycin. Some recommend trimethoprim-sulfamethoxazole although it does not provide ideal coverage against *S. pyogenes* , a potential cause of cellulitis *without* abscess. A randomized trial of 500 children >12 yr and adults did not demonstrate significant differences in treatment failure between those treated with cephalexin alone compared with those treated with a combination of cephalexin and trimethoprim-sulfamethoxazole.

Intravenous antibiotics may be necessary if improvement is not noted or the disease progresses significantly in the 1st 24-48 hr of therapy. Infants and children older than 2 mo with signs of systemic infection, including fever, lymphadenopathy, or constitutional signs, also require hospitalization and treatment with intravenous antibiotics effective against *S. pyogenes* and *S. aureus* , such as clindamycin or a 1st-generation cephalosporin (cefazolin). If the child is severely ill or toxic appearing, consideration should be given to the addition of clindamycin or vancomycin if these antibiotics were not started initially. Other agents for complicated skin and skin structure infections caused by MRSA or *S. pyogenes* have been approved by the US Food and Drug Administration (FDA) in adults, including dalbavancin (intravenous given once weekly), ceftaroline (IV), telavancin (IV*),* linezolid (oral or IV), tedizolid (oral or IV), and oritavancin (IV). Dalbavacin also provides activity against vancomycin-resistant enterococci.

In unimmunized patients, antibiotic treatment may include a 3rd-generation cephalosporin (cefepime, ceftriaxone, or if available cefotaxime) or a β-lactam/β-lactamase inhibitor combination (e.g., ampicillin-sulbactam), which provide coverage for *H. influenzae* type b and *Streptococcus pneumoniae* .

Once the erythema, warmth, edema, and fever have decreased significantly, a 5- to 7-day total course of treatment may be completed on an outpatient basis though treatment should be extended if the infection has not substantially improved with this time period. Elevation of an affected limb, particularly early in the course of therapy, may help reduce swelling and pain. If present, a subcutaneous abscess should be drained.

Necrotizing Fasciitis

Etiology

Necrotizing fasciitis is a subcutaneous tissue infection that involves the deep layer of superficial fascia but may spare adjacent epidermis, deep fascia, and muscle.

Relatively few organisms possess sufficient virulence to cause necrotizing fasciitis when acting alone. Most (55–75%) cases of necrotizing fasciitis are polymicrobial (synergistic necrotizing fasciitis), with an average of 4 different organisms isolated. The organisms most commonly isolated in polymicrobial necrotizing fasciitis are *S. aureus* , streptococcal species, *Klebsiella* species, *E. coli*, and anaerobic bacteria.

The rest of the cases and the most fulminant infections, associated with toxic shock syndrome and a high case fatality rate, are usually caused by *S. pyogenes* (group A streptococcus) (see Chapter 210). Streptococcal necrotizing fasciitis may occur in the absence of toxic shock–like syndrome and is potentially fatal and associated with substantial morbidity. Necrotizing fasciitis can occasionally be caused by *S. aureus; Clostridium perfringens; Clostridium septicum; P. aeruginosa; Vibrio* spp., particularly *Vibrio vulnificus;* and fungi of the order Mucorales, particularly *Rhizopus* spp., *Mucor* spp., and *Absidia* spp. Necrotizing fasciitis has also been reported, on rare occasions, to result from nongroup A streptococci such as group B, C, F, or G streptococci, *S. pneumoniae*, or *H. influenzae* type b.

Infections caused by any organism or combination of organisms cannot be distinguished clinically from one another, although development of **crepitus** signals the presence of gas-forming organisms: *Clostridium* spp. or Gram-negative bacilli such as *E. coli*, *Klebsiella*, *Proteus*, or *Aeromonas.*

Clinical Manifestations

Necrotizing fasciitis may occur anywhere on the body. Polymicrobial infections tend to occur on perineal and trunk areas. The incidence of necrotizing fasciitis is highest in hosts with systemic or local tissue immunocompromise, such as those with diabetes mellitus, neoplasia, or peripheral vascular disease as well as those who have recently undergone surgery, who abuse intravenous drugs, or who are undergoing immunosuppressive treatment, particularly with corticosteroids. The infection can also occur in healthy individuals after minor puncture wounds, abrasions, or lacerations; blunt trauma; surgical procedures, particularly of the abdomen, gastrointestinal or genitourinary tracts, or the perineum; or hypodermic needle injection.

There has been a resurgence of fulminant necrotizing soft-tissue infections caused by *S. pyogenes*, which may occur in previously healthy individuals. Streptococcal necrotizing fasciitis is classically located on an extremity. There may be a history of recent trauma to or operation in the area. Necrotizing fasciitis due to *S. pyogenes* may also occur after superinfection of varicella lesions. Children with this disease have tended to display onset, recrudescence, or persistence of high fever and signs of toxicity after the 3rd or 4th day of varicella. Common predisposing conditions in neonates are omphalitis and balanitis after circumcision.

Necrotizing fasciitis begins with acute onset of local, and at times tense, edema, erythema, tenderness, and heat. Fever is usually present, and pain, tenderness, and constitutional signs are disproportionate to cutaneous signs, especially with involvement of fascia and muscle. Lymphangitis and lymphadenitis may or may not be present. The infection advances along the superficial fascial plane, and initially there may be few cutaneous signs to herald the serious nature and extent of the subcutaneous tissue necrosis that is occurring. Skin changes may appear over 24-48 hr as nutrient vessels are thrombosed and cutaneous ischemia develops. Early clinical findings include ill-defined cutaneous erythema and edema that extends beyond the area of erythema. Additional signs include formation of bullae filled initially with straw-colored and later bluish to hemorrhagic fluid, and darkening of affected tissues from red to purple to blue. Skin anesthesia and, finally, frank tissue gangrene and slough develop owing to the ischemia and necrosis. Vesiculation or bulla formation, ecchymoses, crepitus, anesthesia, and necrosis are ominous signs indicative of advanced disease. Children with varicella lesions may initially show no cutaneous signs of superinfection with invasive *S. pyogenes*, such as erythema or swelling. Significant systemic toxicity may accompany necrotizing fasciitis, including shock, organ failure, and death. Advance of the infection in this setting can be rapid, progressing to death within hours. Patients with involvement of the superficial or deep fascia and muscle tend to be more acutely and systemically ill and have more rapidly advancing disease than those with infection confined solely to subcutaneous tissues above the fascia. In an extremity, a **compartment syndrome** may develop, manifesting as tight edema, pain on motion, and loss of distal sensation and pulses; this is a surgical emergency.

Diagnosis

Definitive diagnosis of necrotizing fasciitis is made by surgical exploration, which should be undertaken as soon as the diagnosis is suspected. Necrotic fascia and subcutaneous tissue are gray and offer little resistance to blunt probing. Although CT and MRI aid in delineating the extent and tissue planes of involvement, these procedures should not delay surgical intervention. Frozen-section incisional biopsy specimens obtained early in the course of the infection can aid management by decreasing the time to diagnosis and helping to establish the margins of involvement. Gram staining of tissue can be particularly useful if chains of Gram-positive cocci, indicative of infection with *S. pyogenes*, are seen.

Treatment

Early supportive care, surgical debridement, and parenteral antibiotic administration are mandatory for necrotizing fasciitis. All devitalized tissue should be removed to freely bleeding edges, and repeat exploration is generally indicated within 24-36 hr to confirm that no necrotic tissue remains. This procedure may need to be repeated on several occasions until devitalized tissue has ceased to form. Meticulous daily wound care is also paramount.

Parenteral antibiotic therapy should be initiated as soon as possible with broad-spectrum agents against all potential pathogens. Initial empirical therapy should be instituted with vancomycin, linezolid, or daptomycin to cover Gram-positive organisms, and piperacillin-tazobactam to cover Gram-negative organisms. An alternative is to add ceftriaxone with metronidazole to cover mixed aerobic–anaerobic organisms. Definitive therapy should then be based on sensitivity of isolated organisms. Penicillin with clindamycin is indicated for necrotizing fasciitis caused by either group A streptococcus or *Clostridium* spp. For group A streptococcus infections, clindamycin is administered until the patient is hemodynamically stable and no longer requires surgical debridement. Unlike penicillin, the effectiveness of clindamycin is not influenced by the infectious burden or bacterial stage of growth, thus its addition early in the course of infection may lead to more rapid bacterial killing. Doxycycline plus either ciprofloxacin or ceftazidime is recommended for *Vibrio vulnificus* necrotizing fasciitis. Duration of therapy for necrotizing fasciitis depends on the course of the illness. Antibiotics are generally continued for at least 5 days after signs and symptoms of local signs and symptoms have resolved; the typical duration of therapy is 4 wk. Many centers employ hyperbaric oxygen therapy, although it should not delay resuscitation of shock or surgical debridement.

Prognosis

The combined case fatality rate among children and adults with necrotizing fasciitis and syndrome due to polymicrobial infection or *S. pyogenes* has been as high as 60%. However, death is less common in children and in cases not complicated by toxic shock–like syndrome.

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685.3

Staphylococcal Scalded Skin Syndrome (Ritter Disease)

Daren A. Diiorio, Stephen R. Humphrey

Etiology and Pathogenesis

Staphylococcal scalded skin syndrome is caused predominantly by phage group 2 staphylococci, particularly strains 71 and 55, which are present at localized sites of infection. Foci of infection include the nasopharynx and, less commonly, the umbilicus, urinary tract, a superficial abrasion, conjunctivae, and blood. The clinical manifestations of staphylococcal scalded skin syndrome are mediated by hematogenous spread, in the absence of specific antitoxin antibody of staphylococcal epidermolytic or exfoliative toxins A or B. The toxins have reproduced the disease in both animal models and human volunteers. Decreased renal clearance of the toxins may account for the fact that the disease is most common in infants and young children, as well as a lack of protection from antitoxin antibodies. Epidermolytic toxin A is heat stable and is encoded by bacterial chromosomal genes. Epidermolytic toxin B is heat labile and is encoded on a 37.5 kb plasmid. The site of blister cleavage is subcorneal. The epidermolytic toxins produce the split by binding to and cleaving desmoglein 1. Intact bullae are consistently sterile, unlike those of bullous impetigo, but culture specimens should be obtained from all suspected sites of localized infection and from the blood to identify the source for elaboration of the epidermolytic toxins.

Clinical Manifestations

Staphylococcal scalded skin syndrome, which occurs predominantly in infants and children younger than 5 yr of age, includes a range of disease from localized bullous impetigo to generalized cutaneous involvement with systemic illness. Onset of the rash may be preceded by malaise, fever, irritability, and exquisite tenderness of the skin. **Scarlatiniform erythema** develops diffusely and is accentuated in flexural and periorificial areas. The conjunctivae are inflamed and occasionally become purulent. The brightly erythematous skin may rapidly acquire a wrinkled appearance, and in severe cases, sterile, flaccid blisters and erosions develop diffusely. Circumoral erythema is characteristically prominent, as is radial crusting and fissuring around the eyes, mouth, and nose. At this stage, areas of the epidermis may separate in response to gentle shear force (Nikolsky sign; Fig. 685.3). As large sheets of epidermis peel away, moist, glistening, denuded areas become apparent, initially in the flexures and subsequently over much of the body surface (Fig. 685.4). This development may lead to secondary cutaneous infection, sepsis, and fluid and electrolyte disturbances. The desquamative phase begins after 2-5 days of cutaneous erythema; healing occurs without scarring in 10-14 days. Patients may have pharyngitis, conjunctivitis, and superficial erosions of the lips, but intraoral mucosal surfaces are spared. Although some patients appear ill, many are reasonably comfortable except for the marked skin tenderness.

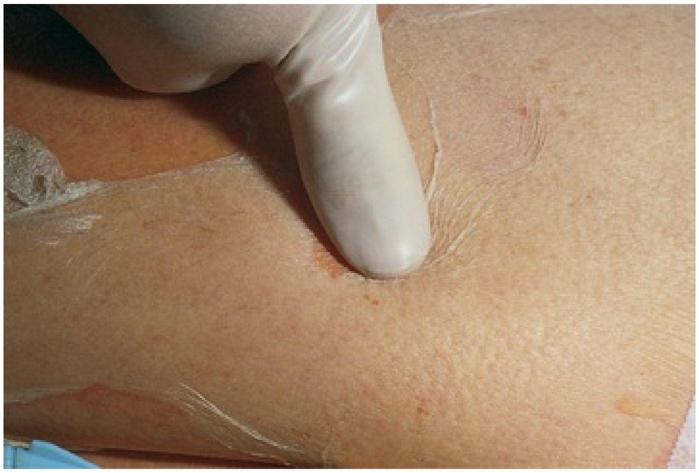

FIG. 685.3 **Nikolsky sign. With slight thumb pressure the skin wrinkles, slides laterally, and separates from the dermis. (From Habif TP, editor: *Clinical dermatology* , ed 4, Philadelphia, 2004, Mosby.)**

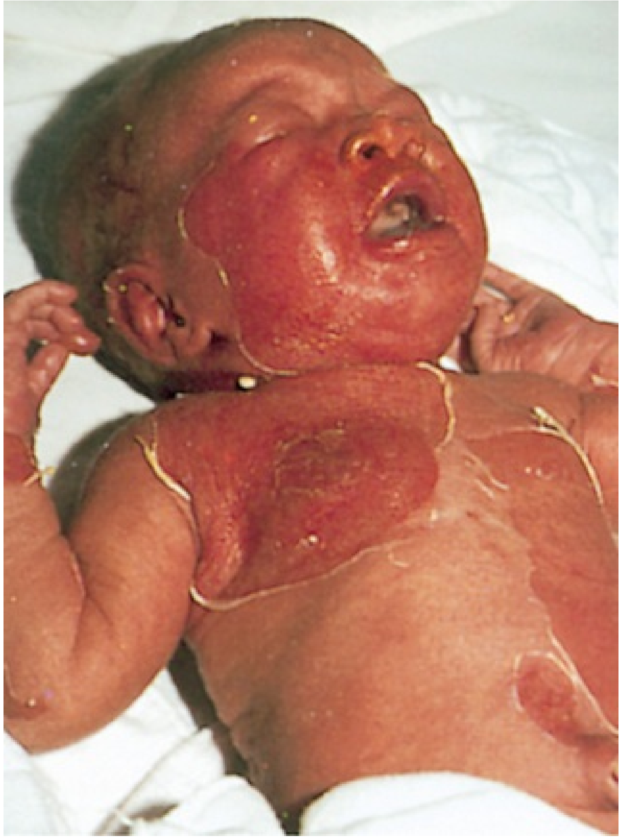

FIG. 685.4 **Infant with staphylococcal scalded skin syndrome.**

Differential Diagnosis

A presumed **abortive** form of the disease manifests as diffuse, scarlatiniform, tender erythroderma that is accentuated in the flexural areas but does not progress to blister formation. In patients with this form, Nikolsky sign may be absent. Although the exanthem is similar to that of streptococcal scarlet fever, strawberry tongue and palatal petechiae are absent. Staphylococcal scalded skin syndrome may be mistaken for a number of other blistering and exfoliating disorders, including bullous impetigo, epidermolysis bullosa, epidermolytic hyperkeratosis, pemphigus, drug eruption, erythema multiforme, and drug-induced toxic epidermal necrolysis. Toxic epidermal necrolysis can often be distinguished by a history of drug ingestion, the presence of Nikolsky sign only at sites of erythema, the absence of perioral crusting, full-thickness epidermal necrosis, and a blister cleavage plane in the lowermost epidermis.

Histology

A subcorneal, granular layer split can be identified on skin biopsy. Absence of an inflammatory infiltrate is characteristic. Histology is identical to that seen in pemphigus foliaceus, bullous impetigo, and subcorneal pustular dermatosis.

Treatment

Systemic therapy, given either orally in cases of localized involvement or parenterally with a semisynthetic antistaphylococcal penicillin (e.g., nafcillin), first-generation cephalosporin (e.g., cefazolin), clindamycin, or vancomycin if MRSA is considered, should be prescribed. Clindamycin is typically used in addition to other agents, as it is thought to inhibit bacterial protein (toxin) synthesis. The skin should be gently moistened and cleansed. Application of an emollient provides lubrication and decreases discomfort. Topical antibiotics are unnecessary. In neonates, or in infants or children with severe infection, hospitalization is mandatory, with attention to fluid and electrolyte management, infection control measures, pain management, and meticulous wound care with contact isolation. In particularly severe disease, care in an intensive care or burn unit is required. Recovery is usually rapid, but complications, such as excessive fluid loss, electrolyte imbalance, faulty temperature regulation, pneumonia, septicemia, and cellulitis, may cause increased morbidity.

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685.4

Ecthyma

Daren A. Diiorio, Stephen R. Humphrey

See also Chapters 208 , 210 , and 232 .

Ecthyma resembles nonbullous impetigo in onset and appearance but gradually evolves into a deeper, more chronic infection. The initial lesion is a vesicle or vesicular pustule with an erythematous base that erodes through the epidermis into the dermis to form an ulcer with elevated margins. The ulcer becomes obscured by a dry, heaped-up, tightly adherent crust (Fig. 685.5) that contributes to the persistence of the infection and scar formation. Lesions may be spread by autoinoculation, may be as large as 4 cm, and occur most frequently on the legs. Predisposing factors include the presence of pruritic lesions, such as insect bites, scabies, or pediculosis, that are subject to frequent scratching; poor hygiene; and malnutrition. Complications include lymphangitis, cellulitis, and, rarely, poststreptococcal glomerulonephritis. The causative agent is usually GABHS; *S. aureus* is also cultured from most lesions but is probably a secondary pathogen. Crusts should be softened with warm compresses and removed. Systemic antibiotic therapy, as for impetigo, is indicated; almost all lesions are responsive to treatment with penicillin.

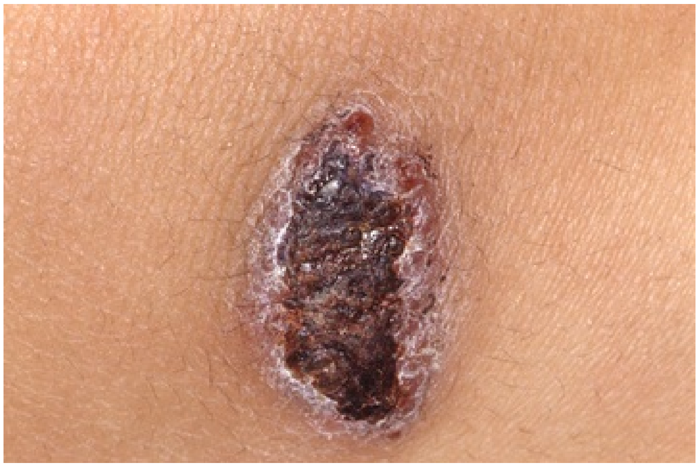

FIG. 685.5 Dry, tightly adherent crust in ecthyma.

Ecthyma gangrenosum is a necrotic ulcer covered with a gray-black eschar. It is usually a sign of *P. aeruginosa* infection, most often occurring in immunosuppressed patients. Neutropenia is a risk factor for ecthyma gangrenosum. Ecthyma gangrenosum occurs in up to 6% of patients with systemic *P. aeruginosa* infection but can also occur as a primary cutaneous infection by inoculation. The lesion begins as a red or purpuric macule that vesiculates and then ulcerates. There is a surrounding rim of pink to violaceous skin. The punched-out ulcer develops raised edges with a dense, black, depressed, crusted center. Lesions may be single or multiple. Patients with bacteremia commonly have lesions in apocrine areas. Clinically similar lesions may also develop as a result of infection with other agents, such as *S. aureus, A. hydrophila, Enterobacter* spp., *Proteus* spp., *Burkholderia cepacia, Serratia marcescens, Aspergillus* spp., Mucorales, *E. coli,* and *Candida* spp. There is bacterial invasion of the adventitia and media of dermal veins but not arteries. The intima and lumina are spared. Blood and skin biopsy specimens for culture should be obtained, and empirical broad-spectrum, systemic therapy that includes coverage for *P. aeruginosa* (e.g., antipseudomonal penicillin and an aminoglycoside, cefepime) should be initiated as soon as possible.

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685.5

Other Cutaneous Bacterial Infections

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Blastomycosis-Like Pyoderma (Pyoderma Vegetans)

Blastomycosis-like pyoderma is an exuberant cutaneous reaction to bacterial infection that occurs primarily in children who are malnourished and immunosuppressed. The organisms most commonly isolated from lesions are *S. aureus* and group A streptococcus, but several other organisms have been associated with these lesions, including *P. aeruginosa, Proteus mirabilis,* diphtheroids, *Bacillus* spp., and *C. perfringens.* Crusted, hyperplastic plaques on the extremities are characteristic, sometimes forming from the coalescence of many pinpoint, purulent, crusted abscesses (Fig. 685.6). Ulceration and sinus tract formation may develop, and additional lesions may appear at sites distant from the site of inoculation. Regional lymphadenopathy is common, but fever is not. Histopathologic examination reveals pseudoepitheliomatous hyperplasia and microabscesses composed of neutrophils and/or eosinophils. Giant cells are usually lacking. The **differential diagnosis** includes deep fungal infection, particularly blastomycosis (Fig. 685.7) and tuberculous and atypical mycobacterial infection. Underlying immunodeficiency should be ruled out, and the selection of antibiotics should be guided by susceptibility testing because the response to antibiotics is often poor.

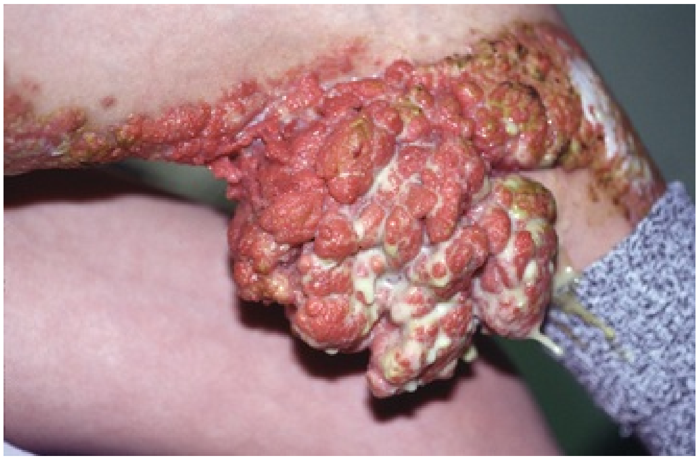

FIG. 685.6 Large vegetating lesion of pyoderma vegetans.

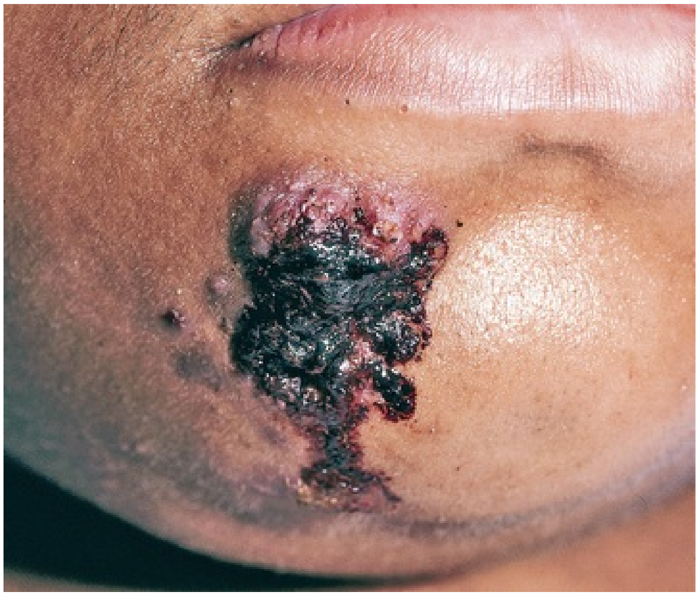

FIG. 685.7 Cutaneous blastomycosis. Verrucous, crusted, erythematous plaque on the chin in a 15-yr-old boy with respiratory symptoms and bone pain. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, Elsevier, Fig. 14.13.)

Blistering Distal Dactylitis

Blistering distal dactylitis is a superficial blistering infection of the volar fat pad on the distal portion of the finger or thumb that typically affects infants and young children. (Fig. 685.8). More than 1 finger may be involved, as may the volar surfaces of the proximal phalanges, palms, and toes. Blisters are filled with a watery purulent fluid; polymorphonuclear leukocytes and Gram-positive cocci are identified on Gram stain. Patients commonly have no preceding history of trauma, and systemic symptoms are generally absent. Poststreptococcal glomerulonephritis has not occurred after blistering distal dactylitis. The infection is caused most commonly by group A streptococcus but has also occurred as a result of infection with *S. aureus*. If left untreated, blisters may continue to enlarge and extend to the paronychial area. The infection responds to incision and drainage and a 10-day course of an antibiotic effective against group A Streptococcus and *S. aureus* (e.g., amoxicillin-clavulanate, clindamycin, cephalexin); patients may require initial intravenous antibiotic therapy.

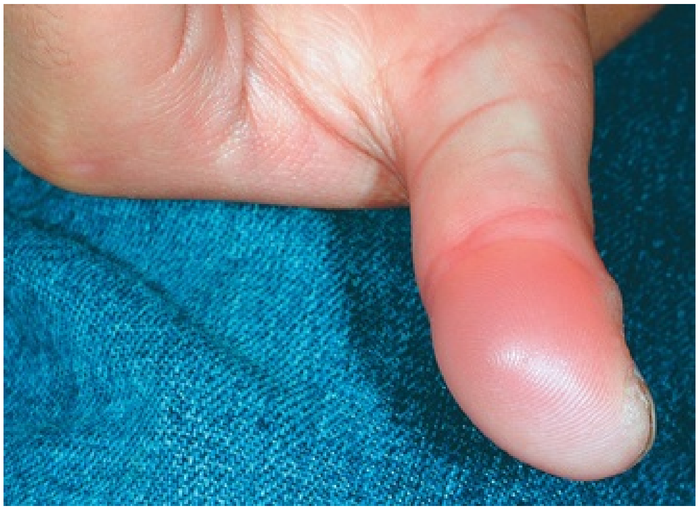

FIG. 685.8 **Blistering dactylitis. Edema and a tense bulla on the thumb of this 7-yr-old girl. Culture of the blister fluid yielded *Staphylococcus aureus* rather than the more commonly seen group A β-hemolytic streptococcus. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, Elsevier, Fig. 14.14.)**

Perianal Infectious Dermatitis

Perianal infectious dermatitis presents most commonly in boys (70% of cases) between the ages of 6 mo and 10 yr as perianal dermatitis (90% of cases) and pruritus (80% of cases; Fig. 685.9). The incidence of perianal infectious dermatitis is not known precisely but ranges from 1 in 2,000 to 1 in 218 patient visits. When GABHS is suspected, it is often referred to as perianal streptococcal dermatitis. The rash is superficial, erythematous, well marginated, nonindurated, and confluent from the anus outward. Acutely (<6 wk), the rash tends to be bright red, moist, and tender to touch. At this stage, a white pseudomembrane may be present. As the rash becomes more chronic, the perianal eruption may consist of painful fissures, a dried mucoid discharge, or psoriasiform plaques with yellow peripheral crust. In girls, the perianal rash may be associated with vulvovaginitis. In boys, the penis may be involved. Approximately 50% of patients have rectal pain, most commonly described as burning inside the anus during defecation, and 33% have blood-streaked stools. Fecal retention is a frequent behavioral response to the infection. Patients also have presented with guttate psoriasis. Although local induration or edema may occur, constitutional symptoms, such as fever, headache, and malaise, are absent, suggesting that subcutaneous involvement, as in cellulitis, is absent. Familial spread of perianal infectious dermatitis is common, particularly when family members bathe together or use the same water.

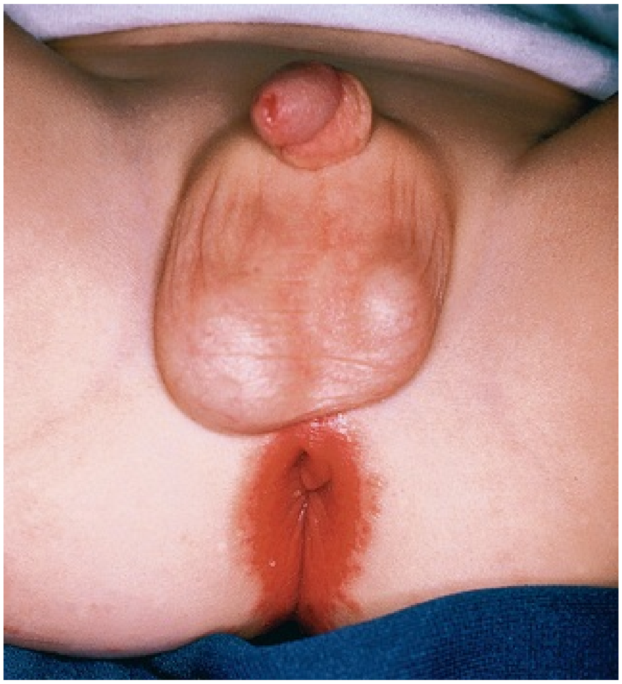

FIG. 685.9 **Perianal streptococcal dermatitis. Bright red erythema with a moist, tender surface. (From Paller AS, Mancini AJ, editors: *Hurwitz clinical pediatric dermatology* , ed 3, Philadelphia, 2006, Elsevier, Fig. 17.38.)**

Perianal infectious dermatitis is usually caused by GABHS, but it may also be caused by *S. aureus.* The index case and family members should undergo culture; follow-up cultures to document bacteriologic cure after a course of treatment are recommended.

The **differential diagnosis** of perianal infectious dermatitis includes psoriasis, seborrheic dermatitis, candidiasis, pinworm infestation, sexual abuse, and inflammatory bowel disease.

For GABHS perianal infectious dermatitis, treatment with a 7-day course of cefuroxime (20 mg/kg/day in 2 divided doses) is superior to treatment with penicillin. Concomitant topical mupirocin ointment 2-3 times a day also may be used. If *S. aureus* is cultured, treatment should be based on sensitivities.

Erysipelas

See Chapter 210 .

Folliculitis

Folliculitis, or superficial infection of the hair follicle, is most often caused by *S. aureus* (Bockhart impetigo). The lesions are typically small, discrete, dome-shaped pustules with an erythematous base, located at the ostium of the pilosebaceous canals (Fig. 685.10). Hair growth is unimpaired, and the lesions heal without scarring. Favored sites include the scalp, buttocks, and extremities. Poor hygiene, maceration, drainage from wounds and abscesses, and shaving of the legs can be provocative factors. Folliculitis can also occur as a result of tar therapy or occlusive wraps. The moist environment encourages bacterial proliferation. In HIV-infected patients, *S. aureus* may produce confluent erythematous patches with satellite pustules in intertriginous areas and violaceous plaques composed of superficial follicular pustules in the scalp, axillae, or groin. The **differential diagnosis** includes *Candida*, which may cause satellite follicular papules and pustules surrounding erythematous patches of intertrigo (particularly in groin/buttocks), and *Malassezia furfur,* which produces 2-3 mm, pruritic, erythematous, perifollicular papules and pustules on the back, chest, and extremities, particularly in patients who have diabetes mellitus or are taking corticosteroids or antibiotics. Diagnosis is made by examining potassium hydroxide–treated scrapings from lesions. Detection of *Malassezia* may require a skin biopsy, demonstrating clusters of yeast and short, branching hyphae (“macaroni and meatballs”) in widened follicular ostia mixed with keratinous debris.

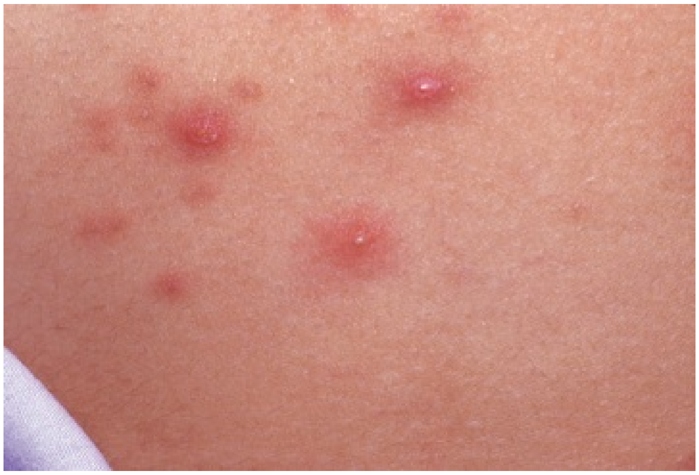

FIG. 685.10 Folliculitis. Multiple follicular pustules.

Topical antibiotic therapy (e.g., clindamycin 1% lotion or solution twice a day) is usually all that is needed for mild cases, but more severe cases may require the use of a systemic antibiotic such as dicloxacillin or cephalexin. Bacterial culture should be performed in treatment-resistant cases. In chronic recurrent folliculitis, daily application of a benzoyl peroxide 5% gel or wash may facilitate resolution. Dilute bleach baths may also be effective in reducing recurrence.

Folliculitis barbae (sycosis barbae) is a deeper, more severe recurrent inflammatory form of folliculitis caused by *S. aureus* that involves the entire depth of the follicle. Erythematous follicular papules and pustules develop on the chin, upper lip, and angle of the jaw, primarily in young black males. Papules may coalesce into plaques, and healing may occur with scarring. Affected individuals are frequently found to be *S. aureus* carriers. Treatment with warm saline compresses and topical antibiotics, such as mupirocin, generally clear the infection. More extensive, recalcitrant cases may require therapy with β-lactamase–resistant systemic antibiotics for several weeks, and elimination of *S. aureus* from the sites of carriage.

Pseudomonal folliculitis (hot tub folliculitis) is attributable to *P. aeruginosa*, predominantly serotype O-11. It occurs after exposure to poorly chlorinated hot tubs/whirlpools and swimming pools, as well as to a contaminated water slide, or loofah sponge. The lesions are pruritic papules and pustules or deeply erythematous to violaceous nodules that develop 8-48 hr after exposure and are most dense in areas covered by a bathing suit (Fig. 685.11). Patients occasionally experience fever, malaise, and lymphadenopathy. The organism is readily cultured from pus. The eruption usually resolves spontaneously in 1-2 wk, often leaving postinflammatory hyperpigmentation. Consideration should be given to the use of systemic antibiotics (ciprofloxacin) in adolescent patients with constitutional symptoms. Immunocompromised children are susceptible to complications of *Pseudomonas* folliculitis (cellulitis) and should avoid hot tubs.

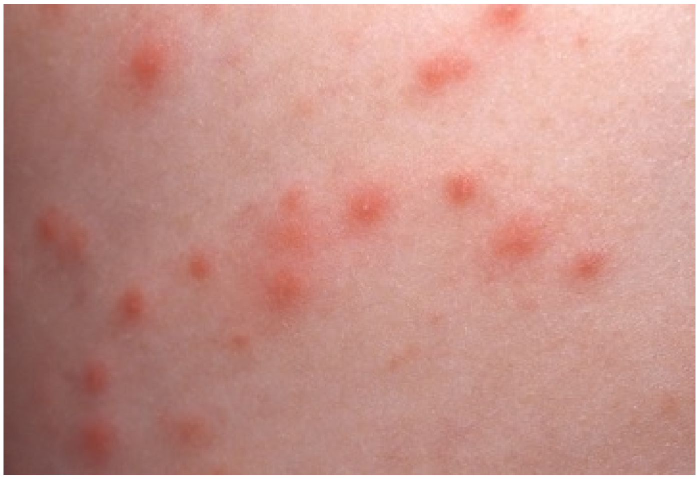

FIG. 685.11 Papules and pustules in hot tub folliculitis.

Abscesses and Furuncles

Etiology

The causative agent in furuncles (“boils”) and carbuncles is usually *S. aureus*, which penetrates abraded perifollicular skin. Conditions predisposing to furuncle formation include obesity, hyperhidrosis, maceration, friction, and preexisting dermatitis. Furunculosis is also more common in individuals with low serum iron levels, diabetes, malnutrition, HIV infection, or other immunodeficiency states. Recurrent furunculosis is frequently associated with carriage of *S. aureus* in the nares, axillae, or perineum, or close contact with someone such as a family member who is a carrier. Other bacteria or fungi may occasionally cause furuncles or carbuncles.

Community-acquired MRSA abscesses can also complicate folliculitis. Community-acquired MRSA infections commonly affect children and young adults, especially athletes where spread of the infection is enhanced by skin-to-skin contact. Infection can also be spread by crowding conditions, shared personal hygiene items, and a compromised skin barrier. They may occur in any location; however, they are most common on the lower abdomen, buttocks, and legs.

Clinical Manifestations

This follicular lesion may originate from a preceding folliculitis or may arise initially as a deep-seated, tender, erythematous, perifollicular nodule. Although lesions are initially indurated, central necrosis and suppuration follow, leading to rupture and discharge of a central core of necrotic tissue and destruction of the follicle (Fig. 685.12). Healing occurs with scar formation. Sites of predilection are the hair-bearing areas on the face, neck, axillae, buttocks, and groin. Pain may be intense if the lesion is situated in an area where the skin is relatively fixed, such as in the external auditory canal or over the nasal cartilages. Patients with furuncles usually have no constitutional symptoms; bacteremia may occasionally ensue. Rarely, lesions on the upper lip or cheek may lead to cavernous sinus thrombosis. Infection of a group of contiguous follicles, with multiple drainage points, accompanied by inflammatory changes in surrounding connective tissue is a **carbuncle** . Carbuncles may be accompanied by fever, leukocytosis, and bacteremia.

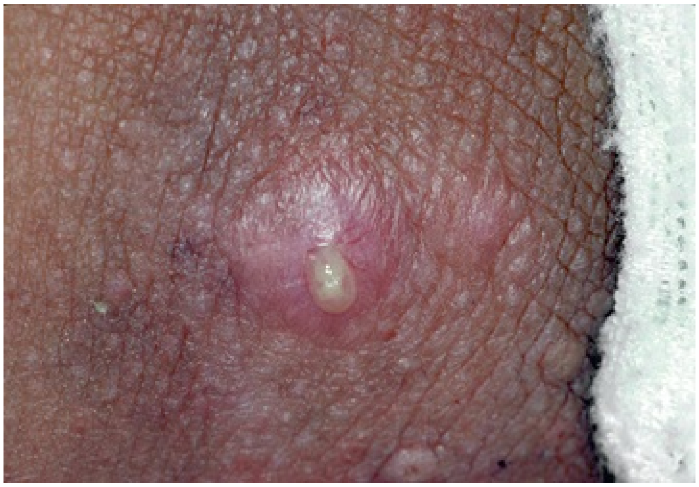

FIG. 685.12 **Rupture and discharge of pus in a furuncle.**

Treatment

Treatment for furuncle and carbuncle includes regular bathing with antimicrobial soaps (chlorhexidine) and wearing of loose-fitting clothing to minimize predisposing factors for furuncle formation. Frequent application of a hot, moist compress may facilitate the drainage of lesions. Large lesions should be drained by a small incision. Carbuncles and large or numerous furuncles should be treated with systemic antibiotics chosen based on culture and sensitivity testing results.

Abscesses are treated with incision and drainage and oral antibiotics (for 7-10 days). Antibiotics with coverage against MRSA are recommended and commonly include oral clindamycin (10-30 mg/kg/day in divided doses) or trimethoprim-sulfamethoxazole (8-12 mg trimethoprim/kg/day in divided doses every 12 hr). Children older than 8 yr may receive doxycycline. To reduce colonization and hence reinfection in children with recurrent infections, mupirocin intranasally (twice daily) and either chlorhexidine (in lieu of soap during showers) or diluted bleach baths [1 teaspoon per gallon of water or ¼ cup per ¼ tub (~13 gallons) of water] (once daily) for 5 days in patients and in family members has been recommended. Recolonization often occurs, typically within 3 mo of the decolonization attempt.

Pitted Keratolysis

Pitted keratolysis occurs most frequently in humid tropical and subtropical climates, particularly in individuals whose feet are moist for prolonged periods, for example, as a result of hyperhidrosis, prolonged wearing of boots, or immersion in water. It occurs most commonly in young males from early adolescence to the late 20s. The lesions consist of 1-7 mm, irregularly shaped, superficial erosions of the horny layer on the soles, particularly at weight-bearing sites (Fig. 685.13). Brownish discoloration of involved areas may be apparent. A rare variant manifests as thinned, erythematous to violaceous plaques in addition to the typical pitted lesions. The condition is frequently malodorous and is painful in approximately 50% of cases. The most likely etiologic agent is *Corynebacterium (Kytococcus) sedentarius*. Treatment of hyperhidrosis is mandatory with prescription-strength aluminum chloride products or 40% formaldehyde in petrolatum ointment. Avoidance of moisture and maceration produces slow, spontaneous resolution of the infection. Topical or systemic erythromycin and topical imidazole creams are standard therapy.

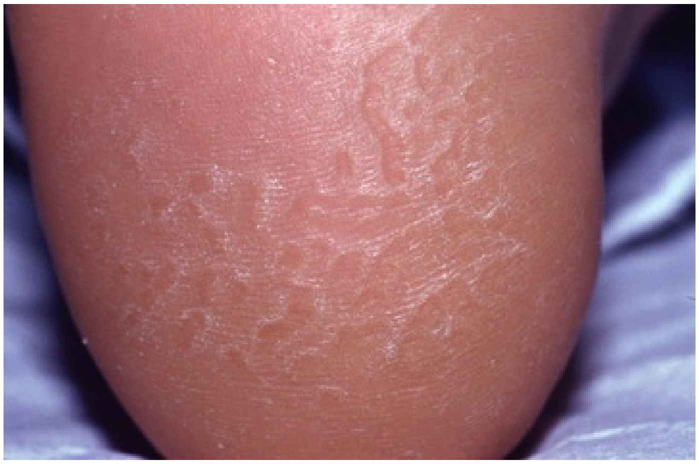

FIG. 685.13 **Superficial erosions of the horny layer in pitted keratolysis.**

Erythrasma

Erythrasma is a benign chronic superficial infection caused by *Corynebacterium minutissimum*. Predisposing factors include heat, humidity, obesity, skin maceration, diabetes mellitus, and poor hygiene. Approximately 20% of affected patients have involvement of the toe webs. Other frequently affected sites are moist, intertriginous areas such as the groin and axillae. The inframammary and perianal regions are occasionally involved. Sharply demarcated, irregularly bordered, slightly scaly, brownish red patches are characteristic of the disease. Mild pruritus is the only constant symptom. *C. minutissimum* is a complex of related organisms that produce porphyrins that fluoresce brilliant coral red under ultraviolet light. The diagnosis is readily made, and erythrasma is differentiated from dermatophyte infection and from tinea versicolor on Wood lamp examination. However, bathing within 20 hr of Wood lamp examination may remove the water-soluble porphyrins. Staining of skin scrapings with methylene blue or Gram stain reveals the pleomorphic, filamentous coccobacillary forms.

Effective treatment can be achieved with topical erythromycin, clindamycin, miconazole, or a 10-14 day course of oral erythromycin or an oral tetracycline (in those older than 8 yr of age).

Erysipeloid

A rare cutaneous infection, erysipeloid is caused by inoculation of *Erysipelothrix* *rhusiopathiae* from handling contaminated animals, birds, fish, or their products. The localized cutaneous form is most common, characterized by well-demarcated diamond-shaped erythematous to violaceous patches at sites of inoculation. Local symptoms are generally not severe, constitutional symptoms are rare, and the lesions resolve spontaneously after weeks but can recur at the same site or develop elsewhere weeks to months later. The diffuse cutaneous form manifests as lesions at several areas of the body in addition to the site of inoculation. It is also self-limited. The systemic form, caused by hematogenous spread, is accompanied by constitutional symptoms and may include endocarditis, septic arthritis, cerebral infarct and abscess, meningitis, and pulmonary effusion. Diagnosis is confirmed by skin biopsy, which reveals the Gram-positive organisms, and culture. The treatment of choice for localized cutaneous infection is oral penicillin for 7 days; ciprofloxacin or a combination of erythromycin and rifampin may be used for penicillin allergic patients. Severe diffuse cutaneous or systemic infection may require parenteral penicillin or ceftriaxone.

Tuberculosis of the Skin

See Chapters 242 and 244 .

Cutaneous tuberculosis infection occurs worldwide, particularly in association with HIV infection, malnutrition, and poor sanitary conditions. Primary cutaneous tuberculosis is rare in the United States. Cutaneous disease is caused by *Mycobacterium tuberculosis, Mycobacterium bovis,* and, occasionally, by the bacillus Calmette-Guérin (BCG), an attenuated vaccine form of *M. bovis.* The manifestations caused by a given organism are indistinguishable from one another. After invasion of the skin, mycobacteria either multiply intracellularly within macrophages, leading to progressive disease, or are controlled by the host immune reaction.

Primary cutaneous tuberculosis (tuberculous chancre) results when *M. tuberculosis* or *M. bovis* gains access to the skin or mucous membranes through trauma in a previously uninfected individual without immunity to the organism. Sites of predilection are the face, lower extremities, and genitals. The initial lesion develops 2-4 wk after introduction of the organism into the damaged tissue. A red-brown papule gradually enlarges to form a shallow, firm, sharply demarcated ulcer. Satellite abscesses may be present. Some lesions acquire a crust resembling impetigo, and others become heaped up and verrucous at the margins. The primary lesion can also manifest as a painless ulcer on the conjunctiva, gingiva, or palate and occasionally as a painless acute paronychia. Painless regional adenopathy may appear several weeks after the development of the primary lesion and may be accompanied by lymphangitis, lymphadenitis, or perforation of the skin surface, forming **scrofuloderma** . Untreated lesions heal with scarring within 12 mo but may reactivate, may form lupus vulgaris (sharply defined red-brown nodules with a gelatinous consistency that represent progressive infection), or, rarely, may progress to the acute miliary form. Therefore, antituberculous therapy is indicated (see Chapter 242).

M. tuberculosis or *M. bovis* can be cultured from the skin lesion and local lymph nodes, but acid-fast staining of histologic sections, particularly of a well-controlled infection, often does not reveal the organism. The **differential diagnosis** is broad, including a syphilitic chancre; deep fungal or atypical mycobacterial infection; leprosy; tularemia; cat-scratch disease; sporotrichosis; nocardiosis; leishmaniasis; reaction to foreign substances such as zirconium, beryllium, silk or nylon sutures, talc, and starch; papular acne rosacea; and lupus miliaris disseminatus faciei.

Scrofuloderma results from enlargement, cold abscess formation, and breakdown of a lymph node, most frequently in a cervical chain, with extension to the overlying skin from underlying foci of tuberculous infection. Linear or serpiginous ulcers and dissecting fistulas and subcutaneous tracts studded with soft nodules may develop. Spontaneous healing may take years, eventuating in cordlike keloid scars. Lupus vulgaris may also develop. Lesions may also originate from an underlying infected joint, tendon, bone, or epididymis. The **differential diagnosis** includes syphilitic gumma, deep fungal infections, actinomycosis, and hidradenitis suppurativa. The course is indolent, and constitutional symptoms are typically absent. Antituberculous therapy is indicated (see Chapter 242).

Direct cutaneous inoculation of the tubercle bacillus into a previously infected individual with a moderate to high degree of immunity initially produces a small papule with surrounding inflammation. **Tuberculosis verrucosa cutis** (warty tuberculosis) forms when the papule becomes hyperkeratotic and warty, and several adjacent papules coalesce or a single papule expands peripherally to form a brownish red to violaceous, exudative, crusted verrucous plaque. Irregular extension of the margins of the plaque produces a serpiginous border. Children have the lesions most commonly on the lower extremities after trauma and contact with infected material such as sputum or soil. Regional lymph nodes are involved only rarely. Spontaneous healing with atrophic scarring takes place over months to years. Healing is also gradual with antituberculous therapy.

Lupus vulgaris is a rare, chronic, progressive form of cutaneous tuberculosis that develops in individuals with a moderate to high degree of tuberculin sensitivity induced by previous infection. The incidence is greater in cool, moist climates, particularly in females. Lupus vulgaris develops as a result of direct extension from underlying joints or lymph nodes; through lymphatic or hematogenous spread; or, rarely, by cutaneous inoculation with the BCG vaccine. It most commonly follows cervical adenitis or pulmonary tuberculosis. Approximately 33% of cases are preceded by scrofuloderma, and 90% of cases manifest on the head and neck, most commonly on the nose or cheek. Involvement of the trunk is uncommon. A typical solitary lesion consists of a soft, brownish red papule that has an apple-jelly color when examined by diascopy. Peripheral expansion of the papule or, occasionally, the coalescence of several papules forms an irregular lesion of variable size and form. One or several lesions may develop, including nodules or plaques that are flat and serpiginous, hypertrophic and verrucous, or edematous in appearance. Spontaneous healing occurs centrally, and lesions characteristically reappear within the area of atrophy. Chronicity is characteristic, and persistence and progression of plaques over many years is common. Lymphadenitis is present in 40% of those with lupus vulgaris, and 10–20% has infection of the lungs, bones, or joints. Extensive deformities may be caused by vegetative masses and ulceration involving the nasal, buccal, or conjunctival mucosa; the palate; the gingiva; or the oropharynx. Squamous cell carcinoma, with a relatively high metastatic potential, may develop, usually after several years of the disease. After a temporary impairment in immunity, particularly after measles infection (lupus exanthematicus), multiple lesions may form at distant sites as a result of hematogenous spread from a latent focus of infection. The histopathology reveals a tuberculoid granuloma without caseation; organisms are extremely difficult to demonstrate. The **differential diagnosis** includes sarcoidosis, atypical mycobacterial infection, blastomycosis, chromoblastomycosis, actinomycosis, leishmaniasis, tertiary syphilis, leprosy, hypertrophic lichen planus, psoriasis, lupus erythematosus, lymphocytoma, and Bowen disease. Small lesions can be excised. Antituberculous drug therapy usually halts further spread and induces involution.

Orificial tuberculosis (tuberculosis cutis orificialis) appears on the mucous membranes and periorificial skin after autoinoculation of mycobacteria from sites of progressive infection. It is a sign of advanced internal disease and carries a poor prognosis, and it occurs in a sensitized host with impaired cellular immunity. Lesions appear as painful, yellowish or red nodules that form punched-out ulcers with inflammation and edema of the surrounding mucosa. Treatment consists of identification of the source of infection and initiation of antituberculous therapy.

Miliary tuberculosis (hematogenous primary tuberculosis) rarely manifests cutaneously and occurs most commonly in infants and in individuals who are immunosuppressed after chemotherapy or infection with measles or HIV. The eruption consists of crops of symmetrically distributed, minute, erythematous to purpuric macules, papules, or vesicles. The lesions may ulcerate, drain, crust, and form sinus tracts or may form subcutaneous gummas, especially in malnourished children with impaired immunity. Constitutional signs and symptoms are common, and a leukemoid reaction or aplastic anemia may develop. Tubercle bacilli are readily identified in an active lesion. A fulminant course should be anticipated, and aggressive antituberculous therapy is indicated.

Single or multiple metastatic tuberculous abscesses (**tuberculous gummas**) may develop on the extremities and trunk by hematogenous spread from a primary focus of infection during a period of decreased immunity, particularly in malnourished and immunosuppressed children. The fluctuant, nontender, erythematous subcutaneous nodules may ulcerate and form fistulas.

Vaccination with BCG characteristically produces a papule approximately 2 wk after vaccination. The papule expands in size, typically ulcerates within 2-4 mo, and heals slowly with scarring. In 1-2 per million vaccinations, a complication caused specifically by the BCG organism occurs, including regional lymphadenitis, lupus vulgaris, scrofuloderma, and subcutaneous abscess formation.

Tuberculids are skin reactions that exhibit tuberculoid features histologically but do not contain detectable mycobacteria. The lesions appear in a host who usually has moderate to strong tuberculin reactivity, has a history of previous tuberculosis of other organs, and usually shows a therapeutic response to antituberculous therapy. The cause of tuberculids is poorly understood. Most affected patients are in good health with no clear focus of disease at the time of the eruption. The most commonly observed tuberculid is the papulonecrotic tuberculid. Recurrent crops of symmetrically distributed, asymptomatic, firm, sterile, dusky-red papules appear on the extensor aspects of the limbs, the dorsum of the hands and feet, and the buttocks. The papules may undergo central ulceration and eventually heal, leaving sharply delineated, circular, depressed scars. The duration of the eruption is variable, but it usually disappears promptly after treatment of the primary infection. Lichen scrofulosorum, another form of tuberculid, is characterized by asymptomatic, grouped, pinhead-sized, often follicular pink or red papules that form discoid plaques, mainly on the trunk. Healing occurs without scarring.

Atypical mycobacterial infection may cause cutaneous lesions in children. *Mycobacterium marinum* is found in saltwater, freshwater, and diseased fish. In the United States, it is most commonly acquired from tropical fish tanks and swimming pools. Traumatic abrasion of the skin serves as a portal of entry for the organism. Approximately 3 wk after inoculation, a single reddish papule develops and enlarges slowly to form a violaceous nodule or, occasionally, a warty plaque (Fig. 685.14). The lesion occasionally breaks down to form a crusted ulcer or a suppurating abscess. Sporotrichoid erythematous nodules along lymphatics may also suppurate and drain. Lesions are most common on the elbows, knees, and feet of swimmers, and on the hands and fingers in persons with aquarium-acquired infection. Systemic signs and symptoms are absent. Regional lymph nodes occasionally become slightly enlarged but do not break down. Rarely, the infection becomes disseminated, particularly in an immunosuppressed host. A biopsy specimen of a fully developed lesion demonstrates a granulomatous infiltrate with tuberculoid architecture. Treatment with 2 active agents is generally recommended with a combination of clarithromycin and ethambutol providing a reasonable balance between effectiveness and tolerability. Rifampin should be added to clarithromycin and ethambutol for deep tissue involvement. Other agents with activity against *M. marinum* include trimethoprim-sulfamethoxazole, doxycycline, minocycline, and ciprofloxacin. While azithromycin has been used as an alternative to clarithromycin for some mycobacterial infections, its effectiveness against *M. marinum* is not known. Treatment should continue for 1-2 mo after resolution of lesions with a minimum treatment duration of 6 mo. The application of heat to the affected site may be a useful adjunctive therapy (see Chapter 244).

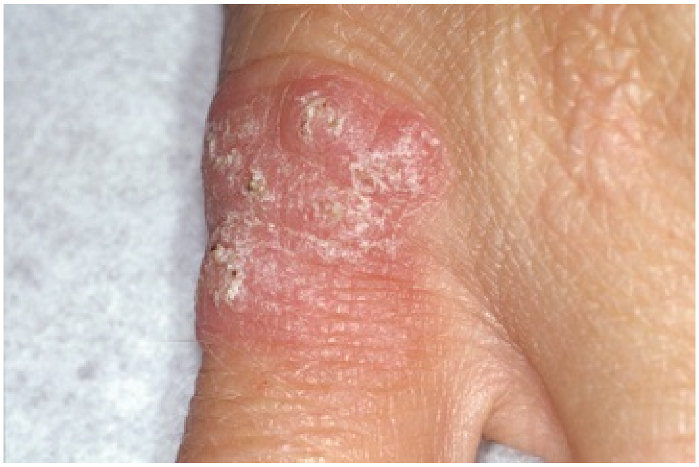

FIG. 685.14 **Violaceous, warty plaque of *Mycobacterium marinum* infection.**

Mycobacterium kansasii primarily causes pulmonary disease; skin disease is rare, often occurring in an immunocompromised host. Most commonly, sporotrichoid nodules develop after inoculation of traumatized skin. Lesions may develop into ulcerated, crusted, or verrucous plaques. The organism is relatively sensitive to antituberculous medications, which should be chosen on the basis of susceptibility testing.

Mycobacterium scrofulaceum causes cervical lymphadenitis (scrofuloderma) in young children, typically in the submandibular region. Nodes enlarge over several weeks, ulcerate, and drain. The local reaction is nontender and circumscribed, constitutional symptoms are absent, and there generally is no evidence of lung or other organ involvement. Other atypical mycobacteria may cause a similar presentation, including *Mycobacterium avium* complex, *Mycobacterium kansasii,* and *Mycobacterium fortuitum.* Treatment is accomplished by excision and administration of antituberculous drugs (see Chapter 244).

Mycobacterium ulcerans (Buruli ulcer) causes a painless subcutaneous nodule after inoculation of abraded skin. Most infections occur in children in tropical rain forests. The nodule usually ulcerates, develops undermined edges, and may spread over large areas, most commonly on an extremity. Local necrosis of subcutaneous fat, producing a septal panniculitis, is characteristic. Ulcers persist for months to years before healing spontaneously with scarring, sometimes with contractures (if over a joint) and lymphedema. Constitutional symptoms and lymphadenopathy are absent. Diagnosis is made by culturing the organism at 32-33°C (89.6-91.4°F). **Treatment of choice** is an 8-wk course of rifampin and streptomycin with surgical debridement for larger lesions. Local heat therapy and oral chemotherapy may benefit some patients.

M. avium complex, composed of more than 20 subtypes, most commonly causes chronic pulmonary infection. Cervical lymphadenitis and osteomyelitis occur occasionally, and papules or purulent leg ulcers occur rarely by primary inoculation. Skin lesions may be an early sign of disseminated infection. The lesions may take various forms, including erythematous papules, pustules, nodules, abscesses, ulcers, panniculitis, and sporotrichoid spread along lymphatics. For treatment, see Chapter 244 .

M. fortuitum complex causes disease in an immunocompetent host principally by primary cutaneous inoculation after traumatic injury, injection, or surgery. A nodule, abscess, or cellulitis develops 4-6 wk after inoculation. In an immunocompromised host, numerous subcutaneous nodules may form, break down, and drain. Treatment is based on identification and susceptibility testing of the organism. Isolates are usually susceptible to fluoroquinolones, doxycycline, minocycline, sulfonamides, cefoxitin, and imipenem; macrolides should be used with caution because many *M. fortuitum* isolates have the erythromycin methylase *(erm)* gene, which confers inducible resistance to macrolides despite “susceptible” minimum inhibitory concentrations.

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CHAPTER 686

Cutaneous Fungal Infections

Daren A. Diiorio, Stephen R. Humphrey

Tinea Versicolor

A common, innocuous, chronic fungal infection of the stratum corneum, tinea versicolor is most often caused by the dimorphic yeast *Malassezia globosa*, with *Malassezia furfur* and *Malassezia sympodialis* as less frequent causative agents. The synonyms *Pityrosporum ovale* and *Pityrosporum orbiculare* were used previously to identify the causal organism.

Etiology

M. globosa is part of the normal indigenous skin flora, predominantly in the yeast form, and is found particularly in areas of skin that are rich in sebum production. Proliferation of filamentous forms occurs in the disease state. Predisposing factors include a warm, humid environment, excessive sweating, occlusion, high plasma cortisol levels, immunosuppression, malnourishment, and genetically determined susceptibility. The disease is most prevalent in adolescents and young adults.

Clinical Manifestations

The lesions of tinea versicolor vary widely in color. In white individuals, they are typically reddish brown, whereas in black individuals they may be either hypopigmented or hyperpigmented. The characteristic macules are covered with a fine scale. They often begin in a perifollicular location, enlarge, and merge to form confluent patches, most commonly on the neck, upper chest, back, and upper arms (Fig. 686.1). Facial lesions are common in adolescents; lesions occasionally appear on the forearms, dorsum of the hands, and pubis. There may be little or no pruritus. Involved areas do not tan after sun exposure. A papulopustular perifollicular variant of the disorder may occur on the back, chest, and sometimes the extremities. These pustules tend to be monomorphic.

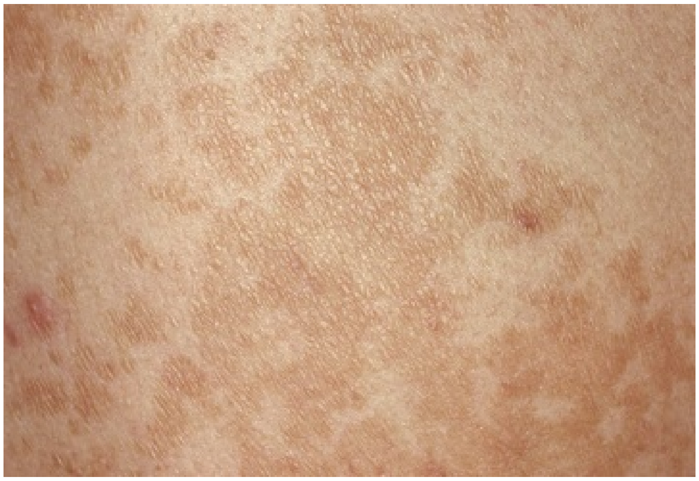

FIG. 686.1 **Hyperpigmented, sharply demarcated macules of varying sizes on the upper trunk characteristic of tinea versicolor.**

Differential Diagnosis

Examination with a Wood lamp discloses a yellowish gold fluorescence. A potassium hydroxide (KOH) preparation of scrapings is diagnostic, demonstrating groups of thick-walled spores and myriad short, thick, angular hyphae resembling macaroni/spaghetti and meatballs. Skin biopsy, including culture and special stains for fungi (periodic acid–Schiff), are often necessary to make the diagnosis in cases of primarily follicular involvement. Microscopically, organisms and keratinous debris can be seen within dilated follicular ostia.

Tinea versicolor must be distinguished from dermatophyte infections, seborrheic dermatitis, pityriasis alba, pityriasis rosea, and secondary syphilis. Tinea versicolor may mimic nonscaling pigmentary disorders, such as postinflammatory pigmentary change, if a patient has removed the scales by scrubbing. *M. globosa* folliculitis must be distinguished from the other forms of folliculitis.

Treatment

Many therapeutic agents can be used to treat this disease successfully. The causative agent, a normal human saprophyte, is not eradicated from the skin, however, and the disorder recurs in predisposed individuals. Appropriate topical therapy may include 1 of the following: selenium 2% shampoo applied for 10 min before rinsing for 1 wk; ketoconazole 2% shampoo once daily for 3 days; and terbinafine spray once to twice daily for 1-2 wk. Antifungal creams are available and can be used; however, these can be impractical to apply given the large surface of skin involved. Oral therapy may be more convenient and may be achieved successfully with fluconazole, 300 mg/wk for 2-4 wk, or itraconazole, 200 mg/24 hr for 5-7 days. Recurrent episodes continue to respond promptly to these agents. Oral therapy is particularly helpful in those with severe disease or recurrent disease, or in those where topical therapies have failed. Maintenance therapy with selenium sulfide shampoo or ketoconazole 2% shampoo once a week may be used.

Dermatophytoses

Dermatophytoses are caused by a group of closely related filamentous fungi with a propensity for invading the stratum corneum, hair, and nails. The 3 principal genera responsible for infections are *Trichophyton, Microsporum*, and *Epidermophyton.*

Etiology

Trichophyton spp. cause lesions of all keratinized tissue, including skin, nails, and hair. *Trichophyton rubrum* is the most common dermatophyte pathogen. *Microsporum* spp. principally invade the hair, and the *Epidermophyton* spp. invade the intertriginous skin. Dermatophyte infections are designated by the word **tinea** followed by the Latin word for the anatomic site of involvement. The dermatophytes are also classified according to source and natural habitat. Fungi acquired from the soil are called *geophilic* . They infect humans sporadically, inciting an inflammatory reaction. Dermatophytes that are acquired from animals are *zoophilic* . Transmission may be through direct contact or indirectly by infected animal hair or clothing. Infected animals are frequently asymptomatic. Dermatophytes acquired from humans are referred to as *anthropophilic* . These infestations range from chronic low-grade to acute inflammatory disease. *Epidermophyton* infections are transmitted only by humans, but various species of *Trichophyton* and *Microsporum* can be acquired from both human and nonhuman sources.

Epidemiology

Host defense has an important influence on the severity of the infection. Disease tends to be more severe in individuals with diabetes mellitus, lymphoid malignancies, immunosuppression, and states with high plasma cortisol levels, such as Cushing syndrome. Some dermatophytes, most notably the zoophilic species, tend to elicit more severe, suppurative inflammation in humans. Some degree of resistance to reinfection is acquired by most infected persons and may be associated with a delayed hypersensitivity response. However, no relationship has been demonstrated between antibody levels and resistance to infection. The frequency and severity of infection are also affected by the geographic locale, the genetic susceptibility of the host, and the virulence of the strain of dermatophyte. Additional local factors that predispose to infection include trauma to the skin, hydration of the skin with maceration, occlusion, and elevated temperature.

Occasionally, a secondary skin eruption, referred to as a dermatophytid or “id” reaction, appears in sensitized individuals and has been attributed to circulating fungal antigens derived from the primary infection. The eruption is characterized by grouped papules (Fig. 686.2) and vesicles and, occasionally, by sterile pustules. Symmetric urticarial lesions and a more generalized maculopapular eruption also can occur. Id reactions are most often associated with tinea pedis but they also occur with tinea capitis.

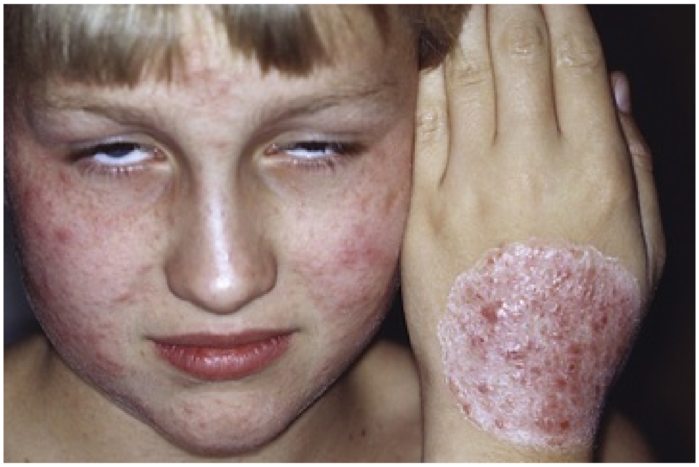

FIG. 686.2 **Id reaction. Papular eruption of the face associated with severe tinea infection of the hand.**

Tinea Capitis

Clinical Manifestations

Tinea capitis is a dermatophyte infection of the scalp most often caused by *Trichophyton tonsurans*, occasionally by *Microsporum canis* , and, much less commonly, by other *Microsporum* and *Trichophyton* spp. It is particularly common in black children age 4-14 yr. In *Microsporum* and some *Trichophyton* infections, the spores are distributed in a sheath-like fashion around the hair shaft (**ectothrix** infection), whereas *T. tonsurans* produces an infection within the hair shaft (endothrix). **Endothrix** infections may continue past the anagen phase of hair growth into telogen and are more chronic than infections with ectothrix organisms that persist only during the anagen phase. *T. tonsurans* is an anthropophilic species acquired most often by contact with infected hairs and epithelial cells that are on such surfaces as theater seats, hats, and combs. Dermatophyte spores may also be airborne within the immediate environment, and high carriage rates have been demonstrated in noninfected schoolmates and household members. *M. canis* is a zoophilic species that is acquired from cats and dogs.

The clinical presentation of tinea capitis varies with the infecting organism. Endothrix infections such as those caused by *T. tonsurans* create a pattern known as “black-dot ringworm,” characterized initially by many small circular patches of alopecia in which hairs are broken off close to the hair follicle (Fig. 686.3). Another clinical variant manifests as diffuse scaling, with minimal hair loss secondary. It strongly resembles seborrheic dermatitis, psoriasis, or atopic dermatitis (Fig. 686.4). *T. tonsurans* may also produce a chronic and more diffuse alopecia. Lymphadenopathy is common (Fig. 686.5). A severe inflammatory response produces elevated, boggy granulomatous masses (**kerion**), which are often studded with pustules (Fig. 686.6*A*). Fever, pain, and regional adenopathy are common, and permanent scarring and alopecia may result (see Fig. 686.6*B*). The zoophilic organism *M. canis* or the geophilic organism *Microsporum gypseum* also may cause kerion formation. The pattern produced by *Microsporum audouinii* , the most common cause of tinea capitis in the 1940s and 1950s, is characterized initially by a small papule at the base of a hair follicle. The infection spreads peripherally, forming an erythematous and scaly circular plaque (**ringworm**) within which the infected hairs become brittle and broken. Numerous confluent patches of alopecia develop, and patients may complain of severe pruritus. *M. audouinii* infection is no longer common in the United States. **Favus** is a chronic form of tinea capitis that is rare in the United States and is caused by the fungus *Trichophyton schoenleinii*. Favus starts as yellowish red papules at the opening of hair follicles. The papules expand and coalesce to form cup-shaped, yellowish, crusted patches that fluoresce dull green under a Wood lamp.

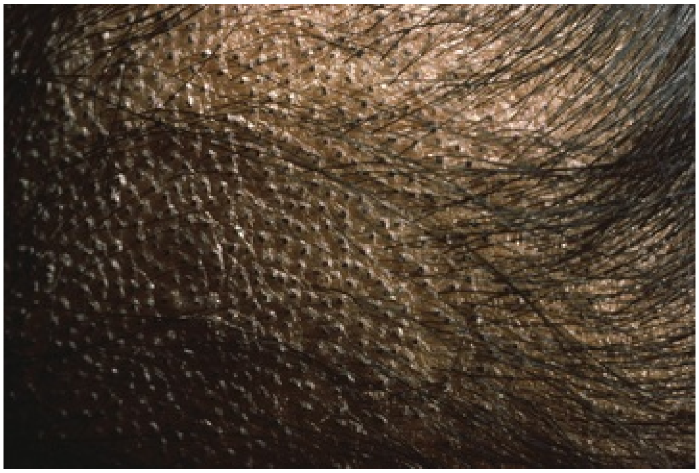

FIG. 686.3 **Black-dot ringworm with hairs broken off at the scalp.**

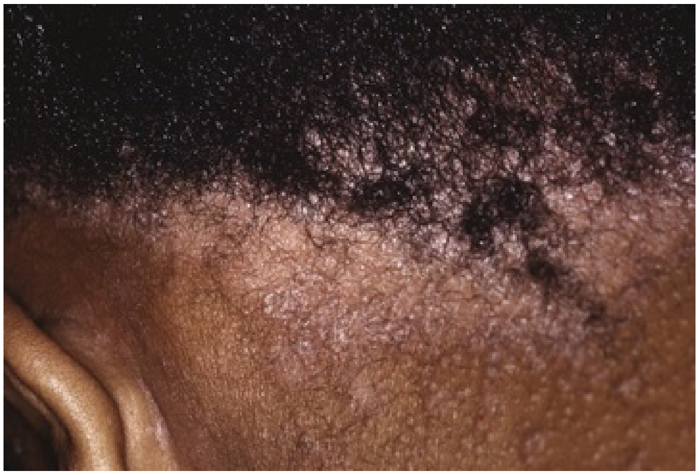

FIG. 686.4 Tinea capitis mimicking seborrheic dermatitis.

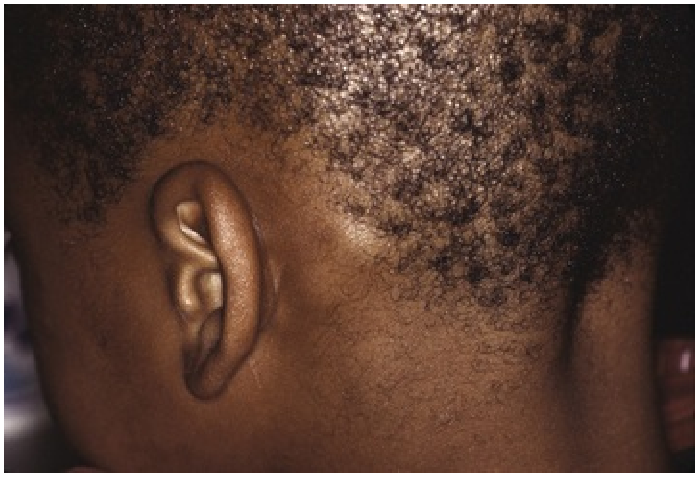

FIG. 686.5 Lymphadenopathy associated with tinea capitis.

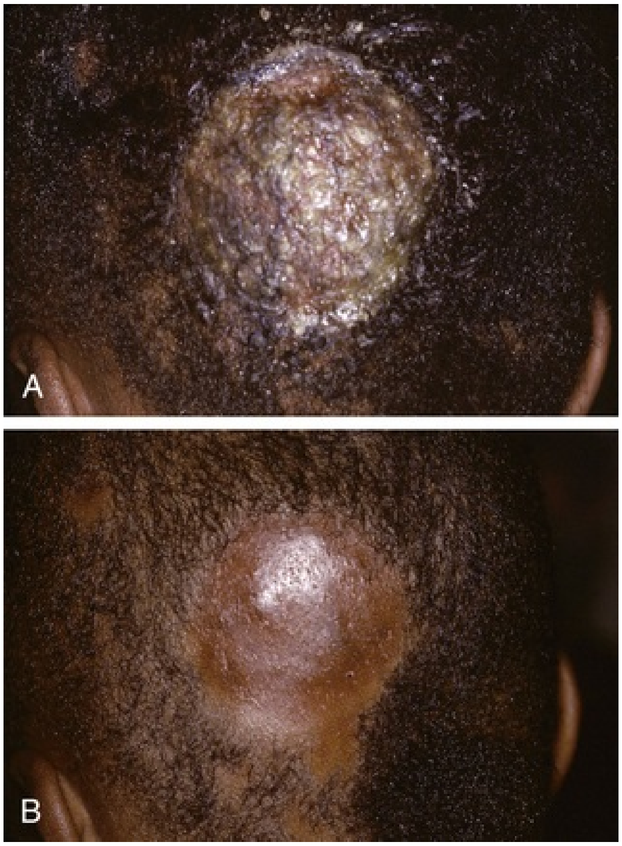

FIG. 686.6 **A,** Kerion. Boggy granulomatous mass of the scalp. **B,** Scarring after kerion.

Differential Diagnosis

Tinea capitis can be confused with seborrheic dermatitis, psoriasis, alopecia areata, trichotillomania, and certain dystrophic hair disorders. When inflammation is pronounced, as in kerion, primary or secondary bacterial infection must also be considered. In adolescents, the patchy, moth-eaten type of alopecia associated with secondary syphilis may resemble tinea capitis. If scarring occurs, discoid lupus erythematosus and lichen planopilaris must also be considered in the differential diagnosis.

The important diagnostic procedures for the various dermatophyte diseases include examination of infected hairs with a Wood lamp, microscopic examination of KOH preparations of infected material, and identification of the etiologic agent by culture. Hairs infected with common *Microsporum* spp. fluoresce a bright blue-green. Most *Trichophyton* -infected hairs do not fluoresce.

Microscopic examination of a KOH preparation of infected hair from the active border of a lesion discloses tiny spores surrounding the hair shaft in *Microsporum* infections and chains of spores within the hair shaft in *T. tonsurans* infections. Fungal elements are not usually seen in scales. A specific etiologic diagnosis of tinea capitis may be obtained by planting broken-off infected hairs on Sabouraud medium with reagents to inhibit growth of other organisms. Such identification may require 2 wk or more.

Treatment

Oral administration of griseofulvin microcrystalline (20-25 mg/kg/day with a maximum daily dose of 1000 mg, or 10-15 mg/kg/day with a maximum daily dose of 750 mg if the ultramicrosize form is used) is the recommended treatment for all forms of tinea capitis. Absorption of griseofulvin is enhanced by the ingestion of a fatty meal and should be recommended for the patient. A minimum of 8 wk of treatment is usually required, though longer courses are sometimes needed. Repeat fungal cultures may help guide treatment length. Treatment for 1 mo after a negative culture result minimizes the risk of recurrence. Adverse reactions to griseofulvin are rare but include nausea, vomiting, headache, blood dyscrasias, phototoxicity, and hepatotoxicity. Terbinafine is also effective at a dosage of 3-6 mg/kg/24 hr for 4-6 wk or possibly in pulse therapy, although it has limited activity against *M. canis*. The oral granules formulation of terbinafine is approved by the U.S. Food and Drug Administration (FDA) for tinea capitis in children 4 yr of age and older. Oral itraconazole is useful in instances of griseofulvin resistance, intolerance, or allergy. Itraconazole is given for 4-6 wk at a dosage of 3-5 mg/kg/24 hr with food. Capsules are preferable to the syrup, which may cause diarrhea. Itraconazole is not approved by the FDA for treatment of dermatophyte infections in the pediatric population. Topical therapy alone is ineffective, but it may be an important adjunct because it may decrease the shedding of spores, and should be recommended in all patients. Asymptomatic dermatophyte carriage in family members is common. Because 1 in 3 families have at least 1 member who is a carrier, treatment of both patient and potential carriers with a sporicidal shampoo may hasten clinical resolution. Vigorous shampooing with a 2.5% selenium sulfide, zinc pyrithione, or ketoconazole shampoo is helpful. It is not necessary to shave the scalp.

Tinea Corporis

Clinical Manifestations

Tinea corporis, defined as infection of the glabrous skin, excluding the palms, soles, and groin, can be caused by most of the dermatophyte species, although *T. rubrum* and *Trichophyton mentagrophytes* are the most prevalent etiologic organisms. In children, infections with *M. canis* are also common. Tinea corporis can be acquired by direct contact with infected persons or by contact with infected scales or hairs deposited on environmental surfaces. *M. canis* infections are usually acquired from infected pets.

The most typical clinical lesion begins as a dry, mildly erythematous, elevated, scaly papule or plaque that spreads centrifugally and clears centrally to form the characteristic annular lesion responsible for the designation of ringworm (Fig. 686.7). At times, plaques with advancing borders may spread over large areas. Grouped pustules are another variant. Most lesions clear spontaneously within several months, but some may become chronic. Central clearing does not always occur (Fig. 686.8), and differences in host response may result in wide variability in the clinical appearance; for example, granulomatous lesions called **Majocchi granuloma,** which are caused by the penetration of organisms along the hair follicle to the level of the dermis, produce a fungal folliculitis and perifolliculitis (Fig. 686.9), and the kerion-like lesions referred to as tinea profunda. Majocchi granuloma is more common after inappropriate treatment with topical corticosteroids, especially the superpotent class.

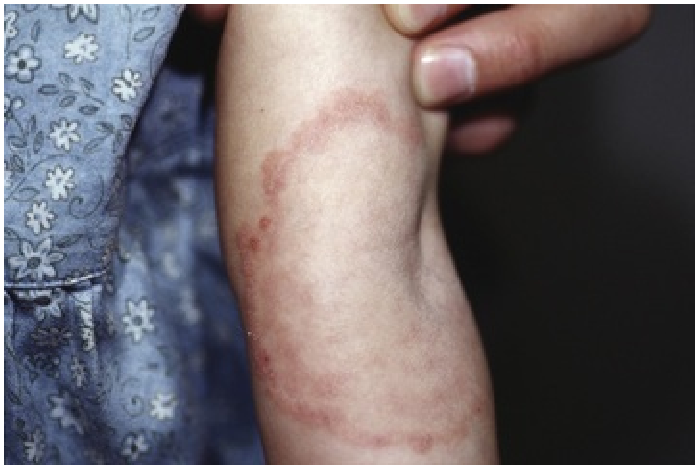

FIG. 686.7 **Annular plaque of tinea corporis with central clearing.**

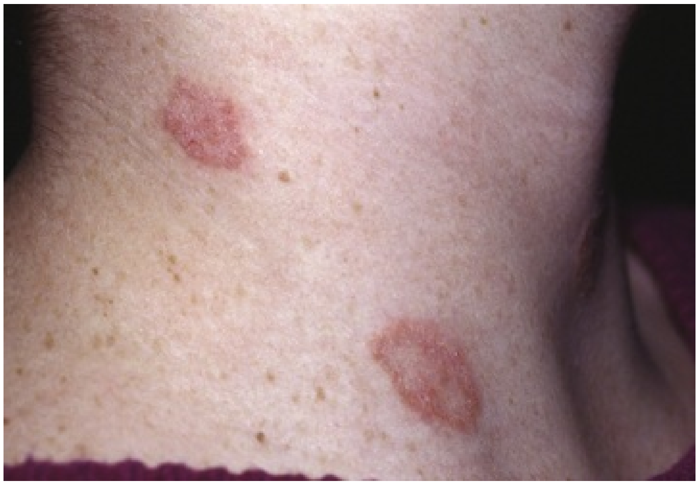

FIG. 686.8 Minimal central clearing with tinea corporis.

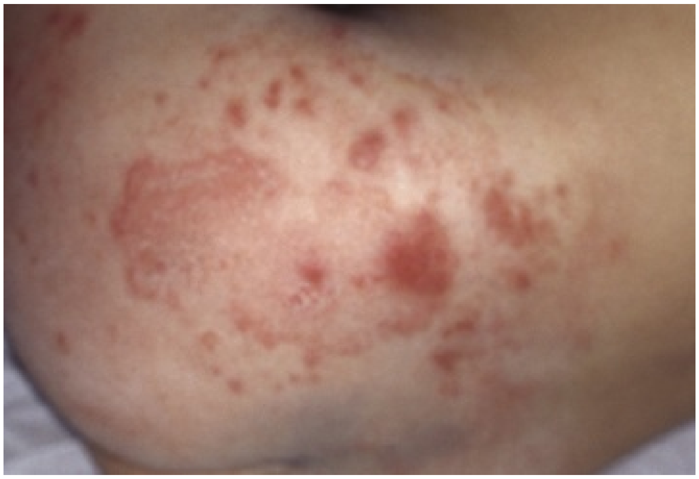

FIG. 686.9 Follicular papule and pustule in Majocchi granuloma after use of a superpotent topical steroid.

Differential Diagnosis

Many skin lesions, both infectious and noninfectious, must be differentiated from the lesions of tinea corporis. Those most frequently confused are granuloma annulare, nummular eczema, pityriasis rosea, psoriasis, seborrheic dermatitis, erythema chronicum migrans, and tinea versicolor. Microscopic examination of KOH wet mount preparations and cultures should always be performed when fungal infection is considered. Tinea corporis usually does not fluoresce with a Wood lamp.

Treatment

Tinea corporis usually responds to treatment with one of the topical antifungal agents (e.g., imidazoles, terbinafine, butenafine, naftifine) twice daily for 2-4 wk. In unusually severe or extensive disease, a course of therapy with oral griseofulvin microcrystalline may be required for 4 wk. Terbinafine for 2 wk can also be used. Itraconazole has produced excellent results in many cases with a 1-2 wk course of oral therapy. Combination topical corticosteroid/antifungal preparations should not be used as they may result in worsening or persistent infection.

Tinea Cruris

Clinical Manifestations

Tinea cruris, or infection of the groin, occurs most often in adolescent males and is usually caused by the anthropophilic species *Epidermophyton floccosum* or *T. rubrum*, but occasionally by the zoophilic species *T. mentagrophytes*.

The initial clinical lesion is a small, raised, scaly, erythematous patch on the inner aspect of the thigh. This spreads peripherally, often developing numerous tiny vesicles at the advancing margin. It eventually forms bilateral, irregular, sharply bordered patches with hyperpigmented scaly centers. In some cases, particularly in infections with *T. mentagrophytes*, the inflammatory reaction is more intense and the infection may spread beyond the crural region. The scrotum and labia are usually not involved in the infection, which is an important distinction from candidosis. Pruritus may be severe initially but abates as the inflammatory reaction subsides. Bacterial superinfection may alter the clinical appearance, and erythrasma or candidosis may coexist. Tinea cruris is more prevalent in obese persons and in persons who perspire excessively and wear tight-fitting clothing. It is a good idea to examine a patient's feet, which can be a source for tinea cruris.

Differential Diagnosis

The diagnosis of tinea cruris is confirmed by culture and by demonstration of septate hyphae on a KOH preparation of epidermal scrapings. The disorder must be differentiated from intertrigo, allergic contact dermatitis, candidosis, and erythrasma. Bacterial superinfection must be precluded when there is a severe inflammatory reaction.

Treatment

Patients should be advised to wear loose cotton underwear. Topical treatment with an imidazole twice a day for 3-4 wk is recommended for severe infection, especially because these agents are effective in mixed candidal-dermatophytic infections. Oral treatments, as mentioned earlier, may also be used.

Tinea Pedis

Clinical Manifestations

Tinea pedis (athlete's foot), infection of the toe webs and soles of the feet, is uncommon in young children but occurs with some frequency in preadolescent and adolescent males. The usual etiologic agents are *T. rubrum, T. mentagrophytes,* and *E. floccosum.*

Most commonly, the lateral toe webs (3rd to 4th and 4th to 5th interdigital spaces) and the subdigital crevice are fissured, with maceration and peeling of the surrounding skin (Fig. 686.10). Severe tenderness, itching, and a persistent foul odor are characteristic. These lesions may become chronic. This type of infection may involve overgrowth by bacterial flora, including *Kytococcus sedentarius, Brevibacterium epidermidis,* and Gram-negative organisms. Less commonly, a chronic diffuse hyperkeratosis of the sole of the foot occurs with only mild erythema (Fig. 686.11). In some cases, 2 feet and 1 hand are involved. This type of infection is more refractory to treatment and tends to recur. An inflammatory vesicular type of reaction may occur with *T. mentagrophytes* infection. This type is most common in young children. The lesions involve any area of the foot, including the dorsal surface, and are usually circumscribed. The initial papules progress to vesicles and bullae that may become pustular (Fig. 686.12). A number of factors, such as occlusive footwear and warm, humid weather, predispose to infection. Tinea pedis may be transmitted in shower facilities and swimming pool areas.

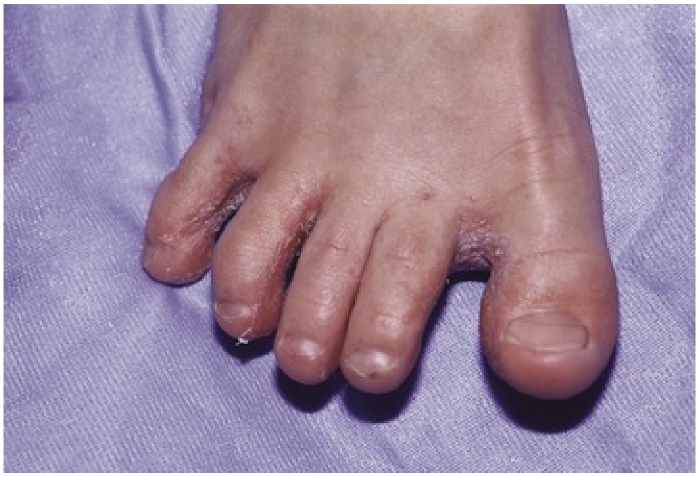

FIG. 686.10 Interdigital tinea pedis.

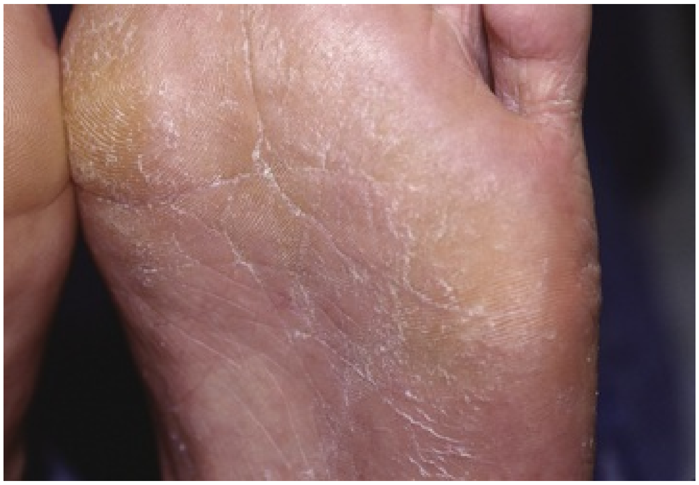

FIG. 686.11 Diffuse, minimally erythematous tinea pedis.

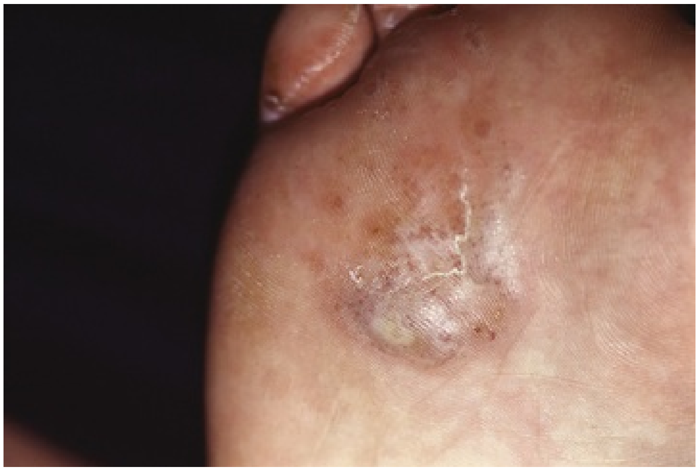

FIG. 686.12 Vesicobullous tinea pedis.

Differential Diagnosis

Tinea pedis must be differentiated from simple maceration and peeling of the interdigital spaces, which is common in children. Infection with *Candida albicans* and various bacterial organisms (erythrasma) may cause confusion or may coexist with primary tinea pedis. Contact dermatitis, vesicular foot dermatitis, atopic dermatitis, and juvenile plantar dermatitis also simulate tinea pedis. Fungal mycelia can be seen on microscopic examination of a KOH preparation or by culture.

Treatment

Treatment for mild infections includes simple measures such as avoidance of occlusive footwear, careful drying between the toes after bathing, and the use of an absorbent antifungal powder such as zinc undecylenate. Topical therapy with an imidazole is curative in most cases. Each of these agents is also effective against candidal infection. Several weeks of therapy may be necessary, and low-grade, chronic infections, particularly those caused by *T. rubrum* , may be refractory. In refractory cases, oral griseofulvin therapy may effect a cure, but recurrences are common.

Tinea Unguium

Clinical Manifestations

Tinea unguium (onychomycosis) is a dermatophyte infection of the nail plate. It occurs most often in patients with tinea pedis, but it may occur as a primary infection. It can be caused by a number of dermatophytes, of which *T. rubrum* and *T. mentagrophytes* are the most common.

The most superficial form of tinea unguium (i.e., white superficial onychomycosis) is caused by *T. mentagrophytes*. It manifests as irregular single or numerous white patches on the surface of the nail unassociated with paronychial inflammation or deep infection. *T. rubrum* generally causes a more invasive, subungual infection that is initiated at the lateral distal margins of the nail and is often preceded by mild paronychia. The middle and ventral layers of the nail plate, and perhaps the nail bed, are the sites of infection. The nail initially develops a yellowish discoloration and slowly becomes thickened, brittle, and loosened from the nail bed (Fig. 686.13). In advanced infection, the nail may turn dark brown to black and may crack or break off.

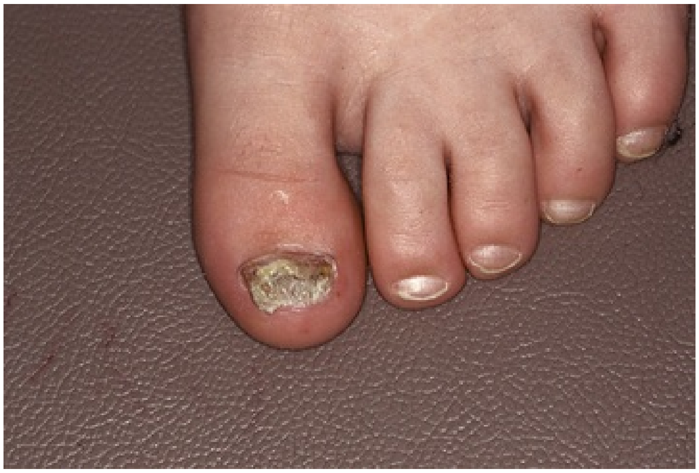

FIG. 686.13 **Hyperkeratotic nail in onychomycosis.**

Differential Diagnosis

Tinea unguium must be differentiated from various dystrophic nail disorders. Changes as a result of trauma, psoriasis, lichen planus, eczema, and trachyonychia can all be confused with tinea unguium. Nails infected with *C. albicans* have several distinguishing features; most prominently, a pronounced paronychial swelling. Thin shavings taken from the infected nail, preferably from the deeper areas, should be examined microscopically with KOH and cultured. Repeated attempts may be required to demonstrate the fungus.

Histologic evaluation of nail clippings with special stains for dermatophytes can be diagnostic.

Treatment

Systemic antifungals are more effective at treating onychomycosis than topical antifungals. The long half-life of itraconazole in the nail has led to promising trials of intermittent short courses of therapy (double the normal dose for 1 wk of each month for 3-4 mo). Oral terbinafine is also used for the treatment of onychomycosis. Terbinafine once daily for 12 wk is more effective than itraconazole pulse therapy. Pulse terbinafine treatment has also been used in adults and has been effective. Topical antifungals may be an acceptable treatment for mild disease without matrix involvement. Several topical agents have been FDA approved for the treatment of onychomycosis in adults including ciclopirox, efinaconazole, and tavaborole. Small clinical trials have demonstrated efficacy of ciclopirox in children. The safety and efficacy of efinaconazole and tavaborole have not yet been established in children.

Tinea Nigra Palmaris

Tinea nigra palmaris is a rare but distinctive superficial fungal infection that occurs principally in children and adolescents. It is caused by the dimorphic fungus *Phaeoannellomyces werneckii,* which imparts a gray-black color to the affected palm. The characteristic lesion is a well-defined hyperpigmented macule. Scaling and erythema are rare, and the lesions are asymptomatic. Tinea nigra is often mistaken for a junctional nevus, melanoma, or staining of the skin by contactants. Treatment is with an imidazole antifungal. *Keratolytic agents, such as salicylic acid, once to twice daily* can also be used.

Candidal Infections (Candidosis, Candidiasis, and Moniliasis)

See Chapter 261 .

The dimorphic yeasts of the genus *Candida* are ubiquitous in the environment, but *C. albicans* usually causes candidosis in children. This yeast is not part of the indigenous skin flora, but it is a frequent transient on skin and may colonize the human alimentary tract and the vagina as a saprophytic organism. Certain environmental conditions, notably elevated temperature and humidity, are associated with an increased frequency of isolation of *C. albicans* from the skin. Many bacterial species inhibit the growth of *C. albicans*, and alteration of normal flora by the use of antibiotics may promote overgrowth of the yeast.

Chronic mucocutaneous candidiasis is associated with a diverse group of primary immunodeficiency diseases (Table 686.1). Chronic mucocutaneous candidiasis is characterized by chronic or recurrent *Candida* infections of the oral cavity, esophagus, genitals, nails, and skin. Chronic mucocutaneous candidiasis may also be seen as an acquired infection in patients with HIV infection, and during immunosuppressive treatments.

Table 686.1

Primary Immunodeficiencies Underlying Fungal Infections

DISEASE	ASSOCIATED INFECTIONS	IMMUNOLOGIC PHENOTYPE	GENE, TRANSMISSION
CMC			
SCID	Bacteria, viruses, fungi, mycobacteria	No T cells, with or without B and/or NK cell lymphopenia	>30 genes: *IL2RG*, X-linked; *JAK3*, autosomal recessive; RAG1, autosomal recessive; *RAG2*, autosomal recessive; *ARTEMIS*, autosomal recessive; *ADA*, autosomal recessive; *CD3*, autosomal recessive, etc.
CID			
CD25 deficiency	Viruses and bacteria	T cell defect	*IL2RA*, autosomal recessive
NEMO or iκBγ deficiency	Pyogenic bacteria, mycobacteria, viruses		*NEMO* or *IKBG* X-linked
IκBα GOF mutation			*IKBA*, autosomal dominant
DOCK8 deficiency	Viruses, bacteria and fungi		*DOCK8*, autosomal recessive
TCR-α deficiency	Viruses and bacteria		*TCRA*, autosomal recessive
CRACM1 deficiency	Viruses, mycobacteria, bacteria and fungi		*CRACM1*, autosomal recessive
MST1/STK4 deficiency	Viruses and bacteria		*MST1/STK4*, autosomal recessive
MHC class II deficiency	Viruses, bacteria and fungi		*CIITA*, *RFXANK*, *RFXC*, *RFXAP*, all autosomal recessive
Idiopathic CD4	*Pneumocystis*,	CD4 T cells <300	*UNC119*, autosomal dominant, *MAGT1* X-linked,

lymphopenia	*Cryptococcus* , virus	cells/mm^3	*RAG1*, autosomal recessive
SYNDROMIC CMC			
Interleukin-12Rβ1 and interleukin-12p40 deficiencies	*Mycobacteria, Salmonella*	Deficit of interleukin-17–producing T cells	*IL12RB1*, autosomal recessive, *IL12B*, autosomal recessive
STAT3 deficiency (autosomal dominant-HIES)	*Staphylococcus aureus, Aspergillus*	Hyperimmunoglobulin E, deficit of interleukin-17–producing T cells	*STAT3*, autosomal dominant
APECED/APS-1	No	Neutralizing antiinterleukin-17A, antiinterleukin-17F, and/or antiinterleukin-22 autoantibodies	*AIRE*, autosomal recessive
CARD9 deficiency	Dermatophytes, *Candida* , brain abscess	Deficit of interleukin-17–producing T cells	*CARD9*, autosomal recessive
CMCD			
Complete interleukin-17RA deficiency	*S. aureus*	No interleukin-17 response	*IL17RA*, autosomal recessive
Partial interleukin-17F deficiency	*S. aureus*	Impaired interleukin-17F, interleukin-17A/F function	*IL17F*, autosomal dominant
STAT1 GOF mutations	Bacteria, viruses, fungi, mycobacteria	Low interleukin-17–producing T cells	*STAT1*, autosomal dominant

CMC, chronic mucocutaneous candidiasis; SCID, severe combined immunodeficiency; NK, natural killer; CID, combined immunodeficiency; NEMO, nuclear factor κB essential modulator; iκBγ, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B-cells, gamma; IκBα, inhibitor of nuclear factor of kappa light polypeptide gene enhancer in B-cells, alpha; GOF, gain-of-function; DOCK8, dedicator of cytokinesis 8; TCR, T-cell receptor; CRACM1, calcium release-activated calcium modulator 1; MST1, macrophage stimulating 1; STK4, serine/threonine protein kinase 4; MHC, major histocompatibility complex; STAT, signal transducer and activator of transcription; HIES, hyperimmunoglobulin E syndrome; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APS-1, autoimmune polyendocrinopathy syndrome type 1; AIRE, autoimmune regulator; CARD9, caspase recruitment domain-containing protein 9; CMCD, chronic mucocutaneous candidiasis disease.

From Lanternier F, Cypowyj S, Picard, C, et al: Primary immunodeficiencies underlying fungal infections. *Curr Opin Pediatr* 25:736–747, 2013.

Oral Candidiasis (Thrush)

See Chapter 261 .

Vaginal Candidiasis

See Chapters 146 and 261 .

C. albicans is an inhabitant of the vagina in 5–10% of women, and vaginal candidosis is not uncommon in adolescent girls. A number of factors can predispose to this infection, including antibiotic therapy, corticosteroid therapy, diabetes mellitus, pregnancy, and the use of oral contraceptives. The infection manifests as cheesy white plaques on an erythematous vaginal mucosa and a thick white-yellow discharge. The disease may be relatively mild or may produce pronounced inflammation and scaling of the external genitals and surrounding skin with progression to vesiculation and ulceration. Patients often complain of severe itching and burning in the vaginal area. Before treatment is initiated, the diagnosis should be confirmed by microscopic examination and/or culture. The infection may be eradicated by insertion of nystatin or imidazole vaginal tablets, suppositories, creams, or foam. If these products are ineffective, the addition of one dose of fluconazole (150 mg) is effective.

Congenital Cutaneous Candidiasis

See Chapter 261 .

Candidal Diaper Dermatitis

Candidal diaper dermatitis is a ubiquitous problem in infants and, although relatively benign, is often frustrating because of its tendency to recur. Predisposed infants usually carry *C. albicans* in their intestinal tracts, and the warm, moist, occluded skin of the diaper area provides an optimal environment for its growth. A seborrheic, atopic, or primary irritant contact dermatitis usually provides a portal of entry for the yeast.

The primary clinical manifestation consists of an intensely erythematous, confluent plaque with a scalloped border and a sharply demarcated edge. It is formed by the confluence of numerous papules and vesicular pustules. Satellite pustules, those that stud the contiguous skin, are a hallmark of localized candidal infections. The perianal skin, inguinal folds, perineum, and lower abdomen are usually involved (Fig. 686.14). In males, the entire scrotum and penis may be involved, with an erosive balanitis of the perimeatal skin. In females, the lesions may be found on the vaginal mucosa and labia. In some infants, the process is generalized, with erythematous lesions distant from the diaper area. In some cases, the generalized process may represent a fungal id (hypersensitivity) reaction.

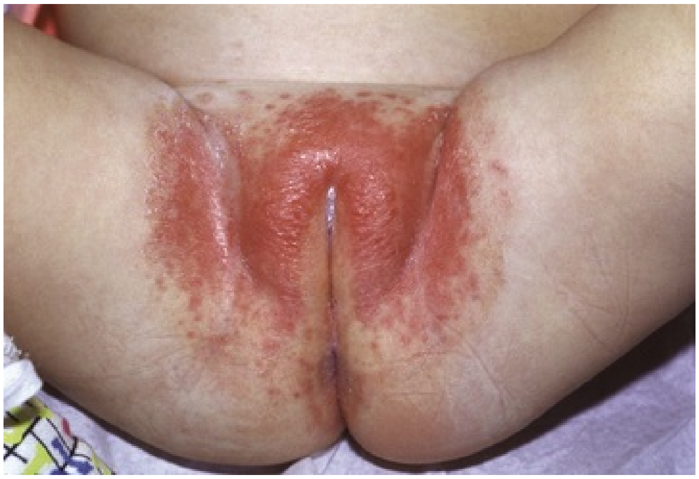

FIG. 686.14 Erythematous confluent plaque caused by candidal infection.

The differential diagnosis of candidal diaper dermatitis includes other eruptions of the diaper area that may coexist with candidal infection. For this reason, it is important to establish a diagnosis by means of KOH preparation or culture.

Treatment consists of applications of an imidazole cream 2 times daily. The combination of a corticosteroid and an antifungal agent may be justified if inflammation is severe but may confuse the situation if the diagnosis is not firmly established. Corticosteroid should not be continued for more than a few days. Protection of the diaper area by an application of thick zinc oxide paste overlying the anticandidal preparation may be helpful. The paste is more easily removed with mineral oil than with soap and water. Fungal id reactions gradually abate with successful treatment of the diaper dermatitis or may be treated with a mild corticosteroid preparation. When recurrences of diaper candidiasis are frequent, it may be helpful to prescribe a course of oral anticandidal therapy to decrease the yeast population in the gastrointestinal tract. Some infants seem to be receptive hosts for *C. albicans* and may reacquire the organism from a colonized adult.

Intertriginous Candidiasis

Intertriginous candidiasis occurs most often in the axillae and groin, on the neck (Fig. 686.15) under the breasts, under pendulous abdominal fat folds, in the umbilicus, and in the gluteal cleft. Typical lesions are large, confluent areas of moist, denuded, erythematous skin with an irregular, macerated, scaly border. Satellite lesions are characteristic and consist of small vesicles or pustules on an erythematous base. With time, intertriginous candidal lesions may become lichenified, dry, scaly plaques. The lesions develop on skin subjected to irritation and maceration. Candidal superinfection is more likely to occur under conditions that lead to excessive perspiration, especially in obese children and in children with underlying disorders, such as diabetes mellitus. A similar condition, interdigital candidiasis, commonly occurs in individuals whose hands are constantly immersed in water. Fissures occur between the fingers and have red denuded centers, with an overhanging white epithelial fringe. Similar lesions between the toes may be secondary to occlusive footwear. Treatment is the same as for other candidal infections.

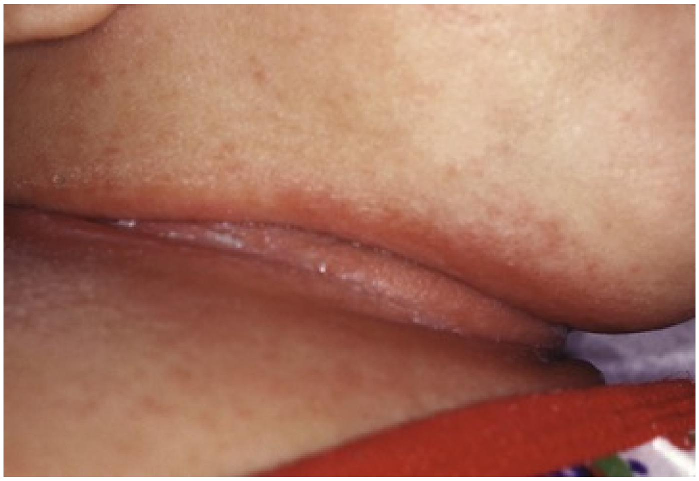

FIG. 686.15 **Intertriginous candidosis of the neck.**

Perianal Candidiasis

Perianal dermatitis develops at sites of skin irritation as a result of occlusion, constant moisture, poor hygiene, anal fissures, and pruritus from pinworm infestation. It may become superinfected with *C. albicans*, especially in children who are receiving oral antibiotic or corticosteroid medication. The involved skin becomes erythematous, macerated, and excoriated, and the lesions are identical to those of candidal intertrigo or candidal diaper rash. Application of a topical antifungal agent in conjunction with improved hygiene is usually effective. Underlying disorders such as pinworm infection must also be treated (see Chapter 319).

Candidal Paronychia and Onychia

See Chapter 683 .

Candidal Granuloma

Candidal granuloma is a rare response to an invasive candidal infection of skin. The lesions appear as crusted, verrucous plaques and hornlike projections on the scalp, face, and distal limbs. Affected patients may have single or numerous defects in immune mechanisms, and the granulomas are often refractory to topical therapy. A systemic anticandidal agent may be required for palliation or eradication of the infection.

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CHAPTER 687

Cutaneous Viral Infections

Daren A. Diiorio, Stephen R. Humphrey

Wart (Verruca)

Etiology

Human papillomaviruses (HPVs) cause a spectrum of disease from warts (verrucae vulgaris) to squamous cell carcinoma of the skin and mucous membranes, including the larynx (see Chapter 417.2). The HPVs are classified by genus, species, and type. More than 200 types are known, and the entire genomes of approximately 100 are completely sequenced. The incidence of all types of warts is highest in children and adolescents. HPV is spread by direct contact and autoinoculation; transmission within families and by fomites occurs. The clinical manifestations of infection develop 1 mo or longer after inoculation and depend on the HPV type, the size of the inoculum, the immune status of the host, and the anatomic site.

Clinical Manifestations

Cutaneous warts develop in 5–10% of children. **Common warts** (verruca vulgaris), caused most commonly by HPV types 2 and 4, occur most frequently on the fingers, dorsum of the hands (Fig. 687.1), paronychial areas, face, knees, and elbows. They are well-circumscribed papules with an irregular, roughened, keratotic surface. When the surface is pared away, many black dots representing thrombosed dermal capillary loops are often visible. **Periungual warts** are often painful and may spread beneath the nail plate, separating it from the nail bed (Fig. 687.2). **Plantar warts (verruca plantaris),** although similar to the common wart, are caused by HPV type 1 and are usually flush with the surface of the sole because of the constant pressure from weight bearing. When plantar warts become hyperkeratotic (Fig. 687.3), they may be painful. Similar lesions (palmar–verruca palmaris) can also occur on the palms. They are sharply demarcated, often with a ring of thick callus. The surface keratotic material must sometimes be removed before the boundaries of the wart can be appreciated. Several contiguous warts (HPV type 4) may fuse to form a large plaque, the so-called mosaic wart. **Flat warts (verruca plana),** caused by HPV types 3 and 10, are slightly elevated, minimally hyperkeratotic papules that usually remain <3 mm in diameter and vary in color from pink to brown. They may occur in profusion on the face, arms, dorsum of the hands, and knees. The distribution of several lesions along a line of cutaneous trauma (Koebnerization) is a helpful diagnostic feature (Fig. 687.4). Lesions may be disseminated in the beard area and on the legs by shaving and from the hairline onto the scalp by combing the hair. **Epidermodysplasia verruciformis** (*EVER1*, *EVER2* genes), caused primarily by HPV types 5 and 8 (β-papillomaviruses, species 1), manifests as many diffuse verrucous papules. Wart types 9, 12, 14, 15, 17, 25, 36, 38, 47, and 50 may also be involved. Inheritance is thought to be primarily autosomal recessive, but an X-linked recessive form also has been postulated. Warts progress to **squamous cell carcinoma** in 10% of patients with epidermodysplasia verruciformis.

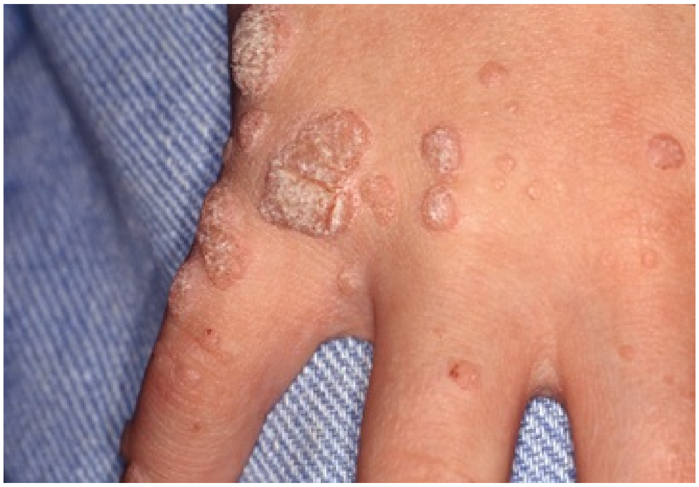

FIG. 687.1 Verrucous papules on the back of the hand.

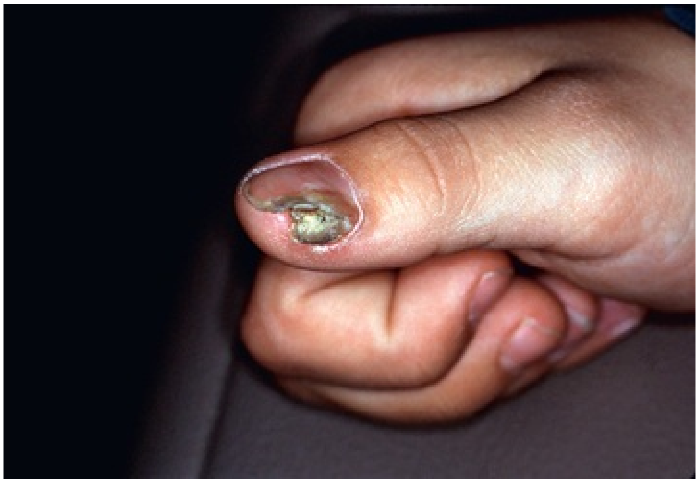

FIG. 687.2 Periungual wart with disruption of nail growth.

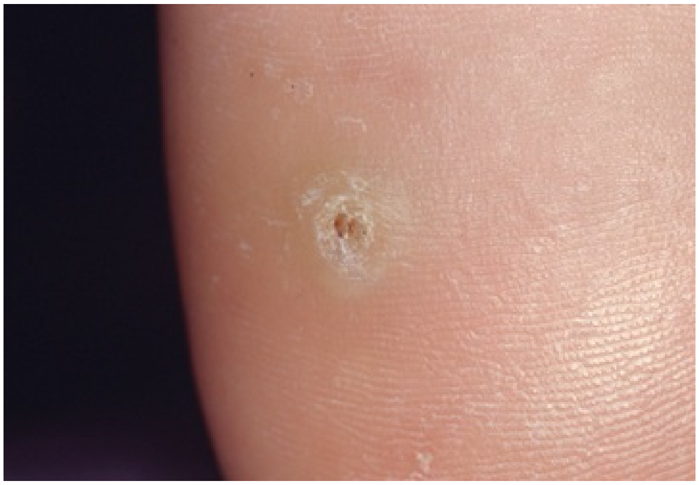

FIG. 687.3 Hyperkeratotic plantar wart.

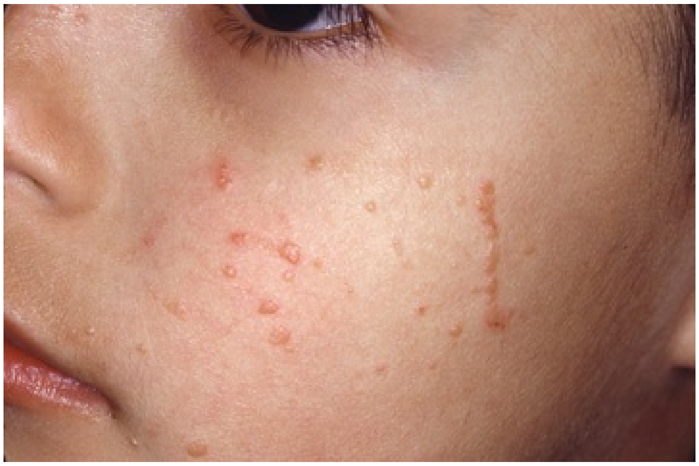

FIG. 687.4 **Multiple flat warts on the face with lesions in line of trauma.**

Genital HPV infection occurs in sexually active adolescents, most commonly as a result of infection with HPV types 6 and 11. **Condylomata acuminata** (mucous membrane warts) are moist, fleshy, papillomatous lesions that occur on the perianal mucosa (Fig. 687.5), labia, vaginal introitus, and perineal raphe, and on the shaft, corona, and glans penis. Occasionally, they obstruct the urethral meatus or the vaginal introitus. Because they are located in intertriginous areas, they may become moist and friable. When untreated, condylomata proliferate and become confluent, at times forming large cauliflower-like masses. Lesions can also occur on the lips, gingivae, tongue, and conjunctivae. Genital warts in children may occur after inoculation during birth through an infected birth canal, as a consequence of sexual abuse, or from incidental spread from cutaneous warts. A significant proportion of genital warts in children contain HPV types that are usually isolated from cutaneous warts. HPV infection of the cervix is a major risk factor for the development of carcinoma, particularly if the infection is caused by HPV type 16, 18, 31, 33, 35, 39, 45, 52, 59, 67, 68, or 70. Immunization against types 6, 11, 16, and 18 is available (see Chapter. 417.2). Laryngeal (respiratory) papillomas contain the same HPV types as in anogenital papillomas. Transmission is believed to occur from mothers with a genital HPV infection to neonates who aspirate infectious virus during birth and may develop laryngeal papillomatosis.

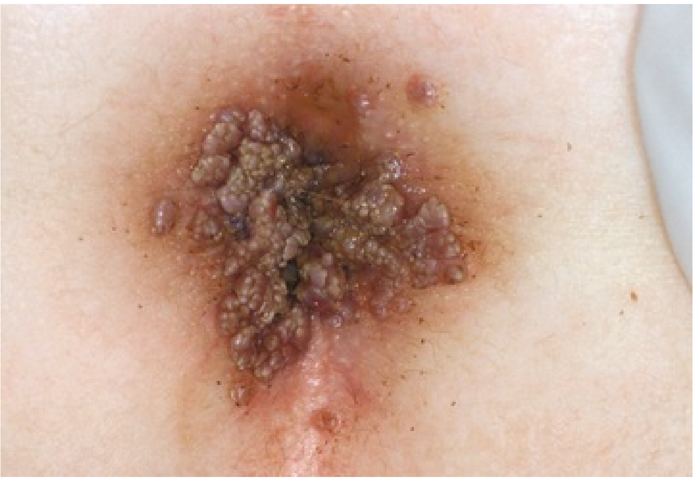

FIG. 687.5 **Condylomata acuminata in the perianal area of a toddler.**

Histology

The various types of warts share the basic changes of hyperplasia of the epidermal cells and vacuolation of the spinous keratinocytes, which may contain basophilic intranuclear inclusions (viral particles). Warts are confined to the epidermis and do not have “roots.” Individuals with impaired cell-mediated immunity are particularly susceptible to HPV infection. Antibodies occur in response to infection but appear to have little protective effect.

Differential Diagnosis

Common warts are most often confused with molluscum contagiosum. Plantar and palmar warts may be difficult to distinguish from punctate keratoses, corns, and calluses. In contrast to calluses, warts obliterate normal skin markings. Juvenile flat warts mimic lichen planus, lichen nitidus, angiofibromas, syringomas, milia, and acne. Condylomata acuminata may resemble condylomata lata of secondary syphilis.

Treatment

Various therapeutic measures are effective in the treatment of warts. More than 65% of warts disappear spontaneously within 2 yr. Warts are epidermal lesions and do not produce scarring unless they are managed surgically or treated in an overly aggressive fashion. Hyperkeratotic lesions (common, plantar, and palmar warts) are more responsive to therapy if the excess keratotic debris is gently pared with a scalpel until thrombosed capillaries are apparent; further paring induces bleeding. Treatment is most successful when performed regularly and frequently (every 2-4 wk).

Common warts can be destroyed by applications of liquid nitrogen or by pulsed dye laser . Daily application of salicylic acid in flexible collodion or as a stick is a slow but painless method of removal that is effective in some patients. Plantar and palmar warts may be treated with 40% salicylic acid plasters. These should be applied for 5 days at a time with a 2-day rest period between applications. Following removal of the plaster and prolonged soaking in hot water, keratotic debris can be removed with an emery board or pumice stone. Condylomata respond best to weekly applications of 25% podophyllin in tincture of benzoin. The medication should be left on the warts for 4-6 hr and then removed by bathing. Keratinized warts near the genitalia (buttocks) do not respond to podophyllin. Imiquimod (5% cream) applied 3 times weekly is also beneficial. Imiquimod is not only indicated for genital warts, but also has been used successfully to treat warts in other locations; however, it can cause inflammation and irritation, particularly in occluded areas. For nongenital warts, imiquimod should be applied daily. Cimetidine 30-40 mg/kg/day by mouth has been used in children with multiple warts unresponsive to other treatments. Immunotherapy with intralesional candida or Trichophyton antigen may also be employed especially when lesions are numerous or resistant to other therapies. Immunotherapy is performed in clinic and multiple treatments every month (at least 3-4) are usually required. With all types of therapy, care should be taken to protect the surrounding normal skin from irritation. Other treatments include 5-fluorouracil, a chemotherapy agent, which can be helpful, particularly when used with occlusion and sometimes in combination with salicylic acid.

Molluscum Contagiosum

Etiology

The poxvirus that causes molluscum contagiosum is a large double-stranded DNA virus that replicates in the cytoplasm of host epithelial cells. The 3 types cannot be differentiated on the basis of clinical appearance, location of lesions, or a patient's age or sex. Type 1 virus causes most infections. The disease is acquired by direct contact with an infected person or from fomites and is spread by autoinoculation. Children aged 2-6 yr who are otherwise well, and individuals who are immunosuppressed, are most commonly affected. The incubation period is estimated to be 2 wk or longer.

Clinical Manifestations

Discrete, pearly, skin-colored, smooth, dome-shaped, papules vary in size from 1 to 5 mm. They typically have a central umbilication from which a plug of cheesy material can be expressed. The papules may occur anywhere on the body, but the face, eyelids, neck, axillae, and thighs are sites of predilection (Fig. 687.6). They may be found in clusters on the genitals or in the groin of adolescents and may be associated with other venereal diseases in sexually active individuals. Lesions commonly involve the genital area in children but are not acquired by sexual transmission in most cases. Mild surrounding erythema or an eczematous dermatitis may accompany the papules (Fig. 687.7). Lesions on patients with AIDS tend to be large and numerous, particularly on the face. Exuberant lesions may also be found in children with leukemia and other immunodeficiencies. Children with atopic dermatitis are susceptible to widespread involvement in areas of dermatitis. A pustular eruption at the site of individual molluscum lesions is seen (Fig. 687.8). It is not a secondary bacterial infection, but rather an immunologic reaction to the molluscum virus, and it should not be treated with antibiotics. Atrophic scars are often seen after this type of reaction.

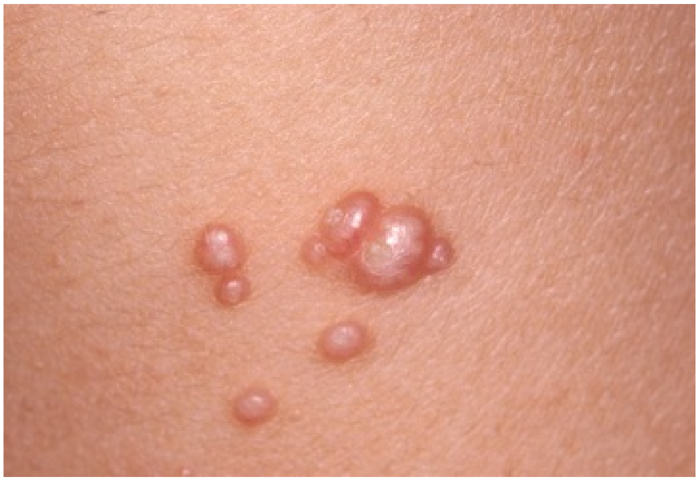

FIG. 687.6 **Grouped molluscum.**

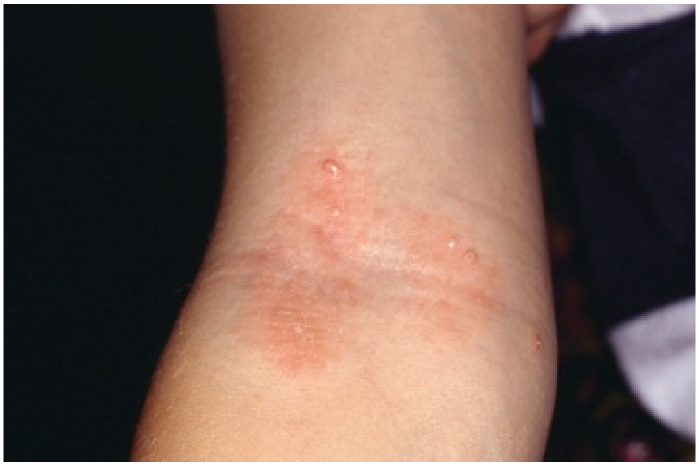

FIG. 687.7 **Molluscum with surrounding dermatitis.**

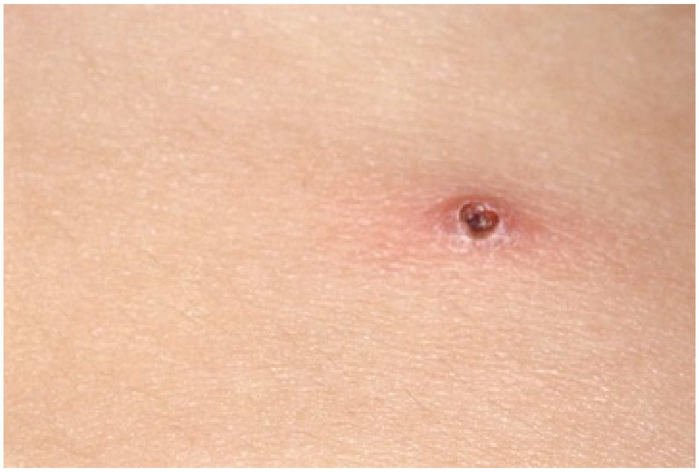

FIG. 687.8 **Inflamed molluscum. Crusted papule at the site of a previous molluscum.**

Differential Diagnosis

Differential diagnosis of molluscum contagiosum includes trichoepithelioma, basal cell carcinoma, ectopic sebaceous glands, syringoma, hidrocystoma, keratoacanthoma, juvenile xanthogranulomas, and warty dyskeratoma. In individuals with AIDS, cryptococcosis may be indistinguishable clinically from molluscum contagiosum. Rarely, coccidioidomycosis, histoplasmosis, or *Penicillium marneffei* infection masquerades as molluscum-like lesions in an immunocompromised host.

Histology

The epidermis is hyperplastic and hypertrophied, extending into the underlying dermis and projecting above the skin surface. The central plug of material, which is composed of virus-laden cells, may be shelled out from a lesion and examined under the microscope. The rounded, cup-shaped mass of homogeneous cells, often with identifiable lobules, is diagnostic. A specific antibody against molluscum contagiosum virus is detectable in most infected individuals, but it is of uncertain immunologic significance. Cell-mediated immunity is thought to be important in host defense.

Treatment

Molluscum contagiosum is a self-limited disease. The average attack lasts 6-9 mo. However, lesions can persist for years, can spread to distant sites, and may be transmitted to others. Affected patients should be advised to avoid shared baths and towels until the infection is clear. Infection may spread rapidly and produce hundreds of lesions in children with atopic dermatitis or immunodeficiency. *Immunotherapy with either candida or trichophyton antigen is the most commonly used treatment* . This is repeated every 4 wk until resolution. If lesions are limited in number, then depending on the age of the patient, individual lesions can be treated with liquid nitrogen cryotherapy. For younger children, cantharidin may be applied to the lesions and covered with adhesive bandages to prevent unwanted spread of the blistering agent. A blister forms at the site of application, and the molluscum is removed with the blister. Cantharidin should not be used on the face. Cantharidin availability is very limited or completely unavailable in the United States. Imiquimod has not been proven more effective than placebo in randomized trials. Molluscum is an epidermal disease and should not be overtreated such that scarring results.

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CHAPTER 688

Arthropod Bites and Infestations

688.1

Arthropod Bites

Daren A. Diiorio, Stephen R. Humphrey

Arthropod bites are a common affliction of children and occasionally pose a problem in diagnosis. A patient may be unaware of the source of the lesions or may deny being bitten, making interpretation of the eruption difficult. In these cases, knowledge of the habits, life cycle, and clinical signs of the more common arthropod pests of humans may help lead to a correct diagnosis (Table 688.1).

Table 688.1

Bed Bugs Versus Other Arthropod Bites: Main Clinical and Epidemiologic Features*

ARTHROPOD	CLINICAL FEATURES ON EXAMINATION	LOCATION	TIMING OF PRURITUS	CONTEXT
Bed bugs	3-4 Bites in a line or curve	Uncovered areas	Morning	Traveling
Fleas	3-4 Bites in a line or curve	Legs and buttocks	Daytime	Pet owners or rural living
Mosquitoes	Nonspecific urticarial papules	Potentially anywhere	*Anopheles* spp. night; *Culex* spp. night; *Aedes* spp. day	Worldwide distribution
Head lice	Live lice on the head associated with itchy,	Scalp, ears, and neck	Any	Children, parents, or contact with children

	scratched lesions			
Body lice	Excoriated papules and hyperpigmentation; live lice inside clothes	Back	Any	Homeless people, developing countries
Sarcoptes scabiei mites (scabies)	Vesicles, burrows, nodules, and nonspecific secondary lesions	Interdigital spaces, forearms, breasts, genitalia	Night	Sexually transmitted, households or institutions
Ticks	Erythema migrans or ulcer	Potentially anywhere	Asymptomatic	Pet owners or hikers
Pyemotes X ventricosus	Comet sign, a linear erythematous macular tract	Under clothes	Any time when inside habitat	People exposed to woodworm contaminated furniture (*Pediculoides ventricosus* is a woodworm parasite)
Spiders	Necrosis (uncommon)	Face and arms	Immediate pain, no itching	Rural living

[*] It is difficult to diagnose a bite. Diagnosis relies on an array of arguments, none of which is specific by itself; it is the association of elements that is suggestive. Any arthropod bite can be totally asymptomatic.

From Bernardeschi C, Le Cleach L, Delaunay P, Chosidow O: Bed bug infestation. *BMJ* 346:f138, 2013.

Clinical Manifestations

The type of reaction that occurs after an arthropod bite depends on the species of insect and the age group and reactivity of the human host. Arthropods may cause injury to a host by various mechanisms, including mechanical trauma, such as the lacerating bite of a tsetse fly; invasion of host tissues, as in myiasis; contact dermatitis, as seen with repeated exposure to cockroach antigens; granulomatous reaction to retained mouthparts; transmission of systemic disease; injection of irritant cytotoxic or pharmacologically active substances, such as hyaluronidase, proteases, peptidases, and phospholipases in sting venom; and induction of anaphylaxis. Most reactions to arthropod bites depend on antibody formation to antigenic substances in saliva or venom. The type of reaction is determined primarily by the degree of previous exposure to the same or a related species of arthropod. When someone is bitten for the first time, no reaction develops. An immediate petechial reaction is occasionally seen. After repeated bites, sensitivity develops, producing a pruritic papule (Fig. 688.1) approximately 24 hr after the bite. This is the most common reaction seen in young children. With prolonged, repeated exposure, a wheal develops within minutes after a bite, followed 24 hr later by papule, vesicle, or bullae formation. By adolescence or adulthood, only a wheal may form, unaccompanied by the delayed papular reaction. Thus, adults in the same household as affected children may be unaffected. Ultimately, as a person becomes insensitive to the bite, no reaction occurs at all. This stage of nonreactivity is maintained only as long as the individual continues to be bitten regularly. Individuals in whom papular urticaria develops are in the transitional phase between development of a primarily delayed papular reaction and development of an immediate urticarial reaction.

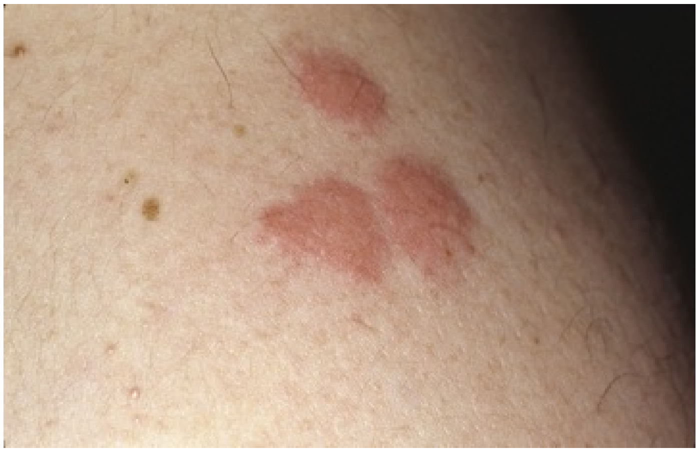

FIG. 688.1 **Pruritic papules after bedbug bites.**

Arthropod bites may occur as solitary, numerous, or profuse lesions, depending on the feeding habits of the perpetrator. Fleas tend to sample their host several times within a small localized area, whereas mosquitoes tend to attack a host at more randomly scattered sites. Delayed hypersensitivity reactions to insect bites—the predominant lesions in the young and uninitiated—are characterized by firm, persistent papules that may become hyperpigmented and are often excoriated and crusted. Pruritus may be mild or severe, transient or persistent. A central punctum is usually visible but may disappear as the lesion ages or is scratched. The immediate hypersensitivity reaction is characterized by an evanescent, erythematous wheal. If edema is marked, a tiny vesicle may surmount the wheal. Certain beetles produce bullous lesions through the action of cantharidin, and various insects, including beetles and spiders, may cause hemorrhagic nodules and ulcers. Bites on the lower extremities are more likely to be severe or persistent or become bullous than those located elsewhere. Complications of arthropod bites include development of impetigo, folliculitis, cellulitis, lymphangitis, and severe anaphylactic hypersensitivity reactions, particularly after the bite of certain hymenopterans. The histopathologic changes are variable, depending on the arthropod, the age of the lesion, and the reactivity of the host. Acute urticarial lesions tend to show central vesiculation in which eosinophils are numerous. Papules most commonly show dermal edema and a mixed superficial and deep perivascular inflammatory infiltrate, often including a number of eosinophils. At times, however, the dermal cellular infiltrate is so dense that a lymphoma is suspected. Many young children demonstrate extensive dermal but nonerythematous, nontender edema in response to mosquito bites (**Skeeter syndrome**), which responds to oral antihistamines; this must be distinguished from cellulitis, which tends to be painful, tender, and red. Retained mouthparts may stimulate a foreign body type of granulomatous reaction.

Papular urticaria occurs principally in the first decade of life. It may occur at any time of the year. The most common culprits are species of fleas, mites, bedbugs, gnats, mosquitoes, chiggers, and animal lice. Individuals with papular urticaria have predominantly transitional lesions in various stages of evolution between delayed-onset papules and immediate-onset wheals. The most characteristic lesion is an edematous, red-brown papule (Fig. 688.2). An individual lesion frequently starts as a wheal that, in turn, is replaced by a papule. A given bite may incite an id reaction at distant sites of quiescent bites in the form of erythematous macules, papules, or urticarial plaques. After a season or two, the reaction progresses from a transitional to a primarily immediate hypersensitivity urticarial reaction.

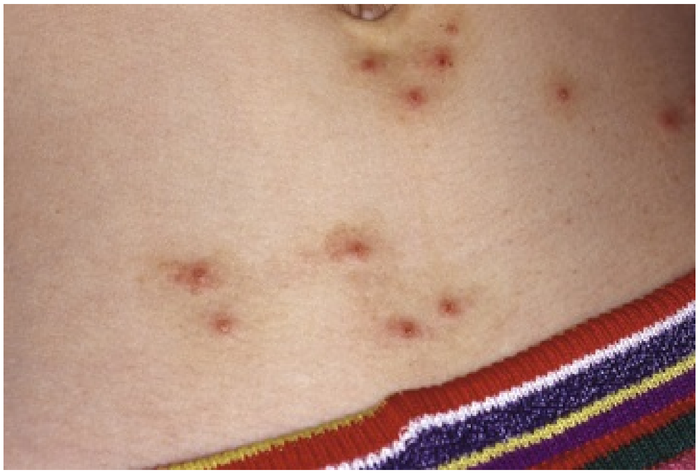

FIG. 688.2 **Red-brown papules in papular urticaria.**

One of the most commonly encountered arthropod bites is that resulting from human, cat, or dog fleas (family *Pulicidae*). Eggs, which are generally laid in dusty areas and cracks between floorboards, give rise to larvae that then form cocoons. The cocoon stage can persist for up to 1 yr, and the flea emerges in response to vibrations from footsteps, accounting for the assaults that frequently befall the new owners of a recently reopened dwelling. Adult dog fleas can live without a blood meal for approximately 60 days. Attacks from fleas are more likely to occur when the fleas do not have access to their usual host; cat or dog fleas are more voracious and problematic when one visits an area frequented by the pet than when the pet is encountered directly. Flea bites tend to be grouped in lines or irregular clusters on the lower extremities. Fleas are often not seen on the body of a pet. Diagnosis of flea bites is aided by examination of debris from the animal's bedding material. The debris is collected by shaking the bedding into a plastic bag and examining the contents for fleas or their eggs, larvae, or feces.

Treatment

Treatment is directed at alleviation of pruritus by oral antihistamines and cool compresses. Potent topical corticosteroids are helpful. Topical antihistamines are potent immunologic sensitizers and have no role in the treatment of insect bite reactions. A short course of systemic steroids may be helpful if many severe reactions occur, particularly around the eyes. Insect repellents containing *N,N* -diethyl-3-methylbenzamide (DEET) may afford moderate protection against mosquitoes, fleas, flies, chiggers, and ticks, but are relatively ineffective against wasps, bees, and hornets. DEET must be applied to exposed skin and clothing to be effective. The most effective protection against mosquitoes, the human body louse, and other blood-feeding arthropods is the use of DEET and permethrin-impregnated clothing. However, these measures are not effective against the phlebotomine sand fly, which transmits leishmaniasis. Because of the potential for toxicity, the lowest effective DEET dose should be selected. Additional insect repellents include picaridin (flies, mosquitoes, chiggers, ticks), IR3535 (mosquitoes), oil of lemon, eucalyptus (mosquitoes), and citronella (mosquitoes). Table 688.2 lists methods to eliminate bed bugs.

Table 688.2

Patient Education to Eliminate Bed Bugs

Detection

- Look for brown insects no bigger than apple seeds on the mattress, sofa, and curtains and in darker places in the room (especially cracks in the walls, crevices in box springs, and furniture)
- Look for black spots on the mattress or blood traces on the sheets

Elimination

- Contact a pest management company
- Wash clothes at 60°C (140°F) or freeze delicate clothing, vacuum, and clean your home before the pest manager visits
- Collaborate with professionals who are used to dealing with bed bug infestation to increase eradication efficacy

Prevention

- Carefully examine secondhand furniture to assure the absence of bed bugs before purchase so as not to contaminate your home
- When sleeping in a hotel, even an upmarket establishment, lift mattresses to look for bed bugs or black spots
- Do not leave luggage in dark places, near furniture, or close to your bed. Before going to bed, close suitcases and put them in the bathroom—in the bathtub or shower stall

From Bernardeschi C, Le Cleach L, Delaunay P, Chosidow O: Bed bug infestation. *BMJ* 346:f138, 2013.

An effort should be made to identify and eradicate the etiologic agent. Pets should be carefully inspected. Crawl spaces, eaves, and other sites of the house or outbuildings frequented by animals and birds should be decontaminated, and baseboard crevices, mattresses, rugs, furniture, and animal sleeping quarters should be decontaminated. Agents that are effective for ridding the home of fleas include lindane, pyrethroids, and organic thiocyanates. Flea-infested pets may be treated with powders containing rotenone, pyrethroids, Malathion, or methoxychlor. Lufenuron, an agent that prevents fleas from reproducing, is effective for animals in oral and injectable formulations. Fipronil is effective as a topical agent for the prevention of flea infestation.

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688.2

Scabies

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Scabies is caused by burrowing and release of toxic or antigenic substances by the female mite *Sarcoptes scabiei* var. *hominis* . The most important factor that determines spread of scabies is the extent and duration of physical contact with an affected individual. Children and sexual partners of affected individuals are most at risk. Scabies is transmitted only rarely by fomites because the isolated mite dies within 2-3 days.

Etiology and Pathogenesis

An adult female mite measures approximately 0.4 mm in length, has 4 sets of legs, and has a hemispheric body marked by transverse corrugations, brown spines, and bristles on the dorsal surface. A male mite is approximately half her size and is similar in configuration. After impregnation on the skin surface, a gravid female exudes a keratolytic substance and burrows into the stratum corneum, often forming a shallow well within 30 min. She gradually extends this tract by 0.5-5.0 mm/24 hr along the boundary with the stratum granulosum. She deposits 10-25 oval eggs and numerous brown fecal pellets (scybala) daily. When egg laying is completed, in 4-5 wk, she dies within the burrow. The eggs hatch in 3-5 days, releasing larvae that move to the skin surface to molt into nymphs. Maturity is achieved in approximately 2-3 wk. Mating occurs, and the gravid female invades the skin to complete the life cycle.

Clinical Manifestations

In an immunocompetent host, scabies is frequently heralded by intense pruritus, particularly at night (Table 688.3). The first sign of the infestation often consists of 1-2 mm red papules, some of which are excoriated, crusted, or scaling. Threadlike burrows are the classic lesion of scabies (Figs. 688.3 and 688.4) but may not be seen in infants. In infants, bullae and pustules are relatively common. The eruption may also include wheals, papules, vesicles, and a superimposed eczematous dermatitis (Fig. 688.5). The palms, soles, and scalp are often affected. In older children and adolescents, the clinical pattern is similar to that in adults, in whom preferred sites are the interdigital spaces, wrist flexors, anterior axillary folds, ankles, buttocks, umbilicus and belt line, groin, genitals in men, and areolas in women. The head, neck, palms, and soles are generally spared. Infants will often have a diffuse eczematous eruption that will involve the scalp, neck, and face. Red-brown nodules, most often located in covered areas such as the axillae, groin, and genitals, predominate in the less common variant called nodular scabies. Additional clues include facial sparing, affected family members, poor response to topical antibiotics, and transient response to topical steroids. Untreated, scabies may lead to eczematous dermatitis, impetigo, ecthyma, folliculitis, furunculosis, cellulitis, lymphangitis, and id reaction. Glomerulonephritis has developed in children from streptococcal impetiginization of scabies lesions. In some tropical areas, scabies is the predominant underlying cause of pyoderma. A latent period of approximately 1 mo follows an initial infestation. Thus, itching may be absent and lesions may be relatively inapparent in contacts who are asymptomatic carriers. However, on reinfestation, reactions to mite antigens are noted within hours.

Table 688.3

Different Presenting Forms of Scabies

PRESENTING FORMS OF SCABIES	SPECIFIC HIGH-RISK POPULATIONS	CLINICAL MANIFESTATIONS	LIMITED DIFFERENTIAL DIAGNOSES
Classic scabies (scabies vulgaris)	Infants and children; sexually active adults; men who have sex with men	Intense generalized pruritus, worse at night; inflammatory pruritic papules localized to finger webs, flexor aspects of wrists, elbows, axillae, buttocks, genitalia, female breasts; lesions and pruritus spare the face, head, and neck; secondary lesions include eczematization, excoriation, impetigo	Dermatitis herpetiformis, drug reactions, eczema, pediculosis corporis, lichen planus, pityriasis rosea
Scalp scabies	Infants and children; institutionalized older adults; AIDS patients; patients with preexisting crusted scabies	Atypical crusted papular lesions of the scalp, face, palms, and soles	Dermatomyositis, ringworm, seborrheic dermatitis
Crusted scabies (Norwegian scabies, scabies norvegica, scabies crustosa)	Institutionalized older adults; institutionalized developmentally disabled (Down syndrome); homeless, especially HIV-positive; all immunocompromised patients, particularly those with AIDS or positive for HIV or HTLV-1; transplant recipients; patients on prolonged systemic corticosteroids and chemotherapy	Psoriasiform hyperkeratotic papular lesions of the scalp, face, neck, hands, feet, with extensive nail involvement; eczematization and impetigo common	Contact dermatitis, drug reactions, eczema, erythroderma, ichthyosis, psoriasis
Nodular scabies	Sexually active adults; men who have sex with men; HIV-positive men > HIV-positive women	Violaceous pruritic nodules localized to male genitalia, groin, axillae, representing hypersensitivity reaction to mite antigens	Acropustulosis, atopic dermatitis, Darier disease, lupus erythematosus,

			lymphomatoid papulosis, papular urticaria, necrotizing vasculitis, secondary syphilis

HTLV-1, human T-cell lymphotropic virus type 1.

From Bennett JE, Blaser MJ, Dolin R, et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* , ed 8, Philadelphia, 2015, Elsevier/Saunders, Table 295.1, p 3252.

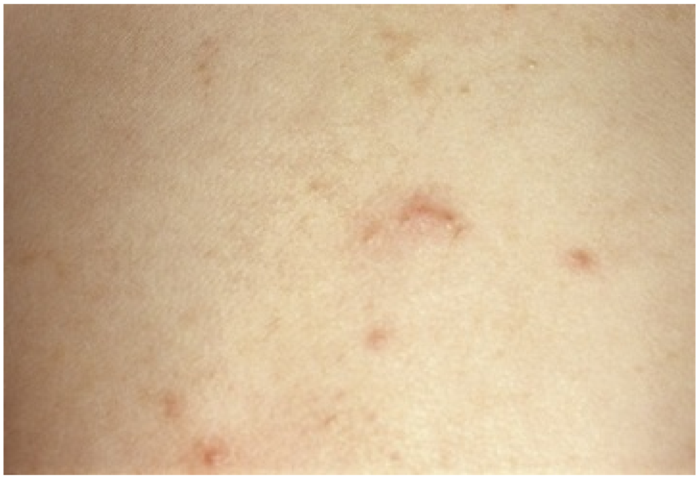

FIG. 688.3 **Classic scabies burrow.**

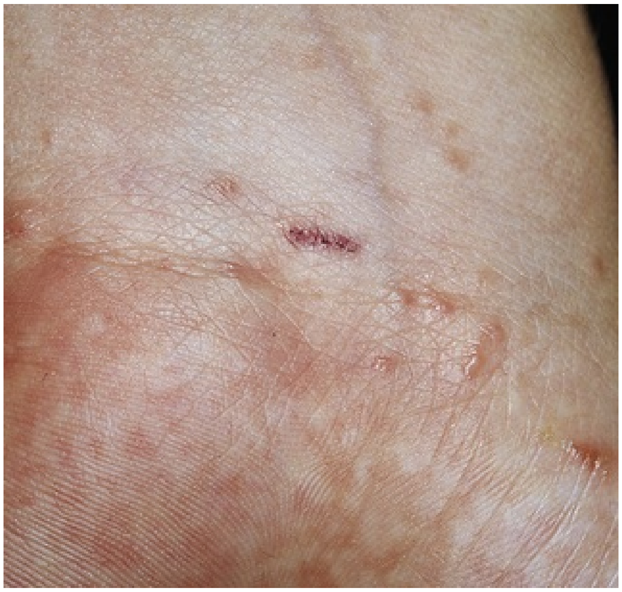

FIG. 688.4 **Scabies. Felt-tipped ink pen has penetrated and highlighted a burrow. The ink is retained after the surface is wiped clean with an alcohol swab. (From Habif TP: *Clinical dermatology,* ed 6, Philadelphia, 2016, Elsevier. Fig 15-16.)**

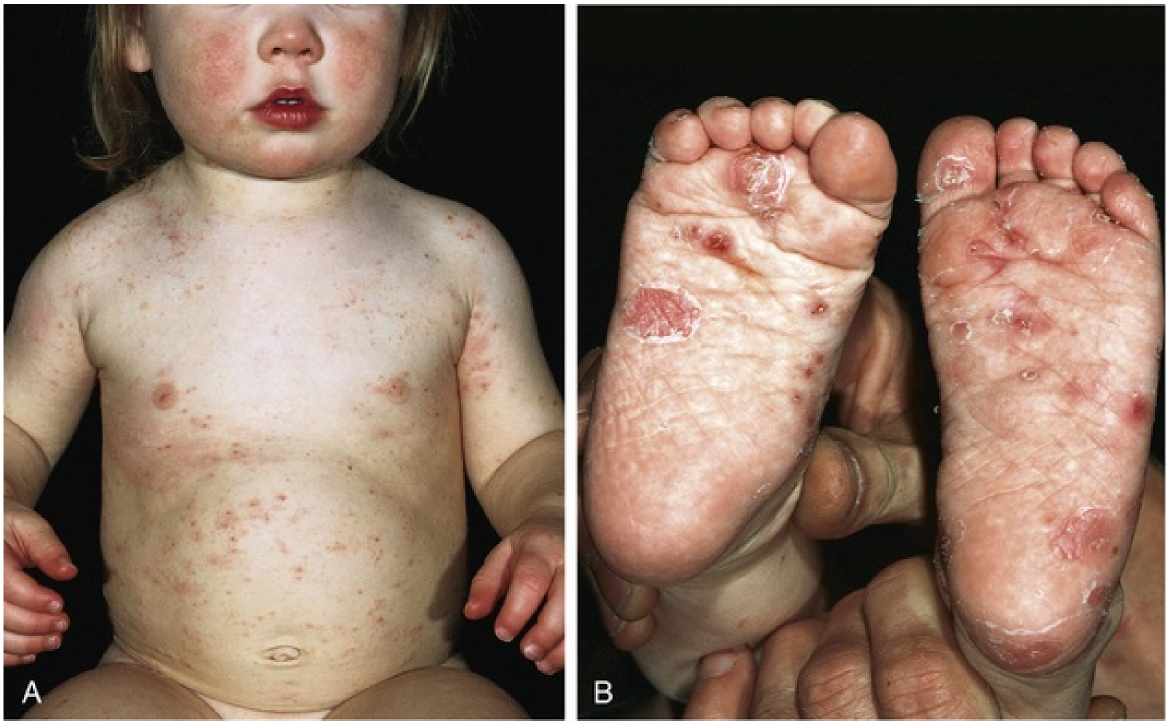

FIG. 688.5 **A,** Diffuse scabies on an infant. The face is clear. The lesions are most numerous around the axillae, chest, and abdomen. **B,** Scabies. Infestation of the palms and soles is common in infants. The vesicular lesions have all ruptured. (From Habif TP, editor: *Clinical dermatology* , ed

4, Philadelphia, 2004, Mosby, Figs. 15.8 and 15.9.)

Differential Diagnosis

Differential diagnosis of scabies can often be made clinically but is confirmed by microscopic identification of mites (Fig. 688.6*A*), ova, and scybala (see Fig. 688.6*B*) in epithelial debris. Scrapings most often test positive when obtained from burrows or fresh papules. A reliable method is application of a drop of mineral oil on the selected lesion, scraping of it with a No. 15 blade, and transferring the oil and scrapings to a glass slide.

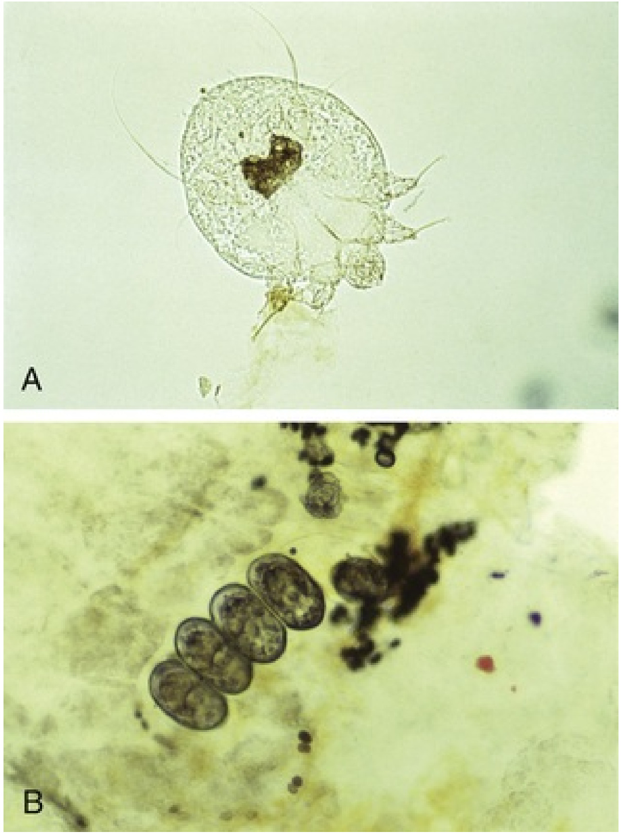

FIG. 688.6 **A,** Human scabies mite obtained from scraping. **B,** Scabies ova and scybala.

The differential diagnosis depends on the types of lesions present. Burrows are virtually pathognomonic for human scabies. Papulovesicular lesions are confused with papular urticaria, canine scabies, chickenpox, viral exanthems, drug eruptions, dermatitis herpetiformis, and folliculitis. Eczematous lesions may mimic atopic dermatitis and seborrheic dermatitis, and the less common bullous disorders of childhood may be suspected in infants with predominantly bullous lesions. Nodular scabies is frequently misdiagnosed as urticaria pigmentosa and Langerhans cell histiocytosis. The histopathologic appearance of nodular scabies, consisting of a deep, dense, perivascular infiltrate of lymphocytes, histiocytes, plasma cells, and atypical mononuclear cells, may mimic malignant lymphoid neoplasms.

Treatment

The treatment of choice for scabies is permethrin 5% cream (Elimite) applied to the entire body from the neck down, with particular attention to intensely involved areas, which is also standard therapy (Table 688.4). Scabies is frequently found above the neck in infants (younger than 2 yr old), necessitating treatment of the scalp. The medication is left on the skin for 8-12 hr and should be reapplied in 1 wk for another 8-12 hr period. Additional therapies include sulfur ointment 5–10%, and crotamiton 10% lotion or cream. Lindane 1% lotion or cream should only be used as an alternative therapy, given risk of systemic toxicity. For severe infestations or in immunocompromised patients, oral ivermectin 200 µg/kg per dose given orally for 2 doses, 2 wk apart can be used (off-label use). Single dose ivermectin (200 µg/kg) has also been effective in immunocompetent patients with improvement (cure) noted in 60% at 2 wk and 89% at 4 wk after treatment (see Table 688.4).

Table 688.4

Currently Recommended Treatment for Scabies

SCABICIDES	FDA APPROVED?	PREGNANCY CATEGORY*	DOSING SCHEDULE	SAFETY PROFILE	CONTRAINDICATIONS
5% Permethrin cream (Actin, Nix, Elimite)	Yes	B	Apply from neck down; wash off after 8-14 hr; good residual activity, but second application recommended after 1 wk	Excellent; itching and stinging on application	Prior allergic reactions; infants <2 mo of age; breast-feeding

1% Lindane lotion or cream	Yes	B	Apply 30-60 mL from neck down; wash off after 8-12 hr; no residual activity; increasing drug resistance	Potential for central nervous system toxicity from organochloride poisoning, usually manifesting as seizures, with overapplication and ingestions	Preexisting seizure disorder; infants and children <6 mo of age; pregnancy; breastfeeding
10% Crotamiton cream or lotion (Eurax)	Yes	C	Apply from neck down on 2 consecutive nights; wash off 24 hr after second application	Excellent; not very effective; exacerbates pruritus	None
2–10% Sulfur in petrolatum ointments	No	C	Apply for 2-3 days, then wash	Excellent; not very effective	Preexisting sulfur allergy
10–25% Benzoyl benzoate lotion	No	None	Two applications for 24 hr with 1-day to 1-wk interval	Irritant; exacerbates pruritus; can induce contact irritant dermatitis and pruritic cutaneous xerosis	Preexisting eczema
0.5% Malathion lotion (Ovide), 1% malathion shampoo (unavailable in the United States)	No	B	95% ovicidal; rapid (5 min) killing; good residual activity; increasing drug resistance	Flammable 78% isopropyl alcohol vehicle stings eyes, skin, mucosa; increasing drug resistance; organophosphate poisoning risk with overapplication and ingestions	Infants and children <6 mo of age; pregnancy; breast-feeding
Ivermectin (Stromectol)	Yes	C	200-µg/kg single PO dose, may be repeated in 14-15 days; not ovicidal, second dose on day 14 or 15 highly recommended; recommended for endemic or epidemic	Excellent; may cause nausea and vomiting; take on empty stomach with water	Safety in pregnancy uncertain; probably safe during breastfeeding; not recommended for children younger than 5 yr of age or weighing <15 kg

			scabies in institutions and refugee camps		

[*] U.S. Food and Drug Administration safety in pregnancy categories: A, safety established; B, presumed safe; C, uncertain safety; D, unsafe; X, highly unsafe.

From Bennett JE, Blaser MJ, Dolin R, et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases* , ed 8, Philadelphia, 2015, Elsevier/Saunders, Table 295.2, p 3253.

Transmission of mites is unlikely more than 24 hr after treatment. Pruritus, which is a result of hypersensitivity to mite antigens, may persist for a number of days to weeks, and may be alleviated by a topical corticosteroid preparation. If pruritus persists for >2 wk after treatment and new lesions are occurring, the patient should be reexamined for mites. Nodules are extremely resistant to treatment and may take several months to resolve. The entire family should be treated, as should caretakers of the infested child. Clothing, bed linens, and towels should be washed in hot water and dried using high heat. Clothing or other items (e.g., stuffed animals) that cannot be washed may be dry cleaned or stored in bags for 3 days to 1 wk, as the mite will die when separated from the human host.

Norwegian (Crusted) Scabies

The Norwegian variant of human scabies is highly contagious and occurs mainly in individuals who are cognitively and physically debilitated, particularly those who are institutionalized and those with Down syndrome; in patients with poor cutaneous sensation (leprosy, spina bifida); in patients who have severe systemic illness (leukemia, diabetes); and in immunosuppressed patients (HIV infection). Affected individuals are infested by a myriad of mites that inhabit the crusts and exfoliating scales of the skin and scalp (Fig. 688.7). The nails may become thickened and dystrophic. The subungual debris is densely populated by mites. The infestation is often accompanied by generalized lymphadenopathy and eosinophilia. There is massive orthokeratosis and parakeratosis with numerous interspersed mites, psoriasiform epidermal hyperplasia, foci of spongiosis, and neutrophilic abscesses. Norwegian scabies is thought to represent a deficient host immune response to the organism. Management is difficult, requiring scrupulous isolation measures, removal of the thick scales, and repeated but careful applications of permethrin 5% cream. Ivermectin (200-250 µg/kg) has been used successfully as single-dose therapy in refractory cases, particularly in

HIV-infected patients. A second dose may be needed a week later. The U.S. Food and Drug Administration has not approved this agent for the treatment of scabies.

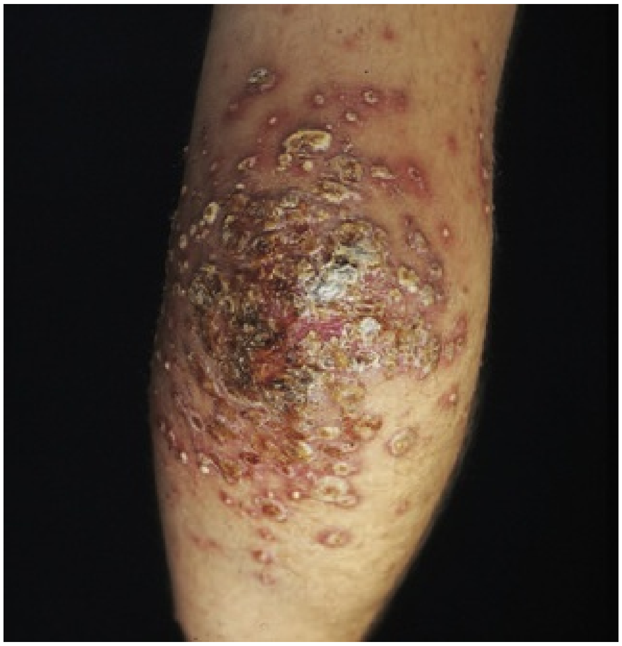

FIG. 688.7 Crusted (Norwegian) scabies on the extensor surface of the elbow secondarily infected with *Staphylococcus aureus* . Note the confluence of the crusts and pustules and the similarity of the lesion to psoriasis, both in its hyperkeratotic appearance and in its location on an extensor surface. Risk factors for crusted scabies include immunocompromise by advanced age, prolonged glucocorticoid therapy, cancer chemotherapy, and HIV or human T-cell lymphotropic virus type 1 infection. (From Fitzpatrick TB, Johnson RA, Wolff K, Suurmond D: *Color atlas and synopsis of clinical dermatology* , ed 4, New York, 2001, McGraw-Hill, p 841.)

Canine Scabies

Canine scabies is caused by *S. scabiei* var. *canis*, the dog mite that is associated with mange. The eruption in humans, which is most frequently acquired by cuddling an infested puppy, consists of tiny papules, vesicles, wheals, and excoriated eczematous plaques. Burrows are not present because the mite infrequently inhabits human stratum corneum. The rash is pruritic and has a predilection for the arms, chest, and abdomen, the usual sites of contact with dogs. Onset is sudden and usually follows exposure by 1-10 days, possibly resulting from development of a hypersensitivity reaction to mite antigens.

Recovery of mites or ova from scrapings of human skin is rare. The disease is self-limited because humans are not a suitable host. Bathing and changing clothes are generally sufficient. Removal or treatment of the infested animal is necessary. Symptomatic therapy for itching is helpful. In rare cases in which mites are demonstrated in scrapings from an affected child, they can be eradicated by the same measures applicable to human scabies.

Other Types of Scabies

Other mites that occasionally bite humans include the chigger or harvest mite *(Eutrombicula alfreddugesi)*, which prefers to live on grass, shrubs, vines, and stems of grain. Larvae have hooked mouthparts, which allow the chigger to attach to the skin, but not to burrow, to obtain a blood meal, most commonly on the lower legs. Avian mites may affect those who come into close contact with chickens or pet gerbils. Humans may occasionally be assaulted by avian mites that have infested a nest outside a window, an attic, heating vents, or an air conditioner. The dermatitis is variable, including grouped papules, wheals, and vesicular lesions on the wrists, neck, breasts, umbilicus, and anterior axillary folds. A prolonged investigation is often undertaken before the cause and source of the dermatitis are discovered.

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688.3

Pediculosis

Daren A. Diiorio, Stephen R. Humphrey

Three types of lice are obligate parasites of the human host: body or clothing lice *(Pediculus humanus corporis)*, head lice *(Pediculus humanus capitis)*, and pubic or crab lice *(Phthirus pubis)*. Only the body louse serves as a vector of human disease (typhus, trench fever, relapsing fever). Body and head lice have similar physical characteristics. They are approximately 2-4 mm in length. Pubic lice are only 1-2 mm in length and are greater in width than length, giving them a crab-like appearance. Female lice live for approximately 1 mo and deposit 3-10 eggs daily on the human host. However, body lice generally lay eggs in or near the seams of clothing. The ova or nits are glued to hairs or fibers of clothing but not directly on the body. Ova hatch in 1-2 wk and require another week to mature. Once the eggs hatch, the nits remain attached to the hair as empty sacs of chitin. Freshly hatched larvae die unless a meal is obtained within 24 hr and every few days thereafter. Both nymphs and adult lice feed on human blood, injecting their salivary juices into the host and depositing their fecal matter on the skin. Symptoms of infestation do not appear immediately but develop as an individual becomes sensitized. The hallmark of all types of pediculosis is pruritus.

Pediculosis corporis is rare in children except under conditions of poor hygiene, especially in colder climates when the opportunity to change clothes on a regular basis is lacking. The parasite is transmitted mainly on contaminated clothing or bedding. The primary lesion is a small, intensely pruritic, red macule or papule with a central hemorrhagic punctum, located on the shoulders, trunk, or buttocks. Additional lesions include excoriations, wheals, and eczematous, secondarily infected plaques. Massive infestation may be associated with constitutional symptoms of fever, malaise, and headache. Chronic infestation may lead to “vagabond's skin,” which manifests as lichenified, scaling, hyperpigmented plaques, most commonly on the trunk. Lice are found on the skin only transiently when they are feeding. At other times, they inhabit the seams of clothing. Nits are attached firmly to fibers in the cloth and may remain viable for up to 1 mo. Nits hatch when they encounter warmth from the host's body when the clothes are worn again. Therapy consists of improved hygiene and hot water laundering of all infested clothing and bedding. A uniform temperature of 65°C (149°F), wet or dry, for 15-30 min kills all eggs and lice. Alternatively, eggs hatch and nymphs starve if clothing is stored for 2 wk at 23.9-29.4°C (75-85°F).

Pediculosis capitis is an intensely pruritic infestation of lice in the scalp hair. It is the most common form of lice to affect children, in particular those between the ages of 3 and 12 yr. Fomites and head-to-head contact are important modes of transmission. In summer months in many areas of the United States and in the tropics at all times of the year, shared combs, brushes, or towels have a more important role in louse transmission. Translucent 0.5 mm eggs are laid near the proximal portion of the hair shaft and become adherent to one side of the shaft (Fig. 688.8). A nit cannot be moved along or knocked off the hair shaft with the fingers. Secondary pyoderma, after trauma from scratching, may result in matting together of the hair and cervical and occipital lymphadenopathy. Hair loss does not result from pediculosis but may accompany the secondary pyoderma. Head lice are a major cause of numerous pyodermas of the scalp, particularly in tropical environments. Lice are not always visible, but nits are detectable on the hairs, most commonly in the occipital region and above the ears, rarely on beard or pubic hair. Dermatitis may also be noted on the neck and pinnae. An id reaction, consisting of erythematous patches and plaques, may develop, particularly on the trunk. Head lice rarely infest African Americans and this is possibly related to the diameter, shape, or twisted nature of their hair shafts (which makes grasping of the shaft more difficult for the louse).

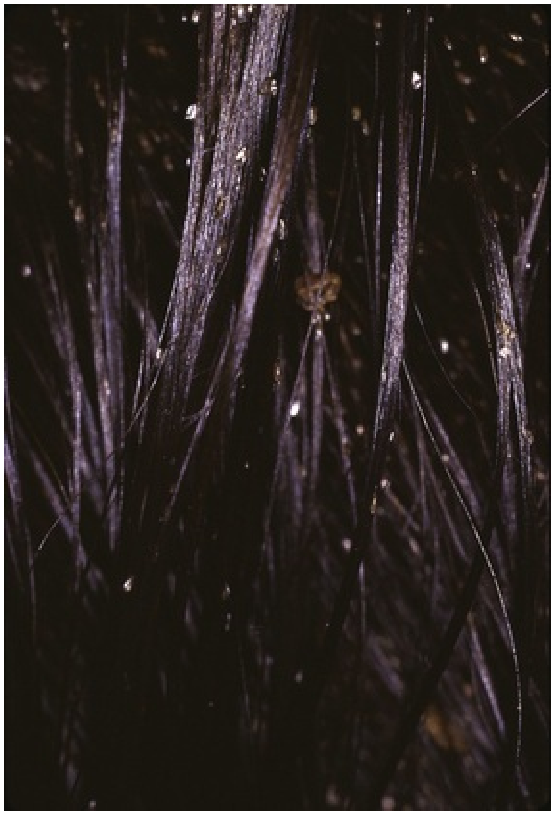

FIG. 688.8 **Intact nits on human hairs.**

In the cases of resistance (which is common) of head lice to pyrethroids, malathion 0.5% in isopropanol is the treatment of choice and should be applied to dry hair until hair and scalp are wet, and left on for 12 hr. A second application, 7-9 days after the initial treatment may be necessary. This product is flammable, so care should be taken to avoid open flames. Malathion, like lindane shampoo, is not indicated for use in neonates and infants; however, additional approved therapies include spinosad (if >6 mo), benzyl alcohol lotion (if >6 mo), and ivermectin for difficult-to-treat head lice (Table 688.5). All household members should be treated at the same time. Nits can be removed with a fine-toothed comb after application of a damp towel to the scalp for 30 min. Clothing and bed linens should be laundered in very hot (>130°F) water and then dried for at least 10 min at the highest setting or dry-cleaned; brushes and combs should be discarded or coated with a pediculicide for 15 min and then thoroughly cleaned in boiling water. If the object cannot be washed, it can be sealed in a plastic bag for 48 hr. Children may return to school after the initial treatment.

Table 688.5

Drugs for Head Lice

DRUG	RESISTANCE	FDA-APPROVED LOWER AGE OR WEIGHT LIMIT	DOSAGE AND ADMINISTRATION	COST[*]/SIZE
Ivermectin 0.5% lotion–Sklice (Arbor)	No	6 mo	Apply to dry hair and scalp for 10 min, then rinse [†]	$297.60/4 oz
Ivermectin tablets [‡] –Stromectol (MSD)	No	15 kg [§]	200-400 µg/kg PO once; repeat 7-10 days later	$9.30 [‖]
Spinosad 0.9% suspension–Natroba (ParaPro)	No	6 mo	Apply to dry hair for 10 min, then rinse; repeat 7 days later if necessary [¶]	$246.10/4 oz
Benzyl alcohol 5% lotion–Ulesfia (Lachlan)	No	6 mo	Apply to dry hair for 10 min, then rinse; repeat 7 days later[**]	$181.30/8 oz
Pyrethrins with piperonyl butoxide shampoo [††] –Generic Rid (Bayer)	Yes	2 yr	Apply to dry hair for 10 min, then shampoo; repeat 7-10 days later	$15.00/8 oz [‡‡] $20.00/8 oz [‡‡]
Permethrin 1% creme rinse [††] –Generic Nix (Insight)	Yes	2 mo	Apply to shampooed, towel-dried hair for 10 min, then rinse; repeat 7 days later	$18.00/4 oz [‡‡] $21.00/4 oz [‡‡]
Malathion 0.5% lotion–Generic Ovide (Taro)	Not in the United States	6 yr [§§]	Apply to dry hair for 8-12 hr, then shampoo; repeat 7-9 days later if necessary [‖‖, ¶¶]	$221.70/2 oz $246.40/2 oz

[*] Approximate WAC for the indicated size. WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource Monthly. November 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. Copyright 2016. www.fdbhealth.com/policies/drug-pricing-policy . Total cost of treatment may vary based on hair length and number of applications required to completely eradicate lice.

[†] The manufacturer recommends using up to one single-use, 4-oz tube of topical ivermectin lotion per application.

[‡] Not FDA approved for treatment of head lice.

[§] The safety and effectiveness of oral ivermectin have not been established in children weighing <15 kg.

[||] Cost of two 3 mg tablets (one dose for a 30-kg child at the lowest dosage).

[¶] The manufacturer recommends using up to one 4 oz (120 mL) bottle of spinosad 0.9% suspension per application.

[**] The amount of benzoyl alcohol 5% lotion recommended per application depends on hair length.

[††] Available without a prescription.

[‡‡] Approximate cost according to walgreens.com . Accessed November 10, 2016.

[§§] The safety and effectiveness of malathion lotion have not been established in children <6 yr old; it is contraindicated in children <24 mo old.

[||||] In clinical trials, patients used a maximum of 2 fl oz of malathion lotion per application.

[¶¶] One or two 20 min applications have also been effective (Meinking TL, Vicaria M, Eyerdam DH, et al: Efficacy of a reduced application time of Ovide lotion (0.5% malathion) compared to Nix creme rinse (1% permethrin) for the treatment of head lice. *Pediatr Dermatol* 21:670–674, 2004.)

FDA, U.S. Food and Drug Administration; MSD, Merck Sharp Dohme; WAC, wholesaler acquisition cost or manufacturer's published price to wholesalers.

From The Medical Letter: Drugs for head lice. *Med Lett Drugs Ther* 58:150–152, 2016.

Pediculosis pubis is transmitted by skin-to-skin or sexual contact with an infested individual; the chance of acquiring the lice with 1 sexual exposure is 95%. The infestation is usually encountered in adolescents, although small children may occasionally acquire pubic lice on the eyelashes. Patients experience moderate to severe pruritus and may develop a secondary pyoderma from scratching. Excoriations tend to be shallow, and the incidence of secondary infection is lower than in pediculosis corporis. Maculae ceruleae are steel-gray spots, usually <1 cm in diameter, which may appear in the pubic area and on the chest, abdomen, and thighs. Oval translucent nits, which are firmly attached to the hair shafts, may be visible to the naked eye or may be readily identified by a hand lens or by microscopic examination (see Fig. 688.8). Grittiness, as a result of adherent nits, may sometimes be detected when the fingers are run through infested hair. Adult lice are more difficult to detect than head or body lice because of their lower level of activity and smaller, translucent bodies. Because pubic lice occasionally may wander or may be transferred to other sites on fomites, terminal hair on the trunk, thighs, axillary region, beard area, and eyelashes should be examined for nits. The coexistence of other venereal diseases should be considered. Treatment with a 10-min application of a pyrethrin preparation is usually effective. Retreatment may be required in 7-10 days. Infestation of eyelashes is eradicated by petrolatum applied 3-5 times per 24 hr for 8-10 days. Clothing, towels, and bed linens may be contaminated with nit-bearing hairs and should be thoroughly laundered or dry-cleaned.

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688.4

Seabather's Eruption

Daren A. Diiorio, Stephen R. Humphrey

Seabather's eruption is a severely pruritic dermatosis of inflammatory papules that develops within about 12 hr of bathing in saltwater, primarily on body sites that were covered by a bathing suit. The eruption has been described primarily in connection with bathing in the waters of Florida and the Caribbean. Lesions, which may include pustules, vesicles, and urticarial plaques, are more numerous in individuals who keep their bathing suits on for an extended period after leaving the water. The eruption may be accompanied by systemic symptoms of fatigue, malaise, fever, chills, nausea, and headache; in one large series, ~40% of children younger than 16 yr of age had fever. Duration of the pruritus and skin eruption is 1-2 wk. Lesions consist of a superficial and deep perivascular and interstitial infiltrate of lymphocytes, eosinophils, and neutrophils. The eruption appears to be due to an allergic hypersensitivity reaction to venom from larvae of the thimble jellyfish *(Linuche unguiculata)*. Treatment is largely symptomatic. Potent topical corticosteroids have been shown to provide relief to some patients.

CHAPTER 689

Acne

Wendy E. Kim

Acne Vulgaris

Acne, particularly the comedonal form, occurs in 80% of adolescents.

Pathogenesis

Lesions of acne vulgaris develop in sebaceous follicles, which consist of large multilobular sebaceous glands that drain their products into the follicular canals. The initial lesion of acne is a microcomedone, which progresses to a comedone. A comedone is a dilated epithelium-lined follicular sac filled with lamellated keratinaceous material, lipid, and bacteria. An open comedone, known as a **blackhead,** has a patulous pilosebaceous orifice that permits visualization of the plug. An open comedone becomes inflammatory less commonly than does a closed comedone or whitehead, which has only a pinpoint opening. An inflammatory papule or nodule develops from a comedone that has ruptured and extruded its follicular contents into the subadjacent dermis, inducing a neutrophilic inflammatory response. If the inflammatory reaction is close to the surface, a papule or pustule develops. If the inflammatory infiltrate develops deeper in the dermis, a nodule forms. Suppuration and an occasional giant cell reaction to keratin and hair are the cause of nodulocystic lesions. These are not true cysts but liquefied masses of inflammatory debris.

The primary pathogenetic alterations in acne are (1) abnormal keratinization of the follicular epithelium, resulting in impaction of keratinized cells within the follicular lumen; (2) increased sebaceous gland production of sebum; (3) proliferation of *Cutibacterium acnes* (formerly *Propionibacterium acnes*) within the follicle; and (4) inflammation. **Comedonal acne** (Fig. 689.1), particularly of the central face, is frequently the first sign of pubertal maturation. At puberty, the sebaceus gland enlarges and sebum production increases in response to the increased activities of androgens of primarily adrenal origin. Most patients with acne do not have endocrine abnormalities. Hyperresponsiveness of the sebocyte to androgens is likely involved in determining the severity of acne in a given individual. Sebocytes and follicular keratinocytes contain 5α-reductase and 3β- and 17β-hydroxyl-steroid dehydrogenase, which are capable of metabolizing androgens. A significant number of women with acne (25–50%), particularly those with relatively mild papulopustular acne, note that their acne flares about 1 wk before menstruation.

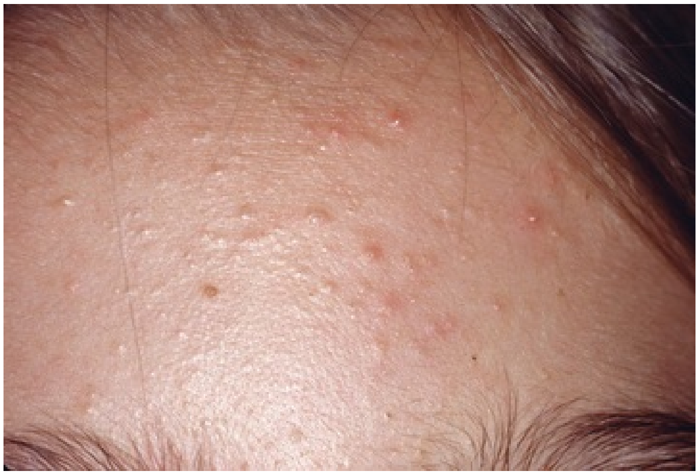

FIG. 689.1 **Primarily comedonal acne in a 7 yr old girl.**

Freshly formed sebum consists of a mixture of triglycerides, wax esters, squalene, and sterol esters. Normal follicular bacteria produce lipases that hydrolyze sebum triglycerides to free fatty acids. Those of medium-chain length (C8-C14) may be provocative factors in initiating an inflammatory reaction. Sebum also provides a favorable substrate for proliferation of bacteria. *C. acnes* appears to be largely responsible for the formation of free fatty acids. Skin surface *C. acnes* counts do not correlate with the severity of acne. There is a correlation between reduction of *C. acnes* count and improvement in acne vulgaris. It is probable that bacterial proteases, hyaluronidases, and hydrolytic enzymes produce biologically active extracellular materials that increase the permeability of the follicular epithelium. Chemotactic factors released by the intrafollicular bacteria attract neutrophils and monocytes. Lysosomal enzymes from the neutrophils, released in the process of phagocytizing the bacteria, further disrupt the integrity of the follicular wall and intensify the inflammatory reaction.

Clinical Manifestations

Acne vulgaris is characterized by 4 basic types of lesions: open and closed comedones, papules, pustules (Fig. 689.2), and nodulocystic lesions (Fig. 689.3 and Table 689.1). One or more types of lesions may predominate. In its mildest form, which is often seen early in adolescence, lesions are limited to comedones on the central area of the face. Lesions may also involve the chest, upper back, and deltoid areas. A predominance of lesions on the forehead, particularly closed comedones, is often attributable to prolonged use of greasy hair preparations (pomade acne) (Fig. 689.4). Marked involvement on the trunk is most often seen in males. Lesions often heal with temporary postinflammatory erythema and hyperpigmentation. Pitted, atrophic, or hypertrophic scars may be interspersed, depending on the severity, depth, and chronicity of the process. Diagnosis of acne is rarely difficult, although flat warts, folliculitis, and other types of acne (drug-induced: glucocorticoid agents, anabolic steroids, gold, dactinomycin, isoniazid, lithium, phenytoin, progestins) may be confused with acne vulgaris. The differential diagnosis includes sarcoidosis, angiofibromas, keratosis pilaris, chloracne, rosacea, and fibrofolliculomas.

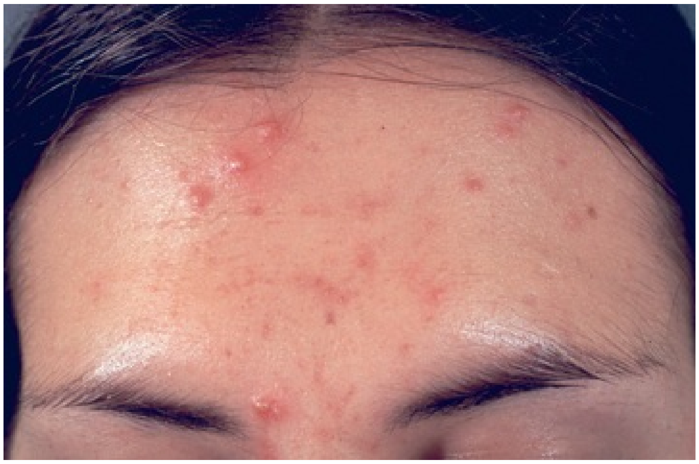

FIG. 689.2 **Inflammatory papules and pustules.**

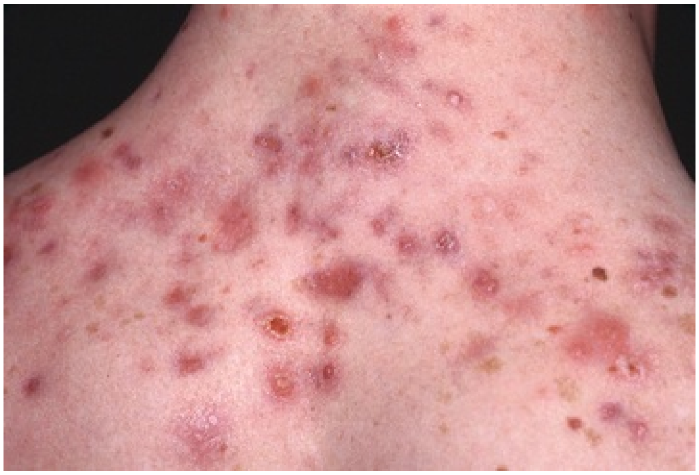

FIG. 689.3 **Severe nodulocystic acne.**

Table 689.1

One Approach to the Classification of Acne

SEVERITY	DESCRIPTION
Mild	Comedones (noninflammatory lesions) are the main lesions. Papules and pustules may be present but are small and few in number (generally <10).
Moderate	Moderate numbers of papules and pustules (10-40) and comedones (10-40) are present. Mild disease of the back and trunk may also be present.
Moderately severe	Numerous papules and pustules are present (40-100), usually with many comedones (40-100) and occasional larger, deeper nodular inflammatory lesions (up to 5). Widespread affected areas usually involve the face, chest, and back.
Severe	Nodulocystic acne and conglobate acne including many large inflammatory, painful nodular or pustular lesions along with many smaller papules, pustules, and comedones.

The American Academy of Dermatology acknowledges that there is no universally agreed upon grading/severity classification for acne.

Modified from James WD: Clinical practice: acne. *N Engl J Med* 352:1463–1472, 2005.

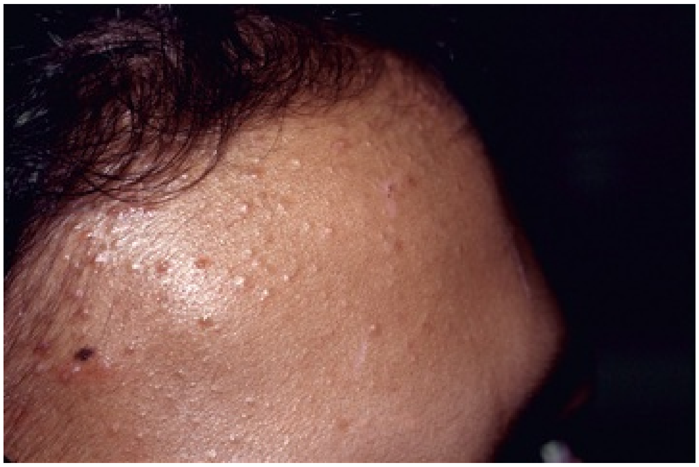

FIG. 689.4 Pomade acne along the hairline.

Treatment

With the exception of isotretinoin therapy, no evidence shows that early treatment alters the course of acne. Acne can be controlled and severe scarring prevented by judicious maintenance therapy that is continued until the disease process has abated spontaneously. Therapy must be individualized and aimed at preventing microcomedone formation through reduction of follicular hyperkeratosis, sebum production, the *C. acnes* population in follicular orifices, and free fatty acid production. Initial control takes at least 6-8 wk, depending on the severity of the acne (Table 689.2 and Fig. 689.5).

Table 689.2

Typical Treatment Regimens for Acne

Comedonal Acne

Topical retinoid *or*
  Azelaic acid *or*
  Salicylic acid

Mild Papulopustular Acne

Topical retinoid *plus*
  Benzoyl peroxide *or*
  Benzoyl peroxide/topical antibiotic *or*
  Benzoyl peroxide/oral antibiotic

Severe Papulopustular or Nodular Acne

Topical retinoid *plus*
Benzoyl peroxide and oral antibiotic *or*
Isotretinoin 1 mg/kg/day

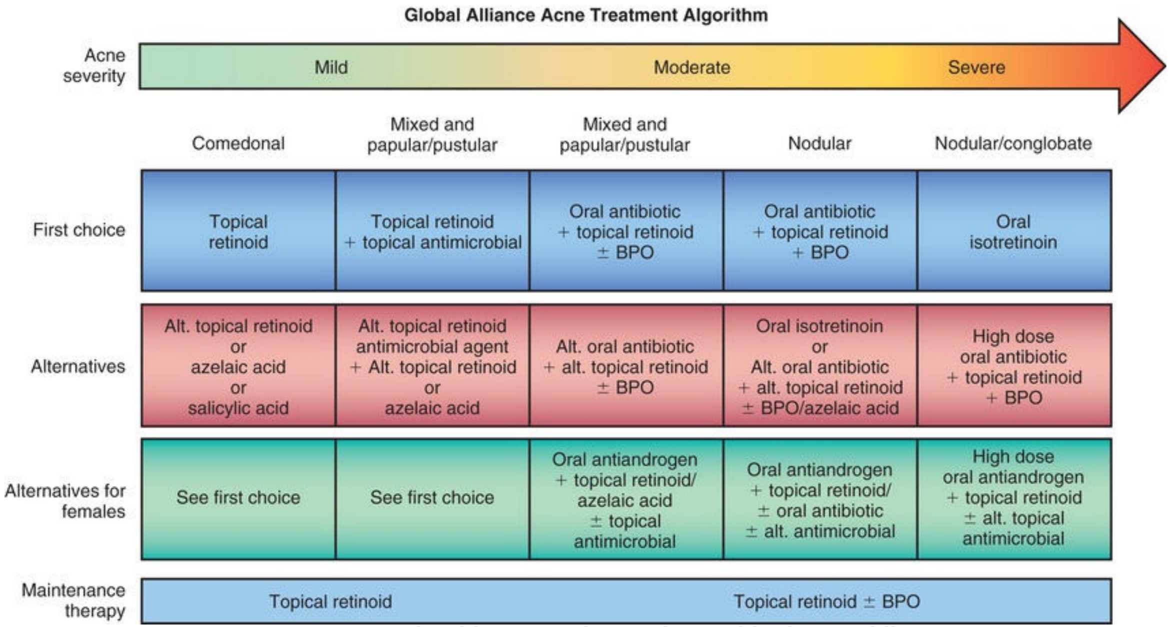

Global Alliance Acne Treatment Algorithm

Acne severity	Mild		Moderate		Severe
	Comedonal	Mixed and papular/pustular	Mixed and papular/pustular	Nodular	Nodular/conglobate
First choice	Topical retinoid	Topical retinoid + topical antimicrobial	Oral antibiotic + topical retinoid ± BPO	Oral antibiotic + topical retinoid + BPO	Oral isotretinoin
Alternatives	Alt. topical retinoid or azelaic acid or salicylic acid	Alt. topical retinoid antimicrobial agent + Alt. topical retinoid or azelaic acid	Alt. oral antibiotic + alt. topical retinoid ± BPO	Oral isotretinoin or Alt. oral antibiotic + alt. topical retinoid ± BPO/azelaic acid	High dose oral antibiotic + topical retinoid + BPO
Alternatives for females	See first choice	See first choice	Oral antiandrogen + topical retinoid/ azelaic acid ± topical antimicrobial	Oral antiandrogen + topical retinoid/ ± oral antibiotic ± alt. antimicrobial	High dose oral antiandrogen + topical retinoid ± alt. topical antimicrobial
Maintenance therapy	Topical retinoid		Topical retinoid ± BPO		

FIG. 689.5 Acne treatment algorithm. BPO, benzoyl peroxide. (From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al: New insights into the management of acne: an update from the Global Allegiance to Improve Outcomes in Acne. *J Am Acad Dermatol* 60:S1–S50, 2009.)

It is also important to address the potentially severe emotional impact of acne on adolescents. The pediatrician must be aware of the frequently poor correlation between acne severity and psychosocial impact, particularly in adolescents. As adolescents become preoccupied with their appearance, offering treatment even to the youngster whose acne is mild may enhance self-image.

Diet

Little evidence shows that the ingestion of particular foods can trigger acne flares. When a patient is convinced that certain dietary items exacerbate acne, it is prudent for the patient to omit those foods provided that such omissions do not lead to excessive dietary restrictions.

Climate

Climate appears to influence acne in that improvement frequently occurs in summer and flares are more common in winter. Remission in summer may relate partly to the relative absence of stress. Emotional tension and fatigue seem to exacerbate acne in many individuals; the mechanism is unclear but has been proposed to relate to an increased adrenocortical response.

Cleansing

Cleansing with soap and water removes surface lipid and renders the skin less oily in appearance, but no evidence shows that surface lipid has a role in generating acne lesions. Only superficial drying and peeling are achieved by cleansing, and almost any mild soap or astringent is adequate. Repetitive cleansing can be harmful because it irritates and chaps the skin. Cleansing agents that contain abrasives and keratolytic agents—such as sulfur, resorcinol, and salicylic acid—may temporarily remove sebum from the skin surface. They exert a mild drying and peeling effect and suppress lesions to a limited degree. They do not prevent microcomedones from forming. No evidence shows that preparations containing alcohol or hexachlorophene decrease acne, because surface bacteria are not involved in the pathogenesis. Greasy cosmetic and hair preparations must be discontinued because they exacerbate preexisting acne and cause further plugging of follicular pores. Manipulation and squeezing of facial lesions only ruptures intact lesions and provokes a localized inflammatory reaction.

Topical Therapy

All topical preparations must be used for 6-8 wk before their effectiveness can be assessed. Retinoids may be used alone for mild acne, but combination therapy is frequently more effective. A popular and effective combination is use of benzoyl peroxide gel in the morning and a retinoid at night (Table 689.3).

Table 689.3

Recommendations for Topical Therapies

- Benzoyl peroxide or combinations with erythromycin or clindamycin are effective acne treatments and are recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne.

- Benzoyl peroxide is effective in the prevention of bacterial resistance and is recommended for patients on topical or systemic antibiotic therapy.
- Topical antibiotics (e.g., erythromycin and clindamycin) are effective acne treatments but are not recommended as monotherapy because of the risk of bacterial resistance.
- Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions.
- Treatment with multiple topical agents that affect different aspects of acne pathogenesis can be useful. Combination therapy should be used in the majority of patients with acne.
- Topical adapalene, tretinoin, and benzoyl peroxide can be safely used in the management of preadolescent acne in children.
- Azelaic acid is a useful adjunctive acne treatment and is recommended in the treatment of postinflammatory dyspigmentation.
- Topical dapsone 5% gel is recommended for inflammatory acne, particularly in adult females with acne.
- There is limited evidence to support recommendations for sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc in the treatment of acne.

From Zaenglein AL, Pathy AL, Scholsser BJ, et al: Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 74(5):945–973, 2016 (Table V, p 951).

Retinoids.

A topical retinoid should be the **primary treatment** for acne vulgaris. Topical retinoids have multiple actions, including inhibition of the formation and number of microcomedones, reduction of mature comedones, reduction of inflammatory lesions, and production of normal desquamation of the follicular epithelium. Retinoids should be applied daily to all the affected areas. The main side effects of retinoids are irritation and dryness. Not all patients initially tolerate daily use of a retinoid. It is prudent to begin therapy every other or every third day and slowly increase the frequency of application as tolerated. Tretinoin, adapalene, and tazarotene (Table 689.4) are the available retinoids. They vary in strength and efficacy, although adapalene tends to be less irritating and tazarotene is more irritating but may be more effective.

Table 689.4

Medications for the Treatment of Acne

DRUG	DOSE	SIDE EFFECTS	OTHER CONSIDERATIONS
TOPICAL AGENTS			
Retinoids			
Tretinoin	Applied once nightly; strengths of 0.025–0.1% available*	Irritation (redness and scaling)	Generics available.
Adapalene	Applied once daily, at night or in the morning; 0.1% and 0.3%*	Minimal irritation	0.1% generic available.
Tazarotene †	Applied once nightly; 0.05% and 0.1%*	Irritation	Limited data suggest tazarotene is more effective than alternatives.
Antimicrobials			
Benzoyl peroxide, alone or with zinc, 2.5–10%	Applied once or twice daily	Benzoyl peroxide can bleach clothing and bedding	Available over the counter; 2.5–5% concentrations as effective as and less drying than 10% concentration.
Clindamycin, erythromycin ‡	Applied once or twice daily	Propensity to resistance	Most effective for inflammatory lesions (rather than comedones); resistance a concern when used alone.
Combination benzoyl peroxide and clindamycin or erythromycin; combination tretinoin and clindamycin	Applied once or twice daily	Side effects from benzoyl peroxide (bleach clothing or bedding) and from topical antibiotics (propensity to resistance)	Combination more effective than topical antibiotics alone; limits development of resistance; use of individual products in combination less expensive and appears similarly effective.
Other Topical Agents			
Azelaic acid, sodium sulfacetamide-sulfur, salicylic	Applied once or twice daily	Well tolerated	Good adjunctive or alternative treatments.

acid [‡]			
ORAL ANTIBIOTICS [§]			
Tetracycline [‖]	250-500 mg once or twice daily	Gastrointestinal upset, intracranial hypertension	Inexpensive; dosing limited by need to take on empty stomach.
Doxycycline [‖]	50-100 mg once or twice daily	Phototoxicity, intracranial hypertension, pill esophagitis, gastrointestinal upset	20-mg dose antiinflammatory only; limited data on efficacy.
Minocycline [‖]	50-100 mg once or twice daily	Hyperpigmentation of teeth, oral mucosa, and skin; lupus-like reactions with long-term treatment, intracranial hypertension, drug hypersensitivity	
Trimethoprim-sulfamethoxazole	One dose (160 mg trimethoprim, 800 mg sulfamethoxazole) twice daily	Toxic epidermal necrolysis and allergic eruptions	Trimethoprim may be used alone in a 300-mg dose twice daily; limited data available.
Erythromycin [‡]	250-500 mg twice daily	Gastrointestinal upset	Resistance problematic; efficacy is limited.
HORMONAL AGENTS [¶]			
Spironolactone [‖]	50-200 mg in 1-2 divided doses	Menstrual irregularities, breast tenderness	Higher doses more effective but cause more side effects; best given in combination with oral contraceptives.
Estrogen-containing oral contraceptives	Daily	Potential side effects include thromboembolism	
ORAL RETINOID			
Isotretinoin[**] (Accutane)	0.5-1.0 mg/kg/day in 2 divided doses	Birth defects; adherence to pregnancy prevention program outlined by drug manufacturer, including 2 initial negative pregnancy tests, is essential; hypertriglyceridemia, elevated results on liver function tests, abnormal night vision, benign intracranial hypertension, dryness of the lips, ocular, nasal, and oral mucosa and skin, secondary staphylococcal infections, arthralgias, and mood disturbances are possible common or important side effects; laboratory testing of lipid profiles and liver function tests monthly should be performed monthly until dose is stabilized	Relapse rate higher if patient is younger than age 16 yr at initial treatment, if acne is of high severity and involves the trunk, or if drug is used in adult women

[*] As cream or gel.

[†] Tazarotene is in pregnancy category X: contraindicated in pregnancy.

[‡] Clindamycin, erythromycin, and azelaic acid are in pregnancy category B: no evidence of risk in humans.

[§] Oral antibiotics are indicated for moderate to severe disease; for the treatment of acne on the chest, back, or shoulders; and in patients with inflammatory disease in whom topical combinations have failed or are not tolerated.

[||] This drug is in pregnancy category D: positive evidence of risk in humans.

[¶] Hormonal agents are for use in women only.

[**] Isotretinoin is in pregnancy category X: contraindicated in pregnancy. It should be used only in patients with severe acne that does not clear with combined oral and topical therapy.

Modified from James WD: Clinical practice: acne. *N Engl J Med* 352:1463–1472, 2005.

Benzoyl Peroxide.

Benzoyl peroxide is primarily an antimicrobial agent. It has an advantage over topical antibiotics in that it does not enhance antimicrobial resistance. It is available in multiple formulations and concentrations. The gel formulations are preferred, owing to better stability and more consistent release of the active ingredient. Washes and cleansers are useful for covering large surface areas such as the chest and back. As with retinoids, the main side effects are irritation and drying. Benzoyl peroxide can also bleach clothing.

Topical Antibiotics.

Topical antibiotics are indicated for the treatment of inflammatory acne. Clindamycin is the most commonly used. It is not as effective as oral antibiotics. It should not be used as monotherapy because it does not inhibit microcomedone formation and has the potential to induce antimicrobial resistance. Irritation and dryness are generally less than with retinoids or benzoyl peroxide. Topical antibiotics are best used as combination products. The most common is benzoyl peroxide/clindamycin. A combination tretinoin/clindamycin product may also be used.

Azelaic Acid.

Azelaic acid (20% cream) has mild antimicrobial and keratolytic properties. It can also help expedite resolution of postinflammatory hyperpigmentation.

Systemic Therapy

Antibiotics, especially tetracycline and its derivatives (see Table 689.4), are indicated for the treatment of patients whose acne has not responded to topical medications, who have moderate to severe inflammatory papulopustular and nodulocystic acne, and who have a propensity for scarring (Table 689.5).

Tetracycline and its derivatives act by reducing the growth and metabolism of *C. acnes*. They also have antiinflammatory properties. For most adolescent patients, therapy may be initiated twice daily, for at least 6-8 wk, followed by a gradual decrease to the minimal effective dose. The drugs should always be administered in combination with a topical retinoid and topical benzoyl peroxide but not with topical antibiotics. Tetracycline absorption is inhibited by food, milk, iron supplements, and calcium-magnesium salts. It should be taken on an empty stomach 1 hr before or 2 hr after meals. Minocycline and doxycycline may be taken with food. Side effects of tetracycline and derivatives are rare. Side effects of tetracycline include vaginal candidosis, particularly in those who take tetracycline concurrently with oral contraceptives; gastrointestinal irritation; phototoxic reactions, including onycholysis and brown discoloration of nails; esophageal ulceration; inhibition of fetal skeletal growth; and staining of growing teeth, precluding its use during pregnancy and in those younger than 8 yr of age. Doxycycline is the most photosensitizing of the tetracycline derivatives and is also more likely to cause pill esophagitis. Rarely, minocycline causes dizziness, intracranial hypertension, bluish discoloration of the skin and mucous membranes, hepatitis, a lupus-like syndrome, and drug hypersensitivity. A possible complication of prolonged systemic antibiotic use is proliferation of Gram-negative organisms—particularly *Enterobacter, Klebsiella, Escherichia coli*, and *Pseudomonas aeruginosa*— producing severe refractory folliculitis.

Table 689.5

Recommendations for Systemic Antibiotics

• Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments.
• Doxycycline and minocycline are more effective than tetracycline.
• Although oral erythromycin or azithromycin can be effective in treating acne, its use should be limited to those who cannot use the tetracyclines (i.e., pregnant women or children <8 yr of age). Erythromycin use should be restricted because of its increased risk of bacterial resistance.
• Use of systemic antibiotics other than the tetracyclines and macrolides is discouraged because there are limited data for their use in acne. Trimethoprim-sulfamethoxazole and trimethoprim use should be restricted to patients who are unable to tolerate tetracyclines or to treatment-resistant patients.
• The use of systemic antibiotic should be limited to the shortest possible duration. Reevaluate at 3-4 mo to minimize the development of bacterial resistance. Monotherapy with systemic antibiotics is not recommended.
• Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy.

From Zaenglein AL, Pathy AL, Scholsser BJ, et al: Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016;74(5):945–973 (Table

VI, p 952).

Women who have acne and hormonal abnormalities, whose acne is unresponsive to antibiotic therapy, or who are not candidates for isotretinoin therapy should be considered for a trial of hormonal therapy. Combined oral contraceptive pills are the primary form of hormonal therapy. Spironolactone has also shown effectiveness.

Isotretinoin (13-*cis* -retinoic acid; Accutane) is indicated for severe nodulocystic acne and moderate to severe acne that has not responded to conventional therapy. The recommended dosage is 0.5-1.0 mg/kg/day. A standard course in the United States lasts 16-20 wk. At the end of one course of isotretinoin, 70–80% of patients are cured, 10-20% need conventional topical and/or oral medications to maintain adequate control, and 10-20% have relapses and need an additional course of isotretinoin. Dosages <0.5 mg/kg/day or a cumulative dose of <120 mg/kg are associated with a significantly higher rate of treatment failure and relapse. If the disease process is not in remission 2 mo after the first course of isotretinoin, a second course should be considered. Isotretinoin reduces size and secretion of sebaceous glands, normalizes follicular keratinization, prevents new microcomedone formation, decreases the population of *C. acnes,* and exerts an anti-inflammatory effect.

Isotretinoin use has many side effects. It is highly **teratogenic** and is **absolutely contraindicated** in pregnancy. Pregnancy should be avoided for 6 wk after discontinuation of therapy. Two forms of birth control are required, as are monthly pregnancy tests. *Concerns over cases of pregnancy despite warnings have prompted a manufacturer registration program, iPLEDGE (www.ipledgeprogram.com), which requires physician enrollment and careful patient pregnancy screening to prescribe isotretinoin.* Many patients also experience cheilitis, xerosis, periodic epistaxis, and blepharoconjunctivitis. Increased serum triglyceride and cholesterol levels are also common. It is important to rule out preexisting liver disease and hyperlipidemia before initiating therapy and to recheck laboratory values 4 wk after commencement of therapy. Less common but significant side effects include arthralgias, myalgias, temporary thinning of the hair, paronychia, increased susceptibility to sunburn, formation of pyogenic granulomas, and colonization of the skin with *Staphylococcus aureus,* leading to impetigo, secondarily infected dermatitis, and scalp folliculitis. Rarely, hyperostotic lesions of the spine develop after more than 1 course of isotretinoin. Concomitant use of tetracycline and isotretinoin is contraindicated because either drug, but particularly when they are used together, can cause benign intracranial hypertension. Although no cause-and-effect relationship has been established, drug-induced mood changes and depression and/or suicide have mandated close attention to psychiatric well-being before and during isotretinoin prescription. An increased risk of inflammatory bowel disease with the use of isotretinoin is debated.

Surgical Therapy

Intralesional injection of low-dose (3-5 mg/mL) midpotency glucocorticoids (e.g., triamcinolone) with a 30-gauge needle on a tuberculin syringe may hasten the healing of individual painful nodulocystic lesions. Dermabrasion or laser peel to minimize scarring should be considered only after the active process is quiescent. Fig. 689.6 describes the management of scarring.

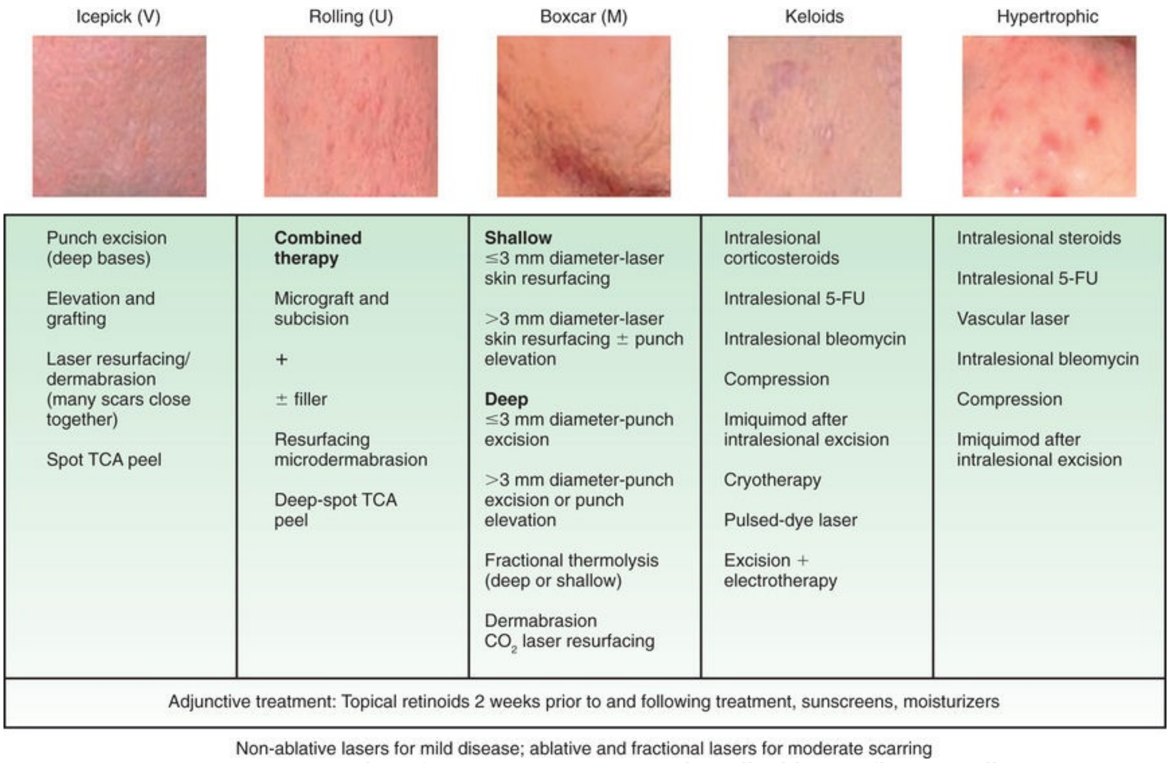

Icepick (V)	Rolling (U)	Boxcar (M)	Keloids	Hypertrophic
Punch excision (deep bases) Elevation and grafting Laser resurfacing/ dermabrasion (many scars close together) Spot TCA peel	**Combined therapy** Micrograft and subcision + ± filler Resurfacing microdermabrasion Deep-spot TCA peel	**Shallow** ≤3 mm diameter-laser skin resurfacing >3 mm diameter-laser skin resurfacing ± punch elevation **Deep** ≤3 mm diameter-punch excision >3 mm diameter-punch excision or punch elevation Fractional thermolysis (deep or shallow) Dermabrasion CO_2 laser resurfacing	Intralesional corticosteroids Intralesional 5-FU Intralesional bleomycin Compression Imiquimod after intralesional excision Cryotherapy Pulsed-dye laser Excision + electrotherapy	Intralesional steroids Intralesional 5-FU Vascular laser Intralesional bleomycin Compression Imiquimod after intralesional excision
Adjunctive treatment: Topical retinoids 2 weeks prior to and following treatment, sunscreens, moisturizers				

Non-ablative lasers for mild disease; ablative and fractional lasers for moderate scarring

FIG. 689.6 **Treatment options for acne scars. CO_2 , carbon dioxide; FU, fluorouracil; TCA, trichloroacetic acid. (From Thiboutot D, Gollnick H; Global Alliance to Improve Acne, et al: New insights into the management of acne: an update from the Global Allegiance to Improve Outcomes in Acne. *J Am Acad Dermatol* 60:S1–S50, 2009.)**

The role of pulsed-dye laser in the treatment of inflammatory acne is controversial and inconclusive.

Drug-Induced Acne

Pubertal and postpubertal patients who are receiving systemic corticosteroid therapy are predisposed to steroid-induced acne. This monomorphous folliculitis occurs primarily on the face, neck, chest (Fig. 689.7), shoulders, upper back, arms, and, rarely, on the scalp. Onset follows the initiation of steroid therapy by approximately 2 wk. The lesions are small, erythematous papules or pustules that may erupt in profusion and are all in the same stage of development. Comedones may occur subsequently, but nodulocystic lesions and scarring are rare. Pruritus is occasional. Although steroid acne is relatively refractory if the medication is continued, the eruption may respond to the use of tretinoin and a benzoyl peroxide gel.

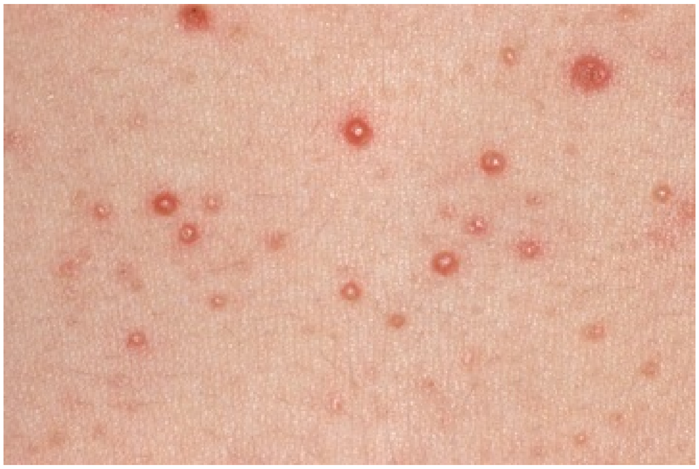

FIG. 689.7 **Monomorphous papular eruption of steroid acne.**

Other **drugs** that can induce **acneiform lesions** in susceptible individuals include isoniazid, phenytoin, phenobarbital, trimethadione, lithium carbonate, androgens (anabolic steroids), and vitamin B_{12} .

Halogen Acne

Administration of medications containing iodides or bromides or, rarely, ingestion of massive amounts of vitamin-mineral preparations or iodine-containing “health foods” such as kelp may induce halogen acne. The lesions are often very inflammatory. Discontinuation of the provocative agent and appropriate topical preparations usually achieve reasonable therapeutic results.

Chloracne

Chloracne is a result of external contact with, inhalation of, or ingestion of halogenated aromatic hydrocarbons, including polyhalogenated biphenyls, polyhalogenated naphthalenes, and dioxins. Lesions are primarily comedonal. Inflammatory lesions are infrequent but may include papules, pustules, nodules, and cysts. Healing occurs with atrophic or hypertrophic scarring. The face, postauricular regions, neck, axillae, genitals, and chest are most commonly involved. The nose is often spared. In cases of severe exposure, associated findings may include hepatitis, production of porphyrins, bulla formation on sun-exposed skin, hyperpigmentation, hypertrichosis, and palmar and plantar hyperhidrosis. Topical or oral retinoids may be effective; benzoyl peroxide and antibiotics are generally ineffective.

Neonatal Acne

Approximately 20% of normal neonates demonstrate acne in the 1st mo of life. Small inflammatory papules and pustules predominate on the cheeks and forehead (Fig. 689.8); comedones are absent. The cause of neonatal acne is unknown but it has been theorized that it may be an inflammatory reaction to *Pityrosporum* species rather than true acne; therefore the term *neonatal cephalic pustulosis* has been proposed. Other theories include placental transfer of maternal androgens, hyperactive neonatal adrenal glands, and a hypersensitive neonatal end-organ response to androgenic hormones. The eruption involutes spontaneously over a few months. **Treatment** is usually unnecessary. If desired, the lesions can be treated effectively with topical antifungals and/or benzoyl peroxide.

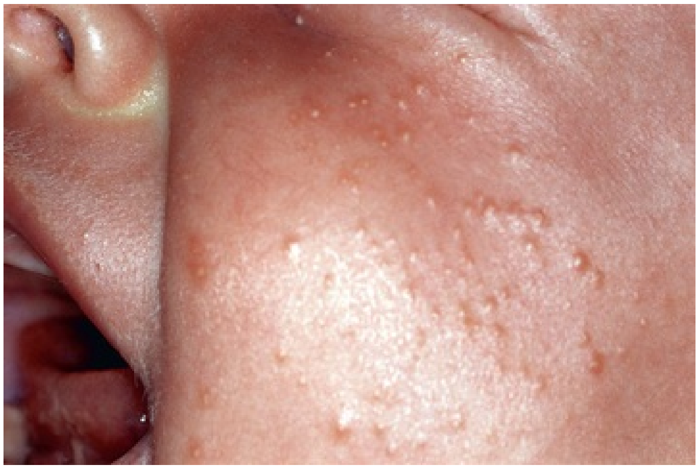

FIG. 689.8 Comedonal acne in a neonate.

Infantile Acne

Infantile acne usually manifests between 3 mo and 1 yr of age, more commonly in boys than in girls. Acne lesions are more numerous, pleomorphic, severe, and persistent than in the case of neonatal acne (Fig. 689.9). Open and closed comedones predominate on the face. Papules and pustules occur frequently, but only occasionally do nodulocystic lesions develop. Pitted scarring is seen in 10–15%. The course may be relatively brief, or the lesions may persist for many months or years, although the eruption generally resolves by 4 yr of age. Use of topical benzoyl peroxide gel and tretinoin usually clears the eruption within a few weeks. Oral erythromycin is occasionally necessary. A child with refractory acne warrants a search for an abnormal source of androgens, such as a virilizing tumor or congenital adrenal hyperplasia.

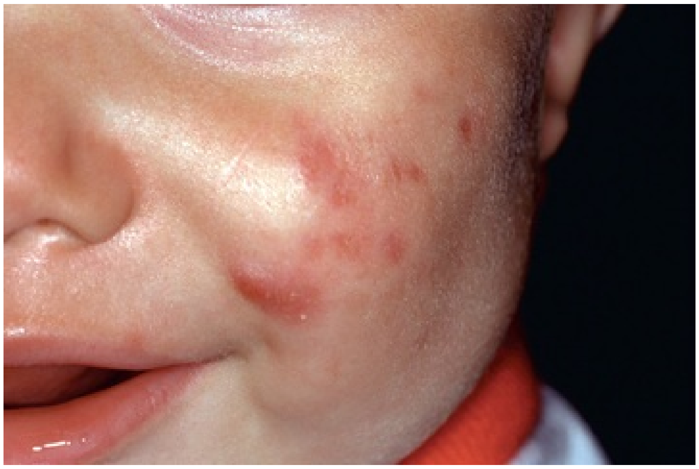

FIG. 689.9 **Inflammatory infantile acne.**

Mid-Childhood Acne

Acne that begins between 1 and 7 yr of age is not considered normal. Although the neonatal adrenal gland secretes high levels of androgens through the 1st year of life, it becomes quiescent until adrenarche, which occurs around age 7. Underlying endocrine abnormality should be considered in those presenting with acne in middle childhood. Precocious puberty, late-onset congenital adrenal hyperplasia, or an androgen-secreting tumor may underlie acne in this age group. Workup for androgen excess is indicated.

Tropical Acne

A severe form of acne occurs in tropical climates; it is believed to be caused by the intense heat and humidity. Hydration of the pilosebaceous duct pore may accentuate blockage of the duct. Affected individuals tend to have an antecedent history of adolescent acne that is quiescent at the time of the eruption. Lesions occur mainly on the entire back, chest, buttocks, and thighs, with a predominance of suppurating papules and nodules. Secondary infection with *S. aureus* may be a complication. The eruption is refractory to acne therapy if the environmental factors are not eliminated.

Acne Conglobata

Acne conglobata, or conglobate acne, is a chronic progressive inflammatory disease that occurs mainly in men and more commonly in white than in black individuals, but it may begin during adolescence. Patients usually have a history of preexisting acne vulgaris. The principal lesion is the nodule, although there is often a mixture of comedones with multiple pores, papules, pustules, nodules, cysts, abscesses, and subcutaneous dissection with formation of multichannel sinus tracts. Severe scarring is characteristic. The face is relatively spared, but in addition to the back and chest, the buttocks, abdomen, arms, and thighs may be involved. Constitutional symptoms and anemia may accompany the inflammatory process. Coagulase-positive staphylococci and β-hemolytic streptococci are frequently cultured from lesions but do not appear to be primarily involved in the pathogenesis. Acne conglobata occasionally occurs in association with hidradenitis suppurativa and dissecting cellulitis of the scalp (as the follicular occlusion triad) and may be complicated by erosive arthritis and ankylosing spondyloarthritis. Endocrinologic studies are not revealing. Routine acne therapy is generally ineffective. Systemic therapy with a corticosteroid may be required to suppress the intense inflammatory activity. Isotretinoin is the most effective form of therapy for some patients but may produce a flare after its initiation.

Acne Fulminans (Acute Febrile Ulcerative Acne)

Acne fulminans is characterized by abrupt onset of extensive inflammatory, tender, ulcerative acneiform lesions on the back and chest of male teenagers. The distinctive feature is the tendency for large nodules to form exudative, necrotic, ulcerated, crusted plaques. Lesions often spare the face and heal with scarring. A preceding history of mild papulopustular or nodular acne is noted in most patients. Constitutional symptoms and signs are common, including fever, debilitation, arthralgias, myalgias, weight loss, and leukocytosis. Blood cultures are sterile. Lesions of **erythema nodosum** sometimes develop on the shins. **Osteolytic bone** lesions may develop in the clavicle, sternum, and epiphyseal growth plates; affected bones appear normal or have slight sclerosis or thickening on healing. Salicylates may be helpful for the myalgias, arthralgias, and fever. Corticosteroids (1 mg/kg of prednisone) are started first. Then, 1 wk later, isotretinoin (0.5-1.0 mg/kg) is added. Dapsone may be effective if isotretinoin cannot be used. The corticosteroid dosage is tapered over approximately 6 wk. Antibiotics are not indicated unless there is evidence of secondary infection. Compared with acne conglobata, acne fulminans occurs in younger patients, is more explosive in onset, more commonly has associated constitutional symptoms and ulcerated crusted lesions, and less commonly has multiheaded comedones or involves the face.

Pyogenic Arthritis with Pyoderma Gangrenosum and Acne (PAPA Syndrome) (see Chapter 188).

Chronic Recurrent Multifocal Osteomyelitis/Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) Syndrome (see Chapter 188).

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CHAPTER 690

Tumors of the Skin

Jesse P. Hirner, Kari L. Martin

See also Chapters 614 .

Epidermal Inclusion Cyst (Epidermoid Cyst)

Epidermoid cysts are the nodules most commonly seen in children. Such a cyst is a sharply circumscribed, dome-shaped, firm, freely movable, skin-colored nodule (Fig. 690.1), often with a central dimple or punctum that is a plugged, dilated pore of a pilosebaceous follicle. Epidermoid cysts form most frequently on the face, neck, chest, or upper back and may periodically become inflamed and infected secondarily, particularly in association with acne vulgaris. The cyst wall may also rupture and induce an inflammatory reaction in the dermis. The wall of the cyst is derived from the follicular infundibulum. A mass of layered keratinized material that may have a cheesy consistency fills the cavity. Epidermoid cysts may arise from occlusion of pilosebaceous follicles, implantation of epidermal cells into the dermis as a result of an injury that penetrates the epidermis, and rests of epidermal cells. Multiple epidermoid cysts may be present in Gardner syndrome and the nevoid basal cell carcinoma syndrome. Excision of the cyst with removal of the entire sac and its contents is indicated, particularly if the cyst becomes recurrently inflamed. A fluctuant cyst should be incised and drained and, if there is surrounding erythema, treated with antibiotics or intralesional corticosteroids. After the inflammation subsides, the cyst should be removed.

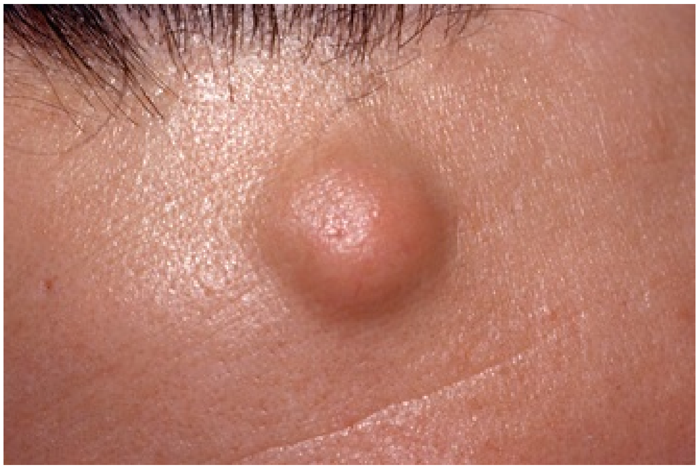

FIG. 690.1 **Flesh-colored cyst on the forehead.**

Milium

Milium is a 1-2 mm, firm, pearly white or yellowish subepidermal keratin cyst. Milia in newborns are discussed in Chapter 666 . Secondary milia occur in association with subepidermal blistering diseases and after dermabrasion or other injury to the skin. They are retention cysts caused by hyperproliferation of injured epithelium and are indistinguishable histopathologically from primary milia. Those that develop after blistering usually arise from the eccrine sweat duct, but they may develop from the hair follicle, sebaceous duct, or epidermis. A milium body differs from an epidermoid cyst only in its small size and superficial location.

Fibrofolliculomas

These lesions usually appear in late adolescents or in young adults and are characterized by multiple dome-shaped clear-white papules appearing on the nose, cheeks, and neck, and at times the trunk or ears (Fig. 690.2). They are associated with the familial cancer syndrome of **Birt-Hogg-Dubé,** an autosomal dominant disorder that results from a mutation in the folliculin *(FLCN)* tumor suppressor gene. Associated features include pulmonary cysts, pneumothorax, renal cell carcinoma, and other benign or malignant tumors.

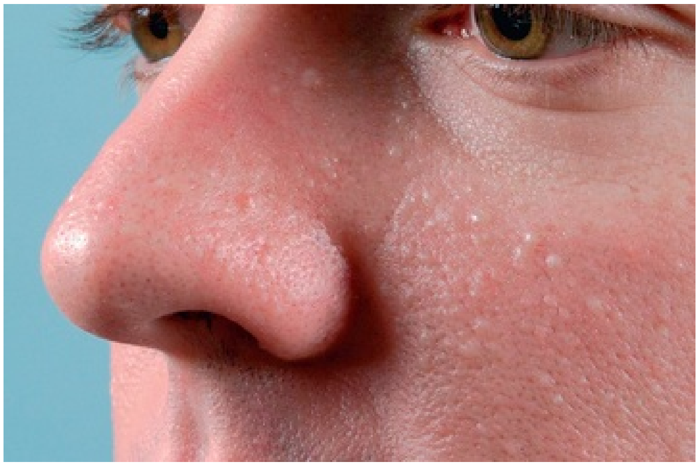

FIG. 690.2 **Multiple, dome-shaped, whitish papules on the nose and cheeks in a 31 yr old carrier of an *FLCN* mutation. (From Menko FH, van Steensel MAM, Giraud S, et al: Birt-Hogg-Dubé syndrome: diagnosis and management. *Lancet* 10:1199–1206, 2009, Fig. 1.)**

Pilar Cyst (Trichilemmal Cyst)

A pilar cyst may be clinically indistinguishable from an epidermoid cyst. It manifests as a smooth, firm, mobile nodule, predominantly on the scalp (Fig. 690.3). Pilar cysts occasionally develop on the face, neck, or trunk. A cyst may become inflamed and may occasionally suppurate and ulcerate. The cyst wall is composed of stratified squamous epithelium with indistinct intercellular bridges. The peripheral cell layer of the wall shows a palisade arrangement, which is not seen in an epidermoid cyst. No granular layer is present. The cyst cavity contains dense homogeneous eosinophilic keratinous material, and foci of calcification are seen in 25% of cases. The propensity for development of pilar cysts may be inherited in an autosomal dominant manner. More than one cyst generally develops in a patient. Numerous pilar and epidermoid cysts, desmoid tumors, fibromas, lipomas, or osteomas may be associated with colonic polyposis or adenocarcinoma in Gardner syndrome. Pilar cysts shell out easily from the dermis.

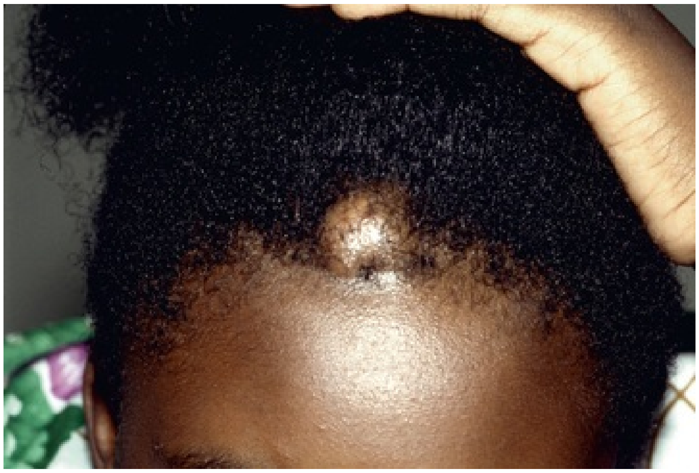

FIG. 690.3 Pilar cyst of the anterior scalp.

Pilomatricoma (Pilomatrixoma)

The second most common nodule seen in children, pilomatricoma is a benign tumor that manifests as a 3-30 mm, firm, solitary, deep dermal or subcutaneous tumor on the head, neck, or upper extremities. The overlying epidermis is usually normal. The tumor may occasionally be located more superficially, however, tinting the overlying skin blue-red (Fig. 690.4). Multiple pilomatricomas are seen in myotonic dystrophy, Gardner syndrome, Rubinstein-Taybi syndrome, and Turner syndrome. In general, however, pilomatricomas are not hereditary. Histopathologically, irregularly shaped islands of epithelial cells with eosinophilic, anucleate “ghost cells” are embedded in a cellular stroma. Calcium deposits are found in 75% of tumors. Pilomatricomas are caused by mutations in β-catenin.

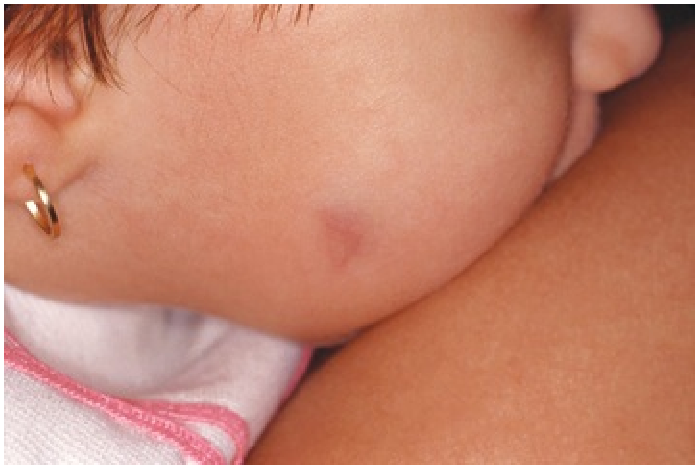

FIG. 690.4 **Pilomatricoma. Firm tumor with overlying bluish discoloration of the skin.**

Trichoepithelioma

A 2-8 mm, smooth, round, firm, skin-colored papule, trichoepithelioma is derived from an immature hair follicle. Trichoepitheliomas generally occur singly on the face in childhood or early adulthood. Multiple trichoepitheliomas are inherited autosomal dominantly (type 1: *CYLD* gene; type 2: 9p21 gene currently unidentified), appear in childhood or at puberty, and gradually increase in number on the nasofacial folds, nose, forehead, and upper lip; occasionally they occur on the scalp, neck, and upper trunk. Microscopically, these benign tumors are characterized by horn cysts composed of a fully keratinized center surrounded by basophilic cells in an adenoid network. Topical imiquimod therapy may be beneficial. Surgical excision has been used for therapy, as have cryotherapy, electrosurgery, and laser vaporization.

Eruptive Vellus Hair Cysts

Eruptive vellus hair cysts are 1-3 mm, asymptomatic, soft, skin-colored follicular papules on the central chest (Fig. 690.5). They may become crusted or umbilicated. Abnormal vellus hair follicles become occluded at the level of the infundibulum, resulting in retention of hairs within an epithelium-lined cystic dilation of the proximal part of the follicle. Most cases are chronic, but spontaneous regression has been reported.

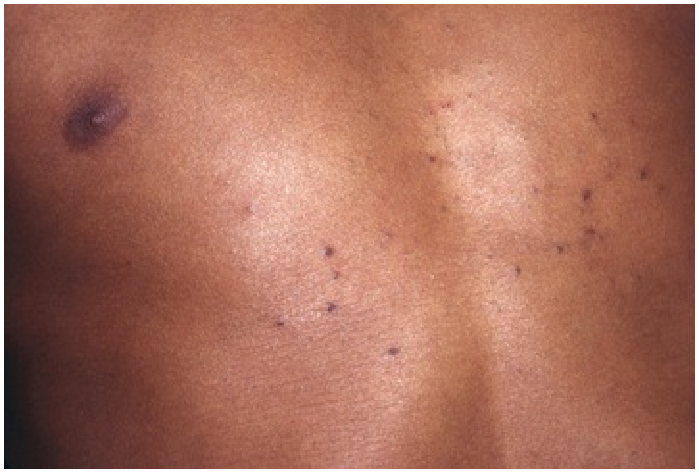

FIG. 690.5 Eruptive vellus hair cysts. Multiple papules on the chest.

Steatocystoma Multiplex

An autosomal dominant (*KRT17* gene) condition, steatocystoma multiplex usually manifests in adolescence or early adulthood as numerous soft to firm cystic nodules that are adherent to the underlying skin and are 3 mm to 3 cm in diameter. When punctured, the cysts may drain oily or cheesy material. Sites of predilection include the sternal region, axillae, arms, and scrotal skin. The multiply folded cyst wall is lined on the luminal side with a thick, homogeneous, eosinophilic horny layer; there is no granular layer. Flattened sebaceous gland lobules are often visible in the cyst wall, and lanugo hairs may be present in a cystic cavity that appears otherwise empty (a processing artifact).

Syringoma

The benign tumors known as syringomas are soft, small, skin-colored or yellowish brown papules that develop on the face, particularly in the periorbital regions (Fig. 690.6). Other sites of predilection include the axillae and umbilical and pubic areas. They often develop during puberty and are more frequent in females. Eruptive syringomas develop in crops over the anterior trunk during childhood or adolescence. A syringoma is derived from an intraepidermal sweat gland duct. Syringomas are of cosmetic significance only. Sparse lesions may be excised, but they are often too numerous to remove.

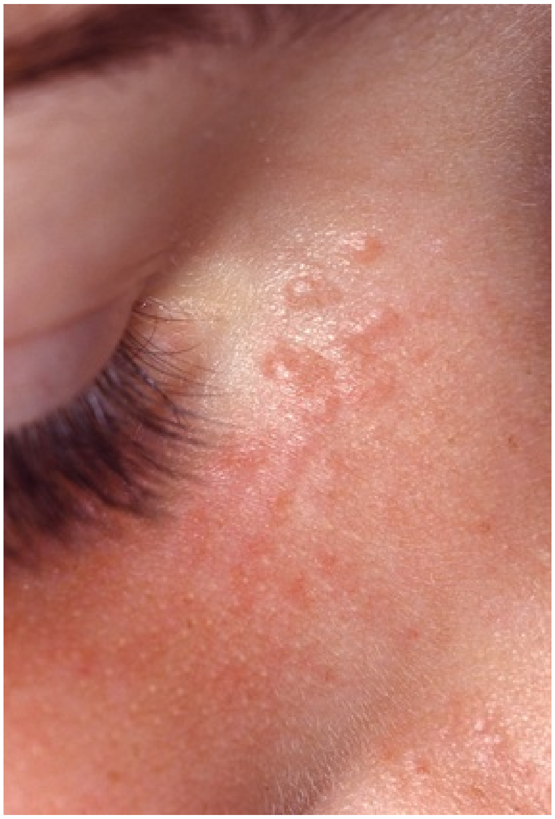

FIG. 690.6 **Syringomas. Multiple yellow papules near the eye.**

Infantile Digital Fibroma

Infantile digital fibroma is a smooth, firm, erythematous or skin-colored nodule on the dorsal or lateral surface of a distal phalanx of a finger or toe. More than 80% of tumors occur in infancy or may be present at birth. Lesions may be solitary or multiple and may manifest as “kissing” tumors on opposing digits. They are usually asymptomatic, but flexion deformity of the digits may occur. Clinically the lesion resembles a fibroma, leiomyoma, angiofibroma, acquired digital fibrokeratoma, accessory digit, or mucous cyst. The diagnosis is confirmed by the finding of numerous spindle-shaped fibroblasts that contain small, round, dense eosinophilic cytoplasmic inclusion bodies composed of collections of actin microfilaments. Local recurrence after simple excision of this tumor has been reported in 75% of patients. Because the tumor does not metastasize and may regress spontaneously in 2-3 yr, a course of expectant observation is advised. If functional impairment or flexion deformity of the digit becomes apparent, prompt full excision of the tumor is indicated.

Dermatofibroma (Histiocytoma)

A benign dermal tumor, dermatofibroma may be pedunculated, nodular (Fig. 690.7), or flat and is usually well circumscribed and firm but occasionally feels soft on palpation. The overlying skin is usually hyperpigmented; it may be shiny or keratotic and dimples when the tumor is pinched. Dermatofibromas range in size from 0.5-10.0 mm, arise most frequently on the limbs, and are usually asymptomatic but may occasionally be pruritic. They are composed of fibroblasts, young and mature collagen, capillaries, and histiocytes in varying proportions, forming a nodule in the dermis that has poorly defined edges. The cause of these tumors is unknown, but trauma such as an insect bite or folliculitis appears to induce reactive fibroplasia. The differential diagnosis includes epidermal inclusion cyst, juvenile xanthogranuloma, hypertrophic scar, and neurofibroma. Dermatofibromas may be excised or left intact, according to the patient's preference. They usually persist indefinitely.

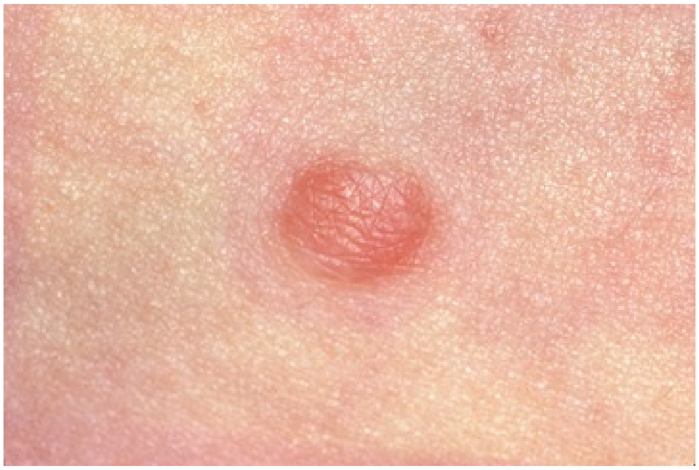

FIG. 690.7 **Dermatofibroma. Red-brown nodular variant.**

Juvenile Xanthogranuloma

A firm, dome-shaped, yellow, pink, or orange papule or nodule (Fig. 690.8), juvenile xanthogranuloma varies from 5 mm to approximately 4 cm in diameter. The average age at onset is 2 yr. These nodules are 10 times more common in white than in African American individuals. Sites of predilection are the scalp, face, and upper trunk, where they may erupt in profusion or remain as solitary lesions. Nodular lesions may appear on the oral mucosa. The diagnosis is usually made clinically. Mature lesions are characterized histopathologically by a dermal infiltrate of lipid-laden histiocytes, admixed inflammatory cells, and Touton giant cells. Clinically the lesions may resemble papulonodular urticaria pigmentosa, dermatofibromas, or xanthomas of hyperlipoproteinemia, but they can be distinguished from these entities histopathologically.

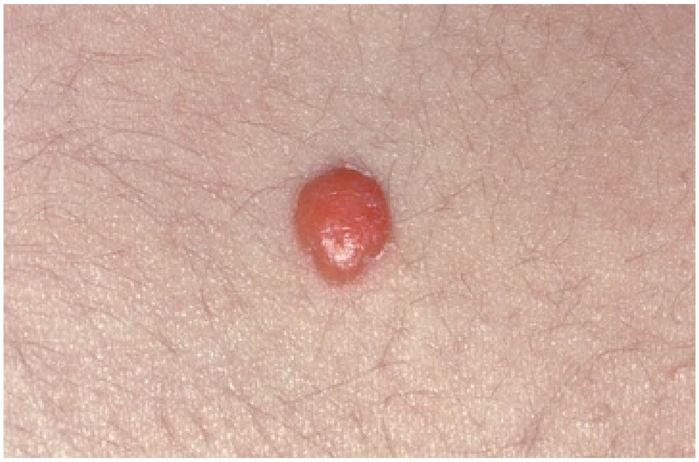

FIG. 690.8 **Juvenile xanthogranuloma. Solitary orange papule.**

Affected infants are nearly always otherwise normal, and blood lipid values are not elevated. Café-au-lait macules are found on 20% of patients with juvenile xanthogranuloma. Xanthogranulomatous infiltrates occur occasionally in ocular tissues. This process may result in glaucoma, hyphema, uveitis, heterochromia iridis, iritis, or sudden proptosis. When seen in patients <2 yr of age, multiple lesions and periocular location may heighten concerns for intraocular involvement. There appears to be an association among juvenile xanthogranuloma, neurofibromatosis, and childhood leukemia, most frequently juvenile chronic myelogenous leukemia. There is no need to remove the benign lesions of juvenile xanthogranuloma because most of them regress spontaneously in the first few years. Residual dyspigmentation and atrophy may result.

Lipoma

A benign collection of fatty tissue, lipoma appears on the trunk, neck, or proximal portions of the limbs. Lipomas are soft, compressible, lobulated subcutaneous masses. Multiple lesions may occur occasionally, as in Gardner syndrome. Atrophy, calcification, liquefaction, or xanthomatous change may sometimes complicate their course. A lipoma is composed of normal fat cells surrounded by a thin connective tissue capsule. Lipomas represent a cosmetic defect and may be surgically excised. Multiple lipomas, identical to those that occur singly, are inherited in an autosomal dominant fashion and often appear by the 3rd decade in patients with familial multiple lipomatosis. Lipomas may appear intra-abdominally, intramuscularly, and subcutaneously. Congenital lipomatosis manifests in the 1st few mo of life as large subcutaneous fatty masses on the chest with extension into skeletal muscle. Congenital lipomatosis can also be a manifestation of **Proteus syndrome** (overgrowth/hyperplasia skin, connective tissue, mutation in *AKT1*). Angiolipomas usually manifest as numerous painful subcutaneous nodules on the arms and trunk.

CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal and spinal anomalies) is usually a sporadic disorder caused by a mutation in the ***PIK3CA*** gene with an asymmetric truncal lipomatous mass present at birth. Additional features include macrodactyly, vascular malformations (low flow), linear epidermal nevus, and renal anomalies. The differential diagnosis includes Proteus, Klippel-Trenaunay, and Bannayan-Riley-Ruvalcaba syndromes.

PIK3CA somatic mutations and mutations in the related AKT-mTOR pathway (*PIK3CA* -related overgrowth spectrum) are associated with segmental overgrowth syndromes (Figs. 690.9 and 690.10). In addition to regional/localized tissue overgrowth, there is a spectrum of malformations (hemimegalencephaly, macrodactyly, lymphatic, muscle hemihypertrophy, epidermal nevi, capillary, polydactyly, syndactyly).

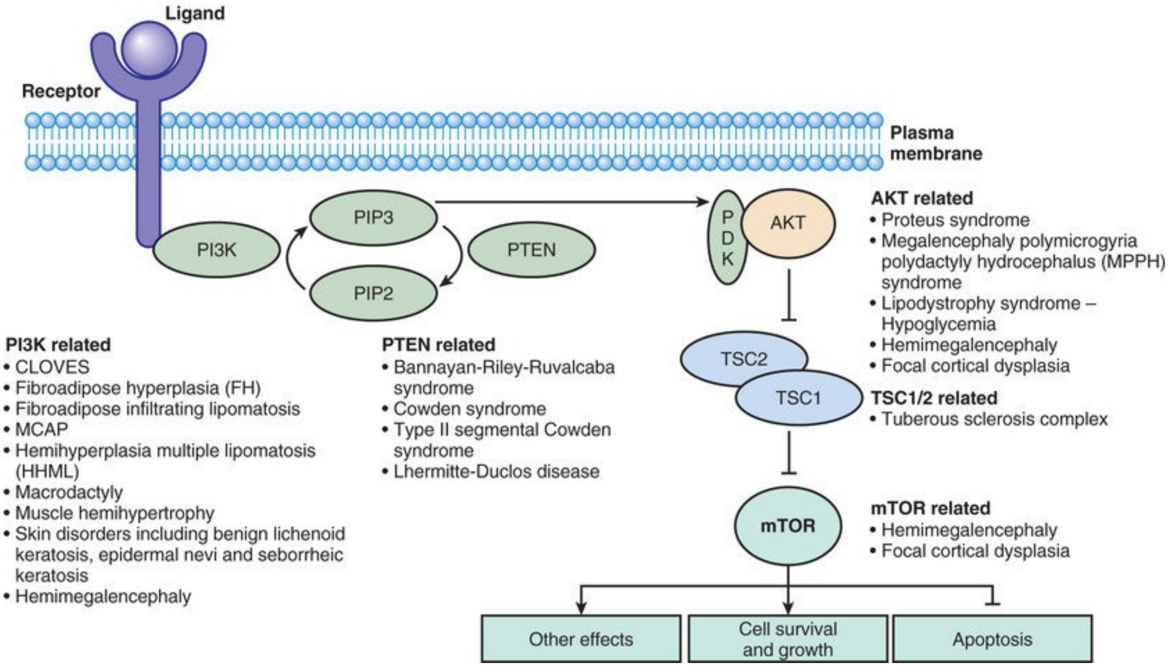
Ligand
Receptor
Plasma membrane
PI3K
PIP3
PIP2
PTEN
P D K
AKT
TSC2
TSC1
mTOR
AKT related
• Proteus syndrome
• Megalencephaly polymicrogyria polydactyly hydrocephalus (MPPH) syndrome
• Lipodystrophy syndrome – Hypoglycemia
• Hemimegalencephaly
• Focal cortical dysplasia
TSC1/2 related
• Tuberous sclerosis complex
mTOR related
• Hemimegalencephaly
• Focal cortical dysplasia
PI3K related
• CLOVES
• Fibroadipose hyperplasia (FH)
• Fibroadipose infiltrating lipomatosis
• MCAP
• Hemihyperplasia multiple lipomatosis (HHML)
• Macrodactyly
• Muscle hemihypertrophy
• Skin disorders including benign lichenoid keratosis, epidermal nevi and seborrheic keratosis
• Hemimegalencephaly
PTEN related
• Bannayan-Riley-Ruvalcaba syndrome
• Cowden syndrome
• Type II segmental Cowden syndrome
• Lhermitte-Duclos disease
Other effects
Cell survival and growth
Apoptosis

FIG. 690.9 Simplified PI3K-AKT-mTOR pathway and associated clinical overgrowth disorders. PDK, phosphatidylinositol-dependent kinase; PIP, phosphatidylinositol polyphosphate; PTEN, phosphatase and tensin homolog. (From Kang H, Baek ST, Song S, et al: Clinical and genetic aspects of the segmental overgrowth spectrum due to somatic mutations in PIK3CA. *J Pediatr* 167(5):957–962, 2015.)

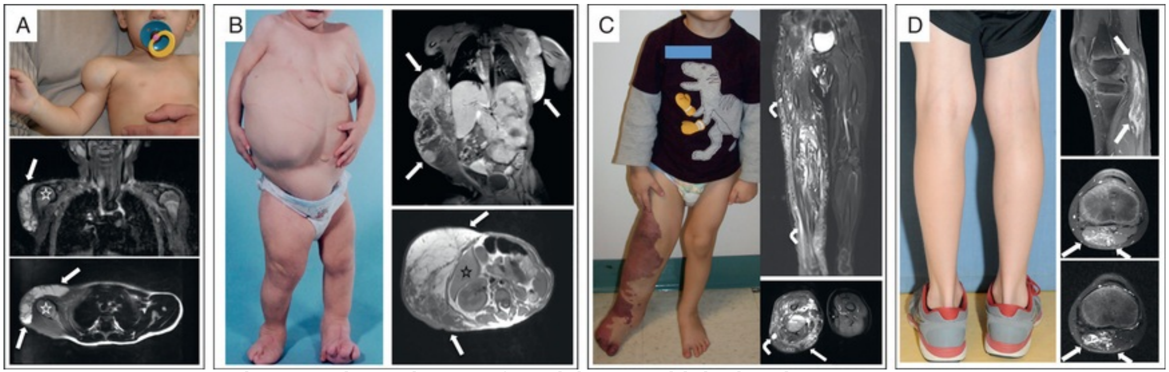

FIG. 690.10 Photographs and MRIs of participants with isolated LM, CLOVES, KTS, and FAVA. A, An 8 mo old boy (LM1) with isolated LM. Note swelling in deltoid region without cutaneous vascular signs. Coronal and sagittal fat-saturated T2-weighted MRI demonstrates macrocystic LM (a multilocular cystic mass) involving the anterolateral aspects of the right shoulder without muscular infiltration *(arrows)* ; humeral head *(asterisk)* . B, A 19 mo old female (CL12) with CLOVES syndrome. Note asymmetric distribution of truncal lipomatous masses and bilateral lower extremity involvement. Coronal fat-saturated T1-weighted MRI following contrast administration demonstrates moderate heterogeneous enhancement of the bilateral truncal masses *(arrows)* . Axial T1-weighted MRI without contrast depicts truncal lipomatous overgrowth *(arrows)* ; segment VI of the liver *(asterisk)* . C, A 3 yr old boy (KT4) with KTS. Note capillary LM and overgrowth involving the right lower extremity. Coronal and axial fat-saturated T2-weighted MRI shows the persistent marginal vein system *(bent arrows)* and marked enlargement of the subcutaneous tissues due to a combination of lymphatic fluid and

fat *(straight arrow)* . There are also intramuscular venous malformations. D, A 9 yr old boy (F8) with FAVA of the left gastrocnemius muscle; note absence of overgrowth and cutaneous vascular anomalies. Sagittal fat-saturated T1-weighted MRI following contrast administration demonstrates the longitudinal distribution of the diffuse FAVA *(arrows)* . Axial fat-saturated T2-weighted MRI with *(upper)* and without *(lower)* contrast. Note that the right head of the gastrocnemius muscle is diffusely replaced by a contrast-enhancing heterogeneous soft tissue lesion *(arrows)* . CLOVES, congenital lipomatous overgrowth with vascular, epidermal, and skeletal anomalies; FAVA, fibroadipose vascular anomaly; KTS, Klippel-Trenaunay syndrome; LM, lymphatic malformation. (From Luks VL, Kamitaki N, Vivero MP, et al: Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *J Pediatr* 166:1048–1054, 2015 [Fig. 1, p 1051].)

Basal Cell Carcinoma

Basal cell carcinoma is very rare in children in the absence of a predisposing condition, such as nevoid basal cell carcinoma syndrome, xeroderma pigmentosum, nevus sebaceus of Jadassohn, arsenic intake, or exposure to irradiation. The lesions are smooth, pearly, pink telangiectatic papules that enlarge slowly and may bleed or ulcerate. Sites of predilection are the face, scalp, and upper back. The differential diagnosis includes pyogenic granuloma, nevocellular nevus, epidermal inclusion cyst, closed comedo, dermatofibroma, and adnexal tumor. Depending on the site of occurrence and associated disease of the host, electrodesiccation and curettage or simple excision of basal cell carcinoma is usually curative. When the tumor is recurrent, >2 cm in diameter, located on problematic anatomic areas such as the midface or ears, or is an aggressive histopathologic type, Mohs microscopically controlled surgery may be the most appropriate treatment.

Nevoid Basal Cell Carcinoma Syndrome (Basal Cell Nevus Syndrome, Gorlin Syndrome)

The autosomal dominant entity known as nevoid basal cell carcinoma syndrome is caused by mutations in the *PTCH1* , *PTCH2* (“patched”), and *SUFU* genes. These tumor-suppressor genes, part of the hedgehog signaling pathway, are important in determining embryonic patterning and cell fate in a number of structures in the developing embryo. Mutations in these genes produce dysregulation of several genes involved in organogenesis and carcinogenesis.

Consequently the syndrome includes a wide spectrum of defects involving the skin, eyes, central nervous and endocrine systems, and bones. The predominant features are early-onset basal cell carcinomas and mandibular cysts. Approximately 20% of those in whom a basal cell carcinoma develops before age 19 yr have this syndrome. Basal cell carcinomas appear between puberty and age 35 yr, erupting in crops of tumors that vary in size, color, and number; they may be difficult to distinguish from other types of skin lesions. Sites of predilection are the periorbital skin, nose, malar areas, and upper lip, but the lesions can also develop on the trunk and limbs and are not restricted to sun-exposed areas. Ulceration, bleeding, crusting, and local invasion can occur. Small milia, epidermal cysts, pigmented lesions, hirsutism, and palmar and plantar pits are additional cutaneous findings.

The facies of patients with this syndrome are characterized by temporoparietal bossing, prominent supraorbital ridges, a broad nasal root, ocular hypertelorism or dystopia canthorum, and prognathism. Keratinized cysts (odontogenic keratocysts) in the maxilla and mandible occur in most patients. These cysts range in size from a few millimeters to several centimeters, may result in maldevelopment of the teeth, and cause pain, swelling of the jaw, facial deformity, bone erosion, pathologic fractures, and suppurating sinus tracts. Osseous defects such as anomalous rib development, spina bifida, kyphoscoliosis, and brachymetacarpalism occur in 60% of patients, and ocular abnormalities—including cataracts, glaucoma, coloboma, strabismus, and blindness—occur in approximately 25%. Some males have hypogonadism, and the testes are absent or undescended. Kidney malformations have also been reported. Neurologic manifestations include calcification of the falx, seizures, mental retardation, partial agenesis of the corpus callosum, hydrocephalus, and nerve deafness. The incidence of medulloblastoma, ameloblastoma of the oral cavity, fibrosarcoma of the jaw, teratoma, cystadenoma, cardiac fibroma, ovarian fibroma, and fetal onset rhabdomyoma is higher in patients with nevoid basal cell carcinoma syndrome.

Treatment of these patients requires the participation of various specialists according to individual clinical problems. Basal cell carcinomas should not be treated with irradiation. Most of the basal cell carcinomas have a clinically benign course, and it is often impossible to remove them all. Those with an aggressive growth pattern and those on the central areas of the face, however, should be removed promptly. Treatment options include surgery, Mohs micrographic surgery, laser ablation, cryotherapy, photodynamic therapy, topical

5% imiquimod and oral retinoids (0.5-1.0 mg/kg/day). Vismodegib, which inhibits smoothened protein in the hedgehog pathway, is a targeted therapy available for unresectable basal cell carcinomas. Genetic counseling is also indicated.

Melanoma

The incidence of melanoma in persons younger than 20 yr of age in the United States is approximately 5-6 cases per 1 million, with 73% occurring in 15 to 19 yr olds, 17% in 10 to 14 yr olds, and 10% in children younger than 10 yr of age. Melanoma is more common among adolescent females than males. Ultraviolet (UV) light, especially sun exposure, is a well-known risk factor for melanoma in adults and contributes to teenage melanoma, as shown by the tendency of lesions to develop on sun-exposed areas in this age group. In younger patients, melanoma does not appear to be associated with sun exposure and often occurs in skin that is not frequently exposed to the sun. Pediatricians should counsel patients regarding the avoidance of sun exposure and the use of tanning beds to decrease the risk of later development of melanoma. Patients with fair skin and a family history of melanoma are at particularly high risk. Known risk factors for children are a giant congenital melanocytic nevus (>40 cm), dysplastic nevus syndrome, and xeroderma pigmentosum. These conditions merit total skin examination at least annually.

Findings of a rapidly enlarging skin lesion that is dark, has changed colors, has irregular borders, or bleeds easily should raise a concern of melanoma. However, many pediatric melanomas are clinically amelanotic, and can easily be confused with a wart or other benign finding. Diagnosis is based on pathology, and an excisional biopsy, such as elliptical, punch or saucerization biopsy, is preferred. A shave biopsy may transect the base of the lesion, preventing the pathologist from being able to discern the Breslow depth, which is an important prognostic factor. Extra care must be taken in the diagnosis of melanoma in children because making the distinction from other lesions, particularly Spitz nevus, can be difficult. Management in a center with expertise in pediatric melanoma may be advisable, especially for anything other than thin melanomas (Breslow thickness of 1 mm or greater).

Prognosis and treatment recommendations have previously been extrapolated from adult data; however, specific prognostic factors for pediatric melanoma are starting to accrue. Biopsy sites that test positive for melanoma should be reexcised with appropriate margins based on thickness. Lymph node mapping and sentinel node biopsy should be performed for all melanomas with a Breslow thickness >0.76-1 mm. If the sentinel node is positive, completion lymph node dissection should be considered. To date, the treatment of childhood melanoma still mirrors treatment of adult melanoma. High-dose adjuvant interferon shows some efficacy in the treatment of adult melanoma, whereas chemotherapy in combination with biologic agents and vaccine therapy has been used to treat advanced melanoma. Although novel therapies such as targeted B-Raf inhibitors and immune-modulating agents have received regulatory approval for the treatment of adult melanoma, their use in children is still investigational.

Mucosal Neuroma Syndrome (Multiple Endocrine Neoplasia Type Iib)

Mucosal neuroma syndrome, an autosomal dominant trait, is characterized by an asthenic or marfanoid habitus with scoliosis, pectus excavatum, pes cavus, and muscular hypotonia. The syndrome is caused by mutations in the tyrosine kinase domain of the *RET* gene. Patients have thick, patulous lips and soft-tissue prognathism simulating acromegaly. Multiple mucosal neuromas or neurofibromas appear as pink, pedunculated, or sessile nodules on the anterior third of the tongue, at the commissures of the lips, and on the buccal mucosa and palpebral conjunctiva. Various ophthalmologic defects and intestinal ganglioneuromatosis with recurrent diarrhea are additional common findings. There is a high incidence of medullary thyroid carcinoma in association with high calcitonin levels, pheochromocytoma, and hyperparathyroidism in patients with this syndrome. Periodic screening tests for the associated malignant tumors are mandatory.

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CHAPTER 691

Nutritional Dermatoses

Joel C. Joyce

Acrodermatitis Enteropathica

Acrodermatitis enteropathica is a rare autosomal recessive disorder caused by an inability to absorb sufficient zinc from the diet. The genetic defect is in the intestinal zinc-specific transporter gene *SLC39A4*. Initial signs and symptoms usually occur in the 1st few months of life, often after weaning from breast milk to cow's milk. The cutaneous eruption consists of vesiculobullous, eczematous, dry, scaly, or psoriasiform skin lesions symmetrically distributed in the perioral, acral, and perineal areas (Fig. 691.1) and on the cheeks, knees, and elbows (Fig. 691.2). The hair often has a peculiar, reddish tint, and alopecia of some degree is characteristic. Ocular manifestations include photophobia, conjunctivitis, blepharitis, and corneal dystrophy detectable by slit-lamp examination. Associated manifestations include chronic diarrhea, stomatitis, glossitis, paronychia, nail dystrophy, growth retardation, irritability, delayed wound healing, intercurrent bacterial infections, and superinfection with *Candida albicans* . Lymphocyte function and free radical scavenging are impaired. Without treatment the course is chronic and intermittent but often relentlessly progressive. When the disease is less severe, only growth retardation and delayed development may be apparent.

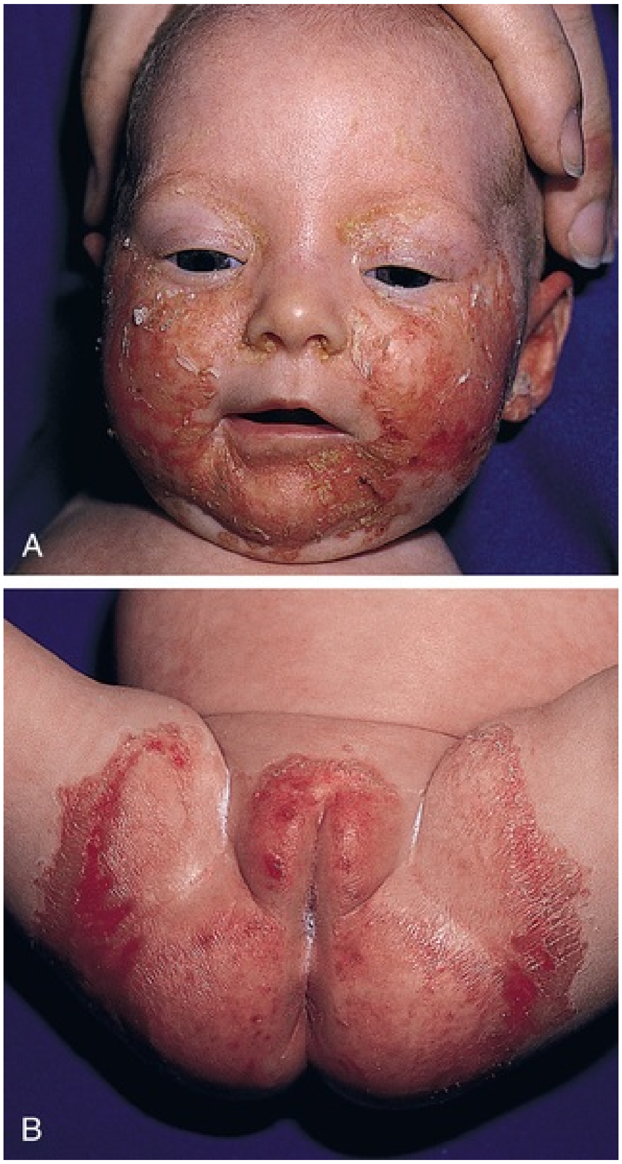

FIG. 691.1 **A,** Periorificial eruption. **B,** Diaper rash. The skin findings are typical of zinc deficiency, in this case caused by low levels of zinc in breast milk. (From Eichenfield LF, Frieden IJ, Esterly NB: *Textbook of neonatal dermatology,* Philadelphia, 2001, WB Saunders, Fig. 14.14.)

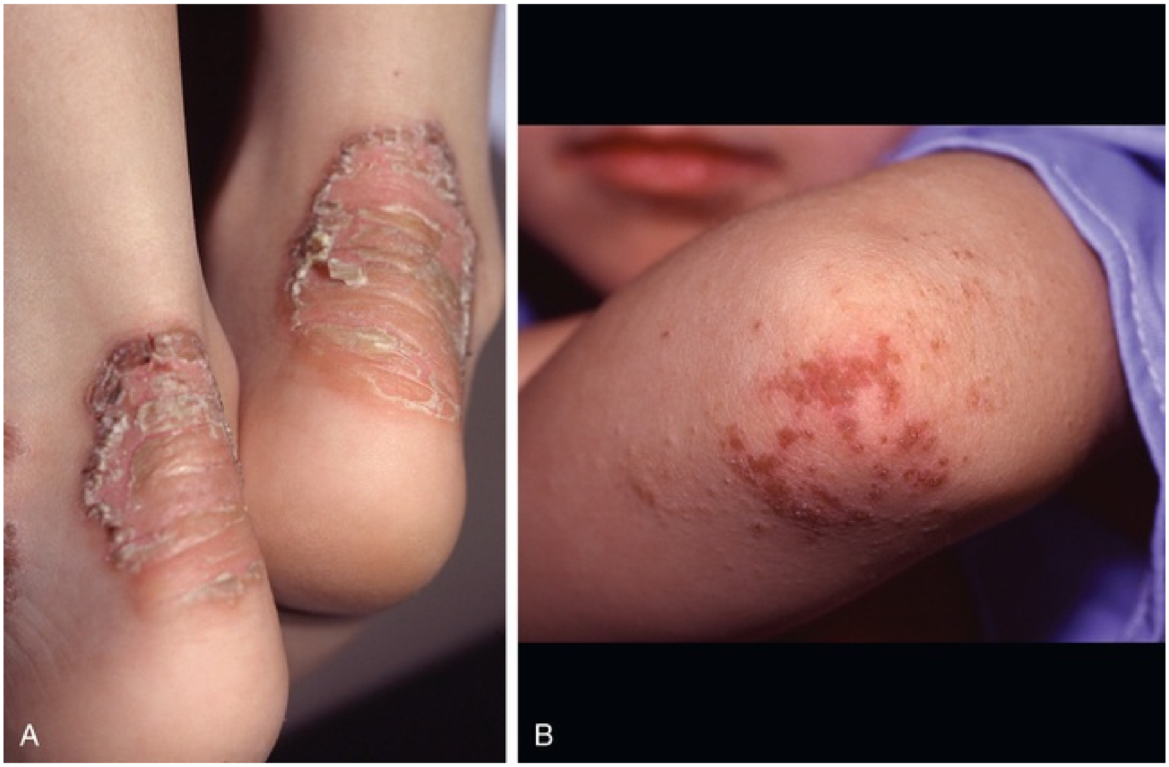

FIG. 691.2 **A,** Psoriasiform lesion of zinc deficiency dermatitis on the ankles. **B,** Similar lesions on the elbows.

The diagnosis is established by the constellation of clinical findings and detection of a low plasma zinc concentration. A serum zinc level less than 50 µg/dL is suggestive but not diagnostic of acrodermatitis enteropathica. Levels of alkaline phosphatase, a zinc-dependent enzyme, may also be decreased. Histopathologic changes in the skin are nonspecific and include parakeratosis and pallor of the upper epidermis. The variety of manifestations of the syndrome may stem from the fact that zinc has a role in numerous metabolic pathways—including those of copper, protein, essential fatty acids, and prostaglandins—and that zinc is incorporated into many zinc metalloenzymes. Other nutritional deficiencies may produce similar findings (Table 691.1), although the classic findings are highly suggestive of acrodermatitis enteropathica.

Table 691.1

Cutaneous Manifestations Due to Nutrient Deficiency

NUTRIENT	FOOD SOURCE	RECOMMENDED DAILY INTAKE	DERMATOLOGIC MANIFESTATIONS OF DEFICIENCY	SYSTEMIC MANIFESTATIONS OF DEFICIENCY

Biotin	Egg yolks, liver, whole cereals, walnuts, peanuts, mushrooms, cow's milk, soybeans	Infants and children: 5-25 mg/day Adults: 30 μg/day	Periorificial and perianal seborrheic-like dermatitis; alopecia	Metabolic disturbance Neurologic: encephalopathy, irritability, hypotonia, ataxia, seizures, developmental delay
Vitamin B_2	Milk, other dairy products, organ meats, fish, eggs, green leafy vegetables, and whole grains	Infants and children: 0.3-13 mg/day Adults: 1.1-1.3 mg/day	Oral-ocular-genital syndrome: cheilitis, angular stomatitis, glossitis, scaling dermatitis in seborrheic/anogenital distribution	Mental retardation, electroencephalographic changes, anemia
Vitamin B_6	Fish, beef liver, organ meats, potatoes, starchy vegetables, noncitrus fruits	Birth to 6 mo: 0.3 mg Adults: 1.3-1.7 mg/day	Seborrheic eruption on scalp, trunk, buttocks, perineum; pellagra-like dermatitis	Anorexia, nausea, vomiting, neurologic weakness, diarrhea Neurologic: weakness, somnolence, confusion, seizures Hematologic: anemia, eosinophilia, lymphopenia
Essential fatty acids	Fish oils, nuts, meat, dairy	omega-6/omega-3 fatty acid ratio of 2	Generalized eczematous eruption, intertriginous erosions, alopecia	Growth impairment, fatty liver change, poor wound healing, anemia, thrombocytopenia, impaired wound healing
Zinc	Oysters, red meat, poultry, seafood, fortified cereals, beans, nuts, whole grains, dairy	Birth to 6 mo: 2 mg/day Adults: 8-11 mg/day	Periorificial and acral dermatitis, alopecia, hypopigmentation, paronychia, stomatitis	Anorexia, dysgeusia. growth impairment, immune deficiency, gastrointestinal changes

From Lakdawala N, Grant-Kels J: Acrodermatitis enteropathica and other nutritional diseases of the folds (intertriginous areas). *Clin Dermatol* 33:414–419, 2015 (Table 1, p 418).

Oral therapy with zinc compounds is the treatment of choice. Replacement for individuals with inherited acrodermatitis enteropathica is with elemental zinc, 3 mg/kg/24 hr, in the form of zinc sulfate, gluconate, or acetate (i.e., 220 mg of zinc sulfate contains 50 mg of elemental zinc). Zinc gluconate carries less risk of gastrointestinal distress. However, plasma zinc levels should be monitored every 3-6 mo so as to individualize the dosage. Zinc therapy rapidly abolishes the manifestations of the disease. *Supplementation is for life.* A syndrome resembling acrodermatitis enteropathica has been observed in patients with secondary zinc deficiency resulting from long-term total parenteral nutrition without supplemental zinc or to chronic malabsorption syndromes. A rash similar to that of acrodermatitis enteropathica has also been reported in infants fed breast milk that is low in zinc and in those with maple syrup urine disease, organic aciduria, methylmalonic acidemia, biotinidase deficiency, essential fatty acid deficiency, severe protein malnutrition (kwashiorkor), and cystic fibrosis. Cutaneous manifestations tend to appear in more severe forms. For those individuals with acquired zinc deficiency, oral replacement with elemental zinc, 0.5-1.0 mg/kg/24 hr, should be undertaken and the cause of underlying malnutrition should be addressed.

Essential Fatty Acid Deficiency

Essential fatty acid deficiency causes a generalized scaly dermatitis composed of thickened, erythematous, desquamating plaques. Individuals may also show failure to thrive, growth retardation, alopecia, thrombocytopenia, and poor wound healing. The eruption has been induced experimentally in animals fed a fat-free diet and has been observed in patients with chronic severe malabsorption, as in short-gut syndrome, and in those sustained on a fat-free diet or fat-free parenteral alimentation. Linoleic acid (18 : 2 n-6) and arachidonic acid (20 : 4 n-6) are deficient, and an abnormal metabolite, 5,8,11-eicosatrienoic acid (20 : 3 n-9), is present in the plasma. Alterations in the triene/tetraene ratio are diagnostic (arachidonic acid/eicosatrienoic acid ratio >0.4 or linoleic acid/arachidonic acid ratio >2.3). The horny layer of the skin contains microscopic cracks, the barrier function of the skin is disturbed, and transepidermal water loss is increased. Topical application of linoleic acid, which is present in sunflower seed and safflower oils, may ameliorate the clinical and biochemical skin manifestations, although absorption can be inconsistent. Oral and/or parenteral therapy can also be considered. Appropriate nutrition should be provided, with the recommendation that 1–4% of total calories should be from linoleic acid.

Kwashiorkor

Severe protein and essential amino acid deprivation in association with adequate caloric intake can lead to kwashiorkor, particularly at the time of weaning to a diet that consists primarily of corn, rice (or rice milk), or beans (see Chapter 57

). Children can be fed such a restricted diet for cultural reasons or because of misdiagnosis on the part of the child's parents or health care providers of perceived food allergies. Diffuse fine reddish brown scaling (enamel/flaky paint sign) is the classic cutaneous finding. In severe cases, erosions and linear fissures develop (Fig. 691.3). Nails are thin and soft, and hair is sparse, thin, and depigmented, sometimes displaying a “flag sign” consisting of alternating light and dark bands that reflect alternating periods of adequate and inadequate nutrition. The cutaneous manifestations may closely resemble those of acrodermatitis enteropathica; however, edema of the extremities and face (“moon facies”) and a protuberant abdomen (“pot belly”) are key features uniformly observed in kwashiorkor. The serum zinc level is often deficient; in some cases skin lesions of kwashiorkor heal more rapidly when zinc is applied topically. See Chapter 57 for treatment recommendations.

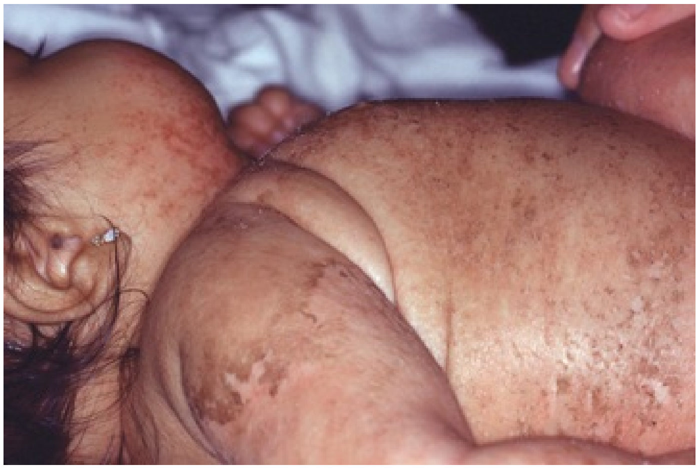

FIG. 691.3 Erosions and scaling in kwashiorkor.

Cystic Fibrosis

See Chapter 432 .

Protein-calorie malnutrition develops in 5–10% of patients with cystic fibrosis. Rash in infants with cystic fibrosis and malnutrition is rare but may appear by age 6 mo. The initial eruption consists of scaling, erythematous papules and progresses in 1-3 mo to extensive desquamating plaques. The rash is accentuated around the mouth and perineum and on the extremities (lower greater than upper). Alopecia may be present, but mucous membranes and nails are uninvolved.

Pellagra

See Chapter 62 .

Pellagra manifests as edema, erythema, and burning of sun-exposed skin on the face, neck, and dorsal aspects of the hands, forearms, and feet. Lesions of pellagra may also be provoked by burns, pressure, friction, and inflammation. The eruption on the face frequently follows a butterfly distribution, and the dermatitis encircling the neck has been termed “Casal's necklace.” Blisters and scales develop, and the skin increasingly becomes dry, rough, thickened, cracked, and hyperpigmented. Skin infections may be unusually severe. Pellagra develops in patients with insufficient dietary intake or malabsorption of niacin and/or tryptophan. Administration of isoniazid, 6-mercaptopurine, or 5-fluorouracil may also produce pellagra. Hartnup disease (see Chapter 103), caused by a mutation in *SLC6A19*. which encodes a neutral amino acid transporter, is a rare autosomal recessive disorder that presents in infancy with a “pellagra-like syndrome” as a result of decreased absorption of tryptophan. Nicotinamide supplementation and sun avoidance are the mainstays of therapy in pellagra. See Chapter 62 for treatment recommendations.

Scurvy (Vitamin C or Ascorbic Acid Deficiency)

See Chapter 63 .

Scurvy manifests initially as follicular hyperkeratosis, or coiling of the hair on the upper arms, back, buttocks, and lower extremities. Other features are perifollicular erythema and hemorrhage, particularly on the legs and advancing to involve large areas of hemorrhage; swollen, erythematous gums; stomatitis; and subperiosteal hematomas. In children, the most common risk factors are behavioral or psychiatric disease resulting in poor nutrition. The best method of confirmation of a clinical diagnosis of scurvy is a trial of vitamin C supplementation. Treatment is with 100-200 mg/day of vitamin C supplementation orally or parenterally for up to 3 mo.

Vitamin a Deficiency

See Chapter 61 .

Vitamin A deficiency manifests initially as impairment of visual adaptation to the dark. Cutaneous changes include xerosis and hyperkeratosis and hyperplasia of the epidermis, particularly the lining of hair follicles and sebaceous glands. In severe cases, desquamation may be prominent. See Chapter 61 for treatment recommendations.

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PART XXXI

Bone and Joint Disorders

OUTLINE

Section 1 Orthopedic Problems
Section 2 Sports Medicine
Section 3 The Skeletal Dysplasias
Section 4 Metabolic Bone Disease

SECTION 1

Orthopedic Problems

OUTLINE

Chapter 692 Growth and Development
Chapter 693 Orthopedic Evaluation of the Child
Chapter 694 The Foot and Toes
Chapter 695 Torsional and Angular Deformities of the Limb
Chapter 696 Leg-Length Discrepancy
Chapter 697 The Knee
Chapter 698 The Hip
Chapter 699 The Spine
Chapter 700 The Neck
Chapter 701 The Upper Limb
Chapter 702 Arthrogryposis
Chapter 703 Common Fractures
Chapter 704 Osteomyelitis
Chapter 705 Septic Arthritis

CHAPTER 692

Growth and Development

Keith D. Baldwin, Lawrence Wells

Normal values are often defined as those that fall within 2 standard deviations of the mean value for the population, a range that accounts for approximately 95% of values. *Statistically normal* should not be confused with *ideal* in any given person's or parent's mind. Table 692.1 lists terms used to describe some common deviations from normal. Congenital anomalies can be categorized into production problems and packaging problems. Production problems include abnormalities caused by malformation, dysplasia, or disruption that will not spontaneously resolve (see Chapter 128). Packaging problems include deformations caused by mechanical causes, including in utero positioning and molding, and they usually resolve with time.

Table 692.1

Terminologies for Deviations

TERMINOLOGY	DESCRIPTION
Congenital	Anomaly that is apparent at birth
Deformation	A normally formed structure that is pushed out of shape by mechanical forces
Deformity	A body part altered in shape from normal, outside the normal range
Developmental	A deviation that occurs over time; one that might not be present or apparent at birth
Disruption	A structure undergoing normal development that stops developing or is destroyed or removed
Dysplasia	A tissue that is abnormal or wrongly constructed
Malformation	A structure that is wrongly built; failure of embryologic development or differentiation resulting in abnormal or missing structures

In Utero Positioning

In utero positioning produces temporary joint and muscle contractures, and affects the torsional alignment of the long bones, particularly those of the lower extremities. Normal full-term newborns can have up to 20-30 degree hip and knee flexion contractures. These contractures tend to resolve by 4-6 mo of age. The newborn hip externally rotates in extension up to 80-90 degrees and has limited internal rotation to approximately 0-10 degrees. The lower leg often has inward rotation (internal tibial torsion). The face may also be distorted; the spine and upper extremities are less affected by the in utero position. The effects of in utero positioning, therefore, are physiologic in origin and resolve by 3-4 mo of age.

Growth and Development

Consideration of growth and development helps formulate treatment strategies designed to preserve or restore normal growth potential. Growth is subject to many variables, including genetics, nutrition, general health, endocrine status, mechanical forces, and physiologic age. Growth also varies between two anatomic regions and even between two bones of the same region.

Bone formation or ossification occurs in two different ways. In **endochondral ossification** , mesenchymal cells undergo chondrogenesis to form cartilage that matures to become bone. Most bones in the axial and appendicular skeleton are formed in this manner. In **intramembranous ossification** , osteoblasts are formed by direct differentiation of mesenchymal cells into bone. Flat bones of the skull and clavicle are examples of this pattern of bone formation.

Centers of Ossification

At the beginning of the fetal period, the chondrocytes in the midshaft of the long bones form the **primary** centers of growth from which the bone eventually lengthens. **Secondary** centers of ossification appear in the chondroepiphysis and mostly appear postnatally. They direct the formation of bone throughout growth, particularly joint development. The ossification centers that are typically present at birth are the distal femur, proximal tibia, calcaneus, and talus (Fig. 692.1).

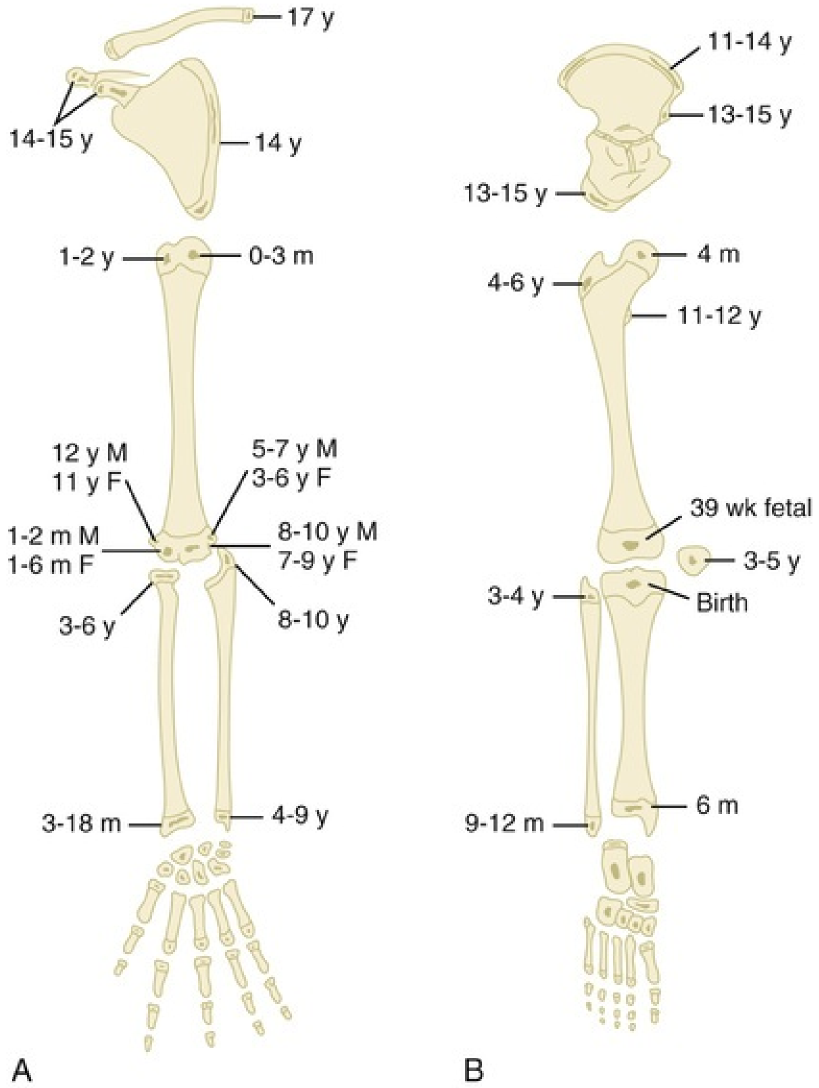
17 y
14-15 y
14 y
1-2 y
0-3 m
12 y M
11 y F
5-7 y M
3-6 y F
1-2 m M
1-6 m F
8-10 y M
7-9 y F
3-6 y
8-10 y
3-18 m
4-9 y
A
11-14 y
13-15 y
13-15 y
4 m
4-6 y
11-12 y
39 wk fetal
3-5 y
3-4 y
Birth
6 m
9-12 m
B

FIG. 692.1 Ages of onset of secondary (epiphyseal and apophyseal) ossification of the major bones of the upper **(A)** and lower **(B)** extremity. *F,* Female; *M,* male; *m,* month; *wk,* week; *y,* year. (From Caffey J. *Pediatric X-ray Diagnosis* , 8th ed. Chicago: Year Book, 1985.)

Anatomic Locations: Descriptive Terms

Typical **long bones** are divided into the physis, epiphysis, metaphysis, diaphysis, and perichondrial ring (Figs. 692.2 and 692.3). The physis is the growth plate located at the end of bone. The epiphysis is typically a secondary ossification center that contributes to joint development. The metaphysis is the bone adjacent to the physis on the side away from the joint. The diaphysis is the central part or shaft of long bones. The perichondrial ring contributes to appositional growth.

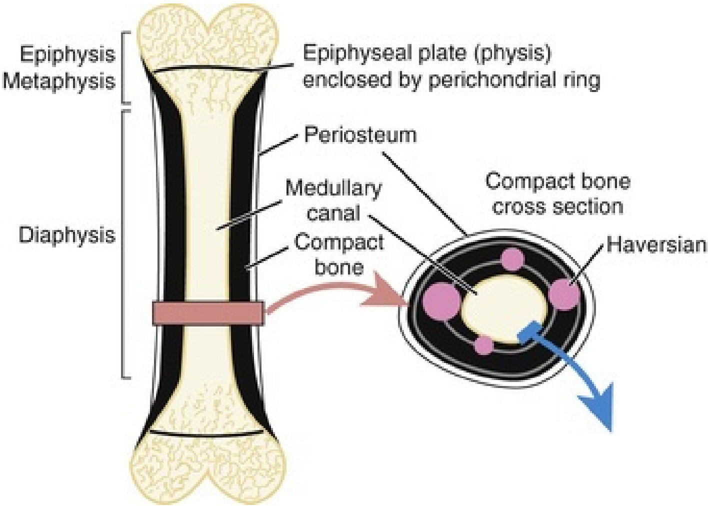
Epiphysis
Metaphysis
Diaphysis
Epiphyseal plate (physis) enclosed by perichondrial ring
Periosteum
Medullary canal
Compact bone
Compact bone cross section
Haversian

FIG. 692.2 **Diagram showing typical long bone divisions.**

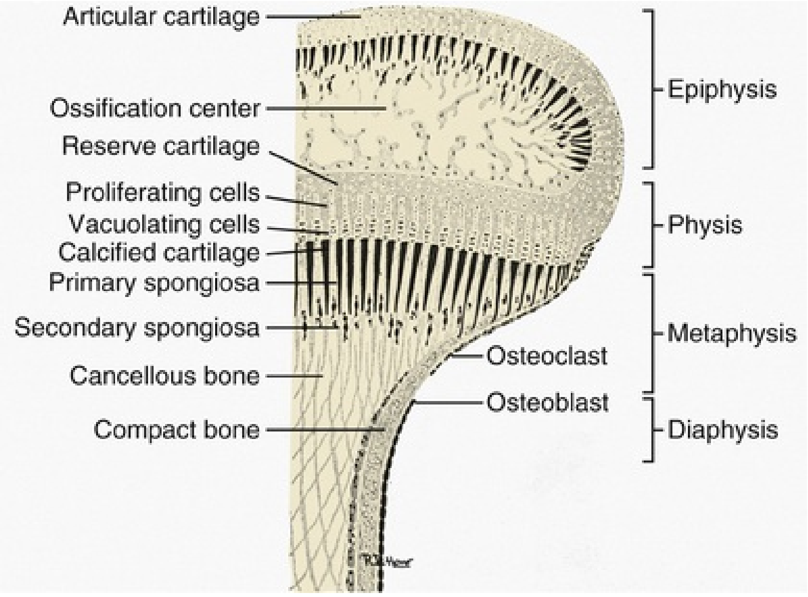
Articular cartilage
Ossification center
Reserve cartilage
Proliferating cells
Vacuolating cells
Calcified cartilage
Primary spongiosa
Secondary spongiosa
Cancellous bone
Compact bone
Osteoclast
Osteoblast
Epiphysis
Physis
Metaphysis
Diaphysis

FIG. 692.3 **Functional components of the growing end of a tubular bone and their anatomic substrate. (From Kan JH, Strouse PJ: Embryology, anatomy, and normal findings. In Coley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 12, Philadelphia, 2013, Saunders, Fig. 129-5).**

The articular cartilage also contributes to the growth of the epiphysis. The perichondrial ring, which surrounds the physes, and the perichondrium around the epiphyses and periosteum, which surrounds the metaphysis and diaphyseal regions of the bone, contribute to appositional or circumferential growth. Bones without physes (pelvis, scapulae, carpals, tarsals) grow by appositional bone growth from their surrounding perichondrium and periosteum. Other bones (metacarpals, metatarsals, phalanges, spine) grow by a combination of appositional and endochondral ossification.

Important Growth and Developmental Milestones

Table 692.2 summarizes some important musculoskeletal growth considerations.

Table 692.2

Skeletal Growth Considerations

- Abnormal stature can be assessed as “proportionate” or “disproportionate” based on comparing the ratio of sitting height with sub-ischial height (lower limbs).
- Normally the arm span is almost equal to standing height.
- The head is disproportionately large at birth, and the ratio of head height to total height is approximately 1:4 at birth, which changes to 1:7.5 at skeletal maturity.
- Lower extremities account for approximately 15% of height at birth and 30% at skeletal maturity.
- The rate of height and growth increase is not constant and varies with growth spurts.
- By age 5 yr, birth height usually doubles and the child is approximately 60% of adult height. The child is approximately 80% of final height at 9 yr. During puberty, the standing height increases by approximately 1 cm/mo.
- Bone age is more important than chronologic age in determining future growth potential.

Growth Patterns in Upper and Lower Extremities

The upper extremity grows longitudinally, primarily from physes of the proximal humeral physis and the distal radial and ulnar physes. In the lower extremity, most of the longitudinal growth occurs around the knee, in the distal femoral and the proximal tibial physes (Fig. 692.4).

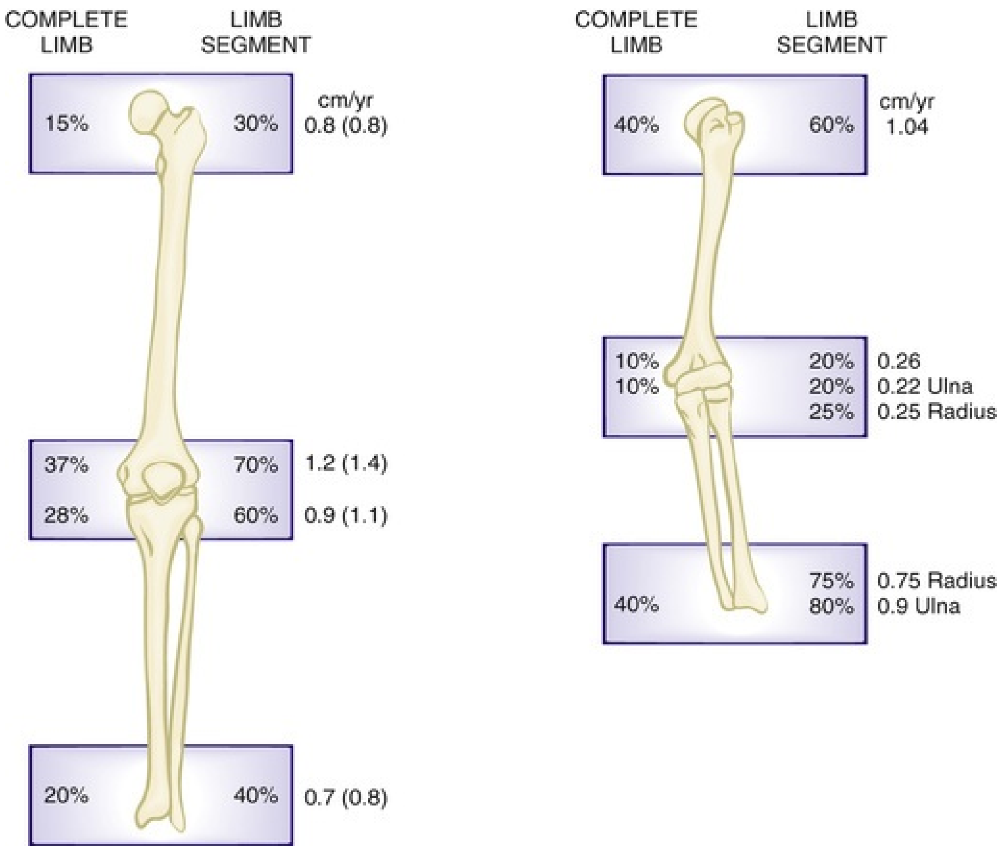
COMPLETE LIMB
LIMB SEGMENT
15%
30%
cm/yr
0.8 (0.8)
37%
70%
1.2 (1.4)
28%
60%
0.9 (1.1)
20%
40%
0.7 (0.8)
COMPLETE LIMB
LIMB SEGMENT
40%
60%
cm/yr
1.04
10%
10%
20%
20%
25%
0.26
0.22 Ulna
0.25 Radius
40%
75%
80%
0.75 Radius
0.9 Ulna

FIG. 692.4 **The contribution (%) of each physis to the overall length of the extremities. (From Morrissy R, Weinstein S, editors: *Lovell and Winter's pediatric orthopedics* , ed 5, Philadelphia, 2001, Lippincott Williams & Wilkins.)**

In the hip joint, the acetabulum forms with the convergence of 3 primary ossification centers: ischium, ilium, and pubis.

Gait/Functional Maturation

Functional mobility develops in infants in a predictable fashion (Table 692.3). Failure to achieve functional milestones is an indication for referral to a neurologist to determine if a central nervous system problem exists. Central nervous system maturation contributes significantly to the development of gait. In early ambulation (at 8-15 mo), the child usually has a wide-based gait with hyperflexion of hips and knees, and initial contact with the heel. By the age of 2 yr, the wide gait diminishes, reciprocal arm swing begins, and there is increased stride length and velocity. Adult fluid gait patterns usually start developing by 3 yr and mature to an adult-like pattern by age 7 yr.

Table 692.3

Functional Milestones

MILESTONE	ACHIEVED BY
Head control	3-6 mo
Sitting	6-9 mo
Crawling	8 mo
Pulling to stand	8-12 mo
Ambulating	12-18 mo

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CHAPTER 693

Orthopedic Evaluation of the Child

Keith D. Baldwin, Lawrence Wells

A detailed history and thorough physical examination are critical to the evaluation of a child with an orthopedic problem. The child's family and acquaintances are important sources of information, especially in younger children and infants. Appropriate radiographic imaging and, occasionally, laboratory testing may be necessary to support the clinical diagnosis.

History

A comprehensive history should include details about the prenatal, perinatal, and postnatal periods. Prenatal history should include maternal health issues: smoking, prenatal vitamins, illicit use of drugs or narcotics, alcohol consumption, diabetes, immunization status (including receipt of rubella vaccine), and sexually transmitted infections. The child's prenatal and perinatal history should include information about the length of pregnancy, length of labor, type of labor (induced or spontaneous), presentation of fetus, evidence of any fetal distress at delivery, requirement for supplemental oxygen following the delivery, birth length and weight, Apgar score, muscle tone at birth, feeding history, and period of hospitalization. In older infants and young children, evaluation of developmental milestones for posture, locomotion, dexterity, social activities, and speech are important. Specific orthopedic questions should focus on joint, muscular, appendicular, or axial skeleton complaints. Information regarding pain or other symptoms in any of these areas should be elicited (Table 693.1). The family history can give clues to heritable disorders. It also can forecast expectations of the child's future development and allow appropriate interventions as necessary.

Table 693.1

Characterization of Pain and Presenting Symptom

Location: Whether pain is localized to a particular segment or involves a larger area.

Intensity: Usually on a pain scale of 1-10.

Quality: Tumor pain is often unrelenting, progressive, and often present during the night. Pain at night particularly suggests osteoid osteoma. Pain in inflammation and infection is usually continuous.

Onset: Was it acute and related to specific trauma or was it insidious? Acute pain and history of trauma are more commonly associated with fractures.

Duration: Whether transient, only lasting for minutes, or lasting for hours or days. Pain lasting for longer than 3-4 wk suggests a serious underlying problem.

Progress: Whether static, increasing, or decreasing.

Radiation: Pain radiating to upper or lower extremities or complaints of numbness, tingling, or weakness require appropriate workup.

Aggravating factors: Relationship to any activities such as swimming or diving or any particular position

Alleviating factors: Is the pain relieved by rest, heat, and/or medication? Conditions such as spondylolysis, Scheuermann disease, inflammatory spondyloarthropathy, muscle pulls, or overuse are improved by bed rest.

Gait and posture: Disturbances associated with pain.

Physical Examination

The orthopedic physical examination includes a thorough examination of the musculoskeletal system along with a comprehensive neurologic examination. The musculoskeletal examination includes inspection, palpation, and evaluation of motion, stability, and gait. A basic neurologic examination includes sensory examination, motor function, and reflexes. The orthopedic physical examination requires basic knowledge of anatomy of joint range of motion, alignment, and stability. Many common musculoskeletal disorders can be diagnosed by the history and physical examination alone. One screening tool that has been useful in adults has now been adapted and evaluated for use in children: the pediatric gait, arms, legs, spine (pGALS) test, the components of which are listed in Fig. 693.1 .

Gait

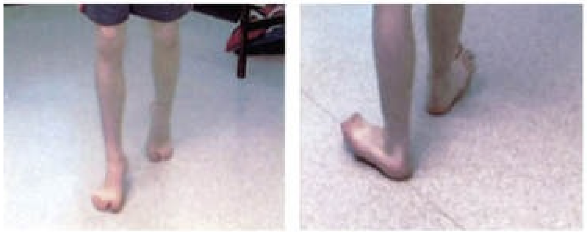

A "Walk on your tip-toes." *Observe the child walking

B "Walk on your heels." *Observe the child walking

Arms

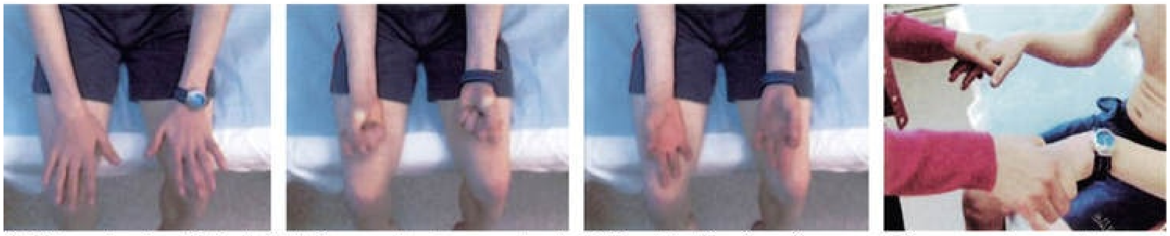

C "Put your hands out in front of you."

D "Turn your hands over and make a fist. Pinch your index finger and thumb together."

E "Touch the tips of your fingers with your thumb."

F Squeeze metacarpophalangeal joints

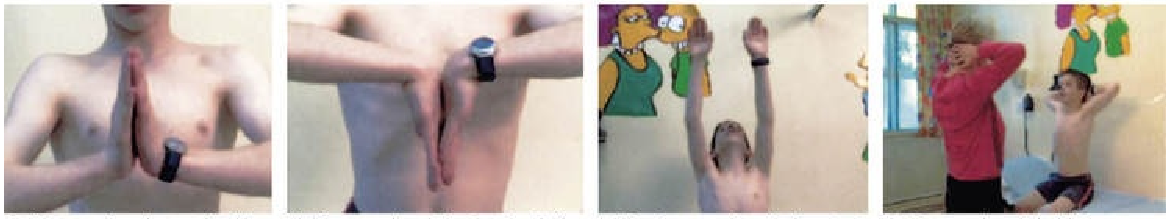

G "Put your hands together."*

H "Put your hands back to back."*

I "Reach up and touch the sky." Look at the ceiling."

J "Put your hands behind your neck."

Legs

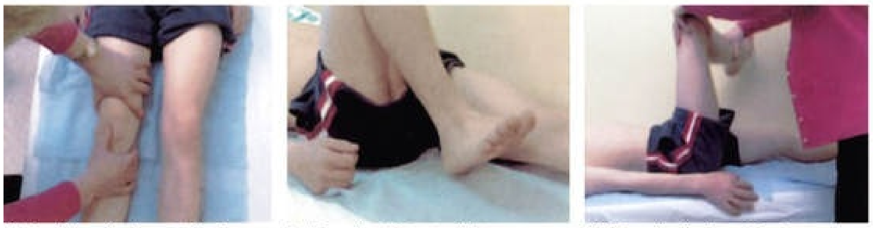

K Feel for effusion at the knee

L "Bend and the straighten your knee." (active movement of knees and examiner feels for crepitus)

M Passive flexion (90 degrees) with internal rotation of hip

Spine

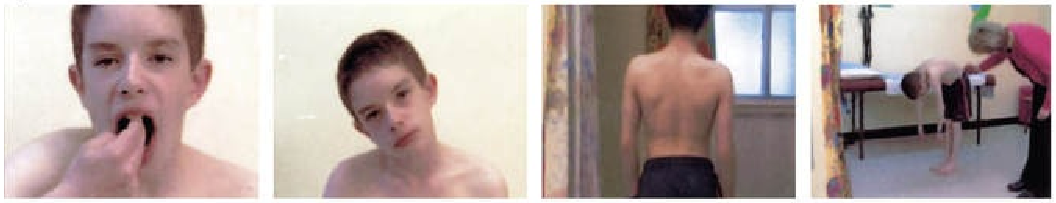

N "Open your mouth and put 3 of your (child's own) fingers in your mouth."*

O Lateral flexion of cervical spine: "Try and touch your shoulder with your ear."

P Observe spine from behind

Q "Can you bend and touch your toes?" Observe curve of spine from side and behind

FIG. 693.1 **The components of pediatric gait, arms, legs, spine (pGALS) screen, with**

illustration of movement. Screening questions: (1) Do you have any pain or stiffness in your joints, muscles, or back? (2) Do you have any difficulty getting yourself dressed without any help? (3) Do you have any difficulty going up and down stairs? *Additions and amendments to the original adult gait, arms, legs, spine screen. (From Foster HE, Kay LJ, Friswell M, et al: Musculoskeletal screening examination [pGALS] for school-age children based on the adult GALS screen. *Arthritis Rheum* 55:709–716, 2006.)

Inspection

Initial examination of the child begins with inspection. The clinician should use the guidelines listed in Table 693.2 during inspection.

Table 693.2

Guidelines During Inspection of a Child With Musculoskeletal Problem

- The patient should be *comfortable with adequate exposure and well-lit surroundings* (lest some important physical finding be missed). Infants or young children may be examined on their parent's lap so that they feel more secure and are more likely to be cooperative.
- It is important to inspect how the patient moves about in the room before and during the examination, as well as during various maneuvers. *Balance, posture, and gait pattern* should also be checked.
- *General examination* findings should include inspection for skin rashes, café-au-lait spots, hairy patches, dimples, cysts, tuft of hair, or evidence of spinal midline defects that can indicate serious underlying problems that need review.
- *General body habitus,* including signs of cachexia, pallor, and nutritional deficiencies, should be noted.
- Note any obvious spinal asymmetry, axial or appendicular deformities, trunk decompensation, and evidence of muscle spasm or contractures. The *forward bending test* is valuable in assessing asymmetry and movement of the spine.
- It is essential to perform and document a *thorough neurologic examination* . Motor, sensory, and reflex testing should be performed and recorded.
- Any *discrepancies in limb lengths* , as well as *muscle atrophy* , should be recorded.

- The range of motion of all joints, their stability, and any evidence of hyperlaxity, peripheral pulsations, and lymphadenopathy should also be noted.

Palpation

Palpation of the involved region should include assessment of local temperature and tenderness; assessment for a swelling or mass, spasticity or contracture, and bone or joint deformity; and evaluation of anatomic axis of limb and of limb lengths.

Contractures are a loss of mobility of a joint from congenital or acquired causes and are caused by periarticular soft tissue fibrosis or involvement of muscles crossing the joint. Congenital contractures are common in **arthrogryposis** (see Chapter 702). Spasticity is an abnormal increase in tone associated with hyperreflexia and is common in cerebral palsy.

Deformity of the bone or joint is an abnormal fixed shape or position from congenital or acquired causes. It is important to assess the type of deformity, its location, and degree of deformity upon clinical examination. It is also important to assess whether the deformity is fixed or can be passively or actively corrected, and whether there is any associated muscle spasm, local tenderness, or pain on motion. Classification of the deformity depends on the plane of deformity: **varus** (away from midline) or **valgus** (apex toward midline), or **recurvatum** (backward curvature) or **flexion** deformity (sagittal plane). In the axial skeleton, especially the spine, deformity can be defined as scoliosis, kyphosis, hyperlordosis, and kyphoscoliosis.

Range of Motion

Active and passive joint motion should be assessed, recorded, and compared with the opposite side. Objective evaluation should be done with a goniometer and recorded.

Vocabulary for direction of joint motion is as follows:

Abduction: Away from the midline
Adduction: Toward the midline
Flexion: Movement of bending from the starting position
Extension: Movement from bending to the starting position

Supination: Rotating the forearm to face the palm upward
Pronation: Rotating the forearm to face the palm downward
Inversion: Turning the hindfoot inward
Eversion: Turning the hindfoot outward
Plantar flexion: Pointing the toes away from the body (toward the floor)
Dorsiflexion: Pointing the toes toward the body (toward the ceiling)
Internal rotation: Turning inward toward the axis of the body
External rotation: Turning outward away from the axis of the body

Gait Assessment

Children typically begin walking between 8 and 16 mo of age. Early ambulation is characterized by short stride length, a fast cadence, and slow velocity with a wide-based stance. Gait cycle is a single sequence of functions that starts with heel strike, toe off, swing, and heel strike. The four events describe one gait cycle and include two phases: stance and swing. The stance phase is the period during which the foot is in contact with the ground. The swing phase is the portion of the gait cycle during which a limb is being advanced forward without ground contact. Normal gait is a symmetric and smooth process. Deviation from the norm indicates potential abnormality and should trigger investigation.

Neurologic maturation is necessary for the development of gait and the normal progression of developmental milestones. A child's gait changes with neurologic maturation. Infants normally walk with greater hip and knee flexion, flexed arms, and a wider base of gait than older children. As the neurologic system continues to develop in the cephalocaudal direction, the efficiency and smoothness of gait increase. The gait characteristics of a 7 yr old child are similar to those of an adult. When the neurologic system is abnormal (cerebral palsy), gait can be disturbed, exhibiting pathologic reflexes and abnormal movements.

Deviations from normal gait occur in a variety of orthopedic conditions. Disorders that result in muscle weakness (e.g., spina bifida, muscular dystrophy), spasticity (e.g., cerebral palsy), or contractures (e.g., arthrogryposis) lead to abnormalities in gait. Other causes of gait disturbances include limp, pain, torsional variations (in-toeing and out-toeing), toe walking, joint abnormalities, and leg-length discrepancy (Table 693.3).

Table 693.3

Causes of Gait Disturbances

Mechanical

- Acute injuries (accidental or nonaccidental)
- Overuse conditions (mainly sports-related)
- Dysplastic lesions
- Limb length discrepancy

Osseous

- Legg-Calvé-Perthes disease
- Osteochondritis dissecans of knee and talus
- Slipped capital femoral epiphysis
- Osteomyelitis
- Diskitis
- Osteoid osteoma or other primary bone tumor

Articular

- Developmental hip dysplasia
- Septic arthritis
- Transient synovitis
- Rheumatic disease (juvenile idiopathic arthritis, systemic lupus erythematosus)
- Hemophilia-related hemorrhage
- Ankylosis of a joint

Neurologic

- Guillain-Barré syndrome and other peripheral neuropathies
- Intoxication
- Cerebellar ataxia
- Brain tumor
- Lesion occupying spinal cord space

Posterior column spinal cord disorders
Myopathy
Hemiplegia
Complex regional pain syndrome
Cerebral palsy

Hematologic/Oncologic

Sickle cell pain crisis
Leukemia, lymphoma
Metastatic tumor
Langerhans cell histiocytosis

Other

Soft tissue infection
Myositis
Fasciitis
Bursitis
Kawasaki disease
Conversion disorder
Gaucher disease
Phlebitis
Scurvy
Rickets
Peritonitis

From Kliegman RM, Lye PS, Bordini BJ, Toth H, Basel D, editors: *Nelson pediatric symptom-based diagnosis* , Philadelphia, 2018, Elsevier, Table 34.1, p. 615.

Limping

A thorough history and clinical examination are the first steps toward early identification of the underlying problem causing a limp. Limping can be considered as either **painful (antalgic)** or painless, with the differential diagnosis ranging from benign to serious causes (septic hip, tumor). In a painful gait, the stance phase is shortened as the child decreases the time spent on the painful extremity. In a painless gait, which indicates underlying proximal muscle weakness or hip instability, the stance phase is equal between the involved and uninvolved sides, but the child leans or shifts the center of gravity over the involved extremity for balance. A bilateral disorder produces a waddling gait. **Trendelenburg gait** (i.e., trunk lists to the affected side with each step) is produced by weak abnormal hip abductors. When the patient stands on one foot, a Trendelenburg sign (i.e., sagging rather than rising of the unsupported buttock) can often be elicited when abductors are weak.

Disorders most commonly responsible for an abnormal gait generally vary based on the age of the patient. The differential diagnosis of limping varies based on age group (Table 693.4) or mechanism (Table 693.5). Neurologic disorders, especially spinal cord, muscle, or peripheral nerve disorders, can also produce limping and difficult walking. Antalgic gait is predominantly a result of trauma, infection, or pathologic fracture. Trendelenburg gait is generally caused by congenital, developmental, or muscular disorders. In some cases, limping also may be caused by nonskeletal causes such as testicular torsion, inguinal hernia, and appendicitis.

Table 693.4

Differential Diagnosis of Limping in Children

AGE GROUP	DIAGNOSTIC CONSIDERATIONS
Early walker: 1-3 yr of age	**Painful limp** Septic arthritis and osteomyelitis Transient synovitis Occult trauma (“toddler's fracture”) Intervertebral diskitis Malignancy Abuse **Painless limp** Developmental dysplasia of the hip Neuromuscular disorder Polio Cerebral palsy Lower extremity length inequality
Child: 3-10 yr of age	**Painful limp** Septic arthritis, osteomyelitis, myositis Transient synovitis Trauma

	Rheumatologic disorders Juvenile idiopathic arthritis Intervertebral diskitis Malignancy **Painless limp** Developmental dysplasia of the hip Legg-Calvé-Perthes disease Lower extremity length inequality Neuromuscular disorder Polio Cerebral palsy Muscular dystrophy (Duchenne)
Adolescent: 11 yr of age to maturity	**Painful limp** Septic arthritis, osteomyelitis, myositis Trauma Rheumatologic disorder Slipped capital femoral epiphysis (acute, unstable) Malignancy **Painless limp** Slipped capital femoral epiphysis (chronic, stable) Developmental dysplasia of the hip (acetabular dysplasia) Lower extremity length inequality Neuromuscular disorder

From Marcdante K, Kliegman R, eds. Nelson Essentials of Pediatrics. 7th ed. Philadelphia: Saunders; 2015.

Table 693.5

Differential Diagnosis of Limping

Antalgic Gait

Congenital

Tarsal coalition

Acquired

Legg-Calvé-Perthes disease
Slipped capital femoral epiphysis

Trauma

Sprains, strains, contusions
Fractures
Occult

Toddler's fracture
Abuse

Neoplasia

Benign
  - Unicameral bone cyst
  - Osteoid osteoma

Malignant
  - Osteogenic sarcoma
  - Ewing sarcoma
  - Leukemia
  - Neuroblastoma
  - Spinal cord tumors

Infectious

Septic arthritis
Reactive arthritis
Osteomyelitis
  - Acute
  - Subacute

Diskitis

Rheumatologic

Juvenile idiopathic arthritis
Hip monoarticular synovitis (transient synovitis)

Trendelenburg

Developmental

Developmental dysplasia of the hip
Leg-length discrepancy

Neuromuscular

Cerebral palsy
Poliomyelitis

From Thompson GH: Gait disturbances. In Kliegman RM, editor: *Practical strategies of pediatric diagnosis and therapy*, Philadelphia, 1996, WB Saunders, pp 757–778.

Back Pain

Children frequently have a specific skeletal pathology as the cause of back pain. The most common causes of back pain in children are trauma, spondylolysis, spondylolisthesis, and infection (see Chapter 699.5). Tumor and tumor-like lesions that cause back pain in children are likely to be missed unless a thorough clinical assessment and adequate workup are performed when required. Nonorthopedic causes of back pain include urinary tract infections, nephrolithiasis, and pneumonia.

Neurologic Evaluation

A careful neurologic evaluation is a part of every pediatric musculoskeletal examination (see Chapter 608). The assessment should include evaluation of developmental milestones, muscle strength, sensory assessment, muscle tone, and deep tendon reflexes. The neurologic evaluation should also assess the spine and identify any deformity, such as scoliosis and kyphosis, or abnormal spinal mobility. The hips and feet should also be examined specifically, along with torsional abnormalities of the lower extremity, which are vastly more common in the neurologically involved population. Specific peripheral nerve examinations may be necessary.

As the nervous system matures, the developing cerebral cortex normally inhibits rudimentary reflexes that are often present at birth (see Chapter 608). Therefore persistence of these reflexes can indicate neurologic abnormality. The most commonly performed deep tendon reflex tests include biceps, triceps, quadriceps, and gastrocnemius and soleus tendons. Upper motor neuron signs should also be noted. The Ashworth scale is often used to grade spasticity (Table

693.6). Upper-extremity motor control is often graded, and these grades are useful both diagnostically and prognostically. Passive range of motion should be assessed to determine contractures (Table 693.7). Localized or diffuse weakness must be determined and documented. A thorough assessment and grading of muscle strength is mandatory in all cases of neuromuscular disorders.

Table 693.6

Ashworth Scale of Spasticity

0	No increase in muscle tone
1	Slight increase in muscle tone, usually a catch or minimal resistance at end range of motion
2	Moderate tone throughout range of motion
3	Considerable increase in tone; passive range of motion difficult
4	Rigid in flexion or extension

Table 693.7

Clinical Scale of Upper Extremity Motor Control

GRADE	DEFINITION
Grade 1	Hypotonic, no volitional motion
Grade 2	Hypertonic, no volitional motion
Grade 3	Mass flexion or extension in response to a stimulus
Grade 4	Patient can initiate movement but results in mass flexion or extension
Grade 5	Slow volitional movement; stress or rapid movement results in mass action
Grade 6	Volitional control of specific joints/muscles

Radiographic Assessment

Plain radiographs are the first step in evaluation of most musculoskeletal disorders. Advanced imaging includes special procedures such as MRI, nuclear bone scans, ultrasonography, CT, and positron emission tomography. Rapid STIR MRI is a valuable screening test if a specific location is not well defined.

Plain Radiographs

Routine radiographs are the first step and consist of anteroposterior and lateral views of the involved area with one joint above and below. Comparison views of the opposite side, if uninvolved, may be helpful in difficult situations but are not always necessary. It is important for the clinician to be aware of normal radiographic variants of the immature skeleton. Several synchondroses may be mistaken for fractures. A patient with “normal” plain radiographic appearance but having persistent pain or symptoms might need to be evaluated further with additional imaging studies.

Ultrasonography

Ultrasonography is useful to evaluate suspected fluid-filled lesions such as popliteal cyst and hip joint effusions. Major indications for ultrasonography are fetal studies of the extremities and spine, including detection of congenital anomalies like spondylocostal dysostosis, fractures suggesting osteogenesis imperfecta, developmental dysplasia of the hip, joint effusions, occult *neonatal* spinal dysraphism, foreign bodies in soft tissues, and popliteal cysts of the knee.

Magnetic Resonance Imaging

MRI is the **imaging modality of choice** for defining the exact anatomic extent of most musculoskeletal lesions (particularly if the structure is soft tissue). MRI avoids ionizing radiation, and doing so does not produce any known harmful effects. It produces excellent anatomic images of the musculoskeletal system, including the soft tissue, bone marrow cavity, spinal cord, and brain. It is especially useful for defining the extent of soft tissue lesions, infections, and injuries. Tissue planes are well delineated, allowing more accurate assessment of tumor invasion into adjacent structures. Cartilage structures can be visualized (articular cartilage of the knee can be distinguished from the fibrocartilage of the meniscus). MRI is also helpful in visualizing unossified joints in the pediatric population, including the shoulders, elbows, and hips of young infants.

Magnetic Resonance Angiography

Magnetic resonance angiography has largely replaced routine angiography in the preoperative assessment of vascular lesions and bone tumors. Magnetic resonance angiography provides good visualization of peripheral vascular branches and tumor neovascularity in patients with primary bone tumors.

Computed Tomography

CT has enhanced the evaluation of multiple musculoskeletal disorders. Coronal, sagittal, and axial imaging is possible with CT, including 3-dimensional reconstructions that can be beneficial in evaluating complex lesions of the axial and appendicular skeleton. It allows visualization of the detailed bone anatomy and the relationship of bones to contiguous structures. CT is useful to readily evaluate tarsal coalition, accessory navicular bone, infection, growth plate arrest, osteoid osteoma, pseudoarthrosis, bone and soft tissue tumors, spondylolysis, and spondylolisthesis. CT is superior to MRI for assessing bone involvement and cortical destruction (even subtle changes), including calcification or ossification and fracture (particularly if displacement of an articular fracture is suspected).

Nuclear Medicine Imaging

A bone scan displays physiologic information rather than pure anatomy and relies on the emission of energy from the nucleotide injected into the patient. Indications include early septic arthritis, osteomyelitis, avascular necrosis, tumors (osteoid osteoma), metastatic lesions, occult and stress fractures, and cases of child abuse.

Total-body radionuclide scan (technetium-99) is useful to identify bony lesions, inflammatory tumors, and stress fractures. Tumor vascularity can also be inferred from the flow phase and the blood pool images. Gallium or indium scans have high sensitivity for local infections. Thallium-201 chloride scintiscans have >90% sensitivity and between 80% and 90% accuracy in detecting malignant bone or soft tissue tumors. MRI has supplanted nuclear medicine imaging in many circumstances.

Laboratory Studies

Laboratory tests are occasionally necessary in the evaluation of a child with musculoskeletal disorder. These may include a complete blood cell count; erythrocyte sedimentation rate; C-reactive protein assay; Lyme titers; and blood, wound, joint, periosteum, or bone cultures for infectious conditions such as septic arthritis or osteomyelitis. Rheumatoid factor, antinuclear antibodies, and human leukocyte antigen B27 may be necessary for children with suspected rheumatologic disorders. Creatine kinase, aldolase, aspartate aminotransferase, and dystrophin testing are indicated in children with suspected disorders of striated muscle, such as Duchenne muscular dystrophy.

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CHAPTER 694

The Foot and Toes

Jennifer J. Winell, Richard S. Davidson

Abnormalities affecting the osseous and articular structures of the foot may be congenital, developmental, neuromuscular, inflammatory, or acquired. Problems with the foot and/or toes may be associated with a host of connective tissue diseases and syndromes; overuse syndromes are commonly observed in young athletes. Symptoms may include pain and abnormal shoe wear; cosmetic concerns are common. The foot may be divided into the **forefoot** (toes and metatarsals), the **midfoot** (cuneiforms, navicular, cuboid), and the **hindfoot** (talus and calcaneus). While the tibiotalar joint (ankle) provides plantarflexion and dorsiflexion, the subtalar joint (between the talus and calcaneus) is oriented obliquely, providing inversion and eversion. Inversion represents a combination of plantarflexion and varus, while eversion involves dorsiflexion and valgus. The subtalar joint is especially important for walking on uneven surfaces. Inversion of the transverse tarsal (Chopart) joint locks the midfoot to provide a stable base on which to perform toe-off during the gait cycle. Eversion of the transverse tarsal joint unlocks the **hindfoot** to provide accommodation during heel strike of the of the gait cycle. The talonavicular and calcaneocuboid joints connect the midfoot with the hindfoot.

694.1

Metatarsus Adductus

Jennifer J. Winell, Richard S. Davidson

Metatarsus adductus involves adduction of the forefoot relative to the hindfoot. When the forefoot is supinated and adducted, the deformity is termed *metatarsus varus* (Fig. 694.1). The disorder is common in newborns, most frequently caused by intrauterine molding; the deformity is bilateral in 50% of cases. As with other intrauterine positional foot deformities, a careful hip and neck examination should always be performed to look for other abnormalities associated with intrauterine positioning.

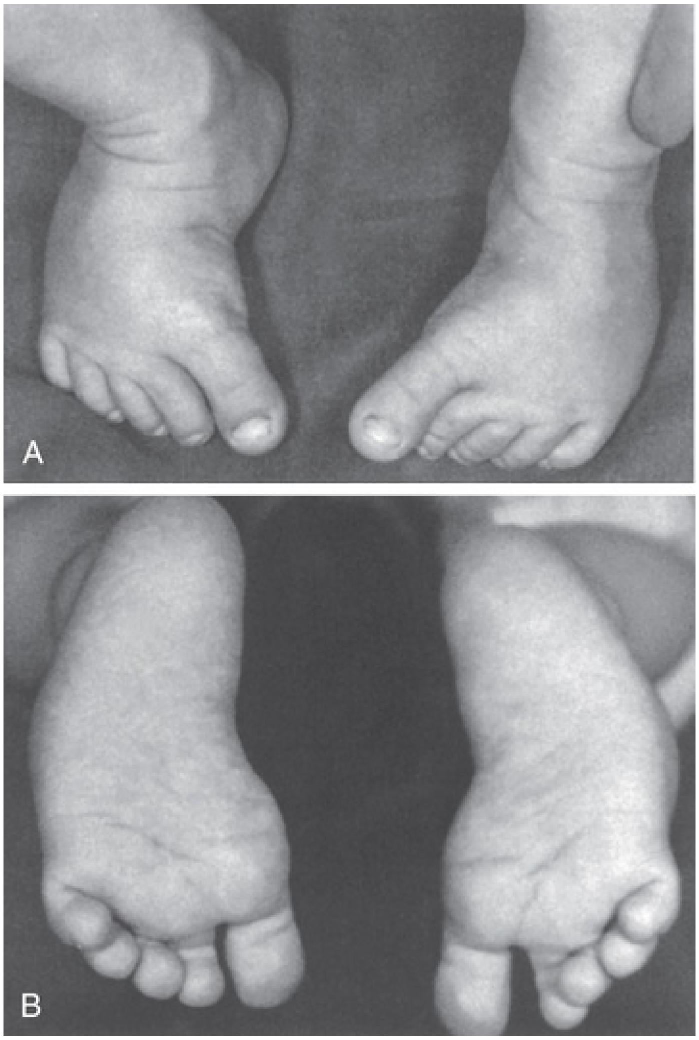

FIG. 694.1 **Bilateral mild metatarsus adductus. A, Dorsal view showing medial deviation of all the metatarsals. B, Plantar view showing the "bean-shaped" foot. This type of foot is easily corrected with serial casting. (From Ricco AI, Richards BS, Herring JA: Disorders of the foot. In Herring JA, editor: *Tachdjian's pediatric orthopaedics* , ed 5, Philadelphia, 2014, Elsevier, Fig. 23-19.)**

Clinical Manifestations

The forefoot is adducted (occasionally supinated), whereas the midfoot and hindfoot are normal. The lateral border of the foot is convex, and the base of the 5th metatarsal appears prominent. Range of motion at the ankle and subtalar joints is normal. Both the magnitude and the degree of flexibility should be documented. When the foot is viewed from the plantar surface, a line through the midpoint of (and parallel to) the heel should normally extend through the 2nd toe. Flexibility is assessed by stabilizing the hindfoot and midfoot in a neutral position with one hand and applying pressure over the 1st metatarsal head with the other. Correction with little pressure is indicative of a more flexible deformity. In the walking child with an uncorrected metatarsus adductus deformity, an in-toe gait and abnormal shoe wear may occur. A subset of patients will also have a dynamic adduction deformity of the great toe (hallux varus), which is often most noticeable during ambulation. This usually improves spontaneously and does not require treatment.

Radiographic Evaluation

Radiographs are not performed routinely in infants. Older children with residual deformity should have anteroposterior (AP) and lateral weight-bearing or simulated weight-bearing radiographs. The AP radiographs demonstrate adduction of the metatarsals at the tarsometatarsal articulation and an increased intermetatarsal angle between the 1st and 2nd metatarsals.

Treatment

The treatment of metatarsus adductus is based on the rigidity of the deformity; most children respond to nonoperative treatment. Deformities that are flexible and overcorrect into abduction with passive manipulation may be observed. Those feet that correct just to a neutral position may benefit from stretching exercises, which can be demonstrated to the parents in the office. In a walking child, the parents can try reversing the shoes as well. If this is not effective, reverse-last shoes to maintain the abducted position of foot can be prescribed. These are worn full-time (22 hr/day), and the condition is reevaluated in 4-6 wk. If improvement occurs, treatment can be continued. If there is no improvement, serial plaster casts should be considered. When stretching a foot with metatarsus adductus, care should be taken to maintain the hindfoot in neutral to slight varus alignment to avoid creating hindfoot valgus. Feet that cannot be corrected to a neutral position may benefit from serial casting; the best results are obtained when treatment is started before 8 mo of age. In addition to stretching the soft tissues, the goal is to alter physeal growth and stimulate remodeling, resulting in permanent correction. Once flexibility and alignment are restored, orthoses or corrective shoes are generally recommended for an additional period. A dynamic hallux varus usually improves spontaneously, and no active treatment is required.

Surgical treatment may be considered in the small subset of patients with symptomatic residual deformities who have not responded to previous treatment. Surgery is generally delayed until children are 4-6 yr of age. Cosmesis is often a concern, and pain and/or the inability to wear certain types of shoes may occasionally lead patients to consider surgery. Options for surgical treatment include either soft tissue releases or osteotomies. An osteotomy (midfoot or multiple metatarsals) is most likely to result in permanent restoration of alignment.

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694.2

Calcaneovalgus Feet

Jennifer J. Winell, Richard S. Davidson

A common finding in the newborn, the calcaneovalgus foot is secondary to in utero positioning. Excessive dorsiflexion and eversion are observed in the hindfoot, and the forefoot may be abducted. There may be an associated external tibial torsion (see Chapter 695).

Clinical Manifestations

The infant typically presents with the foot dorsiflexed and everted, and occasionally the dorsum of the foot or toes will be in contact with the anterolateral surface of the lower leg (Fig. 694.2). Dimpling may be indicative of reduced subcutaneous fat at the dorsolateral ankle. Plantarflexion and inversion are often restricted. As with other intrauterine positional deformities, a careful hip examination should be performed; if there is any concern, hip ultrasonography should be considered. When comparing risk for developmental dysplasia of the hip (DDH) with other congenital foot deformities, congenital calcaneovalgus has the highest association, with 19.4% of patients having coexisting DDH. The calcaneovalgus foot may be confused with a congenital vertical talus and may rarely be associated with a posteromedial bow of the tibia. A calcaneovalgus deformity may also be seen in older patients, typically those with a neuromuscular imbalance involving weakness or paralysis of the gastrocsoleus muscle (polio, myelomeningocele).

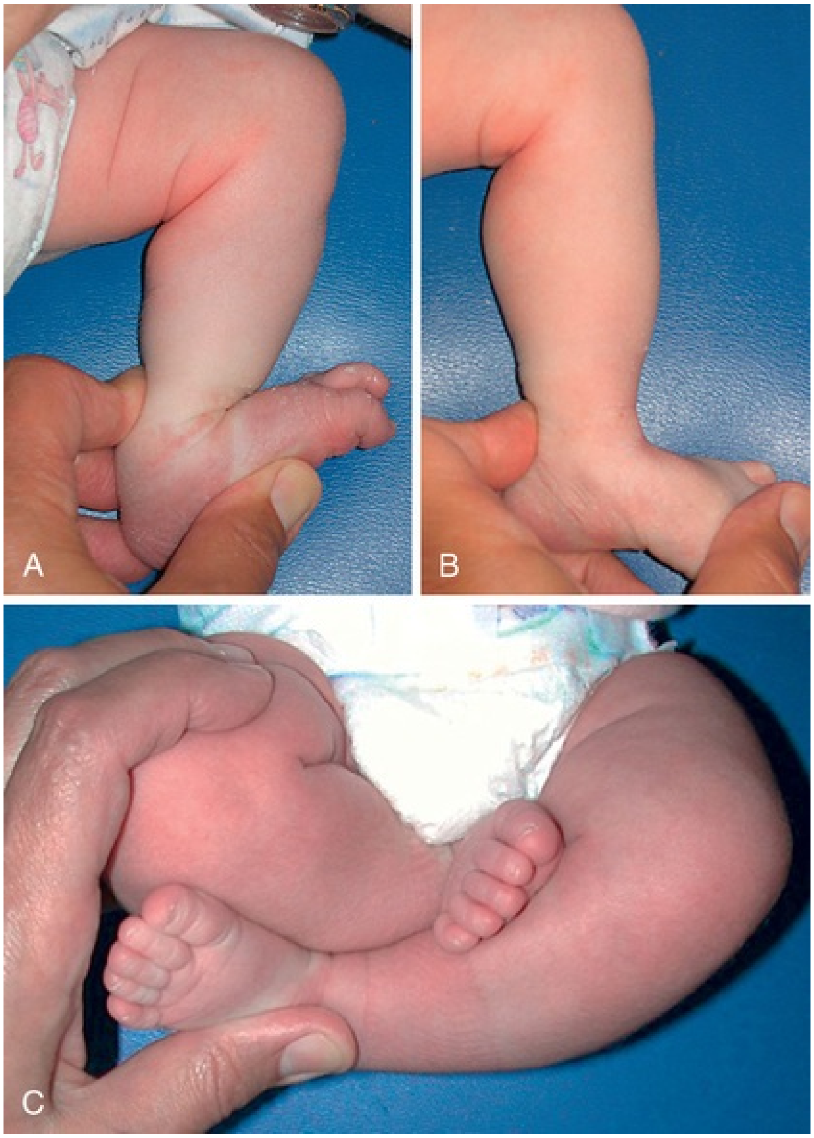

FIG. 694.2 Clinical picture of calcaneovalgus foot **(A)** that is passively correctable **(B)** because of intrauterine positioning **(C)** .

Radiographic Evaluation

Radiographs are usually not required but should be ordered if the deformity fails to correct spontaneously or with early treatment. AP and lateral radiographs along with a lateral radiograph of the foot in maximal plantarflexion may help distinguish calcaneovalgus from a congenital vertical talus or congenital oblique talus. Evaluation of the position of the talus in relation to the navicular in both the lateral and maximally plantarflexed lateral view confirm congenital vertical or oblique talus. If a posteromedial bow of the tibia is suspected, AP and lateral radiographs of the tibia and fibula are necessary. In posteromedial bowing of the tibia, the deformity is located in the tibia with the apex of deformity positioned posterior and medial. All three conditions may be confused clinically with calcaneovalgus feet.

Treatment

Mild cases of calcaneovalgus foot, in which full passive range of motion is present at birth, require no active treatment. These usually resolve within the first few weeks of life. A gentle stretching program, focusing on plantarflexion and inversion, is recommended for cases with some restriction in motion. For cases with a greater restriction in mobility, serial casts may be considered to restore motion and alignment. Casting is rarely required in the treatment of calcaneovalgus feet. The management for those cases associated with a posteromedial bow of the tibia is similar.

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694.3

Talipes Equinovarus (Clubfoot)

Jennifer J. Winell, Richard S. Davidson

Clubfoot or congenital talipes equinovarus (CTEV) is the term used to describe a deformity involving malalignment of the calcaneotalar-navicular complex. Components of this deformity may be best understood using the mnemonic **CAVE** (cavus, adductus, varus, equinus). Although this is predominantly a hindfoot deformity, there are plantarflexion (cavus) of the first ray and adduction of the forefoot/midfoot on the hindfoot. The hindfoot is in varus and equinus. The clubfoot deformity may be positional, congenital, associated with a variety of underlying diagnoses (neuromuscular or syndromic), or a focal dysplasia of musculoskeletal tissue distal to the knee.

The **positional (or postural) clubfoot** is a normal foot that has been held in a deformed position in utero and is found to be flexible on examination in the newborn nursery. The **congenital clubfoot** can either be idiopathic or syndromic. There is a spectrum of severity, but clubfoot associated with neuromuscular diagnoses or syndromes is typically rigid and more difficult to treat. Clubfoot is also extremely common in patients with myelodysplasia, arthrogryposis, and chromosomal syndromes such as trisomy 18 and chromosome 22q11 deletion syndrome (see Chapter 98).

Congenital clubfoot is seen in approximately 1 in 1,000 births and most likely results from a complex multifactorial polygenic inheritance. The risk is approximately 1 in 4 when both a parent and one sibling have clubfeet. It occurs more commonly in males (2 : 1) and is bilateral in 50% of cases. The pathoanatomy involves both abnormal tarsal morphology (plantar and medial deviation of the head and neck of the talus) and abnormal relationships between the tarsal bones in all three planes, as well as associated contracture of the soft tissues on the plantar and medial aspects of the foot.

Clinical Manifestations

A complete physical examination should be performed to rule out coexisting musculoskeletal and neuromuscular problems. The spine should be inspected for signs of occult dysraphism. Examination of the infant clubfoot demonstrates forefoot cavus and adductus, and hindfoot varus and equinus (Fig. 694.3). The degree of flexibility varies, and all patients will exhibit calf atrophy. Internal tibial torsion, foot length shortening, and leg-length discrepancy (shortening of the ipsilateral extremity) will be observed in a subset of cases. Although classically not associated with DDH (see Chapter 698.1), there is a higher association of CTEV and DDH than in the general population.

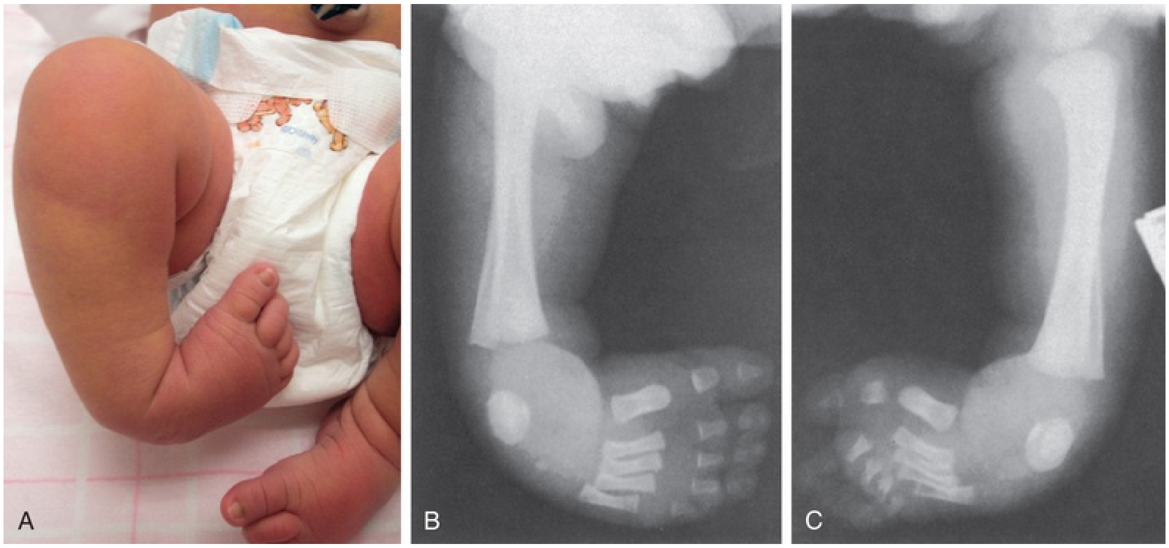

FIG. 694.3 **Talipes equinovarus in a newborn. A, Clinical appearance of an untreated clubfoot. B and C, Initial radiographic appearance of bilateral untreated clubfeet. (From Ricco AI, Richards BS, Herring JA: Disorders of the foot. In Herring JA, editor: *Tachdjian's pediatric orthopaedics* , ed 5, Philadelphia, 2014, Elsevier, Fig. 23-42.)**

Radiographic Evaluation

AP and lateral radiographs are not recommended for idiopathic clubfoot. For arthrogrypotic or syndromic feet, x-rays may be helpful but must be performed, with the foot held in the maximally corrected position. Multiple radiographic measurements can be made to describe malalignment between the tarsal bones. The navicular bone does not ossify until 3-6 yr of age, so the focus of radiographic interpretation is the relationships between segments of the foot, forefoot to hindfoot. A common radiographic finding is “parallelism” between lines drawn through the axis of the talus and the calcaneus on the lateral radiograph, indicating hindfoot varus. X-ray may be particularly useful for older children with persistent or recurrent deformities that are difficult to assess.

Treatment

Nonoperative treatment is initiated in all infants and should be started as soon as possible following birth. Techniques have included taping and strapping, manipulation and serial casting, and functional treatment. Historically, a significant percentage of patients treated by manipulation and casting required a surgical release, which was usually performed between 3 and 12 mo of age. Although many feet remain well aligned after surgical releases, a significant percentage of patients have required additional surgery for recurrent or residual deformities. Stiffness remains a concern at long-term follow-up. While pain is uncommon in childhood and adolescence, symptoms may appear during adulthood. These concerns have led to considerable interest in less-invasive methods for treating the deformity. The Ponseti method of clubfoot treatment, which has now become the standard of initial treatment, involves a specific technique for manipulation and serial casting, and may be best described as minimally invasive rather than nonoperative. The order of correction follows the mnemonic **CAVE** . Weekly cast changes are performed; 5-10 casts are typically required. The most difficult deformity to correct is the hindfoot equinus, and approximately 90% of patients will require a percutaneous tenotomy of the heel cord as an outpatient. Following the tenotomy, a long leg cast with the foot in maximal abduction (up to 70 degrees) and dorsiflexion is worn for 3-4 wk; the patient then begins a bracing program. An abduction brace is worn full-time for 3 mo and then at nighttime for 3-5 yr. A small subset of patients (up to 20%) with recurrent, dynamic supination deformity will require transfer of the tibialis anterior tendon to the middle cuneiform for recurrence. Although most patients require some form of surgery, the procedures are minimal in comparison with extensive surgical release, which requires lengthening and/or release of muscles and tendons about the ankle, and capsulotomy of the major joints to reposition the foot. The results of the Ponseti method are excellent, at up to 40 yr of follow-up. Despite casting, children do not have much dysfunction or delay in achieving normal motor milestones. Compliance with the splinting program is essential; recurrence is common if the brace is not worn as recommended. Functional treatment, or the “French method,” involves daily manipulations (supervised by a physical therapist) and splinting with elastic tape, as well as continuous passive motion (machine required) while the baby sleeps. While results are promising, it is usually performed in the inpatient setting, as the method is labor intensive. Implementation on an outpatient basis may be challenging, although just as successful. It remains unclear whether the technique will gain popularity in the United States. These minimally invasive methods are most successful when treatment is begun at birth or during the first few months of life and with good compliance with postmanipulation bracing. As there are varying degrees of severity for idiopathic CTEV, grading systems have been proposed based on rigidity and magnitude of deformity.

Aggressive surgical realignment has a definite role in the management of clubfeet, especially in the minority of congenital clubfeet that have failed nonoperative or minimally invasive methods, and for the rigid neuromuscular and syndromic clubfeet. In such cases, nonoperative methods such as the Ponseti technique may potentially be of value in decreasing the magnitude of surgery required. Common surgical approaches include a release of the involved joints (realignment of the tarsal bones), a lengthening of the shortened posteromedial musculotendinous units, and usually pinning of the foot in the corrected position. The "a la carte" method allows the surgeon to apply the principles to be tailored to the unique characteristics of each deformity. For older children with untreated clubfeet or those in whom a recurrence or residual deformity is observed, bony procedures (osteotomies) may be required in addition to soft tissue surgery. Triple arthrodesis is reserved as salvage for painful, deformed feet in adolescents and adults.

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694.4

Congenital Vertical Talus

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Congenital vertical talus is an uncommon foot deformity in which the midfoot is dorsally dislocated on the hindfoot and the ankle is in fixed equinus. There is nearly an even split between idiopathic cases and cases with an underlying neuromuscular condition or a syndrome. Neurologic causes include myelodysplasia, tethered cord, and sacral agenesis. Other associated conditions include arthrogryposis, Larsen syndrome, multiple pterygium syndrome, and chromosomal abnormalities (trisomy 13-15, 19; see Chapter 98). Depending on the age at diagnosis, the differential diagnosis may include a calcaneovalgus foot, oblique talus (talonavicular joint reduces passively), flexible flatfoot with a tight Achilles tendon, and tarsal coalition. Genetic studies are ongoing regarding abnormal muscle morphology on biopsy.

Clinical Manifestations

Congenital vertical talus has also been described as a **rocker-bottom foot** (Fig. 694.4) or a Persian slipper foot. The plantar surface of the foot is convex, and the talar head is prominent along the medial border of the midfoot. The fore part of the foot is dorsiflexed (dorsally dislocated on the hindfoot) and abducted relative to the hindfoot, and the hindfoot is in equinus and valgus. There is an associated contracture of the anterolateral (tibialis anterior, toe extensors) and the posterior (Achilles tendon, peroneals) soft tissues. The deformity is typically rigid. Physical examination is required to identify any coexisting neurologic and/or musculoskeletal abnormalities.

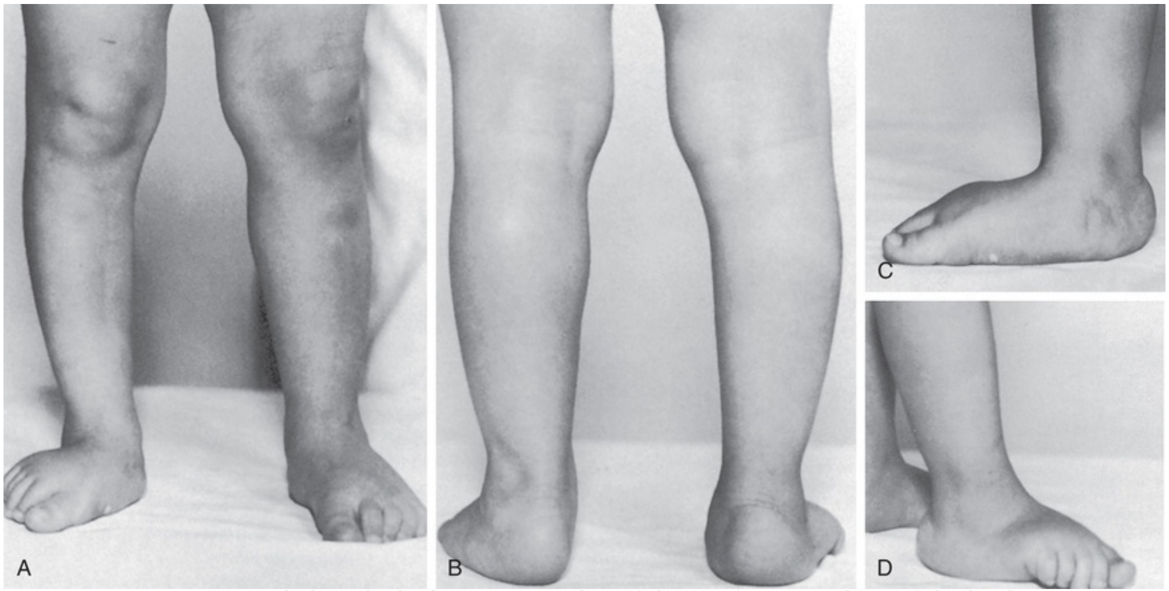

FIG. 694.4 **Congenital vertical talus. A, Pronation of the forefoot. B, Valgus of the heel. C, Absence of an arch, the rocker bottom deformity. D, Elevation of the lateral toes and tight peroneal tendons. (From Ricco AI, Richards BS, Herring JA: Disorders of the foot. In Herring JA, editor: *Tachdjian's pediatric orthopaedics* , ed 5, Philadelphia, 2014, Elsevier, Fig. 23-67.)**

Radiographic Evaluation

AP, lateral, and maximal plantarflexion and dorsiflexion lateral radiographs should be obtained when the diagnosis is suspected. The plantarflexion view helps determine whether the dorsal subluxation or dislocation of the midfoot on the hindfoot can be reduced passively. The dorsiflexion lateral view confirms the equinus contracture of the ankle. Although the navicular does not ossify until 3-6 yr of age, the relationship between the talus and the 1st metatarsal may be evaluated.

Treatment

The initial management consists of serial manipulation and casting, which is started shortly after birth. A “reverse” Ponseti method of casting is particularly useful in stretching out the dorsiflexion and valgus deformities. Open reduction and pin fixation can then stabilize the midfoot, allowing simultaneous heel cord tenotomy and dorsiflexion with casting to correct the ankle equinus.

In recalcitrant cases, the competing deformities of the midfoot and the hindfoot make conservative treatment difficult. Initially an attempt is made to reduce the dorsal dislocation of the forefoot/midfoot on the hindfoot. Once this has been achieved, attention can be directed toward stretching the hindfoot contracture. These deformities are typically rigid, and surgical intervention is required in the majority of cases. In such cases, casting helps to stretch out the contracted soft tissues. Surgery is generally performed between 6 and 12 mo of age; a soft tissue release is performed as a 1 or 2 stage procedure. One component involves release/lengthening of the contracted anterior soft tissues in concert with an open reduction of the talonavicular joint, while the other involves a posterior release with lengthening of the contracted musculotendinous units. Fixation with Kirschner wires is commonly performed to maintain alignment. Postoperatively, casting is employed for a variable period of time; patients often require the use of an orthosis for extended periods, depending on the underlying diagnosis. Salvage options for recurrent or residual deformities in older children include a subtalar or triple arthrodesis.

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694.5

Hypermobile Pes Planus (Flexible Flatfeet)

Jennifer J. Winell, Richard S. Davidson

Flatfoot is a common diagnosis; it has been estimated that up to 23% of the public may be affected, depending on the diagnostic criteria. Three types of flatfeet may be identified: a flexible flatfoot, a flexible flatfoot with a tendo-Achilles contracture, and a rigid flatfoot. Flatfoot describes a change in foot shape, and there are several abnormalities in alignment between the tarsal bones. There is eversion of the subtalar complex. The hindfoot is aligned in valgus. There is midfoot sag at the naviculocuneiform and/or the talonavicular joints. The forefoot is abducted relative to the hindfoot, and the head of the talus is uncovered and prominent along the plantar and medial border of the midfoot/hindfoot. Although hypermobile or flexible pes planus represents a common source of concern for parents, these children are rarely symptomatic. Flatfeet are common in neonates and toddlers and are associated with physiologic ligamentous laxity. Improvement may be seen when the longitudinal arch develops between 5 and 10 yr of age. Flatfoot is less common in societies where shoes are not worn during infancy and childhood. In general, comfortable flexible-soled shoes are recommended for children. Flexible flatfeet persisting into adolescence and adulthood are usually associated with **familial ligamentous laxity (hypermobility syndromes)** and can often be identified in other family members.

Clinical Manifestations

Patients typically have a normal longitudinal arch when examined in a non–weight-bearing position or standing on the toes, but the arch disappears when standing flat. The hindfoot collapses into valgus, and the midfoot sag becomes evident. Generalized hypermobility and ligamentous laxity are often observed. Range of motion should be assessed at both the subtalar and the ankle joints and will be normal in patients with a flexible flatfoot. When assessing range of motion at the ankle, the foot should always be inverted while testing dorsiflexion. If the foot is neutral or everted, spurious dorsiflexion may occur through the midfoot, masking a tendo-Achilles contracture. If subtalar motion is restricted, then the flatfoot is not hypermobile/flexible, and other diagnoses, such as tarsal coalition and juvenile rheumatoid arthritis, must be considered. On occasion, there may be tenderness and/or callus formation under the talar head medially. The shoes should be assessed as well and may have evidence of excessive wear along the medial border.

Radiographic Evaluation

Routine radiographs of asymptomatic flexible flatfeet are usually not indicated. If obtained for diagnostic reasons, weight-bearing radiographs (AP and lateral) are required to assess the deformity. On the AP radiograph, there is widening of the angle between the longitudinal axis of the talus and the calcaneus, indicating excessive heel valgus. The lateral view shows distortion of the normal straight-line relationship between the long axis of the talus and the 1st metatarsal with sag, either of the talonavicular or naviculocuneiform joint, resulting in flattening of the normal medial longitudinal arch (Fig. 694.5).

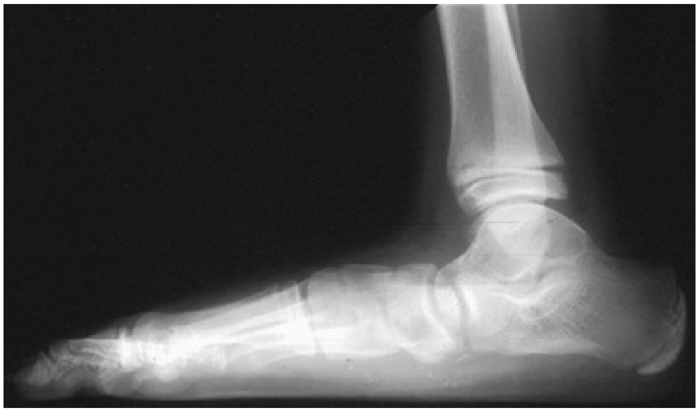

FIG. 694.5 Lateral weight-bearing radiograph demonstrating features of flatfoot.

Treatment

Although the natural history of the flexible flatfoot remains unknown, there is little evidence to suggest that this condition results in long-term problems or disability. As such, treatment is reserved for the small subset of patients who develop symptoms. Patients may complain of hindfoot pain, abnormal shoe wear, or fatigue after long walking. These patients may benefit from an nonprescription orthosis, such as a medial arch support. Severe cases, often associated with an underlying connective tissue disorder such as Ehlers-Danlos syndrome (see Chapter 679) or Down syndrome (see Chapter 98), may benefit from a custom orthosis such as the UCBL (University of California Biomechanics Laboratory) orthosis to better control the hindfoot and prevent collapse of the arch. Although an orthosis may relieve symptoms, there is no evidence to suggest any permanent change in the shape of the foot or alignment of the tarsal bones. Patients with a flexible flatfoot and a tight tendo-Achilles should be treated with stretching exercises. Often patients are referred to physical therapy to ensure that they are stretching appropriately. On occasion, the muscle will need to be lengthened surgically. For the few patients with persistent pain, surgical treatment can be considered. There has been considerable interest in a lateral column lengthening, which addresses all components of the deformity. The procedure involves an osteotomy of the calcaneus, with placement of a trapezoidal bone graft. A lengthening of the tendo-Achilles is required, often with a plantarflexion osteotomy of the medial cuneiform. This procedure preserves the mobility of the hindfoot joints, in contrast to a subtalar or triple arthrodesis. While a hindfoot arthrodesis may correct the deformity adequately, the stress transfer to neighboring joints may result in late-onset, painful degenerative changes.

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694.6

Tarsal Coalition

Jennifer J. Winell, Richard S. Davidson

Tarsal coalition, also known as **peroneal spastic flatfoot** , is characterized by a painful, rigid flatfoot deformity and peroneal (lateral calf) muscle spasm but without true spasticity. It represents a congenital fusion or failure of segmentation between two or more tarsal bones. Any condition that alters the normal gliding and rotatory motion of the subtalar joint may produce the clinical appearance of a tarsal coalition. Thus congenital malformations, arthritis or inflammatory disorders, infection, neoplasms, and trauma can be possible causes.

The most common tarsal coalitions occur at the medial talocalcaneal (subtalar) facet and between the calcaneus and navicular (calcaneonavicular). Coalitions can be fibrous, cartilaginous, or osseous. Tarsal coalition occurs in approximately 1% of the general population and appears to be inherited as an autosomal dominant trait with nearly full penetrance. Approximately 60% of calcaneonavicular and 50% of the medial facet talocalcaneal coalitions are bilateral.

Clinical Manifestations

Approximately 25% of patients will become symptomatic, typically during the 2nd decade of life. Although the flatfoot and a decrease in subtalar motion may have been present since early childhood, the onset of symptoms may correlate with the additional restriction in motion that occurs as a cartilaginous bar ossifies. Recurrent “ankle sprains” often accompany the presenting symptoms. The timing of ossification varies between the talonavicular (3-5 yr of age), the calcaneonavicular (8-12 yr of age), and the talocalcaneal (12-16 yr of age) coalitions. Hindfoot pain is commonly observed, especially in the region of the sinus tarsi and also under the head of the talus. Symptoms are activity related and are often increased with running or prolonged walking, especially on uneven surfaces. There may be tenderness over the site of the coalition and/or pain with testing of subtalar motion. The clinical appearance of a flatfoot is seen in both the weight-bearing and non–weight-bearing positions. There is a restriction in subtalar motion.

Radiographic Evaluation

AP and lateral weight-bearing radiographs and an oblique radiograph of the foot should be obtained (Table 694.1). A calcaneonavicular coalition is seen best on the oblique radiograph. On the lateral radiograph, there may be elongation of the anterior process of the calcaneus, known as the “anteater sign” (Fig. 694.6). A talocalcaneal coalition may be seen on a Harris (axial) view of the heel. On the lateral radiograph, there may be narrowing of the posterior facet of the subtalar joint, or a C-shaped line along the medial outline of the talar dome and the inferior outline of the sustentaculum tali (“C sign”; Fig. 694.7). This “C sign” is made up of the sustentaculum talus of the calcaneus in continuity with the coalition. Beaking of the anterior aspect of the talus on the lateral view is seen with some frequency, and results from an alteration in the distribution of stress. This finding does not imply the presence of degenerative arthritis. Irregularity in the subchondral bony surfaces may be seen in patients with a cartilaginous coalition, in contrast to a well-formed bony bridge in those with an osseous coalition. A fibrous coalition may require additional imaging studies to diagnose. While plain films may be diagnostic, a CT scan is the *imaging modality of choice* when a coalition is suspected (see Fig. 694.7). In addition to securing the diagnosis, this study helps define the degree of joint involvement in patients with a talocalcaneal coalition. Although uncommon, more than 1 tarsal coalition may be observed in the same patient. Only in young children, MRI may be more effective in identifying either the coalition or a differential diagnosis for the foot pain. MRI offers less radiation exposure but requires more time and may necessitate sedation.

Table 694.1

Radiographic Secondary Signs Associated With Tarsal Conditions

Talar breaking
Posterior subtalar facet narrowing
Rounding and flattening of the lateral talar process
Hypoplasia of the talus, shortening of the talar neck
Anterior nose sign
Ball-and-socket ankle joint
Continuous C-sign
Flatfoot deformity
Altered navicular morphology (wide or laterally tapering)
Dysmorphic sustentaculum tali (enlarged and ovoid on lateral radiograph)

From Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, vol 2, Philadelphia, 2008, Mosby, p. 2604.

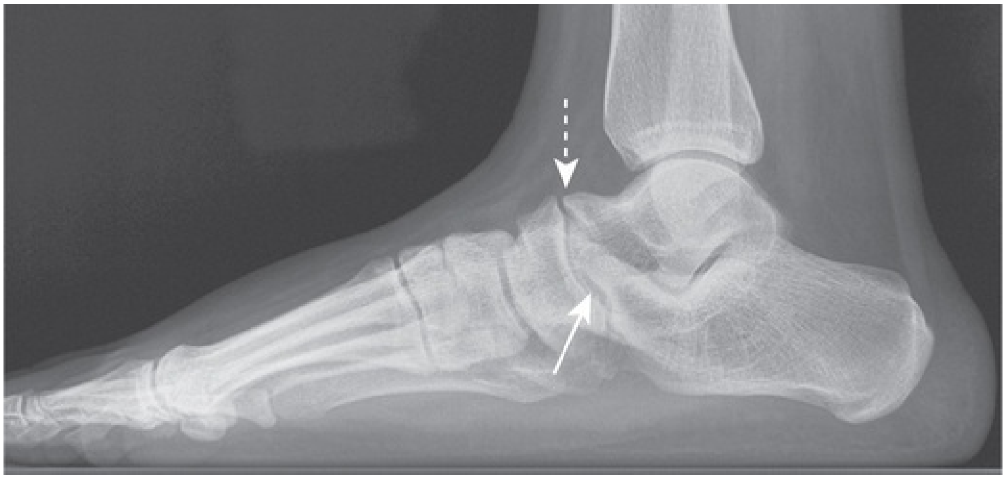

FIG. 694.6 The anteater sign in a child with a calcaneonavicular coalition *(arrow)* and talar beak *(dotted arrow)* . Elongation of the anterior calcaneus resembling the nose of an anteater is present. (From Laor T, Kan JH: Congenital anomalies of bone. In Colley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 12. Philadelphia, 2013, Saunders, Fig. 132-11.)

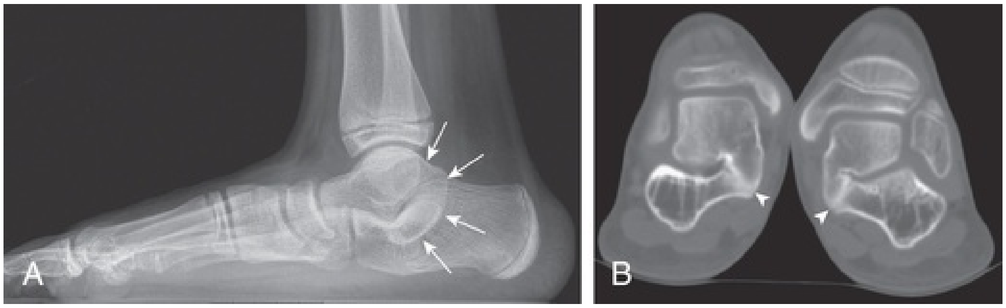

FIG. 694.7 **Talocalcaneal coalition. A, A lateral radiograph demonstrates the C sign *(arrows)* , ovoid, elongated sustentaculum tali, and pes planus. B, Computed tomography with coronal reformats in a different patient demonstrates bilateral middle facet subtalar coalitions *(arrowheads)* . (From Laor T, Kan JH: Congenital anomalies of bone. In Colley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 12, Philadelphia, 2013, Saunders, Fig. 132-13.)**

Treatment

The treatment of symptomatic tarsal coalitions varies according to the type and extent of coalition, the age of the patient, and the presence and magnitude of symptoms. Treatment is required only for symptomatic coalitions, and the initial management consists of activity restriction and nonsteroidal antiinflammatory medications, with or without a shoe insert. Immobilization in a short leg walking cast for 4-6 wk may be required in patients with more pronounced symptoms. For patients with chronic pain despite an adequate trial of nonoperative therapy, surgical treatment should be considered, and options include resection of the coalition, osteotomy, or arthrodesis. For the calcaneonavicular coalition, resection and interposition of the extensor digitorum brevis muscle have been successful. Often, concomitant hindfoot valgus and contracture of the gastrocnemius-soleus are present. In these patients, more reliable pain relief can be obtained with resection of the coalition, correction of the hindfoot valgus by calcaneal lengthening osteotomy with bank bone graft, and lengthening of the gastrocnemius-soleus. For those with extensive involvement of the joint and/or degenerative changes, a triple arthrodesis may be the best option; however, this is rarely needed in adolescents.

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694.7

Cavus Feet

Jennifer J. Winell, Richard S. Davidson

Cavus is a deformity involving plantarflexion of the forefoot or midfoot on the hindfoot, and may involve the entire forepart of the foot or just the medial column. The result is an elevation of the medial longitudinal arch (Fig. 694.8). A deformity of the hindfoot will often develop to compensate for the primary forefoot abnormality. While familial cavus may occur, the majority of patients with this deformity will have an underlying neuromuscular etiology. The initial goal is to rule out (and treat) any underlying causes. These diagnoses may relate to abnormalities of the spinal cord (occult dysraphism, tethered cord, polio, myelodysplasia, etc.) and peripheral nerves (hereditary motor and sensory neuropathies [see Chapter 631], such as Charcot-Marie-Tooth [CMT] disease, Dejerine-Sottas disease, or Refsum disease). Although a unilateral cavus foot is most likely to result from an occult intraspinal anomaly, bilateral involvement usually suggests an underlying nerve or muscle disease. Cavus is commonly observed in association with a hindfoot deformity. Two thirds of CMT patients have pes cavovarus, while 80% of pes cavovarus is most commonly seen in patients with the hereditary motor and sensory neuropathies, 80% of CMT patients having pes cavovarus and 65% of patients with cavovarus having CMT. In patients with hereditary motor and sensory neuropathies, progressive weakness and muscle imbalance result in plantarflexion of the 1st ray/medial column. To obtain a plantigrade foot, the hindfoot must roll into varus. With equinocavus, the hindfoot is in equinus, whereas in calcaneocavus (usually seen in polio or myelodysplasia), the hindfoot is in calcaneus (excessive dorsiflexion).

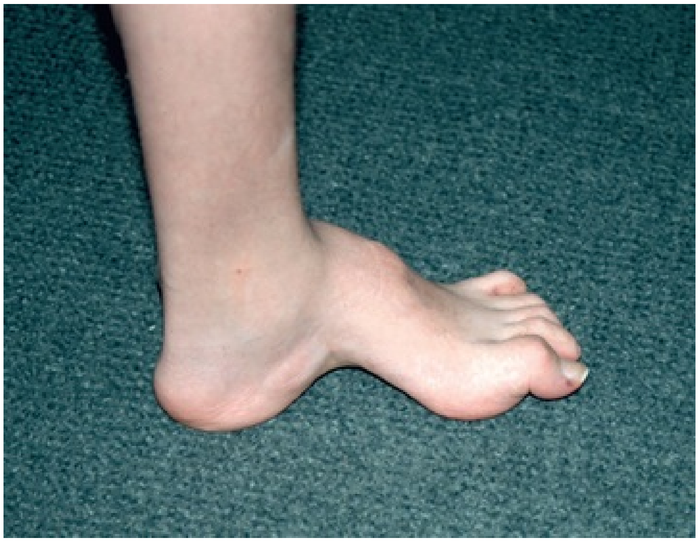

FIG. 694.8 Clinical picture demonstrating pes cavus.

Treatment

Any underlying diagnosis must be identified, as this knowledge also helps address the specific disorder and formulate the proper management strategy. With mild deformities, stretching through physical therapy or serial casting of the plantar fascia and contracted muscles with exercises to strengthen weakened muscles may help delay progression. An ankle–foot orthosis may be necessary to stabilize the foot and improve ambulation. Surgical treatment is indicated for progressive or symptomatic deformities that have failed to respond to nonoperative measures or in the foot that is no longer braceable. The specific procedures recommended depend on the degree of deformity and the underlying diagnosis. In the case of a progressive neuromuscular condition, recurrence of deformity is commonly observed, and additional procedures may be required to maintain a plantigrade foot. Families should be counseled in detail regarding the disease process and the expected gains from the surgery. The goal of surgery is to restore motion and alignment, and to improve muscle balance. For milder deformities, a soft tissue release of the plantar fascia, often combined with a tendon transfer, may suffice. For patients with a fixed bony deformity of the forefoot, midfoot, and/or the hindfoot, 1 or more osteotomies may be required for realignment. A triple arthrodesis (calcaneocuboid, talonavicular, and subtalar) may be required for severe feet (or recurrent deformities) in older patients. Long-term bracing is usually helpful in preventing recurrence.

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694.8

Osteochondroses/Apophysitis

Jennifer J. Winell, Richard S. Davidson

Osteochondroses are idiopathic avascular necroses of bones, which may involve tarsal bones as well. Although rare, they may be observed in the tarsal navicular **(Köhler disease)** or the 2nd or 3rd metatarsal head **(Freiberg infraction** ; Fig. 694.9). These are generally self-limited conditions that commonly result in activity-related pain, which can at times be disabling. The treatment is based on the degree of symptoms and commonly includes restriction of activity. The diagnosis is often made by history and physical exam in conjunction with concordant radiographic findings. The navicular is particularly sensitive, as it is the last tarsal bone to ossify, which may lead to compression from adjacent ossified bones. For patients with Köhler disease, nonsurgical treatment with a short leg cast for 6-8 wk may provide significant relief. Patients with Freiberg infraction may benefit from a period of casting and/or shoe modifications such as a rocker-bottom sole, a stiff-soled shoe, or a metatarsal bar. Degenerative changes and collapse of the metatarsal head will occasionally occur following the gradual healing process, and surgical intervention is required in a small subset of cases. Procedures have included joint debridement, bone grafting, redirectional osteotomy, subtotal or complete excision of the metatarsal head, and joint replacement.

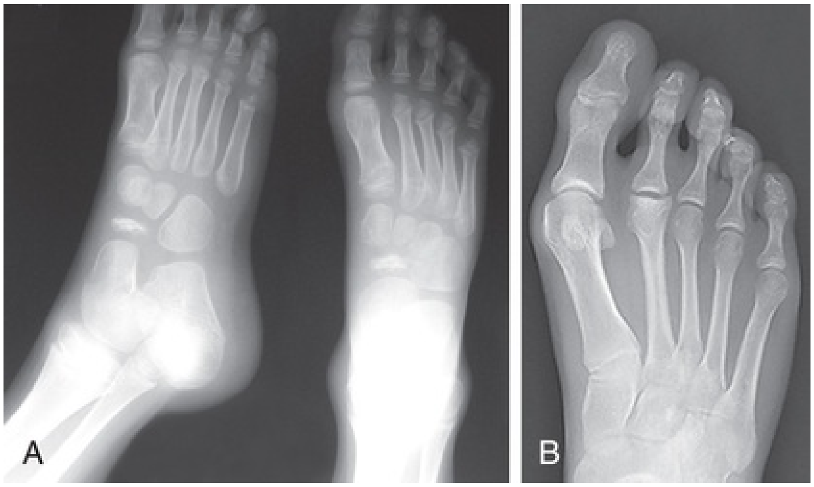

FIG. 694.9 **Radiographs of Köhler disease (A) and Freiberg infraction (B) .**

Apophysitis represents inflammation at the tendinous insertion of a muscle from repetitive tensile loading and is most commonly observed during periods of rapid growth. These stresses result in microfractures at the fibrocartilaginous insertion site, associated with inflammation. Calcaneal apophysitis **(Sever disease)** is the most common cause of heel pain in children; treatment includes activity modification, nonsteroidal antiinflammatory medications, heel cord stretching exercises, and heel cushions or arch supports. **Iselin disease** represents an apophysitis at the 5th metatarsal base where the peroneus brevis attaches and is less common. Even though the mandate for imaging heel pain in all children remains controversial, radiographs should be considered when the symptoms are unilateral or with a failure to respond to treatment. A period of rest (6-8 wk) and avoidance of sports will often resolve symptoms, although recurrence is common until maturity when the apophyses close.

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694.9

Puncture Wounds of the Foot

Jennifer J. Winell, Richard S. Davidson

Most puncture wound injuries to the foot may be adequately managed in the emergency department. **Treatment** involves a thorough irrigation and a tetanus booster, if appropriate; many clinicians will recommend antibiotics. Using this approach, the majority will heal without complication. A subset of cases may develop cellulitis, most often caused by *Staphylococcus aureus* , and require intravenous antibiotics with or without surgical drainage. Persistent signs of infection should be investigated more thoroughly. Deep infection is uncommon and may be associated with septic arthritis, infectious chondritis, or osteomyelitis. The most common organisms are *S. aureus* and *Pseudomonas aeruginosa* ; the treatment involves a thorough surgical debridement followed by a short course (10-14 days) of systemic antibiotics. Although plain radiographs will demonstrate any metallic fragments or other radiopaque foreign bodies, ultrasonography (or advanced imaging such as CT or MRI) may be necessary to identify radiolucent objects such as glass, plastic, or wood. Routine empiric exploration and removal of foreign bodies are not required, but may be necessary when symptoms are present, with recurrences, or when an infection is suspected. Pain and/or gait disturbance is more likely with superficial objects under the plantar surface of the foot.

A special situation occurs when a puncture wound from a nail comes through a rubber sneaker or running shoe. This situation presents a high risk of a

Pseudomonas infection, and consideration should be given to a thorough irrigation and debridement under general anesthesia followed by systemic antibiotics for 10-14 days. Foreign-body entrapment of rubber may also occur.

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694.10

Toe Deformities

Jennifer J. Winell, Richard S. Davidson

Juvenile Hallux Valgus (Bunion)

Juvenile hallux valgus is most common in females (~10-fold), and while a family history is uncommon, it is typically associated with familial ligamentous laxity. The etiology is multifactorial, and important factors include genetic factors, ligamentous laxity, pes planus, wearing shoes with a narrow toe box, and occasionally spasticity (cerebral palsy).

Clinical Manifestations

There is prominence of the 1st metatarsophalangeal (MTP) joint and often erythema and callus from chronic irritation. The great toe is in valgus and is usually pronated, and there is splaying of the forefoot. Pes planus, with or without an associated heel cord contracture, is also observed commonly. Although cosmesis is perhaps the most common concern, patients may have pain in the region of the 1st MTP joint and/or difficulty with shoe wear.

Radiographic Evaluation

Weight-bearing AP and lateral radiographs of the feet are obtained. On the AP view, common measurements include the angular relationships between the 1st and 2nd metatarsals (intermetatarsal angle, <10 degrees is normal) and between the 1st metatarsal and the proximal phalanx (hallux valgus angle, <25 degrees is normal). The orientation of the 1st metatarsal–medial cuneiform joint is also documented. On the lateral radiograph, the angular relationship between the talus and the 1st metatarsal helps identify a midfoot break associated with pes planus. Radiographs are more helpful in surgical planning than in establishing the diagnosis.

Treatment

Conservative management of adolescent bunions consists primarily of shoe modifications. It is important that footwear accommodate the width of the forefoot. Patients should avoid wearing shoes with a narrow toe box and/or a high heel. Shoe modifications, such as a soft upper, bunion last, or heel cup, may also be recommended. In the presence of a pes planus, an orthotic to restore the medial longitudinal arch may be beneficial. If a tendo-Achilles contracture is present, stretching exercises are recommended. The value of night splinting remains to be determined. Surgical treatment is reserved for those patients with persistent and disabling pain who have failed a course of nonoperative therapy. Surgery is not advised purely for cosmesis. Surgery is usually delayed until skeletal maturity to decrease the risk of recurrence or overcorrection. Radiographs are essential in preoperative planning to assess both the magnitude of deformity (hallux valgus angle, intermetatarsal angle, distal metatarsal articular angle) and associated features such as obliquity of the 1st metatarsal–medial cuneiform joint. Surgical treatment often involves a soft tissue release and or rebalancing procedure at the 1st MTP joint, and a single or double osteotomy of the 1st metatarsal to decrease foot width and realign the joints along the medial column of the forefoot. An arthrodesis of the 1st MTP joint may be indicated in patients with spasticity to prevent recurrence.

Curly Toes

A curly toe is caused by contracture of the flexor digitorum longus, and there is flexion at the MTP and the interphalangeal (IP) joints associated with medial deviation of the toe. The toe usually lies underneath its neighbor, and the 4th and 5th toes are most commonly involved. The deformity rarely causes symptoms, and active treatment (stretching, splinting, or taping) is not required. Most cases improve over time, and a subset will resolve completely. For the rare case in which there is chronic pain or skin irritation, release of the flexor digitorum longus muscle at the distal IP joint may be considered when the child is older.

Overlapping 5Th Toe

Congenital digitus minimus varus, or varus 5th toe, involves dorsiflexion and adduction of the 5th toe. The 5th toe typically overlaps the 4th. There is also a rotatory deformity of the toe, and the nail tends to point outward. The deformity is usually bilateral and may have a genetic basis. Symptoms are frequent and involve pain over the dorsum of the toe from shoe wear. Nonoperative treatment has not been successful. For symptomatic patients, several different options for reconstruction have been described. Common features include releasing the contracted extensor tendon and the MTP joint capsule (dorsal, dorsomedial, or complete). A partial removal of the proximal phalanx and creation of a syndactyly between the 4th and 5th toes have been performed in conjunction with the release as well.

Polydactyly

Polydactyly is the most common congenital toe deformity and is seen in approximately 2 : 1,000 births, where it is bilateral in 50% of cases. Polydactyly may be preaxial (great toe) or postaxial (5th toe), and occasionally one of the central toes is duplicated. Associated anomalies are found in approximately 10% of the preaxial and 20% of postaxial polydactyly. One third of patients will also have polydactyly of the hand. Conditions that may be associated with polydactyly include Ellis-Van Creveld (chondroectodermal dysplasia), longitudinal deficiency of the tibia, and Down syndrome. The extra digit may be either rudimentary or well formed, and plain radiographs of the foot help define the anatomy and evaluate any coexisting bony anomalies. Treatment is indicated for cosmesis and to allow for fitting with standard shoes. This involves surgical removal of the extra digit, and the procedure is generally performed between 9 and 12 mo of age. Rudimentary digits may be surgically excised earlier, but should not be "tied off."

Syndactyly

Syndactyly involves webbing of the toes, which may be incomplete or complete (extends to the tip of the toes), and the toenails may be confluent. There is often a positive family history, and the 3rd and 4th toes are involved most commonly. Symptoms are extremely rare, and cosmetic concerns are infrequent. Treatment is only required for a subset of cases in which there is an associated polydactyly (Fig. 694.10). In such cases, the border digit is excised, and the extra skin facilitates coverage of the wound. If the syndactyly does not involve the extra toe, then it can be observed. A complex syndactyly may be seen in patients with Apert syndrome.

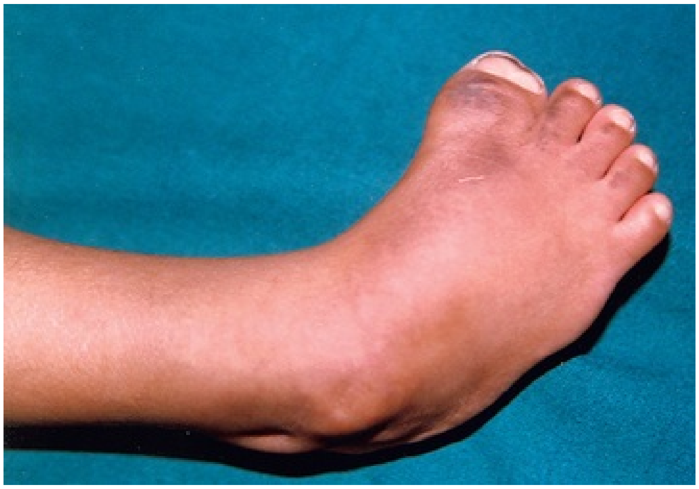

FIG. 694.10 **Clinical picture of polysyndactyly involving the great toe.**

Hammer Toe

A hammer toe involves flexion at the proximal IP (PIP) joint with or without the distal IP (DIP) joint, and the MTP joint may be hyperextended. This deformity may be distinguished from a curly toe by the absence of rotation. The 2nd toe is most commonly involved, and a painful callus may develop over the dorsum of the toe where it rubs on the shoe. Nonoperative therapy is rarely successful, and surgery is recommended for symptomatic cases. A release of the flexor tendons will suffice in the majority of cases. Some authors recommend a transfer of the flexor tendon to the extensor tendon. For severe cases with significant rigidity, especially in older patients, a partial or complete resection of the proximal phalanx and a PIP fusion may be required.

Mallet Toe

Mallet toe involves a flexion contracture at the DIP joint and results from congenital shortening of the flexor digitorum longus tendon. Patients may develop a painful callus on the plantar surface of the tuft. As nonoperative therapy is usually unsuccessful, surgery is required for patients with chronic symptoms. For flexible deformities in younger children, release of the flexor digitorum longus tendon is recommended. For stiffer deformities in older patients, resection of the head of the middle phalanx, or arthrodesis of the DIP joint, may be considered.

Claw Toe

A claw toe deformity involves hyperextension at the MTP joint and flexion at both the PIP and DIP joints, often associated with dorsal subluxation of the MTP joint. The majority are associated with an underlying neurologic disorder such as CMT disease. The etiology is usually muscle imbalance, and the extensor tendons are recruited to substitute for weakening of the tibialis anterior muscle. If treatment is elected, then surgery is required. Transfer of the extensor digitorum (or hallucis) tendon to the metatarsal neck is commonly performed along with a dorsal capsulotomy of the MTP joint and fusion of the PIP joint (IP joint of the great toe).

Annular Bands

Bands of amniotic tissue associated with amniotic disruption syndrome (early amniotic rupture sequence, congenital constriction band syndrome, annular band syndrome) may become entwined along the extremities, resulting in a spectrum of problems from in utero amputation (Fig. 694.11) to a constriction ring along a digit (Fig. 694.12 ; see Chapter 128). These rings, if deep enough, may result in impairment of arterial or venous blood flow. Even though concerns regarding tissue viability are less common, swelling from impairment in venous return is often a great problem. The treatment of annular bands usually involves observation; however, circumferential release of the band may be required emergently if arterial inflow is obstructed or electively to relieve venous congestion.

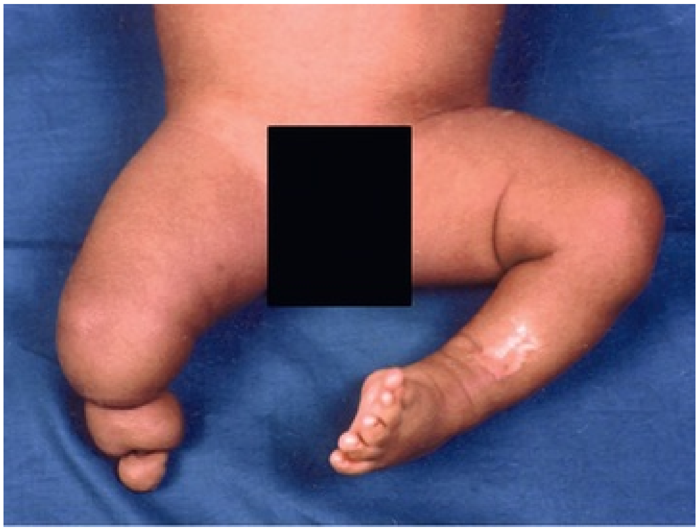

FIG. 694.11 Constriction band syndrome with congenital amputation.

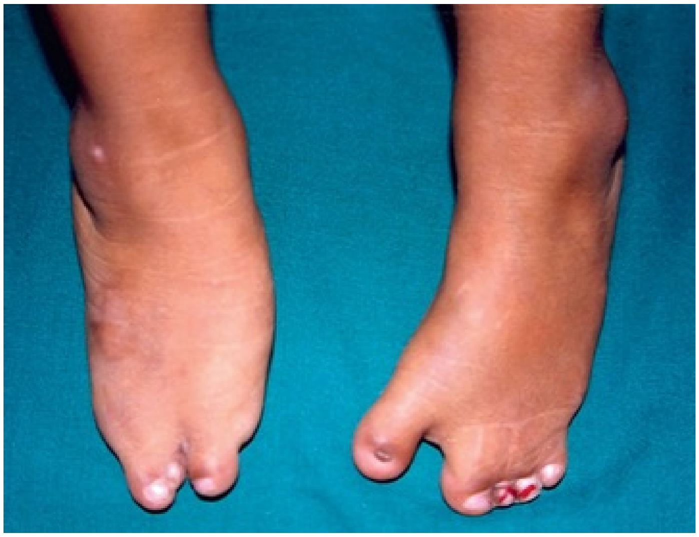

FIG. 694.12 **Constriction band syndrome with foot involvement.**

Macrodactyly

Macrodactyly represents an enlargement of the toes and may occur as an isolated problem or in association with a variety of other conditions such as Proteus syndrome (Fig. 694.13), neurofibromatosis, tuberous sclerosis, and Klippel-Trenaunay-Weber syndrome. This condition results from a deregulation of growth, and there is hyperplasia of one or more of the underlying tissues (osseous, nervous, lymphatic, vascular, fibrofatty). Macrodactyly of the toes may be seen in isolation (localized gigantism) or with enlargement of the entire foot. In addition to cosmetic concerns, patients may have difficulty wearing standard shoes. The treatment is observation, if possible. This is a difficult condition to treat surgically, and complications are frequent. For involvement of a single toe, the best option may be a resection of the ray (including the metatarsal). For greater degrees of involvement, debulking of the various tissues is required. Often a growth arrest of the underlying osseous structures is performed. Stiffness and wound problems are common. The rate of recurrence is high, and more than one debulking may be required. Patients may elect to have an amputation if the process cannot be controlled by less extensive procedures.

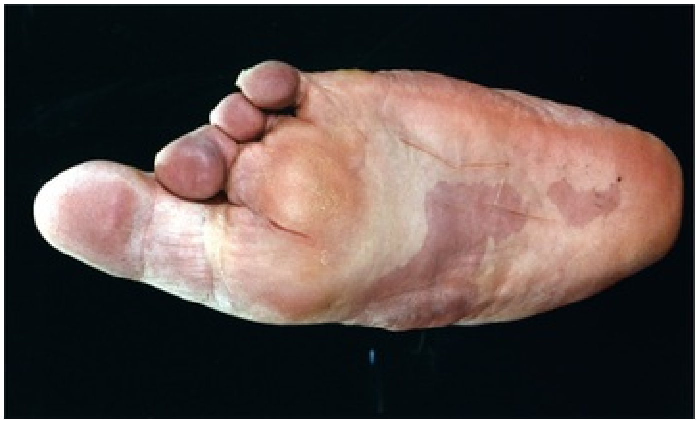

FIG. 694.13 Macrodactyly of the great toe in a case of Proteus syndrome.

Subungual Exostosis

A subungual exostosis is a mass of normal bone tissue that projects out from the dorsal and medial surface of a toe, under the nail. The etiology is unknown but may relate to minor, repetitive trauma. The great toe is involved most often. Patients present with discomfort, and the toenail may be elevated. The lesion may be demonstrated on plain radiographs, and histologically involves normal bone with a fibrocartilaginous cap. The treatment for symptomatic lesions is excision, and the recurrence rate is in the range of 10%.

Ingrown Toenail

Ingrown toenails are relatively common in infants and young children, and usually involve the medial or lateral border of the great toe. Symptoms include chronic irritation and discomfort, and recurrent infection is seen in some cases. Parents should be instructed when cutting toe nails to cut straight across the distal aspect of the nail, rather than curve inwards at the nail edges. If conservative measures including shoe modifications, warm soaks, and appropriate nail trimming fail to control the symptoms, then surgical removal of a portion of the nail should be considered.

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694.11

Painful Foot

Jennifer J. Winell, Richard S. Davidson

Table 694.2 shows a differential diagnosis for foot pain in different age ranges. In addition to the history and physical examination, plain radiographs are most helpful in establishing the diagnosis. Occasionally more sophisticated imaging modalities such as CT or MRI will be required.

Table 694.2

Differential Diagnosis of Foot Pain According to Age

AGE GROUP	DIAGNOSTIC CONSIDERATIONS
0-6 yr	Poorly fitting shoes Fracture Puncture wound Foreign body Osteomyelitis Cellulitis Juvenile idiopathic arthritis Hair tourniquet Dactylitis Leukemia
6-12 yr	Poorly fitting shoes Trauma (fracture, sprain) Juvenile idiopathic arthritis (enthesopathy) Puncture wound Sever disease (calcaneal apophysitis) Accessory tarsal navicular bone

	Hypermobile flatfoot Tarsal coalition Oncologic (Ewing sarcoma, leukemia)
12-18 yr	Poorly fitting shoes Stress fracture Trauma (fracture, sprain) Foreign body Ingrown toenail Metatarsalgia Plantar fasciitis Achilles tendinopathy Accessory ossicles (navicular, os trigonum) Tarsal coalition Avascular necrosis of metatarsal (Freiberg infarction) or navicular (Kohler disease) bones Plantar warts

From Marcdante K, Kliegman R, eds. Nelson Essentials of Pediatrics. 7th ed. Philadelphia: Saunders; 2015.

694.12

Shoes

Jennifer J. Winell, Richard S. Davidson

In toddlers and children, a well-fitting shoe with a **flexible** sole is recommended. This recommendation is in part based on studies suggesting that the development of the longitudinal arch seems to be best in societies where shoes are not worn and flatfeet are more common in shod children. Well-cushioned, shock-absorbing shoes are helpful in the child and adolescent athlete to decrease the chances of developing an overuse injury. Otherwise, shoe modifications are generally reserved for abnormalities in either alignment between segments of the foot or symptoms from an underlying condition (such as a limb-length discrepancy). Numerous modifications are available.

As a rule, shoes protect the foot from abnormal temperature as well as rough surfaces and sharp objects, but have not been shown to help the normal foot develop. Poorly fitting shoes may create problems.

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CHAPTER 695

Torsional and Angular Deformities of the Limb

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695.1

Normal Limb Development

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Keywords

femoral anteversion
medial tibial torsion
metatarsus adductus
genu valgum
genu varum

Pediatricians must understand normal limb development to recognize pathologic conditions during routine and targeted exams. During the 7th wk of intrauterine life, the lower limb rotates medially to bring the great toe toward the midline. The hip joint forms by the 11th wk; the proximal femur and acetabulum continue to develop until physeal closure in adolescence. The first component of rotation is the femoral neck, which is rotated approximately 40 degrees anteriorly at birth. This anterior rotation is referred to as **anteversion** (the angle between the axis of the femoral neck and the transcondylar axis). The increased anteversion results in increased internal rotation of the hip. In most children, femoral anteversion decreases to 15-20 degrees by 8-10 yr of age. Conditions such as cerebral palsy that involve spasticity of the lower extremities can result in the persistence of fetal anteversion. This results in torsional abnormalities of the lower limb and gait disturbances. The second component of limb rotation is found in the tibia. Tibial torsion is the angular difference between the axis of the knee and the transmalleolar axis. Infants can have 30 degrees of medial rotation of the tibia. When skeletally mature, the rotation is between 5 degrees of medial rotation and 15 degrees of lateral rotation (Fig. 695.1). Excessive medial rotation of tibia is referred to as **medial tibial torsion** . This is very common and, although very concerning to parents, very rarely requires treatment. The medial or lateral rotation beyond ±2 SDs from the mean is considered abnormal rotation. The third component of rotational (axial) abnormalities of the lower extremity derives from the foot. Metatarsus adductus can cause the foot to curve medially, pointing the toes inward. It is assessed by observing the medial and lateral borders of the foot.

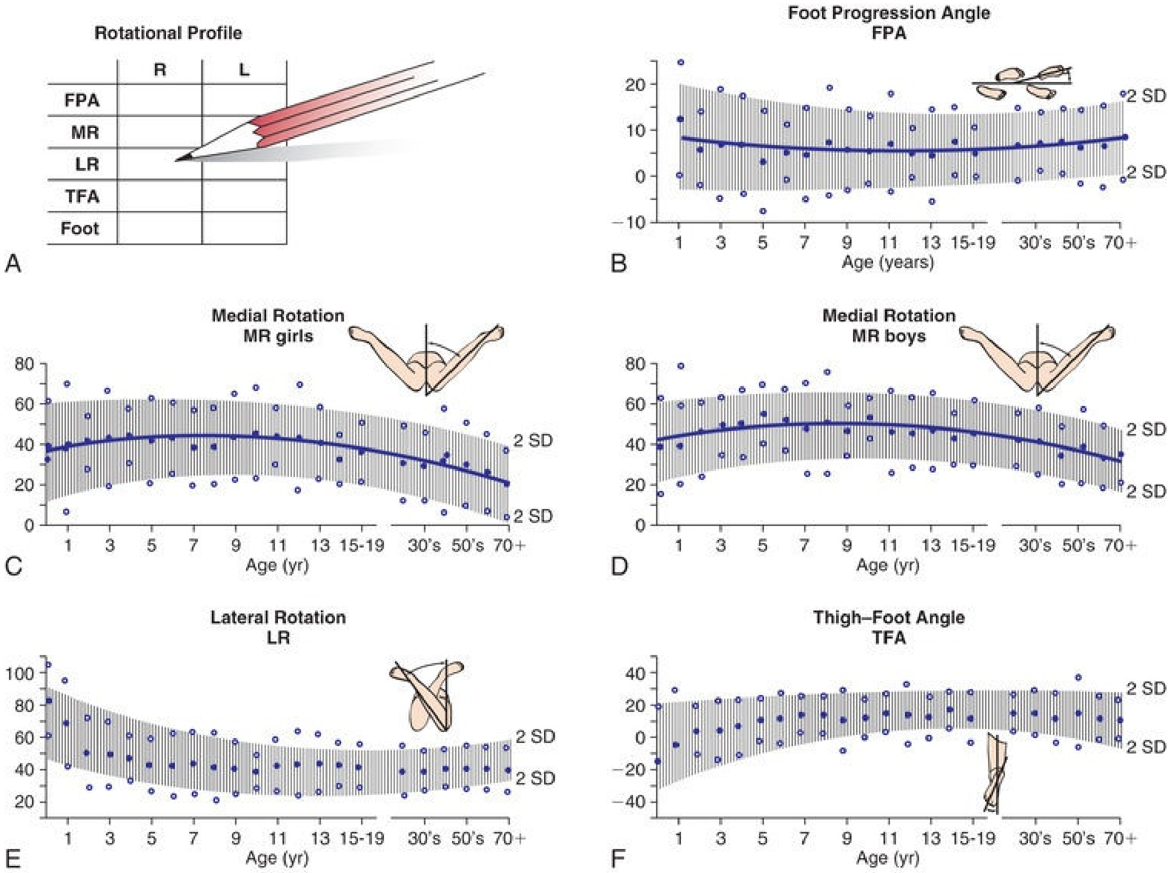

FIG. 695.1 A-F, The rotational profile from birth to maturity is depicted graphically. All graphs include 2 SD from the mean for the foot progression angle *(FPA)* for femoral medial rotation *(MR)* and lateral rotation *(LR)* (for boys and girls), and the thigh-foot angle *(TFA)* . (From Morrissey RT, Weinstein SL, editors: *Lovell and Winter's pediatric orthopaedics,* ed 3, Philadelphia, 1990, Lippincott Williams & Wilkins.)

Torsional deformity may be simple, involving a single component, or complex, involving multiple components. Complex deformities may be additive (internal tibial torsion and internal femoral torsion are additive) or compensatory (external tibial torsion and internal femoral torsion are compensatory).

The normal tibiofemoral angle at birth is 10-15 degrees of physiologic varus. The alignment changes to 0 degrees by 18 mo, and physiologic valgus up to 12 degrees is reached in between 3 and 4 yr of age. The normal valgus of 7 degrees is achieved by 5-8 yr of age (Fig. 695.2). Persistence of varus beyond 2 yr of age may be pathologic and is seen in conditions such as Blount disease. Overall, 95% of developmental physiologic genu varum and genu valgum cases resolve with growth. Persistent genu valgum or valgus into adolescence is considered pathologic and deserves further evaluation.

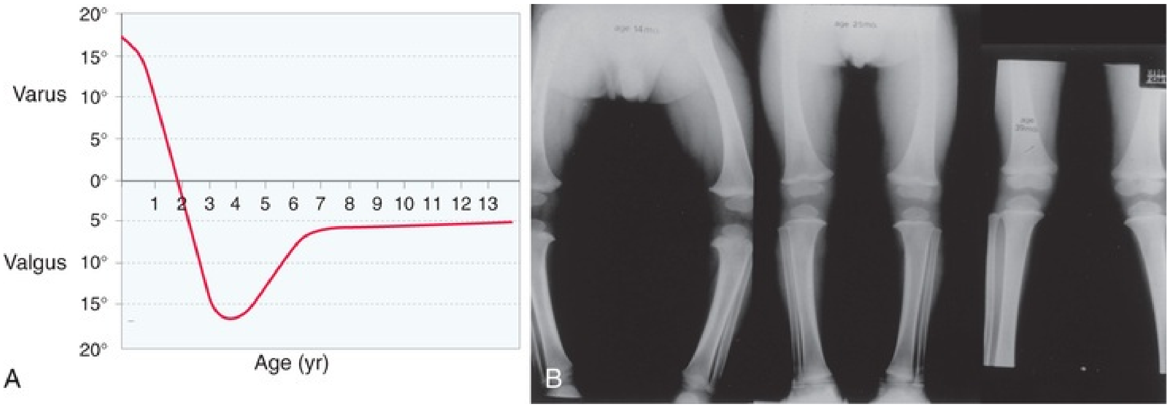

FIG. 695.2 A, Development of the tibiofemoral angle during growth (after Salenius). B, Serial radiographs demonstrating normal transition from varus alignment at 14 months to neutral position at 25 months to valgus tibiofemoral alignment at 39 months. (From Johnston CE, Young M: Disorders of the leg. In Herring JA: Tachdjian's pediatric orthopaedics, ed 5, Philadelphia, 2014, Elsevier, Fig 22-3.)

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695.2

Evaluation

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Keywords

foot progression angle
femoral anteversion
transmalleolar angle
thigh-foot angle
heel bisector line

When evaluating concerns regarding the limb, the pediatrician should obtain a history documenting onset, progression, functional limitations, previous treatment, evidence of neuromuscular disorder, and any significant family history. The examination should assess the exact torsional profile and include (1) foot progression angle, (2) femoral anteversion, (3) tibial version with thigh-foot angle, and (4) assessment of foot adduction and abduction.

Foot Progression Angle

Limb position during gait is expressed as the **foot progression angle** and represents the angular difference between the axis of the foot with the direction in which the child is walking. Its value is usually estimated by asking the child to walk in the clinic hallway (Fig. 695.3). Inward rotation of the foot is assigned a negative value, and outward rotation is designated with positive value. The normal foot progression angle in children and adolescents is 10 degrees (range: −5 to 20 degrees). The foot progression angle delineates whether there is an in-toeing or out-toeing gait.

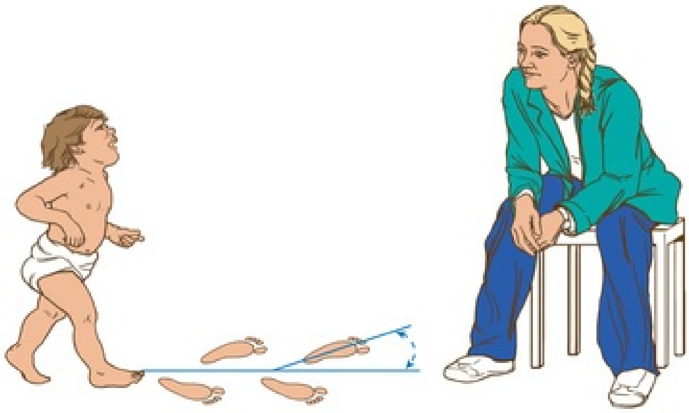

FIG. 695.3 **Foot progression angle. The long axis of the foot is compared with the direction in which the child is walking. If the long axis of the foot is directed outward, the angle is positive. If the foot is directed inward, the angle is negative and indicates in-toeing. (From Thompson GH: Gait disturbances. In Kliegman RM, editor: *Practical strategies in pediatric diagnosis and therapy* , Philadelphia, 2004, WB Saunders.)**

Femoral Anteversion

Hip rotation is measured with the child in a prone position, the hip in neutral flexion or extension, thighs together, and the knees flexed to 90 degrees (Fig. 695.4). Both hips are assessed at the same time. Internal rotation of the hip is measured by rotating the leg ipsilaterally and external rotation is measured by rotating the leg contralaterally. Excessive anteversion has increased internal rotation, whereas retroversion has increased external rotation. The amount of anteversion can be approximately estimated by palpating the greater trochanter of the hip while internally rotating the limb. Femoral anteversion should be measured at the point when the greater trochanter is most prominent laterally during this rotation (Craig's test).

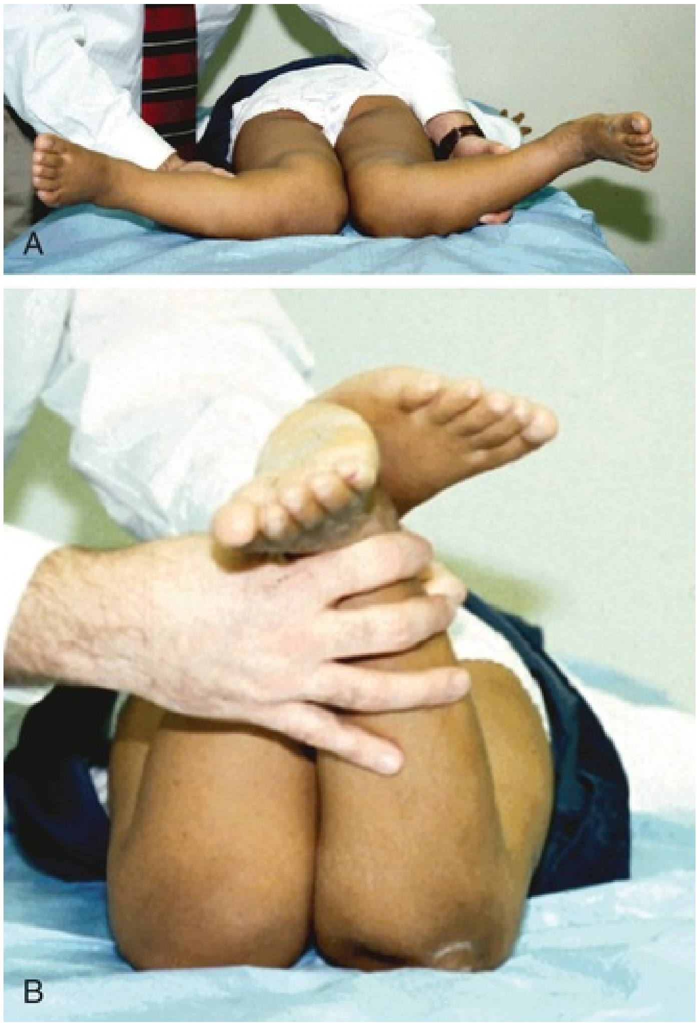

FIG. 695.4 **Anteversion measured by medial rotation of hip (A) and lateral rotation of hip (B) .**

Tibial Rotation

Tibial rotation is measured using the **transmalleolar angle.** The transmalleolar angle is the angle between the longitudinal axis of the thigh with a line perpendicular to the axis of the medial and lateral malleolus (Fig. 695.5). In the absence of foot deformity, the **thigh-foot angle** is preferred (Fig. 695.6). It is measured with the child lying prone. The angle is formed between the longitudinal axis of the thigh and the longitudinal axis of the foot. It measures the tibial and hindfoot rotational status. Inward rotation is assigned a negative value, and outward rotation is assigned a positive value. Inward rotation indicates medial tibial torsion, whereas outward rotation represents lateral tibial torsion. Infants have a mean angle of −5 degrees (range: −35 to 40 degrees) as a consequence of normal in utero position. In mid-childhood through adult life, the mean thigh-foot angle is 10 degrees (range: −5 to 30 degrees).

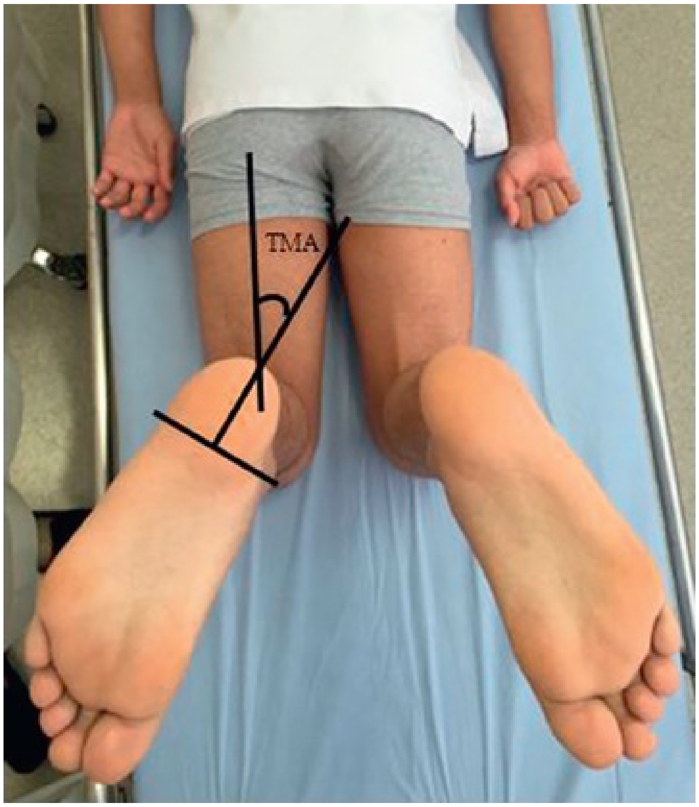

FIG. 695.5 Measurement of transmalleolar angle (TMA). (From Guler O, Isyar M, Karataş D, et al: Investigating the relationship between internal tibial torsion and medial collateral ligament injury in patients undergoing knee arthroscopy due to tears in the posterior one third of the medial meniscus. The Knee 23(4):655-658, 2016. Fig 2.)

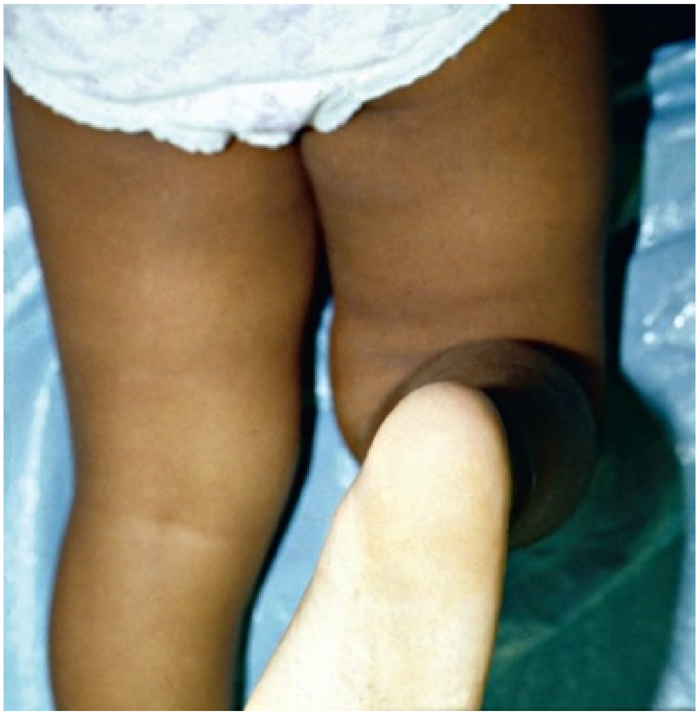

FIG. 695.6 Thigh-foot angle.

Foot Shape and Position

The foot is observed for any deformities in prone and standing position. The **heel bisector line** (HBL) is used to evaluate the foot adduction and abduction deformities. The HBL is a line that divides the heel in two equal halves along the longitudinal axis (Fig. 695.7). It normally extends through the center of the second toe. When the HBL points medial to the second toe, the forefoot is abducted, and when the HBL is lateral to the second toe, the forefoot is adducted. Other lower-extremity problems, such as heel varus or valgus, can make assessment of axial plane issues more difficult.

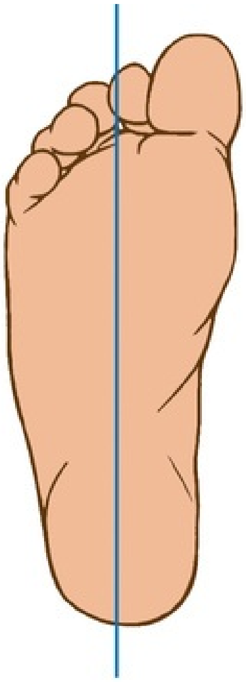

FIG. 695.7 **Schematic demonstration of heel bisector line.**

It is also important to screen children with these foot deformities for associated hip dysplasia and neuromuscular problems (cerebral palsy).

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695.3

Torsional Deformities

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Keywords

femoral anteversion
medial tibial torsion
genu valgum
genu varum
slipped capital femoral epiphysis
lateral tibial torsion
calcaneovalgus foot
metatarsus adductus

Femoral Anteversion

In-toeing gait most commonly results from excessive femoral anteversion. It occurs more commonly in girls than boys (2 : 1) in children 3-6 yr of age. Most orthopedic surgeons agree that this is congenital, resulting from persistent infantile anteversion. On examination, many children with this condition will have **generalized ligamentous laxity** . Gait examination reveals that the entire leg is inwardly rotated. Internal hip rotation is increased beyond 70 degrees, and consequently the external rotation is restricted to 10-20 degrees. Clinically, the patellae point inwards when the foot is straight, and compensatory external rotation of the tibia is demonstrated. This is frequently mistaken as “genu valgum.” The amount of anteversion can be roughly estimated by palpating the greater trochanter of the hip while internally rotating the limb. The point of maximal prominence of the greater trochanter laterally during this rotation corresponds to the degree of femoral anteversion.

Diagnosis is made clinically on examination; CT can provide objective measurements but is rarely indicated. The treatment is predominantly **observation and reassurance** . The torsion usually corrects with longitudinal growth by 8-10 yr of age. Although rare, persistent deformity, unacceptable cosmesis, functional impairment, anteversion >45 degrees, and no external rotation beyond neutral are indications for operative intervention. Surgery involves a derotation osteotomy of the femur.

Medial Tibial Torsion

Medial (internal) tibial torsion manifests with **in-toeing gait.** It is commonly associated with congenital metatarsus varus, genu valgum, or femoral anteversion. This condition is usually seen during the second year of life. It is often noticed after the child begins to walk independently. Many parents are concerned with a “bowed” appearance of the legs. Normally at birth, the medial malleolus lies behind the lateral malleolus, but by adulthood, it is reversed, with the tibia in 15 degrees of external rotation. The treatment is essentially **observation and reassurance** because spontaneous resolution with normal growth and development can be anticipated. Correction can be seen as early as 4 yr of age and in some children by 8-10 yr of age. Persistent deformity with functional impairment is treated with supramalleolar osteotomy, which is rarely necessary.

External Femoral Torsion

External femoral torsion can follow a **slipped capital femoral epiphysis** . There should be a low threshold to perform radiographs of the hips in children older than 10 yr of age who present with hip or knee pain and decreased internal rotation of the hip on clinical exam. Femoral retrotorsion, when of idiopathic origin, is usually bilateral. The disorder is associated with an **out-toeing gait** and increased incidence of degenerative arthritis. The clinical examination of external femoral torsion shows excessive hip external rotation and limitation of internal rotation. The hip will externally rotate up to 70-90 degrees and internally rotate to only 0-20 degrees. If a slipped capital femoral epiphysis is detected, it is treated surgically. Occasionally, persistent femoral retroversion after slipped capital femoral epiphysis can produce functional impairment resulting in a severe out-toed gait and difficulty opposing one's knees in the sitting position. The latter can be disabling to adolescent girls. Should this occur, a Southwick osteotomy or surgical realignment might be necessary.

Lateral Tibial Torsion

Lateral (external) tibial torsion is less common than medial rotation and is often associated with a **calcaneovalgus foot** . It can be compensatory to persistent femoral anteversion or secondary to a tight iliotibial band. Natural growth rotates the tibia externally, and therefore external tibial torsion can become worse with time. Clinically, the patella faces outward when the foot is straight. The thigh-foot angle and the transmalleolar angle are increased. There may be associated patellofemoral instability with knee pain. Although some correction can occur with growth, extremely symptomatic children may need a supramalleolar osteotomy, which is usually done by 10-12 yr of age.

Metatarsus Adductus

Metatarsus adductus (see Chapter 694.1) manifests with forefoot adduction and medial rotation of all metatarsals. Ten percent to 15% of children with metatarsus adductus have hip dysplasia. The prognosis is good, because the majority get better with nonoperative intervention. Feet that correct actively with stimulation of the lateral border of the foot are treated with stretching exercises alone. Feet that are flexible and correctable to neutral with manipulation are treated with stretching, reverse last shoes, or serial casting. Feet that do not correct fully with conservative care or rigid deformities are treated with medial capsulotomy of the 1st metatarsal cuneiform joint and soft-tissue release by 2 yr of age. Osteotomies of the base of the metatarsal may be performed after 6 yr of age.

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695.4

Coronal Plane Deformities

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Keywords

genu varum
genu valgum
Blount disease

Genu varum and genu valgum are common pediatric deformities of the knee. Fig. 695.2 presents the age-appropriate normal values for knee angle. Tibial bowing is common during the first year, bowlegs are common during the second year, and knock-knees are most prominent between 3 and 4 yr of age.

Genu Varum

Physiologic bowleg is a common torsional combination that is secondary to normal in utero positioning (Fig. 695.8). Spontaneous resolution with normal growth and development can be anticipated. Persistence of varus beyond 2 yr of age may be pathologic. Causes of pathologic bowing include metabolic bone disease (vitamin D deficiency, rickets, hypophosphatasia), asymmetric growth arrest (trauma, infection, tumor, Blount), bone dysplasia (dwarfism, metaphyseal dysplasia), and congenital and neuromuscular disorders (Table 695.1). It is important to differentiate physiologic bowing from Blount disease (Table 695.2). Physiologic bowing should also be differentiated from rickets and skeletal dysplasia. Rickets has classic bony changes seen on plain radiographs with trumpeting widening and fraying of the metaphysis along with widening of the physis (see Chapter 64).

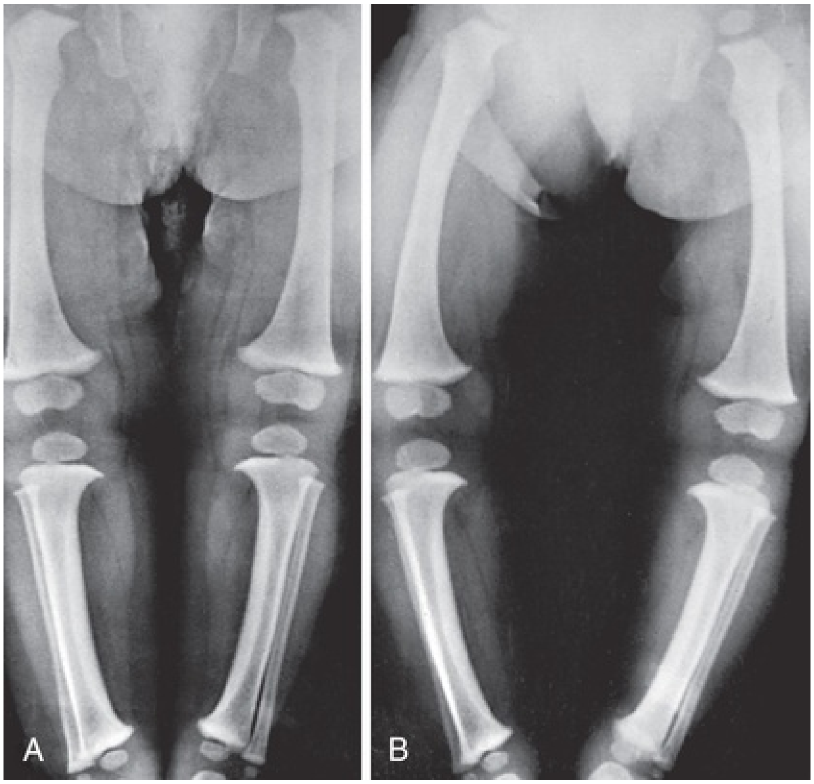

FIG. 695.8 **A,** In recumbent position, tibia and femora are bowed but the legs do not appear bowed. **B,** In erect position during weight bearing and with ankles in apposition, the legs are bowed. (From Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby.)

Table 695.1

Classification of Genu Varum (Bowlegs)

Physiologic

ASYMMETRIC GROWTH

- Tibia vara (Blount disease)
  - Infantile
  - Juvenile
  - Adolescent
- Focal fibrocartilaginous dysplasia
- Physeal injury
- Trauma
- Infection
- Tumor

Metabolic Disorders

- Vitamin D deficiency (nutritional rickets)
- Vitamin D–resistant rickets
- Hypophosphatasia

Skeletal Dysplasia

- Metaphyseal dysplasia
- Achondroplasia
- Enchondromatosis

Modified from Thompson GH: Angular deformities of the lower extremities. In Chapman MW, editor: *Operative orthopedics* , ed 2, Philadelphia, 1993, JB Lippincott, Table 222.1, p. 3132.

Table 695.2

Differentiation of Leg Bowing

PHYSIOLOGIC BOWING	BLOUNT DISEASE
Gentle and symmetric deformity	Asymmetric, abrupt, and sharp angulation
Metaphyseal–diaphyseal angle <11 degrees	Metaphyseal-diaphyseal angle >11 degrees
Normal appearance of the proximal tibial growth plate	Medial sloping of the epiphysis Widening of the physis Fragmentation of the metaphysis
No significant lateral thrust	Significant lateral thrust

Tibia Vara

Idiopathic tibia vara, or **Blount disease** , is a developmental deformity resulting from abnormal endochondral ossification of the medial aspect of the proximal tibial physis leading to varus angulation and medial rotation of the tibia (Fig. 695.9). The incidence is greater in African Americans and in overweight toddlers. It is also higher in patients who have an affected family member or started walking early in life. It has been classified into three types, depending on the age at onset: infantile (1-3 yr of age), juvenile (4-10 yr of age), and adolescent (11 yr or older). The juvenile and adolescent forms are commonly combined as late-onset tibia vara. The exact cause of tibia vara remains unknown, although it is thought to result from abnormal growth of the physis due to excessive weight.

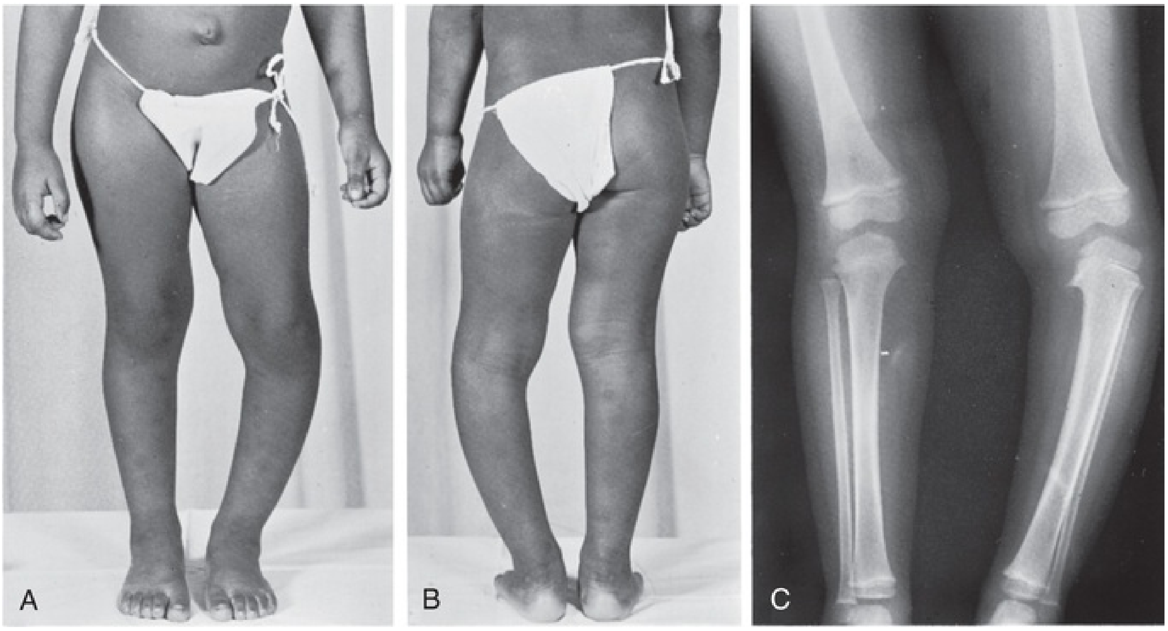

FIG. 695.9 Blount disease in a 5-year-old girl. **A** and **B,** Preoperative clinical appearance. Note the abrupt medial deviation of the tibia just below the knee. Lateral "thrust" of the knee during weight bearing exacerbates the "limp." **C,** Radiograph demonstrating abrupt angulation at the epiphyseal-metaphyseal junction and medial metaphyseal radiolucency and beaking with apparent lateral subluxation of the proximal end of the tibia. (From Johnston CE, Young M: Disorders of the leg. In Herring JA, editor: Tachdjian's pediatric orthopaedics, ed 5, Philadelphia, 2014, Elsevier, Fig 22-4.)

The **infantile** form of tibia vara is the most common. There is a predominance in black females. Approximately 80% are bilateral with a prominent medial metaphyseal beak, internal tibial torsion, and leg-length discrepancy. The characteristics of the **juvenile** and **adolescent** forms (late onset) include predominance in black males, normal or greater than normal height, approximately 50% bilateral involvement, slowly progressive genu varum deformity, pain rather than deformity as the primary initial complaint, no palpable proximal medial metaphyseal beak, minimal internal tibial torsion, mild medial collateral ligament laxity, and mild lower extremity length discrepancy. The infantile group has the greatest potential for progression.

An anteroposterior standing radiograph of both lower extremities with patellae facing forward and a lateral radiograph of the involved extremity should be obtained (Fig. 695.10). Weight-bearing radiographs are preferred and allow maximal presentation of the clinical deformity. The metaphyseal-diaphyseal angle can be measured and is useful in distinguishing between physiologic genu varum and early tibia vara (Fig. 695.11). Langenskiöld has 6 stages on radiographs (Fig. 695.12). The differentiation is based on fragmentation of the epiphysis, beaking of the medial tibial epiphysis, depression of the medial tibial plateau, and formation of a bony bar. Occasionally, CT with 3-dimensional reconstructions, or MRI, may be necessary to assess the meniscus, the articular surface of the proximal tibia including the posteromedial slope, or the integrity of the proximal tibial physis.

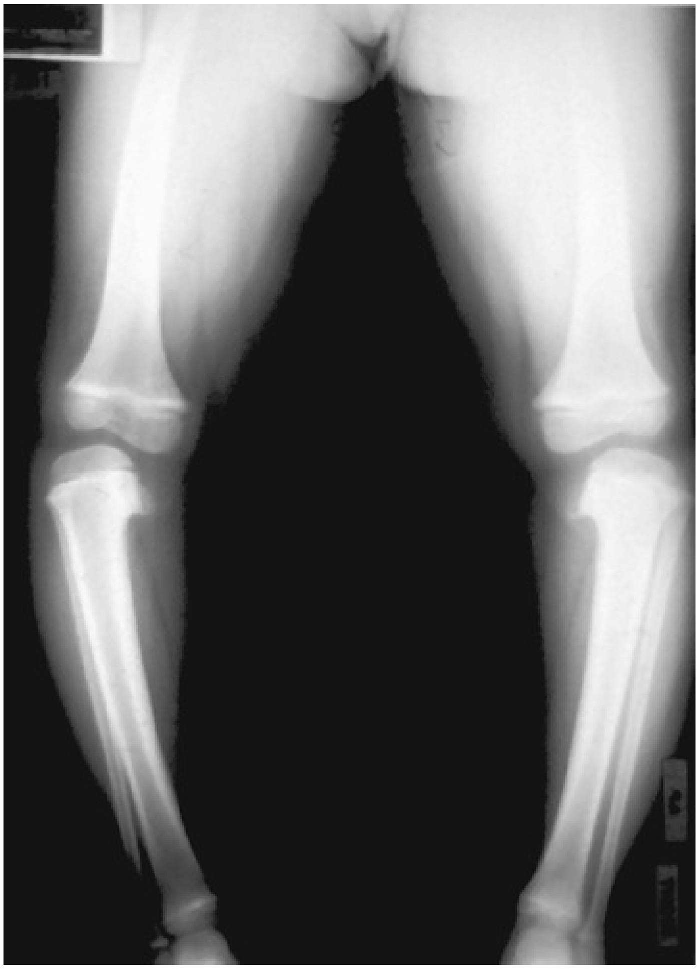

FIG. 695.10 **Anteroposterior radiograph of both knees in Blount disease.**

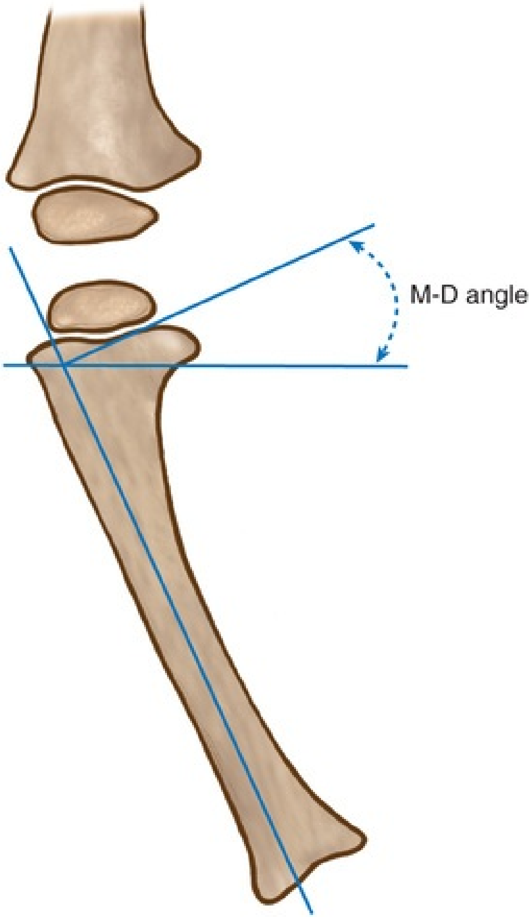

FIG. 695.11 Metaphyseal-diaphyseal *(M-D)* angle. Draw a line on the radiograph through the proximal tibial physis. Draw another line along the lateral tibial cortex. Last, draw a line perpendicular to the shaft line as demonstrated in the diagram. (From Morrissey RT, Weinstein SL, editors: *Lovell and Winter's pediatric orthopaedics* , ed 3, Philadelphia, 1990, Lippincott Williams & Wilkins.)

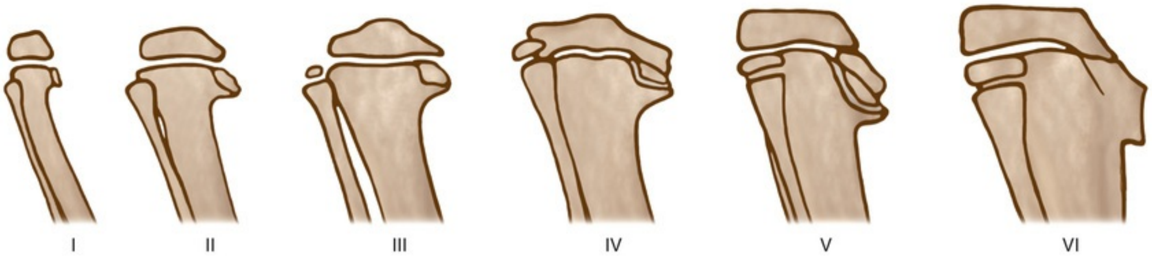

FIG. 695.12 Depiction of the stages of infantile Blount disease. (From Langeskiöld A: Tibia vara (osteochondrosis deformans tibiae): a survey of 23 cases. *Acta Chir Scand* 103:1, 1952.)

Management is based on the stage of the disease, the age of the child, and nature of presentation (primary or recurrent deformity). In children younger than 3 yr and Langenskiöld stage <3, bracing is effective and can prevent progression in 50% of patients. A maximal trial of 1 yr of orthotic management is recommended. If complete correction is not obtained after 1 yr or if progression occurs during this time, a corrective osteotomy is indicated. Surgical treatment is also indicated in children >4 yr of age, those at Langenskiöld stage >3, and those with severe deformities. A proximal tibial valgus osteotomy and associated fibular diaphyseal osteotomy are usually the procedures of choice. In late-onset tibia vara, correction is also necessary to restore the mechanical axis of the knee. Hemiplateau elevation with correction of posteromedial slope has been established as a treatment modality in relapsed cases.

Genu Valgum (Knock-Knees)

The appearance of symmetric bilateral genu valgum most pronounced around age 4 is part of the normal physiologic process of leg development. However, variation of up to 15 degrees of valgus is possible until 6 yr of age. The majority of physiologic valgus has a good chance of correction until this age. The intermalleolar distance with the knees approximated is normally <2 cm, and in a severe valgus deformity it could measure >10 cm. Pathologic conditions leading to valgus are metabolic bone disease (rickets, renal osteodystrophy), skeletal dysplasia, posttraumatic physeal arrest, tumors, and infection. The increased valgus at the knee causes lateral deviation of the mechanical axis with stretching of the medial aspect of the knee leading to knee pain. Deformities >15 degrees and occurring after 6 yr of age are unlikely to correct with growth and require surgical management. In the skeletally immature, medial tibial epiphyseal hemiepiphysiodesis or stapling (guided growth) is attempted for correction. In the skeletally mature, osteotomy is necessary at the center of rotation of angulation and is usually situated in the distal femur. Long-length anteroposterior radiographs of the leg in a weight-bearing stance are necessary for preoperative planning.

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695.5

Congenital Angular Deformities of the Tibia and Fibula

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Keywords

posteromedial tibial bowing
calcaneovalgus foot
anteromedial tibial bowing
fibular hemimelia
anterolateral tibial bowing
congenital pseudoarthrosis of the tibia
neurofibromatosis
tibial longitudinal deficiency

Posteromedial Tibial Bowing

Congenital posteromedial bowing is typically associated with a calcaneovalgus foot and rarely with secondary valgus of the tibia. The exact cause is unknown. Early operative intervention is not indicated because this bowing generally corrects with growth. However, despite the correction of angulation, there can be residual shortening in the tibia and fibula. The mean growth inhibition is 12–13% (range: 5–27%). The mean leg length discrepancy at maturity is 4 cm (range: 3-7 cm). The diagnosis of bowing is confirmed on radiographs, which show the posteromedial angulation without any other osseous abnormalities. The calcaneovalgus deformity of the foot improves with stretching or modified shoe wear and occasionally ankle-foot orthosis. Predicted leg length discrepancy <4 cm is managed with age-appropriate epiphysiodesis of the normal leg. Leg length discrepancy >4 cm is managed with combination of contralateral epiphysiodesis and ipsilateral lengthening. A corrective osteotomy for distal valgus may be required and can be done in the same setting while correcting leg length discrepancy.

Anteromedial Tibial Bowing (Postaxial Hemimelia)

Fibular hemimelia is the most common cause of anteromedial bowing of the tibia. The fibular deficiency can occur with complete absence of fibula or with partial fibular development both proximally and distally. It is associated with deformities of femur, knee, tibia, ankle, and foot. The femur is short and has lateral condylar hypoplasia, causing patellar instability and genu valgum deformity. The tibia has anteromedial bowing with reduced growth potential. The keys for management are addressing the ankle stability and foot deformities. The ankle resembles a ball-and-socket joint with lateral instability. The foot deformities are characterized by the absence of lateral digits, equinocavovarus foot, and tarsal coalition.

Various surgical options have been described, and the treatment is tailored to the patient's needs and parents’ acceptance. A severely deformed foot may be best managed with Syme or Boyd amputation and prosthesis as early as 1 yr of age. In the salvageable foot, leg length discrepancy can be treated with contralateral leg epiphysiodesis or ipsilateral limb lengthening.

Anterolateral Tibial Bowing

Anterolateral tibial bowing is associated with congenital **pseudarthrosis of tibia** . Fifty percent of the patients have **neurofibromatosis** , but only 10% of the neurofibromatosis patients, have this lesion. The pseudarthrosis or site of nonunion is typically situated at the middle third and distal third of the tibia. Boyd has classified it in increasing severity depending on the presence of cystic and dysplastic changes. The treatment for this condition has been very frustrating, with poor results. Bracing has been recommended to prevent fracture early in the course; however, it has not been successful. Numerous surgical interventions have been attempted to achieve union, such as single- and dual-onlay grafting with rigid internal fixation, intramedullary pinning with or without bone grafting, and an Ilizarov device. With the advent of microsurgery, live fibular grafts have been used with varying results. Because of the poor chances of successful union and considerable leg length discrepancy, a below-knee amputation with early rehabilitation may be preferred. It is important not to attempt any osteotomy for correction of the tibial bowing.

Tibial Longitudinal Deficiency

Tibial longitudinal deficiency follows an autosomal dominant inheritance pattern and has been divided into four types depending which part of the tibia is deficient. The other associated anomalies are foot deformities, hip dysplasia, and symphalangism of the hand. The treatment revolves around presence of proximal tibial anlage and a functional quadriceps mechanism. In type Ia deformity, the proximal tibial anlage is absent and knee disarticulation with prosthesis is recommended. In types Ib and II, the tibial anlage is present and the management consists of an early Syme amputation, followed later by synostosis of the fibula with the tibia, and a below-knee prosthesis. Type III is rare, and the principal management is with Syme amputation and a prosthesis. Type IV deformity is associated with ankle diastasis, which requires stabilization of the ankle and correction of leg length discrepancy at a later stage.

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CHAPTER 696

Leg-Length Discrepancy

Richard S. Davidson

A discrepancy in leg lengths may result from a variety of congenital or acquired conditions (Table 696.1). Although up to 25% of adults may have a difference of more than 1 cm, only a small percentage have more than a 2 cm difference. The main consequence is gait asymmetry. An increase in vertical pelvic motion is observed, and more energy must be expended during ambulation. Although a small compensatory lumbar curvature may develop, there is little evidence to suggest that leg-length discrepancy results in back pain, structural scoliosis, or degenerative arthritis. The goal of treatment is to have a discrepancy of <2-2.5 cm at skeletal maturity, and several treatment methods are available to achieve this objective. Knowledge of the underlying etiology, coupled with regular follow-up to assess limb growth and skeletal maturity, allows the treating physician to project the discrepancy at skeletal maturity and to plan treatment. A subset of patients will have coexisting abnormalities in the viscera or musculoskeletal system, which must also be identified and treated.

Table 696.1

Causes of Lower Extremity Length Discrepancy

SHORTENING	LENGTHENING
CONGENITAL Hemiatrophy* Skeletal dysplasias Short femur Proximal focal femoral deficiency* Fibular, tibial hemimelia Developmental dysplasia of the hip*	**CONGENITAL** Hemihypertrophy* Local vascular malformation
TUMOR Developmental Neurofibromatosis Multiple exostosis	**TUMOR** Developmental Neurofibromatosis Soft tissue hemangioma

Enchondromatosis (Ollier disease) Osteochondromatosis Fibrous dysplasia (Albright syndrome) Punctate epiphyseal dysplasia Dysplasia epiphysealis hemimelica (Trevor disease) Radiation therapy before skeletal maturity (physeal arrest)* Resection of benign or malignant neoplasm	Arteriovenous malformation Hemihypertrophy with Wilms tumor Aneurysm
INFECTION Osteomyelitis* Septic arthritis Tuberculosis	**INFECTION** Inflammation Metaphyseal osteomyelitis Rheumatoid arthritis Hemarthrosis (hemophilia)
TRAUMA Physeal injury* Failed joint replacement Osteotomy, atrophic nonunion Overlapping, malposition of fracture fragments* Burns	**TRAUMA** Metaphyseal, diaphyseal fracture Diaphyseal operations (bone grafts, osteosynthesis, periosteal stripping)
NEUROMUSCULAR DISEASE Poliomyelitis Cerebral palsy* Myelomeningocele Peripheral neuropathy Focal cerebral lesions (hemiplegia)	
OTHER Legg–Calvé–Perthes disease* Slipped capital femoral epiphysis	**OTHER** Russell Silver syndrome Klippel-Trénaunay-Weber syndrome

* Common.

Modified from Moseley C. Leg-length discrepancy. *Pediatr Clin North Am* 33(6):1385, 1986.

Diagnosis and Clinical Findings

Gait asymmetry is the most frequent complaint. The long leg is often kept flexed in stance to level the pelvis. The diagnosis is made on physical examination, and specialized radiographs help to quantify the existing discrepancy and predict what the discrepancy will be at maturity. The discrepancy may be caused by hypoplasia, hyperplasia, or angular deformity (structural discrepancy), by soft-tissue contracture at the hips, knees, or ankles (apparent or functional shortening), or by a combination of these conditions. Other contributing factors include joint subluxation or dislocation (hip), a decrease in the height of the foot (congenital or neuromuscular) or structural disorders of the pelvis. A careful physical examination is required to identify all factors contributing to the discrepancy. Muscle contracture about the hip will also create the appearance of leg-length inequality. For example, to bear weight on an abducted hip, the patient must hike up the contralateral hip and pelvis, making the contralateral leg appear short.

There are several clinical methods for measuring limb length. Our preference is to perform a standing examination, in which blocks of various sizes are placed under the short leg until the pelvis is leveled (Fig. 696.1). An alternate method is to measure the length of each leg with the patient supine by the Galeazzi and Alis tests. The traditional method of using a tape measure is very inaccurate because of, for example, the line of measurement used, muscle atrophy, and moving patients. The range of motion at the hip, knee, and ankle must be also assessed to identify any causes of apparent discrepancy. A 10-degree fixed abduction (or adduction) contracture of the hip will create an apparent leg-length discrepancy of 2-3 cm. Similarly, a flexion contracture of the hip and/or knee will create apparent shortening of the extremity, whereas an equinus contracture at the ankle will create apparent lengthening of the extremity. A rigid lumbar scoliosis (suprapelvic contracture) will create pelvic obliquity and an associated limb length inequality. Once a discrepancy is quantified, it must be followed at regular intervals until maturity. Assessments at 6-12 mo intervals are most common.

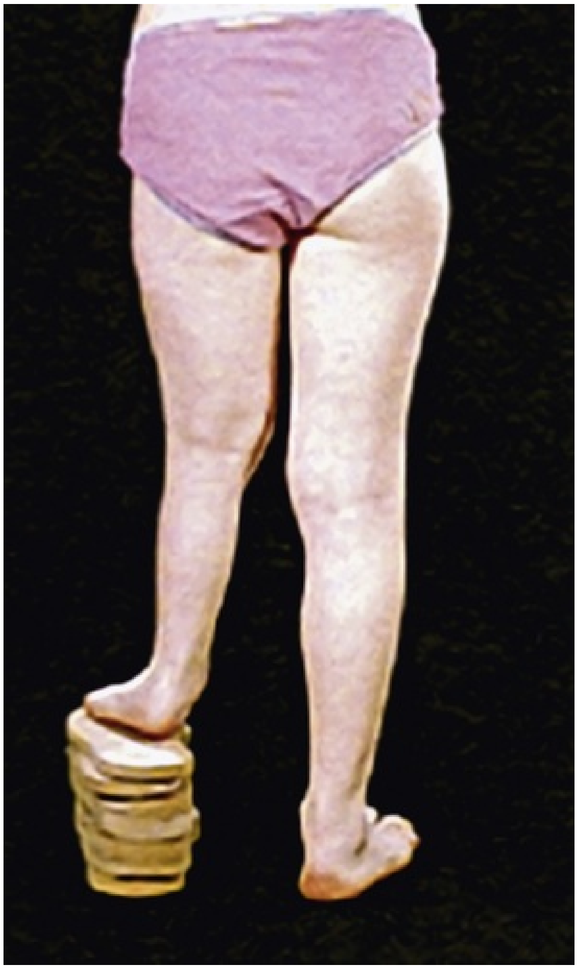

FIG. 696.1 **Examination with blocks under short leg until the pelvis is squared.**

Radiographic Evaluation

Radiologic evaluation complements the clinical examination; both are typically used when making treatment decisions. Five different techniques are available. The **teleoroentgenogram** is a single radiographic exposure of both lower extremities (standing) and requires a long cassette. A ruler is placed on the film, and direct measurements are made, factoring in a 6% magnification error. One advantage is that angular deformities may be assessed. Its primary indication is for young children. Unfortunately, because only one exposure is used for the leg and because the ankle is less dense than the hip, it may be difficult to “see” the whole leg. In addition, because the x-ray source is at the knee projecting up to the hip and down to the ankle, this method projects the hip and ankle along the ruler, making the leg appear longer than it really is, particularly in obese patients.

The **orthoroentgenogram** consists of three separate exposures of the hips, knees, and ankles on a long cassette. The patient is supine, and a ruler is placed on the cassette for measurement of bone length. However, the patient must lie still for the three exposures, which is often difficult to achieve in younger children. Because the x-ray beam is pointed at the hip, knee, and ankle in each of the 3 exposures, the length measurement is accurate and each of the three joints can be exposed properly. The x-rays expose from the top of the pelvis to the mid femur, from the mid femur to the mid tibia, and from the mid tibia to below the foot for each of the 3 exposures, respectively, permitting angular deformity assessment in the frontal plane only. The **scanogram** also consists of separate exposures of the hips, knees, and ankles on a cassette with a radiographic ruler; a chest-sized film cassette is used (Fig. 696.2). There is no magnification error; patients must remain still for the 3 exposures, and angular deformities cannot be assessed. Although ***CT*** is an accurate technique, the assessment is time-consuming, and the technique is not available in most centers. In addition, a radiologist must normalize the axis of the leg to the screen to accurately measure the limbs. Another technique, called ***EOS*** , uses a 3D, low-dose ($^1/_7$ to $^1/_{10}$ the radiation) scanner but requires a sophisticated radiologist to correctly align the limbs for computer measurement. Regardless of the technique, it is critical that the patellae be pointed forward, that measurements be made in the plane of the limb, and that the same method be used in sequential measurements to be compared.

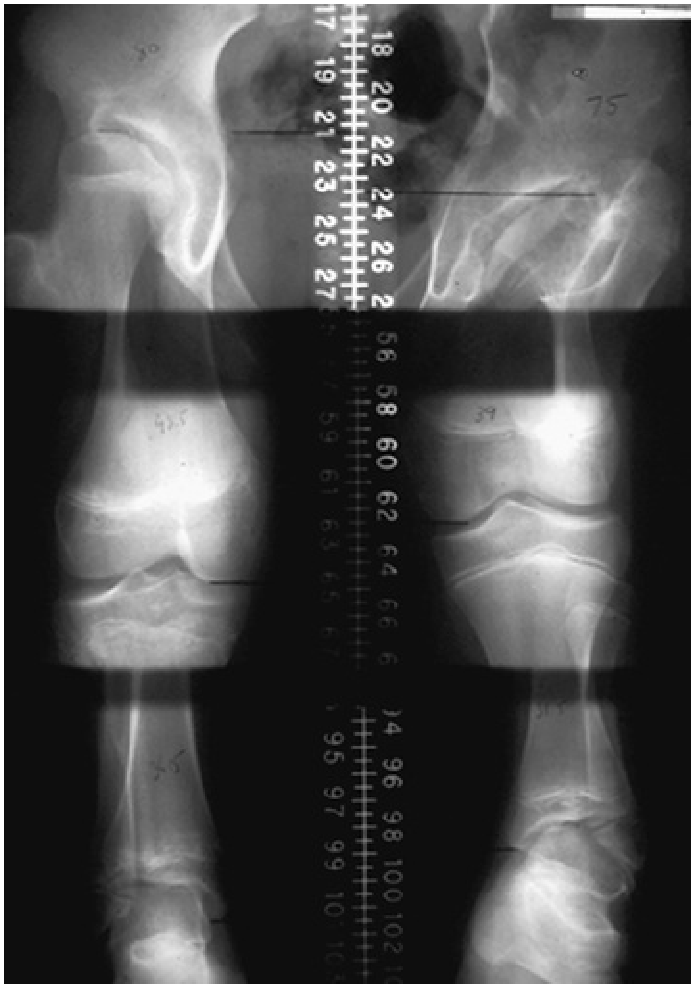

FIG. 696.2 **Scanogram to demonstrate exact leg-length discrepancy.**

In the presence of flexion or extension deformities, each bone should be x-rayed individually with a ruler where the x-ray beam is perpendicular to the bone and the ruler parallel to the bone.

In addition to quantifying the discrepancy, it is essential to determine skeletal age (bone age). An anteroposterior radiograph of the hand and wrist is usually obtained at each visit and compared with the standards in the Greulich and Pyle Atlas to estimate skeletal age. Although more accurate techniques are available, most are time-consuming and impractical for routine clinical application. The range of variability using the atlas is approximately 9 mo, so the method is most accurate when multiple data points have been collected.

Treatment

Options for treatment include observation, a shoe lift or custom orthosis, a limb-shortening procedure (acute shortening and internal fixation versus gradual shortening by growth arrest or guided growth), a limb-lengthening procedure (with internal or external fixation), or a combination of these. Deformity correction is often accomplished simultaneously. In the congenital deficiencies (femur, tibia, fibula) in which the predicted limb-length inequality will require more than three lengthening operations (more than 20 cm), an early foot amputation may be the best option to achieve an optimal functional outcome. In addition to the magnitude of discrepancy predicted at skeletal maturity, both the anticipated adult height of the patient (estimated from family members) and the desires of the patient and the patient's family are important considerations.

Discrepancies of up to 2.5 cm may be treated by observation or a shoe lift. Up to 1 cm may be placed within the shoe, and up to 5 cm may be placed on the outside of the shoe. Complete correction of inequality is not required, and the height of the lift should be adjusted based on the patient's gait and comfort. An orthotic may be used as a temporizing measure prior to definitive treatment. For extended discrepancies, “foot in foot” prostheses are a reasonable alternative until limb length can be accomplished or for patients who cannot or do not wish to undergo surgical correction.

For patients with a discrepancy between 2 and 5 cm, an **epiphysiodesis** is offered in skeletally immature patients, and an acute shortening may be performed in a skeletally mature patient. Epiphysiodesis refers to a temporary or permanent cessation of growth at one or more physes. A permanent growth arrest is most commonly performed when sufficient data are available with which to accurately predict when to perform the procedure. Approximately 65% of the growth of the lower extremity comes from the distal femur (37%, 9 mm/yr) and proximal tibia (28%, 6 mm/yr). Males typically grow until 16 yr of age, whereas females grow until 14 yr of age. As such, performing an epiphysiodesis of both the distal femur and the proximal tibia in a patient with 3 yr of growth remaining should achieve approximately 4.5 cm of correction. Techniques used to determine the timing of epiphysiodesis are the Menelaus method (“rule of thumb”), the Green and Anderson method, the Moseley straight-line graph, and the multiplier method (Figs. 696.3 to 696.5). The most common surgical technique is the percutaneous epiphysiodesis, in which the physis is ablated with a drill and curette under image intensification. This is an outpatient procedure with few complications. Insertion of plates and screws or just screws across the physis is an alternative but usually requires a second operation to remove the hardware. For patients for whom sufficient data are unavailable or those for whom the underlying diagnosis is associated with an unpredictable pattern of growth, then a reversible technique, such as staples, plates, and/or screws, may be considered. Once equalization has been achieved, the hardware can be removed, allowing growth to resume. When the patient is skeletally mature or if it is deemed appropriate to wait until maturity before treatment, acute shortening may be the best option. Acute shortening is typically performed at the femur (several techniques have been described), given the increased risk of complications (compartment syndrome, neurovascular problems) associated with shortening of the tibia and fibula.

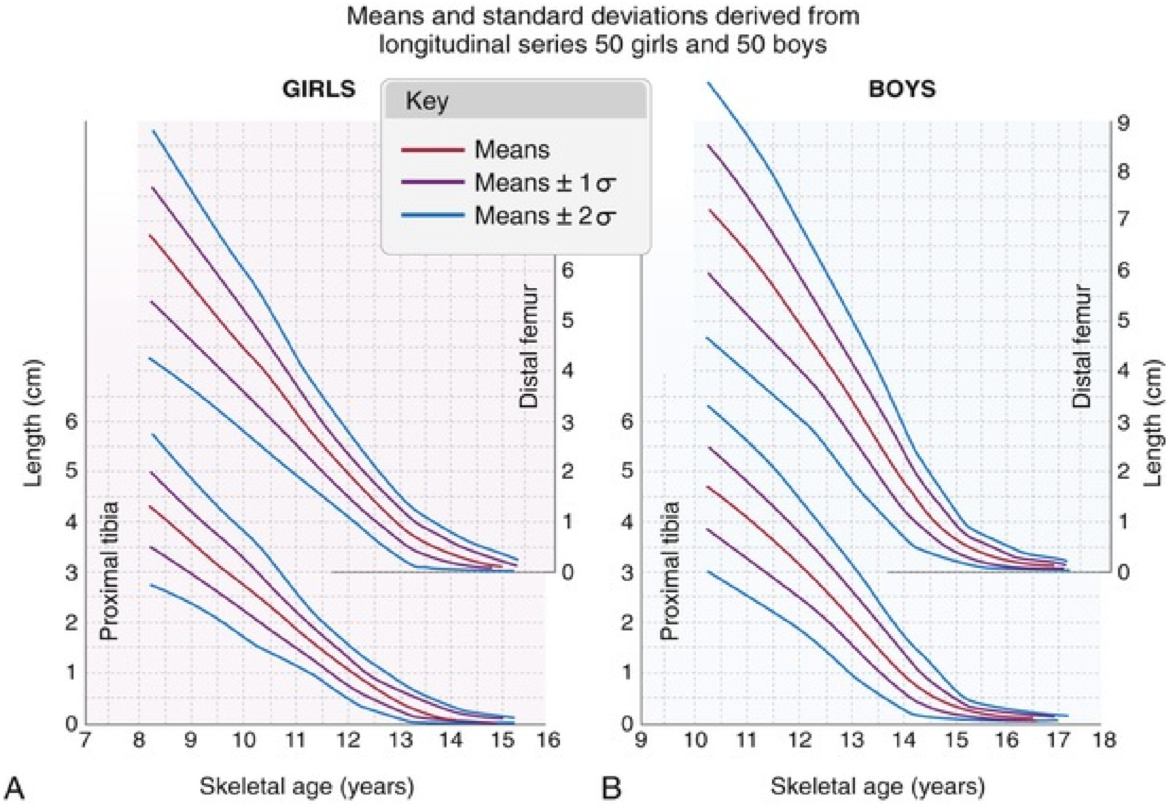

FIG. 696.3 Growth remaining charts for the distal femur and proximal tibia for girls (A) and boys (B). These charts are based on the growth data and an estimate of the contribution to growth of the distal femur (70%) and the proximal tibia (56%) to the total length of the respective bone. Data are presented relative to skeletal age from age 8 yr to skeletal maturity. (From Herring JA: Limb length discrepancy. In Herring JA, editor: Tachdjian's pediatric orthopaedics, ed 5, Philadelphia, 2014, Elsevier, Fig 24-13.)

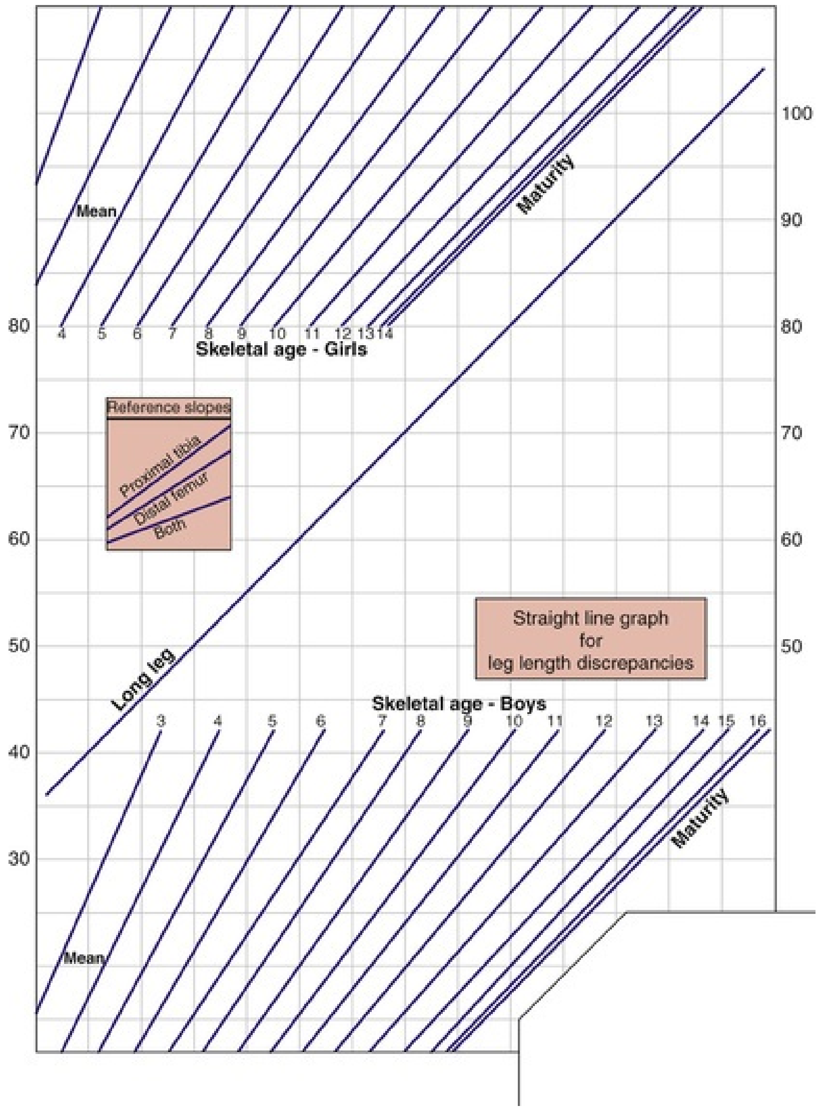

FIG. 696.4 The Moseley straight-line graph for the assessment of leg-length inequalities. This allows simultaneous correlation of the normal leg, short leg, and bone age of the child. It will accurately predict lengths of each extremity at skeletal maturity. The reference slopes are used as a guide in determining when appropriate treatment should be performed. (From Moseley CF: A straight-line graph for leg-length discrepancies. *J Bone Joint Surg Am* 59:174–179, 1977.)

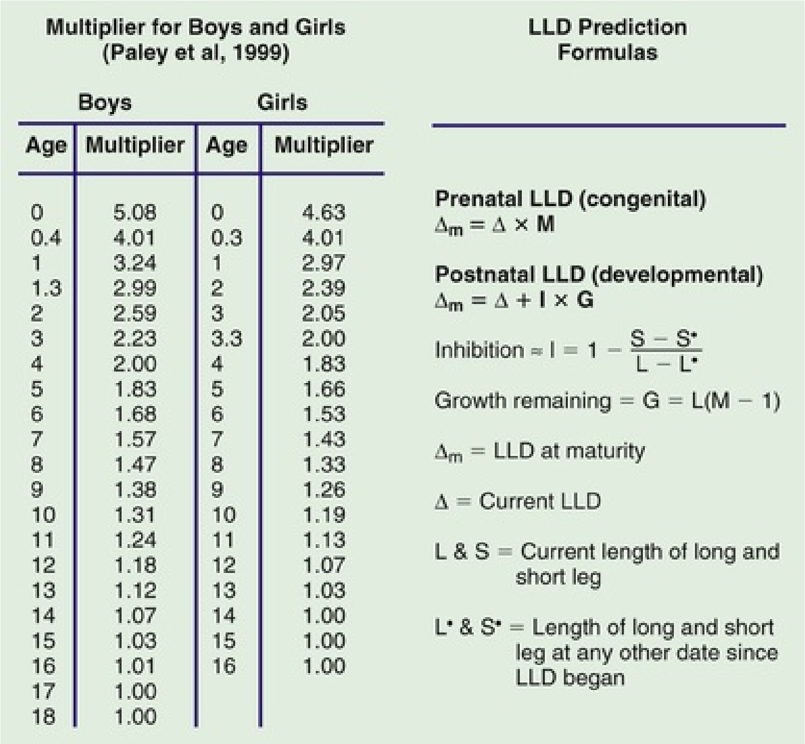

Multiplier for Boys and Girls (Paley et al, 1999)

Boys		Girls	
Age	Multiplier	Age	Multiplier
0	5.08	0	4.63
0.4	4.01	0.3	4.01
1	3.24	1	2.97
1.3	2.99	2	2.39
2	2.59	3	2.05
3	2.23	3.3	2.00
4	2.00	4	1.83
5	1.83	5	1.66
6	1.68	6	1.53
7	1.57	7	1.43
8	1.47	8	1.33
9	1.38	9	1.26
10	1.31	10	1.19
11	1.24	11	1.13
12	1.18	12	1.07
13	1.12	13	1.03
14	1.07	14	1.00
15	1.03	15	1.00
16	1.01	16	1.00
17	1.00		
18	1.00		

LLD Prediction Formulas

Prenatal LLD (congenital)

$\Delta_m = \Delta \times M$

Postnatal LLD (developmental)

$\Delta_m = \Delta + I \times G$

Inhibition $= I = 1 - \frac{S - S'}{L - L'}$

Growth remaining $= G = L(M - 1)$

Δ_m = LLD at maturity

Δ = Current LLD

L & S = Current length of long and short leg

L' & S' = Length of long and short leg at any other date since LLD began

FIG. 696.5 **Paley multiplier. This is a simple method of determining the leg-length discrepancy *(LLD)* at maturation. This is applicable for shortening conditions in which growth retardation is consistent. (From Paley D, Bhave A, Herzenberg JE, Bowen JR: Multiplier methods for predicting limb-length discrepancy. *J Bone Joint Surg Am* 82;1432–1446, 2000.)**

For discrepancies >5 cm, lengthening of the short limb is the procedure of choice. An exception would be a discrepancy secondary to overgrowth of one limb, in which limb shortening would be preferred so as to preserve body proportions, for which acute or gradual shortening of the abnormal limb is preferred. Patients with anticipated discrepancies >8-10 cm often require 1 or more limb-lengthening procedures (several years apart) with or without an epiphysiodesis. The most common technique used for limb lengthening involves placement of an external fixator, either a ring fixator such as the Ilizarov device or a monolateral device (Fig. 696.6). The bone is cut at the metaphyseal-diaphyseal junction, and lengthening is achieved gradually through distraction at the corticotomy. The usual rate of lengthening is 1 mm/day, and it takes approximately 1 mo wearing the fixator for each centimeter of length gained with a minimum of 3 mo in the fixator. Additional time in the fixation may be required for pathologic bone or for metabolic diseases affecting bone formation. A maximum of 15–25% of the original length of the bone may be gained at each session. An advantage of the circular fixator or multiaxial external fixators is the ability to correct coexisting angular deformities at the same time. Technologic advances have allowed the development of intramedullary lengthening and compression rods driven by external magnets. These may provide improvements in patient satisfaction and reduced complications.

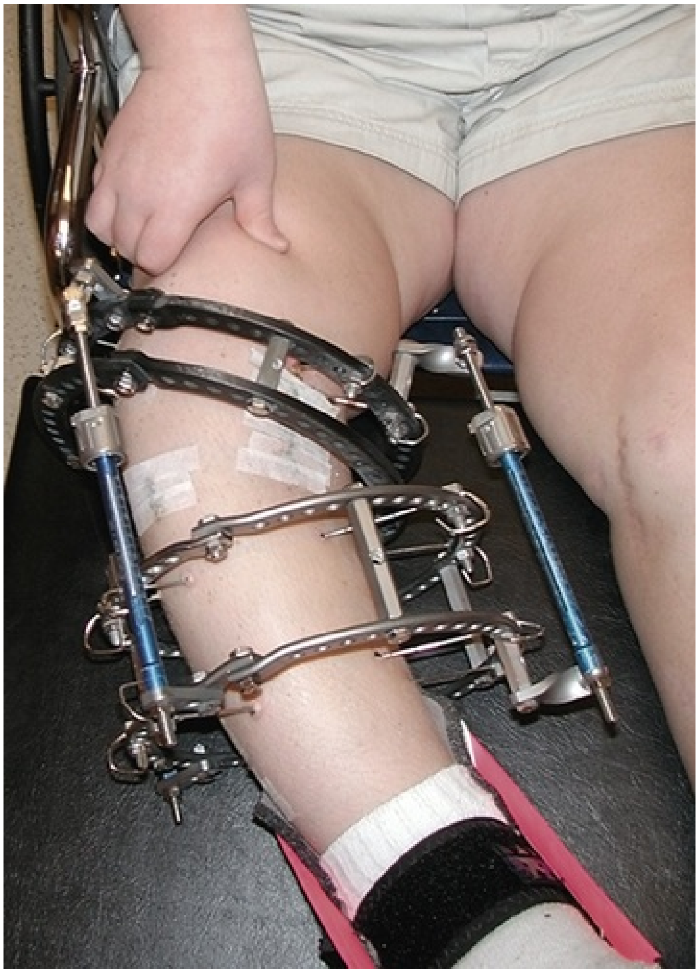

FIG. 696.6 Ilizarov device demonstrating bone lengthening by distraction osteogenesis.

Complications include pin tract infection (most common), wound infection, hypertension, joint subluxation, muscle contracture, premature consolidation, delayed union, implant-related problems, and fractures after implant removal. Finally, early amputation and prosthetic fitting may provide the best long-term function in patients with projected discrepancies in excess of 18-20 cm, especially when there are coexisting deformities or deficiencies of the ipsilateral foot (Figs. 696.7 and 696.8). The alternative would be multiple reconstructive procedures throughout childhood and adolescence. The impact of multiple procedures on the child's psychosocial development must also be kept in mind when formulating the treatment plan in these complex cases.

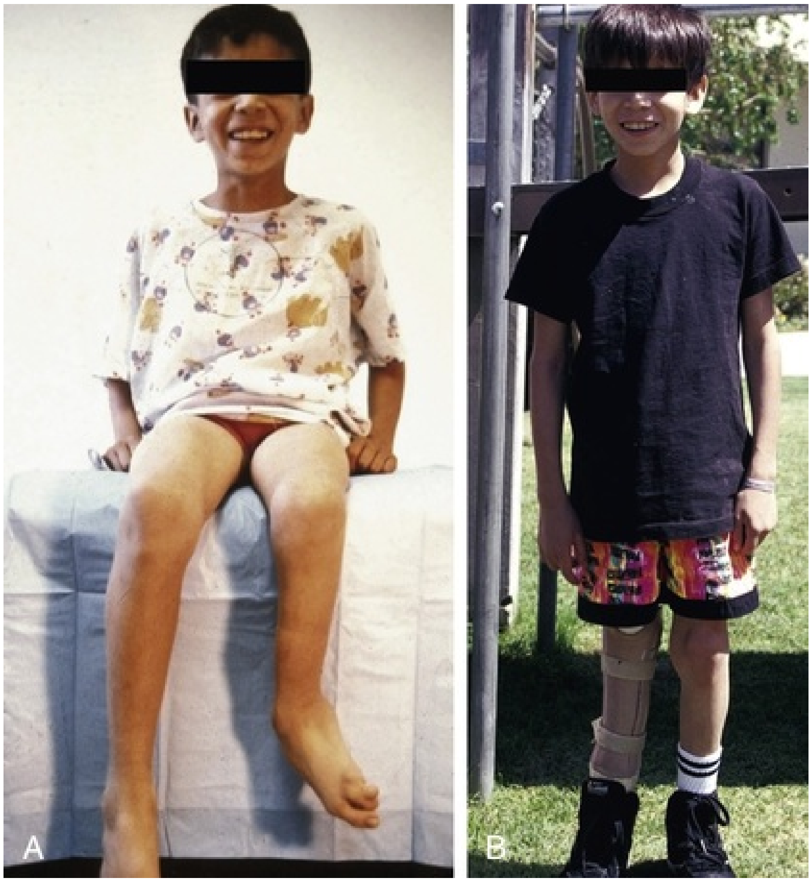

FIG. 696.7 **Extension prosthesis leg-length discrepancy (A) and compensated with extension prosthesis (B).**

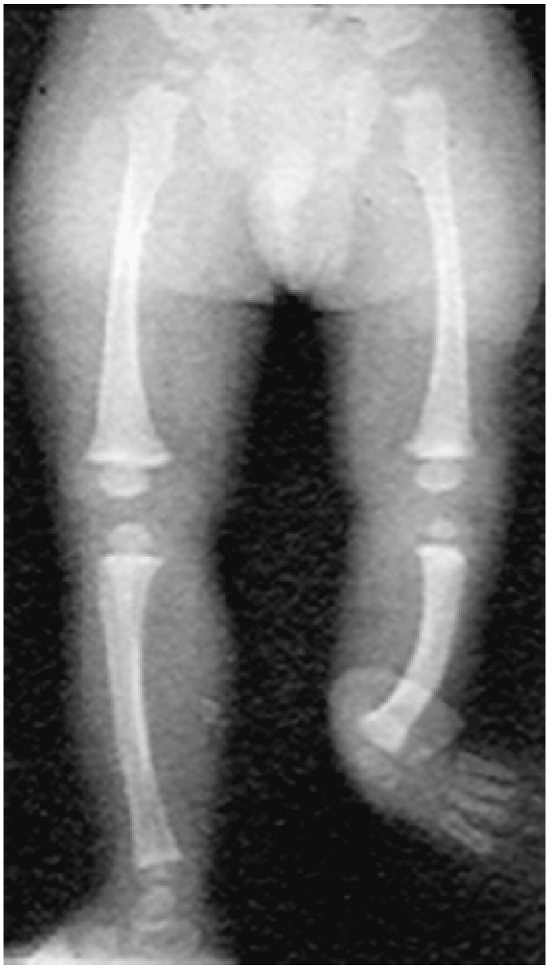

FIG. 696.8 Anteroposterior radiograph of fibular hemimelia with leg-length discrepancy.

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CHAPTER 697

The Knee

J. Todd R. Lawrence

Normal Development of the Knee

The knee is a synovial joint and forms between the 3rd and 4th month of fetal development. Secondary ossification centers form between the 6th and 9th fetal months at the distal femur and between the 8th fetal month and the first postnatal month at the proximal tibia. The patellar ossification center does not appear until 2 and 4 yr in girls and 3 and 5 yr in boys.

Anatomy and Range of Motion

The knee is the largest joint in the body and acts primarily as a modified hinge. The distal femur is cam shaped with the medial and lateral femoral condyles having slightly different shapes. This allows for a posterior gliding motion of the femur on the tibial plateau to occur during knee flexion. This also permits about 8-12 degrees of rotation through the flexion and extension arc. The normal range of motion of the knee is from neutral (or fully straight) to 140 degrees of flexion. Increased ligament laxity, including hyperextension of up to 10-15 degrees, can be normal in many children. Most activities can be performed in the flexion arc of 0-70 degrees.

The knee consists of three articulations: *patellofemoral* , *tibiofemoral* , and *tibiofibular* . The anterior and posterior cruciate ligaments as well as medial and lateral collateral ligaments stabilize the knee during movement. The medial and lateral menisci provide support under compressive forces, helping to redistribute the forces from the more rounded distal femur to the more flat proximal tibia. The medial patellofemoral ligament is the primary static soft-tissue restraint against lateral patellar displacement. There are also several bursae located about the knee to cushion and reduce friction on tendons acting across the knee joint.

697.1

Discoid Lateral Meniscus

J. Todd R. Lawrence

Discoid lateral meniscus (DLM) is a congenital anatomic variation of the lateral meniscus that may be asymptomatic or cause the classic *snapping knee syndrome* . Because many cases can be asymptomatic for years, the true incidence is difficult to determine, but it is estimated to occur in 3–5% of children and adolescents. Up to 25% of DLM cases may be bilateral.

Anatomically, the normal meniscus (Fig. 697.1*A*) is attached around its periphery and at the tips of the “C” anteriorly and posteriorly onto the tibia. During knee motion, the meniscus translates anteriorly and posteriorly to match the slight rollback of the lateral femoral condyle on the tibia with knee flexion. However, with DLM, the meniscal tissue trapped between the articular surfaces is pushed anteriorly as the knee flexes. These abnormal forces, over time, result in tears in the meniscal tissue, the peripheral attachments, or both. Tearing or stretching of this tissue allows for excessive meniscal displacement during knee range of motion. Usually a pop is heard or sensed when flexing at about 90-120 degrees of knee flexion as the meniscus is extruded anteriorly and a loud click or clunk is heard when extending the knee in the last 30 degrees of extension as the meniscus reduces back between the joint surfaces.

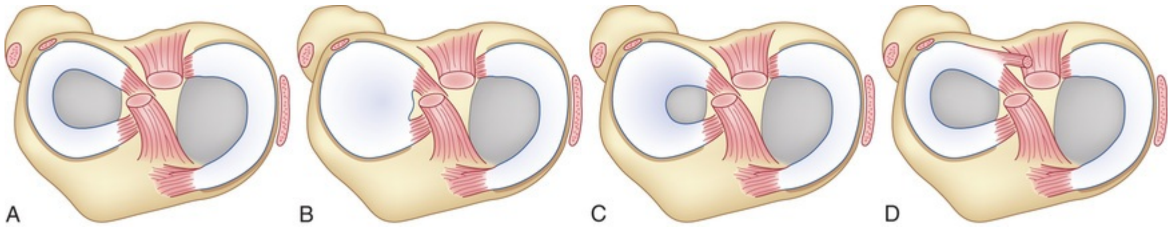

FIG. 697.1 **The anatomy of the normal meniscus and discoid variants. A, The lateral**

meniscus normally has a C shape with circumferential and root attachments. B, A type I, or complete, discoid lateral meniscus covers the entire tibial plateau and has normal attachments. C, A type II, or incomplete, discoid lateral meniscus partially covers the tibial plateau and also has normal attachments. D, A type III, or Wrisberg ligament type, appears similar in shape to a normal lateral meniscus but lacks sufficient attachments posteriorly resulting in a hypermobile meniscus. The ligament of Wrisberg secures the posterior horn of the meniscus to the lateral aspect of the medial femoral condyle.

There are three types of DLM, according to the widely used **Watanabe classification** . Type I, or a **complete discoid lateral meniscus** , most commonly produces symptoms and is characterized by a thickened lateral meniscus with complete coverage of the tibial surface (see Fig. 697.1*B*). Meniscus tissue is always between the joint surfaces. Type II, or an **incomplete discoid lateral meniscus** , is of variable size and covers a lower percentage of the tibial surface (see Fig. 697.1*C*) compared to the complete type. Although the meniscus can become stretched or torn over time, both the complete and the incomplete types are thought to develop with normal peripheral attachments. Type III, or the **Wrisberg variant lateral meniscus** , has no peripheral attachments posteriorly. Instead it is stabilized posteriorly by a prominent meniscofemoral ligament, or ligament of Wrisberg, that secures the posterior horn of the lateral meniscus to the lateral surface of the medial femoral condyle (see Fig. 697.1*D*). As a result, the Wrisberg ligament type of DLM is extremely mobile. Although its shape is not necessarily discoid, the hypermobility of the posterior portion of the meniscus allows it to be extruded anteriorly with flexion and for it to pop back into place with extension, as is characteristic of the other DLM variants.

Clinical Manifestations and Diagnosis

All types of DLM can be asymptomatic, especially if they have stable peripheral attachments. A symptomatic DLM in early childhood is usually caused by a meniscal tear or absent peripheral attachments, allowing for the anterior extrusion during flexion and reduction with extension, producing the classical *snapping knee* . While patients can present as early as 2 yr of age, presentation after 6 yr of age is typical with most presenting during their teenage years. As these patients gain weight in their adolescent growth spurt, they place increasing static and dynamic loads on the tissue, often during high-level sports. Degeneration in the central portion of the DLM with direct weight bearing makes the meniscus highly susceptible to injury and tears, producing lateral pain and swelling in the knee. Often, the classic popping is not appreciated in these

patients.

Younger children usually present with no history of trauma or an acute inciting event but rather with a complaint of popping in the knee with occasional swelling. Older children and adolescents often can recall an inciting event and will sometimes report the mechanical popping, but more often note the lateral joint line pain and knee swelling. Physical examination might show a mild effusion and tenderness over the lateral joint line. With knee flexion, a pop with a slight protuberance along the lateral joint line anteriorly can sometimes be appreciated as the meniscus is extruded anteriorly. As the knee is brought back into extension at approximately 20-30 degrees short of full extension, the meniscus can be felt to snap back in place and the protuberance at the lateral joint line disappears.

A high level of suspicion is necessary based on history and clinical exam findings as many patients will present with a complaint that their knee is “dislocating.” Standard anteroposterior, lateral, merchant (patellar), and 45 degrees flexed posteroanterior (tunnel) views should be obtained if this diagnosis is considered. Radiography of the knee may show widening of the lateral aspect of the knee joint; flattening of the lateral femoral condyle, resulting in a squared-off appearance; and cupping of the lateral aspect of the tibial plateau. Because these findings are very nonspecific, with any history or physical examination findings suggestive of a DLM, evaluation using MRI will provide a definitive diagnosis.

Treatment

Patients with asymptomatic or incidentally found DLM without evidence of a tear or meniscal instability do not require treatment. They should be educated on symptoms to anticipate, but activity restriction is not usually necessary. If knee pain or mechanical symptoms limit activity or a meniscal tear develops, surgical intervention should be considered. Partial meniscectomy, referred to as saucerization, is often performed to reshape the meniscus arthroscopically with the goal of obtaining an anatomically normal-appearing meniscus (Fig. 697.2). Tears remaining in what would be the normal rim of meniscal tissue are either repaired or excised. Meniscal instability is also addressed with repairs as appropriate. Because tears that extend from the center of the meniscal tissue all the way to the peripheral rim are difficult to repair and removing this much meniscal tissue leaves the joint surfaces unprotected leading to early osteoarthritis, addressing DLM tears as soon as they develop and before they extend to the periphery is preferred.

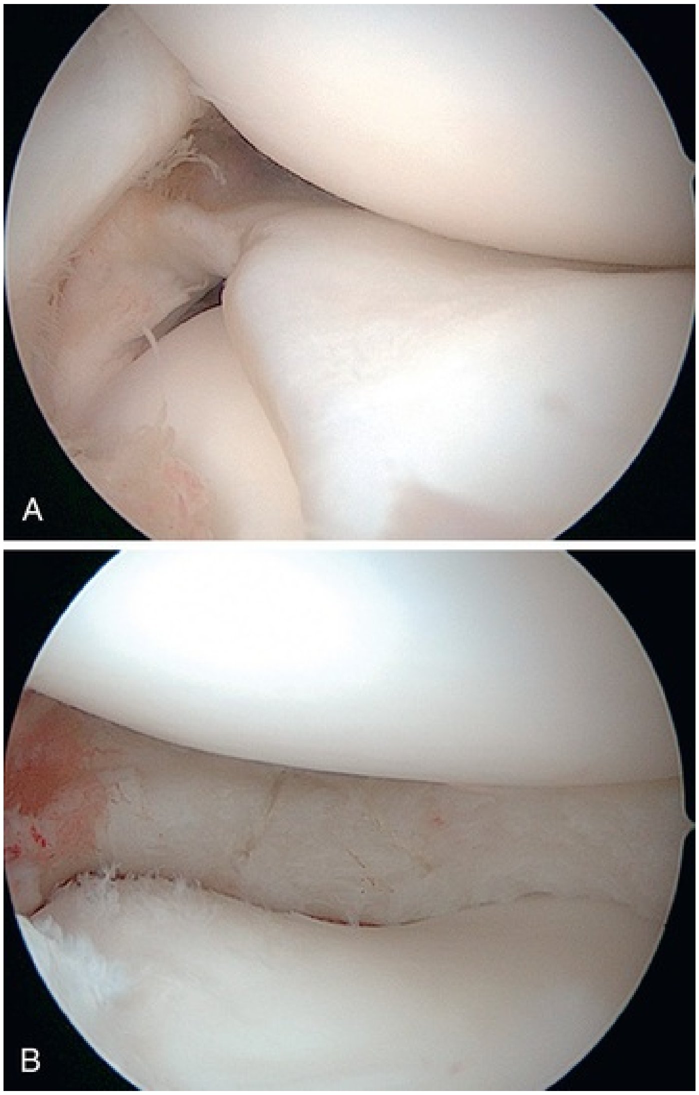

FIG. 697.2 Surgical treatment of discoid lateral meniscus. Arthroscopic images of a complete discoid lateral meniscus before (A) and after (B) partial meniscectomy.

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697.2

Popliteal Cysts (Baker Cysts)

J. Todd R. Lawrence

Popliteal cysts, or **Baker cysts,** are simple cystic masses filled with gelatinous material that develop in the popliteal fossa, the shallow depression located at the posterior part of the knee. They are considered rare in children. They most commonly occur in the region of the medial head of the gastrocnemius and semimembranosus muscles. They occur as an isolated fluid-filled bursa or via herniation through the posterior joint capsule of the knee into this same location. Histologically, the cysts are classified as fibrous, synovial, inflammatory, or transitional. Typically, popliteal cysts resolve spontaneously, although the process may take several years.

Clinical Manifestations and Diagnosis

Patients commonly present with a mass behind the knee that may be fairly large when first noted. There are usually no symptoms of internal derangement of the knee. Physical examination reveals a firm but compressible mass in the popliteal fossa, often medially located and distal to the popliteal crease. The mass is usually most prominent when the knee is extended. Transillumination of the cyst on physical examination is a simple diagnostic test. Knee radiographs are normal, but should be obtained to identify other lesions, such as osteochondromas, osteochondritis dissecans, and malignancies. Ultrasonography, MRI, or aspiration may confirm the diagnosis. Ultrasound can be used to confirm a simple cystic lesion in the expected anatomical location and is often the only diagnostic test necessary to confirm the diagnosis with these reassuring findings. If a solid mass, a vascular lesion, or a complex cystic lesion is identified on ultrasound, an MRI may be used to evaluate the mass. In the presence of a knee effusion, consideration should be given to perform an MRI to evaluate for knee intraarticular pathology that may be causing the swelling.

These children should also be assessed for *other pathology* that may cause recurrent or intermittent knee effusions, including Lyme disease, juvenile idiopathic arthritis, or other autoimmune processes. The presence of a solid mass detected on ultrasound or MRI warrants additional diagnostic testing and referral for biopsy consideration.

Treatment

In most cases, reassurance is all that is needed for popliteal cysts because they often resolve spontaneously. Rest and leg elevation can be suggested to promote drainage of the fluid accumulating within the cyst. In rare cases, aspiration can reduce the size of the cyst, and a corticosteroid injection can reduce inflammation. However, since cysts will often recur after aspiration, the risk of the procedure is not often worth the benefits. Surgical excision of a popliteal cyst is indicated only when symptoms are debilitating and have not resolved after an extended period of conservative treatment.

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697.3

Juvenile Osteochondritis Dissecans

J. Todd R. Lawrence

Osteochondritis dissecans (OCD) is a localized pathologic process of the subchondral bone that secondarily affects the overlying articular cartilage and can progress to joint instability and cartilage separation and fragmentation. Emerging evidence suggests that the cause of OCD is vascular insult to the developing knee that is unable to heal due to repetitive microtrauma. The disorder is being seen with rising frequency in children and adolescents, likely in large part because of the increased sports participation of young athletes. The natural history of juvenile OCD is not the same as that seen in adults. In the knee, OCDs most commonly affect the lateral aspect of the medial femoral condyle; however, the lateral femoral condyle and patella may also be affected. Failure of both the bone and the cartilage surface to heal completely is associated with an increased risk for developing premature osteoarthritis.

Clinical Manifestations and Diagnosis

The most common presenting complaint is a vague or **deep knee pain** that is often activity related. If the osteochondral fragment becomes unstable, the patient may also develop **mechanical symptoms** , such as catching or locking. Physical exam findings include effusion, tenderness to palpation over the femoral condyles, quadriceps atrophy, and diminished range of motion.

Because most OCD lesions are located more on the posterior aspect of the femoral condyle, a posteroanterior radiograph with a 45-degree flexed knee (tunnel view) is often required to evaluate for the presence of an OCD. Many of these patients also have some degree of patellar-related pain, necessitating merchant (patellar) view plain films. Thus, standard radiographic evaluation of nontraumatic adolescent knee pain should routinely include anteroposterior, lateral, tunnel, and merchant radiographs of the knee. An early lesion may appear as a small radiolucency at the articular surface. A more advanced lesion may have a well-demarcated segment of subchondral bone with a lucent line demonstrating separation from the condyle. The clinical significance of irregularities in the ossification center of the developing epiphysis in children less than 10 yr is unclear.

MRI is useful for determining the size of the OCD, the integrity of the articular cartilage, and the presence of loose bodies. Fluid observed between the fragment and subchondral bone suggests an unstable lesion and a high risk for detachment. Any linear signal through the articular cartilage or displacement of the fragment indicates a potentially unstable lesion as well. For an unstable-appearing OCD, either based on the patients' symptoms and signs, or the imaging, arthroscopy should be performed to evaluate the status of the lesion.

Treatment

Treatment for juvenile OCD includes nonoperative and surgical management, with treatment decisions being based on many factors, including the growth status and skeletal maturity of the patient, the presence of symptoms, the size of the lesion, whether the lesion appears intact and stable, or if there is any suggestion of instability. Skeletal immaturity (i.e., younger age), smaller lesion size, and the absence of mechanical symptoms or pain have been associated with a higher likelihood of OCD healing with nonoperative treatment. Unstable lesions will not usually heal with conservative treatment.

Thus, young patients with stable lesions, as evidenced by an intact articular surface on imaging (Fig. 697.3*A*), are deemed to have an acceptable probability of healing and are often initially managed conservatively with a period of restricted weight bearing and immobilization, followed by a period of strict activity restriction and physical therapy for 3-6 mo. OCD healing is followed with radiographs, usually at approximately 3 mo intervals, until lesion healing has been noted. If healing has not been radiographically confirmed in 3-6 mo, surgical intervention is often considered. Because of the low rate of healing in skeletally mature patients, even intact lesions are not usually managed conservatively in this patient population but recommended for surgery.

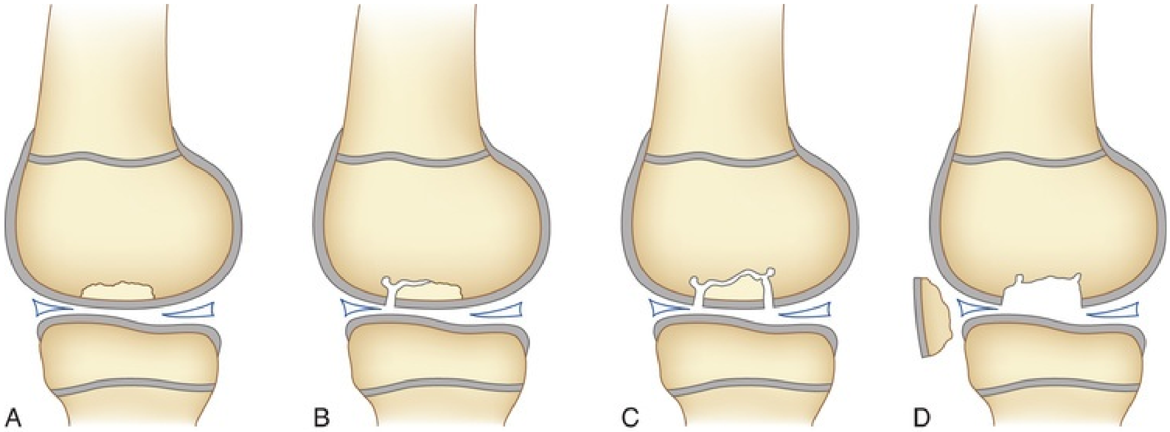

FIG. 697.3 **The spectrum of osteochondritis dissecans (OCD) pathology of the knee. A, A stable and intact lesion without breach of the overlying articular cartilage. B, An OCD with fluid beneath the fragment, subchondral cyst formation, and partial fragment detachment. C, An unstable but located lesion with fluid beneath the fragment, multiple subchondral cysts, and complete fragment detachment. D, A dislodged OCD lesion, resulting in a loose body within the knee joint space.**

Although nonsurgical treatment can be successful in intact lesions, surgical treatment of intact lesions is often more successful and induces healing at a faster rate. Consequently, patients often choose to pursue early surgical intervention. For stable and intact lesions, surgical management involves arthroscopic evaluation of the joint followed by either a transarticular or retroarticular drilling to stimulate bony healing by creating channels in the subchondral bone that allow revascularization to occur. Both techniques are comparably effective in producing short-term patient-oriented outcomes and radiographic healing.

More advanced lesions with edema beneath the fragment, subchondral cyst formation, and partial (see Fig. 697.3*B*) or complete (see Fig. 697.3*C*) fragment detachment on arthroscopy are potentially salvageable and should be treated surgically. Treatment involves drilling or fixation with possible bone grafting. OCD lesions may progress and become unstable and dislodge into the joint space (see Fig. 697.3*D*). Removal of the loose body in addition to cartilage repair and restoration are typically performed for unsalvageable lesions. In the postoperative period, patients usually require physical therapy to regain strength and range of motion, with a gradual return to baseline activity levels once full healing has been observed. Early identification and treatment of OCD lesions often prevents recurrent symptoms in adulthood and reduces the risk of early onset osteoarthritis.

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697.4

Osgood-Schlatter Disease and Sinding-Larsen-Johansson Syndrome

Eric J. Sarkissian, J. Todd R. Lawrence

In skeletally immature patients, the tibial tubercle apophysis is an extension of the proximal tibial epiphysis. As the femur rapidly grows in length, patients often develop tight musculature, particularly of the quadriceps, across the knee joint. These patients also develop movement patterns that preferentially place stress on the knees during physical activity instead of distributing that stress across other joints in the lower extremity. The repetitive tensile microtrauma sustained during sports or other athletic activities creates traction injuries at the weak points in the extensor mechanism at the knee, as the stress exceeds the developing skeleton's ability to repair the damage.

Sinding-Larsen-Johansson (SLJ) syndrome is an insertional periostitis at the inferior pole of the patella. **Osgood-Schlatter (OS) disease** is an irritation of the patellar tendon at its insertion into the tibial tubercle or a traction apophysitis of the tibial tubercle growth plate. These conditions typically present during periods of relative accelerated growth. Sinding-Larsen-Johansson syndrome tends to occur in a slightly younger patient population, whereas OS disease presents in slightly older patients with most symptomatic between the ages of 10 and 15 yr. These conditions are most common in very physically active children.

Clinical Manifestations and Diagnosis

Anterior knee pain, very specifically localized to the inferior pole of the patella (Sinding-Larsen-Johansson syndrome) or over the tibial tubercle (OS disease) is the most common patient complaint. Localized soft tissue swelling, along with an eventual firm and fixed increased prominence at the tibial tubercle, may occur with OS disease and may also be part of the initial complaint (Fig. 697.4). There is typically no acute traumatic inciting event, and the history of an acute traumatic onset of symptoms should raise the possibility of a tibial tubercle fracture or patellar sleeve fracture. The pain is aggravated by sports activities but may often persist with regular daily activities and even at rest. Physical examination reveals point tenderness over the inferior pole of the patella (SLJ) or over the tibial tubercle and the distal portion of the patellar tendon (OS disease). The presence of a knee effusion should raise the possibility of other intra-articular pathology. Diagnosis is usually made clinically, but radiographs may reveal fragmentation of the tibial tubercle and soft tissue swelling (Fig. 697.5).

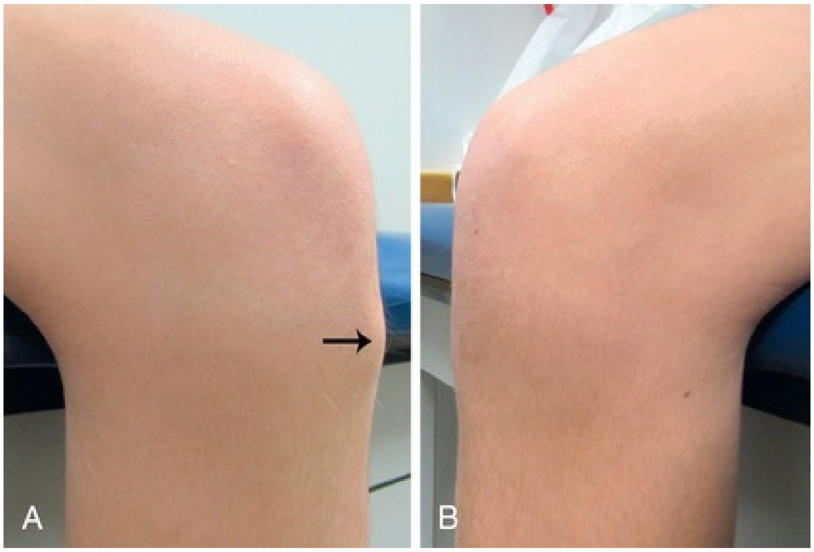

FIG. 697.4 Clinical manifestations of Osgood-Schlatter disease. The increased prominence of the tibial tubercle, indicated by the *arrow,* (A) from traction apophysitis in a 15 yr old boy's knee is contrasted with the normal appearance of the tibial tubercle (B) in his contralateral, unaffected knee.

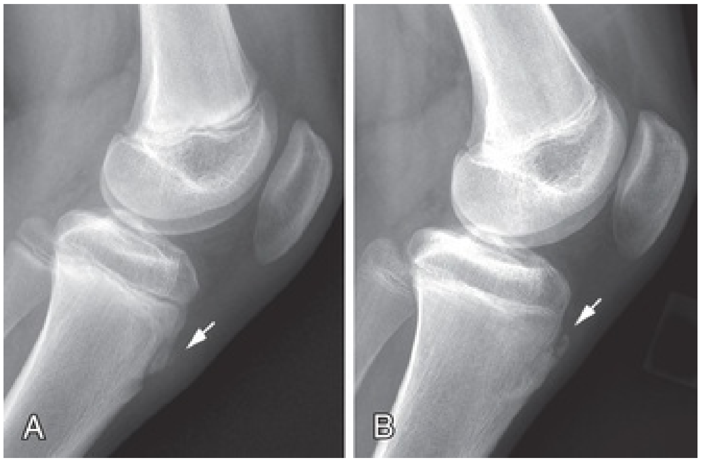

FIG. 697.5 Radiographic findings of Osgood-Schlatter disease. A, Lateral radiograph of the knee of a 13 yr old male demonstrates a sliver of new bone formation *(arrow)* at the tibial tubercle. B, Lateral radiograph of the same child at 15 yr of age demonstrates characteristic fragmentation *(arrow)* of the tibial tubercle.

Treatment

In most patients, SLJ syndrome and OS disease are self-limited processes and resolve with rest. Patients are treated with increasing levels of activity restriction or immobilization to get them to a pain-free state before advancing their activities. For instance, if they have pain only with running, but are pain free with normal daily activities, they may be restricted from running but perform daily activities for 2 wk before advancing. In more severe cases, a knee immobilizer or even crutches with restricted weight bearing are required to help the patient reach a pain-free state. Patients are usually advised to maintain this pain-free level of activity for 1-2 wk before attempting to advance to the next level. Sports and other dynamic activities are restricted until the patient has been pain free during palpation with daily activities for at least 2 wk. During this rest period, addressing some of the contributing factors, such as muscular tightness, can help prevent a recurrence with activity resumption. A self-directed stretching regimen, concentrating on the quadriceps and hamstrings, may be provided. Some patients and resistant cases may benefit from formal instruction in these exercises with a physical therapist.

Reassurance is important because some patients and parents fear that the swollen tubercle may be a sign of a more significant pathology. Patients and family members should be advised that the tibial tubercle swelling will not likely resolve. Hyperosmolar dextrose local injections may improve outcomes in patients with recalcitrant disease. Removal of ossicles from the tubercle is rarely necessary in pediatric patients, but it may be required with persistent disabling symptoms in young adults. Complications are rare and include early closure of the tibial tubercle with recurvatum or hyperextension, deformity, and, rarely, patellar tendon rupture or avulsion fracture of the tibial tubercle. Although rare, these complications can have significant long-term consequences and should thus prompt counseling to avoid playing through the pain.

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697.5

Patellofemoral Pain Syndrome

J. Todd R. Lawrence

Also known as anterior knee pain syndrome, patellofemoral pain syndrome (PFPS) is one of the most common causes of knee pain, particularly in adolescent females. Previously, PFPS was thought to arise from a deranged patellar articular surface, hence, the former term chondromalacia patella. Increasing evidence shows that anterior knee pain is frequently present even with normal articular cartilage of the patella, resulting in more appropriate labeling of the condition. The precise etiology of the knee pain remains unknown and is likely multifactorial.

Clinical Manifestations and Diagnosis

Pain beneath or near the patella is the most common symptom. Bent knee activities, such as walking up and down stairs, put the patella under high compressive loads and tend to aggravate the pain. Squatting, running, and other vigorous physical activities also exacerbate the anterior knee pain. Sitting in a flexed knee position for an extended period of time, the so-called **theater sign** , is another common complaint. The onset of symptoms in usually gradual with no history of trauma. If a traumatic etiology is noted, consideration for other etiologies should be entertained. Buckling or a sense of the knee *giving way* can occur, but there is rarely any true patellar or knee instability. Swelling is not common and, if present, should prompt further investigation. Pain is often relieved through knee extension.

Physical exam reveals tenderness with palpation about the medial or lateral aspects of the patella. With the knee extended and the quadriceps relaxed, placing pressure on the patella and translating it distally into the top of the trochlear groove, the so-called **grind test** , often also causes pain. Reproduction of the patient's pain with these maneuvers is an important component of the exam. Active and passive range of motion of the knee, alignment of the lower extremity, knee ligamentous stability, patellar tracking, and gait should be evaluated to identify any obvious causes of malalignment or an unstable patella. These patients often have tight quadriceps, hamstrings, and heel cords, along with weak hip musculature and poor overall balance. A single leg squat can often highlight the hip weakness and balance and alignment issues that contribute to this condition. Routine radiographs of the knee, including anteroposterior, lateral, tunnel (posteroanterior with 45 degrees flexed knee), and merchant (patellar) views, are usually normal, but are helpful in eliminating other etiologies of vague knee pain, such as OCD. Radiographs of the hip should be considered in suspected cases to rule out hip pathology, such as a slipped capital femoral epiphysis (SCFE), which can manifest as ill-defined knee pain in adolescents as well. An MRI is not routinely required for evaluation but should be considered in any patient with a history of mechanical symptoms or an effusion. MRI should be considered in cases refractory to standard treatments as well.

Treatment

Several methods of nonoperative treatment are utilized to address PFPS. The mainstay of treatment is continued physiotherapy, involving overall lower-extremity stretching and strengthening, including short-arc quadriceps strengthening, hip and core strengthening, and exercises designed to address balance and overall body positioning during dynamic activities. No one particular regime seems to demonstrate results superior to the others. Home exercise programs can be effective for the properly disciplined and motivated patient, but formal physical therapy should be considered in resistant cases or in patients who may not have the motivation or wherewithal to adhere to a self-directed program. Orthoses, including patellar taping, knee sleeves, customized knee braces, or even shoe inserts are often used in conjunction with physical therapy. However, evidence for long-term benefit from orthotic use is unclear. Treatment with Botulinum toxin injections, nonsteroidal antiinflammatory medications, or therapeutic ultrasound is not substantiated. Most cases of PFPS resolve spontaneously over time, although pain can persist in up to about a third of patients. Surgical treatment of PFPS is rarely necessary.

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697.6

Patellofemoral Instability

J. Todd R. Lawrence

The stable tracking of the patellofemoral joint in the front of the knee depends on a balance of the static restraints and the dynamic forces acting on the patella. These include the restraining ligaments and the articular anatomy of the patellofemoral groove that serve to balance the dynamic forces of the quadriceps mechanism and overall limb positioning. During knee flexion, the pull of the quadriceps mechanism tends to place an overall lateral displacing force at the patella. The **Q angle** refers to the deviation between the angle of the patellar tendon and the line of the quadriceps. Wider hips and valgus (knock-kneed) positioning increase the Q angle and thus the lateral force applied at the patella. In extension, the static restraints, including the medial restraining ligaments, primarily the medial patellofemoral ligament (MPFL), are responsible for guiding the patella into the trochlear grove in the distal femur. The pull of the vastus medialis obliquus is the only dynamic restraint. Once in the trochlea, the bony congruity becomes the primary restraint to the net lateral muscular forces.

Factors that contribute to patellofemoral instability are multifactorial and include ligamentous laxity; trochlear dysplasia, creating a shallow sulcus; condylar hypoplasia; patella alta (a high-riding patella); or malalignment, which effectively increases the Q angle, such as genu valgum, increased femoral anteversion, or a lateralized tibial tubercle.

Acute patellofemoral dislocation is the most common acute knee disorder in children and adolescents and often occurs after a sudden valgus strain during sports participation, but it may be the result of direct trauma. **Recurrent patellofemoral subluxation** is more than one episode of patellar subluxation without frank dislocation. Lateral malalignment of the quadriceps mechanism is the most common etiologic factor. **Habitual dislocation of the patella** describes patellar dislocation occurring during every knee flexion/extension cycle. A dysplastic knee with contracture of the lateral portion of the quadriceps mechanism is often associated. Several syndromes are associated with patellar instability, including Down syndrome (see Chapter 98), Turner syndrome (see Chapter 98), Kabuki syndrome, and Rubinstein-Taybi syndrome.

Clinical Manifestations and Diagnosis

With an acute patellar dislocation, patients will recall the acute event and the sensation that their “kneecap” was out of place. Straightening the knee is all that is usually required to reduce the patella, but sometimes this requires medical attention. Swelling is usually apparent immediately following the injury and appreciable on examination as a large effusion. The patella may appear laterally displaced when the knee is fully extended or higher than normal with the knee slightly flexed. Pain along the medial knee from the medial patella to the medial epicondyle of the femur is common. Lateral patellar translocation with the knee slightly flexed should be tested with the **patellar apprehension test** . In the acute setting, there will be increased translation and pain and a feeling of insecurity. Patellar tracking is also an important component of the exam but may not be possible due to pain in the acute setting. The **J sign** refers to the inverted J-path the patella takes, beginning in a laterally subluxated position and then suddenly shifting medially to engage the femoral groove with early knee flexion. The torsional profile of the patient is also important to assess to rule out possible rotational abnormalities of the femur or tibia.

Radiographs of a patient with patellar instability should include anteroposterior, lateral, and merchant views (obtained with the knee bent 45 degrees, with the beam of the x-ray through the knee from head to toe) of the patella. Radiographs should also be carefully examined for occult fractures. In the presence of a significant knee effusion, mechanical symptoms, acute traumatic patellar dislocation, or uncertainty in the diagnosis, further investigation should include an MRI to evaluate for loose bodies or cartilage damage. MRI will demonstrate bone bruise patterns typical of patellar dislocation at the medial patellar facet and at the lateral femoral condyle and a tear in the medial patellofemoral ligament.

Treatment

Nonoperative management is initially recommended for acute patellar dislocation and recurrent patellar subluxation, unless a large osteochondral fracture or additional intra-articular pathology is seen on imaging studies. Although early physical therapy has also been shown to be successful, a brief 4-6 wk period of immobilization in extension may help with healing of the medial knee restraints following an initial traumatic dislocation. After this, transition to a patellar stabilizing brace usually improves symptoms. Successful treatment is usually achieved with formal physical therapy aimed at improving extensor muscle tone, particularly the vastus medialis obliquus, activity-related body positioning, and hip and core muscle strengthening. The reported redislocation rate following an initial traumatic patellar dislocation ranges from 15% to 44% and seems to be higher in younger patients and in patients with more significant trochlear dysplasia (shallow trochlea).

Failure to improve after nonoperative treatment and persistent episodes of patellar subluxation or dislocation are indications for surgical intervention to address patellofemoral instability. Patients with loose bodies, osteochondral fractures, or chondral damage are surgical candidates for early intervention. Many different types of surgical procedures exist to prevent lateral translation of the patella, but almost all include reconstruction of the medial patellofemoral ligament. Distal realignment of the patellar tendon insertion with a tibial tubercle osteotomy can help improve overall alignment and is often included as part of the stabilization procedure in skeletally mature adolescents. Guided growth techniques can be used in patients with growth remaining to correct overall alignment. The surgical approach is ideally individualized for each patient depending on the pathoanatomy contributing to the recurrent instability.

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697.7

Anterior Cruciate Ligament Rupture

J. Todd R. Lawrence

Pediatric anterior cruciate ligament (ACL) reconstruction has become more prevalent as ACL tears in skeletally immature patients have greatly increased in recent years. Increased sports participation, increased intensity of training and competition, participation on multiple teams, heightened awareness, and improved methods for diagnosis are all likely contributing factors to the growing awareness of ACL injuries in children and adolescents.

Females are also known to have a greater risk for ACL injury than males. The gender-specific discrepancy appears to be caused mostly by insufficient neuromuscular activation patterns in females, resulting in increased dynamic **genu valgum** , or knock-knee, biased landing, and, therefore, a heightened tendency toward landing or stopping in an injury prone position. Other nonmodifiable risk factors include generalized joint laxity, knee recurvatum (hyperextension), femoral anteversion, and contralateral ACL injury; trauma is unusual. Various pediatric ACL injury prevention programs have shown benefits in not only reducing the rate of injuries but also in increasing athletic strength and performance. Studies also indicate that universal implementation of injury prevention programs would be a cost-effective prevention strategy.

Clinical Manifestations and Diagnosis

The majority of ACL tears occur as a result of a noncontact injury. Patients may report a pop associated with the acute onset of knee pain. Later they develop swelling, limited range of motion, and sometimes a sensation of instability. After the initial injury, patients may have surprisingly little pain. On physical exam, the anterior drawer sign or **Lachman test** may indicate increased anterior tibial translation. The Lachman examination is performed by applying an anteriorly directed force to the proximal tibia with the femur stabilized and the knee flexed 20-30 degrees. The amount of translation and the end point are assessed, with increased translation and an indistinct end point indicating a positive test. A pivot shift test can also be performed to confirm the diagnosis, but it is rarely successful in the conscious patient. It is conducted by gently bending the knee while just supporting the lower leg. A gentle valgus stress and slight internal rotation can enhance the shift.

Radiographs of the knee are performed, including anteroposterior, lateral, tunnel (posteroanterior with 45 degrees flexed knee), and merchant (patellar) views, to assess for other potential injuries common in pediatric and adolescent patients, such as tibial spine avulsion fractures or OCD. In traumatic injuries, internal and external oblique radiographs can also be helpful. Ultimately, knee MRI is usually necessary to confirm the presence of an intrasubstance ACL tear, and any associated meniscal or chondral pathology (Fig. 697.6). Arthroscopic evaluation is the gold standard for diagnosis and treatment.

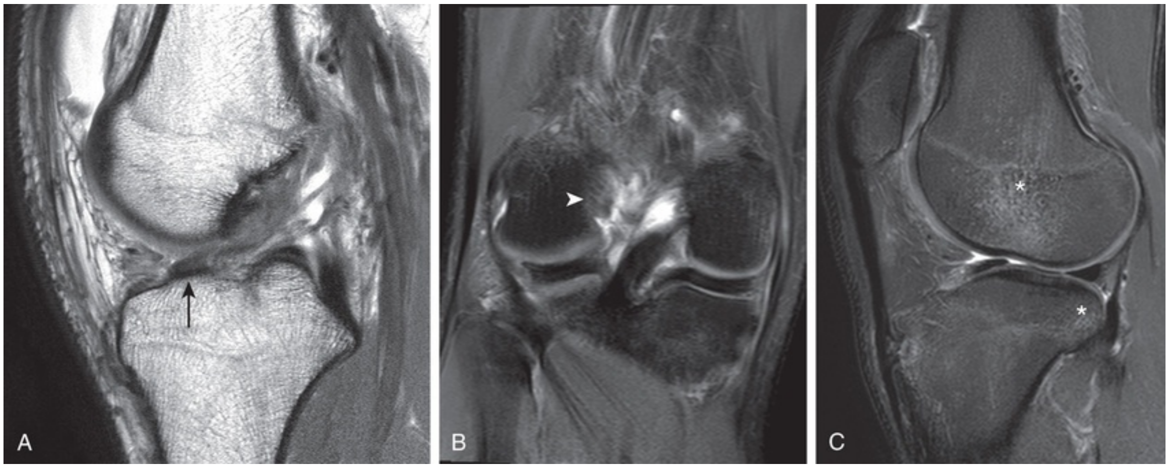

FIG. 697.6 **A 16 yr old boy with full-thickness anterior cruciate ligament (ACL) tear. A, Proton density sagittal image demonstrates a full-thickness tear of the ACL near its femoral origin with residual tibial insertion fibers *(arrow)* . B, Proton density fat**

suppression coronal image demonstrates a full-thickness tear with residual femoral origin ACL fibers *(arrowhead)* . C, A T2-weighted fat suppression sagittal image demonstrates a characteristic kissing contusion pattern related to an ACL mechanism injury *(asterisk)* . (From Kan JH: Sports medicine. In Colley BD, editor: *Caffey's pediatric diagnostic imaging* , 12/e. Philadelphia, 2013, Elsevier, Fig. 145.20.)

Treatment

The management of ACL injury in this patient population can be challenging, and the severity of the ACL tear and the degree of knee instability are important in directing treatment. Incomplete or partial ACL tears that still maintain a firm endpoint on examination may be treated nonoperatively, and the patient's and family's understanding and willingness to adhere to a protocol of bracing and activity restriction are important factors in optimizing outcomes. For complete tears of the ACL, due to the risk of ongoing knee damage if stabilization of the knee is delayed, surgical reconstruction is usually the preferred treatment for patients who are physically, mentally, and emotionally capable of maintaining precautions and complying with the long rehabilitation course after the procedure. Nevertheless, the ultimate treatment course is an individual decision for the patient and family to make in a shared way in consultation with their physician. Growth-respecting ACL reconstruction techniques, such as all-epiphyseal, partial transphyseal, or traditional transphyseal reconstruction techniques, are used based upon the skeletal maturity of the patient to minimize the risk for growth disturbance across the distal femoral and proximal tibial physes.

Depending on the technique used for reconstruction and any associated meniscal pathology addressed, weight bearing is restricted, and a brace is used for the 1st first 4-6 wk postoperatively. Physical therapy is used postoperatively and continued until strength and functional testing are equal to the contralateral, unaffected limb. Injury prevention through neuromuscular training is built into the final phases of the rehabilitation and final screening tests to try to minimize the risk of re-injury. Patients return to sports typically at a minimum of 9-12 mo postoperatively and are followed on a yearly basis thereafter until skeletal maturity to monitor progress and for any signs of growth disturbance. Despite extensive prevention efforts, secondary injury rates remain very high with a return to risky sports.

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CHAPTER 698

The Hip

Wudbhav N. Sankar, Jennifer J. Winell, B. David Horn, Lawrence Wells

Anatomically, the hip joint is a ball-and-socket articulation between the femoral head and acetabulum. The hip joint is a pivotal joint of the lower extremity, and its functional demands require both stability and flexibility.

Growth and Development

The hip joint begins to develop at about the 7th wk of gestation, when a cleft appears in the mesenchyme of the primitive limb bud. These precartilaginous cells differentiate into a fully formed cartilaginous **femoral head** and **acetabulum** by the 11th wk of gestation (see Chapter 20). At birth, the neonatal acetabulum is completely composed of cartilage, with a thin rim of fibrocartilage called the **labrum** .

The very cellular hyaline cartilage of the acetabulum is continuous with the triradiate cartilages, which divide and interconnect the three osseous components of the pelvis (the **ilium** , **ischium** , and **pubis**). The concave shape of the hip joint is determined by the presence of a spherical femoral head.

Several factors determine acetabular depth, including interstitial growth within the acetabular cartilage, appositional growth under the perichondrium, and growth of adjacent bones (the ilium, ischium, and pubis). In the neonate, the entire proximal femur is a cartilaginous structure, which includes the femoral head and the greater and lesser trochanters. The three main growth areas are the physeal plate, the growth plate of the greater trochanter, and the femoral neck isthmus. Between the 4th and 7th mo of life, the proximal femoral ossification center (in the center of the femoral head) appears. This ossification center continues to enlarge, along with its cartilaginous anlage, until adult life, when only a thin layer of articular cartilage remains. During this period of growth, the thickness of the cartilage surrounding this bony nucleus gradually decreases, as does the thickness of the acetabular cartilage. The growth of the proximal femur is affected by muscle pull, the forces transmitted across the hip joint with weight bearing, normal joint nutrition, circulation, and muscle tone. Alterations in these factors can cause profound changes in the development of the proximal femur.

Vascular Supply

The blood supply to the capital femoral epiphysis is complex and changes with growth of the proximal femur. The proximal femur receives its arterial supply from intraosseous (primarily the medial femoral circumflex artery) and extraosseous vessels (Fig. 698.1). The **retinacular vessels** (extraosseous) lie on the surface of the femoral neck but are intracapsular because they enter the epiphysis from the periphery. This makes the blood supply vulnerable to damage from septic arthritis, trauma, thrombosis, and other vascular insults. Interruption of this tenuous blood supply can lead to avascular necrosis of the femoral head and permanent deformity of the hip.

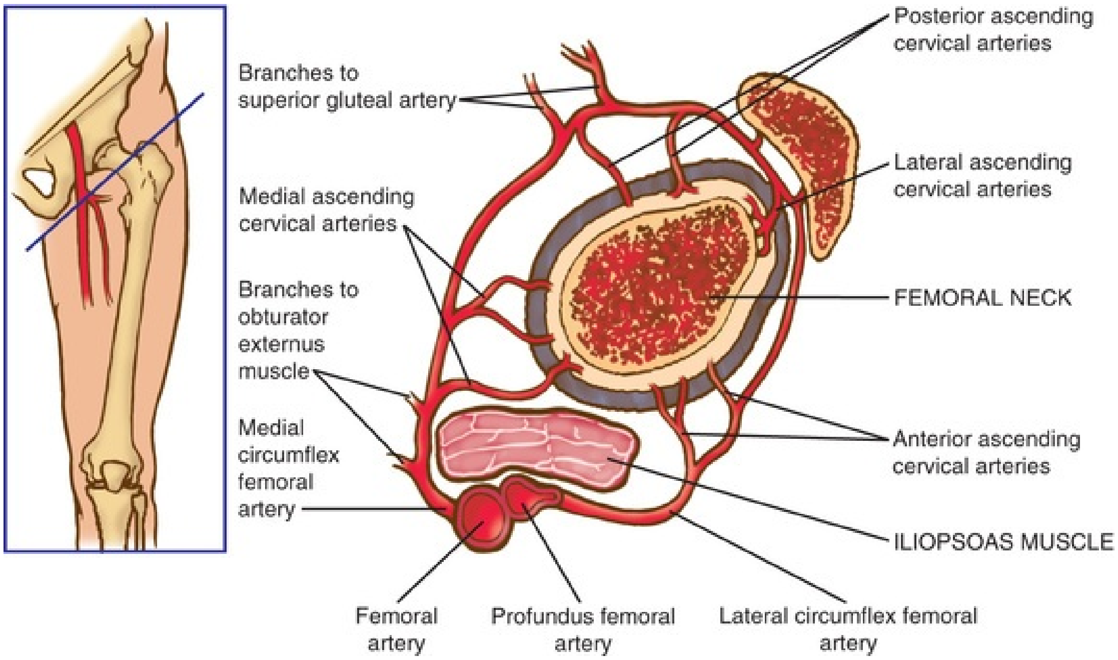
Posterior ascending cervical arteries
Branches to superior gluteal artery
Lateral ascending cervical arteries
Medial ascending cervical arteries
Branches to obturator externus muscle
FEMORAL NECK
Medial circumflex femoral artery
Anterior ascending cervical arteries
ILIOPSOAS MUSCLE
Femoral artery
Profundus femoral artery
Lateral circumflex femoral artery

FIG. 698.1 Diagram of vascular anatomy of the proximal femur.

698.1

Developmental Dysplasia of the Hip

Wudbhav N. Sankar, B. David Horn, Jennifer J. Winell, Lawrence Wells

Keywords

dysplasia
subluxation
dislocation
teratologic
torticollis
metatarsus adductus
Barlow
Galeazzi
Ortolani
hip click
Trendelenburg sign
Pavlik harness
avascular necrosis

Developmental dysplasia of the hip (DDH) refers to a spectrum of pathology in the development of the immature hip joint. Formerly called *congenital dislocation of the hip* , DDH more accurately describes the variable presentation of the disorder, encompassing mild dysplasia as well as frank dislocation.

Classification

Acetabular **dysplasia** refers to abnormal morphology and development of the acetabulum. Hip **subluxation** is defined as only partial contact between the femoral head and acetabulum. Hip **dislocation** refers to a hip with no contact between the articulating surfaces of the hip. DDH is classified into two major groups**:** **typical** and **teratologic** . Typical DDH occurs in otherwise normal patients or those without defined syndromes or genetic conditions. Teratologic hip dislocations usually have identifiable causes, such as arthrogryposis or a genetic syndrome, and occur before birth.

Etiology and Risk Factors

Although the etiology remains unknown, the final common pathway in the development of DDH is increased laxity of the joint, which fails to maintain a stable femoroacetabular articulation. This increased laxity is probably the result of a combination of hormonal, mechanical, and genetic factors. A positive family history for DDH is found in 12–33% of affected patients. DDH is more common among female patients (80%), which is thought to be because of the greater susceptibility of female fetuses to maternal hormones, such as relaxin, which increases ligamentous laxity. Although only 2–3% of all babies are born in breech presentation, the incidence of DDH in these patients is 16–25%.

Any condition that leads to a tighter intrauterine space and, consequently, less room for normal fetal motion may be associated with DDH. These conditions include oligohydramnios, large birth weight, and first pregnancy. The high rate of association of DDH with other *intrauterine molding abnormalities* , such as torticollis and metatarsus adductus, supports the theory that the *crowding phenomenon* has a role in the pathogenesis. The left hip is the most commonly affected hip. In the most common fetal position, the left hip is usually forced into adduction by the mother's sacrum.

Epidemiology

Although most newborn screening studies suggest that some degree of hip instability can be detected in 1 in 100 to 1 in 250 babies, actual dislocated or dislocatable hips are much less common, being found in 1-1.5 of 1,000 live births.

There is marked geographic and racial variation in the incidence of DDH. The reported incidence based on geography ranges from 1.7 in 1,000 babies in Sweden to 75 in 1,000 in Yugoslavia to 188.5 in 1,000 in a district in Manitoba, Canada. The incidence of DDH is almost 0% in Chinese and African newborns, whereas it is 1% for hip dysplasia and 0.1% for hip dislocation in white newborns. These differences may result from environmental factors, such as child-rearing practices, rather than genetic predisposition. African and Asian caregivers have traditionally carried babies against their bodies in a shawl so that a child's hips are flexed, abducted, and free to move. This keeps the hips in the optimal position for stability and for dynamic molding of the developing acetabulum by the cartilaginous femoral head. Children in Native American and Eastern European cultures, which have a relatively high incidence of DDH, have historically been swaddled in confining clothes that bring their hips into extension. This position increases the tension of the psoas muscle-tendon unit and might predispose the hips to displace and eventually dislocate laterally and superiorly.

Pathoanatomy

In DDH, several secondary anatomic changes can prevent reduction. Both the fatty tissue in the depths of the socket, known as the pulvinar, and the ligamentum teres can hypertrophy, blocking reduction of the femoral head. The transverse acetabular ligament usually thickens as well, which effectively narrows the opening of the acetabulum. In addition, the shortened iliopsoas tendon becomes taut across the front of the hip, creating an hourglass shape to the hip capsule, which limits access to the acetabulum. Over time, the dislocated femoral head places pressure on the acetabular rim and labrum, causing the labrum to infold and become thick.

The shape of a normal femoral head and acetabulum depends on a concentric reduction between the two. The more time that a hip spends dislocated, the more likely that the acetabulum will develop abnormally. Without a femoral head to provide a template, the acetabulum will become progressively shallow, with an oblique acetabular roof and a thickened medial wall.

Clinical Findings

The Neonate

DDH in the neonate is asymptomatic and must be screened for by specific maneuvers. Physical examination must be carried out with the infant unclothed and placed supine in a warm, comfortable setting on a flat examination table. A feeding just prior to examination is preferable.

The **Barlow** provocative maneuver assesses the potential for dislocation of an initially nondisplaced hip. The examiner adducts the flexed hip and gently pushes the thigh posteriorly in an effort to dislocate the femoral head (Fig. 698.2). In a positive test, the hip is felt to slide out of the acetabulum. As the examiner relaxes the proximal push, the hip can be felt to slip back into the acetabulum.

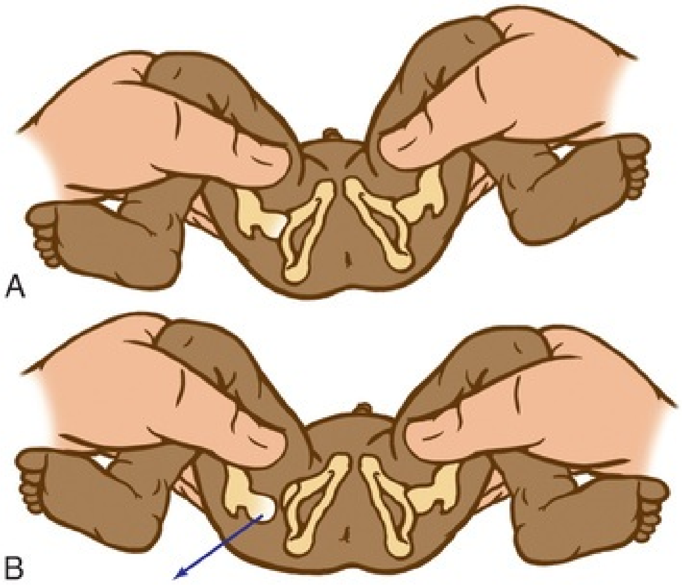

FIG. 698.2 **The Barlow provocative test is performed with the patient's knees and hips flexed. A, Holding the patient's limbs gently, with the thigh in adduction, the examiner applies a posteriorly directed force. B, This test is positive in a dislocatable hip.**

The **Ortolani** test is the reverse of the Barlow test: The examiner attempts to reduce a hip that is dislocated at rest (Fig. 698.3). The examiner grasps the child's thigh between the thumb and index finger and, with the 4th and 5th fingers, lifts the greater trochanter while simultaneously abducting the hip. When the test is positive, the femoral head will slip into the socket with a delicate clunk that is palpable but usually not audible. It should be a gentle, nonforced maneuver.

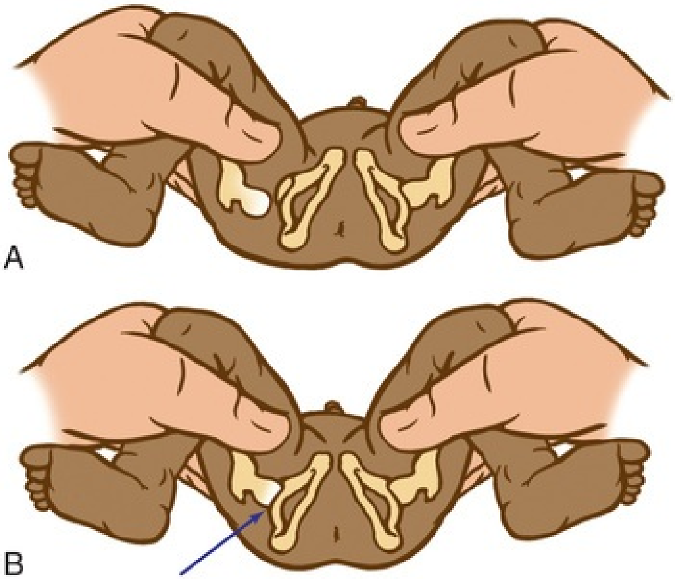

FIG. 698.3 **The Ortolani maneuver is the sign of the ball of the femoral head moving in and out of the acetabulum. A, The examiner holds the patient's thigh and gently abducts the hip while lifting the greater trochanter with 2 fingers. B, When the test is positive, the dislocated femoral head falls back into the acetabulum with a palpable clunk as the hip is abducted.**

A **hip click** is the high-pitched sensation (or sound) felt at the very end of abduction during testing for DDH with Barlow and Ortolani maneuvers. A hip click can be differentiated from a **hip clunk** , which is felt as the femoral head goes in and out of joint. Hip clicks usually originate in the ligamentum teres or occasionally in the fascia lata or psoas tendon and do not indicate a significant hip abnormality.

The Infant

As the baby enters the 2nd and 3rd mo of life, the soft tissues begin to tighten, and the Ortolani and Barlow tests are no longer reliable. In this age group, the examiner must look for other specific physical findings, including limited hip abduction, apparent shortening of the thigh, proximal location of the greater trochanter, asymmetry of the gluteal or thigh folds (Fig. 698.4), and positioning of the hip. Limitation of abduction is the most reliable sign of a dislocated hip in this age group.

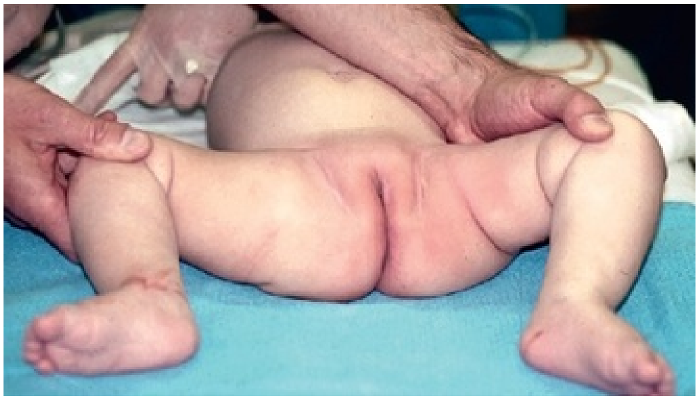

FIG. 698.4 Asymmetry of thigh folds in a child with developmental dysplasia of the hip.

Shortening of the thigh, the **Galeazzi sign,** is best appreciated by placing both hips in 90 degrees of flexion and comparing the height of the knees, looking for asymmetry (Fig. 698.5). Asymmetry of gluteal skin creases may be a sign of hip dysplasia. Another helpful test is the **Klisic test,** in which the examiner places the 3rd finger over the greater trochanter and the index finger of the same hand on the anterior superior iliac spine. In a normal hip, an imaginary line drawn between the two fingers points to the umbilicus. In the dislocated hip, the trochanter is elevated, and the line projects halfway between the umbilicus and the pubis (Fig. 698.6).

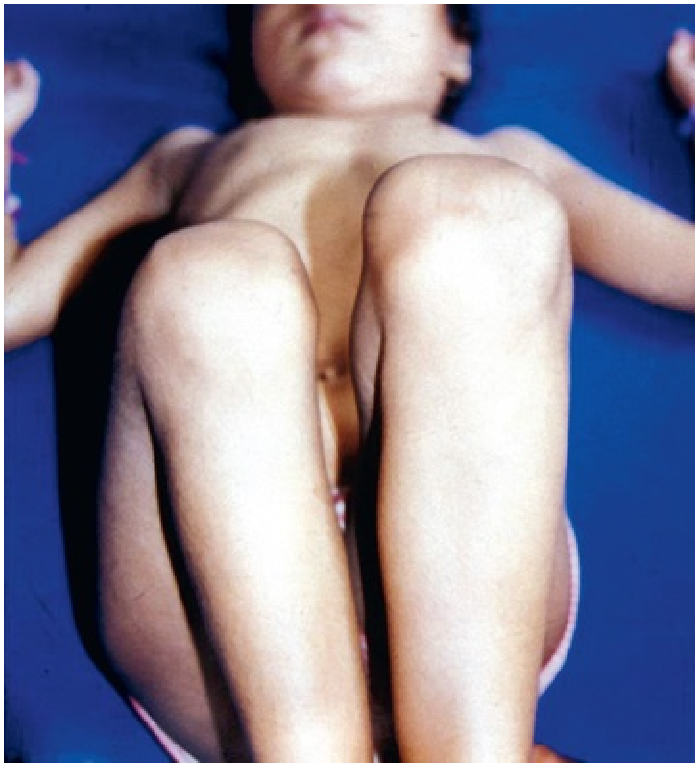

FIG. 698.5 Positive Galeazzi sign noted in a case of untreated developmental dysplasia of the hip.

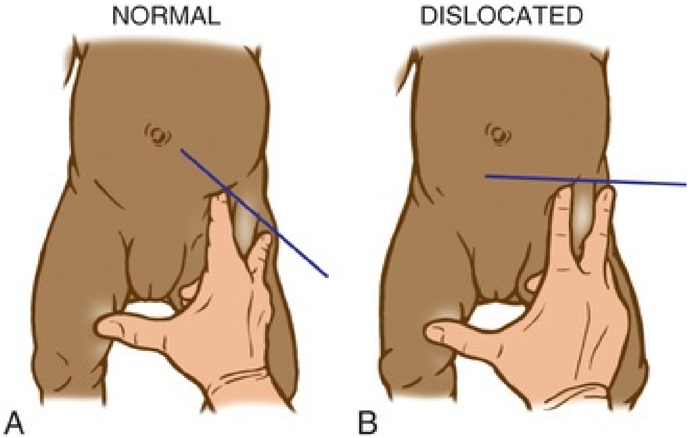

FIG. 698.6 Klisic test. A, In a normal hip, an imaginary line drawn down through the tip of an index finger placed on the patient's iliac crest and the tip of the long finger placed on the patient's greater trochanter should point to the umbilicus. B, In a dislocated hip, this line drawn through the 2 fingertips runs below the umbilicus because the greater trochanter is abnormally high.

The Walking Child

The walking child often presents to the physician after the family has noticed a limp, a waddling gait, or a leg-length discrepancy. The affected side appears shorter than the normal extremity, and the child toe-walks on the affected side. The Trendelenburg sign (see Chapter 693) is positive in these children, and an abductor lurch is usually observed when the child walks. As in the younger child, there is limited hip abduction on the affected side and the knees are at different levels when the hips are flexed (the Galeazzi sign). Excessive lordosis, which develops secondary to altered hip mechanics, is common and is often the presenting complaint.

Diagnostic Testing

Ultrasonography

Because it is superior to radiographs for evaluating cartilaginous structures, ultrasonography is the diagnostic modality of choice for DDH before the appearance of the femoral head ossific nucleus (4-6 mo). During the early newborn period (0-4 wk), however, physical examination is preferred over ultrasonography because there is a high incidence of false-positive sonograms in this age group. Therefore, waiting to obtain an ultrasound until the infant is at least 1 mo of age is preferred unless the child has a strongly positive physical exam. In addition to elucidating the static relationship of the femur to the acetabulum, ultrasonography provides dynamic information about the stability of the hip joint. The ultrasound examination can be used to monitor acetabular development, particularly of infants in Pavlik harness treatment; this method can minimize the number of radiographs taken and might allow the clinician to detect treatment failure earlier.

In the Graf technique, the transducer is placed over the greater trochanter, which allows visualization of the ilium, the bony acetabulum, the labrum, and the femoral epiphysis (Fig. 698.7). The angle formed by the line of the ilium and a line tangential to the boney roof of the acetabulum is termed the **α angle** and represents the depth of the acetabulum. Values >60 degrees are considered normal, and those <60 degrees imply acetabular dysplasia. The **β angle** is formed by a line drawn tangential to the labrum and the line of the ilium; this represents the cartilaginous roof of the acetabulum. A normal β angle is <55 degrees; as the femoral head subluxates, the β angle increases. Another useful test is to evaluate the position of the center of the head compared to the vertical line of the ilium. If the line of the ilium falls lateral to the center of the head, the epiphysis is considered reduced. If the line falls medial to the center of the head, the epiphysis is uncovered and is either subluxated or dislocated.

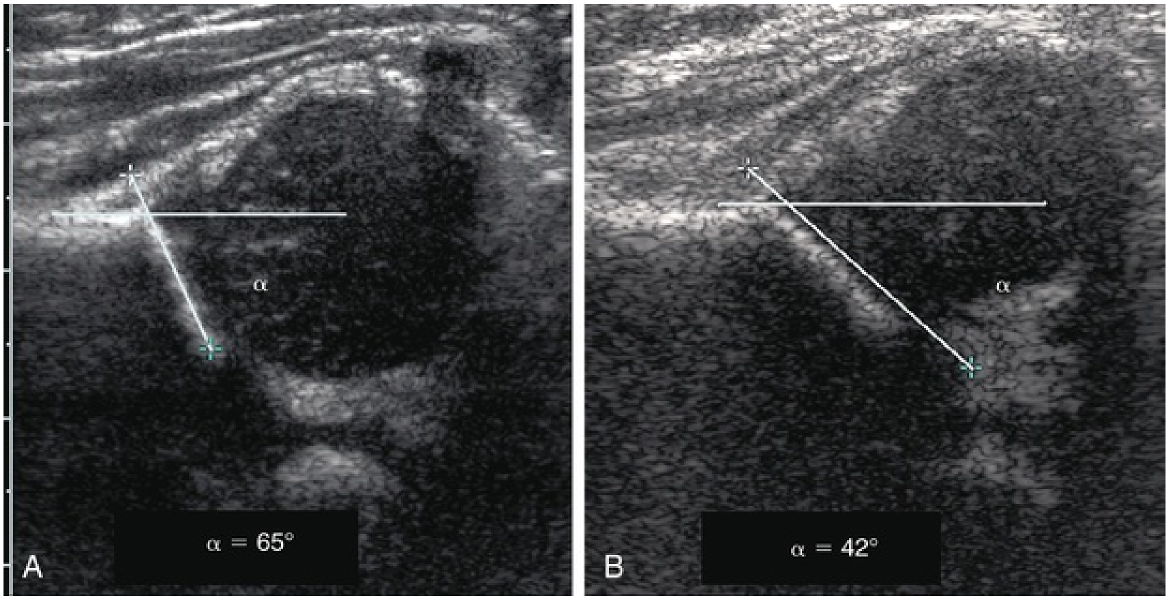

FIG. 698.7 **A,** Normal ultrasonographic image of the hip in an infant. The α angle is >60 degrees. Note that a line drawn tangential to the ilium falls lateral to the center of the femoral head. **B,** In this child with developmental dysplasia of the hip, the left hip demonstrates an α angle of 42 degrees, and a line drawn tangential to the ilium shows that <50% of the femoral head is contained within the acetabulum.

Screening for DDH with ultrasound remains controversial. Although routinely performed in Europe, meta-analyses indicate that data are insufficient to give clear recommendations. In the United States, the current recommendations are that every newborn undergo a clinical examination for hip instability. Children who have findings suspicious for DDH should be followed up with ultrasound. Most authors agree that infants with *risk factors* for DDH (breech position, family history, torticollis) should be screened with ultrasound regardless of the clinical findings.

Radiography

Radiographs are recommended for an infant once the proximal femoral epiphysis ossifies, usually by 4-6 mo. In infants of this age, radiographs have proven to be more effective, less costly, and less operator dependent than an ultrasound examination. An anteroposterior (AP) view of the pelvis can be interpreted with the aid of several classic lines drawn on it (Fig. 698.8).

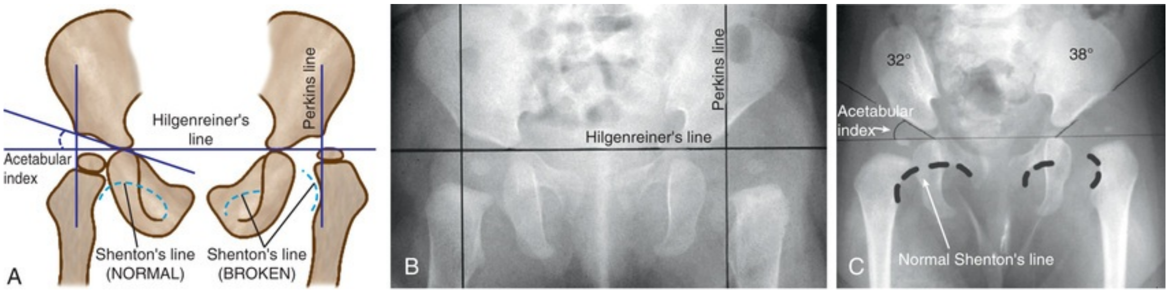

FIG. 698.8 **A-C,** Radiographic measurements are useful in evaluating developmental dysplasia of the hip. Hilgenreiner line is drawn through the triradiate cartilages. Perkins line is drawn perpendicular to Hilgenreiner line at the lateral edge of the acetabulum. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these 2 lines. Shenton's line curves along the femoral metaphysis and connects smoothly to the inner margin of the pubis. In a child with hip subluxation or dislocation, this line consists of 2 separate arcs and is described as broken. The acetabular index is the angle between a line drawn along the margin of the acetabulum and Hilgenreiner line; in normal newborns, it averages 27.5 degrees and decreases with age.

Hilgenreiner's line is a horizontal line drawn through the top of both triradiate cartilages (the clear area in the depth of the acetabulum). **Perkins line** is a vertical line through the most lateral ossified margin of the roof of the acetabulum, drawn perpendicular to Hilgenreiner's line. The ossific nucleus of the femoral head should be located in the medial lower quadrant of the intersection of these two lines. **Shenton's line** is a curved line drawn from the medial aspect of the femoral neck to the lower border of the superior pubic ramus. In a child with normal hips, this line is a continuous contour. In a child with hip subluxation or dislocation, this line consists of two separate arcs and is described as “broken.”

The **acetabular index** is the angle formed between Hilgenreiner's line and a line drawn from the depth of the acetabular socket to the most lateral ossified margin of the roof of the acetabulum. This angle measures the development of the osseous roof of the acetabulum. In the newborn, the acetabular index can be up to 40 degrees; by 4 mo in the normal infant, it should be no more than 30 degrees. In the older child, the **center-edge angle** is a useful measure of femoral head coverage. This angle is formed at the juncture of the Perkins line and a line connecting the lateral margin of the acetabulum to the center of the femoral head. In children 6-13 yr old, an angle >19 degrees is normal, whereas in children 14 yr and older, an angle >25 degrees is considered normal.

Treatment

The goals in the management of DDH are to obtain and maintain a concentric reduction of the femoral head within the acetabulum to provide the optimal environment for the normal development of both the femoral head and acetabulum. The later the diagnosis of DDH is made, the more difficult it is to achieve these goals, the less potential there is for acetabular and proximal femoral remodeling, and the more complex the required treatments.

Newborns and Infants Younger Than 6 Months

Newborns hips that are Barlow-positive (reduced but dislocatable) or Ortolani-positive (dislocated but reducible) should generally be treated with a Pavlik harness as soon as the diagnosis is made. The management of newborns with dysplasia who are younger than 4 wk of age is less clear. A significant proportion of these hips normalize within 3-4 wk; consequently, many physicians prefer to reexamine these newborns after a few weeks before making treatment decisions. A study of 128 newborns with mildly dysplastic hips based on the results of an ultrasound (alpha angles between 43 and 50 degrees) who were randomly assigned to receive immediate abduction splinting or active sonographic surveillance from birth with Frejka splinting (if treatment was subsequently needed), revealed no difference in radiologic findings at 6 yr of age.

Triple diapers or abduction diapers *have no place* in the treatment of DDH in the newborn; they are usually ineffective and give the family a false sense of security. Acetabular dysplasia, subluxation, or dislocation can all be readily managed with the Pavlik harness. Although other braces are available (von Rosen splint, Frejka pillow), the Pavlik harness remains the most commonly used device worldwide (Fig. 698.9). By maintaining the Ortolani-positive hip in a Pavlik harness on a full-time basis for 6 wk, hip instability resolves in approximately 75% of cases. After 6 mo of age, the failure rate for the Pavlik harness is >50% because it is difficult to maintain the increasingly active and crawling child in the harness. Frequent examinations and readjustments are necessary to ensure that the harness is correctly fitted. The anterior straps of the harness should be set to maintain the hips in flexion (usually ~90-100 degrees); excessive flexion is discouraged because of the risk of femoral nerve palsy. The posterior straps are designed to encourage abduction. These are generally set to allow adduction just to neutral, as forced abduction by the harness can lead to avascular necrosis of the femoral epiphysis.

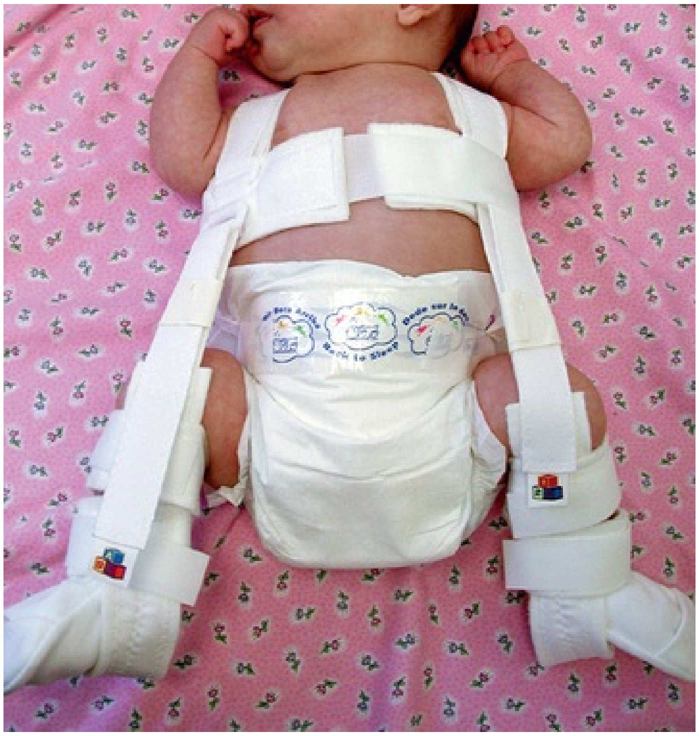

FIG. 698.9 **Photograph of a Pavlik harness.**

If follow-up examinations and ultrasounds do not demonstrate concentric reduction of the hip after 3-4 wk of Pavlik harness treatment, the harness should be abandoned. Continued use of the harness beyond this period in a persistently dislocated hip can cause *Pavlik harness disease* or wearing away of the posterior aspect of the acetabulum, which can make the ultimate reduction less stable.

Children 6 Months to 2 Years of Age

The principal goals in the treatment of late-diagnosed dysplasia are to obtain and maintain reduction of the hip without damaging the femoral head. Closed reductions are performed in the operating room under general anesthesia. The hip is moved to determine the range of motion in which it remains reduced. This is compared to the maximal range of motion to construct a "safe zone" (Fig. 698.10). An arthrogram obtained at the time of reduction is very helpful for evaluating the depth and stability of the reduction (Fig. 698.11). The reduction is maintained in a well-molded spica cast, with the "human position" of moderate flexion and abduction being the preferred position. After the procedure, single-cut CT or MRI may be used to confirm the reduction. Twelve weeks after closed reduction, the plaster cast is removed; an abduction orthosis is often used at this point to encourage further remodeling of the acetabulum. Failure to obtain a stable hip with a closed reduction indicates the need for an open reduction. In patients younger than 18 mo of age, a concomitant acetabular or femoral procedure is rarely required. The potential for acetabular development after closed or open reduction is excellent and continues for 4-8 yr after the procedure.

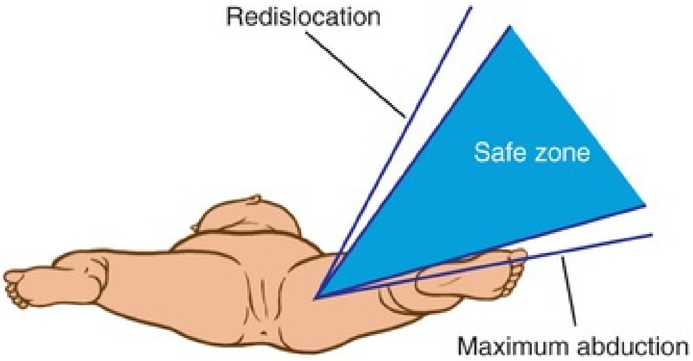

FIG. 698.10 **Diagram of the safe zone of Ramsey.**

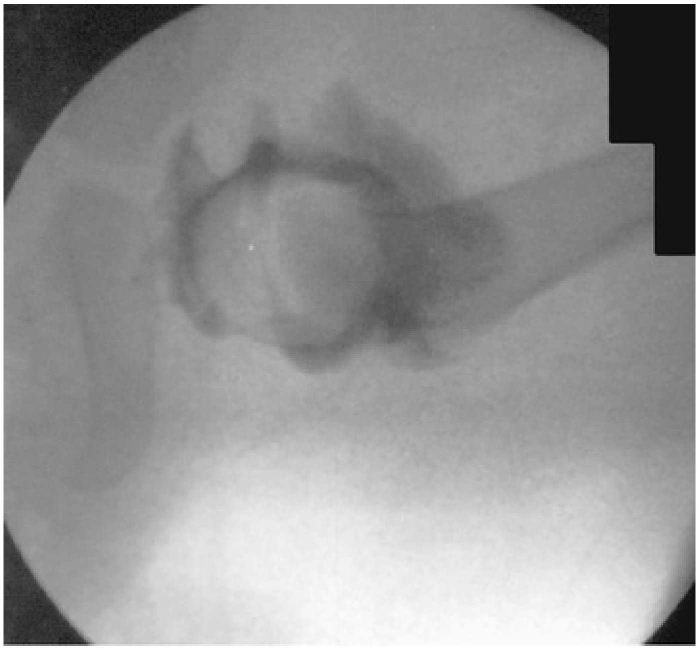

FIG. 698.11 Arthrogram of a reduced hip for evaluating the stability of reduction.

Children Older Than 2 Years

Children 2-6 yr of age with a hip dislocation usually require an open reduction. In this age group, a concomitant femoral shortening osteotomy is often performed to reduce the pressure on the proximal femur and minimize the risk of osteonecrosis. Because the potential for acetabular development is markedly diminished in these older children, a pelvic osteotomy is usually performed in conjunction with the open reduction. Postoperatively, patients are immobilized in a spica cast for 6-12 wk.

Complications

The most important complication of DDH is **avascular necrosis** of the femoral epiphysis. Reduction of the femoral head under pressure or in extreme abduction can result in occlusion of the epiphyseal vessels and produce either partial or total infarction of the epiphysis. Revascularization soon follows, but if the physis is severely damaged, abnormal growth and development can occur. Management, as previously outlined, is designed to minimize this complication. With appropriate treatment, the incidence of avascular necrosis for DDH is reduced to 5–15%. Other complications in DDH include redislocation, residual subluxation, acetabular dysplasia, and postoperative complications, including wound infections.

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698.2

Transient Monoarticular Synovitis (Toxic Synovitis)

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Keywords

transient synovitis
toxic synovitis

Transient synovitis (toxic synovitis) is a reactive arthritis and is one of the most common causes of hip pain in young children.

Etiology

The cause of transient synovitis remains unknown. It has been variously described as a nonspecific inflammatory condition or as a postviral immunologic synovitis because it tends to follow recent viral illnesses.

Clinical Manifestations

Although transient synovitis can occur in all age groups, it is most prevalent in children between 3 and 8 yr of age, with a mean onset at age 6 yr. Approximately 70% of all affected children have had a nonspecific upper respiratory tract infection the 7-14 days before symptom onset. Symptoms often develop acutely and usually consist of pain in the groin, anterior thigh, or knee, which may be referred from the hip. These children are usually able to bear weight on the affected limb and typically walk with an antalgic gait with the foot externally rotated. The hip is not held flexed, abducted, or laterally rotated unless a significant effusion is present. They are often afebrile or have a low-grade fever <38°C (100.4°F).

Diagnosis

Transient synovitis is a clinical diagnosis, but laboratory and radiographic tests can be useful to rule out other more serious conditions. In transient synovitis, infection labs (erythrocyte sedimentation rate, serum C-reactive protein, and white blood cell counts) are relatively normal, but on occasion a mild elevation in the erythrocyte sedimentation rate is observed. AP and Lauenstein (frog-leg) lateral radiographs of the pelvis may be acquired and are also usually found to be normal. Ultrasonography of the hip *is preferred* to x-rays and often demonstrates a small joint effusion.

The most important condition to exclude before confirming a diagnosis of toxic synovitis is septic arthritis. Children with septic arthritis usually appear more systemically ill than those with transient synovitis. The pain associated with septic arthritis is more severe, and children often refuse to walk or move their hip at all. High fever, refusal to walk, and elevations of the erythrocyte sedimentation rate, serum C-reactive protein, and white blood cell count all suggest a diagnosis of septic arthritis. If the clinical scenario is suspicious for septic arthritis, an ultrasound-guided aspiration of the hip joint should be performed to make the definitive diagnosis (see Chapter 705). An exception to these criteria is hip septic arthritis due to *Kingella kingae* , which may have minimal inflammation and low-grade or no fever (see Chapter 705). MRI may be needed to detect an associated osteomyelitis.

Treatment

The treatment of transient monoarticular synovitis of the hip is symptomatic. Recommended therapies include activity limitation and relief of weight bearing until the pain subsides. Antiinflammatory agents and analgesics can shorten the duration of pain. Most children recover completely within 3-6 wk.

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698.3

Legg-Calvé-Perthes Disease

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Keywords

Legg-Calvé-Perthes disease
Catterall
Herring

Legg-Calvé-Perthes disease (LCPD) is a hip disorder of unknown etiology that results from temporary interruption of the blood supply to the proximal femoral epiphysis, leading to osteonecrosis and femoral head deformity.

Etiology

Although the underlying etiology remains obscure, most authors agree that the final common pathway in the development of LCPD is disruption of the vascular supply to the femoral epiphysis, which results in ischemia and osteonecrosis. Infection, trauma, and transient synovitis have all been proposed as causative factors but are unsubstantiated. Factors leading to thrombophilia, an increased tendency to develop thrombosis and a reduced ability to lyse thrombi have been identified. Factor V Leiden mutation, deficiency of proteins C and S, lupus anticoagulant, anticardiolipin antibodies, antitrypsin, and plasminogen activator might play a role in the abnormal clotting mechanism. These abnormalities in the clotting cascade are thought to increase blood viscosity and the risk for venous thrombosis. Poor venous outflow leads to increased intraosseous pressure, which, in turn, impedes arterial inflow, causing ischemia and cell death.

Epidemiology

The incidence of LCPD in the United States is 1 in 1,200 children with boys 4-5 times more likely to be affected than girls. The peak incidence of the disease is between the ages of 4 and 8 yr. Bilateral involvement is seen in approximately 10% of the patients, but the hips are usually in different stages of collapse. East Asians have the lowest incidence of the disease and whites the highest.

Pathogenesis

Early pathologic changes in the femoral head are the result of ischemia and necrosis; subsequent changes result from the repair process. The disease course may have 4 stages, although variations have been described. The **initial** stage of the disease, which often lasts 6 mo, is characterized by synovitis, joint irritability, and early necrosis of the femoral head. Revascularization then leads to osteoclastic-mediated resorption of the necrotic segment. The necrotic bone is replaced by fibrovascular tissue rather than new bone, which compromises the structural integrity of the femoral epiphysis. The second stage is the **fragmentation** stage, which typically lasts 8 mo. During this stage, the femoral epiphysis begins to collapse, usually laterally, and begins to extrude from the acetabulum. The **healing** stage, which lasts approximately 4 yr, begins with new bone formation in the subchondral region. Reossification begins centrally and expands in all directions. The degree of femoral head deformity depends on the severity of collapse and the amount of remodeling that occurs. The final stage is the **residual** stage, which begins after the entire head has reossified. A mild amount of remodeling of the femoral head still occurs until the child reaches skeletal maturity. LCPD often damages the proximal femoral physis leading to a short neck (coxa breva) and trochanteric overgrowth.

Clinical Manifestations

The most common presenting symptom is a limp of varying duration. Pain, if present, is usually activity related and may be localized in the groin or referred to the anteromedial thigh or knee region. *Failure to recognize that thigh or knee pain in a child may be secondary to hip pathology can cause further delay in the diagnosis*. Less commonly, the onset of the disease may be much more acute and may be associated with a failure to ambulate.

Antalgic gait (a limp characterized by a shortening of gait phase on the injured side to alleviate weight-bearing pain) may be particularly prominent after strenuous activity at the end of the day. Hip motion, primarily internal rotation and abduction, is limited. Early in the course of the disease, the limited abduction is secondary to synovitis and muscle spasm in the adductor group; however, with time and the subsequent deformities that can develop, the limitation of abduction can become permanent. A mild hip flexion contracture of 10-20 degrees may be present. Atrophy of the muscles of the thigh, calf, or buttock from disuse secondary to pain may be evident. An apparent leg-length inequality may be caused by an adduction contracture or true shortening on the involved side from femoral head collapse.

Diagnosis

Routine plain radiographs are the primary diagnostic tool for LCPD. AP and Lauenstein (frog-leg) lateral views are used to diagnose, stage, provide prognosis for, and follow the course of the disease (Fig. 698.12). It is important when evaluating disease progression that all radiographs be viewed sequentially and compared with previous radiographs to assess the stage of the disease and to determine the true extent of epiphyseal involvement.

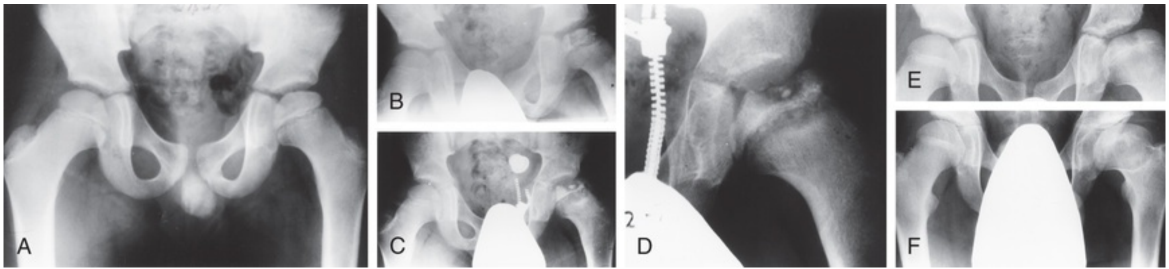

FIG. 698.12 **Radiographic evolution of Legg-Calvé-Perthes disease, with onset in a boy at 10 yr 11 mo of age. Despite the late age of onset, the femoral head remodels well as the patient approaches skeletal maturity. A, Anteroposterior (AP) radiograph obtained at onset of the disorder shows increased density in the femoral head and apparent widening of the joint space (Waldenström's initial stage). B, AP radiograph obtained 9 mo after onset shows the head entering the fragmentation stage. The central fragment remains dense and has collapsed relative to the lateral portion (lateral pillar) of the femoral head. The lateral pillar is lucent but has not collapsed, and the hip is classified as group B in the lateral pillar classification system. The joint space has widened further. C, AP radiograph obtained 17 mo after onset shows early reossification of the femoral head (the healing stage). D, A closer view of the femoral head at 22 mo after onset of disease. There is still widening of the joint space, and the acetabulum has a bicompartmental appearance. E, AP radiograph obtained 4 yr after onset. The femoral head is healed and in the residual state. There is still widening of the joint space and incongruity of the head with the acetabulum. F, AP radiograph obtained 6 yr after onset shows improved roundness of the femoral head and better joint congruity. (From Kim HK, Herring JA: Legg-Calvé-Perthes disease. In Herring JA, editor: *Tachdjian's pediatric orthopaedics* , 5/e. Philadelphia, 2014, Elsevier, Fig. 17.18.)**

In the initial stage of LCPD, the radiographic changes include a decreased size of the ossification center, lateralization of the femoral head with widening of the medial joint space, a subchondral fracture, and physeal irregularity. In the fragmentation stage, the epiphysis appears fragmented, and there are scattered areas of increased radiolucency and radiodensity. During the reossification stage, the bone density returns to normal via new (woven) bone formation. The residual stage is marked by the reossification of the femoral head, gradual remodeling of head shape until skeletal maturity, and remodeling of the acetabulum.

In addition to these radiographic changes, several classic radiographic signs have been reported that describe a “head at risk” for severe deformity. Lateral extrusion of the epiphysis, a horizontal physis, calcification lateral to the epiphysis, subluxation of the hip, and a radiolucent horizontal V in the lateral aspect of the physis (Gage's sign) are all associated with a poor prognosis.

In the absence of changes on plain radiographs, particularly in the early stages of the disease, MRI is useful to diagnose early infarction and determine the degree of impaired perfusion. It is being used more in early stages to help determine prognosis. During the remodeling or residual stages, MRI is extremely helpful to define the abnormal anatomy and determine the extent of intra-articular injury. Arthrography can be useful to dynamically assess the shape of the femoral head, demonstrate whether a hip can be contained, and diagnose hinge abduction. Table 698.1 outlines the differential diagnosis.

Table 698.1

Differential Diagnosis of Legg-Calvé-Perthes Disease

Other Causes of Avascular Necrosis

Sickle cell disease
Other hemoglobinopathies (e.g., thalassemia)
Chronic myelogenous leukemia
Steroid medication
Sequela of traumatic hip dislocation
Treatment of developmental dysplasia of the hip
Septic arthritis

Epiphyseal Dysplasias

Multiple epiphyseal dysplasia
Spondyloepiphyseal dysplasia

Mucopolysaccharidoses
Hypothyroidism

Other Syndromes

Osteochondromatosis
Metachondromatosis
Schwartz-Jampel syndrome
Trichorhinophalangeal syndrome
Maroteaux-Lamy syndrome
Martsolf syndrome

From Kim HKW, Herring JA: Legg-Calvé-Perthes disease. In Herring JA, editor: *Tachdjian's pediatric orthopaedics*, ed 5. Philadelphia, 2014, WB Saunders, Box 17.6, p. 613.

Classification

Catterall proposed a four-group classification based on the amount of femoral epiphysis involvement and a set of radiographic "head at-risk" signs. Group I hips have anterior femoral head involvement of 25%, no sequestrum (an island of dead bone within the epiphysis), and no metaphyseal abnormalities. Group II hips have up to 50% involvement and a clear demarcation between involved and uninvolved segments. Metaphyseal cysts may be present. Group III hips display up to 75% involvement and a large sequestrum. In group IV, the entire femoral head is involved. Use of the Catterall classification system has been limited because of a high degree of interobserver variability.

The **Herring lateral pillar classification** is the most widely used radiographic classification system for determining treatment and prognosis during the active stage of the disease (Fig. 698.13). Unlike the Catterall system, the Herring classification has a high degree of interobserver reliability. Classification is based on several radiographs taken during the early fragmentation stage. The lateral pillar classification system for LCPD evaluates the shape of the femoral head epiphysis on AP radiograph of the hip. The head is divided into three sections or pillars. The lateral pillar occupies the lateral 15–30% of the head width, the central pillar is approximately 50% of the head width, and the medial pillar is 20–35% of the head width. The degree of involvement of the lateral pillar can be subdivided into three groups. In group A, the lateral pillar is radiographically normal. In group B, the lateral pillar has some lucency, but >50% of the lateral pillar height is maintained. In group C, the lateral pillar is more lucent than in group B, and <50% of the pillar height remains. Herring has added a B/C border group to the classification system to describe patients with approximately 50% collapse of the lateral pillar.

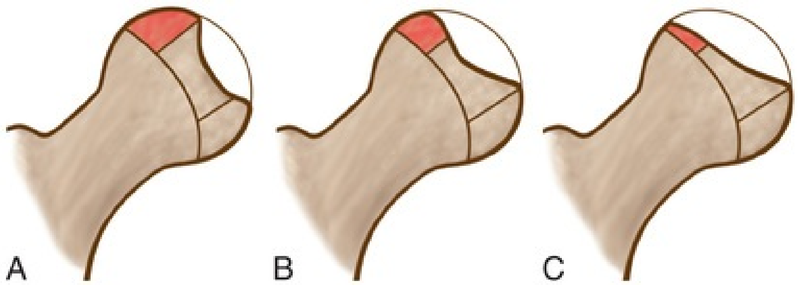

FIG. 698.13 **Lateral pillar classification for Legg-Calvé-Perthes disease. A, There is no involvement of the lateral pillar. B, More than 50% of the lateral pillar height is maintained. C, Less than 50% of the lateral pillar height is maintained.**

Natural History and Prognosis

Children who develop signs and symptoms of LCPD before the age of 6 yr tend to recover with fewer residual problems. Patients older than 9 yr of age at presentation usually have a poor prognosis. The reason for this difference is that the remodeling potential of the femoral head is higher in younger children. Greater extent of femoral head involvement and duration of the disease process are additional factors associated with a poor prognosis. Hips classified as Catterall groups III and IV and lateral pillar group C generally have a poor prognosis.

Treatment

The goal of treatment in LCPD is preservation of a spherical, well-covered femoral head and maintenance of hip range of motion that is close to normal. Although the treatment of LCPD remains controversial, most authors agree that the general approach to these patients should be guided by the principle of containment. This principle is predicated on the fact that while the femoral head is fragmenting, and therefore in a softened condition, it is best to contain it entirely within the acetabulum; by doing so, the acetabulum acts as a mold for the regenerating femoral head. Conversely, failure to contain the head permits it to deform, with resulting extrusion and impingement on the lateral edge of the acetabulum. To be successful, containment must be instituted early while the femoral head is still moldable; once the head has healed, repositioning the femoral epiphysis will not aid remodeling and can, in fact, worsen symptoms.

Initial options to manage symptoms include activity limitation, protected weight bearing, and nonsteroidal antiinflammatory medications. Nonoperative containment can be achieved by using a Petrie cast to restore abduction and to direct the femoral head deeper into the acetabulum. Petrie casts are two long-leg casts that are connected by a bar and can be helpful to keep the hips in abduction and internal rotation (the best position for containment). Casting is generally done in conjunction with an arthrogram to confirm containment and a tenotomy of the adductor tendons. After 6 wk, patients can be transitioned into an abduction orthosis with limited weight bearing. Several older studies did not support the efficacy of casting and long-term bracing as a means of containment, but a subsequent large series reported excellent results with this form of treatment.

Surgical containment may be approached from the femoral side, the acetabular side, or both sides of the hip joint. A varus osteotomy of the proximal femur is the most common procedure. Pelvic osteotomies in LCPD are divided into three categories: acetabular rotational osteotomies, shelf procedures, and medial displacement or Chiari osteotomies. Any of these procedures can be combined with a proximal femoral varus osteotomy when severe deformity of the femoral head cannot be contained by a pelvic osteotomy alone.

After healing of the epiphysis, surgical treatment shifts from containment to management of the residual deformity. Patients with hinge abduction or joint incongruity might benefit from a valgus-producing proximal femoral osteotomy. Coxa breva and overgrowth of the greater trochanter can be managed by performing an advancement of the trochanter. This helps restore the length–tension relationship of the abductor mechanism and can alleviate abductor fatigue. Patients with femoroacetabular impingement from irregularity of the femoral head can often be helped with an osteoplasty or cheilectomy of the offending prominence.

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698.4

Slipped Capital Femoral Epiphysis

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Keywords

slipped capital femoral epiphysis
physis
Klein's line
osteonecrosis
chondrolysis

Slipped capital femoral epiphysis (SCFE) is a hip disorder that affects adolescents, most often between 10 and 16 yr of age, and involves failure of the physis and displacement of the femoral head relative to the neck.

Classification

SCFEs may be classified temporally, according to onset of symptoms (acute, chronic, acute-on-chronic); functionally, according to patient's ability to bear weight (stable or unstable); or morphologically, as the extent of displacement of the femoral epiphysis relative to the neck (mild, moderate, or severe), as estimated by measurement on radiographic or CT images.

An **acute** SCFE is characterized as one occurring in a patient who has prodromal symptoms for ≤3 wk and should be distinguished from a purely traumatic separation of the epiphysis in a previously normal hip (a true Salter-Harris type I fracture; see Chapter 703). The patient with an acute slip usually has some prodromal pain in the groin, thigh, or knee, and usually reports a relatively minor injury (a twist or fall) that is not sufficiently violent to produce an acute fracture of this severity.

Chronic SCFE is the most common form of presentation. Typically, an adolescent presents with a few months’ history of vague groin, thigh, or knee pain and a limp. Radiographs show a variable amount of posterior and inferior migration of the femoral epiphysis and remodeling of the femoral neck in the same direction.

Children with **acute-on-chronic** SCFE can have features of both acute and chronic conditions. Prodromal symptoms have been present for >3 wk with a sudden exacerbation of pain. Radiographs demonstrate femoral neck remodeling and further displacement of the capital epiphysis beyond the remodeled point of the femoral neck.

The stability classification separates patients based on their ability to ambulate and is more useful in predicting prognosis and establishing a treatment plan. The SCFE is considered **stable** when the child is able to walk with or without crutches. A child with an **unstable** SCFE is unable to walk with or without walking aids. Patients with unstable SCFE have a much higher prevalence of osteonecrosis (up to 50%) compared to those with stable SCFE (nearly 0%). This is most likely because of the vascular injury caused at the time of initial displacement.

SCFE may also be categorized by the degree of displacement of the epiphysis on the femoral neck. The head-shaft angle difference is <30 degrees in mild slips, between 30 and 60 degrees in moderate slips, and >60 degrees in severe slips, compared to the normal contralateral side.

Etiology and Pathogenesis

SCFEs are most likely caused by a combination of mechanical and endocrine factors. The plane of cleavage in most SCFEs occurs through the hypertrophic zone of the physis. During normal puberty, the physis becomes more vertically oriented, which converts mechanical forces from compression to shear. In addition, the hypertrophic zone becomes elongated in pubertal adolescents due to high levels of circulating hormones. This widening of the physis decreases the threshold for mechanical failure. Normal ossification depends on a number of different factors, including the thyroid hormone, vitamin D, and calcium. Consequently, it is not surprising that SCFEs occur with increased incidence in children with medical disorders, such as hypothyroidism, hypopituitarism, and renal osteodystrophy. Obesity, one of the largest risk factors for SCFE, affects both the mechanical load on the physis and the level of circulating hormones. The combination of mechanical and endocrine factors results in gradual failure of the physis, which allows posterior and inferior displacement of the head in relation to the femoral neck.

Epidemiology

The annual incidence of SCFE is 2 per 100,000 in the general population. Incidence has ranged from 0.2 per 100,000 in eastern Japan to 10.08 per 100,000 in the northeastern United States. The African American and Polynesian populations are reported to have an increased incidence of SCFE. Obesity is the most closely associated risk factor in the development of SCFE; approximately 65% of the patients are >90th percentile in weight-for-age profiles. There is a predilection for males to be affected more often than females and for the left hip to be affected more often than the right. Bilateral involvement has been reported in as many as 60% of cases, nearly half of which may be present at the time of initial presentation.

Clinical Manifestations

The classic patient presenting with a SCFE is an obese African American male between the ages of 11 and 16 yr. Females present earlier, usually between 10 and 14 yr of age. Patients with chronic and stable SCFEs tend to present after weeks to months of symptoms. Patients usually limp to some degree and have an externally rotated lower extremity. Physical examination of the affected hip reveals a restriction of internal rotation, abduction, and flexion. Commonly, the examiner notes that as the affected hip is flexed, the thigh tends to rotate progressively into more external rotation with increased flexion (Fig. 698.14). Most patients complain of groin symptoms, but isolated thigh or knee pain is a common presentation from referred pain along the course of the obturator nerve. Missed or delayed diagnosis often occurs in children who present with knee pain and do not receive appropriate imaging of the hip. Patients with unstable SCFEs usually present in an urgent fashion. Children typically refuse to allow any range of motion of the hip; much like a hip fracture, the extremity is shortened, abducted, and externally rotated.

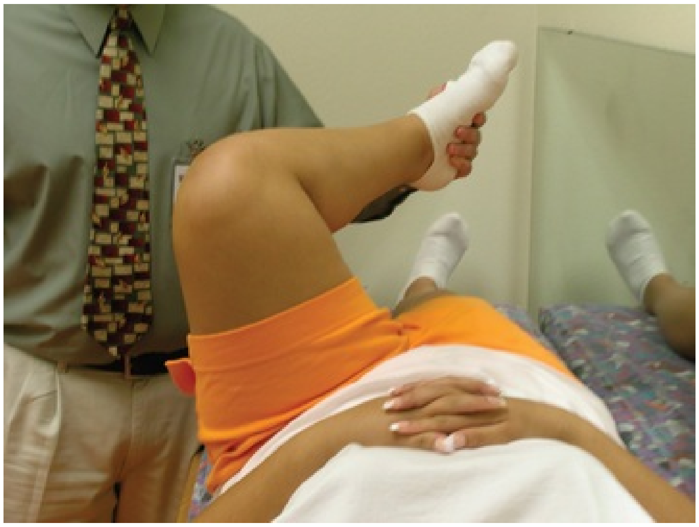

FIG. 698.14 **Clinical examination of a patient with a stable slipped capital femoral epiphysis. Hip flexion and external rotation are limited. With flexion of the affected hip, the limb rotates externally. (From Herring JA: Slipped capital femoral epiphysis. In Herring JA, editor: *Tachdjian's pediatric orthopaedics* , 5/e. Philadelphia, 2014, Elsevier, Fig.18.5.)**

Diagnostic Studies

AP and frog-leg lateral radiographic views of both hips are usually the only imaging studies needed to make the diagnosis. Because approximately 25% of patients have a contralateral slip on initial presentation, it is critical that both hips be carefully evaluated by the treating physician. Radiographic findings include widening and irregularity of the physis, a decrease in epiphyseal height in the center of the acetabulum, a crescent-shaped area of increased density in the proximal portion of the femoral neck, and the “blanch sign of Steel” corresponding to the double density created from the anteriorly displaced femoral neck overlying the femoral head. In an unaffected patient, Klein's line, a straight line drawn along the superior cortex of the femoral neck on the AP radiograph, should intersect some portion of the lateral capital femoral epiphysis. With progressive displacement of the epiphysis, Klein's line no longer intersects the epiphysis (Fig. 698.15). Although some of these radiographic findings can be subtle, most diagnoses can be readily made on the frog-leg lateral view, which reveals the characteristic posterior and inferior displacement of the epiphysis in relation to the femoral neck (Fig. 698.16).

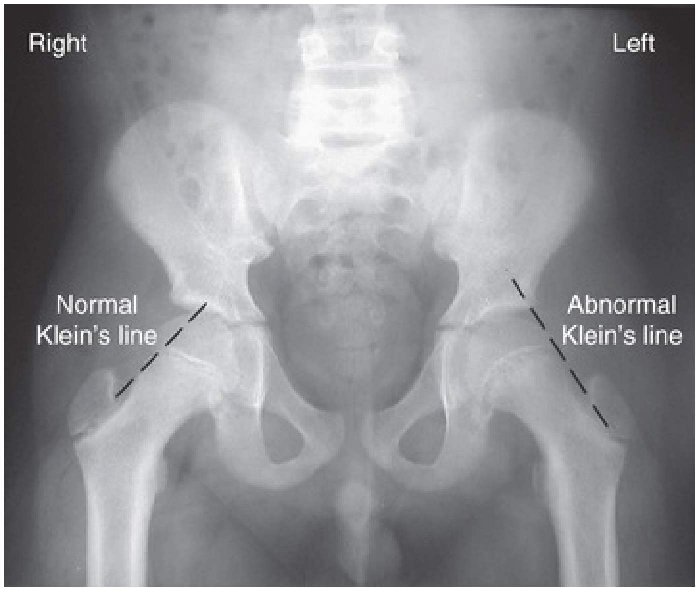

FIG. 698.15 Illustration of Klein's line.

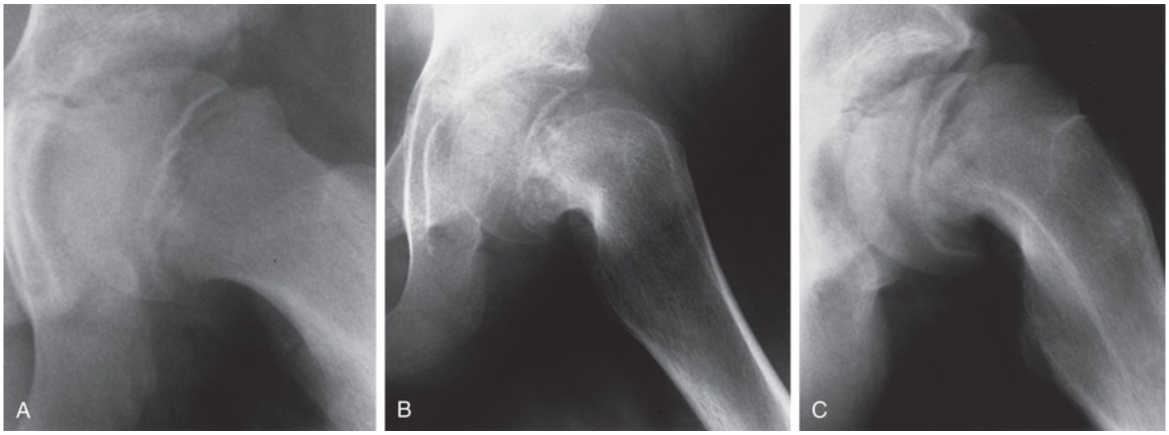

FIG. 698.16 Radiographic appearance of slipped capital femoral epiphysis (SCFE) on presentation. A, Appearance of acute SCFE on a frog-leg lateral view. The displacement of the epiphysis is suggestive of a Salter-Harris type I fracture of the upper femoral physis. There are no secondary adaptive changes noted in the femoral neck. B, Frog-leg lateral radiographs in a patient with many months of thigh discomfort and a chronic slipped epiphysis. Adaptive changes in the femoral neck predominate, and the epiphysis is centered on the adapted femoral neck. C, Frog-leg lateral radiographs of a patient with acute-on-chronic SCFE. The patient had several months of vague thigh pain, with sudden, severe exacerbation of that pain. The acute displacement of the epiphysis is evident. Unlike in acute SCFE (see A), secondary adaptive remodeling changes are also present in the femoral neck, beyond which the epiphysis has acutely displaced. (From Herring JA: Slipped capital femoral epiphysis. In Herring JA, editor: *Tachdjian's pediatric orthopaedics* , ed 5, Philadelphia, 2014, WB Saunders, Fig. 18.1, p. 632.)

Treatment

Once the diagnosis is made, the patient should be admitted to the hospital immediately and placed on bed rest. Allowing the child to go home without definitive treatment increases the risk that a stable SCFE will become an unstable SCFE and that further displacement will occur. Children with atypical presentations (younger than 10 yr of age, thin body habitus) should have screening labs sent to rule out an underlying endocrinopathy.

The goal of treatment is to prevent further progression of the slip and to stabilize (i.e., close) the physis. Although various forms of treatment have been used in the past, including spica casting, the current gold standard for the treatment of SCFE is in situ pinning with a single large screw (Fig. 698.17). The term *in situ* implies that no attempt is made to reduce the displacement between the epiphysis and femoral neck because doing so increases the risk of osteonecrosis. Screws are typically placed percutaneously under fluoroscopic guidance. Postoperatively, most patients are allowed partial weight bearing with crutches for 4-6 wk, followed by a gradual return to normal activities. Patients should be monitored with serial radiographs to be sure that the physis is closing and that the slip is stable. After healing from the initial stabilization, patients with severe residual deformity may be candidates for proximal femoral osteotomy to correct the deformity, reduce impingement, and improve range of motion.

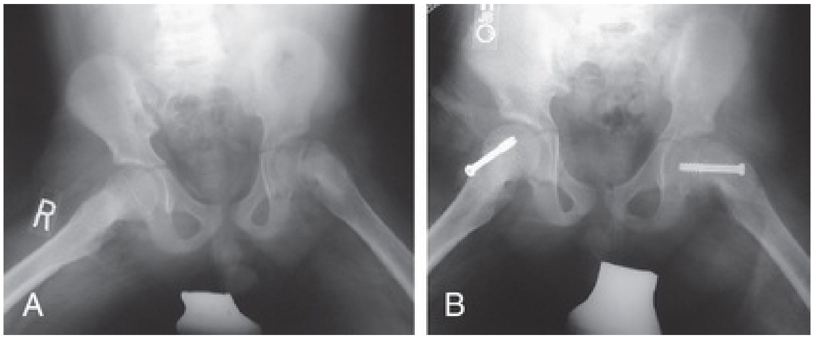

FIG. 698.17 Preoperative **(A)** and postoperative **(B)** radiographs demonstrating the in situ pinning in a case of slipped capital femoral epiphysis.

Because 20–40% of children will develop a contralateral SCFE at some point, many orthopedists advocate prophylactic pin fixation of the contralateral (normal) side in patients with a unilateral SCFE. The benefits of preventing a possible slip must be balanced with the risks of performing a potentially unnecessary surgery. Several recent studies have attempted to analyze decision models for prophylactic pinning, but controversy remains regarding the optimal course of treatment.

Complications

Osteonecrosis and chondrolysis are the 2 most serious complications of SCFE. Osteonecrosis, or avascular necrosis, usually occurs as a result of injury to the retinacular vessels. This can be caused by an initial force of injury, particularly in unstable slips, forced manipulation of an acute or unstable SCFE, compression from intracapsular hematoma, or as a direct injury during surgery. Partial forms of osteonecrosis can also appear following internal fixation; this can be caused by a disruption of the intraepiphyseal blood vessels. Chondrolysis, on the other hand, is an acute dissolution of articular cartilage in the hip. There are no clear causes of this complication, but it is believed to be associated with more severe slips, to occur more commonly among African Americans and girls, and to be associated with pins or screws protruding out of the femoral head.

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CHAPTER 699

The Spine

R. Justin Mistovich, David A. Spiegel

Abnormalities of the spine can result from a variety of causes including congenital, developmental, and traumatic. In addition to spinal deformities, back pain is also prevalent in children and adolescents. A thoughtful diagnostic evaluation is required to establish the diagnosis while minimizing the overutilization of health care resources. The most common spinal deformities are scoliosis and kyphosis. An early diagnosis is important, as a subset of patients may be candidates for bracing or other early interventions to prevent curve progression. For example, bracing has been proven to reduce the number of patients with curve progressing to require surgery in adolescent idiopathic scoliosis (AIS).

Scoliosis may be idiopathic, due to congenital bony deformities, or may be associated with a variety of underlying conditions, including neuromuscular diseases, connective tissue diseases, or genetic syndromes. Oftentimes, the pediatrician is the first to diagnose these conditions. A familiarity with the physical examination, the natural history, and treatment options will help the pediatrician to not only establish an early diagnosis, but also to provide counseling for the patient and family regarding the diagnosis, general prognosis, and whether a referral or further workup might be indicated.

While parents and families are often most concerned about the resulting cosmetic abnormalities, the physician diagnosing a patient with a spinal deformity must carefully consider both the potential for underlying causes requiring treatment and the patient's long-term prognosis. For example, progressive curvatures in the neuromuscular population may result in respiratory insufficiency in addition to a loss of sitting balance. Other conditions such as neurofibromatosis are associated with a specific dystrophic curve pattern that can rapidly progress. Sometimes, the curve might be the first sign of an underlying syndrome. Parents and the patient must have an understanding of the deformity, how it may progress, and potential complications associated with the diagnosis. A classification of common spinal abnormalities is presented in Table 699.1 .

Table 699.1

Classification of Spinal Deformities

Scoliosis

Idiopathic

- Infantile
- Juvenile
- Adolescent

Congenital

- Failure of formation
    - Wedge vertebrae
    - Hemivertebrae
- Failure of segmentation
    - Unilateral bar
    - Block vertebra
    - Mixed

Neuromuscular

- Neuropathic diseases
    - Upper motor neuron
        - Cerebral palsy
        - Spinocerebellar degeneration (Friedreich ataxia, Charcot Marie-Tooth disease)
        - Syringomyelia
        - Spinal cord tumor
        - Spinal cord trauma
    - Lower motor neuron

Poliomyelitis
Spinal muscular atrophy

Myopathies

- Duchenne muscular dystrophy
- Arthrogryposis
- Other muscular dystrophies

Syndromes

- Neurofibromatosis
- Marfan syndrome

Compensatory

- Leg-length discrepancy

Kyphosis

- Postural kyphosis (flexible)
- Scheuermann disease
- Congenital kyphosis
  - Failure of formation
  - Failure of segmentation
  - Mixed

Adapted from the Terminology Committee, Scoliosis Research Society: A glossary of scoliosis terms. *Spine* 1:57, 1976.

Normal Spinal Curvatures

A normal spinal column is straight in the anteroposterior (coronal) plane but normally has curvatures in the lateral (sagittal) plane. Normal cervical lordosis, thoracic kyphosis, and lumbar lordosis regions are biomechanically advantageous as they maintain relationships of the body relative to the forces of gravity, which is important for balance. These curvatures also help to conserve energy by minimizing the amount of muscular activity required to maintain an upright posture.

Abnormalities affecting these normal curvatures, termed *sagittal plane imbalances* , can be measured on a lateral spine radiograph. A vertical line, or *plumb line* , drawn from the center of the 7th cervical vertebra should normally fall through the posterosuperior corner of the sacrum. Disorders affecting sagittal alignment include thoracic hyperkyphosis and lumbar hyperlordosis. In contrast, while scoliosis is actually a 3-dimensional deformity not limited to a single anatomic plane, it is most commonly described as a frontal or coronal plane deformity with curvatures away from the midline in this plane.

699.1

Idiopathic Scoliosis

R. Justin Mistovich, David A. Spiegel

Keywords

Cobb angle
growing rods
scoliosis
vertical expandable prosthetic titanium rib

Definition

The word *scoliosis* takes its origin from the Greek word *skolios* , meaning bent or curved. Scoliosis is a complex, 3-dimensional spinal deformity, defined in the coronal plane as a curve of at least 10 degrees on a posteroanterior (PA) radiograph of the spine. Affected vertebrae are axially rotated, causing the visible prominence on the Adams forward bend test. The sagittal plane is also affected, leading to abnormalities such as decreased thoracic kyphosis.

Etiology

The etiology of idiopathic scoliosis remains unknown despite a considerable body of research. It is likely that the disease has multifactorial causes, with genetic, hormonal, cellular, and anatomic contributions.

A genetic link has been proposed with sex-linked dominant, autosomal dominant, and polygenetic inheritance patterns all suggested. Genetic involvement has been substantiated in studies of twins, demonstrating a 73% concordance rate for AIS in monozygotic twins compared to a 36% concordance rate in dizygotic twins.

AIS is 2-10 times more common in females than males. Investigators have attempted to explain this difference as a genetic effect: it has been hypothesized that males are not as susceptible to the involved genes as females. Therefore affected males must inherit a larger number of susceptibility genes to have a scoliosis phenotype. Males would pass more susceptibility genes onto their children and would therefore have more affected children. Fathers with AIS “transmit” scoliosis to 80% of their children, but mothers with AIS “transmit” it to only 56% of their children.

Earlier genetic studies have demonstrated that certain polymorphisms in the estrogen receptor gene are associated with AIS, though other studies have not corroborated these findings. An exome sequencing study identified mutations in the *COL11A2* collagen gene in 32% of AIS cases. Additional studies have noted that females who have first-degree relatives with AIS have more severe curves and longer arms spans than females who have a “spontaneous” case. Despite these genetic studies, no currently available test accurately predicts patients at genetic risk of curve progression.

Other factors have also been identified in having a possible role in the disease pathology. Lower plasma melatonin levels have been noted in patients with progressive curvatures. Abnormal levels of growth hormone and IGF-1 have also been discovered. Leptin, the hormone responsible for satiety, is found at lower levels in patients with AIS. Calcitonin levels in females with AIS have been reported to be twofold lower than in matched controls.

Cellular structures may be involved in the disease process. Calmodulin, a regulator of the contractile properties of muscle, occurs at increased levels in the platelets of patients with progressive AIS. One study identified abnormalities and asymmetric responses in the upper extremity responses to motor evoked potential and somatosensory evoked potential testing in patients with operative AIS curves. Other functional evaluations of patients with AIS have noted abnormalities in proprioception and postural balance. Yet another study has demonstrated that patients with AIS have differences in vestibular-evoked myogenic potentials, suggesting that otolith system dysfunction may play a role in the disease.

MRI studies of the brain in patients with AIS versus controls have found that the cerebellum of affected patients is hypertrophied in areas involving the somatosensory tracts, motor control, and response to visual stimulation. These areas of hypertrophy may be a compensation for impaired balance resulting from malalignment of the spine. Other studies have noted a decrease in regional brain volumes and white matter in the corpus callosum and internal capsule between patients affected with AIS and normal adolescents. Females with AIS have also been noted to have a larger foramen magnum. The importance of these imaging findings remains unclear.

The density of bone in patients with AIS has also been studied. Approximately one third of females with AIS have osteopenia on DEXA studies, and of these, 80% will have lifelong osteopenia. Osteopenia has been linked to an increased risk of curve progression.

Epidemiology

Idiopathic scoliosis is the most common type of spinal curvature. Out of all possible causes of scoliosis, 80% of cases are idiopathic. The overall prevalence of idiopathic scoliosis in skeletally immature patients ranges from 1% to 3% of the population. Most curves are mild and do not require treatment, with only 0.5% >20 degrees and 0.3% exceeding 30 degrees. While curves of ≤10 degrees occur equally between males and females, those requiring an intervention occur in a 7 : 1 female to male ratio.

Classification of Idiopathic Scoliosis

Idiopathic scoliosis is classified according to the age at onset. Infantile scoliosis is rare, comprising 0.5–4% of all cases of idiopathic scoliosis. It describes patients with spinal curves aged from birth to 3 yr of age. Juvenile scoliosis accounts for 8–16% of cases of idiopathic scoliosis and affects children aged 3-10 yr. AIS affects patients 11 yr of age and older, and comprises 70–80% of all cases of idiopathic scoliosis.

Clinical Presentation of Idiopathic Scoliosis

When evaluating a patient with a structural spinal curvature, a thorough history and physical examination are required because idiopathic scoliosis is a diagnosis of exclusion. All other potential causes, including congenital bone malformations, neuromuscular and syndromic diseases, and tumors must systematically be excluded.

The curvature is frequently found on a positive screening by primary care physicians, through a school screening program, or because patients (or their family or friends) have noticed a cosmetic deformity. In the past, partially due to the unclear evidence regarding the ability to decrease the incidence of patients requiring surgery through interventions such as bracing, the cost versus benefit of scoliosis screening programs has been controversial. The British Orthopaedic Association and the United States Preventive Services Task Force had both issued statements recommending against routine screening. However, citing the need for early identification of scoliosis to reduce the risk of operative complications with correction of large, neglected curves, the Scoliosis Research Society, an international organization of spine surgeons, continued to advocate for school screening. Now, with the publication of the BRAIST study, which demonstrated definitively that patients treated with Boston braces for 18 hr a day have a significantly lower incidence of curves progressing to the surgical range, we expect that public health entities may also begin to advocate for screening programs.

Back pain is not commonly a primary presenting complaint of patients with scoliosis, though when questioned, one third of adolescents with idiopathic scoliosis will endorse some degree of back discomfort at some point in time. To keep this finding in perspective, approximately 35% of healthy adolescents complain of episodes of low back pain and discomfort. However, if a patient presents with the complaint of significant back pain associated with a curvature, do a careful physical exam, check spine radiographs, and rule out any diagnostic red flags. Look for other causes of pain in these patients including spondylosis, spondylolisthesis, tethered cord, syrinx, herniated disc, or tumor such as osteoid osteoma or spinal cord tumor.

Physical Examination of Idiopathic Scoliosis

Evaluate the patient in the standing position, from both the front and the side, to identify any asymmetry in the chest wall, trunk, or shoulders.

Begin the examination focusing on the back. The earliest abnormality noted on physical exam in patients with scoliosis is asymmetry of the posterior chest wall on forward bending. This test, called the Adams forward-bending test (Fig. 699.1), is performed by placing a scoliometer at the apex of the deformity with the patient bending 45 degrees forward. An inclination measuring 7 degrees or more has been suggested as the cutoff for orthopedic referral. Keep in mind that scoliosis is a 3-dimensional deformity. Patients develop a posterior rib hump on the convex side of the spinal curve as a result of the rotational component of the deformity. The anterior chest wall may be prominent on the concavity of the curve due to outward rib rotation. Other associated findings may include shoulder imbalance, a lateral shift of the trunk, or an apparent leg-length discrepancy due to pelvic obliquity. A primary limb length discrepancy may also present as a lumbar spinal deformity. This lumbar curvature is compensatory and flexible, with the apex toward the shorter leg.

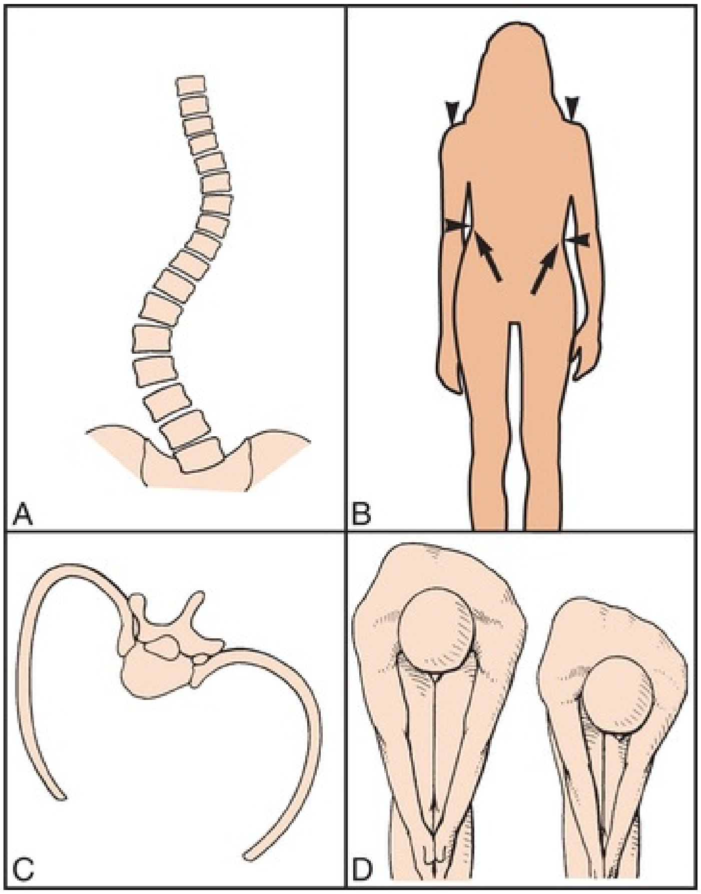

FIG. 699.1 Structural changes in idiopathic scoliosis. A , As curvature increases, alterations in body configuration develop in both the primary and compensatory curve regions. B, Asymmetry of shoulder height, waistline, and elbow-to-flank distance are common findings. C, Vertebral rotation and associated posterior displacement of the ribs on the convex side of the curve are responsible for the characteristic deformity of the chest wall in scoliosis patients. D, In the school screening examination for scoliosis, the patient bends forward at the waist. Rib asymmetry of even a small degree is obvious. (From Scoles PV: Spinal deformity in childhood and adolescence. In Behrman RE, Vaughn VC III, editors: *Nelson textbook of pediatrics, update 5,* Philadelphia, 1989, WB Saunders.)

Next, examine the patient from the side to evaluate the degree of kyphosis and lordosis. The upper thoracic spine normally has a smooth, gently rounded kyphotic curve with an apex in the midthoracic region. The cervical spine and lower lumbar spine have concave, or lordotic curves. The magnitude of these sagittal contours varies with age. Children have less cervical lordosis and more lumbar lordosis than do adults or adolescents. When examining a patient with idiopathic scoliosis, a common finding is a loss of the normal thoracic kyphosis, resulting in what is called a relative thoracic lordosis or hypokyphosis.

Another common, benign finding in normal adolescent thoracic spines is a flexible round back, or postural kyphosis. This can be corrected voluntarily when the patient extends his or her spine. This is different from sharp, abrupt, or accentuated forward angulation in the thoracic or thoracolumbar region, which is indicative of a pathologic kyphotic deformity.

The final exam component is a careful neurologic examination, as scoliosis may be associated with an underlying neurologic diagnosis. Check abdominal superficial reflexes, extremity deep tendon reflexes, muscle strength, atrophy and examine for clonus. A high suspicion is necessary in patients with infantile and juvenile idiopathic scoliosis because up to 25% have an associated intraspinal abnormality such as a tethered spinal cord or syringomyelia. The index of suspicion for neurologic involvement is further raised in the presence of back pain or neurologic symptoms, café-au-lait spots, a sacral dimple, midline cutaneous abnormalities such as a hair patch or skin tag, unilateral foot deformity, or an atypical curve pattern.

Radiographic Evaluation of Idiopathic Scoliosis

Standing, high-quality PA and lateral radiographs of the *entire* spine are recommended at the initial evaluation for patients with clinical findings suggestive of a spinal deformity. If your center is unable to perform the appropriate full-length films, it is best to allow the consulting orthopedic surgeon to obtain the films in their clinic, thereby avoiding unnecessary radiation and inappropriate radiographs. On the PA radiograph, the degree of curvature is determined by the Cobb method, in which the angle between the superior and inferior vertebrae most tilted into the curve is measured (Fig. 699.2).

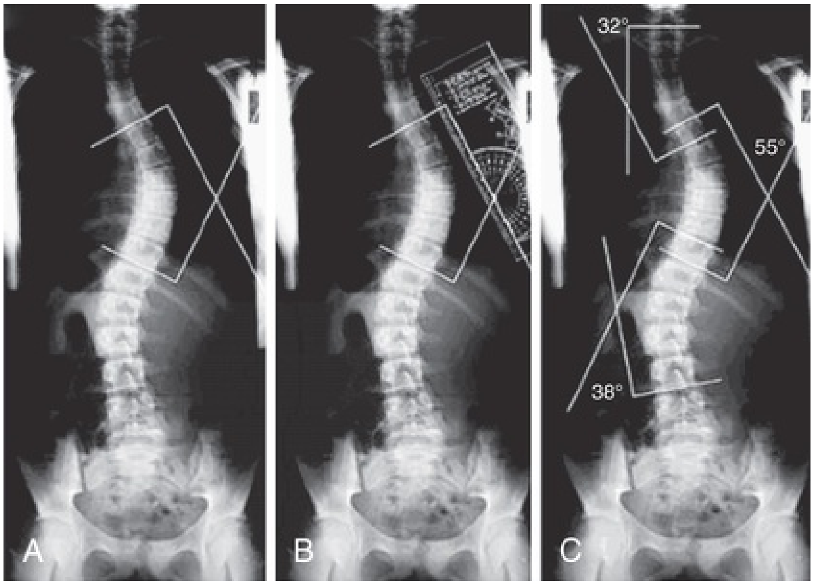

FIG. 699.2 **A-C, Cobb angles measurements. (From Morrissy RT, Weinstein SL: *Lovell & Winter's pediatric orthopaedics,* ed 6, Philadelphia, 2006, Lippincott Williams & Wilkins.)**

Although the indications for performing an MRI are variable, it is helpful when an underlying cause for the scoliosis such as spinal cord abnormality is suspected based on age (infantile or juvenile curves), abnormal findings on the history or physical examination, and atypical radiographic features, including abnormal curve patterns. **Atypical radiographic findings** include curve patterns such as a left thoracic curve, double thoracic curves, or high thoracic curves. Other radiographic abnormalities include widening of the spinal canal and erosive or dysplastic changes in the vertebral body or ribs. On the lateral radiograph, an increase in thoracic kyphosis or an absence of segmental lordosis may be suggestive of an underlying neurologic abnormality.

Low-dose, 3-dimensional imaging systems have been developed. These imaging modalities allow for a lower radiation exposure while delivering higher fidelity imaging and three-dimensional modeling of the vertebrae for both clinical and research applications. Many centers are adopting this approach to imaging in their spinal deformity programs.

Natural History of Idiopathic Scoliosis

Treatment decisions for affected patients are based on the natural history of idiopathic scoliosis. Uniquely, infantile idiopathic scoliosis may spontaneously resolve in 20–90% of cases. Patients with infantile scoliosis who have cognitive disabilities, curves presenting after 1 yr of age, and larger magnitude curves are more likely to progress. A radiographic parameter called the Mehta angle can also be used to predict curve progression in infantile scoliosis. This measurement examines the vertebra at the apex of the thoracic curve. It measures the angle formed by a line perpendicular from the vertebral end plate and a line down the center of the rib. The measurement is calculated on the convex and concave side, and the final rib vertebral angle difference (RVAD) is calculated by subtracting the convex side from the concave side. A curve with an RVAD <20 degrees will resolve in about 80% of cases, while one with an RVAD >20 degrees will progress in over 80% of cases. Curves that resolve typically do so before 2 yr of age.

There are several factors affecting the rate of curve progression in patients with AIS. Curves are more likely to progress in younger, more skeletally immature patients with significant growth remaining. Findings associated with significant growth remaining are younger age, premenarchal status, Tanner stage I or II, and Risser sign (a radiographic measurement of ossification of the iliac crest) of 0 or 1. Other factors affecting curve progression are the current curve magnitude, curve pattern, and patient gender. Three-dimensional spinal measurements of vertebral wedging, axial rotation, and torsion have been correlated to curve progression. Risk factors for progression in AIS patients have recently been studied using the Sanders Skeletal Maturity Staging System, which examines skeletal maturity using a single PA radiograph of the left hand, and associating this value with the current curve magnitude. Higher magnitude curves in more skeletally immature patients are more likely to progress.

In general, female patients are more likely than males to have curves that progress. Younger, premenarchal females with curves between 20 and 30 degrees have a significantly higher risk of progression than do females 2 yr after menarche with similar curves, demonstrating the significance of age on progression. In fact, the older group is unlikely to have any progression at all while premenarchal females with the same curve are likely to progress. Thoracic curves <30 degrees rarely progress after skeletal maturity, while those >50 degrees may progress approximately 1 degree/yr through life, and surgical stabilization is commonly offered.

Functionally, there are not many significant, clinically detrimental effects of smaller curves. There is conflicting literature regarding the exact curve magnitude and curve morphology in idiopathic thoracic scoliosis that leads to cardiopulmonary impairment. A study of curve morphology and pulmonary function found that thoracic curves >70 degrees were associated with below normal pulmonary function. However, patients with curve magnitudes <50 degrees may also have some degree of pulmonary impairment, suggesting that magnitude alone cannot fully predict pulmonary function. Factors such as thoracic kyphosis, curve stiffness, location of curve apex, and degree of vertebral rotation may also impact pulmonary function. Surgical correction is correlated with improved total lung capacity in patients with severe restrictive pulmonary function preoperatively.

Long-term studies have demonstrated that back pain is common in patients with scoliosis, although there is no definitive connection between pain and the curve magnitude or location. Furthermore, nearly 70% of patients with pain reported low or moderate severity of symptoms, stating that the pain does not interfere with normal activities.

Treatment of Idiopathic Scoliosis

Brace treatment has recently been proven to decrease the incidence of curve progression. The BRAIST study, examining the effect of Boston braces in patients treated for 18 hr a day, was stopped prior to study completion—the benefits of bracing became so clear that it was unethical to continue patients in the nonbraced control arm of the study. Treatment success (preventing curve progression to 50 degrees) in the bracing group was 72% while only 48% of those patients observed without bracing avoided progression to the surgical range.

The bracing success rate depends upon the amount of growth remaining. For example, patients with infantile or juvenile scoliosis are much more likely to require a surgical procedure than those with adolescent scoliosis and limited remaining growth. Patients at Risser 0, or very skeletally immature, are at a higher risk of surgery even if they are braced. It is recommended that these skeletally immature patients with curves that are otherwise thought of as small magnitude (>30 degrees) should be braced full time for a minimum of 18 hr daily. In addition to the effect of skeletal maturity, adherence with the recommended protocol for wearing the brace will influence the outcome. Adherence can be a challenge in the adolescent population. Braces are offered for treatment of skeletally immature patients with curves >30 degrees at the first visit, or in patients who are being followed and have developed progression of their curvature beyond 25 degrees. Bracing is ineffective in curvatures >45 degrees, as these patients have already reached the threshold for surgical intervention. The brace is worn until cessation of growth in males, but in females some authors will consider weaning from the brace when the patient is more than 1.5 yr postmenarchal, is a Risser 4 or greater and/or has grown less than a centimeter over the previous 6 mo.

Traditional surgical treatment involves spinal instrumentation and fusion and is usually recommended for skeletally immature patients with progressive curves >45 degrees and skeletally mature patients with curves >50 degrees. The goals of surgery are to arrest progression of the deformity, to improve cosmesis, and to achieve a balanced spine, all while minimizing the number of vertebral segments that are stabilized to preserve as much motion as possible.

Implants including pedicle screws, sublaminar wires, and hooks are attached to two longitudinal rods (Fig. 699.3). Another implant is the sublaminar band, which can be tensioned to progressively correct the curvature. All implants function by allowing the application of mechanical forces to the spine, correcting the deformity in both the frontal and lateral planes to achieve normal frontal and sagittal spinal balance. Pedicle screw constructs also allow for derotational maneuvers, correcting the rib prominences associated the axial component of the deformity. After instrumentation, the spine is decorticated, and bone graft is placed for the fusion portion of the procedure. The strength of modern spinal implants maintains correction without requiring a postoperative brace in most cases.

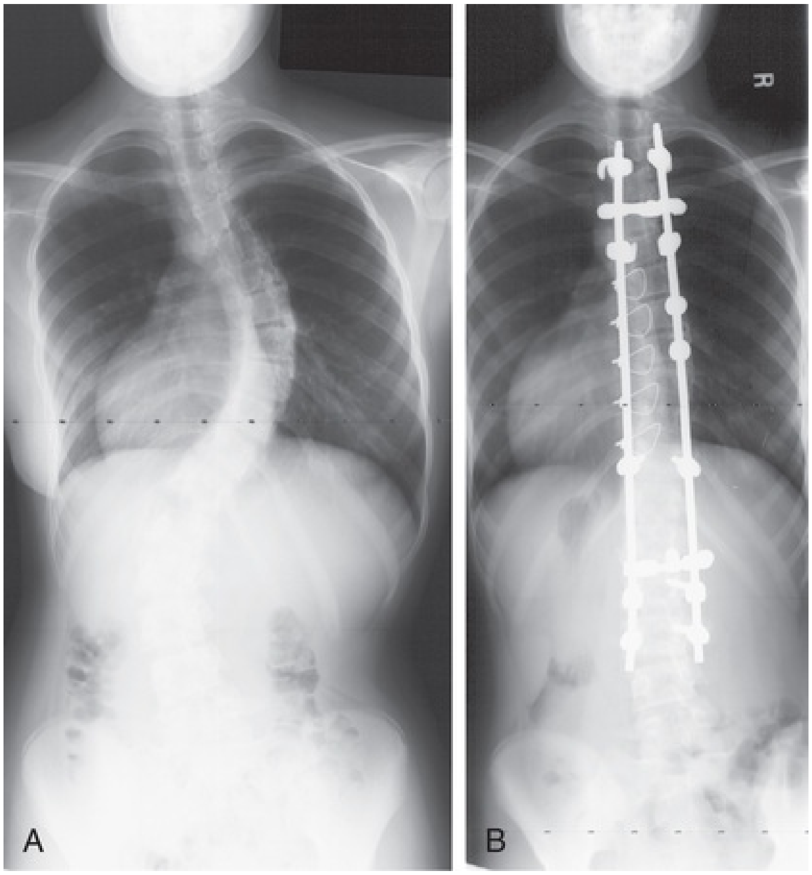

FIG. 699.3 Preoperative standing posteroanterior radiograph of a 14 yr old girl who was skeletally immature and developed a 68-degree right thoracic and a 53-degree left lumbar scoliosis **(A)** . Her trunk was shifted to the right, and the left shoulder was slightly depressed. Based upon the risk of future progression, she was treated by an instrumented posterior spinal fusion from T3 to L3 with correction of the right thoracic curve to 20 degrees and the left lumbar curve to 10 degrees **(B).** Coronal spinal balance was restored, and shoulder height was maintained.

Most procedures are performed posteriorly using pedicle screw fixation, which affords excellent correction, especially of the rotational component of the deformity. Posterior osteotomies are often added to enhance flexibility and improve the degree of correction in stiffer curves. Anterior spinal releases requiring a thoracotomy are now performed infrequently due to the efficacy of pedicle screw instrumentation. Open anterior thoracic and thoracolumbar procedures violate the chest wall and often the diaphragm. Pulmonary function may take up to 2 yr to return to normal values. While thoracoscopic techniques may be utilized to perform anterior spinal release with or without instrumentation and fusion, their use has been limited in recent years, again due to the efficacy of posterior pedicle screw constructs. However, patients with conditions such as neurofibromatosis and myelomeningocele have a higher likelihood of achieving a nonunion of their fusion, and an anterior fusion is considered in addition to the posterior fusion in these groups. Additionally, patients with severe, neglected deformities may still benefit from combined anterior and posterior procedures.

Younger patients, in whom the triradiate cartilage remains open, are at risk for "crankshafting," or progressive deformity due to continued anterior spinal growth, after a posterior fusion. Traditionally, these patients were treated by simultaneous anterior fusion to remove this growth potential; however, the rigidity pedicle screw constructs have negated the need for this additional surgery. While an anterior fusion with instrumentation can be considered for idiopathic thoracolumbar and lumbar curves, the posterior approach with pedicle screw fixation is being used more frequently to avoid the need for anterior surgery and chest wall violation.

Several emerging techniques are being evaluated in the management of idiopathic scoliosis. These include new approaches to the spine, attempts to preserve remaining growth in younger patients, and even specialized treatments to save the lives of young patients with curves so significant they result in mortality secondary to inadequate pulmonary volume.

In addition to fusion surgeries, there has been an interest in developing techniques to correct curves without limiting future growth and even to modulate spinal growth and prevent future fusion surgeries. The FDA-approved VEPTR, or vertical expandable prosthetic titanium rib (Fig. 699.4), has been developed to help young children with thoracic insufficiency syndrome due to severe spinal curves with restrictive lung disease, often associated with a high mortality rate. The chest wall device can enlarge the thorax and indirectly correct scoliosis without requiring spinal fusion and likely triggering lung growth by increasing thoracic volume. After implantation, it is lengthened twice a year by minor surgery. Long-term survival rates are favorable for these extremely severe deformity patients treated by VEPTR. The device obtains and maintains correction without fusing the spine, which allows for alveolar development and maximizes trunk height prior to definitive spinal fusion.

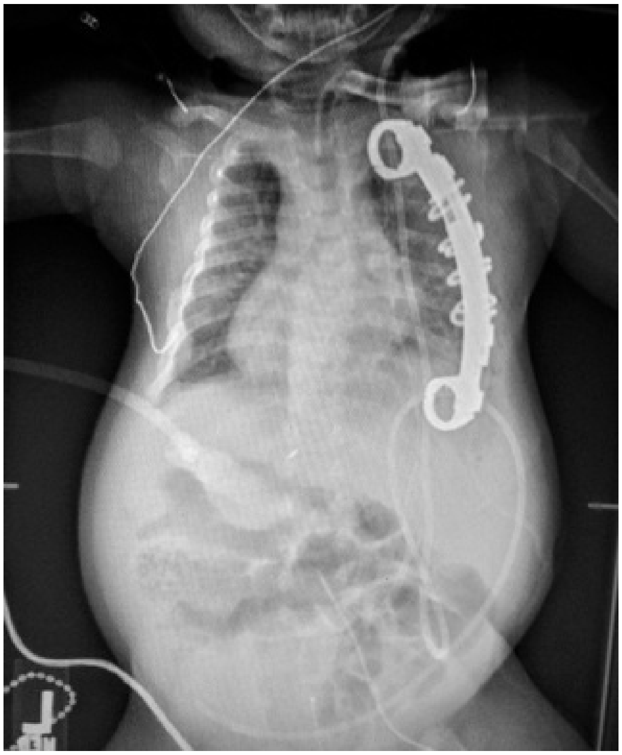

FIG. 699.4 A postoperative posteroanterior radiograph of a patient with Jeune syndrome after placement of a right rib-to-rib VEPTR.

Growing rods have also been used in young children with scoliosis. These devices have fixation points placed at the proximal and distal ends of the spinal deformity, with expandable rods placed subcutaneously, spanning the length of the deformity (Fig. 699.5). Similar to the VEPTR, growing rods require additional minor operations to lengthen the rods twice a year until skeletal maturity or definitive spinal fusion. Technological advancements have led to the development of magnetically controlled growing rods. These devices, once inserted, can be lengthened in the clinic without the need for further surgeries. However, complications are still possible with these devices, requiring revision surgery. Additionally, final fusion is still indicated after achieving adult thoracic height.

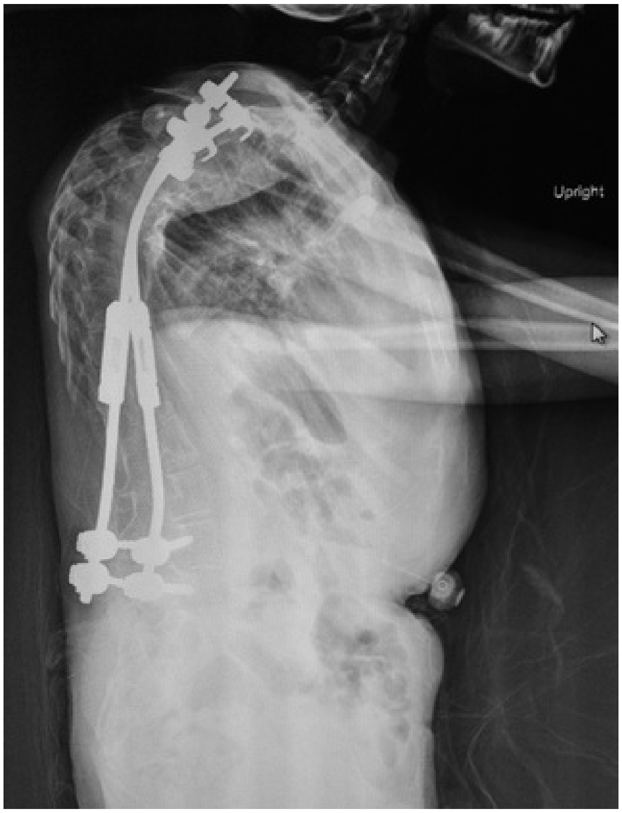

FIG. 699.5 A postoperative lateral radiograph of a skeletally immature patient with severe syndromic scoliosis after placement of growing rods.

The Shilla growth guidance technique has also been developed to allow growth during treatment of early onset scoliosis without requiring frequent lengthening procedures. A limited fusion is performed at the apex of the curve, and a sliding pedicle screw and rod construct allows the spine to lengthen. However, early reports of complication rates remain high.

Another technique is intervertebral stapling. This technique attempts to dynamically modify spinal growth in immature individuals with smaller curves. Staples are placed through either an open or thoracoscopic approach across the intervertebral disk space (growth zone) on the convex side of the curve. This technique holds the spine in a corrected position and limits growth on the convex side, preventing further curvature, and achieving correction through concave growth. Like stapling, intervertebral tethers, consisting of a flexible cord attached with screws to affected vertebrae, may allow for correction of a curve dynamically while allowing more motion than staples. The indications for tethering remain undetermined. Theoretically, patients with somewhat flexible curves and with enough growth remaining to allow for correction of the deformity but not the potential for over-correction or need for additional surgery are the appropriate candidates. It remains to be seen whether these techniques will play a definitive role in the management of patients with idiopathic scoliosis.

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699.2

Congenital Scoliosis

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Keywords

Cobb angle
growing rods
Jarcho-Levin syndrome
scoliosis
spondylothoracic dysplasia
thoracic insufficiency syndrome
vertical expandable prosthetic titanium rib

Definition

Congenital scoliosis is a spinal deformity that results from abnormal development of the vertebrae. Asymmetric spinal growth due to one or more vertebral anomalies leads to spinal curvature. While the malformation is present at birth, it may not become clinically apparent until a later time as growth progresses.

Etiology

Embryologic development of the spine begins at the 5th wk of gestation. An insult to the normal developmental process occurs, resulting in abnormal growth of one or more vertebrae. Oftentimes, this abnormal development is associated with additional developmental anomalies or a known syndromic condition.

Associated Conditions

The developmental insult is typically not limited to the spine alone: it is extremely common for children with congenital scoliosis to have associated malformations in other organ systems, which must be ruled out. Nearly 60% of patients with congenital scoliosis have other developmental malformations.

Genitourinary abnormalities are identified in 20–40% of children with congenital scoliosis and include unilateral renal agenesis, ureteral duplication, horseshoe kidney, and genital anomalies. Approximately 2% of these patients have a silent obstructive uropathy that may be life threatening. Renal ultrasonography should be performed early on in all children with congenital scoliosis, and other studies such as CT or MRI may also be required.

Cardiac anomalies are identified in 10–25% of patients. A thorough cardiac examination should be performed. Some clinicians recommend routine echocardiography.

Intraspinal anomalies are identified in approximately 15–40% of patients. Spinal dysraphism is the general term applied to such lesions (see Chapters 609 and 667). Examples include diastematomyelia, split cord malformations, intraspinal lipomas, arachnoid cysts, teratomas, dermoid sinuses, fibrous bands, and tight filum terminale. Cutaneous findings that may be seen in patients with closed spinal dysraphism include hair patches, skin tags or dimples, sinuses, and hemangiomas. Infants with these cutaneous abnormalities overlying the spine may benefit from ultrasonography to rule out an occult spinal dysraphic condition. MRI is often delayed in older patients until a clinical indication is present, such as tethering of the spinal cord, which may present as back or leg pain, calf atrophy, progressive unilateral foot deformity (especially cavovarus), and problems with bowel or bladder function.

Classification of Congenital Scoliosis

Congenital scoliosis is classified by the type of developmental abnormality: either a failure of formation or a failure of segmentation. The deformities are then further described by the anatomic features of the affected vertebrae. Failure of formation results in wedge vertebrae or hemivertebrae. Failure of segmentation results in unilateral bar vertebrae or block vertebrae. Lastly, some instances of congenital scoliosis result from a combination of both failure of formation and failure of segmentation (Fig. 699.6). One or more bony anomalies may occur in isolation or in combination.

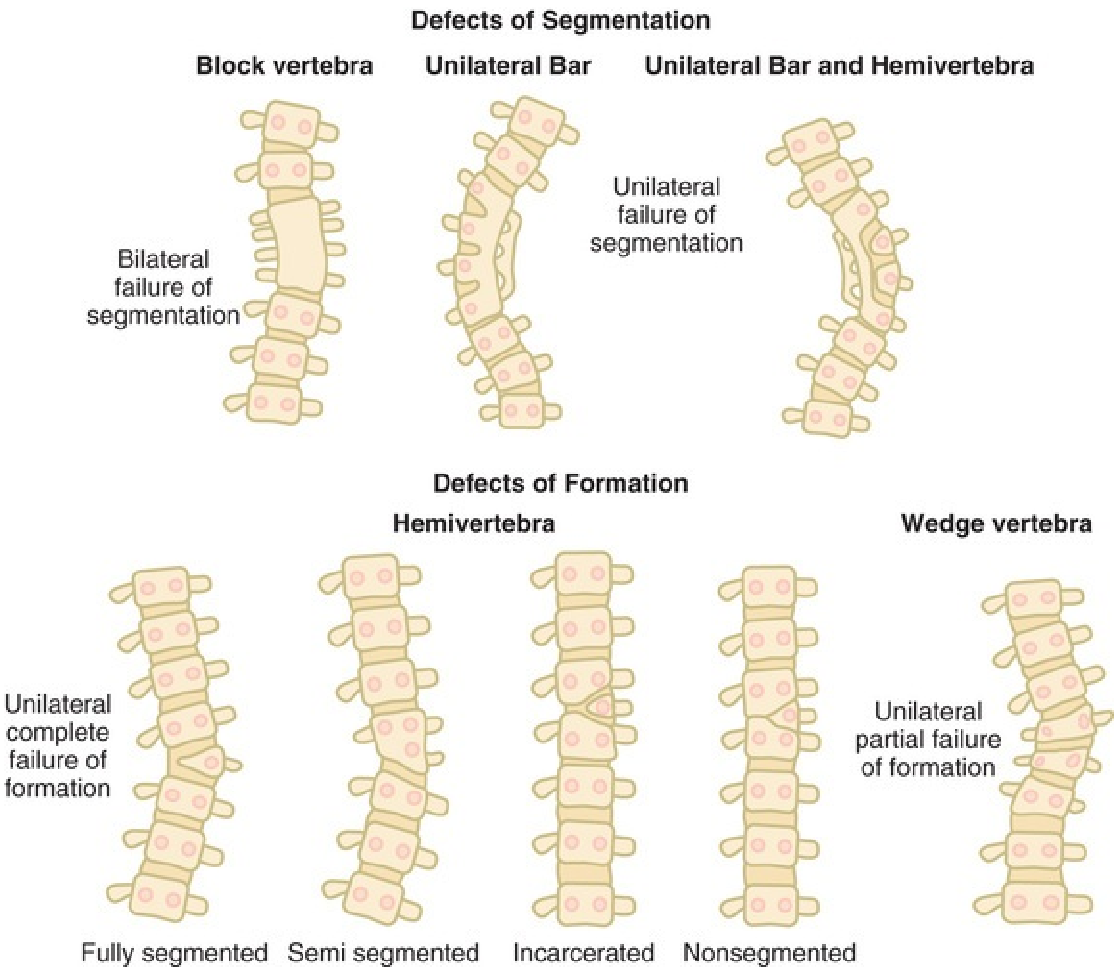
Defects of Segmentation
Block vertebra
Unilateral Bar
Unilateral Bar and Hemivertebra
Bilateral failure of segmentation
Unilateral failure of segmentation
Defects of Formation
Hemivertebra
Wedge vertebra
Unilateral complete failure of formation
Unilateral partial failure of formation
Fully segmented
Semi segmented
Incarcerated
Nonsegmented

FIG. 699.6 The defects of segmentation and formation that can occur during spinal development. (From McMaster MJ: Congenital scoliosis. In Weinstein SL, editor: *The pediatric spine: principles and practice, ed 2,* Philadelphia, 2001, Lippincott Williams & Wilkins, p 163.)

Natural History of Congenital Scoliosis

The risk of progression depends on the growth potential of each anomaly, which may vary considerably. Close radiographic follow-up is required. Progression of these curves is most pronounced during periods of rapid growth associated with the first 2-3 yr of life and during the adolescent growth spurt.

The anatomic characteristics of the malformed vertebra play a significant role in the progression of deformity. The most severe form of congenital scoliosis is a unilateral unsegmented bar with a contralateral hemivertebra. In this anomaly, the spine is fused to the side of the unsegmented bar but also has a growth center on the other side at the location of the hemivertebra at the same level. This combination of deformities in the bony spine results in a rapidly progressive curve. As a result, all affected patients usually require surgical stabilization. A unilateral unsegmented bar is also associated with significant progression and in most cases will require surgical intervention. An isolated hemivertebra must be followed closely, and many, but not all, of these will be associated with a progressive deformity that requires surgical intervention. In contrast, an isolated block vertebra has little growth potential and rarely requires treatment.

Treatment of Congenital Scoliosis

Early diagnosis and prompt treatment of progressive curves are essential. Bracing is not indicated for most congenital curves due to their structural nature, except in rare cases to control additional curves not associated with the bony abnormality or to attempt the delay of inevitable surgery until a safer age for a surgical procedure. The definitive treatment of progressive curves is spinal fusion. Once a bony abnormality is identified that is likely to progress, surgery is performed before progression occurs, preventing development or further inevitable progression of spinal deformity. If the deformity has already developed, surgical correction is difficult to achieve, and the risk of neurologic complications is high.

Both anterior and posterior spinal fusion is often required, though with pedicle screw constructs, a posterior fusion may be sufficient in some cases. Other procedures can also be indicated for congenital scoliosis. A convex hemiepiphysiodesis can be performed with certain deformities, fusing only one side of the spine to allow some correction of the deformity by permitting growth on the noninvolved side of the curve. Complete excision of a hemivertebra, along with fusion of a short segment of the spine, can be performed via a posterior approach and may result in better correction and spinal balance in selected cases. Oftentimes, a definitive fusion is still required at skeletal maturity. Additionally, growing spine constructs or VEPTR can be used to span curvatures secondary to deformities.

Surgery in these young, syndromic patients is not without risk; there may be a complication rate of nearly 85% and a mortality rate of over 15% in patients who underwent operative treatment for all types of early onset scoliosis, including those with congenital scoliosis as well as other associated syndromes producing early onset scoliosis.

Special Circumstance: Thoracic Insufficiency Syndrome

When multiple levels of the thoracic spine are involved in the presence of fused ribs, a progressive 3-dimensional deformity of the chest wall may impair lung development and function. This development is termed *thoracic insufficiency syndrome* . As a result of thoracic insufficiency syndrome, the chest wall cannot support normal respiration resulting in decreased life expectancy.

Thoracic insufficiency syndrome may be seen in patients with several recognized conditions such as Jarcho-Levin syndrome (spondylocostal or spondylothoracic dysplasia) and Jeune syndrome (asphyxiating thoracic dystrophy) as well as patients with severe spinal deformities. These difficult cases are being treated with a technique called *expansion thoracoplasty* , in which the thoracic cage is gradually expanded over time by progressive lengthening of the chest wall on the concavity of the spinal deformity (or in some cases on both sides of the spine). The procedure involves an opening wedge thoracostomy, followed by placement of a vertical expandable titanium prosthetic rib or VEPTR. The implant is then lengthened at regular intervals (Fig. 699.7). The primary goal is to gradually correct the chest wall deformity to improve pulmonary function, and a secondary goal is correction of an associated spinal deformity. Several studies have examined VEPTR in the use of patients with congenital scoliosis. In patients with associated fused ribs, insertion of a VEPTR with an opening wedge thoracostomy results in improved pulmonary function. Additionally, VEPTR has been studied in patients without fused ribs but with congenital scoliosis. These patients also demonstrate improved thoracic spinal height and associated curve correction.

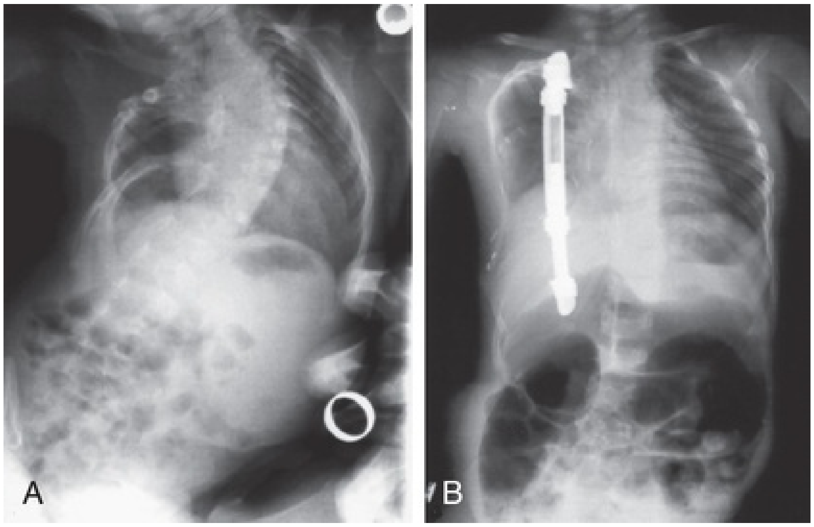

FIG. 699.7 **A,** Anteroposterior preoperative radiograph of a 7 mo old boy with congenital scoliosis and fused ribs. A three-dimensional reconstruction of a CT scan of the chest of this infant estimated his lung volume to be 173.2 mL^3 . **B,** Anteroposterior radiograph after implantation of a vertically expandable prosthetic titanium rib and several expansions over 33 mo. The lung volume now measures 330.3 mL^3 , an increase of 90.7%. (From Gollogly S, Smith JT, Campbell RM: Determining lung volume with three-dimensional reconstructions of CT scan data: a pilot study to evaluate the effects of expansion thoracoplasty on children with severe spinal deformities. *J Pediatr Orthop* 23:323–328, 2004.)

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699.3

Neuromuscular Scoliosis, Genetic Syndromes, and Compensatory

Scoliosis

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Keywords

arthrodesis
Duchenne muscular dystrophy

Neuromuscular Scoliosis

Scoliosis is frequently identified in children with neuromuscular diseases such as cerebral palsy, muscular dystrophies, myopathies, spinal muscular atrophy, Friedreich's ataxia, myelomeningocele, polio, and arthrogryposis. Children with spinal cord injuries are also at high risk to develop a progressive curvature. The etiology and natural history of these patients differ from idiopathic and congenital scoliosis. Most cases result from weakness and/or imbalance of the trunk musculature. Spasticity may also contribute to spinal curvatures. In some cases, such as myelomeningocele, coexisting congenital vertebral anomalies may be present, further contributing to curve development.

A spinal deformity is more common in patients with higher degrees of neurologic impairment, namely those who are nonambulatory with inadequate control of their trunk. It is diagnosed in more than 70% of nonambulatory patients with cerebral palsy, and over 90% of patients with Duchenne muscular dystrophy.

The diagnosis is suspected on physical examination. In nonambulators, the most common curve pattern is a long, sweeping “C”-shaped thoracolumbar or lumbar curve (Fig. 699.8). The curve is typically associated with pelvic obliquity which may impact seating balance. In contrast, ambulatory patients with diagnoses such as Friedreich ataxia may have curve patterns more similar to idiopathic scoliosis.

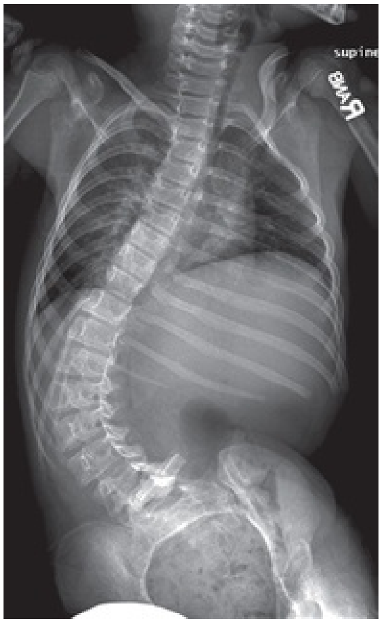

FIG. 699.8 Imaging shows a long C-shaped curve with convexity to the left side and significant pelvic obliquity, a curve pattern often seen in patients with neuromuscular scoliosis. (From Pruthi S. Scoliosis. In Coley BD, editor. *Caffey's pediatric diagnostic imaging,* ed 12, Philadelphia, 2013, WB Saunders, pp 135-10B.)

In ambulatory patients, the examination is similar to the previously described physical examination for idiopathic scoliosis. In nonambulators, the back is inspected with the patient sitting upright. Any asymmetry should be noted. These patients often need manual support to maintain an upright position. If any progressive asymmetry is observed, sitting PA and lateral radiographs should be obtained. Since prophylactic treatment or bracing cannot alter the natural history of the disease, our own preference is to establish the diagnosis clinically and obtain radiographs if the curve is noted to progress.

The clinical course of patients with neuromuscular scoliosis depends on the severity of neuromuscular involvement as well as the nature of the underlying disease process. Progressive diseases are often associated with progressive curvatures. The consequences of a progressive scoliosis in the neuromuscular population involve both function, especially sitting and standing balance, and ease of hygiene and personal care. Pulmonary dysfunction may be expected with the gradual deformation of the rib cage and vertebra-pelvic axis, as well as collapse of the spine with the pelvis impinging on the rib cage. Diaphragmatic function is impaired, and changes in chest volume and chest wall architecture will undoubtedly exacerbate the pulmonary dysfunction owing to underlying muscle weakness. Pulmonary function may be difficult to document in some patient populations, especially those with severe cerebral palsy. Additionally, patients with initial marginal ambulatory function may lose the ability to walk altogether as their scoliosis advances. Curves associated with pelvic obliquity result in asymmetric seating pressures, which may limit sitting endurance and may cause skin breakdown and decubitus ulcers. Patients may also experience pain from impingement of the rib cage on the iliac crest.

The treatment of neuromuscular scoliosis depends on the age of the patient, the underlying diagnosis, and the magnitude of the deformity. The goal is to achieve or maintain a straight spine over a level pelvis, especially in the nonambulatory population, and to intervene early before curve magnitude and rigidity become severe. Neuromuscular curves often continue to progress after skeletal maturity. Curves of >40-50 degrees will continue to worsen over time. Brace treatment does not affect the natural history of neuromuscular scoliosis, and standard braces used for idiopathic scoliosis are poorly tolerated in neuromuscular patients. A soft spinal orthosis may improve sitting balance and ease of care, although it does not ultimately change the natural history of the curvature.

A spinal arthrodesis is offered to patients with progressive curvatures over 40-50 degrees. The indications will differ somewhat based on the underlying diagnosis. For example, patients with Duchenne muscular dystrophy are often offered surgery when their curves progress beyond 20-30 degrees, before their anticipated decline in pulmonary or cardiac function makes the procedure riskier or preclude their ability to tolerate surgery. Ambulatory patients with curvatures similar to those seen in idiopathic scoliosis are managed by similar principles to idiopathic etiologies. Patients who are nonambulatory with pelvic obliquity are usually managed by a long spinal fusion extending from the upper thoracic spine to the pelvis, or the lower lumbar spine in selected cases. A brace is not required following this procedure. Treatment decisions must be individualized in those nonambulatory patients with spastic quadriplegia, and are based on loss of function, the potential to improve hygiene or personal care, and the desires of the family and/or caregivers. These treatment decisions are complex, and recent research has demonstrated the benefit of formal decision aids for families to assist with understanding treatment risks and benefits.

Although complications are relatively frequent in comparison to patients with nonneuromuscular curves, the available literature suggests that most patients benefit in terms of function and ease of care. To better identify patients at risk of complications, many studies have focused on identifying risk factors for perioperative complications. One study identified nonambulatory patients and those with curves ≥60 degrees as having a significantly increased risk of postoperative major complications, including ileus, pneumonia, infection, and wound problems. Baclofen pumps have not been associated with increased risk of complications. Another study recently identified G-tube dependence as a risk factor for postoperative complications. Increased blood loss was found to be an independent risk factor for major perioperative complications in another study. ASA classification ≥3, BMI ≥95th percentile, and extension of fusion to the pelvis have also been found to be associated with postoperative infections. One study subclassified patients with Gross Motor Function Classification System (GMFCS) level 5 in terms of their risk for complications from spinal fusion. These patients have severe functional limitations and are at a high risk of perioperative complications, although not all are identical in terms of risk factors. They identified four subgroups, based on the associated presence of a gastrostomy tube, tracheostomy, history of seizures, and nonverbal status. Patients with none of these risk factors were subclassified as 5.0; 1 associated risk factor was 5.1; two were 5.2; and three or more were 5.3. The rate of major complications for patients with 5.0 GMFCS levels was 12%, while patients with 5.3 GMFCS level had a 49% rate of major complications.

Syndromes and Genetic Disorders

This diverse group of diagnoses includes neurofibromatosis (see Chapter 614.1), osteogenesis imperfecta (see Chapter 721), connective tissue diseases such as Marfan syndrome (see Chapter 722) and Ehlers-Danlos syndrome (see Chapter 679), and Prader-Willi syndrome (see Chapter 98)—among many others. Patients with these diagnoses should have their spine examined routinely during visits to their primary care physician. Similar to other types of scoliosis, the follow-up and treatment are based on the age of the patient, the degree of deformity, whether progression has been documented, and the underlying diagnosis.

Compensatory Scoliosis

Leg-length inequality is a common clinical diagnosis and is usually associated with a small compensatory lumbar curvature (see Chapter 696). This is one cause of false-positive screening examinations. Patients with leg-length inequality may have the pelvis become tilted toward the shorter limb and subsequently develop an associated lumbar curve. The apex of the curve points toward the short leg. There is little evidence to suggest that a small compensatory lumbar curve places the patient at risk of progression or back pain. However, children with leg-length inequality may also have idiopathic or congenital scoliosis. A standing radiograph may be obtained with a block under the foot on the short side, which corrects the leg-length discrepancy and levels the pelvis. If the curvature disappears when the limb-length discrepancy is corrected, then a diagnosis of a compensatory curve is made. An alternative imaging study is a PA radiograph with the patient seated.

In neuromuscular disorders such as polio (see Chapter 276) or cerebral palsy (see Chapter 616.1), an adduction or abduction contracture of the hip, described as a fixed infrapelvic contracture, may have an associated compensatory lumbar scoliosis to maintain standing balance. For patients who ambulate, a 10-degree fixed contracture will result in up to 3-cm apparent leg-length discrepancy.

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699.4

Kyphosis

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Keywords

hyperkyphosis
Milwaukee brace
Scheuermann disease
Schmorl nodes

The normal thoracic spine has 20-50 degrees of kyphosis as measured from T3 to T12 using the Cobb method on a standing lateral radiograph of the spine. A thoracic kyphosis in excess of the normal range of values is termed hyperkyphosis. These patients may present with cosmetic concerns, back pain, or both. A flexible or postural kyphosis may be overcorrected voluntarily or with postural adjustment while a rigid kyphosis cannot be corrected passively. Causes of rigid kyphosis include Scheuermann disease and congenital kyphosis among others. Table 699.2 lists conditions associated with hyperkyphosis.

Table 699.2

Conditions Associated With Hyperkyphosis

- Trauma causing spinal fractures
- Spinal infections resulting from bacteria, tuberculosis, and fungi
- Metabolic diseases such as osteogenesis imperfecta or osteoporosis
- Iatrogenic (laminectomy, spinal irradiation)
- Neuromuscular diseases
- Neoplasms
- Congenital/developmental
    - Disorders of collagen such as Marfan syndrome
    - Dysplasias such as neurofibromatosis, achondroplasia, and mucopolysaccharidoses

The evaluation and treatment depend on the underlying diagnosis, the degree of deformity and its flexibility, whether the deformity is progressive, and whether any symptoms are present.

Flexible Kyphosis (Postural Kyphosis)

Postural kyphosis is a common cosmetic concern and is most often recognized by parents or peers. Adolescents with postural kyphosis can correct the curvature voluntarily. A standing lateral radiograph will show an increase in kyphosis but no pathologic changes of the involved vertebrae. There is no evidence to suggest that postural kyphosis progresses to a structural deformity. While mild aching discomfort is sometimes reported, there is no evidence that the condition leads to long-term symptoms, alterations in function, or quality of life. The mainstay of treatment is reassurance. Physical therapy can be considered for muscular discomfort. While core strengthening is certainly beneficial to most all patients, there are no data to suggest that a permanent alteration in alignment can be maintained. Neither bracing nor surgery plays a role in the management of this condition.

Structural Kyphosis

Scheuermann Kyphosis

Scheuermann disease is the most common form of structural hyperkyphosis and is defined by wedging of >5 degrees of three or more consecutive vertebral bodies at the apex of the deformity on a lateral radiograph. In addition, the apex of the thoracic kyphosis is lower than expected. Other radiographic findings include irregularities of the vertebral end plates and Schmorl nodes, which are herniations of the vertebral disc into the surface of the vertebral body. The etiology remains unknown, but most likely involves the influence of mechanical forces in a genetically susceptible individual. Histologic specimens taken of patients with Scheuermann disease have shown a disordered pattern of endochondral ossification. However, it remains unclear whether these findings are the primary result of a genetic or metabolic pathologic process, or simply the secondary result of mechanical overload. The reported incidence varies from 0.4% to 10% affecting males 3 times more frequently than females.

Physical Exam and Clinical Manifestations

Examine the patient from the side. There is a hyperkyphosis of the thoracic spine typically associated with a sharp contour. The apex of the deformity will often be in the lower thoracic spine. Patients are unable to correct the deformity voluntarily. Pain is a relatively common complaint. It is typically mild and near the apex of the kyphosis. The symptoms are intermittent, rarely severe, and occasionally limit certain activities. Neurologic symptoms are uncommon.

Radiographic Evaluation

The standard imaging protocol includes standing PA and lateral radiographs (Fig. 699.9). A specific, standardized technique in which the arms are folded across the chest is recommended for the lateral view. In addition to the diagnostic findings noted above, a mild scoliosis is commonly seen. Less frequently, a spondylolisthesis may be identified on the lateral radiograph.

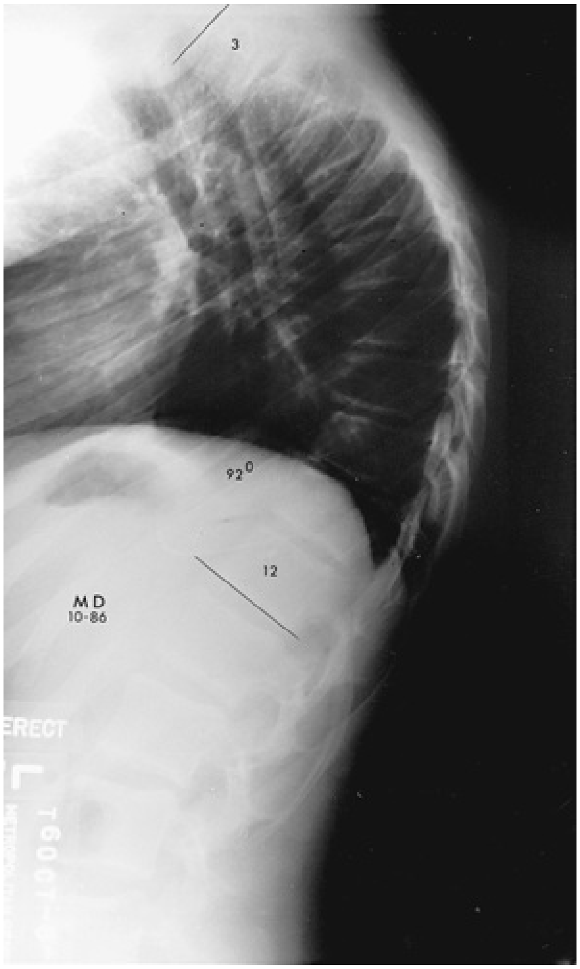

FIG. 699.9 Standing lateral radiograph of a 14 yr old boy with severe Scheuermann kyphosis. This measures 92 degrees between T3 and T12. Note the wedging of the vertebrae at T6, T7, T8, and T9. The normal thoracic kyphosis is ≤40 degrees.

Natural History

Treatment depends on the age of the patient, the degree of deformity, and whether any symptoms are present. As adolescents, patients with Scheuermann kyphosis may have more complaints of back pain compared to other adolescents, but this often improves after skeletal maturity. With regard to back pain, several studies have found no difference between Scheuermann patients and controls, while others have noted an increased incidence of constant back pain. Patients' self-esteem, participation in activities of daily living and recreational activities, and level of education are not different than in the general population. Kyphotic deformities >90 degrees are more likely to be aesthetically unacceptable, symptomatic, and progressive. Deformities more than 100 degrees may be associated with restrictive pulmonary dysfunction.

Treatment

There are few absolute guidelines for treatment, and decisions must therefore be individualized. Skeletally immature patients with mild deformity may benefit from a hyperextension exercise program, but the effects of this strategy on pain relief and spinal alignment, or the natural history, remain unknown. Patients with more than 1 yr of growth remaining and a kyphosis of >55-60 degrees may benefit from a bracing program. A Milwaukee brace, which extends up to the neck, is recommended for curves with an apex above T7, while curves with a lower apex may often be treated by a thoracolumbar orthosis. The brace should be worn for up to 23 hr daily. Consideration may also be given to a serial casting or stretching program to gain flexibility prior to instituting the brace program. The goal of the brace is to prevent progression. A permanent improvement in alignment is seen less frequently. Skeletally mature patients with little or no pain and acceptable cosmesis are not treated. In the rare patient with progressive deformity >70-80 degrees who is dissatisfied with his or her cosmetic appearance or has persistent back pain despite nonoperative measures, a spinal fusion may be considered. A recent study from the Spinal Deformity Study Group found that patients undergoing surgical management had worse pain scores and larger BMI than those successfully treated conservatively. An instrumented posterior spinal fusion from the upper thoracic to the mid lumbar spine is commonly performed, with spinal osteotomies to promote shortening of the spine when correcting with compressive forces. Some surgeons have recommended an anterior spinal release (discectomies and fusion) in addition to the posterior spinal fusion; however, this procedure has been performed less frequently due to the increased neurologic risks of this combined procedure since the spine is lengthened during the correction. As a whole, these surgical procedures carry a higher risk than fusions performed for AIS. A recent study found that major complications were 3.9 times more likely after surgery for Scheuermann kyphosis than AIS, with a greater number of levels fused being an independent risk factor for complications.

Congenital Kyphosis

Congenital kyphosis results from congenital anomalies of the vertebrae. In an anterior failure of formation (type I), a portion of the vertebral body fails to form. The resulting kyphosis is typically identified after birth and carries a high risk of progression and neurologic dysfunction. Spinal cord dysfunction commonly results from compression at the apex of the deformity. The second type of congenital kyphosis involves an anterior failure of segmentation, in which two vertebrae are fused (type II). The posterior elements of the spine continue to grow but the anterior spine does not, resulting in a variably progressive kyphosis and a much lower risk of neurologic dysfunction. Patients must be followed closely, and treatment is required in a significant number of cases. Similar to congenital scoliosis, abnormalities of other organ systems should be ruled out.

The treatment depends on the type of malformation, the degree of deformity, and whether neurologic symptoms are present. Bracing is ineffective, and surgical treatment is the only option for progressive curves. Since the natural history is so poor for type I deformities, spinal fusion is usually performed shortly after the diagnosis is made. The surgical goals are to prevent or treat kyphotic deformities and avoid neurologic deterioration while maximizing spinal growth to the extent possible. This usually involves some form of limited spinal fusion, which may include anterior and/or posterior components, with or without resection of the vertebral remnant, and spinal instrumentation. Ideally, only a short segment of the spine will be fused to try and maximize trunk height. Deformities due to anterior failure of segmentation also require spinal stabilization in some cases, but progression is typically slower, and patients are often followed over years to determine whether surgical stabilization will be required.

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699.5

Back Pain in Children

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Keywords

Faber test
spondylolysis

With a lifetime prevalence of over 70%, only the common cold affects individuals more frequently than back pain. Back pain is a frequent complaint in the pediatric and adolescent patient, with studies demonstrating 1-yr prevalence rates between 7% and 58% of adolescents. Reported risk factors include increasing growth, female gender, family history, excessive sport participation or manual labor, and possibly carrying a heavy backpack. Back pain may also be a physical manifestation of psychosocial factors in adolescents, similar to adults. Traditionally, the younger pediatric patient presenting with back pain warranted an aggressive clinical evaluation since the probability of establishing a specific diagnosis is high. However, the incidence of both pediatric and adolescent back pain has increased (or has been better studied), while the proportion of patients having a diagnosable pathology is decreasing. One large cohort study found no diagnosable pathology in 78% of patients. These trends add further complexity to determining the proper approach to diagnosis and treatment. The differential diagnosis is extensive (Table 699.3). Given the potential for serious pathology, a complete history and careful physical exam must be performed on all patients presenting with back pain, ruling out all diagnostic red flags.

Table 699.3

Differential Diagnosis of Back Pain

Inflammatory Diseases

Diskitis*
Vertebral osteomyelitis (pyogenic, tuberculosis)
Spinal epidural abscess
Transverse myelitis
Pyelonephritis*
Perinephric abscess
Pancreatitis
Paraspinal muscle abscess, myositis
Psoas abscess
Endocarditis
Pelvic osteomyelitis or myositis
Pelvic inflammatory disease

Rheumatologic Diseases

Pauciarticular juvenile rheumatoid arthritis*
Reactive arthritis
Ankylosing spondylitis
Psoriatic arthritis
Ulcerative colitis, Crohn disease
Fibrositis, fibromyalgia

Developmental Diseases

Spondylolysis (in adolescence)*
Spondylolisthesis (in adolescence)*
Scheuermann syndrome (in adolescence)*
Scoliosis
Chiari malformation type 1 with or without syringomyelia
Spinal dysraphism

Mechanical Trauma and Abnormalities

Muscle strain/sprain*
Hip/pelvic anomalies
Herniated disk (rare)
Juvenile osteoporosis (rare)
Overuse syndromes (common with athletic training and in gymnasts and dancers)*
Vertebral stress fractures
Lumbosacral sprain*
Seatbelt injury
Trauma (direct injury; e.g., motor vehicle crash)*
Strain from heavy knapsacks

Neoplastic Diseases

Primary vertebral tumors (osteogenic sarcoma, Ewing sarcoma)
Metastatic tumor (neuroblastoma, rhabdomyosarcoma)
Primary spinal tumor (neuroblastoma, lipoma, cysts, astrocytoma, ependymoma)
Malignancy of bone marrow (ALL, lymphoma)
Benign tumors (eosinophilic granuloma, osteoid osteoma, osteoblastoma, bone cyst)

Other

Disk space calcification (idiopathic, after diskitis)
Conversion reaction
Sickle cell anemia*
Nephrolithiasis
Hemolysis (acute)
Hematocolpos
Post-procedure pain after lumbar puncture

ALL , Acute lymphocytic leukemia; *S/P* , status post.

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* Common.

Modified from Behrman R, Kliegman R, editors: *Nelson essentials of pediatrics,* ed 2, Philadelphia, 1994, WB Saunders, p 711.

Clinical Evaluation

Take a full, careful history. Identify the location, character, and duration of symptoms. Any history of acute trauma or repetitive physical activities should be sought. Identify patients with at-risk athletic pursuits, including football linemen or gymnasts, who have a high incidence of spondylolysis. Symptoms consistent with a neoplastic or infectious etiology include pain that is constant or unrelenting, not relieved by rest, and wakes the patient from sleep. Fevers, chills, night sweats, or constitutional symptoms of weight loss or malaise are additional red flags for infectious or neoplastic processes.

Symptoms of neurologic dysfunction must also be uncovered. Patients should be questioned about the presence of any radicular symptoms, gait disturbance, muscle weakness, alterations in sensation, muscle atrophy, and changes in bowel or bladder function.

The physical examination includes a complete musculoskeletal and neurologic assessment. The patient should be adequately undressed for the clinical exam. Inspect the patient from the back and the side, identifying any changes in alignment in the frontal or sagittal plane. Assess range of motion in flexion, extension, and lateral bending. Recall that pain with extension suggests pathology within the posterior elements of the spine such as spondylolysis.

Forward flexion will exacerbate pain linked to abnormalities of the anterior column of the spine (vertebral body or disc), such as a herniated disc or discitis. Younger children may be asked to pick up an object off the floor to assess spinal flexion.

Palpation will reveal any areas of point tenderness over the posterior bony elements of the spinal column or the muscles and identify muscle spasm or strain.

As spinal pain may be referred, an abdominal examination should be performed, and a gynecologic evaluation should also be considered. Pathology at the sacroiliac joint may also mimic low back pain. This joint should be stressed by compression of the iliac wings or by external rotation at the hip (Faber test).

A detailed neurologic examination should be performed, including manual muscle testing, sensation, proprioception, and reflexes. Examine for myelopathy by performing the Babinski test, assessing for hyperreflexia, and checking for sustained, or >3 beats, of clonus. The superficial cutaneous abdominal reflex should be tested by gently stroking the skin on each of the four quadrants surrounding the umbilicus. Normally, the umbilicus will move toward the area stimulated. A normal examination includes symmetry in the response on both sides of the midline, even if the reflex cannot be elicited on either side. An abnormal test suggests the presence of a subtle abnormality of spinal cord function, most commonly syringomyelia. Perform a straight leg raise test to check for nerve root tension due to a herniated disk, slipped vertebral apophysis, or other pathology. This examination should reproduce any neurologic symptoms distal to the knee.

Medical Decision Making

A detailed history and physical exam are the most important components of the initial evaluation, and should focus on identifying “red flags” and differentiating between mechanical and nonmechanical back pain. Findings consistent with a nonmechanical etiology warrant a more aggressive evaluation and/or prompt referral (Table 699.4).

Table 699.4

Findings Consistent With a Nonmechanical Etiology of Back Pain

- History of trauma (including assessment for nonaccidental trauma)
- Pain which wakes the patient from sleep
- Constant pain unrelieved by rest
- Constitutional or systemic symptoms of fevers, chills, malaise, or weight loss
- Any neurologic dysfunction including weakness, numbness, radicular pain, gait changes, or bowel and bladder changes
- Abnormalities in spinal alignment
- Bony tenderness to palpation or vertebral step-offs
- Significant pain with provocative tests (spinal flexion or extension)
- Positive straight leg raise test for neurologic symptoms below the knee
- Abnormal neurologic exam

Patients with mechanical or muscular back pain and symptoms that are activity-related and improve with rest are typically treated by rest or activity restrictions and nonnarcotic analgesics. Physical therapy for core strengthening can be considered. The patient is asked to return for a follow-up appointment after 4-6 wk. Plain radiographs are commonly obtained at the discretion of individual practitioners. If no red flags are present though, consider deferring radiographs due to the cumulative adverse effects of radiation exposure. Patients presenting with red flags or those who have not improved after 6 wk of conservative care are subjected to further investigation.

Radiographic and Laboratory Evaluation

When further workup is indicated, PA and lateral radiographs of the involved region of the spine are the initial images of choice. Some clinicians will also use oblique radiographs of the lumber spine when spondylolysis is in the differential diagnosis. If plain radiographs are normal, advanced imaging modalities are considered including a 3-phase technetium bone scan, a bone scan with single photon emission computed tomography (SPECT) if spondylolysis is suspected, computed tomography for viewing osseous detail, and magnetic resonance imaging for viewing soft tissue detail or bony areas of inflammation. There are advantages and disadvantages with each, and no evidence-based guidelines are available for the workup or back pain in the pediatric population.

When systemic signs or constitutional symptoms are present, a complete blood cell count with differential, erythrocyte sedimentation rate, and C-reactive protein should be ordered. In certain cases, laboratory tests to evaluate for inflammatory diseases such as juvenile idiopathic arthritis, sero-negative spondyloarthropathies, and ankylosing spondylitis, are indicated.

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699.6

Spondylolysis and Spondylolisthesis

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Keywords

arthrodesis
pseudarthrosis
spinal hyperextension
spondyloptosis

Spondylolysis represents a defect in the pars interarticularis, the segment of bone connecting the superior and inferior articular facets in the vertebra. It is thought to result from repetitive hyperextension stresses, in which compressive forces are transmitted from the inferior articular facet of the superior vertebra to the pars interarticularis of the inferior vertebra. A stress fracture, unilateral or bilateral, may progress to a spondylolysis. In many cases, this stress fracture does not heal, resulting in a pseudarthrosis, or false joint, and thereby allowing motion through this bony area where motion should not normally exist.

Spondylolysis is common in athletes who engage in repetitive spinal hyperextension, especially gymnasts, football interior linemen, weight lifters, and wrestlers. Approximately 4–8% of the entire pediatric population is affected, making it the most common cause of back pain in adolescents when a diagnosis can be established. Patients with excessive lordosis in the lumbar spine may be predisposed to developing a spondylolysis, and a genetic component has also been suggested. The lesion is most common at L5, but it may be identified at upper lumbar levels as well.

Spondylolisthesis represents a forward slippage of one vertebra on another and is identified in approximately 4–5% of the population. There are multiple causes of spondylolisthesis including dysplastic/congenital, isthmic (due to a pars stress fracture), traumatic, and neoplastic. In children and adolescents, the most common types are dysplastic and isthmic. Between 5% and 15% of patients with spondylolysis will develop *spondylolisthesis* .

Spondylolisthesis is assessed on a standing lateral radiograph of the lumbosacral junction according to (1) percentage of forward translation of one vertebra on the other, (2) the slip angle, measuring the rotation of the involved vertebrae in the sagittal plane, and (3) relative position of the sacrum during upright posture. For example, a grade 1 slip of L5 on S1 has <25% of the width of the vertebral body of L5 translated anteriorly on S1. Similarly, grade 2 is 25–50%, grade 3 is 50–75%, and grade 4 is 75–100%. *Spondyloptosis* , or grade 5, describes a complete displacement of one vertebral body on the level below. The slip angle, which demonstrates the degree to which the superior vertebra is flexed forward relative to the underlying vertebra, and the verticality of the sacrum both have a significant effect on sagittal balance, or relationship of the sagittal weight-bearing axis to the body segments. Abnormalities in sagittal spinal balance may be associated with compensatory flexion of the knees during ambulation, hamstring spasm and/or contracture, and back pain.

Clinical Manifestations

Spondylolysis may occasionally be asymptomatic and diagnosed incidentally on imaging obtained for other reasons. Usually, though, it presents with mechanical low back pain that may radiate to the buttocks, with or without spasm of the hamstring muscles. Neurologic symptoms are rare in patients with spondylolysis. However, patients with spondylolisthesis may experience neurologic symptoms from compression and/or stretching of the nerve roots causing radiculopathy or even the surgical emergency of cauda equina in which bowel and bladder function is affected.

Physical Exam

Patients with spondylolysis often have discomfort with spinal extension or hyperextension. Provocative testing may include keeping the spine extended for 10-20 sec to see if back pain can be reproduced. There may be discomfort with palpation of the spinous process of the involved vertebra. Patients with higher grades of spondylolisthesis demonstrate loss of lumbar lordosis, flattening of the buttocks on visual inspection, and a vertical sacrum due to posterior rotation of the pelvis. A step-off may be palpated between the spinous processes of the involved vertebrae. Hamstring contracture is testing by measuring the popliteal angle. The hip is flexed to 90 degrees while fully extending the contralateral hip to level the pelvis. The knee is then passively extended, and the popliteal angle represents the angle between the thigh (vertical) and the lower leg axis. A careful, complete neurologic examination is essential.

Radiographic Evaluation

The initial evaluation of the lumbar region should include high-quality AP and lateral radiographs. Some authors also prefer to obtain oblique radiographs, which demonstrate the classic “Scotty dog” finding on the parts interarticularis. The lumbar spine in oblique radiograph projections normally appears to form the figure of a “Scotty dog” (i.e., Scottish terrier) with the transverse process forming the nose and the pedicle forming the eye, and the pars interarticularis forming the neck; in spondylolysis, the pars interarticularis will have a defect or a break, mimicking a “collar” on the radiograph. One recent study has suggested that a four-view series may not offer greater diagnostic accuracy than two views. Standing PA and lateral radiographs of the entire spine are obtained if findings suggestive of scoliosis or hyperkyphosis are also present (Figs. 699.10 and 699.11). In patients with normal plain films, traditional imaging studies included a bone scan with SPECT to diagnose a spondylolysis during the earliest stage of a stress reaction, prior to the formation of a stress fracture or an established pseudarthrosis. The radiation exposure from this test, though, is substantial—bone scans have 7-9 times the radiation dose of two-view plain films. In comparison, CT scans only carry 2 times the radiation dose of two-view plain films. The sensitivity of MRI magnets using STIR imaging is comparable to SPECT and led the authors of a systematic review to recommend this imaging modality in acute cases where plain films could not make a diagnosis over bone scans. MRI sequences will demonstrate inflammation associated with an acute spondylolysis while avoiding radiation exposure. A CT scan with thin cuts may provide additional information to establish the presence of a pars defect and may be indicated in chronic, refractory cases. MRI is also indicated in the presence of signs or symptoms of cauda equina or nerve root involvement.

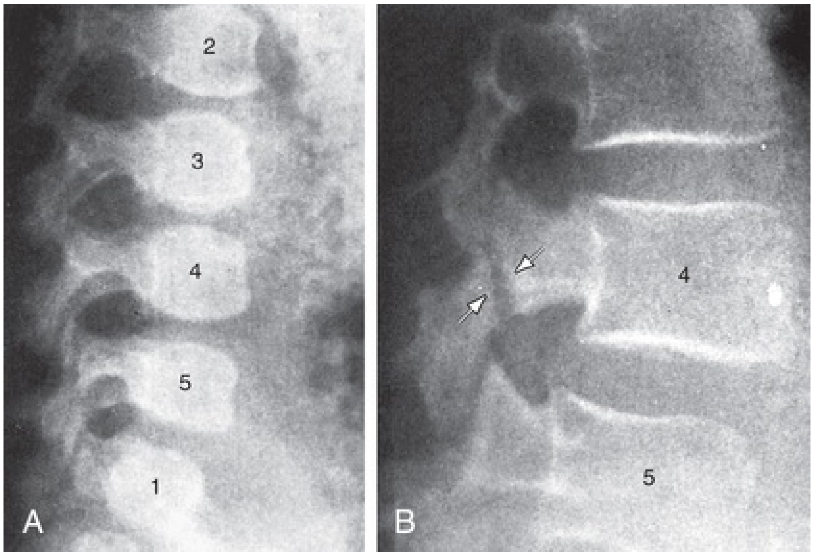

FIG. 699.10 **A,** Normal spine at 9 mo of age. **B,** Spondylolysis in the L4 vertebra at 10 yr of age. (From Silverman FN, Kuhn JP: *Essentials of Caffrey's pediatric X-ray diagnosis,* Chicago, 1990, Year Book Medical Publishers, p 94.)

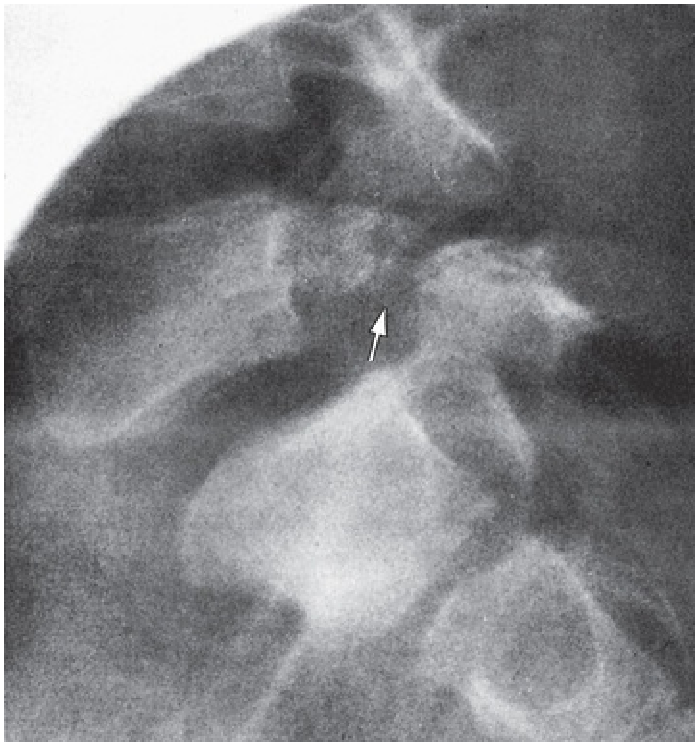

FIG. 699.11 Defect in the pars interarticularis *(arrow)* of the neural arch of L5 (spondylolysis) that has permitted the body of L5 to slip forward (spondylolisthesis) on the body of S1. (From Silverman FN, Kuhn JP: *Essentials of Caffrey's pediatric X-ray diagnosis,* Chicago, 1990, Year Book Medical Publishers, p 95.)

Treatment

The asymptomatic patient with **spondylolysis** requires no treatment. Patients with pain are treated initially by activity modification, physical therapy for core strengthening, and antiinflammatory medication. The use of a lumbosacral orthosis, which immobilizes the spine in slight flexion to decompress the posterior elements, may lead to a faster resolution of symptoms. This orthosis is typically worn for 3-4 mo. Participation in sports or other activities that exacerbate pain should be restricted until the symptoms have resolved.

Most patients experience resolution of their symptoms even though the spondylolysis heals in only a small number of patients. Surgery is offered for chronic, refractory back pain when conservative measures have failed. For those with spondylolysis at L5, a posterior spinal fusion from L5 to S1 is indicated as the mobility at this joint is limited relative to that observed at higher levels in the spine. For the infrequent cases in which the defect is at higher levels in the lumbar spine, techniques for repairing the pseudarthrosis without fusion are considered.

Recommendations for the management of **spondylolisthesis** depend on the age of the patient, the presence of pain or neurologic symptoms, and the degree of deformity. For low-grade lesions, the management is similar to that for spondylolysis. As progressive slippage may occur in a subset of skeletally immature patients, patients must be followed through skeletal maturity. Guidelines for the timing of follow-up, and whether or not to obtain routine radiographs at each follow-up, differ between individuals and institutions. The authors typically follow asymptomatic patients yearly with a standing lateral of the lumbosacral junction. Nonoperative management in minimally symptomatic or asymptomatic patients even with high-grade spondylolisthesis is safe and does not lead to significant problems. Additionally, delayed surgical treatment does not lead to worsened outcomes.

For low-grade slips with persistent symptoms despite nonoperative measures, an in situ posterior spinal arthrodesis is suggested. Additionally, patients with a more kyphotic slip angle have been shown to have poorer prognosis, although operative treatment did not significantly improve their outcome. The surgical approach for high-grade slips varies between surgeons and institutions. The main principle is to stabilize the unstable segment of the spine and avoid neurologic complications. The typical components of these complex procedures include (1) posterior decompression of the L5 and S1 nerve roots (laminectomy and takedown of pseudarthrosis), (2) instrumented posterior spinal fusion from L4 or L5 to S1 and occasionally the pelvis is included in the instrumentation, (3) discectomy at L5-S1 with placement of anterior column support (transforaminal cage or fibular allograft from sacrum to L5), and (4) reduction of the slippage by positioning the hips in extension or by an “instrumented reduction” utilizing the spinal implants. The risk of neurologic complications is higher when an instrumented reduction is attempted.

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699.7

Spine Infection

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Keywords

diskitis
Kingella kingeae

spondylitis
Staphylococcus aureus

Spondylitis, meaning inflammation of the vertebrae, is most commonly due to autoimmune or infectious processes. Both diskitis and vertebral osteomyelitis are causes of infectious spondylitis. The most common etiology of infectious spondylitis is from hematogenous spread of bacteria. Diskitis involves bacterial infection of the disc space and is generally seen in children younger than 5 yr of age; it is often associated with vertebral body osteomyelitis. In contrast, isolated osteomyelitis of the vertebral body most often occurs in older children and adolescents. Differences in the anatomic location of the infection relate to the vascular development of the spine. Patients in the younger age range have vascular channels between the vertebral end plate and the disc space, explaining the prevalence of diskitis with osteomyelitis. In older children, these channels have closed and the infection remains in the vertebra causing osteomyelitis.

Staphylococcus aureus is the most common organism causing spine infections. Other organisms include *Kingella kingae,* and less often group A streptococcus, and *Escherichia coli* . Rare causes of vertebral bone infection include tuberculosis, *Serratia marcescens* , brucellosis, and cat-scratch disease. Blood cultures have a sensitivity of only 30%. Percutaneous or open biopsy of the disc space is positive only 50–85% of the time; PCR is indicated for the diagnosis of *Kingella* .

Clinical Manifestations

A high index of suspicion is required to establish the diagnosis of infectious spondylitis. Patients may experience back pain, abdominal pain, fever, or malaise. Fever is less common, and may only be present in 30% of patients. Toddlers may develop a limp, or refuse to walk or sit. In an effort to reduce the pain associated with spinal motion, the child will hold the spine in a rigid position. There may also be a paraspinal muscle spasm. Local point tenderness over the affected spinous process is common. There may be a “list” or leaning of the trunk when the patient is viewed from the front or back, and from the side there may be a loss of lumbar lordosis. Neurologic manifestations are rare and if present suggest that an epidural abscess may be present.

Spine flexion compresses the anterior elements of the spine and will elicit an increase in pain. Asking a child to pick up an object from the ground is a simple way to elicit this provocative test.

While the white blood count may remain normal, the erythrocyte sedimentation rate is elevated in 80% of cases, and the C-reactive protein is also elevated. It is therefore important to order the appropriate laboratory studies in any patient demonstrating clinical symptoms.

Radiographic Evaluation

The earliest radiographic finding is loss of lumbar lordosis. The characteristic features on plain radiographs are disc space narrowing, or loss of disc height, and irregularity of the adjacent vertebral end plates. However, these findings do not develop until 2-3 wk after the onset of symptoms. The diagnosis may be established earlier using either a technetium bone scan or MRI; MRI is the most sensitive and specific imaging to diagnose osteomyelitis and to identify abscesses and/or neural compression.

Treatment

Once the diagnosis is suspected clinically, the treatment involves symptomatic care and empiric antistaphylococcal antibiotics. A first-generation cephalosporin (e.g., cefazolin) or semisynthetic antistaphylococcal penicillin (e.g., oxacillin) is recommended in areas where methicillin-resistant *S. aureus* is not prevalent. Clindamycin should be considered in areas where methicillin-resistant *S. aureus* is more common. Some areas of the world report increasing clindamycin resistance among both methicillin-resistant and methicillin-susceptible *S. aureus* isolates, leading to consideration of vancomycin or linezolid in these areas. Blood cultures should be obtained *prior* to the administration of antibiotics. The antibiotic agent may be modified if blood cultures are positive. Symptomatic care includes rest and analgesics, and a spinal orthosis may also be considered. The typical antibiotic course is from 4 to 6 wk, and data in osteomyelitis suggest that conversion from intravenous to oral agents may be acceptable after several days depending on the clinical course (see Chapter 704). A CT-guided needle biopsy of the disk space is usually reserved for patients who do not respond to empiric antibiotics. Surgical treatment is rarely required, and indications include establishing the diagnosis in patients who fail to respond to empiric antibiotics, and those in whom an abscess and/or neurologic involvement are identified.

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699.8

Intervertebral Disc Herniation/Slipped Vertebral Apophysis

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Keywords

laminotomy
spinal fusion

Apophysis

Intervertebral disc herniation is the result of a tear in the outer layer of the vertebral disc, called the annulus fibrosus, which then allows for protrusion of the inner nucleus pulposus. At times, a free fragment of disc can rupture and compress the nerve roots or spinal cord. Bulging of the annulus without rupture may also be observed, resulting in back pain and occasionally radicular symptoms. Symptoms are due to either direct mechanical compression or a local inflammatory response.

Slipped vertebral apophysis, also called a posterior ring apophysis separation, is due to an injury and is only found in the skeletally immature. A small fragment of bone from the posterior corner of the vertebral body apophysis avulses and may cause direct mechanical compression to the spinal cord or nerve root, similar to a disc herniation. (An apophysis is a normal outgrowth of bone with its own physis, or growth plate. Another example is the tibial tubercle.) Both disc herniations and ring apophysis separations can cause back pain, radicular symptoms (nerve root compression or irritation), or spinal cord compression.

Etiology

Predisposing activities for both conditions include heavy lifting, repetitive axial loading activities, and occasionally traumatic injury such as a fall. Approximately 30–60% of patients with symptomatic herniated discs have a history of a trauma or sports-related injury. Other associations include preexisting disc degeneration, congenital malformation, and genetic or environmental factors. There may be a potential association between disc degeneration and the herpes virus.

Clinical Manifestations

Symptoms of intervertebral disc herniation or slipped vertebral apophysis in adolescents are similar to adult herniated disc symptoms. The major complaint is back pain, present in nearly 90% of patients. Over 30% of patients complain of radicular symptoms, or radiating sciatic-type pain into the legs. The back pain is often made worse by coughing, a Valsalva maneuver, or sitting. Pain may be relieved by standing or back extension, which increases the disc space between vertebral bodies. Inquire about weight loss, fever, or other constitutional symptoms to rule out an infectious or neoplastic etiology.

On physical examination, both paraspinal muscle spasm and a generalized spinal stiffness are common. Patients may lean toward the unaffected side to increase the size of the affected neural foramen thereby partially relieving symptoms. This results in a reactive scoliosis—not a true spinal curve—which improves with symptom resolution. While overt signs of neurologic involvement are absent in most patients, a positive straight leg raise test, causing radicular pain to shoot down the affected leg, is usually present. Pain is also worsened by spinal flexion.

It is critical to perform a full neurologic evaluation. Evaluate sensation to light touch, pinprick, and proprioception. Check muscle strength and reflexes. It is critical to evaluate for perineal numbness, or saddle anesthesia. This finding, combined with changes in bowel or bladder function, which is also critical to specifically discern in the history, is indicative of cauda equina syndrome, a surgical emergency in which the nerve roots at the caudal end of the spinal cord are compressed or damaged.

Radiographic Evaluation

Radiographs often show loss of lumbar lordosis, which is due to muscle spasm, and sometimes a mild lumbar scoliosis. Other radiographic findings include degenerative changes and a loss of intervertebral disc height. MRI is the best study to establish the diagnosis of a disc herniation. CT is especially helpful to visualize a partially ossified fragment associated with a slipped apophysis.

Treatment

The initial treatment is nonoperative in the vast majority of patients—even if symptoms or findings of radiculopathy are observed. Treatment focuses on rest, activity modification, NSAIDs, and physical therapy. An orthosis may provide additional symptomatic relief. Complete bed rest is not recommended. Epidural steroid injection (ESI) may be discussed with patients after approximately 6 wk of symptomatic treatment if symptoms persist, though the evidence is not yet definitive. However, in our opinion, if patients elect to undergo an ESI, they should not have more than a single injection if the first did not provide any relief. Clinical experience has demonstrated that multiple injections are no more likely to provide relief than a single injection, and expose patients to additional risks of infection, scarring, and neural injury. If a patient experiences substantial relief from an ESI and has a later recurrence of symptoms, consideration may be given for a repeat injection after performing a complete physical exam and ruling out any new pathology.

Surgical treatment should be considered when nonoperative measures have failed or when a profound neurologic deficit such as cauda equina syndrome is present or evolving. Unfortunately, children and adolescents respond less favorably to nonoperative therapy compared with adults, and a significant percentage will require surgical intervention. While patients with disc herniation may improve with reduction in the local inflammatory response around the nerve root, and also as the disc material loses water volume and shrinks which eliminates mechanical compression, patients with symptomatic ring apophyseal separations have a bony fragment causing their symptoms and are unlikely to improve spontaneously.

The surgical technique involves removing a small area of the lamina via a posterior approach, called a *laminotomy* , which allows exposure of the neural elements and underlying disc. Any loose fragments are removed. A bulging disc may also be opened surgically to decompress the area compressing the neural elements, although a complete discectomy is inadvisable. The surgical approach is similar in the case of a slipped vertebral apophysis, in which fragments of bone and cartilage must also be removed. This often requires a bilateral laminotomy to completely address the pathology.

The initial results are excellent in the majority of patients. However, literature suggests that up to one-third of patients may have recurrent herniations and resultant symptoms of back or leg pain at longer-term follow-up. These recurrences are initially treated nonoperatively. A spinal fusion may be required when there is instability due to a spondylolisthesis or other etiology.

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699.9

Tumors

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Keywords

aneurysmal bone cyst
eosinophilic granuloma
Ewing sarcoma
ganglioneuroma
osteoid osteoma
osteoblastoma
osteosarcoma

Back pain may be the most common presenting complaint in children who have a tumor involving the vertebral column or the spinal cord. Other associated symptoms may include weakness of the lower extremities, scoliosis, and loss of sphincter control. The majority of tumors are benign (see Chapter 528), including osteoid osteoma, osteoblastoma, aneurysmal bone cyst, and eosinophilic granuloma. Malignant tumors involving the vertebral column may be osseous, such as osteosarcoma or Ewing sarcoma. They may involve the spinal cord and sympathetic or parasympathetic nerves, in cases of ganglioneuroma, ganglioneuroblastoma, and neuroblastoma. Tumors from other primary sites can also metastasize to the spine.

In addition to high-quality plain radiographs, useful imaging modalities include bone scans, which help with localization and identification of other lesions; MRI, which is helpful to identify soft tissue extension and neurologic compression; and CT, which provides excellent bony detail.

A biopsy is usually required to establish the diagnosis. Treatment of tumors of the spinal column may require a multidisciplinary approach. These cases should ideally be managed in centers with experience in the care patients with these lesions.

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CHAPTER 700

The Neck

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700.1

Torticollis

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Keywords

Grisel syndrome
metatarsus adductus
plagiocephaly
Sandifer syndrome

Torticollis, literally meaning “twisted neck,” is not a diagnosis but rather a clinical manifestation of a variety of underlying conditions (Table 700.1). Common names associated with this condition include “wry-neck” and “cock-robin” deformity.

Table 700.1

Differential Diagnosis of Torticollis

Congenital

- Muscular torticollis
- Positional deformation
- Hemivertebra (cervical spine)
- Unilateral atlanto-occipital fusion
- Klippel-Feil syndrome
- Unilateral absence of sternocleidomastoid
- Pterygium colli

Trauma

- Muscular injury (cervical muscles)
- Atlanto-occipital subluxation
- Atlantoaxial subluxation
- C2-3 subluxation
- Rotary subluxation
- Fractures

Inflammation

- Cervical lymphadenitis
- Retropharyngeal abscess
- Cervical vertebral osteomyelitis
- Rheumatoid arthritis
- Grisel syndrome (nontraumatic subluxation of the atlantoaxial joint due to local inflammation)
- Upper lobe pneumonia

Neurologic

- Visual disturbances (nystagmus, superior oblique or lateral rectus paresis)
- Dystonic drug reactions (phenothiazines, haloperidol, metoclopramide)
- Cervical cord tumor
- Posterior fossa brain tumor
- Syringomyelia
- Wilson disease
- Dystonia musculorum deformans

Other

- Acute cervical disk calcification
- Sandifer syndrome (gastroesophageal reflux, hiatal hernia)
- Benign paroxysmal torticollis
- Bone tumors (eosinophilic granuloma)
- Soft tissue tumor
- Psychogenic

Congenital Muscular Torticollis

The most common diagnosis during infancy is congenital muscular torticollis (CMT). A contracture of the sternocleidomastoid muscle results in a **tilting** of the head and neck **ipsilaterally** toward the side of the contracted muscle with head **rotation contralaterally** , toward the opposite side. In most cases (75%), the right sternocleidomastoid muscle is involved, causing the patient's face and chin to point to the left side.

CMT is hypothesized to result from an intrauterine deformation or compression problem and is more common in first pregnancies. CMT may be associated with the presence of a palpable mass of fibrous tissue within the substance of the sternocleidomastoid muscle in approximately 50% of cases. The mass disappears during infancy and is eventually replaced by a fibrous band.

Information from muscle biopsies and magnetic resonance imaging has led to the hypothesis that sternocleidomastoid muscle injury, resulting from compression or stretch, may create localized ischemia resulting in fibrosis and subsequent contracture—essentially an intramuscular compartment syndrome. In other more rare cases, the condition can result from hereditary muscle aplasia.

Associated findings with CMT include plagiocephaly, facial asymmetry, and positional musculoskeletal deformities, such as metatarsus adductus (15%) and calcaneovalgus feet. Hip dysplasia may be identified in 8–20% of affected patients. Because of the association with hip dysplasia, it is worthwhile to obtain either an ultrasound scan at 6 wk of age or a plain radiograph of the pelvis at 4-6 mo of age even if the physical exam is normal.

A stretching program is successful in >90% of patients with congenital muscular torticollis, especially when treatment is started within the first 3 mo of life. While firm guidelines for imaging the cervical spine have not been established, consideration may be given to obtaining anteroposterior and lateral radiographs of the cervical spine when the typical clinical features associated with congenital muscular torticollis are absent or if the deformity does not respond to the stretching treatment, as torticollis in infants may also be due to **congenital vertebral anomalies** .

Surgical release of the sternocleidomastoid is considered in patients with persistent deformity after failure of conservative treatment. The muscle may be released at its insertion on the clavicle (unipolar release) or at both its origin and insertion (bipolar release). There is no agreement as to the most appropriate time for the surgical release, but surgical treatment is typically delayed until after 18 mo of age. Some even suggest waiting until the child is approaching school age. While range of motion can be improved following surgical release even during the teenage years, remodeling of facial asymmetry and plagiocephaly may be less predictable in patients older than infancy. Surgical management results in satisfactory function and acceptable cosmesis in more than 90% of patients; however, with early diagnosis and treatment, surgery should only be required in a minority of cases.

Other Causes of Torticollis

The evaluation of torticollis becomes more complex when the typical findings associated with CMT are absent, the usual clinical response is not observed, or when the deformity presents at a later age. In addition to a careful history and physical examination, consultation with an ophthalmologist and neurologist will be helpful. Plain radiographs should be obtained, and an MRI of the brain and cervical spine will be required in a subset of cases.

The **differential diagnosis** is extensive (see Table 700.1). Neurogenic torticollis is uncommon and results from tumors of the posterior fossa or brainstem, syringomyelia, and Arnold-Chiari malformation. In addition to the neurologic examination, MRI of the brain and cervical spine is required to establish the diagnosis. **Paroxysmal torticollis** of infancy is also uncommon and may be due to vestibular dysfunction. Episodes may last from minutes to days, and the side of the deformity may alternate. The condition is self-limiting, and no specific treatment is required other than ruling out other treatable causes. Torticollis may also be seen in association with discitis or vertebral osteomyelitis; juvenile idiopathic arthritis; cervical disk calcification; visual problems, such as congenital nystagmus or paresis of the superior oblique or lateral rectus muscle; benign or malignant bone tumors; and in patients with cerebral palsy and chronic gastroesophageal reflux (Sandifer syndrome).

Atlantoaxial Rotatory Displacement

Atlantoaxial rotatory displacement (AARD) represents a spectrum of rotational malalignments from subluxation to frank dislocation between the atlas (C1) and the axis (C2) and may best be described as a pathologic “stickiness” in the arc of joint motion. In some cases, there is fixed malalignment between C1 and C2 (atlantoaxial rotary fixation), which results in a 50% loss of cervical rotation. The malalignment is often reducible initially but may become irreducible and fixed after weeks to months. Therefore, prompt diagnosis and treatment are essential.

AARD may be diagnosed after infection or inflammation of the tissues of the upper airway, neck, or pharynx (**Grisel syndrome**), following minor traumatic injuries, and as a complication of surgical procedures in the oropharynx, ear, or nose. The diagnosis is established using a dynamic rotational computerized tomography scan, in which axial images are obtained through the upper cervical spine with the head rotated maximally toward both the right and the left. The patient must be relaxed and comfortable, and some clinicians may choose to treat empirically if the clinical findings are characteristic, reserving advanced imaging study for patients who have not responded clinically. If the patient is seen within a few days of the onset of symptoms, then a trial of analgesics and a soft collar may be attempted. Patients with symptoms for more than a week are often admitted to the hospital for analgesia, muscle relaxants, and a period of cervical traction. If this fails to reduce the displacement, halo traction may be attempted. If the joint can be reduced, patients are typically immobilized for at least 6 wk in a halo vest. Patients with a longstanding fixed deformity may require a posterior atlantoaxial fusion to stabilize the articulation.

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700.2

Klippel-Feil Syndrome

R. Justin Mistovich, David A. Spiegel

Keywords

Duane anomaly
scoliosis
Sprengel's deformity
Wildervanck syndrome

Klippel-Feil syndrome (KFS) includes the classic triad of a low posterior hairline, short neck, and decreased cervical range of motion (Fig. 700.1). However, these clinical findings are present in <50% of patients with KFS. Limited cervical motion may be the most common finding, present in 64.5% of patients, while only 9.7% of patients had all three findings. Patients have a congenital fusion (failure of segmentation) of one or more cervical motion segments at the cranio-cervical junction or in the subaxial spine, and often have additional associated congenital anomalies of the cervical spine and other organ systems.

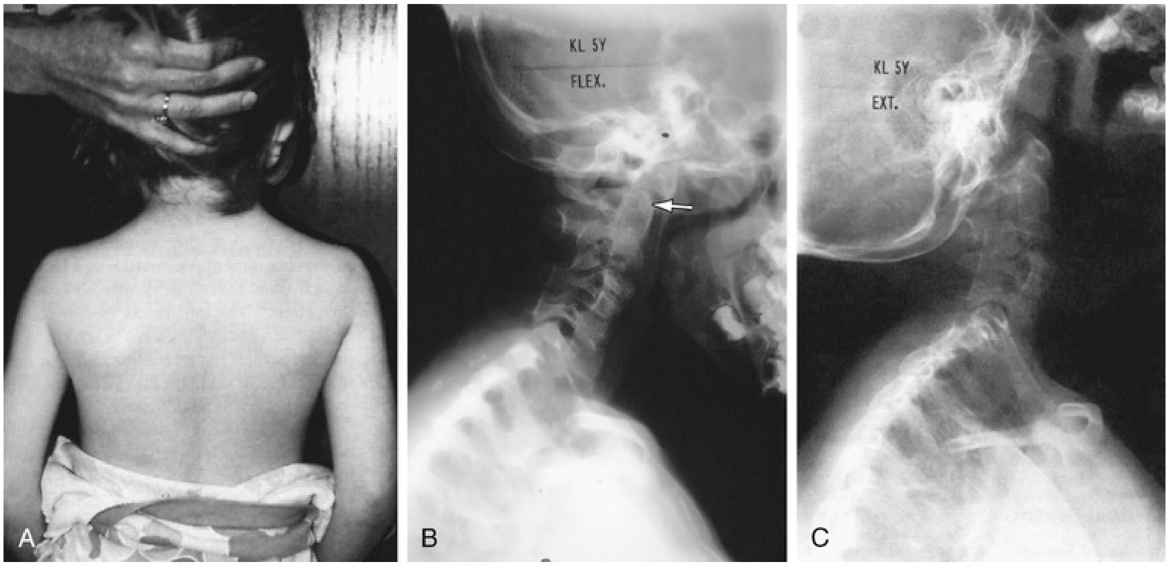

FIG. 700.1 Clinical picture of a 5 yr old with Klippel-Feil syndrome. **A,** Note short neck and low hairline. **B** and **C,** Radiographs of the cervical spine (**B** , flexion; **C** , extension) demonstrate congenital fusion and evidence of spinal instability *(arrow)* . (From Drummond DS: Pediatric cervical instability. In Weisel SE, Boden DS, Wisnecki RI, editors: *Seminars in spine surgery* , Philadelphia, 1996, WB Saunders, pp 292–309.)

Additional findings in the cervical spine include occipitocervical synostosis, odontoid abnormalities, and basilar invagination (proximal migration of the C2 vertebra). Other associations include Sprengel's deformity (congenital elevation of the scapula), congenital scoliosis, genitourinary anomalies (25–35%), sensorineural hearing loss (5%), and congenital heart disease (5–10%). Renal abnormalities include double collecting systems, renal aplasia, and horseshoe kidney. The cervical spine anomalies seen in patients with Klippel-Feil syndrome may also be seen with Goldenhar syndrome, Mohr syndrome, VACTERL syndrome, and fetal alcohol syndrome.

Clinical problems are more common in adults and include pain or neurologic symptoms from spinal instability or stenosis. The incidence has been estimated at 1 : 40,000-42,000 births. However, not every patient with the condition is diagnosed.

Etiology and Classification

Several candidate genes have been proposed for patients with KFS. One recent study identified a mutation affecting RNA polymerase via whole exome sequencing. Other studies report mutations in the *MEOX1*, *GDF6*, or *GDF3* genes, which all affect somite development.

Traditionally, the classification of Klippel-Feil syndrome has been based on the anatomical distribution of the cervical fusions and the kinematics of the cervical spine in flexion and extension. As more information regarding the genetics of this condition has become available, the classification system has incorporated these changes. **KFS1** involves a fusion at C1 with or without a more caudal fusion level and is associated with severe anomalies. **KFS2** has a fusion of C2 and C3 with or without a more caudal fusion. **KFS3** has an isolated fusion caudal to C1 and C2/3. **KFS4** is synonymous with Wildervanck's syndrome, which involves congenital cervical synostosis associated with hearing loss and Duane anomaly (a rare congenital type of strabismus).

Clinical Presentation

Klippel-Feil syndrome is present at birth but does not usually become clinically apparent until the 2nd or 3rd decades. Patients at this point present with pain, loss of motion, or neurologic symptoms. Given that the same physiologic stresses are applied to a smaller number of mobile spinal segments, patients are at risk for the development of hypermobility and often instability, especially at motion segments adjacent to the fused vertebrae. Weakness or clumsiness consistent with **myelopathy** may be the presenting symptoms.

Physical Examination

A comprehensive musculoskeletal and neurologic examination is required, given associated anomalies in the musculoskeletal and visceral systems. Scoliosis is present in more than 50% of patients with Klippel-Feil syndrome, and congenital anomalies may be identified in other regions of the spine as well. The neurological exam focuses on identifying any signs of radiculopathy or myelopathy. Spinal cord compression, or myelopathy, may result from stenosis or instability. A physical exam will demonstrate upper motor neuron signs such as hyperreflexia, Hoffman's sign, Babinski's sign, and sustained clonus, with more than three beats considered pathological. Nerve root compression, or radiculopathy, may be due to stenosis and is identified by weakness or decreased sensation in the muscles or dermatomes served by a particular nerve root.

Radiologic Investigation

Initial radiological evaluation should include an anteroposterior, lateral, and oblique view of the cervical spine. The characteristic finding is a congenital fusion of two or more vertebrae resulting from a failure of segmentation; however, multiple vertebrae may be involved. Since congenital anomalies may exist in more than one region of the spine, radiographs of the thoracic and lumbosacral spine should be routinely obtained. Flexion-extension lateral views of the cervical spine may help to identify segments with excessive motion. Referral to an orthopedist is appropriate once the diagnosis is established. Patients with this condition usually undergo computerized tomography and magnetic resonance imaging of the spine to accurately characterize the bony anomalies and also identify any coexisting neural pathology. A renal ultrasound is routinely obtained to identify associated anomalies (e.g., duplicated collecting system, absence of a kidney, horseshoe kidney). Additional imaging, such as echocardiogram, may identify cardiovascular anomalies, mainly septal defects.

Audiologic evaluation is indicated for patients diagnosed with Klippel-Feil syndrome; hearing impairment may be identified in up to one-third of affected patients.

Treatment

The three patterns commonly associated with instability include: (1) C2/C3 fusion with occipitocervical synostosis; (2) extensive fusion over multiple levels with an abnormal occipitocervical junction; and (3) two fused segments separated by an open joint space.

Pain may often be controlled by activity restriction, intermittent immobilization, or other nonoperative modalities. Patients who are chronically symptomatic, have instability with positive neurologic symptoms or exam findings, or are felt to be at increased risk for neurologic deterioration are candidates for surgical treatment. Operative interventions include decompression of nerve roots or the spinal cord itself or spinal fusion to address spinal instability.

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700.3

Cervical Anomalies and Instabilities

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Keywords

Down syndrome
ligamentous laxity
occipitalization

Anomalies of the craniovertebral junction or lower cervical spine may be seen in isolation or in association with other conditions. These include genetic syndromes, skeletal dysplasias, connective tissue disorders, and metabolic disorders. These anomalies may be congenital or developmental. While most anomalies remain asymptomatic and undiagnosed, a subset will place the patient at risk of neurologic injury as a result of instability or spinal canal stenosis. The most frequently encountered causes of cervical spine instability in children can be categorized etiologically (Table 700.2). Patients with conditions that have known associations involving the cervical spine should have a complete evaluation, including history, physical examination, and initial radiographic examination.

Table 700.2

Causes of Pediatric Cervical Instability

CAUSES	SUBTYPES
Congenital	Cranio-occipital defects (occipital vertebrae, basilar impression, occipital dysplasias, condylar hypoplasia, occipitalized atlas)
	Atlantoaxial defects (aplasia of atlas arch, aplasia of odontoid process)
	Subaxial anomalies (failure of segmentation and/or fusion, spina bifida, spondylolisthesis)
	Syndromic disorders (e.g., Down syndrome, Klippel-Feil syndrome, 22q11.2 deletion syndrome, Larsen syndrome, Marfan syndrome, Ehlers-Danlos syndrome)
Acquired	Trauma
	Infection (pyogenic/granulomatous)
	Tumor (including neurofibromatosis)
	Inflammatory conditions (e.g., juvenile rheumatoid arthritis)
	Osteochondrodysplasias (e.g., achondroplasia, diastrophic dysplasia, metatropic dysplasia, spondyloepiphyseal dysplasia)

	Storage disorders (e.g., mucopolysaccharidoses)
	Metabolic disorders (rickets)
	Miscellaneous (including osteogenesis imperfecta, post-surgery)

Patients may complain of neck pain or neurologic symptoms. Radicular symptoms include pain, weakness, and numbness within the distribution of a nerve root. Myelopathic symptoms include generalized weakness, gait disturbance, increased fatigue with ambulation, upper extremity clumsiness, and abnormalities in bowel or bladder function. Physical exam findings may include restricted cervical mobility, cervical tenderness or spasm, and neurologic abnormalities.

While the upper cervical spine has limited flexion and extension, roughly 50% of cervical rotation occurs at the atlantoaxial (C1-2) joint. The main constraints to motion in the upper cervical spine are soft tissue (ligaments and joint capsules) rather than osseous. Excessive motion or instability may result in a compressive injury to the brainstem or spinal cord. Anomalies at the craniovertebral junction include congenital fusion of the occiput to C1 (occipitalization of the atlas), basilar impression and invagination (proximal migration of the C2 vertebra as the result of softening of the bones and with normal bones, respectively), and accessory vertebrae. Aplasia or hypoplasia of the atlas or the axis may result in atlantoaxial instability.

OS Odontoideum

Os odontoideum is the most common anomaly of the odontoid, or dens, and radiographically appears as an oval-shaped, well-corticated bony ossicle that is positioned cephalad to the body of the axis. There is a discontinuity in the mid-portion of the dens, and the upper portion of the dens moves with the ring of C1, narrowing the space available for the spinal cord, placing the spinal cord at risk for injury. The body of the dens is mesenchymal in origin and originates from the first cervical vertebra. Subsequent separation allows it to then fuse with the C2 vertebra. It is formed by two separate ossification centers, one on either side of the midline that eventually fuse and are visible at birth. There are three etiologies that have been proposed: (1) the os odontoideum represents a fracture nonunion of the dens, (2) the os odontoideum represents damage to the epiphyseal plate that has occurred in the first year of life, or (3) the os odontoideum represents a congenital malformation of the dens itself. The most widely accepted etiology is that a fracture of the dens occurs and subsequently develops a nonunion.

The symptoms and physical findings vary with the location of the compression or impingement. Fielding et al, in the largest published series (35 patients) reported an average age at presentation of 18.9 yr. The most common presenting symptom was neck pain followed by upper and lower limb paresthesia. Torticollis, neck stiffness, gait disturbance, and headaches were uncommon symptoms at presentation. Neurological examination may reveal a combination of both upper and lower motor neuron signs. Some patients are completely asymptomatic with the anomaly noted incidentally on a lateral cervical spine radiograph.

The radiographic evaluation begins with anteroposterior, lateral, and open mouth odontoid views, which may be supplemented by flexion and extension lateral radiographs. CT provides the best bony detail and is useful in defining each anomaly. MRI, including dynamic images in flexion and extension, is best for evaluating neurologic impingement. Symptomatic treatment may be helpful; however, patients with cervical instability and/or neurologic impingement require surgical decompression and stabilization.

Down Syndrome

Ligamentous hyperlaxity is a characteristic feature of Down syndrome and may result in hypermobility or instability at the occipitoatlantal or the atlantoaxial joints in 10–30% of patients (see Chapter 98.2). These patients may also have coexisting congenital or developmental anomalies of the cervical spine, such as occipitalization of the atlas, atlantal arch hypoplasia, basilar invagination, and os odontoideum.

While the natural history of this spectrum of pathology remains unknown, a subset of patients may develop or be at significant risk of developing neurologic dysfunction. The clinical diagnosis of neurologic dysfunction may be challenging, with subtle findings, such as decreased exercise tolerance and gait abnormalities, including increased tripping or falling, presenting as the earliest signs of myelopathy. In addition to a neurologic examination focusing on the presence of long tract signs, imaging studies including plain films and MRI are required to evaluate patients suspected of having neurologic involvement.

All patients require screening by history and physical examination (at regular intervals) and at least a single series of cervical spinal radiographs, including a lateral view in flexion and extension. Plain radiographs are the preliminary imaging modality used to evaluate for hypermobility or instability. The atlanto-dens interval (ADI) is used to evaluate the relationship between C1 and C2 (atlantoaxial joint) and is measured as the space between the dens and the anterior ring of C1 on lateral radiographs in neutral, flexion, and extension (Fig. 700.2). While the ADI should be 3 mm or less in the population without Down syndrome, a normal ADI in children with Down syndrome is <4.5 mm. Hypermobility is diagnosed as an ADI between 4.5 and 10 mm, while an ADI >10 mm represents instability and carries a significant risk of neurologic injury. MRI is indicated to detect neurologic involvement in patients with radiographic instability.

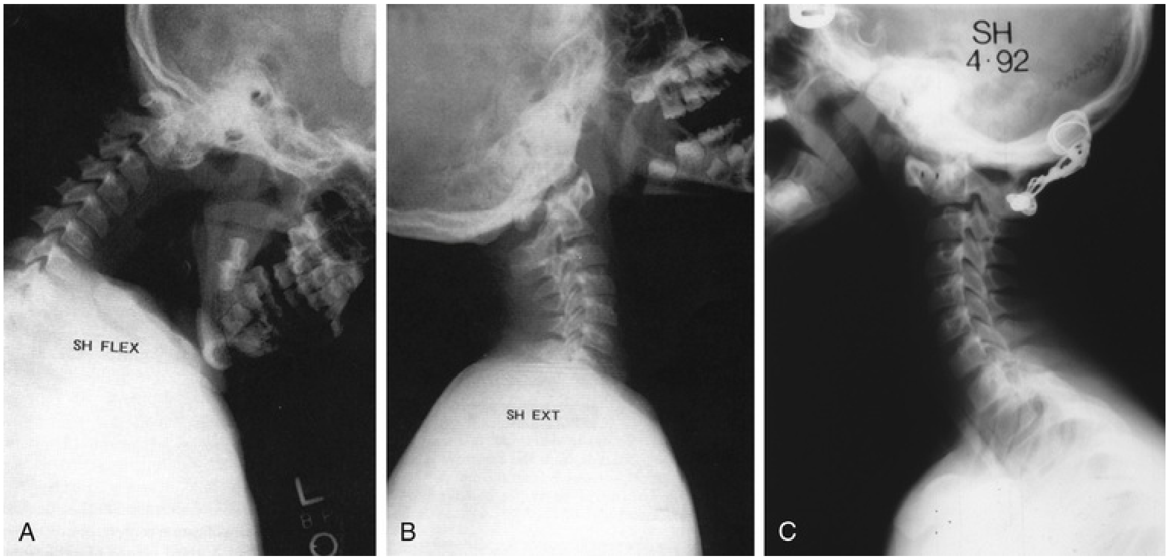

FIG. 700.2 Flexion **(A)** and extension **(B)** radiographs of a case of Down syndrome demonstrating atlanto-occipital hypermobility and subluxation. **C,** Instability and symptoms were relieved by an occipitoaxial arthrodesis.

Recommendations for surveillance of the cervical spine in children with Down syndrome remain varied. While routine clinical evaluations, including a neurologic examination, should be performed, the indications for repeated imaging studies in the absence of clinical symptoms or findings have not been defined. Surveillance helps to define the most appropriate level of physical activity and to identify the small subset of those with either progressive hyperlaxity or instability. Although the specific recommendations vary between states, both clinical and radiographic screenings are also required prior to participation in the Special Olympics. Patients with normal radiographs who are also neurologically normal may be allowed to participate in full activity. Those who are diagnosed with hypermobility may be restricted from contact sports and other high-risk activities that increase the risk of trauma to the cervical spine. Patients with C1-2 instability with or without neurologic findings are candidates for an atlantoaxial fusion. The risks of a major complication are extremely high for a posterior cervical fusion in this population and include death, neurologic deterioration, and pseudarthrosis with or without graft resorption.

Although hypermobility at the occipito-atlantal joint is present in >50% of children with Down syndrome, most patients do not develop instability or neurologic symptoms. The relationships at this articulation are difficult to measure reliably on plain radiographs. An MRI in flexion and extension is required to evaluate any questionable radiographic findings, especially in the presence of clinical symptoms. Involvement of the subaxial spine is less common and is typically encountered in the adult population of patients with Down syndrome. Degenerative changes or instability may result in pain, radiculopathy, and/or myelopathy.

22Q11.2 Deletion Syndrome

The chromosome abnormality deletion of 22q11.2 is a common genetic syndrome, with an overall prevalence of 1 in 5,950 births and encompasses a wide spectrum of abnormalities. There are characteristic facial features, cleft palate, and cardiac anomalies. Cervical spine anomalies are also common phenotypic features of this syndrome.

At least one developmental variation of the occiput or cervical spine is noted in all patients. The occipital variations observed include platybasia, an abnormal flattening of the base of the skull, and basilar impression. Variations in anatomy of C1 include dysmorphic shape, an open posterior arch, and occipitalization, while axis variations include a dysmorphic dens and “C2 swoosh” (upswept lamina and posterior elements). A range of cervical vertebral fusions is noted in these patients, the most common being at the C2-3 level. Increased segmental motion is commonly observed but symptomatic instability is quite uncommon. With frequent occurrence of upper cervical spine anomalies in 22q11.2 deletion syndrome patients (Fig. 700.3), advanced imaging of the upper cervical spine and regular follow-up of patients to clarify their clinical course is recommended.

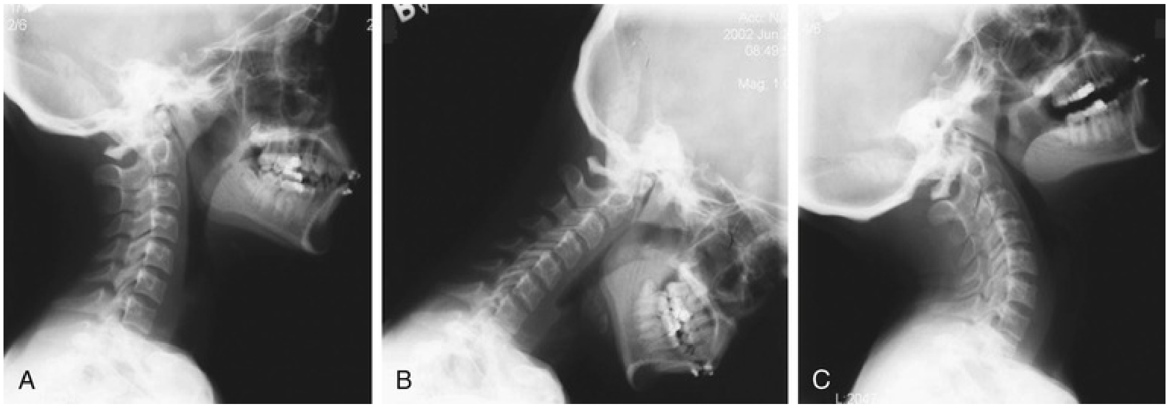

FIG. 700.3 Radiographs of the cervical spine in a child with 22q11.2 deletion syndrome showing evidence of platybasia, occipitocervical, and atlantoaxial instability. **A,** Neutral radiograph. **B,** Flexion. **C,** Extension. (From Drummond DS: Pediatric cervical instability. In Weisel SE, Boden SD, Wisnecki RI, editors: *Seminars in spine surgery* . Philadelphia, 1996, WB Saunders, pp 292–309.)

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CHAPTER 701

The Upper Limb

Robert B. Carrigan

Shoulder

The shoulder is a ball-and-socket joint similar to the hip; however, there are several anatomic differences between the two. The shoulder is a very shallow joint compared with the hip and is thus more prone to dislocation. In addition, the shoulder range of motion (ROM) is much greater than that of the hip. This is due to the size of the humeral head relative to the glenoid, as well as to the presence of scapulothoracic motion. The shoulder positions the hand along the surface of a theoretical sphere in space, with its center at the glenohumeral joint.

Sprengel Deformity

Sprengel deformity, or congenital elevation of the scapula, is a disorder of development that involves a high scapula and limited scapulothoracic motion. The scapula originates in early embryogenesis at a level posterior to the 4th cervical vertebra, but it descends during development to below the 7th cervical vertebra. Failure of this descent, either unilateral or bilateral, is the Sprengel deformity. The severity of the deformity depends on the location of the scapula and associated anomalies. The scapula in mild cases is simply rotated, with a palpable or visible bump corresponding to the superomedial corner of the scapula in the region of the trapezius muscle. Function is generally good. In moderate cases, the scapula is higher on the neck and connected to the spine with an abnormal omovertebral ligament or even bone. Shoulder motion, particularly abduction, is limited. In severe cases, the scapula is small and positioned on the posterior neck, and the neck may be webbed. The majority of patients have associated anomalies of the musculoskeletal system, especially in the spine, making spinal evaluation important.

Treatment

In mild cases, treatment is generally unnecessary, although a prominent and unsightly superomedial corner of the scapula can be excised. In more severe cases, surgical repositioning of the scapula with rebalancing of parascapular muscles can significantly improve both function and appearance.

Congenital Pseudoarthrosis of the Clavicle

The clavicle is a tubular S-shaped bone that articulates with the sternum and acromion. It acts as a strut to keep the shoulder from protracting forward. Congenital pseudoarthrosis of the clavicle is a failure of the two primary ossification centers of the clavicle to fuse during embryogenesis (Fig. 701.1). The condition presents exclusively on the right side and may be confused for an acute clavicle fracture sustained during birth. A thorough history and physical exam will help to distinguish between the two conditions. Both a birth-related clavicle fracture and a congenital pseudoarthrosis present with a bump or prominence over the midclavicle. The child with a birth-related clavicle fracture will have tenderness to palpation on exam; the parents may also report that the child is fussy with feeding and changing. Congenital pseudoarthrosis of the clavicle will be painless on exam. Radiographically the congenital pseudoarthrosis clavicle will have to rounded edges at the midportion with signs of hypertrophy.

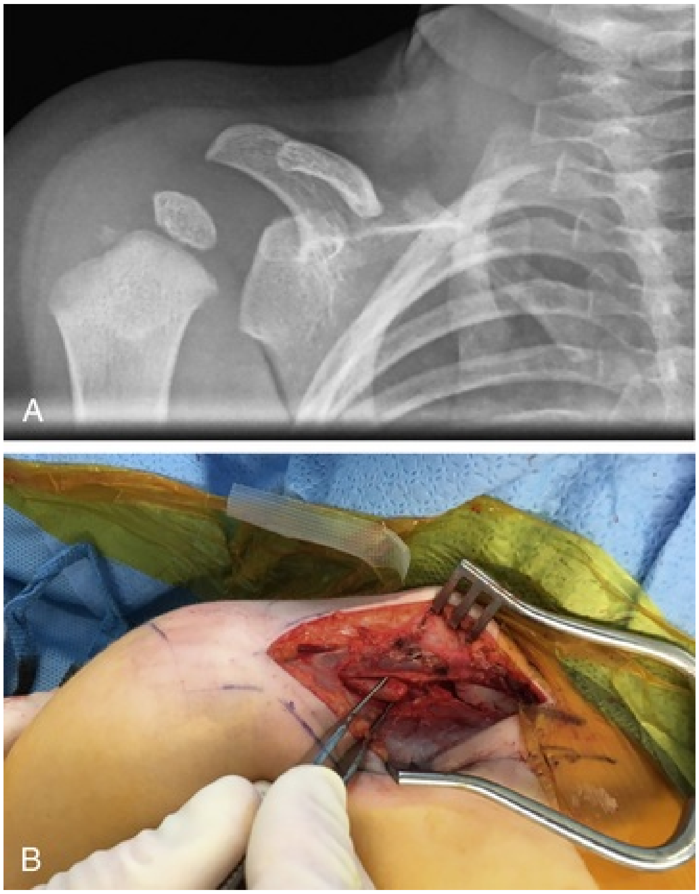

FIG. 701.1 **A,** Radiograph of congenital pseudoarthrosis of the clavicle. **B,** Intraoperative photo of pseudoarthrosis of the clavicle.

Treatment

Treatment of congenital pseudoarthrosis of the clavicle is varied, without a clear consensus. Some advocate for operative treatment, citing concerns for vascular and neurologic impingement of the clavicle on the brachial plexus and subclavian vessels, others advocate for observation and only considering operative treatment in symptomatic cases.

The operative treatment of congenital pseudoarthrosis of the clavicle consists of opening the pseudoarthrosis site, preserving the periosteum, debriding the hypertrophic ends, bone grafting, and stabilization.

Elbow

The elbow is the most congruent joint in the body. The stability of the elbow is imparted via this bony congruity, as well as through the medial and radial collateral ligaments. Where the shoulder positions the hand along the surface of a theoretical sphere, the elbow positions the hand within that sphere. The elbow allows extension and flexion through the ulnohumeral articulation and pronation and supination through the radiocapitellar articulation.

Panner Disease

Panner disease is a disruption of the blood flow to the articular cartilage and subchondral bone to the capitellum (Fig. 701.2). It typically occurs in boys between the ages of 5 and 13 yr. Presenting symptoms include lateral elbow pain, loss of motion, and, in advanced cases, mechanical symptoms of the elbow (loose bodies).

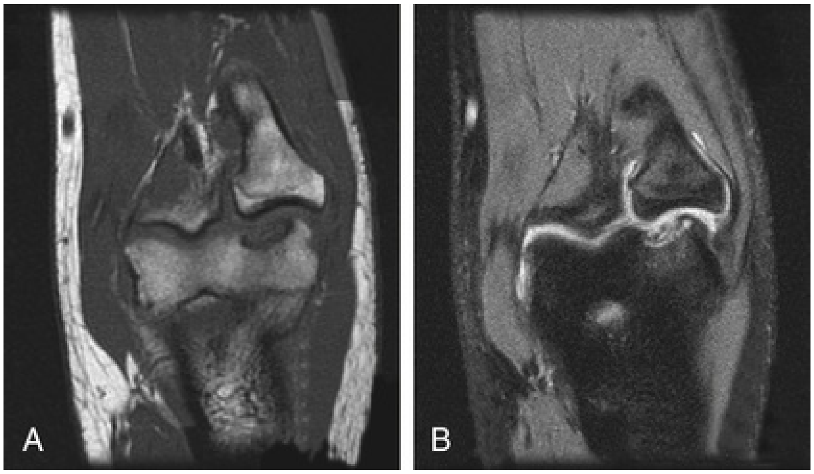

FIG. 701.2 T1 **(A)** and T2 **(B)** coronal MRI images of the elbow depicting Panner disease of the elbow.

The mechanism of injury can be impaction or overloading of the joint, as seen with sports such as gymnastics and baseball. It can also be idiopathic. Radiographs of the elbow may be normal, but they may also show a small lucency within the subchondral bone of the capitellum. MRI is the study of choice to evaluate a suspected capitellar lesion. MRI can demonstrate the extent of the involvement in the subchondral bone, as well as the integrity of the cartilage of the articular surface.

Treatment

Treatment is typically conservative. Rest, activity modification, and patient education are initial treatment options. In cases where the articular cartilage fragments and loose bodies form, arthroscopy of the elbow is warranted to remove the loose bodies. When the cartilage defect in the capitellum is large and symptomatic, procedures to restore the articular cartilage may be considered. These procedures include drilling of the subchondral bone (microfracture) to promote scar cartilage and osteochondral autograft transplantation (OATS).

Radial Longitudinal Deficiency

Radial longitudinal deficiency of the forearm comprises a spectrum of conditions and diseases that result in hypoplasia or absence of the radius (Table 701.1). This process was formerly referred to as *radial club hand*, but the name has been changed to *radial longitudinal deficiency,* which better characterizes the condition. Clinical characteristics consist of a small, shortened limb with the hand and wrist in excessive radial deviation. Partial or complete absence of the radial structures of the forearm and hand are observed (Fig. 701.3).

Table 701.1

Syndromes Commonly Associated With Radial Deficiency

SYNDROME	CHARACTERISTICS
Holt-Oram syndrome	Heart defects, most commonly atrial septal defects
Thrombocytopenia absent radius	Thrombocytopenia present at birth but improves over time
VACTERL association	Vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula, esophageal atresia, renal defects, radial dysplasia, lower limb abnormalities
Fanconi anemia	Aplastic anemia not present at birth, develops about 6 yr of age; fatal without bone marrow transplant; chromosomal breakage challenge test available for early diagnosis

From Trumble T, Budoff J, Cornwall R, editors: *Core knowledge in orthopedics: hand, elbow, shoulder* , Philadelphia, 2005, Elsevier, p 425.

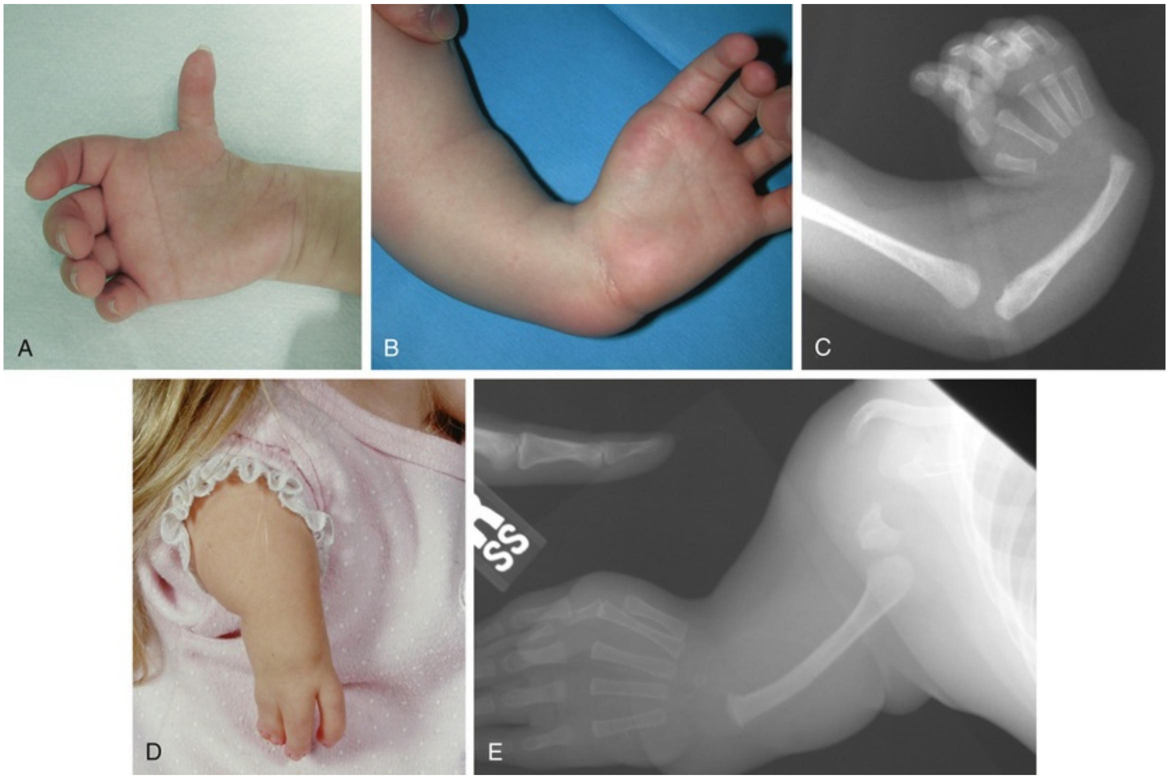

FIG. 701.3 Spectrum of phenotypes of radial dysplasia. **A,** Type 1 radius with a hypoplastic thumb. **B,** Type IV radius with an absent thumb. **C,** Radiograph of a type IV radius. **D** and **E,** Phocomelic radial deficiency. (From Ho C: Disorders of the upper extremity. In Herring JA, editor: *Tachdjian's pediatric orthopaedics* , ed 5, Philadelphia, 2014, WB Saunders. Fig. 15.72, p. 391.)

Radial longitudinal deficiency has been classified into four types according to Bayne and Klug (Table 701.2). Radial longitudinal deficiency can be associated with other syndromes such as Holt-Oram and Fanconi anemia (see Chapter 495).

Table 701.2

Classification of Radial Longitudinal Deficiency

TYPE	CHARACTERISTICS
I	Short radius Minor radial deviation of the hand
II	Hypoplastic radius with abnormal growth at proximal and distal ends Moderate radial deviation of the hand
III	Partial absence of the radius Severe radial deviation of the hand
IV	Complete absence of the radius The most common type

Adapted from Bayne LG, Klug MS: Long-term review of the surgical treatment of radial deficiencies. *J Hand Surg Am* 12(2):169–179, 1987.

Treatment

The goals for the treatment of radial longitudinal deficiency include centralizing the hand and wrist on the forearm, balancing the wrist, and maintaining appropriate thumb and digital motion. Shortly after birth, parents are encouraged to passively stretch the wrist and hand to elongate the contracted radial soft tissues. Serial casting and splinting are ineffective at this time, due to the small size of the arm.

Surgery for correction of the wrist deformity remains controversial. Historically for children with good elbow motion, centralization of the wrist on the forearm was performed. However, recurrence of the deformity was often observed, leading some surgeons to abandon this procedure.

When considering a centralization procedure, the preoperative plan begins with careful examination of the patient; considerations in regard to thumb and elbow function must be made before surgery. The surgery typically occurs when the child is 1 yr of age. Correction of the radial deviation, as well as centralization of the wrist, can be accomplished with a variety of different surgical techniques. These techniques include open release, capsular reefing, and tendon rebalancing. External fixation techniques have also been described.

Nursemaid Elbow

Nursemaid elbow is a subluxation of a ligament rather than a subluxation or dislocation of the radial head. The proximal end of the radius, or radial head, is anchored to the proximal ulna by the annular ligament, which wraps like a leash from the ulna, around the radial head, and back to the ulna. If the radius is pulled distally, the annular ligament can slip proximally off the radial head and into the joint between the radial head and the humerus (Fig. 701.4). The injury is typically produced when a longitudinal traction force is applied to the arm, such as when a falling child is caught by the hand, or when a child is pulled by the hand. The injury usually occurs in toddlers and rarely occurs in children >5 yr of age. Subluxation of the annular ligament produces immediate pain and limitation of supination. Flexion and extension of the elbow are not limited, and swelling is generally absent. The diagnosis is made by history and physical examination because radiographs are typically normal.

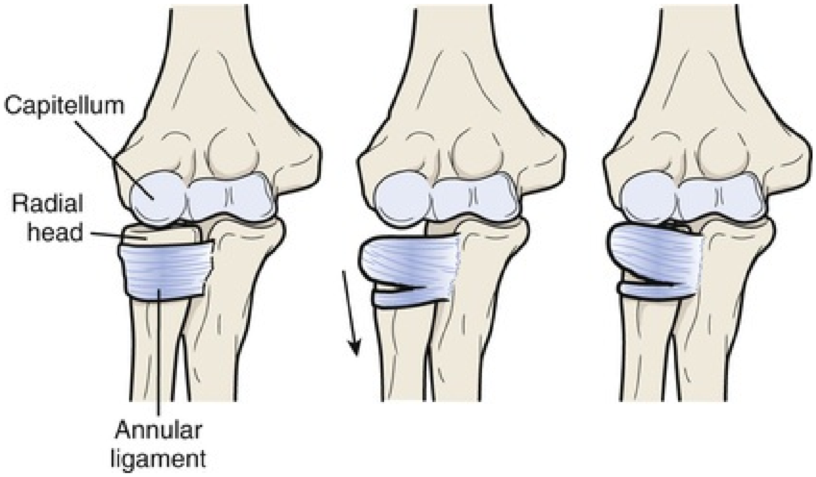

FIG. 701.4 Nursemaid's elbow. Illustration depicting subluxation of the radial head inferior to the annular ligament, with interposition of the ligament to the radiocapitellar joint space. This entity is sometimes in the differential in the setting of upper extremity injury in a small child. Radiographs are negative and serve only to exclude the presence of bony injury when the diagnosis is not clear. (From Walters MM, Robertson RL, editors: *Pediatric radiology: the requisites* , ed 4, Philadelphia, 2017, Elsevier. Fig. 7.102.)

Treatment

The annular ligament is reduced by rotating the forearm into supination while holding pressure over the radial head. A palpable click or clunk can be felt. This maneuver usually provides immediate relief of discomfort and recovery of active supination. Immobilization is not required, but recurrent annular ligament subluxations can occur, and the parents should avoid activities that apply traction to the elbows. Parents can learn reduction maneuvers for recurrent episodes to avoid trips to the emergency department or pediatrician's office. Recurrent subluxation beyond 5 yr of age is rare. Irreducible subluxations tend to resolve spontaneously, with gradual resolution of symptoms over days to weeks; surgery is rarely indicated.

Wrist

The wrist is composed of the two forearm bones and the eight carpal bones. The wrist allows flexion, extension, and radial and ulnar deviation through the radiocarpal and midcarpal articulations. Pronation and supination occur, at the wrist, through the distal radial ulnar joint. The wrist is a complex joint with numerous ligamentous and soft tissue attachments. Its complex kinematics allow for a generous ROM, but when these kinematics are altered, significant dysfunction can occur.

Madelung Deformity

Madelung deformity is a deformity of the wrist that is characterized as radial and palmar angulations of the distal aspect of the radius (Fig. 701.5). Growth arrest of the palmar and ulnar aspect of the distal radial physis is the underlying cause of this deformity. Bony physeal lesions and an abnormal radiolunate ligament (Vickers ligament) have been implicated. The deformity can be bilateral and affects girls more than boys.

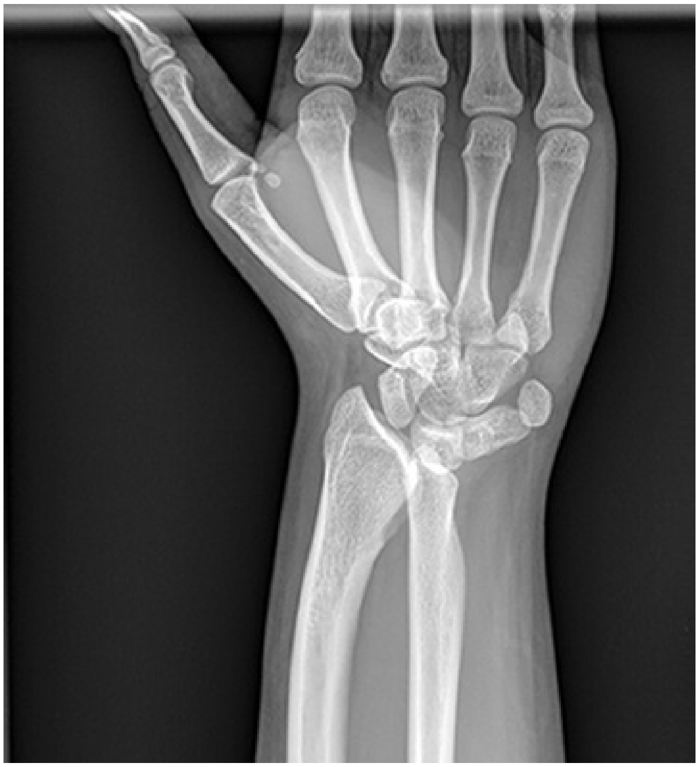

FIG. 701.5 Radiograph of an adolescent with Madelung deformity.

Treatment

Treatment of Madelung deformity is typically observation. Mild deformities can be observed until skeletal maturity. Moderate to severe deformities that either are painful or limit function may be candidates for surgical intervention. Surgical treatment for Madelung deformity is often motivated by appearance. Patients and their families may be concerned about the palmar angulation of the wrist, as well as the resulting prominent distal ulna.

There are a multitude of surgical options for treating Madelung deformity. For the skeletally immature patient, resection of the tethering soft tissue (Vickers ligament) and physiolysis (fat grafting of any bony lesion seen within the physis) is often the first option. When Madelung deformity is encountered in skeletally mature patients, an osteotomy may be considered. Dorsal closing wedge, dome, and ulnar shortening osteotomies may be used alone or in combination to achieve the desired result.

Long-term considerations of Madelung deformity concern the incongruity of the distal radial ulnar joint and resulting premature arthritis of the joint.

Gymnast's Wrist

Gymnast's wrist refers to the changes observed in the physis of the distal radius in the setting of repetitive stress associated with gymnastics (Fig. 701.6). Symptoms include pain with weight bearing, swelling, and loss of motion (mainly wrist extension). The pain is typically mild at first and worsens with time and increased activity. Children will have pain over the distal radial physis on palpation. The child should also be examined for coexisting wrist pathology, including distal radial-ulnar joint instability and triangular fibrocartilage complex tears. Radiographs are often normal but may show chronic changes in the distal radial physis, including widening, sclerosis, and partial physeal arrest. Ulnar positive variance may also be observed because of partial growth arrest of the radius. MRI may be useful to examine the extent of physeal involvement, as well as triangular fibrocartilage complex pathology.

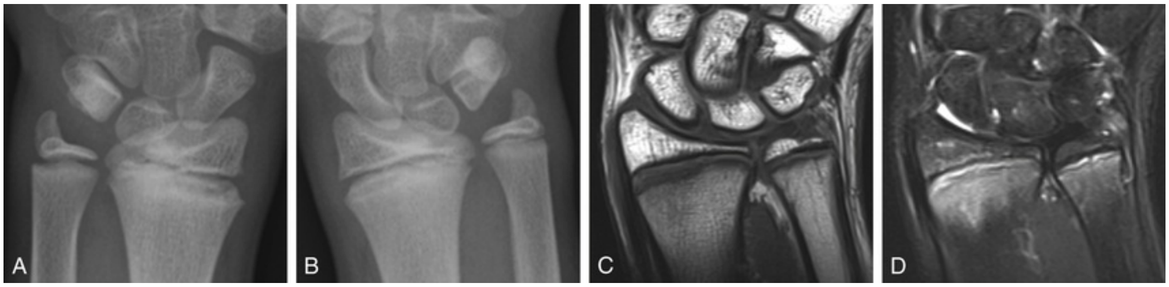

FIG. 701.6 Gymnast's wrist. **A** and **B,** Posteroanterior radiographs of the

bilateral wrists show widening and irregularity of the distal radial physis. Abnormal linear lucency is seen in the metaphyses, with surrounding sclerosis noted. Findings reflect disrupted growth at the physes. **C,** Coronal T1 and **D** , coronal T2 magnetic resonance images with fat saturation show similar abnormality at the distal radial physis, along with abnormal increased fluid signal along the metaphysis. (From Walters MM, Robertson RL, editors: Pediatric radiology: the requisites, ed 4, Philadelphia, 2017, Elsevier. Fig. 7.107.)

Treatment

Treatment of gymnast's wrist begins with rest. Typically, the child is prohibited from weight-bearing activities for a period of 6 wk, until symptoms resolve. The child may gradually resume his or her routine. If symptoms return during the recovery phase, then rest is reinitiated. It is not uncommon for relapses to occur when returning to competition. This may be difficult for the child and parents to understand because gymnasts and gymnasts' families are often very motivated to continue their sport. Use of wrist supports or braces may help to limit the amount of force transmitted to the wrist and in turn help with injury prevention.

In cases where significant damage is seen in the distal radius physis, surgery may be indicated to prevent future morphologic changes in the wrist. Surgery may include epiphysiodesis of the radius and ulna, shortening of the ulna, and triangular fibrocartilage complex repair.

Ganglion

As a synovial joint, the wrist articulation is lubricated with synovial fluid, which is produced by the synovial lining of the joint and maintained within the joint by the joint capsule. A defect in the capsule can allow fluid to leak from the joint into the soft tissues, resulting in a ganglion. The term *cyst* is a misnomer, because this extraarticular collection of fluid does not have its own true lining. The defect in the capsule can occur as a traumatic event, although trauma is rarely a feature of the presenting history. The fluid usually exits the joint in the interval between the scaphoid and lunate, resulting in a ganglion located at the dorsoradial aspect of the wrist. Ganglia can occur at other locations, such as the volar aspect of the wrist, or in the palm as a result of leakage of fluid from the flexor tendon sheaths. Pain is not commonly associated with ganglia in children, and when it is, it is unclear whether the cyst is the cause of the pain. The diagnosis is usually evident on physical examination, especially if the lesion transilluminates. Extensor tenosynovitis and anomalous muscles can mimic ganglion cysts, but radiography or MRI is not routinely required. Ultrasonography is an effective, noninvasive tool to support the diagnosis and reassure the patient and family.

Treatment

Treatment of ganglia may include aspiration, excision, injection, and observation; ultrasound can confirm the diagnosis (AEIOU).

- **Aspiration** : Simple aspiration of the fluid has a high recurrence rate and is painful for children given the large-bore needle required to aspirate the gelatinous fluid. However, this approach may be reasonable, particularly in older children, to attempt cyst decompression as a less invasive alternative to surgery.
- **Excision:** Surgical excision, including excision of the stalk connecting the ganglion to its joint of origin, has a high success rate, although the ganglion can recur.
- **Injection** : Aspiration of the cyst and a simultaneous injection of a corticosteroid is effective in treating recurrence in children.
- **Observation:** Up to 80% of ganglia in children <10 yr of age resolve spontaneously within 1 yr of being noticed. If the ganglion is painful or bothersome and the child is >10 yr of age, treatment may be warranted.
- **Ultrasound:** For children's parents who are concerned about the mass and want a radiographic study to confirm the diagnosis, ultrasound is a noninvasive test to confirm the diagnosis.

Hand

The hand and fingers allow for complex and fine manipulations. An intricate balance among extrinsic flexors, extensors, and intrinsic muscles allow these complex motions to occur. Congenital anomalies of the hand and upper extremity rank just behind cardiac anomalies in incidence. Like cardiac anomalies, if they are not properly identified and remedied, they may have long-term consequences.

Camptodactyly

Camptodactyly is a nontraumatic flexion contracture of the proximal interphalangeal joint that is often progressive. The small and ring fingers are most often affected. Bilateralism is observed two thirds of the time. The etiology of camptodactyly is varied. Several different hypotheses have been offered as to the cause of this condition. Camptodactyly can be divided into three different types (Table 701.3).

Table 701.3

Classification of Camptodactyly

TYPE	CHARACTERISTICS
I	Congenital, no sex bias, small finger only
II	Acquired between 7 and 11 yr, typically progressive
III	Severe, significant contracture, bilateral and associated with other musculoskeletal syndromes

Adapted from Kozin SH: Pediatric hand surgery. In Beredjiklian PK, Bozentka DJ, editors: *Review of hand surgery,* Philadelphia, 2004, WB Saunders, pp 223–245.

Treatment

Mild contractures of <30 degrees are usually well tolerated and do not need treatment. Serial casting and static and dynamic splinting are the treatments of choice for preventing progression of contractures. This should be performed until the child is skeletally mature.

Surgical treatment is limited to the treatment of severe contractures. At the time of surgery, all contracted and anomalous structures are released. Results of contracture release for camptodactyly are mixed; often a loss of flexion results from an attempt to improve extension.

Clinodactyly

Angular deformity of the digit in the coronal plane, distal to the metacarpophalangeal joint, is clinodactyly. The most commonly observed finding is a mild radial deviation of the small finger at the level of the distal interphalangeal joint. This is often due to a triangular or trapezoidal middle phalanx. In some cases, a disruption of the physis at the middle phalanx produces a longitudinal epiphysial bracket. This bracket is thought to be the underlying cause for the formation the “delta phalanx” that is often observed in clinodactyly. Clinodactyly has been observed in other fingers, including the thumb (Fig. 701.7) and ring finger.

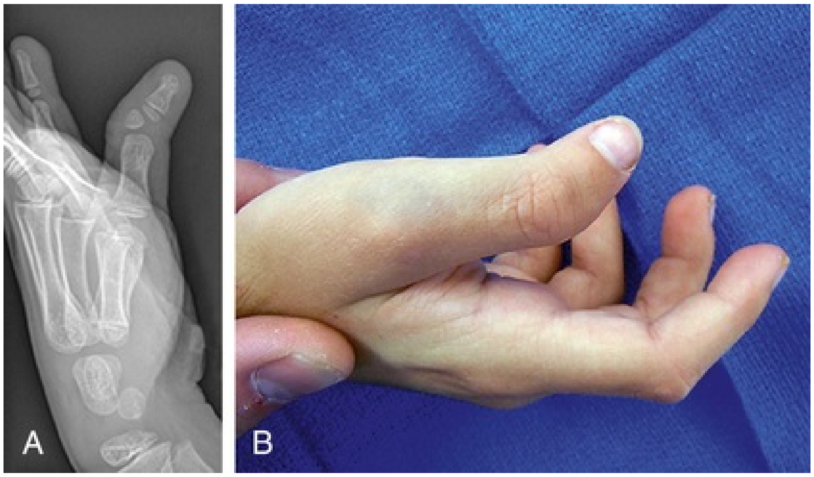

FIG. 701.7 Clinodactyly of the thumb.

Treatment

Often the treatment for clinodactyly is observation and not surgery. For severe deformities and for those affecting the thumb, surgery may be indicated. Surgery is technically demanding. Bracket resections, corrective osteotomies, and growth plate ablations are the most common procedures performed to correct the observed angular deformities. Results are good and recurrences are uncommon when an appropriate procedure is performed.

Polydactyly

Polydactyly or duplication of a digit can occur either as a preaxial deformity (involving the thumb) or as a post axial deformity (involving the small finger) (Table 701.4). Each has an inherited and genetic component. Duplication of the thumb occurs more in whites and Asians and is often unilateral, whereas duplication of the small finger occurs more frequently in African-Americans and may be bilateral. Transmission is typically in an autosomal dominant pattern and has been linked to defects in genes localized to chromosome 2.

Table 701.4

Syndromes Associated With Polydactyly

Carpenter syndrome
Ellis-van Creveld syndrome
Meckel-Gruber syndrome
Polysyndactyly
Trisomy 13
Orofaciodigital syndrome
Rubinstein-Taybi syndrome

Duplication of the thumb was extensively studied by Wassel. Wassel subdivided thumb duplication based on the degree of duplication. The seven types according to Wassel are listed in Table 701.5 . Small finger duplication has been further subdivided into two types. Type A is a well-formed digit. Type B is a small, often underdeveloped supernumerary digit.

Table 701.5

Wassel Classification of Radial Polydactyly: Opposable Thumb Duplications

TYPE	%	DESCRIPTION
I	~2-3	Bifid distal phalanx
II	~15-19	Duplicate distal phalanx
III	~6-8	Bifid proximal phalanx
IV	~40-50	Duplicate proximal phalanx
V	~10-12	Bifid metacarpal
VI	~4	Duplicate metacarpal
VII	~20	Triphalangeal component

Treatment

Thumb and small finger duplication is typically treated with ablation of the supernumerary digit. Treatment options vary based on the degree of involvement. Less well-formed digits can be treated with suture ligation. Well-formed digits require reconstructive procedures that preserve important structures such as the collateral ligaments and nail folds (Fig. 701.8).

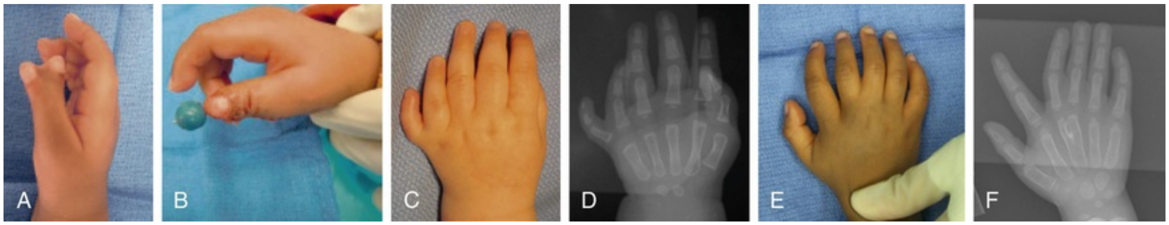

FIG. 701.8 **A and B,** Preoperative and postoperative pictures of a Wassel II thumb duplication. **C,** Clinical photograph. **D,** Radiograph postaxial polydactyly. **E,** Clinical photograph. **F,** Radiograph of central polydactyly.

Thumb Hypoplasia

Hypoplasia of the thumb is a challenging condition for both the patient and the doctor. The thumb represents about 40% of hand function. A less-than-optimal thumb can severely limit a patient's function as he or she grows and develops. Hypoplasia of the thumb can range from being mild with slight shortening and underdeveloped musculature to complete absence of the thumb. Radiographs are useful to help determine osseous abnormalities. The most important finding on physical exam is the presence or absence of a stable carpometacarpal (CMC) joint. This finding helps to guide surgical treatment.

Treatment

If the thumb has a stable CMC joint, reconstruction is advised. Key elements of thumb reconstruction include rebuilding the ulnar collateral ligament of the metacarpophalangeal joint, tendon transfers to aid thumb abduction, and procedures to deepen the web space.

If a stable CMC joint is not present or the thumb is completely absent (Fig. 701.9), **pollicization** (surgical construction of a thumb from a finger) is the definitive treatment. Pollicization is a complex procedure rotating the index finger along its neurovascular pedicle to form a thumb. This procedure is typically performed at around 1 yr of age and may be followed by subsequent procedures to deepen the web space or augment abduction (Fig. 701.10).

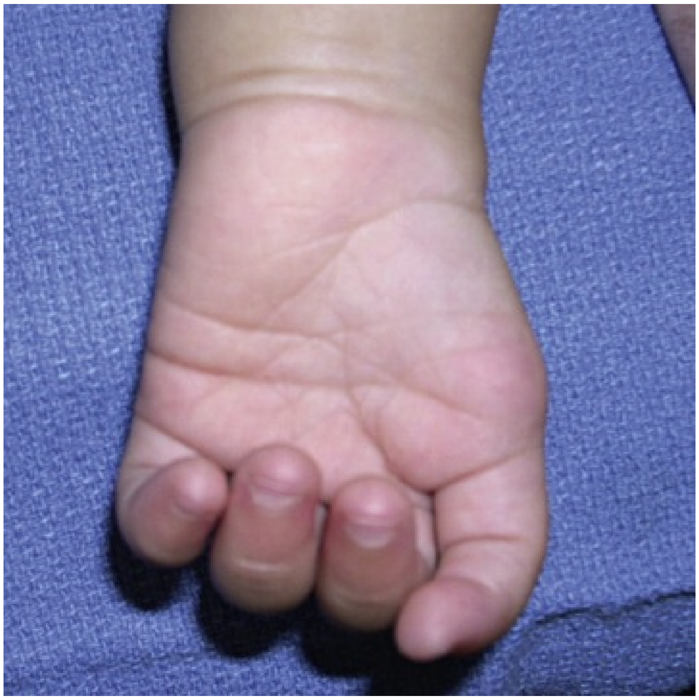

FIG. 701.9 Congenital absence of the thumb.

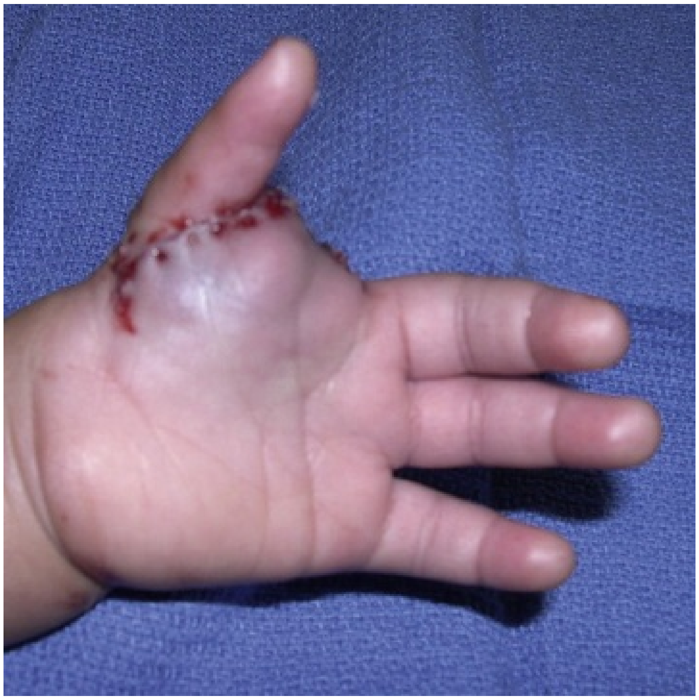

FIG. 701.10 Postsurgical image after pollicization.

Syndactyly

Failure of the individual digits to separate during development produces syndactyly. Syndactyly is one of the more common anomalies observed in the upper limb (Table 701.6). It is seen in 0.5 of 1,000 live births. Syndactyly can be classified as simple (skin attachments only), complicated (bone and tendon attachments), complete (fusion to the tips, including the nail), or incomplete (simple webbing).

Table 701.6

Syndromes Associated With Syndactyly

- Apert syndrome
- Carpenter syndrome
- de Lange syndrome
- Holt-Oram syndrome
- Orofaciodigital syndrome
- Polysyndactyly
- Trisomy 21
- Fetal hydantoin syndrome
- Laurence-Moon-Biedl syndrome
- Fanconi pancytopenia
- Trisomy 13
- Trisomy 18

Treatment

Division of the conjoined digits should be considered before the 2nd yr of life. Border digits should be divided earlier (3-6 mo) because of concern for tethered growth of digits of unequal length. Digits of similar size, such as the ring and middle, may wait until the child is older to consider separation. Reconstruction of the web space and nail folds, as well as appropriate skin-grafting techniques, must be used to ensure the best possible functional and cosmetic result (Fig. 701.11).

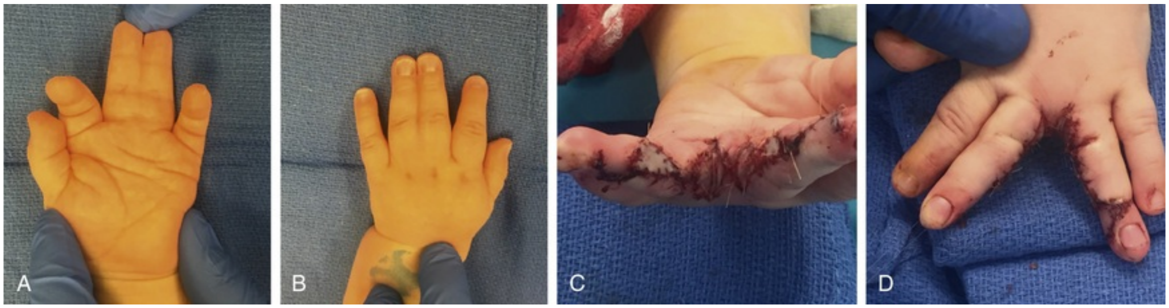

FIG. 701.11 Preoperative **(A and B)** and postoperative **(C and D)** pictures of a simple syndactyly.

Fingertip Injuries

Young children are fascinated with door-jambs or car doors and other tight spaces, making crush injuries to the fingertips quite common. Injury can range from a simple subungual hematoma to complete amputation of part or the entire fingertip. Radiographs are important to rule out fractures. Physeal fractures associated with nailbed injuries are **open fractures** with a higher risk of osteomyelitis, growth arrest, and deformity if not treated promptly with formal surgical debridement and reduction. Tuft fractures involving the very distal portion of the distal phalanx are common and require little specific treatment other than that for the soft tissue injury.

The treatment of the soft tissue injury depends on the type of injury. For suture repairs, only absorbable sutures should be used, because suture removal from a young child's fingertip can require sedation or general anesthesia. If a subungual hematoma exists but the nail is normal and no displaced fracture exists, the nail need not be removed for nailbed repair. If the nail is torn or avulsed, the nail should be removed, the nail bed and skin should be repaired with absorbable sutures, and the nail (or a piece of foil if the nail is absent) should be replaced under the eponychial fold to prevent scar adhesion of the eponychial fold to the nail bed that can prevent nail regrowth.

If the fingertip is completely amputated, treatment depends on the level of amputation and the age of the child. Distal amputations of skin and fat in children <2 yr of age can be replaced as a composite graft with a reasonable chance of surviving. Similar amputations in older children can heal without replacing the skin as long as no bone is exposed and the amputated area is small. A variety of coverage procedures exist for amputations through the midportion of the nail. Amputations at or proximal to the proximal edge of the fingernail should be referred emergently to a replant center for consideration for microvascular replantation. When referring, all amputated parts should be saved, wrapped in saline-soaked gauze, placed in a watertight bag, and then placed in ice water. Ice should never directly contact the part, because it can cause severe osmotic and thermal injury.

Trigger Thumb and Fingers

The flexor tendons for the thumb and fingers pass through fibrous tunnels made up of a series of pulleys on the volar surface of the digits. These tunnels, for reasons that are not well understood, can become tight at the most proximal or 1st annular pulley. Swelling of the underlying tendon occurs, and the tendon no longer glides under the pulley. In children, the most common digit involved is the thumb. It has classically been thought to be a congenital problem, but prospective screening studies of large numbers of neonates have failed to find a single case in a newborn child. The incidence of trigger thumb is approximately 3 per 1,000 children at 1 yr of age. Trauma is rarely a feature of the history, and the condition is often painless. Overall function is rarely impaired. A trigger thumb typically manifests with the inability to fully extend the thumb interphalangeal joint. A palpable nodule can be felt in the flexor pollicis longus tendon at the base of the thumb metacarpal phalangeal joint volarly. Other conditions can mimic trigger thumb, including the thumb-in-palm deformity of cerebral palsy. Similar findings in the fingers (index through small) are much less common and may be associated with inflammatory conditions such as juvenile rheumatoid arthritis (Fig. 701.12).

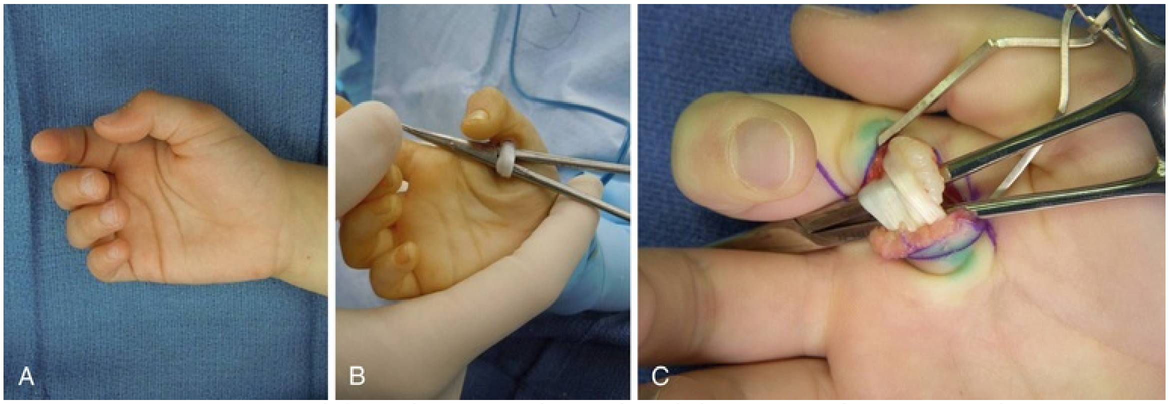

FIG. 701.12 **A,** Clinical picture of trigger thumb in a 2 yr old; note flexed posture of the interphalangeal joint. **B,** Intraoperative picture of flexor

tendon following release of A1 pulley. **C,** Intraoperative picture of benign growth along flexor tendon causing triggering in an index finger.

Treatment

Trigger thumbs spontaneously resolve in up to 30% of children in whom they are diagnosed before 1 yr of age. Spontaneous resolution beyond that age is not common. Corticosteroid injections are effective in adults but are not effective in children and risk injury to the nearby digital nerves. Surgical release of the 1st annular pulley is curative and is generally performed between 1 and 3 yr of age. Treatment of trigger fingers other than the thumb in children involves evaluation and treatment of any underlying inflammatory process and in some cases surgical decompression of the flexor sheath and possible flexor tendon partial excision.

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CHAPTER 702

Arthrogryposis

Helen M. Horstmann, Richard S. Davidson

Arthrogryposis multiplex congenita refers to a heterogeneous group of muscular, neurologic, and connective tissue anomalies that present with two or more joint contractures at birth as well as muscle weakness. It is associated with abnormal contraction of muscle fibers, causing reduced mobility with a decreased active and passive arc of motion. Arthrogryposis is not a specific diagnosis but a descriptive term with various etiologies and complex clinical features, including multiple congenital contractures of various limb joints. It is associated with over 300 different disorders encompassing malformation, malfunction, and neurologic deficiency.

Approximately 1% of all births show some form of contractures of the joints ranging from unilateral clubfoot to the most severe amyoplasia, a condition characterized by pervasive, crippling contractures involving many joints. The overall incidence of arthrogryposis is 1 in 5,000-10,000 live births with equal gender ratios.

Although children with arthrogryposis have many other problems, such as micrognathia and feeding issues, focus is on the orthopedic problems frequently seen in this group of children. In the absence of central nervous system lesions, many children have normal intelligence.

Etiology

The main cause of arthrogryposis is fetal akinesia or decreased fetal movement. The associated pattern of abnormalities is often referred to as the **fetal akinesia deformation sequence** . This sequence manifests as multiple joint contractures, polyhydramnios, craniofacial anomalies (e.g., micrognathia), and pulmonary hypoplasia due to lack of movement of the diaphragm and intercostal muscles.

Intrinsic and extrinsic causes of fetal akinesia are categorized into six groups (Fig. 702.1) and include a multitude of disorders (Table 702.1).

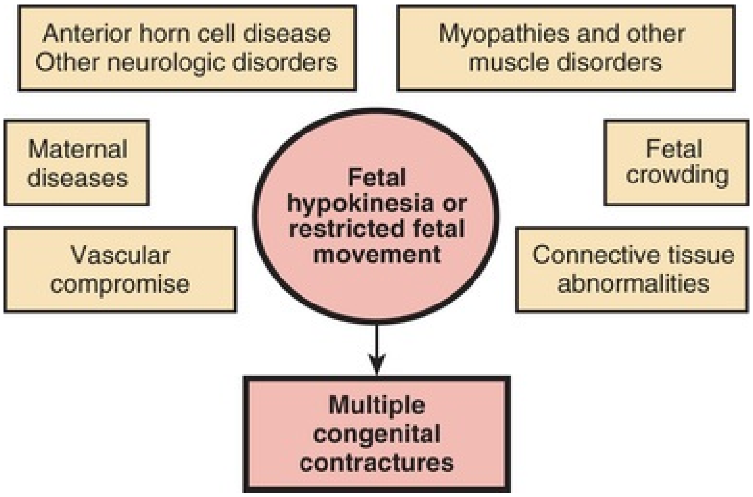
Anterior horn cell disease
Other neurologic disorders
Myopathies and other muscle disorders
Maternal diseases
Fetal crowding
Fetal hypokinesia or restricted fetal movement
Vascular compromise
Connective tissue abnormalities
Multiple congenital contractures

FIG. 702.1 Etiology of arthrogryposis. (Data from Hall JG: Arthrogryposis multiplex congenital: Etiology, genetics, classification, diagnostic approach, and general aspects. *J Pediatr Orthop B* 6:159–166, 1996.)

Table 702.1

Associated Etiologies of Arthrogryposis

Arthrogryposis Caused by Nervous System Disorders

- Focal anterior horn cell deficiency
- Generalized anterior horn cell deficiency
- Structural brain disorder/damage
- Uncertain location

(Spastic conditions are excluded)

Distal Arthrogryposis Syndromes

- Type I dominant distal
- Type IIa dominant distal (Freeman-Sheldon syndrome)
- Digitotalar dysmorphism

- Trismus pseudocamptodactyly
- Distal distribution, type not specified

Pterygium Syndromes

- Multiple pterygium syndrome
- Lethal multiple pterygium syndrome
- Popliteal pterygium syndrome
- Ptosis, scoliosis, pterygia
- Antecubital webbing syndrome (Liebenberg)

Myopathies

- Emery-Dreifuss muscular dystrophy
- Hypotonia, myopathy, mild contractures

Abnormalities of Joints and Contiguous Tissue

- Congenital contractural arachnodactyly
- Freeman-Sheldon syndrome
- Laxity or hypertonicity with intrauterine dislocation and contractures
- Larsen syndrome
- Spondyloepimetaphyseal dysplasia with joint laxity
- Trisomy 18, extended breech position with bilateral hip dislocation
- Siblings with bifid humeri, hypertelorism, and hip and knee joint dislocations

Skeletal Disorders

- Diastrophic dysplasia
- Parastremmatic dysplasia
- Kniest dysplasia
- Metatropic dysplasia

- Campomelic dysplasia
- Schwartz syndrome
- Fetal alcohol syndrome with synostoses
- Osteogenesis imperfecta with bowing/contractures

Intrauterine/Maternal Factors

- Fetal alcohol syndrome with contractures
- Infections
- Untreated maternal systemic lupus erythematosus
- Intrauterine fetal constraint
- Deformity (pressure)
- Amniotic fluid leakage
- Multiple pregnancies
- Intrauterine tumors
- Disruption (bands)

Miscellaneous

- Pseudotrisomy 18 with contractures
- Roberts pseudothalidomide syndrome
- Deafness with distal contractures
- VACTERL association
- Multiple abnormalities and contractures not otherwise specified
- ARC

Single Joint

- Campomelia
- Symphalangism
- “Trigger” finger

ARC , Arthrogryposis, renal tubular acidosis, cholestasis; *VACTERL* , vertebral defects, imperforate anus, congenital heart disease, tracheoesophageal fistula, renal and limb defects.

Modified from Mennen U, Van Heest A, Ezaki MB, et al: Arthrogryposis multiplex congenita. *J Hand Surg Br* 30(5):468–474, 2005. Copyright 2005 The British Society for Surgery of the Hand.

Neurologic Abnormalities

As one of the most common causes of arthrogryposis, neurologic abnormalities are present in 70–80% of cases. Patchy damage to the anterior horn cells of the spinal cord can lead to characteristic limb posturing of arthrogryposis. Neurologic disorders, such as spinal muscular atrophy and anterior horn disease, are associated with arthrogryposis; however, the type of anterior horn cell involvement is usually not from spinal muscular atrophy syndrome. Other, less-common neurologic disorders include neonatal myasthenia, myotonic dystrophy, olivo-ponto-cerebellar disorders, and neuronal migration anomalies.

Muscular Abnormalities

These rare abnormalities affect the function and structure of the muscles. Some muscular diseases associated with arthrogryposis are muscular dystrophies, congenital myopathies (central core, nemaline, centronuclear), intrauterine myositis, and mitochondrial diseases.

Limited Intrauterine Spacing

With a less than 0.1% occurrence rate, uterine constraint is rarely the primary cause of arthrogryposis. Maternal uterine anomalies will occasionally increase contractures of fetal limbs with arthrogryposis already existing. Other known causes are lack of amniotic fluid within the uterus and tumors, such as fibroids, that can prevent movement by impinging on uterine space.

Connective Tissue Abnormalities

When the tendons, bones, joints, and joint lining develop atypically, decrease in fetal movement causes congenital contractures. Diseases such as diastrophic dysplasia, campomelic dysplasia, and metatropic dysplasia result from connective tissue not developing properly. These are specific diagnoses resulting in limited joint motion and not true distal arthrogryposis. Other cases show that individuals who lack normal joint movement have distal joint involvement because the connective tissue develops normally but does not attach to the proper location around a joint bone or joint.

Maternal Diseases

Maternal diseases, such as multiple sclerosis, diabetes mellitus, myasthenia gravis, maternal hyperthermia, infection, drugs, and trauma, are associated with an increased incidence of arthrogryposis. In approximately 10% of neonates born to mothers with myasthenia gravis, maternal antibodies enter the fetal circulation through the placenta, causing transient myasthenia gravis; this inhibits fetal acetylcholine receptors, which leads to damaged fetal muscles.

Intrauterine Vascular Compromise

Inadequate vascular supply to the fetus causes fetal hypoxia resulting in anterior horn cell death, which decreases neurologic and myopathic function, resulting in fetal akinesia and secondary joint contractures. Multiple congenital contractures have been reported in individuals after bleeding throughout pregnancy or after a failed attempt at terminating the pregnancy.

Classification

Arthrogryposis multiplex congenita is divided into subgroups with different signs, symptoms, and causes as a practical way to make a differential diagnosis. Disorders involving primarily limbs such as **amyoplasia** and **distal arthrogryposis** are the most common subgroups (Table 702.2). Disorders involving limbs *and* other body parts typically represent a form of *multiple pterygium*, which is characterized by a weblike membrane that forms across joints affecting a child's ability to extend and causing fixed flexion. Disorders with limb involvement and abnormal neurologic function are caused by atypical central nervous system, peripheral nervous system, and damaged or absent anterior horn cells.

Table 702.2

A Classification System and Clinical Features of Distal Arthrogryposes

TYPE	DESCRIPTION
I	Characteristic clinical features are camptodactyly and talipes equinovarus with possible concomitant shoulder and hip contractures. The DA1 variant is determined by a gene located on chromosome 9.
II	The phenotype was first described in 1938 as the Freeman-Sheldon syndrome, where contractures of fingers and toes are accompanied by kyphosis, scoliosis, and malformations of the facial skeleton with characteristic facial appearance: narrow mouth, wide cheeks, an H -shaped chin dimple, small wide-based nose, high palate, and small tongue. Growth retardation, inguinal hernia, and cryptorchidism have also been reported. Another name of this syndrome is "whistling face" syndrome. The Freeman-Sheldon syndrome is currently classified as DA2A, as a separate DA2B subtype, known as Sheldon-Hall syndrome has been described; this syndrome combines clinical features of DA1 (hand and foot contractures) and some features of DA2 (prominent nasolabial folds, slanted down-facing eyes, and narrow mouth) and is currently considered to be probably the most common type of distal arthrogryposis.
III	Also known as Gordon syndrome, this rare syndrome is characterized by low stature and palatoschisis.
IV	Rare. Contractures with severe scoliosis.
V	Contractures with ocular signs and symptoms such as limited eye motion, ptosis, strabismus, and the absence of typical hand flexion creases. Chest wall muscle abnormalities have also been observed, potentially causing restricted respiratory movements and, consequently, pulmonary hypertension.
VI	Similar to DA3, DA4; very rare, characterized by sensorineural auditory abnormalities.
VII	Difficulties in mouth opening (trismus) and pseudocamptodactyly: wrists position in palmar flexion with MCP joints in extension. Sometimes accompanied by low stature and knee flexion contractures.
VIII	Autosomal dominant multiple pterygium syndrome.
IX	Beals syndrome, i.e., congenital arachnodactyly with contractures of small joints of the fingers. Patients with this type of arthrogryposis are tall and slender, phenotypically resembling Marfan syndrome but without cardiovascular abnormalities.
X	Congenital plantar flexion contractures of the foot.

From Kowalczyk B, Feluś J: Arthrogryposis: an update on clinical aspects, etiology, and treatment strategies. *Arch Med Sci* 12(1):10–24, 2016 (Table 1, p 16).

Amyoplasia, also known as *classic arthrogryposis*, is a sporadic symmetric disorder that causes fibrotic replacement of the muscles. Symptoms include internally rotated and adducted shoulders, extended elbows, pronated forearms, flexed fingers and wrists, dislocated hips, feet with severe equinovarus contractures, and extended knees. Involved muscles are hypoplastic and fibrotic. Often patients have midfacial hemangioma. Intelligence is usually normal (Figs. 702.2 and 702.3).

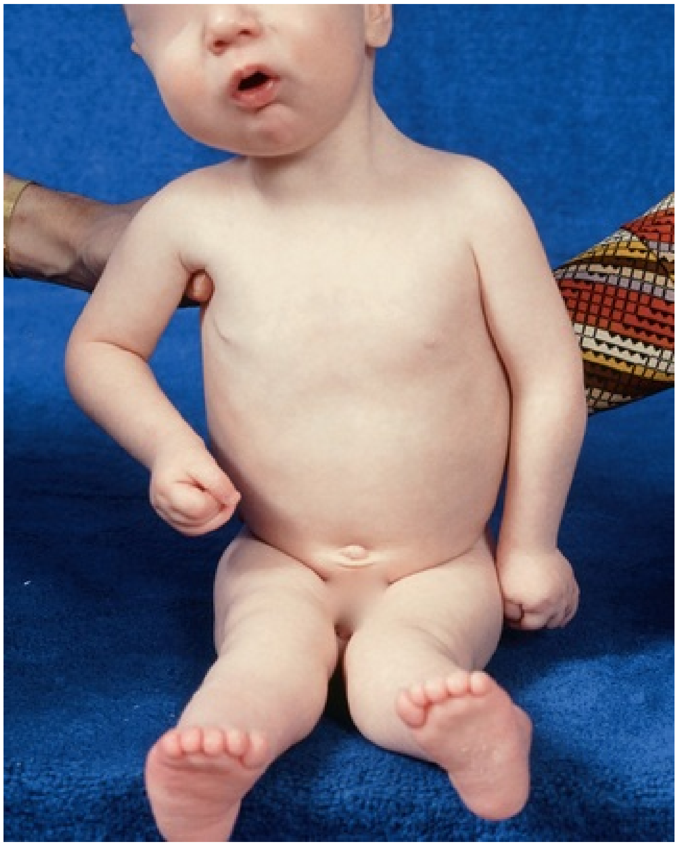

FIG. 702.2 Infant with stiff elbows, wrists, fingers, dislocated left hip, valgus stiff knees, and clubfeet.

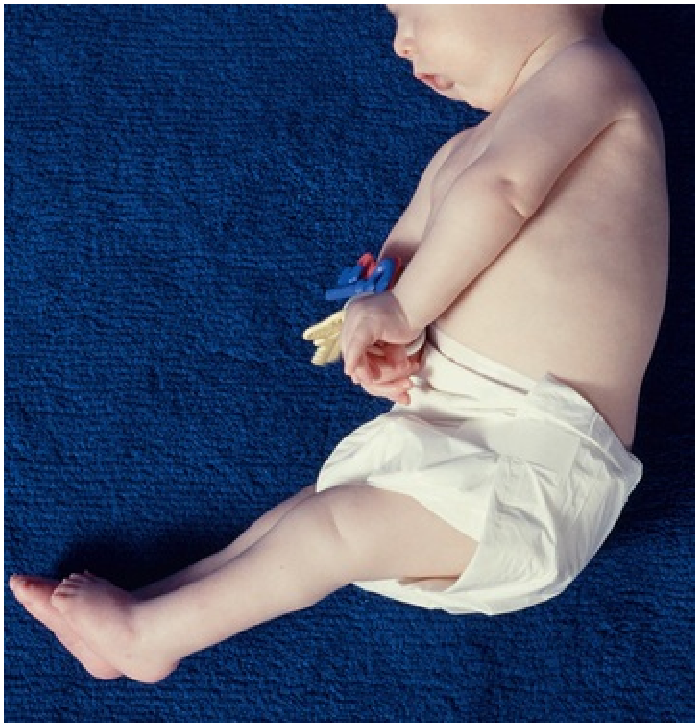

FIG. 702.3 Infant with stiff elbows, wrists, fingers, dislocated left hip, clubfeet, and micrognathia.

Distal arthrogryposis is an autosomal dominant disorder that primarily affects the distal joints of the limbs. Characteristics of the upper limbs are medially overlapping fingers, clenched fists, ulnar deviation of fingers, camptodactyly, and hypoplasia. Lower limbs show talipes equinovarus, calcaneovalgus, vertical talus, or metatarsus varus (Fig. 702.4).

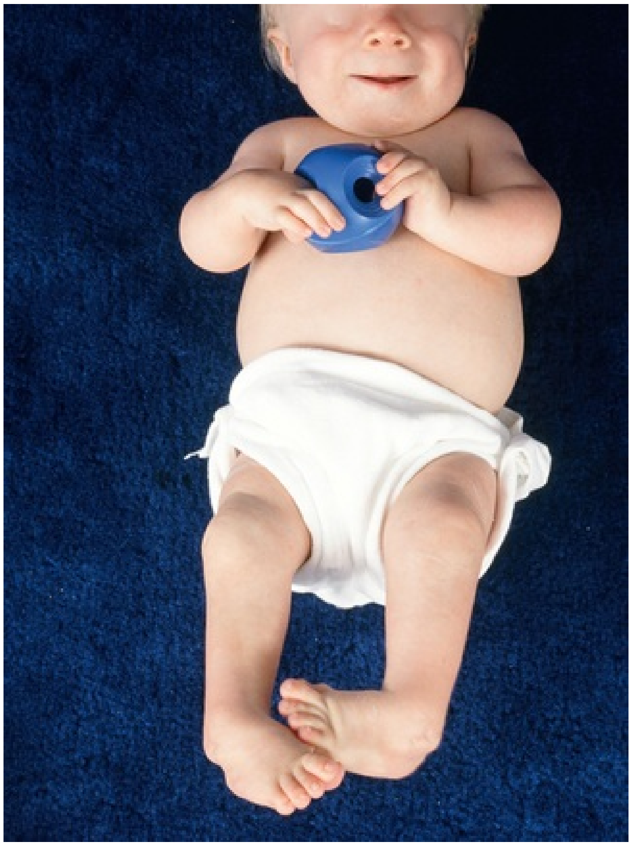

FIG. 702.4 **Infant with club feet, stiff knees, dislocated hips, stiff fingers, and facial hemangioma.**

Ten different types of distal arthrogryposis have been categorized based on specific traits they share with each other.

Management of Orthopedic Problems of Arthrogryposis

When a child is born with arthrogryposis, the many stiff or dislocated joints pose issues of timing and best practices of management. Typically, a child can have stiff elbows, dislocated hips, dislocated, hyperextended, or contracted knees, and clubfeet (Fig. 702.5). The stiffness and deformity need to be aggressively addressed through a combination of modalities. A team of clinicians, including therapists for the upper and lower extremities, orthotists, and orthopedic surgeons, will be involved.

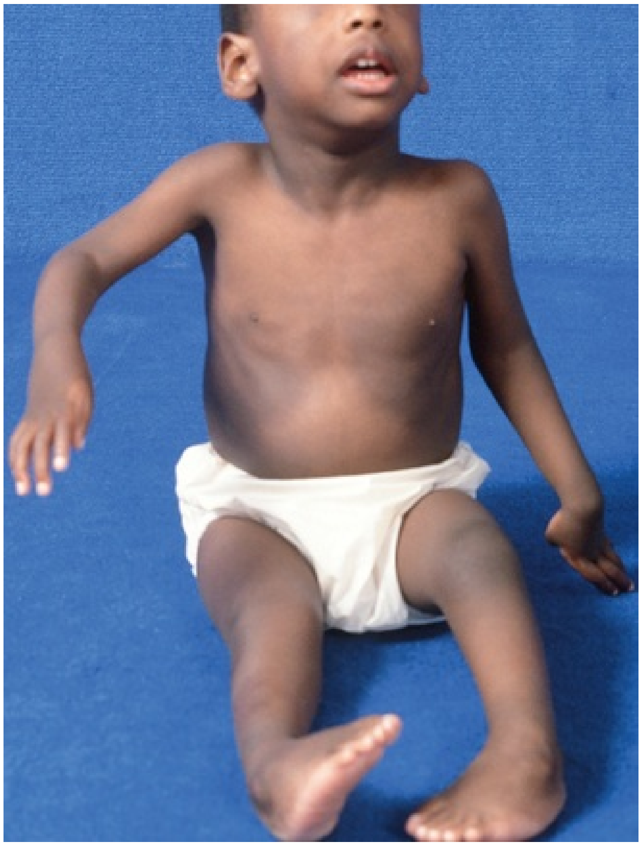

FIG. 702.5 Child with stiff elbows, wrists, knees, and clubfeet.

Initially, passive range-of-motion exercises and judicious splinting directed and assisted by physical and occupational therapy will help to address the various deformities. Splinting and casting can be augmented by a taping program which can be taught to the family so that the taping can be redone frequently to take advantage of improved range of motion. The ingenuity of the therapists and/or orthotists to create the right splints and braces using appropriate thermoplastics, neoprene, Velcro, and other materials can be simple yet effective (Fig. 702.6).

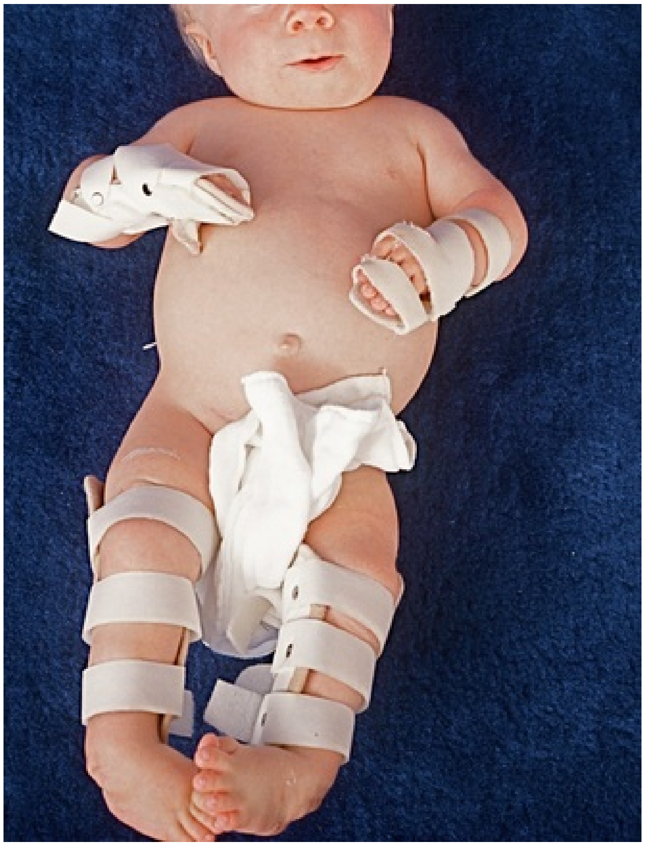

FIG. 702.6 Infant with splints to extend metatarsophalangeal joints, wrists, and knees.

The therapeutic and orthopedic goal for the child with arthrogrypotic limb deformities is to achieve maximal joint motion and to optimize joint position for function. In the lower extremities, the foot needs to be plantigrade. The knees need to have optimal motion for sitting and standing. Hips need to be stabilized especially if the child has walking potential. In the upper extremities, the goals should include positioning of 1 arm for feeding and the other for toileting in cases where there is extreme stiffness. Two-handed activities require some symmetry, which can be a challenging goal with extreme contractures and limited muscle strength.

Although scoliosis is common, it usually does not become a problem until adolescence.

Foot Problems

Clubfoot deformities are the most commonly seen deformities with arthrogryposis (Fig. 702.7). A clubfoot has components of hindfoot equinus, midfoot varus, and forefoot adduction. Feet in arthrogryposis tend to be resistant to improvement but the traditional methods of treatment are nevertheless employed. Casting is begun shortly after birth in a method known as the Ponseti method. Casts are changed weekly until a plateau is reached and heel cord lengthening is needed. Other deformities such as vertical talus are also seen and are addressed in a similar approach although with appropriately differing techniques.

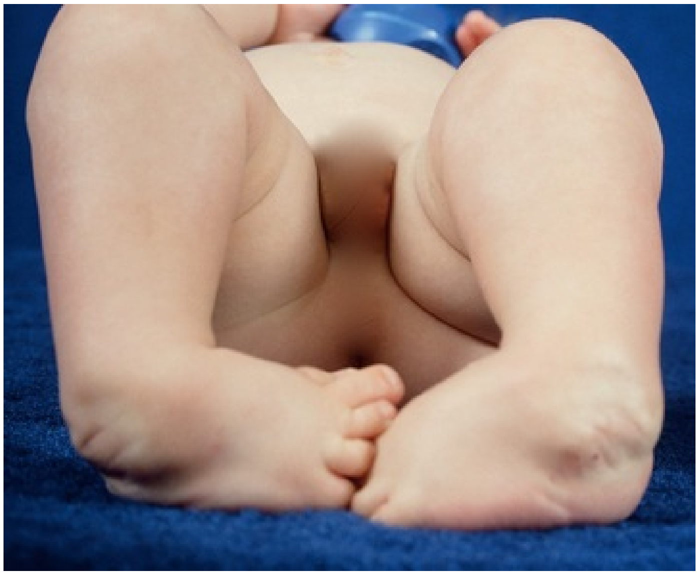

FIG. 702.7 **Clubfeet in infant with arthrogryposis.**

Persistent stiffness often leads to more comprehensive soft tissue releases. This is typically done around age 6-12 mo and is followed by 3 mo of further casting and additional bracing as needed, especially as the foot is growing. When deformities are not corrected in early childhood, additional bony surgery may be needed later. Some of the approaches to this involve bony wedge osteotomies, lateral column lengthening, bone decancellation, or talectomy. Ilizarov ring or multiaxial monolateral external fixation with or without osteotomies are used in late correction of residual deformities.

Children with significant deformities are often in ankle foot orthoses through much of their lives to avoid deformity recurrence and to augment the standing base due to weak leg muscles. A plantigrade, pain free, stable foot is the goal of foot management. Foot stiffness is anticipated and unavoidable in arthrogryposis involving the foot.

Knee Problems

Knee issues, including knee extension or flexion, subluxation, and stiffness, respond well to therapy and splinting. Knee flexion is more common in arthrogryposis. Infrequently it can structurally be complex and associated with skin webbing known as pterygiums. Pterygiums are resistant to nonsurgical intervention and require plastic Z lengthenings. In the case of a flexion contracture, the quadriceps musculature is often deficient and weak. Sometimes the casting and splinting of the knee contractures is insufficient. Hamstring lengthenings with additional posterior knee capsular releases are often needed.

In the case of knee hyperextension, the quadriceps are sometimes fibrotic and weak in spite of seeming to overpower the hamstrings. Casting and splinting should begin shortly after birth, which can be done in conjunction with clubfoot casting following the principles of Ponseti. If splinting and therapy fail, lengthening of the quadriceps can be achieved through release of the lateral medial quadriceps, with proximal detachment of the rectus femoris, lengthening of the quadriceps either percutaneously or through a mini open procedure which may minimize scarring.

Long-standing stiffness may lead to joint surface flattening permanently reducing the arc of motion. Repositioning the arc of motion may improve sitting or standing, a choice to be made by the patient, family, and physician. Follow-up bracing can help to compensate for weak, fibrotic muscles of the legs.

Hip Problems

Teratologic hip dislocations are common within the spectrum of arthrogryposis and usually require open reduction of the hip. Hips in a child with less upper-extremity involvement and more supple hips that are not pathologically stiff *may* respond to early treatment with a Pavlik harness. Knee hyperextension can often be treated with physical therapy and serial casting. Careful observation of the hip during knee flexion as tightening of the quadriceps and hip flexors can push the hip into posterior dislocation. Once some knee flexion has been achieved, the Pavlik harness can be useful in further flexing the knee and maintaining hip stability in the infant. Most often, the hips are stiff and not reducible closed. For these, open reduction with pelvic reconstruction and femoral osteotomy are commonly required, typically at 1 yr of age. There is some controversy about reducing bilateral hip dislocations as a high failure rate can result in asymmetry of the pelvis, pain, leg length inequality, and stiffness. If a child has little ambulation potential, he may do as well retaining the bilateral hip dislocations and positioning the hips for sitting. Management judgment should be made in conjunction with the family guided by a pediatric hip surgeon.

Ambulation

As would be expected, walking is more difficult for children with arthrogryposis due to the muscle weakness and limited joint motion. Children with arthrogryposis who walk have lower activity levels and take fewer steps than their peers. Not surprisingly, muscle fatigue and pain on exertion were noted in a study that included adults with distal arthrogryposis.

Upper-Extremity Problems

If splinting and a movement exercise program do not result in optimally functional upper extremities, surgical management may improve use of the arms of the child with arthrogryposis. A typical child with arthrogrypotic involvement of the upper extremities has internally rotated arms, extended elbows, flexed wrists, and thumb-in-palm or clasp-thumb deformities (see Figs. 702.2 and 702.3).

Treatment is geared toward optimizing use of the arms and hands particularly for critical activities of daily living, such as feeding and toileting. Therapy to improve motion of the joints is started immediately after birth. Pediatric hand therapists are the optimal leaders of the mobility treatment program. Therapy is augmented by use of splints so that less-extensive surgery will be required. The elbow is the critical length adjuster of the arm, allowing the arm to reach out as is necessary for toileting or to approach the mouth for feeding. If necessary, lack of these motions can be compensated by modified silverware and other adaptive equipment, including arm extenders for grabbing.

Surgery of the Upper Extremity

Surgical correction of arthrogrypotic upper extremity contractures should be started after 1-3 mo and completed by age 12 mo so that the child can optimize his or her motor development. This allows for improved results optimizing the joint growth remodeling plasticity. One-stage procedures yield the best results.

Delays in surgery result in more problems of intraarticular adhesions as well as fixed joint incongruity.

Shoulder

Because of the rotational capacity of the shoulder, derotation osteotomy of the humerus is only occasionally needed. This is usually done in later childhood.

Elbow

A stiff elbow that does not respond to therapy requires surgical intervention starting with soft tissue and capsular release. Capsulotomy of the posterior elbow combined with a V-Y or Z reconstructive lengthening of the triceps allows improved elbow flexion. The triceps may need to be lengthened. Muscle transfer to the forearm can permit active elbow flexion. Each child needs individual assessment as to available flexor source. Most commonly available is the triceps. An elbow with some flexion is extremely important for arm function. Use of the triceps can create elbow flexion overpowering and contracture.

Wrist

Wrist flexion deformity is improved with soft tissue balancing as well as partial carpectomies. The carpectomies need to be trapezoidal with more removed from the dorsum and the radial side to balance the wrist flexion contracture as well as the tendency for ulnar deviation. Thumb adduction may require an adductor release with an opponensplasty. Tendon transfers such as transfer of the extensor indicis pollicis to the extensor pollicis longus is helpful for improved function of the thumb in clasp thumb deformity.

Finger stiffness and wrist contractures often respond to therapy and bracing without need for surgery.

Scoliosis

Scoliosis is frequent in arthrogrypotic children, although the reported incidence of between 28% and 66% is probably skewed upward in reports as they reflect the experience of scoliosis surgeons. Scoliosis can be congenital or paralytic. The scoliosis is often accompanied by hip contractures associated with hip dislocation and compensatory lumbar lordosis. Curves <30 degrees can be treated initially with bracing in a thoracolumbar spinal orthosis (TLSO brace). After 40 degrees, spinal fusion is warranted.

Surgical Staging

Surgical treatment of the lower limbs usually begins distally and works proximally. The feet are corrected around 6 mo of age, the knees around 8 mo of age, and the hips around 12 mo of age as pelvic osteotomy is often needed to stabilize the hips properly.

The upper extremities are corrected during infancy when the child is seen early. Hand, physical, and occupational therapy are a critical part of the team to optimize function prior to and after surgery. Further surgery during childhood may be needed to tweak and optimize functional use of the upper and lower extremities.

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CHAPTER 703

Common Fractures

Keith D. Baldwin, Apurva S. Shah, Lawrence Wells, Alexandre Arkader

Trauma is a leading cause of death and disability in children older than 1 yr of age (see Chapter 13). Several factors make fractures of the immature skeleton different from those involving the mature skeleton. The anatomy, biomechanics, and physiology of the pediatric skeletal system differ from those of adults, resulting in different fracture patterns (Fig. 703.1), diagnostic challenges, and management techniques. Children have a high functional demand and expectations, while carrying concerns regarding remaining skeletal growth and development.

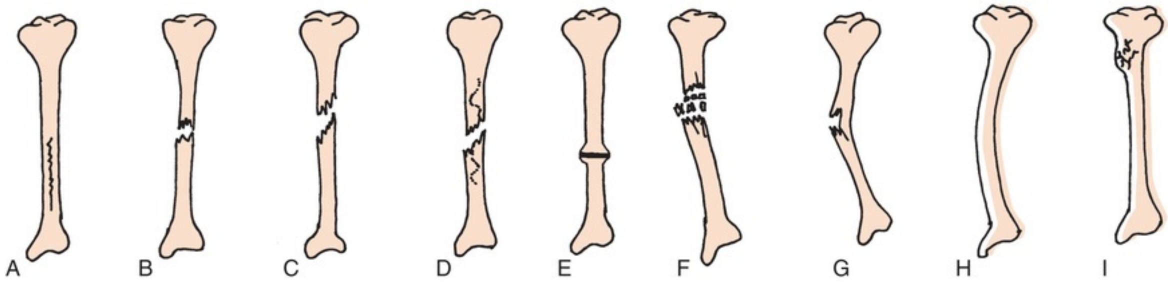

FIG. 703.1 **Illustration of fracture patterns. A, Longitudinal fracture line parallel to bony axis. B, Transverse fracture line perpendicular to bony axis. C, Oblique fracture line at angle to bony axis. D, Spiral fracture line runs a curvilinear course to the bony axis. E, Impacted fractured bone ends compressed together. F, Comminuted fragmentation of bone into 3 or more parts. G, Greenstick bending of bone with incomplete fracture of convex side. H, Bowing bone plastic deformation. I, Torus buckling fracture. (From White N, Sty R: Radiological evaluation and classification of pediatric fractures. *Clin Pediatr Emerg Med* 3:94–105, 2002.)**

Epiphyseal lines, rarefaction, dense growth lines, congenital fractures, and pseudofractures appear on radiographs, which make it challenging to identify and differentiate an acute fracture. Although most fractures in children heal well, some fractures terminate disastrously if handled with insufficient expertise. The differences in the pediatric skeletal system predispose children to injuries different from those of adults. Important differences are the presence of periosseous cartilage, physes, and a thicker, stronger, more osteogenic periosteum that produces new bone, called *callus* , more rapidly and in greater amounts. The pediatric bone is less dense and more porous. The low density is from lower mineral content and the increased porosity is the result of an increased number of haversian canals and vascular channels. These differences result in a comparatively lower modulus of elasticity and lower bending strength. The bone in children can fail either in tension or in compression; because the fracture lines do not propagate as in adults, there is less chance of comminuted fractures. Hence, pediatric bone can crush, splinter, and break incompletely (e.g., buckle fracture, greenstick fracture), as opposed to adult bone which generally breaks like glass and may comminute.

A common teaching is that joint injuries, dislocation, and ligament disruptions are infrequent in children. Damage to a contiguous physis is more likely. Although this is generally true, MRI studies show that ligament damage in ankle injuries may not be as unusual as once thought. Interdigitating mammillary bodies and the perichondrial ring enhance the strength of the physes. Biomechanically, the physes are not as strong as the ligaments or metaphyseal bone. The physis is most resistant to traction and least resistant to torsional forces. The periosteum is loosely attached to the shaft of bone and adheres densely to the physeal periphery. The periosteum is usually injured in all fractures, but it is less likely to have complete circumferential rupture, because of its loose attachment to the shaft. This intact hinge or sleeve of periosteum lessens the extent of fracture displacement and assists in reduction and maintenance of fracture reduction. The thick periosteum can also act as an impediment to closed reduction, particularly if the fracture has penetrated the periosteum, or in reduction of a displaced growth plate.

703.1

Unique Characteristics of Pediatric Fractures

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Keywords

pediatric fractures
physis
physeal fractures
remodeling

Fracture Remodeling

Remodeling is the third and final phase in the biology of fracture healing; it is preceded by the inflammatory and reparative phases. This occurs from a combination of appositional bone deposition on the concavity of deformity, resorption on the convexity, and asymmetric physeal growth. Thus reduction accuracy is somewhat less important than it is in adults (exceptions include intra-articular fractures) (Fig. 703.2). The three major factors that have a bearing on the potential for angular correction are skeletal age, distance to the physis, and orientation to the joint axis. The rotational deformity and angular deformity not in the axis of the joint motion have less potential for remodeling. Remodeling is best when the fracture occurs close to the physis, the child has more years of growth remaining, has less deformity to remodel, and is adjacent to a rapidly growing physis (e.g., the proximal humerus or distal radius). Remodeling typically occurs over a several months period following the fracture until skeletal maturity. Generally, skeletal maturity is reached in postmenarchal girls between 13 and 15 yr of age, and in boys between 15 and 17 yr of age.

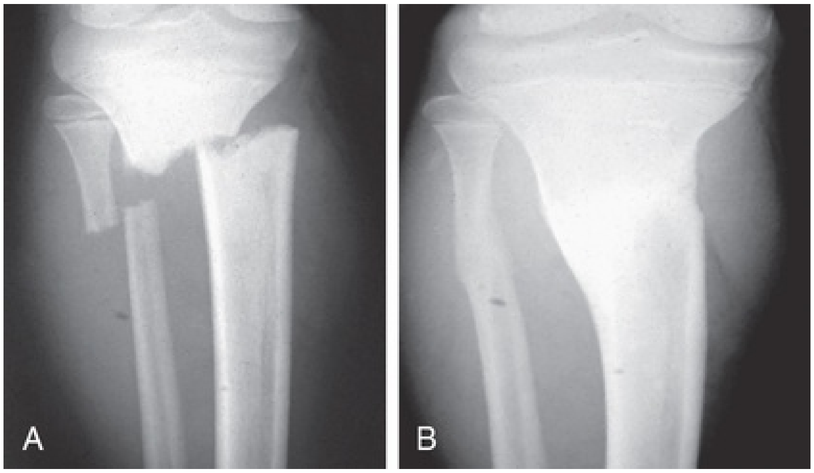

FIG. 703.2 Remodeling in children is often extensive, as in this proximal tibial fracture **(A)** and as seen 1 yr later **(B).** (From Dormans JP: *Pediatric orthopedics: introduction to trauma* , Philadelphia, 2005, Mosby, p. 38.)

Overgrowth

Physeal stimulation from the hyperemia associated with fracture healing may also cause overgrowth. It is usually more prominent in lower extremity long bones such as the femur. The growth acceleration is usually present for 6 mo to 1 yr following the injury. Femoral fractures in children younger than 10 yr of age may overgrow up to 1-3 cm. If external fixation or casting is employed, bayonet apposition of bone may be preferred for younger children to compensate for the expected overgrowth. This overgrowth phenomenon will result in equal or near equal limb lengths at the conclusion of fracture remodeling if the fracture shortens less than 2 cm. After 10 yr of age, overgrowth does not tend to occur, and anatomic alignment is recommended. In physeal injuries, growth stimulation is associated with use of implants or fixation hardware that can cause stimulus for longitudinal growth.

Progressive Deformity

Injuries to the physes can be complicated by permanent or temporary growth arrest, leading to progressive limb deformity. The most common cause is complete or partial closure of the growth plate. This can occur in any long bone but is particularly seen in fractures involving the distal ulna, distal femur, and proximal tibia growth plates. An MRI is helpful for early diagnosis of growth arrest, as well as measurement of percent of physeal closure after such an injury. Harris growth arrest lines may be observed in the setting of asymmetric growth and will point toward the area of growth arrest (Fig. 703.3). If these lines are parallel to the physis, this finding indicates that the growth plate is healthy. As a consequence of growth arrest, angular deformity or shortening, or both, can occur. The partial arrest may be peripheral, central, or combined. The magnitude of deformity depends on the specific physis involved, the degree of involvement, and the amount of growth remaining.

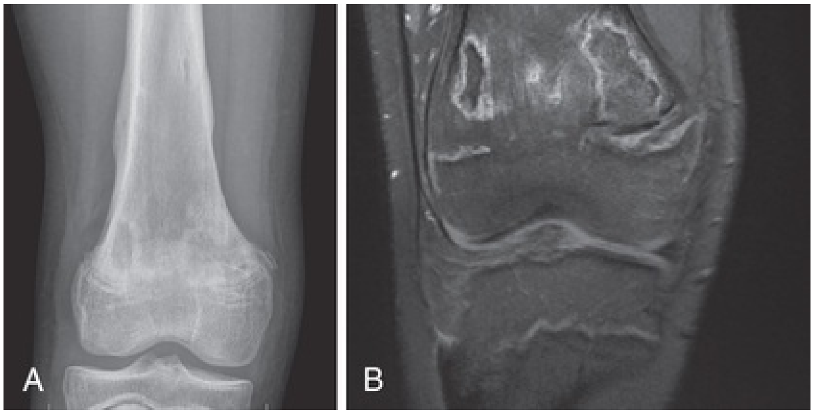

FIG. 703.3 **A,** Harris growth arrest lines on either side of the femur pointing centrally in the femur indicating a central growth arrest. **B,** Corresponding MRI image showing central growth arrest. (**A,** Courtesy Keith D. Baldwin, MD, MPH, Children's Hospital of Philadelphia.)

Rapid Healing

Children's fractures heal more quickly than adults as a result of children's growth potential and thicker, more active periosteum. As children approach adolescence and maturity, the rate of healing slows and becomes similar to that of an adult.

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703.2

Pediatric Fracture Patterns

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Keywords

pediatric fractures
physis
physeal fractures

The different pediatric fracture patterns are the reflection of a child's characteristic skeletal system. The majority of pediatric fractures can be managed by closed methods and heal well.

Plastic Deformation

Plastic deformation is unique to children. It is most commonly seen in the forearm and occasionally the fibula. The fracture results from a force that produces microscopic failure on the tensile side of bone and does not propagate to the concave side (Fig. 703.4). The concave side of bone also shows evidence of microscopic failure in compression. The bone is angulated beyond its elastic limit, but the energy is insufficient to produce a fracture. Thus no fracture line is visible radiographically (Fig. 703.5). While the plastic deformation is permanent, it is important to remember that children have great remodeling capability, for example, a 20-degree bend in the ulna of a 4 yr old child is expected to correct completely with growth. These findings inform “acceptability” of fracture alignment.

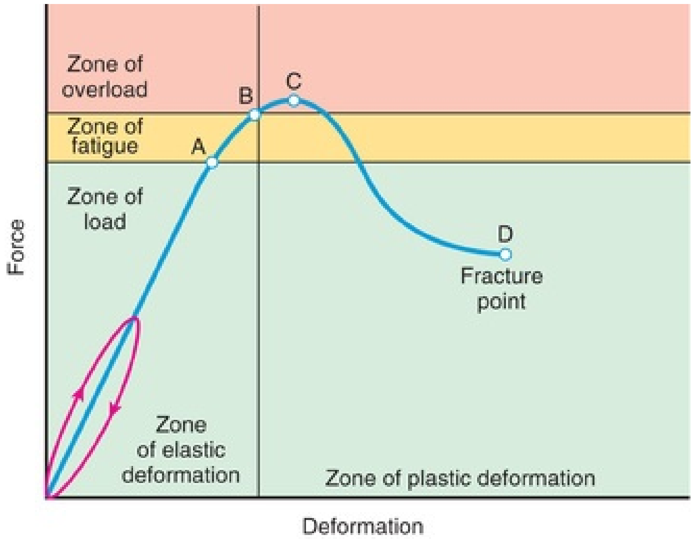

FIG. 703.4 Graphic relation of bony deformation (bowing) and force (longitudinal compression) showing that the limit of an elastic response is not a fracture but plastic deformation. If the force continues, a fracture results. **A,** Reversible bowing with stress; **B,** microfractures occur; **C,** point of maximal strength; between **C** and **D,** bowing fractures; **D,** linear fracture occurs. (Modified from Borden S IV: Roentgen recognition of acute plastic bowing of the forearm in children. *Am J Roentgenol Radium Ther Nucl Med* 125:524–530, 1975.)

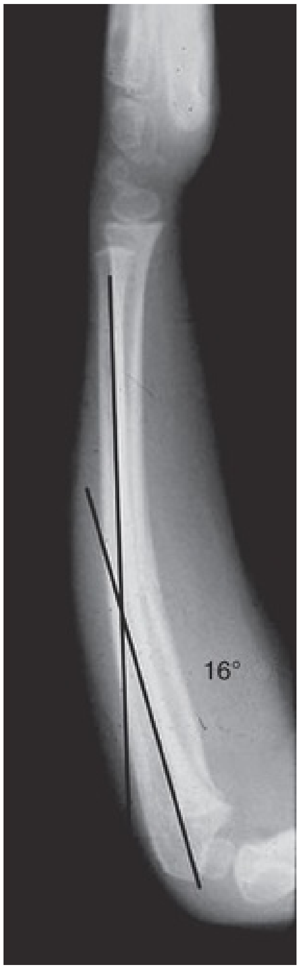

FIG. 703.5 **Plastic deformation is a microfailure in tension without a visible fracture line. (Courtesy of Dr. John Flynn, Children's Hospital, Philadelphia.)**

Buckle or Torus Fracture

This fracture represents a failure in compression of the bone, usually occurring at the junction of the metaphysis and diaphysis. The distal radius is the most common location, but it may occur in other areas as well (Fig. 703.6). This injury is referred to as a *torus fracture* because of its similarity to the raised band around the base of a classic Greek column. They are inherently stable, usually associated with an acceptable amount of angulation, and heal in 3-4 wk with simple immobilization.

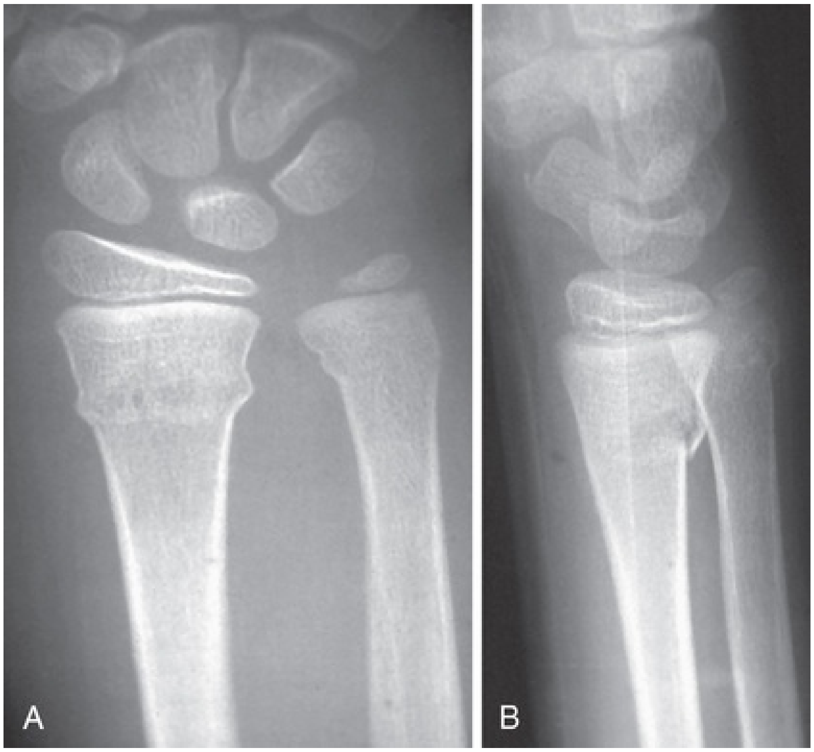

FIG. 703.6 Buckle fracture is a partial failure in compression: anteroposterior **(A)** and lateral **(B)** radiographs of the distal radius. (From Dormans JP: *Pediatric orthopedics: introduction to trauma* , Philadelphia, 2005, Mosby, p. 37.)

Greenstick Fracture

These fractures occur when the bone is bent, and there is failure on the tensile (convex) side of the bone. The fracture line does not propagate to the concave side of the bone (Fig. 703.7). The concave side shows evidence of microscopic failure with plastic deformation. If the angulation at the fracture site is unacceptable, it is usually necessary to break the bone on the concave side because the plastic deformation recoils it back to the deformed position. It is important to distinguish this unicortical fracture pattern from buckle fractures, as these fractures are at greater risk of loss of reduction and often need a longer period of immobilization.

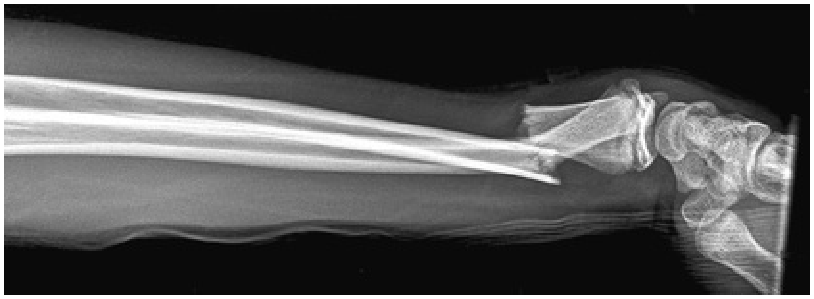

FIG. 703.7 This displaced distal radius fracture has an ulna fracture that is a greenstick (complete failure on the tensile side with microscopic failure on the compression side).

Complete Fractures

Fractures that propagate completely through the bone are called *complete fractures* . These fractures may be classified as spiral, transverse, or oblique, depending on the direction and shape of the fracture lines. A rotational force is responsible for spiral fractures, and most of these fractures are stable and heal quickly due to the large surface area; however, spiral fractures as a result of a high-energy trauma may present with shortening of the bone and loss of alignment. Oblique fractures are defined by a 30-degree angle to the axis of the bone and are often unstable. The transverse fracture pattern occurs following a 3-point bending force and are amenable to successful reduction by using the intact periosteum from the concave side as a hinge.

Epiphyseal Fractures

Fractures involving the epiphysis often involve the growth plate; therefore there is a potential for growth disturbance leading to deformity or discrepancy, and hence long-term observation is necessary. The distal radial physis is the most commonly injured physis. Salter and Harris (SH) classified epiphyseal injuries into five groups (Table 703.1 and Fig. 703.8). This classification helps to predict the outcome of the injury and offers guidelines in formulating treatment. Most SH type I and II fractures usually can be managed by closed reduction techniques and do not require perfect alignment, because they tend to remodel with growth, as long as there is enough growth remaining. One classic exception is the distal femur, where SH type II fractures are unstable and require anatomic reduction with adequate fixation. The SH type III and IV epiphyseal fractures involve the articular surface and require anatomic alignment (<2 mm displacement) to prevent any step off and realign the growth cells of the physis. SH type V fractures are usually not diagnosed initially. They manifest in the future with growth disturbance. Other injuries to the epiphysis are avulsion injuries of the tibial spine and muscle attachments to the pelvis. Osteochondral fractures are also defined as physeal injuries that do not involve the growth plate.

Table 703.1

Salter-Harris Classification

SALTER-HARRIS TYPE	CHARACTERISTICS
I	Separation through the physis, usually through the zones of hypertrophic and degenerating cartilage cell columns
II	Fracture through a portion of the physis but extending through the metaphyses
III	Fracture through a portion of the physis extending through the epiphysis and into the joint
IV	Fracture across the metaphysis, physis, and epiphysis
V	Crush injury to the physis

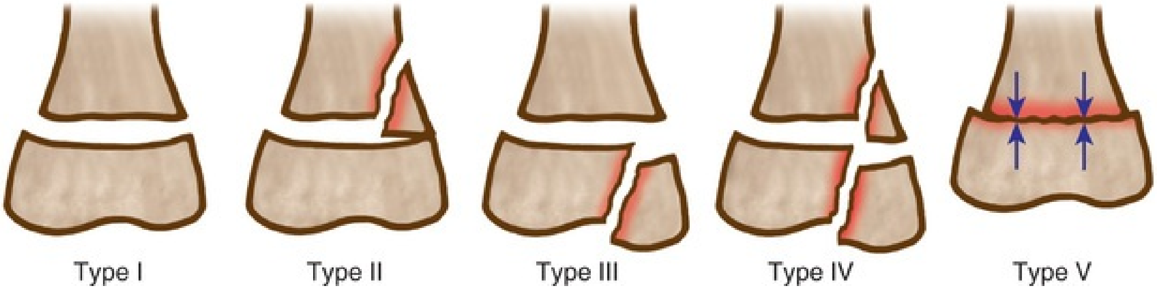

FIG. 703.8 Salter-Harris classification of physeal fractures, types I-V.

Child Abuse

(See also Chapter 16 .)

Fractures are the second most common manifestation of child abuse after skin injury (bruises, burns/abrasions). The orthopedic surgeon sees 30–50% of all nonaccidental traumas. Child abuse should be suspected in nonambulatory children with lower-extremity long-bone fractures. No fracture pattern or types are pathognomonic for child abuse; any type of fracture can result from nonaccidental trauma. **Transverse fractures** in long bones are the most prevalent, while **corner fractures** in the metaphysis are the most classic. The fractures that suggest nonaccidental injury include femur fractures in nonambulatory children (younger than age18 mo), distal femoral metaphyseal corner fractures, posterior rib fractures, scapular spinous process fractures, and proximal humeral fractures. Fractures that were unwitnessed or carry a suspicious or changing story or delayed presentation also warrant investigation. A full skeletal survey (as opposed to a "babygram") is essential in every suspected case of child abuse, because it can demonstrate other fractures in different stages of healing. Radiographically, some systemic diseases mimic signs of child abuse, such as osteogenesis imperfecta, osteomyelitis, Caffey disease, and fatigue fractures. Many hospitals have a multidisciplinary team to evaluate and treat patients who are victims of child abuse; these teams are critical to engage early and preferably in the emergency room setting, as difficulty arises managing these emotionally charged issues in a clinic setting. Dedicated teams are most well equipped to identify and manage these issues. It is mandatory to report these cases to social welfare agencies.

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703.3

Upper Extremity Fractures

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Keywords

pediatric fractures
physis
physeal fractures

Phalangeal Fractures

Finger fractures are among the most common fracture types in children. The different phalangeal fracture patterns in children include physeal, diaphyseal, and tuft fractures. The mechanism of injury varies from a direct blow to the finger to a finger trapped in a door (see Chapter 701). Crush injuries of the distal phalanx manifest with severe comminution of the underlying bone (tuft fracture), disruption of the nail bed, and significant soft tissue injury. These injuries are best managed with irrigation, tetanus prophylaxis, and antibiotic prophylaxis; antibiotics effective against staphylococci (e.g., first-generation cephalosporins) are usually appropriate, although the mechanism of injury may warrant other antibiotic coverage. Radiographs in patients with fingertip crush injuries should be scrutinized for evidence of a Seymour's fracture, an open physeal fracture of the distal phalanx with possible interposition of the nail matrix. These patients are at higher risk of nail plate deformity and infection without surgical treatment. A **mallet finger** deformity is the inability to extend the distal portion of the digit and is caused by a hyperflexion injury. It represents an avulsion fracture of the physis of the distal phalanx. The treatment is continuous splinting the digit in extension for 6 wk. The physeal injuries of the proximal and middle phalanx are similarly treated with cast immobilization. The most common physeal finger fracture results from an abduction injury to the small finger. These fractures often require a closed reduction prior to immobilization. Diaphyseal fractures may be oblique, spiral, or transverse in fracture geometry. They are assessed for angular and rotational deformity with the finger in flexion. The patient should be asked to make a fist. All fingers should point toward the scaphoid. If they do not, a malrotation is suspected, even in the presence of x-rays which appear minimally displaced. Malrotation or angular deformity may require correction to avoid finger cross-over and to optimize hand function. These deformities are corrected with closed reduction, and if unstable, they need stabilization.

Forearm Fractures

Fractures of the wrist and forearm are very common fractures in children, accounting for nearly half of all fractures seen in the skeletally immature. The most common mechanism of injury is a fall on the outstretched hand. Eighty percent of forearm fractures involve the distal radius and ulna, 15% involve the middle third, and the rest are rare fractures of the proximal third of the radius or ulnar shaft (Fig. 703.9). Most forearm fractures in younger children are torus or greenstick fractures. The torus fracture is an impacted fracture, and there is minimal soft tissue swelling or hemorrhage. They are best treated in a short arm (below the elbow) cast and usually heal within 3-4 wk. Wrist buckle fractures have also been successfully treated with a removable splint. Impacted greenstick fractures of the forearm tend to be intrinsically stable (no cortical disruption) and may be managed with a soft bandage rather than casting.

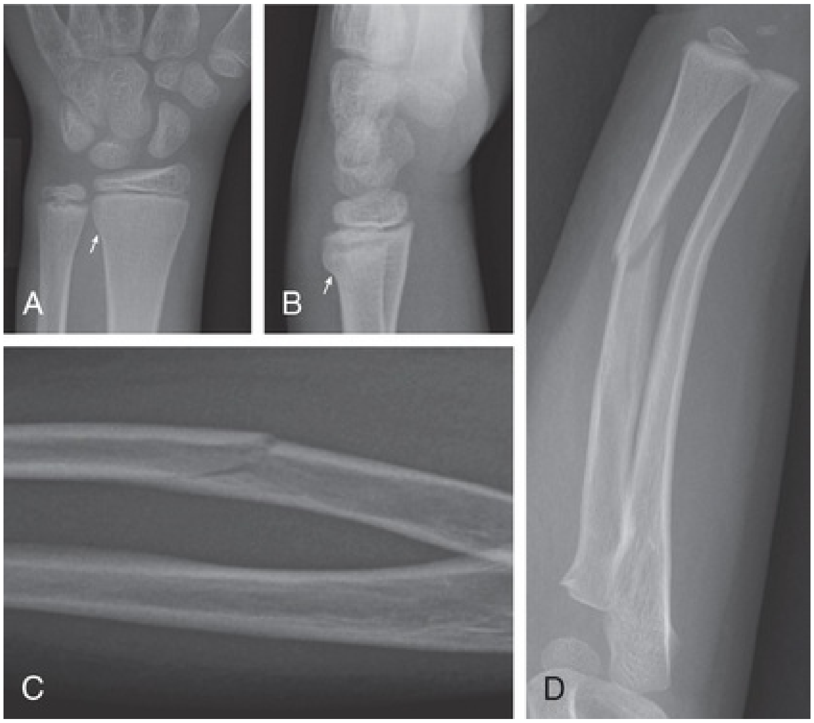

FIG. 703.9 **Common pediatric fracture patterns. A, Posteroanterior and (B) lateral radiographs of the wrist demonstrate a buckle fracture of the distal radial metaphysis (*arrows*). C, Radiograph of the forearm demonstrates a greenstick fracture of the radial shaft, with the fracture extending through a single cortex. D, Anteroposterior radiograph of the forearm shows an oblique fracture through the distal radial shaft, with plastic bowing deformity of the adjacent distal ulna. (From Walters MM, Robertson RL, editors: *Pediatric radiology: the requisites* , ed 4, Philadelphia, 2015, Elsevier. Fig. 7.90, p. 243.)**

Diaphyseal fractures can be more difficult to treat because the limits of acceptable reduction are much more stringent than for distal radial fractures. A significant malunion of a forearm diaphyseal fracture can lead to a permanent loss of pronation and supination, leading to functional difficulties. This is particularly true with malrotation of the fragments. Diaphyseal fractures are vulnerable to rotational malalignment due to insertion of the pronator muscle groups and the supinator groups. This malalignment is particularly hard to assess because the deformity is in the axial plane and is evaluated with anteroposterior (AP) and lateral radiographs (Fig. 703.10). The physical examination focuses on soft tissue injuries and ruling out any neurovascular involvement. The AP and lateral radiographs of the forearm and wrist confirm the diagnosis. Displaced and angulated fractures require manipulative closed reduction under general anesthesia or conscious sedation. They are immobilized in an above-elbow cast for at least 6 wk. Both bone fractures in older children and adolescents (>10 yr of age) must be followed carefully as they often lose reduction. Loss of reduction and unstable fractures require open reduction and internal fixation. Fixation may be with intramedullary nails or plate fixation, which yield similar results.

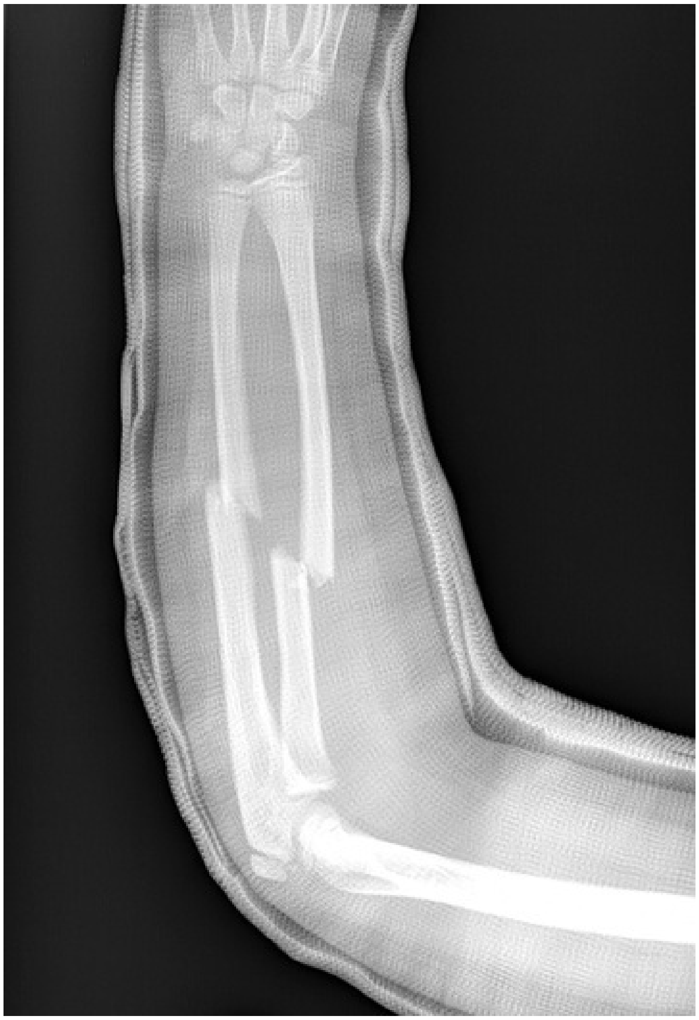

FIG. 703.10 A rotationally malaligned forearm fracture that initially had good alignment but lost reduction in the cast. Note that the radial styloid is visible, but the biceps tuberosity is not. The 2 should normally be 180 degrees from one another. These landmarks are sometimes hard to appreciate in children but were visible on other views in this child.

Distal Humeral Fractures

Fractures around the elbow receive more attention because more aggressive management is needed to achieve a good result. Many injuries are intraarticular, involve the physeal cartilage, and can result in malunion or nonunion. As the distal humerus develops from a series of ossification centers, these ossification centers can be mistaken for fractures by inexperienced eyes. Careful radiographic evaluation is an essential part of diagnosing and managing distal humeral injuries. It is important to remember that the distal humerus is only responsible for 20% of the growth of the humerus; therefore there is very low potential for remodeling. Observation of soft tissue swelling and tenderness is critical to pick up subtle injuries. Common fractures include separation of the distal humeral epiphysis (transcondylar fracture), supracondylar fractures of the distal humerus, and epiphyseal fractures of the lateral condyle or medial epicondyle. The mechanism of injury is a fall on an outstretched arm. The physical examination includes noting the location and extent of soft tissue swelling, ruling out any neurovascular injury, specifically anterior interosseous nerve involvement or evidence of compartment syndrome. *A transphyseal fracture in a very young child, who does not have the reflex to keep the arm outstretched during to break a fall, should raise suspicion of child abuse.* AP and lateral radiographs of the involved extremity are necessary for the diagnosis. If the fracture is not visible, but there is an altered relationship between the humerus and the radius and ulna or the presence of a posterior fat pad sign, a transcondylar fracture or an occult fracture should be suspected (Fig. 703.11). Imaging studies such as oblique radiographs, CT, MRI, and ultrasonography may be required for further confirmation. Displaced supracondylar fractures may be associated with concomitant neurovascular injury (Fig. 703.12) or, rarely, a compartment syndrome. Ulnar nerve injury is identified by decreased sensation over the cutaneous innervation of the lateral aspects of the hand as well as a motor deficit of abduction and adduction. Neurologic injury may also appear in the postoperative period. Careful neurologic examination of the hand before and after is needed to document and treat nerve injury. Most nerve injuries associated with displaced supracondylar fractures are neuropraxias and will resolve in several months.

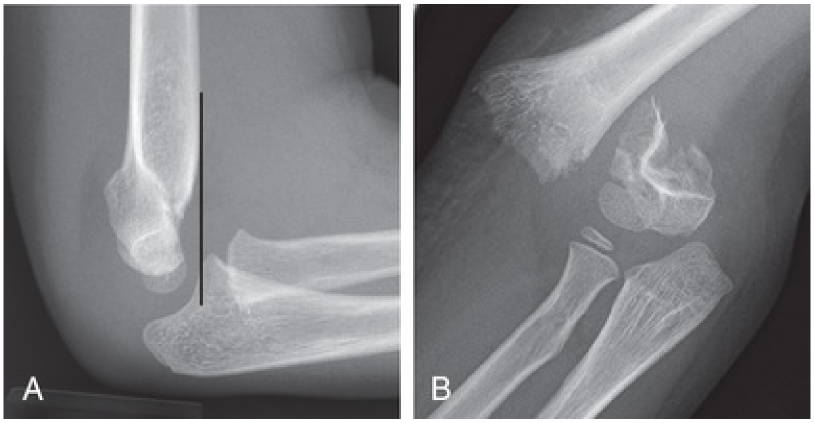

FIG. 703.11 **Supracondylar humerus fracture. A, Lateral radiograph of the elbow**

demonstrates a type II supracondylar humerus fracture, with disruption of the anterior humeral line *(black line).* This line normally passes through the middle third of the capitellum. Here the capitellum is displaced behind the line. A large joint effusion is noted. B, Anteroposterior radiograph of the elbow shows a type III supracondylar humerus fracture. There is no cortical continuity and significant displacement and overlap of fracture fragments. (From Walters MM, Robertson RL, editors: ***Pediatric radiology: the requisites*** , ed 4, Philadelphia, 2015, Elsevier. Fig. 7.97.)

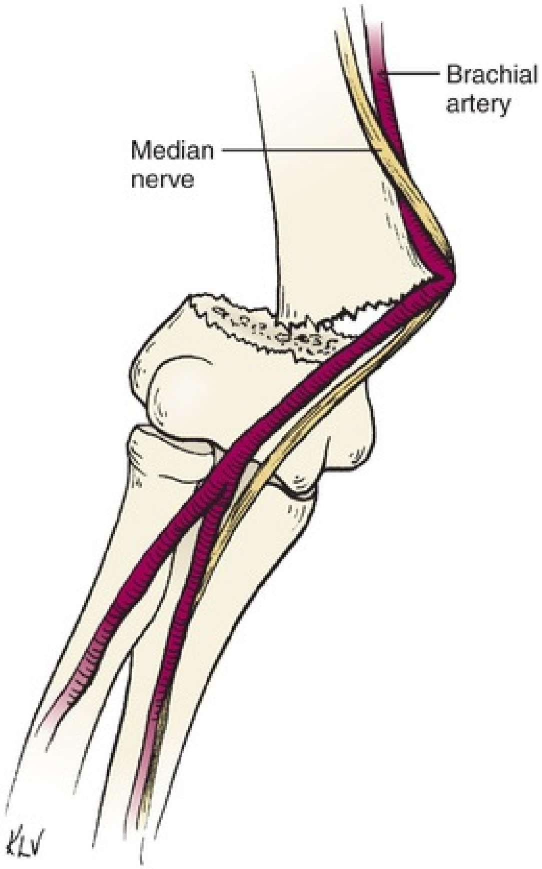

FIG. 703.12 Posterolaterally displaced type III (extension-type) supracondylar humeral fracture. The proximal fragment displaces anteromedially. Thus placing the brachial artery and median nerve at risk. (From Herring JA, Ho C: Upper extremity injuries. In Herring JA, editor: ***Tachdjian's pediatric orthopaedics*** , ed 5, Philadelphia, 2014, WB Saunders, Fig. 33.36, p. 1268.)

In general, distal humeral fractures need restoration of anatomic alignment. This is necessary to prevent deformity and to allow for normal growth and development. Closed reduction alone, or in association with percutaneous fixation, is the preferred method. Open reduction is indicated for fractures that cannot be reduced by closed methods, fractures with vascular compromise following closed reduction, open fractures, or interarticular fractures, particularly in older children. Inadequate reductions can lead to loss of motion, cubitus varus, cubitus valgus, and rare nonunion or elbow instability. Elbow stiffness is not as common as in adult fractures but may occur with fractures which are severe or intraarticular.

Proximal Humerus Fractures

Fractures of the proximal humerus account for <5% of fractures in children. They usually result from a fall onto an outstretched arm, or direct trauma. The fracture pattern tends to vary with the age group. Physeal and metaphyseal fractures are both common. Among physeal fractures of the proximal humerus, children younger than 5 yr of age have an SH I injury, those 5-10 yr of age have metaphyseal fractures, and children older than 11 yr of age have SH II injury. Examination includes a thorough neurologic evaluation, especially of the axillary nerve. The diagnosis is made on AP radiographs of the shoulder. An axillary view is obtained to rule out any dislocation, and to assess angular deformity in an orthogonal plane. Many children are too uncomfortable to tolerate this view. In this case, a Velpeau axillary can be obtained while the arm remains in a sling. SH I injuries do not require reduction because they have excellent remodeling capacity, and simple immobilization in a sling for 2-3 wk is sufficient. Metaphyseal fractures usually do not need reduction unless the angulation is >50 degrees. In general, sling immobilization is all that is required. SH II fractures with <30 degrees of angulation and <50% displacement are managed in a sling. Displaced fractures are treated with closed reduction and further stabilization if unstable. Occasionally, open reduction is required because of button-holing of the fracture spike through the deltoid or interposition of the tendon of biceps. The majority of longitudinal growth (80%) of the limb comes from the proximal humeral physis. Additionally, the glenohumeral joint is capable of a large amount of motion. As such, this area is extremely tolerant to deformity. Indications for open reduction are rare. However, as adolescents approach adulthood, these fractures will remodel less.

Clavicular Fractures

Neonatal fractures occur as a result of direct trauma during birth, most often through a narrow pelvis or following shoulder dystocia. They can be missed initially and can appear with pseudoparalysis. Childhood fractures are usually the result of a fall on the affected shoulder or direct trauma to the clavicle. The most common site for fracture is the junction of the middle and lateral 3rd clavicle. Tenderness over the clavicle will make the diagnosis. A thorough neurovascular examination is important to diagnose any associated **brachial plexus injury.** Biceps function is important to assess, as it is a prognostic indicator for future function.

An AP radiograph of the clavicle demonstrates the fracture and can show overlap of the fragments. Physeal injuries occur through the medial or lateral growth plate and are sometimes difficult to differentiate from dislocations of the acromioclavicular or sternoclavicular joint. Further imaging such as a CT scan may be necessary to further define the injury. Posterior medial clavicular physeal injuries are particularly problematic due to their proximity to the great vessels and the trachea. Closed versus open reduction with a cardiac/thoracic team on standby is necessary. This can be delayed if there is no sign of vascular or respiratory compromise.

The treatment of most clavicle fractures consists of an application of a figure-of-eight clavicle strap or a simple sling. A figure-of-eight strap will extend the shoulders and minimize the amount of overlap of the fracture fragments. Evidence exists for adults—that fractures that are shortened or displaced result in strength loss of the shoulder without anatomic reduction and fixation. Many centers are extending that indication to older adolescents, although the data are currently not as strong as for adults. If a fracture is tenting the skin, or open or resulting in neurovascular compromise, surgery is indicated. The physeal fractures are treated with simple sling immobilization without any reduction attempt. Often, anatomic alignment is not achieved, nor is it necessary. The fractures heal rapidly usually in 3-6 wk. A palpable mass of callus is usually visible in thin children. This remodels satisfactorily in 6-12 mo. Complete restoration of shoulder motion and function is uniformly achieved.

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703.4

Lower Extremity Fractures

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Keywords

pediatric fractures
physis
physeal fractures

Hip Fracture

Hip fractures in children account for <1% of all children's fractures. These injuries result from high-energy trauma and can be associated to injury to the chest, head, or abdomen. Treatment of hip fractures in children entails a complication rate of up to 60%, an overall avascular necrosis rate of 50%, and a malunion rate of up to 30%. The unique blood supply to the femoral head accounts for the high rate of avascular necrosis. Fractures are classified by the Delbet classification as transphyseal separations, transcervical fractures, cervicotrochanteric fractures, and intertrochanteric fractures. The management principle includes urgent anatomic reduction (either open or closed), stable internal fixation (avoiding the physis if possible), and spica casting if the child is younger. Urgent management has been associated with a lower rate of avascular necrosis and superior overall outcomes. Capsular decompression also has been advocated as decreasing overall pressure on the epiphyseal vessels and has been demonstrated experimentally. The clinical results have been mixed.

Femoral Shaft Fractures

Fractures of the femur in children are common. All age groups, from early childhood to adolescence, can be affected. The mechanism of injury varies from low-energy twisting type injuries to high-velocity injuries in vehicular accidents. *Femur fractures in children younger than age 2 yr should raise the concern for child abuse.* A thorough physical examination is necessary to rule out other injuries and assess the neurovascular status. In the case of high-energy trauma, any signs of hemodynamic instability should prompt the examiner to look for other sources of bleeding. AP and lateral radiographs of the femur demonstrate the fracture. An AP radiograph of the pelvis is obtained to rule out any associated pelvic fracture. Treatment of shaft fractures varies with the age group, as described in Table 703.2 .

Table 703.2

Femoral Shaft Fracture: Treatment Options by Age

TREATMENT OPTIONS	0-2 YR	3-5 YR	6-10 YR	>11 YR
Spica cast	x	x		
Traction and spica cast		x	x	x
Intramedullary rod		x	x	x
External fixator		x*	x*	x*
Screw or plate		x	x	x

* Open fracture.

Modified from Wells L: Trauma related to the lower extremity. In Dormans JP, editor: *Pediatric orthopaedics: core knowledge in orthopaedics* , Philadelphia, 2005, Mosby, p. 93.

Proximal Tibia Fractures

Proximal tibia fractures can be physeal injuries, metaphyseal injuries, or avulsion injuries of the tibial spine or tubercle. Physeal injuries can be either isolated or as part of tibial tubercle fracture. If the distal segment is displaced posteriorly the trifurcation of the popliteal vessels may be involved. Careful neurovascular examination is warranted both pre- and postreduction. Anatomic reduction and pin fixation is preferred with unstable fractures or displaced SH III or IV fractures.

Proximal tibial metaphyseal fractures, or the so-called cozen fracture, are most common in the 3-6 yr old age group. They may result in a late valgus deformity even if anatomically reduced. This deformity tends to remodel within 1-2 yr but can cause great distress to parents and treating clinicians.

Tibial eminence fractures are fractures of the bony prominence that is the attachment of the anterior cruciate ligament. The mechanism of injury is similar to an anterior cruciate ligament tear in an adult. Displaced fractures require surgical reduction and fixation. This may be done either open or arthroscopically.

Tibial tubercle fractures are common in patients with Osgood-Schlatter syndrome. Care must be taken to observe for compartment syndrome as the injury is associated with injury of the recurrent anterior tibial artery. The injury may be treated nonoperatively if the fracture is displaced <2 mm and the patient has no extensor lag (rare). Open reduction and internal fixation is preferred otherwise.

Tibia and Fibula Shaft Fractures

The tibia is the most commonly fractured bone of the lower limb in children. This fracture generally results from a direct injury. Most tibial fractures are associated with a fibular fracture, and the mean age of presentation is 8 yr. The child has pain, swelling, and deformity of the affected leg and is unable to bear weight. Distal neurovascular examination is important in assessment. The AP and lateral radiographs should include the knee and ankle. Closed reduction and immobilization are the standard method of treatment. Most fractures heal well, and children usually have excellent results. Open fractures need to undergo irrigation and debridement, and antibiotic treatment. The tibia is a subcutaneous bone. Severe soft tissue loss may necessitate plastic surgery consultation. Definitive external fixation versus internal fixation and simultaneous soft tissue coverage are alternate treatment strategies to minimize infection. Tibia fractures are associated with compartment syndrome. Vigilance is necessary to avoid disastrous outcomes in the setting of missed compartment syndrome. *Emergent* *fasciotomy is indicated as soon as compartment syndrome is diagnosed.* Several return trips to the operating room are often necessary to close, versus cover, the fasciotomy wounds.

Toddler Fracture

Toddler fractures occur in young ambulatory children. The age range for this fracture is typically from around 1-4 yr (Fig. 703.13). The injury often occurs after a seemingly harmless twist or fall and is often unwitnessed. It is a result of a torsional injury. The children in this age group are usually unable to articulate the mechanism of injury clearly or to describe the area of injury well. The radiographs may show no fracture; the diagnosis is made by physical examination. The classic symptom is refusal to bear weight, which can manifest as pulling up the affected extremity or florid display of protest. The other common sign is point tenderness at the fracture site. The AP and lateral views of the tibia-fibula might show a nondisplaced spiral fracture of the distal tibial metaphysis. An oblique view is often helpful because the fracture line may be visible in only one of the three views. Often the fracture line is not visualized until 2-3 wk later, when periosteal reaction and resorption at fracture site allow better visualization. Inflammatory markers may be ordered to rule out infectious processes if the diagnosis is in doubt. Bone scans were employed in the past but impart a large amount of radiation to the child. The fracture can be safely treated with a below-knee cast for approximately 3 wk.

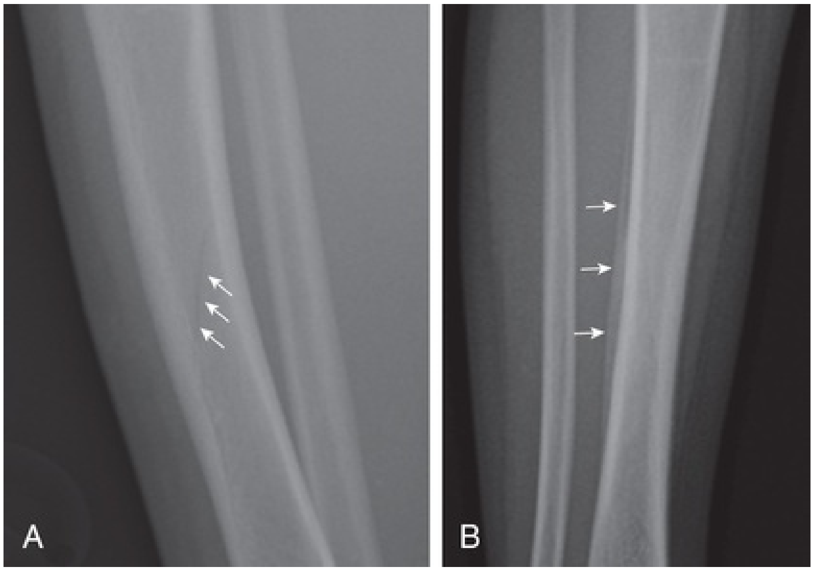

FIG. 703.13 **Toddler's fracture of the tibia in a 2 yr old girl presenting with a limp and no history of trauma. A, Lateral radiograph of the lower leg shows a subtle, nondisplaced, oblique fracture through the tibial shaft *(arrows)* . B, Anteroposterior radiograph obtained 10 days later shows healing, with subperiosteal new bone formation along the tibial shaft (*arrows*). (From Walters MM, Robertson RL, editors: *Pediatric radiology: the requisites* , ed 4, Philadelphia, 2015, Elsevier. Fig. 7.117, p. 256).**

Triplane and Tillaux Fractures

Triplane and Tillaux fracture patterns occur at the end of the growth period and are based on relative strength of the bone–physis junction and asymmetric closure of the tibial physis. The triplane fractures are so named because the injury has coronal, sagittal, and transverse components (Fig. 703.14). The Tillaux fracture is an avulsion fracture of the anterolateral aspect of the distal tibial epiphysis. Radiographs and further imaging with CT and 3-dimensional reconstructions are necessary to analyze the fracture geometry. The triplane fracture involves the articular surface and hence anatomic reduction is necessary. The reduction is further stabilized with internal fixation. The Tillaux fracture is treated by closed reduction. Open reduction is recommended if a residual intraarticular step-off persists.

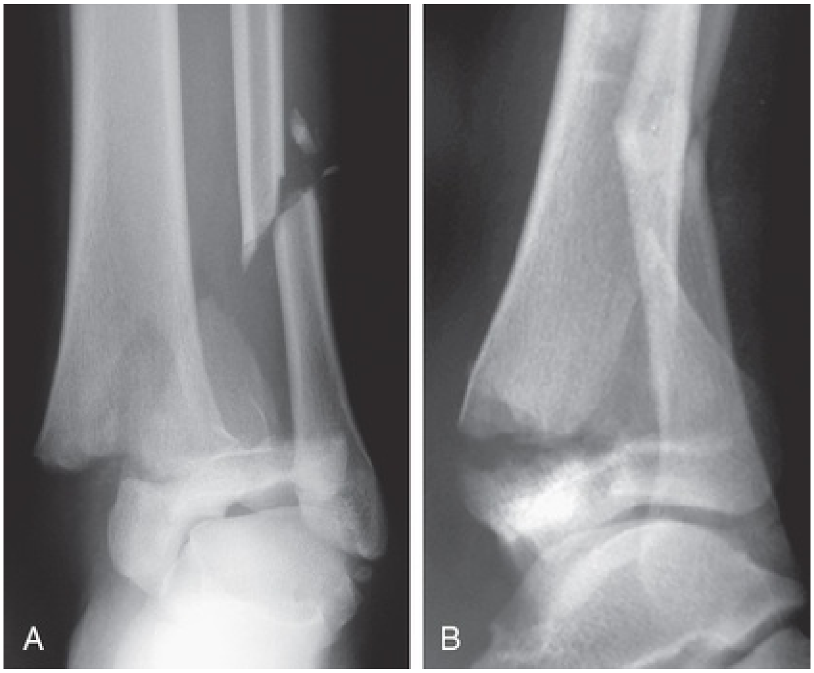

FIG. 703.14 **The triplane fracture is a transitional fracture: anteroposterior (A) and lateral (B) radiographs. (From Dormans JP: *Pediatric orthopedics: introduction to trauma* , Philadelphia, 2005, Mosby, p. 38.)**

Metatarsal Fractures

Metatarsal fractures are common in children. They usually result from direct trauma to the dorsum of the foot. High-energy trauma or multiple fractures of the metatarsal base are associated with significant swelling. A high index for compartment syndrome of the foot must be maintained and compartment pressures must be measured if indicated. Diagnosis is obtained by AP, lateral, and oblique radiographs of the foot. Most metatarsal fractures can be treated by closed methods in a below-knee cast. Weight bearing is allowed as tolerated. Displaced fractures can require closed or open reduction with internal fixation. Percutaneous, smooth Kirschner wires generally provide sufficient internal fixation for these injuries. If the compartment pressure is increased, complete release of all compartments in the foot is necessary.

Toe Phalangeal Fractures

Fractures of the lesser toes are common and are usually secondary to direct blows. They commonly occur when the child is barefoot. The toes are swollen, ecchymotic, and tender. There may be a mild deformity. Diagnosis is made radiographically. Bleeding suggests the possibility of an open fracture. The lesser toes usually do not require closed reduction unless significantly displaced. If necessary, reduction can usually be accomplished with longitudinal traction on the toe. Casting is not usually necessary. Buddy taping of the fractured toe to an adjacent stable toe usually provides satisfactory alignment and relief of symptoms. Crutches and heel walking may be beneficial for several days until the soft tissue swelling and the discomfort decrease.

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703.5

Operative Treatment of Fractures

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Keywords

pediatric fractures
physis
physeal fractures
surgical treatment

Surgery is required for 4–5% of pediatric fractures. The common indications for operative treatment in children and adolescents include displaced physeal fractures, displaced intraarticular fractures, unstable fractures, multiple injuries, open fractures, failure to achieve adequate reduction in older children, failure to maintain an adequate reduction, and certain pathologic fractures.

The aim of operative intervention is to obtain anatomic alignment and relative stability. Rigid fixation is not necessary as it is in adults for early mobilization. The relatively stable construct can be supplemented with external immobilization. SH types III and IV injuries require anatomic alignment, and if they are unstable, internal fixation is used (smooth Kirschner wires, preferably avoiding the course across the growth plate). Multiple closed reductions of an epiphyseal fracture are contraindicated because they can cause permanent damage to the germinal cells of the physis.

Surgical Techniques

It is important to take great care with soft tissues and skin. The other indications for open reduction and internal fixation are unstable fractures of the spine, ipsilateral fractures of the femur and tibia, neurovascular injuries requiring repair, and open fractures. Closed reduction and minimally invasive fixation are specifically used for supracondylar fractures of the distal humerus and most phalangeal fractures. Failure to obtain anatomic alignment by closed means is an indication for an open reduction. Percutaneous techniques such as intramedullary fixation and minimally invasive plate osteosynthesis are increasingly popular as well.

As children become older and more similar to adults, techniques become more similar to adult techniques. The classic example of this is the femoral shaft fracture. Newborns may be treated with a soft dressing or Pavlik harness; young children may have a spica cast; older children will often be treated with flexible nails. Adolescents will frequently be treated with rigid intramedullary fixation similar to their adult counterparts.

Table 703.3 summarizes the main indications for external fixation. The advantages of external fixation include rigid immobilization of the fractures, access to open wounds for continued management, and easier patient mobilization for treatment of other injuries and transportation for diagnostic and therapeutic procedures. The majority of complications with external fixation are pin tract infections, chronic osteomyelitis, and refractures after pin removal.

Table 703.3

Common Indications for External Fixation in Pediatric Fractures

Grades II and III open fractures
Fractures associated with severe burns
Fractures with soft tissue loss requiring free flaps or skin grafts
Fractures requiring distractions such as those with significant bone loss
Unstable pelvic fractures
Fractures in children with associated head injuries and spasticity
Fractures associated with vascular or nerve repairs or reconstruction

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703.6

Complications of Fractures in

Children

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Keywords

pediatric fractures
physis
physeal fractures
complications

Complications of fractures in children can be categorized as (1) complications of the injury itself, (2) complications of treatment, and (3) late complications resulting from growth disturbance or deformity.

Complications Resulting From Injury

Growth arrest is possible in physeal fractures, particularly widely displaced physeal fractures about the distal femur, proximal tibia, or distal ulna. Fractures about the hip may cause avascular necrosis or premature physeal closure, particularly when the fracture involves the proximal femoral physis. Unacceptable alignment may cause loss of motion or limb malalignment. Fracture malunion may cause cosmetically unappealing bumps or curves in the limb, and at times functional impairment. Compartment syndrome can occur, particularly in diaphyseal tibia fractures or high energy or open both bone forearm fractures. Supracondylar humerus fractures, distal femur fractures, and proximal tibia fractures may result in neurovascular compromise. Nonunions are rare in children, but can be seen with intraarticular fractures, such as distal humerus lateral condyle. Malunions (or missed) of Monteggia fracture dislocations about the elbow can cause permanent stiffness and loss of function if the deformity is not corrected. Displaced intraarticular fractures can result in posttraumatic arthritis and early joint degeneration. Open fractures can result in infection and osteomyelitis if inadequately treated. Older children with severe injuries of the lower extremity can be vulnerable to deep vein thrombosis.

Complications of Treatment

Treatment may complicate fractures. Cast immobilization can result in cast ulcers, either from inadequate padding of bony prominences or from patients placing objects in the cast. Casts that are too tight can cause neurovascular compromise and compartment syndrome. Patients can get cast saw burns from using cast saws that are too dull to remove the cast. Safe operation of a cast saw requires monitoring of blade temperature. The saw blade should be intermittently cooled with a wet towel to avoid overheating and thermal injury to the skin. Improperly placed casts can promote fracture displacement and malunion. Surgical treatment can be complicated by blood loss, neurovascular compromise, iatrogenic physeal damage, and hardware complications such as infection or hardware failure. Symptomatic hardware may require later removal.

Late Complications of Trauma

Late effects of trauma can be from partial or complete closure of the physis, or malunion of the fracture. This can lead to limb angular deformity, shortening, or incongruency. Angular deformities can be treated by hemiepiphysiodesis or osteotomy. Joint incongruency may be a very difficult problem to deal with and may ultimately lead to early degenerative joint disease. Reflex sympathetic dystrophy is another poorly understood late effect of trauma but can be debilitating. Distal radius fractures have been observed to have a higher than average rate of reflex sympathetic dystrophy relative to other injuries. Physical and occupational therapists are very helpful in managing this condition. Some evidence exists that vitamin C may be useful in the acute setting of high-risk injuries to prevent this complication.

CHAPTER 704

Osteomyelitis

Eric Robinette, Samir S. Shah

Bone infections in children are relatively common. Early recognition of osteomyelitis in young patients is of critical importance; prompt institution of appropriate medical and surgical therapy before extensive infection develops will minimize permanent damage. The risk is greatest if the physis (the growth plate of bone) is damaged.

Etiology

Bacteria are the most common pathogens in acute skeletal infections. *Staphylococcus aureus* (see Chapter 208.1) is the most common infecting organism in osteomyelitis among all age groups, including newborns. The prevalence of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) as a cause of osteomyelitis varies by region. Most studies have shown an equal or higher prevalence of methicillin-susceptible strains in otherwise healthy children with acute hematogenous osteomyelitis.

Group B streptococcus (see Chapter 211) and Gram-negative enteric bacilli (*Escherichia coli*, see Chapter 227) are also prominent pathogens in neonates; group A streptococcus (see Chapter 210) constitutes <10% of all cases. After 6 yr of age, most cases of osteomyelitis are caused by *S. aureus*, group A streptococci, or *Pseudomonas aeruginosa* (see Chapter 232.1). Cases of *Pseudomonas* infection are related almost exclusively to puncture wounds of the foot, with direct inoculation of *P. aeruginosa* from the foam padding of the shoe into bone or cartilage, which develops as osteochondritis. *Salmonella* species (see Chapter 225) and *S. aureus* are the two most common causes of osteomyelitis in children with sickle cell disease (see Chapter 489.1). *Streptococcus pneumoniae* (see Chapter 209) most commonly causes osteomyelitis in children younger than 24 mo of age and in children with sickle cell disease, but its frequency has declined because of pneumococcal conjugate vaccines. *Bartonella henselae* (see Chapter 236) can cause osteomyelitis of any bone but especially in pelvic and vertebral bones.

Kingella kingae (see Chapter 220) is the second most common cause of osteomyelitis in children younger than 4 yr of age. The organism is established as a cause of osteomyelitis, spondylodiskitis, and septic arthritis (see Chapter 705) in this age group, especially when there is a subacute presentation. *K. kingae* can be difficult to detect unless polymerase chain reaction (PCR) testing is used.

Infection with atypical mycobacteria (see Chapter 244), *S. aureus*, or *Pseudomonas* can occur after penetrating injuries. These organisms, as well as coagulase-negative staphylococci or Gram-negative enteric bacteria, may cause bone infection related to implanted materials such as orthopedic hardware. Fungal infections usually occur as part of multisystem disseminated disease; *Candida* (see Chapter 261) osteomyelitis sometimes complicates fungemia in neonates with or without indwelling vascular catheters. Blastomycosis causes multiple bone lesions in endemic areas.

A microbial etiology is confirmed in approximately 60% of cases of osteomyelitis. Blood cultures are positive in approximately 50% of patients.

Epidemiology

The median age of children with musculoskeletal infections is approximately 6 yr. Bone infections are more common in boys than girls; the behavior of boys might predispose them to traumatic events. Except for the increased incidence of skeletal infection in patients with sickle cell disease, there is no predilection for osteomyelitis based on race.

Most osteomyelitis cases in previously healthy children are hematogenous. Minor closed trauma is a common preceding event in cases of osteomyelitis, occurring in approximately 30% of patients. Infection of bones can also follow penetrating injuries or open fractures. Bone infection following orthopedic surgery is unusually associated with an implanted surgical device. Impaired host defenses also increase the risk of skeletal infection. Table 704.1 lists other risk factors.

Table 704.1

Microorganisms Isolated From Patients With Osteomyelitis and Their Clinical Associations

MOST COMMON CLINICAL ASSOCIATION	MICROORGANISM
Frequent microorganism in any type of osteomyelitis	*Staphylococcus aureus* (susceptible or resistant to methicillin)
Associated with septic arthritis, diskitis, long or unusual bones, age <4 yr, mild symptoms	*Kingella kingae*
Foreign body–associated infection	Coagulase-negative staphylococci, other skin flora, atypical mycobacteria, fungi
Common in nosocomial infections	*Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Candida* spp.
Decubitus ulcer or ulceration associated with sensory autonomic neuropathies	*S. aureus* , streptococci, Gram-negative enterics, and/or anaerobic bacteria; polymicrobial infections are common
Sickle cell disease	*Salmonella* spp., *S. aureus*, or *Streptococcus pneumoniae*
Exposure to kittens	*Bartonella henselae*
Human or animal bites	*Pasteurella multocida* or *Eikenella corrodens*
Immunocompromised patients	*Aspergillus* spp., *Candida albicans*, or *Mycobacteria* spp.
Populations in which tuberculosis is prevalent	*Mycobacterium tuberculosis*
Populations in which these pathogens are endemic	*Brucella* spp., *Coxiella burnetii* , fungi found in specific geographic areas (coccidioidomycosis, blastomycosis, histoplasmosis)

Modified from Lew DP, Waldvogel FA: Osteomyelitis. *Lancet* 364:369–379, 2004.

Pathogenesis

The unique anatomy and circulation of the ends of long bones result in the predilection for localization of bloodborne bacteria. In the metaphysis, nutrient arteries branch into nonanastomosing capillaries under the physis, which make a sharp loop before entering venous sinusoids draining into the marrow. Low-velocity blood flow in this area predisposes to bacterial invasion. Once a bacterial focus is established, phagocytes migrate to the site and produce an inflammatory exudate (metaphyseal abscess). The generation of proteolytic enzymes, toxic oxygen radicals, and cytokines results in decreased oxygen tension, decreased pH, osteolysis, and tissue destruction. As the inflammatory exudate progresses, pressure increases spread through the porous metaphyseal space via the haversian system and Volkmann canals into the subperiosteal space. Purulence beneath the periosteum may lift the periosteal membrane of the bony surface, further impairing blood supply to the cortex and metaphysis.

In newborns and young infants, transphyseal blood vessels connect the metaphysis and epiphysis, so it is common for pus from the metaphysis to enter the joint space. This extension through the physis has the potential to result in abnormal growth and bone or joint deformity. During the latter part of the 1st year of life, the physis forms, obliterating the transphyseal blood vessels. Joint involvement, once the physis forms, can occur in joints where the metaphysis is intraarticular (hip, ankle, shoulder, and elbow), and subperiosteal pus ruptures into the joint space.

In later childhood, the periosteum becomes more adherent, favoring pus to decompress through the periosteum. Once the growth plate closes in late adolescence, hematogenous osteomyelitis more often begins in the diaphysis and can spread to the entire intramedullary canal. Septic arthritis contiguous with a site of osteomyelitis is also seen in older children with *S. aureus* osteomyelitis, which may be related to simultaneous hematogenous inoculation of bone and joint space.

Clinical Manifestations

The earliest signs and symptoms of osteomyelitis, often subtle and nonspecific, generally depend on patient age. Neonates might exhibit **pseudoparalysis** or pain with movement of the affected extremity (e.g., diaper changes). Half of neonates do not have fever and might not appear ill. Older infants and children are more likely to have pain, fever, and localizing signs such as edema, erythema, and warmth. With involvement of the lower extremities, limp, or refusal to walk is seen in approximately half of patients.

Focal tenderness over a long bone can be an important finding. Local swelling and redness with osteomyelitis suggests spread of infection beyond the metaphysis and into the subperiosteal space, representing a secondary soft tissue inflammatory response. Pelvic osteomyelitis can manifest with subtle findings such as hip, thigh, groin, or abdominal pain. Vertebral osteomyelitis typically presents as back pain with or without tenderness to palpation over the vertebral processes.

Long bones are principally involved in osteomyelitis (Table 704.2); the femur and tibia are equally affected and together constitute almost half of all cases. The bones of the upper extremities account for 25% of all cases. Flat bones are less commonly affected.

Table 704.2

Site of Involvement in Acute Hematogenous Osteomyelitis Data

SITE	%
TUBULAR BONE	
Femur	25.0
Tibia	24
Humerus	13
Phalanges	5
Fibula	4
Radius	4
Ulna	2
Metatarsal	2
Clavicle	0.5
Metacarpal	0.5
CUBOIDAL BONE	
Calcaneus	5
Talus	0.8
Carpals	0.5
Cuneiform	0.5
Cuboid	0.3
IRREGULAR BONE	
Ischium	4
Ilium	2
Vertebra	2
Pubis	0.8
Sacrum	0.8
FLAT BONE	
Skull	1
Rib	0.5
Sternum	0.5
Scapula	0.5
Maxilla	0.3
Mandible	0.3

From Krogstad P: Osteomyelitis. In Cherry JD, Harrison GJ, Kaplan SL, et al (eds): Feigin and Cherry's textbook of pediatric infectious diseases, ed 7, Philadelphia, 2014, Elsevier, Table 55-2.

Usually only a single site of bone or joint is involved, although multiple sites of osteomyelitis may be noted in up to 20% of children with *S. aureus* infections. In neonates, 2 or more bones are involved in almost half of the cases. Multifocal disease may also be seen with tuberculosis, cat-scratch disease, and brucellosis. Children with subacute symptoms and focal findings in the metaphyseal area (usually of tibia) might have a **Brodie abscess,** with radiographic lucency and surrounding reactive bone. Typically, the contents of Brodie abscesses are sterile (Fig. 704.1).

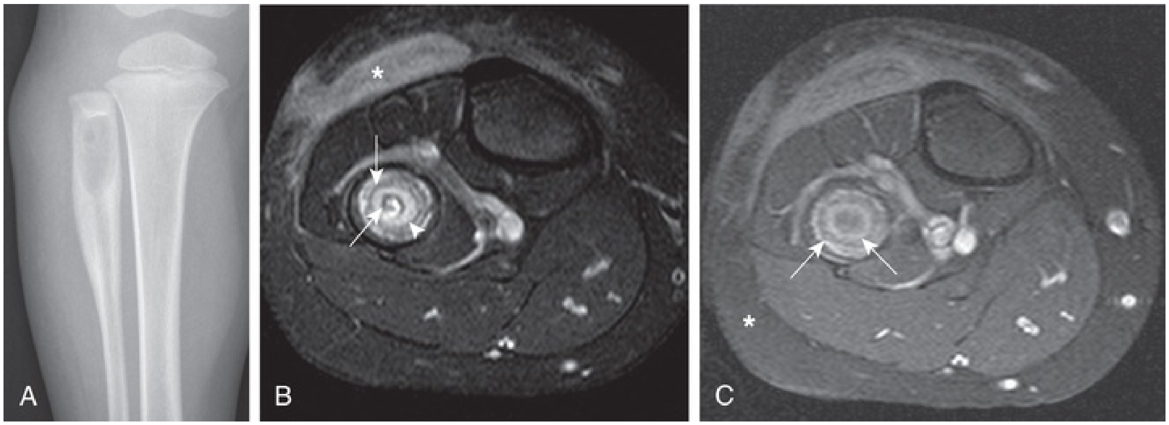

FIG. 704.1 **A,** Radiograph demonstrates a lytic lesion in the proximal fibula with laminated thick periostitis. T2-weighted fat-saturated axial **(B)** and T1-weighted fat-saturated postgadolinium axial **(C)** magnetic resonance images demonstrate a Brodie abscess with sclerotic outer rim *(asterisk)* and inner granulation tissue with enhancement *(arrowhead).* Note the nonenhancing central abscess, which contains a small sequestrum *(arrows)* that is only seen on the T2-weighted fat-saturated sequence. (From Kan JH, Azouz EM: Musculoskeletal infections. In Coley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 12, Philadelphia, 2013, WB Saunders, Fig. 138-15, p. 1477.)

Some patients with osteomyelitis due to *S. aureus* develop a deep venous thrombosis adjacent to the affected bone which can produce septic pulmonary emboli; these patients are often critically ill.

Diagnosis

The diagnosis of osteomyelitis begins with clinical suspicion and requires appropriate cultures and imaging studies. *Blood cultures should be performed in all suspected cases.* Depending on the results of imaging studies (see later), aspiration or biopsy of bone or subperiosteal abscess for Gram stain, culture, PCR for *K. kingae,* and possibly bone histology provides the optimal specimen for culture to confirm the diagnosis and significantly increases the yield compared with blood culture alone. These specimens are often obtained by the interventional radiologist or at the time of surgical drainage by the orthopedic surgeon. Direct inoculation of clinical specimens into aerobic blood culture bottles can improve the recovery of *K. kingae,* particularly if held for 1 wk. PCR is the most sensitive technique to detect *K. kingae* , even up to 6 days after antibiotics are initiated.

There are no specific laboratory tests for osteomyelitis. The white blood cell count and differential, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP) are generally elevated in children with bone infections but are nonspecific and not helpful in distinguishing between skeletal infection and other inflammatory processes. The leukocyte count and ESR may be normal during the 1st few days of infection, and normal test results do not preclude the diagnosis of skeletal infection. However, most children with acute hematogenous osteomyelitis have elevations in the ESR and/or CRP. Monitoring elevated CRP may be of value in assessing response to therapy or identifying complications.

Radiographic Evaluation

Radiographic studies play a crucial role in the evaluation of osteomyelitis. Conventional radiographs and MRI are the primary modalities. Ultrasonography, CT, and radionuclide studies can also contribute to establishing the diagnosis in selected cases.

Plain Radiographs

Within 72 hr of onset of symptoms of osteomyelitis, plain radiographs of the involved site using soft tissue technique and compared with the opposite extremity, if necessary, can show displacement of the deep muscle planes from the adjacent metaphysis caused by deep-tissue edema. Lytic bone changes are not visible on radiographs until 30–50% of the bony matrix is destroyed. Tubular long bones do not show lytic changes for 7-14 days after onset of infection. Infection in flat and irregular bones can take longer to appear. Radiographs in children with possible osteomyelitis are important to exclude other possible causes (e.g., fracture) of the presenting symptoms and signs.

Magnetic Resonance Imaging and Computed Tomography

MRI is more sensitive than CT or radionuclide imaging in acute osteomyelitis and is the best radiographic imaging technique for identifying abscesses and for differentiating between bone and soft tissue infection. MRI provides precise anatomic detail of subperiosteal pus and accumulation of purulent debris in the bone marrow and metaphyses for possible surgical intervention. In acute osteomyelitis, purulent debris and edema appear dark, with decreased signal intensity on T1-weighted images, with fat appearing bright (Figs. 704.2 and 704.3). The opposite is seen in T2-weighted images. The signal from fat can be diminished with fat-suppression techniques to enhance visualization. Gadolinium administration can also enhance MRI. Cellulitis and sinus tracts appear as areas of high signal intensity on T2-weighted images. Short tau inversion recovery MRI is a rapid imaging modality for osteomyelitis (Fig. 704.4). MRI can also demonstrate a contiguous or isolated septic arthritis, pyomyositis, or venous thrombosis. Whole body rapid STIR MRI has emerged as an effective alternative to radionuclide imaging where multiple sites of infection are suspected or the site of infection cannot be clearly localized. CT can demonstrate osseous and soft tissue abnormalities and is ideal for detecting gas in soft tissues but has poor sensitivity for detecting the presence of osteomyelitis.

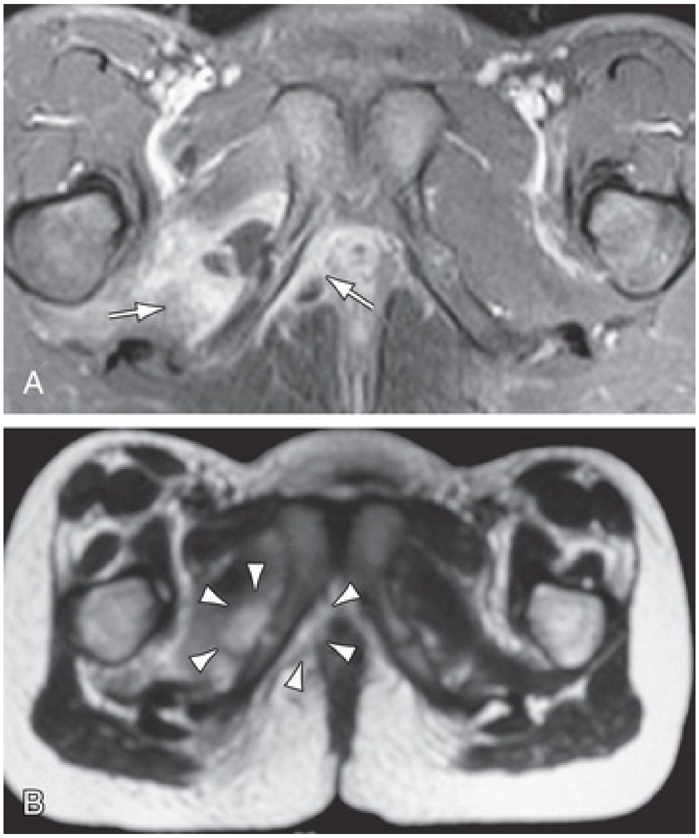

FIG. 704.2 MRI of an 8 yr old girl with acute pelvic hematogenous osteomyelitis. A, Axial T1-weighted contrast-enhanced MRI with fat saturation reveals a nonenhancing fluid collection adjacent to the inflamed pubic synchondrosis. B, The fluid collection appears hyperintense on the corresponding T2-weighted image *(arrowheads).* In addition, a contrast enhancement within the adjacent internal obturator muscle is seen *(arrow),* indicating pelvic acute pelvic hematogenous osteomyelitis with complicating

adjacent abscess formation and soft tissue inflammation. (From Weber-Chrysochoou C, Corti N, Goetschel P, et al: Pelvic osteomyelitis: a diagnostic challenge in children. *J Pediatr Surg* 42:553–557, 2007.)

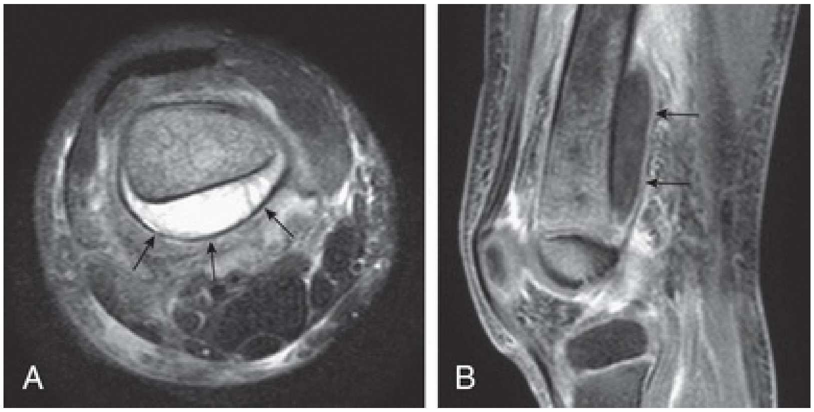

FIG. 704.3 Acute osteomyelitis of the distal femur in a 5 yr old boy. A, T2-weighted fat-saturated axial MRI shows a large subperiosteal abscess *(arrows)* at the posterior aspect of the femur. Increased signal is seen within the bone, and there is adjacent soft tissue edema. B, T1-weighted fat-saturated postgadolinium sagittal MRI shows the longitudinal extent of the subperiosteal abscess with enhancing wall *(arrows).* (From Kan JH, Azouz EM: Musculoskeletal infections. In Coley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 12, Philadelphia, 2013, WB Saunders, Fig. 138-13, p. 1476.)

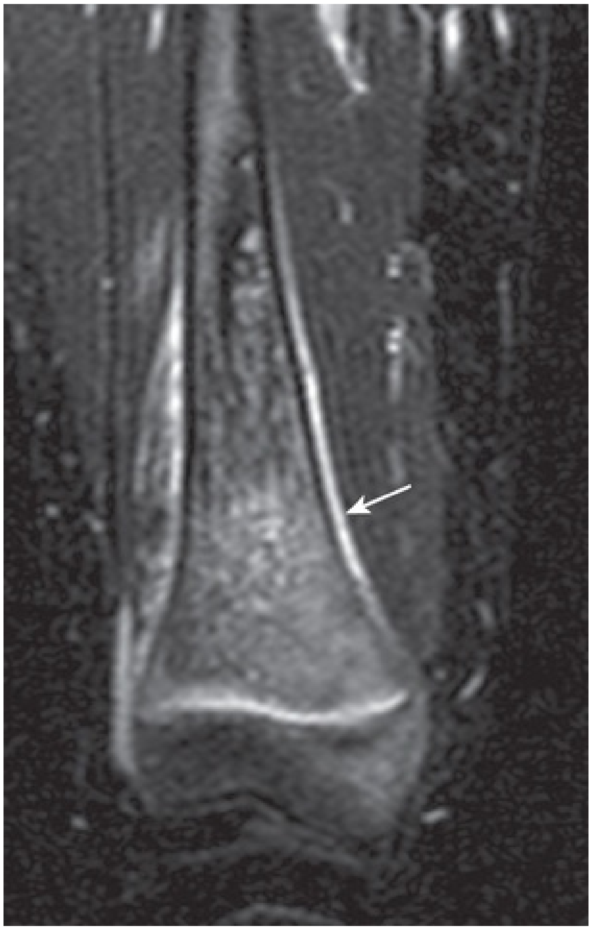

FIG. 704.4 Short tau inversion recovery coronal magnetic resonance image demonstrates a salt-and-pepper appearance to marrow edema and periosteal reaction *(arrow).* (From Kan JH, Azouz EM: Musculoskeletal infections. In Coley BD, editor: *Caffey's pediatric diagnostic imaging* , ed 12, Philadelphia, 2013, WB Saunders, Fig. 138-14, p. 1477.)

Radionuclide Studies

Radionuclide imaging, an alternative to MRI, may be useful if multiple foci are suspected. Technetium-99 methylene diphosphonate (^{99m} Tc), which accumulates in areas of increased bone turnover, is the preferred agent for radionuclide bone imaging (3-phase bone scan). Any areas of increased blood flow or inflammation can cause increased uptake of ^{99m} Tc in the 1st and 2nd phases, but osteomyelitis causes increased uptake of ^{99m} Tc in the 3rd phase (4-6 hr). Three-phase imaging with ^{99m} Tc has excellent sensitivity (84–100%) and specificity (70–96%) in hematogenous osteomyelitis and can detect osteomyelitis within 24-48 hr after onset of symptoms. The sensitivity in neonates is much lower because of poor bone mineralization. Advantages include infrequent need for sedation and the ability to image the entire skeleton for detection of multiple foci. Disadvantages include exposure to radiation, inability to image surrounding soft tissues, and overall lack of detail, which limits the tests' utility for preoperative planning.

Differential Diagnosis

Distinguishing osteomyelitis from cellulitis or trauma (accidental or abuse) is the most common clinical circumstance. Myositis or pyomyositis can also appear similar to osteomyelitis with fever, warm and swollen extremities, and limping; tenderness to palpation of the affected soft tissue area is generally more diffuse than noted in acute osteomyelitis. Nevertheless, distinguishing myositis and pyomyositis from osteomyelitis clinically may be difficult. Myositis and pyomyositis may be isolated but are often found adjacent to an osteomyelitis on MRI. Pyomyositis is most often caused by *S. aureus*, followed by group A streptococcus. The pelvic muscles are a common site of pyomyositis and can mimic a pelvic osteomyelitis. MRI is the definitive study to identify and localize pelvic pyomyositis (Fig. 704.5). An iliopsoas abscess can manifest with thigh pain, limp, and fever and must be considered in the differential diagnosis of osteomyelitis. The iliopsoas abscess may be primary (hematogenous: *S. aureus*) or secondary to infection in adjacent bone *(S. aureus)*, kidney *(E. coli)* or intestine (*E. coli* , *Bacteroides* spp.). *Mycobacterium tuberculosis* has been reported in patients with HIV infection. Any child with negative x-ray imaging and a negative hip aspiration, who presents with fever, limp, and elevated inflammatory marks should be evaluated for pyomyositis.

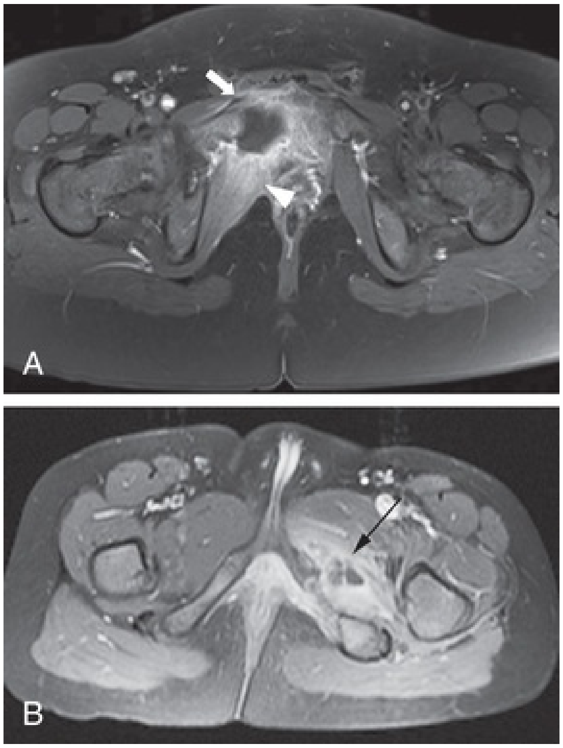

FIG. 704.5 **A,** Pelvic pyomyositis in a 10-year-old boy presenting with limping. Pelvis MRI demonstrates an avid contrast enhancement of the internal obturator muscle *(arrowhead)* with an abscess on T1-weighted fat-saturated postcontrast axial image *(arrow)* . **B,** Pyomyositis in a 7-year-old boy with left pelvic pain and fever. Axial T1 fat-saturated postcontrast image through the inferior ramus of the obturator ring demonstrates multiloculated, rim-enhancing fluid collections in the adductor muscles *(arrow)* , which is characteristic of pyomyositis. (**A,** From Bartoloni A, Gómez A, Pilar M, et al. Imaging of the limping child. *Eur J Radiol* 109:155–170, 2018, Fig 13; **B,** from Pruthi S, Thapa MM. Infectious and inflammatory disorders. *Magn Reson Imaging Clin North Am* 17:423, 2009, Fig 7.)

Appendicitis, urinary tract infection, and gynecologic disease are among the conditions in the differential diagnosis of pelvic osteomyelitis. Children with leukemia commonly have bone pain or joint pain as an early symptom. Neuroblastoma with bone involvement may be mistaken for osteomyelitis. Primary bone tumors need to be considered, but fever and other signs of illness are generally absent except in Ewing sarcoma. In patients with sickle cell disease, distinguishing bone infection from infarction may be challenging.

Chronic recurrent multifocal osteomyelitis (CRMO) is a nonpyrogenic, sterile inflammatory bone disease that is considered an autoinflammatory disorder (see Chapter 188). It is also associated with a family history of autoimmune disease; the affected patient may also have other inflammatory diseases such as Crohn disease, Sweet syndrome, psoriasis, and palmar plantar pustulosis. CRMO in children has many similarities with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome (SAPHO), seen in adults. In addition, CRMO has similarities to Majeed syndrome, an autosomal recessive disorder with a microcytic dyserythropoietic anemia and with a deficiency of interleukin-1 receptor antagonist, an autosomal recessive autoinflammatory disease.

In contrast to infectious osteomyelitis, CRMO is multifocal and recurrent and may involve bones not typical of osteomyelitis (spine, pelvis, clavicle, mandible, calcaneus). Plain radiographs reveal osteolytic lesions or sclerosis; whole body short tau inversion recovery MRI imaging is the diagnostic study of choice (Fig. 704.6).

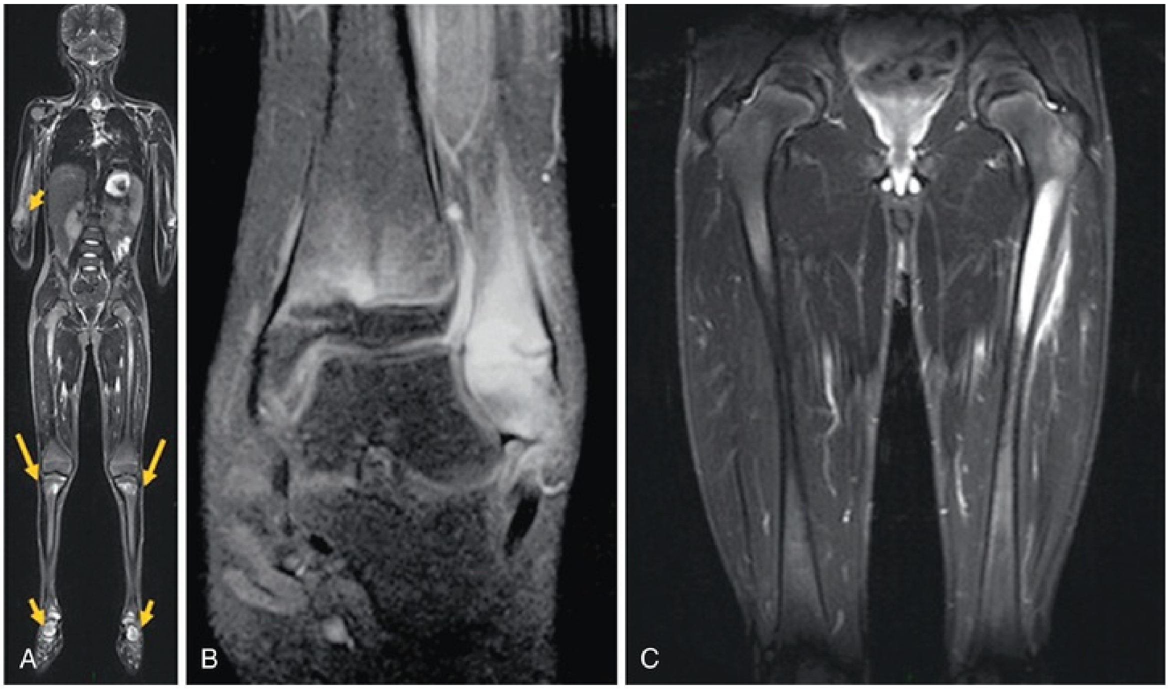

FIG. 704.6 MRI in a patient with chronic recurrent multifocal osteomyelitis. **A,** Whole body image showing multiple foci of osteomyelitis *(arrows)* , some of which are distributed symmetrically. **B,** Image of the ankle showing inflammatory metaphyseal and epiphyseal lesions. **C,** Image of the left femur showing involvement of the diaphysis with a soft tissue reaction. (From Wipff J, Adamsbaum C, Kahan A, Job-Deslandre C: chronic recurrent multifocal osteomyelitis. *Joint Bone Spine* 78:555–560, 2011, Fig. 3, p. 557.)

Pain in CRMO is usually insidious, noted at night; fever is not always present.

The mean age of onset is 10 yr. The ESR and CRP may be elevated but are not as high as in bacterial osteomyelitis. Pain usually responds to nonsteroidal antiinflammatory drugs. Second line treatments include systemic corticosteroids or tumor necrosis factor alpha inhibitors.

Treatment

Optimal treatment of skeletal infections requires collaborative efforts of pediatricians, orthopedic surgeons, and interventional radiologists. Obtaining a blood culture **before** antibiotics are given is essential. Most patients with osteomyelitis have an indolent, non–life-threatening condition, and in these circumstances antibiotics may be deferred until a decision about whether to obtain additional diagnostic cultures (periosteal abscess, bone) has been made. A short duration of antibiotic pretreatment (<24 hr) for osteomyelitis caused by *S. aureus* has a minimal impact on culture yield from abscess or bone specimens. In critically ill patients, empirical antimicrobial therapy should be initiated without delay.

Antimicrobial Therapy

The initial empirical antimicrobial therapy is based on knowledge of likely bacterial pathogens at various ages, the results of the Gram stain of aspirated material, and additional considerations. In neonates, an antistaphylococcal penicillin, such as nafcillin or oxacillin (150-200 mg/kg/24 hr divided q6h IV), and a broad-spectrum cephalosporin, such as cefepime (100 to 150 mg/kg/24 hr divided q12h IV), provide coverage for the methicillin-susceptible *S. aureus*, group B streptococcus, and Gram-negative bacilli. If methicillin-resistant *Staphylococcus* is suspected, vancomycin is substituted for nafcillin. If the neonate is a small premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (Gram-negative enteric, *Pseudomonas*, or *S. aureus*) or fungi *(Candida* spp.*)* should be considered. In older infants and children, the principal pathogens are *S. aureus*, *K. kingae*, and group A streptococcus.

Cefazolin (150 mg/kg/24 hr divided q6h IV) or nafcillin (150-200 mg/kg/24 hr divided q6h) is the agent of choice for parenteral treatment of osteomyelitis caused by methicillin-susceptible *S. aureus* and is the backbone of empirical treatment for acute hematogenous osteomyelitis. A major factor influencing the selection of empirical therapy is the rate of methicillin resistance among community *S. aureus* isolates. Vancomycin (60 mg/kg/24 hr divided q6h IV) is the “gold standard” agent for treating invasive MRSA infections. In areas with a high local prevalence of CA-MRSA infection, the addition of vancomycin to a beta-lactam should be considered, especially if the child is critically ill. Because β-lactams are superior to vancomycin for the treatment of MSSA, dual drug therapy in critically ill children should be continued until the causative organism is identified and susceptibilities are known. Rapid molecular diagnostic tests which can accurately differentiate MRSA from MSSA within hours of blood culture positivity can help to avoid prolonged exposure to multiple agents. Clindamycin (40 mg/kg/24 hr divided q6h IV) is the best studied alternative therapy for susceptible isolates of MRSA and for MSSA when a β-lactam cannot otherwise be used. Clindamycin can also be considered for empirical treatment when the rate of clindamycin resistance is low among community *S. aureus* isolates, the child is not severely ill, and bacteremia is not a concern or blood cultures are known to be negative. Penicillin is first line therapy for treating osteomyelitis caused by susceptible strains of *S. pneumoniae,* as well as all group A streptococci. Cefotaxime or ceftriaxone is recommended for pneumococcal isolates with resistance to penicillin and for most *Salmonella* spp.

Special situations dictate deviations from the usual empirical antibiotic selection. In patients with sickle cell disease with osteomyelitis, Gram-negative enteric bacteria *(Salmonella)* are common pathogens, as well as *S. aureus,* so a broad-spectrum cephalosporin such as cefepime (150 mg/kg/24 hr q8h IV) is used in addition to vancomycin or clindamycin. Clindamycin (40 mg/kg/24 hr divided q6h IV) is a useful alternative drug for patients allergic to β-lactam drugs. In addition to good antistaphylococcal activity, clindamycin has broad activity against anaerobes and is useful for treating infections secondary to penetrating injuries or compound fractures. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime, cefepime, or piperacillin-tazobactam, with or without an aminoglycoside. *K. kingae* responds to β-lactam antibiotics, including penicillin and cephalosporins, but some isolates produce a β-lactamase. Thus a first-generation cephalosporin (cefazolin) is a reasonable component of empirical therapy in children younger than 4 yr of age. Although the efficacy of treating osteomyelitis caused by *B. henselae* is uncertain, azithromycin plus rifampin may be considered.

When the pathogen is identified and antibiotic susceptibilities are determined, appropriate adjustments in antibiotics are made as necessary. If a pathogen is not identified and a patient's condition is improving, therapy is continued with the initially selected antibiotic. This selection is more complicated owing to the presence of MRSA isolates in the community. If a pathogen is not identified and a patient's condition is not improving, reaspiration or biopsy and the possibility of a noninfectious condition should be considered.

Duration of antibiotic therapy is individualized depending on the organism isolated and clinical course. For most infections including those caused by *S. aureus* , the minimal duration of antibiotics is 21-28 days, provided that the patient shows prompt resolution of signs and symptoms (within 5-7 days) and the CRP has normalized; a total of 4-6 wk of therapy may be required for those with slower resolution of symptoms or normalization of CRP. For group A streptococcus, *S. pneumoniae*, or *Haemophilus influenzae* type b, treatment duration may be shorter. A total of 7-10 postoperative days of treatment is adequate for *Pseudomonas* osteochondritis from a foot puncture wound, when curettage of infected tissue has been performed. Immunocompromised patients generally require prolonged courses of therapy, as do patients with mycobacterial or fungal infection.

For typical cases, antimicrobial agents may be changed from intravenous to oral administration when a patient's condition clearly has improved, the child is afebrile, and bacteremia has resolved. Oral cephalexin (100-150 mg/kg/24 hr q8h) may be used for susceptible staphylococcal or streptococcal infections. Oral clindamycin (30-40 mg/kg/24 hr q8h) can be used to complete therapy for children with clindamycin-susceptible CA-MRSA or for patients who are seriously allergic or cannot tolerate β-lactam antibiotics. The oral regimen decreases the risk of complications related to prolonged intravenous therapy, is more comfortable for patients, and permits treatment outside the hospital if adherence to treatment can be ensured. Outpatient intravenous antibiotic therapy via a central venous catheter can be used for completing therapy at home for (1) patients unable or unwilling to take oral medication; (2) patients with underlying medical conditions that make enteral drug absorption unreliable; (3) patients without comparable oral antibiotic options (e.g., resistant bacteria, drug allergy); and (4) patients with disseminated infection (e.g., pulmonary septic emboli). Catheter-related complications, including infection or mechanical problems, can lead to readmission or emergency department visits.

In children with venous thrombosis complicating osteomyelitis, administration of anticoagulants under the supervision of a hematologist until the thrombus has resolved is a generally accepted practice, although high-quality evidence to support this practice is lacking; antibacterial therapy alone may be sufficient.

Surgical Therapy

When frank pus is obtained from subperiosteal or metaphyseal aspiration or is suspected based on MRI findings, a surgical drainage procedure is usually indicated. Surgical intervention is also often indicated after a penetrating injury and when a retained foreign body is possible. In selected cases, catheter drainage performed by an interventional radiologist is adequate.

Treatment of chronic osteomyelitis consists of surgical removal of sinus tracts and sequestrum, if present. Antimicrobial therapy is continued for several months or longer until clinical and radiographic findings suggest that healing has occurred. Normalization of ESR and CRP is expected in successful treatment of chronic osteomyelitis but does not by itself indicate clearance of the underlying infection. Many patients with chronic osteomyelitis have a normal CRP and ESR even at the onset of illness.

Physical Therapy

The major role of physical medicine is a preventive one. If a child is allowed to lie in bed with an extremity in flexion, limitation of extension can develop within a few days. The affected extremity should be kept in extension with sandbags, splints, or, if necessary, a temporary cast. Casts are also indicated when there is a potential for pathologic fracture. After 2-3 days, when pain is easing, passive range of motion exercises are started and continued until the child resumes normal activity. In neglected cases with flexion contractures, prolonged physical therapy is required.

Prognosis

When pus is drained and appropriate antibiotic therapy is given, the improvement in signs and symptoms is rapid. Failure to improve or worsening by 48-72 hr requires review of the appropriateness of the antibiotic therapy, the need for surgical intervention, or the accuracy of the diagnosis. Acute phase reactants may be useful as monitors. The serum CRP typically decreases below 2 mg/dL within 7-10 days after starting treatment, whereas the ESR typically rises for 5-7 days and then falls slowly, dropping sharply after 10-14 days. Failure of either of these acute phase reactants to follow the usual course should raise concerns about the adequacy of therapy. The prognostic significance of a minimally elevated ESR in the 4th week of therapy where CRP has normalized is not clear. Recurrence of disease and development of chronic infection after treatment occur in <10% of patients.

Because children are in a dynamic state of growth, sequelae of skeletal infections might not become apparent for months or years; therefore long-term follow-up is necessary with close attention to range of motion of joints and bone length. Although firm data about the impact of delayed treatment on outcome are not available, it appears that initiation of medical and surgical therapy within 1 wk of onset of symptoms provides a better prognosis than delayed treatment.

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CHAPTER 705

Septic Arthritis

Eric Robinette, Samir S. Shah

Without early recognition and prompt institution of appropriate medical and surgical therapy, septic arthritis in infants and children has the potential to damage to the synovium, adjacent cartilage, and bone, and cause permanent disability.

Etiology

Staphylococcus aureus (see Chapter 208.1) is the most common cause of bacterial arthritis in all age groups. Methicillin-resistant *S. aureus* (MRSA) accounts for a high proportion (>25%) of community *S. aureus* isolates in many areas of the United States and throughout the world. Group A streptococcus (see Chapter 210) and *Streptococcus pneumoniae* (pneumococcus; see Chapter 209) historically cause 10–20%; *S. pneumoniae* is most likely in the 1st 2 yr of life, but its frequency has declined since the introduction of the pneumococcal conjugate vaccines. *Kingella kingae* is recognized as a relatively common etiology with improved culture and polymerase chain reaction (PCR) methods in children younger than 4 yr (see Chapters 220 and 704). In sexually active adolescents, gonococcus (see Chapter 219) is a common cause of septic arthritis and tenosynovitis, usually of small joints or as a monoarticular infection of a large joint (knee). *Neisseria meningitidis* (see Chapter 218) can cause either a septic arthritis that occurs in the first few days of illness or a reactive arthritis that is typically seen several days after antibiotics have been initiated. Group B streptococcus (see Chapter 211) is an important cause of septic arthritis in neonates. Q fever and brucellosis should be considered in endemic areas and with an exposure risk.

Fungal infections usually occur as part of multisystem disseminated disease;

Candida arthritis can complicate systemic infection in neonates with or without indwelling vascular catheters. Primary viral infections of joints are rare, but arthritis accompanies many viral (parvovirus, mumps, rubella live vaccines) syndromes, suggesting an immune-mediated pathogenesis.

A microbial etiology is confirmed in approximately 65% of cases of septic arthritis. In addition, some cases treated as bacterial arthritis are actually postinfectious (gastrointestinal or genitourinary) reactive arthritis (see Chapter 182) rather than primary infection. Lyme disease produces an arthritis more like a rheumatologic disorder and not typically suppurative.

Epidemiology

Septic arthritis is more common in young children. Half of all cases occur by 2 yr of age and three fourths of all cases occur by 5 yr of age. Adolescents and neonates are at risk of gonococcal septic arthritis.

Most infections in otherwise healthy children arise hematogenously. Less commonly, infection of joints can follow penetrating injuries or procedures such as trauma, arthroscopy, prosthetic joint surgery, intraarticular steroid injection, and orthopedic surgery. Immunocompromised patients and those with rheumatologic joint disease are also at increased risk of joint infection.

Pathogenesis

Septic arthritis primarily occurs as a result of hematogenous seeding of the synovial space. Less often, organisms enter the joint space by direct inoculation or extension from a contiguous focus. The synovial membrane has a rich vascular supply and lacks a basement membrane, providing an ideal environment for hematogenous seeding. The presence of bacterial products (endotoxin or other toxins) within the joint space stimulates cytokine production (tumor necrosis factor-α, interleukin-1) within the joint, triggering an inflammatory cascade. The cytokines stimulate chemotaxis of neutrophils into the joint space, where proteolytic enzymes and elastases are released by neutrophils, damaging the cartilage. Proteolytic enzymes released from the synovial cells and chondrocytes also contribute to destruction of cartilage and synovium. Bacterial hyaluronidase breaks down the hyaluronic acid in the synovial fluid, making the fluid less viscous and diminishing its ability to lubricate and protect the joint cartilage. Damage to the cartilage can occur through increased friction, especially for weight-bearing joints. The increased pressure within the joint space from accumulation of purulent material can compromise the vascular supply and induce pressure necrosis of the cartilage. Synovial and cartilage destruction results from a combination of proteolytic enzymes and mechanical factors.

Clinical Manifestations

Most septic arthritides are monoarticular. The signs and symptoms of septic arthritis depend on the age of the patient. Early signs and symptoms may be subtle, particularly in neonates. As with osteomyelitis, neonates might exhibit **pseudoparalysis** or pain which limits voluntary movement of the affected extremity (e.g., diaper changes). Septic arthritis in neonates and young infants is often associated with adjacent osteomyelitis caused by transphyseal spread of infection, although osteomyelitis contiguous with an infected joint can be seen at any age (see Chapter 704).

Older infants and children might have fever and pain, with localizing signs such as swelling, erythema, and warmth of the affected joint. With involvement of joints of the pelvis and lower extremities, limp or refusal to walk often occurs.

Erythema and edema of the skin and soft tissue overlying the site of infection are seen earlier in septic arthritis than in osteomyelitis because the bulging infected synovium is usually more superficial, whereas the metaphysis is located more deeply. Septic arthritis of the hip is an exception because of the deep location of the hip joint. With Lyme arthritis, joint swelling is typically quite prominent and may be disproportionate to the relatively lesser degree of pain and limited range of motion when compared with suppurative arthritis. Lyme arthritis has a predilection for large joints, particularly the knees and hips, and may be either monoarticular or pauciarticular at presentation.

Joints of the lower extremity constitute 75% of all cases of septic arthritis (Table 705.1). The elbow, wrist, and shoulder joints are involved in approximately 25% of cases, and small joints are uncommonly infected, except in gonococcal arthritis. Suppurative infections of the hip, shoulder, elbow, and ankle in infants and children may be associated with an adjacent osteomyelitis of the proximal femur, proximal humerus, proximal radius, and distal tibia because the metaphysis extends intraarticularly. Concomitant osteomyelitis is less common in older children and adolescents as their anatomy and physiology become more adult-like.

Table 705.1

Distribution of Hematogenous Bacterial Arthritis*

BONE	PERCENT (%)
Knee	~35
Hip	~25
Ankle	~10
Elbow	~10
Wrist	~4
Shoulder	~5
Small joints	~1-2

* Excludes Lyme disease and immune-complex postinfectious arthritis. Viral (rubella, mumps, chikungunya) infectious arthritis is often small and multiple joints. Septic bursitis (shoulder, prepatellar) may be confused with bacterial joint infections.

Diagnosis

The white blood cell count and differential, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are generally elevated in children with joint infections but elevations are nonspecific and might not be helpful in distinguishing between infection and other inflammatory processes. Most children with septic arthritis will have normal leukocyte counts and ESR at presentation, and normal test results do not preclude the diagnosis of septic arthritis.

Blood cultures should be performed in all cases of suspected septic arthritis but are positive in 20% or fewer cases of proven or probable septic arthritis. Cervical, anal, and throat cultures should be obtained when gonococcus is suspected. Aspiration of the joint fluid provides the optimal specimen to confirm the diagnosis. Most large joint spaces are easy to aspirate, but the hip can pose technical problems; ultrasound guidance facilitates aspiration. Although yield for joint aspirate cultures is higher than from blood cultures, the overall culture yield when combining both methods remains less than 50%. Multiplex bacterial PCR panels appear to have a yield around 50% from joint fluid specimens, but this increase over culture is almost entirely due to their enhanced ability to detect *K. kingae*. Other strategies to increase detection of *K. kingae* include prompt inoculation onto solid media and inoculation of the joint fluid in blood culture bottles. A diagnosis of Lyme arthritis is made through via a two-step test of an ELISA or IFA followed by a reflex Western blot for samples that are positive or equivocal by the first methodology. Patients with Lyme arthritis are seropositive because arthritis is a late manifestation of infection. PCR is rarely necessary but can detect *Borrelia burgdorferi* in joint aspirate specimens in cases of Lyme arthritis.

Synovial fluid analysis for cell count, differential, protein, and glucose has limited utility in diagnosing infectious arthritis. Joint fluid white blood cell counts >50,000 cells/mm^3 suggest bacterial infection as the most likely etiology, but this finding is neither sensitive nor specific enough to exclude or confirm a bacterial infection in isolation. When the results of joint aspirate cell counts and culture are not strongly suggestive of a joint infection but the clinical presentation is worrisome for a bacterial etiology, infectious causes of sympathetic joint effusions such as adjacent pyomyositis and osteomyelitis should be investigated by MRI (see Chapter 704).

Monitoring elevated CRP may be of value in assessing response to therapy or identifying complications. In addition, patients with adjacent infections complicating septic arthritis more frequently have a CRP >10-13 mg/dL compared with patients with septic arthritis alone. Other findings such as older age, prolonged symptoms, bacteremia, alterations in other lab values (such as elevated ANC and thrombocytopenia), and failure to rapidly improve with therapy have been less consistently associated with adjacent infection. Nonetheless, adjacent infection should be considered in patients demonstrating such multiple risk factors.

Radiographic Evaluation

Radiographic studies play a crucial role in evaluating septic arthritis. Conventional radiographs and ultrasonography are performed as part of the routine workup. CT, MRI, and radionuclide studies can all contribute to establishing the diagnosis in selected cases (Fig. 705.1).

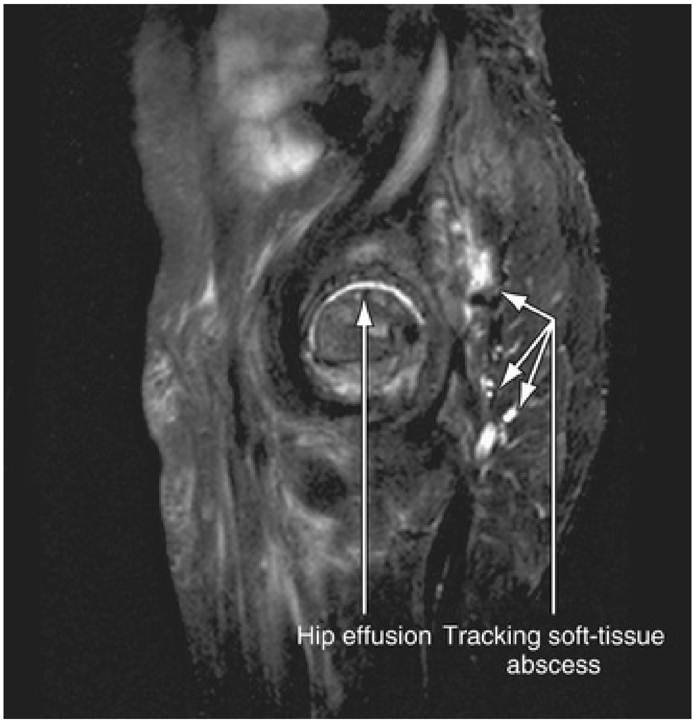

FIG. 705.1 **MRI of staphylococcal septic arthritis of left hip, with fluid collections between planes of gluteal muscles. *Arrows* indicate fluid collection. (From Matthews CJ, Weston VC, Jones A, et al: Bacterial septic arthritis in adults. *Lancet* 375:846–854, 2010.)**

Plain Radiographs

Plain films can suggest the diagnosis of septic arthritis by showing: widening of the joint capsule, soft tissue edema, and obliteration of normal fat lines. Plain films can also help to exclude other causes of joint pain such as fractures. Plain films of the hip can show medial displacement of the obturator muscle into the pelvis (the obturator sign), lateral displacement or obliteration of the gluteal fat lines, and elevation of Shenton's line with a widened arc.

Ultrasonography

Ultrasonography is included with plain films in routine evaluations because it is particularly helpful in detecting joint effusion and fluid collection in the soft tissue and subperiosteal regions. Ultrasonography is highly sensitive in detecting joint effusion, particularly for the hip joint, where plain radiographs are normal in more than 50% of cases of septic arthritis of the hip. Ultrasonography can serve as an aid in performing hip aspiration.

Magnetic Resonance Imaging and Computed Tomography

MRI and CT can confirm the presence of joint fluid in patients with suspected osteoarthritis infections but are not routinely indicated. MRI is useful in evaluating for adjacent osteomyelitis or pyomyositis but is typically reserved for cases when the index of suspicion for these conditions is high. Considerations include: patient factors such as younger age, the clinical presentation (e.g., protracted pain preceding joint swelling), the results of laboratory investigations such as joint aspiration and CRP, and response to therapy.

Radionuclide Imaging

Radionuclide imaging, although not routinely indicated, is more sensitive than plain radiographs in providing supportive evidence of the diagnosis of septic arthritis; a scan may be positive within 2 days of the onset of symptoms. Three-phase imaging with technetium-99 methylene diphosphonate shows symmetric uptake on both sides of the joint, limited to the bony structures adjacent to the joint. Radionuclide imaging is also useful for evaluating the sacroiliac joint.

Differential Diagnosis

The differential diagnosis of septic arthritis depends on the joint or joints involved and the age of the patient. For the hip, toxic synovitis, pyomyositis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, psoas abscess, and proximal femoral, pelvic, or vertebral osteomyelitis, as well as diskitis, should be considered. For the knee, distal femoral or proximal tibial osteomyelitis, pauciarticular rheumatoid arthritis, and referred pain from the hip should be considered. Knee or thigh pain may be referred from the hip. Other conditions such as trauma, cellulitis, pyomyositis, sickle cell disease, hemophilia, Lyme arthritis, and Henoch-Schönlein purpura can mimic purulent arthritis. When several joints are involved, serum sickness, collagen vascular disease, rheumatic fever, and Henoch-Schönlein purpura should be considered. Arthritis is one of the extraintestinal manifestations of inflammatory bowel disease. Reactive arthritis following a variety of bacterial (gastrointestinal or genital) and parasitic infections, streptococcal pharyngitis, or viral hepatitis can resemble acute septic arthritis (see Chapter 182).

Treatment

Optimal treatment of septic arthritis requires cooperation of pediatricians, orthopedic surgeons, and radiologists.

Antimicrobial Therapy

The initial empirical antimicrobial therapy is based on likely bacterial pathogens at various ages, the results of the Gram stain of aspirated material, and additional considerations. In neonates, an antistaphylococcal penicillin, such as nafcillin or oxacillin (150-200 mg/kg/24 hr divided q6h IV), and a broad-spectrum cephalosporin, such as cefepime (100 to 150 mg/kg/24 he divided q 12 IV), provide coverage for the *S. aureus,* group B streptococcus, and Gram-negative bacilli. If MRSA is a concern, vancomycin is selected instead of nafcillin or oxacillin. If the neonate is a small premature infant or has a central vascular catheter, the possibility of nosocomial bacteria (*S. aureus* , Gram-negative enterics, or *Pseudomonas aeruginosa*) or fungi *(Candida)* should be considered.

In older infants and children with septic arthritis, empirical therapy to cover for *S. aureus* , streptococci, and *K. kingae* includes at minimum cefazolin (100-150 mg/kg/24 hr divided q8h) or nafcillin (150-200 mg/kg/24 hr divided q6h).

In areas where methicillin resistance is noted in ≥10–15% of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains, adding an antimicrobial that is effective against local CA-MRSA isolates is suggested. Vancomycin (15 mg/kg q6h IV) is preferred in patients who are ill-appearing, suspected to be bacteremic, or if local clindamycin resistance is more than 10–15%. Clindamycin (40 mg/kg divided q6h) is a reasonable alternative when treating CA-MRSA infections. For immunocompromised patients, combination therapy is usually initiated, such as with vancomycin and ceftazidime, cefepime, or piperacillin/tazobactam, with or without an aminoglycoside. Adjunct therapy with dexamethasone for 4 days with antibiotic therapy has been shown to decrease the duration of fever and promote a more rapid decline in inflammatory markers. These studies have had some significant limitations and a favorable impact on long-term outcomes has not yet been clearly demonstrated in humans thus this practice has not yet been adopted as part of routine care. **Lyme arthritis** is treated with doxycycline (4 mg/kg/24 hr divided Q12 PO) for 28 days in children >8 yr old. For children < 8 yr old, amoxicillin (50 mg/kg/24 hr divided Q8 PO) or cefuroxime (30 mg/kg/24 hr divided Q12) is recommended.

A second 28-day course may be considered for patients with persistent or recurrent symptoms after completing the initial course of treatment. Intravenous ceftriaxone (50 mg/kg Q24 IV) for 14-28 days may be considered as an initial or second course of therapy for severe or refractory cases.

Empirical antimicrobials are narrowed to targeted therapy when the pathogen is identified. If a pathogen is not identified and a patient's condition is improving, therapy is continued with the antibiotic selected initially. If a pathogen is not identified and a patient's condition is not improving, consideration should be given to the need for reaspiration, the presence of an extraarticular infection requiring surgical debridement or the possibility of a noninfectious etiology. In such cases, MRI may be performed to assist with subsequent management decisions.

Duration of antibiotic therapy is individualized depending on the organism isolated and the clinical course. Ten to 14 days is usually adequate for streptococci, *S. pneumoniae* , and *K. kingae;* longer therapy may be needed for *S. aureus* and Gram-negative infections (3 wk), concomitant osteomyelitis (4 wk), extensive disease, or slow response to treatment. Normalization of CRP in addition to a normal examination supports discontinuing antibiotic therapy. The prognostic significance of an improved but still minimally elevated ESR in the 3rd or 4th week of therapy is not clear if all other clinical and laboratory parameters are favorable. In selected patients, obtaining a plain radiograph of the joint before completing therapy can provide evidence (typically periosteal new bone) of a previously unappreciated contiguous site of osteomyelitis that would likely prolong antibiotic treatment. Oral antibiotics can be used to complete therapy once the patient is afebrile for 48-72 hr and is clearly improving.

Surgical Therapy

Infection of the hip is generally considered a surgical emergency because of the vulnerability of the blood supply to the head of the femur. For joints other than the hip, daily aspirations of synovial fluid may be required. In general, one or two subsequent aspirations suffice. If fluid continues to accumulate after 4-5 days, arthrotomy or video-assisted arthroscopy is needed. At the time of surgery, the joint is flushed with sterile saline solution. Antibiotics are not instilled because they are irritating to synovial tissue, and adequate amounts of antibiotic are achieved in joint fluid with systemic administration.

Prognosis

Improvement in signs and symptoms occurs rapidly following joint drainage and antibiotic administration. Failure to improve or worsening by 48-72 hr requires review of the appropriateness of the antibiotic therapy, the need for surgical intervention, and the correctness of the diagnosis. Acute phase reactants may be useful as monitors. Failure of either of these acute phase reactants to follow the usual course should raise concerns about the adequacy of therapy. Recurrence of disease and development of chronic infection after treatment occur in <10% of patients.

Septic arthritis can lead to numerous long-term sequelae in children, including leg-length discrepancy or angular deformity from growth arrest, limitations in range of motion due to chondral damage, and avascular necrosis of the femoral head from septic arthritis of the hip. The overall rate of these sequelae with current therapies is <5%. However, children are in a dynamic state of growth, so these abnormalities might not become apparent for months or years; therefore long-term follow-up is necessary, with close attention to range of motion of joints and bone length. Involvement of the hip is associated with a higher rate of sequelae. Although firm data about the impact of delayed treatment on outcome are not available, it appears that initiation of medical and surgical therapy within 1 wk of onset of symptoms provides a better prognosis than delayed treatment.

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SECTION 2

Sports Medicine

OUTLINE

Chapter 706 Epidemiology and Prevention of Injuries

Chapter 707 Management of Musculoskeletal Injury

Chapter 708 Sports-Related Traumatic Brain Injury (Concussion)

Chapter 709 Cervical Spine Injuries

Chapter 710 Heat Injuries

Chapter 711 Female Athletes Menstrual Problems and the Risk of Osteopenia

Chapter 712 Performance-Enhancing Aids

Chapter 713 Specific Sports and Associated Injuries

CHAPTER 706

Epidemiology and Prevention of Injuries

Gregory L. Landry

The Centers for Disease Control and Prevention recommend moderate to vigorous physical activity on a regular basis for all adolescents. Physical activity has favorable effects on hypertension, obesity, and serum lipid levels in youths and is associated with lower rates of cardiovascular disease, type 2 diabetes mellitus, osteoporosis, and colon and breast cancer among adults.

Pediatricians should promote physical activity to their patients, especially those with lower rates of physical activity and sports participation, including children with special healthcare needs (see Chapter 734) and those from lower socioeconomic groups. Physicians also have the responsibility of providing medical clearance for participation in physical activity and sports and for diagnosis and rehabilitation of injuries.

Approximately 30 million children and adolescents participate in organized sports in the United States. Approximately 3 million injuries occur annually, if injury is defined as time lost from the sport. Deaths in sports are rare, with the majority of nontraumatic deaths caused by cardiac diseases (see Chapter 463). Nonetheless, approximately 30% of life-threatening injuries in children presenting to an emergency room are sports related. Overall, injury rates and injury severity in sports increase with age and pubertal development, related to the greater speed, strength, and intensity of competition.

Identifying mechanisms of injury and establishing and enforcing rules that reduce the likelihood of that mechanism of injury, including penalizing dangerous play, have reduced catastrophic injury rates. Injury rates also have been reduced by removing environmental hazards, such as trampolines in gymnastics and stationary (vs. breakaway) bases in softball, and by modifying heat injury rates in soccer tournaments by adding water breaks and reducing the playing time. Wearing equipment such as mouth guards can reduce dental injuries. A common reason for reinjury is lack of rehabilitation of old injuries; appropriate rehabilitation reduces injury rates. Preseason training for high school athletes, with an emphasis on speed, agility, jump training, and flexibility, is associated with lower injury rates in soccer and fewer serious knee injuries in female athletes. Traditional stretching maneuvers or massage have not been demonstrated to reduce the risk of injury or muscle soreness, but ankle taping and use of lace-up ankle braces are helpful particularly to prevent reinjury of the ankle. One setting for implementing some of these prevention strategies and for detecting unrehabilitated injuries and medical problems that could affect participation in sports is the preparticipation sports examination (PSE).

Preparticipation Sports Examination

The PSE is performed with a directed history and a directed physical examination, including a screening musculoskeletal examination. It identifies possible problems in 1–8% of athletes and excludes fewer than 1% from participation. The PSE is not a substitute for the recommended comprehensive annual evaluation, which looks at behaviors that are potentially harmful to teens, such as sexual activity, drug use, and violence, and assesses for depression and suicidal ideation and addresses broader issues of prevention. Table 706.1 identifies the purposes of the PSE. If possible, the PSE should be combined with the comprehensive annual health visit with emphasis on preventive healthcare (see Chapters 12 and 28).

Table 706.1

Objectives of the Preparticipation Sports Examination

- Determination of the general health of the athlete
- Disclosure of defects that may limit participation
- Detection of conditions that may predispose the athlete to injury
- Determination of optimal level of performance
- Classification of the athlete according to individual qualifications
- Fulfillment of legal and insurance requirements for organized athletic

programs

- Evaluation of size and level of maturation of younger athletes
- Improvement of fitness and performance
- Provision of opportunities for students to compete who have either physiologic or pathologic health conditions that may preclude blanket approval
- Provision of the opportunity to counsel youths and answer health and personal questions
- Entry of the athlete into the local sports medicine system establishing a doctor-patient relationship that continues

From Sanders B, Blackburn TA, Boucher B: Preparticipation screening-the sports physical therapy perspective. *Int J Sports Phys Ther* 8(2):180–193, 2013, Table 1.

State requirements for how often a youth needs a PSE differ, ranging from annually to entry to a new school level (middle school, high school, college). At a minimum, a focused, annual interim evaluation should be done on an otherwise healthy young athlete. The PSE is optimally performed 3-6 wk before the start of practice.

History and Physical Examination

The essential components of the PSE are the history and focused medical and musculoskeletal screening examinations. Identified problems require more investigation (Tables 706.2 and 706.3). In the absence of symptoms, no screening laboratory tests are required.

Table 706.2

Preparticipation Sports Examination

COMPONENT OF THE PHYSICAL EXAMINATION	CONDITION TO BE DETECTED
Vital signs	Hypertension, cardiac disease, bradycardia or tachycardia
Height and weight	Obesity, eating disorders, malabsorption
Vision and pupil size	Legal blindness, absent eye, anisocoria, amblyopia
Lymph node	Infectious diseases, malignancy
Cardiac (performed standing and supine)	Heart murmur, prior surgery, dysrhythmia

Pulmonary	Recurrent and exercise-induced bronchospasm, chronic lung disease
Abdomen	Organomegaly, abdominal mass
Skin	Contagious diseases (impetigo, herpes, staphylococcal, streptococcal)
Genitourinary	Varicocele, undescended testes, tumor, hernia
Musculoskeletal	Acute and chronic injuries, physical anomalies (scoliosis)

Table 706.3

Medical Conditions and Sports Participation

CONDITION	**MAY PARTICIPATE**	**EXPLANATION**
Atlantoaxial instability (instability of the joint between cervical vertebrae 1 and 2)	Qualified yes	Athlete (particularly if the athlete has Down syndrome or juvenile idiopathic arthritis with cervical involvement) needs evaluation to assess the risk of spinal cord injury during sports participation, especially when using a trampoline
Bleeding disorder	Qualified yes	Athlete needs evaluation
Diabetes mellitus	Yes	All sports can be played with proper attention and appropriate adjustments to diet (particularly carbohydrate intake), blood glucose concentrations, hydration, and insulin therapy Blood glucose concentrations should be monitored before exercise, every 30 min during continuous exercise, 15 min after completion of exercise, and at bedtime
Eating disorders	Qualified yes	Athlete with an eating disorder needs medical and psychiatric assessment before participation
Fever	No	Elevated core temperature can indicate a pathologic medical condition (infection or disease) that is often manifest by increased resting metabolism and heart rate. Accordingly, during the athlete's usual exercise regimen, fever can result in greater heat storage, decreased heat tolerance, increased risk of heat illness, increased cardiopulmonary effort, reduced maximal exercise capacity, and increased risk of hypotension because of altered vascular tone and dehydration. On rare occasions, fever accompanies myocarditis or other conditions that can make usual exercise dangerous
Heat illness, history of	Qualified yes	Because of the likelihood of recurrence, the athlete needs individual assessment to determine the presence of predisposing conditions and behavior and to develop a prevention strategy that includes sufficient acclimatization (to the environment and to exercise intensity and duration), conditioning, hydration, and salt intake, as well as other effective measures to improve heat tolerance and to reduce heat injury risk (e.g., protective equipment and uniform configurations)
HIV infection	Yes	Because of the apparent minimal risk to others, all sports may be played as athlete's state of health allows (especially if viral load is undetectable or very low) For all athletes, skin lesions should be covered properly, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood Certain sports (such as wrestling and boxing) can create a situation that favors viral transmission (likely bleeding plus skin breaks); if viral load is detectable, then athletes should be

		advised to avoid such high-contact sports
Malignant neoplasm	Qualified yes	Athlete needs individual assessment
Musculoskeletal disorders	Qualified yes	Athlete needs individual assessment
Myopathies	Qualified yes	Athlete needs individual assessment
Obesity	Yes	Because of the increased risk of heat illness and cardiovascular strain, obese athletes particularly need careful acclimatization (to the environment and to exercise intensity and duration), sufficient hydration, and potential activity and recovery modifications during competition and training.
Organ transplant recipient (and those taking immunosuppressive medications)	Qualified yes	Athlete needs individual assessment for contact, collision, and limited-contact sports In addition to potential risk of infections, some medications (e.g., prednisone) increase tendency for bruising
Skin infections, including herpes simplex, molluscum contagiosum, verrucae (warts), staphylococcal and streptococcal infections (furuncles [boils], carbuncles, impetigo, methicillin-resistant *Staphylococcus aureus* [cellulitis and/or abscesses]), scabies, and tinea	Qualified yes	During contagious periods, participation in gymnastics or cheerleading with mats, martial arts, wrestling, or other collision, contact, or limited-contact sports is not allowed
Spleen, enlarged	Qualified yes	If the spleen is acutely enlarged, then participation should be avoided because of risk of rupture If the spleen is chronically enlarged, then individual assessment is needed before collision, contact, or limited-contact sports are played
CARDIOVASCULAR		
Carditis (inflammation of the heart)	No	Carditis can result in sudden death with exertion
Active pericarditis	Qualified no	Athlete needs individual assessment
Hypertension (high blood pressure)	Qualified yes	Those with hypertension >5 mm Hg above the 99th percentile for age, sex, and height should avoid heavy weightlifting and power lifting, bodybuilding, and high-static component sports Those with sustained hypertension (>95th percentile for age, sex, and height) need evaluation The National High Blood Pressure Education Program Working Group report defined prehypertension and stage 1 and stage 2 hypertension in children and adolescents younger than 18 yr of age
Congenital heart disease (structural heart defects present at birth)	Qualified yes	Consultation with a cardiologist is recommended Those who have mild forms may participate fully in most cases; those who have moderate or severe forms or who have undergone surgery need evaluation The 36th Bethesda Conference defined mild, moderate, and severe disease for common cardiac lesions
Heart murmur	Qualified yes	If the murmur is innocent (does not indicate heart disease), full participation is permitted; otherwise, athlete needs evaluation (see structural heart disease, especially hypertrophic cardiomyopathy and

		mitral valve prolapse)
Dysrhythmia (Irregular Heart Rhythm)		
Long QT syndrome	Qualified yes	Consultation with a cardiologist is advised. Those with symptoms (chest pain, syncope, near-syncope, dizziness, shortness of breath, or other symptoms of possible dysrhythmia) or evidence of mitral regurgitation on physical examination need evaluation; all others may participate fully Genetic testing for a channelopathy is recommended.
Malignant ventricular arrhythmias	Qualified yes	
Symptomatic Wolff-Parkinson-White syndrome	Qualified yes	
Advanced heart block	Qualified yes	
Family history of sudden death or previous sudden cardiac event	Qualified yes	
Implantation of a cardioverter-defibrillator	Qualified yes	
Structural or Acquired Heart Disease		
Hypertrophic cardiomyopathy (symptomatic)	Qualified no	Consultation with a cardiologist is recommended. The 36th Bethesda Conference provided detailed recommendations. Most of these conditions carry a significant risk of sudden cardiac death associated with intense physical exercise. Hypertrophic cardiomyopathy requires thorough and repeated evaluations, because disease can change manifestations during later adolescence. Marfan syndrome with an aortic aneurysm also can cause sudden death during intense physical exercise. An athlete who has ever received chemotherapy with anthracyclines may be at increased risk for cardiac problems owing to the cardiotoxic effects of the medications, and resistance training in this population should be approached with caution; strength training that avoids isometric contractions may be permitted. Athlete needs evaluation
Dilated cardiomyopathy (symptomatic)	Qualified no	
Coronary artery anomalies	Qualified no	
Arrhythmogenic right ventricular cardiomyopathy	Qualified no	
Acute rheumatic fever with carditis	Qualified no	
Ehlers-Danlos syndrome, vascular form	Qualified no	
Marfan syndrome	Qualified yes	
Mitral valve prolapse	Qualified yes	
Anthracycline use	Qualified yes	
Vasculitis, vascular disease	Qualified yes	
Kawasaki disease (coronary artery vasculitis)	Qualified yes	Consultation with a cardiologist is recommended. Athlete needs individual evaluation to assess risk on the basis of disease activity, pathologic changes, and medical regimen
Pulmonary hypertension	Qualified yes	
EYES		
Functionally 1-eyed athlete	Qualified yes	A functionally 1-eyed athlete is defined as having best-corrected visual acuity worse than 20/40 in the poorer-seeing eye. Such an athlete would suffer significant disability if the better eye were seriously injured, as would an athlete with loss of an eye. Specifically, boxing and full-contact martial arts are not recommended for functionally 1-eyed athletes, because eye protection is impractical and/or not permitted. Some athletes who previously underwent intraocular eye surgery or had a serious eye injury may have increased risk of injury because of weakened eye tissue. Availability of eye guards approved by the American Society for Testing and Materials and other protective equipment might allow participation in most sports, but this must be judged on an individual basis
Loss of an eye	Qualified yes	
Detached retina or family history of retinal detachment at young age	Qualified yes	
High myopia	Qualified yes	
Connective tissue disorder, such as Marfan or Stickler syndrome	Qualified yes	
Previous intraocular eye surgery or serious eye injury	Qualified yes	
Conjunctivitis, infectious	Qualified no	Athlete with active infectious conjunctivitis should be excluded from swimming

GASTROINTESTINAL		
Malabsorption syndromes (celiac disease or cystic fibrosis)	Qualified yes	Athlete needs individual assessment for general malnutrition or specific deficits resulting in coagulation or other defects; with appropriate treatment, these deficits can be treated adequately to permit normal activities
Short bowel syndrome or other disorders requiring specialized nutritional support, including parenteral or enteral nutrition	Qualified yes	Athlete needs individual assessment for collision, contact, or limited-contact sports Central or peripheral indwelling venous catheter might require special considerations for activities and emergency preparedness for unexpected trauma to the device(s)
Hepatitis, infectious (primarily hepatitis C)	Yes	All athletes should receive hepatitis B vaccination before participation. Because of the apparent minimal risk to others, all sports may be played as the athlete's state of health allows For all athletes, skin lesions should be covered properly, and athletic personnel should use universal precautions when handling blood or body fluids with visible blood
Liver, enlarged	Qualified yes	If the liver is acutely enlarged, participation should be avoided because of risk of rupture If the liver is chronically enlarged, individual assessment is needed before collision, contact, or limited-contact sports are played Patients with chronic liver disease can have changes in liver function that affect stamina, mental status, coagulation, or nutritional status
Diarrhea, infectious	Qualified no	Unless symptoms are mild and athlete is fully hydrated, no participation is permitted, because diarrhea can increase risk of dehydration and heat illness (see fever)
GENITOURINARY		
Kidney, absence of one	Qualified yes	Athlete needs individual assessment for contact, collision, and limited-contact sports Protective equipment can reduce risk of injury to the remaining kidney sufficiently to allow participation in most sports, providing such equipment remains in place during the activity
Ovary, absence of one	Yes	Risk of severe injury to remaining ovary is minimal
Pregnancy and postpartum period	Qualified yes	Athlete needs individual assessment As pregnancy progresses, modifications to usual exercise routines become necessary; activities with high risk of falling or abdominal trauma should be avoided Scuba diving and activities posing risk of altitude sickness should also be avoided during pregnancy After the birth, physiologic and morphologic changes of pregnancy take 4-6 wk to return to baseline
Testicle, undescended or absence of one testicle	Yes	Certain sports require a protective cup
NEUROLOGIC		
Cerebral palsy	Qualified yes	Athlete needs evaluation to assess functional capacity to perform sports-specific activity
History of serious head or spine trauma or abnormality, including craniotomy, epidural bleeding, subdural hematoma, intracerebral hemorrhage, second-	Qualified yes	Athlete needs individual assessment for collision, contact, or limited-contact sports

impact syndrome, vascular malformation, and neck fracture		
History of simple concussion (mild traumatic brain injury), multiple simple concussions, and/or complex concussion	Qualified yes	Athlete needs individual assessment Research supports a conservative approach to concussion management, including no athletic participation while symptomatic or when deficits in judgment or cognition are detected, followed by graduated return to full activity
Recurrent headaches	Yes	Athlete needs individual assessment
Seizure disorder, well controlled	Yes	Risk of seizure during participation is minimal
Seizure disorder, poorly controlled	Qualified yes	Athlete needs individual assessment for collision, contact, or limited-contact sports The following noncontact sports should be avoided: archery, riflery, swimming, weightlifting, power lifting, strength training, and sports involving heights; in these sports, a seizure during activity can pose a risk to self or others
Recurrent plexopathy (burner or stinger) and cervical cord neurapraxia with persistent defects	Qualified yes	Athlete needs individual assessment for collision, contact, or limited-contact sports; regaining normal strength is an important benchmark for return to play
RESPIRATORY		
Pulmonary compromise, including cystic fibrosis	Qualified yes	Athlete needs individual assessment but generally all sports may be played if oxygenation remains satisfactory during graded exercise test Athletes with cystic fibrosis need acclimatization and good hydration to reduce risk of heat illness
Asthma	Yes	With proper medication and education, only athletes with severe asthma need to modify their participation For those using inhalers, recommend having a written action plan and using a peak flowmeter daily Athletes with asthma might encounter risks when scuba diving
Acute upper respiratory infection	Qualified yes	Upper respiratory obstruction can affect pulmonary function Athlete needs individual assessment for all except mild disease (see fever)
RHEUMATOLOGIC		
Juvenile idiopathic arthritis	Qualified yes	Athletes with systemic or polyarticular juvenile idiopathic arthritis and history of cervical spine involvement need radiographs of C1 and C2 to assess risk of spinal cord injury Athletes with systemic or HLA-B27–associated arthritis require cardiovascular assessment for possible cardiac complications during exercise For those with micrognathia (open bite and exposed teeth), mouth guards are helpful If uveitis is present, risk of eye damage from trauma is increased; ophthalmologic assessment is recommended In visually impaired athletes, guidelines for functionally 1-eyed athletes should be followed
Juvenile dermatomyositis, idiopathic myositis	Qualified yes	Athlete with juvenile dermatomyositis or systemic lupus erythematosus with cardiac involvement requires cardiology assessment before participation. Athletes receiving systemic corticosteroid therapy are at higher risk for osteoporotic fractures and avascular necrosis, which should be assessed before clearance; those receiving immunosuppressive medications are at higher risk
Systemic lupus erythematosus	Qualified yes	

Raynaud phenomenon	Qualified yes	for serious infection. Sports activities should be avoided when myositis is active. Rhabdomyolysis during intensive exercise can cause renal injury in athletes with idiopathic myositis and other myopathies. Because of photosensitivity with juvenile dermatomyositis and systemic lupus erythematosus, sun protection is necessary during outdoor activities. With Raynaud phenomenon, exposure to the cold presents risk to hands and feet
SICKLE CELL		
Sickle cell disease	Qualified yes	Athlete needs individual assessment In general, if illness status permits, all sports may be played; however, any sport or activity that entails overexertion, overheating, dehydration, or chilling should be avoided Participation at high altitude, especially when not acclimatized, also poses risk of sickle cell crisis
Sickle cell trait	Yes	Athletes with sickle cell trait generally do not have increased risk of sudden death or other medical problems during athletic participation under normal environmental conditions; however, when high exertional activity is performed under extreme conditions of heat and humidity or increased altitude, such catastrophic complications have occurred rarely Athletes with sickle cell trait, like all athletes, should be progressively acclimatized to the environment and to the intensity and duration of activities and should be sufficiently hydrated to reduce the risk of exertional heat illness and/or rhabdomyolysis According to National Institutes of Health management guidelines, sickle cell trait is not a contraindication to participation in competitive athletics, and there is no requirement for screening before participation More research is needed to fully assess potential risks and benefits of screening athletes for sickle cell trait

This table is intended for use by medical and nonmedical personnel. “Needs evaluation” means that a physician with appropriate knowledge and experience should assess the safety of a given sport for an athlete with the listed medical condition. Unless otherwise noted, this need for special consideration is because of variability in the severity of the disease, the risk of injury for the specific sports, or both.

From Rice SG; the Council on Sports Medicine and Fitness, American Academy of Pediatrics: Medical conditions affecting sports participation. *Pediatrics* 121:841–848, 2008.

Seventy-five percent of significant findings are identified by the history; a standardized questionnaire given to the parent and athlete is important because the young athlete might not know or might forget important aspects of his or her history. The questionnaire should include questions about the family history and the patient's previous medical, surgical, cardiac, pulmonary, neurologic, dermatologic, visual, psychologic, musculoskeletal, and menstrual problems, as well as about heat illness, medications, allergies, immunizations, and diet. The most commonly identified problems are *unrehabilitated injuries* . An investigation of previous injuries, including diagnostic tests, treatment, and present functional status, is indicated.

Sudden death during sports can result from undetected cardiac disease such as hypertrophic or other **cardiomyopathies** (see Chapter 466), **anomalous coronary vessels** (see Chapter 459.2), or a ruptured aorta in **Marfan syndrome** (see Chapter 722). In many cases, the underlying heart disease is not suspected, and death is the first sign of heart disease (see Chapter 463). However, in approximately 25–50% of cases, in retrospect there were preceding symptoms of dizziness, chest pain, syncope, palpitations, shortness of breath, and/or a family history of early, unexpected death. Chest radiographs, electrocardiograms, and echocardiograms are not recommended as routine screening tests in the United States. If there is a suspicion of heart disease, such as a history of syncope, presyncope, palpitations, or excessive dyspnea with exercise, or a family history of a condition such as hypertrophic cardiomyopathy or prolonged QT or Marfan syndrome, the evaluation should be complete and include a 12-lead electrocardiogram, an echocardiogram, Holter or event-capture monitoring, and a stress test with electrocardiographic monitoring. Recommendations for participation with identified cardiac disease should be made in consultation with a cardiologist.

Disqualification and limitations for sports participation among various medical conditions are available from the American Academy of Pediatrics (see Table 706.3). Sports may also be classified by intensity (Fig. 706.1) and contact (Table 706.4). Athletes may seek to participate in sports against medical advice and have done so successfully for professional sports. Section 504(a) of the Rehabilitation Act of 1973 prohibits discrimination against disabled athletes if they have the capabilities or skills required to play a competitive sport. This was reinforced through the Americans with Disabilities Act of 1990. An amateur athlete has no absolute right to decide whether to participate in competitive sports. Participation in competitive sports is considered a privilege, not a right. *Knapp v Northwestern University* established that “difficult medical decisions involving complex medical problems can be made by responsible physicians exercising prudent judgment (which will be necessarily conservative when definitive scientific evidence is lacking or conflicting) and relying on the recommendations of specialist consultants or guidelines established by a panel of experts.”

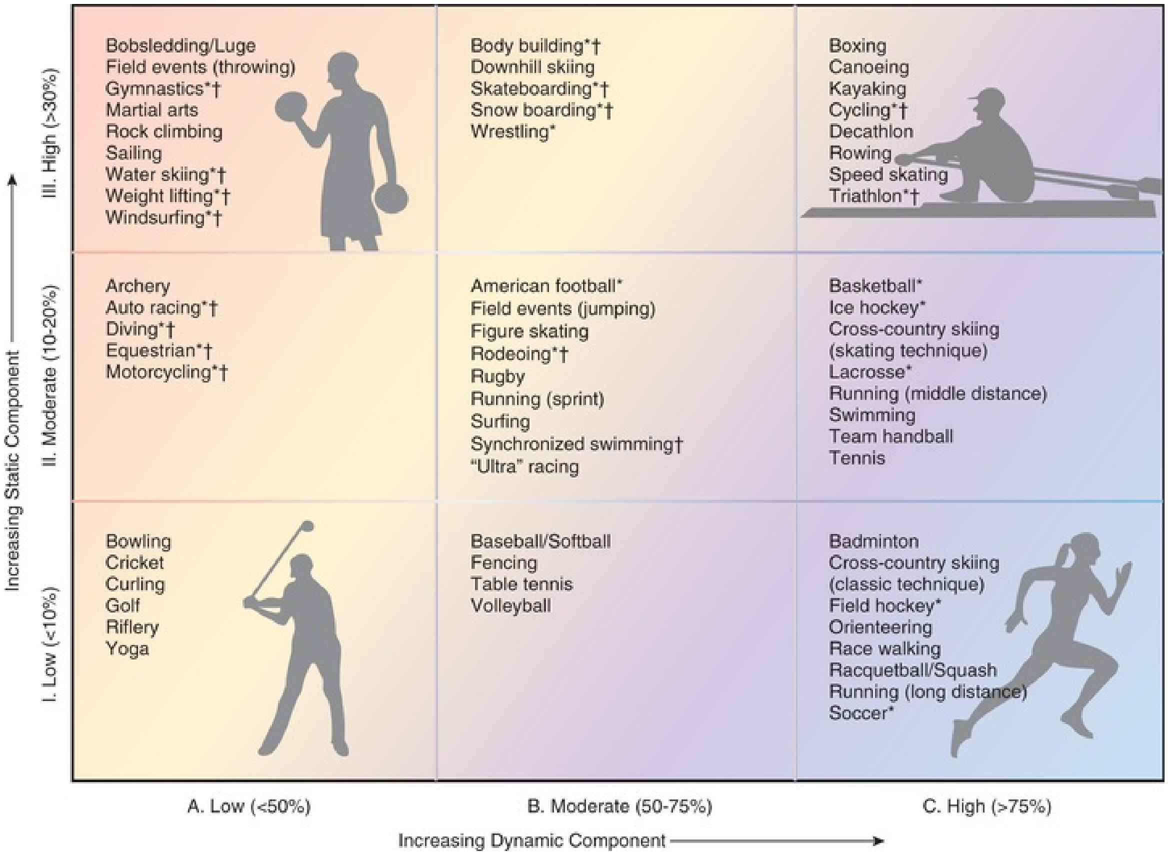

	A. Low (<50%)	B. Moderate (50-75%)	C. High (>75%)
III. High (>30%)	Bobsledding/Luge Field events (throwing) Gymnastics*† Martial arts Rock climbing Sailing Water skiing*† Weight lifting*† Windsurfing*†	Body building*† Downhill skiing Skateboarding*† Snow boarding*† Wrestling*	Boxing Canoeing Kayaking Cycling*† Decathlon Rowing Speed skating Triathlon*†
II. Moderate (10-20%)	Archery Auto racing*† Diving*† Equestrian*† Motorcycling*†	American football* Field events (jumping) Figure skating Rodeoing*† Rugby Running (sprint) Surfing Synchronized swimming† “Ultra” racing	Basketball* Ice hockey* Cross-country skiing (skating technique) Lacrosse* Running (middle distance) Swimming Team handball Tennis
I. Low (<10%)	Bowling Cricket Curling Golf Riflery Yoga	Baseball/Softball Fencing Table tennis Volleyball	Badminton Cross-country skiing (classic technique) Field hockey* Orienteering Race walking Racquetball/Squash Running (long distance) Soccer*

FIG. 706.1 Classification of sports. This classification is based on peak static and dynamic components achieved during competition; however, higher values may be reached during training. The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake (Vo_{2max}) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percentage of maximal voluntary contraction reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are shown in the palest color, with increasing dynamic load depicted by increasing blue intensity and increasing static load by increasing red intensity. Note the graded transition between categories, which should be individualized on the basis of player position and style of play. *Danger of bodily collision (see Table 706.4 for more detail on collision risk). †Increased risk if syncope occurs. (Modified from Mitchell JH, Haskell W, Snell P, et al: 36th Bethesda conference. Task force 8: classification of sports. *J Am Coll Cardiol* 45:1364–1367, 2005.)

Table 706.4

Sports According to Risk of Impact and Educational Background

	JUNIOR HIGH SCHOOL	HIGH SCHOOL/COLLEGE
Impact expected	American football Ice hockey Lacrosse Wrestling	American football Soccer Ice hockey Lacrosse

	Karate/judo Fencing Boxing	Basketball Wrestling Karate/judo Downhill skiing Squash Fencing Boxing
Impact may occur	Soccer Basketball Field hockey Downhill skiing Equestrian Squash Cycling	Field hockey Equestrian Cycling Baseball/softball Gymnastics Figure skating
Impact not expected	Baseball/softball Cricket Golf Riflery Gymnastics Volleyball Swimming Track and field Tennis Figure skating Cross-country skiing Rowing Sailing Archery Weightlifting Badminton	Cricket Golf Riflery Volleyball Swimming Track and field Tennis Cross-country skiing Rowing Sailing Archery Weightlifting Badminton

From Levine BD, Baggish AL, Kovacs RJ, et al: Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task force 1: classification of sports: dynamic, static, and impact: a scientific statement from the American Heart Association and American College of Cardiology. *J Am Coll Cardiol* 66(21):2350–2355, 2015.)

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CHAPTER 707

Management of Musculoskeletal Injury

Aaron M. Karlin, Nicholas P. Goyeneche, Kevin P. Murphy

Mechanism of Injury

Acute Injuries

Sprains, strains, and contusions account for the majority of musculoskeletal injuries. A **sprain** is an injury to a ligament or joint capsule. Most sprains are graded I-III. A *grade I* sprain is defined as mild damage to a ligament or ligaments without instability of the affected joint. A *grade II* sprain is considered a partial tear to the ligament, stretched to the point that it exhibits excessive laxity. A *grade III* sprain is a complete tear of the ligament with instability to the affected joint. A **strain** is an injury to a muscle or tendon and these, too, are graded I-III. *Grade I* muscle strains involve disruption of only a few muscle fibers, pain is mild to moderate and range of motion and strength are at or near normal. *Grade II* strains represent a more significant partial tear of the muscle and frequently involve loss of range of motion and strength. *Grade III* strains are defined as complete rupture of the musculotendinous unit. On examination, *grade III* strains, and often *grade II* strains, present with ecchymosis and a palpable step-off at the site of injury. A **contusion** is a crush injury to any soft tissue. The history of the injury is especially helpful in assessing musculoskeletal trauma. More severe injuries, indicating internal derangement of a joint, may have acute signs and symptoms such as immediate swelling, deformity, numbness or “give-way” weakness, a loud painful pop, mechanical locking of the joint, or instability.

Overuse Injuries

Overuse injuries are caused by repetitive microtrauma that exceeds the body's rate of repair. This occurs in muscles, tendons, bone, bursae, cartilage, and nerves. Overuse injuries occur essentially in all sports but are more commonly seen in sports emphasizing repetitive motion such as swimming, running, tennis, and gymnastics. Factors leading to overuse injuries can be categorized as extrinsic (i.e., training errors, poor equipment, or workout surface) and intrinsic (i.e., athlete's anatomy or medical conditions). Training error is the most commonly identified factor. As an example of this, at the beginning of the training program, athletes might violate the 10% rule: Do not increase the duration or intensity of workouts more than 10% per week. Intrinsic factors include abnormal biomechanics—due to anatomical causes such as leg-length discrepancy, pes planus, pes cavus, tarsal coalition, valgus heel, external tibial torsion, and femoral anteversion; muscle imbalance, inflexibility, and medical conditions (deconditioning, nutritional deficits, amenorrhea, and obesity). The athlete should be questioned about the specifics of their training. Specifically, runners, for example, should be asked about their shoes, orthotics, running surface, weekly mileage or time spent running per week, speed or hill workouts, and previous injuries and rehabilitation. When causative factors are identified, they can be modified or eliminated so that after rehabilitation the athlete does not resume the same regimen and suffer re-injury.

For athletes engaged in excessive training that causes an overuse injury, curtailing all exercise may not be necessary. Treatment incorporates a reduction of training load (relative rest) combined with a rehabilitation program designed to return athletes to their sport as soon as possible while minimizing exposure to re-injury. Early identification of an overuse injury requires less alteration of the workout regimen.

It has become more commonplace for young athletes to specialize in a single sport, and engage in year-round training. This practice should be counseled against as research has correlated this with burnout and decreased motivation and enjoyment, as well as increases in overuse injuries. This is especially evident in the sport of baseball, where the highly repetitive and forceful throwing motion can do damage to the tissues in the elbow and shoulder in a growing athlete. The athlete and their parents should be counseled to diversify their sport participation which may increase their enjoyment and performance in sport.

The goals of treatment in overuse injuries are to control pain and spasm to rehabilitate flexibility, strength, endurance, and proprioceptive deficits (Table 707.1). In many overuse injuries, the role of inflammation in the process is minimal. For most injuries to tendons, the term *tendinitis* is no longer used as there is little or no inflammation on histopathology of the affected tendons. Instead, there is evidence of microscopic trauma to the tissue. Most of these entities are more appropriately called **tendinosis** and, when the tendon tissue is scarred and when markedly abnormal, **tendinopathy** . With tendinosis, there is less of a role for antiinflammatory medication in the treatment, except as an analgesic.

Table 707.1

Staging of Overuse Injuries

GRADE	GRADING SYMPTOMS	TREATMENT
I	Pain only after activity Does not interfere with performance or intensity Generalized tenderness Disappears before next session	Modification of activity, consider cross-training, home rehabilitation program
II	Minimal pain with activity Does not interfere with performance More localized tenderness	Modification of activity, cross-training, home rehabilitation program
III	Pain interferes with activity and performance Definite area of tenderness Usually disappears between sessions	Significant modification of activity, strongly encourage cross-training, home rehabilitation program, and outpatient physical therapy
IV	Pain with activities of daily living Pain does not disappear between sessions Marked interference with performance and training intensity	Discontinue activity temporarily, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy
V	Pain interferes with activities of daily living Signs of tissue injury (e.g., edema) Chronic or recurrent symptoms	Prolonged discontinuation of activity, cross-training only, oral analgesic, home rehabilitation program, and intensive outpatient physical therapy

Novel treatments are emerging for the effective treatment of chronic tendinopathies, alongside the advancement and implementation of musculoskeletal ultrasound in clinical practice. Under ultrasound guidance, pathologic areas of tendon tissue can be targeted with injectates of autologous blood or platelet-rich plasma to stimulate a pro-inflammatory and more robust healing response. Although platelet-rich plasma is a popular therapy, the evidence for its effectiveness is inconclusive. Pathologic tissue can also be targeted with percutaneous needle fenestration or tenotomy, and tendon-fat pad adhesions can also be addressed through mechanical needle scraping or hydrodissection techniques utilizing ultrasound.

Initial Evaluation of the Injured Extremity

Initially, the examiner should determine the quality of the peripheral pulses and capillary refill rate as well as the gross motor and sensory function to assess for neurovascular injury. The first priorities are to maintain vascular integrity and skeletal stability.

Criteria for immediate attention and rapid orthopedic consultation include vascular compromise, nerve compromise, and open fracture. With the latter, the exposed wound should be covered with sterile saline-soaked gauze, and the injured limb should be padded and splinted. Pressure should be applied to any site of excessive bleeding. Additional criteria include deep laceration over a joint, unreducible dislocation, grade III (complete) tear of a muscle–tendon unit, and displaced, significantly angulated fractures.

Transition From Immediate Management to Return to Play

Rehabilitation of a musculoskeletal injury should be initiated on the day of the injury.

Phase 1

Limit further injury, control swelling and pain, and minimize strength and flexibility losses. **PRICE** principles (**P** rotection, **R** est, **I** ce, **C** ompression, and **E** levation) need to be applied. Crutches, air stirrups for ankle sprains, slings for arm injuries and elastic wraps (4-8 inches) for compression are a helpful inventory of medical supplies. Ice can be placed directly over the injury as tolerated for 20 min continuously 3-4 times per day until the swelling resolves. Compression limits further bleeding and swelling but should not be so tight that it limits perfusion. Elevation of the extremity promotes venous return and limits swelling. A nonsteroidal antiinflammatory drug or acetaminophen are indicated for analgesia.

Pain-free isometric strengthening, and range of motion exercises should be initiated as soon as possible. Pain inhibits full muscle contraction; deconditioning results if the pain and resultant nonuse persist for days to weeks, thus delaying recovery. Education about the nature of the injury and the specifics of rehabilitation exercises, including handouts with written instructions and drawings demonstrating the exercises, are helpful.

Phase 2

Improve strength and range of motion (e.g., flexibility) while allowing the injured structures to heal . Protective devices are removed when the patient's strength and flexibility improve, and activities of daily living are pain free. Flexibility can then be addressed by a program of specific stretches, held for 15-30 sec for 3-5 repetitions, once or twice daily. A physical therapist or athletic trainer is invaluable in guiding the athlete through this process. Protective devices might need to be used during sports participation. Swimming, water jogging, and stationary cycling are good, low-impact aerobic exercises that can allow the injured extremity to be used pain free while maintaining cardiovascular fitness.

Phase 3

Achieve near-normal strength and flexibility of the injured structures and further improve or maintain cardiovascular fitness. Strength and endurance are improved under controlled conditions using elastic bands and closed kinetic chain exercises at this point and then progressing next to utilizing exercise equipment followed by free weights. Additional sensory proprioceptive training allows the athlete to redevelop the kinesthetic sense critical to joint function and stability.

Phase 4

Return to exercise or competition without restriction. When the athlete has reached normal range of motion, strength, proprioception, and endurance, the athlete can initiate sports-specific exercises. The athlete will transition from the rehabilitation program to functional rehabilitation appropriate for the sport. Substituting sports participation for rehabilitation is inappropriate; rather, there should be progressive stepwise functional return to a full activity or play program. For instance, a basketball player recovering from an ankle injury might begin a walk-run-sprint-cut program before returning to competition. At any point in this progression, if pain is experienced, the athlete needs to stop, apply ice, avoid running for 1-2 days, continue to perform ankle stabilizing exercises, and then resume running at a lower intensity and progress accordingly.

Relative Rest and Return-to-Play Guidelines

Relative rest refers to the concept that the athlete participates in rehab and return to sport activities provided the injured structures do not hurt during or within 24 hr of the activity. Exercising beyond the pain threshold delays recovery.

Imaging

Traditional imaging modalities such as x-ray, MRI, and CT are well established in the routine diagnostic workup of musculoskeletal injury. Diagnostic ultrasound is gaining in popularity as technology continues to advance image resolution and the practicality of placement of the equipment in a clinic setting. An obvious advantage of ultrasound is a lack of radiation. It is also better tolerated by younger children who may have difficulty complying with MRI or CT protocols. Dynamic movement or stressing of a limb, joint, or structure can provide valuable diagnostic information, and can easily be compared to the contralateral side for comparison. Snapping or popping sensations, suspected intramuscular hematomas, stress fractures, and prognostic scrutiny of strains, sprains, and tendinopathies are all high-yield applications of diagnostic musculoskeletal sonography. Ultrasound imaging can also increase the accuracy of therapeutic injections, improving injection efficacy while simultaneously reducing adverse outcomes by erroneous needle placement.

Differential Diagnoses of Musculoskeletal Pain

Traumatic, rheumatologic, infectious, hematologic, psychologic, congenital, and oncologic processes—especially under the age of 12 yr—can cause the presenting complaint of musculoskeletal pain. Symptoms such as fatigue, weight loss, rash, multiple joint complaints, fever, chronic or recent illness, and persistent pain despite conservative care suggest a diagnosis other than sports-related trauma. The possibility of child abuse, including sexual abuse, as an etiology is not to be overlooked permeating all socioeconomic strata. Incongruity between the patient's history and physical examination findings should lead to further evaluation. A negative review of systems with an injury history consistent with the physical findings suggests a sports-related etiology.

707.1

Growth Plate Injuries

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Approximately 20% of pediatric sports injuries seen in the emergency department are fractures, and 25% of those fractures involve an epiphyseal growth plate or physis (see Chapter 703). Growth in long bones occurs in three areas and is susceptible to injury. Immature bone can be acutely injured at the physis (e.g., Salter-Harris fractures, see Chapter 703.2), the articular surface (e.g., osteochondritis dissecans [OCD]), or the apophysis (e.g., avulsion fractures). Males suffer nearly twice as many physeal fractures as females; the highest incidence of fracture is during peak height velocity (females: age 12 ± 2.5 yr; males: age 14 ± 2 yr). The physis is a pressure growth plate and is responsible for longitudinal growth in bone. The apophysis is a bony outgrowth at the attachment of a tendon and is a traction physis. The epiphysis is the end of a long bone, distal or proximal to the long bone, and contains articular cartilage at the joint.

Physeal injuries of the upper extremity are most commonly seen at the distal radius occurring in the growing child or adolescent, and are typically due to excessive force applied to the upper extremity. Injuries of this nature can be seen in athletes, including those participating in gymnastics, cheerleading, ice skating, hockey, and weight lifting. Mechanisms of injury include falls onto an outstretched hand or repetitive dorsiflexion and axial loading through the distal radius (see Chapter 713). Chronic wrist pain can be seen in up to 79% of young gymnasts—particularly female gymnasts between the ages of 12 and 14 yr, and is commonly termed **gymnasts' wrist** (see Chapter 701). With repetitive axial loading, temporary metaphyseal ischemia may be induced preventing cartilage calcification and causing the physis to widen. With widening of the distal radial physis, microfractures can develop. Clinical features involve radial wrist pain particularly dorsal with passive and active hyperextension activities relieved with suspension of the offending activity. Tenderness or focal pain around the circumference of the distal radius is often noted. Differential diagnosis includes metacarpal fractures, scaphoid fracture and in the older child or adolescent, and de Quervain tenosynovitis. Juvenile idiopathic arthritis always needs to be considered in a child with a painful swollen wrist not to exclude malignancy or an infectious process. X-rays of the wrist can be helpful particularly when compared to the contralateral extremity. Radiographs can show physeal widening with cystic changes involving the metaphyseal segment, breaking of the distal epiphysis and in later stages, positive ulnar variance. Bone scan may be helpful for stress fractures followed by MRI if subsequently needed. PRICE principles are followed with nonnarcotic pain management. Salter-Harris fractures types I and II can be treated with closed reduction and immobilization. Ulnar-shortening osteotomy may be necessary in the athlete with significant ulnar positive variance. Physeal injuries at the knee (distal femur, proximal tibia) are rare while those at the ankle (distal fibula most commonly) are more frequent —typically occurring as a result of an inversion injury—and predominantly Salter-Harris I fractures.

Growth disturbance following a growth plate injury is a function of location and the part of the physis fractured. These factors influence the probability that a physeal bar will form, resulting in growth arrest. In the upper extremity, the areas making the largest contribution to longitudinal growth are the proximal humerus and distal radius and ulna; in the lower extremities, the distal femur and the proximal tibia and fibula are the greatest contributors to longitudinal growth. Injuries to these areas are more likely to cause growth disturbance compared with physeal injuries at the other end of these long bones. The type of physis fracture relative to the risk of growth disturbance is described by the Salter-Harris classification system (see Table 706.2). A grade I injury is least likely to result in growth disturbance while grade V is the most likely fracture to result in growth disturbance.

Osteochondritis dissecans (OCD) affects the subchondral bone and overlying articular surface (see Chapter 697). With avascular necrosis of subchondral bone, the articular surface can flatten, soften, or break off in fragments. The etiology is unknown but may be related to repetitive stress injury in some patients. OCD most commonly presents in the lower extremities at the knee affecting the lateral aspect of the medial femoral condyle in 70% of patients, the lateral femoral condyle in 20%, and the patella in 10% (Fig. 707.1). In the upper extremities it is most frequently seen at the elbow—affecting the capitellum—and is often associated with repetitive overhead throwing or swinging activities (e.g., baseball). Other sites where OCD lesions are also seen are the ankle (talus) and radial head. OCD classically affects athletes in their seconds decade. The most common presentation is poorly localized vague joint pain. There is rarely a history of recent acute trauma. Some OCD lesions are asymptomatic—diagnosed on “routine” radiographs—whereas others are manifested as joint effusion, pain, decreased range of motion, and mechanical symptoms (e.g., locking, popping, or catching). Activity usually worsens the pain.

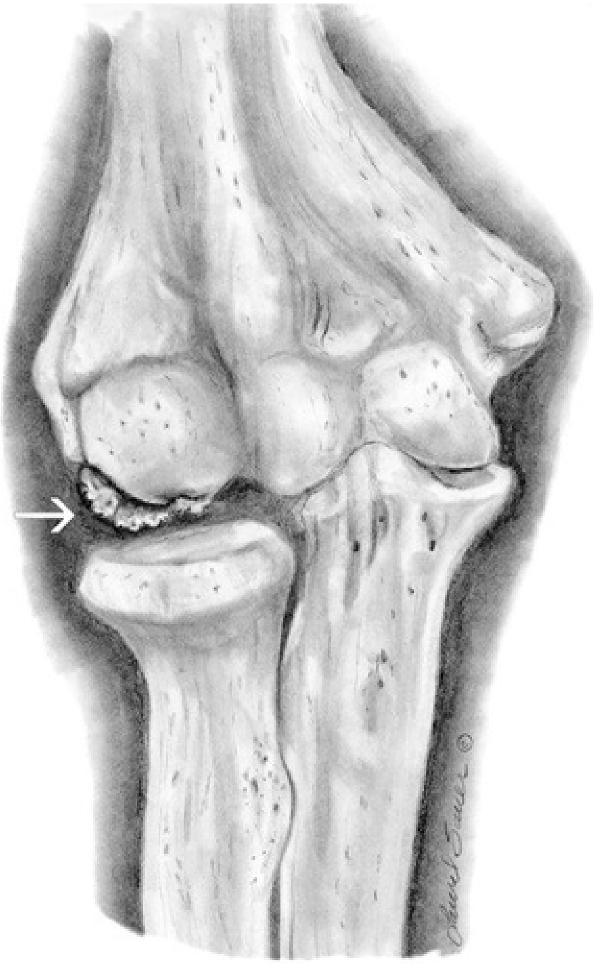

FIG. 707.1 Osteochondritis dissecans in the elbow. (Copyright Laurel Sauer, 2017.)

Physical examination might show no specific findings. Sometimes tenderness over the involved condyle can be elicited by deep palpation. Diagnosis is usually made with plain radiographs. When concerned about OCD at the knee, a tunnel view radiograph can be obtained to better view the posterior two thirds of the femoral condyle. Treatment of OCD remains controversial. Intact lesions can often be treated symptomatically with or without activity modification, reduced weight bearing, or immobilization. Free fragments generally require surgical removal. Drilling techniques can be utilized and are helpful in stimulating new bone formation, healing, and return of mobile bodies to their original donor sites. Long-term sequelae can be seen in up to 25% with atypical lesions, older age, effusion, and lesions of large size.

Avulsion fractures occur when a forceful muscle contraction dislodges the apophysis from the bone. They occur most commonly around the hip (Fig. 707.2) and are treated nonsurgically. Acute fractures to other apophyses (i.e., knee and elbow) require urgent orthopedic consultation. Chronically increased traction at the muscle–apophysis attachment can lead to repetitive microtrauma and pain at the apophysis. The most common areas affected are the knee (**Osgood-Schlatter** and **Sinding-Larsen-Johansson disease**), the ankle (**Sever disease**) (Fig. 707.3), and the medial epicondyle (**Little Leaguer's elbow**). Traction apophysitis of the knee and ankle can often be treated in a primary care setting. The main goal of treatment is to minimize the intensity and incidence of pain and disability. Exercises that increase the strength, flexibility, and endurance of the muscles attached at the apophysis, using the relative rest principle, are appropriate. The use of a patellar strap can provide benefit in reducing the traction force placed upon the tibial apophysis during activity. Symptoms can last for 12-24 mo if untreated. As growth slows, symptoms abate.

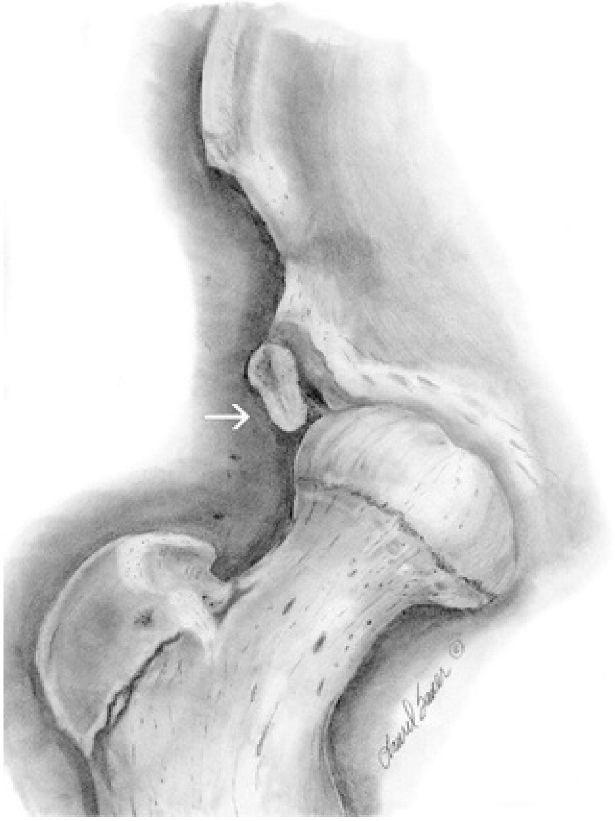

FIG. 707.2 **Anterior inferior iliac spine avulsion. (Copyright Laurel Sauer, 2017.)**

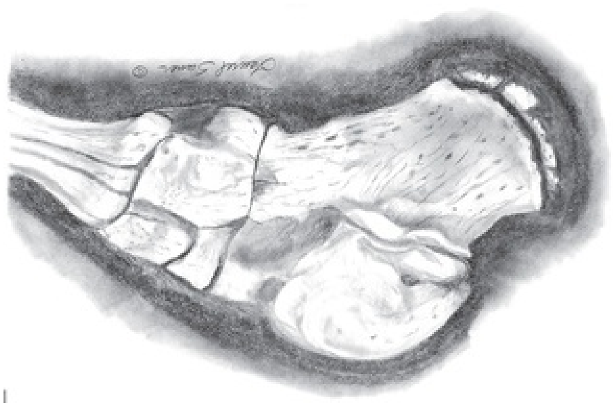

FIG. 707.3 Calcaneal apophysitis (sever disease). (Copyright Laurel Sauer, 2017.)

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707.2

Shoulder Injuries

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Shoulder pain associated with radiating symptoms down the arm should raise the possibility of a neck injury. *Neck pain and tenderness or limitation of cervical range of motion requires that the cervical spine be immobilized and that the athlete be transferred for further evaluation.* If there is no neck pain, tenderness or limitation of motion of the cervical spine, the shoulder is likely the site of the primary injury.

Clavicle Fractures

Clavicle fracture is one of the most common shoulder injuries. Injury is usually sustained by a fall on the lateral shoulder, on an outstretched hand, or by direct blow. Approximately 80% of fractures occur in the middle third of the clavicle. With younger children, plastic bowing of the clavicle may be present instead of an overt fracture and should be treated in the same fashion. Treatment is conservative and includes the use of an arm sling or figure of eight brace for comfort and protection. Healing time is shorter in comparison to adults—generally 4-6 wk. An additional 2-3 wk period of protection from contact/collision activities is recommended after clinical and radiographic healing is achieved to prevent reinjury. If nondisplaced, most medial and lateral clavicular fractures can be managed similar to middle third clavicular fractures. Displaced lateral and medial third fractures require orthopedic consultation because of a higher incidence of acromioclavicular (AC) osteoarthritis (lateral) and physeal involvement (medial). Distal clavicular osteolysis is likely an overuse injury associated with slow dissolution and resorption of bone. The cause of injury is unclear, appearing most consistent with a stress reaction or fracture at the site of considerable force. This lesion is commonly seen in weightlifting athletes and can be seen in older children. Nonoperative treatment including activity limitations, ice, nonsteroidal antiinflammatory agents, and cortisone injections can be helpful. Gripping the barbell at a greater distance for the weightlifter may be helpful. For those not willing to modify weightlifting activity, or those with persistent symptoms despite conservative care, surgery can be very successful and involves removal of the distal clavicle (approximately 1 cm) with no loss of strength and full return to activity anticipated.

Acromioclavicular Joint Separation

An AC joint separation most commonly occurs when an athlete sustains a direct blow to the acromion with the humerus in an adducted position, forcing the acromion inferiorly and medially. Force is directed toward the AC joint and coracoclavicular ligaments because of the inherent stability of the sternoclavicular joint. Patients have point tenderness at the AC joint, pain with lifting their arms above the level of their shoulder, and may have an apparent step-off between the distal clavicle and the acromion (Fig. 707.4).

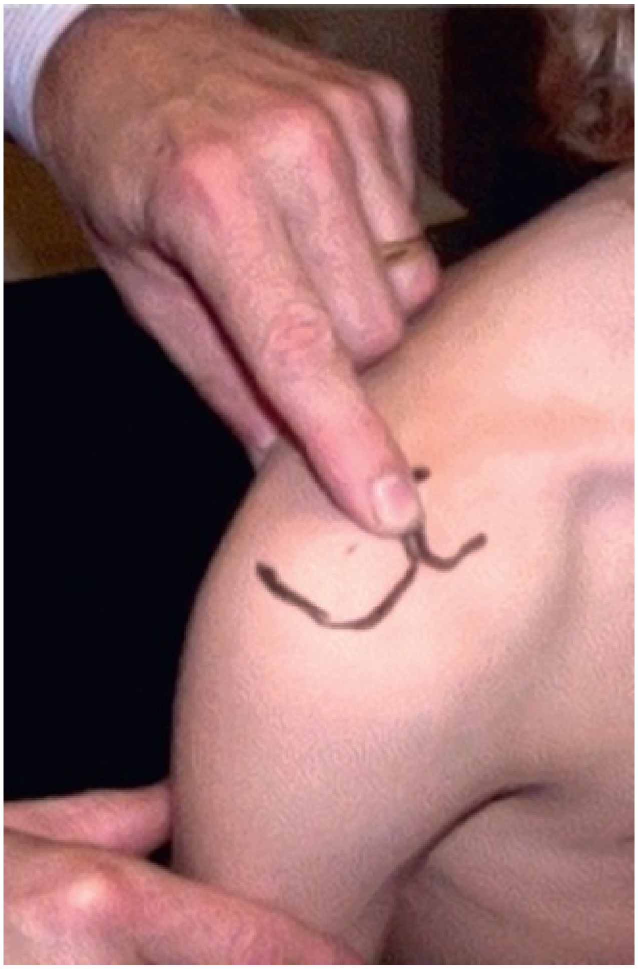

FIG. 707.4 **Palpitation of acromioclavicular joint. (From Anderson SJ: Sports injuries. *Curr Probl Pediatr Adolesc Health* 35:105–176, 2005.)**

Type I AC joint injuries involve isolated sprain of the AC ligament with the periosteal sleeve intact. There is no visible deformity and the radiographs are normal. Pain is elicited with adduction of the humerus across the chest. **Type II** injuries involve the AC ligament and coracoclavicular ligament, as well as partial disruption of the periosteal sleeve. Radiographs may show slight widening of the AC joint though the distance between the clavicle and the coracoid process is unchanged in comparison to the uninjured shoulder. Treatment of type I and type II AC injuries is conservative and nonoperative and consists of ice, nonsteroidal antiinflammatories, a sling for immobilization, and acute pain control. Shoulder range of motion exercises and strengthening of the rotator cuff, deltoid, and trapezius musculature are incorporated early in the rehabilitative course once pain-free range of motion is achieved in order to prevent residual joint stiffness. A short course of physical therapy may be helpful if range of motion limitations are present 2-4 wk out from injury. Consideration for return to play is made when the patient no longer has focal AC joint tenderness, exhibits full painless range of motion, has strength sufficient to be functionally protected from a collision or fall, and can perform maneuvers required within their sport. Typically, return to play from a type I AC injury is 1-2 wk, and 2-4 wk for type II.

Type III AC joint injury is more severe involving further tearing of the AC and coracoclavicular ligaments and disruption of the periosteal sleeve with instability of the distal clavicle because of deltotrapezial fascial detachment. Radiographs will commonly show superior displacement of the distal clavicle from the coracoid of 25–100%. The treatment of type III AC injuries is controversial. Many can be treated nonoperatively—similar to that described for types I and II AC injuries—if there is no damage to the overlying skin or neurovascular compromise to the injured limb. The patient should be counseled regarding this injury likely to result in a noticeable defect to ascertain whether this is acceptable. Surgery for type III AC injuries are uncommon and primarily for athletes involved with throwing sports or for cosmesis. **Types IV, V, and VI** AC joint injuries have progressive worsening of ligamentous and fascial disruption with varied locations of the clavicular displacement. These injuries should be referred to an orthopedist for consultation and operative repair.

Anterior Glenohumeral Dislocation

The most common mechanism of injury causing an **anterior glenohumeral dislocation** is making contact with another player with the shoulder abducted to 90 degrees and forcefully rotated externally. Patients complain of severe pain and that their shoulder “popped out of place” or “shifted.” Patients with an unreduced anterior dislocation have a hollow region inferior to the acromion and a bulge in the anterior portion of the shoulder caused by anterior displacement of the humeral head. Abnormal sensation of the lateral deltoid region and the extensor surface of the proximal forearm should be assessed for with regard to concomitant injury to the radial or musculocutaneous nerves, respectively.

Reduction of a dislocated shoulder should be made expediently, assuming no presence of crepitus—which would be concerning for a fracture. Numerous safe methods for closed reduction have been described, including the traction–counter traction technique, the **Stimson maneuver** , and the abduction maneuver. Postreduction radiographs are helpful and may show evidence of a posterior lateral humeral head impaction fracture (Hill-Sachs lesion). Injuries to the surrounding soft tissues, including the anterior capsule and labrum, are best evaluated by MRI—often with an accompanying arthrogram of the glenohumeral joint. Once reduced, initial treatment of a dislocation includes placing the patient into an arm sling for comfort and protection. The duration of immobilization is controversial and may last anywhere from a few days to 4-6 wk. The most significant risk after an acute traumatic dislocation is recurrence. Most sports medicine practitioners encourage early range of motion and strengthening exercises as tolerated. Rehabilitation focuses on progressive strengthening of the rotator cuff, deltoid, and periscapular muscles at increasing degrees of abduction and external rotation. Strengthening of the rotator cuff muscles is extremely important as they are the dynamic stabilizers of the glenohumeral joint, which are integral to the prevention of future dislocation. Plyometric exercises also may be incorporated near the end of rehabilitation to improve proprioceptive function in preparation for return to athletics. Patients can return to play when strength, flexibility, and proprioception are equal to the uninjured shoulder to the extent that they are able to protect the shoulder and perform sports-specific activities without pain. Surgery is to be considered in cases of recurrent dislocations or in those individuals that fail to heal adequately after prolonged rehabilitation. Additionally, early operative repair should be considered for athletes participating in contact or collision sports that inherently have higher recurrence rates.

Rotator Cuff Injury

The muscles of the **rotator cuff** consist of the supraspinatus, infraspinatus, teres minor, and subscapularis. The function of these muscles is to rotate the humerus and stabilize the humeral head against the glenoid. The supraspinatus is most commonly injured, either by an acute strain caused by trauma or chronic tendinosis from overuse. Specifically, rotator cuff tendinosis commonly presents with the complaint of pain with overhead arc of motion, such as with throwing, lifting, or reaching for objects above one's head. Pain is often poorly localized about the shoulder, although it may be referred to the deltoid. The onset of pain is often insidious and is commonly associated with increased frequency or duration of overhead throwing or lifting activities. Pain is exacerbated with these or other activities, but is often present at rest; nighttime pain occurs in more severe cases. On exam, manual muscle testing of the rotator cuff muscles often produces pain and in some cases weakness in comparison to the uninjured shoulder. Supraspinatus tendinosis produces pain with active abduction against resistance in which the patient abducts the arm to 90 degrees, forward flexes to 30 degrees anterior to the parasagittal plane, and internally rotates the humerus.

The treatment of rotator cuff tendinosis includes relative rest from athletics or activities causing pain; the use of ice, analgesia, and/or nonsteroidal antiinflammatory use. Strengthening of the rotator cuff and scapular stabilizer musculature, modifications of technique, and core strengthening are important components of rehabilitation often supervised by a physical therapist. In the young athlete, rotator cuff pain is most commonly a result of glenohumeral instability and not rotator cuff impingement syndrome. The latter is more commonly seen in adults and is caused by impingement of the rotator cuff by the bony structures superior to it. As a result, treatment focusing on stretching alone can make symptoms worse. Return to play often includes gradual increases in load placed upon the rotator cuff as the patient resumes their prior activities, such as an interval throwing program in baseball.

Glenoid labrum tears may present in similar insidious fashion to rotator cuff tendinosis or may be associated with an acute traumatic dislocation. This is frequently manifested with pain in the glenohumeral joint and may be associated with a sensation of clicking or catching in the shoulder. This can frequently be reproduced on exam. One of the most common lesions is a superior labrum anterior and posterior lesion. Throwing athletes are at particular risk. Mechanism of injury is thought to be related to a traction injury along the long head of the biceps at its attachment at the superior glenoid labrum, occurring during the throwing cycle. Radiographs are usually normal. MRI with arthrogram is the best study to identify glenoid labrum pathology (Fig. 707.5).

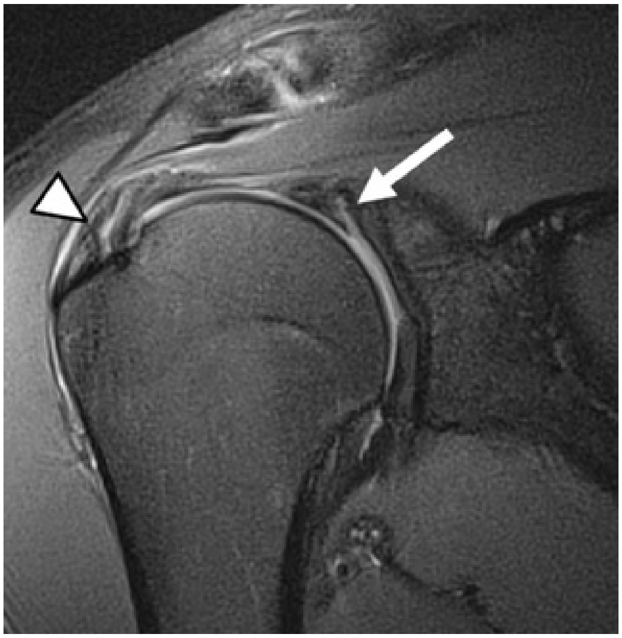

FIG. 707.5 Coronal intermediate-weighted MRI in a different patient showing superior labral tear *(arrow)* and tendinosis of the supraspinatus tendon *(arrowhead)* . There is no adjacent perilabral edema, suggesting chronic injury. (From Chang, I-Yuan J, Polster JM: Pathomechanics and magnetic resonance imaging of the thrower's shoulder. *Radiol Clin N Am* 54(5):801–805, 2016, Fig. 13, p. 811.)

Proximal humeral stress fracture (epiphysiolysis) is an uncommon cause of proximal shoulder pain and is suspected when shoulder pain does not respond to routine measures. Gradual onset of deep shoulder pain occurs in a young (open epiphyseal plates) athlete involved in repetitive overhead motion, such as in baseball, tennis, or swimming, but with no history of trauma. Tenderness is noted over the proximal humerus; the diagnosis is confirmed by detecting a widened epiphyseal plate on plain radiographs, increased uptake on nuclear scan, or edema of the physis on MRI. Treatment is total rest from throwing for 6-8 wk.

Non-sports-related conditions that need to be considered in any child with a painful shoulder include an undiagnosed Sprengel deformity. This deformity involves the scapula, which fails to descend from its cervical region overlying the 1st through 5th ribs. Children often present with a shortened neckline and a lack of normal scapular thoracic motion. Malpositioning of a glenoid can cause limited forward flexion and abduction of the shoulder. An omovertebral bar is present in up to 50% of cases. This bar connects the superior medial angle of the scapula and the cervical spine, and consists of fibrous cartilaginous tissue or bone. Other regional abnormalities can include scoliosis with a prominent scapula on the convex side, congenital rib anomalies, and undiagnosed Klippel-Feil syndrome. Winging of the scapula always raises the question of muscular dystrophy, particularly scapular thoracic. Family histories can be most helpful. Primary bone tumors (see Chapter 528) common to the upper extremities include Ewing sarcoma of the scapula and osteogenic sarcoma of the proximal humerus, in addition to osteoblastomas and chondroblastomas common to the diaphysis and epiphysis of long bones. The most common presenting manifestations of osteosarcoma are pain, upper limb dysfunction, and swelling. Similar presentations can be seen in Ewing sarcoma, along with weight loss and fever. Symptoms not responding to conservative treatment require further investigation and specialty consultation.

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707.3

Elbow Injuries

Aaron M. Karlin, Nicholas P. Goyeneche, Kevin P. Murphy

Acute Injuries

The most commonly dislocated joint in childhood is the elbow. Radial head subluxation, or “nursemaid's elbow,” comprises the majority of these (see Chapter 701). Posterior dislocation is the next most common type of **elbow dislocation** , with its mechanism being that of falling backward onto an outstretched arm with the elbow in extension. The dislocation may be complete or incomplete—termed “perched”—with the trochlea subluxed upon the top of the coronoid process. The ulnar collateral ligament (UCL) is commonly disrupted along with other components of the soft tissue capsule about the elbow. Fractures of the olecranon (> 80% occurrence) or medial epicondyle may be present as well. An obvious deformity is visualized with the olecranon process displaced prominently behind the distal humerus. Careful examination of the distal radius and ulnar pulses to assess vascular integrity of the distal upper arm is important because of the potential for injury to the brachial artery. Sensation to the distal extremity should also be assessed because of possible injury to the radial, median, and ulnar nerves. Reduction should be performed as soon as possible before significant swelling and muscle spasm potentially complicate the procedure. Longitudinal traction is applied to the forearm with gentle upward pressure on the distal humerus so that the coronoid process clears the trochlea. If reduction is unable to be performed, the arm should be placed in a padded splint and sling, and the patient transported to an emergency facility.

Supracondylar humeral fractures can result from the same mechanism of injury as elbow dislocations and can be difficult to distinguish on exam from a posterior dislocation because of significant swelling about the elbow joint. These, too, can be complicated by concomitant injury to the brachial artery and to a lesser extent the median, radial, and ulnar nerves. The injury typically occurs in the first decade of life, which is associated with peak hyperlaxity of the elbow joint in children between the ages of 5 and 8 yr. An acute compartment syndrome can develop after these fractures, which is associated with a fat pad sign (Fig. 707.6). These fractures should be referred for orthopedic consultation and are discussed in more depth in Chapter 703 .

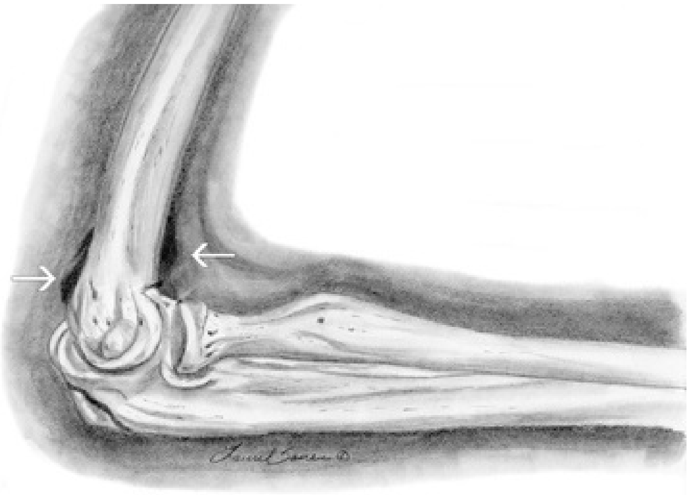

FIG. 707.6 Deflection of the supracondylar fat pad with a joint effusion (fat pad sign) showing evidence of a fracture. (Copyright Laurel Sauer, 2017.)

Direct trauma to the elbow can cause bleeding and inflammation in the olecranon bursa resulting in **olecranon bursitis.** Aspiration is rarely required, and this injury can be managed with ice, compressive dressing, and analgesia (RICE principles). An overlying elbow pad provides comfort during activity and prevention of reinjury.

Chronic Injuries

Overuse injuries in the upper extremities occur primarily in throwing sports, sports that require repetitive wrist flexion or extension, or sports that demand weightbearing on hands (gymnastics).

Little Leaguer's elbow is a broad term for several different elbow problems. Throwing overhand creates valgus stress to the elbow with medial opening of the joint and lateral compressive forces. **Medial elbow pain** is a common complaint of young throwers, resulting from repetitive valgus overload of the wrist flexor-pronator muscle groups and their attachment on the medial apophysis. In preadolescents who still have maturing secondary ossification centers, **traction apophysitis of the medial epicondyle** is likely. Patients have tenderness along the medial epicondyle; pain is exacerbated by valgus stress or resisted wrist flexion and pronation. Wrist pain may be present in more severe cases. Radiographs may show widening of the growth plate at the medial apophysis in comparison to the uninjured elbow. Treatment includes no throwing for 4-6 wk, pain-free strengthening and stretching of the flexor-pronator group followed by a 1-2 wk progressive functional throwing program with careful rehabilitation.

Incorporation of core strengthening and scapular stabilizing exercises, as well as addressing proper throwing mechanics (to reduce the load upon the medial elbow), are important components of the rehabilitation program. This problem has to be treated with a period of rest from throwing because of the risk of nonunion of the apophysis and chronic pain. If pain occurs acutely, **avulsion fracture of the medial epicondyle** must be considered. Radiographs should be taken in any thrower with acute elbow pain. If the medial epicondyle is avulsed (Fig. 707.7), orthopedic consultation is indicated.

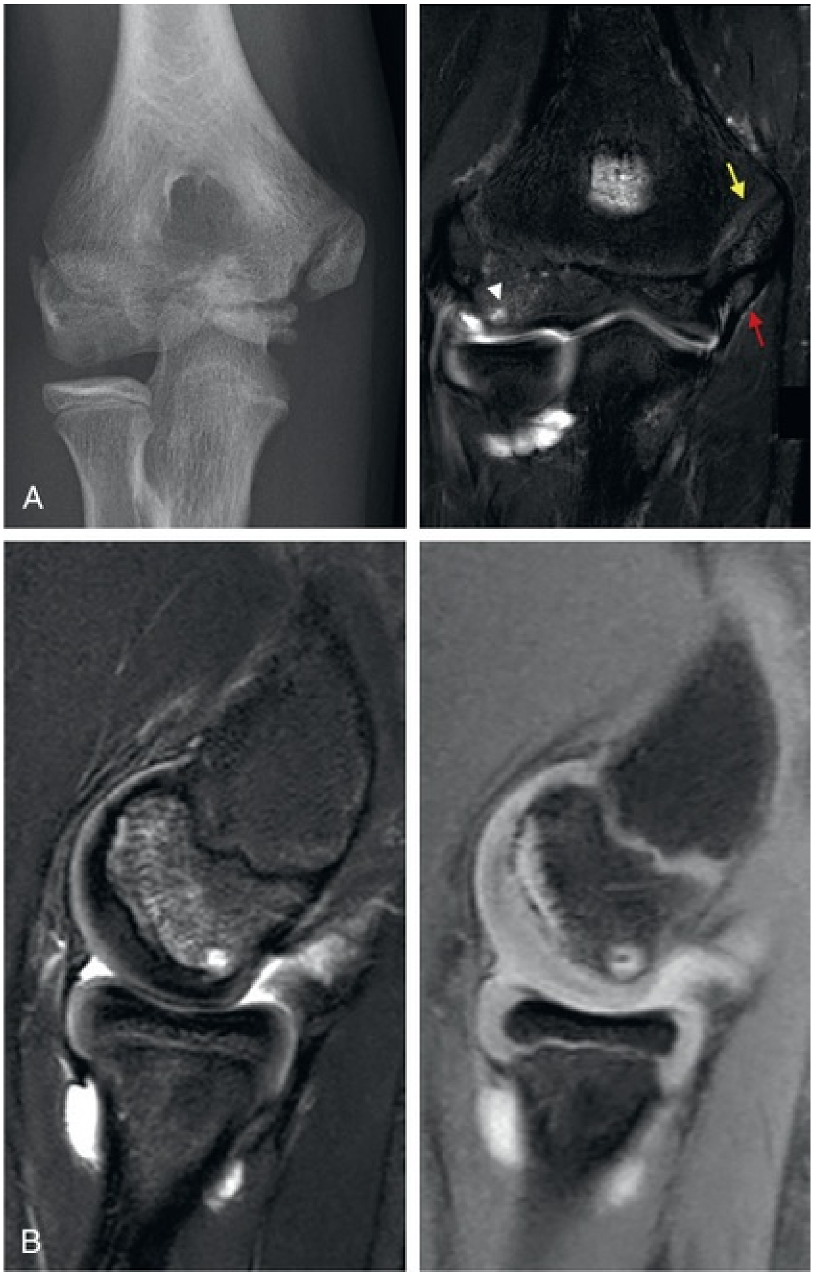

FIG. 707.7 The many faces of little league elbow in a 14-yr-old pitcher. A, AP radiograph and coronal oblique fat-saturated T2-weighted MRI demonstrate features of chronic medial epicondyle stress injury *(yellow arrow)* as well as findings of capitellar osteochondritis dissecans *(white arrowhead)* . Proximal medial ulnar collateral ligament edema/grade 1 sprain also noted at the humeral attachment *(red arrow)* . B, Sagittal short tau inversion recovery and fat-saturated T1-weighted MR arthrogram images emphasize the classic features of injury to the "metaphyseal equivalent" bone deep to the disorganized and obliterated secondary physis of the ossifying capitellum. (From Braithwaite KA, Marshall KW: The skeletally immature and newly mature throwing athlete. *Radiol Clin N Am* 54(5):841–855, 2016, Fig. 11.)

In older adolescents and young adults with a fused apophysis, the structure at the elbow vulnerable to injury is the **ulnar collateral ligament (UCL).** UCL sprains/tears are common in sports requiring high-velocity throwing or overhead activities. Medial elbow pain primarily worse during the acceleration phase of throwing is common. A sensation of elbow joint "opening" during throwing is also frequently described. On exam, focal tenderness to palpation over the UCL is present. Additionally, laxity may be appreciated with valgus stress of the elbow when flexed to 30 and/or 90 degrees. Radiographs are generally unremarkable. Diagnostic ultrasonography or MRI with arthrography is often necessary to assess the integrity of the UCL. Partial tears can be treated with a period of time off from throwing (2-4 wk) followed by careful progressive rehabilitation as discussed above for medial elbow pain. If there is a complete tear, surgical repair is indicated if the athlete desires to continue a pitching career.

Medial epicondylitis, or golfer's elbow, is another common cause of medial elbow pain in the individual with fused apophysis. It is commonly caused by overuse of the flexor pronator muscle groups at their origin at the medial humeral epicondyle. This occurs frequently in athletics or activities with repetitive wrist flexion. Tenderness is noted over the medical epicondyle and exacerbated by passive wrist extension or resisted wrist flexion. Treatment includes rest from the inciting activity, ice, stretching and strengthening of the wrist flexors, forearm straps, counterforce bracing, and analgesia. Ulnar nerve dysfunction can be a complication of valgus overload and can occur with any of the diagnoses previously discussed. Persisting paresthesia or motor weakness in the ulnar nerve distribution should be evaluated with electromyography and nerve conduction studies. Diagnostic ultrasonography can also be of use to assess for focal thickening of the nerve, as a sign of irritation, as well as dynamically visualizing the nerve through the arc of elbow flexion to assess for subluxation over the medial epicondyle (Fig. 707.8).

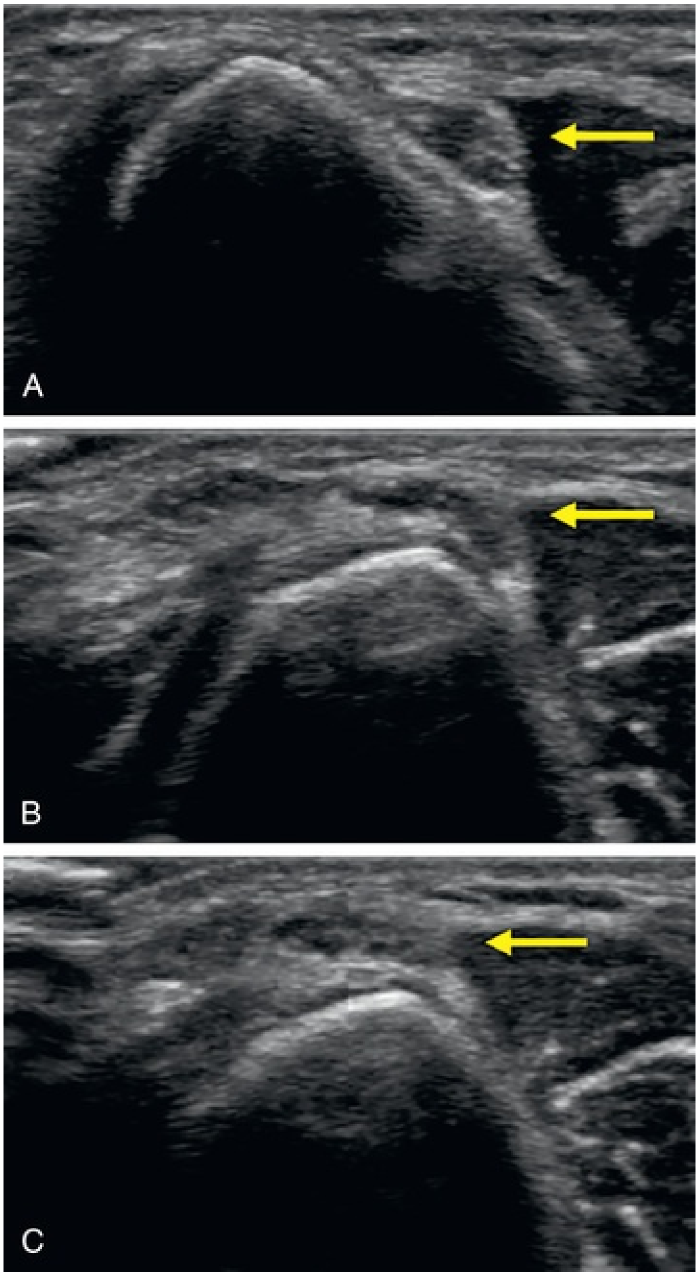

FIG. 707.8 Ulnar nerve subluxation. Dynamic ultrasound imaging of the ulnar nerve *(arrow)* in the ulnar groove at the elbow. A, The ulnar nerve positioned appropriately in the ulnar groove with the elbow extended. With elbow flexion, (B) the nerve becomes perched upon the medial epicondyle. As the elbow moves into terminal flexion, (C) the nerve is completely dislocated anteriorly over the medial epicondyle. (Courtesy Nicholas Goyeneche, MD, ultrasound clinic files, Ochsner Clinic Medical Center.)

Lateral elbow pain can be caused by compression during the throwing motion at the radiocapitellar joint. **Panner disease** is osteochondrosis of the capitellum that occurs between ages 7 and 12 yr (Fig. 707.9). **Osteochondritis dissecans (OCD)** of the capitellum occurs at age 13-16 yr (see Fig. 707.1).

These two entities may represent a continuum of the same disease. Although patients with both conditions present with insidious onset of lateral elbow pain exacerbated by throwing, patients with OCD have mechanical symptoms (popping, locking) and, more commonly, decreased range of motion. Patients with Panner disease have no mechanical symptoms and often have normal range of motion. The prognosis of Panner disease is excellent, and treatments consist of relative rest (no throwing), brief immobilization, and repeat radiographs in 6-12 wk to assess bone remodeling. In OCD, radiographs show a more focal lesion in the capitellum with eventual flattening and potentially fragmentation. An MRI scan can be very helpful in the diagnosis early on and with subsequent staging. A diagnosis of OCD requires orthopedic consultation with treatment dependent upon the severity of the lesion and fragmentation.

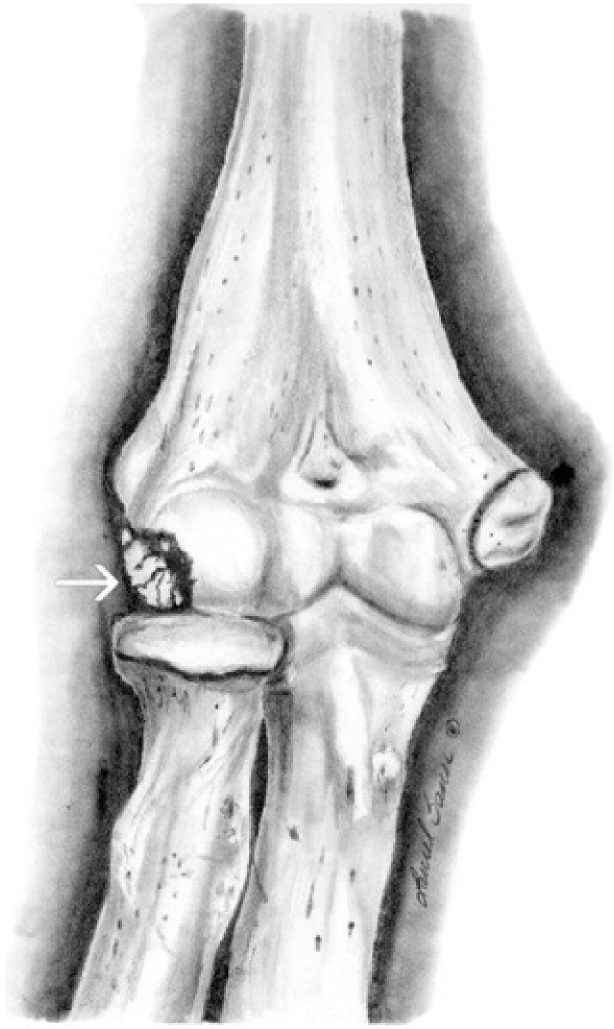

FIG. 707.9 **Panner disease. Note fragmentation of the humeral capitellum and flattening of the articular surface *(arrow).* (Copyright Laurel Sauer, 2017.)**

Lateral epicondylitis, or "tennis elbow," is the most common overuse elbow injury in adults but is relatively uncommon in children and adolescents (Fig. 707.10). It is a tendinosis of the extensor muscle origin at the lateral humeral epicondyle, which is commonly found in individuals performing activities requiring repetitive or prolonged grip. Tenderness is localized over the upper lateral epicondyle and is worsened with passive wrist flexion or resisted wrist extension. Treatment includes relative rest, analgesia, and specific stretching and strengthening exercises for the elbow and forearm. Improper equipment (i.e., wrong grip size or overstrung racket) and poor technique can contribute to the onset of symptoms. Return to play should be gradual and progressive to prevent reinjury.

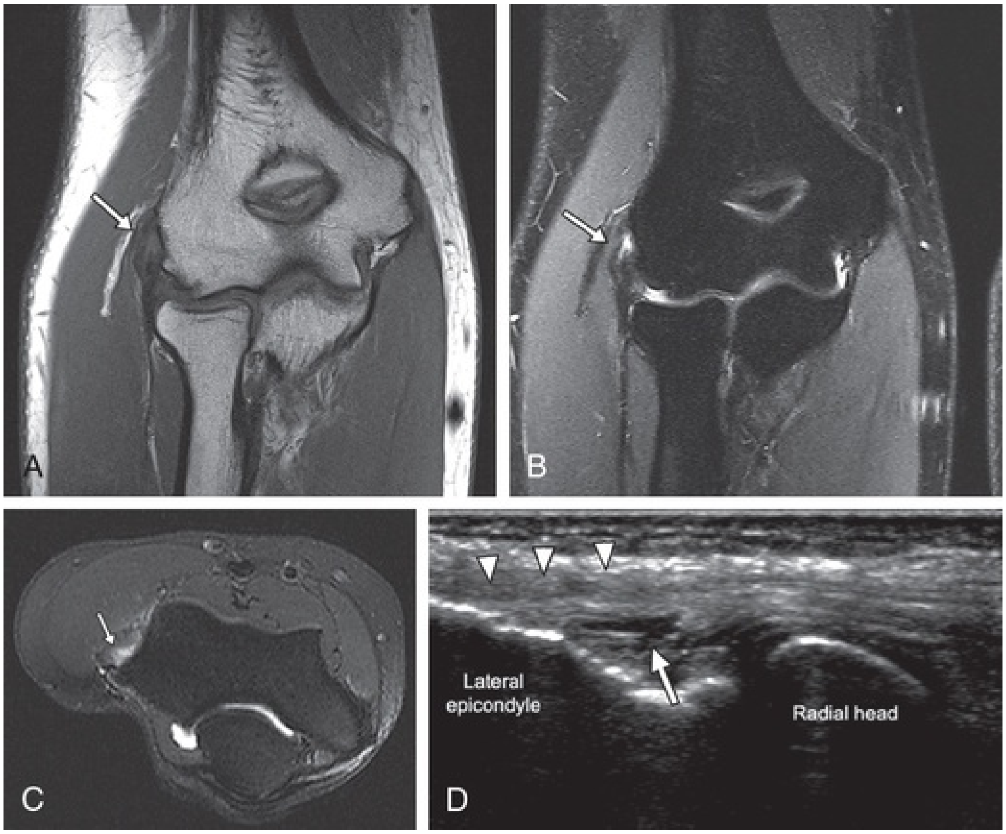

FIG. 707.10 **A 22-yr-old tennis player with persistent lateral elbow pain despite 3 mo of physical therapy. A, Coronal T1 sequence shows thickening and intermediate signal in the common extensor tendon (CET; *arrow*). B, Coronal T2 fat suppression (FS) (CET; *arrow*) and (C) axial proton density FS sequences reveal fluid signal within the CET and discontinuity of tendon fibers, consistent with a partial-thickness tear (CET; *arrow*). D, Corresponding long axis ultrasound image shows an anechoic fluid cleft *(arrow)* in**

the undersurface of the CET *(arrowheads).* (From Gustas CN, Lee KS: Current imaging concepts and image-guided treatments for the injured thrower's elbow. *Radiol Clin N Am* 54(5):817–839, 2016, Fig. 2, p. 821.)

Elbow injuries can be minimized but not necessarily prevented by preseason stretching and strengthening exercises. The importance of core strengthening and scapular stabilization with respect to preventing elbow and shoulder injuries in the throwing athlete cannot be overstated. The most important consideration for preventing elbow injuries in throwers is limitation of the number of pitches and advising players, coaches, and athletes that they should stop immediately when they experience elbow pain. If it persists, they need medical evaluation. It has been recommended that a young pitcher have age-specific limits on pitch counts, including the number of pitches thrown per game and per week, as well as maintaining appropriate days off between games pitched. A good rule of thumb is that the maximal number of pitches per game should be approximately 6 times the pitcher's age in years.

Other less-common problems that cause elbow pain are ulnar neuropathy/subluxation, tricipital or bicipital tendonitis (distal), olecranon apophysitis, and loose bodies. Non-sports-related injuries that need to be considered in the child with a painful elbow include undiagnosed congenital conditions, such as radial dysplasia, including radial ulnar synostosis and mild persistent brachial plexus palsy. The elbow is not an uncommon site for inflammatory arthritides, including juvenile idiopathic arthritis, sepsis, hemophilia, and sickle cell disease. Neoplasia to consider includes osteoblastomas and chondroblastomas, which are common in the diaphysis and epiphysis of longer bones, in addition to osteosarcoma. As always, in the child with persistent symptoms who is not responding to conservative care, further diagnostic workup is indicated.

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707.4

Low Back Injuries

Aaron M. Karlin, Nicholas P. Goyeneche, Kevin P. Murphy

Spondylolysis, Spondylolisthesis, and Facet Syndrome

Spondylolysis

Spondylolysis, a common cause of back pain in athletes, is a stress fracture of the pars interarticularis (see Chapter 699.6). It can occur at any vertebral level but is most likely at L4 or L5. Complete spondylolysis has never been found in the newborn. Its occurrence increases between the ages of 5.5 and 6.5 yr to a rate of 5%, close to the frequency of 5.8% in the white population. Prevalence in adolescent athletes evaluated for low back pain is 13–47%. Besides acute hyperextension that causes an acute fracture, the mechanism of injury is either a congenital defect or hypoplastic pars. This is exacerbated by repetitive lumbar extension loading. Ballet, weightlifting, gymnastics, and football are examples of sports in which repetitive extension loading of the lumbar spine frequently occurs.

Patients often present with pain of insidious onset. However, there may be a precipitating injury, such as a fall, or a single episode of hyperextension. The pain is worse with extension, may radiate to the buttocks, and can eventually affect activities of daily living. Rest or supine positioning usually alleviates the pain.

On examination, the pain is reproduced with lumbar extension while standing, especially when standing on one leg (single-leg hyperextension test). Limited forward spinal flexion and tight hamstrings may be seen. Neurologic examination is generally normal. There is often well-localized tenderness to deep palpation just lateral to the spinous process on the affected side—frequently at the level of L4 or L5.

The diagnosis is confirmed by finding a pars defect on an oblique lumbar spine radiograph. The defect is rarely seen on anteroposterior (AP) and lateral views. Bone single-photon emission CT is needed to confirm diagnosis if radiographs are normal. A plain CT scan can help to identify the degree of bony involvement and is sometimes used to assess healing.

Treatment includes pain relief and activity restriction. Rehabilitation consisting of trunk strengthening, hip flexor stretching, and hamstring stretching is important in most cases. A thoracic lumbar sacral orthotic on a temporary basis may be helpful for the spondylolytic stress fracture resistant to healing by alternative conservative means.

Spondylolisthesis and Facet Syndrome

Spondylolysis, spondylolisthesis, and facet syndrome are injuries to the posterior elements of the vertebrae. **Spondylolisthesis** occurs when bilateral pars defects exist and forward displacement or slippage of a vertebra occurs upon the vertebra inferior to it (see Chapter 699.6). **Facet syndrome** has a similar history and physical examination findings as spondylolysis. It is caused by instability or injury to the facet joint, posterior to the pars interarticularis and at the interface of the inferior and superior articulating processes. Facet syndrome can be established by identifying facet abnormalities on CT or by exclusion, requiring a nondiagnostic radiograph and nuclear scan to rule out spondylolysis.

Treatment of posterior element injuries is conservative, directed at reducing the extension-loading activity, often for 2-3 mo. Body mechanics, posture principals, core strengthening, and lumbar pelvic stabilization routines can be very helpful in the functional recovery of the motivated athlete. Walking, swimming, and cycling can be appropriate exercises also during the rehabilitation phase. Rarely spinal segmental fusion can be indicated in the athlete with spondylolisthesis and persistent symptomatic segmental instability despite further conservative care.

Lumbar Disk Herniation, Strain, and Contusion

Intervertebral disc injury in children and the young athlete is uncommon. In contrast to the selective motor and sensory deficits often observed in adults with disc herniation, athletes younger than 20 yr of age have pain or tenderness less commonly identified over the course of the sciatic nerve. Physical examination findings may be minimal but usually include pain with forward flexion and lateral bending. It is unusual to have a positive straight leg test or any neurologic deficit in the young athlete with an injured disc. There may be tenderness of the vertebral spinous process at the level of the disc injury. A general aching sensation in the lower back or upper buttocks may be present. MRI usually confirms a clinical diagnosis. Assuming the herniation is not large, and the pain is not intractable, the treatment of choice is conservative with analgesia and physical therapy. Surgery is rarely necessary.

Acute lumbar strain or contusion can be seen in the younger athlete and is usually associated with precipitating activity often outside of the normal routine. Physical examination reveals tenderness in the paraspinal and lateral soft tissues often associated with recreating the mechanisms of injury. Thoracic and lumbar strain in the school-age child is frequently associated with obesity, deconditioning, positive family history, and poorly supervised and equipped recreational activity. Up to 20% of youths have experienced back pain at some point in their life prior to age 15 yr. The school-used backpack is rapidly becoming the most common cause of back pain of a benign nature in children. Up to 74% of school backpackers experience pain. Back pain is more common with the heavy backpack (>10–20% of body weight), female gender, large body mass index, and single shoulder strap.

Treatment is conservative including analgesia, myofascial release, massage, and physical therapy, as tolerated. The natural history of acute back strain in adults is that 50% are better in 1 wk, 80% in 1 mo, and 90% in 2 mo, regardless of therapy. The course of back pain in young athletes is likely similar given the elimination of obvious precipitating influence and/or activities, as discussed above.

Sacroiliitis manifests as pain over the sacroiliac joints; it is usually chronic but is occasionally associated with a history of trauma. Patients have a positive result with the **Patrick test,** which includes resting the foot of the affected side on the opposite knee (hip flexed 90 degrees), stabilizing the opposite iliac crest, and externally rotating the hip on the affected side (pushing the knee down and lateral). Symptomatic improvement with knee-to-chest maneuvers and subsequent posterior pelvic tilt may be present. A radiograph of the sacroiliac joints is indicated, and if results are positive, exploration for a rheumatologic disease (ankylosing spondylitis [see Chapter 181], juvenile idiopathic arthritis [see Chapter 180], or inflammatory bowel disease [see Chapter 362]) is warranted.

Treatment is with relative rest, nonsteroidal antiinflammatory drugs (NSAIDs), and physical therapy. Ankylosing spondylitis is more likely if the onset of lower back pain is before 40 yr of age, if there is morning stiffness demonstrating improvement with activity, and if the pain has a gradual onset having lasted longer than 3 mo.

Other Causes

Non-sports-related causes of low back pain in the young athlete are numerous and include infection (osteomyelitis, diskitis) and neoplasia. These should be considered in patients with fever, weight loss, other constitutional signs, or lack of response to initial therapy. Osteomyelitis of the lower back or pelvis is often, but not always, associated with fever. Undiagnosed **Scheuermann's disease** needs to be considered with a history of chronic back pain; it is more common in males and younger adolescents, and should be distinguished from symptomatic postural roundback and congenital decompensating kyphosis. Atypical Scheuermann's disease or thoracolumbar apophysitis can progress and become the pediatric equivalent of an adult compression fracture. Benign tumors of the spine include osteoid osteoma with intense focal nighttime pain, not activity related and almost always relieved by aspirin or nonsteroidal antiinflammatory agents. Undiagnosed osteoblastoma, eosinophilic granuloma, aneurismal bone cyst, and fibrous dysplasia are additional benign tumors not to be excluded. Malignant spinal tumors include the Ewing sarcoma (onion skin appearance) and osteogenic sarcoma (sunburst pattern) both associated with the Codman triangle. Metastatic tumors of the spine include neuroblastoma, spinal cord tumors, leukemia, and lymphoma. Wilms tumor can also metastasize to the spine and be associated with hemihypertrophy. Referred pain to the spine always needs to be considered. Conditions that can refer pain include pyelonephritis, renal osteodystrophy, pneumonia, endocarditis, cholecystitis, nephrolithiasis, pancreatitis, megacolon, constipation/ileus, hiatal hernia/reflux, pelvic inflammatory disease, and sickle cell crisis. Undiagnosed pregnancy is always a consideration in the age-appropriate female. Psychogenic pain and fibromyalgia can be seen in children. Child abuse can present in the spine with soft tissue injuries more common than fractures. Posterior rib and spinous process fractures can be seen in up to 30% of abused children. Skeletal survey can be helpful in diagnosing abuse with multiple injuries in multiple stages of healing.

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707.5

Hip and Pelvis Injuries

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Injuries to the hip and pelvis represent a small percentage of sports injuries, but they are potentially severe and require prompt diagnosis. Hip pathology can manifest as knee pain and normal findings on knee examination.

In children, **transient synovitis** is the most common nontraumatic cause of hip pain. It usually manifests with acute onset of a limp, with the child refusing to use the affected leg and having painful range of motion on examination. There may be a history of minor trauma. This is a self-limiting condition that usually resolves in 48-72 hr.

Legg-Calvé-Perthes disease (avascular necrosis of the femoral head) also manifests in childhood with insidious onset of limp and hip pain (see Chapter 698.3).

Until skeletal maturity (Table 707.2), younger athletes are susceptible to apophyseal injuries (e.g., the anterior superior iliac spine). **Apophysitis** develops from overuse or from direct trauma. **Avulsion fractures** occur in adolescents playing sports requiring sudden, explosive bursts of speed (see Fig. 707.2). Large muscles contract and create force greater than the strength of the attachment of the muscle to the apophysis. Biomechanical susceptibility of the pelvis allows separation to occur in the cartilaginous region between the apophysis and the adjoining bone. The most common sites of **pelvic avulsion fractures** are the anterior superior iliac spine (sartorius and tensor fasciae lata), anterior inferior iliac spine (rectus femoris), lesser femoral trochanter (iliopsoas), ischial tuberosity (hamstrings), and the iliac crest (abdominal muscles). Symptoms include localized pain and swelling, with decreased strength and range of motion. Bilateral radiographs are important in order to allow for comparison to assess for displacement, if any, of the fracture fragment. Significant displacement or the presence of a large fragment may require orthopedic consultation. Initial treatment includes ice, analgesics, rest, and pain-free range of motion exercises. Crutches are usually needed for ambulation. Surgery is usually not indicated because most of these fractures—even large or displaced ones—heal well. Direct contact to the bone around the hip and pelvis causes exquisitely tender subperiosteal hematomas called “**hip pointers** . ” These injuries are more commonly seen around the anterior superior iliac spine and the iliac crest. Limited active range of motion can be identified about the hip brought on by contracture of locally attached musculature such as hip flexors and hip abductors. Symptomatic care includes rest, ice, analgesia, and protection from re-injury.

Table 707.2

Age of Appearance and Fusion of Apophyses in Hip and Pelvis

APOPHYSIS	APPEARANCE (YR)	FUSION (YR)	RELATED MUSCLE GROUP(S)
Anterior inferior iliac spine	13-15	16-18	Quadriceps
Anterior superior iliac spine	13-15	21-25	Sartorius
Lesser trochanter	11-12	16-17	Iliopsoas
Greater trochanter	2-3	16-17	Gluteal
Ischial tuberosity	13-15	20-25	Hamstrings
Iliac crest	13-15	21-25	Abdominal obliques Latissimus dorsi

From Waite BL, Krabak BJ: Examination and treatment of pediatric injuries of the hip and pelvis. *Phys Med Rehabil Clin N Am* 19:305–318, ix, 2008.

Slipped capital femoral epiphysis usually occurs in the 11-15 yr age range during the time of rapid linear bone growth (see Chapter 698.4) and often presents with complaints of pain in the groin area or, on occasion, referred pain felt at the knee.

A **femoral neck stress fracture** can manifest as vague progressive hip pain in an endurance athlete. Girls with the female athlete triad are especially at risk. This diagnosis should always be kept in mind in the running athlete with vague anterior thigh pain. On examination, there may be pain with passive stretch of the hip flexors and pain with hip rotation. If radiographs do not demonstrate a periosteal reaction consistent with a stress fracture, a bone scan or MRI may be required. Orthopedic consultation is necessary in femoral neck stress fractures because of their predisposition to nonunion and displacement with minor trauma or continued weight bearing. These fractures carry increased risk of avascular necrosis of the femoral head.

Osteitis pubis is an inflammation at the pubic symphysis that may be caused by excessive side-to-side rocking of the pelvis. It can be seen in an athlete in any running sport and is more common in sports requiring additional use of the adductor muscles such as ice hockey, soccer, and inline skating. Athletes typically present with vague groin pain that may be unilateral or bilateral. On physical examination, there is tenderness over the symphysis and sometimes over the proximal adductors. Adduction strength testing causes discomfort. Radiographic evidence (irregularity, sclerosis, widening of the pubic symphysis with osteolysis) might not be present until symptoms are present for 6-8 wk; a bone scan and MRI are more sensitive to early changes. Relative rest for 6-12 wk may be required. Some patients require corticosteroid injection as adjunctive therapy. Ultrasound needle guidance may be used to improve the accuracy of the injection while simultaneously avoiding injury to surrounding structures, such as the bladder, and vascular structures of the genitalia.

Acetabular labrum tears can occur in the hip, similar to glenoid labrum tears in the shoulder. Athletes might have a history of trauma and complain of sharp anterior hip pain associated with a clicking or catching sensation. Clinical diagnosis is difficult; magnetic resonance arthrography is useful for diagnosis.

Snapping hip syndrome is caused by the iliopsoas musculotendinous unit riding over the pectineal eminence of the pelvis, anterior hip capsule, or the iliotibial band (ITB) over the greater trochanter. Lack of flexibility in these muscles results in snapping, as the musculotendinous unit slides over the associated bony prominence. It is most commonly seen in ballet dancers and runners, and it can occur as an acute or, more commonly, an overuse injury. Athletes present with either a painful or painless click or snap in the hip, usually located lateral or anterior and deep within the joint. Examination often reproduces the symptoms. Radiographs are not usually needed in the workup. Ultrasound examination can be useful to visualize the anatomic structures in question causing the snapping sensation. Core weakness may be present, leading to excessive movement about the hip girdle contributing to increased sliding of the tight muscle over the boney prominence. Treatment involves analgesia, relative rest, biomechanical assessment, core flexibility, with stretching and strengthening of the involved soft tissue. The athlete may return to activity as tolerated. Common soft tissue injuries around the hip and pelvis include strain and tendinosis of the hip flexors (groin) and hamstrings in addition to quadriceps contusions and greater trochanteric bursitis.

The term **athletic pubalgia** is more commonly used to describe a number of different pathologies that may cause lower abdominal or groin pain. Often called a sports hernia, this is a source of confusion as no true hernia exists through the inguinal canal or abdominal wall. The pathophysiology stems from tissue injury to the structures that comprise the pubic aponeurosis, most commonly the tendinous attachment of the abdominal and hip adductor musculature. Like a true hernia, pain may radiate into the anterior thigh, inguinal region, perineum, and/or scrotum. Physical exam may exhibit tenderness over, or adjacent to, the pubic ramus, and/or reproduction of pain with resisted abdominal flexion or hip adduction. MRI, CT scan, and bone scan can be helpful in ruling out other diagnoses, but usually are negative. Some radiology departments may have specialized athletic pubalgia MRI protocols that may provide more detailed imaging of the pathologic area. Patients who continue with symptoms despite conservative care, such as physical therapy, may be surgical candidates. Surgical repair can be 95% successful if anatomical lesions are identified.

Femoroacetabular impingement (FAI) may coexist with athletic pubalgia to produce groin pain. FAI is defined as an abnormal contact between the femoral neck and the acetabulum due to excessive bone on the acetabular rim, the femoral neck, or both. X-rays and MRI can be diagnostic. As in athletic pubalgia, a period of rest and rehabilitation should be attempted, and those that fail conservative treatment should be referred to a sports medicine specialist.

As with any child or adolescent presenting with a painful hip or pelvis, undiagnosed non-sports-related conditions need to be considered. Differential diagnoses may also include the epiphyseal dysplasias, congenital or developmental hip dysplasia, additional causes of avascular necrosis including sickle cell anemia, Gaucher disease, rheumatoid arthritis, and other collagen disorders including steroid therapy. Inguinal hernia should be recognized in those patients with groin pain exacerbated with coughing/Valsalva and a palpable mass in the groin. Traumatic hip dislocations are relatively rare in children but are not to be overlooked. Leg-length discrepancies (usually over 1 cm), can be symptomatic at the hip in an otherwise able-bodied child. Common tumors in the lower extremities include osteosarcoma along with osteoblastoma, aneurismal bone cysts, and fibrous dysplasia (more common in the pelvis). Metastatic tumors to the lower extremities include neuroblastoma and lymphomas of various types, not to exclude leukemic infiltration with joint arthralgia. Child abuse always needs to be considered in a young patient with musculoskeletal pain, no matter what the socioeconomic status.

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707.6

Knee Injuries

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Knee pain is common among adolescents. Acute knee injuries that cause immediate disability and/or effusion are likely to be due to fracture, patellar dislocation, anterior or posterior cruciate ligament (ACL or PCL) injury, or meniscal tear. The mechanism of injury is usually a weight-bearing event. If the knee swells more immediately (within several hours of injury), the swelling is likely caused by a hemarthrosis and more severe injury. The injury most likely to occur with a hemarthrosis is an ACL injury. This injury (rare in children younger than 12 yr) is usually caused from being hit directly, landing off-balance from a jump, quickly changing direction while running, or hyperextension. Instability is often present but may be hard to detect in the presence of significant swelling. Females are more than twice as likely as males to disrupt their ACL, with a soccer injury a common scenario. Often, these injuries are associated with an avulsion injury of the anterior tibial spine. Most athletes with significant ACL injury need orthopedic consultation with consideration of ACL reconstruction. Chronic ACL insufficiency may increase the risk of meniscal injury and further joint dysfunction. Additional physeal-sparing reconstructions with minimal risk of growth arrest or angular deformity have been reported with success in children younger than 12 yr and adolescents.

Posterior cruciate ligament (PCL) injury occurs from a direct blow to the region of the proximal tibia, such as might occur with a dashboard injury or a fall to the knees in volleyball. PCL injuries are rare and are usually treated nonsurgically.

Medial collateral ligament injuries result from a valgus blow to the outside of the knee. Isolated **lateral collateral ligament** injuries are uncommon and result from significant varus knee stress. Because they are extra-articular, lateral collateral ligament injuries should not produce much of a knee effusion and are generally less disabling. Isolated medial and lateral collateral injuries are generally managed nonsurgically with conservative care and appropriate rehabilitation.

Meniscal tears generally occur by the same mechanisms as ACL injuries. They are often associated with less hemarthrosis, significant joint line pain, and increased pain with full knee flexion. MRI scan will often yield the diagnosis; conservative care, including **PRICE** principles, is therapeutic for smaller injuries. Orthopedic consultation is indicated for larger tears not healing with conservative care and causing significant dysfunction inhibiting quality of life or return to athletics. An isolated meniscal tear in a child younger than 10 yr of age is unusual, with surgery, again, only if conservative measures fail. The choice is often repair of the meniscus rather than surgical resection because of the increased potential in children for cartilaginous healing. Physeal injuries tend to predominate in younger patients, whereas the more skeletally mature adolescents tend to sustain medial collateral ligament injuries. Discoid meniscus (an anatomical variant covering lateral tibial plateau) always needs to be considered, particularly in children younger than 12 yr of age.

Patellar dislocation occurs most often as a noncontact injury when the quadriceps muscles forcefully contract to extend the knee while the tibia is externally rotated in relation to the femur. Patellar dislocation is the 2nd most common cause of hemarthrosis. The patella is almost always dislocated laterally, and this motion tears the medial patellar retinaculum, causing bleeding in the joint. Recurrent episodes of patellar instability are associated with less swelling. Patellar dislocations are often associated with genu valgum, external tibial torsion, and general ligamentous hyperlaxity. Exercises to strengthen the quadriceps, particularly the vastus medialis, and the use of patella-tracking braces may be helpful. Recurrent instability can require surgical intervention. Surgical stabilization of the medial patellar tissues and lateral retinacular release can be helpful in more difficult cases.

Initial Treatment of Acute Knee Injuries

The physician should inspect for an effusion and obvious deformities; if any deformity is present, the physician should assess neurovascular status and transfer the patient for emergency care as indicated. If no gross deformities are present and neurovascular integrity is intact, initial maneuvers include full passive extension and gentle valgus and varus stress to the knee while in extension. Comparison to the noninjured knee is always helpful for assessing degrees of laxity and range of motion. The patient's ability to contract the quadriceps should be noted. Pain occurring with quadriceps contraction, or the inability to contract the quadriceps muscle, implies an injury to the extensor mechanism. Tenderness over the medial patella, medial retinaculum, or above the adductor tubercle is associated with a patellar dislocation (usually lateral). Point tenderness is consistent with fracture or injury to the underlying structure. Meniscal tears usually manifest as tenderness along the joint line, accentuated with flexion of the knee often beyond 90 degrees. Pain or limitation in either flexion or extension while rotating the tibia implies a meniscal injury. Ligament injury is manifested as pain or laxity with the appropriate maneuver (Fig. 707.11).

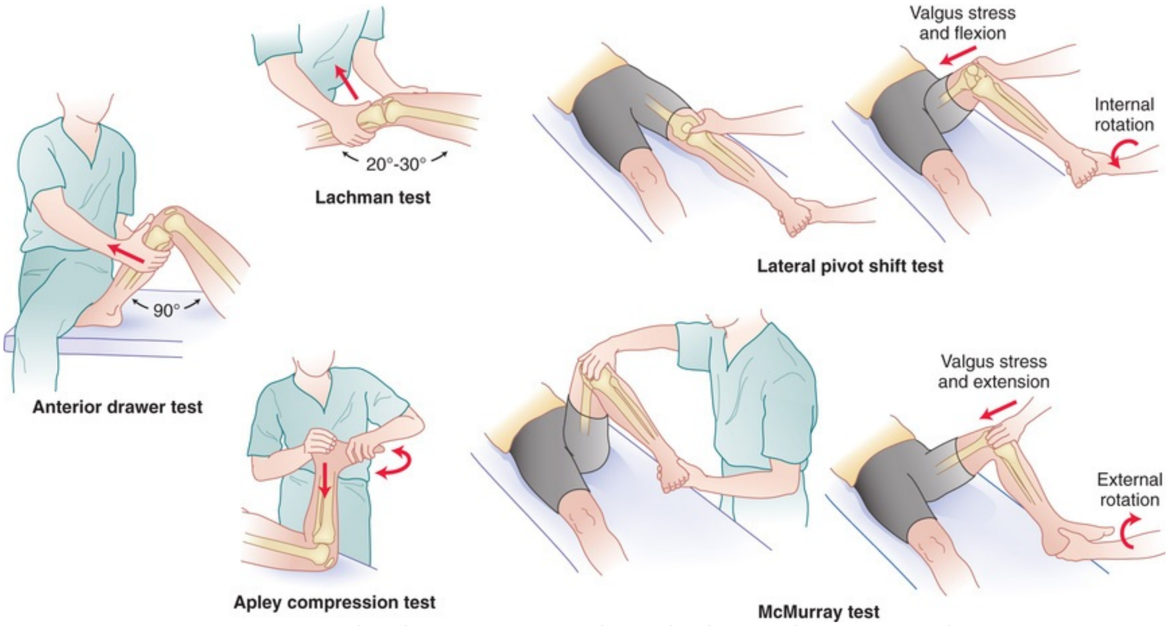
Lachman test
20°-30°
Anterior drawer test
90°
Lateral pivot shift test
Valgus stress and flexion
Internal rotation
Apley compression test
McMurray test
Valgus stress and extension
External rotation

FIG. 707.11 Examination maneuvers include the Lachman, anterior drawer, lateral pivot shift, Apley compression, and McMurray tests (the right knee is shown). The Lachman test, performed to detect anterior cruciate ligament (ACL) injuries, is conducted with the patient supine and the knee flexed 20-30 degrees. The anterior drawer test detects ACL injuries and is performed with the patient supine and the knee in 90 degrees of flexion. The lateral pivot shift test is performed with the patient supine, the hip flexed 45 degrees, and the knee in full extension. Internal rotation is applied to the tibia while the knee is flexed to 40 degrees under a valgus stress (pushing the outside of the knee medially). The Apley compression test, used to assess meniscal integrity, is performed with the patient prone and the examiner's knee over the patient's posterior thigh. The tibia is externally rotated while a downward compressive force is applied over the tibia. The McMurray test, used to assess meniscal integrity, is performed with the patient supine and the examiner standing on the side of the affected knee.

If a patient cannot weight-bear pain free, or has clinical signs of instability, significant swelling, or any other major concern, the knee should be immobilized, crutches provided, and plain radiographs obtained. If the patella is dislocated, reduction may be achieved with gentle active assistive knee extension. Straight-leg immobilizers offer no structural support and are only used for comfort and reminding the patient to be careful with any weight bearing. A derotational hinge brace may be indicated for stabilization, such as an injury when both ACL and medial collateral ligament have been traumatized. The leg should be elevated and an elastic wrap can be applied for compression (PRICE principles).

Chronic Injuries

Patellofemoral Stress Syndrome

Patellofemoral stress syndrome (PFSS), or **runner's knee** , is the most common cause of anterior knee pain. PFSS is also known as **patellofemoral pain syndrome** or **patellofemoral dysfunction** (see Chapter 697.5). It is a diagnosis of exclusion used to describe anterior knee pain that has no other identifiable pathology. Chondromalacia may be seen in association with softening of the articular cartilage underneath the patellar surface. Pain is usually difficult to localize. Patients indicate a diffuse area over the anterior knee as the source, or they might feel as if the pain is originating from underneath the patella. Bilateral pain is common, and pain is often worse going up stairs, after sitting for prolonged periods, or after squatting or running. There should be a negative history for significant swelling, which would indicate a more serious injury. History of change in activity is common, such as altered training surface or terrain, increased training regimen, or performance of new tasks.

Examination should include evaluation of stance and gait for lower limb alignment, musculature, and midfoot hyperpronation. Flexibility of the hamstrings, ITB, and gastrocnemius should be assessed, because stress is increased across the patellofemoral joint when these structures are excessively tight. Hip range of motion should be assessed to rule out hip pathology. Medial patellar tenderness or pain with compression of the patellofemoral joint confirms the diagnosis in the absence of a significant effusion and other positive findings. PFSS is a clinical diagnosis usually managed without imaging.

Treatment focuses on assessing and improving flexibility, strength, and gait abnormalities. In the presence of midfoot hyperpronation (ankle valgus), new shoes, or the use of arch supports, can improve patellofemoral mechanics and improve pain. Ice and an analgesic can be used to help control pain. Reduced overall activity or training is important initially in rehabilitation along with limiting knee flexion no greater than 60 degrees as possible. Short arc quadriceps strengthening exercises can be helpful: active knee extension with or without resistance between 0 and 30 degrees of knee flexion. Therapeutic taping techniques to help improve patella tracking within the trochlear groove can be helpful with the assistance of a sports physical therapist. The use of a patellar stabilizing brace with a lateral buttress to maintain patellar alignment may be of benefit in more chronic, cases as well.

Osgood-Schlatter Disease

Osgood-Schlatter disease is a traction apophysitis occurring at the insertion of the patellar tendon on the tibial tuberosity (see Chapter 697.4). Because it is also related to overuse of the extensor mechanism, Osgood-Schlatter disease is treated like PFSS. A protective pad to protect the tibial tubercle from direct trauma can be used. Therapeutic taping of the tibial tubercle may provide comfort, along with well-fitted knee sleeves and/or straps. NSAIDs are often prescribed as well. Pain-free strengthening of weightbearing soft tissues using closed-kinetic chain techniques may be best. PRICE principles apply. Make certain that patients and parents are aware that resolution is usually slow, often requiring 12-18 mo. Complications are rare and can include growth arrest with recurvatum deformity and rupture or avulsion of the patellar tendon/tibial tubercle.

Other Chronic Injuries

Sinding-Larsen-Johansson disease is a traction apophysitis occurring at the inferior pole of the patella. It occurs most often in volleyball and basketball athletes. Treatment is similar to PFSS and Osgood-Schlatter disease.

Patellar tendinosis, or jumper's knee , is caused by repetitive microtrauma of the patellar tendon, usually at the inferior pole of the patella. In approximately 10% of the cases, the quadriceps tendon above the patella is affected. It is associated with jumping sports but may occur in runners as well. Treatment is similar to that for PFSS, with an emphasis on eccentric strengthening in physical therapy. Relative rest is more important in patellar tendinosis because chronic pain can be associated with irreversible changes in the tendon. In these cases, recalcitrant to rest, activity modifications, and physical therapy, there may be a role of biologic injections such as platelet rich plasma to the pathologic area. Surgical techniques also have a good success rate if needed.

Iliotibial band (ITB) friction syndrome is the most common cause of chronic lateral knee pain. Generally, it is not associated with swelling or instability. It is from friction of the ITB along the lateral knee, resulting in bursitis. Tenderness is elicited along the ITB as it courses over the lateral femoral condyle, or at its insertion at Gerdy's tubercle along the lateral tibial plateau. Tightness of the ITB is also noted using the Ober test. To perform an Ober test, the athlete lies on one side, the inferior hip is flexed, and the superior hip is extended with the knee flexed. The examiner holds the superior foot in midair, and if the superior knee drops inferiorly toward the exam table, it implies a flexible ITB and a negative Ober test. If the knee and leg stay in midair, the Ober test is positive, suggesting a tight ITB. Treatment principles follow those for PFSS, except the emphasis is on improving flexibility of the ITB.

Other soft tissue injuries not to be excluded include prepatellar and pes anserine **bursitis** , plical syndromes, and Hoffa syndrome. The pes anserine bursa lies just under the conjoined tendon of the sartorius, gracilis, and semitendinosus muscles as it attaches medially to the proximal tibia. In **Hoffa syndrome** , the fat pad beneath the patella and posterior to the patella ligament becomes pinched with anterior pain on knee extension. These conditions are generally more common in adolescents, those with genu recurvatum, and long-distance runners. Undiagnosed non-sports-related conditions, again, always need to be considered in the context of any child with a painful knee, particularly those younger than age 12 yr. These include conditions such as osteochondritis dissecans (see Chapter 697.3), which is most common on the lateral aspect of the medial femoral condyle. Inflammatory and infectious arthritis, **Baker's cyst** (see Chapter 697.2), and hip pain referred to the knee are additional considerations. Tumors more common to the knee joint include osteogenic sarcoma (distal femoral and proximal tibial), histiocytosis X in the diaphysis, and eosinophilic granuloma in the epiphysis of long bones. Metastatic tumors to the lower extremities include neuroblastoma and lymphomas of various types. As with any musculoskeletal injury in a child not responding to conservative care, more in-depth diagnostic pursuit for alternative pathology is mandatory; child abuse not excluded.

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707.7

Lower Leg Exertional Pain: Shin Splints, Stress Fractures, and Chronic Compartment Syndrome

Aaron M. Karlin, Nicholas P. Goyeneche, Kevin P. Murphy

Stress injury to the bones of the lower leg occurs on a continuum from mild injury (shin splints) to stress fracture. All occur by an overuse mechanism.

Medial tibial stress syndrome , **or shin splints,** manifests with pain along the medial tibia and is the most common overuse injury of the lower leg. The pain initially appears toward the end of exercise, and if exercise continues without rehabilitation, the pain worsens and occurs earlier in the exercise period.

There is diffuse tenderness over the lower third to half of the distal medial tibia. Any focal tenderness or tenderness of the proximal tibia is suspicious for a stress fracture. A stress fracture tends to be painful during the entire workout. Shin splints can often be distinguished from a **tibial stress fracture** in which the tenderness is more focal (2-5 cm) and more severe. Shin splints and stress fracture represent a continuum of stress injury to the tibia and are thought to be related to traction of the soleus on the tibia. Eccentric contraction of the medial aspect of the soleus is required to control pronation from initial contact to mid-stance with running. This contraction increases the stress of the fascial origin of the soleus, possibly through Sharpey's fibers, causing disruption to the tibial periosteum and fibrocartilaginous attachments.

The diagnosis can be made by history and physical examination. Findings on plain radiographs of the tibia are typically unremarkable with shin splints—as well as with tibial stress fractures within the first 2 wk of injury. Beyond this time frame, the radiographs may demonstrate periosteal reaction if a stress fracture is present. Sensitivity of plain radiographs can be increased by obtaining 4 views of the tibia; AP, lateral, and both oblique views. A bone scan is the most sensitive test to diagnose stress fractures. It demonstrates discrete tracer uptake at the site(s) of the stress fracture. Increased uptake may be noted in the presence of shin splints, but in a fusiform pattern along the periosteal surface suggestive of stress reaction but not fracture. If results of the bone scan are normal, the diagnosis is likely to be shin splints or chronic compartment syndrome. MRI has replaced bone scan as the most sensitive tool for diagnosing stress fractures in long bones in many medical centers.

The treatment of shin splints and tibial stress fractures is similar, involving relative rest, correcting training errors, and addressing quartile muscle imbalances and abnormal mechanical alignment. Orthotics and/or new shoes may be useful in patients who hyperpronate. Fitness can be maintained with non-weight-bearing activities, such as swimming, cycling, and water jogging. With shin splints, after 7-10 days, patients can usually start on the walk–jog program. If pain worsens, 2-3 pain-free days are required before resuming the walk–jog program. Ice should be used daily and an analgesic should be used for pain control. Stretching the plantar flexors, hamstrings, and strengthening the ankle dorsiflexors may be useful. Therapeutic taping and wrapping techniques to support the soft tissue attachments have been useful in some when directed by a skilled sports therapist. Being pain free for 7-10 days is recommended before exercises are commenced. Individuals with pain at rest and who are not responsive to treatment require continued suspicion for stress fracture.

Chronic compartment syndrome occurs in an athlete in a running sport, usually during a period of heavy training. It is caused by muscle hypertrophy and increased intracompartmental pressure with exercise. There is typically a pain-free period of about 10 min at the beginning of a workout before onset of constant throbbing pain that is difficult to localize. It lasts for minutes to hours after exercise and is relieved by ice and elevation. Classically, there is numbness of the foot associated with high pressure within the corresponding muscle compartment. The most common compartment affected is the anterolateral compartment with compression of the fibular nerve followed by the deep posterior compartment. The physical examination in the office is often normal, but weakness of the extensor hallucis longus (anterolateral compartment) and decreased sensation between the 1st and 2nd toe may be present. X-rays, bone scan, and MRI are typically negative and are used more to rule out other conditions. Compartment pressure measurements are the test of choice. Treatment involves reduction of activity, antiinflammatory medication, orthotics (hyperpronation), heel cord stretching, light strengthening of distal musculature, optimal footwear, and cross-training (swimming, cycling, and water jogging). Cryotherapy and superficial heat can also be of help. Persistent systems, despite conservative care, may require fasciotomy (successful in up to 90% of cases).

Popliteal artery entrapment syndrome occurs when the popliteal artery is compressed by the medial head of the gastrocnemius muscle and the fascial band of the soleus with activity; the entrapment may be anatomic or functional (from hypertrophy). Patients may have claudication and paresthesia (involvement of the tibial nerve), and calf swelling (primary venous obstruction). Most patients have exertional leg pain with no symptoms at rest; pain may be unilateral or bilateral depending on the type of entrapment syndrome. The tibial or dorsalis pedis pulse may be reduced or absent with passive ankle dorsiflexion with the knee extended. Doppler exam in the neutral and flexion position confirms the diagnosis in most; MRA or CT angiography may be needed if the Doppler exam is inconclusive. Surgical correction is the treatment of choice and involves medical gastrocnemius fasciotomy, take down of the soleus tibial attachments, and resection of the fibula soleus band. If the artery is injured, it requires bypass surgery.

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707.8

Ankle Injuries

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Ankle injuries are the most common acute athletic injury. Approximately 85% of ankle injuries are ankle sprains, and 85% of these are inversion injuries (foot planted with the lateral fibula moving toward the ground), 5% are eversion injuries (foot planted with the medial malleolus moving toward the ground), and 10% are combined.

Examination and Injury Grading Scale

In obvious cases of fracture or dislocation, evaluating neurovascular status with as little movement as possible is the initial priority. If no deformity is obvious, the next step is inspection for edema, ecchymosis, and anatomic variants. Key sites to palpate for tenderness are the entire length of the fibula; the medial and lateral malleoli; the base of the 5th metatarsal; the anterior, medial and lateral joint lines; the navicular; and the Achilles tendon complex. Assessment of active range of motion (patient alone) in dorsiflexion, plantar flexion, inversion, and eversion along with gentle resisted range of motion can be helpful.

Provocative testing attempts to evaluate the integrity of the ligaments. In a patient with a markedly swollen, painful ankle, provocative testing is difficult because of muscle spasm and involuntary guarding. It is more useful on the field before much bleeding and edema have occurred. The anterior drawer test assesses for anterior translation of the talus and competence of the anterior talofibular ligament. The inversion stress test examines the competence of the anterior talofibular and calcaneofibular ligaments (Fig. 707.12). In the acute setting, the integrity of the tibiofibular ligaments and syndesmosis is examined by the syndesmosis squeeze test. Pain at the ankle joint with squeezing the superior aspect of the lower leg implies injury to the interosseous membrane and syndesmosis between the tibia and fibula—suspicious for a high ankle sprain or more severe injury. Athletes with this injury cannot bear any weight and have severe pain with external rotation of the foot. Occasionally, the peroneal tendon dislocates from the fibular groove simultaneously with an ankle sprain. To assess for peroneal tendon instability, the examiner applies pressure from behind the peroneal tendon with resisted eversion and plantar flexion, and the tendon pops anteriorly. If either a significant syndesmotic injury or an acute peroneal dislocation is suspected, orthopedic consultation should be sought.

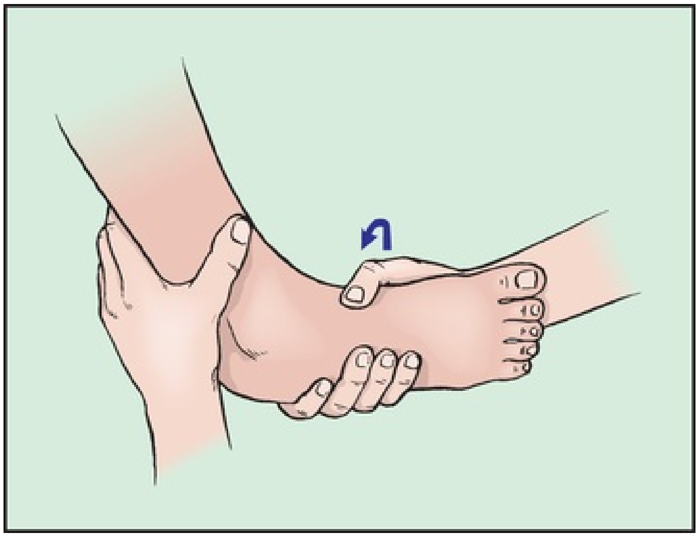

FIG. 707.12 **Inversion stress tilt test for ankle instability. (From Hergenroeder AC: Diagnosis and treatment of ankle sprains. A review. *Am J Dis Child* 144:809–814, 1990.)**

Radiographs

AP, lateral, and mortise views of the ankle are obtained when patients have pain in the area of the malleoli, are unable to bear weight, or have focal bone tenderness over the distal tibia or fibula. The **Ottawa ankle rules** help define who requires radiographs (Fig. 707.13). A foot series (AP, lateral, and oblique views) should be obtained when patients have pain in the area of the midfoot or bone tenderness over the navicular or fifth metatarsal. It is important to differentiate an **avulsion fracture of the 5th metatarsal base (dancer's fracture)** from the more distal **Jones fracture of the proximal 5th metatarsal** (located about 2 cm distal to the proximal end). The former is treated more like an ankle sprain; the latter fracture has an increased risk of nonunion and requires orthopedic consultation. Injury to the deltoid ligament of the medial ankle is rare but should raise the question of proximal fibular fracture. In this circumstance more proximal tibial imaging may be necessary. A **talar dome fracture** is manifested as an ankle sprain that does not improve. Radiographs on initial presentation can have subtle abnormalities. Any suspicion on the initial radiographs of a talar dome fracture warrants orthopedic consultation and further imaging. In the early adolescent, always look carefully at the tibial epiphysis. Nondisplaced Salter III fractures can be subtle and need to be recognized early and referred to an orthopedic surgeon promptly. Diagnostic ultrasound, when available at the point of care, can efficiently provide prognostic information by direct visualization of injured ligaments. Additionally, dynamic stress can be applied during ligament visualization to assess for gaping of the joint, which is indicative of more complete tearing with an increased duration of expected recovery.

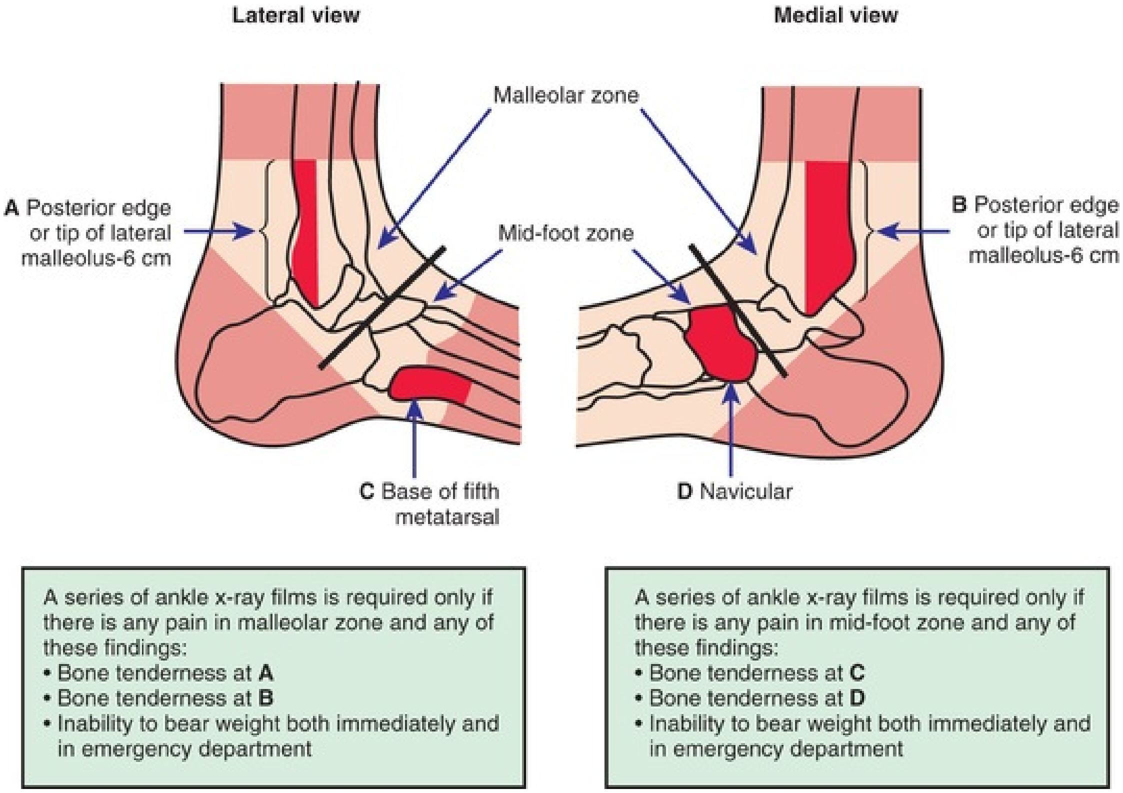
Lateral view
Medial view
Malleolar zone
A Posterior edge or tip of lateral malleolus-6 cm
Mid-foot zone
B Posterior edge or tip of lateral malleolus-6 cm
C Base of fifth metatarsal
D Navicular

A series of ankle x-ray films is required only if there is any pain in malleolar zone and any of these findings:

- Bone tenderness at **A**
- Bone tenderness at **B**
- Inability to bear weight both immediately and in emergency department

A series of ankle x-ray films is required only if there is any pain in mid-foot zone and any of these findings:

- Bone tenderness at **C**
- Bone tenderness at **D**
- Inability to bear weight both immediately and in emergency department

FIG. 707.13 Ottawa ankle rules. (From Bachmann LM, Kolb E, Koller MT, et al: Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot; systematic review. *BMJ* 326:417–419, 2003.)

Initial Treatment of Ankle Sprains

Ankle sprains need to be treated with **PRICE** . This should be followed for the first 48-72 hr after the injury to minimize bleeding and edema. For an ankle injury, this might consist of crutches and an elastic wrap, although other compression devices, such as an air stirrup splint, work quite well. This allows early weight bearing with protection and can be removed for rehabilitation. It is important to start a rehabilitation program as soon as possible.

Rehabilitation

Rehabilitation should begin the day of injury; for patients who have pain with movement, isometric strengthening can be started. Early phase intervention includes restoration of functional range of motion, strengthening with emphasis on peroneal musculature and early sensory proprioceptive training. Later intervention includes higher-level balance activities, advanced proprioception exercises, and endurance training. When determining when an athlete is ready for running, there must be full range of motion and nearly full strength compared to the uninjured side. While standing on the uninjured side only, the athlete is instructed to hop 8-10 times, if possible. When this can be achieved without pain on the injured side, the athlete can begin to run, starting out with jogging and gradually progressing in speed, and finally to sprints. The athlete must stop if there is significant pain or limp. Finally, before returning to sport, the athlete must be able to sprint and change directions off the injured ankle comfortably. Performing some sport-related tasks is also helpful in determining readiness for return to play.

Recurrent ankle injuries are more likely in patients who have not undergone complete rehabilitation. Ankle sprains are less likely in players wearing high-top shoes. Proper taping of the ankle with adhesive tape can provide functional support but loosens with use and is often unavailable. Lace-up ankle supports are felt by many to be more useful for preventing recurrences. They are more supportive than tape and can be tightened repeatedly during the course of a practice or a game. Many sports physicians recommend their use indefinitely to help prevent further sprains. Surgery is a consideration for chronic mechanical instability with lateral complex ligamentous laxity in the failure of more conservative care. Salter-Harris grade I distal fibular fractures need careful consideration, particularly in the child younger than 12 yr old. The physeal plates are generally the weakest link in the musculoskeletal chain and tend to slide or pull apart before the surrounding soft tissue and/or ligaments tear in this younger population. **Toddler's fracture** also needs to be considered especially in those younger than age 8 yr. The proposed mechanism involves sheer stress with lack of displacement because of the periosteum that is relatively strong compared to the elastic bone in younger children. Additional radiographs may be inconspicuous (a faint spiral oblique line) or even normal. After 1 or 2 wk callous develops. The condition can be mistaken for osteomyelitis, transient synovitis, and/or even child abuse. Toddler's fracture usually occurs in the lower third of the tibia, whereas nonaccidental injury typically affects the upper two-thirds or midshaft of the tibia. Other, less common conditions that cannot be excluded include os fibulare, a congenital unfused secondary ossification center of the distal fibula. This can be seen in younger patients with recurrent ankle sprains, particularly as their body weight and activity increase during the early academic years. Undiagnosed tarsal coalitions can be seen also in the presence of ankle sprains in younger children the most common being talocalcaneal and calcaneal navicular. Muscular strains and/or tendinoses are more prevalent in the older child and adolescent, and include peroneal, posterior tibialis, and gastrocnemius/Achilles types. Tarsal tunnel syndrome is also more prevalent in the adolescent/younger adult and is commonly associated with medial ankle pain and burning or tingling into the sole of the foot.

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707.9

Foot Injuries

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Metatarsal stress fractures can occur in any running athlete. The history is often one of insidious pain with activity that is getting worse. Examination reveals point tenderness over the mid-shaft of the metatarsal, most commonly the 2nd or 3rd metatarsal. Radiographs might not show the periosteal reaction before pain has been present for 2 wk or more. Treatment is relative rest for 6-8 wk. Shoes with good arch supports reduce stress to the metatarsals.

Vague dorsal foot pain in an athlete in a running sport can represent a **navicular stress fracture.** Unlike other stress fractures, it might not localize well on examination. If there is any tenderness around the navicular, a stress fracture should be suspected. This stress fracture can take many weeks to show up on plain radiographs, so a bone scan or MRI should be obtained to make the diagnosis. Because this fracture is at high risk of nonunion, immobilization, and nonweight bearing for 8 wk is the usual **treatment.** A CT scan should be obtained to document full healing after the period of immobilization.

Sever's disease (calcaneal apophysitis) occurs at the insertion of the Achilles tendon on the calcaneus and manifests as activity-related pain (see Fig. 707.3). It is more common in boys, is often bilateral, and usually occurs between ages 8 and 13 yr. Tenderness is elicited at the insertion of the Achilles tendon into the calcaneus, especially with squeezing the heel (positive squeeze test). Sever disease is associated with tight Achilles tendons and mid-foot hyperpronation that puts more stress on the plantar flexors of the foot. Treatment includes relative rest, ice, massage, stretching, and strengthening the Achilles tendon. Correcting the mid-foot hyperpronation with orthotics, arch supports, or stabilizing shoe wear is important in most athletes with Sever's disease. If the foot is neutral or there is mild hyperpronation, cushioned heel lifts can be helpful to unload the Achilles tendon and its insertion. With optimal management, symptoms frequently improve in 4-8 wk. Generally, if there is no limp during the athletic activity, young athletes with Sever disease should be allowed to play.

Plantar fasciitis is an overuse injury resulting in degeneration of the plantar aponeurosis. Rare in prepubertal children, this diagnosis is more likely seen in the adolescent or young adult. Athletes report heel pain with activity that is worse with the first steps of the day or after several hours of nonweight bearing. Tenderness is elicited on the medial calcaneal tuberosity. Relative rest from weight-bearing activity is helpful. Athletes get plantar fasciitis when shoes are worn with inadequate arch supports. New shoes or use of semi-rigid arch supports often lessen the pain. Stretching the calves and plantar fascia helps, assisted at times with therapeutic ultrasound treatment. Some patients benefit from night splints even though they can make sleep difficult. As long as there is no limping with athletic activity, the athlete may continue participation. Complete recovery is usually seen at 6 mo. Corticosteroid injection, extracorporeal shock-wave therapy, or injections of platelet-rich plasma can be considered in those cases recalcitrant to conservative treatments.

Calcaneal stress fracture is seen in the older adolescent or young adult involved in a running sport. There is heel pain with any weight-bearing activity. The physical examination reveals pain with squeezing the calcaneus. Sclerosis can show up on the AP and lateral radiographs after 2-3 wk of pain. A bone scan or MRI needs to be performed to clinch the diagnosis in some cases. The calcaneus is an uncommon location for a stress fracture; it is associated with osteopenia (amenorrheic girls). Treatment is rest from running and other weight-bearing activity for at least 8 wk. Immobilization is rarely necessary.

Pes planus, or “flat feet,” may be termed “flexible” or “rigid.” **Flexible pes planus** is usually asymptomatic, at least in the early years and is the most common type found in children. Scaphoid pads or medial inserts may be helpful to create plantigrade weight-bearing posture. Untreated sports progression may occur with compensatory hallux valgus, planovalgus, and secondary bunion and toe deformities. With progression, pain may develop along with shortening in the peroneal musculature. **Rigid pes planus** is a congenital deformity associated with other anomalies in 50% of cases. It is caused by failure of the tarsal bones to separate leaving a bony cartilaginous or fibrous bridge or coalition between two or more tarsal bones. Talocalcaneal coalitions are more symptomatic between 8 and 12 yr of age, whereas calcaneal navicular coalitions are more symptomatic between 12 and 16 yr of age. Symptoms are insidious with occasional acute arch, ankle, and mid-foot pain, which is at times brought on with sports-related activities. The hindfoot often does not align in its normal varus position on tiptoe maneuvers. Patients are predisposed to ankle sprains secondary to limited subtalar motion, and stress to the subtalar and transverse tarsal joints frequently causes pain. CT scans are diagnostic and initial treatment is conservative with short leg casting and/or molded orthoses and rest. In the case of failure of conservative care, surgical intervention is usually necessary. **Rigid cavus feet** can also be associated with metatarsalgia, clawing, and intrinsic muscle atrophy, which are all possible in the young athlete. With a cavus foot, undiagnosed neurologic conditions, such a Charcot-Marie-Tooth disease, spinal dysraphism, Friedrich ataxia, or spinal tumor, need to be considered. Custom-molded orthotics may be helpful, and family history can be critical. A Coleman block test can help determine hindfoot flexibility and suggest a more rigid versus flexible pes planus. Plantar fascial release is standard for all cavus foot surgical procedures. Accessory navicular bones and sesamoiditis need to be considered in all symptomatic feet, especially those with rigid components. These conditions are more common in the adolescent or younger adult and can be exacerbated with sporting activities.

Other conditions causing foot pain include **Lisfranc sprain** and/or dislocation, which is more common in football linemen or other athletes requiring heavy loading on the mid- and forefoot joints, and gymnasts using the balance beam. The Lisfranc joint is the tarsal metatarsal articulation of the 3 cuneiform bones and the cuboid with the 5 proximal metatarsals. Turf toe can be seen, particularly in the older child and/or adolescent running on artificial or synthetic surfaces. It results from hyperextension through the 1st metatarsal phalangeal joint, spraining the ligaments surrounding the joint often in a football and/or soccer activity.

Iselin apophysitis is an apophysitis that occurs at the tuberosity of the 5th metatarsal. The apophysis at this site appears between the ages of 9 and 14 yr and is located within the insertion of the peroneus brevis tendon. This condition can be a predisposing factor to dancer's fracture (see Chapter 707.8). **Freiberg disease** —which involves the collapse of the articular service and subchondral bone, usually of the 2nd metatarsal—and **Kohler disease** —which involves irregular ossification of the tarsal navicular joint with localized pain and increased density—should always considered in the evaluation **osteochondroses of the foot** (see Chapter 694.8). Freiberg disease is more common in girls between the ages of 12 and 15 yr, whereas Kohler disease occurs in younger individuals, age 2-9 yr, and is frequently reversible with conservative care, including orthoses and casting.

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CHAPTER 708

Sports-Related Traumatic Brain Injury (Concussion)

Christopher W. Liebig, Joseph A. Congeni

Concussion is defined as a traumatic brain injury (TBI) induced by biomechanical forces leading to a transient disturbance of brain function. Concussion may be caused either by a direct blow to the head, face, neck, or elsewhere on the body with an “impulsive” force transmitted to the head, whether these are linear or rotational forces. Although it is disputed where concussion falls on the TBI spectrum, it is important to communicate that it is a **traumatic brain injury** , because the word “concussion” unintentionally and incorrectly has been found to communicate to some families that a brain injury has not occurred, resulting in less-than-adequate follow-up.

Epidemiology

At least 1.6-3.8 million concussions occur in the United States each year, with 1.1-1.9 million occurring in children ≤18 yr old during sports and recreational activities. This number is likely to represent only a fraction of the true incidence because there is underreporting of symptoms by directly withholding information to continue participation or poor understanding of symptoms. From 2007 to 2014 there was a 60% increase in concussion incidence, with a 143% increase in 10-14 yr olds and an 87% increase in 15-19 yr olds. Activities include but are not limited to football, soccer, wrestling, bicycling, hockey, lacrosse, field hockey, basketball, and playground injuries.

Pathophysiology

The pathophysiologic process following a concussion is best described as an *energy crisis* following a neurometabolic cascade. In animal models, these ionic and metabolic events, along with microscopic axonal injury, result in a desperation use of glucose to begin the healing process. The increased energy demand is met with a decreased cerebral blood flow, resulting in less available energy for other brain processes and a true mismatch of energy supply and demand.

Assessment of the Injured Player

A “gold-standard” assessment of suspected concussion has been difficult to ascertain. Particularly difficult is the sideline evaluation, where simply recognizing the injury can be most challenging for medical personnel. Initial sideline evaluation should include cervical spine stabilization, four-limb neurologic testing, and evaluation of ABCs (airway, breathing, circulation). Discussion of the athlete's symptoms with an accepted sideline assessment tool should also be completed.

The most well-established assessment tools are the Sport Concussion Assessment Tool (**SCAT5**) and the **Child-SCAT5** for children ages 5-12, available at: http://bjsm.bmj.com/content/51/11/851 and http://bjsm.bmj.com/content/51/11/862 .

These tests include the Glasgow Coma Scale, observable signs such as stumbling or slowed movements, symptom checklist, memory assessment (“Who scored last?” “What team did you play last week?”), general memory/orientation (date, day of week, time of day), immediate memory (list 5-10 words and have patient repeat), concentration (give 3-6 digits and have patient repeat backwards or months in reverse order), balance testing (double, single, tandem leg stances), coordination, neurologic screen, and delayed recall (repeat list of words).

Additional domains that may be useful include reaction time and oculomotor screening because sensory coordination and vestibular systems can also be affected by concussion. When available, preinjury baseline performance can be compared with the individual's postinjury test. Given the variability in concussion presentation and because it is often an evolving injury with delayed symptoms, medical personnel are encouraged to err on the side of safety by adapting the phrase *when in doubt, sit them out* . If concussion is suspected, an athlete must be removed from participation and forbidden to return on the day of injury.

The signs and symptoms of concussion traditionally fall into four categories: physical, cognitive, emotional, and sleep (Table 708.1). Headache is the most common symptom reported, and a higher number of symptoms and severity are predictive for slower recovery. Transient loss of consciousness occurs in less than 5% of concussions and does not typically correlate with severity of injury. Assessment can be challenging as several or only one of the symptoms listed are identified. Furthermore, patients with preexisting mental health disorders such as depression or attention-deficit/hyperactivity disorder may experience exacerbations in their symptoms.

Table 708.1

Postconcussion Symptom Scale

	NONE	MILD		MODERATE		SEVERE	
Headache	0	1	2	3	4	5	6
“Pressure in head”	0	1	2	3	4	5	6
Neck pain	0	1	2	3	4	5	6
Nausea or vomiting	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6
Blurred vision	0	1	2	3	4	5	6
Balance problems	0	1	2	3	4	5	6
Sensitivity to light	0	1	2	3	4	5	6
Sensitivity to noise	0	1	2	3	4	5	6
Feeling slowed down	0	1	2	3	4	5	6
Feeling like “in a fog”	0	1	2	3	4	5	6
“Don't feel right”	0	1	2	3	4	5	6
Difficulty concentrating	0	1	2	3	4	5	6
Difficulty remembering	0	1	2	3	4	5	6
Fatigue or low energy	0	1	2	3	4	5	6
Confusion	0	1	2	3	4	5	6
Drowsiness	0	1	2	3	4	5	6
More emotional	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Sadness	0	1	2	3	4	5	6
Nervous or anxious	0	1	2	3	4	5	6
Trouble falling asleep (if applicable)	0	1	2	3	4	5	6

From Echemendia RJ, Meeuwisse W, McCrory P, et al: Sport concussion assessment tool—5th edition. *Br J Sports Med* 51:851–858, 2017. doi:10.1136/bjsports-2017-097506SCAT5.

Cognitive functioning is an important component in the overall assessment. Evaluation with neuropsychological testing provides another objective measurement of brain functioning. Computerized neurocognitive tests can be useful to those familiar with the test and when athletes were able to perform baseline testing but are not intended to be sole determining factor for return-to-play decisions.

Concussion lacks structural changes with conventional imaging studies (MRI and CT), limiting their usefulness in evaluation. Neuroimaging should be used if suspicion of intracerebral lesion exists. Advances in functional neuroimaging have shown positive findings in concussion but require further research before clinical use and recommendation. Imaging may be indicated for possible neck injury (see Chapter 709). CT imaging may be indicated for prolonged loss of consciousness, persistent altered mental status, focal neurologic deficits, suspicion of a skull fracture, or signs of clinical deterioration.

Management and Treatment

Initial Phase

Management of a concussion continues to evolve and is primarily based on symptom control while protecting the athlete from activities that may slow recovery. Management should consist of a reduction, not an elimination, in physical and cognitive activity. Light activity is encouraged, while taking caution to stay below their cognitive and physical symptom-exacerbation threshold. Rest for more than a few days may not hasten recovery and may lead to prolonged symptoms. Symptoms may be followed with a postconcussion symptom scale (see Table 708.1), with attention paid to the possible differentiation of clinical symptoms into separate clusters such as somatic/headache, cognitive, affective, cervical, vestibular, and/or oculomotor which may assist in developing targeted rehabilitation. Concussed patients will often complain of increased symptoms with cognitive activities such as reading, video games, music, and texting. They often have difficulty attending school, focusing on schoolwork, and trying to keep up with assignments. Initially, cognitive rest may include shortened school days, reduced workload, or even temporary leave of absence with gradual return to school (Table 708.2). Medication may be considered in those with prolonged recovery and specific symptoms; however, there is no evidence-based pharmacologic treatment for a concussed athlete. Vestibular therapy consisting of balance and oculomotor exercises has shown results in combating dizziness and vertigo; an active rehabilitation program may facilitate recovery.

Table 708.2

Graduated Return to School Strategy

STAGE	AIM	ACTIVITY	GOAL OF EACH STEP
1	Daily activities at home that do not give the child symptoms	Typical activities of the child during the day as long as they do not increase symptoms (e.g., reading, texting, screen time). Start with 5-15 min at a time and gradually build up	Gradual return to typical activities
2	School activities	Homework, reading or other cognitive activities outside of the classroom	Increase tolerance to cognitive work
3	Return to school part-time	Gradual introduction of schoolwork. May need to start with a partial school day or with increased breaks during the day	Increase academic activities
4	Return to school full time	Gradually progress school activities until a full day can be tolerated	Return to full academic activities and catch up on missed work

From McCrory P, Meeuwise WH, Dvorak J, et al: Consensus statement on concussion in sport—the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med* 51:838–847, 2017.

Returning to Sport

No athlete should return to sport until they have returned to preinjury symptom levels and full workload at school without medication use. Each athlete's return should be individually based as recovery occurs at different rates with the majority of youth fully recovered by 4 wk. A **return to play protocol** provides a structured guideline that athletes progress through gradually, provided that the athlete remains asymptomatic for 24 hr at each step (Table 708.3). If no symptoms return, the athlete will take 5 days to complete and return to play. If symptoms have occurred, the athlete is required to rest until asymptomatic for 24 hr and resume at the previous asymptomatic step. It is important to consider individual factors at this juncture that are suspected to prolong recovery or increase patient susceptibility. Evidence exists that the teenage years might be the most vulnerable time for persistent symptoms with females at greater risk for increased severity and longer duration of recovery.

Table 708.3

Graduated Return to Play Protocol

STAGE	AIM	ACTIVITY	GOAL OF EACH STEP

1	Symptom-limited activity	Daily activities that do not provoke symptoms	Gradual reintroduction of work/school activities
2	Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training	Increase heart rate
3	Sport-specific exercise	Running or skating drills. No head impact activities	Add movement
4	Noncontact training drills	Harder training drills (e.g., passing drills). May start progressive resistance training	Exercise, coordination and increased thinking
5	Full contact practice	Following medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6	Return to sport	Normal game play	

NOTE: An initial period of 24-48 hr of both relative physical rest and cognitive rest is recommended before beginning the return to sport progression.

There should be at least 24 hr (or longer) for each step of the progression. If any symptoms worsen during exercise, the athlete should go back to the previous step. Resistance training should be added only in the later stages (stage 3 or 4 at the earliest). If symptoms are persistent (e.g., more than 10-14 days in adults or more than 1 mo in children), the athlete should be referred to a healthcare professional who is an expert in the management of concussion.

From McCrory P, Meeuwise WH, Dvorak J, et al: Consensus statement on concussion in sport–the 5th international conference on concussion in sport held in Berlin, October 2016. *Br J Sports Med* 51:838–847, 2017.

After sustaining a concussion, a child is 2-6-fold more likely to sustain another concussion. This risk is heightened while recovering from an initial injury with a rare, yet catastrophic injury known as second impact syndrome. In this injury, seen more frequently in child athletes, a mild impact may result in brain swelling and death. Previous and repeat concussions may be associated with slower recovery with more cognitive, emotional, and physical symptoms that may require a multidisciplinary and collaborative approach.

Those with multiple concussions may experience a cumulative effect resulting in difficulty in attention and concentration, but long-term effects continue to be heavily researched. **Persistent postconcussive symptoms** are another complication that is most simply noted as symptoms of concussion that persist beyond an expected time frame, most recently suggested as >4 wk in children. Causes and correlations have yet to be determined, but treatments should target specific medical, physical, and psychosocial factors, including possible development of mood disorders. Treatment may include symptom-limited aerobic exercise in those with autonomic instability or deconditioning, physical therapy for cervical spine or vestibular dysfunction, and/or behavioral therapy for mood or other mental health issues. A pre-injury history of mood disorders or migraines is associated with an increased risk of having symptoms >1 mo.

Prevention

Despite ongoing research and technologic advances, personal protective equipment and supplements have not decreased the severity or reduced the incidence of concussion in team sports. Concussion-related legislations have been passed in attempt to improve awareness, recognition, and quality of care with limited success. Therefore educating athletes, coaches, officials, and parents remains paramount.

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CHAPTER 709

Cervical Spine Injuries

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Sports participation has surpassed motor vehicle crashes as the number one cause of cervical spine injuries (primarily involving soft tissue) in youth older than 9 yr of age. American football, hockey, and wrestling have the highest incidence in the United States; internationally, rugby is nearly as high. Catastrophic cervical spine injuries are rare but happen mostly in the scrum or tackling in rugby and tackling in American football.

The normal cervical spine has a lordotic curve, allowing it to absorb shock and dissipate force. When the neck is flexed forward, the spine straightens, losing this shock-absorbing property. Axial loading is when a force is applied to the top of the head in this flexed position, transmitting force through the spine.

Soft Tissue Injury

The most frequent injury resulting from trauma to the head and neck involves the muscles, tendons, and ligamentous structures. Even though strains, sprains, and contusions are common and are managed with cervical, scapulothoracic, and shoulder-strengthening exercises, thorough evaluation is required to rule out more serious injuries. Even without bony abnormalities, the cervical spine may become unstable secondary to soft tissue injury.

Spinal laxity results when most restraining ligaments are injured. When compared with adjacent vertebra, laxity should horizontally be less than 3.5 mm, and angular displacement less than 11 degrees on plain flexion/extension films. However, younger athletes have more baseline laxity making the criteria less applicable and muscle spasm can acutely mask instability. If subluxation is remotely suspected, a hard cervical collar should be placed, and flexion/extension views obtained again at 2-4 wk when inflammation and spasm have subsided. A loss of lordosis on lateral x-ray is associated with significant weakness of cervical muscles, particularly the cervical extensors. Disc injuries are rare in pediatric patients. Rupture or herniation must be considered in any cervical pain differential (see Chapter 83).

Spear Tackler's Spine

This clinical entity is characterized by progressive spinal changes secondary to incorrect tackling form. Findings on plain x-ray consist of: (1) narrowing of cervical spinal canal, (2) loss or reversal of normal cervical lordosis, and (3) preexisting minor posttraumatic x-ray evidence of bony or ligamentous injury. Although rule changes in collision and contact sports have limited the practice of making contact with a “head-down” neck position, this condition still persists.

Many experts argue that this condition disqualifies athletes from return to play. Others argue that if physical therapy and rehabilitation are able to correct the curvature and improper technique is corrected, then athletes are not at a high risk of reinjury and could return. Data are lacking and more research required for a definitive answer.

Cervical Fractures

All significant neck injuries should be treated seriously until cleared with appropriate examination and imaging. Although many cervical fractures are stable, improper management or inadequate evaluation could end with catastrophic results. *Until formally evaluated, the patient should be immobilized and treated as if the patient has an unstable cervical fracture* (see Chapter 83).

Stingers (Burners)

Stingers are unilateral *(never bilateral)* peripheral nerve injuries occurring somewhere between the cervical nerve root and the brachial plexus. Three proposed mechanisms are traction or tensile stretch injury, compressive injury, and direct trauma. Typical presentation is a transient episode of unilateral pain, with or without paresthesia, in an upper extremity. Symptoms of C5 and C6 roots and upper trunk are most common. One should examine for weakness, especially shoulder abduction, external rotation, and elbow flexion. Cervical spine should have pain-free full range of motion and have no tenderness to palpation. The Spurling Compression test helps to assess for cervical radiculopathy as a cause of upper extremity pain. The patient is seated with his or her neck tilted to the affected side. In a positive test, the pain is reproduced with gentle axial compression. The test has high specificity (~93%) but relatively low sensitivity (~30%), meaning that positive tests indicate likely cervical radiculopathy but many patients with cervical radiculopathy will not have a positive test.

Return to play may be considered the same day if the exam is reassuring. This requires complete resolution of symptoms, full range of motion, and normal strength. Multiple stingers, bilateral symptoms, or symptoms persisting for longer than 1 hr should prompt further evaluation before resumption of any physical activities.

Transient Quadriparesis

Transient quadriparesis is a temporary neurologic episode encompassing sensory symptoms with or without motor changes. Transient quadriparesis is also known as *cervical cord neurapraxia* , *burning hands syndrome* , *commotio spinalis* , and *spinal cord concussion* . Transient quadriparesis can be divided into three types: plegia (complete loss of motor function), paresis (motor weakness), and paresthesia (sensory symptoms only). There is also a 3-part grading system: grade 1 symptoms last <15 min, grade 2 symptoms last 15 min to 24 hr, and grade 3 symptoms persist beyond 24 hr. Transient quadriparesis must be differentiated from just a stinger, and the player should be removed from activity and spinal cord injury considered.

Mechanisms of injury include hyperextension, hyperflexion, and axial loading. Anatomically, when the neck is hyperflexed or hyperextended, the spinal canal is narrowed by up to 30%, increasing the likelihood of cord injury.

Burning hands syndrome is the most common presentation. The athlete has intense paresthesias in both upper extremities. This is suggestive of a central cord syndrome and includes burning, tingling, and loss of sensation. Athletes need to be treated with full cervical precautions to prevent injury progression.

Evaluation should start with plain flexion and extension films if stable. CT should be used if cervical fracture is suspected. MRI should then be used to evaluate for intrinsic spinal cord abnormalities or ongoing cord or root compression. Spinal stenosis is discussed later.

Return to play for transient quadriparesis is heavily debated and lacks data to guide decision-making. Some experts argue that one episode is a contraindication to return to contact sports, whereas others agree with using the Return to Play Table (Table 709.1) for absolute and relative contraindications for return. If allowed to return to play and second episode of transient quadriparesis occurs, the complete workup needs repeating.

Table 709.1

Return to Play

NO CONTRAINDICATION TO RTP	
Healed fractures including:	Healed C1 or C2 fracture with normal cervical spine range of motion (ROM)
	Healed subaxial fracture without sagittal plane deformity
	Asymptomatic clay-shoveler's (C7) spinous process avulsion fracture
Congenital conditions	Klippel-Feil (single-level anomaly not C0/C1 articulation)
	Spina bifida occulta
Degenerative/postsurgical conditions	Cervical disc disease (no change in baseline neurologic status)
	Single-level ACF with/without instrumentation
	Single- or multiple-level posterior cervical laminotomy
Recurrent stingers	Less than 3 episodes lasting <24 hr
	Must have full cervical range of motion
	No persisting neurologic deficit
Transient quadriparesis	Single episode
	Full cervical range of motion
	Normal neurologic exam
	No radiologic instability
	Normal spinal reserve (as evidenced on MRI)
RELATIVE CONTRAINDICATION TO RTP	
Stingers/Burners	Prolonged symptomatic burner/stinger
	Three or more stingers
Transient quadriparesis	Transient quadriparesis lasting >24 hr
	More than 1 episode with symptoms of any duration
Postsurgical	Healed 2-level ACF
	PCF with/without instrumentation
ABSOLUTE CONTRAINDICATION TO RTP	
Transient quadriparesis and any 1 or more of:	Cervical myelopathy
	Continued neck discomfort
	Reduced ROM
	Neurologic deficit from baseline after injury
Surgical procedures	C1 + C2 fusion
	Cervical laminectomy
	Three-level ACF or PCF
Soft tissue injuries	Asymptomatic ligamentous laxity (>11 degrees of kyphotic deformity)
	C1 + C2 hypermobility with anterior dens >3.5 mm (adult), >4 mm (child), i.e., Down syndrome (see Chapter 82)
	Symptomatic cervical disc herniation
Other conditions including	Spear tackler's spine

	Multilevel Klippel-Feil anomaly (see Chapter 700.2)
	Healed subaxial fracture with sagittal kyphosis coronal plane abnormality, or cord encroachment
	Ankylosing spondylitis
	Rheumatoid arthritis with spinal abnormalities
	Spinal cord abnormality (cord edema, compression, etc.)
	Arnold-Chiari syndrome
	Basilar invagination
	Occipital-C1 assimilation (occipitalization or connection)
	Spinal stenosis (canal width <13 mm between C3 and C7)

ACF, Anterior cervical fusion; *PCF,* posterior cervical fusion; *RTP* , return to play.

Adapted from Cantu R, Li YM, Abdulhamid M, Chin LS: Return to play after cervical spine injury in sports. *Curr Sports Med Rep* 12:14–17, 2013.

Congenital Spinal Stenosis

Developmental narrowing of the cervical spinal canal predisposes an athlete to higher risk of spinal cord injury. This condition can be found incidentally while working up other conditions. The Torg ratio, the ratio of vertebral body width to canal width on plain lateral film (cutoff for normal is 0.7 or 0.8), remains useful as a diagnostic test in certain clinical settings. Currently, the “gold standard” is an MRI measuring a canal width of <13 mm between C3 and C7 to define stenosis, with “normal” being >15 mm.

Functional stenosis can be seen with dynamic MRI in flexion and extension to see if the canal space decreases with movement. The positioning of the canal in flexion or extension causes narrowing from positioning of the vertebra and ligament, respectively. The measured diameter may be irrelevant if disc protrusion or ligament hypertrophy causes compression. This narrow “reserve space” around the spinal cord puts the athlete at greater risk for injury as compared with the same force on a normal spine.

Spinal Cord Injury

Spinal cord injury is the most dreaded complication of cervical trauma and is categorized into four entities. Hemorrhage and transection are considered irreversible and associated with complete cord injury, whereas contusion and edema are considered to have more potential for recovery (Fig. 709.1). These severe injuries should be managed by providers with expertise in this area.

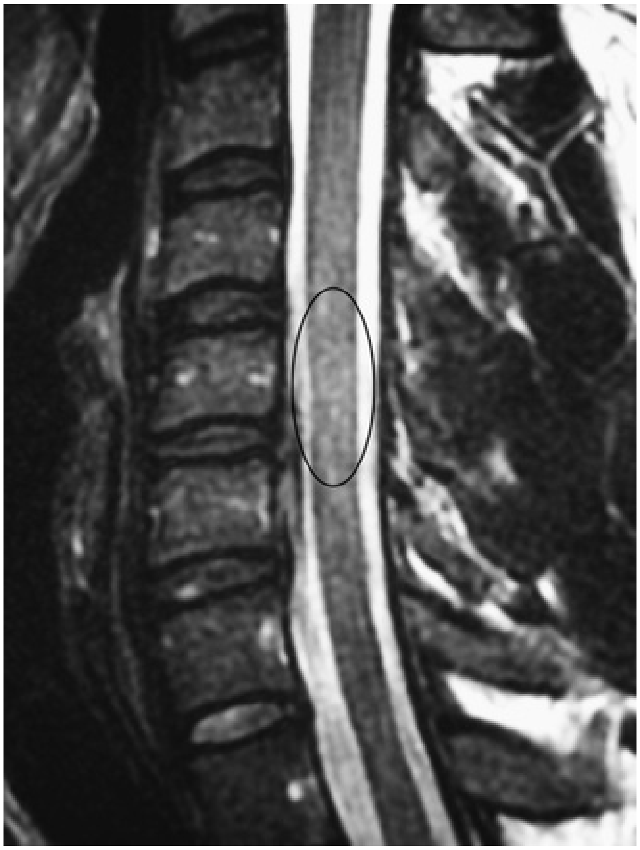

FIG. 709.1 A magnetic resonance image (sagittal) demonstrating spinal cord contusion (edema in central portion of spinal cord). (From Krabak BJ, Kanarek SL: Cervical spine pain in the competitive athlete. *Phys Med Rehabil Clin N Am* 22:459–471, 2011, Fig. 2).

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CHAPTER 710

Heat Injuries

Gregory L. Landry

Heat illness is the 3rd leading cause of death in U.S. high school athletes. It is a continuum of clinical signs and symptoms that can be mild (heat stress) to fatal (heatstroke). Children are more vulnerable to heat illness than adults because they have greater ratio of surface area to body mass and produce greater heat per kilogram of body weight during activity. The sweat rate is lower in children, and the temperature at which sweating occurs is higher. Children can take longer to acclimatize to warmer, more humid environments (typically 8-12 near-consecutive days of 30-45 min exposures). Children also have a blunted thirst response compared with adults and might not consume enough fluid during exercise to prevent dehydration.

Three categories for heat illness are generally used: heat cramps, heat exhaustion, and heat stroke (Table 710.1). However, symptoms of heat illness overlap and advance as the core temperature rises. **Heat cramps** are the most common heat injury and usually occur in mild dehydration and/or salt depletion, usually affecting the calf and hamstring muscles. They tend to occur later in activity, as muscle fatigue is reached, and water loss and sodium loss worsen. They respond to oral rehydration with electrolyte solution and with gentle stretching. The athlete can return to play when ability to perform is not impaired. **Heat syncope** is fainting after prolonged exercise attributed to poor vasomotor tone and depleted intravascular volume, and it responds to fluids, cooling, and supine positioning. **Heat edema** is mild edema of the hands and feet during initial exposure to heat; it resolves with acclimatization. **Heat tetany** is carpopedal tingling or spasms caused by heat-related hyperventilation. It responds to moving to a cooler environment and decreasing respiratory rate (or rebreathing by breathing into a bag).

Table 710.1

Spectrum of Heat Illness

Heat Cramps and Dehydration: ***CAUTIOUS RETURN TO PLAY***

Muscle cramps
Thirst
Fatigue
Light-headedness
Sweating
Flushed face

Heat Exhaustion: ***REMOVE FROM PLAY***

Dizziness
Rapid pulse
Headaches
Nausea
Vomiting
Loss of coordination
Profuse sweating
Core temperature less than 40°C (104°F)

Heat Stroke: ***MEDICAL EMERGENCY, CALL 911***

Core temperature of 40°C (104°F) or higher
Hot dry skin
Multiple system failure
Delirium
Convulsions
Abnormal vital signs

From Merkel DL, Molony JT Jr. Medical sports injuries in the youth athlete: emergency management. *Int J Sports Phys Ther* 7:242–251, 2012, Table 4.

Heat exhaustion is a moderate illness with core temperature 37.7-39.4°C (100-103°F). Performance is obviously affected, but central nervous system dysfunction is mild, if present. It is manifested as headache, nausea, vomiting, dizziness, orthostasis, weakness, piloerection, and possibly syncope. Treatment includes moving to a cool environment, cooling the body with fans, removing excess clothing, and placing ice over the groin and axillae. If a patient is not able to tolerate oral rehydration, IV fluids are indicated. Patients should be monitored, including rectal temperature, for signs of heat stroke. If rapid improvement is not achieved, transport to an emergency facility is recommended.

Heat stroke is a severe illness manifested by central nervous system disturbances and potential tissue damage. It is a medical emergency; *the mortality rate is 50%* . Sports-related heat stroke is characterized by profuse sweating and is related to intense exertion, whereas “classic” heatstroke with dry, hot skin is of slower onset (days) in elderly or chronically ill persons. Rectal temperature is usually >40°C (104°F). Significant damage to the heart, brain, liver, kidneys, and muscle occurs, with possible fatal consequences if untreated. Treatment is immediate whole-body cooling via cold water immersion. Airway, breathing, circulation, core temperature, and central nervous system status should be monitored constantly. Rapid cooling should be ceased when core temperature is approximately 38.3-38.9°C (101-102°F). IV fluid at a rate of 800 mL/m^2 in the 1st hr with normal saline or lactated Ringer solution improves intravascular volume and the body's ability to dissipate heat. Immediate transport to an emergency facility is necessary. Physician clearance is required before return to exercise.

Dehydration is common to all heat illness; consequently, measures to prevent dehydration may also prevent heat illness. Thirst is usually an adequate indicator of hydration status; excessive fluid replacement beyond sweat and urine losses predisposes to hyponatremia. Endurance athletes should be cautioned not to drink beyond thirst. Mild dehydration (2–3%) does not usually affect performance and itself does not cause cramping, fatigue, or heat stroke.

Exercise associated hyponatremia ($Na < 135$ mmol/L) may be asymptomatic or symptomatic (lightheadedness, nausea, headache, confusion, cerebral edema) and is often seen in endurance sports (marathon, triathlon, cycling, swimming), hiking, football, and police or military drills. Major risk factors include overdrinking water or hypotonic sports drinks, weight gain during exercise, exercise duration >4 hr, readily available fluids, and inexperienced or slow pace.

Athletes are advised to be hydrated before exercise and should drink to thirst (Fig. 710.1). Fluids should contain sodium and not be ingested in excess.

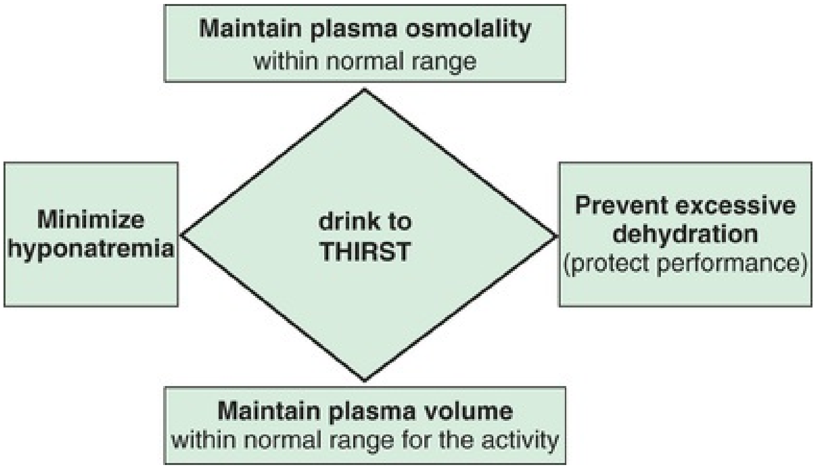

FIG. 710.1 Primary recommended fluid intake strategy to prevent symptomatic exercise-associated hyponatremia. (From Hew-Butler T, Rosner MH, Fowkes-Godek S, et al: Statement of the third international exercise-associated hyponatremia consensus development conference, Carlsbad, California, 2015. *Clin J Sport Med* 25(4):303–320, 2015, Fig. 1, p. 313.)

During a football practice, scheduled breaks every 20-30 min with helmets off to get out of the heat can decrease the cumulative amount of heat exposure. Practices and competition should be scheduled in the early morning or late afternoon to avoid the hottest part of the day. Guidelines have been published about modifying activity related to temperature and humidity (Fig. 710.2). Proper clothing such as shorts and T-shirts without helmets can improve heat dissipation. Prepractice and postpractice weight can be helpful in determining the amount of fluid necessary to replace (8 oz for each pound of weight loss). When practice or performing in a warm environment, gradual acclimatization is recommended.

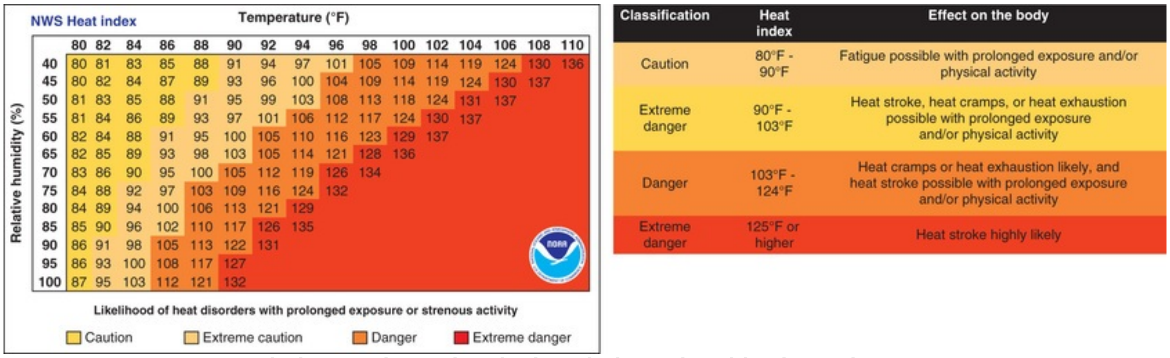

NWS Heat index

Temperature (°F)

Relative humidity (%)	80	82	84	86	88	90	92	94	96	98	100	102	104	106	108	110
40	80	81	83	85	88	91	94	97	101	105	109	114	119	124	130	136
45	80	82	84	87	89	93	96	100	104	109	114	119	124	130	137	
50	81	83	85	88	91	95	99	103	108	113	118	124	131	137		
55	81	84	86	89	93	97	101	106	112	117	124	130	137			
60	82	84	88	91	95	100	105	110	116	123	129	137				
65	82	85	89	93	98	103	105	114	121	128	136					
70	83	86	90	95	100	105	112	119	126	134						
75	84	88	92	97	103	109	116	124	132							
80	84	89	94	100	106	113	121	129								
85	85	90	96	102	110	117	126	135								
90	86	91	98	105	113	122	131									
95	86	93	100	108	117	127										
100	87	95	103	112	121	132										

Likelihood of heat disorders with prolonged exposure or strenous activity

🟨 Caution 🟨 Extreme caution 🟧 Danger 🟥 Extreme danger

Classification	Heat index	Effect on the body
Caution	80°F - 90°F	Fatigue possible with prolonged exposure and/or physical activity
Extreme danger	90°F - 103°F	Heat stroke, heat cramps, or heat exhaustion possible with prolonged exposure and/or physical activity
Danger	103°F - 124°F	Heat cramps or heat exhaustion likely, and heat stroke possible with prolonged exposure and/or physical activity
Extreme danger	125°F or higher	Heat stroke highly likely

FIG. 710.2 Heat index. To determine the heat index using this chart, air temperature and the relative humidity need to be known. For example, if the air temperature is 100° F and the relative humidity is 55%, the heat index will be 124° F. When the relative humidity is low, the apparent temperature can actually be lower than the air temperature. T, air temperature (F); R, relative humidity (percentage). (Courtesy National

Weather Service, United States National Oceanic and Atmospheric Administration. https://www.weather.gov/ama/heatindex .)

Fluids with electrolyte and carbohydrate are more important for persons who exercise for longer than 1 hr. Salt supplements should not be used by most people because of the risk of their causing hypernatremia and delayed gastric emptying. If excessive fluid intake contributes to hyponatremia, salt supplements will not avoid the decline in serum sodium. They may be useful in a person with a high sweat rate or recurrent heat cramps.

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CHAPTER 711

Female Athletes

Menstrual Problems and the Risk of Osteopenia

Gregory L. Landry

Physical training in young women can adversely affect reproductive function and bone mineral status, especially when combined with calorie restriction (Fig. 711.1 ; see Chapters 41 and 142).

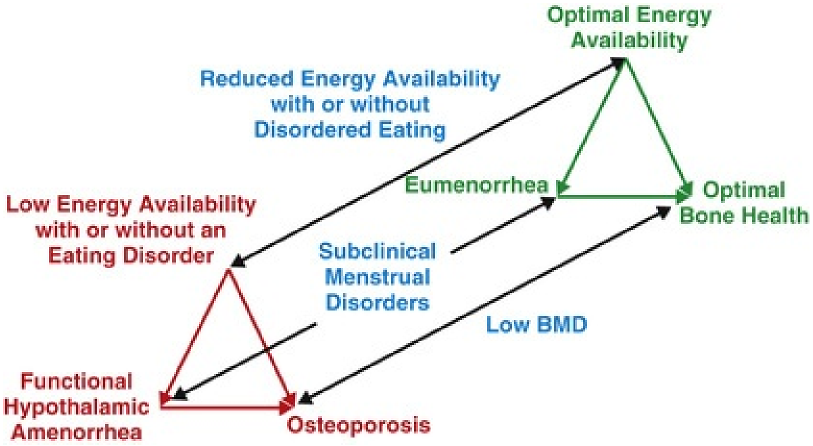
Optimal Energy Availability
Reduced Energy Availability with or without Disordered Eating
Eumenorrhea
Optimal Bone Health
Low Energy Availability with or without an Eating Disorder
Subclinical Menstrual Disorders
Low BMD
Functional Hypothalamic Amenorrhea
Osteoporosis

FIG. 711.1 Spectra of the female athlete triad. The 3 interrelated components of the Female Athlete Triad are energy availability, menstrual status, and bone health. Energy availability directly affects menstrual status, and in turn, energy availability and menstrual status directly influence bone health. Optimal health is indicated by optimal energy availability, eumenorrhea, and optimal bone health, whereas, at the other end of the spectrum, the most severe presentation of the Female Athlete Triad is characterized by low energy availability with or without an eating disorder, functional hypothalamic amenorrhea, and osteoporosis. An athlete's condition moves along each spectrum at different rates depending on her diet and exercise behaviors. *BMD* , Bone mineral density. (Adapted from Nattiv A, Loucks AB, Manore MM, et al.: American College of

Sports Medicine position stand. The female athlete triad. *Med Sci Sports Exerc* 2007;39:1867–1868.)

The majority of bone mass is acquired by the end of the 2nd decade (see Chapter 726). Approximately 60–70% of adult bone mass is genetically determined, and the remaining is influenced by three controllable factors: exercise, calcium intake, and sex steroids, primarily estrogen. Exercise promotes bone mineralization in the majority of young women and is to be encouraged. In females with eating disorders and those who exercise to the point of excessive weight loss with **amenorrhea** or **oligomenorrhea** , exercise can be detrimental to bone mineral acquisition, resulting in reduced bone mineral content, or **osteopenia** .

Specifically, bone mineralization is negatively affected by amenorrhea (absence of menstruation for ≥3 consecutive months). This may be influenced by abnormal eating patterns, or *disordered eating* . When occurring together, disordered eating, amenorrhea, and osteoporosis form the **female athlete triad** . A more inclusive definition refers to the interrelationships among energy availability, menstrual function, and bone mineral density as athletes are distributed along a spectrum of health and disease (see Fig. 711.1). At health supervision visits and the preparticipation physical examination, special attention should be given to screening for any unhealthy features of the triad (Table 711.1).

Table 711.1

Triad Consensus Panel Screening Questions*

- Have you ever had a menstrual period?
- How old were you when you had your 1st menstrual period?
- When was your most recent menstrual period?
- How many periods have you had in the past 12 mo?
- Are you presently taking any female hormones (estrogen, progesterone, birth control pills)?
- Do you worry about your weight?
- Are you trying to or has anyone recommended that you gain or lose weight?
- Are you on a special diet or do you avoid certain types of foods or food groups?

- Have you ever had an eating disorder?
- Have you ever had a stress fracture?
- Have you ever been told you have low bone density (osteopenia or osteoporosis)?

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[*] The Triad Consensus Panel recommends asking these screening questions at the time of the sport preparticipation evaluation.

From De Souza MJ, Nattiv A, Joy E, et al: 2014 female athlete triad coalition consensus statement on treatment and return to play of the female athlete triad. *Br J Sports Med* 48:289, 2014, Box 1, p. 3.

Menstrual abnormalities (including **amenorrhea**) result from suppression of the spontaneous hypothalamic pulsatile secretion of gonadotropin-releasing hormone (Fig. 711.2 ; see Chapter 142.1). It is believed that the amenorrhea results from reduced energy availability, defined as energy intake minus expenditure. Energy availability below a threshold of 30 kcal/kg/day lean body mass is thought to result in menstrual disturbances. Negative energy balance also appears to lower levels of leptin, which affects both nutritional state and the reproductive system. Other causes to be ruled out are pregnancy (see Chapter 144), pituitary tumors, thyroid abnormalities, polycystic ovary syndrome (see Chapter 567), anabolic–androgenic steroid use (see Chapters 140 and 712), and other medication side effects.

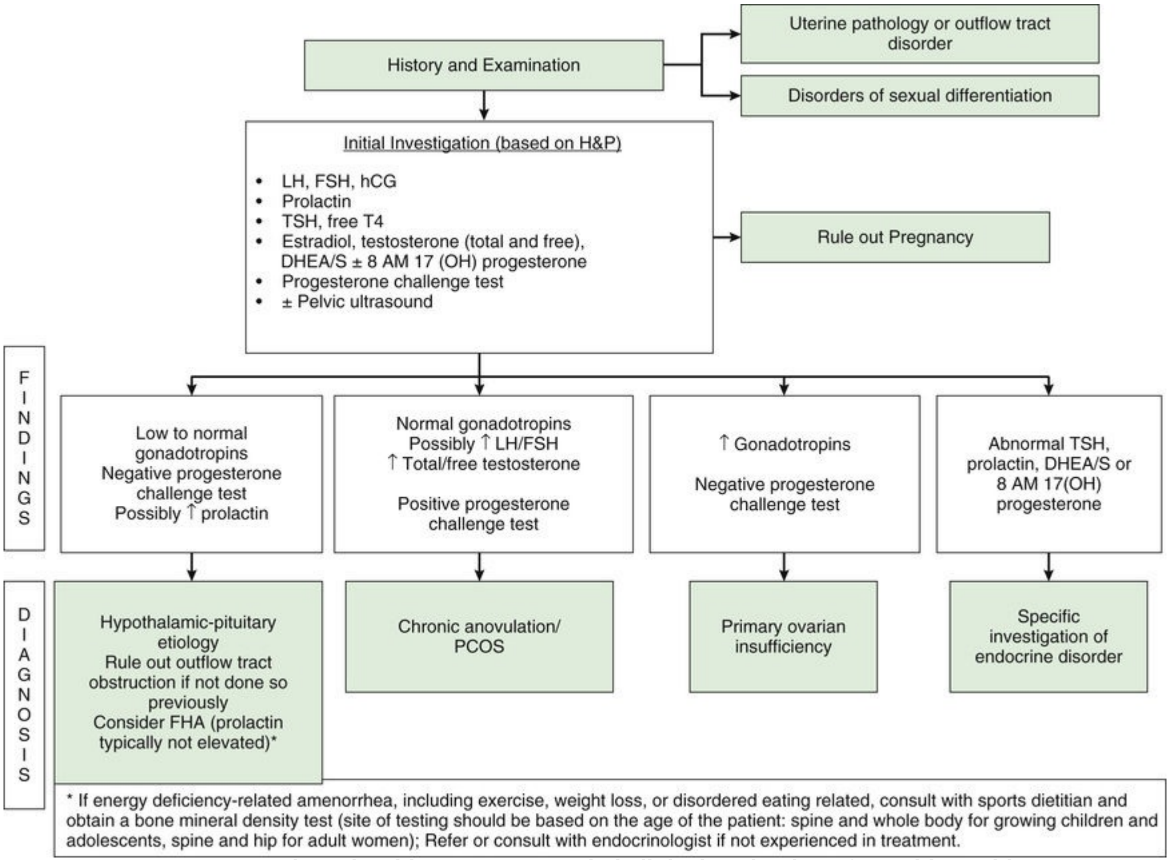
History and Examination
Uterine pathology or outflow tract disorder
Disorders of sexual differentiation
Initial Investigation (based on H&P)
LH, FSH, hCG
Prolactin
TSH, free T4
Estradiol, testosterone (total and free), DHEA/S ± 8 AM 17 (OH) progesterone
Progesterone challenge test
± Pelvic ultrasound
Rule out Pregnancy
FINDINGS
Low to normal gonadotropins Negative progesterone challenge test Possibly ↑ prolactin
Normal gonadotropins Possibly ↑ LH/FSH ↑ Total/free testosterone Positive progesterone challenge test
↑ Gonadotropins Negative progesterone challenge test
Abnormal TSH, prolactin, DHEA/S or 8 AM 17(OH) progesterone
DIAGNOSIS
Hypothalamic-pituitary etiology Rule out outflow tract obstruction if not done so previously Consider FHA (prolactin typically not elevated)*
Chronic anovulation/ PCOS
Primary ovarian insufficiency
Specific investigation of endocrine disorder

* If energy deficiency-related amenorrhea, including exercise, weight loss, or disordered eating related, consult with sports dietitian and obtain a bone mineral density test (site of testing should be based on the age of the patient: spine and whole body for growing children and adolescents, spine and hip for adult women); Refer or consult with endocrinologist if not experienced in treatment.

FIG. 711.2 **Amenorrhea algorithm. Recommended clinical evaluation of an athlete with primary or secondary amenorrhea, or prolonged oligomenorrhea, includes a history and physical examination, initial and follow-up laboratory testing, and diagnosis by a physician. Referral or consultation with endocrinology is recommended if the diagnosing physician is not experienced with treatment of functional hypothalamic amenorrhea or other etiologies of amenorrhea. DHEA/S, dehydroepiandrosterone sulfate; FHA, functional hypothalamic amenorrhea; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; PCOS, polycystic ovarian syndrome; TSH, thyroid-stimulating hormone. (Modified from Jameson JL, De Groot LJ, Illingworth P. Amenorrhea, anovulation, and dysfunctional uterine bleeding. In Jameson JL, De Groot LJ, editors: *Endocrinology adult and pediatric* , ed 6, St. Louis, MO, 2010, Saunders, pp 2341–2355.)**

The low estrogen state of amenorrhea predisposes the female athlete to osteopenia and puts her at risk for stress fractures, especially of the spine and lower extremity. If left unchecked, bone loss is partially irreversible despite resumed menses, estrogen replacement, or calcium supplements. Routine bone mineral density screening is not recommended but can help guide treatment and return to activity in severe cases.

Three eating disorders can occur in the context of amenorrhea. **Anorexia nervosa** manifests as weight <85% of estimated ideal body weight with evidence of starvation manifesting as bradycardia, hypothermia, and orthostatic hypotension or orthostatic tachycardia. **Bulimia nervosa** manifests as recurrent episodes (at least once weekly) of binge eating with a sense of lack of control overeating during an episode with recurrent episodes of compensatory behaviors. A third category, **Unspecified Feeding and Eating Disorder** , is a general description for disorders failing to meet the criteria for the two previous disorders. Many young women who previously were diagnosed as “Unspecified Feeding and Eating Disorder” have a specific diagnosis of anorexia or bulimia. Signs of an eating disorder are weight loss, food restriction, depression, fatigue, and worsened athletic performance, and preoccupation with calories and weight. The athlete might avoid events surrounding food consumption or might hide and discard food. Signs and symptoms include fat depletion, muscle wasting, bradycardia worsened from baseline, orthostatic hypotension, constipation, cold intolerance, hypothermia, gastric motility problems, and in some cases lanugo (see Chapter 41). Electrolyte abnormalities can lead to cardiac dysrhythmias. Psychiatric problems (depression [see Chapter 39], anxiety [see Chapter 38], suicide risk [see Chapter 40]) are of higher incidence in this population.

For treatment of eating disorders, control of the symptoms is a central theme. The first step is confronting the athlete about the abnormal behavior and unhealthy weight. In general, exercise is not recommended if the body weight is <85% of estimated ideal body weight, although there are exceptions, especially if the athlete is eumenorrheic. If the athlete is unable to gain weight with nutrition and medical counseling alone, then psychologic consultation is sought (Fig. 711.3).

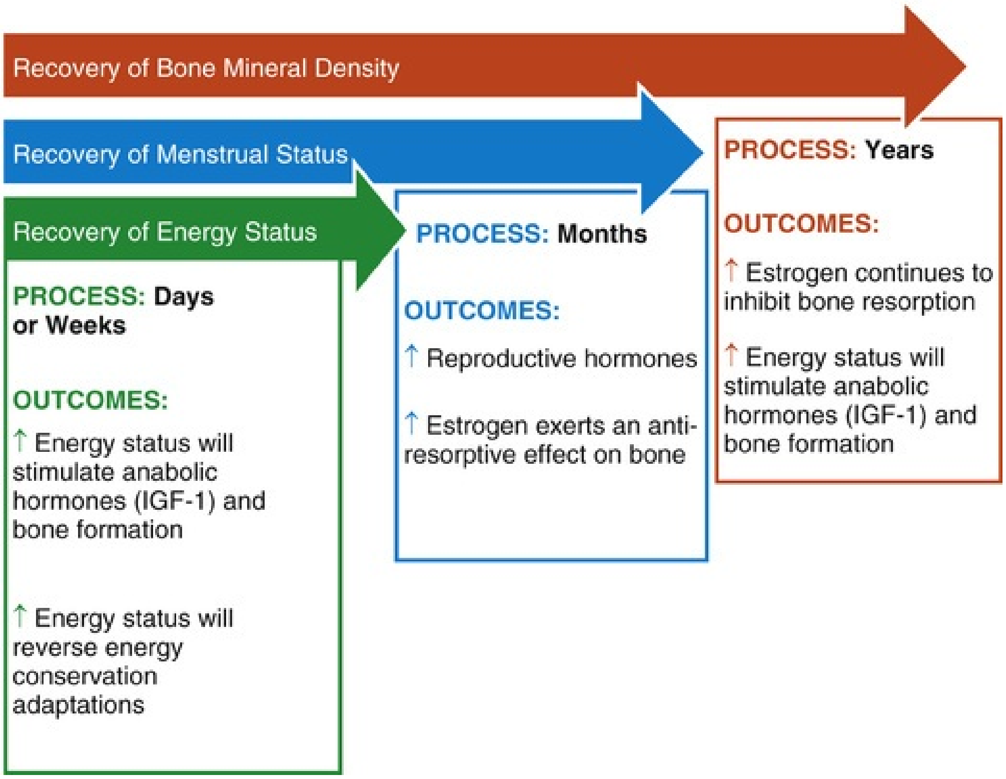
Recovery of Bone Mineral Density
Recovery of Menstrual Status
Recovery of Energy Status
PROCESS: Days or Weeks
OUTCOMES:
↑ Energy status will stimulate anabolic hormones (IGF-1) and bone formation
↑ Energy status will reverse energy conservation adaptations
PROCESS: Months
OUTCOMES:
↑ Reproductive hormones
↑ Estrogen exerts an anti-resorptive effect on bone
PROCESS: Years
OUTCOMES:
↑ Estrogen continues to inhibit bone resorption
↑ Energy status will stimulate anabolic hormones (IGF-1) and bone formation

FIG. 711.3 **Treatment of the female athlete triad. The three components of the Triad recover at different rates with the appropriate treatment. Recovery of energy status is typically observed after days or weeks of increased energy intake and/or decreased energy expenditure. Recovery of menstrual status is typically observed after months of increased energy intake and/or decreased energy expenditure, which improves energy status. Recovery of bone mineral density may not be observed until years after recovery of energy status and menstrual status has been achieved. IGF-1, insulin-like growth factor-1. (From De Souza MJ, Nattiv A, Joy E, et al.: 2014 female athlete triad coalition consensus statement on treatment and return to play of the female athlete triad. *Br J Sports Med* 48:289, 2014, Fig. 3, p. 7.)**

Most athletes will not initially admit a problem, and many are unaware of the serious physical consequences. A helpful technique in talking to these athletes is to sensitively point out performance issues. Education about decreased strength, endurance, and concentration can be a motivating factor for treatment. Often, the athlete's family needs to be involved, and the athlete should be encouraged to reveal necessary information to them. Psychology or psychiatry referral is important in the multidisciplinary approach to treatment of disordered eating. It is important for the physician to monitor the athlete's physical health while the mental health professional is caring for the mental aspects of the eating disorder.

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CHAPTER 712

Performance-Enhancing Aids

Gregory L. Landry

See also Chapter 140 .

Ergogenic aids are substances used for performance enhancement, most of which are unregulated supplements (Table 712.1). The 1994 Dietary Supplement and Health Education Act limited the ability of the U.S. Food and Drug Administration to regulate any product labeled as a supplement. Many agents have significant side effects without proven ergogenic properties. In 2016, the American Academy of Pediatrics published a policy statement strongly condemning their use in children and adolescents. The 2004 Controlled Substance Act outlawed the purchase of steroidal supplements such as androstenediol, and androstenedione, with the exception of dehydroepiandrosterone (DHEA).

Table 712.1

Characteristics of Common Performance-Enhancing Substances

PERFORMANCE-ENHANCING SUBSTANCE	DESIRED EFFECTS	MAJOR ADVERSE EFFECTS	MINOR ADVERSE EFFECTS	STATUS	ROUTE OF ADMINISTRATION
Anabolic–androgenic steroids [1]	Increase muscle size, strength, lean body mass; decrease body fat	Testicular atrophy, CV disease, atherosclerosis, myocardial disease, liver dysfunction, cancer	Acne, gynecomastia	Banned by IOC and all major sporting bodies	Oral, topical, injectable
Creatine	Increase in strength, power output,	Heatstroke	Dehydration	Allowed	Oral

	sprint performance, total work to fatigue, peak force/power; decrease lactate threshold; increase weight and lean body mass				
Human growth hormone [2]	May increase lean body mass and decrease fat mass	Carpal tunnel syndrome, intracranial hypertension, CV disease, hyperlipidemia, insulin resistance	Arthralgias	Banned by IOC and International Federations	Injectable
Amphetamines/stimulants [3] , [4]	Increase in alertness and metabolism; may increase strength, muscular power, speed, acceleration, aerobic power, anaerobic capacity, endurance	Arrhythmias, heat exhaustion, seizures, myocardial infarction, sudden death	Agitation, GI upset, nausea, headaches, insomnia, hallucinations	Banned by IOC, NCAA, NFL	Oral, injectable, inhalable
Erythropoietin/blood doping	Increase in oxygen-carrying capacity, endurance	Hypertension, myocardial infarction, pulmonary embolism, immune reaction	Headaches	Banned by IOC and all major sporting bodies	Injectable
Beta-hydroxy-beta-methylbutyrate	May increase lean body mass, muscle strength, power; enhance recovery	Unknown	Unknown	Allowed	Oral
Protein supplements	Increase lean body mass, improve healing	Unknown in previously healthy athletes	Unknown	Allowed	Oral

[1] Including selective androgen receptor modulators and aromatase inhibitors or estrogen receptor modulators

[2] Including various growth factors (IGF-1, etc.)

[3] Caffeine is commonly used and remains permitted by WADA.

[4] Includes various beta-2-agonists prohibited by WADA, except when needed for therapy of asthma but within therapeutic limits

CV, Cardiovascular; *GI* , gastrointestinal; *IOC* , International Olympic Committee; *LDH* , lactate dehydrogenase; *N/A* , not applicable; *NCAA* , National Collegiate Athletic Association; *NFL* , National Football League; *WADA* , World Anti-Doping Agency.

Modified from Momaya A, Fawal M, Estes R: Performance-enhancing substances in sports: a review of the literature. *Sports Med* 45:517–531, 2015, Table 1, p. 519.

The prevalence of lifetime steroid use is highest among boys in the United States; among a large representative sample in 2014, 3–4% of boys in middle school and 5–6% of those in high school report having used steroids for muscle-enhancement. The European School Survey Project on Alcohol and Other Drugs found that 1% of European youth reported any use of steroids. Steroids in oral, injectable, and skin cream form are taken in various patterns. *Cycling* is a term used to describe taking multiple doses of steroids for a period, ceasing, and then starting again. *Stacking* refers to the use of different types of steroids in both oral and injectable forms. *Pyramiding* involves slowly increasing the steroid dose to a peak amount and then gradually tapering down.

Anabolic–androgenic steroids have been used in supraphysiologic doses for their ability to increase muscle size and strength and decrease body fat. An evidence base does support the increase in muscle mass and strength; the effects appear to be related to the myotrophic action at androgen receptors, as well as competitive antagonism at catabolism-mediating corticosteroid receptors. However, they have significant endocrinologic side effects, such as decreased sperm count and testicular atrophy in men and menstrual irregularities and virilization in women. Hepatic problems include elevated aminotransaminases and γ-glutamyl transferase, cholestatic jaundice, peliosis hepatitis, and a variety of tumors, including hepatocellular carcinoma. There is evidence that anabolic–androgenic steroids might cause cardiovascular problems as well, including higher blood pressure, lower high-density lipoprotein, higher low-density lipoprotein, higher homocysteine, and decreased glucose tolerance. The possible psychologic effects include aggression, several personality disorders, and a variety of other psychologic problems (anxiety, paranoia, mania, depression, psychosis). Physical findings in males include gynecomastia, testicular shrinkage, jaundice, male pattern baldness, acne, and marked striae. Women can develop hirsutism, voice deepening, clitoral hypertrophy, male-pattern baldness, acne, and marked striae.

Testosterone precursors (also known as *prohormones*) include androstenedione and DHEA. Their use in the adolescent population has increased markedly in conjunction with reports of high-profile athletes' use. They are androgenic but have not been proved to be anabolic. If they are anabolic at all, they work by increasing the production of testosterone. They also increase production of estrogenic metabolites. The side effects are similar to those of anabolic–androgenic steroids and far outweigh any ergogenic benefit. Since January 2005, these substances cannot be sold without prescription.

Creatine is an amino acid mostly stored in skeletal muscle. Its key feature is ability to rephosphorylate adenosine diphosphate to adenosine triphosphate, therefore increasing muscle performance. Its use has increased, especially since other supplements have been withdrawn from the market. Thirty percent of high school football players have used creatine. There is evidence that creatine, as a source of increased energy, enhances strength and maximal exercise performance when used during training. There is no evidence that creatine affects hydration or temperature regulation. Concerns about nephritis in case reports have not been supported by controlled studies. However, there are few long-term studies evaluating creatine use.

Caffeine is an active ingredient in energy drinks and some endurance sport supplements. More of a problem as an energy drink when combined with alcohol, excessive caffeine ingestion may result in tachycardia, gastritis, nausea, vomiting, and central nervous system excitation. Overdoses may result in seizures, arrhythmias, and hypotension.

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CHAPTER 713

Specific Sports and Associated Injuries

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Sports Participation, Early Specialization, Injury Risk and Burnout

It is estimated that 60 million youth, ages 6-18 yr, participate in organized athletics, with 44 million participating in multiple sports. It has also been estimated that 69% of girls and 75% of boys ages 8-17 yr participate in at least one organized sport team or club. Participating in sport gives children the opportunity to develop self-esteem and leadership skills, promote peer socialization, and improve general health and fitness. Some parents encourage their children to participate in a *single sport* because they think this will allow the athlete more time to focus on sport-specific skills and will increase the likelihood that their child will be selected for elite teams, a college scholarship, or professional contract. They may also feel pressure from coaches. However, only 0.2–0.5% of U.S. high school athletes rise to the professional level; Olympic level athletes start training in their main sport at an older age than their less elite peers and on average participate in two other sports prior to, or in parallel with, their main sport. A study at the collegiate level revealed that 70% of surveyed athletes did not specialize in their sport until 12 yr of age, and 88% participated in more than one sport. *Multi-sports* athletes, in general, have a more diverse skill set, can transfer skills from one sport to another, have a decreased risk of **overuse injury** , have lower rates of **burnout** , and thus are less likely to quit sports at a younger age. Exposure to multiple sports also allows that athlete to identify the sport that they most enjoy.

Risk of injury in sports increases with age and training volumes. In general, there is an increased risk of injury if a young athlete participates in more weekly organized sport hours than their age. In addition, training more than 16 hr/wk is associated with a significantly increased risk of injury. When young athletes exceed a 2 : 1 ratio of weekly hours in organized sports to weekly hours in unorganized free play, they are more likely to suffer a serious overuse injury. Overuse injuries unique to young athletes include apophyseal injuries and physeal stress injuries secondary to decreased muscle mass, increased joint hypermobility and imbalances in growth and strength. Overuse injuries and fractures are more likely to occur during adolescent growth spurts as physes, apophyses, and articular surfaces in a rapid phase of growth are less resistant to tensile, shear, and compressive forces than either mature bone or more immature prepubescent bone, and because of decreased blood flow to the physes. Another risk factor for overuse injuries in the youth population is overscheduling secondary to participation in a large number of competitive events at young ages. These events often include tournaments, which consist of multiple games in a short period of time. This type of schedule does not allow enough time for rest and recovery.

Sports specialization is defined as “participating in a single sport for greater than 8 mo per year, choosing a single main sport, and/or quitting all other sports to focus on one sport.” Athletes that specialize early sometimes report increased anxiety and stress secondary to worrying about failure, trying to meet adult expectations, or experiencing parental pressure to participate or perform at a certain level, and often feel as though they have a lack of control in sport decision making. All of these feelings can contribute to burnout, which can lead to quitting sports early and ultimately increased inactivity as an adult. To reduce the risk of overuse injury and burnout, one should limit weekly and yearly participation time, limit sport-specific repetitive movements, and ensure adequate rest and recovery periods. Thus, it has been recommended that “intense training in a single sport to the exclusion of others should be delayed until adolescence in order to optimize success while minimizing injury, stress and burnout.”

Football

Football is the sport with the greatest number of participants in the United States, especially at the high school level, and with the highest number and rate of injuries. Most of these injuries are relatively minor, and compared with injuries in many other sports, are less severe, as evidenced by fewer days lost from injury. Age, weight, and position played contribute to injury risk, with older and heavier players and running backs and line backers having higher injury rates. The most common football injuries include joint sprains, muscle strains, and contusions, with the lower extremities injured most frequently.

Although the majority of catastrophic sports injuries in the United States have occurred in football, these injuries are rare. Catastrophic injury is defined as a fatal injury or a severe injury with or without permanent severe functional disability. Disabling injuries include cervical spine and cerebral injuries.

Head and neck injuries in football include concussion, neck sprain, and brachial plexopathy. Compared to other sports, brain injury (concussion) (see Chapter 708) occurs with the highest rate in football, a result of the frequent exposure to contact during practices and games, although more concussions occur in games than practices. When compared to other sports, cervical spine injuries occur at higher rates in football, given the increased risk of high velocity contact, neck flexion, and axial loading. Proper blocking and tackling form with the neck extended rather than flexed is essential to help reduce the risk of cervical spine injury. Although not shown to reduce the concussion rate, helmets can help reduce facial and dental trauma and provide some protection from side head blows. A **“stinger”** or **“burner”** represents a brachial plexus neurapraxia (see Chapter 709). This is the most common nerve injury in football and results from traction, compression, or a direct blow to the upper cervical nerve roots of the brachial plexus caused by forceful lateral neck bending.

Heat illness is possible in pediatric athletes given physiologic factors including increased heat production per body weight, less efficient heat dissipation and higher body temperatures associated with dehydration. Dehydration and associated electrolyte abnormalities and poor acclimatization increase the risk of heat illness. Heat illness risk can be reduced with proper hydration pre-, during, and postpractice, avoiding practice in high heat or humidity, wearing breathable, light-colored clothing, removing the helmet between plays and avoiding certain medications such as antihistamines, anticholinergics, stimulants, and supplements (see Chapter 710).

Contusions to the arm or thigh muscles can result in the development of a large hematoma if not treated aggressively in the acute stage, resulting in prolonged time away from football. Large hematomas and those allowed to persist are at risk for development of **myositis ossificans** .

Low back pain can be caused by **spondylolysis** , especially in players with repetitive hyperextension of the spine (see Chapter 699.6). Education on tackling mechanics, core strengthening, and hamstring flexibility are important in prevention of and/or recovery from a spondylolysis injury. Shoulder trauma can cause glenohumeral joint dislocations, the majority of which are anterior dislocations and have a high rate of recurrence; acromioclavicular joint sprains; and fractures to the clavicle or humerus (see Chapter 703). Knee injuries (see Chapter 707.6) are common and include **anterior cruciate ligament** (ACL) tears and, less frequently, medial collateral ligament (MCL) tears. Knee bracing in high school football players is controversial and lacks significant evidence; however, some studies have shown reduced MCL injury rate and less severe MCL injuries in players in high-risk positions, including offensive lineman, who wear knee braces.

Ankle sprains occur frequently, with lateral ankle sprains resulting in less time away from the sport than high ankle sprains. The risk of re-injury may be reduced by rehabilitation, including strengthening and range of motion, and the use of a lace-up ankle brace (see Chapter 707.8). **Turf toe** , a sprain to the 1st metatarsophalangeal joint, is caused by forceful dorsiflexion of the toe while wearing soft, lightweight, flexible shoes. Calcaneal apophysitis at the insertion of the Achilles tendon on the calcaneus, also known as **Sever's disease** , is an overuse injury that typically presents as heel pain in a cleated athlete who is still growing (typically between ages 7 and 10 yr).

Baseball/Softball

Baseball- and softball-related injury sites are most commonly the shoulder, elbow, ankle, and hip. Facial injuries and concussions are also seen. The most common mechanisms of injury include pitching repetition and being hit by a ball or a bat.

Throwing injuries of the shoulder and elbow are typically seen in pitchers secondary to overuse, with contributory factors including high pitch count, pitch type, and inadequate rest. “**Little League shoulder** ” is a repetitive micro trauma injury to the open proximal humeral physis, and “**Little League elbow** ” is a repetitive micro trauma injury to one or more of the six ossification centers in the elbow (see Chapter 707.3). “Little League shoulder” is the most common injury seen in softball windmill pitching, with similar shoulder stress as seen in overhand pitching. Poor core strength and alteration in biomechanics, especially when fatigued, may contribute to injury risk (Fig. 713.1). Age-related **pitch**

count and rest guidelines, “Pitch Smart,” are available online and are endorsed by Little League. Curve balls and sliders should not be thrown by players younger than 14 yr of age. Current recommendations also advise against participating in multiple leagues and participating in year-round baseball, given the increased risk of injury with this volume of play. Adherence to the guidelines is the responsibility of the athlete, parents, and coaches. Counseling athletes (and coaches) to stop all throwing activities if the player experiences shoulder or elbow pain, with medical evaluation if no resolution with rest, is essential. If injured, a gradual return to throwing protocol under the direction of a physical therapist with additional focus on strengthening and throwing mechanics should be considered. Catchers are more vulnerable to traumatic sprains of the interphalangeal and metacarpal phalangeal joints, head injuries including concussions from the ball striking the mask, and knee injuries associated with the deep squatting posture.

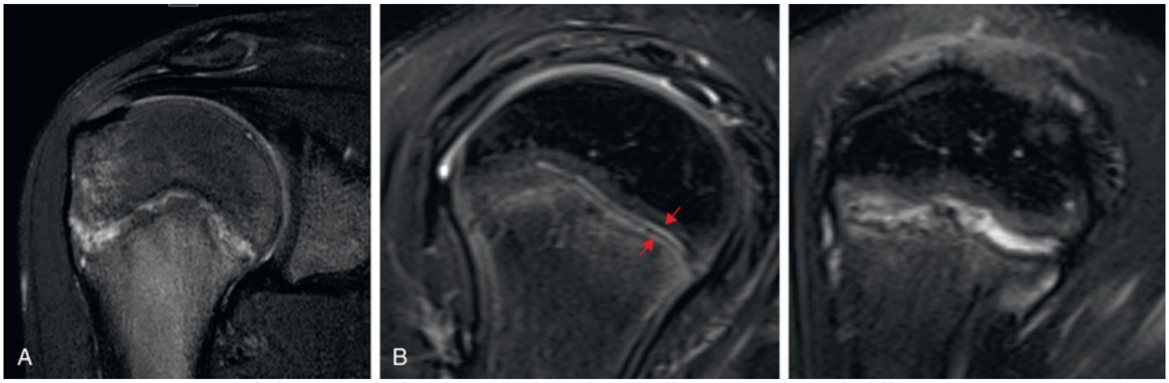

FIG. 713.1 **Little League shoulder MR imaging findings. A, Coronal oblique fat-saturated T2-weighted image in a 12-yr-old pitcher demonstrates diffuse proximal humeral primary physeal widening and undulation with bone marrow edema within the metaphysis and lateral epiphysis. B, Two sagittal oblique fat-saturated T2-weighted images obtained in a 13-yr-old pitcher demonstrate preservation of the normal anterior medial humeral physis *(red arrows)* in contrast to the widened irregular physis posteriorly and laterally. (From Braithwaite KA, Marshall KW: The skeletally immature and newly mature throwing athlete. *Radiol Clin N Am* 54:841–855, 2016.)**

Death or serious injury in baseball is rare, but may result from direct contact by the ball or bat, causing serious head injury or **commotio cordis** , which is a direct blow to the chest during a critical time in the cardiac cycle resulting in a possibly fatal arrhythmia. Batting helmets, with consideration of faceguards, must be worn properly to help prevent face and head injuries. Modifications to the hardness of baseballs used with younger athletes may also be helpful. Chest protectors have not been shown to reduce the risk of commotio cordis.

Sliding causes the most injuries in base runners, including head injury and lower limb injuries. If sliding is allowed, correct sliding technique must be taught as many injuries are secondary to timing issues. Head first sliding is controversial and is not recommended for players younger than 10 yr of age.

Basketball/Volleyball

When combining male and female sports participation, basketball has one of the highest injury rates, even though it is considered a “safe sport” from a contact perspective. Common maneuvers of basketball and volleyball include jumping, pivoting, running, and sudden acceleration and deceleration, which increase the risk for knee and ankle injuries. Similarly, injury to the fingers may result from the passing, catching, and striking of the ball inherent in these sports. Scaphoid fractures may result from falling on an outstretched hand. Injuries to the face and eyes can also occur.

Ankle sprains are the most common injury and are usually caused by inversion with plantar flexion, placing the lateral ligaments on tension. An avulsion fracture of the base of the 5th metatarsal at the insertion of the peroneus brevis tendon is another sequelae of inversion ankle injuries. A “**high ankle sprain** ” or syndesmosis ligament injury typically results from an excessive external rotation in a dorsiflexed position, and these athletes have pain out of proportion to exam.

Foot pain may be secondary to calcaneal apophysitis (Sever's disease), retrocalcaneal bursitis, posterior tibialis tendinosis, accessory tarsal navicular, sesamoiditis, blisters, subungual hematoma, and paronychia (see Chapters 683). Achilles tendinosis is also a common overuse injury.

Knee injuries include those caused by overuse, such as traction apophysitis at the insertion of the patella tendon on the tibial tubercle (**Osgood-Schlatter disease**) (see Chapter 697.4), traction apophysitis at the distal patella (**Sinding-Larsen-Johansson syndrome**) and patellar tendinosis (**jumper's knee**) (see Chapter 707.6). A modest reduction in knee overuse injuries was seen in participants wearing knee pads.

ACL injury occurs in both male and female participants; however, among children 12-17 yr age the frequency of ACL injury in female participants is slightly higher. The exact reason for this discrepancy is unclear; however, some data suggest that female athletes do not exhibit the same neuromuscular adaptions that male athletes exhibit during pubertal growth spurts. Multiple studies on the effect of neuromuscular training and strengthening programs focused on ACL injury prevention in females suggest that these types of programs may reduce the risk of ACL injury. As with other jumping sports, other acute ligament sprains (medial collateral with or without ACLs) can occur. For all participants, a program focused on the strengthening of hip group muscles and hamstrings to prevent dynamic valgus when landing and sport-specific training with jump training can help to reduce knee injury rates.

The overhead nature of volleyball can result in overuse shoulder injuries including rotator cuff tendinosis, shoulder impingement syndrome, labral tears, and glenohumeral instability. Players may want to limit the number of overhead spikes and serves they perform, similar to pitch count limits in baseball, to help reduce the risk of overuse injuries. Finger injuries seen in both basketball and volleyball participants include sprains, dislocations, and fractures.

Eye injuries, although rare, can be reduced by wearing protective eyewear. Facial injuries occur more frequently in male players and typically result from an elbow or hand hitting the opponent's face during rebounding or defending. Head injury can occur in both sports, and in volleyball they can occur when the player makes contact with the net pole. Protective padding of volleyball net poles is required by U.S. volleyball standards.

Tennis

Injury rates in high-level youth tennis players are higher than in adults. Tennis injuries occur twice as often in the lower extremity as in the upper extremity. Lower extremity injuries tend to be more acute while upper extremity and trunk injuries tend to be more chronic, and the incidence of overuse injury is high. Overall injury rates are similar for boys and girls. However, male players aged 5-10 yr were more likely to sustain injuries to the head and neck and suffer injuries due to contact with the net, ball, or racket than other groups.

The most common injury in tennis players is to the ankle, although the knee and thigh are vulnerable as well. Lower extremity injuries are related to the frequent directional changes, creating significant concentric and eccentric loads. Overuse injuries include iliopsoas tendonitis or bursitis, patellofemoral stress syndrome, patellar tendinosis, Osgood-Schlatter disease, medial gastrocnemius strain (“**tennis leg”**), Achilles tendonitis, and Sever's disease. Stress fractures in the lower extremity in elite players are most common at the tarsal navicular, metatarsals, and tibia.

In the upper extremities, **tennis elbow** (lateral epicondylosis with extensor carpi radialis brevis tendinosis) and **extensor carpi ulnaris (ECU) tendinosis** with or without subluxation, are particularly prevalent in the recreational player and are thought to be most likely related to overuse and improper technique (see Fig. 707.10). With repetitive overload of the wrist flexor–pronator muscle groups, traction apophysitis at the medial humeral epicondyle and medial epicondylar fragmentation of the humerus, especially in younger boys, can occur. This can secondarily involve the ulnar collateral ligament and ulnar nerve. Shoulder pain often results from **labral injury** , a common site of injury for overhead athletes. Anteroposterior glenohumeral instability, glenohumeral internal rotation deficit with impingement, rotator cuff strain, and scapular dyskinesis are all possible. Wrist problems include an enlarged dorsal ganglion cyst, radiocarpal joint capsular impingement or synovitis, chronic degenerative tears of the triangular fibrocartilage complex, and acute fracture of the hook of the hamate. Stress fractures may occur in the metacarpals (2nd metacarpal in particular) and less commonly in the humerus, ulna, and radius.

It has been hypothesized that repeated loading during service, particularly using a “topspin” serve at a young age, may contribute to the development of **spondylolysis** (**pars interarticularis fracture**) or spondylolisthesis. However, the most common back injury in tennis is lumbar muscle strain.

The risk of injury is increased with increased training duration and intensity. The volume of play is positively correlated with increased injury rate. Various tennis racket grip mechanics may impact the type of wrist injury. The literature is mixed on the effect of court surface and racquet properties. Recent efforts by the U.S. Tennis Association, such as shrinking the court size and using slower tennis balls for players under 10 yr of age, have been trialed in an attempt to reduce injury rates.

Lacrosse

Lacrosse is one of the fastest growing sports for both male and female youth, high school and college level athletes. Protective equipment and rules are different for male and female players. Required equipment for male players includes mouth guard, helmet, gloves, and elbow and shoulder pads. Required equipment for female players includes eye wear and mouth guard. In youth boys’ games, checking is not permitted, and in girls’/women's games, no intentional contact to the head or body is allowed. The sticks also differ for male and female athletes with a shallower pocket for the female athlete.

Injury rates are nearly 3 times higher in competition than in practice. The most common injuries for all players include lower extremity injuries, primarily ankle and knee sprains, and head injuries. **Ankle sprains** typically occur in the setting of cutting, dodging, and twisting activities. The likelihood of subsequent injury may be reduced with bracing. **ACL tears** are a common knee injury and typically occur in noncontact cutting or pivoting. Prepractice training should include balance, lower extremity strengthening, and neuromuscular feedback activities, as these have been proven to help reduce the ACL injury rate. Injury type and rate may vary by position played; therefore position-specific drills and training should be incorporated into preseason and prepractice training.

Head injury occurs in both male and female players. The head injury rate in male players is second to that of football players. Player to player contact is the typical mechanism for head injury in male players. Incidental contact with the stick is the typical mechanism for head injury in female players. Eye wear for female athletes has been shown to reduce the risk of significant eye injury.

Upper extremity injuries include **acromioclavicular sprains** and hand and thumb fractures, particularly in young men's games given permitted contact and **checking** . Shoulder and elbow injuries are typically secondary to contact injury rather than the throwing mechanism, as the throwing motion incorporates the core and pelvis more than the shoulder and elbow.

As with any sport with significant protective equipment that impedes heat loss, heat illness can occur. Players and coaches should be mindful of hydration, temperature, humidity, and duration of play. Commotio cordis is a rare but possible risk. The use of chest protectors has been evaluated and has not been shown to reduce risk.

Swimming/Diving

In competitive swimming, injuries to the shoulder are most common and are generally a result of chronic overuse. **Swimmer's shoulder** is a general term for shoulder overuse in a swimmer and is typically a combination of subacromial impingement/bursitis and tendinosis of the rotator cuff and long-head of the bicep tendon. Commonly, a narrowed subacromial space, **increased laxity** of the shoulder capsule and relative weakness of the scapular stabilizers result in protracted shoulder posture, which contributes over time to the insidious onset of shoulder pain and possible **scapulohumeral dyskinesis** . Freestyle, back, and butterfly strokes tend to exacerbate the pain. Prevention includes monitoring training load, proper technique, and strengthening exercises. The multiaxial instability of the glenohumeral joint common in swimmers is addressed with rehabilitation focusing on strengthening of the rotator cuff and scapular stabilizer musculature. Differential diagnosis for shoulder region pain should also include 1st rib fracture, which may be seen on rib x-ray.

Knee and hip/groin pain can be exacerbated with breaststroke given the whip kick motion required in this stroke.

Swimmer's ear , or **otitis externa** , presents with pain and often drainage from the external auditory canal. It is caused by bacterial, or less commonly, fungal infection of the external auditory canal due to chronic, excessive wetness (see Chapter 657).

Diving is a sport that many athletes start at a young age with early sport-specific specialized training given the skill required for high-level performance and competition. The most common injury for divers is shoulder strain, given overhead activity and the significant force taken by the shoulder, which is dependent on the angle of entry into the water. Low back pain can be seen in divers, and may be associated with lumbar hyperextension, which is used to compensate for limited shoulder flexibility when entering the water. Compared with football, diving has the second highest percentage of **cervical spine injury** secondary to axial loading.

Soccer

Soccer enjoys a very high level of popularity and participation among youth worldwide. In the United States, the annual rate of injury in soccer more than doubled between 1990 and 2014, and almost 3 million children were seen in U.S. emergency departments for injuries related to soccer during those years. Mechanisms of injury include body-to-body contact, falls, or ball-to-body contact. While lower extremity injuries are by far most common, younger children are more likely to injure an upper extremity, and upper extremity injuries are most likely to be fractures. Torso and significant abdominal injuries can occur. Low back symptoms are relatively less common and are most often muscular in nature.

Injuries in youth soccer occur predominately in the lower extremity and include joint and ligament injuries, abrasions, contusions, muscle strains, and fractures of the ankle, knee, and thigh. Ligamentous injuries to the **ACL** and

MCL at the knee and the **anterior talofibular ligament (ATFL)** at the ankle occur because of the cutting and pivoting maneuvers required during play. ACL injuries, particularly in girls, have gained attention in recent years. ACL injuries are more common in high school girls' soccer than in other girls' sports. Risk factors may include genetics, hormones, age, gender, previous injury, and anthropomorphic factors. **Overuse syndromes** such as patellofemoral dysfunction, Osgood-Schlatter, Sinding-Larsen-Johansson and Sever's disease frequently occur. Hip problems include the **hip pointer** (**iliac crest contusion**), iliac crest apophysitis, and chronic groin pain (muscle strain, **sports hernia** , **osteitis pubis**). The term "sportsman's hernia," "inguinal insufficiency," and "conjoint tendon tear" may comprise a constellation of different pathologic processes producing similar groin pain. These injuries may occur with the combined forceful rotation of the torso and kicking motion. Femoral neck stress fractures, slipped femoral capital epiphysis, and avulsion fractures of the pelvis or femur should also be considered in the differential despite being uncommon. Neuromuscular factors, such as quadriceps and leg dominance, muscle activation patterns and dynamic stability, may be modifiable, thus the American Academy of Pediatrics (AAP), and other organizations support neuromuscular training programs aimed at risk reduction for both genders. Shoes and playing surfaces may influence injury risk; however, more study is required.

Concussion is common in soccer because of contact between players, player and goal post, player and ground, and possibly player and ball (**headers**). As of January 2016, the U.S. Soccer Concussion Initiative updated recommendations to reduce head injury risk in youth soccer players to include a ban on heading the ball for ages 10 and under, and for limited heading of the ball for 11-13 yr olds. There is interest in headbands and other head gear to decrease concussion risk; however, more study is needed.

Ice Hockey

Ice hockey is a fast-paced, collision sport associated with injuries caused by contact from other players, the ice, or the boards, as well as from the puck or stick. With injury rates similar to other boys' high school full-contact sports, concussions, contusions, fractures, ligament sprains, muscle strains, lacerations, joint separations, dislocations, and subluxations are commonly reported. Injuries are more likely to occur in competition than in practice, and overall injury rates appear to be on the rise, possibly related to increased participation.

Concussion was the most commonly reported injury in U.S. high school ice hockey athletes between 2008 and 2013 with head and face injuries accounting for 34% of all of the reported injuries. Injuries to the shoulder and arm are also common and include contusions, strains, **acromioclavicular separations** , and **clavicle fractures** . Over 50% of upper extremity fractures occur in the forearm, wrist, and hand. Other specific hockey injuries include hip pain secondary to **femoroacetabular impingement (FAI)** , high ankle sprains, hip adductor strain, and osteitis pubis. In a 16-yr study of youth hockey players who presented to a level 1 trauma center, about one third of the patients seen in the emergency department were admitted to the hospital, and almost half of those required a minor or major procedure. Brain injury, fractures, and blunt abdominal trauma accounted for the majority of the admissions.

The role of factors, such as of age, size, level of skill, player position, and gender, in injury risk is inconclusive, although recent articles suggest that concussion may be more frequent in girls and fractures more common in boys.

Body checking is the single most common mechanism of injury. In Canada, 11- and 12-yr old Pee Wee hockey players who were allowed to body check had a 3-fold greater risk of injury than those who were not. In 2011, the USA Hockey rules of play disallowed body checking in the 12-yr and under boys' leagues. Body checking is not allowed in girls' leagues of any age. With wide support, in 2014, the AAP published a policy statement recommending the expansion of nonchecking programs and the restriction of body checking to elite levels of boys play after 15 yr of age. AAP recommendations also include the use of protective equipment (helmets and full-face shields), rules to eliminate dangerous play with a zero-tolerance policy for head contact and body contact from behind, and safer play education for coaches and athletes.

Field Hockey

Field hockey is played worldwide by both male and female athletes. Protective equipment, including mouth, shin, and ankle guards, is recommended but not required. Players are twice as likely to be injured in game versus practice. Lower limb injures are the most common with inversion ankle sprain being the most common. Bracing may help with ankle re-injury rates. Other lower extremity injuries include hamstring strain, ACL tears, and contusions. The most common upper limb injury occurs when the hand is struck by a stick or a ball, as field hockey does not require the use of padded gloves for protection. Head injury and facial lacerations occur at a very high rate and are typically caused by contact with the stick or ball. Given the crouched position of the sport, back pain would seem to be common; however, there is little evidence to support this assertion. Injury types and rates may differ based on the position played; however, specific data are lacking.

Injury prevention is important in this sport and can be attained via the use of protective equipment, including permitted head or face protection, and sport-specific training including balance, strengthening, and proprioceptive training activities.

Skiing and Snowboarding

Injury frequency in skiing, snowboarding, and related winter sports has declined over the past several decades, largely secondary to improved equipment (boots, bindings, poles) and slope conditions. Of concern, however, is that **severe head** and **spinal cord injuries** are on the rise due to increased speed and the addition of acrobatic maneuvers (terrain parks, half pipes, aerial tricks). Head and neck injuries are the primary cause of fatal injury. Of the World Cup events, freestyle skiers (particularly aerials and slope style) have a higher incidence of head injury than snowboard and alpine events, although snowboard cross is also particularly risky. Overall, the risk of injury is higher in snowboarders, males, beginners, fatigued athletes, and those with improper equipment.

Lower extremity injuries are more commonly associated with skiing, while head, internal organ, upper extremity, and ankle injuries are more common in snowboarders. The most common lower extremity injury in skiing is ligamentous (**ACL** , **MCL,** and **LCL**) at the knee. Lower-extremity injuries in skiers also include contusions, knee dislocation, femur fractures, spiral fractures of the tibia **(“boot top” fractures),** and high ankle sprains. In snowboarders, femur and tibia/fibula fractures are seen.

Upper-extremity injuries are more common in snowboarding because both of the snowboarder's feet are strapped onto the same board and, without poles, there is an increased risk of falls on outstretched arms. Common injuries include distal radial, ulnar, and metacarpal fractures, sprains, and contusions. Other high incidence upper extremity injuries in snowboarding include shoulder soft tissue injuries, clavicle fractures, acromioclavicular sprains, and glenohumeral joint dislocations. A unique skiing injury is **skier's thumb** , a sprain of the ulnar collateral ligament of the thumb which typically results from a fall with the thumb in abduction and hyperextension around a ski pole. Phalanx fractures and bony avulsions can also be associated with this injury.

Snow sport athletes may experience visceral injuries to the spleen, liver, and kidney. Spine injuries including fracture and strain may also occur.

It is strongly advised that individuals of all ages wear helmets for skiing and snowboarding. Wrist protectors are also recommended for snowboarders. Care should be taken to ensure up to date and properly fitted and adjusted equipment. Preventative measures endorsed by the AAP include participation in formal instruction, such as in a ski school, having adequate supervision, and exercising responsible speed and technique. Cardiovascular fitness, endurance, and muscle strength are believed to be critical components in injury prevention; however, there is limited supportive literature.

Skateboarding

Injuries associated with skateboarding are predominantly acute, including contusions, lacerations, sprains, and fractures, affecting the wrists, forearms, and to a lesser extent, the ankles and head. Fractures involving the upper extremities are more common in younger skateboarders, often from a *fall onto an outstretched arm*. Lower-extremity fractures and head injuries predominate in the adolescent population, which is likely because of higher complexity of the airborne maneuvers and tricks often attempted. Loss of balance leading to a fall when failing to perform a particular maneuver, especially when catching a wheel, is generally the primary cause of injury. These falls can occur at high velocities, with speeds up to 40 mph documented in the literature, placing the skateboarder at risk for serious injuries.

Traumatic brain injuries are not uncommon within this sport; the incidence increases with age and is more common in males than females. In older children and adolescents, the neglected use of helmets and the increased speed of their skating contribute to this fact.

In addition to helmet use, other safety measures recommended include wrist guards as well as **elbow and knee pads** . The building of skateboard parks has been a recent strategy to remove skateboarders from pedestrians, bicyclists, and motor vehicle traffic, while also encouraging adult supervision.

Cycling and Motocross

Bicycle riding has been a beloved childhood recreational activity for decades. Cycling options have expanded to include a variety of events such as track and road racing as well as mountain biking, mountain bike terrain parks or “free-riding,” cyclo-cross, and freestyle BMX. As increased speed, jumps, and other man-made obstacles have been added, risk for injury has increased. Motocross, beginning as early as 4 yr of age, adds further complexity as it utilizes 2-wheeled motorized cycles racing through designed outdoor courses.

Recreational bicycling injuries include abrasions, lacerations, contusions, and fractures. Head and face as well as genitourinary injuries are common. However, the literature is limited regarding risk factors and bicycle safety in youth riders. Helmet use is, of course, strongly encouraged. Upper extremity fractures predominate in mountain bikers and mountain terrain park riders. Risk of injury is increased in mountain biking boys between 10 and 14 yr and in those who admit to riding faster than usual. Motocross riders sustain more serious injuries. Hospital admission is not uncommon, and surgery may be required for injuries of head, bone, and **viscera** . Head injuries include skull fractures and a variety of intracranial bleeds even when using a helmet.

Wrestling

Wrestlers have great fluctuations in weight to meet weight-matched competition standards. Such fluctuations are sometimes associated with fasting, dehydration, and then binging. Counseling wrestlers and their parents regarding impaired performance resulting from these components of disordered eating, especially with respect to decreased speed and strength, is important to deter athletes from incorporating them into routine practice.

Wrestling holds apply a variety of torques or forces to the extremities and spine, producing a number of common injuries. Takedown maneuvers and subsequent impact with the mat can produce concussions, neck strain/sprain, or spinal cord injury. **Spondylolysis** (see Chapter 699.6) is a concern in wrestlers given repetitive lumbar extension, which occurs when an athlete is trying to avoid a pin as well as with certain throws/takedown maneuvers.

Stingers and **burners** —also seen among football players—are caused by stretching or pinching of the brachial plexus (see Chapter 709). Overall, the two most common sites of injury in wrestling are the shoulder and knee.

At the shoulder, subluxation is common. This generally occurs anteriorly with the shoulder forcibly abducted and extended. Patients are commonly aware of their shoulder slipping in and out. Injuries to the hand are less common and typically include metacarpophalangeal and proximal interphalangeal joint sprains.

Knee injuries (see Chapter 707.6) are also common, and include **prepatellar bursitis** , medial and lateral collateral ligament sprains, and medial and lateral meniscus tears. Acute or recurrent traumatic impact to the mat can result in prepatellar bursitis. If the overlying skin is broken, septic bursitis must be considered.

Dermatologic problems associated with wrestling include herpes simplex (see Chapter 279 : **herpes gladiatorum**), impetigo (see Chapter 685.1), staphylococcal furunculosis or folliculitis, superficial fungal infections, and contact dermatitis. Herpes gladiatorum and impetigo are contraindications to wrestling until the lesions have resolved. Washing of the wrestling mats with appropriate antibacterial and antifungal solution is required after daily wrestling sessions to keep the mats disinfected and to prevent the spread of dermatologic contagion.

Auricular hematoma is caused by friction or direct trauma to the auricle (see Chapter 661). If allowed to remain without evacuation, irreversible deformity of the auricle often results, termed cauliflower ear. Properly fitted headgear is the best means of prevention.

Running

Running for sport and exercise has increased in popularity for children and adolescents. Running problems are typically caused by overuse injury related to muscle imbalance; a minor skeletal deformity; repetitive overload; and/or poor flexibility, strength, endurance, or proprioception. With each step while running, the foot impact ranges from 3 to 8 times the athlete's body weight**.** Errors in training, including increasing the distance or intensity of workouts too rapidly, often result in injury to the runner. Minor variations (e.g., malalignment) in anatomy that do not cause problems at rest can predispose to injury at specific sites, such as **over-pronation** contributing to increased **patellofemoral stress** . Muscle fatigue, environmental temperature (see Chapter 710), and running surface (grass vs. unyielding concrete) also contribute to injury. **Barefoot** or **minimalist running** style or shoes involves greater weight distribution through the forefoot during running, and biomechanical research suggests reduced joint forces through the knee and hip. However, increased forces can occur through the foot, ankle, and lower leg in individuals not accustomed to this style of running. Prevention of injuries is possible by muscle-strengthening exercises, incorporating periods of rest into training plans, and the use of good-quality running shoes that match an athlete's foot type. Those who significantly over-pronate may benefit from a motion control shoe for maximal rear foot and arch support. Those who mildly over-pronate may want to utilize a stability shoe that combines extra support in the medial midsole with midsole cushion. Those who supinate excessively could consider a neutral, cushioned shoe with increased shock absorption in the midsole and less arch support.

“**Shin splints,** ” or **medial tibial stress syndrome** , is a descriptive term for pain located diffusely over the distal medial tibia and should be distinguished from tibia stress fracture and chronic exertional compartment syndrome. Medial tibial stress syndrome is a periosteal stress reaction at the insertion of the strong leg muscles. It can be seen in new runners with over-pronation, runners that have markedly increased their training duration in a short period of time, and runners with higher body mass indices (BMIs). Continued loading and stress of medial tibial stress syndrome can lead to a **stress fracture** . Stress fractures of all bones of the lower extremities can occur in runners (see Chapter 703.4) and have been documented at the femoral neck, inferior pubic rami, subtrochanteric area, proximal femoral shaft, proximal tibia, fibula, calcaneus, tarsal navicular, metatarsals, and sesamoids. The most common are in the metatarsals, tibia, and fibula. The anterior proximal tibia, femoral neck (tension or superior-side), tarsal navicular, and sesamoids are most at risk for nonunion.

Muscle strains most frequently affect the hamstrings, followed by the quadriceps, hip adductors, soleus, and gastrocnemius muscles. Lower extremity tendon injuries are more common than apophyseal injuries in young, skeletally immature runners. Tendon injury is most common in the Achilles tendon, followed by the posterior tibial, peroneal, iliopsoas, and proximal hamstring tendons. Achilles tendinosis should be distinguished from retrocalcaneal bursitis.

Knee pain in the runner is frequently anterior in location and is commonly caused by **patellofemoral pain syndrome (runner's knee**), which results from excessive dynamic, usually lateral, motion of the patella in relationship to the femoral intracondylar groove (see Chapter 707.6). The athlete's body habitus (i.e., increased Q-angle, over-pronation) and presence of core and hip abductor weakness may contribute to this overuse injury. Posterior knee pain can be caused by gastrocnemius strain, while posteromedial pain may be caused by proximal tibial stress fracture or semimembranosus/semitendinosus tendinosis.

Lateral knee pain is commonly caused by **iliotibial band syndrome** and less so by **popliteal tendinosis** , which may be precipitated by running downhill. Iliotibial band syndrome may combine both a component of bursitis and tendinosis owing to mechanical friction of the iliotibial band (an extension of the tensor fasciae latae) over the lateral femoral epicondyle. Vague knee pain that worsens with activity or traumatic event should raise suspicion for **osteochondritis dissecans** (OCD) of the lateral aspect of the medial femoral condyle.

Chronic exertional compartment syndrome can involve any of the muscle compartments but the most common is the anterior compartment. There is typically poorly localized throbbing pain that begins 10-15 min into a run. Pain typically prevents further training, thus limiting the risk of nerve injury (see Chapter 707.7).

Plantar fasciitis is an inflammation of the supporting structures of the longitudinal arch of the foot, due to repetitive cyclic loading with foot strike. Pain is typically worst with the first step out of bed in the morning and with running, and is located on the medial aspect of the heel. Pes planus and over pronation are common in these patients. Calcaneal stress fracture should be considered, especially in the amenorrheic distance runner (see Chapter 711).

The **female athlete triad** , referring to abnormalities in energy availability, menstrual function, and bone health, is well documented in adolescent running literature and is an important education topic for the runner, parents, and coaches (see Chapter 711). Poor bone health, specifically impaired bone mineral development, has been seen in the male runner as well.

Cheerleading

Like other sports, cheerleading has become increasingly popular and evolved to become more competitive and athletic. Cheerleading can begin as early as 3-6 yr of age and includes skill levels ranging from recreational to sideline, competition to professional. The sport includes advanced gymnastic tumbling and “stunts” involving athletes lifting and throwing other athletes overhead. This requires repetitive flexion, hyperextension and rotation of the spine as well as compressive loading on landings, and the risk of athlete contact and falls.

Stunting injuries account for the majority of injuries, with bases (the athletes who lift, throw, and catch another athlete) at higher risk of injury than fliers (athletes who are lifted and thrown). The primary mechanism of injury is contact with another athlete. Injuries sustained in tumbling are the second most common.

The overall injury rate in cheerleading is lower than in all other girls' sports combined. However, injuries may be more severe. Of girls' sports, the risk of catastrophic injury is the highest in cheerleading. Following a period of increasing incidence of injury, it appears that injury rates have stabilized.

Head and facial injury accounts for almost one third of injuries sustained. Head trauma primarily results from falls while stunting or from a pyramid formation, which includes the base cheerleaders as well. Following concussion, strains and sprains comprise the most likely injuries, with ankle the most common site followed by wrist and trunk. Fractures are more likely to occur in the upper extremity. Overuse injuries are common.

In 2012, the AAP published a position statement regarding recommendations for the prevention of injury in cheerleading. Strategies to reduce the risk of injury include designating cheerleading as an official sport, ensuring athletes undergo preparticipation exams, participating in conditioning and strength training, utilizing proper lifting technique, avoiding stunting over hard surfaces, and that coaches and trainers be consistently educated about sport safety, including specific rules for the execution of technical skills. The American Association of Cheerleading Coaches and Administrators and others have also set up rules to limit the type of stunts performed, and the National Federation of State High School Associations annually updates rules for spirit events with the intent of improving cheerleading safety.

Gymnastics

Typically, males and females begin gymnastics participation at 4-5 yr of age. The highest level of competition is in the mid-teens followed by retirement, often by 20 yr of age for females and mid-20s for males. Both acute and chronic injuries, with a high incidence of overuse-related injuries, are seen in gymnasts, and commonly involve the wrists, shoulders, ankles, and back. Injury types and rates in the acrobatic and circus arts were similar to those seen in traditional gymnastics.

The injury rate is similar in male versus female gymnasts. Lower-extremity injuries are more common in female gymnasts, whereas upper body injuries occur with higher frequency in male gymnasts. Apparatus competed upon accounts for this discrepancy, such as the horizontal bar and ring exercises for male gymnasts, which place a great deal of stress upon the shoulders, and floor exercise, vault, and balance beam for female gymnasts, stressing the feet and ankles. In addition to mechanical or traumatic injuries, female gymnastics may have delayed menarche and can be at risk for hypothalamic amenorrhea or oligomenorrhea, as well as low body weight for height, which is related to disordered eating. Despite the presence of these two components of the **female athlete triad** (see Chapter 711), the third component, reduced bone density or osteoporosis, is not commonly seen. In fact, bone density tends to be high in most gymnasts, which is thought to be secondary to their performance involving repetitive high-impact activities. Nevertheless, **stress fractures** , in both the upper and lower extremities, are a significant problem. The short stature associated with male and female gymnasts is probably caused by selection bias and not the result of gymnastics training.

The amount of weight bearing through the upper extremities in gymnastics can contribute to the development of both traumatic and overuse injuries. During upper extremity weight bearing, the wrist, particularly over the radial physis, is subjected to a force almost twice the athlete's body weight and up to 16 times the body weight during high impact loading activities. This, along with repetitive motion, axial compression, and torsional forces, contributes to the increasing frequency of wrist pain and injury in gymnastics and acrobatics. Wrist pain and injury is also correlated with training intensity, based on skill level and number of hours of training per week. Wrist injuries typically seen include **distal radial epiphysitis** (**gymnast's wrist**), triangular fibrocartilage complex tears, scaphoid fractures, **scapholunate dissociation** , dorsal ganglion cysts, and wrist sprains (see Chapter 701). Individualized training regimens, including gradual increase in training load and reduced training during growth spurts, as well as the use of wrist orthoses, should be considered for these athletes.

Ankle sprain remains the most common injury in gymnastics, secondary to forces seen in landing and dismounting. Ankle sprains that have not responded to conservative management should be further evaluated for osteochondral defects (OCD) of the talar dome. Heel pain may be secondary to plantar fasciitis, Sever's disease, or calcaneal stress fracture. Patellar tendinopathy may contribute to knee pain in a gymnast.

Spine injuries are notable for a high incidence of **spondylolysis** , a stress fracture of the pars interarticularis, and, in less frequent cases, spondylolisthesis, both related to repetitive extension loading of spine (see Chapter 699.6). Other potential sources of back pain in a gymnast include intervertebral disc pathology,

Scheuermann's disease (juvenile kyphosis) (see Chapter 699.4), and mechanical back pain secondary to biomechanical imbalances.

Dance

Dance, including ballet, modern, dance or drill line, is a highly demanding activity that may be associated with delayed menarche in females and *disordered eating* in both female and male dancers (see Chapter 711). Acute injuries commonly involve the lower extremities. Overuse injuries are common, due to the repetitive nature of maneuvers incorporated into training and performance, and occur at the same rate in amateur male and female dancers. Injuries seen in modern/contemporary dance are similar in type and incidence as those seen in traditional ballet.

Frequently, kinetic chain dysfunction contributes to injury and should be considered when evaluating the dancer. Common mistakes in technique can cause injury, such as forcing excessive “turnout” (external rotation at the hip) in ballet resulting in undue stress placed upon the hip and knees (see Chapter 707.6).

Foot problems are common and include metatarsal stress fractures, subungual hematomas, **sesamoiditis** , **tenosynovitis (especially of the FDL)** , plantar fasciitis, Achilles tendinitis, retrocalcaneal bursitis, calluses, and bunions (see Chapter 707.7). A **dancer's fracture** is an avulsion fracture of the distal shaft of the 5th metatarsal. Beware of delayed healing as a result of the tenuous blood supply in the area, which may necessitate surgical fixation. Common ankle injuries and pain include acute sprains, anterior and posterior impingement syndromes, and OCD of the talus. Soft tissue impingement between the lateral malleolus and talus can cause persistent pain after an inversion injury. Medial tibial stress syndrome (“shin splints”) and tibial stress fractures are noted in the lower leg. A nonrehabilitated ankle sprain may cause favoring of the affected leg, leading to development of a stress fracture of the contralateral tibia. Achilles tendinopathy is seen due to the demands of running and jumping. Patellar malalignment or hypermobility can result in patellofemoral pain syndrome or, less frequently, patellar subluxation/dislocation. Patellar tendinopathy is widely reported. **Internal snapping hip syndrome** , caused by the iliopsoas tendon riding over the anterior hip capsule and iliopectineal eminence, and hip flexor (rectus femoris and iliopsoas) tendinosis are commonly noted in traditional ballet. Gluteal region pain with sciatica may be a result of piriformis syndrome, which occurs because of the repetitive external hip rotation required in ballet (see Chapter 707.5).

The proper time to allow a ballet dancer to go en pointe is a common question asked by dancers and parents alike. An average age to go en pointe is 12 yr. A functional test should be part of that decision: if the young dancer is able to perform a passé steadily away from the barre and maintain an en pointe position without pain or instability, the dancer is likely ready to begin dancing en pointe. **Posterior impingement syndrome** of the ankle can be seen with dancing en pointe, given compression between bony or soft tissue structures during terminal plantarflexion. An **os trigonum** is commonly the cause of bony-related posterior impingement syndrome.

Adaptive Sports

Participation in sports and recreational activities helps to minimize deconditioning; improve strength, endurance and cardiopulmonary fitness; and promote companionship, sense of achievement, and self-esteem. Participation can also support the development of the child's motor coordination and adjustment to physical limitations. However, children with disabilities tend to participate less in physical activity for myriad reasons, including lack of access to activities or opportunities for participation, lack of self-confidence, and fear of injury by the child, parent, or physician. Because of this, children with disabilities are at risk of becoming obese, having poor cardiopulmonary endurance, and having lower self-esteem and greater dependence on others for daily living. Conversations between pediatricians, parents, and the child, regarding health status, safety precautions, interests, and available programs are crucial to encouraging participation and determining the appropriate sports or activities to pursue. Direction into appropriate sports/physical activity rather than excluding them, should be guided by the child's physical or mental challenge, physical exam, including components of pre-participation exam, and consideration of the American Academy of Orthopedic Surgeons “participation possibility chart,” which outlines recommended sports and recreation based on physical disability.

Fear of injury remains a barrier to participation for many; however, the risk of injury for an **adaptive sport** athlete is no greater than for an athlete without disability. Injuries in the adaptive sport athlete are influenced by the specific disability, equipment used, and prosthetic or orthotics worn. Acute soft tissue injuries, including skin abrasions, contusions, sprains, and strains, tend to be the most common injuries; fractures and dislocations tend to be uncommon, given the lower participation in contact sports. Just as in athletes without disability, **overuse injuries** commonly occur in this athlete population. Lower limb injuries are more common in athletes with amputations or cerebral palsy, and upper limb injuries are more common in spinal cord injury and wheelchair-based athletes. Appropriate training to support muscle balance and avoid muscle imbalance, as well as the management of **spasticity** and properly fitting prosthetics and orthotics can help to reduce the risk of overuse injuries. Pressure sores are common in wheelchair-based athletes and can be avoided with vigilant skin care and monitoring, and weight shifting.

Consideration of the athlete's disability and medications is essential, as they may have increased propensity for abnormalities in, for example, thermoregulation, resulting in **heat illness,** and fluid and electrolyte derangements. This should be discussed and monitored with the athlete, parents, athletic trainers, and coaches, as appropriate.

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SECTION 3

The Skeletal Dysplasias

OUTLINE

Chapter 714 General Considerations in Skeletal Dysplasias
Chapter 715 Disorders Involving Cartilage Matrix Proteins
Chapter 716 Disorders Involving Transmembrane Receptors
Chapter 717 Disorders Involving Ion Transporters
Chapter 718 Disorders Involving Transcription Factors
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CHAPTER 714

General Considerations in Skeletal Dysplasias

Julie E. Hoover-Fong, William A. Horton, Jacqueline T. Hecht

Genetic skeletal disorders can be classified into four major categories: chondroosteodysplasias, metabolic bone conditions, dysostoses, and other skeletal malformations. The chondroosteodysplasias, also known as skeletal dysplasias or bone dysplasias, are a genetically and clinically heterogeneous group of disorders with an estimated prevalence of 1 in 4,000 births. The chondroosteodysplasias can be divided into the chondrodysplasias and osteodysplasias. The former includes genetic disorders of cartilage and results in deficient linear growth, typified by achondroplasia. The osteodysplasias are marked by abnormal bone structure with a classic example of osteogenesis imperfecta (see Chapter 721). The clinical picture of the chondroosteodysplasias is dominated by generalized skeletal abnormalities with frequent involvement of nonskeletal tissues. The disorders range in severity from lethal in utero to such mild features as to go undetected. Metabolic bone conditions, such as rickets or hypophosphatasia, are due to abnormal bone mineralization while the dysostoses affect a single bone (e.g., craniosynostosis). Many complex genetic syndromes include skeletal malformations as part of the overall phenotype.

The chondrodysplasias are distinguished from other forms of short stature by a disproportionality of skeletal manifestations. There are two basic categories of skeletal dysplasias: those with predominantly short limbs versus short trunks. Fig. 714.1 notes the importance of cartilage in bone formation. Efforts to define the extent of clinical heterogeneity resulted in the delineation of well over 200 distinct entities (Table 714.1). Many of these disorders result from mutations of a relatively small group of genes, the *chondrodysplasia genes* . The better-defined chondrodysplasia groups, such as the achondroplasia and type II collagenopathy groups, contain graded series of disorders that range from very severe to very mild. This spectrum of severity is increasingly being appreciated for other skeletal dysplasia groups as more mutations have been discovered and the range of clinical phenotypes associated with mutations within a given gene have been defined. These disorders are clinical phenotypes distributed along spectra of phenotypic abnormality associated with mutations of particular genes. For mutations of some genes, such as *COL2A1*, the distribution is fairly continuous, with clinical phenotypes merging into one another across a broad range. There is much less clinical overlap for mutations of some other genes, such as *FGFR3*, in which the distribution is discontinuous. Because most clinicians and most reference materials refer to the disorders as distinct entities, this vernacular continues to be used.

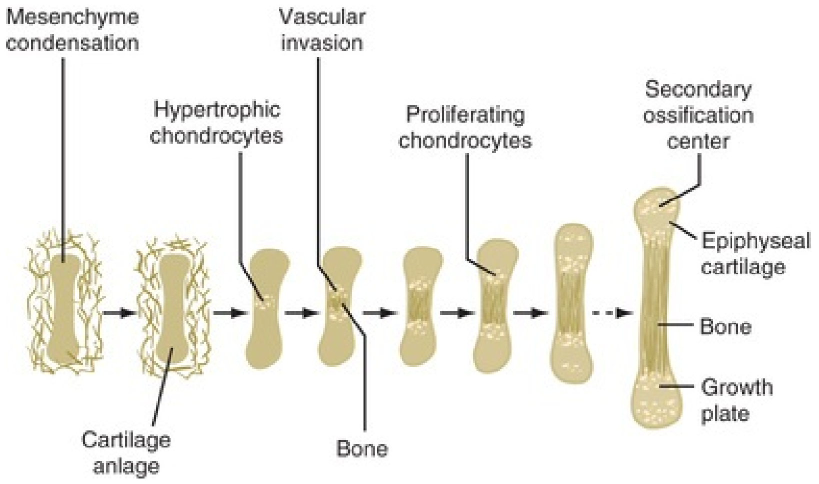
Mesenchyme condensation
Vascular invasion
Hypertrophic chondrocytes
Proliferating chondrocytes
Secondary ossification center
Epiphyseal cartilage
Bone
Growth plate
Cartilage anlage
Bone

FIG. 714.1 **The importance of cartilage in bone formation. (From Horton WA: Skeletal development: Insights from targeting the mouse genome. *Lancet* 362:560, 2005.)**

Table 714.1

Genetics of Skeletal Dysplasias

GENE LOCUS	CHROMOSOME LOCATION	PROTEIN	PROTEIN FUNCTION	CLINICAL PHENOTYPE	MIM	DISE MEC
COL2A1	12q13.1-q13.3	Type II collagen α_1 chain	Cartilage matrix protein	Achondrogenesis II	200610	Domi
				Hypochondrogenesis	200610	Domi
				SED congenital	183900	Domi
				Kniest dysplasia	156550	Domi
				Late-onset SED		Domi
				Stickler dysplasia	108300	Haplc
ACG1	15q26.1	Aggrecan	Cartilage	SED Kimberley	608361	Haplc

			matrix protein	SEMD Aggrecan type	612813	Domi
SEDL	Xp22.2-p22.1	Sedlin	Intracellular transporter	X-linked SED tarda	313400	Loss
COL11A1	1p21	Type XI collagen α_1 chain	Cartilage matrix protein	OSMEDA	184840	Domi
COL11A2	6p21.3	Type XI collagen α_2 chain	Cartilage matrix protein	OSMEDB	215150	Loss
COMP	19p12-p13.1	Cartilage oligomeric matrix protein	Cartilage matrix protein	Pseudoachondroplasia	177170	Domi
				MED	600969	Domi
COL9A2	1p32.2-p33	Type IX collagen α_2 chain	Cartilage matrix protein	MED	600969	Domi
COL9A3	20q13.3	Type IX collagen α_3 chain	Cartilage matrix protein	MED	600969	Domi
MATN3	2p24-p23	Matrilin 3	Cartilage matrix protein	MED	600969	Domi
COL10A1	6q21-q22.3	Type X collagen α_1 chain	Hypertrophic cartilage matrix protein	Schmid metaphyseal chondrodysplasia	156500	Haplo
FGFR3	4p16.3	FGF receptor 3	Tyrosine kinase receptor for FGFs	Thanatophoric dysplasia I	187600	Gain
				Thanatophoric dysplasia II	187601	Gain
				Achondroplasia	100800	Gain
				Hypochondroplasia	146000	Gain
PTHR1	3p21-p22	PTHrP receptor	G protein-coupled receptor for PTH and PTHrP	Jansen metaphyseal chondrodysplasia	156400	Gain
DTDST	5q32-q33	DTD sulfate transporter	Transmembrane sulfate transporter	Achondrogenesis 1B	600972	Loss
				Atelosteogenesis II	256050	Loss
				Diastrophic dysplasia	222600	Loss
SOX9	17q24.3-q25.1	SRY box 9	Transcription factor	Campomelic dysplasia	114290	Haplo
RUNX2 [†]	6p21	Runt-related transcription factor 2	Transcription factor	Cleidocranial dysplasia	119600	Haplo
LMX1B	9q34.1		Transcription factor	Nail-patella dysplasia	161200	Haplo
CTSK	1q21	Cathepsin K	Enzyme	Pyknodysostosis	265800	Loss
RMPR	9p21-p12	Mitochondrial RNA-processing endoribonuclease	RNA-processing enzyme	CHH	250250	Loss
DYNC2H1	11q13.5	Dynein, cytoplasmic 2, heavy chain 1	Cytoplasmic cilia-related protein	ATD	208500	Loss
				SRPIII	613091	Loss
TRPV4	12q24.1-12q24.2	Calcium-permeable TRP ion channel	Transmembrane channel protein	Brachyolmia type 3	113500	Gain
				SMDK	1842522	Gain
				Metatropic dysplasia	156530	Gain

[*] Usually lethal.

[†] Also called CBFA1.

AD, autosomal dominant; SED, spondyloepiphyseal dysplasia; SEMD, spondyloepimetaphyseal dysplasia; AR, autosomal recessive; MED, multiple epiphyseal dysplasia; FGF, fibroblast growth factor; OSMEDA, otospondylomegaepiphyseal dysplasia autosomal dominant; OSMEDB, otospondylomegaepiphyseal dysplasia autosomal recessive; PTHrP, parathyroid hormone-related protein; PTH, parathyroid hormone; DTD, diastrophic dysplasia; SRY, sex-determining region of the Y chromosome; CHH, cartilage-hair hypoplasia; ATD, Jeune asphyxiating thoracic dystrophy; SRPIII, short rib polydactyly syndrome type III; TRPV4, transient receptor potential vanilloid family 4; SMDK, spondyloepimetaphyseal dysplasia Kozlowski type.

Most chondrodysplasias require the analysis of information from the history, physical examination, skeletal radiographs, family history, and laboratory testing to make a diagnosis. The process involves recognizing complex patterns that are characteristic of the different disorders (Tables 714.2 to 714.5). Metaphyseal dysplasias, for example, are characterized by short stature, bowing of the legs, and a waddling gait. Most metaphyseal dysplasias have normal serum levels of calcium and phosphate, alkaline phosphatase activity, and vitamin D metabolites. In addition, subtypes of metaphyseal dysplasias exist and have their own unique features. Metaphyseal chondrodysplasia (**Jansen type,** also see Chapter 716) is typified by cupped and ragged metaphyses, which develop mottled calcification at the distal ends of bone over time (Fig. 714.2). Hypercalcemia can occur. The **Schmid type** of metaphyseal chondrodysplasia is less severe, although the radiographic appearance of the knees and extreme bowing of the lower limbs resemble signs seen in patients with familial hypophosphatemia. It is associated with defects in collagen type X, alpha 1, and the hip abnormalities are more debilitating than in Jansen metaphyseal chondrodysplasia. Patients with both types of metaphyseal chondrodysplasia have lifelong short stature.

Table 714.2

Major Problems Associated With Skeletal Dysplasias

PROBLEM	EXAMPLE
Lethality*	Thanatophoric dysplasia
Associated anomalies †	Ellis-van Creveld syndrome
Short stature	Common to almost all
Cervical spine dislocations	Larsen syndrome
Severe limb bowing	Metaphyseal dysplasia, Schmid type
Spine curvatures	Metatropic dysplasia
Clubfeet	Diastrophic dysplasia
Fractures	Osteogenesis imperfecta
Pneumonias, aspirations	Campomelic dysplasia
Spinal cord compression	Achondroplasia
Joint problems (hips, knees)	Most skeletal dysplasias
Hearing loss	Common (greatest with cleft palate)
Myopia/cataracts	Stickler syndrome

Immunodeficiency [‡]	Cartilage-hair hypoplasia, Schimke immuno-osseous dysplasia
Poor body image	Variable, but common to all
Sex reversal	Campomelic dysplasia

[*] Mostly a result of severely reduced size of thorax.

[†] See Table 714.3 .

[‡] At least 4 additional disorders, all involving the metaphyses, can have immunodeficiency.

Table 714.3

Associated Anomalies in Skeletal Dysplasias

ANOMALY	EXAMPLE
Heart defects	Ellis-van Creveld syndrome, Jeune syndrome
Polydactyly	Short rib polydactyly, Majewski type
Cleft palate	Diastrophic dysplasia
Ear cysts	Diastrophic dysplasia
Spinal cord compression	Achondroplasia
Encephalocele	Dyssegmental dysplasia
Hemivertebrae	Dyssegmental dysplasia
Micrognathia	Campomelic dysplasia
Nail dysplasia	Ellis-van Creveld syndrome
Conical teeth, oligodontia	Ellis-van Creveld syndrome
Multiple oral frenula	Ellis-van Creveld syndrome
Dentinogenesis imperfecta	Osteogenesis imperfecta
Pretibial skin dimples	Campomelic dysplasia
Cataracts, retinal detachment	Stickler syndrome
Intestinal atresia	Saldino-Noonan syndrome
Renal cysts	Saldino-Noonan syndrome
Camptodactyly	Diastrophic dysplasia
Craniosynostosis	Thanatophoric dysplasia
Ichthyosis	Chondrodystrophia punctata
Hitchhiker thumb	Diastrophic dysplasia
Sparse scalp hair	Cartilage-hair hypoplasia
Hypertelorism	Robinow syndrome
Hypoplastic nasal bridge	Acrodysostosis
Clavicular agenesis	Cleidocranial dysplasia
Genital hypoplasia	Robinow syndrome
Tail	Metatropic dysplasia
Omphalocele	Beemer-Langer syndrome
Blue sclera	Osteogenesis imperfecta

Table 714.4

Lethal Neonatal Dwarfism

Usually Fatal[*]

Achondrogenesis (different types)
Thanatophoric dysplasia
Short rib polydactyly (different types)
Homozygous achondroplasia
Campomelic dysplasia
Dyssegmental dysplasia, Silverman-Handmaker type
Osteogenesis imperfecta, type II
Hypophosphatasia (perinatal form)
Chondrodysplasia punctata (rhizomelic form)

Often Fatal

Asphyxiating thoracic dysplasia (Jeune syndrome)

Occasionally Fatal

Ellis-van Creveld syndrome
Diastrophic dysplasia
Metatropic dwarfism
Kniest dysplasia

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[*] A few prolonged survivors have been reported in most of these disorders.

Table 714.5

Usually Nonlethal Dwarfing Conditions Recognizable at Birth or Within 1st Few Mo of Life

Most Common

Achondroplasia
Osteogenesis imperfecta (types I, III, IV)
Spondyloepiphyseal dysplasia congenita
Diastrophic dysplasia

Ellis-van Creveld syndrome

Less Common

Chondrodysplasia punctata (some forms)
Kniest dysplasia
Metatropic dysplasia
Langer mesomelic dysplasia

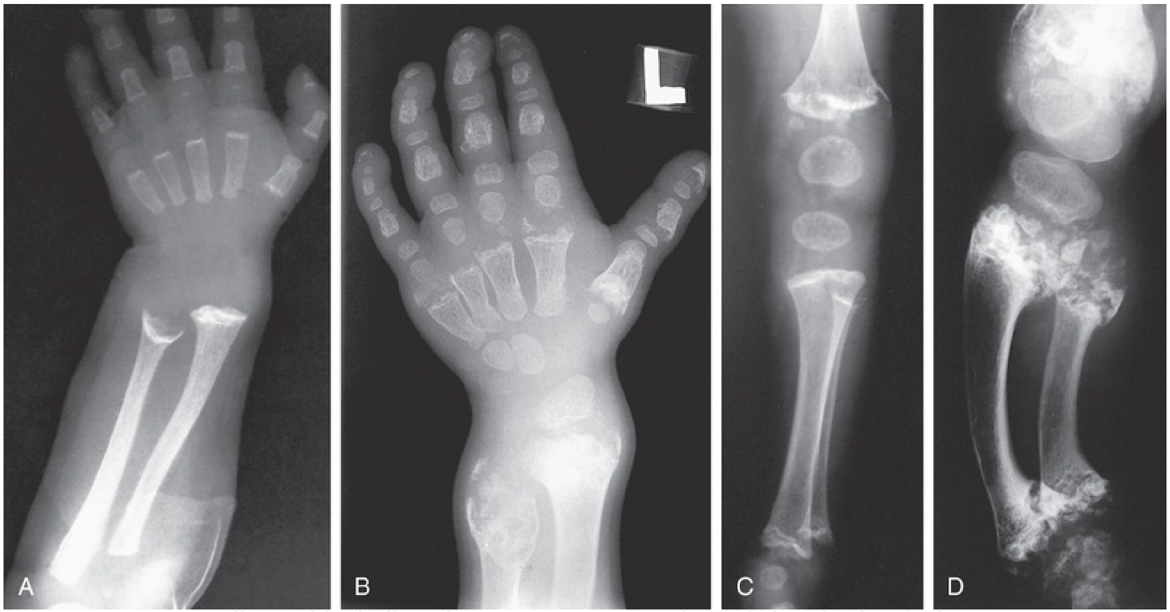

FIG. 714.2 Radiographic findings in Jansen-type metaphyseal chondrodysplasia. A, At age 1 yr there is severe metaphyseal cupping and splaying at the wrists and also in the hand bones. B, At age 7 yr there is increasing metaphyseal change at the wrists with enlarged epiphysis; enlarged epiphyses with wide epiphyseal plates are also present in the hands. C, At age 1 yr there are severe metaphyseal irregularities at the knees and ankles (femur, tibia, and fibula) and enlarged, rounded epiphyses. D, At age 7 yr there are severely fragmented, sclerotic metaphyses, wide epiphyseal plates, and enlarged epiphyses. Radiographic findings in Jansen-type metaphyseal chondrodysplasia. (From Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby.)

Comprehensive descriptions of disorders and references are at the Online Mendelian Inheritance in Man (OMIM) Internet site (http://omim.org/about).

Clinical Manifestations

Growth

The hallmark of the chondrodysplasias is disproportionate short stature. Although this refers to a disproportion between the limbs and the trunk, most disorders exhibit some shortening of both, and subtle degrees of disproportion may be difficult to appreciate, especially in premature, obese, or edematous infants. Disproportionate shortening of the limbs should be suspected if the upper limbs do not reach the mid-pelvis in infancy or the upper thigh after infancy. Disproportionate shortening of the trunk is indicated by a short neck, small chest, and protuberant abdomen. Skeletal disproportion is usually accompanied by short stature (length and height below the 3rd percentile); these measurements are occasionally within the low-normal range early in the course of certain conditions.

There may also be disproportionate shortening of different segments of the limbs; the particular pattern can provide clues for specific diagnoses. Shortening is greatest in the proximal segments (upper arms and legs) in achondroplasia; this is termed **rhizomelic shortening.** Disproportionate shortening of the middle segments (forearms and lower legs) is called **mesomelic shortening; acromelic** shortening involves the hands and feet.

With some exceptions, there is a strong correlation between the age when shortening is appreciated and the clinical severity of the condition. Many of the lethal neonatal chondrodysplasias are evident during routine fetal ultrasound examinations performed at the end of the first trimester of gestation (see Table 714.4). Gestational standards exist for long-bone lengths; discrepancies are often detected between biparietal diameter of the skull and long-bone lengths. Many disorders become apparent around the time of birth; others manifest during the first year of life. A number of disorders manifest in early childhood and a few in late childhood or later.

Non-Growth-Related Manifestations

Most patients also have problems unrelated to growth. Skeletal deformities, such as abnormal joint mobility, protuberances at and around joints, and angular deformities, are common and usually symmetric. Skeletal abnormalities can adversely affect nonskeletal tissues. Impaired growth at the base of the skull and of vertebral pedicles reduces the size of the spinal canal in achondroplasia and can contribute to spinal cord compression. Short ribs reduce thoracic volume, which can compromise breathing in patients with short trunk chondrodysplasias. Cleft palate (see Chapter 336) is common to many disorders, presumably reflecting defective palatal growth.

Manifestations may be unrelated to the skeleton; they reflect the expression of mutant genes in nonskeletal tissues. Examples include retinal detachment in spondyloepiphyseal dysplasia congenita, sex reversal in campomelic dysplasia, congenital heart malformations in Ellis-van Creveld syndrome, immunodeficiency in cartilage-hair hypoplasia, and renal dysfunction in asphyxiating thoracic dysplasia. These nonskeletal problems provide valuable clues to specific diagnoses and must be managed clinically (see Table 714.3).

Family and Reproductive History

A family history might identify relatives with the condition; a mendelian inheritance pattern may be elicited. Because the presentation can vary in some disorders, features that might be related to the disorder should be identified. Special attention should be given to mild degrees of short stature, disproportion, deformities, and other manifestations (e.g., precocious osteoarthritis) because they may be overlooked. Physical examination of relatives may be useful, as may the review of their photographs, radiographs, and medical and laboratory records.

A reproductive history might reveal previous stillbirths, fetal losses, and other abnormal pregnancy outcomes resulting from a skeletal dysplasia. Pregnancy complications, such as polyhydramnios or reduced fetal movement, are common in bone dysplasias, especially neonatal lethal variants.

Even though most of the skeletal dysplasias are genetic, it is common to have no family history of the disorder. New mutations are common for autosomal dominant disorders, especially lethal disorders in the perinatal period (thanatophoric dysplasia, osteogenesis imperfecta). Most cases of achondroplasia result from new mutations. Germ cell mosaicism, in which a parent has clones of mutant germ cells, has been observed in osteogenesis imperfecta and in other dominant disorders. A negative family history is usually seen in recessive disorders. Few of these conditions are caused by X-linked mutations. Prenatal diagnosis is available for disorders that have a genetic locus identified. Appropriateness of the testing depends on many factors, and genetic counseling is warranted for these families.

Radiographic Features

Radiographic evaluation for a chondrodysplasia should include plain films of the entire skeleton. Efforts should be made to identify which bones and which parts of bones (epiphyses, metaphyses, diaphyses) are most affected. If possible, films taken at different ages should be examined because the radiographic changes evolve with time. Films taken before puberty are generally more informative because pubertal closure of the epiphyses obliterates many of the signs needed for a radiographic diagnosis. Prenatal diagnosis may also be possible with fetal ultrasound.

Diagnosis

If an infant or child is short with disproportionate features, a diagnosis is established by matching the observed clinical picture (defined primarily from clinical, family, and gestational histories; physical examination; and radiographic evaluation) with clinical phenotypes of well-documented disorders. Pediatricians should be able to gather most of this information and, in consultation with a radiologist, diagnose the common chondrodysplasias. A number of reference texts and online databases provide information about the disorders and comprehensive lists of current references (http://www.ncbi.nlm.nih.gov/books/NBK1116/). For less-common disorders and for infants and children whose phenotypes do not closely match well-established clinical phenotypes, consultation with experts in the bone dysplasia field is warranted.

Molecular genetic testing for chondrodysplasias is very useful, especially for disorders in which recurrent mutations occur (typical achondroplasia has the same *FGFR3* mutation). Mutation testing for achondroplasia is available, although the diagnosis can be made clinically. The greatest utility for testing may be for prenatal diagnosis for couples where both parents have typical (heterozygous) achondroplasia. Their children are at a 25% risk of the much more severe homozygous achondroplasia, which can be detected by mutation analysis. Preimplantation genetic testing can be used to identify double dominant mutations. Another example of testing is in disorders resulting from mutations of *DTDST.* These disorders are inherited in an autosomal recessive manner, and a limited number of mutant alleles have been found. If the mutations are identified in the patient, they should be detectable in the parents and potentially used for prenatal diagnosis. Mutational analysis is commercially available for many of the skeletal dysplasias and is increasingly used to confirm clinical diagnosis and for future pregnancy planning.

Many of the chondrodysplasias have distinct histologic changes of the skeletal growth plate. Sometimes such tissues obtained at biopsy or discarded from a surgical procedure are helpful diagnostically. It is uncommon to make a diagnosis histologically if it was not already suspected on clinical or radiographic grounds.

Molecular Genetics

A number of chondrodysplasia genes have been identified (see Table 714.1). They encode several categories of proteins, including cartilage matrix proteins, transmembrane receptors, ion transporters, and transcription factors. The number of identified gene loci is smaller than anticipated from the number of recognized clinical phenotypes. The majority of patients have disorders that map to fewer than 10 loci; mutations at 2 loci (*COL2A1* and *FGFR3*) account for more than half of all cases. There may be a limited number of genes whose function is critical to skeletal development, especially linear bone growth; mutations in these genes give rise to a wide range of chondrodysplasia clinical phenotypes. New genes harboring mutations that cause chondrodysplasias continue to be identified with advances in detection technology.

Mutations at the *COL2A1* and *FGFR3* loci illustrate different genetic characteristics. *COL2A1* mutations are distributed throughout the gene, with few instances of recurrence in unrelated persons. In contrast, *FGFR3* mutations are restricted to a few locations within the gene, and the occurrence of new mutations at these sites in unrelated persons is the rule. There is a strong correlation between clinical phenotype and mutation site for *FGFR3,* but not *COL2A1,* mutations.

Pathophysiology

Chondrodysplasia mutations act through different mechanisms. Most mutations involving cartilage matrix proteins cause disease when only one of the two copies (alleles) of the relevant gene is mutated. These mutations usually act through a *dominant negative mechanism* in which the protein products of the mutant allele interfere with the assembly and function of multimeric molecules that contain the protein products of both the normal and mutant alleles. The type II collagen molecule is a triple helix composed of three collagen chains, which are the products of the type II collagen gene *COL2A1*. When chains from both normal and mutant alleles are combined to form triple helices, most molecules contain at least one mutant chain. It is not known how many mutant chains are required to produce a dysfunctional molecule but, depending on the mutation, it theoretically could be as few as one.

Mutations involving type X collagen differ from the model just described. They map to the region of the chain that is responsible for chain recognition; the chains must recognize each other before they can assemble into collagen molecules. Mutations are thought to disrupt this process. As a result, none of the mutant chains are incorporated into molecules. This mechanism is *haploinsufficiency* because the products of the mutant allele are functionally absent and the normal allele is insufficient for normal function. Mutations involving ion transport genes also act through a loss of function of the transporters. Mutations of transmembrane receptors studied to date appear to act through a gain of function; the mutant receptors initiate signals in a constitutive manner independent of their normal ligands.

Regardless of genetic mechanism, the mutations ultimately disrupt endochondral ossification, the biologic process responsible for the development and linear growth of the skeleton (see Fig. 714.1). Indeed, a wide range of morphologic abnormalities of the skeletal growth plate, the anatomic structure in which endochondral ossification occurs, have been described in the chondrodysplasias.

Treatment

The first step is to establish the correct diagnosis. This allows one to provide a prognosis and to anticipate the medical and surgical problems associated with a particular disorder. Establishing a diagnosis helps to distinguish between lethal disorders and nonlethal disorders in a premature or newborn infant (see Tables 714.4 and 714.5). A poor prognosis for long-term survival might argue against initiating extreme lifesaving measures for thanatophoric dysplasia or achondrogenesis types Ib or II, whereas such measures may be indicated for infants with spondyloepiphyseal dysplasia congenita or diastrophic dysplasia, which have a good prognosis if the infant survives the newborn period.

Because there is no definitive therapy to normalize bone growth in any of the disorders, management is directed at preventing and correcting skeletal deformities, treating nonskeletal complications, providing genetic counseling, and helping patients and families learn to cope. Each disorder has its own unique set of problems, and consequently management must be tailored to each disorder.

There are a number of problems common to many chondrodysplasias for which general recommendations can be made. Children with most chondrodysplasias should avoid contact sports and other activities that cause injury or stress to joints. Good dietary habits should be established in childhood to prevent or minimize obesity in adulthood. Dental care should be started early to minimize the crowding and malalignment of teeth. Children and relatives should be given the opportunity to participate in support groups, such as the Little People of America (http://www.lpaonline.org) and Human Growth Foundation (http://www.hgfound.org).

Two controversial approaches have been used to increase bone length. Surgical limb lengthening has been employed for a few disorders. Its greatest success has been in achondroplasia in which nonskeletal tissues tend to be redundant and easily stretched. The procedure is usually performed during adolescence. Pharmacologic doses of human growth hormone comparable to those used to treat Turner syndrome have also been tried in several disorders; the results have been equivocal. Animal studies suggest that C-type natriuretic peptide may promote linear bone growth in achondroplasia. Clinical trials are beginning to test the efficacy of this approach.

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CHAPTER 715

Disorders Involving Cartilage Matrix Proteins

Jacqueline T. Hecht, William A. Horton

Disorders of cartilage matrix proteins resulting in bone and joint disorders can be classified in five categories corresponding to the defective proteins: three collagens and the noncollagenous proteins COMP (cartilage oligomeric matrix protein), matrilin-3, and aggrecan. The clinical phenotypes and clinical severity differ between and within the groups, especially the spondyloepiphyseal dysplasia (SED) group, which are referred to as the type 2 collagenopathies.

Spondyloepiphyseal Dysplasias/Type 2 Collagenopathies

The term *spondyloepiphyseal dysplasia* refers to a heterogeneous group of disorders characterized by shortening of the trunk and, to a lesser extent, the limbs. Severity ranges from achondrogenesis type II to the slightly less-severe hypochondrogenesis (although both types are lethal in the perinatal period) to SED congenita and its variants, including Kniest dysplasia (which is apparent at birth and is usually nonlethal), to late-onset SED (which might not be detected until adolescence or later). The radiographic hallmarks are abnormal development of the vertebral bodies and of epiphyses, the extent of which corresponds with clinical severity. Most of the SEDs result from heterozygous mutations of *COL2A1* ; they are autosomal dominant disorders. The mutations are dispersed throughout the gene; there is a poor correlation between the mutation's location and the resultant clinical phenotype. Molecular testing/confirmation is readily available commercially. Prenatal diagnosis is possible if the mutation is known.

Lethal Spondyloepiphyseal Dysplasias

Achondrogenesis type II (*MIM 200610)* is characterized by severe shortening of the neck and trunk and especially the limbs, and by a large, soft head. Fetal hydrops and prematurity are common; infants are stillborn or die shortly after birth. **Hypochondrogenesis *(MIM 200610)*** refers to a clinical phenotype intermediate between achondrogenesis type II and SED congenita. It is typically lethal in the newborn period.

The severity of radiographic changes correlates with the clinical severity. Both conditions produce short, broad tubular bones with cupped metaphyses. The pelvic bones are hypoplastic, and the cranial bones are not well mineralized. The vertebral bodies are poorly ossified in the entire spine in achondrogenesis type II, and in the cervical and sacral spine in hypochondrogenesis. The pedicles are ossified in both. Both types can be detected prenatally and confirmed by molecular testing.

Spondyloepiphyseal Dysplasia Congenita

The phenotype of this group, SED congenita (MIM 183900), is apparent at birth. The head and face are usually normal, but a cleft palate is common. The neck is short and the chest is barrel shaped (Fig. 715.1). Kyphosis and exaggeration of the normal lumbar lordosis are common. The proximal segments of the limbs are shorter than the hands and feet, which often appear normal. Some infants have clubfoot and/or exhibit hypotonia.

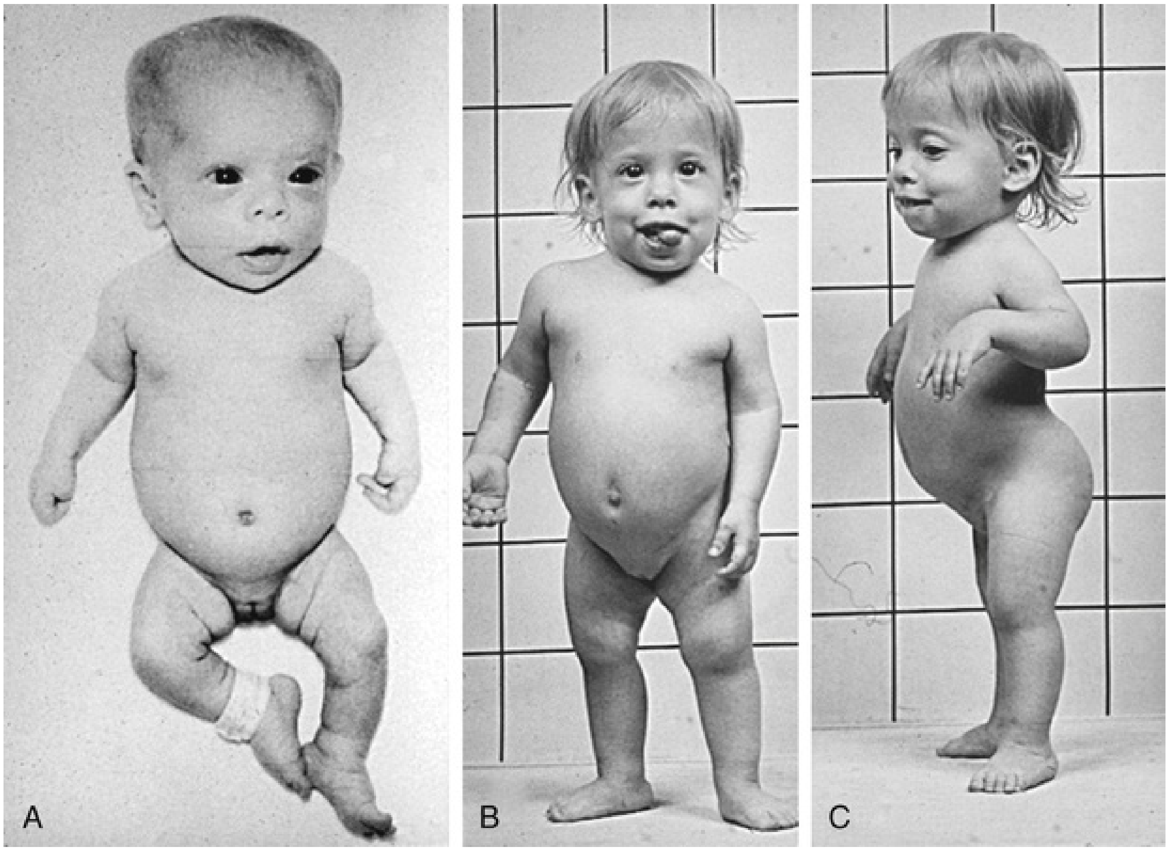

FIG. 715.1 Spondyloepiphyseal dysplasia congenita is shown in infancy **(A)** and early childhood **(B, C)** . Note the short extremities, relatively normal hands, flat facies, and exaggerated lordosis.

Skeletal radiographs of the newborn reveal short tubular bones, delayed ossification of vertebral bodies, and proximal limb bone epiphyses (Fig. 715.2). Hypoplasia of the odontoid process, a short, square pelvis with a poorly ossified symphysis pubis, and mild irregularity of metaphyses are apparent.

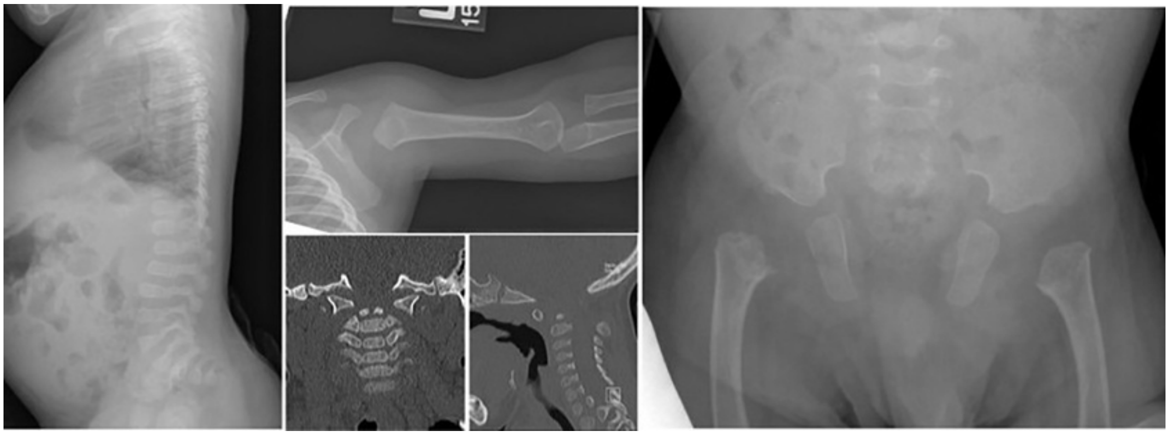

FIG. 715.2 **Spondyloepiphyseal dysplasia. Platyspondyly, delayed epiphyseal ossification (especially femoral heads), dens hypoplasia. (From Campeau P, Schlesinger AE: Skeletal dysplasias. [Updated 2017 Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al, editors. *Endotext [internet].* South Dartmouth, MA, 2000, MDText.com , Inc., Fig. 5. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279130/ .)**

Infants usually have normal developmental milestones; a waddling gait typically appears in early childhood. Childhood complications include respiratory compromise from spinal deformities and spinal cord compression because of cervicomedullary instability. The disproportion and shortening become progressively worse with age, and adult heights range from 95 to 128 cm. Myopia is typical; adults are predisposed to retinal detachment. Precocious osteoarthritis (OA) occurs in early adulthood and requires surgical joint replacement.

Kniest Dysplasia

The Kniest dysplasia variant of SED (MIM 156550) manifests at birth with a short trunk and limbs associated with a flat face, prominent eyes, enlarged joints, cleft palate, and clubfoot (Fig. 715.3). Radiographs show vertebral defects and short tubular bones with epiphyseal irregularities and metaphyseal enlargement that gives rise to a dumbbell appearance.

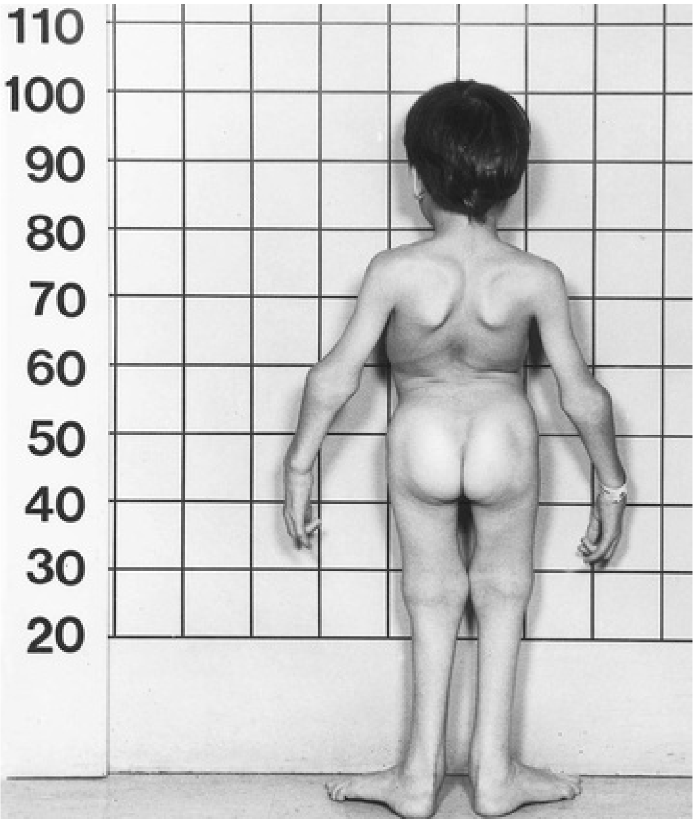

FIG. 715.3 Patient with Kniest dysplasia. The trunk is short, and the epiphyses are broad. There is contracture of the fingers. (From Traboulsi EI: Skeletal and connective tissue disorders with anterior segment manifestations. In Krachmer JH, Mannis MJ, Holland EJ, editors: Cornea, ed 3, Philadelphia, 2011, Elsevier, Fig. 60.9.)

Motor development is often delayed because of the joint deformities, although intelligence is normal. Hearing loss and myopia commonly develop during childhood, and retinal detachment is a common complication. Joint enlargement progresses during childhood and becomes painful; it is accompanied by flexion contractures and muscle atrophy, which may be incapacitating by adolescence.

Late-Onset Spondyloepiphyseal Dysplasia

Late-onset SED is a mild clinical phenotype characterized by slightly short stature associated with mild epiphyseal and vertebral abnormalities on radiographs. It is typically detected during childhood or adolescence but can go unrecognized until adulthood when precocious OA appears. This designation is nosologically distinct from SED tarda, which is clinically similar but results from mutation of the X-linked gene *SEDL*.

Aggrecan-Related Spondyloepiphyseal Dysplasias

Mutations of aggrecan have been detected in three SED-like conditions. SED-Kimberley *(MIM 608361)* is relatively mild, with short stature, stocky build, and early onset OA of weight-bearing joints. Autosomal dominant mutations are etiologic. Autosomal recessive mutations cause a more severe and generalized clinical phenotype, **spondyloepimetaphyseal dysplasia–aggrecan type (*MIM 612813*)** . Radiographic changes include widened metaphyses. A mild condition, **familial osteochondritis dissecans *(MIM 65800)*** is characterized by multiple osteochondritic lesions (separation of cartilage and subchondral bone from the surrounding tissue and primarily affecting the knee, ankle, and elbow joints) in knees and/or hips and/or elbows, disproportionate short stature, and early-onset OA. Autosomal dominant mutations have been found in familial cases.

Stickler Syndrome/Dysplasia (Hereditary Osteoarthroophthalmopathy)

Short stature is not a feature of Stickler dysplasia (MIM 184840). It resembles SED because of its joint and eye manifestations. Mutations of genes encoding type II *(COL2A1),* type XI *(COL11A1 , COL11A2),* and type IX *(COL9A1)* collagens have been identified in Stickler-like disorders *(MIM 184840 , MIM 215150)* . Stickler dysplasia is often identified in the newborn because of cleft palate and micrognathia (Pierre Robin anomaly; see Chapter 337). Of patients with Stickler syndrome, 25% have Pierre Robin anomaly; 30% of patients with Pierre Robin anomaly have Stickler syndrome. Children with Stickler syndrome are often identified in craniofacial clinics. Infants typically have severe myopia and additional ophthalmologic complications, including cataracts and choroidoretinal and vitreous degeneration; retinal detachment is common during childhood (Fig. 715.4). Sensorineural and conductive hearing loss can arise during adolescence, which is when symptoms of significant OA can also begin. Special attention must be given to the eye complications even in childhood. Osteoarticular manifestations include joint hypermobility (especially hip), wide femoral neck, hypoplastic iliac wings, Schmorl nodules, muscle hypotonia, metaphyseal–epiphyseal dysplasia; progressive OA of the spine and peripheral joints (which may require hip replacement surgery before age 30 yr), and decreased bone density. Similar manifestations may be seen in other diseases with mutations in type II and XI collagen genes (Table 715.1).

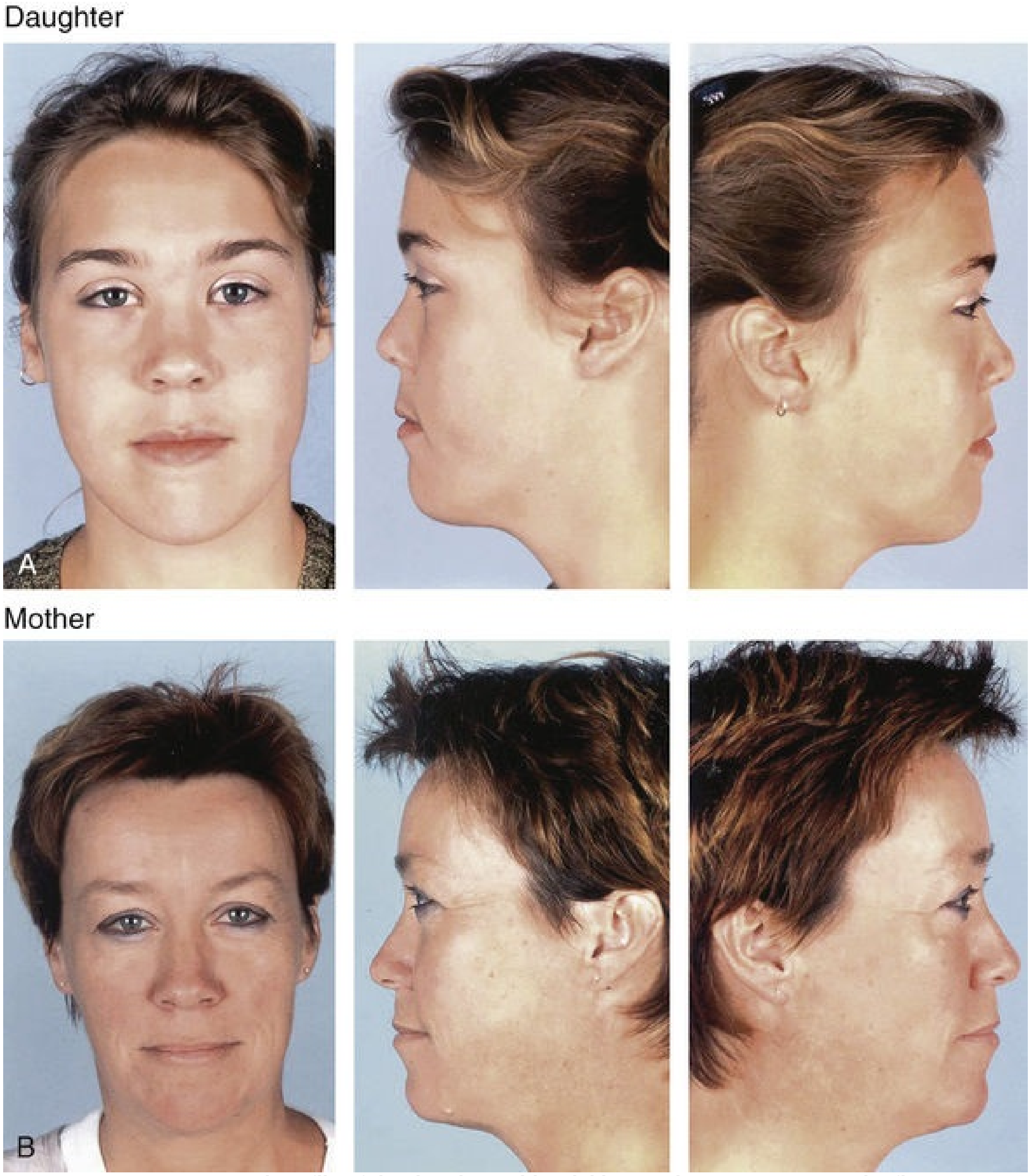

FIG. 715.4 **Face and profile of the daughter with Stickler syndrome type I. Note the flat nasal bridge, the mild epicanthal folds and discrete micrognathia. Face and profile of the mother with Stickler syndrome type I. At first sight, the mother shows no clear facial characteristics of Stickler syndrome. (From Baijens LWJ, De Leenheer EMR, Weekamp HH, et al: Stickler syndrome type I and Stapes ankylosis. *Int J Pediatr Otorhinolaryngol* 68:1573–1580, 2004, Fig. 2.)**

Table 715.1

Other Genetic Diseases Associated With Mutations in Type II and Type XI Collagen Genes, With Clinical Presentations Similar to That of Stickler Syndrome

PHENOTYPES ASSOCIATED WITH *COL2A1* MUTATIONS
Achondrogenesis type II Hypochondrogenesis Spondyloepiphyseal dysplasia congenita Spondyloepimetaphyseal dysplasia, Strudwick type Kniest dysplasia Dysplasia with altered vertebral contours Some of the juvenile joint diseases
PHENOTYPES ASSOCIATED WITH *COL11A1* MUTATIONS
Marshall syndrome
PHENOTYPES ASSOCIATED WITH *COL11A2* MUTATIONS
Otospondylometaphyseal dysplasia Weissenbach-Zweymuller syndrome Some cases of isolated sensorineural deafness

From Couchouron T, Masson C: Early-onset progressive osteoarthritis with hereditary progressive ophthalmology or Stickler syndrome. *Joint Bone Spine* 78:45–49, 2011, Table 1, p. 48.

Schmid Metaphyseal Dysplasia

Schmid metaphyseal dysplasia (MIM 156500) is one of several chondrodysplasias in which metaphyseal abnormalities dominate the radiographic features. It typically manifests in early childhood with mild short stature, bowing of the legs, and a waddling gait (Fig. 715.5). Joints, such as the wrist, may be enlarged. Radiographs show flaring and irregular mineralization of the metaphyses of tubular bones of the proximal limbs (Fig. 715.6). Coxa vara is usually present and can require surgical correction. Short stature becomes more evident with age and affects the lower extremities more than the upper extremities; the manifestations are limited to the skeleton.

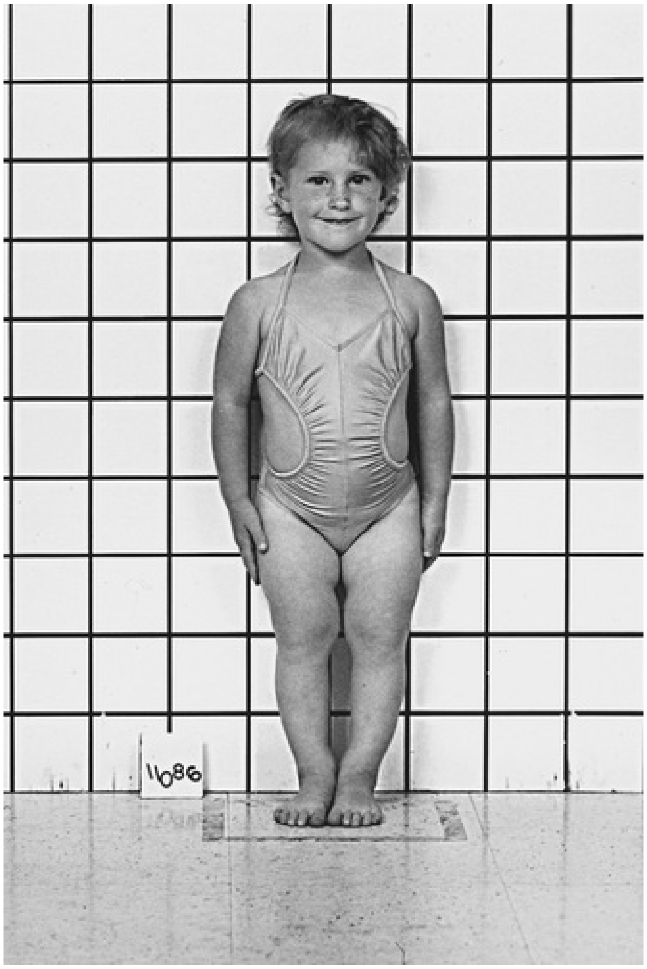

FIG. 715.5 Female patient with metaphyseal dysplasia, type Schmid. The facies are normal and the stature is mildly reduced. Mild tibia vara is present.

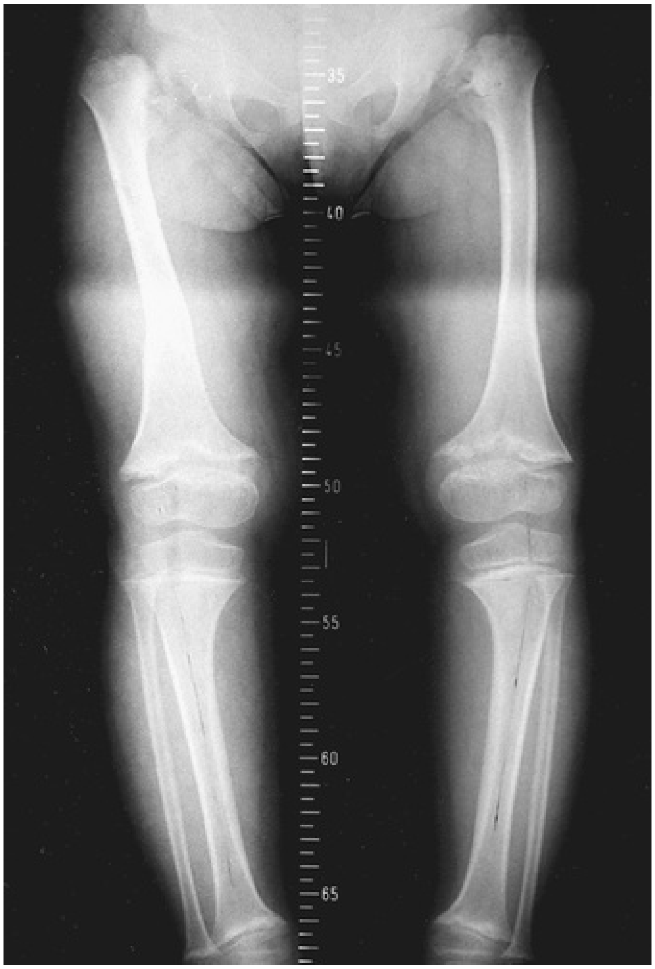

FIG. 715.6 Radiograph of lower extremities in Schmid metaphyseal dysplasia showing short tubular bones and metaphyseal flaring and irregularities, abnormal capital femoral epiphyses, and femoral necks. The epiphyses are normal. Coxa vara is present.

Schmid metaphyseal chondrodysplasia is caused by heterozygous mutations in the gene encoding type X collagen; it is an autosomal dominant trait. The distribution of type X collagen is restricted to the region of growing bone in which cartilage is converted into bone. This might explain why radiographic changes are confined to the metaphyses.

Pseudoachondroplasia and Multiple Epiphyseal Dysplasia

Pseudoachondroplasia (MIM 177170*)* and multiple epiphyseal dysplasia (MED) (MIM 600969) are two distinct phenotypes that are grouped together because they result from mutations of the gene encoding COMP. The mutations are heterozygous in both; they are autosomal dominant traits. The clinical phenotypes are restricted to musculoskeletal tissues.

Newborns with pseudoachondroplasia are average in size and appearance. Gait abnormalities and short stature mainly affect the limbs and become apparent in late infancy. Short stature becomes marked as the child grows and is associated with generalized joint laxity (Fig. 715.7). The hands are short, broad, and deviated in an ulnar direction; the forearms are bowed. Developmental milestones and intelligence are usually normal. Lumbar lordosis and deformities of the knee develop during childhood; the latter often requires surgical correction. Pain is common in weight-bearing joints during childhood and adolescence, and OA develops late in the 2nd decade of life. Adult height ranges from 105 to 128 cm.

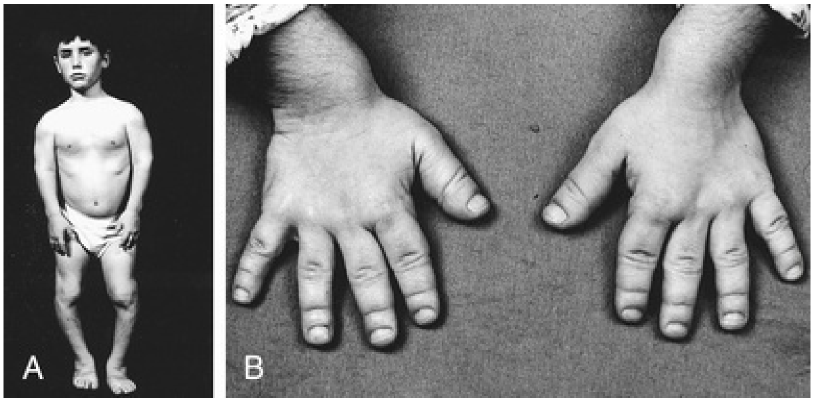

FIG. 715.7 **A,** Pseudoachondroplasia in an adolescent boy. The facies and head circumference are normal. There is shortening of all extremities and bowing of the lower extremities. **B,** Photograph of hands, demonstrating short stubby fingers.

Skeletal radiographs show distinctive abnormalities of vertebral bodies and of both epiphyses and metaphyses of tubular bones (Fig. 715.8).

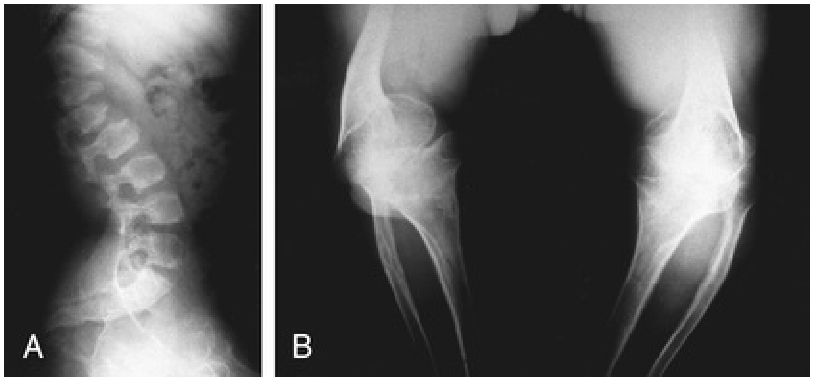

FIG. 715.8 **A,** Lateral thoracolumbar spine radiograph of a patient with pseudoachondroplasia showing central protrusion (tonguing) of the anterior aspect of upper lumbar and lower thoracic vertebrae. Note reduced vertebral body heights (platyspondyly) and secondary lordosis. **B,** Lower-extremity radiograph of a patient with pseudoachondroplasia showing large metaphyses, poorly formed epiphyses, and marked bowing of the long bones.

The MED phenotype has skeletal abnormalities that predominantly affect the epiphyses as noted on radiographs. Two forms, the severe Fairbank type and the mild Ribbing type, are no longer used in classification. Because of overlap in clinical features, and because COMP mutations are found in both types, they are now considered clinical variants.

The more severe clinical phenotype has its onset during childhood, with mild short-limbed short stature, pain in weight-bearing joints, and a waddling gait. Radiographs show delayed and irregular ossification of epiphyses. In more mildly affected patients the disorder might not be recognized until adolescence or adulthood. Radiographic changes may be limited to the capital femoral epiphyses. In the latter case, mild MED must be distinguished from bilateral Legg-Calvé-Perthes disease (see Chapter 698.3). Precocious OA of hips and knees is the major complication in adults with MED. Adult heights range from 136 to 151 cm.

There are families with clinical and radiographic manifestations of MED that are not caused by mutations of COMP. Mutations in the genes encoding all three of the type IX collagen chains have been reported. It has been suggested that COMP and type IX collagen interact functionally in cartilage matrix, thus explaining why mutations of different genes produce similar pictures. Mutations of the genes coding for another cartilage matrix protein, matrilin 3, and the diastrophic dysplasia sulfate transporter have also been found in patients with autosomal dominant and recessive MED, respectively. For familial cases of pseudoachondroplasia and MED resulting from mutation in COMP, prenatal diagnosis is available.

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CHAPTER 716

Disorders Involving Transmembrane Receptors

Julie E. Hoover-Fong, William A. Horton, Jacqueline T. Hecht

Heterozygous mutations of genes encoding *FGFR3* (fibroblast growth factor receptor 3) and *PTHR1* (parathyroid hormone-1 receptor) result in disorders involving transmembrane receptors. The mutations cause the receptors to become activated in the absence of physiologic ligands, which accentuates normal receptor function of negatively regulating bone growth. The mutations act by gain of negative function. In the *FGFR3* mutation group, in which the clinical phenotypes range from severe to mild, the severity appears to correlate with the extent to which the receptor is activated. *PTHR1* and especially *FGFR3* mutations tend to recur in unrelated individuals (Table 716.1).

Table 716.1

FGFR3 Chondrodysplasia Group

GROUP/NAME OF DISORDER	INHER.	OMIM	GR	ORPHA	GENE
Thanatophoric dysplasia type I (TD I)	AD	187600	1366	1860	*FGFR3*
Thanatophoric dysplasia type II (TD II)	AD	187601	1366	93274	*FGFR3*
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)	AD	187600	1455	85165	*FGFR3*
Achondroplasia	AD	100800	1152	15	*FGFR3*
Hypochondroplasia	AD	146000	1477	429	*FGFR3*
Camptodactyly, tall stature, and hearing loss syndrome (CATSHL)	AD	610474			*FGFR3*

Please also refer to group 33 for craniosynostoses syndromes linked to FGFR3 mutations, as well as LADD syndrome in group 39 for another FGFR3-related phenotype.

OMIM, Online Mendelian Inheritance in Man (omim.org); GR, GeneReviews; ORPHA, Orphanet (orpha.net).

From Campeau P, Schlesinger AE: Skeletal dysplasias. [Updated 2017 Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al., editors. *Endotext [internet]* . South Dartmouth, MA, 2000,

MDText.com , Inc. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279130/ .

Achondroplasia Group

The achondroplasia group represents a substantial percentage of patients with chondrodysplasias and contains thanatophoric dysplasia (TD), the most common lethal chondrodysplasia, with a birth prevalence of 1 in 35,000 births; achondroplasia, the most common nonlethal chondrodysplasia, with a birth prevalence of 1 in 15,000 to 1 in 40,000 births; and hypochondroplasia. All three have mutations in a small number of locations in the *FGFR3* gene. There is a strong correlation between the mutation site and the clinical phenotype.

Thanatophoric Dysplasia

TD (MIM 187600, 187601) manifests before or at birth. In the former situation, ultrasonographic examination in mid-gestation or later reveals a large head and very short limbs; the pregnancy is often accompanied by polyhydramnios and premature delivery. Very short limbs, short neck, long narrow thorax, and large head with midfacial hypoplasia dominate the clinical phenotype at birth (Fig. 716.1). The cloverleaf skull deformity known as **kleeblattschädel** is sometimes found. If the affected fetus survives through pregnancy, the newborn will have severe respiratory distress because of their small thorax. Although this distress can be treated by intense respiratory care, the long-term prognosis is poor.

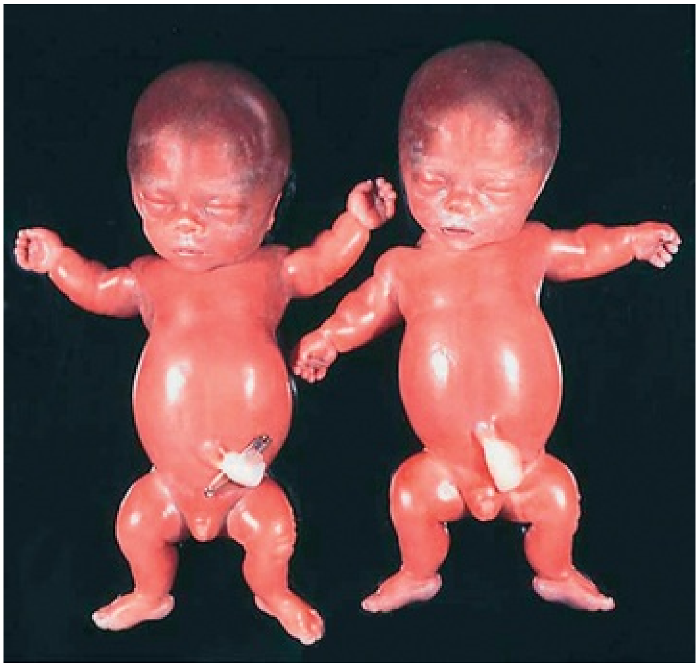

FIG. 716.1 **Identical twins with type I thanatophoric dysplasia. Disproportionately large head, bell-shaped chest, and micromelia. (From Gilbert-Barness E, Kapur RP, Oligny LL, Siebert JR, editors: *Potter's pathology of the fetus, infant and child,* ed 2, Philadelphia, 2007, Elsevier, Fig. 20-47.)**

Skeletal radiographs distinguish two slightly different forms called TD I and TD II. In the more common TD I, radiographs show large calvarium with a small cranial base, marked thinning and flattening of vertebral bodies (platyspondyly) visualized best on lateral view, very short ribs, severe hypoplasia of pelvic bones, and very short and bowed tubular bones with flared metaphyses (Fig. 716.2). The femurs are curved and shaped like a telephone receiver. TD II differs mainly in that there are longer and straighter femurs.

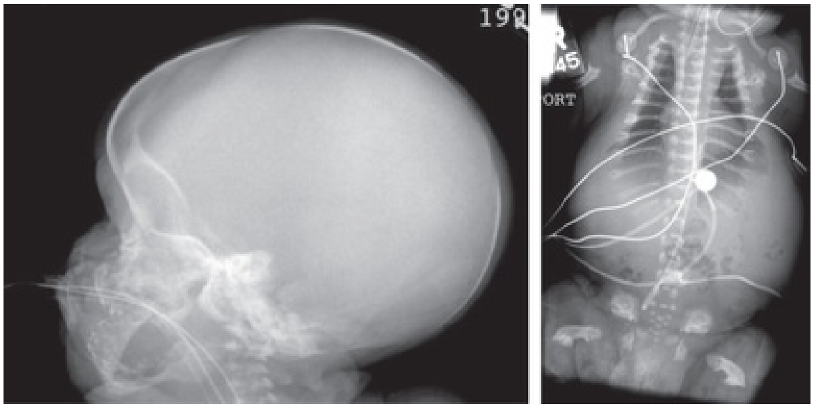

FIG. 716.2 **Thanatophoric dysplasia type I. Severe platyspondyly, very short ribs,**

narrow thorax, short broad pelvis, large skull, very short and bent long bones. (From Campeau P, Schlesinger AE: Skeletal dysplasias. [Updated 2017 Jan 30]. In: De Groot LJ, Chrousos G, Dungan K, et al, editors. *Endotext [internet].* South Dartmouth, MA, 2000, MDText.com , Inc., Fig. 1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279130/ .)

The TD II clinical phenotype is associated with mutations that map to codon 650 of *FGFR3* , causing the substitution of a glutamic acid for the lysine. This activates the tyrosine kinase activity of a receptor that transmits signals to intracellular pathways. Mutation of lysine 650 to methionine is associated with a clinical phenotype intermediate between TD and achondroplasia, referred to as **SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans)** . Mutations of the TD I phenotype mainly map to two regions in the extracellular domain of the receptor, where they substitute cysteine residues for other amino acids. Free cysteine residues are thought to form disulfide bonds promoting dimerization of receptor molecules, leading to activation and signal transmission. TD I and TD II represent new mutations in offspring born to unaffected, average stature parents. The recurrence risk is low. Because the mutated codons in TD are mutable for unknown reasons and because of the theoretical risk of germ cell mosaicism, parents are offered prenatal diagnosis for subsequent pregnancies.

Achondroplasia

Achondroplasia (MIM 100800) is the prototype chondrodysplasia. It typically manifests at birth with short limbs, a long narrow trunk, and a large head with midfacial hypoplasia and prominent forehead (Fig. 716.3). The limb shortening is greatest in the proximal segments, and the fingers often display a trident configuration. Most joints are hyperextensible, but extension is restricted at the elbow. A thoracolumbar gibbus is often found. Birth length may be slightly less than normal but often plots within the low-normal range.

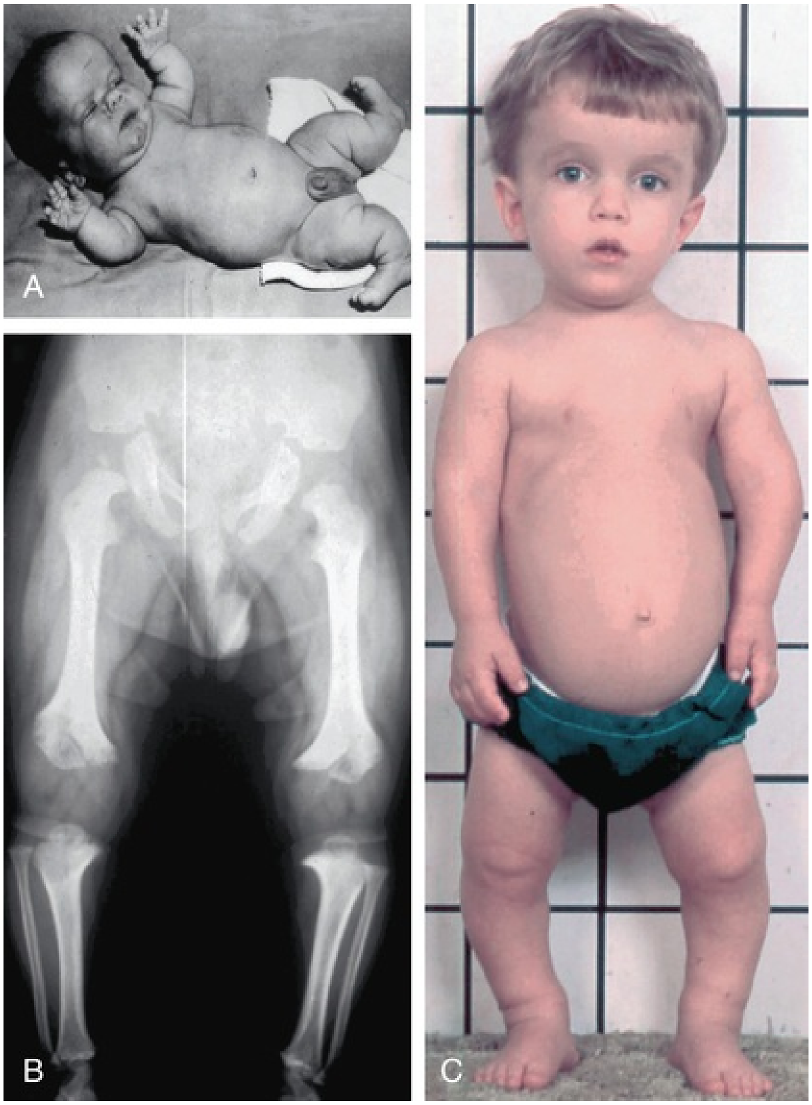

FIG. 716.3 Achondroplasia phenotype at different ages. A, Infant with achondroplasia with macrocephaly, frontal bossing, midface hypoplasia, small chest, rhizomelic shortening of all the limbs, redundant skin folds, and extreme joint laxity. Note the trident hand with short fingers and abducted hips. B, Typical radiographic findings from a child with achondroplasia. All of the tubular bones are short, but the fibula is relatively long compared to the tibia. There is protrusion of the epiphysis into the metaphysis of the distal femur, creating the chevron deformity, and—to a lesser extent—of the proximal tibia. The iliac bones are rounded, the acetabular roof is horizontal, and the sacrosciatic notches are small. C, A 3 yr old with achondroplasia with the typical features shown in A . Note that the redundant skin folds are no longer present and that joint laxity has improved. Rhizomelic shortening of the extremities is more pronounced and accompanied by tibial bowing. (From Horton WA, Hall JG, Hecht JT: Achondroplasia. *Lancet* 370:162–172, 2007.)

Diagnosis

Skeletal radiographs confirm the diagnosis (see Figs. 716.3 and 716.4). The calvarial bones are large, whereas the cranial base and facial bones are small.

The vertebral pedicles are short throughout the spine as noted on a lateral radiograph. The interpedicular distance, which normally increases from the 1st to the 5th lumbar vertebra, decreases in achondroplasia. The iliac bones are short and round, and the acetabular roofs are flat. The tubular bones are short with mildly irregular and flared metaphyses. The fibula is disproportionately long compared with the tibia, which is often bowed.

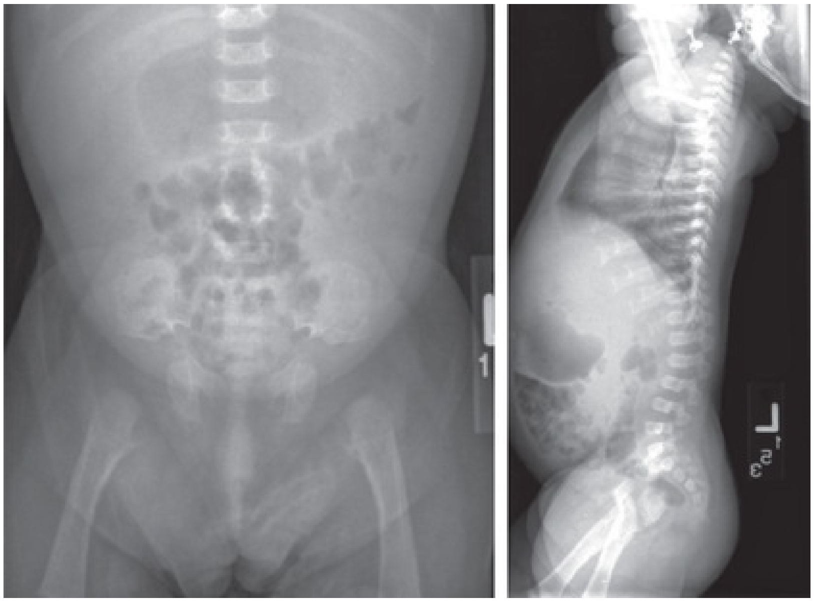

FIG. 716.4 **Achondroplasia. Small rounded iliac bones, horizontal acetabula, decreasing interpediculate distance, normal vertebral body height, short ribs. (From Campeau P, Schlesinger AE: Skeletal dysplasias. [Updated 2017 Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al, editors. *Endotext [internet].* South Dartmouth, MA, 2000, MDText.com , Inc., Fig. 2. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279130/ .)**

Clinical Manifestations

Infants usually exhibit delayed motor milestones, often not walking alone until 18-24 mo. This is because of hypotonia and mechanical difficulty balancing the large head on a normal-sized trunk and short extremities. Intelligence is normal unless central nervous system complications develop. As the child begins to walk, the gibbus usually gives way to an exaggerated lumbar lordosis.

Infants and children with achondroplasia progressively fall below normal standards for length and height. They can be plotted against standards established for achondroplasia. Adult heights typically are 118-145 cm for men and 112-136 cm for women. Surgical limb lengthening and human growth hormone treatment have been used to increase height; however, both are controversial. C-type natriuretic peptide may stimulate bone growth in achondroplasia based on studies in animal models. Clinical trials are underway to study various compounds.

Virtually all infants and children with achondroplasia have large heads, although only a fraction have true hydrocephalus. Head circumference should be carefully monitored using standards developed for achondroplasia, as should neurologic function in general. The spinal canal is stenotic, and spinal cord compression can occur at the foramen magnum and in the lumbar spine. The former usually occurs in infants and small children; it may be associated with hypotonia, failure to thrive, quadriparesis, central and obstructive apnea, and sudden death. Surgical correction may be required for severe stenosis. Lumbar spinal stenosis usually does not occur until early adulthood. Symptoms include paresthesias, numbness, and claudication in the legs. Loss of bladder and bowel control may be late complications. Bowing of the legs is common in patients with achondroplasia and might need to be corrected surgically. Other common problems include dental crowding, articulation difficulties, obesity, and frequent episodes of otitis media, which can contribute to hearing loss.

Genetics

All patients with typical achondroplasia have mutations at *FGFR3* codon 380. The mutation maps to the transmembrane domain of the receptor and is thought to stabilize receptor dimers that enhance receptor signals, the consequences of which inhibit linear bone growth. Achondroplasia behaves as an autosomal dominant trait; most cases arise from a new mutation to average stature parents.

Because of the high frequency of achondroplasia among short stature skeletal dysplasias, it is relatively common for adults with achondroplasia to marry. Such couples have a 50% risk of transmitting their condition, heterozygous achondroplasia, to each offspring, as well as a 25% risk of **homozygous achondroplasia** . The latter condition exhibits intermediate severity between TD and heterozygous achondroplasia and is usually lethal in the newborn period; it is often referred to as “double dominant” inheritance. Prenatal diagnosis is available and has been used to diagnose homozygous achondroplasia. Preimplantation genetic testing can be used to identify double dominant mutations.

Hypochondroplasia

Hypochondroplasia (MIM 146000) resembles achondroplasia but is milder. Usually, it is not apparent until childhood, when mild short stature affecting the limbs becomes evident. Children have a stocky build and slight frontal bossing of the head. Learning disabilities may be more common in this condition. Radiographic changes are mild and consistent with the mild achondroplastic phenotype. Complications are rare; in some patients the condition is never diagnosed. Adult heights range from 116 to 146 cm. An *FGFR3* mutation at codon 540 has been found in many patients with hypochondroplasia. Genetic heterogeneity exists in hypochondroplasia; that is, *SHOX* mutations are associated with a very similar clinical phenotype. Recombinant growth hormone therapy may enhance growth and improve body disproportion.

Jansen Metaphyseal Dysplasia

Jansen metaphyseal chondrodysplasia (MIM 156400) is a rare, dominantly inherited chondrodysplasia characterized by severe shortening of limbs associated with an unusual facial appearance (see Chapter 714). Sometimes it is accompanied by clubfoot and **hypercalcemia** with serum calcium values of 13-15 mg/dL. At birth, a diagnosis can be made from these clinical findings and radiographs that show short tubular bones with characteristic metaphyseal abnormalities that include flaring, irregular mineralization, fragmentation, and widening of the physeal space. The epiphyses are normal. The joints become enlarged and limited in mobility with age. Flexion contractures develop at the knees and hips, producing a bent-over posture. The spine can also be deformed by the irregular growth of vertebrae. Intelligence is normal, although there may be hearing loss.

Jansen metaphyseal chondrodysplasia is caused by activating mutations of *PTHR1* . This G-protein–coupled transmembrane receptor serves as a receptor for both parathyroid hormone and parathyroid hormone-related peptide. Signaling through this receptor serves as a brake on the terminal differentiation of cartilage cells at a critical step in bone growth. Because the mutations activate the receptor, they enhance the braking effect and thereby slow bone growth. Loss-of-function mutations of *PTHR1* are observed in Blomstrand chondrodysplasia, whose clinical features are the mirror image of Jansen metaphyseal chondrodysplasia.

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CHAPTER 717

Disorders Involving Ion Transporters

Jacqueline T. Hecht, William A. Horton, David Rodriguez-Buritica

In order of decreasing severity, the disorders involving ion transporters include achondrogenesis type 1B, atelosteogenesis type II, diastrophic dysplasia, and a rare recessive form of multiple epiphyseal dysplasia (rMED, MIM 226900). They result from the functional loss of the sulfate ion transporter called *diastrophic dysplasia sulfate transporter* (DTDST), which is also referred to as *SLC26A2* (solute carrier family 26, member 2). This protein transports sulfate ions into cells and is important for cartilage cells that add sulfate moieties to newly synthesized proteoglycans destined for cartilage extracellular matrix. Matrix proteoglycans are responsible for many of the properties of cartilage that allow it to serve as a template for skeletal development. The clinical manifestations result from defective sulfation of cartilage proteoglycans.

A number of mutant alleles have been found for the *DTDST* gene; they variably disturb transporter function. The disorders are recessive traits requiring the presence of bi-allelic mutations. The phenotype is determined by the combination of mutant alleles; some alleles are present in more than one disorder.

Autosomal Recessive Multiple Epiphyseal Dysplasia

Although previously regarded as a multiple epiphyseal dysplasia (MIM 606718), according to the new nosology, rMED is now classified among other sulfation disorders. rMED typically presents during adolescence with the gradual onset of hip and knee pain that might resemble rheumatoid arthritis. Later on, patients present with hand, feet, and knee deformities and scoliosis. Fifty percent of individuals present during infancy with club feet and external ear abnormalities. Stature is normal during childhood, but final height might be slightly decreased compared with unaffected siblings. Radiographic findings include flat epiphysis, mild brachydactyly, and double-layered patella. Diagnosis is clinical, based on presentation and radiological findings, but molecular confirmation is available with a detection rate over 90%. Management includes physical therapy, pain control, and orthopedic interventions.

Diastrophic Dysplasia

Diastrophic dysplasia (MIM 22600) is a well-characterized disorder recognized at birth by the presence of very short extremities, clubfoot, and short hands, with proximal displacement of the thumb producing a hitchhiker appearance (Fig. 717.1). The hands are usually deviated in an ulnar direction. Bony fusion of the metacarpophalangeal joints (symphalangism) is common, as is restricted movement of many joints, including the hips, knees, and elbows. The external ears often become inflamed soon after birth. The inflammation resolves spontaneously, but leaves the ears fibrotic and contracted (cauliflower ear deformity). Many newborns have a cleft palate.

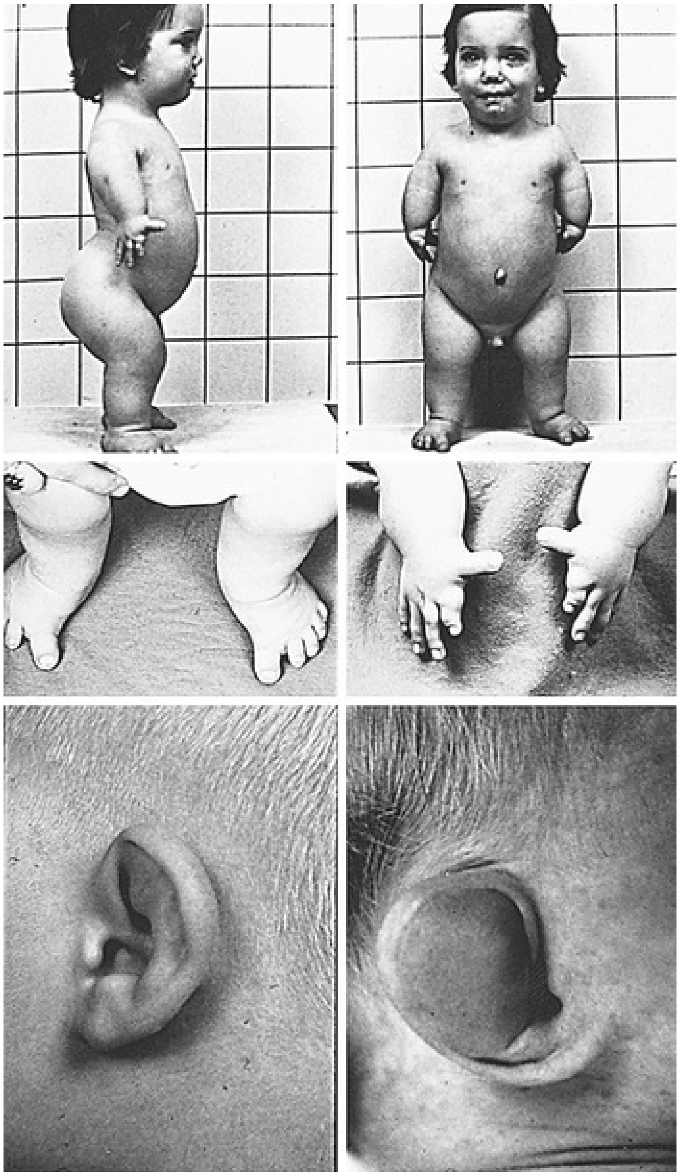

FIG. 717.1 Child with diastrophic dysplasia. The extremities are dramatically shortened *(top)* . Clubfoot is commonly observed *(middle left)* . The fingers are short, especially the index finger; the thumb characteristically is proximally placed and has a hitchhiker appearance *(middle right)* . The upper helix of the ears becomes swollen 3-4 wk postnatally *(lower left)* , and this inflammation spontaneously resolves, leaving a cauliflower deformity of the pinnae *(lower right)* .

Radiographs reveal short and broad tubular bones with flared metaphyses and flat, irregular epiphyses (Fig. 717.2). The capital femoral epiphyses are hypoplastic, and the femoral heads are broad. The ulnas and fibulas are disproportionately short. Carpal centers may be developmentally advanced; the first metacarpal is typically ovoid, and the metatarsals are twisted medially. There may be vertebral abnormalities, including clefts of cervical vertebral lamina and narrowing of the interpedicular distances in the lumbar spine.

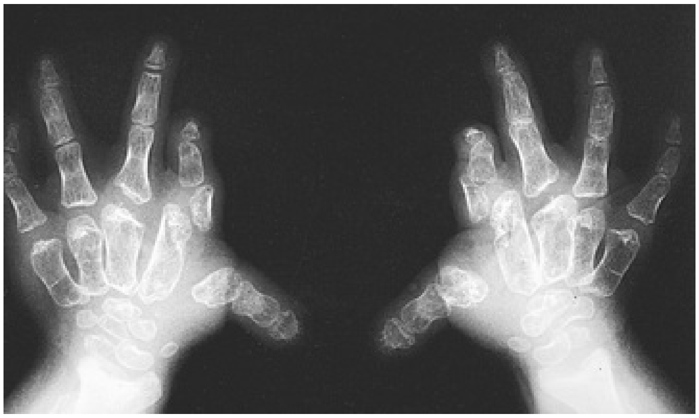

FIG. 717.2 **Radiograph of hands in diastrophic dysplasia. The metacarpals and phalanges are irregular and short. The first metacarpal is ovoid.**

Complications are primarily orthopedic and tend to be severe and progressive. The clubfoot deformity in the newborn resists usual treatments, and multiple corrective surgeries are common. Scoliosis typically develops during early childhood. It often requires multiple surgical procedures to control, and it sometimes compromises respiratory function in older children. Despite the orthopedic problems, patients typically have a normal life span and reach adult heights in the 105-130 cm range, depending on the severity of scoliosis. Growth curves are available for diastrophic dysplasia.

Some patients are mildly affected and exhibit slight short stature and joint contractures, no clubfoot or cleft palate, and correspondingly mild radiographic changes. The mild phenotype tends to recur within families. The recurrence risk of this autosomal recessive condition is 25%. Ultrasonographic examination can be employed for prenatal diagnosis, but if *DTDST* mutations can be identified in the patients or parents, molecular genetic diagnosis is possible.

Achondrogenesis Type 1B and Atelosteogenesis Type 2

Achondrogenesis type 1B (MIM 600972) and atelosteogenesis type 2 (MIM 256050) are rare recessive lethal chondrodysplasias. The most serious is achondrogenesis type 1B, which demonstrates a severe lack of skeletal development usually detected *in utero* or after a miscarriage. The limbs are extremely short, and the head is soft. Skeletal radiographs show poor to missing ossification of skull bones, vertebral bodies, fibulas, and ankle bones. The pelvis is hypoplastic, and the ribs are short. The femurs are short and exhibit a trapezoid shape with irregular metaphyses.

Infants with atelosteogenesis type II are stillborn or die soon after birth; prematurity is common. They exhibit very short limbs, especially the proximal segments. Clubfoot and dislocations of the elbows and knees may be detected. Hypoplasia of vertebral bodies, especially in the cervical and lumbar spine, is found on radiographs. The femora and humeri are hypoplastic and display a club-shaped appearance. The distal limb bones, including the ulna and fibula, are poorly ossified.

Both disorders have a 25% recurrence risk and are potentially detectable *in utero* by mutation analysis if the mutant alleles are identified in the parents. Prenatal diagnosis is possible with fetal imaging and/or mutational testing, which is commercially available.

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CHAPTER 718

Disorders Involving Transcription Factors

Jacqueline T. Hecht, William A. Horton, David Rodriguez-Buritica

There are three well-delineated disorders involving transcription factors that result in bone dysplasias. One, campomelic dysplasia, is historically considered a chondrodysplasia. Cleidocranial dysplasia was initially considered a dysostoses, but in the new nosology is now considered a skeletal dysplasia due to recognition of additional skeletal involvement. Nail-patella syndrome (NPS) continues to be regarded as a dysostoses. The mutant genes that encode these transcription factors are *SOX9, RUNX2 (CBFA1*), and *LMX1B* , respectively, and are members of much larger gene families. For instance, *SOX9* is a member of the *SOX* family of genes related to the *SRY* (sex-determining region of the Y chromosome) gene; *RUNX2 (CBFA1*) belongs to the runt family of transcription factor genes, and *LMX1B* is part of the LIM homeodomain gene family. All three disorders are due to haploinsufficiency of the respective gene products; the disorders are dominant traits. For familial cases of cleidocranial dysplasia and NPS, prenatal diagnosis is possible if the mutations are identified. Campomelic dysplasia results from new mutational events and has a low risk of recurrence in subsequent pregnancies.

Campomelic Dysplasia

Campomelic dysplasia (MIM 114290) is apparent in newborn infants and is characterized by bowing of long bones (especially in the lower legs), short bones, respiratory distress, and other anomalies that include defects of the cervical spine, Pierre-Robin sequence, central nervous system, heart, and kidneys. In some cases, femoral bowing is minimal (acampomelic campomelic dysplasia). A total of 75% of XY individuals have some degree of gonadal dysgenesis that goes from complete to incomplete, presenting with normal female phenotype or ambiguous genitalia, resulting in lack of determination of testicular tissue and undervirilization in 46,XY individuals. 46,XX individuals have an expected female phenotype with normal ovarian differentiation. *Therefore karyotype analysis is indicated in every female with campomelia* . This is due to the importance of *SOX9* function in the differentiation of testicular tissue downstream from *SRY* . Compared with SOX9 haploinsufficiency, duplications cause the gonadal tissue to differentiate into testicular tissue in a 46,XX individual, highlighting the importance of the dose of *SOX9* in gonadal differentiation. Radiographs confirm the bowing and often show hypoplasia of the scapulae and pelvic bones (Fig. 718.1). Affected infants usually die of respiratory distress in the neonatal period, due to rib cage involvement. Complications in children and adolescents who survive include cervical instability, short stature with progressive kyphoscoliosis, recurrent apnea and respiratory infections, hearing loss, and learning difficulties. Due to the effect on gonadal differentiation, 46XY survivors affected with gonadal dysgenesis present with absent thelarche and primary amenorrhea. Mutational testing is commercially available and has a 95% detection rate.

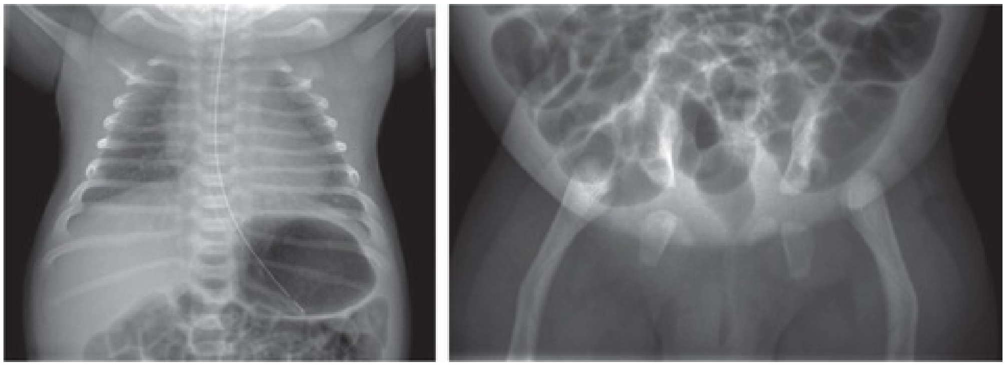

FIG. 718.1 **Campomelic dysplasia. Bell-shaped thorax, hypoplastic scapula, bowed femurs, widely spaced ischial bones. (From Campeau P, Schlesinger AE: Skeletal dysplasias (Fig. 12). [Updated 2017 Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al, editors. *Endotext [internet]* . South Dartmouth, MA, 2000, MDText.com , Inc. https://www.ncbi.nlm.nih.gov/books/NBK279130/ .)**

Cleidocranial Dysplasia

Cleidocranial dysplasia (MIM 114290) might be recognized in infants because of drooping shoulders, open fontanelles, and prominent forehead. Birth length is normal, but mild short stature and dental abnormalities are evident during childhood (Fig. 718.2). The shoulders of patients with Cleidocranial dysplasia can meet in the midline. Radiographs reveal hypoplastic or absent clavicles, delayed ossification of the cranial bones with multiple ossification centers (wormian bones), and delayed ossification of pelvic bones. The anterior fontanelle is wide and might remain open. The course is usually uncomplicated except for dislocations, especially of the shoulders and dental anomalies (numerous teeth) that require therapy, and the risk of hearing loss due to infections. Affected individuals are shorter than unaffected siblings and have an increased risk of genu valgum, pes planus, and scoliosis. Diagnosis is based on clinical and radiographic presentation, but molecular confirmation is available with a detection rate of 70%. The proportion of cases due to de novo mutations is high. Management includes prevention of ear infections, speech therapy, dental, and orthopedic interventions as indicated.

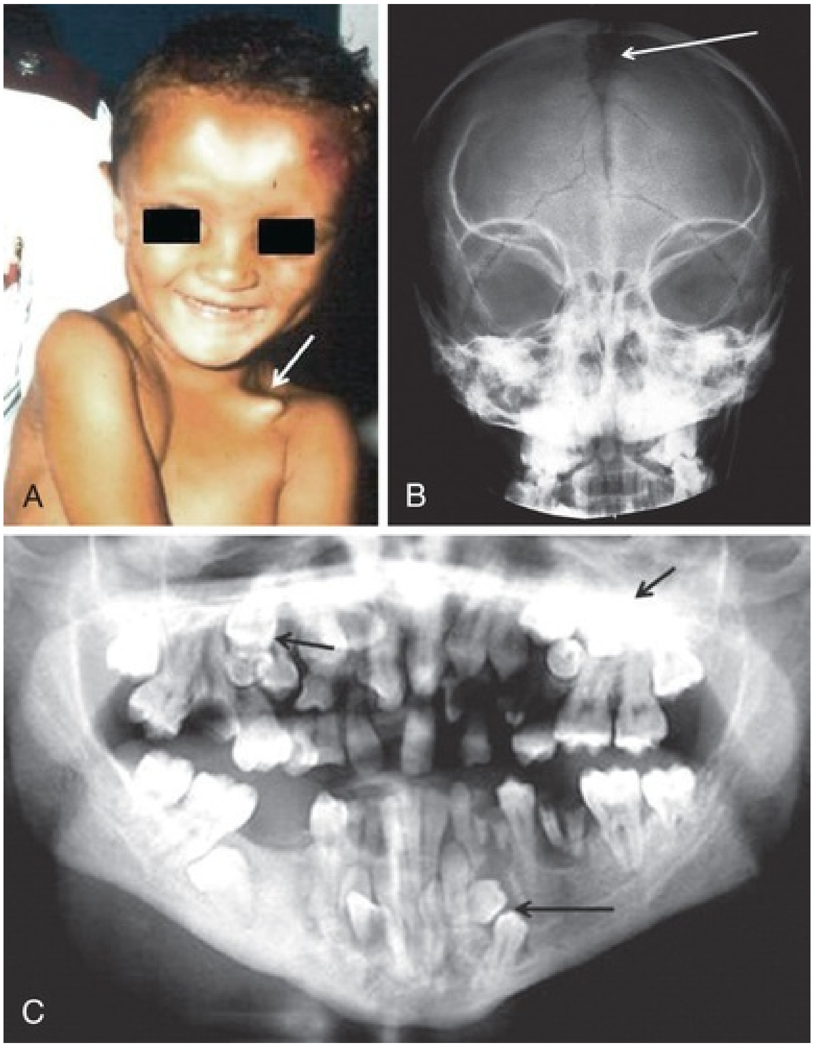

FIG. 718.2 Features of cleidocranial dysplasia displayed. **A,** The forehead is bulky with a central depression, the eyes are widely spaced and the jaw is pointed. The clavicle is misshapen *(arrow)* . **B,** Note patency of the anterior fontanelle. **C,** Hyperdontia pantomogram of an affected male showing supernumerary teeth. (From Roberts T, Stephen L, Beighton P. Cleidocranial dysplasia: a review of the dental, historical, and practical implications with an overview of the South African experience. *Oral Surg Oral Med Oral Pathol Oral Radiol* 115(1):46–55, 2013, Figs. 1, 4, and 6.)

Nail-Patella Syndrome

Dysplasia of the nails, absence or hypoplasia of the patella, abnormalities of the elbow, and spurs or “horns” extending from the iliac bones characterize the NPS (MIM 119600), which is also called *osteo-onychodysostosis.* Penetrance is high, but clinical presentation is extremely variable with a wide spectrum of severity;

some patients present in early childhood, whereas others are asymptomatic as adults. Nail abnormalities are almost universal with a wide variety of manifestations, including absence, hypoplasia, clefts, ridged, thin, or hypertropic nails. Elbow abnormalities include limitation of any of the movements, cubits valgus, and pterygium. The patella might be hypoplastic or absent (Fig. 718.3). Iliac horns project posterior-laterally from the center of the iliac bone. A total of 30% of patients have nephritis that resembles chronic glomerulonephritis that presents with proteinuria with or without hematuria; 5% of cases progress to end-stage renal disease. There is an increased risk of glaucoma for NPS patients; 12% of cases are *de novo* . Diagnosis is based on clinical presentation, and molecular confirmation is available with a 95% detection rate. Management includes treatment of orthopedic complications, surveillance and treatment of renal disease, and ophthalmological follow-up.

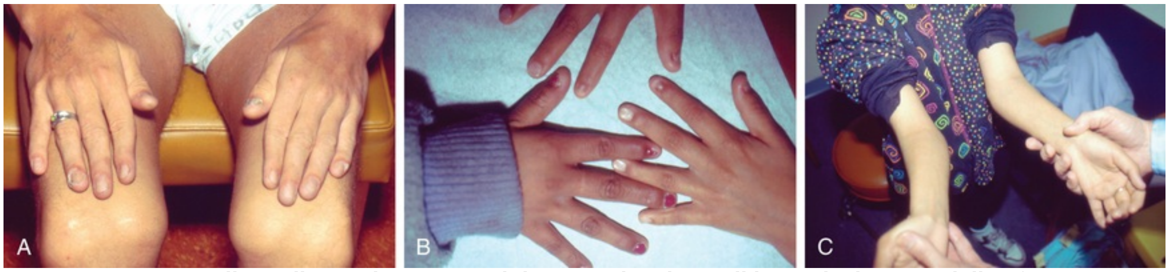

FIG. 718.3 **Nail-patella syndrome. A, Adolescent showing nail hypoplasia, especially of thumbs, and displacement of small patellae. B, Two affected children showing nail dysplasia. C, Incomplete extension of the elbows. (From Jones KL, Jones MC, Del Campo M, editors: *Smith's recognizable patterns of human malformation* , ed 7, Philadelphia, 2013, Elsevier/Saunders, Fig. 1, p. 574.)**

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CHAPTER 719

Disorders Involving Defective Bone Resorption

Jacqueline T. Hecht, William A. Horton, David Rodriguez-Buritica

Bone dysplasias displaying increased bone density are rare. Osteopetrosis, which has many subtypes, and pyknodysostosis result from defective bone resorption.

Osteopetrosis

Two main forms of osteopetrosis have been delineated: a severe autosomal recessive form (MIM 259700) with an incidence of ~1/250,000 births and a mild autosomal dominant form (MIM 166600) occurring in ~1/20,000 births. Intrinsic disturbances of osteoclast function due to mutations in genes encoding osteoclast-specific subunits of the vacuolar proton pump *TCIRG1* , *CLCN7* , *OSTM1* , *SNX10* , *TNFSFR11A*, *TNFSF11*, and *PLEKHM1* are found in most patients with the recessive form. Mutations in *TNFSFR11A and TNFSF11* produce osteoclast-poor osteopetrosis, due to alteration of the RANK-RANKL interaction. Mutations of *CLCN7* are observed in the dominant form of osteopetrosis. All types of mutations lead to disturbances of normal osteoclast function. Mutations in other genes result in additional syndromic presentations like osteopetrosis with renal tubular acidosis due to bi-allelic mutations in *CAII*.

The severe form is usually detected in infancy or earlier because of macrocephaly, hepatosplenomegaly, deafness, blindness, and severe anemia. Radiographs reveal diffuse bone sclerosis and **hypocalcemia** levels may be detected. Later x-rays show the characteristic bone-within-bone appearance (Fig. 719.1). With time, infants typically fail to thrive and show psychomotor delay and worsening of cranial neuropathies and anemia. Dental problems, osteomyelitis of the mandible, and pathologic fractures are common. The most severely affected patients die during infancy; less severely affected patients rarely survive beyond the 2nd decade. Those who survive beyond infancy usually have learning disabilities, but might have normal intelligence despite hearing and vision loss.

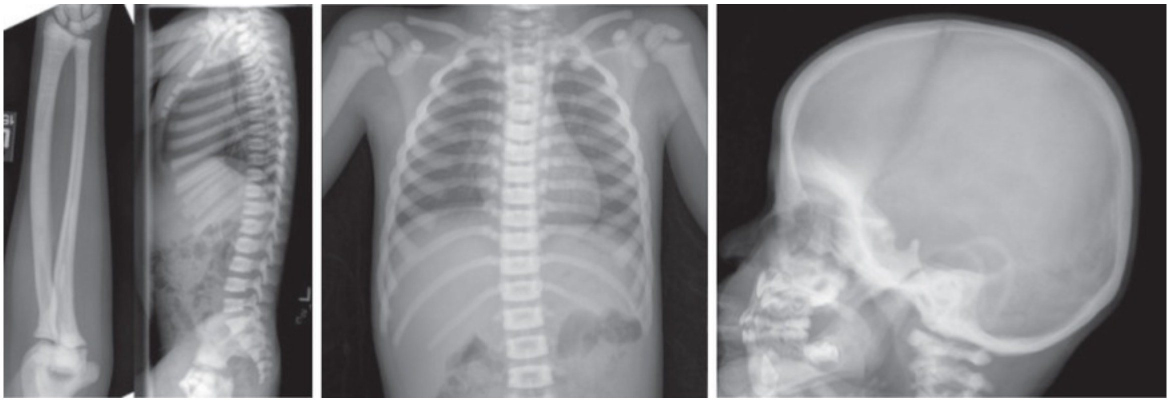

FIG. 719.1 **Osteopetrosis. Thick dense bones, alternating bands of sclerosis, and normal density bone in long bones, rugger jersey spine, dense base of skull. (From Campeau P, Schlesinger AE: Skeletal dysplasias (Fig. 14). [Updated 2017, Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al, editors. *Endotext [internet]* . South Dartmouth, MA, 2000, MDText.com , Inc. https://www.ncbi.nlm.nih.gov/books/NBK279130/ .)**

Clinical Manifestations

Most of the manifestations are due to failure to remodel growing bones. This leads to narrowing of cranial nerve foramina and encroachment on marrow spaces, which results in secondary complications, such as optic and facial nerve dysfunction, and anemia accompanied by compensatory extramedullary hematopoiesis in the liver and spleen. The unusually dense bones are weak, leading to increased risk of fractures.

The autosomal dominant form of osteopetrosis (Albers-Schönberg disease, osteopetrosis tarda, or marble bone disease) usually manifests during childhood or adolescence with fractures and mild anemia and, less often, as cranial nerve dysfunction, dental abnormalities, or osteomyelitis of the mandible. Skeletal radiographs reveal a generalized increase in bone density and clubbing of metaphyses. Alternating bands of lucent and dense bands produce a sandwich appearance to vertebral bodies. The radiographic changes are sometimes incidental findings in otherwise asymptomatic adolescents and adults.

Treatment

Most of the bone manifestations in severe osteopetrosis due to intrinsic osteoclast defects can be prevented or reversed by hematopoietic stem cell transplantation (HSCT), if carried out before development of irreversible secondary complications, such as visual impairment. RANKL replacement therapy may be useful in patients with RANKL deficiency due to *TNFSF11* bi-allelic mutations, who do not benefit from HSCT. Calcitriol and interferon-γ have also been used with equivocal results. Symptomatic care, such as dental care, transfusions for anemia, and antibiotic treatment of infections, is important for patients who survive infancy.

Pyknodysostosis

An autosomal recessive bone dysplasia related to osteopetrosis, pyknodysostosis (MIM 265800) manifests in early childhood with short limbs, characteristic facies, an open anterior fontanel, a large skull with frontal and occipital bossing, and dental abnormalities. The hands and feet are short and broad, and the nails may be dysplastic. The sclerae may be blue. Minimal trauma often leads to fractures. Treatment is symptomatic and focused mainly on the management of dental problems and fractures. The prognosis is generally good, and patients typically reach heights of 130-150 cm.

Skeletal radiographs show a generalized increase in bone density. In contrast to many disorders in this group, the metaphyses are normal. Other changes include wide sutures and wormian bones in the skull, a small mandible, and hypoplasia of the distal phalanges (Fig. 719.2).

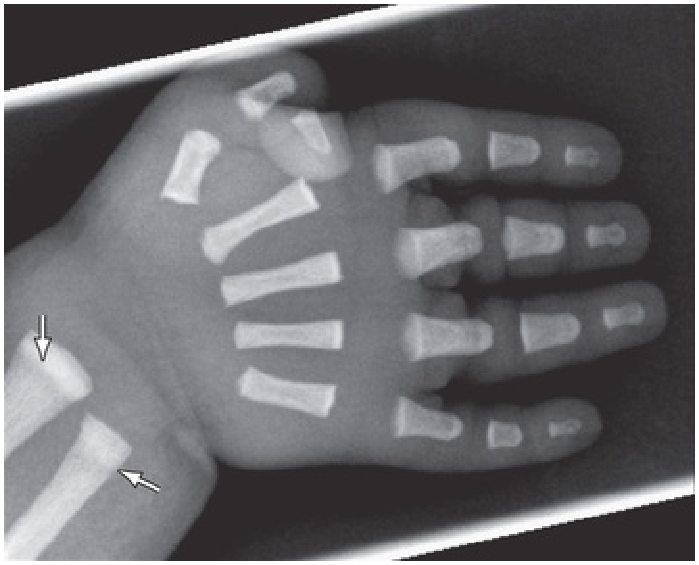

FIG. 719.2 Osteopetrosis. Right-hand radiograph obtained at 2 wk of age. Note metaphyseal lucent bands in the distal ulna and radius *(arrows)* and short tubular bones. (From Stark Z, Savarirayan R: Osteopetrosis. *Orphanet J Rare Dis* 4:5, 2009.)

Several mutations have been found in the gene encoding cathepsin K, a cysteine protease that is highly expressed in osteoclasts. The mutations predict loss of enzyme function, suggesting that there is an inability of osteoclasts to degrade bone matrix and remodel bones.

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CHAPTER 720

Other Inherited Disorders of Skeletal Development

Jacqueline T. Hecht, William A. Horton

Great advances in our understanding have led to delineation of the genetic basis of disorders that were previously poorly understood. Some of these conditions are now classified into a gene family based on their molecular and clinical findings.

Ellis–Van Creveld Syndrome

The Ellis–van Creveld syndrome (MIM 225500), also known as chondroectodermal dysplasia, is a skeletal *and* an ectodermal dysplasia. The skeletal dysplasia presents at birth with short limbs, especially the middle and distal segments, accompanied by postaxial polydactyly of the hands and sometimes of the feet (Fig. 720.1). Nail dysplasia and dental anomalies (including neonatal, absent, premature loss of teeth, and upper lip defects) constitute the ectodermal dysplasia. Common manifestations also include atrial septal defects and other congenital heart defects.

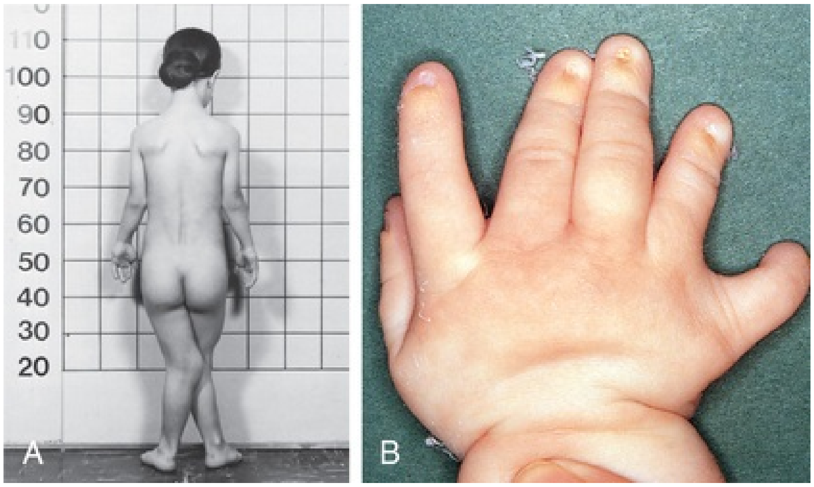

FIG. 720.1 **A,** Ellis–van Creveld syndrome in a young woman. Note short stature, joint contractures at the elbows, and marked genu valgum. **B,** Multiple digits (polydactyly) in a different patient with Ellis–van Creveld syndrome. (A, From Zipes DP, Libby P, Bonow R, Braunwald E, editors: *Braunwald's heart disease: a textbook of cardiovascular medicine* , ed 7, Philadelphia, 2004, WB Saunders, Fig 70.6; B from Beerman LB, Kreutzer J, Allada V: Cardiology. In Zitelli BJ, McIntire SC, Nowalk AJ, editors: *Zitelli and Davis' atlas of pediatric physical diagnosis* , ed 6, Philadelphia, 2012, Elsevier, Fig 5.6.)

Skeletal radiographs reveal short tubular bones with clubbed ends, especially the proximal tibia and ulna (Fig. 720.2). Carpal bones display extra ossification centers and fusion; cone-shaped epiphyses are evident in the hands. A bony spur is often noted above the medial aspect of the acetabulum.

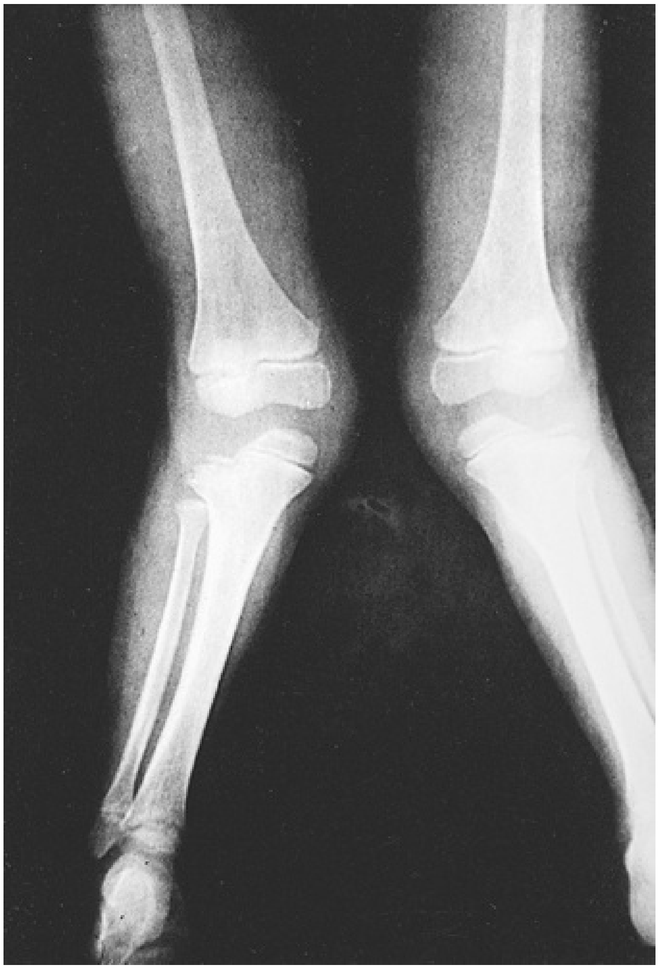

FIG. 720.2 Radiograph of lower extremities in Ellis–van Creveld syndrome. Tubular bones are short, and proximal fibula is short. Ossification is retarded in lateral tibia epiphyses, causing a knock-knee deformity.

Ellis–van Creveld syndrome is an autosomal recessive trait that occurs most often in the Amish. Mutations have been identified in one of two genes, *EVC (EVC1*) or *EVC2 (LIMBIN)* , which map in a head-to-head configuration to chromosome 4p. Mutations of *EVC2* are detected in the allelic condition Weyers acrofacial dysostosis (MIM 193530). EVC and EVC2 proteins are thought to influence hedgehog signaling in cilia by constitutively associating in a ring-like pattern in the ciliary transition zone and transducing extracellular signals to the nucleus via hedgehog signaling. Fgf18 may also play a significant role. This disorder is now classified under the **ciliopathies** with major skeletal involvement.

Approximately 30% of patients die of cardiac or respiratory problems during infancy. Life span is otherwise normal; adult heights range from 119 to 161 cm.

Asphyxiating Thoracic Dystrophy (See Also Chapter 445.3)

Asphyxiating thoracic dystrophy (MIM 208500), or **Jeune syndrome** , is an autosomal recessive chondrodysplasia that resembles Ellis–van Creveld syndrome. Newborn infants present with a long, narrow thorax and respiratory insufficiency associated with pulmonary hypoplasia. Neonates often die. Other neonatal manifestations include slightly short limbs and postaxial polydactyly. This condition results from a disturbance of primary cilia, most often from mutations of the gene encoding cytoplasmic dynein 2 heavy chain 1 (*DYNC2H1*). This disorder is now classified under **ciliopathies** with major skeletal involvement.

Skeletal radiographs show very short ribs with anterior expansion. Tubular limb bones are short with bulbous ends; cone-shaped epiphyses occur in hand bones. The iliac bones are short and square with a spur above the medial aspect of the acetabulum (Fig. 720.3).

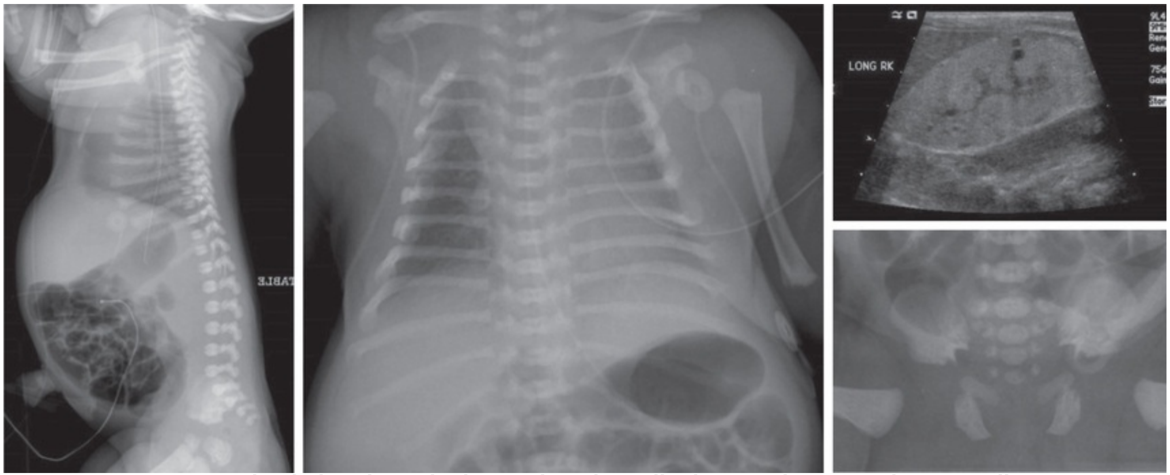

FIG. 720.3 Asphyxiating thoracic dystrophy. Short ribs long and narrow chest, small pelvis, trident acetabula, no platyspondyly (helps differentiate from thanatophoric dysplasia), cystic renal disease. (From Campeau P, Schlesinger AE: Skeletal dysplasias. [Updated 2017 Jan 30]. In De Groot LJ, Chrousos G, Dungan K, et al, editors. *Endotext [internet]* . South Dartmouth, MA, 2000, MDText.com , Inc., Fig 6. https://www.ncbi.nlm.nih.gov/books/NBK279130/)

If infants survive the neonatal period, respiratory function usually improves as the rib cage grows. Surgery that produces lateral thoracic expansion improves rib growth and enhances chest wall dimensions. Progressive renal dysfunction often develops during childhood. Intestinal malabsorption and hepatic dysfunction have also been reported.

Short-Rib Polydactyly Syndromes

These conditions, which share the clinical features of constricted thoracic cage, short ribs, polydactyly, very short extremities, lethality during the newborn period and autosomal recessive inheritance, are grouped into five syndromes (SRP-2-5). Mutations that map to cilia-related genes, *DYNCH2H, TT21B, WDR 19, WDR34, WDR35,* IFT80, *IFT140, IFT172 AND NEK1* , are found in this group of disorders.

Cartilage-Hair Hypoplasia–Anauxetic Spectrum Disorders

Cartilage-hair hypoplasia (CHH; MIM 250250) is also known as **metaphyseal chondrodysplasia–McKusick type** is part of a spectrum of disorders with metaphyseal involvement that includes metaphyseal dysplasia without hypotrichosis and anauxetic dysplasia. All disorders are characterized by severe disproportionate short stature, which is usually recognized at birth; the short limbs can lead to prenatal detection. They all show autosomal recessive inheritance and are caused by mutations in *RMRP* , a gene coding for a large untranslated RNA component of an enzyme complex involved in processing mitochondrial RNA. Loss of this gene product interferes with processing of both messenger RNA and ribosomal RNA, and correlates with the extent of bone dysplasia, whereas loss of messenger RNA processing correlates with the degree of hair hypoplasia, immunodeficiency, and hematologic abnormality. Molecular testing confirms the diagnosis, and prenatal diagnosis is available if the mutation is identified either in the patient or the parents.

Cartilage-Hair Hypoplasia

CHH is recognized during the 2nd year because of growth deficiency affecting the limbs, accompanied by flaring of the lower rib cage, a prominent sternum, and bowing of the legs. The hands and feet are short, and the fingers are very short with extreme ligamentous laxity. The hair is thin, sparse, and light colored; the nails are hypoplastic; and the skin can be hypopigmented.

Radiographs show short tubular bones with flared, irregularly mineralized, and cupped metaphyses (Fig. 720.4). The knees are more affected than are the hips, and the fibula is disproportionately longer than the tibia. The metacarpals and phalanges are short and broad. Spinal radiographs reveal mild platyspondyly.

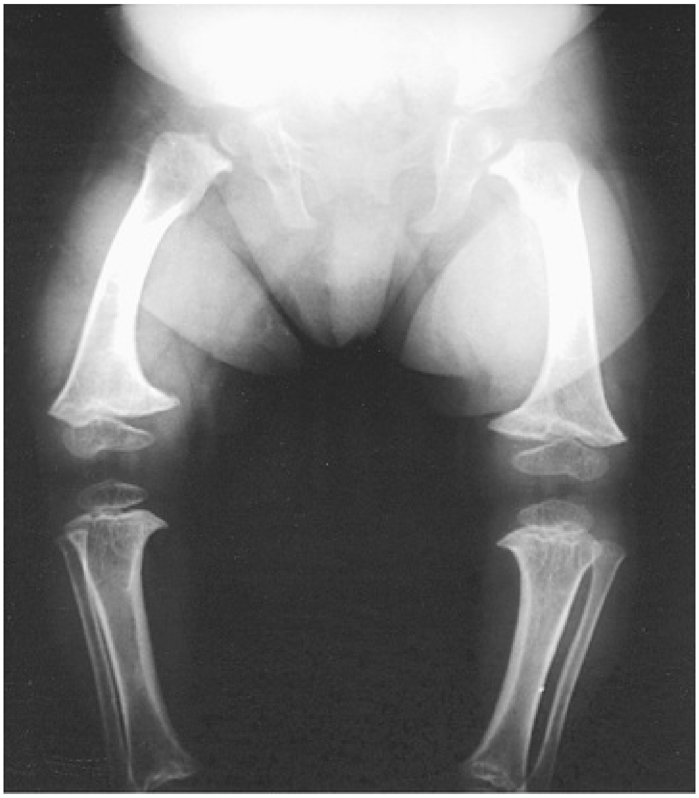

FIG. 720.4 Radiograph of lower extremities in cartilage-hair hypoplasia. The tubular bones are short and the metaphyses are flared and irregular. The fibula is disproportionately long compared with the tibia. The femoral necks are short.

Nonskeletal manifestations associated with CHH include immunodeficiency (T-cell abnormalities, neutropenia, leukopenia, and susceptibility to varicella zoster virus infections; children also may have complications from smallpox and polio vaccinations), malabsorption, celiac disease, and Hirschsprung disease. Adults are at risk for malignancy, especially non-Hodgkin lymphoma and skin tumors. Adult height ranges from 107 to 157 cm.

The highest birth prevalence is in the Amish and Finnish populations because of founder effect. Carrier frequency in the Amish is 1 : 19 with 1 per 1,300 births affected compared to a carrier frequency of 1 : 76 and 1 in 23,000 births affected in Finland. The exact prevalence in the general population is not known, but CHH is relatively rare. However, 2 allelic conditions, metaphyseal dysplasia without hypotrichosis and anauxetic dysplasia expand the phenotypic spectrum. Children with a growth disorder and abnormal hair should be evaluated for RMRP mutations so as to not miss the diagnosis.

Metatropic Dysplasia

Metatropic dysplasia (MIM 156530) is an autosomal dominant disorder resulting from heterozygous mutations of transient receptor potential vanilloid family 4 (TRPV4), which encodes a calcium-permeable cation channel. Newborn infants present with a long narrow trunk and short extremities. A tail-like appendage sometimes extends from the base of the spine. Odontoid hypoplasia is common and may be associated with cervical instability. Kyphoscoliosis appears in late infancy and progresses through childhood, often becoming severe enough to compromise cardiopulmonary function. The joints are large and become progressively restricted in mobility, except in the hands. Contractures often develop in the hips and knees during childhood. Although severely affected infants can die at a young age from respiratory failure, patients usually survive, although they can become disabled as adults from the progressive musculoskeletal deformities. Adult heights range from 110 to 120 cm.

Skeletal radiographs show characteristic changes dominated by severe platyspondyly and short tubular bones with expanded and deformed metaphyses that exhibit a dumbbell appearance (Fig. 720.5). The pelvic bones are hypoplastic and exhibit a halberd appearance because of a small sacrosciatic notch and a notch above the lateral margin of the acetabulum. Metatropic dysplasia is included in the TRPV4 group.

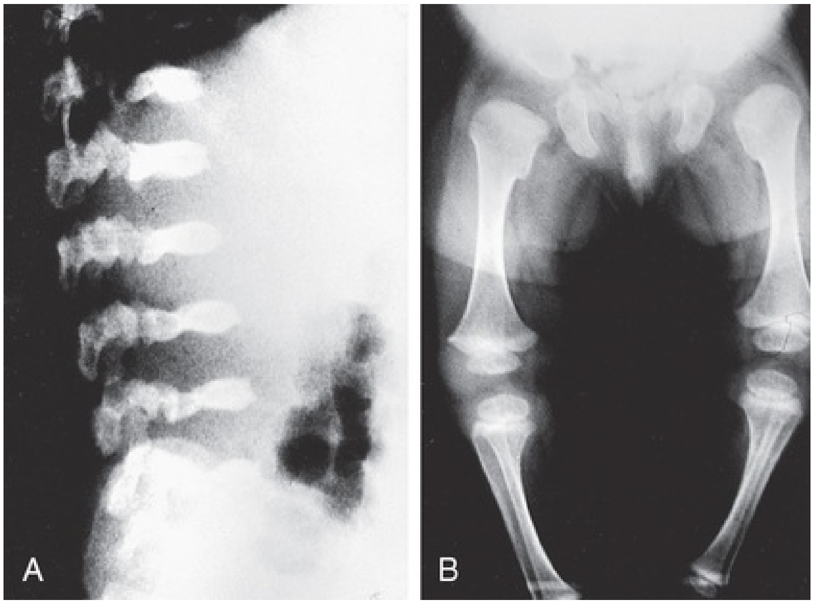

FIG. 720.5 **A,** Radiograph of the lateral thoracolumbar spine in metatropic dysplasia showing severe platyspondyly. **B,** Radiograph of lower extremities in metatropic dysplasia showing short tubular bones with widened metaphyses. The femurs have a dumbbell appearance.

Spondylometaphyseal Dysplasia, Kozlowski Type

Kozlowski type of spondylometaphyseal dysplasia (MIM 184252) is an autosomal dominant allelic disorder to metatropic dysplasia caused by *TRPV4* mutations. Mutations of *TRPV4* have also been identified in autosomal dominant brachyolmia (MIM 113500), whose phenotype is dominated by progressive scoliosis and platyspondyly on x-rays and familial digital arthropathy with brachydactyly (MIM 606835), which is characterized by deforming painful osteoarthritis of the interphalangeal, metacarpophalangeal, and metatarsophalangeal joints starting after the 1st decade of life. The rest of the skeleton is unaffected.

Kozlowski type of spondylometaphyseal dysplasia manifests in early childhood with mild short stature involving mostly the trunk and a waddling gait. The hands and feet may be short and stubby. Radiographs show flattening of vertebral bodies. The metaphyses of tubular bones are widened and irregularly mineralized, especially at the proximal femur. The pelvic bones manifest mild hypoplasia. Scoliosis can develop during adolescence. The disorder is otherwise uncomplicated, and manifestations are limited to the skeleton. Adults reach heights of 130-150 cm.

Disorders Involving Filamins

Mutations of genes encoding filamin A and filamin B proteins have been detected in diverse disorders of skeletal development: filamin A mutations in otopalatodigital syndromes type 1 and 2, frontometaphyseal dysplasia, Melnick-Needles syndrome and terminal osseous dysplasia with pigmentary defects (MIM 311300, 304120, 305620, 309350, 300244) and filamin B mutations in Larsen syndrome and perinatal lethal atelosteogenesis types 1 and 3, spondylo-carpal-tarsal dysplasia and Boomerang dysplasia (MIM 150250, 108720, 108721, 272460, 112310). Filamins functionally connect extracellular to intracellular structural proteins, thereby linking cells to their local microenvironment, which is essential for skeletal development and growth.

Juvenile Osteochondroses

The juvenile osteochondroses are a heterogeneous group of disorders in which regional disturbances in bone growth cause noninflammatory arthropathies. Table 720.1 summarizes the juvenile osteochondroses. Some have localized pain and tenderness (Freiberg disease, Osgood-Schlatter disease [see Chapter 697.4], osteochondritis dissecans [see Chapter 697.3]), whereas others present with painless limitation of joint movement (Legg-Calvé-Perthes disease [see Chapter 698.3], Scheuermann disease [see Chapter 699.4]). Bone growth may be disrupted, leading to deformities. The diagnosis is usually confirmed radiographically, and treatment is symptomatic. The pathogenesis of these disorders is believed to involve ischemic necrosis of primary and secondary ossification centers. Although familial forms have been reported, these disorders usually occur sporadically.

Table 720.1

Juvenile Osteochondroses

EPONYM	AFFECTED REGION	AGE AT PRESENTATION
Legg-Calvé-Perthes disease	Capital femoral epiphysis	3-12 yr
Osgood-Schlatter disease	Tibial tubercle	10-16 yr

Sever disease	Os calcaneus	6-10 yr
Freiberg disease	Head of second metatarsal	10-14 yr
Scheuermann disease	Vertebral bodies	Adolescence
Blount disease	Medial aspect of proximal tibial epiphysis	Infancy or adolescence
Osteochondritis dissecans	Subchondral regions of knee, hip, elbow, and ankle	Adolescence

Caffey Disease (Infantile Cortical Hyperostosis)

This is a rare disorder of unknown etiology characterized by cortical hyperostosis with inflammation of the contiguous fascia and muscle. It is often sporadic, but both autosomal dominant (MIM 244460) and autosomal recessive (MIM 127000) forms have been reported. Mutations in *Fam111A* (family with sequence similarity 111, member A) and *TBCE* (tubulin-specific chaperone E) have been identified in the autosomal dominant and recessive forms, respectively. Caffey dysplasia is classified in the slender bone dysplasia group.

Prenatal and more often postnatal onsets have been described. Prenatal onset may be mild (autosomal dominant) or severe (autosomal recessive). Severe prenatal disease is characterized by typical bone lesions, polyhydramnios, hydrops fetalis, severe respiratory distress, prematurity, and high mortality. Onset in infancy (younger than 6 mo; average: 10 wk) is most common; manifestations include the sudden onset of irritability, swelling of contiguous soft tissue that precedes the cortical thickening of the underlying bones, fever, and anorexia. The swelling is painful with a wood-like induration but with minimal warmth or redness; suppuration is absent. There are unpredictable remissions and relapses; an episode can last 2 wk to 3 mo. The most common bones involved include the mandible (75%) (Fig. 720.6), the clavicle, and the ulna. If swelling is not prominent or visible, the diagnosis might not be evident.

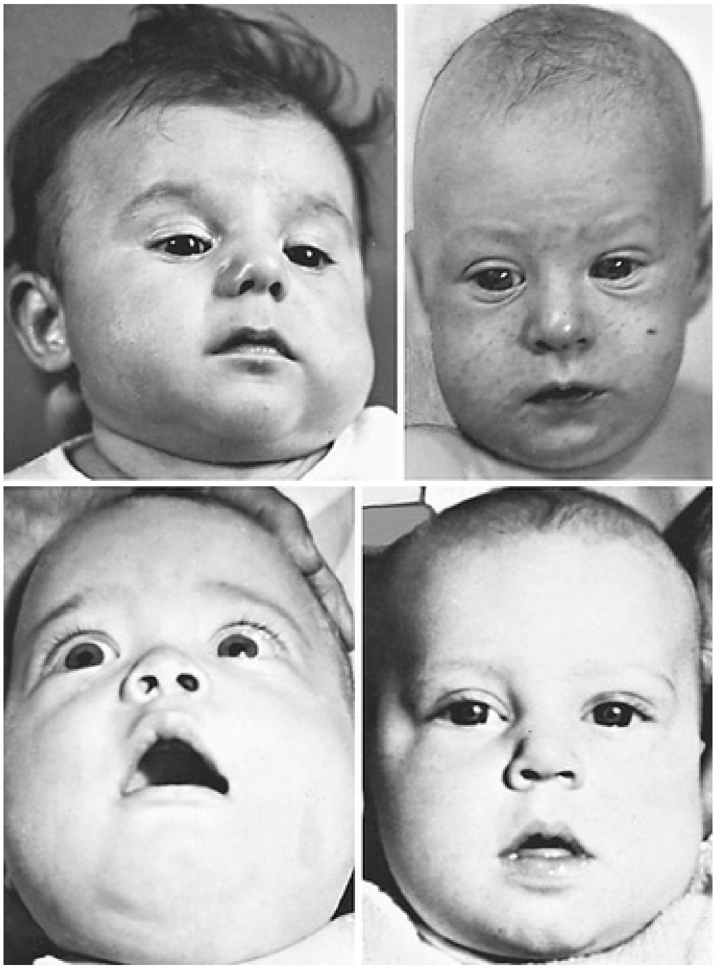

FIG. 720.6 Facies in infantile cortical hyperostosis. In almost all cases, the changes have appeared before the 5th mo of life. Unilateral swelling of the left cheek and left side of the jaw in an infant 12 wk of age. (From Slovis TL: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby.)

Laboratory features include elevated erythrocyte sedimentation rate and serum alkaline phosphatase as well as, in some patients, increased serum prostaglandin E levels. There may be thrombocytosis and anemia. The radiographic features include soft tissue swelling and calcification and cortical hyperostosis (Fig. 720.7). All bones may be affected except the phalanges or vertebral bodies. The **differential diagnosis** includes other causes of hyperostosis such as chronic vitamin A intoxication, prolonged prostaglandin E infusion in children with ductal dependent congenital heart disease, primary bone tumors, and scurvy.

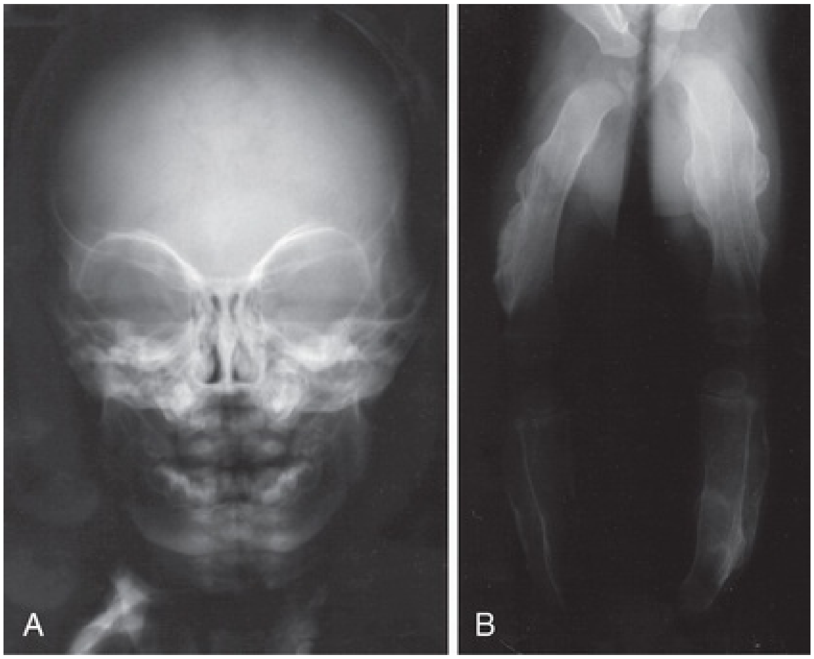

FIG. 720.7 **A,** X-ray of a 5 mo old infant showing hyperostosis of the mandible. **B,** X-ray of a 5 mo old infant showing hyperostosis of both legs. (From Kamoun-Goldrat A, le Merrer M: Infantile cortical hyperostosis (Caffey disease): a review. *J Oral Maxillofac Surg* 66:2145–2150, 2008, Figs. 1 and 2.)

Complications are unusual but include pseudoparalysis with limb or scapula involvement, pleural effusions (rib), torticollis (clavicle), mandibular asymmetry, bone fusion (ribs or ulna and radius), and bone angulation deformities (common with severe prenatal onset). Treatment includes indomethacin and prednisone (if there is a poor response to indomethacin).

Fibrodysplasia Ossificans Progressiva

Fibrodysplasia ossificans progressiva (FOP) (MIM 135100) is a rare and severely disabling disorder characterized by progressive extraskeletal heterotopic bone formation in soft connective tissues including muscles, tendons, ligaments, fascia, and aponeuroses. With the exception of deformity of the large toes, infants are normal at birth. Episodes of painful soft-tissue swelling with inflammation usually begin in early childhood initially involving the upper back and neck, and later the entire trunk and extremities. Repeated episodes (flare-ups) slowly transform the soft tissues into bands or plates of bone that span joints and progressively limit movement and mobility. Episodes are often triggered by injury, intramuscular injections, and viral infection. Most patients are wheelchair bound by their late teens. The average life span is approximately 40 yr, with death usually resulting from complications of thoracic insufficiency.

FOP results from heterozygous activating mutations of the gene *(ACVR1)* encoding the bone morphogenetic protein (BMP) type I receptor, activin A receptor type I *(ALK2)* . Patients with classic FOP have the same missense *ACVR1* mutation, which enhances BMP signaling, which, in turn, induces inflammation and aberrant endochondral ossification through mechanisms that are poorly understood. Environmental factors, such as injury, play an important role in triggering these events. *ACVR1* mutations usually occur sporadically, but autosomal dominant transmission has rarely been observed. FOP is classified in the disorganized development of skeletal components group.

There is currently no definitive treatment for FOP. Supportive care includes avoidance of injury-prone physical activities, intramuscular injections including immunizations and overstretching of the jaw during dental procedures. Corticosteroids and other antiinflammatory agents reduce inflammation and pain during flare-ups, but are unable to prevent heterotopic bone formation. Studies in FOP animal models suggest that BMP type I kinase inhibitors and retinoic acid receptor γ agonists, which block chondrogenesis—the initial step in endochondral ossification—may be useful therapies in the future. An animal FOP study has indicated that mutant ALK2 responds to activin A, induces canonical BMP signaling and leads to heterotopic bone formation, providing an additional possible therapeutic target. Notably, the retinoic acid receptor γ agonist Palovarotene is being tested in an ongoing phase 2 clinical trial with FOP patients (NCT02190747).

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CHAPTER 721

Osteogenesis Imperfecta

Joan C. Marini

Osteoporosis is fragility of the skeletal system and a susceptibility to fractures of the long bones or vertebral compressions from mild or inconsequential trauma (see Chapter 726). **Osteogenesis imperfecta** (**OI**) (brittle bone disease), the most common genetic cause of osteoporosis, is a generalized disorder of connective tissue. The spectrum of OI is extremely broad, ranging from forms that are lethal in the perinatal period to a mild form in which the diagnosis may be equivocal in an adult.

Etiology

Structural or quantitative defects in type I collagen cause the full clinical spectrum of OI (types I-IV). Type I collagen is the primary component of the extracellular matrix of bone and skin. Between 15% and 20% of patients clinically indistinguishable from OI do not have a molecular defect in type I collagen (Table 721.1). These cases are caused by defects in genes whose protein products interact with type I collagen. One group of patients has overmodified collagen, with similar biochemical findings to those with collagen structural defects and severe or lethal OI bone dysplasia. These cases are caused by recessive null mutations in any of the three components of the collagen prolyl 3-hydroxylation complex, prolyl 3-hydroxylase 1 (coded by the *LEPRE1* gene on chromosome 1p34.1) or its associated protein, CRTAP, or cyclophilin B (CyPB, encoded by *PPIB*). A second set of cases without collagen defects have biochemically normal collagen. Defects in *IFITM5* and *SERPINF1* account for defects in mineralization in types V and VI OI, while mutations in *SERPINH1* , encoding the collagen chaperone HSP47, and *FKBP10* , encoding the peptidyl-prolyl *cis-trans* isomerase FKBP65, cause types X and XI OI, respectively. Rare mutations in *BMP1*, the enzyme that processes the C-propeptide of type I collagen, also cause a recessive form of OI. The most recent set of genes added to the recessive OI causative panel (*SP7* , type XIII OI; *TMEM38B* , type XIV OI; *WNT1* , type XV OI; *CREB3L1* , type XVI OI, *SPARC* , type XVII OI, and *MBTPS2* , type XVIII OI) not only are involved in osteoblast differentiation but also affect collagen synthesis and cross linking. There are very few individuals with OI whose genetic defect is not in a known causative gene.

Table 721.1

Osteogenesis Type, Gene Defects, and Phenotypes

OI TYPE	INHERITANCE	DEFECTIVE GENE	DEFECTIVE PROTEIN
DEFECTS IN COLLAGEN SYNTHESIS AND STRUCTURE			
Type I, II, III, IV	AD	*COL1A1 or COL1A2*	α1(1) or α2(1) collagen
DEFECTS IN BONE MINERALIZATION			
Type V	AD	*IFITM5*	BRIL
Type VI	AR	*SERPINF1*	PEDF
DEFECTS IN COLLAGEN MODIFICATION			
Type VII	AR	*CRTAP*	CRTAP
Type VIII	AR	*LEPRE1*	P3H1
Type IX	AR	*PPIB*	PPIB (CyPB)
DEFECTS IN COLLAGEN PROCESSING AND CROSSLINK			
Type X	AR	*SERPINH1*	HSP47
Type XI	AR	*FKBP10*	FKBP65
Unclassified	AR	*PLOD2*	LH2
Type XII	AR	*BMP1*	BMP1
DEFECTS IN OSTEOBLAST DIFFERENTIATION AND FUNCTION			
Type XIII	AR	*SP7*	SP7 (OSTERIX)
Type XIV	AR	*TMEM38B*	TRIC-B
Type XV	AR/AD	*WNT1*	WNT1
Type XVI	AR	*CREB3L1*	OASIS
Type XVII	AR	*SPARC*	SPARC (Osteonectin)
Type XVIII	XR	*MBTPS2*	S2P

AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive.

From Kang H, Aryal ACS, Marini JC: Osteogenesis imperfecta: new genes reveal novel mechanisms in bone dysplasia. *Transl Res* 181:27–48, 2017, Table 1, p. 29.

Epidemiology

The autosomal dominant forms of OI occur equally in all racial and ethnic groups, whereas recessive forms occur predominantly in ethnic groups with consanguineous marriages or as a founder effect in an isolated population. The

West African founder mutation for type VIII OI has a carrier frequency of 1 in 200-300 among African Americans. The collective incidence of all types of OI detectable in infancy is approximately 1 in 20,000. There is a similar incidence of the mild form OI type I.

Pathology

The collagen structural mutations in OI cause the bones to be globally abnormal. The bone matrix contains abnormal type I collagen fibrils and relatively increased levels of types III and V collagen. Several noncollagenous proteins of bone matrix are also reduced. Bone cells contribute to OI pathology, with abnormal osteoblast differentiation and increased numbers of active bone resorbing osteoclasts. The hydroxyapatite crystals deposited on this matrix are poorly aligned with the long axis of fibrils, and there is paradoxical hypermineralization of bone.

Pathogenesis

Type I collagen is a heterotrimer composed of 2 α1(I) chains and 1 α2(I) chain. The chains are synthesized as procollagen molecules with short globular extensions on both ends of the central helical domain. The helical domain is composed of uninterrupted repeats of the sequence Gly-X-Y, where Gly is glycine, X is often proline, and Y is often hydroxyproline. The presence of glycine at every third residue is crucial to helix formation because its small side chain can be accommodated in the interior of the helix. The chains are assembled into trimers at their carboxyl ends; helix formation then proceeds linearly in a carboxyl to amino direction. Concomitant with helix assembly and formation, helical proline and lysine residues are hydroxylated by prolyl 4-hydroxylase and lysyl hydroxylase, and some hydroxylysine residues are glycosylated.

Collagen structural defects are predominantly of two types: 80% are point mutations causing substitutions of helical glycine residues or crucial residues in the C-propeptide by other amino acids, and 20% are single exon splicing defects. The clinically mild OI type I has a quantitative defect, with null mutations in one α1(I) allele leading to a reduced amount of normal collagen.

The glycine substitutions in the two α chains have distinct genotype–

phenotype relationships. One third of mutations in the α_1 chain are lethal, and those in α2(I) are predominantly nonlethal. Two lethal regions in α1(I) align with major ligand binding regions of the collagen helix. Lethal mutations in α2(I) occur in eight regularly spaced clusters along the chain that align with binding regions for matrix proteoglycans in the collagen fibril.

Classical OI (Sillence types I-IV) is an autosomal dominant disorder, as is type V OI. Some familial recurrences of OI are caused by parental mosaicism for dominant collagen mutations. Recessive OI accounts for 7–10% of newly diagnosed OI in North America. Three recessive types are caused by null mutations in the genes coding for the components of the collagen prolyl 3-hydroxylation complex in the endoplasmic reticulum (*LEPRE1* , *CRTAP*, or *PPIB)* . It is not yet clear whether absence of the complex itself or of the modification is the crucial feature of these types of recessive OI. Other recessive types are caused by null mutations in genes whose products are involved in collagen folding (*SERPINH1, FKBP10*), or mineralization (*SERPINF1)* , or defects in osteoblast differentiation and function (*SP7, TMEM38B, WNT1, CREB3L1, SPARC, MBTPS2*).

Clinical Manifestations

Classical OI was described with the triad of fragile bones, blue sclerae, and early deafness, although most cases do not have all of these features. The Sillence classification divides OI into four types based on clinical and radiographic criteria. Types V and VI were later proposed based on histologic distinctions. Subsequent types VII-XVIII were based on identification of the molecular defect, followed by clinical description.

Osteogenesis Imperfecta Type I (Mild)

OI type I is sufficiently mild that it is often found in large pedigrees. Many type I families have blue sclerae, recurrent fractures in childhood, and presenile (i.e. beginning in early adulthood) hearing loss (30–60%). Both types I and IV are divided into A and B subtypes, depending on the absence (A) or presence (B) of **dentinogenesis imperfecta,** a type of dentin dysplasia resulting in discolored (often blue-gray or amber), translucent teeth that wear down rapidly or break. Other possible connective tissue abnormalities include hyperextensible joints, easy bruising, thin skin, joint laxity, scoliosis, wormian bones, hernia, and mild short stature compared with family members. Fractures result from mild to moderate trauma but decrease after puberty.

Osteogenesis Imperfecta Type II (Perinatal Lethal)

Infants with OI type II may be stillborn or die in the 1st yr of life. Birthweight and length are small for gestational age. There is extreme fragility of the skeleton and other connective tissues. There are multiple intrauterine fractures of long bones, which have a crumpled appearance on radiographs. There are striking micromelia and bowing of extremities; the legs are held abducted at right angles to the body in the frogleg position. Multiple rib fractures create a beaded appearance, and the small thorax contributes to respiratory insufficiency. The skull is large for body size, with enlarged anterior and posterior fontanels. Sclerae are dark blue-gray. The cerebral cortex has multiple neuronal migration and other defects (agyria, gliosis, periventricular leukomalacia).

Osteogenesis Imperfecta Type III (Progressive Deforming)

OI type III is the most severe nonlethal form of OI and results in significant physical disability. Birthweight and length are often low normal. Fractures usually occur in utero. There is relative macrocephaly and triangular facies (Fig. 721.1). Postnatally, fractures occur from inconsequential trauma and heal with deformity. Disorganization of the bone matrix results in a “popcorn” appearance at the metaphyses (Fig. 721.2). The rib cage has flaring at the base, and pectal deformity is frequent. Virtually all type III patients have scoliosis and vertebral compression. Growth falls below the curve by the 1st yr; all type III patients have extreme short stature. Scleral hue ranges from white to blue. Dentinogenesis imperfecta, hearing loss, and kyphoscoliosis may be present or develop over time.

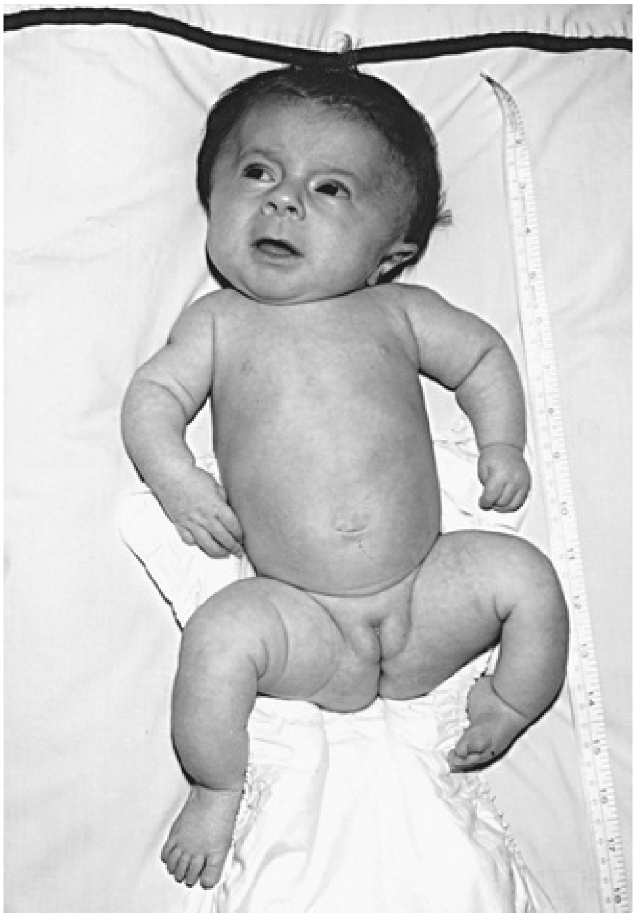

FIG. 721.1 Infant with type III osteogenesis imperfecta displays shortened bowed extremities, thoracic deformity, and relative macrocephaly.

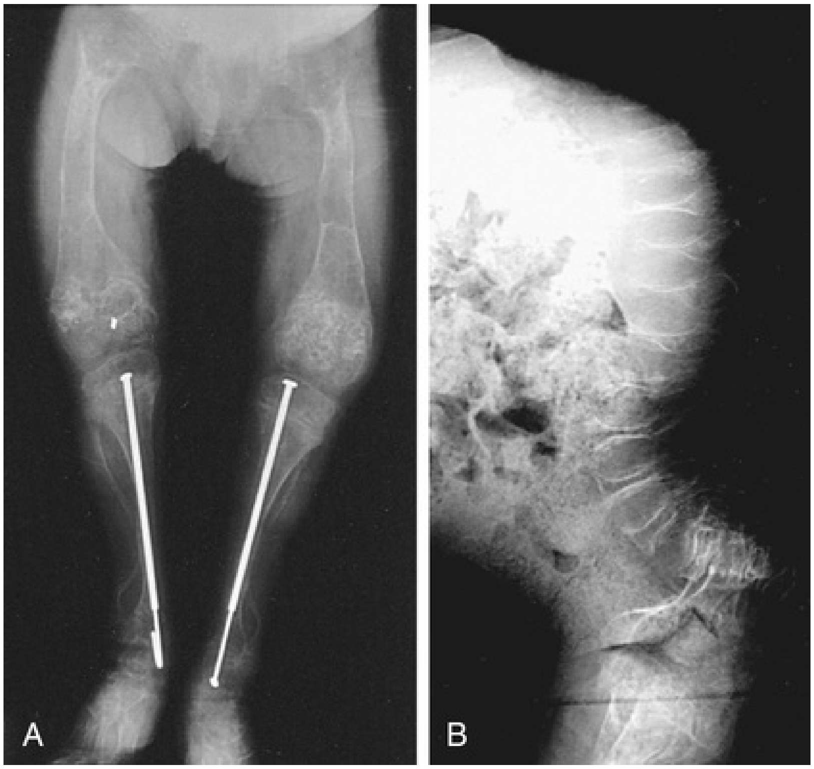

FIG. 721.2 Typical features of type III osteogenesis imperfecta radiographs in a 6 yr old child. **A,** Lower long bones are osteoporotic, with metaphyseal flaring, “popcorn” formation at growth plates, and placement of intramedullary rods. **B,** Vertical bodies are compressed and osteoporotic.

Osteogenesis Imperfecta Type IV (Moderately Severe)

Patients with OI type IV can present at birth with in utero fractures or bowing of lower long bones. They can also present with recurrent fractures after ambulation and have normal to moderate short stature. Most children have moderate bowing even with infrequent fractures. Children with OI type IV require orthopedic and rehabilitation intervention, but they are usually able to attain community ambulation skills. Fracture rates decrease after puberty. Radiographically, they are osteoporotic and have metaphyseal flaring and vertebral compressions. Scleral hue may be blue or white.

Osteogenesis Imperfecta Type V (Hyperplastic Callus) and Type VI Hyperosteoidosis

(Mineralization Defect)

Types V and VI OI patients clinically have OI similar in skeletal severity to types IV and III, respectively, but they have distinct findings on bone histology. Type V patients also usually have some combination of hyperplastic callus, calcification of the interosseous membrane of the forearm, and/or a radiodense metaphyseal band. They constitute <5% of OI cases. All type V OI patients are heterozygous for the same mutation in *IFITM5* , which generates a novel start codon for the bone protein BRIL. Ligamentous laxity may be present; blue sclera or dentinogenesis imperfecta are not present. Patients with type VI OI have progressive deforming OI that does not manifest at birth. They have distinctive bone histology with broad osteoid seams and fish-scale lamellation under polarized light, caused by deficiency of pigment epithelium derived factor, encoded by *SERPINF1* . Types V and VI are connected in intracellular osteoblast pathways—*SERPINF1* transcripts are increased in type V OI, while *IFITM5* transcripts are decreased in type VI OI.

Osteogenesis Imperfecta Types VII, VIII, and IX (Autosomal Recessive)

Types VII and VIII patients overlap clinically with types II and III OI but have distinct features including white sclerae, rhizomelia, and small to normal head circumference. Surviving children have severe osteochondrodysplasia with extreme short stature and dual-energy x-ray absorptiometry L1-L2 z-score in the −6 to −7 range. Type IX OI is very rare (only 8 cases reported). The severity is quite broad, ranging from lethal to moderately severe. These children have white sclerae but do not have rhizomelia.

Osteogenesis Imperfecta Types X and XI (Autosomal Recessive)

There have been several reports of severe to lethal type X OI caused by defects affecting the serine-type endopeptidase inhibitor domain of HSP47. This domain is responsible for the HSP47 chaperone function that helps to maintain the folded state of procollagen heterotrimers. HSP47 and FKBP65, the protein responsible for type XI OI, cooperate in collagen synthesis. Type XI OI is a more prevalent recessive form with a moderate to severe skeletal phenotype, including white sclerae and normal teeth. Congenital contractures of large joints may occur with the same mutations that cause only skeletal fragility, even in sibships. At the opposite end of the spectrum, a deletion of a single tyrosine residue causes Kuskokwim syndrome, a congenital contracture disorder with very mild vertebral findings and osteopenia. Defects in *FKBP10* decrease collagen crosslinking in matrix because FKBP65 is the foldase for lysyl hydroxylase 2, which hydroxylates collagen telopeptide residues important for cross linking.

High Bone Mass Osteogenesis Imperfecta (Cleavage of the Procollagen C-Propeptide)

Autosomal dominant mutations in the C-propeptide cleavage site of procollagen or recessive defects in the enzyme responsible for its cleavage cause bone fragility with normal or elevated dual-energy x-ray absorptiometry bone density z-scores. Individuals with dominant mutations have normal stature, white sclerae and teeth, and mild to moderate OI. Null mutations in *BMP1* lead to a more severe skeletal phenotype with short stature, scoliosis and bone deformity, because *BMP1* has other substrates in addition to type I collagen.

Defects in Osteoblast Differentiation (Types XIII-XVIII OI)

The most recent functional grouping of genes causing recessive OI (types XIII to XVIII) affect osteoblast differentiation and are collagen related. *SP7* (type XIII OI) regulates osteoblast differentiation and is critical for bone formation. *TMEM38B* (type XIV OI) defects are clinically indistinguishable from type IV OI. *TMEM38B* encodes the endoplasmic reticulum membrane cation channel TRIC-B, which affects calcium flux from the endoplasmic reticulum to the cytoplasm. Since many enzymes involved in collagen metabolism are calcium dependent, collagen synthesis is globally dysregulated in the absence of TRIC-B, with significant intracellular retention. Collagen posttranslational modification is also impaired, leading to underhydroxylation of the collagen helix. *WNT1* (type XV OI) recessive defects cause severe progressive deforming OI. Wnt signaling pathway activation through the Frizzled receptor on the osteoblast surface increases bone mass, but deficiency of Wnt decreases it. SPARC (type XVII OI), also known as osteonectin, is a glycoprotein component of extracellular matrix.

Defects in residues important for SPARC binding to collagen were reported in two cases of moderate to severe OI.

The genes *MBTPS2* and *CREB3L1* , causing types XVIII and XVI OI, respectively, encode proteins involved in regulated intramembrane proteolysis (RIP). *MBTPS2* encodes the transmembrane Golgi protein site-2 protease (S2P), that acts in successively with S1P to activate regulatory molecules in times of cell stress. OASIS, encoded by *CREB3L1* , is an RIP substrate.

Interestingly, missense substitutions in S2P in OI patients result in underhydroxylation of the collagen residue important for crosslinking of collagen in matrix, thus impairing bone strength. In OASIS-null mice, collagen transcription has been shown to be impaired.

Other Genes for Osteogenesis Imperfecta

A very small percentage of OI patients cannot be accounted for by mutations known OI genes.

Laboratory Findings

DNA sequencing is the first diagnostic laboratory test; several Clinical Laboratory Improvement Amendments (CLIA)-certified sequencing labs offer panels to test for dominant and recessive OI. Mutation identification is useful to determine the type with certainty and to facilitate family screening and prenatal diagnosis. It is also possible to screen for type VI OI by the determination of serum pigment epithelium-derived factor level, which is severely reduced in this type.

If dermal fibroblasts are obtained these can be useful for determining the level of transcripts of the candidate gene and for collagen biochemical testing, which is positive in most cases of types I-IV and IX OI, and in all cases of VII/VIII OI. In OI type I, the reduced amount of type I collagen results in an increase in the ratio of type III to type I collagen on gel electrophoresis.

Severe OI can be detected prenatally by level II ultrasonography as early as 16 wk of gestation. OI and thanatophoric dysplasia may be confused. Fetal ultrasonography might not detect OI type IV and rarely detects OI type I. For recurrent cases, chorionic villus biopsy can be used for biochemical or molecular studies. Amniocytes produce false-positive biochemical studies but can be used for molecular studies in appropriate cases.

In the neonatal period, the normal to elevated alkaline phosphatase levels present in OI distinguish it from hypophosphatasia. During the school-age period, children with type VI OI have notably elevated serum alkaline phosphatase.

Complications

The morbidity and mortality of OI are cardiopulmonary. Recurrent pneumonias and declining pulmonary function occur in childhood, and cor pulmonale is seen in adults.

Neurologic complications include basilar invagination, brainstem compression, hydrocephalus, and syringohydromyelia. Most children with OI types III and IV have basilar invagination, but brainstem compression is uncommon. Basilar invagination is best detected with spiral CT of the craniocervical junction (Fig. 721.3).

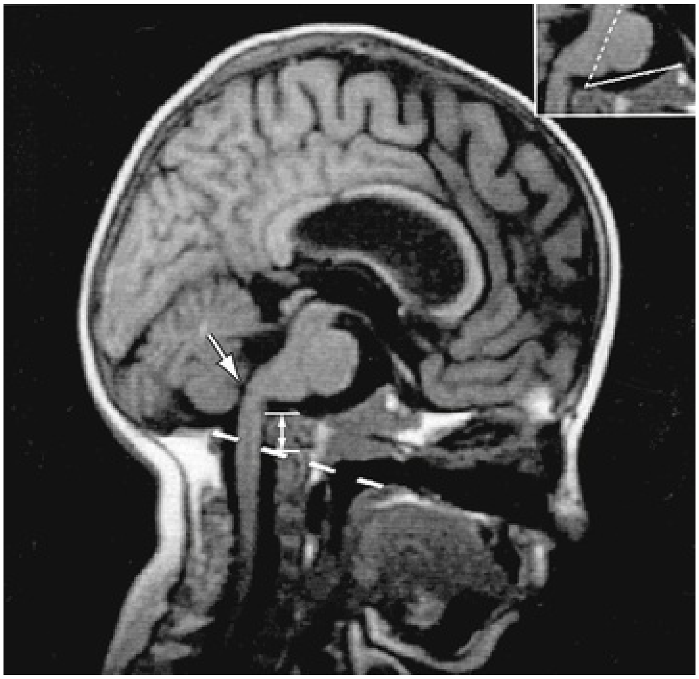

FIG. 721.3 Typical feature of basilar invagination shown in the sagittal MRI of an asymptomatic child with type III osteogenesis imperfecta. There is invagination of the odontoid above the Chamberlain line, causing

compression and kinking at the pontomedullary junction *(arrow).*

Treatment

There is no cure for OI. For severe nonlethal OI, active physical rehabilitation in the early years allows children to attain a higher functional level than orthopedic management alone. Children with OI type I and some with type IV are spontaneous ambulators. Children with types III, IV, V, VI, and XI OI benefit from gait aids and a program of swimming and conditioning. Severely affected patients require a wheelchair for community mobility but can acquire transfer and self-care skills. Teens with OI can require psychologic support with body image issues. Growth hormone improves bone histology in growth-responsive children (usually types I and IV).

Orthopedic management of OI is aimed at fracture management and correction of deformity to enable function. Fractures should be promptly splinted or cast; OI fractures heal well, and cast removal should be aimed at minimizing immobilization osteoporosis. Correction of long-bone deformity requires an osteotomy procedure and placement of an intramedullary rod.

A several-year course of treatment of children with OI with bisphosphonates (IV pamidronate or oral olpadronate or risedronate) confers some benefits. Bisphosphonates decrease bone resorption by osteoclasts; OI patients have increased bone volume that still contains the defective collagen. Bisphosphonates are more beneficial for vertebrae (trabecular bone) than long bones (cortical bone). Treatment for 1-2 yr results in increased L1-L4 dual-energy x-ray absorptiometry and, more importantly, improved vertebral compressions and area. However, follow-up of bisphosphonate-treated children has shown that the incidence of scoliosis is unchanged even in children treated early, although there was a modest delay in progression in type III OI. The relative risk of long-bone fractures is modestly decreased by several years of bisphosphonates. However, the material properties of long bones are weakened by prolonged treatment and nonunion after osteotomy is increased. There is no effect of bisphosphonates on mobility scores, muscle strength, or bone pain. Limiting treatment duration to 2-3 yr in mid-childhood can maximize the benefits and minimize the detriment to cortical material properties. Benefits appear to persist several years after the treatment interval, and alternation of treatment intervals and drug holidays may be beneficial. Side effects include abnormal long-bone remodeling, increased incidence of fracture nonunion, and osteopetrotic-like brittleness to bone.

Prognosis

OI is a chronic condition that limits both life span and functional level. Infants with OI type II usually die within months to 1 yr of life. An occasional child with radiographic type II and extreme growth deficiency survives to the teen years. Persons with OI type III have a reduced life span with clusters of mortality from pulmonary causes in early childhood, the teen years, and the 40s. OI types I, IV, and V OI are compatible with a full life span. The oldest reported individuals with type VIII are in their 3rd decade, and some with type XI are in their 4th decade. The long-term prognosis for most recessive types is still emerging, and many adults with OI have not had molecular testing.

Individuals with OI type III are usually wheelchair dependent. With aggressive rehabilitation, they can attain transfer skills and household ambulation. OI type IV children usually attain community ambulation skills either independently or with gait aids.

Genetic Counseling

For autosomal dominant OI, the risk of an affected individual passing the gene to the individual's offspring is 50%. An affected child usually has about the same severity of OI as the parent; however, there is variability of expression, and the child's condition can be either more or less severe than that of the parent. The empirical recurrence risk to an apparently unaffected couple of having a second child with OI is 5–7%; this is the statistical chance that 1 parent has germline mosaicism. The collagen mutation in the mosaic parent is present in some germ cells and may be present in somatic tissues. If a parent is a mosaic carrier, the risk of recurrence may be as high as 50%.

For recessive OI, the recurrence risk is 25% per pregnancy. No known individual with severe nonlethal recessive OI has had a child.

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CHAPTER 722

Marfan Syndrome

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Marfan syndrome (MFS) is an inherited, systemic, connective tissue disorder caused by mutations in the gene encoding the extracellular matrix (ECM) protein fibrillin-1. It is primarily associated with skeletal, cardiovascular, and ocular pathology. The diagnosis is based on clinical findings, some of which are age dependent.

Epidemiology

The incidence is 1 in 10,000 live births, and approximately 25% of cases are sporadic. The disorder shows autosomal dominant inheritance, with high penetrance, but variable expression; both interfamilial and intrafamilial clinical variation is common. There is no racial or gender preference.

Pathogenesis

MFS is associated with abnormal production, matrix deposition and/or stability of fibrillin-1, a 350-kd ECM protein that is the major constituent of microfibrils, with prominent disruption of microfibrils and elastic fibers in diseased tissues. The fibrillin-1 *(FBN1)* locus resides on the long arm of chromosome 15 (15q21), and the gene is composed of 65 exons. Linkage analysis has suggested an absence of locus heterogeneity, and the involvement of *FBN1* is demonstrated in >90% of cases, with more than 1,000 disease-causing mutations identified to date (the majority of which are missense point mutations and unique to a given family). With the exception of early-onset and severe presentations of the disease associated with some mutations in exons 26-27 and 31-32, no clear genotype-phenotype correlation has been identified. Given that there is considerable intrafamilial variability, genetic, epigenetic, environmental, or other unidentified factors may influence expression of the disease.

MFS was traditionally considered to result from a structural deficiency of connective tissues. Reduced fibrillin-1 was thought to lead to a primary derangement of elastic fiber deposition, because both skin and aorta from affected patients show decreased elastin, along with elastic fiber fragmentation. In response to stress (such as hemodynamic forces in the proximal aorta), affected organs were thought to manifest this structural insufficiency with accelerated degeneration. However, it was difficult to reconcile certain manifestations of the disease, such as bone overgrowth, craniofacial dysmorphism, and low muscle mass or fat stores, with this structural deficiency model.

The transforming growth factor beta (TGF-β) family of cytokines influences a diverse repertoire of cellular processes, including cell proliferation, migration, differentiation, survival, and synthetic activity. The TGF-β ligands (TGF-β1, -β2, or -β3) are synthesized as inactive precursor complexes and sequestered by ECM proteins, including fibrillin-1. Mice heterozygous for a mutation in the fibrillin-1 gene, typical of those that cause MFS in humans, display many of the classic features of MFS, including aortic root aneurysm, which associates with a tissue signature for increased TGF-β signaling, suggesting that failed ECM sequestration of latent TGF-β by fibrillin-1 leads to increased TGF-β activation and signaling. Furthermore, pharmacological antagonism of TGF-β signaling ameliorates aortic aneurysm in mouse models of MFS, demonstrating that high TGF-β signaling is a cause rather than a consequence of disease progression.

Aberrant TGF-β signaling might also play a role in the wider spectrum of manifestations of MFS. Increased TGF-β signaling has been observed in other tissues in MFS mice, including the developing lung, mitral valve, and skeletal muscle. Treatment of these mice with agents that antagonize TGF-β attenuates or prevents pulmonary emphysema, myxomatous degeneration of the mitral valve, and skeletal muscle myopathy. The prominent role of TGF-β dysregulation in the pathogenesis of MFS was further validated by the discovery and characterization of another related aortic aneurysm syndrome, **Loeys-Dietz syndrome (LDS)** , in which patients have mutations in the TGF-β receptors and share many overlapping clinical features with MFS (see differential diagnosis). This is further supported by data showing that **Shprintzen-Goldberg syndrome (SGS)** , which shows phenotypic overlap with both MFS and LDS, is caused by mutations in *SKI* , a known repressor of the TGF-β signaling pathway.

Clinical Manifestations

MFS is a multisystem disorder, with cardinal manifestations in the skeletal, cardiovascular, and ocular systems.

Skeletal System

Overgrowth of the long bones (**dolichostenomelia**) is often the most obvious manifestation of MFS and may produce a reduced upper segment to lower segment ratio (UL/LS) or an arm span to height ratio >1.05 times. Abnormal ratios are US/LS <1 for age 0-5 yr, US/LS <0.95 for 6-7 yr, US/LS <0.9 8-9 yr old, and <0.85 above age 10 yr. Anterior chest deformity is likely the result of excessive rib growth, pushing the sternum either outward (**pectus carinatum**) or inward (**pectus excavatum**). Abnormal curvatures of the spine (most commonly thoracolumbar scoliosis) may also partly result from increased vertebral growth. Other skeletal features include an inward bulging of the acetabulum into the pelvic cavity (protrusio acetabuli), flat feet (pes planus), and joint hypermobility (Fig. 722.1) or joint contractures. Long and slender fingers in relation to the palm of the hand (**arachnodactyly**) are generally a subjective finding. The combination of arachnodactyly and hypermobile joints is examined by the Walker-Murdoch or wrist sign, which is positive if there is full overlap of the distal phalanges of the thumb and 5th finger when wrapped around the contralateral wrist (Fig. 722.2), and the Steinberg or thumb sign, which is present when the distal phalanx of the thumb fully extends beyond the ulnar border of the hand when folded across the palm (see Fig. 722.2). Contracture of the fingers (**camptodactyly**) and elbows is commonly observed. A selection of craniofacial manifestations may be present including a long narrow skull (dolichocephaly), deeply set eyes (enophthalmos), recessed lower mandible (retrognathia) or small chin (micrognathia), flattening of the midface (**malar hypoplasia**), a high-arching palate, and downward-slanting palpebral fissures (Fig. 722.3).

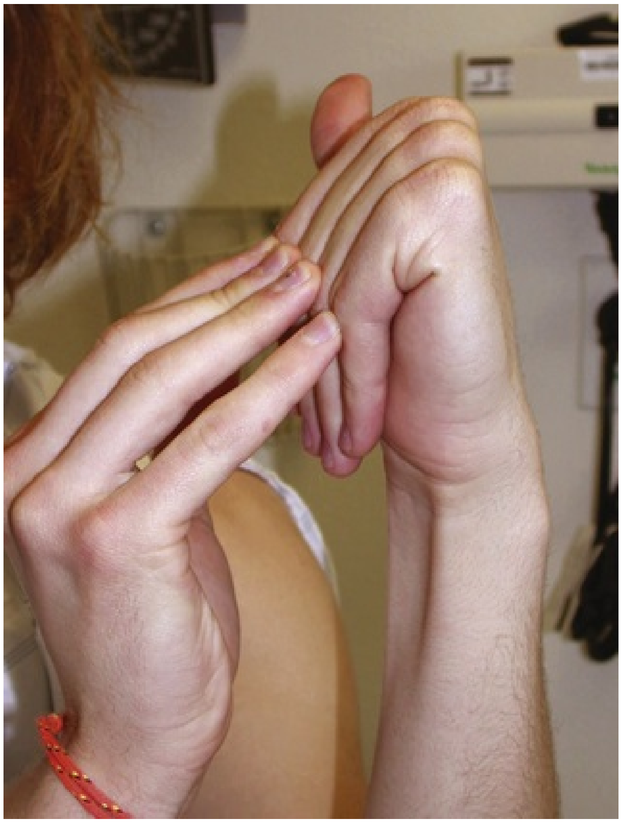

FIG. 722.1 **Joint laxity in a patient with Marfan syndrome.**

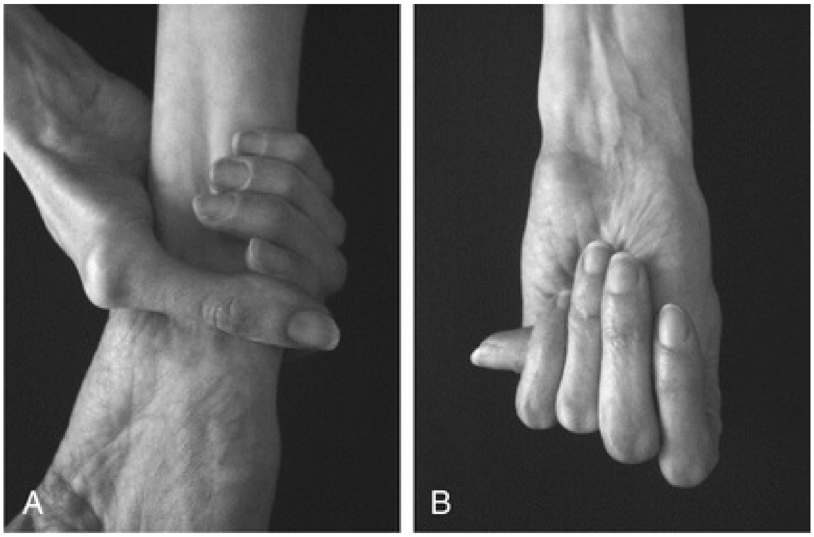

FIG. 722.2 **A,** Wrist (or Walker-Murdoch wrist) sign. When the wrist is grasped by the contralateral hand, the thumb overlaps the terminal phalanx of the 5th digit. **B,** Thumb (or Steinberg thumb) sign. When the hand is clenched without assistance, the entire thumbnail projects beyond the

border of the hand. (*A and B,* From McBride ART, Gargan M: Marfan syndrome, *Curr Orthop* 20:418–423, 2006, Figs 2 and 3.)

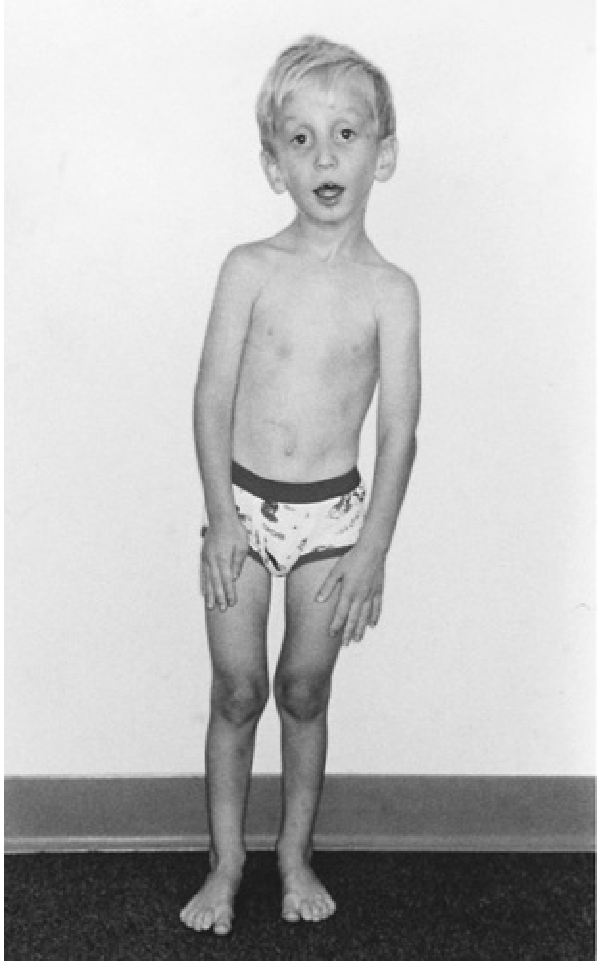

FIG. 722.3 **Marfan syndrome. Note the elongated facies, droopy lids, apparent dolichostenomelia, and mild scoliosis.**

Cardiovascular System

Thickening of the atrioventricular (AV) valves is common and often associated with valvular prolapse. Variable degrees of regurgitation may be present. In children with early onset and severe MFS, insufficiency of the mitral valve can lead to heart failure, pulmonary hypertension, and death in infancy; this manifestation is the leading cause of morbidity and mortality in young children with the disorder. Supraventricular arrhythmias may be seen in association with mitral valve dysfunction. Ventricular dysrhythmias have also been described in children with MFS, and there is an increased prevalence of prolonged QT interval. Dilated cardiomyopathy occurs with increased prevalence in patients with MFS, most often attributed to volume overload imposed by valve regurgitation. Aortic valve dysfunction is generally a late occurrence and attributed to stretching of the aortic annulus by an expanding aortic root aneurysm.

Aortic aneurysm, dissection, and rupture , principally at the level of the sinuses of Valsalva (also known as the aortic root), remain the most life-threatening manifestations of MFS, prompting lifelong monitoring by echocardiography or other imaging modalities. In severe cases, the aneurysm may be present in utero, but in mild examples, it may be absent or never exceed dimensions that require clinical intervention. Aortic dimensions must be interpreted in comparison to age-dependent nomograms. The most important risk factor for aortic dissection is the maximal aortic root size and a positive family history. The characteristic histological findings from aortas of patients with MFS include cystic medial necrosis of the tunica media and disruption of elastic lamellae. Cystic medial necrosis describes the focal apoptosis and disappearance of vascular smooth muscle cells and elastic fibers from the of the tunica media of the aortic wall, and subsequent deposition of mucin-like material in the cystic space. These changes produce a thicker, less distensible and stiffer aorta, which is more prone to aortic dissection. Most patients experiencing acute aortic dissection present with classic symptoms, including sudden-onset, severe, tearing chest pain, often radiating into the back. The dissection typically starts at the aortic root and may remain confined to the ascending aorta (type II) or continue into the descending aorta (type I). Acute-onset heart failure may occur if aortic valve function is compromised, and patients may suffer cerebrovascular injury, depending on the involvement of the carotid arteries. Involvement of the coronary arteries may herald sudden cardiac death, secondary to myocardial infarction or rupture into the pericardial sac with subsequent pericardial tamponade. Chronic aortic dissection usually occurs more insidiously, often without chest pain. Dilatation of the main pulmonary artery is common but does not typically cause any clinical sequelae. Enlargement of the descending thoracic or abdominal aorta can also occur, although relatively rarely.

Ocular System

Dislocation of the ocular lens (**ectopia lentis**) occurs in around 60–70% of patients, although it is not unique to the disorder. Other ocular manifestations include early and severe myopia, flat cornea, increased axial length of the globe, hypoplastic iris, and ciliary muscle hypoplasia, causing decreased miosis. Patients are also predisposed to retinal detachment, early cataracts, and glaucoma.

Other Systems

There is an increase incidence of pulmonary disease in MFS: progressive anterior chest deformity or thoracic scoliosis may contribute to a restrictive pattern of lung disease. Furthermore, a widening of the distal airspaces predisposes patients to spontaneous pneumothorax, which occurs in up to 15% of patients. Assessment of pulmonary volumes and function should account for long bone overgrowth affecting the lower extremities, which can lead to a reduction in the normalized forced vital capacity and total lung capacity. If normalized to thoracic size or sitting height, pulmonary function testing is often normal in patients with the disorder.

MFS patients typically have normal skin texture and elasticity. The most common skin finding is stretch marks—pinkish, scar-like lesions that later become white (**striae atrophicae**), which occur in about ⅓ of patients. These may occur in the absence of obesity, rapid gain in muscle mass, or pregnancy, and at sites not associated with increased skin distension (i.e., the anterior shoulder or lower back). Another common manifestation is congenital or acquired inguinal hernia. There is also an increased risk of surgical and recurrent hernias in the Marfan population.

Widening of the dural sac or root sleeves (dural ectasia) is present in 63–92% of MFS patients. Although dural ectasia can result in lumbar back pain, it is often asymptomatic and should be assessed by lumbosacral imaging with CT or MRI.

Diagnosis

Given the complexity of the clinical examination in MFS and the relevant differential diagnoses, evaluation should be coordinated by a professional with extensive experience, such as a geneticist, cardiologist, or ophthalmologist. The diagnosis is based on a defined set of clinical criteria drawn up by an international panel of experts (the revised Ghent nosology for the Marfan syndrome; Table 722.1).

Table 722.1

Diagnostic Criteria for Marfan Syndrome

In the absence of a family history of MFS, a diagnosis can be established in 4 distinct scenarios:

1. Aortic root Z score ≥2 AND ectopia Lentis*
2. Aortic root Z score ≥2 AND a bona fide *FBN1* mutation (see Table 722.2)
3. Aortic root Z score ≥2 AND a systemic score ≥7* (see Table 722.3)
4. Ectopia lentis AND a bona fide *FBN1* mutation known to cause aortic disease

In the presence of a family history of MFS, a diagnosis can be established in the presence of:

1. Ectopia lentis
2. A systemic score ≥7*
3. Aortic root Z score ≥2 if older than 20 yr or ≥3 if younger than 20 yr*

In the absence of a family history of MFS, alternative diagnoses include:

1. Ectopia lentis ± systemic score AND *FBN1* mutation not known to associate with aortic aneurysm or no *FBN1* mutation = Ectopia lentis syndrome
2. Aortic root Z score <2 AND a systemic score ≥5 (with at least 1 skeletal feature) without ectopia lentis = MASS phenotype
3. Mitral valve prolapse AND Aortic root Z score <2 AND a systemic Score <5 without ectopia lentis = Mitral valve prolapse syndrome

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* Denotes caveat that features suggestive of an alternative diagnosis must be

excluded and appropriate alternative molecular testing should be performed.

In the absence of a conclusive family history of MFS, the diagnosis can be established in four distinct scenarios:

1. The presence of either aortic root dilatation when standardized to age and body size (an aortic root Z score ≥2) or aortic dissection combined with ectopia lentis allows for the unequivocal diagnosis of MFS, irrespective of the presence or absence of any systemic features (see Table 722.1), except when these are indicative of an alternate diagnosis.
2. The presence of aortic root dilatation (Z score ≥2) or aortic dissection and the identification of a bona fide *FBN1* mutation (Table 722.2) are sufficient to establish the diagnosis even if ectopia lentis is absent.

Table 722.2

Criteria for Causal *FBN1* Mutation

- Mutation previously shown to segregate in a Marfan family
- Any 1 of the following de novo mutations (with proven paternity and absence of disease in parents):
  - Nonsense mutation
  - In-frame and out-of-frame deletion/insertion
  - Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
  - Missense mutation affecting/creating cysteine residues
  - Missense mutation affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable number of residues; D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)
  - Other missense mutations: segregation in family if possible AND absence in 400 ethnically matched control chromosomes; if no family history, absence in 400 ethnically matched control chromosomes
  - Linkage of haplotype for $n \geq 6$ meioses to the *FBN1* locus

From Loeys BL, Dietz HC, Braverman AC, et al: The revised Ghent nosology for the Marfan syndrome, *J Med Genet* 2010;47:476–485.

3. When aortic root dilatation (an aortic root Z score ≥2) or aortic dissection is present, but ectopia lentis is absent and the *FBN1* status is either unknown or negative, the diagnosis may be confirmed by the presence of sufficient systemic findings (a systemic score ≥7 points; Table 722.3). However, features suggestive of an alternate diagnosis must be excluded, and the appropriate alternative molecular testing

should be performed.

Table 722.3

Scoring of Systemic Features in Points

- Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)
- Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
- Hind foot deformity = 2 (plain pes planus = 1)
- Pneumothorax = 2
- Dural ectasia = 2
- Protrusio acetabuli = 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis = 1
- Scoliosis or thoracolumbar kyphosis = 1
- Reduced elbow extension = 1
- Facial features (3/5) = 1 (dolichocephaly, enophthalmos, down slanting palpebral fissures, midface hypoplasia, retrognathia)
- Skin striae = 1
- Myopia >3 diopters = 1
- Mitral valve prolapse (all types) = 1

Maximum total: 20 points; score ≥7 indicates systemic involvement. US/LS = upper segment / lower segment ratio.

4. In the presence of ectopia lentis, but absence of aortic root dilatation or aortic dissection, an *FBN1* mutation, which has previously been associated with aortic disease, is required before the diagnosis can be made. If the *FBN1* mutation is not unequivocally associated with cardiovascular disease in either a related or unrelated proband, the patient should be classified as “isolated ectopia lentis syndrome” (see differential diagnosis).

Despite these diagnostic criteria, on occasion sporadic cases in individuals <20 yr old may not fit in one of the four proposed scenarios detailed above. If insufficient systemic features (systemic score <7) and/or borderline aortic root measurements (Z score <3) are present without documented evidence of a bona fide *FBN1* mutation, the term “nonspecific connective tissue disorder” is recommended. In those instances when a *FBN1* mutation is identified, the term “potential MFS” should be used instead.

In an individual with a positive family history of MFS (where a family member has been independently diagnosed using the above criteria), the diagnosis can be established in the presence of:

1. Ectopia lentis
2. A systemic score ≥7 points (see Table 722.3)
3. Aortic root dilatation with Z score ≥2 in adults (≥20 yr old) or Z score ≥3 in individuals <20 yr old

In the case of scenarios 2 and 3, features suggestive of an alternative diagnosis must again be excluded and appropriate alternative molecular testing should be performed.

Differential Diagnosis

The differential diagnosis of MFS includes disorders with aortic aneurysm (Loeys-Dietz syndrome, familial thoracic aortic aneurysm syndrome, and Shprintzen-Goldberg syndrome); ectopia lentis (ectopia lentis syndrome, Weil-Marchesani syndrome, and homocystinuria); or systemic manifestations of MFS (congenital contractural arachnodactyly and mitral valve, aorta, skin, skeletal [MASS] phenotype; Table 722.4).

Table 722.4

Differential Diagnosis of Marfan Syndrome

DIFFERENTIAL DIAGNOSIS	CARDIAC FEATURES	VASCULAR FEATURES	SYSTEMIC FEATURES
AORTIC ANEURYSM SYNDROMES			
Loeys-Dietz syndrome (OMIM: 609192)	Patent ductus arteriosus Atrial septal defect Bicuspid aortic valve	Aortic root aneurysm Arterial tortuosity Widespread aneurysms Vascular dissection at relatively young ages and small aortic dimensions	Hypertelorism Cleft palate Broad or bifid uvula Craniosynostosis Midface hypoplasia Blue sclerae Arachnodactyly Pectus deformity Scoliosis Joint hypermobility Pes planus Rarely Easy bruising Dystrophic scars Translucent skin Rarely

			developmental delay
Familial thoracic aortic aneurysm (OMIM: 132900)	Generally none Rare forms with patent ductus arteriosus	Aortic root aneurysm Ascending aortic aneurysm	Generally none Rarely livedo reticularis and iris flocculi
Shprintzen-Goldberg syndrome (OMIM: 182212)	None	Aortic root aneurysm	Hypertelorism Craniosynostosis Arched palate Arachnodactyly Pectus deformity Scoliosis Joint hypermobility Developmental delay
Bicuspid aortic valve with aortic aneurysm (OMIM: 109730)	Bicuspid aortic valve	Aortic root aneurysm Ascending aortic aneurysm	
Ehlers-Danlos syndrome, type IV (OMIM: 130050)	Mitral valve prolapse	Aneurysm and rupture of any medium to large muscular artery No predisposition for aortic root enlargement	Joint hypermobility Atrophic scars Translucent skin Easy bruising Hernias Rupture of hollow organs
ECTOPIA LENTIS SYNDROMES			
Familial ectopia lentis (OMIM: 129600)	None	None	Nonspecific skeletal features
Homocystinuria (OMIM: 236200)	Mitral valve prolapse	Intravascular thrombosis	Tall stature Ectopia lentis Long-bone overgrowth Developmental delay
SYNDROMES WITH SYSTEMIC MANIFESTATIONS OF MFS			
MASS phenotype (OMIM: 604308)	Mitral valve prolapse	Borderline or nonprogressive	Nonspecific skin and skeletal findings Myopia

Aortic Aneurysm Syndromes

Loeys-Dietz syndrome (LDS) is a systemic connective tissue disorder characterized by the triad of arterial tortuosity and aggressive aneurysm disease, hypertelorism, and bifid uvula or cleft palate, as well as many of the craniofacial and skeletal features found in MFS. Distinction between MFS and LDS is important because aneurysms tend to dissect at younger ages and smaller dimensions in LDS patients, necessitating more aggressive management. LDS was originally classified into type 1 or type 2, depending on whether the mutation is present in the *TGFBR1* or *TGFBR2* gene, which encode the type 1 or type 2 TGF-β receptor subunits, respectively. Each subtype was further subclassified into type 1A and type 1B or type 2A and type 2B, depending on the degree of craniofacial involvement, with patients with type A disease having severe craniofacial abnormalities and those with type B disease having mild or no craniofacial involvement. Several new LDS genes have been described. LDS type 3 is caused by heterozygous mutations in the gene encoding the TGF-β-dependent intracellular signaling molecule SMAD3. LDS type 4 is caused by heterozygous mutations in the extracellular TGF-β receptor ligand TGF-β2, while LDS type 5 is caused by heterozygous mutations in the extracellular TGF-β receptor ligand TGF-β3. Types 3 and 4 are also characterized by widespread arterial tortuosity, aortic aneurysm, and aortic dissection, as well as typical craniofacial and skeletal abnormalities. Patients with *SMAD3* mutations may have early onset osteoarthritis and supraventricular arrhythmias. In contrast to other forms of LDS, type 5 shows no striking arterial tortuosity, and there is no strong evidence for early aortic dissection.

Like MFS, **familial thoracic aortic aneurysm syndrome** segregates as an autosomal dominant trait characterized aortic root aneurysm and dissection. However, other systemic manifestations of MFS are typically absent, and the disorder has reduced penetrance. Disease-causing heterozygous mutations have been identified in several genes with roles in the vascular smooth muscle contractile apparatus, including *MYH11* , *ACTA2* , and *MYLK* , which encode smooth muscle myosin heavy chain 11, vascular smooth muscle α-actin, and myosin light chain kinase. However, these genes only account for a fraction of cases of nonsyndromic familial thoracic aortic aneurysm. In most cases, the management principles that have been generated for MFS have proved effective for this form of familial aortic aneurysm.

Shprintzen-Goldberg syndrome (SGS) is a systemic connective tissue disorder that includes virtually all the craniofacial, skeletal, skin, and cardiovascular manifestations of MFS and LDS, with the additional findings of developmental delay and severe skeletal muscle hypotonia. Most cases are caused by heterozygous mutations in the *SKI* gene, which encodes an intracellular repressor of TGF-β signaling. Vascular involvement tends to be less prevalent and less severe when compared with MFS or LDS.

Ectopia Lentis Syndromes

Both **ectopia lentis syndrome** and **Weill-Marchesani syndrome (WMS)** may also be caused by heterozygous mutations in *FBN1* . Compound heterozygous or homozygous mutations at a 2nd locus, *ADAMTSL4* have recently been shown to cause ectopia lentis syndrome associated with slightly younger age at diagnosis. Interestingly, some *FBN1* mutations can be associated with classical MFS, ectopia lentis syndrome, and ectopia lentis combined with skin, but not cardiovascular, manifestations of MFS, suggesting that these presentations are part of a spectrum of clinical features of the same disease, and highlighting the potential contribution of genetic modifiers of disease.

WMS is a systemic connective tissue disorder characterized by skin, skeletal, and ocular abnormalities, including microspherophakia, ectopia lentis, and myopia. Features inconsistent with the diagnosis of MFS include short stature and brachydactyly. In addition to *FBN1* mutations (type 2), the syndrome may be caused by homozygous or compound heterozygous mutations in *ADAMTS10* (type 1) or homozygous mutations in LTBP2 (type 3), which encode ADAM metallopeptidase with thrombospondin type 1 motif 10 and latent transforming growth factor beta binding protein 2, respectively.

Homocystinuria is a metabolic disorder caused by homozygous or compound heterozygous mutations in the gene encoding cystathionine β-synthase, which leads to increases in both homocysteine and methionine. The clinical features of untreated homocystinuria include ectopia lentis and skeletal abnormalities resembling MFS. However, in contrast to MFS, affected persons often suffer from developmental delay, a predisposition to thromboembolic events, and a high incidence of coronary artery disease.

Syndromes With Systemic Manifestations of MFS

Congenital contractural arachnodactyly (CCA) is a connective tissue disorder caused by heterozygous mutations in the gene encoding fibrillin-2 (*FBN2*). There are a number of clinical features overlapping with MFS, including dolichostenomelia, anterior chest deformity, scoliosis, joint contractures, and arachnodactyly, as well as some craniofacial malformations, including highly arched palate and retrognathia. In addition, both may suffer from severe cardiovascular abnormalities leading to premature death, but the specific cardiac anomalies are different; valvular insufficiency and aortic root dilation are common with MFS, whereas congenital heart defects are more common in CCA. Patients with CCA also suffer from crumpled auricular helices (a hallmark of this condition).

Many patients referred for possible MFS are found to have evidence of a systemic connective tissue disorder, including long limbs, deformity of the thoracic cage, striae atrophicae, mitral valve prolapse, and borderline but nonprogressive dilatation of the aortic root, but do not meet diagnostic criteria for MFS. This constellation of features is referred to by the acronym **MASS phenotype** , emphasizing the mitral, aortic, skin, and skeletal manifestations. The MASS phenotype can segregate in large pedigrees and remain stable over time. The diagnosis is particularly challenging in the context of a young, sporadic patient in whom careful follow-up is needed to distinguish MASS phenotype from emerging MFS. Familial mitral valve prolapse syndrome can also be caused by mutations in the gene encoding fibrillin-1 and include subdiagnostic systemic manifestations.

Laboratory Findings

Laboratory studies should document a negative urinary cyanide nitroprusside test or specific amino acid studies to exclude cystathionine β-synthase deficiency (homocystinuria). Although it is estimated that most, if not all, people with classic MFS have an *FBN1* mutation, the large size of this gene and the extreme allelic heterogeneity in MFS have frustrated efficient molecular diagnosis. The yield of mutation screening varies based on technique and clinical presentation. It remains unclear whether the “missing” mutations are simply atypical in character or location within *FBN1* or located in another gene. Other differential diagnoses, such as MASS phenotype, EL, WMS, and SGS, have been associated with mutations in the *FBN1* gene. It is often difficult or impossible to predict the phenotype from the nature or location of a *FBN1* mutation in MFS. Hence molecular genetic techniques can contribute to the diagnosis, but they do not substitute for comprehensive clinical evaluation and follow-up. The absence or presence of an *FBN1* mutation is not sufficient to exclude or establish the diagnosis, respectively.

Management

Management focuses on preventing complications and genetic counseling. Referral to a multidisciplinary center where a geneticist with experience in MFS works in concert with subspecialists to coordinate a rational approach to monitoring, and treatment is advisable, given the complex nature of some patient's disease. Yearly evaluations for cardiovascular disease, scoliosis, or ophthalmologic problems are imperative.

Current Therapies

Most therapies currently available or under investigation aim to diminish cardiovascular complications, which can be categorized into activity restrictions, aortic surgery, endocarditis prophylaxis, and current pharmacological approaches.

Activity Restrictions

Physical therapy can improve cardiovascular performance, neuromuscular tone, and psychosocial health, and so aerobic exertion in moderation is recommended. However, strenuous physical exertion, competitive or contact sports, and particularly isometric activities such as weight lifting, which invoke a Valsalva maneuver, should be avoided.

Aortic Surgery

Surgical outcome is more favorable if undertaken on an elective rather than an urgent or emergent basis (mortality of 1.5% vs. 2.6% and 11.7%, respectively). Therefore aortic surgery should be recommended for adult patients when their aortic root diameter approaches 50 mm, and early intervention should be considered for those with a rapid rate of enlargement (>5-10 mm/yr) or a family history of early aortic dissection. There are no definitive criteria guiding the timing of surgery in children in whom dissection is extremely rare, irrespective of aortic size. This has prompted many centers to adopt the adult criterion of 50 mm, although early surgery may be undertaken in the presence of a rapid rate of growth (>10 mm/yr) or the emergence of significant aortic regurgitation. Preserving the native aortic valve at the time of repair is desirable to avoid the need for lifelong anticoagulation. Mitral valve repair or replacement is advised for severe mitral valve regurgitation with associated symptoms or progressive left ventricular dilatation or dysfunction.

Pregnancy

There is higher risk of aortic dissection during pregnancy in women with MFS. However, improved awareness and data have indicated the risk is low in patients with an aortic root diameter <40 mm. Prophylactic aortic root replacement can minimize the risk of aortic dissection and death in women with MFS who wish to become pregnant, but the risk of more distal ascending or descending aortic dissection would not be modified by this intervention.

Endocarditis Prophylaxis

The Professional Advisory Board of the National Marfan Foundation believes that patients with MFS should continue to receive prophylaxis for bacterial endocarditis, in part because it remains unknown, but possible, that the myxomatous valves typical of MFS are a preferred substrate for bacterial infection.

Current Pharmacological Approaches

β-Blockers have traditionally been considered the standard of care in MFS, and multiple small observational studies have suggested there is a protective effect on aortic root growth, with the dose typically titrated to achieve a resting heart rate <100 bpm during submaximal exercise. Given the putative role of hemodynamic stress in aortic dilatation and aortic dissection in MFS, these effects are attributed to the negative inotropic and chronotropic effects of β-blockade.

Emerging Therapeutic Strategies

Angiotensin II Receptor Type 1 Blockers

There is extensive evidence linking angiotensin II signaling to TGF-β activation and signaling. In a mouse model of MFS, the angiotensin II receptor type 1 blocker (ARB) losartan was shown to completely prevent pathologic aortic root growth and to normalize both aortic wall thickness and architecture, findings that were absent in placebo-treated and propranolol-treated mice. These data suggest the potential for productive aortic wall remodeling in MFS after TGF-β inhibition. Remarkably, improvements in pulmonary and skeletal muscle pathology in these mice also occurred with losartan, further supporting the conclusion that this treatment works by decreasing TGF-β signaling rather than by simply reducing hemodynamic stress on structurally predisposed tissues.

In support of its relevance to humans, a retrospective study assessing the effect of ARBs in a small cohort of pediatric patients with MFS who had severe aortic root enlargement despite previous alternate medical therapy, showed that ARBs significantly slowed the rate of aortic root and sinotubular junction dilatation (both of which occur in MFS), whereas the distal ascending aorta (which does not normally become dilated in MFS) remained unaffected. Further evidence of a beneficial effect from losartan therapy has been provided by three prospective clinical trials demonstrating that losartan treatment alone or in combination with β-blockade slowed the progression of aortic root dilation in patients with MFS.

A comparison clinical trial assessing the therapeutic benefit of losartan versus atenolol in patients with MFS concluded that both drugs provided significant protection against aortic growth, with no significant difference in therapeutic effect between the two drugs despite the use of conventional dose losartan (FDA-approved dose for hypertension) and an atypically high dose of atenolol (average dose of atenolol was 1.5 times and the maximum dose was 2 times the FDA approved upper limit for the treatment of hypertension). Both treatment arms in this trial showed a very slow rate of aortic root growth and a significant decline in aortic root z-score over time, a performance superior to that observed in untreated Marfan patients or in patients treated with conventional dose atenolol (~1 mg/kg/day). These data strongly suggest that both modalities have therapeutic potential in patients with Marfan syndrome.

ACE Inhibitors

It has been proposed that ACE inhibitors might prove as effective as, or more effective than, ARBs in the treatment of MFS through their ability to limit signaling through both the type 1 and type 2 angiotensin receptors (AT1R and AT2R, respectively). However, experiments in mouse models have demonstrated that the beneficial effect of losartan is mediated by both blocking AT1R receptor signaling as well as diverting signaling through AT2R receptor, and as a consequence enalapril, while superior to placebo, was shown to be less effective than losartan. These findings are concordant with some small studies suggesting there is some protection afforded by ACE inhibitors in patients with MFS; however, additional experimentation and clinical experience is needed to fully resolve this issue.

ERK Inhibitors

It is known that ligand-dependent TGF-β receptor activation can also initiate non-canonical cascades, including the MAPKs. There is an increase in ERK1/2 activation in the aortas of MFS mice, while administration of an orally bioavailable selective inhibitor of ERK1/2 activation, RDEA119, completely prevented pathologic aortic root growth in MFS mice, suggesting that ERK1/2 is a critical mediator of disease pathophysiology and a potential viable therapeutic target.

Prognosis

The major cause of mortality is aortic root dilatation, dissection, and rupture with the majority of fatal events occurring in the 3rd and 4th decades of life. A re-evaluation of life expectancy in MFS suggested that early diagnosis and refined medical and surgical management has greatly improved the prognosis for patients with the condition. Nevertheless, MFS continues to be associated with significant morbidity and selected subgroups are refractory to therapy and continue to show early mortality. In a review of 54 patients diagnosed during infancy, 89% had serious cardiac pathology, and cardiac disease was progressive despite standard care (22% died during childhood, 16% before age 1 yr). In the more classic form of MFS, it is estimated that greater than 90% of individuals will have a cardiovascular event during their lifetime, placing both physical and mental stresses on patients and their families. Awareness of these issues and referral for support services can facilitate a positive perspective toward the condition.

Genetic Counseling

The heritable nature of MFS makes recurrence risk (genetic) counseling mandatory. Fathers of these sporadic cases are, on average, 7 to 10 yr older than fathers in the general population. This paternal age effect suggests that these cases represent new dominant mutations with minimal recurrence risk to the future offspring of the normal parents. Owing to rare reports of gonadal mosaicism in a phenotypically normal parent, the recurrence risk for parents of a sporadic case can be reported as low, but not zero. Each child of an affected parent, however, has a 50% risk of inheriting the MFS mutation and thus being affected. Recurrence risk counseling is best accomplished by professionals with expertise in the issues surrounding the disorder.

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SECTION 4

Metabolic Bone Disease

OUTLINE

Chapter 723 Bone Structure, Growth, and Hormonal Regulation

Chapter 724 Hypophosphatasia

Chapter 725 Hyperphosphatasia

Chapter 726 Osteoporosis

CHAPTER 723

Bone Structure, Growth, and Hormonal Regulation

Catherine M. Gordon

See also Chapters 64 and 588 .

Bone is a rigid organ but metabolically active in that it is constantly being formed **(modeling)** and reformed **(remodeling)** . It is capable of rapid turnover, bearing weight, and withstanding the stresses of various physical activities. Bone is the major body reservoir for calcium, phosphorus, and magnesium. Other functions of bone include organ protection, structure, movement, and sound transmission. It is also an endocrine organ that produces fibroblast growth factor 23 (FGF23), which regulates renal phosphate handling. Disorders that affect this organ and the process of mineralization are designated **metabolic bone diseases** .

The human skeleton consists of a protein matrix, largely composed of a collagen-containing protein, osteoid, on which is deposited a crystalline mineral phase. Collagen-containing osteoid accounts for 90% of bone protein; other proteins, including osteocalcin, which contains γ-carboxyglutamic acid, are also present. Synthesis of osteocalcin depends on vitamin K and vitamin D; in states with high bone turnover, serum osteocalcin values are often elevated. Osteocalcin appears to enhance insulin secretion and sensitivity and reduce fat stores.

The microfibrillar matrix of osteoid permits deposition of highly organized calcium phosphate crystals, including hydroxyapatite [$C_{10}(PO_4)_6 \cdot 6H_2O$] and octacalcium phosphate [$Ca_8(H_2PO_4)_6 \cdot 5H_2O$], plus less-organized amorphous calcium phosphate, calcium carbonate, sodium, magnesium, and citrate. Hydroxyapatite is deep within bone matrix, whereas amorphous calcium phosphate coats the surface of newly formed or remodeled bone.

Because bone growth and turnover rates are high during childhood, many clinical and osseous features of metabolic bone diseases are more prominent in children than in adults.

The growth pattern of bones is an acceleration of bone growth (length) of the limbs during prepubescence, increased growth (length) of the trunk (spine) during early adolescence, and increased bone mineral deposition in late adolescence. The use of **dual-energy x-ray absorptiometry (DXA)** or quantitative CT permits measurement of both mineral content and bone density in healthy subjects and in children with metabolic bone disease. DXA exposes the patient to less radiation than a chest radiograph and significantly less than quantitative CT, and is therefore most commonly used in clinical practice.

Bone growth occurs in children by the process of calcification of the cartilage cells present at the ends of bone. In accord with the prevailing extracellular fluid calcium and phosphate concentrations, mineral is deposited in chondrocytes or cartilage cells set to undergo mineralization. The main function of the vitamin D–parathyroid hormone (PTH)–FGF23–endocrine axis is to maintain the extracellular fluid calcium and phosphate concentrations at appropriate levels to permit mineralization.

Other hormones also appear to regulate the growth and mineralization of cartilage, including growth hormone acting through insulin-like growth factors, thyroid hormones, insulin, leptin, ghrelin, and androgens and estrogens during the pubertal growth spurt. Supraphysiologic concentrations of glucocorticoids impair cartilage function and bone growth and augment bone resorption.

Rates of bone formation are coordinated with alterations in mineral metabolism in both the intestine and kidneys, where a number of hormones regulate the processes. Inadequate dietary intake or intestinal absorption of calcium causes a fall in serum levels of calcium and its ionized fraction. This decrease serves as the signal for parathyroid hormone (PTH) synthesis and secretion, resulting in greater bone resorption (which raises the serum calcium level) and enhanced distal tubular reabsorption of calcium. It also promotes higher rates of renal synthesis of $1,25(OH)_2$ D or calcitriol, the most active metabolite of vitamin D (Fig. 723.1). **Calcium homeostasis** thus is controlled by the intestine because the availability of $1,25(OH)_2$ D ultimately determines the fraction of ingested calcium that is absorbed.

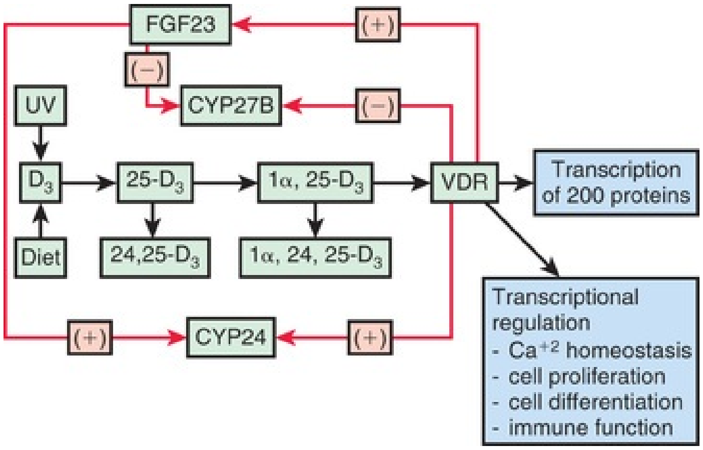

FIG. 723.1 **Vitamin D metabolism. Vitamin D can be synthesized in the skin under the influence of ultraviolet (UV) irradiation, or it can be absorbed from the diet. It is converted to 25(OH)D_3 (vitamin D_3) in the liver and then further converted by the kidney. The enzyme cytochrome P450 (CYP) 27B converts 25(OH)D_3 to 1α,25-$(OH)_2$ D_3 . 1,25$(OH)_2$ D_3 binds to vitamin D receptor (VDR), which, after transport to the nucleus, acts to induce the transcription of more than 200 proteins. The functions of some of the proteins are indicated. VDR activation leads to productions of fibroblast growth factor 23 (FGF23). FGF23 induces phosphaturia (not shown), upregulates CYP 24, and downregulates CYP 27B.**

Phosphate homeostasis is regulated by the kidneys because intestinal phosphate absorption is nearly complete and renal excretion determines the serum level of phosphate. Excessive intestinal phosphate absorption causes a fall in serum levels of ionized calcium and a rise in PTH secretion, resulting in phosphaturia, thus lowering the serum phosphate level and permitting the calcium level to rise. Hypophosphatemia blocks PTH secretion and promotes renal 1,25-dihydroxyvitamin D [1,25$(OH)_2$ D] synthesis. This latter compound also promotes greater intestinal phosphate absorption. The important role of FGF23 in phosphate homeostasis is described later.

Vitamin D can be synthesized in the skin under the influence of ultraviolet (UV) irradiation, or it can be absorbed from the diet. It is converted to 25(OH)D_3 (vitamin D_3) in the liver and then further converted by the kidney. An understanding of the metabolism of vitamin D is necessary to appreciate mineral homeostasis and metabolic bone disease and rickets. The skin contains 7-dehydrocholesterol, which is converted to vitamin D_3 [25(OH)D_3] by UV radiation; other inactive vitamin D sterols are also produced (see Chapter 51). Vitamin D_3 is then transported in the bloodstream to the liver by a vitamin D–binding protein (DBP); DBP binds all forms of vitamin D. The plasma concentration of free or nonbound vitamin D is much lower than the level of DBP-bound vitamin D metabolites.

Vitamin D also can enter the metabolic pathway by ingestion of dietary vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol), both of which are absorbed from the intestine because of the action of bile salts. After absorption, ingested vitamin D is transported by chylomicrons to the liver, where, along with skin-derived vitamin D_3 , it is converted to 25-hydroxyvitamin D [25(OH)D]. The 25(OH)D is next transported by DBP to the kidneys, where it undergoes further metabolism. 25(OH)D is the main circulating vitamin D metabolite in humans (Table 723.1). Because the synthesis of 25(OH)D is weakly regulated by feedback, its plasma level rises in summer and falls in winter. High vitamin D intake raises the plasma level of 25(OH)D to many times above normal, but the parent vitamin D compound itself is absorbed by adipose tissue.

Table 723.1

Vitamin D Metabolic Values in Plasma of Normal Healthy Subjects

METABOLITE	PLASMA VALUE
Vitamin D_2	1-2 ng/mL
Vitamin D_3	1-2 ng/mL
$25(OH)D_2$	4-10 ng/mL
$25(OH)D_3$	26-70 ng/mL
TOTAL 25(OH)D	20-80 ng/mL [The 2010 Institute of Medicine report states that a value of 25(OH)D above 20 ng/mL is the lower limit of normal.]
$24,25(OH)_2$ D	1-4 ng/mL
$1,25(OH)_2$ D	
Infancy	70-100 pg/mL
Childhood	30-50 pg/mL
Adolescence	40-80 pg/mL
Adulthood	20-35 pg/mL

In the kidneys, 25(OH)D undergoes further hydroxylation, depending on the prevailing serum concentration of calcium, phosphate, PTH, and FGF23. If the calcium or phosphate level is reduced or the PTH level is elevated, the enzyme 25(OH)D-1-hydroxylase is activated and $1,25(OH)_2$ D is formed. $1,25(OH)_2$ D_3 binds to a vitamin D receptor, which, after transport to the nucleus, acts to induce the transcription of 200-400 proteins and peptides. The functions of some of the proteins are known.

Another class of proteins important in the regulation of mineral balance and vitamin D synthesis are the **phosphatonins** . Among these are FGF23, sFRP-4 (secreted Frizzled-related protein 4), and MEPE (matrix extracellular phosphoglycoprotein). Overexpression of FGF23 results in hypophosphatemia, phosphaturia, reduced serum $1,25(OH)_2$ D values, and some forms of rickets. Disorders of phosphate balance, including hyper- and hypophosphatemia, can relate to loss or gain of function of these phosphatonins (see Fig. 723.1).

Vitamin D receptor activation by $1,25(OH)_2$ D leads to production of FGF23. FGF23 is produced by osteocytes and targets another organ, the kidney, to promote phosphaturia. FGF23 reduces expression/insertion of 2 sodium phosphate transporters into the renal proximal tubule, resulting in higher levels of urinary phosphate excretion. This bone-derived hormone also inhibits renal hydroxylase activity (CYP 27B1) and promotes 24-hydroxylase activity. Consequently, circulating $1,25(OH)_2$ D levels fall.

The active metabolite, $1,25(OH)_2$ D, circulates at a level that is only 0.1% of the level of 25(OH)D (see Table 723.1) and acts on the intestine to increase the active transport of calcium and stimulate phosphate absorption. Because 1α-hydroxylase is a mitochondrial enzyme that is tightly feedback regulated, the synthesis of $1,25(OH)_2$ D declines after serum calcium or phosphate values return to normal. Excessive $1,25(OH)_2$ D is converted to an inactive metabolite. In the presence of normal or elevated serum calcium or phosphate concentrations, the renal 25(OH)D-24-hydroxylase is activated, producing 24,25-dihydroxyvitamin D [$24,25(OH)_2$ D], which is a pathway for the removal of excess vitamin D; serum levels of $24,25(OH)_2$ D (1-5 ng/mL) increase after ingestion of large amounts of vitamin D (see Fig. 723.1), or in the presence of increased concentrations of FGF23. Although hypervitaminosis D and production of inactive metabolites can occur after oral dosing, extensive skin exposure to sunlight does not usually produce toxic levels of $25(OH)D_3$, suggesting natural regulation of the production of this metabolite in cutaneous tissue.

Serum $1,25(OH)_2$ D levels are higher in children than in adults, are not as subject to seasonal variability, and peak during the 1st yr of life and again during the adolescent growth spurt. These values must be interpreted in light of the prevailing serum calcium, phosphate, and PTH values, and with regard to the entire vitamin D metabolite profile.

Mineral deficiency prevents the normal process of bone mineral deposition. If mineral deficiency occurs at the growth plate, growth slows and bone age is retarded, a condition called **rickets.** Poor mineralization of trabecular bone resulting in a greater proportion of unmineralized osteoid is the condition of osteomalacia. Rickets is found only in growing children before fusion of the epiphyses, whereas osteomalacia is present at all ages. All patients with rickets have osteomalacia, but not all patients with osteomalacia have rickets. These conditions should not be confused with osteoporosis, a condition of equal loss of bone volume and mineral (see Chapter 726).

Rickets may be classified as calcium-deficient or phosphate-deficient rickets. Because both calcium and phosphate ions constitute bone mineral, the insufficiency of either type in the extracellular fluid that bathes the mineralizing surface of bone results in rickets and osteomalacia. The 2 types of rickets are distinguishable by their clinical manifestations (Table 723.2). Rickets can also occur in the face of mineral deficiency, despite adequate vitamin D stores. True dietary calcium deficiency rickets are found in some parts of Africa but rarely in North America or Europe. A form of phosphate-deficiency rickets can occur in infants, given prolonged administration of phosphate-sequestering aluminum salts as a treatment for colic or gastroesophageal reflux. This results in the phosphate depletion syndrome.

Table 723.2

Clinical Variants of Rickets and Related Conditions

TYPE	SERUM CALCIUM LEVEL	SERUM PHOSPHORUS LEVEL	ALKALINE PHOSPHATASE ACTIVITY	URINE CONCENTRATION OF AMINO ACIDS	GENETICS	GE DE KN
CALCIUM DEFICIENCY WITH SECONDARY HYPERPARATHYROIDISM*						
Lack of Vitamin D						
Lack of exposure to sunlight	N or L	L	E	E		
Dietary deficiency of vitamin D	N or L	L	E	E		
Congenital	N or L	L	E	E		
Other Deficiencies						
Malabsorption of vitamin D	N or L	L	E	E		
Liver diseases	N or L	L	E	E		
Anticonvulsant drug	N or L	L	E	E		
Renal osteodystrophy	N or L	E	E	V		
Vitamin D–dependent type I	L	N or L	E	E	AR	Y
PRIMARY PHOSPHATE DEFICIENCY (NO SECONDARY HYPERPARATHYROIDISM)						
Genetic Primary	N	L	E	N	XI, AD, AR	Y

Hypophosphatemia						
X-linked hypophosphatemic rickets					XL	Y
Autosomal dominant hypophosphatemic rickets					AD	Y
Autosomal recessive hypophosphatemic rickets					AR	Y
Fanconi Syndrome						
Cystinosis	N	L	E	E	AR	Y
Tyrosinosis	N	L	E	E	AR	Y
Lowe syndrome	N	L	E	E	XR	Y
Acquired	N	L	E	E		
Phosphate Deficiency or Malabsorption						
Parenteral hyperalimentation	N	L	E	N		
Low phosphate intake	N	L	E	N		
Other						
Renal tubular acidosis, type II proximal	N	L	E	N		Y
Tumor-induced osteomalacia	N	L	E	N		Y
END-ORGAN RESISTANCE TO 1,25(OH)$_2$ D$_3$						
Vitamin D-dependent type II (several variants)	L	L or N	E	E	AR	Y
RELATED CONDITIONS RESEMBLING RICKETS						
Hypophosphatasia	N	N	L	Phosphoethanolamine elevated	AR	Y
Metaphyseal Dysostosis						
Jansen type		N	E	N	AD	Y
Schmid type		N	E	N	AD	Y

[*] Deficiency of vitamin D; low 25(OH)D and no stimulation of higher 1,25(OH)$_2$ D values.

AD, autosomal dominant; AR, autosomal recessive; E, elevated; L, low; N, normal; V, variable; XL, X-linked; Y, yes.

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CHAPTER 724

Hypophosphatasia

Linda A. DiMeglio

Hypophosphatasia is a rare inborn error of metabolism in which tissue-nonspecific (liver, bone, kidney) alkaline phosphatase isoenzyme (TNSALP) activity is deficient, although activity of the intestinal and placental isoenzymes is normal. *ALPL* gene mutations reduce the TNSALP enzyme activity essential for normal skeletal mineralization.

Most of the >100 *ALPL* mutations gene identified to date are missense mutations, although splice-site mutations, small deletions, and frameshift mutations also have been found. Some patients have a regulatory defect involving this enzyme rather than a mutation. There is considerable heterogeneity in disease severity related to the degree of enzyme activity impairment. A nosology that describes seven forms of the condition, ranging from neonatal lethal disease to **odontohypophosphatasia** , which only affects teeth, is employed. The lethal and infantile forms are autosomal recessive; milder forms can be either autosomal recessive or dominant.

The most severe **perinatal hypophosphatasia** cases are lethal in utero or shortly after birth. Affected infants have profound skeletal hypomineralization with short bones and may also have anemia with hemorrhage, pyridoxine-dependent seizures, and hypoplastic lungs (Fig. 724.1*A*). **Infantile hypophosphatasia** is next on the continuum. These infants present prior to 6 months of age with hypercalcemia/ hypercalciuria (leading to nephrocalcinosis), premature cranial suture fusion (that can lead to increased intracranial pressure), irritability, and failure to thrive. X-rays reveal irregular ossification, punched-out areas, and metaphyseal cupping. Prior to the availability of enzyme replacement therapy with **asfotase alfa** , mortality was estimated at 50%; survivors had significant disability. There is also a **benign prenatal** form of hypophosphatasia, seen in newborns who have skeletal abnormalities in utero or at birth that improve spontaneously over time.

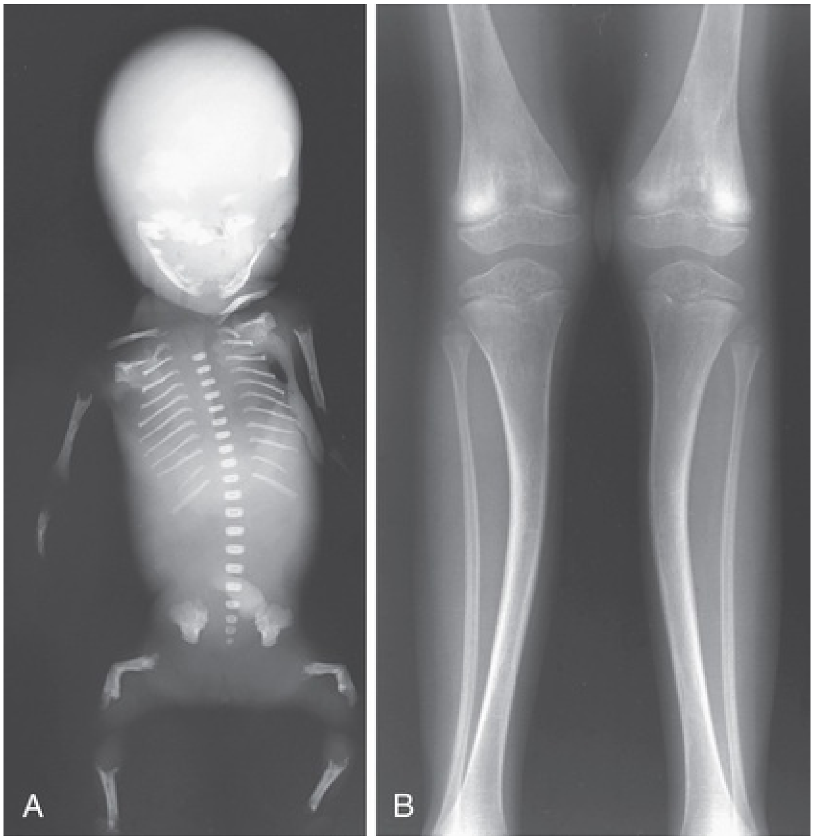

FIG. 724.1 **A,** Fetus with congenital lethal hypophosphatasia showing thin wavy ribs, platyspondyly, missing cervical vertebrae, ossification, and bent femurs. **B,** A 7 yr old with hypophosphatasia tarda showing osteopenia, bent tibias, and punched-out metaphyseal lesions.

The next form of hypophosphatasia is recognized in childhood (after 6 months of life) or late adolescence **(hypophosphatasia tarda)** (see Fig. 724.1*B*). These children present with premature exfoliation of primary teeth (with the root intact due to poorly mineralized dental cementum), mild skeletal deformities, fracture, and variable short stature. Some children have skeletal pain and muscle weakness. Long bones can have characteristic “tongues” of radiolucency.

An **adult hypophosphatasia** form manifests in middle age (although some patients can recount a history of early deciduous tooth loss or rickets). This form is characterized by osteopenia/osteoporosis, recurrent metaphyseal stress fractures (particularly of the metatarsals and tibiae), and femoral pseudofractures. Affected individuals can also have psychiatric symptoms (depression/anxiety) chondrocalcinosis, osteoarthritis, myopathy, nephrocalcinosis, and permanent tooth loss between 40 and 60 years of age.

In hypophosphatasia, large quantities of phosphoethanolamine (PEA) are found in the urine because this compound cannot be degraded in the absence of TNSALP activity. Plasma inorganic pyrophosphate and pyridoxal-5′-phosphate (PLP) levels are elevated for the same reason. Pyridoxal-5-phosphate levels tend to be lower than normal in most other bone diseases and hence can aid in the differential diagnosis of hypophosphatasia. Seizures in patients with the lethal and infantile forms of the disease are related to impaired pyridoxine metabolism.

The clinical course of this condition often improves spontaneously as an affected child matures, although early death from renal failure or flail chest leading to pneumonia can occur in the severe infantile form of the disorder. Enzyme replacement therapy with recombinant human TNSALP improves skeletal healing and mineral content, pulmonary status, and overall physical activity.

Rarely patients presenting with identical clinical and radiographic patterns have normal serum alkaline phosphatase activity but increased concentrations of phosphoethanolamine, inorganic phosphate, and pyridoxal-5′-phosphate. Their disease has been labeled **pseudohypophosphatasia** and might represent the presence of a mutant alkaline phosphatase isoenzyme that reacts to artificial substrates in an alkaline environment (in a test tube), but not in vivo with natural substrates.

An approach to low ALP levels is noted in Fig. 724.2 .

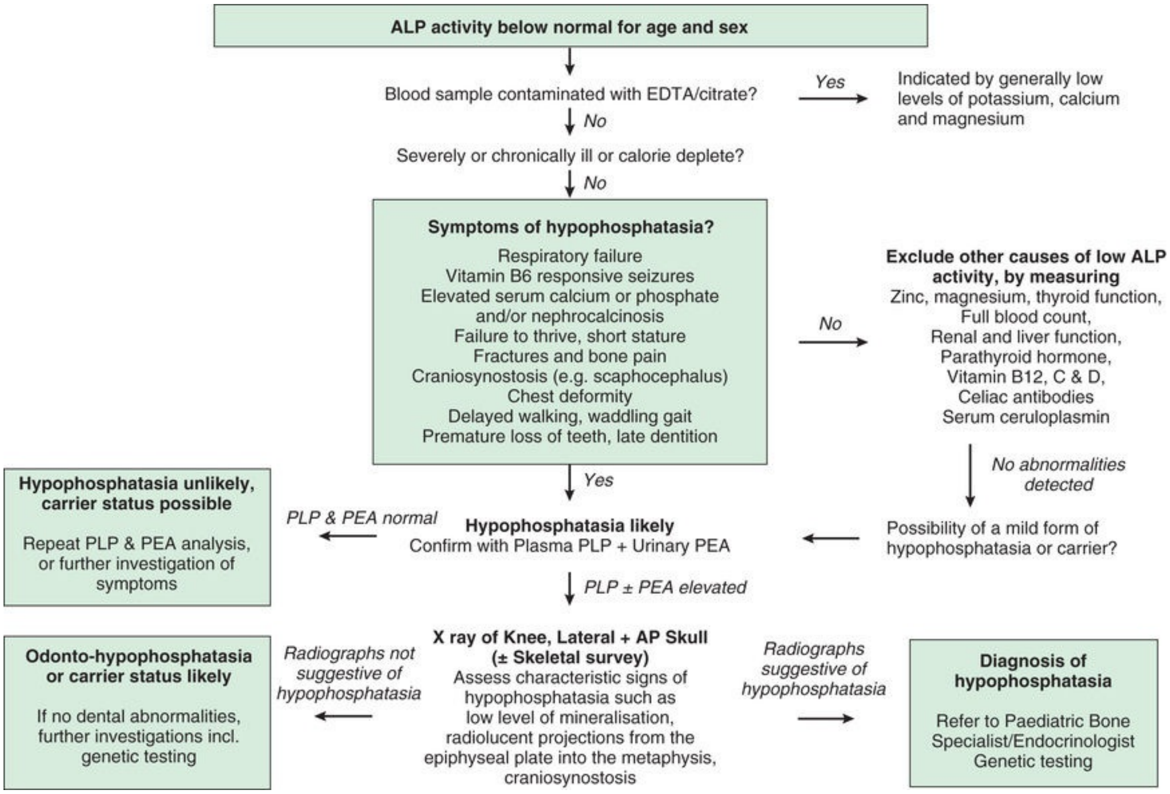
ALP activity below normal for age and sex
Blood sample contaminated with EDTA/citrate?
Yes
Indicated by generally low levels of potassium, calcium and magnesium
No
Severely or chronically ill or calorie deplete?
No
Symptoms of hypophosphatasia?
Respiratory failure
Vitamin B6 responsive seizures
Elevated serum calcium or phosphate and/or nephrocalcinosis
Failure to thrive, short stature
Fractures and bone pain
Craniosynostosis (e.g. scaphocephalus)
Chest deformity
Delayed walking, waddling gait
Premature loss of teeth, late dentition
No
Exclude other causes of low ALP activity, by measuring
Zinc, magnesium, thyroid function,
Full blood count,
Renal and liver function,
Parathyroid hormone,
Vitamin B12, C & D,
Celiac antibodies
Serum ceruloplasmin
No abnormalities detected
Possibility of a mild form of hypophosphatasia or carrier?
Yes
Hypophosphatasia likely
Confirm with Plasma PLP + Urinary PEA
PLP & PEA normal
Hypophosphatasia unlikely, carrier status possible
Repeat PLP & PEA analysis, or further investigation of symptoms
PLP ± PEA elevated
X ray of Knee, Lateral + AP Skull
(± Skeletal survey)
Assess characteristic signs of hypophosphatasia such as low level of mineralisation, radiolucent projections from the epiphyseal plate into the metaphysis, craniosynostosis
Radiographs not suggestive of hypophosphatasia
Odonto-hypophosphatasia or carrier status likely
If no dental abnormalities, further investigations incl. genetic testing
Radiographs suggestive of hypophosphatasia
Diagnosis of hypophosphatasia
Refer to Paediatric Bone Specialist/Endocrinologist
Genetic testing

FIG. 724.2 Diagnostic algorithm for the investigation of children presenting with low ALP activity and/or symptoms of hypophosphatasia. For patients with low ALP, a number of conditions such as nutritional deficiencies (protein/calorie, zinc, folic acid, magnesium, vitamin B6, B12, and vitamin C), vitamin D excess, hypothyroidism, hypoparathyroidism, celiac disease, recent significant blood transfusions, renal osteodystrophy, cardiac surgery and cardiopulmonary bypass, posthepatic resection and transplantation, achondroplasia, and Wilson disease need to be excluded. AP, Anteroposterior; PEA, phosphoethanolamine; PLP, pyridoxal-5'-phosphate. (From Saraff V, Narayanan VK, Lawson AJ, et al: A diagnostic algorithm for children with low alkaline phosphatase activities: Lessons learned from laboratory screening for hypophosphatasia, *J Pediatr* 172:181–186, 2016, Fig. 3.)

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CHAPTER 725

Hyperphosphatasia

Linda A. DiMeglio

Hyperphosphatasia refers to an elevated serum alkaline phosphatase. Increases in alkaline phosphatase are most commonly due to hepatobiliary disease or to bone disorders, including nutritional rickets, characterized by high osteoblast activity; distinguishing liver from bone etiologies requires fractionating alkaline phosphatase isoenzymes or measuring bone-specific alkaline phosphatase as well as other laboratory assessments of liver function or bone turnover/vitamin D status. Pediatric alkaline phosphatase activities are generally higher than those seen in adults because children have higher bone formation rates; age- and gender-appropriate reference ranges should be used.

In children between 6 mo and 2 yr of age, increases in alkaline phosphatase are often due to **transient hyperphosphatasia** . This is usually detected as an incidental finding during screening laboratory evaluations or evaluations performed to assess a specific complaint. Serum alkaline phosphatase values as high as 3,000-6,000 IU/L may be encountered. Liver and bone isoenzyme fractions are both elevated; there are no other clinical or laboratory signs of hepatic or bone disease. Diagnosis can be confirmed by a careful clinical history plus laboratory assessments of: calcium, phosphorus, Cr, AST, ALT, GGT, bilirubin, PTH, and 25-hydroxyvitamin D. The cause may be related to excess sialylation of alkaline phosphatase, which slows clearance. Alkaline phosphatase should be followed serially (every 2-3 mo) until resolution is documented. Resolution usually occurs within 4-6 mo.

Familial hyperphosphatasia is another benign condition. It has an autosomal dominant inheritance and can be distinguished from the transient infantile form by persistent elevations of serum alkaline phosphatase levels.

High bone specific alkaline phosphatase can also be a sign of an underlying genetic bone disorder. **Juvenile Paget disease** is a rare, recessively inherited disorder. Most cases are due to loss-of-function mutations in the *TNFRSF11B* gene, resulting in osteoprotegerin deficiency. The disease usually has its onset by 2-3 yr of age, when painful extremity deformity leads to abnormal gait and sometimes fracture. The skull is large, and the cranium is thickened (widened diploë) and may be deformed. Skull involvement can lead to progressive and profound hearing loss. The disorder is additionally characterized by short stature and progressive bony deformities, including kyphoscoliosis. X-rays show bowing and diaphyseal thickening, along with osteopenia (Fig. 725.1). Radiographically, the bony texture is variable; dense areas (showing a teased cotton-wool appearance) are interspersed with radiolucent areas and general demineralization. Long bones appear cylindrical, lose metaphyseal modeling, and contain pseudocysts that show a dense, bony halo. This disorder, however, is distinct from adult Paget disease (osteitis deformans) because bone histology reveals a lack of normal cortical bone remodeling and an absence of the classic mosaic pattern of lamellar bone found in the adult condition. As in adult-onset Paget disease, bisphosphonates can reduce the rapid bone turnover found in this disorder, preventing deformity and disability and improving hearing.

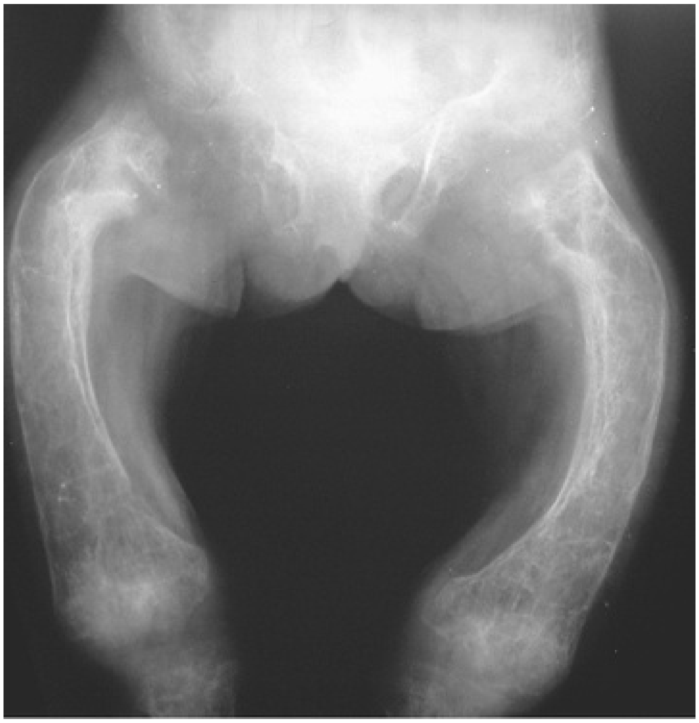

FIG. 725.1 **Juvenile Paget disease showing bowing and thickening of the diaphyses and osteopenia. (From Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, Fig. 167-26, p. 2744.)**

A more serious autosomal dominant disorder, **familial expansile osteolysis** , is characterized by early-onset deafness, premature loss of teeth, progressive hyperostotic widening of long bones causing painful phalanges in the hands, episodic hypercalcemia, and enhanced bone remodeling. This disorder is due to mutations in the *TNFRSF11A* gene encoding the receptor activator of NF-kappa-B (RANK) transmembrane protein, which mediates osteoclastogenesis.

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CHAPTER 726

Osteoporosis

Catherine M. Gordon

Osteoporosis, the most common bone disorder in adults, is relatively uncommon in children, and the criteria that underlie this diagnosis in pediatric patients are a source of debate. This disorder is characterized by diminished bone volume and a marked increase in the prevalence of fractures. In contrast to osteomalacia, which shows undermineralization and normal bone volume, histologic sections of bone in all forms of osteoporosis reveal a normal degree of mineralization but a reduction in the volume of bone, especially trabecular bone (vertebral bone). The diagnosis of osteoporosis in children and adolescents requires evidence of skeletal fragility (fractures) independent of a bone density measurement and, in the pediatric age group, may be primary or secondary (Table 726.1 ; Fig. 726.1). The primary osteoporoses can be divided into heritable disorders of connective tissue, including osteogenesis imperfecta (see Chapter 721), Bruck syndrome, osteoporosis-pseudoglioma syndrome, Ehlers-Danlos syndrome (see Chapter 679), Marfan syndrome (see Chapter 722), homocystinuria, and idiopathic juvenile osteoporosis. Secondary forms of osteoporosis include various neuromuscular disorders, chronic illness, endocrine disorders, and drug-induced and inborn errors of metabolism, including lysinuric protein intolerance and Gaucher disease.

Table 726.1

Diagnoses That Confer Increased Risk for Osteoporosis

Endocrine Disorders

Female Hypogonadism

Turner syndrome
Hypothalamic amenorrhea (female athletic triad)
Anorexia nervosa
Primary ovarian insufficiency
Depot medroxyprogesterone acetate therapy
Estrogen receptor α (ESR1) mutations
Hyperprolactinemia

Male Hypogonadism

Primary gonadal failure (Klinefelter syndrome)
Secondary gonadal failure (idiopathic hypogonadotropic hypogonadism)
Delayed puberty
Hyperthyroidism
Hyperparathyroidism
Hypercortisolism (therapeutic or Cushing disease)
Growth hormone deficiency
Thyrotoxicosis

Inflammatory Disorders

Dermatomyositis
Chronic hepatitis
Juvenile idiopathic arthritis
Systemic lupus erythematosus

Gastrointestinal Disorders

Malabsorption syndromes (cystic fibrosis, celiac disease, biliary atresia)
True or perceived lactose intolerance
Inflammatory bowel disease
Chronic obstructive jaundice
Primary biliary cirrhosis and other cirrhoses
Alactasia
Subtotal gastrectomy

Bone Marrow Disorders

Bone marrow transplant
Lymphoma
Leukemia
Hemolytic anemias (sickle cell anemia, thalassemia)
Systemic mastocytosis

Connective Tissue/Bone Disorders

Idiopathic juvenile osteoporosis
Osteogenesis imperfecta
Ehlers-Danlos syndrome
Marfan syndrome
Homocystinuria
Fibrous dysplasia
Previous or recurrent low impact fractures
Early-onset osteoporosis with WNT1 mutations
X-linked osteoporosis with fractures with PLS3 mutations

Drugs

Alcohol
Heparin
Glucocorticoids
Thyroxine
Anticonvulsants
Gonadotropin-releasing hormone agonists
Cyclosporine
Chemotherapy
Tobacco cigarettes

Miscellaneous Disorders

Immobilization (cerebral palsy, spinal muscular atrophy, Duchenne dystrophy)

Chronic renal disease

Glycogen storage disease type 1

Chronic hepatitis

Hypophosphatasia

Low calcium dietary intake

Gaucher disease

Severe congenital neutropenia

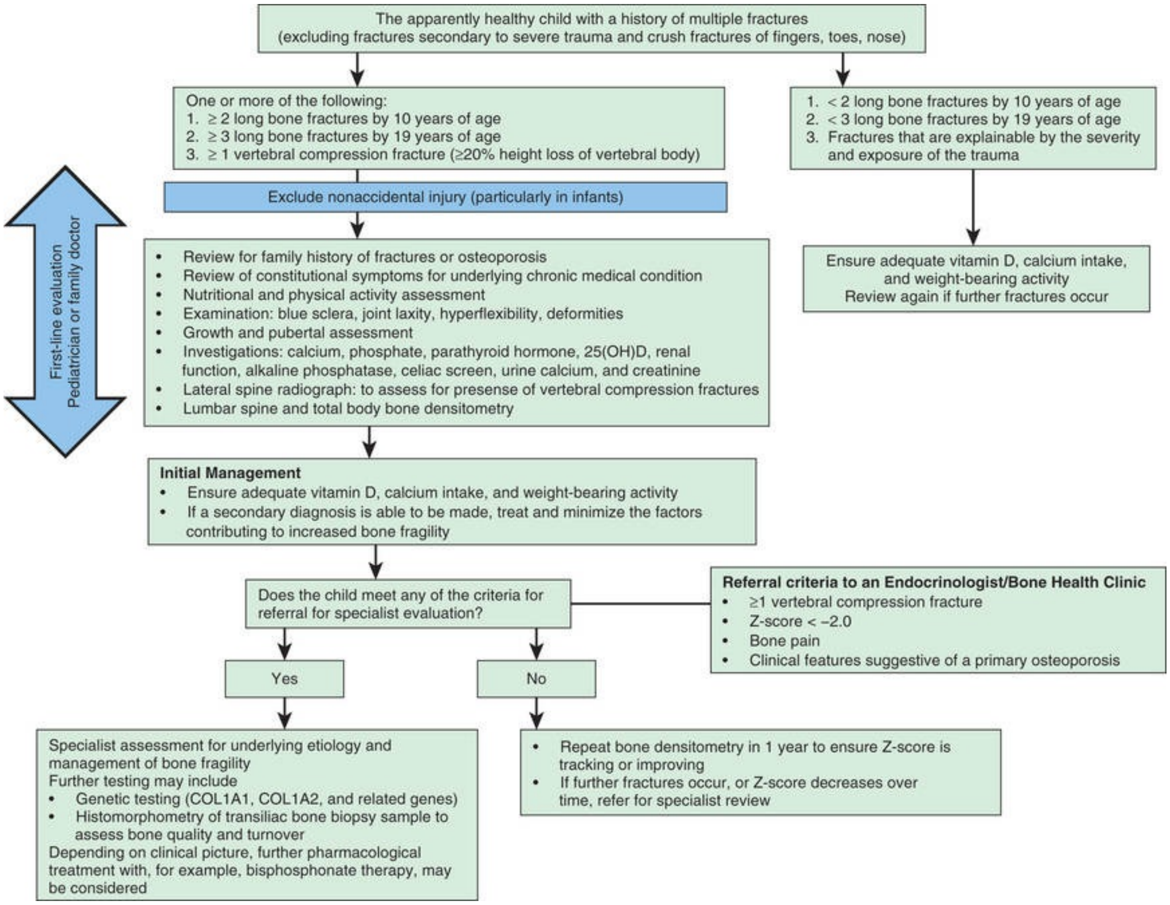
The apparently healthy child with a history of multiple fractures
(excluding fractures secondary to severe trauma and crush fractures of fingers, toes, nose)
One or more of the following:
1. ≥ 2 long bone fractures by 10 years of age
2. ≥ 3 long bone fractures by 19 years of age
3. ≥ 1 vertebral compression fracture (≥20% height loss of vertebral body)
1. < 2 long bone fractures by 10 years of age
2. < 3 long bone fractures by 19 years of age
3. Fractures that are explainable by the severity and exposure of the trauma
Exclude nonaccidental injury (particularly in infants)
First-line evaluation
Pediatrician or family doctor
Review for family history of fractures or osteoporosis
Review of constitutional symptoms for underlying chronic medical condition
Nutritional and physical activity assessment
Examination: blue sclera, joint laxity, hyperflexibility, deformities
Growth and pubertal assessment
Investigations: calcium, phosphate, parathyroid hormone, 25(OH)D, renal function, alkaline phosphatase, celiac screen, urine calcium, and creatinine
Lateral spine radiograph: to assess for presense of vertebral compression fractures
Lumbar spine and total body bone densitometry
Ensure adequate vitamin D, calcium intake, and weight-bearing activity
Review again if further fractures occur
Initial Management
Ensure adequate vitamin D, calcium intake, and weight-bearing activity
If a secondary diagnosis is able to be made, treat and minimize the factors contributing to increased bone fragility
Does the child meet any of the criteria for referral for specialist evaluation?
Referral criteria to an Endocrinologist/Bone Health Clinic
≥1 vertebral compression fracture
Z-score < −2.0
Bone pain
Clinical features suggestive of a primary osteoporosis
Yes
No
Specialist assessment for underlying etiology and management of bone fragility
Further testing may include
Genetic testing (COL1A1, COL1A2, and related genes)
Histomorphometry of transiliac bone biopsy sample to assess bone quality and turnover
Depending on clinical picture, further pharmacological treatment with, for example, bisphosphonate therapy, may be considered
Repeat bone densitometry in 1 year to ensure Z-score is tracking or improving
If further fractures occur, or Z-score decreases over time, refer for specialist review

FIG. 726.1 An algorithm for the management of a child presenting with a clinically significant fracture history, outlining the initial evaluation, management, and when to consider referral for specialist review. (Data from Mayranpaa MK, Viljakainen HT, Toiviainen-Salo S, et al: Impaired bone health and asymptomatic vertebral compressions in fracture-prone children: a case-control study, *J Bone Miner Res* 27(6):1413–1424, 2012; and Bishop N, Arundel P, Clark E, et al: Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 pediatric official positions, *J Clin Densitom* 17(2):275–280, 2014.)

When no obvious primary or secondary cause can be detected, **idiopathic juvenile osteoporosis** should be considered, especially if the following clinical features are evident: onset before puberty, long-bone and lower back pain, vertebral fractures, long-bone and metatarsal fractures, a washed-out appearance of the spine and appendicular skeleton on standard radiographs, and improvement of bone density after puberty. Trabecular bones such as the spine and metatarsals are particularly affected by atraumatic fractures.

In general, blood values of minerals, vitamin D metabolites, alkaline phosphatase, and parathyroid hormone are normal. Evaluation of bone mineral content and bone density by dual-energy x-ray absorptiometry or, less often, quantitative CT shows markedly reduced values. Several modes of therapy (including oral calcium supplements, calcitriol, bisphosphonates, and calcitonin) have been used with some success in individual conditions, but the effect of these treatments is difficult to gauge because spontaneous recovery occurs after the onset of puberty in more than 75% of cases.

Osteoporosis-pseudoglioma syndrome is an autosomal recessive disorder manifested by variable age at onset, low bone mass, fractures in childhood, and abnormal eye development; the defective gene has been mapped to chromosome 11q12-13. The mutation is a loss of function in the gene for low-density lipoprotein receptor-related protein 5. Interestingly, gain-of-function mutations result in a gene product that increases bone density.

The life-cycle implications of either significant demineralization or osteoporosis in childhood need to be stressed. Events in childhood influence peak bone mass, and late adolescence is a period of rapid bone mineral accretion. Peak bone mass is typically achieved by 20-25 yr of age (depending on the bone measured), and the contribution during childhood is considerable. A number of measures influence bone mass: vitamin D, preferably as cholecalciferol (400-800 IU daily), calcium intake (≥1,200 mg/day in adolescents), and weight-bearing exercise throughout childhood. Weight-bearing exercise enhances bone formation and reduces bone resorption. Factors that can prevent acquisition of peak bone mass include the use of alcohol and tobacco. Excellent and convenient sources of dietary calcium include dairy products, but also bony fish, green vegetables, and calcium-supplemented drinks (e.g., orange juice). Yogurt and hard cheeses can be used in many lactase-deficient children. Because it appears that adult-onset osteoporosis stems primarily from genetic factors, representing a complex trait interaction, specific interventions during childhood to augment bone mass are not available.

The treatment of secondary osteoporosis is best achieved by treating the underlying disorder when feasible (see Fig. 726.1). Hypogonadism should be treated with hormone replacement therapy, but in adolescent girls, nutritional issues should first be addressed and, ultimately, prescription of transdermal over oral estrogen (see Chapter 711). Calcium intake should be increased to 1,500-2,000 mg/day. In glucocorticoid-induced osteoporosis, an emphasis is placed on the lowest possible dose to prevent disease activity (e.g., in children with inflammatory bowel disease) with alternate-day dosing or, when appropriate, topical (e.g., eczema) or inhaled (e.g., asthma) glucocorticoids. Special diets for inborn errors of metabolism are also appropriate, as well as enzymatic replacement for diseases such as hypophosphatasia, a genetic disorder leading to deficient endogenous alkaline phosphatase production and defective bone mineralization. Screening for celiac disease should be carried out in unexplained cases of low bone mass, as adherence to a gluten-free diet can significantly enhance bone health in these patients (see Chapter 338.2). Treatment with bisphosphonates that inhibit bone resorption in certain secondary (glucocorticoid-induced) and adult-onset osteoporosis has been successful. Bisphosphonate therapy can also be beneficial for children and adolescents with osteogenesis imperfecta and cerebral palsy.

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PART XXXII

Rehabilitation Medicine

OUTLINE

Chapter 727 Evaluation of the Child for Rehabilitative Services

Chapter 728 Rehabilitation for Severe Traumatic Brain Injury

Chapter 729 Spinal Cord Injury and Autonomic Dysreflexia Management

Chapter 730 Spasticity

Chapter 731 Birth Brachial Plexus Palsy

Chapter 732 Meningomyelocele (Spina Bifida)

Chapter 733 Ambulation Assistance

Chapter 734 Health and Wellness for Children With Disabilities

CHAPTER 727

Evaluation of the Child for Rehabilitative Services

Michael A. Alexander, Nicole Marcantuono

A rehabilitation evaluation starts with determining physiologic impairments and strengths. The strengths may turn out to be pivotal in how well the individual compensates for his or her actual impairments. Physiologic impairments are the biologic factors that limit the child.

Child Characteristics

The assessment begins with **cognitive issues** . Where is the child in the developmental spectrum in language, social, and emotional abilities? How does the child function in the family, school, and community? Does the presence of an impairment act as an impediment to social acceptance? Poor impulse control, stuttering, or speaking loudly, perhaps because of hearing loss, will all distance a child from other children of the same age group.

Sensory issues need to be evaluated. Are vision, hearing, and other senses present and meeting the needs of the child? Impairment of the sense of touch and position sense may affect the child's extremity function, particularly in the area of fine motor activities. Deficiencies in these skills can also affect how others perceive the child.

For a child who has significant disabilities, the evaluation team needs to include educators, neuropsychologists, social workers, physical therapists, occupational therapists, speech therapists, augmentative communication and device technicians, and seating and adaptive equipment specialists, as well as the physician. The pediatric rehabilitation evaluation is a process that not only looks at the actual impairments but looks to see how they affect the functioning of the individual. Functional substitutions and adaptive equipment and strategies need to be applied by the team to minimize the overall impact of the child's impairments on the child's function, maturation, and separation from family and, ultimately, on the child's function as an adult.

Upper-extremity function is assessed to determine strength, range of motion, and agility. Obviously, weakness of both the arms and legs will result in a greater degree of dysfunction than weakness of only the arms or only the legs. Lower-extremity function affects movement in other environments as well.

For a particular child, a manual wheelchair may enhance mobility. But children with arm weakness may need electric wheelchairs, with their associated complications. Problems of accessibility, transport, and cost can become significant issues for the family. Fine motor and prehension tasks (the highly complex motor and sensory tasks performed by the hand) are closely assessed, because some of these children may need to rely on their ability to interface with access joysticks and computers, and strength in these areas may compensate for physical weaknesses.

Skeletal deformities, range-of-motion limitations, and contractures may affect gross motor function, balance, sitting, walking, and climbing. Scoliosis, kyphosis, and pelvic obliquity may limit sitting balance and tolerance, which can secondarily affect upper-extremity function and the amount of time a child is able to socialize.

Family Characteristics

The education, vocation, and mental well-being of the parents or caregivers have a dramatic impact on the child. We know that if a child with impairment is to reach maximum potential, a stable and loving family structure facilitates the child's outcome. Does the family have other stressors, such as illness, death, divorce, and legal problems? What are their healthcare resources?

The Physical Environment

Environment assessment begins with the child's room and home. Access to and inside the home should be discussed. How is this child transported? If the child uses power mobility, does the chair travel with the child, or does it need to reside at the school or home or elsewhere? How is the child mobile in environments in which the power chair is not available? Is the transport of the child the problem? What are the adequacy, cost, and reliability of the van that is being used by the family? How the child gets in and out of the wheelchair is a significant part of the evaluation. Does the child assist with this, or is the child totally and passively dependent on an adult to move the child from, for example, a toilet seat back to the wheelchair?

In the school, does the child have access to all of the building and can the child participate in all activities in the building, such as those in the art and music rooms, cafeteria, science lab, and stage? Does the child participate in clubs, teams, and other activities outside of the home?

The Previously Healthy Child

For children who have established themselves in the general community and functioned in their environment in a normal capacity but then acquire a significant impairment, it becomes incredibly important to understand what their world looked like before they were affected by this new set of problems. If the child is old enough to remember what life had been like, the loss of function can be devastating. Coping with “what could have been” coupled with what was lost will require the help of skilled psychosocial clinicians.

CHAPTER 728

Rehabilitation for Severe Traumatic Brain Injury

Phillip R. Bryant, Chong-Tae Kim

See Chapter 85 .

Traumatic brain injury (TBI) is a major cause of pediatric disability in the United States. TBI due to falls (72.8%) is most common in the 0-4 yr old age range. **Nonaccidental TBI** remains a significant cause of TBI in children 0-4 yr of age (20-30 cases/100,000). Falls (35.1%) and being struck by or against an object (34.9%) are most common in those 5-14 yr of age. Assaults, falls, and motor vehicle injuries make up 85% of the TBI experienced in those 15-24 yr of age. TBI is more common in males than females at all ages.

Pathophysiology

TBI is the consequence of primary and secondary injury. Primary injury results from direct physical impact. It includes coup and counter coup injuries, **acceleration-deceleration injuries** , and **shear forces** . Primary injuries are clinically manifest by focal contusion injuries, hematomas, and swelling. Secondary injury is the consequence of aberrant neurochemical homeostasis following primary injury. This injury mechanism helps to explain why individuals may experience global dysfunction of the brain despite relatively small or focal brain lesions per imaging studies. Minimizing secondary injury is critical to preventing further brain insult after the primary injury.

TBI in children may manifest differently compared to adults. Very young children who have not yet closed their cranial sutures accommodate some increase in intracranial pressure that may result from TBI. However, children have a relatively larger head size compared with their body, higher brain water content, and less myelination, all of which may contribute to greater brain distortion and further brain injury than a comparable injury experienced by an adult.

Severity

The acute severity of TBI is typically classified with the **Glasgow Coma Scale** (GCS) score with severe injury scoring 3-8, moderate scoring 9-12, and mild scoring 13-15 (see Chapter 85). Additional parameters may be helpful in classifying severity. The longer the duration of loss of consciousness (i.e., <30 min, <24 hr, or >24 hr), the more severe the TBI. Longer duration of posttraumatic amnesia (<1 day, between 1 and 7 days, or >7 days) is also reflective of a more severe TBI.

Medical Complications

Disorders of Consciousness

Children with severe TBI manifest various levels of altered consciousness. The levels of consciousness are classified as coma, vegetative state, and minimally conscious state (Table 728.1). The longer the period of impaired consciousness, the poorer the functional recovery. As patients recover from impaired consciousness, they may have altered circadian sleep-wake patterns. In this phase, it is particularly important to **avoid overstimulation at night** , such as procedures, or sedation medications during the day. **A sleep diary** over a period of several days to a week is a useful measure to monitor sleep patterns and determine the effectiveness of medications. **Neurostimulators** (e.g., amantadine, bromocriptine, methylphenidate, or L-dopa) are used for improved arousal during the day. Trazodone or melatonin may help facilitate sleeping at night.

Table 728.1

Level of Consciousness

	COMA	VEGETATIVE STATE	MINIMALLY CONSCIOUS STATE (−)	MINIMALLY CONSCIOUS STATE (+)
Eye opening	None	Spontaneous or to stimulus	Spontaneous	Spontaneous
Brain stem	None	Present	Present	Present

reflexes				
Orientation	None	None	Inconsistent	Consistent
Purposeful Response	None	None	Trivial responses with localization (visual fixation or tracking, localization to pain)	Evident reliable responses with verbal, behavioral, and/or motor

Cognitive-Behavioral Disorders

As patients with severe TBI recover from initial low levels of consciousness, they may demonstrate significant cognitive-behavioral disorders. The **Rancho Los Amigo scale** (RLAS) (Table 728.2) may be used to evaluate the level of this impairment. Common cognitive-behavioral disorders include agitation, aggression, low thresholds of frustration, impulsivity, attention deficits, emotional lability, perseveration, impaired working memory, and poor safety awareness and judgment. It is important to exclude potential exacerbating factors or medical causes of impaired mental status and behavior, including electrolyte abnormalities, infection, marked constipation or urinary retention, and severe pain due to concomitant injuries in patients who incur multiple trauma, including severe TBI.

Table 728.2

Rancho Los Amino Scale

LEVEL	COGNITIVE-BEHAVIORAL CHARACTERISTICS	CLINICAL FEATURES
I	No response	Comatose state
II	Generalized response	Nonpurposeful, reflexive, stereotyped response to simulations
III	Localized response	Specifically localized (head turn, blink eye, grasp), consistent response to stimulations
IV	Confused-agitated	Confused and hyperactive or bizarre behavior
V	Confused-inappropriate	Less agitated and able to follow simple instructions consistently but difficult to follow complicated ones
VI	Confused-appropriate	Still impaired recent memory, needs assistance for unfamiliar situations
VII	Automatic-appropriate	Able to do daily routine independently but has difficulty solving problems
VIII	Purposeful-appropriate	Independent and functional in activities at home and community, but may have some difficulties in stressful situations

Agitation

The first line of management for agitation is to decrease excessive environmental, visual, auditory, and tactile stimulation. Physical constraint is typically implemented as a last resort to prevent harm to the patient and others, and should be removed as soon as the danger has resolved. Posttraumatic loss of memory can be particularly debilitating because it may limit the acquisition and retention of new learning skills. The **Children's Orientation and Amnesia Test** may be helpful in determining when a patients' posttraumatic amnesia has ended, after which these children may be candidates for cognitive rehabilitation. This test assesses **general orientation** (name, age, birthdate, school, etc.), **temporal orientation** (current time, day of the week, year, etc.), and **memory** (verbal and nonverbal). Most patients who have severe TBI will have varying degrees of long-term residual cognitive impairments, including impaired judgment, attention deficits, and impaired working memory.

Posttraumatic Seizure

The incidence of posttraumatic seizure (PTS) is dependent on injury severity and age. About 30–35% of children with severe TBI will experience a PTS. Very early onset PTS develops within 24 hr after TBI, early onset PTS within 7 days, and late onset PTS after 7 days following a TBI. Early onset PTS is more common in children and late onset PTS is more common in adults. The risk of late onset PTS is increased in TBI caused by penetrating injury, with particularly severe brain injuries, and in patients with a history of early onset PTS. Prophylactic treatment with an anti-epileptic medication for 7 days after a TBI is commonly prescribed (see Chapter 85). However, treatment with an anti-epileptic medication beyond 1 week offers no further benefit as a prophylactic agent.

Paroxysmal Sympathetic Hyperactivity

PSH is a constellation of symptoms manifested by hyperthermia, tachycardia, tachypnea, diaphoresis, and increased tone, including dystonic posturing. It is primarily attributable to autonomic dysregulation. The mechanism has not been clearly defined, but is thought to be due to disruption of the inhibitory function of the mesencephalon on the diencephalon. Some drug-related symptoms may mimic the features of PSH and may require discontinuation and use of alternative medication—for example, haloperidol and chlorpromazine may cause neuroleptic malignant syndrome, phenytoin may precipitate a fever, and histamine-2 blockers (cimetidine and ranitidine) may produce extrapyramidal symptoms. There is no current established standard of care for management of PSH, but bromocriptine, propranolol or labetalol, clonidine, amantadine, intrathecal baclofen, morphine, benzodiazepine, and gabapentin have been prescribed with variable success. PSH is a negative factor for short-term but not long-term functional outcomes.

Neuroendocrine Disorders

Deficiencies of growth hormone and gonadotropin are the most common disorders following TBI, resulting in growth retardation and precocious puberty, respectively. About 8% of children with severe TBI sustain chronic pituitary dysfunction. Three different types of salt and water metabolism derangements, diabetes insipidus (DI), syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and cerebral salt wasting (CSW) can develop after a severe TBI. DI results in hypernatremia and is treated with desmopressin. SIADH results in hyponatremia and is treated by restricting fluids. CSW has characteristic laboratory findings of hyponatremic hypo-osmolality in the plasma and hypernatremic hyperosmolality in the urine. In CSW, extracellular fluid volume is depleted; therefore, treatment requires replacement of sodium and water.

Spasticity

Spasticity is a major complication that develops in children with severe TBI (see Chapter 730).

Outcomes Associated With Severe Traumatic Brain Injury

Generally, the younger a child incurs a severe brain injury, the better the functional outcome. However, given the same severity, the outcome of very young children is poorer than that of older children. The age defined as “very young children” (2-5 yr) is variable depending on the studies. The specific reason for this difference in outcomes has not been identified, but a plausible explanation is that although very young children ostensibly have a higher potential for neuroplasticity, their immature and developing brains are more vulnerable to TBI.

The GCS score is a strong prognostic factor for mortality and functional outcome in the acute injury phase, but not for functional outcome in the subacute or chronic phase. Duration of posttraumatic amnesia or time to follow commands are a better prognostic factors for long-term functional outcomes.

Cognitive and behavioral impairments (poor memory-learning and executive skills, hyperactivity, depression, awareness deficits) are the most common and long-lasting sequelae of TBI. These deficits can inhibit successful school re-entry and participation in social activities.

Given the same severity, the long-term functional outcome of children who sustain nonaccidental (inflicted) trauma is worse than that of children who have not been the target of abuse. Children who incur nonaccidental trauma are typically very young. If developmentally delayed prior to their brain injury, they are likely to have poorer long-term functional outcome. The long-term functional outcome of children who sustain a TBI is better than those who sustain a nontraumatic (anoxic) brain injury.

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CHAPTER 729

Spinal Cord Injury and Autonomic Dysreflexia Management

Phillip R. Bryant, Ashlee Jaffe

See Chapter 83 .

Individuals from birth to 21 yr of age account for 26% of all cases of traumatic **spinal cord injury (SCI).** Children are more susceptible to lap-belt injuries, upper cervical injuries, SCIs without radiologic abnormalities (**SCIWORA**), and delayed onset of neurological deficits, ranging from 30 min to 4 days. The most accurate way to evaluate a patient who has sustained a SCI is by performing a standardized physical examination, as endorsed by the International Standards for Neurological and Functional Classification of SCI, recommended for children 6 yr of age and older (Fig. 729.1). Life expectancy is related to the neurologic level of injury and the ASIA impairment scale classification.

ASIA

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY (ISNCSCI)

ISCOS

Patient Name ______________________ Date/Time of Exam ______________

Examiner Name ______________________ Signature ______________

RIGHT		MOTOR KEY MUSCLES	SENSORY KEY SENSORY POINTS Light Touch (LTR)	Pin Prick (PPR)	SENSORY KEY SENSORY POINTS Light Touch (LTL)	Pin Prick (PPL)	MOTOR KEY MUSCLES		LEFT
	C2							C2	
	C3							C3	
	C4							C4	
Elbow flexors	C5							C5	Elbow flexors
Wrist extensors	C6							C6	Wrist extensors
Elbow extensors	C7							C7	Elbow extensors
Finger flexors	C8							C8	Finger flexors
Finger abductors (little finger)	T1							T1	Finger abductors (little finger)
	T2							T2	
	T3							T3	
	T4							T4	
	T5							T5	
	T6							T6	
	T7							T7	
	T8							T8	
	T9							T9	
	T10							T10	
	T11							T11	
	T12							T12	
	L1							L1	
Hip flexors	L2							L2	Hip flexors
Knee extensors	L3							L3	Knee extensors
Ankle dorsiflexors	L4							L4	Ankle dorsiflexors
Long toe extensors	L5							L5	Long toe extensors
Ankle plantar flexors	S1							S1	Ankle plantar flexors
	S2							S2	
	S3							S3	
	S4-5							S4-5	
RIGHT TOTALS									LEFT TOTALS
(MAXIMUM)		(50)	(56)	(56)	(56)	(56)	(50)		(MAXIMUM)

UER (Upper Extremity Right)

LER (Lower Extremity Right)

UEL (Upper Extremity Left)

LEL (Lower Extremity Left)

Comments *(Non-key Muscle? Reason for NT? Pain?):*

(VAC) Voluntary Anal Contraction (Yes/No) ☐

(DAP) Deep Anal Pressure (Yes/No) ☐

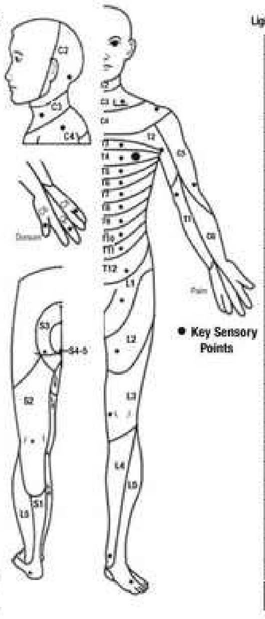

MOTOR
(SCORING ON REVERSE SIDE)

0 = total paralysis
1 = palpable or visible contraction
2 = active movement, gravity eliminated
3 = active movement, against gravity
4 = active movement, against some resistance
5 = active movement, against full resistance
5 = normal corrected for pain/disuse*
NT = not testable

SENSORY
(SCORING ON REVERSE SIDE)

0 = absent *2 = normal*
1 = altered *NT = not testable*

MOTOR SUBSCORES

UER ☐ + UEL ☐ = *UEMS TOTAL* ☐ MAX (25) (25) (50)

LER ☐ + LEL ☐ = *LEMS TOTAL* ☐ MAX (25) (25) (50)

SENSORY SUBSCORES

LTR ☐ + LTL ☐ = *LT TOTAL* ☐ MAX (56) (56) (112)

PPR ☐ + PPL ☐ = *PP TOTAL* ☐ MAX (56) (56) (112)

NEUROLOGICAL LEVELS *Steps 1-5 for classification as on reverse*		R	L
	1. SENSORY	☐	☐
	2. MOTOR	☐	☐

3. NEUROLOGICAL LEVEL OF INJURY (NLI) ☐

4. COMPLETE OR INCOMPLETE? ☐
Incomplete = Any sensory or motor function in S4-5

5. ASIA IMPAIRMENT SCALE (AIS) ☐

(In complete injuries only) *ZONE OF PARTIAL PRESERVATION* *Most caudal level with any innervation*	R	L
SENSORY	☐	☐
MOTOR	☐	☐

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REV 11/15

Muscle Function Grading

0 = total paralysis

1 = palpable or visible contraction

2 = active movement, full range of motion (ROM) with gravity eliminated

3 = active movement, full ROM against gravity

4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

Sensory Grading

0 = *Absent*

1 = *Altered, either decreased/impaired sensation or hypersensitivity*

2 = *Normal*

NT = *Not testable*

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, abduction, adduction, internal and external rotation **Elbow:** Supination	C5
Elbow: Pronation **Wrist:** Flexion	C6
Finger: Flexion at proximal joint, extension. **Thumb:** Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments (S4-S5) by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body.
(This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

ASIA

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI)
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
If voluntary anal contraction = ***No*** *AND all S4-5 sensory scores =* ***0***
AND deep anal pressure = ***No****, then injury is* ***Complete.***
Otherwise, injury is ***Incomplete.***

5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? **If YES, AIS=A** and can record ZPP (lowest dermatome or myotome on each side with some preservation)

NO ↓

Is injury Motor Complete? **If YES, AIS=B**

NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?

NO ↓ **AIS=C**

YES ↓ **AIS=D**

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

FIG. 729.1 American Spinal Injury Association standards worksheet. (From the American Spinal Injury Association: International standards for neurological and functional classification of spinal cord injury (ISNCSCI). Richmond, Virginia, 2016, http://asia-spinalinjury.org/wp-content/uploads/2016/02/International_Stds_Diagram_Worksheet.pdf .)

Clinical Manifestations

Immediately following SCI there is typically a period of **spinal shock** with low tone and absent reflexes. Eventually signs of an **upper motor neuron** lesion may emerge, including spasticity and involuntary muscle spasms. However, if there is a substantial segment of spinal cord infarction present, patients may have persistent flaccid paralysis.

Children with neurologic levels of injury at T6 or above are at particular risk for interruption and decentralization of the autonomic nervous system. The most common manifestations include bradycardia, hypotension, temperature dysregulation, and, once spinal shock has resolved, **autonomic dysreflexia (AD)** . AD is a sustained sympathetic response as a result of a noxious stimulus *below* the level of injury. Symptoms resulting from AD typically include hypertension, bradycardia, headache, and flushing of the skin above the level of injury, although vague symptoms such as fatigue, irritability, or crying may be the presenting symptoms in younger patients. Noxious stimuli are most often localized to bladder or rectal distention, but may include a number of other causes (Table 729.1). Children and adolescents with cervical and upper thoracic level SCI have lower baseline blood pressures compared with the general population. Therefore caution should be used when referencing age appropriate blood pressures, since blood pressure elevations of even 20-40 mm Hg above this lower baseline may be suggestive of AD. *Identification and treatment of the noxious stimulus are typically associated with resolution of symptoms without the use of antihypertensive medication.* If necessary, antihypertensive agents with a rapid onset and short duration, such as nifedipine and nitropaste, are advocated to treat elevated blood pressure while the underlying cause is identified (Fig. 729.2). Emergent management of AD is necessary due to the risk of stroke and additional organ damage resulting from sustained hypertension. Consideration of a medical alert bracelet, education of supervising adults, and carrying of an AD emergency reference card is recommended (Fig.

729.3).

Table 729.1

Potential Etiologies of Noxious Stimuli Causing Autonomic Dysreflexia

Urinary System

- Bladder distention
- Bladder or kidney stones
- Blocked/kinked catheter
- Detrusor sphincter dyssynergia
- Urinary tract infection
- Urologic instrumentation
- Shock wave lithotripsy

Gastrointestinal System

- Bowel distention
- Bowel impaction
- Gallstones
- Appendicitis
- Gastric ulcers
- Gastritis
- Gastrointestinal instrumentation
- Hemorrhoids

Integumentary System

- Constrictive clothing, shoes, or orthotics
- Blisters
- Burns, sunburn, or frostbite
- Ingrown toenail

- Insect bites
- Pressure ulcers

Musculoskeletal System

- Fractures
- Heterotopic ossification
- Functional electrical stimulation

Reproductive System—Male

- Epididymitis
- Scrotal compression (sitting on scrotum)
- Sexual intercourse
- Sexually transmitted infections

Reproductive System—Female

- Menstruation
- Pregnancy, especially labor and delivery
- Vaginitis
- Sexual intercourse
- Sexually transmitted infections

Hematologic System

- Deep vein thrombosis
- Pulmonary embolus

Other Systemic Causes

- Boosting (an episode of autonomic dysreflexia intentionally caused by an athlete with spinal cord injury in an attempt to enhance physical performance).

- Excessive alcohol intake
- Excessive caffeine or diuretic intake
- Over-the-counter or prescribed stimulants
- Substance abuse

From Consortium for Spinal Cord Medicine: Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health-care facilities, Washington, DC, 2001, Paralyzed Veterans of America, pp 10–11.

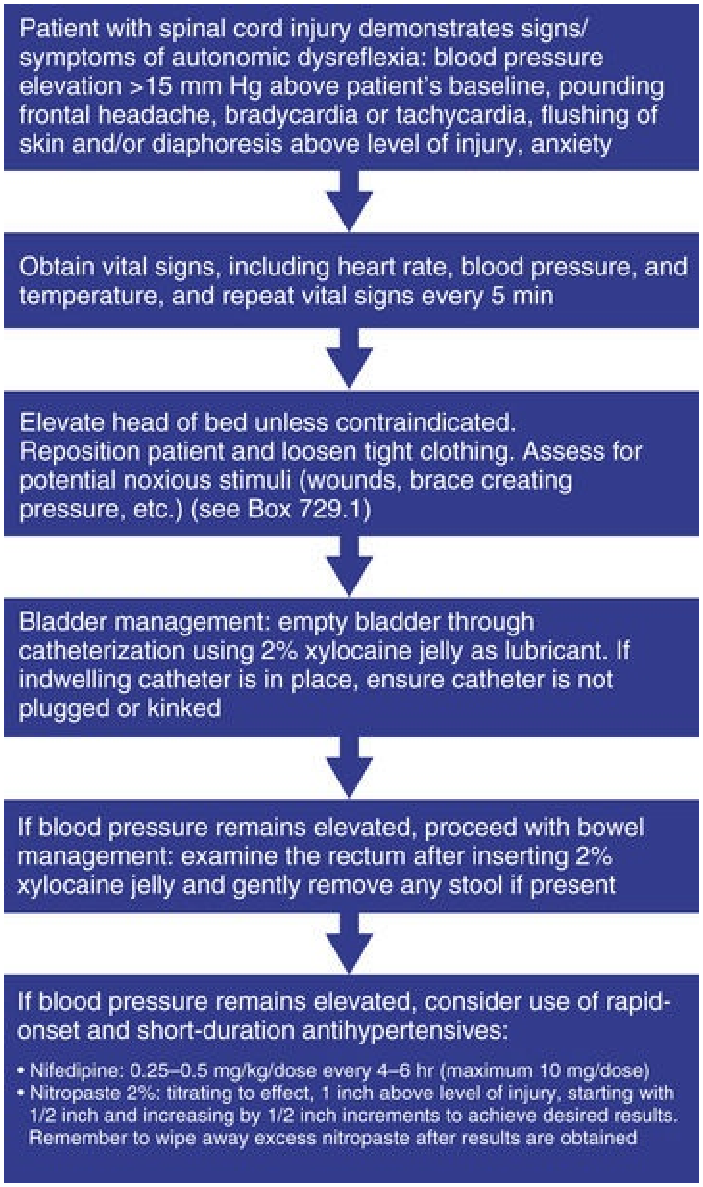

Patient with spinal cord injury demonstrates signs/symptoms of autonomic dysreflexia: blood pressure elevation >15 mm Hg above patient's baseline, pounding frontal headache, bradycardia or tachycardia, flushing of skin and/or diaphoresis above level of injury, anxiety

Obtain vital signs, including heart rate, blood pressure, and temperature, and repeat vital signs every 5 min

Elevate head of bed unless contraindicated.
Reposition patient and loosen tight clothing. Assess for potential noxious stimuli (wounds, brace creating pressure, etc.) (see Box 729.1)

Bladder management: empty bladder through catheterization using 2% xylocaine jelly as lubricant. If indwelling catheter is in place, ensure catheter is not plugged or kinked

If blood pressure remains elevated, proceed with bowel management: examine the rectum after inserting 2% xylocaine jelly and gently remove any stool if present

If blood pressure remains elevated, consider use of rapid-onset and short-duration antihypertensives:

- Nifedipine: 0.25–0.5 mg/kg/dose every 4–6 hr (maximum 10 mg/dose)
- Nitropaste 2%: titrating to effect, 1 inch above level of injury, starting with 1/2 inch and increasing by 1/2 inch increments to achieve desired results. Remember to wipe away excess nitropaste after results are obtained

FIG. 729.2 Algorithm for the management of autonomic dysreflexia.

ATTENTION PHYSICIAN

The following are treatment recommendations for children with Autonomic Dysreflexia (AD)

- Sit patient upright (up to 90 degrees).
- Monitor BP every 2-3 min.
- Quick exam to include abdomen for distended bladder/bowel and any other organ system below the level of injury that can be the source of dysreflexia.
- If an indwelling urinary catheter is not in place, catheterize the individual. If indwelling catheter is in place, check system for kinks, folds, constrictions, or obstructions.
- If systolic BP:
  >120 in children under 5 yrs
  >130 in children 6-12 yrs
  >140 in adolescents
  give an antihypertensive with rapid onset and short duration while cause of AD is being investigated.
- **Nitro Paste**—1/2" (<13y) or 1" (≥13y), apply every 30 min, topically above level of injury, wipe off when BP stable, reapply as needed.
- **Nifedipine** (if Nitro paste NOT available)–0.25-0.5mg/kg per dose (<13y) or 10mg per dose (≥13y), squirt immediate release form sublingually or ask patient to chew, may repeat every 20-30 min as needed.
- **IV Antihypertensives**—only in a monitored setting (I.C.U.)
- Monitor symptoms and BP for at least 2 hrs after the resolution of an AD episode.
- AD can lead to seizures, stroke, or death!

MY INFORMATION

Name:

MEDICAL HISTORY

Baseline Blood Pressure:

Baseline Body Temperature:

Neurological Location of Injury:

Primary Healthcare Provider:

Phone Number:

Allergies:

EMERGENCY CONTACT

In Case of Emergency Call:

Relationship:

Phone Number:

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Pediatric Edition

AUTONOMIC DYSREFLEXIA (AD)

WHAT IT IS:

A blood pressure is the measurement of how well blood moves from the heart to the rest of the body. Autonomic Dysreflexia (AD) affects the blood pressure of people with a spinal cord injury above the thoracic T6 level. Their body gets confused when something harmful or painful is hurting them and they are not able to tell what it is. This causes their body to panic and makes their blood pressure go up. It is unsafe for their blood pressure to get too high. It is important to figure out what is hurting them and take it away. Not fixing this can be dangerous and make that person very sick.

Autonomic Dysreflexia is a Medical Emergency!

COMMON CAUSES:

- Full bladder
- Full bowel/ constipation
- Wounds
- Broken bones
- Skin burns
- Infections
- Ingrown toenails
- Any condition or procedures that may cause pain or discomfort but is located below neurologic injury level.

COMMON SIGNS & SYMPTOMS

ABOVE LEVEL OF INJURY

- Hypertension *(A fast increase in blood pressure, 15 mm Hg systolic higher than usual in children and 15-20 mm Hg systolic higher than usual in adolescents)*
- Bradycardia *(slow heart rate)* or Tachycardia *(fast heart rate)*
- Big headache
- Feeling nervous/worried/scared
- Red cheeks/neck/shoulders
- Blurry vision
- Stuffy nose
- Sweating
- Goosebumps
- Tingling

BELOW LEVEL OF INJURY

- Upset stomach, feels like you need to throw up
- Chills without fever
- Clammy or cold and sweaty
- Cool
- Pale

AUTONOMIC
DYSREFLEXIA
(AD)

WHAT TO DO

☐ **Sit up**—Sit up or raise your head 90 degrees.

IMPORTANT: Stay sitting up until blood pressure is normal.

☐ **Take off**—Take off or loosen anything tight.

☐ **Check blood pressure**—Take your blood pressure every 5 minutes if it's still higher than normal (15 mm above usual pressure Hg in children, and 15-20 mm Hg above usual pressure in adolescents). Make sure the right size blood pressure cuff is being used.

☐ **Check bladder**—Empty your bladder (i.e., catheterize your bladder). If you have an indwelling catheter, check if it's bent or kinked.

☐ **Check bowel**—Check your bowel after using numbing jelly or ointment.

☐ **Check skin**—See if your skin has any new wounds, sores, bruises, burns, bumps, cuts, insect bites, etc.

☐ **Find other source**—Look for anything else that may be hurting you if symptoms have not resolved.

☐ **Find help**—If not able to promptly make the symptoms go away on your own, call your doctor's office to get more help or go to the nearest emergency room.

IMPORTANT: If you go to the hospital, tell the doctors and nurses you may have dysreflexia, need your blood pressure checked, need to stay sitting up, and need to find what's causing it.

CHRISTOPHER & DANA REEVE FOUNDATION
PARALYSIS RESOURCE CENTER

636 Morris Turnpike
Suite 3A
Short Hills, NJ 07078
Phone: (800) 539-7309
Fax: (973) 467-9845
www.paralysis.org

International Center for Spinal Cord Injury
at Kennedy Krieger Institute
Research. Restoration. Recovery.

707 North Broadway
Baltimore, MD 21205
Phone: (443) 923-9230
Fax: (443) 923-9215
www.spinalcordrecovery.org

FIG. 729.3 Example of pediatric autonomic dysreflexia emergency card, which can be downloaded in multiple languages for free from the Christopher & Dana Reeve Foundation Paralysis Resource Center website. (*https://www.christopherreeve.org/living-with-paralysis/free-resources-and-downloads/wallet-cards* .)

Patients with SCI are particularly vulnerable to **deep venous thrombosis** and **pulmonary embolism** because of immobilization of their affected limbs. In children and youth, deep venous thromboses are more common in postpubertal children. Prophylactic treatment is recommended as soon as possible after an SCI (unless contraindicated because of the risk of bleeding or prior allergic response), including low-molecular-weight heparin, graduated compression stockings, and sequential calf compression devices for older children and adolescents. Late-occurring deep venous thrombosis most commonly occurs with prolonged immobilization related to illness or surgery, and prophylactic measures should be continued during these situations as well.

Consequent of SCI, patients often present with varying degrees of bowel and bladder incontinence. Following a SCI, the bladder can be areflexic or hyperreflexic and detrusor sphincter dyssynergia may occur. Clean intermittent catheterization (CIC) of the bladder is typically performed up to 4-6 times/day to prevent urinary retention and vesicoureteral reflux. Constipation can negatively impact the success of a CIC program. Anticholinergic medications may improve bladder storage capacity and prevent urinary incontinence between bladder catheterizations. Antibiotics are recommended for symptomatic urinary tract infections; asymptomatic bacteriuria, without vesicoureteral reflux, is generally due to colonization and typically not treated. Functional independence with bladder and bowel management should be promoted when developmentally appropriate.

Management of **bowel incontinence** requires the use of diet modifications, bowel medications, and planned evacuations. Emptying is facilitated by use of the gastrocolic reflex, digital stimulation, suppositories, and enemas. Individuals with SCI have increased risk for dysphagia, delayed gastric emptying, ileus, gastric ulcerations, pancreatitis, and superior mesenteric artery syndrome. Presentation of an acute abdomen in SCI is challenging to identify because a patient may be incapable of feeling the pain intensity typically associated with an intraabdominal disorder. As a result, an acute abdomen may be manifested by nonspecific signs and symptoms, such as vomiting, poorly localized dull pain, restlessness, fever, and leukocytosis.

Frequent monitoring for **skin breakdown** and **pressure ulcers** is necessary, both acutely as well as lifelong, in individuals with SCI. Pressure ulcers may heal slower in patients with SCI and can significantly impact function. Common locations include the occiput, elbows, sacrum, ischium, and heels. Devices such as halo vests and splints increase the risk of developing a pressure sore. Frequent inspection and repositioning for pressure relief when in bed and when sitting are important measures to minimize the risk of pressure ulcer development.

Depending on the level of the lesion, paralysis of the diaphragm or intercostal and abdominal muscles can result in restrictive ventilatory impairment and ineffective coughing. Respiratory muscle training, abdominal binders, and noninvasive ventilation and airway clearance devices, such as the insufflator–exsufflator cough assist device, should be considered in select patients.

Spasticity typically increases with noxious stimulation and can interfere with sleep, comfort, positioning, and care. Untreated spasticity can lead to contracture development and functional limitations. Management includes pharmacologic therapy, stretching, splinting, and positioning to reduce tone. Focal spasticity can be treated with chemodenervation by injecting botulinum toxin into select hypertonic muscles or phenol perineurally. Intrathecal baclofen may be an option for severe generalized spasticity or spasticity that is predominately in the lower extremities.

Increased bone resorption occurs as a result of prolonged immobilization. If excessive calcium is not adequately excreted by the kidneys, insidious onset of abdominal pain, nausea, vomiting, lethargy, polydipsia, polyuria, and behavior changes may occur. This **immobilization hypercalcemia** is managed with intravenous normal saline and the bisphosphonate pamidronate. Failure to manage the immobilization hypercalcemia may result in nephrocalcinosis, urolithiasis, or renal failure. Osteopenia begins immediately after an SCI occurs and plateaus 6-12 mo later. **Pathologic fractures** may occur as a consequence of loss of bone mineral density. The most common sites of fracture include the supracondylar region of the femur and the proximal tibia. Precautions are necessary because fractures may occur with minor trauma, range of motion exercises, and gait training. Treatment should include the use of removable splints or casts that are well padded over bony prominences to prevent skin breakdown, which is more likely with insensate skin under the cast. Prevention through progressive weight bearing, if feasible and safe, and calcium and vitamin D supplementation is encouraged.

The development of spinal deformities and scoliosis is prevalent in patients sustaining SCI both prior to and during puberty, and some of these children will require surgical correction. Because of the high incidence of scoliosis, radiographs of the thoracolumbar-sacral spine should generally be obtained every 6 mo prior to skeletal maturity and every 12 mo thereafter. Children who sustain injuries prior to puberty are also susceptible to hip dislocation and require periodic screening for this condition. **Heterotopic ossification** is less prevalent in children compared with adults and may occur on average 14 mo after initial injury.

Children and adolescents with SCI are at risk for decreased muscle mass, insulin resistance, decreased glucose transport, dyslipidemia, obesity, and decreased bone health as they age. Nutrition education and monitoring are important for decreasing long-term morbidities. Exercise and activities that promote physical activity and fitness are important for well-being.

Psychological adjustment to SCI is influenced by the developmental age at the time of injury. An SCI will impact the child's psychosocial development, so adjustment should be monitored closely. Long-term outcomes related to coping, depression, and anxiety are better in adults who sustained their injury during childhood, compared with those who sustained their injuries in adulthood. Positive coping strategies and strong social supports are associated with greater social participation. Education regarding sexual development and function with SCI injury should be provided.

Prognosis

Prognosis for functional recovery after a SCI depends on the neurologic level of injury and the level of completeness. Examination at least 72 hr after injury has been determined to be a better indicator of the prognosis than examinations done earlier. Reexamination after recovery from spinal shock provides additional prognostic information. It is prudent for those determining and communicating the diagnosis to understand the limitations of the anorectal examinations, and thus completeness of injury, unique to children. Those individuals with an initial incomplete injury have an increased likelihood of eventual neurologic recovery. The neurologic level of injury can be helpful in determining the level of independence with functional activities (Table 729.2).

Table 729.2

Projected Functional Outcomes at 1 Yr After Injury and/or Diagnosis According to Neurologic Level of Injury

	C1-C4	**C5**	**C6**	**C7**	**C8-T1**
Feeding	Dependent	Independent with adaptive equipment after set-up	Independent with or without adaptive equipment	Independent	Independent
Grooming	Dependent	Minimal assistance with equipment after set-up	Some assistance to independent with adaptive equipment	Independent with adaptive equipment	Independent
Upper-extremity dressing	Dependent	Requires assistance	Independent	Independent	Independent
Lower-extremity dressing	Dependent	Dependent	Requires assistance	Some assistance to independent with adaptive equipment	Usually independent
Bathing	Dependent	Dependent	Some assistance to independent with equipment	Some assistance to independent with equipment	Independent with equipment
Bed mobility	Dependent	Assistance	Assistance	Independent to some assistance	Independent
Weight shifts	Independent in power; dependent in manual wheelchair	Assistance unless in power wheelchair	Independent	Independent	Independent
Transfers	Dependent	Maximum assistance	Some assistance to independence on level surfaces	Independence with or without board for level surfaces	Independent
Wheelchair propulsion	Independent with power; dependent with manual	Independent in power; independent to some assistance, in manual with adaptations on level surfaces	Independent, manual with coated rims on level surfaces	Independent, except curbs and uneven terrain	Independent
Driving	Unable	Independent with adaptations	Independent with adaptations	Car with hand controls or adapted van	Car with hand controls or adapted van
	T2-T9		T10-L2		L3-L5
Activities of daily living (grooming. feeding, dressing bathing)	Independent		Independent		Independent
Bowel/bladder	Independent		Independent		Independent

Transfers	Independent		Independent		Independent
Ambulation	Standing in frame, tilt table, or standing wheelchair Exercise only		Household ambulation with orthosis		Community ambulation is possible

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CHAPTER 730

Spasticity

Joyce L. Oleszek, Loren T. Davidson

Spasticity is a component of the upper motor neuron syndrome characterized by velocity-dependent resistance to passive range of motion, resulting in tonic stretch reflexes and accompanied by exaggerated tendon jerks. Spasticity management is determining what degree of spasticity may be tolerable and of functional benefit versus counterproductive and potentially injurious. When devising a treatment plan, both the positive and negative effects of spasticity on function must be considered; treatment should maximize function while minimizing sedation and adverse effects.

Oral Medications

Oral medications are often used as an early treatment for generalized spasticity (Table 730.1). Although efficacy of certain antispasmodics has been demonstrated, their use should be contingent upon functional benefit, as adverse effects are quite common. Frequently used medications include baclofen, benzodiazepines (diazepam, clonazepam), dantrolene sodium, tizanidine, and clonidine.

Table 730.1

Dosing Guidelines, Pharmacologic Actions, and Adverse Event Profile of Commonly Prescribed Oral Antispasmodic Medications for Children

ORAL MEDICATION (DOSE/FREQ., *AGE/WEIGHT RANGE*)	MODE OF ACTION	ADVERSE EVENTS/PRECAUTIONS

Baclofen (0.125-1 mg/kg/day) *Dosing guideline:* *2-7 yr:* 2.5-10 mg tid-qid (10-40 mg/day) *8-12 yr:* 5-15 mg tid-qid (15-60 mg/day) *12-16 yr:* 5-20 mg tid-qid (20-80 mg/day) Note: Caution advised with renal impairment, consider reducing dose.	• Centrally acting, structural analog of GABA • Binds to GABA_B receptors causing presynaptic inhibition of mono/polysynaptic spinal reflexes • Rapid absorption, blood level peaks in 1 hr, half-life 5.5 hr • Renal excretion (70–80% unchanged) • Hepatic excretion (15%)	• Central nervous system depression (sedation, drowsiness, fatigue) • Nausea • Headache • Dizziness • Confusion • Euphoria • Hallucinations • Hypotonia • Ataxia • Paresthesias **Note: Abrupt withdrawal** may cause seizures, hallucinations, rebound muscle spasms, and hyperpyrexia.
Diazepam (0.12-0.8 mg/kg/day) *Dosing guideline:* *6 mo-12 yr:* 0.12-0.8 mg/kg/day PO divided q 6-8h *>12 yr:* 2-10 mg PO bid-qid Note: Prescription of a *qhs* dose only or proportionately larger dose at bedtime may limit excessive daytime sedation.	• Centrally acting, binds to GABA_A receptors mediating presynaptic inhibition in brain stem reticular formation and spinal polysynaptic pathways • Rapid absorption, blood level peaks in 1 hr, with half-life of 30-60 hr	• Central nervous system depression (sedation, impaired memory and attention) • Ataxia • Dependence/potential for substance abuse/overdose • Withdrawal syndrome (including anxiety, agitation, irritability, tremor, muscle twitching, nausea, insomnia, seizures, hyperpyrexia) • Increased potential for adverse effects with low albumin levels due to being 98% protein bound
Dantrolene sodium (3-12 mg/kg /day) *Dosing guideline:* *For children >5 yr old:* *6-8 mg/kg/d PO divided bid-qid* Start 0.5 mg/kg qd-bid for 7 days, then 0.5 mg/kg tid for 7 days, then 1 mg/kg tid for 7 days, then 2 mg/kg tid to a maximum of 12 mg/kg/d or 400 mg/day	• Peripheral action, blocking release of calcium from sarcoplasmic reticulum with uncoupling of nerve excitation and skeletal muscle contraction • Blood level peaks in 3-6 hr (active metabolite 4-8 hr), with half-life of approx. 15 hr	• Malaise • Fatigue • Nausea • Vomiting • Diarrhea • Muscle weakness with high dose Note: Hepatotoxicity (baseline liver function tests MUST be checked prior to starting dantrolene, tested weekly during dose titration and regularly every 1-2 mo thereafter). Drug ***should be discontinued promptly*** if liver enzymes become elevated.
Tizanidine *Dosing guideline:* *In children <10 yr:* Commence 1 mg orally at bedtime initially, increasing to 0.3-0.5 mg/kg in 4 divided doses *In children >10 yr:* Commence 2 mg orally at bedtime initially, increased according to response, maximum 24 mg/day in 3-4 divided	• Centrally acting, alpha-2 adrenoceptor agonist activity at both spinal and supraspinal sites. Prevents release of excitatory amino acids, facilitating presynaptic inhibition • Good oral absorption, blood level peaks in 1-2 hr, with a half-life of 2.5 hr	• Dry mouth • Drowsiness • Headache • Dizziness • Insomnia • Anxiety • Aggression • Mood swings • Visual hallucinations • Risk of hypotension (although 10 times less anti-hypertensive potency than clonidine) • Nausea • Vomiting • Constipation

doses		Note: Liver function tests should be monitored: baseline and 1 mo after maintenance dose achieved.
Clonidine *Dosing guideline:* 0.025-0.1 mg/kg/day in 2-3 divided doses	• Centrally acting, mixed alpha adrenoceptor agonist with predominant alpha-2 activity causing membrane hyperpolarization at multiple sites in brain, brainstem and dorsal horns of spinal cord • Rapidly absorbed orally, blood level peaks in 1-1½ hr, with a half-life of 6-20 hr	• Drowsiness • Dry mouth • Bradycardia • Orthostatic hypotension Note: Abrupt cessation may result in rebound hypertension.

GABAergic Medications

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter of the central nervous system. The 2 most relevant GABA receptors for the purposes of pharmacologic management of spasticity are GABA_A and GABA_B . **Benzodiazepine medications** exert their effect through GABA_A receptors by increasing the affinity of GABA for the GABA_A receptor. This results in presynaptic inhibition and a net inhibitory effect at both spinal and supraspinal levels. Of the benzodiazepines, **diazepam** is the most commonly used medication to treat spasticity because of its long half-life and need for less-frequent administration. In children <2 yr of age, **clonazepam** is a good option because of the availability of a liquid formulation and dosing guidelines. The cognitive effects of benzodiazepines limit its use in persons with severe spasticity, as dose escalation results in increased sedation. Furthermore, sedation and cognitive slowing limit the usefulness of benzodiazepines in persons with spasticity of cerebral origin, as this may impede recovery in acquired brain injury and cognitive development in congenital developmental delay. The use of benzodiazepines may lead to physiologic dependence, and thus abrupt discontinuation should be avoided to prevent withdrawal.

Baclofen is a GABA_B agonist and is a preferred agent in the treatment of spasticity of spinal origin. Baclofen exerts an inhibitory effect on both monosynaptic and polysynaptic spinal reflexes. Unfortunately, supraspinal receptor sites also exist, resulting in sedation, which is common to all GABAergic medications. In most instances, daytime dosing of oral baclofen is better tolerated than benzodiazepines with regard to sedation. Intrathecal administration of baclofen via a baclofen pump (discussed later) allows greater selectivity of spasticity reduction while minimizing adverse cognitive effects. Abrupt cessation of both oral and intrathecal baclofen (ITB) therapy *must be avoided* , as it may result in a life-threatening withdrawal response.

α_2 -Adrenergic Agents

Clonidine and **tizanidine** are examples of centrally acting α_2 -adrenergic agents that decrease spasticity and have an antinociceptive effect. Clonidine is used more frequently as an antihypertensive agent. Clonidine exerts its effect on spasticity via both presynaptic inhibition of sensory afferents as well as release of glutamate at the level of the spinal cord. Adverse effects of clonidine that limit its use as an antispasmodic include hypotension, bradycardia, sedation, cognitive impairment, and xerostomia.

Tizanidine is an α_2 -noradrenergic agonist that is as effective as diazepam and baclofen in tone reduction. In comparison to clonidine, tizanidine has less-potent hemodynamic effects, which is desirable when it is used primarily for spasticity reduction. The half-life of tizanidine is approximately 2.5 hr, requiring frequent dosing to maintain a steady state. Adverse effects of tizanidine include hypotension, sedation, xerostomia, dizziness, hallucination, and hepatotoxicity.

Peripherally Acting Calcium Blockers

Dantrolene sodium works at the level of skeletal muscle to block calcium release from the sarcoplasmic reticulum. Despite its peripheral site of action, dantrolene may induce sedation, although to a lesser degree than other centrally acting agents. Dantrolene is effective at decreasing both clonus and spasticity but achieves this by weakening skeletal muscle in a nonselective fashion. The resultant generalized weakness seen with dantrolene use limits its utility in ambulatory patients. Dantrolene has a rare but significant adverse event of fatal hepatotoxicity in less than 1% of patients. Hepatotoxicity risk increases with increasing age, increasing dose, and female sex.

Pediatric dosing of spasticity medications is quite variable and needs to be tailored to the response of the child. The choice of medication is often based on personal experience and the impact of benefit vs potential adverse effects. See Table 730.1 for dosing guidelines.

Surgical Management

Surgical management of spasticity should be considered when spasticity causes significant functional impairments that are refractory to more conservative management. Combining treatment options such as injections and systemic medications can be very effective.

Botulinum toxin (BTX) intramuscular injections and **phenol/alcohol neurolysis** are used to treat focal areas of spasticity. These injections are most effective in children with hypertonia localized to specific muscles and those without significant contracture. BTX blocks signal transmission at the neuromuscular junction by preventing the release of acetylcholine from the presynaptic axon of the motor end plate. Treatment with BTX type A is most common, but BTX type B is also used. The period of clinically useful relaxation is usually 12-16 wk, and it is recommended that injections be spaced a minimum of 3 mo apart because of concern for neutralizing antibody formation. Adverse events related to BTX are rare and include injection-site pain and focal muscle weakness. The U.S. Food and Drug Administration (FDA) requires black box labeling on BTX products, cautioning that the effects of the BTX may spread from the area of injection to other areas of the body, causing symptoms similar to botulism. Coadministration of BTX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) should be performed with caution, as the effect of the toxin may be potentiated. BTX-A is an effective and generally safe treatment for spasticity of the upper and lower extremities; evidence regarding functional improvement is conflicting. Long-term use of BTX-A with repeated rounds of injections in children with cerebral palsy is safe and efficacious. BTX-A injections into the gastrocnemius can be combined with serial casting to help improve ankle range and gait.

Phenol perineural injections are typically performed in the large proximal muscles (biceps brachii, hip adductors, hamstrings) and duration of clinical effect may be longer than BTX, varying between 3 and 18 mo. Phenol injection of the anterior branch of the obturator nerve in children with cerebral palsy is safe and effective. The low cost of phenol is a significant advantage over BTX, but the need for electrical stimulation guidance and general anesthesia may offset any cost savings. Combining phenol injections with BTXs allows an increased number of affected muscles to be injected at the maximal recommended dose during a procedure. Phenol is safe in children, but transient sensory dysesthesias occur rarely.

Intrathecal baclofen (ITB) is highly effective in treating severe spasticity. ITB is delivered to the intrathecal space via a surgically implanted infusion pump and catheter. This method of delivery confers an advantage over enteral baclofen, in that central nervous system depressive effects are minimized and dosages can be titrated to functional effect. A preoperative screening bolus dose of baclofen can be delivered via lumbar puncture and is used to evaluate responsiveness and impact on functional abilities. Goals of treatment, whether they are to improve function, comfort, and/or care, need to be firmly established. Cost and maintenance can be prohibitive for some families. Catheter tips are typically positioned at C5-T2 but can be placed intraventricularly for severe dystonia. ITB is effective in children with cerebral palsy; there may be a significant reduction in upper- and lower-extremity spasticity for up to 10 yr. Speech, communication, and saliva control can improve after ITB. The most frequent and serious adverse events related to device and implant procedures are catheter dislodgement from the intrathecal space, catheter break/cut, and implant site infection, including meningitis. Electromagnetic interference and magnetic resonance imaging (MRI) may cause transient operational changes to the pump and changes in flow rate. Although baclofen pumps do not prohibit MRI imaging, it is recommended that the pump be “interrogated” by a programmer after MRI as a precaution. ITB pumps need to be replaced every 5-7 yr for end of battery life. The pump is available in a 20 and 40 mL size, both of which measure 8.75 cm in diameter. The baclofen pump requires regular refills at 2-6 mo intervals, depending on dose rate and pump size, and refills are readily performed in an outpatient clinic setting. **ITB withdrawal** is a medical emergency and needs to be identified early and managed aggressively. Sequelae can include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity that, in rare cases, can advance to rhabdomyolysis, multiple organ–system failure, and death. Prevention of abrupt discontinuation of ITB requires careful attention to programming and monitoring of the infusion system, refill scheduling, and pump alarms. Caregivers need to be educated about the early symptoms of baclofen withdrawal.

Selective dorsal rhizotomy (SDR) is a surgical procedure that has been widely used as a treatment for spasticity. The surgical technique involves single-level or multilevel osteoplastic laminectomies exposing the L2-S1 nerve roots. Typically, 25–70% of dorsal rootlets are selectively cut with the aid of electrophysiologic monitoring. Children 3-8 yr of age with spastic diplegia, minimal upper-limb involvement, good selective motor skills and strength, and minimal contractures are the best candidates for SDR. The preoperative ability to rise from a squatted position with minimal support or a younger child's ability to crawl on hands and knees are positive predictors for a good outcome with SDR. Children must have the cognitive and social capacity for the requisite intensive postoperative therapy program. Long-term outcomes 5 and 20 yr after SDR in children show an improvement in spasticity, motor function, and gait pattern. SDR can reduce the need for orthopedic surgeries, with 35% of children avoiding surgery; this might be more likely if SDR is performed before the age of 5 yr. Long-term complications such as sensory dysfunction, bladder or bowel dysfunction, or back pain are infrequent. A concern with multilevel laminectomies is the potential increased risk of spinal deformities, but there is no clear evidence to support this.

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CHAPTER 731

Birth Brachial Plexus Palsy

Maureen R. Nelson

Birth brachial plexus palsy (BBPP) may cause significant arm weakness and subsequent functional deficits in children. The nerves to the arm are affected with variable degrees of weakness and sensory loss. Most children will have good recovery spontaneously, but functional deficits will remain in 20–30% of children with BBPP (see Chapter 120.6).

The mechanism for birth brachial plexus injury is lateral stretch of the plexus for the vast majority of cases. Anatomic variations in bones, blood vessels, and tendons lead to a very small number of cases. The incidence of BBPP is reported as 0.5-4.6 per 1,000 live births, with variability thought to be attributable to the type of obstetric care and the size of infants around the world.

Risk factors for birth brachial plexus injury include prior infants with BBPP, shoulder dystocia, birth weight >4 kg, multiparous mothers, mothers with excessive weight gain, and diabetic mothers. Delivering twins or triplets, as well as cesarean sections, have been described as protective from BBPP. Factors with a higher risk of poor outcome are birth weight greater than 4 kg, Horner's syndrome, cephalic presentation, and induction or augmentation of labor.

Nerve injuries include neurapraxia, neurotmesis, and axonotmesis. **Neurapraxia** is the least severe of these types and is a reversible loss of nerve conduction. This type will recover. **Neurotmesis** is the most severe and is a total and complete disruption of the nerve. An *avulsion* describes a neurotmesis of a preganglionic lesion, and a *rupture* describes the same event in a postganglionic lesion. **Axonotmesis** is the intermediate form and the most difficult to delineate. There is disruption of the epineurium with variable injury to the axons (Fig. 731.1). Nerves are made of groups of fascicles, which, in turn, are made of groups of axons. The variation of findings in axonotmesis contributes greatly to the diagnostic dilemma and difficulty in prediction of recovery.

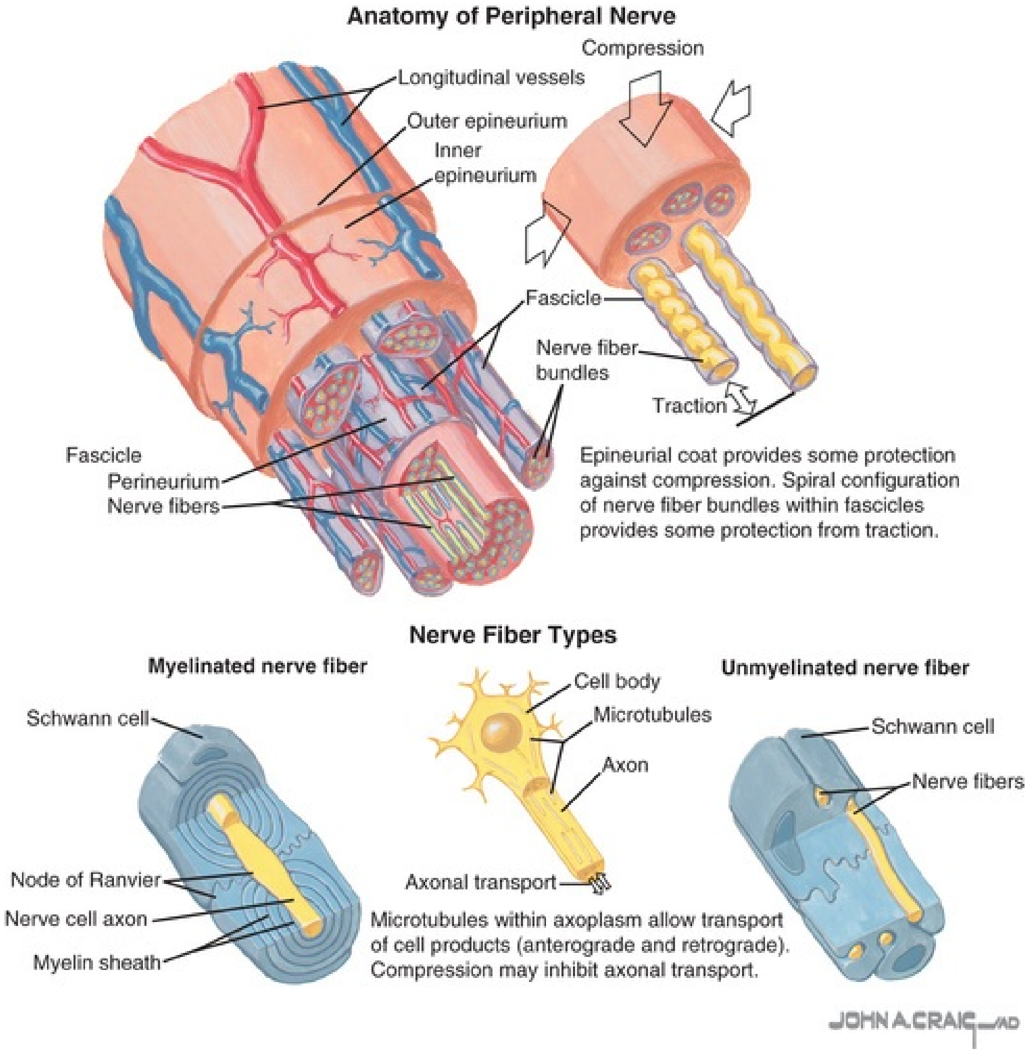
Anatomy of Peripheral Nerve
Compression
Longitudinal vessels
Outer epineurium
Inner epineurium
Fascicle
Nerve fiber bundles
Traction
Fascicle
Perineurium
Nerve fibers
Epineurial coat provides some protection against compression. Spiral configuration of nerve fiber bundles within fascicles provides some protection from traction.
Nerve Fiber Types
Myelinated nerve fiber
Schwann cell
Node of Ranvier
Nerve cell axon
Myelin sheath
Cell body
Microtubules
Axon
Axonal transport
Microtubules within axoplasm allow transport of cell products (anterograde and retrograde). Compression may inhibit axonal transport.
Unmyelinated nerve fiber
Schwann cell
Nerve fibers
JOHN A.CRAIG MD

FIG. 731.1 **Anatomy of peripheral nerve. (Netter illustration from www.netterimages.com . Elsevier, Inc. All rights reserved.)**

The brachial plexus consists of the anterior primary rami, or roots, from C5, C6, C7, C8, and T1 (Fig. 731.2). The trunks of the brachial plexus consist of C5-C6 forming the upper trunk, C7 forming the middle trunk, and C8-T1 forming the lower trunk; each trunk has anterior and posterior divisions. The posterior cord is formed from the posterior division of each trunk. The medial cord comes from the anterior division of the lower trunk. The lateral cord is formed from the anterior divisions of the upper and middle trunks. Evaluation of the roots, trunks, and cords from which the nerves arise helps determine the site of injury.

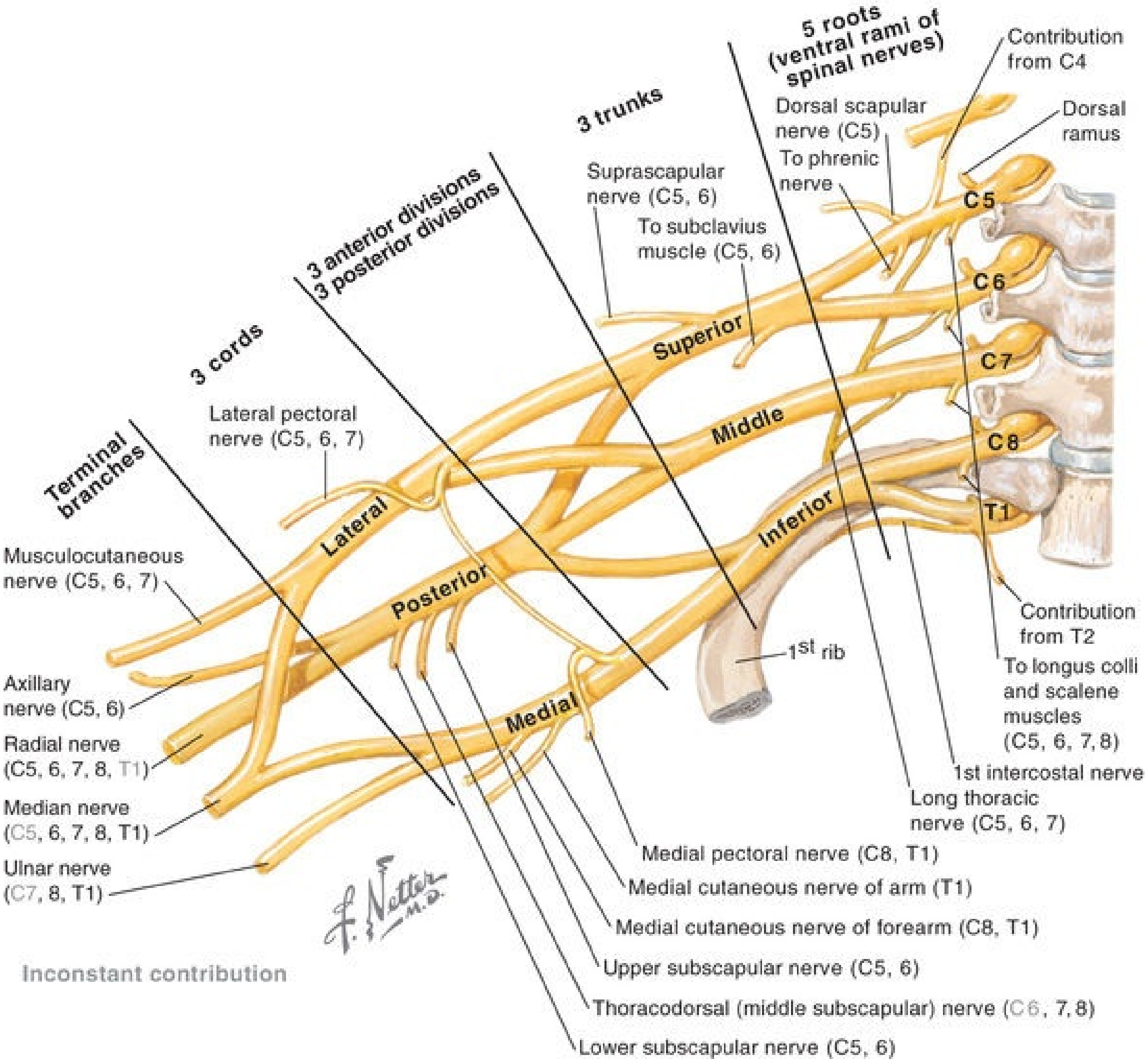
5 roots (ventral rami of spinal nerves)
Contribution from C4
Dorsal ramus
3 trunks
Dorsal scapular nerve (C5)
To phrenic nerve
Suprascapular nerve (C5, 6)
To subclavius muscle (C5, 6)
3 anterior divisions
3 posterior divisions
3 cords
Terminal branches
C5
C6
C7
C8
T1
Superior
Middle
Inferior
Lateral pectoral nerve (C5, 6, 7)
Lateral
Posterior
Medial
Musculocutaneous nerve (C5, 6, 7)
Axillary nerve (C5, 6)
Radial nerve (C5, 6, 7, 8, T1)
Median nerve (C5, 6, 7, 8, T1)
Ulnar nerve (C7, 8, T1)
1st rib
Contribution from T2
To longus colli and scalene muscles (C5, 6, 7, 8)
1st intercostal nerve
Long thoracic nerve (C5, 6, 7)
Medial pectoral nerve (C8, T1)
Medial cutaneous nerve of arm (T1)
Medial cutaneous nerve of forearm (C8, T1)
Upper subscapular nerve (C5, 6)
Thoracodorsal (middle subscapular) nerve (C6, 7, 8)
Lower subscapular nerve (C5, 6)
Inconstant contribution

FIG. 731.2 Schematic of the brachial plexus. (Netter illustration from www.netterimages.com . Elsevier, Inc. All rights reserved.)

Erb's palsy is generally described as the upper trunk or C5-6 palsy. It is by far the most common injury seen in BBPP, and together with C5-7, sometimes called extended Erb's, they make up 75% of all BBPP. These two groups also demonstrate the greatest recovery rate, with 80% and 60%, respectively, resulting in a functional arm. **Klumpke's palsy** , C8-T1, is extremely rare in BBPP, likely not occurring except in the case of anatomic variation. If a baby presents with a C8-T1 deficit, the baby most likely originally had a complete C5-T1 BBPP and then had recovery of the upper portion of the plexus. This can happen because C4, C5, C6, and sometimes C7 are protected coming out from the spinal cord, held in a gutter along the transverse processes by connective tissue, whereas C8 and T1 are not. A C8-T1 deficit may also result from a spinal cord injury. Consequently, it is important to check for any other indications of spinal cord injury throughout the body. Consideration also must be given to the potential of an anatomic variation, such as an anomalous rib or tendon that may actually cause a C8-T1 deficit alone. The sensory fibers are also relatively protected compared with the motor fibers, because the sensory fibers run together until outside of the spinal cord into the dorsal root ganglion, where their cell bodies lie. The motor fibers have the cell bodies within the spinal cord and so are not as cohesive in their path. Therefore the sensory fibers may be spared, while motor fibers show clinical deficits.

Because various parts of the brachial plexus have different risks of injury, the clinical presentation may be quite variable, causing the diagnosis to be challenging. The phrenic nerve may also be involved with its innervation from C3, C4, and C5, with potential respiratory concerns.

Included in the differential diagnosis of an infant with an arm deficit is the possibility of a fracture of the humerus or clavicle, osteomyelitis, a tumor, or congenital varicella infection, all of which may lead to the limited ability to move the arm.

Physical Examination

The physical examination of the child begins with observation. Examination for sensation, particularly examining for sharp sensation, useful in its own right, will also frequently help with active motor evaluation in infants. Assessment of muscle stretch reflexes is important, in that infants with brachial plexus palsy will be areflexive or hyporeflexive in the involved arm. Evaluation of primitive reflexes, particularly the Moro reflex, is helpful, as most of these infants will have C5-6 involvement, and therefore the Moro may show shoulder abduction and elbow flexion on 1 side but not the involved side. Range-of-motion examination is critical. Deficits are commonly seen because of the imbalance of muscles that are active and those that are not. Shoulder adduction and internal rotation is a common position, as is elbow flexion, forearm pronation, and wrist and finger flexion. In children with very severe deficits, the arm may be cooler because of the sympathetic nervous system outflow at T1. Torticollis is commonly present, and almost always with the face turned away from the involved arm. **Horner's syndrome** (ptosis, miosis, and anhidrosis) may be present ipsilaterally. The size of the involved arm eventually is usually smaller, about 95% of the uninvolved arm, because of muscle atrophy and smaller diameter and length of the bone.

Among older infants and children, compensatory movements of the arm may be noted. Common examples are use of trunk momentum to move (particularly to rotate) the proximal arm, hyperlordosis of the lumbar spine to position the arm more advantageously, use of the pectoralis muscle to flex the shoulder, and use of the knee to physically flex the elbow. Examination of the back for symmetry, along with the scapulae for winging, is also relevant. Having the older child manipulate buttons, snaps, or zippers, throw and catch a ball, and write, print, or color may be revealing, along with how s/he removes the shirt for examination.

Evaluation

Radiographic evaluation may be needed. Plain films can be viewed immediately if there is reason to consider clavicle or humerus fracture, infection, osteomyelitis, or tumor. Ultrasound scan (USS) shows the nerves and this is improving as technology advances. Magnetic resonance imaging (MRI) and computed tomography (CT) myelogram are used for evaluation of nerve roots and nerves. USS and MRI are useful in older children to evaluate shoulder abnormalities.

Electrodiagnostic evaluation may also contribute to the diagnosis. Sensory nerve conduction studies are very useful in a child with severe injury who has insensate areas. Normal electrical sensory response in areas where the child cannot feel indicates a *preganglionic neurotmesis* (avulsion). Motor nerve conduction studies are useful to check for continuity of nerve fibers to muscles that are weak or paralyzed. F waves are useful in evaluating proximally, as these responses go from peripheral nerves to the spinal cord and back. Somatosensory evoked potentials are difficult to perform on infants while awake, because of motor artifact obliterating the responses with movement, and are imprecise because of overlapping responses to peripheral stimulation. These are useful intraoperatively, as stimulation can be performed on the nerve roots themselves to determine proximal continuity. **Electromyography (EMG)** can show activation in muscles with paralysis or severe weakness. It is important that these studies be performed by someone who is experienced in the examinations of infants and young children, both for the most precise evaluation and the most comfortable experience for the youngster. There are changes in nerve conduction velocities that occur with age, distances are nonclassic for traditional studies, and electrode placement is challenging because of the very small hands and limbs. The absence of biceps motor unit potentials at 1 mo of age predicts future lack of clinical biceps recovery, though biceps EMG at 3 mo has been reported to overestimate recovery potential.

Treatment

Treatment begins on initial evaluation with instruction to the parents for positioning and early stretching exercises to begin in the 1st days, or at 3-4 wk if humerus or clavicle fracture is present. They are also told of the critical task of maintaining infant awareness of the involved arm, initially by manually mimicking activities with the affected arm that the baby performs with the contralateral arm and by using a wrist rattle on the arm. The parents also are informed of the higher risk of BBPP for future infants, and so the families are encouraged to speak with the obstetrician about optimal management in future deliveries.

The baby will start with occupational or physical therapy at approximately 2 wk of age. The therapist will evaluate the baby as described previously and will reiterate the importance of maximizing the awareness of the involved arm and will teach range-of-motion exercises. The therapist will often do **splinting** , commonly for wrist extension in a baby with wrist-drop, and possibly extending the fingers and abducting the thumb as well. Over time other splinting needs may be evident. There may be a supinator strap used during the therapeutic activities to turn the arm from a pronated position to supination. Shoulder external rotation splints may be useful. **Therapeutic taping** may be done for supination, wrist extension, or, most commonly, for shoulder positioning to minimize an adducted, internally rotated posture. The family is instructed in a home exercise program to be carried out on a daily basis, including stretching exercises, strengthening as a child is able, positioning, and use of splints.

After a few months of age, the child may be able to tolerate **electrical stimulation** . Functional electrical stimulation to the muscles minimizes atrophy and promotes increased size, and therefore strength, of muscle fibers. Ideal parameters for its use have not yet been determined, but a 20-30 min twice-daily program is effective and has been shown to increase bone density. There are also proponents of the use of **constraint-induced movement training** to increase the active use of the involved hand. This is useful for a short-term increase in active use of the arm, but long-term improvements have not been shown.

Biofeedback has been used to attempt to retrain muscles in those with BBPP. **Botulinum toxin injections** are also used to help balance out muscles that are overpowering weak muscles, in order to minimize contractures.

Hand function was evaluated with testing of children with upper-plexus involvement compared with their contralateral hand; 80% of the children had significantly greater-than-predicted decreased performance from the opposite hand. This indicated the hand function is impaired even in children who only have upper plexus involvement.

Secondary problems can increase the negative impact of functional deficits in children with BBPP. Contractures from imbalance due to muscle weakness or paralysis, including shoulder adduction and internal rotation, elbow flexion, forearm pronation, and wrist and finger flexion, are all seen and interfere with function. Botulinum toxin injections are effective in preventing or delaying surgical interventions in children with shoulder and elbow deficits. A decrease in growth of the affected arm in length and atrophy of muscles are often seen. Lack of awareness of the arm, sometimes called *developmental disregard* , in children can have a significant impact on active use of the arm, with functional loss as a consequence. Pain is not usually seen in birth brachial plexus as opposed to injuries that occur later in life. Scapular winging can be problematic both socially and clinically. The change in child development overall can be problematic. Toddlers with sensory loss sometimes chew on their fingers, causing injury.

Infants who do not show satisfactory improvement in muscle strength are candidates for **surgical intervention** . Classically the lack of elbow flexion to 3/5 or greater strength by 3 mo of age merits referral for nerve surgery. The specific criteria and timing remain under debate. Those with a complete brachial plexus palsy with a flaccid arm and lack of sensation are under consideration for surgery at 3 mo of age, and those with upper-plexus involvement are considered between 3 and 6 (or even 9) mo of age. The surgical strategy for complete palsy is early microsurgery, with the initial focus on hand reinnervation. If the shoulder and elbow have continued deficits later, they will undergo secondary musculotendinous procedures.

Nerve transfers, nerve grafting, and neurolysis all are commonly performed in primary surgery. Intraoperative electrical nerve studies can help guide the procedure with somatosensory evoked potentials and nerve conduction studies, both nerve-to-nerve and nerve-to-muscle, commonly performed. These can assist in determining functional electrical continuity of nerve fibers. Nerve grafting is commonly performed using sural nerve fascicles or synthetic nerve conduits, with several fascicles attached at each root level. For those with no intact nerve roots, intercostal nerve and other peripheral nerve transfers or grafts, or a cross C7 graft (from the contralateral plexus), may be performed.

Recovery of muscle function can occur with extremely varied nerve grafts and transfers providing innervation, showing the amazing adaptability of the body and its recuperative power. Postoperative improvement in hand and arm function has been shown to have a negative correlation with age at surgery, and therefore early intervention is recommended.

For older babies and children, muscle, tendon, and bony procedures are generally performed, sometimes combined with a peripheral nerve procedure in a secondary procedure. The Oberlin procedure, using a portion of the ulnar nerve to the musculocutaneous nerve, just as it enters the biceps, is a classic peripheral nerve procedure. The Steindler flexorplasty may be used to obtain elbow flexion by moving the flexor and pronator muscles from the medial epicondyle to the more proximal humerus. Elbow flexion contractures develop in about half of children, with increasing prevalence with age. Botulinum toxin injections and serial casting have both been shown to decrease the contracture, while splinting minimizes progression of the contracture but does not decrease it. For those with very severe arm involvement, the gracilis is sometimes used by transferring this muscle along with the nerve and vascular supply to the arm for elbow flexion and/or wrist extension.

Because the shoulder joint develops as the infant and toddler grows, deficits frequently develop. Glenohumeral dysplasia, sometimes with shoulder dislocation, occurs in 60–80% of those with BBPP. Muscular imbalance across the developing shoulder results in deformity of the skeletally immature glenohumeral joint. The weakness of shoulder external rotation, combined with strong internal rotation, leads to this difficulty. The natural history of this deformity is progression if left untreated. This leads to further functional limitations, even with a strong hand. Treatment aims to minimize this progression. Treatment options include botulinum toxin injections, arthroscopic or open anterior capsule release or release of contracture, musculotendinous lengthening, tendon transfers (commonly transfer of the latissimus dorsi to increase external rotation and abduction strength), and for severe deficits, a derotational humeral osteotomy.

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CHAPTER 732

Meningomyelocele (Spina Bifida)

Pamela Wilson, Janet Stewart

See also Chapter 609 .

Meningomyelocele, or spina bifida, is a congenital neural tube defect that results in the malformation of the spine and a potential dysplastic spinal cord. The severity of defect ranges from spina bifida occulta (see Chapter 609.2) upward to anencephaly (see Chapter 609.6). Recent estimates suggest that spina bifida without anencephaly is the most prevalent nonchromosomal central nervous system (CNS) defect (3.73 per 10,000 births) in the United States and ranks 7th among other non-CNS birth defects based on the CDC data.

Etiology

See Chapter 609.1 .

Prevention

See Chapter 609.1 .

Prenatal Screening

Prenatal screening is recommended for all pregnant women to detect neural tube defects. A simple blood test is done in the 2nd trimester to evaluate alpha-fetal protein (AFP). If a neural tube defect is present, the AFP is often elevated, and further screening using high-resolution ultrasound is indicated. Ultrasound may reveal not only the spinal defect but also abnormal brain development, suggested by the “*lemon* and *banana signs.*” The lemon sign is a medial indentation and scalloping of the frontal bones in the skull, whereas the banana sign is associated with hindbrain herniation of the cerebellum into the foramen magnum. The importance in early identification allows families to plan for delivery and consider fetal interventions, mainly prenatal surgical closure of the defect. Prenatal closure decreases the need for a shunt and lowers the incidence of severe Arnold-Chiari malformations, along with improved motor outcomes. However, there is an increased incidence of preterm delivery and a risk for uterine dehiscence; these risks are reduced with fetoscopic procedures.

Clinical Implications

Meningomyelocele is a multisystem problem that includes characteristic abnormalities within the CNS. The neurologic lesion is assessed by the most caudal intact nerve segment with a motor test of grade 3. Lesions associated with spina bifida are often grouped together as thoracic, upper lumbar (L1-L2), midlumbar (L3), lower lumbar (L4-L5), and sacral. Based on this information a clinician can make inferences on the functional capabilities of the child and answer pertinent questions during the initial encounters (Table 732.1). The most basic question all families ask is: “Will my child walk?”

Table 732.1

Prognosticating in Myelomeningocele

MOTOR LEVEL SPINAL CORD SEGMENT	CRITICAL MOTOR FUNCTION PRESENT	MOBILITY: SCHOOL AGE	RANGE: ADULT	ACTIVITY: ADOLESCENT
T12	Totally paralyzed lower limbs	Standing brace, wheelchair	Wheelchair	Wheelchair, no ambulation
L1-L2	Hip flexor muscles	Crutches, braces, wheelchair	Wheelchair, household ambulation	Wheelchair, nonfunctional ambulation
L3-L4	Quadriceps muscles	Crutches, braces, household ambulation, wheelchair	Crutches, household ambulation, wheelchair	50% Wheelchair, household ambulation with crutches
L5	Medical hamstrings, anterior tibial muscles	Crutches, braces, community ambulation	Crutches, community ambulation	Community ambulation with crutches
S1	Lateral hamstring and peroneal muscles	Community ambulation	Community ambulation	Community ambulation 50% crutch or cane

S2-S3	Mild loss of intrinsic foot muscles possible	Normal	Normal	Limited endurance because of late foot deformities

From Braddon RL, editor: *Physical medicine & rehabilitation* , ed 4, Philadelphia, 2011, WB Saunders, Table 54.1, p. 1284.

Initial surgical interventions are related to closure of the open defect. This is generally done the first day of life. Once the back is closed, the child will be monitored to see if hydrocephalus develops. Hydrocephalus is very common, and related to hindbrain herniation and obstruction of the 4th ventricle. Hydrocephalus may occur at any time, but most frequently within the first few months. Ventricular dilation may precede a change in head circumference or signs of increased intracranial pressure. The occurrence of hydrocephalus is approximately 77–95% and does appear to have an association with level of lesion. Treatment of ventriculomegaly, if mild, may be limited initially to clinical observation. Surgical placement of a ventricular shunt or endoscopic 3rd ventriculostomy is indicated when occipital frontal circumference (OFC) is increasing. The risk for shunt revision in the first 2 yr is 30–50%, which then decreases to 10%.

Hindbrain herniation or the **Chiari type II malformation** is seen in 80–90% of individuals with myelomeningocele. The classic manifestations include caudal displacement of the cerebellum, pons, and medulla and elongation of the 4th ventricle. The Chiari II malformation can be symptomatic (from brainstem herniation/compression) in approximately 20% of children. Respiratory symptoms associated with a Chiari malformation include stridor, vocal cord dysfunction, and central or obstructive apnea. Swallowing and feeding problems may require gastrostomy tube placement. If the child has a symptomatic Chiari II malformation, surgical decompression is indicated. All children with spina bifida are at risk for **tethered cord syndrome** (see Chapter 624.1). After shunt malfunction, this is the second most common cause for neurologic decline. Clinical manifestations of tethered cord syndrome include any change in gait, change in bowel or bladder function, increasing scoliosis, back pain, or orthopedic changes. Surgical detethering procedures are indicated in those with neurologic decline, but the success rate is variable.

The **orthopedic complications** of myelomeningocele are common and have predictable patterns. The spine deformities include scoliosis, lordosis, and kyphosis (see Chapter 699). The development of scoliosis has an association with the neurologic level. Children with thoracic level defects have an 80–100% risk, whereas those with a sacral level are at very low risk. Spine deformities tend to increase more rapidly during growth, especially puberty. Treatment of scoliosis includes both nonsurgical and surgical options. Braces, such as **thoracic-lumbar-sacral orthotics (TLSO)** , therapy, and proper seating options may be beneficial. Surgically implanted growing rods to support the developing spine have been used in younger children. Spine surgery should be considered if the scoliotic spine curvature reaches 45 degrees; the child who is nearing skeletal maturity is a better candidate for spine surgery. Realistic expectations need to be discussed with the child and family. Correction of the spine may improve sitting, posture, and pelvic obliquity, but may have a negative impact on function and ambulation.

The **development of the hip** is also influenced by neurologic level (see Chapter 698). The risk for dislocation is highest for those with lesions at the L3 level, followed by L1-L2. Unilateral hip dislocations should be fixed surgically, as they may result in pelvic obliquity and problems with sitting, whereas bilateral dislocations generally do not require interventions. Contractures of soft tissues are commonly seen in children with higher lesion levels. Hip flexors and knee flexors are commonly involved.

Abnormalities in the foot occur in approximately 90% of children and adolescents. The goal of treatment is to achieve a plantar grade foot for weight bearing and allow shoe wear. Clubfoot deformities are common in babies and treatment includes serial casting and orthotics (see Chapter 694.3). The results are often suboptimal and surgery may be needed. In addition, congenital vertical talus (rocker-bottom feet) is often encountered and needs to be addressed (see Chapter 694.4).

Osteoporosis (see Chapter 726) begins to develop in childhood and is more severe in the higher-level injuries. Fractures of the lower extremities are most common in the femur, followed by the tibia. Preventive treatment includes nutritional approaches such as the use of supplemental calcium and vitamin D. Those with documented fractures should undergo a diagnostic evaluation (see Table 726.1), including dual-energy x-ray absorptiometry (DEXA). The use of bisphosphonates may be considered if the diagnostic evaluation does not reveal other underlying causes. The utility of early weight bearing has been advocated, but passive standing may have little impact on bone density.

Neurogenic bladder and bowel can be anticipated (see Chapters 558 and 624.1). The goals of treatment interventions are to protect kidney function and achieve social continence. The introduction of clean intermittent catheterization (CIC) is the mainstay of management. It is not atypical for newborn babies to be started on a CIC program. Urodynamics and renal ultrasounds are routinely used to monitor for hydronephrosis and track intravesicular pressures. Medications may be used to reduce bladder contractions and improve volume capacity. Surgical techniques are being used to improve continence including bladder augmentation, urethral surgeries, and catheterizable channels. Poor CIC technique and or urinary reflux may lead to urinary tract infection, which is diagnosed by having two findings: a urinalysis with white cell count of >10 and urinary culture >100,000. A good bowel program is generally needed to achieve bowel continence. Nonsurgical interventions include adequate hydration, dietary manipulation, fiber regulation, and use of laxatives and enemas. Surgical interventions, such as the antegrade continence enema (ACE), have improved continence in many of these children and adolescents.

Latex allergies are common in this population. The etiology may be multifactorial but increased early exposure may play a role in development of severe reactions (see Chapter 174). Care providers need to be keenly aware of products that contain latex or that have a cross reactivity, such as foods mixed with avocado, bananas, or kiwi fruit. Radioallergosorbent testing is used for identification of potential severe allergens.

Spina bifida is known to be associated with specific **neuropsychologic problems** . Various cerebral neuronal dysplasia may be present. The hallmark is a nonverbal learning disorder characterized by difficulties in math reasoning, visual spatial perception, and time concepts. In addition, there are weaknesses in executive function, processing speed, and organizational skills. Children with spina bifida typically fall within the average IQ range, although those with a higher lesion tend to cluster on the lower end of the spectrum. Hydrocephalus itself has an impact on cognition as noted by deficits in learning, memory, and executive function. Young children with spina bifida tend to do well early on, as they have good verbal skills, but as the academic demands increase, school problems become more obvious. It is important to have appropriate neuropsychologic/educational testing done to identify difficulties each child or adolescent may encounter. Appropriate early intervention and support programs should be put in place, and individual education plans or 504 plans developed (see Chapter 53). Structure in the home environment plays a key role in teaching self-care, dressing, and mobility skills. The importance of these early interventions cannot be underestimated, as they will impact the quality of life and independence in adolescence and transition to an independent adulthood.

Adolescence and Transition to Adulthood

Clinical care has increased the life span of individuals with spina bifida, and the majority are living well into adulthood. Physical problems in association with the learning disorders make the transition into independent living and competitive employment very difficult. The pediatrician, in conjunction with specialty services, plays a pivotal role in developing future planning. It is important to discuss early on strategies to encourage developmentally appropriate independence and self-help skills. Long-term financial arrangements, such as Special Needs Trusts, should be discussed. Transitional care should be started early, as medical services can be difficult to identify.

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CHAPTER 733

Ambulation Assistance

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Assistive devices, such as orthoses, prostheses, walkers, crutches, and wheelchairs, are key components of the therapeutic prescription for children with physical disabilities. The type of device chosen depends on the underlying diagnosis, functional abilities of the child, prognosis for functional improvement or decline, tone abnormalities, range of motion, strength, and the overall gait pattern. Physicians, licensed independent practitioners, and physical therapists perform the evaluation of a child requiring mobility assistance. The physician or licensed independent practitioner is ultimately responsible for writing the prescription for the assistive device.

Orthoses

An **orthosis** is a device that is applied to the surface of the body to maintain alignment or position, to prevent or assist movement of the body part, or to provide support. Named for the body parts covered, orthoses can be static, made of rigid material and designed to immobilize joints to inhibit movement, or they can be dynamic, allowing movement of the limb to occur. For example, "**AFO** " stands for *ankle-foot orthosis* , a brace worn on the foot that extends from the toes to the midcalf position, supporting the foot and ankle joints (Fig. 733.1). Prefabricated orthoses are available, but many children require custom-made orthoses for optimal fit. Orthoses are modified or replaced during periods of growth or changes in function and can be obtained either directly through the orthotist or through the child's physical therapist. All braces must be prescribed by a physician or licensed independent practitioner.

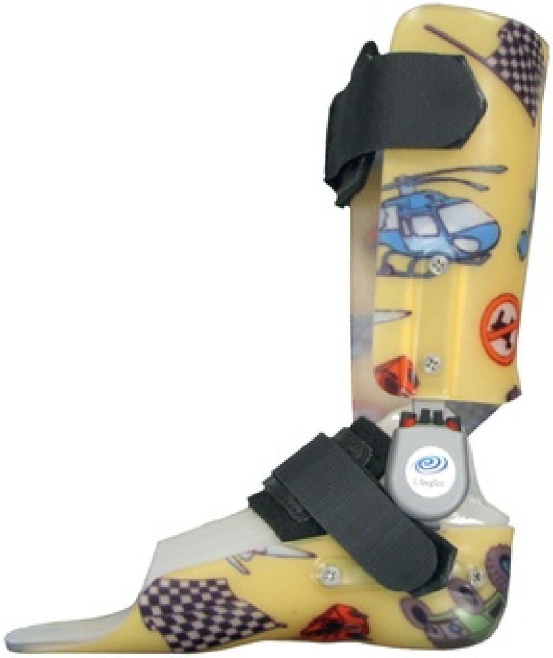

FIG. 733.1 **Hinged ankle-foot orthosis. (Courtesy of Ultraflex Systems, Inc., Pottstown, PA.)**

The type of lower-extremity orthosis prescribed is based on the child's diagnosis, functional status, prognosis, and the goals of treatment with the prescription frequently modified over time as the child changes. Prior to writing a prescription, the provider performs an examination, which may include an evaluation of the child's gait, strength, tone, and range of motion. There are many types of braces that have specific functions to improve gait. Table 733.1 lists examples of these orthoses and their potential uses.

Table 733.1

Orthotic Options

ORTHOSIS	FUNCTION	COMMENTS
Foot orthosis	Provides support of foot only to prevent excessive pronation	Not typically customized
Supramalleolar orthosis	Provides medial-lateral support of foot to prevent excessive pronation or instability	Appropriate for children with low tone such as in Down syndrome
Ankle-foot orthosis	Provides support at the ankle and reduces foot drop or plantarflexion tone by keeping the ankle in a neutral position	Commonly used for ambulatory and nonambulatory children
Ground reaction ankle-foot orthosis	Provides knee extension moment to reduce crouching during standing or walking	Appropriate for children with spina bifida who crouch when walking
Knee-ankle-foot orthosis	Provides support at the knee when there is quadriceps weakness to promote an upright	Less commonly used because of large size of brace but may be appropriate for child with

	posture with standing or walking	spina bifida or spinal cord injury

The most commonly prescribed braces are solid and articulated AFOs. Solid AFOs are used for children with hypertonicity, as they help to biomechanically reduce tone and provide stability with standing and walking. Children who are nonambulatory also benefit from wearing solid AFOs to maintain range of motion of the ankle.

Articulated (hinged) AFOs allow the child to have ankle dorsiflexion by permitting forward movement of the tibia and supporting the foot for heel strike. This design makes ambulating on uneven surfaces and using stairs easier because of the movement allowed at the ankle, while still supporting the foot position and maintaining medial-lateral stability of the ankle. Articulated AFOs should not be used in children with cerebral palsy, spina bifida, or other disorders if they have a crouched gait pattern, as the hinge in the ankle joint may allow further crouching. In crouched gait, the hips and knees are held in flexion and ankles in dorsiflexion throughout the gait cycle, leading to an inefficient gait pattern.

Prostheses

A **prosthesis** is a device that replaces a missing body part, such as an arm or a leg. Lower-extremity prostheses are used to improve mobility, while upper-limb prostheses are not always needed to improve function, as children can be quite independent with a single upper limb. Lower-limb prostheses are used in children with acquired amputations as a result of trauma or cancer and also in congenital transverse amputations or for those that have undergone surgical correction, as often occurs with longitudinal fibular deficiency or proximal femoral focal deficiency.

There are multiple components to lower-limb prostheses, which include the socket and foot, but may also include a hip and knee joint, depending on the level of amputation. A prosthetist works with the child and family to fabricate the prosthesis. A physician or licensed independent practitioner with experience in prostheses provides the prescription for this device.

The type of prosthesis depends on the age of the child, the level of the amputation, and the status of the residual limb. In very young children, use of a lower-extremity prosthesis follows developmental milestones, with the first prosthesis prescribed at the time the child is pulling to stand. Addition of joints to the prosthesis also occurs when developmentally appropriate, such as use of a knee joint around the age of 3 yr when the child is learning to use stairs.

Advances in technology are helping children who use prostheses achieve a fluid gait pattern that makes their prosthetic use virtually undetectable to the untrained eye. New components and designs allow amputees to lead active lifestyles that may include running, swimming, biking, and mountain climbing.

Assistive Mobility Devices

The function of assistive mobility devices is to provide a wider base of support to improve stability during ambulation, reduce the possibility of falls, and improve efficiency of gait. The least supportive device is a traditional single-point cane commonly used following an orthopedic injury. For most children with gait abnormalities secondary to neurologic disorders, this is not a functional option, as a cane does not provide enough stability. More supportive gait aids, such as forearm or Lofstrand crutches, are appropriate in these children; however, use of these devices requires good coordination and strength. Children with cerebral palsy and spina bifida may benefit from these devices.

Walkers provide more support than crutches and canes; they do not require as much strength and coordination to operate. Children with cerebral palsy, for example, may use a reverse walker, which they pull behind them. This reverse configuration provides a wide base of support and stability, helps maintain an erect posture, and allows the child to engage with the environment without the barrier of the walker in front of them. Having the walker behind them also reduces the risk for more serious injury after a forward fall.

For children who require a significant amount of support due to poor head and trunk control, **gait trainers** are often used. These devices allow the child to work on leg movements while the trunk and pelvis are stabilized (Fig. 733.2). While gait trainers provide a child with moderate to severe motor impairments upright supportive mobility, “gait trainer” is a misnomer in that it is not intended to train a child to walk independently.

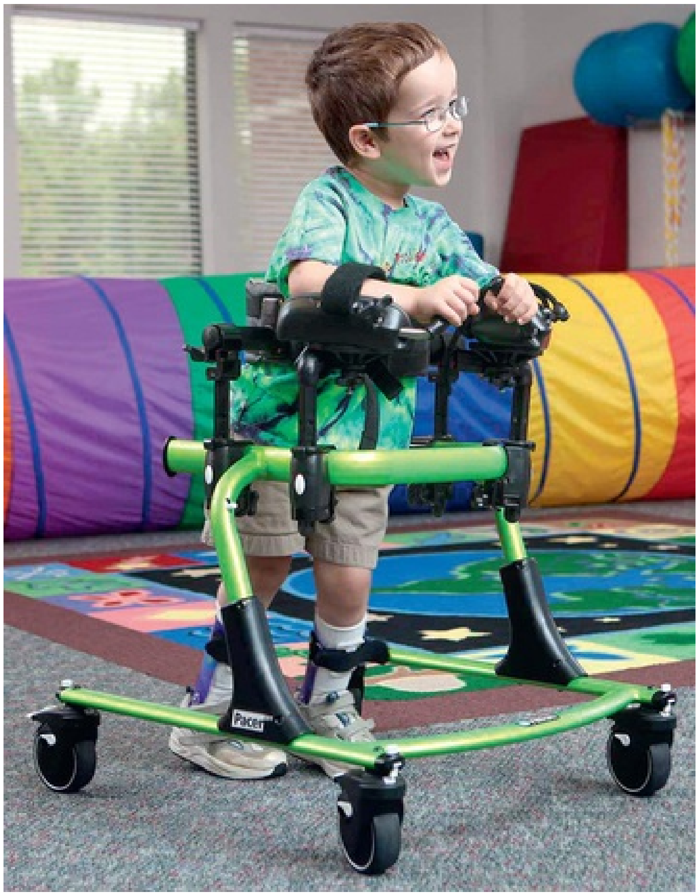

FIG. 733.2 Gait trainer. (Photo copyright 2013 by Rifton Equipment, http://www.rifton.com .)

Wheelchair

Wheelchairs should be considered as a means of mobility when ambulation is not possible or is difficult outside of the home setting. Children with spinal cord injuries, spina bifida, neuromuscular diseases, or cerebral palsy may benefit from the use of a wheelchair. The goal is to provide a wheelchair that will allow the child to move independently about the environment, including home, school, and the community. Children as young as age 2 yr can self-propel a manual wheelchair and operate a power wheelchair. The type of wheelchair prescribed will depend on the child's underlying diagnosis, cognition, vision, motor skills such as head and trunk control, strength and endurance of upper limbs, musculoskeletal deformities, if present, and medical comorbidities. One must also consider future growth or anticipated changes in function over time, as well as the family's ability to transport the chair. An important consideration when ordering a pediatric wheelchair is the adjustability to accommodate growth. A typical wheelchair may last 3-5 yr with periodic adjustments to growth by a seating specialist. There are many components that can be added in order to provide more support in the wheelchair, including head rests, lateral trunk support, hip guides, antitippers that prevent the wheelchair from tipping backward, and specialized tires. The seating system is considered a separate item from the wheelchair itself and should be properly fit for the child's current size and seating needs. The function of a seating system is to promote the upright positioning of the head and trunk. Children with good trunk control will require a simple seat back, while a child with poor trunk control, such as someone with a high cervical spinal cord injury, will require a system that includes a head rest and lateral thoracic supports. Specialized seat cushions are needed for those with decreased sensation to prevent pressure related skin sores.

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CHAPTER 734

Health and Wellness for Children With Disabilities

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See also Chapter 17 .

The expansion of the disability definition to include children with special healthcare needs, chronic conditions, and activity limitations from any cause (e.g., limitations in usual daily activities such as age-appropriate self-care, mobility, communication, and cognition) has made the health issues of the more traditional childhood disability types (e.g., cerebral palsy, intellectual disability, spina bifida, congenital musculoskeletal disorders) more difficult to identify. U.S. data identify developmental, emotional, and behavioral conditions as the leading conditions with activity or functional limitations, with physical health conditions comprising a smaller proportion of self-identified disabilities (although mobility and motor control issues may be noted among the aforementioned nonphysical conditions). Childhood cognitive, mental, and physical health problems contribute to continued economic and health problems into adulthood. Because these problems can respond to childhood and adolescent health promotion interventions, monitoring children with disabilities throughout their development is helpful in providing information and support to children and adolescents, their parents, and families to promote health over a lifetime.

Health Promotion Definitions and Background for Disability

The World Health Organization (WHO) defines *health promotion* as “the process of enabling people to increase control over, and to improve, their health.” For people with disabilities, this concept is important because they are both underserved and have comparatively large health disparities. The WHO further defines health promotion approaches as including more than health education and consisting of community action, supportive and accessible environments, policy changes, health service modifications, and development of personal skills. Health and wellness programs also include traditional preventive management strategies, such as anticipatory guidance. There is ample evidence that engaging in specific areas of health promotion results in improvement, although the evidence for its influence on adult health is less robust.

Children with disabilities encounter many barriers to healthy behaviors (Table 734.1). Both broad and focused health promotion programs consider severity of condition, barriers and resources, and self-efficacy and resiliency to achieve health-promoting behaviors. Children with disabilities may also require modeling or assistance to apply healthy behaviors to their particular disability or economic, social, and environmental circumstances.

Table 734.1

Barriers and Facilitators for Children to Engage in Healthy Behaviors

BARRIERS	FACILITATORS
• Lack of knowledge and skills • Fear of injury or failure • Negative attitudes by parents, peers, healthcare providers • Poor parental healthy behaviors • Stress in the close family network • Personal choices • Fatigue • Lack of initiative • Limited function or capability • Inability to control behaviors • Inaccessible facilities or resources • Needing adult or aid assistance • Economic restrictions • Policies and procedures of facilities or programs • Noninclusive providers • Transport challenges	• Education or knowledge about healthy behaviors • Engaging child in discussions and decisions • Promotion of activities by rehabilitation and other healthcare professionals • Family support and participation • Involvement of friends and peers in activities • Desire to be active • Models or directions for participation with adaptations • Creative and knowledgeable professionals • Making activities a part of the routine—repetition and consistency promote ongoing activities • Accessible facilities and opportunities, with knowledgeable staff • Policies and resources promoting participation • Welcoming and inclusive providers • Adaptable approaches

Children and adults (and their families) often view health differently than those without disabilities. Disability may influence health and vice versa, but their perception of their own health and wellness does not equate with their level of disability. Children with congenital or acquired disabilities have a narrow view of healthy living, concentrating on nutrition and secondarily on physical activity, with little understanding of how they apply to their own condition. Experiences as a child with a disability often foreshadow adult behaviors, especially negative attitudes toward therapy, exercise, and activity. Beliefs of parents, families, and healthcare providers also influence the views of health by children with disabilities. Health promotion programs for these children must (1) understand and support the role and well-being of parents, (2) recognize that parents of children with more functional limitations may require more resources and support, (3) involve children with disabilities in design of programs and decisions about participation, and (4) address barriers to participation, perceived and real (see Table 734.1).

An effective health and wellness program should involve multiple approaches and opportunities for success, including partnerships with families, school staff, and rehabilitation providers. Competency requires addressing any mismatch between the child's positive sense of health and well-being and that expected by the healthcare providers; limitations of an education-only model; engaging the child in discussions about the importance of healthy behaviors, ways to engage in healthy behaviors related to the child's disability and circumstances, and decisions about participation; and parent and family involvement coupled with sensitivity for the already overwhelming support a family provides for the child with a disability.

Anticipatory Guidance, Counseling, and Preventive Care

Preventive healthcare through health education, anticipatory guidance, and participation in screening and immunization schedules is the mainstay of pediatric public health programs (see Chapter 28). *Bright Futures,* developed by the American Academy of Pediatrics and their collaborators and supported by the Maternal and Child Health Bureau, Health Resources and Services Administration, provides a knowledge base for pediatric healthcare providers and the public about anticipatory guidance, health promotion, and prevention for children and adolescents, but it has few references to disability. Anticipatory guidance refers to general information related to growth/development and healthy practices. Counseling refers to advice given regarding specific conditions, which could include discussions of applications of general guidance to children with disabilities. For the general population, 25% of parents receive no information and <50% receive all recommended guidance. Although parents of children with special healthcare needs (the broad inclusive definition of disabilities) report similar or better receipt of general preventive information, it is not clear whether those with higher severity of functional limitations receive this guidance or counseling, and whether it is provided in the context of disability and other circumstances.

Children with special healthcare needs require typical prevention, as well as more specific counseling related to their disability. Some of this more specific counseling can be managed by specialty care providers, although children with special healthcare needs have difficulty obtaining appropriate specialty outpatient services. Additional barriers to care, especially with increasing age of the child, are the lack of accessible medical equipment and facilities. Although discussions of health risks with adolescents about smoking, drinking, and protected sexual activity should be undertaken, the discussions may require a different focus for adolescents with disabilities. Higher violence and abuse rates toward children with disabilities are reported, for which providers must be vigilant.

The recommendation is to recognize the need for modifications to typical guidance, to be alert for any signs of violence, and to broaden counseling to include questions and discussions about conditions associated with the specific disabilities (e.g., epilepsy or cognitive impairments often seen with cerebral palsy, or neurogenic bladder and bowel in spinal cord dysfunction) or secondary conditions, such as pain, osteoporosis/fractures, or fatigue seen in many children and adolescents with disabilities.

Physical Activity and Exercise

National health guidelines recommend at least 60 min of physical activity daily for children, but any activity increase from sedentary levels to even moderate activity (30-40 min of moderate intensity or 20 min of more strenuous activity) provides some health benefit. Health professionals should give specific advice about how children with disability can increase their level of activity. Exercise and activity increase aerobic capacity, functional ability, and quality of life for children with many kinds of disabilities and chronic diseases (e.g., cerebral palsy, spinal cord dysfunction, cystic fibrosis, asthma, intellectual disabilities, diabetes). And yet, most healthcare providers expect sedentary lifestyles for children and adolescents with disabilities, whatever their functional abilities. For children with disabilities, school physical education and recess programs can support activities at or greater than the recommendation, and school requirements can reinforce activity expectations. The need for exercise beyond physical therapy should be clarified to help children understand the benefits and purpose of both. The activities in which youth with disabilities wish to participate can be supported. Children with disabilities who participate in physical activities report social benefits, such as developing friendships, building a support system, gaining knowledge of self, and acquiring a sense of accomplishment. These factors also contribute to higher adherence to activities. Children with disabilities may also be more likely to participate in physical activities when those activities are supervised and organized, as opposed to free play in an open room. In order for children with disabilities to engage in physical activity in supported environments, school and public playgrounds must be made sufficiently accessible to support community physical activity. A number of agencies have endorsed the Commit to Inclusion campaign to promote building healthy, inclusive communities for people of all ages with disability (e.g., the President's Council on Fitness, Sports and Nutrition, along with the National Center on Health, Physical Activity and Disability, the American Association on Health and Disability, and the Center on Disability at the Public Health Institute).

Physical activity for children and adolescents improves fitness and quality of life for youth with developmental disabilities (Table 734.2). These exercise and fitness programs require 2-3 mo of participation, at least twice a week, to achieve any changes, and many of the changes achieved are more-longer lasting than expected. These programs are not traditional therapy, and participation in therapy is not a substitute. These focused fitness and exercise programs generally require the support and direction of rehabilitation professionals, although programs can be community based in nonmedical surroundings.

Table 734.2

Examples of Effective Exercise Programs for Children With Disabilities

PROGRAM	DESCRIPTION	OUTCOMES/COMMENTS
Center-based fitness program and home program*	Children with a variety of disabilities Group exercise: 2×/wk for 14 wk; warm-up, aerobics, strengthening, cool-down Home program: 2×/wk for 12 wk using video exercises	Improved walking efficiency, strength, general function Group treatment more effective by measures and by satisfaction

Group aquatics aerobic exercise program [†]	Children with a variety of disabilities, >50% able to walk 2×/wk for 14 wk Recreation to achieve target heart rate; aquatic strengthening program	Improved walk/run, not strength to isometric testing Required adults monitoring to maintain target heart rates
Group training class [‡]	Children with cerebral palsy able to walk 2×/wk for 4 wk Warm-up, circuit training stations (treadmill, balance, stairs, closed-chain exercises)	Improved muscle strength, mobility, function except fine-motor test–maintained 8 wk later Therapists conducted and monitored
Strength training [§]	Children with cerebral palsy, including a majority able to walk with assistive devices 3×/wk for 6 wk Progressive strength training program, conducted in the home	Improved perceptions of strength, walking, stair management and improved psychologic benefits Clinicians to monitor, problem solve; some need for direct parental involvement
Walking–jogging program [‖]	Children with Down syndrome 3×/wk for 10 wk 30 min sessions, achieving 65–70% peak heart rate	Difficulty promoting increasing activity intensity Improved peak exercise time and grade, but not in aerobic capacity; improved walking capacity
Treadmill training program [¶]	Children with intellectual disabilities Daily for 2 mo Progressive treadmill use with goal of 20-30 min	Improved heart rate with and without activities Therapist developed and monitored, community staff implemented
Peer-guided exercise[**]	Adolescents with intellectual disabilities 2×/wk for 15 wk Typical adolescents and those with disabilities paired to support each other in 1 hr aerobic, weight-training, flexibility activities	Improved curl-ups, 6 min walk, and body mass index High attendance, less compliance with weight training

[*] Fragala-Pinkham MA, Haley SM, Rabin J, Kharasch VS. A fitness program for children with disabilities. *PhysTher* 85(11):1182–1200, 2005.

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Recreation and organized sports are other areas where children and adolescents with disabilities can engage successfully, at times with modifications. Participation improves cardiopulmonary parameters, motor function, social competence, and general sense of well-being. Many children with disabilities require 1-on-1 instruction for development of skills, with a goal of participation in activities with their peers. Perceived barriers to participation in sports differ based on the source: children were concerned about dependency; parents required more information about possible sport participation; professionals noted family's attitudes carried great influence. Programs through Special Olympics International are an opportunity for children and adolescents to engage in supportive and monitored environments for sport and recreation.

Rehabilitation professionals can assist with problem-solving activity participation, such as using computerized technologies for “exergaming” (e.g., Wii, Xbox, PlayStation), developing individual or group challenges with mobile devices (e.g., activity trackers such as FitBit, mobile phone apps), adaptation of equipment (e.g., modified upper-limb prosthesis to allow baseball glove use or modified bicycle equipment), and knowledge of adapted recreation programs in the area (e.g., horseback riding, winter/water sports) to increase participation.

Nutrition and Obesity

See also Chapter 60 .

Managing the combination of nutrition and physical activity is the key ingredient of weight control. Obesity also affects children with special needs. Estimates suggest that children with physical activity limitations were twice as likely as the general population to be overweight, and youth with cognitive impairments are at increased risk. It is unclear if obesity is a cause for the activity limitations or is a result of the limited activity, which may be an important distinction in developing interventions. The concern with obesity contrasts with early life weight gain needs of many children with disabilities, and may be confusing for parents and families when the focus changes to weight decrease. Confounding factors related to monitoring percent body fat in children with disability include (1) the propensity for some disabilities, often those that are genetically mediated, to be associated with obesity; (2) standards of measurement may not be appropriate for certain diagnoses or disability types (e.g., expected body composition differences, short statures, contractures, or limb deficiencies or amputations); (3) obesity may be a side effect of medication and this effect must be balanced against the drug benefits (e.g., antidepressants, mood stabilizers, steroids); and (4) the social network of family, friends, schools, and healthcare providers may unwittingly influence healthy habits in a negative way, including use of food as reward for behavior management. Both children and their parents should be a part of the conversations related to obesity or any weight-related topic. Information must be presented in a direct and understandable way, and modified for the child's and parents’ needs. Discussion of promoting health through nutrition and physical activity, while problem solving challenges to participation, may be a better approach than explaining body composition and metabolic pathways.

Emotional Health and Leisure Activities

Emotional health is often overlooked in children with disabilities, unless mental health or challenging behaviors are the cause for the disability. Youth and adolescents with disabilities appear to be at higher risk for feeling low, stressed, or anxious (especially those with higher levels of limitations), and those with mental health needs may have lower adaptive functioning, a family history of mental illness, or a diagnosis of autism spectrum disorder. Adolescents with physical disabilities participate in fewer social activities, have fewer close or intimate friends, and have few plans for ongoing education. There is a risk for continued isolation into adulthood. Medications may be considered, but effectiveness is not guaranteed, and unwanted side effects may produce more health conditions. Counseling requires insurance support or discretionary funding.

Leisure and recreational activities provide social supports, additional stress-coping mechanisms, and ability to develop social skills and a stronger personal identity. Girls with disabilities tend to engage in social or skill-based activities, and boys in physical activities, with decreasing participation with increasing age. In general, encouraging socialization through leisure activities, recreation, or sports and physical activity can be a part of a routine health visit.

Dental Care

Dental care is a frequently unmet healthcare need for children with disabilities. The principal deficits are in receipt of further or specific dental care (not preventive services) and that the severity of the condition and low income may be associated with unmet dental needs. Condition severity may also predict the degree to which parents are interested in oral health–related education and actually engage in oral health efforts. Challenging behaviors often limit dental care, and the use of behavior management techniques and education programs have been effective in allowing both preventive and additional dental care.

Role of Healthcare Providers

Primary care and other healthcare providers should be mindful of discussing and promoting health and healthy behaviors with children and adolescents with disabilities and their families (Table 734.3). Once initial discussions have ensued, referral to healthcare professionals with expertise in modifications needed for a more tailored approach to health promotion may be indicated.

Table 734.3

Targeting Healthy Behaviors for Children With Disabilities

HEALTH ACTIVITY TARGET	RELEVANCE TO CHILDREN WITH DISABILITIES
General prevention	• Recognize risks for less healthy behaviors, and barriers and facilitators about behavior changes and participation. • Cover typical topics for all children; counsel regarding disability or situation context. • Specifically monitor for abuse and violence. • Provide typical age-appropriate adolescent information about smoking, drinking, substance abuse, sexual contacts; refer if unable to provide. • Monitor for disability-specific health conditions; may require referral.
Physical activity	• Promote exercise and activity—should be an expectation for activity. • Ensure that family and child/adolescent are knowledgeable about benefits and possible adaptation. • Review need for possible dietary changes. • Consider engaging rehabilitation professionals.
Nutrition and obesity	• Recognize obesity can cause limitations, and can be the result of poor dietary habits and limited activity. • Follow percent body fat in a consistent way, recognizing the need for accurate measures or limitations of measures (e.g., weight, BMI, skinfold thickness, other traditional measures) in many disability conditions. • Ensure that family and child/adolescent are knowledgeable about healthy nutrition. • Consider referral to nutritionist or other professional to engage patient and family in modeling/direction or behavior suggestions. • Review need for increased activity level with dietary changes.
Emotional health	• Question for sense of anxiety/feeling low, stress management and ability to adapt, social supports. • Consider medications and counseling based on expected effect, monitor effects/side effects; consider referral, making sure that insurance/payment coverage is available.

	• Consider recreation and leisure activities to promote social support and ability to develop social skills.
Recreation and leisure	• Question about social activities outside the home; promote importance for development of social skills, sense of self, support. • Consider referral to community programs or rehabilitation professionals.
Dental	• Discuss more than preventive dental care. • Suggest behavior strategies if there are problems engaging in dental appointments and refer for this service as needed.

734.1

Home Mechanical Ventilation and Technology Dependence

Robert J. Graham

Keywords

home mechanical ventilation
children with special healthcare needs
technology dependence
medical home
quality of life
chronic illness

See also Chapter 446.4 .

Children with technology dependence represent a particularly complex and potentially vulnerable cohort of children with special healthcare needs (CSHCN).

Following the decision to pursue technology supports for a child, the reality of homecare is daunting. This chapter, coupled with that on Long-term Ventilation (see Chapter 446.4), provides an approach when considering provisions for the CSHCN and their families.

Preparation

There are emotional challenges associated with integration of technology supports into “routine” care and assuming an altered role as a parent and care provider. Addressing practical needs, however, can help attenuate some of the anxiety, as well as allow families to focus on, or revisit, the global goals of care, quality of life, and the role of technology. The family will need to consider each of the following implications.

Financial (e.g., insurance, subsidies, alternative funding, and parental employment): Independent of personal resources, the majority of families with children requiring technology assistance report some degree of financial burden. These costs arise from the direct outlay for equipment and medications, lost work-time or need to discontinue/change vocations, home adaptations, and other indirect costs. Accessing a financial counselor or case manager may help identify and navigate through local, state, and federal resources. Additional considerations should also be paid to personal trusts, wills, and estate planning, as all of these have implications for long-term benefits and financial supports for the individual with special healthcare needs.

Equipment and supplies: Ideally the equipment intended for use at home will be tested before discharge to home. Testing ensures proper function as well as any tolerance. Electrical compatibility with the home service should be confirmed. Delivery of backup devices (e.g., tracheostomy tubes including a smaller size for contingency planning, batteries for ventilators, and portable oxygen tanks to supplement electric oxygen concentrators) as well as emergency supplies (e.g., self-inflating respiratory bags, epinephrine for those who have allergy histories, or prophylactic antiepileptic medication for those prone to breakthrough seizures) should be confirmed. Medication supplies and refills should be sufficient to allow for the scheduling of follow-up visits. Providers responsible for recertification or reordering should be identified.

Training: Standards for training and demonstration of competency varies between institutions and across providers. Families and their medical teams should come to an agreement on minimum safety preparation and the number of responsible parties available to assist in the home. Hospital-based training around ventilator use and troubleshooting, central-line care, tracheostomy tube exchanges and suctioning, wound care, and other interventions could include basic life support classes, 1-on-1 sessions with nurses, respiratory therapists, or other staff, with hands-on or mannequin simulation. Assumption of full care by families while in the hospital can be informative for all stakeholders and reassuring to families; supported replication of the demands of homecare before discharge is ideal.

Augmented staff: Home nursing, hospice, personal care assistants, extended family, and friends represent additional resources for the child and their family. Allowances vary based upon the child's age, independence, medical condition, technology dependence, goals of care, and other factors. These individuals may require additional training, but augmenting numbers of proficient homecare providers is crucial for safety and consistency of care. When considering homecare provision, families should consider the type of personnel and how additional supports would allow the child to attend school, the parent to work or maintain the household, continue care when the parent is sick or incapacitated, or assist with other children.

Monitoring: Continuous direct observation is not practical, or often desirable, in the community setting. Providers and families should agree upon the balance of extrinsic monitoring (e.g., pulse oximetry and heart rate) and intrinsic device alarms (e.g., high and low minute ventilation, disconnect, and pressure ranges on a ventilator), based on the child's individual risks as well as the environmental circumstances. Typically capnography is not available except in cases of central hypoventilation syndromes, but can complement oximetry. Simple audio and video monitors can be used to augment surveillance and may help families in their activities of daily living. Alarm fatigue, as experienced by hospital-based providers, should also be discussed, as it can be of great consequence where the resources are not as robust.

Adaptations to the homecare setting: Modifications to the home may be required to ease care and optimize safety. Ramps for wheelchair access will permit ingress and egress, and lift systems can minimize physical burden and injury risk to providers. Doorways can be expanded to permit access to multiple rooms, and alternative bath and toileting accommodations may be needed. Electrical system upgrades with grounding and increased amperage may be required for some equipment.

Transportation: Discharge planning for a child with technology dependence should include transportation to school, community programs, routine family activities, and scheduled or urgent medical services. Proximity (rural or urban), the child's mobility, weather, and the need for monitoring en route are other considerations. Adaptive car seats or car beds can be purchased. Personal vehicles may need expensive modifications, including lifts and power inverters. Allowances may also be required for one person to drive while another, nurse, parent, or care assistant, tends to the child. If traveling long distances, perhaps on vacation, advanced planning might include identification of hospitals along the route and reciprocal equipment companies to assist with unexpected supply needs.

Air transportation: If a family anticipates travel by plane, contingencies should be made for oxygen support at altitude, recognizing that most commercial airlines pressurize their cabins to the equivalent of 7,000 to 8,000 feet. Portable oxygen sources may have less liter flow capacity than stationary or home devices. Space and limited supplies inflight are also considerations. Power wheelchairs are prone to damage when placed in cargo holds, and ground crews likely require explicit instructions. Providers may need to write letters for airport security and airlines for excess baggage, electronic equipment, medication, and fluid allowance. Families can also consider sending additional supplies to the final destination in advance.

Environmental stressors: Extreme temperatures, heat or cold, variability in humidity, and other environmental variables can greatly impact the well-being of a child with underlying cardiorespiratory insufficiency or other special healthcare needs. Home adaptations to permit climate control for the child's room may be required. Families may consider prewarming, or cooling, vehicles for routine excursions, and limitations on day-to-day activities are warranted at times. Augmented hydration needs should be reviewed with medical providers, along with routine sunscreen and preventative measures.

Preparation for transition to the homecare setting may include a period of quiescence, depending upon the circumstances and family preferences. Establishing a period of stability, when there has been no need to alter in supports, may minimize unplanned readmissions.

Community Resources

The transition from the acute care or rehabilitation facility to homecare setting is often much anticipated and welcomed. This step can also be frightening and overwhelming, whether it represents the first time home or a return after an acute illness or planned surgery. Hospital-based providers can partner with families to alleviate some anxiety as well as avoid potential pitfalls through proactive engagement. Hand-off to outpatient and community stakeholders can include the following:

The community medical practice: Updates on problem lists, projected follow-up, medication and equipment needs, routine health maintenance and preventative measures (e.g., immunizations), special considerations for nutrition, identification of specialty providers and follow-up schedules, and case-specific risks.

First responders: Confirmation that the family has capacity to call emergency services, outreach to police and ambulance services to outline baseline needs, special condition-specific interventions or precautions, identification of equipment that may need to be taken with the child in the event of an emergency, determination of emergency destination (i.e., local hospital or referral center), and clarification of resuscitation status and life-sustaining therapies.

Therapy programs: Physical, occupational, speech-language/feeding, and other therapists benefit from hospital-based assessments as well as outlines of expectations, restrictions, and uncertainties.

Educational programs/schools/day-habilitation: Integration into community services requires evaluation of developmental needs as well as potential adaptive settings, equipment, services, staffing, transportation, and services for all ages.

Power and water: Alerting local housing, social, power, and water authorities to medical necessities can facilitate prioritization of service restoration during natural disasters or other interruptions, as well as identify programs to defray incurred costs with increased technology driven electrical usage (e.g., home ventilators, oxygen concentrators, and climate control).

Families may find additional resources through faith-based institutions, nonprofit and advocacy groups (e.g., Kiwanas, Shriners, Boy Scouts), and condition-specific entities, such as the Muscular Dystrophy Association. Outreach to other families with similar circumstances can also be helpful with the caveat that their recommendations reflect their own goals and lived experience with special healthcare needs.

Subacute Care

Local resources for medical services should be identified in advance. These begin with the primary care and extend to local and regional hospitals. It is important to determine the range of services available as well as to identify specific providers who would familiarize themselves with a given case. The child with technology dependence will experience intercurrent illnesses or unexpected accidents that require evaluation, but may not always necessitate transport to tertiary care or referral centers. Individual care plans can be developed in conjunction with the family and local providers and may include thresholds for transfer.

Families should also consider bringing home equipment and supplies when presenting to urgent and acute care settings. Devices, such as biphasic positive airway pressure (BiPAP) masks and cough assist machines, or compounded medications may not be available at every facility. Short-term evaluations may become protracted, and lack of routine care provision may compound the immediate issues.

Emergency and Acute Care

Providers and families should acknowledge that CSHCN are at risk for repeated hospitalization. Progression of underlying illnesses (e.g., heart failure), planned surgical interventions (e.g., spinal instrumentation, bronchoscopy surveillance, tendon releases), or superimposed acute illnesses (e.g., pneumonia, gastroenteritis, appendicitis, recurrent seizures) may necessitate readmission. Those children who are technology dependent have a higher likelihood of requiring critical care services due to the nature of their needs as well as their vulnerability. Preventable equipment-related issues may be obviated through the planning described previously. Once hospitalized, CSHCN are at greater risk of medical error and incur more interventions when compared with otherwise healthy children. Parents should be encouraged to develop a medical passport and reference list of providers to facilitate communication and consistency of care. Referencing established care guidelines and, again, developing individualized care plans may be helpful.

Quality of Life

CSHCN of increasing complexity and technology dependence are thriving in the homecare setting due to advances in medical care, shared decision-making, community services, and most notably, extensive, vigilant, and proactive care efforts by their families. Adaptations allow for participation in all aspects of family, school, and community activities. While individual trajectory and subsequent needs may be difficult to predict, all stakeholders should acknowledge the impact of chronic care on the family unit and health-related quality of life. The evolution of a medical home for this cohort of children will require provisions for family mental health, sibling supports, respite, and other measures to optimize outcomes.

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PART XXXIII

Environmental Health

OUTLINE

Chapter 735 Overview of Environmental Health and Children
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CHAPTER 735

Overview of Environmental Health and Children

Ruth A. Etzel

Global Climate Change

Pediatricians’ primary goal is prevention. One dominant prevention challenge of the 21st century is global climate change. The assessment of the Intergovernmental Panel on Climate Change concluded with the scientific consensus that the Earth is undergoing adverse global climate change and that anthropogenic (man-made) contributions are significant. These climate changes are creating conditions that affect public health, with disproportionate impacts on certain life stages, including children. Children are especially vulnerable to the impacts of climate change because their bodies are growing and developing, they have unique behaviors and interactions with their environment, and they must rely on parents or caregivers to provide for their basic needs. Climate change will affect children's health as a result of their exposure to elevated temperatures; more frequent, severe, or longer-lasting extreme weather events; transmission rates of food-borne, water-borne, and vector-borne diseases; increases in air pollution from molds, pollens, and the burning of fossil fuels; and mental health stressors (Fig. 735.1). Natural disasters such as floods and hurricanes, damp housing, and mycotoxin-related illnesses are expected to worsen as temperatures and sea levels rise. The impacts likely will be felt most among young children and those who are living in poverty. The need to reduce carbon dioxide in the environment has compelled many countries to sign the Paris Accord. Individual actions are a necessary step in carbon dioxide reduction. Parents and caregivers also can work to reduce their family's carbon footprint. They also can protect children's health by checking the air quality index and pollen counts and considering a limit to children's outdoor play time if levels are high. Parents can watch for signs of dehydration or overheating in their children, and can prevent tick and mosquito bites by using insect repellent and protective clothing. Pediatricians and those who care for children can be highly effective advocates at the community, national, and international level.

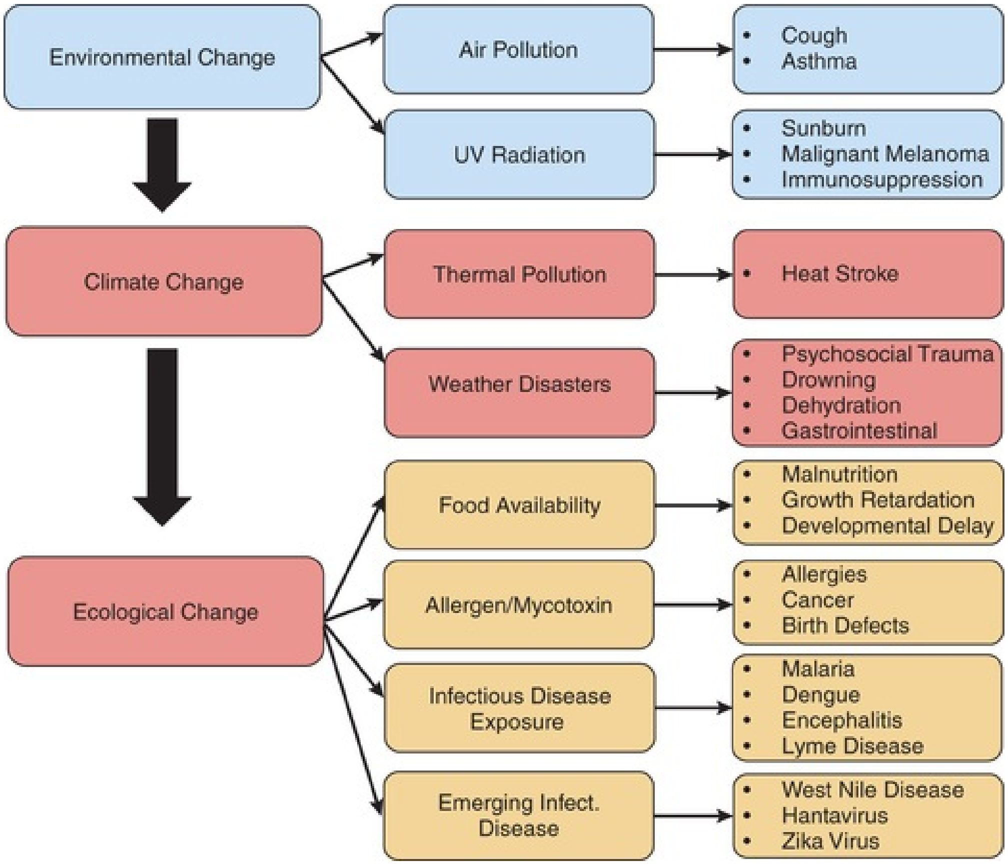
Environmental Change
Air Pollution
Cough
Asthma
UV Radiation
Sunburn
Malignant Melanoma
Immunosuppression
Climate Change
Thermal Pollution
Heat Stroke
Weather Disasters
Psychosocial Trauma
Drowning
Dehydration
Gastrointestinal
Food Availability
Malnutrition
Growth Retardation
Developmental Delay
Ecological Change
Allergen/Mycotoxin
Allergies
Cancer
Birth Defects
Infectious Disease Exposure
Malaria
Dengue
Encephalitis
Lyme Disease
Emerging Infect. Disease
West Nile Disease
Hantavirus
Zika Virus

FIG. 735.1 **The relationship between environmental change, climate change, ecologic change, and child health. (From Bunyavanich S, Landrigan CP, McMichael AJ, Epstein PR: The impact of climate change on child health, *Ambul Pediatr* 3:44–52, 2003, Fig. 2.)**

Localized Environmental Hazards

Localized exposures to a wide variety of chemical, biological, and physical agents can also harm children. Numerous epidemics of disease from chemical, biological, and physical agents (both natural and man-made) over the past 80 yr have documented a variety of adverse outcomes among children (Table 735.1). Some epidemics, such as those caused by the night-time release of methyl isocyanate from a factory in Bhopal, India, the nuclear meltdown in Chernobyl, and the melamine contamination of infant formula in China, received widespread attention and heightened the awareness of parents and pediatricians about hazards in the environment. For many people, the word *epidemic* conjures up images of hospital isolation wards, poor sanitation, and rapidly spreading infectious diseases. Epidemics of environmental origin often have served to elucidate new hazards for children. Many of the routinely used chemicals understood to be toxic to children were initially identified when a cluster of children was exposed and developed symptoms during a relatively short period of time. Unfortunately, the children served as the “canaries in the coal mine” to indicate that specific chemicals (including thallium, mercury, arsenic, and lead) contained in products for children such as diaper rinses, teething powders, and depilatory agents, posed a threat to their health. The comparison of children to canaries is apt: following underground mine explosions, canaries were used by miners throughout recent history to help detect elevated levels of carbon monoxide gas. Canaries were useful “carbon monoxide detectors” because of their rapid breathing rate and high metabolism, making them more sensitive to the effects of gases, including carbon monoxide. Likewise, young children have a rapid breathing rate and a high metabolic rate, and may be more sensitive than adults to chemicals in the environment.

Table 735.1

Epidemics of Environmental Disease Affecting Children

CONTAMINANT	VEHICLE	DATE	COUNTRY	APPROX. # SICKENED	ILLNESS	APPROX. # WHO DIED
Thallium	Depilatory agents	1930	Grenada	16	Thallotoxicosis	13
Methylmercury	Fish and shellfish	1956	Japan	2,265	Cerebral palsy	1,784
Arsenic	Contaminated milk powder	1955	Japan	11,778	Fever, diarrhea darkened skin, swollen abdomen	113
Hexachlorobenzene	In human milk after pregnant women ate HCB-treated seed grain	1957	Turkey	~200	Pembe yara (pink sore) rash, weakness convulsions	<2 yr ~200
Methyl isocyanate	Leak from chemical plant	1984	India	<15 yr 200,000	Coughing, eye irritation choking death	All ages 2,500–5,000
Dioxin	Chemical plant explosion	1976	Italy	193 (88%)	Chloracne	0

Radiation	Chernobyl	1986	Ukraine	<18 yr 4,000	Thyroid cancer	~8
Radiation	Scrapped medical machine stolen from hospital	1987	Goiânia Brazil	249	Acute radiation syndrome	4 (1 child)
Aflatoxin	Grain	2004	Kenya	317	Aflatoxicosis	125
Melamine	Infant formula	2008	China	290,000	Kidney stones	6
Lead	Small-scale gold mining	2010	Nigeria	>2,000	Seizures, death	200

Table 735.1 summarizes major incidents of environmental poisoning that affected children. The characteristics of the environmental exposure and the age and developmental stage of the child affect the likelihood of developing health problems. After the release of methyl isocyanate (used in the production of some pesticides) at Bhopal in 1984, an estimated 200,000 children living near the Bhopal chemical plant were affected by the gas release (see Table 735.1). Methyl isocyanate gas is 1.4 times heavier than air; thus higher concentrations of the gas were found near the ground or floor. Because of their short stature, children's breathing zones are closer to the ground or floor than adults' breathing zones; therefore children likely inhaled higher concentrations of the toxic gas. Children exposed to the same levels of methyl isocyanate as adults may have received larger doses because they have relatively greater lung surface area to body weight ratios and higher minute volume to weight ratios. Based on each of the poisoning events listed in Table 735.1 , additional precautions were taken to avoid children's unnecessary exposure to the specific product or chemical implicated.

Although major poisonings such as those listed in Table 735.1 have caused substantial morbidity and mortality among children, environmental health hazards may also result in more subtle effects that may not manifest until later in life. In addition to the exposures received during large outbreaks, children receive smaller doses of chemicals on an almost daily basis through the water they drink, the food they eat, and the air they breathe. Because of their unique vulnerability, they may exhibit symptoms from these exposures earlier than do adults.

Toxins Versus Toxicants

A toxin is a poisonous substance produced naturally by a living organism (e.g., aflatoxin). A toxicant is a poisonous substance made by humans or introduced into the environment by human activity (e.g., dioxins). Synthetic chemicals are referred to as toxicants.

Mycotoxins

Children's exposures to mycotoxins, the toxins produced by certain fungi on grains, nuts, and other crops, will likely increase as the climate changes because their production is influenced by temperature, humidity, and rainfall. Exposure to mycotoxins results in different health outcomes dependent on the route of exposure. Exposure from eating or drinking may lead to gastrointestinal illness, tremors, and cancer in adulthood; exposure via breathing may result in acute respiratory illness during infancy. There also is emerging evidence linking mycotoxin exposures among children, especially those in developing countries to stunted growth.

Pediatric Conditions Linked to Mycotoxin Exposures

Exposures to mycotoxins have been linked to at least 2 conditions that affect children: neural tube defects and acute pulmonary hemorrhage.

Neural Tube Defects

Studies of an epidemic of birth defects in 1990 in south Texas suggested an association between maternal ingestion during pregnancy of high levels of fumonisin, universally present in corn and in corn-based products, and birth defects such as anencephaly and spina bifida. Fumonisins are known to interfere with cellular folate uptake.

Infant Pulmonary Hemorrhage

Several studies of a 1994 epidemic of acute pulmonary hemorrhage in Cleveland, Ohio, documented a novel association between life-threatening pulmonary hemorrhage and the presence of the toxigenic mold *Stachybotrys* in the water-damaged homes in which the infants were living. *Stachybotrys* produces mycotoxins that are lipid-soluble and readily absorbed by the airways, as well as a hemolysin and several proteinases that can degrade vascular collagen. In subsequent years, *Stachybotrys* and other toxigenic fungi including *Trichoderma* have been associated with acute pulmonary hemorrhage among infants in other areas of the United States and New Zealand. The rapidly growing lungs of infants appear to be vulnerable to the effects of the trichothecene mycotoxins produced by *Stachybotrys* and *Trichoderma* .

Food-Borne Diseases Caused by Environmental Exposures

Contamination of food with viruses and bacteria is a major cause of childhood food-borne diseases (see Chapter 366), and children are also at risk from a variety of non-infectious food-borne hazards in the environment, which include natural hazards such as mycotoxins and synthetic persistent organic pollutants such as dioxins (see Chapter 737 ; Table 735.2).

Table 735.2

Food-Borne Illnesses (Noninfectious)

ETIOLOGY	INCUBATION PERIOD	SIGNS AND SYMPTOMS	DURATION OF ILLNESS	ASSOCIATED FOODS	LABORATORY TESTING	TREA
Antimony	5 min–8 hr. usually <1 hr	Vomiting, metallic taste	Usually self-limited	Metallic container	Identification of metal in beverage or food	Suppo
Arsenic	Few hours	Vomiting, colic, diarrhea	Several days	Contaminated food	Urine; may cause eosinophilia	Gastri BAL (dimer
Cadmium	5 min–8 hr. usually <1 hr	Nausea, vomiting, myalgia, increase in salivation, stomach pain	Usually self-limited	Seafood, oysters, clams, lobster, grains, peanuts	Identification of metal in food	Suppo
Ciguatera fish poisoning (ciguatera toxin)	2–6 hr	**GI:** abdominal pain, nausea, vomiting, diarrhea	Days to weeks to months	A variety of large reef fish, grouper, red snapper, amberjack, and barracuda (most common)	Radioassay for toxin in fish or a consistent history	Suppo care, I manni childre vulner
	3 hr	**Neurologic:** paresthesias, reversal of hot and cold, pain, weakness				
	2–5 days	**Cardiovascular:** bradycardia, hypotension, increase in T wave abnormalities				
Copper	5 min–8 hr usually <1 hr	Nausea, vomiting, blue or green vomitus	Usually self-limited	Metallic container	Identification of metal in beverage or food	Suppo

Mercury	1 wk or longer	Numbness, weakness of legs, spastic paralysis, impaired vision, blindness, coma. Pregnant women and developing fetuses are especially vulnerable	May be protracted	Fish exposed to organic mercury, grains treated with mercury fungicides	Analysis of blood, hair	Suppo
Mushroom toxins, short-acting (museinol, muscarine, psilocybin, coprius artemetaris, ibotenic acid)	<2 hr	Vomiting, diarrhea, confusion, visual disturbance, salivation, diaphoresis, hallucinations, disulfiram-like reaction	Self-limited	Wild mushrooms (cooking may not destroy these toxins)	Typical syndrome and mushroom identified or demonstration of the toxin	Suppo
Mushroom toxin, long-acting (amanitine)	4–8 hr diarrhea; 24–48 hr liver failure	Diarrhea, abdominal cramps, leading to hepatic and renal failure	Often fatal	Mushrooms	Typical syndrome and mushroom identified and/or demonstration of the toxin	Suppo care, li threate may n suppor
Nitrite poisoning	1–2 hr	Nausea, vomiting, cyanosis, headache, dizziness, weakness, loss of consciousness, chocolate brown– colored blood	Usually self-limited	Cured meals, any contaminated foods, spinach exposed to excessive nitrification	Analysis of food, blood	Suppo care, n blue
Pesticides (organophosphates or carbamates)	Few min to few hr	Nausea, vomiting, abdominal cramps, diarrhea, headache, nervousness, blurred vision, twitching, convulsions, salivation, and meiosis	Usually self-limited	Any contaminated food	Analysis of food, blood	Atropi PAM (Pralid is use atropi able to sympt is rare necess carban poison
Puffer fish (tetrodotoxin)	<30 min	Paresthesias, vomiting, diarrhea, abdominal pain, ascending paralysis, respiratory failure	Death usually in 4–6 hr	Puffer fish	Detection of tetrodotoxin in fish	Life-threate may n respira suppor

Scombroid (histamine)	1 min–3 hr	Flushing, rash, burning sensation of skin, mouth, and throat, dizziness, urticaria, paresthesias	3–6 hr	Fish: bluefin, tuna, skipjack, mackerel, marlin, escolar, and mahi mahi	Demonstration of histamine in food or clinical diagnosis	Suppo care, antihis
Shellfish toxins (diarrheic, neurotoxic, amnesic)	Diarrheic shellfish poisoning (DSP)—30 min–2 hr	Nausea, vomiting, diarrhea, and abdominal pain accompanied by chills, headache, and fever	Hours to 2–3 days	A variety of shellfish, primarily mussels, oysters, scallops, and shellfish from the Florida coast and the Gulf of Mexico	Detection of the toxin in shellfish; high-pressure liquid chromatography	Suppo care, g self-li
	Neurotoxic shellfish poisoning (NSP)—few min to hr	Tingling and numbness of lips, tongue, and throat, muscular aches, dizziness, reversal of the sensations of hot and cold, diarrhea, and vomiting				
	Amnesic shellfish poisoning (ASP)—24–48 hr	Vomiting, diarrhea, abdominal pain and neurologic problems such as confusion, memory loss, disorientation, seizure, coma				
Shellfish toxins (paralytic shellfish poisoning)	30 min–3 hr	Diarrhea, nausea, vomiting leading to paresthesias of mouth, lips, weakness, dysphasia, dysphonia, respiratory paralysis	Days	Scallops, mussels, clams, cockles	Detection of toxin in food or water where fish are located; high-pressure liquid chromatography	Life-threate may n respira suppo
Sodium fluoride	Few min to 2 hr	Salty or soapy taste, numbness of mouth, vomiting, diarrhea, dilated pupils, spasms, pallor, shock, collapse	Usually self-limited	Dry foods (e.g., dry milk, flour, baking powder, cake mixes) contaminated with sodium fluoride–containing insecticides and rodenticides	Testing of vomitus or gastric washings, analysis of food	Suppo
Thallium	Few hr	Nausea, vomiting, diarrhea, painful	Several days	Contaminated foods	Urine, hair	Suppo

		paresthesias, motor polyneuropathy, hair loss				
Tin	5 min–8 hr, usually <1 hr	Nausea, vomiting, diarrhea	Usually self-limited	Metallic container	Analysis of food	Suppo
Vomitoxin	Few min to 3 hr	Nausea, headache, abdominal pain, vomiting	Usually self-limited	Grains such as wheat, corn, barley	Analysis of food	Suppo
Zinc	Few hr	Stomach cramps, nausea, vomiting, diarrhea, myalgias	Usually self-limited	Metallic container	Analysis of food, blood, and feces, saliva, or urine	Suppo

Adapted from Centers for Disease Control and Prevention. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. MMWR 53(No. RR-4):1–33, 2004.

Aflatoxins

Aflatoxins are poisonous substances that are formed as a result of mold growth on peanuts, corn, figs, oil-seeds, tobacco, and other products. The International Agency for Research on Cancer (IARC) has classified aflatoxin B1 as a group I carcinogen. Ingestion of elevated levels of aflatoxin also can result in acute aflatoxicosis, characterized by vomiting, abdominal pain, hepatitis, and sometimes death.

Ochratoxin A

The mycotoxin ochratoxin A, produced by many different species of *Aspergillus* molds, is toxic to the kidneys. Ochratoxin A contaminates many foods, including barley, rye, and other cereals, cereal-derived foods, dry fruits, beans, cocoa, coffee, beer, wine, poultry, eggs, pork, and milk. Ochratoxin A is teratogenic, immunotoxic, genotoxic, and mutagenic. The International Agency for Research on Cancer has indicated that ochratoxin is a possible human carcinogen (category 2B).

Fumonisins

Fumonisins are mycotoxins that may contaminate cornmeal and cereals. The fumonisins are known to interfere with sphingolipid metabolism. Consuming foods contaminated with fumonisins during pregnancy has been linked to an increased risk of having a child with a neural tube defect and an increased risk of esophageal cancer in adulthood.

Deoxynivalenol

This mycotoxin, often called vomitoxin because its predominant effect is vomiting, can be present in foods made from wheat and corn. Even after the grain is baked or cooked, vomitoxin retains its toxicity. Multiple epidemics of vomiting illness that occurred in China during 1961 to 1985 were associated with ingesting grain contaminated with vomitoxin. In India in 1987, almost 100 persons started vomiting after they ate wheat products that contained vomitoxin and other mycotoxins. For infants, the estimated tolerable daily intake is 1.5 ug/kg body weight. A suspected epidemic of vomitoxin-related illness that affected about 1,700 school children in the United States was linked to burritos that had measurable levels of vomitoxin of 0.3 ppm (the advisory level set by the US Food and Drug Administration for adults is 1 ppm).

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CHAPTER 736

Biologic Effects of Ionizing Radiation on Children

Samuel L. Brady, Donald P. Frush

Basic Principles

Ionizing radiation is produced when energy is absorbed within an atom such that a bound electron is liberated and the atom becomes ionized. Ionizing radiation exposure is characterized broadly in two categories: the first being **absorbed dose** and the second **equivalent** and **effective dose** . In terms of radiation interaction with humans, absorbed dose is defined as the energy imparted (i.e., absorbed) within a mass of tissue from a radiation source. Absorbed dose is calculated based on the attenuation properties of the irradiated tissue (e.g., attenuation is greater in bony tissue due to its higher electron density and mass than water equivalent solid organs). The units of absorbed dose, as defined by the International Commission of Radiation Units, are the **Gray** (Gy) and the radiation absorbed dose (**rad**). There are different types of radiation—for example, x-ray, γ-ray, α-particles (helium nucleus stripped of all electrons), β-particles (unbound electrons), neutrons, protons, and so on. Not all radiation has the same effect on biologic tissue for a given absorbed dose, namely, β-particles are quite superficial, protons deposit most of their energy deeper within the body, and α-particles and neutrons cause significantly more damage than x-rays or γ-rays. Diagnostic imaging uses x-rays and γ-rays. The therapeutic use of radiation for cancer treatment primarily uses x-rays, β-particles, and protons, depending on their application and location of disease within the body. **Effective dose** is a term used to define the relative effectiveness to cause biological damage. The International Commission on Radiological Protection (ICRP) gives x-rays, γ-rays, and β-particles a relative weighting of 1, protons a weighting of 2, neutrons a weighting of 2.5-20 (neutron weighting factor depends on the energy of the neutron), and α-particles a weighting of 20. **Effective dose** is a term that represents “The sum of the weighted [applying organ and tissue weighting factors] equivalent doses for the radiosensitive tissues and organs of the body” (National Council on Radiation Protection and Measurements). The most recent list of relative organ and tissue weighting factors defined by the ICRP is provided in Table 736.1 . Equivalent dose and effective dose are measured in units of **Sievert** (Sv) and the **rem** (older unit) (Table 736.2). Effective dose is not applied as a metric of individual dose but is a population average. Effective dose is averaged for both genders and is not defined for any population age.

Table 736.1

Table of Tissue Radiosensitive Weighting Factors; International Commission on Radiological Protection Report 103

TISSUE	TISSUE WEIGHTING FACTOR (W_T)	$\sum w_T$
Red bone-marrow, Colon, Lung, Stomach, Breast, Remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, Oesophagus, Liver, Thyroid	0.04	0.16
Bone surface, Brain, Salivary glands, Skin	0.01	0.04
Total		1.00

* Remainder tissues: adrenal glands, extrathoracic region, gall bladder, heart, kidneys, lymph nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix.

Table 736.2

Radiation Measurements

UNITS	RADIOACTIVITY	ABSORBED DOSE	EFFECTIVE DOSE	EXPOSURE
Common units	Curie (Ci)	rad	rem	Roentgen (R)
SI units*	Becquerel (Bq)	Gray (Gy)	Sievert (Sv)	Coulombs/kg
CONVERSION EQUIVALENTS				
1 millicurie (mCi) = 37 megabecquerels (MBq)				
100 rad = 1 Gy (1 rad = 1 cGy)				
100 rem = 1 Sv (1 rem = 10 mSv)				
Background radiation dose is approximately 1 millirad/day (10 µGy/day)				

* SI units: International System of Units

Nuclear medicine and positron emission tomography (PET) imaging examinations are described by the amount of radioactivity injected, also referred to as “administered” (milliCuries or Becquerels), which may be converted to effective dose (in terms of milliSieverts) by applying correction factors provided in ICRP reports 53, 80, and 106.

Ionizing radiation exposure occurs from both natural (50%) and man-made (50%) sources. Radon gas accounts for the majority (37%) of natural radiation. The percent contribution from medical imaging to the total ionizing radiation exposure has dramatically increased to 50% in 2006 from 15% in the mid-1980s, where computed tomography (CT) is responsible for 24% of all radiation exposure and almost half of medical imaging radiation (Fig. 736.1). As the population exposure rate from medical imaging increases, understanding of sources, amounts and potential risks of ionizing radiation can sill be limited; for example, 75% of radiologists and emergency department physicians are reported to underestimate the radiation dose from CT. In addition, some imaging procedures do not produce ionizing radiation (Table 736.3), and not all ionizing radiation-producing modalities expose a child to the same amount of radiation (Table 736.4).

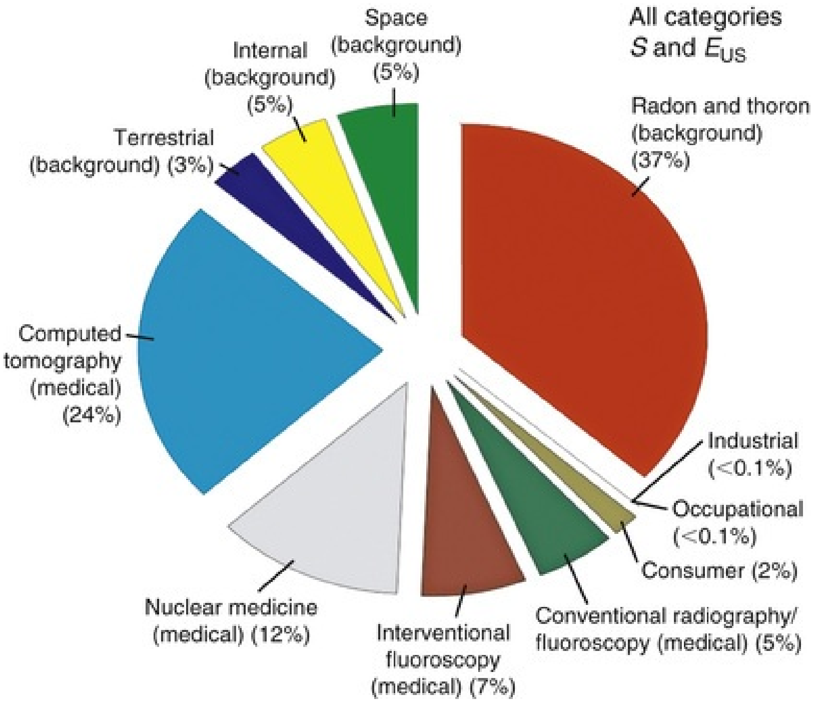

FIG. 736.1 **All exposure categories collective effective dose in adults (percentage) 2006. (Adapted with permission of the National Council on Radiation Protection and Measurements, http://NCRPonline.org .)**

Table 736.3

Imaging Modalities

MODALITY	SOURCE
Digital Radiography (plain film x-ray)	Radiation (x-ray)
Angiography/fluoroscopy	Radiation (x-ray)
Ultrasound	Acoustic sound beams
Computed tomography	Radiation (x-ray)
Magnetic resonance imaging	Magnetic field; Radiofrequency
Nuclear medicine (including positron emission tomography)	Radiation (administered isotope)

Table 736.4

Average Radiation Dose by Imaging Test for Pediatric Population[*]

EXAMINATION (0-18 yr)	EFFECTIVE DOSE (mSv)
Interventional fluoroscopy: AP & Lat abdomen	0.2-1.1 mSv/min
Interventional fluoroscopy: head	0.02-0.08 mSv/min
Interventional fluoroscopy: cardiac	0.1-1 mSv/min
Digital radiography: 2 view chest	0.04-0.06
Digital radiography: 2 view abdomen	0.1-0.4
Computed tomography: brain	0.8-4
Computed tomography: chest	1-4
Computed tomography: abdomen/pelvis [†]	2-7
Nuclear medicine (^{99m}Tc methylene diphosphonate–Bone)	5-7
Positron emission tomography (^{18}F-FDG; whole body)	3-15

[*] Background radiation reference = 0.01 mSv/day or 3 mSv/yr.

[†] Radiation dose upper limit includes adult aged population

Biologic Effects of Radiation

Biologic effects of radiation are divided into two types. The first type, **tissue reactions** (previously **deterministic effects**), are characterized by a threshold absorbed dose, and severity is directly related to the magnitude once the threshold is exceeded. No evidence of tissue reactions has been demonstrated from radiation dose levels (<100 mGy) used in diagnostic examinations but invasive procedures (therapeutic and interventional) have on rare occasions led to these effects. Typical tissue reactions present as temporary hair loss (epilation) and skin reddening (erythema) and occur in regions of peak dose >2 Gy (Table 736.5). Cataracts have also been reported to occur with an acute exposure to

>2.0 Gy or with long-term exposure to >5.0 Gy (international limits have set the threshold at >0.5 Gy).

Table 736.5

Deterministic Dose Levels

INJURY	APPROXIMATE THRESHOLD
SKIN	
Transient erythema	2 Gy (200 rad)
Dry desquamation	8 Gy (800 rad)
Moist desquamation	15 Gy (1,500 rad)
Temporary epilation	2 Gy (200 rad)
Permanent epilation	7 Gy (700 rad)
EYES	
Cataracts (acute)	2.0 Gy (200 rad)*

* Has been reported as occurring between 0.5 and 1.0 Gy.

The second type consists of stochastic (random) effects that are of concern because they may occur at any dose—that is, there is no threshold. The probability of a stochastic effect increases with the rising level of absorbed dose, but the severity of a stochastic effect does not increase with dose. Stochastic effects can be caused by any level of radiation striking vulnerable tissue (most importantly DNA, but cytoplasm also may be at risk) and causing irreversible damage. These effects are represented by the linear no (dose) threshold (LNT) model. This model maintains that no level of radiation exposure is effect free, or does not have a potential effect "(i.e., no threshold), and that the risk of radiation damage". This concept states that no level of radiation exposure can be considered safe.

Radiation can cause permanent cell injury leading to carcinogenesis, genetic mutations, or cell death. The biologic effects of radiation result primarily from damage to DNA. **Direct effect** reactions occur mainly through interactions of high **linear energy transfer (LET)** particles, such as α-particles or neutrons, directly with the DNA structure. Similarly, x-ray or γ-ray photons may interact with, and liberate, an electron from atoms (called a recoil electron) near the DNA structure. The kinetic energy of the recoil electron or high LET particles directly cleaves chemical bonds in the DNA structure. Recoil electrons cause approximately one third of DNA damage.

An **indirect effect** is caused by the formation of free radicals. Approximately 80% of the cell is water, so most of the energy deposited in a cell results in production of aqueous free radicals. Absorbed x-ray or γ-ray photon energy is converted to recoil electrons that create ion radicals (H_2O^+ and H_2O^-). The ion radicals promptly decay (10^{-18} -10^{-3} sec) into free radical species (OH^- , H^+ , H_3O^+). Approximately two thirds of DNA damage is believed to be caused by hydroxyl (OH^-) free radicals, which primarily reacts with DNA by attaching to the hydrogen bound to the deoxyribose carbon, resulting in a base release from the DNA structure and strand break of the DNA helix. The biochemical changes that follow take hours or days, whereas the physiologic changes leading to cancer induction may take years to decades.

The manifestations of DNA injury are variable. The cell containing the damaged DNA might die; cell death (**apoptosis**) is a mechanism for eliminating heavily damaged and potentially mutable cells. Damage to a single base pair is the most prevalent and least significant effect. Ninety percent of single strand DNA breaks are repaired within an hour, and therefore usually have little biologic significance because each strand is repaired with use of the opposite strand as a template, but a mutation can result if misrepair occurs.

Breakage of both strands of DNA (i.e., double strand break) is the least-common event but more problematic. The end result depends on the proximity of the break in each strand. If widely separated, as with a single-strand break, repairs occur rather seamlessly. If the breaks in the two strands are opposite each other (or separated by only a few base pairs), repair is more difficult without a template. Radiation induced double stranded breaks in proximity generally lead to cell death, or chromosomal damage leading to mutations and carcinogenesis.

When DNA damage occurs, aberrations are produced in chromosomes, resulting in an *unstable aberration* (usually lethal to dividing cells) or a *stable aberration.* Stable aberrations can result in failure of chromosomes to reunite (leading to deletions) or in abnormal rearrangement of chromosomes, such as reciprocal translocation or aneuploidy. Although it is logical to think that these abnormalities in chromosomes lead to mutations that can activate oncogenes or proto-oncogenes, or cause mutations in tumor-suppressor genes (see Chapter 519), few radiation-induced cancers show specific translocations that would be associated with activation of specific oncogenes or known tumor-suppressor genes. An exception is the radiation induction of papillary thyroid carcinoma in children, which probably results from activation of the RET oncogene (see Chapter 506.1).

Radiation carcinogenesis seems to be a progressive multistep process composed of three independent stages: morphologic changes, cellular immortality, and tumorigenicity. Radiation exposure induces cellular genomic instability. This instability is transmitted to a cell's progeny, resulting in a continued elevation in the rate at which genetic changes arise in the subsequent generations of the irradiated cell (Fig. 736.2).

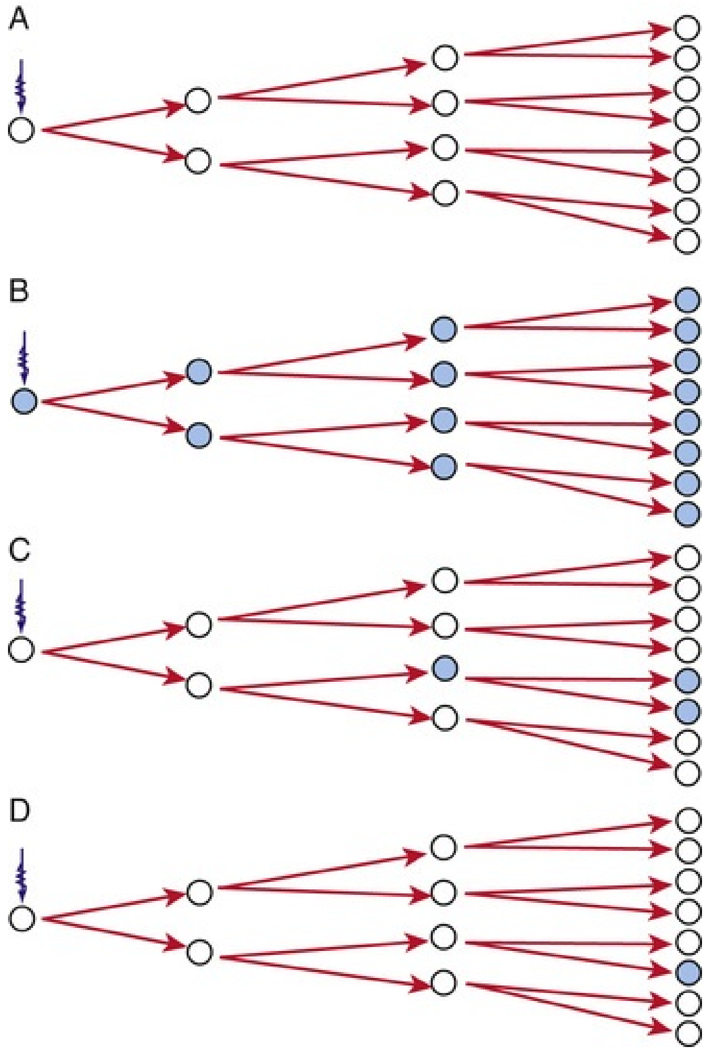

FIG. 736.2 Schematic of radiation-induced mutagenesis. *Open circles* represent normal wild-type cells, whereas *solid blue circles* represent mutated cells. A, Most of the cells in an irradiated population retain the wild-type phenotype. B, Example of a cell directly mutated by radiation exposure; the mutation is transmitted to all of its progeny. C and D are examples of mutations arising as a result of radiation-induced genomic instability. The irradiated cell and its immediate progeny are wild type, but the frequency with which mutations arise among the more distant descendants of the irradiated cell is elevated. (From Little JB: Ionizing radiation. In Kufe DW, Pollock RE, Weichselbaum RR, et al, editors: *Holland-Frei cancer medicine* , ed 3, Ontario, Canada, 2003, BC Decker.)

A longitudinal study of the lifetime risks of excess cancer mortality to irradiation has been evaluated in *atomic bomb survivors* . More than 120,000 survivors have been followed for more than 77 yr since exposure. Individual radiation doses were estimated by considering the person's location in relation to distance from the epicenter and individual shielding situations (such as line of sight with respect to buildings and terrain). Most of the exposure was direct gamma irradiation, with neutron exposure out to approximately 2,000 m. Age at exposure, life style, and other factors were considered in the analytic models when calculating cancer occurrence (Fig. 736.3) and other noncancer diseases. Compared with middle-aged adults, children are generally are 2 times more sensitive to radiation-induced carcinogenesis, and neonates are more sensitive than older children. Because of the higher risks associated with radiation exposure to the breast and thyroid, females are more sensitive than males. It must be understood that cancer rates in this study are mortality figures. The incidence of cancer is approximately two times greater than mortality incidence. Increased biologic vulnerability to stochastic effects to radiation can be seen in the fetus exposed in utero through maternal radiation. The Centers for Disease Control and Prevention (CDC) reports no scientific evidence demonstrating noncancerous effects (e.g., malformations, growth and developmental delay) from in utero exposure <50 mGy, an exposure level that is greater than essentially any single diagnostic examination using ionizing radiation. In addition, noncancerous effects may only increase slightly with exposure levels between 50 and 500 mGy. In utero radiation exposure is associated with an excess risk of developing (all types) childhood cancer: 1% (<50 mGy), 1-6% (50-500 mGy), and >6% (>500 mGy), as compared with 0.3% (natural background exposure only). The fetus and infant are most vulnerable to radiation-induced cancer because (1) they are growing rapidly, with many cells undergoing mitotic activity; (2) radiation-induced tumors (except leukemia) take a long time to develop and children have a longer lifetime; and (3) there is a greater time to have imaging studies, with accumulation of the risks related to doses. Policies relating to the use of therapeutic abortion have been established by the ICRP and American College of Obstetricians and Gynecologists, which state that fetal doses <100 mGy should not be considered a reason for terminating pregnancy, and that every woman should be counseled that exposure from a single diagnostic procedure does not result in tissue effects to the fetus.

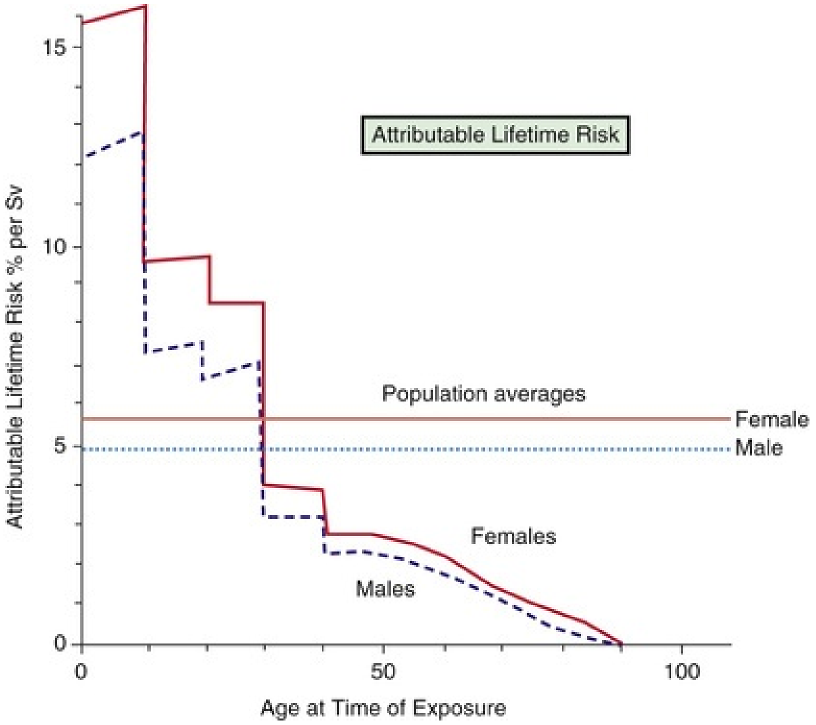

FIG. 736.3 Lifetime risk of excess cancer per Sievert *(Sv)* as a function of age at the time of exposure. Data from the atomic bomb survivors. The average risk across all ages in a population is approximately 5% per Sievert, but the risk varies considerably with age: children are much more sensitive than adults. At early ages, girls are more sensitive than boys. (From Hall EJ: Introduction to session I: Helical CT and cancer risk, *Pediatr Radiol* 32:225–227, 2002.)

Most childhood tumors occur sporadically, but 10–15% of cases have a strong familial association. Familial tumors have specific chromosomal deletions in common. In some of these tumors (retinoblastoma), the two-hit hypothesis by Knudson is apparent (see Chapter 518). It is not coincidental that individuals with many of the congenital diseases are at risk for the development of tumors after irradiation. Table 736.6 lists diseases that are associated with sensitivity to radiation.

Table 736.6

Inherited Human Syndromes Associated With Sensitivities to Ionizing Radiation

Ataxia-telangiectasia
Basal cell nevoid syndrome
Cockayne syndrome
Down syndrome

Fanconi anemia
Gardner syndrome
Nijmegen breakage syndrome
Usher syndrome

Modified from Slovis TL, Frush DP, Berdon WE, et al: Biologic effects of diagnostic radiation on children. In Slovis TL, editor: *Caffey's pediatric diagnostic imaging* , ed 11, Philadelphia, 2008, Mosby, p. 5; and Hall EJ: *Radiobiology for the radiologist* , ed 6, Philadelphia, 2006, Lippincott Williams & Wilkins, p. 41.

Radiation Exposure in Diagnostic Imaging of Children

The use of imaging modalities utilizing ionizing radiation for diagnostic purposes (e.g., CT, nuclear imaging including PET, radiography) has steadily increased over the years. Recent studies have reported utilization rate increases among pediatric CT examinations for various indications (e.g., patients presenting in the ER for abdominal pain, falls) up from 1 to 5% in the late 1990s to 11-15% in the late 2000s. With the increased use of radiation for imaging purposes has come the question of potential long-term risk for cancer induction and mortality. Evidence for **excess lifetime cancer risk (ELCR)** for survivors of the atomic bomb demonstrated clear evidence of radiation-induced cancer risk for whole body exposure >100 mSv, whereas no direct epidemiological data supports exposure <10 mSv, which is the effective dose for most diagnostic imaging examinations. What is unclear is the cancer risk for calculated effective dose levels between 10 and 100 mSv, which is the range in which multiphase or high-dose CT, nuclear cardiology, and some interventional/cardiology fluoroscopic procedures fall. Head and abdominal CT scans in children have been studied, and estimated ELCR vary widely, from as low as 1 : 500 to more than 1 : 10,000 (including the possibility that these doses do not incur a risk). Therefore, since stochastic effects are random but the probability of an effect increases with rising dose, it is important that we use the lowest dose necessary to get sufficiently diagnostic images; it is for this reason that accrediting and governing bodies are requiring a radiation dose estimate to appear in real-time during the imaging examination/procedure and a dose summary available with each completed examination. Ordering physicians and radiologists should be familiar with the specific dose metrics for common diagnostic examinations.

Increasing in popularity are dose reporting and aggregating software. The ability to collect and analyze individual examination doses gives healthcare providers a powerful tool to correct outlier examinations (i.e., over exposures), adjust overutilization, and address other systemic errors present in imaging clinics (such as radiation dose creep with time). However, as reported in the BEIR VII report "Health Risks from Exposure to Low Levels of Ionizing Radiation," the significance of accumulated patient radiation dose, with respect to health risk, is unclear. As previously discussed, the risk for acute single dose levels >100 mSv is well documented, but no evidence of cancer risk from accumulated dose levels <100 mSv derived over short- or long-term has been established.

Decreasing Unnecessary Diagnostic Radiation in Children While Still Obtaining Diagnostic Images

Ultimately the lowest radiation dose examination is the imaging examination performed without ionizing radiation. For an increasing number of indications, utilization of nonionizing radiation modalities such as ultrasound or magnetic resonance imaging (MRI) should be the first consideration for diagnosis. Selecting the correct examination is the responsibility of the ordering physician and may involve consultation with the radiologist, preferably with pediatric expertise. CT does not detect as many abnormalities as MRI, and CT involves ionizing radiation. MRI detects the subtle changes of congenital or acquired anomalies that may be responsible for seizures much more easily. Therefore it is appropriate, *except* in an emergency, to obtain MRI within a reasonable time frame instead of performing two tests (CT followed by an MRI). In addition, examples for the use of ultrasound in place of MRI, digital radiography, or CT include the enhanced diagnostic power when using dynamic testing of muscle-skeleton tissue when performed under stress (e.g., diagnosing rotator cuff tear, or meniscal subluxation of the joint line), or when assessing liver lesions with contrast enhanced ultrasound. Consideration of risks of cognitive impairment from moderate sedation and anesthetic versus potential radiation use risks do come into play at ages where this would be necessary for MR but not for CT.

It has been estimated that perhaps up to 30% of imaging examinations, including CT examinations, are questionably indicated, and may be replaced by another, non-radiation-producing modality, or are performed without evidence-based indications.

Reducing Radiation From the CT Examination

The largest source of medical radiation is CT. CT utilization has increased, in part, due to the ability to acquire high quality volumetric imaging data sets in seconds. We have progressed from a single-image per rotation scanner to scanners that can cover large areas of coverage (e.g., 16 cm) and produce a large number images per rotation in subsecond time. The images may have excellent detail, including multiplanar and 3-dimensional reconstruction of the acquired data. It once took more than 30 min to obtain 10-12 images, but now hundreds to thousands of images are generated in seconds. For many years, adult parameters for CT settings were used for children, which led to dosages for children much higher than the dosage for adults. This occurs because lower-energy x-rays that would have been absorbed in the near field in an adult pass into the entire child, with relatively greater organ irradiation for the same exposure. When comparing dosages given to newborns and adults during CT scanning of the head, with the same parameters in both groups, the dosage given to newborns can be four times that of the dosage given to adults; with abdominal imaging, the dosage is increased by 60%. *It is the role of the radiologist and technologist, with the help of a medical physicist, to tailor the examination to the pediatric patient* .

Modern CT scanners have many tools to help administer the appropriate amount of radiation dose to a pediatric patient and acquire the necessary diagnostic image quality from the imaging examination. Radiologists should work in conjunction with medical physicists and vendor-supplied application specialists to tailor specific examination protocols to the pediatric patient population by establishing appropriate tube current modulation (milliamperage second [mAs]) and tube potential (kilovoltage [kV]) ranges based on patient weight or size, when scanning the body, or age, when scanning the head. In addition, radiologists and medical physicists should establish clear guidelines within an institution's pediatric CT protocols for anatomical scanning coverage; scanned coverage should be limited to only the necessary area for diagnosis (e.g., a chest-only scan should begin at the lung apices and extend to no more than a little below the lowest lung base). Multiphasic scanning should not be the rule but the exception, only obtained when absolutely necessary.

The radiologist has many ways to decrease parameters so that children receive diagnostic imaging without excessive radiation, e.g., decrease kV and increase mA may improve image quality at decreased exposure. In the past, reducing the radiation dose by half, even in adults receiving CT, did not change the diagnostic efficacy of the study and the radiologist's ability to make the proper diagnosis. This required the radiologist to review images of reduced image quality (i.e., “noisier” images); however, modern CT scanners use reconstruction algorithms, such as *statistical iterative reconstruction (IR)* , or model-based IR. These IR algorithms permit the reduction of radiation dose by as much as 90% in some patient populations while maintaining equivalent image quality to the predose reduced image data sets. Historically, improving the quality of the CT image required increasing the radiation dose to the patient. Replacing older CT scanners with more advanced scanners, implementing pediatric-specific size, weight, or age examination protocols, and tracking institution dose utilization have been three successful ways to reduce overall pediatric patient population doses by >50% during the past decade.

Radiation Therapy—Acute and Late Effects

Radiation therapy uses high doses to kill malignant cells. The sensitivity of normal cells is quite close to that of malignant cells, and to achieve significant cure rates, radiation oncologists must accept a given percentage of serious complications (5–10%). Radiation causes tissue loss plus injury to the underlying vasculature. The vascular change may be progressive, leading to arteriocapillary fibrosis and irreparable injury, in turn leading to further tissue loss.

The acute effects of therapy (occurring <3 mo after therapy begins) are usually related to the area of the body being irradiated (except fatigue, which can begin during this time period). These acute effects include radiation-caused pneumonitis, dermatitis, mucositis and esophagitis, cerebral edema, and swelling of the organ irradiated. There may be changes in bowel movement patterns. Of these, one of the most severe acute reactions is pneumonitis. It can be manifest within 24 hr of irradiation when there is an exudation of proteinaceous material into the alveoli and intraalveolar edema. Most often, radiation pneumonitis begins 2-6 mo after the beginning of radiation with a clinical presentation of fever, cough, congestion, and pruritic pain. The late effects of therapy (beginning more than 3 mo after therapy) are numerous (Table 736.7). The most common are abnormalities of pulmonary function, hearing loss, endocrine/reproductive function, cardiac function, and neurocognitive loss.

Table 736.7

Late Effects of Radiation Therapy in Children Treated for Cancer

SYSTEM	LATE EFFECT	DOSE (Gy)
Musculoskeletal	Muscular hypoplasia	>20
	Scoliosis, kyphosis, lordosis	10-20
	Osteocartilaginous exostosis	?
Neuroendocrine (cranial or cranial spinal)	Impaired growth hormone	>18
	Adrenocorticotropic hormone deficiency	>40
	Thyrotropin-releasing deficiency	>40
	Precocious puberty (females mostly)	>20
	Gonadotropin deficiency	<40
Gonad failure	Ovarian failure	4-12
	Testicular failure	>3
Central nervous system dysfunction*	Structured changes	>18
	Cognitive changes	?
Other	Pulmonary fibrosis	
	Nephropathy	
	Liver failure	
	Arteritis	
	Eye impairment	
	Ear impairment	
	Bone marrow dysfunction	
	Cardiac impairment	

* With intrathecal chemotherapy (methotrexate).

Derived from Halperin EC, Constine LS, Tarbell NJ, et al, editors: *Pediatric radiation oncology* , ed 3, Philadelphia, 1999, Lippincott Williams & Wilkins.

Annually, childhood cancer affects 70-160 per million children between the ages of 0 and 14 yr. Because of earlier diagnosis and improved therapy, more than 79% of children who were diagnosed from 1995 to 2001 with cancer are long-term survivors. Approximately 1 in 570 young adults is a long-term survivor of cancer, and up to 25% have a complication related to their therapy. Second cancers account for 6–10% of all cancers in children or adults. Among children in the Childhood Cancer Survivor Study, there is a cumulative incidence of second neoplasms of 3.2% at 20 yr from original diagnosis. Primary malignancies with the highest cumulative incidence of a second neoplasm in the order of frequency are Hodgkin disease (7.6), soft tissue sarcoma (4.0), cancers of bone (3.3), leukemia (2.1), central nervous system (CNS) cancers (2.1), and non-Hodgkin disease lymphoma (1.9). This reflects an overall standard incidence rate of 6.38% (Fig. 736.4). The most prevalent second tumors are bone, breast, thyroid, and CNS lesions (Fig. 736.5). Table 736.8 relates second cancers to primary cancer and latency period. Almost 70% of the second neoplasms are in the field of the original irradiation. Radiation therapy increases the risk of second cancers in a dose-dependent manner for nongenetic neoplasms.

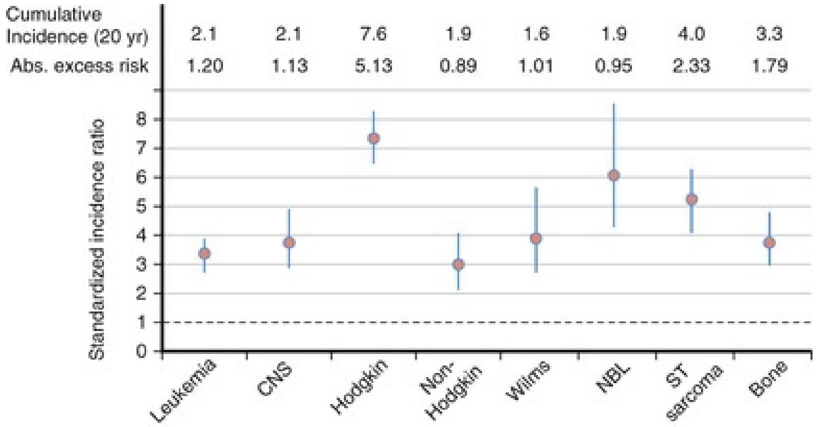

FIG. 736.4 Second malignancies among the Childhood Cancer Survivor Study cohort. ***CNS*** **, Central nervous system;** ***NBL*** **, neuroblastoma;** ***ST*** **, soft tissue. (From Robison LL: Treatment-associated subsequent neoplasms among long-term survivors of childhood cancer: the experience of the Childhood Cancer Survivor Study,** ***Pediatr Radiol*** **39[Suppl 1]:S32–S37, 2009, Fig. 1.)**

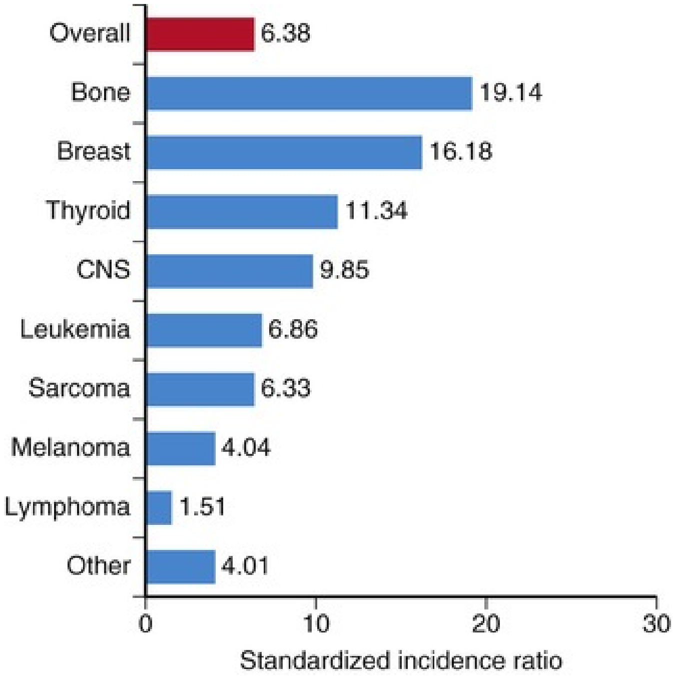

FIG. 736.5 **Standardized incidence ratio by type of 2nd malignancy. *CNS* , Central nervous system. (From Robison LL: Treatment-associated subsequent neoplasms among long-term survivors of childhood cancer: the experience of the Childhood Cancer Survivor Study, *Pediatr Radiol* 39[Suppl 1]:S32–S37, 2009, Fig. 2.)**

Table 736.8

Second Cancers and Their Relationship With Primary Cancers

SECOND CANCERS	PRIMARY CANCERS	LATENCY (MEDIAN IN Yr)	RISK FACTORS
Brain tumors	ALL; brain tumors; HD	9-10	Radiation; younger age
Myelodysplastic syndromes/acute myelogenous leukemia	ALL; HD; bone tumors	3-5	Topoisomerase II inhibitors; alkylating agents
Breast cancer	HD; bone tumors; soft tissue sarcomas; ALL; brain tumors; Wilms tumors; NHL	15-20	Radiation; female gender
Thyroid cancer	ALL: HD; neuroblastoma; soft tissue sarcomas; bone tumors; NHL	13-15	Radiation; younger age; female gender
Bone tumors	Retinoblastoma (heritable); other bone tumors; Ewing sarcoma; soft tissue sarcomas; ALL	9-10	Radiation; alkylating agents; removal of the spleen
Soft tissue sarcomas	Retinoblastoma (heritable); soft tissue sarcomas; HD; Wilms tumors; bone tumors; ALL	10-11	Radiation; younger age; anthracyclines

ALL , Acute lymphocytic leukemia; *HD* , Hodgkin disease; *NHL* , non-Hodgkin lymphoma.

From Bhatia S, Sklar S: Second cancers in survivors of childhood cancer. *Nat Rev Cancer* 2:124–132, 2002.

The exact complications depend on the location of the treatment field. In children, because of the location of many childhood tumors, the normal brain is commonly in the treatment field. Standard irradiation of the brain in children results in cortical atrophy in more than half of patients who receive 20-60 Gy; 26% are left with white matter changes (leukoencephalopathy) and 8% with calcifications. The younger the child is at the time of irradiation, the greater the atrophy. Some patients also demonstrate mineralizing microangiopathy. Radiation-induced changes of the brain are potentiated by methotrexate administered before, during, or after radiation therapy.

Cerebral necrosis is a serious complication of radiation-induced vascular disease. It is usually diagnosed 1-5 yr after irradiation but can occur up to a decade later. Brain necrosis may manifest as headache, increased intracranial pressure, seizures, sensory deficits, and psychotic changes.

Spinal cord irradiation may result in **radiation myelitis,** which may be either transient or permanent. Acute transient myelitis often appears 2-4 mo after irradiation. Patients with myelitis usually present with **Lhermitte sign,** a sensation of little electrical shocks in the arms and legs occurring with neck flexion or other movements that stretch the spinal cord. Reversal of transient myelopathy usually occurs between 8 and 40 wk and does not necessarily progress to delayed necrosis.

Delayed myelopathy occurs after a mean latent period of 20 mo but can occur earlier if the total dose or the dose per fraction is high. It usually manifests as discontinuous deterioration and is irreversible. In the cervical and thoracic regions, sensory dissociation develops, followed by spastic and then flaccid paresis. In the lumbar cord, flaccid paresis is dominant. The mortality for high thoracic and cervical lesions reaches 70%, death being due to pneumonia and urinary tract infections.

CNS irradiation may also affect growth by compromising function of the pituitary-hypothalamic axis and leading to diminishing growth hormone production and release. Non–growth hormone trophins may also be affected by CNS irradiation, leading to gonadotrophin deficiency or precocious puberty. Central hypothyroidism can also develop. CNS irradiation also compromises bone mineral deposition both locally (in the radiation field) and systemically.

Irradiation also has other effects specific to children. Scoliosis and hypoplasia of bones may occur if fractionated treatment schemes exceed 4,000 rad.

Fractionated doses higher than 25 Gy can result in slipped capital femoral epiphyses. An increase in the incidence of benign osteochondromas also has been reported after childhood irradiation. Chest wall irradiation of girls (besides causing breast cancer) may impair breast development and/or cause fibrosis and atrophy of breast tissue.

Whole-Body Irradiation

Uncontrolled Large- or Small-Scale Exposure to Radiation

Large-scale exposure to radiation can occur in an event of nuclear accidents, war, or terrorist attacks (see Chapters 14.2 and 741). Radiation as well as explosive and thermal injury need to be considered.

Clinical Manifestations

A large single exposure of penetrating radiation can result in **acute radiation syndrome.** The signs and symptoms of this syndrome result from damage to major organ systems that have different levels of radiation sensitivity, modulated by the rate at which the radiation exposure occurred. Delivery of 1 Gy in 1 min would be symptomatic, but delivery of 1 cGy/day for 100 days would not be symptomatic.

The **hematopoietic syndrome** results from acute whole-body doses above 0.7-10 Gy, where healthy patients will almost always recover from doses <2 Gy. The dose that kills 50% of a population in 60 days is approximately 3.5-4.5 Gy, where effective blood transfusions and antibiotics may extend the dose range to 5-8 Gy. Doses >8 Gy almost always lead to hematopoietic induced death. Symptoms of exposure consist of a prodromal phase during which the patient will experience nausea/vomiting, diarrhea, and fatigue within the first 12 hr, with symptoms usually lasting up to 48 hr. A latent period of 2-3 wk, during which patients may feel quite well, follows. Although patients are asymptomatic, bone marrow impairment has occurred. The most obvious laboratory finding is lymphocyte depression (Table 736.9). Maximal bone marrow depression occurs approximately 30 days after exposure, when hemorrhage and infection can be major problems. If the bone marrow was not completely eradicated, a recovery phase then ensues. This radiation effect is similar to what occurs when whole-body irradiation (given as 12 Gy in two treatments) is used to obliterate the bone marrow in children with leukemia before bone marrow transplantation.

Table 736.9

Expected Outcome Based on Absolute Lymphocyte Count After Acute Penetrating Whole-Body Irradiation

MINIMAL LYMPHOCYTE COUNT WITHIN FIRST 48 HR AFTER EXPOSURE	PROGNOSIS
1,000-3,000 (normal range)	No significant injury
1,000-1,500	Significant but probably nonlethal injury, good prognosis
500-1,000	Severe injury, fair prognosis
100-500	Very severe injury, poor prognosis
<100	Lethal without compatible bone marrow donor

The **gastrointestinal (GI) syndrome** occurs from acute whole-body doses above 6-10 Gy. Prompt onset of nausea, vomiting, and diarrhea follows. There is a latent period of approximately 1 wk if intense medical treatment is administered. Following the latent period, recurrence of GI symptoms, sepsis, and electrolyte imbalance returns, which results in death at about 2 wk post exposure from GI tract and bone marrow destruction.

At dose levels exceeding 20-50 Gy, the **cardiovascular/CNS syndrome** predominates. Nausea, vomiting, prostration, hypotension, ataxia, and convulsions are almost immediate. The latent period occurs between 4 and 6 hr after exposure, followed by severe manifestation of the initial illness stage and leading to eventual coma and death within 2-3 days.

Treatment

For the hematopoietic and GI syndromes, treatment is supportive, involving transfusions, fluids, antibiotics, and antiviral agents.

Localized Irradiation

Clinical Manifestations

Because localized exposure involves a small amount of tissue, systemic manifestations may be less severe, and patients may survive even if locally absorbed doses are very high. The hand is the most common site for accidental localized irradiation injuries, usually as a result of picking up or playing with lost radiation sources. The second most common accidental site is the thigh and buttocks, predominantly from placing unsuspected highly radioactive sources in the pockets.

Table 736.10 lists the skin changes that occur after a single acute, localized irradiation. As opposed to other forms of thermal burns, signs of irradiation appear a period of days *after* the exposure. Vascular insufficiency may appear months to years later and cause ulcerations or necrosis in formerly healed areas. The penetrability of the radiation is an important factor in the outcome of local radiation injury. Beta-particles from heavy radiation fallout can cause superficial skin burns because they have low penetrability.

Table 736.10

Skin Changes After a Single, Acute, Localized Radiation Exposure

ABSORBED DOSE (Gy)	CHANGE
3-4	Epilation in 2-3 wk
10-15	Threshold for erythema; appears 18-20 days after exposure at lower doses; may appear within a few hours at higher doses
20	Moist desquamation, possible ulceration
25	Ulceration with slow healing
30-50	Blistering, necrosis at 3 wk
100	Blistering, necrosis at 1-2 wk

Data from Gusev I, Guskova AK, Mettler FA Jr, editors: *Medical management of radiation accidents* , ed 2, Boca Raton, FL, 2001, CRC Press.

Some tissues that may receive localized radiation exposure are relatively radiosensitive. **Cataract formation** (see Chapter 646) may occur with single gamma ray exposures in the range of less than 1 Gy to several Gy. Such cataracts usually take from 2 mo to several years to develop. **Oligospermia** may take up to 2 mo to develop. Transient infertility in men may result from doses as low as 15 cGy, and permanent sterility may occur in men at dose levels between 3 and 6 Gy.

Treatment

Skin therapy is directed at prevention of infections. Treatment of localized injuries usually involves plastic surgery and grafting, if the radiation exposure was not very penetrating (see Chapter 92). The nature of the surgery depends on the dose at various depths in tissue and the location of the lesion. The full expression of radiation injury often is not apparent for 1-2 yr, owing to slow arteriolar narrowing that can cause delayed necrosis. After relatively penetrating radiation, amputation may be necessary because of obliterative changes in small vessels.

Internal Contamination

Epidemiology

Accidents involving internal contamination are rare and are usually the result of misadministration in hospital settings or voluntary ingestion of unsuspected contaminated radioactive materials. Other possible causes of internal contamination of children include ingestion of breast milk from mothers who have had diagnostic nuclear medicine scans and radiation exposure when a parent or sibling receives a therapeutic dose of iodine-131.

Clinical Manifestations

The hazards from internal contamination depend on the nature of both the radionuclide (particularly in terms of its solubility in water, half-life, biological half-life, and radioactive emission) and the chemical compound.

Treatment

The most effective treatment requires knowledge of both the radionuclide and the chemical form. Treatment must be instituted quickly to be effective (Table 736.11). **Removal treatment** involves cleaning a contaminated wound and performing stomach lavage or administration of cathartics in the case of ingestion. Administration of alginate-containing antacids (e.g., Gaviscon) also usually helps in removal by decreasing absorption in the GI tract. An example of **blocking therapy** is the administration of potassium iodine or other stable iodine-containing compounds to patients with known internal contamination with radioactive iodine. The stable iodine effectively blocks the thyroid, although its effectiveness decreases rapidly as time elapses after the contamination. The recommended dose of potassium iodine is 16 mg for neonates; 32 mg for children ages 3 yr or younger; and 65 mg for children ages 3-18 yr. Each dose protects for only 1 day. **Dilution therapy** is used in cases of tritium (radioactive hydrogen as water) contamination. Forcing fluids promotes excretion. Cases of internal contamination with transuranic elements (americium and plutonium) may require **chelation therapy** with calcium diethylene triamine pentaacetic acid.

Table 736.11

Specific Therapy for Internal Radiation Contamination

RADIONUCLIDE	THERAPEUTIC APPROACH
Tritium	Dilution (force fluids)
Iodine-125 or iodine-131	Blockage (saturated solution of potassium iodide or potassium iodide), mobilization (antithyroid drugs)
Cesium-134 or cesium-137	Reduction of gastrointestinal absorption (Prussian blue)
Strontium-89 or strontium-90	Reduction of absorption (aluminum phosphate gel antacids), blockage (strontium lactate), displacement (oral phosphate), mobilization (ammonium chloride or parathyroid extract)
Plutonium and other transuranic elements	Chelation with zinc or calcium diethylenetriamine pentaacetic acid (investigational agents)
Unknown	Reduction of absorption (emetics, lavage, charcoal, or laxatives) in cases of ingestion

From Mettler FA, Voelz GL: Major radiation exposure—what to expect and how to respond, *N Engl J Med* 346:1554, 2002.

Prussian blue is a drug approved by the U.S. Food and Drug Administration (FDA) for patients with internal contamination with cesium or thallium. It can speed fecal elimination of radioactive cesium from the body. It acts by intercepting the cesium coming into the gut from the bile. Prussian blue prevents the cesium from being absorbed again from the gut. Prussian blue can be given days after ingestion, unlike potassium iodine, which must be given initially in the 1st 12-24 hr after exposure.

In the case of **breastfeeding** after a nuclear medicine procedure, two primary concerns are considered: (1) the internal dose to the infant passed through the excreted milk and (2) the dose from the radiopharmaceutical absorption in female breast that exposes the infant to external γ-rays while undergoing decay. Most imaging radiopharmaceuticals are below the activity calculated to expose the infant to a dose of 1 mSv via either internal or external mode of exposure. Table 736.12 provides a comprehensive list of radiopharmaceuticals and the recommended period for breastfeeding cessation by the U.S. Nuclear Regulatory Commission. In the case of delaying of breastfeeding, pumped milk may be stored for the times indicated in Table 736.12 , after which it will be safe to feed the infant.

Table 736.12

Nuclear Regulatory Commission Guidelines on Breastfeeding During the Period of a Nuclear Medicine Examination

RADIOPHARMACEUTICAL	SUGGESTED TIME PERIOD OF NO BREASTFEEDING
^{131}-I Sodium iodide	Complete cessation
^{123}-I Sodium iodide	No interruption*
^{123m} I IBG	24 hr
^{99m}-Tc DTPA	No interruption*
^{99m}-Tc MAA	13 hr
^{99m}-Tc pertechnetate	24 hr
^{99m}-Tc IDA agents	No interruption*
^{99m}-Tc glucoheptonate	No interruption*
^{99m}-Tc HAM	No interruption*
^{99m}-Tc MIBI	No interruption*
^{99m}-Tc MDP	No interruption*
^{99m}-Tc PYP	No interruption*
^{99m}-Tc red blood cells	No interruption*
^{99m}-Tc sulfur colloid	6 hr
^{99m}-Tc MAG3	No interruption*
^{99m}-Tc white blood cells	24 hr
^{67} Ga citrate	1 mo
^{51} Cr EDTA	No interruption*
^{111} In white blood cells	1 wk
^{201} Tl chloride	2 wk

* The normally administered activity is below activities that require any interruption.

The guideline for ^{99m} Tc compounds is a 24-hr interruption for >1,110 MBq administered, 12 hr for 444–1,110 MBq, and no interruption for <444 MBq administered.

External Contamination

The presence of external radioactive contamination on a patient's skin is not an immediate medical emergency. Management involves removing and controlling the spread of radioactive materials. If a patient has suspected surface contamination and no physical injuries, decontamination can be performed relatively easily. If substantial physical trauma or other life-threatening injuries are combined with external contamination, surface decontamination should proceed only after the patient has been stabilized physiologically. In many accident situations, essential medical care may be delayed inappropriately by hospital emergency staff because of fear of radiation or spread of contamination in the hospital. After a radiation accident, triaging of patients is critical and is based on exposure and symptoms (Fig. 736.6).

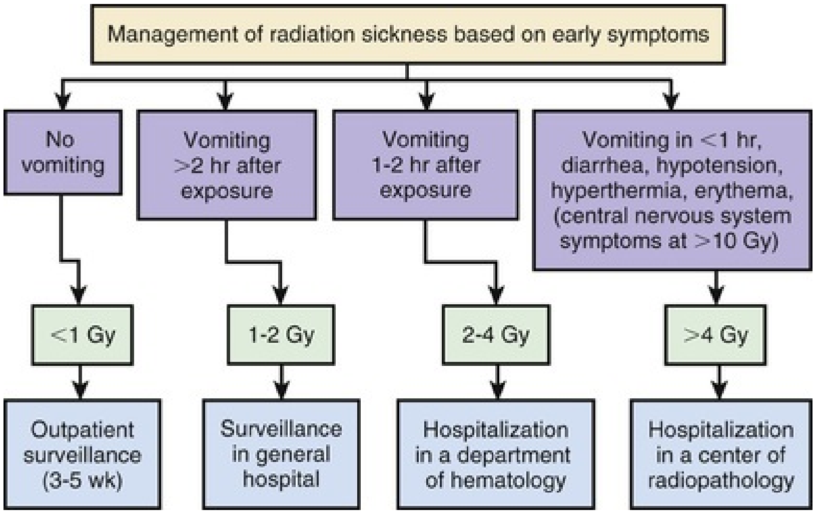
Management of radiation sickness based on early symptoms
No vomiting
Vomiting >2 hr after exposure
Vomiting 1-2 hr after exposure
Vomiting in <1 hr, diarrhea, hypotension, hyperthermia, erythema, (central nervous system symptoms at >10 Gy)
<1 Gy
1-2 Gy
2-4 Gy
>4 Gy
Outpatient surveillance (3-5 wk)
Surveillance in general hospital
Hospitalization in a department of hematology
Hospitalization in a center of radiopathology

FIG. 736.6 **Management of radiation sickness at different levels of medical care, depending on the appearance of early symptoms and the estimated radiation dose to the whole body. (From Turai I, Veress K, Günalp B, et al: Medical response to radiation incidents and radionuclear threats, *BMJ* 328:568–572, 2004.)**

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CHAPTER 737

Chemical Pollutants

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More than 85,000 new synthetic chemicals have been developed in the past 75 yr. Most did not previously exist in nature. These chemicals are used in millions of products, ranging from food packaging to clothing, building materials, motor fuels, cleaning products, cosmetics, medical products, toys, and baby bottles.

Synthetic chemicals are widely disseminated in the environment. The Toxic Release Inventory of the U.S. Environmental Protection Agency (EPA) reports that in 2015 nearly 3.4 billion pounds of chemical wastes were discharged to air, water, and land in the United States. These chemicals are detected today in even the most remote corners of the planet—at the polar icecaps and in the ocean depths.

Children are at daily risk of exposure to synthetic chemicals. Children are especially likely to be exposed to the nearly 3,000 chemicals that are produced in amounts of 1 million pounds or more per year and are designated by EPA as high-production-volume chemicals. Biomonitoring data on blood and urine levels of more than 200 high-production-volume chemicals are obtained annually by the Centers for Disease Control and Prevention in a sample of the U.S. population through the National Health and Nutrition Examination Survey. These data document that most Americans of all ages, including children, are routinely exposed to scores of synthetic chemicals.

Toxic chemicals are exported in ever-increasing quantities to the world's poorer countries as these countries pass through industrial development. Environmental safeguards in those countries are typically not as stringent as in high-income countries, and the potential for serious exposure is therefore high. Examples of tragedies that have resulted from the movement of toxic chemicals to low- and middle-income countries include the Bhopal disaster in India, in which hundreds were killed and thousands injured by methylisocyanate gas released by an explosion in a pesticide production facility, and the ongoing export each year of more than 2 million tons of newly produced asbestos to the world's poorest countries, where this asbestos is responsible for nearly 200,000 deaths annually from asbestosis, lung cancer, and malignant mesothelioma.

Synthetic Chemicals and Human Health

Some synthetic chemicals have greatly benefitted human health. Antibiotics have helped control the major communicable diseases. Chemical disinfectants have reduced deaths from dysentery. Chemotherapy agents have made possible the cure of many childhood cancers.

But new synthetic chemicals have also been responsible for tragic episodes of disease, death, and environmental degradation. Many have resulted in severe injury to children. A recurrent pattern is that chemicals are brought to market with great enthusiasm, presumed harmless, and undergo little or no premarket safety testing. Then years or decades later, after they had come into wide use, the chemicals were found to be harmful to children's health.

Often the first cases of disease caused by these chemicals are clinically severe, but as time passes, evidence of widespread subclinical toxicity comes to light.

Classic historical examples of epidemics caused by inadequately tested toxic chemicals include the following:

- *Tetraethyl lead* , which was added to gasoline in the United States from the early 1920s until 1980. It was responsible for widespread lead poisoning, initially evident as an epidemic of acute toxicity manifesting as encephalopathy, seizures, and even death, but later demonstrated to have caused subclinical neurotoxicity and reduction in IQ across 2 generations of U.S. children (see Chapter 739).
- The pesticide *dichlorodiphenyltrichloroethane (DDT)* , which very nearly led to extinction of the

osprey and the American bald eagle and more recently has been linked to increased risk for breast cancer among women exposed decades ago in utero

◆ *Polychlorinated biphenyls (PCBs)* , highly persistent pollutants banned from production in the United States in 1977, which continue today to contaminate major lakes and rivers and have been found also to be responsible for loss of IQ and disruption of behavior in children

◆ The ozone-destroying *chlorofluorocarbons*

Other examples of synthetic chemicals that came into wide use with little assessment of their safety and now recognized as causing harm to children's health include:

◆ *Phthalates* , chemicals added to plastics, cosmetics, intravenous tubing, and common household products that are now linked to increased risk for reproductive abnormalities in baby boys and heightened risk of behavioral abnormalities (see Chapter 49);

◆ *Polybrominated diphenyl ethers* , used as flame retardants in carpets, furniture, and electronic equipment and now linked to persistent loss of intelligence and disruption of behavior in children; *and*

◆ *Bisphenol A* , a plastics chemical linked to neurodevelopmental disorders.

These chemicals are all produced in volumes of millions of tons per year, are widely disseminated in the environment, and are detectable in the bodies of nearly all Americans. Only decades after their introduction are these chemicals' risks to children beginning to be recognized.

Children's Unique Susceptibility to Synthetic Chemicals

The health effects of synthetic chemicals are especially serious when exposure occurs during windows of vulnerability in early life—during pregnancy, infancy, and early childhood. Children are highly vulnerable to chemical pollutants for several reasons:

1. Children have proportionally greater exposures to environmental pollutants than adults. Because they drink more water, eat more food, and breathe more air per kilogram of body weight, children are more heavily exposed to pollutants in water, food, and air. Children's hand-to-mouth behavior and their play close to the ground further magnify their exposures.
2. Children's metabolic pathways, especially in the 1st few mo after birth, are immature. Although in some instances children are better able than adults to cope with environmental toxicants because they cannot metabolize these chemicals to their active forms, more commonly children are not as well able as adults to detoxify and excrete chemical pollutants.
3. Infants and children are growing and developing, and their complex, fast-moving, and highly choreographed developmental processes are exquisitely sensitive to disruption by chemical pollutants. Exposures to even minute doses of toxic chemicals during windows of vulnerability in early development have been shown to cause a wide array of diseases in childhood and also to increase risk for chronic disease and disability lifelong (Table 737.1).

Table 737.1

Effects of Selected Chemical Pollutants on Infants and Children

CHEMICAL POLLUTANT	EFFECT(S)
Air pollution	Asthma, other respiratory diseases, sudden infant death syndrome
Asbestos	Mesothelioma and lung cancer
Benzene, nitrosamine, vinyl chloride, ionizing radiation	Cancer
Environmental tobacco smoke	Increased risk of sudden infant death syndrome and asthma
Ethyl alcohol	Fetal alcohol syndrome after intrauterine exposure
Lead	Neurobehavioral toxicity from low-dose exposure
Methyl mercury	Developmental neurotoxicity
Organophosphate insecticides	Developmental neurotoxicity
Polychlorinated biphenyls	Developmental neurotoxicity
Polybrominated diphenyl ethers	Developmental neurotoxicity
Phthalates	Developmental neurotoxicity and reproductive impairment
Trichloroethylene	Elevated risk of leukemia after intrauterine exposure

4. Because children have many future years of life, they have time for the development of multistage chronic diseases that may be triggered by early exposures.

The unique susceptibility of infants and children to toxic chemicals—susceptibility that is both quantitatively and qualitatively different from that of adults—is summarized in the phrase “*children are not little adults* .” Many of the impacts on children's health of toxic exposures in early life appear to be mediated through epigenetic changes in gene expression.

Safety Testing of Synthetic Chemicals

Legally mandated testing of chemicals for safety and toxicity coupled with strict controls on dangerous chemicals are the linchpins of chemical safety. Strong chemical safety policies are needed to protect children against disease and death caused by chemicals. A fundamental problem in environmental pediatrics today is that chemical safety policies in many countries are weak. Only approximately 65% of high-production-volume chemicals have been tested for their safety or potential hazard to human health, and fewer than 30% have been assessed for their pediatric or developmental toxicity.

Failure to test chemicals for safety and toxicity reflects the chemical industry's unwillingness to take responsibility for the products they produce coupled with long-standing failure of the previous U.S. federal law on chemical safety, the

Toxic Substances Control Act (TSCA). This law was intended at the time of its passage in 1976 to be bold legislation that would require premarket evaluation of all new chemicals as well as retroactive testing of chemicals already in commerce, but it never fulfilled those intentions. A particularly egregious lapse was a decision made shortly after enactment to assume that all 62,000 chemicals then on the market were safe and to require no testing of them. Since that time, chemicals have been brought to the market with almost no safety testing and presumed to be safe until beyond to cause harm. Only five chemicals have been banned or controlled under the TSCA: PCBs, the ozone-destroying chlorofluorocarbons, and three known human carcinogens—dioxin, asbestos, and hexavalent chromium.

To address the problem of exposure to untested chemicals, countries have begun in recent years to enact chemical safety legislation. In 2007, the European Union enacted the Registration, Evaluation, Authorisation and Restriction of Chemical Substances (REACH) legislation. This law places responsibility on industry to generate data on potential risks of commercial chemicals and to register this information with the European Chemical Agency in Helsinki. The European Union is using this information to craft regulations to protect children's health, and it has banned and restricted certain toxic products.

In June 2016, the United States passed new legislation to revamp TSCA. This law—the Frank R. Lautenberg Chemical Safety for the 21st Century Act—requires that the EPA assess the safety of any new chemical before it is allowed to enter the market; to prioritize safety testing of existing chemicals; and to use a risk-based standard to evaluate chemical safety that considers only hazards to health and is blind to the costs of protective action. This new law holds much promise for improving the protection of children's health against toxic chemicals, but also includes a federal preemption clause that could inhibit state-based protective regulations. Transparency, oversight, and advocacy will be critical to ensuring that the law is implemented in a timely manner that is true to the intent to prioritize children's health. Implementation of the law is just beginning.

UN Environment (formerly the UN Environment Programme, UNEP) is the United Nations agency responsible for chemical safety. UN Environment has called for “a global commitment to the sound management of chemicals. The agency supports and tracks the progress of international agreements and treaties limiting the manufacture, environmental release and global transport of persistent pollutants, pesticides, hazardous waste, and mercury.” The Strategic

Approach to International Chemicals Management, a program supported by UN Environment, provides a platform for coordinating international control of toxic chemicals and hazardous waste across a broad range of stakeholders. UN Environment has worked closely with the World Health Organization to coordinate the removal lead from gasoline in countries around the world.

Synthetic Chemicals and Disease in Children

A large and growing body of evidence documents that toxic chemicals can cause disease, disability, and death in children. High-dose exposures can cause acute, clinically evident disease. Lower-dose exposures can cause subclinical injury—injury that is very real but detectable only through special testing—such as decreases in intelligence, shortening of attention span, reductions in fertility, and slowing of lung growth. When exposure to a neurotoxic pollutant is widespread, the resulting widespread subclinical neurotoxicity can reduce the intelligence, creativity, and economic productivity of entire societies (Fig. 737.1).

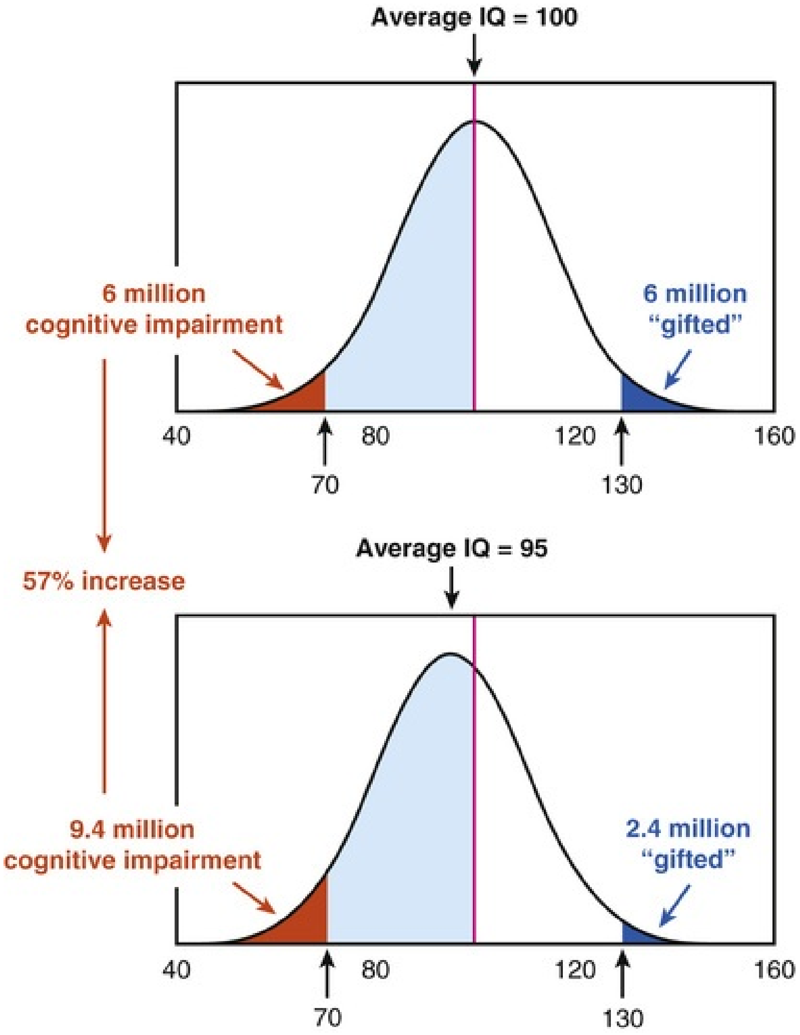

FIG. 737.1 Societal impact of subclinical neurotoxicity. Widespread exposure to a neurotoxic chemical pollutant that reduces average IQ by 5 points can reduce the number of children in a society with truly superior intelligence (IQ scores above 130 points) by more than 50% and likewise cause a more than 50% increase in the number with IQ scores below 70, thus increasing the number of children who do poorly in school, require special education and other remedial programs, and cannot contribute fully to society when they become adults. Although subclinical effects may be small at the individual level, the aggregate effects at a population level can have far-reaching consequences. And until the toxicity is recognized, the damage can proceed unchecked for many years. (From Schettler T, Stein J, Reich F, Valenti M: In harm's way: toxic threats to child development. A report by Greater Boston Physicians for Social Responsibility, 2000, p. 25. Available at: http://www.psr.org/chapters/boston/resources/in-harms-way.html .)

Exposures to toxic chemicals in early life are linked not only to increased risks of disease in childhood, but also to increased risks of disease in later life. This recognition, termed the "developmental origins of health and disease" concept, derives from studies conducted by Barker and colleagues who found that undernutrition in utero is associated decades later with increased risks for hypertension, obesity, diabetes, and cardiovascular disease. Epigenetic programming of gene expression during windows of vulnerability in early development appears to be the underlying mechanism. Increased risks for disease in adult life have now been associated also with early-life exposures to toxic chemicals and also appear to be mediated through epigenetic changes in gene expression. Among the health problems linked to toxic chemical exposures in early life are decreased cognition in adults who were exposed as children to lead, neurobehavioral disorders in children exposed to a range of developmental neurotoxicants, and cancer.

Chemical Pollutants of Major Concern

Air Pollutants

Air pollution—ambient air pollution and household air pollution—is the world's largest environmental threat to health, and according to the World Health Organization is responsible for an estimated 6.5 million deaths each year. The air pollutants of greatest concern for children's health are fine particulates, photochemical oxidants (especially ozone), oxides of nitrogen, sulfur oxides, and carbon monoxide.

Fuel combustion is the principal source of air pollution. In high- and middle-income countries, combustion of fossil fuels—coal, oil, and gas—accounts for most air pollution. In low- and lower-middle-income countries, the major source is burning of biomass: wood, dung, straw, and charcoal. Coal is the single most highly polluting fossil fuel and also the most important source of the greenhouse gas emissions that drive global climate change.

Elevated levels of ambient air pollutants are associated with respiratory problems in children, including decreased expiratory volume, wheezing, exacerbations of asthma, and slowed lung growth. Slowed lung growth leads to decreased lung volume and increases risk for respiratory disease in childhood, adolescence, and adult life.

The effects of household air pollution on children's health are magnified by the fact that many children spend 80–90% of their time indoors. The World Health Organization estimates that more than 2 million children < age 5 yr die each year from acute respiratory infections and that half of these deaths are attributable to indoor burning of biomass fuels. Second-hand tobacco smoke is an especially hazardous constituent of indoor air pollution and a powerful trigger for asthma (see Chapter 737.1). Allergens in indoor air can contribute to respiratory problems and include cockroach, mite, mold, and cat and dog allergens.

Long-term improvements in ambient air quality, especially reductions in levels of particulates and oxides of nitrogen, are associated with statistically and clinically significant improvements in lung growth in children, effects that appear likely to persist into adulthood and to reduce lifetime risk of pulmonary and cardiovascular disease.

Health Hazards of Unconventional Natural Gas Development (Fracking)

Unconventional natural gas development (UNGD) using high-volume horizontal hydraulic fracturing (fracking) has made possible the cost-effective extraction of natural gas from previously inaccessible underground shale deposits and has catalyzed a 30-fold expansion in natural gas production in the United States since 2000. In 2015, there were 17,000 natural gas wells in the United States, and gas has surpassed coal to become the major source of electricity generation in North America.

In fracking, large volumes of water containing a mix of chemicals (whose composition is a closely guarded secret) are injected at very high pressure through deep wells into shale deposits to break apart the rock and allow release of gas. The gas is brought up to the wellhead through return pipes, collected, and sent to market. In some areas, gas and oil occur together, and the gas may be burned off (flared) at the wellhead while the more valuable oil is piped to market.

The hazards of fracking to children's health are only beginning to be examined. They include:

◆ Toxic air pollution by volatile organic compounds released from fracking wells such as benzene, ethyl-benzene, hydrogen sulfide (H_2S), n-hexane, and methane. Benzene and ethyl-benzene are known human carcinogens; H_2S and n-hexane are neurotoxicants; and methane is a climate pollutant that contributes to greenhouse gas emissions.

◆ Traffic-related air pollution resulting from the large volumes of diesel truck traffic required 24/7 to bring piping, chemicals, and water to drilling operations. Diesel exhaust contains coarse and fine particulates, polycyclic aromatic hydrocarbons (PAHs), and formaldehyde, and has been classified by the International Agency for Research on Cancer as a known human carcinogen.

◆ Water pollution by toxic chemicals. Leaks of toxic materials into waterways occur commonly during fracking operations, and in addition, much of the water injected into the wells returns to the surface containing proprietary injected chemicals, along with high concentrations of salt dissolved from underground deposits and naturally occurring radioactive materials. These chemicals have been shown to contaminate both ground and surface waters. Water pollution is a particularly severe problem in arid regions with limited water supplies.

◆ Radon released from underground deposits. Radon has been shown to contaminate air near wellheads, and high concentrations of radon have been identified in shipped gas.

Additional, nonchemical hazards of fracking include incessant noise, high risk of vehicular injury to children from fast-moving heavy trucks on poorly maintained rural roads, societal disruption in rural communities, and extensive degradation of the environment.

Lead

See Chapter 739 .

Mercury

See Chapter 738 .

Asbestos

Between 1947 and 1973, asbestos was sprayed as insulation on classroom walls and ceilings in approximately 10,000 schools in the United States. Subsequent deterioration of this asbestos has released asbestos fibers into the air. Asbestos is not a health hazard so long as it is intact, but once it becomes airborne, it can be inhaled by children to produce adverse health effects. Asbestos is a human carcinogen, and the two principal cancers caused by asbestos are lung cancer and mesothelioma. U.S. federal law requires that all schools be inspected periodically for asbestos and that the results be made public. Removal is required only when asbestos is visibly deteriorating or is within the reach of children. In most cases, placement of barriers (drywall walls or drop ceilings) provides appropriate protection.

Pesticides

Pesticides are a diverse group of chemicals used to control insects, weeds, fungi, and rodents. Approximately 600 pesticide chemicals are registered with the EPA for use in the United States. In 2007, the most recent year for which data are available, 877 million pounds of pesticides were applied in American agriculture. Additional large quantities are used in homes, schools, parks, lawns, gardens, and golf courses.

Children are at risk of exposure to pesticides in their homes and schools. Diet is another major route of exposure, because children are exposed to residual levels of multiple pesticides on fruit and vegetables, especially fruits and vegetables imported from countries where pesticide use is heavier than in the

United States. Children in rural areas can be exposed to pesticide drift from fields that have been sprayed. Children employed in agriculture or living in migrant farm camps are at risk of direct exposure to pesticides.

Children can be acutely overexposed to pesticides and clinically evident poisoning results. High-dose exposure to neurotoxic insecticides such as the **organophosphate** and **carbamate pesticides** can cause acute neurotoxicity. Both classes of pesticides act through inhibition of acetylcholinesterase and are responsible for the largest number of acute poisoning cases. Symptoms include meiosis (although not in all cases), excess salivation, abdominal cramping, vomiting, diarrhea, and muscle fasciculation. In severe cases, the child may experience loss of consciousness, cardiac arrhythmias, and death by respiratory arrest. The war gas sarin is an organophosphate. See Chapter 77 for treatment of poisoning from drugs, chemicals, and plants.

Pesticides can also cause a range of chronic toxic effects that include: polyneuropathy and central nervous system dysfunction (organophosphates); hormonal disruption and reproductive impairment (DDT, kepone, dibromochloropropane); cancer (aldrin, dieldrin, chlorophenoxy herbicides [2,4,5-T]); and pulmonary fibrosis (paraquat).

Prenatal exposure to the organophosphate pesticide chlorpyrifos at levels that produce no evident toxicity in pregnant women has been associated with neurodevelopmental disability in children with reduced cognitive function (lowered IQ), disordered executive function, and functional and anatomic changes in the brain discernible by functional magnetic resonance imaging (fMRI).

Two classes of pesticides of growing concern are synthetic herbicides and the neonicotinoid insecticides. Herbicides account for about 40% of total pesticide use, and their application is increasing sharply. A major use of herbicides is in production of genetically modified (GM) food crops, mainly corn and soybeans that are engineered to be tolerant to **glyphosate (Roundup)** , the most used herbicide worldwide. Herbicides can be sprayed on herbicide-resistant crops throughout the growing season, and glyphosate-resistant, “Roundup-Ready,” genetically modified crops now account for more than 90% of all corn and soybeans planted in the United States. Glyphosate use has increased by more than 250-fold in the past 40 yr—from 0.4 million kg in 1974 to 113 million kg in 2014.

Studies of agricultural workers exposed occupationally to glyphosate and other herbicides have found evidence for increased incidence of non-Hodgkin lymphoma. On the basis of these studies and convergent results from toxicologic studies, the International Agency for Research on Cancer has determined that glyphosate is a “probable human carcinogen.” Measurable levels of glyphosate metabolites are detected in the urine of more than 90% of Americans.

The **neonicotinoids** are a novel class of neurotoxic pesticides developed in the 1980s to replace the organophosphates and carbamates. Use of neonicotinoids has risen dramatically in the past decade, and the neonicotinoid insecticide, Imidacloprid, is now the most widely used insecticide in the world. Agricultural use of neonicotinoids in the United States in 2014 was nearly 8 million pounds. Neonicotinoids target nicotinic acetylcholine receptors (nAChRs) in the insect nervous system, acting as potent agonists of these receptors and impairing neural transmission. A growing body of evidence indicates that neonicotinoids are toxic to bees and other pollinators at concentrations found currently in agricultural areas, and neonicotinoids are suspected of contributing to bee colony collapse disorder. Several European countries have banned or severely restricted neonicotinoid use. Almost no information is available on the possible developmental or pediatric toxicity of the neonicotinoids.

Children's exposures to pesticides can be reduced by minimizing applications to lawns, gardens, schools, and playgrounds; adapting techniques of integrated pest management; and reducing pesticide applications to food crops. *Consumption of organic produce has been shown to dramatically reduce organophosphate pesticide exposure in school-age children.*

Polychlorinated Biphenyls, DDT, Dioxins, Brominated Flame Retardants, and Other Halogenated Hydrocarbons

The chlorinated hydrocarbons are a large and diverse class of chemicals that include insecticides (DDT), plastics (polyvinyl chloride), electrical insulators (PCBs), and solvents (trichloroethylene). Highly toxic chlorinated dioxins and furans are formed during synthesis of chlorinated herbicides or as by-products of plastic combustion. All of these materials are widely dispersed and highly persistent in the environment. Dioxins and furans are known human carcinogens. Brominated flame retardants are used in carpets, furniture, and computers. They too are environmentally persistent.

The embryo, fetus, and young child are at particularly high risk of injury from halogenated hydrocarbons. All of these compounds are lipid-soluble. They readily cross the placenta, and they accumulate in breast milk. Intrauterine exposure to PCBs and brominated flame retardants has been linked to persistent neurobehavioral dysfunction in children manifested by cognitive impairment (reduced IQ), shortening of attention span, and behavioral disorders.

Consumption of fish from contaminated waters is a major source of children's exposure to PCBs. Children can be exposed in utero or through breast milk. To protect children and pregnant women against PCBs in fish, government agencies have issued advisories concerning fish consumption for certain lakes and rivers. Combustion of medical wastes containing polyvinyl chloride and the use of chlorine to bleach paper products are major preventable sources of environmental dioxin emissions and should be discouraged. Older fluorescent light ballasts that were installed decades ago in schools in the United States are another source of PCB exposure. PCB-containing ballasts should be removed from schools as soon as possible to prevent environmental contamination. Removal must be performed by trained workers.

Endocrine Disruptors

Endocrine disruptors are synthetic chemicals that mimic, block, or alter the actions of normal hormones such as estrogen, testosterone, growth hormone, insulin, and thyroid hormone. Synthetic endocrine disruptors are manufactured in volumes of millions of pounds per year. They include phthalates, bisphenol A, perchlorate, certain pesticides, brominated flame retardants, certain metals, and dioxins. These chemicals are widespread today in consumer products such as soaps, shampoos, perfumes, and plastics. They are widely disseminated in the environment and encountered in air, food, and drinking water.

Exposures to endocrine disruptors in early human development are especially hazardous. Even extremely low-dose exposures during critical early periods can lead to lasting impairments in organ function and to increased risk of disease.

Reproductive effects are one consequence of early life exposures to endocrine disruptors. Endocrine disruption is implicated in the epidemiologic observations of a trend toward earlier thelarche and menarche in girls (see Chapter 26), with rising rates of testicular cancer and hypospadias, and with diminishing sperm counts. Among the most clearly documented reproductive effects of early life exposures to endocrine disruptors are **adenocarcinoma** of the vagina in women and **cryptorchidism** in men whose mothers took DES. Another well-documented effect is shortening of the anogenital distance, a measure of in utero feminization, in baby boys whose mothers had elevated exposures to phthalates during pregnancy.

Early life exposures to endocrine disruptors can have adverse effects on brain development. Prenatal exposure to low-molecular-weight phthalates is associated with shortening of attention span in children 4-9 yr old, as well as with increased risk for autistic behaviors. Prenatal exposure to Bisphenol A has also been linked to behavioral anomalies.

Endocrine disruptors have been reported to have adverse impacts on lipid metabolism and to increase risk for obesity. Higher urinary levels of bisphenol A are associated with obesity-related outcomes, such as cardiovascular disease, in a cross-sectional analysis of National Health and Nutrition Examination Survey 2003-2004 data in adults.

Early life exposures to endocrine disruptors, most notably DDT, are linked with increased risk for cancer. A long-term epidemiologic study of women in California found that those who were exposed in utero to high levels of DDT have increased risk for breast cancer in adult life 40-50 yr later.

Environmental Carcinogens

Leukemia and brain cancer, the two most common forms of pediatric malignancy in the United States, both increased in incidence in the 50-yr period from 1972 to 2012, despite declining mortality. The cumulative increase in incidence for childhood leukemia was more than 20%, and for brain and CNS cancer more than 40%. In the same time period, testicular cancer in young men, ages 15-30 yr, more than doubled in incidence and is occurring at younger ages. These increases are too rapid to be of genetic origin and are not likely due to better diagnoses. They are most probably the result of still undefined exposures in the environment. Cancer is now the second-leading cause of death in American children, surpassed only by injuries

Children may be exposed to carcinogenic pollutants in utero or after birth. Children appear more sensitive than adults to certain chemical carcinogens and also to ionizing radiation (see Chapter 736). The potential for chemical carcinogenesis in utero was initially recognized with the discovery that clear cell adenocarcinoma of the vagina could develop in young women who were exposed in utero to DES.

Carcinogenesis may be associated with exposures in the home and community. Children of asbestos workers and children who have grown up near asbestos plants have been found to have an elevated incidence of mesothelioma. Children who attended elementary school in communities containing synthetic rubber plants have been shown to be at increased risk of leukemia as a result of their exposure to 1,3-butadiene, a known human carcinogen and a major component of synthetic rubber. Children who grow up on farms have elevated rates of leukemia; pesticides are suspected of playing an etiologic role. Intrauterine exposure to trichloroethylene via contaminated drinking water has been associated with an increased incidence of leukemia among girls living near an industrial facility and industrial waste site.

Routes of Exposure

Transplacental.

Heavy metals such as lead and mercury, fat-soluble compounds such as PCBs and DDT, and endocrine disruptors such as phthalates, readily cross the placenta. They may have serious and irreversible toxic effects on the developing nervous, endocrine, and reproductive organs, even at very low levels.

Water.

Approximately 200 chemicals have been detected at various levels in water supplies. Lead is an especially common contaminant. Water supplies are generally lead-free at source, but can become contaminated by lead that dissolves from lead pipes and from lead-containing plumbing fixtures. Lead is especially likely to dissolve from pipes and plumbing when the water is acidic, as happened in Flint, Michigan, in 2014. The highest levels of lead occur in water that has been standing in lead pipes overnight. It is wise therefore to run water for 2-3 min each morning before making up infant formula. Solvents and components of gasoline such as methyl tertiary-butyl ether and benzene are commonly encountered in groundwater. Chemical contaminants from gas drilling can contaminate water in areas where fracking is taking place. Herbicides, such as glyphosate and atrazine, are commonly found contaminants in drinking water in agricultural areas.

Air.

Vehicular emissions are the major source of urban air pollution. Diesel exhaust is a human carcinogen. Coal-fired power plants are another major source. In rural areas, wood smoke can contribute to air pollution. Children living in the vicinity of smelters and chemical production plants can be exposed to toxic industrial emissions such as lead, benzene, and 1,3-butadiene.

Food.

Many chemicals are intentionally added to food to improve appearance, taste, texture, or preservation, but many such chemicals have been poorly tested for potential toxicity. Residues of many pesticides are found in both raw and processed foods. Levels of pesticides are lower in organic produce than in conventionally grown fruits and vegetables. Children who consume organic produce have substantially lower urinary pesticide levels than children who eat conventional produce.

Work Clothes.

Illnesses in children sometimes may be traced to contaminated dust from parents' work clothes; toxicity from lead, beryllium, dioxin, organophosphate pesticides, and asbestos has occurred. Such exposure (termed "fouling the nest") can be prevented by providing facilities at work for changing and showering.

School.

Children may be exposed in schools, kindergartens, and nurseries to lead paint, molds, asbestos, tobacco smoke, pesticides, and hazardous arts and crafts materials. Substantial opportunities for prevention exist in the school environment, and pediatricians are often consulted for advice.

Child Labor.

Four to 5 million children and adolescents in the United States work for pay, and child labor is widespread around the world. Working children are at high risk of physical trauma and injury. They also may be exposed to a wide range of toxic chemicals, including pesticides in agriculture and lawn work, asbestos in construction and building demolition, and benzene in pumping gasoline.

The Physician's Role

Pediatricians have time and again played key roles in the initial recognition of diseases caused by toxic chemicals. Every pediatrician needs to be an “alert clinician” ever open to the possibility of discovering new diseases in children caused by hazardous exposures in the environment. In considering the origins of noninfectious disease, pediatricians should ask about the home environment, parental occupation, unusual exposures, and neighborhood factories. An environmental cause is particularly likely when several unusual cases of disease or constellations of findings occur together. Any adolescent with a traumatic injury may have been injured at work.

The history is the single most important instrument for obtaining information on environmental exposures. Information about current and past exposures (including questions about work and travel to or residence in developing countries) should be sought routinely on every new patient and on every patient with illness of unclear causation through a few brief screening questions. Changes in patterns of exposure or new exposures may be especially important. If suspicious information is elicited, more detailed follow-up should be pursued. Referral to a state or local health department or to a Pediatric Environmental Health Specialty Unit may be indicated (https://www.pehsu.net/). Accurate diagnosis of an environmental cause of disease can lead to better care of sick children and prevention of disease in other children.

737.1

Tobacco

Judith A. Groner

Keywords

Second-hand smoke exposure
tobacco smoke
nicotine

Composition of Second-Hand Smoke and Toxicities

Cigarette smoking is the single most preventable cause of morbidity and mortality, contributing to over 438,000 annual deaths in the United States. The reason that people smoke is nicotine addiction. Along with active tobacco use, second-hand tobacco smoke (SHS) exposure is a very serious health hazard for both children and adults. SHS is a mixture of approximately 7,000 constituents and is made up of the mainstream smoke exhaled by the smoker and side-stream smoke expelled from the end of a lit tobacco product. At least 40 carcinogens have been identified in SHS, along with 250 constituents that are toxic to the central nervous system, immune system, heart, and liver.

SHS also contains particulate matter, which is an independent health hazard. Particulate matter is microscopic solid and liquid matter suspended in air, which can be inhaled and enter the circulation. The most studied of these include PAHs and the tobacco-specific nitrosamines, which are both carcinogenic. Most particulate matter in side-stream smoke is unfiltered by the smoker and is in the submicron (<1 μm diameter) range, meaning that it is classified as fine particulate matter. These are smaller than the particles in mainstream smoke and can penetrate deeper into the lungs, resulting in higher toxicity through oxidative stress and inflammation. Short- and long-term exposure to fine particulate matter contributes to the aggravation of asthma and other respiratory diseases, lung and other cancers, cardiovascular disease, and death. SHS can be detected in the indoor environment well after it has been generated. Research shows that about half the particulate matter from SHS is still airborne after 5 to 6 hr. Many constituents, such as nicotine and some polyaromatic hydrocarbons, exist in both the gaseous and the particulate phase of second-hand smoke. Classified as “semivolatile,” their ability to change form according to environmental conditions means that they remain detectable in the indoor environment for longer periods after active smoking has ceased.

SHS concentration in the indoor environment depends on the number of cigarettes smoked in a period, the volume of the room, the ventilation rate, and other processes that eliminate pollutants from the air. The Surgeon General Report (2006) stated that there are multiple mechanisms by which SHS causes injury to the respiratory tract. Injury to the cardiovascular system is due to endothelial cell dysfunction due to smoke exposure and its prothrombotic effects. There is no safe level of tobacco exposure.

Tobacco Use and Exposure Is A Health Risk Disparity

Tobacco use, and hence childhood exposure, is found disproportionately among the socially disadvantaged low-income populations, who can least afford tobacco and SHS-related illness and evidenced-based treatment for nicotine addiction. There has been a profound decrease in smoking rates among the middle and upper classes within the United States since the 1960s (83% decrease), but the rate of decrease is much less (39%) among the lower income groups. The smoking rate for the overall U.S. populations is approximately 17%, but it is as high as 43% among adults with a high school equivalency degree. Because of these disparities in smoking rates among adults, children born into low-income homes are more likely to be exposed to SHS. More than 40% of U.S. children aged 3-11 were exposed to tobacco smoke from 2011 to 2012, based on a biological marker of exposure, serum cotinine levels. Of special concern are children from low-income homes and African American children because they have the highest rates of biologically measured SHS exposure; for every decrease in family income ratio, serum cotinine levels increase by 1.18 ng/L among children. Having a parent who smokes has also been shown to be an independent risk factor for food insecurity in children.

Maternal Smoking During Pregnancy and Tobacco Smoke Exposure During Pregnancy

The effects of maternal smoking on the fetus are profound and can be divided into pregnancy-related and long-term effects. Fetal exposure is one of the most important modifiable risk behaviors for child and long-term health.

Pregnancy-related effects: Maternal smoking increases the risk of placenta-associated complications of pregnancy, with an increased rate of placental abruption and placenta previa among maternal smokers. Both active maternal smoking and second maternal tobacco smoke exposure have been shown to reduce birth weight, and to increase the risk of preterm birth. In utero tobacco exposure from either maternal active tobacco product use or maternal SHS exposure increases the rate of stillbirth. Smoking both during and after pregnancy is a risk factor for **sudden infant death syndrome (SIDS)** ; using the 2005-2009 data, the 2014 Report of the Surgeon General determined that tobacco smoking during pregnancy results in nearly 1,000 infant deaths per year, of 8% of all infant deaths and 17% of all SIDS deaths. These associations are modifiable by public policy. Several countries in Europe have shown decreased perinatal complications after comprehensive smoke-free laws; within the United States, pregnancy complications and SIDS are inversely related to tobacco taxation levels.

Long-term effects : Birth defects: Maternal smoking during pregnancy in early pregnancy is considered causal (Surgeon General Report 2014) for orofacial clefts.

Both active smoking during pregnancy and SHS exposure of the mother increases the child's later risk of being overweight. This finding may appear surprising due to the long known relationship between smoking during pregnancy and low birth weight. This relationship has been shown in multiple epidemiological studies and is robust to adjustment for potential confounders, such as parental BMI, breastfeeding, family diet, and lifestyle. A meta-analysis of seven relevant studies from 1990 to 2011 showed an adjusted OR of 1.47 (95% CI: 1.26-1.73) of being overweight.

Maternal smoking during pregnancy has been associated with both an increased risk of learning problems and neurobehavioral issues during childhood. The adverse effects of prenatal smoking on child neurodevelopment include poor language development and reduction in cognitive functioning. Prenatal exposure to smoking may also reduce the child's motor performance, mental development (measured by the Bayley Scales of Infant Development), IQ scores, and language development through age 3 yr. This exposure may also increase the risks of several child behavioral problems, including externalization of aggressive and hyperactive behavior, prolonged periods of verbal or physical aggression and socially undesirable behavior (conduct disorder) throughout childhood, and delinquency in later childhood. In one study, a dose-response relationship with increasing severity of poor school performance was related to the number of cigarettes the mother smoked during pregnancy. The 2014

Surgeon General report concluded that “the evidence is sufficient to infer that nicotine exposure during fetal development, a critical window for brain development, has lasting adverse consequences.”

Maternal Smoking During Pregnancy and Lung Development

Smoking during pregnancy is associated with poor lung growth and function in the offspring and with a greater risk for wheezing between ages 2 and 4. According to the Surgeon General Report (2014), there is sufficient evidence to consider this relationship to be causal.

Postnatal Second-Hand Smoke Exposure —Effects on the Child

Respiratory: Children exposed to SHS have a higher rate of asthma prevalence and greater asthma severity. The Surgeon General Report (2006) concluded that there is a causal relationship between parental smoking and cough, phlegm, wheezing, and breathlessness, along with asthma, among school-aged children. Children with SHS exposure have a weakened response to inhaled corticosteroids. Asthmatic children who are SHS-exposed are more likely to have an acute care visit, an overnight hospital stay, and a higher number of hospital admissions than asthmatic children with no exposure. The rate of hospital readmissions for asthma has been associated with the level of the child's saliva cotinine, a biomarker of smoke exposure, and this is true even at very low levels of exposure.

Tobacco smoke exposure is a cause of lower respiratory tract infection in children. Findings of the Surgeon General in 2006 were updated by a systemic review of parental and household smoking and risk of lower respiratory tract infections in infancy in 2011. The strongest relationship was for bronchiolitis, where the risk of any household smoke exposure was increased by an OR of 2.51 (95% CI 1.96-3.21) in the 1st 2 yr of life.

SHS exposure during childhood increases the rate of middle ear disease, including acute, recurrent otitis media and chronic middle ear effusion. The Surgeon General Report (2006) rated this evidence as sufficient to infer a causal relationship between parental smoking and middle ear disease in children.

Cardiovascular Effects. Tobacco smoke exposure during adulthood has been linked to an increased risk of cardiovascular disease. Increasing evidence links childhood exposure to findings of preclinical atherosclerosis. These include increased carotid intima-media thickness and decreased flow-mediated dilation, both indirect tests for preclinical changes leading to atherosclerosis during adulthood. Other findings have included increased inflammation as measured by C-reactive protein, abnormal lipid profiles, and higher blood pressure, and increased rates of metabolic syndrome among SHS-exposed children and youth.

Infection . Childhood exposure to SHS is related to increased rates of invasive meningococcal disease in children less than 5 yr old. SHS in the home doubled the risk of invasive meningococcal disease (OR 2.18, 95% CI 1.63-2.92, I^2 = 72%), with some evidence of a dose-response relationship. The strongest effect was seen in children under 5 yr, with SHS exposure more than doubling the rate of meningococcal disease (OR 2.48, 95% CI 1.51-4.09). This relationship was seen both with prenatal smoking (OR 2.93, 95% CI 1.52-5.66) and postnatal exposure (OR 2.26, 95% CI 1.54-3.31).

SHS exposure has also been shown to increase the severity of influenza among children hospitalized for the disease. Children with SHS exposure were 4.7 times more likely to be admitted to intensive care (95% CI 1.4-18.5) and had a 70% longer length of stay (95% CI 12–230%) than nonexposed children, after controlling for multiple potential confounding factors.

Healthcare utilization : Children and teens ages 3-19 who are SHS-exposed had higher healthcare utilization compared with nonexposed peers based on an analysis of NHANES data 2009-2012. Children with high SHS exposure based on serum cotinine were almost 3 times more likely to have an overnight hospital stay (95% CI 1.81-4.34), and two times as likely to have a higher number of total hospital admissions as children with no exposure (95% CI 1.46-287).

Special vulnerable pediatric populations: There is evidence that SHS exposure exacerbates disease processes among children with significant chronic health conditions. Children with sickle cell disease who are exposed to SHS have increased morbidity, specifically increased rates of Emergency Department visits and hospitalizations for vaso-occlusive crisis and acute chest syndrome. In addition, tobacco smoke exposure is also associated with pulmonary function abnormalities among children with sickle cell disease, independent of their baseline disease.

Children with cystic fibrosis (CF) are another vulnerable population in which SHS exposure presents an additive threat to overall health. Core health issues for this group of children include problems with growth, lung function, and pulmonary infections. SHS-exposed children with CF had decreased growth between 4 and 12 mo compared with non-SHS exposed infants. Furthermore, tobacco smoke exposure was associated with increased bronchodilator responsiveness and air trapping, and with increased methicillin-resistant Staphylococcus aureus and anaerobic growth on respiratory culture. Tobacco smoke exposure can be considered a modifiable risk factor for children with sickle cell disease and with CF.

Treatment for Second-Hand Tobacco Smoke Exposure

The best method to treat children's SHS exposure is to eliminate this exposure by helping parents quit smoking. Methods to reduce exposure such as “smoking outside” or wearing a “smoking jacket” have not been shown to eliminate biochemically confirmed SHS exposure. A meta-analysis of six controlled trials aimed specifically at SHS exposure reduction for children (not parental smoking cessation) showed some reduction in tobacco smoke pollution post intervention. However, all homes had significant tobacco-related air pollution at the end of the study period.

The pediatric office has long been considered an excellent venue for pediatricians to screen for parental smokers and children's SHS exposure and intervene with parents. The American Academy of Pediatrics recommends that “Pediatricians inquire about tobacco use and tobacco smoke exposure as part of health supervision visits and visits for diseases that may be caused or exacerbated by tobacco smoke exposure, address parent/caregiver tobacco dependence as part of pediatric health care, and implement systems to identify and offer counseling, treatment, treatment recommendations, and/or referral for tobacco-dependent parents.” The 5 A's method for delivering brief tobacco intervention was developed for the adult primary care office. The steps in this model include: (1) **Ask** (about the patient's tobacco use, (2) **Advise** the patient to quit smoking, (3) **Assess** the patient's willingness to quit, (4) **Assist** the patient with quitting by providing brief counseling, pharmacotherapy, or appropriate referrals, and (5) **Arrange** a follow-up visit. For pediatric offices, this model has been abbreviated to the Ask, Advise, Refer model. These steps are: (1) **Ask** if anyone in the home or who cares for the child smokes, (2) **Advise** the smoker to quit smoking, and (3) **Refer** the smoker to evidence-based cessation treatments, most often a telephone based Quitline or a Text to Quit service. Quitlines provide free population-based treatment to tobacco users and have been shown to increase the chances of quitting smoking compared with minimal intervention.

The Clinical Effort Against Secondhand Smoke Exposure (CEASE) is a program that trains pediatricians and their office staff to systematically provide cessation counseling and interventions to parents and other adults who smoke, while offering more assistance in quitting smoking than Ask/Advise/Refer. The CEASE model is Ask, Assist, Refer, and involves training pediatricians to provide smoking cessation pharmacotherapy to parents who wish to quit smoking. The CEASE module (found at https://www.ceasetobacco.org) includes tools to both change the pediatric healthcare office structure for identifying parents who smoke and facilitate pediatric healthcare providers/delivery of counseling, medications, and referral for tobacco treatment.

Despite the AAP recommendations for pediatricians to incorporate these methods into practice, a meta-analysis in 2016 of controlled trials in routine healthcare settings of child SHS exposure reduction did not show an intervention effect. However, three controlled trials of maternal postpartum smoking relapse prevention did demonstrate beneficial outcomes of the intervention.

Decreasing smoking initiation among youth will prevent the children of the future from SHS exposure.

Eighty percent of youth who are smokers persist in smoking in adulthood. Of those, half will die earlier than their nonsmoking peers. Ninety percent of smokers initiate use before 19 yr of age. By increasing the age of cigarette purchase to 21, a whole generation of smoking can be prevented. The Tobacco 21 movement was begun in 2005 in Needham, Massachusetts, by increasing the age of the purchase of tobacco to 21 yr of age. By 2010, the rate of youth smoking was approximately half (from 12.9 to 6.7%). Since then, many municipalities, including Chicago and New York City, and two states, California and Hawaii, have Tobacco 21 laws.

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CHAPTER 738

Heavy Metal Intoxication

Prashant V. Mahajan

Lead, mercury, arsenic, and cadmium, four of the World Health Organization's (WHO) “Ten chemicals of greatest public health concern,” are the heavy metals posing the greatest threats to humans. The most prevalent of these exposures is lead (see Chapter 739).

Heavy metal intoxication results in diverse multiorgan toxicity through widespread disruption of vital cellular functions. A meticulous history of environmental exposure may be necessary to correctly identify heavy metals as the source of the protean manifestations associated with such exposure. Arsenic exposure can occur from contaminated food or water; globally, more than 140 million people are estimated to be chronically exposed to drinking water containing high arsenic levels. Mercury exposure occurs primarily through food; fish is a major source of methyl mercury exposure.

Arsenic

Epidemiology

Arsenic is a metalloid that exists in four forms: elemental arsenic, arsine gas, inorganic arsenic salts (pentavalent arsenate form or trivalent arsenite form), and organic arsenic compounds. Toxic manifestations are higher in the more soluble and higher-valence compounds. **Arsine gas** is the most toxic form of arsenic. Mass poisonings from exposure to arsenic have occurred throughout history, including one in 1998 in Wakayama, Japan, in which 70 people were poisoned. Children may be poisoned after exposure to inorganic arsenic found in pesticides, herbicides, dyes, homeopathic medicines, and certain contaminated folk remedies from China, India, and Southeast Asia (see Chapter 78). Soil deposits contaminate artesian well water. Groundwater contamination with arsenic is a common problem in developing countries and has been reported to be a common well contaminant in Alaska, Maine, North Carolina, and areas in the western United States. Food products (e.g., rice, organic brown rice syrup, fruit juices) cooked in contaminated water may absorb arsenic, thus concentrating it in the food (Fig. 738.1). The WHO has set 10 µg/L as the upper limit of safety. In many parts of Asia and South America, this limit is frequently exceeded. Arsenic concentrations in a quarter of the wells in Bangladesh exceed 50 µg/L, and 35-77 million of the 125 million inhabitants of Bangladesh regularly consume arsenic-contaminated water. Occupational exposure may occur in industries involved in the manufacturing, mining, smelting, or refining of glass, pottery, electronic and semiconductor components, and lasers. Although arsenic is no longer produced in the United States, it is produced in many countries and is imported into the United States for industrial use. Organic arsenic compounds may be found in seafood, pesticides, and some veterinary pharmaceuticals. In contrast to mercury, the organic forms of arsenic found in seafood are nontoxic.

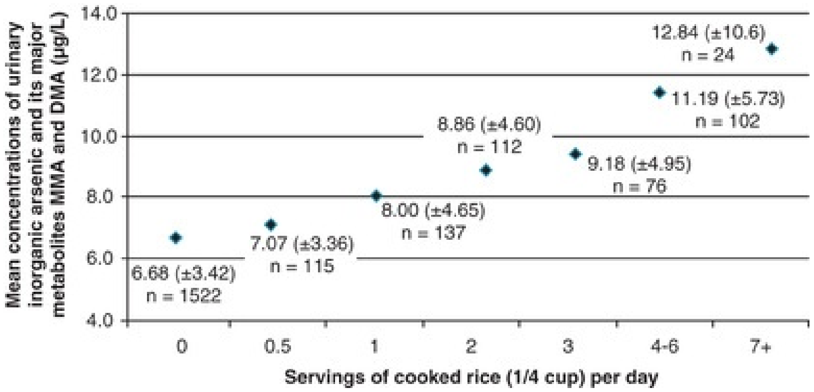

FIG. 738.1 Mean concentrations of urinary inorganic arsenic and its major metabolites monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) by categories of rice intake in children ages 6-17, National Health and Nutrition Examination Survey (NHANES) 2003-2008, excluding subjects with recent seafood consumption. (From Lai PY, Cottingham KL, Steinmaus C, et al: Arsenic and rice: translating research to address health care providers' needs. *J Pediatr* 167(4):797–803, 2015, Fig. 1, p. 799.)

Pharmacokinetics

Elemental arsenic is insoluble in water and bodily fluids, and thus is insignificantly absorbed and nontoxic. Inhaled arsine gas is rapidly absorbed through the lungs. The inorganic arsenic salts are well absorbed through the gastrointestinal tract, lungs, and skin. The organic arsenic compounds are well absorbed through the gastrointestinal tract. After acute exposure, arsenic initially is bound to the protein portion of hemoglobin in the red blood cells (RBCs) and rapidly distributed to all tissues. Inorganic arsenic is methylated and is eliminated predominantly by the kidneys, with approximately 95% excreted in the urine and 5% excreted in the bile. Most of the arsenic is eliminated in the first few days, with the remainder slowly excreted over a period of several weeks. Arsenic concentrates in hair, nails, and skin. Measurement of the distance of **Mees lines** (transverse white striae on the nail) from the nail bed can provide an estimate of time of exposure (nails grow at the rate of 0.4 mm/day).

Pathophysiology

After exposure to arsine gas, absorbed arsine enters RBCs and is oxidized to arsenic dihydride and elemental arsenic. Complexing of these derivatives with red cell sulfhydryl groups results in cell membrane instability and massive hemolysis. The inorganic arsenic salts poison enzymatic processes vital to cellular metabolism. Trivalent arsenic binds to sulfhydryl groups, resulting in decreased production of adenosine triphosphate through the inhibition of enzyme systems such as the pyruvate dehydrogenase and α-ketoglutarate complexes. Pentavalent arsenic may be biotransformed to trivalent arsenic or substituted for phosphate in the glycolytic pathway, resulting in uncoupling of oxidative phosphorylation.

Clinical Manifestations

Arsine gas is colorless, odorless, nonirritating, and highly toxic. Inhalation causes no immediate symptoms. After a latent period of 2-24 hr, exposed individuals experience massive hemolysis, malaise, headache, weakness, dyspnea, nausea, vomiting, abdominal pain, hepatomegaly, pallor, jaundice, hemoglobinuria, and renal failure (Table 738.1). Acute ingestion of arsenic produces gastrointestinal toxicity within minutes to hours and is manifested as nausea, vomiting, abdominal pain, and diarrhea. Hemorrhagic gastroenteritis with extensive fluid loss and third spacing may result in hypovolemic shock.

Cardiovascular toxicity includes QT interval prolongation, polymorphous ventricular tachycardia, congestive cardiomyopathy, pulmonary edema, and cardiogenic shock. Acute neurologic toxicity includes delirium, seizures, cerebral edema, encephalopathy, and coma. Lethal doses of arsenates are 5-50 mg/kg; lethal doses of arsenites are <5 mg/kg.

Table 738.1

Effects of Arsenic on Organ Systems

ORGAN SYSTEM	EFFECTS OF ARSENIC
Gastrointestinal system	Submucosal vesicles, watery or bloody diarrhea, severe hematemesis
Cardiovascular system	Reduced myocardial contractility, prolonged QT intervals, tachyarrhythmias
	Vasodilation, hypotension
Kidneys	Hematuria, proteinuria, acute tubular necrosis
Nervous system	Toxic encephalopathy with seizures, cerebral edema, and coma
	Chronic exposure: peripheral painful sensorimotor neuropathy
Hematologic and lymphatic system	Anemia and thrombocytopenia; acute hemolysis with arsine gas
Liver	Fatty degeneration with central necrosis
Skin	Desquamation, alopecia, hyperkeratosis, nail changes
	Chronic exposure: hyperkeratosis, hyperpigmentation
Teratogenic	Neural tube defects in the fetus
Oncologic	Urologic cancer, other malignancies

Late sequelae include hematuria, proteinuria, and acute tubular necrosis. A delayed sensorimotor peripheral neuropathy may appear days to weeks after acute exposure, secondary to axonal degeneration. Neuropathy manifests as painful dysesthesias followed by diminished vibratory, pain, touch, and temperature sensation; decreased deep tendon reflexes; and in the most severe cases, an ascending paralysis with respiratory failure mimicking Guillain-Barré syndrome (see Chapter 634). Adult survivors of infant arsenic poisoning experience higher mortality from disorders of the nervous system compared with adults without such exposure.

Subacute toxicity is characterized by prolonged fatigue, malaise, weight loss, headache, chronic encephalopathy, peripheral sensorimotor neuropathy, leukopenia, anemia, thrombocytopenia, chronic cough, and gastroenteritis. Mees lines in the nails become apparent 1-2 mo after exposure in approximately 5% of patients. Dermatologic findings include alopecia, oral ulceration, peripheral edema, a pruritic macular rash, and desquamation.

Chronic arsenic toxicity causes significant morbidity in children resulting in skin lesions, lung disease, and defect in intellectual function. **Chronic exposure** to low levels of arsenic is usually from environmental or occupational sources.

Over the course of years, dermatologic lesions develop, including hyperpigmentation, hypopigmentation, hyperkeratoses (especially on the palms and soles), squamous and basal cell carcinomas, and **Bowen disease** (cutaneous squamous cell carcinoma in situ). Encephalopathy and peripheral neuropathy may be present. Hepatomegaly, hypersplenism, noncirrhotic portal fibrosis, and portal hypertension occur. **Blackfoot disease** is an obliterative arterial disease of the lower extremities associated with chronic arsenic exposure that has been described in Taiwan. Carcinogenicity of chronic arsenic exposure is reflected in increased rates of cancers of the skin, lung, liver, bladder, and kidney as well as of angiosarcomas. Arsenic is carcinogenic, possibly through epigenetic dysregulation. The effects of prenatal exposure to arsenic are uncertain but may include low birthweight.

Laboratory Findings

The diagnosis of arsenic intoxication is based on characteristic clinical findings, a history of exposure, and elevated urinary arsenic values, the last of which confirm the exposure. A spot urine arsenic level should be determined for symptomatic patients before chelation, although initially the result may be negative. Because urinary excretion of arsenic is intermittent, definitive diagnosis depends on a 24 hr urine collection. Concentrations greater than 50 µg/L in a 24 hr urine specimen are consistent with arsenic intoxication (Table 738.2). Urine specimens must be collected in metal-free containers. Ingestion of seafood containing nontoxic arsenobetaine and arsenocholine can cause elevations of urinary arsenic. Blood arsenic levels rarely are helpful because of their high variability and the rapid clearance of arsenic from the blood in acute poisonings. Elevated arsenic values in the hair or nails must be interpreted cautiously because of the possibility of external contamination. Abdominal radiographs may demonstrate ingested radiopaque arsenic.

Table 738.2

Acceptable and Toxic Levels of Arsenic and Mercury

	ARSENIC	MERCURY
Molecular weight	74.9 Da	200.59 Da
Acceptable blood level	<5 µg/L (<0.665 nmol/L)	<10 µg/L (<50 nmol/L)
Acceptable urine level	<50 µg/L (<6.65 nmol/L) 24 hr urine sample	<20 µg/L (<100 nmol/L)
Intervene at blood level		>35 µg/L (>175 nmol/L)

Intervene at urine level	>100 µg/L (>13.3 nmol/L) 24 hr urine sample	>150 µg/L (>750 nmol/L)

Later in the course of illness, a complete blood cell count may show anemia, thrombocytopenia, and leukocytosis, followed by leukopenia, karyorrhexis, and basophilic stippling of RBCs. The serum concentrations of creatinine, bilirubin, and transaminases may be elevated; urinalysis may show proteinuria, pyuria, and hematuria; and examination of the cerebrospinal fluid may show protein elevations.

Mercury

Epidemiology

Mercury exists in three forms: elemental mercury, inorganic mercury salts, and organic mercury (Table 738.3). **Elemental mercury** is present in thermometers, sphygmomanometers, barometers, batteries, gold or silver smelting processes, and some latex paints produced before 1991. Workers in industries producing these products may expose their children to the toxin when mercury is brought home on contaminated clothing. Vacuuming of carpets contaminated with mercury and breaking of mercury fluorescent light bulbs may result in elemental mercury vapor exposure. Severe inhalation poisonings have resulted from attempts to separate gold from gold ore by heating mercury and forming a gold-mercury amalgam. Elemental mercury has been used in folk remedies by Asian and Mexican populations for chronic stomach pain, by Latin Americans and Caribbean natives in occult practices, and as a skin-lightening agent. Dental amalgams containing elemental mercury release trace amounts of mercury. An expert panel for the National Institutes of Health concluded that existing scientific evidence does not indicate that dental amalgams pose a health risk and should not be replaced merely to decrease mercury exposure. A 2009 WHO expert panel concluded that a global near-term ban on amalgam would be problematic for public and dental health. However, this committee recommended that alternatives to amalgam should be sought as part of a phase-out of the use of mercury-containing amalgams.

Table 738.3

Differential Characteristics of Mercury Exposure

	ELEMENTAL	INORGANIC (SALT)	ORGANIC (ALKYL)

Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Kidney	CNS, kidney, liver
Clearance	Renal, GI	Renal, GI	Methyl: GI
			Aryl: renal, GI
CLINICAL EFFECTS			
CNS	Tremor	Tremor, erethism (irritability)	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+++	—	—
Gastrointestinal	+	+++ (caustic)	+
Renal	+	+++ (acute tubular necrosis)	+
Acrodynia	+	++	—
Therapy	BAL, DMSA	BAL, DMSA	DMSA (early)

BAL , British antilewisite; *CNS* , central nervous system; *DMSA* , 2,3-dimercaptosuccinic acid; *GI* , gastrointestinal; +, mild; ++, moderate; +++, severe.

From Sue YJ: Mercury (heavy metals). In Nelson LS, Lewin NA, Howland MA, et al, editors: *Goldfrank's toxicologic emergencies,* ed 9, New York, 2011, McGraw-Hill, Table 96.4, p 1330.

Inorganic mercury salts are found in pesticides, disinfectants, antiseptics, pigments, dry batteries, and explosives and as preservatives in some medicinal preparations. **Organic mercury** in the diet, especially fish containing methyl mercury, is a major source of mercury exposure among the general population. Industries that may produce mercury-containing effluents include chlorine and caustic soda production, mining and metallurgy, electroplating, chemical and textile manufacturing, paper and pharmaceutical manufacturing, and leather tanning. Mercury compounds in the environment are methylated to methyl mercury by soil and water microorganisms. Methyl mercury in the water rapidly accumulates in fish (swordfish, king mackerel, fresh tuna, tile fish, shark) and other aquatic organisms, which are in turn consumed by humans. To address concerns that maternal consumption of large quantities of fish during pregnancy may expose the fetus to concentrations of mercury with adverse consequences, the longitudinal Seychelles Child Development Study has been ongoing since the late 1980s. The first cohort of the study involved nearly 800 mother–child pairs, with subsequent cohorts enrolled. Despite a high maternal fish intake (mean of 12 fish meals per wk), follow-up of children at least through 9 yr of age has revealed no consistent adverse developmental effects. Well-known large outbreaks of methyl mercury intoxication include the incidents in Japan in the 1950s (**Minamata disease,** from consumption of contaminated seafood) and in Iraq in 1971 (from consumption of grain treated with a methyl mercury fungicide).

Thimerosal is a mercury-containing preservative used in some vaccines. Thimerosal contains 49.6% mercury by weight and is metabolized to ethyl mercury and thiosalicylate. During an ongoing review of biologic products in response to the U.S. Food and Drug Administration (FDA) Modernization Act of 1997, the FDA determined that infants who received thimerosal-containing vaccines at multiple visits might have been exposed to more mercury than recommended by federal guidelines. As a precautionary measure, the American Academy of Pediatrics, American Academy of Family Physicians, Advisory Committee on Immunization Practices, and U.S. Public Health Service issued a joint recommendation in 1999 that thimerosal be removed from vaccines as quickly as possible. *In the United States, thimerosal has been removed from all vaccines in the recommended childhood immunization schedule.* Infants and children who have received thimerosal-containing vaccines do not need to undergo blood, urine, or hair testing for mercury because the concentrations of mercury would be quite low and would not require treatment. The larger risks of not vaccinating children far outweigh any known risk of exposure to thimerosal-containing vaccines. Studies do *not* demonstrate a link between thimerosal-containing vaccines and autistic spectrum disorders (see Chapter 54), and no evidence supports a change in the standard of practice regarding administration of thimerosal-containing vaccines in areas of the world where they are used. A rise in blood mercury levels following a single dose of hepatitis vaccine was seen in preterm infants, but the clinical significance is unknown.

Pharmacokinetics

Inhaled elemental mercury vapor is 80% absorbed by the lungs and is distributed rapidly to the central nervous system because of its high lipid solubility. The elemental mercury is oxidized by catalase to the mercuric ion, which is the reactive form that causes cellular toxicity. Elemental mercury liquid is poorly absorbed from the gastrointestinal tract, with less than 0.1% being absorbed. The half-life of elemental mercury in the tissues is approximately 60 days, with most of the excretion occurring in the urine.

Inorganic mercury salts are approximately 10% absorbed from the gastrointestinal tract and cross the blood-brain barrier to a lesser extent than elemental mercury. Mercuric salts are more soluble than mercurous salts and therefore produce greater toxicity. Elimination occurs primarily in the urine, with a half-life of approximately 40 days.

Methyl mercury is the most avidly absorbed of the organic mercury compounds, with approximately 90% absorbed from the gastrointestinal tract. The lipophilic, short-chain alkyl structure of methyl mercury allows it to distribute rapidly across the blood-brain barrier and placenta. Methyl mercury is approximately 90% excreted in the bile, with the remainder being excreted in the urine. The half-life is 70 days.

Pathophysiology

After absorption, mercury is distributed to all tissues, particularly the central nervous system and kidneys. Mercury reacts with sulfhydryl, phosphoryl, carboxyl, and amide groups, resulting in disruption of enzymes, transport mechanisms, membranes, and structural proteins. Widespread cellular dysfunction or necrosis results in the multiorgan toxicity characteristic of mercury poisoning.

Clinical Manifestations

Five syndromes describe the clinical presentation of mercury poisoning. **Acute inhalation of elemental mercury vapor** results in rapid onset of cough, dyspnea, chest pain, fever, chills, headaches, and visual disturbances. Gastrointestinal findings include metallic taste, salivation, nausea, vomiting, and diarrhea. Depending on the severity of the exposure, the illness may be self-limited or may progress to necrotizing bronchiolitis, interstitial pneumonitis, pulmonary edema, and death from respiratory failure. Younger children are more susceptible to pulmonary toxicity. Survivors may demonstrate restrictive lung disease. Renal dysfunction and neurologic disturbances (ataxia, persistent weakness, emotional lability) may develop subacutely. Chronic exposure to volatilized elemental mercury in dental amalgams has not been found to be of any clinical significance.

Acute ingestion of inorganic mercury salts (typically secondary to ingestion of a button battery) can manifest in a few hours as corrosive gastroenteritis, signified by metallic taste, oropharyngeal burns, nausea, hematemesis, severe abdominal pain, hematochezia, acute tubular necrosis, cardiovascular collapse, and death.

Chronic inorganic mercury intoxication produces the **classic triad** consisting of tremor, neuropsychiatric disturbances, and gingivostomatitis. The syndrome may result from long-term exposure to elemental mercury, inorganic mercury salts, or certain organic mercury compounds, all of which may be metabolized to mercuric ions. The tremor starts as a fine intention tremor of the fingers that is abolished during sleep but that may later involve the face and progress to choreoathetosis and spasmodic ballismus. Mixed sensorimotor neuropathy and visual disturbances may also be present. The neuropsychiatric disturbances include emotional lability, delirium, headaches, memory loss, insomnia, anorexia, and fatigue. Renal dysfunction ranges from asymptomatic proteinuria to nephrotic syndrome.

Acrodynia , or **pink disease** , is a rare idiosyncratic hypersensitivity reaction to mercury that occurs predominantly in children exposed to mercurous powders. The symptom complex includes generalized pain, paresthesias, and an acral (hands, feet) rash that may spread to involve the face. The rash typically is red-pink, papular, pruritic, and painful; it may progress to desquamation and ulceration. Morbilliform, vesicular, and hemorrhagic variants have been described. Other important features include anorexia, apathy, photophobia, and hypotonia, especially of the pectoral and pelvic girdles. Irritability, tremors, diaphoresis, insomnia, hypertension, and tachycardia may be present. Some cases initially were diagnosed as pheochromocytoma. The outcome is good after removal of the source of mercury exposure.

Methyl mercury intoxication (also known as **Minamata disease** after the widespread mercury poisoning that occurred at Minamata Bay in Japan in people who had ingested contaminated fish) manifests as delayed neurotoxicity that appears after a latent period of weeks to months. It is characterized by ataxia; dysarthria; paresthesias; tremors; movement disorders; impairment of vision, hearing, smell, and taste; memory loss; progressive dementia; and death. Infants exposed in utero are the most severely affected, with low birthweight, microcephaly, profound developmental delay, cerebral palsy, deafness, blindness, and seizures. Although there is significant residual morbidity from methyl mercury neurotoxicity, observations on long-term follow-up of children exposed in Iraq reveal complete or partial resolution in most cases.

Laboratory Findings

The diagnosis of mercury intoxication is based on characteristic clinical findings, a history of exposure, and elevation of whole blood or urine mercury values, the last of which confirms the exposure. Thin-layer and gas chromatographic techniques can be used to distinguish organic from inorganic mercury. Blood should be collected in special tubes for trace elements from laboratories that capably perform those tests. Levels <10 µg/L in whole blood and <20 µg/L in a 24 hr urine specimen are considered normal (see Table 738.2). Although blood mercury levels may reflect acute exposure, they decrease as mercury redistributes into the tissues. Urine mercury levels are most useful for identifying long-term exposures, except in the case of methyl mercury, which undergoes minimal urinary excretion. Urinary mercury levels are used in monitoring efficacy of chelation therapy, whereas blood levels are used primarily in monitoring organic mercury poisonings. Hair analysis for mercury is not reliable because hair reflects both endogenous and exogenous mercury exposure (hair avidly binds mercury from the environment). Abdominal radiographs may demonstrate ingested radiopaque mercury.

Urinary markers of early nephrotoxicity include microalbuminuria, retinol-binding protein, β_2 -microglobulin, and *N* -acetyl-β-D -glucosaminidase. Early neurotoxicity may be detected with neuropsychiatric testing and nerve conduction studies, whereas severe central nervous system toxicity is apparent on CT or MRI.

Treatment of Arsenic and Mercury Intoxication

The principles of management for arsenic and mercury intoxication include prompt removal from the source of poisoning, aggressive stabilization and supportive care, decontamination, and chelation therapy when appropriate. Once the diagnosis is suspected, the local poison control facility should be contacted, and care coordinated with physicians who are familiar with the management of heavy metal poisoning.

Supportive care for patients exposed to arsine gas requires close monitoring for signs of hemolysis, including evaluation of the peripheral blood smear and urinalysis. Transfusion of packed RBCs may be necessary, as may administration of intravenous fluids, sodium bicarbonate, and mannitol to prevent renal failure secondary to the deposition of hemoglobin in the kidneys. After inhalation of elemental mercury vapor, patients require careful monitoring of respiratory status, which may include pulse oximetry, arterial blood gas analysis, and chest radiography. Supportive care involves administration of supplemental oxygen and, in severe cases, intubation and mechanical ventilation.

Acute ingestion of inorganic arsenic and mercury salts results in hemorrhagic gastroenteritis, cardiovascular collapse, and multiorgan dysfunction. Fluid resuscitation, pressor agents, and transfusion of blood products may be required for management of cardiovascular instability. Severe respiratory distress, coma with loss of airway reflexes, intractable seizures, and respiratory paralysis are indications for intubation and mechanical ventilation. Renal function must be monitored carefully for signs of renal failure and the need for hemodialysis.

Gastrointestinal decontamination after ingestion of the inorganic arsenic and mercury salts has not been well studied. Because of the corrosive effects of these compounds, induced emesis is not recommended, and endoscopy may be considered before gastric lavage. Arsenic and mercury are not well adsorbed to activated charcoal, but its use may be helpful if coingestants are suspected. Whole-bowel irrigation is used to remove any radiopaque material remaining in the gastrointestinal tract.

Chelation for acute arsenic and mercury poisoning is most effective when administered as soon as possible after the exposure. Chelation should be continued until 24 hr urinary arsenic or mercury levels return to normal (<50 µg/L for arsenic and <20 µg/L for mercury), the patient is symptom-free, or the remaining toxic effects are believed to be irreversible. The efficacy of chelation in long-term exposures is reduced because heavy metal in the tissue compartment is relatively nonexchangeable and some degree of irreversible toxicity has already occurred.

Dimercaprol , also known as *2,3-dimercaptopropanol* or *British antilewisite (BAL)* , is the chelator of choice for a patient who cannot tolerate oral therapy, as often is true for critically ill patients and after ingestion of the corrosive inorganic arsenic and mercury salts. BAL is available suspended in peanut oil and benzyl benzoate in 3 mL ampules at a concentration of 100 mg/mL for deep intramuscular (IM) injection. For **arsenic poisoning** , the recommended regimen of BAL is 2.5 mg/kg IM q6h for the 1st 2 days, 2.5 mg/kg IM q12h on the 3rd day, and then 2.5 mg/kg/day IM for 10 days. For severe arsenic poisoning, the dose of BAL is increased to 3 mg/kg IM q4h for 2 days, 3 mg/kg IM q6h on day 3, and then 3 mg/kg IM q12h for 10 days. The dose of BAL for **inorganic mercury poisoning** is 5 mg/kg IM on the 1st day, and then 2.5 mg/kg IM q12-24h for 10 days. The BAL–heavy metal complex is excreted in the urine and bile. A period of 5 days between courses of chelation is recommended. Adverse effects of BAL include pain at the injection site, hypertension, tachycardia, diaphoresis, nausea, vomiting, abdominal pain, a burning sensation in the oropharynx, and a feeling of constriction in the chest. BAL may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient individuals. It is important to note that BAL is contraindicated for chelation of methyl mercury because BAL redistributes methyl mercury to the brain from other tissue sites, resulting in increased neurotoxicity.

D -Penicillamine is an orally administered chelator that can be considered for less-severe mercury poisoning or as an adjunct to BAL therapy in arsenic poisoning, but its use is largely restricted because of the potential for significant leukopenia, thrombocytopenia, and proteinuria. A newer investigational analog, *N* -acetyl-D ,L -penicillamine, is used with variable success in mercury poisoning.

Oral chelating agents are used to replace the painful BAL injections when the patient is stable enough to tolerate oral therapy and prolonged chelation is necessary. **Succimer** , also known as *2,3-dimercaptosuccinic acid* (DMSA), is an orally administered water-soluble derivative of BAL. DMSA is available in 100 mg capsules. The recommended regimen of DMSA is 10 mg/kg orally every 8 hr for 5 days. The DMSA–heavy metal complex is excreted in the urine and bile. A period of 2 wk between courses of chelation is recommended. Mild adverse effects include nausea, vomiting, diarrhea, loss of appetite, and transient elevations in liver enzyme levels. DMSA also may cause hemolysis in glucose-6-phosphate dehydrogenase–deficient patients. Patients with ingestion of elemental mercury require no follow-up unless there is an underlying disease that decreases the gastrointestinal transit time. Serial abdominal radiographs to document the progression of the metal are recommended. Acute inhalation of mercury fumes and ingestion of inorganic mercury require hospitalization to monitor the respiratory and gastrointestinal status, respectively. Therapeutic abortion may be considered in pregnant patients, because of the teratogenic effect of mercury.

Strategies to reduce arsenic exposure in rice are noted in Table 738.4 .

Table 738.4

Potential Strategies for Reducing Exposure of Arsenic in Rice

1. Diversify the diet

  - Eat a well-balanced diet and a variety of grains [†, ‡, §]
  - Identify children at risk for high consumption of rice and rice products (e.g., gluten-free diets, highly allergic)

2. Consider alternatives to rice for first food
  - Start infants on barley, oats, or other grains [†, ‡]
  - If rice cereal must be used for infants, limit to 1 serving per day [§]

3. Adopt strategies that help minimize exposure
  - Rinse rice in a colander prior to cooking [§]
  - Cook rice like pasta, with plenty of extra water [§]
  - Choose lower-arsenic varieties of rice (e.g., basmati) [§]
  - Avoid or limit use of rice milk or other rice beverages for infants [‡] and children under 5 yr old [§, ¶]
  - Read labels of processed foods: choose alternatives to foods sweetened with brown rice syrup or thickened with rice products

4. Regulatory action
  - Federal agencies should establish regulatory limits for arsenic content in rice and rice products [§]

[†] FDA.

[‡] AAP.

[§] Consumer Reports.

[¶] United Kingdom Food Standard Agency.

From Lai PY, Cottingham KL, Steinmaus C, et al: Arsenic and rice: translating research to address health care providers' needs. *J Pediatr* 167(4):797–803, 2015, Table, p. 801.

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CHAPTER 739

Lead Poisoning

Morri Markowitz

Lead is a metal that exists in four isotopic forms. Clinically it is purely a toxicant; no organism has an essential function that is lead dependent. Chemically its low melting point and ability to form stable compounds have made it useful in the manufacture of hundreds of products; this commercial attractiveness has resulted in the processing of millions of tons of lead ore, leading to widespread dissemination of lead in the human environment.

The blood lead level (BLL) is the gold standard for determining health effects. The threshold level at which lead begins to cause biochemical, subclinical, or clinical disturbance remains to be determined. In 2012, the Centers for Disease Control and Prevention (CDC) designated 5 µg/dL as the *“reference value based on the 97.5th percentile of the population of US children aged 1-5 years.”* In other words, it is the BLL that identifies the 2.5% of children with the highest BLLs as of 2012. As a measure of the distribution of BLLs in young American children rather than a toxicity threshold, this number will change in a manner dependent on the epidemiology of BLLs. Surveillance by the CDC has shown that the prevalence of elevated BLLs has declined markedly. Approximately 100,000 children ages 1-5 yr currently have BLLs ≥5 µg/dL. Fortunately, children with levels high enough to be life-threatening (>100 µg/dL) are rarely seen in the United States. Although stated as a reference value, it is likely that clinicians and departments of health will consider this a threshold for action.

Public Health History

In the late 1970s, nearly all preschool-age children in the United States had BLLs above the current reference value of 5 µg/dL. Over the next 25 yr, government regulations resulted in the significant reduction of three main contributors to lead exposure by means of (1) the elimination of the use of tetraethyl lead as a gasoline additive, (2) the banning of lead-containing solder to seal food- and beverage-containing cans, and (3) the application of a federal rule that limited the amount of lead allowed in paint intended for household use to less than 0.06% by weight (further reduced by the Consumer Product Safety Commission to 0.009% in 2008). Factors that indicate increased risk of lead poisoning, in addition to preschool age, include low socioeconomic status; living in older housing, built primarily before 1960; urban location; and African American race. Another high-risk group that has been identified consists of recent immigrants from less wealthy countries, including adoptees.

Progress is also being made globally. In Mexico, the introduction of unleaded gasoline in 1990 was associated with a decline in BLLs among 1st-grade students, from 17 µg/dL in 1990 to 6.2 µg/dL in 1997. As of 2014, only 6 countries continue to use leaded gasoline (Afghanistan, Algeria, Iraq, North Korea, Myanmar, and Yemen), and these are expected to phase out its use. In Malta, after the import of red lead paint was banned and the use of lead-treated wood for fuel in bakeries was prohibited, mean BLLs of pregnant women and newborns decreased by 45%. After it was documented that children living in the neighborhood of a battery factory in Nicaragua had a mean BLL of 17.2 µg/dL, whereas children in the control community had a mean BLL of 7.4 µg/dL, the factory was closed. Despite these advances, the World Health Organization estimates that nearly a quarter billion people have BLLs above 5 µg/dL; of those that are children, 90% live in developing countries, where, in some regions, BLLs may be 10-20–fold higher than in developed countries.

Unfortunately, lead-related disasters continue to occur. When the water source for Flint, Michigan, was changed (2014) to the Flint River and utilized a water treatment plant with poor corrosion control, the lead level of Flint tap water increased, as did the BLL of children <5 yr of age. The risk of a BLL ≥ 5 µg/dL after the water source switched was significantly highest during the summer and fall seasons for children 1-2 yr of age. Subsequently, other cities are evaluating the lead content of their drinking water.

In 2010, the CDC identified numerous lead-contaminated villages in northern Nigeria. The grinding of ore to extract gold caused widespread leaded dust dissemination. It is likely that hundreds of children died because of this activity, and all remaining children in the villages initially assessed at that time were lead poisoned, with 97% having a BLL ≥45 µg/dL.

Sources of Exposure

Lead poisoning may occur in utero because lead readily crosses the placenta from maternal blood. The spectrum of toxicity is similar to that experienced by children after birth. The source of maternal blood lead content is either redistribution from endogenous stores (i.e., the mother's skeleton) or lead newly acquired from ongoing environmental exposure.

Several hundred products contain lead, including batteries, cable sheathing, cosmetics, mineral supplements, plastics, toys (Table 739.1), and traditional medicines (Table 739.2). Major sources of exposure vary among and within countries; the major source of exposure in the United States remains old lead-based paint. Approximately 37 million homes, mainly built before 1950, have lead-based paint (2011 estimate). As paint deteriorates, it chalks, flakes, and turns to dust. Improper rehabilitation work of painted surfaces (e.g., sanding) can result in dissemination of lead-containing dust throughout a home. The dust can coat all surfaces, including children's hands. All of these forms of lead can be ingested. If heat is used to strip paint, then lead vapor concentrations in the room can reach levels sufficient to cause lead poisoning via inhalation. More recently, there is an increased awareness that tap water in both homes and schools may have substantial amounts of lead. This arose from the discovery in 2015 of contaminated water in Flint, Michigan, originating in corroding pipes that resulted in elevated BLLs in Flint children. Moreover, this occurrence raised questions about the safety of the EPA lead in water standard of 15 ppb (µg of Pb/liter of water) that water distribution companies must meet in at least 90% of homes in their service areas. This standard was not based on achieving health safety but rather on what the water companies felt was financially feasible. It is under review at the EPA.

Table 739.1

Sources of Lead

Paint chips
Dust
Soil
Parent's or older child's occupational exposure (auto repair, smelting, construction, remodeling, plumbing, gun/bullet exposure, painting, e-scrap)

Glazed ceramics
Herbal remedies (e.g., Ayurvedic medications)
Home remedies, including antiperspirants, deodorants (litargirio)
Jewelry (toys or parents')
Stored battery casings (or living near a battery smelter)
Lead-based gasoline
Moonshine alcohol
Mexican candies; Ecuadorian chocolates
Indoor firing ranges
Retained bullet fragments
Imported spices (*svanuri marili, zafron, kuzhambu*)
Lead-based cosmetics (kohl, surma)
Lead plumbing (water)
Imported foods in lead-containing cans
Imported toys
Home renovations
Antique toys or furniture

Table 739.2

Cases of Lead Encephalopathy Associated With Traditional Medicines by Type of Medication

TRADITIONAL MEDICAL SYSTEM	CASES OF LEAD ENCEPHALOPATHY N (%)	N (%) PEDIATRIC CASES WITHIN CAM SYSTEM OR MEDICATION
Ayurveda	5 (7)	1 (20)
Ghasard	1 (1)	1 (100)
Traditional Middle Eastern practices	66 (87)	66 (100)
Azarcon and Greta	2 (3)	2 (100)
Traditional Chinese medicine	2 (3)	2 (100)
Total	76 (100)	72 (95)

CAM , Complementary and alternative medicines.

From Karri SK, Saper RB, Kales SN: Lead encephalopathy due to traditional medicines. *Curr Drug Saf* 3:54–59, 2008.

Metabolism

The nonnutritive hand-to-mouth activity of young children is the most common pathway for lead to enter the body. In most cases, lead is ingested, either as a component of dust licked off of surfaces or in swallowed paint chips, through water contaminated by its flow through lead pipes or brass fixtures, or from contaminated foods or liquids. Cutaneous contamination with inorganic lead compounds, such as those found in pigments, does not result in a substantial amount of absorption. Organic lead compounds, such as tetraethyl lead, may penetrate through skin, however.

The percentage of lead absorbed from the gut depends on several factors: particle size, pH, other material in the gut, and nutritional status of essential elements. Large paint chips are difficult to digest and are mainly excreted; this chemical characteristic of lead compounds is fortunate, as a single chip may contain a potentially lethal dose of lead. Fine dust can be dissolved more readily, especially in an acid medium. Lead eaten on an empty stomach is better absorbed than that taken with a meal. The presence of calcium and iron may decrease lead absorption by direct competition for binding sites; iron (and probably calcium) deficiency results in enhanced lead absorption, retention, and toxicity.

After absorption, lead is disseminated throughout the body via blood. It circulates bound to erythrocytes; approximately 97% in blood is bound on or in the red blood cells. The plasma fraction is too small to be measured by conventional techniques employing atomic absorption spectroscopy or anodic stripping voltammetry; it is presumably the plasma portion that may enter cells and induce toxicity. Thus clinical laboratories report the BLL, not the serum or plasma lead level. The increasing availability and decreasing cost of inductively coupled plasma mass spectrometry, which is capable of measuring lead in ng/dL quantities, may eventually result in clinical availability of tools to measure plasma lead.

Most retained lead accumulates in bone, where it resides for years. But in all cells, lead has multiple effects. It binds to enzymes, particularly those with available sulfhydryl groups, changing the contour and diminishing function. For example, 3 of the 8 enzymes in the ubiquitously distributed heme pathway are susceptible to lead inhibitory effects. The accumulation of excess amounts of heme precursors also is toxic. The last enzyme in this pathway, ferrochelatase, enables protoporphyrin to chelate iron, thus forming heme. Erythrocyte protoporphyrin (EP) levels higher than 35 µg/dL (laboratory dependent) are abnormal and are consistent with lead poisoning, iron deficiency, or recent inflammatory disease. Measurement of the EP level is thus a useful tool for monitoring biochemical lead toxicity. EP levels begin to rise several weeks after BLLs have reached 20 µg/dL in a susceptible portion of the population and are elevated in nearly all children with BLLs higher than 50 µg/dL. A drop in EP levels also lags behind a decline in BLLs by several weeks because it depends on both cell turnover and cessation of further overproduction by marrow red blood cell precursors. The test can be ordered either as the free EP or the zinc protoporphyrin. The latter is generally not corrected for hematocrit.

A second mechanism of lead toxicity works via its competition with calcium. Many calcium-binding proteins have a higher affinity for lead than for calcium. Lead bound to these proteins may alter function, resulting in abnormal intracellular and intercellular signaling. Neurotransmitter release is, in part, a calcium-dependent process that is adversely affected by lead.

Although these 2 mechanisms of toxicity may be reversible, a third mechanism prevents the development of the normal tertiary brain structure. In immature mammals the normal neuronal pruning process that results in elimination of multiple intercellular brain connections is affected by lead. Failure to construct the appropriate tertiary brain structure during infancy and childhood may result in a permanent abnormality. It is tempting to extrapolate from these anatomic findings to the clinical correlate of attention-deficit/hyperactivity disorder observed in lead-poisoned children.

Clinical Effects

The BLL is the best-studied measure of the lead burden in children. Although subclinical and clinical findings correlate with BLLs in populations, there is considerable interindividual variability in this relationship. **Lead encephalopathy** is more likely to be observed in children with BLLs higher than 100 µg/dL; however, one child with a BLL of 300 µg/dL may have no symptoms, whereas another with the same level may be comatose. Susceptibility may be associated with polymorphisms in genes coding for lead-binding proteins, such as Δ-aminolevulinic acid dehydratase, an enzyme in the heme pathway.

Several **subclinical effects** of lead have been demonstrated in cross-sectional epidemiologic studies. Hearing and height are inversely related to BLLs in children; in neither case, however, does the lead effect reach a level that would bring an individual child to medical attention. As BLLs increase in the study populations, more sound (at all frequencies) is needed to reach the hearing threshold. Children with higher BLLs are shorter than those with lower levels; for every 10 µg increase in the BLL, the children are 1 cm shorter. Chronic lead exposure also may delay puberty.

Several longitudinal studies have followed cohorts of children from birth for as long as 20 yr and examined the relationship between BLLs and cognitive test scores over time. In general, there is agreement that BLLs, expressed either as levels obtained concurrently with cognitive testing or as a measure that integrates multiple BLLs drawn from subjects over time, are inversely related to cognitive test scores. From these studies, no BLL above 0 µg/dL appears safe. On average, for each 1 µg/dL elevation in BLL, the cognitive score is approximately 0.25-0.50 points lower, though the relationship is not linear across the BLL spectrum. Because the BLLs from early childhood are predictors of the cognitive test results performed years later, this finding implies that the effects of lead can be permanent.

The effect of in utero lead exposure is less clear. Scores on the Bayley Scale of Mental Development were obtained repeatedly every 6 mo for the 1st 2 yr of life in a cohort of infants born to middle-class families. Results correlated inversely with cord BLLs, a measure of in utero exposure. However, after 2 yr of age, all other cognitive tests performed on the cohort over the next 10 yr correlated with the BLLs at age 2 yr but not with cord BLLs, indicating that the effects of prenatal lead exposure on brain function were superseded by early childhood events and later BLLs. Later studies, performed in cohorts of Mexican children monitored from the prenatal period, confirm the association between in utero lead exposure and later cognitive outcomes. In these studies, maternal plasma Pb levels obtained, especially during the 1st trimester, were more strongly associated with cognitive scores in the offspring than in maternal BLLs.

Behavior also is adversely affected by lead exposure. Hyperactivity is noted in young school-age children with histories of lead poisoning or with concurrent elevations in BLL. Older children with higher bone lead content are more likely to be aggressive and to have behaviors that are predictive of later juvenile delinquency. One report supports the concept of long-term effects of early lead exposure. In this longitudinal study, the mothers of a cohort were enrolled during their pregnancies. BLLs were obtained early in pregnancy, at birth, and then multiple times in the offspring during the 1st 6 yr. The investigators report that the relative rate of arrests, especially for violent crimes, increased significantly in relationship to the presence of these BLLs early in life. For every 5 µg/dL increase in BLL, the adjusted arrest rate was 1.40 for prenatal BLLs and 1.27 for

6 yr BLLs. Epidemiologic data support the findings in this observational study. In an analysis that combined two national datasets, total annual leaded gasoline use (U.S. Geological Survey), and total reported violent criminal acts (U.S. Department of Justice), the amount of leaded gasoline used yearly was found to be strongly associated with violent criminal behavior with a lag time of 23 yr—that is, early exposure was followed 2 decades later by violent behavior rising and falling in close tandem. A similar association was found, this time between urban air lead levels and later violent crime, with a similar best-fit model employing a lag of approximately 22 yr.

An intervention study, in which children with moderate lead poisoning and initial BLLs of 20-55 µg/dL were aggressively managed over 6 mo, addressed the issue of the effects of treatment on cognitive development. Components of treatment included education regarding sources of lead and its abatement, nutritional guidance, multiple home and clinic visits, and for a subset, chelation therapy. Average BLLs declined, and cognitive scores were inversely related to the change in BLLs. For every 1 µg/dL fall in BLLs, cognitive scores were 0.25 point higher. A randomized placebo-controlled treatment study of 2 yr old children with initial BLLs of 20-44 µg/dL that employed the chelating agent succimer administered over 6 mo found no difference in *mean* cognitive scores at age 4 yr. However, as in the earlier treatment study, regression analysis did find an inverse relation between *change* scores—that is, a change in BLLs was associated with a change in cognitive scores.

Whether the behavioral effects of lead are reversible is unclear. In one small, short-term study, 7 yr old hyperactive children with BLLs in the 20s were randomly allocated to receive a chelating agent (penicillamine), methylphenidate, or placebo. Teacher and parent ratings of behavior improved for the first two groups but not the placebo group. BLLs declined only in the chelated group. Two yr old lead-poisoned children enrolled in a placebo-controlled trial of the chelating agent succimer showed no mean difference in behavior at 4 or 7 yr of age. However, mean BLLs were also not different in the 2 groups at those ages.

These studies support the concept that early exposure to lead can result in long-term deficits in cognition and behavior; they also hold out the possibility that reductions in lead burden may be associated with improvement in cognitive test scores.

Clinical Symptoms

Gastrointestinal symptoms of lead poisoning include anorexia, abdominal pain, vomiting, and constipation, often occurring and recurring over a period of weeks. Children with BLLs higher than 20 µg/dL are twice as likely to have gastrointestinal complaints as those with lower BLLs. **Central nervous system** symptoms are related to worsening cerebral edema and increased intracranial pressure. Headaches, change in mentation, lethargy, papilledema, seizures, and coma leading to death are rarely seen at levels lower than 100 µg/dL but have been reported in children with a BLL as low as 70 µg/dL. The last-reported death directly attributable to lead toxicity in the United States was in 2006 in a child with a BLL of 180 µg/dL. There is no clear cutoff BLL value for the appearance of hyperactivity, but it is more likely to be observed in children who have levels higher than 20 µg/dL.

Other organs also may be affected by lead toxicity, but symptoms usually are not apparent in children. At high levels (>100 µg/dL), renal tubular dysfunction is observed. Lead may induce a reversible Fanconi syndrome (see Chapter 547.1). In addition, at high BLLs, red blood cell survival is shortened, possibly contributing to a hemolytic anemia, although most cases of anemia in lead-poisoned children are a result of other factors, such as iron deficiency and hemoglobinopathies. Older patients may develop a peripheral neuropathy leading to wrist drop and footdrop, as well as hypertension.

Diagnosis

Screening

It is estimated that 99% of lead-poisoned children are identified by screening procedures rather than through clinical recognition of lead-related symptoms. Until 1997, universal screening by blood lead testing of all children at ages 12 and 24 mo was the standard in the United States. Given the national decline in the prevalence of lead poisoning, the recommendations have been revised to target blood lead testing of high-risk populations. High risk is based on an evaluation of the likelihood of lead exposure. Departments of health are responsible for determining the local prevalence of lead poisoning, as well as the percentage of housing built before 1950, the period of peak leaded paint use. When this information is available, informed screening guidelines for practitioners can be issued. For instance, in New York State, where a large percentage of housing was built before 1950, the Department of Health mandates that all children be tested for lead poisoning via blood analyses. *In the absence of such data, the practitioner should continue to test all children at both 12 and 24 mo.* In areas where the prevalence of lead poisoning and old housing is low, targeted screening may be performed on the basis of a risk assessment. Three questions form the basis of most published questionnaires (Table 739.3), and items that are pertinent to the locale or individual may be added. If there is a lead-based industry in the child's neighborhood, the child is a recent immigrant from a country that still permits use of leaded gasoline, or the child has pica or developmental delay, blood lead testing would be appropriate. All Medicaid-eligible children should be screened by blood lead testing. Venous sampling is preferred to capillary sampling because the chances of false-positive and false-negative results are less with the former.

Table 739.3

Minimum Personal Risk Questionnaire

1. Does the child live in or visit regularly a house that was built before 1950? (Include settings such as daycare, babysitter's or relative's home.)
2. Does the child live in or regularly visit a house built before 1978 with recent (past 6 mo) or ongoing renovations or remodeling?
3. Does the child have a sibling or playmate who has or did have lead poisoning?

From Screening young children for lead poisoning: guidance for state and local public health officials, Atlanta, 1997, Centers for Disease Control and Prevention.

The threshold for lead effects and the reference level for risk management purposes are not the same. Laboratory issues make the interpretation of values between 0 and 5 µg/dL more difficult. Some labs certified as proficient by the CDC or other testing programs can accurately measure BLLs to 2 µg/dL; others only to 5 µg/dL. A screening value at or above 5 µg/dL is consistent with exposure and requires a second round of testing for a diagnosis and to determine the appropriate intervention. The timing for the “repeat” evaluation depends on the initial value (Table 739.4). If the diagnostic (second) test confirms that the

BLL is elevated, then further testing is required by the recommended schedule (Table 739.5). A confirmed venous BLL of 45 µg/dL or higher requires prompt chelation therapy.

Table 739.4

Follow-Up of Blood Lead Level Screening

BLOOD (µg/dL)	TIME TO CONFIRMATION TESTING
≥ Reference value -5	1-3 mo
5-44	1 wk-1 mo*
45-59	48 hr
60-69	24 hr
≥70	Urgently as emergency test

CDC (2012).

Table 739.5

Summary of Recommendations for Children With Confirmed (Venous) Elevated Blood Lead Concentrations

BLOOD LEAD CONCENTRATION (µg/dL)	FOLLOW-UP TESTING	RECOMMENDATIONS
≥ Reference value-5	3 mo	As levels approach 5 µg/dL use the 5-19 µg/dL recommendations
5-19	1-3 mo	Lead education (sources, route of entry) Dietary counseling (Ca/Fe) Environmental (methods for hazard elimination)
20-24	1-3 mo	Proceed as for 10-19 plus: Shorter intervals if blood lead level rising
25-44	2 wk-1 mo	Proceed as for 20-24 plus: Complete history and physical examination Hemoglobin or hematocrit Iron status Neurodevelopmental monitoring
45-69	As soon as possible	Proceed as for 25-44 plus: Hospitalize and commence chelation therapy Laboratory studies: Hemoglobin or hematocrit Iron status Free erythrocyte protoporphyrin or zinc protoporphyrin Renal and liver function tests Abdominal radiography (if particulate lead ingestion is suspected) with bowel decontamination if indicated
≥70	As soon as possible	Proceed as for 45-69 µg/dL plus: Commence chelation therapy with 2 drugs
NOT RECOMMENDED AT ANY BLOOD LEAD CONCENTRATION Searching for gingival lead lines Testing of hair, teeth, or fingernails for lead		

Radiographic imaging of long bones
X-ray fluorescence of long bones

Data from American Academy of Pediatrics: Lead exposure in children: prevention, defection, and management, *Pediatrics* 116:1036–1046, 2005, and; Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention Report of the Advisory Committee on Childhood Lead Poisoning Prevention. CDC (2012).

Other Tools for Assessment

BLL determinations remain the gold standard for evaluating children because of ready availability and its correlation with health outcomes in populations. Techniques are available to measure lead in other tissues and body fluids. Experimentally, the method of x-ray fluorescence (XRF) allows direct and noninvasive assessment of bone lead stores. XRF methodology was used to evaluate a population that had long-term exposure to lead from a polluting battery-recycling factory. The study found that the school-aged children had elevated lead levels in bone but not in venous blood, a finding that is consistent with our understanding of the slow turnover of lead in bone, which is measurable in years, in contrast to that in blood, which is measurable in weeks. It also indicates that children may have substantial lead in their bodies that is not detected by routine blood lead testing. This stored lead may be released to toxic levels if bone resorption rates suddenly increase, as occurs with prolonged immobilization of longer than a week and during pregnancy. Thus children with histories of elevated BLLs are potentially at risk for recrudescence of lead toxicity long after ingestion has stopped and may pass this lead to the next generation. XRF methodology is not available for clinical use in children.

Lead also can be measured in urine. Spontaneous excretion, even in children with high BLLs, is usually low. Lead excretion may be stimulated by treatment with chelating agents, and this property of these drugs forms the basis of their use as a component of lead treatment. It also has been used to develop a test that differentiates children with lead burdens responsive to chelation therapy, the **lead mobilization test** . In this test, a timed urine collection follows one or two doses of chelating agent and the lead content is determined. However, this test is no longer recommended.

Lead in hair, nails, and saliva also is measurable but has problems of contamination and interpretability. Further research is required before indications for testing these materials are established. Other tests are used as indirect assessments of lead exposure and accumulation. Radiographs of long bones may show dense bands at the metaphyses, which may be difficult to distinguish from growth arrest lines but, if caused by lead, are indicative of months to years of exposure. For children with acute symptoms, when a BLL result is not immediately available, a **kidneys-ureters-bladder (KUB) radiograph** may reveal **radiopaque flecks** in the intestinal tract, a finding that is consistent with recent ingestion of lead-containing plaster or paint chips. The absence of radiographic findings does not rule out lead poisoning, however.

Because BLLs reflect recent ingestion or redistribution from other tissues but do not necessarily correlate with the body burden of lead or lead toxicity in an individual child, tests of lead effects also may be useful. After several weeks of lead accumulation and a BLL higher than 20 µg/dL, increases in EP values to more than 35 µg/dL may occur. An elevated EP value that cannot be attributed to iron deficiency or recent inflammatory illness is both an indicator of lead effect and a useful means of assessing the success of the treatment; the EP level will begin to fall a few weeks after successful interventions that reduce lead ingestion and increase lead excretion. Since EP is light sensitive, whole blood samples should be covered in aluminum foil (or equivalent) until analyzed.

Treatment

Once lead is in bone, it is released slowly and is difficult to remove even with chelating agents. Because the cognitive/behavioral effects of lead may be irreversible, the main effort in treating lead poisoning is to prevent it from occurring and to prevent further ingestion by already-poisoned children. The main components in the effort to eliminate lead poisoning are universally applicable to all children (and adults) and are as follows: (1) identification and elimination of environmental sources of lead exposure, (2) behavioral modification to reduce nonnutritive hand-to-mouth activity, and (3) dietary counseling to ensure sufficient intake of the essential elements calcium and iron. For the small minority of children with more-severe lead poisoning, drug treatment is available that enhances lead excretion.

During health maintenance visits a limited risk assessment is warranted, which includes questions pertaining to the most common sources of lead exposure: the condition of old paint, secondary occupational exposure via an adult living in the home, and/or proximity to an industrial source of pollution. If such a source is identified, its elimination usually requires the assistance of public health and housing agencies as well as education for the parents. The family should move out of a lead-contaminated apartment until repairs are completed. During repairs, repeated washes of surfaces and the use of high-efficiency particle accumulator (HEPA) vacuum cleaners help reduce exposure to lead-containing dust. Careful selection of a contractor who is certified to perform lead abatement work is necessary. Sloppy work can cause dissemination of lead-containing dust and chips throughout a home or building and result in further elevation of a child's BLL. After the work is completed, dust wipe samples should be collected from floors and windowsills or wells to verify that the risk from lead has abated.

A single case of lead poisoning is often discovered in a household with multiple affected family members, including other young children, even in a household with a common source of exposure such as peeling lead-based paint. The mere presence of lead in an environment does not produce lead poisoning. Parental efforts at reducing the hand-to-mouth activity of the affected child are necessary to reduce the risk of lead ingestion. Handwashing effectively removes lead, but in a home with lead-containing dust, lead rapidly begins to reaccumulate on the child's hands after washing. Therefore, handwashing is best limited to the period immediately before nutritive hand-to-mouth activity occurs.

Because there is competition between lead and essential minerals, it is reasonable to promote a healthy diet that is sufficient in calcium and iron. The recommended daily intakes of these metals vary somewhat with age. In general, for children 1 yr of age and up, a calcium intake of about 1 g/day is sufficient and convenient to remember (roughly the calcium content of a quart of milk [≈1,200 mg/qt] or calcium-fortified orange juice). Calcium absorption is vitamin D dependent; milk is fortified with vitamin D, but other nutritional sources of calcium often are not. A multivitamin containing vitamin D may be prescribed for children who do not drink sufficient milk or who have inadequate sunlight exposure. Iron requirements also vary with age, ranging from 6 mg/day for infants to 12 mg/day for adolescents. For children identified biochemically as being iron deficient, therapeutic iron at a daily dose of 5-6 mg/kg for 3 mo is appropriate. Iron absorption is enhanced when iron is ingested with ascorbic acid (citrus juices). Giving additional calcium or iron above the recommended daily intakes to mineral-sufficient children has not been shown to be of therapeutic benefit in the treatment of lead poisoning.

Drug treatment to remove lead is lifesaving for children with lead encephalopathy. In nonencephalopathic children, it prevents symptom progression and further toxicity. Guidelines for **chelation** are based on the BLL.

A child with a venous BLL of 45 µg/dL or higher should be treated. Four drugs are available in the United States: 2,3-dimercaptosuccinic acid (DMSA [succimer]), $CaNa_2$ EDTA (versenate), British antilewisite (BAL [dimercaprol]), and penicillamine. DMSA and penicillamine can be given orally, whereas $CaNa_2$ EDTA and BAL can be administered only parenterally. The choice of agent is guided by the severity of the lead poisoning, the effectiveness of the drug, and the ease of administration (Table 739.6). Children with BLLs of 44-70 µg/dL may be treated with a single drug, preferably DMSA. Those with BLLs of 70 µg/dL or greater require two-drug treatment: $CaNa_2$ EDTA in combination with either DMSA or BAL for those without evidence of encephalopathy, or $CaNa_2$ EDTA and BAL for those with encephalopathy. Published data on the combined treatment with $CaNa_2$ EDTA and DMSA for children with BLLs higher than 100 µg/dL are very limited. However, anecdotal information derived from the treatment of hundreds of severely lead poisoned children in northern Nigeria indicates that single-drug treatment with DMSA is lifesaving, although the degree of residual damage in survivors has not been reported.

Table 739.6

Chelation Therapy

NAME	SYNONYM	DOSE	TOXICITY
Succimer	Chemet, 2,3-dimercaptosuccinic acid	350 mg/m^2 body surface area/dose (***not 10 mg/kg***) q8h, PO for 5 days, then q12h for 14 days	Gastrointestinal distress, rashes; elevated LFTs, depressed white blood cell count
Edetate	$CaNa_2$ EDTA (**calcium** disodium edetate), versenate	1,000-1,500 mg/m^2 body surface area/day; IV infusion—continuous or intermittent; IM divided q6h or q12h for 5 days	Proteinuria, pyuria, rising blood urea nitrogen/creatinine—all rare Hypercalcemia if too rapid an infusion Tissue inflammation if infusion infiltrates
British antilewisite	Dimercaprol, British antilewisite	300-500 mg/m^2 body surface area/day; **IM only** divided q4h for 3-5 days. Only for blood lead level ≥70 µg/dL	GI distress, altered mentation; elevated LFTs, hemolysis if glucose-6-phosphate dehydrogenase deficiency; no concomitant **iron** treatment
D-Pen	Penicillamine	10 mg/kg/day for 2 wk increasing to 25-40 mg/kg/day; oral, divided q12h. For 12-20 wk	Rashes, fever; blood dyscrasias, elevated LFTs, proteinuria Allergic cross-reactivity with penicillin

From Markowitz ME: Lead poisoning. *Pediatr Rev* 21:327–335, 2000.

Drug-related toxicities are minor and reversible. These include gastrointestinal distress, transient elevations in transaminases, active urinary sediment, and neutropenia. These types of events are least common for $CaNa_2$ EDTA and DMSA, and more common for BAL and penicillamine. All of the drugs are effective in reducing BLLs when given in sufficient doses and for the prescribed time. These drugs also may increase lead absorption from the gut and should be administered to children in lead-free environments. Some authorities also recommend the administration of a cathartic immediately prior to or concomitant with the initiation of chelation to eliminate any lead already in the gut.

None of these agents removes all lead from the body. Within days to weeks after completion of a course of therapy, the BLL rises, even in the absence of new lead ingestion. The source of this rebound in the BLL is believed to be bone. Serial examinations of bone lead content have shown that chelation with $CaNa_2$ EDTA is associated with a decline in bone lead levels but that residual bone lead remains detectable even after multiple courses of treatment.

Repeat chelation is indicated if the BLL rebounds to 45 µg/dL or higher. Children with initial BLLs higher than 70 µg/dL are likely to require more than one course. A minimum of 3 days between courses is recommended to prevent treatment-related toxicities, especially in the kidney.

The indication for chelation therapy for children with BLLs <45 µg/dL is less clear. Although use of these drugs in children with BLLs from 20 to 45 µg/dL will result in transient lowered BLLs, and in some cases reversal of lead-induced enzyme inhibition, few such children increase their excretion of lead significantly during chelation, raising the question of whether any long-term benefit is achieved. A study of 2 yr old children with BLLs of 20-44 µg/dL who were randomized to receive either DMSA or placebo found that the drop in BLLs was greater in the 1st 6 mo after enrollment in the DMSA-treated group, but the levels converged by 1 yr of follow-up. Mean cognitive test scores obtained at 4 and 7 yr of age were not statistically different between the groups. Chelation with DMSA (and $CaNa_2$ EDTA) is not recommended for all children with BLLs <45 µg/dL. Further work needs to be done to determine whether there are subgroups of children with BLLs lower than 45 µg/dL who might benefit from chelation. For example, if children are selected for chelation after demonstrating responsiveness to a test dose of a chelating agent with an enhanced lead diuresis—an indication that the drug is effective at removing lead permanently from the body—will there be better clinical/subclinical outcomes? It also remains to be demonstrated whether other chelating agents available in the United States or elsewhere are effective at either substantially reducing body stores (bone) of lead or reversing the cognitive deficits attributable to lead at these BLLs.

With successful intervention, BLLs decline, with the greatest fall in BLL occurring in the 1st 2 mo after therapy is initiated. Subsequently, the rate of change in BLL declines slowly, so that by 6-12 mo after identification, the BLL of the average child with moderate lead poisoning (BLL >20 µg/dL) will be 50% lower. Children with more markedly elevated BLLs may take years to reach the current CDC reference level, 5 µg/dL, even if all sources of lead exposure have been eliminated, behavior has been modified, and nutrition has been maximized. Early screening remains the best way of avoiding and therefore obviating the need for the treatment of lead poisoning.

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CHAPTER 740

Nonbacterial Food Poisoning

740.1

Mushroom Poisoning

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Keywords

mushroom
mycotoxin
food poisoning

Mushrooms are an ideal food. They are low in calories, fat free, and high in protein, making them a great source of nutrition. Unfortunately, some are highly toxic if ingested. Picking (foraging) and consumption of wild mushrooms are increasingly popular in the United States. This rise in popularity has led to increased reports of severe and fatal mushroom poisonings.

The clinical syndromes produced by mushroom poisoning are divided according to the rapidity of onset of symptoms and the predominant system involved (Table 740.1). The symptoms are caused by the principal toxin present in the ingested mushrooms. The 8 major toxins produced by mushrooms are categorized as cyclopeptides, monomethylhydrazine, muscarine, hallucinogenic indoles, isoxazole, coprine (disulfiram-like reaction), orellanine, and gastrointestinal tract–specific irritants. The edible wild mushroom *Tricholoma* *equestre* is associated with delayed rhabdomyolysis, and *Clitocybe amoenolens* and *Clitocybe acromelalga* have been reported to cause erythromelalgia. The toxins responsible for these effects are unknown, and diagnostic testing methods are limited.

Table 740.1

Summary of Common Mushroom-Associated Syndromes

SYNDROME	**CLINICAL COURSE**	**TOXIN(S)**	**TYPICAL CAUSATIVE MUSHROOM(S)**
Delayed gastroenteritis followed by hepatorenal syndrome	Stage 1: 24 hr after ingestion: onset of nausea, vomiting, profuse cholera-like diarrhea, abdominal pain, hematuria Stage 2: 12-48 hr after ingestion: apparent recovery; levels of hepatic enzymes are rising during this stage Stage 3: 24-72 hr after ingestion: progressive hepatic and renal failure, coagulopathy, cardiomyopathy, encephalopathy, convulsions, coma, death	Cyclopeptides, principally amatoxins	“Deadly *Amanitas* ,” *Galerina* species
Hyperactivity, delirium, coma	30 min to 2 hr after ingestion: delirium, hallucinations, and coma	Muscimol, ibotenic acid	*Amanita muscaria*, *Amanita pantherina*
Delayed gastroenteritis with central nervous system abnormalities	6-24 hr after ingestion: nausea, vomiting, diarrhea, abdominal pain, muscle cramps, delirium, convulsions, coma; hemolysis and methemoglobinemia may occur	Gyromitrin	*Gyromitra esculenta* (“false morel”)
Cholinergic syndrome	30 min to 2 hr after ingestion: bradycardia, bronchorrhea, bronchospasm, salivation, perspiration, lacrimation, convulsions, coma	Muscarine	*Boletus* species, *Clitocybe* species, *Inocybe* species, *Amanita* species
Disulfiram-like reaction with ethanol	30 min after drinking ethanol (may occur up to 1 wk after eating coprine-containing mushrooms): flushing of skin of face and trunk, hypotension, tachycardia, chest pain, dyspnea, nausea, vomiting, extreme apprehension	Coprine	*Coprinus atramentarius*
Hallucinations	30 min to 3 hr after ingestion: hallucinations, euphoria, drowsiness, compulsive behavior, agitation	Psilocybin and psilocin	*Psilocybe* species
Delayed gastritis and renal failure	Abdominal pain, anorexia, vomiting starting over 30 hr after ingestion, followed by progressive renal failure 3-14 days later	Orelline, orellanine	*Cortinarius* species
Immune-mediated hemolytic anemia	Syncope, gastroenteritis, oliguria, hemoglobinuria, back pain, hemolysis	Immunoglobulin mediated	*Paxillus involutus*
General gastrointestinal irritants	30 min to 2 hr after ingestion: nausea, vomiting, abdominal cramping, diarrhea; may recover without treatment	Unidentified, probably multiple	*Chlorophyllum molybdites* , backyard mushrooms (“little brown

			mushrooms”), many others

From Brent J, Palmer RB: Mushrooms. In Shannon MW, Borron SW, Burns MJ, editors: *Haddad and Winchester's clinical management of poisoning and drug overdose* , ed 4, Philadelphia, 2007, WB Saunders, Table 23-1.

Symptoms after eating mushrooms may not be the direct effect of a toxin but may be an allergic reaction or a toxic effect of pesticides or other contaminants. In addition, all who ate the same mushroom may not become sick, or if they do, they may become sick at different intervals. Table 740.2 lists general principles of management.

Table 740.2

General Management of Mushroom Ingestion

1. Determine history of ingestion: how many types of mushrooms ingested, what time, if anyone else ate them, and what symptoms are present.
2. Attempt to determine which of the possible syndromes (see Table 740.1) the patient may have. For example, gastrointestinal symptoms occurring more than 6 hr after ingestion strongly suggest cyclopeptide, gyromitrin, or *Cortinarius* poisoning.
3. Administer activated charcoal. If the patient has diarrhea, do not give a cathartic. If a cathartic is used, give it only with the first dose of activated charcoal. Use repeated doses of activated charcoal for suspected amatoxin poisonings.
4. If feasible and when indicated, send gastric aspirate or emesis, along with any remaining mushrooms, to a mycologist for identification.
5. Try to perform a preliminary identification of mushroom and spores. Start to develop a spore print as soon as possible.
6. Maintain supportive measures, including airway support, intravenous fluids, and vasopressors (if needed). Monitor volume status.
7. Avoid antispasmodics for gastrointestinal symptoms.
8. Anticipate the clinical course.

From Brent J, Palmer RB: Mushrooms. In Shannon MW, Borron SW, Burns MJ, editors: *Haddad and Winchester's clinical management of poisoning and drug overdose* , ed 4, Philadelphia, 2007, WB Saunders, Box 23.1.

Gastrointestinal: Delayed Onset

Amanita Poisoning

Poisonings by species of *Amanita* (death cap mushroom) and *Galerina* account for 95% of the fatalities from mushroom intoxication; the mortality rate for this group is 5–10%. Most species produce two classes of cyclopeptide toxins: (1) phallotoxins, which are heptapeptides believed to be responsible for the early symptoms of *Amanita* poisoning, and (2) amatoxins, octapeptides that inhibit nuclear RNA polymerase II and subsequent production of messenger RNA leading to impaired protein synthesis and cell death. Cells with high turnover rates, such as those in the gastrointestinal mucosa, kidneys, and liver, are the most severely affected. Other suggested toxin effects are induction of apoptosis, glutathione depletion in the liver, and oxygen free radical formation. Acute yellow atrophy of the liver and necrosis of the proximal renal tubules are found in lethal cases.

The clinical course of poisoning with *Amanita* or *Galerina* species is biphasic. Nausea, vomiting, and severe abdominal pain ensue 6-24 hr after ingestion. Profuse watery diarrhea follows shortly thereafter and may last for 12-24 hr or longer. During this time, patients become severely dehydrated. From 24 to 48 hr after poisoning, jaundice, hypertransaminasemia (peaking at 72-96 hr), renal failure, and coma occur. Death occurs 4-7 days after the ingestion. A prothrombin time less than 10% of control is a poor prognostic factor.

Treatment

Treatment for *Amanita* poisoning is both supportive and specific. Fluid loss from severe diarrhea during the early course of the illness is profound, requiring aggressive correction of fluid loss, electrolytes, and acid–base disturbances. In the late phase of the disease, management of renal and hepatic failure is also necessary.

Specific therapy for *Amanita* poisoning is designed to remove the toxin rapidly and to block binding at its target site. Oral activated charcoal is recommended as part of the initial treatment for children with *Amanita* poisoning. For significant ingestions, consider silibinin (5 mg/kg IV over 1 hr followed by a continuous intravenous infusion of 20 mg/kg/24 hr) for 3 days postingestion. If silibinin is not available, intravenous penicillin G (400,000 units/kg/24 hr) may be used. Silibinin and penicillin G inhibit binding of both toxins, interrupt enterohepatic recirculation of amatoxin, and protect the liver from further injury, although their effectiveness is controversial. Acetylcysteine should be given for hepatoprotective effect. Hemodialysis and hemoperfusion are also recommended as part of the initial treatment for intoxicated children. Orthotopic liver transplantation may be required for children with severe hepatic failure.

Monomethylhydrazine Intoxication

Species of *Gyromitra* contain gyromitrin, which decomposes in the stomach to form monomethylhydrazine (CH_3 $NHNH_2$) and inhibits central nervous system (CNS) enzymatic production of γ-aminobutyric acid. Monomethylhydrazine also oxidizes iron in hemoglobin, resulting in methemoglobinemia. Children with *Gyromitra* poisoning experience vomiting, diarrhea, hematochezia, and abdominal pain within 6-24 hr of ingestion of the toxin. CNS symptoms such as vertigo, diplopia, headache, ataxia, and seizures develop later in the clinical course. Hemolysis and methemoglobinemia (see Chapter 489.6) are rare but potential life-threatening complications of gyromitrin poisoning.

Treatment

Hypovolemia from gastrointestinal fluid losses and seizures require supportive intervention. Pyridoxal phosphate, the coenzyme that catalyzes the production of γ-aminobutyric acid, can reverse the effects of monomethylhydrazine when administered in high doses. Pyridoxine hydrochloride (25 mg/kg infused over 30 min) is given at a frequency that is dependent on clinical improvement. Diazepam is given for persistent seizures. Parenteral administration of methylene blue is indicated if the methemoglobin concentration exceeds 30%. Blood transfusions may be required for significant hemolysis.

Renal: Delayed Onset

Orellanine Poisoning

Species of *Cortinarius* contain the heat-stable toxin bipyridyl orellanine, which causes severe nonglomerular renal injury characterized by interstitial fibrosis and acute tubular necrosis. Although the exact mechanism of injury is not fully understood, a metabolite of orellanine is thought to inhibit renal protein synthesis. *Cortinarius* poisoning is characterized by nausea, vomiting, and diarrhea that manifest 36-48 hr after ingestion. Although the initial symptoms may be trivial, more serious renal toxicity occurs in several days. Acute renal failure occurs in 30–50% of those affected, beginning with polyuria and progressing to renal failure (see Chapter 550).

Treatment

Treatment for orellanine poisoning is supportive. Early presentation, within 4-6 hr after ingestion, can be treated with activated charcoal and gastric lavage. Hemodialysis may be needed in patients suffering from renal failure. Most patients recover within 1 mo, but chronic renal insufficiency develops in one third to one half of patients, who subsequently require renal transplantation.

Autonomic Nervous System: Rapid Onset

Muscarine Poisoning

Mushrooms of the genera *Inocybe* and, to a lesser degree, *Clitocybe* contain muscarine or muscarine-related compounds. These quaternary ammonium derivatives bind to postsynaptic receptors, producing an exaggerated cholinergic response.

The onset of symptoms is rapid (30 min to 2 hr after consumption), and intoxication is characterized by symptoms of cholinergic excess: diaphoresis, excessive lacrimation, salivation, miosis, bradycardia, hypotension, urinary and fecal incontinence, and vomiting. Respiratory distress caused by bronchospasm and increased bronchopulmonary secretions is the most serious complication. The symptoms subside spontaneously within 6-24 hr.

Treatment

Atropine sulfate, the specific antidote, is administered intravenously (0.01 mg/kg; maximum: 2 mg). This is repeated until the pulmonary symptoms resolve or the patient becomes overtly tachycardic.

Coprine Ingestion

Coprinus atramentarius and *Clitocybe clavipes* contain coprine. Like disulfiram (Antabuse; Odyssey Pharmaceuticals, Inc.), coprine inhibits the metabolism of acetaldehyde after ethanol ingestion. The clinical manifestations result from accumulation of acetaldehyde.

Coprine intoxication becomes apparent after ethanol ingestion and may occur up to 5 days after consumption of the mushroom. Hyperemia of the face and trunk, tingling of the hands, metallic taste, tachycardia, and vomiting occur acutely. Hypotension may result from intense peripheral vasodilation.

The syndrome typically is self-limited and lasts only several hours. No specific antidote is available. If hypotension is severe, vascular reexpansion with isotonic parenteral solutions may be required. Small oral doses of propranolol have also been suggested.

Central Nervous System: Rapid Onset

Isoxazole Intoxication

Although *Amanita muscaria* and *Amanita pantherina* may contain muscarine, the toxins responsible for the CNS symptoms after ingestion of these mushrooms are primarily muscimol and ibotenic acid, the heat-stable derivatives of the isoxazoles. Muscimol, a hallucinogen, and ibotenic acid, an insecticide, act as γ-aminobutyric acid agonists. From 30 min to 3 hr after ingestion, CNS symptoms appear: obtundation, alternating lethargy and agitation, and occasionally seizures. Nausea and vomiting are uncommon. If large amounts of muscarine are contained in the mushroom, symptoms of cholinergic crisis also may occur.

Specific therapy must be carefully selected. If an exaggerated cholinergic response is observed, atropine should be administered. Conversely, because ingestions of *A. muscaria* or *A. pantherina* may cause anticholinergic findings, the acetylcholinesterase inhibitor physostigmine can be used to reverse the delirium and coma. Benzodiazepines also are used for the agitation and delirium. Seizures can be controlled with diazepam. In most cases, however, early supportive care and close observation are all that is required.

Indole Intoxication

Mushrooms belonging to the genus *Psilocybe* (“magic mushrooms”) contain psilocybin and psilocin, 2 psychotropic compounds. Within 30 min after ingestion, patients experience euphoria and hallucinations, often accompanied by tachycardia and mydriasis. Fever and seizures have also been observed in children with psilocybin poisoning. These symptoms are short-lived, usually lasting for 6 hr after consumption of the mushroom. Treatment consists of rest and observation in a quiet environment. Severely agitated patients may respond to diazepam.

Gastrointestinal: Rapid Onset

Many mushrooms from various genera produce local gastrointestinal manifestations. The causative toxins are diverse and largely unknown. Within 1 hr of ingestion, patients experience acute abdominal pain, nausea, vomiting, and diarrhea. Symptoms may last from hours to days, depending on the species of mushroom.

Treatment is mainly supportive. Children with large fluid losses may require parenteral fluid therapy. It is imperative to differentiate ingestion of mushrooms of this class from ingestion of *Amanita* and *Galerina* species containing cyclopeptide toxins.

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740.2

Solanine Poisoning

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Keywords

solanine
Solanaceae
poisoning

Solanine is an alkaloid found in plants of the nightshade family (Solanaceae), specifically tomatoes, eggplant, and most significantly, potatoes. The majority of solanine poisoning reported has arisen from the ingestion of greened potatoes. When exposed to light and allowed to turn green and/or sprout, potatoes produce a number of alkaloid glycosides containing the cholesterol derivative *solanidine* . Two of these glycosides, α-solanine and α-chaconine, are found in highest concentration in the peels and sprouts. Some solanine can be removed by boiling but not by baking. The major effect of α-solanine and α-chaconine is the reversible inhibition of cholinesterase. Cardiotoxic and teratogenic effects have also been reported.

Clinical manifestations of solanine and chaconine poisoning intoxication occur within 7-19 hr after ingestion. The most common symptoms are vomiting, abdominal pain, and diarrhea; in more severe instances of poisoning, neurologic symptoms, including drowsiness, apathy, confusion, weakness, and vision disturbances, are rarely followed by coma or death.

Treatment of solanine poisoning is largely supportive. In the most severe cases, symptoms resolve within 1-2 wk.

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740.3

Seafood Poisoning

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Keywords

seafood

ciguatera
ciguatoxins
poisoning
harmful algal blooms
shellfish poisoning
saxitoxin
tetrodotoxin
pufferfish

Ciguatera Fish Poisoning

The most frequently reported seafood-toxin illness in the world, ciguatera fish poisoning, has been reported in Florida, Hawaii, French Polynesia, the Marshall Islands, Caribbean and South Pacific Islands, and the Virgin Islands. With modern methods of transportation, the illness now occurs worldwide. Grouper is the most commonly identified source of the toxin, followed by snapper, kingfish, amberjack, dolphin, eel, and barracuda. Poisoning has also been associated with farm-raised salmon.

The dinoflagellate *Gambierdiscus toxicus,* a microscopic unicellular organism found along coral reefs, produces high concentrations of ciguatoxin and maitotoxin. The toxins are passed along the food chain from small herbivorous fish that consume the dinoflagellate to larger predatory fish and then to humans. These toxins are harmless in fish but produce distinct clinical symptoms in humans.

Ciguatoxins are odorless, colorless, and tasteless, and are not destroyed by cooking or freezing. Ciguatoxins increase the sodium ion permeability of excitable membranes and depolarize nerve cells, actions that are inhibited by calcium and tetrodotoxin.

Between 2 and 30 hr after ingestion, ciguatera fish poisoning typically produces a biphasic illness. The initial symptoms are nonspecific and are of gastrointestinal origin (diarrhea, vomiting, nausea, and abdominal pain). The second phase occurs within a few days of ingestion and consists of intense itching, anxiety, myalgias, painful intercourse, feeling of loose teeth, and rash on palms and soles; the neurologic symptoms of circumoral dysesthesias and cold allodynia (reversal of hot and cold sensation) are characteristic of this disease and may last for months. Tachycardia, bradycardia, hypotension, and death occur very infrequently. Eating fish organs, roe, or viscera is associated with greater symptom severity. The diagnosis of ciguatera fish poisoning is based on clinical presentation and a compatible epidemiologic history; the diagnosis is confirmed by testing the ingested fish for toxin. There is no human biomarker to confirm ciguatera fish poisoning.

Treatment

Treatment of ciguatera fish poisoning is supportive. Intravenous fluids may be required for severe diarrhea, and parenteral administration of calcium can be used to treat hypotension. Once adequate hydration is established, mannitol (0.5-1.0 g/kg, IV over 30-45 min), given within 48-72 hr of the toxic fish ingestion, is recommended for reduction of acute symptoms (especially neurologic symptoms) and possible prevention of chronic neurologic symptoms. Various other medications and herbal remedies have been tried, with variable results. Most cases are self-limited with a favorable prognosis.

Scombroid (Pseudoallergic) Fish Poisoning

Ingestion of members of the Scombridae families, including albacore, mackerel, tuna, bonita, and kingfish, have been linked to major outbreaks of pseudoallergic fish poisoning. Nonscombroid fish and marine mammals, such as mahi-mahi (dolphin fish), swordfish, and bluefish, also are associated with poisoning.

The bacterial transformation of histidine to histamine is responsible for the clinical syndrome. Histidine is found in high concentrations in the flesh of scombroid fish; if refrigeration is inadequate, the action of bacterial decarboxylases during putrefaction converts histidine to histamine. Fish containing more than 20 mg of histamine per 100 g of flesh are toxic. In patients receiving isoniazid, a potent histaminase blocker, ingestion of fish flesh containing a lower concentration of histamine may be toxic.

The onset of clinical manifestations is acute and occurs within 10 min to 2 hr of ingestion. The most common symptoms and signs are diarrhea, erythema, sweating, flushing, diaphoresis, urticaria, nausea, and headache (Fig. 740.1). Abdominal pain, tachycardia, oral burning or numbness, dizziness, respiratory distress, hives, and facial swelling also occur. The illness is usually self-limited, terminating within 8-24 hr.

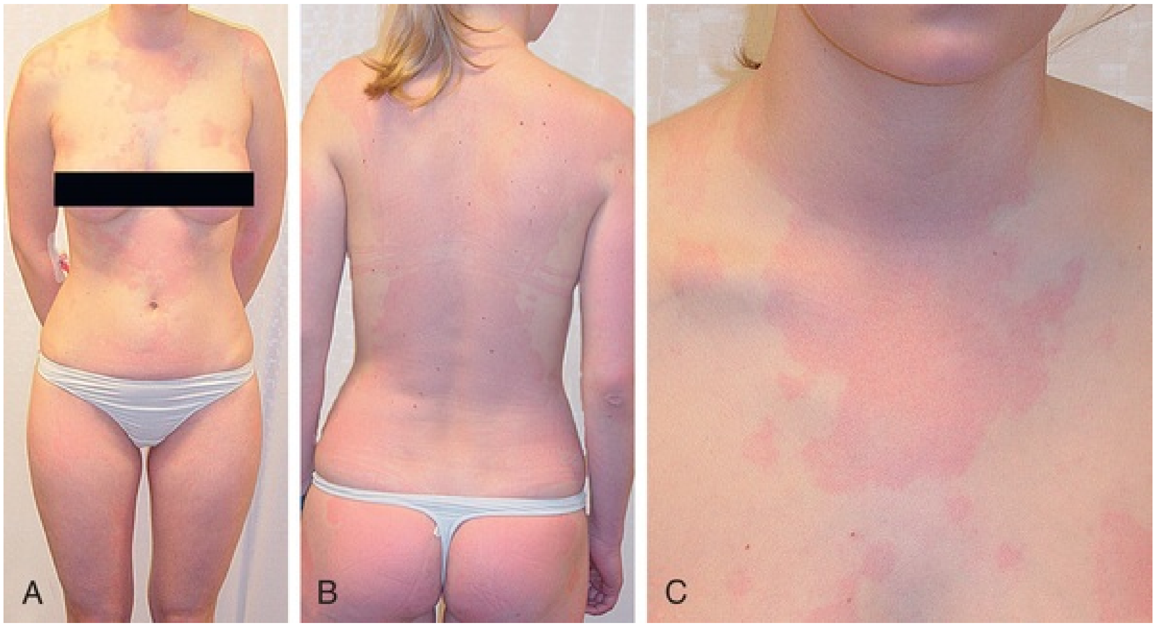

FIG. 740.1 A and B, Widespread erythematous rash predominantly on the face (not shown) and trunk of patient 1. C, Close-up view of the upper chest area. Note the absence of wheals. (From Jantschitsch C, Kinaciyan T, Manafi M, et al: Severe scombroid fish poisoning: an underrecognized dermatologic emergency. *J Am Acad Dermatol* 65(1):246–247, 2011, Fig. 1.)

Treatment

Treatment is mainly supportive. With severe diarrhea, fluid replacement may be necessary. Antihistamines and antiemetics have been variably successful.

Paralytic Shellfish Poisoning

Mussels, clams, oysters, scallops, and other filter-feeding mollusks may become contaminated during dinoflagellate blooms or “red tides.” During periods of contamination, water in coastal areas can be colored red by the algae; this sign is the origin of the term *red tide* . (Such discoloration does not necessarily indicate the presence of toxin, and toxin may be present in high quantities without discoloration. Nonetheless, discolored water should be regarded with suspicion.) The dinoflagellates *Alexandrium* spp. and *Gymnodinium catenatum* often are responsible for these red tides and contain several potent neurotoxins. Paralytic shellfish poisoning is a distinctive neurologic illness caused by 20 closely related heat-stable paralytic shellfish toxins, generally referred to as saxitoxins. These compounds prevent nerve conduction by inhibiting the sodium–potassium pump.

Consumption of bivalves, such as mussels, scallops, and clams, is the usual pathway of intoxication, although crustaceans and fish have been implicated as well.

The onset of clinical manifestations of paralytic shellfish poisoning occurs rapidly, 30 min to 2 hr after ingestion. Abdominal pain and nausea are common. Paresthesias are common and occur circumorally or in a stocking–glove distribution, or both. Perioral numbness or tingling, diplopia, ataxia, dysarthria, and the sensation of floating are seen less commonly. In severe cases, respiratory failure from diaphragmatic paralysis may result. Swimming in the water during a red tide episode does not appear to have neurologic sequelae, although skin or mucosal irritation may result.

Treatment

No antidote for paralytic shellfish poisoning is known. Supportive care, including mechanical ventilation, may be needed. Although the symptoms are usually self-limited and short-lived, weakness and malaise may persist for weeks after ingestion.

Neurotoxic Shellfish Poisoning

Neurotoxic shellfish poisoning is a rare disease that occurs after consumption of molluscan shellfish contaminated with brevetoxins. Shellfish harvested along the Gulf of Mexico during or right after a red tide are at risk of contamination with brevetoxins produced by the dinoflagellate *Karenia brevis* . There has also been recent evidence of brevetoxin production by raphidophytes (*Chattonella* spp.). Brevetoxins are a group of more than 10 lipid-soluble neurotoxins that activate sodium ion channels, causing nerve membrane depolarization. Shellfish are not affected by the brevetoxins. Rinsing, cleaning, cooking, and freezing do not destroy the toxins, which also cannot be detected by taste or smell.

The onset of clinical manifestations of neurotoxic shellfish poisoning occurs from within a few min up to 18 hr after consumption. Most symptoms are gastrointestinal (nausea, vomiting, and diarrhea) or neurologic (numbness and tingling of the lips, mouth, face, and extremities, ataxia, partial limb paralysis, reversal of hot and cold sensation, slurred speech, headache, and fatigue). Neurotoxic shellfish poisoning is similar to a mild case of paralytic shellfish poisoning.

Treatment

There are no specific antidotes for brevetoxins. Treatment involves mostly supportive care. Brevenal, a natural antagonist of brevetoxin produced by *K. brevis* , may be used as a form of treatment in the future.

Diarrhetic Shellfish Poisoning

Several outbreaks of diarrhetic shellfish poisoning have been reported in Europe after consumption of mussels, cockles, and other shellfish. The dinoflagellates *Dinophysis* and *Prorocentrum* produce okadaic acid and its derivatives, the dinophysistoxins. These compounds inhibit protein phosphatases. The intracellular accumulation of phosphorylated proteins causes increased fluid secretion by gut cells via calcium influx, which is mediated by cyclic adenosine monophosphate and prostaglandins.

Patients have severe diarrhea. Care is supportive and directed at rehydration. The illness is self-limited, and recovery occurs in 3-4 days; few patients require hospitalization.

Amnesic Shellfish Poisoning

Amnesic shellfish poisoning was first reported in 1987 in Canada when a group of people demonstrated severe gastroenteritis as well as neurologic symptoms, including memory loss, after eating mussels from Prince Edward Island. Subsequent cases have been identified after consumption of shellfish from the United States, Spain, and the United Kingdom. The responsible toxin, domoic acid, comes from a diatom, *Pseudonitzschia multiseries* , and is a potent glutamate agonist, disrupting neurochemical transmission in the brain. It also binds to glutamate receptors, which increase calcium influx, producing neuronal swelling in the hippocampal area of the brain and death.

The initial clinical manifestations are gastrointestinal. Memory loss is closely related to advanced age. Those patients <40 yr are more likely to suffer only from diarrhea, whereas those >50 yr suffer from memory loss lasting months to years.

Pufferfish Poisoning

The consumption of pufferfish (blowfish) in certain geographic areas such as Japan and the Indo-Pacific Ocean is associated with a lethal neurotoxic illness due to tetrodotoxin. Fugu, a Japanese delicacy, is sought after in part because of the subtle neurotoxic effects experienced upon eating, including perioral paresthesias and a dissociative feeling. While a trained fugu chef will remove the most toxic parts of the fish, the toxin is still found in varying degrees.

Tetrodotoxin, which is also found in the blue-ringed octopus, causes a paralytic illness due to the blockade of voltage-dependent sodium channels. Early symptoms include paresthesias, nausea, and dizziness, which progresses to weakness, numbness, and incoordination. Autonomic compromise may also occur with bradycardia and hypotension. In the most severe of cases, respiratory compromise requires assisted ventilation.

There is no specific antidote for tetrodotoxin pufferfish poisoning.

Azaspiracid Poisoning

The azaspiracids are a class of algal toxins associated with **harmful algal blooms (HAB)** . Azaspiracid poisoning results from ingestion of contaminated bivalve shellfish, especially mussels. Azaspiracid toxins are distributed throughout the muscle tissue in the shellfish. Azaspiracid is cytotoxic to cells and an inhibitor of Ca^{2+} channels in plasma membranes. Symptoms start 6-18 hr after ingestion and include nausea, vomiting, severe stomach cramps, and diarrhea, which often persist up to 5 days.

Cyanobacteria (blue-green algae) also produce HAB; exposure is usually during recreational water sports and may be cutaneous or gastrointestinal. Symptoms include rash, cough, abdominal pain, diarrhea, nausea, emesis, muscle aches, watery eyes, weakness, or sore throat.

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740.4

Melamine Poisoning

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Keywords

melamine
renal failure

Melamine (1,3,5-triazine-2,4,6-triamine, or $C_3H_6N_6$), a compound developed in the 1830s, is found in many plastics, adhesives, laminated products, cement, cleansers, fire retardant paint, and more. Melamine poisoning from food products was unheard of until 2007, when melamine-tainted pet food caused the death of many dogs and cats in the United States. In 2008, feeding of melamine-tainted infant formula to more than 300,000 children resulted in kidney injuries, 50,000 hospitalizations, and 6 deaths in China. This was the first reported epidemic of melamine-tainted milk products.

Melamine contains 66% nitrogen by mass. The illegal addition of melamine to infant formula can give the formula a milky appearance and falsely raise the protein content as measured by nitrogen testing. Melamine, combined with cyanuric acid, forms cyanurate crystals in the kidneys. Along with protein, uric acid, and phosphate, melamine forms renal calculi.

Clinical manifestations are initially subtle and nonspecific. The severity is dose related. The first symptoms in affected infants are unexplained crying (especially when urinating), vomiting, and discolored urine caused by the formation of stones and gravel in the urinary tract. Urinary obstruction and acute renal failure follow. In the absence of a specific diagnosis, death from renal failure may occur. Whether children with melamine-induced renal failure will have chronic sequelae is currently unknown. Animal studies have shown that melamine may cause cognitive impairment, but further investigation is needed.

The melamine stones and gravel can be treated with hydration, alkalinization, or lithotripsy. Acute renal failure requires supportive care and dialysis if needed.

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CHAPTER 741

Biologic and Chemical Terrorism*

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In April of 2017, an attack on the town of Khan Shaykhun in Syria employed a poisonous “nerve agent” (likely Sarin) and resulted in the deaths of at least 92 civilians, many of them young children. The attack intentionally targeted civilian neighborhoods at the time children were getting ready for school—strong evidence that its purpose was terror, not warfare. Terrorist actions targeting children are not novel. Brought to the forefront of American consciousness by Timothy McVeigh's references to child fatalities as “collateral damage” during the Oklahoma City bombing in April 1995, the intentional targeting of children became firmly ensconced as a global reality with the attack upon a school in Beslan, Russia, in September 2004. The attack, which left 334 (including 186 children) dead, presaged additional attacks specifically directed against children at an Amish school in Pennsylvania in 2006, at a camp for teenagers in Utoya, Norway, in 2011, and at Sandy Hook Elementary School in Connecticut in 2012, among others.

Paralleling the targeting of children is an apparent trend toward the use of “unconventional” weapons of terror. In 1984, members of the Rajneeshee cult employed *Salmonella typhi* in a wave of intentional poisonings that affected 751 persons, including 142 teenage patrons of a popular pizza parlor. In 1995, the Aum Shinrikyo cult killed 12 and sickened thousands by intentionally releasing sarin nerve agent in the Tokyo subway system. A disgruntled scientist allegedly deployed anthrax spores via the U.S. mail in October 2001, killing 5 and injuring 17 in an attack upon a nation already reeling in the wake of the 9/11 attacks.

These developments remind us that terrorists can strike at any time, utilizing any number of unconventional weapons, including biologic and chemical agents. Children will not be spared in these attacks on civilians, and indeed schools and daycare sites may be the targets of these actions.

Etiology

Terrorists may choose to use **weapons of opportunity,** agents that for some reason are readily available to some member of the terrorist group. The motives of terrorists often are obscure and difficult to predict. Prevention and response strategies should thus concentrate not on those agents most likely to be used but, rather, on those agents that, if used, would constitute the gravest potential threats to public health and security.

Biologic threat agents, including pathogens and toxins, have been divided by the Centers for Disease Control and Prevention into three categories, with **category A** including diseases caused by those six agents posing the greatest threat: anthrax, plague (see Chapter 230.3), tularemia (see Chapter 233), smallpox, botulism (see Chapter 237), and the viral hemorrhagic fevers (see Chapter 297).

Terrorists could also procure and release a vast array of potentially harmful chemicals. Tank cars full of flammable industrial gases and liquids, corrosive industrial acids and bases, poisonous compounds such as cyanides and nitrites, pesticides, dioxins, and explosives traverse our railways and roads daily. Four classes of "military-grade" chemicals with a history of use in warfare or manufactured specifically for use as weapons include the organophosphate-based nerve agents, vesicants, cyanides (misleadingly referred to as "blood agents"), and certain pulmonary irritants or "choking agents."

Epidemiology and Pediatric-Specific Concerns

Large-scale attacks on civilian targets will likely involve pediatric victims, and children may be more susceptible than adults to the effects of certain biologic and chemical agents (see Chapter 737). A thinner and less-keratinized epidermis makes dermally active agents, such as mustard or trichothecene mycotoxins, a greater risk to children than adults. A larger surface area per unit volume further increases the problem. A small relative blood volume makes children more susceptible to the volume losses associated with enteric infections such as cholera and to gastrointestinal intoxications such as might be seen with exposure to the staphylococcal enterotoxins. Children's high minute ventilation, compared with that of adults, increases the threat of agents delivered via the inhalational route. The fact that children live “closer to the ground” compounds this effect when heavier-than-air chemicals are involved. An immature blood-brain barrier may heighten the risk of central nervous system toxicity from nerve agents. Developmental considerations make it less likely that a child would readily flee an area of danger, thereby increasing exposure to these various adverse effects. Moreover, children are more likely to be terrified at the sight of responders in personal protective ensembles.

Children appear to have a unique susceptibility to certain potential agents that might be used by terrorists. Although adults generally suffer only a brief, self-limited incapacitating illness after infection with Venezuelan equine encephalitis virus, young children are more likely to experience seizures, permanent neurologic sequelae, and death. In the case of smallpox, waning herd immunity may disproportionately affect children. Vaccine-induced immunity to smallpox probably diminishes significantly after ages 3-10 yr. Although most adults are considered susceptible to smallpox, given that routine civilian immunization ceased in the early 1970s, older adults may have some residual protection from death, if not from the development of disease. Today's children are among the first to grow up in a world without any individual or herd immunity to smallpox.

Children also may experience unique disease manifestations not seen in adults. Suppurative parotitis is a common characteristic finding among children with melioidosis but is not generally seen in adults with *Burkholderia pseudomallei* infection (see Chapter 232.2). Seizures, often the presenting symptom of cyanide or nerve agent poisoning, may clinically be much harder to recognize in children than in adults, looking more like unresponsiveness or change in mental status than tonic-clonic phenomena.

Pediatricians are likely to experience unique problems in managing childhood victims of biologic or chemical attack. Many of the drugs useful in treating such casualties are unfamiliar to pediatricians or have relative contraindications in childhood. The fluoroquinolones and tetracyclines are commonly cited as agents of choice in the treatment and prophylaxis of anthrax, plague, tularemia, brucellosis, and Q fever. Both drug classes are often avoided in children, although the risk of morbidity and mortality from diseases induced by agents of bioterrorism far outweighs the minor risk associated with short-term use of these agents. Ciprofloxacin received, as its first licensed pediatric indication, FDA approval for use in the prophylaxis of anthrax after inhalational exposure during a terrorist attack. Doxycycline and levofloxacin are licensed specifically in children for the same indication, and levofloxacin is also licensed for postexposure prophylaxis of children against plague. Immunizations potentially useful in preventing biologic agent–induced diseases are often not approved for use in pediatric patients. The available anthrax vaccine is licensed only for those between 18 and 65 yr. The plague vaccine, currently out of production and probably ineffective against inhalational exposures, was approved only for individuals ages 18-61 yr. The smallpox vaccine, a live vaccine employing vaccinia virus, can cause fetal demise when given to pregnant women.

Many otherwise useful pharmaceutical agents are not available in pediatric dosing regimens. The military distributes nerve agent antidote kits consisting of prefilled autoinjectors designed for the rapid administration of atropine and pralidoxime. Many emergency departments and some ambulances stock these kits. The doses of agents contained in the nerve agent antidote kit are calculated for soldiers and thus are excessive of those appropriate for young children, and pediatric pralidoxime autoinjectors are not yet available. Atropine autoinjectors specifically formulated for children are approved by the FDA and are available. Even though these products exist, children smaller than 15 pounds are too small for safe use of the autoinjectors, and obtaining venous access via cutdown will not only be time-consuming but extremely difficult in a contaminated environment.

Although physical protective measures and devices (e.g., “gas masks”) are likely to be of little utility in a civilian terrorism setting, such commercially available devices are not often available in pediatric sizes. The Israeli experience during the first Gulf War suggests that frightened parents may improperly use such masks on their children, resulting in inadvertent suffocation.

In the event of a large-scale terrorist attack, there may be an insufficient number of pediatric hospital beds. In any large disaster, excess bed capacity might potentially be provided at civilian and veterans hospitals under the auspices of the National Disaster Medical System, but that system makes no specific provision for pediatric beds. The situation is even more dire regarding burn unit beds, which may be needed in an attack with vesicants like sulfur mustard.

Clinical Manifestations

Should a terrorist attack occur, clinicians may be called on to make prompt diagnoses and render rapid lifesaving treatments before the results of confirmatory diagnostic tests are available. Although each potential agent of terrorism produces its own unique clinical manifestations, it is useful to consider their effects in terms of a limited number of distinct clinical syndromes. This approach helps clinicians make prompt, rational decisions regarding empirical therapy. Casualties resulting from a terrorist attack would either experience symptoms immediately upon exposure to an agent (or within the first several hours after exposure) or, alternatively, would see their symptoms develop slowly over a period of days to weeks. In the former case, the sinister nature of the event is often obvious and the etiology more likely to be conventional or chemical in nature.

Biologic agents differ from conventional, chemical (see Chapter 737), and nuclear (see Chapter 736) weapons in that they have inherent incubation periods. Consequently, patients are likely to present distant in time and place from the point of an unannounced and unnoticed exposure to a biologic agent. Whereas traditional first responders, such as firefighters and paramedics, may be at the forefront of a conventional or chemical terrorism response, the primary care physician or emergency room is likely to constitute the first line of defense against the effects of a biologic agent.

Casualties can thus be categorized as either immediate or delayed in presentation. Within each of these categories, patients can be further classified as having primarily respiratory, neuromuscular, or dermatologic manifestations (Table 741.1). A limited number of agents may cause each particular syndrome, permitting institution of empiric therapy targeted at a short list of potential etiologies. The viral hemorrhagic fevers might manifest as fever and a bleeding diathesis; these agents are considered separately in Chapter 297 . In most cases, supportive care is the mainstay of hemorrhagic fever treatment.

Table 741.1

Diseases Caused by Agents of Chemical and Biologic Terrorism, Classified by Syndrome

	NEUROMUSCULAR SYMPTOMS PROMINENT	RESPIRATORY SYMPTOMS PROMINENT	DERMATOLOGIC FINDINGS PROMINENT
Sudden onset or intermediate onset	Nerve agents	Chlorine Phosgene Cyanide	Mustard Lewisite
Delayed onset	Botulism	Anthrax Plague Tularemia	Smallpox

		Ricin	

Sudden-Onset Neuromuscular Syndrome: Nerve Agents

The very rapid onset of neuromuscular symptoms after an exposure should lead the clinician to consider nerve agent intoxication. The nerve agents (*tabun, sarin, soman,* and *VX*) are **organophosphate** analogs of common pesticides that act as potent inhibitors of the enzyme acetylcholinesterase. They are hazardous via ingestion, inhalation, or cutaneous absorption (see Chapter 77).

The inhibition of cholinesterase by these compounds results in the accumulation of acetylcholine at neural and neuromuscular junctions, causing excess stimulation. The resultant **cholinergic syndrome** involves central, nicotinic, and muscarinic effects. Central effects are both muscarinically and nicotinically mediated, and include altered mental status progressing rapidly to lethargy and coma, as well as ataxia, convulsions, and central respiratory depression. Studies on pesticide exposure suggest that children may be more prone to central neurologic dysfunction with organophosphate toxicity than adults. The most lethal effects are respiratory, which result not only from central effects but also from direct paralysis of the diaphragm and other respiratory muscles (nicotinic effects), as well as bronchospasm and bronchorrhea (muscarinic effects). Nicotinic effects include muscle fasciculations and twitching, followed by weakness, which can progress to flaccid paralysis as muscles fatigue. Importantly, flaccid paralysis is not present initially, as in a patient with botulinum toxin poisoning; in botulinum toxin poisoning, neurotransmitter cannot be released from the presynaptic terminal, whereas in nerve agent poisoning, excess neurotransmitter accumulates because acetylcholinesterase, the enzyme that turns off the transmitter, is inhibited. Muscarinic effects include miosis (the clinical hallmark of a patient who has suffered a non-life-threatening nerve agent challenge), visual blurring, profuse lacrimation, and watery rhinorrhea. Bronchospasm and increased bronchial secretions lead to cough, wheezing, dyspnea, and cyanosis. Cardiovascular manifestations include bradycardia, hypotension, and atrioventricular block. Flushing, sweating, salivation, nausea, vomiting, diarrhea, abdominal cramps, and urinary incontinence are also seen. In the absence of prompt intervention, death can quickly result from a combination of central effects and respiratory muscle paralysis.

The classic neuromuscular syndrome of extremely acute symptoms most commonly results from an aerosol or vapor challenge, the most likely route in a terrorist attack. But nerve agents are liquids at standard temperature and pressure, and do not cause immediate irritation to skin, so liquid nerve agent can be contagious person-to-person, pass through the skin, and cause the cholinergic crisis syndrome that way. This is often delayed by minutes to hours, depending upon dose and body site. In children, because the stratum corneum of the skin forms only gradually, skin transit time will be reduced. The most important clinical pearl is that miosis may be a late development. *If the clinician suspects that the child may have been exposed to nerve agent via the skin route, she or he should immediately treat, even if miosis has not yet developed.*

Cyanide poisoning is a major differential diagnosis of nerve agent poisoning in an attack scenario. Cyanide poisons cytochrome a3 in the mitochondrial electron transport chain and can cause an almost immediate and rather similar syndrome of loss of consciousness, immediate rapid breathing, status epilepticus, and rapid progression to cardiac arrest. Important clinical differential points include miosis, which is usually absent in cyanide poisoning, and the usual lack of cyanosis (ironically) due to the tissues' inability to use oxygen from the blood, causing venous blood to retain oxygen and remain red. In a real emergency, it may be necessary to treat for both nerve agent and cyanide poisoning until the cause is definitively identified.

Delayed-Onset Neuromuscular Syndrome: Botulism

The delayed onset (hours to days after exposure) of neuromuscular symptoms is characteristic of botulism. Botulism occurs after exposure to 1 of 7 related neurotoxins produced by certain strains of *Clostridium botulinum,* a strictly anaerobic, spore-forming, Gram-positive bacillus commonly found in soil. Naturally occurring botulism (see Chapter 237) usually follows ingestion of preformed toxin (food poisoning) or results from intestinal toxin production (infantile botulism). An aerosol exposure would likely result in a case of clinical botulism indistinguishable from that caused by natural exposures.

Following exposure to botulinum toxin, clinical manifestations typically begin with bulbar palsies, causing patients to complain of ptosis, photophobia, and blurred vision resulting from difficulty in accommodation. Symptoms can progress to include dysarthria, dysphonia, and dysphagia, and finally, a descending symmetric paralysis. Sensation and sensorium are typically not affected. In the absence of intervention, death often results from respiratory muscle failure. The mechanism of action of botulinum toxin is almost the exact opposite of that of nerve agent. Seizures, loss of consciousness, and peripheral twitching and fasciculations, typical of nerve agent poisoning, are not seen in botulism.

Sudden-Onset Respiratory Syndrome: Chlorine, Phosgene, and Cyanide

The acute onset of respiratory symptoms shortly after exposure should prompt the clinician to consider a range of potential chemical agents. Of note, nerve agents, discussed previously, may affect respiration via massive bronchial hypersecretion, bronchospasm, and respiratory muscle paresis. However, the nerve agent casualty will likely have generalized muscle involvement and central nervous system manifestations. In contrast, the toxic inhalants chlorine and phosgene produce respiratory distress without neuromuscular involvement.

Chlorine is a dense, acrid, yellow-green gas that is heavier than air. After mild to moderate exposure, ocular and nasal irritation occurs, followed by cough, a choking sensation, bronchospasm, and substernal chest tightness. Pulmonary edema, mediated by hydrochloric acid and free oxygen radical generation, follows moderate to severe exposures within 30 min to several hours. Hypoxemia and hypovolemia secondary to pulmonary edema are the factors responsible for death when it occurs.

Phosgene, like chlorine, is a common industrial compound that was used as a weapon on the battlefields of World War I. Its odor has been described as similar to “new-mown hay.” Like chlorine, phosgene also is thought to result in the generation of hydrochloric acid, contributing particularly to upper airway, nasal, and conjunctival irritation. Acylation reactions caused by the effects of phosgene on the pulmonary alveolar-capillary membrane lead to pulmonary edema. Phosgene lung injury also may be mediated, in part, by an inflammatory reaction associated with leukotriene production. Patients with mild to moderate exposures to phosgene may be asymptomatic, a fact that may cause victims to remain in a contaminated area. Noncardiogenic pulmonary edema or “dry land drowning” occurs 4-24 hr after exposure and is dose dependent, with heavier exposures causing earlier symptoms. Dyspnea may precede radiologic findings. In severe exposures, pulmonary edema may be so marked as to result in hypovolemia and hypotension. As in the case of chlorine, death results from hypoxemia and asphyxia.

Cyanide is a cellular poison, with protean clinical manifestations. Initially, cyanide toxicity is most likely to manifest as tachypnea and hyperpnea, progressing rapidly to apnea in cases with significant exposure (see Chapter 77). The efficacy of cyanide as a chemical terrorism agent is limited by its volatility in open air and relatively low lethality in comparison with nerve agents. Released in a closed room, however, cyanide could have devastating effects, as evidenced by its use in the Nazi gas chambers during World War II. Cyanide inhibits cytochrome a_3 , interfering with normal mitochondrial oxidative metabolism and leading to cellular anoxia and lactic acidosis. In addition to respiratory distress, early findings among cyanide victims include tachycardia, flushing, dizziness, headache, diaphoresis, nausea, and vomiting. With greater exposure, seizures, coma, apnea, and cardiac arrest may follow within minutes. An elevated anion gap metabolic acidosis is typically present, and decreased peripheral oxygen utilization leads to an elevated mixed venous oxygen saturation value.

Delayed-Onset Respiratory Syndrome: Anthrax, Plague, Tularemia, and Ricin

A delayed onset of respiratory symptoms (days after exposure) is characteristic of several infectious diseases and 1 toxin that might be adapted for sinister purposes by terrorists. Among the most threatening and problematic of these are anthrax, plague, tularemia, and ricin, the latter having garnered considerable media attention in recent years.

Anthrax is caused by infection with the Gram-positive spore-forming rod *Bacillus anthracis*. Its ability to form a spore enables the anthrax bacillus to survive for long periods in the environment and enhances its potential as a weapon.

The vast majority of naturally occurring anthrax cases are cutaneous, acquired by close contact with the hides, wool, bone, and other by-products of infected ruminants (principally cattle, sheep, and goats). Cutaneous anthrax is amenable to therapy with a variety of antibiotics and is readily recognizable to experienced clinicians in endemic areas; consequently, it is rarely fatal. Although it is common in parts of Asia and sub-Saharan Africa, only two cases of cutaneous anthrax had occurred in the United States in the 9 yr that preceded the attacks of

2001 (when 11 cutaneous cases were seen). Gastrointestinal anthrax has been described only once in the United States, in a drum circle participant whose drum heads were made from imported animal hides. In general, however, it occurs after the ingestion of contaminated meat. In the past, inhalational anthrax, or **woolsorters' disease** , was an occupational hazard of abattoir and textile workers. Now eliminated as a naturally occurring disease in the United States, it is this inhalational form of anthrax that poses the greatest terror threat. Following an inadvertent release in 1979 from a bioweapons facility at Sverdlovsk in the former Soviet Union, 66 of 77 (86%) known adult victims of inhalational anthrax died. In the 2001 attacks involving contaminated mail in the United States, 5 of 11 (46%) patients with inhalational anthrax died. Whether better intensive care modalities, changes in antibiotic therapy, or earlier recognition accounted for this improved mortality rate remains unknown.

Symptomatic *inhalational* anthrax typically begins 1-6 days after exposure, although incubation periods of up to several weeks have been reported. The disease begins as a flulike illness, characterized by fever, myalgia, headache, and cough. A brief intervening period of improvement sometimes follows, but rapid deterioration then ensues; high fever, dyspnea, cyanosis, and shock mark this second phase. Hemorrhagic meningitis occurs in up to 50% of cases. Chest radiographs obtained late in the course of illness may reveal a widened mediastinum or prominent mediastinal lymphadenopathy; pleural effusions also may be seen. Bacteremia is often so profound that Gram stains of peripheral blood may demonstrate the organism at this stage. Prompt treatment is imperative; death occurs in as many as 95% of inhalational anthrax cases if such treatment is begun more than 48 hr after the onset of symptoms.

Whereas inhalational anthrax is a disease primarily of mediastinal lymphatic tissue, exposure to aerosolized plague bacilli typically leads to a primary pneumonia. Endemic **plague** is usually transmitted via the bites of fleas and is discussed in Chapter 230.3 . The causative organism of all forms of human plague, *Yersinia pestis,* is a bipolar-staining, Gram-negative facultative intracellular bacillus. An ability to survive within the macrophage aids its dissemination to distant sites following inoculation or inhalation. “Buboes,” markedly swollen, tender regional lymph nodes in the distribution of a bite, are the hallmark feature of bubonic plague. Fever and malaise are typically present, and septicemia often develops as bacteria gain access to the circulation. Petechiae, purpura, and overwhelming disseminated intravascular coagulopathy commonly occur, and 80% of bubonic plague victims ultimately have positive blood culture results. Plague is extremely infective and lethal, as illustrated by the fact that the "Black Death" eliminated one third of the population of Europe during the Middle Ages.

Intentional aerosol dissemination of *Y. pestis* would likely result in a preponderance of pneumonic plague cases. Pneumonic plague may also arise secondarily after seeding of the lungs of septicemic patients. Symptoms include fever, chills, malaise, headache, and cough. Chest radiographs may reveal a patchy consolidation, and the classic clinical finding is blood-streaked sputum. Disseminated intravascular coagulation and overwhelming sepsis typically develop as the disease progresses. Untreated pneumonic plague has a fatality rate approaching 100%.

Tularemia is a highly infectious disease caused by the Gram-negative coccobacillus *Francisella tularensis*. Naturally occurring tularemia is discussed in Chapter 233 . The high degree of infectivity of *F. tularensis* (<10 organisms are thought to be necessary to produce infection via inhalation), as well as its survivability in the environment, contributes to its inclusion on the list of agents of concern. Several clinical forms of endemic tularemia are known, but inhalational exposure resulting from a terrorist attack would likely lead to a plague-like primary pneumonia or to typhoidal tularemia, manifesting as a variety of nonspecific symptoms, including fever, malaise, and abdominal pain.

Ricin is a protein toxin derived from the castor bean plant *(Ricinus communis)* that inhibits ribosomal protein synthesis. It is highly toxic in animal studies when inhaled, and may result in the delayed onset of respiratory distress, pulmonary edema, and acute respiratory failure. One case series of 8 persons from the 1940s described a febrile respiratory illness after inhalational exposure. If injected, it may cause a sepsis-like syndrome that may progress to multiorgan system failure; ingestion can lead to severe gastroenteritis. Ricin-containing letters were mailed to a U.S. Senate office building in 2004, and again to President Obama and New York City Mayor Bloomberg in 2013, although no persons were sickened in either attack.

Intermediate-Onset Dermatologic Syndrome: Mustard and Lewisite

The development of skin lesions within hours to days of exposure is characteristic of the chemical vesicants. These compounds, often referred to as **blistering agents** , are cellular poisons and include the alkylating agent mustard and the organic arsenical agent lewisite. Tissue injury to rapidly reproducing cells begins within minutes of contact with these agents. Clinical effects typically become evident several hours after exposure to mustard, whereas patients exposed to lewisite feel immediate pain. Both mustard and lewisite affect the eyes and respiratory tract, and their inadvertent ingestion may produce significant gastrointestinal symptoms. Mustard exposure may lead several days later to bone marrow suppression. With a large challenge, mustard may also cause an acute respiratory syndrome, particularly affecting the upper airway and presenting with laryngospasm and stridor.

Delayed-Onset Dermatologic Syndrome: Smallpox

The appearance of an exanthem days to weeks after exposure is likely to be a presenting feature of smallpox. Caused by infection with variola virus, a member of the orthopoxvirus family, smallpox has an incubation period of 7-17 days. This would likely permit the wide dispersal of asymptomatic exposed persons, thus contributing to the spread of an outbreak. During the incubation period, the virus replicates in the upper respiratory tract. A primary viremia ensues, during which time seeding of the liver and spleen occurs. A secondary viremia then develops, the skin is seeded, and the classic exanthem of smallpox appears.

Symptoms of smallpox begin abruptly during the phase of secondary viremia and include fever, rigors, vomiting, headache, backache, and extreme malaise. Within 2-4 days, macules appear on the face and extremities and then progress in synchronous fashion to papules, pustules, and finally scabs. As the scabs separate, survivors often are left with disfiguring, depigmented scars. The synchronous nature of the rash and its centrifugal distribution distinguish smallpox from chickenpox, which has a centripetal distribution. Historically, smallpox had a 30% mortality rate, with death typically resulting from visceral organ involvement.

Diagnosis

In some cases, the terrorist nature of a chemical or biologic attack may be obvious—for example, a chemical attack in which victims succumb in close temporal and geographic proximity to a dispersal device or terrorists announce their attack. In other instances, the clinician may need to rely on epidemiologic clues to suspect an intentional release of chemical or biologic agents. The presence of large numbers of victims clustered in time and space should raise the index of suspicion, as should cases of unexpected death or unexpectedly severe disease. Diseases unusual in a given locale, in a given age group, or during a certain season likewise may warrant further investigation. Simultaneous outbreaks of a disease in noncontiguous areas should cause one to consider an intentional release (as in the 2001 mail-borne anthrax attacks), as should outbreaks of multiple diseases in the same area. Even a single case of a rare disorder such as anthrax or certain viral hemorrhagic fevers would be suspicious, and a single case of smallpox would almost certainly be the result of an intentional dissemination. Large numbers of dying animals might provide evidence of an unnatural aerosol release, as would evidence of disparate attack rates between those known to be indoors and outdoors at a given time.

In a mass casualty setting, diagnoses may be made largely on clinical grounds. The diagnosis of nerve agent intoxication is based primarily on clinical recognition and patient response to antidotal therapy. Several simple rapid detection devices developed for military use can detect the presence of nerve agents in the environment. Some of these are now commercially available and are stocked in certain emergency departments and public safety vehicles. Measurements of acetylcholinesterase in plasma or erythrocytes of nerve agent victims may be helpful in long-term prognostication, but the correlation between cholinesterase levels and clinical effects is often poor, and the test rarely is available on an emergency basis.

Botulism should be suspected clinically among patients presenting with a symmetric, descending, flaccid paralysis. Although the differential diagnosis of botulism includes other uncommon neurologic disorders, such as myasthenia gravis and the Guillain-Barré syndrome, the presence of multiple casualties with similar symptoms should aid in the determination of a botulism outbreak. Electromyography is useful in supporting the diagnosis.

Initially the diagnosis of **cyanide poisoning** also will likely be made on clinical grounds in the presence of the appropriate toxidrome. An unusually high anion gap metabolic acidosis with elevated serum lactate and an oxygen concentration greater than expected in mixed venous blood lend support to the clinical diagnosis. Elevated blood cyanide concentrations can confirm the clinical suspicion.

Of all the chemical and biological agents, the only ones for which immediate therapy without waiting for definitive diagnosis is potentially life-saving and mandatory are nerve agents and cyanide poisoning. If these are suspected, they should be treated before waiting for further diagnostic certainty, since they can kill so quickly.

Anthrax should be suspected upon finding Gram-positive bacilli in skin biopsy material (in the case of cutaneous disease), blood smears, pleural fluid, or spinal fluid. Chest radiographs demonstrating a widened mediastinum in the context of fever and constitutional signs and, in the absence of another obvious explanation (e.g., blunt trauma or postsurgical infection), should also lead one to consider the diagnosis. Confirmation can be obtained by blood culture.

A diagnosis of **plague** can be suspected on finding bipolar “safety-pin”–staining bacilli in Gram or Wayson stains of sputum or aspirated lymph node material; confirmation is obtained by culturing *Y. pestis* from blood, sputum, or lymph node aspirate. The organism grows on standard blood or MacConkey TRA agars, but it is often misidentified by automated systems. *F. tularensis* , the causative agent of tularemia, grows poorly on standard media; its growth is enhanced on media containing cysteine. Because of its extreme infectivity, however, many laboratories prefer to make a diagnosis via polymerase chain reaction or serologically using an enzyme-linked immunosorbent assay or serum agglutination assay.

Smallpox should be suspected on clinical grounds and can be confirmed by culture or electron microscopy of scabs or vesicular fluid, although the manipulation of clinical material from suspected smallpox victims should be attempted only at public health laboratories able to employ maximum biocontainment (Biosafety Level 4) precautions. Similar caution should be exercised with specimens from patients with various viral hemorrhagic fevers.

Prevention

Preventive measures can be considered in both a preexposure and a postexposure context. **Preexposure protection** against a chemical or biologic attack may consist of physical, chemical, or immunologic measures. **Physical protection** against primary attack often involves gas masks and protective suits; such equipment is used by the military and by certain hazardous materials response teams, but it is unlikely to be available to civilians at the precise moment that a release occurs. Medical personnel need to understand the principles of physical protection as they apply to infection control and the spread of contamination.

Pneumonic plague is spread through respiratory droplets. Droplet precautions, including the use of simple surgical masks, are thus warranted for providers caring for patients with plague. Smallpox is transmitted by droplet nuclei. Airborne precautions, including (ideally) a high-efficiency particulate air filter mask, are thus warranted with smallpox victims. Patients with certain viral hemorrhagic fevers, such as those caused by filoviruses (Ebola, Marburg) and arenaviruses, should be managed using a combination of droplet and contact precautions, ideally in a specialized biocontainment unit. Most other biologic agent victims can be safely cared for with the use of standard precautions. In the case of chemical agents, residual mustard or nerve agent on the skin or clothing of victims might potentially pose a hazard to medical personnel. For such victims, whenever possible, clothing should be removed, and the patients decontaminated using copious amounts of water before extensive medical care is rendered. Most other chemical agents are volatile enough that spread of an agent among patients or from patient to caregiver is unlikely.

Preexposure chemical prophylaxis might be used on the basis of credible intelligence reports. Should officials deem that the threatened release of a specific biologic agent appears imminent, antibiotics might be distributed to a population prior to exposure. Opportunities to employ such a strategy are likely to be limited, although federal and state officials are examining various mechanisms for such employment. In military settings, pyridostigmine is FDA-approved as pretreatment against expected nerve agent attack. It is not approved for use in children, and it is not likely to be recommended in civilian settings.

Although licensed vaccines **(preexposure immunologic measures)** against anthrax and smallpox have been developed, widespread use of either vaccine is likely to be problematic, especially in children. The anthrax vaccine is licensed only for those persons age 18 yr and older, is given as a five-dose series over 18 mo, and requires annual booster doses. These considerations make civilian employment of the current anthrax vaccine on a large scale unlikely, although a new recombinant anthrax vaccine is in development and being studied as a three-dose series.

Significant obstacles to the widespread employment of smallpox vaccine also exist, although public health officials have contemplated the resumption of a smallpox vaccination campaign. Whereas in the past smallpox vaccine (prepared from vaccinia virus, an orthopoxvirus related to variola) was used safely and successfully in young infants, it has a relatively high rate of serious complications in certain patients. *Fetal vaccinia* and demise can occur when pregnant women are vaccinated. *Vaccinia gangrenosa* , an often fatal complication, can occur when immunocompromised persons are vaccinated. *Eczema vaccinatum* occurs in those with preexisting dermatoses (atopic dermatitis). Severe vaccine-related encephalitis was well known during the era of widespread vaccination; because it occurs only in primary vaccines, it would disproportionately affect pediatric patients. Autoinoculation can occur when the virus present at the site of vaccination is manually transferred to other areas of skin or to the eye. Young children would presumably be at greater risk for such inadvertent transmission. Myocarditis has been reported following vaccinations of military recruits.

To manage these complications, vaccinia immune globulin should be available when one is undertaking a vaccination campaign. Vaccinia immune globulin (0.6 mg/kg IM) may be given to vaccine recipients who experience severe complications or to significantly immunocompromised individuals exposed to smallpox and in whom vaccination would be unsafe. A compound, tecovirimat, has been used successfully under an Investigational New Drug permit to treat persons (including children) experiencing severe complications from vaccine. The current cell-culture–derived vaccine (ACAM2000), as well as vaccinia immune globulin and tecovirimat, can be obtained as needed upon consultation with officials at the Centers for Disease Control and Prevention. In addition to a potential role in preexposure prophylaxis, vaccination may be effective in postexposure prophylaxis if given within the 1st 4 days or so after exposure.

Anthrax vaccine might similarly be employed in a postexposure setting. Some authorities recommend three doses of this vaccine as an adjunct to postexposure chemoprophylaxis after documented exposure to aerosolized anthrax spores. Nonetheless, postexposure administration of oral antibiotics constitutes the mainstay of management for asymptomatic victims believed to have been exposed to anthrax as well as to other bacterial agents such as plague and tularemia. Table 741.2 lists appropriate prophylactic regimens for various biologic exposures.

Table 741.2

Critical Biologic Agents of Terrorism

DISEASE	CLINICAL FINDINGS	INCUBATION PERIOD (DAYS)	ISOLATION PRECAUTIONS	INITIAL TREATMENT	PROPHYLAXIS
Anthrax	Febrile	1-5	Standard	See Table 741.3	**Ciprofloxacin 30**

(inhalational) Patients who are clinically stable after 14 days can be switched to a single oral agent (as described in the prophylaxis section of this table) to complete a 60-day course*	prodrome with rapid progression to mediastinal lymphadenitis and mediastinitis, sepsis, shock, and meningitis				**mg/kg/day PO divided q12h** [†] (max 500 mg/dose) *or* **Doxycycline 4.4 mg/kg/day PO divided q12h** (max 100 mg/dose) *or* Clindamycin 30 mg/kg/day PO divided q8h (max 900 mg/dose) *or* Levofloxacin 16 mg/kg/day PO divided q12h (max 250 mg/dose) *or* **Amoxicillin 75 mg/kg/day PO divided q8h** [‡] (max 1 g/dose) *or* Penicillin VK 50-75 mg/kg/day divided q6-8h
Plague (pneumonic)	Febrile prodrome with rapid progression to fulminant pneumonia, hemoptysis, sepsis, disseminated intravascular coagulation	2-3	Droplet (for 1st 3 days of therapy)	Gentamicin 2.5 mg/kg IV q8h *or* doxycycline 2.2 mg/kg IV q12h *or* ciprofloxacin 15 mg/kg IV q12h	Doxycycline 2.2 mg/kg PO q12h *or* ciprofloxacin 20 mg/kg PO q12h
Tularemia	Pneumonic: abrupt onset of fever with fulminant pneumonia Typhoidal: fever, malaise, abdominal pain	2-10	Standard	Same as for plague	Same as for plague
Smallpox	Febrile prodrome with synchronous, centrifugal, vesiculopustular exanthema	7-17	Airborne (+ contact)	Supportive care	Vaccination may be effective if given within the 1st several days after exposure
Botulism	Afebrile descending symmetric flaccid paralysis with cranial	1-5	Standard	Supportive care; antitoxin (see text) may halt the progression of	None

	nerve palsies			symptoms but is unlikely to reverse them	
Viral hemorrhagic fevers	Febrile prodrome with rapid progression to shock, purpura, and bleeding diatheses	4-21	Contact (consider airborne in cases of massive hemorrhage)	Supportive care; ribavirin may be beneficial in treating Lassa fever, and perhaps other arenaviral hemorrhagic fevers	Ribavirin has been shown to be efficacious in the postexposure prophylaxis of Lassa fever

[†] Preferred drugs are shown in bold font.

[‡] Penicillin and amoxicillin should only be used when the strain of Bacillus anthracis is known to be susceptible.

Treatment

Tables 741.2 , 741.3 , and 741.4 provide recommended therapies for overt diseases caused by various chemical and biologic agents. It is likely that the clinician attending to victims will need to make therapeutic decisions before the results of confirmatory diagnostic tests are available and in situations in which the diagnosis is not known with certainty. In particular, decontamination by hospital personnel in appropriate personal protective equipment is required for patients exposed to chemical agents who have not been adequately decontaminated in the prehospital setting (see Table 741.4). In such cases, it is useful to note that many diseases and symptoms caused by chemical and biologic agents will resolve spontaneously, with only supportive care required. Most cases of chlorine or phosgene exposure can be successfully managed by providing meticulous attention to oxygenation and fluid balance. Mustard victims may require intensive multisystem support, but no specific antidote or therapy is available. Many viral diseases, such as smallpox, most viral hemorrhagic fevers, and the equine encephalitides, are also managed supportively.

Table 741.3

Treatment of Inhalational Anthrax in Children

WHEN MENINGITIS HAS NOT BEEN RULED OUT*	WHEN MENINGITIS CAN BE RULED OUT
1. A Bactericidal Fluoroquinolone:	1. A Bactericidal Antimicrobial:

1. A Bactericidal Fluoroquinolone: Ciprofloxacin 30 mg/kg/day IV divided q8h [†] (max 400 mg/dose) *or* Levofloxacin 16 mg/kg/day IV divided q12h (max 250 mg/dose) *or* Moxifloxacin 12 mg/kg/day IV divided q12h (max 200 mg/dose; for children 3 mo-2 yr old); 10 mg/kg/day IV divided q12h (for children 2-5 yr old); 8 mg/kg/day IV divided q12h (for children 6-11 yr old); 400 mg IV qd (for children >12 yr old and >45 kg)	1. A Bactericidal Antimicrobial: Ciprofloxacin 30 mg/kg/day IV divided q8h (max 400 mg/dose) *or* Levofloxacin 20 mg/kg/day IV divided q12h (max 250 mg/dose) *or* Imipenem 100 mg/kg/day IV divided q6h (max 1 g/dose) *or* Vancomycin 60 mg/kg/day IV divided q8h *or* **Penicillin G 400,000 U/kg/day IV divided q4h** (max 4 MU/dose) *or* Ampicillin 200 mg/kg/day IV divided q6h (max 3 g/dose)
2. A 2nd Bactericidal Antimicrobial: Meropenem 120 mg/kg/day IV divided q8h (max 2 g/dose) *or* Imipenem 100 mg/kg/day IV divided q6h (max 1 g/dose) *or* Doripenem 120 mg/kg/day IV divided q8h (max 1 g/dose) *or* Vancomycin 60 mg/kg/day IV divided q8h *or* **Penicillin G 400,000 U/kg/day IV divided q4h** [‡] (max 4 MU/dose) *or* Ampicillin 400 mg/kg/day IV divided q6h (max 3 g/dose)	
3. A Protein Synthesis Inhibitor **Linezolid 30 mg/kg/day IV divided q8h** (for children <12 yr old); 30 mg/kg/day IV divided q12h (for children >12 yr old; max 600 mg/dose) *or* Clindamycin 40 mg/kg/day IV divided q8h (max 900 mg/dose) *or* Rifampin 20/mg/kg/day IV divided q12h (max 300 mg/dose) *or* Chloramphenicol 100 mg/kg/day IV divided q6h	2. A Protein Synthesis Inhibitor **Clindamycin 40 mg/kg/day IV divided q8h** (max 900 mg/dose) or Linezolid 30 mg/kg/d IV divided q8h (for children <12 yr old); 30 mg/kg/day IV divided q12h (for children >12 yr old; max 600 mg/dose) *or* Rifampin 20/mg/kg/day IV divided q12h (max 300 mg/dose) *or* Doxycycline 4.4 mg/kg/day IV loading dose (for children <45 kg; max 200 mg), followed by 4.4 mg/kg/day IV divided q12h; 200 mg IV loading dose, followed by 100 MG IV q12h (for children >45 kg)

[*] Meningitis occurs in approximately 50% of patients with inhalational anthrax.

[†] Preferred drugs are shown in bold font.

[‡] Penicillin and ampicillin should only be used when the strain of Bacillus anthracis is known to be susceptible.

Table 741.4

Critical Chemical Agents of Terrorism

AGENT	TOXICITY	CLINICAL FINDINGS	ONSET	DECONTAMINATION[*]	MANAGEM
NERVE AGENTS					
Tabun, sarin, soman,	Anticholinesterase: muscarinic, nicotinic, central	Vapor: miosis, rhinorrhea, dyspnea	Seconds: vapor Minutes to	Vapor: fresh air, remove clothes, wash hair	ABCs. A 0.05 mg/

VX	nervous system effects	Liquid: diaphoresis, vomiting Both: coma, paralysis, seizures, apnea	hours: liquid	Liquid: remove clothes, wash skin, hair with copious soap and water, ocular irrigation	‡ (min: 0. 5 mg), re min prn f secretions bronchos Pralidoxi mg/kg IV (max: 1 g IM), may within 30 prn, then for 1 or 2 for persis weakness atropine r Diazepam mg/kg (m IV; loraze mg/kg IV 4 mg); mi 0.2 mg/kg mg) IM p seizures c exposure
VESICANTS					
Mustard	Alkylation	Skin: erythema, vesicles Eye: inflammation Respiratory tract: inflammation	Hours	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Symptomatic
Lewisite	Arsenical		Immediate pain	Skin: soap and water Eyes: water (effective only if done within minutes of exposure)	Possibly Brit antilewisite (mg/kg IM q4 systemic effe lewisite in se
PULMONARY AGENTS					
Chlorine, phosgene	Liberate hydrochloric acid, alkylation	Eye, nose, and throat irritation (especially chlorine) Respiratory: bronchospasm, pulmonary edema (especially phosgene)	Minutes: eye, nose, and throat irritation, bronchospasm Hours: pulmonary edema	Fresh air Skin: water	Symptomatic text)
CYANIDE					
	Cytochrome oxidase	Tachypnea, coma, seizures, apnea	Seconds	Fresh air	ABCs, 100%
	Inhibition: cellular anoxia, lactic			Skin: soap and water	Na bicarbona metabolic aci

	acidosis				hydroxocoba mg/kg IV (m nitrite/thiosul as follows (se	
					Na nitrite (3%): dose (mL/kg) (max: 10 mL)	*E h c (g*
					0.27	1
					0.33	1 fo c
					0.39	1
					followed by Na thiosulfate (25%): 1.65 mL/kg (max: 50 mL)	

[*] Decontamination, especially for patients with significant nerve agent or vesicant exposure, should be performed by healthcare providers garbed in adequate personal protective equipment. For emergency department staff, this equipment consists of a nonencapsulated, chemically resistant body suit, boots, and gloves with a full-face air-purifier mask/hood.

[†] Intraosseous route is likely equivalent to intravenous.

[‡] Atropine might have some benefit via endotracheal tube or inhalation, as might aerosolized ipratropium. See also Table 741.5 .

[§] Pralidoxime is reconstituted to 50 mg/mL (1 g in 20 mL water) for IV administration, and the total dose infused over 30 min, or may be given by continuous infusion (loading dose 25 mg/kg over 30 min, and then 10 mg/kg/hr). For IM use, it might be diluted to a concentration of 300 mg/mL (1 g added to 3 mL water—by analogy to the U.S. Army's Mark 1 autoinjector concentration), to effect a reasonable volume for injection. See also Table 741.5 .

ABCs, Airway, breathing, and circulatory support; max, maximum; min, minimum; prn, as needed.

Adapted from Henretig FH, Cieslak TJ, Eitzen EM: Biological and chemical terrorism. *J Pediatr* 141:311–326, 2002.

In addition to ensuring adequate oxygenation, ventilation, and hydration, the clinician may need to provide specific empiric therapies on an urgent basis. Patients suffering from the sudden onset of severe neuromuscular symptoms may have nerve agent intoxication and should be given atropine (0.05 mg/kg) promptly for its antimuscarinic effects. Although atropine relieves bronchospasm and bradycardia, reduces bronchial secretions, and ameliorates the gastrointestinal effects of nausea, vomiting, and diarrhea, it does not improve skeletal muscle paralysis. Pralidoxime (also known as *2-PAM*) cleaves the organophosphate moiety from cholinesterase and regenerates intact enzyme if “aging” has not occurred. The effect is most prominent at the neuromuscular junction and leads to improved muscle strength. Its prompt use (at a dose of 25 mg/kg) as an adjunct to atropine is recommended in all serious cases.

Ideally, both atropine and pralidoxime should be administered intravenously in severe cases, although the intraosseous route may be acceptable. Some experts recommend that atropine be given intramuscularly in the presence of hypoxia to avoid arrhythmias associated with intravenous administration. Many emergency management services stock military-style autoinjector kits consisting of atropine and 2-PAM for intramuscular injection. Pediatric atropine autoinjectors are licensed, although kits intended for adults (with 2 mg of atropine and 600 mg of pralidoxime) might be used in children >2-3 yr (Table 741.5). Autoinjectors cannot easily be used in the smallest infants.

Table 741.5

Pediatric Autoinjector Recommendations for Mass Casualties or Prehospital Care*

ATROPINE AUTOINJECTOR THERAPY			
APPROXIMATE AGE	APPROXIMATE WEIGHT (kg)	AUTOINJECTOR SIZE (mg)	
<6 mo	<7.5	0.25	
6 mo-4 yr	7.5-18	0.5	
5-10 yr	18-30	1.0	
>10 yr	>30	2.0	
PRALIDOXIME AUTOINJECTOR THERAPY			
APPROXIMATE AGE (yr)	APPROXIMATE WEIGHT (kg)	NUMBER OF AUTOINJECTORS	PRALIDOXIME DOSE (mg/kg)
3-7	13-25	1	24-46
8-14	26-50	2	24-46
>14	>50	3	<35

* Consider adult pralidoxime autoinjector use for severely affected mass casualties when IV access or more precise mg/kg IM dosing is logistically impractical. The initial dose using atropine autoinjectors is 1 autoinjector of each recommended size. The initial dose using pralidoxime autoinjectors is the recommended number of (adult-intended, 600 mg) autoinjectors. These latter may also be injected into an empty sterile vile; the contents redrawn through a filter needle into a small syringe may then provide a ready source of concentrated (300 mg/mL) pralidoxime solution for IM injection to infants. Autoinjectors may become available that provide adult doses of both atropine and pralidoxime in 1 injector; these could be used in children ≥3 yr in lieu of 2 individual injectors and dosed as noted previously for pralidoxime alone.

Animal studies support the routine prophylactic administration of anticonvulsant doses of benzodiazepines, even in the absence of observable convulsive activity. At present, the approved benzodiazepine is diazepam, but FDA approval of midazolam, which shows superior activity against nerve agent-induced seizures in multiple animal models, is anticipated within the next few years.

Delayed neuromuscular symptoms in the setting of terrorism might be due to botulism. Supportive care, with meticulous attention to ventilatory support, is the mainstay of botulism treatment. Such support may be necessary for several months, making the management of a large-scale botulism outbreak especially problematic in terms of medical resources. A licensed heptavalent antitoxin (types A-G) is available through the Centers for Disease Control (1-800-232-4636). Administration of this antitoxin is unlikely to reverse disease in symptomatic patients but may prevent further progression. In addition, a pentavalent (containing antibody against toxin types A to E, but licensed only for treatment of type A or B intoxication) product, Botulism Immune Globulin Intravenous (Human), BabyBIG, is available through the California Department of Health Services (1-916-327-1400) specifically for the treatment of infant botulism.

The **rapid onset of respiratory symptoms** may signal an exposure to chlorine, phosgene, cyanide, or a number of other toxic industrial chemicals. Although the mainstay of therapy in virtually all of these exposures consists of removal to fresh air and intensive supportive care, cyanide intoxication often requires the administration of specific antidotes.

The classic **cyanide antidote** utilizes a nitrite along with sodium thiosulfate and is given in 2 stages. The methemoglobin-forming agent (e.g., sodium nitrite) is administered first, because methemoglobin has a high affinity for cyanide and causes it to dissociate from cytochrome oxidase. Nitrite dosing in children should be based on body weight to avoid excessive methemoglobin formation and nitrite-induced hypotension. For the same reasons, nitrites should be infused slowly over 5-10 min. A sulfur donor, such as sodium thiosulfate, is given next. This compound is used as a substrate by the hepatic enzyme rhodanese, which converts cyanide to thiocyanate, a less toxic compound excreted in the urine. Thiosulfate treatment itself is efficacious and relatively benign, and may be used alone for mild to moderate cases. Sodium nitrite and sodium thiosulfate are packaged together in standard antidote kits, along with amyl nitrite, a sodium nitrite substitute that can be inhaled in prehospital settings in which intravenous access is not available.

Another antidote available in the United States is hydroxocobalamin, which exchanges its hydroxy group for cyanide, forming harmless cyanocobalamin (vitamin B_{12}), which is subsequently excreted by the kidneys. Hydroxocobalamin use is not complicated by the potential for nitrite-induced hypotension or methemoglobinemia, and it has low toxicity. The recommended dose is 5 g in adults or 70 mg/kg in children, administered IV over 15 min. A second dose (2.5-5 g in adults; 35-70 mg/kg in children) may be repeated in severely affected patients. Side effects include modest hypertension and reddening of skin, mucous membranes, and urine that may last several days. Although no human controlled trials are currently available to compare hydroxocobalamin with nitrite/thiosulfate-based therapies, many authorities believe that hydroxocobalamin's efficacy and safety profile favor it as the cyanide antidote of choice, especially for children in the mass casualty context. To use hydroxocobalamin, however, the solution must be mixed immediately before use, in the field if need be, so first responders need to be properly trained to employ it.

Animal research suggests a modest benefit of steroid therapy in mitigating lung injury after chlorine inhalation, and thus steroids may be considered for patients with chlorine exposure, especially as an adjunct to bronchodilators in those manifesting bronchospasm and/or a history of asthma. Further, symptomatic relief has also been reported following chlorine exposure with nebulized 3.75% sodium bicarbonate therapy, though the impact of this regimen on pulmonary damage is unknown. Animal models have also suggested a benefit from antiinflammatory agents, including ibuprofen and *N* -acetylcysteine, which appear to ameliorate phosgene-induced pulmonary edema, as well as the utilization of low tidal volume ventilation (protective ventilation), although the results of such interventions have not yet been reported in clinical trials.

In cases in which the **delayed onset of respiratory symptoms** may be the result of a terrorist attack, consideration should be given to the empirical administration of an antibiotic effective against anthrax, plague, and tularemia. Ciprofloxacin (10-15 mg/kg IV q12h), levofloxacin (8 mg/kg IV q12h), or doxycycline (2.2 mg/kg IV q12h) is a reasonable choice. Although naturally occurring strains of *B. anthracis* usually are quite sensitive to penicillin G, these agents are chosen because penicillin-resistant strains of *B. anthracis* exist. Moreover, ciprofloxacin and doxycycline are effective against almost all known strains of *Y. pestis* and *F. tularensis.* Concerns about inducible β-lactamases in *B. anthracis* have led experts to recommend 1 or 2 additional antibiotics in patients with inhalational anthrax. Rifampin, vancomycin, penicillin or ampicillin, clindamycin, imipenem, and clarithromycin are reasonable choices based on in vitro sensitivity data. Because *B. anthracis* relies on the production of 2 protein toxins, edema toxin and lethal toxin, for its virulence, drugs that act at the ribosome to disrupt protein synthesis (e.g., clindamycin, the macrolides) provide a theoretical advantage. Frequent meningeal involvement among inhalational anthrax victims makes agents with superior central nervous system penetration desirable. The treatment of anthrax is detailed in Table 741.3 .

Raxibacumab, a monoclonal antibody that inhibits anthrax antigen binding to cell receptors, thus preventing toxins from entering cells, is approved for the treatment of inhalation anthrax in combination with antibiotics, as is obiltoxaximab, which neutralizes anthrax toxins. The adult dose of raxibacumab is 40 mg/kg given IV over 2 hr and 15 min. The dose for children is weight based; ≤15 kg: 80 mg/kg; >15-50 kg: 60 mg/kg; >50 kg: 40 mg/kg. Premedication with diphenhydramine IV or PO is recommended 1 hr before the infusion.

In patients in whom a diagnosis of plague or tularemia is established, streptomycin (15 mg/kg IM q12h) has historically been considered the drug of choice. Because this drug is generally unavailable, many experts consider gentamicin (2.5 mg/kg IV/IM q8h) the preferred choice for therapy. In addition to ciprofloxacin, levofloxacin, or doxycycline, chloramphenicol (25 mg/kg IV q6h) should be employed in the 6% of pneumonic plague cases with concomitant meningitis. To be effective, therapy for pneumonic plague must be initiated within 24 hr of the onset of symptoms. There is little clinical experience with ricin-induced pulmonary injury. The mainstay of therapy is expected to be supportive care.

The management of **vesicant-induced injury** is similar to that for burn victims and is largely symptomatic (see Chapter 92). The major difference between thermal burns and vesicant burns is that vesicant casualties do not need the large volumes of fluid required by thermal burn victims, as their epidermis remains intact. These patients risk overhydration if treated using thermal burn protocols. Mustard victims will benefit from the application of soothing skin lotions such as calamine and the administration of analgesics. Early intubation of severely exposed patients is warranted to guard against edematous airway compromise. Oxygen and mechanical ventilation may be needed, and meticulous attention to hydration is of paramount importance. Ongoing research suggests a role for oral *N* -acetylcysteine in mitigating chronic pulmonary effects due to mustard injury. Lewisite victims can be managed in much the same manner as mustard victims. In addition, dimercaprol (British antilewisite) in peanut oil, given intramuscularly, may help ameliorate the systemic effects of lewisite.

The management of symptomatic smallpox victims also is largely supportive, with attention to pain control, hydration status, and respiratory sufficiency again of primary importance. The parenteral antiviral compound cidofovir, licensed for the treatment of cytomegalovirus retinitis in HIV-infected patients, has in vitro efficacy against variola and other orthopoxviruses. Its utility in treating smallpox victims is untested. Moreover, in the face of a large outbreak of disease, wide parenteral use of this drug would be problematic. Tecovirimat, mentioned previously, demonstrates excellent in vitro activity against orthopoxviruses, but its utility in treating patients with smallpox is likewise untested.

In all chemical casualties, but especially if a liquid agent such as VX or mustard is suspected, decontamination is crucial and should be considered a primary medical intervention. While this has been part of casualty doctrine in the civilian and military environments for decades, only recently has information become available to quantify its value. In recent unpublished work funded by the U.S. government and carried out by Public Health England and the University of Hertfordshire, disrobing eliminated 90% of contamination in normal volunteers, and following this with showering using water or soap and water eliminated 99% of contamination. This has huge implications for the hospital management of possibly contaminated casualties, including children, and hospitals must plan to execute the decontamination mission at all levels.

A useful planning tool for clinicians faced with an acute chemical emergency is the National Library of Medicine's website, Chemical Emergency Medical Management (http://chemm.nlm.nih.gov), which contains a quick tool assisting the clinician in quick syndromic identification similar to that used in this chapter.

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CHAPTER 742

Mass Psychogenic Illness

Jonathan W. Mink

Mass psychogenic illness refers to the rapid spread of illness signs and symptoms affecting members of a cohesive group, originating from a nervous system disturbance involving excitation, loss, or alteration of function, whereby physical complaints that are exhibited unconsciously have no corresponding organic etiology. Mass psychogenic illness shares features in common with conversion disorder (Chapter 35) in that the symptoms are not consciously produced and are typically sensorimotor in nature. The physical symptoms are associated with significant distress and impairment; they commonly interfere with function at school or home and affect peer relationships. Mass psychogenic illness has also been called “mass hysteria” in the past, although most of the medical community has moved away from the term “hysteria.” Some experts have argued that “functional” is a better used term than “psychogenic” because it does not imply etiology and does not reinforce dualist thinking about the mind being separate from the brain. Nonetheless, *mass psychogenic illness* is the term in widest use today.

Much less is known about the biological underpinnings and clinical features of mass psychogenic illness than is known about conversion disorder and other somatic symptom disorders. However, there are some important features in common with conversion disorder. These include sudden abrupt onset, inconsistency with known anatomy and physiology, atypical features, and inconsistency of symptoms over time. Specific features of mass psychogenic illness are the occurrence of these symptoms in a cohesive group; the presence of increased anxiety; spread of symptoms via sight, sound, or oral communication (including social media); and a high female:male ratio.

Clinical Features and Diagnosis

There are many examples of mass psychogenic illness throughout history. The best known is perhaps that of the Salem “witches.” Most widely reported examples of mass psychogenic illness are in adults, but there are several reports in children too. For example, in 2004, 10 teenage girls from a school in rural North Carolina developed paroxysmal episodes resembling epilepsy or syncope. These girls were from a cohesive social group (school-age students in a small school) and had similar symptoms. The symptoms were shown not to be consistent with either syncope or epilepsy and they eventually resolved after a 2-wk holiday break from school. Another episode in Le Roy, NY, was an outbreak of a “tic-like” illness among high school students. The symptoms were atypical for tics because they were not preceded by a premonitory urge and could not be suppressed with effort. In addition, the symptoms were remarkably similar across the affected patients. Symptoms resolved over time. In the Le Roy example, there was likely an exacerbating role of both social media and mass media, which amplified the cohesiveness of the group.

In a study of 280 environmental chemical incidents in the United Kingdom between 2007 and 2008, 7% were classified as mass psychogenic illness according to 5 diagnostic criteria: (1) presence of somatic (bodily) symptoms; (2) preexisting social connection between two or more of the affected people; (3) epidemic spread of symptoms; (4) attribution of symptoms by affected individuals (or by their parents or caregivers) to a threatening external agent of a physical (usually chemical, biologic, or radiologic) or spiritual nature; and (5) symptoms and signs that are not compatible with the environmental exposure specified by the affected individuals nor with any other environmental exposure that could reasonably be expected to have been present at the time of (or shortly before) the onset of symptoms.

One study has examined experimentally induced mass psychogenic illness. In a randomized controlled experiment, participants were assigned to one of three groups to study the effects of a simulated biologic threat and elements of social contagion. The three groups were (1) no-intervention control group, (2) psychogenic illness induction group, and (3) psychogenic illness induction plus media group. Groups 2 and 3 were told that the purpose of the study was to test the side effects of a carrier compound for an antiinfluenza medication. They were told that the compound did not produce serious side effects but was being evaluated with regard to mild side effects. In groups 2 and 3, professional actors were placed among the participants to feign illness during the study with symptoms of nausea, dizziness, and headache. Group 3 was also shown a documentary about the 1918 flu pandemic. The video contained interviews with survivors and vivid images of death and illness. The two psychogenic induction groups had 11 times more symptoms than did the control group. If a subject had a lifetime history of a traumatic event of depression, he or she was more likely to have symptoms. The documentary viewing was not associated with a higher rate of symptoms. This study confirmed the role of **“social contagion”** in mass psychogenic illness and provided a model for future studies of factors leading to such contagion.

Treatment Strategies

Mass psychogenic illness is usually self-limited, but treatment requires careful reassurance and communication between physician and patient. Explanation models should be communicated in a sensitive manner so as not to appear dismissive of symptoms. When doctors and patients do not agree on the “reality” of the illness, the prognosis is worse. Thus, media attention, medical and scientific disagreement, and legal proceedings must be managed in a way that does not exacerbate the symptoms or the illness.

In the Le Roy illness described earlier, treatment varied across individuals. The treatment strategies included cognitive behavioral therapy, supportive psychotherapy, education, pharmacotherapy for co-existing anxiety, and alteration of social setting. Many of the patients sought multiple medical opinions. There were frequent discussions among public health and other medical officials and the local media outlets. Reduced media attention seemed to lead to more rapid improvement of symptoms in some patients.

It is helpful for healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered as being either physically *or* psychologically based. In contrast, a biobehavioral continuum of disease better characterizes illness as occurring across a spectrum ranging from a predominantly biologic etiology on one end to a predominantly psychosocial etiology on the other. It is beneficial to the patient for the treating physician to try to shift the emphasis from understanding the etiology to a path toward recovery.

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CHAPTER 743

Animal and Human Bites

David A. Hunstad

Many animals besides domestic and stray dogs and cats inflict bites on humans. The profile of such bites varies by country and region, based on living conditions, indigenous species, and opportunity for encounter.

Epidemiology

Worldwide there are tens of millions of dog bites, resulting in approximately 55,000 deaths annually from rabies (see Chapter 300). **Dog bites** represent approximately 80–90% of all bites in the United States; 5–15% are from cats, 2–5% from rodents, and the remainder from rabbits, ferrets, farm animals, monkeys, and reptiles. An estimated 4.5 million persons in the United States are bitten by dogs annually; approximately 885,000 of those bitten seek medical care. Bites from dogs are also most common in Bangladesh, India, Pakistan, and Myanmar, whereas in Nepal cattle and buffalo account for more than half of bites, followed by dogs, pigs, and horses. Approximately 1% of dog bite wounds and 6% of cat bite wounds in the United States require hospitalization. During the past 3 decades, there have been approximately 20 deaths per year in the United States from dog-inflicted injuries; 65% of these occurred in children under 11 years of age. The breed of dog involved in attacks on children varies; Table 743.1 depicts the risk index of fatal dog bites by breed. Compared with other breeds, bites by pit bulls account for higher rates of hospital admission, lower Glasgow scores at admission, and an increased risk of death. Unaltered male dogs account for approximately 75% of attacks; nursing dams often inflict injury to humans when children attempt to handle their puppies.

Table 743.1

Breeds of Dog Associated With Involvement in Fatal Attacks, 2007 National Registration Data From the American Kennel Club, and Relative Risk of Fatal Attack

BREED*	NUMBER OF DOGS INVOLVED IN FATAL ATTACKS	NUMBER OF DOGS REGISTERED WITH THE AKC	RELATIVE RISK OF FATAL ATTACK PER DOG †
Pit bull ‡	113	2,239	2,520
Neapolitan Mastiff	2	357	280
Chow Chow	2	1,567	65
Rottweiler	18	14,211	65
Great Pyrenees	2	1,916	50
Parson Russell Terrier	1	1,096	45
Old English Sheepdog	1	1,206	40
Siberian Husky	6	9,048	35
Bull Mastiff	1	3,735	15
Doberman Pinscher	2	11,381	10
Australian Shepherd or mix	1	6,471	10
Mastiff mix	1	7,160	5
German Shepherd	4	43,376	5
Boxer	1	33,548	1.5
Golden Retriever or mix	1	39,659	1.5
Labrador Retriever or mix	2	114,110	1
Total	**158**		

[*] Data are presented only for dog breeds for which registration information is available from the American Kennel Club (AKC). The AKC does not register the Perro de Presa Canario, Wolf Hybrids, or dogs of unknown mixed breed.

[†] Data for Labrador Retrievers and Labrador mix are combined. Relative risk is normalized to Labrador Retriever and Labrador mix.

[‡] The term *pit bull* refers to dogs from the following breeds: American Pit Bull Terrier, American Staffordshire Terrier, and Staffordshire Bull Terrier.

AKC, American Kennel Club.

From Bini JK, Cohn SM, Acosta SM, McFarland MJ, Muir MT, Michalek JE; TRISAT Clinical Trials:

Group. Mortality, mauling, and maiming by vicious dogs. *Ann Surg* 253(4):791–797, 2011, Table 2.

The majority of dog attacks on children in the United States occur between the ages of 6 and 11 years, with a slight predominance of males. Approximately 65% of attacks occur around the home, 75% of biting animals are known by the children, and almost 50% of attacks are said to be unprovoked. Similar statistics apply in Canada, where 70% of all bites reported in one study were sustained by children aged 2-14 years; 65% of dogs involved in biting were part of the family or extended family.

Of the approximately 450,000 reported **cat bites** per year occurring in the United States, nearly all are inflicted by known household animals. Because rodent bites (rat, mouse, gerbil) do not represent reportable conditions, little is known about the epidemiology of these injuries or the incidence of infection after rodent-inflicted bites or scratches.

Few data exist on the incidence and demographics of **human bite** injuries in pediatric patients; however, preschool and early school-age children appear to be at greatest risk of sustaining an injury from a human bite, often in daycare or preschool settings. In some series, the proportion of human bites is highest among adolescents, an age group in which fist-to-tooth injuries (so-called fight bites) become more common.

Clinical Manifestations

Dog bite–related injuries can be divided into three categories of almost equal incidence: abrasions, puncture wounds, and lacerations with or without an associated avulsion of tissue. Dog bites may also involve crush injury to tissues. In contrast, the most common type of injury from cat and rat bites is a puncture wound. Cat bites often penetrate to deep tissue. Human bite injuries are of two types: an occlusion injury that is incurred when the upper and lower teeth come together on a body part or a clenched-fist injury that occurs when the injured fist, usually on the dominant hand, strikes the teeth of another individual.

Diagnosis

Management of the bite victim should begin with a thorough history and physical examination. Careful attention should be paid to the circumstances surrounding the bite event (e.g., species and number of animals, type of animal [domestic or wild], whether the attack was provoked or unprovoked, location of the attack); a history of drug allergies; and the immunization status of the child (tetanus) and animal (rabies). During physical examination, meticulous attention should be paid to the type, size, and depth of the injury; the presence of any foreign material in the wound; the status of underlying structures; and, when the bite is on an extremity, the exact location of the injury, an assessment of possibly involved structures, and the range of motion of the affected area. A diagram of the injury should be recorded in the patient's medical record. Radiographs of the affected part should be considered if it is likely that a bone or joint was penetrated or fractured or if foreign material is present in the wound. The possibility of a fracture or penetrating injury of the skull should particularly be considered in infants who have sustained dog bite injuries to the face or head.

Complications

Infection is the most common complication of bite injuries regardless of the species of biting animal. The decision to obtain material for culture from a wound depends on the species of the biting animal, the length of time that has elapsed since the injury, the depth of the wound, the presence of foreign material contaminating the wound, and whether there is clinical evidence of infection. Although potentially pathogenic bacteria have been isolated from up to 80% of dog bite wounds that are brought to medical attention within 8 hr of the bite, the infection rate for wounds receiving medical attention in <8 hr is relatively low (2.5–20%). If the dog bite(s) is (are) not deep and/or extensive, wounds that are <8 hr old do not require cultures unless there are early signs of infection or the patient is immunocompromised. *Capnocytophaga canimorsus* is isolated from approximately 5% of infected wounds in immunocompromised patients and can cause serious systemic infection in these individuals. The infection rate in **cat bite** wounds, even those that receive prompt medical attention, is >50%; therefore it is prudent to obtain material for culture from all but the most trivial cat-bite wounds. Cultures should be taken from *all* other animal bite wounds regardless of species that are not brought to medical attention within 8 hr.

The rate of infection after **rodent bite** injuries is not known. Most of the oral flora of rats is similar to that of other mammals; however, approximately 50% and 25% of rats harbor strains of *Streptobacillus moniliformis* and *Spirillum minus*, respectively, both of which cause **rat bite fever** (see Chapter 744).

All **human bite** wounds, regardless of the mechanism of injury, should be considered to carry a high risk for infection and should be cultured. Because of the high incidence of anaerobic infection after bite wounds, it is important to obtain material for anaerobic as well as aerobic cultures.

Table 743.2 lists common causes of soft tissue bacterial infections after dog, cat, or other animal bites. Bites of humans or cats, those in which treatment is delayed, those in immunocompromised patients, and those associated with deep puncture wounds or significant crush injury carry a higher risk for infection. An elevated risk for infection is also present if the bite is to certain anatomic regions (e.g., hand, foot, or genitals) or there is penetration of bone or tendons.

Table 743.2

Microorganisms Associated With Bites

Dog Bites

Staphylococcus species
Streptococcus species
Eikenella species
Pasteurella species
Proteus species
Klebsiella species
Haemophilus species
Enterobacter species
Capnocytophaga canimorsus
Bacteroides species
Moraxella species
Corynebacterium species
Neisseria species
Fusobacterium species
Prevotella species
Porphyromonas species

Cat Bites

Pasteurella species
Actinomyces species
Propionibacterium species

Bacteroides species
Fusobacterium species
Clostridium species
Wolinella species
Peptostreptococcus species
Staphylococcus species
Streptococcus species

Herbivore Bites

Actinobacillus lignieresii
Actinobacillus suis
Pasteurella multocida
Pasteurella caballi
Staphylococcus hyicus subsp. *hyicus*

Swine Bites

Pasteurella aerogenes
Pasteurella multocida
Bacteroides species
Proteus species
Actinobacillus suis
Streptococcus species
Flavobacterium species
Mycoplasma species

Rodent Bites—Rat Bite Fever

Streptobacillus moniliformis
Spirillum minus

Primate Bites

Bacteroides species

Fusobacterium species
Eikenella corrodens
Streptococcus species
Enterococcus species
Staphylococcus species
Enterobacteriaceae
Simian herpesvirus

Large Reptile (Crocodile, Alligator) Bites

Aeromonas hydrophila
Pseudomonas pseudomallei
Pseudomonas aeruginosa
Proteus species
Enterococcus species
Clostridium species

Adapted from Perkins Garth A, Harris NS: Animal bites. http://emedicine.medscape.com/article/768875-overview . Reprinted with permission from eMedicine.com , 2009.

Treatment

Table 743.3 describes the prophylactic management of human or animal bite wounds to prevent infection.

Table 743.3

Management of Bite Wounds

History
Animal bite: Ascertain the type of animal, whether the bite was provoked or unprovoked, and the situation/environment in which the bite occurred. Follow rabies guidelines for details on management of bites that carry a risk of rabies.
Patient: Obtain information on antimicrobial allergies, current medications, splenectomy, liver disease, or immunosuppressive conditions.
Physical Examination
If possible, record a diagram of the wound with the location, type, and approximate depth of injury; range of motion; possibility of joint penetration; presence of edema or crush injury; nerve and tendon function; signs of infection; and odor of exudate.

Culture
Aerobic and anaerobic cultures should be taken from infected wounds.
Irrigation
Copious amounts of normal saline should be used for irrigation.
Débridement
Devitalized or necrotic tissue should be cautiously débrided.
Radiographs
Plain radiographs should be obtained if bony penetration is possible and to provide a baseline for future evaluation of osteomyelitis.
Wound Closure
Primary wound closure is not usually advocated. Wound closure may be necessary for selected, fresh, uninfected wounds, especially large facial wounds. For larger wounds, edges may be approximated with adhesive strips in selected cases.
Antimicrobial Therapy
Early presenting (uninfected) wounds: provide antimicrobial therapy for (1) moderate-to-severe injuries less than 8 hours old, especially if edema or significant crush injury is present; (2) bone or joint space penetration; (3) deep hand wounds; (4) immunocompromised patients (including those with mastectomy, advanced liver disease, asplenia, or chronic steroid therapy); (5) wounds adjacent to a prosthetic joint; and (6) wounds in close proximity to the genital area. In most cases, coverage should include *Pasteurella* (*Eikenella* in human bites), *Staphylococcus, Streptococcus,* and anaerobes including *Fusobacterium, Porphyromonas, Prevotella,* and *Bacteroides* spp.
Infected wounds: Cover *Pasteurella* (*Eikenella* in human bites), *Staphylococcus, Streptococcus,* and anaerobes including *Fusobacterium, Porphyromonas, Prevotella,* and *Bacteroides* spp. The following antimicrobials can be considered for most terrestrial animal and human bites. **DOSAGES ARE FOR ADULTS.**

• First choice: Amoxicillin/clavulanic acid
• Penicillin allergy: No alternative treatment for animal bites has been established for penicillin-allergic patients. The following regimens can be considered.
  • Clindamycin 300 mg PO qid *plus* either ciprofloxacin 500 mg PO bid or levofloxacin 500 mg PO daily or trimethoprim-sulfamethoxazole one double-strength tablet PO bid
  • Doxycycline 100 mg PO bid
  • Moxifloxacin 400 mg PO daily
  • In highly penicillin-allergic pregnant patients, macrolides have been used, but because of poor antimicrobial coverage against anaerobic pathogens, the wounds must be closely followed.
• In cases where intravenous antibiotics are deemed necessary, single antimicrobial choices can include ampicillin/sulbactam, cefoxitin, ertapenem, or moxifloxacin.
• Empirical regimens for marine- and freshwater-acquired infection should also cover *Vibrio* and *Aeromonas* spp. respectively, with agents such as third-generation cephalosporins (e.g., cefotaxime) and fluoroquinolones.

Hospitalization
Indications include signs and symptoms of systemic toxicity and worsening infection.
Immunizations
Provide tetanus and rabies immunization, if indicated.
Elevation
Elevation may be required if any edema is present. Lack of elevation is a common cause of therapeutic failure.
Immobilization
For significant injures, immobilize the extremity, especially the hands, with a splint.
Follow-up
Patients should be reminded to follow up within 48 hours or sooner for worsening or unresolved infections and continuous pain.
Reporting
Reporting the incident to a local health department may be required.

bid, two times a day; PO, orally; qid, four times a day; tid, three times a day.

From Goldstein EJC, Abrahamian FM: Bites. IN Bennett JE, Dolin R, Blaswer MJ, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ed 8, Philadelphia, 2015, Elsevier, Table 320-3.

After appropriate material has been obtained for culture, the wound should be anesthetized, cleaned, and vigorously irrigated with copious amounts of sterile saline. Irrigation with antibiotic-containing solutions provides no advantage over irrigation with saline alone and may cause local irritation of the tissues. Puncture wounds should be thoroughly cleansed and gently irrigated with a catheter or blunt-tipped needle; high-pressure irrigation should not be employed. Avulsed or devitalized tissue should be debrided and any fluctuant areas incised and drained.

Insufficient data exist to settle questions of whether bite wounds should undergo primary closure, delayed primary closure (3-5 days), or healing by secondary intention. Factors to be considered are the type, size, and depth of the wound; the anatomic location; the presence of infection; the time since the injury; and the potential for cosmetic disfigurement. Appropriate surgical consultation (e.g., general pediatric surgery; plastic, hand, or orthopedic surgery) should be obtained for all patients with deep or extensive wounds; wounds involving the hands, face, or bones and joints; and infected wounds that require open drainage. Although there is general agreement that visibly infected wounds and those that are more than 24 hr old should not be sutured, there is variation in practice regarding the efficacy and safety of closing wounds <8 hr old with no evidence of infection. Because all **hand wounds** are at high risk for infection, particularly if there has been disruption of the tendons or penetration of the bones, surgical consultation is almost always indicated, and delayed primary closure is recommended for many bite wounds of the hands. **Facial lacerations** are at smaller risk for secondary infection because of the more luxuriant blood supply to this region. Given this fact and cosmetic considerations, many plastic surgeons advocate primary closure of facial bite wounds that have been brought to medical attention within 6 hr and after thorough irrigation and debridement.

Similarly, there are few studies addressing the efficacy and selection of antimicrobial agents for **prophylaxis** of bite injuries. The bacteriology of bite wound infections is primarily a reflection of the oral flora of the biting animal more than the skin flora of the victim (see Table 743.2). Because many of the aerobic and anaerobic bacterial species colonizing the oral cavity of the biting animal have the potential to invade local tissue, multiply, and cause tissue destruction, most bite wound infections are polymicrobial.

Despite the large degree of homology in the bacterial flora of the oral cavity among humans, dogs, and cats, important differences exist between the biting species, and they are reflected in the type of wound infections that occur. The predominant bacterial species isolated from infected dog bite wounds are *Staphylococcus aureus* (20–30%), *Pasteurella multocida* (20–30%), *Staphylococcus intermedius* (25%), and *C. canimorsus;* approximately one-half of dog bite wound infections also contain mixed anaerobes. Similar species are isolated from infected cat bite wounds; however, *P. multocida* is the predominant species in at least 50% of cat bite wound infections. At least 50% of rats harbor strains of *S. moniliformis* in the oropharynx, and approximately 25% harbor *Spirillum minor,* an aerobic Gram-negative organism. In human bite wounds, nontypable strains of *Haemophilus influenzae, Eikenella corrodens, S. aureus,* α-hemolytic streptococci, and β-lactamase–producing aerobes (~50%) are the predominant species. Clenched-fist injuries are particularly prone to infection by *Eikenella* spp. (25%) and anaerobic bacteria (50%).

The choice between oral and parenteral antimicrobial agents should be based on the severity of the wound, the presence and degree of overt infection, signs of systemic toxicity, and the patient's immune status. Amoxicillin–clavulanate is an excellent choice for empirical oral therapy for human and animal bite wounds because of its activity against most bacteria that have been isolated from infected bites. Similarly, piperacillin-tazobactam or ampicillin-sulbactam is preferred for patients who require empirical parenteral therapy. Penicillin G remains the drug of choice for prophylaxis and treatment of rat-inflicted injuries, as this agent has excellent activity against *S. moniliformis* and *S. minor* . Because first-generation cephalosporins have limited activity against *P. multocida* and *E. corrodens* , they should not be used for prophylaxis or empirical initial therapy of bite wound infections. Therapeutic alternatives for penicillin-allergic patients are limited because the traditional alternative agents are generally inactive against one or more of the multiple pathogens that cause bite wound infections. Clindamycin plus trimethoprim-sulfamethoxazole is the most commonly suggested regimen for these patients. Tetracycline is the drug of choice for penicillin-allergic patients who have sustained rat bite injuries.

Although **tetanus** occurs only rarely after human or animal bite injuries, it is important to obtain a careful immunization history and to provide tetanus toxoid to all patients who are incompletely immunized or who have gone longer than 5 years since their last tetanus immunization. The need for postexposure **rabies** vaccination in victims of dog and cat bites depends on whether the biting animal is known to have been vaccinated and, most importantly, on local experience with rabid animals in the community. Bites from bats, foxes, skunks, and raccoons should be considered to carry a high risk of rabies, and postexposure prophylaxis is indicated. For dogs, cats, and other animals that are known or can be captured, observation for 7-10 days by the local animal control department is indicated. If a biting dog or cat has escaped, a decision about rabies prophylaxis can be based on the circumstances surrounding the bite and advice from local infectious diseases specialists and/or health department officials. Annually worldwide, animal bites and contacts result in more than 10 million postexposure courses. Postexposure prophylaxis for hepatitis B should be considered in the rare instance in which a susceptible individual has sustained a human bite from an individual who is at high risk for hepatitis B.

Prevention

It is possible to reduce the risk of animal bite injury with anticipatory guidance (Table 743.4). Parents should be routinely counseled during prenatal visits and routine health maintenance examinations about the risks of having potentially biting pets in the household. All patients should be cautioned against harboring exotic animals for pets. Additionally, parents should be made aware of the proclivity of certain breeds of dogs to inflict serious injuries and the protective instincts of nursing dams. All young children should be closely supervised, particularly when in the presence of animals, and from a very early age should be taught to respect animals and to be aware of their potential to inflict injury. Reduction of the rate of human bite injuries, particularly in daycare centers and schools, can be achieved by good surveillance of the children and adequate teacher-to-child ratios.

Table 743.4

Measures for Preventing Dog Bites

- Realistically evaluate environment and lifestyle and consult with a professional (e.g., veterinarian, animal behaviorist, or responsible breeder) to determine suitable breeds of dogs for consideration.
- Dogs with histories of aggression are inappropriate in households with children.
- Be sensitive to cues that a child is fearful or apprehensive about a dog and if so, delay acquiring a dog.

- Spend time with a dog before buying or adopting it. Use caution when bringing a dog or puppy into the home of an infant or toddler.
- Spay/neuter virtually all dogs (this frequently reduces aggressive tendencies).
- Never leave an infant or young child alone with any dog.
- Properly socialize and train any dog entering the household. Teach the dog submissive behaviors (e.g., rolling over to expose abdomen and relinquishing food without growling).
- Immediately seek professional advice (e.g., from veterinarians, animal behaviorists, or responsible breeders) if the dog develops aggressive or undesirable behaviors.
- Do not play aggressive games with your dog (e.g., wrestling).
- Teach children basic safety around dogs and review regularly:
    - Never approach an unfamiliar dog.
    - Never run from a dog and scream.
    - Remain motionless when approached by an unfamiliar dog (e.g., “be still like a tree”).
    - If knocked over by a dog, roll into a ball and lie still (e.g., “be still like a log”).
    - Never allow a child to play with a dog unless supervised by an adult.
    - Immediately report stray dogs or dogs displaying unusual behavior to an appropriate person.
    - Avoid direct eye contact with a dog.
    - Do not disturb a dog who is sleeping, eating, or caring for puppies.
    - Do not pet a dog without allowing it to see and sniff you first.
    - If bitten, immediately report the bite to an adult.

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CHAPTER 744

Rat Bite Fever

David A. Hunstad

Etiology

Rat bite fever is a generic term that has been applied to at least two distinct clinical syndromes, each caused by a different microbial agent. Rat bite fever caused by *Streptobacillus moniliformis* is most commonly reported in the United States as well as in Brazil, Canada, Mexico, Paraguay, Great Britain, and France; it has been identified elsewhere in Europe and in Australia. *S. moniliformis* is a Gram-negative bacillus that is present in the nasopharyngeal flora of many laboratory and wild rats. Infection with *S. moniliformis* most commonly occurs following the bite of a rat; however, infection has also been reported in individuals who have been scratched by rats, in those who have handled dead rats, and in those who have ingested milk contaminated with the bacterium (termed **Haverhill fever**). Rat bite fever may also be transmitted by bites from wild mice. Rat bite fever caused by *Spirillum minus*, called **sodoku,** is most commonly reported in Asia. *S. minus* is a small, spiral, aerobic Gram-negative organism. Reports of rat bite fever from Africa are rare, suggesting underrecognition rather than absence of the disease.

Clinical Course

The incubation period for the streptobacillary form of rat bite fever is variable, ranging from 3 to 10 days. The illness is characterized by an *abrupt* onset of fever up to 41°C (105.8°F) (fever occurring in more than 90% of reported cases), severe throbbing headache, intense myalgia, chills, and vomiting. In virtually all instances, the lesion at the cutaneous inoculation site has healed by the time the systemic systems first appear. Shortly after the onset of the fever, a polymorphous rash occurs in up to 75% of patients. In most patients, the rash consists of blotchy red maculopapular lesions that often have a petechial component; the distribution of the rash is variable, but it is typically most dense on the extremities (Fig. 744.1*A* and *B*). Hemorrhagic vesicles may develop on the hands and feet and are very tender to palpation (Fig. 744.2).

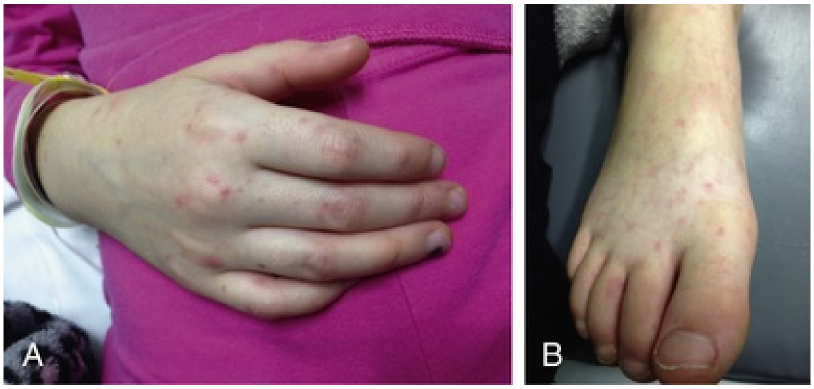

FIG. 744.1 Morbilliform rash on the hands/palms **(A)** and feet **(B)** of a patient with rat bite fever. (From Vetter NM, Feder Jr HM, Ratzan RM: Rat bite fever caused by a kiss, *Am J Emer Med* 34(6):1190.e3–1190.e4, 2015. Figs. 1 and 3.)

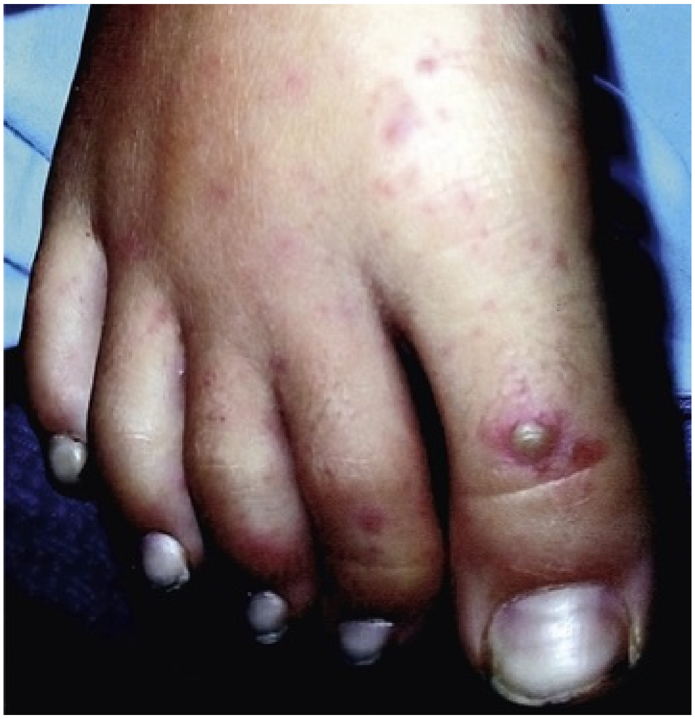

FIG. 744.2 Hemorrhagic vesicles on the first and third toes of a patient with advanced rat bite fever. (From Elliott SP: Rat bite fever and Streptobacillus moniliformis, *Clin Microbiol Rev* 20:13–22, 2007. Fig. 3.)

Approximately 50% of patients have arthritis, which first manifests toward the end of the 1st week of disease; early on, the arthritis may be migratory. If untreated, fever, rash, and arthritis last from 14 to 21 days, often with a biphasic pattern to the fever and arthritis. A wide range of complications are reported in patients with rat bite fever, the most common being pneumonia, persistent arthritis, brain and soft tissue abscesses, and, less commonly, myocarditis or endocarditis. The mortality rate due to untreated rat bite fever is estimated to be approximately 13%.

The incubation period of sodoku is longer (14-21 days) than that of the streptobacillary form of disease. The hallmark of *Spirillum* -induced disease is fever associated with an indurated, often suppurative, nonhealing lesion at the bite site. Lymphadenitis and lymphadenopathy are invariably present in the regional nodes that drain the inoculation site, and many patients have a generalized macular rash most prominent when fever is present. In untreated patients, sodoku has a relapsing and remitting course; symptoms abate after 5-7 days of chills and fever but recur 7-10 days later. There may be multiple cycles if the disease is not recognized and treated.

Diagnosis

Diagnosis of the streptobacillary form of rat bite fever is difficult because the disease is uncommon and can be confused with Rocky Mountain spotted fever or (less commonly) meningococcemia. Furthermore, *S. moniliformis* is difficult both to isolate and to identify with classic bacteriologic techniques. The organism is fastidious, requires enriched media for growth, and is inhibited by sodium polyanethol sulfonate, an additive present in many commercial blood culture bottles. A definitive diagnosis is made when the organism is recovered from blood or joint fluid or is identified in human samples with molecular technology such as polymerase chain reaction analysis, which has been used successfully in humans and laboratory animals.

Diagnosis of sodoku is made on clinical grounds because there are no diagnostic serologic tests and *S. minus* has not been cultured on artificial media. Rarely, the organism may be identified in Gram-stained smears of pus from the inoculation site. Approximately 50% have a false positive VDRL.

Treatment

Penicillin is the drug of choice for both forms of rat bite fever. Intravenous penicillin G or intramuscular penicillin G procaine is recommended for 7-10 days; a regimen of IV penicillin G for 5-7 days followed by oral penicillin V for an additional 7 days has also been used. Doxycycline, gentamicin, or streptomycin represent effective alternatives for penicillin-allergic patients. Patients with endocarditis caused by *S. moniliformis* require high-dose penicillin G for 4 weeks; the addition of streptomycin or gentamicin might be helpful.

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CHAPTER 745

Monkeypox

David A. Hunstad

Etiology

Since the eradication of smallpox (variola), monkeypox virus, causing the disease monkeypox, has, for humans, become the most important member of the genus *Orthopoxvirus* . Monkeys are the predominant host for the virus; however, it may be endemic in African rainforest squirrels and is present in African rats, mice, domestic pigs, hedgehogs, and opossums. It has also been identified in and transmitted by prairie dogs in the United States and has affected elephants in zoos. Severity of infection varies by viral strain and by host; for example, disease is relatively mild in cynomolgus monkeys but severe in orangutans.

Monkeypox virus was first observed in humans from West and Central Africa in the 1970s at the time that smallpox had been eradicated from the area. In the 1970s, the secondary attack rate was around 3% (a stark comparison to the 80% seen in unvaccinated smallpox contacts). Few cases were observed over the next 2 decades; however, during a subsequent outbreak in the 1990s, when immunity to smallpox was no longer prevalent in the population, the secondary attack rate exceeded 75%. Monkeypox outbreaks have also been reported in the Sudan. Monkeypox was inadvertently introduced into the United States in 2003, presumably through rodents from Ghana that infected prairie dogs that were subsequently distributed as pets; this outbreak affected more than 70 persons. Primary transmission of the disease from infected animal to human is by bite or by human contact with an infected animal's blood, wound discharge, or other body fluids. Human-to-human transmission of infection is uncommon but is believed to have been an important source for the transmission of new cases during the U.S. outbreak.

Clinical Course

The clinical signs, symptoms, and course of monkeypox are similar to those of smallpox, although typically milder. After an incubation period of 10-14 days, during which the virus replicates in lymphoid tissues, humans experience an abrupt onset of malaise, fever, myalgia, headache, and severe backache. Nonproductive cough, nausea, vomiting, and abdominal pain may be present. Generalized lymphadenopathy, a finding unusual in smallpox, is invariably present during the acute stages of monkeypox illness. After a prodrome of 2-4 days, an exanthem appears in cephalad-to-caudal progression. As the rash progresses, fevers begin to abate. The rash is initially macular but transforms within hours to firm papules that rapidly vesiculate and become pustular over 2-3 days. Unlike smallpox lesions but similar to chickenpox lesions, the lesions of monkeypox tend to occur in crops (Fig. 745.1). Late into the second week of illness, the lesions begin to desiccate, crust, scab, and fall off.

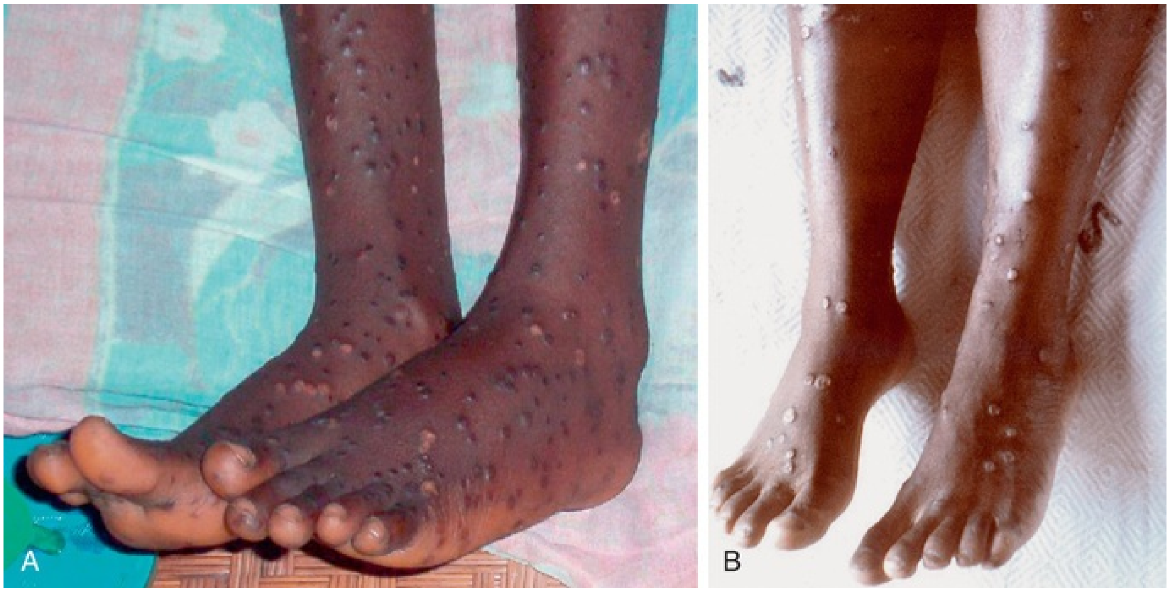

FIG. 745.1 **A,** Legs and feet of a monkeypox patient. **B,** Legs and feet of a smallpox patient at an analogous stage of rash (pustular). (**A,** courtesy Joseph M. Harvey, MD. **B,** courtesy J. Nobel, Jr, MD, Centers for Disease Control and Prevention.)

Monkeypox should be suspected in any child who has the characteristic prodrome associated with an atypical form of chickenpox and a history of contact with prairie dogs or exotic mammals such as Gambian rats and rope squirrels. Diagnosis is by isolation of monkeypox virus in culture, demonstration by polymerase chain reaction of viral DNA in a clinical specimen, or microscopic demonstration of an orthopoxvirus in a clinical specimen in the absence of other orthopoxvirus exposure.

Treatment

There is no proven effective therapy for monkeypox. Despite evidence that preexposure administration of smallpox vaccine is 85% effective in preventing or attenuating monkeypox disease, the rarity of monkeypox infection does not warrant universal vaccination. In instances of known exposure or in outbreak situations, there may be an indication for administering smallpox vaccine. Consideration should be given to vaccinating close family contacts and healthcare workers who provide care to infected individuals. Vaccine is said to be preventive if given within 2 wk of exposure. Individuals with a compromised immune system and those with life-threatening allergies to latex or to smallpox vaccine or any of its components (polymyxin B, streptomycin, tetracycline, neomycin) also should not receive smallpox vaccine.

Although there are data indicating that cidofovir has in vitro activity against monkeypox virus and has been effective in preventing monkeypox infection in animals, there are no data to support its effectiveness in humans. Careful attention should be paid to skin hygiene, maintenance of adequate nutrition and hydration, and prompt implementation of local or systemic therapy for secondary bacterial infection that may occur. For prevention of human-to-human spread of disease, a combination of contact, droplet, and airborne infection control procedures should be implemented.

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CHAPTER 746

Envenomations

Sing-Yi Feng, Collin S. Goto

Envenomations due to snakes, spiders, scorpions, and other venomous animals can cause significant morbidity and mortality, although the majority cause only localized pain and swelling. In the 2014 report of the American Association of Poison Control Centers, approximately 55,000 out of 2.3 million phone consultations were related to bites and stings of various creatures, with approximately 18,000 involving children <19 yr of age. There were six fatalities, one pediatric fatality from a crotalid envenomation, four adult fatalities from crotalid envenomations, and one adult fatality from a hymenoptera sting.

Not every bite from a venomous creature is harmful. In many cases no venom is injected; these are so-called dry bites. A dry bite may occur for many reasons, including failure of the venom delivery mechanism and depletion of venom. Up to 20% of pit viper, 80% of coral snake, and approximately 50% of all venomous snake bites are dry.

General Approach to the Envenomated Child

Children may be bitten or stung as they play and explore their environment. The evaluation may be hampered by an unclear history of the circumstances and the possible offending organism, particularly with preverbal children. The overall effects of some venomous bites and stings may be relatively more severe in children than in adults because children generally receive a similar venom load from the offending animal yet have less circulating blood volume to dilute its effects.

General Management

The majority of envenomations require local wound care, pain control, and reassurance. However, the severely envenomated child may require advanced life support interventions including endotracheal intubation and mechanical ventilation. Intravenous access should be obtained in an unaffected extremity if possible (see Chapters 69 and 70) to provide intravenous fluids and vasopressors as needed. Early hypotension is usually due to vasodilation and should be treated with volume expansion using appropriate infusion of intravenous crystalloid solution (normal saline boluses of 20 mL/kg; repeated as needed up to 3 times). Shock unresponsive to volume repletion may require addition of a vasopressive agent such as epinephrine or norepinephrine (in addition to antivenom administration if appropriate). If the presentation is suspicious for an anaphylactic reaction to venom, treatment (including epinephrine) should be initiated as soon as possible (see Chapter 174) along with the appropriate antivenom.

The affected body part should be immobilized in a position of function and any areas of edema should be marked, measured, and monitored. If antivenom is available for the envenomation, efforts should be initiated to locate and secure an adequate amount to treat the patient. In the United States, regional poison control centers are available via the national phone number 1-800-222-1222 to facilitate this effort, especially if the species is exotic. Guidance in dosing the antivenom should be obtained from experienced toxicologists via the regional poison center.

General Wound Care

Bites and stings require basic wound care, including copious tap water or normal saline irrigation under pressure when possible. For small puncture wounds, this is impractical, but the skin should still be thoroughly cleansed with soap and water. Tetanus immunization should be updated as needed. Intact bullae should be left to act as a natural sterile dressing to prevent infection, whereas ruptured bullae should be debrided. Exposed tissue should be covered with wet to dry dressings. Necrotic wounds, as seen in some snake and spider bites, should be judiciously debrided, with removal of only clearly necrotic tissue. Reconstructive surgery with skin grafts or muscle/tendon grafts may be necessary at a later date. Prophylactic antibiotics are usually not necessary because venom is bacteriostatic. Antibiotics should generally be reserved for signs of established secondary infection.

Snake Bites

Most snake bites are inflicted by nonvenomous species and are of no more consequence than a potentially contaminated puncture wound (Fig. 746.1). Medically important venomous snakes in the United States belong to two families—Crotalinae and Elapidae (Table 746.1). Most snakebites occur from April through September, when snakes are at their most active. Males sustain 75% of bites and children <5 yr of age account for 10–15%. Bites are usually located on extremities, although other parts of the body have been reported. In the United States, approximately 98% of venomous snake bites are inflicted by pit vipers (Crotalinae). A small fraction of bites is caused by coral snakes (Elapidae) in the southern and southwestern states and by pet exotic snakes that have been imported.

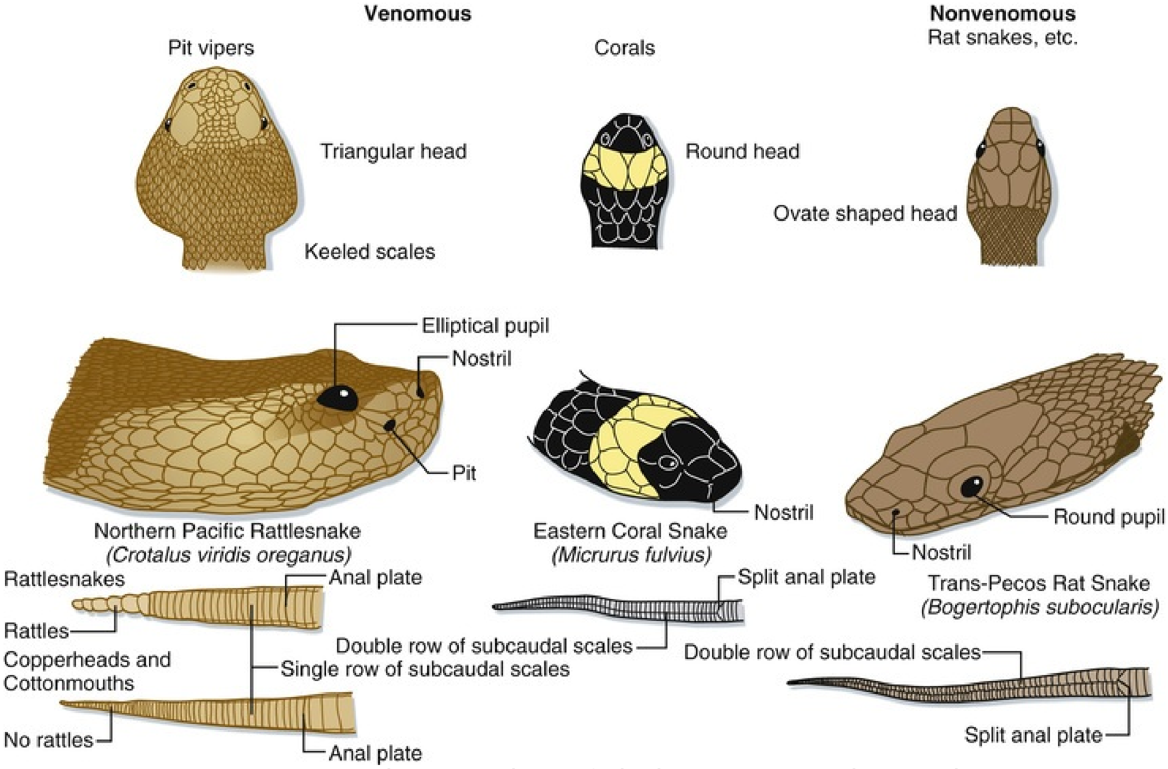
Venomous
Nonvenomous
Rat snakes, etc.
Pit vipers
Corals
Triangular head
Round head
Ovate shaped head
Keeled scales
Elliptical pupil
Nostril
Pit
Nostril
Round pupil
Nostril
Northern Pacific Rattlesnake
(Crotalus viridis oreganus)
Eastern Coral Snake
(Micrurus fulvius)
Trans-Pecos Rat Snake
(Bogertophis subocularis)
Rattlesnakes
Anal plate
Split anal plate
Rattles
Copperheads and Cottonmouths
Double row of subcaudal scales
Single row of subcaudal scales
Double row of subcaudal scales
No rattles
Anal plate
Split anal plate

FIG. 746.1 Anatomic comparison of pit vipers, coral snakes, and nonvenomous snakes of the United States. (Modified from Adams JG, et al, editors: Emergency medicine, Philadelphia, 2008, WB Saunders. Drawing by Marlin Sawyer.)

Table 746.1

Important Venomous Snake Families in the United States

FAMILY	EXAMPLES	TOXIN EFFECTS/OTHER COMMENTS	ANTIVENOM
Crotalinae (pit vipers)	Rattlesnakes (*Crotalus* and *Sistrurus* spp.), cottonmouths and copperheads (*Agkistrodon* spp.)	Heat-sensing "pit" between each eye and nostril Toxins cause tissue damage, coagulopathy, cardiovascular collapse Exception: Mojave rattlesnake (*Crotalus scutulatus*) – neurotoxic venom	*Crotalinae* polyvalent immune Fab
Elapidae	Coral snakes (*Micrurus* spp.)	Venom is neurotoxic	Antivenin (*Micrurus fulvius*)

Venoms and Effects

Snake venoms are complex mixtures of proteins including enzymes that cause local tissue destruction and other enzymes that have potentially lethal systemic effects including coagulopathy and neurotoxicity. The symptoms and severity of an envenomation vary according to the type of snake, the amount of venom injected, and the location of the bite. About 25% of snakebites are "dry bites," where the patient has fang marks and puncture wounds but no pain, swelling, or systemic effects as no venom was injected. Most pit viper bites cause significant local pain, swelling, and ecchymosis and may result in necrosis of the affected extremity (Fig. 746.2). Pain and swelling typically begin quickly after the bite and may progress over hours to days. Serious envenomation may result in a consumptive coagulopathy, hypotension, and respiratory distress. In contrast, venom from the Elapidae is neurotoxic with little or no local tissue damage. These bites cause variable local pain, and the onset of systemic effects can be delayed for hours. Manifestations of neurotoxicity generally are caused by curare-like blockade at the neuromuscular junction. Symptoms usually begin with cranial nerve palsies such as ptosis, dysarthria, and dysphagia and may progress to respiratory failure and complete paralysis. Some pit vipers, including the Southern Pacific rattlesnake *(Crotalus oreganus helleri),* western diamondback rattlesnake *(Crotalus atrox),* timber rattlesnake *(Crotalus horridus*

horridus), and Mojave rattlesnake *(Crotalus scutulatus),* can also cause significant neurotoxicity, like the Elapidae. Regional poison control centers and toxicologists should be consulted early in the course of treatment.

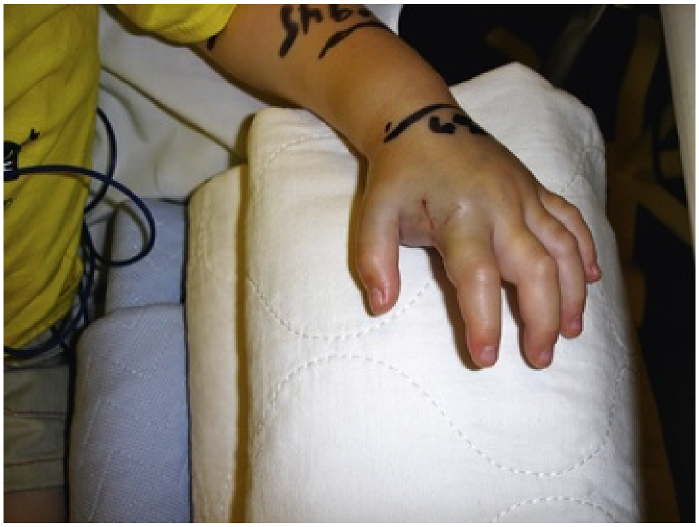

FIG. 746.2 Southern Pacific rattlesnake bite *(Crotalus oreganus helleri)* in a 2 yr old boy. Note the fang marks, swelling, and bruising of the tissues (photograph taken 2 hr following the bite). (Courtesy Sean Bush, MD.)

Management

Prehospital care should focus on rapid transport to the emergency department while providing supportive care. Constrictive clothing, jewelry, and watches should be removed, and the injured body part should be immobilized in a position of function at the level of the heart. Many popularized field treatments for snake bites—such as tourniquets, ice, electric shock, incision, and suction—have proven ineffective or deleterious.

At the hospital, supportive care should be continued as an effort is made to identify the offending snake and secure the appropriate antivenom. In severe envenomations, advanced respiratory support may be required, including endotracheal intubation and mechanical ventilation. Intravenous access should be established in an unaffected extremity, intravenous fluids administered as needed, and standard laboratory specimens obtained, including complete blood count, coagulation studies, fibrinogen concentration, and serum chemistry analysis including total creatine kinase. Laboratory studies should initially be repeated every 4-6 hr to monitor the patient's progress and response to therapy. If tourniquets are placed in the field, they should be cautiously removed after venous access is obtained due to possible adverse effects that may follow from a sudden release of venom into the systemic circulation. The bitten extremity should be marked with the leading edge of the erythema and edema as well as the time to monitor progression of the swelling.

Assessment of the severity of the envenomation in the field and at the hospital is essential in determining the appropriateness of antivenom therapy for the snakebite victim (Table 746.2). Antivenoms are relatively specific for the genus of snake whose venom they are designed to neutralize. If it is determined that the patient requires antivenom, appropriating the correct antivenom should begin as soon as possible by discussing the matter with the hospital pharmacy, regional poison control center, and perhaps local zoos and museums that keep captive snakes because they often stock exotic snake antivenom.

Table 746.2

Snakebite Severity Score and Indication for Crotaline Fab Antivenom (FabAV)

SEVERITY SCORE	CLASSIFICATION	SIGNS AND SYMPTOMS	FabAV
0	No envenomation	Fang marks, minimal pain	−
1	Minimal envenomation	Fang marks, pain, 1-5 inches of edema, erythema during 1st 12 hr, no systemic symptoms	±
2	Moderate envenomation	Fang marks, pain, 6-12 inches of edema, erythema in 1st 12 hr, systemic symptoms may be present along with rapid progression from grade 1; bloody ooze from bite site may be seen	+
3	Severe envenomation	Fang marks, pain, edema greater than 12 inches, systemic symptoms, including coagulation defects after pit viper bites; signs of grades 1 and 2 in rapid progression, with immediate signs and symptoms	++
4	Very severe envenomation	Local reaction develops rapidly; edema may involve ipsilateral trunk; ecchymosis, necrosis, and blebs and blisters develop; at tightly restrictive fascial planes tension may even be great enough to restrict arterial flow	+++

Adapted from Dart RC, Hurlbut KM, Garcia R, Boren J: Validation of a Severity Score for the Assessment of Crotalid Snakebite, *Ann Emerg Med* 27(3):321–326, 1996.

Table 746.3 lists the indications for administering antivenom. In October 2000, a Crotalinae polyvalent immune Fab antivenom (FabAV) marketed as CroFab was approved by the U.S. Food and Drug Administration (FDA) for use in crotalid envenomations. FabAV is derived from sheep (ovine) antibodies to crotalid snake venom and replaces the previously used whole equine immunoglobulin antivenom. The most important advantage of this antivenom is fewer hypersensitivity reactions, including both immediate and delayed reactions. This is because the much smaller Fab fragment is considerably less antigenic than the entire immunoglobulin.

Table 746.3

Crotaline Fab Antivenom Dosing Guidelines

DOSE	RECOMMENDATIONS
Initial dose: 4-6 vials IV	• Reconstitute each vial of FabAV in 10 mL sterile water for injection and mix with gentle swirling. • Dilute 4-6 vials of reconstituted FabAV in 250 mL normal saline. • Infuse FabAV over 1 hr IV. • Start with slow infusion rate of 25-50 mL/hr for 10 min. • If no acute allergic reaction occurs, increase rate to 250 mL/hr to complete infusion. • The volume of the infusion may be decreased for the very small child or volume-sensitive patient. • Observe 1 hr after initial dose to assess for control of envenomation. • Repeat 4-6 vials of FabAV as needed to gain initial control.
Maintenance dose: 2 vials IV every 6 hr × 3 doses	• Monitor for delayed or recurrent toxicity requiring additional FabAV. • Antivenom dose requirements vary depending on the individual patient's response and clinical course. • Patients with mild envenomation may not require maintenance dosing beyond the initial dose.

Adapted from Goto CS, Feng SY: Crotalidae polyvalent immune Fab for the treatment of pediatric crotaline envenomations, *Ped Emerg Care* 25(4):273–279, 2009.

FabAV is derived from four snakes, three from the genus *Crotalus* (the eastern diamondback rattlesnake, the western diamondback rattlesnake, and the Mojave rattlesnake) and one from the genus *Agkistrodon* (the cottonmouth or water moccasin). It is effective against the venoms of all Crotalinae snakes in the United States. There is cross-reactivity with FabAV against venom from copperhead snakes *(Agkistrodon contortrix)* . However, copperhead bites often do not require treatment with antivenom because they cause fewer systemic effects and less severe local tissue damage. Most copperhead envenomations cause only local tissue swelling, ecchymosis, and pain and generally do well with good supportive care and pain control. Any child with evidence of systemic toxicity should receive FabAV.

Initial dosing of FabAV is aimed at control of symptoms (progressive tissue swelling, thrombocytopenia, coagulopathy, neurotoxicity, or systemic toxicity). The dose is repeated until initial control of toxicity is achieved (Table 746.3).

Subsequent maintenance dosing may be needed to prevent or treat recurrence of venom effects because, due to its small molecular size, the half-life of FabAV is considerably shorter than that of crotalid venom constituents. Patients with significant envenomation should be followed for late hematologic abnormalities (coagulopathy) that can occur up to 2 wk after the bite. Although these tend to be mild laboratory coagulopathies without clinical bleeding, rare cases of severe delayed bleeding have been reported. Further antivenom therapy should be considered for such delayed or recurrent coagulopathy as outlined in Table 746.4 .

Table 746.4

Indications for Administration of Additional Antivenom in Patients with Recurrent Coagulopathy or Thrombocytopenia After Initial Control

- Evidence of clinically significant bleeding
- Platelet count below 25,000/mm^3
- International normalized ratio (INR) >3
- Activated partial thromboplastin time (aPTT) >50 sec
- Fibrinogen <50 mg/dL
- Presence of multicomponent coagulopathy
- Worsening trend in a patient with prior severe coagulopathy
- High-risk behavior for trauma
- Certain comorbid conditions (e.g., systemic vasculitis, seizure disorders, prior stroke)

From Norris RL, Bush SP, Smith J: Bites by venomous reptiles in Canada, the U.S. and Mexico. In Auerbach PS, editor: *Wilderness medicine* , ed 6, Philadelphia, 2012, Elsevier.

Envenomation of the extremities can mimic compartment syndrome, with severe pain and swelling. It is important to treat these patients aggressively with FabAV and opioid pain control to control the severe pain and swelling. Although fasciotomy was once advocated for the treatment of crotalid snakebites of the extremities, it is now a treatment of last resort only if aggressive FabAV treatment is unable to stop the progression of pain and swelling and true compartment syndrome is documented with measurement of intracompartmental pressure.

Antivenom *(Micrurus fulvius)* has been the recommended treatment for envenomation by the eastern coral snake *(Micrurus fulvius)* and the Texas coral snake *(Micrurus tener)* . Indications for this antivenom are the development of any neurologic signs and symptoms of coral snake envenomation including paresthesias, slurred speech, respiratory difficulties, muscle weakness, and fasciculations. However, the antivenom may not be readily available since the manufacturer temporarily stopped production. It is not known how soon a new supply will become available. Respiratory supportive care including endotracheal intubation and mechanical ventilation for respiratory failure remains the mainstay of treatment.

Disposition

If, after observation for 6-8 hr, a child exhibits only fang-induced puncture marks with no local or systemic symptoms, the wounds can be considered dry bites and the child can be safely discharged home. Patients with significant toxicity and those requiring treatment with antivenom should be admitted to the hospital. Patients with a history of eastern or Texas coral snakebite should be admitted to a monitored setting for 24 hr to observe for neurologic toxicity so that respiratory support can be provided as needed. Children should be admitted to an intensive care setting if they develop severe and progressive local tissue toxicity or evidence of systemic toxicity including coagulopathy, neurotoxicity, hemodynamic instability, or respiratory difficulties.

Spider Bites

In the United States, 18 genera of spiders have been identified that cause clinically significant envenomation. The spiders of importance in the United States include the *Latrodectus* species (the widow spiders) and the *Loxosceles* species (the recluse spiders).

Latrodectus Spiders

The *Latrodectus* species are found throughout the United States and include *L. mactans* Fig. 746.3 (black widow spider), *L. hesperus* (western black widow), *L. bishop* (red widow spider), *L. variolus* , and *L. geometricus* (brown widow spider). They are indigenous to every state except Alaska. The classic hourglass-shape marking is found only in *L. mactans* . They like to live close to the ground in secluded and dimly lit areas such as barns, sheds, and garages.

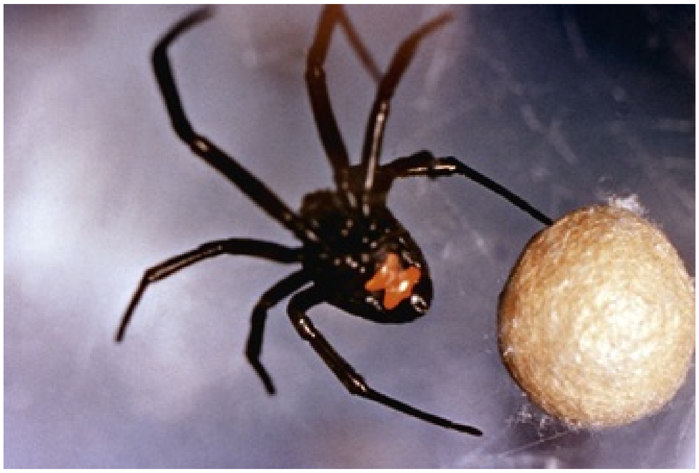

FIG. 746.3 Female black widow spider *(Latrodectus mactans)* . Note the red hourglass-shaped marking on the underside of her abdomen. (From The Centers for Disease Control and Prevention Public Health Image Library, Image #5449.)

Venoms and Effects

Latrodectu s spiders possess venoms that act at neuromuscular and autonomic nervous system synapses, resulting in excessive release of neurotransmitters. All of the widow spiders possess similar venoms, with the most important neurotoxin being α-latrotoxin.

Bites by the neurotoxic spiders tend to be very painful, and the offending spider is often seen. Systemic effects may include hypertension, tachycardia, bradycardia, hypersalivation, diaphoresis, and diffuse muscle spasm. Nausea, vomiting, abdominal pain, and abdominal rigidity may mimic appendicitis or another acute abdominal emergency.

Management

The management of a neurotoxic spider envenomation centers on sound supportive care. Generous doses of opioid analgesics and benzodiazepines should be utilized to ease severe pain and muscle spasm. *Latrodectus* antivenom (Wyeth) is equine-derived and may be considered to reverse severe systemic effects of widow spider envenomation. Although effective, it is associated with anaphylaxis, serum sickness, and anaphylactoid reactions and should be reserved for high-risk patients such as pregnant women at risk of spontaneous abortion due to the severe pain. One vial is administered via intravenous infusion. Efficacy is usually noted within 1 hr of administration, with reversal of systemic toxicity and relief of pain. Occasionally a second vial is necessary. Owing to the possibility of severe or life-threatening reactions, the risks and benefits should be carefully considered and the antivenom infused slowly with continuous monitoring and preparation to treat anaphylaxis should it occur.

Loxosceles Spiders

Venoms and Effects

The spiders most notorious for their dermonecrotic potential are the recluse spiders of the genus *Loxosceles* . The best-known member of this genus is the **brown recluse** (*Loxosceles reclusa* ; Fig. 746.4), found in the midwestern and southern regions of the United States. The venom of *Loxosceles* spiders contains a phospholipase enzyme, sphingomyelinase D, as well as hyaluronidase. Hyaluronidase is the spreading factor that enables the venom to penetrate tissues, but it does not induce tissue damage. Sphingomyelinase D causes necrosis, red blood cell hemolysis, and platelet serotonin release. The bite of this spider is generally painless and initially goes unnoticed. A few hours after the bite, the area begins to blister and bleed and become painful. Within a day or two, the site will ulcerate and develop violaceous necrosis with surrounding ecchymosis and a rim of pale ischemia (“red, white, and blue” reaction). The lesion may gradually expand over a period of days to weeks until necrotic tissue sloughs and healing begins (Fig. 746.5).

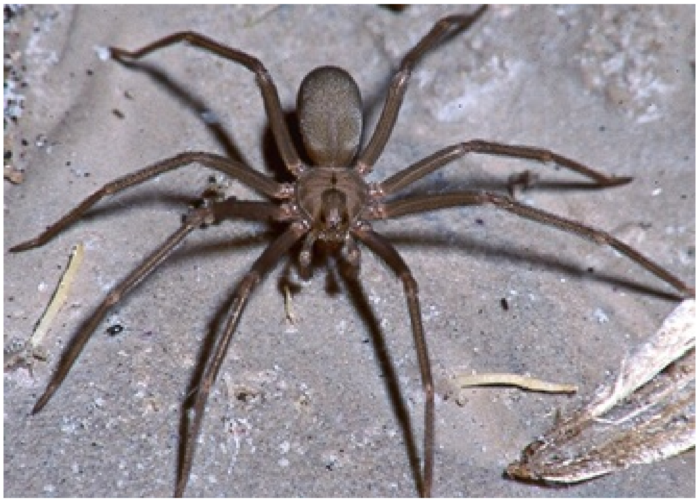

FIG. 746.4 Male recluse spider (*Loxosceles* spp.). Note the distinct violin-shaped marking on the dorsum of the cephalothorax. (Courtesy Michael Cardwell/Extreme Wildlife Photography.)

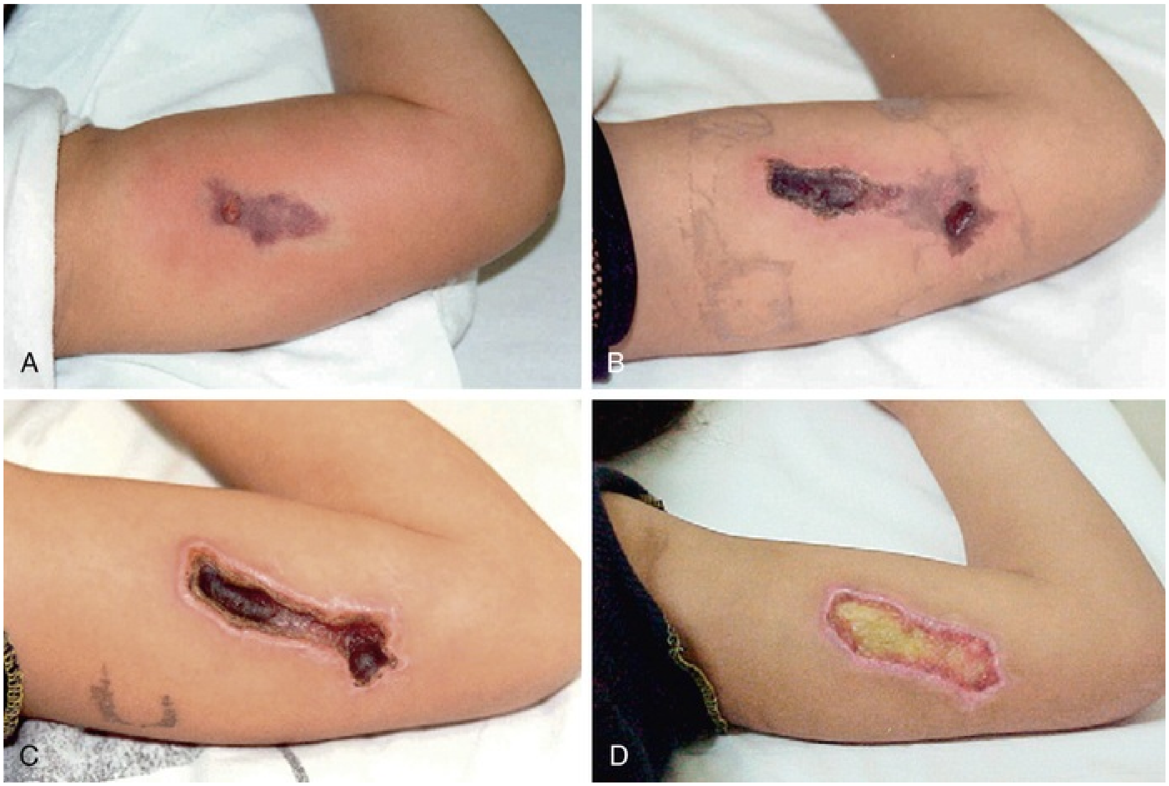

FIG. 746.5 Progression of cutaneous loxoscelism in a Brazilian patient who was bitten inside a house while putting on a shirt. Ulceration and necrosis at day 1 **(A)** , day 9 **(B)** , day 16 **(C)** , and day 25 **(D)** . (From Isbister G, Fan HW: Spider bite, *Lancet* 378:2039–2046, 2011, Fig. 3. Photographs by Ceila MS Malaque.)

Rare cases of systemic loxoscelism appear to be more common in young children. Patients present with systemic toxicity, including fever, chills, nausea, malaise, diffuse macular rash, and petechiae; they may experience hemolysis, coagulopathy, and renal failure.

In cases of necrotic dermal lesions with no identified spider as the culprit, a broad differential diagnosis must be considered to ensure appropriate management. The differential diagnosis includes skin infections (particularly methicillin-resistant *Staphylococcus aureus;* see Chapter 208), pyoderma gangrenosum, or ecthyma gangrenosum.

Management

The management of necrotizing spider bites includes good wound care, updating of tetanus status, and administration of antibiotics if there is secondary bacterial infection. Daily wound cleansing and splinting of the affected area should be provided until the wound has healed.

No therapy has been definitively proven effective in limiting the extent of necrosis following a recluse spider bite, including steroids, dapsone, colchicine, cyproheptadine, nitroglycerine, hyperbaric oxygen, and early excision of tissue. Meticulous wound care is the mainstay of treatment, and large lesions may require delayed secondary closure with skin grafting after clear tissue demarcation has occurred.

Patients with signs and symptoms of systemic loxoscelism should be admitted to the hospital for supportive treatment of hypovolemia, coagulopathy, hemolysis, and acute kidney injury. There is no commercially available antivenom in the United States for the management of necrotizing spider bites such as those from *Loxosceles* species.

Disposition

Victims with necrotic skin lesions should be monitored with frequent outpatient wound checks to determine progression of the lesion. Children with rapidly progressive dermonecrosis or systemic toxicity should be admitted to the hospital for supportive therapy, which may include intensive care admission for hemolysis, coagulopathy, renal failure, or hypotension.

Scorpion Stings

There are more than 650 species of scorpions worldwide, some of which are capable of causing severe or lethal envenomation. In the United States, there are two clinically significant scorpions: *Centruroides exilicauda* (the bark scorpion) and *Centruroides vittatus* . Most scorpion envenomations occur in the southwestern United States, and fatalities are rare. In other regions of the world —especially Latin America, Africa, the Middle East, and Asia—a number of scorpions regularly cause fatalities.

Venoms and Effects

Centruroides scorpion venom contains phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins, resulting in severe pain and paresthesias as well as systemic symptoms of excessive nerve depolarization and release of acetylcholine and catecholamines. The manifestations of scorpion stings in children vary from mild to severe and can include autonomic and somatic toxicity. Autonomic toxicity includes hypertension, tachycardia, hypersalivation, emesis, diaphoresis, and bronchoconstriction, although respiratory failure is rare. Somatic motor toxicity includes ataxia, fasciculations, myoclonus, and opsoclonus. Patients are often restless or agitated, and cranial nerve dysfunction may occur.

Management

Most scorpion stings do not produce severe effects and require only wound care and orally administered pain medications. However, patients with more severe symptoms may require intravenous opioids for analgesia and benzodiazepines for severe muscle spasm or agitation.

In August 2011, the FDA approved a bark scorpion–specific antivenom, Anascorp (Bioclon, Mexico). This antivenom is recommended for critically ill patients with neurotoxicity or other severe symptoms, including intractable pain that is not responsive to adequate doses of opioid analgesics. Small children are more likely than adults to develop such severe symptoms. It is best to discuss antivenom therapy with the regional poison control center for guidance.

Disposition

Patients who have had mild scorpion stings with only local effects can be safely discharged home with wound care instructions, analgesics, and close outpatient follow up. Patients with evolving symptoms, intractable pain, neurotoxicity, or other systemic toxicity should be admitted to the hospital, especially if scorpion antivenom is being considered. Those with severe toxicity should be admitted to an intensive care unit.

Hymenoptera Stings

The insect order Hymenoptera includes the stinging ants, bees, and wasps, which are characterized by the presence of a modified ovipositor (the "sting" or "stinger") at the end of the abdomen through which venom is injected. Various members of the order can be found throughout the world.

Venoms and Effects

Hymenoptera venom is a complex mixture of proteins, enzymes, and vasoactive substances that result in local tissue injury and inflammation. Most stings cause only local pain, redness, and swelling followed by itching and resolution. Some patients experience a large local reaction in which swelling progresses beyond the sting site, possibly involving the entire extremity. Approximately 0.4–0.8% of children and 3% of adults are at risk for acute, life-threatening allergic reactions as a result of hymenoptera venom sensitivity. Deaths from hymenoptera envenomation due to anaphylaxis used to be a major cause of mortality; however, from 2008 to 2011 only 2 deaths due to hymenoptera envenomation were reported to poison control centers in the United States (see Chapter 171). Rare cases of delayed serum sickness can follow hymenoptera stings (see Chapter 175). Africanized honeybees *(Apis mellifera scutellata)* , an aggressive hybrid of western honeybee species with African bee species, can cause massive stinging episodes resulting in systemic venom toxicity with hypotension, respiratory failure, shock, hemolysis, and renal failure.

Management

Children with typical local reactions can be treated with supportive care including analgesics and antihistamines as needed. Children with large local reactions should also receive a course of oral corticosteroids and a prescription for an epinephrine autoinjection kit including instructions in its use prior to discharge. Patients presenting with urticaria, angioedema, wheezing, or hypotension should be treated with aggressive supportive care including standard therapy for anaphylaxis such as intramuscular epinephrine, corticosteroids, antihistamines, intravenous fluids, oxygen, and airway management as needed (see Chapter 174). Children suffering massive stinging episodes may also require critical care resuscitation.

Disposition

Children with local reactions can be discharged with continued outpatient care that may include analgesia and antihistamines. More difficult disposition decisions are involved for children with systemic manifestations. Children with only diffuse urticaria who are stable after a period of observation can be discharged home to continue a short course of antihistamines and steroids and to carry an epinephrine self-administration kit. These children are at low risk for progressing to systemic anaphylaxis with future stings. Children suffering more than simple urticaria (e.g., wheezing, evidence of laryngeal edema or cardiovascular instability) should be treated aggressively and admitted for at least 24 hr of observation. They should receive a referral to allergy/immunology to test for hymenoptera venom sensitivity and possible immunotherapy. Immunotherapy reduces the risk of systemic anaphylaxis from future stings in high-risk patients from somewhere between 30% and 60% to <5%.

Marine Envenomation

The classes of venomous marine animals that cause the most morbidity and mortality in humans are the Cnidaria (including jellyfish, the Portuguese man-of-war, Pacific blue bottle, fire coral, sea nettles, anemones, and others), Mollusca (blue-ringed octopus and cone snails), Chondrichthyes (stingrays), and members of the family Scorpaenidae (lionfish, scorpionfish, and stonefish).

Venoms and Effects

All members of the Cnidaria have unique stinging cells called nematocysts. These cells contain a highly folded tubule that discharges on contact, penetrates the skin, and injects venom. The venom is antigenic and can be dermonecrotic, hemolytic, cardiotoxic, or neuropathic, depending on the species. The **Pacific**

box jellyfish *(Chironex fleckeri)* of Australia, with its cardiotoxic venom, is known to cause stings that are rapidly fatal due to cardiac arrest and pulmonary edema. Although fatal anaphylaxis to jellyfish stings has been reported in coastal waters of the United States, these events are rare. For clinicians in the Americas, the primary concern with Cnidaria envenomation is localized pain that may be associated with paresthesias or pruritus. Occasionally, victims may have systemic symptoms such as nausea, vomiting, headache, and chills.

The phylum Mollusca includes octopi and cone snails (*Conus* sp.). The **octopus** of toxicologic significance is the *Hapalochlaena maculosa* (blue-ringed octopus), which is primarily found in Australian waters. The blue-ringed octopus secretes tetrodotoxin (the same toxin found in pufferfish) in its salivary gland. The beak of the octopus punctures the skin and delivers the tetrodotoxin. Tetrodotoxin blocks sodium channels in neurons, leading to paralysis. The venom also contains other toxins, including vasoactive agents and enzymes that cause local tissue injury. **Cone snails** have a hollow proboscis with a tooth that can be extended to inject venom into the victim. Venom of the *Conus* species contains conotoxins that target multiple receptors, including voltage, ligand, and G-mediated receptors. Conotoxins cause a variety of symptoms including severe pain, weakness, tissue ischemia, cyanosis, and numbness. Systemic symptoms are usually neurological and include aphonia, aphasia, weakness, paralysis, respiratory failure, cardiovascular collapse, and ultimately death.

The stingray has a sharp, retroserrated spine and associated venom gland at the base of its tail. Envenomation often occurs when the victim steps on the animal hidden in the surf and the tail is whipped around to puncture the lower extremity. Injuries involve jagged lacerations from the spine, often with retained debris (spine fragments, glandular tissue, and sand). The venom has vasoconstrictive properties that can result in tissue necrosis and poor wound healing. Stingray envenomations are noteworthy for immediate and intense pain at the site of injury that lasts 24-48 hr. Some patients experience nausea, vomiting, and muscle cramps. Rarely, hypotension or seizures occur.

The Scorpaenidae have venomous dorsal, pelvic, and anal spines that become erect when the animal is threatened. The venom glands associated with these spines contain multiple toxins, enzymes, and vasoactive substances. Envenomation causes immediate severe pain that may persist for hours or days. Victims may experience local tissue destruction, and superinfections are common. Systemic symptoms include diaphoresis, nausea, vomiting, diarrhea, abdominal pain, muscle cramping, and headache. In severe cases, paralysis, respiratory failure, hypotension, dysrhythmias, and cardiovascular collapse have been reported.

Management

Treatment of Cnidaria stings should begin immediately after envenomation. Dousing the sting site with vinegar has been shown to inhibit nematocyst discharge. Visible tentacle fragments should be removed with a gloved hand or forceps, and microscopic fragments may be removed by gently shaving the affected area. Folk remedies such as rubbing the sting with sand and applying urine are not helpful and cause more irritation. Meat tenderizer is usually not effective. Antihistamines and corticosteroids are indicated for swelling and urticaria. An acute anaphylactic reaction should be treated with intramuscular epinephrine. Antibiotics are usually not necessary.

Patients who have been envenomated by Mollusca are treated supportively. There are no antivenoms available for either the blue-ringed octopus or the cone snails. Adequate pain control should be provided as needed. Cardiovascular support may be required and severe neurological toxicity such as respiratory failure should be managed via airway management and mechanical ventilation.

Treatment of stingray and Scorpaenidae stings is similar. These toxins are heat-labile, and immersion in hot water (approximately 42°C [107.6°F]) for 30-60 min denatures the protein constituents and decreases pain significantly. The wounds should be thoroughly cleansed and explored with use of local or regional anesthesia to rule out retention of spine or integument fragments. Stingray spines are radiopaque and may be seen on radiographs or identified by ultrasonography. Lacerations should be treated with delayed primary closure or allowed to heal by secondary intention. Systemic analgesia should be provided as needed. Because of the risk of secondary bacterial infection, there should be a low threshold for administering prophylactic antibiotics to cover *Staphylococcus* , *Streptococcus,* and *Vibrio* species, and wounds should be rechecked daily for a few days. An equine Fab stonefish antivenom is available for severe stonefish envenomation with systemic toxicity or intractable pain.

Disposition

After wound care and effective analgesia, most victims can be discharged home. If there are significant systemic effects, the patient should be admitted for monitoring and further care as needed.

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PART XXXIV
Laboratory Medicine

OUTLINE

Chapter 747 Laboratory Testing in Infants and Children
Chapter 748 Reference Intervals for Laboratory Tests and Procedures

CHAPTER 747

Laboratory Testing in Infants and Children

Stanley F. Lo

Normal values (**reference intervals**) are difficult to establish within the pediatric population. Differences in genetic composition, physiologic development, environmental influences, and subclinical disease are variables that need to be considered when developing reference intervals. Other considerations for further defining reference intervals include partitioning based on sex and age. The most commonly used reference range is generally given as the **mean** of the reference population ±2 standard deviations (SD). This is acceptable when the distribution of results for the tested population is essentially gaussian (normal). The serum sodium concentration in children, which is tightly controlled physiologically, has a distribution that is essentially gaussian; the mean value ±2 SD gives a range very close to that actually observed in 95% of children (Table 747.1). However, not all analytes have a gaussian distribution. The serum creatine kinase level, which is subject to diverse influences and is not actively controlled, does not show a gaussian distribution, as evidenced by the lack of agreement between the range actually observed and that predicted by the mean value ±2 SD. In these cases, a reference interval defining the 2.5-97.5 percentiles is typically used.

Table 747.1

Gaussian and Nongaussian Laboratory Values in 458 Normal Schoolchildren 7-14 Yr Old

	SERUM SODIUM (mmol/L)	SERUM CREATINE KINASE (units/L)
Mean	141	68
SD	1.7	34
Mean ±2 SD	138-144	0-136

Actual 95% range	137-144	24-162

Reference cutoffs are typically established from large studies with a large reference population. Examples of these cutoffs are illustrated by reference cutoffs established for cholesterol, lipoproteins, and neonatal bilirubin. Patient results exceeding these cutoffs have a future risk of acquiring disease. A final modification needed for reporting reference intervals is referencing the Tanner stage of sexual maturation (sexual maturity rating scale), which is most useful in assessing pituitary and gonadal function.

The establishment of common reference intervals remains an elusive target. Although some patient results are directly comparable between laboratories and methods, most are not. Careful interpretation of patient results must consider when testing was performed and what method was used. **Higher-order methods** , methods that are more accurate and precise, continue to be slowly developed. These will be critical to the standardization of tests and the establishment of common reference intervals.

Accuracy and Precision of Laboratory Tests

Technical accuracy, or trueness, is an important consideration in interpreting the results of a laboratory test. Because of improvements in methods of analysis and elimination of analytic interference, the accuracy of most tests is limited primarily by their precision. **Accuracy** is a measure of the nearness of a test result to the actual value, whereas **precision** is a measure of the reproducibility of a result. No test can be more accurate than it is precise. Analysis of precision by repetitive measurements of a single sample gives rise to a gaussian distribution with a mean and an SD. The estimate of precision is the coefficient of variation (CV):

$$\mathrm{CV} = \frac{\mathrm{SD}}{\mathrm{Mean}} \times 100$$

The CV is not likely to be constant over the full range of values obtained in clinical testing, but it is approximately 5% in the normal range. The CV is generally not reported but is always known by the laboratory. It is particularly important in assessing the significance of changes in laboratory results. For example, a common situation is the need to assess hepatotoxicity incurred because of the administration of a therapeutic drug and reflected in the serum alanine transaminase (aminotransferase) (ALT) value. If serum ALT increases from 25 units/L to 40 units/L, is the change significant? The CV for ALT is 7%. Using the value obtained ±2 × CV to express the extremes of imprecision, a value of 25 units/L is unlikely to reflect an actual concentration of >29 units/L, and a value of 40 units/L is unlikely to reflect an actual concentration of <34 units/L. Therefore, the change in the value as obtained by testing is likely to reflect a real change in circulating ALT levels. Continued monitoring of serum ALT is indicated, even though both values for ALT are within normal limits. *Likely* in this case is only a probability. Inherent biologic variability is such that the results of 2 successive tests may suggest a trend that will disappear on further testing.

The precision of a test may also be indicated by providing *confidence limits* for a given result. Usually, 95% confidence limits are used, indicating that it is 95% certain that the value obtained lies between the 2 limits reported. Confidence limits are calculated using the mean and SD of replicate determinations:

$$95\%\ \text{confidence limits} = \text{Mean} \pm t \times \text{SD}$$

where *t* is a constant derived from the number of replications. In most cases, $t = 2$.

Accuracy is expressed by determining the difference, or **bias** , between results from a comparative method and a definitive or reference method. A **definitive** or **reference** method provides results with increased precision and accuracy compared to the clinical laboratory. When these methods are used, along with highly purified materials (i.e., Standard Reference Materials from the National Institute of Standards and Technology) to establish values for assay calibrators used in the clinical laboratory, the accuracy of patient results is improved. Creatinine, hemoglobin A_{1c} , and neonatal bilirubin are examples in which the accuracy of these tests has been improved.

Sensitivity, Accuracy, and Analytic

Testing

In some circumstances, the sensitivity and accuracy of an analysis are reduced or increased as functions of clinical purpose. For example, ion exchange chromatography of plasma amino acids for the diagnosis of inborn errors of metabolism is usually performed at an analytic sensitivity that allows measurement of all the amino acids with a single set of standards. The range of values is approximately 20-800 µmol/L, and accuracy is poor at values ≤20 µmol/L. The detection of homocysteine in this type of analysis suggests an inborn error of methionine metabolism. If the analysis is adjusted to achieve greater analytic sensitivity, it is possible to measure homocysteine accurately in normal plasma (3-12 µmol/L). This more sensitive test is used to assess cobalamin status and analyze risk factors for atherosclerotic cardiovascular disease.

Predictive Value of Laboratory Tests

Predictive value (PV) theory deals with the usefulness of tests as defined by their clinical **sensitivity** (ability to detect a disease) and **specificity** (ability to define the absence of a disease).

$$\text{Sensitivity} = \frac{\text{Number positive by test}}{\text{Total number positive}} \times 100$$

$$\text{Specificity} = \frac{\text{Number negative by test}}{\text{Total number without disease}} \times 100$$

$$\text{PV of a positive test result} = \frac{\text{True-positive results}}{\text{Total positive results}} \times 100$$

$$\text{PV of a negative test result} = \frac{\text{True-negative results}}{\text{Total negative results}} \times 100$$

The problems addressed by PV theory are *false-negative* and *false-positive* test results. Both are major considerations in interpreting the results of screening tests in general and neonatal screening tests in particular.

Testing for human immunodeficiency virus (HIV) seroreactivity illustrates some of these considerations. If it is assumed that approximately 1,100,000 of 284,000,000 residents of the United States are infected with HIV (prevalence = 0.39%) and that 90% of those infected demonstrate antibodies to HIV, then we can consider the usefulness of a simple test with 99% sensitivity and 99.5% specificity (see Chapter 302). If the entire population of the United States were screened, it would be possible to identify most of those infected with HIV:

$$1,100,000 \times 0.9 \times 0.99 = 980,100\ (89.1\%)$$

However, there will be 119,900 false-negative test results. Even with 99.5% specificity, the number of false-positive test results would be larger than the number of true-positive results:

$$284,000,000 \times 0.0005 = 1,420,000$$

In addition, there will be 281,480,000 true-negative results:

$$\text{PV of positive test result} = \frac{980,100}{(980,100 + 1,420,000)} \times 100 = 41\%$$

$$\text{PV of negative test result} = \frac{281,480,000}{(281,480,000 + 119,900)} \times 100$$
$$= 99.96\%$$

Given the high cost associated with follow-up and the anguish produced by a false-positive result, it is easy to see why universal screening for HIV seropositivity received a low priority immediately after the introduction of testing for HIV infection.

By contrast, we can consider the screening of 100,000 individuals from groups at increased risk for HIV in whom the overall prevalence of disease is 10%, with all other considerations being unchanged.

$$\text{True-positive results} = 0.9 \times 0.99 \times 10,000 = 8,910$$

$$\text{False-positive results} = 0.005 \times 90,000 = 450$$

$$\text{False-negative results} = 10,000 - 8,910 = 1,090$$

$$\text{PV of positive test result} = \frac{8,910}{8,910 + 450} \times 100 = 95\%$$

$$\text{PV of negative test result} = \frac{89,500}{89,550 + 1,090} \times 100 = 99\%$$

These two hypothetical testing strategies show that the diagnostic efficiency of testing depends heavily on the prevalence of the disease being tested for, even with a superior test, such as the test for HIV antibodies. Because the treatment of pregnant women infected with HIV is effective in preventing vertical transmission of the infection, screening has now been expanded to all pregnant women. The proven effectiveness of current therapy in preventing neonatal infection has intensified screening for HIV early in pregnancy.

However, because of the long time needed to test for HIV antibodies, it was difficult to screen women during labor and provide the necessary therapy. Rapid HIV antibody testing procedures using a fingerstick or venipuncture to obtain whole blood, plasma, or serum, and tests using oral fluid were approved (Table

747.2). The HIV test results are usually obtained in <20 min. The collection of oral fluid samples provides an alternative for individuals who avoid HIV testing because of their dislike of needlesticks. HIV testing using whole blood or oral fluid is classified as a waived test under the **Clinical Laboratory Improvement Amendments of 1988 (CLIA),** and these tests are allowed in a point-of-care setting. *Waived tests* are simple laboratory procedures that use methodologies that are so simple and accurate as to render the likelihood of an erroneous result by the user negligible. A positive rapid HIV test result is then confirmed by Western blot analysis or immunofluorescence assay.

Table 747.2

Rapid HIV Antibody Tests and Status Under CLIA

RAPID HIV TEST	SPECIMEN TYPE	CLIA CATEGORY	TIME FOR PERFORMING ASSAY	WAIT TIME TO READ RESULTS	MANUFACTURER
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	Oral fluid Whole blood (fingerstick or venipuncture)	Waived Waived	<5 min	20-40 min	OraSure Technologies www.orasure.com
	Plasma	Moderate complexity			
Uni-Gold Recombigen HIV-1	Whole blood (fingerstick or venipuncture)	Waived	<5 min	10-12 min	Trinity Biotech www.trinitybiotech.com
	Serum and plasma	Moderate complexity			
Reveal G4 Rapid HIV-1 Antibody Test	Serum and plasma	Moderate complexity	<5 min	Read result immediately	MedMira www.medmira.com
MultiSpot HIV-1/HIV-2 Rapid Test	Serum and plasma	Moderate complexity	10-15 min	Result can be read immediately or up to 4 hr later	BioRad Laboratories www.bio-rad.com
Clearview HIV 1/2 STAT-PAK and Clearview COMPLETE HIV 1/2	Whole blood (fingerstick or venipuncture)	Waived	5 min	15-20 min	Alere www.alere.com
	Serum and plasma	Waived	5 min	15-20 min	Alere
Clearview Determine HIV1/2 Ag/Ab Combo	Whole blood (fingerstick or venipuncture)	Waived	5 min	20 min	Alere

	Serum and plasma	Waived	5 min	20 min	Chembio Diagnostic Systems; distributed by Alere

Ag/Ab, Antigen/antibody; CLIA, Clinical Laboratory Improvement Amendments of 1988; HIV, human immunodeficiency virus.

According to the U.S. Centers for Disease Control and Prevention (CDC), 174 infants were born with HIV in 2014 in the United States. Rapid HIV testing during labor allows for implementation of antiretroviral therapy for HIV-infected women who have not been tested or are unaware of their HIV status. The initiation of therapy at the time of labor or within the first 12 hr of an infant's birth significantly reduces the risk of mother-to-child transmission. In the mother–infant rapid intervention at delivery study, it was shown that the sensitivity and specificity of a rapid whole blood test for HIV during labor were 100% and 99.9%, respectively, with a positive PV of 90%. The median turnaround time for obtaining results from blood collection to patient notification was only 66 min. The performance of the rapid blood test was better than that of the standard HIV enzyme immunoassay, which had sensitivity and specificity of 100% and 99.8%, respectively, with a positive PV of 76%. In addition, the median turnaround time from blood collection to patient notification was 28 hr. As a result, rapid whole blood HIV testing is now the standard of care for women in labor with undocumented HIV status.

Rapid HIV testing can also be used in developing countries. In resource-poor settings, because of the lack of properly equipped laboratories, skilled technologists, and basic resources, such as electricity and water, these self-contained, point-of-care HIV tests are very attractive. In areas of Asia and Africa where HIV is epidemic, screening pregnant women with rapid HIV tests and offering antiretroviral therapy can significantly reduce the transmission of HIV to hundreds of thousands of infants.

Neonatal Screening Tests

Almost all the diseases detected in neonatal screening programs have a very low prevalence, and for the most part, the tests are *quantitative* rather than qualitative. In general, the strategy is to use the initial screening test to separate a highly suspect group of patients from normal infants (i.e., to increase the prevalence) and then to follow this suspect group aggressively. Two common strategies are used to detect congenital hypothyroidism (see Chapter 581): one uses thyroid-stimulating hormone for the initial screen and the other uses thyroxine. In the **thyroxine** strategy for congenital hypothyroidism, which has a prevalence of 25 in 100,000 liveborn infants, the initial test performed is for thyroxine in whole blood. Infants with the lowest 10% of test results are considered suspect. If all infants with hypothyroidism were included in the suspect group, the prevalence of disease in this group would be 250 in 100,000 infants. The original samples obtained from the suspect group are retested for thyroxine and are tested for thyroid-stimulating hormone. This second round of testing results in an even more highly suspect group composed of 0.1% of the infants screened and having a prevalence of hypothyroidism of 25,000 in 100,000 individuals. This final group is aggressively pursued for further testing and treatment. Even with a 1,000-fold increase in prevalence, 75% of the aggressively tested population is euthyroid. The justifications advanced for the program are that treatment is easy and effective and that the alternative, if congenital hypothyroidism is undetected and untreated—long-term custodial care—is both unsatisfactory and expensive.

At its inception, newborn screening was driven by the selection of genetic diseases whose clinical manifestations developed postnatally, such as phenylketonuria, galactosemia, and hypothyroidism. Diseases selected for screening typically had to meet certain criteria. The prevalence of disease had to meet a minimum, typically 1 in 100,000. Disease selection required demonstrated reduction in morbidity and mortality in the neonatal period. Effective therapies needed to be available, and the cost of screening and the feasibility of laboratory testing were also considerations in this selection process.

More common diseases have also become targets for neonatal screening programs. **Sickle cell disease** (see Chapter 489.1), easily detected using liquid chromatography or isoelectric focusing, can be treated more effectively if it is diagnosed before clinical signs appear. In addition, the results of neonatal screening for **cystic fibrosis** (CF; see Chapter 432) show clear benefits associated with preclinical diagnosis, but also some inherent difficulties associated with genetic screening for complex autosomal recessive diseases that are common and are caused by a rather large number of mutations (>1,500) of a single gene. The definitive diagnostic test for CF is the measurement of concentrations of chloride in sweat, a test that is not practical during the first week of life. Neonates with CF generally have elevations in whole blood trypsinogen. This test allows the identification of a group of neonates at risk for CF. Unfortunately, trypsinogen as an initial screening test has a high false-positive rate, an unfavorable characteristic that creates unnecessary anxiety among newborn parents and families and is costly because of the time and expense for medical follow-up. Performing DNA analysis for common mutations that cause CF reduces the size of the suspect group and identifies neonates with a higher likelihood of disease. This 2-tiered strategy identifies a manageable number of infants for whom to perform sweat tests. Problems include the following: (1) uncommon mutations are not included in the screening panel; thus cases of CF caused by these mutations can be missed; (2) common mutations that cause clinically innocent elevations of whole blood trypsinogen in heterozygous neonates cause potentially alarming false-positive findings; and (3) CF in patients with normal sweat test results is rare but is likely to be missed.

Tandem mass spectrometry (MS/MS) is a technically advanced method in which many compounds are initially fragmented and separated by molecular weight. Each compound is then fragmented again. Identification of compounds is based on characteristic fragments. The process requires approximately 2 min per sample and can detect 20 or more inborn errors of metabolism. The effects of prematurity, neonatal illness, and intensive neonatal management on metabolites in blood complicate the interpretation of results. The PV of a positive screening result is likely to be <10%; that is, 90% of positive results are not indicative of a genetic disorder of metabolism. Nonetheless, MS/MS permits a diagnosis to be made before clinical illness develops and has revolutionized the purpose and ability of newborn screening. MS/MS is not directed toward diseases defined as treatable, but it is directed toward all the diseases, each of which is rare, that the technique can identify.

Electrospray MS/MS permits the detection of rare inborn errors of metabolism and has been introduced as a newborn screening tool worldwide. Since 1998, when mass spectrometry was implemented in Australia, the rate of detection per 100,000 births has been 15.7, significantly higher than the rate of 8.6-9.5 in the six preceding 4 yr periods. Disorders of fatty acid oxidation, particularly medium-chain acyl coenzyme A dehydrogenase deficiency (see Chapter 104), accounted for the majority of increased diagnoses. Expanded newborn screening programs using MS/MS increase the detection of inherited metabolic disorders. All states in the United States use MS/MS in their neonatal screening programs; the metabolic conditions screened range from 31 to >50.

In an attempt to standardize newborn screening programs, the American College of Medical Genetics (ACMG) recommended that every baby born in the United States be screened for a core panel of 29 disorders (Table 747.3). An additional 25 conditions were recommended as secondary targets because they may be identified while screening for the core panel disorders. The March of Dimes and the American Academy of Pediatrics also endorse the ACMG recommendations. However, expansion of the screening test menu raises several issues. The cost of implementation can be significant because many states will need multiple MS/MS systems. Staffing the laboratory with qualified technical personnel to run the MS/MS system and qualified clinical scientists to interpret the profiles can be a challenge. A number of false-positive results will also be obtained with these newborn screening programs. Many of these findings are the result of parenteral nutrition, biologic variation, or treatment and are *not* the result of an inborn error of metabolism. Consequently, qualified staff will be needed to ensure that patients with abnormal results are contacted and receive follow-up testing and counseling, if needed. Even with these concerns, the ACMG report is a step in the right direction toward standardizing guidelines for state newborn screening programs.

Table 747.3

American College of Medical Genetics Core Panel of Neonatal Screening Tests

Isovalericacidemia
Glutaric aciduria type 1
3-Hydroxy-3-methylglutaricaciduria
Multiple coenzyme A (CoA) carboxylase deficiency
Methylmalonic acidemia (mutase deficiency)
3-Methylcrotonyl CoA carboxylase deficiency
Methylmalonic acidemia (cobalamin [Cbl] A, B)
Propionic acidemia
β-Ketothiolase deficiency
Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake deficiency
Phenylketonuria
Maple syrup urine disease
Homocystinuria (because of cystathionine β-synthase deficiency)
Citrullinemia
Argininosuccinic acidemia
Tyrosinemia type 1
Sickle cell anemia (Hb SS disease)
Hemoglobin (Hb) S/β-thalassemia
Hb S/C disease
Congenital hypothyroidism
Biotinidase deficiency

Congenital adrenal hyperplasia (21-hydroxylase deficiency)
Classic galactosemia
Hearing loss
Cystic fibrosis

Testing in Refining a Differential Diagnosis

The use of laboratory tests in refining a differential diagnosis satisfies PV theory because a correct differential diagnosis should result in a relatively high prevalence of the disease under consideration. An example of testing in refining a differential diagnosis is the measurement of urinary vanillylmandelic acid (VMA) for the diagnosis of **neuroblastoma** (see Chapter 525). A simple spot test for VMA is not useful in general screening programs because of the low prevalence of neuroblastoma (3 cases/100,000) and the low sensitivity of the test (69%). Even though the specificity of urinary VMA is 99.6%, testing of 100,000 children would produce 2 true-positive test results, 400 false-positive results, and 1 false-negative result. The PV of a positive result in this setting is 0.5%, and the PV of a negative result is 99.99%, not much different from the assumption that neuroblastoma is not present. Testing for urinary VMA in a 3 yr old child with an abdominal mass, however, gives a useful result because the prevalence of neuroblastoma is at least 50% in 3 yr old children with abdominal masses. If 100 such children are tested and the prevalence of neuroblastoma in the group is assumed to be 50%, a satisfactory PV is obtained.

$$\text{PV of positive test result} = \frac{0.69\times 50}{0.69\times 50+(0.004\times 50)}\times 100 = 99\%$$

$$\text{PV of negative test result} = \frac{0.996\times 50}{0.996\times 50+(0.31\times 50)}\times 100 = 76\%$$

Thus, in this situation, a test with low sensitivity is powerful in refining the differential diagnosis because the PV of a positive result is almost 100% in the setting of high prevalence.

Serologic Testing

Using laboratory testing to refine a differential diagnosis poses problems, as exemplified by serologic testing for **Lyme disease** , which is a tick-borne infection by *Borrelia burgdorferi* that has various manifestations in both early and late stages of infection (see Chapter 249). Direct demonstration of the organism is difficult, and serologic test results for Lyme disease are not reliably positive in young patients presenting early with erythema chronicum migrans. These results become positive after a few weeks of infection and remain positive for a number of years. In an older population being evaluated for late-stage Lyme disease, some individuals will have recovered from either clinical or subclinical Lyme disease, and some will have active Lyme disease, with both groups having true-positive serologic test results. Of individuals without Lyme disease, some will have true-negative serologic test results, but a significant percentage will have antibodies to other organisms that cross-react with *B. burgdorferi* antigens.

This set of circumstances gives rise to a number of problems. First, the protean nature of Lyme disease makes it difficult to ensure a high prevalence of disease in persons to be tested. Second, the most appropriate antibodies to be detected are imperfectly defined, leading to a wide variety of tests with varying false-positive and false-negative rates. Third, the natural history of the antibody response to infection and the difficulty of showing the causative organism directly combine to make laboratory diagnosis of early Lyme disease difficult. Fourth, in the diagnosis of late-stage Lyme disease in older individuals, the laboratory diagnosis is plagued by misleading positive (either false-positive or true-positive, but not clinically relevant) results, typically an enzyme-linked immunosorbent assay (ELISA) that uses whole *B. burgdorferi* organisms. In a review of 788 patients referred to a specialty clinic with the diagnosis of Lyme disease, the diagnosis was correct in 180 patients, 156 patients had true seropositivity without active Lyme disease, and 452 had never had Lyme disease, even though 45% of them were found to be seropositive by at least one test before referral.

A 2-step approach, similar to that used in HIV testing, is often used: a screening test that has high sensitivity (e.g., ELISA) and excellent negative PV, followed by a very specific confirmatory test for verification of positive screening test results (e.g., Western blot to detect antibodies to selected bacterial antigens). Negative screening test results and negative verification test results are reported as negative. Positive verification test results are reported as positive. However, standardization of the testing procedures is difficult in North America, where only 1 pathogenic strain of *B. burgdorferi* is found, and is more difficult elsewhere in the Northern hemisphere, where as many as 3 pathogenic strains are present. Identification of microbial DNA in body fluids by polymerase chain reaction is definitive but invasive.

Laboratory Screening

Screening profiles are used as part of a complete review of systems, to establish a baseline value, or to facilitate patient care in specific circumstances, such as (1) when a patient clearly has an illness, but a specific diagnosis remains elusive; (2) when a patient requires intensive care; (3) for postmarketing surveillance and evaluation of a new drug; and (4) when a drug is used that is known to have systemic adverse effects. Laboratory screening tests should be used in a targeted manner to supplement, not supplant, a complete history and physical examination (Table 747.4).

Table 747.4

Laboratory Profile as a Review of Systems

LABORATORY TEST	ASSESSMENT FACILITATED BY TESTS
Complete blood cell count and platelets	Nutrition, status of formed elements
Complete urinalysis	Renal function/genitourinary tract inflammation
Albumin and cholesterol	Nutrition
ALT, bilirubin, GGT	Liver function
BUN, creatinine	Renal function, nutrition
Sodium, potassium, chloride, bicarbonate	Electrolyte homeostasis
Calcium and phosphorus	Calcium homeostasis

ALT, Alanine transaminase; BUN, blood urea nitrogen; GGT, γ-glutamyltransferase.

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CHAPTER 748

Reference Intervals for Laboratory Tests and Procedures

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In Tables 748.1 through 748.5 , the reference intervals apply to infants, children, and adolescents when possible. For many analyses, separate reference intervals for children and adolescents are not well delineated. When interpreting a test result, the reference interval supplied by the laboratory performing the test should always be used, because these intervals are instrument and/or method dependent. Figs. 748.1 and 748.2 provide estimations related to dosages. Fig. 748.3 is a nomogram for risk assessment of hyperbilirubinemia.

Table 748.1

Prefixes Denoting Decimal Factors in Table 748.5

PREFIX	SYMBOL	FACTOR
mega-	M	10^6
kilo-	k	10^3
hecto-	h	10^2
deka-	da	10^1
deci-	d	10^{-1}
centi-	c	10^{-2}
milli-	m	10^{-3}
micro-	µ	10^{-6}
nano-	n	10^{-9}
pico-	p	10^{-12}
femto-	f	10^{-15}

Table 748.2

Abbreviations Used in Table 748.5

Abbreviations Used in Table 748.5

Ab	Absorbance
AU	Arbitrary unit
BB	Brain isoenzyme of creatine kinase
cap	Capillary
CH_{50}	Dilution required to lyse 50% of indicator red blood cells; indicates complement activity
Cr	Creatinine
CSF	Cerebrospinal fluid
F	Female
g	Gram, grams
G6PD	Glucose-6-phosphate dehydrogenase
Hb	Hemoglobin
HbCO	Carboxyhemoglobin
hpf	High-power field
hr	Hour, hours
IU	International unit(s) of hormone activity
L	Liter
M	Male
MB	Heart isoenzyme of creatine kinase
mEq/L	Milliequivalents per liter
min	Minute, minutes
mm^3	Cubic millimeter, microliter (μL)
mm Hg	Millimeters of mercury
mmol	Millimole
mo	Month, months
mol	Mole
mOsm	Milliosmole
MW	Relative molecular weight
ND	Not detected
nm	Nanometer (wavelength)
Pa	Pascal(s)
pc	Postprandial
RBC	Red blood cell(s), erythrocyte(s)
RT	Room temperature
SD	Standard deviation
sec	Second, seconds
Tr	Trace
U	International unit(s) of enzyme activity
V	Volume
WBC	White blood cell(s)
WHO	World Health Organization
wk	Week, weeks
yr	Year, years

Table 748.3

Abbreviations for Specimens in Table 748.5

S	Serum
P	Plasma

(H)	Heparin
(LiH)	Lithium heparin
(E)	Ethylenediaminetetraacetic acid (EDTA)
(C)	Citrate
(O)	Oxalate
W	Whole blood
(NH_4 H)	Ammonium heparinate

Table 748.4

Key to Comments Section of Table 748.5

30°C, 37°C	Temperature of enzymatic analysis (Celsius)
a	Values obtained are significantly method dependent
b	Values in older males are higher than those in older females
c	Values in older females are higher than those in older males
d	Atomic absorption
e	Borate affinity chromatography
f	Cation-exchange chromatography
g	Vitros, a proprietary analytic system of Ortho Clinical Diagnostics
i	Electrophoresis
j	Enzymatic assay
k	Enzyme-amplified immunoassay
l	Fluorometric method
m	Fluorescence-activated cell sorting (FACS)
n	Fluorescence polarization
o	Gas chromatography
p	High-performance liquid chromatography (HPLC)
q	Indirect fluorescence antibody (IFA) assay
r	Ion-selective electrode
s	Nephelometry
t	Optical density
u	Radial immunodiffusion (RID)
v	Radioimmunoassay (RIA)
w	Spectrophotometry

Table 748.5

Reference Intervals[*]

ANALYTE OR PROCEDURE	SPECIMEN	REFERENCE VALUES (U.S.) [†]		CONVERSION FACTOR	REFERENCE VALUES (SI) [†]
COMPLETE BLOOD COUNT					
Hematocrit (HCT, Hct)	W(E)		% of packed red cells (V red cells/V whole blood cells × 100)		Volume fraction (V red cells/V whole blood)
Calculated from mean		0-30 days	44-70%	×0.01	0.44-0.70

corpuscular volume (MCV) and RBC count (electronic displacement or laser)		1-23 mo	32-42%		0.32-0.42
		2-9 yr	33-43%		0.33-0.43
		10-17 yr M	36-47%		0.36-0.47
		F	35-45%		0.35-0.45
		>18-99 yr M	42-52%		0.42-0.52
		F	37-47%		0.37-0.47
Hemoglobin (Hb)	W(E)		g/dL		mmol/L
		0-30 days	15.0-24.0	×0.155	2.32-3.72
		1-23 mo	10.5-14.0		1.63-2.17
		2-9 yr	11.5-14.5		1.78-2.25
		10-17 yr M	12.5-16.1		1.93-2.50
		F	12.0-15.0		1.86-2.32
		>18-99 yr M	13.5-18.0		2.09-2.79
		F	12.5-16.0		1.93-2.48
	P(H)	See Chemical Elements			
Erythrocyte indices (RBC indices)					
Mean corpuscular hemoglobin (MCH)	W(E)		pg/cell		fmol/cell
		0-30 days	33-39	×0.0155	0.51-0.60
		1-23 mo	24-30		0.37-0.46
		2-9 yr	25-31		0.39-0.48
		10-17 yr M	26-32		0.26-0.32
		F	26-32		0.26-0.32
		>18-99 yr M	27-31		0.27-0.31
		F	27-31		0.27-0.31
Mean corpuscular hemoglobin concentration (MCHC)	W(E)		% Hb/cell or g Hb/dL RBC		mmol Hb/L RBC
			32-36	×0.155	4.96-5.58
Mean corpuscular volume (MCV)	W(E)		µm^3		fL
		0-30 days	99-115	×1	99-115
		1-23 mo	72-88		72-88
		2-9 yr	76-90		76-90
		10-17 yr	78-95		78-95
		>18-99 yr	78-100		78-100
Leukocyte count (WBC count)	W(E)	×1,000 cells/mm^3 (µL)			$\times 10^9$ cells/L
		0-30 days	9.1-34.0	×1	9.1-34.0
		1-23 mo	6.0-14.0		6.0-14.0
		2-9 yr	4.0-12.0		45.0-12.0
		10-17 yr	4.0-10.5		4.0-10.5
		18-99 yr	4.0-10.5		4.0-10.5
Leukocyte differential	W(E)	%			Number fraction
Myelocytes		0%		×0.01	0
Neutrophils (“bands”)		3-5%			0.03-0.05
Neutrophils (“segs”)		54-62%			0.54-0.62
Lymphocytes		25-33%			0.25-0.33
Monocytes		3-7%			0.03-0.07
Eosinophils		1-3%			0.01-0.03
Basophils		0-0.75%			0-0.0075
		Cells/mm^3 (µL)			$\times 10^6$ cells/L
Myelocytes		0		×1	0
Neutrophils (“bands”)		150-400			150-400

Neutrophils (“segs”)		3,000-5,800			3,000-5,800
Lymphocytes		1,500-3,000			1,500-3,000
Monocytes		285-500			285-500
Eosinophils		50-250			50-250
Basophils		15-50			15-50
Platelet count (thrombocyte count)	W(E)	$\times 10^3$ /mm^3 (µL)			$\times 10^9$ /L
		Newborn 84-478 (after 1 wk, same as adult)		$\times 10^6$	84-478
		Adult 150-400			150-400
Reticulocyte count	W(E,H,O)	Adults 0.5-1.5% of erythrocytes or 25,000-75,000/mm^3 (µL)		×0.01 $\times 10^6$	0.005-0.015 (number fraction) or 25,000-75,000 × 10^6 /L
			%		Number fraction
	W(cap)	1 day	0.4-6.0	×0.01	0.004-0.060
		7 days	<0.1-1.3		<0.001-0.013
		1-4 wk	<1.0-1.2		<0.001-0.012
		5-6 wk	<0.1-2.4		<0.001-0.024
		7-8 wk	0.1-2.9		0.001-0.029
		9-10 wk	<0.1-2.6		<0.001-0.026
		11-12 wk	0.1-1.3		0.001-0.013
Alanine transaminase (aminotransferase) (ALT, SGPT)	S	0-7 days	6-40 U/L	×1	6-40 U/L
		8-30 days M	10-40		10-40
		F	8-32		8-32
		1-12 mo	12-45		12-45
		1-19 yr	5-45		5-45
Albumin (BCG)	P	Premature 1 day	1.8-3.0 g/dL	×10	18-30 g/dL
		Full term <6 days	2.5-3.4		25-34
		8 days-1 yr	1.9-4.9		19-49
		1-3 yr	3.4-4.2		34-42
		4-19 yr	3.5-5.6		35-56
Ammonia	P		11-35 µmol/L	×1	11-35 µmol/L
Amylase	S,P	1-19 yr	30-100 U/L	×1	30-100 U/L
			% pancreatic fraction		% pancreatic fraction
Amylase isoenzymes	S,P(H)	Cord-8 mo	0-34%	×0.01	0-0.34%
		9 mo-4 yr	5-56%		0.05-0.56%
		5-19 yr	23-59%		0.23-0.59%
Anion gap (sodium − [chloride + bicarbonate])	P(H)	7-16 mEq/L		×1	7-16 mEq/L
Antideoxyribonuclease B titer (anti-DNase B titer)	S	Age	Upper limit of normal		Upper limit of normal
		4-6 yr	240-480 U	×1	240-480 U
		7-12 yr	480-800 U		480-800 U
Antidiuretic hormone (hADH, vasopressin)	P(E)	Plasma osmolarity	Plasma ADH (pg/mL)		Plasma ADH ng/L

		(mOsm/kg)					
		270-280	<1.5	×1	<1.5		
		280-285	<2.5		<2.5		
		285-290	1-5		1-5		
		290-295	2-7		2-7		
		295-300	4-12		4-12		
Antistreptolysin-O titer (ASO titer)	S	Age	Upper limit of normal		Upper limit of normal		
		2-5 yr	120-160 Todd units	×1	120-160 Todd units		
		6-9 yr	240 Todd units		240 Todd units		
		10-12 yr	320 Todd units		320 Todd units		
Aspartate transaminase (aminotransferase) (AST, SGOT)	S		U/L		U/L		
		0-7 days M	30-100	×1	35-100		
		F	24-95		24-95		
		8-30 days	22-71		22-71		
		1-12 mo	22-63		22-63		
		1-3 yr	20-60		20-60		
		3-9 yr	15-50		15-50		
		10-15 yr	10-40		10-40		
		16-19 yr M	15-45		15-45		
		F	5-30		5-30		
Base excess	W(H)		mmol/L		mmol/L		
		Newborn	(−10)-(−2)	×1	(−10)-(−2)		
		Infant	(−7)-(−1)		(−7)-(−1)		
		Child	(−4)-(+2)		(−4)-(+2)		
		Thereafter	(−3)-(+3)		(−3)-(−3)		
Bicarbonate	S,P		mmol/L		mmol/L		
		Arterial	21-28	×1	21-28		
		Venous	22-29		22-29		
Bilirubin, total	S		mg/dL		µmol/L		
		Newborn	See Bhutani nomogram (Fig. 748.3)	×17.1			
		1 mo-adult	<1.0		<17		
C-reactive protein (high sensitivity)	S						
			M (mg/dL)	F (mg/dL)		M (mg/L)	F (mg/L)
		0-90 days	0.08-1.58	0.09-1.58	×10	0.8-15.8	0.9-15.8
		91 days-12 mo	0.08-1.12	0.05-0.79		0.8-11.2	0.5-7.9
		13 mo-3 yr	0.08-1.12	0.08-0.79		0.8-11.2	0.8-7.9
		4-10 yr	0.06-0.79	0.5-1.0		0.6-7.9	0.5-10.0
		11-14 yr	0.08-0.76	0.06-0.81		0.8-7.6	0.6-8.1
		15-18 yr	0.04-0.79	0.06-0.79		0.4-7.9	0.6-7.9
Calcium, ionized (Ca)	S,P(H),W(H)		mg/dL		mmol/L		
		Cord blood	5.0-6.0	×0.25	1.25-1.50		
		Newborn, 3-24 hr	4.3-5.1		1.07-1.27		
		24-48 hr	4.0-4.7		1.00-1.17		
		Thereafter	4.8-4.92		1.12-1.23		

		or	2.24-2.46 Eq/L	×0.5	1.12-1.23
Calcium, total	S		mg/dL		mmol/L
		Cord blood	9.0-11.5	×0.25	2.25-2.88
		Newborn, 3-24 hr	9.0-10.6		2.3-2.65
		24-48 hr	7.0-12.0		1.75-3.00
		4-7 days	9.0-10.9		2.25-2.73
		Child	8.8-10.8		2.20-2.70
		Thereafter	8.4-10.2		2.10-2.55
Carbon dioxide, partial pressure (PCO$_2$)	W(H)		mm Hg		kPa
		Newborn	27-40	×0.1333	3.6-5.3
		Infant	27-41		3.6-5.5
		Thereafter M	35-48		4.7-6.4
		F	32-45		4.3-6.0
Carbon monoxide (carboxyhemoglobin)	W(E)	Nonsmoker	<2% HbCO	×0.01	HbCO fraction <0.02
		Smoker	<10%		<0.10
		Lethal	>50%		>0.5
Chloride	S,P(H)	Cord blood	96-104 mmol/L	×1	96-104 mmol/L
		Newborn	97-110		97-110
		Thereafter	98-106		98-106
Chloride, sweat	Sweat		mmol/L		
		0-5 mo	≤29	CF unlikely	
			30-59	Intermediate	
			≥60	Indicative of CF	
		≥6 mo	≤39	CF unlikely	
			40-60	Intermediate	
			≥60	Indicative of CF	
Cortisol	S,P(H)		µg/dL		nmol/L
		Newborn	1-24	×27.59	28-662
		Adults, 8 AM	5-23		138-635
		4 PM	3-15		82-413
		8 PM	<50% of 8 AM	×0.01	Fraction of 8 AM
					≤0.50
Creatine kinase	S	Cord blood	70-380 U/L	×1	70-380 U/L
		5-8 hr	214-1,175		214-1,175
		24-33 hr	130-1,200		130-1,200
		72-100 hr	87-725		87-725
		Adult	5-130		5-130
Creatine kinase isoenzymes	S		% MB	% BB	
		Cord blood	0.3-3.1	0.3-10.5	
		5-8 hr	1.7-7.9	3.6-13.4	
		24-33 hr	1.8-5.0	2.3-8.6	
		72-100 hr	1.4-5.4	5.1-13.3	
		Adult	0-2	0	
Creatinine (IDMS)					
Enzymatic	S,P		mg/dL		µmol/L
		0-4 yr	0.03-0.50	×88.4	2.65-44.2
		4-7 yr	0.03-0.59		2.65-52.2
		7-10 yr	0.22-0.59		19.4-52.2
		10-14 yr	0.31-0.88		27.4-77.8
		>14 yr	0.50-1.06		44.2-93.7
Creatinine clearance (endogenous)	S,P,U	Newborn 40-65 mL/min/1.73			

		m^2					
		<40 yr, M 97-137					
		F 88-128					
		Decreases <6.5 mL/min/decade					
Ferritin	S		ng/mL			µg/L	
		0-6 wk	0-400		×1	0-400	
		7 wk-365 days	10-95			10-95	
		1-9 yr	10-60			10-60	
		10-18 yr M	10-300			10-300	
		F	10-70			10-70	
Folate	S	Newborn 7.0-32 ng/mL			×2.265	15.9-72.4 nmol/L	
		Thereafter 1.8-9.0				4.1-20.4	
	W(E)	150-450 ng/mL RBCs				340-1,020 nmol/L cells	
Glucose	S		mg/dL			mmol/L	
		Cord blood	45-96		×0.0555	2.5-5.3	
		Premature	20-60			1.1-3.3	
		Neonate	30-60			1.7-3.3	
		Newborn					
		1 day	40-60			2.2-3.3	
		>1 day	50-90			2.8-5.0	
		Child	60-100			3.3-5.5	
		Adult	70-105			3.9-5.8	
	W(H)	Adult	65-95			3.6-5.3	
Glucose, 2 hr post	S		<120			<6.7	
Glucose tolerance test (GTT) (Chapter 607)	S		mg/dL			mmol/L	
Oral dose							
Adult: 75 g			Normal	Diabetic		Normal	Diabetic
Child: 1.75 g/kg of ideal weight, up to a maximum of 75 g		Fasting	70-105	≥126	×0.0555	3.9-5.8	≥7.0
		120 min	70-120	≥200		3.9-6.7	≥11
G6PD in erythrocytes		W(E,H,C)					
Bishop, modified		Adult				Adult	
		3.4-8.0 U/g Hb			×0.0645	0.22-0.52 mU/mol Hb	
		98.6-232 U/10^{12} RBCs			$\times 10^{-3}$	0.10-0.23 nU/10^6 RBCs	
		1.16-2.72 U/mL RBC			×1	1.16-2.72 kU/L RBC	
		Newborn: 50% higher				Newborn: 50% higher	
γ-Glutamyl transpeptidase (GGT, GGTP)	S		U/L			U/L	
		Cord blood	37-193		×1	37-193	
		0-1 mo	13-147			13-147	
		1-2 mo	12-123			12-123	
		2-4 mo	8-90			8-90	
		4 mo-10 yr	5-32			5-32	
		10-15 yr	5-24			5-24	
Immunoglobulin A (IgA)	S		mg/dL			mg/L	
		Cord blood	1.4-3.6		×10	14-36	
		1-3 mo	1.3-53			13-530	
		4-6 mo	4.4-84			44-840	
		7 mo-1 yr	11-106			110-1,060	
		2-5 yr	14-159			140-1,590	

		6-10 yr	33-236			330-2,360
		Adult	70-312			700-3,120
Immunoglobulin D (IgD)	S	Newborn: none detected				None detected
		Thereafter: 0-8 mg/dL			×10	0-80 mg/L
Immunoglobulin E (IgE)	S	M 0-230 IU/mL			×1	0-230 kIU/L
		F 0-170				0-170
Immunoglobulin G (IgG)	S		mg/dL			g/L
		Cord blood	636-1,606		×0.01	6.36-16.06
		1 mo	251-906			2.51-9.06
		2-4 mo	176-601			1.76-6.01
		5-12 mo	172-1,069			1.72-10.69
		1-5 yr	345-1,236			3.45-12.36
		6-10 yr	608-1,572			6.08-15.72
		Adult	639-1,349			6.39-13.49
Immunoglobulin M (IgM)	S		mg/dL			mg/L
		Cord blood	6.3-25		×10	63-250
		1-4 mo	17-105			170-1,050
		5-9 mo	33-126			330-1,260
		10 mo-1 yr	41-173			410-1,730
		2-8 yr	43-207			430-2,070
		9-10 yr	52-242			520-2,420
		Adult	56-352			560-3,520
Iron	P	All ages	22-184 µg/dL		×0.1791	4-33 µmol/L
Iron-binding capacity, total (TIBC)	S	Infant 100-400 µg/dL			×0.179	17.90-71.60 µmol/L
		Thereafter 250-400				44.75-71.60
L -lactate (perchloric acid)	W		mg/dL			mmol/L
		1-12 mo	10-21		×1	1.1-2.3
		1-7 yr	7-14			0.8-1.5
		7-15 yr	5-8			0.6-0.9
D -lactate	P(H)					
		6 mo-3 yr	0.0-0.3		×1	0.0-0.3
Lactate dehydrogenase (LDH)	S		U/L			U/L
		<1 yr	170-580		×1	170-580
		1-9 yr	150-500			150-500
		10-19 yr	120-330			120-330
Isoenzymes	S		% of total activity			
			1-6 yr	7-19 yr		
		LD1	20-38	20-35		
		LD2	27-38	31-38		
		LD3	16-26	19-28		
		LD4	5-16	7-13		
		LD5	3-13	5-12		
Lead	W(H)		µg/dL			mmol/L
		Child	<5		×0.0483	<0.0024
		Toxic	≥70			≥3.38
Lipase	P,S	1-18 yr	145-216 U/L		×1	145-216 U/L
Magnesium	P(H)		mg/dL			mmol/L

		0-6 days	1.2-2.6		×0.411	0.48-1.05		
		7 days-2 yr	1.6-2.6			0.65-1.05		
		2-14 yr	1.5-2.3			0.60-0.95		
		0.78 ± 0.37% of total Hb			×0.01	0.0078 ± 0.0037 (mass fraction)		
Osmolality	S	Child, adult						
		275-295 mOsm/kg H_2O						
Phosphatase, alkaline	S		U/L			U/L		
		1-9 yr	145-420		×1	145-420		
		10-11 yr	140-560			140-560		
			M	F			M	F
		12-13 yr	200-495	105-420			200-495	105-42
		14-15 yr	130-525	70-230			130-525	70-230
		16-19 yr	65-260	50-130			65-260	50-130
Phosphorus, inorganic	S,P(H)		mg/dL			mmol/L		
		0-5 days	4.8-8.2		×0.3229	1.55-2.65		
		1-3 yr	3.8-6.5			1.25-2.10		
		4-11 yr	3.7-5.6			1.20-1.80		
		12-15 yr	2.9-5.4			0.95-1.75		
		16-19 yr	2.7-4.7			0.90-1.50		
Potassium	S		mmol/L			mmol/L		
		0-1 wk	3.2-5.5		×1	3.3-5.5		
		1 wk-1 mo	3.4-6.0			3.4-6.0		
		1-6 mo	3.5-5.6			3.5-5.6		
		6 mo-1 yr	3.5-6.1			3.5-6.1		
		>1 yr	3.3-4.6			3.3-4.6		
	P(H)	3.5-4.5 mmol/L				3.5-4.5 mmol/L		
Prealbumin (transthyretin)	S		mg/dL			mg/L		
		0-5 days	6.0-21.0		×10	60-210		
		1-5 yr	14.0-30.0			140-300		
		6-9 yr	15.0-30.0			150-300		
		10-13 yr	20.0-36.0			200-360		
		14-19	22.0-45.0			220-450		
Protein, total	S		g/dL			g/L		
		Premature	4.3-7.6		×10	43-76		
		Newborn	4.6-7.4			46-74		
		1-7 yr	6.1-7.9			61-79		
		8-12 yr	6.4-8.1			64-81		
		13-19 yr	6.6-8.2			66-82		
Pyruvate (perchloric acid)	W	7-17 yr	0.076 ± 0.026 mmol/L		×1	0.076 ± 0.026 mmol/L		
Sodium	S,P (LiH, NH_4 H)		mmol/L			mmol/L		
		Newborn	133-146		×1	133-146		
		Infant	134-144			134-144		
		Child	134-143			134-143		
		Thereafter	135-145			135-145		
Thyroid-stimulating	S		µIU/L			µIU/L		

hormone (TSH)		0-3 days	1.00-20.00	×1	1.0-20.00
		3-30 days	0.5-6.5		0.50-6.50
		1-5 mo	0.5-6.0		0.5-6.0
		6 mo-18 yr	0.5-4.5		0.5-4.5
Thyroid uptake of radioactive iodine	Activity over thyroid gland	2 hr	<6%	×0.01	2 hr <0.06
		6 hr	3-20%		6 hr 0.03-0.20
		24 hr	8-30%		24 hr 0.08-0.30
Thyroid uptake of technetium-99m	Activity over thyroid gland	After 24 hr	0.4-3.0%	×0.01	Fractional uptake 0.004-0.030
Thyrotropin-releasing hormone (TRH)	P	5-60 pg/mL		×2.759	14-165 pmol/L
Thyroxine-binding globulin (TBG)	S		mg/dL		mg/L
		Cord blood	1.4-9.4	×10	14-94
		1-4 wk	1.0-9.0		10-90
		1-12 mo	2.0-7.6		20-76
		1-5 yr	2.9-5.4		29-54
		5-10 yr	2.5-5.0		25-50
		10-15 yr	2.1-4.6		21-46
		Adult	1.5-3.4		15-34
Thyroxine (T_4), total	S		µg/dL		nmol/L
		0-3 days	8.0-20.0	×12.9	103-258
		3-30 days	5.0-15.0		64-193
		31-365 days	6.0-14.0		77-180
		1-5 yr	4.5-11.0		58-142
		6-18 yr	4.5-10.0		58-129
Thyroxine (T_4), free	S		ng/dL		pmol/L
		0-3 days	2.00-5.00	×12.9	25.7-64.3
		3-30 days	0.90-2.20		11.6-28.3
		31 days-18 yr	0.7-2.00		9.0-25.7
Thyroxine (T_4), total	W	Newborn screen (filter paper) 6.2-22.0 µg/dL		×12.9	80-283 nmol/L
Triiodothyronine (T_3), free	S		pg/dL		pmol/L
		Cord blood	20-240	×0.01536	0.3-3.7
		1-3 days	200-610		3.1-9.4
		6 wk	240-560		3.7-8.6
		Adult (20-50 yr)	230-660		3.5-10.0
Triiodothyronine (T_3), total	S		ng/dL		nmol/L
		0-3 days	60-300	×0.0154	0.9-4.7
		4-365 days		90-260	
		1-6 yr	90-240		1.4-3.7
		7-11 yr	90-230		1.4-3.6
		12-18 yr	100-210		1.5-3.3
Urea nitrogen	S,P		mg/dL		mmol/L
		Cord blood	21-40	×0.357	7.5-14.3
		Premature (1 wk)	3-25		1.1-9.0
		Newborn	3-12		1.1-4.3

		infant or child	5-18		1.8-6.4
		Thereafter	7-18		2.5-6.4
Uric acid	S		mg/dL		µmol/L
		1-3 yr	1.8-5.0	×59.48	100-300
		4-6 yr	2.2-4.7		130-280
		7-9 yr	2.0-5.0		120-295
		10-11 yr M	2.3-5.4		135-320
		10-11 yr F	3.0-4.7		180-280
		12-13 yr M	2.7-6.7		160-400
		14-15 yr M	2.4-7.8		140-465
		12-15 yr F	3.0-5.8		180-345
		16-19 yr M	4.0-8.6		235-510
		16-19 yr F	3.0-5.9		180-350

[*] In preparing the reference range listings, a number of abbreviations, symbols, and codes were used (see Table 748.2).

[†] Reference values are shown in SI units (International System of Units) and U.S. units (Traditional Units).]

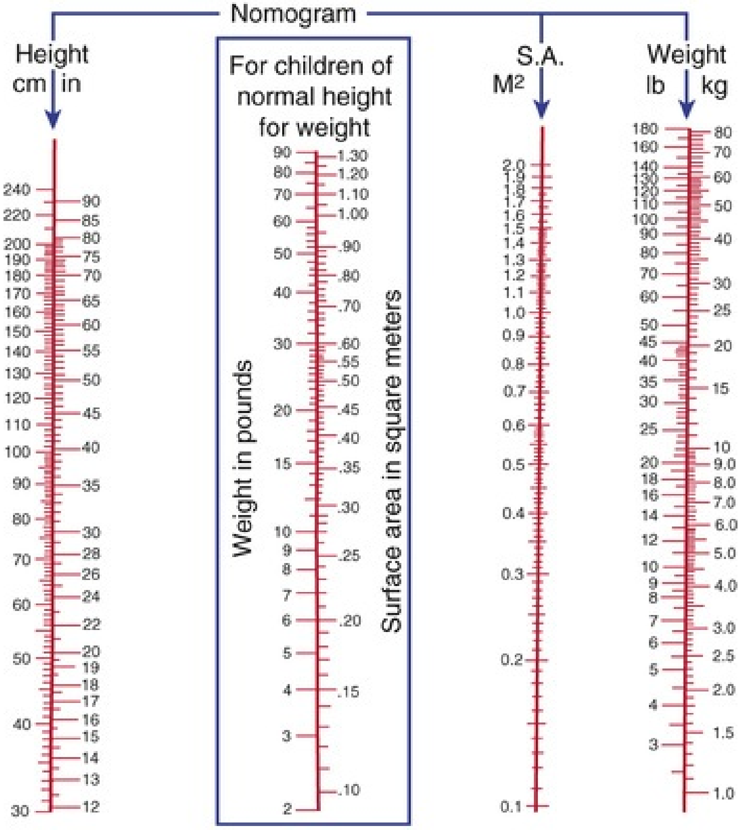
Nomogram
Height
cm in
For children of normal height for weight
Weight in pounds
Surface area in square meters
S.A.
M2
Weight
lb kg

Alternative (Mosteller's formula):

$$\text{Surface area (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3600}}$$

FIG. 748.1 Nomogram for the estimation of surface area. The surface area is indicated where a straight line that connects the height and weight levels intersects the surface area column, or if the patient is roughly of average size, from the weight alone *(enclosed area)* . (Nomogram modified from the data of E. Boyd by C.D. West. See also Briars GL, Bailey BJ: Surface area estimation: pocket calculator v nomogram, *Arch Dis Child* 70:246–247, 1994.)

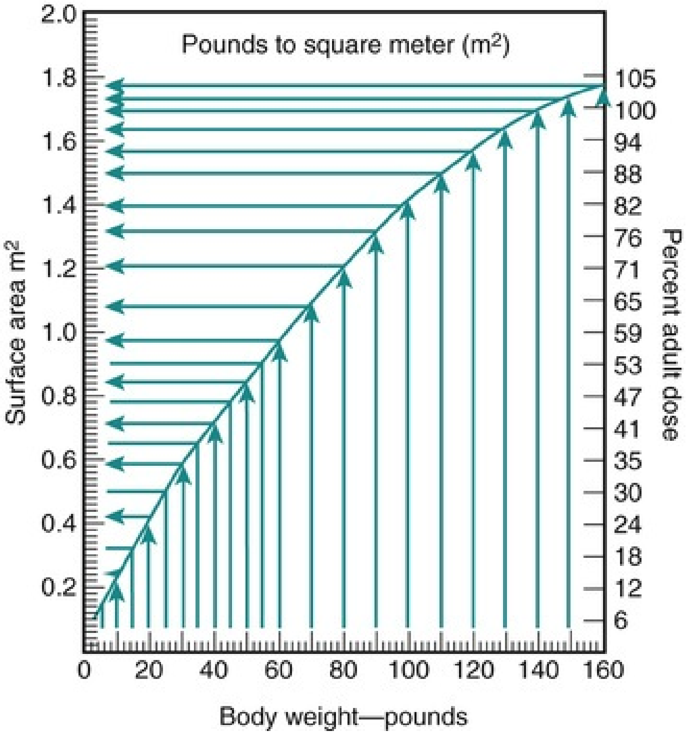

FIG. 748.2 Relationships among body weight (lb), body surface area, and adult dosage. The surface area values correspond with those set forth by Crawford JD, Terry ME, Rourke GM: Simplification of drug dosage calculation by application of the surface area principle, *Pediatrics* 5:783–790, 1950. Note that the 100% adult dose is for a patient weighing approximately 140 lb and having a surface area of approximately 1.7 m^2 . (From Talbot NB, Richie RH, Crawford JH: *Metabolic homeostasis: a syllabus for those concerned with the care of patients,* Cambridge, MA, 1959, Harvard University Press.)

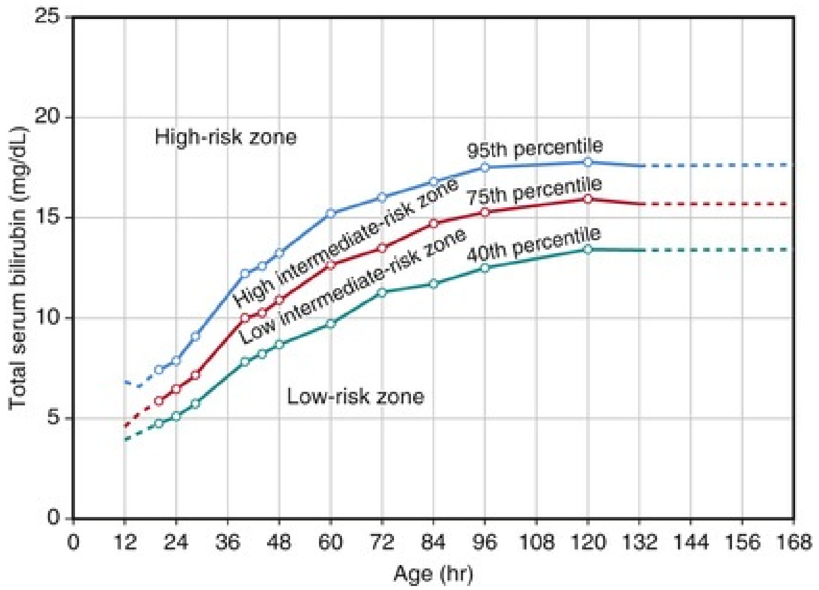

FIG. 748.3 **Nomogram for risk assessment of hyperbilirubinemia. (From Bhutani VK, Johnson L, Sivieri EM: Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns, *Pediatrics* 103:6–14, 1999, Fig 2.)**

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FPIES, Food protein-induced enterocolitis syndrome

FPLD, Familial partial lipodystrophy

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FSGS, Focal segmental glomerulosclerosis

FSH, Follicle-stimulating hormone

FTT, Failure to thrive

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FVC, Forced vital capacity

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GABA, γ-Aminobutyric acid

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- dosages of, 3104*t* –3105*t*
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GBS, Group B streptococcus

GCS, Glasgow Coma Scale

GCTs, Germ cell tumors

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HFO, High-frequency oscillation

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HIDS, Hyperimmunoglobulinemia D with periodic fever

HIF, Hypoxia-inducible factor

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HIT, Heparin-induced thrombocytopenia

HIV/AIDS, Human immunodeficiency virus/acquired immunodeficiency syndrome

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HIV-seronegative host, nontuberculous mycobacteria infection and, 1588*t*

HIV-seropositive host, nontuberculous mycobacteria infection and, 1588*t*

HL, Hodgkin lymphoma

HLA, Human leukocyte antigen

HLH, Hemophagocytic lymphohistiocytosis

HLMs, Hemosiderin-laden macrophages

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HMS, Hyperreactive malarial splenomegaly

HNPCC, Hereditary nonpolyposis colon cancer

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HPFH, Hereditary persistence of fetal hemoglobin

HPS, Hepatopulmonary syndrome

HPV, Human papillomavirus

HRCT bronchiectasis, 2279

HRV-associated wheezing, 1742

HS, Hereditary spherocytosis

HSCT, Hematopoietic stem cell transplantation

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HSILs, High-grade squamous intraepithelial lesions

HSV, Herpes simplex virus

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IAP, Intracisternal A particle

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IBD, Inflammatory bowel disease

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ICF, Intracellular fluid

ICH, Intracranial hemorrhage

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ICP, Intracranial pressure

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IDDM, Insulin-dependent diabetes mellitus

IDEA, Individuals with Disabilities Education Act

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IED, Intermittent explosive disorder

IEM, Inborn errors of metabolism

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IGIM, Immune globulin intramuscular

IGIV, Immune globulin intravenous

IGSC, Immune globulin subcutaneous

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IPD, Infantile Pompe disease

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IPH, Idiopathic pulmonary hemosiderosis

IPNHLRC, International Pediatric Non-Hodgkin Lymphoma Response Criteria

IPNHLSS, International Pediatric Non-Hodgkin Lymphoma Staging System

IPV, Intimate partner violence

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IRIS, Immune reconstitution inflammatory syndrome

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ISF, Insulin sensitivity factor

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ISSVA, International Society for the Study of Vascular Anomalies

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ITP, Idiopathic thrombocytopenic purpura

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IUD, Intrauterine device

IUGR, Intrauterine growth restriction

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IVH, Intraventricular hemorrhage

IVIG, Intravenous immunoglobulin

IWE, Impairment in written expression

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JXG, Juvenile xanthogranuloma

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LMWH, Low molecular weight heparin

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LSIL, Low-grade squamous intraepithelial lesion

LSMT, Life-sustaining medical treatment

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NPRP, National Pediatric Readiness Project

NSAIDs, Nonsteroidal antiinflammatory drugs

NSSI, Nonsuicidal self-injury

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TNSALP, Tissue-nonspecific alkaline phosphatase isoenzyme

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